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Nelson TEXTBOOK *of* PEDIATRICS

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Nelson TEXTBOOK *of* PEDIATRICS

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To the Child's Physician and especially to those who through their expressed confidence in past editions of this book have provided the stimulus for this revision.
Waldo E. Nelson, 9/e, 1969

This is as true in 2015 as it was in 1969.
R.M. Kliegman, 20/e, 2015

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Respiratory Distress and Failure
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Shigella
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Disorders of Phagocyte Function

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Care of Abrasions and Minor Lacerations

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Clostridium difficile *Infection*

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Principles of Antifungal Therapy

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Ankylosing Spondylitis and Other Spondyloarthritides
Reactive and Postinfectious Arthritis

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The Foot and Toes
Leg-Length Discrepancy
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Nonvenereal Treponemal Infections
Leptospira
Relapsing Fever (Borrelia)

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Psychotherapy
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Somatic Symptom and Related Disorders
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Motor Disorders and Habits
Mood Disorders
Suicide and Attempted Suicide
Disruptive, Impulse-Control, and Conduct Disorders
Autism Spectrum Disorder
Childhood Psychoses

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Coronaviruses

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Ascariasis (Ascaris lumbricoides)
Trichuriasis (Trichuris trichiura)
Enterobiasis (Enterobius vermicularis)
Strongyloidiasis (Strongyloides stercoralis)
Lymphatic Filariasis (Brugia malayi, Brugia timori, *and* Wuchereria bancrofti)
Other Tissue Nematodes
Toxocariasis (Visceral and Ocular Larva Migrans)
Trichinosis (Trichinella spiralis)

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Mucolipidoses
Disorders of Glycoprotein Degradation and Structure
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Morphology of the Skin
Evaluation of the Patient
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Hypofunction of the Testes
Pseudoprecocity Resulting from Tumors of the Testes
Gynecomastia
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Vesicoureteral Reflux
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Anomalies of the Bladder
Neuropathic Bladder
Enuresis and Voiding Dysfunction
Anomalies of the Penis and Urethra
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Overview and Assessment of Variability
Assessment of Fetal Growth and Development
The First Year
The Second Year
The Preschool Years
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Nutritional Requirements
Feeding Healthy Infants, Children, and Adolescents

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Inflammatory Bowel Disease

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University of Washington School of Public Health
Adjunct Professor of Pediatrics
University of Washington School of Medicine
Seattle, Washington
Injury Control

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University of Naples Federico II
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Chronic Diarrhea

Reut Gurion, DO
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University Hospitals Case Medical Center
Rainbow Babies & Children's Hospital
Cleveland, Ohio
Miscellaneous Conditions Associated with Arthritis

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Cleveland Clinic Foundation
Cleveland, Ohio
Hereditary Stomatocytosis
Glucose-6-Phosphate Dehydrogenase Deficiency and Related Deficiencies

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University of California, San Diego
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Chief Scientific Officer
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Diagnostic Approach to Respiratory Disease

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Howard W. Smith Professor and Interim Chair
Lawrence Savetsky Professor
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Columbia University College of Physicians and Surgeons
Director, Pediatric Otolaryngology—Head and Neck Surgery
New York-Presbyterian Morgan Stanley Children's Hospital
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Congenital Disorders of the Nose
Acquired Disorders of the Nose
Nasal Polyps
General Considerations and Evaluation (Ear)
Hearing Loss
Congenital Malformations
External Otitis (Otitis Externa)
The Inner Ear and Diseases of the Bony Labyrinth
Traumatic Injuries of the Ear and Temporal Bone
Tumors of the Ear and Temporal Bone

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Maximizing Children's Health: Screening, Anticipatory Guidance, and Counseling

Scott B. Halstead, MD
Professor of Pediatrics and Medical Genetics
University of British Columbia Faculty of Medicine
British Columbia's Children's Hospital
Vancouver, British Columbia, Canada
Arboviral Infections in North America
Arboviral Infections Outside North America
Dengue Fever and Dengue Hemorrhagic Fever
Yellow Fever
Ebola and Other Viral Hemorrhagic Fevers
Hantavirus Pulmonary Syndrome

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Chlamydia (Chlamydophila) pneumoniae
Chlamydia trachomatis
Psittacosis (Chlamydia psittaci)

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Northwestern University Feinberg School of Medicine
Chicago, Illinois
Diffuse Lung Diseases in Childhood

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Seizures in Childhood

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Disorders of Purine and Pyrimidine Metabolism

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Pediatric Emergencies and Resuscitation

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Non–Group A or B Streptococci
Enterococcus

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Cholestasis

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Tuberculosis (Mycobacterium tuberculosis)

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Sudden Infant Death Syndrome

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Influenza Viruses

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UT Health School of Dentistry
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General Considerations (Bone and Joint Disorders)
Disorders Involving Cartilage Matrix Proteins
Disorders Involving Transmembrane Receptors
Disorders Involving Ion Transporters
Disorders Involving Transcription Factors
Disorders Involving Defective Bone Resorption
Disorders for Which Defects Are Poorly Understood or Unknown

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Respiratory Pathophysiology and Regulation

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Sinusitis
Retropharyngeal Abscess, Lateral Pharyngeal (Parapharyngeal) Abscess, and Peritonsillar Cellulitis/Abscess

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Biologic and Chemical Terrorism

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Campylobacter
Yersinia
Aeromonas *and* Plesiomonas

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Headaches

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Retinoblastoma
Gonadal and Germ Cell Neoplasms
Neoplasms of the Liver
Benign Vascular Tumors
Melanoma
Nasopharyngeal Carcinoma
Adenocarcinoma of the Colon and Rectum
Desmoplastic Small Round Cell Tumor

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Lymphoma

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Vulvovaginitis

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Congenital Anomalies of the Larynx, Trachea, and Bronchi
Foreign Bodies in the Airway
Laryngotracheal Stenosis and Subglottic Stenosis
Neoplasms of the Larynx, Trachea, and Bronchi

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Adolescent Physical and Social Development
Transitioning to Adult Care
The Breast

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The Acquired Pancytopenias

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The Hip

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Arthrogryposis

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General Considerations (Bone and Joint Disorders)
Disorders Involving Cartilage Matrix Proteins
Disorders Involving Transmembrane Receptors
Disorders Involving Ion Transporters
Disorders Involving Transcription Factors
Disorders Involving Defective Bone Resorption
Disorders for Which Defects Are Poorly Understood or Unknown

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Hookworms (Necator americanus *and* Ancylostoma *spp.)*

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Liver Transplantation

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Thyroid Development and Physiology
Defects of Thyroxine-Binding Globulin
Hypothyroidism
Thyroiditis
Goiter
Hyperthyroidism
Carcinoma of the Thyroid

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Polycystic Ovary Syndrome and Hirsutism

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Neoplasms of the Kidney

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Growth and Development (Eye)
Examination of the Eye
Abnormalities of Refraction and Accommodation
Disorders of Vision
Abnormalities of Pupil and Iris
Disorders of Eye Movement and Alignment
Abnormalities of the Lids
Disorders of the Lacrimal System
Disorders of the Conjunctiva
Abnormalities of the Cornea
Abnormalities of the Lens
Disorders of the Uveal Tract
Disorders of the Retina and Vitreous
Abnormalities of the Optic Nerve
Childhood Glaucoma
Orbital Abnormalities
Orbital Infections
Injuries to the Eye

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Melanoma

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Gonadal and Germ Cell Neoplasms
Adenocarcinoma of the Colon and Rectum

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Principles of Therapy (Skin)

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Animal and Human Bites

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Sudden Infant Death Syndrome

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Pyloric Stenosis and Other Congenital Anomalies of the Stomach

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Division of Developmental Biology
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Morphogenesis of the Liver and Biliary System

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Somatic Symptom and Related Disorders

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Mitochondrial Hepatopathies

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Actinomyces
Nocardia
Tularemia (Francisella tularensis)
Brucella

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Contraception

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Viral Hepatitis

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Chronic Fatigue Syndrome
Epstein-Barr Virus
Human T-Lymphotropic Viruses (1 and 2)

Chandy C. John, MD, MS
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Indiana University School of Medicine
Riley Hospital for Children at Indiana University Health
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Health Advice for Children Traveling Internationally
Giardiasis and Balantidiasis
Malaria (Plasmodium)

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Disorders of Lipoprotein Metabolism and Transport

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Congenital Anomalies of the Central Nervous System
Encephalopathies

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Monocytes, Macrophages, and Dendritic Cells
The Complement System
Disorders of the Complement System

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Principles of Drug Therapy

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Chronic Fatigue Syndrome

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Vesiculobullous Disorders
Nutritional Dermatoses

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Hyperpigmented Lesions
Cutaneous Bacterial Infections
Cutaneous Fungal Infections
Cutaneous Viral Infections
Arthropod Bites and Infestations

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Headaches

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Cultural Issues in Pediatric Care

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Fever
Fever Without a Focus

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Hypofunction of the Ovaries
Pseudoprecocity Resulting from Lesions of the Ovary

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Osteomyelitis
Septic Arthritis

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Management of Musculoskeletal Injury
Specific Sports and Associated Injuries

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Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases

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Rumination and Pica

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Ascariasis (Ascaris lumbricoides)
Trichuriasis (Trichuris trichiura)
Enterobiasis (Enterobius vermicularis)
Strongyloidiasis (Strongyloides stercoralis)
Lymphatic Filariasis (Brugia malayi, Brugia timori, *and* Wuchereria bancrofti)
Other Tissue Nematodes
Toxocariasis (Visceral and Ocular Larva Migrans)
Trichinosis (Trichinella spiralis)

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Assessment of Growth

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Principles of Drug Therapy

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Congenital Disorders of the Nose
Acquired Disorders of the Nose
Nasal Polyps
General Considerations and Evaluation (Ear)
Hearing Loss
Congenital Malformations
External Otitis (Otitis Externa)
The Inner Ear and Diseases of the Bony Labyrinth
Traumatic Injuries of the Ear and Temporal Bone
Tumors of the Ear and Temporal Bone

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Neurodevelopmental Function and Dysfunction in the School-Age Child

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Foreign Bodies and Bezoars

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Complementary Therapies and Integrative Medicine

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Malrotation
Meckel Diverticulum and Other Remnants of the Omphalomesenteric Duct
Intussusception
Malformations
Ascites

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Effects of War on Children

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Otitis Media

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Embryology, Anatomy, and Function of the Esophagus
Congenital Anomalies: Esophageal Atresia and Tracheoesophageal Fistula
Obstructing and Motility Disorders of the Esophagus
Dysmotility
Hiatal Hernia
Gastroesophageal Reflux Disease
Eosinophilic Esophagitis and Non–Gastroesophageal Reflux Disease Esophagitis
Esophageal Perforation
Esophageal Varices
Ingestions

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Diagnosis of Allergic Disease
Principles of Treatment of Allergic Disease

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Schistosomiasis (Schistosoma)
Flukes (Liver, Lung, and Intestinal)

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Congenital Anomalies of the Central Nervous System

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Pediatric Stroke

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Defects in Metabolism of Carbohydrates

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Rumination and Pica

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Coccidioidomycosis (Coccidioides *species*)

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Interfacility Transport of the Seriously Ill or Injured Pediatric Patient
Acute Care of the Victim of Multiple Trauma

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Blastomycosis (Blastomyces dermatitidis)

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Surgical Conditions of the Anus and Rectum

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Refeeding Syndrome
Liver Abscess
Generalized Arterial Calcification of Infancy/Idiopathic Infantile Arterial Calcification
Arterial Calcifications Caused by Deficiency of CD73
Female Genital Mutilation/Cutting
Reflex Seizures (Stimulus Precipitated Seizures)
Nodding Syndrome

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Parvoviruses

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Chlamydia (Chlamydophila) pneumoniae
Psittacosis (Chlamydia psittaci)

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Brain Tumors in Childhood

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Histiocytosis Syndromes of Childhood

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Thyroid Development and Physiology
Defects of Thyroxine-Binding Globulin
Hypothyroidism
Thyroiditis
Goiter
Hyperthyroidism
Carcinoma of the Thyroid

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Pulmonary Abscess

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Chemical Pollutants

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Epidemiology and Prevention of Injuries
Heat Injuries
Female Athletes: Menstrual Problems and the Risk of Osteopenia
Performance-Enhancing Aids

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Abused and Neglected Children

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Varicella-Zoster Virus Infections

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The Knee

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Integration of Genetics into Pediatric Practice
The Genetic Approach in Pediatric Medicine
The Human Genome
Patterns of Genetic Transmission
Cytogenetics
Genetics of Common Disorders

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Neurologic Evaluation
Chorea, Athetosis, Tremor

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Evaluation of Children with Suspected Intestinal Malabsorption
Enzyme Deficiencies

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The Anemias
Congenital Hypoplastic Anemia (Diamond-Blackfan Anemia)
Pearson Syndrome
Acquired Pure Red Blood Cell Anemia
Anemia of Chronic Disease and Renal Disease
Congenital Dyserythropoietic Anemias
Physiologic Anemia of Infancy
Megaloblastic Anemias

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Bronchopulmonary Dysplasia

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Atopic Dermatitis (Atopic Eczema)

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Normal Digestive Tract Phenomena
Major Symptoms and Signs of Digestive Tract Disorders
Normal Development, Structure, and Function (Stomach)
Pyloric Stenosis and Other Congenital Anomalies of the Stomach
Intestinal Atresia, Stenosis, and Malrotation
Intestinal Duplications, Meckel Diverticulum, and Other Remnants of the Omphalomesenteric Duct
Motility Disorders and Hirschsprung Disease
Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions
Foreign Bodies and Bezoars
Functional Abdominal Pain (Nonorganic Chronic Abdominal Pain)
Malformations
Ascites
Peritonitis

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Growth and Development (Eye)
Examination of the Eye
Abnormalities of Refraction and Accommodation
Disorders of Vision
Abnormalities of Pupil and Iris
Disorders of Eye Movement and Alignment
Abnormalities of the Lids
Disorders of the Lacrimal System
Disorders of the Conjunctiva
Abnormalities of the Cornea
Abnormalities of the Lens
Disorders of the Uveal Tract
Disorders of the Retina and Vitreous
Abnormalities of the Optic Nerve
Childhood Glaucoma
Orbital Abnormalities
Orbital Infections
Injuries to the Eye

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Laboratory Testing in Infants and Children
Reference Intervals for Laboratory Tests and Procedures

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Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation
Hematopoietic Stem Cell Transplantation from Alternative Sources and Donors
Graft-Versus-Host Disease, Rejection, and Venoocclusive Disease
Infectious Complications of Hematopoietic Stem Cell Transplantation
Late Effects of Hematopoietic Stem Cell Transplantation

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Pertussis (Bordetella pertussis *and* Bordetella parapertussis)

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*Pertussis (*Bordetella pertussis *and* Bordetella parapertussis*)*
Pleurisy, Pleural Effusions, and Empyema
Pneumothorax
Hemothorax
Chlyothorax

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Digestive System Disorders
Blood Disorders

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Diabetes Insipidus
Other Abnormalities of Arginine Vasopressin Metabolism and Action

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Genetic Approaches to Rare and Undiagnosed Diseases

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Lead Poisoning

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Principles of Antimycobacterial Therapy

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Diseases of the Neonate
Cutaneous Defects
Ectodermal Dysplasias
Vascular Disorders
Cutaneous Nevi
Disorders of Keratinization
Disorders of the Sweat Glands
Disorders of Hair
Disorders of the Nails
Tumors of the Skin

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Rubella
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Aspartic Acid (Canavan Disease)

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Loss, Separation, and Bereavement

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Pulmonary Tumors
Extrapulmonary Diseases with Pulmonary Manifestations

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Lipidoses (Lysosomal Storage Disorders)
Mucolipidoses
Disorders of Glycoprotein Degradation and Structure

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Failure to Thrive

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Toxoplasmosis (Toxoplasma gondii)

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Hansen Disease (Mycobacterium leprae)
Mycoplasma pneumoniae
Genital Mycoplasmas (Mycoplasma hominis, Mycoplasma genitalium, *and* Ureaplasma urealyticum)

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Leishmaniasis (Leishmania)

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Metabolic Diseases of the Liver

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Seizures in Childhood
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Campylobacter
Yersinia

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Listeria monocytogenes
Pseudomonas, Burkholderia, *and* Stenotrophomonas

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Disorders of Lipoprotein Metabolism and Transport

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Demyelinating Disorders of the Central Nervous System

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Leukopenia
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Fever Without a Focus

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Examination of the Eye
Abnormalities of Refraction and Accommodation
Disorders of Vision
Abnormalities of Pupil and Iris
Disorders of Eye Movement and Alignment
Abnormalities of the Lids
Disorders of the Lacrimal System
Disorders of the Conjunctiva
Abnormalities of the Cornea
Abnormalities of the Lens
Disorders of the Uveal Tract
Disorders of the Retina and Vitreous
Abnormalities of the Optic Nerve
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Obstructing and Motility Disorders of the Esophagus
Dysmotility
Hiatal Hernia
Gastroesophageal Reflux Disease
Eosinophilic Esophagitis and Non–Gastroesophageal Reflux Disease Esophagitis
Esophageal Perforation
Esophageal Varices
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Hemolytic Anemias Resulting from Extracellular Factors—Immune Hemolytic Anemias

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Lower Urinary Tract Causes of Hematuria
Introduction to the Child with Proteinuria
Fixed Proteinuria
Nephrotic Syndrome
Cortical Necrosis

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Streptococcus pneumoniae (*Pneumococcus*)

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Growth and Development (Eye)
Examination of the Eye
Abnormalities of Refraction and Accommodation
Disorders of Vision
Abnormalities of Pupil and Iris
Disorders of Eye Movement and Alignment
Abnormalities of the Lids
Disorders of the Lacrimal System
Disorders of the Conjunctiva
Abnormalities of the Cornea
Abnormalities of the Lens
Disorders of the Uveal Tract
Disorders of the Retina and Vitreous
Abnormalities of the Optic Nerve
Childhood Glaucoma
Orbital Abnormalities
Orbital Infections
Injuries to the Eye

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Upper Urinary Tract Causes of Hematuria
Hematologic Diseases Causing Hematuria
Anatomic Abnormalities Associated with Hematuria
Transient Proteinuria
Orthostatic (Postural) Proteinuria
Tubulointerstitial Nephritis
Toxic Nephropathy

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Treatment of Rheumatic Diseases
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Amebiasis
*Trichomoniasis (*Trichomonas vaginalis*)*
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Amebiasis
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Metabolic Myopathies
Disorders of Neuromuscular Transmission and of Motor Neurons
Hereditary Motor-Sensory Neuropathies
Toxic Neuropathies
Autonomic Neuropathies
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Foreign Bodies in the Airway
Laryngotracheal Stenosis and Subglottic Stenosis
Neoplasms of the Larynx, Trachea, and Bronchi

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The Genetic Approach in Pediatric Medicine
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Patterns of Genetic Transmission

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von Willebrand Disease
Hereditary Predisposition to Thrombosis
Thrombotic Disorders in Children
Postneonatal Vitamin K Deficiency
Liver Disease
Acquired Inhibitors of Coagulation
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Definitions and Classification of Hemolytic Anemias
Hereditary Spherocytosis
Hereditary Elliptocytosis
Hereditary Stomatocytosis
Paroxysmal Nocturnal Hemoglobinuria and Acanthocytosis
Enzymatic Defects
Hemolytic Anemias Resulting from Extracellular Factors—Immune Hemolytic Anemias
Hemolytic Anemias Secondary to Other Extracellular Factors

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Allergic Rhinitis
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Atopic Dermatitis (Atopic Eczema)
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Ocular Allergies
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The Spine
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Nephrogenic Diabetes Insipidus
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Disorders of Vision
Abnormalities of Pupil and Iris
Disorders of Eye Movement and Alignment
Abnormalities of the Lids
Disorders of the Lacrimal System
Disorders of the Conjunctiva
Abnormalities of the Cornea
Abnormalities of the Lens
Disorders of the Uveal Tract
Disorders of the Retina and Vitreous
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Childhood Glaucoma
Orbital Abnormalities
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Preface

Whoever saves one life it is considered as if they saved an entire world.
— Babylonian Talmud

The 20th edition of *Nelson Textbook of Pediatrics* continues in its tradition of being an essential resource for pediatricians as they diagnose and treat the infants, children, and adolescents of the 21st century. The 20th edition has been thoroughly revised, updated, and edited to keep up with the growing data accumulated from basic, clinical, and population-based research. The promise that translational medicine will improve the lives of all children is greater than ever. Knowledge of human development, behavior, and diseases from the molecular to sociologic levels is increasing at fantastic rates, leading to greater understanding of health and illness in children and substantial improvements in health quality for those who have access to health care. These exciting scientific advances also provide hope to effectively address prevention and treatment of new and emerging diseases threatening children and their families.

The field of pediatrics encompasses advocacy for all children throughout the world and must address societal inequalities of important resources required for normal development, as well as protection from natural and manmade disasters. Unfortunately, many children throughout the world have not benefited from the significant advances in the prevention and treatment of health-related problems, primarily because of a lack of political will and misplaced priorities. For our increasing knowledge to benefit all children and youth, medical advances and good clinical practice must always be coupled with effective advocacy.

This new edition of *Nelson Textbook of Pediatrics* attempts to provide the essential information that practitioners, house staff, medical students, and other care providers involved in pediatric health care throughout the world need to understand to effectively address the enormous range of biologic, psychologic, and social problems that our children and youth may face. Our goal is to be comprehensive yet concise and reader friendly, embracing both the new advances in clinical science and the time-honored art of pediatric practice.

The 20th edition is reorganized and revised from the previous edition. There are many additions of new diseases and new chapters, as well as substantial expansion or significant modification of others. In addition many more tables, photographs, imaging studies, and illustrative figures, as well as up-to-date references, have been added. Although, to an ill child and his or her family and physician, even the rarest disorder is of central importance, all health problems cannot possibly be covered with the same degree of detail in one general textbook of pediatrics. Thus, leading articles and subspecialty texts are referenced and should be consulted when more information is desired.

The outstanding value of the 20th edition of the textbook is due to its expert and authoritative contributors. We are all indebted to these dedicated authors for their hard work, knowledge, thoughtfulness, and good judgment. Our sincere appreciation also goes to Kate Dimock and Jennifer Shreiner at Elsevier and to Carolyn Redman at the Pediatric Department of the Medical College of Wisconsin. In addition, we thank Barbara Ruggeri for her excellent library science skills and for keeping us up to date with the literature. We have all worked hard to produce an edition that will be helpful to those who provide care for children and youth and to those desiring to know more about children's health worldwide.

In this edition we have had informal assistance from many faculty and house staff of the departments of pediatrics at the Medical College of Wisconsin, Wayne State University School of Medicine, University of Pennsylvania School of Medicine, and University of Rochester School of Medicine. The help of these individuals and of the many practicing pediatricians from around the world who have taken the time to offer thoughtful feedback and suggestions is always greatly appreciated and helpful.

Last and certainly not least, we especially wish to thank our families for their patience and understanding, without which this textbook would not have been possible.

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VIDEOS

Nelson TEXTBOOK *of* PEDIATRICS

The Field of Pediatrics

PART I

Chapter 1

Overview of Pediatrics

Bonita F. Stanton and Richard E. Behrman

Pediatrics is the only discipline dedicated to all aspects of the well-being of infants, children, and adolescents, including their health; their physical, mental, and psychologic growth and development; and their opportunity to achieve full potential as adults. Pediatricians must be concerned not only with particular organ systems and biologic processes, but also with environmental, social, and political influences, which have a major impact on the health and well-being of children and their families.

Children cannot advocate for themselves. As the professionals whose entire purpose is to advance the well-being of children, pediatricians must be advocates for the individual child and for all children, irrespective of culture, religion, gender, race, or ethnicity or of local, state, or national boundaries. The more politically, economically, or socially disenfranchised a population or a nation is, the greater the need for advocacy for children. The young are often among the most vulnerable or disadvantaged in society and thus their needs require special attention. As divides between nations blur through modern transportation, communication and economics, through global climate change, through contemporary means of warfare, and through uneven development within and across countries, a global, rather than a national, perspective for the field of pediatrics becomes both a reality and a necessity. The interrelation of health issues across the globe has achieved widespread recognition in the wake of the SARS (severe acute respiratory syndrome) and AIDS epidemics, expansions in the pandemics of cholera and West Nile virus, war and bioterrorism, the tsunami of 2004, the global recession beginning in 2008, the "Arab Spring" beginning in 2010, and the growing severity of hurricanes and cyclones.

More than a century ago, pediatrics emerged as a medical specialty in response to increasing awareness that the health problems of children differ from those of adults and that a child's response to illness and stress varies with age. In 1959, the United Nations issued the Declaration of the Rights of the Child, articulating the universal presumption that children everywhere have fundamental needs and rights.

VITAL STATISTICS ABOUT CHILD HEALTH (See Also Chapter 1.1)

From 1990 to 2010, the world population grew at an annual rate of 1.3% per yr, down from 1.8% annually during the prior 20 yr. The annual growth rate from 2010 to 2030 is expected to further decline to 0.9%. Worldwide, children younger than age 18 yr account for 2.2 billion (30%) of the world's 7.02 billion persons. In 2010, there were an estimated 135 million births worldwide, 121 million (90%) of which were in developing countries. India, with 27.2 million births annually, is home to the largest number, followed by China at 16.5 million.

Despite global interconnectedness, the health problems of children and youth vary widely between and within populations in the nations of the world depending on a number of often interrelated factors. These factors include (1) economic considerations (economic disparities); (2) educational, social, and cultural considerations; (3) the prevalence and ecology of infectious agents and their hosts; (4) climate and geography; (5) agricultural resources and practices (nutritional resources); (6) stage of industrialization and urbanization; (7) the gene frequencies for some disorders; (8) the health and social welfare infrastructure available within these countries; and (9) political focus and stability. The state of health of any community is defined by the incidence of illness and by data from studies that show the changes that occur with time and in response to programs of prevention, case finding, therapy, and surveillance. To ensure that the needs of children and adults across the globe were not obscured by local needs, in 2000 the international community established 8 Millennium Development Goals (MDGs) to be achieved by 2015 (http://www.countdown2015mnch.org). Although all 8 MDGs impact child well-being, MDG 4 ("Reduce by two-thirds, between 1990 and 2015, the under-five mortality rate") is exclusively focused on children.

Great strides have been made toward achieving the MDGs. Globally, there has been a reduction in under-5 mortality since 1990 from 90 to 48 deaths per 1,000 live births, with a reduction from 15 to 6 deaths in developed countries and from 99 to 53 deaths in developing countries. With the exception of sub-Saharan Africa and Oceania, all global regions reduced their under-5 mortality rate by more than half from 1990 to 2012. There were nearly 13 million under-5 deaths in 1990; 2006 marked the first year that there were fewer than 10 million deaths (9.7 million), which further decreased to 9.0 million in 2007, 8.8 million in 2008, 7.6 million in 2010, and 6.6 million in 2012. Despite these substantial successes, the annual rate of reduction in the global under-5 mortality rate of 3.9% remains below the MDG targeted rate of 4.4%, necessary to achieve the goal of a ⅔ reduction in the 1990 rate by 2015 (Fig. 1-1).

The infant mortality rate (deaths of children <1 yr) accounts for 83% of the under-5 mortality rate in industrialized countries, but only 64% of the rate in the least-developed nations. Neonatal (<1 mo) death contributes substantially to the under-5 mortality rate, growing in proportion as the under-5 death rate decreases. The neonatal mortality rate has been slower to decline. Globally, the neonatal mortality rate of 23 per 1,000 live births represents 57% of the infant mortality rate of 40 per 1,000 live births and 40% of the under-5 death rate (up from 37% in 1990). The neonatal mortality rate is responsible for 50% of the under-5 mortality rate in industrialized nations, 40% of the rate in developing countries, but only 33% in the least-developed countries. Most of the decline in infant mortality in the United States and other industrialized countries since 1970 is attributable to a decrease in the birthweight-specific infant mortality rate related to neonatal intensive care, not to the prevention of low-birthweight births (see Chapter 93).

Across the globe, there are significant variations in infant mortality rates by nation, by region, by economic status, and by level of industrial development, the categorizations employed by the World Bank and the United Nations (Table 1-1; see also Figs. 1-8 and 1-9). As of 2012 three nations in the world still have an under-5 mortality rate of ≥150 per 1,000 live births (Sierra Leone, 182; Angola, 164, Chad, 150), with an additional 13 nations having ≥100 deaths per 1,000 live births. Although these 3 nations are among the poorest in the world, many of their economic matches have enjoyed greater improvements in child survival in recent years, demonstrating that economics are important but that other factors, such as political will, are also important. Similarly, in 2012, the United States, with one of the 10 highest gross national incomes in the world, had an under-5 mortality rate of 7 per 1,000 live births; 39 nations had lower under-5 mortality rates, with 9 countries having a rate of 3 and 2 countries having a rate of 2 per 1,000 live births.

Causes of under-5 mortality differ markedly between developed and developing nations. In developing countries, 66% of all deaths resulted from infectious and parasitic diseases. Among the 42 countries having

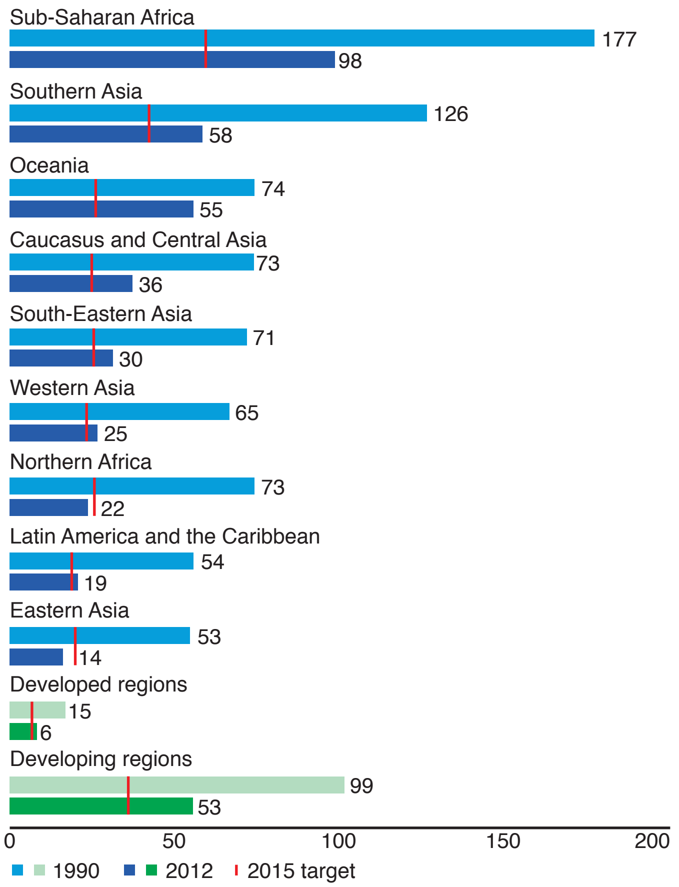

Figure 1-1 Despite substantial progress, the world is still falling short of the MDG child mortality target. Under-5 mortality rate per 1,000 live births, 1990 and 2012 (deaths per 1,000 live births). *(From* Millennium Development Goals Report, 2014. *New York, 2014, United Nations, p. 24.)*

90% of childhood deaths, diarrheal disease accounted for 22% of deaths, pneumonia 21%, malaria 9%, AIDS 3%, and measles 1%. Neonatal causes contributed to 33%. The contribution for AIDS varies greatly by country, being responsible for a substantial proportion of deaths in some countries and negligible amounts in others. Likewise, there is substantial co-occurrence of infections; a child may die with HIV, malaria, measles, and pneumonia. Infectious diseases are still responsible for much of the mortality in developing countries. In the United States, pneumonia (and influenza) accounted for only 2% of under-5 deaths, with only negligible contributions from diarrhea and malaria. Unintentional injury is the most common cause of death among U.S. children ages 1-4 yr, accounting for approximately 33% of deaths, followed by congenital anomalies (11%), homicides (9%), and malignant neoplasms (8%). Other causes accounted for <5% of total mortality within this age group (Table 1-2). Although unintentional injuries in developing countries are proportionately less important causes of mortality than in developed countries, their absolute rates and their contributions to morbidity are substantially greater.

Just as economic status of a country as a whole is closely correlated with child survival, so too is relative wealth within a country. Poorer children in nations worldwide have higher death rates than their wealthier national counterparts (Fig. 1-2).

Causes of death vary by developmental status of the nation. In the United States, the 3 leading causes of death among infants were congenital anomalies, disorders related to gestation and low birthweight, and sudden infant death (see Table 1-2). By contrast, in developing countries, the majority of infant deaths are caused by infectious diseases; even in the neonatal period, 24% of deaths are caused by severe infections and 7% by tetanus. Although immunization rates remain higher in industrialized nations compared to developing nations, this gap is closing. In 2010, immunization percentage rates against diphtheria, pertussis, tetanus, measles, and polio were in the mid-90s; comparable levels in developing countries were in the mid-80s, with rates in the least-developed countries very close. In developing countries, 29% of neonatal deaths are caused by birth asphyxia and 24% are caused by complications of prematurity.

A consistently robust predictor of infant mortality across the globe is a poor level of maternal education (consequently, another of the MDGs addresses the need for universal access to schooling for girls; Fig. 1-3). Other maternal risk characteristics, such as unmarried status, adolescence, and high parity, correlate with increased risk of postneonatal mortality and morbidity and low birthweight.

Table 1-1 Child Health Indicators Worldwide by Region

	Mortality Rate by Yr Per 1,000 Live Births					GROSS NATIONAL PER CAPITA INCOME	LIFE EXPECTANCY AT BIRTH	PRIMARY SCHOOL ATTENDANCE
	UNDER-5		INFANT MORTALITY		NEONATAL MORTALITY			
	1990	2012	1990	2012	2012	2012	2012	2008-2011
Sub-Saharan Africa	177	98	107	64	32	$1,397	56 yr	77%
Eastern and Southern Africa	163	77	101	51	28	$1,729	59 yr	87%
West and Central Africa	195	118	115	76	37	$1,071	54 yr	68%
Middle East and North Africa	71	30	53	24	15	—	71 yr	90%
South Asia	129	60	92	47	32	$1,440	67 yr	93%
East Asia and Pacific	58	20	44	17	11	$5,592	74 yr	97%
Latin America and Caribbean	54	19	43	16	10	$9,212	75 yr	95%
CEE/CIS	47	19	38	16	9	$8,727	70 yr	96%
Least-developed countries	172	85	107	58	30	$779	61 yr	81%
World	90	48	63	35	21	$10,132	71 yr	91%

CEE/CIS, Central and Eastern Europe/Commonwealth of Independent States (formerly the USSR).
Adapted from UNICEF: The state of the world's children 2014: Statistical Table, *New York, 2012, UNICEF, Table 1, p. 35.*

Table 1-2 Leading Causes of Death and Numbers of Deaths, According to Age: United States, 2010

AGE AND RANK ORDER	CAUSE OF DEATH	NUMBER	PERCENT OF TOTAL DEATHS
Under 1 yr	All causes	24,586	100%
	Congenital malformations, deformations, and chromosomal abnormalities	5,107	21%
	Disorders related to short gestation and low birthweight, not elsewhere classified	4,148	17%
	Sudden infant death syndrome	2,063	8%
	Newborn affected by maternal complications of pregnancy	1,561	6%
	Unintentional injuries	1,110	5%
	Newborn affected by complications of placenta, cord, and membranes	1,030	4%
	Bacterial sepsis of newborn	583	2%
	Respiratory distress of newborn	514	2%
	Diseases of the circulatory system	507	2%
	Newborn affected by maternal complications of pregnancy	472	2%
1-4 yr	All causes	4,316	100%
	Unintentional injuries	1,394	32%
	Congenital malformations, deformations, and chromosomal abnormalities	507	12%
	Homicide	385	9%
	Malignant neoplasms	346	8%
	Diseases of heart	159	4%
	Influenza and pneumonia	91	1%
	Septicemia	62	1%
	In situ neoplasms, benign neoplasms, and neoplasms of uncertain or unknown behavior	59	1%
	Certain conditions originating in the perinatal period	52	1%
	Chronic lower respiratory diseases	51	1%
5-14 yr	All causes	5,279	100%
	Unintentional injuries	1,643	31%
	Malignant neoplasms	916	17%
	Congenital malformations, deformations, and chromosomal abnormalities	298	6%
	Suicide	274	5%
	Homicide	261	5%
	Diseases of heart	185	4%
	Chronic lower respiratory diseases	133	3%
	Cerebrovascular diseases	90	2%
	In situ neoplasms, benign neoplasms, and neoplasms of uncertain or unknown behavior	82	2%
	Influenza and pneumonia	71	1%
15-24 yr	All causes	29,551	100%
	Unintentional injuries	12,341	30%
	Homicide	4,678	16%
	Suicide	4,600	16%
	Malignant neoplasms	1,604	5%
	Diseases of heart	1,028	3%
	Congenital malformations, deformations, and chromosomal abnormalities	412	1%
	Cerebrovascular diseases	190	<1%
	Influenza and pneumonia	181	<1%
	Diabetes mellitus	165	<1%
	Pregnancy, childbirth, and the puerperium	163	<1%

Adapted from National Center for Health Statistics: Health, United States, 2013: with special feature on prescription drugs. *Hyattsville, MD, 2014, Department of Health and Human Services, Table 23, p. 98.*

THE CHANGING PEDIATRIC WORLD

A profound improvement in child health within industrialized nations occurred in the 20th century with the introduction of antibacterial disinfectants, antibiotic agents, and vaccines. Efforts to control infectious diseases were complemented by better understanding of nutrition. In the United States, Canada, and parts of Europe, new and continuing discoveries in these areas led to establishment of public well-child clinics for low-income families. Although the timing of control of infectious disease was uneven around the globe, this focus on control was accompanied by significant decreases in morbidity and mortality in all countries. The smallpox eradication program of the 1970s resulted in the global eradication of smallpox in 1977. The introduction in the 1970s of the Expanded Program of Immunizations (universal vaccination against polio, diphtheria, measles, tuberculosis, tetanus, and pertussis) by the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) has resulted in an estimated annual reduction of 1-2 million deaths per year globally. Recognizing the importance of prevention of infectious diseases to the health of children, several countries among the 50 ranked by the World Bank as among the poorest nations (per capita income <$750/yr) have invested heavily in infectious disease control through the development of internal vaccine production capability. From 2000 to 2010, globally there was a 74% decline (with sub-Saharan Africa witnessing an 85% decline) in deaths caused by measles as a result of increased vaccination. As diarrheal diseases continued through the mid-1970s to account for ≈25% of infant and childhood deaths in developing countries (~4 million deaths per year at that time), attention turned to the development and utilization of oral resuscitation fluids to sustain children through potentially life-threatening episodes of acute diarrheal diseases. Oral rehydration solutions are largely credited with the current reduction of diarrheal deaths annually to 1.5 million. Substantial improvements have been witnessed in malaria control (global decrease of incidence by 17% and mortality rate by 25% since 2000). There have been substantial increases in the percent of households having insecticide-treated bed nets and in treatment of children with fever in endemic areas receiving antimalarial drugs.

In the later 20th century, with improved control of infectious diseases (including the elimination of polio in the Western hemisphere)

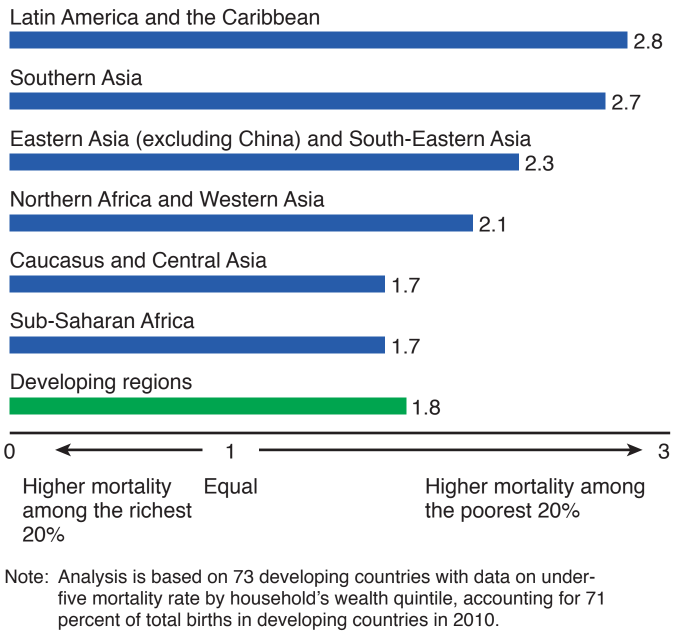

Figure 1-2 Ratio of under-5 mortality rate for children from the poorest 20% quintile of households to children from the richest 20% of households, 2000/2010. *(From* Millennium Development Goals Report, 2012. *New York, 2012, United Nations, p. 28.)*

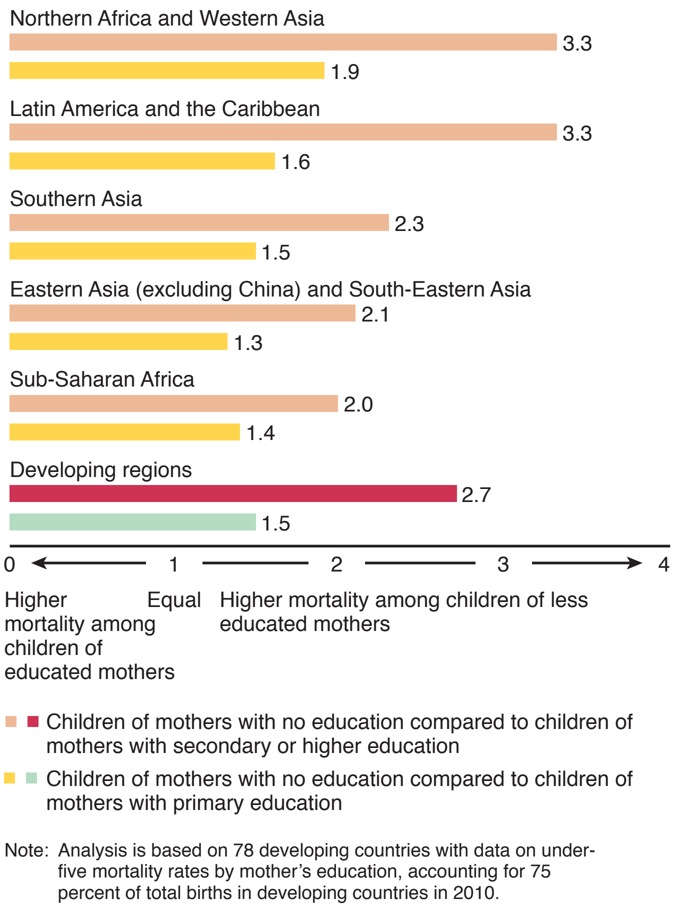

Figure 1-3 Ratio of under-5 mortality rate of children of mothers with no education compared to the rate of children of mothers with higher education. *(From* Millennium Development Goals Report, 2012. *New York, 2012, United Nations, p. 28.)*

through both prevention and treatment, pediatric medicine in industrialized nations increasingly turned its attention to a broad spectrum of conditions. These included both potentially lethal conditions and temporarily or permanently handicapping conditions; among these disorders were leukemia, cystic fibrosis, diseases of the newborn infant, congenital heart disease, mental retardation, genetic defects, rheumatic diseases, renal diseases, and metabolic and endocrine disorders.

Increasing attention has also been given to behavioral and social aspects of child health, ranging from reexamination of child-rearing practices to creation of major programs aimed at prevention and management of abuse and neglect of infants and children. Developmental psychologists, child psychiatrists, neuroscientists, sociologists, anthropologists, ethnologists, and others have brought us new insights into human potential, including new views of the importance of the environmental circumstances during pregnancy, surrounding birth, and in the early years of child rearing. The later 20th century witnessed the beginning of nearly universal acceptance by pediatric professional societies of attention to normal development, child rearing, and psychosocial disorders across the continents. In the past decade, irrespective of level of industrialization, nations have developed programs addressing not only causes of mortality and physical morbidity (such as infectious diseases and protein-calorie malnutrition), but also factors leading to decreased cognition and thwarted psychosocial development, including punitive child-rearing practices (whether at home or in school) and wife abuse, child labor, undernutrition, war, and poor-quality schooling. Obesity is recognized as a major health risk not only in industrialized nations, but increasingly in transitional countries. Progress at the turn of the 21st century in unraveling the human genome offers for the first time the realization that significant genetic screening, individualized pharmacotherapy, and genetic manipulation will be a part of routine pediatric treatment and prevention practices in the future. The prevention implications of the genome project give rise to the possibility of reducing costs for the care of illness but also increase concerns about privacy issues (see Chapter 3).

Although local famines and disasters, and regional and national wars have periodically disrupted the general trend for global improvement in child health indices, it was not until the advent of the AIDS epidemic in the later 20th century that the first substantial global erosion of progress in child health outcomes occurred. This erosion resulted in ever-widening gaps between childhood health indices in sub-Saharan Africa compared to the rest of the world. From 1990 to 2002, life expectancy in sub-Saharan Africa decreased from 50 yr to 46 yr. However, as of 2008, it had returned to 52 yr and in 2012 was 56 yr. Wide distribution of effective antiretroviral therapy (Fig. 1-4), aggressive HIV prevention education, and increased access to antitubercular drugs have been important in these successes, but continued successes will require sustained international support. Despite this positive news, children with HIV remain the least-likely group to receive antiretroviral treatment. Despite these gains, diseases once confined to limited geographic niches, including West Nile virus, and diseases previously uncommon among humans, such as the avian flu virus, increased awareness of the interconnectedness of health around the world and the impact of global warming. Formerly perceived as a problem of industrialized nations, motor vehicle crashes are now recognized as a major cause of mortality in developing countries.

MORBIDITIES AMONG CHILDREN

Adequately addressing special healthcare needs is important in all countries, both to minimize loss of life and to maximize the potential of each individual.

In the United States, ≈70% of all pediatric hospital bed days are for chronic illnesses; 80% of pediatric health expenditures are for 20% of children. Approximately 14% of U.S. children have special healthcare needs, ranging from 10% to 19.8% across the 50 states and the District of Columbia. One in 5 households with children had ≥1 children with special healthcare needs (see Chapter 42). Significantly, more poor children and minority children have special healthcare needs.

Although there are numerous chronic conditions and the prevalence of these disorders vary by population, 2 of these morbidities—asthma

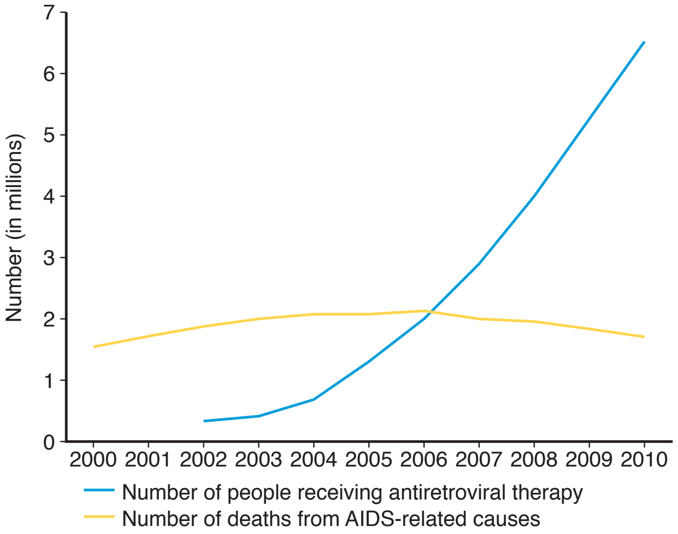

Figure 1-4 Number of persons receiving antiretroviral therapy and deaths caused by HIV over time. *(From* Millennium Development Goals Report, 2012. *New York, 2012, United Nations, p. 41.)*

and nutrition disorders—have an increasing presence worldwide and are associated with substantial health consequences and costs.

More than 80% of **asthma-related deaths** occur among children living in developing countries. The Centers for Disease Control and Prevention estimated that 10% of U.S. children have asthma, with particularly high rates among Puerto Rican and black children. Between 2001 and 2009, the prevalence of asthma increased by 50% among black children. The International Study of Asthma and Allergies in Childhood has presented evidence for a substantial global burden of childhood asthma, although rates vary substantially between and within countries. The highest annual prevalence rates are in the United Kingdom, Australia, New Zealand, and Ireland, with the lowest rates in Eastern European countries, Indonesia, China, Taiwan, India, and Ethiopia (see Chapter 144).

Chronic disorders of nutrition occur in a variety of forms. Long recognized as a major threat to child welfare, malnutrition (undernutrition) has been steadily decreasing over the past decades. Children in industrialized countries have greatly benefitted from a wide range of supplemental feeding programs (see Chapters 45 and 46); malnutrition in such nations is generally a result of selected deficiencies rather than overall undernutrition. An estimated 1% of children in the United States have some form of malnutrition. Moderate and severe malnutrition continue to impact children in developing nations. Although great progress has been made in this regard over the past several decades, children in the poorest nations and children whose families are in the lower economic quintile in a broader range of countries continue to struggle. In the period 2011–2013, 14% of children younger than age 5 yr in developing countries and 25% of those in the least-developed countries suffer from moderate/severe malnutrition; South Asia and West/Central Africa suffer from the highest rates of moderate/severe malnutrition at 42% and 23%, respectively. Rates of stunting (>2 SD below median height for age) are higher, at 29% and 41%, for children in developing and the least-developed countries, respectively (see Chapter 46).

The global epidemic of **overweight/obesity** is also significant. In the United States, 30% of children and adolescents are overweight or obese, representing a 3-fold increase over the past 30 yr. Rates of obesity for boys whose parents did not graduate from high school are 3-fold higher than those whose parents received at least a bachelor's degree; for girls, the difference is 2-fold. Similar rates have been reported from Australia and multiple countries in Europe, Egypt, Chile, Peru, and Mexico (see Chapter 47). The WHO estimates that globally 42 million children younger than the age of 5 yr are overweight; ~35 million of these live in developing countries.

Chronic cognitive morbidities represent another substantial problem. Although different diagnostic criteria have been applied, attention-deficit/hyperactivity disorder has been identified in 5-12% of children in countries across the globe, with a worldwide estimated prevalence of 5.29%. Rates exceeding 10% have been reported in the United States, New Zealand, Australia, Spain, Italy, Colombia, and Great Britain. Variations in cultural tolerance and/or differences in screening approaches or tools may account for some of the differences in prevalence of the disorder by country, but genetic and gene–environmental interactions may also play a role. Despite variations in rate, the condition is universal. Beyond the personal and familial stress caused by the disorder, costs to the educational systems are considerable. In countries where they are available, drug costs are considerable; in the United States, annual costs for drug treatments for attention-deficit/hyperactivity disorder are estimated to exceed $4 billion. In developing countries without resources for special education, these children are unlikely to fulfill their academic potential (see Chapter 33).

Mental retardation affects ≈1-3% of children in the United States, with ~80% of these children having mild retardation. Rates are several fold higher among very-low birthweight infants. In the United States, there is substantial variation in rates of mild retardation by socioeconomic status (9-fold higher in the lowest compared to the highest socioeconomic stratum), but relatively equivalent rates of severe retardation. A similar income-related distribution is found in other countries, including some of the most impoverished countries, such as Bangladesh. Lower overall rates have been reported in some countries, including countries ranging from Saudi Arabia to Sweden to China; the difference is primarily in the prevalence of mild retardation (see Chapter 36).

Posttraumatic stress disorder (PTSD) in children remains underrecognized. PTSD can follow violent attacks and witnessed violence, sexual abuse, natural disasters, motor vehicle accidents, kidnapping, and domestic violence. Female gender, prior exposure to violence, other psychologic disturbances, and low social support are also associated with its appearance after an exposure. The prevalence of childhood PTSD varies considerably around the globe, but in children with substantial exposure to violence, the rates appear to be very high. After the attacks on the World Trade Center towers and the Pentagon in 2001, 33% of U.S. children had experienced 1 or more symptoms of PTSD. The prevalence of PTSD among children and adolescents exposed to the tsunami of 2004 were 57%, 46%, 31%, 10%, and 7% 6 wk, 6 mo, 1 year, 18 mo, and 2 yr post exposure, respectively. Children hit by the waves had significantly higher rates of PTSD.

SITUATIONAL SPECIAL-RISK POPULATIONS

Children at situational special risk have had their futures compromised by actions or policies arising from their families, schools, communities, nations, or the international community. These problems have several causes, whether the end result is homeless children, runaway children, children in foster care, or children in other disadvantaged groups.

Children in Urban Settings

Over half of the world's population is urban dwellers. Although urban settings historically have offered educational, medical, recreational, and employment opportunities, an increasing number of urban dwellers are living in marginal communities with a growing gap in access to clean water, adequate sanitation or dependable electricity as the urban population rapidly increases (Fig. 1-5). As has been seen in Port-au-Prince, Haiti, after the devastating earthquake of 2010, national disasters exact an especially high toll on children and families living in makeshift homes on lands that are not intended for housing.

Children in Poverty

Family income is central to the health and well-being of children. Children living in poor families, especially those located in poor communities, are much more likely than children living in upper- or middle-class families to experience material deprivation and poor health, die during childhood, score lower on standardized tests, be

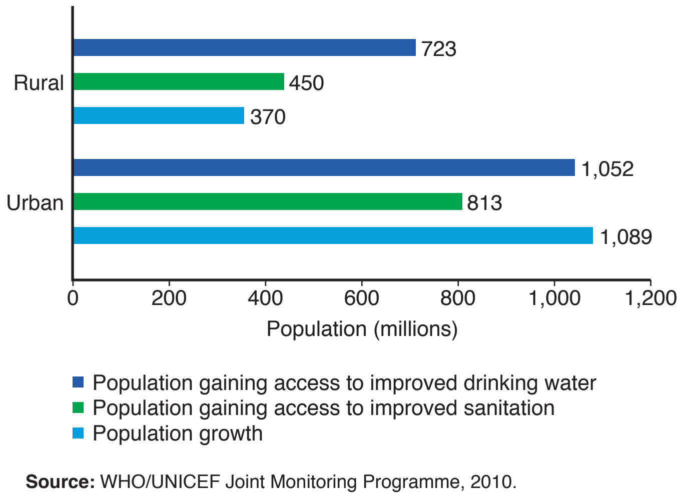

Figure 1-5 In urban areas, access to improved water and sanitation is not keeping pace with population growth. *(From UNICEF,* The state of the world's children, 2012: children in an urban world, *New York, 2012, United Nations, p. 5.)*

retained in a grade or drop out of school, have out-of-wedlock births, experience violent crime, end up as poor adults, and suffer other undesirable outcomes. As of 2010, worldwide, 22% of the population lives below the international poverty line of U.S. $1.25 per capita per day; 47% of sub-Saharan and 50% of the least-developed nations live below this amount. Poverty rates are higher for children than adults and are highest for infants and toddlers. Higher in general in developing countries, within each country, the rate of infant mortality among the poorest quintile of the population is about twice that of the wealthiest quintile (see Fig. 1-2).

In the United States, from 1990 to 2000, the percentage of children <18 yr living below the poverty line had decreased from 21% to 16%. In 2010, 2 yr after the start of the recession, the rate had risen to 22%. Black and Hispanic children consistently have had higher poverty rates than Asian and white children. In 2010, 39% of black children and 35% of Hispanic children lived in poverty, compared to 14% of Asian children and 12% of white children. Sixty-six percent of black and Hispanic children compared to only 33% of Asian and 29% of white children lived below 200% of the poverty level. Children who are poor have higher-than-average rates of death and illness from almost all causes (exceptions being suicide and motor vehicle crashes, which are most common among white, nonpoor children). Many factors associated with poverty are responsible for these illnesses: crowding, poor hygiene and healthcare, poor diet, environmental pollution, poor education, and stress.

Poverty and economic loss diminish the capacity of parents to be supportive, consistent, and involved with their children. Clinicians at all times, but especially in the context of a national or global recession, need to be especially alert to the development and behavior of children whose parents have lost their jobs or who live in permanent poverty. Fathers who become unemployed frequently develop psychosomatic symptoms, and their children often develop similar symptoms. Young children who grew up in the Great Depression in the United States and whose parents were subject to acute poverty suffered more than older children, especially if the older ones were able to take on responsibilities for helping the family economically. Such responsibilities during adolescence seem to give purpose and direction to an adolescent's life. The younger children, faced with parental depression and unable to do anything to help, suffered a higher frequency of illness and a diminished capacity to lead productive lives even as adults.

The pediatric team should ask parents about their economic resources, adverse changes in their financial situation, and the family's attempts to cope. Encouraging concrete methods of coping, suggesting ways to reduce stressful social circumstances while increasing social networks that are supportive, and referring patients and their families to appropriate welfare, job training, and family agencies can significantly improve the health and functioning of children at risk when their families live in poverty. In many cases, special services, especially social services, need to be added to the traditional medical services; outreach is required to find and encourage parents to use health services and bring their children into the healthcare system. Pediatricians also have the responsibility to contribute to, and advocate for, safety net services for impoverished children within and outside the boundaries of their own country. An increasing number of programs are available to help children of greatest need worldwide, such as Project Smile, CARE, Project Hope, and Doctors Without Borders.

Children of Immigrants and Racial Minority Groups Including U.S. Native Americans

Immigrants comprise >15% of the population in >50 countries, including many Western European countries. Thirteen percent of the U.S. population is foreign-born; 24% of all children in the United States <17 yrs have immigrant parents. The United States is experiencing a wave of immigration larger than that occurring in the early 20th century. Until the mid-20th century, emigrants to the United States were primarily white and from Europe. Such individuals now represent only approximately 10% of immigrants; the remainder are overwhelmingly of color and from throughout the world, including 29% from Mexico, 5% from China, and 4% each from India and the Philippines. Although immigrants in the United States have faced discrimination and oppression throughout history, the potential for such discrimination is compounded by the racial differences represented in the current immigrant pool. In the United States, about 240,000 children legally immigrate each year, and, through 2010, an estimated 50,000/yr entered the country illegally. In recent years the number of children from Latin American countries entering illegally has greatly increased, with estimates of more than 90,000 such children entering in 2014 alone. An estimated 5.5 million children have at least 1 illegal immigrant parent; this number doubled from 2000 to 2010.

The immigrant population constitutes a substantial proportion of the low-wage labor market. Immigrants represent 16% of all U.S. workers but 20% of low-wage workers. Immigrants are twice as likely as U.S.–born citizens to earn less than minimum wage. The poverty rate of children in immigrant families is 50% greater than in U.S.–born families; over the past decade children with 2 immigrant parents consistently have a 15% greater likelihood of living below the poverty line than children in nonimmigrant families. Contributing to the lack of access to higher salaried jobs is the lack of proficiency in English (≈52% of immigrants) and the lack of education (40% have not completed high school). Immigrants account for 29% of the uninsured in the United States.

Families of different origins obviously bring different health problems and different cultural backgrounds, which influence health practices and use of medical care. To provide appropriate services, clinicians need to understand these influences (see Chapter 4). The high prevalence of hepatitis among women from Southeast Asia makes use of hepatitis B vaccine essential for their newborns. Children from Southeast Asia and South America have growth patterns that are generally below the norms established for children of Western European origin, as well as high rates of hepatitis, parasitic diseases, and nutritional deficiencies and high degrees of psychosocial stress. Foreign-born children may surpass American-born children in some health outcomes, but their health deteriorates as they become acculturated (see Chapter 4).

Refugee children who escape from war or political violence and whose families have been subjected to extreme stress represent a subset of immigrant children who have faced severe trauma. These children have a particularly high incidence of mental and behavioral problems (see Chapter 39). Armed conflicts in 2011 resulted in an especially high (4 million) number of refugees worldwide.

Linguistically isolated households, in which no one older than 14 yr of age speaks English, often present significant obstacles to providing quality healthcare to children because of difficulties in understanding and communicating basic concerns and instructions, avoiding

compromising privacy and confidentiality interests, and obtaining informed consent (see Chapter 4).

The United States is home to multiple minority populations, including the 2 largest groups, Latinos and African-Americans. The nonwhite minority groups will constitute >50% of the U.S. population by 2050. Nonwhite children in the United States disproportionately experience adverse child health outcomes (Tables 1-3 and 1-4). Infants that are born to African-American mothers experience low birthweight and infant mortality rates twice those with white mothers (see Chapter 93). Rates of these 2 adverse health outcomes are also substantially higher among some groups of Hispanic infants and children, the rates are particularly high among those of Puerto Rican descent (≈1.5 times the rates for white infants). In 2010, the overall infant mortality rate was 6.4 per 1,000 live births, whereas that for non-Hispanic African-America infants was 11.7; for Native Americans, 8.3; and Puerto Ricans, 7.1. Mexicans, Asians, Pacific Islanders, Central and South Americans, and Cubans were below the national average. Latino, Native American, and African-American children are substantially more likely to live in poverty than are white children.

There are approximately 5.1 million Native Americans (including those with mixed races/ethnicities) and 566 federally recognized tribes. The Native American population increased by 26% from 2000 to 2010 compared to a national increase of only 9.7%. Approximately 60% of Native Americans live in urban areas, not on or near native lands. Like their minority immigrant counterparts, they have faced social and economic discrimination. The unemployment and poverty levels of Native Americans are, respectively, 3-fold and 4-fold that of the white population, and far fewer Native Americans graduate from high school or go to college. The rate of low birthweight among Native Americans is more than the white rate but less than the black rate. The neonatal and the postneonatal mortality rates are higher for Native Americans living in urban areas than for urban white Americans. Deaths in the first year of life from sudden infant death syndrome, pneumonia, and influenza are higher than the average in the United States, whereas deaths as a result of congenital anomalies, respiratory distress syndrome, and disorders relating to short gestation and low birthweight are similar.

Unintended injury deaths among Native Americans occur at twice the rate for other U.S. populations; deaths caused by malignant

Table 1-3 Deaths Rates for All Causes Among Children and Young Adults According to Sex, Race, Hispanic Origin, and Age: 2010

	Deaths Per 100,000 Resident Population			
	UNDER 1 yr	1-4 yr	5-14 yr	15-24 yr
All persons	623.4	26.5	12.9	67.7
Male	680.2	29.6	14.6	97.6
Female	564.0	23.3	11.1	36.4
MALES				
White	584.3	27.4	13.8	91.8
Black male (African-American)	1206.5	42.9	19.6	142.8
American Indian or Alaska Native	542.5	34.3	18.1	116.4
Asian or Pacific Islander	434.4	19.3	8.4	43.0
Hispanic or Latino	556.8	25.0	11.4	79.4
White not Hispanic or Latino	594.4	29.3	15.0	100.8
FEMALES				
White	575.9	27.5	14.3	93.4
Black (African-American)	488.0	21.6	10.6	36.2
American Indian or Alaska Native	366.4	24.4	10.5	43.6
Asian or Pacific Islander	341.8	16.3	7.9	17.0
Hispanic or Latino	462.9	20.2	8.9	26.3
White not Hispanic or Latino	480.4	21.8	10.9	38.4

Adapted from National Center for Health Statistics: Health, United States, 2013: with special feature on prescription drugs, *Hyattsville, MD, 2014, Department of Health and Human Services, Table 25, pp. 103–106.*

Table 1-4 Infant, Neonatal, and Postnatal Deaths and Mortality Rates by Specified Race or Origin of Mother: United States, 2009 and 2010

		Mortality Rate Per 1,000 Live Births		
RACE OF MOTHER	YEAR(S)	INFANT	NEONATAL	POSTNATAL
All races	2007	6.4	4.2	2.2
	2008	6.1	4.0	2.1
White	2007	5.3	3.5	1.9
	2008	5.2	3.5	1.8
Black or African American	2007	12.1	8.0	4.2
	2008	11.2	7.3	3.9
American Indian or Alaska Native	2007	8.3	4.3	4.0
Asian or Pacific Islander	2007	4.3	3.0	1.3
Hispanic or Latino	2007	5.3	3.6	1.7
Mexican	2007	5.1	3.5	1.6
Puerto Rican	2007	7.1	4.8	2.3
Cuban	2007	3.8	2.9	2.1*
Central and South American	2007	4.4	3.0	1.4
Other and unknown Hispanic or Latino	2007	6.1	4.0	2.1
Not Hispanic or Latino				
White	2007	5.2	3.4	1.8
Black or African American	2007	11.5	7.5	4.0

Adapted from National Center for Health Statistics: Health, United States, 2013: with special feature on prescription drugs, *Hyattsville, MD, 2014, Department of Health and Human Services, Tables 11, p. 98, and 17, p. 71.*

*2009.

neoplasms are lower. During adolescence and young adulthood, suicide and homicide are the second and third causes of death in this population and occur at about twice the rates of the rest of the population. There may be significant underreporting of deaths of Native American children.

As many as 75% of Native American children have recurrent otitis media and high rates of hearing loss, resulting in learning problems. Tuberculosis and gastroenteritis, formerly much more common among Native Americans, now occur at about the national average. Psychosocial problems are more prevalent in these populations than in the general population: depression, alcoholism, drug abuse, out-of-wedlock teenage pregnancy, school failure and dropout, and child abuse and neglect.

An estimated 300 million indigenous persons live in 70 countries (50% in Asia) and speak ≈4,000 languages. Such children endure lower vaccination rates, lower school entry and higher dropout rates, higher rates of poverty, and lower access to justice. Indigenous children in Latin America account for 66% of the deaths of children younger than age 2 yr.

Children of Migrant Workers

Families facing economic hardship have been forced to leave their land and homes in search of better opportunities; such migrations are often within a country or between neighboring countries.

In the United States, the number of migrant and seasonal farm workers is estimated to exceed 3 million, with 68% born in Mexico; 52% are parents, often accompanied by their children as they travel from site to site. The families experience poor housing, frequent moves, and a socioeconomic system controlled by a crew boss who arranges the jobs, provides transportation, and often, together with the farm owners, provides food, alcohol, and drugs under a "company store" system that leaves migrant families with little money or in debt. Children often go without schooling. English skills are limited, with 35% speaking no English and 27% "a little." The average family income is $17,500 to $19,999. Only 8% report receiving health insurance.

The medical problems of children of migrant farm workers are similar to those of children of homeless families: increased frequency of infections (including HIV), trauma, poor nutrition, poor dental care, low immunization rates, exposures to animals and toxic chemicals, anemia, and developmental delays.

Homeless Children

The number of homeless children in the United States has increased by more than 35% since the recession began in 2007. An estimated 1.6 million children are homeless, living in shelters, with other relatives or on the streets.

Homeless children have an increased frequency of illness, including intestinal infections, anemia, neurologic disorders, seizures, behavioral disorders, mental illness, and dental problems, as well as increased frequency of trauma and substance abuse. Homeless children are admitted to U.S. hospitals at a much higher rate than the national average. They have higher school failure rates, and the likelihood of their being victims of abuse and neglect is much higher. The limited research on homeless children suggests high rates of developmental delays, severe depression, or learning disorders. The increased frequency of maternal psychosocial problems, especially depression, in homeless households has a significant untoward impact on the mental and physical health of these children. Because families tend to break apart under the strain of poverty and homelessness, many homeless children end up in foster care. If their families remain intact, frequent moves make it very difficult for them to receive continuity of medical care or schooling.

Provision of adequate housing, job retraining for the parents, and mental health and social services are necessary to prevent homelessness from occurring. Physicians can have an important role in motivating society to adopt the social policies that will prevent homelessness from occurring by educating policymakers that these homeless children are at greater risk of becoming burdens both to themselves and to society if their special health needs are not met.

Runaway and Thrown-Away Children

Annually in the United States, an estimated 1.6-2.8 million youth run away. Several hundred thousand of these children have no secure and safe place to stay. Black and Hispanic youth, as well as lesbian, homosexual, bisexual, and transgender youth, are disproportionately represented in these numbers. The usual definition of a *runaway* is a youth younger than 18 yr who is gone for at least 1 night from his or her home without parental permission; ~70% of these youth endangers their physical well-being during the runaway episode. Most runaways leave home only once, stay overnight with friends, and have no contact with the police or other agencies. This group is no different from their "healthy" peers in terms of psychological status. A smaller but unknown number become multiple or permanent "runners" and are significantly different from the one-time runners, with less-favorable long-term outcomes.

Thrown-aways include children told directly to leave the household, children who have been away from home and are not allowed to return, abandoned or deserted children, and children who run away but whose caretakers make no effort to recover them or do not appear to care if they return. The same constellation of causes common to many of the other special-risk groups is characteristic of permanent runaways and thrown-aways, including environmental problems (family dysfunction, abuse, poverty) and personal problems of the young person (poor impulse control, psychopathology, substance abuse, or school failure). Thrown-aways experience more violence and conflicts in their families.

In the United States, it is a minority of runaway youths who become homeless street people. These youths have a high frequency of problem behaviors, with 75% engaging in some type of criminal activity and 50% engaging in prostitution. A majority of permanent runaways have serious mental problems; more than 33% are the product of families who engage in repeated physical and sexual abuse (see Chapter 40). These children also have a high frequency of medical problems, including hepatitis, sexually transmitted infections, and drug abuse. Although runaways often distrust most social agencies, they will come to and use medical services. Medical care may become the point of reentry into mainstream society and the path to needed services. U.S. parents who seek a physician's advice about a runaway child should be asked about the child's history of running away, the presence of family dysfunction, and personal aspects of the child's development. If the youth contacts the physician, the latter should examine the youth and assess the youth's health status, as well as willingness to return home. If it is not feasible for the youth to return home, foster care, a group home, or an independent living arrangement should be sought by referral to a social worker or a social agency. Although legal considerations involved in the treatment of homeless minor adolescents may be significant, most states, through their "Good Samaritan" laws and definitions of emancipated minors, authorize treatment of homeless youths. Legal barriers should not be used as an excuse to refuse medical care to runaway or thrown-away youths.

The issue of runaway youths is very complex in many developing nations, where in many instances the youth may be orphaned and/or leaving situations of forced sex or other abusive situations. It is estimated that there are tens of millions of such youth worldwide. Natural disasters such as the 2010 earthquake devastating Haiti also contribute to growing numbers of orphaned children. In 2012, there were an estimated 17.8 million HIV orphans globally, with 14.8 > 15 million in Africa. With school attendance <50% in many parts of sub-Saharan Africa, children who are orphaned are 17% less likely to attend school. Humanitarian and international organizations have begun to focus on this very vulnerable group of youths across the globe. Rates are often uncertain, and in many countries, these children have not even been recognized as an at-risk group, so great is the social chaos and so massive are the unmet needs.

Children Directly Affected By War and Other Forms of Direct Violence

See Chapter 39.2.

There have been ~250 major wars (defined as armed combat with more than 1,000 casualties) since the end of the Second World War.

The majority of these conflicts have been civil wars, many of which have lasted longer than a decade. Sixteen of the world's poorest 20 countries have endured a civil war in the past 20 yr. Poorer countries are more likely to engage in war; a country whose median income is at the 50th percentile is one-half as likely to engage in a civil war as a country whose median income is at the 10th percentile. The distinction between intentional and unintentional injury loses its meaning in such situations; in modern wars, 70-80% of casualties are among women and children. Direct mortality and morbidity to children account for only a portion of war's destructive impact on children. In 1996 the United Nations commissioned a report addressing the full consequences of war on children entitled "Promotion and Protection of the Rights of Children: Impact of Armed Conflict on Children" including (1) the disruption of basic educational and child health pediatric care and services; (2) hardships endured as a result of refugee status; (3) the abuse of the 250,000-300,000 children younger than age 18 yr who are soldiers; and (4) the impact on children when 1 or both parents are deployed to serve.

A growing number of children worldwide are facing acts of violence with a broad reach outside of the context of war, including religious crusades (such as suicide bombers in countries not always engaged in war), countries with extraordinarily high rates of violence (such as certain cities in South Africa and Mexico) and as a result of individuals with uncertain or confused personal motives, such as the mass shooting in an elementary school in Sandy Hook, Connecticut. While the direct consequences of such nonwar violence impact far fewer children than do those from war, the reach of such random acts of violence is increasingly touching a wider swath of our globe.

Inherent Strengths in Vulnerable Children and Interventions

By age 20-30 yr, many children in the United States and other developed countries who were at special risk will have made moderate successes of their lives. Teenage mothers and children who were born prematurely or in poverty demonstrate that, by this age, the majority have made the transition to stable marriages and jobs and are accepted by their communities as responsible citizens. As the numbers of risk factors increases for an individual, the odds for a successful adulthood decline.

Certain biologic characteristics are associated with success, such as being born with an accepting temperament. Avoidance of additional social risks is even more important. Premature infants or preadolescent boys with conduct disorders and poor reading skills, who must also face a broken family, poverty, frequent moves, and family violence, are at much greater risk than children with only 1 of these risks. Perhaps most important are the protective buffers that have been found to enhance children's resilience because these can be aided by an effective healthcare system and community. Children generally do better if they can gain social support, either from family members or from a nonjudgmental adult outside the family, especially an older mentor or peer. Providers of medical services should develop ways to "prescribe" supportive "other" persons for children who are at risk. Promotion of self-esteem and self-efficacy is a central factor in protection against risks. It is essential to promote competence in some area of these children's lives.

A team is needed because it is rare for 1 individual to be able to provide the multiple services needed for high-risk children. Successful programs are characterized by at least 1 caring person who can make personal contact with these children and their families. Most successful programs are relatively small (or are large programs divided into small units) and nonbureaucratic but are intensive, comprehensive, and flexible. They work not only with the individual, but also with the family, school, community, and at broader societal levels. Introduction of remedial programs to children at the youngest possible age appears to increase the chance of success across multiple problem areas. It is also important for services to be continued over a long period.

Global Warming

Global climate change is occurring and will impact everyone; its impact will be harder felt on children and hardest felt are certain categories of vulnerable child, including those living in areas threatened by variations in rainfall, temperatures or hurricanes and cyclones (Fig. 1-6).

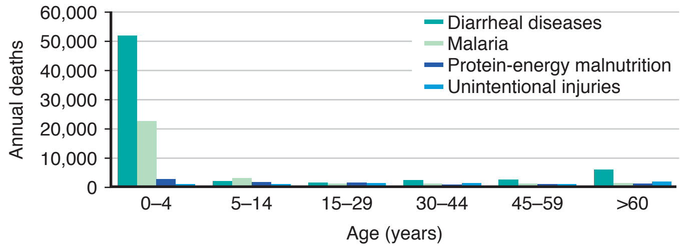

Figure 1-6 Deaths attributable to global climate change: 2004 annual data in total numbers divided by age categories. *(Data from* WHO Global burden of disease: 2004 update. *2008. Available at* http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. *Image from Sheffield PE, Landrigan PJ. Global climate change and children's health: threats and strategies for prevention.* Environ Health Perspect *2011;119:291.)*

The Challenge to Pediatricians

Concerns about the aforementioned problems of children throughout the world have generated 3 sets of goals. The *first set* includes that all families have access to adequate perinatal, preschool, and family planning services; that international and national governmental activities be effectively coordinated at the global, regional, national, and local levels; that services be so organized that they reach populations at special risk; that there be no insurmountable or inequitable financial barriers to adequate care; that the healthcare of children have continuity from prenatal through adolescent age periods; and that every family ultimately have access to all necessary services, including developmental, dental, genetic, and mental health services. A *second set* of goals addresses the need for reducing unintended injuries and environmental risks, for meeting nutritional needs, and for health education aimed at fostering health-promoting lifestyles. A *third set* of goals covers the need for research in biomedical and behavioral science, in fundamentals of bioscience and human biology, and in the particular problems of mothers and children.

PATTERNS OF HEALTHCARE

Healthcare utilization and organization differs significantly among nations, reflecting differences in the geography and wealth of the country; the priority placed on healthcare versus other competing needs and interests within a nation and by the international community; philosophy regarding prevention versus curative care; and the balance between child and adult healthcare needs. An interesting analysis of 2 industrialized countries (United States and Japan) revealed that for comparable symptoms, Japanese children were 2.5 times more likely to visit a community physician's office or emergency clinic, and 11 times more likely to visit a hospital-based outpatient clinic. In most countries, hospitals are sources of both routine and intensive child care, with medical and surgical services that may range from immunization and developmental counseling to open heart surgery and renal transplantation. Clinical conditions and procedures requiring intensive care are also likely to be clustered in university-affiliated centers serving as regional resources—if these resources exist.

In developing countries, external forces may also contribute greatly to the organization of healthcare and possibly to healthcare utilization. This relationship is complex. The significant declines in infant and child mortality enjoyed in many of the developing countries in the past 4 decades have occurred in the context of support from the international community, including agencies such as UNICEF, WHO, and the World Bank; bilateral donors (the aid provided from 1 country to another); and nongovernmental agencies to develop integrated, universal primary pediatric care with an emphasis on primary (vaccination) and selected secondary (oral rehydration solution [ORS], treatment of pneumonia and malaria) prevention strategies. But, as

healthcare systems become dependent on such external support, their populations are increasingly vulnerable to changes in political will over which they have little or no influence.

In the United States, pediatricians report an average of 50 preventive care visits per wk, 33% for infants. The visits average 17-20 min, increasing in length as children become adolescents. The principal diagnoses, accounting for ≈40% of these visits, are well-child visits (15%), middle-ear infections (12%), and injuries (10%). Ambulatory visits by children and youth decrease with age. The opposite occurs with adults. Nonwhite children are more likely than white children to use hospital facilities (including the emergency room) for their ambulatory care; the number of well-child visits annually is almost 80% higher among white infants than black infants. Children with private insurance are more likely than children with public insurance who, in turn, are more likely than uninsured children to receive non–emergency room care. Insurance coverage increases outpatient utilization and receipt of preventive care by approximately 1 visit per year for children. Between 70 and 90 children per 1,000 children are hospitalized per year. These rates are less than those of adults up to age 65 yr, except for the first year of life. Children represent <7% of the total acute hospital discharges; in children's hospitals, ≈70% of admissions are for chronic conditions, and 10-12% of pediatric hospitalizations are related to birth defects and genetic diseases. White children are less likely to be hospitalized than black or Hispanic children, but more likely than Asian children. Poor children are nearly twice as likely as nonpoor children to be hospitalized. Insurance coverage also appears to reduce hospital admissions that are potentially manageable in an ambulatory setting.

PLANNING AND IMPLEMENTING A SYSTEM OF CARE

Access to at least a basic level of quality services to promote health and treat illness is a right of every person. Having health insurance, whether private or governmental, is strongly associated with access to primary care. Efforts to make the delivery of healthcare more efficient and effective have led to the creation of new categories of healthcare providers, such as pediatric nurse practitioners in industrialized nations and trained birth attendants in developing countries, and to participate in new organizations for providing care to children, such as various managed care arrangements.

The U.S. Patient Protection and Affordable Care Act passed in 2010 and upheld by the United States Supreme Court in 2012, contains provisions specific to children, including a requirement that all preexisting conditions be covered and (effective 2014) pregnancy and newborn care be covered, as well as vision and dental care for children.

Health Services for At-Risk Populations

In the United States, the largest vulnerable group is children living in poverty, representing approximately 22% of U.S. children. Substantial proportions of children in other industrialized countries are also living in poverty. The approach to addressing the needs of this group in the United States has been the establishment of a targeted insurance program, Medicaid, which became law in 1965 as a jointly funded cooperative venture between the federal and state governments to assist states in the provision of adequate medical care to eligible needy persons. The federal statute identifies >25 different eligibility categories for which federal funds are available. These statutory categories can be classified into 5 broad coverage groups: children, pregnant women, adults in families with dependent children, individuals with disabilities, and individuals ≥65 yr old. Pediatric care in the United States is highly dependent on Medicaid; however, only a relatively small proportion of the Medicaid funds actually go to child healthcare, with the remainder serving older adults. Following broad national guidelines, each state establishes its own eligibility standards; determines the type, amount, duration, and scope of services; sets the rate of payment for services; and administers its own program. Although Medicaid has made great strides in enrolling low-income children, significant numbers of children remain uninsured. From 1988 to 1998, the proportion of children insured through Medicaid increased from 15.6% to 19.8%, but the percentage of children without health insurance increased from 13.1% to 15.4%. Minority children were disproportionately among those without insurance. The Balanced Budget Act of 1997 created a new children's health insurance program called the State Children's Health Insurance Program (SCHIP). This program gave each state permission to offer health insurance for children, up to age 19 yr, who are not already insured. SCHIP is a state-administered program and each state sets its own guidelines regarding eligibility and services. There is great variation by state, but in many states, the SCHIP program has begun to reduce racial inequities in access to healthcare for children. In 2009, the percent of children without insurance had decreased to 9%.

Many industrialized nations have adapted different "safety net" systems to assure adequate coverage of all youth. Many of these programs provide health insurance for all children, regardless of income, hoping to avoid problems with children losing insurance coverage and access to healthcare as a result of changes in eligibility by providing a single form of insurance that all providers accept. The response of developing countries to the issue of universal access to care for children has been uneven, with some providing no safety net, but many having limited universal or safety net services.

To address the special needs of Native Americans in the United States, the Indian Health Service, established in 1954, has been the responsibility of the Public Health Service, but the 1975 Indian Self-Determination Act gave tribes the option of managing Native American health services in their communities. The Indian Health Service is managed through local administrative units, and some tribes contract outside the Indian Health Service for healthcare. Much of the emphasis is on adult services: treatment for alcoholism, nutrition and dietetic counseling, and public health nursing services. There are also >40 urban programs for Native Americans, with an emphasis on increasing access of this population to existing health services, providing special social services, and developing self-help groups. In an effort to accommodate traditional Western medical, psychologic, and social services to the Native American cultures, such programs include the "Talking Circle," the "Sweat Lodge," and other interventions based on Native American culture (see Chapter 4). The efficacy of any of these programs, especially those to prevent and treat the sociopsychological problems particular to Native Americans, has not been determined.

Recognizing the health needs of migrants in the United States, the U.S. Public Health Service initiated in 1964 the Migrant Health Program to provide funds for local groups to organize medical care for migrant families. Many migrant health projects that were initially staffed by part-time providers and were open for only part of the year have been transformed into community healthcare centers that provide services not only for migrants but also for other local residents. As of 2012, there are >700 Migrant Health Centers and satellite sites operating in 42 states. Health services for migrant farm workers often need to be organized separately from existing primary care programs because the families are migratory. Special record-keeping systems that link the healthcare provided during winter months in the south with the care provided during the migratory season in the north are difficult to maintain in ordinary group practices or individual physicians' offices. Outreach programs that take medical care to the often remote farm sites are necessary, and specially organized Head Start, early education, and remedial education programs should also be provided. Approaches in other countries have also focused on business initiatives for migrant populations to enable them to overcome the cycle of financial dependency on their migratory lifestyle.

The United States has spent >$14 billion through the 1987 McKinney-Vento Act to provide emergency food, shelter, and healthcare; to finance help for young runaways; to aid homeless people in making their way back into the housing market; and to place homeless children in school. Mobile vans, with a team consisting of a physician, nurse, social worker, and welfare worker, have been shown to provide effective comprehensive care, ensure delivery of immunizations, link the children to school health services, and bring the children and their families into a stable relationship with the conventional medical system. Special record-keeping systems have been introduced to enhance continuity and to provide a record of care once the family has moved to a

permanent location. Because of the high frequency of developmental delays in this group, linkage of preschool homeless children to Head Start programs is an especially important service. The Runaway Youth Act, Title III of the Juvenile Justice and Delinquency Prevention Act of 1974 (Public Law 93-414) and its amended version (Public Law 95-509) have supported shelters and provide a toll-free 24 hr telephone number (1-800-621-4000) for youths who wish to contact their parents or request help after having run away.

Other nations have expanded the reality of the "health safety net" for children. In Belgium, Finland, the Netherlands, Portugal, and Spain, the right to housing has been incorporated into the national constitutions. The Finnish government has devised a multifaceted response to the problem, including house building, social welfare and healthcare services, and the obligation to provide a home of minimum standards for every homeless person. The number of homeless in Finland has been reduced by 50%.

Evaluation of Healthcare

The Institute of Medicine issued a report, "Crossing the Quality Chasm: A New Health System for the 21st Century" in 2001. This report, challenging American physicians to renew efforts to focus not just on access and cost, but also on quality of care, has been furthered in several pediatric initiatives, including, but not limited to, specific initiatives for monitoring child health outlined in the Institute of Medicine report "Children's Health, the Nation's Wealth"; challenge/demonstration grants funded by the Robert Wood Johnson Foundation; and the National Initiative for Children's Healthcare Quality. Importantly, each of these initiatives is calling for the establishment of measurable standards for assessment of quality of care and for the establishment of routine plans for periodic reassessment thereof. Efforts have been initiated at some medical centers to establish evidence-based clinical pathways for disorders (such as asthma) where there exists sound evidence to advise these guidelines. Pediatricians have developed tools to evaluate the content and delivery of pediatric preventive "anticipatory guidance," the cornerstone of modern pediatrics (see Chapter 5).

THE INFORMATION EXPLOSION OF THE 21ST CENTURY

There is no touchstone through which physicians can ensure that the process of their own continuing education will keep them abreast of advancing knowledge in the field, but the requirement for "Maintenance of Certification" as opposed to the former practice of lifelong certification by specialty boards actively addresses this issue (see Chapter 2). An essential element of this process may be for physicians to take an active role, such as participating in medical student and resident education. Efforts in continuing self-education will also be fostered if clinical problems can be made a stimulus for a review of standard literature, alone or in consultation with an appropriate colleague or consultant. This continuing review will do much to identify those inconsistencies or contradictions that will indicate, in the ultimate best interest of patients that things are not what they seem or have been said to be. These difficulties may be exacerbated by commercially sponsored education programs and research projects that may, on occasion, put profit before the patient's best interests. Physicians still learn most from their patients, but this will not be the case if they fall into the easy habit of accepting their patients' problems casually or at face value because the problems appear to be simple.

The tools that physicians must use in dealing with the problems of children and their families fall into 3 main categories: *cognitive* (up-to-date factual information about diagnostic and therapeutic issues, available on recall or easily found in readily accessible sources, and the ability to relate this information to the pathophysiology of their patients in the context of individual biologic variability), *interpersonal or manual* (the ability to carry out a productive interview, execute a reliable physical examination, perform a deft venipuncture, or manage cardiac arrest or resuscitation of a depressed newborn infant), and *attitudinal* (the physician's unselfish commitment to the fullest possible implementation of knowledge and skills on behalf of children and their families in an atmosphere of empathic sensitivity and concern). With regard to this last category, it is important that children participate with their families in informed decision making about their own healthcare in a manner appropriate to their stage of development and the nature of the particular health problem.

The workday needs of professional persons for knowledge and skills in care of children vary widely. Primary care physicians need depth in developmental concepts and in the ability to organize an effective system for achieving quality and continuity in assessing and planning for healthcare during the entire period of growth. They may often have little or no need for immediate recall of esoterica. On the other hand, consultants or subspecialists not only need a comfortable grasp of both common and uncommon facts within their field and perhaps within related fields, but also must be able to cope with controversial issues with flexibility that will permit adaptation of various points of view to the best interest of their unique patient.

At whatever level of care (primary, secondary, or tertiary) or in whatever position (student, pediatric nurse practitioner, resident pediatrician, practitioner of pediatrics or family medicine, or pediatric or other subspecialist), professional persons dealing with children must be able to identify their roles of the moment and their levels of engagement with a child's problem; each must determine whether his or her experience and other resources at hand are adequate to deal with this problem and must be ready to seek other help when they are not.

ORGANIZATION OF THE PROFESSION AND THE GROWTH OF SPECIALIZATION

The 20th century witnessed the formation of professional societies of pediatricians around the globe. Some of these societies, such as the European Board of Pediatrics and the American Board of Pediatrics, are concerned with education and the awarding of credentials certifying competence and the continuing maintenance of competence as a pediatrician and/or a pediatric subspecialist to the public. From its inception in 1933 through the beginning of 2014, the American Board of Pediatrics certified 108,879 general pediatricians.

The amount of information relevant to child healthcare is rapidly expanding, and no person can become master of it all. Physicians are increasingly dependent on one another for the highest quality of care for their patients. Approximately 25% of pediatricians in the United States claim an area of special knowledge and skill, including >20,000 who have board certification in 1 of the 14 pediatric subspecialties with board certification. Each year approximately 10% of the ≈3,000 pediatric residents training in the United States are enrolled in a dual-residency training program that will lead to eligibility for board certification in both pediatrics and internal medicine.

In the United States, most subspecialists practice in academic settings or children's hospitals. Likewise, specialists are growing in number in other industrialized countries and in developing nations that are becoming industrialized. Reflecting the diverse cultures, organization of medical care, economic circumstances and the history of medicine within each of the ~200 countries across the globe, is the great diversity in role of pediatricians within the healthcare delivery system to children in each country; Figure 1-7 illustrates the resultant variations in pediatricians per population among some European countries.

Beyond certifying bodies, there are other pediatric societies primarily concerned with organizing members of the profession in their country or region to dedicate their efforts, advocacy and resources toward children. In the United States, the American Academy of Pediatrics currently has a membership of ≈60,000 child health specialists in both academic and private practice. Most general pediatricians in the United States enter private practice; ≈66% are in group practices, 5% enter solo practice, and 5% work in a health maintenance organization. The American Academy of Pediatrics provides a variety of continuing educational services to pediatricians in multiple national and regional settings and tracks the professional activities and practices of its members. A comparable group in India, the Indian Academy of Pediatrics, was formed in 1963, and now has ~16,500 members and 16 subspecialty chapters. Likewise, the Pakistani Pediatrics Association was founded in 1967, the Malaysian

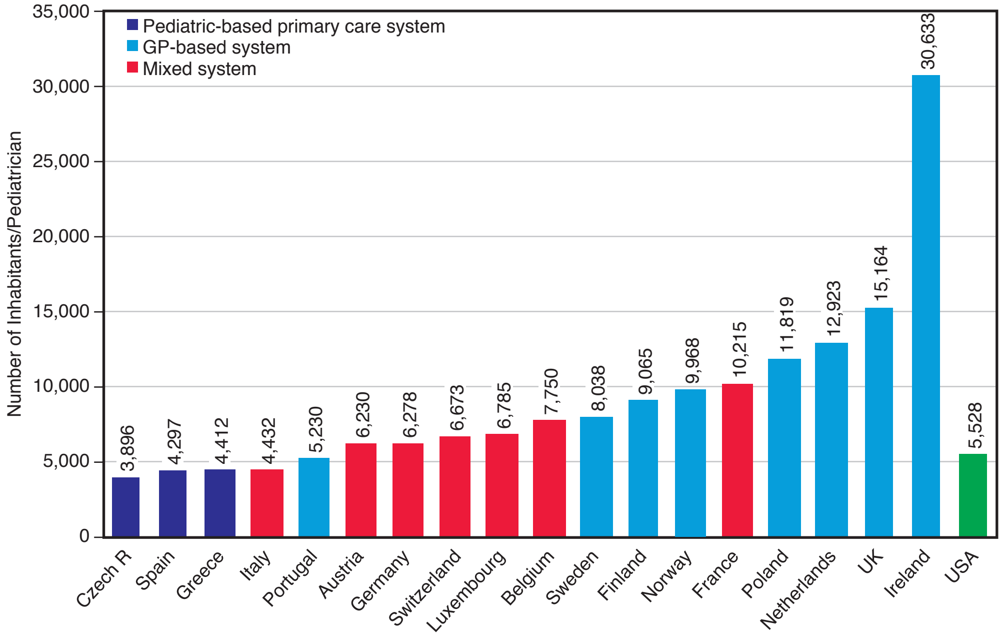

Figure 1-7 Number of inhabitants per pediatrician in some European countries as a function of the differences in primary health care delivery systems, population, and pediatric work force, compared to the current situation in the United States. *(Courtesy of Dr. Alfred Tenore, European Academy of Paediatrics and Chair of Global Pediatric Education Consortium.)*

Pediatric Association was started in 1985, and the Canadian Pediatric Society was founded in 1922. Established in 1974, the Asian Pacific Pediatric Association includes 20 member pediatric societies from throughout eastern Asia, and the International Pediatric Association established in 1910 includes 144 national pediatric societies from 139 countries, 10 regional pediatric societies, and 11 international pediatric specialty societies. The European Academy of Pediatrics is the pediatric specialist organization for the member countries of the European Union and the European Free Trade Association, and the Pediatric Council of the Arab Board of Medical Specializations is the comparable institution for 19 of the world's Arab nations These societies represent but a few of the many national and regional pediatric professional organizations around the world who seek to identify and bring treatments and approaches supporting child well-being to pediatricians worldwide.

Bibliography is available at Expert Consult.

1.1 Innovations in Addressing Child Health and Survival in Low-Income Settings

Zulfiqar Ahmed Bhutta

GLOBAL BURDEN AND MORTALITY TRENDS

The current global burden of neonatal and child death is largely concentrated in Central and sub-Saharan Africa and South Asia (Figs. 1-8 and 1-9; see also Fig. 1-1 and Table 1-1). Ten countries have almost ⅔ of the global burden of maternal and newborn deaths as well as stillbirths.

It is estimated that 6.2 million children younger than 5 yr died in 2012, a 63% reduction from 16.9 million in 1970. However, there are still wide disparities and in 2012, child mortality rates range from a high of 182 per 1,000 in Sierra Leone to 2 per 1,000 in Iceland and Luxembourg. Progress in this regard has been variable, and despite global progress, of the 75 countdown countries that have almost 98% of all maternal and under-5 child deaths, only 13 are on track to reach MDG targets for child mortality. Other global estimates from the Institute of Health Metrics and Evaluation indicate that only 31 developing countries will reach MDG 4 targets by 2015.

From 1990 to 2013, annual rates of decline ranged from 6.7% to –0.9%. In 2013, neonatal deaths account for 41.3% of under-5 deaths, up from 37.6% in 1990. Comparing 2013 with 1990, rising numbers of births, particularly in sub-Saharan Africa, were associated with an additional 1.5 million child deaths. Neonatal mortality reduction has been much slower than that for maternal and child (1-59 mo) mortality, and slowest in the highest burden countries, especially in Africa. The sobering realization is that even in countries that would reach their MDGs 4 and 5 targets, many would still have high numbers of deaths with much scope for improvement.

CAUSES OF NEWBORN AND CHILD DEATHS

The Child Health Epidemiology Reference Group estimated that 40.3% of 7.6 million under-5 deaths in 2010 occurred in the newborn period; 2013 figures from the Institute of Health Metrics and Evaluation corroborate these estimates.

Among newborn deaths, major causes include preterm birth complications (14.1%; 1.078 million), intrapartum-related complications, previously labeled as birth asphyxia (717,000 deaths; 9.4%), and sepsis or meningitis (393,000; 5.4%) neonatal deaths. Among older children, the leading causes of deaths included pneumonia (14.1%; 1.071 million), diarrhea (9.9%; 751,000), and malaria (7.4%; 564,000) (Fig. 1-10*A*). Existing data suggest broadly comparable figures for under-5 deaths (Fig. 1-10*B*), although some categories are different, notably higher proportion of malaria deaths among under-5 children in the Global Burden of Disease study 2010 estimates and lower numbers for pneumonia deaths.

An unaddressed burden of stillbirths exists globally and is not included in the current Global Burden of Disease study estimates. Of an estimated 2.64 million stillbirths worldwide in 2009, 76.2% occurred in south Asia and sub-Saharan Africa, mostly among rural populations. An estimated 45% of these stillbirths occur in the intrapartum period, reflecting a clear extension of the neonatal deaths related to intrapartum events, previously labeled as birth asphyxia deaths. The highest risk time is around birth, when more than 40% of maternal deaths and combined stillbirths during labor and neonatal deaths occur. These deaths occur rapidly, requiring urgent response by healthcare workers. Table 1-5 lists the top 10 countries for risks of intrapartum stillbirths and newborn deaths on the first day of life.

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Neonatal Deaths per 1,000 Live Births in 2011

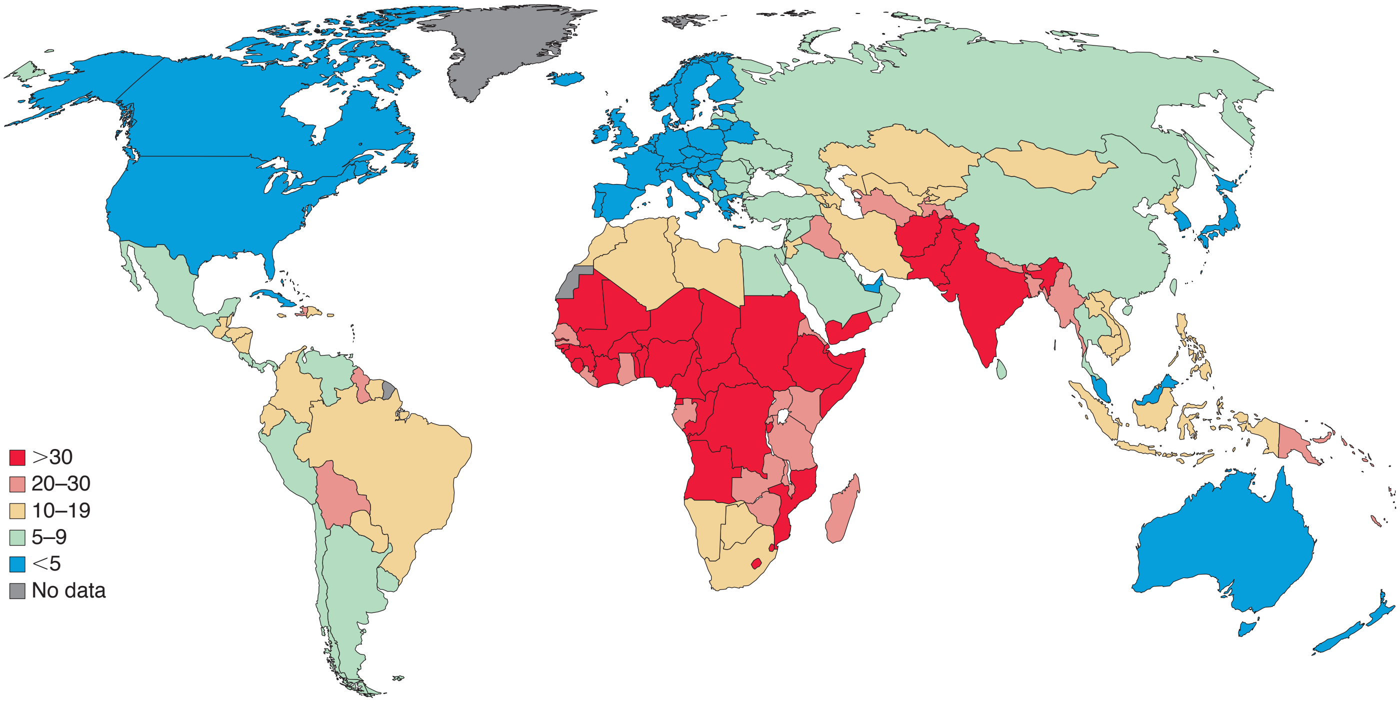

Figure 1-8 Neonatal deaths by country (rates). *(From Bhutta ZA, Black RE. Global maternal, newborn, and child health—so near and yet so far.* N Engl J Med *2013;369:2226–2235.)*

Deaths in Children <5 Yr of Age per 1,000 Live Births in 2011

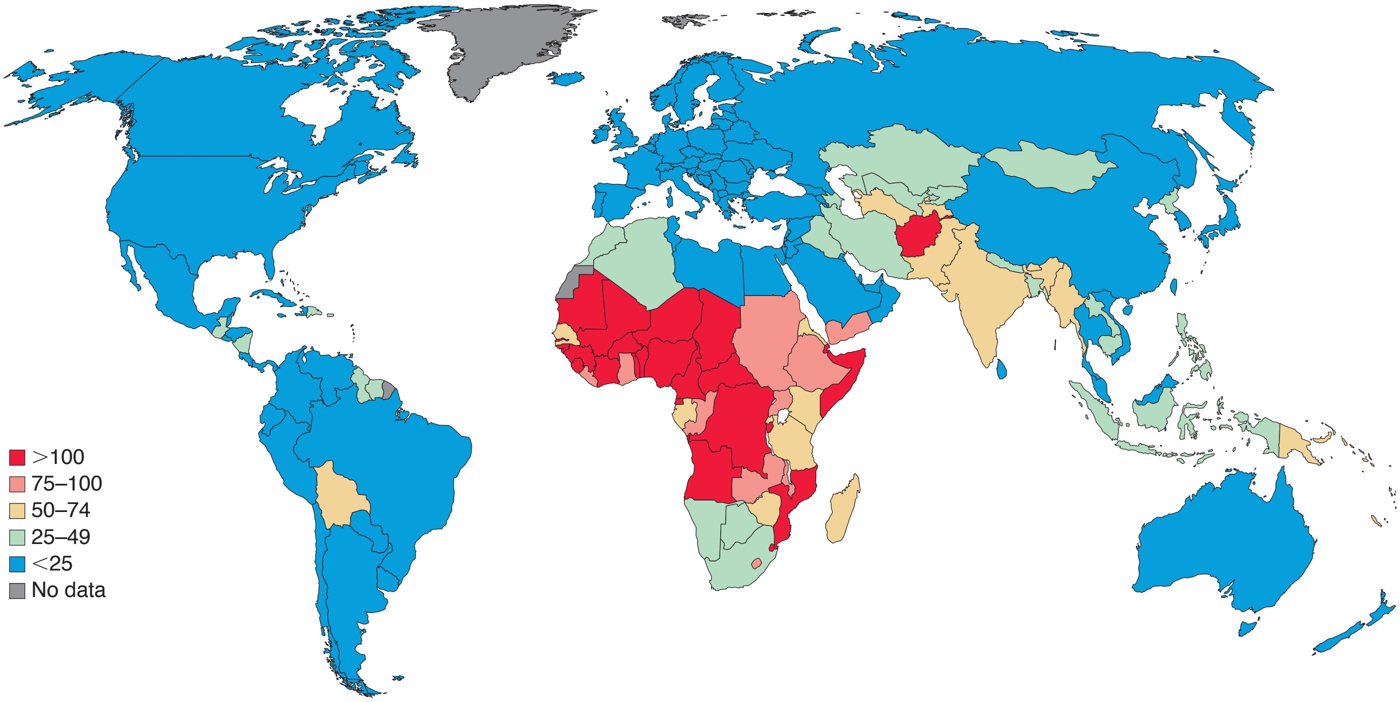

Figure 1-9 Child (1-4 yr) deaths per 1,000 live births. *(From Bhutta ZA, Black RE. Global maternal, newborn, and child health—so near and yet so far.* N Engl J Med *2013;369:2226–2235.)*

Being born small, because of preterm birth or small for gestational age (SGA) or both, is the leading risk factor for neonatal deaths and carries increased risk for postneonatal mortality, growth failure, and adult-onset noncommunicable conditions (see Chapter 97). South Asia has the highest SGA rates and sub-Saharan Africa has the highest preterm birth rates. Babies who are term SGA low birthweight face risks for stunting, and adult-onset metabolic conditions. Fifteen million preterm births, especially those <32 wk gestation, are at highest risk of neonatal death, with ongoing postneonatal mortality risk, significant risk of long-term neurodevelopmental impairment, and stunting, as well as noncommunicable conditions. Four million neonates annually have other life-threatening conditions, including intrapartum-related

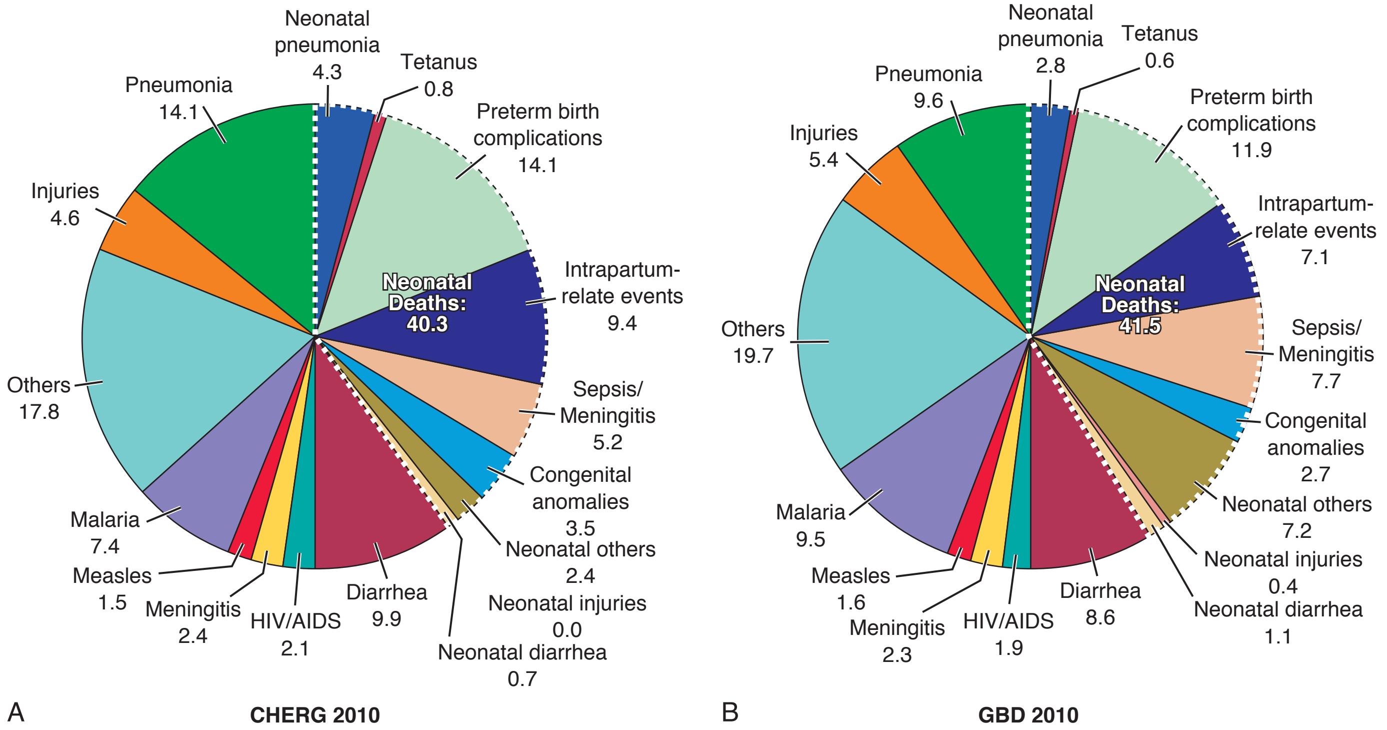

Figure 1-10 Global causes of child deaths. *CHERG, Child Health Epidemiology Reference Group; GBD, Global Burden of Disease study.*

Table 1-5 Ten Countries with the Highest Rate of First-Day Deaths and Stillbirths During Labor

COUNTRY	RISK OF NEONATAL DEATH ON DAY OF BIRTH (PER 1,000 LIVE BIRTHS)	INTRAPARTUM STILLBIRTH RATE (PER 1,000 TOTAL BIRTHS)	INTRAPARTUM STILLBIRTHS AND NEONATAL DEATHS ON DAY OF BIRTH (PER 1,000 TOTAL BIRTHS)
Pakistan	15	26.4	40.7
Nigeria	14	19.4	32.7
Sierra Leone	18	13.9	30.8
Somalia	16	14.0	29.7
Guinea-Bissau	16	13.7	29.4
Afghanistan	13	16.6	29
Bangladesh	9	20.6	28.9
Democratic Republic of Congo	15	13.3	28.3
Lesotho	16	11.8	27.5
Angola	16	11.7	27.4

brain injury, severe bacterial infection, and pathologic jaundice, with 1.4 million neonates surviving with long-term neurodevelopmental impairment. The consequences of not acting to improve birth outcomes by 2035 are estimated at 116 million deaths, 99 million with disability or lost development potential, and many millions of adults with noncommunicable disease following being born SGA and or prematurely.

UNDERSTANDING SOCIAL DETERMINANTS AND BARRIERS FOR CARE

Understanding the causes of deaths allows for better planning and targeting of interventions. Between 2000 and 2010, the bulk of the reduction in under-5 child mortality related to decreases in pneumonia, measles, and diarrhea deaths, whereas corresponding reductions in neonatal causes of deaths other than tetanus (notably those associated with prematurity and intrapartum related events) was minimal.

Poverty is a huge barrier and affects all levels of care because much of the burden of maternal and child mortality and ill health is concentrated among the poorest countries of sub-Saharan Africa and South Asia. In many of these countries, the bulk of the mortality is clustered among the poor, frequently residing in remote and rural populations with limited access to healthcare services. A sizeable proportion of deaths also occur among the urban poor living in slum conditions with limited social support networks and poor living conditions. Other determinants, such as environmental factors (e.g., overcrowding, poor air quality and sanitary conditions), may be much worse in urban slums than in many rural populations. Lack of trained human resources and transportation facilities in rural populations, as well as quality of care in existing primary care settings are also problems. Figures 1-11 and 1-12 illustrate some of the inequities observed across key evidence-based maternal and child interventions across and within large number of developing countries. Interventions that have a relatively narrow

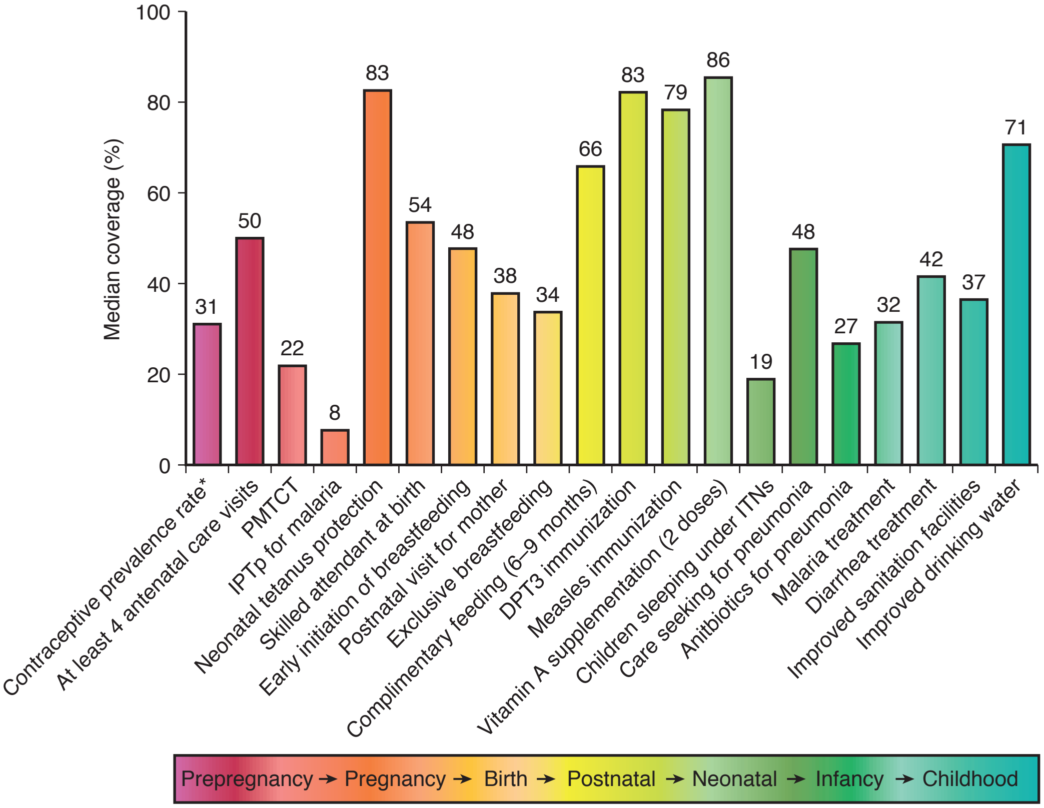

Figure 1-11 Global coverage for 75 countdown countries with 98% of maternal and child deaths. *(From Bhutta ZA, Chopra M, Axelson H, et al: Countdown to 2015 decade report [2000–10]: taking stock of maternal, newborn, and child survival. Lancet 375:2032–2044, 2010, Fig. 2.)*

delivery channel and mandates such as immunizations do achieve high coverage, whereas those that require functional health systems and facilities, such as skilled birth attendance and postnatal care, hardly reach half of the population in need. For others, such as the appropriate use of zinc, ORS, and antibiotics for the treatment of childhood diarrhea or pneumonia, current coverage rates are very low.

Estimates of the impact of various factors on child survival between 1990 and 2013 indicate that while rising numbers of births, particularly in sub-Saharan Africa, led to 1.5 million more child deaths, rising income per capita and maternal education led to 774,000 and 2.4 million fewer deaths, respectively. Technology change alone led to 4.0 million fewer deaths. In 23 developing countries, there is evidence that declines since 2000 have been faster than predicted on the basis of income, education, and technology shift alone.

EVIDENCE-BASED INTERVENTIONS AND INNOVATIONS TO ADDRESS INEQUITIES

There is a range of preventive, promotive and therapeutic interventions that can affect newborn and child survival (Table 1-6).

These services require **appropriate delivery platforms** for scaling up coverage, especially in circumstances where there is widespread **shortage of health workers**, and the **removal of financial barriers** that preclude care seeking and access where such care is not freely available within the public health system. There is also the need to **improve quality of care** within facilities and ensure availability of life saving commodities by well trained and motivated care providers.

COMMUNITY HEALTH WORKERS FOR NEWBORN AND CHILD HEALTH

The global shortage of a skilled health work force has been a key barrier to effective coverage and in many instances policy makers and planners resort to the use of community health workers (CHWs) who are provided basic training in preventive and promotive strategies. Such task-shifting strategies have been shown to yield beneficial results in diverse settings, frequently in malaria and HIV management. Communities should take active part in improving their own health, and the dynamic role of CHWs in delivery of health-related care are well recognized. CHWs work in liaison with frontline health workers and are fastened across the primary healthcare for better success in reaching the goals (Fig. 1-13).

A growing array of interventions delivered by CHWs can significantly improve neonatal and child health and survival; behavioral interventions to promote healthy behavior; preventive interventions, such as immunization; and more complex tasks, such as case management of childhood illnesses (e.g., pneumonia, malaria, and neonatal sepsis). The active involvement and empowerment of communities through CHWs have positive effects on health by changing health beliefs and improving care seeking for illnesses. CHWs increase the proportion of people who receive healthcare and increase the number of children with up-to-date immunization statuses. CHWs who provide some amount of support of breastfeeding, as well as care during pregnancy, help reduce child mortality through various antenatal interventions, including pregnancy surveillance, vitamin supplementation, and promotion of birth preparedness. CHW programs are also dependent upon basic tool kits and a steady and reliable supply of key commodities. Lack of adequate supplies and frequent stock outs are a major impediment to effective programs and implementation.

Women's and community support groups which are largely formulated and facilitated by CHWs have shown reductions in neonatal mortality and morbidity and improvement in domiciliary practices, such as early initiation of breastfeeding and healthcare seeking for their illnesses. These participatory activities empower mothers, emphasize safe delivery practices and encourage care seeking behavior.

Home visits by CHWs may improve coverage of key newborn care practices such as early initiation of breastfeeding, exclusive breastfeeding, skin-to-skin contact, delayed bathing and attention to hygiene, such as hand washing with soap and water, clean umbilical cord care, immunization and early diagnosis, detection of complications,

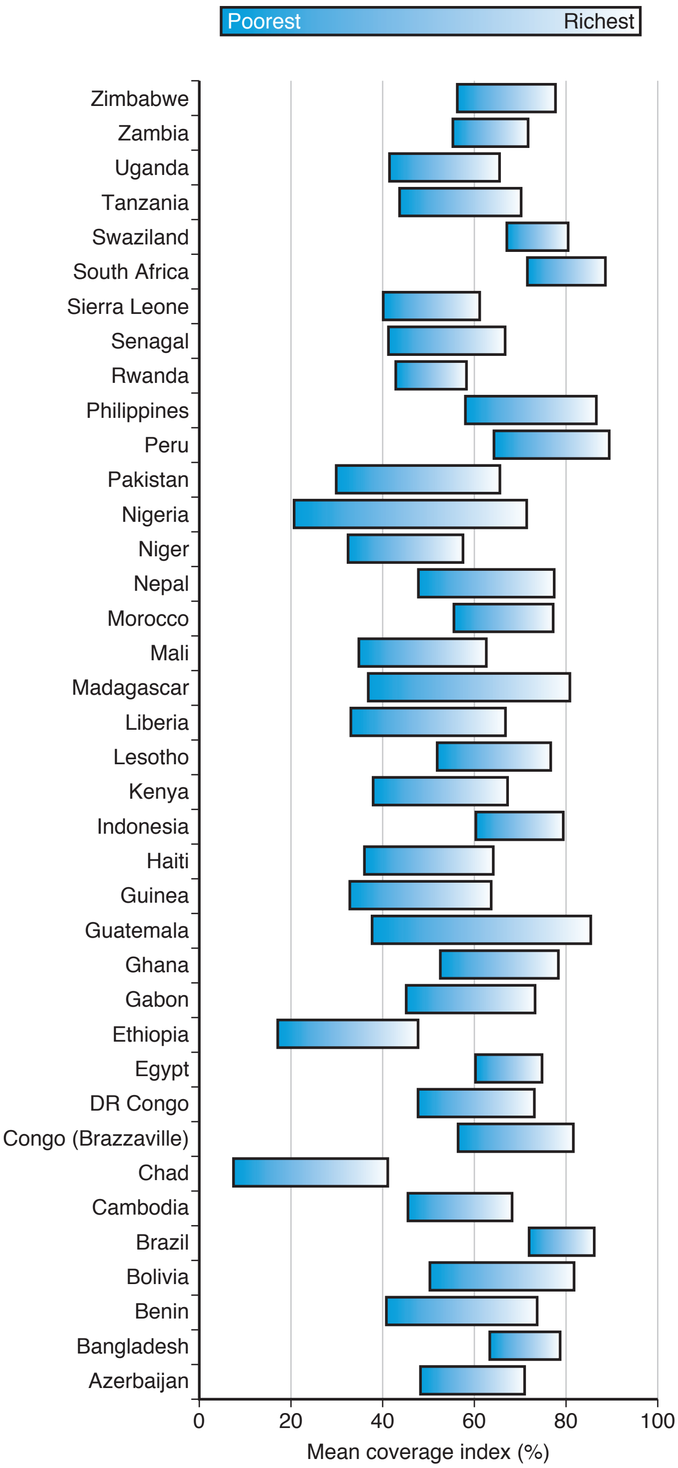

Figure 1-12 Inequities in maternal and child interventions from 38 countdown countries. *(From Bhutta ZA, Chopra M, Axelson H, et al: Countdown to 2015 decade report [2000–10]: taking stock of maternal, newborn, and child survival. Lancet 375:2032–2044, 2010,Fig. 7.)*

and appropriate referrals. Home-based newborn care consisting of therapeutic interventions, case management and referrals, and preventive interventions such as health education have shown reductions in neonatal mortality and in stillbirths.

Implementation of an essential newborn care package along with administration of home-based antibiotic therapy for suspected neonatal sepsis by CHWs has resulted in a 62% reduction in the neonatal mortality rate when 93% of the newborns in the intervention area were provided treatment. In a meta-analysis of trials of community-based case-management of pneumonia all-cause neonatal mortality was 27% lower in the intervention group, whereas pneumonia-specific neonatal mortality in the intervention group was reduced by an even greater amount. Case management of children suffering from pneumonia, malaria, and diarrhea may be the potential way forward in the low-income setting. Case management of pneumonia by CHWs could result in a 70% reduction in mortality from pneumonia in children <5 yr of age. Community-based interventions correlate to a 13% and 9% increase in care seeking for pneumonia and diarrhea, respectively. Case management is associated with increased uptake of ORS and zinc for management of diarrhea. These interventions also lead to a 32% reduction in pneumonia-specific mortality. CHWs can also be trained to perform rapid diagnostic tests for malaria, and manage test-positive children with antimalarials.

CHWs can also play a role in improving the use of anthelminthics in children. Interventions such as preventive chemotherapy, health education to promote general hygiene and sanitation, iron and β-carotene supplementation, construction of latrines, removing cattle from residential areas, staff training and community mobilization can have significant impacts on prevention and management of worm infestations. Evidence suggests that school-based delivery of anthelminthics can significantly reduce soil-transmitted helminthes prevalence, schistosomiasis prevalence, and anemia. Interventions related to handwashing counseling (for individuals or groups) suggested a 30% reduction in the risk of diarrhea as well.

THE ROLE OF INFORMATION TECHNOLOGY AND mHEALTH PLATFORMS

Mobile health, or mHealth, is the use of mobile information and communication technologies for improving health. It can be used for a wide range of purposes, including health promotion and illness prevention, healthcare delivery, training and supervision, electronic payments, and information systems. This is widely regarded as a great equalizer across social strata in increasing access to information and empower health workers to reach marginalized populations. In the simplest forms SMS/text-based campaigns can be an effective way to share health information with people who lack reliable Internet access and in other instances telemedicine can permit specialist access and consultations which were hitherto not possible because of geographic constraints and limitations. mHealth is of particular interest in low- and middle-income countries, where widespread mobile networks and access to devices are connecting people, leap-frogging older technologies to dramatically improve information flow, data collection, social and behavior change, and emergency response.

CASH TRANSFERS TO REDUCE POVERTY BARRIERS AND IMPROVE CHILD HEALTH

Out of pocket expenses by households form the major share of total health expenditure in most low income countries and a substantial share in middle income countries. Financial incentives are becoming widely used to improve healthcare coverage, alleviate poverty and improve access to child health services. Some support platforms have a dual purpose of reducing financial barriers and also strengthening service delivery. Financial incentive programs may include conditional/unconditional cash transfers, conditional/unconditional microcredit, conditional/unconditional voucher, user fee removal and health insurances. Financial incentive programs targeting child health generally focus on breastfeeding practices; vaccination; healthcare use; management of diarrheal diseases; and other preventive health interventions including preventive deworming, vitamin A and iron supplementation. These programs are also directed toward education improvement by improving school enrollment, attendance, and occasionally some measure of performance.

OTHER TECHNOLOGIES AND INNOVATIONS

There has been a massive increase in global knowledge and potential of low-cost technologies to improve diagnosis and care of sick newborn infants and children. These span bedside tools to assess risk of severe

Table 1-6 Evidence-based Interventions to Address Newborn and Child Health and Undernutrition

NEWBORN	NUTRITION	DIARRHEA	PNEUMONIA
Breastfeeding promotion including initiation			
	Improved water source, sanitation, and hygiene Preventive vitamin A supplementation Preventive zinc supplementation		
Periconceptional folic acid supplementation or fortification Multiple micronutrient/iron-folate supplementation in pregnancy Maternal balanced energy protein supplementation Maternal calcium supplementation			
ORS Antibiotics for dysentery		ORS Antibiotics for dysentery	
Case management of pneumonia			Case management of pneumonia
IPTp case management, Syphilis detection and treatment Tetanus toxoid vaccination Diabetes case management Fetal growth restriction detection Hypertensive disease prevention and case management Induction of labor for pregnancies after 41 weeks Active management of the third stage of labor Clean birth practices Labor and delivery management ANS for preterm labor Antibiotics for preterm premature rupture of membranes Immediate assessment and stimulation Neonatal resuscitation Thermal care Chlorhexidine cord application Clean postnatal practices Hospital care of preterm babies including Kangaroo mother care	Appropriate complementary feeding Management of moderate acute malnutrition Management of severe acute malnutrition	Zinc for treatment of diarrhea Rotavirus vaccine	Hib vaccine Pneumococcal vaccine

ANS, antenatal corticosteroid treatment; Hib, *Haemophilus influenzae* type b; IPTp, intermittent preventive treatment of malaria for pregnant women.

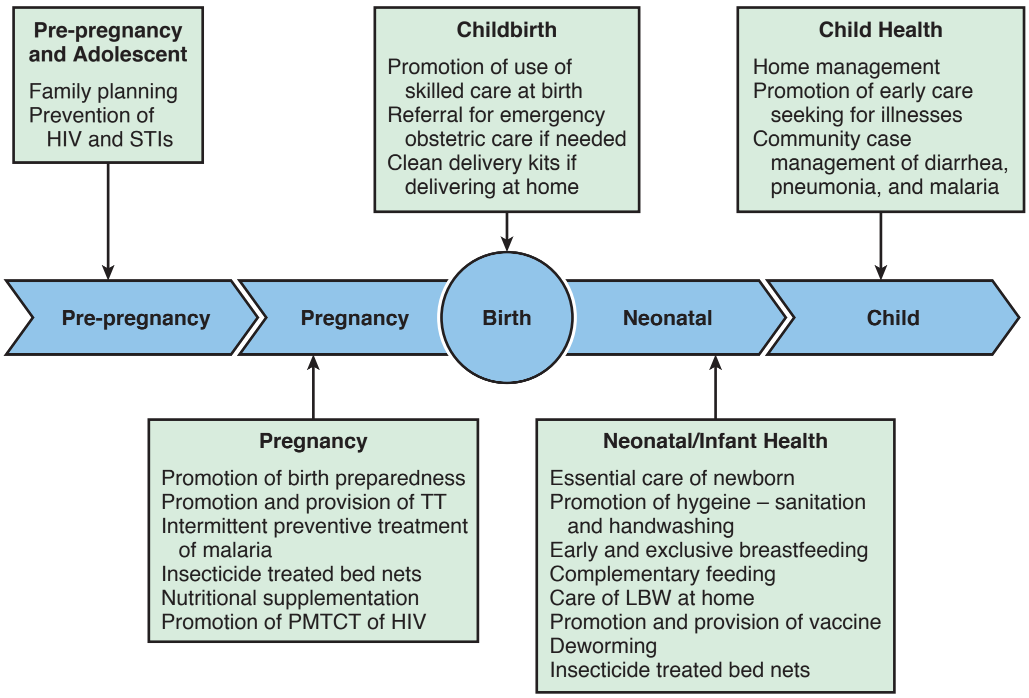

Figure 1-13 Neonatal and child health interventions: delivered by community health workers.

illness such as handheld pulse oximetry devices for children with respiratory infections, development of 4% chlorhexidine gel for prevention of cord infections in newborns, and injection devices to aid health workers such as Uniject systems.

There has been considerable work to achieve consensus across a range of UN agencies, academic bodies, and professional groups on key essential evidence-based interventions for maternal and child health that need implementation and scaling up within health systems.

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Chapter 2

Quality and Safety in Healthcare for Children

Ramesh C. Sachdeva

THE NEED FOR QUALITY IMPROVEMENT

There is a significant quality gap between known, recommended evidence-based care and the actual care that is delivered. Adults receive recommended care slightly higher than 50% of the time, whereas children receive recommended care only approximately 46% of the time. This quality gap exists because of a chasm between knowledge and practice—a chasm made wider by variations in practice and disparities in care from doctor to doctor, institution to institution, geographic region to geographic region, and socioeconomic group to socioeconomic group.

Historically, success in medicine was viewed as advances in technology, identification of new treatments, and the generation of new evidence to improve care. Although these facets of medical advances continue to be important, it is estimated that it takes about 17 yr for new knowledge and research findings to be adopted into clinical practice. Further, the Institute of Medicine's (IOM) report, "To Err is Human: Building a Safer Health System," highlights that ~44,000-98,000 patients die in U.S. hospitals each year because of preventable medical errors. These errors were more likely to occur in environments such as operating rooms, emergency departments, and intensive care units. Preventable medical errors have an economic cost of $17-$29 billion per year. These gaps in quality and related high costs will only be solved when physicians and healthcare systems adopt the emerging new science of **Quality Improvement (QI).**

The need for QI is expanding even further. With the growing concerns of healthcare costs and also the implementation of the Affordable Care Act, the scope of QI has expanded from the level of individual patients to include the notion of the **Triple Aim** proposed by the Institute for Healthcare Improvement–improving the care for *individual patients*, improving the care *for populations*, and improving the *cost effectiveness for healthcare delivery*. Recently, there has been a recognition that QI needs to shift from the sphere of process improvement toward outcomes improvement, and to ensure value from the standpoint of the patient.

WHAT IS QUALITY?

The IOM defines quality of healthcare as the degree to which healthcare services for individuals and populations increases the likelihood of desired health outcomes and are consistent with current professional knowledge. This definition incorporates 2 key concepts related to healthcare quality: the direct relationship between the provision of healthcare services and health outcomes, and the need for healthcare services to be based on current evidence.

To measure healthcare quality, the IOM has identified Six Dimensions of Quality all of which relate to quality of care. The Six Dimensions of Quality are **effectiveness, efficiency, equity, timeliness, patient safety,** and **patient-centered care.** Quality of care needs to be effective, which means that healthcare services should result in benefits and outcomes. Healthcare services also need to be efficient, which incorporates the idea of avoiding waste and improving system cost efficiencies. Healthcare quality should improve patient safety, which incorporates the concept of patient safety as one of the key elements within the Six Dimensions of Quality. Healthcare quality must be timely, thus incorporating the need for appropriate access to care. Healthcare quality should be equitable, which highlights the importance of minimizing variations as a result of ethnicity, gender, geographic location, and socioeconomic status. Healthcare quality should be patient-centered, which underscores the importance of identifying and incorporating individual patient needs, preferences, and values in clinical decision making.

The IOM framework of the Six Dimensions of Quality emphasizes the concept that all Six Dimensions of Quality need to be met for the provision of high quality healthcare. These concepts can be viewed as the overall *value* proposition—that is, the value created for a patient. From the standpoint of the practicing physician, these Six Dimensions of Quality can be categorized into clinical quality and operational quality. To provide high-quality care to children, both aspects of quality—clinical and operational—must be met. Historically, physicians have viewed quality to be limited in scope to clinical quality with the goal of improving clinical outcomes, and have considered efficiency optimization and access as the role of healthcare plans, hospitals, and insurers. Healthcare organizations, which are subject to regular accreditation requirements, viewed the practice of clinical care delivery as the responsibility of physicians and limited their efforts to improve quality largely to process improvement to enhance efficiencies. This is further magnified as many office-based pediatricians have independent clinical practices and interact with hospitals only when they care for hospitalized children.

This traditional perspective is changing. The evolving healthcare system requires physicians, healthcare providers, healthcare organizations, and hospitals to partner together to measure, demonstrate, and improve the overall quality of care to the patients they serve. With many regulatory and accreditation changes such as **Maintenance of Certification (MOC)** requirements of the **American Board of Pediatrics** and the planned Maintenance of Licensure by U.S. state licensing bodies, physicians will be required to understand and implement QI principles into their clinical practice and report the quality of their care delivered by them in a transparent manner.

The recently implemented Patient Protection and Affordable Care Act has at its core quality measurement and QI. The Affordable Care Act aims at enhancing access to care which is a quality dimension. Quality measurement is integral to ensuring transparency and choice across health plans. An important concept for quality within the Affordable Care Act relates to expanding the conventional scope of quality to population health.

Definitions of Quality-Related Terms

Quality includes many concepts—quality measurement, quality reporting and benchmarking, process improvement, performance, and outcomes improvement using quality initiatives (Table 2-1).

FRAMEWORK FOR QUALITY

Quality is broader in scope than QI. As adopted by the *American Academy of Pediatrics*, the approach to quality includes 4 building blocks (Fig. 2-1). First, the standard for quality must be defined (i.e., developing evidence based guidelines, best practices, or policies that guide the clinician for the specific clinical situation). These guidelines should change based upon new evidence. For example, in 2000-2001, the American Academy of Pediatrics had published guidelines for care

Table 2-1 Definitions of Quality-Related Terms

Term	Definition
Quality	"…the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." *U.S. Institute of Medicine*
Quality Initiative	"…systematic, data-guided activities designed to bring about immediate improvements in healthcare delivery in particular settings." *Hastings Center*
Performance Measure	"…yardsticks by which all healthcare providers and organizations can determine how successful they are in delivering recommended care and improving patient outcomes." *U.S. Institute of Medicine*
Performance Management	"…a systematic process by which an organization involves its employees in improving the effectiveness of the organization and achieving the organization's mission and strategic goals. By improving performance and quality, public health systems can save lives, cut costs, and get better results by managing performance." *Public Health Foundation*
Process Improvement	"… the systematic approach to closing of process or system performance gaps through streamlining and cycle time reduction, and identification and elimination of causes of below specifications quality, process variation, and non–value-adding activities." *BusinessDictionary.com*

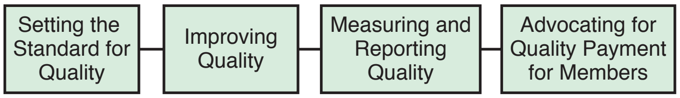

Figure 2-1 The American Academy of Pediatrics model for quality.

of children with attention-deficit/hyperactivity disorder. Subsequently, in 2011, these were updated to highlight a greater emphasis on behavioral interventions rather than pharmacologic options. Second, quality needs to be improved to close the quality gap. The quality gap refers to the difference between the recommended care and the actual care delivered to a patient. This can be achieved by using principles from improvement and implementation science. Improvement science relates to the methods and tools for achieving change. Methods can include learning collaboratives where groups of individuals share their experiences creating a community of learners. With the growth of new technology, including social media, virtual collaboratives are increasingly gaining popularity. Tools for QI can include techniques such as the Improvement Model, LEAN, Six Sigma, and Management Sciences. Implementation science is different than improvement science and relates to the study of methods to successfully spread the improvement to new settings and sustain it in these settings. Third, quality needs to be measured. Quality measures can be developed as measures for accountability and measures for improvement. Accountability measures are developed with a high level of demonstrated rigor as these are used at the macro level for measuring the quality of care at the state level, and for regional use by health plans and health systems. Efforts are ongoing to link such measures to *pay-for-performance (P4P)* for reimbursement at the hospital and individual physician level. In contrast, improvement measures are metrics that can demonstrate the improvement accompanying a QI initiative. These need to be locally relevant and typically have not had rigorous field testing. Finally, the quality measurement effort has to be linked to advocacy. Advocacy should be aimed at ensuring that there is adequate investment in early childhood from a preventive standpoint that will result in significant savings in adulthood from a healthcare perspective.

DEVELOPING GUIDELINES TO ESTABLISH THE STANDARD FOR QUALITY

Guidelines need to be developed based upon accepted recommendations, such as the Grades of Recommendation Assessment, Development and Evaluation system for rating the quality of the evidence and strength of evidence which is crucial for guideline development. Guidelines must adopt a high level of transparency in the development process. This is particularly relevant in the pediatric setting where there may be limited research using methods such as randomized controlled trials which would have a high level of rating from an evidence standpoint. As guidelines and policies related to quality need to be interpreted for specific settings, they should not be interpreted as standards of care.

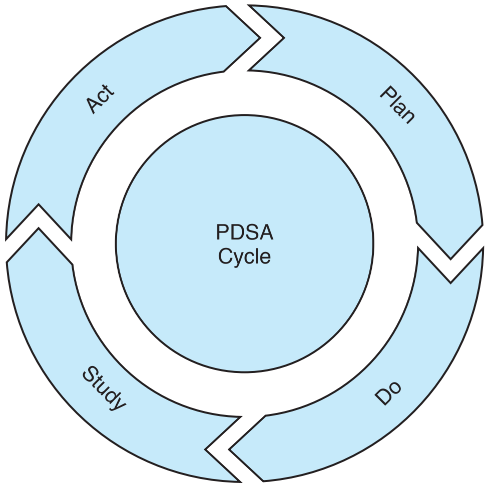

Figure 2-2 The plan-do-study-act cycle. *(From Langley GJ: The improvement guide: a practical guide to enhancing organizational performance, San Francisco, 1996, Jossey-Bass. © 1996 by Gerald J. Langley, Kevin M. Nolan, Thomas W. Nolan, L. Norman, and Lloyd P. Provost.)*

IMPROVING QUALITY

Achieving QI requires the adoption of a 3-step model: "Data → Information → Improvement." Quality needs to be measured. Quality data obtained from the measurement then needs to be converted into meaningful information that can be compared and reported. This quality measurement must also be actionable to achieve improvements in clinical practice. QI is a rapidly growing science. There are currently 4 techniques available for QI.

Model for Improvement

The *Model for Improvement* can be implemented using a framework of rapid cycle improvement also known as the *plan-do-study-act (PDSA) cycle* (Fig. 2-2). The PDSA cycle is typically aimed at testing small changes and then studying the results to plan and implement the next cycle of change (i.e., multiple PDSA cycles build on previous learning from PDSAs). Valuable information can be obtained from PDSA cycles that are successful, and those that are not, to help plan the next iteration of the PDSA cycle. The PDSA cycle specifically requires that improvements be data driven. This is important because many clinicians attempt to make changes for improvement in their practice but do not emphasize the importance of data collection.

The Model for Improvement has been successfully used in the **Vermont Oxford Network (VON)** to achieve improvements in care in

the **neonatal intensive care unit (NICU)** setting. The VON is a global network of collaborating NICUs involved in several studies that have favorably impacted the care of newborns. An example of a successful VON QI effort is a project aimed at reducing rates of chronic lung disease in extremely low birthweight infants. Clinical teams participating in this improvement effort used special reports from the VON database, reviewed the available evidence with content faculty experts, and then identified improvement goals. The teams received QI training through conference calls and emails for a period of 1 year. This effort resulted in a 37% increase in early surfactant administration for preterm infants achieving a high degree of QI.

Another example of a successful QI collaborative using the improvement model relates to the reduction of **catheter-associated bloodstream infections (CA-BSIs)** in the **pediatric intensive care unit (PICU)** setting. Similar to the VON experience, this effort included a group of PICUs that collaborated to impact a serious preventable problem in the PICU—*CA-BSIs*. National content experts and local PICU quality champions monitored and provided performance data at the local level in an almost real-time basis to ensure continued learning and improvement. The engagement of the entire PICU team—physicians, trainees, nurses, respiratory therapists, and others created a culture of quality and accountability. There was a strong emphasis on team learning across the participating institutions. This national collaborative sponsored by the Children's Hospital Association and the American Board of Pediatrics has resulted in a significant measurable reduction in CA-BSI rates across PICUs in the United States and is now in subsequent iterations of the PDSA cycle.

Six Sigma

Six Sigma relates to the reduction in *undesirable variation in processes* (Fig. 2-3). Every process has some level of inherent variation built into it. There are 2 types of variations in a process. *Random variation* relates to the variation that is inherent in the process simply because the process is being performed by humans. A physician completing a history and physical for a patient more than once may have a slightly different process each time, even though it is the same patient and the same physician. Random variation in processes is acceptable. In contrast, *special cause variation* relates to nonrandom variation that can adversely affect a process; when tracking infection rates in a nursery, a sudden increase in the infection rates may be secondary to poor handwashing techniques by a new healthcare provider in the system. This would represent a special cause variation (i.e., once this practice is improved, the infection rates will likely go back to the baseline level). Six Sigma attempts to provide a structured approach to unwanted variations in healthcare processes (Fig. 2-4). Six Sigma approaches have been successfully used in healthcare to improve processes in both the clinical and nonclinical settings.

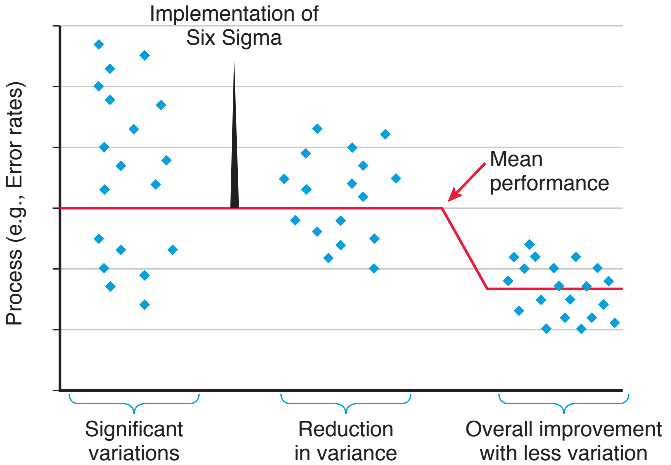

Figure 2-3 Improving quality by reducing variation and shifting the mean.

LEAN

Lean methodology, which stems from the Toyota Production System, aims at reducing waste within a process in a system. Figure 2-5*A* illustrates the steps in the process of a patient coming to the emergency department. After the initial registration, the patient is seen by a nurse and then the physician. In a busy emergency department, a patient may need to wait for hours before registration is complete and the patient is placed in the examination room. This wait time is a waste from the perspective of the patient and the family. By incorporating the registration process after placing the patient in the physician examination room, time can be saved and waste minimized (Fig. 2-5*B*). Lean

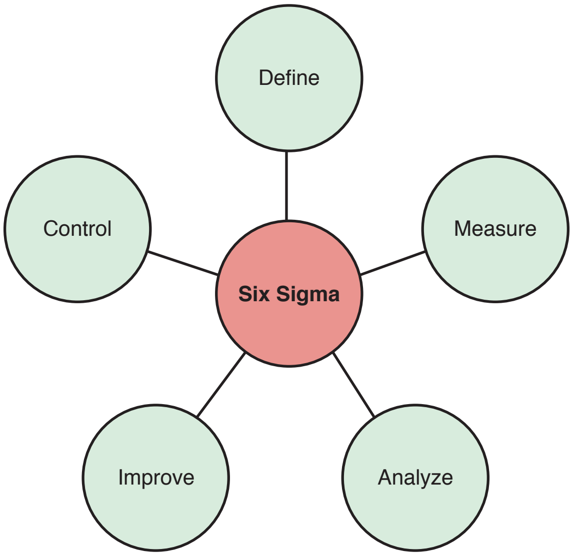

Figure 2-4 Six Sigma DMAIC (define, measure, analyze, improve, control) method.

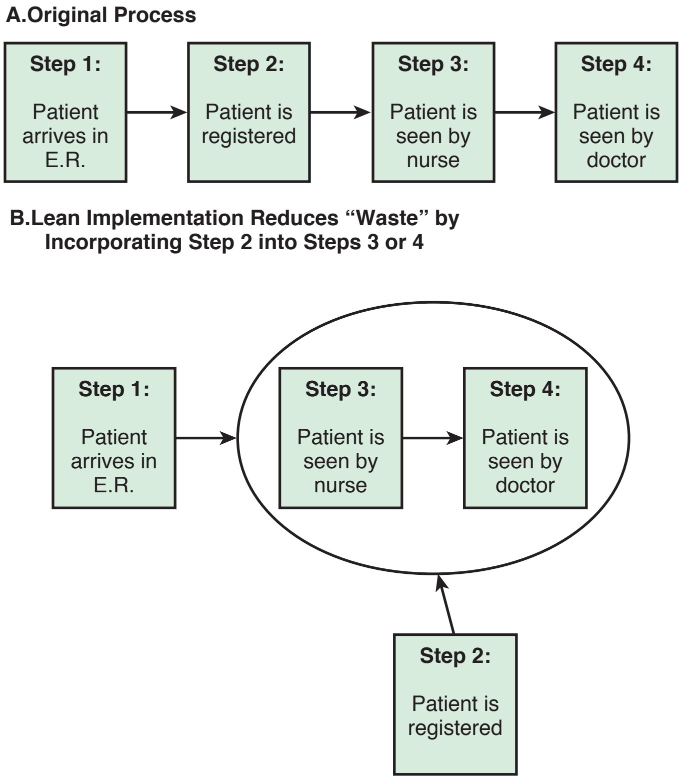

Figure 2-5 **A** and **B**, Lean—waste reduction.

methods have been successfully used in several outpatient and inpatient settings with resulting improvements in efficiency. Lean principles have also been adopted as a core strategy for children's hospitals with the goal of improving efficiencies and reducing waste.

Management Sciences

Management sciences, also known as *operations management*, stems from operations research and relates to the use of mathematical principles to maximize efficiencies within systems. Management sciences has been successfully used in many non–healthcare settings, such as airlines and the military. Management sciences principles have been successful in many European healthcare settings to optimize efficiencies in outpatient primary care office settings, inpatient acute care hospital settings, surgical settings including operating rooms, and also for effective planning of transport and hospital expansion policies. Management sciences principles are being explored for use in the U.S. healthcare system. One of the techniques for management sciences, *discrete event simulation* was used at the Children's Hospital of Wisconsin to effectively plan the expansion of the pediatric critical care services with the goal of improving quality and safety. The discrete event simulation model illustrated in Figure 2-6 depicts the various steps of the process in a PICU. Patients stratified across 3 levels of severity (low, medium, high) are admitted to the PICU, are initially seen by a nurse and physician, then stay in the PICU with ongoing care being provided by physicians and nurses, and are finally discharged from the PICU. The discrete event simulation model is a computer model developed using real estimates of numbers of patients, numbers of physicians and nurses in a PICU, and patient outcomes. Discrete event simulation models are created using real historical data, which allows testing the "what if" scenarios, such as the impact on patient flow and throughput by increasing the number of beds and/or changing nurse and physician staffing.

Another management sciences technique developed in Europe relates to the concept of *cognitive mapping*. Cognitive mapping aims at measuring the soft aspects of management sciences as illustrated in Figure 2-7. Cognitive mapping highlights the importance of perceptions and constructs of healthcare providers and how these constructs are linked in a hierarchical manner. Goals and aspirations of individual healthcare providers are identified by structured interviews and are mapped to strategic issues and problems, and options. By using specialized computer software, complex relationships can be identified to better understand the relationships between different constructs in a system. A discrete event simulation model views patient throughput based on numbers of beds, physicians, and nurses, and accounts for differences in patient mix. It does not account for many other factors, such as individual unit characteristics related to culture. By interviewing healthcare providers, cognitive maps can be developed that can help to better inform decision making.

DES Model

- Mathematically depicts a 24-bed PICU
- Depicts the patient experience from admission to discharge
- Factors the staffing of physicians and nurses in the PICU using historical experience
- DES Model starts with baseline and runs computer iterations to identify predicted outcomes with changing patient flow and staffing
- Results of DES Model provide insight into predicted outcomes of changing bed/staffing assumptions

Illustration of DES Model

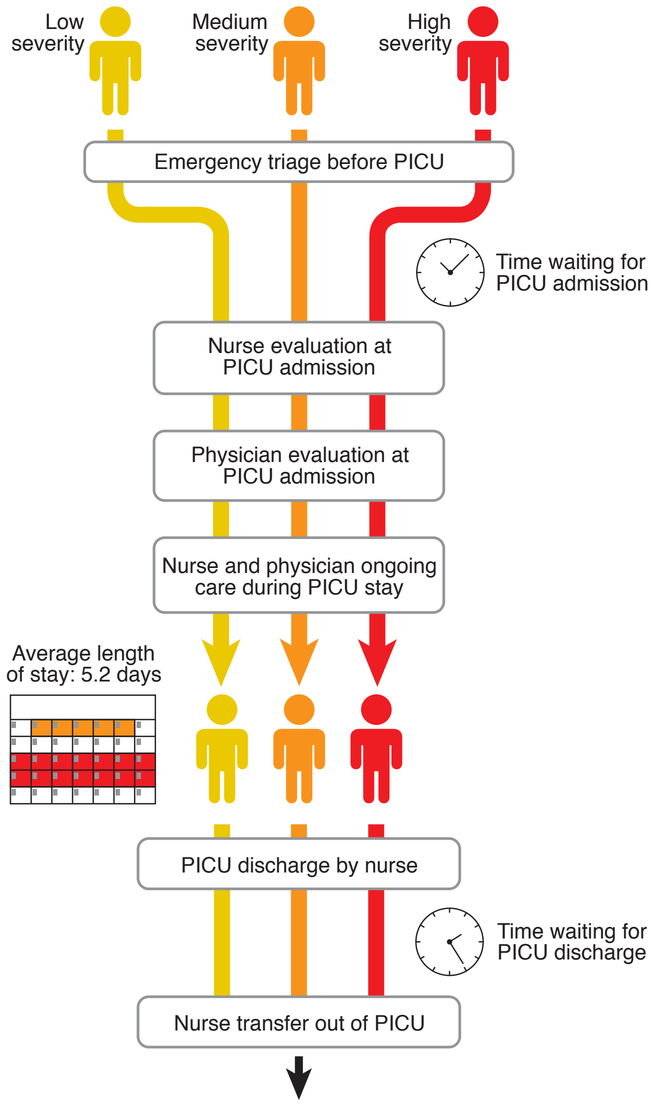

Conclusions

- Simply adding new PICU beds will not improve patient flow in itself
- Critical ratio between MDs, RNs, and beds in PICU adjusted for patient severity is needed to maximize patient flow, safety, and outcomes

Figure 2-6 Management sciences—discrete event stimulation. PICU, pediatric intensive care unit.

MEASURING QUALITY

Robust quality indictors should have clinical and statistical relevance. Clinical relevance ensures that the indicators are meaningful in patient care from the standpoint of patients and clinicians. Statistical relevance ensures that the indicators have measurement properties to allow an acceptable level of accuracy and precision. These concepts are captured in the national recommendations that quality measures must meet the criteria of being valid, reliable, feasible, and usable (Table 2-2). Validity of quality measures relates to the notion that the measure is estimating the true concept of interest. Reliability relates to the notion that the measure is reproducible and provides the same result if retested. It is important that quality measures are feasible in practice. Quality measures must be useable, which means that they should be clinically meaningful. The **Agency for Healthcare Research and Quality** and the **National Quality Forum** have provided specific criteria to be considered when developing quality measures.

Quality indicators can be aimed at measuring the performance within 3 components of healthcare delivery: structure, process, and outcome (Fig. 2-8). Structure relates to the organizational characteristics in healthcare delivery. Examples of organizational characteristics are the number of physicians and nurses in an acute care setting and the availability and use of systems such as electronic health records. Process-related measures estimate how services are provided. Examples of a process measures are the percent of families of children with asthma who receive an asthma action plan as part of their office visit or the percent of hospitalized children who have documentation of

pain assessments as part of their care. Outcome measures relate to the final health status of the child. Examples of outcome measures are risk adjusted survival in an intensive care unit setting, birthweight-adjusted survival in the NICU setting, and functional status of children with chronic conditions such as cystic fibrosis.

It is important to distinguish between measures for accountability and measures for improvement. As illustrated in Figure 2-9, measures, particularly measures for accountability that may be linked to attribution and payment, must be based upon a rigorous process. This can be resource intensive and time-consuming. In contrast, measures for improvement serve a different purpose—to track incremental improvements linked to specific QI efforts. These may not undergo rigorous testing, but they have limited applicability beyond the specific QI setting.

Quality data can be quantitative and qualitative. Quantitative data includes numerical data, which can be continuous (patient satisfaction scores represented as a percentage with higher numbers indicating better satisfaction) or categorical (patient satisfaction scores obtained from a survey where a Likert scale is used indicating satisfactory, unsatisfactory, good, or superior care). Data can also be qualitative in nature, which includes nonnumeric data. Examples of qualitative data can include results from open-ended surveys related to the satisfaction of care in a clinic or hospital setting. It is important to be sensitive to the source and quality of data being obtained to ensure data quality.

Data measuring quality of care can be obtained from a variety of sources, which include chart reviews, patient surveys, existing administrative data sources (billing data from hospitals), disease and specialty databases, and patient registries, which track individual patients over time.

It is important to distinguish between *databases* and *data registries*. Databases are data repositories that can be as simple as a Microsoft Excel spreadsheet or as complex as relational databases using sophisticated servers and information technology platforms. Databases can provide a rich source of aggregated data for both quality measurement and research. Data registries allow tracking individual patients over time; this dynamic and longitudinal characteristic is important for population health management and QI.

Table 2-2 Properties of Robust Quality Measures

ATTRIBUTE	RELEVANCE
Validity	Indicator accurately captures the concept being measured.
Reliability	Measure is reproducible.
Feasibility	Data can be collected using paper or electronic records.
Usability	Measure is useful in clinical practice.

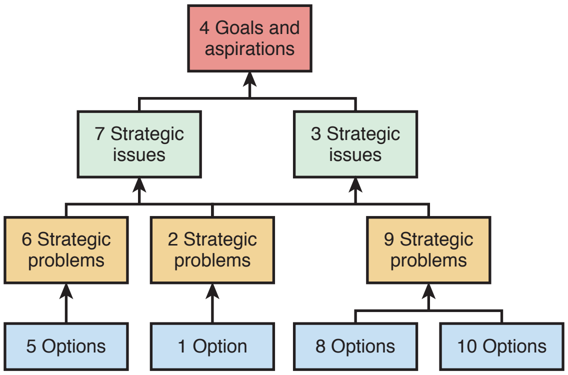

Figure 2-7 Management sciences—cognitive mapping.

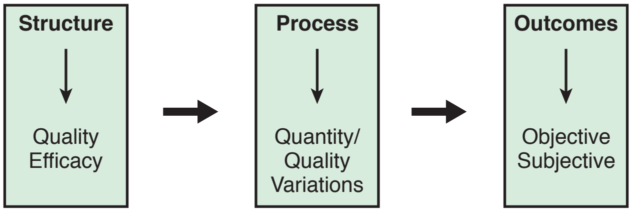

Figure 2-8 Donabedian model.

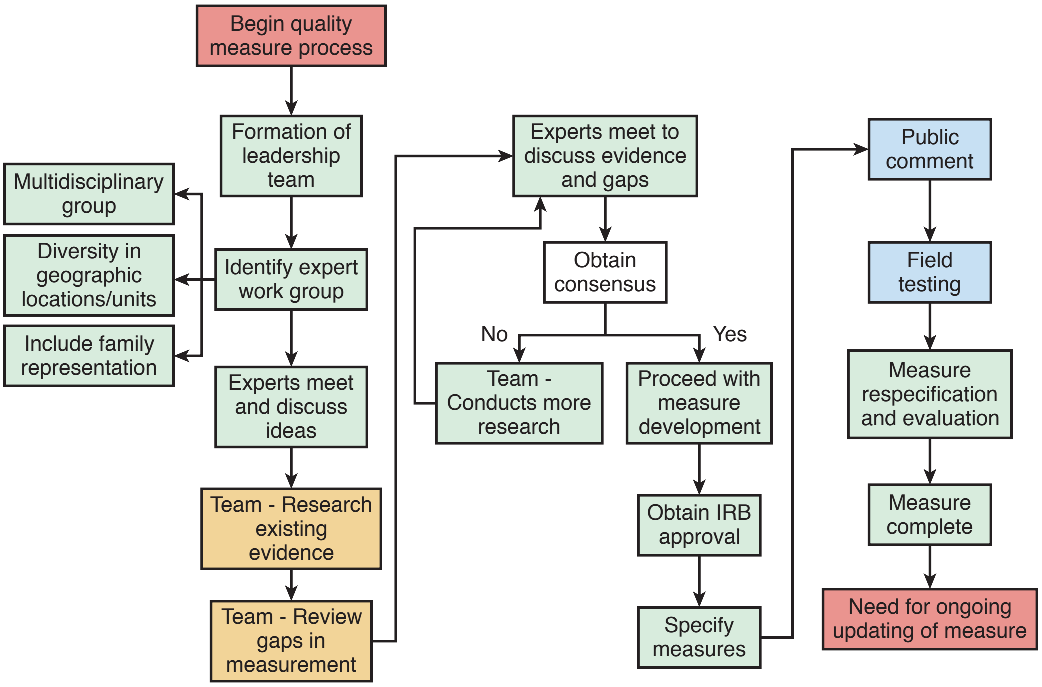

Figure 2-9 Development of a quality measure.

Data quality can become a significant impediment when using data from secondary sources, which can adversely impact the overall quality evaluation. Once data on the quality indicator has been collected, quality measurement can occur at 3 levels: (1) measuring quality status at 1 point in time (e.g., percent of children seen in a primary care office setting who received the recommended 2-year immunizations); (2) tracking performance over time (e.g., change in immunization rates in the primary care office setting for children 2 yr of age); and (3) comparing performance across clinical settings after accounting for epidemiologic confounders (e.g., immunization rates for children <2 yr of age in a primary care office setting stratified by race and socioeconomic status as compared to the rates of other practices in community and rates at national levels).

Pediatric quality measures are being developed nationally. Table 2-3 lists some of the important currently endorsed pediatric national quality indicators.

ANALYZING QUALITY DATA

Three approaches have been used for analyzing and reporting data. The classic approach from a research paradigm has been applied to quality data for statistically comparing trends over time, and differences before and after an intervention. P-values are interpreted as being significant if ≤0.05, which suggests that the likelihood of seeing a difference as extreme as observed has a probability of ≤5% (type I error). Another approach from an improvement science paradigm uses techniques such as run charts and control charts to identify special-cause variation. Special-cause variation attempts to capture observations that are unlikely to reflect random variation. Finally, quality data also has been reported on an individual patient level. This has gained popularity in the patient safety arena where identifying individual patient events in the form of descriptive analysis ("stories") may be more powerful in motivating a culture of change, rather than statistical reporting of aggregate data in the form of rates of adverse patient safety events.

COMPARING AND REPORTING QUALITY

There is an increasing emphasis on quality reporting in the United States. Many states have mandatory policies for the reporting of quality data. This reporting may be tied to reimbursement using the policy of P4P. P4P implies that reimbursements by insurers to hospitals and physicians will be partially based on the quality metrics. P4P can include both incentives and disincentives. Incentives relate to additional payments for meeting certain quality thresholds. Disincentives relate to withholding certain payments for not meeting those quality thresholds. An extension of the P4P concept relates to the implementation of the policy of **nonreimbursable hospital-acquired conditions**, formerly called "never events" by the **Centers for Medicare and Medicaid.** The Centers for Medicare and Medicaid has identified a list of hospital-acquired conditions, which are specific quality events that will result in no payment for care provided to patients (e.g., wrong site surgery, CA-BSI, and decubitus ulcers acquired in the hospital).

Quality reporting is also being used in a voluntary manner as a business growth strategy. Leading children's hospitals across the United States actively compete to have high ratings in national quality evaluations that are reported in publications such as *Parents* (formerly *Child)* magazine and *US News & World Report*. Many children's hospitals have also developed their own websites for voluntarily reporting their quality information for greater transparency. Although greater transparency may provide a competitive advantage to institutions, the underlying goal of transparency is to improve the quality of care being delivered, and for families to be able to make informed choices in selecting hospitals and physicians for their children.

Quality measures may also be used for purposes of certifying individual physicians as part of the MOC process. In the past, specialty and

Table 2-3 Examples of National Pediatric Quality Measures

NQF PEDIATRIC QUALITY INDICATORS	NQF-ENDORSED INPATIENT MEASURES AMONG PICUs	NQF-ENDORSED INPATIENT PEDIATRIC CARE MEASURES	NQF-ENDORSED OUTPATIENT PEDIATRIC CARE MEASURES
Neonatal bloodstream infection rate	PICU standardized mortality ratio	CAC-1 relievers for inpatient asthma	Appropriate testing for children with pharyngitis
Transfusion reaction	PICU severity-adjusted length of stay PICU unplanned readmission rate	CAC-2 systemic corticosteroids for inpatient asthma Admit decision time to ED departure time for admitted patients Follow-up after hospitalization for mental illness (FUH) NHSN Catheter-Associated Urinary Tract Infection (CAUTI) outcome measure NHSN Central Line-Associated Bloodstream Infection (CLABSI) outcome measure Percent of residents or patients assessed and appropriately given the pneumococcal vaccine (short stay) Restraint prevalence (vest and limb) Validated familycentered survey questionnaire for parents' and patients' experiences during inpatient pediatric hospital stay	CAHPS clinician/group surveys (adult primary care, pediatric care, and specialist care surveys) Child and adolescent major depressive disorder: diagnostic evaluation Child and adolescent major depressive disorder: suicide risk assessment Follow-up after hospitalization for mental illness (FUH) Initiation and engagement of alcohol and other drug dependence treatment Median time from ED Arrival to ED departure for discharged ED patients Pediatric symptom checklist (PSC)
Gastroenteritis admission rate		Initiation and engagement of alcohol and other drug dependence treatment (IET) Nursing hours per patient day Preventive care and screening: screening for clinical depression and follow-up plan Skill mix (RN, LVN/LPN, UAP, and contract)	

CAC, Children's Asthma Care; CAHPS, Consumer Assessment of Healthcare Providers and Systems; ED, emergency department; HBIPS, hospital-based inpatient psychiatric services; LVN/LPN, licensed vocational/practical nurse; NHSN, National Healthcare Safety Network; NQF, National Quality Forum; PICU, pediatric intensive care unit; RACHS-1, risk adjustment for congenital heart surgery; RN, registered nurse; UAP, unlicensed assistive personnel.

subspecialty certification in medicine, including pediatrics, was largely based on demonstrating a core fund of knowledge by being successful in an examination. No specific evidence of competency in actual practice needed to be demonstrated beyond successful completion of a training program. There continues to be significant variations in practice patterns even among physicians who are board certified, which highlights the concept that medical knowledge is important, but not sufficient for the delivery of high-quality care. Subsequently, the **American Board of Medical Specialties,** including its member board, the American Board of Pediatrics, implemented the MOC process in 2010. Within the MOC process, there is a specific requirement (Part IV of MOC) for the physician to demonstrate the assessment of quality of care and implementation of improvement strategies as part of recertification in pediatrics and subspecialties. Lifelong learning and the translation of learning into practice are the basis for the MOC process and for an essential competency for physicians professionalism. There are also discussions to adopt a similar requirement for Maintenance of Licensure for physicians by state medical regulatory boards.

The **Accreditation Council for Graduate Medical Education** requires residency programs to incorporate QI curriculum to ensure that systems-based practice and QI are part of the overall competencies within accredited graduate medical training programs. One form of **continuing medical education**, the **performance improvement** continuing medical education, is used for ongoing physician education. These initiatives require physicians to measure the quality of care they deliver to their patients, to compare their performance to peers or known benchmarks, and to work toward improving their care by leveraging QI methods. This forms a feedback loop for continued learning and improvement in practice.

Prior to comparing quality measures data both within and across clinical settings, it is important to perform risk adjustment to the extent that is feasible. **Risk adjustment** is the statistical concept that utilizes measures of underlying severity or risk so that the outcomes can be compared in a meaningful manner. The importance of risk adjustment was highlighted in the PICU setting many years ago. The unadjusted mortality rate for large tertiary care centers was significantly higher than that for smaller hospital settings. By performing severity of illness risk adjustment it was subsequently shown that the risks in tertiary care large PICUs were higher because patients had higher levels of severity of illness. These patients were sicker than other patients, which would explain the higher mortality rate. Although this concept is now intuitive for most clinicians, the use of severity of illness models in this study allowed a mathematical estimate of patient severity using physiologic and laboratory data, which allowed for the statistical adjustment of outcomes. This permits meaningful comparisons of the outcomes of large and small critical care units. Severity of illness models and the concepts of statistical risk adjustment are most developed in pediatric critical care, but these concepts are relevant for all comparisons of outcomes in the hospital settings where sicker patients may be transferred to the larger institutions for care and, therefore, would be expected to have poorer outcomes as compared to other settings with less sick patients.

Risk adjustment can be performed at 3 levels. First, patients who are sicker can be excluded from the analysis, thereby allowing the comparisons to be within homogenous groups. Although this approach is relatively simple to use, it is limited in that it would result in patient groups being excluded from the analysis. Second, risk stratification can be performed using measures of patient acuity. An example of this relates to the use of the **All-Patient Refined Diagnosis-Related Group** system where patients can be grouped or stratified into different severity criteria based on acuity weights. This approach may provide relatively homogenous strata within which comparisons can be performed, but it is not able to predict the overall outcomes within patient risk groups. Third, severity of illness risk adjustment relates to the use of clinical data to predict the outcomes of patient groups. An example of a clinical severity of illness risk adjustment process is the use of the **Pediatric Risk of Mortality (PRISM)** scoring system in the PICU setting. The PRISM score, and its subsequent iterations, composed of a combination of physiologic and laboratory perimeters that are weighted on a statistical logistic scale to predict the risk of mortality within that PICU stay. By comparing the observed and expected outcomes (i.e., mortality or survival), a quantitative estimate of the performance of that PICU can be established which can then be used to compare outcomes with other PICUs (standardized mortality ratio).

Risk-adjustment systems have been effectively incorporated into specialty databases. An example of such a system is the **Virtual Pediatric Intensive Care Unit System (VPS)**, which represents the pediatric critical care database system in the United States. The VPS, comprising more than 100 PICUs and cardiac PICUs across the United States, as well as international PICUs, currently has more than 300,000 patients within its database. The VPS database emphasizes data quality, both data validity and reliability, to ensure that the resulting data are accurate. Data validity has been established using standard data definitions with significant clinical input. Data reliability is established using interrater reliability to ensure that the manual data collection that involves several data collectors within pediatric institutions is consistent. The PRISM scoring system is programmed into the VPS software to allow the rapid estimation of the severity of illness of individual patients. This, in turn, allows risk adjustment of the various outcomes that are compared within institutions over time and across institutions for purposes of QI.

QUALITY AND PATIENT SAFETY

Safety is an important dimension of quality, and errors in healthcare are a leading cause of death and injury. Approximately 3-4% of hospitalized adult patients are harmed by the care that is supposed to help them, and 7% are exposed to a serious medication error that harms or could harm them. Multiple factors contribute to errors: an increasingly complex healthcare system with diffuse accountability; a culture of attributing errors to individuals, which overlooks problematic systems; lack of allegiance between physicians and hospitals, which detracts from patient-centered practices; and reimbursement policies that frequently discourage safety measures.

Medical Errors in Children's Healthcare

Few epidemiologic data are available regarding medication errors in the pediatric setting, and the *potential* for pediatric inpatient medical errors is substantial. This may be partly a result of children having unique clinical experiences that are prone to error. These unique risk factors or safety issues, the "4 Ds," are **developmental change, dependence on adults, different disease epidemiology,** and **demographic characteristics.** *Developmental change* might refer to the unique susceptibility of neonates to infections or the need for weight-based dosing with growth. Children's *dependence on adults* puts them at heightened risk for experiencing medical errors because children do not usually manage their own treatments or provide their own medical history and may not have the insight to question their own care. *Different disease epidemiology* refers to the unique illnesses and medical needs that predispose children to unique safety events as compared with adults (e.g., birth trauma and screening for metabolic abnormalities). Children have distinct *demographic characteristics* and are more likely to live in poverty than any other segment of the population.

Adverse drug events (ADEs) may occur in pediatric patients at a similar rate as in adult patients; the potential ADE rate may be 3 times higher in children. A *potential* ADE is one that is intercepted before causing harm. Most potential ADEs occur at the stage of drug ordering and involve incorrect dosing, antiinfective drugs, and intravenous medications. In an ambulatory setting, 13% of prescriptions for children had potential medication errors. These errors are more common for infants and toddlers, children obtaining multiple prescriptions at the same time, and prescriptions for analgesics/narcotics. Technology software does not always address issues specific to children, such as pediatric dosing calculations and age-based normal ranges. It is estimated that inpatient nonmedication errors involving children result in more than $1 billion in reconciliation costs per year and are associated with significant increases in length of stay, charges, and in-hospital deaths.

Key Issues in Patient Safety

Making care safer requires the identification and control of things that could cause harm to patients. Several key concepts regarding patient safety are summarized in the following sections and are available in curriculum overviews at www.patientsafety.gov, www.npsf.org, and www.va.gov.

Systems Approach

The majority of healthcare errors result from faults intrinsic to the processes by which healthcare is delivered, rather than individual mistakes. This systems approach compels organizations to respond to adverse events not by blaming individuals, but by improving the conditions under which individuals work. An error is viewed as a symptom of trouble in a process that offers an opportunity for improvement and the potential to implement safeguards.

Developing a Culture of Safety

The biggest challenge in making the health system safer is changing the culture from one of treating errors as personal failures to one of treating errors as opportunities to improve the system. Organizations need to foster a culture of learning in which each individual will feel accountable for ensuring a safe and quality program, communication is open, and teamwork is valued. Reporting of errors should be valued, reports of adverse events should be handled confidentially, and those who report errors should be protected from discovery. Developing a culture of learning involves the compassionate and appropriate disclosure of system failures and medical errors to patients and families. It has also been shown that utilizing multiple approaches to identify adverse events may be effective.

Communication. Good communication among the healthcare team is essential for patient safety. Healthcare involves the safe transfer of responsibility for patient care and the transfer of patient information. Poor communication or miscommunication creates the opportunity for incorrect or incomplete transfer of vital information during the transfer of responsibility for patient care from one provider to another, thus placing the patient at risk for serious medical error. The potential for harm is increased when the healthcare team and the patient do not share a native language. Errors in medical interpretation are common, with omissions being the most frequent. Ad hoc interpreters are significantly more likely to commit errors with harmful clinical consequences than are hospital interpreters.

Teamwork and Authority Gradients. Ensuring a systems approach to healthcare safety involves a paradigm shift. Healthcare has tended to be a hierarchical endeavor, with physicians in leadership roles that allowed significant amounts of autonomy. This authority gradient can predispose to communication failures: junior team members may be hesitant to speak up and senior members may resist feedback. A medical student or nursing assistant may be hesitant to inform an attending physician of a potential error. In a culture of safety, team members with different positions of authority must interact to facilitate optimal patient care; all are empowered to voice a safety concern. The composition of the teams may vary day to day because of shifting schedules. Senior leaders must be able to engender trust rapidly among team members, accept that human error is inevitable, and encourage behaviors that prevent or mitigate the harm that results from errors. Healthcare can learn important lessons for safety from industry. Experiences from industries that have standardized and achieved a high level of safety and reliability (e.g., the airline and nuclear industries) can help inform future healthcare systems in both developing and industrialized nations.

Human Factors Engineering. **Human factors engineering (HFE)** is a discipline concerned with the design of tools, machines, and systems that take into account human capabilities, limitations, and characteristics. It builds on ergonomics and utilizes what is known about human performance and system interaction. HFE can play an important role in the optimal design of equipment, the development of effective processes, monitoring for unintended consequences, and the planning for and introduction of new technologies. HFE techniques used to identify hazards or areas for improving safety can be proactive (addressing complex areas of healthcare before implementing an intervention) or reactive (reviewing reports of "close calls" or injuries). Computerized physician order entry, an example of HFE in healthcare, has been shown to decrease the rate of medication errors in pediatric inpatient settings.

The role of a team based approach along with the need to consider human factors requires the creation of systems that are designed to improve outcomes. Recent studies from the nursing literature has identified the positive impact of continuity of nursing care on patient outcomes in high-risk settings, and also the potential detrimental impact on patient outcomes with unduly long nursing shifts in the inpatient acute care setting for children.

Reliability. Reliability in healthcare is defined as the measurable capability of a process, procedure, or health service to perform its intended function in the required time under commonly occurring conditions (i.e., providing intended care on a consistent basis). Most healthcare organizations currently perform at *Level 1 reliability*, which means that processes are performed with only an 80-90% success rate. To achieve *Level 2 performance* (≤5 failures/100 opportunities), processes must be *intentionally designed* with tools and concepts based on the principles of HFE. Performance at *Level 3* (≤5 failures/1,000 opportunities), requires a well-designed system with low variation and cooperative relationships and a state of what has been called "mindfulness," where attention is paid to processes, structure, and their relationship to outcomes. Cincinnati Children's Hospital Medical Center used reliability science and the Model for Improvement to institute a ventilator-associated pneumonia protocol that led to an 87% reduction in ventilator-associated pneumonias per 1,000 ventilator days (from a fiscal year average of 7.5 to an average of only 0.95).

Such efforts are now expanding from individual institutions to the regional level. The Solutions for Patient Safety is a new collaboration of multiple pediatric institutions at a state level to share quality and safety data in a transparent manner, and to create a culture of shared learning.

IMPLICATIONS OF THE U.S. HEALTHCARE REFORM FOR QUALITY

In 2010, the Affordable Care Act was enacted into law. This significant health care legislation attempting to achieve the vision of universal health care includes an emphasis on access to health care, the implementation of consumer protections (e.g., preexisting conditions), and improving quality and lowering the cost of health care.

Regarding quality and safety in health care for children, health care reform has three key implications. First, universal coverage optimizes access and includes expanding coverage for young adults to age 26 yr. Second, various initiatives related to quality, safety, patient-centered outcomes research, and innovation were implemented and funded. For example, the Agency for Healthcare Research and Quality (AHRQ) has funded a national effort to establish seven centers of excellence through the Pediatric Quality Measurement Program (PQMP) to improve existing pediatric quality measures and create new measures that can be used by states and in a variety of other settings to evaluate quality of care for children. Third, a paradigm shift in the existing model of health care delivery system has been vertically integrated toward a model of horizontal integration. This has led to the creation and rapid growth of integrated delivery systems and risk-sharing relationships of accountable care organizations (ACOs).

Accomplishing this strategic direction is resulting in three new areas of rapid growth in the quality arena. "Big Data" relates to the notion of linking potentially disparate sources of data to generate new knowledge, accelerate innovation, and improve outcomes. Big Data is unique in that it aims to link structured and unstructured data sources, including data emerging from databases, registries, clinical records, and social media. A key strength of using a large volume of data across multiple sources by linking it to create Big Data is a significant increase in power for early prediction and new knowledge generation that can be rapidly implemented.

Another area of increasing emphasis is the notion of population health. This is important because it expands the traditional role of

physicians to improve quality of care for individual patients to also improve the quality of care for larger populations. Populations can be defined by geographic constraints or disease/patient condition. The notion of population health is integral for achieving the “triple aim” vision of quality of care. Efforts to link payment and reimbursement for care delivery by physicians and health systems are being increasingly tied to measurable improvements in population health. To achieve a meaningful improvement in population outcome, physician practices will need to embrace the emerging paradigm of practice transformation. Practice transformation has many facets, including the adoption of a “medical home,” the seamless connectivity across the primary care and subspecialty continuum, and a strong connection between the medical and social determinants of health care delivery. To implement successful practice transformation, hospitals are increasingly adopting a broader view to evolve into health care systems that serve children across the entire range of the care continuum, including preventive and primary care, acute hospital care, and partnerships with community organizations for enhancing the social support structure. In addition, new risk-sharing payment models are evolving, resulting in the growth of entities such as ACOs, which represent a financial risk-sharing model across primary and subspecialty care and hospitals, resulting in an unprecedented level of health care integration to improve quality of care.

THE EVOLUTION OF QUALITY TO OUTCOMES TO VALUE

Most efforts at QI tend to emphasize enhancements in the process of healthcare delivery with the assumption that this will lead to improvements in outcomes. With the growing adoption of electronic health records that can allow tracking patients across the continuum of care, it will be possible to measure outcomes. Efforts at quality and outcomes must move toward creating value from the perspective of patients and families. Healthcare delivery systems must be developed based upon patient needs. Healthcare providers should lead this initiative to create value and that outcomes being measured should matter to patients.

INFORMATION TECHNOLOGY AND QUALITY IMPROVEMENT

The underlying goal of the HIT movement is to improve quality and safety. HIT includes electronic health records, personal health records, and health information exchange. The purpose of a well-functioning electronic health record is to allow collection and storage of patient data in an electronic form, to allow this information to be provided to clinicians and healthcare providers, to have the ability to allow clinicians to enter patient care orders through the **computerized physician order entry,** and to have the infrastructure to provide clinical decision support which will improve physician decision making at the level of individual patients. Personal health records will allow patients and families to be more actively engaged in managing their own health by monitoring their clinical progress and laboratory information, and also be able to communicate with their physicians for appointments, obtaining medications, and getting their questions answered. Appropriate, timely, and seamless sharing of patient information across physician networks and healthcare organizations is critical to quality care and to achieve the full vision of a *medical home* for children. Health information exchange would allow the sharing of healthcare information in an electronic format to facilitate the appropriate connections between providers and healthcare organizations within a community or region. However, significant cost and time barriers remain for adoption of HIT. The entire field of HIT as a mechanism to improve quality is likely to continue to be in the forefront of the quality journey for physicians and healthcare organizations for the next several years.

Despite the emphasis on HIT and data, it is important to understand that data does not lead to improvement in itself. Improvement is an affirmative choice and requires translating data (measurement) into clinically relevant information (data that has context and relevance) that is actionable for QI.

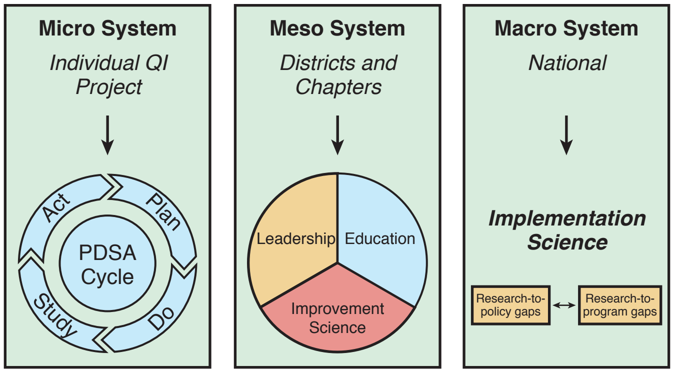

Figure 2-10 Success ingredients for large-scale quality improvement.

QUALITY IMPROVEMENT OR RESEARCH?

Research aims at generating new knowledge. QI aims at implementing the new knowledge into practice. Whereas research aims at developing new generalizable knowledge, QI aims at adopting the available evidence into practice at a local level. With the growing interest of research in the field of QI and efforts to expand the generalizability of QI initiatives, there can be situations in which research and QI overlap. In the future, the gap between QI and research will likely narrow to allow a continuum of active knowledge transfer from research into practice using QI methods.

EXPANDING INDIVIDUAL QUALITY IMPROVEMENT INITIATIVES TO SCALE

Despite the success of individual QI and patient safety projects, the overall progress to achieve large-scale improvements to reach all children across the spectrum of geographic location and socioeconomic status remains limited. This contributes to the health disparities that persist for children with significant differences in access and quality of care. A potential factor that limits the full impact of QI is the lack of strategic alignment of improvement efforts with hospitals, health systems, and across states.

This challenge can be viewed from a system standpoint in being able to conduct and expand QI from a micro level (individual projects), to the meso level (regional), to the macro level (national and international). The learning from individual QI projects for addressing specific challenges can be expanded to the regional level by ensuring that there is optimal leadership, opportunity for education, and adoption of improvement science (Fig. 2-10). To further expand the learning to a national and international level, it is important to leverage implementation science to allow a strategic approach to identification of the key success ingredients to expand the improvement strategy. To fully leverage the synergies to impact the quality of care delivered to children, it is important for national and international healthcare organizations to effectively collaborate from a knowledge management and improvement standpoint (Table 2-4).

INTERNATIONAL EFFORTS FOR QUALITY IMPROVEMENT

The implications of QI for healthcare delivery systems are equally relevant to international venues as to the United States. Many developing and industrialized countries are in the process of expanding their pediatric care delivery systems to have a greater presence of tertiary and quaternary care delivery. The understanding and adoption of QI principles during the early phase of expansion will result in the efficient use of resources with the greatest potential for favorably impacting health outcomes in children. Pediatric clinical practices in many developing countries have already adopted several unique, innovative approaches to allow delivery and creation of healthcare systems despite limited resources. These local innovations need to be expanded to allow for learning across countries. QI provides a unique strategy that can result in linking of a global community for the care of children including real-time learning and sharing of innovative best practices

Table 2-4 National Organizations Involved in Pediatric Quality Improvement

ORGANIZATION	ROLE	ACTIVITIES
American Academy of Pediatrics (AAP)	Represents more than 60,000 pediatricians and pediatric subspecialists worldwide	Resources for QI to improve health for all children, best practices, advocacy, policy, research and practice, and medical home
American Board of Pediatrics (ABP)	Certifying board for pediatrics and pediatric subspecialties	Certification policies and resources for activities such as Maintenance of Certification (MOC)
American Medical Association (AMA)	Physician member association	Physician Consortium for Performance Improvement (PCPI)—physician-led initiative
Children's Hospital Association (CHA)	Formerly the National Association of Children's Hospitals and Related Institutions; and the Child Health Corporation of America	Databases, QI collaboratives, and policy
Institute for Healthcare Improvement (IHI)	QI organization for adult and pediatric care	QI collaboratives, QI educational workshops and materials
National Initiative for Child Health Quality (NICHQ)	QI organization for pediatric care	QI training, improvement networks
Joint Commission	Hospital accreditation organization	Unannounced surveys to evaluate quality of care in hospitals
National Committee for Quality Assurance (NCQA)	QI organization	Healthcare Effectiveness Data and Information Set (HEDIS) and quality measures for improvement
National Quality Forum (NQF)	Multidisciplinary group including healthcare providers, purchases, consumers, and accrediting bodies	Endorsing national quality measures, convening expert groups, and setting national priorities

across the developing and industrialized worlds. Many international efforts to improve QI are already in progress. For example, the World Health Organization (WHO) has highlighted the global progress in adoption of HIT in many countries. A survey performed by WHO between 2005 and 2006 identified that nearly half of 112 countries responding to the survey already have national task forces or related groups to provide the national direction for e-health strategies. Pediatricians have the unique opportunity to provide leadership to evolving governmental-private-public partnerships in designing the next generation of pediatric healthcare delivery systems.

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Chapter 3

Ethics in Pediatric Care

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Pediatric ethics is the branch of bioethics that analyzes moral aspects of decisions made relating to the healthcare of children. In general terms, the **autonomy**-driven framework of adult medical ethics is replaced by a **beneficent** paternalism (or parentalism) in pediatrics. Pediatric ethics is distinctive because the pediatric clinician has an independent fiduciary obligation to act in a younger child's **best interest** that takes moral precedence over the wishes of the child's parent(s). For older children, the concept of **assent** suggests that the voice of the patient must be heard. These factors create the possibility of conflict among child, parent, and clinician. The approach to the ethical issues that arise in pediatric practice ***must*** include respect for parental responsibility and authority balanced with a child's developing capacity and autonomy. Heterogeneity of social, cultural, and religious views about the role of children adds complexity.

ASSENT AND PARENTAL PERMISSION

The doctrine of informed consent has limited direct application to children and adolescents who lack decisional capacity. The capacity for informed decision making in healthcare involves the ability to understand and communicate, to reason and deliberate, and to analyze conflicting elements of a decision using a set of personal values. The age at which a competent patient may legally exercise voluntary and informed consent for medical care varies from state to state and may be limited to specific conditions (sexually transmitted infections, family planning, drug or alcohol abuse).

In contrast to decisions about one's own care, a parent's right to direct a child's medical care is more limited. For this reason, the term *parental consent* is misleading. The concept of parental permission (rather than consent) reflects a *surrogate* or *proxy* decision made by a parent on behalf of a child. It is constrained both by the child's best interest and the independent obligation of clinicians to act in the child's best interest, even if this places them in conflict with a parent. In any given instance, the decision of what is or is not in a child's best interest may be difficult, especially given the diverse views of acceptable child rearing and child welfare. Parents are (and should be) granted wide discretion in raising their children. In cases involving a substantial risk of harm, the moral focus should be on avoiding or preventing harm to the child, not on a parental right to decide. While the term "best" interests may be too high of a threshold requirement, a minimum standard of "basic" interests is ethically obligatory.

Respect for children must account for both a child's vulnerability and developing capacity. This respect encompasses both the protective role of parental permission and the developmental role of **child assent** (the child's affirmative agreement). Understanding the concept of assent is one of the major conceptual challenges in pediatric ethics. The dissent (or disagreement) of a child is the opposite of assent and is also morally relevant. Pediatric ethics ***requires*** clinicians and parents to override a child's dissent when a proposed intervention is essential to the child's welfare. Otherwise, assent should be solicited and dissent should be honored. In seeking younger children's assent, a clinician should help them understand their condition, tell them what they can expect, assess their understanding and whether they feel pressured to assent, and solicit their willingness to participate. All efforts must be made to delineate situations in which the test or procedure will be done regardless of the child's assent/dissent, and in such cases the charade

of soliciting assent should be avoided. There is an important distinction between soliciting assent and respectfully informing a child that a test or procedure will take place regardless of the child's decision. Optimally, an educational process can transpire (if time allows) to gain the trust and assent of the child-patient. When this cannot occur, pediatric ethics requires that clinicians apologize to a child for acting to override dissent.

Older children or adolescents may have the cognitive and emotional capacity to fully participate in healthcare decisions. If so, the adolescent should be provided with the same information as would be given to an adult patient. In cases like this, the patient may be able to provide informed consent ethically but not legally. The adolescent's parent(s) remain in a guiding and protective role. The process of communication and negotiation will be more complex should disagreement arise between the parent and adolescent.

TREATMENT OF CRITICALLY ILL CHILDREN

Infants, children, and adolescents who become critically ill may recover fully, may die, or may survive with new or worsened limitations of function. Uncertainty about outcomes can make planning goals of care difficult, or if misunderstandings between patient, families, and medical staff occur, may drive conflict over treatment proposals. Ethical issues that arise during critical illness include balancing benefits, burdens, and harms of therapy in the face of uncertainty; maintaining a helpful degree of transparency and communication about medical standards of care at an institution; understanding and respecting religious and cultural differences that impact requests for or refusal of treatments; defining limits of therapy based on assessments of medical futility; recognizing the moral equivalence of not starting an ineffective treatment and stopping (although the 2 acts may feel very different to families and providers); and controversies such as withholding medically administered nutrition and hydration.

Transitioning the Goals of Care

Most acutely ill children who die in an ICU do so after a decision has been made to either forgo or withdraw **life-sustaining medical treatment (LSMT)**, and the same may apply in the chronically ill population. LSMT is justified when the anticipated benefit outweighs the burdens to the patient; the availability of technology does not in and of itself obligate its use. Decisions to use, limit, or withdraw LSMT should be made after careful consideration of all pertinent factors recognizable by both family and medical staff, including medical likelihood of particular outcomes, burdens on the patient and family, religious and cultural decision-making frameworks, and input by the patient when possible. Although fear of legal repercussions may sometimes drive treatment and medical advice, ultimate decisions should be based on what is thought to be best for the patient rather than based on fears of litigation.

The concept of **futility** has been used to support unilateral forgoing of LSMT against the wishes of patients and families by holding that clinicians should not provide futile (or useless) interventions. If medical futility is defined narrowly as the impossibility of achieving a desired physiologic outcome, then forgoing a particular intervention is ethically justified. However, this approach may not adequately engage professionals and families in understanding facts and values that might allow the same therapy to reach other goals, and may leave medical and family stakeholders in permanent conflict. If agreement cannot be reached through clear and compassionate communication efforts, further input can be sought from an ethics consultant or committee.

Communication about life-threatening or life-altering illness is challenging, and requires skills learned through both modeling and practice. These skills include choosing a setting conducive to what may become 1 or more long conversations; listening carefully to children's and families' hopes, fears, understanding, and expectations; explaining medical information and uncertainties simply and clearly without complicated terms and concepts; conveying concern and openness to discussion; and being willing to share the burdens of decision-making with families by giving clear recommendations. Discussing difficult topics with children requires an understanding of child development, and can be aided by professionals such as child psychologists or child life specialists. Such conversations and their outcomes have a major impact on the future care of the patient, on families, and on medical staff. For this reason, ongoing evaluation of goals and communication about them is needed with families and within complex medical teams as the course of the illness unfolds.

Experts recognize that good medical care involves providing for communication, symptom management, and a range of supportive services from the onset of acute illness. In this way, if an illness proves to be life-limiting in spite of aggressive therapies, the elements of palliative care are already in place. This concept has had difficulty gaining traction, especially in critical care settings, because of the mistaken conflation of broadly defined palliative measures with hospice care. Palliative care interventions focus on the relief of symptoms and conditions that may detract from quality of life regardless of the impact on a child's underlying disease process, and as such are important whether care is focused on cure or on transitioning to end-of-life care (see Chapter 43). Some interventions regarded as life-sustaining, such as chemotherapy, may be ethically acceptable in the end-of-life setting if their use decreases pain and suffering rather than results only in prolonging death.

Withholding and Withdrawing Life-Sustaining Treatment

Limitation of interventions or withdrawal of existing therapies are ethically acceptable if they are congruent with a plan of care focused on comfort and improved quality at the end of life rather than cure. The prevailing view in Western, traditional medical ethics is that there is no moral distinction between withholding or withdrawing interventions that are not medically indicated. Uncertainty in predicting a child's response to treatment may drive the initiation and continuation of interventions that are no longer supportive of shared goals of care. It is necessary to continually evaluate the results of these treatments and the evolution of the illness to recognize whether such interventions continue to be the best medical and moral choices. Maintaining the focus on the child rather than on the interests of parents or medical staff will help guide decision making.

The decision about whether or not to attempt **cardiopulmonary resuscitation** may become an issue to discuss with parents of children living with life-threatening or terminal conditions. All elements of end-of-life care approaches, including resuscitation status, should be supportive of agreed-on goals of care. It is imperative that decisions and plans are effectively communicated to all caregivers in order to avoid denying medically effective interventions and measures to ensure comfort. Orders about resuscitation status should clarify the plan regarding intubation and mechanical ventilation, the use of cardiac medications, chest compressions, and cardioversion. Because goals of care may change over time, a medical order regarding resuscitation is not irrevocable. Clinicians may assume that the absence of a do-not-attempt-resuscitation (DNAR) order obligates them to perform a prolonged resuscitation. This action may not be ethically supportable if resuscitative efforts will not achieve the desired physiologic endpoint. In all cases, treatments should be tailored to the child's clinical condition, balancing benefits and burdens to the patient. Resuscitation should not be performed solely to mollify parental distress at the tragic time of the loss of their child.

Advance Directives. An advance directive (AD) is a mechanism that allows patients and/or appropriate surrogates to designate the desired medical interventions under applicable circumstances. Discussion and clarification of resuscitation status should be included in advance care planning, and for children attending school in spite of advanced illness, may need to be addressed in that setting. Decisions regarding resuscitation status in the out-of-hospital setting can be an important component of providing comprehensive care.

The 1991 federal Patient Self-Determination Act requires that healthcare institutions ask adult (>18 yr) patients whether they have completed an AD and, if not, inform them of their right to do so. Few states support creation of broad ADs for minors because ADs are

traditionally created by persons with legal decision-making capacity, but some have moved in this direction because it is recognized that minors may be capable of participating in decision making, especially if they have been dealing with chronic disease. However, surrogate decision makers may participate in advance care planning for their children. Most states have approved the implementation of prehospital or portable DNAR orders, through which adults may indicate their desire not to be resuscitated by emergency personnel. On a state-by-state basis, portable orders regarding resuscitation status may also apply to children. If DNAR orders exist for an infant or a child, it is important to communicate effectively about their intent among all potential caregivers, because nonmedical stakeholders such as teachers or sitters may not wish to be in the position of interpreting or honoring them. Some institutions have established local policies and procedures by which an appropriately executed outpatient DNAR order can be honored upon a child's arrival in the emergency department. Key features may include a standardized document format, review by an attending physician, ongoing education, and involvement of a pediatric palliative medicine service.

In cases involving prenatal diagnosis of a lethal or significantly burdensome anomaly, parents may choose to carry their fetus/unborn child to term in order to cherish a short time with the infant after birth, but do not feel that resuscitation or certain other aggressive measures would support their well-considered goals of care. In this setting, a birth plan explaining the reasons for each choice can be developed by the parents and medical staff prior to delivery and shared with involved medical staff. This approach gives staff a chance to find other caregivers if they are uncomfortable with the approach, without abandoning the care of the child. If, after evaluation at birth, the infant's condition is as had been expected, honoring the requested plan is ethically supportable and should be done in a way that optimizes comfort of the infant and family.

Many states utilize **Physician Orders for Life-Sustaining Treatment** or **Medical Orders for Life-Sustaining Treatment** approaches to communicating a patient or surrogates wishes regarding advance care planning. It is important for pediatricians to learn which pathways for communicating goals of care are available in their own states.

Artificial Hydration and Nutrition. Issues surrounding withholding or withdrawing artificial hydration and nutrition are controversial, and interpretations are affected by parental, religious, and medical beliefs. Any adult or child who is fully dependent on the care of others will die as a result of not receiving hydration and nutrition. Case law has supported the withholding of artificially administered nutrition and hydration in the setting of adult vegetative or permanently unconscious patients who can be shown to have previously expressed a wish not to be maintained in such a state. This requires a valid AD, or for a surrogate decision maker to speak on behalf of the patient's known wishes. Because infants and many children have not reached a developmental stage in which such discussions would have been possible, decisions about stopping artificially administered nutrition and hydration as a limitation of treatment are more problematic. These decisions should be based on what families and caregivers decide best support comfort. In the child who is imminently dying, unaware of hunger, does not tolerate enteral feedings, and in whom family and staff agree that IV nutrition and hydration only prolong the dying process, it may be ethically supportable to withhold or withdraw these treatments based on a benefit–burden analysis.

The Doctrine of Double Effect. Treatment decisions at the end of life may include limitations of certain LSMT, or may involve the use of analgesic or sedative medications that some fear may shorten life, thereby causing death. The doctrine of double effect holds that an action with both good and bad effects is morally justifiable if the good effect is the only one intended, and the bad effect is foreseen and accepted, but not desired. In pediatrics, it is most commonly applied in end-of-life cases, when upward titration of medication (opiates) necessary to relieve pain, anxiety, or air hunger can be expected to result in a degree of respiratory depression. In such cases, meeting a provider's obligation to relieve suffering is the intended effect, and this obligation to the patient outweighs the acknowledged but unavoidable side effect. Choosing medications that adequately relieve symptoms with minimal adverse effects would be ethically preferable, but the obligation to provide comfort at the end of life outweighs the foreseeable occurrence of unavoidable side effects. Hastening death as a primary intention is not considered to be morally acceptable.

Providing pain medication guided by the doctrine of double effect should not be confused with active euthanasia. The distinction is clear:

- In active euthanasia, causing death is chosen as a means of relieving the symptoms that cause suffering.
- Under the doctrine of double effect, adequate management of pain, anxiety, or air hunger is recognized as an obligation to dying patients, and is provided by careful titration of medications in response to symptoms. If death occurs sooner as a result, this is accepted.

In both cases the patient dies and in both cases suffering ends, but immediate death is the intended consequence only in the case of euthanasia. Codes of ethics and legislation in many states support the obligation to provide pain and symptom relief at the end of life, even if this requires increasing doses of medication.

CARE OF DISABLED NEWBORNS

In 1982, an infant with Down syndrome and esophageal atresia was allowed to die at 6 days of age at the parents' request. Prior to this case becoming public, prevailing opinion was that withholding aggressive treatments from infants who were predicted to be significantly disabled from conditions such as Down syndrome or meningomyelocele was ethically acceptable, and was being done on advice of physicians who felt that they and families should be able to decide what was best for an individual infant. The public legal controversy resulted in federal legislation called the "Baby Doe Regulations," prohibiting the withholding of medically beneficial treatment from disabled infants except under conditions of permanent unconsciousness, "futile" treatment, and "virtually futile" treatment that imposes excessive burdens on the infant. Today, treatment options and potential outcomes have improved, attitudes toward and social supports for disabled children have evolved, and initial aggressive treatment of infants with severe disabilities has become more common. Studies done since the Baby Doe Regulations went into effect indicate that most pediatricians supported parental rather than government control of such decisions, and felt that they were now constrained to institute treatments that served neither patients nor families well.

One consequence of the legislation was a shift from potential undertreatment to widespread overtreatment (LSMT that does not serve the interests of the child) of severely disabled newborns. The legislation has been difficult to enforce, and subsequent case law has upheld the right of a parent to decide to forgo LSMT in certain instances. The 2002 "Born Alive Act" defined a human being as any infant born alive at any stage of development. It has been thought by some to pose a risk to the ethical practice of providing palliative care for newborns, though many believe that no changes in patient management are necessary.

Active euthanasia of severely suffering disabled newborns has been legalized in the Netherlands, using a protocol designed to minimize risk of abuse and maximize transparency. Although there may be some controversy over the subject in the United States, there is consensus that active euthanasia is not ethically acceptable in the care of infants and children.

DECLARING DEATH AND ORGAN DONATION

Donation of solid organs necessary to support life can occur after a patient is declared dead based on either irreversible cessation of neurologic function of the brain and brainstem (death by neurologic criteria, or "brain death") or a predetermined period of cardiac asystole called "circulatory death." To avoid a potential conflict of interest by surgeons or others caring for a potential organ recipient, the request for organ donation should be separated from the clinical discussion of either brain death or withdrawal of LSMT. Although clinicians may be

the first providers to enter discussion about death and organ donation with family members during conversations about outcomes and options, detailed discussion of organ donation should be done by other individuals who are specifically trained for this purpose. This "decoupling" of clinical decision making from a request for organ donation by trained individuals, perhaps by providing families with expert information without a perceived conflict of interest, has been associated with improved donation rates.

Death by Neurologic Criteria

Death by neurologic criteria (DBNC), commonly referred to as brain death, may be difficult for families to understand when the child appears to be breathing (albeit on a ventilator), pink, and warm to the touch, and when language such as life support is used at the bedside by staff. Studies also document clinician misunderstanding of the diagnosis of DBNC. For these reasons, strict criteria adhering to nationally accepted guidelines must be used to determine when irreversible cessation of brain and brainstem function has occurred, and to adequately document these findings (see Chapter 68.1).

The states of New York and New Jersey allow families to object on religious grounds to the declaration of DBNC. In that situation, the clinical determination of the DBNC sets the stage for a discussion of forgoing LSMT, rather than the death of the patient. A unilateral decision not to initiate new or escalate existing interventions is ethically supportable under these circumstances, given the documented death of the patient. Even though it would seem to follow that a similar unilateral decision to withdraw existing interventions would also be supportable, this act is not in accordance with the intent of the state laws. Institutional procedures for conflict resolution, including involvement of the courts if necessary, should be followed.

Circulatory Death

Protocols allowing for organ donation after determination of circulatory death (DDCD) rather than after DBNC have been developed. DDCD can occur under either controlled (after planned withdrawal of LSMT) or uncontrolled (after failed CPR) circumstances, but in both cases require rapid removal of organs in order for subsequent transplantation to be successful. An increasing number of programs are pursuing DDCD protocols after federal legislation began requiring accredited hospitals to address the issue in hopes of decreasing organ shortages. Hospitals can make policy that either allows or disallows the process. In adults, consent for donation by either means can be obtained from patients or surrogates; for children, parents or guardians would make the decision to donate.

Ethical concerns about DDCD protocols focus on two principles that have served as the basis for organ donation: (1) the "dead donor rule" limiting the donation of vital organs to those who are irreversibly dead (either by circulatory or neurologic criteria, not both), and (2) the absence of conflict of interest between clinical care and organ procurement. With DDCD protocols, irreversibility has been declared at varying times after asystole occurs (usually 2-5 min), to avoid spontaneous return of circulation after forgoing CPR. To avoid a potential conflict of interest during the DDCD process, there is a requirement for strict decoupling of end-of-life care after discontinuation of LSMT and presence of the transplant team. Unlike in the setting of DBNC, a patient who is being considered for DDCD remains alive until after asystole has occurred. Careful evaluation by the transplantation team and organ procurement agency is performed before discontinuation of LSMT. Then, in most DDCD protocols the medical caregivers from the ICU continue to care for the patient until after death by cardiac criteria has been declared, and only then is the surgical transplant team allowed into the room to procure organs.

It is ***ethically imperative*** to correctly diagnose the state of death, whether by neurologic criteria or prior to organ donation after cardiac death. Doing so avoids the danger of removing life-sustaining organs from a living person. Strict adherence to an ethically sound protocol is the best way to prevent both the perception and the potential reality of mistakes related to the pronunciation of death and organ procurement.

RELIGIOUS OR CULTURAL OBJECTIONS TO TREATMENT

Differences in religious beliefs or ethic-based cultural norms may lead to conflict between patients, families, and medical caregivers over the approach to medical care. Pediatricians need to remain sensitive to and maintain an attitude of respect for these differences, yet recognize that an independent obligation exists to provide effective medical treatment to the child. An adult with decision-making capacity is recognized as having the right to refuse treatment on religious or cultural grounds, but children who have not yet developed this capacity are considered a vulnerable population that has a right to treatment. In situations that threaten the life of the child or that may result in substantial harm, legal intervention should be sought if reasonable efforts toward collaborative decision making are ineffective. If a child's life is imminently threatened, medical intervention is ethically justified despite parental objections.

PEDIATRIC ETHICS COMMITTEES AND ETHICS CONSULTATION

Most hospitals have institutional ethics committees to assist with policy development, education, and case consultation. When these committees serve institutions caring for children, they may be referred to as *pediatric ethics committees*. Because of the important differences in approach between adult and pediatric ethics, member expertise on this committee should include those with special insight into the unique ethical issues arising in the care of children. Such committees generally provide ethics consultation advice without mandating action or being determinative. For the vast majority of decisions involving the medical treatment of children (including forgoing LSMT), pediatric clinicians and parents are in agreement about the desirability of the proposed intervention. Because of the ethical importance of assent, the views of older children should also be given considerable weight.

Pediatric ethics committees typically perform at least 3 different functions: (1) the drafting and review of institutional policy on such issues as DNAR orders and forgoing LSMT; (2) the education of healthcare professionals, patients, and families about ethical issues in healthcare; and (3) case consultation and conflict resolution. Although the process of case consultation may vary, ideally the committee (or consultant) should adopt a collaborative approach that uncovers all the readily available and relevant facts, takes into account the values of those involved, and balances the relevant interests, while arriving at a recommendation based on a consistent ethical analysis. One helpful approach involves consideration of the 4 following elements: (1) medical indications, (2) patient preferences, (3) quality of life, and (4) contextual features. Another framework based on principles would suggest attention to respect for persons, beneficence/nonmaleficence, and justice. Pediatric ethics committees often play a constructive role when parents and medical staff cannot agree on the proper course of action. Over the past several decades, these committees have acquired considerable influence and are increasingly recognized by state courts as an important aid in decision making. The membership, policies, and procedures of a pediatric ethics committee should conform to accepted professional standards.

NEWBORN SCREENING AND GENETIC TESTING

The *Oxford Dictionary of Public Health* defines **screening** as "the identification of a previously unrecognized disease or disease precursor, using procedures or tests that can be conducted rapidly and economically on large numbers of people with the aim of sorting them into those who may have the condition(s)…and those who are free from evidence of the condition(s)." Several programs, such as newborn screening for inborn errors of metabolism (see Chapter 84; e.g., phenylketonuria and hypothyroidism), are rightly counted among the triumphs of contemporary pediatrics. The success of such programs sometimes obscures serious ethical issues that continue to arise in proposals to screen for other conditions for which the benefits, risks, and costs have not been clearly established. Advances in genetics and technology have led to exponential growth in the number of conditions

for which screening programs might be considered, with insufficient opportunity to study each proposed testing program (see Chapter 78).

The introduction of screening efforts should be done in a carefully controlled manner that allows for the evaluation of the costs (financial, medical, and psychologic) and benefits of screening, including the effectiveness of follow-up and treatment protocols. New programs should be considered experimental until the risks and benefits can be carefully evaluated. Screening tests that identify candidates for treatment need to have demonstrated sensitivity, specificity, and high predictive value, lest individuals be falsely labeled and subject to possibly toxic treatments or to psychosocial risks. As newborn screening tests are being developed, parents should be given the opportunity to exercise informed parental permission or refusal. However, once a particular screening test has been clearly demonstrated to benefit the individual or public health, a formal, active parental permission process may not be ethically obligatory.

A persistent ethical issue is whether screening should be (1) voluntary ("opt in"), (2) routine, with the ability to "opt out" or refuse, or (3) mandatory. A voluntary approach entails an informed decision by parents before screening. Concern is often expressed that seeking parental permission is ethically misguided for tests of clear benefit, such as phenylketonuria screening, because refusal would constitute neglect. Routine testing with an opt-out approach requires an explicit refusal of screening by parents who object to this intervention. The principal ethical justification for mandatory screening is the claim that society's obligation to promote child welfare through early detection and treatment of selected conditions supersedes any parental right to refuse this simple and low-risk medical intervention. Parental permission is clearly required when there is a research agenda (i.e., for incorporating experimental tests into established screening programs).

Genetic testing of young children for late-onset disorders such as the *BRCA1* and *BRCA2* breast cancer risk genes has been the subject of some ethical controversy. Knowledge of increased risk status may lead to lifestyle changes that can reduce morbidity and the risk of mortality, or may precipitate adverse emotional and psychologic responses and discrimination. Because many adults choose not to be tested for late-onset disorders, one cannot assume that a child would want or will benefit from similar testing. Genetic testing of young children for late-onset disorders is generally inappropriate unless such testing will result in interventions that have been shown to reduce morbidity and mortality when initiated in childhood. Otherwise, such testing should be deferred until the child has the capacity to make an informed and voluntary choice. This ethical approach is founded on the work of philosopher Joel Feinberg's writing on the "child's right to an open future."

ADOLESCENT HEALTHCARE

Adolescent Assent and Consent

Many adolescents are more like adults than children in their capacity to understand healthcare issues and to relate them to their life goals (see Chapter 110). Teenagers may lack legally defined competency, yet they may have developed the capacity meet the elements of informed consent for many aspects of medical care (see Chapter 112). There are also public health reasons for allowing adolescents to consent to their own healthcare with regard to reproductive decisions, such as contraception, abortion, and treatment of sexually transmitted infections. Strict requirements for parental permission may deter adolescents from seeking healthcare, with serious implications for their health and other community interests.

Counterbalancing these arguments are legitimate parental interests to maintain responsibility and authority for child rearing, including the opportunity to influence the sexual attitudes and practices of their children. Others claim that access to treatment such as contraception, abortion, or needle exchange programs implicitly endorses sexual activity or drug use during adolescence. Pediatricians should not impose their own moral beliefs in these disputes. Rather, they should provide unbiased evidence-based information and nonjudgmental support. One guiding principle should be encouragement of children and adolescents to begin taking responsibility, with guidance, for their own health. This requires some input from parents or guardians but also some privacy during decision making as they achieve developmentally anticipated separation from parental control.

Chronic Illness

The normal process of adolescent development involves gradually separating from parents, establishing self-confidence, asserting individuality, developing strong peer relationships, solidifying an ability to function independently outside the family, and taking on increasing autonomy in healthcare decisions. Most developmentally normal children older than age 14 yr understand the implications of well-explained medical options as well as the average adult, and their input into their own care should be respected. For children living with chronic illness, the ability to make medical decisions for themselves may either occur earlier than for those who have been previously healthy, or may occur later if, because of illness, they have not been able to achieve normal developmental milestones or psychological maturity. The clinician's role involves assessment of the individual adolescent patient's ability to understand the medical situation, to support the patient's efforts to express wishes regarding medical treatment, to value and encourage parental support and involvement, and to foster cooperation and mutual understanding. This may be difficult in situations in which parents and adolescents disagree about life-sustaining treatments such as organ transplantation or chemotherapy, but many such conflicts may be resolved by exploring the reasons for the disagreement. Overriding an adolescent's wishes should be done very infrequently, and only after careful consideration of the potential consequences of unwanted interventions.

Decisions in Terminally Ill Adolescents

Most adolescents share end-of-life decision making with family members, although communication may be challenging because of a growing sense of independence. Open communication and flexibility about treatment preferences may help teens cope with fears and uncertainties. Development of an age-appropriate AD may support the patient's emerging autonomy by clarifying the adolescent's wishes, while fostering a collaborative process among the patient, family, and medical caregivers. From the time of diagnosis of a life-threatening condition through the end-of-life phase, children should be included in a developmentally tailored process of communication and shared decision-making that builds a foundation of mutual respect and trust.

RESEARCH

The central ethical challenge of pediatric research is the need to balance protection of children from research risk against the ethical imperative of conducting studies to better the lives of future children. Research is defined in the federal regulations as "a systematic investigation designed to develop or contribute to generalizable knowledge." For any research to be performed, the risks should be minimized and reasonable with respect to any anticipated benefits to the subjects and the importance of the resulting knowledge. The fact that some children derive a direct benefit from participation in research must also be considered, making it important to distinguish research with the prospect of direct benefit from nontherapeutic pediatric research. ***Because children are a vulnerable population, there are restrictions on the research risks to which a child may be exposed*** that contrast with the risk level acceptable for research with consenting adults. These restrictions function by limiting the kind of research institutional review boards (IRBs) are permitted to approve and by specifying the conditions under which parent(s) have the moral and legal authority to permit a child to participate in research.

Nontherapeutic research in children is the most ethically controversial because it holds no expected direct benefit for the subject. The prohibition against using a person (especially a child) solely as a means to an end has led some to argue that children should never be used in nontherapeutic research. The more widely held opinion is that children may be exposed to a limited degree of risk with IRB approval, parental permission, and assent if the child is capable. The federal regulations allow healthy children to participate in minimal-risk research regardless of the potential benefit to the child-subject. More

controversially, the regulations also state that children with a disorder or condition may be exposed to slightly more than minimal risk in nontherapeutic research if the child's experience is similar to everyday life with that condition and the anticipated knowledge is of vital importance for understanding that condition.

In pediatric research with the prospect of direct benefit, the risks must be justified by the anticipated benefit to the child, and the balance of anticipated benefit to the risk should be at least as favorable as that presented by available alternatives. ***The welfare of an individual child must always come before the scientific goals of the research study.***

The regulations in the United States for the protection of human research subjects rest on 2 foundations: (1) independent review of the ethics and science of the research by an IRB **prior to** (2) voluntary and informed consent of the subject/participant. Although it is not amenable to regulation, the integrity of the investigator is probably the most important element contributing to the protection of human research subjects. The standard for informed consent in a research setting is higher than for clinical care because the risks and benefits are typically less clear, the investigator has a conflict of interest, and humans have historically been subjected to unauthorized risks when strict requirements for consent were not respected.

Adolescents who are competent may sometimes consent to be research subjects. Younger children may participate in a process of assent, but this does not imply that a child's signature on an assent document is necessarily a legal or ethical requirement. Children should be given the opportunity to dissent, particularly for nontherapeutic research, when there cannot be a claim that participation is in the child's interest. In the United States, national regulations require that reasonable efforts be made at least to inform children who are capable of understanding that participation is not part of their care and that, therefore, they are free to refuse to participate. In the rare case that the research offers a direct benefit to the child that would not otherwise be available, the regulations do not require child assent but only parental permission.

In addition to the protection that informed consent/parental permission is intended to provide, virtually all research involving human subjects in the United States is reviewed by an IRB, required by federal regulations for institutions receiving federal research funds and for drug research regulated by the U.S. Food and Drug Administration. For research that carries more than a minor increase over minimal risk without prospect of benefit to the child such that a local IRB cannot provide approval, there is a process for federal review of research that "presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." Ultimately, the U.S. Secretary of Health and Human Services has the authority to approve such research.

BALANCING MATERNAL AND FETAL INTERESTS

Some situations require balancing of maternal health and well-being with those of the fetus/unborn child to reach an ethically sound decision. For instance, innovative surgical treatment of a prenatally diagnosed anomaly may help the fetus/unborn child survive, but in the process place the mother at risk of injury or of loss of the pregnancy. Alternatively, a pregnant woman may object to delivery by caesarian section for various reasons in spite of advice that it may protect the fetus/unborn child during birth. A third important situation involves risk-taking behaviors during pregnancy that are known to injure the developing fetus/unborn child, such as drug or alcohol use. These issues raise conflicts over clinicians' responsibility to the living, competent decision-maker—the pregnant mother—as opposed to the interests of the fetus/unborn child.

In certain cases, courts in the United States have decided that a woman can be required to undergo caesarian section against her will when the risk to her health is minimal and the benefit to the otherwise normal, near-term fetus/unborn child is clear, for example, in a case of placenta previa. Other factors, such as prematurity, have led to the opposite legal conclusion in otherwise similar situations because the benefit of intervention was less clear. In general, a clinician should not oppose a pregnant woman's refusal of a recommended intervention unless (1) the risk to the pregnant woman is minimal, (2) the intervention is clearly effective, and (3) the harm to the fetus/unborn child without the intervention would be certain, substantial, and irrevocable. Attempts should be made to persuade the pregnant woman to comply with recommendations in the interest of the fetus/unborn child when these 3 conditions exist, using support strategies such as the influence of other trusted caregivers, clergy, and/or ethics consultation/committee involvement. If these approaches fail and there is time, a clinician may seek judicial intervention as a last resort in the attempt to prevent harm to the fetus/unborn child.

Obstetricians and pediatricians may consider reporting women under child abuse or neglect statutes if ingesting alcohol or illicit drugs during pregnancy is felt to place the fetus/unborn child at risk of injury. However, clinicians must consider the likelihood of benefit from reporting, the harm to the child as well as to the mother if criminal charges or custody changes are sought, and the possible effects that reporting may have on driving pregnant women away from prenatal or postnatal care. The U.S. Supreme Court has held that drug testing of pregnant women without consent was a violation of the Fourth Amendment, which provides protection from unreasonable searches.

JUSTICE AND PEDIATRIC ETHICS

The most serious ethical problem in healthcare in the United States may be inequality in access to healthcare. Children are particularly vulnerable to this disparity, and pediatricians have a moral obligation to advocate for children as a class. Because children do not vote and do not have financial resources at their disposal, they are subject to a greater risk of being uninsured or underinsured. This lack of adequate and affordable healthcare has serious consequences in terms of death, disability, and suffering. The Affordable Care Act may help to ameliorate these problems in the United States. The per capita proportion of healthcare funding spent on adults greatly exceeds that spent on children, and Medicare is available to all adults who turn 65 yr old whereas Medicaid is limited to those beneath a specific income level. Federal dollars intended to support healthcare for children are generally administered and supplemented with state funds, which can create additional barriers. Pediatricians should be familiar with policy issues around the economics of child healthcare so that they will be better able to advocate for their own patients (see Chapter 1).

EMERGING ISSUES

The ready availability of information on the Internet has encouraged parents to become more involved in advocating for specific approaches to the healthcare of their children, requiring physicians to remain aware of the quality of these sources of information in order to adequately counsel parents on treatment choices. Because the range of aggressive, innovative, or exceedingly expensive therapies has increased, without necessarily providing clear benefit to the patient, pediatricians must exercise care and judgment before agreeing to pursue these interventions. A growing number of parents are refusing to immunize their children because of fear of adverse reaction to vaccine. This raises the ethical problem of the "free rider," in which a child may benefit from herd immunity because others have been immunized without contributing to this public good. Outbreaks of preventable infectious disease have been detected in communities where vaccine refusal is prevalent. Pediatricians should manage this issue with ethical sensitivity, educating parents about the safety profile of vaccines and encouraging appropriate immunization. More confrontational approaches are not generally effective or ethically warranted. A second emerging issue relates to children as stem cell or solid organ donors. Here the risk : benefit balance should be carefully weighed, but in general, a permissive policy with regard to stem cell donation and a more restrictive approach to solid-organ donation are ethically justified. Finally, controversial medical and surgical interventions, such as growth attenuation of children with severe cognitive impairment in hopes of prolonging ability to care for them in the home setting, and disorders of sexual development require careful ethical consideration. Attitudes about emerging technologies and treatments

may be influenced by media coverage, special interest groups, and efforts by understandably desperate families to help their children. The clinician attempting to practice ethically must carefully consider all relevant facts in each case, and try to focus families and caregivers on a reasonable best interest assessment for the child. The tension between finding optimal policy for groups of children and doing the right thing for an individual child raises formidable ethical challenges in this context. Ethics consultation may be helpful to frame the issues and design ethically supportable approaches to care.

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Chapter 4

Cultural Issues in Pediatric Care

Linda Kaljee and Bonita F. Stanton

Pediatricians live and work in a multicultural world. Among the world's 7 billion people residing in >200 countries, >6,000 languages are spoken. As the global population becomes more mobile and integrated, ethnic and economic diversity increases in all countries. From 1970 to 2000, the foreign-born population in the United States increased 3-fold. In the 2000 U.S. census, 25-30% of Americans self-identified as belonging to an ethnic or racial minority group. In 2010, 13% of the population was foreign born and 1 or both parents of 24% of children under age 17 yr is foreign born; the 40 million immigrants represents a 28% increase over the number in 2000. Whereas in 1920, 97% of immigrant families in the United States were from Europe or Canada as of 2010 more than 90% of immigrant families are from Asia and Latin America. Nonwhite children are projected to outnumber white children in the United States by the year 2030. Increased migration and diversity in the migrant pool is not limited to the United States; immigrants account for more than 15% of the population in >50 nations.

THE IMPORTANCE OF CULTURE TO MEDICAL PRACTICE

The concept of culture includes the ways in which a group of people share and understand their history, beliefs, and values, and engage in behaviors reflective of these shared worldviews. Although culture is not synonymous with language, ethnicity, nationality, or socioeconomic status, groups with similar backgrounds with respect to these characteristics often share cultural norms and beliefs.

Within cultures, there are frameworks for classifying and organizing kin (family), assigning roles and responsibilities based on age, gender, and other social groupings, and defining concepts such as prosperity, success, knowledge, causes of disease, and health. Disease typology, prevention and intervention efforts, and health practitioners are culturally defined. Health-related cultural-beliefs and practices are integrated within pluralistic health systems that include both biomedicine and traditional medicine.

Tables 4-1 to 4-3 display some cultural values associated with 4 populations in the United States: Latinos, Muslims, Native Americans, and African-Americans, illustrating both areas of significant overlap and great variation that are relevant to health perceptions and health seeking. Latinos may subscribe to the importance of "personalismo," placing great importance on politeness in the face of stress and adversity. Thus expectations may include a display of warmth from their physician, including physical touching such as handshaking, placing hands on the shoulder, and occasionally hugging. By contrast, in the Muslim culture, for a person to touch the body of a member of the opposite gender, including on the arm or a pat on the shoulder, is considered highly inappropriate.

Despite the existence of shared values within a defined population group, there may be substantial variations within subgroups, such as the Latino national subgroups (e.g., Cuban, Puerto Rican, Dominican, Mexican), resulting in great variation in specific health-seeking behaviors. Likewise, within an overarching culture ("American"), persons who are economically and/or politically disenfranchised may use resistance, inverting the values of the dominant socioeconomic group. Such a reaction may include distrust of recommendations regarding healthcare from members of the perceived dominant or controlling group or class. Immunizations have been viewed with distrust among the poor in countries around the globe, as they were believed to be a form of birth control or sterilization and were often offered through institutions associated with "Western" and postcolonial rule. Within cultures, socially constructed categories of gender, sexuality, and age affect perceptions of an individual's vulnerability to a particular disease or condition, as well as the individual's access to health system resources. Adolescents girls living in cultures with strong taboos against premarital sexual relationships (e.g., Chinese, Muslim, Vietnamese) may not have social access to disease and birth control protection (e.g., condoms) resulting in increased risks for HIV, other sexually transmitted infections, and unwanted pregnancies.

There may also be significant generational differences between foreign-born parents and their American-raised children, particularly as these children go through adolescence. Such disparate experiences and cultural identities can result in a generational gap that decreases parent–child communication and subsequently lessens the important positive effects of communication on reducing substance use and engagement in sexual risk behaviors among youth.

Other values may be shared across disparate cultural groups. Multiple ethnic groups, including Latinos and Muslims, as well as Sudanese and Bengalis, share a cultural belief of fatalism, with strong implications for health-seeking behavior.

The perceived role of the physician may also differ between cultures. Pediatricians are trained to offer advice on child rearing, and studies have shown that parents look to pediatricians for this advice. However, parents of differing cultural backgrounds may not desire or may be reluctant to accept such advice.

NEWLY RECOGNIZED CULTURAL GROUPS

Groups that may or may not traditionally have been recognized as distinct cultural groups, (adolescents, gay/lesbian youth, transgender youth, street youth, deaf youth, etc.) have shared values which frequently have implications for health and health seeking. Failure on the part of the pediatrician to recognize accepted language and frame of reference of these groups may result in the unintentional use of offensive terminology or assumptions, leading to loss of the physician's credibility or noncompliance from the patient.

THE CULTURE OF THE MEDICAL PROFESSION

The profession of medicine also has a distinct culture. Like other cultural groups, physicians have a distinct "language" and share a common history, admiring the same role models, sharing the same preparatory courses that must be mastered for entrance into training for the profession, and subscribing to a common meaning of "competence" in medical practice. Physicians learn a new way to describe health and illness, requiring a new vocabulary and a prescribed pattern to the narrative history, which is not shared by those outside medicine. Physician reliance on "evidence-based practice" carries the implication that it is synonymous with truth or real knowledge. Of particular importance in the relationship with patients has been the lack of physician insight into the existence of a physician culture and the potential biases that may be inherent to that culture.

Although physicians around the world recognize the great strides that have been made in child survival through the use of oral rehydration therapy in the treatment of dehydrating diarrheal diseases, parents are often anxious because the treatment does not stop the diarrhea. Physicians may be dependent on a particular style of communication

Table 4-1 Cultural Values* Relevant to Health and Health-Seeking Behavior

CULTURAL GROUP	RELEVANT CULTURAL NORMS	
	Description of Norm	**Consequences of Failure to Appreciate**
Latino	*Fatalismo:* Fate is predetermined, reducing belief in the importance of screening and prevention	Less preventive screening
	Simpatia: Politeness/kindness in the face of adversity—expectation that the physician should be polite and pleasant, not detached	Nonadherence to therapy, failure to make follow-up visits
	Personalismo: Expectation of developing a warm, personal relationship with the clinician, including introductory touching	Refusal to divulge important parts of medical history, dissatisfaction with treatment
	Respecto: Deferential behavior on the basis of age, social stature, and economic position, including reluctance to ask questions	Mistaking a deferential nod of the head/not asking questions for understanding; anger at not receiving due signs of respect
	Familismo: Needs of the extended family outrank those of the individual, and thus family may need to be consulted in medical decision making	Unnecessary conflict, inability to reach a decision
Muslim	*Fasting* during the holy month of Ramadan: fasting from sunrise to sundown, beginning during the teen years. Women are exempted during pregnancy, lactation, and menstruation, and there are exemptions for illness, but an exemption may be associated with a sense of personal failure	Inappropriate therapy; will not take medicines during daytime misinterpreted as noncompliance; misdiagnosed
	Modesty: Women's body including hair, body, arms, and legs not to be seen by men other than in immediate family. Female chaperone and/or husband must be present during exam and only that part of the body being examined should be uncovered	Deep personal outrage, seeking alternative care
	Touch: Forbidden to touch members of the opposite sex other than close family. Even a handshake may be inappropriate	Patient discomfort, seeking care elsewhere
	After death, body belongs to God: Postmortem exam will not be permitted unless required by law; family may wish to perform after-death care	Unnecessary intensification of grief and loss
	Cleanliness essential before prayer: Individual must perform ritual ablutions before prayer, especially elimination of urine and stool. Nurse may need to assist in cleaning if patient is incapable	Affront to religious beliefs
	God's will: God causes all to happen for a reason, and only God can bring about healing	Allopathic medicine will be rejected if it conflicts with religious beliefs, family may not seek healthcare
	Patriarchal, extended family: Older male typically is head of household, and family may defer to him for decision making	Child's mother or even both parents may not be able to make decisions about child's care; emergency decisions may require additional time
	Halal (permitted) vs. *harem* (forbidden) foods and medications: Foods and medicine containing alcohol (some cough and cold syrups) or pork (some gelatin-coated pills) are not permitted	Refusal of medication, religious effrontery
Native American	*Nature* provides the spiritual, emotional, physical, social, and biologic means for human life; by caring for the earth, Native Americans will be provided for. Harmonious living is important	Spiritual living is required of Native Americans; if treatments do not reflect this view, they are likely not to be followed
	Passive forbearance or right of the individual to choose his or her path: Another family member cannot intervene	Mother's failure to intervene in a child's behavior and/or use of noncoercive disciplinary techniques may be mistaken for neglect
	Natural unfolding of the individual: Parents further the development of their children by limiting direct interventions and viewing their natural unfolding	Many pediatric preventive practices will run counter to this philosophy
	Talking circle format to decision-making: Interactive learning format including diverse tribal members	Lecturing, excluding the views of elders is likely to result in advice that will be disregarded
African-American	Great heterogeneity in beliefs and culture among African-Americans	Risk of stereotyping and/or making assumptions that do not apply to a specific patient or family
	Extended family and variations in family size and child care arrangements are common; matriarchal decision making regarding healthcare	Advice/instructions given only to the parent and not to others involved in health decision making may not be effective
	Parenting style often involves stricter adherence to rules than seen in some other cultures	Advice regarding discipline may be disregarded if it is inconsistent with perceived norms; other parenting styles may not be effective
	History-based widespread mistrust of medical profession and strong orientation toward culturally specific alternative/complementary medicine	In patient noncompliance, physicians will be consulted as a last resort
	Greater orientation toward others; the role of an individual is emphasized as it relates to others within a social network	Compliance may be difficult if the needs of 1 individual are stressed above the needs of the group
	Spirituality/religiosity important; church attendance central in most African-American families	Loss of opportunity to work with the church as an ally in healthcare

Table 4-1 Cultural Values* Relevant to Health and Health-Seeking Behavior—cont'd

CULTURAL GROUP	RELEVANT CULTURAL NORMS	
	Description of Norm	**Consequences of Failure to Appreciate**
East and Southeast Asian	Long history of eastern medicines (e.g., Chinese medicine) as well as more localized medical traditions	May engage with multiple health systems (Western biomedical and traditional) for treatment of symptoms and diseases
	Extended families and care networks. Grandparents may provide day-to-day care for children while parents work outside of the home	Parents may not be the only individuals a physician needs to communicate with in regard to symptoms, follow-through on treatments, and preventive behaviors
	Sexually conservative. Strong taboos for premarital sexual relationships, especially for women	Adolescents may be reluctant to talk about issues of sexuality, pregnancy, birth control with physicians. Recent immigrants or native populations may have less knowledge regarding pregnancy prevention, sexually transmitted infections, and HIV.
	Infant/child feeding practices may overemphasize infant's or child's need to eat a certain amount of food to stay "healthy"	Guidelines for child nutrition and feeding practices may not be followed out of concern for child's well-being
	Saving face. This is a complex value whereby an individual may lose prestige or respect of a third party when a second individual says negative or contradictory statements	Avoid statements that are potentially value laden or imply a criticism of an individual. Use statements such as "We have now found that it is better to …" rather than criticizing a practice

*Adherence to these or other beliefs will vary among members of a cultural group based on nation of origin, specific religious sect, degree of acculturation, age of patient, etc.

Table 4-2 Examples of Disease Beliefs or Practices

CULTURAL GROUP	EXAMPLES
Latino	Use of traditional medicines (nopales or cooked prickly pear cactus as a hypoglycemic agent) along with allopathic medicine Recognition of disorders not recognized in Western allopathic medicine (*empacho*, in which food adheres to the intestines or stomach), which are treated with folk remedies but also brought to the pediatrician Cultural interpretation of disease (*caida de mollera* or fallen fontanel) as a cultural interpretation of severe dehydration in infants
Muslim	Female genital mutilation: practiced in some Muslim countries; the majority do not practice it and it is not a direct teaching of the Koran Koranic faith healers: use verses from the Koran, holy water, and specific foods to bring about recovery
Native American	Traditional "interpreters" or "healers" interpret signs and answers to prayers. Their advice may be sought in addition or instead of allopathic medicine Dreams are believed to provide guidance; messages in the dream will be followed
East and Southeast Asian	Concepts of "hot" and "cold," whereby a combination of hot and cold foods and other substances (e.g., coffee, alcohol) combine to cause illness. One important aspect is that Western medicines are considered hot by Vietnamese and, therefore, nonadherence may occur if it is perceived that too much of a medicine will make their child's body hot. *Note:* Hot and cold do not refer to temperatures, but are a typology of different foods; for example, fish is hot and ginger is cold. Foods, teas, and herbs are also important forms of medicine because they provide balance between hot and cold

and they may miss information from patients using alternative narrative styles. Likewise, the physician–researcher forms questions through the prism of the physician–researcher's own beliefs and literature, thereby reducing the likelihood of exploring alternative explanations or questions. Even though vast segments of the world's population understand disease as an imbalance of "hot" and "cold," this belief system has not been well-represented in contemporary medical research.

CULTURAL COMPETENCE

Physicians and patients bring to their interaction personal and professional values from multiple cultural systems that have significant implications for the delivery of healthcare. Consequently, physician "cultural competence" is critical to a successful patient–provider interaction (Fig. 4-1). Campinha-Bacote's model for understanding and assessing culturally competency is frequently used in education and research: (1) learning to value and understand other cultures, in part through self-awareness of one's own cultural values ("cultural awareness"); (2) learning basic fundamentals about other cultures, particularly those of the patients with whom the physician will interact ("cultural knowledge"); (3) developing the ability to apply cultural knowledge in patient encounters ("cultural skills"); (4) seeking exposure to cross-cultural interactions ("cultural encounters"); and (5) being motivated to achieve all of the previous ("cultural desire"). This framework provides an important guide to pediatric education and practice and, thus, will serve as the outline for the remainder of this chapter.

Cultural Awareness

Recognition of the importance of differing cultural expectations and explanations is critical to a pediatrician's successful interactions with patients. Among many cultures (e.g., Muslim), kinship is of great importance and decision making may involve the extended family. The erroneous belief on the part of a physician that a mother may execute independent decision making in relation to her child's healthcare (when in fact she may not be entitled to such a role in her family or culture) may result in an apparent noncompliance on the part of the mother.

Cultural Knowledge

Physicians and patients have differing definitions of health and illness and differing concepts of the origins of disease and therapeutic responses. Understanding the patient perspective will both increase

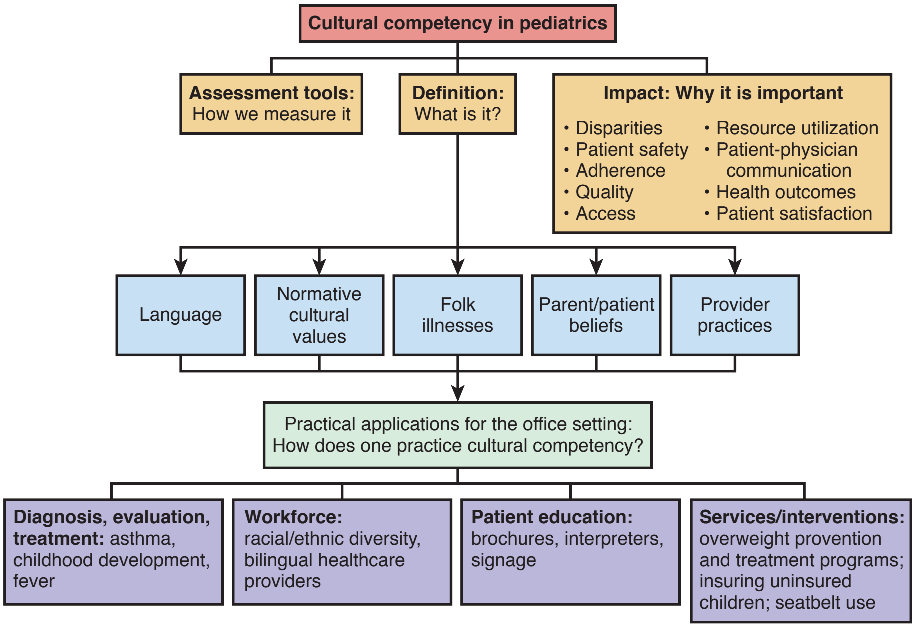

Conceptual framework for cultural competency in pediatrics: (1) what is known about the impact of cultural competency on general pediatric care; (2) the domains of cultural competency; and (3) practical applications of cultural competency for general pediatricians

Figure 4-1 Components of cultural competency in pediatric practice. *(From Brotanek JM, Seeley CE, Flores G: The importance of cultural competency in general pediatrics,* Curr Opin Pediatr *20:711–718, 2008, Fig. 1, p. 712.)*

Table 4-3 Home Remedies for Fever, Colic, and Teething Among African-Americans

CONDITION	REMEDY	KNOWLEDGE, % (N = 107)	USE, % (N = 107)
Fever	Acetaminophen*	98	77.6
	Cool bath*	85	48.3
	Isopropyl alcohol*	71	38.3
	Cool drinks/popsicles†	11.2	0
	Undress child†	10.3	0
	Ibuprofen†	10.3	0
	Warm feet†	8.4	0
	Potatoes or onions in socks†	6.5	0
Colic	Catnip*	34.6	8.4
	Senna extract*	25.2	4.7
	Other (asafetida, paregoric, or bicarbonate)†	13.1	0
	Chamomile*	7.5	0
	Walk†	6.5	0
	Cigarette smoke†	5.6	0
	Simethicone drops†	4.7	0
	Vacuum/steam†	3.7	0
	Cover head†	3.7	0
	Massage†	2.8	0
	Gripe water*	1.9	0
Teething	Nonprescription benzocaine gel*	97.2	57
	Teething object†	35.2	7.5
	Whiskey*	34.6	1.9
	Penny*	16.8	0
	Ice cubes/popsicles†	13.3	0
	Egg†	11.4	0
	Spices (asafetida, cloves, or vanilla)†	4.8	0

*Responses given in closed-ended questions.
†Responses given in open-ended questions.
From Smitherman LC, Janisse J, Mathur A: The use of folk remedies among children in an urban black community: remedies for fever, colic and teething, Pediatrics 115:297–304, 2005, Table 2.

the likelihood of correct diagnosis and patient adherence to therapy and decrease the possibility of misdiagnosis. The belief that becoming chilled causes dysentery is common among rural Chinese, and medical advice that directly challenges or runs contrary to this belief may be disregarded. Likewise, diarrhea among Bangladeshi children during teething may be regarded as normal and would not be identified as a health issue. Thus, asking the parent if the child has been ill might not reveal the presence of diarrhea. Rubbing a coin against a child's skin is thought by some parents in Asia to reduce fever. Failure by the pediatrician to recognize the practice of *coining* could lead to the erroneous

diagnosis of a rash or child abuse. In some instances, particularly in relation to developmental and emotional disorders, the manifestation of symptoms and/or recognition of symptoms by parents or other caregivers may be culturally defined. Autism is a condition characterized by communication and socializing disabilities. Yet expectations of children's language and social skills development are culturally defined, resulting in potentially later identification by family members of a child's disabilities and subsequently delayed treatment seeking.

Cultural Skill

Describing a diagnostic or therapeutic course of action that respects cultural beliefs but is consistent with good medical practice can be challenging. Common among many Latino groups is the belief of *empacho,* a condition wherein food is "stuck" to the stomach or intestinal wall, resulting in obstruction. The condition is believed to cause nausea, vomiting, diarrhea, and anorexia. Although many Latino parents would take a child with *empacho* to the physician for treatment, in Western settings, a pediatrician diagnosing the condition as viral gastroenteritis might only advise supportive management, leaving the parents perplexed and with no option but to seek independent treatment from an alternative or traditional healer. A culturally skilled pediatrician might suggest partnering with the traditional healer in such a situation. Likewise, in response to parents subscribing to a belief in fatalism and, consequently, a notion that preventive medicine or screening is not necessary, a skilled pediatrician might suggest that screening is the mechanism through which their destiny is intended to be reached. Referrals for services may also be affected by a patient's culture and history. The need for psychologic services may be rejected because of cultural stigmas regarding psychological disorders. Likewise, referrals for HIV or sexually transmitted infection testing may be more likely rejected by gay adolescent men from cultures in which homosexuality is highly stigmatized.

Central to "cultural skill" is the employment of language fully comprehended by the child's parents. This goal is best realized if the pediatrician is at least conversant in the parent's language, and thus a requirement for a second language is a reasonable goal for physicians. Familiarity with a language should not be confused with fluency or even competency. Professional interpreters should be available and accessed to overcome the language barriers. Ad hoc use of individuals at the workplace who are known to possess skill in the indicated language and/or use of telephone interpreter services may suffice if a professional interpreter is not available. A genuinely bilingual family member or friend may be helpful, but issues of confidentiality, disruption of social roles, and uncertain or inaccurate translation of medical terms may pose serious problems. Medical errors occur at a significantly higher rate among non–English speaking patients when nonprofessional translators (e.g., family members) are used to obtain a history or give medical advice.

Cultural Encounters

Although cultural knowledge may be acquired through didactic training, the development of cultural skills requires experience that can only be gained through repeated "cultural encounters." Nonminority clinicians provide lower quality of care to Latino and African-American patients, with these children being less likely to receive analgesia and/or nebulizers for asthma. Latino mothers have reported clinician attitudes as a major barrier to seeking care for their children. Participation by physicians in diverse medical educational settings and experience in community clinics has been shown to predict increased cultural knowledge. Cultural knowledge and participation in diverse educational settings, and Latino ethnicity and bilingual skills likewise predict cultural awareness, Cultural awareness predicts culturally competent actions. Consistent with observations that cultural competence may not be valued in the traditional medical culture is the observation that *higher* specialty training (e.g., subspecialty training among internists compared to general physicians, family medicine, or internal medicine generalists) predicted *less* cultural awareness. Children who receive care from practice sites with the highest cultural competence scores are less likely to underutilize preventive asthma medications.

Cultural Desire

Cultural competence is not something that can be achieved and retained in the absence of continued effort. The recognition that culture is integral to health and healing, and to disease and sickness, is central to the concept of "cultural competence." Understanding of the role of culture in health outcomes is nascent; it is not yet known why less acculturated Latinos in the United States demonstrate significantly lower rates of low birthweight, depression, tobacco use, illicit drug use, and older age for sexual debut compared to those who are more acculturated. Likewise, less acculturation among Asian children is associated with lower prevalence of chronic illness. Such findings expose the complexities between individuality, environment, cultures, and biology, and how these integrated factors can affect health-related behaviors and health outcomes.

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Chapter 5

Maximizing Children's Health: Screening, Anticipatory Guidance, and Counseling

Joseph F. Hagan Jr. and Paula M. Duncan

Routine, scheduled care of well infants, children, and adolescents is an essential prevention effort for children and youth worldwide. Children's constantly changing development lends added value to regular and periodic encounters between children and their families and practitioners of pediatric healthcare. Health supervision visits from birth to age 21 yr are the platform for a young person's healthcare. The provision of well care in the medical home, fosters strong relationships between the clinic or practice and the child and family, enabling the provision of appropriate surveillance, screening, and sick care.

To assure the optimal health of the developing child, pediatric care in the United States and other countries evolved into regularly scheduled visits to assure adequate nutrition, detect and immunize against infectious diseases, and observe the child's development. Assessment of immunizations, nutrition and developmental status remain essential elements of the well-child health supervision visit, but changes in the population's health have led to the addition of other components to the content of today's well-child encounter. Preventive care for children and youth is a component of contemporary U.S. health reform activities; this approach offers great opportunity for health cost savings.

A healthy economy requires educated and healthy workers. For children to have a successful educational experience, they must have both physical and emotional health. Educational success is also tied to early childhood developmental competence. Thus health supervision well-child care plays a vital role in promoting adult health, a concept endorsed by business leaders.

Adversity impairs development and adverse factors in life experience increase the risk of disease. Adults who experienced abuse, violence, or other stressors as children have an increased risk for depression, heart disease, and other morbidities. Biology informs us that stress leads to increased heart rate and blood pressure, and increased levels of inflammatory cytokines, cortisol, and other stress hormones, all of which impair brain activity, immune status, and cardiovascular function. There are both a causal model and evidence that

adverse childhood events, including those that could have been prevented, adversely impact the life course.

PERIODICITY

The frequency and content for well-child care activities are derived from evidence-based practice and research. In addition, federal agencies and professional organizations, such as the American Academy of Pediatrics (AAP), have developed evidence informed, expert consensus guidelines for care. The Recommendations for Preventive Pediatric Health Care or Periodicity Schedule (Fig. 5-1) is a compilation of recommendations listed by age-based visits. It is intended to guide practitioners of pediatric primary care to perform certain services and make observations at age-specific visits and it designates the standard for preventive services for children and youth according to the U.S. health reform legislation, the Affordable Care Act of 2010.

GUIDELINES

Comprehensive guides for care of well infants, children, and adolescents have been developed, based on the Periodicity Schedule, which expand and further recommend how practitioners might accomplish the tasks outlined in the Periodicity Schedule. In the United States, the current guideline standard is *The Bright Futures Guidelines for Health Supervision of Infants, Children, and Adolescents,* 4th edition. These guidelines were developed by the AAP under the leadership of the Maternal Child Health Bureau of the U.S. Department of Health and Human Services, in collaboration with the National Association of Pediatric Nurse Practitioners, the American Academy of Family Physicians, the American Medical Association, the American Academy of Pediatric Dentistry, Family Voices, and others.

TASKS OF WELL-CHILD CARE

The well-child encounter intends to promote the physical and emotional well-being of children and youth. Child health professionals, including pediatricians, family medicine physicians, nurse practitioners, and physician assistants, take advantage of the opportunity well-child visits provide to elicit parental questions and concerns, gather relevant family and individual health information, perform a physical examination, and initiate screening tests.

The tasks of each well-child visit include:

- Disease detection
- Disease prevention
- Health promotion
- Anticipatory guidance

To achieve these outcomes, healthcare professionals employ techniques to screen for disease, screen for risk of disease, and provide advice about healthy behaviors. These activities lead to the formulation of appropriate anticipatory guidance and health advice.

Clinical detection of disease in the well-child encounter is accomplished by both surveillance and screening. In well-child care, surveillance occurs in every health encounter and is enhanced by repeated visits and observations with advancing developmental stages. It relies on the experience of a skilled clinician over time. Screening is a more formal process utilizing some form of tool that has been validated and has known sensitivity and specificity. For example, anemia surveillance is accomplished through taking a dietary history and seeking signs of anemia in the physical examination. Anemia screening is done by hematocrit or hemoglobin tests. Developmental surveillance relies on the observations of parents and the watchful eyes of providers of pediatric healthcare who are experienced in child development. Developmental screening uses a structured developmental screening tool by personnel trained in its use or in the scoring and interpretation of parent report questionnaires.

The second essential action of the well-child encounter, *disease prevention,* may include both *primary prevention* activities applied to a whole population and *secondary prevention* activities aimed at patients with specific factors of risk. For example, counseling about reducing fat intake is appropriate for all children and families. Counseling is intensified for overweight and obese youth or in the presence of a family history of hyperlipidemia and its sequelae. The child and adolescent healthcare professional needs to individualize disease prevention strategies to the specific patient, family, and community.

Health promotion and **anticipatory guidance** activities distinguish the well-child health supervision visit from all other encounters with the healthcare system. Disease detection and disease prevention activities are germane to all interactions of children with physicians and other healthcare providers, but health promotion and anticipatory guidance shift the focus to wellness and to the strengths of the family (e.g., what is being done well and how this might be improved). This approach is an opportunity to help the family address relationship issues, broach important safety topics, access community services, and engage with extended family, school, neighborhood, and church.

It is not possible to cover all the topics suggested by comprehensive guidelines such as *Bright Futures* in the average 18 min well-child visit. Child health professionals must prioritize the most important topics to cover. Consideration should be given to a discussion of:

- The agenda the parent or child brings to the health supervision visit.
- The topics where evidence suggests counseling is effective in behavioral change.
- The topics where there is a clear rationale for the issue's critical importance to health, for example, sleep environment to prevent sudden infant death syndrome or attention to diet and physical activity.
- A summary of the child's progress in emotional and social development, physical growth, and strengths.
- Issues that address the questions, concerns, or specific health problems relevant to the individual family.
- Community-specific problems that could significantly impact the child's health (e.g., neighborhood violence from which children need protection or absence of bike paths that would promote activity).

It is important to note that this approach is directed at all children, including those with special health needs. Children with special health needs are no different from other children in their need for guidance about healthy nutrition, physical activity, progress in school, connection with friends, a healthy sense of self-efficacy, and avoidance of risk-taking behaviors. The coordination of specialty consultation, medication monitoring, and functional assessment, which should occur in their periodic visits, needs to be balanced with a discussion of the child's unique ways of accomplishing the emotional, social, and developmental tasks of childhood and adolescence. Comprehensive integrated care planning for children and youth with special healthcare needs supports partnerships between medical homes and families and youth through goal setting and negotiating next steps. In this process, chronic condition management and health surveillance (including adolescent engagement and planning for transition to adult care) occur within an effective patient care relationship, partnering to improve health outcomes and efficiencies of care provision.

INFANCY AND EARLY CHILDHOOD

Nutrition, physical activity, sleep, safety, and emotional, social, and physical growth, along with parental well-being, are critical for all children. For each well-child visit, there are topics that are specific to individual children based on their age, family situation, chronic health condition, or a parental concern, for example, sleep environment to prevent sudden infant death syndrome, activities to lose weight, and fences around swimming pools. Attention should also be focused on the family milieu, including screening for parental depression (especially maternal postpartum depression) and other mental illness, family violence, substance abuse, nutritional inadequacy, or lack of housing. These issues are essential to the care of young children.

Answering parents' questions is the most important priority of the well-child visit. Promoting family-centered care and partnership with parents increases the ability to elicit parent concerns, especially about their child's development, learning, and behavior. It is important to identify children with developmental disorders as early as possible. Developmental surveillance at every visit combined with a structured developmental screening, neuromuscular screening and autism screening at some visits is a way to improve diagnosis, especially for some of

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Each child and family is unique; therefore, these Recommendations for Preventive Pediatric Health Care are designed for the care of children who are receiving competent parenting, have no manifestations of any important health problems, and are growing and developing in satisfactory fashion. Additional visits may become necessary if circumstances suggest variations from normal.

Developmental, psychosocial, and chronic disease issues for children and adolescents may require frequent counseling and treatment visits separate from preventive care visits.

These guidelines represent a consensus by the American Academy of Pediatrics (AAP) and Bright Futures. The AAP continues to emphasize the great importance of continuity of care in comprehensive health supervision and the need to avoid fragmentation of care.

Refer to the specific guidance by age as listed in *Bright Futures* guidelines (Hagan JF, Shaw JS, Duncan PM, eds. *Bright Futures Guidelines for Health Supervision of Infants, Children and Adolescents*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008).

The recommendations in this statement do not indicate an exclusive course of treatment or standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

	INFANCY								EARLY CHILDHOOD							MIDDLE CHILDHOOD						ADOLESCENCE										
AGE[1]	Prenatal[2]	Newborn[3]	3-5 d[4]	By 1 mo	2 mo	4 mo	6 mo	9 mo	12 mo	15 mo	18 mo	24 mo	30 mo	3 y	4 y	5 y	6 y	7 y	8 y	9 y	10 y	11 y	12 y	13 y	14 y	15 y	16 y	17 y	18 y	19 y	20 y	21 y
HISTORY Initial/Interval	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
MEASUREMENTS																																
Length/Height and Weight		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Head Circumference		●	●	●	●	●	●	●	●	●	●	●																				
Weight for Length		●	●	●	●	●	●	●	●	●	●																					
Body Mass Index[5]												●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood Pressure[6]		★	★	★	★	★	★	★	★	★	★	★	★	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
SENSORY SCREENING																																
Vision		★	★	★	★	★	★	★	★	★	★	★	★	●[7]	●	●	●	★	●	★	●	★	●	★	★	●	★	★	●	★	★	★
Hearing		●[8]	★	★	★	★	★	★	★	★	★	★	★	★	●	●	●	★	●	★	●	★	★	★	★	★	★	★	★	★	★	★
DEVELOPMENTAL/BEHAVIORAL ASSESSMENT																																
Developmental Screening[9]								●			●		●																			
Autism Screening[10]											●	●																				
Developmental Surveillance		●	●	●	●	●	●		●	●		●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Psychosocial/Behavioral Assessment		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Alcohol and Drug Use Assessment[11]																						★	★	★	★	★	★	★	★	★	★	★
Depression Screening[12]																						●	●	●	●	●	●	●	●	●	●	●
PHYSICAL EXAMINATION[13]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
PROCEDURES[14]																																
Newborn Blood Screening[15]		←	●	→																												
Critical Congenital Heart Defect Screening[16]		●																														
Immunization[17]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Hematocrit or Hemoglobin[18]						★			●	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Lead Screening[19]							★	★	● or ★[20]		★	● or ★[20]		★	★	★	★															
Tuberculosis Testing[21]				★			★		★			★		★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Dyslipidemia Screening[22]												★			★		★		★	←	●	→	★	★	★	★	★	★	←		●	→
STI/HIV Screening[23]																						★	★	★	★	★	←	●	→	★	★	★
Cervical Dysplasia Screening[24]																																●
ORAL HEALTH[25]							★	★	● or ★		● or ★	● or ★	● or ★	●			●															
ANTICIPATORY GUIDANCE	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

1. If a child comes under care for the first time at any point on the schedule, or if any items are not accomplished at the suggested age, the schedule should be brought up to date at the earliest possible time.
2. A prenatal visit is recommended for parents who are at high risk, for first-time parents, and for those who request a conference. The prenatal visit should include anticipatory guidance, pertinent medical history, and a discussion of benefits of breastfeeding and planned method of feeding, per the 2009 AAP statement "The Prenatal Visit" (http://pediatrics.aappublications.org/content/124/4/1227.full).
3. Every infant should have a newborn evaluation after birth, and breastfeeding should be encouraged (and instruction and support should be offered).
4. Every infant should have an evaluation within 3 to 5 days of birth and within 48 to 72 hours after discharge from the hospital to include evaluation for feeding and jaundice. Breastfeeding infants should receive formal breastfeeding evaluation, and their mothers should receive encouragement and instruction, as recommended in the 2012 AAP statement "Breastfeeding and the Use of Human Milk" (http://pediatrics.aappublications.org/content/129/3/e827.full). Newborn infants discharged less than 48 hours after delivery must be examined within 48 hours of discharge, per the 2010 AAP statement "Hospital Stay for Healthy Term Newborns" (http://pediatrics.aappublications.org/content/125/2/405.full).
5. Screen, per the 2007 AAP statement "Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity: Summary Report" (http://pediatrics.aappublications.org/content/120/Supplement_4/S164.full).
6. Blood pressure measurement in infants and children with specific risk conditions should be performed at visits before age 3 years.
7. If the patient is uncooperative, rescreen within 6 months, per the 2007 AAP statement "Eye Examination in Infants, Children, and Young Adults by Pediatricians" (http://pediatrics.aappublications.org/content/111/4/902.abstract).
8. All newborns should be screened, per the AAP statement "Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs" (http://pediatrics.aappublications.org/content/120/4/898.full).
9. See 2006 AAP statement "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening" (http://pediatrics.aappublications.org/content/118/1/405.full).
10. Screening should occur per the 2007 AAP statement "Identification and Evaluation of Children with Autism Spectrum Disorders" (http://pediatrics.aappublications.org/content/120/5/1183.full).
11. A recommended screening tool is available at http://www.ceasar-boston.org/CRAFFT/index.php.
12. Recommended screening using the Patient Health Questionnaire (PHQ)-2 or other tools available in the GLAD-PC toolkit and at http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf.
13. At each visit, age-appropriate physical examination is essential, with infant totally unclothed and older children undressed and suitably draped. See 2011 AAP statement "Use of Chaperones During the Physical Examination of the Pediatric Patient" (http://pediatrics.aappublications.org/content/127/5/991.full).
14. These may be modified, depending on entry point into schedule and individual need.
15. The Recommended Uniform Newborn Screening Panel (http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/uniformscreeningpanel.pdf), as determined by The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, and state newborn screening laws/regulations (http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/nbsdisorders.pdf), establish the criteria for and coverage of newborn screening procedures and programs. Follow-up must be provided, as appropriate, by the pediatrician.
16. Screening for critical congenital heart disease using pulse oximetry should be performed in newborns, after 24 hours of age, before discharge from the hospital, per the 2011 AAP statement "Endorsement of Health and Human Services Recommendation for Pulse Oximetry Screening for Critical Congenital Heart Disease" (http://pediatrics.aappublications.org/content/129/1/190.full).
17. Schedules, per the AAP Committee on Infectious Diseases, are available at: http://aapredbook.aappublications.org/site/resources/izschedules.xhtml. Every visit should be an opportunity to update and complete a child's immunizations.
18. See 2010 AAP statement "Diagnosis and Prevention of Iron Deficiency and Iron Deficiency Anemia in Infants and Young Children (0-3 Years of Age)" (http://pediatrics.aappublications.org/content/126/5/1040.full).
19. For children at risk of lead exposure, see the 2012 CDC Advisory Committee on Childhood Lead Poisoning Prevention statement "Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention" (http://www.cdc.gov/nceh/lead/ACCLPP/Final_Document_030712.pdf).
20. Perform risk assessments or screenings as appropriate, based on universal screening requirements for patients with Medicaid or in high prevalence areas.
21. Tuberculosis testing per recommendations of the Committee on Infectious Diseases, published in the current edition of *AAP Red Book: Report of the Committee on Infectious Diseases*. Testing should be performed on recognition of high-risk factors.
22. See AAP-endorsed 2011 guidelines from the National Heart Blood and Lung Institute, "Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents" (http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm).
23. Adolescents should be screened for sexually transmitted infections (STIs) per recommendations in the current edition of the *AAP Red Book: Report of the Committee on Infectious Diseases*. Additionally, all adolescents should be screened for HIV according to the AAP statement (http://pediatrics.aappublications.org/content/128/5/1023.full) once between the ages of 16 and 18, making every effort to preserve confidentiality of the adolescent. Those at increased risk of HIV infection, including those who are sexually active, participate in injection drug use, or are being tested for other STIs, should be tested for HIV and reassessed annually.
24. See USPSTF recommendations (http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm). Indications for pelvic examinations prior to age 21 are noted in the 2010 AAP statement "Gynecologic Examination for Adolescents in the Pediatric Office Setting" (http://pediatrics.aappublications.org/content/126/3/583.full).
25. Refer to a dental home, if available. If not available, perform a risk assessment (http://www2.aap.org/oralhealth/docs/RiskAssessmentTool.pdf). If primary water source is deficient in fluoride, consider oral fluoride supplementation. For those at high risk, consider application of fluoride varnish for caries prevention. See 2008 AAP statement "Preventive Oral Health Intervention for Pediatricians" (http://pediatrics.aappublications.org/content/122/6/1387.full) and 2009 AAP statement "Oral Health Risk Assessment Timing and Establishment of the Dental Home" (http://pediatrics.aappublications.org/content/111/5/1113.full).

KEY ● = to be performed ★ = risk assessment to be performed with appropriate action to follow, if positive ← ● → = range during which a service may be provided

Figure 5-1 Recommendations for preventive pediatric healthcare. *(From Bright Futures/American Academy of Pediatrics. Copyright 2014, American Academy of Pediatrics, Elk Grove Village, IL.)*

the more subtle delays or autism spectrum disorders where early intervention is believed to be associated with reduced morbidity.

MIDDLE CHILDHOOD AND ADOLESCENCE

As the child enters school-age years, additional considerations emerge. Attention to developing autonomy requires fostering a clinician–patient relationship separate from the clinician–child-family relationship with increasing needs for privacy and confidentiality as the child ages.

The 6 health behaviors that most significantly impact adolescent and adult morbidity and mortality are inadequate physical activity, poor nutrition, sexuality-related behaviors, substance use and abuse (including tobacco), unintentional injury-related behaviors, and intentional injury-related behaviors. Emotional well-being and early diagnosis and treatment of mental health problems are equally important, with attention to the developmental tasks of adolescence (competence at school and other activities, connection to friends and family, autonomy, empathy, and a sense of self-worth).

OFFICE INTERVENTION FOR BEHAVIORAL AND MENTAL HEALTH ISSUES

One-fifth of primary care encounters with children are for a behavioral or mental health problem, or are sickness visits complicated by a mental health issue. Pediatricians require increased knowledge for diagnosis, treatment, and referral criteria for attention-deficit/hyperactivity disorder (see Chapter 33), depression and other mood disorders (see Chapter 26), anxiety (see Chapter 25), and conduct disorder (see Chapter 29), as well as an understanding of the pharmacology of the frequently prescribed psychotropic medications. Familiarity with available local mental health services and clinicians and knowledge of the types of services indicated are important for effective consultation or referral. Encouragement of behavioral change is also an important responsibility of the clinician. Motivational interviewing provides a structured approach that has been designed to help patients and parents identify the discrepancy between their desire for health and their behavioral choices. It also allows the clinician to use proven strategies that lead to a patient-initiated plan for change.

STRENGTH-BASED APPROACHES AND FRAMEWORK

Questions about school or extracurricular accomplishments or competent personal characteristics should be integrated into the content of the well child visit. Such inquiries set a positive context for the visit, deepen the partnership with the family, acknowledge the child's healthy development, and facilitate discussing social–emotional development with children and their parents. There is a strong relationship between appropriate social–emotional development (e.g., children's strong connection to their family, social friends, and mentors; competence; empathy; and appropriate autonomy) and decreased participation in all the risk behaviors of adolescence (related to drugs, sex, and violence). An organized approach to the identification and encouragement of a child's strengths during health supervision visits provides both the child and parent with an understanding of how to promote healthy achievement of the developmental tasks of childhood and adolescence. Children with special health needs often have a different timetable, but they have an equal need to be encouraged to develop strong family and peer connections, competence in a variety of arenas, ways to do things for others, and appropriate independent decision making.

OFFICE SYSTEM CHANGE FOR QUALITY IMPROVEMENT

Some of the office strategies to improve the preventive services delivered to children and youth include screening schedules and parent handouts, flow sheets, registries, and the use of parent and youth previsit questionnaires. Such tools are available in *The Bright Futures Guidelines Toolkit* and online previsit tools are under construction. These efforts are part of a larger national effort that is built on a coordinated team approach in the office setting and the use of continuous measurement for improvement.

EVIDENCE

Available evidence should be utilized in developing health-promotion and disease-detection recommendations. Revisions to the AAP's *Periodicity Schedule* undergo rigorous evidence assessment; however, many highly valued well-child care activities have not been evaluated for efficacy. Lack of evidence is most often related to absence of study and does not define lack of benefit. Thus the clinical encounter with the well child is also guideline- and recommendation-driven and requires the integration of clinician goals, family needs, and community realities in seeking better health for the child. The rationale for well-child care activities is a balance of evidence from research, clinical practice guidelines, professional recommendations, expert opinion, experience and knowledge of the needs of the patient population in the context of community assets and challenges. Clinical or counseling decisions and recommendations may also be based on legislation (seat belts), on common sense measures not likely to be studied experimentally (lowering water heater temperatures), or on the basis of relational evidence (television watching associated with violent behavior in young children). Most important, sound clinical and counseling decisions are responsive to family needs and desires, and support "patient-centered decision making."

CARING FOR THE CHILD AND YOUTH IN THE CONTEXT OF THE FAMILY AND COMMUNITY

A successful primary care practice for children incorporates families, is family centered, and embraces the concept of the medical home. A medical home is defined by the AAP as primary care that is accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective. In a medical home, a pediatrician works in partnership with the family and patient to assure that all medical and nonmedical needs of the child are met. Through this partnership, the child healthcare professional helps the family/patient access and coordinate specialty care, educational services, out-of-home care, family support, and other public and private community services that are important to the overall health of the child and family.

Ideally, health promotion activities occur not only in the medical home, but also in partnership with community members and other health and education professionals. This rests on a clear understanding of the important role that the community plays in supporting healthy behaviors among families. Communities where children and families feel safe and valued, and have access to positive activities and relationships, provide the important base that the healthcare professional can build on and refer to for needed services that support health but are outside the realm of the healthcare system or primary care medical home. It is important for the medical home and community agencies to identify mutual resources, communicate well with families and each other, and partner in designing service delivery systems. This interaction is the practice of community pediatrics, whose unique feature is its concern for all of the population: those who remain well but need preventive services, those who have symptoms but do not receive effective care, and those who do seek medical care either in a physician's office or in a hospital.

Bibliography is available at Expert Consult.

5.1 Injury Control

Frederick P. Rivara and David C. Grossman

In all high-income countries of the world, and in many low- and middle-income countries, injuries are the most common cause of death during childhood and adolescence beyond the first few months of life and represent 1 of the most important causes of preventable pediatric morbidity and mortality in the United States (see Table 1-2 in Chapter 1 and Fig. 5-2). The identification of risk factors for injuries has led to the development of successful programs for prevention and control. Strategies for injury prevention and control should be pursued

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by the pediatrician in the office, emergency department, hospital, and community setting and be done in a multidisciplinary, multifaceted fashion.

INJURY CONTROL (FORMERLY CALLED ACCIDENT PREVENTION)

Injuries have defined risk and protective factors that can be used to define prevention strategies. The term *accidents* implies an event occurring by chance, without pattern or predictability. In fact, most injuries occur under fairly predictable circumstances to high-risk children and families. Most injuries are preventable.

The reduction of morbidity and mortality from injuries can be accomplished not only through primary prevention (averting the event or injury in the first place), but also through secondary and tertiary prevention. The latter 2 approaches include appropriate emergency medical services for injured children; regionalized trauma care for the child with multiple injuries, severe burns, or traumatic brain injury; and specialized pediatric rehabilitation services that attempt to return children to their previous level of functioning.

Injury control also encompasses intentional injuries (assaults and self-inflicted injuries). These injuries are important in adolescents and young adults, and in some populations, they rank first or second as causes of death in these age groups. Many of the same principles of injury control can be applied to these problems; for example, limiting access to firearms may reduce both unintentional shootings and suicides.

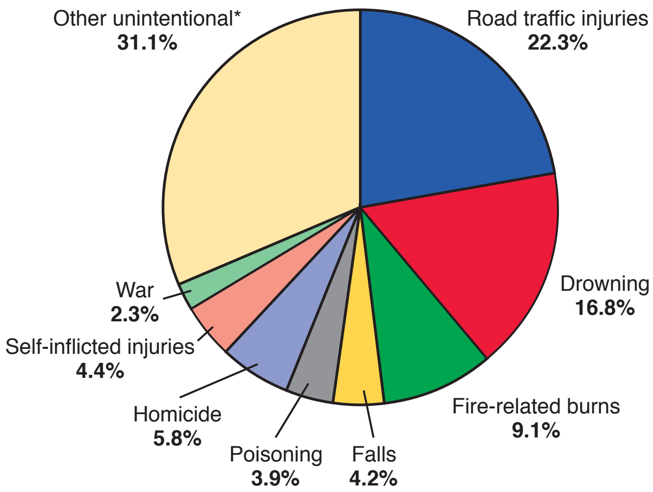

Figure 5-2 Worldwide distribution of global child injury deaths by cause, 0-17 yr of age, 2004. *"Other intentional" includes categories such as smothering, asphyxiation, choking, animal and venomous bites, hypothermia, and hyperthermia, as well as natural disasters. *(From WHO 2008, Global Burden of Disease: 2004 update. www.who.int/violence_injury_prevention/child/injury/wold_report/en/)*

SCOPE OF THE PROBLEM

Mortality

In the United States, injuries cause 41% of deaths among 1-4 yr old children and 3.5 times more deaths than the next leading cause, congenital anomalies. For the rest of childhood and adolescence up to the age of 19 yr, 63% of deaths are a result of injuries, more than all other causes combined. In 2010, injuries caused 13,819 deaths (16 deaths per 100,000) among individuals 19 yr old and younger in the United States (Table 5-1), resulting in more years of potential life lost than any other cause. Unintentional injuries remained the leading cause of death among those <24 yr in 2014 (see Table 1-2).

Motor vehicle injuries lead the list of injury deaths among school-age children and adolescents, and are the second leading cause of injury death for those ages 1-4 yr. In children and adults, motor vehicle **occupant** injuries account for the majority of these deaths. During adolescence, occupant injuries are the leading cause of injury death, accounting for >50% of unintentional trauma mortality in this age group.

Drowning ranks second overall as a cause of unintentional trauma deaths among those ages 1-14 yr, with peaks in the preschool and later teenage years (see Chapter 74). In some areas of the United States, drowning is the leading cause of death from trauma for preschool-age children. The causes of drowning deaths vary with age and geographic area. In young children, bathtub and swimming pool drowning predominate, whereas in older children and adolescents, drowning occurs predominantly in natural bodies of water while the victim is swimming or boating.

Fire and burn deaths account for 8% of all unintentional trauma deaths and 14% in those younger than 5 yr of age (see Chapter 75).

Table 5-1 Injury Deaths in the United States, 2010* [N (Rate per 100,000)]

CAUSE OF DEATH	YOUNGER THAN 1 Yr	1-4 Yr	5-9 Yr	10-14 Yr	15-19 Yr	0-19 Yr
ALL CAUSES	24,586 (623.35)	4316 (26.55)	2330 (11.45)	2949 (14.26)	10887 (49.40)	45068 (54.12)
ALL INJURIES	1529 (38.77)	1862 (11.45)	905 (4.45)	1341 (6.49)	8182 (37.12)	13819 (16.60)
All unintentional	1110 (28.14)	1264 (7.78)	758 (3.73)	885 (4.28)	4537 (20.58)	8684 (10.43)
Motor vehicle occupant	22 (0.56)	95 (0.58)	116 (0/57)	143 (0.69)	1065 (4.83)	1441 (1.73)
Pedestrian	12 (0.30)	206 (1.27)	96 (0.47)	115 (0.56)	315 (1.43)	744 (0.89)
Drowning	39 (0.99)	436 (2.68)	134 (0.66)	117 (0.57)	301 (1.37)	1027 (1.23)
Fire and burn	41(1.04)	281 (1.73)	174 (0.86)	89 (0.47)	102 (0.46)	687 (0.83)
Poisoning	25 (0.63)	65 (0.40)	21 (0.10)	58 (0.28)	938 (4.26)	1107 (1.33)
Bicycle	0	2 (0.01)	17 (0.08)	39 (0.19)	54 (0.25)	112 (0.13)
Firearm	11 (0.28)	71 (0.44)	73 (0.36)	225 (1.09)	2331 (10.58)	2711 (3.26)
Fall	12 (0.30)	25 (0.15)	12 (0.06)	20 ().10)	108 (0.49)	177 (0.21)
Suffocation	959 (24.31)	165 (1.02)	51 (0.25)	239 (1.16)	842 (3.82)	2256 (2.71)
All intentional	311 (7.89)	386 (2.37)	118 (0.58)	418 (2.02)	3508 (15.92)	4741 (5.69)
Suicide	0	0	7 (0.03)	267 (1.29)	1659 (7.53)	1933 (2.32)
Firearm suicide	0	0	1 (—)	80 (0.39)	688 (3.03)	749 (0.90)
Homicide	311 (7.89)	385 (2.37)	111 (0.55)	150 (0.73)	1832 (8.31)	2789 (3.35)
Firearm homicide	11 (0.28)	43 (0.26)	58 (0.29)	107 (0.52)	1554 (7.05)	1773 (2.13)
Undetermined intent	108 (2.74)	82 (0.50)	29 (0.14)	38 (0.18)	137 (0.62)	394 (0.47)

*Injury data from Centers for Disease Control and Prevention: Web-based Injury Statistics Query and Reporting System (WISQARS) (website). National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (producer). Available at http://www.cdc.gov/injury/wisqars/index.html.

All cause data from Centers for Disease Control and Prevention, National Center for Health Statistics. Compressed Mortality File 1999-2010 on CDC WONDER Online Database, released January 2013. Data are compiled from Compressed Mortality File 1999-2010 Series 20 No. 2P, 2013. http://wonder.cdc.gov/cmf-icd10.html

Most of these are a result of house fires; deaths are caused by smoke inhalation and asphyxiation rather than severe burns. Children and the elderly are at greatest risk for these deaths because of difficulty in escaping from burning buildings.

Suffocation accounts for approximately 86% of all unintentional deaths in children younger than 1 yr of age. The majority of these deaths result from choking on food items, such as hot dogs, candy, grapes, and nuts. Nonfood items that can cause choking include undersize infant pacifiers, small balls, and latex balloons. However, some of these deaths may represent misclassification of children dying from sudden infant death syndrome (see Chapter 375).

Homicide is the third leading cause of injury death in children 1-4 yr of age and the second leading cause of injury death in adolescents (15-19 yr old). Homicide in the pediatric age group falls into 2 patterns: infantile and adolescent. Child homicide involves children younger than age 5 yr and represents child abuse (see Chapter 40). The perpetrator is usually a caretaker; death is generally the result of blunt trauma to the head and/or abdomen. The adolescent pattern of homicide involves peers and acquaintances and is caused by firearms in 85% of cases. The majority of these deaths involve handguns. Children between these 2 age groups experience homicides of both types.

Suicide is rare in children younger than age 10 yr; only 1% of all suicides occur in children younger than age 15 yr. The suicide rate increases markedly after the age of 10 yr, with the result that suicide is now the third leading cause of death for 15-19 yr olds. Native American teenagers are at the highest risk, followed by white males; black females have the lowest rate of suicide in this age group. Approximately 40% of teenage suicides involve firearms (see Chapter 27).

In the last decade, there has been a substantial increase in unintentional poisoning deaths among teens and young adults; in 2010 unintentional poisonings were the third leading cause of injury deaths among 15-24 year olds. Many of these were from prescription analgesic and opioid medications.

Nonfatal Injuries

Most childhood injuries do not result in death. Approximately 12% of children and adolescents receive medical care for an injury each year in hospital emergency departments, and at least an equal number are treated in physicians' offices. Of these, 2% require inpatient care and 55% have at least short-term temporary disability as a result of their injuries.

The distribution of these nonfatal injuries is very different from that of fatal trauma (Fig. 5-3). Falls are the leading cause of both emergency department visits and hospitalizations. Bicycle-related trauma is the most common type of sports and recreational injury, accounting for approximately 300,000 emergency department visits annually. Nonfatal injuries, such as anoxic encephalopathy from near-drowning, scarring and disfigurement from burns, and persistent neurologic deficits from head injury, may be associated with severe morbidity, leading to substantial changes in the quality of life for victims and their families.

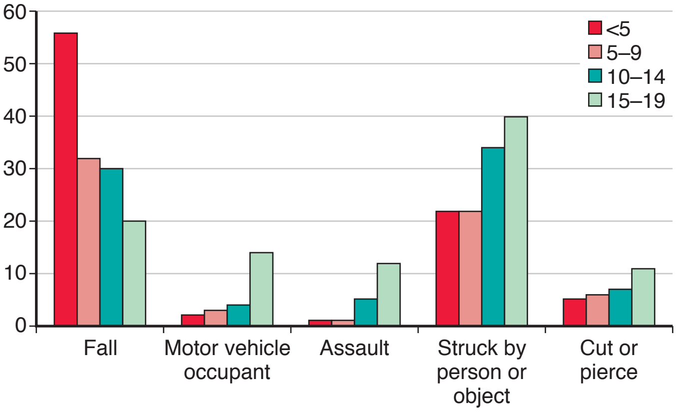

Figure 5-3 Emergency department visits for injuries, 2011. *(Data from NEISS All Injury Program operated by the Consumer Product Safety Commission for numbers of injuries. Bureau of Census for population estimates.)*

Global Child Injuries

Child injuries are a global public health issue and prevention efforts are necessary in low-, middle-, and high-income countries. Between 1990 and 2010 there was a 53% decrease in death rates of people of all ages from communicable, maternal, neonatal, and nutritional disorders whereas injury mortality rates decreased by only 16%. Worldwide, nearly 1 million children and adolescents die from injuries and violence each year, and more than 90% of these deaths are in low- and middle-income countries. As child mortality undergoes an epidemiologic transition because of better control of infectious diseases and malnutrition, injuries have and will increasingly become the leading cause of death for children in the developing world as it now is in all industrialized countries. Drowning is now the 5th most common cause of death for 5-9 yr old children globally, and in some countries, such as Bangladesh, it is the leading cause of death among children beyond the first year of life, with a rate 22 times greater than that in the Americas. An estimated 1 billion people do not currently have access to roads; as industrialization and motorization spreads, the incidence of motor vehicle crashes, injuries, and fatalities will climb. The rate of child injury death in low- and middle-income countries is 3-fold higher than that in high-income countries, and reflects both a higher incidence of many types of injuries as well as a much higher case-fatality ratio in those injured because of a lack of emergency and surgical care. As in high-income countries, prevention of child injuries and consequent morbidity and mortality is feasible with multifaceted approaches, many of which are low cost and of proven effectiveness.

PRINCIPLES OF INJURY CONTROL

Injury prevention once centered on attempts to pinpoint the innate characteristics of a child that result in greater frequency of injury. Most discount the theory of the *accident-prone child.* Although longitudinal studies have demonstrated an association between hyperactivity and impulsivity and increased rates of injury, the sensitivity and specificity of these traits for injury are extremely low. The concept of *accident proneness* is counterproductive in that it shifts attention away from potentially more modifiable factors, such as product design or the environment. It is more appropriate to examine the physical and social environment of children with frequent rates of injury than to try to identify particular personality traits or temperaments, which are difficult to modify. Children at high risk for injury are likely to be relatively poorly supervised, to have disorganized or stressed families, and to live in hazardous environments.

Efforts to control injuries include education or persuasion, changes in product design, and modification of the social and physical environment. Efforts to persuade individuals, particularly parents, to change their behaviors have constituted the greater part of injury control efforts. Speaking with parents specifically about using child car-seat restraints and bicycle helmets, installing smoke detectors, and checking the tap water temperature is likely to be more successful than offering well-meaning but too-general advice about supervising the child closely, being careful, and "childproofing" the home. This information should be geared to the developmental stage of the child and presented in moderate doses in the form of anticipatory guidance at well-child visits. Table 5-2 lists important topics to discuss at each developmental stage.

The most successful injury-prevention strategies generally are those involving changes in product design. These passive interventions protect all individuals in the population, regardless of cooperation or level of skill, and are likely to be more successful than active measures that require repeated behavior change by the parent or child. For some types of injuries, effective passive interventions are not available or feasible; we must rely heavily on attempts to change the behavior of individuals. The most important and effective product changes have been in motor vehicles. Turning down the water heater temperature,

Table 5-2	Injury Prevention Topics for Anticipatory Guidance by the Pediatrician
NEWBORN Car seats Tap water temperature Smoke detectors	
INFANT Car seats Tap water temperature Bath safety	
TODDLER AND PRESCHOOLER Car seats and booster seats Water safety Poison prevention Fall prevention	
PRIMARY SCHOOL CHILD Pedestrian skills training Water skills training Booster seats and seat belts Bicycle helmets Safe storage of firearms	
MIDDLE SCHOOL CHILD Seat belts Safe storage of firearms Water skills training	
HIGH SCHOOL AND OLDER ADOLESCENT Seat belts Alcohol and drug use, especially while driving and swimming Mobile phone use while driving Safe storage of firearms Occupational injuries	

installing smoke detectors, and using child-resistant caps on medicines and household products are other examples of effective product modifications. Many interventions require both active and passive measures. Smoke detectors provide passive protection when fully functional, but behavior change is required to ensure periodic battery changes and proper testing.

Modification of the environment often requires greater changes than individual product modification, but may be very effective in reducing injuries. Safe roadway design, decreased traffic volume and speed limits in neighborhoods, and elimination of guns from households are examples of such interventions. Included in this concept are changes in the social environment through legislation, such as laws mandating child seat restraint and seatbelt use, bicycle helmet use, and graduated driver licensing laws.

Prevention campaigns combining 2 or more of these approaches have been particularly effective in reducing injuries. The classic example is the combination of legislation and education to increase child seat restraint and seatbelt use; other examples are programs to promote bike helmet use among school-aged children and improvements in occupant protection in motor vehicles.

RISK FACTORS FOR CHILDHOOD INJURIES

Major factors associated with an increased risk of injuries to children include age, sex, race and ethnicity, socioeconomic status, rural–urban location, and the environment.

Age

Toddlers are at the greatest risk for burns, drowning, and falling. Poisonings become another risk as these children acquire mobility and exploratory behavior. Young school-age children are at greatest risk for pedestrian injuries, bicycle-related injuries (the most serious of which usually involve motor vehicles), motor vehicle occupant injuries, burns, and drowning. During the teenage years, there is a markedly increased risk from motor vehicle occupant trauma, a continued risk from drowning and burns, and the new risk of intentional trauma. Work-related injuries associated with child labor, especially for 14-16 yr olds, are an additional risk.

Injuries occurring at a particular age represent a window of vulnerability during which a child or an adolescent encounters a new task or hazard that the adolescent may not have the developmental skills to handle successfully. Toddlers do not have the judgment to know that medications can be poisonous or that some houseplants are not to be eaten; they do not understand the hazard presented by a swimming pool or an open second-story window. For young children, parents may inadvertently set up this mismatch between the skills of the child and the demands of the task. Many parents expect young school-age children to walk home from school, the playground, or the local convenience store, tasks for which most children are not developmentally ready. Likewise, the lack of skills and experience to handle many tasks during the teenage years contributes to an increased risk of injuries, particularly motor vehicle injuries. The high rate of motor vehicle crashes among 15-17 yr old teens is caused in part by inexperience, but also appears to reflect their level of development and maturity. Alcohol, other drugs, and mobile phone use substantially add to these limitations.

Age also influences the severity of injury and the risk of long-term disability. Young school-age children have an incompletely developed pelvis. In a motor vehicle crash, the seatbelt does not anchor onto the pelvis, but rides up onto the abdomen, resulting in the risk of serious abdominal injury. Age also interacts with vehicle characteristics in that most children ride in the rear seat, which in the past was equipped only with lap belts and not with lap-shoulder harnesses. Proper restraint for 4-8 yr old children requires the use of booster seats. Children younger than the age of 2 yr have much poorer outcomes from traumatic brain injuries than do older children and adolescents.

Gender

Beginning at 1-2 yr of age and continuing throughout the life span, males have higher rates of fatal injury than females. During childhood, this does not appear to be primarily a result of developmental differences between the sexes, differences in coordination, or differences in muscle strength. Variation in exposure to risk may account for the male predominance in some types of injuries. Although boys in all age groups have higher rates of bicycle-related injuries, adjusting for exposure reduces this excess rate. Boys may have higher rates of injuries because they use bicycles more frequently or for more hours. Sex differences in rates of pedestrian injuries do not appear to be caused by differences in the amount of walking, but rather reflect differences in behavior between young girls and boys. Greater risk-taking behavior, combined with greater frequency of alcohol use, may lead to the disproportionately high rate of motor vehicle crashes among teenage males. The rate of violence related injuries is higher among males because of their risk taking behavior.

Race and Ethnicity

Native Americans have the highest death rate from unintentional injuries. African-American children and adolescents have higher rates of fatal injuries than whites, whereas Asians have lower rates; rates for Hispanic children and adolescents are intermediate between those for African-Americans and those for whites. These discrepancies are even more pronounced for some injuries. The homicide rate for African-Americans age 15-19 yr was 29.6/100,000 in 2010, compared with 6.4/100,000 for American Indians and Alaskan Natives and 4.0/100,000 for whites and 2.0/100,000 for Asians. The suicide rate for Native American youth was 2.2 times the rate for whites and 4.4-fold greater than that for African-Americans. The rate of firearm homicide deaths for African-American youth ages 15-19 is nearly 9-fold higher than that for whites and 21 times that of Asian American youth.

These disparities appear to be primarily related to poverty, the educational status of parents, and the presence of hazardous environments. Homicide rates among African-Americans are nearly equivalent to those among whites, when adjusted for socioeconomic status. It is important to understand racial disparities in injury rates, but

Table 5-3 Recommended Child Restraint Methods

	INFANTS	TODDLERS (1-3)	YOUNG CHILDREN
Recommended age/ weight requirements	*Birth to 1 yr or below weight limit of seat*	*Older than 1 yr and 20-40 lb*	*40-80 lb and under 4′9″ in height; generally between 4 and 8 yr of age*
Type of seat	Infant only or rear-facing convertible	Convertible or forward-facing harness seat	Belt positioning booster seat
Seat position	Rear-facing only. Place in back seat of vehicle	Can be rear-facing until 30 lb if seat allows; generally forward-facing. Place in back seat of vehicle	Forward-facing. Place in back seat of vehicle
Notes	Children should use rear-facing seat until at least 1 yr and at least 20 lb Harness straps should be at or below shoulder level	Harness straps should be at or above shoulder level Most seats require top strap for forward-facing use	Belt positioning booster seats must be used with both lap and shoulder belts Make sure the lap belt fits low and tightly across the lap/upper thigh area and the shoulder belt fits snugly, crossing the chest and shoulder to avoid abdominal injuries

Data from http://www.safercar.gov/parents/CarSeats.htm.

inappropriate to ascribe the etiology of these differences to race or ethnicity.

Socioeconomic Status

Poverty is one of the most important risk factors for childhood injury. Mortality from fires, motor vehicle crashes, and drowning is 2-4 times higher in poor children. Death rates among both African-Americans and whites have an inverse relationship to income level: the higher the income level, the lower the death rate. Native Americans have especially high rates. Other factors are single-parent families, teenage mothers, multiple care providers, family stress, and multiple siblings; these are primarily a function of poverty rather than independent risk factors.

Rural–Urban Location

Injury rates are generally higher in rural than in urban areas. Homicide rates are higher in urban areas, as is violent crime in general. Case fatality from injury is generally twice as high in rural areas than in urban areas, reflecting both the increased severity of some injuries (such as motor vehicle crashes occurring at higher speeds) and poorer access to emergency medical services and definitive trauma care in rural areas. Some injuries are unique to rural areas, such as agricultural injuries to children and adolescents.

Environment

Poverty increases the risk of injury to children, at least in part through its effect on the environment. Children who are poor are at increased risk for injury because they are exposed to more hazards in their living environments. They may live in poor housing, which is more likely to be dilapidated and less likely to be protected by smoke detectors. The roads in their neighborhoods are more likely to be major thoroughfares. Their neighborhoods are more likely to experience higher levels of violence, and they are more likely to be victims of assault than are children and adolescents living in the suburbs. The focus on the environment is also important because it directs attention away from relatively immutable factors, such as family dynamics, poverty, and race, and directs efforts toward factors that can be changed through interventions.

MECHANISMS OF INJURY

Motor Vehicle Injuries

Motor vehicle injuries are the leading cause of serious and fatal injuries for children and adolescents. Large and sustained reductions in motor vehicle crash injuries can be accomplished by identifiable interventions.

Occupants

Injuries to passenger vehicle occupants are the predominant cause of motor vehicle deaths among children and adolescents. The peak injury and death rate for both males and females in the pediatric age group occurs between 15 and 19 yr of age (see Table 5-1). Proper restraint use in vehicles is the single most effective method for preventing serious or fatal injury. Table 5-3 shows the recommended restraints at different ages. Figure 5-4 provides examples of car safety seats.

Much attention has been given to child occupants younger than 8 yr of age. Use of child restraint devices, infant car seats, and booster seats can be expected to reduce fatalities by 71% and the risk of serious injuries by 67% in this age group. All 50 states and the District of Columbia have laws mandating their use, although the upper age limit for booster seat requirements varies by state. Physician reinforcement of the positive benefits of child seat restraints has been successful in improving parent acceptance. Pediatricians should point out to parents that toddlers who normally ride restrained behave better during car trips than children who ride unrestrained.

A detailed guide and list of acceptable devices is available from the AAP (http://www.healthychildren.org/english/safety-prevention/on-the-go/pages/car-safety-seats-information-for-families.aspx) and the National Highway Traffic Safety Administration (http://www.safecar.gov/parents/carseats.htm). Children weighing < 20 lb may use an infant seat or be placed in a convertible infant-toddler child-restraint device. Infants and toddlers younger than 1 to 2 yr or if less than manufacturer's weight limit should be placed in the rear seat facing backward; older toddlers and young children can be placed in the rear seat in a forward-facing child harness seat until it is outgrown. Emphasis must be placed on the correct use of these seats, including placing the seat in the right direction, routing the belt properly, and ensuring that the child is buckled into the seat correctly. Government regulations have made the fit between car seats and the car easier, quicker, and less prone to error. *Children younger than age 13 yr should never sit in the front seat. Inflating airbags can be lethal to infants in rear-facing seats and to small children in the front passenger seat.*

Older children are often not adequately restrained. Many children ride in the rear seat restrained with lap belts only. Booster seats have been shown to decrease the risk of injury by 59%, and should be used by children who are between 40 lb (≈4 yr of age) and 80 lb, are <8 yr of age, and are <4 ft 9 in (145 cm) tall. Many states have extended their car seat laws to include children of booster seat age as well. Shoulder straps placed behind the child or under the arm do not provide adequate crash protection and may increase the risk of serious injury. The use of lap belts alone has been associated an increased risk of seatbelt-related injuries, especially fractures of the lumbar spine and hollow-viscous injuries of the abdomen. These flexion-distraction injuries of the spine are usually accompanied by injuries to the abdominal organs.

The rear seat is clearly much safer than the front seat for both children and adults. One study of children younger than the age of 15 yr found that the risk of injury in a crash was 70% lower for children in the rear seat compared with those sitting in the front seat. Frontal

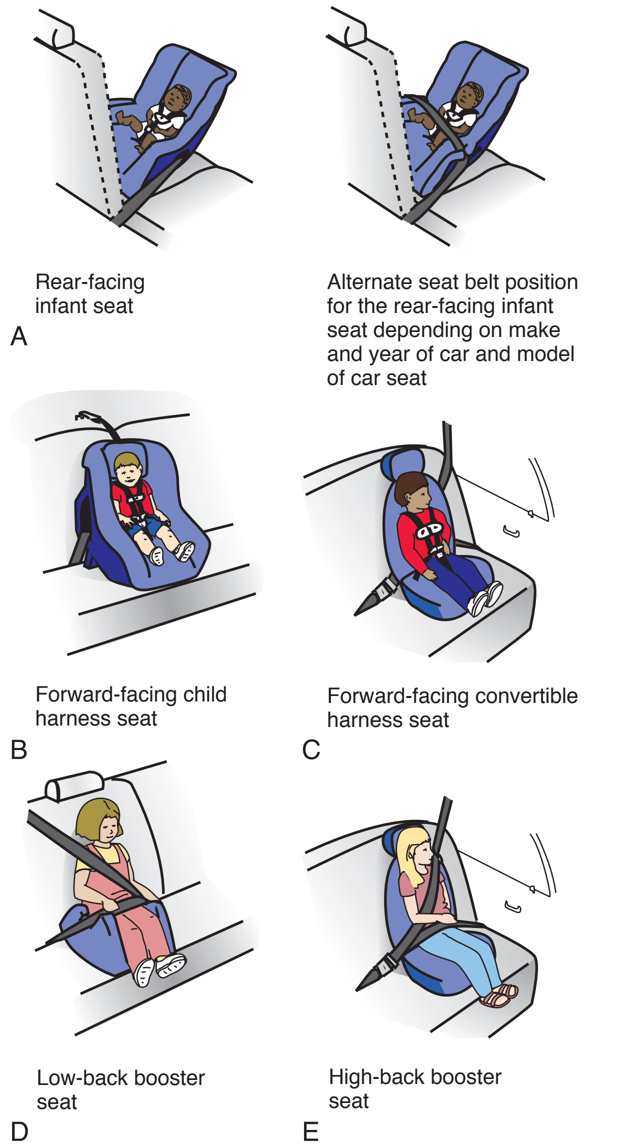

Figure 5-4 Car safety seats. **A,** Rear-facing infant seat. **B,** Forward-facing child harness seat. **C,** Forward-facing convertible harness seat. **D,** Low-back booster seat. **E,** High-back booster seat. *(From Ebel BE, Grossman DC: Crash proof kids? An overview of current motor vehicle child occupant safety strategies, Curr Probl Pediatr Adolesc Health Care 33:33–64, 2003. Source: NHTSA.)*

airbags appear to offer little protection to children in crashes and also present a risk of serious or fatal injury from the airbag itself. Side airbags also pose a risk for children who are in the front seat and are leaning against the door at the time of a crash. The safest place for children is in the rear middle seat, properly restrained for their age and size. Educational and legislative interventions to increase the number of children traveling in the rear seat have been successful.

Transportation of **premature infants** presents special problems. The possibility of oxygen desaturation, sometimes associated with bradycardia, among premature infants while in child seat restraints has led the AAP to recommend an observed trial of infants born at <37 wk of gestational age in the seat before discharge and the use of oxygen or alternative restraints for infants who experience desaturation or bradycardia, such as seats that can be reclined and used as a car bed. Car seats should only be used for travel and not as a general use infant seat around the home.

Children riding in the rear bed of pickup trucks are at special risk for injury because of the possibility of ejection from the truck and resultant serious head injury.

Teenage Drivers

Drivers 15-17 yr of age have more than twice the rate of collisions compared with motorists 18 yr of age and older. Formal driver education courses for young drivers appear to be ineffective as a primary means of decreasing the number of collisions, and in fact may increase risk by allowing younger teens to drive. The risk of serious injury and mortality is directly related to the speed at the time of the crash and inversely related to the size of the vehicle. Small, fast cars greatly increase the risk of a fatal outcome in the event of a crash.

The number of passengers traveling with teen drivers influences the risk of a crash. The risk of death for 17 yr old drivers is 50% greater when driving with 1 passenger compared with driving alone; this risk is 2.6-fold higher with 2 passengers and 3-fold higher with 3 or more passengers. The risk is also increased if the driver is male and the passengers are younger than age 30 yr.

Teens driving at night are overrepresented in crashes and fatal crashes, with nighttime crashes accounting for >33% of teen motor vehicle fatalities. Almost 50% of fatal crashes involving drivers younger than age 18 yr occur in the 4 hr before or after midnight. Teens are 5-10 times more likely to be in a fatal crash while driving at night compared with driving during the day. The difficulty of driving at night combined with the inexperience of teen drivers appears to be a deadly combination.

Another risk factor for motor vehicle crashes for people of all ages, including teens, is distracted driving from the use of mobile devices for texting or talking. In 2011, ⅓ of high school students reported they had texted or emailed while driving in the last 30 days. Dialing on a cell phone increases the risk of a crash nearly 3-fold, and texting may increase the risk as much as 6-fold. Although 44 states have banned text messaging for all drivers, the effect of state laws on prohibiting such behavior well driving is unknown. Parents should set limits on the use of these devices by their teens; technological interventions that can block cell phone signals in a moving vehicle may also be available.

Graduated licensing laws (GLLs) consist of a series of steps over a designated period before a teen can get full, unrestricted driving privileges. In a 3-stage graduated license, the student driver must first pass vision and knowledge-based tests. This is followed by obtaining a learner's permit and once a specific age has been achieved and driving skills advanced, the student driver is eligible to take the driving test. Once given the provisional license, the new driver will have a specified time to do low-risk driving. GLLs usually place initial restrictions on the number of passengers (especially teenaged) allowed in the vehicle and restrict driving during nighttime. There is a decrease in the number of crashes of 10-30% among the youngest drivers in states with a GLL system. The characteristics of GLLs vary substantially across states.

Alcohol use is a major cause of motor vehicle trauma among adolescents. The combination of inexperience in driving and inexperience with alcohol is particularly dangerous. Approximately 20% of all deaths from motor vehicle crashes in this age group are the result of alcohol intoxication, with impairment of driving seen at blood alcohol concentrations as low as 0.05 g/dL. Approximately 30% of adolescents report riding with a driver who had been drinking and approximately 10% report driving after drinking. All states have adopted a zero tolerance policy, which defines any measurable alcohol content as legal intoxication, to adolescent drinking while driving. All adolescent motor vehicle injury victims should have their blood alcohol concentration measured in the emergency department and be screened for high-risk alcohol use with a validated screening test (such as the CRAFFT or Alcohol Use Disorders Identification Test [AUDIT] screening tools) to identify those with alcohol abuse problems (see Chapter 114.1). Individuals who have evidence of alcohol abuse should not leave the emergency department or hospital without plans for appropriate alcohol abuse treatment. Interventions for problem drinking can be effective in decreasing the risk of subsequent motor vehicle crashes. Even brief interventions in the emergency department using motivational interviewing can be successful in decreasing adolescent problem drinking.

Another cause of impaired driving is marijuana use. In 2011, nearly one-quarter of high school students reported using marijuana in the prior 30 days. Marijuana use doubles the risk of a crash; as with alcohol,

this effect may be more pronounced with less experienced drivers. As of this writing, two states (Washington and Colorado) have legalized the sale of marijuana for adults; the effects of this on adolescent injury remains to be determined.

All-Terrain Vehicles. All-terrain vehicles (ATVs) in many parts of the country are an important cause of injuries to children and adolescents. These vehicles can attain high speeds and are prone to rollover because of their high center of gravity. Orthopedic and head injuries are the most common serious injuries seen among children involved in ATV crashes. Helmets can significantly decrease the risk and severity of head injuries among ATV riders, but current use is very low. Voluntary industry efforts to decrease the risk of injuries appear to have had little effect in making ATVs safer. The AAP recommends that children younger than 16 yr of age should not ride on ATVs.

Bicycle Injuries. Each year in the United States, approximately 300,000 children and adolescents are treated in emergency departments for bicycle-related injuries, making this one of the most common reasons that children with trauma visit emergency departments. The majority of severe and fatal bicycle injuries involve head trauma. A logical step in the prevention of these head injuries is the use of helmets. Helmets are very effective, reducing the risk of all head injury by 85% and the risk of traumatic brain injury by 88%. Helmets also reduce injuries to the mid and upper face by as much as 65%. Pediatricians can be effective advocates for the use of bicycle helmets and should incorporate this advice into their anticipatory guidance schedules for parents and children. Appropriate helmets are those with a firm polystyrene liner that fit properly on the child's head. Parents should avoid buying a larger helmet to give the child "growing room."

Promotion of helmet use can and should be extended beyond the pediatrician's office. Community education programs spearheaded by coalitions of physicians, educators, bicycle clubs, and community service organizations have been successful in promoting the use of bicycle helmets to children across the socioeconomic spectrum, resulting in helmet use rates of 60% or more with a concomitant reduction in the number of head injuries. Passage of bicycle helmet laws also leads to increased helmet use.

Consideration should also be given to other types of preventive activities, although the evidence supporting their effectiveness is limited. Bicycle paths are a logical method for separating bicycles and motor vehicles.

Pedestrian Injuries. Pedestrian injuries are an important of traumatic death for children and adolescents in the United States and in most high-income countries. In low-income countries, a much higher proportion of motor vehicle fatalities are pedestrians, especially among 5-14 year olds. Although case fatality rates are <5%, serious nonfatal injuries constitute a much larger problem, resulting in 60,000 emergency department visits annually for children and adolescents. Pedestrian injuries are the most important cause of traumatic coma in children and a frequent cause of serious lower extremity fractures, particularly in school-age children.

Most injuries occur during the day, with a peak in the after-school period. Improved lighting or reflective clothing would be expected to prevent few injuries. Surprisingly, approximately 30% of pedestrian injuries occur while the individual is in a marked crosswalk, perhaps reflecting a false sense of security and decreased vigilance in these areas. The risk of pedestrian injury is greater in neighborhoods with high traffic volumes, speeds greater than ≈25 mph, absence of play space adjacent to the home, household crowding, and low socioeconomic status.

One important risk factor for childhood pedestrian injuries is the developmental level of the child. Children < 5 yr are at risk for being run over in the driveway. Few children < 9 or 10 yr of age have the developmental skills to successfully negotiate traffic 100% of the time. Young children have poor ability to judge the distance and speed of traffic and are easily distracted by playmates or other factors in the environment. Many parents are not aware of this potential mismatch between the abilities of the young school-age child and the skills needed to cross streets safely. The use of mobile phones and devices has become increasingly common while walking, and can increase the risk of being struck by a motor vehicle.

Prevention of pedestrian injuries is difficult, but should consist of a multifaceted approach. Education of the child in pedestrian safety should be initiated at an early age by the parents and continue into the school-age years. Younger children should be taught never to cross streets when alone; older children should be taught (and practice how) to negotiate quiet streets with little traffic. Major streets should not be crossed alone until the child is at least 10 yr of age or older and has been observed to follow safe practices.

Legislation and police enforcement are important components of any campaign to reduce pedestrian injuries. Right-turn-on-red laws increase the hazard to pedestrians. In many cities, few drivers stop for pedestrians in crosswalks, a special hazard for young children. Engineering changes in roadway design are extremely important as passive prevention measures. Most important are measures to slow the speed of traffic and to route traffic away from schools and residential areas; these efforts are endorsed by parents and can decrease the risk of injuries and death by 10-35%. Other modifications include networks of 1-way streets, proper placement of transit or school bus stops, sidewalks in urban and suburban areas, edge stripping in rural areas to delineate the edge of the road, and curb parking regulations. Comprehensive traffic "calming" schemes using these strategies have been very successful in reducing child pedestrian injuries in Sweden, the Netherlands, Germany, and increasingly, the United States.

Ski- and Snowboard-Related Head Injuries. The increasing use of helmets in snow sports, such as skiing and snowboarding, is encouraging .since head injuries are the most common cause of death in these sports, and helmets reduce the risk of head injury by 50% or more. Use of helmets does not result in skiers or snow boarders taking more risks and should be encouraged in all snow sports.

Fire- and Burn-Related Injuries. See Chapter 75.

Poisoning. See Chapter 63.

Drowning. See Chapter 74.

Traumatic Brain Injury. See Chapter 68.

Firearm Injuries. Injuries to children and adolescents involving firearms occur in 3 different situations: unintentional injury, suicide attempt, and assault. The injury induced may be fatal or may result in permanent sequelae.

Unintentional firearm injuries and deaths have continued to decrease and accounted for 134 deaths in 2010, representing only a very small fraction of all firearm injuries among children and adolescents. The majority of these deaths occur to teens during hunting or recreational activities. **Suicide** is the third most common cause of death from all causes in both males and females ages 10-19 yr. During the 1950s to 1970, suicide rates for children and adolescents more than doubled; firearm suicide rates peaked in 1994 and decreased by 59% from this peak by 2010. The difference in the rate of suicide death between males and females is related to the differences in method used during attempts. Women die less often in suicide attempts, partly because they use less-lethal means (mainly drugs) and perhaps have a lower degree of intent. The use of firearms in a suicidal act usually converts an attempt into a fatality.

Homicides are second only to motor vehicle crashes among causes of death in teenagers older than 15 yr. In 2010, 1,832 adolescents age 15-19 yr were homicide victims; African American teenagers accounted for 52% of the total, making homicides the most common cause of death among African-American teenagers. Hispanic teenagers accounted for nearly 17% of the homicide deaths in this age group. In 2010, 85% of homicides among teenage males involved firearms, the majority of which are handguns.

In the United States, approximately 34% of households owned guns in 2012. Handguns account for approximately 30% of the firearms in use today, yet they are involved in 80% of criminal and other firearm misuse. Home ownership of guns increases the risk of adolescent suicide 3- to 10-fold and the risk of adolescent homicide up to 4-fold. In homes with guns, the risk to the occupants is far greater than the chance that the gun will be used against an intruder; for every death

occurring in self-defense, there may be 1.3 unintentional deaths, 4.6 homicides, and 37 suicides.

Of all firearms, handguns pose the greatest risk to children and adolescents. Access to handguns by adolescents is surprisingly common and is not restricted to those involved in gang or criminal activity. Stricter approaches to reduce youth access to handguns, rather than all firearms, would appear to be the most appropriate focus of efforts to reduce shooting injuries in children and adolescents.

Locking and unloading guns as well as storing ammunition locked in a different location substantially reduces the risk of a suicide or unintentional firearm injury among youth by up to 73%. Because up to 30% of handgun-owning households have at least 1 firearm stored unsafely, 1 potential approach to reducing these injuries could focus on improving household firearm storage practices where children and youth reside or visit. The evidence regarding the effectiveness of office-based counseling to influence firearm storage practice is mixed.

Adolescents with mental health conditions and alcoholism are at particularly high risk for firearm injury. In the absence of conclusive evidence, physicians should continue to work with families to eliminate access to guns in these households.

Falls. Falls are the leading cause of nonfatal injury in children and adolescents. Altogether, there were 2.9 million falls that led to emergency department visits in 2011 for children and adolescents; approximately 1.7% of these visits led to a hospitalization. There have been relatively few in-depth analytic studies of falls, except in particular circumstances, such as playground injuries. Strategies to prevent falls depend on the environmental circumstances and social context in which they occur. Window falls have been successfully prevented with the use of devices that prevent egress, and injuries from playground falls can be mitigated through the use of proper surfacing, such as woodchips or other soft, energy-absorbing materials. Alcohol may also contribute to falls among teenagers, and these injuries can be reduced by general strategies to reduce teen alcohol use.

Violent Behavior and Aggression. Although the current rates of homicide are much lower than they were at their peak in the late 1980s and early 1990s, the problem of violence and assault is still large. The origins of adult and teen violence occur during childhood. Adults who commit violent acts usually have a history of violent behavior during childhood or adolescence. Longitudinal studies following groups of individuals from birth have found that aggression occurs among infants and that most children learn to control this aggression early in childhood. Children who later become violent adolescents and adults do not learn to control this aggressive behavior.

The most successful interventions for violence target young children and their families. These include home visits by nurses and paraprofessionals beginning in the prenatal period and continuing for the first few years of life to provide support and guidance to parents, especially parents without other resources. Enrollment in early childhood education programs (e.g. Head Start) starting at age 3 yr has been shown to be effective in improving school success, keeping children in school, and decreasing the chance that the child will be a delinquent adolescent. School-based interventions, including curricula to increase the social skills of children and improve the parenting skills of caregivers, have long-term effects on violence and risk-taking behavior. Early identification of behavior problems by primary care pediatricians can best be accomplished through the routine use of formal screening tools. Interventions in adolescence, such as family therapy, multisystemic therapy, and therapeutic foster care, can decrease problem behavior and a subsequent decline into delinquency and violence.

Psychosocial Consequences of Injuries

Many children and their parents have substantial psychosocial sequelae from trauma. Studies in adults indicate that 10-40% of hospitalized injured patients will have posttraumatic stress disorder (PTSD; see Chapter 25). Among injured children involved in motor vehicle crashes, 90% of families will have symptoms of acute stress disorder after the crash, although the diagnosis of acute stress disorder is not predictive of later PTSD. Standardized questionnaires that collect data from the child, the parents, and the medical record at the time of initial injury can serve as useful screening tests for later development of PTSD. Early mental health intervention, with close follow-up, is important for the treatment of PTSD and for minimizing its effect on the child and family.

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Growth, Development, and Behavior

PART II

Chapter 6
Overview and Assessment of Variability

Susan Feigelman

The field of pediatrics is dedicated to optimizing the growth and development of each child. Pediatricians require knowledge of normal growth, development, and behavior in order to effectively monitor children's progress, identify delays or abnormalities in development, obtain needed services, and counsel parents and caretakers. To alter factors that increase or decrease risk, pediatricians need to understand how biologic and social forces interact within the parent-child relationship, within the family, and between the family and the larger society. Growth is an indicator of overall well-being, status of chronic disease, and interpersonal and psychologic stress. By monitoring children and families over time, pediatricians are uniquely situated to observe the interrelationships between physical growth and cognitive, motor, and emotional development. Observation is enhanced by familiarity with developmental theory and understanding of developmental models which describe normal patterns of behavior and provide guidance for prevention of behavior problems.

BIOPSYCHOSOCIAL MODEL AND ECOBIODEVELOPMENTAL FRAMEWORK: MODELS OF DEVELOPMENT

The medical model presumes that a patient presents with signs and symptoms and a physician focuses on diagnosing and treating diseases of the body. This model neglects the psychologic aspect of a person who exists in the larger realm of the family and society. In the **biopsychosocial model**, higher-level systems are simultaneously considered with the lower-level systems that make up the person and the person's environment (Fig. 6-1). A patient's symptoms are examined and explained in the context of the patient's existence. This basic model can be used to understand health and both acute and chronic disease.

With the advances in neurology, genomics including epigenetics, molecular biology and the social sciences, a more accurate model, the **ecobiodevelopmental framework** has emerged. This framework emphasizes how the ecology of childhood (social and physical environments) interacts with biologic processes to determine outcomes and life trajectories. Early influences, particularly those producing toxic levels of stress, affect the individual through modification of gene expression, without change in DNA sequencing. These **epigenetic changes**, such as DNA methylation and histone acetylation, are a result of environmental insults. Stress responses may produce alterations in brain structure and function, leading to disruption of later coping mechanisms. These changes will produce long-lasting effects on the health and well-being of the individual and may be passed on to future generations (Fig. 6-2).

Critical to learning and remembering (and therefore development) is **neuronal plasticity**, which permits the central nervous system to reorganize neuronal networks in response to environmental stimulation, both positive and negative. An overproduction of neuronal precursors eventually leads to about 100 billion neurons in the adult brain. Each neuron develops on average 15,000 synapses by 3 yr of age. Synapses in frequently used pathways are preserved, whereas less-used ones atrophy, through neuronal "pruning." Changes in the strength and number of synapses and reorganization of neuronal circuits also play important roles in brain plasticity. Increases or decreases in synaptic activity result in persistent increases or decreases in synaptic strength. Thus experience (**environment**) has a direct effect on the physical and therefore functional properties of the brain (**genetics**). Children with different talents and temperaments (already a combination of genetics and environment) further elicit different stimuli from their (differing) environments.

Periods of behavioral development generally correlate with periods of great changes in synaptic numbers in relevant areas of the brain. Accordingly, sensory deprivation during the time when synaptic changes should be occurring has profound effects. The effects of strabismus leading to amblyopia in 1 eye may occur quickly during early childhood; likewise, patching the eye with good vision to reverse amblyopia in the other eye is less effective in late childhood (see Chapter 621). Early experience is particularly important because learning proceeds more efficiently along established synaptic pathways. Traumatic experiences also create enduring alterations in the neurotransmitter and endocrine systems that mediate the stress response, with effects noted later in life. Positive and negative experiences do not determine the total outcome, but shift the probabilities by influencing the child's ability to respond adaptively to future stimuli. The plasticity of the brain continues into adolescence, with further development of the prefrontal cortex, which is important in decision-making, future planning, and emotional control; neurogenesis persists in adulthood in certain areas of the brain, including the subventricular zone of the lateral ventricles and in portions of the hippocampus.

Biologic Influences

Biologic influences on development include genetics, in utero exposure to teratogens, the long-term negative effects of low birthweight (neonatal morbidities plus increased rates of obesity, coronary heart disease, stroke, hypertension, and type 2 diabetes), postnatal illnesses, exposure to hazardous substances, and maturation. Adoption and twin studies consistently show that heredity accounts for approximately 40% of the variance in IQ and in other personality traits, such as sociability and desire for novelty, whereas shared environment accounts for another 50%. The negative effects on development of prenatal exposure to teratogens, such as mercury and alcohol, and of postnatal insults, such as meningitis and traumatic brain injury, have been extensively studied (see Chapters 96 and 99). Any chronic illness can affect growth and development, either directly or through changes in nutrition, parenting, or peer interactions.

The age at which children walk independently is similar around the world, despite great variability in child-rearing practices. The attainment of other skills, such as the use of complex sentences, is less tightly bound to a maturational schedule. Maturational changes also generate behavioral challenges at predictable times. Decrements in growth rate and sleep requirements around 2 yr of age often generate concern about poor appetite and refusal to nap. Although it is possible to accelerate many developmental milestones (toilet training a 12 mo old or teaching a 3 yr old to read), the long-term benefits of such precocious accomplishments are questionable.

In addition to physical changes in size, body proportions, and strength, maturation brings about hormonal changes. Sexual differentiation, both somatic and neurologic, begins in utero. Both stress and reproductive hormones affect brain development as well as behavior throughout development.

Temperament describes the stable, early-appearing individual variations in behavioral dimensions, including emotionality (crying, laughing, sulking), activity level, attention, sociability, and persistence. The classic theory proposes 9 dimensions of temperament (Table 6-1). These characteristics lead to 3 common constellations: (1) the easy, highly adaptable child, who has regular biologic cycles; (2) the difficult child, who withdraws from new stimuli and is easily frustrated; and (3) the slow-to-warm-up child, who needs extra time to adapt to new circumstances. Various combinations of these clusters also occur. Temperament has long been described as biologic or "inherited." Monozygotic twins are rated by their parents as temperamentally similar more often than are dizygotic twins. Estimates of heritability suggest that genetic differences account for approximately 20-60% of the variability of temperament within a population. The remainder of the variance is attributed to the child's environment. Maternal prenatal stress and anxiety is associated with child temperament, possibly through stress hormones. However, certain polymorphisms of specific genes moderate the influence of maternal stress on infant temperament (specifically irritability) illustrating the interplay between genes and environment. Longitudinal twin studies of adult personality indicate that changes in personality over time largely result from non-shared environmental influences, whereas stability of temperament appears to result from genetic factors.

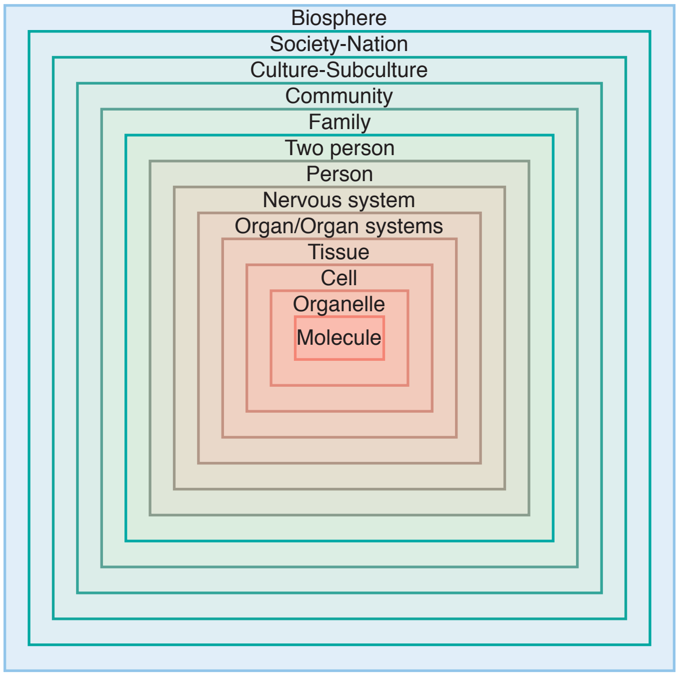

Figure 6-1 Continuum and hierarchy of natural systems in the biopsychosocial model. *(From Engel GL: The clinical application of the biopsychosocial model,* Am J Psychiatry *137:535–544, 1980.)*

The concept of temperament can help parents understand and accept the characteristics of their children without feeling responsible for having caused them. Children who have difficulty adjusting to change may have behavior problems when a new baby arrives or at the time of school entry. In addition, pointing out the child's temperament may allow for adjustment in parenting styles. Behavioral and emotional problems may develop when the temperamental characteristics of children and parents are in conflict.

Psychologic Influences: Attachment and Contingency

The influence of the child-rearing environment dominates most current models of development. Infants in hospitals and orphanages, devoid of opportunities for attachment, have severe developmental deficits. **Attachment** refers to a biologically determined tendency of a young child to seek proximity to the parent during times of stress and also to the relationship that allows securely attached children to use

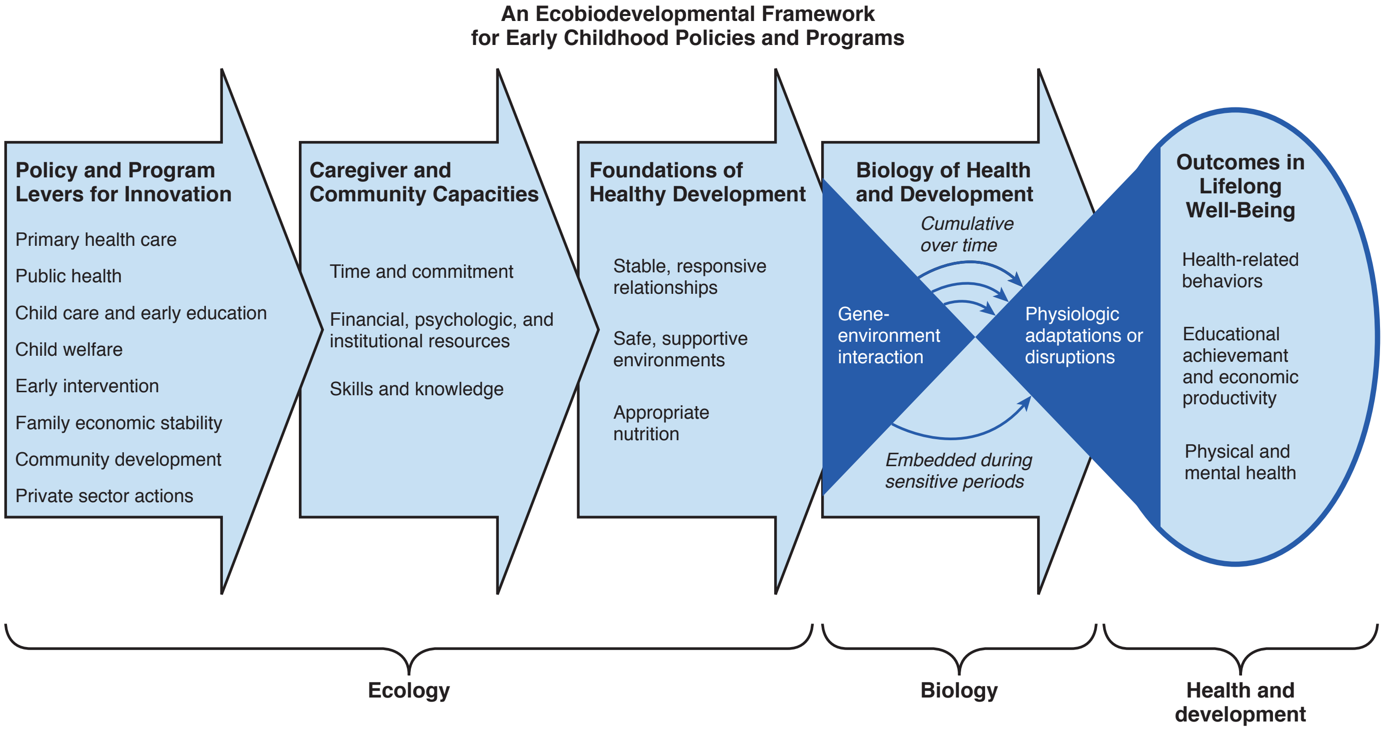

Figure 6-2 An ecobiodevelopmental framework for early childhood policies and programs. *(Adapted from Center on the Developing Child at Harvard University. The foundations of lifelong health are built in early childhood. Available at:* http://developingchild.harvard.edu/index.php/resources/reports_and_working_papers/foundations-of-lifelong-health/ *and published in* Pediatrics: *Shonkoff JP, Garner AS, The Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, and Section of Developmental and Behavioral Pediatrics: The lifelong effects of early childhood adversity and toxic stress.* Pediatrics *129(1):e232–e246, 2012.)*

Table 6-1 Temperamental Characteristics: Descriptions and Examples

CHARACTERISTIC	DESCRIPTION	EXAMPLES*
Activity level	Amount of gross motor movement	"She's constantly on the move." "He would rather sit still than run around."
Rhythmicity	Regularity of biologic cycles	"He's never hungry at the same time each day." "You could set a watch by her nap."
Approach and withdrawal	Initial response to new stimuli	"She rejects every new food at first." "He sleeps well in any place."
Adaptability	Ease of adaptation to novel stimulus	"Changes upset him." "She adjusts to new people quickly."
Threshold of responsiveness	Intensity of stimuli needed to evoke a response (e.g., touch, sound, light)	"He notices all the lumps in his food and objects to them." "She will eat anything, wear anything, do anything."
Intensity of reaction	Energy level of response	"She shouts when she is happy and wails when she is sad." "He never cries much."
Quality of mood	Usual disposition (e.g., pleasant, glum)	"He does not laugh much." "It seems like she is always happy."
Distractibility	How easily diverted from ongoing activity	"She is distracted at mealtime when other children are nearby." "He doesn't even hear me when he is playing."
Attention span and persistence	How long a child pays attention and sticks with difficult tasks	"He goes from toy to toy every minute." "She will keep at a puzzle until she has mastered it."

*Typical statements of parents, reflecting the range for each characteristic from very little to very much.
Based on Chess S, Thomas A: Temperament in clinical practice, *New York, 1986, Guilford.*

their parents to reestablish a sense of well-being after a stressful experience. Insecure attachment may be predictive of later behavioral and learning problems.

At all stages of development, children progress optimally when they have adult caregivers who pay attention to their verbal and nonverbal cues and respond accordingly. In early infancy, such contingent responsiveness to signs of overarousal or underarousal helps maintain infants in a state of quiet alertness and fosters autonomic self-regulation. **Contingent responses** (reinforcement depending on the behavior of the other) to nonverbal gestures create the groundwork for the shared attention and reciprocity that are critical for later language and social development. Children learn best when new challenges are just slightly harder than what they have already mastered, a degree of difficulty dubbed the "zone of proximal development." Psychologic forces, such as attention problems (see Chapter 33) or mood disorders (see Chapter 26), will have profound effects on many aspects of an older child's life.

Social Factors: Family Systems and the Ecologic Model

Contemporary models of child development recognize the critical importance of influences outside of the mother–child dyad. Fathers play critical roles, both in their direct relationships with their children and in supporting mothers. As traditional nuclear families become less dominant, the influence of other family members (grandparents, foster and adoptive parents, same-sex partners) becomes increasingly important. Children are increasingly raised by unrelated caregivers while parents work or while they are in foster care.

Families function as systems, with internal and external boundaries, subsystems, roles, and rules for interaction. In families with rigidly defined parental subsystems, children may be denied any decision-making, exacerbating rebelliousness. In families with poorly defined parent–child boundaries, children may be required to take on responsibilities beyond their years, or may be recruited to play a spousal role.

Family systems theory recognizes that individuals within systems adopt implicit roles. One child may be the troublemaker, whereas another is the negotiator and another is quiet. Birth order may have profound effects on personality development, through its influence on family roles and patterns of interaction. Families are dynamic. Changes in one person's behavior affect every other member of the system; roles shift until a new equilibrium is found. The birth of a new child, attainment of developmental milestones such as independent walking, the onset of nighttime fears, and the death of a grandparent are all changes that require renegotiation of roles within the family and have the potential for healthy adaptation or dysfunction.

The family system, in turn, functions within the larger systems of extended family, subculture, culture, and society. Bronfenbrenner's ecologic model depicts these relationships as concentric circles, with the parent–child dyad at the center (with associated risks and protective factors) and the larger society at the periphery. Changes at any level are reflected in the levels above and below. The shift from an industrial economy to one based on service and information is an obvious example of societal change with profound effects on families and children.

Unifying Concepts: The Transactional Model, Risk, and Resilience

The **transactional model** proposes that a child's status at any point in time is a function of the interaction between biologic and social influences. The influences are bidirectional: Biologic factors, such as temperament and health status, both affect the child-rearing environment and are affected by it. A premature infant may cry little and sleep for long periods; the infant's depressed parent may welcome this good behavior, setting up a cycle that leads to poor nutrition and inadequate growth. The child's failure to thrive may reinforce the parent's sense of failure as a parent. At a later stage, impulsivity and inattention associated with early, prolonged undernutrition may lead to aggressive behavior. The cause of the aggression in this case is not the prematurity, the undernutrition, or the maternal depression, but the interaction of all these factors (Fig. 6-3). Conversely, children with biologic risk factors may nevertheless do well developmentally if the child-rearing environment is supportive. Premature infants with electroencephalographic evidence of neurologic immaturity may be at increased risk for cognitive delay. This risk may only be realized when the quality of parent–child interaction is poor. When parent–child interactions are optimal, prematurity carries a reduced risk of developmental disability.

Children growing up in poverty experience multiple levels of developmental risk: increased exposure to biologic risk factors, such as environmental lead and undernutrition, lack of stimulation in the home, and decreased access to interventional education and therapeutic experiences. As they respond by withdrawal or acting out, they further discourage positive stimulation from those around them.

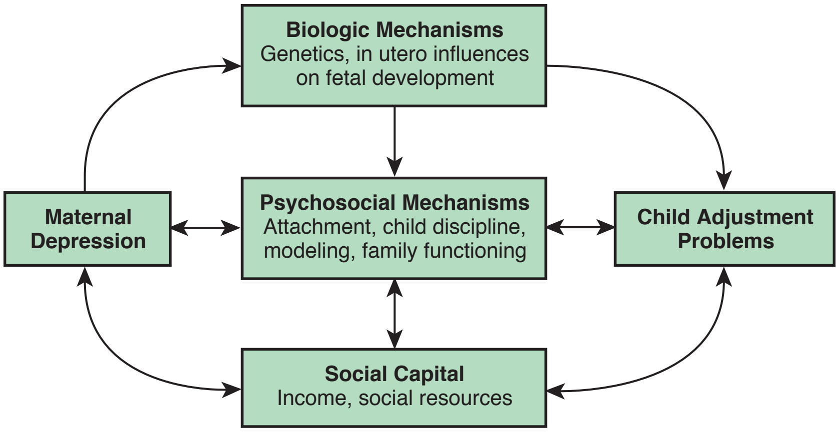

Figure 6-3 Theoretical model of mutual influences on maternal depression and child adjustment. *(From Elgar FJ, McGrath PJ, Waschbusch DA, et al: Mutual influences on maternal depression and child adjustment problems,* Clin Psychol Rev *24:441–459, 2004.)*

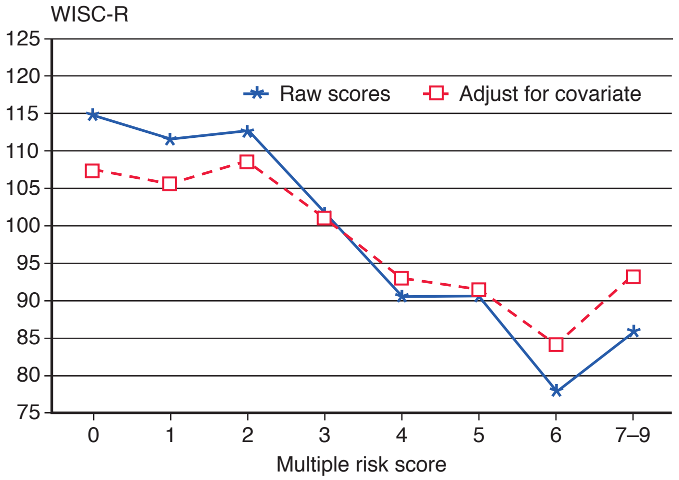

Figure 6-4 Relationship between mean IQ scores at 13 yr (both raw and adjusted for covariation of mother's IQ), as related to the number of risk factors. *WISC-R,* Wechsler Intelligence Scale-Revised. *(From Sameroff AJ, Seifer R, Baldwin A, et al: Stability of intelligence from preschool to adolescence; the influence of social and family risk factors,* Child Dev *64:80–97, 1993.)*

Children of adolescent mothers are also at risk. When early intervention programs provide timely, intensive, comprehensive, and prolonged services, at-risk children show marked and sustained upswings in their developmental trajectory. Early identification of children at developmental risk, along with early intervention to support parenting, is critically important.

An estimate of developmental risk can begin with a tally of risk factors, such as low income, limited parental education, and lack of neighborhood resources. There is a direct relationship between developmental outcome at age 13 yr and the number of social and family risk factors at age 4 yr (Fig. 6-4). Both individual stress and community-level poverty and disorder are associated with shortened telomeres in salivary samples, a link to health disparities. Protective (resilience) factors must also be considered. These factors, like risk factors, may be either biologic (temperamental persistence, athletic talent) or social. The personal histories of children who overcome poverty often include at least 1 trusted adult (parent, grandparent, teacher) with whom the child has a special, supportive, close relationship.

Developmental Domains and Theories of Emotion and Cognition

Child development can also be tracked by the child's developmental progress in particular domains, such as gross motor, fine motor, social, emotional, language, and cognition. Within each of these categories are developmental lines or sequences of changes leading up to particular attainments. Developmental lines in the gross motor domain, leading from rolling to creeping to independent walking, are obvious. Others, such as the line leading to the development of conscience, are more subtle.

The concept of a developmental line implies that a child passes through successive stages. Several psychoanalytic theories are based on stages as qualitatively different epochs in the development of emotion and cognition (Table 6-2). In contrast, behavioral theories rely less on qualitative change and more on the gradual modification of behavior and accumulation of competence.

Psychoanalytic Theories

At the core of **Freudian theory** is the idea of body-centered (or, broadly, "sexual") drives; the emotional health of both the child and the adult depends on adequate resolution of these conflicts. Although Freudian ideas have been challenged, they opened the door to subsequent theories of development.

Erikson recast Freud's stages in terms of the emerging personality (see Table 6-2). The child's sense of basic trust develops through the successful negotiation of infantile needs. As children progress through these psychosocial stages, different issues become salient. It is predictable that a toddler will be preoccupied with establishing a sense of autonomy, whereas a late adolescent may be more focused on establishing meaningful relationships and an occupational identity. Erikson recognized that these stages arise in the context of Western European societal expectations; in other cultures, the salient issues may be quite different.

Erikson's work calls attention to the intrapersonal challenges facing children at different ages in a way that facilitates professional intervention. Knowing that the salient issue for school-age children is industry vs inferiority, pediatricians inquire about a child's experiences of mastery and failure and (if necessary) suggest ways to ensure adequate successes.

Cognitive Theories

Cognitive development is best understood through the work of **Piaget**. A central tenet of Piaget's work is that cognition changes in quality, not just quantity (see Table 6-2). During the sensorimotor stage, an infant's thinking is tied to immediate sensations and a child's ability to manipulate objects. The concept of "in" is embodied in a child's act of putting a block into a cup. With the arrival of language, the nature of thinking changes dramatically; symbols increasingly take the place of objects and actions. Piaget described how children actively construct knowledge for themselves through the linked processes of assimilation (taking in new experiences according to existing schemata) and accommodation (creating new patterns of understanding to adapt to new information). In this way, children are continually and actively reorganizing cognitive processes.

Table 6-2 Classic Stage Theories

	INFANCY (0-1 YR)	TODDLERHOOD (2-3 YR)	PRESCHOOL (3-6 YR)	SCHOOL AGE (6-12 YR)	ADOLESCENCE (12-20 YR)
Freud: psychosexual	Oral	Anal	Phallic/oedipal	Latency	Genital
Erikson: psychosocial	Basic trust vs mistrust	Autonomy vs shame and doubt	Initiative vs guilt	Industry vs inferiority	Identity vs role diffusion
Piaget: cognitive	Sensorimotor	Sensorimotor	Preoperational	Concrete operations	Formal operations
Kohlberg: moral	—	Preconventional: avoid punishment/obtain rewards (stages 1 and 2)	Conventional: conformity (stage 3)	Conventional: law and order (stage 4)	Postconventional: moral principles

Piaget's basic concepts have held up well. Challenges have included questions about the timing of various stages and the extent to which context may affect conclusions about cognitive stage. Children's understanding of cause and effect may be considerably more advanced in the context of sibling relationships than in the manipulation and perception of inanimate objects. In many children, logical thinking appears well before puberty, the age postulated by Piaget. Of undeniable importance is Piaget's focus on cognition as a subject of empirical study, the universality of the progression of cognitive stages, and the image of a child as actively and creatively interpreting the world.

Piaget's work is of special importance to pediatricians for 3 reasons: (1) Piaget's observations provide insight into many puzzling behaviors of infancy, such as the common exacerbation of sleep problems at 9 and 18 mo of age. (2) Piaget's observations often lend themselves to quick replication in the office, with little special equipment. (3) Open-ended questioning, based on Piaget's work, can provide insights into children's understanding of illness and hospitalization.

Based on cognitive development, **Kohlberg** developed a theory of moral development in 6 stages, from early childhood through adulthood. Preschoolers' earliest sense of right and wrong is egocentric, motivated by externally applied controls. In later stages, children perceive equality, fairness, and reciprocity in their understanding of interpersonal interactions through perspective-taking. Most youth will reach stage 4, conventional morality, by mid to late adolescence. The basic theory has been modified to distinguish morality from social conventions. Whereas moral thinking considers interpersonal interactions, justice, and human welfare, social conventions are the agreed-on standards of behavior particular to a social or cultural group. Within each stage of development, children are guided by the basic precepts of moral behavior, but also may take into account local standards, such as dress code, classroom behavior, and dating expectations. Additional studies have even demonstrated some protomorality in infants.

Behavioral Theory

This theoretical perspective distinguishes itself by its lack of concern with a child's inner experience. Its sole focus is on observable behaviors and measurable factors that either increase or decrease the frequency with which these behaviors occur. No stages are implied; children, adults, and, indeed, animals all respond in the same way. In its simplest form, the behaviorist orientation asserts that behaviors that are positively reinforced occur more frequently; behaviors that are negatively reinforced or ignored occur less frequently. The strengths of this position are its simplicity, wide applicability, and conduciveness to scientific verification. A behavioral approach lends itself to interventions for various common problems, such as temper tantrums, aggressive preschool behavior, and eating disorders in which behaviors are broken down into discrete units. In cognitively limited children and children with autism spectrum disorders (see Chapter 30), behavioral interventions using **applied behavior analysis** approaches have demonstrated their ability to teach new, complex behaviors. Applied behavior analysis has been particularly useful in the treatment of early-diagnosed autism (see Chapter 30.1). However, in cases in which misbehavior is symptomatic of an underlying emotional, perceptual, or family problem, an exclusive reliance on behavior therapy risks leaving the cause untreated. Behavioral approaches can be taught to parents to apply at home.

Theories Commonly Employed in Behavioral Interventions

An increasing number of programs or interventions (within and outside of the physician's office) are designed to influence behavior; some of these models are based on behavioral or cognitive theory or may have attributes of both. The most commonly employed models are the Health Belief Model, Theory of Reasoned Action, Theory of Planned Behavior, Social Cognitive Theory, and the Transtheoretical Model, which is also known as Stages of Change Theory. Pediatricians should be aware of these models; Table 6-3 shows the similarities and differences between these models. Interventions based on these theories have been designed for children and adolescents in community, clinic, and hospital-based settings.

Motivational interviewing is a technique often used in clinical settings to bring about behavior change, rather than a behavioral theory. The goal in using the technique is to enhance an individual's motivation to change behavior by exploring and removing ambivalence. This may be practiced by an individual practitioner and is taught in some pediatric residency programs. Motivational interviewing emphasizes the importance of the therapist (which may be a pediatrician, other physician, psychologist, social worker, etc.) understanding the client's perspective and displaying unconditional support. The therapist is a partner rather than an authority figure and recognizes that, ultimately, the patient has control over the patient's choices.

Statistics Used in Describing Growth and Development

(See Chapters 15 and 16.)

In everyday use, the term *normal* is synonymous with *healthy*. In a statistical sense, *normal* means that a set of values generates a normal (bell-shaped or gaussian) distribution. This is the case with anthropometric quantities, such as height and weight, and with many developmental milestones, such as the age of independent standing. For a **normally distributed measurement**, a histogram with the quantity (height, age) on the *x*-axis and the frequency (the number of children of that height, or the number who stand on their own at that age) on the *y*-axis generates a bell-shaped curve. In an ideal bell-shaped curve, the peak corresponds to the arithmetic mean (average) of the sample and to the median and the mode as well. The **median** is the value above and below which 50% of the observations lie; the mode is the value having the highest number of observations. Distributions are termed *skewed* if the mean, median, and mode are not the same number.

The extent to which observed values cluster near the mean determines the width of the bell and can be described mathematically by the **standard deviation (SD)**. In the ideal normal curve, a range of values extending from 1 SD below the mean to 1 SD above the mean includes approximately 68% of the values, and each "tail" above and

Table 6-3 Similar or Identical Elements Within 5 Health-Behavior Theories

CONCEPT	GENERAL TENET OF THE CONCEPT "ENGAGING IN THE BEHAVIOR IS LIKELY IF …"	HEALTH BELIEF MODEL	THEORY OF REASONED ACTION	THEORY OF PLANNED BEHAVIOR	SOCIAL COGNITIVE THEORY	TRANSTHEORETICAL MODEL
ATTITUDINAL BELIEFS						
Appraisal of the positive and negative aspects of the behavior and expected outcome of the behavior	The positive aspects outweigh the negative aspects	Benefits, barriers/ health motive	Behavioral beliefs and evaluation of those beliefs (attitudes)	Behavioral beliefs and evaluation of those beliefs (attitudes)	Outcome expectations/ expectancies	Pros, cons (decisional balance)
SELF-EFFICACY BELIEFS/BELIEFS ABOUT CONTROL OVER THE BEHAVIOR						
Belief in one's ability to perform the behavior; confidence	One believes in their ability to perform the behavior	Self-efficacy	—	Perceived behavioral control	Self-efficacy	Self-efficacy/temptation
NORMATIVE AND NORM-RELATED BELIEFS AND ACTIVITIES						
Belief that others want you to engage in the behavior (and one's motivation to comply); may include actual support of others	One believes that people important to one want one to engage in the behavior; person has others' support	Cues from media, friends (cues to action)	Normative beliefs and motivation to comply (subjective norms)	Normative beliefs and motivation to comply (subjective norms)	Social support	Helping relationships (process of change)
Belief that others (e.g., peers) are engaging in the behavior	One believes that other people are engaging in the behavior	—	—	—	Social environment/ norms; modeling	Social liberation (process of change)
Responses to one's behavior that increase or decrease the likelihood one will engage in the behavior; may include reminders	One receives positive reinforcement from others or creates positive reinforcements for one's self	Cues from media, friends (cues to action)	—	—	Reinforcement	Reinforcement management/stimulus control (processes of change)
RISK-RELATED BELIEFS AND EMOTIONAL RESPONSES						
Belief that one is at risk if one does not engage in the behavior, and that the consequences may be severe; may include actually experiencing negative emotions or symptoms and coping with them	One feels at risk with regard to a negative outcome or disease	Perceived susceptibility/ severity (perceived threat)	—	—	Emotional coping responses/ expectancies about environmental cues	Dramatic relief (process of change)
INTENTION/COMMITMENT/PLANNING						
Intending or planning to perform the behavior; setting goals or making a commitment to perform the behavior	One has formed strong behavioral intentions to engage in the behavior; one has set realistic goals or made a firm commitment to engage in the behavior	—	Behavioral intentions	Behavioral intentions	Self-control/ self-regulation	Contemplation/ preparation (stages of change); self-liberation (process of change)

From Noar SM, Zimmerman RS: Health behavior theory and cumulative knowledge regarding health behaviors: are we moving in the right direction? Health Educ Res *20:275–290, 2005, Table 1.*

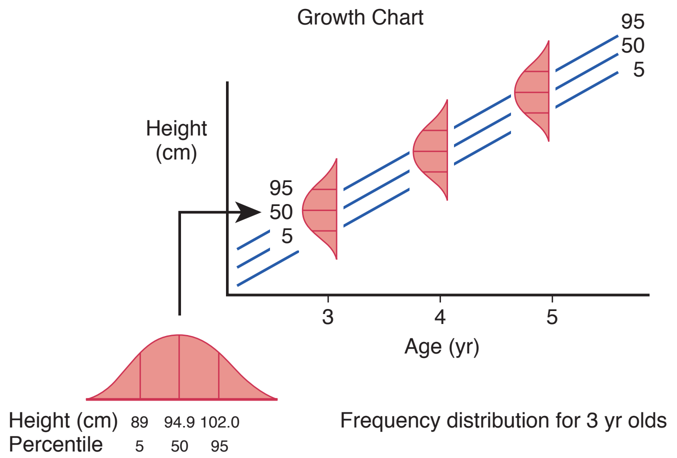

Figure 6-5 Relationship between percentile lines on the growth curve and frequency distributions of height at different ages.

Table 6-4 Relationship Between SD and Normal Range for Normally Distributed Quantities

OBSERVATIONS INCLUDED IN THE NORMAL RANGE		PROBABILITY OF A "NORMAL" MEASUREMENT DEVIATING FROM THE MEAN BY THIS AMOUNT	
SD	**%**	**SD**	**%**
±1	68.3	≥1	16.0
±2	95.4	≥2	2.3
±3	99.7	≥3	0.13

below that range contains 16% of the values. A range encompassing ±2 SD includes 95% of the values (with the upper and lower tails each comprising approximately 2.5% of the values), and ±3 SD encompasses 99.7% of the values (Table 6-4 and Fig. 6-5).

For any single measurement, its distance away from the mean can be expressed in terms of the number of SDs (also called a *z score*); one can then consult a table of the normal distribution to find out what percentage of measurements fall within that distance from the mean. Software to convert anthropometric data into z scores for epidemiologic purposes is available. A measurement that falls "outside the normal range"—arbitrarily defined as 2, or sometimes 3, SDs on either side of the mean—is atypical, but not necessarily indicative of illness. The further a measurement (say, height, weight, or IQ) falls from the mean, the greater the probability that it represents not simply normal variation, but rather a different, potentially pathologic, condition.

Another way of relating an individual to a group uses percentiles. The **percentile** is the percentage of individuals in the group who have achieved a certain measured quantity (e.g., a height of 95 cm) or a developmental milestone (e.g., walking independently). For anthropometric data, the percentile cutoffs can be calculated from the mean and SD. The 5th, 10th, and 25th percentiles correspond to −1.65 SD, −1.3 SD, and −0.7 SD, respectively. Figure 6-4 demonstrates how frequency distributions of a particular parameter (height) at different ages relate to the percentile lines on the growth curve.

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Chapter 7

Cognitive Development: Domains and Theories

Alison Gopnik

From Freud to Skinner to Piaget, philosophers, psychologists, and psychiatrists used to think that babies and young children were solipsistic and egocentric, precausal and illogical, concrete and superficial, restricted to the immediate here and now. That is still the picture most parents and many pediatricians have of babies and young children.

But 3 decades of research shows that just the opposite is true. Even the youngest babies both know more and learn more than we would ever have thought. There are still many controversies about exactly what babies and children know and when they know it. There also are competing theories about how and why children know and learn so much.

METHODOLOGIES

Much of this new understanding is the result of new techniques. Psychoanalysts asked adults to remember their childhood, behaviorists extrapolated from experiments on animals, and even Jean Piaget, the founder of the field of cognitive development, relied on observing the spontaneous behavior of babies, or on clinical interviews in which he asked children to say what they thought about mind and body or life and death. We now have experimental techniques that let children tell us what they know in their own language.

One group of methods involves seeing what babies prefer to look at (visual preferences), or listen to, or even smell. Babies have a choice of two stimuli, such as a mother's voice playing in one speaker, while a stranger's plays in another. We can see if babies turn toward one stimuli or the other.

Other methods use the fact that babies pay more attention to things that are unexpected than to those that are more predictable or familiar. Babies are *habituated* to a stimulus; they look or listen until their attention wanders, and when they see a variant of that stimulus they focus attention to the new stimulus if it is different. In *violation-of-expectation* studies, experimenters present babies with events that are surprising from an adult point of view, for example, one object apparently moving through another, and see whether babies look longer at those events than at similar unsurprising events.

These *looking-time* techniques have a drawback: it is difficult to tell just how babies interpret the stimulus by simply recording whether they look at it. Other technologies have made it possible to actually track babies' eye movements as they look at a stimulus. We can also look at what babies do as well as at what they attend to. Watching where babies reach or what they point to can be highly informative. Babies begin to imitate other people literally from birth and seeing how that imitation unfolds has proved to be a particularly useful tool.

As children grow older their attention patterns become less predictable. On the other hand, we can listen to what toddlers and preschoolers say. Large databases that record and analyze children's spontaneous language are becoming increasingly sophisticated, and can be an invaluable source of insight.

Asking preschoolers what they think often produces a sort of stream-of-consciousness poem, and has undoubtedly contributed to the impression that preschoolers are irrational. Children behave much more intelligently when you ask them about restricted, highly detailed scenarios. Instead of asking "Can someone believe something that isn't true?," researchers tell children a specific story—Max sees some

chocolate in the yellow cupboard, but then it is transferred to the blue cupboard without his knowledge. Preschoolers are even likely to respond to open-ended questions with silence or irrelevance. But they will consistently pick one option over the other when you ask them to choose between them. Four-year-olds can say that Max will look for the chocolate in the blue cupboard rather than the yellow one.

PHYSICAL KNOWLEDGE DEVELOPMENT

From the time infants are very young they understand some of the basic properties of physical objects. In the first few months of life, they know that objects are 3-dimensional and extended in space, that they can't pass through other objects, and that they continue to exist when they move behind a screen. They also have a basic concept of numbers, at least up to 3. In one experiment, infants see a toy disappear behind a screen, and then see another toy move behind the screen. The screen is lifted and 1, 2, or 3 toys appear. The babies look longer if 1 or 3, rather than 2, toys appear.

Infants also have a surprisingly early understanding of relationships that cross sensory modalities. They recognize parallelisms between lip movements and vocal sounds, between the feel of a pacifier and the way it looks, or between the visual image of a bouncing ball and the sound it makes.

Babies also have a surprisingly early and sophisticated understanding of statistics and probability. Before they are 1 yr old, they expect that a ball taken at random from a box of 80 red and 20 white balls is more likely to be red than white. Infants can also recognize statistical patterns in both visual and auditory sequences. You can play babies a string of syllables or tones or show them a sequence of pictures that have a particular pattern. For example “pa” may always follow “ti” but only follow “ko” 75% of the time. Babies seem to figure out these statistical patterns. Later they use them to isolate words or objects or other meaningful units from the torrent of sounds and sights they perceive.

In their second year, babies have a basic understanding of spatial relationships like gravity and containment. They can also categorize objects, recognizing that animals, for example, go together and are different from artifacts. They also gradually come to understand how to use simple tools to accomplish what they want, although they may still make interesting mistakes, like pulling a blanket to try to get a toy even when the toy is beside the blanket instead of on top of it.

Preschoolers continue to learn about the physical world, but they also begin to learn about the biologic world. Three and 4 yr olds are *essentialists*. They assume that categories of animals or plants, such as birds or daisies, will have the same insides and the same *essence* even if they are perceptually diverse. Contrary to conventional wisdom, preschoolers are not restricted to superficial perceptual categories. Preschoolers also have a first understanding of basic biologic ideas like inheritance, growth, and illness, and don't confuse these with psychologic ideas; they are not animists as Piaget thought. However, they still have difficulty understanding biologic concepts in a unified way, and they have little understanding of death.

By 5 yr of age, preschoolers have a more unified concept of something like a *life force*. They believe that the presence of this force makes living things grow and thrive, and its absence leads to illness and death. Interestingly, disadvantaged rural children, for example, Native American children on Indian reservations, who may have more experience of the living world, may develop an understanding of biology earlier than more privileged middle-class children.

Preschoolers also have a much more sophisticated understanding of causal relationships than we previously thought. Infants even understand something about the way physical objects move and interact with other objects. Older children understand the mechanics of simple physical systems.

They can also learn about new causal relationships. We can give young children evidence about how a novel machine works, showing them for instance that a box lights up and plays music only when you put a specific combinations of blocks on it. Children as young as 2 yr of age can figure out how the machine works and can use that information to invent novel ways to make it go. By 4 yr, they can figure out a machine that involves complex interactions of 3 different gears and switches. They can even propose invisible unobserved causes, when that is the best explanation for the pattern of evidence. In fact, they use forms of inductive causal reasoning that are basic to science and that are used in computer learning.

SOCIAL KNOWLEDGE DEVELOPMENT

Some of the most impressive kinds of early knowledge and learning involve children's understanding of other people. These *theory-of-mind* abilities are particularly important for social interaction and appear to be specifically impaired in children with autism. From the time they are born, infants treat people as special. Within the 1st mo infants prefer to look at human faces and listen to human voices, and rapidly prefer the face, voice, and even smell of their caregivers. Newborn infants also imitate facial expressions. To do this they must link what they see on the face of another person and how it feels to be them inside.

Within the 1st yr babies develop an even richer understanding of others. Seven-month-olds appreciate that human actions are directed towards particular goals. You can show the babies a ball and a teddy bear on a table. A hand reaches in and grasps the ball. Now you switch the locations of the 2 toys, so that the teddy bear is where the ball was and vice-versa. Seven-month-olds look longer when the hand goes to the teddy bear instead of the ball. They don't do this if a stick, rather than a hand, touches one object or the other.

One-year-olds don't just imitate actions; they reproduce the results of those actions. A 1 yr old child walks into the lab and sees the experimenter tap his head on a box, making the box light up. A week later she returns to the lab and sees the box on the table. She'll immediately use her own head to get the box to light.

Eighteen-month-olds can imitate in an even more sophisticated way. You can show them an experimenter touching her head to the box, but now she has a blanket wrapped around her so that her hands aren't available. If the other person's hands are free the babies will tap their own heads on the machine. But if she's wrapped up in the blanket and she taps the machine with her head, the babies will instead use their own hands. They've figured out that you would use your hands if you could, but because you can't, you're using your head instead.

In their second year, children also start to understand that their own perceptions, attention, and emotion may be shared by others. At this age babies start to engage in *joint attention behaviors*; they will follow the gaze or point of another person and they will point to objects themselves. They also start to understand that closing your eyes or wearing a blindfold may make it more difficult to see. In *social referencing*, babies will react appropriately to the emotional expression of another person that is directed at an object; if 1 yr olds see someone react to an ambiguous object with fear they will avoid the object themselves.

Babies are also sensitive to the contingency between their own actions and the actions of others, and use contingency patterns to differentiate people and things. If 1 yr olds see a machine that blinks and chirps in coordination with their own actions, they will treat it like a person, following its gaze if it turns toward an object. They will not do this if the machine makes the same noises, but they are not contingent on the baby's actions.

Eighteen-month-olds also start to show an understanding of love. *Attachment* researchers have long noted that different babies behave differently when they are separated from their caregivers and then reunited. *Secure* babies are distressed at separation but are quickly comforted when the caregiver returns. *Avoidant* babies seem to repress their distress; they ignore the caregiver both when she leaves and returns. *Anxious* babies are very distressed and take a long time to comfort.

Secure and insecure babies seem to have different theories of love. In one experiment, 18 mo old babies saw an animated film of a mother figure, a big circle, and a baby figure, which was a small circle that emitted a realistic cry. Then the babies either saw that the mother move toward the baby or move away from the baby. The secure babies expected that the mother would return to the baby and looked longer when she did not. The insecure babies had just the opposite theory; they looked longer when the mother changed course and returned.

From 2-6 yr of age, children discover further fundamental facts about how their own minds and the minds of others work. Even 18 mo olds already seem to understand something about the ways that people's minds might differ. You can show 14 mo olds and 18 mo olds 2 bowls of food: raw broccoli and Goldfish crackers. Then the experimenter tastes a bit of food from each bowl and acts as if she likes the broccoli but not the crackers. She puts out her hand and says, "Can you give me some." Fourteen-month-olds give the experimenter the crackers, but the 18 mo olds give the experimenter broccoli.

Slightly older children can understand the complex causal interactions between desire, perception, and emotion; they can predict all the possible actions that might stem from different psychologic combinations.

Preschoolers also, against conventional wisdom, can understand the difference between the physical and the mental, reality and fantasy, from a very young age. Preschoolers may be intensely emotionally affected by the products of fantasy, from imaginary friends to monsters in the closet. Nevertheless, they recognize the distinction between imaginations, which are private and intangible, and reality, which is public and verifiable.

In addition, around 5 yr of age children start to understand the relationship between our beliefs and the world around us. For example, suppose you show a child a candy box that turns out to be full of pencils. The children are very surprised when they see the pencils. But if you ask them what they thought was in the box 3 yr olds confidently report that they thought there were pencils in there. You see the same thing in the "Max" experiment described earlier. Though 4 yr olds accurately report where Max will look for the chocolate, 3 yr olds say that Max will look for the chocolate where it actually is instead of where he thinks it is.

Similarly, 3 yr olds have difficulty understanding the sources of their beliefs. If you ask them how they learned something, they are likely to think that they saw it directly, even when they actually heard it from someone else—an important consideration in child testimony. In their spontaneous language children only start explaining actions in terms of thoughts and beliefs, especially false thoughts and beliefs, when they are around 4 yr old. There are somewhat controversial studies that suggest that some implicit and unconscious understanding of belief may even be in place earlier, but there are clearly important changes in children's conscious understanding of the mind between 3 and 5 yr of age.

Understanding the mind also allows children to act to change the minds of others. Children who can explain actions in terms of a theory of mind also seem to be more adept, for good or ill, at altering other people's minds. They are more socially skillful, but they are also better liars.

Understanding minds actually also allows us to change our own minds as well as the minds of others. Between 3 and 5 yr of age, children also start to develop capacities for what psychologists call *executive control*, which is the ability to control your own actions, thoughts, and feelings. These capacities seem to be specifically related to *theory-of-mind* abilities. Understanding how your own mind works may help you to control and regulate it.

THEORIES OF COGNITIVE DEVELOPMENT

Several alternative theories have been proposed to explain these developmental processes. The basic conundrum of cognitive development is that even the youngest babies seem to have abstract, highly structured, hierarchical knowledge of the world; knowledge that lets them make wide-ranging new inferences. And yet as children experience more of the world, these representations change in systematic ways; it appears that young children are learning from their experiences.

One classic approach, often called *nativism* suggests that much of this abstract structure is in place innately; babies are born knowing about crucial aspects of the world. Learning is largely just a matter of filling in details. Although babies are far from being blank slates, there also seem to be significant changes in their understanding of the world.

The alternative approach, *empiricism,* suggests that all of children's knowledge is simply the result of a process of associating or combining particular sensory experiences, or detecting the statistics of the environment. Although children are able to associate particular experiences and to detect statistics, those abilities don't seem to be sufficient to explain their remarkable growth of knowledge.

Piaget originally articulated *constructivism* as an alternative to both nativism and empiricism. But Piaget had little to say in detail about how constructivist processes could take place; many of his empirical claims have been disproved. The *theory theory* is the more current version of constructivism. The idea is that children develop their knowledge of the world by constructing every day or intuitive theories, much like scientific theories. The *theory theory*, unlike empiricism, proposes that even babies may be born with innate theories of the world, but unlike nativism, it proposes that those theories may be radically transformed as children learn more about the world. Most recently, *rational constructivism*, a more rigorous and precise version of the *theory theory*, was formulated. It uses mathematical ideas about probabilistic models and bayesian inference to explain how even very young children can learn so much from the evidence they encounter.

Within the constructivist approach, an exciting new set of studies and theoretical ideas confirms something that parents and preschool teachers and others have long thought intuitively: Very young children's play, both their exploratory play and their imaginative and pretend play, contributes greatly to their early learning.

Nativism, empiricism, and constructivism all focus on the process of learning from evidence. Two other approaches describe other factors that contribute to cognitive development. Information-processing approaches stress the development of general abilities to process and organize information, such as memory or attention. Indeed, children do develop such abilities in the first few years of life and those developments contribute to the development of their knowledge.

Sociocultural approaches emphasize the contribution that *expert adults* can make to children's knowledge. There is growing evidence that from very early in infancy babies are specifically and powerfully tuned to information that comes to them from their caregivers. By preschool, what is sometimes called *implicit* or *intuitive* pedagogy plays an increasingly important role in children's learning. Preschoolers tend to give grownup testimony the benefit of the doubt, but they can also distinguish between reliable and unreliable teachers.

However, preschoolers sensitivity to implicit teaching can be a double-edged sword. Some studies show that children are less likely to engage in wide-ranging exploration when adults provide them with answers. Preschoolers left to their own resources are often able to solve complex problems (see Chapter 7.1). In addition because play is such an important component of a preschool-age child's learning process, the learning environment may need to be less structured, more child-focused, and with less emphasis on traditional academic instruction. Sociocultural approaches are especially relevant to the many kinds of learning where there is no right answer such as learning the particular traditions, mythologies, or values of your cultural or ethnic group.

All these factors, innate structure, association and statistics, theory formation and play, information-processing abilities, and cultural transmission, must somehow combine to allow children to learn as much as they do.

Bibliography is available at Expert Consult.

7.1 The Reggio Emilia Educational Approach and Child Development and Learning

Naama Zoran and Rivkie Spalter

Maria Montessori was the first to bring the message of children as competent, and was followed by Loris Malaguzzi who had the same philosophy and developed his approach in Reggio Emilia, a city in Italy. Malaguzzi believed that education is a lifetime experience that has 3

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Box 7-1 Example of Creating an Educational Environment That Recognizes the Child's Social–Emotional Well-Being

The K3 children were working on building an igloo in the playground. When they realized the task was bigger than they anticipated, they decided to invite their parents to help.

M (4 yr old) shared that his dad could not come because he was in the hospital. The teacher dialogued with the child, and together they thought about ways for the father to be part of the process. The decision was to create a book for his father with the story of the igloo. The strong message given to the child was that he has the tools for coping with the situation. This empowered him to approach the situation with joy and creativity. One of the child's ideas was to add some photos of his father's previous visits at school to the book. Seen as competent, he chose the pictures that would go into the pages.

M was so proud of his book. He asked every person who visited our school, whether adult or child, to read his book with him. In addition this book brought emotional stability to a family going through a difficult and scary time. The book was a tool for father and son to communicate and share meaningful conversation.

major elements: the emotional component, the ethical component, and the aesthetic component.

THE EMOTIONAL COMPONENT

Malaguzzi believed that the concept of well-being leads the educational approach. Well-being, especially in early childhood, is the leading developmental task that every child from birth is thriving for as part of each child's sense of self establishment. Creating an educational environment that recognizes the child's social–emotional well-being means creating a place where every child is valued and respected as an individual and as an equal member of a group. Malaguzzi believed that every moment should be enjoyable and satisfactory (Box 7-1).

THE ETHICAL COMPONENT

The following points characterize the Reggio Emilia ethical code:

- Education is not just a technique but is a shared process for revealing values.
- The school is a place that transmits and constructs culture through experiences. The reciprocal relations between transmission and construction gives schools and teachers a responsibility and an active role in sustaining and generating a culture that is based on the past, yet looking ahead to the future.
- The school should focus not only on knowledge but also on concepts, ideas, and values.
- The educator influences the future, and as such needs to generate the connections between the individual and the world.
- Children are born with myriad ways to construct and process knowledge. Those ways are defined as *100 languages*; language is defined as the different ways through which any human being represents, communicates, and expresses thoughts, feelings, concepts, and symbols (Box 7-2).

THE AESTHETIC COMPONENT

Education must focus on the aesthetics because the child knows how to value beauty and is able to interact with all the expressive languages. Malaguzzi's innovative idea for approaching and embracing the expressive–aesthetic aspects to early childhood education was the *atelier*. The atelier is a statement about the importance of imagination, creativity, expression, and aesthetics in the learning and knowledge construction processes. Because children do not separate different disciplinary fields, and because they learn in an interrelated and interdisciplinary way, the learning environment should connect between aesthetics and ways of knowing. The expressive languages and the arts are ways to break the conformist thinking about children and their learning, and to move toward elaborating the opportunities that are given to children while they are exploring, researching, and constructing knowledge.

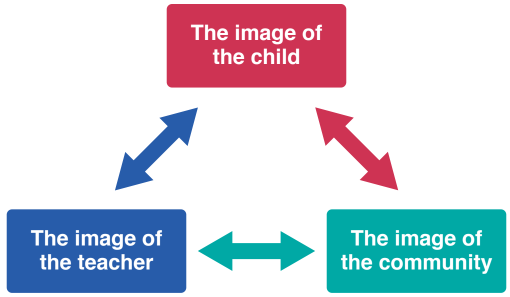

Figure 7-1 Pedagogic thinking: core concepts around 3 major areas.

Box 7-2 Example of Children Processing Information and Solving Problems

When the K4 teacher had an idea to have senior citizens as pen pals for the K4 kids, she thought about a correspondence that might take place every once in a while.

One cold winter day the bus arrived with the seniors for the monthly visit, but the driver notified the school that the bus needed to leave because the lift to lower the seniors off the bus was jammed. When the children heard about the situation, they immediately thought about a way to solve it. They decided as a group to board the bus with the activities that they had planned. They put on their coats and hats and brought the bingo and the brownies, and for the next 2 hr, the children and seniors had an enjoyable afternoon together. It was a moment when we realized that our children have internalized the value of working with seniors and from that place found the appropriate solution to the issue at hand.

PEDAGOGIC THINKING: CORE CONCEPTS AROUND 3 MAJOR AREAS

One of the cornerstones of this approach is the concept of **images** (Fig. 7-1).

An image is a cognitive structure that serves as a container. It keeps and holds all of the tools we have to perceive and interpret the world around us. All of the perceptions and interpretations are organized into clusters that serve as our inner compass and navigate our way in the personal and social–cultural life that we share with others.

When it comes to education, the images play a crucial and determinative role as is reflected in the following quote from Carla Rinaldi: "Everyone (you, us, each parent…) has his or her own image of the child, and, consequently, we have our own educational theories that we develop based on personal, social, cultural, and political experience, and that we construct or acquire as part of our society and culture. Whether we are aware of it or not, we cannot live without theories." Yet, as educators we have a profound responsibility for the awareness level that guides us when we make choices for children.

It is important to note that each person has his or her own image of the child. By saying image we mean personal interpretation that is subjective and unique. The focus is on which point of view being used when thinking about a child. Our points of view about the world around us are dynamic and are consistently changing. We are structuring the impressions we are getting on any concept or experience to create a holistic image in our mind.

The Image of the Child

Loris Malaguzzi said "Each has inside ourselves an image of the child that directs you as you begin to relate to a child. This theory within you pushes you to behave in certain ways." It orients you when you listen to the child, observe the child. It is very difficult for you to act contrary to this internal image.

It is important to emphasize the impact of the image to the awareness of the teachers, as only the awareness would enable the teacher to follow the desired image of children; one that sees and accepts the

Box 7-3 Example of Relating to a Child as a Competent Partner

One day, a child who was questioning about how he is seen by his teacher began to cry, saying, "I cannot do it," referring to pulling on his pants. The teacher who understood it was a question more than a statement about his incompetence, said: "Show me what you **can** do." Her focusing on her perception of the child as competent met the child's inner question and empowered the child to focus on what the child could accomplish. The child was able to complete the task on his own.

child as an active competent partner, plentiful with potential and capabilities. Usually the strength and the talents of children are underestimated and schools tend to suppress the child's potential by creating an environment of transmission, instead of exploration. The environment should be collaborative between teachers and children; they partner together rather than the teacher determining all activities or interactions.

The concept of a "blank slate," first mentioned by the philosopher John Locke, is presented here as a characterizing traditional point of view in education that does not believe in the child's abilities and leaves no room for the child's feelings, thoughts, imagination, and creativity. It also reflects the belief that the child is waiting for the school and society to "write" on, nourish, and fill his or her slate.

Choosing an image calls for a *sense of responsibility*, as we need to commit to the image that was chosen. The chosen image then becomes a compass that guides us in every interaction or practice we are having with the child. Reggio educators believe that the image of **child as competent** brings a point of view that sees children as structuring their sense of self, they generate and construct values, and they establish their rights; the first one is the right that acknowledges and accepts the role childhood has and the unique contribution each person brings to it.

The child is born as a *researcher* that is looking for relationships, hypotheses, and provocations in anything the child is exploring. The choice to see the child as a researcher has major pedagogic implications. The first guiding implication is the understanding that the child is **never** waiting for the adult to actuate the child's need to research, yet the child needs the adult as a **context** for the child's revelations (Box 7-3).

The Image of the Educator

The core component in the image of the teacher is the understanding that to be a high-quality teacher, the educator needs to perceive himself or herself also as a learner. The most meaningful place for learning how to teach is within the educational setting. You learn how to teach by being with children and by reflecting on the processes you have experienced with them; the best key for learning and teaching is **reciprocity**.

The role of the teacher in the above image encompasses the following aspects:

- To define and create the context within which all learning/ teaching processes would occur. The context enables the landscape of learning to emerge and develop.
- To think and plan using symbols and concepts
- To interpret the child concepts and symbols with the group
- To elaborate on the experiences and the interpretations done with the children.
- To review with the children a second round of experiences built on the previous day.
- To add improvisations according to the previous learning processes.

There are reciprocal relationships between the image of the child and the image of the teacher, and each is complementary and bound to the other.

Teachers should never think of the child in the abstract. When we think about a child, that child is already tightly connected and linked to a certain reality. Children have relationships and experiences that they bring to any new environment. Similarly, the teacher brings pieces of his or her life to the educational environment (Box 7-4).

Box 7-4 Example of Reciprocal Relationships Between the Image of the Child and the Image of the Teacher

One morning a child was brought to school and was not willing to take his coat off. The mother did not know how to convince him to take the coat off; the teacher kept asking him to take the coat off; and the child was crying and determined not to take the coat off.

It was only when the teacher changed her **point of view** and was willing to accept the child and meet him where he was that the child stopped crying and was able to join his class activities.

We see this example as a compass for remembering that it is only when you leave your preconceived notions and see yourself as a **place** where children feel that they are seen and heard as equal, active, and competent partners that the quality of relationships you create is elevated and becomes clear and coherent.

The Image of the Contextual Community

The concept at the core of the educational communal life is the idea of the "other" that is the essence of the Reggio Emilia pedagogic approach. The "other" might be the child, the family, or a colleague—in a sense, any person who is interacting with the educational system. All members together, through the relations that are constructed among all, are part of creating a sense of belonging for the system and for its members. The feeling of belonging serves as a foundation for the community life. When people who are part of the system feel they are seen, heard, and known, a culture of participation can be developed. The culture of participation arises out of the integration of the concept of feeling a part of, and its complementary aspect of taking part, and is shared among all children, parents, and teachers.

The focus was and is to develop relationships with the other, with the other's uniqueness and originality, with the other's point of view, and to reach the place where the subjectivity of each partner is open to entering an intersubjective field for a real meeting. The basic assumption is that each family shares its culture with the others.

The idea of crossing the *boundaries of the subjectivity* to arrive at the intersubjective landscape emerges from a very important declaration that the school sends to the community: A declaration of a place that has a defined and solid identity that is based on the perception that the school by nature is a multicultural place, and as such embraces every inhabitant, including each inhabitant's background and culture, knowing that the school point of view is partial, and each is invited to share their points of view, as the school invites each partner to add their point of view for strengthening, elaborating, and accommodating the shared identity of the school.

Concepts like welcoming, plurality, dialog, and intercultural dynamics are explored and new meanings are attributed to them, as a realization that every word/concept or value could have different meanings. That realization creates a place for reworking of the ideas, a place where new questions are generated and discussed.

THE DEVELOPMENTAL THEORIES OF GREENSPAN, VYGOTSKY, AND MALAGUZZI

Greenspan on Well-Being and the Sense of Self

Stanley Greenspan (1941–2010), a psychiatrist, was a leading researcher on the prevention and treatment of emotional and developmental disorders in infants and children. He believed that when you observe or interact with a child, you should take into account not just the child's developmental functioning level, but also the child's background, personal and familial history, and, especially, the quality of relationships the child is experiencing in his or her home and school environment.

Greenspan believed that it is the quality of the interactions children have with meaningful figures that determines the quality of the social–emotional experiences and the level of success in achieving the developmental tasks that are required in every developmental sequence. Greenspan developed a model that shows how in every developmental phase, 2 different processes are possible. Simply stated, high-quality responsive parenting leads to high-quality achievement of the

Table 7-1 Comparison of Greenspan and Malaguzzi Developmental Theories

DEVELOPMENTAL PRINCIPLE	GREENSPAN	MALAGUZZI (REGGIO)
Self-regulation	The ability to reach an inner and outer harmony. The harmony represents the skills needed to create the initial understanding of being in the world.	The school environment is designed and organized in ways that support the concept of being in harmony. In Malaguzzi's words, an "amiable environment."
Attachment and bonding	The ability to create a meaningful, special bond with another; plant the seeds for the notion of to love and be loved.	Well-being is the fountain for all the relationships, and the school is the landscape of well-being that is ready to embrace all kinds of relationships.
Differentiation	The ability to differentiate oneself from any other person is crucial for the sense of separation and uniqueness.	The child is seen as a unique individual, who is at all times an active and equal member of the school community.
Initiation and internalization	The ability to navigate oneself in the world in an active, participatory way, that empowers and leads to the internalization of the sense of self.	One of the core concepts that defines curricular planning and guides teachers' practical choices is the ability of the school to define the educational intents in visible and declarative ways that support the curricular initiatives and their impact on the school community.
Representational thinking	The ability to represent all of the above in a verbal, conceptual, socially and emotionally appropriate way.	The concept of the "hundred languages of children" is a message that there are a hundred ways to represent the knowledge and understanding that was achieved in any learning experience.

developmental tasks needed; and low-quality parenting skills lead to low-quality achievement of the developmental tasks at hand.

The above point of view matches Malaguzzi's concept of the **pedagogy of relationships**. The concept of *pedagogy of relationships* has an extra value for the early childhood period because the early childhood years are considered the most critical period in our lives; the **self** that is the entity that is the core of our being establishes its essential structure in these early years.

Greenspan defined the leading developmental tasks that are connected to the development of the sense of self and that continue to deepen and elaborate throughout life: self-regulation processes, attachment and bonding, differentiation, initiative and internalization, and representational symbolic thinking (Table 7-1).

Vygotsky and the Reggio Emilia Approach

Vygotsky's concept of the **zone of proximal development** states that in any given moment, the person (child or adult) finds himself between 2 developmental points—the *actual* and the *potential* points of development that represent the idea of human competence. Vygotsky saw the actual point of development as the place that reflects the already existing skills in all areas of development, and the potential point of development as the place for the skills on which the person works at that given time. Between those 2 points of development is the land of development, where each of us is using what we already have in order to develop what is potentially waiting to unfold.

Vygotsky believed that the teacher's role is to be with children in a very conscious and attentive way. To use the child's actual point of development as the launching place for challenges that would encourage further exploration and learning.

Malaguzzi believed that being with children in their developmental journey calls for deep engagement and attentiveness by the teacher in order to meet all children individually and in small groups in terms of where they are in their interests, exploration, and research. The main goal is to create the most meaningful learning environment that supports the actualization of their potential. According to Malaguzzi, the level of engagement of the teachers is not narrowed only to their actions but includes investment in observations, interpretations, and reflections that are the grounds for the practical actions.

Vygotsky's social constructive is known for its relevance to the educational field. One of Vygotzky's leading concepts is the scaffolding process that defines a specifi interaction between teachers and learners in which the teacher supports the learning process in situations where the learner cannot explore or research alone. Connected to the scaffolding concept is the question of the relations between scaffolding and giving **help** when it comes to relationships with children. Vygotsky's scaffolding concept highlights the difference between authentic and nonauthentic support of children's learning processes and focuses on giving only the support that would enable the child to move toward the child's potential point of development, according to the child's developmental pace. This was interpreted by Malaguzzi as *things that children can do by themselves should not be done for them*.

It is only when the child needs the bridge between the child's current place and the child's destination that adults should step in delicately and consciously and provide help (Box 7-5).

Box 7-5 Example of Giving Only the Support That Enables a Child to Move Toward the Child's Potential Point of Development, According to the Child's Developmental Pace

The children were playing with a large box that was brought to the school. One of the kids climbed in and suddenly realized he was stuck and could not climb out. The child began to cry. The teacher asked him what he could do to solve the problem, and his response was: "I will ask my friends." He called his friends and they began giving him ideas.

One child tried to pull him out, but the box was too tall. Two other friends came, brought a chair, and tried to pull him out, but still the box was too tall.

Then a fourth child joined and suggested putting a chair INSIDE the box. The children brought a chair that was put inside, and their friend climbed out happy and empowered.

Reggio Approach and Relationships with Parents

In the Reggio approach, the image of the parent parallels the image of the child. In other words, as the child is seen as an equal, active, and competent partner, the parent is also perceived as a competent, active partner to the educational endeavor. The core of the relationship is the value of parent participation with 2 cornerstones. First is the idea of taking part in the different ways parents can participate in school life. Second is the emotional attitude parents establish toward the school. The integration of those 2 cornerstones creates a way of being in the schools that represents a democratic approach to citizenship with solidarity and shared responsibility as core guidelines.

The ethical code for the participatory approach is that each member in the educational process brings his or her forms of knowing, points of view, interpretations of different experiences, and culture. The participation sets the ground to discussions and rich exchanges among the parents and the school that open the door for wide-ranging discussions

and collaborations. The uniqueness of the participatory way of being in the Reggio Emilia approach is the belief that only by accepting other persons from a humanistic point of view, can real acceptance and acknowledgement arise. The parent usually has his or her own image of the child that is based on the relationships, culture, and family traditions, history, and characteristics. The deep relationship with the school enables the parent to gain a different image of his or her child. The opportunity to widen the personal image and to integrate the personal image with the school image opens a door for a wider and deeper relationship between parents and their children.

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Chapter 8

Assessment of Fetal Growth and Development

Susan Feigelman

Table 8-1 Milestones of Prenatal Development

WK	DEVELOPMENTAL EVENTS
1	Fertilization and implantation; beginning of *embryonic* period
2	Endoderm and ectoderm appear (bilaminar embryo)
3	First missed menstrual period; mesoderm appears (trilaminar embryo); somites begin to form
4	Neural folds fuse; folding of embryo into human-like shape; arm and leg buds appear; crown-rump length 4-5 mm
5	Lens placodes, primitive mouth, digital rays on hands
6	Primitive nose, philtrum, primary palate
7	Eyelids begin; crown-rump length 2 cm
8	Ovaries and testes distinguishable
9	*Fetal* period begins; crown-rump length 5 cm; weight 8 g
12	External genitals distinguishable
20	Usual lower limit of viability; weight 460 g; length 19 cm
25	Third trimester begins; weight 900 g; length 24 cm
28	Eyes open; fetus turns head down; weight 1,000-1,300 g
38	Term

The developing fetus is affected by social and environmental influences, including maternal nutritional status; substance use (both legal and illicit); and psychologic trauma. Correspondingly, the psychologic alterations experienced by the parents during the gestation profoundly impact the lives of all members of the family. Growing evidence implicates the importance of these and other maternal and paternal experiences that occur during and prior to the pregnancy (and even among members of earlier generations) on the subsequent development of the individual (*epigenetic effects*). The complex interplay between these forces and the somatic and neurologic transformations occurring in the fetus influence growth and behavior at birth, through infancy, and potentially throughout the individual's life.

SOMATIC DEVELOPMENT

Embryonic Period

Table 8-1 lists milestones of prenatal development. By 6 days postconception age, as implantation begins, the embryo consists of a spherical mass of cells with a central cavity (the *blastocyst*). By 2 wk, implantation is complete and the uteroplacental circulation has begun; the embryo has 2 distinct layers, *endoderm* and *ectoderm*, and the amnion has begun to form. By 3 wk, the 3rd primary germ layer *(mesoderm)* has appeared, along with a primitive neural tube and blood vessels. Paired heart tubes have begun to pump.

During wk 4-8, lateral folding of the embryologic plate, followed by growth at the cranial and caudal ends and the budding of arms and legs, produces a human-like shape. Precursors of skeletal muscle and vertebrae (somites) appear, along with the branchial arches that will form the mandible, maxilla, palate, external ear, and other head and neck structures. Lens placodes appear, marking the site of future eyes; the brain grows rapidly. By the end of wk 8, as the embryonic period closes, the rudiments of all major organ systems have developed; the crown-rump length is 3 cm.

Fetal Period

From the 9th wk on (fetal period), somatic changes consist of rapid body growth as well as differentiation of tissues, organs, and organ systems. Figure 8-1 depicts changes in body proportion. By wk 10, the face is recognizably human. The midgut returns to the abdomen from the umbilical cord, rotating counterclockwise to bring the stomach, small intestine, and large intestine into their normal positions. By wk 12, the gender of the external genitals becomes clearly distinguishable. Lung development proceeds, with the budding of bronchi, bronchioles, and successively smaller divisions. By wk 20-24, primitive alveoli have formed and surfactant production has begun; before that time, the absence of alveoli renders the lungs useless as organs of gas exchange.

During the 3rd trimester, weight triples and length doubles as body stores of protein, fat, iron, and calcium increase.

NEUROLOGIC DEVELOPMENT

During the 3rd wk, a neural plate appears on the ectodermal surface of the trilaminar embryo. Infolding produces a neural tube that will become the central nervous system and a neural crest that will become the peripheral nervous system. Neuroectodermal cells differentiate into neurons, astrocytes, oligodendrocytes, and ependymal cells, whereas microglial cells are derived from mesoderm. By the 5th wk, the 3 main subdivisions of forebrain, midbrain, and hindbrain are evident. The dorsal and ventral horns of the spinal cord have begun to form, along with the peripheral motor and sensory nerves. Myelinization begins at midgestation and continues for years.

By the end of the embryonic period (wk 8), the gross structure of the nervous system has been established. On a cellular level, neurons migrate outward to form the 6 cortical layers. Migration is complete by the 6th mo, but differentiation continues. Axons and dendrites form synaptic connections at a rapid pace, making the central nervous system vulnerable to teratogenic or hypoxic influences throughout gestation. Figure 8-2 shows rates of increase in DNA (a marker of cell number), overall brain weight, and cholesterol (a marker of myelinization). The prenatal and postnatal peaks of DNA probably represent rapid growth of neurons and glia, respectively. By the time of birth, the structure of the brain is complete. Synapses will be pruned back substantially and new connections will be made, largely as a result of experience. Many psychiatric and developmental disorders are thought to result at least in part from disruptions in the **functional connectivity** of brain networks. Disorders of connectivity may begin during fetal life; MRI studies provide a developmental timetable for such connections that lend support to the possible role of disruptions in the establishment of such connections during fetal life.

BEHAVIORAL DEVELOPMENT

No behavioral evidence of neural function is detectable until the 3rd mo. Reflexive responses to tactile stimulation develop in a craniocaudal sequence. By wk 13-14, breathing and swallowing motions appear. The grasp reflex appears at 17 wk and is well developed by 27 wk. Eye

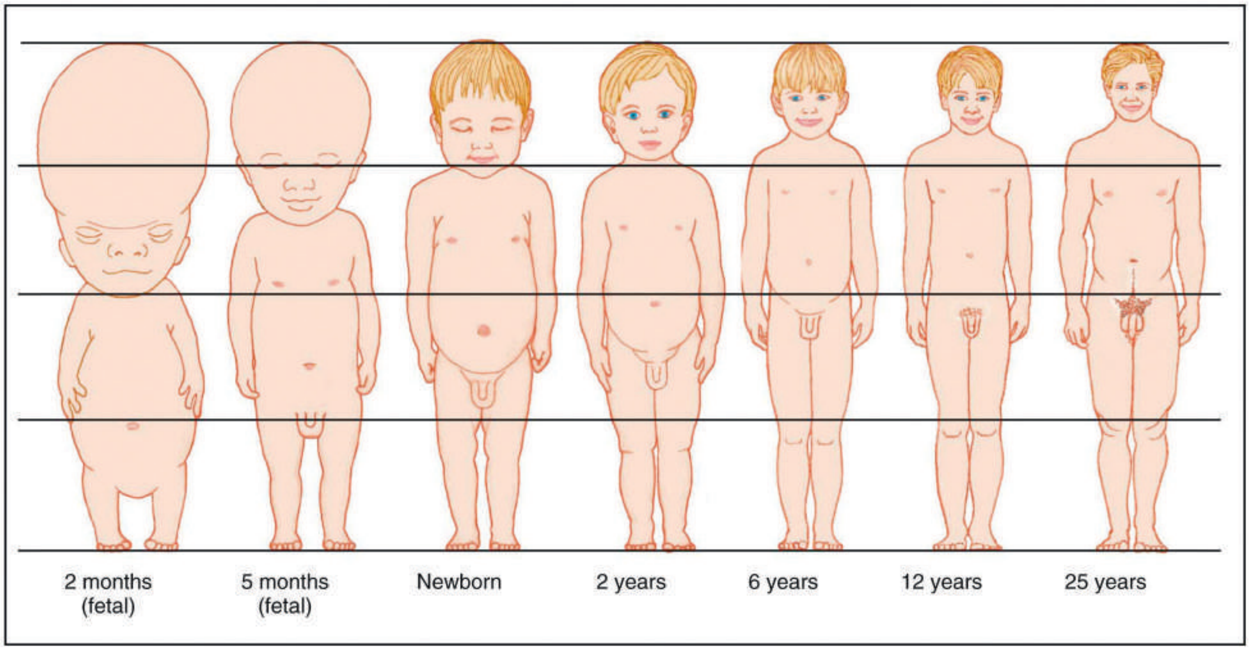

Figure 8-1 Changes in body proportions. Approximate changes in body proportions from fetal life through adulthood are shown. *(From Leifer G:* Introduction to maternity & pediatric nursing, *Philadelphia, 2011, WB Saunders, pp 347–385, Fig. 15-2.)*

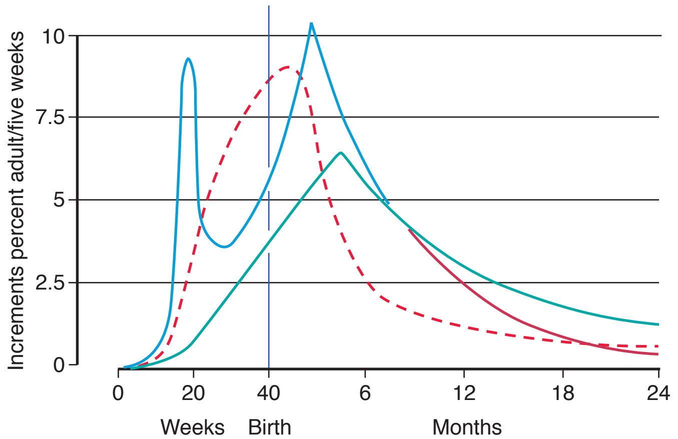

Figure 8-2 Velocity curves of the various components of human brain growth. Solid line with two peaks, DNA; dashed line, brain weight; solid line with a single peak, cholesterol. *(From Brasel JA, Gruen RK. In Falkner F, Tanner JM, editors:* Human growth: a comprehensive treatise, *New York, 1986, Plenum Press, pp 78–95.)*

opening occurs around 26-28 wk. By midgestation, the full range of neonatal movements can be observed.

During the 3rd trimester, fetuses respond to external stimuli with heart rate elevation and body movements (see Chapter 96). As with infants in the postnatal period, reactivity to auditory (vibroacoustic) and visual (bright light) stimuli vary, depending on their behavioral state, which can be characterized as quiet sleep, active sleep, or awake. Individual differences in the level of fetal activity are commonly noted by mothers and have been observed ultrasonographically. Fetal behavior is affected by maternal medications and diet, increasing after ingestion of caffeine. Behavior may be entrained to the mother's diurnal rhythms: asleep during the day, active at night. Abnormal fetal movement patterns are found in neonates with subsequent muscular or neurologic abnormalities.

Fetal movement increases in response to a sudden auditory tone, but decreases after several repetitions. This demonstrates **habituation,** a basic form of learning in which repeated stimulation results in a response decrement. If the tone changes in pitch, the movement increases again, which is evidence that the fetus distinguishes between a familiar, repeated tone and a novel tone. Habituation improves in older fetuses, and decreases in neurologically impaired or physically stressed fetuses. Similar responses to visual and tactile stimuli have been observed.

PSYCHOLOGIC CHANGES IN PARENTS

Many psychologic changes occur during pregnancy. An unplanned pregnancy may be met with anger, denial, or depression. Ambivalent feelings are the norm, whether or not the pregnancy was planned. Elation at the thought of producing a baby and the wish to be the perfect parent compete with fears of inadequacy and of the lifestyle changes that mothering will impose. Parents of an existing child feel protective for the existing child, worried that the existing child may feel less valued. Old conflicts may resurface as a woman psychologically identifies with her own mother and with herself as a child. The father-to-be faces similar mixed feelings, and problems in the parental relationship may intensify.

Tangible evidence that a fetus exists as a separate being, whether as a result of ultrasonic visualization or awareness of fetal movements (at approximately 20 wk), often heightens a woman's feelings. Parents worry about the fetus's healthy development and mentally rehearse what they will do if the child is malformed, including their response to evidence of abnormality through ultrasound, amniocentesis or other fetal laboratory tests. Toward the end of pregnancy, a woman becomes aware of patterns of fetal activity and reactivity and begins to ascribe to her fetus an individual personality and an ability to survive independently. Appreciation of the psychologic vulnerability of the expectant parents and of the powerful contribution of fetal behavior facilitates supportive clinical intervention.

THREATS TO FETAL DEVELOPMENT

Mortality and morbidity are highest during the prenatal period (see Chapter 93). An estimated 50% of all pregnancies end in spontaneous abortion, including 10-20% of all clinically recognized pregnancies. The vast majority occur in the 1st trimester. Some occur as a result of chromosomal or other abnormalities.

Teratogens associated with gross physical and mental abnormalities include various infectious agents (toxoplasmosis, rubella, syphilis); chemical agents (mercury, thalidomide, antiepileptic medications, and ethanol), high temperature, and radiation (see Chapters 96 and 718).

Teratogenic effects may also result in decreased growth and cognitive or behavioral deficits that only become apparent later in life. Nicotine has vasoconstrictor properties and may disrupt dopaminergic and serotonergic pathways. Prenatal exposure to cigarette smoke is associated with lower birthweight, shorter length, and smaller head circumference, as well as changes in neonatal neurodevelopmental assessments. Later, these children are at increased risk for learning problems, externalizing behavior disorders, and long-term health effects. The effects of prenatal exposure to cocaine, also occurring through alternations in placental blood flow and in direct toxic effects to the developing brain, have been followed in several cohorts and are less dramatic than previously believed. Exposed adolescents show small but significant effects in behavior and functioning, but may not show cognitive impairment. The associated risk factors including other prenatal exposures (alcohol and cigarette co-use) as well as "toxic" postnatal environments frequently characterized by instability, multiple caregivers, and violence exposure remain significant (see Chapters 39 and 40).

The association between an inadequate nutrient supply to the fetus and low birthweight has been recognized for decades; this adaptation on the part of the fetus presumably increases the likelihood that the fetus will survive until birth. For any potential fetal insult, the extent and nature of its effects are determined by characteristics of the host as well as the dose and timing of the exposure. Inherited differences in the metabolism of ethanol, timing of exposure, and the mother's diet may explain the variability in fetal alcohol effects. Organ systems are most vulnerable during periods of maximum growth and differentiation, generally during the 1st trimester (organogenesis). http://www2.epa.gov/children/children-are-not-little-adults details critical periods and specific developmental abnormalities.

Fetal adaptations or responses to an adverse situation in utero (referred to as *fetal programming* or *developmental plasticity*) have lifelong implications for the individual. Fetal programming may prepare the fetus for an environment that matches that experienced in utero. Fetal programming in response to some environmental and nutritional signals in utero increase the risk of cardiovascular disease, diabetes, and obesity in later life. These adverse long-term effects appear to represent a mismatch between fetal and neonatal environmental conditions and the conditions that the individual will confront later in life; a fetus deprived of adequate calories may or may not as a child or teenager face famine. One proposed mechanism for fetal programming is **epigenetic imprinting**, in which two genes are inherited but one is turned off through environmentally induced epigenetic modification (see Chapters 80 and 81.1). Imprinted genes play a critical role in fetal growth and thus may be responsible for the subsequent lifelong effects on growth and related disorders.

Just as the fetal adaptations to the in utero environment may increase the likelihood of later metabolic conditions, the fetus adapts to the mother's psychologic distress. In response to the stressful environment, physiologic changes involving the hypothalamic–pituitary–adrenal axis and the autonomic nervous system occur. Dysregulation of the hypothalamic–pituitary–adrenal axis and autonomic nervous system may explain the associations observed in some but not all studies between maternal distress and negative infant outcomes, including low birthweight, spontaneous abortion, prematurity, and decreased head circumference. In addition, children born to mothers experiencing high stress levels have been found to have higher rates of inattention, impulsivity, conduct disorders, and cognitive changes. Although these changes may have been adaptive in primitive cultures, they are maladaptive in modern societies, leading to psychopathology. Genetic variability, timing of stress during sensitive periods, and the quality of postnatal parenting can attenuate or exacerbate these associations.

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Chapter 9

The Newborn

John M. Olsson

(See also Chapter 94.)

Regardless of gestational age, the newborn (neonatal) period begins at birth and includes the 1st mo of life. During this time, marked physiologic transitions occur in all organ systems, and the infant learns to respond to many forms of external stimuli. Because infants thrive physically and psychologically only in the context of their social relationships, any description of the newborn's developmental status has to include consideration of the parents' role as well.

PARENTAL ROLE IN MOTHER–INFANT ATTACHMENT

Parenting a newborn infant requires dedication because a newborn's needs are urgent, continuous, and often unclear. Parents must attend to an infant's signals and respond empathically. Many factors influence parents' ability to assume this role.

Prenatal Factors

Pregnancy is a period of psychologic preparation for the profound demands of parenting. Women may experience ambivalence, particularly (but not exclusively) if the pregnancy was unplanned. If financial worries, physical illness, prior miscarriages or stillbirths, or other crises interfere with psychologic preparation, the neonate may not be welcomed. For adolescent mothers, the demand that they relinquish their own developmental agenda, such as an active social life, may be especially burdensome.

The early experience of being mothered may establish unconsciously held expectations about nurturing relationships that permit mothers to "tune in" to their infants. These expectations are linked with the quality of later infant–parent interactions. Mothers whose early childhoods were marked by traumatic separations, abuse, or neglect may find it especially difficult to provide consistent, responsive care. Instead, they may reenact their childhood experiences with their own infants, as if unable to conceive of the mother–child relationship in any other way. Bonding may be adversely affected by several risk factors during pregnancy and in the postpartum period that undermine the mother–child relationship and may threaten the infant's cognitive and emotional development (Table 9-1).

Social support during pregnancy, particularly support from the father and close family members, is also important. Conversely, conflict with or abandonment by the father during pregnancy may diminish the mother's ability to become absorbed with her infant. Anticipation

Table 9-1 Prenatal Risk Factors for Attachment
Recent death of a loved one
Previous loss of or serious illness in another child
Prior removal of a child
History of depression or serious mental illness
History of infertility or pregnancy loss
Troubled relationship with parents
Financial stress or job loss
Marital discord or poor relationship with the other parent
Recent move or no community ties
No friends or social network
Unwanted pregnancy
No good parenting model
Experience of poor parenting
Drug and/or alcohol abuse
Extreme immaturity

From Dixon SD, Stein MT: Encounters with children: pediatric behavior and development, *ed 3, St. Louis, 2000, Mosby, p 74.*

of an early return to work may make some women reluctant to fall in love with their babies because of anticipated separation. Returning to work should be delayed for at least 6 wk, by which time feeding and basic behavioral adjustments have been established.

Many decisions have to be made by parents in anticipation of the birth of their child. One important choice is that of how the infant will be nourished. Among the important benefits of breastfeeding is its promotion of bonding. Providing breastfeeding education for the parents at the prenatal visit by the pediatrician and by the obstetrician during prenatal care can increase maternal confidence in breastfeeding after delivery and reduce stress during the newborn period (see Chapter 45).

Peripartum and Postpartum Influences

The continuous presence during labor of a woman trained to offer friendly support and encouragement (a **doula**) results in shorter labor, fewer obstetric complications (including cesarean section), and reduced postpartum hospital stays. Early skin-to-skin contact between mothers and infants immediately after birth may correlate with an increased rate and longer duration of breastfeeding. Most new parents value even a brief period of uninterrupted time in which to get to know their new infant, and increased mother–infant contact over the 1st days of life may improve long-term mother–child interactions. Nonetheless, early separation, although predictably very stressful, does not inevitably impair a mother's ability to bond with her infant. Early discharge home from the maternity ward may undermine bonding, particularly when a new mother is required to resume full responsibility for a busy household.

Postpartum depression may occur in the 1st wk or up to 6 mo after delivery and can adversely affect neonatal growth and development. Screening methods are available for use during neonatal and infant visits to the pediatric provider (Table 9-2). Referral for care will greatly accelerate recovery.

THE INFANT'S ROLE IN MOTHER–INFANT ATTACHMENT

The in utero environment contributes greatly but not completely to the future growth and development of the fetus. Abnormalities in maternal–fetal placental circulation and maternal glucose metabolism or the presence of maternal infection can result in abnormal fetal growth. Infants may be small or large for gestational age as a result. These abnormal growth patterns not only predispose infants to an increased requirement for medical intervention, but also may affect their ability to respond behaviorally to their parents.

Physical Examination

Examination of the newborn should include an evaluation of growth and an observation of behavior. The average term newborn weighs approximately 3.4 kg (7.5 lb); boys are slightly heavier than girls. Average weight does vary by ethnicity and socioeconomic status. The average length and head circumference are about 50 cm (20 in) and 35 cm (14 in), respectively, in term infants. Each newborn's growth parameters should be plotted on growth curves specific for that infant's gestational age to determine the appropriateness of size. Likewise specific growth charts for conditions associated with variations in growth patterns have also been developed. The infant's response to being examined may be useful in assessing its vigor, alertness, and tone. Observing how the parents handle their infant, their comfort and affection, is also important. The order of the physical examination should be from the least to the most intrusive maneuver. Assessing visual tracking and response to sound and noting changes of tone with level of activity and alertness are very helpful. Performing this examination and sharing impression with parents is an important opportunity to facilitate bonding (see Chapter 94).

Interactional Abilities

Soon after birth, neonates are alert and ready to interact and nurse. This first alert-awake period may be affected by maternal analgesics and anesthetics or fetal hypoxia. Neonates are nearsighted, having a fixed focal length of 8-12 inches, approximately the distance from the breast to the mother's face, as well as an inborn visual preference for faces. Hearing is well developed, and infants preferentially turn toward a female voice. These innate abilities and predilections increase the likelihood that when a mother gazes at her newborn, the baby will gaze back. The initial period of social interaction, usually lasting about 40 minutes, is followed by a period of somnolence. After that, briefer periods of alertness or excitation alternate with sleep. If a mother misses her baby's first alert-awake period, she may not experience as long a period of social interaction for several days. The hypothalamic–midbrain–limbic–paralimbic–cortical circuit of the parents interact to support responses to the infants that are critical for effective parenting (e.g., emotion, attention, motivation, empathy, and decision making).

Modulation of Arousal

Adaptation to extrauterine life requires rapid and profound physiologic changes, including aeration of the lungs, rerouting of the circulation, and activation of the intestinal tract. The necessary behavioral changes are no less profound. To obtain nourishment, to avoid hypo- and hyperthermia, and to ensure safety, neonates must react appropriately to an expanded range of sensory stimuli. Infants must become aroused in response to stimulation, but not so overaroused that their behavior becomes disorganized. Underaroused infants are not able to feed and interact; overaroused infants show signs of **autonomic instability,** including flushing or mottling, perioral pallor, hiccupping, vomiting, uncontrolled limb movements, and inconsolable crying.

Behavioral States

The organization of infant behavior into discrete behavioral states may reflect an infant's inborn ability to regulate arousal. *Six states* have been described: quiet sleep, active sleep, drowsy, alert, fussy, and crying. In the **alert state,** infants visually fixate on objects or faces and follow them horizontally and (within a month) vertically; they also reliably turn toward a novel sound, as if searching for its source. When overstimulated, they may calm themselves by looking away, yawning, or sucking on their lips or hands, thereby increasing parasympathetic activity and reducing sympathetic nervous activity. The behavioral state determines an infant's muscle tone, spontaneous movement, electroencephalogram pattern, and response to stimuli. In **active sleep,** an infant may show progressively less reaction to a repeated heel stick (habituation), whereas in the **drowsy state,** the same stimulus may push a child into fussing or crying.

Mutual Regulation

Parents actively participate in an infant's state regulation, alternately stimulating and soothing. In turn, they are regulated by the infant's signals, responding to cries of hunger with a letdown of milk (or with a bottle). Such interactions constitute a system directed toward furthering the infant's physiologic homeostasis and physical growth. At the same time, they form the basis for the emerging psychologic relationship between parent and child. Infants come to associate the presence of the parent with the pleasurable reduction of tension (as in feeding) and show this preference by calming more quickly for their mother than for a stranger. This response, in turn, strengthens a mother's sense of efficacy and her connection with her baby.

IMPLICATIONS FOR THE PEDIATRICIAN

The pediatrician can support healthy newborn development in several ways.

Optimal Practices

A prenatal pediatric visit allows pediatricians to assess potential threats to bonding (a tense spousal relationship) and sources of social support. Supportive hospital policies include the use of birthing rooms rather than operating suites and delivery rooms; encouragement for the father or a trusted relative or friend to remain with the mother during labor or the provision of a professional doula; the practice of giving the newborn infant to the mother immediately after drying and a brief assessment; placement of the newborn in the mother's room rather

Table 9-2 Edinburgh Postnatal Depression Scale

INSTRUCTIONS FOR USERS

1. The mother is asked to underline the response that comes closest to how she has been feeling in the previous 7 days.
2. All 10 items must be completed.
3. Care should be taken to avoid the possibility of the mother discussing her answers with others.
4. The mother should complete the scale herself, unless she has limited English or has difficulty with reading.
5. The Edinburgh Postnatal Depression Scale may be used at 6-8 wk to screen postnatal women. The child health clinic, a postnatal checkup, or a home visit may provide a suitable opportunity for its completion.

Edinburgh Postnatal Depression Scale

Name:

Address:

Baby's age:

Because you have recently had a baby, we would like to know how you are feeling. Please underline the answer that comes closest to how you have felt in the past 7 days, not just how you feel today.

Here is an example, already completed.

I have felt happy:
- Yes, all the time
- *Yes, most of the time*
- No, not very often
- No, not at all

This would mean: "I have felt happy most of the time" during the past week. Please complete the other questions in the same way.

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   - As much as I always could
   - Not quite so much now
   - Definitely not so much now
   - Not at all
2. I have looked forward with enjoyment to things
   - As much as I ever did
   - Rather less than I used to
   - Definitely less than I used to
   - Hardly at all

*3. I have blamed myself unnecessarily when things went wrong
   - Yes, most of the time
   - Yes, some of the time
   - Not very often
   - No, never

4. I have been anxious or worried for no good reason
   - No, not at all
   - Hardly ever
   - Yes, sometimes
   - Yes, very often

*5. I have felt scared or panicky for no very good reason
   - Yes, quite a lot
   - Yes, sometimes
   - No, not much
   - No, not at all

*6. Things have been getting on top of me
   - Yes, most of the time I haven't been able to cope at all
   - Yes, sometimes I haven't been coping as well as usual
   - No, most of the time I have coped quite well
   - No, I have been coping as well as ever

*7. I have been so unhappy that I have had difficulty sleeping
   - Yes, most of the time
   - Yes, sometimes
   - Not very often
   - No, not at all

*8. I have felt sad or miserable
   - Yes, most of the time
   - Yes, quite often
   - Not very often
   - No, not at all

*9. I have been so unhappy that I have been crying
   - Yes, most of the time
   - Yes, quite often
   - Only occasionally
   - No, never

*10. The thought of harming myself has occurred to me
   - Yes, quite often
   - Sometimes
   - Hardly ever
   - Never

Response categories are scored 0, 1, 2, and 3 according to increased severity of the symptom. Items marked with an asterisk (*) are reverse scored (i.e., 3, 2, 1, and 0). The total score is calculated by adding the scores for each of the 10 items. Users may reproduce the scale without further permission providing they respect copyright (which remains with the *British Journal of Psychiatry*) by quoting the names of the authors, the title, and the source of the paper in all reproduced copies.

From Currie ML, Rademacher R: The pediatrician's role in recognizing and intervening in postpartum depression, Pediatr Clin North Am *51:785–801, 2004.*

than in a central nursery; and avoiding in-hospital distribution of infant formula. Such policies ("Baby Friendly Hospital") have been shown to significantly increase breastfeeding rates (see Chapter 94.3). After discharge, home visits by nurses and lactation counselors can reduce early feeding problems and identify emerging medical conditions in either mother or baby. Infants requiring transport to another hospital should be brought to see the mother first, if at all possible. On discharge home, fathers can shield mothers from unnecessary visits and calls and take over household duties, allowing mothers and infants time to get to know each other without distractions. The first office visit should occur during the 1st 2 wk after discharge to determine how smoothly the mother and infant are making the transition to life at home. Babies who are discharged early, those who are breastfeeding, and those who are at risk for jaundice should be seen 1-3 days after discharge.

Assessing Parent–Infant Interactions

During a feeding or when infants are alert and face-to-face with their parents, it is normal for the dyad to appear absorbed in one another. Infants who become overstimulated by the mother's voice or activity may turn away or close their eyes, leading to a premature termination of the encounter. Alternatively, the infant may be ready to interact, but the mother may appear preoccupied. Asking a new mother about her own emotional state, and inquiring specifically about a history of depression, facilitates referral for therapy, which may provide long-term benefits to the child. Pediatricians may detect **postpartum depression** using the Edinburgh Postnatal Depression Scale at well-child visits during the 1st yr (see Table 9-2).

Teaching About Individual Competencies

The Newborn Behavior Assessment Scale (NBAS) provides a formal measure of an infant's neurodevelopmental competencies, including state control, autonomic reactivity, reflexes, habituation, and orientation toward auditory and visual stimuli. This examination can also be used to demonstrate to parents an infant's capabilities and vulnerabilities. Parents might learn that they need to undress their infant to increase the level of arousal or to swaddle the infant to reduce overstimulation by containing random arm movements. The NBAS can be

used to support the development of positive early parent-infant relationships. Demonstration of the NBAS to parents in the 1st wk of life has been shown to correlate with improvements in the caretaking environment months later.

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Chapter 10

The First Year

Susan Feigelman

The prenatal period and the 1st yr of life provide the platform for remarkable growth and development, setting the trajectory for a child's life. Neural plasticity, the ability of the brain to be shaped by experience, both positive and negative, is at its peak. Total brain volume doubles in the 1st yr of life and increases by an additional 15% over the 2nd yr. Total brain volume at age 1 mo is approximately 36% of adult volume but by age 1 yr is approximately 72% (83% by 2 yr) (Fig. 10-1). The acquisition of seemingly "simple" skills, such as swallowing, reflect a series of intricate and highly coordinated processes involving multiple levels of neural control distributed among several physiologic systems whose nature and relationships mature throughout the 1st yr of life. Substantial learning of the basic tools of language (phonology, word segmentation) occurs during infancy. Speech processing in older individuals requires defined and precise neuronal networks; the infant brain possesses a structural and functional organization similar to that of adults, suggesting that structural neurologic processing of speech may guide infants to discover the properties of his or her native language. Myelination of the cortex begins at 7-8 mo gestation and continues into adolescence and young adulthood. It proceeds in a posterior to anterior fashion, allowing progressive maturation of sensory, motor, and finally associative pathways. Given the importance of iron, cholesterol, and other nutrients in myelination, adequate stores throughout infancy are critical (see Chapter 45). Inadequate dietary intake, insufficient interactions with caregivers or the wider environment may alter experience-dependent processes that are critical to brain structure development and function during infancy. Although some of these processes may be delayed, as the periods of plasticity close during the rapid developmental changes occurring in infancy, more permanent deficits may result.

The infant acquires new competences in all developmental domains. The concept of developmental trajectories recognizes that complex skills build on simpler ones; it is also important to realize how development in each domain affects functioning in all of the others. All growth parameters should be plotted using the World Heath Organization charts which show how children from birth through 72 mo "should" grow under optimal circumstances (see Figs. 11-1 and 11-2). Table 10-1 presents an overview of key milestones by domain; Table 10-2 presents similar information arranged by age. Table 10-3 presents age at time of appearance on x-ray of centers of ossification. Parents often

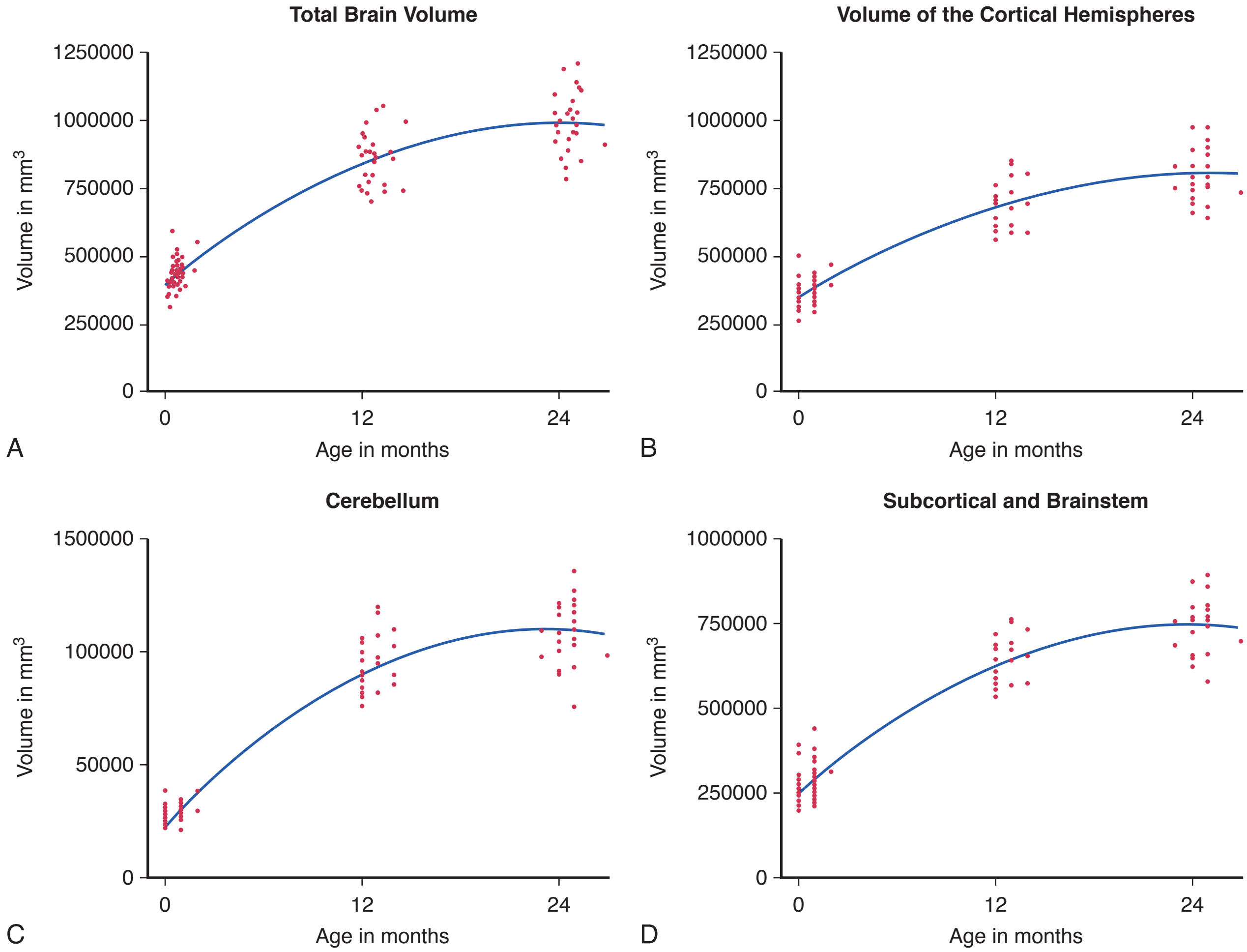

Figure 10-1 Scatterplots showing brain growth in the 1st 2 yr of life. **A,** Total brain volume by age at scan. **B,** Cortical hemispheres. **C,** Cerebellum. **D,** Subcortical region and brainstem. *(From Knickmeyer RC, Gouttard S, Kang C, et al: A structural MRI study of human brain development from birth to 2 years.* J Neurosci *28(47):12176–12182, 2008, Fig. 2.)*

Table 10-1 Developmental Milestones in the 1st 2 Yr of Life

MILESTONE	AVERAGE AGE OF ATTAINMENT (MO)	DEVELOPMENTAL IMPLICATIONS
GROSS MOTOR		
Holds head steady while sitting	2	Allows more visual interaction
Pulls to sit, with no head lag	3	Muscle tone
Brings hands together in midline	3	Self-discovery of hands
Asymmetric tonic neck reflex gone	4	Can inspect hands in midline
Sits without support	6	Increasing exploration
Rolls back to stomach	6.5	Truncal flexion, risk of falls
Walks alone	12	Exploration, control of proximity to parents
Runs	16	Supervision more difficult
FINE MOTOR		
Grasps rattle	3.5	Object use
Reaches for objects	4	Visuomotor coordination
Palmar grasp gone	4	Voluntary release
Transfers object hand to hand	5.5	Comparison of objects
Thumb-finger grasp	8	Able to explore small objects
Turns pages of book	12	Increasing autonomy during book time
Scribbles	13	Visual–motor coordination
Builds tower of 2 cubes	15	Uses objects in combination
Builds tower of 6 cubes	22	Requires visual, gross, and fine motor coordination
COMMUNICATION AND LANGUAGE		
Smiles in response to face, voice	1.5	More active social participant
Monosyllabic babble	6	Experimentation with sound, tactile sense
Inhibits to "no"	7	Response to tone (nonverbal)
Follows one-step command with gesture	7	Nonverbal communication
Follows one-step command without gesture	10	Verbal receptive language (e.g., "Give it to me")
Says "mama" or "dada"	10	Expressive language
Points to objects	10	Interactive communication
Speaks first real word	12	Beginning of labeling
Speaks 4-6 words	15	Acquisition of object and personal names
Speaks 10-15 words	18	Acquisition of object and personal names
Speaks 2-word sentences (e.g., "Mommy shoe")	19	Beginning grammatization, corresponds with 50 word vocabulary
COGNITIVE		
Stares momentarily at spot where object disappeared	2	Lack of object permanence (out of sight, out of mind [e.g., yarn ball dropped])
Stares at own hand	4	Self-discovery, cause and effect
Bangs 2 cubes	8	Active comparison of objects
Uncovers toy (after seeing it hidden)	8	Object permanence
Egocentric symbolic play (e.g., pretends to drink from cup)	12	Beginning symbolic thought
Uses stick to reach toy	17	Able to link actions to solve problems
Pretend play with doll (e.g., gives doll bottle)	17	Symbolic thought

seek information about "normal development" during this period and should be directed to reliable sources, including the American Academy of Pediatrics website (www.AAP.org).

AGE 0-2 MONTHS

In the full-term infant, myelination is present by the time of birth in the dorsal brainstem, cerebellar peduncles, and posterior limb of the internal capsule. The cerebellar white matter acquires myelin by 1 mo of age and is well myelinated by 3 mo of age. The subcortical white matter of the parietal, posterior frontal, temporal, and calcarine cortex is partially myelinated by 3 mo of age. In this period, the infant experiences tremendous growth. Physiologic changes allow the establishment of effective feeding routines and a predictable sleep–wake cycle. The social interactions that occur as parents and infants accomplish these tasks lay the foundation for cognitive and emotional development.

Physical Development

A newborn's weight may initially decrease 10% below birthweight in the 1st wk as a result of excretion of excess extravascular fluid and limited nutritional intake. Nutrition improves as colostrum is replaced by higher-fat breast milk, as infants learn to latch on and suck more efficiently, and as mothers become more comfortable with feeding techniques. Infants regain or exceed birthweight by 2 wk of age and should grow at approximately 30 g (1 oz)/per day during the 1st mo (see Table 15-1). This is the period of fastest postnatal growth. Arms are held to the sides. Limb movements consist largely of uncontrolled writhing, with apparently purposeless opening and closing of the hands. Smiling occurs involuntarily. Eye gaze, head turning, and sucking are under better control and thus can be used to demonstrate infant perception and cognition. An infant's preferential turning toward the mother's voice is evidence of recognition memory.

Six behavioral states have been described (see Chapter 9). Initially, sleep and wakefulness are evenly distributed throughout the 24 hr day (Fig. 10-2). Neurologic maturation accounts for the consolidation of sleep into blocks of 5 or 6 hr at night, with brief awake, feeding periods. Learning also occurs; infants whose parents are consistently more interactive and stimulating during the day learn to concentrate their sleeping during the night.

Cognitive Development

Infants can differentiate among patterns, colors, and consonants. They can recognize facial expressions (smiles) as similar, even when they appear on different faces. They also can match abstract properties of stimuli, such as contour, intensity, or temporal pattern, across sensory modalities. Infants at 2 mo of age can discriminate rhythmic patterns in native vs non-native language. Infants appear to seek stimuli actively,

Table 10-2 Emerging Patterns of Behavior During the 1st Yr of Life*

NEONATAL PERIOD (1ST 4 WK)	
Prone:	Lies in flexed attitude; turns head from side to side; head sags on ventral suspension
Supine:	Generally flexed and a little stiff
Visual:	May fixate face on light in line of vision; "doll's-eye" movement of eyes on turning of the body
Reflex:	Moro response active; stepping and placing reflexes; grasp reflex active
Social:	Visual preference for human face
AT 1 MO	
Prone:	Legs more extended; holds chin up; turns head; head lifted momentarily to plane of body on ventral suspension
Supine:	Tonic neck posture predominates; supple and relaxed; head lags when pulled to sitting position
Visual:	Watches person; follows moving object
Social:	Body movements in cadence with voice of other in social contact; beginning to smile
AT 2 MO	
Prone:	Raises head slightly farther; head sustained in plane of body on ventral suspension
Supine:	Tonic neck posture predominates; head lags when pulled to sitting position
Visual:	Follows moving object 180 degrees
Social:	Smiles on social contact; listens to voice and coos
AT 3 MO	
Prone:	Lifts head and chest with arms extended; head above plane of body on ventral suspension
Supine:	Tonic neck posture predominates; reaches toward and misses objects; waves at toy
Sitting:	Head lag partially compensated when pulled to sitting position; early head control with bobbing motion; back rounded
Reflex:	Typical Moro response has not persisted; makes defensive movements or selective withdrawal reactions
Social:	Sustained social contact; listens to music; says "aah, ngah"
AT 4 MO	
Prone:	Lifts head and chest, with head in approximately vertical axis; legs extended
Supine:	Symmetric posture predominates, hands in midline; reaches and grasps objects and brings them to mouth
Sitting:	No head lag when pulled to sitting position; head steady, tipped forward; enjoys sitting with full truncal support
Standing:	When held erect, pushes with feet
Adaptive:	Sees raisin, but makes no move to reach for it
Social:	Laughs out loud; may show displeasure if social contact is broken; excited at sight of food
AT 7 MO	
Prone:	Rolls over; pivots; crawls or creep-crawls (Knobloch)
Supine:	Lifts head; rolls over; squirms
Sitting:	Sits briefly, with support of pelvis; leans forward on hands; back rounded
Standing:	May support most of weight; bounces actively
Adaptive:	Reaches out for and grasps large object; transfers objects from hand to hand; grasp uses radial palm; rakes at raisin
Language:	Forms polysyllabic vowel sounds
Social:	Prefers mother; babbles; enjoys mirror; responds to changes in emotional content of social contact
AT 10 MO	
Sitting:	Sits up alone and indefinitely without support, with back straight
Standing:	Pulls to standing position; "cruises" or walks holding on to furniture
Motor:	Creeps or crawls
Adaptive:	Grasps objects with thumb and forefinger; pokes at things with forefinger; picks up pellet with assisted pincer movement; uncovers hidden toy; attempts to retrieve dropped object; releases object grasped by other person
Language:	Repetitive consonant sounds ("mama," "dada")
Social:	Responds to sound of name; plays peek-a-boo or pat-a-cake; waves bye-bye
AT 1 YR	
Motor:	Walks with one hand held; rises independently, takes several steps (Knobloch)
Adaptive:	Picks up raisin with unassisted pincer movement of forefinger and thumb; releases object to other person on request or gesture
Language:	Says a few words besides "mama," "dada"
Social:	Plays simple ball game; makes postural adjustment to dressing

*Data are derived from those of Gesell (as revised by Knobloch), Shirley, Provence, Wolf, Bailey, and others.
Data from Knobloch H, Stevens F, Malone AF: Manual of developmental diagnosis, *Hagerstown, MD, 1980, Harper & Row.*

as though satisfying an innate need to make sense of the world. These phenomena point to the integration of sensory inputs in the central nervous system. Caretaking activities provide visual, tactile, olfactory, and auditory stimuli; all of these support the development of cognition. Infants habituate to the familiar, attending less to repeated stimuli and increasing their attention to novel stimuli.

Emotional Development

The infant is dependent on the environment to meet his or her needs. The consistent availability of a trusted adult to meet the infant's urgent needs creates the conditions for secure attachment. Basic trust vs mistrust, the first of Erikson's psychosocial stages (see Chapter 6), depends on attachment and reciprocal maternal bonding. Crying occurs in response to stimuli that may be obvious (a soiled diaper), but are often obscure. Infants who are consistently picked up and held in response to distress cry less at 1 yr and show less-aggressive behavior at 2 yr. Cross-cultural studies show that in societies in which infants are carried close to the mother, babies cry less than in societies in which babies are only periodically carried. Crying normally peaks at about 6 wk of age, when healthy infants may cry up to 3 hr/day, then decreases to 1 hr or less by 3 mo. Infants cry in response to the cry of another infant, which has been interpreted as an early sign of empathy development.

Crying/fussiness is present in 20% of infants younger than 2 mo of age and although in most it is a transient and normal behavioral activity, it is often associated with parental concern and distress. Excessive

Table 10-3 Time of Appearance in X-Rays of Centers of Ossification in Infancy and Childhood

BOYS—AGE AT APPEARANCE*	BONES AND EPIPHYSEAL CENTERS	GIRLS—AGE AT APPEARANCE*
HUMERUS, HEAD		
3 wk		3 wk
CARPAL BONES		
2 mo ± 2 mo	Capitate	2 mo ± 2 mo
3 mo ± 2 mo	Hamate	2 mo ± 2 mo
30 mo ± 16 mo	Triangular†	21 mo ± 14 mo
42 mo ± 19 mo	Lunate†	34 mo ± 13 mo
67 mo ± 19 mo	Trapezium†	47 mo ± 14 mo
69 mo ± 15 mo	Trapezoid†	49 mo ± 12 mo
66 mo ± 15 mo	Scaphoid†	51 mo ± 12 mo
No standards available	Pisiform†	No standards available
METACARPAL BONES		
18 mo ± 5 mo	II	12 mo ± 3 mo
20 mo ± 5 mo	III	13 mo ± 3 mo
23 mo ± 6 mo	IV	15 mo ± 4 mo
26 mo ± 7 mo	V	16 mo ± 5 mo
32 mo ± 9 mo	I	18 mo ± 5 mo
FINGERS (EPIPHYSES)		
16 mo ± 4 mo	Proximal phalanx, 3rd finger	10 mo ± 3 mo
16 mo ± 4 mo	Proximal phalanx, 2nd finger	11 mo ± 3 mo
17 mo ± 5 mo	Proximal phalanx, 4th finger	11 mo ± 3 mo
19 mo ± 7 mo	Distal phalanx, 1st finger	12 mo ± 4 mo
21 mo ± 5 mo	Proximal phalanx, 5th finger	14 mo ± 4 mo
24 mo ± 6 mo	Middle phalanx, 3rd finger	15 mo ± 5 mo
24 mo ± 6 mo	Middle phalanx, 4th finger	15 mo ± 5 mo
26 mo ± 6 mo	Middle phalanx, 2nd finger	16 mo ± 5 mo
28 mo ± 6 mo	Distal phalanx, 3rd finger	18 mo ± 4 mo
28 mo ± 6 mo	Distal phalanx, 4th finger	18 mo ± 5 mo
32 mo ± 7 mo	Proximal phalanx, 1st finger	20 mo ± 5 mo
37 mo ± 9 mo	Distal phalanx, 5th finger	23 mo ± 6 mo
37 mo ± 8 mo	Distal phalanx, 2nd finger	23 mo ± 6 mo
39 mo ± 10 mo	Middle phalanx, 5th finger	22 mo ± 7 mo
152 mo ± 18 mo	Sesamoid (adductor pollicis)	121 mo ± 13 mo
HIP AND KNEE		
Usually present at birth	Femur, distal	Usually present at birth
Usually present at birth	Tibia, proximal	Usually present at birth
4 mo ± 2 mo	Femur, head	4 mo ± 2 mo
46 mo ± 11 mo	Patella	29 mo ± 7 mo
FOOT AND ANKLE‡		

Values represent mean ± standard deviation, when applicable.
*To nearest month.
†Except for the capitate and hamate bones, the variability of carpal centers is too great to make them very useful clinically.
‡Standards for the foot are available, but normal variation is wide, including some familial variants, so this area is of little clinical use.
The norms present a composite of published data from the Fels Research Institute, Yellow Springs, OH (Pyle SI, Sontag L: AJR Am J Roentgenol *49:102, 1943), and unpublished data from the Brush Foundation, Case Western Reserve University, Cleveland, OH, and the Harvard School of Public Health, Boston, MA. Compiled by Lieb, Buehl, and Pyle.*

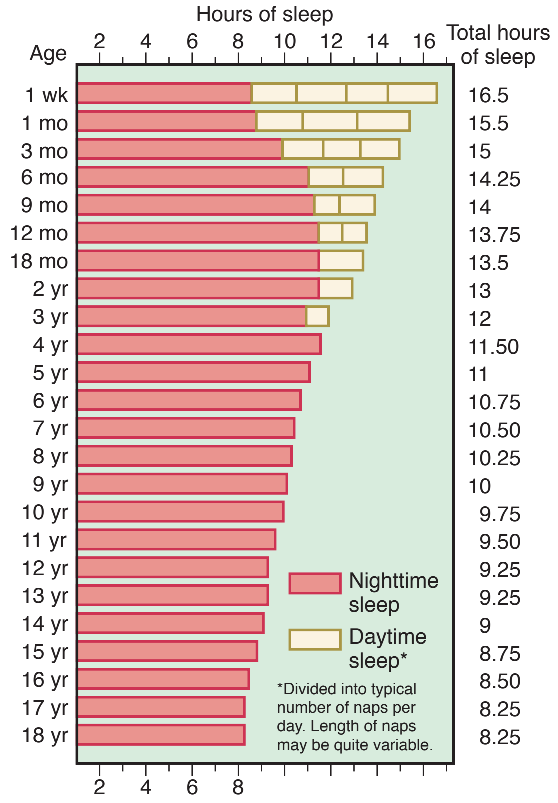

Figure 10-2 Typical sleep requirements in children. *(From Ferber R: Solve your child's sleep problems, New York, 1985, Simon & Schuster.)*

crying (longer than 3 hr/day, longer than 3 days/wk lasting longer than 1 wk) and more often crying/fussiness persisting longer than 3-5 mo might be associated with child abuse, behavioral problems when an older child (anxiety, aggression, hyperactivity), decreased duration of breastfeeding and postnatal depression (uncertain which is the cause or effect). Most infants with crying/fussiness do not have gastroesophageal reflux, lactose intolerance, or cow-milk protein allergy. Some researchers believe excessive crying may be an early manifestation of migraines.

Infants have various signals for their needs and for getting attention from a caregiver. These behaviors progressively increase in intensity in many infants from changes in breathing and color, to postural and movement cures, and then to calm vocalizations. These precry cues, if not attended to, will eventually lead to active crying. Some infants may go directly to crying, perhaps based on temperament; these infants may be less easily consolable and may have feeding problems like refusal of feeds. Sensory integration issues may also be involved with the child being over responsive or sensory deprived.

Management of crying/fussiness should include teaching caregivers about precry cues and responding to the signal for feeding in a calm relaxed manner. If sensory overstimulation is a factor, creating a nondistracting, calm environment may help as well as swaddling. When lack of sensory stimulation is present, mother–infant skin-to-skin contact, and carrying the infant may be beneficial. In all situations, reassurance that this is both normal and transient, with only 5% of infants persisting beyond 3 mo of age, helps the family cope.

The emotional significance of any experience depends on both the individual child's temperament and the parent's responses (see Table 6-1); differing feeding schedules produce differing reactions. Hunger generates increasing tension; as the urgency peaks, the infant cries, the parent offers the breast or bottle and the tension dissipates. Infants fed "on demand" consistently experience this link between their distress, the arrival of the parent, and relief from hunger. Most infants fed on a fixed schedule quickly adapt their hunger cycle to the schedule. Those who cannot because they are temperamentally prone to irregular biologic rhythms experience periods of unrelieved hunger as well as unwanted feedings when they already feel full. Similarly, infants who are fed at the parents' convenience, with neither attention to the infant's hunger cues nor a fixed schedule, may not consistently experience feeding as the pleasurable reduction of tension. Infants with early dysregulation often show increased irritability and physiologic instability (spitting, diarrhea, poor weight gain) as well as later behavioral problems.

Implications for Parents and Pediatricians

Success or failure in establishing feeding and sleep cycles determines parents' feelings of efficacy. When things go well, the parents' anxiety and ambivalence, as well as the exhaustion of the early weeks, decrease. Infant issues (colic) or familial conflict will prevent this from occurring. With physical recovery from delivery and hormonal normalization, the mild postpartum depression that affects many mothers passes. If the mother continues to feel sad, overwhelmed, and anxious, the possibility of moderate to severe postpartum depression, found in 10-15% of postpartum women, needs to be considered. Major **depression** that arises during pregnancy or in the postpartum period threatens the mother–child relationship and is a risk factor for later cognitive and behavioral problems. The pediatrician may be the first professional to encounter the depressed mother and should be instrumental in assisting her in seeking treatment (see Chapter 9).

AGE 2-6 MONTHS

At about age 2 mo, the emergence of voluntary (social) smiles and increasing eye contact mark a change in the parent–child relationship, heightening the parents' sense of being loved reciprocally. During the next months, an infant's range of motor and social control and cognitive engagement increases dramatically. Mutual regulation takes the form of complex social interchanges, resulting in strong mutual attachment and enjoyment. Routines are established. Parents are less fatigued.

Physical Development

Between 3 and 4 mo of age, the rate of growth slows to approximately 20 g/day (see Table 15-1 and Figs. 11-1 and 11-2). By age 4 mo, birth weight is doubled. Early reflexes that limited voluntary movement recede. Disappearance of the asymmetric tonic neck reflex means that infants can begin to examine objects in the midline and manipulate them with both hands (see Chapter 590). Waning of the early grasp reflex allows infants both to hold objects and to let them go voluntarily. A novel object may elicit purposeful, although inefficient, reaching. The quality of spontaneous movements also changes, from larger writhing to smaller, circular movements that have been described as "fidgety." Abnormal or absent fidgety movements may constitute a risk factor for later neurologic abnormalities.

Increasing control of truncal flexion makes intentional rolling possible. Once infants can hold their heads steady while sitting, they can gaze across at things rather than merely looking up at them, opening up a new visual range. They can begin taking food from a spoon. At the same time, maturation of the visual system allows greater depth perception.

In this period, infants achieve stable state regulation and regular sleep–wake cycles. Total sleep requirements are approximately 14-16 hr/24 hr, with about 9-10 hr concentrated at night and 2 naps/day. Approximately 70% of infants sleep for a 6-8 hr stretch by age 6 mo (see Fig. 10-2). By 4-6 mo, the sleep electroencephalogram shows a mature pattern, with demarcation of rapid eye movement and 4 stages of non–rapid eye movement sleep. The sleep cycle remains shorter than in adults (50-60 min vs approximately 90 min). As a result, infants arouse to light sleep or wake frequently during the night, setting the stage for behavioral sleep problems (see Chapter 19).

Cognitive Development

The overall effect of these developments is a qualitative change. At 4 mo of age, infants are described as "hatching" socially, becoming interested in a wider world. During feeding, infants no longer focus exclusively on the mother, but become distracted. In the mother's arms, the infant may literally turn around, preferring to face outward.

Infants at this age also explore their own bodies, staring intently at their hands, vocalizing, blowing bubbles, and touching their ears, cheeks, and genitals. These explorations represent an early stage in the understanding of cause and effect as infants learn that voluntary muscle movements generate predictable tactile and visual sensations. They also have a role in the emergence of a sense of self, separate from the mother. This is the 1st stage of personality development. Infants come to associate certain sensations through frequent repetition. The proprioceptive feeling of holding up the hand and wiggling the fingers always accompanies the sight of the fingers moving. Such self sensations are consistently linked and reproducible at will. In contrast, sensations that are associated with "other" occur with less regularity and in varying combinations. The sound, smell, and feel of the mother sometimes appear promptly in response to crying, but sometimes do not. The satisfaction that the mother or another loving adult provides continues the process of attachment.

Emotional Development and Communication

Babies interact with increasing sophistication and range. The primary emotions of anger, joy, interest, fear, disgust, and surprise appear in appropriate contexts as distinct facial expressions. When face-to-face, the infant and a trusted adult can match affective expressions (smiling or surprise) approximately 30% of the time. Initiating games (singing, hand games) increases social development. Such face-to-face behavior reveals the infant's ability to share emotional states, the 1st step in the development of communication. Infants of depressed parents show a different pattern, spending less time in coordinated movement with their parents and making fewer efforts to reengage. Rather than anger, they show sadness and a loss of energy when the parents continue to be unavailable.

Implications for Parents and Pediatricians

Motor and sensory maturation makes infants at 3-6 mo exciting and interactive. Some parents experience their 4 mo old child's outward turning as a rejection, secretly fearing that their infants no longer love them. For most parents, this is a happy period. Most parents excitedly report that they can hold conversations with their infants, taking turns vocalizing and listening. Pediatricians share in the enjoyment, as the baby coos, makes eye contact, and moves rhythmically. Infants who do not show this reciprocal language and movements are at risk for autism spectrum disorders (see Chapter 30). If this visit does not feel joyful and relaxed, causes such as social stress, family dysfunction, parental mental illness, or problems in the infant–parent relationship should be considered. Parents can be reassured that responding to an infant's emotional needs cannot spoil the infant. Giving vaccines and drawing blood while the child is seated on the parent's lap or nursing at the breast increases pain tolerance.

AGE 6-12 MONTHS

With achievement of the sitting position, increased mobility, and new skills to explore the world around them, 6-12 mo old infants show advances in cognitive understanding and communication, and there are new tensions around the themes of attachment and separation. Infants develop will and intentions, characteristics that most parents welcome, but still find challenging to manage.

Physical Development

Growth slows more (see Table 15-1 and Figs. 11-1 and 11-2). By the 1st birthday, birth weight has tripled, length has increased by 50%, and head circumference has increased by 10 cm. The ability to sit unsupported (6-7 mo) and to pivot while sitting (around 9-10 mo) provides increasing opportunities to manipulate several objects at a time and to experiment with novel combinations of objects. These explorations are aided by the emergence of a thumb–finger grasp (8-9 mo) and a neat pincer grasp by 12 mo. Voluntary release emerges at 9 mo. Many infants begin crawling and pulling to stand around 8 mo, followed by cruising. Some walk by 1 yr. Motor achievements correlate with increasing myelinization and cerebellar growth. These gross motor skills expand infants' exploratory range and create new physical dangers, as well as opportunities for learning. Tooth eruption occurs, usually starting with the mandibular central incisors. Tooth development reflects skeletal maturation and bone age, although there is wide individual variation (see Table 10-3 and Chapter 307).

Cognitive Development

The 6 mo old infant has discovered his hands and will soon learn to manipulate objects. At first, everything is mouthed. In time, novel

objects are picked up, inspected, passed from hand to hand, banged, dropped, and then mouthed. Each action represents a nonverbal idea about what things are for (in Piagetian terms, a *schema;* see Chapter 6). The complexity of an infant's play, how many different schemata are brought to bear, is a useful index of cognitive development at this age. The pleasure, persistence, and energy with which infants tackle these challenges suggest the existence of an intrinsic drive or mastery motivation. Mastery behavior occurs when infants feel secure; those with less secure attachments show limited experimentation and less competence.

A major milestone is the achievement by 9 mo of **object permanence** (**constancy**), the understanding that objects continue to exist, even when not seen. At 4-7 mo of age, infants look down for a yarn ball that has been dropped but quickly give up if it is not seen. With object constancy, infants persist in searching. They will find objects hidden under a cloth or behind the examiner's back. Peek-a-boo brings unlimited pleasure as the child magically brings back the other player. Events seem to occur as a result of the child's own activities.

Emotional Development

The advent of object permanence corresponds with qualitative changes in social and communicative development. Infants look back and forth between an approaching stranger and a parent, and may cling or cry anxiously, demonstrating **stranger anxiety**. Separations often become more difficult. Infants who have been sleeping through the night for mo begin to awaken regularly and cry, as though remembering that the parents are in the next room.

A new demand for autonomy also emerges. Poor weight gain at this age often reflects a struggle between an infant's emerging independence and parent's control of the feeding situation. Use of the 2-spoon method of feeding (1 for the child and 1 for the parent), finger foods, and a high chair with tray table can avert potential problems. Tantrums make their first appearance as the drives for autonomy and mastery come in conflict with parental controls and the infants' still-limited abilities.

Communication

Infants at 7 mo of age are adept at nonverbal communication, expressing a range of emotions and responding to vocal tone and facial expressions. Around 9 mo of age, infants become aware that emotions can be shared between people; they show parents toys as a way of sharing their happy feelings. Between 8 and 10 mo of age, babbling takes on a new complexity, with multisyllabic sounds ("ba-da-ma"); babies can discriminate between languages. Infants in bilingual homes learn the characteristics and rules that govern 2 different languages. Social interaction (attentive adults taking turns vocalizing with the infant) profoundly influences the acquisition and production of new sounds. The first true word (i.e., a sound used consistently to refer to a specific object or person) appears in concert with an infant's discovery of object permanence. Picture books now provide an ideal context for verbal language acquisition. With a familiar book as a shared focus of attention, a parent and child engage in repeated cycles of pointing and labeling, with elaboration and feedback by the parent. The addition of sign language may support infant development while enhancing mother–infant communication.

Implications for Parents and Pediatricians

With the developmental reorganization that occurs around 9 mo of age, previously resolved issues of feeding and sleeping reemerge. Pediatricians can prepare parents at the 6 mo visit so that these problems can be understood as the result of developmental progress and not regression. Parents should be encouraged to plan ahead for necessary, and inevitable, separations (e.g., babysitter, daycare). Routine preparations may make these separations easier. Although controversial, the stability that comes with dual parent employment may be beneficial for long-term social emotional outcomes. Introduction of a **transitional object** may allow the infant to self-comfort in the parents' absence. The object cannot have any potential for asphyxiation or strangulation.

Infants' wariness of strangers often makes the 9 mo examination difficult, particularly if the infant is temperamentally prone to react negatively to unfamiliar situations. Initially, the pediatrician should avoid direct eye contact with the child. Time spent talking with the parent and introducing the child to a small, washable toy will be rewarded with more cooperation. The examination can be continued on the parent's lap when feasible.

Bibliography is available at Expert Consult.

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Chapter 11

The Second Year

Susan Feigelman

The toddler's newly found ability to walk allows separation and independence; however, the toddler continues to need secure attachment to the parents. At approximately 18 mo of age, the emergence of symbolic thought and language causes a reorganization of behavior, with implications across many developmental domains.

AGE 12-18 MONTHS

Physical Development

The toddler continues to experience considerable brain growth and myelination in the 2nd yr, resulting in an increase in head circumference of 2 cm over the year (Fig. 11-1; see also Fig. 10-1). Toddlers have relatively short legs and long torsos, with exaggerated lumbar lordosis and protruding abdomens. Growth in length continues at a steady rate (Fig. 11-2).

Most children begin to walk independently at around 12-15 mo of age. Early walking is not associated with advanced development in other domains. Infants initially toddle with a wide-based gait, with the knees bent and the arms flexed at the elbow; the entire torso rotates with each stride; the toes may point in or out, and the feet strike the floor flat. The appearance is that of genu varus (bowleg). Subsequent refinement leads to greater steadiness and energy efficiency. After several months of practice, the center of gravity shifts back and the torso stabilizes, while the knees extend and the arms swing at the sides for balance. The feet are held in better alignment, and the child is able to stop, pivot, and stoop without toppling over (see Chapters 672 and 673).

Cognitive Development

Exploration of the environment increases in parallel with improved dexterity (reaching, grasping, releasing) and mobility. Learning follows the precepts of Piaget's sensorimotor stage (see Chapter 6). Toddlers manipulate objects in novel ways to create interesting effects, such as stacking blocks or putting things into a computer disk drive. Playthings are also more likely to be used for their intended purposes (combs for hair, cups for drinking). Imitation of parents and older siblings or other children is an important mode of learning. Make-believe (symbolic) play centers on the child's own body (pretending to drink from an empty cup) (Table 11-1; also see Table 10-1).

Emotional Development

Infants who are approaching the developmental milestone of taking their first steps may be irritable. Once they start walking, their predominant mood changes markedly. Toddlers are described as "intoxicated" or "giddy" with their new ability and with the power to control the distance between themselves and their parents. Exploring toddlers orbit around their parents, moving away and then returning for a reassuring touch before moving away again. A securely attached child will

Text continued on p. 75

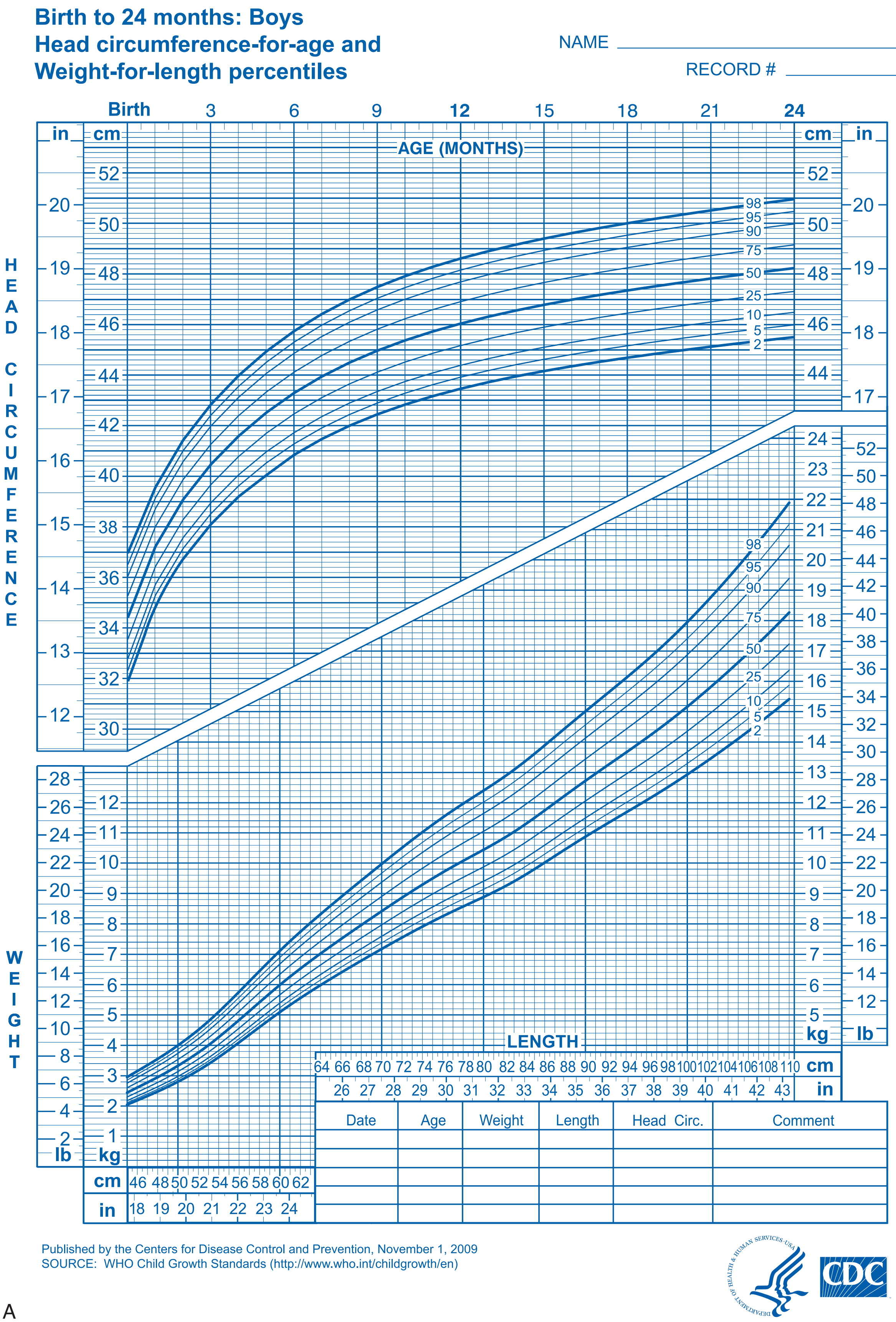

A

Figure 11-1 The World Health Organization Growth Charts. Weight/length and head circumference for boys **(A)** and girls **(B)**. *(Courtesy of the World Health Organization: WHO Child Growth Standards, 2014.* http://www.who.int/childgrowth/standards/en/.*)*

Continued

Birth to 24 months: Girls
Head circumference-for-age and
Weight-for-length percentiles

NAME ______________________

RECORD # __________

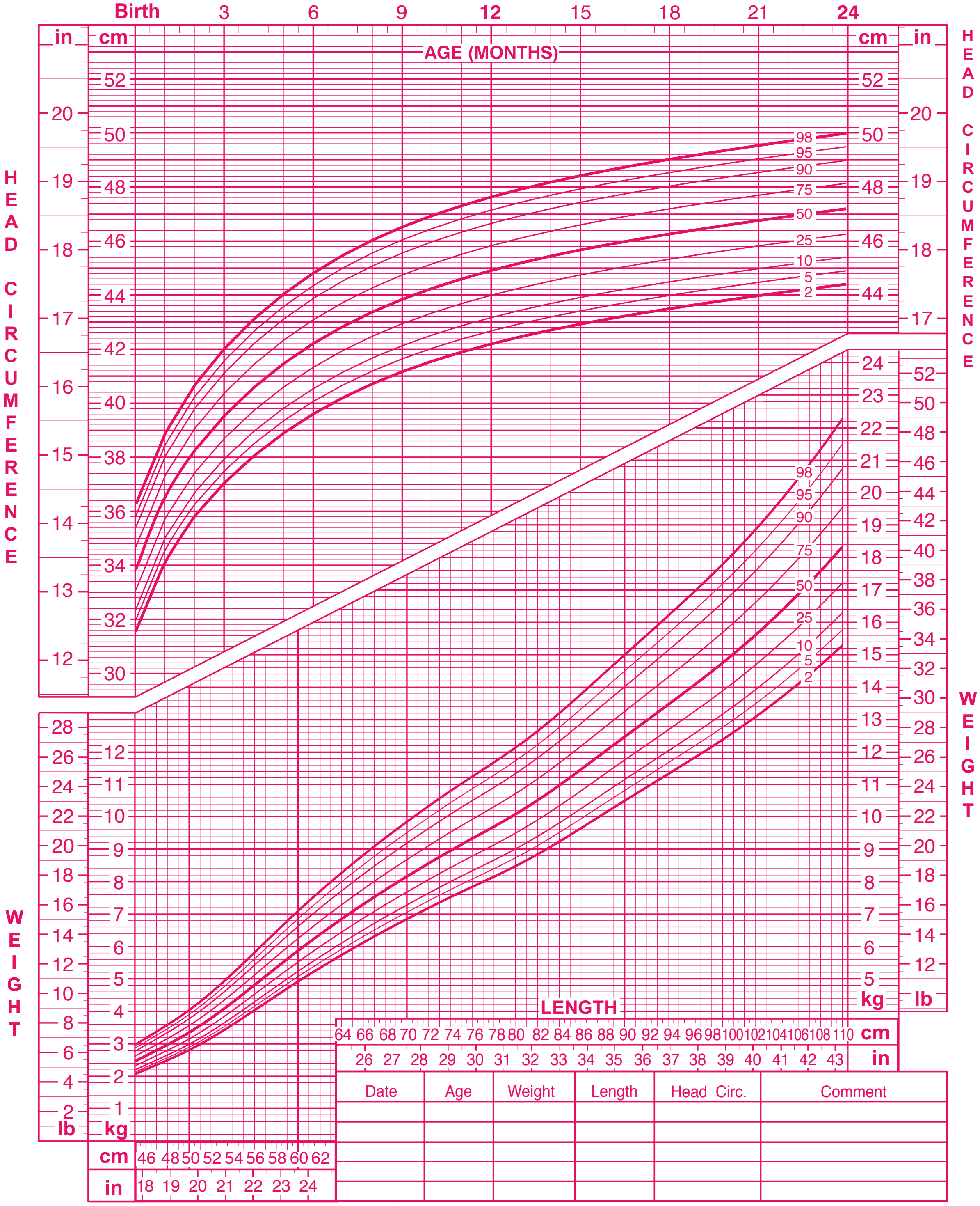

Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

B

Figure 11-1, cont'd

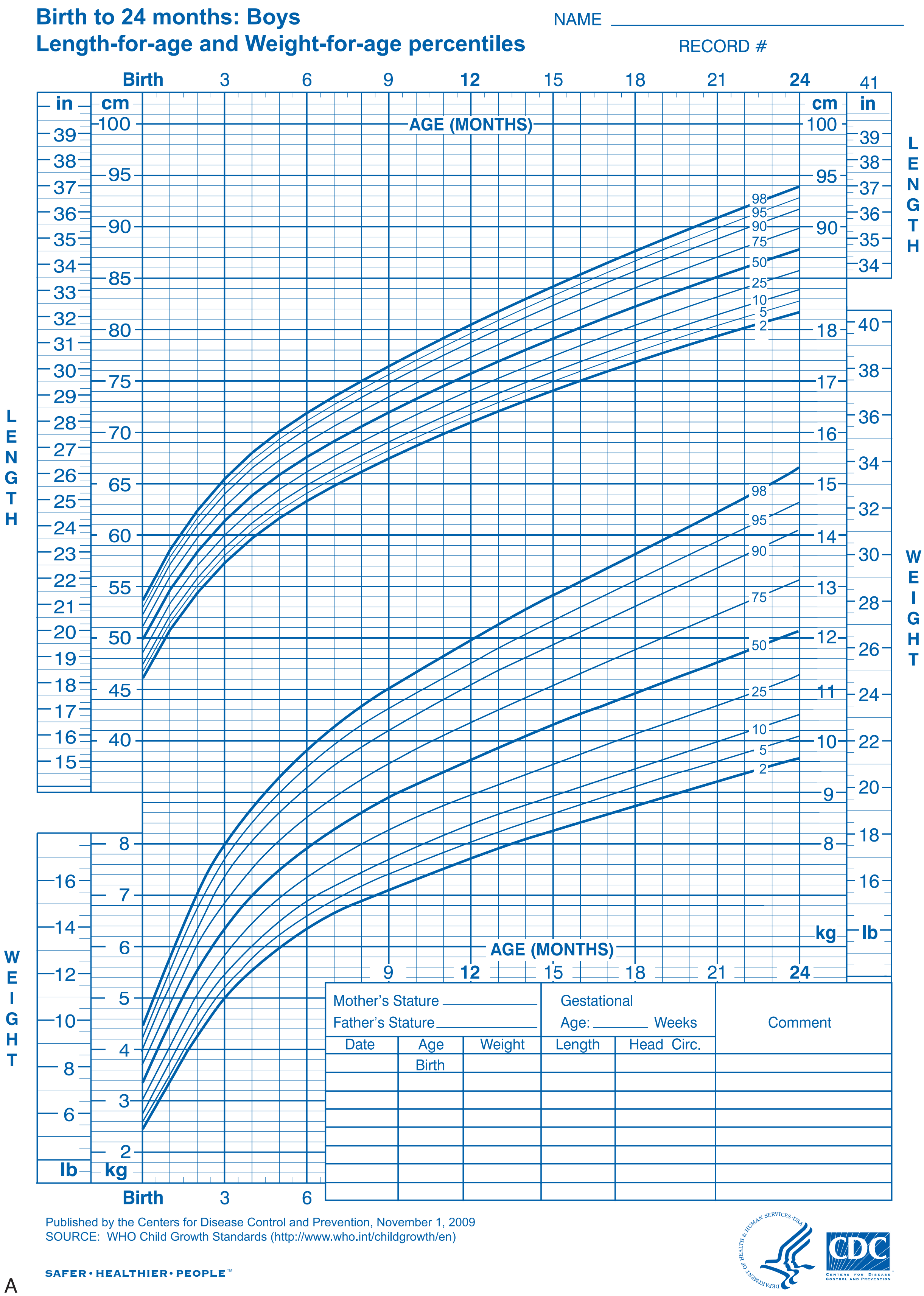

A

Figure 11-2 The World Health Organization Growth Charts. Length for age and weight for age for boys **(A)** and girls **(B)**. *(Courtesy of the World Health Organization: WHO Child Growth Standards, 2014. http://www.who.int/childgrowth/standards/en/.)*

Continued

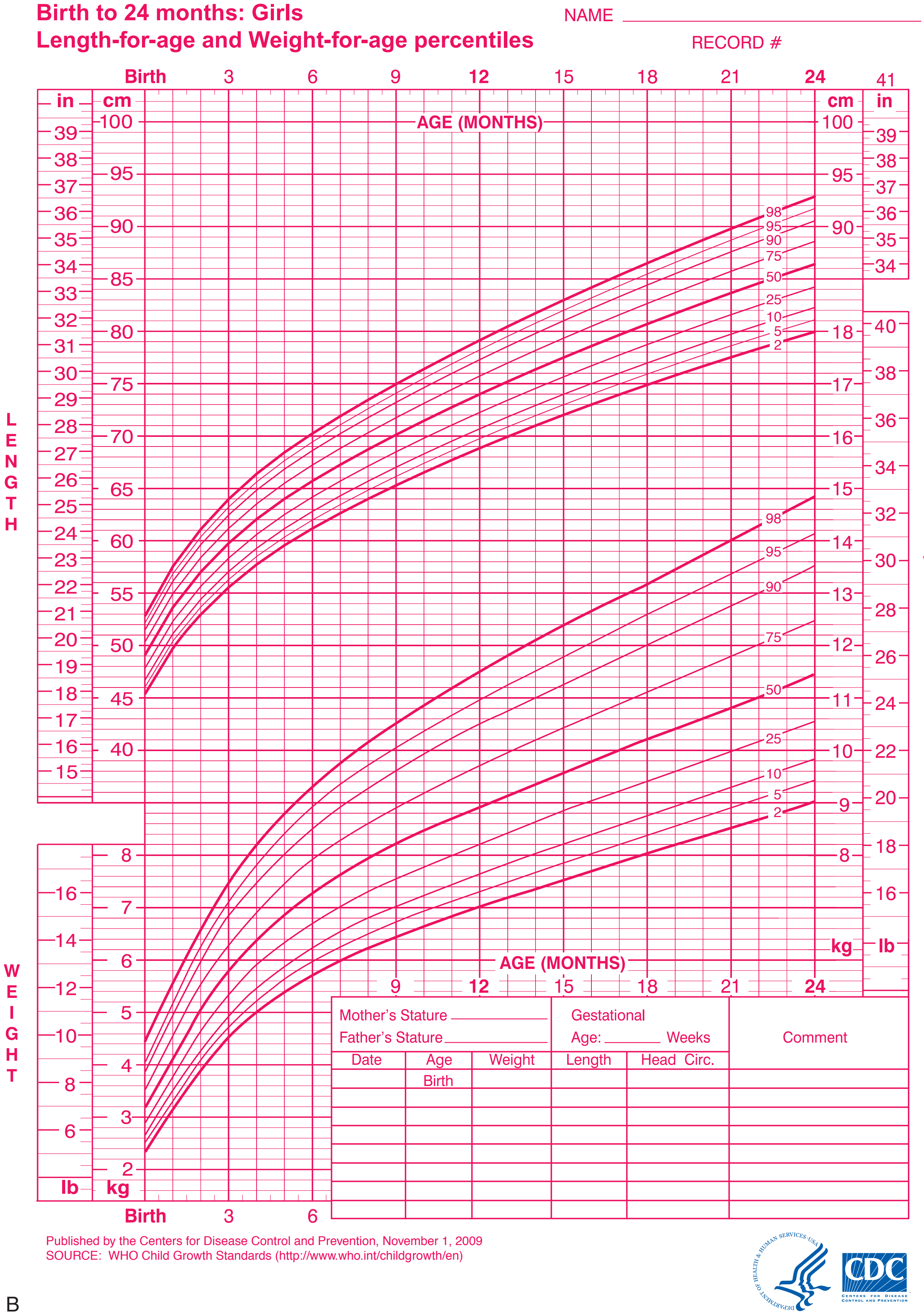

B

Figure 11-2, cont'd

Table 11-1 Emerging Patterns of Behavior from 1-5 Yr of Age*

Age/Domain	Behavior
15 MO	
Motor:	Walks alone; crawls up stairs
Adaptive:	Makes tower of 3 cubes; makes a line with crayon; inserts raisin in bottle
Language:	Jargon; follows simple commands; may name a familiar object (e.g., ball); responds to his/her name
Social:	Indicates some desires or needs by pointing; hugs parents
18 MO	
Motor:	Runs stiffly; sits on small chair; walks up stairs with 1 hand held; explores drawers and wastebaskets
Adaptive:	Makes tower of 4 cubes; imitates scribbling; imitates vertical stroke; dumps raisin from bottle
Language:	10 words (average); names pictures; identifies 1 or more parts of body
Social:	Feeds self; seeks help when in trouble; may complain when wet or soiled; kisses parent with pucker
24 MO	
Motor:	Runs well, walks up and down stairs, 1 step at a time; opens doors; climbs on furniture; jumps
Adaptive:	Makes tower of 7 cubes (6 at 21 mo); scribbles in circular pattern; imitates horizontal stroke; folds paper once imitatively
Language:	Puts 3 words together (subject, verb, object)
Social:	Handles spoon well; often tells about immediate experiences; helps to undress; listens to stories when shown pictures
30 MO	
Motor:	Goes up stairs alternating feet
Adaptive:	Makes tower of 9 cubes; makes vertical and horizontal strokes, but generally will not join them to make cross; imitates circular stroke, forming closed figure
Language:	Refers to self by pronoun "I"; knows full name
Social:	Helps put things away; pretends in play
36 MO	
Motor:	Rides tricycle; stands momentarily on 1 foot
Adaptive:	Makes tower of 10 cubes; imitates construction of "bridge" of 3 cubes; copies circle; imitates cross
Language:	Knows age and sex; counts 3 objects correctly; repeats 3 numbers or a sentence of 6 syllables; most of speech intelligible to strangers
Social:	Plays simple games (in "parallel" with other children); helps in dressing (unbuttons clothing and puts on shoes); washes hands
48 MO	
Motor:	Hops on 1 foot; throws ball overhand; uses scissors to cut out pictures; climbs well
Adaptive:	Copies bridge from model; imitates construction of "gate" of 5 cubes; copies cross and square; draws man with 2-4 parts besides head; identifies longer of 2 lines
Language:	Counts 4 pennies accurately; tells story
Social:	Plays with several children, with beginning of social interaction and role-playing; goes to toilet alone
60 MO	
Motor:	Skips
Adaptive:	Draws triangle from copy; names heavier of 2 weights
Language:	Names 4 colors; repeats sentence of 10 syllables; counts 10 pennies correctly
Social:	Dresses and undresses; asks questions about meaning of words; engages in domestic role-playing

*Data derived from those of Gesell (as revised by Knobloch), Shirley, Provence, Wolf, Bailey, and others. After 6 yr, the Wechsler Intelligence Scales for Children (WISC-IV) and other scales offer the most precise estimates of developmental level. To have their greatest value, they should be administered only by an experienced and qualified person.

use the parent as a secure base from which to explore independently. Proud of her or his accomplishments, the child illustrates Erikson's stage of autonomy and separation (see Chapter 6). The toddler who is overly controlled and discouraged from active exploration will feel doubt, shame, anger, and insecurity. All children will experience tantrums, reflecting their inability to delay gratification, suppress or displace anger, or verbally communicate their emotional states. The quality of the parent–child relationship may moderate negative effects of childcare arrangements when parents work.

Linguistic Development

Receptive language precedes expressive language. By the time infants speak their first words around 12 mo of age, they already respond appropriately to several simple statements, such as "no," "bye-bye," and "give me." By 15 mo, the average child points to major body parts and uses 4-6 words spontaneously and correctly. Toddlers also enjoy **polysyllabic** jargoning (see Tables 10-1 and 11-1), but do not seem upset that no one understands. Most communication of wants and ideas continues to be nonverbal.

Implications for Parents and Pediatricians

Parents who cannot recall any other milestone tend to remember when their child began to walk, perhaps because of the symbolic significance of walking as an act of independence and/or because of the new demands that the ambulating toddler places on his or her parent. All toddlers should be encouraged to explore their environments; a child's ability to wander out of sight also increases the risks of injury and the need for supervision.

In the office setting, many toddlers are comfortable exploring the examination room, but cling to the parents under the stress of the examination. Performing most of the physical examination in the parent's lap may help allay fears of separation. Infants who become more, not less, distressed in their parents' arms or who avoid their parents at times of stress may be insecurely attached. Young children who, when distressed, turn to strangers rather than parents for comfort are particularly worrisome. Children raised in "toxic" stressful environments have increased vulnerability to disease. The conflicts between independence and security manifest in issues of discipline, temper tantrums, toilet training, and changing feeding behaviors. Parents should be counseled on these matters within the framework of normal development.

Parents may express concern about poor food intake as growth slows. The growth chart should provide reassurance. Most children still take two daytime naps, although the duration steadily decreases (see Fig. 10-1).

AGE 18-24 MONTHS

Physical Development

Motor development during this period is reflected in improvements in balance and agility and the emergence of running and stair climbing. Height and weight increase at a steady rate during this year, with a gain of 5 in and 5 lb. By 24 mo, children are about half of their ultimate adult height. Head growth slows slightly. Eighty-five percent of adult head circumference is achieved by age 2 yr, with just an additional 5 cm gain over the next few years (see Fig. 11-1 and Table 15-1).

Cognitive Development

At approximately 18 mo of age, several cognitive changes coalesce, marking the conclusion of the sensory-motor period. These can be observed during self-initiated play. *Object permanence* is firmly established; toddlers anticipate where an object will end up, even though the object was not visible while it was being moved. *Cause and effect* are better understood, and toddlers demonstrate flexibility in problem solving (e.g., using a stick to obtain a toy that is out of reach, figuring out how to wind a mechanical toy). *Symbolic transformations* in play are no longer tied to the toddler's own body, so that a doll can be "fed" from an empty plate. Like the reorganization that occurs at 9 mo (see Chapter 10), the cognitive changes at 18 mo correlate with important changes in the emotional and linguistic domains (see Table 11-1).

Emotional Development

The relative independence of the preceding half-year often gives way to increased clinginess around 18 mo. This stage, described as "rapprochement," may be a reaction to growing awareness of the possibility of separation. Many parents report that they cannot go anywhere without having a small child attached to them. **Separation anxiety** will be manifest at bedtime. Many children use a special blanket or stuffed toy as a **transitional object,** which functions as a symbol of the absent parent. The transitional object remains important until the transition to symbolic thought has been completed and the symbolic presence of the parent has been fully internalized. Despite the attachment to the parent, the child's use of "no" is a way of declaring independence. Individual differences in temperament, in both the child and the parents play a critical role in determining the balance of conflict vs cooperation in the parent–child relationship. As effective language emerges, conflicts become less frequent.

Self-conscious awareness and internalized standards of behavior first appear at this age. Toddlers looking in a mirror will, for the first time, reach for their own face rather than the mirror image if they notice something unusual on their nose. They begin to recognize when toys are broken and may hand them to their parents to fix. Language becomes a means of impulse control, early reasoning, and connection between ideas. When tempted to touch a forbidden object, they may tell themselves "no, no." This is the very beginning of the formation of a conscience. The fact that they often go on to touch the object anyway demonstrates the relative weakness of internalized inhibitions at this stage.

Linguistic Development

Perhaps the most dramatic developments in this period are linguistic. Labeling of objects coincides with the advent of symbolic thought. After the realization that words can stand for things occurs, a child's vocabulary balloons from 10-15 words at 18 mo to between 50 and 100 at 2 yr. After acquiring a vocabulary of about 50 words, toddlers begin to combine them to make simple sentences, the beginning of grammar. At this stage, toddlers understand **2-step commands,** such as "Give me the ball and then get your shoes." Language also gives the toddler a sense of control over the surroundings, as in "night-night" or "bye-bye." The emergence of verbal language marks the end of the sensory-motor period. As toddlers learn to use symbols to express ideas and solve problems, the need for cognition based on direct sensation and motor manipulation wanes.

Implications for Parents and Pediatricians

With children's increasing mobility, physical limits on their explorations become less effective; words become increasingly important for behavior control as well as cognition. Children with delayed language acquisition often have greater behavior problems and frustrations due to problems with communication. Language development is facilitated when parents and caregivers use clear, simple sentences; ask questions; and respond to children's incomplete sentences and gestural communication with the appropriate words. Television viewing, as well as television as background noise, decreases parent–child verbal interactions, whereas looking at picture books and engaging the child in 2-way conversations stimulate language development.

In the office setting, certain procedures may lessen the child's **stranger anxiety.** Avoid direct eye contact initially. Perform as much of the examination as feasible with the child on the parent's lap. Pediatricians can help parents understand the resurgence of problems with separation and the appearance of a treasured blanket or teddy bear as a developmental phenomenon. Parents must understand the importance of exploration. Rather than limiting movement, parents should place toddlers in safe environments or substitute 1 activity for another. Methods of discipline, including corporal punishment, should be discussed; effective alternatives will usually be appreciated. Helping parents to understand and adapt to their children's different temperamental styles can constitute an important intervention (see Table 6-1). Developing daily routines is helpful to all children at this age. Rigidity in those routines reflects a need for mastery over a changing environment.

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Chapter 12

The Preschool Years

Susan Feigelman

The emergence of language and exposure of children to an expanding social sphere represent the critical milestones for children ages 2-5 yr. As toddlers, children learn to walk away and come back to the secure adult or parent. As preschoolers, they explore emotional separation, alternating between stubborn opposition and cheerful compliance, between bold exploration and clinging dependence. Increasing time spent in classrooms and playgrounds challenges a child's ability to adapt to new rules and relationships. Emboldened by their growing array of new skills and accomplishments, preschool children also are increasingly cognizant of the constraints imposed on them by the adult world and their own limited abilities.

STRUCTURAL DEVELOPMENT OF THE BRAIN

The preschool brain experiences dramatic changes in its anatomical and physiologic characteristics, with increases in cortical area, decreases in cortical thickness, and changing cortical volume. These changes are not uniform across the brain, but vary by region. Gray and white matter tissue properties change dramatically, including diffusion properties in the major cerebral fiber tracts. Dramatic increases occur in the brain metabolic demands. In general, a greater number of brain regions are required among younger compared to older children to complete the same cognitive task. This duplication has been interpreted as a form of "scaffolding," which is discarded with increasing age. The preschool brain is characterized by growth and expansion, that will be followed in later years by pruning.

PHYSICAL DEVELOPMENT

Somatic and brain growth slows by the end of the 2nd yr of life, with corresponding decreases in nutritional requirements and appetite, and the emergence of "picky" eating habits (see Table 15-1). Increases of approximately 2 kg (4-5 lb) in weight and 7-8 cm (2-3 in) in height per year are expected. Birthweight quadruples by 2.5 yr of age. An average 4 yr old weighs 40 lb and is 40 in tall. The head will grow only an additional 5-6 cm between ages 3 and 18 yr. Current growth charts, with growth parameters, can be found on the Centers for Disease Control and Prevention website (http://www.cdc.gov/growthcharts/) and in Chapter 15. Children with early adiposity rebound (increase in body mass index) are at increased risk for adult obesity.

Growth of sexual organs is commensurate with somatic growth. The preschooler has genu valgum (knock-knees) and mild pes planus (flatfoot). The torso slims as the legs lengthen. Physical energy peaks, and the need for sleep declines to 11-13 hr/24 hr, with the child eventually dropping the nap (see Fig. 10-1). Visual acuity reaches 20/30 by age 3 yr and 20/20 by age 4 yr. All 20 primary teeth have erupted by 3 yr of age (see Chapter 307).

Most children walk with a mature gait and run steadily before the end of their 3rd yr (see Table 11-1). Beyond this basic level, there is wide variation in ability as the range of motor activities expands to include throwing, catching, and kicking balls; riding on bicycles; climbing on playground structures; dancing; and other complex pattern behaviors. Stylistic features of gross motor activity, such as

tempo, intensity, and cautiousness, also vary significantly. Although toddlers may walk with different styles, toe walking should not persist.

The effects of such individual differences on cognitive and emotional development depend in part on the demands of the social environment. Energetic, coordinated children may thrive emotionally with parents or teachers who encourage physical activity; lower-energy, more cerebral children may thrive with adults who value quiet play.

Handedness is usually established by the 3rd yr. Frustration may result from attempts to change children's hand preference. Variations in fine-motor development reflect both individual proclivities and different opportunities for learning. Children who are restricted from drawing with crayons, for example, develop a mature pencil grasp later.

Bowel and bladder control emerge during this period, with "readiness" for toileting having large individual and cultural variation. Girls tend to train faster and earlier than boys. Bed-wetting is normal up to age 4 yr in girls and age 5 yr in boys (see Chapter 23.3). Many children master toileting with ease, particularly once they are able to verbalize their bodily needs. For others, toilet training can involve a protracted power struggle. Refusal to defecate in the toilet or potty is relatively common and can lead to constipation and parental frustration. Defusing the issue with a temporary cessation of training (and a return to diapers) often allows toilet mastery to proceed.

Implications for Parents and Pediatricians

The normal decrease in appetite at this age may cause parental concern about nutrition; growth charts should reassure parents that the child's intake is adequate. Children normally modulate their food intake to match their somatic needs according to feelings of hunger and satiety. Daily intake fluctuates, at times widely, but intake during the period of a week is relatively stable. A complete multivitamin can be used to assure adequate vitamin and mineral intake. Parents should provide a predictable eating schedule, with 3 meals and 2 snacks per day, allowing the child to choose how much to eat.

Highly active children face increased risks of injury, and parents should be counseled about safety precautions. Parental concerns about possible hyperactivity may reflect inappropriate expectations, heightened fears, or true overactivity. Children who engage in impulsive activity with no apparent regard for personal safety should be evaluated further.

LANGUAGE, COGNITION, AND PLAY

These 3 domains all involve symbolic function, a mode of dealing with the world that emerges during the preschool period.

Language

Our understanding of the acquisition of language is evolving. Preschool children command significant computational skills and understanding of statistical patterns that allow them to learn about both language and causation. The 2 and 3 yr old child employs frequency distributions to identify phonetic units distinguishing words in his or her native language from other languages.

Language development occurs most rapidly between 2 and 5 yr of age. Vocabulary increases from 50-100 words to more than 2,000. Sentence structure advances from telegraphic phrases ("Baby cry") to sentences incorporating all of the major grammatical components. As a rule of thumb, between the ages of 2 and 5 yr, the number of words in a typical sentence equals the child's age (2 by age 2 yr, 3 by age 3 yr, and so on). By 21-24 mo, most children are using possessives ("My ball"), progressives (the "-ing" construction, as in "I playing"), questions, and negatives. By age 4 yr, most children can count to 4 and use the past tense; by age 5 yr, they can use the future tense. Children do not use figurative speech; they will only comprehend the literal meaning of words. Referring to an object as "light as a feather" may produce a quizzical look on a child.

It is important to distinguish between *speech* (the production of intelligible sounds) and *language,* which refers to the underlying mental act. Language includes both expressive and receptive functions. Receptive language (understanding) varies less in its rate of acquisition than does expressive language; therefore, it has greater prognostic importance (see Chapters 16 and 35).

Language acquisition depends critically on environmental input. Key determinants include the amount and variety of speech directed toward children and the frequency with which adults ask questions and encourage verbalization. Children raised in poverty typically perform lower on measures of language development compared to children from economically advantaged families.

Although experience influences the rate of language development, many linguists believe that the basic mechanism for language learning is "hard-wired" in the brain. Children do not simply imitate adult speech; they abstract the complex rules of grammar from the ambient language, generating implicit hypotheses. Evidence for the existence of such implicit rules comes from analysis of grammatical errors, such as the overgeneralized use of "-s" to signify the plural and "-ed" to signify the past ("We seed lots of mouses.").

Language is linked to both cognitive and emotional development. Language delays may be the first indication that a child has an intellectual disability, has an autism spectrum disorder, or has been maltreated. Language plays a critical part in the regulation of behavior through internalized "private speech" in which a child repeats adult prohibitions, first audibly and then mentally. Language also allows children to express feelings, such as anger or frustration, without acting them out; consequently, language-delayed children show higher rates of tantrums and other externalizing behaviors.

Preschool language development lays the foundation for later success in school. Approximately 35% of children in the United States may enter school lacking the language skills that are the prerequisites for acquiring literacy. Children from socially and economically disadvantaged backgrounds have an increased risk of school problems, making early detection, along with referral and enrichment, important. Although children typically learn to read and write in elementary school, critical foundations for literacy are established during the preschool years. Through repeated early exposure to written words, children learn about the uses of writing (telling stories or sending messages) and about its form (left to right, top to bottom). Early errors in writing, like errors in speaking, reveal that literacy acquisition is an active process involving the generation and revision of hypotheses. Programs such as Head Start are especially important for improving language skills for children from bilingual homes. Such parents should be reassured that although bilingual children do initially lag behind their monolingual peers in acquiring language, they learn the differing rules governing both languages. Bilingual children do not follow the same course of language development as monolingual children, but create a different system of language cues. Several cognitive advantages have been repeatedly demonstrated among bilingual compared to monolingual children.

Picture books have a special role not only in familiarizing young children with the printed word but also in the development of verbal language. Children's vocabulary and receptive language improve when their parents or caregivers consistently read to them. Reading aloud with a young child is an interactive process in which a parent repeatedly focuses the child's attention on a particular picture, asks questions, and then gives the child feedback (**dialogic reading**). The elements of shared attention, active participation, immediate feedback, repetition, and graduated difficulty make such routines ideal for language learning. Programs in which physicians provide books to preschool children have shown improvement in language skills among the children.

The period of rapid language acquisition is also when **developmental dysfluency** and **stuttering** are most likely to emerge; these can be traced to activation of the cortical motor, sensory, and cerebellar areas. Common difficulties include pauses and repetitions of initial sounds. Stress or excitement exacerbates these difficulties, which generally resolve on their own. Although 5% of preschool children will stutter, it will resolve in 80% of those children by age 8 yr. Children with stuttering should be referred for evaluation if it is severe, persistent, or associated with anxiety, or if parental concern is elicited. **Treatment** includes guidance to parents to reduce pressures associated with speaking.

Cognition

The preschool period corresponds to Piaget's preoperational (prelogical) stage, characterized by **magical thinking**, **egocentrism**, and **thinking that is dominated by perception**, not abstraction (see Table 6-2). Magical thinking includes confusing coincidence with causality, animism (attributing motivations to inanimate objects and events), and unrealistic beliefs about the power of wishes. A child might believe that people cause it to rain by carrying umbrellas, that the sun goes down because it is tired, or that feeling resentment toward a sibling can actually make that sibling sick. Egocentrism refers to a child's inability to take another's point of view and does not connote selfishness. A child might try to comfort an adult who is upset by bringing the adult a favorite stuffed animal. After 2 yr of age, the child develops a concept of herself or himself as an individual and senses the need to feel "whole."

Piaget demonstrated the dominance of perception over logic. In one experiment, water is poured back and forth between a tall, thin vase and a low, wide dish, and children are asked which container has more water. Invariably, they choose the one that looks larger (usually the tall vase), even when the examiner points out that no water has been added or taken away. Such misunderstandings reflect young children's developing hypotheses about the nature of the world as well as their difficulty in attending simultaneously to multiple aspects of a situation.

Recent work indicating that preschool children do have the ability to understand causal relationships has modified our understanding of the ability of preschool children to engage in abstract thinking. (see Chapter 7)

Imitation, central to the learning experience of preschool children, is now being recognized as a complex act because the of differences in the size of the operators (the adult and the child), different levels of dexterity, and even different outcomes. A child who watches an adult unsuccessfully attempt a simple act (unscrew a lid) will imitate the action—but often with the intended outcome, not the demonstrated but failed outcome. Thus "imitation" goes beyond the mere repetition of observed movements.

By age 3, children have self-identified their sex, and are actively seeking understanding of the meaning of gender identification. There is a developmental progression from rigidity (boys and girls have strict gender roles) in the early preschool years to a more flexible realistic understanding (boys and girls can have a variety of interests).

Play

Play involves learning, physical activity, socialization with peers, and practicing adult roles. Play increases in complexity and imagination, from simple imitation of common experiences, such as shopping and putting baby to bed (2 or 3 yr of age), to more extended scenarios involving singular events, such as going to the zoo or going on a trip (3 or 4 yr of age), to the creation of scenarios that have only been imagined, such as flying to the moon (4 or 5 yr of age). By age 3 yr, cooperative play is seen in activities such as building a tower of blocks together; later, more structured role-play activity, as in playing house, is seen. Play also becomes increasingly governed by rules, from early rules about asking (rather than taking) and sharing (2 or 3 yr of age), to rules that change from moment to moment, according to the desires of the players (4 and 5 yr of age), to the beginning of the recognition of rules as relatively immutable (5 yr of age). Electronic forms of play (games) are best if interactive and educational.

Play also allows for resolution of conflicts and anxiety and for creative outlets. Children can vent anger safely (spanking a doll), take on superpowers (dinosaur and superhero play), and obtain things that are denied in real life (a make-believe friend or stuffed animal). Creativity is particularly apparent in drawing, painting, and other artistic activities. Themes and emotions that emerge in a child's drawings often reflect the emotional issues of greatest importance for the child.

Difficulty distinguishing fantasy from reality colors a child's perception of what the child views in the media, through programming and advertising. One fourth of young children have a television set in their bedroom; a TV in the bedroom is associated with more hours of watching. The number of hours that preschoolers watch TV exceeds guidelines. Interactive quality educational programming in which children develop social relationships with the characters can increase learning. However, exposure to commercial television with violent content is associated with later behavior problems and because children younger than 8 yr are not able to comprehend the concept of persuasive intent, they are more vulnerable to television advertising.

Implications for Parents and Pediatricians

The significance of language as a target for assessment and intervention cannot be overestimated because of its central role as an indicator of cognitive and emotional development and a key factor in behavioral regulation and later school success. As language emerges, parents can support emotional development by using words that describe the child's feeling states ("You sound angry right now.") and urging the child to use words to express, rather than act out, feelings. Active imaginations will come into play when children offer explanations for misbehavior. A parent's best way of dealing with untruths is to address the event, not the child, and have the child participate in making things right.

Parents should have a regular time each day for reading or looking at books with their children. Programs such as Reach Out and Read, in which pediatricians give out picture books along with appropriate guidance during primary care visits, have been effective in increasing reading aloud and thereby promoting language development, particularly in lower-income families. Television and similar media should be limited to 2 hr/day of quality programming, and parents should be watching the programs with their children and debriefing their young children afterward. At-risk children, particularly those living in poverty, can better meet future school challenges if they have early high-quality experiences, such as Head Start.

Preoperational thinking constrains how children understand experiences of illness and treatment. Children begin to understand that bodies have "insides" and "outsides." Children should be given simple, concrete explanations for medical procedures and given some control over procedures if possible. Children should be reassured that they are not to blame when receiving a vaccine or venipuncture. An adhesive bandage will help to make the body whole again in a child's mind.

The active imagination that fuels play and the magical, animist thinking characteristic of preoperational cognition can also generate intense fears. More than 80% of parents report at least 1 fear in their preschool children. Refusal to take baths or to sit on the toilet may arise from the fear of being washed or flushed away, reflecting a child's immature appreciation of relative size. Attempts to demonstrate rationally that there are no monsters in the closet often fail, inasmuch as the fear arises from prerational thinking. However, this same thinking allows parents to be endowed with magical powers that can banish the monsters with "monster spray" or a night light. Parents should acknowledge the fears, offer reassurance and a sense of security, and give the child some sense of control over the situation. Use of the Draw-a-Person, in which a child is asked to draw the best person the child can, may help elucidate a child's viewpoint.

EMOTIONAL AND MORAL DEVELOPMENT

Emotional challenges facing preschool children include accepting limits while maintaining a sense of self-direction, reining in aggressive and sexual impulses, and interacting with a widening circle of adults and peers. At 2 yr of age, behavioral limits are predominantly external; by 5 yr of age, these controls need to be internalized if a child is to function in a typical classroom. Success in achieving this goal relies on prior emotional development, particularly the ability to use internalized images of trusted adults to provide a secure environment in times of stress. The love a child feels for important adults is the main incentive for the development of self-control.

Children learn what behaviors are acceptable and how much power they wield vis-à-vis important adults by testing limits. Testing increases when it elicits attention, even though that attention is often negative, and when limits are inconsistent. Testing often arouses parental anger or inappropriate solicitude as a child struggles to separate, and it gives rise to a corresponding parental challenge: letting go. Excessively tight

limits can undermine a child's sense of initiative, whereas overly loose limits can provoke anxiety in a child who feels that no one is in control.

Control is a central issue. Young children cannot control many aspects of their lives, including where they go, how long they stay, and what they take home from the store. They are also prone to lose internal control, that is, to have temper tantrums. Fear, overtiredness, inconsistent expectations, or physical discomfort can also evoke tantrums. Tantrums normally appear toward the end of the 1st yr of life and peak in prevalence between 2 and 4 yr of age. Tantrums lasting more than 15 min or regularly occurring more than 3 times/day may reflect underlying medical, emotional, or social problems.

Preschool children normally experience complicated feelings toward their parents that can include strong attachment and possessiveness toward the parent of the opposite sex, jealousy and resentment of the other parent, and fear that these negative feelings might lead to abandonment. These emotions, most of which are beyond a child's ability to comprehend or verbalize, often find expression in highly labile moods. The resolution of this crisis (a process extending over years) involves a child's unspoken decision to identify with the parents rather than compete with them. Play and language foster the development of emotional controls by allowing children to express emotions and role play.

Curiosity about genitals and adult sexual organs is normal, as is masturbation. Excessive masturbation interfering with normal activity, acting out sexual intercourse, extreme modesty, or mimicry of adult seductive behavior all suggests the possibility of sexual abuse or inappropriate exposure (see Chapter 40.1). Modesty appears gradually between 4 and 6 yr of age, with wide variations among cultures and families. Parents should begin to teach children about "private" body areas before school entry.

Moral thinking is constrained by a child's cognitive level and language abilities, but develops as the child continues her or his identity with the parents. Beginning before the 2nd birthday, the child's sense of right and wrong stems from the desire to earn approval from the parents and avoid negative consequences. The child's impulses are tempered by external forces; the child has not yet internalized societal rules or a sense of justice and fairness. Over time, as the child internalizes parental admonitions, words are substituted for aggressive behaviors. Finally, the child accepts personal responsibility. Actions will be viewed by damage caused, not by intent. Empathic responses to others' distress arise during the 2nd yr of life, but the ability to consider another child's point of view remains limited throughout this period. In keeping with a child's inability to focus on more than 1 aspect of a situation at a time, fairness is taken to mean equal treatment, regardless of circumstance. A 4 yr old will acknowledge the importance of taking turns, but will complain if he or she didn't get enough time. Rules tend to be absolute, with guilt assigned for bad outcomes, regardless of intentions.

Implications for Parents and Pediatricians

The importance of the preschooler's sense of control over his or her body and surroundings has implications for practice. Preparing the patient by letting the child know how the visit will proceed is reassuring. Tell the child what will happen, but don't ask permission unless you are willing to deal with a "no" answer. A brief introduction to "private parts" is warranted before the genital examination.

The visit of the 4 or 5 yr old should be entertaining, because of the child's ability to communicate, as well as the child's natural curiosity. Physicians should realize that all children are occasionally difficult. Guidance emphasizing appropriate expectations for behavioral and emotional development and acknowledging normal parental feelings of anger, guilt, and confusion should be part of all visits at this time. Parents should be queried about daily routines and their expectations of child behavior. Providing children with choices (all options being acceptable to the parent) and encouraging independence in self-care activities (feeding, dressing, and bathing) will reduce conflicts.

Although some cultures condone the use of corporal punishment for disciplining of young children, it is not an effective means of behavioral control. As children habituate to repeated spanking, parents have to spank ever harder to get the desired response, increasing the risk of serious injury. Sufficiently harsh punishment may inhibit undesired behaviors, but at great psychologic cost. Children mimic the corporal punishment that they receive; children who are spanked will have more aggressive behaviors later. Whereas spanking is the use of force, externally applied, to produce behavior change, **discipline** is the process that allows the child to internalize controls on behavior. Alternative discipline strategies should be offered, such as the "countdown," along with consistent limit setting, clear communication of rules, and frequent approval. Discipline should be immediate, specific to the behavior, and time-limited. Time-out for approximately 1 min/yr of age is very effective. A kitchen timer allows the parent to step back from the situation; the child is free when the timer rings.

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Chapter 13

Middle Childhood

Susan Feigelman

Middle childhood (6-11 yr of age) is the period in which children increasingly separate from parents and seek acceptance from teachers, other adults, and peers. Children begin to feel under pressure to conform to the style and ideals of the peer group. Self-esteem becomes a central issue, as children develop the cognitive ability to consider their own self-evaluations and their perception of how others see them. For the first time, they are judged according to their ability to produce socially valued outputs, such as getting good grades, playing a musical instrument, or hitting home runs.

PHYSICAL DEVELOPMENT

Growth occurs **discontinuously,** in 3-6 irregularly timed spurts each year, but varies both within and among individuals. Growth during the period averages 3-3.5 kg (6.6-7.7 lb) and 6-7 cm (2.4-2.8 in) per year (Fig. 13-1). The head grows only 2 cm in circumference throughout the entire period, reflecting a slowing of brain growth. Myelinization continues into adolescence, with peak gray matter at 12-14 yr. Body habitus is more erect than previously, with long legs compared with the torso.

Growth of the midface and lower face occurs gradually. Loss of deciduous (baby) teeth is a more dramatic sign of maturation, beginning around 6 yr of age. Replacement with adult teeth occurs at a rate of about 4 per year, so that by age 9 yr, children will have 8 permanent incisors and 4 permanent molars. Premolars erupt by 11-12 yr of age (see Chapter 307). Lymphoid tissues hypertrophy, often giving rise to impressive tonsils and adenoids.

Muscular strength, coordination, and stamina increase progressively, as does the ability to perform complex movements, such as dancing or shooting baskets. Such higher-order motor skills are the result of both maturation and training; the degree of accomplishment reflects wide variability in innate skill, interest, and opportunity.

Physical fitness has declined among school-age children. Sedentary habits at this age are associated with increased lifetime risk of obesity, cardiovascular disease, academic achievement, and lower self-esteem (see Chapter 47). The number of overweight children and the degree of overweightness have been increasing, although recently at a slower rate (see Chapter 47). Only 15% of middle and junior high schools require physical education class at least 3 days/wk. One quarter of youth do not engage in any free-time physical activity, despite the recommendation for 1 hr of physical activity per day.

Perceptions of body image develop early during this period; children as young as 5 and 6 yr express dissatisfaction with their body image; by ages 8 and 9 yr many of these youth report trying to diet, often using

2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

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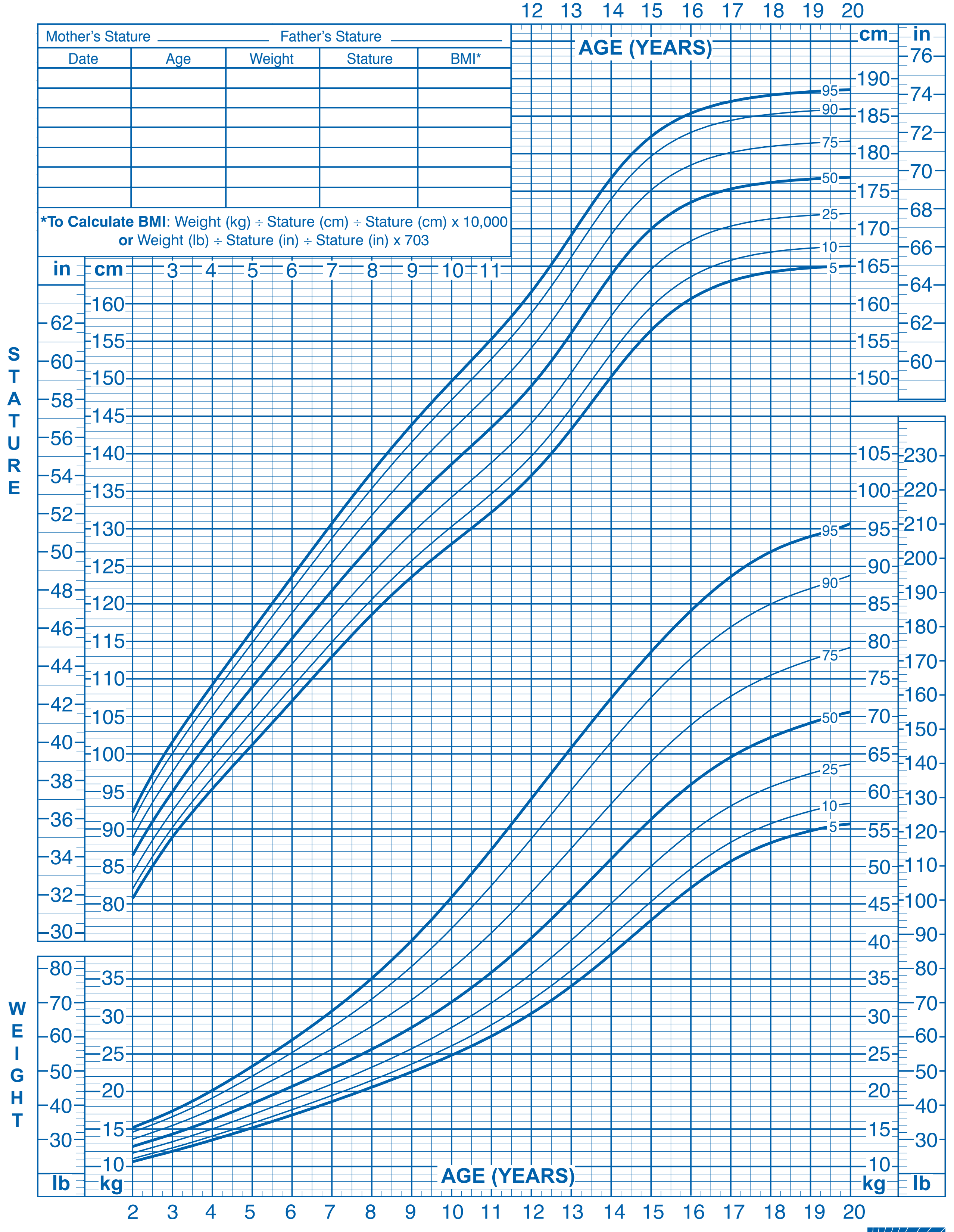

Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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Figure 13-1 Stature (height) for age and weight for boys **(A)** and girls **(B)** ages 2 to 20 years. *(Courtesy the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, 2000. http://www.cdc.gov/growthcharts.)*

2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles

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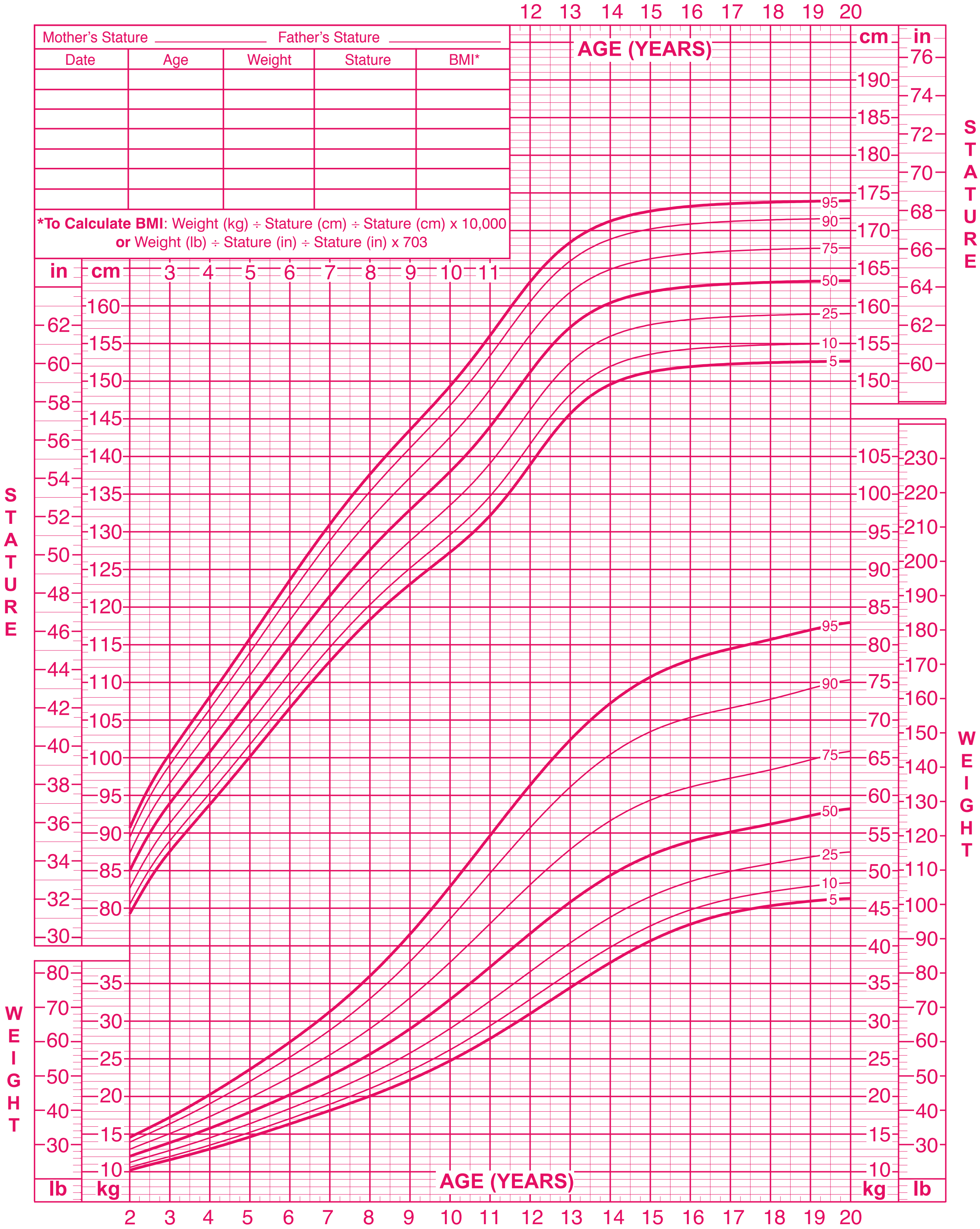

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Figure 13-1, cont'd

ill-advised regimens. Loss of control (binge) eating occurs among approximately 6% of children of this age.

Prior to puberty, the sensitivity of the hypothalamus and the pituitary changes, leading to increased gonadotropin synthesis. Interest in gender differences and sexual behavior increases progressively until puberty. Although this is a period when sexual drives are limited, masturbation is common, and children may be interested in differences between genders. Sexual maturity occurs earlier for both genders in the United States. Rates of maturation differ by geography, ethnicity, and country. These differences in maturation have implications for differing expectations of others about them based on sexual maturation.

Implications for Parents and Pediatricians

Middle childhood is generally a time of excellent health. However, children have variable sizes, shapes, and abilities. Children of this age compare themselves with others, eliciting feelings about their physical attributes and abilities. Fears of being "abnormal" can lead to avoidance of situations in which physical differences might be revealed, such as gym class or medical examinations. Children with actual physical disabilities may face special stresses. Medical, social, and psychologic risks tend to occur together.

Children should be asked about risk factors for obesity. Participation in physical activity, including organized sports or other organized activities can foster skill, teamwork, and fitness, as well as a sense of accomplishment, but pressure to compete when the activity is no longer enjoyable has negative effects. Counseling on establishing healthy eating habits and limited screen time should be given to all families. Prepubertal children should not engage in high-stress, high-impact sports, such as power lifting or tackle football, because skeletal immaturity increases the risk of injury (see Chapter 693).

COGNITIVE DEVELOPMENT

The thinking of early elementary school-age children differs qualitatively from that of preschool children. In place of magical, egocentric, and perception-bound cognition, school-age children increasingly apply rules based on observable phenomena, factor in multiple dimensions and points of view, and interpret their perceptions using physical laws. Piaget documented this shift from *preoperational* to *concrete logical operations.* When 5 yr olds watch a ball of clay being rolled into a snake, they might insist that the snake has "more" because it is longer. In contrast, 7 yr olds typically reply that the ball and the snake must weigh the same because nothing has been added or taken away or because the snake is both longer and thinner. This cognitive reorganization occurs at different rates in different contexts. In the context of social interactions with siblings, young children often demonstrate an ability to understand alternate points of view long before they demonstrate that ability in their thinking about the physical world. Understanding time and space constructs occurs in the later part of this period.

The concept of "**school readiness**" has evolved. The American Academy of Pediatrics recommends following an "interactional relational" model in which the focus is on the child, the environment and the interactions therein. This model aid explicitly asserts that all children can learn and that the educational process is reciprocal between the child and the school. The model is developmentally based as it recognizes the importance of early experiences for later development. Rather than delaying school entry, high quality early education programs may be the key to ultimate school success.

School makes increasing cognitive demands on the child. Mastery of the elementary curriculum requires that a large number of perceptual, cognitive, and language processes work efficiently (Table 13-1), and children are expected to attend to many inputs at once. The 1st 2-3 yr of elementary school are devoted to acquiring the fundamentals: reading, writing, and basic mathematics skills. By 3rd grade, children need to be able to sustain attention through a 45 min period and the curriculum requires more complex tasks. The goal of reading a paragraph is no longer to decode the words, but to understand the content; the goal of writing is no longer spelling or penmanship, but composition. The volume of work increases along with the complexity.

Cognitive abilities interact with a wide array of attitudinal and emotional factors in determining classroom performance. These factors include external rewards (eagerness to please adults and approval from peers) and internal rewards (competitiveness, willingness to work for a delayed reward, belief in one's abilities, and ability to risk trying when

Table 13-1 Selected Perceptual, Cognitive, and Language Processes Required for Elementary School Success

PROCESS	DESCRIPTION	ASSOCIATED PROBLEMS
PERCEPTUAL		
Visual analysis	Ability to break a complex figure into components and understand their spatial relationships	Persistent letter confusion (e.g., between *b, d,* and *g*); difficulty with basic reading and writing and limited "sight" vocabulary
Proprioception and motor control	Ability to obtain information about body position by feel and unconsciously program complex movements	Poor handwriting, requiring inordinate effort, often with overly tight pencil grasp; special difficulty with timed tasks
Phonologic processing	Ability to perceive differences between similar sounding words and to break down words into constituent sounds	Delayed receptive language skill; attention and behavior problems secondary to not understanding directions; delayed acquisition of letter-sound correlations (phonetics)
COGNITIVE		
Long-term memory, both storage and recall	Ability to acquire skills that are "automatic" (i.e., accessible without conscious thought)	Delayed mastery of the alphabet (reading and writing letters); slow handwriting; inability to progress beyond basic mathematics
Selective attention	Ability to attend to important stimuli and ignore distractions	Difficulty following multistep instructions, completing assignments, and behaving well; problems with peer interaction
Sequencing	Ability to remember things in order; facility with time concepts	Difficulty organizing assignments, planning, spelling, and telling time
LANGUAGE		
Receptive language	Ability to comprehend complex constructions, function words (e.g., if, when, only, except), nuances of speech, and extended blocks of language (e.g., paragraphs)	Difficulty following directions; wandering attention during lessons and stories; problems with reading comprehension; problems with peer relationships
Expressive language	Ability to recall required words effortlessly (word finding), control meanings by varying position and word endings, and construct meaningful paragraphs and stories	Difficulty expressing feelings and using words for self-defense, with resulting frustration and physical acting out; struggling during "circle time" and in language-based subjects (e.g., English)

success is not ensured). Success predisposes to success, whereas failure impacts self-esteem and reduces self-efficacy, diminishing a child's ability to take future risks.

Children's intellectual activity extends beyond the classroom. Beginning in the 3rd or 4th grade, children increasingly enjoy strategy games and wordplay (puns and insults) that exercise their growing cognitive and linguistic mastery. Many become experts on subjects of their own choosing, such as sports trivia, or develop hobbies, such as special card collections. Others become avid readers or take on artistic pursuits. Whereas board and card games were once the usual leisure time activity of youth, video, computer and other electronic games currently fill this need.

Implications for Parents and Pediatricians

Pediatricians have an important role in preparing their patients for school entrance by promoting health through immunizations, adequate nutrition, appropriate recreation and screening for physical, developmental, and cognitive disorders. The American Academy of Pediatrics recommends that pediatric providers promote the "5 Rs" of early education: (1) reading as a daily family activity; (2) rhyming, playing, and cuddling together; (3) routines and regular times for meals, play, and sleep; (4) reward through praise for successes; and (5) reciprocal nurturing relationships,

Concrete operations allow children to understand simple explanations for illnesses and necessary treatments, although they may revert to prelogical thinking when under stress. A child with pneumonia may be able to explain about white cells fighting the "germs" in the lungs, but still secretly harbors the belief that the sickness is a punishment for disobedience.

As children are faced with more abstract concepts, academic and classroom behavior problems emerge and come to the pediatrician's attention. Referrals may be made to the school for remediation or to community resources (medical or psychologic) when appropriate. The causes may be one or more of the following: deficits in perception (vision and hearing); specific learning disabilities; global cognitive delay (mental retardation); primary attention deficit; and attention deficits secondary to family dysfunction, depression, anxiety, or chronic illness (see Chapters 16 and 32). Children whose learning style does not fit the classroom culture may have academic difficulties and need assessment before failure sets in. Simply having a child repeat a failed grade rarely has any beneficial effect and often seriously undercuts the child's self-esteem. In addition to finding the problem areas, identifying each child's strengths is important. Educational approaches that value a wide range of talents ("multiple intelligences") beyond the traditional ones of reading, writing, and mathematics may allow more children to succeed.

The change in cognition allows the child to understand "if/when" clauses. Increased responsibilities and expectations accompany increased rights and privileges. Discipline strategies should move toward negotiation and a clear understanding of consequences, including removal of privileges for infringements.

SOCIAL, EMOTIONAL, AND MORAL DEVELOPMENT

Social and Emotional Development

In this period, energy is directed toward creativity and productivity. Changes occur in 3 spheres: the home, the school, and the neighborhood. Of these, the home and family remain the most influential. Increasing independence is marked by the first sleepover at a friend's house and the first time at overnight camp. Parents should make demands for effort in school and extracurricular activities, celebrate successes, and offer unconditional acceptance when failures occur. Regular chores, associated with an allowance, provide an opportunity for children to contribute to family functioning and learn the value of money. These responsibilities may be a testing ground for psychologic separation, leading to conflict. Siblings have critical roles as competitors, loyal supporters, and role models.

The beginning of school coincides with a child's further separation from the family and the increasing importance of teacher and peer relationships. Social groups tend to be same-sex, with frequent changing of membership, contributing to a child's growing social development and competence. Popularity, a central ingredient of self-esteem, may be won through possessions (having the latest electronic gadgets or the right clothes), as well as through personal attractiveness, accomplishments, and actual social skills. Children are aware of racial differences and are beginning to form opinions about racial groups that impact their relationships.

Some children conform readily to the peer norms and enjoy easy social success. Those who adopt individualistic styles or have visible differences may be teased. Such children may be painfully aware that they are different, or they may be puzzled by their lack of popularity. Children with deficits in social skills may go to extreme lengths to win acceptance, only to meet with repeated failure. Attributions conferred by peers, such as funny, stupid, bad, or fat, may become incorporated into a child's self-image and affect the child's personality, as well as school performance. Parents may have their greatest effect indirectly, through actions that change the peer group (moving to a new community or insisting on involvement in structured after-school activities).

In the neighborhood, real dangers, such as busy streets, bullies, and strangers, tax school-age children's common sense and resourcefulness. Interactions with peers without close adult supervision call on increasing conflict resolution or pugilistic skills. Media exposure to adult materialism, sexuality, substance use and violence may be frightening, reinforcing children's feeling of powerlessness in the larger world. Compensatory fantasies of being powerful may fuel the fascination with heroes and superheroes. A balance between fantasy and an appropriate ability to negotiate real-world challenges indicates healthy emotional development.

Moral Development

Although by age 6 yr most children will have a conscience (internalized rules of society), they vary greatly in their level of moral development. For the younger youth, many still subscribe to the notion that, rules are established and enforced by an authority figure (parent or teacher) and decision-making is guided by self-interest (avoidance of negative and receipt of positive consequences). The needs of others are not strongly considered in decision-making. As they grow older, most will recognize not only their own needs and desires, but also those of others, although personal consequences are still the primary driver of behavior. Social behaviors that are socially undesirable are considered to be wrong. By age 10-11 yr the combination of peer pressure, a desire to please authority figures as well as an understanding of reciprocity (treat others as you wish to be treated) shapes the child's behavior.

Implications for Parents and Pediatricians

Children need unconditional support as well as realistic demands as they venture into a world that is often frightening. A daily query from parents over the dinner table or at bedtime about the good and bad things that happened during the child's day may uncover problems early. Parents may have difficulty allowing the child independence or may exert excessive pressure on their children to achieve academic or competitive success. Children who struggle to meet such expectations may have behavior problems or psychosomatic complaints.

Many children face stressors that exceed the normal challenges of separation and success in school and the neighborhood. Divorce affects nearly 50% of children. Domestic violence, parental substance abuse, and other mental health problems may also impair a child's ability to use home as a secure base for refueling emotional energies. In many neighborhoods, random violence makes the normal development of independence extremely dangerous. Older children may join gangs as a means of self-protection and a way to attain recognition and belong to a cohesive group. Children who bully others, and/or are victims of bullying, should be evaluated, since this behavior is associated with mood disorders, family problems, and school adjustment problems. Parents should reduce exposure to hazards where possible. Because of the risk of unintentional firearm injuries to children, parents should be encouraged to ask parents of playmates whether a gun is kept in

their home and, if so, how it is secured. The high prevalence of adjustment disorders among school-age children attests to the effects of such overwhelming stressors on development.

Pediatrician visits are infrequent in this period; therefore each visit is an opportunity to assess children's functioning in all contexts (home, school, neighborhood). Maladaptive behaviors, both internalizing and externalizing, occur when stress in any of these environments overwhelms the child's coping responses. Due to continuous exposure and the strong influence of media (programming and advertisements) on children's beliefs and attitudes, parents must be alert to exposures from the television and Internet. An average American youth spends over 6 hr/day with a variety of media, and ⅔ of these children have a television in their bedrooms. Parents should be advised to remove the television from their children's rooms, limit viewing to 2 hr/day, and monitor what programs children watch. The Draw-a-Person (for ages 3-10 yr, with instructions to "draw a complete person") and Kinetic Family Drawing (beginning at age 5 yr, with instructions to "draw a picture of everyone in your family doing something") are useful office tools to assess a child's functioning.

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Chapter 14

Adolescence

See Part XIII, Chapter 110, Adolescent Development.

Chapter 15

Assessment of Growth

Virginia A. Keane

Many biophysiologic and psychosocial problems can adversely affect growth, and aberrant growth may be the first sign of an underlying problem. The most powerful tool in growth assessment is the growth chart (see Figs. 11-1, 11-2, 13-1, and 15-1) used in combination with accurate measurements of height, weight, head circumference, and calculation of the body mass index (BMI).

PROCEDURES FOR ACCURATE MEASUREMENT

Growth assessment requires accurate measurement. Weight, in pounds or kilograms, must be determined using an accurate scale. For infants and toddlers, weight, length, and head circumference are obtained. These measures should be performed with the infant naked, and ideally, repeated measures should be performed on the same equipment. Head circumference is determined using a flexible tape measure run from the supraorbital ridge to the occiput in the path that leads to the largest possible measurement. Length is most accurately measured by 2 examiners (1 to position the child), with the child supine on a measuring board. For older children, the measure is stature or height, taken without shoes, using a stadiometer. Measurements obtained in alternative manners, such as marking examination paper at the foot and head of a supine infant, or using a simple wall growth chart with a book or ruler on the head can lead to inaccuracy that may render the measurement useless. It is essential to compare measurements with previous growth trends, repeat any that are inconsistent, and plot results longitudinally.

DERIVATION AND INTERPRETATION OF GROWTH CHARTS

In 2000, the Centers for Disease Control and Prevention (CDC) published new growth charts, replacing the 1977 version. Modifications since then have not changed the data points. Set 1 includes the 5th to 95th percentiles; set 2, the 3rd to 97th percentiles. These charts contain data from national surveys conducted by the National Center for Health Statistics between 1963 and 1994. Data are representative of the U.S. population, both demographically and in terms of breastfeeding prevalence. Methodologic steps have assured that the increase in the prevalence of obesity has not unduly raised the upper limits of normal. Several deficiencies of the older charts have been corrected, such as the overrepresentation of bottlefed infants and the reliance on a local data set for the infant charts. The disjunction between length and height, when moving from the infant curves to those for older children, no longer exists. The charts include curves for plotting BMI for ages 2-20 yr rather than weight for height, facilitating identification of obesity.

The data are presented in 5 standard gender-specific charts: (1) weight for age; (2) height (length and stature) for age; (3) head circumference for age; (4) weight for height (length and stature) for infants; and (5) BMI for age for children over 2 yr of age (see Fig. 15-1; also see Figs. 11-1, 11-2, and 13-1). The charts are available at http://www.cdc.gov/growthcharts/.

Each chart is composed of percentile curves, representing the cross-sectional distribution of weight, length, stature, head circumference, weight for length, or BMI at each age. The percentile curve indicates the percentage of children at a given age on the *x*-axis whose measured value falls below the corresponding value on the *y*-axis. On the weight chart for boys 0-36 mo of age (see Fig. 11-2*A*), the 9 mo age line intersects the 25th percentile curve at 8.6 kg, indicating that 25% of the 9 mo old boys in the National Center for Health Statistics sample weigh less than 8.6 kg (75% weigh more). Similarly, a 9 mo old boy weighing more than 11.2 kg is heavier than 95% of his peers. The median or 50th percentile is also termed the *standard value,* in the sense that the standard height for a 7 mo old girl is 67 cm (see Fig. 11-2*B*). The weight-for-height charts (see Fig. 11-1) are constructed in an analogous fashion, with length or stature in place of age on the *x*-axis; the median or standard weight for a girl measuring 110 cm is 18.6 kg.

For infants, the revised CDC charts represent observed but not necessarily optimal growth because they still incorporate data from many bottlefed infants. Rates of initiation of breastfeeding in the United States have more than doubled from 26% in 1970 to 74% in 2005, but nationally only 49% continue to breastfeed at 6 mo, and only 27% continue until 12 mo. Compared with current standards, an exclusively breastfed infant would be expected to plot higher for weight in the 1st 6 mo, but relatively lower in the second half of the 1st yr. Awareness of this growth difference should prevent overidentification of growth problems in breastfed infants.

In an effort to set an internationally usable standard for optimal growth in children, the World Health Organization (WHO) released growth charts based on the Multicenter Growth Reference Study for young children in 2006 and for children 5-19 in 2007. Rather than describing the growth of typical children, the Multicenter Growth Reference Study describes the growth of children who are predominantly breastfed and raised under optimal conditions. Six study sites representing 5 continents were included: United States, Brazil, Norway, Ghana, Oman, and India. Use of the WHO charts in developing nations results in identification of many more children as malnourished and eligible for therapeutic feeding programs. Their use in the United States generally results in many fewer infants being identified as underweight (comparison of curves shown in Fig. 15-2), although studies have found overidentification of poor growth even using these curves. The CDC recommends the use of WHO charts for U.S. children from birth to 24 mo. Adoption of these charts in the United States has been slow. Charts are available online at http://www.who.int/childgrowth/standards/en/.

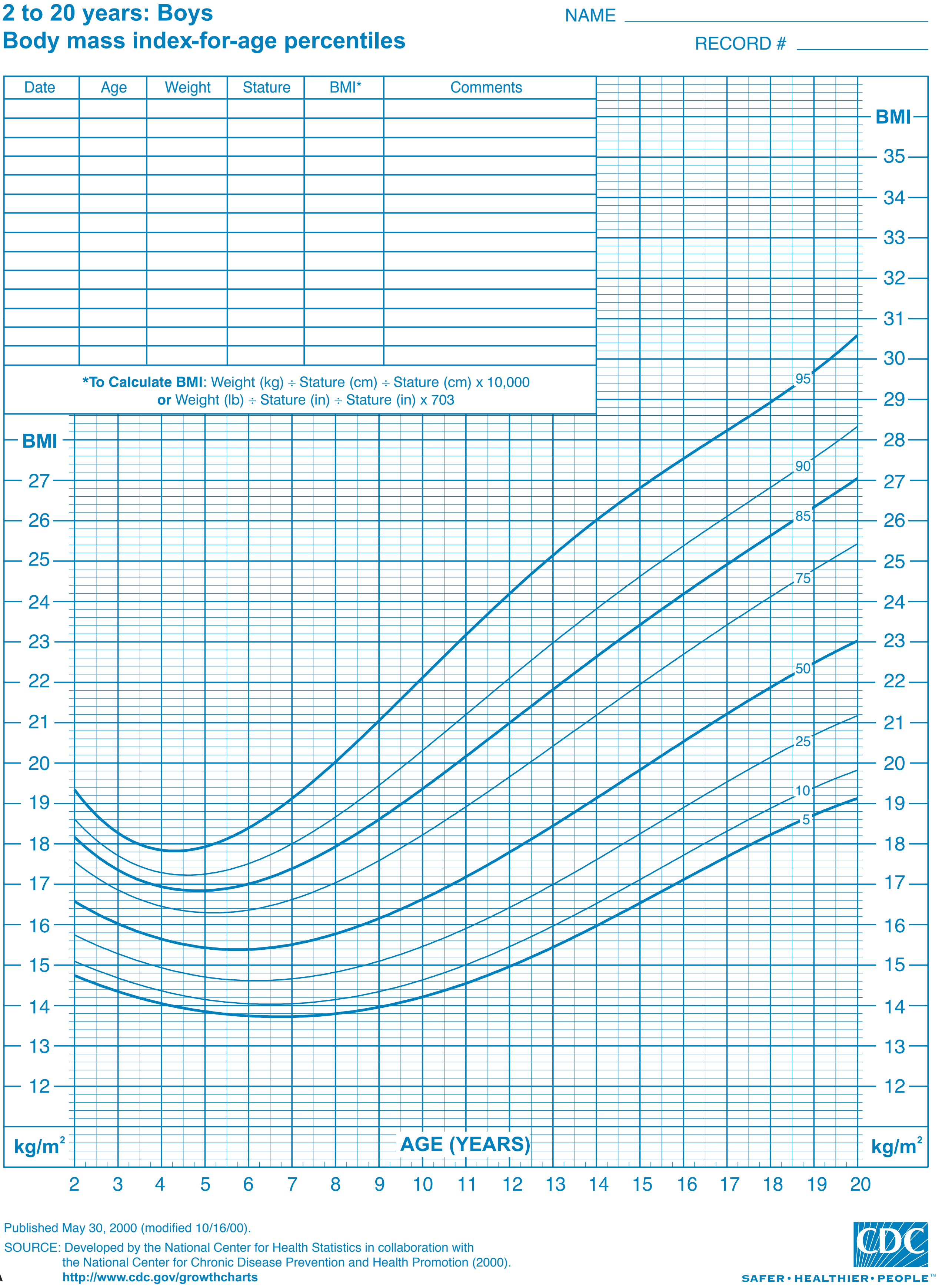

A

Figure 15-1 Body mass index (BMI) percentiles for boys **(A)** and girls **(B)** ages 2-20 yr. *(Official Centers for Disease Control [CDC] growth charts, as described in this chapter. The 85th to 95th percentile is at risk for overweight; >95th percentile is overweight; <5th percentile is underweight. Technical information and interpretation and management guides are available at* www.cdc.gov/nchs*. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, 2000.* http://www.cdc.gov/growthcharts*)*

Continued

2 to 20 years: Girls
Body mass index-for-age percentiles

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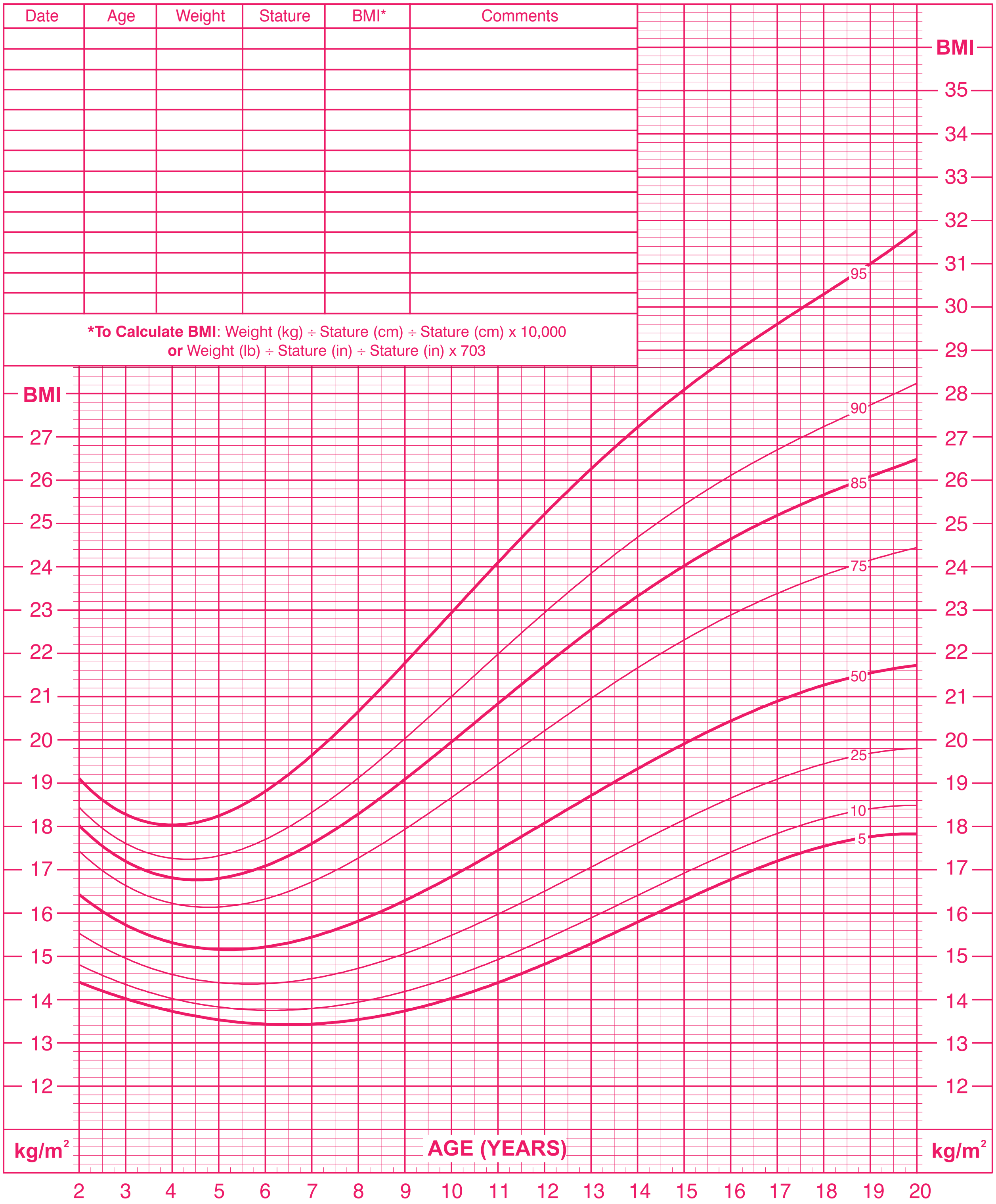

Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
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B

Figure 15-1, cont'd

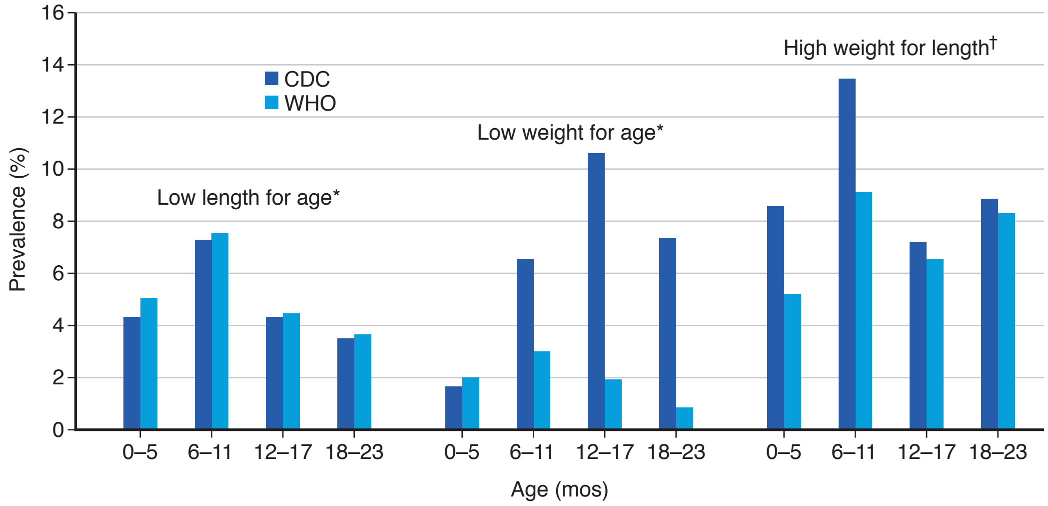

Figure 15-2 Comparison of the WHO and CDC growth chart prevalences of low length for age, low weight for age, and high weight for length among children ages younger than 24 months–United States, 1999-2004. *, ≤5th percentile on the CDC charts; ≤2.3rd percentile on the WHO charts. †, ≥95th percentile on the CDC charts; ≥97.7th percentile on the WHO charts. *(Data from the National Health and Nutrition Examination Survey, 1999-2004; from Grummer-Strawn LM, Reinold C, Krebs NF, Centers for Disease Control and Prevention, Use of World Health Organization and CDC growth charts for children aged 0-59 months in the United States.* MMWR Recomm Rep *59 (RR-9):1-15, 2010, Fig. 6.)*

Table 15-1 Growth and Caloric Requirements

AGE	APPROXIMATE DAILY WEIGHT GAIN (g)	APPROXIMATE MONTHLY WEIGHT GAIN	GROWTH IN LENGTH (cm/mo)	GROWTH IN HEAD CIRCUMFERENCE (cm/mo)	RECOMMENDED DAILY ALLOWANCE (kcal/kg/day)
0-3 mo	30	2 lb	3.5	2.00	115
3-6 mo	20	1.25 lb	2.0	1.00	110
6-9 mo	15	1 lb	1.5	0.50	100
9-12 mo	12	13 oz	1.2	0.50	100
1-3 yr	8	8 oz	1.0	0.25	100
4-6 yr	6	6 oz	3 cm/yr	1 cm/yr	90-100

Adapted from National Research Council, Food and Nutrition Board: Recommended daily allowances, *Washington, DC, 1989, National Academy of Sciences; Frank D, Silva M, Needlman R: Failure to thrive: myth and method,* Contemp Pediatr *10:114, 1993.*

For adolescents, caution must be used in applying cross-sectional charts. Growth during adolescence is linked temporally to the onset of puberty, which varies widely. By using cross-sectional data based on chronological age, the charts combine youth who are at different stages of maturation. Normal variations in the timing of the growth spurt can lead to misdiagnosis of growth abnormalities. The data for 12 yr old boys include both early-maturing boys who are at the peak of their growth spurts and late-maturing ones who are still growing at their prepubertal rate. The net result is to artificially level off the growth peak, making it appear that adolescents grow more gradually and for a longer period than they do. When additional precision is necessary, growth charts derived from longitudinal data, such as the height velocity charts of Tanner and colleagues, are recommended.

Specialized charts have been developed for U.S. children with various conditions, including very-low birthweight and prematurity; Down, Turner, and Klinefelter syndromes; cerebral palsy; and achondroplasia. In addition, growth charts for children of distinct ethnic groups or nationalities may be found on the World Wide Web.

BMI for age complements the standard growth charts for children older than 2 yr of age. BMI can be calculated as weight in kilograms/(height in meters)^2 or weight in pounds/(height in inches)$^2 \times 703$, with fractions of pounds and inches expressed as decimals. Values may be plotted on standard BMI charts (see Fig. 15-1). These calculations can be easily performed electronically using a variety of desktop and handheld devices. BMI percentile varies with age over childhood: a 6 yr old girl with a BMI of 21 is overweight, whereas a 16 yr old girl with the same BMI is just above the 50th percentile.

Electronic medical records (EMRs) include growth charts and usually calculate and plot BMIs. However, the origin of the growth charts that are included in the EMRs used by a pediatrician may be unknown to the pediatrician; consequently, pediatricians are cautioned to contact their EMR company and assure that the CDC and WHO growth charts are available in the EMRs to assure accurate assessment.

Height velocity charts, which evaluate the rate of growth per year, are considered by many to give a more sensitive and specific indicator of abnormal growth. They are used primarily by pediatric endocrinologists. Although many parents think it is important to see growth charts, parents may misinterpret their meaning. Clinicians are cautioned to provide clear interpretation when using growth charts as visual aids.

ANALYSIS OF GROWTH PATTERNS

Growth is a process rather than a static quality. An infant at the 5th percentile of weight for age may be growing normally, may be failing to grow, or may be recovering from growth failure, depending on the trajectory of the growth curve. Infants may lose up to 10% of their birth weight in the 1st wk of life and regain it by the end of the 2nd wk. They will then gain steadily at a rate of 20-30 g/day for the 1st 3 mo. Table 15-1 gives typical growth and calorie requirements for children through age 6 yr. Formulas are available for the estimation of average height

and weight and height for children of various ages, but given their complexity and the easy availability of growth charts, use of the latter is preferable.

Despite the facts that the National Center for Health Statistics charts represent cross-sectional rather than longitudinal data and that children tend to grow in spurts, most children tend to track along a percentile, referred to as *following the curve*. A normal exception commonly occurs between 6 and 18 mo of life. For full-term infants, size at birth reflects the influence of the uterine environment; however, size at 2 yr correlates with mean parental height, reflecting the influence of genes. Between 6 and 18 mo of age, infants may shift percentiles upward or downward toward their genetic potential. Thereafter, most children will track along a growth percentile, with variation within 2 large percentile bands (a small infant might track between the 5th and 25th percentiles, a large one between the 75th and 95th). This tracking often represents the midparental height and a corresponding weight, where **midparental height** is calculated in inches as follows:

- Boys: [(maternal height + 5) + paternal height]/2
- Girls: [maternal height + (paternal height − 5)]/2
- 13 cm (instead of ± 5 in) if using metric units

It is important to correct for various factors in plotting and interpreting growth charts. For **premature infants**, overdiagnosis of growth failure can be avoided by using growth charts developed specifically for this population. A cruder method, subtracting the weeks of prematurity from the postnatal age when plotting growth parameters, does not capture the variability in growth velocity that very-low birthweight infants demonstrate. Although very-low birthweight infants may continue to show catchup growth through early school age, most achieve weight catchup during the 2nd yr and height catchup by 2.5 yr, barring medical complications (see Chapter 97). For children with particularly tall or short parents, there is a risk of overdiagnosing growth disorders if parental height is not taken into account or, conversely, of underdiagnosing growth disorders if parental height is accepted uncritically as the explanation.

The analysis of growth patterns and the detection of aberrant growth patterns provide critical information for the detection of pathologic conditions. Calculation of daily and monthly growth, such as weight gain in g/day (see Table 15-1), allows more precise comparison of growth rate to the norm. Weight loss, or failure to gain normally, is often the first sign of pathology.

The diagnosis of **failure to thrive** (see Chapter 41), usually a diagnosis of children younger than 3 yr of age, is considered if a child's weight is below the 5th percentile, if it drops down more than 2 major percentile lines, or if weight for height is less than the 5th percentile. Weight for height below the 5th percentile remains the single best growth chart indicator of acute undernutrition. A BMI less than the 5th percentile also indicates that a child is underweight. Brief periods of weight loss or poor weight gain are usually rapidly corrected and do not permanently affect size. Children who have been chronically malnourished may be short (stunted) as well as thin, so that their weight-for-height curves may appear relatively normal. Chronic, severe undernutrition in infancy may depress head growth, which may be an ominous predictor of later cognitive disability. Low weight for age or height or weight loss may be referred to as wasting. When growth parameters fall below the 5th percentile, values can be expressed as percentages of the median, or standard, value. A 12 mo old girl weighing 7.1 kg is at 75% of the median weight (9.5 kg) for her age.

Another way to evaluate weight is to determine the ideal body weight for height and compare the current weight to the ideal body weight for length or height. A 15 mo old boy who is 79 cm is at the 50th percentile. The ideal weight is 12 kg. If he weighs 8 kg (<5th percentile), he is 67% of ideal body weight, an indication of severe wasting. Table 15-2 provides interpretation of percent ideal body weight from obese to severe wasting.

Extremes of height or weight can also be expressed in terms of the age for which they would represent the standard or median. For instance, a 30 mo old girl who is 79 cm (<5%) is at the 50th percentile for a 16 mo old. Thus the height age is 16 mo. Weight age can also be expressed this way.

Table 15-2	Interpretation of Percent of Ideal Body Weight
>120%	Obese
110-120%	Overweight
90-110%	Normal variation
80-90%	Mild wasting
70-80%	Moderate wasting
<70%	Severe wasting

Linear growth deficiency (stunting) is more likely to be a result of congenital, constitutional, familial, or endocrine causes than caused by nutritional deficiency (see Chapter 46). In endocrine disorders, length or height declines first or at the same time as weight; weight for height is normal or elevated. In nutritional insufficiency, weight declines before length, and weight for height is low (unless there has been chronic stunting). Figure 15-3 depicts typical growth curves for 4 classes of decreased linear growth. In congenital pathologic short stature, an infant is born small and growth gradually tapers off throughout infancy. Causes include chromosomal abnormalities (Turner syndrome, trisomy 21; see Chapter 81), perinatal infection, extreme prematurity, and teratogens (phenytoin, alcohol) (see Chapter 96). In constitutional growth delay, weight and height decrease near the end of infancy, parallel the norm through middle childhood, and accelerate toward the end of adolescence. Adult size is normal. In familial short stature, both the infant and the parents are small; growth runs parallel to and just below the normal curves.

Obesity affects large numbers of children. Growth charts can confirm an impression of obesity if the weight for height exceeds 120% of the standard (median) weight for height. According to the CDC, a BMI over the 95th percentile indicates obesity and a BMI between the 85th and 95th percentiles indicates overweight. Although widely accepted as the best clinical measure of under- and overweight, BMI may not provide an accurate index of adiposity, because it does not differentiate lean tissue and bone from fat. Measurement of the triceps, subscapular, and suprailiac skinfold thickness can be used to estimate adiposity; considerable experience is needed for accuracy. The *American Academy of Pediatrics Nutrition Handbook,* 6th edition, questions the use of fat folds to estimate total body fat, noting that the method has not been validated in young children and that basic assumptions of the method, that subcutaneous fat is a marker of total fat and that measured sites represent average skin fat thickness, are not true. Other methods of measuring fat, such as hydrodensitometry, bioelectrical impedance, and total body water measurement are used in research, but not in clinical evaluation.

OTHER INDICES OF GROWTH

Body Proportions

Body proportions follow a predictable sequence of changes with development. The head and trunk are relatively large at birth, with progressive lengthening of the limbs throughout development, particularly during puberty. The **lower-body segment** is defined as the length from the symphysis pubis to the floor, and the **upper-body segment** is the height minus the lower-body segment. The ratio of upper-body segment divided by lower-body segment (U/L ratio) equals approximately 1.7 at birth, 1.3 at 3 yr of age, and 1.0 after 7 yr of age. Higher U/L ratios are characteristic of short-limb dwarfism or bone disorders, such as rickets.

Skeletal Maturation

Reference standards for bone maturation facilitate estimation of bone age (see Table 10-3). Bone age correlates well with stage of pubertal development and can be helpful in predicting adult height in early- or late-maturing adolescents. In familial short stature, the bone age is normal (comparable to chronological age). In constitutional delay,

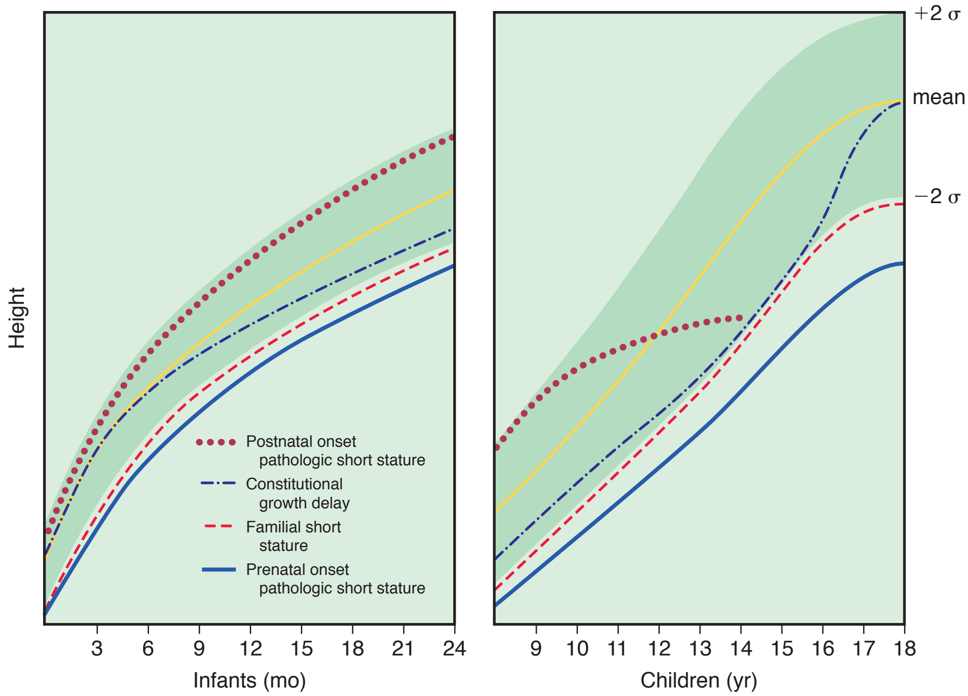

Figure 15-3 Height-for-age curves of the 4 general causes of proportional short stature: postnatal onset pathologic short stature, constitutional growth delay, familial short stature, and prenatal onset short stature. *(From Mahoney CP: Evaluating the child with short stature, Pediatr Clin North Am 34:825, 1987.)*

Table 15-3 Chronology of Human Dentition of Primary or Deciduous and Secondary or Permanent Teeth

	Calcification		Age at Eruption		Age at Shedding	
	BEGINS AT	COMPLETE AT	MAXILLARY	MANDIBULAR	MAXILLARY	MANDIBULAR
PRIMARY TEETH						
Central incisors	5th fetal mo	18-24 mo	6-8 mo	5-7 mo	7-8 yr	6-7 yr
Lateral incisors	5th fetal mo	18-24 mo	8-11 mo	7-10 mo	8-9 yr	7-8 yr
Cuspids (canines)	6th fetal mo	30-36 mo	16-20 mo	16-20 mo	11-12 yr	9-11 yr
First molars	5th fetal mo	24-30 mo	10-16 mo	10-16 mo	10-12 yr	10-12 yr
Second molars	6th fetal mo	36 mo	20-30 mo	20-30 mo	10-12 yr	11-13 yr
SECONDARY TEETH						
Central incisors	3-4 mo	9-10 yr	7-8 yr	6-7 yr		
Lateral incisors	Max, 10-12 mo Mand, 3-4 mo	10-11 yr	8-9 yr	7-8 yr		
Cuspids (canines)	4-5 mo	12-15 yr	11-12 yr	9-11 yr		
First premolars (bicuspids)	18-21 mo	12-13 yr	10-11 yr	10-12 yr		
Second premolars (bicuspids)	24-30 mo	12-14 yr	10-12 yr	11-13 yr		
First molars	Birth	9-10 yr	6-7 yr	6-7 yr		
Second molars	30-36 mo	14-16 yr	12-13 yr	12-13 yr		
Third molars	Max, 7-9 yr Mand, 8-10 yr	18-25 yr	17-22 yr	17-22 yr		

Mand, Mandibular; Max, maxillary.
Adapted from a chart prepared by P.K. Losch, Harvard School of Dental Medicine, who provided the data for this table.

endocrinologic short stature, and undernutrition, the bone age is low and comparable to the height age. Skeletal maturation is linked more closely to sexual maturity rating than to chronological age. It is more rapid and less variable in girls than in boys.

Dental Development

Dental development includes mineralization, eruption, and exfoliation (Table 15-3). Initial mineralization begins as early as the 2nd trimester (mean age for central incisors, 14 wk) and continues through 3 yr of age for the primary (deciduous) teeth and 25 yr of age for the permanent teeth. Mineralization begins at the crown and progresses toward the root. Eruption begins with the central incisors and progresses laterally. Exfoliation begins at about 6 yr of age and continues through 12 yr of age. Eruption of the permanent teeth may follow exfoliation immediately or may lag by 4-5 mo. The timing of dental development is poorly correlated with other processes of growth and maturation. **Delayed eruption** is usually considered when there are no teeth by approximately 13 mo of age (mean + 3 SD). Common causes include hypothyroid, hypoparathyroid, familial, and (the most common) idiopathic. Individual teeth may fail to erupt because of mechanical blockage (crowding, gum fibrosis). Causes of **early exfoliation** include histiocytosis X, cyclic neutropenia, leukemia, trauma, and idiopathic factors. Nutritional and metabolic disturbances, prolonged illness, and certain medications (tetracycline) commonly result in discoloration or malformations of the dental enamel. A discrete line of pitting on the enamel suggests a time-limited insult.

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Chapter 16

Developmental-Behavioral Screening and Surveillance

Frances Page Glascoe, Kevin P. Marks, and Nerissa S. Bauer

The term *developmental–behavioral* refers to children's language, motor, cognitive/academic, self-help, and social–emotional status (a term that also embraces conduct, mental health, attention, and well-being). At well-child visits, development and behavior are the most common topic in parent–professional discussions. Early developmental–behavior problems are common (20-25%) but not benign. Left untreated, early deficits often burgeon into school failure and secondary mental health problems. The consequences include leaving high school before graduating (with rates in inner cities and among minority youth ranging as high as 50%), unemployment, incarceration, and teen pregnancy.

To prevent and address problems, clinicians must screen for existing limitations and risks.

MEASURABLE DELAYS

Among the many types of developmental–behavioral conditions, language problems are the most common (17.5% at 30-36 mo) (see Chapter 35). Delays in language development are often overlooked by healthcare providers, particularly when accurate screening/surveillance tools are not used. Other common conditions are social–emotional/behavioral/mental health disorders (9.5-14.2%), attention-deficit/hyperactivity disorder (7.8%) (see Chapter 33), learning disabilities (6.5%), intellectual disabilities (1.2%) (see Chapter 36), and autism spectrum disorders (0.6-1.1%) (see Chapter 30). Less common conditions include cerebral palsy and other orthopedic/motor impairments (0.23%) (see Chapter 598.1), hearing impairment (0.12%) (see Chapters 636-643), vision impairment (0.8%) (see Chapters 618-635), and conditions associated with disabilities (e.g., Down syndrome and fragile X syndrome [see Chapter 81], traumatic brain injury [see Chapter 68]).

PSYCHOSOCIAL RISK

Many children at risk for school failure lack measurable deficits in early childhood but have markers in the form of multiple risk factors that are strong predictors of future problems. Psychosocial risks include parents with less than a high school education; parental mental health problems such as depression or anxiety; housing or food instability; ethnic or linguistic minority; single parent; 3 or more children in the home; and parenting styles that are neglectful or authoritarian (e.g., highly directive, punitive, limited verbal communication such as talking about children's interests or book-sharing). Such risks eventually lead to developmental–behavioral delays, and result in children entering kindergarten behind their peers, being held back in grade, dropping out of high school, etc. Although psychosocial risk factors are common in children with a history of abuse or neglect, children in many other families are also at-risk.

EARLY INTERVENTION SERVICES AND ELIGIBILITY CRITERIA

If intervention is instituted prior to school entrance, many problems can be prevented and all can be ameliorated. Early intervention takes many forms, requiring varying degrees of intensity.

Developmental–behavioral promotion in primary care is one form of intervention and recommended at all visits. Clinicians identify and intervene with difficulties (e.g., with parent–child interactions and children's behavior), address parents' concerns and provide guidance on child-rearing and other issues. Role-playing, coaching, and verbal advice coupled with take-home information handouts are optimal approaches, although follow-up is needed to determine whether parents capitalized on directives or whether more intensive parent education is needed (e.g., parenting classes). Early intervention in primary care also involves identifying delays, risk factors for future delays, and referring for services more intensive than brief in-office counseling;

For children with psychosocial risk factors but without measurable delays, referrals are needed to a range of services such as Head Start/Early Head Start or quality daycare programs. Families often benefit from parent training classes or mental health interventions and referrals to social work services (e.g., for housing and food assistance, help with domestic violence). Older children with risk factors, benefit from dropout prevention assistance, including after-school tutoring, Boys and Girls Club, summer school, and mentoring programs.

For children with measurable delays (and those at extreme risk such as children in foster care) **referrals are needed to services funded by the Individuals with Disabilities Education Act** (IDEA). Very young children with delays, (i.e., birth to 3 yr of age) are eligible under the broad category of "developmental delay," defined as a single 40% departure or two 25% departures from typical performance in various developmental domains (e.g., receptive language, expressive language, fine motor, gross motor, social–emotional, cognitive/preacademic, and behavior). Because screening measures identify probable strengths and weaknesses but not the extent of deficits, clinicians should refer to IDEA programs for free evaluations to determine eligibility. When children are 3 yr of age, IDEA programs (administered by the public schools) provide detailed evaluations leading to definitive diagnoses and to a range of special education services and adjunctive therapies.

PRIMARY CARE CHALLENGES IN EARLY DETECTION

Despite the serious long-term consequences of psychosocial risk factors, delays and disabilities, only approximately 30% of children with developmental–behavioral problems are detected by primary care providers prior to school entrance, which means that most children with problems miss opportunities for early intervention. There are several reasons for underdetection in primary care:

- **Overconfidence in the effectiveness of informal identification methods** (e.g., ad-hoc questions to parents and milestones checklists such as those embedded in age-specific encounter forms, even if items are drawn from lengthier standardized measures such as the Denver Developmental Screening Test). Informal approaches are of little benefit to patients (or clinicians) because they lack validity, proof of accuracy, and definitive criteria for making referral decisions;
- **Overdependence on clinical judgment and failure to scrutinize the seemingly asymptomatic**. Dysmorphology and organicity are not present in the majority of children with disabilities;
- **Overfocusing on symptoms and thus missing underlying issues**. For example, behavior problems are often the presenting complaint, but many children with developmental deficits act out in frustration due to difficulties understanding what is being asked or expressing thoughts, desires, and feelings in words;
- **Lack of familiarity with and deployment of accurate screening tools effective for busy primary care settings**;
- **An erroneous sense that quality measures take more time than informal approaches**;
- **Excessive optimism about the effectiveness of brief in-office advice when children have measured delays**, and thus deferring rather than referring. Children rarely outgrow developmental–behavioral problems in the absence of intervention;
- **Discomfort at delivering difficult news**. Clinicians require skill at conducting interviews in which difficult news is delivered in a manner that is supportive, positive, and impels families to follow through with recommendations.

POLICIES OF THE AMERICAN ACADEMY OF PEDIATRICS

The American Academy of Pediatrics (AAP) recommends a combination of screening and surveillance at all well-visits.

Screening refers to the administration of brief, standardized, and validated instruments shown to have high sensitivity in detecting children with probable problems and high specificity in determining when children probably do not have problems. Screening for delays should occur across all domains: language (expressive and receptive), motor (gross and fine), cognitive/academic (including features of autism spectrum disorder), self-help, and social–emotional skills (including conduct, attention, and mental health).

Repeated screening compensates for underdetection. Developmental–behavioral problems are a "moving target" and thus require ongoing measurement. Although AAP policies identify specific ages when formal screening should occur (e.g., 9-, 18-, 24- or 30-mo), clinicians should not interpret AAP recommendations to mean that screening/surveillance can cease after 30 mo. Problems (such as language or school readiness) may still be emerging and will not be fully manifested in very young children. The AAP policy states that screening/surveillance should be provided at all well visits and is actively advocating for payers to reimburse for identification efforts with older children.

Although clinicians are often concerned about overidentification, most children with false-positive screens, although ineligible for special education services, have moderate delays in areas predictive of future school failure, that is, language, intelligence, and academic/preacademic skills, along with elevated psychosocial risk. Such children are in need of referrals to other types of intervention programs (e.g., Head Start, after-school tutoring, summer school, and quality preschool or daycare).

Use of accurate screens provides a focus for other well-visit activities. For example, screens relying on parents' concerns identify specific topics for developmental–behavioral promotion. The presence of delays prompts clinicians to conduct a particularly careful physical exam; repeat hearing and vision screening; thoughtfully observe parent–child interactions; take an especially detailed family medical/social history; and similar actions.

Deployment of quality screens provides decision support for the types of interventions needed, including whether clinical advice is sufficient, whether more intensive hands-on services are required, and/or subspecialty medical referrals are needed.

Surveillance refers to ongoing monitoring (tracking over time) of such issues as parental concerns, children's progress with milestones, psychosocial risk and resilience factors, providers' efforts to both detect and address problems, and follow-up regarding child/family outcomes. Surveillance also refers to use of clinical acumen in decision making via the incorporation of screening test results, child/family medical histories, and the physical exam. Repeated accurate screening also serves the tasks of surveillance, but with efficiency and effectiveness. Informal approaches to surveillance are known to be ineffective and of little benefit to families.

OVERCOMING LOGISTICAL CHALLENGES IN PRIMARY CARE EARLY DETECTION AND INTERVENTION

The lists of potential developmental-behavioral topics to be covered at well-child visits are extensive—far more than could be covered in the 14-18 min allotted for such encounters. It is essential to cull topics to those of greatest interest to parents so as to create "the teachable moment" wherein parents are primed to learn most from clinicians' recommendations. Solutions include posters in waiting rooms listing the range of topics on which providers can advise; previsit checklists on which parents indicate topics of interest (and which topics have already been covered in prior visits); and use of use quality screening tests eliciting parents' specific concerns and providing decision support, that is, when advice is probably sufficient vs when referrals are needed.

Clinicians are not always aware of the plethora of services available to families. Approaches to overcome this problem include creating a list of community programs to post in each exam room so that options are visible to parents and providers and encouraging non-medical services to provide prompt feedback on the status of referrals (e.g., establishing two-way consent forms for information sharing), evaluation results and recommendations. Implementing quality screens and patient education in practices requires thoughtful planning and generating enthusiasm among clinic staff who must aid in the process. Clinic flow templates and implementation worksheets are useful tools for establishing efficient implementation procedures.

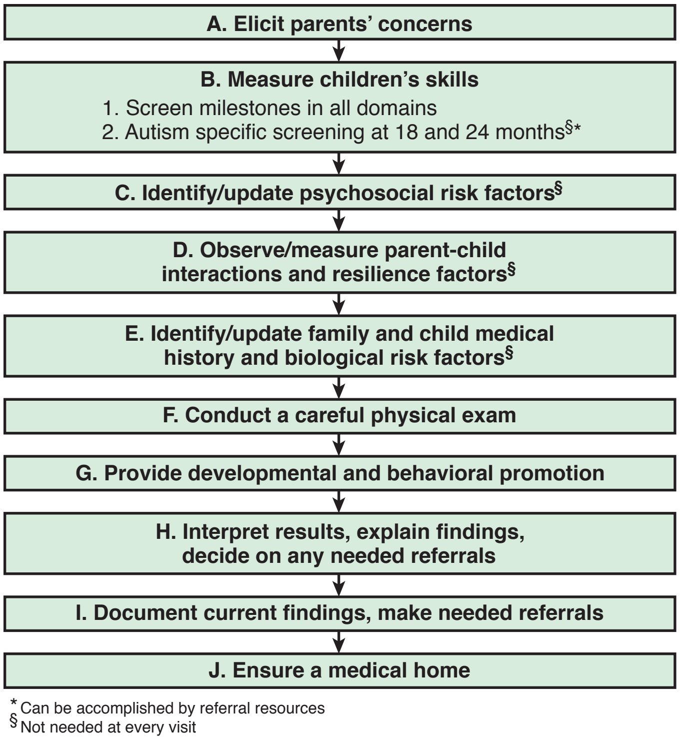

Figure 16-1 Developmental-behavioral surveillance/screening at well-visits with children from birth to 6 yr of age: step-by-step. *(Adapted with permission from Glascoe FP, Marks KP, Poon JK, Macias MM:* Identifying and addressing developmental-behavioral problems: a practical guide for medical and non-medical professionals, trainees, researchers and advocates. *Nolensville, TN, 2013, PEDStest.com, LLC;* http://www.pedstest.com. *Copyright 2013.)*

Evidence-Based Tools

Table 16-1 shows a range of measures useful for early detection of psychosocial risk and resilience, and developmental–behavioral problems, including autism spectrum disorders. Because well-child visits are brief and have enormous agendas (physical exams, immunizations, anticipatory guidance, safety and injury prevention, developmental promotion, and developmental–behavioral screening/surveillance), tools relying on information from parents are ideal because they can be completed in advance of appointments, either online or in writing, whether at home, or while waiting for the encounter to begin. If tools are scored in advance of the patient encounter, clinicians can enter the exam room armed with needed information (e.g., parenting handouts, descriptions of services).

A Workable Process: Step-By-Step

The process of surveillance/screening as drawn from AAP policies is depicted in Figure 16-1 with a description provided in Table 16-2. Many tasks are staggered across visits so that each visit is only minimally burdened with measurement. Red flags are noted in Table 16-3 but are not a substitute for evidence-based screening. Asymptomatic children are those most in need of screening. Those with obvious symptoms simply need referral.

Table 16-2 mentions a range of tools by abbreviations as denoted Table 16-1. The Resources Section (Table 16-4) provides guidance on finding supportive information, practice tools, and the like.

Bibliography is available at Expert Consult.

Table 16-1 Print and Online Tools for Developmental–Behavioral Screening and Surveillance

The following chart is a list of measures meeting standards for screening test accuracy, meaning that they correctly identify, at all ages, at least 70-80% of children with disabilities while also correctly identifying at least 70-80% of children without disabilities. All listed measures were standardized on national samples, proven to be reliable, and validated against a range of diagnostic measures and diagnosed conditions. Not included are measures that fail to meet psychometric standards (limited standardization, absent validation, problematic sensitivity and specificity) such as Denver-II.

The first column provides publication information and the cost of purchasing a specimen set. The "Purpose and Description" column provides details about content and information on alternative ways, if available, to administer measures (e.g., waiting rooms). "Scoring" shows the types of results rendered. The "Accuracy" column shows the percentage of patients with and without problems identified correctly. The "Time Frame/Costs" column shows the costs of materials per visit, along with the costs of professional time (using an average salary of $60/hr) needed to administer each measure, but does not include time needed for generating referral letters. For parent self-report tools, administration time reflects not only scoring of test results, but also the relationship between each test's reading level and the percentage of parents with less than a high school education (who may or may not be able to complete measures in waiting rooms because of literacy problems and thus will need interview administrations).

SCREENS FOR PRIMARY CARE

BEHAVIORAL AND/OR DEVELOPMENTAL SCREENS RELYING ON INFORMATION FROM PARENTS	AGE RANGE	PURPOSE AND DESCRIPTION	SCORING	ACCURACY	TIME FRAME/COSTS
Ages & Stages Questionnaires, Third Edition (ASQ-3) (2009). Paul H. Brookes Publishing Co., Inc., P.O. Box 10624, Baltimore, MD 21285. (800-638-3775) ($295.00) *www.agesandstages.com*. **Training Options:** DVDs for purchase, case examples, and live training **Electronic Options:** See below	1-66 mo	**Purpose:** Screening and surveillance of developmental milestones **Description:** Parents indicate children's developmental skills on 30 items plus overall concerns. The ASQ has a different form (5-8 pages) for each age interval. Written at the 4th–6th grade level. Can be used in mass mail-outs for child-find programs. Manual contains detailed instructions for organizing child-find programs and includes activity handouts for parents. The ASQ-3 is available in English and Spanish; the ASQ-2 is also available in French and Korean with additional translations underway. The ASQ-3 Learning Activities kit is helpful for developmental promotion	Cutoff scores set at 2 SD below the mean, in 5 developmental domains; indicate need for referral or monitoring	**By age:** Sensitivity: 82-89% Specificity: 77-92% **By domain:** Sensitivity: 83% Specificity: 91% **By disabilities:** i.e., cerebral palsy, visual and hearing impairment: Sensitivity: 87%	Scoring time: 2 min Scoring cost: $2.40 Materials: ~$0.36-$0.48 **Total Self-Report: $2.76-$2.88** Interview Time: 12 min. Interview Cost: $14.40 Scoring/Materials: $2.76-$2.88 **Total Interview: $17.28**
Parents' Evaluations of Developmental Status (PEDS). (2013) PEDSTest.com, LLC, 1013 Austin Court, Nolensville, TN 37135 (615-776-4121) ($36.00) www.pedstest.com **Training Options:** offers through its website self-training/train-the-trainer support via downloadable slide shows with notes, case examples, pre-/posttest questions, FAQs, participant handouts, website discussion list (covering all screens), short videos, with some live training available **Electronic Options:** See below	Birth-8 yr	**Purpose:** Screening/surveillance of development/social–emotional/behavior/mental health via parents' concerns **Description:** 10 questions eliciting parents' (and providers') concerns in English, Spanish, Vietnamese and many other languages. Items written at the 5th grade level. Longitudinal Score and Interpretation Forms, assign risk levels, track decision making and offer specific guidance on how to address concerns. Provides screening, longitudinal surveillance, and triage for both developmental and behavioral/social–emotional/mental health problems. PEDS can be used in conjunction with the PEDS: DM (below) for compliance with AAP policies on screening and surveillance, i.e., eliciting and addressing parents' concerns and monitoring milestones	Identifies when to refer and what types of referrals are needed; advise parents; monitor vigilantly; screen further (or refer for screening); or reassure	**By age:** Sensitivity: 91-97% Specificity: 73-86% **By disabilities,** i.e., learning, intellectual, language, mental health, and autism spectrum disorders: Sensitivity: 71-87%	Scoring time: 1 min Scoring cost: $1.20 Materials: $0.39 **Total Self-Report: $1.59** Interview Time: 2 min Interview Cost: $2.40 Scoring/Materials: $1.59 **Total Interview: $3.99**

PEDS: Developmental Milestones (Screening Version) (2008) PEDSTest.com, LLC, 1013 Austin Court, Nolensville, TN 37135 (615-776-4121) ($275.00) *www.pedstest.com* **Training Options:** offers through its website self-training/train-the-trainer support via downloadable slide shows with notes, case examples, pre-/posttest questions, participant handouts, FAQs, website discussion list (covering all screens), short videos, with some live training available. The PEDS: DM manual includes extensive suggestions for training medical students, residents, and nurses **Electronic Options:** See below	Birth-8 yr	**Purpose:** Screening/surveillance of developmental and social–emotional/mental health milestones **Description:** PEDS-DM is designed to replace informal milestones checklists (such as key items from other measures) with evidence. It consists of 6-8 items at each age level. Each item taps a different domain: fine/gross motor, self-help, academics, expressive/receptive language, social-emotional. The PEDS: DM provides screening, triage, and surveillance via a longitudinal score form for tracking milestones progress. Written at the 2nd-3rd grade level and can be completed by self-report, interview, or administered directly to children. Forms are laminated and completed with a dry erase marker. Supplemental measures focused on AAP policy include the M-CHAT, Family Psychosocial Screen, Pictorial PSC-17, the SWILS, the Vanderbilt ADHD scale, and the Brigance Parent-Child Interactions Scale. When combined with PEDS, ensures full compliance with AAP policy. In English, Spanish, Taiwanese, and Portuguese, with other languages in process. The PEDS: DM manual and website contain developmental–behavioral promotion handouts	Pass/fail cutoffs tied to performance above and below the 16th percentile for each item and its domain	**By age:** Sensitivity: 70-94%; Specificity: 77-93% **By developmental domain:** Sensitivity: 75-87%; Specificity: 71-88%	Scoring time: 1 min Scoring cost: $1.20 Materials: $0.02 Total Self-Report: $1.22 Interview Time: 3 min Scoring/Materials: $1.22 Total Interview: $3.82 Direct Admin: 4 min Scoring/Materials: $1.22 Total Direct Admin: $6.10

Parent-report narrow-band screens (for social–emotional/behavioral/mental health, psychosocial risk, and autism spectrum disorder). These are valuable adjuncts in primary care and in other settings but only when preceded by a broadband screen. Narrowband tools should *not* be used as the sole measure of developmental–behavioral status).

NARROWBAND SCREENS RELYING ON INFORMATION FROM PARENTS	AGE RANGE	PURPOSE AND DESCRIPTION	SCORING	ACCURACY	TIME FRAME/COSTS
Modified Checklist for Autism in Toddlers (M-CHAT) (1999). Freely downloadable in multiple languages along with the Follow-up Interview at www.mchatscreen.com Also included in print in PEDS: Developmental Milestones. Commercial software vendors must pay a licensing fee **Training Options:** the site contains a guide to the needed follow-up interview for missed items, and houses research papers and reviews on autism spectrum disorder (ASD) screening **Electronic options:** see below	18-47 mo	**Purpose:** Screening for ASDs **Description:** Parent report of 23 yes-no questions written at 4th-6th grade reading level. Screens for ASD. Downloadable scoring template and Excel files for automated scoring. Requires a follow-up interview for failed items (which can be requested by referral sources). Available in multiple languages	Pass/fail scores based on failing at least 2 critical items, or 3 or more noncritical items	**By age and disability**: i.e., autism spectrum disorders**:** Sensitivity: 90%; Specificity: 99%	Scoring Time: 2 min Scoring costs: $2.40 Materials: $0.06 **Total (Self-Report): $2.46** Interview Time: 5 min (excluding follow-up on any failed items) Interview Cost: $6.00 Scoring/Materials: $2.46 **Total (Interview): $8.46**

Continued

Table 16-1 Print and Online Tools for Developmental–Behavioral Screening and Surveillance—cont'd

NARROWBAND SCREENS RELYING ON INFORMATION FROM PARENTS	AGE RANGE	PURPOSE AND DESCRIPTION	SCORING	ACCURACY	TIME FRAME/COSTS
Brief-Infant-Toddler Social-Emotional Assessment (BITSEA) (2006) Pearson/ Psych Corp, Inc.19500 Bulverde Road, San Antonio, TX 78259 (800-627-7271) ($113.75) www.pearsonassessments.com **Training Options:** none **Electronic Options:** None	12-36 mo	**Purpose:** Screening and surveillance of milestones in social–emotional and mental health **Description:** 42 item parent-report measure (with separate forms if clinical observation is needed). Identifies social–emotional/ behavioral. problems and delays in competence. Written at the 4th-6th grade level. Can be followed by the more detailed ITSEA. Available in Spanish, French, Dutch, Hebrew. Has a CD-ROM for ease of scoring and generating reports and referral letters	Cutpoints based on child age and sex show presence/ absence of problems and competence	**By age and disability:** i.e., internalizing, externalizing, and autism spectrum disorders: Sensitivity: 80-95% Specificity: 80%	Scoring Time: 3 min Scoring costs: $3.60 Materials: $1.56 **Total (Self-Report): $5.16** Interview Time: 6 min Interview Costs: $7.20 Scoring/Materials: $5.16 **Total (Interview): $12.36**
Infant-Toddler Checklist (2002). Paul H. Brookes Publishing Co., Inc., P.O. Box 10624, Baltimore, MD 21285. (800-638-3775) ($99.95) www.brookespublishing.com **Training Options:** live training and research support, downloadable slide shows, abstracts, videos, and references at http://firstwords.fsu.edu **Electronic options**: None	6-24 mo	**Purpose:** Screening and surveillance of language and social milestones **Description:** Parents complete the Checklist's 24 multiple-choice questions. Focuses on screening for language, social communication. Examiners are encouraged to observe child to verify parents' answers via brief observation. Reading level is ~ 3rd grade. Can serve as an entry point into the assessment-level CSBS and also as a monitoring tool. Does not screen for motor milestones. In English, Spanish, Slovenian, Chinese, and German	Cutoff scores for each domain: social, speech and symbolic	**By age and disability**: i.e., developmental disabilities: Sensitivity: 78% Specificity: 84%	Scoring time: ~10 min (by hand), ~3 with CD-ROM Observation time: ~5 min Scoring Costs: $3.60-$12.00 Observation Costs: $6.00 Material Costs: $0.12 **Total (Self-Report/Observation)**: $9.72-$18.12 Interview Time: 8 min Interview Costs: $9.60 Scoring/Materials + Observation: $9.72-$18.12 **Total Interview Costs**: $19.32-$28.72
Ages & Stages Questionnaires: Social–Emotional (ASQ:SE) (2002). Paul H. Brookes Publishing Co., Inc., P.O. Box 10624, Baltimore, MD 21285 (800-638-3775) ($225.00) www.agesandstages.com **Training Options**: training DVD live training, webinars, supporting research on website **Electronic options:** See below	3-66 mo	**Purpose:** Screening and surveillance of milestones in social-emotional and mental health **Description:** Companion measure to ASQ-3. ASQ:SE consists of 8 age-specific forms (each 4-6 pages long) with 22-36 items. Items focus on self-regulation, compliance, communication, adaptive functioning, autonomy, affect, and interaction with people. Readability is 5th-6th grade. Includes activities sheets for families. In English and Spanish	Single cutoff score indicating when a referral is needed	**By age and disability:** i.e., social–emotional problems: Sensitivity: 71-85% Specificity: 90-98%	Scoring Time: 2 min Scoring Cost: $2.40 Material Costs: $0.24-$0.36 **Total (Self-Report): $2.64-$2.76** Interview Time: 10 min Interview Cost: $12.00 Scoring/Materials:$2.64-$2.76 **Total (Interview):** $14.64-$14.76
Psychosocial Risk and Resilience Tools: Not all of the measures below are screens (meaning they do not provide definitive cutoffs) but instead assess a broad array of environmental risk and protective/resilience factors that may affect children's developmental/mental health trajectory—well before delays become obvious. Lack of resilience factors or presence of risk factors, even if all aspects of development are typical at the moment, serve as a call to lower thresholds for referral and to consider a wide-range of community services (e.g., Head Start, parent training, parent mental health programs/parents' own healthcare providers, social services)					

SURVEILLANCE TOOLS FOR RESILIENCE, RISK AND MENTAL HEALTH	AGE RANGE	PURPOSE AND DESCRIPTION	SCORING	ACCURACY	TIME FRAME/COSTS
Family Psychosocial Screen (FPS) (2000) Included within the AAP Pediatric Intake Form (http://www.brightfutures.org), within PEDS: Developmental Milestones, and freely downloadable at www.pedstest.com/TheBook/Chapter10 **Training Options:** none **Electronic Options:** none	Parent	**Purpose:** screening and surveillance of family psychosocial risk **Description:** A 2-page clinic measure of psychosocial risk factors associated with developmental problems, often used for clinic intake. More than 4 risk factors is associated with developmental delays. The FPS also includes: (a) a 4 item screen for parental history of physical abuse as a child; (b) a 6 item measure of parental substance abuse; (c) a 4 item screen for domestic violence; and (d) a 3 item measure of maternal depression. Can be used along with the Brigance Parent-Child Interaction Scale to view parenting risk and resilience. Readability is 4th grade. In English and Spanish	Refer/no refer to available community resources for each of the 4 screens' risk factors	By condition, i.e., parental depression, substance abuse, etc. Depression (3 items): Sensitivity: 100% Specificity: 88% Parental Substance Abuse (7 items): (a) alcohol abuse sensitivity ~90%; (b) drug abuse sensitivity ~88% Parent history of abusive punishment as a child (4 items): Sensitivity: 92-95%; Specificity: 87-92%	Scoring Time: 3 min Scoring Cost: $3.60 Material Costs: photocopied: $0.12 Laminated: $0.00 **Total (Self-Report): $3.60-$3.72**
Brigance Parent-Child Interaction Scale (BPCIS) (2007) PEDSTest.com, LLC. The BPCIS is included in PEDS: Developmental Milestones and in the Brigance Infant and Toddler Screen. It can be freely downloaded at: http://www.pedstest.com/TheBook/Chapter10 **Training Options:** none **Electronic Options:** none	0-30 mo	**Purpose**: Surveillance of parenting behaviors associated with resilience vs psychosocial risk **Description:** Administered by parent-self report or examiner observation, the 18-19 multiple choice items tap whether parents read and talk with their child, enjoy talking with their child, and perceive him/her as interested in communication, whether parents actively teach their child new things, etc. Certain items are associated with resilience while others are associated with accumulating delays (which start to become visible at 6 mo of age and are striking by 12-18 mo)	Item analysis—discrete sets of items reflect resilience factors associated with typical development while others items reflect limited resilience associated with future or current delays	Not applicable	Scoring Time: 1 min Scoring Costs: $1.20 Materials ~$0.06 **Total (Self-Report): $1.26** Interview/Observation Administration time: ~5 min Interview Admin Costs: $6.00 Materials/Scoring ~$1.26 **Total (Direct Admin): $7.26**
Strengths and Difficulties Questionnaire (SDQ) http://www.sdqinfo.org freely downloadable in multiple languages **Training options:** none **Electronic options:** none	4-17 yr	**Purpose:** Resilience and psychosocial risk for mental health/social–emotional, behavioral skills **Description:** 25 items (youth self-report vs parent or teacher report) tapping positive and negative attributes. Generates indicators for conduct problems, hyperactivity, emotional symptoms, peer problems and prosocial behavior. Produces a total strengths vs total difficulties score. Guidance is available on how to aggregate results for epidemiologic and needs-assessment studies. Cross-cultural research and translations are abundant and norming studies have been conducted in Great Britain, the United States and otherwise in European countries	Comparison of factors	Not applicable	Scoring Time: 5 min Scoring Cost: $6.00 Materials: ~$0.12 **Total (Self-Report): $6.12** Interview time: ~5 min Interview Admin costs: $6.00 Materials/Scoring: ~$0.12 **Total (Direct Admin): $12.12**

Continued

Table 16-1 Print and Online Tools for Developmental–Behavioral Screening and Surveillance—cont'd

SCREENS FOR OLDER CHILDREN (These screens focus on academic skills and mental health, including ADHD screening)					
SCREENS FOR OLDER CHILDREN	**AGE RANGE**	**PURPOSE AND DESCRIPTION**	**SCORING**	**ACCURACY**	**TIME FRAME/COSTS**
Safety Word Inventory and Literacy Screener (SWILS). From PEDSTest.com, LLC with items courtesy of Curriculum Associates, Inc. The SWILS is included in PEDS: Developmental Milestones (PEDS:DM) and is freely downloadable at: http://www.pedstest.com/TheBook/Chapter9 **Training Options:** none **Electronic Options:** none	6-14 yr	**Purpose:** Screening and surveillance of academic skills **Description:** Children are asked (by parents or professionals) to read 29 common safety words (e.g., high voltage, wait, poison) aloud. The number of correctly read words is compared to a cutoff score. Results predict performance in math, written language, and a range of reading skills. Test content may serve as a springboard to injury prevention counseling and can be used to screen for parental literacy. Because even non-English speakers living in the United States need to read safety words in English, the measure is only available in English	Single cutoff score by age, indicating the need for a referral	**By age/academic deficits:** Sensitivity: 73-88% Specificity: 77-88%	Scoring Time: 1 min Scoring Costs: $1.20 Materials ~$0.06 **Total (Self-Report): $1.26** Administration time: ~7 min Admin/Scoring Costs: $8.40 Materials/Scoring ~$1.26 **Total (Direct Admin): $9.66**
Pediatric Symptom Checklist (PSC) (1991). Freely downloadable in multiple languages in its 30 question version at http://psc.partners.org **The Pictorial PSC** is useful with low-income Spanish and English speaking families and is included in its 17 item factorable version in PEDS: Developmental Milestones and is available at http://www.pedstest.com/TheBook/Chapter9 **Training Options:** none **Electronic Options:** see below	6-18 yr	**Purpose:** Screening and surveillance of emotional/mental health, and conduct. Serves as a necessary prescreen for sorting attention problems from competing conditions **Description:** Administered by youth/parent self-report or by interview. The PSC/Pictorial PSC are 35 short statements of problem behaviors capturing various mental health challenges. The PSC-17/Pictorial PSC-17 are 17 item versions producing cutoffs for attentional, internalizing (meaning depression or anxiety) and externalizing problems (conduct, impulsivity, etc.) Readability is ~2nd grade. In English, Spanish, Portuguese, Chinese, Dutch, Filipino, French, Somali, and several other languages	For the PSC, a single refer/nonrefer score; for the PSC-17/Pictorial PSC-17, cutoffs for attention, internalizing, and externalizing factors	**PSC/Pictorial PSC by disability:** i.e., mental problems of any kind, across numerous studies: Sensitivity: 80-95% Sensitivity: 68-100% **PSC-17/Pictorial PSC-17 by specific disability:** i.e., ADHD: Sensitivity: 58% Specificity: 91% Internalizing Disorders: Sensitivity: 52-73% Specificity: 74% Externalizing Disorders: Sensitivity: 62% Specificity: 89%	Scoring time: 3 min Scoring Cost: $3.60 Materials ~$0.06 **Total (Self-Report): $3.66** Interview Time: 3 min Interview Cost: $3.60 Materials/Scoring: $3.66 **Total (Interview): $7.26**
CRAFFT (Car, Relax, Alone, Forget, Friends, Trouble): (2009). Freely downloadable from the Center for Adolescent Substance Abuse Research http://www.ceasar-boston.org **Training options:** none **Electronic options:** none	Adolescents (11-21 yr)	**Purpose:** To identify substance use (tobacco, alcohol or other drug abuse) in adolescents **Description:** self-/youth-report questionnaire that contains 3 initial screening questions (A1, A2, A3). If the first 3 questions are all answered "no," then providers should routinely ask 1 more question (B1). If 1 or more of the first 3 screening questions is positive/answered "yes," then the provider should ask 6 more questions (CRAFFT: B1, B2, B3, B4, B5 and B6). If the CRAFFT score is 0 or 1 (0 or 1 item answered "yes"), then give brief advice only. If the CRAFFT score is >2, then this is a positive screen and a brief assessment is needed	For scoring, refer to "description" Note: The AAP has published a recommended algorithm for substance abuse screening, assessment and intervention. Must be completed by youth confidentially	Sensitivity: 76-93% Specificity: 76-94% (positive predictive value [PPV] 29-83%) (negative predictive value [NPV] 91-98%) However, there is no cross cultural data (similar to the PSC and Pictorial PSC)	Scoring time: 1-2 min Scoring cost: $1.20-$2.40 Materials ~$0.06 **Total (Self-Report): $1.26-$2.46** Interview time: 3 min Interview cost: $3.60 Materials/Scoring: $3.66 **Total (Interview):** $4.86-$6.06 but higher if further counseling and intervention is needed

ELECTRONIC RECORDS OPTIONS FOR SCREENING AND SURVEILLANCE WITH QUALITY TOOLS

Essential definitions are:

- Tablet PC—approaches that typically require a stylus to select among multiple-choice answers only;
- Keyboards—approaches enabling users select multiple-choice responses but also type in text-based answers to questions
- Touch-screens applications—these often allow parents to listen to questions and response options and then touch a simple response box (e.g., yes/no) thus reducing literacy demands;
- Online—meaning hosted on a website and thus requiring an Internet connection, preferably high speed;
- PDA—personal digital assistant such as a Palm Pilot or Blackberry usually requiring users to be online, with or without a keyboard
- CD-ROM—offline but still electronic, and requiring installation on the user's computer;
- Parent Portal—online applications wherein parents can complete measures but do not see results; instead, these are sent to a different office computer for retrieval/inclusion in electronic records
- Telephony—automated calling, often along with appointment reminder systems through which multiple-choice screens can be administered;
- Data Aggregation—almost all electronic applications create a database either online or on individuals' computers (in the case of CD-ROMs) where all administered screens can be viewed, overall results summarized, etc. Some web-based scoring services provide exported files; (e.g., Excel compatible) to allow users to view overall results. In all such applications, an administrator of multiple sites can view all results
- Webcasts/webinars—These are training options online, either live on a specific day and, eventually constantly available on publishers' websites.

COMPANY/OFFERINGS	TRAINING/SUPPORT OPTIONS	DESCRIPTION AND PRICING
CHADIS: http://www.chadis.com **ASQ, M-CHAT, PSC, and other measures online for touch-screen, tablet PCs, keyboards, telephony and parent portal methods). Spanish language applications coming soon**	Downloadable guides, live training at exhibits, and other training services on request	CHADIS includes decision support for more than 75 both diagnostic and parent/family focused measures, such as the Vanderbilt ADHD Diagnostic Rating Scale, and various parent and adolescent depression, substance abuse, domestic violence and other inventories. CHADIS offers integration with existing electronic healthcare records (EHRs), works with a range of equipment/applications, and automatically generates reports. Pricing is via site license and ~$695 per year per full-time provider. Includes options for Maintenance of Certification (MOC), quality improvement (QI) credit, and e-chapters for clinicians
PEDS Online: http://www.pedstest.com/online PEDS, PEDS: DM, M-CHAT online (for keyboards) in English and Spanish	Slide shows, website FAQs, email support, online videos, discussion list	This site offers PEDS, PEDS:DM, and the MCHAT for keyboard applications (allowing for actual comments from parents). Offers a parent portal (wherein families do not see the results). Scoring is automated as are summary reports for parents, referral letters when needed, and ICD-9/procedure codes. In English and Spanish. Health Level Seven (HL7)/Health Insurance Portability and Accountability Act (HIPPA)/Family Educational Rights and Privacy Act (FERPA) compliant integration with electronic records is available as is data export and aggregate views of records. $2.00-$2.75 per encounter (depending on volume)
Patient Tools: http://www.patienttools.com (M-CHAT, ASQ, ASQ: SE and other measures online for tablet, i.e., touch-screen PCs)	Webcasts/webinars, live support by phone, email	Patient Tools offers the ASQ (with audio option), ASQ: SE (with audio option), MCHAT, PEDS (in a survey version, i.e., closed-ended questions), PSC, the Vanderbilt ADHD Scales and a wide range of behavioral/mental health measures in multiple languages for adolescents and adults. A practice-based approach provides access in the office via dedicated Survey Tablet equipment, wireless tablet PCs and kiosk PC; or online from home with results available in the office. Access fees are $58.00/mo for ongoing hosting, data storage, reporting, custom programming, telephone technical and installation support. Uses client's PCs or alternately Survey Tablet equipment, including rentable docking stations, lease-purchasing arrangements, or software purchase ($1,525) plus hosting and installation ($58.00/mo) with additional licensing fees for some measures
Ages and Stages-3 and ASQ: SE: http://www.ASQonline.com **Online administration and separately on a CD-ROM for offline administration with keyboards and tablet PCs**	Live training, online training	Web-based management system offers automated scoring, reporting, referral tracking, and customizable letters for parents/providers for ASQ-3 and ASQ: SE. ASQ Pro is designed for single-site programs ($149.95 annual subscription, plus quarterly billing for screens used) and ASQ Enterprise is designed for multisite programs ($499.95 annual subscription, plus quarterly billing for screens used). Online questionnaire completion available through ASQ Family Access ($349.95 annual subscription). ASQ Family Access provides secure, customizable website for parent completion of questionnaires, i.e., a parent portal ($349.95 for an annual subscription plus $79.95 for annual support)

Adapted with permission from Glascoe FP, Marks KP, Poon JK, Macias MM. Identifying and addressing developmental-behavioral problems: a practical guide for medical and non-medical professionals, trainees, researchers and advocates. *Nolensville, TN, 2013, PEDStest.com, LLC; http://www.pedstest.com. Copyright 2013.*

Table 16-2 Annotated Description of Screening/Surveillance in Primary Care

A. **Elicit Parents' Concerns**
At every visit, it is crucial to identify the parent/patient agenda, preferably prior to the encounter, so that clinicians can best prepare for the topics at hand. Informal questions to parents are rarely effective at eliciting their unique issues and do not render the decision support needed to discern which concerns are predictive of problems and which can be addressed with information and monitoring. It is best to use a standardized, validated screening/surveillance measure such as PEDS which is also known to reduce problematic "oh, by the way" concerns, increase the likelihood of attendance at subsequent well-visits, and encourage referral uptake.

B. **Measure/Monitor Children's Skills**
1. Use a broadband milestones-focused screen such as the ASQ or PEDS : DM starting at 6-9 mo and at subsequent well-visits.
2. Use an autism-specific screen such as the M-CHAT at 18 and 24 mo and whenever clinical observation or parents' concerns are worrisome. The requisite M-CHAT Follow-Up Interview (used after a failed M-CHAT) can become a request to referral sources.

Note 1: If using a broadband milestones-focused screen such as the ASQ that does not cover social–emotional/mental health skills, additional screens (e.g., ASQ : SE) should be administered when problems arise and otherwise periodically. When time is limited, referral sources can assist with further evaluations.
Note 2: Use of accurate parent-completed tools prior to the visit is particularly efficient (e.g., from home via electronic screening services, on waiting or exam room computers, paper-pencil, or by staff/clinician interview). As with eliciting parents' concerns, having results available before the encounter gives clinicians an opportunity to prepare referral and/or patient education information.

C. **Measure/Monitor Psychosocial Risk Factors**
At the initial/intake visit (typically the 1st wk of life), a measure such as the Family Psychosocial Screen (FPS) is useful for identifying psychosocial and other risk factors (e.g., substance abuse, domestic violence, housing and food instability, parents' education levels, parental mental health and social support). Four or more risk factors, in the absence of intervention, generally lead to substantial declines in developmental–behavioral status. The FPS also contains a 3-item parental depression screen that should be readministered twice in the 6-15 mo age range to identify and address issues with postpartum dysthymia.

D. **Measure/Monitor Parent–Child Interactions (Resilience Factors)**
Protective (also called resilience) factors are the positive parent–child interactions that promote developmental and behavioral skills (e.g., when parents actively and age-appropriately teach children new things, label objects of interest, share books, and converse with their child [including back-and-forth sound play in infancy, playing peek-a-boo, etc.]). Positive interactions often eclipse psychosocial risk factors and so it is helpful to measure both at the same time. A dearth of positive interactions takes a long-term toll on developmental–behavioral status with marked differences appearing as early as 12-mo of age. Although clinicians sometimes have opportunities to observe parent–child interactions, it is often easier to ask parents to complete a measure such as the Brigance Parent-Child Interactions Scale (BPCIS). Administration at 6 and again at 15 mo is recommended, along with parenting guidance and referrals for parent training when parents have not benefited from in-office advice.

E. **Identify/Update Family and Child Medical History and Biologic Risk Factors**
Child's Medical History: Note in utero exposure to teratogenic/harmful substance, Apgar score less than 5 at 5 min, late or moderate preterm (>32 0/7 to 36 6/7 wk gestational age), very preterm (<32 wk gestational age, low birthweight (<2,500 g), very-low birthweight (<1,500 g), small for gestational age, in utero growth retardation; child's history of: obesity, diabetes, or hypertension, congenital hydrocephalus, meningomyelocele, interventricular hemorrhage (grade III or IV), respiratory distress syndrome, anoxic brain injury, encephalopathy, genetic, metabolic or neurodevelopmental disorder with a high probability of a developmental delay, failure to thrive, iron-deficiency anemia, elevated blood lead level, vision or hearing impairment, HIV, congenital heart disease, obstructive sleep apnea, seizure disorder, etc.
Family Medical/Developmental History: Note any family history of language impairment, learning or intellectual disabilities, autism spectrum disorders, motor disorder, fragile X syndrome, attention-deficit/hyperactivity disorder, mental illness including anxiety disorder, major depression, bipolar disorder, history of deafness, genetic or metabolic disorders, cataract, retinoblastoma, retinal dysplasia, or glaucoma.
In most states, children are automatically eligible for IDEA services if they have a diagnosed condition involving biologic/medical risk factors. In some states, IDEA programs serve children whose parents are mentally ill, intellectually disabled, as well as children in foster care because of a history of abuse or neglect.

F. **Conduct a Careful Physical Exam**
Identify any chronic respiratory or allergic illness, recurrent otitis, head trauma, and sleep problems including symptoms of obstructive sleep apnea. Attend to known symptoms of developmental–behavioral problems, including growth parameters, head shape, and circumference, especially in light of prior visits (e.g., failure to thrive, microcephaly or markedly decelerating head circumference, markedly accelerating head circumference or macrocephaly), facial and other body dysmorphology symptomatic of genetic conditions, eye findings (e.g., cataracts in various inborn errors of metabolism), vascular markings, testicular volume, and signs of neurocutaneous disorders (e.g., >6 café-au-lait spots in neurofibromatosis, hypopigmented macules in tuberous sclerosis), Lisch nodules, ash leaf macules, etc. Neurodevelopmental assessment should include muscle strength, joint laxity, tone, presence of abnormal reflexes, and disturbance of movement.
Focus carefully on physical findings suggestive of abuse or neglect and ensure prompt referrals to social work services.
Newborn hearing screening is essential but even the asymptomatic need follow-up with otoacoustic emissions (OAE) beginning at 6-mo of age and thereafter, as well as tympanometry to evaluate of middle ear pathology. Failed OAEs regardless of middle ear status require an axiomatic referral to an audiologist.
Assess vision at every visit: (a) Abnormal red reflex (may indicate cataract, glaucoma, retinoblastoma, retinal abnormality, or strabismus, or unequal or high refractive error); (b) abnormal ocular alignment (i.e., strabismus) or asymmetrical corneal light reflex; (c) pupillary asymmetry of ≥1 mm (suggestive of neurologic condition); (d) corneal asymmetry (suggestive of glaucoma); (e) unilateral ptosis or other lesions obstructing the visual axis (e.g., eyelid hemangioma), which may cause amblyopia; and (f) nystagmus. For children 3-4 yr of age, measures of visual acuity are needed for which the Lea Symbols are helpful because letter naming is not required. At age 5-6 yr, Snellen Eye Charts can be used. Prompt referral to a pediatric ophthalmologist is warranted when acuity is less than 20/40 in children ages 3-5 yr, or 20/30 in children >6 yr.
Lead screening should be provided whenever developmental–behavioral problems arise, but preferably for all children. Lead screening should be repeated at several points during the 0-6 yr age range. Children living in older homes, near busy streets, with pica, or recently immigrated are at particular risk, as are those who play with adult makeup.
Many of the above findings will automatically qualify children for IDEA Part C programs (birth-3) and so referral for early intervention should be axiomatic in such cases.

Table 16-2 Annotated Description of Screening/Surveillance in Primary Care—cont'd

G. **Provide Developmental–Behavioral Promotion**

Whether or not screening/surveillance identifies problems, parents always need suggestions for what to do at home. The specifics of their concerns should be addressed with parenting information, advice on age-appropriate activities, and anticipatory guidance focused on how developmental changes affect health and safety (e.g., a baby about to crawl will find, mouth, and probably swallow small objects left under furniture). All parents need to be encouraged to promote their child's language and preacademic/academic development. This is most easily accomplished with written patient education materials, by encouraging parents to visit websites with quality information, participating in Reach and Read, or by parent training classes, group well visits, or social work services. A well-organized system for filing and retrieving parent-focused materials is essential (see Table 16-3 for resources). Follow up with families, in 6-8 wk to assess the effectiveness of promotion activities, especially in-office advice about behavior and social skills. If less than successful, encourage parents to engage in more intensive services (e.g., parenting classes, family therapy). Information and referral resources are listed under the Resources section for this chapter.

H. **Interpret Results, Explain Findings, Decide on Any Needed Referrals**

Refer those at psychosocial risk and those with an absence of protective factors for Head Start/Early Head Start, quality daycare, or evidence-based parent-training programs. For all children with positive screens, refer to IDEA programs. Additionally, refer to autism specialty clinics if indicated.

Consider whether medical subspecialty referrals are needed. Electroencephalograms and neuroimaging are not routinely indicated but might be used if there is clinical suspicion of a seizure disorder, hydrocephalus, micro- or macrocephaly, encephalopathy, neurofibromatosis, tuberous sclerosis, brain tumor, or other neurologic problem (not including autism). Extreme handedness at an early age and persistence of fisting after 4 mo is another indicator of potential neuron migration disorders requiring imaging. Uncommonly, surveillance may indicate a need for additional metabolic screens, such as serum electrolytes and glucose, venous blood gas, serum ammonia, urine glycosaminoglycans, endocrine screens (e.g., thyroid-stimulating hormone, free thyroxine), creatinine kinase (CK), genetic testing (chromosomal analysis, DNA for fragile X, etc.), or screens for an infectious disease (e.g., HIV antibody testing, TORCH [toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex] infection testing). Because of the need to discern which tests are needed, referral to a developmental–behavioral or neurodevelopmental pediatrician is wise.

Gather referral information and then explain results to families. Sit down with them and describe referrals in a positive light (e.g., "There is much we can do to help."). Avoid diagnostic labels because in all cases, further evaluation will be provided by referral services. Use euphemisms (e.g., "seems behind others," "seems to be having difficulty with") but use language strong enough that parents will take your concerns seriously. If at all possible, provide a take-home summary report. Most online screening services generate these automatically.

I. **Document Findings and Make Referrals**

A carefully constructed well-visit age-specific encounter form should have space to indicate measures administered and results. A longitudinal problem checklist should be used to briefly document results over time, intervention recommendations, (and will also help identify which measures are needed and when). Billing and coding for optimal reimbursement is essential (in many states, developmental–behavioral screening when coded properly, incurs separate reimbursement). A referral letter is also needed that can be shared with other programs. Be sure to document not only screens administered, results and observations but also health, hearing, and vision status; IDEA requires such information before evaluating children further. Online screening services generate referral letters and thus save a great deal of practice time and expense. If at all possible, make appointments for families because this greatly increases uptake. For examples of age-specific encounter forms, referral letters, and take-home parent summary reports, see www.pedstest.com/thebook.

J. **Ensure a Medical Home**

Children with health and developmental–behavioral problems often receive splintered care with little oversight from primary care providers who, in fact, should be the center of care coordination. Many families do not seek services in a timely manner and so it is critical to establish follow-up dates (e.g., on a longitudinal problem checklist) to determine whether recommendations were followed and whether additional screening or other encouragement is needed.

Establishing communication mechanisms with IDEA and other referral services is helpful so that personnel offer prompt updates on whether appointments were kept, results of further testing, and eligibility for services. Be aware that some referrals will not result in service eligibility due to deficits of insufficient severity. Note that in some, but not all states, IDEA programs for the birth-3 yr age-range can provide ongoing monitoring of ineligible children and suggest to parents other helpful resources. Prompt feedback on the issue of eligibility and ongoing monitoring is needed so that clinicians can refer to other types of intervention programs (e.g., quality daycare, Head Start, parenting training).

In any case, make sure to collaborate with non-medical services by establishing 2-way consent forms for sharing information. Clinicians should also identify communication preferences (e.g., by email, fax, or telephone [including available hours]) and the kind of information to be sent (e.g., evaluation reports, status updates, individual educational plans). Collaboration is facilitated if providers agree to advise intervention programs about medical conditions and medical interventions that may be needed at school.

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Table 16-3 Red Flags in Developmental Screening and Surveillance

These indicators suggest that development is seriously disordered and that the child should be promptly referred to a developmental or community pediatrician.
Note: Most children do not have "red flags" and thus require quality screening to detect any problems.

POSITIVE INDICATORS (THE PRESENCE OF ANY OF THE FOLLOWING)
Loss of developmental skills at any age
Parental or professional concerns about vision, fixing, or following an object or a confirmed visual impairment at any age (simultaneous referral to pediatric ophthalmology)
Hearing loss at any age (simultaneous referral for expert audiologic or ear, nose, and throat assessment)
Persistently low muscle tone or floppiness
No speech by 18 mo, especially if the child does not try to communicate by other means such as gestures (simultaneous referral for urgent hearing test)
Asymmetry of movements or other features suggestive of cerebral palsy, such as increased muscle tone
Persistent toe walking
Complex disabilities
Head circumference above the 99.6th centile or below 0.4th centile. Also, if circumference has crossed 2 centiles (up or down) on the appropriate chart or is disproportionate to parental head circumference
An assessing clinician who is uncertain about any aspect of assessment but thinks that development may be disordered

NEGATIVE INDICATORS (ACTIVITIES THAT THE CHILD CANNOT DO)
Sit unsupported by 12 mo
Walk by 18 mo (boys) or 2 yr (girls) (check creatine kinase urgently)
Walk other than on tiptoes
Run by 2.5 yr
Hold object placed in hand by 5 mo (corrected for gestation)
Reach for objects by 6 mo (corrected for gestation)
Point at objects to share interest with others by 2 yr

From Bellman M, Byrne O, Sege R: Developmental assessment of children. BMJ *346:31–36, 2013.*

Table 16-4 Resources for Developmental–Behavioral Screening/Surveillance in Primary Care

DEVELOPMENTAL–BEHAVIORAL PROMOTION AND PARENT TRAINING
Kids' Health
From the Nemours Foundation, this site has a well-visit guide for each age, anticipatory guidance information, and an easily searchable database for handouts (in English and Spanish) on health and safety, emotional and social development and positive parenting for babies through adolescence.
Reach Out and Read
Offers parenting handouts on how to share books, literacy milestones, and guidance for professionals. Tabs within the site include: Parents and Educators Home, Importance of Reading Aloud, Literacy Milestones, Reading Tips, Books for Children, and Books for Parents.
American Academy of Pediatrics (Information for Families)
The AAP has numerous handouts that can be downloaded for free and available in multiple languages. Provides information on a variety of topics including health conditions, safety and prevention, mental health issues from birth through adolescence.
American Academy of Child and Adolescent Psychiatry
AACAP was one of the first professional organizations to develop handouts for families. These are freely downloadable and cover a wide range of topics as divorce, sleep problems, specific mental health diagnoses, help for military families, and how and where to find a psychiatrist. Handouts are written in many different languages including Spanish, Malaysian, Urdu, Arabic, Icelandic, Polish, and Hebrew. Other site research reviews for professionals, video clips, and links to other resources.

REFERRAL LINKS
American Academy of Pediatrics: Find a Pediatrician
Helps locate developmental–behavioral, neurodevelopmental, general and other subspecialty pediatricians.
Individuals with Disabilities Education Act
Provides links to state, regional and local early intervention programs under the Individuals with Disabilities Education Act, and testing services for young children with suspected or known to have disabilities go to
Early Head Start and Head Start
Provides links to local programs including services for migrant workers, tribal councils, etc.

INTERVENTION SERVICES FOR OLDER CHILDREN
To refer children 3 yr of age and older for evaluations, contact the school district's department of psychology or special education.
For after school/tutoring programs, check with the child's school of zone, and see the websites of the **Boys and Girls Club** and the **YWCA.**

TRAINING AND IMPLEMENTATION PLANNING
Medical Home Initiative
From the AAP and focused on coordinated care for children with special healthcare needs, the site has training materials, rating scales, an e-mail announcement list for providers, how-to information, etc. Medical Home also sponsors several conferences each year.
Harvard University
Includes a helpful video showing providers who, although reluctant to try quality screening, found use of tools far more sensitive and less than time-consuming. The site also provides a helpful implementation guide.
PEDStest.org
Includes downloadable implementation planning forms, workflow charts, two-way consent forms, longitudinal problem checklists, age-specific encounter forms, training guides, slide shows, freely downloadable risk and resilience measures, mental health and academic screens for older children, videos offering a rationale for screening, information about tools, guidance on billing and coding, and links to parenting resources in multiple languages.

Table 16-4 Resources for Developmental–Behavioral Screening/Surveillance in Primary Care—cont'd

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Chapter 17

Childcare: How Pediatricians Can Support Children and Families

Laura Stout Sosinsky and Walter S. Gilliam

In the United States, 61% of all children younger than 5 yr—12.5 million children—were in regular childcare in 2011. Large proportions of young children are in childcare at all ages, with more children entering care as they get older; the majority of children 3 yr of age or older are in regular childcare. Young children of employed mothers spend on average 36 hr per wk in a childcare arrangement.

Childcare is affected by many factors, which derive from family demand, childcare supply, and child and family policy. With increasing movement of mothers into the workplace across the globe, the prime reason most families use childcare is to support maternal employment. At childbirth, unpaid maternity leave is the typical solution among U.S. mothers. The U.S. federal leave program allows for 12 wk of unpaid job-protected leave during pregnancy or after childbirth, but only covers approximately 50% of the workforce, as companies with <50 employees, part-time employees, and those working in informal labor markets are exempt. Four states and the District of Columbia have passed paid family leave laws. In part because of the financial burden of an unpaid maternity leave, many mothers return to work and their children begin childcare very young, sometimes in the 1st few wk after birth. In a 2000 Family and Medical Leave Act survey, only 10% of respondents reported taking more than 60 days for maternity leave. Approximately 44% of mothers in 2005-2007 were working by the time their first child was 3-4 mo of age, and approximately 63% of mothers were working by the time their first child was 12 mo of age. Some mothers face work requirements if they are receiving public benefits given the reforms to welfare passed by Congress in 1996. Many mothers feel strong financial motivation or even pressure to work, especially in single-parent households, or have strong incentive to work for short- and long-term financial security, interest and preference, or all of these. Maternal employment is not the only factor driving childcare use, as young children of unemployed mothers spend on average 21 hr per wk in childcare. Many parents want their children to have childcare experiences for the potential benefits early learning environments can give to their children, particularly preschoolers. Given these realities, childcare quality is of great concern, yet the quality of childcare and early education environments varies widely and the supply of high-quality childcare is largely deemed inadequate.

PROVISION AND REGULATION OF CHILDCARE IN AMERICA

Childcare Settings

Childcare settings vary widely and fall into 4 broad categories, here listed from the least to the most formal:

- Relative care;
- In-home nonrelative care such as nannies, babysitters, or au pairs;
- Family childcare, in which the caregiver provides care in her own home for up to 6 young children often including children of mixed ages, siblings, or the provider's own children; and
- Center-based care, provided in nonresidential facilities for children grouped by age.

Parents more often utilize home-based care for infants and toddlers, partly because of greater preference, flexibility, and availability, and sometimes because of lower cost. Use of center-based childcare is greater among preschoolers (children 3-5 yr old). Childcare centers and early education programs are administered by a wide array of businesses and organizations, including for-profit independent companies and chains, religious organizations, public and private schools, community organizations, cooperatives, and public agencies. Preschool programs (e.g., Head Start, prekindergarten) also may play an important role in childcare. Although early education programs may have a greater focus on educational activities and often only provide limited hours of care per days, the health and safety issues involved with preschool programs are similar to those presented by other group childcare settings.

Childcare Licensing, Regulation, and Accreditation

Licensing and regulatory requirements for the most part mandate basic health and safety standards, such as sanitary practices, child and provider vaccinations, access to a healthcare professional, and facilities and equipment safety, as well as basic structural and caregiver characteristics, such as the ratio of children to staff, group sizes, and minimum caregiver education and training requirements. Most childcare centers and preschools and many family daycare providers are subject to state licensing and regulation. As of this writing, with the exception of Idaho, all states regulate centers, as does the District of Columbia (for the most recent data, see http://www.naralicensing.org/Licensing). Most states also regulate family childcare providers, although some states only license specific types of family childcare homes, and 3 states do not license these providers at all (Idaho, Louisiana, and New Jersey). Seven states (Arizona, Idaho, Louisiana, New Jersey, Ohio, South Dakota, and Virginia) do not license small family childcare homes, and 11 states (Arkansas, Idaho, Kentucky, Louisiana, Maryland, Maine, North Carolina, New Jersey, Vermont, Washington, and Wisconsin) and the District of Columbia do not license large/group family childcare homes. Louisiana has a registration process for family childcare homes with no more than 6 children, but registration is only required when the provider cares for children subsidized by the federal Childcare and Development Fund (which assists low-income families receiving temporary public assistance, or those needing childcare in order to work or receiving training to transition off of public assistance). New Jersey has a voluntary registration process for family childcare homes that is operated by childcare resource and referral agencies in the state.

Many providers are legally exempt from licensing standards. Exemptions for various types of programs vary state to state. The smallest homes (3-4 children in care) are typically license-exempt, encompassing relative, friend, and neighbor caregivers as well as babysitters, nannies and au pairs. These providers fall outside of any regulatory scrutiny, and some may not even think of themselves as offering "childcare"; 31% of 9 mo olds and 22% of 2 yr olds may be in small home-based care settings (3 or fewer children). Fewer are cared for in large home-based settings (4 or more children), typically by nonrelatives. Small family childcare homes are exempt if there are a small number of children in care in 26 states, and large/group family childcare homes are exempt if they are open part-day in 11 states. Unlike exemption rules for homecare providers, which typically are based on size, centers are often exempted if overseen by other organizations such as schools, churches, or local governments, and thus have some external oversight. Many of these entities provide part-day or part-week Head Start or preschool programs, and about half of the states also explicitly exempt such part-time programs. Just 9% of 9 mo olds and 17% of 2 yr olds were cared for in centers. In contrast to care for 4 yr olds (when more than half of children are in center care), few centers caring for younger children were exempt from licensing (35% of centers caring for 4 yr olds were not licensed in contrast to 2% of centers caring for 2 yr olds).

Homes and centers that fall under state licensing guidelines face very different requirements. Size differs greatly between the 2 types of contexts, and such size differences are built into regulations in terms of the maximum number of children that can be cared for in a group and the number of adults that must be present. The most common state-required maximum group size in centers is 8 for infants, 12 for toddlers, and 20 for preschoolers; centers may have numerous classrooms of these sizes. For centers, regulations explicitly state an allowable ratio of children to adults. The most common ratios are 4 : 1 for infants, 6 : 1 for toddlers, and 10 : 1 for preschoolers, meaning that typically there would be 2 adults in a group. States license homes in 2 categories, small and large, with typical maximums of 6 and 12 in the 2 categories (including the provider's own children). More than three-quarters of licensed homes fall within the small category. Thus the total size of a typical home is smaller than just 1 classroom in a center. States less often explicitly lay out child-to-adult ratios for homes, given that many homes involve 1 provider caring for all of the children. Some states restrict the number of younger children that may be in care, or explicitly provide ratios (especially for large homes), although these restrictions vary greatly across states.

Health and safety conditions may be unsatisfactory in unlicensed settings. In most states, licensing and regulatory standards have been found to be inadequate to promote optimal child development, and in many states standards are so low as to endanger child health and safety. Therefore, even licensed providers may be providing care at quality levels far below professional recommendations. A small portion of providers become accredited by National Association for the Education of Young Children (NAEYC), National Association for Family Child Care (NAFCC), or other organizations by voluntarily meeting high-quality, developmentally appropriate, professionally recommended standards. The accreditation process goes far beyond health and safety practices and structural and caregiver characteristics to examine the quality of child–caregiver interactions, which are crucial for child development, as described in the next section. Evidence indicates that childcare programs that complete voluntary accreditation through NAEYC improve in quality and provide an environment that better facilitates children's overall development. Only 10% of childcare centers and 1% of family childcare homes are accredited; this is partly the result of a lack of knowledge, resources, and incentives for providers to improve quality, but it may also be partly because of expenses providers incur in the process of becoming accredited.

State childcare licensing agencies are playing a larger role in various initiatives designed to improve the quality of childcare, working through the infrastructure of the early care and education system. Several states' licensing agencies are part of quality initiatives called quality ratings and improvement systems, such as tiered quality strategies (e.g., tiered reimbursement systems for participating providers who achieve levels of quality beyond basic licensing requirements), public funding to facilitate accreditation, professional development systems, and program assessments and technical assistance.

Sick Children

When children are ill, they may be excluded from out-of-home arrangements, and settings under state licensure are required to exclude children with certain conditions. Guidelines for health and safety in out-of-home care from the American Academy of Pediatrics, the American Public Health Association, and the National Resource Center for Health and Safety in Child Care and Early Education offer recommendations regarding the conditions under which sick children should and should not be excluded from group programs (Table 17-1). State laws typically mirror these guidelines but may be stricter in some states.

Most families need to make arrangements to keep sick children at home (such as staying home from work or having backup plans with an alternative caregiver). Alternative care arrangements outside the home for sick children are relatively rare but may include either (1) care in the child's own center, if it offers special provisions designed for the care of ill children (sometimes called the infirmary model or sick daycare), or (2) care in a center that serves only children with illness or temporary conditions. Although it is important that such arrangements emphasize preventing further spread of disease, one study found no occurrence of additional transmission of communicable disease in children attending a sick center. The impact of group care of ill children on their subsequent health and on the health of their families and community is unknown.

CHILDCARE'S ROLE IN CHILD HEALTH AND DEVELOPMENT

Characteristics of Childcare and Associations with Child Developmental Outcomes

High-quality childcare is characterized by warm, responsive, and stimulating interactions between children and caregivers. In high-quality interactions, caregivers express positive feelings toward their children; are emotionally involved, engaged, and aware of the child's needs and sensitive and responsive to their initiations; speak directly with children in a manner that is elaborative and stimulating while being age-appropriate; and ask questions and encourage children's ideas and verbalizations. Structural quality features of the setting, including ratio of children to adults, group size, and caregiver education and training, act indirectly on child outcomes by facilitating high-quality child–caregiver interactions. It would be difficult for even the most sensitive and stimulating provider to engage in high-quality interactions with each child, if the provider was the sole caregiver of 10 toddlers.

The quality, quantity, type of setting, and stability of childcare experienced by young children contribute to child development. Childcare use by itself does not affect mother–child attachment. Only when combined with low maternal sensitivity and responsiveness does poor-quality childcare, larger quantities of childcare, or multiple childcare arrangements predict greater likelihood of insecure attachment.

Adjusting for family factors (i.e., parental income, education, race/ethnicity, family structure, parental sensitivity) the quality of childcare has a unique and consistent, albeit small, association with child outcomes across most domains of development. The type of childcare setting has unique effects, controlling for quality, with results from numerous studies demonstrating that center-based care is associated with better language and preacademic performance than home-based care. Quantity of care (hours per week) may also have unique effects, but findings are mixed, with some studies demonstrating small associations between greater quantity and elevated behavior problems, and other studies finding no associations for most children. Instability in childcare—over the course of a day, such as with rotating staff or multiple arrangements, or over time, with frequent changes in arrangements—does have negative effects on children's language and internalizing problems. Also, as childcare settings naturally have packages of quality characteristics, which are a mix of lower- and

Table 17-1 Conditions That Do and Do Not Require Exclusion from Group Childcare Settings

CONDITIONS THAT REQUIRE EXCLUSION	COMMENTS
If any of these 3 key criteria for exclusion of children who are ill are met, the child should be temporarily excluded, regardless of the type of illness:	
Illness preventing the child from participating comfortably in activities as determined by the childcare provider	Providers should specify in their policies, approved by the facilities' healthcare consultant, what severity level of illness the facility can manage, and how much and what types of illness will be addressed: • Severity level 1 consists of children whose health condition is accompanied by high interest and complete involvement in activity associated with an absence of symptoms of illness (such as children recovering from pinkeye, rash, or chickenpox), but who need further recuperation time • Severity level 2 encompasses children whose health condition is accompanied by a medium activity level because of symptoms (such as children with low-grade fever, children at the beginning of an illness, and children in the early recovery period of an illness) • Severity level 3 is composed of children whose health condition is accompanied by a low activity level because of symptoms that preclude much involvement
Illness resulting in a greater need for care than the childcare staff can provide without compromising the health and safety of the other children as determined by the childcare provider	
Illness that poses a risk of spread of harmful diseases to others	
In addition to the above key criteria, temporary exclusion is recommended when the child has any of the following conditions:	
Fever (temperature above 38°C [101°F] orally, above 38.9°C [102°F] rectally, or above 37.8°C [100°F] or higher taken axillary [armpit] or measured by an equivalent method) and behavior change or other signs and symptoms (e.g., sore throat, rash, vomiting, diarrhea)	Accompanied by behavior changes or other signs or symptoms of illness until medical professional evaluation finds the child able to be included at the facility
Acute change in behavior including lethargy/lack of responsiveness, inexplicable irritability or persistent crying, difficult breathing, or having a quickly spreading rash	Until evaluation by a medical professional finds the child able to be included at the facility
Diarrhea (defined by watery stools or decreased form of stool that is not associated with changes of diet). Exclusion is required for all diapered children whose stool is not contained in the diaper and toilet-trained children if the diarrhea is causing soiled pants or clothing	Readmission after diarrhea can occur when diapered children have their stool contained by the diaper (even if the stools remain loose) and when toilet-trained children are continent. Special circumstances that require specific exclusion criteria include the following: • Toxin-producing *Escherichia coli* or *Shigella* infection, until stools are formed and test results of 2 stool cultures obtained from stools produced 24-hr apart do not detect these organisms • *Salmonella* serotype Typhi infection, until diarrhea resolves and, in children younger than age 5 yr, 3 negative stool cultures obtained with 24-hr-intervals are obtained
Blood or mucus in stool	Not explained by dietary change, medication, or hard stools
Vomiting illness	More than 2 times in the previous 24 hr, unless the vomiting is determined to be caused by a noninfectious condition and the child remains adequately hydrated
Abdominal pain	Persistent (continues more than 2 hr) or intermittent associated with fever or other signs or symptoms
Mouth sores with drooling	Unless the child's primary care provider or local health department authority states that the child is noninfectious
Rash with fever or behavior changes	Until the primary care provider has determined that the illness is not an infectious disease
Active tuberculosis	Until the child's primary care provider or local health department states child is on appropriate treatment and can return
Impetigo	Until treatment has been started
Streptococcal pharyngitis (i.e., strep throat or other streptococcal infection)	Until 24 hr after treatment has been started
Purulent conjunctivitis	Defined as pink or red conjunctiva with white or yellow eye discharge, until after treatment has been initiated
Pediculosis (head lice)	Until after the first treatment *Note:* Exclusion is not necessary before the end of the program day
Scabies	Until after treatment has been given

Continued

Table 17-1 Conditions That Do and Do Not Require Exclusion from Group Childcare Settings—cont'd

CONDITIONS THAT REQUIRE EXCLUSION	COMMENTS
Varicella-zoster (chickenpox)	Until all lesions have dried or crusted (usually 6 days after onset of rash)
Rubella	Until 6 days after onset of rash
Pertussis	Until 5 days of appropriate antibiotic treatment
Mumps	Until 5 days after onset of parotid gland swelling
Measles	Until 4 days after onset of rash
Hepatitis A virus	Until 1 wk after onset of illness or jaundice if the child's symptoms are mild or as directed by the health department
Any child determined by the local health department to be contributing to the transmission of illness during an outbreak	
CONDITIONS THAT DO NOT REQUIRE EXCLUSION	**COMMENTS**
Common colds, runny noses	Regardless of color or consistency of nasal discharge
A cough not associated with an infectious disease or a fever	
Watery, yellow or white discharge or crusting eye discharge without fever, eye pain, or eyelid redness	
Presence of bacteria or viruses in urine or feces in the absence of illness symptoms, like diarrhea	Exceptions include children infected with highly contagious organisms capable of causing serious illness
Pink eye (bacterial conjunctivitis) indicated by pink or red eyelids after sleep	If 2 unrelated children in the same program have conjunctivitis, the organism causing the conjunctivitis may have a higher risk for transmission and a child healthcare professional should be consulted.
Fever without any signs or symptoms of illness in children who are older than 6 mo regardless of whether acetaminophen or ibuprofen was given	If the child is behaving normally but has a fever of below 38.9°C (102°F) rectally or the equivalent, the child should be monitored, but does not need to be excluded for fever alone
Rash without fever and without behavioral changes	
Lice or nits	Exclusion for treatment of an active lice infestation may be delayed until the end of the day
Ringworm	Exclusion for treatment may be delayed until the end of the day
Molluscum contagiosum	Do not require exclusion or covering of lesions
Thrush (i.e., white spots or patches in the mouth or on the cheeks or gums)	
Fifth disease	Once the rash has appeared
Methicillin-resistant *Staphylococcus aureus* (MRSA) without an infection or illness that would otherwise require exclusion	Known MRSA carriers or colonized individuals should not be excluded
Cytomegalovirus infection	
Chronic hepatitis B infection	
HIV infection	
Asymptomatic children who have been previously evaluated and found to be shedding potentially infectious organisms in the stool	Children who are continent of stool or who are diapered with formed stools that can be contained in the diaper may return to care
Children with chronic infections conditions that can be accommodated in the program according to the legal requirement of federal law in the Americans with Disabilities Act	The act requires that childcare programs make reasonable accommodations for children with disabilities and/or chronic illnesses, considering each child individually

Adapted from American Academy of Pediatrics, American Public Health Association, National Resource Center for Health and Safety in Child Care and Early Education: Stepping stones to caring for our children: national health and safety performance standards: guidelines for early care and education programs, third edition, *Elk Grove Village, IL, 2013, Authors, pp 46–52, available at: http://nrckids.org/index.cfm/products/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/*

higher-quality indicators, the bundle of features in a childcare arrangement may be another meaningful way for a parent to consider the potential effects of an arrangement on their child.

When a healthcare provider talks with a parent about the parent's child's childcare arrangement, it is also important to consider the individual child's characteristics, health concerns, dispositions, and even physiologic responses to the environment. Like all environments, childcare is experienced differently by different children. An average environment can often sufficiently compensate for the typical regulatory capacities of most children, but when an environment lacks adequate support for a child's unique needs, healthy development can be further compromised. Some children may be more vulnerable to bad childcare (or particularly responsive to good childcare), such as children with difficult or fearful temperaments, especially if their home environments are characterized by more risk factors, such as poverty or high conflict with a parent.

Several large studies have found that most U.S. childcare is of "poor to mediocre" quality. In one study, only 14% of centers (8% of

center-based infant care) were found to provide developmentally appropriate care, while 12% scored at minimal levels that compromised health and safety (40% for infant care). In another study, 58% of family daycare homes provided adequate or custodial care, and only 8% provided good care. Children with the greatest amount of family risk may be the most likely to receive childcare that is substandard in quality. Many children from lower-risk families also receive lower-quality care, and despite their advantages at home, these children may not be protected from the negative effects of poor-quality care.

Affordable, accessible, high-quality childcare is hard to find. Middle-class families spend approximately 6% of their annual income on childcare expenses, whereas poor families spend approximately 33% (on par with housing expenses). Infant and toddler care is particularly expensive with fewer available slots. For a married couple with children, the average cost of full-time center care for 1 infant ranges from 7% to approximately 19% of the state median income, depending on the state, and the average cost of center care for one 4 yr old exceeds 10% of the median household income in 21 states and the District of Columbia. For single parents, the average cost of center-based infant care exceeds 25% of median income in every state. The average cost of family childcare is only slightly lower.

In addition to the stress of meeting such a high expense, many parents worry that their child will feel unhappy in group settings, will suffer from separation from the parents, or will be subjected to neglect or abuse. This worry is especially likely among low-income parents with more risk factors, fewer resources, and fewer high-quality options available. Parents are the purchasers but not the recipients of care, and are not in the best position to judge its quality. Many parents are first-time purchasers of childcare with little experience and very immediate needs, selecting care in a market that does little to provide them with useful information about childcare arrangements. In many states, efforts are underway to improve quality and provide parents with quality information, but several states do not have a quality rating and information system, and programs in states that do are still emerging, and testing of effectiveness is still underway. To inform their care decisions, parents may turn to their child's pediatrician as the only professional with expertise in child development with whom they have regular and convenient contact.

Childcare and Child Health

A disproportionate number of sudden infant death syndrome (SIDS) deaths occur in childcare centers or family-based childcare homes (approximately 20%). Infants who are back-sleepers at home, but are put to sleep on their fronts in childcare settings, have a higher risk of SIDS. Providers and parents should be made aware of the importance of placing infants on their backs to sleep (see Chapter 375).

Children enrolled in childcare are also of an age that places them at increased risk for acquiring infectious diseases. Participation in group settings elevates exposure. Children enrolled in such settings have a higher incidence of illness (upper respiratory tract infections, otitis media, diarrhea, hepatitis A infections, skin conditions, and asthma) than those cared for at home, especially in the preschool years; these illnesses have no long-term adverse consequences. Childcare providers that follow childcare licensure guidelines for handwashing, diapering, and food handling, and that manage child illness appropriately, can reduce communicable illnesses.

There is debate about whether childcare exposure serves as a risk or protective factor for asthma. One cross-sectional study found that preschoolers in childcare had increased risk of the common cold and otitis media, and children who began childcare before the age of 2 yr had increased risk of developing recurrent otitis media and asthma. However, a longitudinal study found that children who were exposed to older children at home or to other children at childcare during the 1st 6 mo of life were less likely to have frequent wheezing from age 6-13 yr, suggesting that childcare exposure may protect against the development of asthma and frequent wheezing later in childhood. A 10 yr follow-up of a birth cohort found no association between childcare attendance and respiratory infections, asthma, allergic rhinitis, or skin prick test reactivity. Another study found that in the 1st yr of elementary school, children who had attended childcare had fewer absences from school, half as many episodes of asthma, and less acute respiratory illness than their peers who had never attended childcare. These results are perhaps related to protection against respiratory illness as a result of early exposure or a shift in the age-related peak of illness, though selection of illness-prone children into home care may play a role. Other factors may also be relevant to this issue, such as children in childcare potentially being less exposed to passive smoking than children at home.

Childcare and Children with Special Needs

The needs of children with mental, physical, or emotional disabilities who, because of their chronic illness, require special care and instruction may require particular attention when it comes to their participation in most childcare settings. Guiding principles of services for children with disabilities advocate supporting children in natural environments, including childcare. Furthermore, the Americans with Disabilities Act and Section 504 of the Rehabilitation Act of 1973 prohibit discrimination against children and adults with disabilities by requiring equal access to offered programs and services.

Although many childcare providers and settings are unprepared to identify or administer services for children with special needs, childcare could be utilized for delivery of support services to these children and/or for linking families to services, such as early intervention and doctor referrals. Furthermore, pediatricians can draw upon childcare providers to help provide important evaluative data regarding a child's well-being, as these providers have extensive daily contact with the child and may have broad, professional understanding of normative child development. A childcare provider may be the first to identify a child's potential language delay. Childcare providers are also necessary and valuable partners in the development and administration of early intervention service plans.

Children with special needs may be eligible for services under the Individuals with Disabilities Education Act (IDEA) (see Chapter 36). The purpose of this law is to provide "free appropriate public education," regardless of disability or chronic illness, to all eligible children, birth to 21 yr, in a natural and/or least-restrictive environment. Eligible children include those with mental, physical, or emotional disabilities who, because of their disability or chronic illness, require special instruction to learn. As a part of these services, a formal plan of intervention is to be developed by the service providers, families, and the children's healthcare providers. Federal funds are available to implement a collaborative early intervention system of services for eligible infants and toddlers between the ages of birth and 3 yr and their families. These services include screening, assessment, service coordination, and collaborative development of an **individualized family service plan (IFSP).** The IFSP describes early intervention services for the infant or toddler and family, including family support and the child's health, therapeutic, and educational needs. An understanding of the child's routines and real-life opportunities and activities, such as eating, playing, interacting with others, and working on developmental skills, is crucial to enhancing a child's ability to achieve the functional goals of the IFSP. Therefore it is critical that childcare providers be involved in IFSP development or revision, with parental consent. Childcare providers should also become familiar with the child's IFSP and understand the providers' role and the resources available to support the family and childcare provider.

Additionally, IDEA provides support for eligible preschool age children to receive services through the local school district. This includes development of a written **individualized education program (IEP)**, with implementation being the responsibility of the local education agency in either a public or private preschool setting. As with IFSPs, childcare providers should become familiar with the preschooler's special needs as identified in the IEP and may become involved, with parental consent, in IEP development and review meetings. In cases where children may have or be at risk of developmental delays, a diagnosis is important for obtaining and coordinating services and further evaluation. To this end, pediatricians can partner with childcare providers to screen and monitor children's behavior and development.

Table 17-2 Childcare Information Resources

ORGANIZATION	SPONSOR	WEBSITE AND CONTACT INFORMATION
Child Care Aware	Child Care Aware of America (formerly National Association of Child Care Resource and Referral Agencies)	http://www.childcareaware.org
Healthy Child Care America	American Academy of Pediatrics (AAP)	http://www.healthychildcare.org
National Association for the Education of Young Children (NAEYC)		http://www.naeyc.org
National Association for Sick Child Daycare (NASCD)		http://www.nascd.com
National Association for Family Child Care (NAFCC)		http://www.nafcc.org
National Resource Center for Health and Safety in Child Care and Early Education (NRC)		http://www.nrckids.org For the 2013 report from the AAP, APHA, and NRC, *Stepping Stones to Caring for Our Children: National Health and Safety Performance Standards: Guidelines for Early Care and Education Programs,* Third Edition, go to: http://nrckids.org/index.cfm/products/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/
Office of Child Care (OCC)	U.S. Department of Health and Human Services, Administration for Children & Families	http://www.acf.hhs.gov/programs/occ
Office of Child Care Technical Assistance Network (CCTAN)	U.S. Department of Health and Human Services, Administration for Children & Families, Office of Child Care	https://childcare.gov/

ROLE OF PEDIATRIC PROVIDERS IN CHILDCARE

Advising Parents on Childcare Selection

Organized professional guidance in choosing childcare is insufficient. Pediatricians can help parents understand the importance for their child's development of selecting high-quality care by describing how it looks and providing referrals and tips on how to find and select high-quality childcare (Table 17-2). In addition, pediatricians can help parents determine how to adjust childcare arrangements to best meet their child's specific needs (e.g., allergies, eating and sleeping habits, temperament and stress-regulation capacities). For most parents, finding childcare that they can afford, access, manage, and accept as a good environment for their child is a very difficult process and one many parents find distressing. Many parents are also worried about how their child will fare in childcare (e.g., Will their child feel distressed by group settings, suffer from separation from the parents, or even be subjected to neglect or abuse?). These worries are especially likely among low-income parents with fewer family and community resources to draw upon. A few parents may think of childcare only as babysitting, and may not consider the consequences for their child's cognitive, linguistic, and social development, focusing solely on whether the child is safe and warm. These parents may be less likely to select a high-quality childcare arrangement, which is especially problematic if the family is facing socioeconomic challenges that already place them at risk of receiving lower-quality care for their children. For these parents, it is vital to stress the importance of quality and its implications for their child's cognitive, language, and behavioral development and school readiness.

Advising Parents on Childcare Health Issues

Parents of infants should be advised to ensure that childcare providers put infants on their back to sleep to prevent SIDS. Also, pediatricians should emphasize the importance of following vaccination schedules; most states require compliance for children to participate in licensed group childcare settings.

When children are ill, parents should be advised to follow guidelines for inclusion and exclusion (see Table 17-1). Parents may disagree with childcare staff about whether a child meets or does not meet the exclusion criteria. However, professional guidelines state that "if … the reason for exclusion relates to the child's ability to participate or the caregiver's/teacher's ability to provide care for the other children, the caregiver/teacher should not be required to accept responsibility for the care of the child." (http://nrckids.org/index.cfm/products/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/).

Helping Children with Special Needs

Pediatricians should work with parents and communicate with other service providers and early intervention staff to identify problems, remove access barriers, and coordinate service delivery for children with special needs. They should also encourage involvement of parents and childcare providers in IFSP or IEP plan development.

Consulting and Partnering with Childcare Providers

Most state regulations mandate that licensed programs have a formal relationship with a healthcare provider. Additional state efforts include mental health consultation models to support providers, who are often not well trained in managing child behavior, and build capacity to raise quality for all children. Early childhood mental health consultation links a mental health professional with an early education and care provider in an ongoing problem-solving and capacity-building relationship.

Pediatricians can provide consultation to childcare providers about measures to protect and maintain the health and safety of children and staff. This may include consultation regarding promoting practices to prevent SIDS; preventing and reducing the spread of communicable disease; reducing allergen, toxin, and parasite exposure; ensuring vaccinations for children and staff; removing environmental hazards; and preventing injuries.

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Chapter 18

Loss, Separation, and Bereavement

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All children will experience involuntary separations, whether from illness, death, or other causes, from loved ones at some time in their lives. Relatively brief separations of children from their parents, such as vacations, usually produce minor transient effects, but more enduring and frequent separation may cause sequelae. The potential impact of each event must be considered in light of the age and stage of development of the child, the particular relationship with the absent person, and the nature of the situation.

SEPARATION AND LOSS

Separations may be from temporary causes, such as vacations, parental job restrictions, natural disasters, or parental or sibling illness requiring hospitalization. More long-term separations occur as a result of divorce, placement in foster care, or adoption, whereas permanent separation may occur because of death. The initial reaction of young children to separation of any duration may involve crying, either of a tantrum-like, protesting type, or of a quieter, sadder type. Children's behavior may appear subdued, withdrawn, fussy, or moody, or they may demonstrate resistance to authority. Specific problems may include poor appetite, behavior issues such as acting against caregiver requests, reluctance to go to bed, sleep problems, or regressive behavior, such as requesting a bottle or bed-wetting. School-age children may experience impaired cognitive functioning and poor performance in school. Some children may repeatedly ask for the absent parent and question when the absent parent will return. The child may go to the window or door or out into the neighborhood to look for the absent parent; a few may even leave home or their place of temporary placement to search for their parents. Other children may not refer to the parental absence at all.

A child's response to reunion may surprise or alarm an unprepared parent. A parent who joyfully returns to the family may be met by wary or cautious children. After a brief interchange of affection, children may seem indifferent to the parent's return. This response may indicate anger at being left and wariness that the event will happen again, or the child may feel, as a result of magical thinking, as if the child caused the parent's departure. If the mother who frequently says "Stop it, or you'll give me a headache" is hospitalized, the child may feel at fault and guilty. As a result of these feelings, children may seem to be more closely attached to the other present parent than to the absent one, or even to the grandparent or babysitter who cared for them during their parent's absence. Some children, particularly younger ones, may become more clinging and dependent than they were before the separation, while continuing any regressive behavior that occurred during the separation. Such behavior may engage the returned parent more closely and help to reestablish the bond that the child felt was broken. Such reactions are usually transient and within 1-2 wk, children will have recovered their usual behavior and equilibrium. Recurrent separations may tend to make children more wary and guarded about reestablishing the relationship with the repeatedly absent parent, and these traits may affect other personal relationships. Parents should be advised not to try to ameliorate a child's behavior by threatening to leave.

DIVORCE

More sustained experiences of loss, such as divorce or placement in foster care, can give rise to the same kinds of reactions noted earlier, but they are more intense and possibly more lasting. Currently in the United States, approximately 40% of marriages end in divorce. Divorce has been found to be associated with negative parent functioning, such as parental depression and feelings of incompetence, negative child behavior, such as noncompliance and whining, and negative parent–child interaction, such as inconsistent discipline, decreased communication, and decreased affection. Greater childhood distress is associated with greater parental distress. Continued parental conflict and loss of contact with the noncustodial parent, usually the father, is common. Two of the most important factors that contribute to morbidity of the children in a divorce include parental psychopathology and disrupted parenting before the separation. The year following the divorce is the period when problems are most apparent; these problems tend to dissipate over the next 2 yr. Depression may be present 5 yr later, and educational or occupational decline may occur even 10 yr later. It is difficult to sort out all of the confounding factors. Children may suffer when exposed to parental conflict that continues after divorce, and in some cases may escalate. The degree of interparental conflict may be the most important factor associated with child morbidity. A continued relationship with the noncustodial parent, as long as there is minimal interparental conflict, was a factor associated with more positive outcomes.

School-age children may respond with evident depression, may seem indifferent, or may be markedly angry. Other children appear to deny or avoid the issue, behaviorally or verbally. Most children cling to the hope that the actual placement or separation is not real and are only temporary. The child may experience guilt by feeling that the loss, separation, or placement represents rejection and perhaps punishment for misbehavior. Children may protect a parent and assume guilt, believing that their own "badness" caused the parent to depart. Outwardly blaming parents may be perceived by a child as emotionally risky; parents who discover that a child harbors resentment might punish the child further for these thoughts or feelings. Children who feel that their misbehavior caused their parents to separate or become divorced have the fantasy that their own trivial or recurrent behavioral patterns caused their parents to become angry at each other. Some children have behavioral or psychosomatic symptoms and unwittingly adopt a "sick" role as a strategy for reuniting their parents.

In response to divorce of parents and the subsequent separation and loss, older children and adolescents commonly show intense anger. Five yr after the breakup, approximately ⅓ of children report intense unhappiness and dissatisfaction with their lives and their reconfigured families, another ⅓ show clear evidence of a satisfactory adjustment, whereas the remaining ⅓ demonstrate a mixed picture, with good achievement in some areas and faltering achievement in others. After 10 yr, approximately 45% do well, but 40% may have academic, social, and/or emotional problems. As adults, some are reluctant to form intimate relationships, fearful of repeating their parents' experience. Parental divorce has a moderate long-term negative impact on the adult mental health status of children who had experienced it, even after controlling for changes in economic status and problems before divorce. Good adjustment of children after a divorce is related to ongoing involvement with 2 psychologically healthy parents who minimize conflict, and to the siblings and other relatives who provide a positive support system. Divorcing parents should be encouraged to avoid adversarial processes and to use a trained mediator to resolve disputes if needed. Joint custody arrangements may reduce ongoing parental conflict, but children in joint custody may feel overburdened by the demands of maintaining a strong presence in 2 homes.

When the primary care provider is asked about the effects of divorce, parents should be informed that different children may have different reactions, but that the parents' behavior and the way they interact with each other will have a major and long-term effect on the child's adjustment. The continued presence of both parents in the child's life, with minimal interparental conflict, is most beneficial to the child.

MOVE/FAMILY RELOCATION

A significant proportion of the population of the United States changes residence each year. The effects of this movement on children and families are frequently overlooked. For children, the move is essentially involuntary and out of their control. When such changes in family

structure as divorce or death precipitate moves, children face the stresses created by both the precipitating events and the move itself. Parental sadness surrounding the move may transmit unhappiness to the children. Children who move lose their old friends, the comfort of a familiar bedroom and house, and their ties to school and community. They not only must sever old relationships but also are faced with developing new ones in new neighborhoods and new schools. Children may enter neighborhoods with different customs and values, and because academic standards and curricula vary among communities, children who have performed well in one school may find themselves struggling in a new one. Frequent moves during the school years are likely to have adverse consequences on social and academic performance.

Migrant children and children who emigrate from other countries present with special circumstances. These children not only need to adjust to a new house, school, and community but also need to adjust to a new culture and, in many cases, a new language. Because children have faster language acquisition than adults, they may function as translators for the adults in their families. This powerful position may lead to role reversal and potential conflict within the family. In the evaluation of migrant children and families, it is important to ask about the circumstances of the migration, including legal status, violence or threat of violence, conflict of loyalties, and moral, ethical, and religious differences.

Parents should prepare children well in advance of any move and allow them to express any unhappy feelings or misgivings. Parents should acknowledge their own mixed feelings and agree that they will miss their old home while looking forward to a new one. Visits to the new home in advance are often useful preludes to the actual move. Transient periods of regressive behavior may be noted in preschool children after moving, and these should be understood and accepted. Parents should assist the entry of their children into the new community, and whenever possible, exchanges of letters and visits with old friends should be encouraged.

SEPARATION BECAUSE OF HOSPITALIZATION

Potential challenges for hospitalized children include coping with separation, adapting to the new hospital environment, adjusting to multiple caregivers, seeing very sick children, and sometimes experiencing the disorientation of intensive care, anesthesia, and surgery. To help mitigate potential problems, a preadmission visit to the hospital is important to allow the child to meet the people who will be offering care and ask questions about what will happen. Parents of children younger than 5-6 yr of age should room with the child if feasible. Older children may also benefit from parents staying with them while in the hospital, depending on the severity of their illness. Creative and active recreational or socialization programs with child life specialists, chances to act out feared procedures in play with dolls or mannequins, and liberal visiting hours, including visits from siblings, are all helpful. Sensitive, sympathetic, and accepting attitudes toward children and parents by the hospital staff are very important. Healthcare providers need to remember that parents have the best interest of their children at heart and know their children the best. Whenever possible, school assignments and tutoring for the hospitalized children should be available in order to engage the child intellectually and prevent them from falling behind in their scholastic achievements.

The psychologic aspects of illness should be evaluated from the outset, and physicians should act as a model for parents and children by showing interest in a child's feelings, allowing them a venue for expression, and demonstrating that it is possible and appropriate to communicate discomfort in verbal, symbolic language. Continuity of medical personnel may be reassuring to the child and family.

MILITARY FAMILIES

More than 2 million children live in military families in the United States, and approximately 50% of them obtain medical care in the community rather than at a military medical facility.

Children whose parents are serving in the military may experience loss and separation in multiple ways. These include frequent relocations, relocation to foreign countries, and duty-related separation from parents. In recent years, the most impactful experiences have been repeated wartime deployments of parents and of the deaths of parents during military service.

All branches of the military have increased their focus on preparing and supporting military families for a service member's deployment to improve family coping. Military families composed of young parents and young children are at risk for child maltreatment in the context of repeated or prolonged deployments.

PARENTAL/SIBLING DEATH

Approximately 5-8% of U.S. children will experience parental death; rates are much higher in other parts of the world that are more directly affected by war, AIDS, and natural disasters. Anticipated deaths from chronic illness may place a significant strain on a family, with frequent bouts of illness, hospitalization, disruption of normal home life, absence of the ill parent, and perhaps more responsibilities placed on the child. Additional strains include changes in daily routines, financial pressures, and the need to cope with aggressive treatment options.

Children can and should continue to be involved with the sick parent or sibling, but they need to be prepared for what they will see in the home or hospital setting. The stresses that a child will face include visualizing the physical deterioration of the family member, helplessness, and emotional lability. Forewarning the child that the family member may demonstrate physical changes, such as appearing thinner or losing hair will help the child to adjust. These warnings, combined with simple yet specific explanations of the need for equipment, such as a nasogastric tube for nutrition, an oxygen mask, or a ventilator, will help lessen the child's fear. Children should be honestly informed of what is happening, in language they can understand, allowing them choices, but with parental involvement in decision making. They should be encouraged, but not forced, to see their ill family member. Parents who are caring for a dying spouse or child may be too emotionally depleted to be able to tend to their healthy child's needs or to continue regular routines. Children of a dying parent may suffer the loss of security and belief in the world as a safe place, and the surviving parent may be inclined to impose his or her own need for support and comfort onto the child. However, the well parent and caring relatives must keep in mind that children need to be allowed to remain children, with appropriate support and attention. Sudden, unexpected deaths lead to more anxiety and fear, because there was no time for preparation and uncertainty as to explanations.

GRIEF AND BEREAVEMENT

Grief is a personal, emotional state of bereavement or an anticipated response to loss, such as a death. Common reactions include sadness, anger, guilt, fear, and at times, relief. The normality of these reactions needs to be emphasized. Most bereaved families remain socially connected and expect that life will return to some new, albeit different, sense of normalcy. The pain and suffering imposed by grief should never be automatically deemed "normal" and thus neglected or ignored. In uncomplicated grief reactions, the steadfast concern of the pediatrician can help promote the family's sense of well-being. In more distressing reactions (such as those seen in traumatic grief of sudden deaths), the pediatrician may be a major, first-line force in helping children and families address their loss.

Participation in the care of a child with a life-threatening or terminal illness is a profound experience. Parents experience much anxiety and worry during the final stages of their child's life. In 1 study at a children's hospital, 45% of children dying from cancer died in the pediatric intensive care unit, and parents report that 89% of their children suffered "a lot" or "a great deal" during the last month of life. Physicians consistently underreport children's symptoms in comparison to parents' reports. Better ways are needed to provide for dying children, and to maintain honest and open communication, provide appropriate pain management, and meet the families' wishes as to the preferred location of the child's death, in some cases in their own home. Inclusion of multiple disciplines, such as hospice, clergy, nursing, pain service, child life specialists, and social work, often helps to fully support families during this difficult experience.

The practice of withholding information from children and parents regarding a child's diagnosis and prognosis has generally been abandoned because physicians have learned that protecting parents and patients from the seriousness of their child's condition does not alleviate concerns and anxieties. Even very young children may have a real understanding of their illness. Children who have serious diseases and are undergoing aggressive treatment and medication regimens, but are told by their parents that they are okay, are not reassured by their parents. These children understand that something serious is happening to them, and they are often forced to suffer in silence and isolation because the message they have been given by their parents is to not discuss it and to maintain a cheerful demeanor. Children have the right to know their diagnosis and should be informed early in their treatment. The content and depth of the discussion needs to be tailored to the child's personality and developmental level of understanding. Parents have choices as to how to orchestrate the disclosure. Parents may want to be the ones to inform the child themselves, may choose for the pediatric healthcare provider to do so, or may do it in partnership with the pediatrician.

A death, especially the death of a family member, is the most difficult loss for a child. Many changes in normal patterns of functioning may occur, including loss of love and support from the deceased family member, a change in income, the possible need to relocate, less emotional support from surviving family members, altering of routines, and a possible change in status from sibling to only child. Relationships between family members may become strained, and children may blame themselves or other family members for the death of a parent or sibling. Bereaved children may exhibit many of the emotions discussed earlier as a result of the loss, in addition to behaviors of withdrawal into their own world, sleep disturbances, nightmares, and symptoms such as headache, abdominal pains, or possibly similar to those of the family member who has died. Children 3-5 yr of age who have experienced a family bereavement may show regressive behaviors such as bed-wetting and thumb sucking. School-age children may exhibit nonspecific symptoms, such as headache, abdominal pain, chest pain, fatigue, and lack of energy. Children and adolescents may also demonstrate enhanced anxiety should these symptoms resemble those of the family member who died. The presence of secure and stable adults who can meet the child's needs and who permit discussion about the loss is most important in helping a child to grieve. The pediatrician should help the family understand this necessary presence and encourage the protective functioning of the family unit. More frequent visits to the healthcare professional may be necessary to address these symptoms and provide reassurance when appropriate.

Death, separation, and loss as a result of natural catastrophes and human-made disasters have become increasingly common events in children's lives. Exposure to such disasters occurs either directly or indirectly, where the event is experienced through the media. Examples of indirect exposure include televised scenes of earthquakes, hurricanes, tsunamis, tornadoes and the terrorist attacks at the Boston Marathon in 2013 and in New York on September 11, 2001, with the subsequent news stories about anthrax and heightened states of alert. Children who experience personal loss in disasters tend to watch more television coverage than children who do not. Children without a personal loss watch as a way of participating in the event and may thus experience repetitive exposure to traumatic scenes and stories. The loss and devastation for a child who personally lives through a disaster is significant; the effect of the simultaneous occurrence of disaster and personal loss complicates the bereavement process as grief reactions become interwoven with posttraumatic stress symptoms (see Chapter 25). After a death that occurs as a result of aggressive or traumatic circumstances, access to expert help may be required. Under conditions of threat and fear, children seek proximity to safe, stable, protective figures.

It is important for parents to grieve with their children. Some parents want to protect their children from their grief, so they put on an outwardly brave front or do not talk about the deceased family member. Instead of the desired protective effect, the child receives the message that demonstrating grief or talking about death is wrong, leading the child to feel isolated, to grieve privately, or to delay grieving. The child may also conclude that the parents didn't really care about the deceased because they have forgotten the deceased so easily or demonstrate no emotion. The parents' efforts to avoid talking about the death may cause the parents to isolate themselves from their children at a time when the children most need them. Children need to know that their parents love them and will continue to protect them. Children need opportunities to talk about their relative's death and associated memories. A surviving sibling may feel guilty simply because he or she survived, especially if the death was the result of an accident that involved both children. Siblings' grief, especially when compounded by feelings of guilt, may be manifested by regressive behavior or anger. Parents should be informed of this possibility and encouraged to discuss the possibility with their children.

DEVELOPMENTAL PERSPECTIVE

Children's responses to death reflect the family's current culture, their past heritage, experiences, and the sociopolitical environment. Personal experience with terminal illness and dying may also facilitate children's comprehension of death and familiarity with mourning. Developmental differences in children's efforts to make sense of and master the concept and reality of death do exist and profoundly influence their grief reactions.

Children **younger than 3 yr** of age have little or no understanding of the concept of death. Despair, separation anxiety, and detachment may occur at the withdrawal of nurturing caretakers. Young children may respond in reaction to observing distress in others, such as a parent or sibling who is crying, withdrawn, or angry. Young children also express signs and symptoms of grief in their emotional states, such as irritability or lethargy, and in severe cases, mutism. If the reaction is severe, failure to thrive may occur.

Preschool children are in the preoperational cognitive stage, in which communication takes place through play and fantasy (see Chapter 6). They do not show well-established cause-and-effect reasoning. They feel that death is reversible, analogous to someone going away. In attempts to master the finality and permanence of death, preschoolers frequently ask unrelenting, repeated questions about when the person who died will be returning. This makes it difficult for parents, who may become frustrated because they don't understand why the child keeps asking and do not like the constant reminders of the person's death. The primary care provider has a very important role in helping families understand the child's struggle to comprehend death. Preschool children typically express magical explanations of death events, sometimes resulting in guilt and self-blame ("He died because I wouldn't play with him." "She died because I was mad at her."). Some children have these thoughts, but do not express them verbally because of embarrassment or guilt. Parents and primary care providers need to be aware of magical thinking and must reassure preschool children that their thoughts had nothing to do with the outcome. Children of this age are often frightened by prolonged, powerful expressions of grief by others. Children conceptualize events in the context of their own experiential reality, and therefore consider death in terms of sleep, separation, and injury. Young children express grief intermittently and show marked affective shifts over brief periods. Regression, accompanied by longing, sadness, and anger, may accompany grief.

Younger school-age children think concretely, recognize that death is irreversible, but believe it will not happen to them or affect them, and begin to understand biologic processes of the human body ("You'll die if your body stops working"). Information gathered from the media, peers, and parents forms lasting impressions. Consequently, they may ask candid questions about death that adults will have difficulty addressing ("He must have been blown to pieces, huh?").

Children 9 yr of age and older do understand that death is irreversible and that it may involve them or their families. These children tend to experience more anxiety, overt symptoms of depression, and somatic complaints than do younger children. School-aged children are often left with anger focused on the loved one, those who could not save the deceased, or those presumed responsible for the death. Contact with

the pediatrician may provide great reassurance, especially for the child with somatic symptoms, and particularly when the death followed a medical illness. School and learning problems may also occur, and these reactions are often linked to difficulty concentrating or preoccupation with the death. Close collaboration with the child's school may provide important diagnostic information and offer opportunities to mobilize intervention or support.

At 12-14 yr of age, children begin to use symbolic thinking, reason abstractly, and analyze hypothetical, or "what if," scenarios systematically. Death and the end of life become concepts, rather than events. Teenagers are often ambivalent about dependence and independence and may withdraw emotionally from surviving family members, only to mourn in isolation. Adolescents begin to understand complex physiologic systems in relationship to death. Since they are often egocentric, they may be more concerned about the impact of the death on themselves than about the deceased or other family members. Fascination with dramatic, sensational, or romantic death sometimes occurs and may find expression in copycat behavior, such as cluster suicides, as well as competitive behavior to forge emotional links to the deceased person ("He was my best friend."). Somatic expression of grief may revolve around highly complex syndromes (eating disorders or conversion reactions) as well as symptoms limited to the more immediate perceptions, as with younger children (stomachaches). Quality of life takes on meaning, and the teenager develops a focus on the future. Depression, resentment, mood swings, rage, and risk-taking behaviors can emerge as the adolescent seeks answers to questions of values, safety, evil, and fairness. Alternately, the adolescent may seek philosophical or spiritual explanations ("being at peace") to ease their sense of loss. The death of a peer may be especially traumatic.

Families often struggle with how to inform their children of the death of a family member. The answer depends on the child's developmental level. It is best to avoid misleading euphemisms and metaphor. A child who is told that the relative who died "went to sleep" may become frightened of falling asleep, resulting in sleep problems or nightmares. Children can be told that the person is "no longer living" or "no longer moving or feeling." Using examples of pets that have died sometimes can help children gain a more realistic idea of the meaning of death. Parents who have religious beliefs may comfort their children with explanations, such as "Your sister's soul is in heaven" or "Grandfather is now with God," provided those beliefs are honestly held. If these are not religious beliefs that the parents share, children will sense the insincerity and experience anxiety rather than the hoped-for reassurance. Children's books about death can provide an important source of information, and when read together, these books may help the parent to find the right words, while addressing the child's needs.

ROLE OF THE PEDIATRICIAN IN GRIEF

The pediatrician has an important role in assisting grieving families, because the death of a child has become an uncommon experience in our society. The pediatric healthcare provider who has had a longitudinal relationship with the family will be an important source of support in the disclosure of bad news and critical decision making, during both the dying process and the bereavement period.

The involvement of the healthcare provider may include being present at the time the diagnosis is disclosed, at the hospital or home at the time of death, being available to the family by phone during the bereavement period, sending a sympathy card, attending the funeral, and/or scheduling a follow-up visit. Attendance at the funeral sends a strong message that the family and their child are important, respected by the healthcare provider, and can also help the pediatric healthcare provider to grieve and reach personal closure about the death. A family meeting 1-3 mo later may be helpful because parents may not be able to formulate their questions at the time of death. This meeting allows the family time to ask questions, share concerns, and review autopsy findings (if one was performed), and allows the healthcare provider to determine how the parents and family are adjusting to the death.

Instead of leaving the family feeling abandoned by a healthcare system that they have counted on, this visit allows them to have continued support. This is even more important when the healthcare provider will be continuing to provide care for surviving siblings. The visit can be used to determine how the mourning process is progressing, detect evidence of marital discord, and evaluate how well surviving siblings are coping. This is also an opportunity to evaluate whether referrals to support groups or mental health providers may be of benefit. Continuing to recognize the child who has died is important. Families appreciate the receipt of a card on their child's birthday or the anniversary of their child's death.

The healthcare provider needs to be an educator about disease, death, and grief. The pediatrician can offer a safe environment for the family to talk about painful emotions, express fears, and share memories. By giving families permission to talk and modeling how to address children's concerns, the pediatrician demystifies death. Parents often request practical help. The healthcare provider can offer families resources, such as literature (both fiction and nonfiction), referrals to therapeutic services, and tools to help them learn about illness, loss, and grief. In this way, the physician reinforces the sense that other people understand what they are going through and helps to normalize their distressing emotions. The pediatrician can also facilitate and demystify the grief process by sharing basic tenets of grief therapy. There is no single right or wrong way to grieve. Everyone grieves differently; mothers may grieve differently than fathers, and children mourn differently than adults. Helping family members to respect these differences and reach out to support each other is critical. Grief is not something to "get over," but a lifelong process of adapting, readjusting, and reconnecting.

Parents may need help in knowing what constitutes normal grieving. Hearing, seeing, or feeling their child's presence may be a normal response. Vivid memories or dreams may occur. The pediatrician can help parents to learn that, although their pain and sadness may seem intolerable, other parents have survived similar experiences, and their pain will lessen over time.

Pediatricians are often asked whether children should attend the funeral of a parent or sibling. These rituals allow the family to begin their mourning process. Children older than 4 yr of age should be given a choice. If the child chooses to attend, the child should have a designated, trusted adult, who is not part of the immediate family, stay with the child, offer comfort, and be willing to leave with the child if the experience proves to be overwhelming. If the child chooses not to attend, the child should be offered additional opportunities to share in a ritual, go to the cemetery to view the grave, tell stories about the deceased, or obtain a keepsake object from the deceased family member as a remembrance.

In the era of regionalized tertiary care medicine, the primary care provider and medical home staff may not be informed when one of their patients dies in the hospital. Yet, this communication is critically important. Families assume their pediatrician has been notified, and often feel hurt when they don't receive some symbol of condolence. Because of their longitudinal relationship with the family, primary care providers may offer much needed support. There are practical issues, such as the need to cancel previously made appointments and the need to alert office and nursing staff so that they are prepared should the family return for a follow-up visit or for ongoing health maintenance care with the surviving siblings. Even minor illnesses in the surviving siblings may frighten children. Parents may contribute to this anxiety because their inability to protect the child who has died may leave them with a sense of guilt or helplessness. They may seek medical attention sooner or may be hypervigilant in the care of the siblings because of guilt over the other child's death, concern about their judgment, or the need for continued reassurance. A visit to the pediatrician can do a lot to allay their fears.

Clinicians must remain vigilant for risk factors in each family member and in the family unit as a whole. Primary care providers, who care for families over time, know bereft patients' premorbid functioning and can identify those at current or future risk for physical and psychiatric morbidity. Providers must focus on symptoms that interfere with a patient's normal activities and compromise a child's attainment of developmental tasks. Symptom duration, intensity, and severity, in context with the family's culture, can help identify

complicated grief reactions in need of therapeutic attention. Descriptive words, such as "unrelenting," "intense," "intrusive," or "prolonged," should raise concern. Total absence of signs of mourning, specifically, an inability to discuss the loss or express sadness, also suggests potential problems.

No specific sign, symptom, or cluster of behaviors identifies the child or family in need of help. Further assessment is indicated if the following occur: (1) persistent somatic or psychosomatic complaints of undetermined origin (headache, stomachache, eating and sleeping disorders, conversion symptoms, symptoms related to the deceased's condition, hypochondriasis); (2) unusual circumstances of death or loss (sudden, violent, or traumatic death; inexplicable, unbelievable, or particularly senseless death; prolonged, complicated illness; unexpected separation); (3) school or work difficulties (declining grades or school performance, social withdrawal, aggression); (4) changes in home or family functioning (multiple family stresses, lack of social support, unavailable or ineffective functioning of caretakers, multiple disruptions in routines, lack of safety); (5) concerning psychologic factors (persistent guilt or blame, desire to die or talk of suicide, severe separation distress, disturbing hallucinations, self-abuse, risk-taking behaviors, symptoms of trauma such as hyperarousal or severe flashbacks, grief from previous or multiple deaths). Children who are intellectually impaired may require additional support.

TREATMENT

Suggesting interventions outside the natural support network of family and friends can often prove useful to grieving families. Bereavement counseling should be readily offered if needed or requested by the family. Interventions that enhance or promote attachments and security, as well as give the family a means of expressing and understanding death, help to reduce the likelihood of future or prolonged disturbance, especially in children. Collaboration between pediatric and mental health professionals can help determine the timing and appropriateness of services.

Interventions for children and families who are struggling to cope with a loss in the community include gestures such as sending a card or offering food to the relatives of the deceased and teaching children the etiquette of behaviors and rituals around bereavement and mutual support. Performing community service or joining charitable organizations, such as fund-raising in memory of the deceased, may be useful. In the wake of a disaster, parents and older siblings can give blood or volunteer in search and recovery efforts. When a loss does not involve an actual death (e.g., parental divorce or geographic relocation), empowering the child to join or start a "divorced kids' club" in school or planning a "new kids in town" party may help. Participating in a constructive activity helps move the family away from a sense of helplessness and hopelessness and helps them to find meaning in their loss.

Psychotherapeutic services may benefit the entire family or individual members. Many support or self-help groups focus on specific types of losses (sudden infant death syndrome, suicide, widow/widowers, or AIDS) and provide an opportunity to talk with other people who have experienced similar losses. Family, couple, sibling or individual counseling may be useful, depending on the nature of the residual coping issues. Combinations of approaches may work well for children or parents with evolving needs. A child may participate in family therapy to deal with the loss of a sibling and use individual treatment to address issues of personal ambivalence and guilt related to the death.

The question of pharmacologic intervention for grief reactions often arises. Explaining that medication does not cure grief and often does not reduce the intensity of some symptoms (separation distress) can help. Although medication can blunt reactions, the psychologic work of grieving still must occur. The pediatrician must consider the patient's premorbid psychiatric vulnerability, current level of functioning, other available supports, and the use of additional therapeutic interventions. Medication, as a first line of defense, rarely proves useful in normal or uncomplicated grief reactions. In certain situations (severe sleep disruption, incapacitating anxiety, or intense hyperarousal), use of an anxiolytic or antidepressant medication for symptom relief and to provide the patient with the emotional energy to mourn may help. Medication used in conjunction with some form of psychotherapy, and in consultation with a psychopharmacologist, has optimal results.

Children who are refugees and may have experienced war, violence, or personal torture, while often resilient, may experience post-traumatic stress disorder if exposures were severe or repeated. Sequelae such as depression, anxiety, and grief need to be addressed, and mental health therapy is indicated. Cognitive behavioral treatment, use of journaling and narratives to bear witness to the experiences, and use of translators may be essential.

SPIRITUAL ISSUES

Responding to patients' and families' spiritual beliefs can help in comforting them during family tragedies. Offering to call members of pastoral care teams or their own spiritual leader can be a real support to them and aid in decision-making. Families have found it important to have their beliefs and their need for hope acknowledged in end-of-life care. The majority of patients report welcoming discussions on spirituality, which may help individual patients cope with illness, disease, dying, and death. In addressing spirituality, physicians need to follow certain guidelines, including maintaining respect for the patient's beliefs, following the patient's lead in exploring how spirituality affects the patient's decision making, acknowledging the limits of their own expertise and role in spirituality, and maintaining their own integrity by not saying or doing anything that violates their own spiritual or religious views. Healthcare providers should not impose their own religious or antireligious beliefs on patients, but rather should listen respectfully to their patients. By responding to spiritual needs, physicians may better aid their patients and families in end-of-life care and bereavement and take on the role of healers.

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Chapter 19

Sleep Medicine

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Sleep regulation is also referred to as the *2-process* sleep system because it requires the simultaneous operation of 2 basic, highly coupled processes that govern sleep and wakefulness. The **homeostatic process** ("Process S"), regulates the length and depth of sleep, and may be related to the accumulation of adenosine and other sleep-promoting chemicals ("somnogens"), such as cytokines, during prolonged periods of wakefulness. This sleep pressure appears to build more quickly in infants and young children, thus limiting the duration that wakefulness can be sustained during the day and necessitating periods of daytime sleep (i.e., naps). The endogenous **circadian rhythms** ("Process C"), influence the internal organization of sleep and timing and duration of daily sleep–wake cycles, and govern predictable patterns of alertness throughout the 24 hr day. The "master circadian clock" that controls sleep–wake patterns, of which melatonin secretion is the principal biomarker, is located in the suprachiasmatic nucleus in the ventral hypothalamus. The "circadian clocks" govern the timing of multiple other physiologic systems in the body (e.g., cardiovascular reactivity, hormone levels, renal and pulmonary functions). Because the human circadian clock is actually slightly longer than 24 hr, intrinsic circadian rhythms must be synchronized or "entrained" to the 24 hr day cycle by environmental cues called **zeitgebers**. The **dark–light cycle** is the most powerful of the zeitgebers; light signals are transmitted to the suprachiasmatic nucleus via the circadian photoreceptor system within the retina (functionally and anatomically separate from the visual system), which switch the body's production of the hormone melatonin off

(light) or on (dark) by the pineal gland. Circadian rhythms are also synchronized by other external time cues, such as timing of meals and alarm clocks.

Sleep propensity (the relative level of sleepiness) or alertness experienced at any given time during a 24 hr period is partially determined by the homeostatic *sleep drive*, which, in turn, depends upon the duration and quality of previous sleep and the amount of time awake since the last sleep period. Interacting with this *sleep homeostat* is the 24 hr cyclic pattern or rhythm characterized by clock-dependent periods of maximum sleepiness (*circadian troughs*) and maximum alertness (*circadian nadirs*). There are 2 periods of maximum sleepiness, 1 in the late afternoon (3:00-5:00 PM) and 1 toward the end of the night (3:00-5:00 AM), and 2 periods of maximum alertness, 1 in mid-morning and 1 in the evening, just prior to sleep onset (the so-called forbidden zone or second-wind phenomenon).

There are significant consequences of the failure to meet basic sleep needs, termed insufficient/inadequate sleep or **sleep loss**. Sufficient sleep is a biologic imperative, necessary for optimal functioning and apparently for life. **Slow-wave sleep** (SWS) (i.e., N3, delta, or deep sleep) appears to be the most restorative form of sleep; it is entered into relatively quickly after sleep onset, it is preserved in the face of reduced total sleep time, and it increases (rebounds) after a night of restricted sleep. **Rapid eye movement** (REM) sleep (Stage R or "dream" sleep) appears to be involved in (1) completing vital cognitive functions, such as the consolidation of memory; (2) promoting the plasticity of the central nervous system (CNS); and (3) protecting the brain from injury. Sufficient amounts of both of these sleep stages are necessary for optimal cognitive functioning. Partial sleep loss (sleep restriction) on a chronic basis accumulates in what is termed a **sleep debt** and produces deficits equivalent to those seen under conditions of total sleep deprivation. If the sleep debt becomes large enough and is not voluntarily repaid by obtaining sufficient recovery sleep, the body may respond by overriding voluntary control of wakefulness. This results in periods of decreased alertness, dozing off, and unplanned napping, recognized as excessive daytime sleepiness. The sleep-restricted individual may also experience very brief (several seconds) repeated daytime microsleeps of which the individual may be completely unaware, but which, nonetheless, may result in significant lapses in attention and vigilance. There is also a relationship between the amount of sleep restriction and performance on cognitive tasks, particularly those requiring sustained attention and higher level cognitive skills (*executive functions*), with a decay in performance correlating with declines in sleep amounts.

Both insufficient quantity and poor quality of sleep in children and adolescents usually result in excessive daytime sleepiness and decreased daytime alertness levels. Sleepiness in children may be recognizable as drowsiness, yawning, and other classic "sleepy behaviors," but can also be manifested as mood disturbance, including complaints of moodiness, irritability, emotional lability, depression, and anger; fatigue and daytime lethargy, including increased somatic complaints (headaches, muscle aches); cognitive impairment, including problems with memory, attention, concentration, decision making, and problem solving; daytime behavior problems, including hyperactivity, impulsivity, and noncompliance; and academic problems, including chronic tardiness related to insufficient sleep and school failure resulting from chronic daytime sleepiness.

To evaluate sleep problems, it is important to have an understanding of what constitutes "normal" sleep in children and adolescents. Sleep disturbances, as well as many characteristics of sleep itself, have some distinctly different features in children from sleep and sleep disorders in adults. Changes in sleep architecture and the evolution of sleep patterns and behaviors reflect the physiologic/chronobiologic, developmental, and social/environmental changes that are occurring across childhood. These trends may be summarized as the gradual assumption of more adult sleep patterns as children mature:

1. Sleep is *the* primary activity of the brain during early development; for example, by age 2 yr, the average child has spent 9500 hr (~13 months) asleep compared to 8000 hr awake, and between 2 and 5 yr, the time asleep is equal to the time awake.
2. There is a gradual decline in the average 24 hr sleep duration from infancy through adolescence, which involves a decrease in both diurnal and nocturnal sleep amounts. The decline in daytime sleep (scheduled napping) results in termination of naps typically by around 5 yr of age. There is also a gradual continued decrease in nocturnal sleep amounts into late adolescence; however, the typical adolescent still requires 9-9.25 hr of sleep per night.
3. There is also a decline in the relative percentage of REM sleep from birth (50% of sleep) through early childhood into adulthood (25-30%), and a similar initial predominance of SWS that peaks in early childhood, drops off abruptly after puberty (40-60% decline), and then further decreases over the life span. This SWS preponderance in early life has clinical significance; for example, the high prevalence of partial arousal parasomnias (sleepwalking and sleep terrors) in preschool and early school-age children is related to the relative increased percentage of SWS in this age group.
4. The within-sleep ultradian cycle lengthens from about 50 minutes in the term infant to 90-110 minutes in the school-age child. This, again, has clinical significance in that there is typically a brief arousal or awakening during the night at the termination of each ultradian cycle. As the length of the cycles increase, there is a concomitant decrease in the number of these end-of-cycle arousals ("night wakings").
5. A gradual shift in the circadian sleep–wake rhythm to a delayed (later) sleep onset and offset time, linked to pubertal stage rather than chronological age, begins in middle childhood and accelerates in early to mid-adolescence. This biologic phenomenon often coincides with environmental factors, which further delay bedtime and advance wake time and result in insufficient sleep duration, including exposure to electronic "screens" (i.e., television and computer) in the evening, social networking, academic and extracurricular demands, and early (before 8 AM) high school start times.
6. Increasing irregularity of sleep–wake patterns is typically observed across childhood into adolescence; this is characterized by increasingly larger discrepancies between school night and non–school night bedtimes and wake times, and increased "weekend oversleep" in an attempt to compensate for chronic weekday sleep insufficiency. This practice not only fails to adequately address performance deficits associated with insufficient sleep on school nights, but further exacerbates the normal adolescent phase delay and results in additional circadian disruption (analogous to that experienced by shift workers).

Table 19-1 lists normal developmental changes in children's sleep.

COMMON SLEEP DISORDERS

Childhood sleep problems may be conceptualized as resulting from either inadequate duration of sleep for age and sleep needs (insufficient sleep quantity) or disruption and fragmentation of sleep (poor sleep quality) as a result of frequent, repetitive, and brief arousals during sleep. Less common but important causes of sleep disturbance in childhood involve inappropriate timing of the sleep period (as occurs in circadian rhythm disturbances), or primary disorders of excessive daytime sleepiness (central hypersomnias such as narcolepsy). Insufficient sleep is usually the result of difficulty initiating (delayed sleep onset) and/or maintaining sleep (prolonged night wakings), but, especially in older children and adolescents, may also represent a conscious lifestyle decision to sacrifice sleep in favor of competing priorities, such as homework and social activities. The underlying causes of sleep onset delay/prolonged night wakings or sleep fragmentation may, in turn, be related to primarily behavioral factors (e.g., bedtime resistance resulting in shortened sleep duration) and/or medical causes (e.g., obstructive sleep apnea causing frequent, brief arousals).

Certain pediatric populations are relatively more vulnerable to acute or chronic sleep problems. These include children with medical problems, including chronic illnesses or pain conditions, such as cystic fibrosis, asthma, and rheumatoid arthritis, and acute illnesses, such as otitis media; children taking medications or ingesting substances with

Table 19-1 Normal Developmental Changes in Children's Sleep

AGE CATEGORY	SLEEP DURATION AND SLEEP PATTERNS	ADDITIONAL SLEEP ISSUES	SLEEP DISORDERS
Newborn (0-2 mo)	Total sleep: 10-19 hr per 24 hr (average = 13-14.5 hr), may be higher in premature babies Bottlefed babies generally sleep for longer periods (2-5 hr bouts) than breastfed babies (1-3 hr) Sleep periods are separated by 1-2 hr awake No established nocturnal–diurnal pattern in the 1st few wk; sleep is evenly distributed throughout the day and night, averaging 8.5 hr at night and 5.75 hr during the day	The American Academy of Pediatrics issued a formal recommendation in 2005 advocating against bed sharing in the 1st yr of life, instead encouraging proximate but separate sleeping surfaces for mother and infant. Safe sleep practices for infants: • Place the baby on his or her back to sleep at night and during nap times • Place the baby on a firm mattress with a well-fitting sheet in a safety-approved crib • Do not use pillows or comforters • Cribs should not have corner posts over 1/16 in high or decorative cutouts • Make sure the baby's face and head stay uncovered and clear of blankets and other coverings during sleep	Most sleep issues that are perceived as problematic at this stage represent a discrepancy between parental expectations and developmentally appropriate sleep behaviors Newborns who are noted by parents to be extremely fussy and persistently difficult to console are more likely to have underlying medical issues, such as colic, gastroesophageal reflux, and formula intolerance
Infant (2-12 mo)	Total sleep: average is 12-13 hr (note that there is great individual variability in sleep times during infancy) Nighttime: average is 9-10 hr Naps: average is 3-4 hr	Sleep regulation or self-soothing involves the infant's ability to negotiate the sleep–wake transition, both at sleep onset and following normal awakenings throughout the night. The capacity to self-soothe begins to develop in the 1st 12 wk of life, and is a reflection of both neurodevelopmental maturation and learning Sleep consolidation, or "sleeping through the night," is usually defined by parents as a continuous sleep episode without the need for parental intervention (e.g., feeding, soothing) from the child's bedtime through the early morning. Infants develop the ability to consolidate sleep between 6 wk and 3 mo	Behavioral insomnia of childhood; sleep onset association type Sleep-related rhythmic movements (head banging, body rocking)
Toddler (1-3 yr)	Total sleep: average is 11-13 hr Nighttime: average is 9.5-10.5 hr Naps: average is 2-3 hr; decrease from 2 naps to 1 at average age of 18 mo	Cognitive, motor, social, language developmental issues impact on sleep Nighttime fears develop; transitional objects, bedtime routines important	Behavioral insomnia of childhood, sleep onset association type Behavioral insomnia of childhood, limit setting type
Preschool (3-5 yr)	Nighttime: average is 9-10 hr Naps decrease from 1 nap to no nap Overall, 26% of 4 yr olds and just 15% of 5 yr olds nap	Persistent cosleeping tends to be highly associated with sleep problems in this age group Sleep problems may become chronic	Behavioral insomnia of childhood, limit setting type Sleepwalking Sleep terrors Nighttime fears/nightmares Obstructive sleep apnea
Middle childhood (6-12 hr)	9-11 hr	School and behavior problems may be related to sleep problems Media and electronics, such as television, computer, video games, and the Internet increasingly compete for sleep time Irregularity of sleep–wake schedules reflects increasing discrepancy between school and non–school night bedtimes and wake times	Nightmares Obstructive sleep apnea Insufficient sleep
Adolescence (>12 yr)	Average sleep duration 7-7.5 hr; only 20% of adolescents overall get the recommended 9-9.25 hr of sleep Later bedtimes; increased discrepancy sleep patterns weekdays/weekends	Puberty-mediated phase delay (later sleep onset and wake times), relative to sleep-wake cycles in middle childhood Earlier required wake times Environmental competing priorities for sleep	Insufficient sleep Delayed sleep phase disorder Narcolepsy Restless legs syndrome/periodic limb movement disorder

stimulant (e.g., psychostimulants, caffeine), sleep-disrupting (e.g., corticosteroids), or daytime-sedating (some anticonvulsants, α-agonists) properties; hospitalized children; and children with a variety of psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), depression, bipolar disorder, and anxiety disorders. Children with neurodevelopmental disorders such as blindness, mental retardation, some chromosomal syndromes (e.g., Smith-Magenis, fragile X), and autism spectrum disorders have especially high rates of sleep disturbances for a wide variety of reasons. They may be on sleep-disrupting medications, they are often more prone to nocturnal seizures, they may be less easily entrained by environmental cues and thus more vulnerable to circadian disruption, and are more likely to have

comorbid psychiatric and behavioral conditions which that further predispose them to disrupted sleep.

Insomnia of Childhood

Insomnia is difficulty initiating and/or maintaining sleep that occurs despite age-appropriate time and opportunity for sleep and results in some degree of impairment in daytime functioning for the child and/or family (ranging from fatigue, irritability, lack of energy, and mild cognitive impairment to effects on mood, school performance, and quality of life). Insomnia may be of a short-term and transient nature (usually related to an acute event), or may be characterized as long-term and chronic. Insomnia is a set of *symptoms* with a large number of possible etiologies (e.g., pain, medication, medical and psychiatric conditions, learned behaviors). Insomnia, like many behavioral issues in children, is often primarily defined by parental concerns rather than by objective criteria, and therefore should be viewed in the context of family (i.e., maternal depression, stress), child (i.e., temperament, developmental level), and environmental (i.e., cultural practices, sleeping space) considerations.

One of the most common presentations of insomnia found in infants and toddlers is the **sleep-onset association type.** In this situation, the child learns to fall asleep only under certain conditions or associations, which typically require parental presence, such as being rocked or fed, and does not develop the ability to self-soothe. During the night, when the child experiences the type of brief arousal that normally occurs at the end of an ultradian sleep cycle or awakens for other reasons, the child is not able to get back to sleep without those same associations being present. The infant then "signals" the parent by crying (or coming into the parents' bedroom, if the child is ambulatory) until the necessary associations are provided. The presenting complaint is typically one of prolonged night waking resulting in insufficient sleep (for both child and parent).

Management of night wakings should include establishment of a set sleep schedule and bedtime routine, and implementation of a behavioral program. The treatment approach typically involves a program of rapid withdrawal (extinction) or more gradual withdrawal (graduated extinction) of parental assistance at sleep onset and during the night. Extinction ("cry it out") involves putting the child to bed at a designated bedtime, "drowsy but awake" to maximize sleep propensity. and then systematically ignoring any protests by the child until a set time the next morning. Although it has considerable empirical support, extinction is often not an acceptable choice for families. Graduated extinction involves gradually weaning the child from dependence on parental presence; typically, the parent leaves the room at "lights out" and then returns or "checks" periodically at fixed or successively longer intervals during the sleep–wake transition to provide brief reassurance until the child falls asleep. The exact time interval between checks is generally determined by the parents' tolerance for crying and the child's temperament. The goal is to allow the infant or child to develop skills in self-soothing during the night, as well as at bedtime. In older infants, the introduction of more appropriate sleep associations that will be readily available to the child during the night (transitional objects, such as a blanket or toy), in addition to positive reinforcement (i.e., stickers for remaining in bed), is often beneficial. If the child has become habituated to awaken for nighttime feedings (learned hunger), then these feedings should be slowly eliminated. Parents must be consistent in applying behavioral programs to avoid inadvertent, intermittent reinforcement of night wakings; they should also be forewarned that crying behavior often temporarily escalates at the beginning of treatment (*postextinction burst*).

Bedtime problems, including stalling and refusing to go to bed, are more common in preschool-age and older children. This type of insomnia is frequently related to inadequate **limit setting** and is often the result of parental difficulties in setting limits and managing behavior in general, and the inability or unwillingness to set consistent bedtime rules and enforce a regular bedtime in particular. The situation may be exacerbated by the child's oppositional behavior. In some cases the child's resistance at bedtime is the result of an underlying problem in falling asleep that is caused by other factors (medical conditions, such as asthma or medication use; a sleep disorder, such as restless legs syndrome; or anxiety) or a mismatch between the child's intrinsic circadian rhythm ("night owl") and parental expectations regarding an "appropriate" bedtime.

Table 19-2	Basic Principles of Healthy Sleep for Children

1. **Have a set bedtime and bedtime routine** for your child.
2. **Bedtime and wake-up time should be about the same time on school nights and non–school nights.** There should not be more than about an hour difference from one day to another.
3. **Make the hour before bed shared quiet time.** Avoid high-energy activities, such as rough play, and stimulating activities, such as watching television or playing computer games, just before bed.
4. **Don't send your child to bed hungry.** A *light* snack (such as milk and cookies) before bed is a good idea. Heavy meals within an hour or 2 of bedtime, however, may interfere with sleep.
5. **Avoid products containing caffeine for at least several hours before bedtime.** These include caffeinated sodas, coffee, tea, and chocolate.
6. **Make sure your child spends time outside every day,** whenever possible, and is involved in regular exercise.
7. **Keep your child's bedroom quiet and dark.** A low-level night light is acceptable for children who find completely dark rooms frightening.
8. **Keep your child's bedroom at a comfortable temperature** during the night (<24°C [75°F]).
9. **Don't use your child's bedroom for time-out or punishment.**
10. **Keep the television set out of your child's bedroom.** Children can easily develop the bad habit of "needing" the television to fall asleep. It's also much more difficult to control your child's viewing if the set is in the bedroom.

Successful treatment of limit-setting sleep problems generally involves a combination of parent education regarding appropriate limit setting, decreased parental attention for bedtime-delaying behavior, establishment of bedtime routines, and positive reinforcement (sticker charts) for appropriate behavior at bedtime; other behavioral management strategies that have empirical support include bedtime fading (temporarily setting the bedtime closer to the actual sleep onset time and then gradually advancing the bedtime to an earlier target bedtime). Older children may benefit from being taught relaxation techniques to help themselves fall asleep more readily. Following the principles of healthy sleep practices for children is essential (Table 19-2).

When the insomnia is not primarily a result of parent behavior or secondary to another sleep disturbance, or to a psychiatric or medical problem, it is often referred to as **psychophysiologic** or **primary** or **learned insomnia**. Primary insomnia occurs largely in adolescents and is characterized by a combination of learned sleep-preventing associations and heightened physiologic arousal resulting in a complaint of sleeplessness and decreased daytime functioning. A hallmark of primary insomnia is excessive worry about sleep and an exaggerated concern of the potential daytime consequences. The physiologic arousal can be in the form of cognitive hypervigilance, such as "racing" thoughts; in many individuals with insomnia an increased baseline level of arousal is further intensified by this secondary anxiety about sleeplessness. Treatment usually involves educating the adolescent about the principles of healthy sleep practices (Table 19-3), institution of a consistent sleep–wake schedule, avoidance of daytime napping, instructions to use the bed for sleep only and to get out of bed if unable to fall asleep (stimulus control), restricting time in bed to the actual time asleep (sleep restriction), addressing maladaptive cognitions about sleep, and teaching relaxation techniques to reduce anxiety. Hypnotic medications are rarely needed.

Obstructive Sleep Apnea

Sleep-disordered breathing (SDB) in children encompasses a broad spectrum of respiratory disorders that occur exclusively in or are

Table 19-3	Basic Principles of Healthy Sleep for Adolescents

1. **Wake up and go to bed at about the same time** every night. Bedtime and wake-up time should not differ from school to non–school nights by more than approximately 1 hr.
2. **Avoid sleeping in on weekends** to "catch up" on sleep. This makes it more likely that you will have problems falling asleep.
3. If you take **naps**, they should be **short** (no more than 1 hr) and **scheduled in the early to midafternoon**. However, if you have a problem with falling asleep at night, **napping** during the day may make it worse and should be avoided.
4. **Spend time outside** every day. Exposure to sunlight helps to keep your body's internal clock on track.
5. **Exercise regularly.** Exercise may help you fall asleep and sleep more deeply.
6. **Use your bed for sleeping only.** Don't study, read, listen to music, watch television, etc., on your bed.
7. Make the 30-60 minutes before a **quiet or wind-down time**. Relaxing, calm, enjoyable activities, such as reading a book or listening to calm music, help your body and mind slow down enough to let you get to sleep. Don't study, watch exciting/scary movies, exercise, or get involved in "energizing" activities just before bed.
8. Eat regular meals and **don't go to bed hungry**. A light snack before bed is a good idea; eating a full meal in the hour before bed is not.
9. **Avoid** eating or drinking products containing **caffeine** from dinner time on. These include caffeinated sodas, coffee, tea, and chocolate.
10. **Do not use alcohol.** Alcohol disrupts sleep and may cause you to awaken throughout the night.
11. **Smoking disturbs sleep.** Don't smoke at least 1 hr before bed (and preferably, not at all!).
12. Don't use **sleeping pills, melatonin**, or other **nonprescription sleep aids** to help you sleep unless specifically recommended by your doctor. These can be dangerous, and the sleep problems often return when you stop taking the medicine.

exacerbated by sleep, and includes primary snoring and upper airway resistance syndrome, as well as apnea of prematurity (see Chapter 101.2) and central apnea (see Chapter 418). **Obstructive sleep apnea (OSA)**, the most important clinical entity within the SDB spectrum, is a respiratory disorder that is characterized by repeated episodes of prolonged upper airway obstruction during sleep despite continued or increased respiratory effort, resulting in complete (apnea) or partial (hypopnea; ≥30% reduction in airflow accompanied by ≥3% O_2 desaturation and/or arousal) cessation of airflow at the nose and/or mouth, as well as in disrupted sleep. Both intermittent hypoxia and the multiple arousals resulting from these obstructive events likely contribute to significant metabolic, cardiovascular, and neurocognitive/neurobehavioral morbidity.

Primary snoring is defined as snoring without associated ventilatory abnormalities on overnight polysomnogram (e.g., apneas or hypopneas, hypoxemia, hypercapnia) or respiratory-related arousals, and is a manifestation of the vibrations of the oropharyngeal soft tissue walls that occur when an individual attempts to breathe against increased upper airway resistance during sleep. Although generally considered nonpathologic, primary snoring in children with may still be associated with subtle breathing abnormalities during sleep, including evidence of increased respiratory effort, which, in turn, may be associated with adverse neurodevelopmental outcomes.

Etiology

OSA results from an anatomically or functionally narrowed upper airway; this typically involves some combination of decreased upper airway patency (upper airway obstruction and/or decreased upper airway diameter), increased upper airway collapsibility (reduced pharyngeal muscle tone), and decreased drive to breathe in the face of reduced upper airway patency (reduced central ventilatory drive) (Table 19-4). Upper airway obstruction varies in degree and level (i.e., nose, nasopharynx/oropharynx, hypopharynx) and is most commonly caused by adenotonsillar hypertrophy, although tonsillar size does not necessarily correlate with degree of obstruction, especially in older children. Other causes of airway obstruction include allergies associated with chronic rhinitis/nasal obstruction; craniofacial abnormalities, including hypoplasia/displacement of the maxilla and mandible; gastroesophageal reflux with resulting pharyngeal reactive edema (see Chapter 323); nasal septal deviation (see Chapter 376); and velopharyngeal flap cleft palate repair. Reduced upper airway tone may result from neuromuscular diseases, including hypotonic cerebral palsy and muscular dystrophies (see Chapter 609), or hypothyroidism (see Chapter 565). Reduced central ventilatory drive may be present in some children with Arnold-Chiari malformation (see Chapter 418), rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation, and meningomyelocele (see Chapter 591). In other situations, the etiology is mixed; individuals with Down syndrome (see Chapter 81), by virtue of their facial anatomy, hypotonia, macroglossia, and central adiposity, as well as the increased incidence of hypothyroidism, are at particularly high risk for OSA, with some estimates of as great as 70% prevalence.

Table 19-4	Anatomic Factors That Predispose to Obstructive Sleep Apnea and Hypoventilation in Children

NOSE
Anterior nasal stenosis
Choanal stenosis/atresia
Deviated nasal septum
Seasonal or perennial rhinitis
Nasal polyps, foreign body, hematoma, mass lesion

NASOPHARYNGEAL AND OROPHARYNGEAL
Adenotonsillar hypertrophy
Macroglossia
Cystic hygroma
Velopharyngeal flap repair
Cleft palate repair
Pharyngeal mass lesion

CRANIOFACIAL
Micrognathia/retrognathia
Midface hypoplasia (e.g., trisomy 21, Crouzon, Apert syndrome)
Mandibular hypoplasia (Pierre Robin sequence, Treacher Collins, Cornelia de Lange)
Craniofacial trauma
Skeletal and storage diseases
Achondroplasia
Storage diseases (e.g., glycogen, Hunter, Hurler syndrome)

Although many children with OSA are of normal weight, an increasingly large percentage are overweight or obese, and many of these children are school-age and younger (see Chapter 47). There is a significant correlation between weight and SDB (e.g., habitual snoring, OSA, sleep-related hypoventilation). Although adenotonsillar hypertrophy also plays an important etiologic role in overweight/obese children with OSA, mechanical factors related to an increase in the amount of adipose tissue in the throat (pharyngeal fat pads), neck (increased neck circumference), and chest wall and abdomen can create increased upper airway resistance, worsen gas exchange, and increased work of breathing, particularly in the supine position and during REM sleep. There may be a component of blunted central ventilatory drive in response to hypoxia/hypercapnia and hypoventilation as well (see Chapter 418.3), particularly in children with morbid or syndrome-based (e.g., Prader-Willi) obesity. Overweight and obese children and adolescents are at a particularly high risk for metabolic and cardiovascular complications of SDB, such as insulin resistance and systemic hypertension; morbidly obese children are also be at increased risk for postoperative complications as well as residual OSA following adenotonsillectomy.

Epidemiology

Overall prevalence of parent-reported snoring in the pediatric population is approximately 8%; "always" snoring is reported in 1.5-6%, and "often" snoring in 3-15%. When defined by parent-reported symptoms, the prevalence of OSA is 4-11%. The prevalence of pediatric OSA as documented by overnight sleep studies utilizing ventilatory monitoring procedures (e.g., in-lab polysomnography [PSG], home studies) is 1-4% overall, with a reported range of 0.1-13%. Prevalence is also affected by the demographic characteristics, such as age (increased prevalence between 2 and 8 yr), gender (more common in boys, especially after puberty), race/ethnicity (increased prevalence in African-American and Asian children), history of prematurity, and family history of OSA.

Pathogenesis

The upregulation of inflammatory pathways, as indicated by an increase in peripheral markers of inflammation such as C-reactive protein, appear to be linked to metabolic dysfunction (e.g., insulin resistance, dyslipidemia) in both obese and nonobese children with OSA. Both systemic inflammation and arousal-mediated increases in sympathetic autonomic nervous system activity with altered vasomotor tone may be key contributors to increased cardiovascular risk in both adults and children with OSA. Mechanical stress on the upper airway induced by chronic snoring may also result in both local mucosal inflammation of adenotonsillar tissues and subsequent upregulation of inflammatory molecules, most notably leukotrienes. Another potential mechanism that may mediate cardiovascular sequelae in both adults and children with OSA is altered endothelial function.

One of the primary mechanisms by which OSA is believed to exert negative influences on cognitive function appears to involve repeated episodic arousals from sleep leading to sleep fragmentation and resulting sleepiness. An equally important role may be intermittent hypoxia that leads directly to systemic inflammatory vascular changes in the brain. Levels of inflammatory markers such as C-reactive protein and cytokine interleukin-6 are elevated in children with OSA and are also associated with cognitive dysfunction.

Clinical Manifestations

The clinical manifestations of OSA may be divided into sleep-related and daytime symptoms. The most common nocturnal manifestations of OSA in children and adolescents are loud, frequent, and disruptive snoring, breathing pauses, choking or gasping arousals, restless sleep, and nocturnal diaphoresis. Many children who snore do not have OSA, but very few children with OSA do not snore. Children, like adults, tend to have more frequent and more severe obstructive events in REM sleep and when sleeping in the supine position. Children with OSA may adopt unusual sleeping positions, keeping their necks hyperextended to maintain airway patency. Frequent arousals associated with obstruction may result in nocturnal awakenings, but are more likely to cause fragmented sleep.

Daytime symptoms of OSA include mouth breathing and dry mouth, chronic nasal congestion/rhinorrhea, hyponasal speech, morning headaches, difficulty swallowing, and poor appetite. Children with OSA may have secondary enuresis, which has been postulated to result from the disruption of the normal nocturnal pattern of antidiuretic hormone or atrial natriuretic peptide secretion. Partial arousal parasomnias (sleepwalking and sleep terrors) may occur more frequently in children with OSA, related to the frequent associated arousals and an increased percentage of SWS.

One of the most important but frequently overlooked sequelae of OSA in children is the effect on mood, behavior, learning, and academic functioning. The neurobehavioral consequences of OSA in children include daytime sleepiness with drowsiness, difficulty in morning waking, and unplanned napping or dozing off during activities, although evidence of frank hypersomnolence tends to be less common in children compared to adults with OSA (except in very obese children). Mood changes include increased irritability, mood instability and emotional dysregulation, low frustration tolerance, and depression/anxiety. Behavioral issues include both "internalizing" (i.e., increased somatic complaints and social withdrawal) and "externalizing" behaviors, including aggression, impulsivity, hyperactivity, oppositional behavior, and conduct problems. There is a substantial overlap between the clinical impairments associated with OSA and the diagnostic criteria for ADHD, including inattention, poor concentration, and distractibility (see Chapter 33). There may be a selective impact of OSA specifically on "executive functions," which include cognitive flexibility, task initiation, self-monitoring, planning, organization, and self-regulation of affect and arousal; executive function deficits are also a hallmark of ADHD.

Many of the studies that have looked at changes in behavior and neuropsychologic functioning in children following treatment (usually adenotonsillectomy) for OSA have largely documented significant improvement in outcomes, in both the short and long term, of OSA syndrome posttreatment, including daytime sleepiness, mood, behavior, academics, and quality of life. However, most studies failed to find a dose-dependent relationship between OSA in children and specific neurobehavioral/neurocognitive deficits, suggesting that other factors may influence neurocognitive outcomes, including individual genetic susceptibility, racial/ethnic background, environmental influences such as passive smoking exposure, and comorbid conditions, such as obesity, shortened sleep duration, and the presence of other sleep disorders. In adults, cognitive functions impacted by OSA include deficits in attention, long-term visual and verbal memory, visuospatial functioning, and executive function while language and psychomotor function do not appear to be impacted.

Diagnosis

The 2012 revised American Academy of Pediatrics clinical practice guidelines provide excellent information for the evaluation and management of uncomplicated childhood OSA (Table 19-5). There are no physical examination findings that are truly pathognomonic for OSA, and most healthy children with OSA appear normal; certain physical examination findings may suggest OSA. Growth parameters may be abnormal (obesity or, less commonly, failure to thrive), and there may be evidence of chronic nasal obstruction (hyponasal speech, mouth breathing, septal deviation, "adenoidal facies"), as well as signs of atopic disease (i.e., "allergic shiners"). Oropharyngeal examination may reveal enlarged tonsils, excess soft tissue in the posterior pharynx, and a narrowed posterior pharyngeal space. Any abnormalities of the facial structure, such as retrognathia and/or micrognathia, midfacial hypoplasia, best appreciated by inspection of the lateral facial profile, increase the likelihood of OSA and should be noted. In very severe cases, there may be evidence of pulmonary hypertension, right-sided heart failure, and cor pulmonale; systemic hypertension may occur, especially in obese children.

Because no combination of clinical history and physical findings can accurately predict which children with snoring have OSA, the gold standard for diagnosing OSA remains an in-lab overnight **polysomnogram**.

Overnight PSG is a technician-supervised, monitored study that documents physiologic variables during sleep; sleep staging, arousal measurement, cardiovascular parameters, and body movements (electroencephalography, electrooculography, chin and leg electromyography, electrocardiogram, body position sensors, and video recording), and a combination of breathing monitors (oronasal thermal sensor and nasal air pressure transducer for airflow), chest/abdominal monitors (e.g., inductance plethysmography for respiratory effort, pulse oximeter for O_2 saturation, end-tidal or transcutaneous CO_2 for CO_2 retention, snore microphone). The polysomnographic parameter most commonly used in evaluating for sleep disordered breathing is the apnea-hypopnea index (AHI), which indicates the number of apneic and hypopneic events per hour of sleep. It should be noted that currently there are no universally accepted polysomnographic normal reference values and parameters for diagnosing OSA in children, and it is still unclear which parameters best predict morbidity. Normal preschool and school-age children generally have a total AHI of less than 1.5 (obstructive AHI <1), and this is the most widely used cutoff value for OSA in children 12 yr and below; in older adolescents, the adult cutoff of an AHI ≥5 is generally used. In cases in which the AHI

Table 19-5 American Academy of Pediatrics Clinical Practice Guideline: Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome (September 2012)
Key Action Statement 1: Screening for OSAS As part of routine health maintenance visits, clinicians should inquire whether the child or adolescent snores. If the answer is affirmative or if a child or adolescent presents with signs or symptoms of OSAS, clinicians should perform a more focused evaluation. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 2A: Polysomnography If a child or adolescent snores on a regular basis and has any of the complaints or findings of OSAS, clinicians should either (1) obtain a polysomnogram (Evidence Quality A; Key Action strength: Recommendation) *or* (2) refer the patient to a sleep specialist or otolaryngologist for a more extensive evaluation (Evidence quality D; Key Action strength: Option). (Evidence Quality: Grade A for polysomnography, Grade D for specialist referral; Recommendation Strength: Recommendation.)
Key Action Statement 2B: Alternative Testing If polysomnography is not available, then clinicians may order alternative diagnostic tests, such as nocturnal video recording, nocturnal oximetry, daytime nap polysomnography, or ambulatory polysomnography. (Evidence Quality: Grade C; Recommendation Strength: Option.)
Key Action Statement 3: Adenotonsillectomy If a child is determined to have OSAS, has a clinical examination consistent with adenotonsillar hypertrophy, and does not have a contraindication to surgery, the clinician should recommend adenotonsillectomy as the first line of treatment. If the child has OSAS but does not have adenotonsillar hypertrophy, other treatment should be considered (see Key Action Statement 6). Clinical judgment is required to determine the benefits of adenotonsillectomy compared with other treatments in obese children with varying degrees of adenotonsillar hypertrophy. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 4: High-Risk Patients Undergoing Adenotonsillectomy Clinicians should monitor high-risk patients undergoing adenotonsillectomy as inpatients postoperatively. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 5: Reevaluation Clinicians should clinically reassess all patients with OSAS for persisting signs and symptoms after therapy to determine whether further treatment is required. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 5B: Reevaluation of High-Risk Patients Clinicians should reevaluate high-risk patients for persistent OSAS after adenotonsillectomy, including those who had a significantly abnormal baseline polysomnogram, have sequelae of OSAS, are obese, or remain symptomatic after treatment, with an objective test (see Key Action Statement 2) or refer such patients to a sleep specialist. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 6: CPAP Clinicians should refer patients for CPAP management if symptoms/signs or objective evidence of OSAS persists after adenotonsillectomy or if adenotonsillectomy is not performed. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 7: Weight Loss Clinicians should recommend weight loss in addition to other therapy if a child/adolescent with OSAS is overweight or obese. (Evidence Quality: Grade C; Recommendation Strength: Recommendation.)
Key Action Statement 8: Intranasal Corticosteroids Clinicians may prescribe topical intranasal corticosteroids for children with mild OSAS in whom adenotonsillectomy is contraindicated or for children with mild postoperative OSAS. (Evidence Quality: Grade B; Recommendation Strength: Option.)

Adapted from Marcus CL, Brooks LJ, Draper KA, et al: Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 130:576-584, 2012.

is between 1 and 5 obstructive events per hour, clinical judgment regarding risk factors for SDB, evidence of daytime sequelae, and the technical quality of the overnight sleep study should determine further management.

Treatment

There are presently no universally accepted guidelines regarding the indications for treatment of pediatric SDB (i.e., including primary snoring and OSA). Current recommendations largely emphasize weighing what is known about the potential cardiovascular, metabolic, and neurocognitive sequelae of SDB in children in combination with the individual healthcare professional's clinical judgment. The decision of whether and how to treat OSA specifically in children is contingent on a number of parameters, including severity (nocturnal symptoms, daytime sequelae, sleep study results), duration of disease, and individual patient variables such as age, comorbid conditions, and underlying etiologic factors. Figure 19-1 presents a guide to decision making. In the case of moderate (AHI 5-10) to severe disease (AHI >10), the decision to treat is usually straightforward, and most pediatric sleep experts recommend that any child with an apnea hypopnea index >5 should be treated. However, a large randomized trial of early adenotonsillectomy vs watchful waiting with supportive care, 46% of the control group children normalized on PSG (compared to 79% of the early adenotonsillectomy group) during the 7 mo observation period.

In the majority of cases of pediatric OSA, adenotonsillectomy is the first-line treatment in any child with significant adenotonsillar hypertrophy, even in the presence of additional risk factors such as obesity. Adenotonsillectomy in uncomplicated cases generally (70-90% of children) results in complete resolution of symptoms; regrowth of adenoidal tissue after surgical removal occurs in some cases. Groups considered high-risk include young children (<3 yr old), as well as those with severe OSA documented by PSG, significant clinical sequelae of OSA (e.g., failure to thrive), or associated medical conditions, such as craniofacial syndromes, morbid obesity, and hypotonia. All patients should be reevaluated postoperatively to determine whether additional evaluation, a repeat polysomnogram and/or treatment are required. The American Academy of Sleep Medicine recommends that in high-risk groups (children with obesity, craniofacial anomalies, Down syndrome or moderate-severe OSA) or in children with continued symptoms of OSA, a follow-up sleep study at least 6 wk postadenotonsillectomy is indicated.

Additional treatment measures that may be appropriate include weight loss, positional therapy (attaching a firm object, such as a tennis ball, to the back of a sleep garment to prevent the child from sleeping in the supine position), and aggressive treatment of additional risk factors when present, such as asthma, seasonal allergies, and gastroesophageal reflux; there is evidence that intranasal corticosteroids and leukotriene inhibitors may be helpful in reducing upper airway inflammation in mild OSA. Other surgical procedures, such as

Algorithm for the Diagnosis and Treatment of Pediatric OSA

Step 1. Child is at risk for OSA (one or more):

- Parents report symptoms of OSA
- Physician identifies symptoms of OSA using structured questionnaire
- Conditions predisposing to OSA are present (adenotonsillar hypertrophy-allergic rhinitis, obesity, craniofacial abnormalities, neuromuscular disorders)
- History of prematurity
- Family history of OSA

Step 2a. OSA-related morbidity is recognized (one or more):

- Systolic or diastolic blood pressure >95th percentile for gender, age and height, or pulmonary hypertension
- Daytime sleepiness, hyperactivity, inattention, academic difficulties
- Inadequate somatic growth
- Enuresis

Step 2b. Conditions frequently coexisting with OSA are identified (one or more):

- Recurrent otitis media, tympanostomy tubes
- Recurrent wheezing
- Oral-motor dysfunction
- Metabolic syndrome

Step 3. Factors predicting OSA persistence are present (at least one):

- Male gender
- Increasing Body Mass Index percentile, development of obesity

Step 4. Objective evaluation for OSA severity:

- Overnight polysomnography
- If not available: nocturnal pulse oximetry

Step 5. Child is a potential candidate for treatment if at risk for OSA (step 1) and at least one criterion:

- AHI >5 episodes/h
- AHI 1–5 and OSA morbidity present (step 2a)
- AHI 1–5 and risk factor for OSA persistence (step 3)
- AHI 1–5 and neuromuscular disorder or craniofacial abnormalities present (step 1)
- ≥ 3 SpO_2 drops $<90\%$ and ≥ 3 clusters of desaturation events <u>or</u> alternatively, desaturation ($\geq 3\%$) index ≥ 3.5 episodes/h

Or if polysomnography or oximetry not available:

- Frequently or almost always loud snoring and male gender
- Frequently or almost always loud snoring and sleepiness
- Frequently or almost always loud snoring and learning problems

Priority for treatment increases if coexisting OSA-related conditions are present that may also improve with treatment (step 2b)

Step 6. <u>Stepwise</u> treatment approach:

1. Weight control for obesity
2. Trial of nasal corticosteroids for adenoidal hypertrophy prior to adenoidectomy
3. Adenotonsillectomy for adenotonsillar hypertrophy
4. Orthodontic devices for mandibular malpositioning, narrow maxilla
5. nCPAP for: i) residual OSA after adenotonsillectomy; ii) OSA related to obesity, neuromuscular disorders or craniofacial abnormalities and unresponsive to other measures
6. Craniofacial surgery or tracheostomy if other treatment modalities fail

Notes

1. Information collected in steps 1–4 is used to identify children requiring treatment for OSA (step 5) and to determine the appropriate therapeutic modalities (step 6). Please refer to the text for details.
2. Step 6 represents a hierarchical approach to OSA treatment.

Figure 19-1 Algorithm for the diagnosis and treatment of pediatric OSA. *(From Kaditis A, Kheirandish-Gozal L, Gozal D: Algorithm for the diagnosis and treatment of pediatric OSA: a proposal of two pediatric sleep centers,* Sleep Med *13(3):217–227, 2012, Figure 1.)*

uvulopharyngopalatoplasty, and maxillofacial surgery (e.g., mandibular distraction osteogenesis), are seldom performed in children. Oral appliances, such as mandibular advancing devices and palatal expanders, may be considered in select cases; consultation with a pediatric dentist/orthodontist is recommended. Exercises to address abnormal tongue position and low upper airway tone (i.e., myofunctional therapy) have been shown to be of some benefit in mild cases of OSA.

Continuous or bilevel positive airway pressure is the most common treatment for OSA in adults and can be used successfully in children and adolescents. Positive airway pressure may be recommended if removing the adenoids and tonsils is not indicated, if there is residual disease following adenotonsillectomy, or if there are major risk factors that are not amenable to treatment with surgery (obesity, hypotonia). Positive airway pressure delivers humidified, warmed air through an interface (mask, nasal pillows) that, under pressure, effectively “splints” the upper airway open. Optimal pressure settings (that abolish or significantly reduce respiratory events without increasing arousals or central apneas) are determined in the sleep lab during a full night positive airway pressure titration. Careful attention should be paid to education of the child and family and desensitization protocols should be implemented in most cases to increase the likelihood of adherence. Efficacy studies at the current pressure and retitrations should be conducted periodically with long-term use (at least annually or in association with significant weight changes or resumption of SDB symptoms).

Parasomnias

Parasomnias are episodic nocturnal behaviors that often involve cognitive disorientation and autonomic and skeletal muscle disturbance. Parasomnias may be further characterized as occurring primarily during non-REM sleep (partial arousal parasomnias) or in association with REM sleep, including nightmares, hypnogogic hallucinations, and sleep paralysis; other common parasomnias include sleep-talking and hypnic jerks or “sleep starts” (Fig. 19-2). Sleep-related movement disorders, including restless legs syndrome/periodic limb movement disorder (RLS/PLMD) and rhythmic movement disorder (head banging, body rocking), are reviewed in “Sleep-Related Movement Disorders: Restless Legs Syndrome/Periodic Limb Movement Disorder and Rhythmic Movements” below.

Etiology

Partial arousal parasomnias, which include **sleepwalking, sleep terrors**, and **confusional arousals** are more common in preschool and school-age children because of the relatively higher percentage of SWS in younger children. They typically occur when SWS predominates (i.e., in the first third of the night); in contrast, nightmares, which are much more common than the partial arousal parasomnias but are often confused with them, are concentrated in the last third of the night, when REM sleep is most prominent. Any factor that is associated with an increase in the relative percentage of SWS (certain medications, previous sleep restriction) may increase the frequency of events

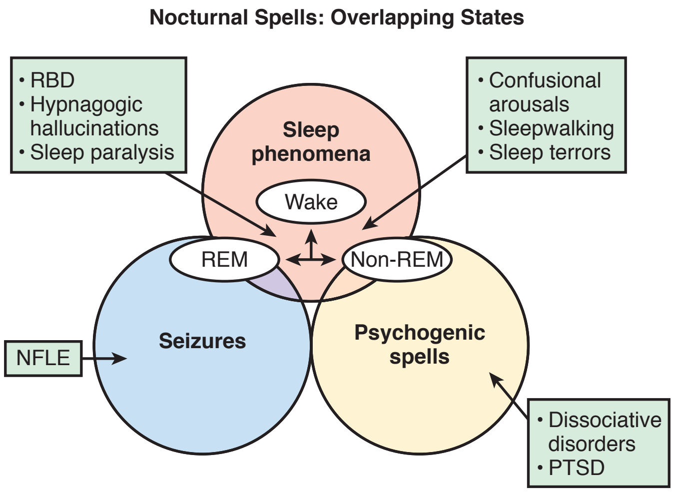

Figure 19-2 **Overlapping states of being.** Parasomnias are explainable on the basic notion that sleep and wakefulness are not mutually exclusive states but may dissociate and oscillate rapidly. The abnormal admixture of the 3 states of being (non-REM sleep, REM sleep, and wakefulness) may overlap, giving rise to parasomnias. REM parasomnias occur because of the abnormal intrusion of wakefulness into REM sleep and likewise non-REM parasomnias, such as sleepwalking, occur because of abnormal intrusions of wakefulness into non-REM sleep. Other nocturnal spells that may be confused with parasomnias include NFLE and psychogenic spells such as posttraumatic stress disorder (PTSD), dissociated disorders. AHI, Apnea–hypopnea index (mean number of central + mixed + obstructive apneas and hypopneas per hour of total sleep); NFLE, nocturnal frontal lobe epilepsy; RBD, REM behavior disorder. *(Modified from Mahowald MW, Schenck CH. Non-rapid eye movement sleep parasomnias.* Neurol Clin *23(4):1078, vii, 2005.)*

in a predisposed child. There appears to be a genetic predisposition for both sleepwalking and night terrors. Partial arousal parasomnias may also be difficult to distinguish from nocturnal seizures. Table 19-6 summarizes similarities and differences among these nocturnal arousal events.

Epidemiology

Many children (15-40%) **sleepwalk** on at least 1 occasion; the prevalence of children who regularly sleepwalk is approximately 17%, and 3-4% have frequent episodes. Sleepwalking (somnambulism) may persist into adulthood, with the prevalence in adults of approximately 4%. The prevalence is approximately 10 times greater in children with a family history of sleepwalking. Approximately 1-3% of children experience **sleep terrors**, primarily during the preschool and elementary school yr, and the age at onset is usually between 4 and 12 yr. Because of the common genetic predisposition, the prevalence of sleep terrors in children who sleepwalk is approximately 10%. Although sleep terrors can occur at any age from infancy through adulthood, most individuals outgrow sleep terrors by adolescence. **Confusional arousals** (sleep drunkenness, sleep inertia) commonly co-occur with sleepwalking and sleep terrors; prevalence rates have been estimated to be upward of 15% in children ages 3-13 yr.

Clinical Manifestations

The partial arousal parasomnias have several features in common. Because they typically occur at the transition out of "deep" or SWS, partial arousal parasomnias have clinical features of both the awake (ambulation, vocalizations) and the sleeping (high arousal threshold, unresponsiveness to the environment) states; there is usually amnesia for the events. The duration is typically a few minutes (sleep terrors) to 30-40 minutes (confusional arousals). Sleep terrors are sudden in onset and characteristically involve a high degree of autonomic arousal (i.e., tachycardia, dilated pupils), whereas confusional arousals typically arise more gradually from sleep, may involve thrashing around but usually not displacement from bed, and are often accompanied by slow mentation, disorientation and confusion on forced arousal from SWS or upon waking in the morning. Sleepwalking may be associated with safety concerns (e.g., falling out of windows, wandering outside). Avoidance of, or increased agitation with, comforting by parents or attempts at awakening are also common features of all partial arousal parasomnias.

REM sleep behavior disorder, is characterized by episodes of arousal during REM sleep, loss of REM atonia, and acting out of dreams including vocalizations during night-time sleep or naps. Some patients have CNS lesions (tumors), narcolepsy, seizures, neuropsychiatric medications, or neurodegenerative diseases.

Treatment

Management of partial arousal parasomnias involves some combination of parental education and reassurance, healthy sleep practices, and avoidance of exacerbating factors such as sleep restriction and caffeine. Particularly in the case of sleepwalking, it is important to institute safety precautions such as use of gates in doorways and at the top of staircases, locking of outside doors and windows, and installation of parent notification systems such as bedroom door alarms. Scheduled awakenings, a behavioral intervention that involves having the parent wake the child approximately 15-30 min before the time of night that the first parasomnia episode is most likely to be successful in situations in which partial arousal episodes occur on a nightly basis. Pharmacotherapy is rarely necessary, but may be indicated in cases of frequent or severe episodes, high risk of injury, violent behavior, or serious disruption to the family; the primary pharmacologic agents used are potent SWS suppressants, primarily benzodiazepines and tricyclic antidepressants.

Sleep-Related Movement Disorders: Restless Legs Syndrome/Periodic Limb Movement Disorder and Rhythmic Movements

RLS (Willis Ekbom syndrome) is a chronic neurologic disorder, characterized by an almost irresistible urge to move the legs, often accompanied by uncomfortable sensations in the lower extremities. Both the urge to move and the sensations are usually worse at rest and in the evening and are at least partially relieved by movement, including walking, stretching, and rubbing, but only as long as the motion continues. RLS is a clinical diagnosis that is based on the presence of these key symptoms. PLMD is characterized by periodic, repetitive, brief (0.5-10 sec), and highly stereotyped limb jerks typically occurring at 20-40 sec intervals. These movements occur primarily during sleep, most commonly occur in the legs, and frequently consist of rhythmic extension of the big toe and dorsiflexion at the ankle. The diagnosis of **periodic limb movements** (PLMs) requires overnight PSG to document the characteristic limb movements with anterior tibialis electromyography leads.

Etiology

"Early-onset" RLS (i.e., onset of symptoms before 35-40 yr of age), often termed "primary" RLS, appears to have a particularly strong genetic component, with a 6-7 fold increase in prevalence in first-degree relatives of RLS patients. The mode of inheritance is complex and several genetic loci have been identified (*MEIS1, BTBD9, MAP2K5*). Low serum iron levels in both adults and children may be an important etiologic factor for the presence and severity of both RLS symptoms and PLMs. As a marker of decreased iron stores, serum ferritin levels in both children and adults with RLS are frequently low (i.e., less than 50 µg/mL). The underlying mechanism that has been postulated is related to the role of iron as a cofactor in tyrosine hydroxylation, a rate-limiting step in dopamine synthesis; in turn, dopaminergic dysfunction has been implicated as playing a key role particularly in the genesis of the sensory component of RLS, as well as in PLMD. Certain medical conditions, including diabetes mellitus, end-stage renal disease, cancer, rheumatoid arthritis, hypothyroidism, and pregnancy, may also be associated with RLS/PLMD, as are specific medications

Table 19-6 Key Similarities and Differentiating Features Between Non-REM and REM Parasomnias as Well as Nocturnal Seizures

	CONFUSIONAL AROUSALS	SLEEP TERRORS	SLEEPWALKING	NIGHTMARES	RBD	NOCTURNAL SEIZURES
Time	Early	Early	Early-Mid	Late	Late	Any
Sleep stage	SWA	SWA	SWA	REM	REM	Any
EEG discharges	–	–	–	–	–	+
Scream	–	++++	–	++	+	+
Autonomic activation	+	++++	+	+	+	+
Motor activity	–	+	+++	+	++++	++++
Awakens	–	–	–	+	+	+
Duration (minutes)	0.5–10	1–10	2–30	3–20	1–10	5–15
Postevent confusion	+	+	+	–	–	+
Age	Child	Child	Child	Child–Young Adult	Older Adult	Adolescent, Young Adult
Genetics	+	+	+	–	–	±
Organic CNS lesion	–	–	–	–	++	++++

EEG, Electroencephalogram; RBD, REM behavior disorder; REM, rapid eye movement; SWA, slow-wave arousal

From Avidan A, Kaplish N: The parasomnias: epidemiology, clinical features and diagnostic approach. Clin Chest Med *31:353–370, 2010.*

(e.g., antihistamines such as diphenhydramine, antidepressants, and H_2 blockers such as cimetidine) and substances (notably, caffeine).

Epidemiology

Previous studies found prevalence rates of RLS in the pediatric population ranging from 1-6%; approximately 2% of 8-17 yr olds meet the criteria for "definite" RLS. Prevalence rates of PLMs greater than 5 per hour in clinical populations of children referred for sleep studies range from 5-27%; in survey studies of PLM symptoms, rates are 8-12%. Several studies in referral populations have found that PLMs occur in as much as 25% of children diagnosed with ADHD.

Clinical Manifestations

In addition to the urge to move the legs and the sensory component, most RLS episodes begin or are exacerbated by rest or inactivity, such as lying in bed to fall asleep or riding in a car for prolonged periods. A unique feature of RLS is that the timing of symptoms also appears to have a circadian component, in that they often peak in the evening hours. Some children may complain of "growing pains," although this is considered a nonspecific feature. Because RLS symptoms are usually worse in the evening, bedtime struggles and difficulty falling asleep are 2 of the most common presenting complaints. In contrast to patients with RLS, individuals with PLMs are usually unaware of these movements, but children may complain of morning muscle pain or fatigue; these movements may result in arousals during sleep and consequent significant sleep disruption. Parents of children with RLS/PLMD may report that their child is a restless sleeper, moves around or even falls out of bed during the night.

Treatment

The decision of whether and how to treat RLS depends on the level of severity (intensity, frequency, and periodicity) of sensory symptoms, the degree of interference with sleep, and the impact of daytime sequelae in a particular child or adolescent. With PLMs, for an index (PLMs per hour) less than 5, usually no treatment is recommended; for an index greater than 5, the decision to specifically treat PLMs should be based on the presence or absence of nocturnal symptoms (restless or nonrestorative sleep) and daytime clinical sequelae. The acronym AIMS represents a comprehensive approach to the treatment of RLS: A = avoidance of exacerbating factors such as caffeine and drugs which increase symptoms, I = iron supplementation when appropriate, M = muscle activity (increased physical activity, muscle relaxation, application of heat/cold compresses), and S = sleep (regular sleep schedule and sufficient sleep for age). Iron supplements should be instituted if serum ferritin levels are <50; it should be kept in mind that ferritin is an acute-phase reactant and thus may be falsely elevated (i.e., normal) in the setting of a concomitant illness. The recommended dose of ferrous sulfate is typically in the range of 3-6 mg/kg/day for a duration of 3 mo. Medications that increase dopamine levels in the CNS, such as ropinirole and pramipexole, have been found to be effective in relieving RLS/PLMD symptoms in adults; data in children are extremely limited.

Sleep-related rhythmic movements, including head banging, body rocking, and head rolling, are characterized by repetitive, stereotyped, and rhythmic movements or behaviors that involve large muscle groups. These behaviors typically occur with the transition at sleep at bedtime, but also at nap times and following nighttime arousals. Children typically engage in these behaviors as a means of soothing themselves to (or back to) sleep; they are much more common in the 1st yr of life and usually disappear by preschool age. In most instances, rhythmic movement behaviors are benign, because sleep is not significantly disrupted as a result of these movements and associated significant injury is rare. These behaviors typically occur in normally developing children, and in the vast majority of cases their presence does not indicate that there is some underlying neurologic or psychologic problem. Usually, the most important aspect in management of sleep-related rhythmic movements is reassurance to the family that this behavior is normal, common, benign, and self-limited.

Narcolepsy

Hypersomnia is a clinical term that is used to describe a group of disorders characterized by recurrent episodes of **excessive daytime sleepiness (EDS)**, reduced baseline alertness, and/or prolonged nighttime sleep periods that interfere with normal daily functioning. It is important to recognize that there are many potential causes of EDS, which may be broadly grouped as "extrinsic" (e.g., secondary to insufficient and/or fragmented sleep) or "intrinsic" (e.g., resulting from an increased need for sleep). **Narcolepsy** is a chronic lifelong CNS disorder, typically presenting in adolescence and early adulthood, that is characterized by profound daytime sleepiness and resultant significant functional impairment. Other symptoms frequently associated with narcolepsy, including cataplexy (sudden and temporary loss of muscle tone), hypnogogic/hypnopompic (immediately before falling asleep/awakening) hallucinations, and sleep paralysis, may be conceptualized

as representing the "intrusion" of REM sleep features into the waking state (see further descriptions below).

Etiology

The genesis of narcolepsy with cataplexy (type 1) is thought to be related to a specific deficit in the hypothalamic orexin/hypocretin neurotransmitter system. The underlying pathogenesis of narcolepsy involves selective loss of cells that secrete hypocretin/orexin in the lateral hypothalamus; it has been postulated that autoimmune mechanisms, possibly triggered by viral infections, in combination with a genetic predisposition and environmental factors, may be involved. Human leukocyte antigen testing also shows a strong association with narcolepsy; however, the vast majority of individuals with this antigen do not have narcolepsy, and most (90%), but not all, patients with narcolepsy with cataplexy are HLA-DQB1*0602–positive. Patients with narcolepsy without cataplexy (type 2) are increasingly thought to have a significantly different pathophysiology; they are much less likely to be HLA-DQB1*0602–positive. Although the majority of cases of narcolepsy are considered idiopathic, "secondary" narcolepsy with cataplexy is associated with CNS insults, including hypothalamic tumors and cranial irradiation, and specific genetic syndromes (Prader-Willi [see Chapter 81.8] and Niemann-Pick type C [see Chapter 86.4]). Narcolepsy has been reported in Finnish children after immunization with the AS03 adjuvanted AH1N1 influenza vaccine.

Epidemiology

The prevalence of narcolepsy is reported to be between 3 and 16 per 10,000, with the prevalence of narcolepsy with cataplexy approximately 0.2-0.5/10,000. The risk of developing narcolepsy with cataplexy in a 1st-degree relative of a narcoleptic patient is estimated at 1-2%; this represents an increase of 10-40–fold compared to the general population.

Clinical Manifestations and Diagnosis

The typical onset of symptoms of narcolepsy is in adolescence and early adulthood, although symptoms may initially present in school-age and even younger children. The early manifestations of narcolepsy are often ignored, misinterpreted, or misdiagnosed as other medical, neurologic, and psychiatric conditions, and the appropriate diagnosis is frequently delayed for a number of years.

The most prominent clinical manifestation of narcolepsy is profound daytime sleepiness, characterized by both an increased baseline level of daytime drowsiness and by the repeated occurrence of sudden and unpredictable sleep episodes. These "**sleep attacks**" are often described as "irresistible" in that the child or adolescent is unable to stay awake despite considerable effort, and they occur even in the context of normally stimulating activities (e.g., during meals, in the middle of a conversation). Very brief (several seconds) sleep attacks may also occur in which the individual may "stare off," appear unresponsive, or continue to engage in an ongoing activity (automatic behavior). EDS may also be manifested by increased nighttime sleep needs and extreme difficulty waking in the morning or after a nap. **Cataplexy** is considered pathognomonic for narcolepsy. Cataplexy is rarely the first symptom of narcolepsy, but it often develops within the 1st yr of the onset of EDS. It is described as an abrupt, bilateral, partial (especially knees and head/jaw) or complete loss of muscle tone, without loss of consciousness, classically triggered by an intense positive emotion (e.g., laughter, surprise). The cataplectic attacks are typically brief (seconds to minutes) but in children may last for hours or days ("status cataplecticus"), and they are fully reversible, with complete recovery of normal tone when the episode ends. "Cataplectic facies" is a clinical feature unique to the pediatric population and is characterized by slack facial musculature, a protruding tongue, and slurred speech. **Hypnogogic/hypnopompic hallucinations** involve vivid visual, auditory, and sometimes tactile sensory experiences occurring during transitions between sleep and wakefulness, primarily at sleep offset (hypnopompic) and sleep onset (hypnogogic). **Sleep paralysis** is the inability to move or speak for a few seconds or minutes at sleep onset or offset, and often accompanies the hallucinations. Other symptoms associated with narcolepsy include disrupted nocturnal sleep, impaired cognition, inattention, and behavioral and mood dysregulation.

Overnight PSG followed by a multiple sleep latency test are strongly recommended components of the evaluation of a patient with profound unexplained daytime sleepiness or suspected narcolepsy. The purpose of the overnight PSG is to evaluate for primary sleep disorders, such as OSA that may cause EDS. The multiple sleep latency test involves a series of 5 opportunities to nap (20 min long), during which narcoleptics demonstrate a pathologically shortened mean sleep onset latency (typically less than 5 minutes) as well as at least 2 periods of REM sleep occurring immediately after sleep onset.

Treatment

An individualized narcolepsy treatment plan usually involves education, good sleep hygiene, behavioral changes, and medication. Scheduled naps are often helpful. Medications such as psychostimulants and modafinil are often prescribed to control the EDS, whereas antidepressants (serotonin reuptake inhibitors, venlafaxine) may also be used to reduce cataplexy. Sodium oxybate is a drug that appears to both positively impact daytime sleepiness and REM-associated phenomena, such as cataplexy, hypnogogic hallucinations, and sleep paralysis. Most of these medications are not approved for use in children. The goal should be to allow the fullest possible return of normal functioning in school, at home, and in social situations.

Delayed Sleep Phase Disorder

Delayed sleep phase disorder (DSPD), a circadian rhythm disorder, involves a significant, persistent, and intractable phase shift in sleep–wake schedule (later sleep onset and wake time) that conflicts with the individual's normal school, work, and/or lifestyle demands. DSPD may occur at any age, but is most common in adolescents and young adults.

Etiology

Individuals with DSPD often start out as night owls; that is, they have an underlying predisposition or circadian preference for staying up late at night and sleeping late in the morning, especially on weekends, holidays, and summer vacations. The underlying pathophysiology of DSPD is still unknown, although some authors have theorized that it involves an intrinsic abnormality in the circadian oscillators that govern the timing of the sleep period.

Epidemiology

Studies indicate that the prevalence of DSPD may be as high as 7-16% in adolescents and young adults.

Clinical Manifestations

The most common clinical presentation is sleep initiation insomnia when the individual attempts to fall asleep at a "socially acceptable" desired bedtime, accompanied by extreme difficulty getting up in the morning even for desired activities, and daytime sleepiness. Sleep maintenance is generally not problematic, and no sleep onset insomnia is experienced if bedtime coincides with the preferred sleep onset time (e.g., on weekends, school vacations). School tardiness and frequent absenteeism with a decline in academic performance are often present.

Treatment

The treatment of DSPD usually has 3 components, all directed toward the goals of shifting the sleep–wake schedule to an earlier more desirable time, and maintaining the new schedule. The initial step involves shifting the sleep–wake schedule to the desired earlier times, usually with gradual (i.e., in 15-30 min increments every few days) advancement of bedtime in the evening and rise time in the morning; more significant phase delays (i.e., difference between current sleep onset and desired bedtime) may require "chronotherapy," which involves delaying bedtime and wake time by 2-3 hr every 24 hr "forward around the clock" until the target bedtime is reached. Because melatonin secretion is highly sensitive to light, exposure to light in the morning (either natural light or a "light box," which typically produces predominantly

blue light) and avoidance of evening light exposure are often beneficial. Exogenous oral melatonin supplementation may also be used; larger mildly sedating doses (i.e., 5 mg) are typically given at bedtime, but some studies have suggested that physiologic doses of oral melatonin (0.3-0.5 mg) administered in the afternoon or early evening (i.e., 5-7 hr before the habitual sleep onset time) seem to be most effective in advancing the sleep phase.

HEALTH SUPERVISION

It is especially important for pediatricians to both screen for and recognize sleep disorders in children and adolescents during health encounters. The well-child visit is an opportunity to educate parents about normal sleep in children and to teach strategies to prevent sleep problems from developing (primary prevention) or from becoming chronic, if problems already exist (secondary prevention). Developmentally appropriate screening for sleep disturbances should take place in the context of every well child visit and should include a range of potential sleep problems; one Table 19-7 outlines a simple sleep screening algorithm, the "BEARS." Because parents may not always be aware of sleep problems, especially in older children and adolescents, it is also important to question the child directly about sleep concerns. The recognition and evaluation of sleep problems in children requires both an understanding of the association between sleep disturbances and daytime consequences, such as irritability, inattention, and poor impulse control, and familiarity with the developmentally appropriate differential diagnoses of common presenting sleep complaints (difficulty initiating and maintaining sleep, episodic nocturnal events). In particular, an assessment of sleep patterns and possible sleep problems should be part of the initial evaluation of every child presenting with behavioral and/or academic problems, especially ADHD.

Effective preventive measures include educating parents of newborns about normal sleep amounts and patterns. The ability to regulate sleep, or control internal states of arousal to fall asleep at bedtime and to fall back asleep during the night, begins to develop in the 1st 8-12 wk of life. Thus, it is important to recommend that parents put their 2-4 mo old infants to bed "drowsy but awake" if they wish to avoid dependence on parental presence at sleep onset and foster the infants' ability to self-soothe. Other important sleep issues include discussing the importance of regular bedtimes, bedtime routines, and transitional objects for toddlers, and providing parents and children with basic information about healthy sleep practices, recommended sleep amounts at different ages, and education regarding signs that a child is not getting sufficient sleep (i.e., wakes with difficulty in the morning, sleeps longer when allowed on weekends and vacation days).

The cultural and family context within which sleep problems in children occur should be considered; for example, cosleeping of infants and parents is a common and accepted practice in many racial/ethnic groups and the goal of independent self-soothing in young infants may not be shared by these families. Anticipatory guidance needs to balance cultural awareness with the critical importance of "safe sleep" conditions in sudden infant death syndrome prevention (i.e., sleeping in the supine position, avoidance of bed-sharing but encouragement of room-sharing in the 1st yr of life) (see Chapter 375). On the other hand, the institution of cosleeping by parents as an attempt to address a child's underlying sleep problem (so-called reactive cosleeping), rather than as a conscious family decision, is likely to yield only a temporary respite from the problem and may set the stage for more significant sleep issues.

EVALUATION OF PEDIATRIC SLEEP PROBLEMS

The clinical evaluation of a child presenting with a sleep problem involves obtaining a careful medical history to assess for potential medical causes of sleep disturbances, such as allergies, concomitant medications, and acute or chronic pain conditions. A developmental history is important because of the aforementioned increased risk of sleep problems in children with neurodevelopmental disorders.

Table 19-7 BEARS Sleep Screening Algorithm

The BEARS instrument is divided into 5 major sleep domains, providing a comprehensive screen for the major sleep disorders affecting children 2-18 yr old. Each sleep domain has a set of age-appropriate "trigger questions" for use in the clinical interview.
B = Bedtime problems
E = Excessive daytime sleepiness
A = Awakenings during the night
R = Regularity and duration of sleep
S = Snoring

Examples of Developmentally Appropriate Trigger Questions			
	TODDLER/PRESCHOOL CHILD (2-5 YR)	**SCHOOL-AGED CHILD (6-12 YR)**	**ADOLESCENT (13-18 YR)**
1. Bedtime problems	Does your child have any problems going to bed? Falling asleep?	Does your child have any problems at bedtime? (P) Do you any problems going to bed? (C)	Do you have any problems falling asleep at bedtime? (C)
2. Excessive daytime sleepiness	Does your child seem overtired or sleepy a lot during the day? Does your child still take naps?	Does your child have difficulty waking in the morning, seem sleepy during the day, or take naps? (P) Do you feel tired a lot? (C)	Do you feel sleepy a lot during the day? In school? While driving? (C)
3. Awakenings during the night	Does your child wake up a lot at night?	Does your child seem to wake up a lot at night? Any sleepwalking or nightmares? (P) Do you wake up a lot at night? Do you have trouble getting back to sleep? (C)	Do you wake up a lot at night? Do you have trouble getting back to sleep? (C)
4. Regularity and duration of sleep	Does your child have a regular bedtime and wake time? What are they?	What time does your child go to bed and get up on school days? Weekends? Do you think your child is getting enough sleep? (P)	What time do you usually go to bed on school nights? Weekends? How much sleep do you usually get? (C)
5. Snoring	Does your child snore a lot or have difficulty breathing at night?	Does your child have loud or nightly snoring or any breathing difficulties at night? (P)	Does your teenager snore loudly or nightly? (P)

C, child; P, parent.

Assessment of the child's current level of functioning (school, home) is a key part of evaluating possible mood, behavioral, and neurocognitive sequelae of sleep problems. Current sleep patterns, including the usual sleep duration and sleep–wake schedule, are often best assessed with a sleep diary, in which a parent (or adolescent) records daily sleep behaviors for an extended period (1-2 wk). A review of sleep habits, such as bedtime routines, daily caffeine intake, and the sleeping environment (e.g., temperature, noise level) may reveal environmental factors that contribute to the sleep problems. Nocturnal symptoms that may be indicative of a medically based sleep disorder, such as OSA (loud snoring, choking or gasping, sweating) or PLMs (restless sleep, repetitive kicking movements), should be elicited. An overnight sleep study is not routinely warranted in the evaluation of a child with sleep problems unless there are symptoms suggestive of OSA or periodic leg movements, unusual features of episodic nocturnal events, or daytime sleepiness that is unexplained.

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Behavioral and Psychiatric Disorders

PART III

Chapter 20

Assessment and Interviewing

Heather J. Walter and David R. DeMaso

It is estimated that 13-20% of children living in the United States experience a mental illness in a given year, at a cost of nearly $300 billion. In children, mental illness is more prevalent than leukemia, diabetes, and AIDS combined; more money is spent on mental disorders than on any other childhood illness, including asthma, trauma, upper respiratory infections, and infectious diseases. Although nearly 1 in 5 youths suffers from a psychiatric disorder, 75-80% do not receive needed mental health services. Those who do, primarily receive services in nonspecialty sectors (primary care, schools, child welfare, juvenile justice) where mental health expertise may be limited. Untreated or inadequately treated psychiatric disorders are associated with significant adverse sequelae, including increased morbidity and mortality, failure to achieve mastery in life's developmental tasks (education, occupation, marriage, child-rearing), cross-generational transmission of disadvantage, and substantial costs to society. Psychiatric disorders negatively affect the course of physical illness, adherence to treatment regimens, and use of medical resources. The strong continuity into adulthood of child psychiatric disorders further underscores the importance of early identification and treatment.

AIMS OF ASSESSMENT

A psychosocial assessment in the pediatric setting should determine whether there are signs and symptoms of cognitive, developmental, emotional, behavioral, or social difficulties and characterize these signs and symptoms sufficiently to determine their appropriate management. The focus of the assessment varies with the nature of the presenting problem and the clinical setting. Under emergency circumstances, the focus may be limited to an assessment of dangerousness to self or others for the purpose of determining the safest level of care. In routine circumstances (well-child visits), the focus may be broader, involving a screen for symptoms and functional impairment in all major psychosocial domains. The challenge for the pediatric practitioner will be to determine as accurately as possible whether the presenting signs and symptoms are likely to meet criteria for a psychiatric disorder and whether the severity and complexity of the disorder suggests referral to a mental health specialist or management in the pediatric setting.

PRESENTING PROBLEMS

Infants are presented for clinical attention because of problems with eating and/or sleep regulation, concerns about failure to gain weight and length, poor social responsiveness, limited vocalization, apathy or disinterest, and response to strangers that is excessively fearful or overly familiar. Psychiatric disorders most commonly diagnosed during this period are rumination and reactive attachment disorders.

Toddlers are assessed for concerns about sleep problems, language delay, motor hyperactivity, extreme misbehavior, extreme shyness, inflexible adherence to routine, difficulty separating from parents, struggles over toilet training, dietary issues, and testing limits. Developmental delays and more subtle physiologic, sensory, and motor processing problems can be presented as concerns. Problems with goodness of fit between the child's temperament and the parents' expectations can create relationship difficulties that also require assessment. Psychiatric disorders most commonly diagnosed during this period are autism spectrum and reactive attachment disorders.

Presenting problems in *preschoolers* include elimination difficulties, sibling jealousy, lack of friends, self-destructive impulsiveness, multiple fears, nightmares, refusal to follow directions, somatization, speech that is difficult to understand, and temper tantrums. Psychiatric disorders most commonly diagnosed in this period are autism spectrum, communication, disruptive, attention-deficit/hyperactivity, anxiety (separation, selective mutism), reactive attachment, gender dysphoria, and sleep disorders.

Older children are brought to clinical attention because of concerns about angry or sad mood, bedwetting, overactivity, impulsiveness, distractibility, learning problems, arguing, defiance, nightmares, school refusal, bullying or being bullied, worries and fears, somatization, communication problems, tics, and withdrawal or isolation. Psychiatric disorders most commonly diagnosed during this period are attention-deficit/hyperactivity, disruptive, anxiety (generalized, phobias), elimination, somatic symptom, specific learning, and tic disorders.

Adolescents are assessed for concerns about the family situation, experimentation with sexuality and drugs, delinquency and gang involvement, friendship patterns, issues of independence, identity formation, self-esteem, and morality. Psychiatric disorders most commonly diagnosed during this period are anxiety (panic, social anxiety), depressive, bipolar, psychotic, obsessive-compulsive, impulse control, conduct, substance-related, and eating disorders.

GENERAL PRINCIPLES OF THE PSYCHOSOCIAL INTERVIEW

Psychosocial interviewing in the context of a routine pediatric visit requires adequate time and privacy. The purpose of this line of inquiry should be explained to the child and parents ("to make sure things are going OK at home, at school, and with friends"), along with the limits of confidentiality. Thereafter, the first goal of the interview is to build rapport with both the child and the parents.

With the parents, this rapport is grounded in respect for the parents' knowledge of their child, their role as the central influence in their child's life, and their desire to make a better life for their child. Parents often feel anxious or guilty because they believe that problems in a child imply that their parenting skills are inadequate. Parents' experiences of their own childhood influence the meaning a parent places on a child's feelings and behavior. A good working alliance allows mutual discovery of the past as it is active in the present and permits potential distortions to be modified more readily. Developmentally appropriate overtures can facilitate rapport with the child. Examples include playing peek-a-boo with an infant, racing toy cars with a preschooler, commenting on sports with a child who is wearing a baseball cap, and discussing music with a teenager who is wearing a rock music t-shirt.

After an overture with the child, it is helpful to begin with family-centered interviewing, in which the parent is invited to present any psychosocial concerns (development, thinking, feelings, behavior, peer relationships) about the child. With adolescent patients, it is important to conduct a separate interview to give the adolescent an opportunity to confirm or refute the parent's presentation and to present the problem from his or her perspective. Following the family's undirected presentation of the primary problem, it is important to shift to direct questioning to clarify the duration, frequency, and severity of symptoms, associated distress or functional impairment, and the developmental and environmental context in which the symptoms occur.

Because of the high degree of comorbidity of psychosocial problems in children, after eliciting the presenting problem, the pediatric practitioner should then briefly screen for problems in all of the major

Table 20-1	Mental Health Action Signs

- Feeling very sad or withdrawn for more than 2 weeks
- Seriously trying to harm or kill yourself, or making plans to do so
- Sudden overwhelming fear for no reason, sometimes with a racing heart or fast breathing
- Involvement in many fights, using a weapon, or wanting to badly hurt others
- Severe out-of-control behavior that can hurt yourself or others
- Not eating, throwing up, or using laxatives to make yourself lose weight
- Intense worries or fears that get in the way of your daily activities
- Extreme difficulty in concentrating or staying still that puts you in physical danger or causes school failure
- Repeated use of drugs or alcohol
- Severe mood swings that cause problems in relationships
- Drastic changes in your behavior or personality

From The Action Signs Project, Center for the Advancement of Children's Mental Health at Columbia University.

developmentally appropriate categories of cognitive, developmental, emotional, behavioral, and social disturbance, including problems with mood, anxiety, attention, behavior, thinking and perception, substance use, social relatedness, eating, elimination, development, language, and learning. This can be preceded by a transition statement such as, "Now I'd like to ask about some other issues that I ask all parents and kids about."

A useful guide for this area of inquiry is provided by the "11 Action Signs" (Table 20-1), which was designed to give frontline clinicians the tools needed to recognize early symptoms of mental disorders. Functional impairment can be assessed by inquiring about symptoms and function in the major life domains, including home and family, school, peers, and community. These domains are included in the HEADSS (home, education, activities, drugs, sexuality, suicide/depression) interview guide, often used in the screening of adolescents (Table 20-2).

The nature and severity of the presenting problem(s) can be further characterized through the use of a standardized self-, parent-, or teacher-informant rating scale (Table 20-3 lists some of the scales in the public domain). A rating scale is a type of measure that provides a relatively rapid assessment of a specific construct with an easily derived numerical score that is readily interpreted. The use of rating scales can ensure systematic coverage of relevant symptoms, quantify symptom severity, and document a baseline against which treatment effects can be measured.

Clinical experience and methodologic studies suggest that parents and teachers are more likely than the child to report externalizing problems (disruptive, impulsive, overactive, or antisocial behavior). Children may be more likely to report anxious or depressive feelings, including suicidal thoughts and acts, of which the parents may be unaware. Functional impairment also can be assessed with self and other rating scales. Although concerns have been raised about children's competence as self-reporters (because of limitations in linguistic skills; self-reflection; emotional awareness; ability to monitor behavior, thoughts, and feelings; and tendency toward social desirability), children and adolescents can be reliable and valid self-reporters.

Clinicians are encouraged to become familiar with the psychometric characteristics and appropriate use of at least 1 broad-based measure of psychosocial problems, such as the *Strengths and Difficulties Questionnaire* (SDQ) (http://www.sdqinfo.org/py/sdqinfo/b0.py), the *Pediatric Symptom Checklist* (PSC) (http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_sympton_chklst.pdf), or the *Swanson, Nolan, and Pelham–IV* (SNAP-IV) (http://psychiatryassociatespc.com/doc/SNAP-IV_Parent&Teacher.pdf). These measures are available in multiple languages. If the interview or broad-based rating scale suggests difficulties in one or more specific symptom areas, the clinician can follow with a psychometrically sound, appropriate narrow-band instrument such as the *Vanderbilt ADHD Diagnostic Rating Scale* for attention, behavior, and learning problems, the *Center for Epidemiological Studies Depression Scale for Children* (CES-DC) or *Mood and Feelings Questionnaire* (MFQ) for depression, or the *Screen for Child Anxiety Related Emotional Disorders* (SCARED) for anxiety.

Table 20-2	HEADSS Screening Interview for Taking a Rapid Psychosocial History

PARENT INTERVIEW

Home
- How well does the family get along with each other?

Education
- How well does your child do in school?

Activities
- What does your child like to do?
- Does your child do anything that has you really concerned?
- How does your child get along with peers?

Drugs
- Has your child used drugs or alcohol?

Sexuality
- Are there any issues regarding sexuality or sexual activity that are of concern to you?

Suicide/depression
- Has your child ever been treated for an emotional problem?
- Has your child ever intentionally tried to hurt him-/herself or made threats to others?

ADOLESCENT INTERVIEW

Home
- How do you get along with your parents?

Education
- How do you like school and your teachers?
- How well do you do in school?

Activities
- Do you have a best friend or group of good friends?
- What do you like to do?

Drugs
- Have you used drugs or alcohol?

Sexuality
- Are there any issues regarding sexuality or sexual activity that are of concern to you?

Suicide/depression
- Everyone feels sad or angry some of the time. How about you?
- Did you ever feel so upset that you wished you were not alive or so angry you wanted to hurt someone else badly?

HEADSS, home, education, activities, drugs, sexuality, suicide/depression.
From Cohen E, MacKenzie RG, Yates GL: HEADSS, a psychosocial risk assessment instrument: implications for designing effective intervention programs for runaway youth, J Adolesc Health *12:539–544, 1991.*

Children and adolescents scoring above standardized cutpoints in most cases should be referred to a qualified mental health professional for assessment and treatment, because scores in this range are highly correlated with clinically significant psychiatric disorders. Youths scoring just below or slightly above cutpoints (e.g., subsyndromal or mild mood, anxiety, or disruptive behavior disorders) may be appropriate for management in the pediatric setting, as may youths scoring well above cutpoints for certain neurodevelopmental disorders (attention-deficit/hyperactivity, autism spectrum, tic).

The safety of the child in the context of the home and community is of paramount importance. The interview should sensitively assess whether the child has been exposed to any frightening events, including abuse, neglect, bullying, marital discord, or domestic or community violence; whether the child shows any indication of dangerousness to self or others or a severely altered mental status (psychosis, intoxication, rage, hopelessness); or whether the child (if age-appropriate) has been involved in any risky behavior, including running away, staying out without permission, truancy, gang involvement, experimentation with substances, and unprotected sexuality. The interview also should assess the capacity of the parents to adequately provide for the child's

Table 20-3 Select List of Mental Health Rating Scales in the Public Domain

INSTRUMENTS	FOR AGES (yr)	INFORMANT: NUMBER OF ITEMS	TIME TO COMPLETE (min)	AVAILABLE AT
BROAD BAND				
Pediatric Symptom Checklist (PSC)	3-18	Parent: 35, 17 Youth: 35, 17	5-10	www.massgeneral.org/psychiatry
SNAP-IV Rating Scale	6-18	Parent, Teacher: 90	10	www.adhd.net
Strengths & Difficulties Questionnaire (SDQ)	16 4-17	Parent, Teacher, Child: 25	5	www.sdqinfo.com
NARROW BAND				
Anxiety				
Self-Report for Childhood Anxiety Related Emotional Disorders (SCARED)	8-18	Parent, Child: 41	5	www.wpic.pitt.edu/research
Attention and Behavior				
Vanderbilt ADHD Diagnostic Rating Scale	6-12	Parent: 55 Teacher: 43	10	www.brightfutures.org
Autism				
Modified Checklist for Autism in Toddlers (M-CHAT)	16-30 months	Parent: 23	5-10	https://www.m-chat.org/index.php
Depression				
Center for Epidemiological Studies Depression Scale for Children (CES-DC)	6-18	Child: 20	5	www.brightfutures.org
Mood and Feelings Questionnaire (MFQ) Short Version	7-18	Parent: 34 Child: 33	<5	www.devepi.duhs.duke.edu/mfq.html

physical, emotional, and social needs or whether parental capacity has been diminished by psychiatric disorder, family dysfunction, or the sequelae of disadvantaged socioeconomic status. Any indications of threats to the child's safety should be immediately followed by thorough assessment and protective action.

INDICATIONS FOR REFERRAL

There is variability in the level of confidence pediatric practitioners perceive in diagnosing psychosocial problems in children and adolescents. Pediatric practitioners who have familiarity with psychiatric diagnostic criteria may feel confident diagnosing certain disorders, particularly the neurodevelopmental and other biologically based disorders (attention-deficit/hyperactivity, autism spectrum, and tic disorders, enuresis, encopresis, insomnia, anorexia). The disorders about which pediatric practitioners might have less diagnostic confidence include the disruptive/impulse control/conduct, depressive, bipolar, anxiety, psychotic, obsessive-compulsive, trauma-related, somatic symptom, and substance-related disorders. Pediatric practitioners should refer to a qualified mental health practitioner whenever they experience diagnostic uncertainty with a child who has distressing or functionally impairing psychosocial symptoms. Children who upon initial assessment are found to have indicators of dangerousness always should be immediately referred to a qualified mental health professional.

PSYCHIATRIC DIAGNOSTIC EVALUATION

The objectives of the psychiatric diagnostic evaluation of the child and adolescent are to determine whether psychopathology or developmental risk is present and if so, to establish an explanatory formulation and a differential diagnosis, and to determine whether treatment is indicated and if so, to develop a treatment plan and facilitate the parents' and child's involvement in the plan. The aims of the diagnostic evaluation are to clarify the reasons for the referral; to obtain an accurate accounting of the child's developmental functioning and the nature and extent of the child's psychosocial difficulties, functional impairment, and subjective distress; and to identify potential individual, family, or environmental factors that might account for, influence, or ameliorate these difficulties. The issues relevant to diagnosis and treatment planning can span genetic, constitutional, and temperamental factors; individual psychodynamics; cognitive, language, and social skills; family patterns of interaction and child- rearing practices; and community, school, and socioeconomic influences.

The focus of the evaluation is developmental; it seeks to describe the child's functioning in various realms and to assess the child's adaptation in these areas relative to that expected for the child's age and phase of development. The developmental perspective extends beyond current difficulties to vulnerabilities that can affect future development and as such are important targets for preventive intervention. Vulnerabilities may include subthreshold or subsyndromal difficulties that, especially when manifold, often are accompanied by significant distress or impairment and as such are important as potential harbingers of future problems.

Throughout the assessment, the clinician focuses on identifying a realistic balance of vulnerabilities and strengths in the child, in the parents, and in the parent–child interactions. From this strength-based approach, over time a hopeful family narrative is co-constructed to frame the child's current developmental progress and predict the child's ongoing progress within the scope of current risk and protective factors.

Although the scope of the evaluation will vary with the clinical circumstance, the full *psychiatric diagnostic evaluation* has 12 major components: the presenting problem(s) and the context in which they occur; a review of psychiatric symptoms; a risk assessment; a history of psychiatric treatment; a medical history, a developmental history; an educational history; a family history; a mental status examination; a biopsychosocial clinical formulation; a *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) diagnosis; and a treatment plan. For infants and young children, the presenting problem and historical information is derived from parents and other informants. As children mature, they become increasingly important contributors to the information base, and they become the primary source of information in later adolescence. Information relevant to formulation and differential diagnosis is derived in multiple ways, including directive and nondirective questioning, interactive play, and observation of the child alone and together with the caregiver(s).

The *explication of the presenting problem(s)* includes information about onset, duration, frequency, and severity of symptoms, associated

distress and/or functional impairment, and predisposing, precipitating, perpetuating, and ameliorating contextual factors. The *symptom review* assesses potential comorbidity in the major domains of child and adolescent psychopathology, including problems with intellectual, communication, motor, learning, and developmental capabilities; attention deficits; angry, sad, or elated mood; anxiety; obsessions or compulsions; trauma or stress reactions; somatic symptoms; eating, elimination, sleep, or gender disturbances; disruptive, impulse-control, or conduct problems; psychosis; or substance abuse or addiction. The *risk assessment* includes a careful assessment of risk status, including suicidality, homicidality, assaultiveness, self-injuriousness, and involvement in risky behavior or situations. The *history of psychiatric treatment* includes gathering information about prior emergency mental health assessments, psychiatric hospitalizations, day treatment, psychotherapy, pharmacotherapy, and nontraditional treatments.

The *medical history* includes information about the source of primary care, the frequency of health supervision, past and current medical illnesses and treatments, and the youth and family's history of adherence to medical treatment. A systematic review of organ or functional systems facilitates the identification of abnormalities that require investigation or monitoring by the pediatric practitioner, as well as the identification of cautionary factors related to the prescription of psychotropic medication. The *developmental history* includes information about the circumstances of conception, pregnancy, or adoption; pre-, peri-, or postnatal insults; attachment and temperament; cognitive, motor, linguistic, emotional, social, and moral development; health habits, sexuality, and substance use (as age-appropriate), coping and defensive structure, future orientation, and perceived strengths. The *educational history* includes schools attended; typical grades, attendance, and behavior; special education services; disciplinary actions; social relationships; extracurricular activities; and barriers to learning. The *family history* assesses family composition; sociodemographic and neighborhood characteristics; domiciliary arrangements; parenting capacities; family function; medical and psychiatric histories of family members; and cultural/religious affiliations. The *mental status examination* assesses appearance, relatedness, cognition, communication, mood, affective expression, behavior, memory, orientation, and perception.

The evaluation culminates in a *biopsychosocial formulation and diagnosis*. The *biopsychosocial formulation* is derived from an assessment of vulnerabilities and strengths in the biologic, psychologic, and social domains and serves to identify targets for intervention and treatment. In the biologic domain, major vulnerabilities include a family history of psychiatric disorder and personality or behavior problems, and a personal history of pre-, peri-, or postnatal insults; cognitive or linguistic impairments; physical illness; and a difficult temperament. In the psychological domain, major vulnerabilities include failure to achieve developmental tasks and maladaptive coping and defensive styles. In the social domain, major vulnerabilities include parental incapacity; unskilled parenting; family dysfunction; social isolation; unfavorable school setting; unsupportive community structures; and sociodemographic disadvantage. Major strengths include cognitive and linguistic capability; physical health and attractiveness; stable, moderate temperamental characteristics; and stable and supportive parenting, family, peer, and community structures. The biopsychosocial formulation can be organized to reflect predisposing, precipitating, perpetuating, and protective (ameliorating) factors (the "4 Ps") influencing the development of the observed psychopathology.

The *diagnosis* must be made in accordance with the nomenclature in the DSM-5. This nomenclature categorizes cross-sectional phenomenology into discrete clinical syndromes and seeks to improve diagnostic accuracy at the expense of theories of causation and dimensional presentations. By DSM-5 convention, if diagnostic criteria are met, the diagnosis is given (except where hierarchical rules apply); consequently psychiatric comorbidity is a common occurrence.

The psychiatric diagnostic evaluation culminates in a *treatment plan* that brings the broad array of targeted psychosocial interventions to the service of the child. Diagnoses drive the choice of evidence-based psychotherapeutic and psychopharmacologic treatments. The formulation drives the selection of interventions targeted at biologic, psychologic, and social vulnerabilities and strengths. Many of these treatments and interventions are described in the succeeding chapters.

SPECIAL CONSIDERATIONS IN THE DIAGNOSTIC EVALUATION OF INFANTS AND YOUNG CHILDREN

Psychiatric evaluation of infants and young children includes the domains of physiology, temperament, motor behavior, affective behavior, social behavior, and communication. Although much of the information in these domains will be derived from parent report, much also can be gleaned from nonverbal behavior and observation of the parent-child interaction. Observations should include predominant affective tone of parent and child (positive, negative, apathetic); involvement in the situation (curiosity, disinterest); social responsiveness (mutuality of gaze, auditory responsiveness); and reactions to transitions (including separation).

A screen for maternal depression (see http://www.medicalhomeportal.org/clinical-practice/screening-and-prevention/maternal-depression for several examples) is critical at this stage, as is an assessment of the mother's (or other caregiver's) ability to rapidly respond on a contingent basis to the child's expressed needs, regulate the child's rapid shifts of emotion and behavior, and provide a stimulus shelter to prevent the child from being overwhelmed.

Standardized screening instruments *(Bayley Scales of Infant Development)* designed for this age group can be helpful in systematizing the evaluation. In addition, the *Infant, Toddler and Preschool Mental Status Exam* (ITP-MSE) is a reference tool that describes how traditional categories of the mental status exam can be adapted to observations of young children. Additional categories, including sensory and state regulation, have been added that reflect important areas of development in young children.

Diagnostic systems that are more age-appropriate than DSM-5 have been developed for infants and young children. These systems include the *Research Diagnostic Criteria—Preschool Age* (RDC-PA) and the *Zero to Three Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood-Revised* (DC: 0-3R). The DC: 0-3R includes relationship classification that assesses the range of interactional adaptation in each parent–child relationship and regulation disorders of sensory processing that identify a range of constitutionally and maturationally based sensory reactivity patterns, motor patterns, and behavior patterns that together can dysregulate a child internally and the child's interactions with caregivers.

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Chapter 21

Psychological Treatment of Children and Adolescents

David R. DeMaso and Heather J. Walter

Three-quarters of children with mental health problems are seen in primary care. About half of the treatment for psychiatric disorders is provided in primary care settings and most psychotropic prescriptions for youth are written by primary care practitioners. Barriers that prevent children and their families from obtaining needed mental health services include stigma, shortages of mental health

professionals, inadequate coverage of mental health services in public and private health insurance programs, inadequately trained clinicians, inadequate time for primary care providers to identify mental health issues, and fragmented service delivery systems.

The provision of supportive counseling, anticipatory guidance, and parent psychoeducation about mental health problems combined with medication management of neurodevelopmental (attention-deficit/hyperactivity [ADHD], autism spectrum, tic), sleep, and elimination disorders are commonly undertaken by the pediatric practitioner. Youth with other psychiatric disorders (psychotic, bipolar, depressive, anxiety, obsessive-compulsive, trauma-related, somatic symptom, dissociative, gender dysphoric, disruptive/impulse-control/conduct, and substance-related) require initial evaluation, treatment planning, and stabilization by child-trained mental health clinicians. However, the pediatric practitioner often resumes the care of these youth once stabilized.

Barriers to providing mental health services in the primary care setting include lack of mental health training for staff, insufficient time, lack of knowledge about community mental healthcare resources, and inadequate reimbursement. In the face of these challenges, safe and effective mental healthcare of children and adolescents requires effective collaboration between pediatric and mental health practitioners. Several models of effective collaboration in the primary care setting have been advanced; most converge in recommending the following components: (1) screening for and early detection of mental health problems; (2) triage/referral to appropriate mental health treatment; (3) timely access to mental health consultation and direct mental health assessment (in-person or via telepsychiatry); (4) care coordination (by a designated care coordinator in the primary care setting); (5) access to specialty mental health treatment services; and (6) education of primary care practitioners around the accurate assessment and safe and effective treatment of child and adolescent psychiatric disorders.

Bibliography is available at Expert Consult.

Table 21-1 Best Principles for Use of Psychotropic Medications

1. Before initiating pharmacotherapy, a psychiatric evaluation is completed.
2. Before initiating pharmacotherapy, a medical history is obtained and a medical evaluation is considered when appropriate.
3. The prescriber communicates with other professionals to obtain collateral history and collaborate in the monitoring of outcome and side effects during the medication trial.
4. The prescriber develops a psychosocial and psychopharmacological treatment plan based upon the best available evidence.
5. The prescriber develops a plan to monitor the patient during the medication trial.
6. The prescriber is cautious when the medication trial cannot be appropriately monitored.
7. The prescriber educates the patient and family about the patient's diagnosis and treatment plan.
8. The prescriber obtains and documents informed consent before initiating the medication trial and at appropriate intervals during the trial.
9. The informed consent process focuses on the risks and benefits of the proposed and alternative treatments.
10. The medication trial should involve an adequate dose of medication for an adequate duration.
11. The prescriber reassesses the patient if the patient fails to respond to the medication trial as expected.
12. The prescriber has a clear rationale for using medication combinations.
13. The prescriber has a specific plan for medication discontinuation.

Modified from American Academy of Child and Adolescent Psychiatry: Practice parameter on the use of psychotropic medication in children and adolescents. J Am Acad Child Adolesc Psychiatry *48(9):961–973, 2009.*

21.1 Psychopharmacology

David R. DeMaso and Heather J. Walter

Data are available regarding the safety and efficacy for the use of *single* psychotropic medications for the treatment of a number of childhood psychiatric disorders, including depressive, obsessive-compulsive, ADHD, anxiety, bipolar, psychotic, and tic disorders. Evidence also supports the use of psychotropic medications for agitation, aggression and serious problems with impulse control in disruptive/impulse-control/conduct and autism spectrum disorders.

The evidence for using multiple psychotropic medications at the same time is much smaller. Combinations of medications are used to address complex comorbid conditions, manage side effects, increase treatment response, and/or address symptoms hypothesized to be associated with multiple underlying neurotransmitter abnormalities (dopamine agonists for hyperactivity and serotonin agonists for anxiety).

To ensure safe and appropriate use of psychotropic medications, prescribers should follow best practice principles that underlie medication prescribing (Table 21-1). The use of medication involves a series of interconnected steps, including performing an assessment, deciding on treatment and a monitoring plan, obtaining treatment assent and/or consent, and implementing treatment. Cognitive, emotional, and/or behavior symptoms are targets for medication intervention when there is no response to available evidence-based psychosocial interventions, there is a significant risk of harm, and/or there is significant distress or functional impairment. Commonly encountered target symptom domains include agitation, aggression, anxiety, depression, hyperactivity, inattention, impulsivity, mania, and psychosis (Table 21-2).

Table 21-2 Target Symptom Approach to Psychopharmacologic Management

TARGET SYMPTOM	MEDICATION CONSIDERATIONS
Agitation	Atypical antipsychotic Typical antipsychotic Anxiolytic (e.g., benzodiazepine)
Aggression	Stimulant Atypical antipsychotic
Anxiety	Antidepressant Anxiolytic
Depression	Antidepressant
Hyperactivity, inattention, impulsivity	Stimulant Atomoxetine Alpha-agonist
Mania	Atypical antipsychotic
Psychosis	Atypical antipsychotic

Modified from Shaw RJ, DeMaso DR: Clinical manual of pediatric psychosomatic medicine: mental health consultation with physically ill children and adolescents, *Washington, DC, 2006, American Psychiatric Press, p. 306.*

STIMULANTS AND OTHER ADHD MEDICATIONS

Stimulants are sympathomimetic drugs that act both in the central nervous system and peripherally by enhancing dopaminergic and noradrenergic transmission (Table 21-3). There is strong evidence for the effectiveness of these medications for the treatment of ADHD (***number needed to treat*** [**NNT**] approximates 4) as well as aggression (NNT approximates 4), and moderate evidence for the treatment of hyperactivity in autism spectrum disorder. In some cases, stimulants are used as an adjunct in the treatment of depression and for fatigue

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Table 21-3 Medications for ADHD Symptoms

NAME	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	USUAL DAILY DOSAGE RANGE	SUGGESTED TOP END OF DAILY DOSAGE RANGE
STIMULANTS *Long Acting* Methylphenidate (Concerta)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	6-12: 18-54 mg >12: 18-72 mg	6-12: 54 mg >12: 72 mg
Dexmethylphenidate (Focalin XR)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	Child: 5-30 mg	Child: 30 mg
Amphetamine combination (Adderall XR)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	6-12: 5-10 mg >12: 10-20 mg	6-12: 30 mg >12: 40 mg
Dextroamphetamine (Dexedrine Spansule)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	5-40 mg	40 mg
Intermediate Acting Methylphenidate (Metadate CD, Metadate ER, Ritalin LA, Ritalin SR)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	10-60 mg	60 mg
Short Acting				
Dexmethylphenidate (Focalin)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	2.5-20 mg	20 mg
Methylphenidate (Ritalin, Methylin)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	5-30 mg	60 mg
Amphetamine combination (Adderall)	ADHD (3 and up)	Inattention Hyperactivity Impulsivity	3-5: 2.5-40 mg >6: 5-40 mg	40 mg
Dextroamphetamine (Dexedrine)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	2.5-40 mg	40 mg
SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITOR Atomoxetine (Strattera)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	<70 kg: 0.5-1.2 mg/kg >70 kg: 40-80 mg	<70 kg: 1.4 mg/kg >70 kg: 100 mg
α-AGONISTS Clonidine (Catapres)	Not approved for ADHD in children & adolescents	Inattention Hyperactivity Impulsivity	27-40.5 kg: 0.05-0.2 mg 40.5-45 kg: 0.05-0.3 mg >45 kg: 0.05-0.4 mg	27-40.5 kg: 0.2 mg 40.5-45 kg: 0.3 mg >45 kg: 0.4 mg
Clonidine (Kapvay)	ADHD (6-17)	Inattention Hyperactivity Impulsivity	0.1-0.4 mg/day	0.4 mg
Guanfacine (Tenex)	Not approved for ADHD in children & adolescents	Inattention Hyperactivity Impulsivity	27-40.5 kg: 0.5-2 mg 40.5-45 kg: 0.5-3 mg >45 kg: 0.5-4 mg	27-40.5 kg: 2 mg 40.5-45 kg: 3 mg >45 kg: 4 mg
Guanfacine (Intuniv)	ADHD (6-17)	Inattention Hyperactivity Impulsivity	1-4 mg	4 mg

ADHD, attention-deficit/hyperactivity disorder.

or malaise associated with chronic physical illnesses. There is a range of stimulant options, including those with short half-lives (typically 4 hr) and those with long half-lives (8-12 hr). The most commonly reported side effects are appetite suppression and sleep disturbances. Nervousness, headaches, abdominal pain, dizziness, palpitations, tachycardia have also been reported. More serious reactions include psychosis, mania, hypertension, dependency, and abuse. Anorexia and weight loss have been noted with controversy about their impact on ultimate height attainment.

Sudden death has been reported in association with the use of stimulants in children, although a large study did not find an increased rate of serious cardiac events.. Currently, no routine pretreatment cardiology evaluation is indicated unless the patient has a structural cardiac abnormality and/or cardiac-related symptoms; in this situation, cardiology clearance is recommended.

Atomoxetine is a selective inhibitor of presynaptic norepinephrine transporters; it increases dopamine and norepinephrine in the prefrontal cortex. It is effective in treating ADHD for 24 hr despite a plasma half-life of 4 hr. Common side effects include headache, abdominal pain, insomnia, somnolence, erectile dysfunction, irritability, fatigue, weight loss, and dizziness along with nonclinical increases in heart rate and blood pressure. More serious reactions include psychosis, mania, aggressive behavior, suicidal ideation, depression, seizures, and hepatoxicity.

The α-adrenergic agents (clonidine and guanfacine) are presynaptic adrenergic agonists that appear to stimulate inhibitory presynaptic autoreceptors in the central nervous system. These medications (see Table 21-5) have moderate evidence for the treatment of ADHD and ADHD with oppositional defiant disorder, and weak evidence for the treatment of agitation in autism. Two longer-acting preparations of each agent (Kapvay and Intuniv) have recently received FDA approval for use in ADHD. Sedation, hypotension, dry mouth, depression, and confusion are potential side effects. Abrupt withdrawal can result in rebound hypertension. Guanfacine appears to be less sedating and to have a longer duration of action than clonidine.

ANTIDEPRESSANTS

Antidepressant drugs act on pre- and postsynaptic receptors affecting the release and reuptake of brain neurotransmitters, including norepinephrine, serotonin, and dopamine (Table 21-4). There is strong evidence for the effectiveness of antidepressant medications in the treatment of anxiety and obsessive-compulsive disorders (NNT approximates 3 and 6, respectively), and weaker evidence for the treatment of depressive disorders (NNT approximates 10). Suicidal

Table 21-4 Medications for Depression and Anxiety Symptoms

NAME	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	USUAL DAILY DOSAGE RANGE	SUGGESTED TOP END OF DAILY DOSAGE
SELECTIVE SEROTONIN REUPTAKE INHIBITORS				
Citalopram (Celexa)	Not approved for anxiety & depression in children & adolescents	Depression Anxiety Obsessions/compulsions	20-40 mg	40 mg
Escitalopram (Lexapro)	Depression (12-17)	Depression Anxiety Obsessions/compulsions	10-20 mg	20 mg
Fluoxetine (Prozac)	Depression (8-17) OCD (7-17)	Depression Anxiety Obsessions/compulsions	10-60 mg	60 mg
Sertraline (Zoloft)	OCD (6-17)	Depression Anxiety Obsessions/compulsions	25-200 mg	200 mg
TRICYCLIC ANTIDEPRESSANTS				
Clomipramine (Anafranil)	OCD (10-17)	Obsessions/compulsions	25-100 mg	Lesser of 200 mg or 3 mg/kg
ATYPICAL ANTIDEPRESSANTS				
Bupropion (Wellbutrin XL)	Not approved for depression in children & adolescents	Depression	150-300 mg	450 mg
Venlafaxine (Effexor XR)	Not approved for anxiety & depression in children & adolescents	Depression Anxiety	75-225 mg	225 mg
ANXIOLYTIC AGENTS				
Lorazepam (Ativan)	Not approved for anxiety	Anxiety	0.5-6 mg	10 mg
Clonazepam (Klonopin)	Not approved for panic in children & adolescents	Panic	0.5-1 mg	4 mg
Buspirone (BuSpar)	Not approved for anxiety & depression in children & adolescents	Anxiety	15-30 mg	60 mg
Hydroxyzine (Atarax, Vistaril)	Anxiety	Anxiety	50 mg >6: 50-100 mg	<6: 2 mg/kg 50 mg >6: 100 mg

ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder.

Table 21-5 Medications for Psychosis and Agitation

NAME	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	USUAL DAILY DOSAGE RANGE	SUGGESTED TOP END OF DAILY DOSAGE
ATYPICAL ANTIPSYCHOTICS				
Aripiprazole (Abilify)	Bipolar disorder (10-17) Schizophrenia (13-17) Irritability in autism (6-17)	Psychosis Mania Irritability Aggression Agitation	2-30 mg qd	30 mg Autism: 15 mg
Olanzapine (Zyprexa)	Bipolar disorder (13-17) Schizophrenia (13-17)	Psychosis Mania Agitation	2.5-10 mg qd	20 mg
Quetiapine (Seroquel)	Bipolar disorder (10-17) Schizophrenia (13-17)	Psychosis Mania Agitation	Bipolar: 400-600 mg Schizophrenia: 400-800 mg	Bipolar: 600 mg Schizophrenia: 800 mg
Risperidone (Risperdal)	Bipolar disorder (10-17) Schizophrenia (13-17) Irritability in autism (5-17)	Psychosis Mania Aggression Agitation Irritability	0.5-6 mg Autism: 15-20 kg: 0.25 mg-0.5 mg >20 kg: 0.5-1 mg	Bipolar & Schizophrenia: 6 mg Autism: 3 mg
Ziprasidone (Geodon)	Not approved for psychosis, mania, aggression, or agitation in children & adolescents	Psychosis Mania Agitation	40-160 mg	200 mg
TYPICAL ANTIPSYCHOTICS				
Haloperidol (Haldol)	Psychosis (3-17) Tourette (3-17) Severe behavioral disorders (3-17) Agitation (3-17)	Psychosis Mania Aggression Agitation	3-12: 0.05-0.15 mg/kg >12: 0.5-5 mg Agitation: 3-12: 0.01-0.03 mg/kg >12: 0.5-10 mg	3-12: 0.15 mg/kg/day >12: maximum 100 mg for severe refractory cases

thoughts have been reported during treatment with all antidepressant medications. The overall risk difference of suicidal ideation/attempts across all randomized controlled antidepressant trials and indications has been reported to be 0.7%, corresponding to a ***number needed to harm*** of 143.

The ***selective serotonin reuptake inhibitors*** **(SSRIs)**, which, as their name suggests, inhibit the reuptake of serotonin, have a large margin of safety with no appreciable cardiovascular effects. Side effects include irritability, insomnia, appetite changes, gastrointestinal symptoms, headaches, diaphoresis, restlessness, behavioral activation, and sexual dysfunction. Withdrawal symptoms are more common in short-acting SSRIs (sertraline, citalopram, escitalopram), leading to a recommendation for divided doses if these medications are used.

The ***tricyclic antidepressants*** **(TCAs)** have mixed mechanisms of action (e.g., clomipramine is primarily serotonergic; imipramine is both noradrenergic and serotonergic). With the advent of the SSRIs, the lack of efficacy studies (particularly in depression), and more serious side effects, the use of TCAs in children has declined. They continue to be used in the treatment of some anxiety disorders (particularly obsessive-compulsive disorder) and, unlike the SSRIs, can be helpful in pain disorders. They have a narrow therapeutic index, with overdoses being potentially fatal (see Chapter 63). Anticholinergic symptoms (e.g., dry mouth, blurred vision, and constipation) are the most common side effects. TCAs can have cardiac conduction effects in doses higher than 3.5 mg/kg. Blood pressure and electrocardiographic monitoring is indicated at doses above this level.

The **atypical antidepressants** include bupropion and venlafaxine (see Table 21-4); because of their sparse evidence base, they are third-line medications (after fluoxetine and the other SSRIs) for anxiety and depressive disorders. Bupropion has also been used for smoking cessation and ADHD. Bupropion appears to have an indirect mixed agonist effect on dopamine and norepinephrine transmission. Common side effects include irritability, nausea, anorexia, headache, and insomnia. Venlafaxine has both serotonergic and noradrenergic properties. Side effects are similar to SSRIs, including irritability, insomnia, headaches, anorexia, nervousness, dizziness, and blood pressure changes.

Anxiolytic agents (including lorazepam, clonazepam, buspirone, and hydroxyzine) have all been effectively used for acute situational anxiety (see Table 21-4). Their efficacy as chronic medication is poorer, particularly when used as a monotherapy agent.

ANTIPSYCHOTICS

Based on their mechanism of action, antipsychotic medications can be divided into typical (blocking dopamine D_2 receptors) and atypical (mixed dopaminergic and serotoninergic [$5\text{-}HT_2$] activity) agents (Table 21-5).

The **atypical antipsychotics** have relatively strong antagonistic interactions with $5\text{-}HT_2$ receptors and perhaps more variable activity at central adrenergic, cholinergic, and histaminic sites, which might account for varying side effects noted among these agents. These medications have strong evidence for the treatment of agitation in autism (NNT approximates 2-7), and for the treatment of schizophrenia (NNT approximates 4-10), bipolar disorder (NNT approximates 3-4), and aggression (NNT approximates 2-5). Risperidone and aripiprazole are 2 of the most well-studied and commonly used medications in this class.

The atypical antipsychotics have significant side effects including extrapyramidal symptoms (e.g., restlessness and dyskinesias), weight gain, metabolic syndrome, diabetes, hyperlipidemia, hyperprolactinemia, hematologic adverse effects (e.g., leukopenia or neutropenia), seizures, hepatotoxicity, neuroleptic malignant syndrome, and cardiovascular effects. For all atypical antipsychotics, body mass index, blood pressure, fasting blood glucose, fasting lipid profiles, and abnormal movements should be closely monitored. If there is a family or personal history suggestive of cardiac disease, electrocardiograms should also be monitored.

Table 21-6 Medications for Mania

	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	USUAL DAILY DOSAGE RANGE	SUGGESTED TOP END OF DAILY DOSAGE
MOOD STABILIZERS				
Lithium carbonate (Eskalith, Eskalith CR, Lithobid)	Bipolar disorder (12-17)	Mania Depression	<22 kg: 600 mg 22-41 kg: 900 mg >41 kg: 1200 mg	1800 mg
Divalproex (Depakote, Depakote ER)	Not approved for mania in children & adolescents	Mania	Teen: 10-60 mg/kg *(Blood valproic acid level 50-100 μg/mL)*	60 mg/kg
ATYPICAL ANTIPSYCHOTICS				
Aripiprazole (Abilify)	Bipolar disorder (10-17) Schizophrenia (13-17) Irritability in autism (6-17)	Irritability Psychosis Mania Aggression Agitation	2-30 mg	30 mg Autism: 15 mg
Risperidone (Risperdal)	Bipolar disorder (10-17) Schizophrenia (13-17) Irritability in autism (5-17)	Psychosis Mania Aggression Agitation Irritability	0.5-6 mg Autism: 15-20 kg: 0.25 mg-0.5 mg >20 kg: 0.5-1 mg	Bipolar & Schizophrenia: 6 mg Autism: 3 mg

Haloperidol is a high-potency butyrophenone that is the typical antipsychotic most commonly used. This medication is useful in psychosis, Tourette disorder, and severe agitation. Side effects include anticholinergic effects, weight gain, drowsiness, and extrapyramidal symptoms (dystonia, rigidity, tremor, and akathisia). There is a risk of tardive dyskinesia (see Chapter 597.3) with chronic administration.

MOOD STABILIZERS

Because of their limited evidence of effectiveness and concerns about safety, mood stabilizer medications (Table 21-6) have limited use in the treatment of child and adolescent psychiatric disorders. For the treatment of bipolar mania in adolescents, atypical antipsychotics are considered first-line therapy.

Lithium's mechanism of action is not well understood; proposed theories relate to neurotransmission, endocrine effects, circadian rhythm, and cellular processes. Common side effects include polyuria and polydipsia and central nervous system symptoms (tremor, somnolence, and memory impairment). Periodic monitoring of lithium levels along with thyroid and renal function is needed. Lithium serum levels of 0.8-1.2 mEq/L are targeted for acute episodes and 0.6-0.9 mEq/L are targeted for maintenance therapy.

Valproic acid is an anticonvulsant with a therapeutic plasma concentration range of 50-100 μg/mL. Common side effects include sedation, gastrointestinal symptoms, and hair thinning. Idiosyncratic bone marrow suppression and liver toxicity have been reported, necessitating monitoring of blood counts as well as liver and kidney function.

MEDICATION USE IN PHYSICAL ILLNESS

There are special considerations in the use of psychotropic medications with physically ill children. Between 80% and 95% of psychotropic medications are protein bound, with the exceptions being lithium (0%), methylphenidate (10-30%), venlafaxine (25-30%), gabapentin (0-3%), and topiramate (9-17%). As a result, psychotropic levels may be directly affected because albumin binding is reduced in many physical illnesses. Metabolism is primarily through the liver and gastrointestinal tract, with excretion via the kidney. Therefore, dosages may need to be adjusted in children with hepatic or renal impairment.

Hepatic Disease

Lower doses of medications may be required in in patients with hepatic disease. Initial dosing of medications should be reduced and titration should proceed slowly. In steady-state situations, changes in protein binding can result in elevated unbound medication, resulting in increased drug action even in the presence of normal serum drug concentrations. Because it is often difficult to predict changes in protein binding, it is important to maintain attention to the clinical effects of psychotropic medications and not rely exclusively on serum drug concentrations.

In acute hepatitis, there is generally no need to modify dosing because metabolism is only minimally altered. In chronic hepatitis and cirrhosis, hepatocytes are destroyed and doses may need to be modified.

Medications with high baseline rates of liver clearance (e.g., haloperidol, sertraline, venlafaxine, TCAs) are significantly affected by hepatic disease. For drugs that have significant hepatic metabolism, intravenous administration may be preferred because parenteral administration avoids first-pass liver metabolic effects and the dosing and action of parenteral medications are similar to those in patients with normal hepatic function. Valproic acid can impair the metabolism of the hepatocyte disproportionate to the degree of hepatocellular damage. In patients with valproate-induced liver injury, low albumin, high prothrombin, and high ammonia may be seen without significant elevation in liver transaminases.

Gastrointestinal Disease

Medications with anticholinergic side effects can slow gastrointestinal motility, affecting absorption and causing constipation. SSRIs increase gastric motility and can cause diarrhea. SSRIs have the potential to increase the risk of gastrointestinal bleeding, especially when they are co-administered with nonsteroidal anti-inflammatory drugs. Extended-release or controlled-release preparations of medications can reduce gastrointestinal side effects, particularly where gastric distress is related to rapid increases in plasma drug concentrations.

Kidney Disease

With the exceptions of lithium and gabapentin, psychotropic medications do not generally require significant dosing adjustments in kidney failure. It is important to monitor serum concentrations in renal insufficiency, particularly for medications with a narrow therapeutic index; cyclosporine can elevate serum lithium levels by decreasing lithium excretion. Patients with kidney failure and those on dialysis appear to be more sensitive to TCA side effects, possibly because of the accumulation of hydroxylated tricyclic metabolites.

Because most psychotropic medications are highly protein-bound, they are not significantly cleared by dialysis. Lithium, gabapentin, and topiramate are essentially completely removed by dialysis, and the common practice is to administer these medications after dialysis. Patients on dialysis often have significant fluid shifts and are at risk for dehydration, with neuroleptic malignant syndrome being more likely in these situations.

Heart Disease

Cardiovascular effects of psychotropic medications can include orthostatic hypotension, conduction disturbances, and arrhythmias. Orthostatic hypotension is one of the most common cardiovascular side effects of TCAs. Trazodone can cause orthostatic hypotension and exacerbate myocardial instability; SSRIs and bupropion are preferred as antidepressant agents in patients with heart disease.

There is the potential for increased morbidity and mortality in patients with preexisting cardiac conduction problems. Some of the calcium channel-blocking agents (e.g., verapamil) can slow atrioventricular conduction and can theoretically interact with a TCA. Patients with Wolff-Parkinson-White syndrome (see Chapter 435.3) who have a short PR interval (<0.12 sec) and widened QRS interval associated with paroxysmal tachycardia are at high risk for life-threatening ventricular tachycardia that may be exacerbated by the use of a TCA. Quinidine-like effects of TCAs and the antipsychotic agents can lead to prolongation of the QTc interval, with increased risk of ventricular tachycardia and ventricular fibrillation, particularly in patients with structural heart disease. Patients with a baseline QTc interval of >440 msec should be considered at particular risk. The range of normal QTc values in children is 400 msec ± 25-30 msec. A QTc value that exceeds 2 SD (>450-460 msec) is considered too long and may be associated with increased mortality. An increase in the QTc from baseline of >60 msec is also associated with increased mortality.

Respiratory Disease

Anxiolytic agents can increase the risk of respiratory suppression in patients with pulmonary disease. SSRIs and buspirone are good alternative medications for treating anxiety. Consideration should be given to possible airway compromise due to acute laryngospasm when dopamine-blocking agents such as antipsychotic or antiemetic medications are used.

Neurologic Disease

Psychotropic medications can be used safely with epilepsy following consideration of potential interactions between the psychotropic medication, the seizure disorder, and the anticonvulsant medication. Any behavioral toxicity of anticonvulsants used either alone or in combination should be considered before proceeding with psychotropic treatment. Simplification of combination anticonvulsant therapy or a change to another agent can result in a reduction of behavioral or emotional symptoms and obviate the need for psychotropic intervention. Clomipramine and bupropion possess significant seizure-inducing properties and should be avoided when the risk of seizures is present.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome is a rare and potentially fatal reaction that can occur during treatment with antipsychotic agents (see Chapter 176). The syndrome generally manifests with fever, muscle rigidity, autonomic instability, and delirium. It is associated with elevated serum creatine phosphokinase levels, a metabolic acidosis, and high end-tidal CO_2 excretion. It has been estimated to occur in 0.2-1% of patients treated with dopamine-blocking agents. Malnutrition and dehydration in the context of an organic brain syndrome and simultaneous treatment with lithium and antipsychotic agents can increase the risk. Mortality rates may be as high as 20-30% as a result of dehydration, aspiration, kidney failure, and respiratory collapse. Differential diagnosis of neuroleptic malignant syndrome includes infections, heat stroke, malignant hyperthermia, lethal catatonia, agitated delirium, thyrotoxicosis, serotonin syndrome, drug withdrawal, and anticholinergic or amphetamine, ecstasy, salicylate toxicity.

Serotonin Syndrome

Serotonin syndrome is characterized by a triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities (see Chapter 63). It is the result of an excess agonism of the central and peripheral nervous system serotonergic receptors and can be caused by a range of drugs including SSRIs, valproate, and lithium. Drug-drug interactions that can cause serotonin syndrome include linezolid (an antibiotic that has monoamine oxidase inhibitor properties) and anti-migraine preparations used with an SSRI, as well as combinations of SSRI, trazodone, buspirone, and venlafaxine. It is generally self-limited and can resolve spontaneously after the serotonergic agents are discontinued. Severe cases require the control of agitation, autonomic instability, and hyperthermia as well as the administration of 5-HT_{2A} antagonists (e.g., cyproheptadine).

Bibliography is available at Expert Consult.

21.2 Psychotherapy

David R. DeMaso and Heather J. Walter

Psychotherapy in children may also be effective in reducing patient symptomatology. Effect sizes in research studies range from 0.71 to 0.84, which are as large as or larger than the effects of psychiatric medications or medicines for many physical illnesses. Despite benefit, only a minority of patients achieve the same level of functioning as average children, because in community settings the effect size of psychotherapy approaches zero. This poor response might reflect the fact that treatment in real-world community settings involves complex and co-occurring disorders, as opposed to the research or academic setting, where comorbid conditions are often excluded.

A variety of psychotherapeutic approaches exist with varying levels of evidence regarding their effectiveness. Differences between therapeutic approaches may be less pronounced in practice than in theory. The quality of the therapist–patient alliance consistently has been shown to be the strongest predictor of treatment outcome. A positive therapeutic relationship, expecting change to occur, facing problems assertively, increasing mastery, and attributing change to the participation in the therapy have all been connected to effective therapy.

The use of psychotherapy involves a series of interconnected steps including performing an assessment, deciding upon treatment and a monitoring plan, obtaining treatment assent or consent, and implementing treatment. Cognitive, emotional, and/or behavioral symptoms are identified that become the targets for evidence-based psychotherapeutic interventions. Psychotherapists ideally develop a treatment plan by combining known evidence-based practices about specific interventions with their clinical judgment to arrive at a specific intervention plan for the individual patient. It is not unusual for the psychotherapist to use elements from more than one treatment approach, including psychopharmacology.

BEHAVIOR THERAPY

Behavior therapy is based upon both classic (pavlovian) and operant (skinnerian) conditioning. Both of these approaches do not concern themselves with the inner motives of the individual, but instead address the antecedent stimuli and consequent responses. The treatment begins with a behavioral assessment with interview, observation, diary, and rating scale components, along with a functional analysis of the setting context, immediately preceding external events, and real-world consequences of the behavior. A treatment plan is then developed to modify the maladaptive functions of the behavior, using tools such as positive and negative reinforcement, social and tangible rewards, shaping, modeling, and prompting to increase positive behavior, and extinction, stimulus control, punishment, response cost, overcorrection, differential reinforcement of incompatible behavior, graded exposure/

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systematic desensitization, flooding, modeling, and role playing to decrease negative behavior.

Behavior therapy has shown applicability to anxiety disorders, obsessive-compulsive and related disorders, posttraumatic stress disorder, behavior disorders, ADHD, nocturnal enuresis, autism spectrum disorder, and intellectual disability.

COGNITIVE-BEHAVIORAL THERAPY

Cognitive-behavioral therapy (CBT) is based on social and cognitive learning theories and extends behavior therapy to address the influence of cognitive processes on behavior. These cognitive processes include social information processing (automatic and controlled), fixed patterns of thinking or beliefs (cognitive schema), and emotional effects mediating cognitive attributions and behavior. CBT is problem-oriented treatment that seeks to identify and change cognitive distortions (e.g., learned helplessness or irrational fears), identify and avoid distressing situations, and identify and practice distress-reducing behavior. Self-monitoring (daily thought record), self-instruction (brief sentences asserting thoughts that are comforting and/or adaptive), and self-reinforcement (rewarding oneself) are key tools used to facilitate achievement of the CBT treatment goals.

CBT has shown applicability to the treatment of behavior, depressive, and anxiety disorders. Specially modified versions of CBT have shown applicability to the treatment of other disorders. ***Trauma-focused CBT*** involves a combination of psychoeducation, teaching effective relaxation, affective modulation, and cognitive coping and processing skills, engaging in a trauma narrative, mastering trauma reminders, and enhancing future safety and development, and is considered the first-line treatment for posttraumatic stress disorder. ***Dialectical behavioral therapy*** combines standard CBT with concepts of distress tolerance, emotional regulation, interpersonal effectiveness, and mindfulness drawn from Buddhist meditative practice. Dialectical behavioral therapy has shown promise for the treatment of borderline personality disorder, bipolar disorder, suicidal behavior, and other manifestations of emotional and behavioral dysregulation.

FAMILY THERAPY

Although family therapy covers a broad range of approaches, the core idea in family therapy is that the cause of problems in individuals is thought to lie in patterns of family interaction, with other family members helping to maintain the problem. Family dysfunction can take a variety of forms, including enmeshment, disengagement, role-reversal or confusion, and maladaptive communication patterns. Family therapy begins with an assessment of the family system, including observing patterns of interaction, assessing family beliefs and the meanings attached to behaviors, defining social and cultural contexts, exploring the presenting problem in the context of individual and family development, assessing the family's style of dealing with problems, and identifying family strengths and weaknesses. Family therapy techniques are drawn from 2 major theoretical models: structural and behavioral. Structural family therapy develops capacities believed to foster well-functioning families, including clear and flexible boundaries between individuals, well-defined roles, and an appropriate balance between closeness and independence. Behavioral family therapy focuses on behavioral sequences that occur in daily life, and attempts to interrupt unhelpful patterns and strengthen positive patterns through effective communication and problem solving.

Family therapy has shown applicability to anorexia and substance abuse, and for these disorders is the treatment of choice. For other disorders (e.g., depressive, anxiety, obsessive-compulsive, and behavior), the evidence is more limited.

PSYCHODYNAMIC PSYCHOTHERAPY

At the core of psychodynamic psychotherapy lies a *dynamic* interaction between different parts or aspects of the mind. This approach is based on the belief that much of one's mental activity occurs outside one's awareness. The patient is often unaware of internal conflicts because threatening or painful emotions, impulses, and memories are repressed. Behavior is then controlled by what the patient does not know about himself or herself. Therapy objectives are to increase self-understanding, increase acceptance of feelings, shift to mature defense mechanisms, and develop realistic relationships between self and others. This therapy is nondirective to allow the patient's characteristic patterns to emerge so that self-understanding and a corrective emotional experience can then be fostered by the therapist.

Psychodynamic psychotherapy has shown applicability for the treatment of emotional problems (e.g., anxiety, depression) as well as maladaptive aspects of personality. Limited applicability has been shown for behavior, eating, and trauma-related disorders. Brief, time-limited psychodynamic psychotherapy can be appropriate for youth who are in acute situational distress, while long-term therapy can be appropriate when the biological or social factors destabilizing the child's adaptation and development are chronic, or the psychological difficulties due to comorbidities are complex, or entrenched conflicts and developmental interferences are present.

SUPPORTIVE PSYCHOTHERAPY

Supportive psychotherapy aims to minimize levels of emotional distress through the provision of individual and contextual support. Treatment is focused on the here and now. The therapist is active and helpful in providing the patient with symptomatic relief by containing anxiety, sadness, and anger. The therapist provides education and encouragement to bolster a patient's existing coping mechanisms. The therapist also facilitates problem solving and social and instrumental support for contextual symptom-generating problems.

PARENTING INTERVENTIONS

Parenting interventions are based upon attachment and social learning theory. Attachment theory proposes that the quality of care provided to the child, particularly sensitivity and responsiveness, leads to a secure or insecure attachment, which in turn influences the development of internal working models of self and others. A history of consistent and sensitive care by a parent is expected to lead to the child developing a model of self as lovable and others as loving and helpful. Social learning theory hypothesizes that children's real-life experiences and exposures directly or indirectly shape behavior, and that new positive experiences and exposures can change behavior favorably.

Parenting interventions seek to address both attachment and social learning deficits by improving both the parent–child relationship and parenting skills. Core attachment skills include spending quality time with the child, increasing verbal interaction, showing physical affection, providing contingent praise, and engaging in child-directed play. Core parenting skills include increasing reinforcement of positive behaviors, decreasing reinforcement of negative behaviors, applying consequences for dangerous/destructive behavior, and making parental response predictable, contingent, and immediate.

Parenting interventions have shown applicability for the behavior disorders and ADHD.

Bibliography is available at Expert Consult.

21.3 Psychiatric Hospitalization

David R. DeMaso and Heather J. Walter

Psychiatric hospital programs are meant to address the serious risks and severe impairments caused by the most acute and complex forms of psychiatric disorder that cannot be managed effectively at any other level of care. Their goal is to produce rapid clinical stabilization that allows an expeditious, safe, and appropriate treatment transition to a less-intensive level of mental healthcare outside of the hospital.

High levels of illness severity combined with significant functional impairment signal a need for hospitalization. Admission criteria must include significant signs and symptoms of active psychiatric disorder(s). Functional admission indicators generally include a significant risk of self-harm and/or harm to others, although in some cases the patient is unable to meet basic self-care or healthcare needs, jeopardizing

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well-being. Serious emotional disturbances that prevent participation in family, school, or community life can also rise to a level of global impairment that can only be addressed on an inpatient basis.

Discharge planning begins at the time of admission, when efforts are made to coordinate care with services and resources that are already in place for the child or adolescent in the community. Step-down care might be needed in partial hospital or residential settings if integrated services in a single location remain indicated after sufficient clinical stabilization has occurred in the hospital setting. Transition from the hospital entails active collaboration and communication with pediatric practitioners in the child's medical home.

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Chapter 22

Somatic Symptom and Related Disorders

Patricia I. Ibeziako and David R. DeMaso

Pediatric psychosomatic medicine deals with the relation between physiologic and psychological factors in the causation or maintenance of disease states. The process whereby distress is experienced and/or expressed in physical symptoms is referred to as ***somatization*** or ***psychosomatic illness***. Even though somatic symptoms are present in virtually every psychiatric disorder, they are most prominent in the various somatic symptom disorders.

In the *Diagnostic Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), illnesses previously referred to as somatoform disorders are defined as ***somatic symptom disorders***. Somatic symptom disorders are classified on the basis of distressing physical symptoms and excessive thoughts, feelings or behaviors in relation to these symptoms rather than the absence of a medical explanation for somatic symptoms. These disorders form a continuum that can range from pain to disabling neurological symptoms and they generally interfere with school, home life and peer relationships. The DSM-5 Somatic Symptom and Related Disorders category includes the following disorders related to children and adolescents: ***conversion disorder*** (or functional neurologic symptom disorder), ***somatic symptom disorder***, ***factitious disorder***, ***psychological factors affecting other medical conditions***, and ***other specified/unspecified somatic symptom disorders*** (Tables 22-1 through 22-5 identify the DSM-5 diagnostic criteria).

Multiple terms used to describe somatic symptom disorders include "functional," "psychosomatic," or "medically unexplained symptoms." Additionally, most patients are seen by general practitioners and specialists and may receive specialty-specific syndrome diagnoses such as visceral hyperalgesia, irritable bowel syndrome, chronic fatigue syndrome, or noncardiac chest pain. The diagnostic heterogeneity that exists across the different medical specialists contributes to the different diagnostic labels. Studies indicate a significant overlap in the symptoms and presentation of patients with somatic symptoms who have received different diagnoses from different specialties.

Moreover, functional syndromes share similarities in etiology, pathophysiology, neurobiology, psychological mechanisms, patient characteristics, and management and treatment response, which is indicative of a single spectrum of disorders. It is helpful for healthcare providers to avoid the dichotomy of approaching illness using a medical model in which diseases are considered as being either organic

Table 22-1 DSM-5 Diagnostic Criteria for Conversion Disorder or Functional Neurologic Symptom Disorder

A. One or more symptoms or deficits affecting voluntary motor or sensory function.
B. Clinical findings provide evidence of incompatibility between the symptom and recognized neurologic or medical conditions.
C. The symptom or deficit is not better explained by another medical or mental disorder.
D. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

Specify symptom type: weakness or paralysis, abnormal movements, swallowing symptoms, speech symptom, attacks/seizures, or anesthesia/sensory loss, special sensory symptom (visual, olfactory, or hearing), or mixed symptoms.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 318.

Table 22-2 DSM-5 Diagnostic Criteria for Somatic Symptom Disorder

A. One or more somatic symptoms that are distressing or result in significant disruption of daily life.
B. Excessive thoughts, feelings or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following:
   1. Disproportionate and persistent thoughts about the seriousness of one's symptoms.
   2. Persistent high level of anxiety about health and symptoms.
   3. Excessive time and energy devoted to these symptoms or health concerns.
C. Although any 1 somatic symptom may not be continuously present, the state of being symptomatic is persistent.

Specify if:

With predominant pain (previously known as pain disorder in DSM IV-TR): for individuals whose somatic symptoms predominantly involve pain.

Persistent: A persistent course is characterized by severe symptoms, marked impairment, and long duration (more than 6 mo).

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 311.

Table 22-3 DSM-5 Diagnostic Criterial for Psychological Factors Affecting Other Medical Conditions

A. A medical symptom or condition (other than a mental disorder) is present.
B. Psychological or behavioral factors adversely affect the medical condition in 1 of the following ways:
   1. The factors have influenced the course of the medical condition as shown by a close temporal association between the psychological factors and the development or exacerbation of, or delayed recovery from, the medical condition.
   2. The factors interfere with the treatment of the medical condition (e.g., poor adherence).
   3. The factors constitute additional well-established health risks for the individual.
   4. The factors influence the underlying pathophysiology, precipitating or exacerbating symptoms or necessitating medical attention.
C. The psychological and behavioral factors in Criterion B are not better explained by another mental disorder (e.g., panic disorder, major depressive disorder, posttraumatic stress disorder).

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 322.

Table 22-4 DSM-5 Diagnostic Criteria for Factitious Disorders

Factitious Disorder Imposed on Self

A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with identified deception.
B. The individual presents himself or herself to others as ill, impaired, or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.
D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Factitious Disorder Imposed on Another (Previously Factitious Disorder by Proxy)

A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, in another, associated with identified deception.
B. The individual presents another individual (victim) to others as ill, impaired or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.
D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Note: The perpetrator, not the victim, receives this diagnosis

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 324.

Table 22-5 DSM-5 Diagnostic Criteria for Other Specified/Unspecified Somatic Symptom and Related Disorders

Other Specified

This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet full criteria for any of the disorders in the somatic symptom and related disorders diagnostic class.

Examples of presentations that can be specified using the "other specified" designation include the following:

1. Brief somatic symptom disorder: Duration of symptoms is <6 mo.
2. Brief illness anxiety disorder: Duration of symptoms is <6 mo.
3. Illness anxiety disorder without excessive health-related behaviors: Criterion D for illness anxiety disorder is not met.
4. Pseudocyesis: A false belief of being pregnant that is associated with objective signs and reported symptoms of pregnancy.

Unspecified

This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in functioning predominate but do not meet criteria for any of the other disorders in the somatic symptom and related disorders diagnostic class.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 327.

or psychologically based. In contrast, a biobehavioral continuum of disease characterizes illness as occurring across a spectrum ranging from a biologic etiology on one end to predominantly a psychosocial etiology on the other.

EPIDEMIOLOGY

Between 10% and 30% of children worldwide experience physical symptoms that are described as "functional" or unexplained by a physical illness. Estimated prevalence varies greatly between studies based on the type of symptoms and the study methodology. The frequency and heterogeneity of complaints increase with age with symptoms occurring more frequently in females.

The majority of children with persistent complaints of abdominal pain meet criteria for functional abdominal pain or somatic symptom disorder with predominant pain in DSM-5. In a prospective study, patients with functional abdominal pain carry long-term vulnerability to anxiety that begins in childhood and persists into late adolescence and early adulthood, even if abdominal pain resolves.

Headaches, back pain, limb pain and chest pain, as well as other gastrointestinal symptoms, are also frequently occurring pain symptoms in adolescents. Prevalence rates of conversion disorder in adolescents are 0.3-10%. Nonepileptic seizures, loss of consciousness, and motor conversion symptoms are common somatic neurologic complaints across cultures.

RISK FACTORS

Family and Environmental

Genetic

A possible genetic etiology in somatization disorders is suggested by findings of a 29% concordance rate in monozygotic twin studies and 10-20% of 1st-degree relatives of patients meeting criteria for this disorder. Further evidence is seen in studies showing a familial link between somatic symptom disorders and other psychiatric disorders (e.g., higher rates of anxiety and depression in the family members).

Symptom Modeling

Multiple studies have found evidence that a significant proportion of patients with somatic symptom disorders had recently encountered similar symptoms in their local environment or live with family members who complain of similar physical symptoms (e.g., a child with nonepileptic seizures who has a parent or sibling with a seizure disorder).

Parental Responses

Parent beliefs about the significance of symptoms influence the amount of symptoms the child reports. Having a somatic complaint may be more acceptable or noticed in some households than the expression of strong emotions (e.g., anxiety, fear or anger). In such an environment, a child may garner minimal attention for emotional distress, but obtain more attention and sympathy for physical symptoms. Multiple studies have shown that parental protectiveness predicts child functional disability and parental responses (e.g., discouraging activity, expressing concern, and providing comfort) may serve to inadvertently reinforce and maintain illness behaviors.

School and Family Stressors

External environmental factors (e.g., school stress or change in family situation) are common in children presenting with somatic symptom disorders. Common school stressors include bullying, beginning the school year, fear of academic failure, or participation in extracurricular school activities. Dysfunction and less support within the family system are common in somatic symptom disorders. A transition within the family system including death of a family member, birth of a sibling, parental divorce, physical punishment by parents and an increase in the number of arguments between parents have all been linked to somatic symptoms. Nevertheless, there is a significant minority of patients with somatic symptom disorders who do not appear to have obvious psychosocial precipitants for their symptoms. It is unclear whether the absence of recorded stressful events in these patients is because they were unwilling or unable to report relevant stressors or if they were simply absent.

Trauma

Elevated rates of childhood trauma (e.g., childhood sexual, physical, or emotional abuse) have been found in patients with somatic symptom disorders although the trauma prevalence rates in studies vary widely.

Individual

Childhood Physical Illness

There does appear to be a connection between childhood physical illness and the later development of somatization. Many children with somatic symptom disorders have other medical conditions. An antecedent history (e.g., of an accident, viral illness) may trigger onset of symptoms and lead to prolonged recovery or recurrence of symptoms after illness should have subsided. Children who tend to somatize may have a tendency to experience normal somatic sensations as "intense, noxious and disturbing," referred to as *somatosensory amplification*. Children with somatic symptom disorders may also have histories of disabling and poorly explained physical symptoms.

Temperament/Coping Styles

Somatic symptoms have been found to be more common in children who are conscientious, sensitive, insecure, internalizers, anxious, and in those who strive for high academic achievement. Somatization may also occur in youngsters who are unable to verbalize emotional distress. Somatic symptoms are often seen as a form of psychological defense against intrapsychic distress that allows the child to avoid confronting anxieties or conflicts, a process referred to as *primary gain*. "Primary gain" is obtained by keeping the conflict from consciousness and minimizing anxiety. The symptoms may also lead to what is described as "secondary gain" if the symptom results in the child being allowed to avoid unwanted responsibilities or consequences.

Learned Behavior

Somatic complaints may be reinforced (e.g., through a decrease in responsibilities or expectations by others and/or through receiving attention and sympathy as a result of the physical symptoms). Many youngsters may have an antecedent underlying general medical condition that may then be reinforced by parental and/or peer attention as well as additional medical attention in the form of unnecessary tests and investigations.

Psychiatric Comorbidity

There is an association between somatization and other psychiatric illness, in particular depressive and anxiety disorders.

Other Biologic Factors

Research into the pathophysiology of somatic symptom disorders has suggested some unifying mechanisms, including aberrant functions of efferent neural pathways, such as the autonomic nervous system and the hypothalamic–pituitary axis, and alterations in central processing of sensory input. Hyperactivity of the anterior cingulate cortex has been found in patients with conversion disorder, along with impaired activity of the dorsolateral prefrontal cortex. In studies of chronic pain, including migraine and tension type headache, there appears to be progressive loss of gray matter density in brain structures involved in registering pain such as the somatosensory cortex, anterior cingulate cortex and insula. Additionally when there is a strong expectation of pain, the anterior insular cortex is activated in proportion to this expectation.

ASSESSMENT

The majority of patients with somatic symptom and related disorders present in the pediatric rather than mental health settings. It is important for pediatricians to make their diagnosis on the basis of positive symptoms and signs (distressing somatic symptoms plus abnormal thoughts, feelings, and behaviors in response to these symptoms) rather than the absence of a medical explanation. As such, the evaluation of suspected disorders should include an assessment of biologic, psychological, social, and developmental realms both separately and in relation to each other. An integrated approach where both pediatric and mental health clinician are involved in the assessment, management, and treatment is indicated.

Medical

The presence of a physical illness does not exclude the possibility of somatization playing an important role in the child's presentation. Somatic symptoms early in a disease course that can be directly attributed to a specific physical illness (e.g., acute respiratory illness) may evolve into psychologically based symptoms, particularly in situations in which the child may experience benefit from adopting the sick role. Somatic symptoms may also occur in excess of what would be expected of the symptoms experienced in an existing physical illness. Physical findings may occur secondary to the effects of the somatic symptom disorder, especially when chronic and/or severe (e.g., deconditioning, disuse atrophy and contractures from prolonged immobilization, nutritional deficiency, gastroparesis and constipation from chronic poor oral intake.)

A comprehensive medical work-up to rule out serious physical illness must be carefully balanced with efforts to avoid unnecessary and potentially harmful tests and procedures. The physical examination will find that the child's symptoms may fluctuate in different contexts, may be anatomically inconsistent or may be in excess of what would be expected from the physical findings.

Psychological

If somatization is suspected, psychiatric consultation should be included early in the diagnostic workup. The reason for consultation should be carefully explained to the family to help avoid the perception that their child's symptoms are not being taken seriously by the pediatric team (i.e., "it's in her head"). It should be explained that a complete work-up involves a thorough assessment of the physical and psychological domains of the child and the psychiatric consultation can provide further understanding of the origins of the child's distress, what perpetuates it and which treatments are likely to be most effective.

The mental health interview should include a careful assessment of the psychological and social stressors and risk factors including a thorough family psychiatric and medical history. The nature of current physical symptoms and any history of prior episodes of somatic symptoms should be included in the assessment, in addition to the child's emotional, social and academic functioning, coping strategies and family functioning. The evaluation should provide the clinical team with a biopsychosocial explanation of the child's symptoms, which will inform the treatment plan.

Differential Diagnoses

The primary differential diagnosis is between that of somatic symptom disorder and a physical illness. It is important, however, to be aware that these disorders are not mutually exclusive and often coexist. Mood and anxiety disorders frequently include the presence of physical symptoms which tend to remit with treatment of the primary mood or anxiety symptoms and which appear distinct from physical complaints seen in somatic symptom disorders. Chronic pain syndromes may be caused by fibromyalgia and small fiber autonomic neuropathy (see Chapter 168).

MANAGEMENT

With the completion of medical and psychological assessments, a multidisciplinary team meeting of medical and mental health clinicians should be arranged to review all the specialty evaluations and tests, discuss the formulation, diagnostic impressions and treatment recommendations. This should occur to ensure that a consensus has been reached regarding the diagnosis and treatment plan and to facilitate adequate and consistent communication among all providers.

An informing meeting or conference with the family should be facilitated after the above meeting to convey the multidisciplinary team's diagnostic impressions and treatment recommendations to the patient/family. Medical and mental health clinicians together should communicate the diagnosis (or diagnoses) in a way that families can understand using a comprehensive biopsychosocial formulation. Medical and psychiatric findings should be acknowledged and discussed. Patients and families with somatic symptom disorders often present with the belief that there is primarily a medical cause for their problem and psychosocial contributors are often resisted. Following exhaustive medical investigations which do not yield any unifying

results, labeling the symptoms as "psychiatric" can effectively shift the search for the cause onto family functioning, resulting in youngsters and parents feeling blamed for the symptoms. The team should help the family move towards an understanding of the mind–body connection and shift their approach from searching for the cause of the symptoms to increasing functioning. Providing education about the benefits of treatment and risks of nontreatment is helpful to move the family through the treatment steps.

Treatment

An integrated multidisciplinary rehabilitation model is the most suitable for patients with somatic symptom disorders. A rehabilitation model approach provides a useful framework for the treatment that shifts the focus away from finding a cure for symptoms, and instead emphasizes a return to normal adaptive functioning. This includes increased activities of daily living, improved nutrition, enhanced mobility, return to school and socialization with peers.

Cognitive behavioral interventions are evidence-based treatments of choice. Cognitive behavioral interventions modify symptom experience including pain perception and restore central nervous system abnormalities that are linked with functional impairment. Components of cognitive behavioral techniques (e.g., relaxation training, biofeedback, and hypnosis) can be used to teach patients the control they can have over certain physiological processes such as autonomic system activity. Cognitive restructuring is effective in addressing and altering dysfunctional thoughts regarding symptoms and their implications for functioning. Treatments that encourage active coping strategies, emotional expression and modulation and limit adolescent reliance on emotional support provided by parents are particularly helpful to more effectively reduce symptoms and improve functioning. Modifying parental response patterns that are overly protective and potentially reinforcing (e.g., allowing the child to sleep late or to stay home from school in response to symptoms) help to decrease disability.

Psychopharmacologic treatment may be considered when other psychiatric disorders are co-occurring, specifically depressive and anxiety disorders. A combination of pharmacotherapy, physical therapy, and psychological interventions in multicomponent management programs has been shown to be effective.

Treatment Setting

The majority of patients can be managed in the outpatient setting with appropriate mental health follow-up. Scheduled follow up visits with the primary care provider (PCP) and other specialists are important to maintain alliance and investment in treatment, prevent doctor shopping, and avoid unnecessary invasive tests and procedures.

Because of the nature of their symptoms, most patients with somatic symptom disorders do not present in mental health settings for their physical complaints and only patients displaying prominent emotional symptoms or who have a concurrent mental disorder are referred to psychiatric services. Medical specialists treat "their own" specialty functional somatic syndrome within their service as a natural consequence of the large number of patients with these disorders presenting at their clinics. The management in these clinics is often monodisciplinary and with primarily medically based treatments and interventions. The existence of various syndrome-specific clinics perpetuates the separate, specialty-dominated approach to somatic symptom disorders and can perpetuate fragmented care rather than moving toward a more integrated model. Although specialized clinics play an important role in the provision of the expertise needed in the evaluation of these patients, they are often not prepared to manage patients who have symptoms involving multiple organ systems. These patients may attend several clinics simultaneously and receive several, parallel, uncoordinated treatments.

A medical home model with mental health clinicians working in collaboration with PCPs and/or different medical specialists may prove to be the most suitable approach for patients with somatic symptom disorders. Collocated medical and mental health services improve communication, decrease fragmentation of services, and decrease the stigma and resistance some families may have with attending psychiatric clinics. The efficacy of a treatment program with comprehensive multidisciplinary services and cognitive behavioral treatment has been studied in a randomized, controlled trial, and the results showed immediate, clinically relevant benefits that were sustained at the 1-year follow-up.

Patients with profound and pervasive functional impairment likely will need more intensive psychiatric treatment (e.g., a medical-psychiatric partial hospital program or inpatient unit). Multidisciplinary inpatient rehabilitation programs have a great deal to offer these patients as they are designed to support both physical and psychological recovery. Families feel reassured that multidisciplinary staff can continue to monitor symptoms, thus ensuring that any missed diagnoses will be recognized quickly.

Children with a high level of impairment often miss a significant amount of school; communication with the school in such cases is often crucial in helping a successful transition back and improving overall functioning. In addition to discussions with the school guidance counselor and nurse, a letter for the school providing education and recommended approaches for patient's symptoms is often beneficial. Ongoing communication between the school and PCP for monitoring of further symptoms is recommended.

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Chapter 23

Rumination and Pica

Emily R. Katz, Robert L. Kitts, and David R. DeMaso

23.1 Rumination Disorder

Emily R. Katz, Robert L. Kitts, and David R. DeMaso

Rumination disorder is the repeated regurgitation of food, where the regurgitated food may be rechewed, reswallowed, or spit out, for a period of at least 1 mo following a period of normal functioning. Regurgitation is typically frequent and daily; it does not occur during sleep. It is not caused by an associated gastrointestinal illness or other medical condition (e.g., gastroesophageal reflux or pyloric stenosis). It does not occur exclusively during the course of anorexia nervosa, bulimia nervosa, binge-eating disorder, or avoidant/restrictive food intake disorder. If the symptoms occur in the context of an intellectual developmental disorder or another neurodevelopmental disorder, they must be sufficiently severe to warrant additional clinical attention.

Weight loss and failure to make expected weight are common features in infants with rumination disorder. Infants may display a characteristic position of straining and arching the back with the head held back, making sucking movements with their tongue. In infants and older individuals with intellectual disability, the rumination behavior may appear to have a self-soothing or self-stimulating function. Malnutrition may occur in older children and adults, particularly when the regurgitation is associated with restricted food intake (which may be designed to avoid regurgitation in front of others). They may attempt to hide the regurgitation behavior or avoid eating among others.

EPIDEMIOLOGY

Originally thought of as a disorder predominantly seen in infants and those with intellectual disability, rumination disorder has also been recognized in healthy individuals across the life span. Prevalence data

for rumination disorder are inconclusive. In otherwise healthy children, this disorder typically appears in the first year of life, generally between the ages of 3 and 12 mo. The disorder can have an episodic course or occur continuously until treatment is initiated. In infants, the disorder frequently remits spontaneously, but can be protracted with problematic and even life-threatening malnutrition. Additional complications related to the secondary effects of malnutrition included growth delay and negative effect on development and learning potential.

ETIOLOGY AND DIFFERENTIAL DIAGNOSIS

Risk factors for rumination disorder in infants and young children include a disturbed relationship with primary caregivers, lack of an appropriately stimulating environment, neglect, stressful life situations, learned behavior reinforced by pleasurable sensations, distraction from negative emotions, and/or inadvertent reinforcement (attention) from primary caregivers. The differential diagnosis includes congenital gastrointestinal system anomalies, pyloric stenosis (see Chapter 329), Sandifer syndrome (see Chapter 323), gastroparesis, hiatal hernia (see Chapter 322), increased intracranial pressure, diencephalic tumors, adrenal insufficiency, and inborn errors of metabolism. Older children and adults with anorexia nervosa or bulimia nervosa may also engage in regurgitation because of concerns about weight gain. The diagnosis of rumination disorder is appropriate only when the severity of the disturbance exceeds that routinely associated with a concurrent physical illness or mental disorder.

TREATMENT

This first step in treatment begins with a behavioral analysis to determine if the disorder serves as a self-stimulation purpose and/or is socially motivated. The behavior may begin as self-stimulation, but it subsequently becomes reinforced and maintained by the social attention given to the behavior. The central focus of behavioral treatment is to reinforce correct eating behavior while minimizing attention to rumination. Diaphragmatic breathing and postprandial gum chewing when used as a competing response have been shown to be helpful. Aversive conditioning techniques (e.g., withdrawal of positive attention) are considered when a child's health is jeopardized.

Successful behavioral treatment requires the child's primary caregivers to be involved in the intervention. The caretakers need education and counseling around responding adaptively to the child's behavior as well as altering any maladaptive responses. There is no current evidence supporting a psychopharmacologic intervention for this disorder. In more severe or intractable cases (e.g., severe dehydration and malnutrition), an intensive integrated medical-behavioral treatment program afforded on a medical or medical-psychiatric unit may be necessary.

Bibliography is available at Expert Consult.

23.2 Pica

Emily R. Katz, Robert L. Kitts, and David R. DeMaso

Pica involves the persistent eating of nonnutritive, nonfood substances (e.g., paper, soap, plaster, charcoal, clay, wool, ashes, paint, earth) over a period of at least 1 mo. The eating behavior is inappropriate to the developmental level (e.g., the normal mouthing and tasting of objects in infants and toddlers) and, therefore, a minimum age of 2 yr is suggested. The eating behavior is not part of a culturally supported or socially normative practice. A diagnosis of pica may be assigned in the presence of any other feeding and eating disorder.

EPIDEMIOLOGY

Pica can occur throughout the lifetime, but occurs most commonly in childhood. It appears to be more common in those with intellectual disability and autism spectrum disorders, and to a lesser degree in obsessive-compulsive and schizophrenic disorders. The prevalence of pica is unclear, although it appears to increase with the severity of an intellectual disability. It usually remits in childhood but can continue into adolescence and adulthood. *Geophagia* (eating earth) is associated with pregnancy and is not seen as abnormal in some cultures (e.g., rural or preindustrial societies in parts of Africa and India). Children with pica are at increased risk for lead poisoning (see Chapter 721), iron-deficiency anemia (see Chapter 455), mechanical bowel problems, intestinal obstruction, intestinal perforations, dental injury, and parasitic infections. It can be fatal based on substances ingested.

ETIOLOGY AND DIFFERENTIAL DIAGNOSIS

Numerous etiologies have been proposed but not proved, ranging from psychosocial causes to physical ones. They include nutritional deficiencies (e.g., iron, zinc, and calcium), low socioeconomic factors (e.g., lead paint exposure), child abuse and neglect, family disorganization (e.g., poor supervision), mental disorder, learned behavior, underlying (but undetermined) biochemical disorder, and cultural and familial factors. The differential diagnosis includes anorexia nervosa (see Chapter 28), factitious disorder, and nonsuicidal self-injury in personality disorders. A separate diagnosis of pica should be made only if the eating behavior is sufficiently severe enough to warrant additional clinical attention.

TREATMENT

Combined behavioral, social, and medical approaches are generally indicated for pica. Assessment for neglect and family supervision combined with a psychiatric assessment for cooccurring mental disorders and developmental delay are important in developing an effective intervention strategy for pica. Behavioral treatment interventions, particularly applied behavioral analysis in patients with intellectual disability or autism spectrum disorders, have increasing evidence for being helpful. The sequelae related to an ingested item can require specific treatment (e.g., lead toxicity, iron-deficiency anemia, parasitic infestation). Ingestion of hair can require medical or surgical intervention for a gastric bezoar (see Chapter 334.2).

Bibliography is available at Expert Consult.

23.3 Enuresis (Bed-Wetting)

See Chapter 543.

23.4 Encopresis

See Chapter 332.2.

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Chapter 24

Motor Disorders and Habits

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Motor disorders are interrelated sets of psychiatric symptoms characterized by abnormal motor movements and associated phenomena. In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), motors disorders include tic, stereotypic movement, and developmental coordination disorders. Tic disorders (Tourette, persistent motor or vocal tic, provisional tic) and stereotypic movement

disorder will be addressed in this chapter. Although not DSM-5 motor disorders, habits present as repetitive and often problematic motor behaviors (specifically thumb sucking and teeth grinding).

24.1 Tic Disorders

Colleen A. Ryan, Michael L. Trieu, David R. DeMaso, and Heather J. Walter

Tourette disorder **(TD),** ***persistent (chronic) motor or vocal tic*** **(PTD),** and provisional tic disorders (Table 24-1) are characterized by involuntary, rapid, repetitive, single or multiple motor and/or vocal/phonic tics that wax and wane in frequency but have persisted for more than 1 year since first tic onset (<1 year for provisional tic disorder). PTD is differentiated from TD in that PTD is limited to either motor or vocal tics (not both), whereas TD has both motor and vocal tics at some point in the illness (although not necessarily concurrently). The tic disorders are hierarchical in order (i.e., TD followed by PTD followed by provisional tic disorder), such that once a tic disorder at one level of the hierarchy is diagnosed, a lower hierarchy diagnosis cannot be made.

DESCRIPTION

Tics are sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations. Simple motor tics (e.g., eye blinking, neck jerking, shoulder shrugging, extension of the extremities) are fast, brief movements involving one or a few muscle groups, while complex motor tics involve sequentially and/or simultaneously produced relatively coordinated movements that can seem purposeful (e.g., brushing back one's hair bangs, tapping the foot, imitating someone else's movement [echopraxia], or making a sexual or obscene gesture [copropraxia]). Simple vocal tics (e.g., throat clearing, sniffing, coughing) are solitary, meaningless sounds and noises, whereas complex vocal tics (e.g., partial words [syllables], words out of context, coprolalia [obscenities or slurs], palilalia [repeating one's own sounds or words], or echolalia [repeating the last heard word or phrase]) are meaningful utterances and verbalizations.

Sensory phenomena (premonitory urges) that precede and trigger the urge to tic have been described. Individuals with tics can suppress them for varying periods of time, particularly when external demands exert their influence, when deeply engaged in a focused task or activity, or during sleep. Tics are often suggestible and are worsened by anxiety, excitement, or exhaustion. Although parents have described increasing frequency of tics at the end of the day, research has not supported volitional suppressing of tics leading to tic rebound.

Table 24-1 DSM-5 Diagnostic Criteria for Tic Disorders

Note: A tic is a sudden, rapid, recurrent, nonrhythmic motor movement or vocalization.

TOURETTE'S DISORDER

A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).

PERSISTENT (CHRONIC) MOTOR OR VOCAL TIC DISORDER

A. Single or multiple motor or vocal tics have been present during the illness, but not both motor and vocal.
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).
E. Criteria have never been met for Tourette's disorder.

Specify if:
With motor tics only
With vocal tics only

PROVISIONAL TIC DISORDER

A. Single or multiple motor and/or vocal tics.
B. The tics have been present for less than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).
E. Criteria have never been met for Tourette's disorder or persistent (chronic) motor or vocal tic disorder.

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 81.

CLINICAL COURSE

Onset of tics is typically between ages 4 and 6 yr. Peak severity occurs between ages 10 and 12 yr, with marked attenuation of tic severity in most individuals (65%) by age 18-20 yr. A small percentage will have worsening tics into adulthood. New onset of tics in adulthood is very rare and most often is associated with exposure to drugs or insults to the central nervous system. Tics manifest similarly in all age groups and change in affected muscle groups and vocalizations over time. Some individuals may have tic-free periods of weeks to months.

EPIDEMIOLOGY

Prevalence rates for all tics range from 6-18% for boys and 3-11% for girls, with the rate of TD alone estimated as 0.3-0.8%. In general, PTD/TD has a male preponderance with a gender ratio varying from 2 : 1 to 4 : 1. Evidence supports higher rates in white compared to African-American or Hispanic youth.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes the repetitive movements of childhood (Table 24-2). Tics may be difficult to differentiate from stereotypies. Although stereotypies may resemble tics, stereotypies are typically rhythmic movements and do not demonstrate the change in body location or movement type over time that is typical of tics. Compulsions may be difficult to differentiate from tics when tics have premonitory urges. Tics should be differentiated from a variety of developmental and benign movement disorders (e.g., benign paroxysmal torticollis, Sandifer syndrome, benign jitteriness of newborns, and shuddering attacks). Tics may present in various neurologic illnesses (e.g., Wilson disease, neuroacanthocytosis, Huntington syndrome, and a variety of frontal-subcortical brain lesions); it is rare for tics to be the only manifestation of these disorders. Individuals presenting with tics in the context of declining motor or cognitive function should be referred for neurologic assessment. Some substances/medications that are reported to worsen tics include stimulants, selective serotonin reuptake inhibitors, lamotrigine, and cocaine. If tics develop in close temporal relationship to the use of a substance/medication and then remit when use of the substance is discontinued, a causal relationship is possible. Although a long-time clinical concern, there is no scientific evidence in controlled studies that stimulants increase tics.

COMORBIDITIES

Co-occurring psychiatric disorders are common, often with both the patient and family viewing the accompanying condition as more problematic than the tics per se. There is a bidirectional association between PTD/TD (especially TD) and obsessive-compulsive disorder (OCD; see Chapter 25), with 20-60% of TD patients meeting OCD criteria and 20-40% of OCD patients reporting tics (Fig. 24-1). Attention-deficit/hyperactivity disorder (ADHD; see Chapter 33) co-occurs in approximately 50% of all childhood PTD/TD, but estimates

Table 24-2 Repetitive Movements of Childhood

	DESCRIPTION	TYPICAL DISORDERS WHERE PRESENT
Tics	Sudden rapid, recurrent, nonrhythmic, stereotyped, vocalization or motor movement	Transient tics, Tourette disorder, persistent tic disorder
Dystonia	Involuntary, sustained, or intermittent muscle contractions that cause twisting and repetitive movements, abnormal postures, or both	DYT1 Gene, Wilson, myoclonic dystonia, extrapyramidal symptoms caused by dopamine blocking agents
Chorea	Involuntary, random, quick, jerking movements, most often of the proximal extremities, that flow from joint to joint. Movements are abrupt, nonrepetitive, and arrhythmic and have variable frequency and intensity	Sydenham chorea, Huntington chorea
Stereotypies	Stereotyped, rhythmic, repetitive movements or patterns of speech, with lack of variation over time	Autism, stereotypic movement disorder, intellectual disability
Compulsions	A repetitive, excessive, meaningless activity or mental exercise that a person performs in an attempt to avoid distress or worry	Obsessive-compulsive disorder, anorexia, body dysmorphic disorder, trichotillomania, excoriation disorder
Myoclonus	Shock-like involuntary muscle jerk that may affect a single body region, one side of the body, or the entire body; may occur as a single jerk or repetitive jerks	Hiccups, hypnic jerks, Lennox-Gastaut syndrome, juvenile myoclonic epilepsy, mitochondrial encephalopathies, metabolic disorders
Akathisia	Unpleasant sensations of "inner" restlessness, often prompting movements in an effort to reduce the sensations	Extrapyramidal adverse effects from dopamine blocking agents; anxiety
Volitional behaviors	Behavior that may be impulsive or due to boredom like tapping peers, making sounds (animal noises)	Attention-deficit/hyperactivity disorder, oppositional defiant disorder, sensory integration disorders

Adapted from Murphy TK, Lewin AB, Storch EA, et al: Practice parameter for the assessment and treatment of children and adolescents with chronic tic disorders, J Am Acad Child Adolesc Psychiatry *52(12):1341–1359, 2013.*

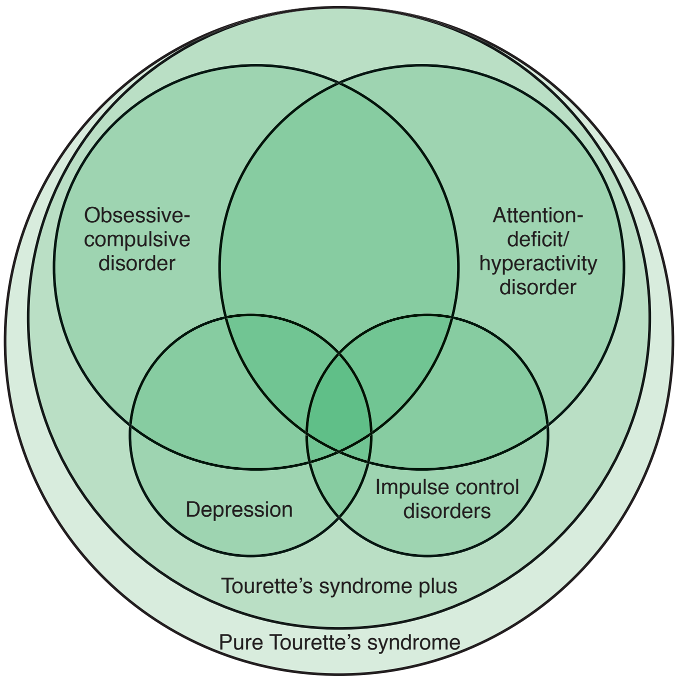

Figure 24-1 **Schematic representation of the behavioral spectrum in Tourette syndrome.** The size of each area is proportional to the estimated prevalence of the symptoms; the background color intensity is proportional to the complexity of the clinical presentation. *From Cavanna AE, Seri S: Tourette's syndrome. BMJ 347:f4964, 2013.*

in clinically referred patients suggest much higher rates (60-80%). PTD/TD is often accompanied by behavior problems including poor frustration tolerance, temper outbursts, and oppositionality. Learning disabilities have been found in more than 20% of these patients. The co-occurrence of anxiety and depression also has been observed. Some patients with PTD/TD will display symptoms of ***autism spectrum disorders*** (**ASDs**; see Chapter 30); careful assessment is required to determine which disorder is primary.

ETIOLOGY

Tics are proposed to be the result of dysfunctional corticostriatal–thalamocortical motor pathways in the basal ganglia, striatum, and frontal lobes associated with abnormalities in the dopamine, serotonin and norepinephrine neurotransmitter systems. Male predominance in PTD/TD may be attributable to influences of sex hormones on the neurodevelopment of these motor pathways, as reflected by the effects of antiandrogens in the treatment of TD.

Family studies suggest a 10-100–fold increase in the risk of PTD/TD among 1st-degree relatives compared to rates in the general population. Twin studies also support a genetic link, with approximately 80% of monozygotic twins and 30% of dizygotic twins showing concordance for PTD/TD. To date, candidate-gene association and nonparametric linkage studies have not shown specific susceptibility genes for PTD/TD.

Autoimmune mediated mechanisms have been hypothesized as having a potential etiologic role in some tic disorders. The ***pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection*** (**PANDAS**; see Chapter 183) designation has been used to describe cases of acute childhood onset of OCD and/or tics following a streptococcal infection. More recently, **PANS *(pediatric acute-onset neuropsychiatric syndrome)*** has been used to describe a subtype of acute childhood onset OCD (tics are not a required feature) in which a link to a prior streptococcal infection is not evident suggesting that other infectious agents may also be responsible (Table 24-3). In addition to a diagnosis of OCD and/or tics, children with PANS/PANDAS have been reported to have symptoms of separation anxiety, nightmares, personality change, oppositional behaviors, and deterioration in math skills and handwriting. Although some studies suggest a prior history of infections may increase the risk for developing tic disorder, this remains controversial.

Premorbid stress has been hypothesized to act as a sensitizing agent in the pathogenesis of TD among susceptible individuals by affecting

Table 24-3 Diagnostic Criteria Proposed for Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

CRITERION	DESCRIPTION
I.	Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake
II.	Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least 2 of the following 7 categories (see text for full description): 1. Anxiety 2. Emotional lability and/or depression 3. Irritability, aggression and/or severely oppositional behaviors 4. Behavioral (developmental) regression 5. Deterioration in school performance 6. Sensory or motor abnormalities 7. Somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency
III.	Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder or others. *Note:* The diagnostic work-up of patients suspected of PANS must be comprehensive enough to rule out these and other relevant disorders. The nature of the co-occurring symptoms will dictate the necessary assessments, which may include MRI scan, lumbar puncture, electroencephalogram or other diagnostic tests.

From Swedo SE, Leckman JF, Rose NR: From research subgroup to clinical syndrome: modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). Pediatr Therapeut *2:113, 2012, Table 2.*

stress responsive biologic systems such as the hypothalamic–pituitary–adrenal axis.

SEQUELAE

Many individuals with mild to moderate tics express little to no distress or functional impairment and may even be unaware of their tics. Even individuals with moderate to severe tics can experience little functional impairment, but psychological distress may occur. Uncommonly, the presence of tics can lead to social isolation, social victimization, inability to work or attend school, or impaired quality of life.

SCREENING

Pediatricians should routinely screen for unusual movements and vocalizations. As an adjunct to a verbal screen, commonly used broadband symptom rating scales such as the *Child Behavior Checklist* (CBCL) and the *Swanson, Nolan, and Pelham* (SNAP) include specific tic questions. Often families are unaware that frequent sniffing, coughing, or blinking may be indicative of tics, attributing these behaviors to medical problems (e.g., allergies, visual problems). A careful assessment of the timing, triggers, and specific characteristics may differentiate tics from other medical problems. If differentiation is difficult, a referral to a pediatric specialist in the affected system is warranted.

ASSESSMENT

If the screening suggests the presence of a tic disorder, a more comprehensive evaluation should ensue, including the age of onset, types of tics, tic frequency, alleviating and aggravating factors, and a family history of tics. Symptom rating scales specific for tics (e.g., the *Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey* [MOVES], *Tic Self Report Scale*, *Tourette's Disorder Scale*, *Parent Tic Questionnaire* (PTQ; hppt://www.uab.edu/ot/practice/tourette-syndrome-clinic/parent-tic-questionnaire), and the *Child Tourette's Disorder Impairment Scale–Parent Version* can supplement the assessment. For clinician-rated tic severity, the most commonly used instrument is the *Yale Global Tic Severity Scale* (YGTSS); the *Tourette Syndrome Severity Scale* (TSSS), and the *Tourette Syndrome Global Scale* (TSGS) also can be useful.

A medical workup should be considered for new-onset tics, particularly for presentations characterized by sudden onset, atypicality, or mental status abnormalities. Basic laboratory measures (hemogram, renal/hepatic function panel, thyroid panel and ferritin along with urine drug screen for adolescents) should be considered. For new sudden (overnight) onset or severe symptom exacerbation, pediatricians may assess for co-occurring acute infection (e.g., culture, rapid viral tests, etc.). Electroencephalogram and brain imaging are not routinely recommended and should be reserved for cases with other neurologic findings that might suggest an autoimmune encephalitis syndrome (limbic encephalitis) (see Chapter 598.4). Cooccurring psychiatric disorders (e.g., OCD, ADHD, ASD) should be investigated.

TREATMENT

The decision to treat tics is made with the child and family based upon the level of impairment and distress caused by the tics. If tics are mild in severity, there may be no need for intervention after psychoeducation is provided.

Psychoeducation should include common symptom presentations, implications of co-occurring conditions, course and prognosis, and treatment options (including no treatment). The youth's typical exacerbating and alleviating factors should be reviewed. The clinician can direct the family and youth to informational websites, including the Tourette Syndrome Association (www.tsa-usa.org) or the Tourette Syndrome "Plus" website (www.tourettesyndrome.net).

Nearly 75% of children with TD/PTD receive some form of classroom accommodation (most often ignoring the tics and permission to leave the room as needed). The accommodations may need to be formalized in an ***Individualized Education Plan*** **(IEP)** or 504 Plan.

Referral to a behavioral treatment specialist should be considered when tics are distressing or functionally impairing. The behavioral intervention with the strongest empirical support is ***habit reversal therapy*** **(HRT)**. The typical components of HRT include premonitory urge awareness training, building a competing response to the urge to tic, and social support. In a large randomized trial comparing an HRT protocol to a psychosocial control, the effect size favoring the intervention was 0.64; nearly all intervention subjects were also prescribed medication. To date, there are no studies comparing HRT to medication or combined (medication plus HRT) therapy.

Behavioral treatment may also address less-adaptive coping strategies (e.g., avoidance, social withdrawal) that develop secondary to tics and contribute to impairment. Skill-based therapies such as cognitive-behavioral therapy can be beneficial in reducing maladaptive coping strategies, anxiety, and compulsive behavior.

Medications should be considered when the tics are causing severe impairment in the quality of life, or when medication-responsive psychiatric comorbidities are present that target both tic symptoms and comorbid conditions. The only 2 FDA-approved medications to treat TD are haloperidol and pimozide, although most clinicians use atypical antipsychotics (risperidone) before the FDA-approved agents because of the more favorable side-effect profile of the atypicals. Others use α_2-agonists as 1st-line agents because of their less-adverse side-effect profile compared to the antipsychotics.

The α_2-adrenergic agonists (clonidine and guanfacine) have demonstrated an effect size of 0.5 for amelioration of tics. A meta-analysis found that agonist trials enrolling subjects with comorbid ADHD demonstrated a much higher effect size (0.68) than trials enrolling subjects without comorbid ADHD (0.15). The starting dose for clonidine is 0.025-0.05 mg/day with gradual increases up to 0.1-0.4 mg/day, administered in divided doses (3-4 times a day). A transdermal patch of clonidine is available, as is a sustained-release formulation that has been FDA-approved for the treatment of ADHD, but has not been studied for the treatment of tics. Sedation and low blood pressure are

common side effects that require careful monitoring, particularly when initiating treatment. The role of guanfacine, which is a less-sedating α_2-agonist, has not been firmly established but trials are underway.

The D_2 dopamine receptor-blocking medications (haloperidol and pimozide) are effective in reducing tics, but the side-effect burden (e.g., extrapyramidal symptoms) have limited their use as 1st-line treatment. Risperidone, an atypical antipsychotic medication, has appeared in 4 randomized control trials to be an effective treatment, although concerns for neuromotor and metabolic side effects exist. The starting dose for risperidone is 0.125-0.5 mg/day with a usual dose range of 0.75-3.0 mg/day.

The side effects of all antipsychotic medications warrant close monitoring: abnormal movements should be monitored periodically using a standardized methodology (such as the *Abnormal Involuntary Movement Scale [AIMS] checklist*); blood pressure, body mass index and fasting glucose and lipids should be checked at baseline and at regular intervals thereafter, according to standard guidelines. Consideration of weight management interventions and increased monitoring of blood glucose and lipid levels should be implemented if weight gain exceeds 90th percentile body mass index for age, or a change of 5 body mass index units occurs in youths who were obese at the beginning of treatment. In patients with a personal or family history of cardiac abnormalities, including syncope, palpitations, arrhythmias, or sudden unexplained death, a baseline electrocardiogram with subsequent monitoring should be considered, along with cardiology consultation. Alternative pharmacology should be considered if the resting heart rate exceeds 130 beats/min, or the PR, QRS, and QTc exceed 200, 120, and 460 msec, respectively.

Children with tic disorders may benefit from selective serotonin reuptake inhibitors (SSRIs) for the treatment of comorbid OCD, anxiety, or depressive disorders. Augmentation of SSRIs with an atypical antipsychotic medication has been a consideration in patients with co-occurring tic disorders and OCD responding poorly to an SSRI alone. The presence of tics does not preclude the use of stimulants to address comorbid ADHD. However, close clinical monitoring is required for possible exacerbation of tics during stimulant treatment. Anger and rage outbursts are not uncommon among youth with tics (up to 80% in clinically referred samples). Behavioral therapies that address anger management may be useful. There are no controlled pharmacologic studies in youth with tics disorders with anger outbursts. There also is no scientific evidence to support the use of deep brain stimulation, repetitive magnetic stimulation, and dietary supplements in the treatment of TD/PTD.

24.2 Stereotypic Movement Disorder

Colleen A. Ryan, Michael L. Trieu, David R. DeMaso, and Heather J. Walter

In DSM-5, ***stereotypic movement disorder*** **(SMD)** is defined as a neurodevelopmental disorder characterized by repetitive, seemingly driven, and apparently purposeless motor behavior (stereotypy) that interferes with social, academic, or other activities that may result in self-injury. The onset of SMD is the early developmental period (often before age 3 yr), and the symptoms are not attributable to the physiologic effects of a substance or neurologic condition and are not better explained by another neurodevelopmental or mental disorder. The disorder is considered mild if symptoms are easily suppressed by sensory stimulus or distraction, and severe if continuous monitoring and protective measures are required to prevent serious injury, with moderate falling between mild and severe.

DESCRIPTION

Examples of stereotypic movements include hand shaking or waving, body rocking, head banging, self-biting, and hitting one's own body. The presentation depends on the nature of the stereotypic movement and level of the child's awareness of the behavior. Among typically developing children, the repetitive movements may be stopped when attention is directed to them or when the child is distracted from performing them. Among children with neurodevelopmental disorders, the behaviors are typically less responsive to such efforts. Each individual presents with his or her own uniquely patterned behavior. Stereotypic movements may occur many times during a day, lasting a few seconds to several minutes or longer. The behaviors may occur in multiple contexts, including when the individual is excited, stressed, fatigued, or bored.

CLINICAL COURSE

Stereotypic movements typically begin within the first 3 yr of life. In children who develop complex motor stereotypies, the great majority exhibit symptoms before 24 mo of age. In most typically developing children, these movements resolve over time. Among individuals with intellectual disability, the stereotyped behaviors may persist for years, although the pattern may change over time.

EPIDEMIOLOGY

Simple stereotypic movements (e.g., rocking) are common in typically developing young children. Self-injurious habits, such as self-biting or head banging, can occur in up to 25% of typically developing toddlers, but they are almost invariably associated with developmental delay in children older than age 5 yr. Complex stereotypic movements are much less common (occurring in approximately 3-4% of children). Between 4% and 16% of individuals with intellectual disability engage in stereotypic movements.

COMORBIDITY

Stereotypic movements are a common manifestation of a variety of neurogenetic disorders, such as Lesch-Nyhan syndrome, Rett syndrome (see Chapter 599), fragile X syndrome (see Chapter 81), Cornelia de Lange syndrome, and Smith-Magenis syndrome.

DIFFERENTIAL DIAGNOSIS

According to DSM-5, stereotypic movements must be differentiated from normal development, **ASDs**, tic disorders, **OCDs**, and other neurologic and medical conditions. Simple stereotypic movements occurring in the context of normal development usually resolve with age. Stereotypic movements may be a presenting symptom of ASD, but SMD does not include the deficits in social communication characteristic of ASD. When ASD is present, SMD is diagnosed only when there is self-injury or when the stereotypic behaviors are sufficiently severe to become a focus of treatment. Typically, SMD has an earlier age of onset than the tic disorders, and the movements are fixed in their pattern. SMD is distinguished from OCD by the absence of obsessions as well as the nature of the repetitive behaviors, which in OCD are purposeful (e.g., in response to obsessions). The diagnosis of stereotypic movements requires the exclusion of habits, mannerisms, paroxysmal dyskinesias, and benign hereditary chorea. A neurologic history and examination are required to assess features suggestive of other disorders, such as myoclonus, dystonia, and chorea.

ETIOLOGY

There is a possible evolutionary link between repetitive abnormal grooming-like behaviors and early human experience with adversity. Brain regions implicated in this model (e.g., amygdala and hippocampus) are those involved in navigating human experience through unpredictable, anxiety-provoked emotional states as well as regions (e.g., nucleus accumbens) related to pleasure and reward seeking. The latter involves the hypothesis that individuals experience some level of gratification from performing the habit behavior.

Social isolation with insufficient stimulation (e.g., severe neglect; see Chapter 40) is a risk factor for self-stimulation that may progress into stereotypies (particularly repetitive rocking or spinning). Environmental stress may trigger stereotypic behaviors. Repetitive self-injurious behavior may be a behavioral phenotype in neurogenetic syndromes (e.g., Lesch-Nyhan, Rett, and Cornelia de Lange syndromes). Lower cognitive functioning is also linked to greater risk of stereotypic behaviors.

TREATMENT

The initial approach to helping children with mild stereotypy is for parents to ignore the undesired behavior, encourage substitute behavior, and not convey worry to their child. These behaviors may disappear with time and elimination of attention in young children. However, in children with neurodevelopmental disorders, stereotypies are more refractory to treatment than in normally developing children, and may necessitate referral to a behavioral psychologist and/or child and adolescent psychiatrist for behavioral and/or psychopharmacologic management. The pediatrician should consider and rule out neglect of the child, which can be associated with repetitive rocking, spinning, or other stereotypic movements.

Behavior therapy is the mainstay of treatment, using a variety of strategies including habit reversal, relaxation training, self-monitoring, contingency management, competing responses, and negative practice. The environment should also be modified to reduce risk of injury to those engaging in self-injurious behavior.

Atypical antipsychotic medications appear to be helpful in reducing stereotypic movements in youth with ASD. Patients with co-occurring with anxiety and obsessive-compulsive behaviors treated with SSRIs for these disorders may show improvement in their stereotypic movements.

HABITS

Habits involve an action or pattern of behavior that is repeated often. Habits are common in childhood and range from benign and transient (thumb sucking, nail biting) to more problematic (trichotillomania, bruxism). In DSM-5, habits are not included as a diagnostic category as they are not viewed as disorders causing clinically significant distress or impairment in functioning. Treatment with HRT has been effective as a 1st-line approach (Table 24-4).

Table 24-4 Components of Habit Reversal Procedure

Increase Individual's Awareness of Habit
Response description—have individual describe behavior to therapist in detail while reenacting the behavior and looking in a mirror.
Response detection—inform individual of each occurrence of the behavior until each occurrence is detected without assistance.
Early warning—have individual practice identifying earliest signs of the target behavior.
Situation awareness—have individual describe all situations in which the target behavior is likely to occur.
Teach Competing Response to Habit
The competing response must result in isometric contraction of muscles involved in the habit, be capable of being maintained for 3 min, and be socially inconspicuous and compatible with normal ongoing activities but incompatible with the habit (e.g., clenching one's fist, grasping and clenching an object). For vocal tics and stuttering, deep relaxed breathing with a slight exhale before speech has been used as the competing response.
Sustain Compliance
Habit inconvenience review—have individual review in detail all problems associated with target behavior.
Social support procedure—family members and friends provide high levels of praise when a habit-free period is noted.
Public display—individual demonstrates to others that he or she can control the target behavior in situations in which the behavior occurred in the past.
Facilitate Generalization—Symbolic Rehearsal Procedure
For each situation identified in situation awareness procedure, individual imagines himself or herself beginning the target behavior but stopping and engaging in the competing response.

From Carey WB, Crocker AC, Coleman WL, Elias ER, Feldman HM, editors: Developmental-behavioral pediatrics, *ed 4, Philadelphia, 2009, Elsevier/Saunders, Table 65-4, p. 639.*

Thumb Sucking

Thumb sucking is common in infancy and in as many as 25% of children age 2 yr and 15% of children age 5 yr. Thumb sucking beyond 5 yr may be associated with sequelae (paronychia, anterior open bite). Like other rhythmic patterns of behavior, thumb sucking is self-soothing. Basic behavioral management, including encouraging parents to ignore thumb sucking and instead focus on praising the child for substitute behaviors, is often effective treatment. Simple reminders and reinforcers, such as giving the child a sticker (or other rewards) for each block of time that he or she does not suck the thumb can also be considered. Although some suggest the use of noxious agents (bitter salves) this approach should rarely be necessary.

Bruxism

Bruxism or teeth grinding is common (5-30% of children), can begin in the first 5 yr of life, and may be associated with daytime anxiety. Persistent bruxism can manifest as muscular or temporomandibular joint pain. Untreated bruxism can cause problems with dental occlusion. Helping the child find ways to reduce anxiety might relieve the problem; bedtime can be made more relaxing by reading or talking with the child and allowing the child to discuss fears. Praise and other emotional support are useful. Persistent bruxism requires referral to a dentist given the risk for dental occlusion.

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Chapter 25

Anxiety Disorders

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Anxiety, defined as dread or apprehension is not considered pathologic, is seen across the life span, and can be adaptive (e.g., the anxiety one might feel during an automobile crash). Anxiety has both a cognitive and behavioral component, expressed in worrying and wariness, and a physiologic component, mediated by the autonomic nervous system. Anxiety disorders are characterized by pathologic anxiety in which anxiety becomes disabling, interfering with social interactions, development, and achievement of goals or quality of life, and can lead to low self-esteem, social withdrawal, and academic underachievement. The average age of onset of anxiety disorder is 11 yr. Diagnosis of a particular anxiety disorder in a child requires significant interference in the child's psychosocial and/or academic or occupational functioning, which can occur even with subthreshold symptoms that do not meet criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). Anxiety may have physical manifestations such as weight loss, pallor, tachycardia, tremors, muscle cramps, paresthesias, hyperhidrosis, flushing, hyperreflexia, and abdominal tenderness.

Separation anxiety disorder (**SAD**), childhood-onset social phobia or social anxiety disorder, generalized anxiety disorder (**GAD**), obsessive-compulsive disorder (**OCD**), phobias, posttraumatic stress disorder (**PTSD**), and panic disorder (**PD**) are all defined by the occurrence of either diffuse or specific anxiety, often related to predictable situations or cues. Anxiety disorders are the most common psychiatric disorders of childhood; they occur in 5-18% of all children and adolescents, prevalence rates comparable to physical disorders such as asthma and diabetes. Anxiety disorders are often comorbid with other psychiatric and medical disorders (including a second anxiety disorder); significant impairment in day-to-day functioning is common. High levels of fear in adolescence are also a significant risk factor for experiencing later episodes of major depression in adulthood. Anxiety

and depressive disorder in adolescence predict increased risk of anxiety and depressive symptoms (including suicide attempts) in adulthood, underscoring the need to diagnose and treat these underreported, yet prevalent, conditions early.

Because anxiety is both a normal phenomenon and, when highly activated, strongly associated with impairment, the pediatrician must be able to differentiate normal anxiety from abnormal anxiety across development. Anxiety has an identifiable developmental progression for most children; most infants exhibit stranger wariness or anxiety beginning at 7-9 mo of age. Behavioral inhibition to the unfamiliar (withdrawal or fearfulness to novel stimuli associated with physiologic arousal) is evident in approximately 10-15% of the population at 12 mo of age and is moderately stable. Most children who show behavioral inhibition do not develop impairing levels of anxiety. A family history of anxiety disorders and maternal over involvement or enmeshment predicts later clinically significant anxiety in behaviorally inhibited infants. The infant who is excessively clingy and difficult to calm during pediatric visits should be followed for signs of increasing levels of anxiety.

Preschoolers typically have specific fears related to the dark, animals, and imaginary situations, in addition to normative separation anxiety. Preoccupation with orderliness and routines (*just right* phenomena) often takes on a quality of anxiety for preschool children. Parents' reassurance is usually sufficient to help the child through this period. Although most school-age children abandon the imaginary fears of early childhood, some replace them with fears of bodily harm or other worries (Table 25-1). In adolescence, general worrying about school performance and worrying about social competence are common and remit as the teen matures.

Table 25-1	DSM-5 Diagnostic Criteria for Specific Phobia

Diagnostic Criteria

A. Marked fear or anxiety about a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood).

Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, or clinging.

B. The phobic object or situation almost always provokes immediate fear or anxiety.

C. The phobic object or situation is actively avoided or endured with intense fear or anxiety.

D. The fear or anxiety is out of proportion to the actual danger posed by the specific object or situation and to the sociocultural context.

E. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.

F. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

G. The disturbance is not better explained by the symptoms of another mental disorder, including fear, anxiety and avoidance or situations associated with panic-like symptoms or other incapacitating symptoms (as in agoraphobia); objects or situations related to obsessions (as in obsessive-compulsive disorder); remainders of traumatic events (as in posttraumatic stress disorder); separation from home or attachment figures (as in separation anxiety disorder); or social situations (as in social anxiety disorder).

Specify if:

Code based on the phobic stimulus:

Animal (e.g., spiders, insects, dogs).

Natural environment (e.g., heights, storms, water).

Blood-injection-injury (e.g., needles, invasive medical procedures).

Situational (e.g., airplanes, elevators, enclosed places).

Other (e.g., situations that may lead to choking or vomiting; in children, e.g., loud sounds or costumed characters).

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 197–198.

Genetic or temperamental factors contribute more to the development of some anxiety disorders, whereas environmental factors are closely linked to the cause of others. Specifically, behavioral inhibition appears to be a heritable tendency and is linked with social phobia, generalized anxiety, and selective mutism. OCD and other disorders associated with OCD-like behaviors, such as Tourette syndrome and other tic disorders, tend to have high genetic risk as well (see Chapter 24.1). Environmental factors, such as parent–infant attachment and exposure to trauma, contribute more to SAD and PTSD. Parental anxiety disorder is associated with an increased risk of anxiety disorder in offspring. Differences in the size of the amygdala and hippocampus are noted in patients with anxiety symptoms.

SAD is one of the most common childhood anxiety disorders with a prevalence of 3.5-5.4%. Approximately 30% of children presenting to an outpatient anxiety disorder clinic have SAD as a primary diagnosis. Separation anxiety is developmentally normal when it begins about 10 mo of age and tapers off by 18 mo. By 3 yr of age, most children can accept the temporary absence of their mother or primary caregiver.

SAD is more common in prepubertal children, with an average age of onset of 7.5 yr. Girls are more commonly affected than boys. SAD is characterized by unrealistic and persistent worries about separation from the home or a major attachment figure. Concerns include possible harm befalling the affected child or the child's primary caregivers, reluctance to go to school or to sleep without being near the parents, persistent avoidance of being alone, nightmares involving themes of separation, numerous somatic symptoms, and complaints of subjective distress. The first clinical sign might not appear until 3rd or 4th grade, typically after a holiday or a period where the child has been home because of illness, or when the stability of the family structure has been threatened by illness, divorce, or other psychosocial stressor.

Symptoms vary depending on the child's age: Children younger than 8 yr often have associated school refusal and excessive fear that harm will come to a parent; children 9-12 yr have excessive distress when separated from a parent; and those 13-16 yr often have school refusal and physical complaints. SAD may be more likely to develop in children with lower levels of psychosocial maturity. Parents are often unable to be assertive in returning the child to school. Mothers of children with SAD often have a history of an anxiety disorder. In these cases, the pediatrician should screen for parental depression or anxiety. Often referral for parental treatment or family therapy is necessary before SAD and concomitant school refusal can be successfully treated.

Comorbidity is common in SAD. In children with comorbid tic disorders and anxiety, SAD is especially associated with tic severity. SAD is a predictor for early onset of PD. Children with SAD compared to those without SAD are 3 times more likely to develop PD in adolescence.

When a child reports recurring acute severe anxiety, antidepressant or anxiolytic medication is often necessary. Controlled studies of tricyclic antidepressants (imipramine) and benzodiazepines (clonazepam) show that these agents are not generally effective. Data support the use of cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) (see Table 21-4 in Chapter 21). One study of children 7-17 yr of age with a primary diagnosis of SAD compared 12 wk of treatment with CBT, the SSRI sertraline, their combination, and placebo. Nearly 81% of those treated with combination therapy improved, 55% for SSRI alone, 60% for CBT. All treatments were superior to placebo (24% response rate). The SSRI was well tolerated and had few side effects; adverse events, including suicidal and homicidal ideation, did not differ between the SSRI and placebo groups and there were no attempted suicides. CBT was associated with less insomnia, fatigue, sedation, and restlessness than SSRI. Combining SSRI with CBT may be the best approach to achieving a positive response; long-term SSRI treatment can provide additional benefit. Findings from this study are consistent with a meta-analysis of published and unpublished randomized controlled trials of antidepressants for pediatric patients with SAD, social phobia, or GAD.

Childhood-onset social phobia (social anxiety disorder) is characterized by excessive anxiety in social settings (including the presence

Table 25-2	DSM-5 Diagnostic Criteria for Social Anxiety Disorder (Social Phobia)

Diagnostic Criteria

A. Marked fear or anxiety about 1 or more social situations in which the individual is exposed to possible scrutiny by others. Examples include social interactions (e.g., having a conversation, meeting unfamiliar people), being observed (e.g., eating or drinking), and performing in front of others (e.g., giving a speech).
B. The individual fears that he or she will act in a way or show anxiety symptoms that will be negatively evaluated (i.e., will be humiliating or embarrassing; will lead to rejection or offend others).
C. The social situations almost always provoke fear or anxiety.

Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, clinging, shrinking, or failing to speak in social situations.

D. The social situations are avoided or endured with intense fear or anxiety.
E. The fear or anxiety is out of proportion to the actual threat posed by the social situation and to the sociocultural context.
F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.
G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
H. The fear, anxiety, or avoidance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
I. The fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder, such as panic disorder, body dysmorphic disorder, or autism spectrum disorder.
J. If another medical condition (e.g., Parkinson disease, obesity, disfigurement from burns or injury) is present, the anxiety or avoidance is clearly unrelated or is excessive.

Specify if:

Performance only: If the fear is restricted to speaking or performing in public.

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of unfamiliar peers, or unfamiliar adults) or performance situations, leading to social isolation (Table 25-2) and is associated with social scrutiny and fear of doing something embarrassing. Fear of social settings can also occur in other disorders, such as GAD. Avoidance or escape from the situation usually dissipates anxiety in **social phobia (SP),** unlike GAD, where worry persists. Children and adolescents with SP often maintain the desire for involvement with family and familiar peers. When severe, the anxiety can manifest as a panic attack.

SP is associated with a decreased quality of life, with increased likelihood of having failed at least 1 grade, and a 38% likelihood of not graduating from high school. Its onset is typically during or before adolescence and is more common in girls. A family history of SP or extreme shyness is common. Approximately 70-80% of patients with SP have at least 1 comorbid psychiatric disorder. Most shy patients do not have a SP.

Social effectiveness therapy for children (SET-C), alone or with SSRIs, is considered the treatment of choice for SP (see Table 21-4 in Chapter 21). SSRI and SET-C are superior to placebo in reducing social distress and behavioral avoidance and increasing general functioning. SET-C may be better than SSRI in reducing these symptoms. SET-C, but not SSRI, may be superior to placebo in improving social skills, decreasing anxiety in specific social interactions, and enhancing social competence. SSRIs have a maximum effect by 8 wk; SET-C provides continued improvement through 12 wk. A combination of SSRI and CBT is superior to either treatment alone in reducing severity of anxiety in children with SP and other anxiety disorders. β-Adrenergic blocking agents are used to treat SP, particularly the subtype with performance anxiety and stage fright. β-Blockers are not FDA approved for SP.

School refusal, which occurs in approximately 1-2% of children, is associated with anxiety in 40-50% of cases, depression in 50-60% of cases, and oppositional behavior in 50% of cases. Younger anxious children who refuse to attend school are more likely to have SAD, whereas older anxious children usually refuse to attend school because of SP. Somatic symptoms, especially abdominal pain and/or headaches, are common. There may be increasing tension in the parent–child relationship or other indicators of family disruption (domestic violence, divorce, or other major stressors) contributing to school refusal.

Management of school refusal typically requires parent management training and family therapy. Working with school personnel is always indicated; anxious children often require special attention from teachers, counselors, or school nurses. Parents who are coached to calmly send the child to school and to reward the child for each completed day of school are usually successful. In cases of ongoing school refusal, referral to a child and adolescent psychiatrist and psychologist is indicated. SSRI treatment may be helpful. Young children with affective symptoms have a good prognosis, whereas adolescents with more insidious onset or with significant somatic complaints have a more guarded prognosis.

Selective mutism is conceptualized as a disorder that overlaps with SP. Children with selective mutism talk almost exclusively at home, although they are reticent in other settings, such as school, daycare, or even relatives' homes. The mutism must be present for ≥1 mo. Often, 1 or more stressors, such as a new classroom or conflicts with parents or siblings, drive an already shy child to become reluctant to speak. It may be helpful to obtain history of normal language use in at least 1 situation to rule out any communication disorder (fluency disorder), neurologic disorder, or pervasive developmental disorder (autism, schizophrenia) as a cause of mutism. Fluoxetine in combination with behavioral therapy is effective for children whose school performance is severely limited by their symptoms (see Chapter 35). Other SSRIs may also be effective.

PD is a syndrome of recurrent, discrete episodes of marked fear or discomfort in which patients experience abrupt onset of physical and psychologic symptoms called *panic attacks* (Table 25-3). Physical symptoms can include palpitations, sweating, shaking, shortness of breath, dizziness, chest pain, and nausea. Children can present with acute respiratory distress but without fever, wheezing, or stridor, ruling out organic causes of the distress. The associated psychologic symptoms include fear of death, impending doom, loss of control, persistent concerns about having future attacks, and avoidance of settings where attacks have occurred (agoraphobia, Table 25-4).

PD is uncommon before adolescence, with the peak age of onset at 15-19 yr of age, occurring more often in girls. The postadolescence prevalence of PD is 1-2%. Early-onset PD and adult-onset PD do not differ in symptom severity or social functioning. Early-onset PD is associated with greater comorbidity, which can result from greater familial loading for anxiety disorders in the early-onset subtype. Children of parents with PD are much more likely to develop PD. A predisposition to react to autonomic arousal with anxiety may be a specific risk factor leading to PD. Twin studies suggest that 30-40% of the variance is attributed to genetics. The increasing rates of panic attack are also directly related to earlier sexual maturity. Cued panic attacks can be present in other anxiety disorders and differ from the uncued "out-of-the-blue" attacks in PD.

No randomized controlled trials have evaluated the effectiveness of antidepressant medication in youth with PD. Open-label studies with SSRIs appear to show effectiveness in the treatment of adolescents (see Table 21-4 in Chapter 21). CBT may also be helpful. The recovery rate is approximately 70%.

GAD occurs in children who often experience unrealistic worries about different events or activities for at least 6 mo (Table 25-5) with at least 1 somatic complaint. The diffuse nature of the anxiety symptoms differentiates it from other anxiety disorders. Worries in children with GAD commonly center around concerns about competence and performance in school and athletics. GAD often manifests with somatic symptoms including restlessness, fatigue, problems concentrating, irritability, muscle tension, and sleep disturbance. Given the somatic

Table 25-3 DSM-5 Diagnostic Criteria for Panic Disorder

A. Recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time 4 (or more) of the following symptoms occur:

Note: The abrupt surge can occur from a calm state or an anxious state.

1. Palpitations, pounding heart, or accelerated heart rate.
2. Sweating
3. Trembling or shaking.
4. Sensations of shortness of breath or smothering.
5. Feelings of choking.
6. Chest pain or discomfort.
7. Nausea or abdominal distress.
8. Feeling dizzy, unsteady, light-headed, or faint.
9. Chills or heart sensations.
10. Paresthesias (numbness or tingling sensations).
11. Derealizations (feeling or unreality) or depersonalization (being detached from one-self).
12. Fear of losing control or "going crazy."
13. Fear of dying.

Note: Culture-specific symptoms (e.g., tinnitus, neck soreness, headache, uncontrollable screaming or crying) may be seen. Such symptoms should not count as 1 of the 4 required symptoms.

B. At least 1 of the attacks has been followed by 1 mo (or more) of 1 or both of the following:
1. Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, "going crazy").
2. A significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).

C. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).

D. The disturbance is not better explained by another mental disorder (e.g., the panic attacks do not occur only in response to feared social situations, as in social anxiety disorder; in response to circumscribed phobic objects or situations, as in specific phobia; in response to obsessions, as in obsessive-compulsive disorder; or in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder).

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Table 25-4 DSM-5 Diagnostic Criteria for Agoraphobia

A. Marked fear or anxiety about 2 (or more) if the following 5 situations:
1. Using public transportation (e.g., automobiles, buses, trains, ships, planes).
2. Being in open spaces (e.g., parking lots, marketplaces, bridges).
3. Being in enclosed places (e.g., shops, theaters, cinemas).
4. Standing in line or being in a crowd.
5. Being outside of the home alone.

B. The individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of a developing panic-like symptoms or other incapacitating or embarrassing symptoms (e.g., fear or falling in the elderly, fear of incontinence).

C. The agoraphobic situations almost always provoke fear or anxiety.

D. The agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety.

E. The fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and to the sociocultural context.

F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.

G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational or other important area of functioning.

H. If another medical condition (e.g., inflammatory bowel disease, Parkinson disease) is present, the fear, anxiety, or avoidance is clearly excessive.

I. The fear, anxiety, or avoidance is not better explained by the symptoms or another mental disorder—for example, the symptoms are not confined to specific phobia, situational type; do not involve only social situations (as in social anxiety disorder); and are not related exclusively to obsessions (as in obsessive-compulsive disorder), reminders or traumatic events (as in posttraumatic stress disorder), or fear of separation (as in separation anxiety disorder).

Note: Agoraphobia is diagnosed irrespective of the presence of panic disorder. If an individual's presentation meets criteria for panic disorder and agoraphobia, both diagnoses should be assigned.

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symptoms characteristic of GAD, the differential diagnosis must consider other medical causes. Excessive use of caffeine or other stimulants in adolescence is common and should be determined with a careful history. When the history or physical exam is suggestive, the pediatrician should rule out hyperthyroidism, hypoglycemia, lupus, and pheochromocytoma.

Children with GAD are markedly self-conscious and perfectionistic and struggle with more intense distress than is evident to parents or others around them. They often have other anxiety disorders, such as simple phobia and PD. Onset may be gradual or sudden, although GAD does not often become manifest until puberty. Boys and girls are equally affected before puberty, when GAD becomes more prevalent in girls. The prevalence of GAD ranges from 2.5-6% of children. Hypermetabolism in frontal precortical area and increased blood flow in the right dorsolateral prefrontal cortex may be present.

Children with GAD are good candidates for CBT, an SSRI, or their combination (see Table 21-4 in Chapter 21). Buspirone may be used as an adjunct to SSRI therapy. Combination of CBT and SSRI often results in a superior response in pediatric patients with anxiety disorders, including GAD. The recovery rate is approximately 80%.

It is important to distinguish children with GAD from those who present with specific repetitive thoughts that invade consciousness **(obsessions)** or repetitive rituals or movements that are driven by anxiety **(compulsions)**. The most common obsessions are concerned with bodily wastes and secretions, the fear that something calamitous will happen, or the need for sameness. The most common compulsions are hand washing, continual checking of locks, and touching. At times of stress (bedtime, preparing for school), some children touch certain objects, say certain words, or wash their hands repeatedly. OCD is diagnosed when the thoughts or rituals cause distress, consume time, or interfere with occupational or social functioning (Table 25-6). In the DSM-5, OCD and related disorders (such as trichotillomania, excoriation, body dysmorphic disorder, and hoarding) are listed separately and are no longer included under anxiety disorders.

OCD is a chronically disabling illness characterized by repetitive, ritualistic behaviors over which the patient has little or no control. OCD has a lifetime prevalence of 1-3% worldwide, and as many as 80% of all cases have their onset in childhood and adolescence. Common obsessions include contamination (35%) and thoughts of harming loved ones or oneself (30%). Washing and cleaning compulsions are common in children (75%), as are checking (40%) and straightening (35%). Many children are observed to have visuospatial irregularities, memory problems, and attention deficits, causing academic problems not explained by OCD symptoms alone.

Table 25-5 DSM-5 Diagnostic Criteria for Generalized Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 mo, about a number of events or activities (such as work or school performance).
B. The individual finds it difficult to control the worry.
C. The anxiety and worry are associated with 3 (or more) of the following 6 symptoms (with at least some symptoms having been present for more days than not for the past 6 mo):
Note: Only 1 item is required in children.
1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D. The anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or other medical condition (e.g., hyperthyroidism).
F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, remainders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

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The Children's Yale-Brown Obsessive-Compulsive Scale (C-YBOCS) and the Anxiety Disorders Interview Schedule for Children (ADIS-C) are reliable and valid methods for identifying children with OCD. The C-YBOCS is helpful in following the progression of symptoms with treatment. The Leyton Obsessional Inventory (LOI) is a self-report measure of OCD symptoms that is quite sensitive. Patients with OCD have consistently identified abnormalities in the frontostriatal-thalamic circuitry associated with severity of illness and treatment response. Comorbidity is common in OCD, with 30% of patients having comorbid tic disorders, 26% having comorbid major depression, and 24% having comorbid developmental disorders.

Consensus guidelines recommend that children and adolescents with OCD begin treatment with either CBT alone or CBT in combination with SSRI, when symptoms are moderate to severe (YBOCS >21). In OCD patients with comorbid tics, SSRIs are no more effective than placebo, and combination of CBT and SSRI is superior to CBT; CBT alone is superior to placebo. Pediatric OCD patients with comorbid tics should begin treatment with CBT alone or the combination of CBT and SSRI. Pediatric patients with OCD who have a family history of OCD may be significantly less responsive to CBT alone than patients without a family history of OCD.

There are 4 FDA-approved medications for pediatric OCD: fluoxetine, sertraline, fluvoxamine, and clomipramine. Clomipramine, a heterocyclic antidepressant and nonselective serotonin and norepinephrine reuptake inhibitor, is only indicated when a patient has failed 2 or more SSRI trials. There may be a role for glutamate-modulating medications in the treatment of OCD. The glutamate inhibitor riluzole (Rilutek) is FDA-approved for amyotrophic lateral sclerosis (see Chapter 612.3) and has a good safety record. The most common adverse event with riluzole is transient increase in liver transaminases. Riluzole in children with treatment-resistant OCD may be beneficial and is well tolerated. Other glutamate-modulating agents, such as memantine, *N*-acetyl-cysteine, and D-cycloserine, have been used with some success in patients with OCD. Referral of patients with OCD to a mental health professional is always indicated.

Table 25-6 DSM-5 Diagnostic Criteria for Obsessive-Compulsive Disorder

A. Presence of obsessions, compulsions, or both:
Obsessions are defined by (1) and (2):
1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.
2. The individual attempts to ignore or suppress such thoughts, urges or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).

Compulsions are defined by (1) and (2):
1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.
2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.

B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hr per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The obsessive-compulsive symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder; stereotypies, as in stereotypic movement disorder; ritualized eating disorder, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control and conduct disorders; guilty ruminations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).

Specify if:
With good or fair insight: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true.
With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true.
With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true.
Specify if:
Tic-related: The individual has a current or past history of a tic disorder.

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In 10% of children with OCD, symptoms are triggered or exacerbated by group A β-hemolytic streptococcal infection (see Chapter 183). Group A β-hemolytic streptococcal bacteria trigger antineuronal antibodies that cross-react with basal ganglia neural tissue in genetically susceptible hosts, leading to swelling of this region and resultant obsessions and compulsions. This subtype of OCD, called **pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS),** is characterized by sudden and dramatic onset or exacerbation of OCD or tic symptoms, associated neurologic findings, and a recent streptococcal infection. Increased

antibody titers of antistreptolysin O and antideoxyribonuclease B correlates with increased basal ganglia volumes. Plasmapheresis is effective in reducing OCD symptoms in some patients with PANDAS and also decreasing enlarged basal ganglia volume. OCD has also followed episodes of acute disseminated encephalomyelitis (see Chapter 600.3) The pediatrician should be aware of the infectious cause of some cases of tic disorders, attention-deficit disorder, and OCD and follow management guidelines (see Chapter 24).

Children with **phobias** avoid specific objects or situations that reliably trigger physiologic arousal (e.g., dogs or spiders) (see Table 25-1). The fear is excessive and unreasonable and can be cued by the presence or anticipation of the feared trigger, with anxiety symptoms occurring immediately. Neither obsessions nor compulsions are associated with the fear response; phobias only rarely interfere with social, educational, or interpersonal functioning. Assault by a relative and verbal aggression between parents can influence the onset of specific phobias. The parents of phobic children should remain calm in the face of the child's anxiety or panic. Parents who become anxious themselves may reinforce their children's anxiety, and the pediatrician can usefully interrupt this cycle by calmly noting that phobias are not unusual and rarely cause impairment. The prevalence of specific phobias in childhood is 0.5-2%.

Systematic desensitization is a form of behavior therapy that gradually exposes the patient to the fear-inducing situation or object, while simultaneously teaching relaxation techniques for anxiety management. Successful repeated exposure leads to extinguishing anxiety for that stimulus. When phobias are particularly severe, SSRIs can be used with behavioral intervention. Low-dose SSRI treatment may be especially effective for some children with severe, refractory choking phobia.

PTSD (see Chapter 39) is typically precipitated by an extreme stressor. PTSD is an anxiety disorder resulting from the long- and short-term effects of trauma that cause behavioral and physiologic sequelae in toddlers, children, and adolescents (Table 25-7). Another

Table 25-7 DSM-5 Diagnostic Criteria for Posttraumatic Stress Disorder

POSTTRAUMATIC STRESS DISORDER

Note: The following criteria apply to adults, adolescents, and children older than 6 yr. For children 6 yr and younger, see corresponding criteria below.

A. Exposure to actual or threatened death, serious injury, or sexual violence in 1 (or more) of the following ways:
   1. Directly experiencing the traumatic event(s).
   2. Witnessing, in person, the event(s) as it occurred to others.
   3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
   4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., 1st responders collecting human remains; police officers repeatedly exposed to details of child abuse).

Note: Criterion A4 does not apply to exposure through electronic media, television, movies or pictures, unless this exposure is work related.

B. Presence of 1 (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
   1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).

Note: In children older than 6 yr, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.

   2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).

Note: In children, there may be frightening dreams without recognizable content.

   3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the more extreme expression being a complete loss or awareness of present surroundings.)

Note: In children, trauma-specific reenactment may occur in play.

   4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
   5. Marked physiologic reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by 1 or both of the following:
   1. Avoidance of or efforts to avoid distressing memories, thoughts or feelings about or closely associated with the traumatic event(s).
   2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that around distressing memories, thoughts or feelings about or closely associated with the traumatic event(s).

D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by 2 (or more) of the following:
   1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
   2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
   3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
   4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
   5. Markedly diminished interest or participation in significant activities.
   6. Feelings of detachment or estrangement from others.
   7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by 2 (or more) of the following:
   1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed by verbal or physical aggression toward people or objects.
   2. Reckless or self-destructive behavior.
   3. Hypervigilance.
   4. Exaggerated startle response.
   5. Problems with concentration.
   6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 mo.

G. The disturbance causes clinically significant distress or impairment in social, occupational or other important areas of functioning.

H. The disturbance is not attributable to the physiologic effects of a substance (e.g., medication, alcohol) or another medical condition.

Continued

Table 25-7 DSM-5 Diagnostic Criteria for Posttraumatic Stress Disorder—cont'd

Specify whether

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: to use this subtype, the dissociative symptoms must not be attributable to the physiologic effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 mo after the event (although the onset and expression of some symptoms may be immediate).

POSTTRAUMATIC STRESS DISORDER FOR CHILDREN 6 YR AND YOUNGER

A. In children 6 yr and younger, exposure to actual or threatened death, serious injury, or sexual violence in 1 (or more) of the following ways:
   1. Directly experiencing the traumatic event(s).
   2. Witnessing, in person, the event(s) as it occurred to others, especially primary caregivers.

Note: Witnessing does not include events that are only in electronic media, television, movies, or pictures.

   3. Learning that the traumatic event(s) occurred to a parent or caregiving figure.

B. Presence of 1 (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
   1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).

Note: Spontaneous and intrusive memories may not necessarily appear distressing and may be expressed as play reenactment.

   2. Recurrent distressing dreams in which the content and/or affect of the dream is related to the traumatic event(s).

Note: It may not be possible to ascertain that the frightening content is related to the traumatic event.

   3. Dissociative reactions (e.g., flashbacks) in which the child feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Such trauma-specific reenactment may occur in play.
   4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. One (or more) of the following symptoms, representing either persistent avoidance of stimuli associated with the traumatic event(s) or negative alterations in cognitions and mood associated with the traumatic event(s), must be present, beginning after the event(s) or worsening after the event(s):

Persistent Avoidance of Stimuli

   1. Avoidance of or efforts to avoid activities, places, or physical reminders that arouse recollections or the traumatic event(s).
   2. Avoidance of or efforts to avoid people, conversations, or interpersonal situations that around recollections of the traumatic event(s).

Negative Alterations in Cognitions

   3. Substantially increased frequency of negative emotional states (e.g., fear, guilt, sadness, shame, confusion).
   4. Markedly diminished interest or participation in significant activities, including constriction of play.
   5. Socially withdrawn behavior.
   6. Persistent reduction in expression of positive emotions.

D. Alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by 2 (or more) of the following:
   1. Irritable behavior and angry outbursts (with little or no provocation), typically expressed as verbal and physical aggression toward people or objects (including extreme temper tantrums).
   2. Hypervigilance.
   3. Exaggerated startle response.
   4. Problems with concentration.
   5. Sleep disturbance (e.g., difficulty falling asleep or staying asleep or restless sleep).

E. The duration of the disturbance is more than 1 mo.

F. The disturbance causes clinically significant distress or impairment in relationships with parents, siblings, peers, or other caregivers or with school behavior.

G. The disturbance is not attributable to the physiologic effects of a substance (e.g., medication or alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: to use this subtype, the dissociative symptoms must not be attributable to the physiologic effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 mo after the event (although the onset and expression of some symptoms may be immediate).

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diagnostic category, **acute stress disorder**, reflects the fact that traumatic events often cause acute symptoms that may or may not resolve. Previous trauma exposure, a history of other psychopathology, and symptoms of PTSD in parents predict childhood-onset PTSD. Many adolescent and adult psychopathologic conditions, such as conduct disorder, depression, and some personality disorders, might relate to previous trauma. PTSD is also linked to mood disorders and disruptive behavior. Separation anxiety is common in children with PTSD. The lifetime prevalence of PTSD by age 18 yr is approximately 6%. Up to 40% show symptoms, but do not fulfill the diagnostic criteria.

Events that pose physical injury, harm, or death to the child, to the child's caregiver, or to others close to the child and that produce considerable stress, fear, and/or helplessness are required to make the diagnosis of PTSD. Three clusters of symptoms are also essential for diagnosis: reexperiencing, avoidance, and hyperarousal. Persistent reexperiencing of the stressor through intrusive recollections, nightmares, and reenactment in play are typical responses in children. Persistent avoidance of reminders and numbing of emotional responsiveness, such as isolation, amnesia, and avoidance, constitute the second cluster of behaviors. Symptoms of hyperarousal, such as hypervigilance, poor concentration, extreme startle responses, agitation, and sleep problems, complete the symptom profile of PTSD. Occasionally, children regress in some of their developmental milestones after a traumatic event. Avoidance symptoms are commonly observable in younger children, whereas older children may be more able to describe reexperiencing and hyperarousal symptoms. Repetitive play involving the event, psychosomatic symptoms, and nightmares may also be observed.

Initial interventions after a trauma should focus on reunification with a parent and attending to the child's physical needs in a safe place. Aggressive treatment of pain might decrease the likelihood of PTSD, and facilitating a return to comforting routines, including regular sleep, is indicated. Long-term treatment may include individual, group, school-based, or family therapy, as well as pharmacotherapy, in selected cases. Individual treatment involves transforming the child's concept of himself or herself as victim to that of survivor and can occur through play therapy, psychodynamic therapy, or CBT. Group work is also helpful for identifying which children might need more intensive assistance. Goals of family work include helping the child establish a sense of security, validating the child's emotions, and anticipating situations when the child will need more support from the family. Clonidine or guanfacine may be helpful for sleep disturbance, persistent arousal, and exaggerated startle response. Recent randomized controlled trials in children and adolescents with PTSD did not find a significant difference between SSRI and placebo. SSRIs may be considered in pediatric patients with PTSD who have comorbid conditions responsive to SSRIs, for example, depression, affective numbing, and anxiety (see Table 21.4 in Chapter 21). As for many other anxiety disorders, CBT is the psychotherapeutic intervention with the most empiric support.

ANXIETY ASSOCIATED WITH MEDICAL CONDITIONS

It is prudent to rule out organic conditions such as hyperthyroidism, caffeinism (carbonated beverages), hypoglycemia, central nervous system disorders (delirium, encephalopathy, brain tumors), migraine, asthma, lead poisoning, cardiac arrhythmias, and, rarely, pulmonary embolism, hyperparathyroidism, systemic lupus erythematosus, anaphylaxis, porphyria or pheochromocytoma, before making a diagnosis of an anxiety disorder. Some prescription drugs with side effects that can mimic anxiety include antiasthmatic agents, steroids, sympathomimetics, SSRIs (initiation), anticholinergic agents, and antipsychotics. Nonprescription drugs causing anxiety include diet pills, antihistamines, stimulate drugs of abuse, drug withdrawal, and cold medicines.

Chronic illness is also an underlying cause of anxiety. Children are not often emotionally and cognitively competent to understand the implications of a serious and prolonged illness. In addition to the physiologic implications of illness they must also attend to the hospitalizations, procedures and medications that permeate their everyday schedule. This experience affects their schooling, friendships, activities, and dynamics of the nuclear family including the experiences of their well siblings.

School issues surrounding both prolonged absences and school re-entry following a medical condition can cause, or reinforce and escalate existing anxiety. School is a foundation not only for learning, but it is central to children's social experiences and feelings of normalcy. It is often impeded and stunted by illness. Academic struggles can result from missing classes, medication and emotional status. Children with chronic conditions are also socially disadvantaged with friendship networks hampered by unstable attendance or by social rejection for being different. Consulting with the school psychologist can be beneficial in preparing teachers and classmates before the child returns to school. An agreement between the student and school staff should be implemented outlining a plan for taking medication, needing rest or consulting on other needs. If the child and family wish, an informational meeting with students and teachers can normalize the situation. Explaining the condition makes it less scary for children who catastrophize or worry about contagion. Classmates and teachers are a natural and accessible resource and can be an incredible support and community. Medication may also be warranted to supplement social supports.

The experiences of the siblings of children with chronic illness are often forgotten with familial resources focused on medical and financial consequences, and the emotional and physical functioning of the ill child. It is not uncommon for the siblings of ill children to experience depression and anxiety as well. Assessing their social support systems, communication opportunities with parents and emotional outlets are critical to maintaining healthy functioning. Maintaining a redefined schedule of after-school activities and social engagements are helpful in allowing siblings to continue in school.

SAFETY AND EFFICACY CONCERNS ABOUT SSRIS

No empiric evidence suggests the superiority of one SSRI over another. Data are limited as far as combining medications are concerned. SSRIs are usually well tolerated by most children and adolescents. The FDA issued a black box warning of increased agitation and suicidality among adolescents and children on these medications. This warning was based on review of studies in children and adolescents with major depression and not anxiety disorders. Close monitoring is always warranted.

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Chapter 26

Mood Disorders

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Mood disorders are interrelated sets of psychiatric symptoms characterized by a core deficit in emotional self-regulation. Classically, the mood disorders have been divided into depressive and bipolar disorders, representing the 2 emotional polarities (dysphoric ["low"] and euphoric ["high"] mood).

26.1 Major and Other Depressive Disorders

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The depressive disorders include major depressive, persistent depressive, disruptive mood dysregulation, other specified/unspecified

Table 26-1 DSM-5 Diagnostic Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2 wk period and represent a change from previous functioning; at least 1 of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
  1. Depressed most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
  2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
  3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gain.
  4. Insomnia or hypersomnia nearly every day.
  5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
  6. Fatigue or loss of energy nearly every day.
  7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
  8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
  9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A-C represent a major depressive episode.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. There has never been a manic episode or a hypomanic episode.

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Table 26-2 DSM-5 Diagnostic Criteria for Persistent Depressive Disorder

A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 yr.

Note: In children and adolescents, mood can be irritable and duration must be at least 1 yr.

B. Presence, while depressed, of 2 (or more) of the following:
  1. Poor appetite or overeating.
  2. Insomnia or hypersomnia.
  3. Low energy or fatigue.
  4. Low self-esteem.
  5. Poor concentration or difficulty making decisions.
  6. Feelings of hopelessness.

C. During the 2 yr period (1 yr for children or adolescents) of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than 2 mo at a time.
D. Criteria for a major depressive disorder may be continuously present for 2 yr.
E. There has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder.
F. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
G. The symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism).
H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: Because the criteria for a major depressive episode include 4 symptoms that are absent from the symptom list for persistent depressive disorder (dysthymia), a very limited number of individuals will have depressive symptoms that have persisted longer than 2 yr but will not meet criteria for persistent depressive disorder. If full criteria for a major depressive episode have been met at some point during the current episode of illness, they should be given a diagnosis of major depressive disorder. Otherwise, a diagnosis of other specified depressive disorder or unspecified depressive disorder is warranted.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 168–169.

depressive, premenstrual dysphoric, and substance/medication-induced disorders, as well as depressive disorder caused by another medical condition.

DESCRIPTION

Major depressive disorder (**MDD**) is characterized by a distinct period of at least 2 wk (an episode; Table 26-1) in which there is a depressed or irritable mood and/or loss of interest or pleasure in almost all activities that is present for most of the day, nearly every day. Major depression is associated with characteristic vegetative and cognitive symptoms, including disturbances in appetite, sleep, energy, and activity level; impaired concentration; thoughts of worthlessness or guilt; and suicidal thoughts or actions. Major depression is considered to be mild if few or no, symptoms in excess of those required to make the diagnosis are present, and the symptoms are mildly distressing and manageable and result in minor functional impairment. Major depression is considered to be severe if symptoms substantially in excess of those required to make the diagnosis are present, and the symptoms are highly distressing and unmanageable and markedly impair function. Moderate major depression is intermediate in severity between mild and severe.

Persistent depressive disorder (dysthymia) (Table 26-2) is characterized by depressed or irritable mood for more days than not, for at least 1 yr (in children/adolescents). As with major depression, this chronic form of depression is associated with characteristic vegetative and cognitive symptoms; however, the cognitive symptoms of persistent depression are less severe (e.g., low self-esteem rather than worthlessness, hopelessness rather than suicidality). In the same way as major depression, persistent depressive disorder is characterized as mild, moderate, or severe.

Overall, the clinical presentation of major and persistent depressive disorders in children and adolescents is similar to that in adults. The prominence of the symptoms can change with age: irritability and somatic complaints may be more common in children, and energy, activity level, appetite, and sleep disturbances may be more common in adolescents. Because of the cognitive and linguistic immaturities of young children, symptoms of depression in that age group may be more likely to be observed than self-reported.

The core feature of ***disruptive mood dysregulation disorder*** (**DMDD**) (Table 26-3) is severe, persistent irritability evident for at least 12 mo in multiple settings (at home, at school, with peers). This irritability is characterized by frequent and severe temper outbursts (verbal and/or physical) and a persistently irritable or angry mood that is present for most of the day, nearly every day. This diagnosis is intended to more accurately characterize the extreme irritability heretofore considered by some investigators to be a developmental presentation of bipolar disorder (see Chapter 26.2), and to distinguish extreme irritability from the milder presentations characteristic of oppositional defiant and intermittent explosive disorders (see Chapter 29).

Table 26-3 DSM-5 Diagnostic Criteria for Disruptive Mood Dysregulation Disorder

A. Severe recurrent temper outbursts manifested verbally (e.g., verbal rages) and/or behaviorally (e.g., physical aggression toward people or property) that are grossly out of proportion in intensity or duration to the situation or provocation.
B. The temper outbursts are inconsistent with developmental level.
C. The temper outbursts occur, on average, 3 or more times per week.
D. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observable by others (e.g., parents, teachers, peers).
E. Criteria A-D have been present for 12 or more months. Throughout that time, the individual has not had a period lasting 3 or more consecutive months without all of the symptoms in Criteria A-D.
F. Criteria A and D are present in at least 2 of 3 settings (i.e., at home, at school, with peers) and are severe in at least 1 of these.
G. The diagnosis should not be made for the first time before age 6 yr or after age 18 yr.
H. By history or observation, the age at onset of Criteria A-E is before 10 yr.
I. There has never been a distinct period lasting more than 1 day during which the full symptom criteria, except duration, for a manic or hypomanic episode have been met.

Note: Developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation, should not be considered as a symptom of mania or hypomania.

J. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by another mental disorder (e.g., autism spectrum disorder, posttraumatic stress disorder, separation anxiety disorder, persistent depressive disorder [dysthymia]).

Note: The diagnosis cannot coexist with oppositional defiant disorder, intermittent explosive disorder, or bipolar disorder, though it can coexist with others, including major depressive disorder, attention-deficit/hyperactivity disorder, conduct disorder, and substance use disorders. Individuals whose symptoms meet criteria for both disruptive mood dysregulation disorder and oppositional defiant disorder should only be given the diagnosis of disruptive mood dysregulation disorder. If an individual has ever experienced a manic or hypomanic episode, the diagnosis of disruptive mood dysregulation disorder should not be assigned.

K. The symptoms are not attributable to the physiologic effects of a substance or to another medical or neurologic condition.

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 156.

Other specified/unspecified depressive disorder (subsyndromal depressive disorder) applies to presentations in which symptoms characteristic of a depressive disorder are present and cause clinically significant distress or functional impairment, but do not meet the full criteria for any of the disorders in this diagnostic class.

EPIDEMIOLOGY

The overall prevalence of parent-reported diagnosis of depressive disorder in the United States (excluding DMDD) among 3-17 yr old children is ~2.1% (current) and ~3.9% (ever); the prevalence rate increases to ~12.8% (lifetime) for 12-17 yr olds. The male : female ratio (excluding DMDD) approximates 1 : 1 during childhood and beginning in early adolescence rises to 1 : 1.5-3.0 in adulthood.

Based upon rates of chronic and severe persistent irritability, which is the core feature of DMDD, the overall 6 mo to 1 yr prevalence has been estimated to fall within the 2-5% range. In 3 community samples, the 3 mo prevalence rate of DMDD ranged from 0.8-3.3%, with the highest rates occurring in preschoolers. Approximately 5-10% of children and adolescents are estimated to have subsyndromal (unspecified) depression.

CLINICAL COURSE

Major depression may first appear at any age, but the likelihood of onset increases markedly with puberty. Incidence appears to peak in the 20s. The median duration of a major depressive episode approximates 5-8 mo for clinically referred youth and 3-6 mo for community samples. The course is quite variable in that some individuals rarely or never experience remission, whereas others experience many years with few or no symptoms between episodes. Persistent depressive disorder often has an early and insidious onset, and by definition, a chronic course (average untreated duration in both clinical and community samples: 3.5 yr).

Prepubertal depressive disorders exhibit more heterotypic than homotypic continuity; depressed children appear to be more likely to develop nondepressive psychiatric disorders in adulthood than depressive disorders. Adolescents exhibit greater homotypic continuity, with the probability of recurrence of depression reaching 50%-70% after 5 yr. The persistence of even mild depressive symptoms during remission is a powerful predictor of recurrence; other negative prognostic factors include more severe symptoms, longer time to remission, history of maltreatment, and comorbid psychiatric disorders. Up to 20% of depressed adolescents develop a bipolar disorder; the risk is higher among adolescents who have a high family loading for bipolar disorder, who have psychotic depression, or who have had pharmacologically induced mania.

DIFFERENTIAL DIAGNOSIS

A number of psychiatric disorders, general medical conditions, and medications can generate symptoms of depression or irritability and must be distinguished from the depressive disorders. The psychiatric disorders include autism spectrum (see Chapter 30), attention-deficit/hyperactivity (ADHD; see Chapter 33), bipolar, anxiety (see Chapter 25), trauma- and stressor-related, disruptive/impulse control/conduct, and substance-related disorders. Medical conditions include neurologic disorders, endocrine disorders, infectious diseases, tumors, anemia, uremia, failure to thrive, chronic fatigue disorder, and pain disorder. Medications include narcotics, chemotherapy agents, β-blockers, corticosteroids, and contraceptives. The diagnosis of a depressive disorder should be made after these other explanations for the observed symptoms have been ruled out.

COMORBIDITY

Major and persistent depressive disorders often co-occur with other psychiatric disorders. Depending on the setting and source of referral, 40-90% of youths with a depressive disorder have other psychiatric disorders, and up to 50% have 2 or more comorbid diagnoses. The most common comorbid diagnosis is an anxiety disorder and as such may reflect a common diathesis; other common comorbidities include ADHD and disruptive behavior, eating, and substance use disorders. The development of depressive disorders can both lead and follow the development of the comorbid disorders.

Preliminary data suggests the co-occurrence of DMDD with other psychiatric disorders, including other depressive disorders, ADHD, conduct disorder, and substance use disorders, from 60-90% of the time. Because the symptoms of DMDD overlap in part with symptoms of bipolar disorder (see Chapter 26.2), oppositional defiant disorder (see Chapter 29), and intermittent explosive disorder (see Chapter 29), by *Diagnostic Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) convention hierarchical diagnostic rules apply (i.e., bipolar disorder takes precedence over DMDD if a manic/hypomanic episode has ever occurred; DMDD takes precedence over oppositional defiant disorder and intermittent explosive disorder if full criteria for DMDD are met).

SEQUELAE

Approximately 60% of youths with MDD report thinking about suicide, and 30% actually attempt suicide. The risk of suicidal behavior increases if there is a history of suicide attempts, exposure to adverse psychosocial circumstances, a family history of suicidal behavior, or comorbid psychiatric disorders. Youths with depressive disorders are also at high

risk of substance abuse, impaired family and peer relationships, early pregnancy, legal problems, educational and occupational underachievement, and poor adjustment to life stressors, including physical illness.

Children with DMDD have displayed elevated rates of social impairments, school suspension, and service use. Irritability in adolescence has predicted the development of major depressive and dysthymic disorders and generalized anxiety disorder (but not bipolar disorder) 20 yr later, as well as lower educational attainment and income.

ETIOLOGY AND RISK FACTORS

Current models of vulnerability to depressive disorders are grounded in gene by environment pathways. Genetic studies have repeatedly demonstrated the heritability of depressive disorders, with monozygotic twin studies finding concordance rates of 40-65%. In families, both bottom-up (children to parents) and top-down (parents to children) studies have shown a 2-4–fold bidirectional increase in depression among 1st-degree relatives. The exact nature of genetic expression remains unclear. Cerebral variations in structure and function (particularly serotonergic), the function of the hypothalamic–pituitary–adrenal axis, difficult temperament/personality (i.e., negative affectivity), and ruminative, self-devaluating cognitive style have been implicated as components of biologic vulnerability. The great majority of depressive disorders arise in youth with long-standing psychosocial difficulties, among the most predictive of which are physical/sexual abuse, neglect, chronic illness, school difficulties (bullying, academic failure), social isolation, family or marital disharmony, divorce/separation, parental psychopathology, and domestic violence. Longitudinal studies demonstrate the greater importance of environmental influences in children who become depressed compared to adults who become depressed. Factors shown to be protective against the development of depression include a positive relationship with a parent, better family function, closer parental supervision/monitoring/involvement, a prosocial peer group, higher IQ, and greater educational aspirations.

PREVENTION

Numerous experimental trials have sought to demonstrate the effectiveness of psychological or educational strategies in preventing the onset of depressive disorders in children and adolescents. These programs generally have provided information about the link between depressed mood and depressogenic thoughts and behaviors, and training in skills intended to modify these thoughts and behaviors. A meta-analytic review found small to moderate effects of these programs at both postintervention and follow-up (overall mean effect size: 0.16), with selective programs (targeted at high-risk groups) performing better than universal programs. A Cochrane review found some evidence that depression prevention programs may have a small favorable effect compared with no intervention, but no effect compared to attention controls.

SCREENING/CASE FINDING

Adolescents presenting in the primary care setting should be queried, along with their parent(s), about depressed mood as part of the routine clinical interview. A typical screening question would be "Everyone feels sad or angry some of the time, how about you (or your teen)?" The parents of younger children can be queried about overt signs of depression, such as tearfulness, irritability, boredom, or social isolation. A number of standardized broadband screening instruments widely used in the primary care setting (e.g., *Pediatric Symptom Checklist*, *Strengths and Difficulties Questionnaire*, *Vanderbilt ADHD Diagnostic Rating Scales*) have items specific to sad mood, and as such can be used to focus the interview.

The role of universal depression screening using standardized narrowband (depression-specific) instruments is unclear. A Cochrane review found that the use of depression screening in primary care has little or no impact on the recognition, management, or outcome of depression. The United States Preventive Services Task Force recommends the use of depression screening instruments only among adolescents, and only when systems are in place to ensure adequate follow-up. Targeted screening of known high-risk groups (e.g., youth who are homeless, refugees, attracted to the same sex, involved with child welfare or juvenile justice) or of youth experiencing known psychosocial adversities (see "Etiology/Risk Factors" above) or self-reporting a dysphoric mood may be a higher-yield case-finding strategy than universal screening (Fig. 26-1).

STEPPED MANAGEMENT

Because of the high rates of response to placebo and attention comparators as well as to brief therapy in the treatment of pediatric depression, clinical practice guidelines increasingly are advocating a stepped approach to the management of depressed youth. The stepped approach involves active case finding and initial management in the primary care setting if appropriate, with referral to increasingly intensive and specialized interventions as indicated by the clinical status of the patient.

EARLY INTERVENTION

Youth and/or their parents presenting in the primary care setting who self-report, or respond affirmatively to queries about, a distressing life experience or a depressed or irritable mood, should be offered the opportunity to talk about the situation with the pediatric practitioner (in private with the older youth as indicated). By engaging in active listening (e.g., "I hear how upset you have been feeling, tell me more about what happened to make you feel that way"), the pediatric practitioner can begin to assess the onset, duration, context, and severity of the symptoms, and associated dangerousness, distress, and functional impairment. In the absence of acute dangerousness (e.g., suicidality, psychosis, substance abuse) and significant distress or functional impairment, the pediatric practitioner can schedule a follow-up appointment within 1-2 wk to conduct a depression assessment. At this follow-up visit, to assist with decision making around appropriate level of care, a depression screening instrument can be administered (Table 26-4) and additional risk factors (see "Etiology/Risk Factors" above) can be explored.

For mild symptoms (manageable and not functionally impairing) and in the absence of major risk factors (e.g., suicidality, psychosis, substance use, history of depression, mania, or traumatic exposures, parental psychopathology [particularly depression]) or severe family dysfunction), guided self-help (anticipatory guidance) with watchful waiting may suffice. Guided self-help can include provision of educational materials (e.g., pamphlets, books, workbooks, internet sites) that provide information to the youth about dealing with stressful situations; and advice to parents about strengthening the parent-child relationship and modifying adverse environmental exposures (e.g., taking action against bullying, increasing opportunities for social interaction/support, protecting the child from exposure to marital discord) as depressogenic buffers. During the period of guided self-help, additional follow-up visits should be scheduled.

For youth who continue to have mild depression after a few weeks of guided self-help, supportive therapy by a mental health professional (ideally colocated in the primary care, school, or community setting) may be an appropriate subsequent step. Supportive psychotherapy, which can be delivered in individual or group formats, focuses on teaching thoughts (e.g., positive self-talk) and behaviors (e.g., pleasurable activities, relaxation, problem-solving, effective communication) known to ameliorate depressive symptoms, as well as providing concrete social or material problem-solving assistance to the youth or family as needed.

TREATMENT

For youth who have not responded to approximately 4-8 wk of supportive psychotherapy, or who from the outset exhibit moderate to severe, comorbid, or recurrent depression or suicidality, or who have a history of mania, traumatic exposures or severe family dysfunction or psychopathology, assessment and treatment in the specialty mental health setting by a child-trained mental health clinician should be provided (see Chapter 20). The mental health clinician should be

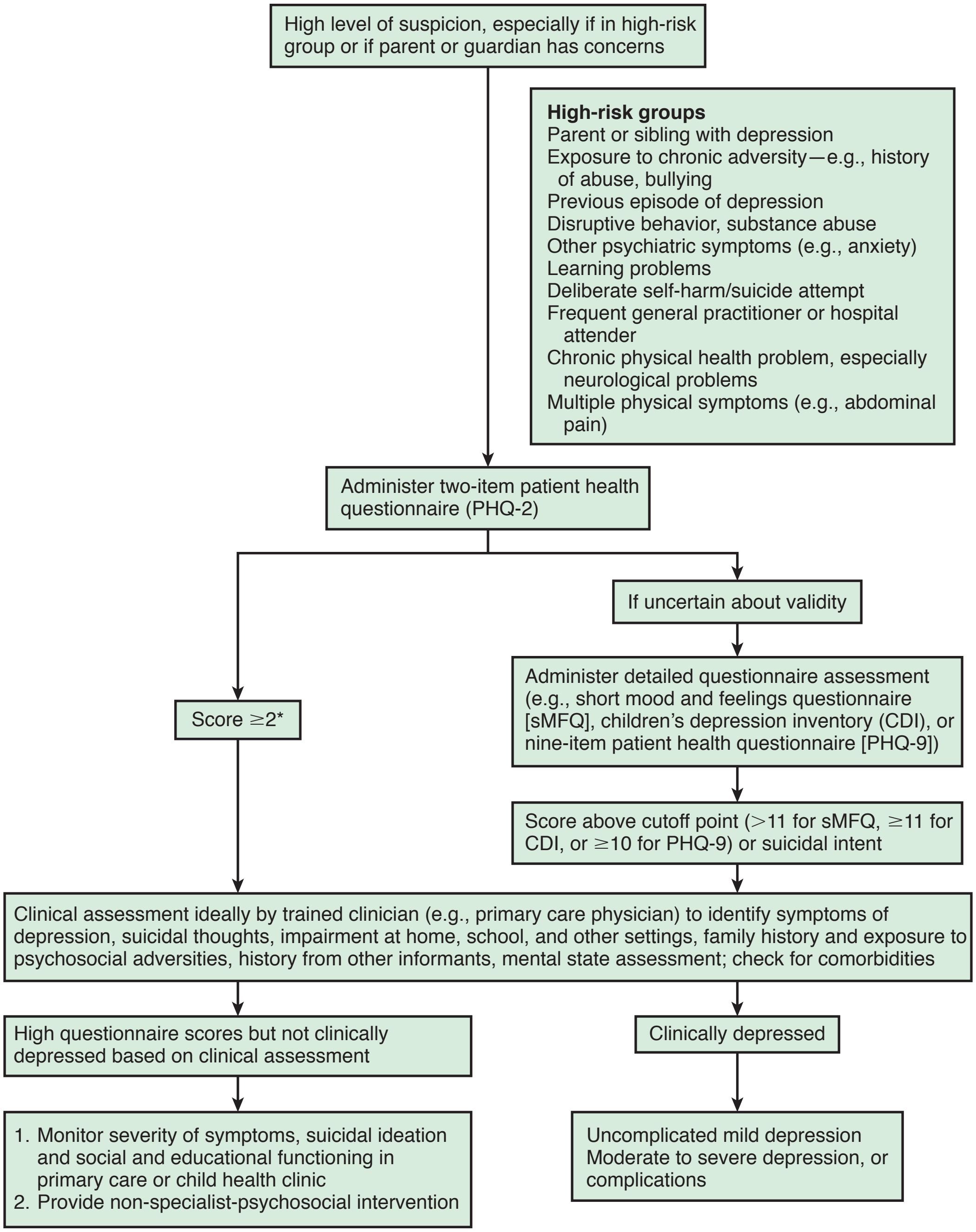

Figure 26-1 Detection of depression in adolescents in nonspecialist settings. *If patient scores < 2, generally no further action is needed. *(From Thapar A, Collishaw S, Pine DS, Thapar AK: Depression in adolescence.* Lancet *379:1056–1066, 2012. Fig. 1.)*

trained to the appropriate level of competence in the specific services he/she is asked to provide.

For moderate to severe depression, specific manualized psychotherapies, antidepressant medication, or a combination of the two should be provided. At present, there is insufficient evidence upon which to base definitive conclusions about the relative effectiveness of these treatments. The main goal of the acute treatment phase is to achieve response, which typically is defined as at least a 50% reduction in depressive symptoms as assessed by a standardized rating scale (see Table 26-4). Full recovery (i.e., absence of a depressive diagnosis) should be the ultimate treatment goal.

Clinical trials of acute treatments have generated support for the efficacy of ***cognitive-behavioral therapy*** **(CBT)** and ***interpersonal therapy*** as monotherapies in depressed youth, but effect sizes are modest (0.35 and 0.26, respectively). CBT focuses on identifying and correcting cognitive distortions that may lead to depressed mood and teaches problem-solving, behavior activation, social communication, and emotional regulation skills to combat depression. interpersonal therapy focuses on enhancing interpersonal problem solving and social communication to decrease interpersonal conflicts. Each of these therapies typically involves approximately 8-12 weekly visits.

Limited evidence suggests that family therapy may be more effective than no treatment on decreasing depression and improving family functioning. Because of the heterogeneity of the evidence base, however, the use of better supported therapies would at this time seem to be preferable over family therapy.

Two ***selective serotonin reuptake inhibitors*** **(SSRIs),** fluoxetine and escitalopram, are the only antidepressants approved by the FDA

Table 26-4 Depression-Specific Screening Instruments

NAME OF INSTRUMENT	INFORMANT(S)	AGE RANGE	NUMBER OF ITEMS
Preschool Feelings Checklist	Parent	3-5.6 yr	20
Preschool Symptom	Self-Report Youth, Parent, Teacher	3-5 yr	25
Center for Epidemiologic Studies-Depression-Children	Youth	6-18 yr	20
Children's Depression Rating Scale-Revised	Youth, Parent, Clinician	6-18 yr	47
Children's Depression Inventory-Second Edition	Youth, Parent, Teacher	7-17 yr	28/17/12
Depression Self-Rating Scale	Youth	7-13 yr	18
Beck Depression Inventory for Youth	Youth	7-14 yr	20
Mood and Feelings Questionnaire	Youth, Parent	7-18 yr	33-34
Reynolds Child Depression Scale	Youth	8-13 yr	30
Reynolds Adolescent Depression Scale-Second Edition	Youth	11-20 yr	30
Beck Depression Inventory	Youth	13+ yr	21
Patient Health Questionnaire-9	Youth	13-17 yr	9

for the treatment of depression, and fluoxetine alone is approved for preadolescents (see Chapter 21.1). These agents should be 1st-line for pharmacotherapy of pediatric depression, unless other factors (e.g., comorbidities, side-effect profiles, personal or family history of response to a specific medication) favor an alternative SSRI (preferably sertraline or citalopram). Resource limitations may necessitate provision of pharmacotherapy in the primary care setting; the safety and efficacy of this practice can be enhanced by regular consultation with a child and adolescent psychiatrist.

Randomized controlled trials **(RCTs)** of the effectiveness of antidepressants are mixed. Based on a large meta-analysis of RCTs, approximately 60% of youths with depression respond to antidepressants (vs. 50% for placebo), yielding a ***number needed to treat*** of 10, but only around 30% of medicated depressed youth experience symptom remission. Fluoxetine has consistently demonstrated greater efficacy, with a number needed to treat of 6, and is the only SSRI separating from placebo in studies of depressed preadolescents. Studies of other classes of antidepressant medications have not demonstrated clear superiority over placebo, and tricyclic medications and paroxetine in particular are not currently recommended for use in youth because of their clearly unfavorable risk : benefit profiles. The absolute risk for suicidal thoughts in youth with major depression approximates 3% (treated with antidepressant) versus 2% (given placebo), translating to a ***number needed to harm*** of 112.

Clinical severity, comorbidity, family conflict, low drug concentration, nonadherence, anhedonia, sleep difficulties, subsyndromal manic symptoms, and child maltreatment have all been related to treatment resistance. Approximately 50% of depressed youth failing to respond to the first SSRI respond after switching to a second antidepressant medication plus CBT, versus approximately 40% who respond to a second medication alone. For youth with psychotic depression, augmenting the antidepressant with an atypical antipsychotic medication should be considered, while monitoring closely for side effects.

The SSRIs have been well tolerated by children and adolescents. The most common side effects include irritability, gastrointestinal symptoms, sleep disturbance, restlessness, diaphoresis, headaches, changes in appetite, dizziness, dry mouth, and sexual dysfunction. Approximately 5% of youths, particularly children, develop increased impulsivity, agitation, and irritability (behavioral activation) on SSRIs, but the symptoms quickly resolve when the medication dose is reduced or the medication is discontinued. More rarely, the use of antidepressants has been associated with serotonin toxicity, increased predisposition to bleeding, abnormal heart rhythms (citalopram causes dose-dependent QT-interval prolongation and should not be prescribed at doses greater than 40 mg/day) and increased suicidal thoughts.

The initial dose of SSRI medication should be approximately one-half of the adult dose (e.g., 10 mg of fluoxetine). Some studies have reported that the half-lives of SSRIs other than fluoxetine are much shorter in children than in adults; therefore daily withdrawal side effects can be observed with these medications if they are administered once daily. Clinical response, tolerability, and emergence of behavioral activation, mania, or suicidal thoughts should be assessed frequently (preferably weekly) for the first 4 wk. If the youth has safely tolerated the antidepressant, the initial dose may be doubled at 4 wk if an adequate response (at least 50% reduction in symptom severity as measured by standardized rating scales) has not been achieved, with biweekly monitoring recommended. Patients who have responded by 8 wk can then be monitored less frequently (up to monthly) until remission (no longer meets diagnostic criteria) has been achieved. Patients treated in the primary care setting who have not responded by 8 wk or remitted by 12 wk should be referred to the specialty mental health setting for advanced care.

Because of the high rate of recurrence, successful treatment should continue for 6-12 mo. At the conclusion of treatment, all antidepressants should be discontinued gradually to avoid withdrawal symptoms (gastrointestinal upset, disequilibrium, sleep disruption, flu-like symptoms, sensory disturbances). Patients with recurrent (2 or more), chronic, or severe major depression can require treatment beyond 12 mo.

Table 26-5 summarizes screening, assessment, and treatment recommendations for depression.

LEVEL OF CARE

Most children and adolescents with mild to moderate depressive disorders can be safely and effectively treated as outpatients, provided that a clinically appropriate schedule of visits can be maintained through the phases of treatment. Inpatient treatment should be considered for youth who present with a high risk of suicide, serious self-harm, or self-neglect, or when the family is not able to provide an appropriate level of supervision or follow-up with outpatient treatment recommendations, or when comprehensive assessment for diagnostic clarity is needed. When considering inpatient admission for a young person with depression, the benefits of inpatient treatment needs to be balanced against potential detrimental effects, such as the loss of family and community support.

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Table 26-5 Screening and Treatment for Major Depressive Disorder in Youths

RECOMMENDATION	ADOLESCENTS (12-18 Yr)	CHILDREN (7-11 Yr)
Screening	Screen (when systems for diagnosis, treatment, and follow-up are in place) Grade B	No recommendations Grade I (insufficient evidence)
Risk assessment	Risk factors for major depressive disorder include parental depression, having comorbid mental health or chronic medical conditions, and having experienced a major negative life event	
Screening tests	The following have been shown to do well in teens in primary care settings: Patient Health Questionnaire for Adolescents (PHQ-A) Beck Depression Inventory—Primary Care version (BDI-PC)	Screening instruments perform less well in younger children
Treatments	Among pharmacotherapies, fluoxetine, a SSRI, has been found efficacious. However, because of risk of suicidality, SSRIs should be considered only if clinical monitoring is possible. Various modes of psychotherapy, and pharmacotherapy combined with psychotherapy, have been found efficacious	Evidence on the balance of benefits and harms of treatment of younger children is insufficient for a recommendation

For a summary of the evidence systematically reviewed in making these recommendations, the full recommendation statement, and supporting documents, please go to http://www.AHRQ.gov/clinic/USPSTF/USPSCHDEPR.htm.

26.2 Bipolar and Related Disorders

Heather J. Walter, Natalija Bogdanovic, and David R. DeMaso

DESCRIPTION

The bipolar and related disorders include bipolar I, bipolar II, cyclothymic, and other specified/unspecified bipolar and related disorders, as well as bipolar and related disorder caused by another medical condition.

A manic episode (Table 26-6) is characterized by a distinct period of at least 1 wk in which there is an abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy that is present for most of the day, nearly every day (or any duration if hospitalization is necessary). The episode is associated with characteristic cognitive and behavioral symptoms, including disturbances in self-regard, speech, attention, thought, activity, impulsivity, and sleep. To diagnose ***bipolar I disorder***, criteria must be met for at least 1 manic episode, and the episode must not be better explained by a psychotic disorder. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes. Bipolar I disorder is rated as mild, moderate, or severe in the same way as the depressive disorders (see Description section of Chapter 26.1).

To diagnose **bipolar II disorder,** criteria must be met for at least 1 hypomanic episode and at least 1 major depressive episode. A hypomanic episode is similar to a manic episode, but is briefer (at least 4 days) and less severe (causes less impairment in functioning, is not associated with psychosis, and would not require hospitalization). In bipolar II disorder, there must never have been a manic disorder, the episodes must not be better explained by a psychotic disorder, and the symptoms of depression or the unpredictability caused by frequent alternation between periods of depression and hypomania must cause clinically significant distress or functional impairment. Bipolar II disorder is rated as mild, moderate, or severe in the same way as bipolar I disorder.

Cyclothymic disorder is characterized by a period of at least 1 yr (in children and adolescents) in which there are numerous periods with hypomanic and depressive symptoms that do not meet criteria for a hypomanic episode or a major depressive episode, respectively.

Other specified/unspecified bipolar and related disorders (subsyndromal bipolar disorder) applies to presentations in which symptoms characteristic of a bipolar and related disorder are present and cause distress or functional impairment, but do not meet the full criteria for any of the disorders in this diagnostic class. Although this diagnosis (formerly known as bipolar disorder, not otherwise specified)

Table 26-6 DSM-5 Diagnostic Criteria for a Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 wk and present most of the day, nearly every day (or any duration if hospitalization is necessary).
B. During the period of mood disturbance and increased energy or activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
 1. Inflated self-esteem or grandiosity.
 2. Decreased need for sleep (e.g., feels rested after only 3 hr of sleep).
 3. More talkative than usual or pressure to keep talking.
 4. Flight of ideas or subjective experience that thoughts are racing.
 5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
 6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
 7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
D. The episode is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiologic effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

Note: Criteria A-D constitute a manic episode. At least 1 lifetime manic episode is required for the diagnosis of bipolar I disorder.

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 124.

heretofore had frequently been applied to children with severe and chronic mood and behavioral dysregulation who did not precisely fit other diagnostic categories, the empiric support for the validity of this practice has been sparse. Many children who formerly received this diagnosis will meet criteria for DMDD (see Chapter 26.1).

In adolescents, the clinical manifestations of bipolar disorder are similar to those in adults, and psychosis (delusions, hallucinations) often is an associated symptom. Mood in a manic episode is often described as euphoric, excessively cheerful, high, or "feeling on top of the world." During the episode, the adolescent may engage in multiple new projects that are initiated with little knowledge of the topic and often at unusual hours (in the middle of the night). Inflated self-esteem is usually present, ranging from uncritical self-confidence to marked grandiosity, and may reach delusional proportions. The adolescent may sleep little if at all for days at a time and nonetheless feel rested and full of energy. Speech can be rapid, pressured, and loud and characterized by jokes, puns, amusing irrelevancies, and theatricality. Frequently there is a flight of ideas evidenced by a nearly continuous flow of accelerated speech, with abrupt shifts from one topic to another. Distractibility is evidenced by an inability to censor irrelevant extraneous stimuli, which often prevents an individual with mania from engaging in a rational conversation. The expansive mood, grandiosity, and poor judgment often lead to reckless involvement in activities with high potential for personal harm.

There is controversy about the applicability of the bipolar diagnostic criteria to prepubertal children. It may be developmentally normal for children to be elated, expansive, grandiose, or talkative, reducing the specificity of these symptoms to this disorder. In addition, the distractibility, overactivity, and impulsivity formerly ascribed to bipolar disorder by some investigators may be better explained by a diagnosis of ADHD. The presentations of severe irritability formerly diagnosed as bipolar disorder may be better captured by the diagnosis of DMDD.

EPIDEMIOLOGY

The lifetime prevalence of the bipolar disorders among adults approximates 1-3%; rates among youth generally have been less than 1%. For bipolar I, the male : female ratio approximates 1.1 : 1.

CLINICAL COURSE

The mean age of onset of the first manic episode is approximately 18 yr for bipolar I disorder. Premorbid problems are common in bipolar disorder, especially difficulties with mood and behavioral regulation. Premorbid anxiety also is common. The early course of adolescent-onset bipolar disorder appears to be more chronic and refractory to treatment than adult-onset bipolar disorder. Comorbidity predicts functional impairment and age at onset predicts duration of episodes. Sleep impairment and family conflict are inversely related to favorable treatment response, suggesting important targets for treatment. The bipolar disorders are highly recurrent, and more than 80% of bipolar I patients go on to have additional mood episodes. Recurrent episodes can approximate 4 in 10 yr, with the interepisode interval shortening as the patient ages. Although the majority of patients with bipolar I return to a fully functional level between episodes, approximately one-third continue to be symptomatic and functionally impaired between episodes. In a 14 yr follow-up study, children 4-16 yr of age exceeding the clinical cutpoint for the dysregulation ("bipolar") profile on the Child Behavior Checklist were found to have increased rates of anxiety, mood, disruptive behavior, and substance abuse disorders in adulthood.

DIFFERENTIAL DIAGNOSIS

A number of psychiatric disorders, general medical conditions, and medications can generate manic-like symptoms and must be distinguished from the bipolar and related disorders. The psychiatric disorders include ADHD, oppositional defiant, intermittent explosive, posttraumatic stress, depressive, anxiety, substance abuse, and borderline personality disorders. Medical conditions include neurologic disorders, endocrine disorders, infectious diseases, tumors, anemia, uremia, and vitamin deficiencies. Medications include androgens, bronchodilators, cardiovascular medications, corticosteroids, chemotherapy agents, thyroid preparations, and certain psychiatric medications (benzodiazepines, antidepressants, stimulants). The diagnosis of a bipolar disorder should be made after these other explanations for the observed symptoms have been ruled out.

COMORBIDITY

Nearly 75% of individuals with bipolar disorders have co-occurring anxiety disorders, and nearly 50% have co-occurring attention, disruptive/impulse control/conduct, and substance use disorders.

SEQUELAE

The lifetime risk of suicide in individuals with bipolar disorder is estimated to be at least 15 times that of the general population. Youths with bipolar disorders are also at high risk for substance abuse, antisocial behavior, impaired academic performance, impaired family and peer relationships, and poor adjustment to life stressors.

ETIOLOGY/RISK FACTORS

Twin studies suggest the heritability of bipolar disorder is greater than 60%. Offspring of parents with bipolar disorders are at high risk for early-onset bipolar disorders, and there is an average 10-fold increased risk among adult relatives of individuals with bipolar disorder, with the magnitude of risk increasing with the degree of kinship. Bipolar disorder and schizophrenia likely share a genetic origin, reflected in familial co-aggregation of the two disorders.

Dysthymic (sad), cyclothymic (labile), or hyperthymic (irritable) temperaments may presage eventual bipolar disorder. Premorbid anxiety and dysphoria also are common, and approximately 20% of youth with major depression go on to experience manic episodes by adulthood. Similar to findings in adults, factors that predict the eventual development of mania in depressed youth include a depressive episode characterized by rapid onset, psychomotor retardation, and psychotic features, a family history of affective disorders, especially bipolar disorder, and a history of mania or hypomania after treatment with antidepressants.

PREVENTION

Although empiric support is sparse, 1 randomized controlled study demonstrated the effectiveness of family-focused treatment versus an educational control in hastening and sustaining recovery from mood symptoms in a high familial risk cohort of youth with subsyndromal symptoms of mania. Family-focused treatment is a manualized psychoeducational intervention designed to reduce family stress, conflict, and affective arousal by enhancing communication and problem-solving between youth and their caregivers. Pharmacologic interventions for subsyndromal mania have produced equivocal results.

CASE FINDING

Cardinal manic symptoms of elation and grandiosity occurring in adolescents as a discrete episode should alert pediatric practitioners to the possibility of a bipolar or related disorder. Because of the complexity of these disorders, any suspected cases should be referred to the specialty mental health setting for comprehensive assessment (see Chapter 20) and treatment (see Chapter 21).

TREATMENT

For mania in bipolar I disorder, medication is the primary treatment. Among traditional mood stabilizer medications (lithium carbonate, divalproex sodium, carbamazepine), only lithium is approved by the FDA for the treatment of bipolar disorder from age 12 yr (see Chapter 21.1). At present lithium has only open-label empirical support, with an overall response rate approximating 40%. There is no RCT evidence supporting the efficacy of divalproex sodium or carbamazepine. No other anticonvulsant medications sometimes used for the treatment of mania (oxcarbazepine, lamotrigine, topiramate) have FDA approval or RCT evidence of efficacy. In contrast, atypical antipsychotic medications (e.g., quetiapine, aripiprazole, ziprasidone, risperidone, olanzapine) have an overall 66% response with significant separation from placebo/active comparator in RCTs, and as such are considered to be

1st-line treatments for mania. The FDA has approved aripiprazole, risperidone, and quetiapine for the treatment of bipolar disorder from age 10 yr, and olanzapine from age 13 yr (see Chapter 21.1). The choice of antipsychotic medication is based upon factors such as side-effect profiles, adherence considerations, and a positive response of a family member.

Medication trials should be systematic, and the duration of trials should be sufficient (generally 6-8 wk) to determine the agent's effectiveness. Care should be taken to avoid unnecessary polypharmacy, in part by discontinuing agents that have not demonstrated significant benefit. Because all of these medications are associated with significant side effects, careful monitoring of baseline and follow-up indices is imperative. Side effects of lithium include reduced urine concentrating ability, hypothyroidism, hyperparathyroidism, weight gain, and renal failure. Acute overdose (level > 1.5 mEq/L) manifests with neurologic symptoms (tremor, ataxia, nystagmus, hyperreflexia, myoclonus, slurred speech, delirium, coma, seizures), and altered renal function. Toxicity is enhanced when dehydrated or with drugs that affect renal function (nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibition) Neuroleptic malignant syndrome has been reported in patients also taking antipsychotic drugs. Atypical antipsychotics cause weight gain, metabolic aberrations (diabetes, hyperlipidemia), and cardiac effects. Withdrawal of medication has been associated with increased risk of relapse.

The regimen needed to stabilize acute mania should be maintained for 12-24 mo. Maintenance therapy is often needed for adolescents with bipolar I disorder, and some patients need lifelong medication. Any attempts to discontinue prophylactic medication should be done gradually, while closely monitoring the patient for relapse.

For depression in bipolar II disorder, antidepressant medication may be used once a mood-stabilizing medication has been initiated. Lamotrigine as adjunctive or monotherapy also may be helpful for adolescents with bipolar depression. Comorbid ADHD can be treated with stimulant medication once a mood-stabilizing medication has been initiated.

Psychotherapy is a potentially important adjunctive treatment for the bipolar disorders. However, a Cochrane review of 7 RCTs of family interventions found only heterogeneous evidence of effectiveness, precluding definitive conclusions about their use. Factors known to adversely influence response to therapy include high-conflict families and sleep impairment, suggesting the importance of targeting these factors in treatment.

LEVEL OF CARE

Most youths with bipolar disorders can be safely and effectively treated as outpatients, provided that an appropriate schedule of visits and laboratory monitoring can be maintained through the course of treatment. Youths who are suicidal or psychotic typically require inpatient care.

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Chapter 27
Suicide and Attempted Suicide

David R. DeMaso, Heather J. Walter, and Elizabeth A. Wharff

Youth suicide is a major and tragic public health problem. For youth between the ages of 15 and 24 yr in the United States, suicide is the 3rd leading cause of death, with approximately 4,600 lives lost each year. Globally, suicide rates for youth ages 15-19 yr are 7.4/100,000 persons, the 4th leading cause of death for males and the 3rd for females. There are a number of psychiatric, social, cultural, and environmental risk factors for suicidal behavior, and knowledge of these risk factors can facilitate identification of youths at highest risk (Fig. 27-1).

EPIDEMIOLOGY

Suicidal Ideation and Attempts

Based on the 2011 Youth Risk Behavior Survey, almost one-third of 9th through 12th grade students nationwide in the United States felt so sad or hopeless almost every day for 2 or more wk in a row during the previous year that they stopped doing some usual activities. During that same time period, nearly 16% of the students reported that they had seriously considered attempting suicide and 8% reported that they had actually attempted suicide. A suicide attempt in the previous year that resulted in an injury, poisoning, or overdose that had to be treated by a doctor or nurse was reported by more than 2% of students.

It is estimated that for every completed youth suicide, as many as 200 suicide attempts are made. Ingestion of medication is the most common method of attempted suicide. The 15-19 yr old age group is the most likely to intentionally harm themselves by ingestion, receive treatment in emergency departments, and survive. Attempts are more common in adolescent females than males (approximately 4 : 1), and in Hispanic females compared to their non-Hispanic counterparts. Gay, lesbian, bisexual, and transgender youths also have disproportionately high rates of suicide attempts. Attempters who have made prior suicide attempts, who used a method other than ingestion, and who still want to die are at increased risk for completed suicide.

Suicide Completions

In the United States, completed suicide is very rare before puberty. Rates of completed suicide increase steadily across adolescence into young adulthood, peaking in the early 20s. In the past 60 yr, the suicide rate has quadrupled among 15-24 year old males and has doubled for females of the same age. The male : female ratio for completed suicide rises with age from 3 : 1 in children to approximately 4 : 1 in 15-24 yr olds, and to greater than 6 : 1 among 20-24 yr olds.

Native Americans/Alaska Natives have highest rates of completed suicide of all ethnic groups, with nearly 21 deaths per 100,000. White youth are the next highest at almost 12 deaths per 100,000. The ethnic groups with the lowest risk are African-Americans, Hispanics, Asians, and Pacific Islanders. Over time the suicide rate among African-American, Hispanic, and other minority males has increased, while the rate among white males has remained steady.

Access to means has been linked to suicide rates among different groups in the population and different geographical areas of the world (Fig. 27-2). Firearms are the most common method used to complete suicide in the United States, and account for 56% of male suicides and 30% of female suicides. In females, poisonous ingestions, especially overdoses of medications, are the most common method used to complete suicide, and account for 37% of female suicides, compared to only 12% of male suicides. Hanging is the third most common method used to complete suicide and accounts for 25% of male and female suicides. Firearms are the most lethal method of suicide completion; the death rate with respect to firearms is approximately 80-90%, whereas the death rate is only 1.5-4% for overdoses.

RISK FACTORS

In addition to age, race/ethnicity, and a history of a previous suicide attempt, there are multiple risk factors that predispose youths to suicide (Table 27-1).

Preexisting Mental Disorder

Approximately 90% of youths who complete suicide have a preexisting psychiatric illness, most commonly major depression (see Chapter 26.1). Among females, chronic anxiety, especially panic disorder, also is associated with suicide attempts and completion (see Chapter 25).

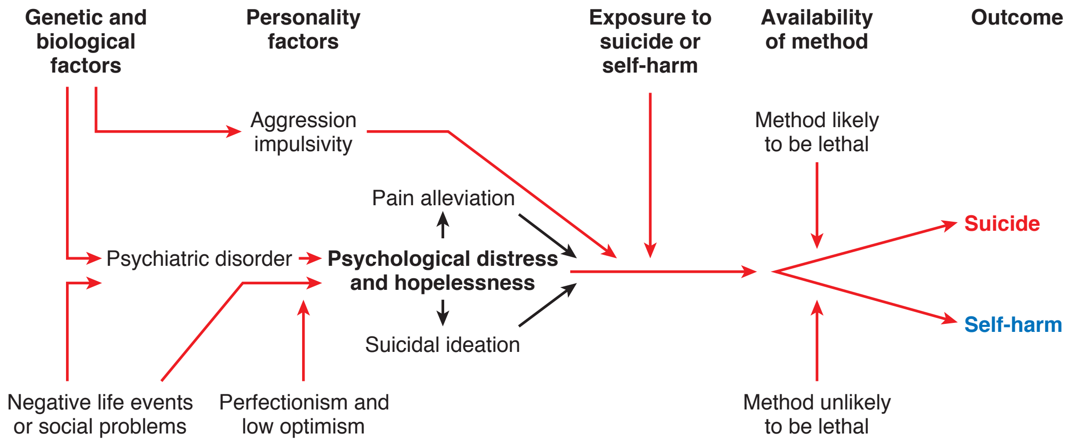

Figure 27-1 Key risk factors for adolescent self-harm and suicide. *(From Hawton K, Saunders KEA, O'Connor RC: Self-harm and suicide in adolescents.* Lancet *379:2373–2380, 2012, Fig. 2.)*

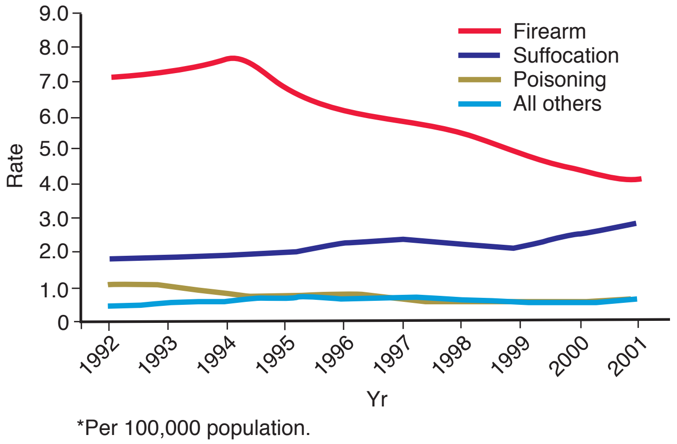

Figure 27-2 Annual suicide rates among persons age 15-19 yr, by year and method, United States, 1992-2001. *(From Centers for Disease Control and Prevention: Methods of suicide among persons aged 10-19 years, United States, 1992-2001.* MMWR Morb Mortal Wkly Rep *53:471-474, 2004.)*

Among males, conduct disorder and substance use convey increased risk. Comorbidity of a substance use disorder (see Chapter 114), a depressive disorder (see Chapter 26.1), and conduct disorder (see Chapter 29.1) are linked to suicide by firearm. Schizophrenia spectrum disorders (see Chapter 31) are linked to suicide attempts and completions.

Cognitive Distortions

Negative self-attributions can contribute to the hopelessness that is commonly associated with suicidality; hopelessness may contribute to approximately 55% of the explained variance in continued suicidal ideation. Many youth who are suicidal hold negative views of their own competence, have poor self-esteem, and have difficulty identifying sources of support or reasons to live. Many youngsters lack the coping strategies necessary to manage strong emotions and instead tend to catastrophize and engage in all-or-nothing thinking.

Biologic Factors

Postmortem studies show that there are observable differences between the brains of individuals who have completed suicide and those who died from other causes. The brain systems that may be related to suicide completion are the serotonergic system, adrenergic system, and the hypothalamic–pituitary axis. Family history of mental disorders also is linked to completed suicide.

Table 27-1	Risk Factors for Self-Harm and Suicide in Adolescents
SOCIODEMOGRAPHIC AND EDUCATIONAL FACTORS	
Sex (female for self-harm and male for suicide)—most countries*	
Low socioeconomic status*	
Lesbian, gay, bisexual, or transgender sexual orientation	
Restricted educational achievement*	
INDIVIDUAL NEGATIVE LIFE EVENTS AND FAMILY ADVERSITY	
Parental separation or divorce*	
Parental death*	
Adverse childhood experiences*	
History of physical or sexual abuse	
Parental mental disorder*	
Family history of suicidal behavior*	
Marital or family discord	
Bullying	
Interpersonal difficulties*	
PSYCHIATRIC AND PSYCHOLOGICAL FACTORS	
Mental disorder,* especially depression, anxiety, attention deficit hyperactivity disorder	
Drug and alcohol misuse*	
Impulsivity	
Low self-esteem	
Poor social problem-solving	
Perfectionism	
Hopelessness*	

All the factors in the panel have been shown to be related to self-harm.
*Shown to be related to suicide.
From Hawton K, Saunders KEA, O'Connor: Self-harm and suicide in adolescents. Lancet *379:2373–2380, 2012, Panel 1, p. 2375.*

Social, Environmental, and Cultural Factors

Of youths who attempt suicide, 65% can name a precipitating event for their action. Most adolescent suicide attempts are precipitated by stressful life events (e.g., academic or social problems, being bullied, trouble with the law, family instability, questioning one's sexual orientation, a newly diagnosed medical condition, or a recent or anticipated loss).

Suicide attempts may also be precipitated by exposure to news of another person's suicide or by reading about or viewing a suicide portrayed in a romantic light in the media. Media coverage of suicide is linked to fluctuating incidence rates of suicides, particularly among adolescents. Glorification or sensationalization of suicide in the media has found to be associated with an increase in suicides. When media coverage includes a detailed description of specific means used, the use of that particular method may increase in the overall population.

For some immigrants, suicidal ideation can be associated with high levels of acculturative stress, especially in the context of family separation and limited access to supportive resources. Physical and sexual abuse can also increase one's risk of suicide with 15-20% of female suicide attempters having had a history of abuse. There is a general association between family conflict and suicide attempts; this association is strongest in children and early adolescents. Family psychopathology and a family history of suicidal behavior convey excess risk. The lack of supportive social relations with peers, parents, and school personnel have an interactive relationship in increasing the risk of suicide among youth.

Protective Factors

Protective factors can provide a counterbalance for those contemplating suicide. They may include a sense of family responsibility, life satisfaction, social support, coping and problem-solving skills, religious faith, intact reality testing, and solid therapeutic relationships (e.g., pediatrician, teacher, therapist).

ASSESSMENT AND INTERVENTION

Pediatric practitioners should consider suicide potential and the need for mental health assessment in the context of adverse information elicited in child/parent psychosocial histories (e.g., HEADSS Psychosocial Risk Assessment; see Table 20-2 in Chapter 20), screening measure scores out of the normal range (e.g., Pediatric Symptom Checklist), or self-reported statements or behaviors from patients and/or parents.

All suicidal ideation and attempts should be taken seriously and require a thorough assessment by a child-trained mental health clinician to evaluate the youth's current state of mind, underlying psychiatric conditions, and ongoing risk of harm. Emergency mental health assessment is needed for immediate threat to self (i.e., suicidal intent and plan); urgent mental health assessment (48-72 hr) is needed for severe psychiatric symptoms, significant change in overall functioning, and/or suicidal ideation without intent or plan. Routine mental health assessment is appropriate for mild to moderate psychiatric symptoms without suicidal ideation.

Pediatric practitioners should expect the mental health clinician to evaluate the presence and degree of suicidality and underlying risk factors. The reliability and validity of child interviewing is affected by the child's level of cognitive development and well as their understanding of the relationship between their emotions and behavior. Confirmation of the youth's suicidal behavior can be obtained from information gathered by interviewing others who know the child or adolescent. It is not unusual for there to be a discrepancy between patient and parent reports, with both children and adolescents being more likely to disclose suicidal ideation and suicidal actions than their parents.

In the mental health assessment, suicidal ideation can be assessed by explicit questions posed in a nonjudgmental, noncondescending, matter-of-fact approach. The *Ask Suicide-Screening Questionnaire* is a validated 4-item measure that has been shown in the emergency room setting to have high sensitivity and negative predictive value in identifying youth at risk for suicide ideation and behavior: *(1) In the past few weeks, have you felt that you or your family would be better off if you were dead? (2) In the past few weeks, have you wished you were dead? (3) In the past weeks, have you been having thoughts about killing yourself? (4) Have you ever tried to kill yourself?*

The assessment of a suicidal attempt should include a detailed exploration of the hours immediately preceding the attempt to identify precipitants as well as the circumstances of the attempt itself so as to fully understand the patient's intent and potential lethality. The calculation of the level of suicide concern is complex requiring a determination across a spectrum of risk (Fig. 27-3). At the low end of the risk spectrum are youth with thoughts of death or wanting to die, but without suicidal thoughts, intent, or a plan. Those with highly specific suicide plans, preparatory acts or suicide rehearsals, and clearly articulated intent are at the high end. A suicidal history, presently impaired judgment (as seen in altered mental states including depression, mania, anxiety, intoxication, substance abuse, psychosis, trauma-reactive, hopelessness, rage, humiliation, impulsivity) as well as poor social support further exacerbates the heightened risk. Among adolescents who consider self-harm, those who carry out (enactors) self-injury are more likely to have family or friends (or think that their peers) engaged in self harm, and are more impulsive than those who only have thoughts of self-harm (ideators).

For youth who are an imminent danger to themselves, inpatient level of psychiatric care is necessary to ensure safety, clarify diagnoses, and comprehensively plan treatment. These patients can be hospitalized voluntarily or involuntarily. It is helpful for the pediatric practitioner to have an office protocol to follow in these situations. This protocol should take into consideration state laws regarding involuntary hospitalization, transportation options, nearest emergency assessment site, necessary forms for hospitalization, and available emergency mental health consultants.

For those youth suitable for treatment in the outpatient setting, an appointment should be scheduled within a few days with a mental health clinician. Ideally, this appointment should be scheduled before leaving the assessment venue, as nearly 50% of those who attempt suicide fail to follow through with the mental health referral. A procedure should be in place to contact the family if the family fails to complete the referral.

Through follow-up office visits, pediatric practitioners can help support and facilitate the implementation of psychotherapies (e.g., cognitive-behavioral therapy, dialectical behavioral therapy, interpersonal therapy, and/or family therapy) that target the specific psychiatric disorders and the emotional dysphoria or behavioral dysregulation that accompany suicidal ideation or behavior. In conjunction with a child and adolescent child psychiatrist, psychotropic medications may be used as indicated to treat underlying psychiatric disorders. Pediatric practitioners also can encourage social connectedness to peers and to community organizations (e.g., school or church), as well as promote help-seeking (e.g., talking to a trusted adult when distressed) and wellness (e.g., sleep, exercise, relaxation, nutrition) behaviors. In the unfortunate circumstance of a completed suicide, pediatricians can offer support to the family, particularly by monitoring for adverse bereavement responses in siblings and parents.

PREVENTION

Suicide prevention is of high global importance. Yet, even in high-risk populations suicide is a comparatively rare event. Even the aforementioned risk factors associated with suicide are relatively common and individually not strong predictors of suicide. The assessment is complicated by patients that may attempt to conceal their suicide thoughts and by those who express suicidal thoughts without serious intent. Suicide screening has been challenging because most screening instruments have variable sensitivity and specificity. In addition, the burden of follow-up mental health evaluations for those who screen positive has been daunting. Although primary care–feasible screening tools may be help to identify some adults at increased risk for suicide, they have, to date, demonstrated limited ability to detect suicide risk in adolescents.

Prevention strategies in the pediatric medical home include training staff to recognize and respond to the warning signs of suicide, screening for and treating depression, educating patients/parents about warning signs for suicide, and restricting access to modes of lethal self-harm. Youth have increased rates of suicide attempts and completions if they live in homes where firearms are present and available. When recommended by their primary care providers, most parents restrict access of their children to guns and medications. Pediatric practitioners should consider counseling parents to either remove firearms from the home entirely or securely lock guns and ammunition in separate locations. Anecdotal evidence suggests youth frequently know where guns and keys to gun cabinets are kept, even though parents may think they do not. The same recommendation applies to restricting access to potentially lethal prescription and nonprescription

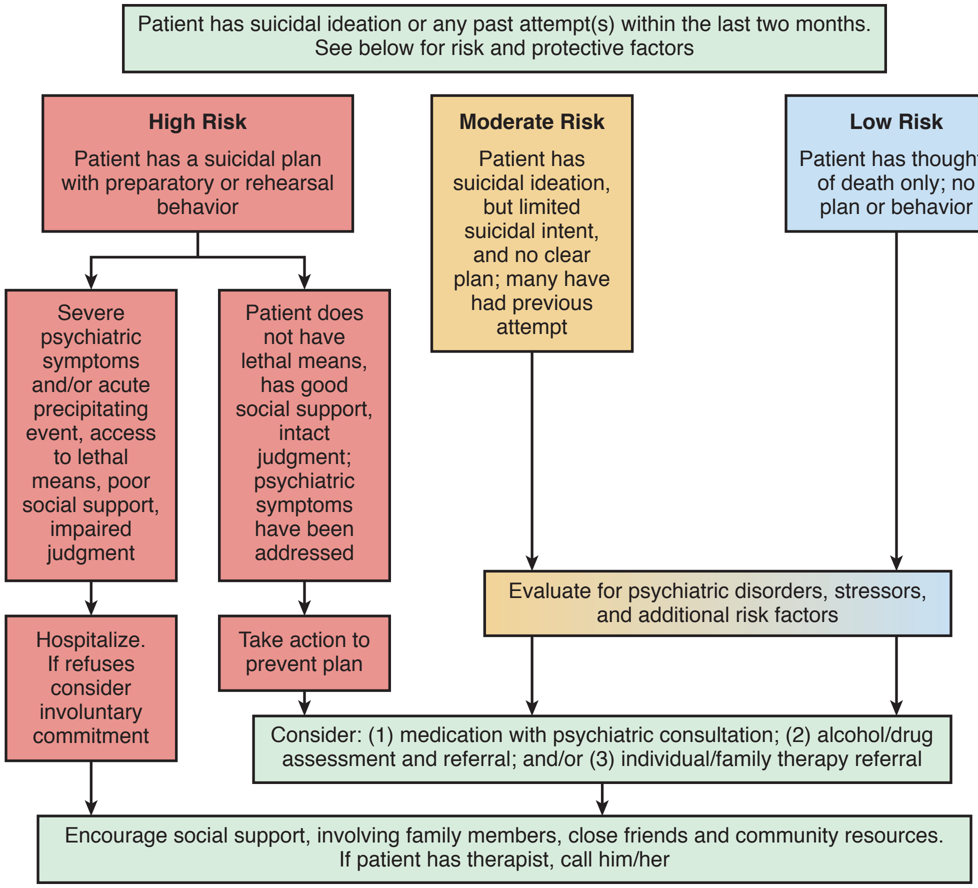

Risk Factors
- **Suicidal behavior:** history of prior suicide attempts, aborted suicide attempts, or self-injurious behavior.
- **Family history:** of suicide, attempts, or psychiatric diagnoses, especially those requiring hospitalization.
- **Current/past psychiatric disorders:** especially mood disorders (e.g., depression, bipolar disorder), psychotic disorders, alcohol/substance abuse, TBI, PTSD, personality disorders (e.g., borderline PD). ***Co-morbidity*** *with other psychiatric and/or substance abuse disorders and recent onset of illness increase risk.*
- **Key symptoms:** anhedonia, impulsivity, hopelessness, anxiety/panic, insomnia, command hallucinations, intoxication, oppositionality, and conduct problems.
- **Precipitants/stressors:** triggering events leading to humiliation, shame or despair (i.e., loss of relationship, financial, or health status – real or anticipated).
- **Chronic medical illness** (esp. CNS disorders, pain)
- **History of current abuse or neglect.**

Protective Factors
Protective factors, even if present, may not counteract significant acute risk.
- **Internal:** ability to cope with stress, religious beliefs, frustration tolerance.
- **External:** responsibility to family, positive therapeutic relationships, social supports

Figure 27-3 Assessment and interventions with potentially suicidal patients. *(Adapted from Suicide Prevention Resource Center, WICHE Center for Mental Health Program.* Suicide prevention primer. *Available at* http://www.sprc.org/sites/sprc.org/files/primer.pdf.*)*

medications (e.g., containers of more than 25 acetaminophen tablets) and alcohol. *These approaches emphasize the importance of restriction of access to means for suicide to prevent self-harm.*

Screening for suicide in schools is also fraught with problems related to low specificity of the screening instrument and paucity of referral sites, as well as poor acceptability among school administrators. Gatekeeper (e.g., student support personnel) training appears effective in improving skills among school personnel and is highly acceptable to administrators but has not been shown to prevent suicide. School curricula (e.g., *Signs of Suicide*) have shown some preventive potential by teaching students to recognize the signs of depression and suicide in themselves and others, and to provide students with specific action steps necessary for responding to these signs. Peer helpers have not generally been shown to be efficacious.

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Chapter 28

Eating Disorders

Richard E. Kreipe

Eating disorders (EDs) are characterized by body dissatisfaction related to overvaluation of a thin body ideal associated with dysfunctional patterns of cognition and weight-control behaviors that result in significant biologic, psychological, and social complications. Although largely affecting white, adolescent girls, EDs also affect boys and cross all racial, ethnic, and cultural boundaries. Early intervention in EDs improves outcome.

Table 28-1 DSM-5 Diagnostic Criteria for Anorexia Nervosa

A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
B. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Specify whether:

Restricting type (ICD-10-CM code F50.01): During the last 3 mo, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.

Binge-eating/purging type (ICD-10-CM code F50.02): During the last 3 mo, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Specify if:

In partial remission: After full criteria for anorexia nervosa were previously met, Criterion A (low body weight) has not been met for a sustained period, but either Criterion B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) or Criterion C (disturbances in self-perception of weight and shape) is still met.

In full remission: After full criteria for anorexia nervosa were previously met, none of the criteria have been met for a sustained period of time.

Specify current severity:

The minimum level of severity is based, for adults, on current body mass index (BMI) (see below) or, for children and adolescents, on BMI percentile. **The ranges below are derived from World Health Organization categories for thinness in adults; for children and adolescents, corresponding BMI percentiles should be used.** The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and the need for supervision.

Mild: BMI ≥ 17 kg/m^2
Moderate: BMI 16–16.99 kg/m^2
Severe: BMI 15–15.99 kg/m^2
Extreme: BMI < 15 kg/m^2

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 338–339.

Table 28-2 DSM-5 Diagnostic Criteria for Bulimia Nervosa

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
   1. Eating, in a discrete period of time (e.g., within any 2 hr period), an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances.
   2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).
B. Recurrent inappropriate compensatory behaviors in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.
C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 mo.
D. Self-evaluation is unduly influenced by body shape and weight.
E. The disturbance does not occur exclusively during episodes of anorexia nervosa.

Specify if:

In partial remission: After full criteria for bulimia nervosa were previously met, some, but not all, of the criteria have been met for a sustained period of time.

In full remission: After full criteria for bulimia nervosa were previously met, none of the criteria have been met for a sustained period of time.

Specify current severity:

The minimum level of severity is based on the frequency of inappropriate compensatory behaviors (see below). The level of severity may be increased to reflect other symptoms and the degree of functional disability.

Mild: An average of 1-3 episodes of inappropriate compensatory behaviors per week.
Moderate: An average of 4-7 episodes of inappropriate compensatory behaviors per week.
Severe: An average of 8-13 episodes of inappropriate compensatory behaviors per week.
Extreme: An average of 14 or more episodes of inappropriate compensatory behaviors per week.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 345.

DEFINITIONS

Anorexia nervosa (AN) involves significant overestimation of body size and shape, with a relentless pursuit of thinness that typically combines excessive dieting and compulsive exercising in the **restrictive** subtype; in the **binge-purge** subtype, patients might intermittently overeat and then attempt to rid themselves of calories by vomiting or taking laxatives, still with a strong drive for thinness (Table 28-1). **Bulimia nervosa (BN)** is characterized by episodes of eating large amounts of food in a brief period, followed by compensatory vomiting, laxative use, and exercise or fasting to rid the body of the effects of overeating in an effort to avoid obesity (Table 28-2).

Children and adolescents with EDs may not fulfill criteria for AN or BN in the new *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) but fall into a new subcategory of **Atypical AN,** or a new category of **Avoidant Restrictive Food Intake Disorder (ARFID)** (Table 28-3), that includes a group of conditions in which food intake is restricted or avoided due to adverse feeding or eating experiences or the sensory qualities of food, resulting in significant nutritional deficiencies and problems with social interactions. **Binge eating disorder (BED)**, in which binge eating is not followed regularly by any compensatory behaviors (vomiting, laxatives) is a stand-alone category in DSM-5 but shares many features with obesity (see Chapter 47). ED-NOS, often called "disordered eating," can worsen into full syndrome EDs.

EPIDEMIOLOGY

The classic features of AN include a white, early to middle adolescent girl of above-average intelligence and socioeconomic status, who is a conflict-avoidant, risk-aversive, perfectionist struggling with disturbances of anxiety and/or mood. BN tends to emerge in later adolescence, sometimes evolving from AN, and is typified by impulsivity and features of borderline personality disorder that are associated with depression and mood swings. The 0.5-1% and 3-5% incidence rates among younger and older adolescent females for AN and BN, respectively, probably reflect ascertainment bias in sampling and underdiagnosis in cases not fitting the typical profile. The same may be true of the significant gender disparity, in which female patients account for approximately 90% of patients with diagnosed EDs. Ten percent or more of some adolescent female populations have ED-NOS.

No single factor causes the development of an ED; sociocultural studies indicate a complex interplay of culture, ethnicity, gender, peers, and family. The gender dimorphism is presumably related to females having a stronger relationship between body image and self-evaluation, as well as the influence of the Western culture's thin body ideal on the development of EDs. Race and ethnicity appear to moderate the

Table 28-3 DSM-5 Diagnostic Criteria for Avoidant/Restrictive Food Intake Disorder

A. An eating or feeding disturbance (e.g., apparent lack of interest in eating or food; avoidance based on the sensory characteristics of food; concern about aversive consequences of eating) as manifested by persistent failure to meet appropriate nutritional and/or energy needs associated with one (or more) of the following:
   1. Significant weight loss (or failure to achieve expected weight gain or faltering growth in children).
   2. Significant nutritional deficiency.
   3. Dependence on enteral feeding or oral nutritional supplements.
   4. Marked interference with psychosocial functioning.

B. The disturbance is not better explained by lack of available food or by an associated culturally sanctioned practice.

C. The eating disturbance does not occur exclusively during the course of anorexia nervosa or bulimia nervosa, and there is no evidence of a disturbance in the way in which one's body weight or shape is experienced.

D. The eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder. When the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the condition or disorder and warrants additional clinical attention.

Specify if:

In remission: After full criteria for avoidant/restrictive food intake disorder were previously met, the criteria have not been met for a sustained period of time.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 334.

association between risk factors and disordered eating, with African-American and Caribbean females reporting lower body dissatisfaction and less dieting than Hispanic and non-Hispanic white females. Because peer acceptance is central to healthy adolescent growth and development, especially in early adolescence when AN tends to have its initial prevalence peak, the potential influence of peers on EDs is significant, as are the relationships among peers, body image, and eating. Teasing by peers or by family members (especially male) may be a contributing factor for overweight females.

Family influence in the development of EDs is even more complex because of the interplay of environmental and genetic factors; shared elements of the family environment and immutable genetic factors account for significant (about equal) variance in disordered eating. There are associations between parents' and children's eating behaviors; dieting and physical activity levels suggest parental reinforcement of body-related societal messages. The influence of inherited genetic factors on the emergence of EDs during adolescence is also significant, but not in a direct fashion. Rather, the risk for developing an ED appears to be mediated through a genetic predisposition to anxiety (see Chapter 25), depression (see Chapter 26), or obsessive-compulsive traits that may be modulated through the internal milieu of puberty. There is little evidence that parents "cause" an ED in their child or adolescent; the importance of parents in treatment and recovery cannot be overestimated.

PATHOLOGY AND PATHOGENESIS

The emergence of EDs coinciding with the processes of adolescence (e.g., puberty, identity, autonomy, cognition) indicates the central role of development. A history of sexual trauma is not significantly more common in EDs than in the population at large, but when present it makes recovery more difficult and is more common in BN. EDs may be viewed as a final common pathway, with a number of *predisposing* factors that increase the risk of developing an ED, *precipitating* factors often related to developmental processes of adolescence triggering the emergence of the ED, and *perpetuating* factors that cause an ED to persist. EDs often begin with dieting but gradually progress to unhealthy habits that lessen the negative impact of associated psychosocial problems to which the affected person is vulnerable because of premorbid biologic and psychologic characteristics, family interactions, and social climate. When persistent, the biologic effects of starvation and malnutrition (e.g., true loss of appetite, hypothermia, gastric atony, amenorrhea, sleep disturbance, fatigue, weakness, and depression) combined with the psychologic rewards of increased sense of mastery and reduced emotional reactivity, actually maintain and reward pathologic ED behaviors. This positive reinforcement of behaviors and consequences, generally viewed by parents and others as negative, helps to explain why affected persons characteristically deny that a problem exists and resist treatment. Although noxious, purging can be reinforcing owing to a reduction in anxiety triggered by overeating; purging also can result in short-term, but reinforcing, improvement in mood that is related to changes in neurotransmitters. In addition to an imbalance in neurotransmitters, most notably serotonin and dopamine, there are also alterations in functional anatomy that support the concept of EDs as brain disorders. The cause-and-effect relationship in central nervous system alterations in EDs is not clear, nor is their reversibility.

CLINICAL MANIFESTATIONS

A central feature of EDs is the overestimation of body size, shape or parts (e.g., abdomen, thighs) leading to weight-control practices intended to reduce weight (AN) or prevent weight gain (BN). Associated practices include severe restriction of caloric intake and behaviors intended to reduce the effect of calories ingested, such as compulsive exercising or purging by inducing vomiting or taking laxatives. Eating and weight loss habits commonly found in EDs can result in a wide range of energy intake and output, the balance of which leads to a wide range in weight from extreme loss of weight in AN to fluctuation around a normal to moderately high weight in BN. Reported eating and weight-control habits (Table 28-4) thus inform the initial primary care approach.

Although weight-control patterns guide the initial pediatric approach, an assessment of commonly reported symptoms and findings on physical examination is essential to identify targets for intervention. When reported symptoms of excessive weight loss (feeling tired and cold; lacking energy; orthostasis; difficulty concentrating) are explicitly linked by the clinician to their associated physical signs (hypothermia with acrocyanosis and slow capillary refill, loss of muscle mass, bradycardia with orthostasis), it becomes more difficult for the patient to deny that a problem exists. Furthermore, awareness that bothersome symptoms can be eliminated by healthier eating and activity patterns can increase a patient's motivation to engage in treatment. Tables 28-5 and 28-6 detail common symptoms and signs that should be addressed in a pediatric assessment of a suspected ED.

DIFFERENTIAL DIAGNOSIS

In addition to identifying symptoms and signs that deserve targeted intervention for patients who have an ED or disordered eating, a comprehensive history and physical examination are required in the assessment of a suspected ED to rule out other conditions in the differential diagnosis. Weight loss can occur with any condition in which there is increased catabolism (e.g., malignancy or occult chronic infection) or malabsorption (e.g., inflammatory bowel disease or celiac disease), but these illnesses are generally associated with other findings and are not usually associated with decreased caloric intake. Patients with inflammatory bowel disease can reduce intake to minimize abdominal cramping; eating can cause abdominal discomfort and early satiety in AN because of gastric atony associated with significant weight loss, not malabsorption. Likewise, signs of weight loss in AN might include hypothermia, acrocyanosis with slow capillary refill, and neutropenia suggesting overwhelming sepsis, but the overall picture in EDs is one of relative cardiovascular stability compared to sepsis. Endocrinopathies are also in the differential of EDs. With BN, voracious appetite in the face of weight loss might suggest diabetes mellitus, but blood glucose levels are normal or low in EDs. Adrenal insufficiency mimics

Table 28-4 Eating and Weight Control Habits Commonly Found in Children and Adolescents with an Eating Disorder

	Prominent Feature		Clinical Comments Regarding Eating Disorder Habits	
HABIT	**ANOREXIA NERVOSA**	**BULIMIA NERVOSA**	**ANOREXIA NERVOSA**	**BULIMIA NERVOSA**
Overall intake	Inadequate energy (calories), although volume of food and beverages may be high because of very low caloric density of intake as a result of "diet" and nonfat choices	Variable, but calories normal to high; intake in binges often "forbidden" food or drink that differs from intake at meals	Consistent inadequate caloric intake leading to wasting of the body is an essential feature of diagnosis	Inconsistent balance of intake, exercise and vomiting, but severe caloric restriction is short-lived
Food	Counts and limits calories, especially from fat; Emphasis on "healthy food choices" with reduced caloric density Monotonous, limited "good" food choices, often leading to vegetarian or vegan diet Strong feelings of guilt after eating more than planned leads to exercise and renewed dieting	Aware of calories and fat, but less regimented in avoidance than AN Frequent dieting interspersed with overeating, often triggered by depression, isolation, or anger	Obsessive-compulsive attention to nutritional data on food labels and may have "logical" reasons for food choices in highly regimented pattern, such as sports participation or family history of lipid disorder	Choices less structured, with more frequent diets
Beverages	Water or other low- or no-calorie drinks; nonfat milk	Variable, diet soda common; may drink alcohol to excess	Fluids often restricted to avoid weight gain	Fluids ingested to aid vomiting or replace losses
Meals	Consistent schedule and structure to meal plan Reduced or eliminated caloric content, often starting with breakfast, then lunch, then dinner Volume can increase with fresh fruits, vegetables, and salads as primary food sources	Meals less regimented and planned than in AN; more likely impulsive and unregulated, often eliminated following a binge-purge episode	Rigid adherence to "rules" governing eating leads to sense of control, confidence, and mastery	Elimination of a meal following a binge-purge only reinforces the drive for binge later in the day
Snacks	Reduced or eliminated from meal plan	Often avoided in meal plans, but then impulsively eaten	Snack foods removed early because "unhealthy"	Snack "comfort foods" can trigger a binge
Dieting	Initial habit that becomes progressively restrictive, although often appearing superficially "healthy" Beliefs and "rules" about the patient's idiosyncratic nutritional requirements and response to foods are strongly held	Initial dieting gives way to chaotic eating, often interpreted by the patient as evidence of being "weak" or "lazy"	Distinguishing between healthy meal planning with reduced calories and dieting in ED may be difficult	Dieting tends to be impulsive and short-lived, with "diets" often resulting in unintended weight gain
Binge eating	None in restrictive subtype, but an essential feature in binge-purge subtype	Essential feature, often secretive Shame and guilt prominent afterward	Often "subjective" (more than planned but not large)	Relieves emotional distress, may be planned
Exercise	Characteristically obsessive-compulsive, ritualistic, and progressive May excel in dance, long-distance running	Less predictable May be athletic, or may avoid exercise entirely	May be difficult to distinguish active thin vs. ED	Males often use exercise as means of "purging"
Vomiting	Characteristic of binge-purge subtype May chew, then spit out, rather than swallow, food as a variant	Most common habit intended to reduce effects of overeating Can occur after meal as well as a binge	Physiologic and emotional instability prominent	Strongly "addictive" and self-punishing, but does not eliminate calories ingested—many still absorbed
Laxatives	If used, generally to relieve constipation in restrictive subtype, but as a cathartic in binge-purge subtype	Second most common habit used to reduce or avoid weight gain, often used in increasing doses for cathartic effect	Physiologic and emotional instability prominent	Strongly "addictive," self-punishing, but ineffective means to reduce weight (calories are absorbed in the small intestine, but laxatives work in the colon)
Diet pills	Very rare, if used; more common in binge-purge subtype	Used to either reduce appetite or increase metabolism	Use of diet pills implies inability to control eating	Control over eating may be sought by any means

AN, anorexia nervosa; BN, bulimia nervosa; ED, eating disorder.

Table 28-5 Symptoms Commonly Reported by Patients with an Eating Disorder

SYMPTOMS	Diagnosis: ANOREXIA NERVOSA	Diagnosis: BULIMIA NERVOSA	CLINICAL COMMENTS REGARDING ED SYMPTOMS
Body image	Feels fat, even with extreme emaciation, often with specific body distortions (e.g., stomach, thighs); Strong drive for thinness, with self-efficacy closely tied to appraisal of body shape, size, and/or weight	Variable body image distortion and dissatisfaction, but drive for thinness is less than the desire to avoid gaining weight	Challenging a patient's body image is both ineffective and counter-therapeutic clinically Accepting the patient's expressed body image but noting its discrepancy with symptoms and signs reinforces concept that patient can "feel" fat but also "be" too thin and unhealthy
Metabolism	Hypometabolic symptoms include feeling cold, tired, and weak and lacking energy May be both bothersome and reinforcing	Variable, depending on balance of intake and output and hydration	Symptoms are evidence of body's "shutting down" in an attempt to conserve calories with an inadequate diet Emphasizing reversibility of symptoms with healthy eating and weight gain can motivate patients to cooperate with treatment
Skin	Dry skin, delayed healing, easy bruising, goose flesh Orange-yellow skin on hands	No characteristic symptom, self-injurious behavior may be seen	Skin lacks good blood flow and the ability to heal in low weight Carotenemia with large intake of β-carotene foods; reversible
Hair	Lanugo-type hair growth on face and upper body Slow growth and increased loss of scalp hair	No characteristic symptom	Body hair growth conserves energy Scalp hair loss can worsen during refeeding "telogen effluvium" (resting hair is replaced by growing hair) Reversible with continued healthy eating
Eyes	No characteristic symptom	Subconjunctival hemorrhage	Caused by increased intrathoracic pressure during vomiting
Teeth	No characteristic symptom	Erosion of dental enamel erosion Decay, fracture, and loss of teeth	Intraoral stomach acid resulting from vomiting etches dental enamel, exposing softer dental elements
Salivary glands	No characteristic symptom	Enlargement (no to mild tenderness)	Caused by chronic binge eating and induced vomiting, with parotid enlargement more prominent than submandibular; reversible
Heart	Dizziness, fainting in restrictive subtype Palpitations more common in binge-purge subtype	Dizziness, fainting, palpitations	Dizziness and fainting due to postural orthostatic tachycardia and dysregulation at hypothalamic and cardiac level with weight loss, as a result of hypovolemia with binge-purge Palpitations and arrhythmias often caused by electrolyte disturbance Symptoms reverse with weight gain and/or cessation of binge-purge
Abdomen	Early fullness and discomfort with eating Constipation Perceives contour as "fat," often preferring well-defined abdominal musculature	Discomfort after a binge Cramps and diarrhea with laxative abuse	Weight loss is associated with reduced volume and tone of GI tract musculature, especially the stomach Laxatives may be used to relieve constipation or as a cathartic Symptom reduction with healthy eating can take weeks to occur
Extremities and musculoskeletal	Cold, blue hands and feet	No characteristic symptoms Self-cutting or burning on wrists or arms	Energy-conserving low body temperature with slow blood flow most notable peripherally Quickly reversed with healthy eating
Nervous system	No characteristic symptom	No characteristic symptom	Neurologic symptoms suggest a diagnosis other than an ED
Mental status	Depression, anxiety, obsessive-compulsive symptoms, alone or in combination	Depression; PTSD; borderline personality disorder traits	Underlying mood disturbances can worsen with dysfunctional weight control practices and can improve with healthy eating AN patients might report emotional "numbness" with starvation, preferable to emotionality associated with healthy eating

AN, anorexia nervosa; BN, bulimia nervosa; ED, eating disorder; GI, gastrointestinal; PTSD, posttraumatic stress disorder.

Table 28-6 Signs Commonly Found in Patients with Eating Disorders Relative to Prominent Feature of Weight Control

PHYSICAL SIGN	Prominent Feature: RESTRICTIVE INTAKE	Prominent Feature: BINGE EATING/PURGING	CLINICAL COMMENTS RELATED TO EATING DISORDER SIGNS
General appearance	Thin to cachetic, depending on balance of intake and output Might wear bulky clothing to hide thinness and might resist being examined	Thin to overweight, depending on the balance of intake and output through various means	Examine in hospital gown Weight loss more rapid with reduced intake and excessive exercise Binge eating can result in large weight gain, regardless of purging behavior Appearance depends on balance of intake and output and overall weight control habits
Weight	Low and falling (if previously overweight may be normal or high); may be falsely elevated if patient drinks fluids or adds weights to body before being weighed	Highly variable, depending on balance of intake and output and state of hydration Falsification of weight is unusual	Weigh in hospital gown with no underwear, after voiding (measure urine SG) Remain in gown until physical exam completed to identify possible fluid loading (low urine SG, palpable bladder) or adding weights to body
Metabolism	Hypothermia: temp < 35.5°C (95.9°F), pulse < 60 beats/min Slowed psychomotor response with very low core temperature	Variable, but hypometabolic state is less common than in AN	Hypometabolism related to disruption of hypothalamic control mechanisms as a result of weight loss Signs of hypometabolism (cold skin, slow capillary refill, acrocyanosis) most evident in hands and feet, where energy conservation is most active
Skin	Dry Increased prominence of hair follicles Orange or yellow hands	Calluses over proximal knuckle joints of hand (Russell's sign)	Carotenemia with large intake of β-carotene foods Russell's sign: maxillary incisors abrasion develops into callus with chronic digital pharyngeal stimulation, usually on dominant hand
Hair	Lanugo-type hair growth on face and upper body Scalp hair loss, especially prominent in parietal region	No characteristic sign	Body hair growth conserves energy Scalp hair loss "telogen effluvium" can worsen weeks after refeeding begins, as hair in resting phase is replaced by growing hair
Eyes	No characteristic sign	Subconjunctival hemorrhage	Increased intrathoracic pressure during vomiting
Teeth	No characteristic sign	Eroded dental enamel and decayed, fractured, missing teeth	Perimolysis, worse on lingual surfaces of maxillary teeth, is intensified by brushing teeth without preceding water rinse
Salivary glands	No characteristic sign	Enlargement, relatively nontender	Parotid > submandibular involvement with frequent and chronic binge eating and induced vomiting
Throat	No characteristic sign	Absent gag reflex	Extinction of gag response with repeated pharyngeal stimulation
Heart	Bradycardia, hypotension, and orthostatic pulse differential > 25 beats/min	Hypovolemia if dehydrated	Changes in AN resulting from central hypothalamic and intrinsic cardiac function Orthostatic changes less prominent if athletic, more prominent if associated with purging
Abdomen	Scaphoid, organs may be palpable but not enlarged, stool-filled left lower quadrant	Increased bowel sounds if recent laxative use	Presence of organomegaly requires investigation to determine cause Constipation prominent with weight loss
Extremities and musculoskeletal system	Cold, acrocyanosis, slow capillary refill Edema of feet Loss of muscle, subcutaneous, and fat tissue	No characteristic sign, but may have rebound edema after stopping chronic laxative use	Signs of hypometabolism (cold) and cardiovascular dysfunction (slow capillary refill and acrocyanosis) in hands and feet Edema, caused by capillary fragility more than hypoproteinemia in AN, can worsen in early phase of refeeding
Nervous system	No characteristic sign	No characteristic sign	Water loading before weigh-ins can cause acute hyponatremia
Mental status	Anxiety about body image, irritability, depressed mood, oppositional to change	Depression, evidence of PTSD, more likely suicidal than AN	Mental status often improves with healthier eating and weight; SSRIs only shown to be effective for BN

AN, anorexia nervosa; BN, bulimia nervosa; PTSD, posttraumatic stress disorder; SG, specific gravity; SSRI, selective serotonin reuptake inhibitor.

many physical symptoms and signs found in restrictive AN but is associated with elevated potassium levels and hyperpigmentation. Although thyroid disorders are often considered, because of changes in weight and other symptoms in AN, the overall presentation includes symptoms of both underactive and overactive thyroid, such as hypothermia, bradycardia, and constipation, as well as weight loss and excessive physical activity, respectively.

In the central nervous system, craniopharyngiomas and Rathke pouch tumors can mimic some of the findings of AN, such as weight loss and growth failure, and even some body image disturbances, but the latter are less fixed than in typical EDs and are associated with other findings, including evidence of increased intracranial pressure. Mitochondrial neurogastrointestinal encephalomyopathy, caused by a mutation in the *TYMP* gene, presents with gastrointestinal dysmotility, cachexia, ptosis, peripheral neuropathy, ophthalmoplegia, and leukoencephalopathy. Symptoms begin during the second decade of life and are often initially diagnosed as AN. Early satiety, vomiting, cramps, constipation, and pseudoobstruction result in weight loss often before the neurologic features are noticed.

Any patient with an atypical presentation of an ED, based on age, sex, or other factors not typical for AN or BN deserves a scrupulous search for an alternative explanation. Patients can have both an underlying illness and an ED. The core features of dysfunctional eating habits—body image disturbance and change in weight—can coexist with conditions such as diabetes mellitus, where patients might manipulate their insulin dosing to lose weight.

LABORATORY FINDINGS

Because the diagnosis of an ED is made clinically, there is no confirmatory laboratory test. Laboratory abnormalities, when found, are the result of malnutrition, weight-control habits used, or medical complications; studies should be chosen based on history and physical examination. A routine screening battery typically includes complete blood count, erythrocyte sedimentation rate (should be normal), and biochemical profile. Common abnormalities in ED include low white blood cell count with normal hemoglobin and differential; hypokalemic, hypochloremic metabolic alkalosis with severe vomiting; mildly elevated liver enzymes, cholesterol, and cortisol levels; low gonadotropins and blood glucose with marked weight loss; and generally normal total protein, albumin, and renal function. An electrocardiogram may be useful when profound bradycardia or arrhythmia is detected; the electrocardiogram usually has low voltage, with nonspecific ST or T wave changes. Although prolonged QTc has been reported, prospective studies have not found an increased risk for this.

COMPLICATIONS

No organ is spared the harmful effects of dysfunctional weight-control habits, but the most concerning targets of medical complications are the heart, brain, gonads, and bones. Some **heart** findings in EDs (e.g., sinus bradycardia and hypotension) are *physiologic* adaptations to starvation that conserve calories and reduce afterload. Cold, blue hands and feet with slow capillary refill that can result in tissue perfusion insufficient to meet demands also represent energy-conserving responses associated with inadequate intake. All of these acute changes are reversible with restoration of nutrition and weight. Significant orthostatic pulse changes, prolonged corrected QT interval, ventricular dysrhythmias, or reduced myocardial contractility reflect myocardial impairment that can be lethal. In addition, with extremely low weight, **refeeding syndrome** (a result of the rapid drop in serum phosphorous, magnesium, and potassium with excessive reintroduction of calories, especially carbohydrates), is associated with acute heart failure and neurologic symptoms. With long-term malnutrition, the myocardium appears to be more prone to tachyarrhythmias, the second most common cause of death after suicide. In BN, dysrhythmias can also be related to electrolyte imbalance.

Clinically, the primary **brain** area affected acutely in EDs, especially with weight loss, is the hypothalamus. Hypothalamic dysfunction is reflected in problems with thermoregulation (warming and cooling), satiety, sleep, autonomic cardioregulatory imbalance (orthostasis), and endocrine function (reduced gonadal and excessive adrenal cortex stimulation), all of which are reversible. Anatomic studies of the brain in ED have focused on AN, with the most common finding being increased ventricular and sulcal volumes that normalize with weight restoration. Persistent gray-matter deficits following recovery, related to the degree of weight loss, have been reported. Elevated medial temporal lobe cerebral blood flow on positron emission tomography similar to that found in psychotic patients, suggests that these changes may be related to body image distortion. Also, visualizing high-calorie foods is associated with exaggerated responses in the visual association cortex that are similar to those seen in patients with specific phobias. Patients with AN might have an imbalance between serotonin and dopamine pathways related to neurocircuits in which dietary restraint reduces anxiety.

Reduced **gonadal** function occurs in male and female patients; it is clinically manifested in AN as amenorrhea in female patients and erectile dysfunction in males. It is related to understimulation from the hypothalamus as well as cortical suppression related to physical and emotional stress. Amenorrhea precedes significant dieting and weight loss in up to 30% of females with AN, and most adolescents with EDs perceive the absence of menses positively. The primary health concern is the negative effect of decreased ovarian function and estrogen on **bones**. Decreased bone mineral density (BMD) with osteopenia or the more severe osteoporosis is a significant complication of EDs (more pronounced in AN than BN). Data do not support the use of sex hormone replacement therapy because this alone does not improve other causes of low BMD (low body weight, lean body mass, and insulin-like growth factor-1; high cortisol).

TREATMENT

Principles Guiding Primary Care Treatment

The approach in primary care should facilitate the acceptance by the patient (and parents) of the diagnosis and initial treatment recommendations. A **nurturant–authoritative** approach using the **biopsychosocial** model is useful. A pediatrician who explicitly acknowledges that the patient may disagree with the diagnosis and treatment recommendations and be ambivalent about changing eating habits, while also acknowledging that recovery requires strength, courage, will-power and determination, demonstrates *nurturance*. Parents also find it easier to be nurturant once they learn that the development of an ED is neither a willful decision by the patient nor a reflection of bad parenting. Framing the ED as a coping mechanism for a complex variety of issues with both positive and negative aspects avoids blame or guilt and can prepare the family for professional help that will focus on strengths and restoring health, rather than on the deficits in the adolescent or the family.

The **authoritative** aspect of a physician's role comes from expertise in health, growth, and physical development. A goal of primary care treatment should be attaining and maintaining health—not merely weight gain—although weight gain is a means to the goal of wellness. Providers who frame themselves as consultants to the patient with *authoritative* knowledge about health can avoid a countertherapeutic authoritarian stance. Primary care health-focused activities include monitoring the patient's physical status, setting limits on behaviors that threaten the patient's health, involving specialists with expertise in EDs on the treatment team, and continuing to provide primary care for health maintenance, acute illness, or injury.

The **biopsychosocial** model uses a broad ecologic framework, starting with the biologic impairments of physical health related to dysfunctional weight control practices, evidenced by symptoms and signs. Explicitly linking ED behaviors to symptoms and signs can increase motivation to change. In addition, there are usually unresolved psychosocial conflicts in both the intrapersonal (self-esteem, self-efficacy) and interpersonal (family, peers, school) domains. Weight-control practices initiated as coping mechanisms become reinforced because of positive feedback. That is, external rewards (e.g., compliments about improved physical appearance) and internal rewards (e.g., perceived mastery over what is eaten or what is done to minimize the effects of overeating through exercise or purging) are more powerful to maintain

behavior than negative feedback (e.g., conflict with parents, peers, and others about eating) is to change it. Thus, when definitive treatment is initiated, more productive alternative means of coping must be developed.

Nutrition and Physical Activity

The primary care provider generally begins the process of prescribing nutrition, although a dietitian should be involved eventually in the meal planning and nutritional education of patients with AN or BN. Framing food as fuel for the body and the source of energy for daily activities emphasizes the health goal of increasing the patient's energy level, endurance, and strength. For patients with AN and low weight, the nutrition prescription should work toward gradually increasing weight at the rate of about 0.5-1 lb/wk, by increasing energy intake by 100-200 kcal increments every few days toward a target of approximately 90% of average body weight for sex, height, and age. Weight gain will not occur until intake exceeds output, and eventual intake for continued weight gain can exceed 4,000 kcal/day, especially for patients who are anxious and have high levels of thermogenesis from nonexercise activity. Stabilizing intake is the goal for patients with BN, with a gradual introduction of forbidden foods while also limiting foods that might trigger a binge.

When initiating treatment of an ED in a primary care setting, the clinician should be aware of common cognitive patterns. Patients with AN typically have all-or-none thinking (related to perfectionism) with a tendency to overgeneralize and jump to catastrophic conclusions, while assuming that their body is governed by rules that do not apply to others. These tendencies lead to the dichotomization of foods into good or bad categories, having a day ruined because of 1 unexpected event, or choosing foods based on rigid self-imposed restrictions. These thoughts may be related to neurocircuitry and neurotransmitter abnormalities related to executive function and rewards.

A standard nutritional balance of 15-20% calories from protein, 50-55% from carbohydrate, and 25-30% from fat is appropriate. The fat content may need to be lowered to 15-20% early in the treatment of AN because of continued fat phobia. With the risk of low BMD in patients with AN, calcium and vitamin D supplements are often needed to attain the recommended 1,300 mg/day intake of calcium. Refeeding can be accomplished with frequent small meals and snacks consisting of a variety of foods and beverages (with minimal diet or fat-free products), rather than fewer high-volume high-calorie meals. Some patients find it easier to take in part of the additional nutrition as canned supplements (medicine) rather than food. Regardless of the source of energy intake, the risk for refeeding syndrome (acute tachycardia and heart failure with neurologic symptoms associated primarily with acute decline in serum phosphate and magnesium) increases with the degree of weight loss and the rapidity of caloric increases. Therefore, if the weight has fallen below 80% of expected weight for height, refeeding should proceed cautiously, possibly in the hospital (Table 28-7).

Patients with AN tend to have a highly structured day with restrictive intake, in contrast to BN, which is characterized by a lack of structure, resulting in chaotic eating patterns and binge-purge episodes. All patients with AN, BN, or ED-NOS benefit from a daily structure for healthy eating that includes 3 meals and at least 1 snack a day, distributed evenly over the day, based on balanced meal planning. Breakfast deserves special emphasis because it is often the first meal eliminated in AN and is often avoided the morning after a binge-purge episode in BN. In addition to structuring meals and snacks, patients should plan structure in their activities. Although overexercising is common in AN, completely prohibiting exercise can lead to further restriction of intake or to surreptitious exercise; inactivity should be limited to situations in which weight loss is dramatic or there is physiologic instability. Also, healthy exercise (once a day, for no more than 30 minutes, at no more than moderate intensity) can improve mood and make increasing calories more acceptable. Because patients with AN often are unaware of their level of activity and tend toward progressively increasing their output, exercising without either a partner or supervision is not recommended.

Table 28-7	Indications for Inpatient Medical Hospitalization of Patients with Anorexia Nervosa
PHYSICAL AND LABORATORY	
Heart rate < 50 beats/min	
Other cardiac rhythm disturbances	
Blood pressure < 80/50 mm Hg	
Postural hypotension resulting in a >10 mm Hg drop or a >25 beats/min increase	
Hypokalemia	
Hypophosphatemia	
Hypoglycemia	
Dehydration	
Body temperature < 36.1°C (97°F)	
<80% healthy body weight	
Hepatic, cardiac, or renal compromise	
PSYCHIATRIC	
Suicidal intent and plan	
Very poor motivation to recover (in family and patient)	
Preoccupation with ego-syntonic thoughts	
Coexisting psychiatric disorders	
MISCELLANEOUS	
Requires supervision after meals and while using the restroom	
Failed day treatment	

Primary Care Treatment

Follow-up primary care visits are essential in the management of EDs; close monitoring of the response of the patient and the family to suggested interventions is required to determine which patients can remain in primary care treatment (patients with early, mildly disordered eating), which patients need to be referred to individual specialists for co-management (mildly progressive disordered eating), and which patients need to be referred for interdisciplinary team management (EDs). Between the initial and subsequent visits, the patient can record daily caloric intake (food, drink, amount, time, location), physical activity (type, duration, intensity), and emotional state (e.g., angry, sad, worried) in a journal that is reviewed jointly with the patient in follow-up. Focusing on the recorded data helps the clinician to identify dietary and activity deficiencies and excesses as well as behavioral and mental health patterns, and the patient to become objectively aware of the relevant issues to address in recovery.

Given the tendency of patients with AN to overestimate their caloric intake and underestimate their activity level, before reviewing the journal record it is important at each visit to measure weight, without underwear, in a hospital gown after voiding; urine specific gravity; temperature; and blood pressure and pulse in supine, sitting, and standing positions as objective data. In addition, a targeted physical examination focused on hypometabolism, cardiovascular stability, and mental status, as well as any related symptoms, should occur at each visit to monitor progress (or regression).

Referral to Mental Health Services

In addition to referral to a registered dietitian, mental health services are an important element of treatment of EDs. Depending on availability and experience, these services can be provided by a psychiatric social worker, psychologist, or psychiatrist, who should team with the primary care provider. Although patients with AN often are prescribed a selective serotonin reuptake inhibitor (SSRI) because of depressive symptoms, there is no evidence of efficacy for patients at low weight; food remains the initial treatment of choice to treat depression in AN. SSRIs, very effective in reducing binge-purge behaviors regardless of depression, are considered a standard element of therapy in BN. SSRI dosage in BN, however, may need to increase to an equivalent of more than 60 mg of fluoxetine to maintain effectiveness.

Cognitive-behavioral therapy, which focuses on restructuring "thinking errors" and establishing adaptive patterns of behavior, is more effective than interpersonal or psychoanalytic approaches.

Dialectical behavioral therapy, in which distorted thoughts and emotional responses are challenged, analyzed, and replaced with healthier ones, with an emphasis on "mindfulness," requires adult thinking skills and is useful for older patients with BN. **Group therapy** can provide much needed support, but it requires a skilled clinician. Combining patients at various levels of recovery who experience variable reinforcement from dysfunctional coping behaviors can be challenging if group therapy patients compete with each other to be "thinner" or take up new behaviors such as vomiting.

The younger the patient, the more intimately the parents need to be involved in therapy. The only treatment approach with evidence-based effectiveness in the treatment of AN in children and adolescents is **family-based treatment**, exemplified by the Maudsley approach. This 3-phase intensive outpatient model helps parents play a positive role in restoring their child's eating and weight to normal, then returns control of eating to the child who has demonstrated the ability to maintain healthy weight, and then encourages healthy progression in the other domains of adolescent development. Features of effective family treatment include an agnostic approach in which the cause of the disease is unknown and irrelevant to weight gain, emphasizing that parents are *not* to blame for EDs; parents being actively nurturing and supportive of their child's healthy eating while reinforcing limits on dysfunctional habits, rather than an authoritarian food police or complete hands-off approach; and reinforcement of parents as the best resource for recovery for almost all patients, with professionals serving as consultants and advisors to help parents address challenges.

Referral to an Interdisciplinary Eating Disorder Team

The treatment of a child or adolescent diagnosed with an ED is ideally provided by an interdisciplinary team (physician, nurse, dietitian, mental health provider) with expertise treating pediatric patients. Because such teams, often led by specialists in adolescent medicine at medical centers, are not widely available, the primary care provider might need to convene such a team. Adolescent medicine–based programs report encouraging treatment outcomes, possibly related to patients entering earlier into care and the stigma that some patients and parents may associate with psychiatry-based programs. Specialty centers focused on treating EDs are generally based in psychiatry and often have separate tracks for younger and adult patients. The elements of treatment noted earlier (cognitive-behavioral therapy, dialectical behavioral therapy, and family-based therapy), as well as individual and group treatment should all be available as part of interdisciplinary team treatment. Comprehensive services ideally include intensive outpatient and/or partial hospitalization as well as inpatient treatment. Regardless of the intensity, type, or location of the treatment services, the patient, parents, and primary care provider are essential members of the treatment team. A recurring theme in effective treatment is helping patients and families re-establish connections that are disrupted by the ED.

Inpatient medical treatment of EDs is generally limited to patients with AN, to stabilize and treat life-threatening starvation and to provide supportive mental health services. Inpatient medical care may be required to avoid refeeding syndrome in severely malnourished patients, provide nasogastric tube feeding for patients unable or unwilling to eat, or initiate mental health services, especially family-based treatment, if this has not occurred on an outpatient basis (see Table 28-7). Admission to a general pediatric or hospital unit is advised only for short-term stabilization in preparation for transfer to a medical unit with expertise in treating pediatric EDs. Inpatient psychiatric care of EDs should be provided on a unit with expertise in managing the often challenging behaviors (e.g., hiding or discarding food, vomiting, surreptitious exercise) and emotional problems (e.g., depression, anxiety). Suicidal risk is small, but patients with AN might threaten suicide if made to eat or gain weight in an effort to get their parents to back off.

An ED **partial hospital program** offers outpatient services that are less intensive than round-the-clock inpatient care. Generally held 4-5 days a wk for 6 to 9 hr each session, partial hospital program services typically are group-based and include eating at least 2 meals as well as opportunities to address issues in a setting that more closely approximates "real life" than inpatient treatment. That is, patients sleep at home and are free-living on weekends, exposing them to challenges that can be processed during the 25-40 hr in program, also sharing group and family experiences.

Supportive Care

In relation to pediatric EDs, support groups are primarily designed for parents. Because their daughter or son with an ED often resists the diagnosis and treatment, parents often feel helpless and hopeless. Because of the historical precedent of blaming parents for causing EDs, parents often express feelings of shame and isolation (www.maudsleyparents.org). Support groups and multifamily therapy sessions bring parents together with other parents whose families are at various stages of recovery from an ED in ways that are educational and encouraging. Patients often benefit from support groups after intensive treatment or at the end of treatment because of residual body image or other issues after eating and weight have normalized.

PROGNOSIS

With early diagnosis and effective treatment, 80% or more of youth with AN recover: They develop normal eating and weight control habits, resume menses, maintain average weight for height, and function in school, work, and relationships, although some still have poor body image. With weight restoration, fertility returns as well, although the weight for resumption of menses (approximately 92% of average body weight for height) may be lower than the weight for ovulation. The prognosis for BN is less-well established, but outcome improves with multidimensional treatment that includes SSRIs and attention to mood, past trauma, impulsivity, and any existing psychopathology. Atypical AN and ED-NOS may still have significant morbidity.

PREVENTION

Given the complexity of the pathogenesis of EDs, prevention is difficult. Targeted preventive interventions can reduce risk factors in older adolescents and college-age women. Universal prevention efforts to promote healthy weight regulation and discourage unhealthy dieting have not shown effectiveness in middle-school students. Programs that include recovered patients or focus on the problems associated with EDs can inadvertently normalize or even glamorize EDs and should be discouraged.

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Chapter 29

Disruptive, Impulse-Control, and Conduct Disorders

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The disruptive, impulse-control, and conduct disorders are interrelated sets of psychiatric symptoms characterized by a core deficit in self-regulation of anger, aggression, defiance, and antisocial behaviors. The disruptive, impulse-control, and conduct disorders include oppositional defiant, intermittent explosive, conduct, other specified/unspecified disruptive, impulse control, and conduct, and antisocial personality disorders, as well as pyromania and kleptomania.

Table 29-1 DSM-5 Diagnostic Criteria for Oppositional Defiant Disorder

A. A pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness lasting at least 6 mo as evidenced by at least 4 symptoms from any of the following categories, and exhibited during interaction with at least 1 individual who is not a sibling.

Angry/Irritable Mood

1. Often loses temper.
2. Is often touchy or easily annoyed.
3. Is often angry and resentful.

Argumentative/Defiant Behavior

4. Often argues with authority figures or, for children and adolescents, with adults.
5. Often actively defies or refuses to comply with requests from authority figures or with rules.
6. Often deliberately annoys others.
7. Often blames others for his or her mistakes or misbehavior.

Vindictiveness

8. Has been spiteful or vindictive at least twice within the past 6 mo.

Note: The persistence and frequency of these behaviors should be used to distinguish a behavior that is within normal limits from a behavior that is symptomatic. For children younger than 5 yr, the behavior should occur on most days for a period of at least 6 mo unless otherwise noted (Criterion A8). For individuals 5 yr or older, the behavior should occur at least once per week for at least 6 mo, unless otherwise noted (Criterion A8). While these frequency criteria provide guidance on a minimal level of frequency to define symptoms, other factors should be considered, such as whether the frequency and intensity of the behaviors are outside a range that is normative for the individual's developmental level, gender, and culture.

B. The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context (e.g., family, peer group, work colleagues), or it impacts negatively on social, educational, occupational, or other important areas of functioning.

C. The behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 462–463.

Table 29-2 DSM-5 Diagnostic Criteria for Intermittent Explosive Disorder

A. Recurrent behavioral outbursts representing a failure to control aggressive impulses as manifested by either of the following:
   1. Verbal aggression (e.g., temper tantrums, tirades, verbal arguments or fights) or physical aggression toward property, animals, or other individuals, occurring twice weekly, on average, for a period of 3 mo. The physical aggression does not result in damage or destruction of property and does not result in physical injury to animals or other individuals.
   2. Three behavioral outbursts involving damage or destruction of property and/or physical assault involving physical injury against animals or other individuals occurring with a 12-mo period.

B. The magnitude of aggressiveness expressed during the recurrent outbursts is grossly out of proportion to the provocation or to any precipitating psychosocial stressors.

C. The recurrent aggressive outbursts are not premeditated (i.e., they are impulsive and/or anger-based) and are not committed to achieve some tangible objective (e.g., money, power, intimidation).

D. The recurrent aggressive outbursts cause either marked distress in the individual or impairment in occupational or interpersonal functioning, or as associated with financial or legal consequences.

E. Chronological age is at least 6 yr (or equivalent developmental level).

F. The recurrent aggressive outbursts are not better explained by another mental disorder (e.g., major depressive disorder, bipolar disorder, disruptive mood dysregulation disorder, a psychotic disorder, antisocial personality disorder, borderline personality disorder) and are not attributable to another medical condition (e.g., head trauma, Alzheimer disease) or to the physiologic effects of a substance (e.g., a drug of abuse, a medication). For children ages 6-18 yr, aggressive behavior that occurs as part of an adjustment disorder should not be considered for this diagnosis.

Note: This diagnosis can be made in addition to the diagnosis of attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder, or autism spectrum disorder when recurrent impulsive aggressive outbursts are in excess of those usually seen in these disorders and warrant clinical attention.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 466.

DESCRIPTION

Oppositional defiant disorder (**ODD**) is characterized by a pattern lasting at least 6 mo of angry, irritable mood, argumentative/defiant behavior, or vindictiveness exhibited during interaction with at least 1 individual who is not a sibling (Table 29-1). For preschool children, the behavior must occur on most days whereas in school-age children, the behavior must occur at least once a week. The severity of the disorder is considered to be mild if symptoms are confined to only 1 setting (e.g., at home, at school, at work, with peers), moderate if symptoms are present in at least 2 settings, and severe if symptoms are present in 3 or more settings.

Intermittent explosive disorder (**IED**) is characterized by recurrent verbal or physical aggression that is grossly disproportionate to the provocation or to any precipitating psychosocial stressors (Table 29-2). The outbursts, which are impulsive and/or anger-based rather than premeditated and/or instrumental, typically last for less than 30 min and commonly occur in response to a minor provocation by a close intimate.

Conduct disorder (**CD**) is characterized by a repetitive and persistent pattern over at least 12 mo of serious rule-violating behavior in which the basic rights of others or major societal norms or rules are violated (Table 29-3). The symptoms of CD are divided into 4 major categories: *aggression to people and animals*, *destruction of property*, *deceitfulness or theft*, and *serious rule violations* (e.g., truancy, running away). Three subtypes of CD (which have different prognostic significance) are based on the age of onset: *childhood-onset type*, *adolescent onset type*, and *unspecified*. A small proportion of individuals with CD exhibit characteristics (lack of remorse/guilt, callous/lack of empathy, unconcerned about performance, shallow/deficient affect) that qualify for the "*with limited prosocial emotions*" specifier. CD is classified as mild if few if any symptoms in excess of those required for the diagnosis are present, and the symptoms cause relatively minor harm to others. CD is classified as severe if many symptoms in excess of those required for the diagnosis are present, and the symptoms cause considerable harm to others. Moderate severity is intermediate between mild and severe.

Other specified/unspecified disruptive, impulse-control, and CD (subsyndromal disorder) applies to presentations in which symptoms characteristic of the disorders in this class are present and cause clinically significant distress or functional impairment, but do not meet full diagnostic criteria for any of the disorders in this class.

EPIDEMIOLOGY

The prevalence of ODD approximates 3% and in preadolescents is more common in males than females (1.4 : 1). One-year prevalence rates for IED and CD approximate 3% and 4%, respectively. For CD, prevalence rates rise from childhood to adolescence and are higher

Table 29-3 DSM-5 Diagnostic Criteria for Conduct Disorder

A. A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of at least 3 of the following 15 criteria in the past 12 mo from any of the categories below, with at least 1 criterion present in the past 6 mo:

Aggression to People and Animals

1. Often bullies, threatens, or intimidates others.
2. Often initiates physical fights.
3. Has used a weapon that can cause serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun).
4. Has been physically cruel to people.
5. Has been physically cruel to animals.
6. Has stolen while confronting a victim (e.g., mugging, purse snatching, extortion, armed robbery).
7. Has forced someone into sexual activity.

Destruction of Property

8. Has deliberately engaged in fire setting with the intention of causing serious damage.
9. Has deliberately destroyed others' property (other than by fire setting).

Deceitfulness or Theft

10. Has broken into someone else's house, building, or car.
11. Often lies to obtain good or favors or to avoid obligations (i.e., "cons" others).
12. Has stolen items of nontrivial value without confronting a victim (e.g., shoplifting, but without breaking and entering; forgery).

Serious Violations of Rules

13. Often stays out at night despite parental prohibitions, beginning before age 13 yr.
14. Has run away from home overnight at least twice while living in the parental or parental surrogate home, or once without returning for a lengthy period.
15. Is often truant from school, beginning before age 13 yr.

B. The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.

C. If the individual is age 18 yr or older, criteria are not met for antisocial personality disorder.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 469–471.

among males than among females. The prevalence of these disorders has been shown to be higher in lower socioeconomic classes.

CLINICAL COURSE

Oppositional behavior can occur in all children and adolescents from time to time, particularly during the toddler and early teenage periods when autonomy and independence are normative developmental tasks. Oppositional behavior becomes a concern when it is intense, persistent, and pervasive and when it affects the child's social, family, and academic life.

Some of the earliest manifestations of oppositionality are stubbornness (3 yr), defiance and temper tantrums (4-5 yr), and argumentativeness (6 yr). Approximately 65% of children with ODD exit from the diagnosis after a 3 yr follow-up; earlier age at onset of oppositional symptoms conveys a poorer prognosis. ODD often precedes the development of CD (approximately 30% higher likelihood with comorbid attention-deficit/hyperactivity disorder [ADHD; see Chapter 33]), but also increases the risk for the development of depressive and anxiety disorders. The defiant and vindictive symptoms carry most of the risk for CD, whereas the angry-irritable mood symptoms carry most of the risk for anxiety and depression.

IED most commonly begins in late childhood or adolescence and appears to follow a chronic and persistent course over many years.

The onset of CD may occur as early as the preschool years, but the first significant symptoms usually emerge during the period from middle childhood through middle adolescence; onset is rare after age 16 yr. Symptoms of CD vary with age as the individual develops increased physical strength, cognitive abilities, and sexual maturity. Symptoms that emerge first tend to be less serious (e.g., lying), while those emerging later tend to be more severe (e.g., sexual or physical assault). Severe behaviors emerging at an early age convey a poor prognosis. In the majority of individuals, the disorder remits by adulthood; in a substantial fraction, antisocial personality disorder develops. Individuals with CD also are at risk for the later development of mood, anxiety, posttraumatic stress, impulse control, psychotic, somatic symptom, and substance-related disorders.

DIFFERENTIAL DIAGNOSIS

The disorders in this diagnostic class share a number of characteristics with each other as well as with disorders from other classes, and as such must be carefully differentiated. ODD can be distinguished from CD by the absence of physical aggression and destructiveness, and by the presence of angry/irritable mood; ODD can be distinguished from IED by the lack of serious aggression (physical assault). IED can be distinguished from CD by the lack of predatory aggression and other nonaggressive symptoms of CD.

The oppositionality seen in ODD must be distinguished from that seen in ADHD, depressive and bipolar disorders (including ***disruptive mood dysregulation disorder*** [see Chapter 26]), language disorders and intellectual disability, and social anxiety disorder. ODD should not be diagnosed if the behaviors occur exclusively during the course of a psychotic, substance use, depressive or bipolar disorder, and if criteria are met for disruptive mood dysregulation disorder. IED should not be diagnosed if the behavior can be better explained by a depressive, bipolar, disruptive mood dysregulation, psychotic, antisocial personality, or borderline personality disorder. The aggression seen in CD must be distinguished from that seen in ADHD and intermittent explosive, depressive, bipolar, and adjustment disorders.

COMORBIDITY

Rates of ODD are much higher in children with ADHD, which suggests shared temperamental risk factors. Depressive, anxiety, and substance use disorders are most commonly comorbid with IED. ADHD and ODD are both common in individuals with CD, and this comorbid presentation predicts worse outcomes. CD also may co-occur with anxiety, depressive, bipolar, learning, language, and substance-related disorders.

SEQUELAE

The disruptive, impulse-control, and CDs are associated with a wide range of psychiatric disorders in adulthood and with many other adverse outcomes, such as suicidal behavior, physical injury, delinquency and criminality, legal problems, substance use, unplanned pregnancy, social instability, marital failure, and academic and occupational underachievement.

ETIOLOGY AND RISK FACTORS

At the individual level, a number of neurobiologic markers (lower heart rate and skin conductance reactivity, reduced basal cortisol reactivity, abnormalities in the prefrontal cortex and amygdala, serotonergic abnormalities) have been variously associated with aggressive behavior disorders. Other biologic risk factors include pre-, peri-, and postnatal insults, cognitive and linguistic impairment (particularly language-based learning deficits); difficult temperamental characteristics (particularly negative affectivity, poor frustration tolerance, impulsivity); certain personality characteristics (novelty seeking, reduced harm avoidance, and reward dependence); and certain cognitive characteristics (cognitive rigidity, hostile attributions for ambiguous social cues).

At the family level, a consistently demonstrated risk factor is ineffective parenting. Parents of behaviorally disordered children have been found to be more inconsistent in their use of rules; to issue more and unclear commands; to be more likely to respond to their child on the basis of their mood rather than the child's behavior; to be less

Table 29-4 Anger/Aggression-Specific Screening Instruments

NAME OF INSTRUMENT	INFORMANT(S)	AGE RANGE	NUMBER OF ITEMS
Children's Aggression Scale	Parent, Teacher	5-18 y	33 (P), 23 (T)
Eyberg Child Behavior Inventory	Parent	2-16 y	36
Outburst Monitoring Scale	Parent	12-17 y	20
Sutter-Eyberg Student Behavior Inventory–Revised	Teacher	2-16 y	38

likely to monitor their children's whereabouts; and to be relatively unresponsive to their children's prosocial behavior. Complicating this association is the consistent finding that temperamentally difficult children are more likely to elicit negative parenting responses, including physical punishment, which can exacerbate anger and oppositionality in the child. Other important family-level influences include impaired parent–child attachment, child maltreatment (physical and sexual abuse), exposure to marital conflict and domestic violence, family poverty and crime, and family genetic liability (family histories of the disorders in this class as well as substance use, depressive, bipolar, schizophrenic, somatization, and personality disorders, as well as ADHD, have all been shown to be associated with the development of behavior disorders).

Peer-level influence on the development of behavior problems include peer rejection in childhood and antisocial peer groups, while neighborhood influences include social processes such as collective efficacy and social control.

PREVENTION

A number of studies have assessed the efficacy of programs targeted at the prevention of problem behaviors in children. One of the best researched programs is *Fast Track* (http://fasttrackproject.org), which is a multicomponent school-based intervention comprising a classroom curriculum targeted at conflict resolution and interpersonal skills, parent training, and interventions targeted at the school environment. Implemented in 1st through 10th grade, outcomes at grade 12 demonstrated that intervention decreased the lifetime prevalence of CD, ODD, and ADHD, but only among those at highest initial risk. Another well-researched program, the *Seattle Social Development Project* (http://ssdp-tip.org/SSDP/index.html), also is a multicomponent school-based intervention made up of teacher, parent, and student components targeting classroom management, interpersonal problem-solving skills, child behavior management skills, and academic support skills. Implemented in 1st through 6th grades, outcomes at age 18 yr demonstrated that the intervention decreased school misbehavior and disciplinary actions and violent delinquent acts, as well as demonstrating other favorable academic and behavioral outcomes.

SCREENING/CASE FINDING

The parents of children presenting in the primary care setting should be queried about angry mood or aggressive, defiant, or antisocial behavior as part of the routine clinical interview. A typical screening question would be "Does [name] have a lot of trouble controlling [his/her] anger or behavior?" A number of standardized broad-band screening instruments widely used in the primary care setting *(Pediatric Symptom Checklist*, *Strengths and Difficulties Questionnaire*, *Vanderbilt ADHD Diagnostic Rating Scales)* have items specific to angry mood and/or aggressive behavior, and as such can be used to focus the interview.

Stepped Management

Because of the high rates of response to brief interventions, including bibliotherapy (use of books and other printed material to address emotional or behavioral issues with or without psychotherapy) and other media interventions, clinical practice guidelines increasingly are advocating a stepped approach to the management of youth with behavior problems. The stepped approach involves active case finding and initial management in the primary care setting if appropriate, with referral to increasingly intensive and specialized interventions as indicated by the clinical status of the patient.

Early Intervention

Youth and/or their parents presenting in the primary care setting who self-report or respond affirmatively to queries about difficulties managing angry mood or aggressive or antisocial behavior should be afforded the opportunity to talk about the situation with the pediatric practitioner (in private with the older youth as indicated). By engaging in active listening (e.g., "I hear how you have been feeling. Tell me more about what happened to make you feel that way"), the pediatric practitioner can begin to assess the onset, duration, context, and severity of the symptoms, and associated dangerousness, distress, and functional impairment. In the absence of acute dangerousness (e.g., homicidality, assaultiveness, psychosis, substance abuse) and significant distress or functional impairment, the pediatric practitioner can schedule a follow-up appointment within 1-2 wk to conduct a behavior assessment. At this follow-up visit, to assist with decision making around appropriate level of care, a behavior screening instrument can be administered (Table 29-4) and additional risk factors (see "Etiology/Risk Factors" above) can be explored.

For mild symptoms (manageable by the parent and not functionally impairing) and in the absence of major risk factors (homicidality, assaultiveness, psychosis, substance use, child maltreatment, parental psychopathology, or severe family dysfunction), guided self-help (anticipatory guidance) with watchful waiting may suffice. Guided self-help can include provision of educational materials (pamphlets, books, DVDs, workbooks, Internet sites) that provide information to the youth about dealing with anger-provoking situations, and advice to parents about strengthening the parent–child relationship, effective parenting strategies, and the effects of adverse environmental exposures on the development of behavior problems. An example of a self-help program for parents is the *Positive Parenting Program* (Triple P; www.triplep.net), self-directed version, in which parents are provided with a workbook outlining a 10 wk self-guided program that includes readings and homework tasks. In a Cochrane review, media-based parenting interventions were found to have a moderate, if variable, effect on child behavior problems. If the problematic behavior is occurring predominantly at school, the parent can be advised about the role of a special education evaluation in the assessment and management of the child's misbehavior, including the development of a behavioral intervention plan. During the period of guided self-help, follow-up visits should be scheduled.

If a mental health clinician has been colocated or integrated into the primary care setting, all parents of young children (universal prevention) as well as the parents of youth with behavior problems (indicated prevention) can be provided with a brief version of parent training. For example, *Incredible Years* has a 6-8 session universal prevention version designed for the parents of 2-6 yr old children, and the Triple P program has a universal prevention communications system (print and electronic media) for the parents of youth from birth to the teenage years. For children with behavior problems, the Triple P program has seminar (three 90 min sessions), brief (15-30 min consultations), and primary care (four 20-30 min consultations) versions for the parents

of youth from birth to the teenage years that have been specifically designed for implementation in the primary care setting. These brief interventions focus on strengthening the parent–child relationship, identifying and monitoring the frequency of a problem behavior, and implementing and reviewing the effects of a targeted behavior plan.

Treatment

For youth who continue to have mild to moderate behavior problems after several weeks of guided self-help or a brief course of parent training, or who from the outset exhibit moderate to severe or comorbid aggression, homicidality, assaultiveness, psychosis, or substance use, or who have a history of child maltreatment or severe family dysfunction or psychopathology, assessment (see Chapter 20) and treatment (see Chapter 21) in the specialty mental health setting by a child-trained mental health clinician should be provided. The mental health clinician should be trained to the appropriate level of competence in the specific services the clinician is asked to provide.

The youth's problem behavior may predominantly occur at home, at school, with peers, or in the community, or it may be pervasive. If possible, interventions need to address each context specifically, rather than assuming generalizability of treatment. Thus, for behaviors mostly manifested in the home setting, parent training would be the treatment of choice, whereas for behaviors manifested mostly at school, consultation with the teacher and recommendation of a special education evaluation for service eligibility can be useful. When there are pervasive problems, including aggression toward peers, anger management training can be employed in addition to the other interventions.

Parent training has been extensively studied for the treatment of youth problem behavior. These programs, typically 10-15 wk in duration, focus on some combination of the following components: understanding social learning principles, developing a warm, supportive relationship with the child, encouraging child-directed interaction and play, providing a predictable, structured household environment, setting clear and simple household rules, consistently praising and materially rewarding positive behavior, consistently ignoring annoying behavior (followed by praise when the annoying behavior ceases), and consistently giving consequences (such as time out or loss of privileges) for dangerous or destructive behavior. Other important targets for parenting training include understanding developmentally appropriate moods and behavior, managing difficult temperamental characteristics, fostering the child's social and emotional development, and protecting the child from traumatic exposures. Several of these programs have demonstrated moderate to large effect sizes (0.5-0.8) in multiple randomized trials for short-term reductions in behavior problems. A Cochrane review found group parenting programs to be effective and cost-effective for improving child behavior problems (***standardized mean difference* [SMD]:** –0.53 to –0.72), parental mental health (SMD: –0.36), and parenting skills (SMD: –0.47 to –0.53) among parents of 3-12 yr old children. An earlier Cochrane review concluded that parenting programs can be effective in improving the emotional and behavioral adjustment of 0-3 yr old children.

Parenting programs with effect sizes exceeding 0.20 include *Parent–Child Interaction Therapy*, Triple P, *Helping the Noncompliant Child, Incredible Years,* and *Parent Management Training Oregon.* Parenting programs have been found to be effective in disadvantaged community settings as well as in DVD format (Incredible Years) and over the Internet (Triple P Online), and for some programs effects have been found to be durable over a number of years. Predictors of nonresponse to these interventions have included greater initial symptom severity as well as involvement of the parent with child protection services.

Adherence to the complete treatment regimen has limited the effectiveness of parent training programs. Estimates of premature termination are as high as 50-60%, and termination within 5 treatment sessions is not uncommon. Predictors of premature termination of parent training programs have included single parent status, low family income, low parental education levels, young maternal age, minority group status, and life stresses.

Anger management training programs for misbehaving youth also have been extensively studied. These programs, typically 16-20 weekly sessions in duration, focus on some combination of the following components: emotion awareness, perspective taking, anger management, social problem solving, and goal settings. Among the programs with effect sizes exceeding 0.20 include *Coping Power* and *Problem-Solving Skills Training*.

Multicomponent treatments for serious behavior disorders (such as CD) that target the broader social context include ***Multidimensional Treatment Foster Care*** and ***Multisystemic Therapy***. Multidimensional Treatment Foster Care, delivered in a foster care setting for 6-9 mo, typically includes foster parent training and support; family therapy for biologic parents; youth anger management, social skills, and problem-solving training; school-based behavioral interventions and academic support; and psychiatric consultation and medication management, when needed. Multisystemic Therapy, typically lasting 3-5 mo, generally includes social competence training, parent and family skills training, medications, academic engagement and skills building, school interventions and peer mediation, mentoring and after-school programs, and involvement of child-serving agencies. These multicomponent programs have been designated probably efficacious because of the limited rigorous supporting evidence. Predictors of nonresponse to multicomponent treatments have included higher frequency of rule-breaking behavior and predatory aggression, higher psychopathy scores, and comorbid mood disorders.

Two classes of medication, stimulants and atypical antipsychotics, have strong evidence for the management of impulsive, anger-driven aggressive behavior, although neither are FDA approved for this indication. Resource limitations may necessitate provision of pharmacotherapy in the primary care setting; the safety and efficacy of this practice can be enhanced by regular consultation with a child and adolescent psychiatrist.

In a meta-analysis of pharmacologic treatments for aggression in youth, stimulants had a pooled mean effect size of 0.78. In a systematic review of placebo-controlled efficacy of stimulants for rating-scale assessed aggression, stimulants had a pooled effect size of 0.6 and a ***number needed to treat*** of 4. The doses of stimulants used for aggression are similar to those used for ADHD (average dose for methylphenidate: approximately 1 mg/kg/day).

Stimulants have been well-tolerated by children and adolescents, and all formulations have similar adverse event profiles. The most common (generally dose-dependent) side effects include headache, stomachache, appetite suppression, weight loss, blood pressure and heart rate increases, and delayed sleep onset. Rare side effects include irritability (particularly in younger children) and hallucinations. The cardiac effects of stimulants have been extensively studied, the most recent of which has demonstrated a hazard ratio for serious cardiovascular events of 0.75. Stimulants should be avoided in the presence of structural cardiac abnormalities and patient symptoms (syncope, palpitations, arrhythmias), or family history (e.g., unexplained sudden death) suggestive of cardiovascular disease, without cardiology consultation.

In studies of risperidone in youth with aggressive behavior, the mean effect size for aggression was 0.72. For maintenance treatment, mean effect size was 0.40. The usual daily dose of risperidone for aggression has been suggested to be 1.5-2 mg for children and 2-4 mg for adolescents. The initial starting doses have been suggested to be 0.25 mg for children and 0.5 mg for adolescents, titrating upward to the usual daily dose as indicated and tolerated.

Side effects of antipsychotic medications include sedation, extrapyramidal side effects, withdrawal dyskinesia, hyperprolactinemia, elevated liver transaminases, weight gain, cardiovascular effects, and metabolic abnormalities (elevated glucose and lipids). Ziprasidone is associated with the lowest weight gain followed by aripiprazole, quetiapine, risperidone, and olanzapine. However, ziprasidone has not been recommended for use in children and adolescents due to lack of efficacy data. The excessive weight gain associated with olanzapine precludes its choice as a 1st-line agent.

The side effects of antipsychotic medications warrant close monitoring: abnormal movements should be monitored periodically using a standardized methodology (such as the Abnormal Involuntary

Movement Scale [AIMS] checklist); blood pressure, body mass index and fasting glucose and lipids should be checked at baseline and at regular intervals thereafter, according to standard guidelines. Consideration of weight management interventions and increased monitoring of blood glucose and lipid levels should be implemented if weight gain exceeds 90th percentile body mass index for age, or a change of 5 body mass index units occurs in youths who were obese at the beginning of treatment. In patients with a personal or family history of cardiac abnormalities, including syncope, palpitations, arrhythmias, or sudden unexplained death, a baseline electrocardiogram with subsequent monitoring should be considered, along with cardiology consultation. Alternative pharmacology should be considered if the resting heart rate exceeds 130 beats/min, or the PR, QRS, and QTc exceed 200, 120, and 460 msec, respectively.

Medication trials should be systematic, and the duration of trials should be sufficient (generally 6-8 wk) to determine the agent's effectiveness. The immediate goal of treatment is to achieve at least a 50% reduction in aggressive symptoms as assessed by a standardized rating scale (see Table 29-4). A second medication of the same class can be considered if there is insufficient evidence of response to the maximal tolerated dose by 8 wk. Care should be taken to avoid unnecessary polypharmacy, in part by discontinuing agents that have not demonstrated significant benefit. Discontinuation of the medication should be considered after a symptom-free interval.

LEVEL OF CARE

Most children and adolescents with a behavior disorder can be safely and effectively treated in the outpatient setting. Youths with intractable CD may benefit from residential or specialized foster care treatment, where more intensive treatments can be provided.

Bibliography is available at Expert Consult.

29.1 Age-Specific Behavioral Disturbances

Lovern R. Moseley, Heather J. Walter, and David R. DeMaso

INFANCY AND TODDLERHOOD

Temper tantrums and breath-holding spells are common during the first years of life and are age-typical expressions of frustration or anger. Parents who respond to toddler defiance with punitive anger can reinforce oppositional behavior. Parents are best advised to attempt to avert defiance by giving the child choices; once the child has begun a tantrum, the child can be given a timeout. It is useful to advise parents to tell their child, once he or she is calm, that the reasons for frustration are understandable, but that defiance is not acceptable.

Parents are occasionally concerned about **breath-holding spells.** Although some children hold their breath until they lose consciousness, sometimes leading to a brief seizure, there is no increased risk of seizure disorders in children who have had a seizure during a breath-holding spell. Parents are best advised to ignore breath holding once it has started. Without sufficient reinforcement, breath holding generally disappears.

Subtypes of breath holding spells include cyanotic, pallid, or mixed episodes. Cyanotic are the dominant type and may include a brief loss of consciousness and a very brief tonic-clonic seizure. Pallid spells may be similar to vasovagal related syncopal events in older children and initiated from similar stimuli (see Chapter 69). Iron deficiency with or without anemia may be present and some children with breath-holding spells respond to iron therapy. Medical conditions to consider should include seizures, Chiari crisis, dysautonomia, cardiac arrhythmias, and central nervous system lesions.

The first key to the office management of temper tantrums and breath-holding spells is to help parents to intercede before the child is highly distressed. The pediatrician should advise parents to intercede early in defiant behavior by calmly placing the child in timeout for a period of time approximating 1 min for each year of age. When breath holding does not respond to the parent's coaching or is accompanied by head banging or high levels of aggression, referral for a mental health evaluation is indicated.

If behavioral measures such as timeout fail, pediatricians must assess how the parents handle anger before making further recommendations about how to approach the child. Children can be frightened by the intensity of their own angry feelings and by angry feelings they arouse in their parents. Parents should model the anger control that they wish their children to exhibit. Some parents are unable to see that they lose control themselves; their own angry behavior does not help their children to internalize controls. Advising parents to calmly provide simple choices will help the child to feel more in control and to develop a sense of autonomy. Providing the child with options also typically helps reduce the child's feelings of anger and shame, which can later have adverse effects on social and emotional development.

Lying can be used by 2-4 yr olds as a method of playing with the language. By observing the reactions of parents, preschoolers learn about expectations for honesty in communication. Lying can also be a form of fantasy for children, who describe things as they wish them to be rather than as they are. To avoid an unpleasant confrontation, a child who has not done something that a parent wanted may say that it has been done. The child's sense of time and reason does not permit the realization that this only postpones a confrontation.

CHILDHOOD AND ADOLESCENCE

Lying

In **school-age children,** lying is generally an effort to cover up something that the child does not want to accept in his or her own behavior. The lie is invented to achieve a temporary good feeling and to protect the child against a loss of self-esteem. Habitual lying also can be promoted by poor adult modeling. Many adolescents lie to avoid adults' disapproval; lying may be used as a method of rebellion. Chronic lying can occur in combination with several other antisocial behaviors and is a sign of underlying psychopathology or family dysfunction.

Regardless of age or developmental level, when lying becomes a common way of managing conflict, intervention is warranted. Initially, the parents should confront the child to give a clear message of what is acceptable. Sensitivity and support combined with limit-setting are necessary for a successful intervention. If this behavior cannot be resolved through the parents' understanding of the situation and the child's understanding that lying is not a reasonable alternative, a mental health evaluation is indicated.

Stealing

Many children **steal** something at some point in their lives. When preschoolers and school-age children steal more than once or twice, the behavior may be a response to stressful environmental circumstances. Stealing can be an expression of anger or revenge for perceived frustrations with parents. In some instances, stealing becomes 1 way the child or adolescent can manipulate and attempt to control the child's or adolescent's world. Stealing also can be learned from adults.

It is important for parents to help the child undo the theft by returning the stolen articles or by rendering their equivalent either in money that the child can earn or in services. When stealing is part of a pattern of conduct problems, referral for a mental health evaluation is warranted.

Truancy and Running Away

Truancy and running away are never developmentally appropriate. Truancy may represent disorganization within the home, caretaking needs of younger siblings, developing conduct problems, or emotional problems including depression or anxiety. Whereas younger children may threaten to run away out of frustration or a desire to get back at parents, older children who run away are almost always expressing a serious underlying problem within themselves or their family, including violence, abuse, and neglect. Adolescent runaways are at high risk for substance abuse, unsafe sexual activity, and other risk-taking behaviors. Youth exhibiting truancy or running away should be referred for a mental health evaluation.

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Fire Setting

Although interest in fire is common in early childhood, unsupervised **fire setting** is always inappropriate because of its extreme dangerousness. School-age children may set fires accidentally, or because of curiosity or latent hostility. These young children usually set fires by themselves within their homes. In adolescence, fire setting can be a sign of delinquency or a signal of traumatic experiences. Fire setting always requires intervention by a mental health clinician. A thorough mental health evaluation is necessary to plan the components of a successful treatment program.

Aggression and Bullying

See also Chapter 39.1.

Aggression and bullying are serious symptoms and are associated with significant morbidity and mortality. Children might not grow out of this behavior; early intervention is indicated for persistent aggressive behavior. Aggressive tendencies are heritable, although environmental factors can promote aggression in susceptible children. Both enduring and temporary stressors affecting a family can increase aggressive behavior in children. Aggression in childhood is correlated with a chaotic and impoverished family home that could be the result of chronic unemployment, family discord, exposure to community and domestic violence, criminality and psychiatric disorders as well as births to teenage mothers and those with limited resources and support. Boys are almost universally reported to be more aggressive than girls. A difficult temperament and later aggressiveness are related, although there is evidence that these children elicit punitive caregiving within the family environment, setting up a cycle of increasing aggression. Aggressive children often misperceive social cues and react with inappropriate hostility toward peers and parents.

Clinically, it is important to differentiate the causes and motives for childhood aggression. Intentional aggression may be primarily instrumental, to achieve an end, primarily hostile, to inflict physical or psychologic pain, or primarily angry and impulsive. Children who are callous and not empathetic and who are often aggressive require mental health intervention. These children are at high risk for suspension from school and eventual school failure. Learning disorders are common, and aggressive children should be screened. Other forms of psychopathology may be present; in particular, aggressive children might have ADHD, ODD, IED, CD, and/or disruptive mood dysregulation disorder.

Aggressive behavior in boys is relatively consistent from the preschool period through adolescence; a boy with a high level of aggressive behavior at 3-6 yr of age has a high probability of carrying this behavior into adolescence, especially without effective intervention. The developmental progression of aggression among girls is less-well studied. There are fewer girls with physically aggressive behavior in early childhood; interpersonal coercive behavior, especially in peer relationships, is not uncommon among girls and may be related to the development of more physical aggression in adolescence (fighting, stealing).

Children exposed to aggressive models on television, in video games, or in play show more aggressive behavior compared with children not exposed to these models. Parents' anger and aggressive or harsh punishment model behavior that children might imitate when they are physically or psychologically hurt. Parents' abuse may be transmitted to the next generation by several modes: children imitate aggression that they have witnessed, abuse can cause brain injury (which itself predisposes the child to violence), and internalized rage often results from abuse.

Cutting and Other Self-Injurious Behaviors

Cutting and other self-injurious behaviors have been occurring in increased rates among children as young as age 11 yr through adolescence. Rates are higher in girls than boys, but cutting and other self-injurious behaviors do occur in both. The behavior involves the deliberate carving, cutting, scratching, or burning of the skin with fingernails or other objects sharp enough to cause injury (razors, scissors, broken glass, hard plastic, knives, staples, fire). Oftentimes the behavior does not occur with the intention of suicide but can be associated with it and can unintentionally result in significant harm or even death. Youth often report that they have friends who "cut" and have reported that it is a way to feel better and so they have tried it as well. There is increased access to message boards and websites on the internet where youth have shared their stories of self-injury; these postings may have contributed to experimentation. The behavior is usually triggered by psychological distress and is also correlated with depression, anxiety, peer victimization, low self-esteem, substance abuse, eating disorders, impulsivity, delinquency, and neglectful or highly punitive parenting practices, as well as a history of physical or sexual abuse. Parents should be advised to monitor their children's media access and be aware of their peer group. Learning that their child has been engaging in this behavior can be very frightening for parents as they are unsure of what to do or the reasons why their child is engaging in this behavior. It is imperative that they seek mental healthcare for their child.

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Chapter 30

Autism Spectrum Disorder

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The essential features of ***autism spectrum disorder* (ASD)** are persistent impairment in reciprocal social communication and interaction, and restricted, repetitive patterns of behavior or interests (Table 30-1). ASD encompasses disorders previously referred to as early infantile autism, childhood autism, Kanner autism, high functioning autism, atypical autism, Asperger disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified. These specific diagnoses are not reliably distinguishable or consistently applied across different treatment centers. Individuals diagnosed with one of these previous diagnoses should be given the diagnosis of ASD.

DESCRIPTION

Social Communication and Interaction Deficits

Aberrant development of social communication and impaired ability to engage in reciprocal social interactions are hallmark symptoms of ASD. Deficits in social–emotional reciprocity (the ability to engage with others and share thoughts and feelings) are evident early in children with ASD who show little or no initiation of social interaction and little or no sharing of emotions or imitative behaviors. Children may present with abnormal social approach, failure of back-and-forth conversation, and difficulties processing and responding to complex social cues. Infants <6 mo of age may or may not demonstrate features typical of ASD.

Impairments in nonverbal social communication are manifested by absent, reduced, or atypical use of eye contact, gestures, facial expressions, body orientation, or speech intonation. Youth may fail to smile, orient to name, or use gestures to point or show. Abnormal eye contact with failure to follow someone's pointing or eye gaze is characteristic. In patients with fluent language, poorly integrated verbal and nonverbal communication may result in odd, wooden, or exaggerated body language during social interactions (Table 30-2).

Children with ASD may demonstrate absent, reduced, or atypical social interest, manifested by rejection of others, passivity, or inappropriate approaches that seem aggressive and disruptive. In young children, lack of shared, age-appropriate flexible pretend and symbolic play is seen, with children often insistent on playing by very fixed rules.

Table 30-1 DSM-5 Diagnostic Criteria for Autism Spectrum Disorder

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
   1. Deficits in social-emotional reciprocity.
   2. Deficits in nonverbal communicative behaviors used for social interaction.
   3. Deficits in developing, maintaining, and understanding relationships.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history:
   1. Stereotyped or repetitive motor movements, use of objects, or speech.
   2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior.
   3. Highly restricted, fixated interests that are abnormal in intensity or focus.
   4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment.

C. Symptoms must be present in the early developmental period (may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 50–51.

Children with ASD may prefer solitary activities and interactions with much younger or older people. A desire to establish friendships without complete understanding of the components of friendship (one-sided friendships based solely on shared special interests) can be seen in some children, while an absence of interest in peers may be seen in others. Some youth show deficits in empathy and understanding what another person might be thinking.

Restricted and Repetitive Patterns

The second core characteristic of ASD is restricted, repetitive patterns of behavior, interests, or activities. These include stereotyped movements (hand flapping, finger flicking), repetitive use of objects (spinning coins, lining up toys), repetitive and abnormal speech (echolalia [delayed or immediate parroting of heard words], pronoun reversal, nonsense rhyming, idiosyncratic phrases); insistence on sameness and inflexible adherence to routines or ritualized patterns of behavior (distress at small changes, insistence on adherence to rules, rituals and routines, rigid thinking, repetitive questioning); highly restricted and fixed interests of abnormal intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests); and hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., extreme responses to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects, apparent indifference to pain, heat, or cold) (see Table 30-2).

The symptoms of ASD must be present in the early developmental period, must cause clinically significant functional impairment, and must not be better explained by intellectual disability or global developmental delay.

Severity

The severity of ASD is based on evaluations of impairment caused by both deficits in social communication and in restricted, repetitive behaviors. Within these 2 categories, severity is rated levels 1-3, with level 3 implying most severe deficit with a need for the most substantial support (Table 30-3).

Specifiers/Associated Features

ASD is specified as occurring with or without accompanying intellectual and language impairment, and associated with a known medical or genetic condition, environmental factor, or other neurodevelopmental, mental, or behavioral disorder. Children with ASD vary in their verbal abilities. Language level in individuals with ASD "without accompanying language impairment" may speak in full sentences or have fluent speech. ASD specified "with accompanying language impairment" can range from nonverbal speech to single word or phrase speech (capable of imitating songs, rhymes, or television commercials). Receptive language may lag behind expressive language development in ASD. Early abnormal language concerns include absent babbling or gestures by 12 mo, absent single words by 16 mo, and absent 2-word purposeful phrases by 24 mo, as well as any loss of language or social skills at any time. Language, if present, is often one-sided, lacking social reciprocity, idiosyncratic, repetitive, and used to request or label rather than comment, share feelings, or converse.

Intellectual functioning can vary from intellectual impairment (intellectual developmental disorder) to superior intellectual functioning in select areas (splinter skills, savant behavior) ("with or without accompanying intellectual impairment"). Some children show typical development in certain skills and can even show areas of strength in specific areas (puzzles, art, or music). The intellectual profile of an individual may be uneven, with gaps in verbal and nonverbal learning ability and intellectual and adaptive functional skills.

Motor deficits, including odd gait, clumsiness, dyspraxia, and other abnormal motor signs (e.g., walking on tiptoes) are often present. Stereotypic movement or tic disorders may go unnoticed given aforementioned restricted behavioral patterns. Self-injury (head banging, biting the wrist) may occur. Some youth develop catatonic-like motor behavior (slowing and "freezing" mid-action) though most do not go onto develop a full episode with mutism, posturing, grimacing, and waxy flexibility.

Epilepsy is a common comorbidity, and any type of seizure may be observed in ASD. Epilepsy is associated with greater intellectual disability and lower verbal ability. Mutations in the *BCKD-kinase* gene is a syndrome associated with autism, epilepsy and intellectual disability. Youth with ASD are also prone to anxiety and depression as well as abnormalities in attention and hyperactivity.

Language, social, or a mixed pattern of regression may occur in the first 1-2 years. In some, a diagnosis of Landau Kleffner syndrome is identified; in others regression may be due to the onset of epilepsy or abnormal EEG findings in the absence of clinical seizures. Levetiracetam also causes a reversible autistic regression syndrome.

EPIDEMIOLOGY

The Centers for Disease Control and Prevention estimates the prevalence of ASD in the United States as 11.3/1,000 (prior estimated prevalence range: 0.7/10,000 to 72.6/10,000 across 36 earlier surveys). Recent higher reported rates of the disorder appear to be related to differences in diagnostic criteria and practices, inclusion of subthreshold cases, age of children screened, and location of the study. The male : female ratio is estimated to be 4 : 1. The incidence of ASD may be higher in immigrant populations.

ETIOLOGY/RISK FACTORS

Genetic and Familial Factors

There is a high recurrence risk (2-19%) for ASD among siblings, as well as a higher concordance rate (37-90%) in twin studies. Closer spacing of pregnancies, advanced maternal or paternal age, and extremely premature birth (<26 wk gestational age) as well as family members with learning problems, psychiatric disorders, and social disability, have been identified as risk factors. Multiple genes are viewed as involved in autism with studies supporting a role for both common (>5% of general population) and rare genetic variations contributing to the disorder. For example, Timothy syndrome, characterized by

Table 30-2 Signs and Symptoms of Possible Autism in Preschool Children (or Equivalent Mental Age)

Social interaction and reciprocal communication behaviors

Spoken language
- Language delay (in babble or words—for example, using fewer than 10 words by the age of 2 yr)
- Regression in or loss of use of speech
- Spoken language (if present) may include unusual features, such as: vocalizations that are not speech-like; odd or flat intonation; frequent repetition of set words and phrases (echolalia); reference to self by name or "you" or "she" or "he" beyond age 3 yr
- Reduced and/or infrequent use of language for communication—for example, use of single words, although able to speak in sentences

Responding to others
- Absent or delayed response to name being called, despite normal hearing
- Reduced or absent responsive social smiling
- Reduced or absent responsiveness to other people's facial expressions or feelings
- Unusually negative response to the requests of others ("demand avoidance" behavior)
- Rejection of cuddles initiated by parent or carer, although the child himself or herself may initiate cuddles

Interacting with others
- Reduced or absent awareness of personal space, or unusually intolerant of people entering their personal space
- Reduced or absent social interest in others, including children of his or her own age—may reject others; if interested in others, he or she may approach others inappropriately, seeming to be aggressive or disruptive
- Reduced or absent imitation of others' actions
- Reduced or absent initiation of social play with others, plays alone
- Reduced or absent enjoyment of situations that most children like—for example, birthday parties
- Reduced or absent sharing of enjoyment

Eye contact, pointing, and other gestures
- Reduced or absent use of gestures and facial expressions to communicate (although may place an adult's hand on objects)
- Reduced and poorly integrated gestures, facial expressions, body orientation, eye contact (looking at people's eyes when speaking), and speech used in social communication
- Reduced or absent social use of eye contact (assuming adequate vision)
- Reduced or absent "joint attention" (when 1 person alerts another to something by means of gazing, finger pointing, or other verbal or nonverbal indication for the purpose of sharing interest). This would be evident in the child from lack of:
  - Gaze switching
  - Following a point (looking where the other person points to—may look at hand)
  - Using pointing at or showing objects to share interest

Ideas and imagination
- Reduced or absent imagination and variety of pretend play

Unusual or restricted interests and/or rigid and repetitive behaviors
- Repetitive "stereotypical" movements such as hand flapping; body rocking while standing; spinning; finger flicking
- Repetitive or stereotyped play—for example, opening and closing doors
- Over focused or unusual interests
- Excessive insistence on following own agenda
- Extremes of emotional reactivity to change or new situations; insistence on things being "the same"
- Over-reaction or under-reaction to sensory stimuli, such as textures, sounds, smells
- Excessive reaction to the taste, smell, texture, or appearance of food, or having extreme food fads

From Baird G, Douglas HR, Murphy MS: Recognizing and diagnosing autism in children and young people: summary of NICE guidance. BMJ 343:d6360, 2011, Box 1, p. 901.

Table 30-3 DSM-5 Severity Levels for Autism Spectrum Disorder

SEVERITY LEVEL	SOCIAL COMMUNICATION	RESTRICTED, REPETITIVE BEHAVIORS
Level 3 "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. *For example,* a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches	Inflexibility of behavior, extreme difficulty coping with change, or other restricted/repetitive behaviors markedly interfere with functioning in all spheres. Great distress/difficulty changing focus or action.
Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. *For example,* a person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communication	Inflexibility of behavior, difficulty coping with change, or other restricted/repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.
Level 1 "Requiring support"	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions. *For example,* a person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 52.

dysmorphic facies, congenital heart disease, prolonged QT interval, and developmental delay, is caused by a mutation in the L-type calcium channel $Ca_v1.2$ and also has ASD features. In addition, ASD is associated with multiple abnormalities of mitochondrial DNA.

Neurobiologic Factors

The high rates of seizure disorder suggest a role for neurobiologic factors in ASD. The number of different areas of the brain affected by autism suggests a diverse and widely distributed set of affected neural systems. Postmortem studies reveal various abnormalities, particularly within the limbic system. Structural MRI reveals an overall increase of brain size, and diffusion tensor imaging studies suggest aberrations in white matter tract development. Functional MRI identifies difficulties in tasks involving social and affective judgments and differences in the processing of face and nonface stimuli. Poor neuronal connectivity in various brain regions also is reported. Elevated peripheral levels of serotonin are a replicated neurochemical finding of unclear significance. A role for dopamine is suggested given the problems with overactivity and stereotyped mannerisms and the positive response of such behaviors to antipsychotic medications.

Neuropsychological correlates of ASD include impairments in executive functioning (e.g., simultaneously engaging in multiple tasks), weak central coherence (integrating information into meaningful wholes), and deficits in theory of mind tasks (taking the perspective of another person). The empathizing-systemizing personality theory describes the autistic mind in terms of impaired empathy alongside intact or even superior systemizing (the drive to analyze or construct systems).

Environmental exposures early in the 1st trimester of pregnancy that have been linked to ASD in epidemiologic studies include thalidomide, misoprostol, rubella infection, valproic acid, and the organophosphate insecticide chlorpyrifos. Prenatal folic acid supplementation may reduce the risk of ASD. There has been concern about vaccines as a postnatal environmental cause for ASD. The focus has been on either the measles-mumps-rubella vaccine or the thimerosal preservative as a causative factor. All available data have not supported either hypothesis.

Neuropathology Factors

The head circumference in ASD is normal or slightly smaller than normal at birth until 2 mo of age. Afterward, children with ASD show an abnormally rapid increase in head circumference from 6-14 mo of age, increased brain volume in 2-4 yr olds, increased volume of the cerebellum, cerebrum, and amygdala, and marked abnormal growth in the frontal, temporal, cerebellar, and limbic regions of the brain. Early, accelerated brain growth during the first several years of life is followed by abnormally slow or arrested growth, resulting in areas of underdeveloped and abnormal circuitry in parts of the brain. Areas of the brain responsible for higher-order cognitive, language, emotional, and social functions are most affected.

CLINICAL COURSE

ASD symptoms are typically recognized during the 2nd yr of life but can been seen earlier than 12 mo if developmental delays are severe. Initial symptoms most frequently involve delayed language accompanied by lack of social interest or odd play patterns. During the 2nd yr, odd and repetitive behaviors and the absence of typical play become more apparent. It is typical for parents to report that there was no period of normal development or that there was a history of unusual behaviors. Less commonly (in 20-40% of cases), a period of apparently normal development is reported before a loss of skills. In adolescence, a small number of individuals with ASD make marked developmental gains; another subgroup will deteriorate (self-injury, aggression).

DIFFERENTIAL DIAGNOSIS

ASD must be differentiated from communication disorders (especially social communication disorder), intellectual disability (see Chapter 36), sensory impairments (especially deafness), reactive attachment disorder, obsessive-compulsive and related disorders, anxiety disorders (see Chapter 25) including selective mutism, schizophrenia (see Chapter 31), stereotypic movement disorder (see Chapter 24.2), attention-deficit/hyperactivity disorder (ADHD), and Rett syndrome (see Chapter 599).

Autistic-like behavior has been noted in many metabolic syndromic and genetic disorders. These include adenylosuccinate lyase deficiency, PKU, glucose-6-phosphatase deficiency, adenosine deaminase deficiency, succinic semialdehyde dehydrogenase deficiency, disorders of creatine transport and metabolism, propionic acidemia, MELAS and other mitochondrial disorders, Danan disease, tuberous sclerosia, fragile X syndrome, Smith Lemli Opitz syndrome, myotonic dystrophy, dystrophinopathies, Cohen and Myhre syndromes, muscle-eye-brain disease, and various genetic microdeletions or duplications, including deletion 22q11.2.

Developmental language disorders and intellectual disability have an impact on socialization and may be mistaken for ASD. The distinction is particularly difficult in preschool children. When an individual shows impairment in social communication and social interactions but without abnormal nonverbal communication or restricted, repetitive patterns of behavior, a diagnosis of *social communication disorder* should be considered. If there is no apparent discrepancy between the level of social-communicative skills and other intellectual skills, a diagnosis of intellectual disability should be considered.

Children with reactive attachment disorder (typically occurring in the face of emotional neglect; see Chapter 40) may exhibit deficits in attachment and therefore inappropriate social responsivity, but these usually improve substantially if adequate caretaking is provided. Obsessive-compulsive disorder (see Chapter 25) has a later onset than ASD, is not typically associated with social and communicative impairments, and is characterized by repetitive patterns of behavior that are ego dystonic. Symptoms that characterize anxiety disorders, such as excessive worry, the need for reassurance, the inability to relax, and feelings of self-consciousness are also seen in ASD, particularly among higher functioning individuals. However, the 2 conditions can be differentiated by the prominent social and communicative impairments seen in ASD but not anxiety disorders, and the developed social insight of children with anxiety disorders, which is not seen in ASD. Differentiating childhood schizophrenia from autism can be difficult, as both are characterized by social impairments and odd patterns of thinking; florid delusions and hallucinations are rarely seen in autism.

Motor stereotypies are among the diagnostic criteria for ASD, so an additional diagnosis of stereotypic movement disorder should not be given if the movements are better explained by ASD. However when stereotypies cause self-injury and become a focus of treatment, both diagnoses may be appropriate. Similarly, an additional diagnosis of ADHD should only be given when attentional difficulties or hyperactivity exceed those typically observed in children of comparable mental age.

During the regressive phase of Rett syndrome (ages 1-4 yr), disruptive social interaction may be observed and affected children may meet diagnostic criteria for ASD. After this phase, social communication improves and an additional diagnosis of ASD should be considered only if all criteria for ASD are met.

COMORBIDITIES

Given difficulties in communication (mutism) and cognitive impairment, issues of comorbidity in ASD can be quite complex. The process of diagnostic overshadowing (the tendency to fail to diagnosis other comorbid conditions when a more noticeable condition is present) may occur. Most studies do show increased rates of anxiety and attentional disorders.

In most epidemiologically based samples of persons with autistic disorder, approximately 50% exhibit severe or profound intellectual disability, 35% exhibit mild to moderate intellectual disability, and the remaining 20% have IQs in the normal range. Verbal skills are typically more impaired than nonverbal skills. Intellectual impairment is not an essential diagnostic feature of autism; it is necessary and important for the diagnosis of intellectual disability to be made.

Neurologic comorbidities include epilepsy, sleep dysfunction, motor delay, dyspraxia, incoordination, and gait disturbances.

A range of behavioral difficulties can be observed in ASD including hyperactivity, obsessive compulsive phenomena, self-injury, aggression, stereotypies, tics, and affective symptoms. The issue of whether these qualify as additional disorders is complex. Affective symptoms are frequently observed and include lability, inappropriate affective responses, anxiety, and depression. Impairments in emotion regulation processes can lead to under- and overreactivity. Overt clinical depression is sometimes observed, and this may be particularly true for adolescents. Case reports and case series suggest possible associations with bipolar disorders and tic disorders. Attentional difficulties (ADHD) are also frequent in autism, reflecting cognitive, language, and social problems.

SEQUELAE

Most persons with ASD remain within the spectrum as adults, and regardless of their intellectual functioning, continue to experience problems with independent living, employment, social relationships, and mental health. Some children, especially those with communication abilities, can grow up to live self-sufficient lives in the community with employment. Others remain dependent on their family or require placement in facilities outside the home. Because early, intensive therapy can improve language and social function, delayed diagnosis can lead to a poorer outcome. A better prognosis is associated with higher intelligence, functional speech, and less-bizarre symptoms and behavior. The symptom profile for some children might change as they grow older, and risk of seizures or self-injurious behavior becomes more common. ASD is not a degenerative disorder and it is typical for learning and compensation to continue throughout life.

SCREENING/CASE FINDING

All children should receive autism-specific screening at 18 and 24 mo of age, in addition to broad developmental screening at 9, 18, and 24 mo (Fig. 30-1). In some instances screening may be relevant to older children, such as those who are more intellectually able and whose

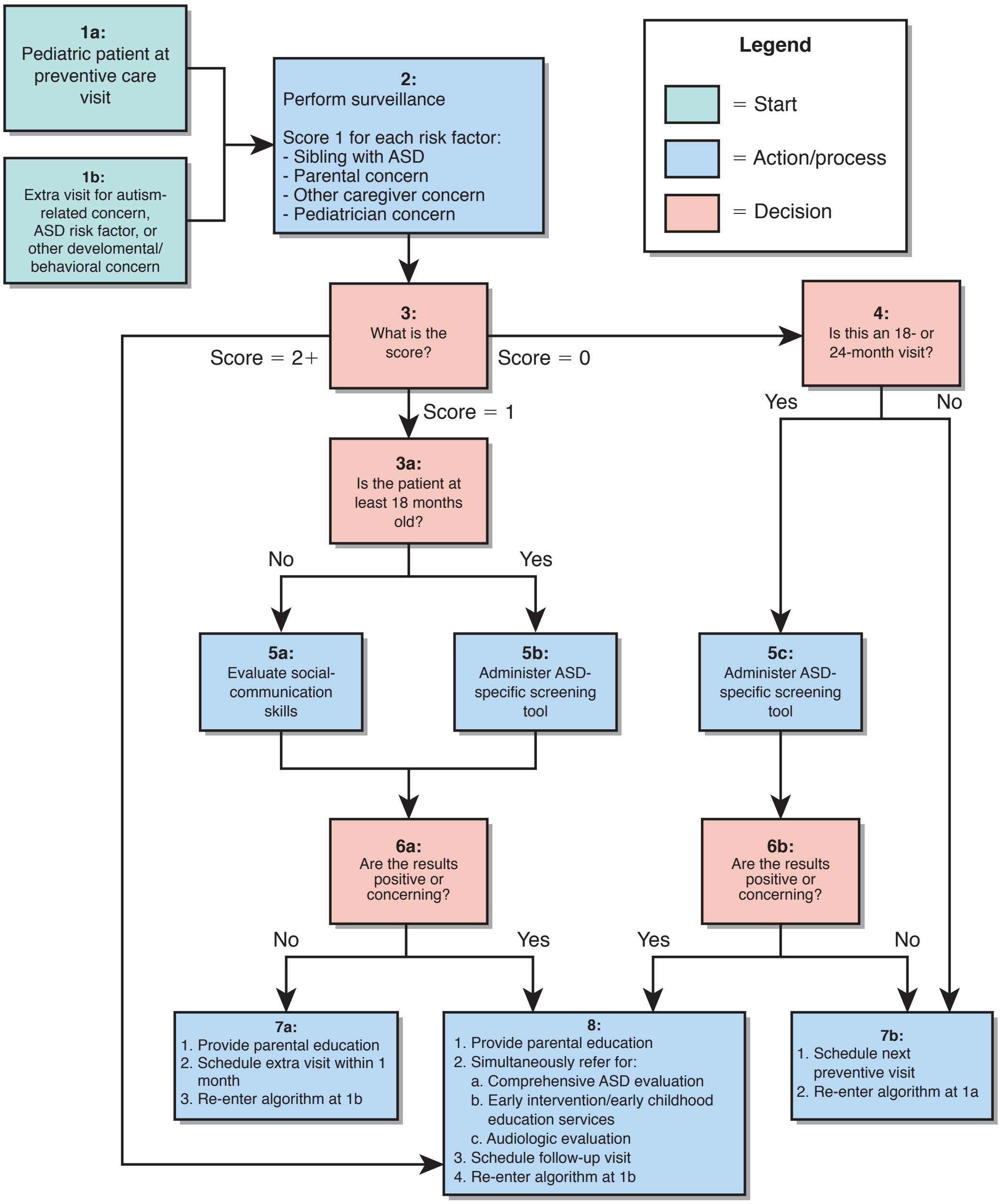

Figure 30-1 Surveillance and screening algorithm: autism spectrum disorders (ASDs). *(From Plauche Johnson C, Myers SM, Council on Children with Disabilities: Identification and evaluation of children with autism spectrum disorders, Pediatrics 120:1183–1215, 2007.)*

1a:
Pediatric patient at preventive care visit

1a - Developmental concerns, including those about social skill deficits should be included as one of several health topics addressed at each pediatric preventive care visit through the first 5 years of life. *(Go to step 2)*

1b:
Extra visit for autism-related concern, asd risk factor, or other developmental/behavioral concern

1b - At the parents' request, or when a concern is identified in a previous visit, a child may be scheduled for a "problem-targeted" clinic visit because of concerns about ASD. Parent concerns may be based on observed behaviors, social or language deficits, issues raised by other caregivers, or heightened anxiety produced by ASD coverage in the media. *(Go to step 2)*

2:
Perform surveillance

Score 1 for each risk factor:
- Sibling with ASD
- Parental concern
- Other caregiver concern
- Pediatrician concern

2 - Developmental surveillance is a flexible, longitudinal, continuous, and cumulative process whereby health care professionals identify children who may have developmental problems. There are 5 components of developmental surveillance: eliciting and attending to the parents' concerns about their child's development, documenting and maintaining a developmental history, making accurate observations of the child, identifying the risk and protective factors, and maintaining an accurate record and documenting the process and findings. The concerns of parents, other caregivers, and pediatricians all should be included in determining whether surveillance suggests that the child may be at risk of an ASD. In addition, younger siblings of children with an ASD should also be considered at risk, because they are 10 times more likely to develop symptoms of an ASD than children without a sibling with an ASD. Scoring risk factors will help determine the next steps, *(Go to step 3)*

For more information on developmental surveillance, see "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening" (Pediatrics 2006; 118:405-420).

3:
What is the score?

3 - Scoring risk factors:

- If the child does not have a sibling with an ASD and there are no concerns from the parents, other caregivers, or pediatrician: Score = 0 *(Go to step 4)*
- If the child has only 1 risk factor, either a sibling with ASD or the concern of a parent, caregiver, or pediatrician: Score = 1 *(Go to step 3a)*
- If the child has 2 or more risk factors: Score = 2+ *(Go to step 8)*

3a:
Is the patient at least 18 months old?

3a -

- If the child's age is $<$18 months, *(Go to step 5a)*
- If the child's age is ≥18 months, *(Go to step 5b)*

4:
Is this an 18-or 24-month visit?

4 - In the absence of established risk factors and parental/provider concerns (score = 0), a level-1 ASD-specific tool should be administered at the 18- and 24-month visits. *(Go to step 5c)* If this is not an 18- or 24-month visit, *(Go to step 7b)*.

Note: In the AAP policy, "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening", a general developmental screen is recommended at the 9-, 18-, and 24-or 30-month visits and an ASD screening is recommended at the 18-month visit. This clinical report also recommends an ASD screening at the 24-month visit to identify children who may regress after 18 months of age.

5a:
Evaluate social-communication skills

5a - If the child's age is $<$18 months, the pediatrician should use a tool that specifically addresses the clinical characteristics of ASDs, such as those that target social-communication skills. *(Go to step 6a)*

5b:
Administer ASD-specific screening tool

5b - If the child's age is ≥18 months, the pediatrician should use an ASD-specific screening tool. *(Go to step 6a)*

5c:
Administer ASD-specific screening tool

5c - For all children ages 18 or 24 months, (regardless of risk factors), the pediatrician should use an ASD-specific screening tool. *(Go to step 6b)*

AAP-recommended strategies for using ASD screening tools: "Autism: Caring for Children with Autism Spectrum Disorders: A Resource Toolkit for Clinicians" (in press)*

6a:
Are the results positive or concerning?

6a - When the result of the screening is *negative*, *Go to step 7a*

When the result of the screening is *positive*, *Go to step 8*

6b:
Are the results positive or concerning?

6b - When the result of the ASD screening (at 18- and 24-month visits) is *negative*, *Go to step 7b*

When the result of the ASD screening (at 18- and 24-month visits) is *positive*, *Go to step 8*

7a:
1. Provide parental education
2. Schedule extra visit within 1 month
3. Re-enter algorithm at 1b

7a - If the child demonstrates risk but has a negative screening result, information about ASDs should be provided to parents. The pediatrician should schedule an extra visit within 1 month to address any residual ASD concerns or additional developmental/behavioral concerns after a negative screening result. The child will then re-enter the algorithm at 1b. A "wait-and-see" approach is discouraged. If the only risk factor is a sibling with an ASD, the pediatrician should maintain a higher index of suspicion and address ASD symptoms at each preventive care visit, but an early follow-up within 1 month is not necessary unless a parental concern subsequently arises.

7b:
1. Schedule next preventive visit
2. Re-enter algorithm at 1a

7b - If this is not an 18- or 24-month visit, or when the result of the ASD screening is *negative*, the pediatrician can inform the parents and schedule the next routine preventive visit. The child will then re-enter the algorithm at 1a.

8:
1. Provide parental education
2. Simultaneously refer for:
   a. Comprehensive ASD evaluation
   b. Early intervention/early childhood education services
   c. Audiologic evaluation
3. Schedule follow-up visit
4. Re-enter algorithm at 1b

8 - If the screening result is *positive* for possible ASD in step 6a or 6b, the pediatrician should provide peer reviewed and/or consensus-developed ASD materials. Because a positive screening result does not determine a diagnosis of ASD, the child should be referred for a comprehensive ASD evaluation, to early intervention/early childhood education services (depending on child's age), and an audiologic evaluation. A categorical diagnosis is not needed to access intervention services. These programs often provide evaluations and other services even before a medical evaluation is complete. A referral to intervention services or school also is indicated when other developmental/behavioral concerns exist, even though the ASD screening result is negative. The child should be scheduled for a follow-up visit and will then re-enter the algorithm at 1b. All communication between the referral sources and the pediatrician should be coordinated.

AAP information for parents about ASDs includes: "*Is Your One-Year-Old Communicating with You?*" and "*Understanding Autism Spectrum Disorders.*"

*Available at www.aap.org

Figure 30-1, cont'd

social disability is therefore more likely to be detected later. A number of screening instruments for ASD have been developed that may be helpful to the pediatric practitioner. For example, the Modified Checklist for Autism in Toddlers (M-CHAT) is a free online 23-item autism screening tool designed to identify children 16-30 mo of age who should receive a more thorough assessment for possible early signs of ASD or developmental delay (https://www.m-chat.org/index.php).

ASSESSMENT

If screening indicates ASD symptomatology, a thorough diagnostic assessment should be performed to determine whether full criteria are met. Multidisciplinary assessment is optimal in facilitating early diagnosis, treatment, and coordinated multiagency collaboration. Evaluations from various professionals, including a developmental pediatrician or pediatric neurologist, medical geneticist, child and adolescent psychiatrist, speech-language pathologist, occupational or physical therapist, or medical social worker may be indicated. The *Autism Diagnostic Observation Schedule* (ADOS), which is a semistructured interactive examination by a professional trained in its administration, is the standard diagnostic tool. *The use of such instruments supplements, but does not replace, informed clinical judgment*.

All children with ASD should have a medical assessment, which typically includes a physical examination, a hearing screen, a Wood's lamp examination for signs of tuberous sclerosis (see Chapter 596.2), and genetic testing, which should include ***chromosomal microarray* (CMA)**. In a community sample of children with ASD, diagnostic yield 0.57% for fragile X testing, and 24% for CMA. CMA is recommended by medical geneticists as the standard of care for the initial evaluation of children with ASD, but does not always detect fragile X or Rett syndromes.

Unusual features in the child (dysmorphology, staring spells) should prompt additional evaluations. The categories of potential organic etiologies includes infectious (encephalitis or meningitis), endocrinologic (hypothyroidism), metabolic (homocystinuria, phenylketonuria), traumatic (head injury), toxic (fetal alcohol syndrome), or genetic (chromosomal abnormality). Certain developmental disorders, most notably Landau-Kleffner syndrome, should be ruled out (characterized by a highly distinctive electroencephalogram abnormality and marked aphasia). Neuroimaging, electroencephalography, and additional laboratory tests should be obtained when relevant, based on examination or history (testing for the *MeCP2* gene in females for possible Rett disorder). Table 30-4 summarizes potential medical tests in the assessment of ASD.

Psychological assessments that clarify cognitive ability and adaptive skills are indicated for treatment planning. Deficits in language and socialization often make it difficult to obtain an accurate estimate of a child's intellectual potential. Some children with ASD perform adequately on nonverbal tests, and those with developed speech can show adequate intellectual capacity. Communication assessment, including measures of both receptive and expressive vocabulary as well as language use (particularly social or pragmatic), is also helpful relative to diagnosis and treatment planning. Occupational and physical therapy evaluations may be needed to evaluate sensory and/or motor difficulties. Sleep is also an important variable to assess.

Table 30-4 Medical and Genetic Evaluation of Children with Autism Spectrum Disorder

Recommended evaluations
Careful physical examination to identify dysmorphic physical features
Macrocephaly
Wood's lamp examination for tuberous sclerosis
Formal audiologic evaluation
Lead test; repeat periodically in children with pica
Chromosomal microarray
Consider if results of above evaluation are normal and if accompanying intellectual impairment
FISH test for region 15q11q13 to rule out duplications in Prader-Willi/Angelman syndrome
Fluorescence in situ hybridization (FISH) test for telomeric abnormalities
Test for mutations in *MECP2* gene (Rett syndrome) in females
DNA testing for fragile X syndrome
Metabolic testing to consider based on clinical features (emesis, hypotonia, lethargy, ataxia, coarse facial features of a storage disease, multiple organs involved)
Fasting blood glucose
Plasma amino acids
Ammonia and lactate
Fatty acid profile, paroxysmal
Carnitine
Acylcarnitine, quantitative
Homocysteine
Urine amino acids
Urine organic acids
Urine purine/pyrimidines
Urine acylglycine, random
Plasma 7-dehydrocholesterol (Smith-Lemli-Opitz disease screening)
Medical testing to consider based on clinical features
Complete blood cell count
Liver enzymes
Biotinidase
Thyroxine, thyroid-stimulating hormone
Ceruloplasmin/serum copper
EEG if the following clinical features are noted
Clinically observable seizures
History of significant regression in social or communication functioning

Adapted from Barbaresi WJ, Katusic SK, Voigt R. Autism: A review of the state of the science for pediatric primary care clinicians, Arch Pediatr Adolesc Med *160:1169-1175, 2006.*

TREATMENT

The pediatric practitioner should aim to foster a long-term collaborative relationship with the family that will vary in intensity over time. For young children, diagnosis and identification of treatment programs will generally be the major focus, whereas for school age children behavioral and medication issues will often become a priority. Vocational training along with future self-sufficiency planning becomes critical in adolescence and early adulthood. It is helpful to the family for the pediatric practitioner to maintain an active role in long-term treatment planning, providing family support, and navigating the healthcare and educational systems.

Psychosocial Interventions

Structured behavioral, educational, and communication interventions are effective for many children with ASD and are associated with better outcomes. Several comprehensive treatment approaches are effective for certain groups of children, although none of the approaches has clearly emerged as superior.

***Applied behavioral analysis* (ABA)** is a behavioral intervention that is informed by basic and empirically supported learning principles. A widely disseminated comprehensive ABA program is *Early Intensive Behavioral Intervention*. Early Intensive Behavioral Intervention is intensive and highly individualized with up to 40 hr per week of one-to-one direct teaching, initially using discrete trials to teach simple skills and progressing to more complex skills such as initiating verbal behavior. ABA techniques have efficacy for specific problem behaviors and to be effective when applied to academic tasks, adaptive living skills, communication, social skills, and vocational skills.

Older children and adolescents with relatively higher intelligence, but with poor social skills and psychiatric symptoms, can benefit from more intensive behavioral or cognitive-behavioral therapy and/or supportive psychotherapy. The focus is on achieving social communication competence, emotional and behavioral regulation, and functional adaptive skills necessary for independence.

Children with ASD need a structured educational approach with explicit teaching. Effective programs typically involve planned, intensive, individualized intervention with an experienced, interdisciplinary

Table 30-5 Level of Evidence for Pharmacologic Treatment of Target Symptoms in Autism Spectrum Disorder

CLASS	AGENT	PRIMARY TARGET SYMPTOM(S)	LEVEL OF EVIDENCE
α_2-Agonist	Clonidine	Hyperactivity	Insufficient
	Guanfacine	Hyperactivity	Insufficient
Antipsychotics	Aripiprazole	Irritability, hyperactivity, stereotypy	Established
	Haloperidol	Behavioral symptoms	Established
	Risperidone	Irritability, hyperactivity	Established
	Risperidone	Repetitive behavior, stereotypy	Preliminary
	Olanzapine	Global functioning	Insufficient
Mood stabilizers	Divalproex sodium/Valproic acid	Irritability, repetitive behavior	Insufficient
	Lamotrigine	Irritability, social behavior	Insufficient
	Levetiracetam	Irritability	Insufficient
Norepinephrine reuptake inhibitors	Atomoxetine	Hyperactivity	Preliminary
Serotonin reuptake inhibitors	Citalopram	Repetitive behavior	Insufficient
	Fluoxetine	Repetitive behavior	Insufficient
	Clomipramine	Repetitive behavior, stereotypy, irritability, hyperactivity	Insufficient
Stimulants	Methylphenidate	Hyperactivity	Promising
Miscellaneous	Amantadine	Hyperactivity, irritability	Insufficient
	Naltrexone	Social behavior, communication, Indiscriminant learning, SIB	Insufficient
	Naltrexone	Hyperactivity	Preliminary
	Pentoxifylline	Irritability, social withdrawal	Preliminary

Established, >2 strong studies or >4 adequate studies in separate settings; Insufficient, lack of research or mixed outcomes; Preliminary, >1 adequate study; Promising, >2 adequate studies.

Adapted from Siegel M, Beaulieu AA. Psychotropic medications in child with autism spectrum disorders: A systematic review and synthesis for evidenced based practice. J Autism Dev Disord *42(8):1592–1605, 2012.*

team of providers, and family involvement to ensure generalization of skills. Two structured educational models with demonstrated efficacy include the *Early Start Denver Model* and the *Treatment and Education of Autism and related Communication handicapped Children* (TEACCH) program. The ***individualized educational plan*** **(IEP)** should reflect an accurate assessment of the child's strengths and vulnerabilities with an explicit description of services to be provided, goals and objectives, and procedures for monitoring effectiveness. Development of an appropriate IEP is central in providing effective service to the child and family.

Communication is generally addressed in the child's IEP in coordination with the speech-language pathologist. Children who do not yet use words can be helped through use of alternative communication modalities such as sign language, electronic communication boards, visual supports, picture exchange, and other forms of augmentative communication. For individuals with fluent speech, the focus should be on pragmatic (social) language skills training.

There is a lack of evidence for most other forms of psychosocial intervention. Studies of sensory-oriented interventions, such as auditory integration training, sensory integration therapy, and touch therapy/massage have contained methodologic flaws and have yet to show replicable improvements. There is also limited evidence thus far for what are usually termed developmental, social-pragmatic models of intervention. Children with ASD are psychiatrically hospitalized at substantially higher rates than the non-ASD population. The efficacy of this level of care is unknown, although there is preliminary evidence for the efficacy of hospital psychiatry units that specialize in this population.

Pharmacotherapy

Pharmacologic interventions (Table 30-5) may increase the ability of children with ASD to benefit from educational and other interventions as well as to remain in less-restrictive environments through the management of challenging behavior. Common targets for pharmacologic intervention include associated comorbid conditions (anxiety, depression) and problematic target symptoms (e.g., irritability, hyperactivity, repetitive behavior, stereotypy, self-injurious behavior).

The FDA has approved risperidone (ages 5-16 yr) and aripiprazole (ages 6-17 yr) for the treatment of irritability in ASD, as evidenced by physical aggression, self-injury, and severe tantrum behavior. In youth weighing < 20 kg, the initial dose of risperidone is 0.25 mg/day with a target dose of 0.5 mg/day, and maximum does of 3 mg/day. In those weighing ≥ 20 kg, the initial dose of risperidone is 0.5 mg/day with a target dose of 1 mg/day, and maximum dose of 3 mg/day. For aripiprazole, the initial dose is 2 mg/day with a target dose of 5-10 mg/day, and maximum dose of 15 mg/day.

The atypical antipsychotic agents also reduce hyperactivity in ASD, though stimulants and atomoxetine appear to be promising for hyperactivity. There is also evidence that repetitive behaviors and stereotypies in ASD may respond to the antipsychotics. Selective serotonin reuptake inhibitors do not have evidence supporting their use for repetitive behaviors or irritability in ASD; they may have efficacy for the treatment of co-occurring depressive and anxiety disorders. The doses of these latter medications would parallel clinical prescribing practices for the specific target symptom (hyperactivity) and/or mental disorders. There is insufficient evidence to support the use of mood stabilizers.

Combining medication with parent training appears to be moderately more efficacious than medication alone for reducing serious behavioral disturbance, and modestly more efficacious for adaptive functioning. Individuals with ASD may be non-verbal, so response to medication is often judged by caregiver report. While this may help assess the effectiveness of the selected medication, it must be remembered that the overall goal of pharmacotherapy is to facilitate the child's adjustment and engagement with behavioral, educational, and communication interventions.

Intranasal oxytocin (IO) is a novel approach to treating ASD. In preliminary studies, IO leads to increased social interactions, better speech comprehension, reduced repetitive behaviors, and functional MRI evidence of improved social attunement. There is currently a large clinical trial testing the efficacy of IO.

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Chapter 31

Childhood Psychoses

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Psychosis is a severe disruption of thought, perception, and behavior resulting in **loss of reality testing.** Delusions, hallucinations, disorganized thinking, grossly disorganized behavior, and negative symptoms are key features that define psychotic disorders. **Delusions** are fixed, unchangeable, false beliefs even in light of conflicting evidence. They may include a variety of themes (persecutory, referential, somatic, religious, or grandiose). Delusions are considered bizarre if they are clearly implausible. **Hallucinations** are vivid and clear perception-like experiences that occur without external stimulus and have the full force and impact of normal perceptions. They may occur in any sensory modality; auditory hallucinations are the most common. **Disorganized thinking** is typically inferred from an individual's speech (loose associations, tangentiality, or incoherence). **Grossly disorganized behavior** may range from child-like silliness to catatonic behavior. **Negative symptoms** include diminished emotional expression, avolition, alogia (lack of speech), anhedonia (inability to experience pleasure), and asociality. They generally account for a substantial portion of the morbidity associated with schizophrenia.

31.1 Schizophrenia Spectrum and Other Psychotic Disorders

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Schizophrenia spectrum and other psychotic disorders include brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, substance/medication-induced psychotic disorder (see Chapter 114), psychotic disorder caused by another medical condition, catatonia associated with another mental disorder, catatonic disorder caused by another medical condition, unspecified catatonia, delusional disorder, schizotypal personality disorder, and other specified/unspecified schizophrenia spectrum and other psychotic disorders.

DESCRIPTION

The schizophrenia spectrum and other psychotic disorders are primarily characterized by the active (or positive) symptoms of psychosis, specifically delusions, hallucinations, disorganized speech, or grossly disorganized behavior. **Brief psychotic disorder** is characterized by the sudden onset (within 2 wk from baseline function) of these symptoms in the context of emotional turmoil or overwhelming confusion, followed by complete resolution (Table 31-1). Although brief, the level of impairment in this disorder may be severe enough that supervision may be required to ensure that basic needs are met and the individual is protected from the consequences of poor judgment and cognitive impairment.

If the psychotic symptoms persist for up to 6 mo, the condition is called **schizophreniform disorder** (Table 31-2), whereas in **schizophrenia**, there are continuous signs of the disturbance for at least 6 mo (Table 31-3). Active symptoms must have been present for a significant portion of time during a 1 mo period, and the level of psychosocial functioning must be markedly below the level achieved prior to the onset (or there is failure in children to achieve the expected level of functioning).

Table 31-1 DSM-5 Diagnostic Criteria for Brief Psychotic Disorder

A. Presence of 1 (or more) of the following symptoms. At least 1 of these must be (1), (2), or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g., frequent derailment or incoherence).
   4. Grossly disorganized or catatonic behavior.

   Note: Do not include a symptom if it is a culturally sanctioned response.

B. Duration of an episode of the disturbance is at least 1 day but less than 1 mo, with eventual full return to premorbid level of functioning.

C. The disturbance is not better explained by major depressive or bipolar disorder with psychotic features or another psychotic disorder such as schizophrenia or catatonia, and is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specify if:

With marked stressor(s) (brief reactive psychosis): If symptoms occur in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the individual's culture.

Without marked stressor(s): If the symptoms do not occur in response to events that, singly or together, would be would be markedly stressful to almost anyone in similar circumstances in the individual's culture.

With postpartum onset: If onset is during pregnancy or within 4 wk postpartum.

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Table 31-2 DSM-5 Diagnostic Criteria for Schizophreniform Disorder

A. Two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least 1 of these must be (1), (2), or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g., frequent derailment or incoherence).
   4. Grossly disorganized or catatonic behavior.
   5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. An episode of the disorder lasts at least 1 mo but less than 6 mo. When the diagnosis must be made without waiting for recovery, it should qualified as "provisional."

C. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

D. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specify if:

With good prognostic features: This specifier requires the presence of at least 2 of the following features: onset of prominent psychotic symptoms within 4 wk of the first noticeable change in usual behavior or functioning; confusion or perplexity; good premorbid social and occupational functioning; and absence of blunted or flat affect.

Without good prognostic features: This specifier is applied if 2 or more of the above features have not been present.

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Table 31-3	DSM-5 Diagnostic Criteria for Schizophrenia

A. Two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least 1 of these must be (1), (2), or (3):
 1. Delusions.
 2. Hallucinations.
 3. Disorganized speech (e.g., frequent derailment or incoherence).
 4. Grossly disorganized or catatonic behavior.
 5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. For a significant portion of the time since the onset of the disturbance, level of functioning in 1 or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 mo. This 6 mo period must include at least 1 mo of symptoms (or less if successfully treated) that meet criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least a month (or less if successfully treated).

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Table 31-4	Medical Conditions Associated with Psychotic-like Behavior

Medications (steroids, β-blocking agents, cyclosporine)
Drugs of abuse (intoxication, overdose or withdrawal)
Central nervous system infections
Autoimmune encephalitis (anti–*N*-methyl-D-aspartate [NMDA] receptor/limbic/paraneoplastic)
Acute disseminated encephalomyelitis (ADEM)
Systemic lupus erythematosus (SLE)
Syndromes (fragile X, trisomy 21, tuberous sclerosis)
Wilson disease
Porphyria
Nonconvulsive status (seizures)
Hyper-/hypoparathyroidism
Hyper-/hypothyroidism
Hyper-/hypoadrenalism
Hypoglycemia
Thiamine deficiency
Vitamin B_{12} deficiency
Inborn errors of metabolism (see Table 31-5)

Schizophrenia is a heterogeneous clinical syndrome with a range of cognitive, behavioral, and emotional dysfunctions. Prodromal symptoms often precede the active phase, in which individuals may express a variety of unusual or odd beliefs and may have unusual perceptual experiences; their speech may be generally understandable but vague; and their behavior may be unusual but not grossly disorganized. Individuals who had been socially active may become withdrawn.

Individuals with schizophrenia can display inappropriate affect, dysphoric moods, disturbed sleep patterns, and lack of interest in eating or food refusal. Depersonalization, derealization, somatic concerns, and anxiety and phobias are common. Cognitive deficits are observed, including decrements in declarative memory, working memory, language function, and other executive functions, as well as slower processing speed. These individuals may have no insight or awareness of their disorder, which is a predictor of nonadherence to treatment, higher relapse rates, and poorer illness course. Hostility and aggression can be associated with schizophrenia, although spontaneous or random assault is uncommon. Aggression is more frequent for younger males and for individuals with a past history of violence, non-adherence with treatment, substance abuse, and impulsivity.

The essential features of schizophrenia are the same in childhood, but it is more difficult to make the diagnosis. In children, delusions and hallucinations may be less elaborate, and visual hallucinations may be more common. Disorganized speech and behavior occur in many childhood onset psychiatric disorders, and should not be attributed to schizophrenia unless more common disorders are ruled out.

EPIDEMIOLOGY

Brief psychotic disorders have been reported to account for 9% of cases of first-onset psychosis in the United States with a 2 : 1 ratio in favor of females. The incidence of schizophreniform disorders in the United States and other developed countries appears as much as 5-fold less than that of schizophrenia, whereas in developing countries the incidence is higher (approaching that of schizophrenia), particularly when associated with good prognostic features.

The lifetime prevalence of schizophrenia is approximately 0.3-0.7%, although there are reported variations by race/ethnicity, across countries, and by geographic origin for immigrants. The male : female ratio is approximately 1.4 : 1. Males generally have a worse premorbid adjustment, lower educational achievement, more prominent negative symptoms, and more cognitive impairment than females.

CLINICAL COURSE

Brief psychotic disorder may appear in adolescence or early adulthood, with the average age of onset in the mid-30s. By definition, a diagnosis of brief psychotic disorder requires full remission within 1 mo of onset. The development of schizophreniform disorder is similar to that of schizophrenia. About one-third of individuals with an initial diagnosis of schizophreniform disorder recover within a 6 mo period; the majority of the remaining two-thirds will eventually receive a diagnosis of schizophrenia or schizoaffective disorder.

Schizophrenia typically develops between the late teens and the mid-30s; onset prior to adolescence is rare. The peak age at onset for the first psychotic episode is in the early to mid-20s for males and in the late-20s for females. The onset may be abrupt or insidious, but the majority of individuals manifest a slow and gradual development, with around one-half of individuals complaining of depressive symptoms. The predictors of course and outcome are largely unexplained. The course appears to be favorable in approximately 20% of cases, and a small number of individuals are reported to recover completely. Most individuals require daily living supports. Psychotic symptoms tend to diminish over time, while negative symptoms are the most persistent, along with cognitive deficits.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the psychotic disorders is broad, and includes substances/medications (dextromethorphan, LSD, hallucinogenic mushrooms, psilocybin, peyote, cannabis, stimulants, and inhalants; corticosteroids, anesthetics, anticholinergics, antihistamines, amphetamines), other medical conditions (Tables 31-4 and 31-5), other disorders within the same class, depressive and bipolar disorders

Table 31-5 Psychiatric Signs in Inborn Errors of Metabolism in Adolescents and Adults: Review of the Literature and Personal Experience

	CONFUSION	MENTAL RETARDATION	BEHAVIORAL DISTURBANCES	CATATONIA	VISUAL HALLUCINATIONS	PSYCHOSIS (SCHIZOPHRENIA)	DEPRESSION
Urea cycle defects	+	+/–	+	+	+	+	+
Cbl (C, G)	+	+	+		+		+
MTHFR deficiency	+	+	+	+	+	+	+
Porphyria	+		+	+		+	+
Wilson disease		+/–	+	+		+/–	+
CBS deficiency		+	+			+/–	+
CTX		+	+	+		+	
MLD			+			+	
GM_2 gangliosidosis			+	+	+	+	+
NPC			+	+	+	+	+
α-Mannosidosis		+	+		+	+	
β-Mannosidosis		+	+				
ALDc			+			+	+
Nonketotic hyperglycinemia		+	+				
Monoamine oxidase A deficiency		+	+				
Creatine transporter deficiency		+	+				
Succinic semialdehyde dehydrogenase deficiency		+	+				

+, Frequently reported; +/–, unusual; empty cell, not reported; ALDc, cerebral adrenoleukodystrophy; CBS, cystathionine β-synthase; CTX, cerebrotendinous xanthomatosis; MLD, metachromatic leukodystrophy; MTHFR, methylene tetrahydrofolate reductase; NPC, Niemann-Pick type C.

From Sedel F, Baumann N, Turpin JC, et al: Psychiatric manifestations revealing inborn errors of metabolism in adolescent and adults. J Inherit Metab Dis *30:631–641, 2007, Table 3, p. 635.*

(see Chapter 26), malingering and factitious disorders, obsessive-compulsive (see Chapter 25) and body dysmorphic disorder, posttraumatic stress disorder (see Chapter 25), autism spectrum disorder (see Chapter 30) or other communication disorders (see Chapter 35), and personality disorders.

Autoimmune encephalitis caused by anti–*N*-methyl-D-aspartate (NMDA) receptor or other autoantibodies may manifest with psychosis, anxiety, depression, agitation, aggression, delusions, catatonia, hallucinations, and paranoia in combination with sleep disturbances, autonomic dysfunction (hypoventilation), dyskinesias, movement disorders, seizures, and a depressed level of consciousness. The electroencephalogram (EEG), cerebral spinal fluid, and MRI are usually, but not always, abnormal. The constellation of psychosis and encephalitic features should suggest the diagnosis; however, at presentation behavioral problems may be the dominant feature (see Chapter 598.4).

Differentiating medical from psychiatric causes of abnormal behavior may be difficult. In general, medical causes are often associated with abnormalities in vital signs and the neurologic exam (including level of consciousness). In medical causes of abnormal behavior, there may not be a positive family history or a prior personal history of psychiatric illness. Furthermore, in medical causes, there are often impairments in attention, orientation, recent memory, and intellectual function. Hallucinations may be present with medical disease, but they are often tactile, visual, or olfactory rather than auditory (noted in psychiatric disease). Medical patients may be able to reality test about their hallucinations, stating they are aware they are not real.

The diagnosis of a psychotic disorder should be made only after these other explanations for the observed symptoms have been ruled out. Most children who report hallucinations do not meet criteria for the schizophrenia spectrum disorders, and most do not have psychosis. Normative childhood experiences, including overactive imaginations and vivid fantasies, can be mistaken for psychosis.

COMORBIDITY

Rates of comorbidity with substance-related disorders are high in schizophrenia. Other common comorbidities are anxiety disorders and obsessive-compulsive disorders.

SEQUELAE

Follow-up studies of early onset schizophrenia suggest moderate to severe impairment across the life span. Poor outcome is predicted by low premorbid functioning, insidious onset, higher rates of negative symptoms, childhood onset, and low intellectual functioning. When followed into adulthood, youth with schizophrenia demonstrated greater social deficits, lower levels of employment, and were less likely to live independently, relative to those with other childhood psychotic disorders.

Approximately 5-6% of individuals with schizophrenia die by suicide, approximately 20% attempt suicide on 1 or more occasions, and many more have suicidal ideation. Life expectancy is reduced in individuals with schizophrenia because of associated medical conditions; a shared vulnerability for psychosis and medical disorders may explain some of the medical comorbidity of schizophrenia.

ETIOLOGY AND RISK FACTORS

Etiologic evidence for schizophrenia supports a neurodevelopmental and neurodegenerative model with multiple genetic and environmental exposures playing important roles. It has been hypothesized that while psychotic disorders likely have their origins in early development, but it is not until they are in their mid-teens that the underlying neural structures manifest the disabling functional deficits and resultant psychotic symptoms.

Genetic Factors

The lifetime risk of developing schizophrenia is 5-20 times higher in 1st-degree relatives of affected probands compared to the general population. Concordance rates of 40-60% and 5-15% have been reported, respectively, in monozygotic and dizygotic twins. Genome-wide association studies, using large collaborative international cohorts, have implicated different genomic loci and genes, including the major histocompatibility complex (6p21.1), MIR137, and ZNF804a. Structural mutations arising at genomic "hotspots," including 1q21.1, 15q13.3, and 22q11.2, may be responsible for 0.5-1.0% of cases.

Childhood schizophrenia appears to be associated with a higher rate of large cytogenetic abnormalities and rare structural variants than reported in adults. The majority of rare copy number errors detected in affected persons are found at different genetic loci, and many are unique to 1 individual or family.

Environmental Factors

In utero exposure to maternal famine, advanced paternal age, prenatal infections, obstetric complications, marijuana use and immigration have been hypothesized to contribute to the development of schizophrenia. Environmental exposures may mediate disease risk via direct neurologic damage, gene by environment interactions, epigenetic effects and/or de novo mutations. There is no evidence that psychological or social factors cause schizophrenia. Rather, environmental factors may potentially interact with biologic risk factors to mediate the timing of onset, course, and severity of the disorder. Expressed emotion within the family setting can influence the onset and/or exacerbation of acute episodes and relapse rates.

Neuroanatomical Abnormalities

Increased lateral ventricle volumes along with reductions in hippocampus, thalamus, and frontal lobe volumes have been reported in schizophrenia. Youth in particular have reductions in grey matter volumes and reduced cortical folding. Neurotransmitter systems, particularly central nervous system dopamine circuits, are hypothesized to have a key role in the pathophysiology of schizophrenia. The dopamine hypothesis is derived in part from the identification of D_2 receptor blockade as the mechanism for the action of antipsychotic medications.

PREVENTION

There has been significant interest in prospectively identifying youth at risk for schizophrenia spectrum and other psychotic disorders in an effort to provide early intervention prior to the development of a full-blown psychotic disorder. Various names including ***attenuated psychosis syndrome*** **(APS)**, psychosis risk syndrome, ultrahigh risk, clinical high risk, at-risk mental state, and prodromal stage have been used to describe patients that present with troubling symptoms suggestive of early psychosis.

APS is characterized by the presence of delusions, hallucinations, or disorganized speech in an attenuated form, with relatively intact reality testing, but of sufficient frequency to warrant clinical attention. The symptoms are described as being present at least once per week for the past month and have begun/worsened over the past year. The symptoms are less severe and more transient than a psychotic disorder, although nearly 20-40% with these attenuated symptoms appear to go on to a psychotic disorder within 3 yr of symptom presentation. There is evidence that premorbid lower cognitive and social skills as well as a history of substance abuse contribute to the risk of developing a full-blown psychotic disorder in individuals with APS.

There is some evidence that antipsychotic medication may delay conversion of attenuated to full-blown psychosis and ameliorate attenuated symptoms in active treatment, yet there appear to be no lasting effects after the medication is withdrawn. In addition, there is concern that the long-term use of even low-dose antipsychotic medication may cause heightened sensitization of brain dopamine receptors, which, in turn, could lead to a rapid-onset of psychosis following discontinuation of the medication.

Antidepressants have been associated with symptomatic improvement in adolescents with APS. In a randomized control trial, omega-3 fish oils reduced attenuated positive, negative, and general symptoms. Psychological interventions (social skills, cognitive, and interaction training programs, as well as psychoeducational family interventions and cognitive-behavioral therapy) are reported to improve symptoms and psychosocial functioning in youth with early symptoms.

Despite improvements in diagnostic predictive validity, significant concern remains regarding a high false-positive rate (identifying an individual as prodromal who does not go on to develop psychosis) that may cause individuals to be stigmatized or exposed to unnecessary treatment. In this context, youth with early symptoms suggestive of psychosis should be referred to a child and adolescent psychiatrist and/or a specialized research program.

SCREENING/CASE FINDING

Pediatric practitioners can make general inquiries of youth and their parents regarding problems with thinking or perceptions. For the older youth, questions like *"Does your mind ever play tricks on you?," "Do you hear voices talking to you when no one is there?," and/or "Does your mind ever feel confused?"* can help elicit symptoms. For younger children, the clinician must ensure that the child understands the questions. True psychotic symptoms are generally confusing to the individual, and highly descriptive, detailed, organized, and/or situation-specific reports are less likely to represent true psychosis. Overt signs of the illness should be evident on mental status exam; without overt evidence of psychosis, the validity of symptom reports needs to be carefully scrutinized. For youth presenting with what could be psychosis, assessment and treatment in the specialty mental health setting by a child and adolescent psychiatrist should be provided.

ASSESSMENT

The diagnostic assessment of schizophrenia in youth is uniquely complicated and misdiagnosis is common. Most children who report hallucinations do not meet criteria for schizophrenia, and many do not have a psychotic illness. Normative childhood experiences, including overactive imaginations and vivid fantasies, can be misinterpreted as psychosis. Expertise in childhood psychopathology and experience in assessing reports of psychotic symptoms in youth are important prerequisite skills for clinicians evaluating youth for possible psychosis. Comprehensive diagnostic assessments, which reconcile mental status findings with the rigorous application of diagnostic criteria, help improve accuracy.

There are no neuroimaging, psychological or laboratory tests that establish a diagnosis of schizophrenic spectrum disorders. The medical evaluation focuses on ruling out nonpsychiatric causes of psychosis, while also establishing baseline laboratory parameters for monitoring medication therapy. Routine laboratory testing typically includes blood counts, basic metabolic panel, liver and renal functions, metabolic parameters, and thyroid functions. More extensive evaluation is indicated for atypical presentations, such as a gross deterioration in cognitive and motor abilities, focal neurologic symptoms, or delirium. Neuroimaging may be indicated when neurologic symptoms are present, or an EEG is indicated for a clinical history suggestive of seizures. Toxicology screens are indicated for acute onset or exacerbations of psychosis, when exposure to drugs of abuse cannot be ruled out. Genetic testing is indicated if there are associated dysmorphic or syndromic features. Tests to rule out specific syndromes or diseases (e.g., amino acid screens for inborn errors of metabolism, ceruloplasmin for Wilson disease [see Chapter 357.2], porphobilinogen for acute intermittent porphyria [see Chapter 91]) are indicated for clinical presentations suggestive of a specific syndrome. Neuropsychological testing cannot establish the diagnosis, but may be important for documenting cognitive deficits for academic planning.

TREATMENT

There are hallmark phases important to recognize in the assessment and management of schizophrenia. In the prodrome phase, most patients experience functional deteriorations (i.e., social withdrawal, idiosyncratic preoccupations, unusual behaviors, academic failure, deteriorating self-care skills, and/or dysphoria) prior to the onset of psychotic symptoms. The acute phase is characterized by prominent positive symptoms and deterioration in functioning. The recuperative/recovery phase is marked by a several-month period of impairment and predominantly negative symptoms. The residual phase (if reached) has no positive symptoms though negative symptoms may contribute to some level of impairment.

Treatment goals include decreasing psychotic symptomology, directing the child toward a developmentally typical trajectory, and reintegrating the child into the home and community. Children and families facing schizophrenia spectrum disorders require an array of mental health services to address their psychological, social, educational, and cultural needs. Given the insidious onset and chronic course of these disorders, the patient must be followed longitudinally, with periodic reassessment to hone diagnostic accuracy and tailor services to meet the patient's and family's needs. Integrated psychopharmacologic, psychotherapeutic, psychoeducational, and case-management services are often necessary.

Psychoeducation about the illness with an assessment of the potential role of stigma in treatment participation is critical for improving adherence with treatment recommendations. Assessing a child's strengths and vulnerabilities as well as available environmental resources is critical in devising an effective treatment plan. School and community liaison work to develop and maintain a day-to-day schedule for the patient is important. Specialized educational programs should be considered within the school system. Cognitive remediation has shown some promising results in planning ability and cognitive flexibility. Effective and collaborative communication among the family, the pediatrician, a child and adolescent psychiatrist, and other mental health providers increases the potential for the patient's optimal functioning.

Pharmacotherapy

First-generation (typical) and second-generation (atypical) antipsychotic medications have been shown to be effective in reducing psychotic symptoms with the latter the preferred medication choice (see Chapter 21). Haloperidol, risperidone, aripiprazole, quetiapine, paliperidone, and olanzapine are FDA approved for treating schizophrenia in ages 13 yr and older. The choice of which agent to use first is typically based on FDA approval status, side-effect profile, patient and family preference, clinician familiarity, and cost. Depot antipsychotics have not been studied in pediatric age groups and have inherent risks with long-term exposure to side effects. Although clozapine is effective in treating both positive and negative symptoms, its risk for agranulocytosis and seizures limits its use to those patients with treatment-resistant disorders.

Most patients require long-term treatment and are at significant risk to relapse if their medication is discontinued. The goal is to maintain the medication at the lowest effective dose so as to minimize potential adverse events. Many patients will continue to experience some degree of positive or negative symptoms, requiring ongoing treatment. Patients should maintain regular physician contact so as to monitor symptom course, side effects, and adherence.

Individuals prescribed antipsychotic medications need to be systematically monitored for side effects, including sedation, abnormal movements, weight gain, hyperprolactinemia, elevated liver transaminases, diabetes, hyperlipidemia, hematologic effects (leukopenia or neutropenia), seizures, neuroleptic malignant syndrome, and cardiovascular effects. For atypical antipsychotics, body mass index, fasting blood glucose, fasting triglycerides/cholesterol, waist circumference, high-density lipoprotein/low-density lipoprotein, blood pressure, and symptoms of diabetes should be checked at baseline and at regular intervals thereafter. Regular physical activity and nutritional balance should be part of a comprehensive treatment plan.

Abnormal movements (dystonia, akathisia, tardive dyskinesia) need periodic assessment preferably using a standardized instrument such as the *Abnormal Involuntary Movement Scale* (AIMS). The need for antiparkinsonian agents may be a consideration for patients, particularly those at risk for acute dystonia or who have a previous history of dystonic reactions. In patients with a personal or family history of cardiac abnormalities, including syncope, palpitations, arrhythmias, or sudden unexplained death, a baseline electrocardiogram with subsequent monitoring should be considered, along with cardiology consultation. Alternative pharmacology should be considered if the resting

heart rate exceeds 130 beats/min, or the PR, QRS, and QTc exceed 200, 120, and 460 msec, respectively.

Electroconvulsive therapy (ECT) may be used with severely impaired adolescents if medications are either not helpful or cannot be tolerated. It has not been systematically studied in children.

Bibliography is available at Expert Consult.

31.2 Psychosis Associated with Epilepsy

David R. DeMaso

Schizophrenia spectrum and other psychotic disorders include *psychotic disorder due to another medical condition* (Table 31-6). *Psychosis associated with epilepsy* has been reported in children and adults. Also called *schizophrenic-like psychosis of epilepsy*, the disorder manifests with delusions or hallucinations, along with poor insight. The characterization is complicated by the fact that anticonvulsant drugs can present with psychosis and antipsychotic drugs can lower the seizure threshold, producing seizures.

Psychosis associated with epilepsy can be further differentiated into ictal, interictal, and postictal psychosis. Ictal-induced psychosis is a form of **nonconvulsive status epilepticus**, usually complex partial status that can last for hours to days and is associated with periods of impaired consciousness. Brief interictal psychosis can last days to weeks and is associated with paranoia, delusions, and auditory hallucinations. Chronic interictal psychosis resembles schizophrenia and manifests with paranoia, visual hallucinations, and catatonia. Postictal psychosis is the most common type (observed in 2-7% of patients with epilepsy); it lasts up to 1 wk and then spontaneously remits.

The diagnosis requires a strong index of suspicion and EEG monitoring. Treatment requires appropriate anticonvulsant drugs and, if the psychosis persists, initiating low-dose antipsychotic medication.

Bibliography is available at Expert Consult.

31.3 Catatonia in Children and Adolescents

Bonita F. Stanton

Catatonia is a poorly defined state presenting as an unusual manifestation of decreased or increased muscle tone and decreased responsiveness (although agitation may be present) occurring in association with a broad array of conditions affecting children, adolescents and adults. These conditions include psychosis, autism spectrum disorder, developmental disorders, drug-induced conditions, affective disorders and a wide range of medical disorders (Table 31-7). Not surprising given the ill-defined nature of the condition, the prevalence of catatonia in children and adolescents is unknown, although it is generally believed to be significantly underdiagnosed. Recognition of catatonia by a clinician is very important because the disorder is generally very responsive to treatment with benzodiazepines and/or ECT.

DIAGNOSIS AND TREATMENT

Catatonia is defined as 3 or more of the 12 symptoms listed in Table 31-8. An important next step is the evaluation and possible elimination of medications being administered to the child for their potential to induce catatonic symptoms, a not-infrequent side effect of many medical and psychiatric medications. Of particular importance, antipsychotic agents should be discontinued as they have been associated with an increased incidence of malignant catatonia or neuroleptic malignant syndrome (see Chapter 21).

Benzodiazepams (typically lorazepam) and **ECT** are effective in adults and appear to be effective in children. A treatment algorithm using a lorazepam challenge test (by mouth, intravenous, or intramuscular administration of lorazepam 1-2 mg) is shown in Figure 31-1. If the challenge test does reverse symptoms, increasing doses of lorazepam are indicated, with careful monitoring to avoid side effects. ECT may be indicated alone (if no improvement with lorazepam) or in combination with lorazepam if some but incomplete improvement is noted.

Table 31-6 DSM-5 Diagnostic Criteria for Psychotic Disorder Due to Another Medical Condition

A. Prominent hallucinations or delusions.
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition.
C. The disturbance is not better explained by another mental disorder.
D. The disturbance does not occur exclusively during the course of a delirium.
E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify whether:

With delusions: If delusions are the predominant symptom.
With hallucinations: If hallucinations are the predominant symptom.

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Table 31-7 Conditions Associated with Catatonia

Psychotic disorders
- Paranoid schizophrenia, catatonic schizophrenia, psychosis, autism, Prader-Willi syndrome, intellectual impairment

Mood disorders
- Bipolar disorder- manic or mixed episodes

Major depressive disorder

Medical conditions
- Endocrine abnormalities, infections, electrolyte imbalances

Neurologic conditions
- Epilepsy, strokes, traumatic brain injury, multiple sclerosis, encephalitis

Drugs
- Withdrawal: Benzodiazepines, L-dopa, gabapentin
- Overdose: LSD, phencyclidine (PCP), cocaine, Ecstasy, disulfiram, levetiracetam

Adapted from Weder ND, Muralee S, Penland H, Tampi RR: Catatonia: a review. Ann Clin Psychiatry *20(2):97–107, 2008, Table 2.*

Table 31-8 Diagnostic Criteria of Catatonia in the DSM-5

Catatonia is defined as the presence of 3 or more of the following

1. Catalepsy (i.e., passive induction of a posture held against gravity)
2. Waxy flexibility (i.e., slight and even resistance to positioning by examiner)
3. Stupor (no psychomotor activity; not actively relating to environment)
4. Agitation, not influenced by external stimuli
5. Mutism (i.e., no, or very little, verbal response [*Note:* not applicable if there is an established aphasia])
6. Negativism (i.e., opposing or not responding to instructions or external stimuli)
7. Posturing (i.e., spontaneous and active maintenance of a posture against gravity)
8. Mannerisms (i.e., odd caricature of normal actions)
9. Stereotypies (i.e., repetitive, abnormally frequent, non–goal-directed movements)
10. Grimacing
11. Echolalia (i.e., mimicking another's speech)
12. Echopraxia (i.e., mimicking another's movements)

From Tandon R, Heckers S, Bustillo J, et al: Catatonia in DSM-5. Schizophr Res *150(1):26-30, 2013, Table 1.*

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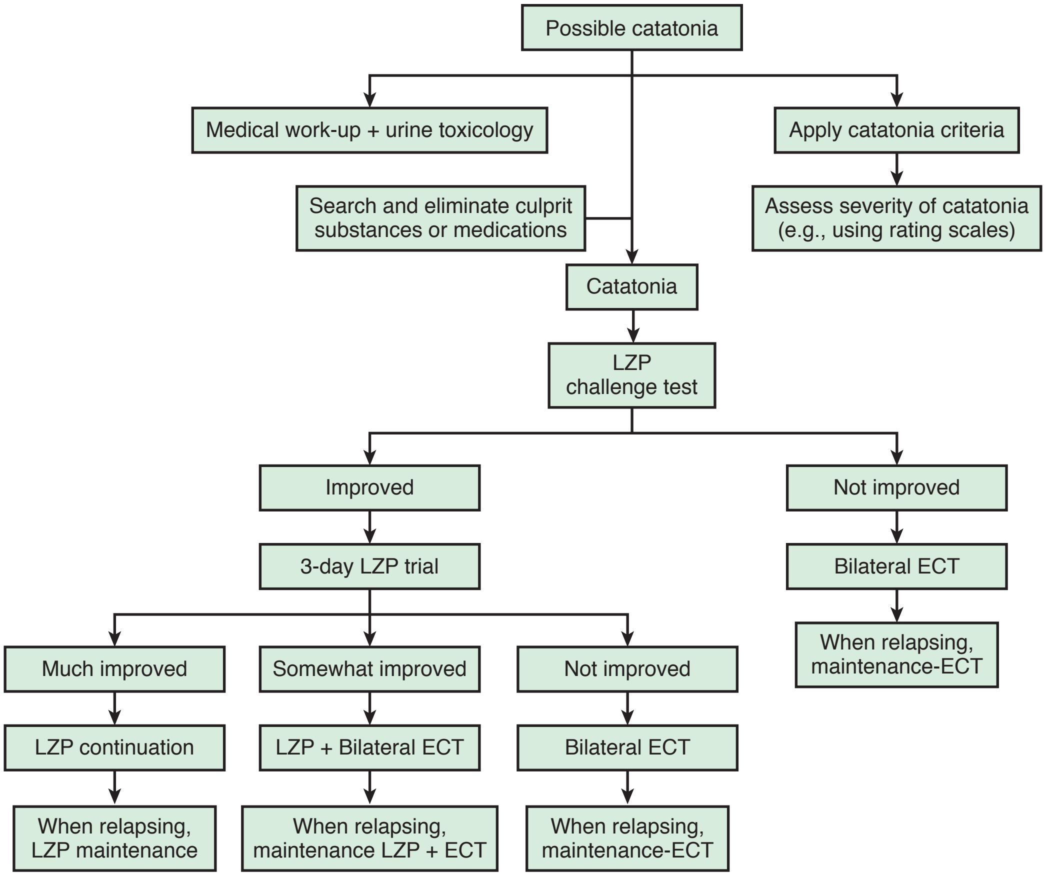

Figure 31-1 Evaluation, diagnosis and treatment of catatonia in children and adolescents. ECT, electroconvulsive therapy; LZP, lorazepam. *(From Dhossche DM, Wilson C, Wachtel LE: Catatonia in childhood and adolescents: implications for the DSM-5. Prim Psychiatry 17(4):23–26, 2010.)*

The outlook for catatonia is greatly impacted by that of the associated condition(s). The long-term outcome for individuals treated with ECT is unknown, but mortality rates in catatonic patients declined after the introduction of ECT in treatment.

Bibliography is available at Expert Consult.

31.4 Acute Phobic Hallucinations of Childhood

Giuseppe J. Raviola, Michael L. Trieu, David R. DeMaso, and Heather J. Walter

Among adults, hallucinations are viewed as synonymous with psychosis and as harbingers of serious psychopathology. In children, hallucinations can be part of normal development or can be associated with nonpsychotic psychopathology, psychosocial stressors, drug intoxication, or physical illness. The first clinical task in evaluating youth who report hallucinations is to sort out those that are associated with severe mental illness from those that derive from other causes (Fig. 31-2).

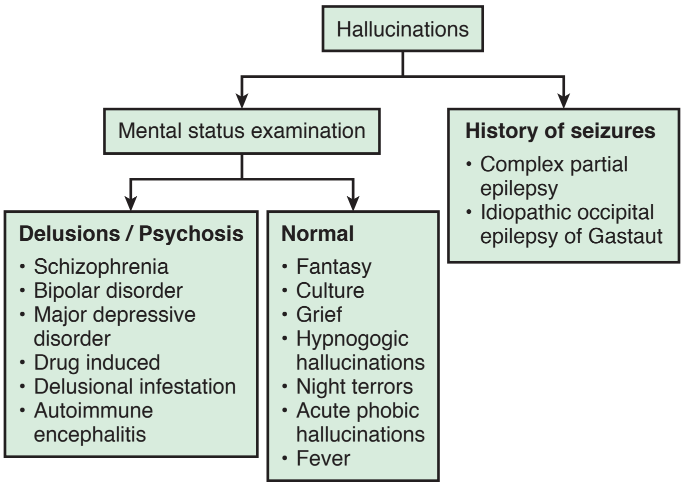

Figure 31-2 Evaluation of hallucinations.

CLINICAL MANIFESTATIONS

Hallucinations are perceptions (typically auditory, visual, tactile, or olfactory) that occur in the absence of identifiable external stimuli. Hallucinations can be further categorized as nondiagnostic (hearing footsteps, knocking, or one's name) and diagnostic (hearing 1 or more voices saying words other than one's own name).

In children with nonpsychotic hallucinations, the symptoms of psychosis are absent. Nonpsychotic hallucinations commonly occur in the context of severe traumatic stress, developmental difficulties, social and emotional deprivation, parents whose own psychopathology promotes a breakdown in the child's sense of reality, cultural beliefs in mysticism, and unresolved mourning. Auditory hallucinations of voices telling the child to do bad things may be more often associated with disruptive behavior disorders than with psychotic diagnoses. Hearing a voice invoking suicide is often associated with depression. Trauma-related auditory hallucinations are commonly associated with posttraumatic stress disorder or a brief psychotic disorder with marked stressors. The content of the hallucinations may be relevant in understanding the underlying psychopathology and/or developmental issues.

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DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Acute phobic hallucinations are benign and common and occur in previously healthy preschool children. The hallucinations are often visual or tactile, last 10-60 minutes, and occur at any time but most often at night. The child is quite frightened and might complain that bugs or snakes are crawling over him or her and attempt to remove them. The cause is unknown. The differential diagnosis includes drug overdose or poisoning, high fever, encephalitis, and psychosis. The child's fear is not alleviated by reassurance by the parents or physician, and the child is not amenable to reason. Findings on physical and mental status examinations are otherwise normal. Symptoms can persist for 1-3 days, slowly abating over 1-2 wk.

The differential diagnosis of hallucinations comprises a broad range of mental disorders, including diagnoses in which hallucinations are not the hallmark feature, but may be viewed as associated symptoms (posttraumatic stress disorder, nonpsychotic mood disorders, and disruptive, impulse-control, and conduct disorders); diagnoses that are defined by psychotic features (brief psychotic disorder, schizophrenia, major depressive or bipolar disorder with psychotic features); and at-risk clinical states (poor reality testing). In addition, other medical conditions can manifest with hallucinations, including drug intoxications (cannabis, LSD, cocaine, amphetamines, barbiturates), medication side effects (e.g., steroids, anticholinergic medications, stimulant medications), and physical illnesses (e.g., thyroid, parathyroid, and adrenal disorders; Wilson disease; electrolyte imbalances; infections; migraines; seizures; and neoplasms).

TREATMENT

The evaluation of the underlying condition directs the type of treatment needed. Nonpsychotic hallucinations suggest the need for disorder-specific psychotherapy (e.g., trauma-focused cognitive behavioral therapy for posttraumatic stress disorder) and perhaps adjunctive medication (e.g., an antidepressant for depression or anxiety, or a brief trial of antipsychotic medication for agitation). Cognitive-behavioral therapy focused on helping the youth understand the origin of the hallucinations and on developing coping strategies for stressful situations may be helpful for older children and adolescents. True psychotic hallucinations suggest the need for antipsychotic medication.

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Learning Disorders

PART IV

Chapter 32

Neurodevelopmental Function and Dysfunction in the School-Age Child

Desmond P. Kelly and Mindo J. Natale

TERMINOLOGY AND EPIDEMIOLOGY

A **neurodevelopmental function** is a basic brain process needed for learning and productivity. **Neurodevelopmental variation** refers to differences in neurodevelopmental functioning. Wide variations in these functions exist within and between individuals. These differences can change over time and need not represent pathology or abnormality.

Neurodevelopmental dysfunctions reflect disruptions of neuroanatomic structure or psychophysiologic function and place a child at-risk for developmental, cognitive, emotional, behavioral, psychosocial and adaptive challenges. For the school-age child, an area of particular focus is academic skill development. Academic disorders have been diagnostically classified as **Specific Learning Disorder** (SLD) by the revised *Diagnostic and Statistical Manual of Mental Disorder Fifth Edition* (DSM-5). Changes in DSM-5 (compared to DSM-IV) involve a broadening of the diagnostic criteria in an effort to recognize factors that may interrupt the effective acquisition of academic skills that include **reading**, **written language, spelling** and **mathematics.** The *International Classification of Diseases* (ICD) of the World Health Organization, 10th Edition (ICD-10) categorizes **Specific Developmental Disorders of Scholastic Skills** that include **Reading Disorder, Spelling Disorder, Disorder of Arithmetical Skills,** and **Mixed Disorder of Scholastic Skills**. **Dyslexia** (reading disorder) is included in ICD-10 in a separate category of symbolic dysfunction. The terms, **Dyscalculia** (mathematics disorder), and **Dysgraphia** (written language disorder) are also used by investigators and clinicians, but their inclusion in diagnostic classification systems has been inconsistent and a source of some disagreement among experts.

Traditionally, the educational system has identified SLDs through the process of psychoeducational testing. Through this process, students experiencing academic problems would be evaluated psychometrically. Typical testing batteries have usually included measures of overall intelligence and academic skills. A student exhibiting a significant discrepancy between scores on tests of intelligence and tests of academic achievement could be classified as a student with an SLD, and would subsequently be eligible for Special Education Services. The degree of discrepancy required for such classification often differed between states and even between school districts. In a marked change in approach to the identification of SLDs, the reauthorization of the Individuals with Disabilities Education Act (IDEA) in 2004 introduced the Response to Intervention (RTI) model, which does not necessitate that schools use the discrepancy model for determining if a student has an SLD. Instead, schools may employ research-based intervention approaches and monitor a student's response to that intervention before initiating psychoeducational testing. This approach has been met with some disapproval, as those who challenge its effectiveness argue that the RTI model, in and of itself, should not be used to identify children with SLD. The underlying view behind this objection rests with the notion that children may fail to respond to RTI for a variety of reasons (e.g., underlying neurocognitive weakness), not just because a SLD exists.

Overall estimates of the prevalence of SLD's range from 3-10%. Some data indicate that approximately 8% of children 3-17 yr of age have, at one point, been identified as having a SLD. Prevalence estimates can vary owing to numerous factors, including differences in definitions and criteria used for classification and diagnosis, as well as differences in methods of assessment.

ETIOLOGY AND PATHOGENESIS

Neurodevelopmental dysfunction may present for any number of reasons. These include pre-/perinatal, genetic, medical, psychologic, environmental and sociocultural influences. Genes that contribute to neurodevelopmental dysfunction have been identified. Reading disorders can be both familial and heritable, and studies have linked some reading disabilities to specific gene loci on chromosomes 6 and 15. Chromosomal abnormalities can lead to unique patterns of dysfunction, such as visual–spatial deficits in girls diagnosed with Turner syndrome or language deficits in children with fragile X syndrome (see Chapter 81). Chromosome 22q11.2 deletion syndrome (DiGeorge or velocardiofacial syndrome [see Chapter 125]) is associated with predictable patterns of neurodevelopmental dysfunction, including a higher prevalence of intellectual disability, and deficits in visual–spatial processing, executive function, attention, working memory, verbal learning, arithmetic, and language with relative strengths in selected reading and spelling skills. Investigations of the neuroanatomical substrates have also yielded important information about the underlying causes of neurodevelopmental dysfunction. Multiple investigations have identified differences in the left parietotemporal and left occipitotemporal brain regions of individuals with dyslexia compared to those without reading difficulties (see Chapter 34). Studies also describe the neural circuitry, primarily in the parietal cortex, underlying mathematical competencies such as the processing of numerical magnitude, and mental arithmetic investigations support a broader role for the white matter in active learning and memory than was previously estimated.

Perinatal risk factors that are associated with neurodevelopmental dysfunction include very-low birthweight, severe intrauterine growth restriction, perinatal hypoxic–ischemia encephalopathy, and prenatal exposure to substances such as alcohol and drugs (see Chapter 96). Increased risk of academic and frontal lobe disorders also is associated with environmental toxins, including lead (see Chapter 721); drugs such as cocaine; infections such as meningitis and HIV; and brain injury secondary to intraventricular hemorrhage, periventricular leukomalacia, or head trauma.

Early psychologic trauma can result in both structural and neurochemical changes in the developing brain, which may contribute to neurodevelopmental dysfunction. Findings suggest that the effects of exposure to trauma (see Chapter 39) and/or abuse (see Chapter 40) early in the developmental course can induce disruption of the brain's regulatory system with connections in the orbitofrontal cortex, and may influence right-hemisphere function with associated risk for problems with information processing, memory, and frontal lobe related operations (e.g., focus and self-regulation). Environmental and sociocultural deprivation can lead to, or potentiate, neurodevelopmental dysfunction, which most often results from a combination of contributing factors, rather than a single cause.

CORE NEURODEVELOPMENTAL FUNCTIONS

The neurodevelopmental processes that are critical for academic success may best be understood as falling within **core neurodevelopmental domains**.

Sensory and Motor Development

Sensory development (e.g., auditory, visual, tactile, proprioceptive) begins well before birth. This neurodevelopmental process is crucial in helping children experience, understand, and manipulate their environments. Through sensory experiences, children's brains mature as new neuronal pathways are created and existing pathways are strengthened. Any interruption of this process may result in sensory-motor deficits and delays (e.g., apraxia) that can interfere with early development and academic performance.

Sensory development for the school-age child progresses in association with environmental exposure and with the development of other cognitive processes such as motor development.

There are 3 distinct, yet related, forms of neuromotor ability: graphomotor, fine motor, and gross motor coordination.

Graphomotor function refers to the specific motor aspects of written output. Several subtypes of graphomotor dysfunction significantly impede writing. Some children harbor weaknesses of visualization during writing. They have trouble picturing the configurations of letters and words as they write (orthographics). Their written output tends to be poorly legible, with inconsistent spacing between words. Others have weaknesses in orthographic memory, which interferes with their ability to recall and/or reproduce letter and number forms rapidly and accurately. They may labor over individual letters and prefer printing (manuscript) to cursive writing. Some exhibit signs of finger agnosia or weak graphomotor feedback; they have trouble localizing their fingers while they write. As a result, they need to keep their eyes very close to the page and tend to apply excessive pressure to the pencil. Others struggle with graphomotor production deficits. For these children, trouble producing the highly coordinated motor sequences needed for writing results in difficulty assigning writing roles to specific muscle groups in their hands. This phenomenon has also been described as **dyspraxic dysgraphia.** It is important to emphasize that a child may show excellent fine motor dexterity (as revealed in mechanical or artistic domains) but very poor graphomotor fluency (with labored or poorly legible writing).

For the school-age child, problems with **fine motor function** can disrupt their ability to communicate in written form, to excel in artistic and crafts activities, and can interfere with learning a musical instrument or mastering a computer keyboard. The term **dyspraxia** relates to difficulty in developing an ideomotor plan and activating coordinated and integrated visual motor actions to complete a task or solve a motor problem, such as assembling a model.

Some children exhibit **gross motor incoordination.** They have problems in processing "outer spatial" information to guide gross motor actions. Affected children may be inept at catching or throwing a ball because they cannot form accurate judgments about trajectories in space. Others demonstrate diminished body position sense. They do not efficiently receive or interpret proprioceptive and kinesthetic feedback from peripheral joints and muscles. They are likely to evidence difficulties when activities demand balance and ongoing tracking of body movement. Others are unable to satisfy the motor praxis demands of certain gross motor activities. It may be hard for them to recall or plan complex motor procedures such as those needed for dancing, gymnastics, or swimming. Children with gross motor problems can incur considerable embarrassment in physical education classes. Gross motor weaknesses can lead to social rejection, withdrawal, and generalized feelings of inadequacy.

Language

Language is one of the most critical and complex cognitive functions and can be broadly divided into r**eceptive** (auditory comprehension/understanding) and e**xpressive** (speech and language production and/or communication) functions. Children who primarily experience receptive language problems may have difficulty understanding verbal information, following instructions and explanations, and interpreting what they hear. Expressive language weaknesses can result from problems with speech production and/or problems with higher level language development (see Chapter 35). Speech production difficulties include oromotor problems affecting articulation, verbal fluency, and naming. Some children have trouble with sound sequencing within words. Others find it hard to regulate the rhythm or prosody of their verbal output. Their speech may be dysfluent, hesitant, and inappropriate in tone. Problems with word retrieval can result in problems in finding exact words when needed (as in a class discussion) or substituting definitions for words (circumlocution). Children who evidence higher level expressive language impediments have trouble formulating sentences, using grammar acceptably, and organizing spoken (and possibly written) narratives.

In considering disordered language, whether in reception or expression, it is vital to ascertain the potential underlying difficulties that are contributing. Some children, for example, have particular problems with **phonology** (see Chapter 35). Commonly, a weak phonologic sense has a negative effect not only on language processing, but also on the development of reading, writing and even mathematics (e.g., word problems). Children with **semantic deficits** have trouble learning the meaning of words, and as a result, may use words improperly (e.g., out of context). Other common language deficiencies include difficulty with **syntax** (word order), problems with **discourse** (paragraphs and passages), an underdeveloped sense of **metalinguistics** (the ability to think about and analyze how language works), and trouble with drawing appropriate inferences (supplying missing information) from language. Difficulty with language **pragmatics**, or the social understanding and application of language, can be another significant impediment.

Language weaknesses not only contribute to problems with reading, writing and math, but can also manifest in the content areas, such as the sciences, which necessitate the processing of dense verbal material in textbooks and the rapid convergent recall of facts, and social studies courses that often entail the use of sophisticated language and verbal abstract concepts (e.g., democracy). Learning foreign languages can be a serious problem. In contrast, children who possess strong language skills are often able to make use of their linguistic facility to compensate for any academic problems; it may be possible to verbalize one's way through a mathematics curriculum, thereby circumventing a tendency to be confused by predominantly nonverbal concepts (e.g., ratio, equation, and diameter).

To one degree or another, all academic skills are taught largely through language, and thus it is not surprising that children who experience language dysfunction often experience problems with academic performance. In fact, some studies suggest that up to 80% of children who present with a SLD also experience language-based weaknesses.

Visual–Spatial/Visual–Perceptual Function

The process of visual development begins well before birth, with continued development and refinement throughout childhood (see Chapter 621). Important structures involved in the development and function of the visual system, beyond the eyes themselves, include the retina, optic cells (e.g., rods and cones), the optic chiasm, the optic nerves, the brainstem (control of automatic responses like pupil dilation), the thalamus (e.g., lateral geniculate nucleus for form, motion, color), and the primary (visual space and orientation) and secondary (color perception) visual processing regions located in and around the occipital lobe. Other brain areas, considered to be outside of the primary visual system, are also important to visual function, helping to process *what* (temporal lobe) is seen and *where* it is located in space (parietal lobe). The left and right cerebral hemispheres interact considerably in visual processes, with each hemisphere possessing more specialized functions, including left hemisphere mediated processing of details, patterns, and linear information, and right hemisphere processing of the gestalt and overall form.

Some of the more critical aspects of visual processing to develop in the school-age child include **spatial relations**—the ability to accurately perceive objects in space in relation to other objects; **visual**

discrimination—the ability to differentiate and identify objects based on their individual attributes such as size, shape, color, form, and position; and, **visual closure—**the ability to recognize or identify an object even when the entire object cannot be seen.

Children with subtle visual deficits are often misidentified and/or missed completely. Indications of visual processing deficits in the school-age child may include difficulty learning to draw and write, and problems with art activities. These children might also have trouble discriminating between left and right. They might encounter problems recognizing letters and words, resulting in delayed reading, spelling, and writing.

Visual–spatial processing dysfunctions are not a common cause of chronic reading disorders, but more recent investigations have established that deficits in orthographic coding (visual–spatial analysis of character-based systems) can contribute to reading disorders. Spelling and writing can emerge as a weakness because children with visual processing problems commonly have trouble with the precise visual configurations of words. In mathematics, these children often have difficulty with visual–spatial orientation, with resultant difficulty aligning digits in columns when performing calculations and/or difficulty managing geometric material. In the social realm, intact visual processing allows a child to make use of visual or physical cues when communicating and interpreting the paralinguistic aspects of language. Secure visual functions are also necessary to process proprioceptive and kinesthetic feedback and to coordinate movements during physical activities. Children with visual processing deficits are thus susceptible to problems such as social isolation and withdrawal and consequent behavioral and/or emotional difficulties.

Intellectual Function

The concept of intellectual function, or intelligence, has had many definitions and theoretical models, and achieving a consensus on the subject has been challenging. Well-known theories include Spearman's unitary concept of "the g-factor," the "verbal and nonverbal" theories (e.g., Binet, Thorndike), the 2-factor theory from Catell (crystallized vs fluid intelligence), Luria's simultaneous and successive processing model, and more recent models that view intelligence as a global construct composed of more-specific cognitive functions (e.g., auditory and visual–perceptual processing, spatial abilities, processing speed, and working memory). A useful definition of **intellectual function** is the capacity to think in the abstract, reason, problem solve and comprehend.

The expression of intellect is mediated by many factors, including language development, sensorimotor abilities, genetics, heredity, environment, and neurodevelopmental dysfunction or neuropathology. When an individual's intelligence is measured at a standard score of 70 or lower, and significant weaknesses in adaptive skills are indicated, consideration of the diagnosis of Intellectual Disability would be warranted. In DSM-5, the previous diagnostic term of Mental Retardation has been changed to **Intellectual Disability**. DSM-5 also includes the term **Intellectual Developmental Disorder** to indicate weaknesses in intellectual functioning that begin during the early developmental period (Chapter 36).

The clinical assessment of intellectual functioning has proved useful in identifying intellectual disability, informing treatment strategies, and in predicting future functionality (e.g., academic, occupational and social). Notwithstanding, intelligence test scores (e.g., IQ) reflect only part of an individual's ability profile. Functionally, there are some common characteristics that distinguish children with deficient intellectual functioning from those with average or above average abilities. Typically, those at the lowest end of the spectrum (e.g., profound or severe intellectual deficiencies) are incapable of independent function, and require a highly structured environment with constant aid and supervision (see Chapter 36). At the other end of the spectrum are those with unusually well-developed intellect (e.g., gifted). Although this level of intellectual functioning offers many opportunities, it can also be associated with functional challenges related to socialization, learning style, and communication and perceptual differences. Individuals whose intellect falls in the below average range (sometimes referred to as the "borderline" or "*slow learner" range*) tend to experience greater difficulty processing and managing information that is abstract, making connections between concepts and ideas, and generalizing information (e.g., may be able to comprehend a concept in one setting but are unable to carry it over and apply it in different situation). In general, these individuals tend to do better when information is presented in more concrete and explicit terms, and when working with rote information (e.g., memorizing specific material). Stronger intellect is associated with better-developed concept formation, critical thinking, problem solving, understanding and formulation of rules, brainstorming and creativity, and metacognition (the ability to "think about thinking")

Frontal Lobe Functioning

Attention

Most brain processes are heavily dependent on functional arousal, alertness, and attention. Any malfunction within or across these systems will likely cause some degree of breakdown in other cognitive processes. Functional attention subsumes intact neuroanatomic and neurochemical brain systems. Structurally, brain regions involved include subcortical, cortical, and association areas throughout the brain. Primary structures involved include brainstem regions (e.g., basal ganglia), the limbic system (e.g., amygdala and hippocampus), and the frontal lobes (e.g., prefrontal cortex). The neurotransmitter dopamine, along with its neuronal pathways, has been identified as a major chemical modulator of attention. It is through the cognitive mechanisms of attention and executive functions that the child's brain acquires, organizes, and processes information. These mechanisms also allow the child to regulate, plan, and monitor their behaviors and thoughts. Children with attention dysfunction comprise a widely heterogeneous group who show various patterns of impairment of these systems (see Chapter 33). The resulting symptoms not only affect behavior, learning, and academic skills development, but also have an impact on the child's emotional, social, and adaptive development and functioning.

Attention is far from a unitary, independent, or specific function. This may be illustrated best through the phenotype associated with **Attention-Deficit/Hyperactivity Disorder (ADHD).** ADHD is not only a disorder of impaired focus, but also includes a host of symptoms related to problems with vigilance, distractibility, impulsivity in thought and behavior, hyperactivity, and flexibility. Disordered attention can occur owing to faulty mechanisms in and/or across subdomains of attention. These subdomains include **selective attention** (the ability to focus attention to a particular stimulus and to discriminate relevant from irrelevant information), **divided attention** (the ability to orient to more than one stimulus at a given time), **sustained attention** (the ability to maintain one's focus), and **alternating attention** (the capacity to shift focus between stimuli).

Attention problems in school-age children can manifest at any point in the process, from arousal through output. Children with diminished alertness and arousal can exhibit signs of mental fatigue in a classroom or when engaged in any activity requiring sustained focus. They might yawn, stretch, fidget, and daydream. They can become overactive in an effort to attain or maintain a higher level of arousal. They are apt to have difficulty allocating and sustaining their concentration, and their efforts may be erratic and unpredictable, with extreme performance inconsistency. These children can also have difficulty discriminating between important and unimportant information. Such weaknesses of determining saliency often result in focusing on the wrong stimuli, at home, in school, and socially, and can result in the child's missing important information and can impede their ability to take notes, to summarize information, or to recognize what to study for a test. In the social context, poor attention may result in inept social interaction (e.g., because of factors such as not "hearing" what others say). Some children present with what has been termed *sluggish cognitive tempo*. Children with sluggish cognitive tempo have many inattentive features without a history of significant hyperactivity and/or impulsiveness. Some researchers believe that sluggish cognitive tempo may be a different disorder from ADHD, with its own characteristics, including hypoactivity, lethargy, confusion, and mental "fogginess."

Distractibility can take the form of listening to extraneous noises instead of a teacher, staring out the window, or constantly thinking about the future. These children often show evidence of superficial concentration, where their level of focus is not of sufficient intensity to capture specific information. As a result, these children are often described as "forgetful" because directions and explanations need to be repeated and details (e.g., changes in operational signs in mathematics) may be missed. These children can also exhibit difficulties with cognitive activation and generalization, passively processing and not linking information with prior knowledge and experience, or overrelying on prior experience.

Attention dysfunction can affect the output of work, behavior, and/or social activity. These children have a tendency to perform or act without previewing a likely outcome or thinking through the potential consequences of what they are about to do or say. Their impulsivity can lead to careless mistakes in academic work and unintended misbehavior. It is important to appreciate that most children with attentional dysfunction also harbor other forms of neurodevelopmental dysfunction that can be associated with academic disorders (with some estimates suggesting up to 60% comorbidity).

Executive Functioning

There is considerable overlap between attention and **executive functioning**. Additions to the ICD classification system include a code for *Frontal Lobe and Executive Function Deficit* (799.55). Executive functioning is an umbrella term used to describe specific cognitive processes involved in regulating, guiding, organizing, and monitoring of thoughts and actions (cognitive, behavioral, and emotional functions) to achieve a specific goal. Processes considered to be executive in nature include inhibition control, flexibility (the ability to shift between activities or thoughts), emotional control, initiation skills, planning, organization, working memory, and self-monitoring.

Studies indicate that executive functioning can be strengthened in children as young as age 4 yr, which suggests that executive functioning is actively developing in the preschool-age child.

Executive function deficits that have particular impact on school function include **inhibition**, or **inhibitory control**, the ability to control a response, whether it be cognitive or behavioral. Children with inhibitory control deficits may answers questions prematurely and fail to check their work. Behaviorally, these children may speak without first considering the impact of what they say. In the social context, disinhibited children may interrupt others and demonstrate other impulsive behaviors that often interfere with interpersonal relationships (see Chapter 33).

The function of **working memory** has been the focus of significant research efforts. Working memory can be defined as the ability to hold, manipulate, and store information for short periods. In its simplest form, working memory involves the interaction of short-term verbal and visual processes (e.g., memory, phonologic, awareness and spatial skills) with a centralized control mechanism that is responsible for coordinating all of the cognitive processes involved (e.g., temporarily suspending information in memory while working with it). Developmentally, working memory capacity can double or triple between the preschool years and adolescence. A child with working memory dysfunction might carry a number and then forget what it was that the child intended to do after carrying that number. Working memory is an equally important underlying function for reading, where it enables the child to remember the beginning of a paragraph when the child arrives at the end of it. In writing, working memory helps children remember what they intend to express in written form while they are performing another task, like placing a comma or working on spelling a word correctly. Working memory also enables the linkage between new incoming information in short-term memory with prior knowledge or skills held in longer-term memory (Table 32-1).

Table 32-1 Symptom Expression of Executive Dysfunction

EXECUTIVE FUNCTION DEFICIT	SYMPTOM EXPRESSION
Disinhibition	Impulsivity/poor behavioral regulation Interrupts "Blurts" things out
Shifting	Problems with transitioning from one task/activity to another Unable to adjust to unexpected change Repeats unsuccessful problem-solving approaches
Initiation	Difficulty independently beginning tasks/activities Lacks initiative Difficulty developing ideas or making decisions
Working memory	Challenges following multistep instruction (e.g., only completes 1 of 3 steps) Forgetfulness
Organization and planning	Fails to plan ahead Work is often disorganized Procrastinates and does not complete tasks "Messy" child
Self-monitoring	Fails to recognize errors and check work Does not appreciate impact of actions on others Poor self-awareness
Affect control	Experiences behavioral and emotional outbursts (e.g., tantrums) Easily upset/frustrated Frequent mod changes

Memory

Memory is a term used to describe the cognitive mechanism by which information is acquired, retained, and recalled. Structurally, some major brain areas involved in memory processing include the hippocampus, the fornix, the temporal lobes, and the cerebellum, with connections in and between most brain regions. The memory system can be partitioned into subsystems based on processing sequences; the form, time span, and method of recall; whether memories are consciously or unconsciously recalled; and the types of memory impairments that can occur.

Once information has been identified (through auditory, visual, tactile, and/or other sensory processes), it needs to be **encoded and registered,** a mental process that constructs a representation of the information into the memory system. The period of time (typically seconds) during which this information is being held and/or manipulated for registration, and ultimately encoded, consolidated, and retained, is referred to as **working memory** (see above). Other descriptors include **short-term memory** and **immediate memory**. **Consolidation** and **storage** represent the process by which information in short-term memory is transferred into **long-term memory**. Information in long-term memory can be available for hours or as long as a life span. Long-term memories are generally thought to be housed, in whole or in part, in specific brain regions (e.g., the cortex, cerebellum). Ordinarily, consolidation in long-term memory is accomplished in 1 or more of 4 ways: pairing 2 bits of information (such as a group of letters and the English sound it represents); storing procedures (consolidating new skills, such as the steps in solving mathematics problems); classifying data in categories (filing all insects together in memory); and linking new information to established rules, patterns, or systems of organization (rule-based learning).

Once information finds its way into long-term memory, it must be accessed. In general, information can be retrieved spontaneously (a process known as **free recall**) or with the aid of cues (**cued or recognition recall**). Some other common descriptors of memory include **anterograde memory** (the capacity to learn from a single point in time

forward), **retrograde memory** (the capacity to recall information that was already learned), and **explicit memory** (conscious awareness of recall), **implicit memory** (subconscious recall: no awareness that the memory system is being activated), **procedural memory** (memory for how to do things), and **prospective memory** or *remembering to remember*.

As children proceed through school, the demands for the efficient use of memory progressively increase. By secondary school, rapid and precise recall is heavily emphasized. Children can have trouble with 1 or more memory mechanisms. They might struggle with the initial registration of information in short-term memory. Others might have difficulty storing newly introduced information. Other children might have difficulty accessing (retrieving) information, despite having registered and stored it effectively. Children can experience frustration in their efforts at consolidating information into long-term memory and/or encounter difficulty with simultaneous recall (retrieval of several facts or procedures at once). Some students exhibit delayed **automatization:** not enough of what they have learned in the past is accessible to them instantaneously and with no expenditure of effort. Such skills as forming letters, mastering mathematical facts, and decoding words must ultimately become automatic if students are to make good academic progress.

Weaknesses with memory processing can be highly specific and/or dependent on the material. Some children struggle to learn visual-spatial material, whereas others may be deficient in learning auditory information. Some have difficulty processing linear data or sequential information. Some can experience difficulty with rote data (e.g., word lists) yet have little or no difficulty registering information in context (e.g., a narrative). Although in-depth examination (e.g., neuropsychologic testing) is often necessary to differentiate potential memory weaknesses and their impact on the child's overall functioning, screening for memory problems should be part of any well-child examination.

Social Cognition

For the school-age child, the development and effective use of social skills is of immeasurable importance. It is heavily dependent on secure **social cognition**, which is composed of mental processes that allow an individual to understand and interact with the social environment. Although some evidence shows that social cognition exists as a discrete area of neurodevelopmental function, multiple cognitive processes are involved with social cognition. These include the ability to recognize, interpret, and make sense of the thoughts, communications (verbal and nonverbal), and actions of others, the ability to understand that others' perceptions, perspectives, and intentions might differ from our own (commonly referred to as "theory of mind"), the ability to use language to communicate with others socially (pragmatic language), and the ability to make inferences about others and/or the environment based on contextual information. It can also be argued that social cognition involves processes associated with memory and executive functions like flexibility.

CLINICAL MANIFESTATIONS

School-age children with neurodevelopmental dysfunctions vary widely with regard to clinical presentations. Their specific patterns of academic performance and behavior represent final common pathways, the convergence of many forces, including interacting cognitive strengths and deficits; environmental, social, or cultural factors; temperament; educational experience; and intrinsic resilience (Table 32-2). Symptoms of academic disorders differ with age. Children in preschool or kindergarten might present with delayed language development, including problems with articulation, vocabulary development, word finding and rhyming. They often experience early challenges with learning colors, shapes, letters and numbers, the alphabet, and days of the week. Difficulty following instructions, overactivity, and distractibility may be early symptoms of emerging attention and inhibitory control weaknesses. Difficulties with fine motor development (e.g., grasping crayons and pencils, coloring or drawing) and social interaction are not uncommon. As these children enter elementary school, they can evidence problems integrating and associating letters and sounds and problems with semantic knowledge such as mixing up their words (like go and eat). While learning to read and spell, challenges with reversals (b/d), inversions (m/w), transpositions (felt/left), and substitutions (house/home) might persist. Reading comprehension may be weak.

Table 32-2 Neurodevelopmental Dysfunction Underlying Academic Disorders

ACADEMIC DISORDER	POTENTIAL UNDERLYING NEURODEVELOPMENTAL DYSFUNCTION
Reading	Language • Phonologic processing • Verbal fluency • Syntactic and semantic skills Memory • Working memory Sequencing Visual–spatial Attention
Written expression, spelling	Language • Phonologic processing • Syntactic and semantic skills Graphomotor Visual–spatial Memory • Working memory Sequencing Attention
Mathematics	Visual–spatial Memory • Working memory Language Sequencing Graphomotor Attention

Isolated neurodevelopmental dysfunction can lead to a specific academic disorder, but more often there is a combination of factors underlying weak academic performance. In addition to the dysfunction in neurodevelopmental domains as listed in the table, the clinician must also consider the possibility of limitations of intellectual and cognitive abilities or associated social and emotional problems.

Children with early signs of a mathematics weakness might have difficulty with concepts of quantity or with adding or subtracting without using concrete representation (e.g., their fingers when calculating). Difficulty learning time concepts and confusion with directions (right/left) might also be observed. Sequencing problems are noted in reading, spelling and writing, and mathematics. Poor fine motor control and coordination and poor planning can lead to spelling and writing problems. Attention and behavioral regulation weaknesses observed earlier can continue, and together with executive functioning weaknesses (e.g., organization, initiation skills), further complicate the child's ability to acquire and generalize new knowledge.

Middle school brings with it a significant shift in cognitive, academic, and regulatory demands, as children in this age group are expected to be increasingly independent, causing further difficulties for a child with existing attention, inhibitory, and/or executive challenges. In reading and writing, middle school children might present with transposition and sequencing errors; might struggle with root words, prefixes, and suffixes; might have difficulty with written expression; and might avoid reading and writing altogether. Challenges completing word problems in math are common. Difficulty with recall of information might also be experienced. Although observable in both lower and more advanced grades, behavioral, emotional, and/or social difficulties tend to become more salient in middle school children who experience cognitive and/or academic problems.

Many of these challenges continue well into high school. High school students can present with deficient reading comprehension, written expression, and slower processing efficiency. Trouble answering

open-ended questions, dealing with abstract information, and producing executive control (e.g., self-monitoring, organization, planning, and self-starting) is often reported.

Reading

Reading disorders (see Chapter 34), also termed **dyslexia,** can stem from any number of neurodevelopmental dysfunctions as described earlier (see Table 32-2). Most commonly, language and/or auditory processing weaknesses are present as evidenced by poor **phonologic processing.** Challenges with phonologic processing often result in deficiencies at the level of decoding individual words and, consequently, a delay in automaticity (e.g., acquiring a repertoire of words they can identify instantly) that causes reading to be slow, laborious, and frustrating. Without effective identification and intervention, reading comprehension, and ultimately the acquisition of knowledge may be seriously compromised. Deficits in other core neurodevelopmental domains might also be present. Weak working memory might make it difficult for a child to hold sounds and/or symbols in mind while breaking down words into their component sounds or might cause reading comprehension problems. Some children experience temporal-ordering weaknesses and struggle with reblending phonemes into correct sequences. Memory dysfunction can cause problems with recall and summarization of what was read. Some children with higher-order cognitive deficiencies have trouble understanding what they read because they lack a strong grasp of the concepts in a text. Although relatively rare as a cause of reading difficulty, problems with visual–spatial functions (e.g., visual perception) can cause children difficulty in recognizing letters. It is not unusual for children with reading problems to avoid reading practice, and a delay in reading proficiency becomes increasingly pronounced and difficult to remediate.

Spelling and Writing

Spelling and writing impairments share many related underlying processing deficits with reading, so it is not surprising that the 2 disorders often occur simultaneously in school-age children (see Table 32-2). Core neurodevelopmental weaknesses can include phonologic and decoding difficulties, **orthographic** problems (coding letters and words into memory), and **morphologic** deficits (use of suffixes, prefixes, and root words). Problems in these areas can manifest as phonetically poor, yet visually comparable approximations to the actual word (*faght* for *fight*), spelling that is phonetically correct but visually incorrect (*fite* for *fight*), and inadequate spelling patterns (*played* as *plade).* Children with memory disorders might misspell words because of coding weaknesses. Others misspell because of poor auditory working memory that interferes with their ability to process letters. Sequencing weaknesses often result in transposition errors when spelling. Overall, the careful analysis of a child's errors can provide valuable insights into the nature of their spelling problems. As children proceed through school, demands increase for large amounts of well-organized written output.

Writing difficulties have been classified as **disorder of written expression**, or **dysgraphia** (see Table 32-2). Although many of the same dysfunctions described for reading and spelling can contribute to problems with writing, written expression is the most complex of the language arts, requiring synthesis of many neurodevelopmental functions (e.g., auditory, visual–spatial, memory, executive). Deficits in any of these domains can be problematic. Even when a child's phonologic and/or orthographic skills are functional, the child can experience writing problems owing to weaknesses with language, attention, sequencing and/or fine motor development. These weaknesses can occur in written output that is difficult to comprehend, disjointed, and/or poorly organized. The child with working memory challenges can lose track of what the child intended to write. Attention deficits can make it hard for a child to mobilize and sustain the mental effort, pacing, and self-monitoring demands necessary for writing. In many cases, writing is laborious because of an underlying graphomotor dysfunction (e.g., fluency does not keep pace with ideation and language production). Thoughts may also be forgotten or underdeveloped during writing because the mechanical effort is so taxing.

Mathematics

Delays in mathematical ability, known as **mathematics disorder** or **dyscalculia,** can be especially refractory to correction, partly because math involves the assimilation of both procedural knowledge (e.g., calculations) and higher-order cognitive processes (e.g., working memory) (see Table 32-2). A school-based study found that no student who was delayed for longer than 6 mo in mathematics in 6th grade ever caught up; another study found persistence of severe arithmetic disorder in half of affected preteen children. Factors associated with persistence of difficulties included the disorder's severity and heritability. Significant mathematical weaknesses can become virtually insurmountable because the subject is so cumulative in its structure.

Some children experience mathematics failure because of weaknesses in reasoning and problem solving (e.g., intellectual functioning). It may be hard for them to grasp and apply concepts effectively and/or systematically. Good mathematicians are able to use both verbal and perceptual conceptualization to understand such concepts as fractions, percentages, equations, and proportion. Children with language dysfunctions have difficulty in mathematics because they have trouble understanding their teachers' verbal explanations of quantitative concepts and operations and are likely to experience frustration in solving word problems and in processing the vast network of technical vocabulary in math. Mathematics also relies on visualization. Children who have difficulty forming and recalling visual imagery may be at a disadvantage in acquiring mathematical skills. They might experience problems writing numbers correctly, placing value locations, and processing geometric shapes or fractions. Children with attention, inhibitory control, or executive deficits (e.g., working memory) may be unable to focus on fine detail (such as operational signs), might take an impulsive approach to problem solving, engage in little or no self-monitoring, forget components of the same problem, or commit careless errors. When a child's memory system is weak, the child might have difficulty recalling appropriate procedures and automatizing mathematical facts (e.g., multiplication tables). Moreover, it is not unusual for children with mathematical disabilities to have superimposed mathematics phobias. Anxiety over mathematics can be especially debilitating.

Nonacademic Problems

Neurodevelopmental dysfunctions commonly have effects that extend far beyond academic performance. These effects may be related to the dysfunctions themselves or to secondary sequelae (e.g., persistent failure and frustration). The impulsivity and lack of effective self-monitoring of children with attention and impulse-control deficits can lead to unacceptable actions that were unintentional. Children with neurodevelopmental dysfunctions can experience excessive performance anxiety or clinical depression, and sadness, self-deprecatory comments, declining self-esteem, chronic fatigue, loss of interests, and even suicidal ideation can ensue. Some children lose motivation. They tend to give up and exhibit learned helplessness, a sense that they have no control over their destiny. Therefore, they feel no need to exert effort and develop future goals. These children may be easily led toward dysfunctional interpersonal relationships, detrimental behaviors (e.g., delinquency), and the development of mental health and personality disorders, such as mood disorders (see Chapter 26) or antisocial personality disorder.

ASSESSMENT AND DIAGNOSIS

The primary care pediatrician has a critical role in identifying and evaluating the child with an academic disorder. A system of screening and surveillance should be incorporated into routine office visits to promote early identification of academic difficulties. The pediatrician should be aware of a family medical history that includes a parent who still struggles with reading or time management, or an older sibling who has failed at school. Factors in the child's medical history should be flagged, such as extreme prematurity or chronic medical conditions. Children with low birthweight and those born prematurely who appear to have been spared more serious neurologic problems might only manifest academic problems later in their school career and they

warrant particular attention. Children falling into these high risk categories should be flagged for an increased level of scrutiny at routine well-child visits as well as acute-care visits, especially if physical complaints are nonspecific. There should be a low threshold for initiating further school performance screening and assessment of these children. Warning signs might be subtle or absent and problems will not be recognized unless there is a system of eliciting and identifying school problems as part of the routine well-child visit. Parents might have concerns about their child's learning progress but be reluctant to share these with the pediatrician unless prompted such as through completion of a standard developmental screening questionnaires or direct questioning of parents regarding possible concerns about their child's school performance. Inconsistency in report from grade to grade may sometimes be caused by a difference in teaching styles or classroom demands. The type of deficit will also be influential; for example, problems with basic phonemic awareness would be more apparent earlier, while reading comprehension difficulties would emerge later.

Review of school report cards can provide useful clues to patterns of neurodevelopmental dysfunction. In addition to the patterns of grades in the various academic skill areas, it is also important to review ratings of classroom behavior, sometimes listed under headings such as deportment, behavior, conduct, effort/work habits, or citizenship. Review of standardized testing is helpful, and poor scores could be caused by a learning disorder, ADHD, anxiety, lack of motivation, or some combination thereof. Conversely, above-average scores tend to rule out learning or attention problems, but motivation or adjustment issues could then explain a discrepancy between standardized scores and classroom performance. Comparison of how long the homework should take, and how long it takes the child is recommended. Children with ADHD, learning disorders, or emotional/behavioral issues often find homework to be a contentious activity.

The primary care physician is responsible for identifying or ruling out any underlying or associated medical problems that could be impeding the academic performance of the patient who is struggling in school. Vision and hearing screening are critical components of the medical evaluation and any suspicion of sensory difficulty should warrant referral for more definitive testing. The influence of chronic medical problems or potential side effects of medications should be considered. Sleep deprivation is increasingly being recognized as a contributor to academic problems and the possibility of substance abuse must always be a consideration, especially in the adolescent who was previously achieving well at school and has manifested a rapid decline in academic performance.

The physician should be alert for dysmorphic physical features, minor congenital anomalies, or constellations of physical findings (such as cardiac anomalies and palatal anomalies in velocardiofacial syndrome) and should perform a detailed neurologic examination. Special investigations, such as electroencephalograms or brain scans, are not indicated in the absence of specific medical findings. Measures of brain function, such as functional MRI, offer insight into possible areas of neurodevelopmental dysfunction, but they largely remain only research tools with limited application in the general clinical setting at this time.

If problems emerge, the pediatrician should address medical causes or associated conditions. The pediatrician can advise and assist parents in obtaining necessary psychoeducational and/or emotional evaluations through the school or by referral to independent clinicians.

Those physicians with a particular interest in learning disorders can extend their participation in the evaluation process. They can obtain data on neurodevelopmental function through the use of questionnaires completed by the parents, the school, and (if old enough) the child, providing information about behavioral adjustment, patterns of academic performance, and traits associated with specific developmental dysfunctions. Screening instruments such as the Pediatric Symptoms Checklist and standardized behavioral questionnaires, including the Child Behavior Checklist (CBCL) and the Behavior Assessment System for Children–Second Edition (BASC-2) can aid in evaluation (see Chapter 20).

The physician may also perform an extended neurologic and developmental assessment. Available pediatric neurodevelopmental examination instruments that facilitate direct sampling of various neurodevelopmental functions, such as attention, memory, and language, include the Pediatric Early Elementary Examination (PEEX II) and the Pediatric Examination of Educational Readiness at Middle Childhood (PEERAMID II). Examinations of this type also include direct behavioral observations and assessment of minor neurologic indicators (sometimes called *soft signs*). The latter include various associated movements and other phenomena often associated with neurodevelopmental dysfunction.

A child who is functioning poorly during the school years usually requires a *multidisciplinary evaluation*, including a pediatrician, a psychologist, and, if possible, a psychoeducational specialist (sometimes called an *educational diagnostician*) who can undertake a detailed analysis of academic skills and subskills. Other professionals should become involved, as needed, in individual cases, such as a speech-language pathologist, an occupational therapist, a neurologist, and a social worker. In some cases, more in-depth examination of a child's neurocognitive status is warranted. This is particularly true for children who present with developmental or cognitive difficulties in the presence of a medical condition (e.g., epilepsy, traumatic brain injury, childhood cancers/brain tumors, genetic conditions). A neuropsychologic evaluation involves comprehensive assessment of brain function as a means of understanding brain function across domains. The goal of neuropsychologic assessment is to understand brain function via identification of a child's profile of cognitive strengths and weaknesses. Neuropsychologic data are often analyzed together with other tests (e.g., structural), such as MRIs, to look for supporting evidence of any areas of difficulty (e.g., memory weaknesses associated with temporal lobe anomalies).

Many children undergo evaluations in school. Such assessments are guaranteed in the United States under Public Law 101-476, the IDEA. In addition, children found to have attentional dysfunction and other disorders might qualify for educational accommodations under Section 504 of the Rehabilitation Act of 1973.

Multidisciplinary evaluations conducted in schools are usually very helpful, but they are focused primarily on determining whether a student meets the eligibility criteria for special education services. School budgeting constraints or lack of personnel can also affect the quality of evaluations and the extent of recommended services. Many parents seek independent evaluations or second opinions outside of the school setting, and pediatricians can facilitate such outside assessments.

Psychoeducational testing can yield relevant data, especially when such assessments include careful analyses that pinpoint where breakdowns are occurring in the processes of reading, spelling, writing, and mathematics. Input from multiple sources can be used in formulating specific recommendations for regular and special educational teachers and for interventions that can be implemented at home. A mental health specialist can be valuable in identifying family-based issues or psychiatric disorders that may be complicating or aggravating neurodevelopmental dysfunctions.

TREATMENT

There are a number of standard approaches that should be incorporated into any management plan for a student who is struggling academically. The primary physician can play an important role as a consultant in overseeing and monitoring the implementation of these steps. Management of children with neurodevelopmental dysfunctions often needs to be multidisciplinary. Most children require several of the following forms of intervention.

Demystification

Many children with neurodevelopmental dysfunctions have little or no understanding of the nature or sources of their academic difficulties. Once an appropriate descriptive assessment has been performed, it is important to explain to the child the nature of the dysfunction while delineating the child's strengths. This explanation should be provided

in nontechnical language, communicating a sense of optimism and a desire to be helpful and supportive.

Bypass Strategies (Accommodations)

Numerous techniques can enable a child to circumvent neurodevelopmental dysfunctions. Such bypass strategies are ordinarily used in the regular classroom. Examples of bypass strategies include using a calculator while solving mathematical problems, writing essays with a word processor, presenting oral instead of written reports, solving fewer mathematical problems, being seated near the teacher to minimize distraction, presenting correctly solved mathematical problems visually, and taking standardized tests untimed. These bypass strategies do not cure neurodevelopmental dysfunctions, but they minimize their academic and nonacademic effects and can provide a scaffold for more successful academic achievement.

Interventions (Remediation of Skills)

Interventions can be implemented at home and in school to strengthen the weak links in academic skills. Reading specialists, mathematics tutors, and other such professionals can use diagnostic data to select techniques that use a student's neurodevelopmental strengths in an effort to improve decoding skills, writing ability, or mathematical computation skills. Remediation need not focus exclusively on specific academic areas. Many students need assistance in acquiring study skills, cognitive strategies, and productive organizational habits.

Early identification is critical so that appropriate instructional interventions can be introduced in an effort to minimize the long-term effects of academic disorders. Any interventions should be empirically supported (e.g., phonologically based reading intervention has been shown to significantly improve reading skills in school-age children). Remediation may take place in a resource room or learning center at school and is usually limited to children who have met the educational criteria for special education resource services as described earlier.

Interventions that can be implemented at home could include drills to aid the automatization of subskills, such as arithmetic facts or letter formations, or the use of phonologically based reading programs.

There are a number of treatment/intervention approaches to strengthening executive function that have demonstrated positive findings. These include computerized training programs such as CogMed (Pearson) that has been demonstrated to strengthen working memory skills in children via a computer game model. Curriculum-based classroom programs, such as the Tools of the Mind (Tools) and PATHS (Promoting Alternative Thinking Strategies) also have accumulating research support. These programs employ approaches such as social play and target areas such as self-control and problem-solving to teach and strengthen executive functions. Aerobic exercise and martial arts such as Tae Kwon Do, which stresses discipline and emphasizes the development of self-regulation (e.g., impulse control), have demonstrated improvements that generalize in many aspects of executive functions and attention.

Developmental Therapy

Controversy exists about the efficacy of treatments to enhance weak developmental functions. Nevertheless, some forms of developmental therapy are widely accepted. Speech-language pathologists commonly offer intervention for children with various forms of language disability. Occupational therapists strive to improve the motor skills of certain students with writing problems, and physical therapists address gross motor clumsiness.

Curriculum Modifications

Many children with neurodevelopmental dysfunctions require alterations in the school curriculum to succeed, especially as they progress through secondary school. Students with memory weaknesses might need to have their courses selected for them so that they do not have an inordinate cumulative memory load in any single semester. The timing of foreign language learning, the selection of a mathematics curriculum, and the choice of science courses are critical issues for many of these struggling adolescents.

Strengthening of Strengths

Affected children need to have their affinities, potentials, and talents identified clearly and exploited widely. It is as important to augment strengths as it is to attempt to remedy deficiencies. Athletic skills, artistic inclinations, creative talents, and mechanical abilities are among the potential assets of certain students who are underachieving academically. Parents and school personnel need to create opportunities for such students to build on these assets and to achieve respect and praise for their efforts. These well-developed personal assets can ultimately have implications for the transition into young adulthood, including career or college selection.

Individual and Family Counseling

When academic difficulties are complicated by family problems or identifiable psychiatric disorders, psychotherapy may be indicated. Clinical psychologists or child psychiatrists may offer long- or short-term therapy. Such intervention may involve the child alone or the entire family. Cognitive-behavioral therapy is a technique that is increasingly popular. It is essential that the therapist have a firm understanding of the nature of a child's neurodevelopmental dysfunctions.

Controversial Therapies

A variety of treatment methods for neurodevelopmental dysfunctions have been proposed that currently have no known scientific evidence base of efficacy. This list includes dietary interventions (vitamins, elimination of food additives or potential allergens), neuromotor programs or medications to address vestibular dysfunction, eye exercises, filters, tinted lenses, and various technologic devices. Parents should be cautioned against expending the excessive amounts of time and financial resources usually demanded by these remedies. In many cases, it is difficult to distinguish the nonspecific beneficial effects of increased support and attention paid to the child from the supposed target effects of the intervention.

Medication

Psychopharmacologic agents may be especially helpful in lessening the toll of neurodevelopmental dysfunctions. Most commonly, stimulant medications are used in the treatment of children with attention deficits. Although most children with attention deficits have other associated dysfunctions (such as language disorders, memory problems, motor weaknesses, or social skill deficits), medications such as methylphenidate, dextroamphetamine, lisdexamfetamine, mixed amphetamine salts, and atomoxetine can be important adjuncts to treatment by helping some children focus more selectively and control their impulsivity. When depression or excessive anxiety is a significant component of the clinical picture, antidepressants or antianxiety drugs may be helpful. Other drugs may improve behavioral control (see Chapter 21). Children receiving medication need regular follow-up visits that include a history to check for side effects, a review of current behavioral checklists, a complete physical examination, and appropriate modifications of the medication dose. Periodic trials off medication are recommended to establish whether the medication is still necessary.

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Chapter 33

Attention-Deficit/ Hyperactivity Disorder

David K. Urion

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood and one of among the most prevalent chronic health conditions affecting school-age children. ADHD is characterized by inattention, including increased distractibility and difficulty sustaining attention; poor impulse control and decreased self-inhibitory capacity; and motor overactivity and motor restlessness (Table 33-1). Definitions vary in different countries (Table 33-2). Affected children commonly experience academic underachievement, problems with interpersonal relationships with family members and peers, and low self-esteem. ADHD often co-occurs with other emotional, behavioral, language, and learning disorders (Table 33-3). For 40-50% of affected children, the disorder appears to continue with varying manifestations into adulthood, and leads to significant under- and unemployment, social dysfunction, and an increased risk of antisocial behaviors including substance abuse, difficulties maintaining relationships, and encounters with the law.

ETIOLOGY

ADHD may be a final common pathway for a variety of complex brain developmental processes. Mothers of children with ADHD are more likely to experience birth complications, such as toxemia, lengthy labor, and complicated delivery. Maternal drug use, smoking and alcohol use during pregnancy, lead or mercury exposure (prenatal or postnatal) are commonly linked to attentional difficulties associated with the development of ADHD. Food colorings and preservatives have inconsistently been associated with hyperactivity in previously hyperactive children.

There is a very strong genetic component to ADHD. Genetic studies have primarily implicated at least 2 candidate genes, the dopamine transporter gene *(DAT1)* and a particular form of the dopamine 4 receptor gene *(DRD4),* in the development of ADHD. Additional genes that might contribute to ADHD include *DOCK2* associated with a pericentric inversion 46N inv(3)(p14:q21) involved in cytokine regulation, a sodium-hydrogen exchange gene, other dopaminergic genes *(DRD5),* serotonergic genes *(5HTT, HTR1B),* and the synaptosomal-associated protein, SNAP-25.

Abnormal brain structures are linked to an increased risk of ADHD; 20% of children with severe traumatic brain injury are reported to have subsequent onset of substantial symptoms of impulsivity and inattention. Children with head or other injury and in whom ADHD is later diagnosed might have impaired balance or impulsive behavior as part of the ADHD, thus predisposing them to injury. Structural and functional abnormalities have been identified in children with ADHD without preexisting identifiable brain injury. These include dysregulation of the frontal subcortical circuits, small cortical volumes in this region, widespread small-volume reduction throughout the brain, and abnormalities of the cerebellum, particularly midline/vermian elements. Abnormalities in neural networks or circuits have been identified with functional MRI.

Psychosocial family stressors can also contribute to or exacerbate the symptoms of ADHD, including poverty, exposure to violence, and under- or malnutrition.

EPIDEMIOLOGY

Studies of the prevalence of ADHD across the globe have generally reported that 9% of school-age children are affected, although rates vary considerably by country, perhaps partly as a result of differing sampling and testing techniques. Rates may be higher if symptoms (inattention, impulsivity, hyperactivity) are considered in the absence of functional impairment. The prevalence rate in adolescent samples is 2-6%. Approximately 2% of adults have ADHD. ADHD is often underdiagnosed in children and adolescents. Youth with ADHD are often undertreated with respect to what is known about the needed and appropriate doses of medications. Many children with ADHD also present with comorbid neuropsychiatric diagnoses, including opposition defiant disorder, conduct disorder, learning disabilities, depression, and anxiety disorders. The incidence of ADHD appears increased in children with neurologic disorders such as epilepsies, neurofibromatosis, tuberous sclerosis (see Table 33-3).

PATHOGENESIS

MRI studies indicate that a loss of normal asymmetry in the brain, in addition to smaller brain volumes of specific structures, such as the prefrontal cortex and basal ganglia, is seen in the brains of children with ADHD. Children with ADHD have approximately a 5-10% reduction in the volume of these brain structures. Functional MRI findings suggest low blood flow to the striatum. Functional MRI data also suggest deficits in a widespread functional networks for selective and tonic attention in ADHD, that include the striatum, prefrontal regions, parietal lobe, and temporal lobe. The prefrontal cortex and basal ganglia are rich in dopamine receptors. This knowledge, plus data about the dopaminergic mechanisms of action of medication treatment for ADHD, has led to the **dopamine hypothesis,** which postulates that disturbances in the dopamine system may be related to the onset of ADHD. Fluorodopa positron emission tomography scans also support the dopamine hypothesis through the identification of low levels of dopamine activity in adults.

CLINICAL MANIFESTATIONS

Development of the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) criteria leading to the diagnosis of ADHD occurred mainly in field trials with children 5-12 yr of age. Fewer studies utilizing *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria are available, but those that are available suggest a good correlation with data from DSM-IV criteria-based studies, despite the broadened age-based definition for onset of symptoms in DSM-5 (see Table 33-1). The current DSM-5 criteria state that the behavior must be developmentally inappropriate (substantially different from that of other children of the same age and developmental level), must begin before age 12 yr, must be present for at least 6 mo, must be present in 2 or more settings and reported as such by independent observers, and must not be secondary to another disorder. DSM-5 identifies 3 subtypes of ADHD. The first subtype, *ADHD, predominantly inattentive type,* often includes cognitive impairment and is more common in females. The other 2 subtypes, *ADHD, predominantly hyperactive-impulsive type,* and *ADHD, combined type,* are more commonly diagnosed in males. Clinical manifestations of ADHD may change with age. The symptoms may vary from motor restlessness and aggressive and disruptive behavior, which are common in preschool children, to disorganized, distractible, and inattentive symptoms, which are more typical in older adolescents and adults. ADHD is often difficult to diagnose in preschoolers because distractibility and inattention are may be considered developmental norms during this period.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A diagnosis of ADHD is made primarily in clinical settings after a thorough evaluation, including a careful history and clinical interview to rule in or to identify other causes or contributing factors; completion of behavior rating scales by different observers from at least 2 settings (e.g., teacher and parent); a physical examination; and any necessary or indicated laboratory tests which arise from conditions suspected based on history and/or physical examination. It is important to systematically gather and evaluate information from a variety of sources, including the child, parents, teachers, physicians, and, when appropriate, other caretakers, over the course of both diagnosis and subsequent management.

Table 33-1 DSM-5 Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder

DIAGNOSTIC CRITERIA

1. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):
   1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
      - **Note:** The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
      1. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
      2. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
      3. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
      4. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
      5. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
      6. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
      7. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
      8. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
      9. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).
   2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
      - **Note:** The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
      1. Often fidgets with or taps hands or feet or squirms in seat.
      2. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
      3. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
      4. Often unable to play or engage in leisure activities quietly.
      5. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
      6. Often talks excessively.
      7. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
      8. Often has difficulty waiting his or her turn (e.g., while waiting in line).
      9. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).
2. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
3. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
4. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
5. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:
- **Combined presentation:** If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.
- **Predominantly inattentive presentation:** If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.
- **Predominantly hyperactive/impulsive presentation:** If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Specify if:
- **In partial remission:** When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:
- **Mild:** Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.
- **Moderate:** Symptoms or functional impairment between "mild" and "severe" are present.
- **Severe:** Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

Clinical Interview and History

The clinical interview allows a comprehensive understanding as to whether the symptoms meet the diagnostic criteria for ADHD. During the interview, the clinician should gather information pertaining to the history of the presenting problems, the child's overall health and development, and the social and family history. The interview should emphasize factors that might affect the development or integrity of the central nervous system or reveal chronic illness, sensory impairments, or medication use that might affect the child's functioning. Disruptive social factors, such as family discord, situational stress, and abuse or neglect, can result in hyperactive or anxious behaviors. A family history of 1st-degree relatives with ADHD, mood or anxiety disorders, learning disability, antisocial disorder, or alcohol or substance abuse might indicate an increased risk of ADHD and/or comorbid conditions.

Table 33-2 Differences Between U.S. and European Criteria for ADHD or HKD

DSM-5 ADHD	ICD-10 HKD
SYMPTOMS	
Either or both of following: At least 6 of 9 inattentive symptoms At least 6 of 9 hyperactive or impulsive symptoms	All of following: At least 6 of 8 inattentive symptoms At least 3 of 5 hyperactive symptoms At least 1 of 4 impulsive symptoms
PERVASIVENESS	
Some impairment from symptoms is present in >1 setting	Criteria are met for >1 setting

ADHD, attention-deficit/hyperactivity disorder; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; HKD, hyperkinetic disorder; ICD-10, *International Classification of Diseases, 10th edition.*

Adapted from Biederman J, Faraone S: Attention-deficit hyperactivity disorder, Lancet *366:237–248, 2005.*

Table 33-3 Differential Diagnosis of Attention-Deficit/Hyperactivity Disorder

PSYCHOSOCIAL FACTORS
Response to physical or sexual abuse
Response to inappropriate parenting practices
Response to parental psychopathology
Response to acculturation
Response to inappropriate classroom setting
DIAGNOSES ASSOCIATED WITH ADHD BEHAVIORS
Fragile X syndrome
Fetal alcohol syndrome
Pervasive developmental disorders
Obsessive-compulsive disorder
Gilles de la Tourette syndrome
Attachment disorder with mixed emotions and conduct
MEDICAL AND NEUROLOGIC CONDITIONS
Thyroid disorders (including general resistance to thyroid hormone)
Heavy metal poisoning (including lead)
Adverse effects of medications
Effects of abused substances
Sensory deficits (hearing and vision)
Auditory and visual processing disorders
Neurodegenerative disorder, especially leukodystrophies
Posttraumatic head injury
Postencephalitic disorder

Note: Coexisting conditions with possible ADHD presentation include oppositional defiant disorder, anxiety disorders, conduct disorder, depressive disorders, learning disorders, and language disorders. Presence of 1 or more of the symptoms of these disorders can fall within the spectrum of normal behavior, whereas a range of these symptoms may be problematic but fall short of meeting the full criteria for the disorder.

From Reiff MI, Stein MT: Attention-deficit/hyperactivity disorder evaluation and diagnosis: a practical approach in office practice, Pediatr Clin North Am *50:1019–1048, 2003. Adapted from Reiff MI: Attention-deficit/hyperactivity disorders. In Bergman AB, editor:* 20 Common problems in pediatrics, *New York, 2001, McGraw-Hill, p 273.*

Behavior Rating Scales

Behavior rating scales are useful in establishing the magnitude and pervasiveness of the symptoms, but are not sufficient alone to make a diagnosis of ADHD. There are a variety of well-established behavior rating scales that have obtained good results in discriminating between children with ADHD and control subjects. These measures include, but are not limited to, the Vanderbilt ADHD Diagnostic Rating Scale; the Conner Rating Scales (parent and teacher); the ADHD Index; the Swanson, Nolan, and Pelham Checklist (SNAP); and the ADD-H: Comprehensive Teacher Rating Scale (ACTeRS). Other broadband checklists, such as the Achenbach Child Behavior Checklist (CBCL) or Behavioral Assessment Scale for Children (BASC), are useful, particularly in instances where the child may be experiencing co-occurring problems in other areas (anxiety, depression, conduct problems). Some, such as the BASC, include a validation scale to help determine the reliability of a given observer's assessment of the child.

Physical Examination and Laboratory Findings

There are no standard laboratory tests available to identify ADHD in children. The presence of hypertension, ataxia, or a thyroid disorder should prompt further diagnostic evaluation. Impaired fine motor movement and poor coordination and other **subtle neurologic motor signs** (difficulties with finger tapping, alternating movements, finger-to-nose, skipping, tracing a maze, cutting paper) are common, but they are not sufficiently specific to contribute to a diagnosis of ADHD. The clinician should also identify any possible vision or hearing problems. The clinician should consider testing for elevated lead levels in children who present with some or all of the diagnostic criteria, if these children are exposed to environmental factors that might put them at risk (substandard housing, old paint, proximity to a highway which led to deposition of lead in the topsoil from automobile exhaust years ago). Behavior in the structured laboratory setting might not reflect the child's typical behavior in the home or school environment. Therefore, reliance on observed behavior in a physician's office can result in an incorrect diagnosis. Computerized attentional tasks and electroencephalographic assessments are not needed to make the diagnosis, and compared to the clinical gold standard they are subject to false-positive and false-negative errors. Nonetheless, the FDA has approved the Neuropsychiatric EEG-Based Assessment Aide (NEBA) system, which may identify an abnormal theta : beta wave ratio associated with ADHD.

Differential Diagnosis

Chronic illnesses, such as migraine headaches, absence seizures, asthma and allergies, hematologic disorders, diabetes, childhood cancer, affect up to 20% of children in the United States and can impair children's attention and school performance, either because of the disease itself or because of the medications used to treat or control the underlying illness (medications for asthma, steroids, anticonvulsants, antihistamines) (see Table 33-3). In older children and adolescents, **substance abuse** (see Chapter 114) can result in declining school performance and inattentive behavior.

Sleep disorders, including those secondary to chronic upper airway obstruction from enlarged tonsils and adenoids, often result in behavioral and emotional symptoms, although such problems are not likely to be principal contributing causes of ADHD (see Chapter 19). Periodic leg movements of sleep/restless leg syndrome is associated with attentional symptoms, and inquiry regarding this should be made during the history. Behavioral and emotional disorders can cause disrupted sleep patterns as well.

Depression and anxiety disorders (see Chapters 25 and 26) can cause many of the same symptoms as ADHD (inattention, restlessness, inability to focus and concentrate on work, poor organization, forgetfulness), but can also be comorbid conditions. Obsessive-compulsive disorder can mimic ADHD, particularly when recurrent and persistent thoughts, impulses, or images are intrusive and interfere with normal daily activities. Adjustment disorders secondary to major life stresses (death of a close family member, parents' divorce, family violence, parents' substance abuse, a move, shared social trauma such as bombings or other attacks) or parent–child relationship disorders involving conflicts over discipline, overt child abuse and/or neglect, or overprotection can result in symptoms similar to those of ADHD.

Although ADHD is believed to result from primary impairment of attention, impulse control, and motor activity, there is a high prevalence of comorbidity with other neuropsychiatric disorders (see Table 33-3). Of children with ADHD, 15-25% have learning disabilities, 30-35% have developmental language disorders, 15-20% have

diagnosed mood disorders, and 20-25% have coexisting anxiety disorders. Children with ADHD can also have co-occurring diagnoses of sleep disorders, memory impairment, and decreased motor skills.

TREATMENT

Psychosocial Treatments

Once the diagnosis of ADHD is established, the caregiver should discuss with the parents and child the ways ADHD can affect learning, behavior, self-esteem, social skills, and family function. The clinician should set goals for the family to improve the child's interpersonal relationships, develop study skills, and decrease disruptive behaviors. Parent support groups with appropriate professional consultation to such groups can be very helpful.

Behaviorally Oriented Treatments

Treatments geared toward behavioral management often occur in the time frame of 8-12 sessions. The goal of such treatment is for the clinician to identify targeted behaviors that cause impairment in the child's life (disruptive behavior, difficulty in completing homework, failure to obey home or school rules) and for the child to work on progressively improving the child's skill in these areas. The clinician should guide the parents and teachers in implementing rules, consequences, and rewards to encourage desired behaviors. In short-term comparison trials, stimulants have been more effective than behavioral treatments used alone; behavioral interventions are only modestly successful at improving behavior, but they may be particularly useful for children with complex comorbidities and family stressors, when combined with medication.

Medications

The most widely used medications for the treatment of ADHD and the treatment of choice are the presynaptic dopaminergic agonists, commonly called psychostimulant medications, including methylphenidate (Ritalin, Concerta, Metadate, Focalin, Daytrana), amphetamine, and/or various amphetamine and dextroamphetamine preparations (Dexedrine, Adderall, Vyvanse) (Table 33-4). Longer-acting, once-daily forms of each of the major types of stimulant medications are available and facilitate compliance with treatment and coverage over a longer period of time. The clinician should prescribe a stimulant treatment, either methylphenidate or an amphetamine compound. If a full range of methylphenidate dosages is used, approximately 25% of patients have an optimal response on a low (<0.5 mg/kg/day for methylphenidate, <0.25 mg/kg/day for amphetamines), 25% on medium (0.5-1.0 mg/kg/day for methylphenidate, 0.25-0.5 mg/kg/day for amphetamines), or high (1.0-1.5 mg/day for methylphenidate, 0.5-0.75 mg/kg/day for amphetamine) daily dosage; another 25% will be unresponsive or will have side effects, making that drug particularly unpalatable for the family.

Over the first 4 wk of treatment, the physician should increase the medication dose as tolerated (keeping side effects minimal to absent) to achieve maximum benefit. If this strategy does not yield satisfactory results, or if side effects prevent further dose adjustment in the presence of persisting symptoms, the clinician should use an alternative class of stimulants that was not used previously. If a methylphenidate compound is unsuccessful, the clinician should switch to an amphetamine product. If satisfactory treatment results are not obtained with the second stimulant, clinicians may choose to prescribe atomoxetine, a noradrenergic reuptake inhibitor that is superior to placebo in the treatment of ADHD in children, adolescents, and adults and that has been approved by the FDA for this indication. Atomoxetine should be initiated at a dose of 0.3 mg/kg/day and titrated over 1-3 wk to a maximum total daily dosage of 1.2-1.8 mg/kg/day. The dose should be divided into twice-daily portions. Once-daily dosing appears to be associated with a high incidence of treatment failure. Guanfacine, originally developed as an antihypertensive agent, is also FDA approved for the treatment of ADHD, although it appears to be less successful for hyperactivity and more likely to assist with impulsivity. It can also treat motor and vocal tics, and so may be a reasonable choice in a child with a comorbid tic disorder.

The clinician should recognize that careful monitoring of medication is a necessary component of treatment in children with ADHD. When physicians prescribe medications for the treatment of ADHD, they tend to use lower-than-optimal doses. Optimal treatment usually requires somewhat higher doses than those typically used in routine practice settings. All-day preparations are also useful to maximize positive effects and minimize side effects, and regular medication follow-up visits should be offered (4 or more times per year) as opposed to the twice-yearly medication visits often used in standard community-care settings.

Medication alone is not always sufficient to treat ADHD in children, particularly in instances where children have multiple psychiatric disorders or stressed home environments. When children do not respond to medication, it may be appropriate to refer them to a mental health specialist. Consultation with a child psychiatrist or psychologist can also be beneficial to determine the next steps for treatment, including adding other components and supports to the overall treatment program. Evidence suggests that children who receive careful medication management, accompanied by frequent treatment follow-up, all within the context of an educative, supportive relationship with the primary care provider, are likely to experience behavioral gains for up to 24 mo.

Stimulant drugs used to treat ADHD may be associated with an increased risk of adverse cardiovascular events, including sudden cardiac death, myocardial infarction, and stroke in young adults and rarely in children. In some of the reported cases, the patient had an underlying disorder, such as hypertrophic obstructive cardiomyopathy, which is made worse by sympathomimetic agents. These events are rare, but they nonetheless warrant consideration before initiating treatment and during monitoring of treatment with stimulant medications. Children with a positive or personal family history of cardiomyopathy, or arrhythmias, or syncope require an electrocardiogram and possible cardiology consultation before a stimulant is prescribed (Fig. 33-1).

PROGNOSIS

A childhood diagnosis of ADHD often leads to persistent ADHD throughout the life span. From 60-80% of children with ADHD continue to experience symptoms in adolescence, and up to 60% of adolescents exhibit ADHD symptoms into adulthood. In children with ADHD, a reduction in hyperactive behavior often occurs with age. Other symptoms associated with ADHD can become more prominent with age, such as inattention, impulsivity, and disorganization, and

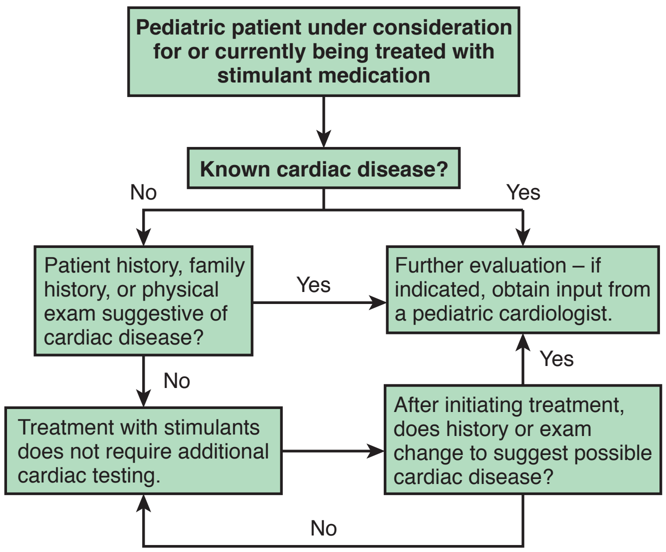

Figure 33-1 Cardiac evaluation of children and adolescents receiving or being considered for stimulant medications. *(From Perrin JM, Friedman RA, Knilans TK: Cardiovascular monitoring and stimulant drugs for attention-deficit/hyperactivity disorder,* Pediatrics *122:451–453, 2008.)*

Table 33-4 Medications Used in the Treatment of Attention-Deficit/Hyperactivity Disorder

GENERIC NAME	BRAND NAME	DURATION	DOSAGE RANGE	SIDE EFFECTS
METHYLPHENIDATE				
Immediate-release	Ritalin, Methylin	3-4 hr	5, 10, 20 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics, priapism
Extended-release	Metadate ER, Methylin ER,	4-6 hr	10, 20 mg extended-release tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics, priapism
	Metadate-CD	8-10 hr	10, 20, 30 mg extended-release caps	
	Ritalin LA	8-10 hr	20, 30, 40 mg caps	
	Concerta	10-12 hr	18, 27, 36, 54 mg caps	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Sustained-release	Ritalin SR, Methylphenidate SR	4-6 hr	20 mg sustained-release tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics, priapism
Transdermal system	Daytrana	≥12 hr	Patch	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics, priapism
DEXMETHYLPHENIDATE				
	Focalin	4-6 hr	2.5, 5, 10 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Extended-release	Focalin XR	6-8 hr		Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
DEXTROAMPHETAMINE				
Short-acting	Dexedrine, DextroStat	4-6 hr	5, 10, 15 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Intermediate-acting	Dexedrine, Spansule	6-8 hr	5, 10, 20 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Lisdexamfetamine	Vyvanse	≤12 hr	30 mg, 50 mg, 70 mg tablets	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
MIXED AMPHETAMINE SALTS				
Intermediate-acting	Adderall	4-6 hr	5, 10, 20 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Extended-release	Adderall XR	8-12 hr	5, 10, 15, 20, 25, 30 mg caps	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
ATOMOXETINE				
Extended-release	Strattera	12 hr	10, 18, 25, 40, 60 mg caps	Nervousness, sleep problems, fatigue, stomach upset, dizziness, dry mouth Can lead in rare cases to severe liver injury or to suicidal ideation
Bupropion	Wellbutrin	4-5 hr	100, 150 mg tabs	Difficulty sleeping, headache, seizures
Bupropion	Wellbutrin SR, Wellbutrin XL		100, 150, 200 mg tabs	
TRICYCLIC ANTIDEPRESSANTS				
Imipramine	Tofranil	Variable	See Table 21-4	Nervousness, sleep problems, fatigue, stomach upset, dizziness, dry mouth, accelerated heart rate
Desipramine*	Norpramin			
Nortriptyline	Aventyl, Pamelor			
α-AGONISTS				
Clonidine	Catapres, Kapvay	6-12 hr	3-10 µg/kg/day bid-qid	Sedation, depression, dry mouth, rebound hypertension on discontinuing, confusion
Guanfacine	Tenex, Intuniv	6-12 hr	1, 2, 3 mg tabs	Hypotension, lightheadedness

cap, capsule; tab, tablet.
*Associated with deaths from cardiac problems. Not recommended for children.

these exact a heavy toll on young adult functioning. A variety of risk factors can affect children with untreated ADHD as they become adults. These risk factors include engaging in risk-taking behaviors (sexual activity, delinquent behaviors, substance use), educational underachievement or employment difficulties, and relationship difficulties. With proper treatment, the risks associated with the disorder can be significantly reduced. It appears that consistent treatment with medication and adjuvant therapies can lower the risk of adverse outcomes, such as substance abuse.

PREVENTION

Parent training can lead to significant improvements in preschool children with ADHD symptoms, and parent training for preschool youth with ADHD can reduce oppositional behavior. To the extent that parents, teachers, physicians, and policymakers support efforts for earlier detection, diagnosis, and treatment, prevention of long-term adverse effects of ADHD on affected children's lives should be reconsidered within the lens of prevention. Given the effective treatments for ADHD now available, and the well-documented evidence about the long-term effects of untreated or ineffectively treated ADHD on children and youth, prevention of these consequences should be within the grasp of physicians and the children and families with ADHD for whom we are responsible.

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Chapter **34**

Dyslexia

Sally E. Shaywitz and Bennett A. Shaywitz

Dyslexia is defined in this chapter as an *unexpected difficulty* in reading, that is, unexpected in relation to intelligence, chronological age/grade level, education, or professional status. In typical readers, development of reading and IQ are dynamically linked over time, but in dyslexic readers there is a developmental uncoupling between reading and IQ (Fig. 34-1). These findings provide an explanation for the "unexpected" nature of dyslexia and provide the long sought empirical evidence for the seeming paradox between cognition and reading in individuals with developmental dyslexia.

ETIOLOGY

Dyslexia is both familial and heritable. Dyslexia is observed in 50% of children who have a parent with dyslexia; 50% of the siblings of dyslexic persons; and 50% of the parents of dyslexics. Dyslexia reflects a multifactorial model of the interaction between genetic and environmental factors. Multiple genes can influence the disorder, with each gene individually contributing a small amount of variance and with a single etiologic factor insufficient to cause or explain dyslexia. The neural systems are the final common pathway for multiple influences, and it is unlikely that a single gene or even several genes cause or explain dyslexia.

EPIDEMIOLOGY

Dyslexia is the most common and most comprehensively studied of the **learning disabilities,** affecting 80% of children identified as learning disabled. Dyslexia may be the most common neurobehavioral disorder affecting children, with prevalence rates ranging from 5-10% in clinic- and school-identified samples to 17.5% in unselected population-based samples in the United States and other countries. Dyslexia fits a dimensional model in which reading ability and disability occur along a continuum, with dyslexia representing the lower tail of a normal distribution of reading ability. Although more boys than girls are identified by schools as dyslexic, in studies based on survey samples in which *all* children are assessed, there are no significant gender differences in dyslexia.

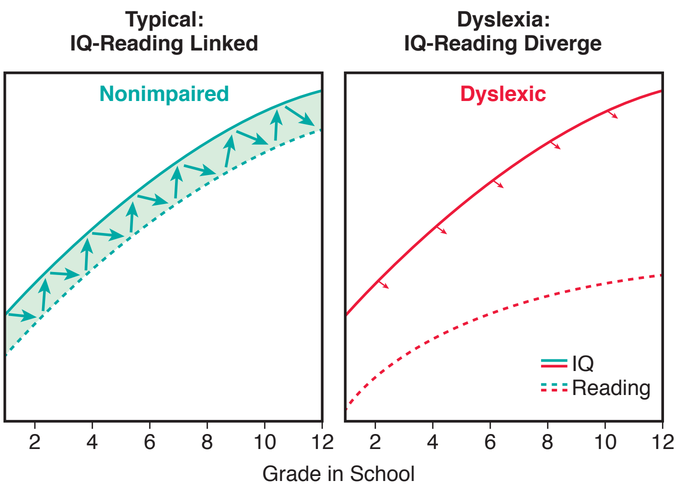

Figure 34-1 **Uncoupling of reading and IQ over time: empirical evidence for a definition of dyslexia.** *Left* panel shows that in typical readers, reading and IQ development are dynamically linked over time. In contrast, *right* panel, dyslexic readers, shows that reading and IQ development are dissociated and one does not influence the other. *(Data adapted from Ferrer E, Shaywitz BA, Holahan JM, et al: Uncoupling of reading and IQ over time: empirical evidence for a definition of dyslexia,* Psychol Sci *21(1):93–101, 2010.)*

PATHOGENESIS

Evidence from a number of lines of investigation indicates that dyslexia reflects deficits within the language system, and more specifically, within the phonologic component of the language system engaged in processing the sounds of speech. Dyslexic individuals have difficulty developing an awareness that spoken words can be segmented into smaller elemental units of sound **(phonemes),** an essential ability given that reading requires that the reader map or link printed symbols to sound. Increasing evidence indicates that disruption of attentional mechanisms may also play an important role in reading difficulties.

Functional brain imaging in both children with dyslexia and adult dyslexic readers demonstrates an inefficient functioning of left hemisphere posterior brain systems, a pattern referred to as the *neural signature of dyslexia* (Fig. 34-2). Although functional MRI consistently demonstrates differences between *groups* of dyslexic compared to typical readers, brain imaging is not able to differentiate an *individual* case of dyslexic reader from a typical reader and so brain imaging is not useful in diagnosing dyslexia.

CLINICAL MANIFESTATIONS

Reflecting the underlying phonologic weakness, children and adults with dyslexia manifest problems in both spoken and written language. Spoken language difficulties are typically manifest by mispronunciations, lack of glibness, speech that lacks fluency with many pauses or hesitations and "ums," word-finding difficulties with the need for time to summon an oral response and the inability to come up with a verbal response quickly when questioned; these reflect sound-based, and not semantic or knowledge-based difficulties.

Struggles in decoding and word recognition can vary according to age and developmental level. The cardinal signs of dyslexia observed in school-age children and adults are a labored, effortful approach to reading involving decoding, word recognition, and text reading. Listening comprehension is typically robust. Older children improve reading accuracy over time, albeit without commensurate gains in reading fluency; they remain slow readers. Difficulties in spelling typically reflect the phonologically based difficulties observed in oral reading. Handwriting is often affected as well.

History often reveals early subtle language difficulties in dyslexic children. During the preschool and kindergarten years, at-risk children display difficulties playing rhyming games and learning the names for letters and numbers. Kindergarten assessments of these language skills can help identify children at risk for dyslexia. Although a dyslexic child enjoys and benefits from being read to, the child might avoid reading aloud to the parent or reading independently.

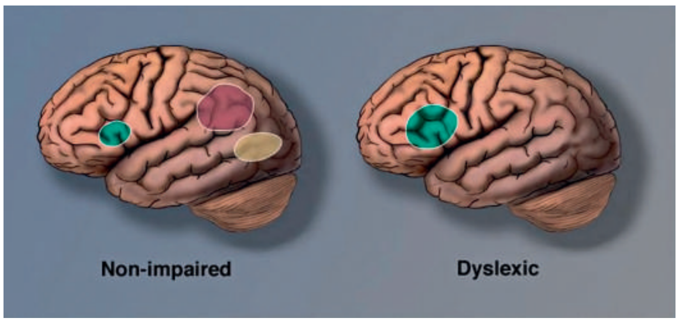

Figure 34-2 **A neural signature for dyslexia.** The *left* side of the figure shows a schematic of left hemisphere brain systems in in typical (non-impaired) readers. The 3 systems for reading are an anterior system in the region of the inferior frontal gyrus (Broca's area), serving articulation and word analysis, and 2 posterior systems, 1 in the occipitotemporal region serving word analysis, and a second in the occipitotemporal region (the word-form area) serving the rapid, automatic, fluent identification of words. In dyslexic readers (*right* side of figure), the 2 posterior systems are functioning inefficiently and appear underactivated. This pattern of underactivation in left posterior reading systems is referred to as the neural signature for dyslexia. *(Adapted from Shaywitz S:* Overcoming dyslexia: a new and complete science-based program for reading problems at any level. *New York, 2003, Alfred A. Knopf. Copyright 2003 by S. Shaywitz. Adapted with permission.)*

Dyslexia may co-occur with attention-deficit/hyperactivity disorder (see Chapter 33); this comorbidity has been documented in both referred samples (40% comorbidity) and nonreferred samples (15% comorbidity).

DIAGNOSIS

Dyslexia is a clinical diagnosis, and history is especially critical. The clinician seeks to determine through history, observation, and psychometric assessment, if there are unexpected difficulties in reading (based on the person's intelligence, chronological/grade, level of education or professional status) and associated linguistic problems at the level of phonologic processing. There is no single test score that is pathognomonic of dyslexia. The diagnosis of dyslexia should reflect a thoughtful synthesis of all clinical data available.

Dyslexia is distinguished from other disorders that can prominently feature reading difficulties by the unique, circumscribed nature of the phonologic deficit, one that does not intrude into other linguistic or cognitive domains. Family history, teacher and classroom observation, and tests of language (particularly phonology), reading including fluency, and spelling represent a core assessment for the diagnosis of dyslexia in children; additional tests of intellectual ability, attention, memory, general language skills, and mathematics may be administered as part of a more comprehensive evaluation of cognitive, linguistic, and academic function. Once a diagnosis has been made, dyslexia is a permanent diagnosis and need not be reconfirmed by new assessments.

For informal screening, in addition to a careful history, the primary care physician in an office setting can listen to the child read aloud from the child's own grade-level reader. Keeping a set of graded readers available in the office serves the same purpose and eliminates the need for the child to bring in schoolbooks. Oral reading is a sensitive measure of reading accuracy and fluency. The most consistent and telling sign of a reading disability in an accomplished young adult is slow and laborious reading and writing. In attempting to read aloud, most children and adults with dyslexia display an effortful approach to decoding and recognizing single words, an approach in children characterized by hesitations, mispronunciations, and repeated attempts to sound out unfamiliar words. In contrast to the difficulties they experience in decoding single words, persons with dyslexia typically possess the vocabulary, syntax, and other higher-level abilities involved in comprehension.

The failure either to recognize or to measure the lack of fluency in reading is perhaps the most common error in the diagnosis of dyslexia in older children and accomplished young adults. Simple word identification tasks will not detect dyslexia in a person who is accomplished enough to be in honors high school classes or to graduate from college or obtain a graduate degree. Tests relying on the accuracy of word identification alone are inappropriate to use to diagnose dyslexia because they show little to nothing of the struggle to read. Because they assess reading accuracy but not automaticity (speed), the kinds of reading tests commonly used for school-age children might provide misleading data on bright adolescents and young adults. The most critical tests are those that are timed; they are the most sensitive in detecting dyslexia in a bright adult. There are few standardized tests for young adult readers that are administered under timed and untimed conditions; the Nelson-Denny Reading Test is an exception. The helpful Test of Word Reading Efficiency (TOWRE) examines simple word reading under timed conditions. Any scores obtained on testing must be considered relative to peers with the same degree of education or professional training.

MANAGEMENT

The management of dyslexia demands a life-span perspective. Early on, the focus is on remediation of the reading problem. Application of knowledge of the importance of early language, including vocabulary and phonologic skills, leads to significant improvements in children's reading accuracy, even in predisposed children. As a child matures and enters the more time-demanding setting of secondary school, the emphasis shifts to the important role of providing accommodations. Based on the work of the National Reading Panel, evidence-based reading intervention methods and programs are identified. Effective intervention programs provide systematic instruction in 5 key areas: phonemic awareness, phonics, fluency, vocabulary, and comprehension strategies. These programs also provide ample opportunities for writing, reading, and discussing literature.

Taking each component of the reading process in turn, effective interventions improve **phonemic awareness:** the ability to focus on and manipulate phonemes (speech sounds) in **spoken** syllables and words. The elements found to be most effective in enhancing phonemic awareness, reading, and spelling skills include teaching children to manipulate phonemes with letters; focusing the instruction on 1 or 2 types of phoneme manipulations rather than multiple types; and teaching children in small groups. Providing instruction in phonemic awareness is necessary but not sufficient to teach children to read. Effective intervention programs include teaching **phonics,** or making sure that the beginning reader understands how letters are linked to sounds (phonemes) to form letter-sound correspondences and spelling patterns. The instruction should be explicit and systematic; phonics instruction enhances children's success in learning to read, and systematic phonics instruction is more effective than instruction that teaches little or no phonics or teaches phonics casually or haphazardly.

Fluency is of critical importance because it allows the automatic, rapid recognition of words and while it is generally recognized that fluency is an important component of skilled reading, it has proven difficult to teach. Interventions for **vocabulary development and reading comprehension** are not as well established. The most effective methods to teach reading comprehension involve teaching **vocabulary** and **strategies** that encourage active interaction between the reader and the text. Emerging science indicates that it is not only teacher content knowledge but the teacher's skill in engaging the student and focusing the student's attention on the reading task at hand that is required for effective instruction.

For those in high school, college, and graduate school, provision of accommodations most often represents a highly effective approach to dyslexia. Imaging studies now provide neurobiologic evidence for the need for extra time for dyslexic students; accordingly, college students with a childhood history of dyslexia require extra time in reading and writing assignments as well as examinations. Many adolescent and adult students have been able to improve their reading accuracy but without commensurate gains in reading speed. The accommodation of extra time reconciles the individual's often high cognitive ability and slow reading so that the exam is a measure of that person's ability rather than his disability. Another important accommodation is teaching the dyslexic student to listen to texts. Programs such as Kurzweil, WYNN, Learning Ally, and Bookshare are available, as are programs such as Dragon Dictate that provide voice-to-text conversion. Other helpful accommodations include the use of laptop computers with spelling checkers, access to lecture notes, tutorial services, and a separate quiet room for taking tests. In addition, the impact of the primary phonologic weakness mandates special consideration during oral examinations so that students are not graded on their lack of glibness or speech hesitancies but on their content knowledge. Unfortunately, often speech hesitancies or difficulties in word retrieval are wrongly confused with insecure content knowledge.

PROGNOSIS

Application of evidence-based methods to young children (kindergarten to grade 3), when provided with sufficient intensity and duration, can result in improvements in reading accuracy and, to a much lesser extent, fluency. In older children and adults, interventions result in improved accuracy, but not an appreciable improvement in fluency. Accommodations are critical in allowing the dyslexic child to demonstrate his or her knowledge. Parents should be informed that with proper support, dyslexic children can succeed in a range of future occupations that might seem out of the reach of dyslexic children including medicine, law, journalism, and writing.

Bibliography is available at Expert Consult.

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Chapter **35**

Language Development and Communication Disorders

Mark D. Simms

Most children learn to communicate in their native language without specific instruction or intervention other than exposure to a language-rich environment. Normal development of speech and language is predicated on the infant's ability to hear, see, comprehend, remember, and socially interact with others. The infant must also possess sufficient motor skills to imitate oral motor movements.

NORMAL LANGUAGE DEVELOPMENT

Language can be subdivided into several essential components. **Communication** consists of a wide range of behaviors and skills. At the level of basic verbal ability, **phonology** refers the correct use of speech sounds to form words, **semantics** refers to the correct use of words, and **syntax** refers to the appropriate use of grammar to make sentences. At a more abstract level, verbal skills include the ability to link thoughts together in a coherent fashion and to maintain a topic of conversation. **Pragmatic** abilities include verbal and nonverbal skills that facilitate the exchange of ideas, including the appropriate choice of language for the situation and circumstance and the appropriate use of body language (i.e., posture, eye contact, gestures). Social pragmatic and behavioral skills also play an important role in effective interactions with communication partners (i.e., engaging, responding, and maintaining reciprocal exchanges).

It is customary to divide language skills into receptive (hearing and understanding) and expressive (talking) abilities. Language development usually follows a fairly predictable pattern and parallels general intellectual development (Table 35-1).

Receptive Language Development

The peripheral auditory system is mature by 26 wk gestation and the fetus responds to and discriminates speech sounds. Anatomical asymmetry in the *planum temporale*, the structural brain region specialized for language processing, is present by 31 wk gestation. At birth, the full-term newborn appears to have functionally organized neural networks that are sensitive to different properties of language input. The normal newborn demonstrates preferential response to human voices over inanimate sound, and recognizes the mother's voice, reacting stronger to it than to a stranger's voice. Even more remarkable is the ability of the newborn to discriminate sentences in their "native" (mother's) language from sentences in a "foreign" language. In research settings, infants of monolingual mothers showed a preference only for that language, while infants of bilingual mothers showed a preference for both exposed languages over any other language.

Between 4 and 6 mo, infants visually search for the source of sounds, again showing a preference for the human voice over other environmental sounds. By 5 mo, infants can passively follow the adult's line of visual regard, resulting in a "joint reference" to the same objects and events in the environment. The ability to share the same experience is critical to the development of further language, social, and cognitive skills as the infant "maps" specific meanings onto his or her experiences. By 8 mo, the infant can actively show, give, and point to objects. Comprehension of words often becomes apparent by 9 mo, when the infant selectively responds to his or her name and appears to comprehend the word "no." Social games, such as "peek-a-boo," "so big," and waving "bye-bye" can be elicited by simply mentioning the words. At 12 mo, many children can follow a simple, one-step request without a gesture (e.g., "Give it to me!").

Between 1 and 2 yr, comprehension of language accelerates rapidly. Toddlers can point to body parts on command, identify pictures in books when named, and respond to simple questions (e.g., "Where's your shoe?"). The 2 yr old is able to follow a 2-step command, employing unrelated tasks (e.g., "Take off your shoes, then go sit at the table"), and can point to objects described by their use (e.g., "Give me the one we drink from"). By 3 yr, children typically understand simple "wh-" question forms (e.g., who, what, where, why). By 4 yr, most children can follow adult conversation. They can listen to a short story and answer simple questions about it. Five yr olds typically have a receptive vocabulary of more than 2000 words and can follow 3- and 4-step commands.

Expressive Language Development

Cooing noises are established by 4-6 wk of age. Over the first 3 mo of life, parents may distinguish their infant's different vocal sounds for pleasure, pain, fussing, tiredness, etc. Many 3 mo old infants vocalize in a reciprocal fashion with an adult to maintain a social interaction ("vocal tennis"). By 4 mo, infants begin to make bilabial ("raspberry") sounds, and by 5 mo, monosyllables and laughing are noticeable. Between 6 and 8 mo, polysyllabic babbling ("lalala" or "mamama") is heard and the infant might begin to communicate with gestures. Between 8 and 10 mo, babbling makes a phonologic shift toward the particular sound patterns of the child's native language (i.e., they produce more native sounds than nonnative sounds). At 9-10 mo, babbling becomes truncated into specific words (e.g., "mama," or "dada") for their parents.

Over the next several months, infants learn 1 or 2 words for common objects and begin to imitate words presented by an adult. These words might appear to come and go from the child's repertoire until a stable group of 10 or more words is established. The rate of acquisition of new words is approximately 1 new word per wk at 12 mo, but it accelerates to approximately 1 new word per day by 2 yr. The first words to appear are used primarily to label objects (nouns) or to ask for objects and people (requests). By 18-20 mo, toddlers should use a minimum of 20 words and produce jargon (strings of word-like sounds) with language-like inflection patterns (rising and falling speech patterns). This jargon usually contains some embedded true words. Spontaneous 2-word phrases (pivotal speech), consisting of the flexible juxtaposition of words with clear intention (e.g., "Want juice!" or "Me down!"), is characteristic of 2 yr olds and reflects the emergence of grammatical ability (syntax).

Two-word, combinational phrases do not usually emerge until the child has acquired 50-100 words in their lexicon. Thereafter, the acquisition of new words accelerates rapidly. As knowledge of grammar increases, there is a proportional increase in verbs, adjectives, and other words that serve to define the relation between objects and people (predicates). By 3 yr, sentence length increases and the child uses pronouns and simple present tense verb forms. These 3-5 word sentences typically have a subject and verb but lack conjunctions, articles, and complex verb forms. The Sesame Street character Cookie Monster ("Me want cookie!") typifies the "telegraphic" nature of the 3 yr old's sentences. By 4-5 yr, children should be able to carry on conversations using adult-like grammatical forms and use sentences that provide details (e.g., "I like to read my books").

Variations of Normal

Language milestones have been found to be largely universal across languages and cultures, with some variations depending on the complexity of the grammatical structure of individual languages. In Italian (where verbs often occupy a prominent position at the beginning or end of sentences), 14 month-olds produce a greater proportion of verbs compared with English speaking infants. Within a given language, development usually follows a fairly predictable pattern, paralleling general cognitive development. Although the sequences are predictable, the exact timing of achievement is not. There are marked variations among normal children in the rate of development of babbling, comprehension of words, production of single words, and use of combinational forms within the first 2-3 yr of life.

Table 35-1 Normal Language Milestones

HEARING AND UNDERSTANDING	TALKING
BIRTH TO 3 MONTHS	
Startles to loud sounds Quiets or smiles when spoken to Seems to recognize your voice and quiets if crying Increases or decreases sucking behavior in response to sound	Makes pleasure sounds (cooing, gooing) Cries differently for different needs Smiles when sees you
4-6 MO	
Moves eyes in direction of sounds Responds to changes in tone of your voice Notices toys that make sounds Pays attention to music	Babbling sounds more speech-like, with many different sounds, including *p*, *b*, and *m* Vocalizes excitement and displeasure Makes gurgling sounds when left alone and when playing with you
7 MO-1 YEAR	
Enjoys games such as peekaboo and pat-a-cake Turns and looks in direction of sounds Listens when spoken to Recognizes words for common items, such as *cup*, *shoe*, and *juice* Begins to respond to requests *(Come here. Want more?)*	Babbling has both long and short groups of sounds, such as *tata upup bibibibi.* Uses speech or noncrying sounds to get and keep attention Imitates different speech sounds Has 1 or 2 words *(bye-bye, Dada, Mama),* although they might not be clear
1-2 YR	
Points to a few body parts when asked Follows simple commands and understands simple questions *(Roll the ball. Kiss the baby. Where's your shoe?)* Listens to simple stories, songs, and rhymes Points to pictures in a book when named	Says more words every month Uses some 1-2 word questions *(Where kitty? Go bye-bye? What's that?)* Puts 2 words together *(more cookie, no juice, mommy book)* Uses many different consonant sounds at the beginning of words
2-3 YR	
Understands differences in meaning (e.g., go–stop, in–on, big–little, up–down) Follows 2-step requests *(Get the book and put it on the table.)*	Has a word for almost everything Uses 2-3 word "sentences" to talk about and ask for things Speech is understood by familiar listeners most of the time Often asks for or directs attention to objects by naming them
3-4 YR	
Hears you when you call from another room Hears television or radio at the same loudness level as other family members Understands simple *who, what, where, why* questions	Talks about activities at school or at friends' homes Usually understood by people outside the family Uses a lot of sentences that have ≥4 words Usually talks easily without repeating syllables or words
4-5 YR	
Pays attention to a short story and answers simple questions about it Hears and understands most of what is said at home and in school	Voice sounds as clear as other children's Uses sentences that include details *(I like to read my books.)* Tells stories that stick to a topic Communicates easily with other children and adults Says most sounds correctly except a few, such as *l, s, r, v, z, ch, sh,* and *th* Uses the same grammar as the rest of the family

Adapted from American Speech-Language-Hearing Association, 2005. http://www.asha.org/public/speech/development/chart.htm.

Two basic patterns of language learning have been identified: "analytic" and "holistic." The analytic pattern is the most common and reflects the mastery of increasingly larger units of language form. As reflected in the previous discussion of milestones, the child's analytic skills proceed from simple to more complex and lengthy forms. Children who follow a holistic or gestalt learning pattern might start by using relatively large chunks of speech in familiar contexts. They might memorize familiar phrases or dialogs from movies or stories and repeat them in an over-generalized fashion. Their sentences often have a formulaic pattern, reflecting inadequate mastery of the use of grammar to flexibly and spontaneously combine words appropriately in the child's own unique utterance. Over time, these children gradually break down the meanings of phrases and sentences into their component parts, and they learn to analyze the linguistic units of these memorized forms. As this occurs, more original speech productions emerge and the child is able to assemble thoughts in a more flexible manner. Both analytic and holistic learning processes are necessary for normal language development to occur.

LANGUAGE AND COMMUNICATION DISORDERS

Epidemiology

Disorders of speech and language are very common in preschool-age children. Nearly 20% of 2 yr olds are thought to have delayed onset of speech. By age 5 yr, approximately 6% of children are identified as having a speech impairment, 5% as having both speech and language impairment, and 8% as having language impairment. Boys are nearly twice as likely to have an identified speech or language impairment as girls.

Etiology

Normal language ability is a complex function that is widely distributed across the brain through interconnected neural networks that are synchronized for specific activities. Although there are clinical similarities between acquired aphasia in adults and childhood language disorders, unilateral, focal lesions acquired in early life do not seem to have the same effects in children as in adults. Risk factors for neurologic injury are absent in the vast majority of children with language impairment.

Genetic factors appear to play a major role in influencing how children learn to talk. Language disorders cluster in families. A careful family history may identify current or past speech or language problems in up to 30% of 1st-degree relatives of proband children. Although children who are exposed to parents with language difficulty might be expected to experience poor language stimulation and inappropriate language modeling, studies of twins have shown the concordance rate for low language test score and/or a history of speech therapy to be approximately 50% in dizygotic pairs, rising to over 90% in

monozygotic pairs. A number of potential gene loci have been identified, but no consistent genetic markers have been established.

The most plausible genetic mechanism involves a disruption in the timing of early prenatal neurodevelopmental events affecting migration of nerve cells from the germinal matrix to the cerebral cortex. Chromosomal lesions and point mutations of the *FOXP2* gene and polymorphisms of the *CNTNAP2* gene are associated with an uncommon but distinct speech and language disorder characterized by difficulties in learning and producing oral movement sequences (childhood apraxia of speech). Affected children have a spectrum of impairment in expressive and receptive language as well as problems understanding grammar.

Pathogenesis

Language disorders are associated with a fundamental deficit in the brain's capacity to process complex information rapidly. Simultaneous evaluation of words (semantics), sentences (syntax), prosody (tone of voice), and social cues can overtax the child's ability to comprehend and respond appropriately in a verbal setting. Limitations in the amount of information that can be stored in verbal working memory can further limit the rate at which language information is processed. Electrophysiologic studies show abnormal latency in the early phase of auditory processing in children with language disorders. Neuroimaging studies identify an array of anatomic abnormalities in regions of the brain that are central to language processing. MRI scans in children with **specific language impairment (SLI)** may reveal white matter lesions, white matter volume loss, ventricular enlargement, focal gray matter heterotopia within the right and left parietotemporal white matter, abnormal morphology of the inferior frontal gyrus, atypical patterns of asymmetry of language cortex, or increased thickness of the corpus callosum in a minority of affected children. Postmortem studies of children with language disorders found evidence of atypical symmetry in the plana temporale and cortical dysplasia in the region of the Sylvian fissure. A high incidence of paroxysmal electroencephalogram (EEG) anomalies during sleep has been identified in children with SLI. Although these findings might represent a mild variant of the Landau-Kleffner syndrome (acquired verbal auditory agnosia), they likely represent an epiphenomenon in which paroxysmal activity is related to architectural dysplasia. In support of a genetic mechanism affecting cerebral development, a high rate of atypical perisylvian asymmetries has also been documented in the parents of children with SLI.

Clinical Manifestations

Primary disorders of speech and language development are often found in the absence of more generalized cognitive or motor dysfunction. Disorders of communication are the most common comorbid condition in persons with generalized cognitive disorders (intellectual disability or autism), structural anomalies of the organs of speech (velopharyngeal insufficiency from cleft palate), and neuromotor conditions affecting oral motor coordination (dysarthria from cerebral palsy or other neuromuscular disorders).

Classification

Each professional discipline has adopted a somewhat different classification system, based on cluster patterns of symptoms. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) organized communication disorders into: (1) language disorder (which combines expressive and mixed receptive-expressive language disorders), speech sound disorder (phonologic disorder), and childhood-onset fluency disorder (stuttering); and (2) social (pragmatic) communication disorder, which is persistent difficulties in the social uses of verbal and nonverbal communication (Table 35-2). In clinical practice, childhood speech and language disorders occur as a number of distinct entities.

Specific Language Impairment

Also referred to as **developmental dysphasia**, or developmental language disorder, SLI is characterized by a significant discrepancy between the child's overall cognitive level (typically nonverbal measures of intelligence) and functional language level. These children also follow an atypical pattern of language acquisition and use. Closer examination of the child's skills might reveal deficits in understanding and use of word meaning (semantics) and grammar (syntax). Often, children with SLI are delayed in starting to talk. Most significantly, they usually have difficulty understanding spoken language. The problem may stem from insufficient understanding of single words or from the inability to deconstruct and analyze the meaning of sentences. Many affected children show a holistic pattern of language development, repeating memorized phrases or dialog from movies or stories (echolalia). In contrast to their difficulty with spoken language, children with SLI appear to learn visually and demonstrate their ability on nonverbal tests of intelligence.

After children with SLI become fluent talkers, they are generally less proficient at producing oral narratives compared with their peers. Their stories tend to be shorter and include fewer propositions, main story ideas, or story grammar elements. Older children include fewer mental state descriptions (e.g., references to what their characters think and how they feel). Their narratives contain fewer cohesive devices and the story line may be difficult to follow.

Although they have difficulty interacting with peers who are more verbally adept, many children with SLI play appropriately with younger or older children. Despite their communication impairment, they engage in pretend play, show imagination, share emotions (affective reciprocity), and demonstrate joint referencing behaviors appropriate to their age. Of note is the high incidence of fine motor coordination difficulty found in these children. A combination of increased joint mobility and mild muscular hypotonia often results in motor clumsiness.

Many children with SLI show difficulties with social interaction, particularly with same-age peers. Social interaction is mediated by oral communication, and a child deficient in communication is at a distinct disadvantage in the social arena. Children with SLI tend to be more dependent on older children or adults, who can adapt their communication to match the child's level of function. Generally, social interaction skills are more closely correlated with language level than with nonverbal cognitive level. Using this as a guide, one usually sees a developmental progression of increasingly more sophisticated social interaction as the child's language abilities improve. In this context, social ineptitude is not necessarily a sign of asocial distancing (e.g., autism) but rather a delay in the ability to negotiate social interactions.

Higher-Level Language Disorder

As children mature, the ability to communicate effectively with others depends on mastery of a range of skills that go beyond basic understanding of words and rules of grammar. Higher-level language skills include the development of advanced vocabulary, the understanding of word relationships, reasoning skills (including drawing correct inferences and conclusions), the ability to understand things from another person's perspective, and the ability to paraphrase and rephrase with ease. In addition, higher-order language abilities include pragmatic skills that serve as the foundation for social interactions. These skills include knowledge and understanding of one's conversational partner, knowledge of the social context in which the conversation is taking place, and general knowledge of the world. Social and linguistic aspects of communication are often difficult to separate, and persons who have trouble interpreting these relatively abstract aspects of communication typically experience difficulty forming and maintaining relationships. DSM-5 Identified Social (Pragmatic) Communication Disorder (SPCD) as a category of communication disorder (Table 35-2). Symptoms of pragmatic difficulty include extreme literalness and inappropriate verbal and social interactions. Proper use and understanding of humor, slang, and sarcasm depend on correct interpretation of the meaning and the context of language and the ability to draw proper inferences. Failure to provide a sufficient referential base to one's conversational partner—to take the perspective of another person—results in the appearance of talking or behaving randomly or incoherently. SPCD often occurs in the context of SLI and autism spectrum disorder (ASD) and it has been recognized as a symptom of a wide range of disorders, including right-hemisphere damage to the

Table 35-2 DSM-5 Diagnostic Criteria for Communication Disorders

Language Disorder	A. Persistent difficulties in the acquisition and use of language across modalities (i.e., spoken, written, sign language, or other) due to deficits in comprehension or production that include the following: 1. Reduced vocabulary (word knowledge and use) 2. Limited sentence structure (ability to put words and word endings together to form sentences based on the rules of grammar and morphology). 3. Impairments in discourse (ability to use vocabulary and connect sentences to explain or describe a topic or series of events or have a conversation). B. Language abilities are substantially and quantifiably below those expected for age, resulting in functional limitations in effective communication, social participation, academic achievement, or occupational performance, individually or in any combination. C. Onset of symptoms is in the early developmental period. D. The difficulties are not attributable to hearing or other sensory impairment, motor dysfunction, or another medical or neurological condition and are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.
Speech Sound Disorder	A. Persistent difficulty with speech sound production that interferes with speech intelligibility or prevents verbal communication of messages. B. The disturbance causes limitations in effective communication that interfere with social participation, academic achievement, or occupational performance, individually or in any combination. C. Onset of symptoms is in the early developmental period. D. The difficulties are not attributable to congenital or acquired conditions, such as cerebral palsy, cleft palate, deafness or hearing loss, traumatic brain injury, or other medical or neurological conditions.
Social (Pragmatic) Communication Disorder	A. Persistent difficulties in the social use of verbal and nonverbal communication as manifested by all of the following: 1. Deficits in using communication for social purposes, such as greeting and sharing information, in a manner that is appropriate for the social context. 2. Impairment of the ability to change communication to match context or the needs of the listener, such as speaking differently in a classroom than on a playground, talking differently to a child than to an adult, and avoiding use of overly formal language. 3. Difficulties following rules for conversation and storytelling, such as taking turns in conversation, rephrasing when misunderstood, and knowing how to use verbal and nonverbal signals to regulate interaction. 4. Difficulties understanding what is not explicitly stated (e.g., making inferences) and nonliteral or ambiguous meanings of language (e.g., idioms, humor, metaphors, multiple meanings that depend on the context for interpretation). B. The deficits result in functional limitations in effective communication, social participation, social relationships, academic achievement, or occupational performance, individually or in combination. C. The onset of the symptoms is in the early developmental period (but deficits may not become fully manifest until social communication demands exceed limited capacities). D. The symptoms are not attributable to another medical or neurological condition or to low abilities in the domains of word structure and grammar, and are not better explained by autism spectrum disorder, intellectual disability (intellectual developmental disorder), global developmental delay, or another mental disorder.

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brain, Williams syndrome, and nonverbal learning disabilities. SPCD can also occur independently of other disorders. In school settings, children with SPCD may be socially ostracized and/or bullied.

Intellectual Disability

Most children with a mild degree of intellectual disability learn to talk at a slower-than-normal rate; they follow a normal sequence of language acquisition and eventually master basic communication skills. Difficulties may be encountered with higher-level language concepts and use. Persons with moderate to severe degrees of intellectual disability can have great difficulty in acquiring basic communication skills. About half of persons with an IQ of <50 are able to communicate using single words or simple phrases; the rest are typically nonverbal.

Autism and Pervasive Developmental Disorders

A disordered pattern of language development is one of the core features of autism and other pervasive developmental disorders (see Chapter 28). The language profile of children with autism is often indistinguishable from that in children with SLIs. The key points of distinction between these conditions are the lack of reciprocal social relationships that characterizes children with autism, limitation in the ability to develop functional, symbolic, or pretend play, and an obsessive need for sameness and resistance to change. Approximately 75-80% of children with autism are also intellectually disabled, and this can limit their ability to develop functional communication skills.

Language abilities can range from absent to grammatically intact, but with limited pragmatic features and/or odd prosody patterns. Some autistic persons have highly specialized, but isolated, "savant" skills, such as calendar calculations and hyperlexia (the precocious ability to recognize written words beyond expectation based on general intellectual ability). Regression in language and social skills (**autistic regression**) occurs in approximately one-third of children with autism, usually before 2 yr of age. No explanation for this phenomenon has been identified. Once the regression has "stabilized," recovery of function does not usually occur (Fig. 35-1).

Asperger Syndrome

(See Chapter 28.2.)

Although sharing many characteristics of autism (deficits in social relatedness and restricted range of interests), individuals with Asperger syndrome typically show normal early language development (syntax and semantics). As they mature, higher-order social and language pragmatic impairments become prominent features of this disorder. Affected children have an unusually circumscribed range of interests, which are all-absorbing and interfere with learning of other skills and with social adaptation. These children may engage in long-winded, verbose monologues about their topics of special interest, with little regard to the reaction of others. Their inflection pattern (prosody) may be inappropriate to the content of their conversation, and they might not adjust their rate of speech or vocal volume to the setting.

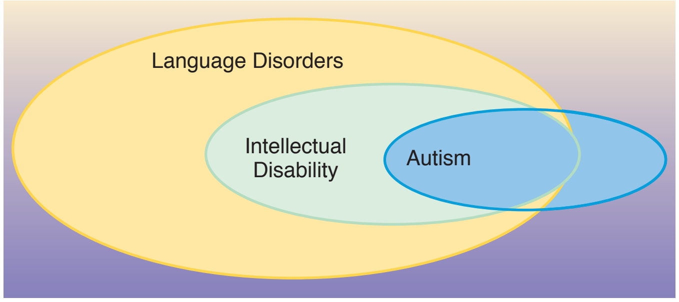

Figure 35-1 Relationship of autism, language disorders, and intellectual disability. *(From Simms MD, Schum RL: Preschool children who have atypical patterns of development,* Pediatr Rev *21:147–158, 2000.)*

Selective Mutism

Selective mutism is defined as a failure to speak in specific social situations despite speaking in other situations, and it is typically a symptom of an underlying **anxiety disorder**. Children with selective mutism can speak normally in certain settings, such as within their home or when they are alone with their parents. They fail to speak in other social settings, such as at school or at other places outside their home. Other symptoms associated with selective mutism can include excessive shyness, withdrawal, dependency on parents, and oppositional behavior. Most cases of selective mutism are not the result of a single traumatic event, but rather are the manifestation of a chronic pattern of anxiety. Mutism is not passive–aggressive behavior. Mute children report that they want to speak in social settings but are afraid to do so. It is important to emphasize that the underlying anxiety disorder is the likely origin of selective mutism. Often, one or both parents of a child with selective mutism has a history of anxiety symptoms, including childhood shyness, social anxiety, or panic attacks. This suggests that the child's anxiety represents a familial trait. For some unknown reason, the child converts the anxiety into the mute symptom. Mutism is highly functional for the child in that it reduces anxiety and protects the child from the perceived challenge of social interaction. Treatment of selective mutism should focus on reducing the general anxiety, rather than focusing only on the mute behaviors (see Chapter 25). Selective mutism reflects a difficulty of social interaction and not a disorder of language processing.

Isolated Expressive Language Disorder

More commonly seen in boys than girls, isolated expressive language disorder (late talker syndrome) is a diagnosis best made in retrospect. These children have age-appropriate receptive language and social ability. Once they start talking, their speech is clear. There is no increased risk for language or learning disability as they progress through school. A family history of other males with a similar developmental pattern is often reported. This pattern of language development likely reflects a variation of normal.

MOTOR SPEECH DISORDERS

Dysarthria

Motor speech disorders can originate from neuromotor disorders such as cerebral palsy, muscular dystrophy, myopathy, facial palsy. The resulting dysarthria affects both speech and nonspeech functions (smiling and chewing). Lack of strength and muscular control manifests as slurring of words and distorting of vowels. Speech patterns are often slow and labored. Poor velopharyngeal function can result in mixed nasal resonance (hyper- or hyponasal speech). In many cases, feeding difficulty, drooling, open mouth posture, and a protruding tongue accompany the dysarthric speech.

Childhood Apraxia of Speech

Difficulty in planning and coordinating movements for speech production can result in inconsistent distortion of speech sounds. The same word may be pronounced differently each time. Intelligibility tends to decline as the length and complexity of the child's speech increases. Consonants may be deleted and sounds transposed. As they try to talk spontaneously, or imitate other's speech, children with childhood apraxia of speech may display oral groping or struggling behaviors. Children with childhood apraxia of speech frequently have a history of early feeding difficulty, limited sound production as infants, and delayed onset of spoken words. They may point, grunt, or develop an elaborate gestural communication system in an attempt to overcome their verbal difficulty. Apraxia may be limited to oral-motor function, or it may be a more generalized problem affecting fine and/or gross motor coordination.

Phonologic Disorder

Children with phonologic speech disorder are often unintelligible, even to their parents. Articulation errors are not the result of neuromotor impairment but seem to reflect an inability to correctly process the words they hear. As a result, they lack understanding of how to fit sounds together properly to create words. In contrast to children with childhood apraxia of speech, those with phonologic disorder are fluent—although unintelligible—and produce a consistent, highly predictable pattern of articulation errors. Children with phonologic speech disorder are at high risk for later reading and learning disability.

HEARING IMPAIRMENT

Hearing loss can be a major cause of delayed or disordered language development (see Chapter 637). Approximately 16-30 per 1,000 children have mild to severe hearing loss, significant enough to affect educational progress. In addition to these "hard of hearing" children, approximately another 1 per 1,000 are deaf (profound bilateral hearing loss). Hearing loss can be present at birth or acquired postnatally. Newborn screening programs can identify many forms of congenital hearing loss, but children can develop progressive hearing loss or acquire deafness after birth.

The most common types of hearing loss are attributable to conductive (middle ear) or sensorineural deficit. Although it is not possible to accurately predict the impact of hearing loss on a child's language development, the type and degree of hearing loss, the age of onset, and the duration of the auditory impairment clearly play important roles. Children with significant hearing impairment often have problems developing facility with language and often have related academic difficulties. Presumably, the language impairment is caused by lack of exposure to fluent language models starting in infancy.

Approximately 30% of hearing-impaired children have at least one other disability that affects development of speech and language (e.g., intellectual disability, cerebral palsy, craniofacial anomalies). Any child who shows developmental warning signs of a speech or language problem should have a hearing assessment by an audiologist and an examination by a geneticist as part of a comprehensive evaluation.

HYDROCEPHALUS

Some children with hydrocephalus may be described as having "cocktail-party syndrome." Although they may use sophisticated words, their comprehension of abstract concepts is limited, and their pragmatic conversational skills are weak. As a result, they speak superficially about topics and appear to be carrying on a monologue (see Chapter 591.11).

RARE CAUSES OF LANGUAGE IMPAIRMENT

Hyperlexia

Hyperlexia is the precocious development of reading single words that spontaneously occurs in some young children (ages 2-5 yr) without specific instruction. It is often associated with children who have a pervasive developmental disorder (see Chapter 30) or SLI. It stands in contrast to precocious reading development in young children who do not have any other developmental disorders. Hyperlexia is a variation seen in young children with disordered language who do not have the social deficits or restricted or repetitive behaviors associated with autism. A typical manifestation is for a child with SLI to orally read single words, or match pictures with single words. Although hyperlexic children show early and well-developed word-decoding skills, they

usually have no precocious ability for comprehension of text. Rather, text comprehension is closely intertwined with oral comprehension, and children who have difficulty decoding the syntax of language are also at risk for having reading comprehension problems.

Landau-Kleffner Syndrome (Verbal Auditory Agnosia)

Children with Landau-Kleffner syndrome have a history of normal language development until they experience a regression in their ability to comprehend spoken language (verbal auditory agnosia). The regression may be sudden or gradual, and it usually occurs between 3 and 7 yr of age. Expressive language skills typically deteriorate, and some children may become mute. Despite their language regression, these children typically retain appropriate play patterns and the ability to interact in a socially appropriate manner. An EEG might show a distinct pattern of status epilepticus in sleep (continuous spike wave in slow-wave sleep), and up to 80% of children with this condition eventually exhibit clinical seizures. A number of treatment approaches have been reported, including antiepileptic medication, steroids, and intravenous gamma globulin, with varying results. The prognosis for return of normal language ability is uncertain, even with resolution of the EEG abnormality. Epileptic interictal discharges are more frequently found on EEGs of children with language impairments than in otherwise normally developing children, even in those without any history of language regression. However, this phenomenon is believed to represent a manifestation of an underlying disorder of brain structure or function that is distinct from the language impairment, as there has been little evidence of improvement in language function when the EEG was normalized after administration of antiepileptic medication. Unless there is a clear pattern of either seizure symptoms or regression in language ability, a routine EEG is not recommended as part of the evaluation for a child with speech and/or language impairment.

Metabolic and Neurodegenerative Disorders

(See also Part XI.)

Regression of language development may accompany loss of neuromotor function at the outset of a number of metabolic diseases including lysosomal storage disorders (metachromatic leukodystrophy), peroxisomal disorders (adrenal leukodystrophy), ceroid lipofuscinosis (Batten disease), and mucopolysaccharidosis (Hunter disease, Hurler disease). Recently, creatine transporter deficiency was identified as an X-linked disorder that manifests with language delay in boys and mild learning disability in female carriers.

Screening

Developmental surveillance at each well child visit should include specific questions about normal language developmental milestones and observations of the child's behavior. Clinical judgment, defined as eliciting and responding to parents' concerns, can detect the majority of children with speech and language problems. Many clinicians employ standardized developmental screening questionnaires and observation checklists designed for use in a pediatrics office (see Chapter 14).

The U.S. Preventive Services Task Force reviewed screening instruments for speech and language delays in young children that can be used in primary care settings. The Task Force focused on brief measures that require <10 min to complete. There was insufficient evidence that screening instruments are more effective than using physician's clinical observations and parents' concerns to identify children who require further evaluation. The Task Force noted that there is no single gold standard for screening, owing to inconsistent measures and terminology, and did not recommend the use of screening instruments. Furthermore, the Task Force determined that the use of formal measures was not time or cost efficient and deferred to pediatrician's and parents' concerns as indicators of potential problems. Table 35-3 offers guidelines for raising concerns and referring a child for specialized speech and language evaluation. Because of the high prevalence of speech and language disorders in the general population, referral to a speech-language pathologist for further evaluation should be made whenever there is a suspicion of delay.

NONCAUSES OF LANGUAGE DELAY

Twinning, birth order, "laziness," exposure to multiple languages (bilingualism), tongue-tie, or otitis media are not adequate explanations for significant language delay. Normal twins learn to talk at the same age as normal single-born children, and birth order effects on language development have not been consistently found. The drive to communicate and the rewards for successful verbal interaction are so strong that children who let others talk for them usually can't talk for themselves and are not "lazy." Toddlers exposed to more than 1 language can show a mild delay in starting to talk, and they can initially mix elements (vocabulary and syntax) of the different languages they are learning (code switching). However, they learn to segregate each language by 24-30 mo and are equal to their monolingual peers by 3 yr of age. An extremely tight lingual frenulum (tongue-tie) can affect feeding and speech articulation, but does not prevent the acquisition of language abilities. Finally, prospective studies show that frequent ear infections and/or serous otitis media in early childhood does not result in persisting language disorder.

Diagnostic Evaluation

It is important to distinguish developmental delay (abnormal timing) from developmental disorder (abnormal patterns or sequences). A child's language and communication skills must also be interpreted within the context of the child's overall cognitive and physical abilities. Finally, it is important to evaluate the child's use of language to communicate with others in the broadest sense (communicative intent). Thus, a multidisciplinary evaluation is often warranted. At a minimum this should include psychologic evaluation, neurodevelopmental pediatric assessment, and speech and language examination.

Psychologic Evaluation

There are 2 main goals for the psychologic evaluation of a young child with a communication disorder. Nonverbal cognitive ability must be assessed to determine if the child has an intellectually disability, and the child's social behaviors must be assessed to determine whether

Table 35-3 Speech and Language Screening

REFER FOR SPEECH–LANGUAGE EVALUATION IF:		
AT AGE	**RECEPTIVE**	**EXPRESSIVE**
15 mo	Does not look/point at 5-10 objects	Is not using 3 words
18 mo	Does not follow simple directions ("get your shoes")	Is not using Mama, Dad, or other names
24 mo	Does not point to pictures or body parts when they are named	Is not using 25 words
30 mo	Does not verbally respond or nod/shake head to questions	Is not using unique 2-word phrases, including noun–verb combinations
36 mo	Does not understand prepositions or action words; does not follow 2-step directions	Has a vocabulary of <200 words; does not ask for things; echolalia to questions; language regression after attaining 2-word phrases

autism spectrum disorder (ASD) is present. Additional diagnostic considerations may include emotional disorders such as anxiety, depression, mood disorder, obsessive-compulsive disorder, academic learning disorders, and attention-deficit/hyperactivity disorder (ADHD).

Cognitive Assessment

Intellectual disability is defined as deficits in cognitive abilities and adaptive behaviors. In this context, children with intellectual disability show delayed development of communication skills; however, delayed communication does not necessarily signal intellectual disability. Therefore, a broad-based cognitive assessment is an important component to the evaluation of children with language delays, including evaluation of both verbal and nonverbal skills. If a child has intellectual disability, both verbal and nonverbal scores will be low compared to norms (≤2nd percentile). In contrast, a typical cognitive profile for a child with SLI includes a significant difference between nonverbal and verbal abilities, with nonverbal IQ being greater than verbal IQ and the nonverbal score within an average range.

Evaluation of Social Behaviors

Social interest is the key difference between children with a primary language disorder (SLI) and those with a communication disorder secondary to ASD. Children with SLI have an interest in social interaction, but they may have difficulty enacting their interest because of their limitations to communication. In contrast, autistic children show little social interest. Four key nonverbal behaviors that are often shown by children with SLI—but not autistic children (especially toddlers and preschoolers)—are joint attention, affective reciprocity, pretend play, and direct imitation.

Relationship of Language and Social Behaviors to Mental Age

Cognitive assessment provides a mental age for the child, and the child's behavior must be evaluated in that context. Most 4 yr old children typically engage peers in interactive play, but most 2 yr olds are playful but primarily focused on interactions with adult caretakers. A 4 yr old with mild to moderate intellectual disability and a mental age of 2 yr might not play with peers yet because of cognitive limitation, not a lack of desire for social interaction.

Speech and Language Evaluation

A certified speech-language pathologist should perform a speech and language evaluation. A typical evaluation includes assessment of language, speech, and the physical mechanisms associated with speech production. Both expressive and receptive language is assessed by a combination of standardized measures and informal interactions and observations. All components of language are assessed, including syntax, semantics, pragmatics, and fluency. Speech assessment similarly uses a combination of standardized measures and informal observations. Assessment of physical structures includes oral structures and function, respiratory function, and vocal quality. In many settings, a speech-language pathologist works in conjunction with an audiologist, who can do appropriate hearing evaluation of the child. If an audiologist is not available in that setting, then a separate referral should be made. No child is too young for a speech and language or hearing evaluation. A referral for evaluation is appropriate whenever there is suspicion of language impairment.

Medical Evaluation

As in any developmental disorder, careful history and physical examination should focus on the identification of potential contributors to the child's language and communication difficulties. A family history of delay in talking, need for speech and language therapy, or academic difficulty can suggest a genetic predisposition to language disorders. Pregnancy history might reveal risk factors for prenatal developmental anomalies, such as polyhydramnios or decreased fetal movement patterns. Small size for gestational age at birth, symptoms of neonatal encephalopathy, or early and persistent oral-motor feeding difficulty may presage speech and language difficulty. Developmental history should focus on the age at which various language skills were mastered and the sequences and patterns of milestone acquisition. Regression or loss of acquired skills should raise immediate concern.

Physical examination should include measurement of height (length), weight, and head circumference. The skin should be examined for lesions consistent with phakomatosis (e.g., tuberous sclerosis, neurofibromatosis, Sturge-Weber syndrome) and other disruptions of pigment (hypomelanosis of Ito). Anomalies of the head and neck, such as white forelock and hypertelorism (Waardenburg syndrome), ear malformations (Goldenhar syndrome), facial and cardiac anomalies (Williams syndrome, velocardiofacial syndrome), retrognathism of the chin (Pierre-Robin anomaly), or cleft lip and/or palate, are associated with hearing and speech abnormalities. Neurologic examination might reveal muscular hypertonia or hypotonia, both of which can affect neuromuscular control of speech. Generalized muscular hypotonia, with increased range of motion of the joints, is commonly seen in children with SLI. The reason for this association is not clear but it might account for the fine and gross motor clumsiness often seen in these children. However, mild hypotonia is not a sufficient explanation for the impairments of expressive and receptive language.

No routine diagnostic studies are indicated for SLI or isolated language disorders. When language delay is a part of a generalized cognitive or physical disorder, referral for further genetic evaluation, chromosome testing (including high resolution banding karyotype, fragile X testing, and microarray comparative genomic hybridization), neuroimaging studies, and EEG may be considered, if clinically indicated.

TREATMENT

Laws emanating from the federal Individuals with Disabilities Education Act (IDEA) require that schools provide special education services to children who have learning difficulties. This includes children with speech and language disorders. Services are provided to children from birth through 21 yr of age. States have various methods for providing services, and for young children these can include Birth-to-Three, Early Childhood, and Early Learning programs. These programs provide speech–language therapy as part of public education, in conjunction with other special education resources. Children can also receive therapy from nonprofit service agencies, hospital and rehabilitation centers, and speech pathologists in private practice.

Of concern is the fact that many children with identified speech and language deficits do not receive appropriate intervention services. Population-based surveys in both the United States and Canada have found that less than half of children identified by kindergarten entry receive speech and language interventions, even when their parents have been educated about the nature of their child's condition. In one study, children with deficits in speech–sound production were much more likely to receive services (41%) than those who had problems with language alone (9%). These findings are troubling because poor educational outcome, especially in reading, social and behavioral adjustment, are more highly associated with language than with speech–sound disorders. Therefore, the children at greatest risk are least likely to receive intervention services. Boys were twice as likely to receive speech intervention as girls, regardless of their speech–language diagnosis. Social and demographic factors did not appear to influence whether identified children received interventions services.

Speech–language therapy includes a variety of goals. Sometimes both speech and language activities are incorporated in therapy. The speech goals focus on development of more intelligible speech. Language goals can focus on expanding vocabulary (lexicon) and understanding of the meaning of words (semantics), improving syntax by using proper forms or learning to expand single words into sentences, and social use of language (pragmatics). Therapy can include individual sessions, group sessions, and mainstream classroom integration. Individual sessions may use drill activities for older children or play activities for younger children to target specific goals. Group sessions can include several children with similar language goals to help them practice peer communication activities and to help them bridge the gap into more naturalistic communication situations. Classroom

integration might include the therapist team-teaching or consulting with the teacher to facilitate the child's use of language in common academic situations.

For children with severe language impairment, alternative methods of communication are often included in therapy. These may include use of manual sign language, use of pictures (e.g., Picture Exchange Communication System), and computerized devices for speech output. Often the ultimate goal is to achieve better spoken language. Early use of signs or pictures can help the child to establish better functional communication and help the child to understand the symbolic nature of words to facilitate the language process. There is no evidence that use of signs or pictures interferes with development of oral language if the child has the capacity to speak. Many clinicians believe that these alternative methods accelerate the learning of language. They also reduce frustration of parents and children who cannot communicate for basic needs.

Parents can consult with their child's speech-language therapist about home activities to enhance language development and extend therapy activities through appropriate language-stimulating activities and recreational reading. Parents' language activities should focus on emerging communication skills that are within the child's repertoire, rather than teaching the child new skills. The speech pathologist can guide parents on effective modeling and eliciting communication from their child.

Recreational reading focuses on expanding the child's comprehension of language. Sometimes the child's avoidance of reading is a sign that the parent is presenting material that is too complex for the child. The speech-language therapist can guide the parent in selecting an appropriate level of reading material.

PROGNOSIS

Children with isolated expressive language disorder ("late talkers") have an excellent prognosis for both language, learning, and social–emotional adjustment.

Over time, children with SLI respond to therapeutic/educational interventions and show a trend toward improvement of communication skills. Adults with a history of childhood language disorder continue to show evidence of impaired language ability, even when surface features of the communication difficulty have improved considerably. This suggests that many persons find successful ways of adapting to their impairment. Although the majority of children improve their communication ability with time, 50-80% of preschoolers with language delay and normal nonverbal intelligence continue to experience difficulty with language and social development up to 20 yr beyond the initial diagnosis. Language disorders often interfere with the child's ability to conceptualize the increasingly complex and ambiguous worlds of social relationship and emotions. As a consequence, in later childhood and adolescence, children with persisting symptoms of SLI are about twice as likely as their typical language peers to show clinical levels of emotional problems and twice as likely to show behavioral difficulties. A Danish study found that adults with SLI were less likely to have completed formal education beyond high school and to have lower occupational and socioeconomic success than the general population. Fifty-six percent held a paid job (vs 84% of the same age general population), of which 35% were unskilled and 40% were skilled workers. Eighty percent of the adults reported having had difficulty reading while in school and most had received remedial teaching, and 50% continued to report reading difficulty as adults (compared with 5% of Danish adults). Lower non-verbal intelligence and comorbid psychiatric and/or neurologic disorders independently contributed to a worse prognosis. These results were consistent with previous reports of adult outcomes of children with SLI from Canada and the United Kingdom.

Academic Disorders

Early language difficulty is strongly related to later reading disorder. Approximately 50% of children with early language difficulty develop reading disorder, and 55% of children with reading disorder have a history of impaired early oral language development. By the time they enter kindergarten, many children with early language deficits may have improved significantly, and they may begin to show early literacy skills, identifying and sounding out letters. However, as they progress through school, they are often unable to keep up with the increasing demands for both oral and written language. Despite their ability to read words, these children lack oral and reading comprehension and struggle with a wide range of academic subjects. This "illusory recovery" of early language skill may result in children losing speech–language services or other special education support in early grades only to be identified later with academic problems. In addition, children with subtle, but persisting language impairments may appear inattentive or anxious in language-rich classroom environments and be misdiagnosed as having an attention disorder.

A study from Australia found that at 7-9 yr of age, children with communication impairments were reported by their parents and teachers to be making slower progress in reading, writing, and overall school achievement than other children their age. The children reported a higher incidence of bullying, poorer peer relationships, and less overall enjoyment of school than their typically developing peers.

COMORBID DISORDERS

Emotional and Behavioral Difficulty

Early language disorder, particularly difficulty with auditory comprehension, appears to be a specific risk factor for later emotional dysfunction. Boys and girls with language disorder have a higher than expected rate of anxiety disorder (principally social phobia). Boys with language disorder are more likely to develop symptoms of ADHD, conduct disorder, and antisocial personality disorder compared with normally developing peers. Language disorders are common in children referred for psychiatric services, but they are often underdiagnosed, and their impact on children's behavior and emotional development is often overlooked.

Preschoolers with language difficulty commonly express their frustration through anxious, socially withdrawn, or aggressive behavior. As their ability to communicate improves, parallel improvements are usually noted in their behavior, suggesting a cause-and-effect relationship between language and behavior. However, the persistence of emotional and behavioral problems over the life span of persons with early language disability suggests a strong biologic or genetic connection between language development and subsequent emotional disorders.

The full impact of environmental and education support on these emotional and behavioral difficulties is not known at this time, but many children with SLI need psychologic support. Efforts should be made to support the child's resilience, emotional competency, and coping abilities. Parents and teachers should be encouraged to strengthen the child's prosocial behavior and to reduce noncompliant and aggressive behaviors.

Motor and Coordination Delays

Approximately one-third to one-half of children with speech and/or language disorders have some degree of motor coordination impairment that may have an important impact on their ability to carry out activities of daily living (dressing, eating, and bathing), school tasks (writing, drawing, coloring), and social/recreational activities (participation in sports and other playground activities). Motor difficulties are not related to the type of language impairment (i.e., they are found in both children with only receptive delays and in those with both expressive and receptive delays). The patterns of motor difficulties seen in children with language impairments are not distinctly "abnormal" and the motor profiles of children with language impairments resemble those of younger children, suggesting that they result from delayed maturation of motor development rather than from a neurologic impairment. Several researchers have postulated that language impairments and motor difficulties may have a common neurodevelopmental basis. Because attention may be focused on the child's language delays, the need for intervention and support for the child's comorbid motor impairment may be overlooked.

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35.1 Childhood-Onset Fluency Disorder: Dysfluency (Stuttering, Stammering)

Kenneth L. Grizzle

Fluent speech requires timely synchronization of phonatory and articulatory muscle groups. There is also an important interaction between speech and language skills. Stuttering involves involuntary frequent repetitions, lengthenings (prolongations) or arrests (blocks, pauses) of syllables, or sounds that are exacerbated by emotionally or syntactically demanding speech. The World Health Organization's definition of *stuttering* is a disorder in the rhythm of speech in which the person knows precisely what he or she wishes to say but at the same time may have difficulty saying it because of an involuntary repetition, prolongation, or cessation of sound. Table 35-4 describes the DSM-5 definition. Stuttering often leads to frustration and avoidance of speaking situations. Stuttering can lead to being bullied or teased and to speech-related anxiety and social phobia.

EPIDEMIOLOGY AND ETIOLOGY

Stuttering usually begins at 2-4 yr of age and is seen more often in boys (4 : 1). Approximately 3-5% of preschool children stutter to some degree; only 0.7-1% of young adults stutter. Stuttering is common in families. Genetic studies suggest genes located on chromosome 12. Stuttering may occur suddenly and often begins when word combinations are involved. Higher vocabulary at age 2 yr and higher material education may also be associated with stuttering. Girls and those with a family history of recovery are most likely to have spontaneous recovery by adolescence. This recovery is not related to the severity of the stuttering. Approximately 75% of boys stop stuttering by adolescence; approximately 90% of girls stop by adolescence.

Adolescent/young adult onset stuttering may be related to central nervous system pathology. In contrast to childhood onset, adolescents may have dysfluency with each word whereas childhood onset usually manifests stuttering on the first word or syllable of a phrase.

Stuttering may be caused by impaired timing between areas of the brain involved in language preparation and execution. Adults who stutter and those with fluent speech activate similar areas of the brain. In addition, adults who stutter overactivate parts of the motor cortex and cerebellar vermis, show right-sided laterality, and have no auditory activation on hearing their own speech.

DIAGNOSIS

Stuttering must be differentiated from the normal developmental dysfluency of preschool children (Tables 35-5 and 35-6). Developmental dysfluency is characterized by brief periods of stuttering that resolve by school age, and it usually involves whole words, with <10 dysfluencies per 100 words. Table 35-4 lists the DSM-5 diagnostic criteria for stuttering. Stuttering often improves while singing, reading aloud, or talking to pets or toys. It increases in intensity with anxiety-inducing situations such as reading or speaking in public or on the phone. Some children who stutter develop behavior routines such as eye blinking, grimacing, head turning, and arm or neck movements. Stuttering that persists and is associated with tics may be a manifestation of **Tourette syndrome** (see Chapters 24.1 and 597.4). Additional disorders in the

Table 35-4 Childhood-Onset Fluency Disorder (Stuttering)

Diagnostic Criteria

A. Disturbances in the normal fluency and time patterning of speech that are inappropriate for the individual's age and language skills, persist over time, and are characterized by frequent and marked occurrences of one (or more) of the following:
   1. Sound and syllable repetitions.
   2. Sound prolongations of consonants as well as vowels.
   3. Broken words (e.g., pauses within a word).
   4. Audible or silent blocking (filled or unfilled pauses in speech).
   5. Circumlocutions (word substitutions to avoid problematic words).
   6. Words produced with an excess of physical tension.
   7. Monosyllabic whole-word repetitions (e.g., "I-I-I-I see him").

B. The disturbance causes anxiety about speaking or limitations in effective communication, social participation, or academic or occupational performance, individually or in any combination.

C. The onset of symptoms is in the early developmental period. (Note: Later-onset cases are diagnosed as 307.0 [F98.5] adult-onset fluency disorder.)

D. The disturbance is not attributable to a speech-motor or sensory deficit, dysfluency associated with neurological insult (e.g., stroke, tumor, trauma), or another medical condition and is not better explained by another mental disorder.

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Table 35-5 Differences Between Stuttering and Developmental Dysfluency

BEHAVIOR	STUTTERING	DEVELOPMENTAL DYSFLUENCY
Frequency of syllable repetition per word	≥2	≤1
Tempo	Faster than normal	Normal
Airflow	Often interrupted	Rarely interrupted
Vocal tension	Often apparent	Absent
Frequency of prolongations per 100 words	≥2	≤1
Duration of prolongation	≥2 sec	≤1 sec
Tension	Often present	Absent
Silent pauses within a word	May be present	Absent
Silent pauses before a speech attempt	Unusually long	Not marked
Silent pauses after the dysfluency	May be present	Absent
Articulating postures	May be inappropriate	Appropriate
Reaction to stress	More broken words	No change in dysfluency
Frustration	May be present	Absent
Eye contact	May waver	Normal

Adapted with permission from Van Riper C: The nature of stuttering, *Englewood Cliffs, NJ, Prentice-Hall, 1971, p 28. From Lawrence M, Barclay DM III: Stuttering: a brief review,* Am Fam Physician *57:2175–2178, 1998.*

Table 35-6	Examples of Normal Dysfluency in Preschoolers
TYPE OF DYSFLUENCY	**EXAMPLES**
Voiced repetitions	Occasionally 2 word parts *(mi…milk)* Single-syllable words *(I…I see you)* Multisyllabic words *(Barney…Barney is coming!)* Phrases *(I want…I want Elmo.)*
Interjections	*We went to the…uh…cottage.*
Revisions: incomplete phrases	*I lost my.…Where is Daddy going?*
Prolongations	*I am Toooommy Baker.*
Tense pauses	Lips together, no sound produced

From Costa D, Kroll R: Stuttering: an update for physicians, CMAJ *162:1849–1855, 2000.*

differential diagnosis include hearing impairment, medication effects, cluttering, and in adolescent onset stuttering, central nervous system disorders.

TREATMENT

Preschool children with normal developmental dysfluency (see Table 35-6) can be observed with parental education and reassurance. Parents should not reprimand the child or create undue anxiety. Preschool or older children with stuttering should be referred to a speech pathologist. Therapy is most effective if started during the preschool period. In addition to the risks noted in Table 35-4, indications for referral include 3 or more dysfluencies per 100 syllables (*b-b-but; th-th-the; you, you, you*), avoidances or escapes (pauses, head nod, blinking), discomfort or anxiety while speaking, and suspicion of an associated neurologic or psychotic disorder.

Most preschool children respond to interventions taught by speech pathologists and to behavioral feedback by parents. Parents should not yell at the child, but should calmly praise periods of fluency ("That was smooth") or nonjudgmentally note episodes of stuttering ("That was a bit bumpy"). The child can be involved with self-correction and respond to requests ("Can you say that again?") made by a calm parent. Such treatment greatly improves dysfluency but it may never be completely eliminated.

Adolescents and adults have also been treated (off label) with risperidone or olanzapine with varying but usually positive results if behavioral speech therapy is unsuccessful. Speech therapy in adolescents may be different from that in young children and involves speech restructuring with the development of a new speech pattern.

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Chapter 36

Intellectual Disability

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Intellectual disability refers to a group of disorders that have in common deficits of adaptive and intellectual function and an age of onset before maturity is reached.

DEFINITION

Contemporary conceptualizations of intellectual disability emphasize functioning and social interaction rather than test scores. The definitions of intellectual disability by the World Health Organization International Classification of Diseases, Individuals with Disabilities Education Act (IDEA), the American Psychiatric Association (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [DSM-5]) and the American Association on Intellectual and Developmental Disabilities (AAIDD) all include significant impairment in general intellectual function, social skills, and adaptive behavior. This focus on the conceptual, social, and practical enables the development of individual treatment plans designed to enhance functioning. Consistent across these definitions is onset of symptoms before age 18 yr or adulthood or during childhood, even if the diagnosis is made later in life.

Significant impairment in general intellectual function refers to performance on an individually administered test of intelligence that is approximately 2 SD below the mean. For a test that has a mean of 100 and SD of 15, IQ scores below 70 would meet these criteria. If the standard error of measurement is considered, the upper limits of subaverage intellectual function may extend to an IQ of 75. Using a score of 75 to delineate intellectual disability might double the number of children with intellectual disability, but the requirement for impairment of adaptive skills limits the false positives. Children with intellectual disability often show a variable pattern of strengths and weaknesses. Not all of their partial scores on IQ tests fall into the significantly subaverage range.

Significant impairment in adaptive behavior reflects the degree that the cognitive dysfunction impairs daily function. Adaptive behavior refers to the skills that are required for people to function in their everyday lives. The AAIDD and DSM-5 classifications of adaptive behavior addresses 3 broad sets of skills: conceptual, social, and practical. Conceptual skills include language, reading and writing, money concepts, and self-direction. Social skills include interpersonal skills, personal responsibility, self-esteem, gullibility, naiveté, and ability to follow rules, obey laws, and avoid victimization. Representative practical skills are performance of activities of daily living (dressing, feeding, toileting and bathing, mobility), instrumental activities of daily living (e.g., housework, managing money, taking medication, shopping, preparing meals, using the telephone), occupational skills, and the maintenance of a safe environment. For a deficit in adaptive behavior to be present, a significant delay in 1 of the 3 areas must be present. The rationale for requiring only 1 of the 3 areas is the empirically derived finding that people with intellectual disability can have varying patterns of ability and may not have deficits in all 3 areas.

The requirement for adaptive behavior deficits is the most controversial aspect of the diagnostic formulation. The controversy centers on 2 broad areas: whether impairments in adaptive behavior are necessary for the construct of intellectual disability and what to measure. The adaptive behavior criterion may be irrelevant for many children; adaptive behavior is impaired in virtually all children who have IQ scores <50. The major utility of the adaptive behavior criterion is to confirm intellectual disability in children with IQ scores in the 65-75 range. It should be noted that deficits in adaptive behavior are often found in disorders such as autism spectrum disorders (see Chapter 30) and attention-deficit/hyperactivity disorder (ADHD) (see Chapter 33) in the presence of typical intellectual function.

The issues of measurement are important as well. The independence of the 3 domains of adaptive behavior has not been validated with research. The relationship between adaptive behavior and IQ performance is insufficiently explored. Most adults with mild intellectual disability do not have significant impairments in practical skills. It should be noted that adaptive behavior deficits must be distinguished from maladaptive behavior (e.g., aggression, inappropriate sexual contact).

Onset before age 18 yr or adulthood distinguishes dysfunctions that originate during the developmental period. The diagnosis of intellectual disability may be made after 18 yr of age or childhood, but the cognitive and adaptive dysfunction must have been manifested before age 18 or adulthood (e.g., during "childhood").

The term **mental retardation** should be cast aside because it is stigmatizing, has been used to limit the achievements of the individual, and has not met its initial objective of providing assistance to people with the disorder. The term **intellectual disability** is increasingly used

Table 36-1 Identification of Cause in Children with Severe Intellectual Disability

CAUSE	EXAMPLES	PERCENT OF TOTAL
Chromosomal disorder	Trisomies 21, 18, 13, Deletion 1p36 Klinefelter syndrome Wolf Hirschhorn syndrome	~20
Genetic syndrome	Fragile X syndrome Prader-Willi syndrome Rett syndrome	~20
Nonsyndromic autosomal mutations	Variations in copy number, de novo mutations in *SYNGAP1*, *GRIK2*, *TUSC3*, oligosaccharyl transferase, and others	~10
Developmental brain abnormality	Hydrocephalus ± meningomyelocele, lissencephaly	~8
Inborn errors of metabolism or neurodegenerative disorder	PKU, Tay-Sachs, various storage diseases	~7
Congenital infections	HIV, toxoplasmosis, rubella, CMV, syphilis, herpes simplex	~3
Familial intellectual disability	Environment, syndromic, or genetic	~5
Perinatal causes	HIE, meningitis, IVH, PVL, fetal alcohol syndrome	4
Postnatal causes	Trauma (abuse), meningitis, hypothyroidism	~4
Unknown	Cerebral palsy	20

CMV, Cytomegalovirus; HIE, hypoxic ischemic encephalopathy; HIV, human immunodeficiency virus; IVH, intraventricular hemorrhage; PKU, phenylketonuria; PVL, periventricular leukomalacia.

Modified from Stromme P, Hayberg G: Aetiology in severe and mild mental retardation: a population based study of Norwegian children, Dev Med Child Neurol *42:76–86, 2000.*

in its place, but has not been adopted universally. In the United States, some existing laws and their attendant entitlements still use the term mental retardation. In Europe, the term **learning disability** is often used to describe intellectual disability. **Global developmental delay** is a term often used to describe young children whose limitations have not yet resulted in a formal diagnosis of intellectual disability; it is often inappropriately used beyond the point when it is clear the child has intellectual disability, usually age 3 yr. Developmental delay is a classification that may be used by IDEA until age 9 yr.

ETIOLOGY

There appear to be 2 overlapping populations of children with intellectual disability: mild (IQ 50-70), which is more associated with environmental influences, and severe (IQ <50), which is more frequently linked to biologic and genetic causes. Mild intellectual disability is 4 times more likely to be found in the offspring of women who have not completed high school than in women who have graduated. This is presumably a consequence of both genetic (children can inherit an intellectual impairment) and socioeconomic (poverty, malnutrition) factors. The specific causes of mild intellectual disability are identifiable in <50% of affected individuals. The most common biologic causes of mild intellectual disability include genetic or chromosomal syndromes with multiple, major, or minor congenital anomalies (velocardiofacial syndrome, Williams syndrome, Noonan syndrome), intrauterine growth restriction, prematurity, perinatal insults, intrauterine exposure to drugs of abuse (including alcohol), and sex chromosomal abnormalities. Familial clustering is common.

In children with severe intellectual disability, a biologic cause (most commonly prenatal) can be identified in more than 75% of cases. Causes include chromosomal (e.g., Down syndrome Wolf-Hirschhorn syndrome, deletion 1p36 syndrome) and other genetic and epigenetic disorders (e.g., fragile X syndrome, Rett syndrome, Angelman and Prader-Willi syndromes), abnormalities of brain development (e.g., lissencephaly), and inborn errors of metabolism or neurodegenerative disorders (e.g., mucopolysaccharidoses) (Table 36-1). Nonsyndromic severe intellectual disability may be a result of inherited or de novo gene mutations, as well as microdeletions or microduplications not detected on standard chromosome analysis. More than 400 genes may be associated with nonsyndromic intellectual disability, with many detected by exomic sequencing. These de novo point mutations may also cause other phenotype features such as seizures or autism; the absence of these features suggests more pleotropic manifestations of genetic mutations. Consistent with the finding that disorders that alter early embryogenesis are the most common and severe, the earlier the problem occurs in development, the more severe its consequences tend to be.

EPIDEMIOLOGY

The prevalence of intellectual disability depends on the definition, the method of ascertainment, and the population. According to statistics, 2.5% of the population should have intellectual disability, and 75% of these individuals should fall into the mild to moderate range. Rates vary across populations. Globally, the prevalence of intellectual disability has been estimated to be approximately 16.41/1,000 persons in low income countries, approximately 15.94/1,000 for middle-income countries, and approximately 9.21/1,000 in high-income countries. Overall, intellectual disability occurs more in boys than in girls: 2 : 1 in mild intellectual disability and 1.5 : 1 in severe intellectual disability. In part this may be a consequence of the many X-linked disorders associated with intellectual disability, the most prominent being fragile X syndrome (see Chapter 81.5).

In 2009-2010 in the United States, approximately 463,000 or 0.9% of school-age children received services for intellectual disability in federally supported school programs. For several reasons, fewer children than predicted are identified as having mild intellectual disability. Because it is more difficult to diagnose mild intellectual disability than the more severe forms, professionals might defer the diagnosis and give the benefit of the doubt to the child. Other reasons that contribute to the discrepancy are use of instruments that underidentify young children with mild intellectual disability (Chapter 30), some children being diagnosed as having autism spectrum disorders and their intellectual disability not addressed, and a disinclination to make the diagnosis in poor or minority students because of previous overdiagnosis.

Young children might show cognitive limitations without significant delays in adaptive behavior. As a result, new cases of mild intellectual disability continue to be diagnosed among children up to 9 yr of age. Children with intellectual disability also may be incorporated into another diagnosis (e.g., autism, cerebral palsy). Furthermore, it

is possible that the number of children with mild intellectual disability is actually decreasing as a result of public health and education measures to prevent prematurity and provide early intervention and head start programs. In fact, the number of school children who receive services for intellectual disability has decreased since 1999, but if developmental delay is included, the numbers have not changed appreciably.

Unlike mild intellectual disability, where the prevalence may be decreasing, the occurrence of severe intellectual disability has not changed appreciably since the 1940s and is 0.3-0.5% of the population. Many of the causes of severe intellectual disability involve genetic or congenital brain malformations that can neither be anticipated nor treated at present. In addition, new populations with severe intellectual disability have offset the decreases in the prevalence of severe intellectual disability that have resulted from improved healthcare. Although prenatal diagnosis and subsequent pregnancy terminations have resulted in a decreased prevalence of Down syndrome (see Chapter 81), and newborn screening with early treatment has virtually eliminated intellectual disability caused by phenylketonuria and congenital hypothyroidism, an increased prevalence of maternal prenatal drug use (see Chapter 96.4) and improved survival of very-low birthweight premature infants has counterbalanced this effect.

PATHOLOGY AND PATHOGENESIS

The limitations in our knowledge of the neuropathology of intellectual disability are exemplified by the fact that 10-20% of brains of persons with severe intellectual disability appear entirely normal by standard neuropathologic study. The majority of brains of these persons show only mild, nonspecific changes that correlate poorly with the degree of intellectual disability. These changes include microcephaly, gray matter heterotopias in the subcortical white matter, unusually regular columnar arrangement of the cortex, and neurons that are more tightly packed than usual. Only a minority of the brain shows more specific changes in dendritic and synaptic organization, with dysgenesis of dendritic spines or cortical pyramidal neurons, or impaired growth of dendritic trees. The programming of the central nervous system (CNS) involves a process of induction; CNS maturation is defined in terms of genetic, molecular, autocrine, paracrine, and endocrine influences. Receptors, signaling molecules, and genes are critical to brain development. The maintenance of different neuronal phenotypes in the adult brain involves the same genetic transcripts that play a crucial role during fetal development, with activation of similar intracellular signal transduction mechanisms. Several syndromes that were thought to involve complex chromosomal abnormalities are, in fact, caused by single-gene mutations involving induction. Rubinstein-Taybi syndrome (see Chapter 81), a disorder marked clinically by broad thumbs and great toes, characteristic facies, and severe intellectual disability, results from a mutation in the gene encoding for the transcriptional coactivator CREB-binding protein (CBP), a factor important in the control of gene expression in early embryogenesis.

CLINICAL MANIFESTATIONS

Early diagnosis of intellectual disability facilitates earlier intervention, identification of abilities, realistic goal setting, easing of parental anxiety, and greater acceptance of the child in the community. Most children with intellectual disability first come to the pediatrician's attention in infancy because of dysmorphisms, associated developmental disabilities, or failure to meet age-appropriate developmental milestones. There are no specific physical characteristics of intellectual disability, but dysmorphisms may be the earliest signs that bring children to the attention of the pediatrician. They might fall within a genetic syndrome such as Down syndrome or be isolated, as in microcephaly or failure to thrive. Associated developmental disabilities include seizure disorders, cerebral palsy, hypotonia, and autism; these conditions are seen more commonly in conjunction with intellectual disability than in the general population.

Most children with intellectual disability do not keep up with their peers and fail to meet age-expected norms. In early infancy, failure to meet age-appropriate expectations can include a lack of visual or auditory responsiveness, unusual muscle tone (hypo- or hypertonia) or posture, and feeding difficulties. Between 6 and 18 mo of age, gross motor delay (lack of sitting, crawling, walking) is the most common complaint. Language delay and behavior problems are common concerns after 18 mo (Table 36-2). Earlier identification of atypical development is likely to occur with more severe impairments; and intellectual disability is usually identifiable by age 3 yr.

For some children with mild intellectual disability the diagnosis remains uncertain during the early school years. It is only after the demands of the school setting increase over the years, changing from "learning to read" to "reading to learn," that the child's limitations are clarified.

Adolescents with mild intellectual disability can present a diagnostic challenge. Typically they are up to date on current trends and are conversant as to who, what, and where. It isn't until the "why" and "how" questions are asked that their limitations become apparent. If allowed to interact at a superficial level, their mild intellectual disability might not be appreciated, even by professionals who may be their special education teachers or healthcare providers. Because of the stigma associated with intellectual disability, they may use euphemisms to avoid being thought of as "stupid" or "retarded" and refer to themselves as learning disabled, dyslexic, language disordered, or slow learners. Some people with intellectual disability emulate their social milieu to be accepted. They may be social chameleons and assume the morals of the group to which they are attached. Some would rather be thought "bad" than "incompetent."

LABORATORY FINDINGS

The most commonly used medical diagnostic testing for children with intellectual disability include neuroimaging; metabolic, genetic, and chromosomal testing; microarray analysis; and electroencephalography. These tests should not be used as screening tools for all children with an intellectual disability. In some children, there is a reasonable yield for testing, whereas in others the yield of <1% does not support its use. Decisions on diagnostic testing should be based on the medical and family history, physical examination, testing by other disciplines, and the family's wishes. Table 36-3 summarizes clinical practice guidelines that have been published and the yields of testing to assist in evaluating the child with global developmental delay or intellectual disability. Microarray analysis has replaced karyotyping as the preferred approach for children with multiple anomalies or a positive family history. Microarray analysis has the ability to discern abnormalities that are below the resolution of karyotyping. For example, deletion 1p36 syndrome, the most common subtelomeric microdeletion syndrome (1 : 5,000 births), accounts for approximately 1% of

Table 36-2 Common Presentations of Intellectual Disability By Age

AGE	AREA OF CONCERN
Newborn	Dysmorphic syndromes, (multiple congenital anomalies), microcephaly Major organ system dysfunction (e.g., feeding and breathing)
Early infancy (2-4 mo)	Failure to interact with the environment Concerns about vision and hearing impairments
Later infancy (6-18 mo)	Gross motor delay
Toddlers (2-3 yr)	Language delays or difficulties
Preschool (3-5 yr)	Language difficulties or delays Behavior difficulties, including play Delays in fine motor skills: cutting, coloring, drawing
School age (>5 yr)	Academic underachievement Behavior difficulties (attention, anxiety, mood, conduct, etc.)

children with developmental disabilities and is characterized by failure to thrive, microcephaly, deep-set eyes, midface hypoplasia, broad nasal bridge, heart deficits, and CNS anomalies. Noncompaction cardiomyopathy and seizures are also noted. The diagnosis is made by standard chromosomes in only approximately 20% and requires fluorescent in situ hybridization or microarray comparative genomic hybridization methods for remaining patients. Microarray analysis may identify variants of unknown significance or benign variants, and therefore should be used in conjunction with a genetic consultation. Karyotyping has a role for children whose array analysis is unrevealing and concern is present for inversions, balanced insertions, and reciprocal translocations. Fluorescent in situ hybridization and subtelomeric analysis have been largely replaced by microarray analysis but continue to be used for specific indications. If microarray analysis is not diagnostic whole exome sequencing increases the diagnostic yield in many children with nonsyndromic severe intellectual disability.

Molecular genetic testing for fragile X syndrome is appropriate for a boy with moderate intellectual disability, unusual physical features, and/or a family history of intellectual disability, or for a girl with more subtle cognitive deficits associated with severe shyness and a relevant family history. For children with a strong history of X-linked intellectual disability, specific testing of genes or the entire chromosome may be revealing. MECP2 (methyl CpG binding protein 2 [Rett syndrome]) testing should be considered in girls with moderate to severe disability.

A child with a progressive neurologic disorder, developmental regression, or acute behavioral changes needs metabolic investigation (urinary organic acids, plasma amino acids, blood lactate, lysosomal enzymes in lymphocytes), although many of these disorders are detectable as part of newborn screening; a child with seizure-like episodes should have an electroencephalography performed. Children with micro- or macrocephaly or changes in head growth trajectory or asymmetric head shapes, as well as those with new or focal neurologic findings, including seizures, should have a neuroimaging procedure.

MRI scans identify a significant number of subtle markers of cerebral dysgenesis in children with intellectual disability. Formes frustes

Table 36-3 Suggested Evaluation of the Child with Intellectual Disability/Global Developmental Delay

TEST	COMMENT
In-depth history	Includes pre-, peri-, and postnatal events (including seizures); developmental attainments; and 3-generation pedigree in family history
Physical examination	Particular attention to minor or subtle abnormalities; neurologic examination for focality and skull abnormalities Behavioral phenotype
Vision and hearing evaluation	Essential to detect and treat; can mask as developmental delay
Gene microarray analysis	A 7.8% yield overall (10% in syndromic and 6.5% in nonsyndromic intellectual disability) Better resolution than Karyotype. May identify up to twice as many abnormalities as karyotyping. Excellent in detecting de novo microdeletions or microduplications
Karyotype	Yield 4% in global developmental delay/intellectual disability Best for inversions and balanced insertions, reciprocal translocations, and polyploidy
Fragile X screen	Combined yield 2% Preselection on clinical grounds can increase yield to 7.6%
X-linked candidate intellectual disability genes	May explain up to 10% of intellectual disability Yield may be as high as 42% if there is a definite family history and as high as 17% from a possibly linked kindred
Exomic gene sequencing	Detects inherited and de novo point mutations especially in nonsyndromic severe intellectual disability
Neuroimaging	MRI preferred. Positives increased by abnormalities of skull contour or microcephaly and macrocephaly, or focal neurologic examination. Overall has a higher yield Identification of specific etiologies is rare. Most conditions that are found do not alter the treatment plan. Need to weigh risk of sedation against possible yield
Thyroid (T_4, TSH)	Near 0% in settings with universal newborn screening program
Serum lead	If there are identifiable risk factors for excessive environmental lead exposure
Metabolic testing	Yield 0.2-4.6% based on clinical indicators and tests performed Urine organic acids, plasma amino acids, ammonia, lactate, and a capillary blood gas. Focused testing based on clinical findings is warranted Tandem mass spectrometry newborn screening has allowed for identification of many disorders in perinatal period and have decreased yield in older children. Other disorders have emerged; e.g., congenital disorders of glycosylation and disorders of creatine synthesis and transport
MECP2 for Rett syndrome	1.5% of females with severe intellectual disability 0.5% of males
EEG	May be deferred in absence of history of seizures
Repeated history and physical examination	Can give time for maturation of physical and behavioral phenotype. New technology may be available for evaluation

EEG, Electroencephalogram; CGH, comparative genomic hybridization; MECP2, methyl CpG binding protein 2; T_4, thyroxine; TSH, thyroid-stimulating hormone.

Based on Michelson DJ, Shevell MI, Sherr EH, et al: Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of Child Neurology. Neurology 77:1629-35, 2011; Curry CJ, Stevenson RE, Aughton D, et al: Evaluation of mental retardation: recommendations of a Consensus Conference: American College of Medical Genetics. Am J Med Genet 12:72:468-477, 1997. Shapiro BK, Batshaw ML: Mental retardation. In Burg FD, Ingelfinger JR, Polin RA, et al: Gellis and Kagan's current pediatric therapy, *ed 18, Philadelphia, 2005, WB Saunders, used with permission; and Shevell M, Ashwal S, Donley D, et al: Practice parameter: evaluation of the child with global developmental delay,* Neurology *60:367–380, 2003.*

of amino acid and organic acid disorders are associated with intellectual disability in the absence of the more commonly associated manifestations of behavior change, lethargy, and coma.

Some children with more subtle physical or neurologic findings can also have determinable biologic causes of their intellectual disability (see Chapter 83). How intensively one investigates the cause of a child's intellectual disability is based on a number of factors:

- What is the degree of intellectual disability? One is less likely to find a biologic cause in a child with mild intellectual disability than in a child with a severe intellectual disability.
- Is there a specific diagnostic path to follow? If there is a medical history or a family history, or if physical findings pointing to a specific disorder, a diagnosis is more likely to be made. In the absence of these indicators, it is difficult to choose specific tests to perform.
- Are the parents planning on having additional children? If so, one would be more likely to intensively seek disorders for which prenatal diagnosis or a specific early treatment option is available.
- What are the parents' wishes? Some parents have little interest in searching for the cause of the intellectual disability and focus exclusively on treatment. Others are so focused on obtaining a diagnosis that they have difficulty following through on interventions until a cause has been found. The entire spectrum of responses must be respected, and supportive guidance should be provided in the context of the parents' education.

DIFFERENTIAL DIAGNOSIS

One of the important roles of pediatricians is the early recognition and diagnosis of cognitive deficits. The developmental surveillance approach to early diagnosis of intellectual disability should be multifaceted. Parents' concerns and observations about their child's development should be listened to carefully, because their observations have been found to be as accurate as developmental screening tests. Medical, genetic, and environmental risk factors should be recognized. Infants at high risk (prematurity, maternal substance abuse, perinatal insult) should be registered in newborn follow-up programs in which they are evaluated periodically for developmental lags in the first 2 yr of life; they should be referred to early intervention programs as appropriate. Developmental milestones should be recorded routinely during healthcare maintenance visits. The American Academy of Pediatrics has formulated a schema for developmental surveillance and screening. Whether developmental surveillance is a more effective technique for identifying than recognizing failure to meet age-appropriate milestones has not been clearly established.

Before making the diagnosis of intellectual disability, other disorders that affect cognitive abilities and adaptive behavior should be considered. These include conditions that mimic intellectual disability and others that involve intellectual disability as an associated impairment. Sensory deficits (severe hearing and vision loss), communication disorders, and poorly controlled seizure disorders can mimic intellectual disability; certain progressive neurologic disorders can appear as intellectual disability before regression is appreciated. More than half of children with cerebral palsy (see Chapter 598) or autism spectrum disorders (see Chapter 30) also have intellectual disability as an associated deficit. Differentiation of isolated **cerebral palsy** from intellectual disability relies on motor skills being more affected than cognitive skills and on the presence of pathologic reflexes and tone changes. In **autism spectrum disorders,** language and social adaptive skills are more affected than nonverbal reasoning skills, whereas in intellectual disability there are usually more equivalent deficits in social, fine motor, adaptive, and cognitive skills.

DIAGNOSTIC PSYCHOLOGIC TESTING

The formal diagnosis of intellectual disability requires the administration of individual tests of intelligence and adaptive functioning.

The Bayley Scales of Infant Development (BSID-III), the most commonly used infant intelligence scale, assesses language, visual problem-solving skills, behavior, fine motor skills, and gross motor skills in children between 1 mo and 42 mo of age. A Mental Developmental Index (MDI) and a Psychomotor Development Index (PDI, a measure of motor competence) score are derived from the results. This test permits the differentiation of infants with severe intellectual disability from typically developing infants, but it is less helpful in distinguishing between a typical child and one with mild intellectual disability.

The most commonly used psychologic tests for children older than 3 yr of age are the Wechsler Scales. The Wechsler Preschool and Primary Scale of Intelligence, 4th edition (WPPSI-IV) is used for children with mental ages of 2.5-7.6 yr. The Wechsler Intelligence Scale for Children, 4th edition (WISC-IV), is used for children who function above a 6 yr mental age. Both scales contain a number of subtests in the areas of verbal and performance skills. Although children with intellectual disability usually score below average on all subscale scores, they occasionally score in the average range in 1 or more performance areas.

The most commonly used test of adaptive behavior is the **Vineland Adaptive Behavior Scale** (VABS), which involves semi structured interviews with parents and/or caregivers and teachers that assess adaptive behavior in four domains: communication, daily living skills, socialization, and motor skills. Other tests of adaptive behavior include the Woodcock-Johnson Scales of Independent Behavior–Revised, the American Association on Intellectual and Developmental Disability Adaptive Behavior Scale (ABS-2nd edition), and the Adaptive Behavior Assessment System (ABAS-2nd edition). There is usually (but not always) a good correlation between scores on the intelligence and adaptive scales. Basic adaptive abilities (feeding, dressing, hygiene) are more responsive to remedial efforts than is the IQ score. Adaptive abilities are also more variable, which can relate to the underlying condition and to environmental expectations. Although persons with Prader-Willi syndrome (see Chapter 81) have stability of adaptive skills through adulthood, those with fragile X syndrome may have increasing deficits over time.

COMPLICATIONS

Children with intellectual disability have higher rates of vision, hearing, neurologic, orthopedic, and behavioral or emotional disorders than do typically developing children. These other problems are often detected later in children with intellectual disability. If untreated, the associated impairments can potentially adversely affect the individual's outcome more than the intellectual disability itself.

The most common associated deficits are motor impairments, behavioral and emotional disorders, medical complications, and seizures. The more severe the intellectual disability, the greater are the number and severity of associated impairments. Knowing the cause of the intellectual disability can help predict which associated impairments are most likely to occur. Fragile X syndrome and fetal alcohol syndrome (see Chapter 106.2) are associated with a high rate of behavioral disorders; Down syndrome has many medical complications (hypothyroidism, celiac disease, congenital heart disease, atlantoaxial subluxation). Associated impairments can require ongoing physical therapy, occupational therapy, speech-language therapy, adaptive equipment, glasses, hearing aids, and medication. Failure to identify and treat these impairments adequately can hinder successful habilitation and result in difficulties in the school, home, and/or neighborhood environment.

PREVENTION

Examples of primary programs to prevent intellectual disability include:

- Increasing the public's awareness of the adverse effects of alcohol and other drugs of abuse on the fetus
- Preventing teen pregnancy and promoting early prenatal care
- Preventing traumatic injury by encouraging the use of guards and railings to prevent falls and other avoidable injuries in the home; using appropriate seat restraints when driving and wearing a safety helmet when biking or skateboarding; teaching firearms safety
- Preventing poisonings by teaching parents about locking up medications and potential poisons

- Encouraging safe sexual practices to prevent the transmission of diseases
- Implementing immunization programs to reduce the risk of intellectual disability caused by encephalitis, meningitis, and congenital infection

Presymptomatic detection of certain disorders can result in treatment that prevents adverse consequences. State newborn screening by tandem mass spectrometry (now including >50 rare genetic disorders in most states), newborn hearing screening, and preschool lead poisoning prevention programs are examples. Thyroid screening in a child with Down syndrome is an example of presymptomatic testing in a disorder associated with intellectual disability.

TREATMENT

Although intellectual disability is not treatable, many associated impairments are amenable to intervention and therefore benefit from early identification. Most children with an intellectual disability do not have a behavioral or emotional disorder as an associated impairment, but challenging behaviors (aggression, self-injury, oppositional defiant behavior) and mental illness (mood and anxiety disorders) occur with greater frequency in this population than among children with typical intelligence. These behavioral and emotional disorders are the primary cause for out-of-home placements, reduced employment prospects, and decreased opportunities for social integration. Some behavioral and emotional disorders are difficult to diagnose in children with more severe intellectual disability because of the child's limited abilities to understand, communicate, interpret, or generalize. Other disorders are masked by the intellectual disability. The detection of ADHD (see Chapter 33) in the presence of moderate to severe intellectual disability may be difficult, as may be discerning a thought disorder (psychosis) in someone with autism and intellectual disability.

Although mental illness is generally of biologic origin and responds to medication, behavioral disorders can result from a mismatch between the child's abilities and the demands of the situation, organic problems, and/or family difficulties. They may represent attempts by the child to communicate, gain attention, or avoid frustration. In assessing the challenging behavior, one must also consider whether it is inappropriate for the child's *mental age,* rather than the *chronological age.* When intervention is needed, an environmental change, such as a more appropriate classroom setting, may improve certain behavior problems. Behavior management techniques are useful; psychopharmacologic agents may be appropriate in certain situations.

Medication is not useful in treating the core symptoms of intellectual disability; no agent has been found to improve intellectual function. Medication may be helpful in treating associated behavioral and psychiatric disorders. Psychopharmacology is generally directed at specific symptom complexes including ADHD (stimulant medication), self-injurious behavior and aggression (neuroleptics), and anxiety obsessive-compulsive disorder, and depression (selective serotonin reuptake inhibitors). Before long-term therapy with any psychopharmacologic agent is initiated, a short trial should be conducted. Even if a medication proves successful, its use should be reevaluated at least yearly to assess the need for continued treatment.

SUPPORTIVE CARE AND MANAGEMENT

Each child with intellectual disability needs a medical home with a pediatrician who is readily accessible to the family to answer questions, help coordinate care, and discuss concerns. Pediatricians can have effects on patients and their families that are still felt decades later. The role of the pediatrician includes involvement in prevention efforts, early diagnosis, identification of associated deficits, referral for appropriate diagnostic and therapeutic services, interdisciplinary management, provision of primary care, and advocacy for the child and family. The management strategies for children with an intellectual disability should be multimodal, with efforts directed at all aspects of the child's life: health, education, social and recreational activities, behavior problems, and associated impairments. Support for parents and siblings should also be provided.

Primary Care

For children with an intellectual disability, primary care has a number of important components:

- Provision of the same primary care received by all other children of similar chronological age (see Chapter 5)
- Anticipatory guidance relevant to the child's level of function: feeding, toileting, school, accident prevention, sexuality education
- Assessment of issues that are relevant to that child's disorder: e.g., examination of the teeth in children who exhibit bruxism, thyroid function in children with Down syndrome, cardiac function in Williams syndrome (see Chapter 108)

The American Academy of Pediatrics has published a series of guidelines for children with specific genetic disorders associated with intellectual disability (Down syndrome, fragile X syndrome, and Williams syndrome). Goals should be considered and programs adjusted as needed during the primary care visit. Decisions should also be made about what additional information is required for future planning or to explain why the child is not meeting expectations. Other evaluations, such as formal psychologic or educational testing, may need to be scheduled.

Interdisciplinary Management

The pediatrician has the responsibility for consulting with other disciplines to make the diagnosis of intellectual disability and coordinate treatment services. Consultant services may include psychology, speech-language pathology, physical therapy, occupational therapy, audiology, nutrition, nursing, and/or social work, as well as medical specialties such as neurodevelopmental disabilities, neurology, genetics, psychiatry, developmental-behavioral pediatricians, and/or surgical specialties. Contact with early intervention and school personnel is equally important to help prepare the child's Individual Family Service Plan/Individual Educational Plan. The family should be an integral part of the planning and direction of this process. Care should be family centered and culturally sensitive; for older children, their participation in planning and decision making should be promoted to whatever extent possible.

Periodic Reevaluation

The child's abilities and the family's needs change over time. As the child grows, more information must be provided to the child and family, goals must be reassessed, and programming needs should be adjusted. A periodic review should include information about the child's health status as well as the child's functioning at home, at school, and in other community settings. Other information, such as formal psychologic or educational testing, may be helpful. Reevaluation should be undertaken at routine intervals (6-12 mo during early childhood), at any time the child is not meeting expectations, or when the child is moving from one service delivery system to another. This is especially true during the transition to adulthood, beginning at age 14 yr as mandated by the IDEA Amendments of 2004. This transitioning should include the transfer of care to the adult healthcare system by age 21 yr.

Educational Services

Education is the single most important discipline involved in the treatment of children with an intellectual disability. The educational program must be relevant to the child's needs and address the child's individual strengths and weaknesses. The child's developmental level, the child's requirements for support, and goals for independence provide a basis for establishing an Individualized Education Program for school-age children, as mandated by federal legislation.

Leisure and Recreational Activities

The child's social and recreational needs should be addressed. Although young children with intellectual disability are generally included in play activities with children who have typical development, adolescents with intellectual disability often do not have opportunities for appropriate social interactions. Participation in sports should be encouraged, even if the child is not competitive, because it offers many benefits,

Table 36-4 Severity of Intellectual Disability and Adult Age Functioning

LEVEL	MENTAL AGE AS ADULT*	ADULT ADAPTATION
Mild	9-11 yr	Reads at 4th-5th grade level; simple multiplication and division; writes simple letter, lists; completes job application; basic independent job skills (arrive on time, stay at task, interact with coworkers); uses public transportation, might qualify for driver's license; keeps house, cooks using recipes
Moderate	6-8 yr	Sight-word reading; copies information, e.g., address from card to job application; matches written number to number of items; recognizes time on clock; communicates; some independence in self-care; housekeeping with supervision or cue cards; meal preparation, can follow picture recipe cards; job skills learned with much repetition; uses public transportation with some supervision
Severe	3-5 yr	Needs continuous support and supervision; might communicate wants and needs, sometimes with augmentative communication techniques
Profound	<3 yr	Limitations of self-care, continence, communication, and mobility; might need complete custodial or nursing care

*WHO, *International Statistical Classification of Diseases and Related Health Problems,* 10th revision, Geneva, Switzerland, 2011, World Health Organization.

including weight management, development of physical coordination, maintenance of cardiovascular fitness, and improvement of self-image. Social activities are equally important, including dances, trips, dating, and other typical social and recreational events.

Family Counseling

Many families adapt well to having a child with intellectual disability, but some have emotional or social difficulties. The risks of parents' depression and child abuse and neglect are higher in this group of children than in the general population. Among the factors that have been associated with good family coping and parenting skills are stability of the marriage, good parental self-esteem, limited number of siblings, higher socioeconomic status, lower degree of disability or associated impairments, parents' appropriate expectations and acceptance of the diagnosis, supportive extended family members, and availability of community programs and respite care services. In families in which the emotional burden of having a child with intellectual disability is great, family counseling, parent support groups, respite care, and home health services should be an integral part of the treatment plan.

PROGNOSIS

In children with severe intellectual disability, the prognosis is often evident by early childhood. Mild intellectual disability might not always be a lifelong disorder. Children might meet criteria for intellectual disability at an early age, but later the disability can evolve into a more specific developmental disorder (communication disorder, autism, slow learner, or borderline normal intelligence). Others with a diagnosis of mild intellectual disability during their school years develop sufficient adaptive behavior skills so that they no longer fit the diagnosis as adolescents, or the effects of maturation and plasticity can result in children moving from one diagnostic category to another (from moderate to mild retardation). Some children who have a diagnosis of a specific learning disability or communication disorder might not maintain their rate of cognitive growth and fall into the range of intellectual disability over time. By adolescence, the diagnosis has generally stabilized.

The apparent higher prevalence of intellectual disability in low and middle income group countries is of concern given the limitations in available resources. While community-based rehabilitation is being implemented in more than 90 countries, the efficacy of such programs has not been established.

The long-term outcome of persons with intellectual disability depends on the underlying cause, the degree of cognitive and adaptive deficits, the presence of associated medical and developmental impairments, the capabilities of the families, and the school and community supports, services, and training provided to the child and family (Table 36-4). As adults, many persons with mild intellectual disability are capable of gaining economic and social independence with functional literacy. They might need periodic supervision, especially when under social or economic stress. Most live successfully in the community, either independently or in supervised settings. Life expectancy is not adversely affected by intellectual disability itself.

For persons with moderate intellectual disability, the goals of education are to enhance adaptive abilities and "survival" academic and vocational skills so they are better able to live in the adult world (see Table 36-4). The concept of supported employment has been very beneficial to these individuals; the person is trained by a coach to do a specific job in the setting in which the person is to work. This bypasses the need for a sheltered workshop experience and has resulted in successful work adaptation in the community for many people with an intellectual disability. These persons generally live at home or in a supervised setting in the community.

As adults, people with severe to profound intellectual disability usually require extensive to pervasive supports (see Table 36-4). These individuals may have associated impairments, such as cerebral palsy, behavioral disorders, epilepsy, or sensory impairments, that further limit their adaptive functioning. They can perform simple tasks in supervised settings. Most people with this level of intellectual disability are able to live in the community with appropriate supports.

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Children with Special Needs

PART V

Chapter 37

Adoption

Samantha L. Wilson and Mark D. Simms

Adoption is a social, emotional, and legal process that provides a new family for a child when the birth family is unable or unwilling to parent. In the United States, about 1 million children <18 yr of age are adopted; 2-4% of all American families have adopted. Annually across the globe, approximately 250,000 children are adopted; approximately 30,000 of adoptions are between nations. In the United States approximately **136,000 children were adopted in 2008, a** 15% increase since 1990. Of these, approximately 40% were stepparent or relative adoptions. Of non-stepparent adoptions, approximately 60% were from the child welfare system, 25% were international, and 15% were voluntarily adoption-placed domestic infants. Public agencies support approximately 50% of total annual adoptions in the United States, private agencies facilitate approximately 25% of adoptions, and independent practitioners, for example, lawyers, handle approximately 15% of adoptions. Compared to 19% of the general population, approximately 39% of adopted children have special healthcare needs.

The Adoption and Safe Families Act (P.L. 105-89) requires children in foster care to be placed with adoptive families if they cannot be safely returned to their families within a reasonable period of time. In fiscal year (FY) 2011, there were 104,236 children waiting for adoption, including 61,361 whose biological parents' rights had been terminated. Many children awaiting adoption have "special needs" because they are of school age, part of a sibling group, members of historically oppressed racial/ethnic groups, or because they have considerable physical, emotional, or developmental needs. A number of policy efforts are aimed at increasing adoption opportunities for these children, including federal adoption subsidies, tax credits, recruitment efforts to identify ethnically diverse adults willing to adopt, increased preplacement services, and expanding adoption opportunities to single adults, gay/lesbian partners, and older couples.

Along with foster care adoptions, international adoptions are a way of providing stable, long-term care to vulnerable children throughout the world. There is concern that in some countries of origin the rapid growth of international adoption has outpaced regulation and oversight to protect vulnerable children/families. Opportunities for financial gain have led to abuses, including the sale and abduction of children, bribery, and financial coercion of families, though the extent and scope of the potential concern is difficult to ascertain. Increasing global efforts, such as the Hague Convention on Protection of Children and Co-Operation In Respect of Intercountry Adoption, have promoted political cooperation between nations and established international law to reduce potential for child abduction/trafficking and to ensure that the best interests of the child are paramount in decision making. Participating nations, including the United States, are working to address the myriad sociopolitical conditions that create the need for out-of-family care, and are working to support children within their nations' borders. International adoption is increasingly considered a measure of last resort if the child cannot be cared for within the child's birth family (including extended relatives), the immediate community, or within the larger national culture. As a result, children adopted internationally into the United States are more likely to enter their families at older ages or with complex medical/developmental/social-emotional needs.

Although the vast majority of children adopted internationally *enter* the United States for purposes of adoption, there are a small, but growing, number of children who *exit* the United States for adoption into other countries. For example, in FY 2012, 99 children exited the United States for adoption by families in other countries (e.g., Canada, Netherlands, Ireland, United Kingdom). Little is known about the circumstances surrounding these adoptions and the eventual outcomes of the children who are adopted internationally *from* the United States.

In 2012, U.S. families adopted 8,868 children from other countries (compared with a peak of 22,884 in 2004). Children from China, Ethiopia, Russia, and South Korea represented 65% of children adopted internationally into the United States in 2012; 33% were from China alone. Although individual experiences vary, most children placed for international adoption have some history of poverty and social hardship in their home countries, and approximately 65% are adopted from orphanage/institutional settings. Many young infants are placed into orphanage care shortly after birth, while some older children have experienced family disruption resulting from parental illness, war, or natural disasters. Still others enter orphanage care following determination of significant abuse/neglect within their biologic families. The effects of institutionalization and other life stresses impact all areas of early growth and development. As a result, many children require specialized support and understanding to overcome the impact of stress and early adversity and to reach their full potential.

ROLE OF PEDIATRICIANS

Preadoption Medical Record Reviews

Adoption agencies are making increased efforts to obtain biological family health information and genetic histories to share with adoptive families prior to adoption. Pediatricians can help prospective adoptive parents understand the health and developmental history of a child and available background information from birth families in order to assess actual and potential medical risk factors to support adult decision making about the family's ability to parent the waiting child. Under the Hague Convention on Protection of Children and Co-operation in Respect of Intercountry Adoption, agencies in the United States that arrange international adoptions must make efforts to obtain accurate and complete health histories on children awaiting adoption.

The nature and quality of medical and genetic information, when available, varies greatly. Poor translation and use of medical terminology and medications that are unfamiliar to U.S.-trained physicians are quite common. Results of specific diagnostic studies and laboratory tests performed outside of the United States should not be relied on and **should be repeated** once the child arrives in the United States. Paradoxically, review of the child's medical records may raise more questions than provide answers. Each medical diagnosis should be considered carefully before being rejected or accepted. Country-specific growth curves should be avoided as they may be inaccurate or reflect a general level of poor health and nutrition in the country of origin. Instead, serial growth data should be plotted on U.S. standard growth curves; they may reveal a pattern of poor growth as a consequence of malnutrition or other chronic illness. Photographs or videotapes/DVDs may provide the only "objective" information from which medical status can be determined. Full-face photographs may reveal dysmorphic features consistent with fetal alcohol syndrome (see Chapter 106.2) or findings suggestive of other congenital disorders.

Preadoptive medical record reviews are also of potential value within the context of U.S. domestic adoptions. Biological family health information and genetic histories are often shared with adoptive families prior to adoption, and such information may become increasingly

relevant to the child as the child ages. The increase in "open" domestic adoptions, which encourages some degree of communication between participating biological and adoptive family members, may provide opportunities for long-term communication about medical and genetic conditions that might affect the adopted child.

In both international and domestic adoptions, frank interpretations of available information should be shared with the prospective adoptive parents. As noted by the American Academy of Pediatrics Committee on Early Childhood, Adoption and Dependent Care (1991), "It is not the pediatrician's role to judge the advisability of a proposed adoption, but it is appropriate and necessary that the prospective parents and any involved agency be apprised clearly and honestly of any special health needs detected now or anticipated in the future."

Postadoption Medical Care

Arrival Visit–International Adoption

All children with symptoms of an acute illness should receive immediate medical care after arriving in the United States. However, a significant number of children adopted internationally have acute or chronic medical problems that are not always immediately evident, including growth deficiencies, anemia, elevated blood lead, dental decay, strabismus, birth defects, developmental delay, feeding and sensory difficulty, and social-emotional concerns (see Chapter 37.1 below). After the child is settled in the new home, pediatricians should encourage adoptive parents to seek a comprehensive assessment of the child's growth and development. The American Academy of Pediatrics recommends that all children who are adopted from other countries undergo routine screening for infectious diseases and disorders of growth, development, vision, and hearing (Tables 37-1 and 37-2). Additional tests (e.g., malaria) should be ordered depending on the prevalence of disease in the child's country of origin (see Centers for Disease Control and Prevention's interactive malaria map at http://www.cdc.gov/malaria/map/). If the child's purified protein derivative is negative, a repeat skin test should be performed in 4-6 mo; children may have false-negative tests because of poor nutrition. A positive purified protein derivative should be followed by a QuantiFERON-TB Gold test to determine if the response is the result of prior bacillus Calmette-Guérin vaccination (see Chapter 215). If they have not received hepatitis A vaccine prior to arriving in the United States, parents, other caregivers, and family members (siblings, grandparents, etc.) should also be immunized. In 1 survey, 65% of internationally adopted children had no written records of overseas immunizations; however, those with records appeared to have valid records, although doses were not necessarily acceptable according to the U.S. schedule (see Chapter 172). The diverse medical and developmental needs of internationally adopted children have led to the creation of specialty clinics throughout the United States, which may be a valuable resource for adoptive families at all stages in the adoption process.

Table 37-1 Recommended Screening Tests for International Adoptees Upon U.S. Arrival

Screening tests
- Complete blood cell count
- Hemoglobin identification
- Blood lead level
- Urinalysis
- Newborn screening (children <12 mo)
- Vision and hearing screening
- Developmental testing

Other screening tests to consider based on clinical findings and age of the child
- Detection of *Helicobacter pylori* antibody or ^{13}C-urea breath test
- Stool cultures for bacterial pathogens
- Glucose-6-phosphate dehydrogenase deficiency screening
- Sickle cell
- Urine pregnancy test

Infectious disease screening (see Table 37-2)

Developmental Delays

At the time of adoption, many children exhibit delays in at least 1 area of development, but most exhibit significant gains within the first 12 mo after adoption. Those adopted before 6 mo of age usually demonstrate typical development, whereas those adopted at older ages have more variable outcomes. In the immediate postadoption period, it may be impossible to determine with any certainty whether a child's developmental delays will be transient or long-lasting. Careful monitoring of development within the first year of adoption can identify a "developmental trend" over time that may be more predictive of long-term functioning than assessment at any specific point in time.

Growth Delays

Physical growth delays are common in both domestically and internationally adopted children, and may represent the combined result of many factors, for example, unknown/untreated medical conditions, malnutrition, and psychological deprivation. Weight and height at the time of adoption have been negatively correlated with the amount of time the child spent in adverse environments (i.e., orphanage care or in the care of highly neglectful biological families). Though most children experience a significant catch-up in physical growth following adoption, many remain shorter than their U.S. peers.

Language Development

For both domestic and international adoptees, genetic or biologic risk factors for poor language development may not have been identified preadoptively. Children adopted internationally typically have had little exposure to English, and it may not be possible to assess a child's language abilities until they have had a chance to learn English. Most internationally adopted children of pre–school-age are able to attain English language skills equal to those born in the United States within 24 mo postadoption. In older children, delays in native language skills often predict delays in English acquisition. If language concerns persist following 1-2 yr in an enriching environment, assessment by a speech-language pathologist may be warranted.

Table 37-2 Screening Tests for Infectious Diseases in International Adoptees

RECOMMENDED TESTS

Hepatitis B virus serologic testing*
- Hepatitis B surface antigen (HBsAg)
- Antibody to hepatitis B surface antigen (anti-HBs)

Hepatitis C virus serologic testing*†
Hepatitis A virus serologic testing†
Varicella virus serologic testing†
Syphilis serologic testing
- Nontreponemal test (RPR, VDRL, or ART)
- Treponemal test (MHA-TP or FTA-ABS)

Human immunodeficiency viruses 1 and 2 testing (ELISA if >18 mo, PCR if <18 mo)*
Complete blood cell count with red blood cell indices and differential (if eosinophilia, see text)
Stool examination for ova and parasites (2-3 specimens)†
Stool examination for *Giardia lamblia* and *Cryptosporidium* antigen (1 specimen)†
Tuberculin skin test (with CXR if >5 mm induration) or interferon-γ release assay*†

OPTIONAL TESTS (FOR SPECIAL POPULATIONS OR CIRCUMSTANCES)

GC/Chlamydia
Chagas disease serology
Malaria thick and thin smears
Urine for O&P for schistosomiasis, if hematuria present

*Repeat 3-6 mo after arrival.
†See text.
ART, automated reagin test; CXR, chest radiograph; ELISA, enzyme-linked immunosorbent assay; FTA-ABS, fluorescent treponemal antibody absorption; GC, gonococcus; MHA-TP, microhemagglutination test for *Treponema pallidum*; O&P, ova and parasites; PCR, polymerase chain reaction; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratories.

Eating Concerns

Initial concerns about eating, sleep regulation, and repetitive (e.g., self-stimulating or self-soothing) behaviors are common, especially among children adopted following a high degree of neglect or developmental trauma. Feeding concerns are sometimes linked to limited exposure to textured or solid foods during later infancy/toddlerhood. Children who have experienced chronic lack of food may not have developed an awareness of satiation cues, leading to hoarding or frequent vomiting. Feeding concerns often subside gradually with introduction of age-appropriate foods and parental support for positive feeding practices. Many children who were adopted following a significant period of malnutrition may eat an excessive amount of food. Unless the child is eating to the point of vomiting (which would indicate little awareness of satiation cues), it is generally best to allow them to eat until satiation. Typically within 6 mo, the child will regulate food intake appropriately. Occasionally, additional support from a speech pathologist or feeding specialist is warranted to address possible physical/psychological concerns that could impede proper feeding.

Sleep Concerns

Sleep is often disrupted as the child reacts to changes in routines and environments. Efforts to create continuity between the preadoption and postadoption environment can be helpful. Within the first 3-6 mo, as the child's emotional self-regulation improves, many sleep concerns subside. Similarly, stereotypic behaviors, such as rocking or head banging, often diminish within the first few months following adoption.

Social and Emotional Development

Dyadic interactions between child and caretaker are a critical component to later regulatory functioning and social-emotional development. The amount and quality of individualized caretaking children have received prior to their adoption is usually unknown. In many instances, entry into a secure, stable home setting with consistent child-caring routines is sufficient to support the child's emerging social-emotional development. At times, the child's prior experiences or biologic disposition may result in behavior that is confusing to the adoptive parents. The child's reactions may be subtle or difficult to interpret, interfering with the parents' ability to respond in a sensitive manner. In these circumstances, additional support may be helpful to foster the emerging relationships and behavioral regulation in the newly formed family.

Racial Identity Development

An estimated 22% of adoptive families are interracial (where the racial background of the child differs from that of the parent/parents). In the vast majority of these adoptive placements, children of color have been adopted by white parents. Racial identity development, including ways to understand and respond to discrimination, is increasingly recognized as important in the overall development of children. Surveys of adults adopted transracially indicate that racial identity is of central importance at many ages, and tends to increase in significance during young adulthood. Integrating race/ethnicity into identity can be a complex process for all children, but it may be especially complicated when they are raised in a family where racial differences are noted. Adults raised within interracial families have noted the value of attending racially diverse schools and of having adult role models (e.g., teachers, doctors, coaches) who share their racial background. Parents who adopt transracially are often encouraged to support interactions within diverse communities and to discuss race (and associated discrimination) often within the family.

Toxic Stress

The cumulative amount of early adversity (e.g., numerous years within international orphanage care, extensive abuse/neglect prior to removal from biological family, or multiple foster care placements) experienced by a child prior to adoption, referred to as "toxic stress," can impact both immediate placement stability and long-term functioning. The degree of presumed toxic stress may be helpful in interpreting a child's behavior and supporting family functioning (see video at http://developingchild.harvard.edu/resources/multimedia/videos/three_core_concepts/toxic_stress/).

Family Support

There are unique aspects to adoptive family formation that can create familial stress and impact child and family functioning. Some adoptive families may have to address infertility, creation of a multiracial family, disclosure of adoptive status, concerns and questions the child may have about their biologic origins, and ongoing scrutiny by adoption agencies. In the case of gay/lesbian parents, there are often additional psychosocial stressors, including continued barriers to legal recognition of both parents in a gay/lesbian partnership that can negatively impact family functioning. Although most families acclimate well to adoption-related stressors, some parents experience post adoption depression and may benefit from additional support to ease the family's transition.

Adoption Narrative

Families are encouraged to speak openly and repeatedly about adoption with their child, beginning in the toddler years and continuing through adolescence. Creating a "Lifebook" for the adopted child provides a way to support family communication about the child's history and significant relationships (including birth family members) and to document the child's important life transitions (e.g., through foster care or immigration to the United States). It is common, and normal, for children to have questions about adoption and their biological family throughout their development. An increase in cognitive understanding between ages 7 and 10 yr can sometimes increase adoption-related questions and/or distress. Youth who have questions about biological family members are increasingly able to access information via web-based searching, raising the importance of ongoing open communication about adoption. Pediatricians may need to respond to increased concerns/questions when the adoptee's health and genetic history is incomplete or unknown. At any time, concerns about development, behavior, and social-emotional functioning may or may not be related to the child's adoption history.

The vast majority of adopted children and families adjust well and lead healthy, productive lives. It is not common for adoptions to disrupt; disruption rates are higher among children adopted from foster care, which research associates with their age at time of adoption and/or a history of multiple placements prior to adoption. As a result of a greater understanding of the needs of families who adopt children from foster care, agencies are placing greater emphasis on the preparation of adoptive parents and ensuring the availability of a full range of postadoption services, including physical health, mental health, and developmental services for their adopted children.

Bibliography is available at Expert Consult.

37.1 Medical Evaluation of Immigrant (Foreign-Born) Children for Infectious Diseases

Stacene R. Maroushek

More than 210,000 foreign-born children (≤16 yr old) enter the United States each year as asylees, refugees, and immigrants including international adoptees. This number does not include undocumented children living and working in the United States, the U.S.-born children of foreign-born parents, or the approximately 2.7 million nonimmigrant visitors ≤16 yr old who legally enter the United States annually with temporary visas. With the exception of internationally adopted children, pediatric guidelines for screening these newly arrived children are sparse. The diverse countries of origin and patterns of infectious disease, the possibility of previous high-risk living circumstances (e.g., refugee camps, orphanages, foster care, rural/urban poor), the

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limited availability of reliable healthcare in many economically developing countries, the generally unknown past medical histories, and interactions with parents who may have limited English proficiency, varied educational, or economic experiences, make the medical evaluation of immigrant children a challenging but important task.

Before admission into the United States, all immigrant children are required to have a medical examination performed by a physician designated by the U.S. Department of State in their country of origin. This examination is limited to completing legal requirements for screening for certain communicable diseases and examination for serious physical or mental defects that would prevent issuing a permanent residency visa. This evaluation is not a comprehensive assessment of the child's health and, except in limited circumstances, laboratory or radiographic screening for infectious diseases **is not required** for children <15 yr old. After entry into the United States, health screenings of refugees, but not other immigrants, are recommended to be done by the resettlement state. There is little tracking of refugees as they move to different cities or states. Thus, many foreign-born children have had minimal prearrival or postarrival screening for infectious diseases or other health issues.

Immunization requirements and records also vary depending on entry status. Internationally adopted children who are younger than 10 yr are exempt from Immigration and Nationality Act regulations pertaining to immunization of immigrants before arrival in the United States. Adoptive parents are required to sign a waiver indicating their intention to comply with U.S.-recommended immunizations, whereas older immigrants need only show evidence of up-to-date, not necessarily complete, immunizations before application for permanent resident (green card) status after arrival in the United States.

Infectious diseases are among the most common medical diagnoses identified in immigrant children after arrival in the United States. Children may be asymptomatic; therefore, diagnoses must be made by screening tests in addition to history and physical examination. Because of inconsistent perinatal screening for hepatitis B and hepatitis C viruses, syphilis, and HIV, and the high prevalence of certain intestinal parasites and tuberculosis, all foreign-born children should be screened for these infections on arrival in the United States. Table 37-2 lists suggested screening tests for infectious diseases. In addition to these infections, other medical and developmental issues, including hearing, vision, dental, and mental health assessments; evaluation of growth and development; nutritional assessment; lead exposure risk; complete blood cell count with red blood cell indices; microscopic urinalysis; newborn screening (this could be done in nonneonates, too) and/or measurement of thyroid-stimulating hormone concentration; and examination for congenital anomalies (including fetal alcohol syndrome) should be considered as part of the initial evaluation of any immigrant child.

Children should be examined within 1 mo of arrival in the United States or earlier if there are immediate health concerns, but foreign-born parents may not access the healthcare system with their children unless prompted by illness, school vaccination, or other legal requirements. I**t is important to assess the completeness of previous medical screenings at any first visit with a foreign-born child**.

Clinicians should be aware of potential diseases in high-risk immigrant children and their clinical manifestations. Some diseases, such as central nervous system cysticercosis, may have incubation periods as long as several years, and thus may not be detected during initial screening. On the basis of findings at the initial evaluation, consideration should be given to a repeat evaluation 6 mo after arrival. In most cases, the longer the interval from arrival to development of a clinical syndrome, the less likely the syndrome can be attributed to a pathogen acquired in the country of origin.

COMMONLY ENCOUNTERED INFECTIONS

Hepatitis B

See Chapter 350.

The prevalence of hepatitis B surface antigen (HBsAg) in international adoptees and refugee children ranges from 1-5% and 4-14%, respectively, depending on the country of origin, age, and year studied. Prevalence of markers of past hepatitis B virus (HBV) infection is higher. HBV infection is most prevalent in immigrants from Asia, Africa, and some countries in Central and Eastern Europe, as well as the former Soviet Union (e.g., Bulgaria, Romania, Russia, and Ukraine), but also occurs in immigrants born in other countries. All immigrant children, even if previously vaccinated, coming from high-risk countries (HBsAg seropositivity >2%) should undergo serologic testing for HBV infection, including both HBsAg and antibody to HBsAg (anti-HBs), to identify current or chronic infection, past resolved infection, or evidence of previous immunization. Because HBV has a long incubation period (6 wk to 6 mo), the child may have become infected at or near the time of migration and initial testing might be falsely negative. Therefore, strong consideration should be given to a repeated evaluation 6 mo after arrival for all children, especially those from highly endemic countries. Chronic HBV infection is indicated by persistence of HBsAg for more than 6 mo. Children with HBsAg-positive test results should be evaluated to identify the presence of chronic HBV infection because chronic hepatitis B infection occurs in >90% of infants infected at birth or in the first year of life, and in 30% of children exposed at ages 1-5 yr. Once identified as being infected, additional testing to assess for biochemical evidence of severe or chronic liver disease or liver cancer should take place.

Hepatitis A

See Chapter 358.

Hepatitis C

See also Chapter 358.

The decision to screen children should depend on history (e.g., receipt of blood products; traditional percutaneous procedures such as tattooing, body piercing, circumcisions, or other exposures to reused, unsterile medical devices) and the prevalence of infection in the child's country of origin. Children from Eastern Mediterranean and Western Pacific countries, Africa, China, and Southeast Asia should be considered for hepatitis C infection screening. All children coming from Egypt, which has the highest known seroprevalence (12% nationally and 40% in some villages), should be tested for hepatitis C.

Intestinal Pathogens

Fecal examinations for ova and parasites by an experienced laboratory will identify a pathogen in 15-35% of internationally adopted children; prevalence rates in immigrants and refugees range from 8-86%. The prevalence of intestinal parasites varies by country of origin, time period when studied, previous living conditions (including water quality, sanitation, and access to footwear) and the age of the child, with toddler/young school-age children being most affected. If documented predeparture treatment was given, an eosinophil count should be performed. An absolute eosinophil count of >400 cells/µL, if persistently elevated for 3-6 mo after arrival, should prompt further investigation for tissue-invasive parasites such as *Strongyloides* (see Chapter 295) and *Schistosoma* (see Chapter 300) species. If no documented predeparture treatment was given, 2 stool ova and parasite specimens obtained from separate morning stools should be examined by the concentration method, and an eosinophil count should be performed. If the child is symptomatic, including evidence of poor physical growth, but no eosinophilia is present, a single stool specimen should also be sent for *Giardia lamblia* (see Chapter 282) and *Cryptosporidium parvum* (see Chapter 283) antigen detection. All potentially pathogenic parasites found should be treated appropriately. All nonpregnant refugees >2 yr of age coming from sub-Saharan Africa and Southeast Asia should be presumptively treated with predeparture albendazole.

Tuberculosis

See also Chapter 215.

Tuberculosis (TB) commonly is encountered in immigrants from all countries because *Mycobacterium tuberculosis* infects approximately 30% of the world's population. Latent TB infection rates range from 0.6-30% in adoptees and up to 60% in some refugee children from North Africa and the Middle East. Prior to 2007, chest radiographs or

tuberculin skin tests were generally not administered in children <15 yr of age and reports indicate that 1-2% of these unscreened children may enter the United States with undiagnosed active TB disease.

Since 2007, TB Technical Instructions for Medical Evaluation of Aliens have required that children ages 2-14 yr undergo a TB skin test if they are medically screened in countries where the TB rate is 20 cases or more per 100,000 population. If the skin test is positive, a chest x-ray is required. If the chest x-ray suggests TB, cultures and 3 sputum smears are required, all before arrival in the United States. This requirement is being phased in over a number of years, and some countries with a case rate of 20 per 100,000 may not currently be screening children. Check with the Centers for Disease Control and Prevention, Division of Global Migration and Quarantine for latest information (www.cdc.gov/ncidod/dq/technica.htm).

Congenital Syphilis

See Chapter 218.

HIV Infection

See Chapter 276.

Immunizations

See Chapter 172.

Immigrant children and adolescents should receive immunizations according to the recommended schedules in the United States for healthy children and adolescents. Some immigrants will have written documentation of immunizations received in their birth or home country. Although immunizations such as bacillus Calmette-Guérin, diphtheria and tetanus toxoids, and pertussis (DTP), poliovirus, measles, and hepatitis B virus vaccines often are documented, other immunizations, such as *Haemophilus influenzae* type b, mumps, and rubella vaccines, are given less frequently, and *Streptococcus pneumoniae*, human papillomavirus, meningococcal, and varicella vaccines are given rarely. When doubt exists, an equally acceptable alternative is to reimmunize the child. Because the rate of more serious local reactions after diphtheria, tetanus toxoid, and acellular pertussis vaccine increases with the number of doses administered, serologic testing for antibody to tetanus and diphtheria toxins before reimmunizing, or if a serious reaction occurs, can decrease risk.

In children older than 6 mo with or without written documentation of immunization, testing for antibodies to diphtheria and tetanus toxoid and poliovirus may be considered to determine whether the child has protective antibody concentrations. If the child has protective concentrations, then the immunization series should be completed as appropriate for that child's age. In children older than 12 mo, measles, mumps, rubella, and varicella antibody concentrations may be measured to determine whether the child is immune; these antibody tests should not be performed in children younger than 12 mo because of the potential presence of maternal antibody.

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Chapter 38

Foster and Kinship Care

Moira Szilagyi

The placement of children in out-of-home care has served the needs of children in many societies worldwide throughout history. The institution of foster care was developed in the United States as a temporary resource for children during times of family crisis and is rooted in the principle that children fare best when raised in family settings. The 1989 United Nations Convention on the Rights of the Child, a legally binding international instrument, addresses the need for such care for all children worldwide. Regardless of its setting, the mission of foster care is to provide for the safety, permanency, and well-being of children while assisting their families with services to promote reunification.

EPIDEMIOLOGY

The number of children in foster care worldwide is unknown, although it has been estimated that 8 million may be in foster and residential care. On September 11, 2011, approximately 400,540 children in the United States resided in foster care, representing a downward trend since 1999, when the daily average of children in care was 567,000. This decrease has occurred despite an increase in maltreatment reports, as child welfare offers families more preventive services and placement with relatives or nonrelative caregivers (kinship care) as an alternative to removal, resulting in fewer admissions. Reunification rates and adoption of children from foster care have also increased. Court ordered and informal kinship care have increased, accounting for up to 7% of children.

Approximately 33% of children in foster care in the United States are younger than the age of 5 yr and 35% are older than age 12 yr. The largest subset is white (41%) with significant percentages of black (27%) and Hispanic (21%) children. The average length of stay has dropped to a mean of 23.9 mo (median: 13.5 mo), although 31% of children remain in foster care for more than 2 yr. Only approximately 52% of children achieve reunification. Approximately 8% go to relatives, while approximately 20% (50,000 children) are adopted out of foster care annually. Among remaining children, 11% emancipate, 6% enter into long-term state guardianship, 1% run away, and 2% transfer to other institutions. In 2011, there were 343 deaths in foster care.

Most children live in nonrelative foster (47%) or certified relative foster (27%) family care, and 4% reside in a preadoptive home, although this is less than 20% of the children who are awaiting adoption. Approximately 15%, mostly adolescents, live in group homes or residential settings. The average number of placements a child experiences in foster care is not included in Adoption and Foster Care Reporting System, but important predictors include severe behavioral and/or developmental problems, larger sibling group size, and longer time spent in foster care. Within 12 months, nearly all emancipated youth have at least one homeless night and, within a decade, less than half have a high school degree and most are living in poverty and have high rates of posttraumatic stress disorder and depression.

LEGISLATION IN THE UNITED STATES

In the United States, the Adoption and Safe Families Act (P.L. 105-89), passed in 1997, requires that a permanency plan be made for each child no later than 12 months after entry into foster care and that a petition to terminate parental rights typically be filed when a child has been in foster care for at least 15 of the previous 22 months. The Fostering Connections and Promoting Adoptions Act of 2009 (P.L. 110-351) focused on incentives for guardianship and adoption, supports for the young adults at the age of emancipation, and rights of Native American children to care within their tribe. This latter act also contained a clause requiring states to develop and coordinate healthcare systems for children in foster care in collaboration with Medicaid and pediatricians.

EARLY CHILDHOOD TRAUMA LEADS TO POOR HEALTH OUTCOMES

Children in foster care have high rates of early childhood trauma and adversity. More than 70% have a history of abuse, neglect, or both. More than 80% have experienced significant domestic and/or community violence. Birth parents have high rates of mental illness, criminal justice system involvement, substance abuse, unemployment, and cognitive impairment. Many children have had prenatal substance exposure, multiple caregivers of varying quality, and are from families with long involvement with child protective services.

Removal from the family of origin may compound trauma although some children experience relief at removal from a chaotic, abusive, or dangerous home. Most children miss their family, worry about their parents and siblings, and long for reunification. Separation, loss and grief, unpredictable contact with birth parents, placement changes, the process of terminating parental rights, and the sheer uncertainty of foster care may further erode a child's well-being.

Childhood trauma is correlated with poor developmental, behavioral and health outcomes. Early trauma and chronic stress adversely affect the neurobiology of the developing brain, especially those areas involved in attention, emotional regulation, memory, executive function, and cognition. As a result, shortened attention span, hyperactivity, poorer cognitive function, aggression, and memory issues are problems encountered frequently encountered among children in foster care.

HEALTH ISSUES

Multiple childhood adversities and the receipt of fragmented and inadequate health services before placement into foster care mean that children enter foster care with a high prevalence of chronic medical, mental health, developmental, dental, and educational problems (Table 38-1), and so are defined as children with special healthcare needs. The greatest single healthcare need of this population is for high-quality, evidence-based mental health services to address the impacts of prior and ongoing trauma, loss, and unpredictability. In addition, they have higher rates of asthma, growth failure, obesity, vertically transmitted infections, and neurologic conditions than the general pediatric population. Adolescents need access to reproductive health and substance abuse services. Up to 60% of children <5 yr have a developmental delay in at least 1 domain and more than 40% of school-age children qualify for special education services. Unfortunately, educational difficulties persist despite improvements in school attendance and performance after placement in foster care.

Table 38-1 Health Issues of Children in Foster Care
CHRONIC MEDICAL PROBLEMS Affect 40-60% of children Asthma, dermatologic, neurologic, obesity, growth failure, hearing, and vision problems are most common
ABUSE AND NEGLECT >70% of children have a history of abuse and neglect at entry into foster care Monitor at all health visits for abuse or neglect
COMPLEX CHRONIC MEDICAL PROBLEMS Involves 10% of children in foster care Children may be dependent on medical technologies or have multiple disabilities
MENTAL HEALTH CONCERNS Affects 80% of children >4 yr of age Result of childhood trauma and adversity Most common diagnoses are adjustment disorder, posttraumatic stress disorder, attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder Externalizing problems are more likely to result in therapy
DEVELOPMENTAL PROBLEMS 60% of children <5 yr of age have at least 1 documented delay Commonly affect communication, cognition, problem-solving, and personal-social domains
DENTAL PROBLEMS 35% of children have significant dental disease
ADOLESCENT HEALTH ISSUES High rates of sexually transmitted infections, high-risk behaviors, and substance abuse
EDUCATIONAL PROBLEMS Half of special education placements relate to behavioral or emotional issues, not cognitive Only 32% of adolescents eventually graduate from high school; 32% obtain a General Equivalency Diploma
FAMILY RELATIONSHIP PROBLEMS 100% of children have family relationship problems

Although children in foster care are children with special healthcare needs, often they lack access to the services they need. Most public and private child welfare agencies do not have formal arrangements for accessing the needed array of health services and rely on local physicians and/or health clinics funded by Medicaid. Health histories are often sparse at admission because many have lacked regular care or their biological parents may not be available or forthcoming. Once children enter foster care, there is often a diffusion of responsibility across caregivers and child welfare. Foster parents usually receive little information about a child's healthcare needs, but they are typically expected to decide when and where children receive healthcare services. Child welfare case workers are responsible for ensuring that a child's health needs are addressed but coordination across multiple healthcare providers may be daunting. Uncertainty about who is legally responsible for making healthcare treatment decisions and who may have access to health information may delay or result in the denial of healthcare services.

HEALTHCARE FOR CHILDREN AND ADOLESCENTS IN FOSTER CARE

The American Academy of Pediatrics (AAP) and Child Welfare League of America published updated general guidelines for the healthcare of this special needs population in 2007. The AAP has published detailed healthcare standards for children in foster care, available on the *Healthy Foster Care America* website. Children should receive healthcare services in a medical home setting where they receive comprehensive healthcare that is continuous over time (Table 38-2). Compassionate, culturally competent healthcare that is trauma-informed means that health staff should understand the effects of past trauma and ongoing uncertainty and loss on a child's health and well-being, and that of their birth and foster families. Children should be seen early and often when they first enter foster care to identify all their health issues, and to support the child and foster parent through a major transition that involves considerable loss and adjustment for the child and many challenges for the foster parent.

The AAP recommends that every child in foster care have comprehensive medical, dental, developmental, and mental health assessments within 30 days of entering foster care. Almost every child in foster care deserves a full mental health evaluation to assess for the impact of trauma and loss on emotional well-being. Psychotropic medication should only be considered, if at all, after a thorough high-quality mental health evaluation by a pediatric-trained mental health professional. It is wise for the pediatrician to remember that inattention, impulsivity and hyperactivity may reflect the impact of past trauma on the developing brain rather than attention-deficit/hyperactivity disorder (see Chapter 33). Childhood trauma impairs cognition and memory (see Chapter 40) so that children <6 yr of age should receive a comprehensive developmental assessment, while older children should receive a comprehensive educational assessment. The caseworker should provide consents for healthcare and any available health history, and encourage the appropriate involvement of the birth parent. The primary care provider should help caseworkers and foster parents obtain and interpret the results of these assessments. Pediatricians, caregivers, and caseworkers should share health information.

Foster parents are the major therapeutic intervention of the foster care system, and pediatricians should provide them with appropriate education and support. Important topics include positive parenting strategies, supporting children through transitions, providing a consistent and nurturing environment, and helping children heal from past trauma and adversity (Table 38-3). Foster and birth parents may need extensive education about behavioral and emotional problems within the context of the child's trauma history to remove blame and promote healing. Minimizing conflict among caregivers is extremely important as a child ideally has affection and loyalty for all of the child's caregivers. Pediatricians should focus on both caregiver (foster and birth

Table 38-2 Pediatric Medical Home for Children in Foster Care

CHARACTERISTIC	APPLICATION IN FOSTER CARE
Comprehensive healthcare	Perform comprehensive admission assessment within 30 days of entry Ensure access to mental health, developmental, and dental evaluation and services Screen and refer as needed for abuse and neglect
Coordination of care	Make timely referrals and follow up subspecialist visits Communicate with caseworkers, foster parents, and legal professionals Maintain a comprehensive medical record despite changes in placement
Compassionate care	Understand and educate children, families, and other healthcare professionals on the impact of early childhood adversities, trauma and ongoing uncertainties of foster care on the developing child Promote positive purposeful parenting strategies and minimizing conflict among caregivers
Child-centered and family-focused care	Prioritize the needs of children first and foremost Partner with families to increase understanding of a child's needs Focus on the strengths of children and families
Continuity of care	Invite children to remain patients throughout their stay in foster care, and beyond when feasible
Cultural competence	Extend this concept to include the microculture of foster care and the multiple transitions that can further erode a child's well-being. Understand the roles of caseworkers, foster parents, law guardians, etc.
Accessibility	Create a welcoming environment for children and all of their families (birth, foster, kin, preadoptive)

Table 38-3 Anticipatory Guidance for Children in Foster Care

SITUATION	ANTICIPATORY GUIDANCE FOR FOSTER PARENTS
Preparing for visits	Educate foster/kinship parents about impact of visitation on children Send familiar object with child to visit Have child draw picture to give birth parent Reassure child that foster parent will be there when child returns from visits Advise all caregivers to minimize conflict with and negativity toward each other
Returning from visits and other transitions	Greet child warmly and help with unpacking Establish reentry rituals, such as quiet play, reading together, having a healthy snack
Relationship with birth parent(s)	Encourage caseworker to have birth parents keep child's rituals and routines consistent with those in foster home (vice versa when appropriate) Focus on birth parent's positive qualities; maintain a neutral affect
Building on child's strengths	Encourage participation in child-directed play. Encourage participation in normalizing activities (such as hobbies or sports) "Catch the child being good" Encourage specific praise Provide child with words for emotions Ignore negative behavior unless there is a safety issue
Preparing for court dates	Foster/kinship parent, caseworker or law guardian should explain purpose of court hearings to child in simple terms
School	If changing schools, visit school together a few times, and meet the teacher Check in regularly (weekly or monthly depending on need) with child's teacher
Adolescent	Decide what issues demand firm limits and guidelines (curfews, no smoking, party at a friend's house, etc.), what issues are not important and can be left up to teen (hair length and color, etc.) and what issues are ideal for negotiation (transportation to a school function, style of dress etc.) Encourage responsible decision-making by recognizing and complimenting it. Encourage after-school activities. Teach driving when age and developmentally appropriate Encourage teen to seek employment and teach job skills Help teen to identify mentors and focus on the future

parent) and child strengths. For teens and young adults in foster care, the pediatrician should provide anticipatory guidance around education, identity formation in the face of past trauma, independent decision making, health promotion, and developing the skills and competencies needed for a successful future life. The pediatrician should advocate for placement stability in a nurturing and responsive foster family where caregivers possess the appropriate skills to help children and youth heal.

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Chapter 39

Impact of Violence on Children

Marilyn C. Augustyn and
Barry S. Zuckerman

The reach of violence, whether as the victim, perpetrator, or witness, whether in person or through the media, is far, deep, and long-standing across the globe (see Chapter 1). Exposure to violence disrupts the healthy development of children in a myriad of ways. Pediatric clinicians must be competent to address these issues in impacted children and families under their care and also have a wider responsibility to advocate on local, state, national, and international levels for safer environments in which all children can grow and thrive.

Witnessing violence is detrimental to children. Because their scars as bystanders are emotional and not physical, the pediatric clinician may not fully appreciate their distress and thereby miss an opportunity to provide needed interventions. For children not living in war zones, the source of first exposure to violence is often **intimate partner violence.** According to data from the National Center for Posttraumatic Stress Disorder (PTSD), 20-30% of American women will be physically abused by a partner at least once in their lifetimes. Similarly in the 2010 National Intimate Partner and Sexual Violence Survey administered by the Centers for Disease Control and Prevention (CDC), 1 in 4 women and 1 in 7 men have been the victim of severe physical violence by an intimate partner, affecting more than 12 million people each year. Slightly more than half of female victims of intimate partner violence live in households with children <12 yr of age; family violence is most likely to be perpetrated by those between the ages of 18 and 30 yr and most victims are impacting before 24 yr of age. Across studies, 7-23% of youths in general population surveys experienced exposure to intimate partner violence, 36-39% of youth in intimate partner violence cases have witnessed the violence, and 45-46% of primary caregivers in child maltreatment investigations have experienced intimate partner violence. In a national survey, 50% of the men who frequently assaulted their wives also frequently abused their children. Most of the children were injured when they intervened to protect their mother from her partner (see Chapter 40). Children who witness domestic violence are at higher risk for negative medical outcomes including increased risk of obesity, asthma, and PTSD. In addition, these children are at higher risk for other traumatic events; for example, in a sample of 120 preschool children (age 4-6 yr) exposed to intimate partner violence in the past 2 yr, 38% were exposed to additional traumatic events, including sexual assaults by family members, physical assaults, serious accidents, and/or life-threatening illnesses.

Another source of witnessed violence is **community violence.** Community violence in the United States is a serious problem that disproportionately affects children from low-income areas. According to the 2011 National Survey of Children's Exposure to Violence, approximately 22% of children had witnessed violence in their family or in their community in the year prior to the survey, and of all the horrors the survey inquired about—assaults and bullying, sexual victimization, maltreatment by a caregiver, and theft or vandalism—nearly 60% of children had experienced or witnessed one of them. Young children living in high crime and violence areas observe death more frequently and at younger ages than do children growing up in more secure surroundings. Witnessing acts of violence may be a significant stressor in children's lives. If children's coping skills are not sufficient to deal with violent situations, stress may be manifested as psychological, physical, or behavioral symptoms.

Table 39-1	Public Health Recommendations to Reduce Effects of Media Violence on Children and Adolescents

Parents should:
- Be made aware of the risks associated with children viewing violent imagery, as it promotes aggressive attitudes, antisocial behavior, fear, and desensitization
- Review the nature, extent, and context of violence in media available to their children before children view
- Assist children's understanding of violent imagery appropriate to their developmental level

Professionals should:
- Offer support and advice to parents who allow their children unsupervised access to extreme violent imagery as this could be seen as a form of emotional abuse and neglect
- Educate all young people in critical film appraisal, in terms of realism, justification, and consequences
- Exercise greater control over access to inappropriate violent media entertainment by young people in secure institutions
- Use violent film material in anger management programs under guidance

Media producers should:
- Reduce violent content and promote antiviolence themes and publicity campaigns
- Ensure that when violence is presented it is in context and associated with remorse, criticism, and penalty
- Ensure that violent action is not justified or its consequences understated

Policy makers should:
- Monitor the nature, extent, and context of violence in all forms of media and implement appropriate guidelines, standards, and penalties
- Ensure that education in media awareness is a priority and a part of school curricula

From Browne KD, Hamilton-Giachritsis C: The influence of violent media on children and adolescents: a public-health approach, Lancet *365:702-710, 2005.*

The most ubiquitous source of witnessing violence for children in the United States is **media violence.** The average child 2-5 yr of age watches 20-30 hr of television a week, hours that are increasingly filled with scenes of violence, not only on commercial television but also on news outlets. In addition, the wider array of "screen time" children are exposed to, including computer, smart phones, and video games, increases the opportunities for violent events to enter the lives of children. In particular, recent tragic events, including mass shootings and acts of terrorism, have increased the specter of fear among children. Although exposure to media violence cannot be equated to exposure to real-life violence, many studies confirm that media violence desensitizes children to the meaning and impact of violent behavior. Not all children are equally affected by media violence. Children most at risk from viewing violence may be children who are also exposed regularly to real-life violence in their homes and communities. Table 39-1 lists interventions to reduce exposure to media violence.

IMPACTS OF VIOLENCE

The violence children experience and witness also has a profound impact on health and development. In a cross-sectional analysis of a Head Start preschool-age cohort, being abused, exposure to domestic violence, and having a mother using substances were associated with a higher number of health problems. Beyond injuries, violence affects children psychologically and behaviorally; it may influence how they view the world and their place in it. Children can come to see the world as a dangerous and unpredictable place. This fear may thwart their exploration of the environment, which is essential to learning in childhood. Children may experience overwhelming terror, helplessness, and fear even if they are not immediately in danger. Preschoolers are most vulnerable to threats that involve the safety (or perceived safety) of their caretakers. High exposure to violence in older children correlates

with poorer performances in school, symptoms of anxiety and depression, and lower self-esteem. Violence, particularly domestic violence, can also teach children especially powerful early lessons about the role of violence in relationships. Violence may change the way that children view their future; they may believe that they could die at an early age and thus take more risks, such as drinking alcohol, abusing drugs, not wearing a seatbelt, and not taking prescribed medication.

Some children exposed to severe and/or chronic violence may suffer from PTSD, exhibiting constricted emotions, difficulty concentrating, autonomic disturbances, and reenactment of the trauma through play or action (see Chapters 1 and 25). Although young children may not fully meet these criteria, certain behavioral changes are commonly associated with exposure to trauma, such as sleep disturbances, aggressive behavior, new fears, and increased anxiety about separations ("clinginess"). A particular challenge in treating and diagnosing pediatric PTSD is that a child's caregiver exposed to the same trauma may be suffering from it as well.

Diagnosis and Follow-up

The simplest way to recognize whether violence has become a problem in a family is to screen both the parents and the children (after ≈8 yr of age) on a regular basis. This practice is particularly important during pregnancy and the immediate postpartum period when women may be at highest risk for being abused. It is important to assure families that they are not being singled out, but that all families are asked about their exposure to violence. A direct approach may be useful: "Violence is a major problem in our world today and one that impacts everyone in our society. Thus I have started asking all my patients and families about violence that they are experiencing in their lives. …" In other cases, beginning with general questions and then moving to the specific may be helpful. "Do you feel safe in your home and neighborhood? Has anyone ever hurt you or your child?" When violence has impacted the child, it is important to gather details about symptoms and behaviors.

The pediatric clinician can effectively counsel many parents and children who have been exposed to violence. Regardless of the type of violence to which the child has been exposed, the following components are part of the guidance: careful review of the facts and details of the event, gaining access to support services, providing information about the symptoms and behaviors common in children exposed to violence, assistance in restoring a sense of stability to the family in order to enhance the child's feelings of safety, and helping parents talk to their children about the event. When the symptoms are chronic (>6 mo in duration) or not improving, if the violent event involved the death or departure of a parent, if the caregivers are unable to empathize with the child, or if the ongoing safety of the child is a concern, it is important that the family be referred to mental health professionals for additional treatment.

Bibliography is available at Expert Consult.

39.1 Bullying, Cyberbullying, and School Violence

Douglas Vanderbilt and Marilyn C. Augustyn

BULLYING ("TRADITIONAL BULLYING")

Bullying is the assertion of power through social, emotional, or physical means of aggression that involves a bully repeatedly and intentionally targeting a weaker victim. Bullying affects a large number of children and lays the groundwork for long-term depression, suicidality, psychotic symptoms, conduct problems, and psychosomatic concerns seen in children. Children can move between being a bully, victim, bully-victim (both a bully and a victim at different times), or bystander. Bullying can be **direct,** involving physical aggression such as hitting, stealing, and threatening with a weapon or verbal aggression such as name-calling, public humiliation, and intimidation, or it can be **indirect,** involving relational aggression such as spreading rumors, social rejection, exclusion from peer groups, and ignoring. Bullying occurs most frequently at school when there is minimal supervision during breaks, recess, and lunch at playgrounds, in hallways, and en route to and from school.

CYBERBULLYING

Cyberbullying is an emerging form of bullying that takes place using electronic technology (text messaging, mass emailing, Internet chat rooms, social networking sites, etc.). In contrast to traditional bullying, it allows complete anonymity to the bully and has enormous capacity for "reach." Given its recent recognition and ongoing evolution, much remains unknown about its causes and therefore prevention strategies; what is clear is that the psychological consequences can be devastating for the victim. Victims of cyberbullying may be at higher risk for suicide (see Chapter 27) than victims of traditional bullying.

Epidemiology

Bullying is a common occurrence for schoolchildren. Bullying occurs in all countries, affecting anywhere from 9-54% of youth. Apparent rates of bullying are influenced by the manner in which questions are asked; youth are more willing to acknowledge having engaged in activities which can be categorized as forms of "bullying" than they are to respond to a question asking them if they have acted in a bullying manner or have been a bully.

The 2011 Indicators of School Crime and Safety reported that 28% of youth (31% females and 25% males) ages 12 to 18 yr had been bullied at school, 18% were ridiculed, 18% were the subject of rumors, 9% were cyberbullied, 8% were purposefully pushed, shoved, or tripped (leading to injury in about 1/5), 6% were purposefully excluded from activities, 5% were threatened with harm, and 3% had personal property that had been purposefully destroyed.

With regard to traditional bulling, the 2009 Youth Health Risk Behavior Survey (YHRBS), concurred that males and females were equally likely to report having been bullied (victims); males were 2.5 times more likely than females to report having bullied others. Rates of bullying or being bullied did not differ by race/ethnicity, except that Hispanics were less likely to report having bullied someone. Other surveys have found that students who carry weapons, smoke, and drink alcohol more than 5-6 days/wk were at greatest risk for moderate bullying. Those who carry weapons, smoke, have more than 1 alcoholic drink per day, have above-average academic performance, moderate/high family affluence, and feel irritable or bad-tempered daily were at greatest risk for frequent bullying. Negative parenting behavior is related to a moderate increase of risk for becoming a bully/victim and small to moderate effects on victim status at school.

Rates of cyberbullying victimization have ranged from 4-72% and of cyberbullying from 3-23%, in part reflecting variations in definitions and sampling design. According to the 2009 YHRBS, males and females were equally likely to experience cyberbullying, but males were >3-fold likely to report having been a cyberbully. Rates of cyberbullying (as victim or perpetrator) did not differ by race/ethnicity. Seniors were more likely to be involved in cyberbullying than youth in other grades.

A separate study conducted among 918 students in grades 6 through 12, found considerable overlap between traditional and cyberbullying/victimization; three-fourths were not involved as victim or bully in either traditional or cyberbullying. Most victims of traditional bullying were not involved in cyberbullying, but those with involvement were more likely to be victims. Most traditional bullies were not involved in cyberbullying but those who were, were generally bullies.

Health Outcomes

Involvement in bullying is associated with poorer psychosocial adjustment; bullies, victims, and bully-victims report greater health problems and poorer emotional and social adjustment. Victims tend to be either physically weak and emotionally vulnerable or provocative, with attention or conduct problems and have lower social status and higher social marginalization and isolation. Overall, **both** victim and

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American Academy of Pediatrics Children and Disasters http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Children-and-Disasters/Pages/About.aspx.

National Child Traumatic Stress Network http://www.nctsn.org/.

bully-victims have been described as anxious, insecure, lonely, and lacking social skills. They may have learning disabilities, autism spectrum disorder, or poor physical skills. They have more depression, psychosomatic complaints, medication use, and suicidality. Chronic or severe victimization in childhood has been shown to be associated with psychotic symptoms in early adolescence. Long-term consequences in adulthood of being bullied as a child include depression, poor self-esteem, and abusive relationships. In the 2009 YHRBS, traditional bullying victimization was a significant predictor of depression for males and females and a direct contributor to suicidal behavior for females.

Bullies have higher rates of both conduct disorders and social standing. They have the lowest rates of adjustment problems because of their higher social status. They make friends that support their bullying behavior but other peers avoid them. Bullies who acknowledge their behavior have higher rates of depression and psychologic distress compared to those who deny their bullying behavior. In the 2009 YHRBS data, traditional bullying predicted depression in females but not in males. Depression significantly mediated the relationship between bullying and suicidal behavior among both genders. They have higher negative attitudes toward school and use more tobacco, alcohol, and other drugs. Childhood bullies have a 4-fold increase in criminal behavior by their mid-20s and are at higher risk of dropping out of school. They have lower likelihood of being employed and having stable long-term romantic relationships. The bully-victim has problems with peer relationships and high rates of depression, loneliness, alcohol use, and weapon carrying.

Less is known about the characteristics of cyber bullies or victims and their long-term consequences. In the 2009 YHRBS data, cyber victimization was associated with depression in women but not men, and contributed to suicidal behavior among women. Cyberbullying was not associated with depression among men or women. Lower academic achievement and lower self-esteem are associated with cyberbullying perpetration and victimization, and anxiety symptoms with cyberbullying perpetration.

SCHOOL VIOLENCE

Epidemiology

School violence is a common but nonnormative aspect of development occurring throughout the world. Almost 40% of U.S. schools report a least 1 violent incident to police, with more than 600,000 victims of violent crime per year. Among 9th to 12th graders, 8% were threatened or injured on school property in the last 12 mo, and 14% were involved in a physical fight over the last year. School-associated violent deaths are rare. Seventeen homicides of children ages 5-18 yr occurred at school during the 2009-2010 school year. Of all youth homicides, less than 2% occur at school. These are more likely to occur at the beginning of each semester with perpetrators previously giving warning signals. Whereas urban schools experience more episodes of violence, the episodes of rare "rampage" gun violence in rural and suburban schools demonstrate that no region is immune to lethal violence.

Risk Factors

Bullying and weapon carrying may be important precursors to more serious school violence. Among perpetrators of violent deaths at school, 20% had been bullying victims, and 6% of all students carried a weapon to school in the last 30 days. Nonlethal violence, mental health problems, racial tensions, student attacks on teachers, and the effects of rapid economic change in communities can all lead to school violence. Individual risk factors for violence include prior history of violence, drug, alcohol, or tobacco use, association with delinquent peers, poor family functioning, poor grades in school, and poverty in the community.

Family risk factors include early childbearing, low parental attachment and involvement, authoritarian or permissive parenting styles, and poverty. There is more school violence in areas with higher crime rates and more street gangs, with little improvement with additional security measures. These risks take away students' ability to learn in a safe environment and leave many children with traumatic stress and grief reactions. Behavioral genetics and developmental psychology are beginning to elucidate the bidirectional gene-environment interactions that promote these endemic episodes of violence.

TREATMENT AND PREVENTION OF BULLYING AND SCHOOL VIOLENCE

Pediatric providers are in a unique position to screen, treat, and advocate for reducing the impact of school violence by assisting those affected and seeking to prevent further occurrences. **Signs** of a child being bullied include physical complaints such as insomnia, stomachaches, headaches, and new-onset enuresis (see Chapter 23.3). **Psychologic symptoms,** such as depression (see Chapter 26), loneliness, anxiety (see Chapter 25), and suicidal ideation, may occur. **Behavioral changes,** such as irritability, poor concentration, school avoidance, and substance abuse, are common. **School problems,** such as academic failure, social problems, and lack of friends, can also occur. Additional vigilance must be made for those children with chronic medical illnesses, obesity, physical deformities, and learning disabilities or autism spectrum disorder who may be potential targets. A bully may be more difficult to identify because of the bully's desire to obscure the behavior. Children who are aggressive, overly confident, lacking in empathy, and having conduct problems may need careful screening. The physical, behavioral, psychologic, and school symptoms of bullying may overlap with other conditions such as medical illness, learning problems, and psychologic disorders.

Simple questions to ask children include **BORRIS**: Have you been **bullied** or bullied anyone? Have you **observed** bullying going on? How did you **respond**? Do you feel like you are **repetitively** singled out as a bully or a victim? Have you sent or receiving things over the **Internet** that you think may represent bullying? Do you feel **stuck** in bullying situations? And for parents **WART**: Have you **witnessed** or heard about your child being picked on or picking on other kids? Have there been any recent changes about your child's **attitude,** attention and concentration changes? What are your community **rules** about bullying? Has your child **talked** to you about being picked on or witnessing other kids being picked on?

Management of bullying and school violence involves systemic interventions with parents, victims, bullies, and the school. Interventions should include supporting families, victims, and bullies; identifying and referring those children in need of further academic and mental health services; and expecting behavioral change from the bully and social change from the school environment. The clinician should listen empathetically to the child to help empower and reassure the child. The clinician should not blame the victim or trivialize the child's concern. Suggestions should include having the child seek social support from teachers and friends and avoiding situations where the bullying may occur. Role-playing an encounter can be helpful for the child. Extracurricular activities, like drama clubs, mentoring programs, and sports, can be used to help to bolster the child's self-esteem. The clinician should identify safety issues, such as suicidal ideation and plans, substance abuse, and other high-risk behaviors.

Once a bully is identified and appropriate screening for family risk factors is completed, the clinician should educate the parents and child about the seriousness of the behavior and its potential consequences. The clinician should label the behavior as the problem and help the family and child to acknowledge the behavior as hurtful. For example: "Do you feel bad when other children hurt your feelings?" "Bullying hurts other children's feelings." The school and parents should ensure accountability for the child's subsequent behavior. Parental mental health and resource risk factors should also be addressed.

Beyond individual- and family-based interactions, providers also can advocate for systemic interventions through **school-community violence and bullying prevention programs**. Targeted school curriculums or social skills group interventions have not been found to reduce bullying in several well-done studies. Successful interventions involve whole school approaches that involve multiple disciplines. These broad-based programs simultaneously include school-wide rules and

sanctions, teacher training, classroom curriculum, conflict resolution training, and individual counseling. Mentoring programs and an increased number of social workers can also be helpful in reducing bullying. Addressing access to firearms, involving community organizations and parents, enhancing the built environment of schools and community, and supporting youth self-esteem are important in creating a safe school climate. Targeting larger societal risk promoters of violence in the neighborhood and school culture are also avenues for improving school violence. In Denmark, an intensive national-level policy has led to the reduction in school bullying prevalence from 25% to 11%.

Prevention programs for cyberbullying are at a more nascent stage, reflecting uncertainty about the prevalence of the practice, who is perpetrating it and from where, and how students respond when they are victimized. One study of approximately 800 parents and 1200 of their children found that although 80% of parents had set rules regarding conduct on the Internet, 85% of the children who had engaged in cyberbullying had done so from their homes. Therefore, if the bullying is reported to the police, the police could track the IP address to find the bully. However, rates vary tremendously by survey (and country) regarding student notification of adults when cyberbullied, with less than 10% of students in a Swedish survey, one-third in a Canadian survey, and a majority in an Austrian survey having reported the victimization to an adult. Many schools have established cyberbullying policies and are increasingly involved with teaching youth about guidelines for appropriate online interactions, and monitoring for cyberbullying problems. As of July 2013, 49 states (plus Washington, DC) have enacted legislation aimed to prevent bullying and 47 states (plus Washington, DC) have specific legislation regarding electronic harassment. Pediatric clinicians must be aware of local legislative action to support children in this difficult topic. (See http://www.cyberbullying.us/Bullying_and_Cyberbullying_Laws.pdf)

Bibliography is available at Expert Consult.

39.2 Effects of War on Children

Isaiah D. Wexler and Eitan Kerem

The adverse consequences of war on children are endless—death, pain, dismemberment and other physical and cognitive disabilities, acute and chronic psychological suffering, temporary and permanent loss of family members, rape, conscription into armed service, forced relocation, famine, drought, and a litany of other untoward consequences lasting for decades after hostilities have ceased. More than 1 billion children <18 yr live in countries involved in war. The majority of sexual victims in war-torn nations are <17 yr of age. The United Nations Children's Fund (UNICEF) estimates that of the 3.6 million people killed as a result of military conflict between the years 1990 and 2003, 90% were civilian and 50% were children.

Mortality and morbidity related to the long-term effects of war and civil strife are often higher than that occurring during actual fighting. War and violence are not listed as leading causes of childhood mortality, but the regions with the highest levels of child mortality, especially among children <5 yr of age, are the same locations involved in military conflicts. Nations, especially but not limited to the least developed, devote substantial portions of their budgets to military expenditures at the expense of the healthcare infrastructure; a substantial proportion of deaths attributed to malnutrition, environmentally related infectious disease, or inadequate immunization are related to the effects of war. For example, an analysis of postwar (2003) Iraq found that mortality rates were 5.5/1,000/yr preinvasion (occurred in March 2003), and 13.2/1,000/yr for the 40 mo postinvasion; through mid-2006, there had been an estimated 654,965 fatalities above the preinvasion death rate, of which 601,027 were from violent causes. The largest group of deaths among females occurred among those <15 yr; infant and <5 yr of age mortality rates had not returned to their 1991 pre-Gulf War levels.

Table 39-2 Impact of War on Children
PHYSICAL
Death
Rape
Injuries
Amputations and fractures
Head trauma
Ballistic wounds
Blast injuries
Burns
Chemical and biologic induced
Malnutrition and starvation
Infectious disease
Displacement
PSYCHOSOCIAL
Loss of caregivers and family members
Separation from community
Lack of education
Inappropriate socialization
Acute stress reaction
Posttraumatic stress disorder
Depression
Maladaptive behavior
EXPLOITATION
Conscription as soldiers
Coerced involvement in terrorist activities
Prostitution
Slavery
Forced adoption

During wartime, customary patterns of behavior are forced to change, overcrowding is frequent, and essential resources, such as water and food staples, may be polluted or contaminated. War is associated with plagues and epidemics and novel disease entities can develop or reemerge. African nodding disease, Konzo (cassava-associated cyanide intoxication), polio, and other epidemics have been attributed to the effects of war.

The morbidity of children exposed to conflicts is significant (Table 39-2). Many more children are physically harmed than killed. Children bear the psychological scars of war resulting from exposure to violent events, loss of primary caregivers, and forced removal from their homes. During periods of war, children are more susceptible to exploitation in the forms of forced conscription as soldiers, sexual exploitation, and slavery. There are approximately 300,000 soldiers younger than the age of 18 yr who are actively participating in military conflicts worldwide. Lacking the appropriate education and socialization, the moral compass of these children is often misaligned. They are not capable of understanding the sources of conflict or why they have been targeted. Their thought processes are more concrete; it is easier for them to dehumanize their adversaries. Children, who themselves are exposed to violence and cruelty, often become the worst perpetrators of atrocities.

After cessation of hostilities, children are still at risk for life-endangering injuries from landmines and unexploded ordnance. Prior to the signing of the international treaty to ban landmines in 1997, an estimated 20,000-25,000 casualties occurred annually from landmines. In 1999, that number had decreased to 8,807 and by 2011 to 4,286. The CDC reported for a 5 yr period ending in 2006 that of the 5,741 individuals who were killed or injured by landmines or unexploded ordnance, 47.2% were children younger than the age of 18 yr. Injuries and death tended to occur while children were either playing or involved in household chores, and in contrast to adults, a large proportion of the injuries involved upper-extremity amputation. After the end of armed conflict, the continued proliferation of small arms and light weapons, which are easily handled by children, continues to take its toll on human life and hinders stabilization in postconflict societies.

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Website Resources

www.cdc.gov/ViolencePrevention/youthviolence/schoolviolence/index.html.
www.aap.org/ConnectedKids/.
www.stopbullying.gov/index.html.
www.safeyouth.org/scripts/index.asp.
http://www.ncsl.org/issues-research/educ/cyberbullying.aspx.

SUSCEPTIBILITY OF CHILDREN IN TIMES OF WAR

Children do not have the physical or intellectual capabilities to defend themselves. It is easier for adults to victimize children than to victimize other adults. Older children's curiosity, desire for adventure, and imperfect assessment of risk often lead them to participate in dangerous behavior. Younger children, because of their small size and immature physiology, are more susceptible to disease and starvation, and are more likely to sustain fatal injuries from ballistic projectiles and explosive devices such as mines. Blast injuries, which are now the most common cause of battle-related injuries, have a more devastating impact on children as compared to adults. Specific types of military engagement can have a disproportionate effect on children. In a survey of war-related mortality in Iraq from 2003-2008, it was found that approximately 10% of the violence-related fatalities were children. Most children succumbed to either small-arms gunfire or suicide bombs (35%). When compared to adults, a proportionately higher rate of children died as a result of the usage of indiscriminant types of weaponry such as mortars, missiles, and aircraft-delivered bombs; 40% of the total casualties in these types of attacks were children.

During times of war, there is a breakdown of social inhibitions and cultural norms. Aberrant behavior such as rape, torture, and pillaging, which would be nearly inconceivable in times of peace, is common during war. Children may be attacked or used as human shields.

The changing nature of war has adversely affected children. Conventional warfare in which armies of professional soldiers representing different countries battle each other has become less common. Intrastate conflicts in the form of civil war are more frequent. Of the approximately 200 armed conflicts occurring after World War II, three-quarters have been intrastate. These conflicts are often rooted in ethnic or religious differences, and the participants are frequently nonprofessional "irregulars" who lack discipline and accountability to higher echelons, and are directed by those who do not acknowledge or respect international accords governing warfare. Often the military resources of the antagonists are disproportionate, leading the weaker protagonist to develop compensatory tactics that can include guerrilla, paramilitary, and terrorist activities, while the stronger side often resorts to the disproportionate use of force. Low-intensity conflicts have become more common. These types of conflicts are often characterized by military activities targeting civilian populations with the goal of disrupting normal routines and generating publicity for the perpetrators. Children are often victims, as this serves to maximize the impact of terrorist activity.

Terrorism and organized urban-based gang warfare violence have become more prevalent. Violence perpetrated by terrorists groups or gangs is designed to coerce and/or intimidate both individuals and entire societies. The destruction of the New York City World Trade Center Towers in 2001 and the nearly 3,000 fatalities showed that highly organized and motivated terrorists have few inhibitions and can strike anywhere. Biologic and chemical terrorism have also been realized, with the most recent example being the use of sarin gas, a deadly volatile nerve agent, in the Syrian civil war. Children are more susceptible to chemical and biologic toxins because of their higher respiratory rates, more permeable skin, and other developmental vulnerabilities (see Chapter 723).

The media has had a significant role in exacerbating the effects of war on children. Media coverage of war and terrorist events is extensive and graphic. Children, who are more impressionable than adults, often view this material in an uncontrolled fashion. Uncensored pictures of victims, unbridled violence, people in shock, or family members searching through ruins for relatives may traumatize children and even encourage inappropriate behavior. Overt broadcast propaganda glorifying war and violence may sway children to participate in militaristic or antisocial activities.

PSYCHOLOGIC IMPACT OF WAR

Exposure to war and violence can have a significant impact on a child's psychosocial development. Displacement, loss of caregivers, physical suffering, and the lack of appropriate socialization all contribute to abnormal child development (see Table 39-2). Often the reactions are age-specific (Table 39-3). Preschoolers may have an increase in somatic complaints and sleep disturbances, and have acting-out behavior such as tantrums or excessively clinging behavior. School-age children will show regressive behavior such as enuresis and thumb sucking. They, too, have an increase in somatic complaints; there is often a negative impact on school performance. For teenagers, psychological withdrawal and depression are common. Adolescents often exhibit trauma-stimulated acting-out behavior. Motivated by the desire for revenge, they may be quick to join in the violence and contribute to the continuation of conflict.

Table 39-3	Manifestations of Stress Reactions in Children and Adolescents Exposed to War, Terrorism, and Urban Violence
CHILDREN ≤6 YEARS	
Excessive fear of separation	
Clinging behavior	
Uncontrollable crying or screaming	
Freezing (persistent immobility)	
Sleep disorders	
Terrified affect	
Regressive behavior	
Expressions of helplessness and passivity	
CHILDREN 7-11 YEARS	
Decline in school performance	
Truancy	
Sleep disorders	
Somatization	
Depressive affect	
Abnormally aggressive or violent behavior	
Irrational fears	
Regressive and childish behavior	
Expressions of fearfulness, withdrawal, and worry	
ADOLESCENTS 12-17 YEARS	
Decline in school performance	
Sleep disturbances	
Flashbacks	
Emotional numbness	
Antisocial behavior	
Substance abuse	
Revenge fantasies	
Suicidal ideation	
Withdrawal	

There is an increased incidence of both acute stress reactions and PTSD (see Chapter 25). The true incidence is difficult to assess because of the heterogeneous nature of war, degree of exposure to violence, and methodological challenges related to the precise characterization of PTSD. The incidence of PTSD among children and adolescents living in Middle East countries that have experienced substantial armed conflict appear to be high: 5-8% in Israel, 23-70% in Palestine, and 10-30% in Iraq. Risk factors for having a more serious psychological response to a violent event include severity of the incident, personal involvement (physical injury, proximity, loss of a relative), prior history of exposure to traumatic events, female gender, and a dysfunctional parental response to the same event. It is not unusual for children to develop PTSD many years after the traumatic event. Children do not have to be directly exposed to violent activity, and media coverage of terrorist events may be sufficient to trigger PTSD.

The trauma experienced by children during war can have lifelong effects. Studies on children imprisoned in concentration camps or evacuated from their homes in London during the Battle of Britain show that these individuals were at greater risk for PTSD, anxiety disorders, and a higher level of dissatisfaction with life. Individuals who suffered wartime trauma can pass on certain traits to their children, including a greater propensity for PTSD. However, children are resilient. With appropriate support from family and community

together with timely and intensive psychological intervention, children can recover and lead normal, productive lives despite the searing trauma that they may have experienced.

EFFORTS TO PROTECT CHILDREN FROM THE EFFECTS OF WAR

International Conventions

War and terror violate the human rights of children, including the right to life, the right to be nurtured and protected, the right to develop appropriately, the right to be with family and community, and the right to a healthy existence. Several international treaties and conventions have been ratified, beginning with the **Fourth Geneva Convention** (1949) that set forth guidelines regarding appropriate treatment of children in times of war. The **United Nations Convention on the Rights of the Child** (1990) delineated specific human rights inherent to every child (defined as any individual younger than the age of 18 yr), and the subsequent **First Optional Protocol** (2000), which prohibits conscripting or recruiting children for military activities. **The Rome Statute of the International Criminal Court,** which was enacted in 2002, declared that the conscription or enlistment of children younger than the age of 15 yr is a prosecutable war crime. As of 2010, a decade since their passage, the number of armed conflicts in which children were serving as soldiers had decreased from 36 to 16 worldwide.

Although these treaties and conventions define the extent of protection afforded to children, the means of enforcement available to the international community is limited. Individuals, motivated by religious fervor, nationalistic zeal, or ethnic xenophobia, are unlikely to curb their activities because of fear of prosecution. These treaties better serve in heightening awareness regarding the protected status of children in wartime, and perhaps deter high-ranking leaders who fear being held accountable for war crimes.

Humanitarian Efforts

Several organizations, either nongovernmental or under the auspices of the United Nations, are involved in mitigating the effects of war on children. These organizations, which include the International Red Cross, UNICEF, United Nations Refugee Agency (UNCHR), International Rescue Committee, World Health Organization, and Médicins Sans Frontières (Doctors Without Borders), have had a significant impact on reducing violence-related casualties in war-torn regions. The infusion of humanitarian aid into developing countries often improves overall mortality and morbidity by increasing the level of medical and social services available to the general population. Other organizations, such as Amnesty International, Stockholm International Peace Research Institute, and Physicians for Human Rights, actively monitor human rights abuses involving children and other civilian groups. In 2005, the United Nations Security Council approved the establishment of a monitoring and reporting system designed to protect children exposed to war. United Nations–led task forces conduct active surveillance in war-stricken regions reporting on the *6 grave violations against children during armed conflict:* the killing or injuring of children, recruitment of child soldiers, attacks directed against schools or hospitals, sexual violence against children, abduction of children, and denial of humanitarian access for children.

THE ROLE OF PEDIATRICIANS AND ALLIED HEALTH PROFESSIONALS

War is a chronic condition and health providers need to be prepared to treat childhood casualties resulting from military or terrorist activity as well as caring for children suffering from the aftermath of war or related violence. Community and hospital pediatricians need to be involved in community disaster planning. General disaster planning should not ignore the unique needs and requirements of children; in planning for a possible chemical attack, appropriate resuscitation equipment suitable for children needs to be stockpiled. The signs of biologic infection or chemical intoxication are different for children, and pediatricians and emergency personnel need to be aware of these differences (see Chapters 719 and 723). Surveys of pediatricians and other healthcare providers indicate that many feel unprepared for bioterrorism attacks. Professional organizations such as the American Academy of Pediatrics and the CDC have published position papers; there is a special section in the American Academy of Pediatrics *Red Book* that presents guidelines for treating specific pathogens likely to be utilized in biologic warfare. In regions where violent terrorist activity is likely, pediatricians, nurses, and rescue personnel should consider becoming certified in the Red Cross Basic and Advanced Trauma Life Support.

Pediatricians need to be cognizant of the effects that war and terror can have on parents and children. Parents, who themselves are under tremendous strain, may not be sensitive to the effects that the same stressors have on their children. Pediatricians should draw out both parents and children, and encourage them to talk freely about their feelings. Child healthcare providers can be instrumental in educating parents to be more aware of inappropriate responses by children to war and violence. When necessary, pediatricians can serve their families by referring them to appropriate support services.

Just as it is important to administer first aid for physical trauma, it is also critical to provide psychologic first aid to victims of trauma. An excellent source of online information for both providers and caregivers is provided by the National Child Traumatic Stress Network (www.nctsn.org). In day-to-day patient interactions, a pediatrician is most likely to confront situations related to stress reactions such as PTSD or depressive disorders. Recognition of PTSD is essential so that early treatment can be initiated. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* stipulates that for a diagnosis of PTSD, there has to be manifestations from each of four symptom clusters: intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity. The DSM-V also established a special preschool subtype of PTSD which has the same four symptom clusters but with specific manifestations that are typical of preschoolers exposed to trauma (see Chapter 25). Clues to the presence of PTSD and acute anxiety reactions include changes in behavior, school performance, affect, and sleep patterns, and an increase in somatic complaints. Even when the triggering event is neither temporally nor physically proximate, it should not dissuade the pediatrician from making an appropriate referral to mental health professionals who are expert in childhood stress disorders.

Medical professional standards demand from each physician that the physician treat all patients equitably without regard to their background. Both international law and professional medical societies ban physicians from actively participating in torture or other activities that infringe on human rights, including those of children. It is difficult to countenance any situation in which a health professional, even acting as a representative of his or her country, might directly or indirectly injure a minor.

Health professionals have an important role in preventing the atrocities that occur to children. In their role as advocates for the rights of children, pediatricians can be instrumental in focusing public attention on the precarious situation of children exposed to brutality and mayhem that are part and parcel of organized violence. They can promulgate the message that war and terror should not be allowed to rob children of their childhood.

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Chapter 40

Abused and Neglected Children

Howard Dubowitz and Wendy G. Lane

The maltreatment (including abuse and neglect) of children is a pervasive problem in nations throughout the world (Fig. 40-1), with short- and long-term physical and mental health and social consequences to the child, family, community, and society at-large. In addition to the child healthcare professionals' responsibility to identify maltreated children and help ensure their protection and health, they should assume vital roles related to prevention, treatment, and advocacy. Rates and policies vary greatly among nations and often within nations. Rates of maltreatment and provision of services are affected by the overall policies of the country, province, or state governing recognition and responses to child abuse and neglect. Two broad approaches have been identified: a child and family welfare approach, with a focus on the family as a whole, and a child safety approach, with the focus on the child perceived to be at risk. The United States has primarily had a child safety approach.

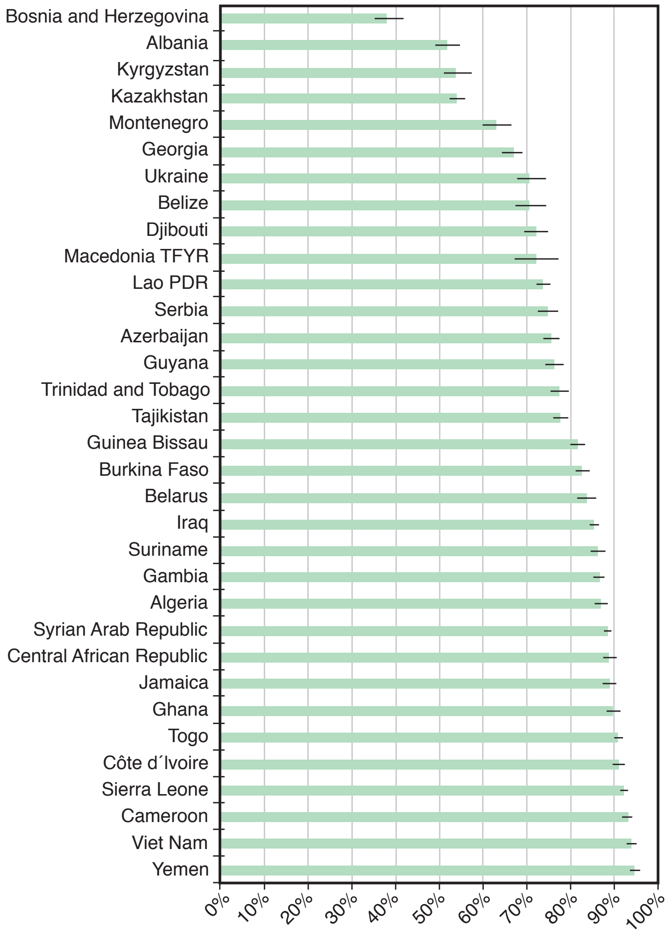

Figure 40-1 Percentage of children ages 2-14 yr who experienced any violent discipline (physical punishment and/or psychological aggression) in the past month, by country. *(From UNICEF,* Child disciplinary practices at home: evidence from a range of low- and middle-income countries, 2010. http://www.childinfo.org/discipline.html.*)*

DEFINITIONS

Abuse is defined as acts of commission and **neglect** as acts of omission. The U.S. government defines child abuse as "any recent act or failure to act on the part of a parent or caretaker, which results in death, serious physical or emotional harm, sexual abuse or exploitation, or an act or failure to act which presents an imminent risk of serious harm." Some states in the United States also include other household members. Children may be found in situations in which no actual harm has occurred and no imminent risk of serious harm is evident, but potential harm may be a concern. Many states include potential harm in their child abuse laws. Consideration of potential harm enables preventive intervention, although predicting potential harm is inherently difficult. Two aspects should be considered. One is the likelihood of harm; the other is the severity of that harm.

Physical abuse includes beating, shaking, burning, and biting. Corporal punishment in any form is increasingly being prohibited. The Global Initiative to End All Corporal Punishment of Children reported that 33 countries have prohibited corporal punishment in all settings, including the home. Governments in at least an additional 18 countries are publicly committed to prohibition in all settings. The majority of countries have prohibited corporal punishment in settings outside the home—in schools (117 countries), in penal institutions (121 countries), and as a sentence of the courts (157 countries). In the United States, corporal punishment in the home is lawful in all states, but 31 states have banned corporal punishment in public schools and the Supreme Court has ruled it unlawful as punishment for a crime.

Internationally, a high proportion of children continue to experience corporal punishment. At the beginning of 2013, 33 countries had banned all corporal punishment, while in 165 some form of corporal punishment is permitted, including 41 countries in which children can be sentenced to corporal punishment for committing a crime.

The threshold for defining corporal punishment as abuse is unclear. One can consider any injury beyond transient redness as abuse. If parents spank a child, it should be limited to the buttocks, should occur over clothing, and should never involve the head and neck. When parents use objects other than a hand, the potential for serious harm increases. Acts of serious violence (e.g., throwing a hard object, slapping an infant's face) should be seen as abusive even if no injury ensues; significant risk of harm exists. Although some child healthcare professionals think that hitting is acceptable under limited conditions, almost all believe that more constructive approaches to discipline are preferable. Although many think that hitting a child should never be acceptable, and many studies have documented the potential harm, there remains a reluctance in the United States to label hitting as abuse unless there is an injury. It is clear that the emotional impact of being hit may leave the most worrisome scar, long after the bruises fade and the fracture heals.

Sexual abuse has been defined as "the involvement of dependent, developmentally immature children and adolescents in sexual activities which they do not fully comprehend, to which they are unable to give consent, or that violate the social taboos of family roles." Sexual abuse includes exposure to sexually explicit materials, oral–genital contact, genital-to-genital contact, genital-to-anal contact, and genital fondling. Any touching of "private parts" by parents or caregivers in a context other than necessary care is inappropriate.

Neglect refers to omissions in care, resulting in actual or potential harm. Omissions include inadequate healthcare, education, supervision, protection from hazards in the environment, and unmet physical needs (e.g., clothing, food) and emotional support. A preferable alternative to focusing on caregiver omissions is to instead consider the basic needs (or rights) of children (e.g., adequate food, clothing, shelter, healthcare, education, nurturance); neglect occurs when a need is not adequately met and results in actual or potential harm, whatever the reasons. A child whose health is jeopardized or harmed by not receiving necessary care experiences medical neglect. Not all such situations

necessarily require a report to **child protective services (CPS)**; less-intrusive initial efforts may be appropriate.

Psychological abuse includes verbal abuse and humiliation and acts that scare or terrorize a child. Although this form of abuse may be extremely harmful to children, resulting in depression, anxiety, poor self-esteem, or lack of empathy, CPS seldom becomes involved because of the difficulty in proving such allegations. Child healthcare professionals should still carefully consider this form of maltreatment, even if the concern fails to reach a legal or agency threshold for reporting. These children and families can benefit from counseling and social support. Many children experience more than 1 form of maltreatment; CPS may be more likely to address psychological abuse in the context of other forms of maltreatment.

Internationally, problems of **trafficking** in children, for purposes of cheap labor and/or sexual exploitation, expose children to all of the forms of abuse just noted.

INCIDENCE AND PREVALENCE

Global Situation

Child abuse and neglect are not rare and occur worldwide. Based on international studies, the World Health Organization (WHO) has estimated that approximately 20% of women and 5-10% of men report being sexually abused as children, while 25-50% of all children report being physically abused. Many children experience emotional abuse and neglect. Rates of child abuse overall and both corporal and psychological vary greatly by this sample of lower- and middle-income nations. Although more difficult to detect and therefore probably underestimated, reports of psychological abuse tend to be somewhat higher than those of physical abuse (Fig. 40-2).

Situation in the United States

Abuse and neglect mostly occur behind closed doors and often are a well-kept secret. Nevertheless, there were 3.4 million reports to CPS involving 6.2 million children in the United States in 2011. Of the 681,000 children with substantiated reports, 78.5% experienced neglect, 17.6% physical abuse, 9.1% sexual abuse, and 9% psychological maltreatment. These rates of substantiated maltreatment continue a trend where neglect has remained at a steady rate since the early 1990s, whereas both sexual and physical abuse rates have declined by approximately 50%. Medical personnel made 8.4% of all reports. The rate of hospitalized children with serious physical abuse has *not* declined in recent years, raising the possibility of CPS trends not necessarily representing a true decline.

Etiology

Child maltreatment seldom has a single cause; rather, multiple and interacting biopsychosocial **risk factors** at 4 levels usually exist. To illustrate, at the *individual level*, a child's disability or a parent's depression or substance abuse predispose a child to maltreatment. At the *familial level*, intimate partner (or domestic) violence presents risks for children. Influential *community factors* include stressors such as dangerous neighborhoods or a lack of recreational facilities. Professional inaction may contribute to neglect, such as when the treatment plan is not clearly communicated. Broad *societal factors*, such as poverty and its associated burdens, also contribute to maltreatment. WHO estimates the rate of homicide of children is approximately 2-fold higher in low-income compared to high-income countries (2.58 vs. 1.21 per 100,000 population), but clearly homicide occurs in high-income countries. Children in all social classes can be maltreated, and child healthcare professionals need to guard against biases concerning low-income families.

Protective factors, such as family supports, or a mother's concern for her child, may buffer risk factors and protect children from maltreatment. Identifying and building on protective factors can be vital to intervening effectively. One can say to a parent, for example, "I can see how much you love ____. What can we do to keep her out of the hospital?" Child maltreatment results from a complex interplay among risk and protective factors. A single mother who has a colicky baby and who recently lost her job is at risk for maltreatment, but a loving

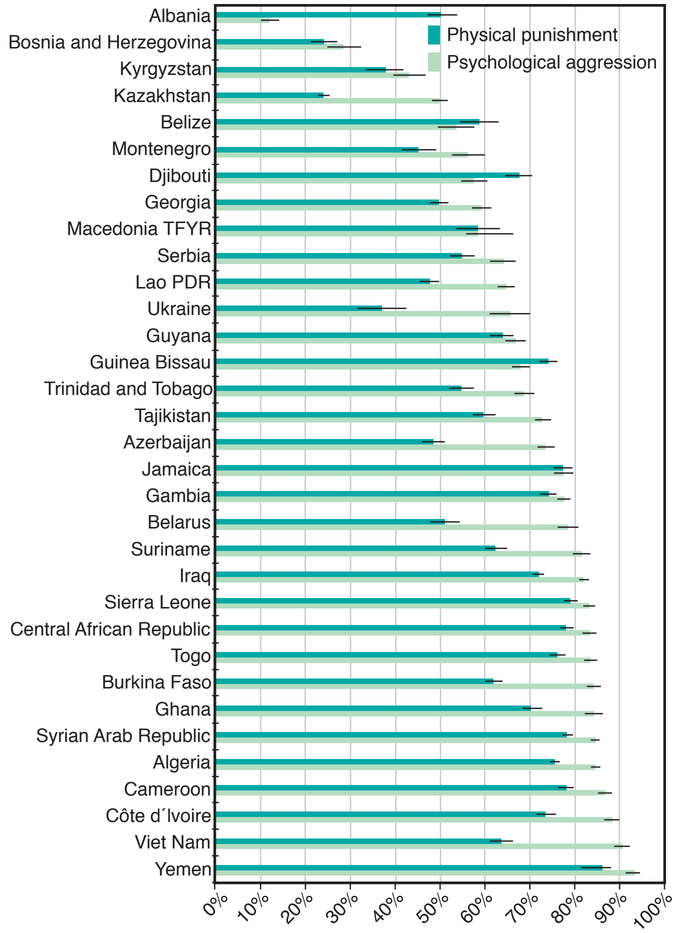

Figure 40-2 Percentage of children ages 2-14 yr who experienced psychological aggression and percentage of children ages 2-14 yr who experienced physical punishment in the past month, by country, 2005-2006. *(From UNICEF,* Child disciplinary practices at home: evidence from a range of low- and middle-income countries, 2010. http://www.childinfo.org/discipline.html.*)*

grandmother may be protective. A good understanding of factors that contribute to maltreatment, as well as those that are protective, should guide an appropriate response.

Clinical Manifestations

Child abuse and neglect can manifest in many different ways. With regard to physical abuse, a critical element is the lack of a plausible history other than inflicted trauma. Signs of abuse may precede the eventual diagnosis of child abuse. These **sentinel injuries** may be noted in approximately 25% of abused infants and may precede the diagnosis by weeks or even months from the sentinel event. Bruising and intraoral injury, in addition to symptoms of an acute life-threatening event, may be early clues of abuse. As with any medical condition, the onus is on the clinician to carefully consider the differential diagnosis and not jump to conclusions.

Bruises are the most common manifestation of physical abuse. Features suggestive of inflicted bruises include (a) bruising in a preambulatory infant (occurring in just 2% of infants), (b) bruising of padded and less-exposed areas (buttocks, cheeks, under the chin, genitalia), (c) patterned bruising or burns conforming to shape of an object or ligatures around the wrists (Table 40-1, Figs. 40-3 and 40-4), and (d) multiple bruises, especially if clearly of different ages. Earlier suggestions for estimating the age of bruises have been discredited. It is very difficult to precisely determine the ages of bruises.

Other conditions, such as birthmarks and mongolian spots can be confused with bruises and abuse. These skin markings are not tender

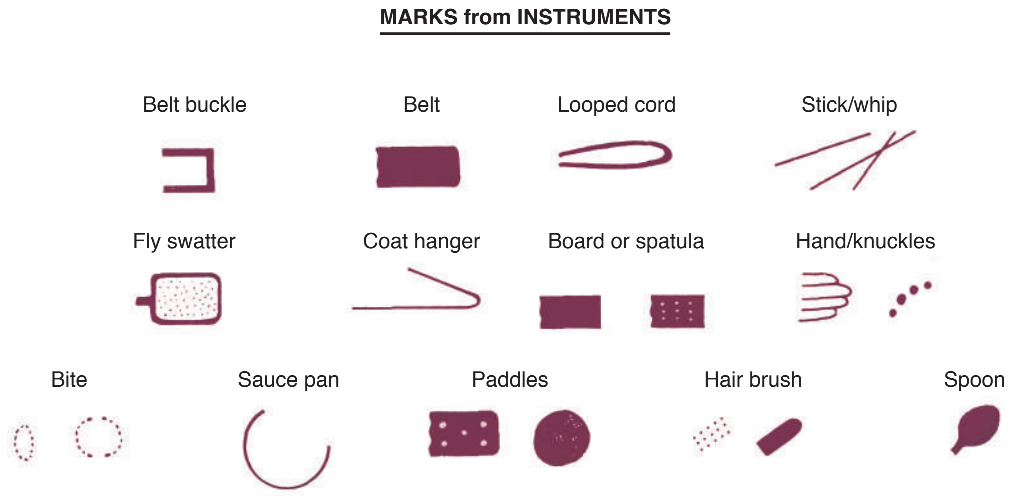

Figure 40-3 A variety of instruments may be used to inflict injury on a child. Often the choice of an instrument is a matter of convenience. Marks tend to silhouette or outline the shape of the instrument. The possibility of intentional trauma should prompt a high degree of suspicion when injuries to a child are geometric, paired, mirrored, of various ages or types, or on relatively protected parts of the body. Early recognition of intentional trauma is important to provide therapy and prevent escalation to more serious injury.

Table 40-1 Injury Patterns

METHOD OF INJURY/IMPLEMENT	PATTERN OBSERVED
Grip/grab	Relatively round marks that correspond with fingertips and/or thumb
Closed-fist punch	Series of round bruises that correspond with the knuckles of the hand
Slap	Parallel, linear bruises (usually petechial) separated by areas of central sparing
Belt/electrical cord	Loop marks or parallel lines of petechiae (the width of the belt/cord) with central sparing; may see triangular marks from the end of the belt, small circular lesions caused by the holes in the tongue of the belt, and/or a buckle pattern
Rope	Areas of bruising interspersed with areas of abrasion
Other objects/household implements	Injury in shape of object/implement (e.g., rods, switches, and wires cause linear bruising)
Human bite	Two arches forming a circular or oval shape, may cause bruising and/or abrasion
Strangulation	Petechiae of the head and/or neck, including mucous membranes; may see subconjunctival hemorrhages
Binding/ligature	Marks around the wrists, ankles, or neck; sometimes accompanied by petechiae or edema distal to the ligature mark Marks adjacent to the mouth if the child has been gagged
Excessive hincar (punishment by kneeling on salt or other rough substance)	Abrasions/burns, especially to knees
Hair pulling	Traumatic alopecia; may see petechiae on underlying scalp, or swelling or tenderness of the scalp (from subgaleal hematoma)
Tattooing or intentional scarring	Abusive cases have been described, but can also be a cultural phenomenon (e.g., Maori body ornamentation)

and do not rapidly change color or size. An underlying medical explanation for bruises may exist, such as connective tissue disorders or blood dyscrasias (see Chapters 476, 477, and 484). The history or examination usually provides clues to these conditions. Henoch-Schönlein purpura, the most common vasculitis in young children, may be confused with abuse. The pattern and location of bruises caused by abuse are usually different from those caused by a coagulopathy. Noninflicted bruises are characteristically anterior and over bony prominences, such as chin, ankles, elbows, shins, and forehead. The presence of a medical disorder does not preclude abuse.

Cultural practices can cause bruising. Cao gio, or *coining*, is a Southeast Asian folkloric therapy. A hard object is vigorously rubbed on the skin, causing petechiae or purpura. Cupping is another approach, popular in the Middle East. A heated glass is applied to the skin, often on the back. As it cools, a vacuum forms, leading to perfectly circular bruises. The context here is important, and such circumstances should not be considered abusive (see Chapter 4).

A careful history of bleeding problems in the patient and first degree relatives is needed. If a bleeding disorder is suspected, a complete blood count including platelet count, prothrombin time, and partial thromboplastin time should be obtained. More extensive testing, such as factors VIII, IX, and XI activity and a von Willebrand evaluation, should be considered in consultation with a hematologist.

Bites have a characteristic pattern of 1 or 2 opposing arches with multiple bruises (see Fig. 40-3). They can be inflicted by an adult, another child, an animal, or the patient. Bites by a child (younger than approximately 8 yr with primary teeth) typically have a distance of less than 2.5 cm between the canines—often the most prominent bruises.

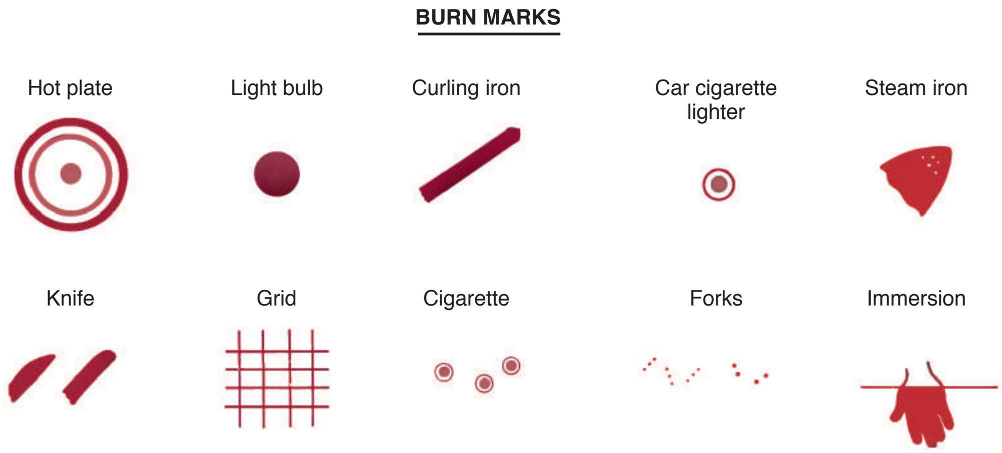

Figure 40-4 Marks from heated objects cause burns in a pattern that duplicates that of the object. Familiarity with the common heated objects that are used to traumatize children facilitates recognition of possible intentional injuries. The location of the burn is important in determining its cause. Children tend to explore surfaces with the palmar surface of the hand and rarely touch a heated object repeatedly or for a long time.

Figure 40-5 Immersion injury patterns. **A,** Sparing of the flexor creases. **B,** Immersion "stocking" burn. **C,** Immersion "glove" burn. **D,** Immersion buttocks burn. *(From Jenny C:* Child abuse and neglect: diagnosis, treatment, and evidence, *Philadelphia, 2011, Saunders, p. 225, Fig. 28-3.)*

The appearance of animal bites is variable; they usually have narrower arches than human bites and are often deep (see Chapter 724). Self-inflicted bites are on accessible areas, particularly the hands. Adult bites raise concern for abuse. Multiple bites by another child suggest inadequate supervision and neglect.

Burns may be inflicted or a result of inadequate supervision. Scalding burns may result from immersion or splash. Immersion burns, when a child is forcibly held in hot water, show clear delineation between the burned and healthy skin, and uniform depth. They may have a sock or glove distribution. Splash marks are usually absent, unlike when a child inadvertently encounters hot water. Symmetric burns are especially suggestive of abuse as are burns of the buttocks and perineum. Although most often accidental, splash burn may also result from abuse. Burns from hot objects such as curling irons, radiators, steam irons, metal grids, hot knives, and cigarettes leave patterns representing the object. A child is likely to try to rapidly escape from a hot object; thus burns that are extensive and deep reflect more than fleeting contact and are suggestive of abuse (Fig. 40-5).

Several conditions mimic abusive burns, such as brushing against a hot radiator, car seat burns, hemangiomas, and folk remedies, such as moxibustion. Impetigo may resemble cigarette burns. Cigarette burns are usually 7-10 mm across, whereas impetigo has lesions of varying size (see Chapter 665.1). Noninflicted cigarette burns are usually oval and superficial.

Neglect frequently contributes to childhood burns. Children, home alone, may be burned in house fires. A parent taking drugs may cause a fire and may be unable to protect a child. Exploring children may pull hot liquids left unattended onto themselves. Liquids cool as they flow downward so that the burn is most severe and broad proximally. If the child is wearing a diaper or clothing, the fabric may absorb the

hot water and cause burns worse than otherwise expected. Some circumstances are difficult to foresee, and a single burn resulting from a momentary lapse in supervision should not automatically be seen as neglectful parenting.

Concluding whether a burn was inflicted depends on the history, burn pattern, and the child's capabilities. A delay in seeking healthcare may result from the burn initially appearing minor, before blistering or becoming infected. This circumstance may represent reasonable behavior and should not be automatically deemed neglectful. A home investigation is often valuable (e.g., testing the water temperature).

Fractures that strongly suggest abuse include classic metaphyseal lesions, posterior rib fractures, and fractures of the scapula, sternum, and spinous processes, especially in young children (Table 40-2). These fractures all require more force than would be expected from a minor fall or routine handling and activities of a child. Rib and sternal fractures rarely result from cardiopulmonary resuscitation, even when performed by untrained adults. It is possible, however, that the recommended 2-finger or 2-thumb technique recommended for infants since 2005 may produce anterolateral rib fractures. In abused infants, rib (Fig. 40-6), metaphyseal (Fig. 40-7), and skull fractures are most common. Femoral and humeral fractures in nonambulatory infants are also highly suggestive for abuse. With increasing mobility and running, toddlers can fall with enough rotational force to cause a spiral, femoral fracture. Multiple fractures in various stages of healing are suggestive of abuse; nevertheless, underlying conditions need to be considered. Clavicular, femoral, supracondylar humeral, and distal extremity fractures in children older than 2 yr are most likely noninflicted unless they are multiple or accompanied by other signs of abuse. Few fractures are pathognomonic of abuse; all must be considered in light of the history.

Table 40-2 Skeletal Injuries from Abuse
High-specificity findings
• Classic metaphyseal corner lesions
• Posterior rib fracture
• Scapular fracture
• Sternal fracture
• Spinous process fracture
• First rib fracture
Moderate-specificity findings
• Multiple fractures
• Fractures of differing age
• Spine fracture
• Complex skull fracture
• Physeal fractures of the long bones
• Digital fractures
Low-specificity findings
• Diaphyseal fractures of the long bones
• Simple skull fractures
• Clavicle fracture

Modified from Kleinman PK. Diagnostic imaging of child abuse, *ed 2, St. Louis, 1998, Mosby.*

Figure 40-6 A high-detail oblique view of the ribs of a 6 mo old infant shows multiple healing posteromedial rib fractures (*arrowheads*). The level of detail in this image is far greater than what would be present on a standard chest radiograph. *(From Dwek JR: The radiographic approach to child abuse.* Clin Orthop Relat Res *469:776-789, 2011, p. 780, Fig. 4.)*

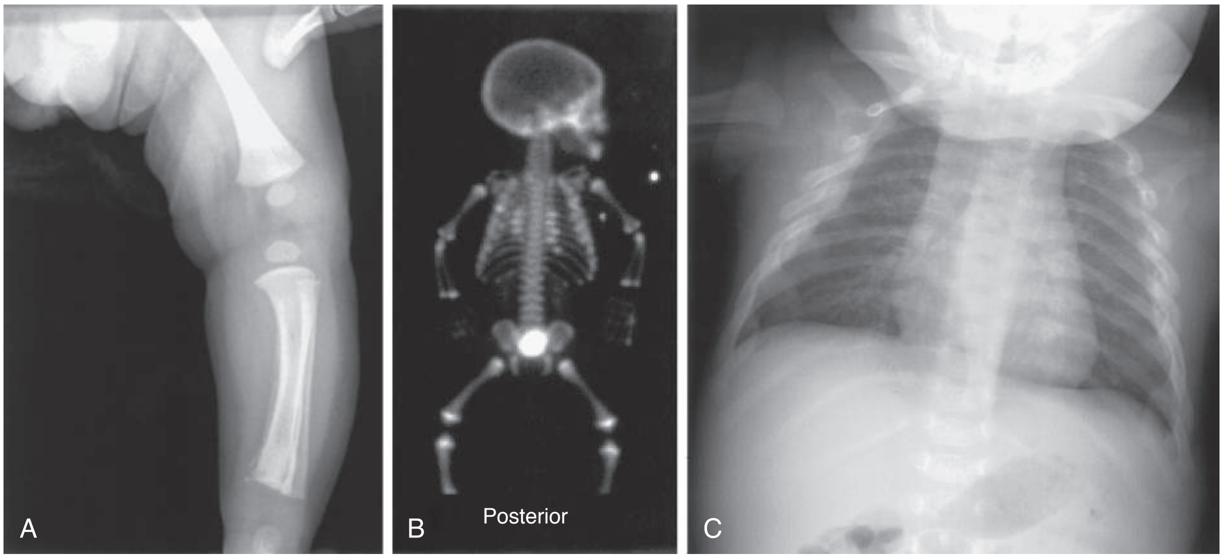

Figure 40-7 A, Metaphyseal fracture of the distal tibia in a 3 mo old infant admitted to the hospital with severe head injury. There is also periosteal new bone formation of the tibia, perhaps from previous injury. **B,** Bone scan of same infant. Initial chest x-ray showed a single fracture of the right posterior 4th rib. A radionuclide bone scan performed 2 days later revealed multiple previously unrecognized fractures of the posterior and lateral ribs. **C,** Follow-up radiographs 2 wk later showed multiple healing rib fractures. This pattern of fracture is highly specific for child abuse. The mechanism of these injuries is usually violent squeezing of the chest.

The *differential diagnosis* includes conditions that increase susceptibility to fractures, such as osteopenia of prematurity and osteogenesis imperfecta, metabolic and nutritional disorders (e.g., scurvy, copper deficiency, rickets), renal osteodystrophy, osteomyelitis, congenital syphilis, congenital insensitivity to pain, Caffey disease, and neoplasia. Some have pointed to possible rickets and low but subclinical levels of vitamin D as being responsible for fractures thought to be abusive. The evidence to date does not support this supposition. Features of congenital or metabolic conditions associated with nonabusive fractures include family history of recurrent fractures after minor trauma, abnormally shaped cranium, dentinogenesis imperfecta, blue sclera, wormian bones, craniotabes, ligamentous laxity, bowed legs, hernia, and translucent skin. Subperiosteal new bone formation is a nonspecific finding seen in infectious, traumatic, and metabolic disorders. In young infants, new bone formation may be a normal physiologic finding, usually bilateral, symmetric, and less than 2 mm in depth.

The evaluation of a fracture should include a skeletal survey in children <2 yr of age when abuse seems possible. Multiple films with different views are needed (Table 40-3); "babygrams" (1 or 2 films of the entire body) should be avoided. If the survey is normal, but concern for an occult injury remains, a radionucleotide bone scan should be performed to detect a possible acute injury. Follow-up films after 2 wk may also reveal fractures not apparent initially.

In corroborating the history and the injury, the age of a fracture can be crudely estimated (Table 40-4). Soft-tissue swelling subsides in 2-21 days. Periosteal new bone is visible within 4-21 days. Loss of definition of the fracture line occurs between 10-21 days. Soft callus can be visible after 10 days and hard callus between 14-90 days. These time frames are shorter in infancy and longer in children with poor nutritional status or a chronic underlying disease. Fractures of flat bones such as the skull do not form callus and cannot be aged, although soft-tissue swelling indicates approximate recency (i.e., within the prior week).

Abusive head trauma (AHT) results in the most significant morbidity and mortality. Abusive injury may be caused by direct impact, asphyxia, or shaking. Subdural hematomas (Fig. 40-8), retinal hemorrhages (Fig. 40-9), particularly when extensive and involving multiple layers, and diffuse axonal injury strongly suggest AHT, especially when they co-occur. The poor neck muscle tone and relatively large heads of infants make them vulnerable to acceleration–deceleration forces associated with shaking, leading to AHT. Children may lack external signs of injury, even with serious intracranial trauma. Signs and symptoms may be nonspecific, ranging from lethargy, vomiting (without diarrhea), changing neurologic status or seizures, and coma. In all preverbal children, an index of suspicion for AHT should exist when children present with these signs and symptoms. Asymptomatic subdural hemorrhage may occur after vaginal or cesarean birth. These resolve by 1 mo of age and prior to resolution the infant remains asymptomatic.

Skull fractures are common in abuse, reflecting impact injury. There is no specific pattern of skull fracture that is diagnostic of abuse. Acute intracranial trauma is best evaluated via initial and follow-up CT. MRIs are helpful in differentiating extra axial fluid, determining timing of injuries, assessing parenchymal injury, and identifying vascular anomalies. MRIs are best obtained 5-7 days after an acute injury. Glutaric aciduria type 1 can present with intracranial bleeding and should be considered. Other causes of subdural hemorrhage in infants include arteriovenous malformations, coagulopathies, birth trauma, tumor, or infections. When AHT is suspected, injuries elsewhere—skeletal and abdominal—should be ruled out.

Table 40-3 Skeletal Survey for Infants and Children Under 2 Yr of Age*

- Anteroposterior (AP) and lateral of skull (Townes view optional; add if any fracture seen)
- Lateral spine (C-spine may be included on skull radiographs; AP spine is included on AP chest and AP pelvis to include entire spine)
- AP, right posterior oblique, left posterior oblique of chest—rib technique
- AP pelvis
- AP of each femur
- AP of each leg
- AP of each humerus
- AP of each forearm
- Posteroanterior of each hand
- AP (dorsoventral) of each foot

*Images are checked by a radiologist before the patient leaves. Poorly positioned or otherwise suboptimal images should be repeated. Lateral views are added for positive or equivocal findings in the extremities. Coned views of positive or equivocal findings (i.e., at the ends of the long bones, ribs) may be obtained.

From Coley BD: Caffey's pediatric diagnostic imaging, *ed. 12, Vol. 2, Philadelphia, 2013, Mosby/Elsevier, p. 1588, Box 144-1.*

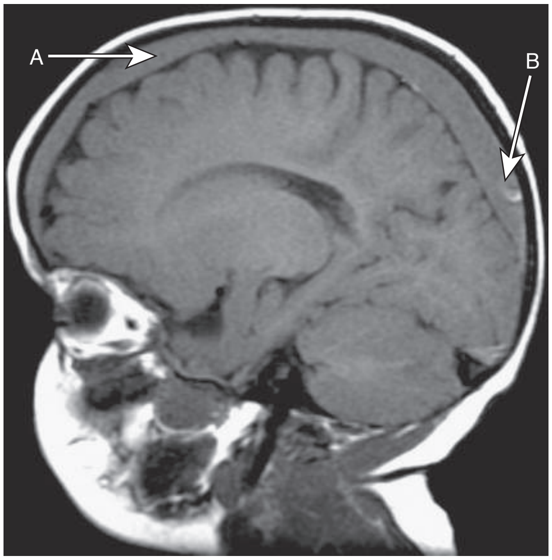

Figure 40-8 CT scan indicating intracranial bleeding. *A*, Older blood. *B*, New blood.

Table 40-4 Timetable of Radiologic Changes in Children's Fractures*

CATEGORY	EARLY	PEAK	LATE
1. Resolution of soft-tissue swelling	2-5 days	4-10 days	10-21 days
2. Subperiosteal new bone formation	4-10 days	10-14 days	14-21 day
3. Loss of fracture line definition, days		10-14 days	14-21 days
4. Soft callus		10-14 days	14-21 days
5. Hard callus	14-21 days	21-42 days	42-90 days
6. Remodeling of fracture	3 mo	1 yr	2 yr to physeal closure

*Repetitive injuries may prolong categories 1, 2, 5, and 6.

From Kleinman PK: Diagnostic imaging of child abuse, *ed. 2, St. Louis, 1998, Mosby, p. 176.*

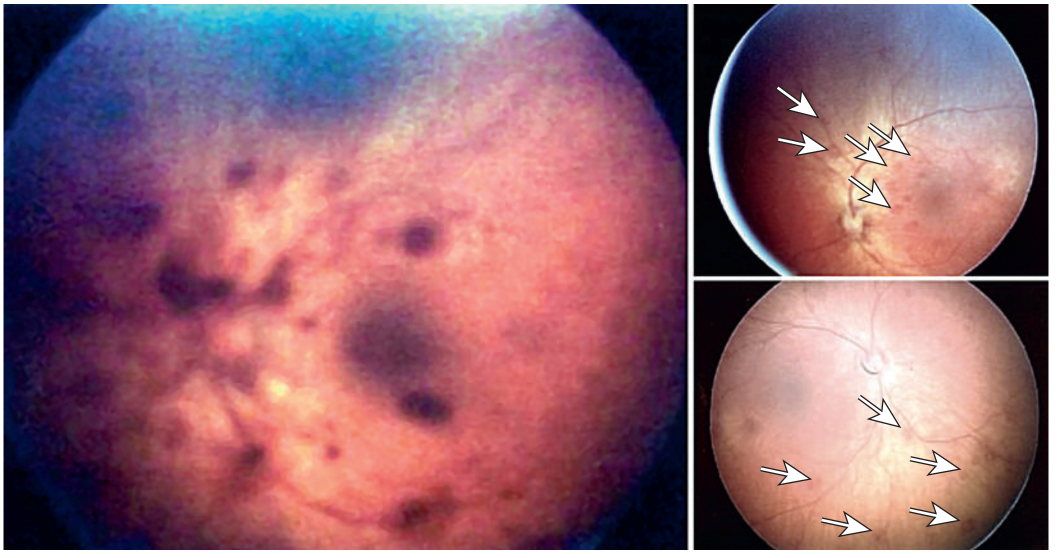

Figure 40-9 Retinal hemorrhages. Arrows point to hemorrhages of various sizes.

Retinal hemorrhages are an important marker of AHT (see Fig. 40-9). Whenever AHT is being considered, a dilated indirect eye examination by a pediatric ophthalmologist should be performed. Although retinal hemorrhages can be found in other conditions, hemorrhages that are multiple, involve more than one layer of the retina, and extend to the periphery (outside the posterior pole) are very suspicious for abuse. The mechanism is likely repeated acceleration–deceleration as a consequence of shaking. Traumatic retinoschisis points strongly to abuse.

There are other causes of retinal hemorrhages, although the pattern is usually different than that seen in child abuse. After normal spontaneous vaginal delivery, 25% of term neonates may have retinal hemorrhages (lower with caesarian section, higher with vacuum assisted delivery). These hemorrhages are in the posterior pole and are intraretinal; 80% resolve by 10 days, 100% by 6-8 wk. Coagulopathies (particularly leukemia), retinal diseases, carbon monoxide poisoning, or glutaric aciduria may be responsible. Severe noninflicted direct crush injury to the head can rarely cause an extensive hemorrhagic retinopathy. Cardiopulmonary resuscitation rarely, if ever, causes retinal hemorrhage in infants and children; if present, there a few hemorrhages in the posterior pole. Hemoglobinopathies, diabetes mellitus, routine play, minor noninflicted head trauma, and vaccinations do not appear to cause retinal hemorrhage in children. Severe coughing or seizures rarely cause retinal hemorrhages that could be confused with AHT. Retinal hemorrhages are rare in children with increased cranial pressure.

The dilemma frequently posed is whether minor, "everyday" forces can explain the findings seen in AHT. Simple linear skull fractures in the absence of other suggestive evidence can be explained by a short fall, although even that is rare (1-2%), and underlying brain injury from short falls is exceedingly rare. Timing of brain injuries in cases of abuse is not precise. In fatal cases, however, the trauma most likely occurred very soon before the child became symptomatic.

Other manifestations of AHT may be seen. "Raccoon" eyes occur in association with subgaleal hematomas after traction on the anterior hair and scalp or after a blow to the forehead. Neuroblastoma can present similarly, and should be considered (see Chapter 498). Bruises from attempted strangulation may be visible on the neck. Choking or suffocation can cause hypoxic brain injury, often with no external signs.

Abdominal trauma accounts for significant morbidity and mortality in abused children. Young children are especially vulnerable because of their relatively large abdomens and lax abdominal musculature. A forceful blow or kick can cause hematomas of solid organs (liver, spleen, kidney) from compression against the spine, as well as hematoma (duodenal) or rupture (stomach) of hollow organs. Intraabdominal bleeding may result from trauma to an organ or from shearing of a vessel. More than one organ may be affected. Children may present with cardiovascular failure or an acute condition of the abdomen, often after a delay in care. Bilious vomiting without fever or peritoneal irritation suggests a duodenal hematoma, often caused by abuse.

The manifestations of abdominal trauma are often subtle, even with severe injuries. Bruising of the abdominal wall is unusual, and symptoms may evolve slowly. Delayed perforation may occur days after the injury; bowel strictures or a pancreatic pseudocyst may occur weeks or months later. Child healthcare professionals should consider screening for occult abdominal trauma when other evidence of physical abuse exists. Screening should include liver and pancreatic enzyme levels, and testing urine for blood. Children with lab results indicating possible injury should have abdominal CT performed. CT or ultrasound should also be performed if there is concern about possible splenic, adrenal, or reproductive organ injury.

Neglect is the most prevalent form of child maltreatment, with potentially severe and lasting sequelae. It may manifest in many ways, depending on which needs are not adequately met. Nonadherence to medical treatment may aggravate the condition, as may a delay in seeking care. Inadequate food may manifest as impaired growth; inattention to obesity may compound that problem. Poor hygiene may contribute to infected cuts or lesions. Inadequate supervision contributes to injuries and ingestions. Children's needs for mental healthcare, dental care, and other health-related needs may be unmet, manifesting as neglect in those areas. Educational needs, particularly for children with learning disabilities, are often not met.

The evaluation of possible neglect requires addressing several critical questions. "Is this neglect?" "Have the circumstances harmed the child, or jeopardized the child's health and safety?" Suboptimal treatment adherence may lead to few or no clear consequences. Inadequacies in the care children receive naturally fall along a continuum, requiring a range of responses tailored to the individual situation. Legal considerations or CPS policies may discourage physicians from labeling many circumstances as neglect. Even if neglect does not meet a threshold for reporting to CPS, child healthcare professionals can still help ensure children's needs are adequately met.

GENERAL PRINCIPLES FOR ASSESSING POSSIBLE ABUSE AND NEGLECT

The heterogeneity of circumstances in situations of child maltreatment precludes specific details. The following are useful general principles.

- Given the complexity and possible ramifications of determining child maltreatment, an interdisciplinary assessment is optimal, with input from all involved professionals. Consultation with a physician expert in child maltreatment is recommended.

- A thorough history should be obtained from the parent(s) optimally via separate interviews.
- Verbal children should be interviewed separately, in a developmentally appropriate manner. Open-ended questions (e.g., "Tell me what happened") are best. Some children need more directed questioning (e.g., "How did you get that bruise?"); others need multiple choice questions. Leading questions (e.g., "Did your daddy hit you?") must be avoided.
- A thorough physical examination is necessary.
- Careful documentation of the history and physical is essential. Verbatim quotes are valuable, including the question that prompted the response. Photographs are helpful.
- For abuse: What is the evidence for concluding abuse? Have other diagnoses been ruled out? What is the likely mechanism of the injury? When did the injury likely occur?
- For neglect: Do the circumstances indicate that the child's needs have not been adequately met? Is there evidence of actual harm? Is there evidence of potential harm and on what basis? What is the nature of the neglect? Is there a pattern of neglect?
- Are there indications of other forms of maltreatment? Has there been prior CPS involvement?
- A child's safety is a paramount concern. What is the risk of imminent harm, and of what severity?
- What is contributing to the maltreatment? Consider the categories described in the section on etiology.
- What strengths/resources are there? This is as important as identifying problems.
- What interventions have been tried, with what results? Knowing the nature of these interventions can be useful, including from the parent's perspective.
- What is the prognosis? Is the family motivated to improve the circumstances and accept help, or resistant? Are suitable resources, formal and informal, available?
- Are there other children in the home who should be assessed for maltreatment?

GENERAL PRINCIPLES FOR ADDRESSING CHILD MALTREATMENT

The circumstances surrounding each child and/or incident of suspected abuse or neglect may be complex and highly variable, precluding specific steps. The following are general principles.

- Treat any medical problems.
- Help ensure the child's safety, often in conjunction with CPS; this is a priority.
- Convey concerns of maltreatment to parents, kindly but forthrightly. Avoid blaming. It is natural to feel anger or pain towards parents of maltreated children, but they need support and deserve respect.
- Have a means of addressing the difficult emotions child maltreatment can evoke in us.
- Be empathic and state interest in helping, or suggest another pediatrician.
- Know your national and state laws and/or local CPS policies on reporting child maltreatment. In the United States, the legal threshold for reporting is typically "reason to believe"; one does not need to be certain. Physical abuse and moderate to severe neglect warrant a report. In less-severe neglect, less-intrusive interventions may be an appropriate initial response. For example, if an infant's mild failure to thrive is a result of an error in mixing the formula, parent education and perhaps a visiting nurse should be tried. In contrast, severe failure to thrive may require hospitalization, and if the contributing factors are particularly serious (e.g., a psychotic mother), out-of-home placement may be needed. CPS can assess the home environment, providing valuable insights.
- Reporting child maltreatment is never easy. Parental inadequacy or culpability is at least implicit, and parents may express considerable anger. Child healthcare professionals should supportively inform families directly of the report; it can be explained as an effort to clarify the situation and provide help, as well as a professional (and legal) responsibility. Explaining what the ensuing process is likely to entail (e.g., a visit from a CPS worker and sometimes a police officer) may ease a parent's anxiety. Parents are frequently concerned that they might lose their child. Child healthcare professionals can cautiously reassure parents that CPS is responsible for helping children and families and that, in most instances, children remain with their parents. Even when CPS does not accept a report or when a report is not substantiated, they may offer voluntary supportive services such as food, shelter, homemaker services, and child care. Child healthcare professionals can be a useful liaison between the family and the public agencies, and should try to remain involved after reporting to CPS.
- Help address contributory factors, prioritizing those most important and amenable to being remedied. Concrete needs should not be overlooked; accessing nutrition programs, obtaining health insurance, enrolling children in preschool programs, and help finding safe housing can make a valuable difference. Parents may need their own problems addressed to enable them to adequately care for their children.
- Establish specific objectives (e.g., no hitting, diabetes will be adequately controlled), with measurable outcomes (e.g., urine dipsticks, hemoglobin A_{1c}). Similarly, advice should be specific and limited to a few reasonable steps. A written contract can be very helpful.
- Engage the family in developing the plan, solicit their input and agreement.
- Build on strengths; there are always some. These provide a valuable way to engage parents.
- Encourage informal supports (e.g., family, friends; invite fathers to office visits). This is where most people get their support, not from professionals. Consider support available through a family's religious affiliation.
- Consider children's specific needs. Too often, maltreated children do not receive direct services.
- Be knowledgeable about community resources, and facilitate appropriate referrals.
- Provide support, follow-up, review of progress, and adjust the plan if needed.
- Recognize that maltreatment often requires long-term intervention with ongoing support and monitoring.

OUTCOMES OF CHILD MALTREATMENT

Child maltreatment often has significant short- and long-term medical, mental health, and social sequelae. Physically abused children are at risk for many problems, including conduct disorders, aggressive behavior, decreased cognitive functioning, and poor academic performance. Neglect is similarly associated with many potential problems. Even if a maltreated child appears to be functioning well, healthcare professionals and parents need to be sensitive to the possibility of later problems. Maltreatment is associated with increased risk in adulthood for several health risk behaviors and physical and mental health problems. Maltreated children are at risk for becoming abusive parents. The neurobiologic effects of child abuse and neglect on the developing brain may partly explain some of these sequelae.

Some children appear to be resilient and may not exhibit sequelae of maltreatment, perhaps owing to protective factors or interventions. The benefits of intervention have been found in even the most severely neglected children, such as those from Romanian orphanages, who were adopted—the earlier the better.

PREVENTION OF CHILD ABUSE AND NEGLECT

An important aspect of prevention is that many of the efforts to strengthen families and support parents should promote children's health, development, and safety, as well as prevent child abuse and neglect. Medical responses to child maltreatment have typically occurred after the fact; preventing the problem is preferable. Child healthcare professionals can help in several ways. An ongoing relationship offers opportunities to develop trust and knowledge of a family's

circumstances. Astute observation of parent–child interactions can reveal useful information.

Parent and child education regarding medical conditions helps to ensure implementation of the treatment plan and to prevent neglect. Possible barriers to treatment should be addressed. Practical strategies such as writing down the plan can help. In addition, anticipatory guidance may help with child rearing, diminishing the risk of maltreatment. Hospital-based programs that educate parents about infant crying and the risks of shaking the infant may help prevent AHT.

Screening for major psychosocial risk factors for maltreatment (depression, substance abuse, intimate partner violence, major stress), and helping address identified problems, often via referrals, may help prevent maltreatment. The primary care focus on prevention offers excellent opportunities to screen briefly for psychosocial problems. The traditional organ system–focused review of systems can be expanded to probe areas such as feelings about the child, the parent's own functioning, possible depression, substance abuse, intimate partner violence, disciplinary approaches, stressors, and supports. The Safe Environment for Every Kid (SEEK) model offers a promising approach for pediatric primary care to identify and help address prevalent psychosocial problems. So doing can strengthen families, support parents, promote children's health, development and safety, and, help prevent child maltreatment.

Obtaining information directly from children or youth is also important, especially given that separate interviews with teens have become the norm. Any concerns identified on such screens require at least brief assessment and initial management, which may lead to a referral for further evaluation and treatment. More frequent office visits can be scheduled for support and counseling while monitoring the situation. Other key family members (e.g., fathers) might be invited to participate, thereby encouraging informal support. Practices might arrange parent groups through which problems and solutions are shared.

Advocacy

Child health professionals can assist in understanding what contributed to the child's maltreatment. When advocating for the best interest of the child and family, addressing risk factors at the individual, family, and community levels is optimal. At the individual level, an example of advocating on behalf of a child is explaining to a parent that an active toddler is behaving normally and not intentionally challenging the parent. Encouraging a mother to seek help dealing with a violent spouse, saying for example, "You and your life are very important," asking about substance abuse and helping parents obtain health insurance for their children are all forms of advocacy. Child abuse can and does occur even in families in which one spouse does not support or condone the abusive behavior (Fig. 40-10).

Efforts to improve family functioning, such as encouraging fathers' involvement in child care are also examples of advocacy. Remaining involved after a report to CPS and helping ensure appropriate services are provided is advocacy as well. In the community, child health professionals can be influential advocates for maximizing resources devoted to children and families. These include parenting programs, services for abused women and children, and recreational facilities. Finally, child health professionals can play an important role in advocating for policies and programs at the local, state, and national levels to benefit children and families. Child maltreatment is a complex problem that has no easy solutions.

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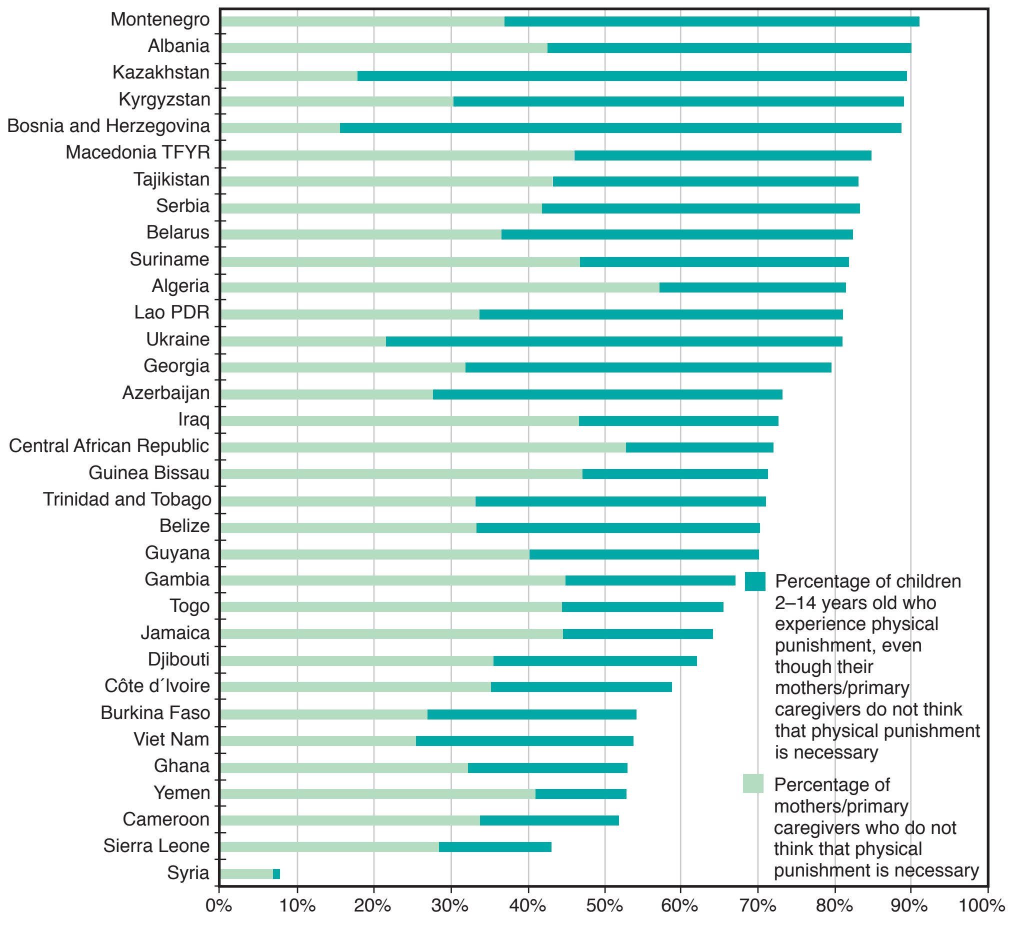

Figure 40-10 Percentage of mothers/primary caregivers who do not think that physical punishment is necessary and percentage of children 2-14 yr old who experience physical punishment, even though their mothers/primary caregivers do not think that physical punishment is necessary, in selected countries with available data. *(From UNICEF global databases 2011, from DHS, MICS and other national surveys, 2005-2006. http://www.childinfo.org/discipline.html.)*

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40.1 Sexual Abuse

Wendy G. Lane and Howard Dubowitz

See also Chapter 119, Adolescent Rape.

Approximately 25% of girls and 10% of boys in the United States will be sexually abused at some point during their childhood. Rates vary across the globe, with children in some countries experiencing even higher rates. Whether children and families share this information with their pediatrician will depend, in large part, on the pediatrician's comfort with and openness to discussing possible sexual abuse with families.

Pediatricians may play a number of different roles in addressing sexual abuse, including identification, reporting to CPS, testing for and treating sexually transmitted infections, and providing support and reassurance to children and families. Pediatricians may also play a role in the prevention of sexual abuse by advising parents and children about ways to help keep safe from sexual abuse. In many jurisdictions throughout the United States, general pediatricians will play a triage role, with the definitive medical evaluation conducted by a child abuse specialist.

DEFINITION

Sexual abuse may be defined as any sexual behavior or action toward a child that is unwanted or exploitative. Some legal definitions distinguish sexual abuse from sexual assault; the former being committed by a caregiver or household member, and the latter being committed by someone with a noncustodial relationship or no relationship with the child. For this chapter, the term *sexual abuse* encompasses both abuse and assault. Sexual abuse does *not* have to involve direct touching or contact by the perpetrator. Showing pornography to a child, filming or photographing a child in sexually explicit poses, and encouraging or forcing one child to perform sex acts on another also constitute sexual abuse.

PRESENTATION OF SEXUAL ABUSE

Caregivers may become concerned about the possibility of sexual abuse when children exhibit sexually explicit behavior. This behavior includes that which is outside the norm for a child's age and developmental level. For preschool and school-age children, sexually explicit behavior may include compulsive masturbation, attempting to perform sex acts on adults or other children, or asking adults or children to perform sex acts on them. Teenagers may become sexually promiscuous and even engage in prostitution. Older children and teenagers may respond by sexually abusing younger children. It is important to recognize that this behavior could also result from accidental exposure (e.g., the child who enters his parent's bedroom at night to find his parents having sex), or from neglect (e.g., watching pornographic movies where a child can see them).

Children who have been sexually abused sometimes provide a clear, spontaneous disclosure to a trusted adult. Often the signs of sexual abuse are much more subtle. For some children, behavioral changes are the first indication that something is amiss. Nonspecific behavior changes such as social withdrawal, acting out, increased clinginess or fearfulness, distractibility, and learning difficulties may be attributed to a variety of life changes or stressors. Regression in developmental milestones, including new-onset bedwetting or encopresis (see Chapter 23), is another behavior that caregivers may overlook as an indicator of sexual abuse. Teenagers may respond by becoming depressed, experimenting with drugs or alcohol, or running away from home. Because nonspecific symptoms are very common among children who have been sexually abused, it should nearly always be included in one's differential diagnosis of child behavior changes.

Some children may not exhibit behavioral changes or provide any other indication that something is wrong. For these children, sexual abuse may be discovered when another person witnesses the abuse or discovers evidence such as sexually explicit photographs or videos. Pregnancy may be another way that sexual abuse is identified. There are also children, with and without symptoms, who will not be identified at any point during their childhood.

THE ROLE OF THE GENERAL PEDIATRICIAN IN THE ASSESSMENT AND MANAGEMENT OF POSSIBLE SEXUAL ABUSE

Before determining where and how a child with suspected sexual abuse is evaluated, it is important to assess for and rule out any medical problems that can be confused with abuse. A number of genital findings may raise concern about abuse but often have alternative explanations. Genital redness in a prepubertal child is more often caused by nonspecific vulvovaginitis, eczema, or infection with staphylococcus, group A streptococcus, *Haemophilus*, *Neisseria*, or yeast. Lichen sclerosis is a less-common cause of redness. Vaginal discharge can be caused by sexually transmitted infections, but also by vaginal foreign body, onset of puberty, or infection with *Salmonella*, *Shigella*, or *Yersinia*. Genital ulcers can be caused by herpes simplex virus and syphilis, but also by Epstein-Barr virus, varicella-zoster, Crohn disease, and Behçet disease. Genital bleeding can be caused by urethral prolapse, vaginal foreign body, accidental trauma, and vaginal tumor.

When other medical conditions are not under consideration, have been ruled out, or are less likely than abuse, the possibility for suspected sexual abuse should be probed (Fig. 40-11). Where and how a child with suspected sexual abuse is evaluated should be determined by how long ago the last incident of abuse likely occurred, and whether the child is prepubertal or postpubertal. For the prepubertal child, if abuse has occurred in the previous 72 hr, forensic evidence collection (e.g., external genital, vaginal, anal, and oral swabs, sometimes referred to as a "rape kit") is often indicated, and the child should be referred to a site equipped to collect forensic evidence. Depending on the jurisdiction, this site may be an emergency department, a child advocacy center, or an outpatient clinic. If the last incident of abuse occurred more than 72 hr prior, the likelihood of recovering forensic evidence is extremely low, and forensic evidence collection is not necessary. For postpubertal females, many experts recommend forensic evidence collection up to 120 hr following the abuse—the same time limit as for adult women. The extended time frame is justified because some studies have demonstrated that semen can remain in the postpubertal vaginal vault for more than 72 hr.

The referral site may be different when the child does not present until after the cutoff for an acute exam. Because emergency departments may not have a child abuse expert, and can be busy, noisy, and lacking in privacy, examination at an alternate location such as a child

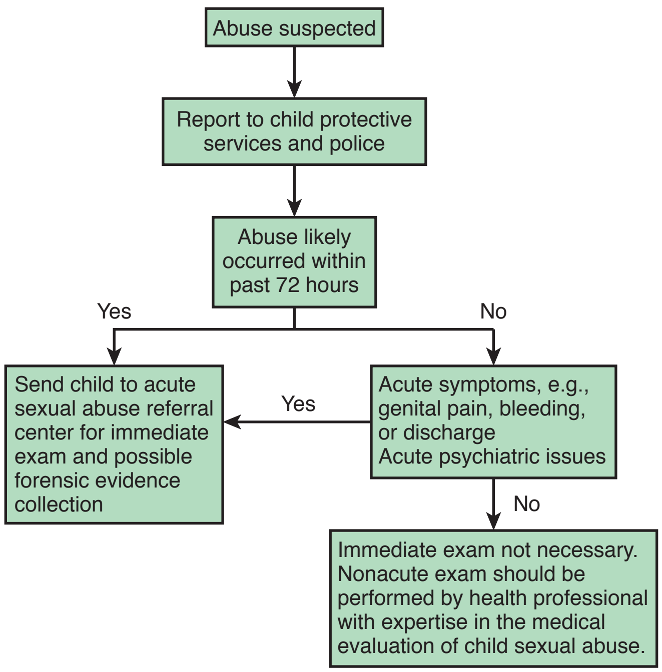

Figure 40-11 Triage protocol for children with suspected sexual abuse.

advocacy center or outpatient clinic is recommended. If the exam is not urgent, waiting until the next morning is recommended because it is easier to interview and examine a child who is not tired and cranky. Referring physicians should be familiar with the triage procedures in their communities, including the referral sites for both acute and chronic exams, and whether there are separate referral sites for prepubertal and postpubertal children.

Children with suspected sexual abuse may present to the pediatrician's office with a clear disclosure of abuse or more subtle indicators. In this situation, a private, brief conversation between pediatrician and child can provide an opportunity for the child to speak in the child's own words without the parent speaking for the child. Doing this may be especially important when the caregiver does not believe the child, or is unwilling or unable to offer emotional support and protection. Telling caregivers that a private conversation is part of the routine assessment for the child's concerns can help comfort a hesitant parent.

When speaking with the child, experts recommend establishing rapport by starting with general and open-ended questions; for example: "Who lives at home?" and "What are your favorite things to do?" Questions about sexual abuse should be nonleading. A pediatrician should explain that sometimes children are hurt or bothered by others, and that the physician wonders whether that might have happened to the child. Open-ended questions, such as "Can you tell me more about that?" allow the child to provide additional information and clarification in the child's own words. It is *not* necessary to obtain extensive information about what happened because the child will usually have a forensic interview once a report is made to CPS and an investigation begins. Very young children and those with developmental delay may lack the verbal skills to describe what happened. In this situation, the caregiver's history may provide enough information to warrant a report to CPS without interviewing the child.

All 50 U.S. states (and a growing number of other nations) mandate that professionals report suspected maltreatment to CPS. The specific criteria for "reason to suspect" are generally not defined by state law. It is clear that reporting does not require certainty that abuse has occurred. Therefore, it may be appropriate to report a child with sexual behavior concerns when no accidental sexual exposure can be identified and the child does not clearly confirm or deny abuse during your conversation with her.

PHYSICAL EXAMINATION OF THE CHILD WITH SUSPECTED SEXUAL ABUSE

Many physicians are unfamiliar with genital anatomy and examination, particularly in the prepubertal child (Figs. 40-12 and 40-13). Because approximately 95% of children who undergo a medical evaluation following sexual abuse have normal exams, the role of the primary care provider is often simply to be able to distinguish a normal exam from findings indicative of common medical concerns or trauma. The absence of physical findings can often be explained by the type of sexual contact that has occurred. Abusive acts such as fondling or even

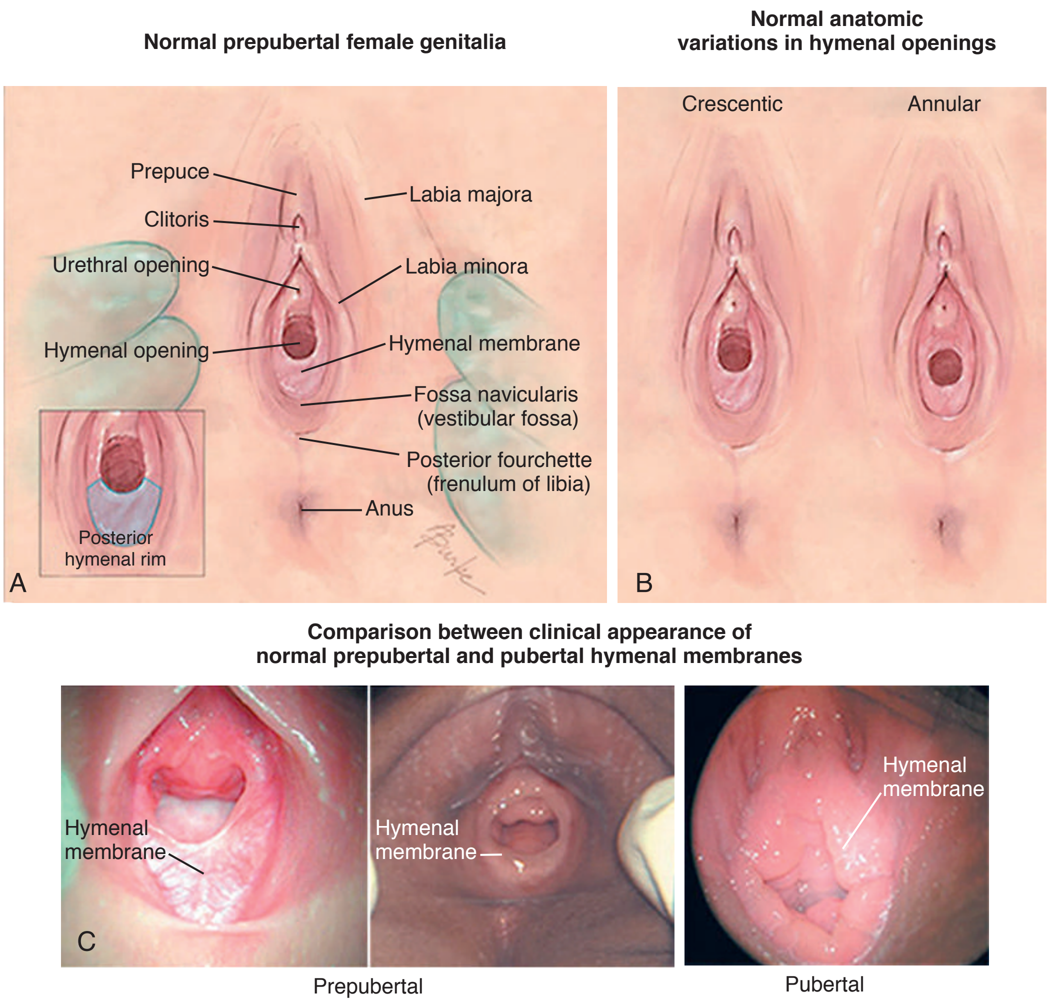

Figure 40-12 Female prepubertal genital anatomy. **A,** Inset shows the region defined as the posterior hymenal rim, between the 4 o'clock and 8 o'clock positions (*shaded blue*). **B,** There is a range of normal anatomic variations in hymenal openings. Crescentic and annular are two of the most common shapes. **C,** Photographs illustrate the range of normal prepubertal and pubertal hymenal membranes. In most children, the hymen becomes thicker and more redundant during puberty. *(From Berkoff MC, Zolotor AJ, Makoroff KL, et al: Has this prepubertal girl been sexually abused?* JAMA *300:2779-2792, 2008.)*

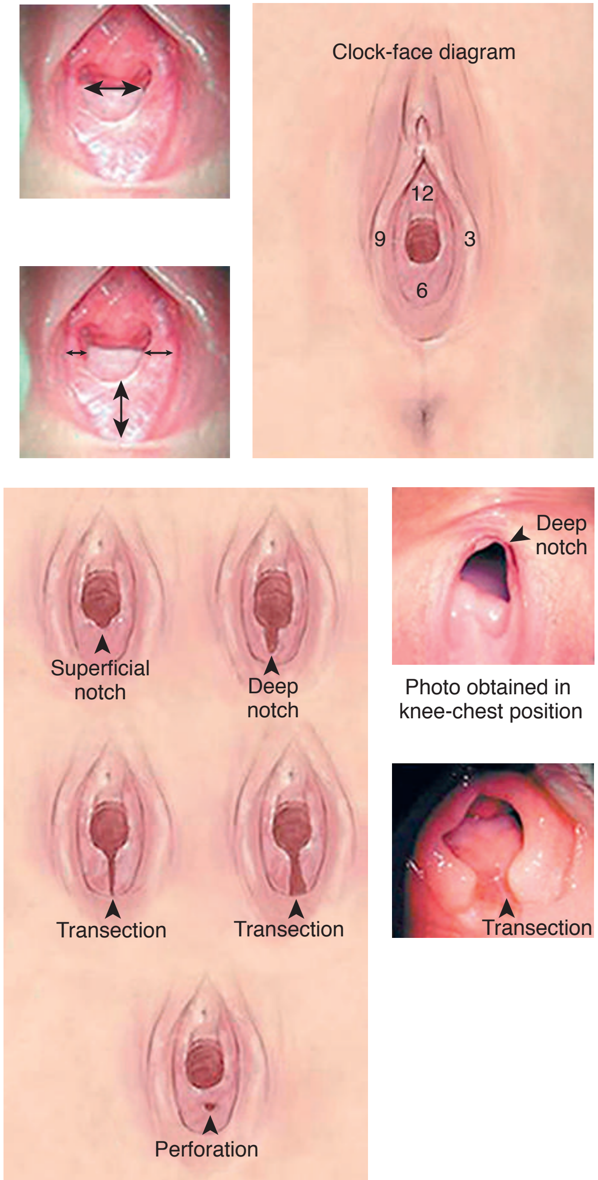

Figure 40-13 **Hymenal membrane characteristics.** When considering the possibility of sexual abuse during an examination, the examiner should document pertinent positive and negative findings. In addition to the clinical signs depicted in the figure, other possible findings include prominent hymenal vessels, bumps, tags, longitudinal intravaginal ridge, external ridge, periurethral bands, or vestibular bands. Perforation of the hymen is not a finding commonly discussed in the literature. *(From Berkoff MC, Zolotor AJ, Makoroff KL, et al: Has this prepubertal girl been sexually abused?* JAMA *300:2779-2792, 2008.)*

digital penetration can occur without causing injury. Many children do not disclose abuse until days, weeks, months, or even years after the abuse has occurred; because genital injuries can heal rapidly, injuries are often completely healed by the time a child presents for medical evaluation. A normal genital exam does not rule out the possibility of abuse, and should not influence the decision to report to CPS.

Even with the high proportion of normal genital exams, there is value in conducting a thorough physical exam. Unsuspected injuries or medical problems, such as labial adhesions, imperforate hymen, or a small urethral prolapse, may be identified. In addition, reassurance about the child's physical health may allay fears and reduce anxiety for the child and family.

Few findings on the genital examination are diagnostic for sexual abuse. In the acute time frame, lacerations or bruising of the labia,

Table 40-5	Situations Involving a High Risk for Transmission of Sexually Transmitted Infections

1. Child has signs or symptoms of STI, including vaginal discharge or pain, genital itching or odor, urinary symptoms, and genital ulcers or lesions.
2. The suspected perpetrator is known to have an STI, or is at high risk for having an STI because of multiple partners, substance abuse, or other reasons.
3. Any other person living in the child's household has an STI.
4. There is evidence of genital, oral, or anal penetration or ejaculation.
5. The patient or parent requests testing.

STI, sexually transmitted infection.

From Centers for Disease Control and Prevention, Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2010, MMWR Recomm Rep *59(RR-12):1-114, 2010.*

penis, scrotum, perianal tissues, or perineum are indicative of trauma. Likewise, hymenal bruising and lacerations, and perianal lacerations extending deep to the external anal sphincter indicate penetrating trauma. Several nonacute findings are also concerning for sexual abuse. A complete transection of the hymen to the base between the 4 and 8 o'clock positions (i.e., absence of hymenal tissue in the posterior rim) is considered diagnostic for trauma (see Fig. 40-13). For all of these findings, the cause of injury must be elucidated through the child and caregiver history. If there is any concern that the finding may be the result of sexual abuse, CPS should be notified and a medical evaluation should be performed by an experienced child abuse pediatrician.

Testing for sexually transmitted infections is not indicated for all children, but is warranted in the situations described in Table 40-5. Until recently, culture was considered the gold standard for the diagnosis of vaginal gonorrhea (see Chapter 192) and chlamydia (see Chapter 226) infections in children. There is growing evidence that **nucleic acid amplification testing (NAAT)** for gonorrhea and chlamydia by either vaginal swab or urine in prepubertal girls is as (or possibly more) sensitive, than culture. Current guidelines from the Centers for Disease Control and Prevention (CDC) allow for NAAT testing by vaginal swab or urine as an alternative to culture in girls. Because obtaining vaginal swabs can be uncomfortable for prepubertal children, urine testing is preferable. Culture remains the preferred method for testing of rectal and pharyngeal specimens in boys and girls. Little data on the use of urine NAAT testing in prepubertal boys is available. Therefore, the CDC continues to recommend urine or urethral culture for boys. Many child abuse experts perform urine NAAT testing on prepubertal boys because urethral swabs are uncomfortable, and there are good data to support urine NAAT testing in girls. For all NAAT testing in both genders, the child should *not* receive presumptive treatment at the time of testing. Instead, a positive NAAT test should be confirmed by culture or an alternate NAAT test prior to treatment. Because gonorrhea and chlamydia in prepubertal children do not typically cause ascending infection, waiting for a definitive diagnosis before treatment will not increase the risk for pelvic inflammatory disease.

A number of sexually transmitted infections should raise concern for abuse (Table 40-6). In a prepubertal child, a positive culture for gonorrhea beyond the neonatal period, trichomonas beyond 1 yr of age, or chlamydia beyond 3 yr of age indicates that the child has had some contact with infected genital secretions, almost always as a result of sexual abuse. Syphilis (see Chapter 218) and HIV are diagnostic for sexual abuse if other means of transmission have been excluded. Because of the potential for transmission either perinatally or through nonsexual contact, the presence of genital warts has a low specificity for sexual abuse. The possibility of sexual abuse should be considered and addressed with the family, especially in children whose warts first appear beyond 3 yr of age. Type 1 or 2 genital herpes is concerning for sexual abuse, but not diagnostic given other possible routes of

Table 40-6 Implications of Commonly Encountered Sexually Transmitted (ST) or Sexually Associated (SA) Infections for Diagnosis and Reporting of Sexual Abuse Among Infants and Prepubertal Children

ST/SA CONFIRMED	EVIDENCE FOR SEXUAL ABUSE	SUGGESTED ACTION
Gonorrhea*	Diagnostic†	Report‡
Syphilis*	Diagnostic	Report‡
HIV§	Diagnostic	Report‡
*Chlamydia trachomatis**	Diagnostic†	Report‡
Trichomonas vaginalis	Highly suspicious	Report‡
Condylomata acuminate (anogenital warts)	Suspicious	Report‡
Genital herpes*	Suspicious	Report‡¶
Bacterial vaginosis	Inconclusive	Medical follow-up

*Report if not likely to be perinatally acquired and rare nonsexual vertical transmission is excluded.
†Although culture is the gold standard, current studies are investigating the use of nucleic acid amplification tests as an alternative diagnostic method.
‡Report to the agency mandated to receive reports of suspected child abuse.
§Report if not likely to be acquired perinatally or through transfusion.
¶Report unless a clear history of autoinoculation is evident.
From MMWR 2010 STD guidelines. Adapted from Kellogg N, American Academy of Pediatrics Committee on Child Abuse and Neglect: The evaluation of sexual abuse in children, Pediatrics *116:506-512, 2005.*

transmission. For both human papillomavirus and herpes simplex virus, the American Academy of Pediatrics recommends reporting to CPS unless perinatal or horizontal transmission is considered likely.

SEXUAL ABUSE PREVENTION

Pediatricians can play a role in the prevention of sexual abuse by educating parents and children about sexual safety at well child visits. During the genital exam the pediatrician can inform the child that only the doctor and select adult caregivers should be permitted to see their "private parts," and that a trusted adult should be told if anyone else attempts to do so. Pediatricians can raise parental awareness that sometimes older kids or adults may try engage in sexual behavior with children. The pediatrician can teach parents how to minimize the opportunity for perpetrators to access children, for example, by limiting 1-adult/1-child situations and being sensitive to any adult's unusual interest in young children. In addition, pediatricians can help parents talk to children about what to do if confronted with a potentially abusive situation. Some examples include telling children to say "no," to leave, and to tell a parent and/or another adult. If abuse does occur, the pediatrician can tell parents how to recognize possible signs and symptoms, and how to reassure the child that she or he was not at fault. Finally, pediatricians can provide parents with suggestions about how to maintain open communication with their children so that these conversations can occur with minimal parent and child discomfort.

Bibliography is available at Expert Consult.

40.2 Medical Child Abuse (Factitious Disorder by Proxy, Munchausen Syndrome by Proxy)

Howard Dubowitz and Wendy G. Lane

The term *Munchausen syndrome* is used to describe situations in which adults falsify their own symptoms. In *Munchausen syndrome by proxy*, a parent, typically a mother, simulates or causes disease in her child. Several terms have been suggested to describe this phenomenon: factitious disorder by proxy, pediatric condition falsification, caregiver fabricated illness, and **medical child abuse (MCA)**. In some instances, such as partial suffocation, "child abuse" may be most appropriate.

The core dynamic is that a parent falsely presents a child for medical attention. This may be via fabricating a history, such as reporting seizures that never occurred. A parent may directly cause a child's illness by exposing a child to a toxin, medication, or infectious agent (e.g., injecting stool into an intravenous line). Signs or symptoms may also be manufactured, such as when a parent smothers a child, or alters laboratory samples or temperature measurements. Each of these actions may lead to unnecessary medical care, sometimes including intrusive tests and surgeries. The "problems" often recur repeatedly over several years. In addition to the physical concomitants of testing and treatment, there are potentially serious and lasting social and psychologic sequelae.

Child health professionals are typically misled into thinking that the child really has a medical problem. Parents, sometimes working in a medical field, may be adept at constructing somewhat plausible presentations; a convincing seizure history may be offered, and a normal electroencephalogram cannot fully rule out the possibility of a seizure disorder. Even after extensive testing fails to lead to a diagnosis or treatment proves ineffective, health professionals may think they are confronting a "new or rare disease." Unwittingly, this can lead to continued testing and interventions, thus perpetuating the MCA. Pediatricians generally rely on and trust parents to provide an accurate history. As with other forms of child maltreatment, accurate diagnosis of MCA requires that the pediatrician maintain a healthy skepticism under certain circumstances.

CLINICAL MANIFESTATIONS

As with other forms of child abuse, the presentation of MCA may vary in nature and severity. Consideration of MCA should be triggered when the reported symptoms are repeatedly noted by only one parent, appropriate testing fails to confirm a diagnosis, and seemingly appropriate treatment is ineffective. The child's symptoms, their course, or the response to treatment may be incompatible with any recognized disease. Preverbal children are usually involved, although older children may be convinced by parents that they have a particular problem and become dependent on the increased attention; this may lead to feigning symptoms.

Symptoms in young children are mostly associated with proximity of the offending caregiver to the child. The mother may present as a devoted or even model parent who forms close relationships with members of the healthcare team. While appearing very interested in her child's condition, she may be relatively distant emotionally. She may have a history of Munchausen syndrome, though not necessarily diagnosed as such. **Bleeding** is a particularly common presentation. This may be caused by adding dyes to samples, adding blood (e.g., from the mother) to the child's sample, or giving the child an anticoagulant (e.g., warfarin).

Seizures are a common manifestation, with a history easy to fabricate, and the difficulty of excluding the problem based on testing. A parent may report that another physician diagnosed seizures, and the myth may be continued if there is no effort to confirm the basis for the "diagnosis." Alternatively, seizures may be induced by toxins, medications (e.g., insulin), water, or salts. Physicians need to be familiar with the substances available to families and the possible consequences of exposure.

Apnea is another common presentation. The observation may be falsified or created by partial suffocation. A history of a sibling with the same problem, perhaps dying from it, should be cause for concern. Parents of children hospitalized for apparent life-threatening events have been videotaped attempting to suffocate their child while in the hospital.

Gastrointestinal signs or symptoms are another common manifestation. Forced ingestion of medications such as ipecac may cause chronic vomiting, or laxatives may cause diarrhea.

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The **skin**, easily accessible, may be burned, dyed, tattooed, lacerated, or punctured to simulate acute or chronic skin conditions.

Recurrent sepsis may be caused by infectious agents being administered; intravenous lines during hospitalization may provide a convenient portal. Urine and blood samples may be contaminated with foreign material, blood or stool.

DIAGNOSIS

In assessing possible MCA, several explanations should be considered in addition to a true medical problem. Some parents may be extremely anxious and genuinely concerned about possible problems. There may be many reasons underpinning this anxiety, such as a personality trait, the death of neighbor's child, or something read on the Internet. Alternatively, parents may believe something told to them by a trusted physician despite subsequent evidence to the contrary and efforts to correct the earlier misdiagnosis. Physicians may unwittingly contribute to a parent's belief that a real problem exists by, perhaps reasonably, persistently pursuing a medical diagnosis. There is a need to discern commonly used hyperbole (e.g., exaggerating the height of the fever) in order to evoke concern and perhaps justify a visit to an emergency department. In the end, a diagnosis of MCA rests on clear evidence of a child repeatedly being subjected to unnecessary medical tests and treatment, primarily stemming from a parent's actions. Determining the parent's underlying psychopathology is the responsibility of mental health professionals.

Once MCA is suspected, gathering and reviewing **all** the child's medical records is an onerous but critical first step. It is often important to confer with other treating physicians about what specifically was conveyed to the family. A mother may report that the child's physician insisted that a certain test be done when it may be the mother instead who demanded the test. It is also necessary to confirm the basis for a given diagnosis, rather than simply accepting a parent's account.

Pediatricians may face the dilemma of when to accept that all plausible diagnoses have been reasonably ruled out, the circumstances fit MCA, and further testing and treatment should cease. The likelihood of MCA must be balanced with concerns about possibly missing an important diagnosis. Consultation with a pediatrician expert in child abuse is recommended. In evaluating possible MCA, specimens should be carefully collected, with no opportunity for tampering with them. Similarly, temperature measurements should be closely observed.

Depending on the severity and complexity, hospitalization may be needed for careful observation to help make the diagnosis. In some instances, such as repeated apparent life-threatening events, covert video surveillance accompanied by close monitoring (to rapidly intervene in case a parent attempts to suffocate a child) can be valuable. It is important that there be close coordination among hospital staff, especially as some may side with the mother and resent even the possibility of MCA being raised. Parents should not be informed of the evaluation for MCA until the diagnosis is made. Doing so could naturally influence their behavior and jeopardize establishing the diagnosis. All steps in making the diagnosis and all pertinent information should be very carefully documented, perhaps using a "shadow" chart that the parent does not have access to.

TREATMENT

Once the diagnosis is established, the treatment plan should be worked out by the medical team and CPS; it may require out-of-home placement and should include mental healthcare for the offending parent as well as for older affected children. Further medical care should be carefully organized and coordinated by one primary care provider. CPS should be encouraged to meet with the family only after the medical team has informed the offending parent of the diagnosis; their earlier involvement may hamper the evaluation. Parents often respond with resistance, denial, and threats. It may be prudent to have hospital security in the vicinity.

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Chapter 41

Failure to Thrive

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Failure to thrive (FTT) results from inadequate usable calories necessary for a child's metabolic and growth demands. No single set of growth parameters provides the criteria for a universal definition. FTT has classically been grouped into organic and nonorganic types; this construct is outmoded and not useful to clinicians seeking to address underlying causes, which are often multifactorial. Many would consider a weight for height ratio less than 2 SD (or <3 or 5 percentile) for age and gender diagnostic of FTT; others would use weight crossing 2 major percentiles on the growth curve. Patients with FTT may either have growth deceleration, faltering growth, or even weight loss.

A biopsychosocial model helps explain the complex interplay between even minor illnesses, the mental health of caregivers, and the home environment. The interaction between the child and parent is often complex; parent expectations of child behavior and the actual temperament of the infant create a transactional model where at times it is often difficult to separate cause and effect (action and reaction). The infant brings to this model an innate temperament with behavioral domains such as activity, adaptability, distractibility, response to new stimuli, and intensity of responses. Some infants are "easy babies," whereas others are more "difficult." These behaviors may interact with different maternal expectations or understanding of child behavior. Additional maternal contributions to this model may include postpartum depression, and the mother's own history of abuse or neglect as a child, as well as home environmental issues such as family stress, poor social/emotional support, poverty, and a chaotic lifestyle. In addition, many medical causes of FTT are associated with these same psychosocial risk factors; both need to be addressed in the management of FTT.

CLINICAL MANIFESTATIONS

Inadequate weight for corrected age, weight for height, and body mass index, as well as failure to gain adequate weight over a period of time, help define FTT (see Chapter 15). Growth parameters should be measured serially and plotted on growth charts appropriate for the child's sex, age, and, if preterm, postconceptual age. Growth charts are also available for some known chromosomal abnormalities, such as Down syndrome and Turner syndrome (see Chapter 81).

ETIOLOGY AND DIAGNOSIS

The causes of insufficient growth include (1) failure of the child to ingest and utilize sufficient calories, (2) malabsorption, and (3) increased metabolic demands. Focus the diagnostic approach on the cause of undernutrition. History, physical examination, and observation of the parent–child interaction in the clinical or home environment usually suggest the most likely etiologies and thus direct appropriate workup and management. A complete history should include a detailed nutritional, family, and prenatal history; documentation of child and caregiver interaction, the quantity, quality and frequency of meals, and further information regarding the onset of the growth failure (Table 41-1).

Many children with FTT will be solely categorized because of deprivation and/or psychological problems and rarely just because of child neglect. These families often share risk factors with neglect, such as poverty, social isolation, and caregiver mental health issues.

The medical causes of FTT may involve every organ system. The clinician may approach the diagnosis in terms of cause (Tables 41-2 and 41-3) or signs and symptoms (Table 41-4). The onset of growth deficiency can indicate a cause, such as the introduction of gluten into the diet of a child with celiac disease or a coincidental psychosocial event. A chromosomal abnormality, intrauterine infection, or

Table 41-1 Historical Factors About the Period After the Neonatal Period to Be Considered in an Evaluation of Growth Failure Using a Biopsychosocial Model

BIOLOGICAL SPHERE	PSYCHOSOCIAL SPHERES
Frequency and source of routine medical care Growth measurements Immunization status Medical illnesses Hospitalizations Medications Allergies—medications, food, other Surgeries Injuries, including bruises on infants Feeding issues—vigorous or difficult feeder Breastfeeding: • Milk letdown • Sense of fullness/emptying • Frequency and duration of feedings • Maternal observation of baby swallowing • Maternal diet and medical problems while breastfeeding Formula feeding: • Type • Method of mixing (concentration) • Frequency and quantity of feedings Other intake in first few months of life, such as: • Water • Juice • Tea • Soda • Cereal Sleep schedule Baby's temperament Developmental milestones Use of alternative or complementary medicines	Provision of baby care, especially feeding Maternal sleep deprivation Postnatal depression or other mental illness Type and amount of social support Availability of respite for mother Involvement of father and/or other intimate partner Intimate partner violence Financial resources, including money for baby supplies Enrollment in governmental aid programs Parental reaction to fussing/crying Who lives with baby Reactions of others in the home to the baby Parental employment Use of daycare or babysitting Caregiver perception of weight gain and general appearance

From Jenny C: Child abuse and neglect: diagnosis, treatment, and evidence, *Philadelphia, 2011, Elsevier/Saunders, p. 554, Table 57-5.*

Table 41-2 Diagnostic Classification of Causes and Selected Examples of Failure to Thrive

INADEQUATE INTAKE	MALABSORPTION
Inadequate food offered • Food insecurity • Poor knowledge of child's needs • Formula dilution or excessive juice • Breastfeeding difficulties • Medical child abuse/caregiver fabricated illness (Munchausen by proxy) • Medical neglect • Food fads including "rice" milk as substitute for formula or cow milk **Child not taking enough food** • Oromotor dysfunction, neurologic disease • Developmental delay • Behavioral feeding problem (altered oromotor sensitivity, pain and conditioned aversion) • Anorexia from systemic causes **Emesis** • Pyloric stenosis • Gastroesophageal reflux • Eosinophilic esophagitis • Vascular rings • Malrotation with intermittent volvulus • Increased intracranial pressure and other neurologic disorders • Inborn errors of metabolism • Rumination • Cyclic vomiting	Cystic fibrosis Celiac disease Hepatobiliary disease Food protein allergy, insensitivity, or intolerance Infection (giardiasis) Short gut syndrome INCREASED METABOLIC DEMAND Insulin resistance (intrauterine growth restriction) Congenital infections (human immunodeficiency virus, TORCHES) Syndromes (Russell-Silver, Turner, Down) Malignancy Chronic disease (cardiac, pulmonary, renal) Metabolic disorders Immunodeficiency/autoinflammatory disorders Endocrine (diabetes mellitus, diabetes insipidus, hyperthyroidism)

TORCHES, toxoplasma, other agents, rubella, cytomegalovirus, herpes simplex.

Data from Jaffe A: Failure to thrive: current clinical concepts, Pediatr Rev *32:100-108, 2011.*

Table 41-3 Failure to Thrive: Differential Diagnosis by System

PSYCHOSOCIAL/BEHAVIORAL Inadequate diet because of poverty/food insufficiency, errors in food preparation Poor parenting skills (lack of knowledge of sufficient diet) Child/parent interaction problems (autonomy struggles, coercive feeding, maternal depression) Food refusal Rumination Parental cognitive or mental health problems Child abuse or neglect; emotional deprivation	**GASTROINTESTINAL** Pyloric stenosis Gastroesophageal reflux Repair of tracheoesophageal fistula Malrotation Malabsorption syndromes Celiac disease Milk intolerance: lactose, protein Pancreatic insufficiency syndromes (cystic fibrosis) Chronic cholestasis Inflammatory bowel disease Chronic congenital diarrhea states Short bowel syndrome Pseudoobstruction Hirschsprung disease Food allergy
NEUROLOGIC Cerebral palsy Hypothalamic and other central nervous system tumors (diencephalic syndrome) Neuromuscular disorders Neurodegenerative disorders	**CARDIAC** Cyanotic heart lesions Congestive heart failure Vascular rings
RENAL Recurrent urinary tract infection Renal tubular acidosis Renal failure	**PULMONARY/RESPIRATORY** Severe asthma Cystic fibrosis; bronchiectasis Chronic respiratory failure Bronchopulmonary dysplasia Adenoid/tonsillar hypertrophy Obstructive sleep apnea
ENDOCRINE Diabetes mellitus Diabetes insipidus Hypothyroidism/hyperthyroidism Growth hormone deficiency Adrenal insufficiency	**MISCELLANEOUS** Collagen-vascular disease Malignancy Primary immunodeficiency Transplantation
GENETIC/METABOLIC/CONGENITAL Sickle cell disease Inborn errors of metabolism (organic acidosis, hyperammonemia, storage disease) Fetal alcohol syndrome Skeletal dysplasias Chromosomal disorders Multiple congenital anomaly syndromes (VATER, CHARGE)	**INFECTIONS** Perinatal infection (TORCHES) Occult/chronic infections Parasitic infestation Tuberculosis HIV

CHARGE, coloboma, heart disease, atresia choanae, retarded growth and retarded development and/or central nervous system anomalies, genital hypoplasia, and ear anomalies and/or deafness; TORCHES, toxoplasma, other agents, rubella, cytomegalovirus, herpes simplex; VATER, vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia.

Table 41-4 Approach to Failure to Thrive Based on Signs and Symptoms

HISTORY/PHYSICAL EXAMINATION	DIAGNOSTIC CONSIDERATION
Spitting, vomiting, food refusal	Gastroesophageal reflux, chronic tonsillitis, food allergies, eosinophilic esophagitis
Diarrhea, fatty stools	Malabsorption, intestinal parasites, milk protein intolerance, pancreatic insufficiency, celiac disease, immunodeficiency, inflammatory bowel disease
Snoring, mouth breathing, enlarged tonsils	Adenoid hypertrophy, obstructive sleep apnea
Recurrent wheezing, pulmonary infections	Asthma, aspiration, food allergy, cystic fibrosis, immunodeficiency
Recurrent infections	HIV or congenital immunodeficiency diseases, anatomic defects
Travel to/from developing countries	Parasitic or bacterial infections of the gastrointestinal tract

teratogen exposure should be considered in a child with symmetric growth failure since birth. Investigation for metabolic disorders should be considered in children with FTT accompanied by 1 of the following factors: history of acute, severe, and potentially life-threatening symptoms, recurrent vomiting, liver dysfunction, neurologic symptoms, cardiomyopathy and myopathy, impairment of special senses, renal symptoms, or distinct dysmorphic features and/or organomegaly.

The physical examination should focus on identifying chronic illnesses, recognizing syndromes that may alter growth, and documenting the effects of malnutrition (Table 41-5).

Laboratory evaluation of children with FTT should be judicious and based on findings from the history and physical. Obtaining the state's newborn screening results, a complete blood count, and urinalysis represent a reasonable initial screen. Testing for celiac disease is indicated in children if the poor growth coincided with gluten exposure (see Chapter 338).

TREATMENT

Treatment requires a multidisciplinary approach and an understanding of all the medical and psychosocial elements that contribute to a child's

Table 41-5	Approach to Physical Examination
Vital signs	Blood pressure, if over 2 yr, temperature, pulse, respirations, oxygen saturation, anthropometry (growth percentiles, body mass index)
General appearance	Activity, affect, posture
Skin	Hygiene, rashes, trauma (bruises, burns, scars)
Head	Hair whorls, color and pluckability of hair, occipital alopecia, fontanel size and patency, frontal bossing, sutures, shape, facial dysmorphisms, philtrum
Eyes	Ptosis, strabismus, fundoscopic examination where possible, palpebral fissures, conjunctival pallor, icterus, cataracts
Ears	External form, rotation, tympanic membranes
Mouth, nose, throat	Thinness of lip, hydration, dental eruption and hygiene caries, glossitis, cheilosis, gum bleeding, marked tonsillar enlargement
Neck	Hairline, masses, lymphadenopathy
Cardiovascular	Evidence of congestive heart failure, cyanosis
Abdomen	Protuberance, hepatosplenomegaly, masses
Genitalia	Malformations, hygiene, trauma
Rectum	Fissures, trauma, hemorrhoids
Extremities	Edema, dysmorphisms, rachitic changes, nails and nail beds
Neurologic	Cranial nerves, reflexes, tone, retention of primitive reflexes, quality of voluntary movement

From American Academy of Pediatrics Committee on Nutrition: Failure to thrive. In Kleinman RE, Greer FR, editors: Pediatric nutrition, *ed 7, Elk Grove Village, IL, 2014, American Academy of Pediatrics, Tab 27-3.*

growth: a child's health and nutritional status, family issues, and the parent–child interaction. An appropriate feeding atmosphere at home is important for all children with FTT.

Indications for hospitalization include severe malnutrition or failure of outpatient management. If a child requiring hospitalization has not responded after 2-3 mo of outpatient management, a specialized, multidisciplinary inpatient assessment should be considered. Inpatient care may include further diagnostic and laboratory evaluation, an assessment and implementation of adequate nutrition, and evaluation of the parent–child feeding interaction.

Children with severe malnutrition must be refed carefully, with an incremental increase in calories to avoid refeeding syndrome (see Chapter 46). The type of caloric supplementation is based on the severity of FTT and the underlying medical condition. The response to feeding depends on the specific diagnosis, medical treatment, and severity of FTT. Minimal catch-up growth should generally be 2-3 times the average weight gain for corrected age. Multivitamin supplementation should be given to all children with FTT to meet the recommended dietary allowance, because these children commonly have iron, zinc, and vitamin D deficiencies, as well as increased micronutrient demands with catch-up growth.

Therapy for the psychosocial factors should be specific for the underlying issue (maternal depression, insufficient funds for food). In addition, parent education should focus on what is normal infant development and correcting any parental misconceptions about feeding and temperament, as well as learning the infant cues for hunger, satiety, and sleep. Some children who develop feeding aversion behaviors will require treatment by a specialized feeding team. If abuse or purposeful neglect is a concern, the family should be referred to the child protective service team.

PROGNOSIS

FTT early in life, regardless of cause, is concerning because maximal postnatal brain growth occurs in the first 6 mo of life. Studies investigating the long-term sequelae of FTT in young infants and children have been conflicting, and there is no clear consensus regarding the long-term emotional, cognitive and metabolic effects. Despite inconclusive long-term outcomes in children who have FTT, investigators support early nutritional interventions for children who have poor growth. Early FTT may be associated with increased risk factors (including dyslipidemia, hypertension, and glucose intolerance) for cardiovascular disease as an adult perhaps relating to epigenetic responses to impaired nutrition and/or inflammation. The growing importance of cardiovascular disease among adults in lower and middle income nations where many children still have inadequate nutrition offers yet another reason why early FTT should be cause for concern globally.

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Chapter 42

Chronic Illness in Childhood

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EPIDEMIOLOGY

Patterns of chronic illness in childhood are complex and dynamic. Serious chronic illness in children is less common than that among adults and widely heterogeneous. These differences have profound implications for the organization of children's health services, as pediatricians have the difficult task of identifying and caring for children with unusual and varied conditions. Child health services have become far more reliant on standardized screening programs and formal systems of referral to regional specialty care programs than are health-care systems for adults. Pediatrics has been characterized by rapid progress in preventing serious acute illnesses and extending the lives of children who previously would have succumbed to their illness early in life. These factors have made the epidemiology of childhood far more dynamic than that of the adult world.

National survey data suggest that 30% of all children have some form of chronic health condition (Table 42-1). If allergies, eczema, minor visual impairments, and other conditions not likely to generate serious consequences are excluded, then between 15% and 20% of all children have a chronic physical, learning, or developmental disorder. Boys have higher rates of chronic illness than do girls. There is considerable variation in the nature and severity of chronic illnesses in children (Table 42-2). The most common serious chronic condition is asthma, with 12% of children having received a diagnosis of asthma at some time in their lives; half of these children were reported to have experienced asthma symptoms in the prior 12 mo (see Chapter 144). Mental health and behavioral conditions represent a large and growing number of children with chronic illness. It has been estimated that almost 21% of U.S. children between 9 and 17 yr of age have a diagnosable mental or addictive disorder associated with some impairment; approximately 11% had significant impairment. Estimates suggest that 5% had major depression (see Chapter 26) and approximately 9.5% have attention-deficit/hyperactivity disorder (see Chapter 33). Overweight is not usually defined as a chronic health condition, but in 2013, the American Medical Association characterized obesity as a disease. In 2010 12% of 2-5 yr olds, 18% of 6-11 yr olds, and nearly 18% of all

Table 42-1 Prevalence and Activity Limitation for Selected Chronic Diseases in Children <18 Yr of Age: United States, 2000-2003

CONDITION	NUMBER (IN THOUSANDS)	PREVALENCE (PER 100,000 CHILDREN)	ACTIVITY LIMITATION* (% OF CHILDREN WITH CONDITION)
Asthma	9,017	12,419	6.9
ADHD/ADD	4,034	6,078	5.5
Developmental delay	2,061	3,145	16.7
Congenital and other heart conditions	957	1,318	9.76
Intellectual disability	447	677	27.7
Cerebral palsy	273	375	36.24
Autism	234	322	18.2
Sickle cell anemia	151	209	23.91
Diabetes	120	166	4.8
Down syndrome	104	141	23.9
Arthritis	73	101	37.11
Muscular dystrophy	35	48	81.3
Cystic fibrosis	29	40	33.9

*Presence of an impairment or health problem that limits the ability to crawl, walk, run, or play. Figures based on weighted and age-adjusted national sample.
ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder.
Data from National Health Interview Survey, 2000-2003. National Center for Health Statistics, Centers for Disease Control and Prevention.

Table 42-2 Quality Measures for Healthcare Received by Children with Special Healthcare Needs by Family Income: United States, 2005-2006 (Percent Meeting Quality Measure)

	MEDICAL PARTNERSHIP AND SATISFACTION WITH SERVICES*	MEDICAL HOME†	ADEQUATE INSURANCE‡	EARLY AND CONTINUOUS SCREENING§	COMMUNITY-BASED SERVICES‖	TRANSITION TO ADULT LIFE¶
<99% FPL	50.0	34.0	56.8	47.7	85.7	24.3
100-199% FPL	52.7	41.3	57.4	56.9	86.7	33.7
200-399% FPL	58.7	51.0	61.8	66.8	90.3	43.5
>399% FPL	64.8	56.2	69.1	76.8	92.0	53.7

*Families of children and youth with special healthcare needs partner in decision-making at all levels and are satisfied with the services they receive.
†Children and youth with special healthcare needs receive coordinated ongoing comprehensive care within a medical home.
‡Families of children with special healthcare needs have adequate private and/or public insurance to pay for the services they need.
§Children are screened early and continuously for special healthcare needs.
‖Community-based services for children and youth with special healthcare needs are organized so families can use them easily.
¶Youth with special healthcare needs receive the services necessary to make transitions to all aspects of adult life, including adult healthcare, work, and independence.
FPL, federal poverty line ($19,350 for family of 4 for the 48 contiguous states and the District of Columbia in 2005).
From U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau: *The national survey of children with special health care needs, chartbook 2005-2006*, Rockville, MD, 2008, U.S. Department of Health and Human Services.

children age 12 through 19 yr have a body mass index above the 95th percentile (see Chapter 47). Comorbid conditions, such as hypertension and a variety of metabolic disorders, may exist.

The severity and impact of chronic illnesses can vary significantly. Approximately 9% of all children have activity limitations as a consequence of 1 or more chronic illnesses, which has been relatively stable since 2001. Of these children, 40% have developmental or learning disorders, 35% have chronic physical conditions, and 25% report chronic mental health disorders. Approximately 2% of children have chronic conditions and activity limitation severe enough to meet eligibility criteria for the Supplemental Security Income program. Between 12% and 18% of all children meet the chronic illness and elevated service needs of the **children with special healthcare needs (CSHCN)** definition, depending on the data set that is examined.

These current prevalence figures represent a substantial increase in childhood chronic illness in the past several decades. In 2009, approximately 9% of children were reported to have a chronic health condition that limited their activities; the comparable figure in 1960 was only 2%. Although the increase in childhood chronic illness is likely partly a result of changes in survey methodologies, improvements in diagnosis, and expanded public awareness of behavioral and developmental disorders, there is strong evidence that the prevalence of certain important chronic child health conditions has increased. Asthma rates rose from <4% in 1980 to 9.5% in 2011, with the highest rates among the poorest children. The prevalence of attention-deficit/hyperactivity disorder and autism (see Chapter 30) has also increased considerably. Although improvements in the survival of infants and young children from prematurity, congenital anomalies, and genetic disorders have also

contributed to the rising prevalence rates, this source accounts for only a small portion of all chronic illness in childhood.

Chronic illness accounts for a growing portion of child healthcare expenditures, serious illness, hospitalizations, and deaths among children in the United States. Across 37 children's hospitals, 19% of admission and 23% of inpatient charges were accounted for by only 3% of patients with frequent recurrent hospitalizations. Children with a chronic illness are hospitalized approximately 4 times more often and spend more than 7 times as many days in the hospital as children without a chronic illness. Estimates suggest that chronic illness accounts for the majority of all nontraumatic hospitalizations for children, a figure that has more than doubled in the past 4 decades, and children with chronic illnesses are experiencing increasing lengths of stay. Multiple admissions in any given year have also risen substantially: a child with a chronic condition is more likely to be readmitted, particularly for children with malignancies and neurologic conditions, although up to 25% of these may be planned admissions. The majority of all non–trauma-related deaths in children are now a result of chronic disorders. This historical shift in the distribution of pediatric hospitalization and mortality reflects not only the rise in the prevalence of childhood chronic illness, but also marked reductions in the incidence of serious acute pediatric illness.

Chronic illness is also contributing more profoundly to **social disparities** in child health. There are somewhat conflicting data on the association of poverty and the prevalence of chronic disorders in children, although most studies suggest a moderate elevation among poor children. Children enrolled in welfare cash assistance programs are more likely to have a chronic illness, and poor and African-American children have greater limitations in activity because of chronic conditions. Latino school-age children have rates of chronic illness that are similar to non-Latino whites; however, there remains little information on the prevalence and impact of chronic illness and its functional impact among the different subgroups of Latino children, as well as subgroups of Asian and Pacific Islanders.

ENHANCED NEEDS OF CHILDREN WITH CHRONIC ILLNESS AND THEIR FAMILIES

Although the nature and severity of chronic illness in children is quite heterogeneous, there are important clinical considerations that are common to virtually all such conditions regardless of their specific diagnosis or specialty group.

Financial Costs

The care required by children with serious chronic illnesses is usually associated with high financial costs. Even though the majority of children with chronic illness have coverage, 38% report being inadequately insured, experiencing gaps in coverage, and having costs or services not covered. Most states have some mechanism to facilitate health insurance coverage for children, although the nature and scope of these programs can vary considerably. A growing number of private and public health insurance plans require deductibles and copayments, which can accumulate rapidly for a child with a chronic illness. Some plans offer coverage up to a designated cost, period of hospitalization, or for a certain number of specialty visits. Once this cap has been reached, a larger portion or all of the costs may be borne by the family. This financial burden has been increasing over time, more so for families with private insurance: 20% of families have out-of-pocket expenses exceeding 10% of the family's income. The Family Opportunity Act of 2005 allows families of children with disabilities who are not financially eligible for Medicaid to buy into the program on a sliding scale. This program was created to fill the gap when children are underinsured because of private insurance limiting essential services, such as durable medical equipment and uncovered prescription drugs. The implementation of this program varies widely by state. The Patient Protection and Affordable Care Act, known colloquially as the ACA or "Obamacare," protects children with serious illness by instituting new insurance industry regulations, ending the practice of denying coverage to individuals with preexisting conditions, and allowing children to remain on their parents' insurance policies to the age of 26 yr.

Of great importance for children with serious chronic disorders, many new procedures, medications, and therapeutic regimens may be considered "experimental" by some insurers and not covered. Insurance coverage policies often generate strong incentives for hospital rather than outpatient care, even if the latter is indicated. Frequent medical visits and hospitalizations can interfere with parental employment and undermine job performance and security.

Complex Clinical Management

Children with serious chronic disorders usually require intense clinical management both in community and hospital settings. Close surveillance of disease progression, symptoms and functioning, and adverse medication effects often necessitate frequent communication and office visits. Managing hospital admissions and discharge planning may also prove complex and involve a variety of clinicians and community resources. As pressure to reduce hospitalization has grown, the burden on outpatient systems has increased accordingly. An uncoordinated approach to the multitude of required clinical visits can prove highly burdensome to the family and can undermine even the most committed family's attempts to comply. New models of care including **accountable care organizations (ACOs)** link care across the continuum, from quaternary to primary care by incentivizing multidisciplinary care teams to manage patients focusing on care coordination and prevention. The ability to capture savings through decreased admissions and emergency department use has been largely derived from the experiences of adult-focused programs; the feasibility and utility of pediatric ACOs, particularly for large populations of poor children, remain unexplored. The impact of ACOs and related financial arrangements on highly regionalized specialty service systems for children is of particular concern.

Pain

Many seriously ill children suffer from chronic pain (rheumatoid arthritis, spastic cerebral palsy), recurrent pain during exacerbations of underlying disease (inflammatory bowel diseases, sickle cell anemia), or acute pain related to procedures, surgeries, or diagnostic tests. This pain can alter a child's affect and influence their academic and social development, while also decreasing the family's quality of life (see Chapter 62). Assessing pain in young children or those with developmental disorders can be difficult and should always consider sociocultural and psychologic factors as well as developmental stage. Because serious, chronic pain is relatively unusual in children, its management may require the involvement of pediatric pain subspecialists who may practice with multidisciplinary teams in regional centers. The emotional toll on parents of children experiencing chronic pain can also be profound and require close attention by medical personnel.

Behavioral and Adjustment Issues

Although chronic illness in children elevates the likelihood that they will experience psychologic and behavioral problems, most children with chronic illness will experience the same level of psychologic and behavioral issues as other children their age. Behavioral and adjustment problems are more likely to occur the earlier the onset of the illness, particularly if it emerges in infancy. The risk of psychologic and behavioral problems does not appear to be associated with the severity of the chronic illness per se. These effects can occur across all diagnoses, although they are more profound for disorders that affect the central nervous system, including cerebral palsy, head trauma, and treatment-related complications that affect the brain, such as chemotherapy for cancer. Children with higher levels of cognitive ability appear to be less likely to develop serious behavioral or adjustment problems. Familial strife and mental illness, particularly depression in the mother, have been associated with an enhanced risk for psychologic and behavioral consequences.

Impact on Families

Like all children, a child with a chronic illness usually brings a mix of challenges and joy to a family. The presence of a chronic illness can add extra burdens, which can be expressed in a variety of forms. First,

the daily requirements of care should never be underestimated, particularly when the child is unable to perform tasks such as bathing, dressing, using the toilet, and feeding. Second, the care required by the child with chronic illness may divert needed attention from siblings and strain normal family dynamics. Third, the ultimate burden faced by families of children with a chronic illness is the emotional toll exacted by the daily struggles, pain, and, occasionally, early death that chronic illness can imply. Fourth, among the most difficult attributes of childhood chronic illness is the inherent unpredictability of its course and ultimate impact. Clinicians should be sensitive to how difficult it can be living with a child whose condition can worsen at any moment and without apparent cause. If conditions worsen to the point where medical care is futile, the evolving field of pediatric palliative care (see Chapter 43) can provide critical medical services and offer comprehensive support for grieving families. Fifth, children with serious chronic illness and their parents may harbor powerful hopes for new breakthroughs or divine intervention. Clinicians should understand the importance of these hopes for the families under their care and should explore related hopes for lesser, more incremental steps, such as attending school, playing sports, or taking a special trip.

Comprehensive Care and the Medical Home

All children require a clinician who takes responsibility for their comprehensive healthcare needs. To meet this responsibility, the coordinated implementation of a series of essential practice components, often termed the **medical home,** is recommended. These services should be provided within a broader system of care that emphasizes partnering in decision making between the family and medical providers, coordination of services among medical and community service providers, adequate health insurance coverage, ongoing screening for special healthcare needs, critical educational and community-based services, and special attention to the needs of older children as they transition to adult life and healthcare systems. Innovative new models are being suggested, including linkages between **community health centers** and academic medical partnerships, which combine the subspecialist expertise, medical technology, and inpatient care of local academic medical centers with the primary care expertise of community health centers, to create a distinctive form of ACO. Evidence suggests that the extent to which these care requirements are being met for families with children with special healthcare needs is highly variable (see Table 42-1) and thus new models are needed. Although essential for all children, these practice elements take on special importance for children with chronic disorders and are outlined as follows.

Preventive Services

Primary, preventive care is an essential component of healthcare for children with chronic disease. Although overall CSHCN use preventive medical and dental services at rates similar to those of other children, primary preventive services can easily be overlooked in addressing the more specialized needs of these patients. The most common unmet healthcare need for CSHCN is dental care. Children with chronic disorders are commonly less-well immunized than their healthy counterparts. Well child care may be disrupted by visits for acute exacerbations of the chronic disorder and clinicians should carefully evaluate whether the chronic illness or its symptoms are contraindications to immunization. A family's reliance on specialty services can be so great that the need for primary care services is overlooked. Special effort may be required to ensure the provision of high-quality primary care to children with chronic illness.

Continuity of Care

Children with chronic illnesses are particularly dependent on a stable, ongoing relationship with clinicians and the healthcare system. The duration and complexity of chronic illness in children require that the clinician responsible for coordinating the child's care have a good understanding of the child's clinical history, including patterns of exacerbation and response to medications and other interventions. Continuity of care also serves as a basis for building trust and effective communication between affected families and clinicians, a prerequisite for high-quality care. Practice structures, therefore, should ensure the identification of a principal clinical provider and facilitate the provider's involvement in all necessary care. Transitioning of care as the child reaches adulthood is also critical, but is not experienced equally across the spectrum of medical need. The greatest difficulty in transitioning care occurs in youth with more complex conditions, those with cognitive impairments, and youth from racial/ethnic minority backgrounds. The transition requires planning, coordination and recognition of the emotional bonds that likely have developed between the child (and the child's family) and the practitioner (see Chapter 112.3).

Access to Urgent Care

Clinicians should expect that children with chronic illness will have enhanced requirements for urgent consultation, emergency care, and hospitalization. Practice mechanisms that ensure rapid access to medical consultation both by telephone and office visitation are essential. Procedures for urgent referral to appropriate facilities for emergency evaluation and hospitalization should also be established. This is particularly important in managed care systems that may require primary care referral or approval for care at referral sites.

Access to Specialty Care

Children with chronic illness commonly require specialized care. The need for specialty referral is particularly important in pediatrics because serious disorders are relatively rare in children. In many countries, including the United States, there is a shortage of many pediatric subspecialists. The ACA includes provisions to encourage pediatric residents to pursue pediatric subspecialty training. Regional systems of specialty referral and hospitalization have been formalized in the past several decades, particularly for perinatal care, pediatric trauma, and children with serious chronic illness. These systems of "regionalized" specialty care have been shown to reduce dramatically morbidity and mortality among affected children. It is crucial that policymakers who develop and implement health insurance products through new marketplaces or exchanges understand the need to include access to children's hospitals and pediatric subspecialists for children with special healthcare needs. Pediatricians can play a crucial role in conveying to policymakers the special dependence of modern pediatrics on established regionalized systems of care. Regionalized care heavily relies on specialty care referrals, responsive communication between primary care practices and specialty programs is essential, particularly in conveying the reasons for referral, patient history, the nature and findings of the specialty evaluation, hospital course, and the collaborative development of a follow-up management plan.

Enhanced Information Systems

Children with chronic illness often require careful monitoring of their clinical status and the rapid evaluation of exacerbations. On-call and related coverage systems must include immediate access to up-to-date medical record information for children with complex histories and management regimens. Electronic medical records and systems that permit parent or other caretakers routine access to computerized medical record information may also prove useful. Access to current medical information, laboratory results, as well as clinical protocols and decision support algorithms could prove particularly helpful for children with complex healthcare requirements.

Linkage to Schools, Support Groups, and Community Services

Children with chronic illnesses often have special educational needs and may require the active participation of teachers and school health personnel in medical care plans. An important first step in creating a care plan is to assess the level of medical expertise available at the school site because many schools no longer have a nurse present. Special mechanisms should be established to ensure close coordination with schools, including provisions for collaborative evaluations of needs, monitoring of educational performance and social interactions, and the ongoing refinement of medical and educational management

regimens. Clinicians can prevent the isolation many families feel by connecting them to support and advocacy groups composed of other parents with similarly affected children. Such connections have been facilitated by use of the Internet, which can link children and families over wide geographic areas.

Logistic Access

The difficulties that families can experience in transporting children with serious physical or behavioral disorders should never be underestimated. Particularly for older children or those requiring wheelchairs or other equipment, urban public transportation systems may be seriously impractical. In suburban and rural areas, transportation may involve traveling over great distances. For parents who have daytime employment, extended clinic hours may be required. Many communities have implemented innovative transportation programs for families in need of health and social services, particularly when available means of travel to clinical facilities is deemed unsafe or if it requires specially equipped vehicles or the assistance of trained personnel. In a growing number of areas, a variety of forms of telemedicine have enhanced access to medical and particularly, specialty care consultation.

Cultural Sensitivity and Language Concordance

See also Chapter 4.

Clinicians must possess a basic understanding of the meaning of illness and traditions of healing in the communities they serve. Cultural competency education is a required component of pediatric residency training, empowering a new generation of pediatricians with tools needed to bridge cultural divides. Although such cultural competence of individual providers is important, access also depends on creating clinical programs that respond to local perceptions and social institutions. Cultural competence not only reduces the likelihood of misunderstandings and medical errors, but also helps ensure that clinical programs can take full advantage of the many strengths that exist in culturally defined communities.

The most basic element of communication between clinicians and families of children with a chronic illness is that they share a common language. Clinicians should not overestimate their own or a parent's basic command of a language and must ensure that conveyed information is well understood. Children should not be used as interpreters despite the fact that they often have a better command of English than do their parents. Given the complex issues chronic illness can generate, it is far more useful to integrate trained interpreters into programs for chronically ill children in locations characterized by diverse language groups.

Nondiscrimination in Access and Clinical Decision Making

Clinicians who care for children with chronic illness must recognize the power of social status to define access to care. A history of inadequate service provision or different levels of service for distinct social groups can generate deep resentment and distrust for the medical system. **Family centered care**, defined in 1987 and incorporated into The Maternal and Child Health Bureau's core objectives, includes principles that build on family strengths, honor diversity, and emphasize the centrality of community-based services among others. Many studies have suggested that even when patients have adequate health insurance, poor and minority patients are less likely to be offered recommended diagnostic and therapeutic interventions. Although the precise reasons for these observations remain unclear, it is important that provider preconceptions do not replace a careful consideration of the true desires and capabilities of families, particularly in association with new, specialized, or home-based interventions. Strategies to confront these issues include implementing a family centered care approach training and recruitment of minority health providers, educational programs for clinicians, and the active assessment of clinical decision-making and family experiences at clinical facilities.

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Chapter 43

Pediatric Palliative Care

Christina Ullrich, Janet Duncan, Marsha Joselow, and Joanne Wolfe

The World Health Organization defines palliative care for children as "…the active total care of the child's body, mind and spirit, and also involves giving support to the family.…Optimally, this care begins when a life-threatening illness or condition is diagnosed and continues regardless of whether or not a child receives treatment directed at the underlying illness." Provision of palliative care applies to children with a range of acute and chronic diseases, both life-threatening and life-altering, including, but not limited to, cancer, mitochondrial disorders, cardiac disease, neurodegenerative diseases, and trauma with life-threatening sequelae (Table 43-1). In fact, medical and technological advances have resulted in children living longer, often with significant dependence on new and complex technologies. These children have complex chronic conditions across the spectrum of congenital and acquired life-threatening disorders (see Chapter 42). Children with complex chronic conditions benefit from integration of palliative care strategies. These children, who often survive near-death crises followed by the renewed need for rehabilitative and life-prolonging treatments, are best served by a system that is flexible and responsive to changing needs.

Table 43-1	Conditions Appropriate for Pediatric Palliative Care
CONDITIONS FOR WHICH CURATIVE TREATMENT IS POSSIBLE BUT MAY NOT SUCCEED	
Advanced or progressive cancer or cancer with a poor prognosis	
Complex and severe congenital or acquired heart disease	
CONDITIONS FOR WHICH THERE IS INTENSIVE LONG-TERM TREATMENT AIMED AT PROLONGING LIFE AND MAINTAINING QUALITY OF LIFE BUT PREMATURE DEATH IS STILL POSSIBLE	
Human immunodeficiency virus infection	
Cystic fibrosis	
Severe immunodeficiency	
High-risk solid-organ transplant candidates and/or recipients such as lung or multivisceral	
Chronic or severe respiratory failure	
Muscular dystrophy	
Primary pulmonary hypertension	
PROGRESSIVE CONDITIONS FOR WHICH THERE IS NO CURATIVE OPTION AND IN WHICH TREATMENT IS ALMOST EXCLUSIVELY PALLIATIVE AFTER DIAGNOSIS	
Progressive metabolic disorders (e.g. mucopolysaccharidosis, Tay Sachs)	
Batten disease	
Severe forms of osteogenesis imperfecta	
CONDITIONS INVOLVING SEVERE, NONPROGRESSIVE DISABILITY, CAUSING EXTREME VULNERABILITY TO HEALTH COMPLICATIONS	
Severe cerebral palsy with recurrent infection or difficult-to-control symptoms	
Severe neurologic sequelae of infectious disease	
Hypoxic or anoxic brain injury	
Brain malformations such as holoprosencephaly or lissencephaly	

Adapted from The Together for Short Lives (formerly the Association for Children's Palliative Care [ACT]) Life-limiting/Life-threatening Condition Categories available at http://www.togetherforshortlives.org.uk/professionals/childrens_palliative_care_essentials/approach

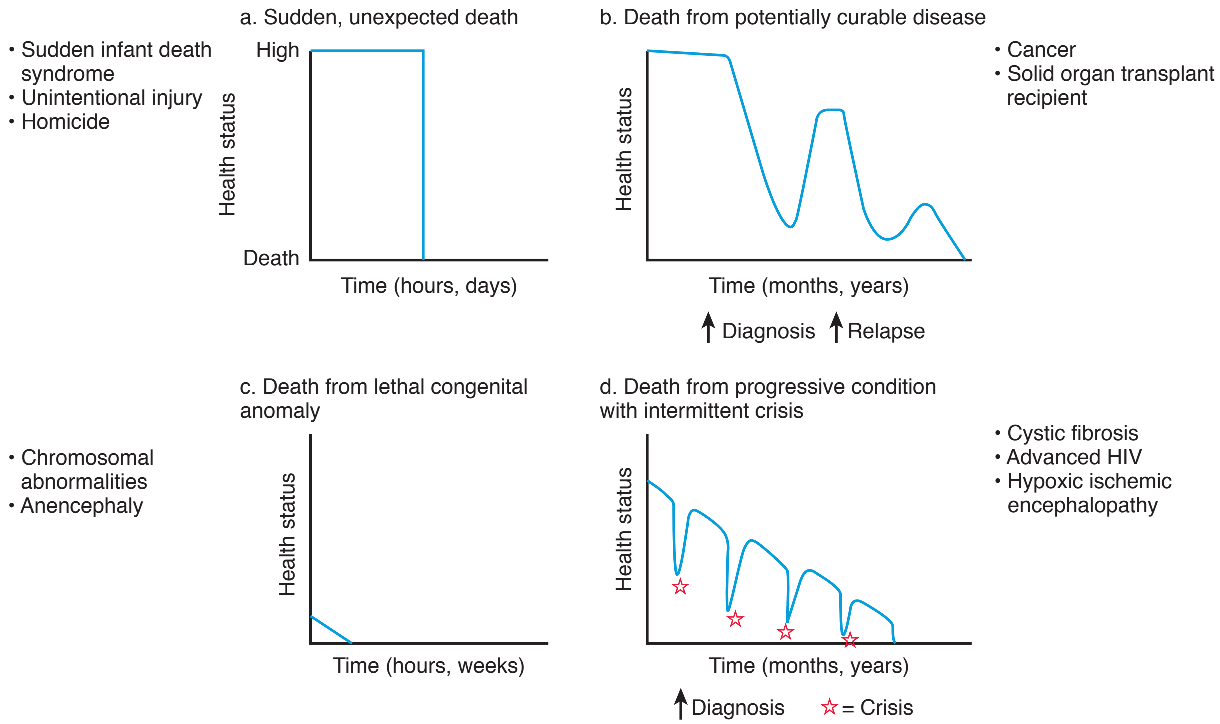

Figure 43-1 Typical illness trajectories for children with life-threatening illness. *(From Field M, Behrman R, editors:* When children die: improving palliative and end-of-life care for children and their families, *Washington, DC, 2003, National Academies Press, p. 74, Fig 3.1.)*

Although palliative care is often mistakenly understood as equivalent to end-of-life care, its scope and potential benefit extend before and well after end-of-life and is *applicable throughout the illness trajectory*. Palliative care emphasizes optimization of quality of life, communication, and symptom control, aims that may be congruent with maximal treatment aimed at sustaining life.

The mandate of the pediatrician and other pediatric clinicians to attend to children's physical, mental, and emotional health and development includes the provision of palliative care for those children who live with a significant possibility of death before adulthood (Fig. 43-1). Such comprehensive physical, psychological, social, and spiritual care requires an interdisciplinary approach. This is often possible with creative use of professional hospital and community-based providers.

In the United States, the healthcare and reimbursement structure combined with frequent use of medical technology (e.g., home ventilatory support) or continuous home nursing historically precluded formal enrollment of children on the hospice benefit when they were otherwise eligible (i.e., had an estimated prognosis of 6 mo or less). Section 2302 of the Patient Protection and Affordable Care Act, termed the **concurrent care for children requirement** eliminated the requirement that Medicaid patients <21 yr of age forgo curative or life-prolonging therapies to be eligible for hospice. Although Medicaid programs in every state are now required to provide concurrent curative/life-prolonging treatment and hospice services for hospice-eligible children, development of systems to make such concurrent care a reality has been slow. A limitation of the concurrent care for children requirement is that it does not expand access to hospice for children with life-threatening illness who do not meet hospice eligibility criteria (i.e., have a prognosis that cannot be estimated to be <6 mo). A number of state-based pediatric palliative care coalitions have formed in recent years to improve access to home-based pediatric hospice/palliative care services, using strategies such as Medicaid waivers or state plan amendments to increase coverage for hospice services. A growing number of home care agencies have also developed palliative care programs that serve as a bridge to hospice services for children not yet meeting hospice eligibility criteria. Provision of hospice or palliative care for children is often also limited by the availability of clinicians who have training or experience in caring for seriously ill children.

CARE SETTINGS

Pediatric palliative care should be provided across settings, including the hospital, outpatient settings, the home, pediatric nursing facilities, and inpatient hospice houses. **Home care** for the child with a life-threatening illness requires 24 hr per day access to experts in pediatric palliative care, a team approach, and an identified coordinator who serves as a link between hospitals, the community, and specialists and who may assist in preventing and/or arranging for hospital admissions, respite care, and increased home care support as needed. Adequate home care support and respite care, though very important, are often not readily available or families may feel using respite care is a personal failure, or they may worry that others cannot adequately care for their child's special needs.

At the end of life, children and families may need intensive support. About half of pediatric deaths occur in acute-care hospitals, and end-of-life care may thus be provided in the home, hospital, pediatric nursing facility or hospice house. Families need to feel safe and well cared for and given permission, if possible, to choose location of care. In tertiary care hospitals, most children die in the neonatal and pediatric ICUs. The philosophy of palliative care can be successfully integrated into a hospital setting, including the ICU, when the focus of care also includes the prevention or amelioration of suffering and improving comfort and quality of life. All interventions that affect the child and family need to be assessed in relationship to these goals. This proactive approach asks the question, "What can we offer that will improve the quality of this child's life and provide the most meaning and control for their family?" instead of, "What therapies are we no longer going to offer this patient?" Staff may benefit from education, support, and guidance as pediatric palliative care, like other types of intensive care, is an area of specialty. Regardless of the care setting, comprehensive palliative care requires an interdisciplinary approach that may include nurses, physicians, psychologists, psychiatrists, social workers, chaplains/clergy, child-life specialists, and trained volunteers.

PRIMARY AND SUBSPECIALTY PALLIATIVE CARE

Not all children with serious illness require care by a hospice and palliative medicine subspecialist or pediatric palliative care team. Basic palliative care knowledge, skills, and behaviors should be known to all clinicians who care for children with life-threatening illnesses and conditions. The role of the Hospice and Palliative Medicine subspecialist and team is to provide clinical consultation for more complex situations, to provide education and training, and to improve palliative care outcomes for all children and families through quality improvement and research.

COMMUNICATION, ADVANCE CARE PLANNING, AND ANTICIPATORY GUIDANCE

Although accurate prognostication is a particular challenge in pediatrics, the medical team often recognizes a terminal prognosis before the prognosis is understood by parents. This time delay may impede informed decision making about how the child lives at the end of life. Given the inherent prognostic uncertainty of a life-threatening diagnosis, discussions concerning resuscitation, symptom control, and end-of-life care planning should be initiated when the physician recognizes that a significant possibility of patient mortality exists. Having these conversations in the midst of a crisis is not ideal. Whenever possible, they should occur well in advance of the crisis or when the patient has recovered from a crisis, but is at high risk for others.

Patients and families are most comfortable being cared for by physicians and other care providers with whom they have an established relationship. Even in the face of long-standing and highly connected relationships, *clinicians often hold assumptions about parent prognostic awareness, and parent readiness and willingness to have such discussions*. In an attempt to protect families, clinicians may avoid conversations that they perceive as promoting hopelessness. However, parents greatly value honesty, and such conversations can promote parent hopefulness. A consultative palliative care team may provide the family with an opportunity to engage in sensitive conversations that are not as comfortably initiated with the primary team.

The population of children who die before reaching adulthood includes a disproportionate number of nonverbal and preverbal children who are developmentally unable to make autonomous care decisions. Although parents are usually the primary decision-makers, children should be as fully involved in discussions and decisions about their care as appropriate for their developmental status. Utilizing communication experts, child-life therapists, chaplains, social workers, psychologists, or psychiatrists to allow children to express themselves through art, play, music, talk, and writing will enhance the provider's knowledge of the child's understanding and hopes. Tools such as "Five Wishes" (for adults), "Voicing My Choices" (for adolescents), and "My Wishes" (for school-age children), have been useful in helping to gently introduce advance care planning to children, adolescents, and their families (http://www.agingwithdignity.org/index.php).

The Parents

From a parent's perspective, compassionate communication with medical providers who understand their child's illness, treatment options, and family beliefs and goals is the cornerstone of caring for children with life-threatening illness. During this period of time, one of the most significant relationships is that with the child's pediatrician, who often has an enduring relationship with the child and family, including healthy siblings. Parents need to know that their child's pediatrician will not abandon them as the goals of care evolve. A family's goals may change with the child's evolving clinical condition and other variable factors. A flexible approach rooted in ongoing communication and guidance that incorporates understanding of the family's values, goals, and religious, cultural, spiritual, and personal beliefs is of paramount importance.

Pediatricians should recognize the important role they have in continuing to care for the child and family as the primary goal of treatment may simultaneously be prolongation of life and comfort, relief of suffering, and promoting quality of life. Regular meetings between caregivers and the family are essential in order to reassess and manage symptoms, explore the impact of illness on immediate family members, and provide anticipatory guidance. At these meetings, important issues with lifelong implications for parents and their child may be discussed. Such discussions should be planned with care, ensuring that adequate time for in-depth conversation is allotted; a private, physical setting is arranged; devices silenced; and that both parents and/or others who might be identified by the family as primary supports are present. Strategies for facilitating conversations related to goals of care and decision-making are detailed below.

Families may look to their pediatrician for assurance that all treatment options have been explored. Assisting a patient's family to arrange a second opinion may be helpful. Listening to families and children speak about the future even in the face of poor prognosis may help keep the focus on living even while the child may be dying. Hoping for a miracle can coexist for parents even as they are facing and accepting the more likely reality of death.

Parents also need to know about the availability of home care, respite services, web-based support educational materials other media, and support groups. Responding to parent requests or need for counseling referrals for themselves, other children, or family is essential. Attending to the concrete needs of families such as financial, insurance and housing needs can be paramount in freeing them of worries that might interfere or compete with their ability to be fully present in their child's care.

When closer to end of life, while broaching the topic may seem daunting, exploration of how parents envision their child's death, addressing their previous loss experiences (most often with death of an adult relative) and any misconceptions they may have, is often a great relief to parents. Learning about cultural, spiritual, and family values regarding pain management, suffering, and the preferred place of end-of-life care is essential before death. Even raising thoughts about funeral arrangements, the possibility of autopsy, and organ/tissue donation can be helpful to give parents choices and know that these considerations can be discussed without fear.

A major worry of many parents is in how to involve and communicate with siblings as well as the child about the fact that most likely death is going to occur. Evidence shows that parents who have open conversations with their child about death and dying do not regret having done so. Clear communication around end-of-life issues, delivered with sensitivity and caring are directly correlated with ratings of high satisfaction with physician care. Such communication includes speaking directly to the child when appropriate. Communication is complicated by an assumed need for mutual protection in which the child wants to protect his or her parents and likewise the parents want to protect their child from painful information or sadness. Honoring the uniqueness of the child as well as understanding and respecting the family's communication style, values, spirituality, and culture, is critical in these highly sensitive conversations.

In communications with the child and family, the physician should avoid giving specific estimates of survival length, even when the child or family explicitly asks for them. These predictions are invariably inaccurate because population-based statistics do not predict the course for individual patients. A more honest approach may be to *explore ranges of time in general terms* ("weeks to months," "months to years"). The physician can also ask parents what they might do differently if they knew how long their child would live and then assist them in thinking through the options relating to their specific concerns (suggest celebrating upcoming holidays/important events earlier in order to take advantage of times when the child may be feeling better). It is generally wise to suggest that relatives who wish to visit might do so earlier rather than later, given the unpredictable trajectory of many conditions.

For the child and family, the integration of bad news is a process, not an event, and when done sensitively does not take away hope or alter the relationship between the family and physician. The physician should expect that some issues previously discussed may not be fully resolved for the child and parents (do-not-resuscitate [DNR] orders, artificial nutrition or hydration) and may need to be revisited over

time. Parents of a child with chronic illness may reject the reality of an impending death because past predictions may not have been accurate. Whether they are parents of a child with a chronic illness or of a child whose death is the result of accident or sudden catastrophic illness, they may experience great anxiety, guilt, or despair.

The Child

Truthful communication that takes into account the child's developmental stage and unique lived experience can help to address the fear and anxiety commonly experienced among children with life-threatening illness. Responding in a developmentally appropriate fashion (Table 43-2) to a child's questions about death, such as "What's happening to me?" or "Am I dying?" requires a careful exploration of what is already known by the child, what is really being asked (the question behind the question), and why the question is being asked at this particular time and in this setting. It may signal a need to be with someone who is comfortable listening to such unanswerable questions. Many children find nonverbal expression much easier than talking; art, play therapy, and storytelling may be more helpful than direct conversation.

A child's perception of death depends on the child's conceptual understanding of *universality* (that all things inevitably die), *irreversibility* (that dead people cannot come back to life), *nonfunctionality* (that being dead means that all biologic functions cease), and *causality* (that there are objective causes of death).

Very young children may struggle with the concepts of irreversibility and nonfunctionality. For young, school-age children, who are beginning to understand the finality of death, worries may include magical thinking in which their thoughts, wishes, or bad behavior might be the underlying cause for their illness. Older children seek more factual information to gain some control over the situation.

Table 43-2 Developmental Questions, Thoughts, and Concepts of Dying and with Responsive Strategies

TYPICAL QUESTIONS AND STATEMENTS ABOUT DYING	THOUGHTS THAT GUIDE BEHAVIOR	DEVELOPMENTAL UNDERSTANDING OF DEATH	STRATEGIES AND RESPONSES
MONTHS-3 YR			
"Mommy, don't cry." *"Daddy, will you still tickle me when I'm dead?"*	Limited understanding of events, future and past, and of the difference between living and nonliving.	May have "sense" that something is wrong. Death is often viewed as continuous with life (analogous to being awake and being asleep).	Optimize comfort, and consistency; familiar persons, objects, routines. Use soothing songs, words, and touch. *"I will always love you."* *"I will always take care of you."* *"I will tickle you forever."*
3-5 YR			
"I did something bad and so I will die." *"Can I eat anything I want in heaven?"*	Concepts are simple and reversible. Variations between reality and fantasy.	The child may see death as temporary and reversible, and not universal. May feel responsible for illness. Death may be perceived as an external force that can get you.	Assure child that illness is not the child's fault. Provide consistent caregivers. Promote honest simple language. Use books to explain the life cycle and promote questions and answers. *"You did not do anything to cause this."* *"You are so special to us and we will always love you."* *"We know (God, Jesus, Grandma, Grandpa) are waiting to see you."*
5-10 YR			
"How will I die?" *"Will it hurt?"* *"Is dying scary?"*	The child begins to demonstrate organized, logical thought. Thinking becomes less esoteric. The child begins to problem solve concretely, reason logically, and organize thoughts coherently. However, the child has limited abstract reasoning.	The child begins to understand death as real and permanent. Death means that your heart stops, your blood does not circulate, and you do not breathe. It may be viewed as a violent event. The child may not accept death could happen to himself or herself or anyone the child knows, but starts to realize that people the child knows will die.	Be honest and provide specific details if they are requested. Help and support the child's need for control. Permit and encourage the child's participation in decision making. *"We will work together to help you feel comfortable. It is very important that you let us know how you are feeling and what you need. We will always be with you so that you do not need to be afraid."*
10-18 YR			
"I'm afraid if I die my mom will just break down." *"I'm too young to die. I want to get married and have children."* *"Why is God letting this happen?"*	Abstract thoughts and logic possible. Body image is important. Need peer relationships for support and for validation. Altruistic values • staying alive for family • parents, siblings • donating organs/tissue Disbelief that he/she is dying.	Understand death as irreversible, inevitable and universal. Needs reassurance of continued care and love. Search for meaning and purpose of life.	Reinforce child/adolescent's self-esteem, sense of worth, and self-respect. Allow need for privacy, independence, access to friends and peers. Tolerate expression of strong emotions and permit participation in decision making. *"I can't imagine how you must be feeling. Despite it all, you are doing an incredible job. I wonder how I can help?"* *"What's most important to you now?"* *"What are your hopes…your worries?"* *"You have taught me so much, I will always remember you."*

Adapted from Hurwitz C, Duncan J, Wolfe J: Caring for the child with cancer at the close of life, *JAMA* 292:2141-2149, 2003.

Children's fears of death are often centered on the concrete fear of being separated from parents and other loved ones and what will happen to their parents rather than themselves. This can be true for teens and young adults as well. This fear may be responded to in different ways: some families may give reassurance that loving relatives will be waiting, while others use religious figures to refer to an eternal spiritual connection.

Even though adolescents may have a conceptual understanding of death similar to that of adults, working with the adolescent with life-threatening illness presents unique concerns and issues. The developmental work of adolescence includes separating from their parents, developing strong peer relationships, and moving towards independent adulthood. For this particular population, the teenager's developmental need to separate is complicated by the often increasing dependence both physically and emotionally on the teenager's parents. At the same time, adolescents are often asked to be part of the decision-making process without always having the emotional experience to fully understand the impact.

In addition to developmental considerations, understanding related to the child's life experiences, the length of the child's illness, the understanding of the nature and prognosis of the illness, the child's role in the family (peacemaker, clown, troublemaker, the "good" child) should be considered in communication with children.

Parents have an instinctive and strong desire to protect their children from harm. When facing the death of their child, many parents attempt to keep the reality of impending death hidden from their child with the hope that the child can be "protected" from the harsh reality. Although it is important to respect parental wishes, it is also true that most children already have a sense of what is happening to their bodies even when it has been purposely left unspoken. Children may blame themselves for their illness and the hardships that it causes for their loved ones. Perpetuating the myth that "everything is going to be all right" takes away the chance to explore fears and provide reassurance. Honest communication also allows opportunities for memory and legacy making and saying goodbye.

School is the "work" of childhood and is important in optimizing quality of life for a child seeking "normalcy" in the face of illness. Finding ways to help children and their families to maintain these connections through modification of the school day and exploring options to promote educational and social connections into the home or into the hospital room can be meaningful in the event that a child is not well enough to attend school. Video conferencing can readily be arranged from almost any setting. As with the younger child, finding ways to help the adolescent maintain peer relationships and school based programming can be important in maximizing quality of life.

The Siblings

Brothers and sisters are at special risk both during their sibling's illness and after the death. Because of the extraordinary demands placed on parents to meet the needs of their ill child and their own needs, healthy siblings may feel that their own needs are not being acknowledged or fulfilled. These feelings of neglect may then trigger guilt about their own good health and resentment toward their parents and ill sibling. Younger siblings may react to the stress by becoming seemingly oblivious to the turmoil around them. Some younger siblings may feel guilty as a result of "wishing" the affected child would die so they could get their parents back; preschool children may believe that their wishes caused the death of their sibling ("magical thinking"; see Chapter 7). Parents need to know that these are normal responses, and siblings should be encouraged to maintain the typical routines of daily living. Siblings who are most involved with their sick brothers or sisters before death usually adjust better both at the time of and after the death. Acknowledging and validating sibling feelings, being honest and open, and appropriately involving them in the life of their sick sibling provide a good foundation for the grief process. It is often helpful to identify a person in the family (such as a loving aunt) or school (such as a counselor) to offer confidential and supportive opportunities for the sibling to reflect on their family experience.

The Staff

Adequate support for the staff providing palliative care is necessary to prevent depression, emotional withdrawal, and/or other symptoms. Offering educational opportunities and emotional support for staff at various stages of caring for a child with life-threatening illness can be helpful in bettering patient/family care and preventing staff from experiencing compassion fatigue, burn out and long-term repercussions, including the possibility of leaving the field.

Goals of Care and Decision Making

In the course of a child's life-limiting illness, a series of important decisions may arise in relation to location of care, medications with risks and benefits, not starting and or discontinuing life-prolonging treatments, experimental treatments in research protocols, and the use of integrative therapies (see Chapters 3 and 64). Such family decisions are greatly facilitated by opportunities for in-depth and guided discussions around **goals of care** for their child. This is often accomplished by eliciting parent (and child) understanding of the child's condition and asking open-ended questions that explore the parent's and child's hopes, worries, and family values. Goals of care conversations include what is most important for them as a family, considerations of their child's clinical condition, and their values and beliefs, including cultural, religious, and spiritual considerations. Table 43-3 lists specific questions that can effectively guide these discussions. The conversation should also include a review of previous discussions, active listening to concerns and issues as they are raised, opportunities to repeat back elements of the discussion to ensure clarity, and provision of honest, factual answers even in areas of uncertainty.

Decision making should be focused on the goals of care, as opposed to limitations of care; "This is what we can offer" instead of "There is nothing more we can do." Instead of meeting specifically to discuss "withdrawing support" or a DNR order, a more general discussion centered on the goals of care will naturally lead to considering which interventions are in the **child's best interests and can present an opportunity for the clinicians to make recommendations based on these goals.** By offering medical recommendations based on family goals and the clinical reality, the team can decrease the burden of responsibility for decision making that parents carry.

Resuscitation Status

The legal mandate requiring attempted resuscitation for cardiorespiratory arrest unless a written DNR order is in place is a complex and confusing concept for many parents. In broaching this topic, rather than asking parents if they want to forgo cardiopulmonary resuscitation for their child (and placing the full burden of decision making on them), it is preferable to discuss whether or not resuscitative interventions are likely to benefit the child. *It is important to make recommendations based on overall goals of care and medical knowledge of potential benefit and/or harm of these interventions*. Once the goals of therapy are agreed upon, the physician is required to write a formal order. Out-of-hospital DNR verification forms are available in many states, which, if completed on behalf of the child, affirm that rather than initiating resuscitative efforts, emergency response teams are obligated to provide comfort measures when called to the scene. Some states have implemented the **physician orders for life-sustaining treatment (POLST)** system. A POLST order is completed for children with life-threatening illness, translating the expressed wishes of the parents (and

Table 43-3	Five Basic Questions to Guide Goals of Care Conversation
Tell us about your child as a person; what does your child enjoy? What is your understanding of your child's illness/condition? In light of your understanding, what is most important to you regarding your child's care? What are you hoping for? What are your worries? In the face of your child's illness/condition, what gives you strength?	

in some cases, of the child) into actionable orders (www.polst.org). It may also be beneficial to write a letter delineating decisions regarding resuscitation interventions and supportive care measures to be undertaken for the child, particularly if POLST are not available. The letter should be as detailed as possible, including recommendations for comfort medications and contact information for caregivers best known to the patient. Such a letter, given to the parents, with copies to involved caregivers and institutions, can be a useful communication aid, especially in times of crisis. If a child may die in the home setting, and the parents opt to use on out-of-hospital DNR verification form or POLST, plans to pronounce the child and provide support for the family must be in place. If the child has been referred to hospice, the hospice personnel usually fulfill those responsibilities.

Conflicts in decision making can occur within families, within healthcare teams, between the child and family, and between the family and professional caregivers. For children who are developmentally unable to provide guidance in decision making (neonates, very young children, or children with cognitive impairment), parents and healthcare professionals may come to different conclusions as to what is in the child's best interests. Given the shifting boundary that separates childhood from adulthood, decision making around the care of adolescents presents specific challenges. In some families and cultures, truth telling and autonomy are secondary to maintaining the integrity of the family. (see Chapter 4). Although frequently encountered, differences in opinion are often manageable for all involved when lines of communication are kept open, team and family meetings are held, and the goals of care are clear.

Symptom Management

Intensive symptom management is another cornerstone of pediatric palliative care. Alleviation of symptoms reduces suffering of the child and family, and allows them to focus on other concerns and participate in meaningful experiences. Despite increasing attention to symptoms, and pharmacologic and technical advances in medicine, children often suffer from multiple symptoms. Table 43-4 lists key elements and general approaches to managing symptoms.

Pain is a complex sensation triggered by actual or potential tissue damage and influenced by cognitive, behavioral, emotional, social, and cultural factors. Effective pain relief is essential to prevent central sensitization, a central hyperexcitation response that may lead to escalating pain, and to diminish a stress response that may have a variety of physiologic effects. Assessment tools include self-report tools for children who are able to communicate their pain verbally, as well as tools based on behavioral cues for children who are unable to do so because of developmental delays, medical conditions or cognitive limitations. Tables 43-5 to 43-7 address management of pain (see Chapter 62).

Table 43-4	Key Elements of Effective Symptom Management

Establish and periodically revisit goals of care and ensure that goals are communicated to entire care team.
Anticipate and plan for symptoms before they occur.
Assess the child for symptoms regularly, using consistent and developmentally appropriate assessment tools.
- Utilize self-report, if the child is able to reliably report symptoms.
- Evaluate all aspects of the symptom, including quality, frequency, duration, and intensity.

Consider the holistic nature of symptoms.
- Explore the meaning that symptoms may have for families in their social, cultural, religious context.
- Assess distress caused by the symptom.
- Evaluate the degree of functional impairment from the symptom.

Understand the pathophysiology of the symptom and establish a complete differential diagnosis.
Treat the underlying cause if possible, weighing benefits and risks, in the context of goals of care.
Choose the least-invasive route for medications—by mouth whenever possible.
Prescribe regular medications for constant symptoms, and consider prn doses for breakthrough or uncontrolled symptoms.
Consider both pharmacologic and nonpharmacologic approaches.
Reassess the symptom and response to interventions regularly.
- For refractory symptoms, revisit the differential diagnosis and review potentially contributing factors.
- Effective interventions relieve the symptom and reduce distress and functional impairment.

Partner with families to identify and address any barriers to optimal control of symptoms.
Address spiritual, emotional, and existential suffering in addition to physical suffering as these are often interrelated.

Table 43-5	Guidelines for Pain Management

Utilize nonopioid analgesics as monotherapy for mild pain and together with opioids for more severe pain.
- Nonopioid analgesics include acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), salicylates, and selective cyclooxygenase (COX-2) inhibitors.

For moderate or severe pain, start with a short-acting opioid at regular intervals.
- When dose requirements have stabilized, consider converting opioid to a long-acting formulation with doses available for breakthrough or uncontrolled pain, as needed.
- For uncontrolled pain, increase opioid dose by 30-50%; for severe pain increase by 50-100%.
- Avoid codeine and opioids with mixed agonist activity (e.g., butorphanol, pentazocine).

Administer medications via the simplest, most effective, and least-distressing route.
Dispel the myth that strong medications should be saved for extreme situations or the very end of life.
- Opioids do not have a "ceiling effect," and escalating symptoms may be treated with an increase in dose.

Clarify for families the differences between tolerance, physical dependence, and addiction.
Anticipate and treat/prevent common analgesic side effects (gastritis with NSAIDs; constipation, pruritus, nausea, sedation with opioids).
- Always initiate a bowel regimen to prevent constipation when starting opioids.
- Consider a stimulant for opioid-induced somnolence.
- Pruritus rarely indicates a true allergy. If not responsive to an antihistamine, consider low-dose naloxone or switching opioids.
- Consider switching to a different opioid for intolerable side effects or neurotoxicity (e.g., myoclonus).
- Use an equianalgesic conversion table when switching opioids, and account for incomplete cross-tolerance.

Consider the use of adjuvant drugs for specific pain syndromes, and for their opioid-sparing effect:
- Antidepressants (e.g., amitriptyline, nortriptyline) and anticonvulsants (e.g., gabapentin, carbamazepine, topiramate) for neuropathic pain.
- Steroids or NSAIDs for bone pain.
- Sedatives and hypnotics for anxiety and muscle spasm.
- To enhance analgesia from opioids, consider clonidine or ketamine.
  - Use topical local anesthetics (lidocaine, prilocaine, bupivacaine) when possible.
  - Consider anesthetic blocks for regional pain.
  - Consider palliative radiation therapy.
  - Consider psychological approaches (e.g., cognitive or behavioral therapy) and integrative therapies (e.g., acupuncture, massage).

Table 43-6 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Pain—mild	Acetaminophen	15 mg/kg po q 4 hr, max 4 g/day	Available po (including liquid), pr, IV
	Ibuprofen	10 mg/kg po q 6 hr	PO (including liquid) only; avoid if risk of bleeding; use only in infants ≥6 mo. Use with caution in congestive heart failure. Chewable tablets contain phenylalanine
	Trilisate	10-15 mg/kg po tid	Trilisate may have less antiplatelet activity and therefore pose less risk for bleeding than other salicylates. Salicylates, however, have been associated with Reye syndrome in children <2 yr
Pain—moderate/severe	Morphine immediate release (i.e., MSIR)	0.3 mg/kg po q 4 hr if <50 kg; 5-10 mg po q 4 hr[*,†]	Also available in IV/SQ formulation[‡,§]
	Oxycodone	0.1 mg/kg po q 4 hr if <50 kg; 5-10 mg po q 4 hr if >50 kg[*,†]	No injectable formulation[‡,§]
	Hydromorphone	0.05 mg/kg po q 4 hr if <50 kg; 1-2 mg po q 4 hr if >50 kg[*,†]	Also available in IV/SQ formulation. Injectable form very concentrated, facilitating subcutaneous delivery[‡,§]
	Fentanyl	0.5-1.5 μg/kg IV/SQ q 30 min[*,†]	Rapid infusion may cause chest wall rigidity[‡,§]
	Methadone	Starting dose 0.1-0.2 mg/kg po bid. May give tid if needed. Recommend consultation with experienced clinician for equivalence dosing from other opioids.[*,†]	Only opioid with immediate and prolonged effect available as a liquid; do not adjust dose more often than every 72 hr as prolonged biologic half-life > than therapeutic half-life. Knowledge of the pharmacokinetics of methadone is needed for converting to and from doses of other opioids. Also available IV/SQ. May cause QT interval prolongation (consider ECG), especially in adults on >200 mg/day or in those at risk for QT prolongation. Interacts with several antiretrovirals[§]
Pain—sustained release	MS Contin Kadian (contains sustained-release pellets), Avinza (contains immediate and extended release beads)	Total daily dose of MSIR divided bid-tid	Do not crush MS Contin. For those unable to swallow pills, Kadian and Avinza capsules may be opened and contents mixed with food but *cannot be chewed*. Kadian contents may be mixed in 10 mL water and given via 16-French G-tube. Avoid alcohol with Avinza. Larger dose formulation may not be suitable for small children[§]
	Oramorph		
	OxyContin	Total daily dose of oxycodone divided bid-tid	Do not crush[§]
	Transdermal fentanyl patch	Divide 24-hr po morphine dose by 2 to determine starting dose of transdermal fentanyl. There is no data on the equianalgesic conversion from transdermal fentanyl to any oral opioid	Smallest patch size may be too high for small children. For children >2 yr. Apply to upper back in young children. Patch may not be cut. Typically for patients on at least 60 mg morphine/day or its equivalent. Not appropriate when dosage changes are frequent or for opioid-naïve patients. Fever >40°C results in higher serum concentrations[§]
Pain—neuropathic	Nortriptyline	0.5 mg/kg po at bedtime to maximum of 150 mg/day	Fewer anticholinergic side effects than amitriptyline. May cause constipation, sedation, postural hypotension, dry mouth. May cause QT interval prolongation (consider ECG). At higher doses monitor ECG and plasma levels
	Gabapentin	Start at 5 mg/kg/day at bedtime and gradually increase to 10-15 mg/kg/day divided tid; titrate up by 5 mg/kg/day every 3-4 days as needed but not to exceed 50-75 mg/kg/day (3600 mg/day)	May cause neuropsychiatric events in children (aggression, emotional lability, hyperkinesia), usually mild but may require discontinuation of gabapentin. May cause dizziness, drowsiness, tremor, nystagmus, ataxia, swelling
	Pregabalin	Start at 1 mg/kg/dose po at bedtime for 3 days, then increase to 1 mg/kg/dose bid. Increase every 3 days to 3 mg/kg/dose po bid (maximum: 6 mg/kg/dose)	
	Methadone	See previous listing	See previous listing
Dyspnea	Morphine, immediate release (i.e., MSIR)	0.1 mg/kg po q 4 hr prn[*,†]	All opioids may relieve dyspnea. For dyspnea, the starting dose is 30% of the dose that would be administered for pain[§]
	Lorazepam	0.025-0.05 mg/kg IV/po q 6 hr, up to 2 mg/dose	See previous listing

Table 43-6 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness—cont'd

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Respiratory secretions	Scopolamine patch	1.5 mg patch, change q 72 hr	Excessive drying of secretions can cause mucus plugging of airways. Good for motion-induced nausea and vomiting. Handling patch and contacting eye may cause anisocoria and blurry vision. May fold patches but do not cut them. Anticholinergic side effects possible
	Glycopyrrolate	0.04-0.1 mg/kg po q 4-8 hr	Powerful antisialagogue. Excessive drying of secretions can cause mucus plugging of airways. Anticholinergic side effects possible. Quaternary ammonium structure limits its ability to cross lipid membranes, such as the blood–brain barrier (in contrast to atropine, scopolamine and hyoscyamine sulfate), so may exert fewer central anticholinergic effects
	Hyoscyamine sulfate	4 gtt po q 4 hr prn if <2 yr; 8 gtt po q 4 hr prn if 2-12 yr; do not exceed 24 gtt/24 hr	Anticholinergic side effects possible, including sedation. May be given sublingually
	Atropine	1-2 gtt SL q 4-6 hr prn	Give 0.5% ophthalmic drops sublingually
Nausea	Metoclopramide	0.1-0.2 mg/kg/dose q 6 hr, up to 10 mg/dose (prokinetic and mild nausea dosing). For chemotherapy-associated nausea 0.5-1 mg/kg q 6 hr prn po/IV/SC, give with diphenhydramine and continue diphenhydramine for 24 hr after last dose of high-dose metoclopramide to prevent extrapyramidal reaction	Helpful when dysmotility is an issue; may cause extrapyramidal reactions, particularly in children following IV administration of high doses. Contraindicated in complete bowel obstruction or pheochromocytoma
	Ondansetron	0.15 mg/kg dose IV/po q 8 hr prn. No single intravenous dose should exceed 16 mg because of risk of QT prolongation	Significant experience in pediatrics. Good empiric therapy for nausea in palliative care population. Oral dissolving tablet contains phenylalanine. Higher doses used with chemotherapy although single 32 mg IV dose is no longer available (risk for QT prolongation). Consider ECG monitoring in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or in patients on other medications with the potential to cause QT prolongation
	Dexamethasone	0.1 mg/kg/dose tid po/IV; max dose 10 mg/day	Also helpful with hepatic capsular distention, bowel wall edema, anorexia, increased intracranial pressure. May cause mood swings or psychosis
	Lorazepam	See previous listing	See previous listing
	Dronabinol	2.5-5 mg/m^2/dose q 3-4 hr	Available in 2.5- and 5-mg capsules. May remove liquid contents from capsules for children who cannot swallow capsules. Avoid in patients with sesame oil hypersensitivity or history of schizophrenia. May cause euphoria, dysphoria or other mood changes. Tolerance to central nervous system side effects usually develops in 1-3 days of continuous use. Avoid in patients with depression or mania
	Scopolamine patch	See previous listing	See previous listing
Anxiety	Lorazepam	See previous listing	See previous listing
Agitation	Haloperidol	0.01 mg/kg po tid prn for acute onset: 0.025-0.050 mg/kg po, may repeat 0.025 mg/kg in 1 hr prn	May cause extrapyramidal reactions, which can be reversed with diphenhydramine or Cogentin. Safety not established in children <3 yr
Sleep disturbance/ insomnia	Lorazepam	See previous listing	See previous listing
	Trazodone	Children 6-18 yr: 0.75-1 mg/kg/dose, given bid-tid if needed If >18 yr, start at 25-50 mg/dose, given bid-tid if needed	Potentially arrhythmogenic
Fatigue	Methylphenidate	0.3 mg/kg/dose titrated as needed, up to 60 mg/day	Rapid antidepressant effect; also improves cognition. Administer before meals to avoid appetite suppression. Use with caution in children at risk for cardiac arrhythmia. Available as liquid and chewable tablet

Continued

Table 43-6 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness—cont'd

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Pruritus	Diphenhydramine	0.5-1 mg/kg q 6 hr IV/po (100 mg max per day)	May reverse phenothiazine-induced dystonic reactions. Topical formulation on large areas of the skin or open area may cause toxic reactions. May cause paradoxical reaction in young children
	Hydroxyzine	0.5-1 mg/kg q 6 hr IV/po (600 mg maximum per day)	
Constipation	Docusate	40-150 mg/day po in 1-4 divided doses	Stool softener available as liquid or capsule
	MiraLAX	<5 yr: ½ scoop (8.5 g) in 4 oz of water daily >5 yr: 1 scoop (17 g) in 8 oz of water daily	Tasteless powder may be mixed in beverage of choice. Now available nonprescription
	Lactulose	5-10 mL po up to q 2 hr until bowel movement	Bowel stimulant; dosing q 2 hr may cause cramping
	Senna	2.5 mL po daily (for children weighing >27 kg)	Bowel stimulant; available as granules
	Dulcolax	3-12 yr: 5-10 mg po daily >12 yr 5-15 mg po daily	Available in oral or rectal formulation
	Pediatric Fleets Enema	2.5 oz pediatric enema for children 2-11 yr; adult enema for children ≥12 yr	May repeat ×1 if needed. Do not use in neutropenic patients
	Methylnaltrexone	10-20 kg: 2 mg SC 21-33 kg: 4 mg SC 34-46 kg: 6 mg SC 47-62 kg: 8 mg SC 63-114 kg: 12 mg SC ≥155 kg: 0.15 mg/kg SC Administer 1 dose every other day as needed; maximum of 1 dose per 24 hr	A peripherally acting opioid antagonist for opioid-induced constipation. Usually works within 30-60 minutes of administration
Muscle spasm	Diazepam	0.5 mg/kg/dose IV/po q 6 hr prn; initial dose for children <5 yr is 5 mg dose; for children ≥5 yr dose is 10 mg/dose	May be irritating if given by peripheral IV
	Baclofen	5 mg po tid, increase by 5 mg/dose as needed	Helpful with neuropathic pain and spasticity; abrupt withdrawal may result in hallucinations and seizures; not for children <10 yr
Seizures	Lorazepam	0.1 mg/kg IV/po/SL/PR; repeat q 10 min ×2	
	Diazepam	0.1 mg/kg q 6 hr (max 5 mg/dose if <5 yr; max 10 mg/dose if >5 yr)	May be given pr as Diastat (0.2 mg/kg/dose q 15 minutes ×3 doses)
Neuroirritability	Gabapentin	See previous listing	
	Clonidine	Starting dose: 0.05 mg/day. May increase every 3-5 days by 0.05 mg/day to 3-5 µg/kg/day given in divided doses 3-4 times/day; maximum dose is 0.3 mg/day May switch from oral to transdermal route once optimal oral dose is established; Transdermal dose is equivalent to the total oral daily dose (e.g., if total oral dose is 0.1 mg/day, apply 1 patch (delivers 0.1 mg/day). Change patch every 7 days.	Transdermal patch may contain metal (e.g., aluminum) that may cause burns if worn during MRI scan. Remove patch prior to MRI. Patch may be cut into quarter or half fractions based on dose needed
	Clonazepam	<10 yr or <30 kg Initial dose: 0.01-0.03 mg/kg/day divided tid; ≥10 yr (≥30 kg) Initial dose: up to 0.25 mg po tid; may increase by 0.5-1 mg/day every 3 days Maintenance dose: 0.05-0.2 mg/kg/day up to 20 mg/day	
Anorexia	Megestrol acetate	10 mg/kg/day in 1-4 divided doses, may titrate up to 15 mg/kg/day or 800 mg/day	For children >10 yr. Acute adrenal insufficiency may occur with abrupt withdrawal after long-term use. Use with caution in patients with diabetes mellitus or history of thromboembolism. May cause photosensitivity
	Dronabinol	See previous listing	See previous listing
	Cyproheptadine	Children ≥2 yr and adolescents: 0.08 mg/kg po q 8 hr; if no benefit in 5 days, increase dose by 0.04-0.08 mg/kg/dose maximum daily dose: ≤6 yr: 12 mg/day; 7-14 yr: 16 mg/day; ≥15 yr: 32 mg/day	Potent antihistamine and serotonin antagonist

*Infants <6 mo should receive 25-30% of the usual opioid starting dose.

†Although the usual opioid starting dose is presented, dose may be titrated as needed. There is no ceiling/maximum dose for opioids.

‡Breakthrough dose is 10% of 24 hr dose. See Chapter 62 for information regarding titration of opioids.

§Side effects from opioids include constipation, respiratory depression, pruritus, nausea, urinary retention, physical dependence.

ECG, electrocardiogram; gtt, drops; hr, hr; IV, intravenously; po, by mouth; pr, rectally; prn, as needed; SC, subcutaneously; SL, sublingually.

Adapted from Ullrich C, Wolfe J: Pediatric pain and symptom control. In Walsh TD, Caraceni AT, Fainsinger R, et al: *Palliative medicine*, Philadelphia, 2008, Saunders, pp. 1101-1102, Table 198.3.

Table 43-7 Nonpharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness

SYMPTOM	APPROACH TO MANAGEMENT
Pain	Prevent pain when possible by limiting unnecessary painful procedures, providing sedation, and giving pre-emptive analgesia prior to a procedure (e.g., including sucrose for procedures in neonates) Address coincident depression, anxiety, sense of fear or lack of control Consider guided imagery, relaxation, hypnosis, art/pet/play therapy, acupuncture/acupressure, biofeedback, massage, heat/cold, yoga, transcutaneous electric nerve stimulation, distraction
Dyspnea or air hunger	Suction secretions if present, positioning, comfortable loose clothing, fan to provide cool, blowing air Limit volume of IV fluids, consider diuretics if fluid overload/pulmonary edema present Behavioral strategies including breathing exercises, guided imagery, relaxation, music, distraction
Fatigue	Sleep hygiene (establish a routine, promote habits for restorative sleep) Regular, gentle exercise; Prioritize or modify activities Address potentially contributing factors (e.g., anemia, depression, side effects of medications) Aromatherapy*: peppermint, rosemary, basil
Nausea/vomiting	Consider dietary modifications (bland, soft, adjust timing/volume of foods or feeds) Aromatherapy*: ginger, peppermint, lavender acupuncture/acupressure
Constipation	Increase fiber in diet, encourage fluids, ambulation (if possible)
Oral lesions/dysphagia	Oral hygiene and appropriate liquid, solid and oral medication formulation (texture, taste, fluidity). Treat infections, complications (mucositis, pharyngitis, dental abscess, esophagitis) Oropharyngeal motility study and speech (feeding team) consultation
Anorexia/cachexia	Manage treatable lesions causing oral pain, dysphagia, or anorexia. Support caloric intake during phase of illness when anorexia is reversible. Acknowledge that anorexia/cachexia is intrinsic to the dying process and may not be reversible Prevent/treat coexisting constipation
Pruritus	Moisturize skin Trim child's nails to prevent excoriation Try specialized antiitch lotions Apply cold packs Counterstimulation, distraction, relaxation
Diarrhea	Evaluate/treat if due to obstipation Assess and treat infection Dietary modification
Depression	Psychotherapy, behavioral techniques, setting attainable daily goals Aromatherapy*: bergamot, lavender
Anxiety	Psychotherapy (individual and family), behavioral techniques Aromatherapy*: clary sage, angelica, mandarin, lavender
Agitation/terminal restlessness	Evaluate for organic or drug causes Educate family Orient and reassure child; provide calm, nonstimulating environment, use familiar music, verse, voice, touch Aromatherapy*: frankincense, ylang ylang

*Best if aromatherapy is administered by a practitioner trained in aromatherapy.
From Sourkes B, Frankel L, Brown M, et al: Food, toys, and love: pediatric palliative care, *Curr Probl Pediatr Adolesc Health Care* 35:345-392, 2005.

Many children with life-threatening illness experience pain that requires opioids for adequate relief at some point in their illness trajectory. Although it was previously recommended, prescribing codeine should generally be avoided because of its side-effect profile and lack of superiority over nonopioid analgesics. Furthermore, relatively common genetic polymorphisms in the CYP2D6 gene lead to wide variation in codeine metabolism. Specifically, 10-40% of individuals carry polymorphisms causing them to be "poor metabolizers" who cannot convert codeine to its active form, morphine, and therefore are at risk for inadequate pain control; others are "ultrametabolizers" who may even experience respiratory depression from rapid generation of morphine from codeine. It is therefore preferable to use a known amount of the active agent, morphine.

It is important to explore with families, as well as members of the care team, misconceptions that they may have regarding respiratory suppression, addiction, dependence, the symbolic meaning of starting an opioid such as methadone or morphine and/or a morphine drip, and the potential for opioids to hasten death. There is no association between administration or escalation of opioids and length of survival. Evidence supports longer survival in individuals with symptoms that are well controlled.

Children also often experience a multitude of **nonpain symptoms**. A combination of both pharmacologic (see Table 43-6) and nonpharmacologic approaches (see Table 43-7) is often optimal. **Fatigue** is one of the most common symptoms in children with advanced illness. Children may experience fatigue as a physical symptom (e.g., weakness or somnolence), a decline in cognition (e.g., diminished attention or concentration), and/or impaired emotional function (e.g., depressed mood or decreased motivation). Because of its multidimensional and incapacitating nature, fatigue can prevent children from participating in meaningful or pleasurable activities, thereby impairing quality of life. Fatigue is usually multifactorial in etiology. A careful history may reveal contributing physical factors (uncontrolled symptoms, medication side effects), psychological factors (anxiety, depression), spiritual distress, or sleep disturbance. Interventions to reduce fatigue include treatment of contributing factors, exercise, pharmacologic agents, and behavior modification strategies. Challenges to effectively addressing fatigue include the common belief that fatigue is inevitable, lack of communication between families and care teams about it, and limited awareness of potential interventions for fatigue.

Dyspnea (the subjective sensation of shortness of breath) is caused by a mismatch between afferent sensory input to the brain and the

outgoing motor signal from the brain. It may stem from respiratory causes (e.g., airway secretions, obstruction, infection) or other factors (e.g., cardiac), and may also be influenced by psychological factors (e.g., anxiety). Respiratory parameters such as respiratory rate and oxygen saturation correlate unreliably with the degree of dyspnea. Therefore, giving oxygen to a cyanotic or hypoxic child who is otherwise quiet and relaxed may relieve staff discomfort while having no impact on patient distress and may also add burden if the child cannot tolerate the mask or canula. Dyspnea can be relieved with the use of regularly scheduled *and* as-needed doses of opioids. Opioids work *directly* on the brainstem to reduce the sensation of respiratory distress, as opposed to relieving dyspnea via sedation. The dose of opioid needed to reduce dyspnea is as little as 25% of the amount that would be given for analgesia. Nonpharmacologic interventions, including guided imagery or hypnosis to reduce anxiety, or cool, flowing air, aimed toward the face, are also frequently helpful in alleviating dyspnea. While oxygen may relieve hypoxemia-related headaches, it is no more effective than blowing room air in reducing the distressing sensation of shortness of breath.

As death approaches, a buildup of secretions may result in noisy respiration sometimes referred to as a "death rattle." Patients at this stage are usually unconscious, and noisy respirations are often more distressing for others than for the child. It is often helpful to discuss this anticipated phenomenon with families in advance, and if it occurs, to point out the child's lack of distress from it. If treatment is needed, an anticholinergic medication, such as glycopyrrolate, may reduce secretions.

Neurologic symptoms include **seizures** that are often part of the antecedent illness but may increase in frequency and severity toward the end of life. A plan for managing seizures should be made in advance and anticonvulsants should be readily available in the event of seizure. Parents can be taught to use rectal diazepam at home. Increased **neuroirritability** accompanies some neurodegenerative disorders; it may be particularly disruptive because of the resultant break in normal sleep–wake patterns and the difficulty in finding respite facilities for children who have prolonged crying. Such neuroirritability may respond to gabapentin. Judicious use of sedatives, benzodiazepines, clonidine, nortriptyline, or methadone may also reduce irritability without inducing excessive sedation; such treatment can dramatically improve the quality of life for both child and caregivers. **Increased intracranial pressure** and **spinal cord compression** are most often encountered in children with brain tumors or metastatic and solid tumors. Depending on the clinical situation and the goals of care, radiation therapy, surgical interventions, and steroids are potential therapeutic options.

Feeding and hydration issues can raise ethical questions that evoke intense emotions in families and medical caregivers alike. Options that may be considered to artificially support nutrition and hydration in a child who can no longer feed by mouth include nasogastric and gastrostomy feedings or intravenous nutrition or hydration. These complex decisions require evaluating the risks and benefits of artificial feedings and taking into consideration the child's functional level and prognosis. At times, it may be appropriate to initiate a trial of tube feedings with the understanding that they may be discontinued at a later stage of the illness. A commonly held but unsubstantiated belief is that artificial nutrition and hydration are "comfort measures," without which a child may suffer from starvation or thirst. This may result in well-meaning but disruptive and invasive attempts to administer nutrition or fluids to a dying child. In dying adults, the sensation of thirst may be alleviated by careful efforts to keep the mouth moist and clean. There may also be deleterious side effects to artificial hydration in the form of increased secretions, need for frequent urination, edema and exacerbation of dyspnea. For these reasons, it is important to educate families about anticipated decreases in appetite/thirst and therefore little need for nutrition and hydration as the child approaches death. In addition, exploring the meaning that provision of nutrition and hydration may hold for families, as well as helping families anticipate the changes in their child's appearance and exploring alternative ways that they may love and nurture their child, may ease distress around this issue. **Nausea and vomiting** may be the result of a variety of causes, including medications/toxins, irritation to or obstruction of the gastrointestinal tract, motion, and emotions. Drugs such as metoclopramide, 5-hydroxytryptamine antagonists, steroids, and aprepitant may be used, and should be chosen depending on the underlying pathophysiology and neurotransmitters involved. Vomiting may accompany nausea but may also occur without nausea, such as in the instance of increased intracranial pressure. **Constipation** is commonly encountered in children with neurologic impairment or children receiving medications that impair gastrointestinal motility (most notably, opioids). Stool frequency and quantity should be evaluated in the context of the child's diet and usual bowel pattern. Children on regular opioids should routinely be placed on stool softeners (docusate) in addition to a laxative agent (e.g., senna). **Diarrhea** may be particularly difficult for the child and family and may be treated with loperamide (an opioid that does not cross the blood–brain barrier), and in some cases cholestyramine or octreotide may be indicated. Paradoxical diarrhea, a result of overflow resulting from constipation, should also be included in the differential diagnosis.

Hematologic issues include consideration of anemia and thrombocytopenia or bleeding. If the child has symptomatic anemia (weakness, dizziness, shortness of breath, tachycardia), red blood cell transfusions may be considered. Platelet transfusions may be an option if the child has symptoms of bleeding. Life-ending hemorrhage is disturbing for all concerned, and a plan involving the use of fast-acting sedatives should be prepared in advance if such an event is a possibility.

Skin care issues include primary prevention of problems by ongoing and timely assessment including observation of indwelling lines and tubes, and frequent turning and repositioning and alleviating pressure wherever possible (e.g., elevating heels with pillows). Pruritus may be secondary to systemic disorders or drug therapy. Treatment includes avoiding excessive use of drying soaps, using moisturizers, trimming fingernails, and wearing loose-fitting clothing, in addition to administering topical or systemic steroids. Oral antihistamines and other specific therapies may also be indicated (e.g., cholestyramine in biliary disease). Although opioids can cause histamine release from mast cells, this does not account for most of the pruritus caused by opioids. A trial of diphenhydramine may provide relief; alternatively, rotating opioids or instituting a low dose of opioid antagonist may be needed for refractory pruritus.

Children with life-threatening illness may experience psychological symptoms such as **anxiety** and **depression.** Such symptoms are frequently multifactorial, and sometimes interrelated with uncontrolled symptoms such as pain and fatigue. Diagnosing depression in the context of serious illness may pose challenges since neurovegetative symptoms may not be reliable indicators. Instead, expressions of hopelessness, helplessness, worthlessness, and guilt may be more useful. Pharmacologic agents such as antidepressants may be helpful, although their effect is often preceded by a significant lag phase. Because of its immediate and positive effect on mood, methylphenidate may be an effective antidepressant for children at end of life, when there may not be time for a traditional antidepressant to take effect. Interventions and opportunities for children to explore worries, hopes, and concerns in an open, supportive, and nonjudgmental setting are equally if not more important approaches to psychological distress. Skilled members from a variety of disciplines, including psychology, social work, chaplaincy, child life, and expressive therapy, among others, may help children and their families in this regard. Such opportunities may in fact create positive moments in which meaning, connection, and new definitions of hope are found.

Discussions with adolescent patients or with the parents of any ill child, about possible therapies or interventions should include **integrative therapies** such as massage therapy, Reiki, acupuncture, clinical aromatherapy, prayer, and nutritional supplements. Many families use integrative therapy, but do not bring it up with their physician unless explicitly asked (see Chapter 64). Although largely unproven, some therapies are inexpensive and provide relief to individual

patients. Other therapies may be expensive, painful, intrusive, and even toxic. By initiating conversation and inviting discussion in a nonjudgmental way, the clinician can offer advice on the safety of different therapies and may help avoid expensive, dangerous, or burdensome interventions.

Intensive Symptom Management

At end of life, when intensive efforts to relieve the symptom have been exhausted, or when efforts to address suffering are incapable of providing relief with acceptable toxicity/morbidity or in an acceptable time frame, **palliative sedation** may be considered. Palliative sedation may relieve suffering from refractory symptoms by reducing a child's level of consciousness. It is most often used for intractable pain, dyspnea, or agitation, but is not limited to these distressing indications. Palliative sedation requires opportunities for parents, staff, and primary clinicians to discuss the indication and goals for sedation, as well as questions or concerns about this therapy, both before and after initiation of sedation.

The *principle of double effect* is often invoked to justify escalation of symptom-relieving medications or palliative sedation for uncontrolled symptoms at the end of life. Use of this principle emphasizes the risk of hastening death posed by escalating opioids or sedation, which is theoretical and unproven. There is mounting evidence that patients with well-controlled symptoms live longer.

The Terminal Phase

As death seems imminent, the major task of the physician and team are to help the child have as many good days as possible and not suffer. If not already in place, a referral to **hospice** may provide the most comprehensive care for the child and family. Gently preparing the family for what to expect and offering choices, when possible, will allow them a sense of control in the midst of tragic circumstances. Before death, it can be very helpful to discuss:

- Support of siblings or other family members
- Resuscitation status
- Limiting technology when no longer beneficial to the child
- Cultural, spiritual, or religious needs
- Location of death
  - Who will pronounce if death occurs at home
- Funeral arrangements
  - Offering siblings choice and appropriate support to attend
- Autopsy and/or tissue or organ donation
  - Legacy building, benefits others, informs science and family

Offered the opportunity, families will often tolerate thinking and speaking about their hopes and fears regarding their child's end of life, and some even express relief when the door to such conversation in opened by the care team. It may help to let the family know these conversations are not about *whether* the child will die, but about *how* the child may die.

Families gain tremendous support from having a physician and team who will continue to stay involved in the child's care. If the child is at home or hospitalized, regular phone calls or visits, assisting with symptom management, and offering emotional support is invaluable for families.

In an intensive care setting, where technology can be overwhelming and put distance between the child and parent, the physician can offer discontinuation of that which is not benefiting the child or adding to quality of life. Parents may be afraid to ask about holding or sleeping next to their child. They may need reassurance and assistance in holding, touching, and speaking with their child, despite tubes and technology, even if the child appears unresponsive.

It is believed that hearing and the ability to sense touch is often present until death; all family members should be encouraged to continue interacting with their loved one through the dying process. Parents may be afraid to leave the bedside so that their child will not die alone. Offering parents other supports such as chaplaincy/clergy, social work and extended family members may be helpful. In most instances the moment of death cannot be predicted. Some propose that children wait to die until parents are "ready," an important event has passed, or until they are given permission. Caregivers need not dispute this, nor the hope for a miracle often held by families until the child takes the very last breath.

For the family, the moment of death is an event that is recalled in detail for years to come, and so enhancing opportunity for dignity and limited suffering is essential. Research suggests that improved symptom control and easing of difficult moments at the time of death may lessen the long-term distress of bereaved parents. Clinical experience has shown that families often find solace in clinician "presence," whether at home or in the hospital. After death, families should be given the option of remaining with their child for as long as they would like. During this time, physicians and other professionals may ask permission to "say goodbye." The family may be invited to bathe and dress the body as a final act of caring for the child.

The physician's decision to attend the funeral is a personal one. Participation may serve the dual purpose of showing respect as well as helping the clinician cope with a personal sense of loss. If unable to attend services, families report highly valuing the importance of receiving a card or note from the physician. To know that their child made a difference and will not be forgotten is often very important to families in their bereavement.

The Pediatrician

While optimal palliative care for children entails caregivers from a variety of disciplines, pediatricians are well-positioned to support children and their families, particularly if they have a long-standing relationship with multiple family members. A pediatrician who has cared for a family over time may already know and care for other family members, understand preexisting stressors for the family, and may be familiar with coping strategies used by family members. Pediatricians are familiar with the process of eliciting concerns and providing anticipatory guidance for parents, as well as developmentally appropriate explanations for children.

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Nutrition

PART VI

Chapter 44

Nutritional Requirements

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Nutritional intakes for infants, children, and adolescents should provide for maintenance of current weight and support normal growth and development. The infancy growth period is rapid, critical for neurocognitive development, and has the highest energy and nutrient requirements relative to body size compared with other periods of growth. It is followed by the childhood period of growth, during which 60% of total growth occurs, and is finally followed by the puberty phase. Nutrition and growth during the first 3 years of life predict adult stature and some health outcomes. The major risk period for growth stunting (impaired linear growth) is between 4 and 24 months of age. It is critical to identify nutrient deficiencies promptly and to address them aggressively early in life, because they can impart lasting adverse effects on growth and development. Dietary intake not only meets energy requirements but also provides macronutrients and micronutrients essential for sustaining the functioning of multiple vital processes. Nutrient deficiencies can limit growth, impair immune function, and increase morbidity and mortality. The significant global burden of malnutrition and undernutrition is the leading worldwide cause of acquired immunodeficiency and the major underlying factor for morbidity and mortality globally for children <5 yr of age.

The nutrition transition in many developing countries as populations change from traditional diets to the Western diet has resulted in increased life expectancy and adult stature in these populations. Unfortunately, this nutrition transition is also frequently accompanied by decreased physical activity, and in parallel to decreases in the incidence and prevalence of communicable (infectious) diseases, there are increases in the incidence and prevalence of noncommunicable diseases such as noninsulin-dependent diabetes, cardiovascular disease, obesity, inflammatory bowel disease, and certain cancers.

Consequently, it is important to view the impact of nutrition on health from various perspectives: to prevent deficiency, to promote adequacy, and to prevent or reduce the risk for acquiring diseases associated with excess intakes, such as obesity, diabetes, and cardiovascular disease. Advances in our understanding of the roles of vitamin D, polyunsaturated fatty acids (PUFAs), and total fiber have changed our focus from recommendations for deficiency to nutritional intakes associated with optimal health. In addition, the 2006 World Health Organization (WHO) growth charts, *which are recommended for all children until 2 years of age*, are not only descriptive, but are also proscriptive on how children with adequate nutrition and health care should grow. Identification and provision of appropriate and adequate nutrition in infancy and childhood are critical to not only support normal growth and development, but also to provide the foundation for lifelong health and well-being.

DIETARY REFERENCE INTAKES

The dietary reference intake (DRI) established by the Food and Nutrition Board of the Institute of Medicine provides guidance as to nutrient needs for individuals and groups across different life stages and by gender (Tables 44-1 to 44-4).

Key DRI concepts include the estimated average requirement (EAR), the recommended dietary allowance (RDA), and the tolerable upper limit of intake (UL) (Fig. 44-1). The EAR is the average daily nutrient intake level estimated to meet the requirements for 50% of the population, assuming normal distribution; the RDA is an estimate of the daily average nutrient intake to meet the nutritional needs of >97% of the individuals in a population, and it can be used as a guideline for individuals to avoid deficiency in the population. When an EAR cannot be derived, an RDA cannot be calculated; therefore, an adequate intake (AI) is developed as a guideline for individuals based on the best available data and scientific consensus. The UL denotes the highest average daily intake at which no adverse health effects are associated for almost all individuals in a particular group. The relationships among EAR, RDA, and UL are characterized in Figure 44-2.

ENERGY

Energy includes both intake and expenditure. Deficits and excesses of energy intake yield undesirable health consequences. Inadequate energy intake can lead to growth faltering, catabolism of body tissues and inability to provide energy substrate, whereas excess energy intakes can increase the risk for obesity. Adequacy of energy intake in adults is associated with maintenance of a healthy weight. The 3 components of energy expenditure in adults are the basal metabolic rate, thermal effect of food (energy required for digestion and absorption), and energy for physical activity. Additional energy intake is required to support growth and development for children.

The **estimated energy requirement (EER)** is the average dietary energy intake predicted to maintain energy balance in a healthy individual and accounts for age, gender, weight, stature, and physical activity level (see Table 44-1). The Dietary Guidelines for Americans 2010 recommend 60 min of moderately intense daily activity for children >2 yr of age to maintain a healthy weight and to prevent or delay progression of chronic noncommunicable diseases such as obesity and cardiovascular disease. The EER was determined based on empirical research in healthy persons at different physical activity levels, including levels different from the recommended levels. *They do not necessarily apply to children with acute or chronic diseases*. EER is estimated by equations that account for total energy expenditure, as well as energy deposition for healthy growth. The EER for infants, relative to body weight, are approximately twice those for adults because of the increased metabolic rate and requirements for weight maintenance and tissue accretion affecting growth.

The nutrients that provide energy intake in the child's diet are fats (~9 kcal/g), carbohydrates (~4 kcal/g), and proteins (~4 kcal/g). They are referred to as **macronutrients**. Alcohol intake also contributes to energy intake (~7 kcal/g). The EER does not specify the relative energy contributions of macronutrients. Once the minimal intakes of each of the respective macronutrients are attained to meet physiologic requirements and to achieve adequacy (sufficient protein intake to meet specific amino acid requirements, fat for essential fatty acids, and neurologic development), the remainder of the intake is used to meet energy requirements with some degrees of freedom and interchangeability among fats, carbohydrates, and proteins. This forms the basis for the acceptable macronutrient distribution ranges (AMDRs) (see Table 44-2), expressed as a function of total energy intake.

Table 44-1	Equations to Estimate Energy Requirement
INFANTS AND YOUNG CHILDREN: EER (KCAL/DAY) = TEE + ED	
0-3 mo	EER = (89 × weight [kg] − 100) + 175
4-6 mo	EER = (89 × weight [kg] − 100) + 56
7-12 mo	EER = (89 × weight [kg] − 100) + 22
13-36 mo	EER = (89 × weight [kg] − 100) + 20
CHILDREN AND ADOLESCENTS 3-18 YR: EER (KCAL/DAY) = TEE + ED	
Boys	
3-8 yr	EER = 88.5 − (61.9 × age [yr] + PA × [(26.7 × weight [kg] + (903 × height [m])] + 20
9-18 yr	EER = 88.5 − (61.9 × age [yr] + PA × [(26.7 × weight [kg] + (903 × height [m])] + 25
Girls	
3-8 yr	EER = 135.3 − (30.8 × age [yr] + PA [(10 × weight [kg] + (934 × height [m])] + 20
9-18 yr	EER = 135.3 − (30.8 × age [yr] + PA [(10 × weight [kg] + (934 × height [m])] + 25

ED, energy deposition; EER, estimated energy requirement; TEE, total energy expenditure.

PA indicates the physical activity coefficient:

For boys:
- PA = 1.00 (sedentary, estimated physical activity level 1.0-1.4)
- PA = 1.13 (low active, estimated physical activity level 1.4-1.6)
- PA = 1.26 (active, estimated physical activity level 1.6-1.9)
- PA = 1.42 (very active, estimated physical activity level 1.9-2.5)

For girls:
- PA = 1.00 (sedentary, estimated physical activity level 1.0-1.4)
- PA = 1.16 (low active, estimated physical activity level 1.4-1.6)
- PA = 1.31 (active, estimated physical activity level 1.6-1.9)
- PA = 1.56 (very active, estimated physical activity level 1.9-2.5)

Adapted from Kleinman RE, editor: Pediatric nutrition handbook, *ed 6, Elk Grove Village, IL, 2009, American Academy of Pediatrics.*

FAT

Fat is the most calorically dense macronutrient, providing approximately 9 kcal/g. For infants, human milk/formula are the main dietary sources of fat, whereas older children get fat from animal products, vegetable oils, and margarine. The AMDR for fats is 30-40% of total energy intake for children 1-3 yr and 25-35% for children 4-18 yr of age. In addition to being energy-dense, fats provide essential fatty acids and play structural and functional roles; cholesterol moieties are precursors for cell membranes, hormones, and bile acids. Fat intake facilitates absorption of fat-soluble vitamins A, D, E, and K. Both roles are particularly relevant in the context of neurological and ocular development.

Table 44-2 Acceptable Macronutrient Distribution Ranges

	AMDR (% OF ENERGY)	
	Children 1-3 yr	**Children 4-18 yr**
Fat	30-40	25-35
ω6 PUFAs (linoleic acid)	5-10	5-10
ω3 PUFAs (α-linolenic acid)	0.6-1.2	0.6-1.2
Carbohydrate	45-65	45-65
Protein	5-20	10-30

AMDR, acceptable macronutrient distribution range; PUFA, polyunsaturated fatty acid.

Adapted from Otten JJ, Hellwig JP, Meyers LD, editors; Institute of Medicine: Dietary reference intakes: the essential guide to nutrient requirements, *Washington, DC, 2006, National Academies Press.*

Table 44-3 Dietary Reference Intakes: Macronutrients

FUNCTION	LIFE STAGE GROUP	RDA OR AI* (g/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION
TOTAL DIGESTIBLE CARBOHYDRATE				
RDA based on its role as the primary energy source for the brain AMDR based on its role as a source of kcal to maintain body weight	*Infants* 0-6 mo 7-12 mo *Children* >1 yr *Pregnancy* ≤18 yr 19-30 yr	 60* 95* **130** **175** **175**	Major types: starches and sugars Grains and vegetables (corn, pasta, rice, potatoes, breads) are sources of starch Natural sugars are found in fruits and juices Sources of added sugars: soft drinks, candy, fruit drinks, desserts	No defined intake level for potential adverse effects of total digestible carbohydrate is identified, but the upper end of the AMDR was based on decreasing risk of chronic disease and providing adequate intake of other nutrients It is suggested that the maximal intake of added sugars be limited to providing no more than 25% of energy
TOTAL FIBER				
Improves laxation, reduces risk of coronary heart disease, assists in maintaining normal blood glucose levels	*Infants* 0-6 mo 7-12 mo *Children* 1-3 yr 4-8 yr *Males* 9-13 yr 14-18 yr 19-21 *Females* 9-13 yr 14-18 yr 19-21 yr *Pregnancy* ≤18 yr 19-21 yr	 ND ND 190* 25* 31* 38* 38* 26* 26* 25* 28* 28*	Includes dietary fiber naturally present in grains (e.g., oats, wheat, unmilled rice) and functional fiber synthesized or isolated from plants or animals and shown to be of benefit to health	Dietary fiber can have variable compositions; therefore, it is difficult to link a specific source of fiber with a particular adverse effect, especially when phytate is also present in the natural fiber source As part of an overall healthy diet, a high intake of dietary fiber will not produce deleterious effects in healthy persons Occasional adverse GI symptoms are observed when consuming some isolated or synthetic fibers, but serious chronic adverse effects have not been observed Owing to the bulky nature of fibers, excess consumption is likely to be self-limiting; therefore, an UL was not set for individual functional fibers

Continued

Table 44-3 Dietary Reference Intakes: Macronutrients—cont'd

FUNCTION	LIFE STAGE GROUP	RDA OR AI* (g/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION
TOTAL FAT				
Energy source When found in foods, is a source of ω3 and ω6 PUFAs Facilitates absorption of fat-soluble vitamins	*Infants* 0-6 mo 7-12 mo 1-18 yr	 31* 30* Insufficient evidence to determine AI or EAR; see AMDR Table 41-4	Infants: Human milk or infant formula Older children: butter, margarine, vegetable oils, whole milk, visible fat on meat and poultry products, invisible fat in fish, shellfish, some plant products such as seeds and nuts, bakery products	UL not set because there is no defined intake of fat at which adverse effects occur. High fat intake will lead to obesity. The upper end of AMDR is also based on decreasing risk of chronic disease and providing adequate intake of other nutrients Low fat intake (with high carbohydrate) has been shown to increase plasma triacylglycerol concentrations and decrease HDL cholesterol
ω6 POLYUNSATURATED FATTY ACIDS				
Essential component of structural membrane lipids, involved with cell signaling, precursor of eicosanoids Required for normal skin function	*Infants* 0-6 mo 7-12 mo *Children* 1-3 yr 4-8 yr *Males* 9-13 yr 14-18 yr 19-21 yr *Females* 9-13 yr 14-18 yr 19-21 yr *Pregnancy* ≤18 yr 19-21 yr *Lactation* ≤18 yr 19-21 yr	 4.4* 4.6* 7* 10* 12* 16* 17* 10* 11* 12* 13* 13* 13* 13*	Nuts, seeds; vegetable oils such as soybean, safflower, corn oil	No defined intake of ω6 level at which adverse effects occur Upper end of the AMDR is based on the lack of evidence that demonstrates long-term safety and human in vitro studies that show increased free-radical formation and lipid peroxidation with higher amounts of ω6 fatty acids Lipid peroxidation is thought to be a component of atherosclerotic plaques
ω3 POLYUNSATURATED FATTY ACIDS				
Involved with neurologic development and growth Precursor of eicosanoids	*Infants* 0-6 mo 7-12 mo *Children* 1-3 yr 4-8 yr *Males* 9-13 yr 14-18 yr 19-21 yr *Females* 9-13 yr 14-18 yr 19-21 yr *Pregnancy* ≤18 yr 19-21 yr *Lactation* ≤18 yr 19-21 yr	 0.5* 0.5* 0.7* 0.9* 1.2* 1.6* 1.6* 1.0* 1.1* 1.1* 1.1* 1.4* 1.3* 1.3*	Vegetable oils, e.g., soybean, canola, flax seed oil; fish oils, fatty fish; smaller amounts in meats and eggs	No defined intake level for potential adverse effects of ω3 PUFAs is identified Upper end of AMDR is based on maintaining the appropriate balance with ω6 fatty acids and on the lack of evidence that demonstrates long-term safety, along with human in vitro studies that show increased free-radical formation and lipid peroxidation with higher amounts of PUFAs Because the longer-chain *n*-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are biologically more potent than their precursor, linolenic acid, much of the work on the adverse effects of this group of fatty acids has been on DHA and EPA Lipid peroxidation is thought to be a component in the development of atherosclerotic plaques
SATURATED AND *TRANS* FATTY ACIDS				
The body can synthesize its needs for saturated fatty acids from other sources		No dietary requirement	Saturated fatty acids are present in animal fats (meat fats and butter fat), and coconut and palm kernel oils *Trans* fat: stick margarines, foods containing hydrogenated or partially hydrogenated vegetable shortenings	There is an incremental increase in plasma total and LDL cholesterol concentrations with increased intake of saturated or *trans* fatty acids; therefore, the intakes of each should be minimized while consuming a nutritionally adequate diet

Table 44-3 Dietary Reference Intakes: Macronutrients—cont'd

FUNCTION	LIFE STAGE GROUP	RDA OR AI* (g/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION
CHOLESTEROL				
		No dietary requirement	Sources: liver, eggs, foods that contain eggs, e.g., cheesecake, custard pie	
PROTEIN AND AMINO ACIDS†				
Major structural component of all cells in the body Functions as enzymes, in membranes, as transport carriers, and as some hormones During digestion and absorption, dietary proteins are broken down to amino acids, which become the building blocks of these structural and functional compounds Nine indispensable amino acids must be provided in the diet; the body can make the other amino acids needed to synthesize specific structures from other amino acids	*Infants*		Proteins from animal sources, e.g., meat, poultry, fish, eggs, milk, cheese, yogurt, provide all 9 indispensable amino acids in adequate amounts and are considered "complete proteins" Proteins from plants, legumes, grains, nuts, seeds, and vegetables tend to be deficient in ≥1 of the indispensable amino acids and are called "incomplete proteins" Vegan diets adequate in total protein content can be "complete" by combining sources of incomplete proteins, which lack different indispensable amino acids	No defined intake level for potential adverse effects of protein is identified Upper end of AMDR was based on complementing the AMDR for carbohydrate and fat for the various age groups Lower end of AMDR is set at approximately the RDA
	0-6 mo	9.1*		
	7-12 mo	**11.0**		
	Children			
	1-3 yr	**13**		
	4-8 yr	**19**		
	Males			
	9-13 yr	**34**		
	14-18 yr	**52**		
	≥19 yr	**56**		
	Females			
	9-13 yr	**34**		
	≥14 yr	**46**		
	≤18 yr			
	19-21 yr	**71**		

Note: Starred numbers are AI; bold numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97-98% of members in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life-stage and gender groups is believed to cover the needs of all members of the group, but lack of data prevents specifying with confidence the percentage covered by this intake. AMDR is the range of intake for a particular energy source that is associated with reduced risk of chronic disease while providing intakes of essential nutrients. With consumption in excess of the AMDR, there is a potential for increasing the risk of chronic diseases and/or insufficient intakes of essential nutrients. ND amounts are not determinable because of a lack of data regarding adverse effects in this age group and concern with regard to a lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

*Adequate intake.

†Based on 1.5 g/kg/day for infants, 1.1 g/kg/day for 1-3 yr, 0.95 g/kg/day for 4-13 yr, 0.85 g/kg/day for 14-18 yr, 0.8 g/kg/day for adults, and 1.1 g/kg/day for pregnant (using prepregnancy weight) and lactating women.

AI, adequate intake; AMDR, acceptable macronutrient distribution range; GI, gastrointestinal; LDL, low-density lipoprotein (cholesterol); ND, not determinable; PUFA, polyunsaturated fatty acid; RDA, recommended dietary allowance; UL, upper limit.

Adapted from Food and Nutrition Board, Institute of Medicine: Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids *http://www.iom.edu/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx*.

Table 44-4 Indispensable, Dispensable, and Conditionally Indispensable Amino Acids in the Human Diet

INDISPENSABLE	DISPENSABLE	CONDITIONALLY INDISPENSABLE*	PRECURSORS OF CONDITIONALLY INDISPENSABLE
Histidine†	Alanine	Arginine	Glutamine/glutamate, aspartate
Isoleucine	Aspartic acid	Cysteine	Methionine, serine
Leucine	Asparagine	Glutamine	Glutamic acid/ammonia
Lysine	Glutamic acid	Glycine	Serine, choline
Methionine	Serine	Proline	Glutamate
Phenylalanine		Tyrosine	Phenylalanine
Threonine			
Tryptophan			
Valine			

*Conditionally indispensable is defined as requiring a dietary source when endogenous synthesis cannot meet metabolic need.

†Although histidine is considered indispensable, unlike the other 8 indispensable amino acids, it does not fulfill the criteria of reducing protein deposition and inducing negative nitrogen balance promptly upon removal from the diet.

Adapted from Otten JJ, Hellwig JP, Meyers LD, editors; Institute of Medicine: Dietary reference intakes: the essential guide to nutrient requirements, *Washington, DC, 2006, National Academies Press.*

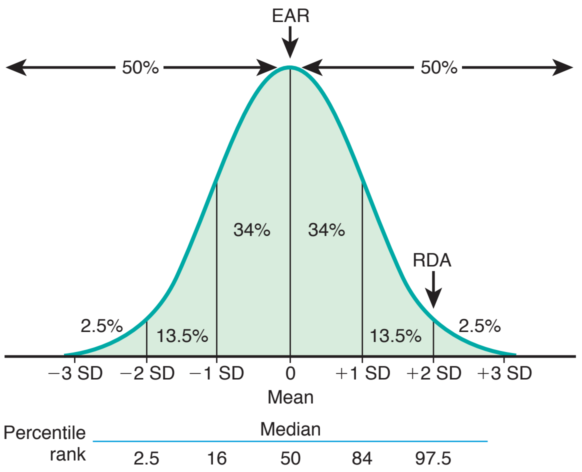

Figure 44-1 **Dietary reference intakes.** Normal requirement distribution of hypothetical nutrient showing percentile rank and placement of the estimated average requirement (EAR) and the recommended dietary allowance (RDA) on the distribution. SD, standard deviation.

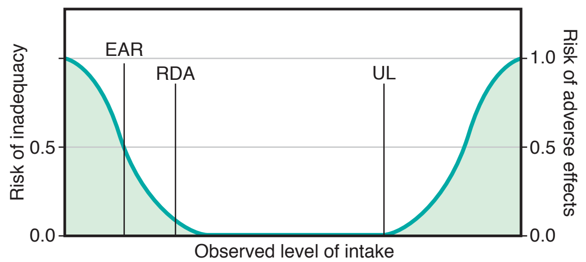

Figure 44-2 **Dietary reference intakes: the relationship among the estimated average requirement (EAR), the recommended dietary allowance (RDA), and the tolerable upper limit of intake (UL).** This figure shows that the EAR is the intake at which the risk of inadequacy is estimated to be 0.5 (50%). The RDA is the intake at which the risk of inadequacy would be very small—only 0.02 to 0.03 (2-3%). At intakes between the RDA and the UL, the risk of inadequacy and of excess are estimated to be close to 0.0. At intakes above the UL, the potential risk of adverse effects can increase.

Triglycerides are the most common form of dietary fat and are composed of 1 glycerol molecule and 3 fatty acids. Triglycerides are found in animal and vegetable fats. Simple sugars (refined grains and high sugar drinks) are converted to triglycerides in the liver. Elevated serum triglycerides are a risk factor for cardiovascular disease and part of the metabolic syndrome. Decreasing simple sugars and increasing complex carbohydrate intake reduce serum triglyceride levels.

Dietary saturated fatty acids (found primarily in animal fat and dairy products), *trans* fats (found in hydrogenated margarines and oils), and cholesterol increase the low-density lipoprotein (LDL) fraction of serum cholesterol, a risk factor for the development of atherosclerosis. Autopsy studies demonstrate that atherosclerosis begins early in childhood, even in infancy. Therefore, dietary advice to optimize cardiovascular health should be dispensed for children starting at age 2 yr when sufficient fat intake to sustain growth and brain development is less of a concern.

Because saturated and monounsaturated fats can be synthesized endogenously to support adequate structural and physiologic requirements, there is no AI or RDA set for these dietary components. *Trans* fats have no known beneficial effects in humans; therefore, no corresponding AI or RDA has been set. Similarly, an UL has not been set for cholesterol, saturated, or *trans* fats because there is a positive linear association between intake of these fats and increased risk for cardiovascular disease, without a threshold level at which risk is increased. Diets low in saturated fats and cholesterol and without *trans* fats are therefore preferred. For optimal cardiovascular health in the general population, rather than limiting the total amount of fat intake, in most cases, advice should focus on changing the type of fat that is consumed. With respect to preventing obesity, all types of fatty acids have about the same energy content and can contribute to increasing the risk for obesity. The current dietary guidelines for children and adolescents recommend that total fat should account for <30% of total daily energy and saturated fat less than 10%, dietary cholesterol <300 mg/day, with no *trans* fat.

Humans are incapable of synthesizing the precursor omega (ω) 3 (α-linolenic acid; ALA) and ω6 (linoleic acid; LA) PUFAs, and are dependent on diet for these essential fatty acids. **Essential fatty acid (EFA) deficiency** is associated with desquamating skin rashes, alopecia, thrombocytopenia, impaired immunity, and growth deficits, but is rare in the general population. Essential fatty acids are enzymatically elongated and desaturated into longer-chain fatty acids; ALA can be converted to eicosapentaenoic (EPA) and docosahexaenoic (DHA) ω3 PUFAs. LA is converted to arachidonic acid (ARA). Long-chain PUFAs such as DHA and ARA play a variety of structural and functional roles; they influence membrane fluidity and function as well as gene expression, and modulate the inflammatory response. ARA and DHA are present in breast milk, often supplemented in infant formulas, and are required for normal growth and development. DHA is present in the retina and is involved in the visual evoked response in infants.

The conversion of ALA to EPA and DHA and of LA to ARA is influenced by many factors, including type and amounts of dietary fats and by enzymatic substrate affinity among competing ω3, ω6, ω9, saturated, and *trans* fatty acids. The efficiency in conversion of ALA to a longer-chain PUFA is minimal and variable. Approximately 0.5% of dietary ALA is converted to DHA and 5% of ALA intake converted to EPA; therefore, dietary intake of longer-chain PUFAs is an important determinant of serum and tissue long-chain PUFA status. The biologic activity and health benefits of ALA are thought to be derived via the longer-chain PUFA products EPA and DHA. Consistent with these findings of limited conversion of ALA to EPA and DHA, and that EPA and DHA appear to confer the biologic role and health benefits, the DRI stipulates that up to 10% of the AI for ω3 PUFA (ALA being the major dietary constituent) can be replaced by DHA and EPA to support normal neural development and growth.

The ratio of dietary intake of each type of PUFA influences their relative amounts in different tissue compartments. A dietary ω6:ω3 PUFA ratio of 4-5 : 1 may be beneficial in reducing risk of disease and may be associated with improved health outcomes, as compared to the current 15-30 : 1 ratio observed in the United States.

PROTEINS

Proteins and amino acids have structural and functional roles in every cell in the body. Proteins also provide approximately 4 kcal/g; however, dietary protein intake is required to replenish the turnover of proteins and to meet amino acid needs for growth. Dietary protein intake also provides energy substrate when in excess or during periods of catabolism. Inadequate energy intake and/or inadequate protein intake increases catabolism of body protein reservoirs (i.e., lean body mass) so as to provide substrate for energy and free amino acids required to support normal physiologic function. Nitrogen losses, derived from proteins, occur through urine, stool, and other bodily excretions. Increased protein intake may be required for rare hypermetabolic states, such as extensive burns. Protein energy malnutrition, although relatively rare in the noninstitutionalized U.S. population, is more common in the developing world. Protein energy malnutrition impairs brain, immune system and intestinal mucosal functions.

DRI for protein is provided in Table 44-3. An UL for protein has not been set. Intake of proteins or specific amino acids needs to be limited in some health conditions, such as renal disease and metabolic diseases, such as phenylketonuria and maple syrup urine disease, in which specific amino acids can be toxic.

The amino acid content of dietary protein is also important. Certain amino acids are **indispensable** and humans depend on dietary sources to meet adequacy and prevent deficiency. Certain amino acids are

termed **conditional essential/indispensable**, meaning they become essential in patients affected by some diseases or during a certain life stage, such as with cysteine, tyrosine and arginine in newborns because of enzymes immaturity (see Table 44-4). Human milk contains both the indispensable and conditionally indispensable amino acids and therefore meets the protein requirements for infants. Breast milk is considered the optimal source of proteins for infants and is the reference amino acid composition by which biologic quality is determined for infants. If a single amino acid in a food protein source is low or absent but is required to support normal metabolism, that specific amino acid becomes the limiting nutrient. For soy-based infant formula, supplementation with the limiting amino acid (methionine) is necessary.

To ensure appropriate growth and to promote satiety, children should consume the recommended amount of protein. Specific recommendations for appropriate dietary protein sources to meet indispensable amino acid requirements are available for groups adopting specific diets, such as vegetarians and vegans. Inclusion of legumes and corn, as well as the use of a variety of food sources to provide all of the required amino acids is a strategy advocated for vegetarians and vegans.

CARBOHYDRATES

Carbohydrates are abundant in many foods, including cereals, grains, fruits, and vegetables, and provide approximately 4 kcal/g. Dietary carbohydrates include monosaccharides, which contain 1 sugar molecule (glucose, fructose), disaccharides that contain 2 sugar molecules (sucrose, lactose), oligosaccharides, polysaccharides (which contain multiple sugar molecules in a chain or complex configuration) (starch), and sugar alcohols. Carbohydrates (glucose) serve as an essential energy source for erythrocytes and the central nervous system and a major energy source for all cells. The requirements for carbohydrates are based on the average minimum amount of glucose utilized by the brain. Chronic low carbohydrate intake results in ketosis. Although an UL for carbohydrates has not been set, a maximal intake of <25% or <10% of total energy intake from added sugars has been proposed in various dietary guidelines. Higher intakes of added sugar can displace other macro- and micronutrients and increase risk for nutrient deficiency and excessive energy intake. There is no distinct advantage or benefit obtained from discretionary calorie intake such as that provided by the consumption of added sugars.

The recommended AMDR for carbohydrates (see Table 44-2) were based upon data suggesting a risk for coronary heart disease with diets high in carbohydrates and low in fat. These diets, compared to higher fat intakes, result in high triglycerides, low high-density lipoprotein (HDL) cholesterol, and small LDL cholesterol particles and are associated with a high risk of coronary heart disease, especially in sedentary overweight individuals. Diets within the AMDR for carbohydrates and fats minimize the risks of diabetes, obesity and coronary heart disease. Diets with less than the minimum AMDR for carbohydrate most likely do not meet the AI for fiber (see Table 44-3).

The majority of carbohydrates are present as starches or sugars in food. Simple sugars (mono- and disaccharides) are often added to foods and beverages during food preparation, processing, and packaging to enhance palatability and as preservatives. Nondiet soft drinks, juice drinks, iced tea, and sport drinks are among the major contributors to added sugars in the diet of U.S. children and adolescents. Added sugars increase the risk for obesity, diabetes, and dental caries. Fructose is one such added sugar in the form of high-fructose corn syrup, which is nearly ubiquitous in the U.S. diet. Fructose increases HDL and triglyceride production in the liver and serum uric acid levels which increase systolic blood pressure and is associated with fatty liver disease and metabolic syndrome. Excessive fructose intake, such as in the form of fruit juices, is associated with diarrhea, abdominal pain, and failure to thrive in children.

The **glycemic index** is a measure of the height of blood sugar levels 2 hours following ingestion against the reference standard (a slice of white bread). The glycemic index has predictable effects on blood glucose, hemoglobin A_{1C}, insulin, triglycerides, and HDL cholesterol levels. Lower glycemic index foods are recommended and may reduce the risk of insulin resistance and cardiovascular disease.

FIBER

Fiber consists of nondigestible carbohydrates mostly derived from plant sources, such as whole grain, fruits, and vegetables, that escape digestion and reach the colon nearly 100% intact. These compounds were previously classified as being water soluble versus insoluble, which may be a relatively less meaningful distinction, although still commonly used. The DRI classification lists **dietary fiber** (nondigestible carbohydrates and lignin that are intrinsic and intact in plants), **functional fiber** (with known physiologic benefits in humans), and **total fiber** (dietary plus functional).

Although fiber intake does not contribute significantly to energy intake, it does play several important roles. The metabolic fate of fiber is influenced primarily by the colonic bacteria, which depending on the structure of the fiber, can render it susceptible to fermentation (e.g., pectin and oat bran). Common by-products of colonic fermentation include carbon dioxide, methane (in addition to other gases), **oligofructases** (also known as prebiotics-substrates that nourish beneficial commensurate gastrointestinal microbiota), and **short-chain fatty acids (SCFAs)**. The common SCFAs produced by fermentation include acetate, butyrate, and propionate. There is dynamic interplay between the colonic bacterial milieu and the diet. SCFAs influence colonic physiology by stimulating colonic blood flow and fluid and electrolyte uptake. Butyrate is the preferred fuel for the colonocyte, and it might have a role in maintaining the normal phenotype in these cells.

Dietary fiber might play an important role by diluting toxins, carcinogens, and tumor promoters; by decreasing transit time, thereby decreasing colonic mucosal exposure; and by promoting their expulsion in the fecal stream. Dietary fiber resistant to colonic degradation might also play a role in maintaining and promoting stool bulk and in the regulation of intraluminal pressure and colonic wall resistance, disordered colonic motility, or both. Lack of dietary fiber is associated with constipation and diverticulosis.

All fiber slows gastric emptying and promotes satiety, and thus may help to regulate appetite. Dietary fiber may decrease the rate of release and absorption of simple sugars, and help in the regulation of blood sugar, with lower postprandial blood sugars observed. Dietary fiber has a low glycemic index, and may have a beneficial effect on insulin sensitivity. Fiber also binds luminal cholesterol and reduces absorption and/or enterohepatic circulation of the cholesterol in bile salts (with the intake of more viscous forms of dietary fiber, such as pectin). Soluble fiber types (such as guar gum, oat products, pectin) lower serum cholesterol, while insoluble fiber may reduce serum triglycerides. However, fiber such as psyllium, resistant dextrins, and resistant starch may also have a role in lowering both serum LDL and triglycerides. Decreased fiber intake in Western society has been associated with the increasing incidence and prevalence of diabetes, obesity, cardiovascular disease, colon cancer, and inflammatory bowel disease.

Data are insufficient to establish an EAR for dietary fiber. An AI for dietary fiber has been established based on the intake levels associated with reducing risk for cardiovascular disease and in lowering or normalizing serum cholesterol (see Table 44-3). An UL has not been established for fibers, which are not thought to be harmful to human health. A general rule of thumb used for fiber intake in children is: *age (in years) + 5 = grams of fiber intake per day*.

MICRONUTRIENTS

Vitamins and trace minerals or **micronutrients** play an essential role in growth and development and contribute to a host of physiologic functions. Many U.S. children have suboptimal intake of iron, zinc, potassium, calcium, vitamin D, and vitamin K, and excess intakes of sodium. Dietary recommendations for micronutrients were originally established to prevent deficiency but also include the impact of micronutrients on long-term health outcomes (Table 44-5). Food fortification is an effective strategy to prevent some nutrient deficiencies, and

Text continued on p. 281

Table 44-5 Dietary Reference Intakes for Vitamins

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Biotin	Coenzyme in synthesis of fat, glycogen, and amino acids	*Infants (μg/day)*			Liver Smaller amounts in fruits and meats	No adverse effects of biotin in humans or animals have been found; this does not mean there is no potential for adverse effects resulting from high intakes Because data on the adverse effects of biotin are limited, caution may be warranted	None
		0-6 mo	5*	ND			
		7-12 mo	6*	ND			
		Children (μg/day)					
		1-3 yr	8*	ND			
		4-8 yr	12*	ND			
		Males (μg/day)					
		9-13 yr	20*	ND			
		14-18 yr	25*	ND			
		19-21 yr	30*	ND			
		Females (μg/day)					
		9-13 yr	20*	ND			
		14-18 yr	25*	ND			
		19-21 yr	30*	ND			
		Pregnancy (μg/day)					
		≤18 yr	30*	ND			
		19-21 yr	30*	ND			
		Lactation (μg/day)					
		≤18 yr	35*	ND			
		19-21 yr	35*	ND			
Choline	Precursor for acetylcholine, phospholipids, and betaine	*Infants (mg/day)*			Milk, liver, eggs, peanuts	Fishy body odor, sweating, salivation, hypotension, hepatotoxicity	Patients with trimethylaminuria, renal disease, liver disease, depression, and Parkinson disease may be at risk for adverse effects with choline intakes at the UL AIs have been set for choline, but there is little data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and the choline requirement might be met by endogenous synthesis at some of these stages
		0-6 mo	125*	ND			
		7-12 mo	150*	ND			
		Children (mg/day)					
		1-3 yr	200*	1,000			
		4-8 yr	250*	1,000			
		Males (mg/day)					
		9-13 yr	375*	2,000			
		14-18 yr	550*	3,000			
		19-21 yr	550*	3,500			
		Females (mg/day)					
		9-13 yr	375*	2,000			
		14-18 yr	400*	3,000			
		19-21 yr	425*	3,500			
		Pregnancy (mg/day)					
		≤18 yr	450*	3,000			
		19-21 yr	450*	3,500			
		Lactation (mg/day)					
		≤18 yr	550*	3,000			
		19-21 yr	550*	3,500			

Folate aka folic acid, folacin, pteroyl-polyglutamates given as dietary folate equivalents (DFE) 1 DFE = 1 μg food folate = 0.6 μg folate from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach	Coenzyme in the metabolism of nucleic and amino acids Prevents megaloblastic anemia	*Infants (μg/day)*			Enriched cereal, grains, dark leafy vegetables, enriched and whole-grain breads and bread products, fortified ready-to-eat cereals	Masks neurologic complications in people with vit B12 deficiency No adverse effects associated with folate from food or supplements have been reported; this does not mean that there is no potential for adverse effects resulting from high intakes Because data on adverse effects of folate are limited, caution may be warranted UL for folate applies to synthetic forms obtained from supplements and/or fortified foods	In view of evidence linking poor folate intake with neural tube defects, all women who can become pregnant should consume 400 μg/day from supplements or fortified foods in addition to intake of food folate from a varied diet
		0-6 mo	65*	ND			
		7-12 mo	80*	ND			
		Children (μg/day)					
		1-3 yr	**150**	300			
		4-8 yr	**200**	400			
		Males (μg/day)					
		9-13 yr	**300**	600			
		14-18 yr	**400**	800			
		19-21 yr	**400**	1,000			
		Females (μg/day)					
		9-13 yr	**300**	600			
		14-18 yr	**400**	800			
		19-21 yr	**400**	1,000			
		Pregnancy (μg/day)					
		≤18 yr	**600**	800			
		19-21 yr	**600**	1,000			
		Lactation (μg/day)					
		≤18 yr	**500**	800			
		19-21 yr	**500**	1,000			
Niacin Includes nicotinic acid amide, nicotinic acid (pyridine-3 carboxylic acid), and derivatives that exhibit the biologic activity of nicotinamide Given as niacin equivalents (NE) 1 mg niacin = 60 mg tryptophan 0-6 mo = preformed niacin (not NE)	Coenzyme or cosubstrate in many biologic reduction and oxidation reactions, thus required for energy metabolism	*Infants (mg/day)*			Meat, fish, poultry, enriched and whole-grain breads and bread products, fortified ready-to-eat cereals	No evidence of adverse effects from consuming naturally occurring niacin in food Adverse effects from niacin-containing supplements can include flushing and GI distress UL for niacin applies to synthetic forms obtained from supplements, fortified food, or a combination of these	Extra niacin may be required by persons treated with hemodialysis or peritoneal dialysis or those with malabsorption syndrome
		0-6 mo	2*	ND			
		7-12 mo	4*	ND			
		Children (mg/day)					
		1-3 yr	**6**	10			
		4-8 yr	**8**	15			
		Males (mg/day)					
		9-13 yr	**12**	20			
		14-18 yr	**16**	30			
		19-21 yr	**16**	35			
		Females (mg/day)					
		9-13 yr	**12**	20			
		14-18 yr	**14**	30			
		19-21 yr	**14**	35			
		Pregnancy (mg/day)					
		≤18 yr	**18**	30			
		19-21 yr	**18**	35			
		Lactation (mg/day)					
		≤18 yr	**17**	30			
		19-21 yr	**17**	35			

Continued

Table 44-5 Dietary Reference Intakes for Vitamins—cont'd

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Pantothenic acid	Coenzyme in fatty acid metabolism	*Infants (mg/day)*			Chicken, beef, potatoes, oats, cereals, tomato products, liver, kidney, yeast, egg yolk, broccoli, whole grains	No adverse effects associated with pantothenic acid from food or supplements have been reported; this does not mean there is no potential for adverse effects resulting from high intakes Because data on adverse effects of pantothenic acid are limited, caution may be warranted	None
		0-6 mo	1.7*	ND			
		7-12 mo	1.8*	ND			
		Children (mg/day)					
		1-3 yr	2*	ND			
		4-8 yr	3*	ND			
		Males (mg/day)					
		9-13 yr	4*	ND			
		14-18 yr	5*	ND			
		19-21 yr	5*	ND			
		Females (mg/day)					
		9-13 yr	4*	ND			
		14-18 yr	5*	ND			
		19-21 yr	5*	ND			
		Pregnancy (mg/day)					
		≤18 yr	6*	ND			
		19-21 yr	6*	ND			
		Lactation (mg/day)					
		≤18 yr	7*	ND			
		19-21 yr	7*	ND			
Riboflavin aka vitamin B_2	Coenzyme in numerous redox reactions	*Infants (mg/day)*			Organ meats, milk, bread products, fortified cereals	No adverse effects associated with vitamin B_2 consumption from food or supplements have been reported; this does not mean there is no potential for adverse effects resulting from high intake Because data on adverse effects of vitamin B_2 are limited, caution may be warranted	None
		0-6 mo	0.3*	ND			
		7-12 mo	0.4*	ND			
		Children (mg/day)					
		1-3 yr	**0.5**	ND			
		4-8 yr	**0.6**	ND			
		Males (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.3**	ND			
		19-21 yr	**1.3**	ND			
		Females (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.0**	ND			
		19-21 yr	**1.1**	ND			
		Pregnancy (mg/day)					
		≤18 yr	**1.4**	ND			
		19-21 yr	**1.4**	ND			
		Lactation (mg/day)					
		≤18 yr	**1.6**	ND			
		19-21 yr	**1.6**	ND			

Thiamin aka vitamin B_1, aneurin	Coenzyme in the metabolism of carbohydrates and branched-chain amino acids	*Infants (mg/day)*			Enriched, fortified, or whole-grain products, bread and bread products, mixed foods whose main ingredient is grain, ready-to-eat cereals	No adverse effects associated with vitamin B_1 consumption from food or supplements have been reported; this does not mean there is no potential for adverse effects resulting from high intake Because data on adverse effects of vitamin B_1 are limited, caution may be warranted	Persons who might have increased need for vitamin B_1 include those being treated with hemodialysis or persons with a malabsorption syndrome
		0-6 mo	0.2*	ND			
		7-12 mo	0.3*	ND			
		Children (mg/day)					
		1-3 yr	**0.5**	ND			
		4-8 yr	**0.6**	ND			
		Males (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.2**	ND			
		19-21 yr	**1.2**	ND			
		Females (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.0**	ND			
		19-21 yr	**1.1**	ND			
		Pregnancy (mg/day)					
		≤18 yr	**1.4**	ND			
		19-21 yr	**1.4**	ND			
		Lactation (mg/day)					
		≤18 yr	**1.4**	ND			
		19-21 yr	**1.4**	ND			
Vitamin A Includes provitamin A carotenoids that are dietary precursors of retinol Given as retinol activity equivalents (RAEs) 1 RAE = 1 µg retinol, 12 µg β-carotene, 24 µg α-carotene, or 24 µg β-cryptoxanthin To calculate RAEs from REs of provitamin A carotenoids in food, divide the REs by 2 For preformed vitamin A in food or supplements and for provitamin A carotenoids in supplements, 1 RE = 1 RAE	Required for normal vision, gene expression, reproduction, embryonic development, and immune function	*Infants (µg/day)*			Liver, dairy products, fish, dark-colored fruit, leafy vegetables	Teratologic effects, liver toxicity (from preformed vitamin A only)	Persons with high alcohol intake, pre-existing liver disease, hyperlipidemia, or severe protein malnutrition may be distinctly susceptible to the adverse effects of excess preformed vitamin A intake β-Carotene supplements are advised only to serve as a provitamin A source for persons at risk for vitamin A deficiency
		0-6 mo	400*	600			
		7-12 mo	500*	600			
		Children (µg/day)					
		1-3 yr	**300**	600			
		4-8 yr	**400**	900			
		Males (µg/day)					
		9-13 yr	**600**	1,700			
		14-18 yr	**900**	2,800			
		19-21 yr	**900**	3,000			
		Females (µg/day)					
		9-13 yr	**600**	1,700			
		14-18 yr	**700**	2,800			
		19-21 yr	**700**	3,000			
		Pregnancy (µg/day)					
		≤18 yr	**750**	2,800			
		19-21 yr	**770**	3,000			
		Lactation (µg/day)					
		≤18 yr	**1,200**	2,800			
		19-21 yr	**1,300**	3,000			

Continued

Table 44-5 Dietary Reference Intakes for Vitamins—cont'd

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Vitamin B_6 Comprises a group of 6 related compounds: pyridoxal, pyridoxine, pyridoxamine, and 5′-phosphates (PLP, PNP, PMP)	Coenzyme in the metabolism of amino acids, glycogen, and sphingoid bases	*Infants (mg/day)*			Fortified cereals, organ meats, fortified soy-based meat substitutes	No adverse effects associated with vitamin B_6 from food have been reported; this does not mean there is no potential for adverse effects resulting from high intake Because data on adverse effects of vitamin B_6 are limited, caution may be warranted Sensory neuropathy has occurred from high intakes of supplemental forms	None
		0-6 mo	0.1*	ND			
		7-12 mo	0.3*	ND			
		Children (mg/day)					
		1-3 yr	**0.5**	30			
		4-8 yr	**0.6**	40			
		Males (mg/day)					
		9-13 yr	**1.0**	60			
		14-18 yr	**1.3**	80			
		19-21 yr	**1.3**	100			
		Females (mg/day)					
		9-13 yr	**1.0**	60			
		14-18 yr	**1.2**	80			
		19-21 yr	**1.3**	100			
		Pregnancy (mg/day)					
		≤18 yr	**1.9**	80			
		19-21 yr	**1.9**	100			
		Lactation (mg/day)					
		≤18 yr	**2.0**	80			
		19-21 yr	**2.0**	100			
Vitamin B_{12} aka cobalamin	Coenzyme in nucleic acid metabolism Prevents megaloblastic anemia	*Infants (μg/day)*			Fortified cereals, meat, fish, poultry	No adverse effects have been associated with consumption of the amounts of vitamin B_{12} normally found in food or supplements; this does not mean there is no potential for adverse effects resulting from high intake Because data on adverse effects of vitamin B_{12} are limited, caution may be warranted	Because 10-30% of older people malabsorb food-bound vitamin B_{12}, those >50 yr are advised to meet their RDA mainly by consuming foods fortified with vitamin B_{12} or a supplement containing vitamin B_{12}
		0-6 mo	0.4*	ND			
		7-12 mo	0.5*	ND			
		Children (μg/day)					
		1-3 yr	**0.9**	ND			
		4-8 yr	**1.2**	ND			
		Males (μg/day)					
		9-13 yr	**1.8**	ND			
		14-18 yr	**2.4**	ND			
		19-21 yr	**2.4**	ND			
		Females (μg/day)					
		9-13 yr	**1.8**	ND			
		14-18 yr	**2.4**	ND			
		19-21 yr	**2.4**	ND			
		Pregnancy (μg/day)					
		≤18 yr	**2.6**	ND			
		19-21 yr	**2.6**	ND			
		Lactation (μg/day)					
		≤18 yr	**2.8**	ND			
		19-21 yr	**2.8**	ND			

Vitamin C aka ascorbic acid, dehydroascorbic acid (DHA)	Cofactor for reactions requiring reduced copper or iron metalloenzyme and as a protective antioxidant	*Infants (mg/day)*			Citrus fruit, tomatoes, tomato juice, potatoes, Brussels sprouts, cauliflower, broccoli, strawberries, cabbage, spinach	GI disturbances, kidney stones, excess iron absorption	Smokers require additional 35 mg/day of vitamin C over that needed by nonsmokers Nonsmokers regularly exposed to tobacco smoke should ensure they meet the RDA for vitamin C
		0-6 mo	40*	ND			
		7-12 mo	50*	ND			
		Children (mg/day)					
		1-3 yr	**15**	400			
		4-8 yr	**25**	650			
		Males (mg/day)					
		9-13 yr	**45**	1,200			
		14-18 yr	**75**	1,800			
		19-21 yr	**90**	2,000			
		Females (mg/day)					
		9-13 yr	**45**	1,200			
		14-18 yr	**65**	1,800			
		19-21 yr	**75**	2,000			
		Pregnancy (mg/day)					
		≤18 yr	**80**	1,800			
		19-21 yr	**85**	2,000			
		Lactation (mg/day)					
		≤18 yr	**115**	1,800			
		19-21 yr	**120**	2,000			
Vitamin E aka α-tocopherol α-Tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the *2R*-stereoisomeric forms of α-tocopherol (*RRR*-, *RSR*-, RRS-, and *RSS*-α-tocopherol) that occur in fortified foods and supplements It does not include the *2S*-stereoisomeric forms of α-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol), also found in fortified foods and supplements	A metabolic function has not yet been identified Vitamin E's major function appears to be as a nonspecific chain-breaking antioxidant	*Infants (mg/day)*			Vegetable oil, unprocessed cereal grains, nuts, fruit, vegetables, meat	No evidence of adverse effects from consuming vitamin E naturally occurring in food Adverse effects from vitamin E–containing supplements may include hemorrhagic toxicity UL for vitamin E applies to any form of α-tocopherol obtained from supplements, fortified foods, or a combination of these	Patients on anticoagulant therapy should be monitored when taking vitamin E supplements
		0-6 mo	4*	ND			
		7-12 mo	5*	ND			
		Children (mg/day)					
		1-3 yr	**6**	200			
		4-8 yr	**7**	300			
		Males (mg/day)					
		9-13 yr	**11**	600			
		14-18 yr	**15**	800			
		19-21 yr	**15**	1,000			
		Females (mg/day)					
		9-13 yr	**11**	600			
		14-18 yr	**15**	800			
		19-21 yr	**15**	1,000			
		Pregnancy (mg/day)					
		≤18 yr	**15**	800			
		19-21 yr	**15**	1,000			
		Lactation (mg/day)					
		≤18 yr	**19**	800			
		19-21 yr	**19**	1,000			

Continued

Table 44-5 Dietary Reference Intakes for Vitamins—cont'd

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Vitamin K	Coenzyme during the synthesis of many proteins involved in blood clotting and bone metabolism	*Infants (μg/day)*			Green vegetables (collards, spinach, salad greens, broccoli), Brussels sprouts, cabbage, plant oil, margarine	No adverse effects associated with vitamin K consumption from food or supplements have been reported in humans or animals; this does not mean there is no potential for adverse effects resulting from high intake Because data on adverse effects of vitamin K are limited, caution may be warranted	Patients on anticoagulant therapy should monitor vitamin K intake
		0-6 mo	2.0*	ND			
		7-12 mo	2.5*	ND			
		Children (μg/day)					
		1-3 yr	30*	ND			
		4-8 yr	55*	ND			
		Males (μg/day)					
		9-13 yr	60*	ND			
		14-18 yr	75*	ND			
		19-21 yr	120*	ND			
		Females (μg/day)					
		9-13 yr	60*	ND			
		14-18 yr	75*	ND			
		19-21 yr	90*	ND			
		Pregnancy (μg/day)					
		≤18 yr	75*	ND			
		19-21 yr	90*	ND			
		Lactation (μg/day)					
		≤18 yr	75*	ND			
		19-21 yr	90*	ND			

Note: Starred numbers are AI, and bold numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97-98% of members in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all members of the group, but lack of data prevents specifying with confidence the percentage covered by this intake.

UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Because of a lack of suitable data, ULs could not be established for potassium, water, and inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

ND amounts are not determinable because of a lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

*Adequate intake. *RDA for vitamin D in IU/day: 400 if <1 yr age, 600 if >1 yr, lactating, or pregnant.

AI, adequate intake; GI, gastrointestinal; ND, not determinable; PLP, pyridoxal phosphate; PMP, pyridoxamine phosphate; PNP, pyridoxine phosphate; RDA, recommended dietary allowance; UL, upper limit.

Adapted from Food and Nutrition Board, Institute of Medicine: Dietary reference intakes for calcium, phosphorous, magnesium, vitamin D, and fluoride *(website),* www.nap.edu/openbook.php?record_id=5776; Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline *(website),* www.nap.edu/openbook.php?record_id=6015; Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids *(website),* www.nap.edu/openbook.php?record_id=9810; *and* Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc *(website),* www.nap.edu/openbook.php?record_id=10026.

has been successfully implemented to prevent iodine and folate deficiency.

Breast milk provides optimal intake of most nutrients including iron and zinc. Although they present in lower amounts than in infant formula, they are more bioavailable and sufficient to meet infant needs until ~4-6 mo of age. After 4-6 mo of age, iron and zinc are required from complementary foods, such as iron-fortified cereal and pureed meats.

Iron requirements are higher during infancy and childhood as compared to later life stages, and are higher for menstruating females as compared to males of similar age groups (see Chapter 54). Iron present in animal protein is more bioavailable than that found in vegetables and other foods because it is already incorporated into heme moieties in blood and muscle. Iron deficiency is the most common micronutrient deficiency and is associated with iron-deficiency anemia and neurocognitive deficits. **Zinc** deficiency affects millions of children and is associated with increased risk for impaired linear growth (stunting), impaired immune function, and increased risk for respiratory and diarrheal diseases.

Breast milk is a poor source of **vitamin D** (see Chapter 51). Vitamin D insufficiency is more common than previously thought in infants and children. Vitamin D is central to calcium and bone metabolism, but is also an important determinant of various nonosseous health outcomes. Vitamin D is absorbed in the skin from sunlight and is also present naturally in some foods and fortified in all cow milk products, regardless of fat content, soy milk, almond milk, and orange juice. Sunlight exposure varies by season. Therefore, for populations residing in northern latitudes and/or who have darker skin, sunlight exposure is unlikely to meet the vitamin D needs over the year; in these groups, additional sunlight exposure and/or vitamin D supplementation may be required to achieve optimal status.

Children with darker skin and those who do not consume fortified products should be screened for vitamin D deficiency. The DRI for vitamin D is based on its effects on calcium status and bone health. The goal is to achieve serum levels of 25(OH) D levels above 50 nmol/L (30 ng/dL), which is often achieved using vitamin D supplementation. In 2010, the American Academy of Pediatrics increased total vitamin D intake recommendations to 600 IU/day for infants and children. A supplement was recommended for all breast-fed infants to ensure sufficient intake.

Calcium adequacy is determined in part as a function of bone health as measured by bone mineral content and density. The main storage organs for calcium are the bones and teeth. Bone mineral accretion occurs primarily in the pediatric age range, with peak bone mass being achieved by the 2nd to 3rd decade of life. Calcium recommendations vary by age and were also increased from AI to RDA, and the UL was increased in 9-18 yr olds (Table 44-6).

Vitamin K is an important determinant of bone health, but is also an important cofactor for coagulation factors (factors II, VII, IX, and X; protein C; and protein S) (see Chapter 53). Status can be assessed by prothrombin time, protein in the absence of vitamin K (PIVKA-II) and the vitamin K–dependent coagulation factor levels. Neonates are at risk for suboptimal vitamin K status, leading to an increased risk for hemorrhagic disease of the newborn. Vitamin K prophylaxis at birth is recommended for all newborn infants.

Potassium and sodium are the main intra- and extracellular cations, respectively, and are involved in transport of fluids and nutrients across the cellular membrane. There is an AI set for **potassium** related to its effects in maintaining a healthy blood pressure, reducing risk for nephrolithiasis, and supporting bone health. Moderate potassium deficiency can occur even in the absence of hypokalemia and can result in increased blood pressure, stroke, and other cardiovascular disease. Most American children have potassium intake below the current recommendations. African-Americans in particular are at increased risk for potassium deficiency. For people at increased risk for hypertension and who are salt sensitive, reducing sodium intake and increasing potassium intake is advised. Leafy green vegetables, vine fruit (such as tomatoes) and root vegetables are good food sources of potassium (see Table 44-6). People with impaired renal function may need to reduce potassium intake as hyperkalemia can increase risk for fatal cardiac arrhythmias among these patients.

Sodium has an AI, but given the risk of hypertension, an UL has also been set. The UL threshold may be even lower in African-Americans, who, on average, are more salt sensitive, and for those with hypertension or preexisting renal disease. Dietary sodium intake also displaces potassium intake. Elevated sodium: potassium ratios can increase the risk for nephrolithiasis. Intakes of <2,300 mg (approximately 1 tsp) per day are recommended. The average daily salt intake for most people in the United States and Canada exceeds both the AI and UL. Most dietary salt in the United States is found in processed foods, breads, condiments, and as a food preservative, and to enhance palatability. *For populations with or at risk for hypertension and renal disease, sodium intake should be decreased to <1,500 mg/day and potassium intake increased to >4,700 mg/day.* For persons with hypertension, additional dietary guidelines are available from the Dietary Approaches to Stop Hypertension (DASH) eating plan.

WATER

The water requirement and content as a proportion of body weight are highest in infants and decrease with age. Water intake is achieved with liquid and food intake, and losses include excretion in the urine and stool as well as insensible and evaporative losses through the skin and respiratory tract. An AI has been established for water (see Table 44-6). Special considerations are required by life stages and by basal metabolic rate, physical activity, body proportions (surface area to volume), environment, and underlying medical conditions. Breast milk and infant formula provide adequate water, and additional water intake is not required until complementary foods are introduced. Although water contains no calories, the concern is that water intake might actually decrease breast milk intake and displace the intake of essential nutrients during this metabolically very active life stage. The increased fluid needs of infants and young children can be explained in part by the high ratio of body surface area to volume in infancy and high respiratory rate.

The consequences of inadequate fluid intake include dehydration, impaired thermoregulation and heat dissipation, reduced activity tolerance and performance, and reduced intravascular fluid. These deficits can result in an increased compensatory heart rate, hypotension and syncope, and, if uncorrected, renal injury or nephrolithiasis. Excess free water intake is usually better tolerated by healthy adults than by younger children, who may be at increased risk for water intoxication. Hyponatremia can result from excess free water intake coupled with inadequate sodium intake. Fluid intake requirements and restrictions are also influenced by underlying renal and hormonal disorders, including diabetes, the syndrome of inappropriate antidiuretic hormone secretion, and diabetes insipidus.

MEASURING NUTRITIONAL ADEQUACY

Growth according to expected patterns can be tracked using the 2000 Centers for Disease Control and Prevention (CDC) and 2006 WHO growth charts (see Chapters 6 and 15). The WHO growth charts are derived from longitudinal and cross-sectional data obtained from a sample of healthy breast-fed infants and children (0-5 yr) who were receiving adequate nutritional intake and medical care from Brazil, Ghana, India, Norway, Oman, and the United States. Consequently, the WHO growth charts are not only descriptive of population average and distribution, but are also prescriptive regarding how adequately nourished healthy children under best-care practices should grow. The CDC and American Academy of Pediatrics recommend the use of the WHO charts to monitor growth of all infants and children (breast and bottle or infant formula fed) from birth to 2 yr of age, and the use of the CDC 2000 growth charts for children 2 to 20 yr of age.

Although the WHO and CDC growth charts are recommended for growth and nutritional assessment, a number of disease-specific charts are available. It is noteworthy that many other disease- or syndrome-specific growth charts are based on small samples of children, and include children with suboptimal nutritional status. For these patient

Text continued on p. 286

Table 44-6 Dietary Reference Intakes for Select Micronutrients and Water

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	AI (mg/day)	UL (mg/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Sodium	Maintains fluid volume outside of cells and thus normal cell function	*Infants*			Processed foods with added sodium chloride (salt), benzoate, phosphate; salted meats, bread, nuts, cold cuts; margarine; butter; salt added to foods in cooking or at the table Salt is ~ 40% sodium by weight	Hypertension Increased risk of cardiovascular disease and stroke	AI is set based on ability to obtain a nutritionally adequate diet for other nutrients and to meet the needs for sweat losses for persons engaged in recommended levels of physical activity Persons engaged in activity at higher levels or in humid climates resulting in excessive sweat might need more than the AI UL applies to apparently healthy persons without hypertension; it thus may be too high for persons who already have hypertension or who are under the care of a health professional
		0-6 mo	120	ND			
		7-12 mo	370	ND			
		Children					
		1-3 yr	1,000	1,500			
		4-8 yr	1,200	1,900			
		Males					
		9-13 yr	1,500	2,200			
		14-21 yr	1,500	2,300			
		Females					
		9-13 yr	1,500	2,200			
		13-21 yr	1,500	2,300			
		Pregnancy and Lactation					
		≥14 yr	1,500	2,300			
Chloride	With sodium, maintains fluid volume outside of cells and thus normal cell function	*Infants*			Processed foods with added sodium chloride (salt), benzoate, phosphate; salted meats, nuts, cold cuts; margarine; butter; salt added to foods in cooking or at the table Salt is ~60% chloride by weight	In concert with sodium, results in hypertension	Chloride is lost, usually with sodium, in sweat, as well as in vomiting and diarrhea AI and UL are equimolar in amount to sodium because most of sodium in diet comes as sodium chloride (salt)
		0-6 mo	180	ND			
		7-12 mo	570	ND			
		Children					
		1-3 yr	1,500	2,300			
		4-8 yr	1,900	2,900			
		Males					
		9-13 yr	2,300	3,400			
		14-21 yr	2,300	3,600			
		Females					
		9-13 yr	2,300	3,400			
		13-21 yr	2,300	3,600			
		Pregnancy and Lactation					
		≥14 yr	2,300	3,600			
Potassium	Maintains fluid volume inside/outside of cells and thus normal cell function; acts to blunt the rise of blood pressure in response to excess sodium intake, and decrease markers of bone turnover and recurrence of kidney stones	*Infants*			Fruits and vegetables, dried peas, dairy products, meats, nuts	None documented from food alone, but potassium from supplements or salt substitutes can result in hyperkalemia and possibly sudden death if excess is consumed by persons with chronic renal insufficiency (kidney disease) or diabetes	Persons taking drugs for cardiovascular disease such as ACE inhibitors, ARBs, or potassium-sparing diuretics should be careful not to consume supplements containing potassium and might need to consume less than the AI
		0-6 mo	400	None set			
		7-12 mo	700				
		Children					
		1-3 yr	3,000	No UL			
		4-8 yr	3,800				
		Males					
		9-13 yr	4,500				
		14-21 yr	4,700				
		Females					
		9-13 yr	4,500				
		13-21 yr	4,700				
		Pregnancy					
		≥14 yr	4,700				
		Lactation					
		≥14 yr	5,100				

Vitamin D aka calciferol **1 µg calciferol = 40 IU vitamin D** DRI values are based on absence of adequate exposure to sunlight	Maintains serum calcium and phosphorus concentrations	*Infants (µg/day)**			Fish liver oils, flesh of fatty fish, liver and fat from seals and polar bears, eggs from hens that have been fed vitamin D, fortified milk products, fortified cereals	Elevated plasma 25(OH)D concentration causing hypercalcemia	Patients on glucocorticoid therapy might require additional vitamin D
		0-6 mo	10	**25**			
		7-12 mo	10	**38**			
		*Children (µg/day)**					
		1-3 yr	**15**	**63**			
		4-8 yr	**15**	**75**			
		*Males (µg/day)**					
		9-21yr	**15**	**100**			
		*Females (µg/day)**					
		9-21 yr	**15**	**100**			
		*Pregnancy (µg/day)**					
		≤18 yr	15	**100**			
		Lactation (µg/day)					
		≤18 yr	15	**100**			
		19-21 yr	**15**	**100**			
Calcium	Essential role in blood clotting, muscle contraction, nerve transmission, and bone and tooth formation	*Infants*			Milk, cheese, yogurt, corn tortillas, calcium-set tofu, Chinese cabbage, kale, broccoli	Kidney stones, hypercalcemia, milk alkali syndrome, and renal insufficiency	Amenorrheic women (exercise- or anorexia nervosa–induced) have reduced net calcium absorption
		0-6 mo	200	**1,000**			
		7-12 mo	260	**1,500**			
		Children					
		1-3 yr	**700**	**2,500**			
		4-8 yr	**1,000**	**2,500**			
		Males					
		9-18 yr	**1,300**	3,000			
		19-21 yr	**1,000**	**2,500**			
		Females					
		9-18 yr	**1,300**	**3,000**			
		19-21 yr					
		Pregnancy					
		≤18 yr	**1,300**	**3,000**			
		19-21 yr	**1,000**	**2,500**			
		Lactation					
		≤18 yr	**1,300**	**3,000**			
		19-21 yr	**1,000**	**2,500**			

Continued

Table 44-6 Dietary Reference Intakes for Select Micronutrients and Water—cont'd

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	AI (mg/day)	UL (mg/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Iron	Critical component of enzymes, cytochromes, myoglobin, and hemoglobin	*Infants*			Heme sources: meat, poultry, fish Nonheme sources: dairy, eggs, plant-based foods, breads, cereals, breakfast foods	GI distress	Persons with decreased gastric acidity may be at increased risk for deficiency Cow's milk is a poor source of bioavailable iron and is not recommended for children <1 yr old Neurocognitive deficits have been reported in infants with iron deficiency RDA for females increases with menarche related to increased losses during menstruation Vegans and vegetarians might require iron supplementation or intake of iron-fortified foods GI parasites can increase iron losses via GI bleeds Iron supplements can interfere with zinc absorption and vice versa; if supplements are being used, the doses should be staggered
		0-6 mo	0.27	40			
		7-12 mo	**11**	40			
		Children					
		1-3 yr	**7**	40			
		4-8 yr	**10**	40			
		Males					
		9-13 yr	**8**	40			
		14-18 yr	**11**	45			
		19-21 yr	**8**	45			
		Females					
		9-13 yr	**8**	40			
		14-18 yr	**15**	45			
		19-21 yr	**18**	45			
		Pregnancy					
		≤18 yr	**27**	45			
		19-21 yr	**27**	45			
		Lactation					
		≤18 yr	**10**	45			
		19-21 yr	**9**	45			
Zinc	Essential for proper growth and development, and an important catalyst for 100 specific enzymes	*Infants*			Meats, shellfish, legumes, fortified cereals, whole grains	Acutely zinc supplements cause GI irritation and headache; chronic effects of zinc supplementation include impaired immune function, changes in lipoprotein and cholesterol levels, and reduced copper status	Zinc supplements interfere with iron absorption and vice versa; therefore, if supplements are being used, the doses should be staggered Zinc deficiency can be associated with stunting or impaired linear growth
		0-6 mo	2	4			
		7-12 mo	**3**	5			
		Children					
		1-3 yr	**3**	7			
		4-8 yr	**5**	12			
		Males					
		9-13 yr	**8**	23			
		14-18 yr	**11**	34			
		19-21 yr	**11**	40			
		Females					
		9-13 yr	**8**	23			
		14-18 yr	**9**	34			
		19-21 yr	**8**	40			
		Pregnancy					
		≤18 yr	**12**	34			
		19-21 yr	**11**	40			
		Lactation					
		≤18 yr	**13**	34			
		19-21 yr	**12**	40			

Water	Maintains homeostasis in the body Allows transport of nutrients to cells and removal and excretion of waste products of metabolism	*Infants (L/day)*			All beverages, including water Moisture in foods High-moisture foods include watermelon, meats, soups	No UL because normally functioning kidneys can handle >0.7 L (24 oz) of fluid per hour Symptoms of water intoxication include hyponatremia, which can result in heart failure, and rhabdomyolysis (skeletal muscle tissue injury), which can lead to kidney failure	Recommended intakes for water are based on median intakes of generally healthy persons who are adequately hydrated Persons can be adequately hydrated at levels above or below the AIs provided; AIs provided are for total water in temperate climates All sources can contribute to total water needs: beverages (tea, coffee, juice, soda, and drinking water) and moisture found in foods Moisture in food accounts for ~ 20% of total water intake Thirst and consumption of beverages at meals are adequate to maintain hydration
		0-6 mo	0.7	None set			
		7-12 mo	0.8				
		Children					
		1-3 yr	1.3				
		4-8 yr	1.7				
		Males (L/day)					
		9-13 yr	2.4				
		14-18 yr	3.3				
		≥19 yr	3.7				
		Females (L/day)					
		9-13 yr	2.1				
		14-18 yr	2.3				
		≥19 yr	2.7				
		Pregnancy (L/day)					
		≥14 yr	3.0				
		Lactation (L/day)					
		≥14 yr	3.8				

Note: Bold numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97-98% of members in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life-stage and gender groups is believed to cover the needs of all members of a group, but lack of data prevents specifying with confidence the percentage covered by this intake. UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Because of a lack of suitable data, ULs could not be established for potassium, water, and inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes. ND amounts are not determinable because of a lack of data on adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

*Vitamin D RDA in IU/day: 40 if <1 yr, 600 if >1 yr of age or pregnant or lactating.

ACE, angiotensin-converting enzyme; AI, adequate intake; ARB, angiotensin receptor blocker; GI, gastrointestinal; ND, not determinable; RDA, recommended dietary allowance; UL, upper limit.

Adapted from Food and Nutrition Board, Institute of Medicine: Dietary reference intakes for water, potassium, sodium, chloride, and sulfate *(website). http://www.nap.edu/openbook.php?record_id=10925.*

groups, disease-specific charts may be helpful to use in conjunction with the WHO or CDC growth charts for comparison to children of similar age and sex from the general population. The goal should be to use this information to approximate growth as closely to that of the general population as possible in these subsets of children, where and when possible. In addition to anthropometry, other nutrient biomarkers can be used to assess status. For infants and children with specific dietary or health concerns, consultation with lactation consultants, registered dieticians, and/or physician nutrition specialists may also be indicated.

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Chapter 45

Feeding Healthy Infants, Children, and Adolescents

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Early nutrition plays an important role in the origin of adult diseases such as type 2 diabetes, hypertension, obesity, and the metabolic syndrome; therefore, appropriate feeding practices should be established in the neonatal period and continued throughout childhood and adolescence to adulthood. Healthy feeding in children requires partnerships between family members, the healthcare system, schools, the community, and the government.

FEEDING DURING THE FIRST YEAR OF LIFE

Breastfeeding

The American Academy of Pediatrics (AAP) and World Health Organization (WHO) have declared breastfeeding and the administration of human milk to be the normative practice for infant feeding and nutrition. Breastfeeding has documented short- and long-term medical and neurodevelopmental advantages (Tables 45-1 and 45-2) and rare contraindications (Table 45-3). Thus the decision to breastfeed should be considered a public health issue and not only a lifestyle choice. The AAP and the WHO recommend that infants should be exclusively breastfed or given breast milk for 6 months. Breastfeeding should be continued with the introduction of complementary foods for 1 year or longer, as mutually desired by mother and infant. The success of breastfeeding initiation and continuation depends on multiple factors, such as education about breastfeeding, hospital breastfeeding practices and policies, routine and timely follow-up care, and family and societal support (Table 45-4).

Feedings should be initiated soon after birth unless medical conditions preclude them. Mothers should be encouraged to nurse at each breast at each feeding starting with the breast offered second at the last feeding. It is not unusual for an infant to fall asleep after the first breast and refuse the second. It is preferable to empty the first breast before offering the second in order to allow complete emptying of both breasts and therefore better milk production. Table 45-5 summarizes patterns of milk supply in the 1st week.

New mothers should be instructed about infant hunger cues, correct nipple latch, positioning of the infant on the breast, and feeding frequency. It is also suggested that someone trained in lactation observe a feeding to evaluate positioning, latch, milk transfer and maternal responses, and infant satiety. Attention to these issues during the birth hospitalization allows dialogue with the mother and family and can prevent problems that could occur with improper technique or knowledge of breastfeeding. As part of the discharge teaching process, issues surrounding infant feeding, elimination patterns, breast engorgement, basic breast care, and maternal nutrition should be discussed. A follow-up appointment is recommended within 24-48 hr after hospital discharge.

Table 45-1 Selected Beneficial Properties of Human Milk Compared to Infant Formula

Secretory IgA	Specific antigen-targeted antiinfective action
Lactoferrin	Immunomodulation, iron chelation, antimicrobial action, antiadhesive, trophic for intestinal growth
κ-Casein	Antiadhesive, bacterial flora
Oligosaccharides	Prevention of bacterial attachment
Cytokines	Antiinflammatory, epithelial barrier function
Growth factors	
Epidermal growth factor	Luminal surveillance, repair of intestine
Transforming growth factor (TGF)	Promotes epithelial cell growth (TGF-β) Suppresses lymphocyte function (TGF-β)
Nerve growth factor	Promotes neural growth
Enzymes	
Platelet-activating factor-acetylhydrolase	Blocks action of platelet-activating factor
Glutathione peroxidase	Prevents lipid oxidation
Nucleotides	Enhance antibody responses, bacterial flora

Adapted from Hamosh M: Bioactive factors in human milk, Pediatr Clin North Am *48:69–86, 2001.*

Table 45-2 Conditions for Which Human Milk Has Been Suggested to Possibly Have a Protective Effect

Acute disorders	Crohn disease
Diarrhea	Childhood cancer
Otitis media	Lymphoma
Urinary tract infection	Leukemia
Necrotizing enterocolitis	Recurrent otitis media
Septicemia	Allergy
Infant botulism	Obesity and overweight
Insulin-dependent diabetes mellitus	Hospitalizations
Celiac disease	Infant mortality

Nipple Pain

Nipple pain is one of the most common complaints of breastfeeding mothers in the immediate postpartum period. Poor infant positioning and improper latch are the most common reasons for nipple pain beyond the mild discomfort felt early in breastfeeding. If the problem persists and the infant refuses to feed, consideration needs to be given to nipple candidiasis. If present the mother should be treated with an antifungal cream that is wiped away before feeding, and the infant treated with oral medication.

Engorgement

In the second stage of lactogenesis, physiologic fullness of the breast occurs. Breasts may become engorged: firm, overfilled, and painful as the pattern and volume of milk production is adjusting to the infant's feeding schedule. Incomplete removal of milk as a result of poor breastfeeding technique or infant illness can cause engorgement. Breastfeeding immediately at signs of infant hunger will eventually prevent this

Table 45-3 Absolute and Relative Contraindications to Breastfeeding Because of Maternal Health Conditions

MATERNAL HEALTH CONDITION	DEGREE OF RISK
HIV and HTLV infection	In the United States, breastfeeding is contraindicated In other settings, health risks of not breastfeeding must be weighed against the risk of transmitting virus to the infant
Tuberculosis infection	Breastfeeding is contraindicated until completion of approximately 2 wk of appropriate maternal therapy
Varicella-zoster infection	Infant should not have direct contact to active lesions Infant should receive immune globulin
Herpes simplex infection	Breastfeeding is contraindicated with active herpetic lesions of the breast
CMV infection	May be found in milk of mothers who are CMV seropositive Transmission through human milk causing symptomatic illness in term infants is uncommon
Hepatitis B infection	Infants routinely receive hepatitis B immune globulin and hepatitis B vaccine if mother is HbsAg positive No delay in initiation of breastfeeding is required
Hepatitis C infection	Breast-feeding is not contraindicated
Alcohol intake	Limit maternal alcohol intake to <0.5 g/kg/day (for a woman of average weight, this is the equivalent of 2 cans of beer, 2 glasses of wine, or 2 oz of liquor)
Cigarette smoking	Discourage cigarette smoking, but smoking is not a contraindication to breastfeeding
Chemotherapy, radiopharmaceuticals	Breastfeeding is generally contraindicated

CMV, cytomegalovirus; HbsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus.

Data from Schanler RJ, Krebs NF, Mass SB (eds): Breastfeeding handbook for physicians, *ed 2, Elk Grove Village, IL, 2014, American Academy of Pediatrics, pp 223–226.*

from occurring. To reduce engorgement, breasts should be softened prior to infant feeding with a combination of hot compresses and expression of milk. Between feedings a supportive bra should be worn, cold compresses applied, and oral nonsteroidal antiinflammatory medications administered.

Mastitis

Mastitis occurs in 2-3% of lactating women and is usually unilateral, manifesting with localized warmth, tenderness, edema, and erythema after the second postdelivery week. Sudden onset of breast pain, myalgia, and fever with fatigue, nausea, vomiting, and headache can also occur. Organisms implicated in mastitis include *Staphylococcus aureus, Escherichia coli,* group A streptococcus, *Haemophilus influenzae, Klebsiella pneumoniae,* and *Bacteroides* spp. Diagnosis is confirmed by physical examination. Oral antibiotics and analgesics, while promoting breastfeeding or emptying of the affected breast, usually resolve the infection. A breast abscess is a less common complication of mastitis, but it is a more serious infection that requires intravenous antibiotics, incision, and drainage, along with temporary cessation of feeding from that breast.

Table 45-4 Recommendations on Breastfeeding Management for Healthy Term Infants

1. Exclusive breastfeeding for about 6 months
   - Breastfeeding preferred; alternatively expressed mother's milk, or donor breast milk
   - To continue for at least the first year and beyond as long as mutually desired by mother and child
   - Complementary foods rich in iron and other micronutrients should be introduced at about 6 mo of age
2. Peripartum policies and practices that optimize breastfeeding initiation and maintenance should be compatible with the AAP and Academy of Breastfeeding Medicine Model Hospital Policy and include the following:
   - Direct skin-to-skin contact with mothers immediately after delivery until the first feeding is accomplished and encouraged throughout the postpartum period
   - Delay in routine procedures (weighing, measuring, bathing, blood tests, vaccines, and eye prophylaxis) until after the first feeding is completed
   - Delay in administration of intramuscular vitamin K until after the first feeding is completed but within 6 hr of birth
   - Ensure 8-12 feedings at the breast every 24 hr
   - Ensure formal evaluation and documentation of breastfeeding by trained caregivers (including position, latch, milk transfer, examination) at least once for each nursing shift
   - Give no supplements (water, glucose water, commercial infant formula, or other fluids) to breastfeeding newborn infants unless medically indicated using standard evidence-based guidelines for the management of hyperbilirubinemia and hypoglycemia
   - Avoid routine pacifier use in the postpartum period
   - Begin daily oral vitamin D drops (400 IU) at hospital discharge
3. All breastfeeding infants should be seen by a pediatrician within 48 to 72 hr after discharge from the hospital
   - Evaluate hydration (elimination patterns)
   - Evaluate body weight gain (body weight loss no more than 7% from birth and no further weight loss by day 5: assess feeding and consider more frequent follow-up)
   - Discuss maternal/infant issues
   - Observe feeding
4. Mother and infant should sleep in proximity to each other to facilitate breastfeeding
5. Pacifier should be offered, while placing infant in back-to-sleep-position, no earlier than 3 to 4 weeks of age and after breastfeeding has been established

From American Academy of Pediatrics: Breast-feeding and the use of human milk, Pediatrics *129:e827–e841, 2012.*

Inadequate Milk Intake

Insufficient milk intake, dehydration, and jaundice in the infant can become evident within the first week of life. Signs of insufficient milk intake include: lethargy, delayed stooling, decreased urine output, weight loss >7% of birth weight, hypernatremic dehydration, inconsolable crying and increased hunger. Insufficient milk intake may be caused by insufficient milk production, failure of established breastfeeding, and health conditions in the infant that prevent proper breast stimulation. Parents should be counseled that breastfed neonates feed 8-12 times a day with a minimum of 8 times per day. Careful attention to prenatal history can identify maternal factors that may be associated with this problem (failure of breasts to enlarge during pregnancy or within the first few days after delivery). Direct observation of breastfeeding can help identify improper technique. If a large volume of milk is expressed manually after breastfeeding, then the infant might not be extracting enough milk, eventually leading to decreased milk output. Late preterm infants (34-36 wk) are at risk for insufficient milk syndrome because of poor suck and swallow patterns or medical issues.

Jaundice

Breastfeeding jaundice is a common reason for hospital readmission of healthy breastfed infants and is largely related to insufficient fluid

Table 45-5 Patterns of Milk Supply

DAY OF LIFE	MILK SUPPLY
Day 1	Some milk (~5 mL) may be expressed
Days 2-4	Lactogenesis, milk production increases
Day 5	Milk present, fullness, leaking felt
Day 6 onward	Breasts should feel “empty” after feeding

Adapted from Neifert MR: Clinical aspects of lactation: promoting breastfeeding success, Clin Perinatol *26:281–306, 1999.*

intake during the first week of life (see Chapter 102.3). It may also be associated with dehydration and hypernatremia. **Breast milk jaundice** is a different disorder that causes persistently high serum indirect bilirubin in a thriving healthy baby that becomes evident later than breastfeeding jaundice, but which generally declines in the 2nd to 3rd wk of life. Infants with severe or persistent jaundice should be evaluated for other medical causes (see Chapter 102.3) before ascribing the jaundice to breast milk that might contain inhibitors of glucuronyl transferase or enhanced absorption of bilirubin from the gut. Persistently high bilirubin levels may require changing from breast milk to infant formula for 24-48 hr and/or treatment with phototherapy without cessation of breastfeeding. Breastfeeding should resume after the decline in serum bilirubin. Parents should be reassured and encouraged to continue collecting breast milk during the period when the infant is taking formula.

Collecting Breast Milk

The pumping of breast milk is a common practice when the mother and baby are separated for work, illness, or hospitalization of mother or infant. Good hand washing and hygiene should be emphasized. Electric breast pumps are more efficient and better tolerated by mothers than mechanical pumps or manual expression. Collection kits should be cleaned with hot soapy water, rinsed, and air dried after each use. Glass or plastic containers should be used to collect the milk, and milk should be refrigerated and then used within 48 hr. Expressed breast milk can be frozen and used for up to 6 mo. Milk should be thawed rapidly by holding under running tepid water and used completely within 24 hr after thawing. *Milk should never be microwaved.*

Growth of the Breastfed Infant

The rate of weight gain of the breastfed infant differs from that of the formula-fed infant, and the infant’s risk for excess weight gain during late infancy may be associated with bottle feeding. The WHO growth charts are based on the growth of healthy breastfed infants through the 1st yr of life. These standards (http://www.who.int/childgrowth) are the result of a study in which >8,000 children were selected from 6 countries. The infants were selected based on healthy feeding practices (breastfeeding), good health care, high socioeconomic status, and nonsmoking mothers, so that they reflect the growth of breastfed infants in the optimal conditions and can be used as prescriptive rather than normative curves. Charts are available for growth monitoring from birth to age 6 yr. The Centers for Disease Control and Prevention (CDC) recommends use of the WHO growth charts for infants 0-23 months of age, and CDC growth charts for ages 24 mo to 20 yr.

Formula Feeding (Fig. 45-1)

Despite efforts to promote exclusive breastfeeding through 6 months, less than 50% of women continue to breastfeed at 6 months. Most women make their infant feeding choices early in pregnancy. Parental preference is the most common reason for using infant formula. However, infant formula is also indicated in infants whose intake of breast milk is contraindicated for infant factors (e.g. inborn errors of metabolism), and maternal factors (see Table 45-3). In addition infant formula is used as a supplement to support inadequate weight gain in breastfed infants.

Infant formulas marketed in the United States are safe and nutritionally adequate as the sole source of nutrition for healthy infants for the first 6 months of life. Infant formulas are available in ready-to-feed, concentrated liquid or powder forms. Ready-to-feed products generally provide 20 kcal/30 mL (1 oz) and approximately 67 kcal/dL. Concentrated liquid products, when diluted according to instructions, provide a preparation with the same concentration. Powder formulas come in single or multiple servings and when mixed according to instructions will result in similar caloric density.

Although infant formulas are manufactured in adherence to good manufacturing practices and are regulated by the U.S. Food and Drug Administration (FDA), there are still potential safety issues. Powder preparations are not sterile, and although the number of bacterial colony-forming units per gram of formula is generally lower than allowable limits, outbreaks of infections with *Enterobacter sakazakii* have been documented, especially in premature infants. The powder preparations can contain other coliform bacteria but have not been linked to disease in healthy term infants. Care must be taken in following the mixing instructions to avoid over- or underdilution, to use boiled or sterilized water, and to use the specific scoops provided by the manufacturer as scoop sizes vary. Water that has been boiled should be allowed to cool fully to prevent degradation of heat labile nutrients, specifically vitamin C. Well water should be tested regularly for bacteria and toxin contamination. Municipal water can contain variable concentrations of fluoride, and if the concentrations are high, bottled water that is defluoridated should be used to avoid toxicity.

Parents should be instructed to use proper handwashing techniques when preparing formula and feedings for the infant. Guidance to follow written instructions for storage should also be given. Once opened, ready-to-feed and concentrated liquid containers can be covered with aluminum foil or plastic wrap and stored in the refrigerator for no longer than 48 hr. Powder formula should be stored in a cool, dry place; once opened, cans should be covered with the original plastic cap or aluminum foil, and the powdered product can be used within 4 weeks. Once prepared, all bottles regardless of type of formula should be used within 24 hours. Formula should be used within 2 hours of removal from the refrigerator and once a feeding has started, that formula should be used within an hour or be discarded. Prepared formula stored in the refrigerator should be warmed by placing the container in warm water for ~5 min. Formula should not be heated in a microwave, because it can heat unevenly and result in burns despite appearing to be at the right temperature when tested.

Formula feedings should be ad libitum, with the goal of achieving growth and development to the child’s genetic potential. The usual intake to allow a weight gain of 25-30 g/day will be 140-200 mL/kg/day in the first 3 months of life. The rate of weight gain declines from 3-12 months of age.

COW MILK PROTEIN–BASED FORMULAS

Intact cow milk–based formulas in the United States contain a protein concentration varying from 1.8 to 3 g/100 kcal or (1.45-1.6 g/dL), considerably higher than in mature breast milk (1.5 g/100 kcal). This increased concentration is designed to meet the needs of the youngest infants but leads to excess protein intake for older infants. In contrast, breastfed infants receive protein intakes that match their needs at various ages. The whey : casein ratio varies from 18 : 82 to 60 : 40; one manufacturer markets a formula that is 100% whey. The predominant whey protein is β-globulin in cow milk and α-lactalbumin in human milk. This and other differences between human milk and cow milk–based formulas result in different plasma amino acid profiles in infants on different feeding patterns, but a clinical significance of these differences has not been demonstrated.

Plant or a mixture of plant and animal oils are the source of fat in infant formulas; fat provides 40-50% of the energy in cow milk–based formulas. Fat blends are better absorbed than dairy fat and provide saturated, monounsaturated, and polyunsaturated fatty acids (PUFAs). All infant formulas are supplemented with long-chain PUFAs, docosahexaenoic acid (DHA), and arachidonic acid (ARA) at varying

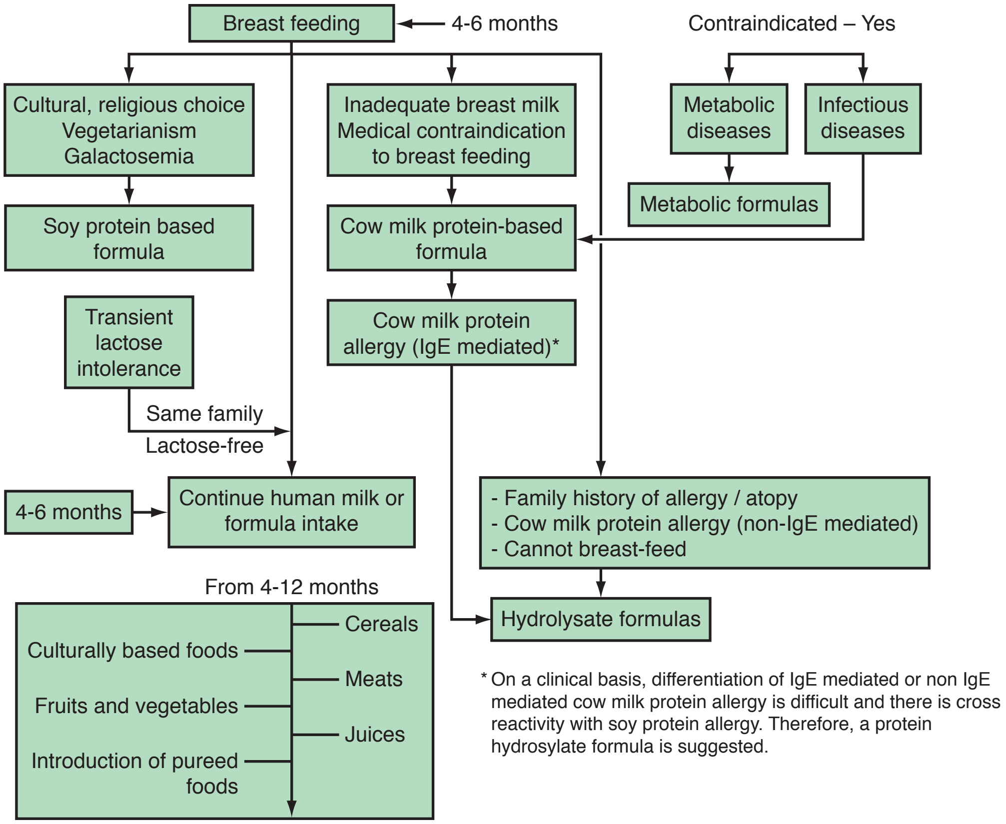

Figure 45-1 Feeding algorithm for term infants. *(From Gamble Y, Bunyapen C, Bhatia J: Feeding the term infant. In Berdanier CD, Dwyer J, Feldman EB, editors:* Handbook of nutrition and food, *Boca Raton, FL, 2008, CRC Press, pp 271–284,* Fig. 15-3.*)*

concentrations. ARA and DHA are found at varying concentrations in human milk and vary by geographic region and maternal diet. No studies in term infants have found a negative effect of DHA and ARA supplementation, and some studies have demonstrated positive effects on visual acuity and neurocognitive development. A critical review concluded that there are no consistent effects of long-chain PUFAs on visual acuity in term infants. A Cochrane review concluded that routine supplementation of milk formula with long chain PUFAs to improve the physical, neurodevelopmental, or visual outcomes of term infants cannot be recommended based on the current evidence. DHA and ARA are derived from single-cell microfungi and microalgae and are classified as generally recognized as safe for use in infant formulas at approved concentrations and ratios.

Lactose is the major carbohydrate in breast milk and in standard cow milk–based formulas for term infants. Formulas for term infants may also contain modified starch or other complex carbohydrates. Carbohydrates comprise 69-75g/L of cow milk–based formula.

SOY FORMULAS

Soy protein–based formulas on the market are all free of cow milk–based protein and lactose and use sucrose, corn syrup solids, and/or maltodextrin to provide 67 kcal/dL. They meet the vitamin, mineral, and electrolyte guidelines from the AAP and the FDA for feeding term infants. The protein is a soy isolate supplemented with L-methionine, L-carnitine, and taurine to provide a protein content of 2.45-2.8 g per 100 kcal or 1.7-1.8 g/dL.

The quantity of specific fats varies by manufacturer and is usually similar to the manufacturer's corresponding cow milk–based formula. The fat content is 5.0-5.5 g per 100 kcal or 3.4-3.6 g/dL. The oils used in both cow milk and soy formula include soy, palm, sunflower, olein, safflower, and coconut. DHA and ARA are also added.

In term infants, although soy protein–based formulas have been used to provide nutrition resulting in normal growth patterns, there are few indications for use in place of cow milk–based formula. Indications for soy formula include galactosemia and hereditary lactase deficiency, because soy–based formulas are lactose-free; and situations in which a vegetarian diet is preferred. Most healthy infants with acute gastroenteritis can be managed after rehydration with continued use of breast milk or cow–based formulas and do not require a lactose-free formula, such as soy-based formula. However, soy protein–based formulas may be indicated when documented secondary lactose intolerance occurs. Soy protein–based formulas have no advantage over cow protein–based formulas as a supplement for the breastfed infant, unless the infant has one of the indications noted previously and are not recommended for preterm infants. The routine use of soy protein–based formula has no proven value in the prevention or management of infantile colic, fussiness, or atopic disease. Infants with documented cow protein–induced enteropathy or enterocolitis often are also sensitive to soy protein and should not be given isolated soy protein–based formula. They should be provided formula derived from extensively hydrolyzed protein or synthetic amino acids. Soy formulas contain phytoestrogens, which have been shown to have physiologic activity in rodent models but a meta-analysis of the topic done by the Center for the Evaluation of Risks to Human Reproduction concluded that there is minimal concern for adverse developmental effects in infants fed soy formula.

PROTEIN HYDROLYSATE FORMULA

Protein hydrolysate formulas may be *partially hydrolyzed*, containing oligopeptides with a molecular weight of <5000 Da, or *extensively hydrolyzed*, containing peptides with a molecular weight <3000 Da. Partially hydrolyzed proteins have fat blends similar to cow milk–based formulas, and carbohydrates are supplied by corn maltodextrin or corn syrup solids. Because the protein is not extensively hydrolyzed, these formulas should not be fed to infants who are allergic to cow protein. In studies of formula fed infants who are at high risk of developing

atopic disease there is modest evidence that childhood atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolyzed formulas, compared with cow milk–based formula. Comparative studies of the various hydrolyzed formulas have also indicated that not all formulas have the same protective benefit. Extensively hydrolyzed formulas may be more effective than partially hydrolyzed in preventing atopic disease. Extensively hydrolyzed formulas are recommended for infants intolerant to cow milk or soy proteins. These formulas are lactose free and can include medium-chain triglycerides, making them useful in infants with gastrointestinal malabsorption as a consequence of cystic fibrosis, short gut syndrome, prolonged diarrhea, and hepatobiliary disease.

AMINO ACID FORMULAS

Amino acid formulas are peptide-free formulas that contain mixtures of essential and nonessential amino acids. They are designed for infants with dairy protein allergy who failed to thrive on extensively hydrolyzed protein formulas. The effectiveness of amino acid formulas to prevent atopic disease has not been studied.

Milk and Other Fluids

Neither breastfed nor formula-fed infants require additional water unless dictated by high environmental temperature. Vomiting and spitting up are common in infants. When weight gain and general well-being are noted, no change in formula is necessary.

Whole cow milk should not be introduced until 12 mo of age. In children between 12 and 24 mo of age for whom being overweight or obesity is a concern or who have a family history of obesity, dyslipidemia, or cardiovascular disease, the use of reduced-fat milk is appropriate. Otherwise whole milk is recommended until age 24 months changing to 2% at 24 months, and 1% at 3 yr of age for healthy children. Regardless of the type, all milk consumed should be pasteurized. Infants and young children are particularly susceptible to infections such as *E. coli*, *Campylobacter*, and *Salmonella* found in raw or unpasteurized milk. For cultural and other reasons, such as parental preference, goat milk is sometimes given in place of formula although this is not recommended. Goat milk has been shown to cause significant electrolyte disturbances and anemia because it has low folic acid concentrations.

COMPLEMENTARY FEEDING

The timely introduction of complementary foods (solid and liquid foods other than breast milk or formula, also called weaning foods or beikost) during infancy is necessary to enable transition from milk feedings to other table foods and is important for nutritional and developmental reasons (Table 45-6). The ability of exclusive breastfeeding to meet macronutrient and micronutrient requirements becomes limiting with increasing age of the infant. The recommendation for timing of complementary feed initiation is based on the benefits on neurodevelopment and prevention of future comorbidities (see Table 45-2) from exclusive breastfeeding for 6 months. The AAP, WHO, and European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition all recommend exclusive breastfeeding for the first 6 months. Similar data on the benefits of the exclusive use of formula for 6 months have not been published.

Some complementary foods are more nutritionally appropriate than others to complement breast milk or infant formula. The food consumption patterns of U.S. infants and toddlers demonstrate that nearly all infants ≤12 mo consumed some form of milk every day; infants >4 mo consumed more formula than human milk, and by 9-11 mo of age 20% consumed whole cow milk and 25% consumed nonfat or reduced-fat milk.

The most commonly fed complementary foods between 4 and 11 mo of age are infant cereals. Nearly 45% of infants between 9 and 11 mo of age consumed noninfant cereals. Infant eating patterns also vary, with up to 61% of infants 4-11 mo of age consuming no vegetables. Among those who consumed vegetables, French fries were the most common vegetables in toddlers. Positive changes in the last decade include increased duration of breastfeeding, delayed introduction of complementary foods, and decreased juice consumption. Continuing concerns included lack of fruits and vegetables, diets low in iron, essential fatty acids, fiber and whole grains, and high in saturated fat and sodium. Table 45-6 summarizes the AAP recommendations for initiating complementary foods.

The complementary foods should be varied to ensure adequate macro- and micronutrient intake. In addition to complementary foods introduced at 6 mo of age, continued breastfeeding or the use of infant formula for the entire 1st year of life should be encouraged. Overconsumption of energy-dense complementary foods can lead to excessive weight gain in infancy, resulting in an increased risk of obesity in childhood.

Table 45-6 Important Principles for Weaning
Begin at 6 mo of age
At the proper age, encourage a cup rather than a bottle
Introduce 1 food at a time
Energy density should exceed that of breast milk
Iron-containing foods (meat, iron-supplemented cereals) are required
Zinc intake should be encouraged with foods such as meat, dairy products, wheat, and rice
Phytate intake should be low to enhance mineral absorption
Breast milk should continue to 12 mo, formula or cow milk is then substituted
Give no more than 24 oz/day of cow milk
Fluids other than breast milk, formula, and water should be discouraged
Give no more than 4-6 oz/day of fruit juices; no sugar sweetened beverages

Adapted from American Academy of Pediatrics: Pediatric nutrition handbook, *ed 6, Elk Grove Village, IL, 2008, American Academy of Pediatrics.*

FEEDING TODDLERS AND PRESCHOOL-AGE CHILDREN

Toddlerhood is a period when eating behavior and healthful habits can be established and is often a confusing and anxiety-generating period. Growth after the 1st yr slows, motor activity increases, and appetite decreases. Birth weight triples during the 1st year of life and quadruples by 2 yr of age, reflecting this slowing in growth velocity. Eating behavior is erratic, and the child appears distracted as the child explores the environment. Children consume a limited variety of foods and often only "like" a particular food for a period of time and then reject the favored food. The use of growth charts to demonstrate adequate growth and to provide guidance about typical behavior and eating habits will help allay concerns of parents. Important goals of early childhood nutrition are to foster healthful eating habits and to offer foods that are developmentally appropriate.

Feeding Practices

The period starting after 6 mo until 15 mo is characterized by the acquisition of self-feeding skills because the infant can grasp finger foods, learn to use a spoon, and eat soft foods (Table 45-7). Around 12 mo of age, the child learns to drink from a cup and may still breastfeed or desire formula bottle feeding. Bottle weaning should begin around 12-15 mo and bedtime bottles should be discouraged because of the association with dental carries. Unless being used at mealtime, the sippy cup should only contain water to prevent caries. Sugar-sweetened beverages and 100% fruit juice should also be discouraged from being used in bottles in all infants at all times. Cups without a lid can be used for no more than 4-6 oz/day of 100% fruit juice for toddlers. In the 2nd year of life, self-feeding becomes a norm and provides the opportunity for the family to eat together with less stress. Self-feeding allows the child to limit the child's intake. Child feeding is an interactive process. Children receive cues regarding appropriate feeding behaviors from parents. Parents should ignore negative eating behaviors unless the behavior jeopardizes the health and safety of the child. In addition, parents should eat with their

Table 45-7 Feeding Skills Birth to 36 Months

AGE (mo)	FEEDING/ORAL SENSORIMOTOR
Birth to 4-6	Nipple feeding, breast, or bottle Hand on bottle during feeding (2-4 mo) Maintains semiflexed posture during feeding Promotion of infant–parent interaction
6-9 (transition feeding)	Feeding more in upright position Spoon feeding thin, pureed foods Both hands to hold bottle Finger feeding introduced Vertical munching of easily dissolvable solids Preference for parents to feed
9-12	Cup drinking Eats lumpy, mashed food Finger feeding for easily dissolvable solids Chewing includes rotary jaw action
12-18	Self-feeding; grasps spoon with whole hand Holds cup with 2 hands Drinking with 4-5 consecutive swallows Holding and tipping bottle
>18-24	Swallowing with lip closure Self-feeding predominates Chewing broad range food Up–down tongue movements precise
24-36	Circulatory jaw rotations Chewing with lips closed One-handed cup holding and open cup drinking with no spilling Using fingers to fill spoon Eating wide range of solid food Total self-feeding, using fork

Adapted from Arvedson JC. Swallowing and feeding in infants and young children. GI Motility online *(2006) doi:10.1038/gimo17.*

toddlers and not simply feed them in order to model positive eating behaviors.

The 2 yr old child should progress from small pieces of soft food to prepared table foods with precautions. At this stage, the child is not capable of completely chewing and swallowing foods, and particular attention should be paid to foods with a choking risk. Hard candies, nuts, and raw carrots should be avoided. Hot dogs, sausages, and grapes should be sliced length wise. Caregivers should always be vigilant and present during feeding, and the child should be placed in a high chair or booster seat. The AAP discourages eating in the presence of distractions such as television, tablets, mobile devices, and other screens, or eating in a car where an adult cannot adequately observe the child.

Young children have a natural preference for sweetened foods and beverages that begins in infancy. Reluctance to accept new foods is a common developmental phase. A new food should be offered multiple times (8-15) before being considered rejected by the child.

Toddlers need to eat 3 healthy meals and 2 snacks daily. Milk continues to be an important source of nutrition. Guidelines for vitamin D supplementation recommend a daily vitamin D intake of 600 IU/day for all infants beginning in the first few days of life, and for children and adolescents who are ingesting <1000 mL/day of vitamin D-fortified milk or formula. Toddlers and preschool children often fail to meet the recommended servings of fruits, vegetables, and fiber, whereas intakes of food with fat and added sugar are high. Giving vegetables at the beginning of the meal and increasing the portion size of vegetables served during meals can be an effective strategy for increasing vegetable consumption in preschool children.

Eating in the Daycare Setting

Many U.S. toddlers and preschool children attend daycare and receive meals and snacks in this setting. There is a wide variation in the quality

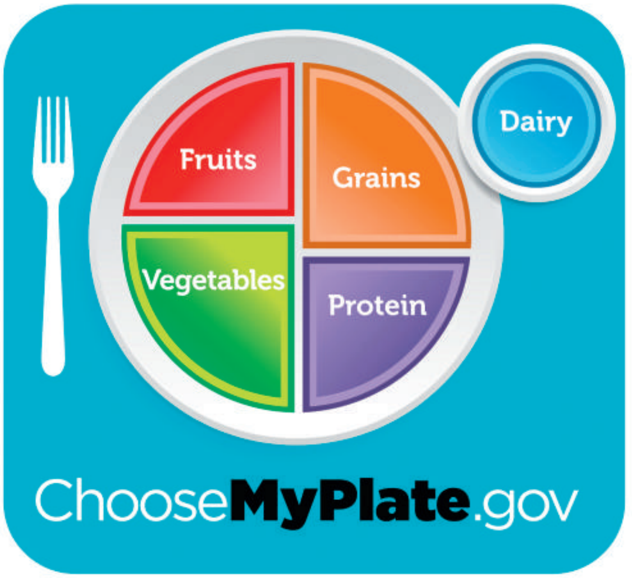

Figure 45-2 MyPlate food guide. *(From U.S. Department of Agriculture: mypyramid.gov. http://www.choosemyplate.gov/.)*

of the food offered and the level of supervision during meals. Parents are encouraged to assess the quality of the food served at daycare by asking questions, visiting the center, and taking part in parent committees. Free or reduced-price snacks and meals are provided in daycare centers for low- and medium-income communities through the U.S. Department of Agriculture (USDA) Child and Adult Care Food Program. Participating programs are required to provide meals and snacks that meet the meal regulations set by the USDA, guaranteeing a certain level of food quality. However, often for monetary reasons, many daycare centers still struggle to provide high-quality meals and snacks.

FEEDING SCHOOL-AGE CHILDREN AND ADOLESCENTS

MyPlate

The USDA MyPlate (www.choosemyplate.gov) is a basis for building an optimal diet for children and adults (Fig. 45-2). MyPlate is based on the *Dietary Guidelines for Americans, 2010* and replaces MyPyramid. MyPlate is aimed at the general public to provide a visual representation of the different food groups and their portion sizes. In addition to food group information, the website provides discretionary calorie information. It provides weight management strategies, and abilities to track calories and physical activity goals. A personalized eating plan based on these guidelines provide, on average over a few days, all the essential nutrients necessary for health and growth, while limiting nutrients associated with chronic disease development. MyPlate can also be used as an Internet interactive tool that allows customization of recommendations, based on age, sex, physical activity, and, for some populations, weight and height. Print material is also available for families without Internet access.

Recommendations based on MyPlate emphasize making half the plate vegetables and fruit, one half of the plate protein and grains, with protein having the smallest section. Protein replaces the meat category as many protein sources are not from animals. A separate dairy section is included. Physical activity recommendations to achieve a healthful energy balance are not visually displayed, but are provided on the website. MyPlate has removed foods that have low nutritional value, such as sweetened sugar beverages, and sweetened bakery products.

In the United States and in an increasing number of other countries, the vast majority of children and adolescents do not consume a diet that follows the recommendations of MyPlate. The intake of

discretionary calories is much higher than recommended, with frequent consumption of sweetened sugar beverages (soda, juice drinks, iced tea, sport drinks), snack foods, high-fat meat (bacon, sausage), and high-fat dairy products (cheese, ice cream). Intake of dark green and orange vegetables (as opposed to fried white potatoes), whole fruits, reduced-fat dairy products, and whole grain is typically lower than recommended. Furthermore, unhealthful eating habits such as larger-than-recommended portion sizes; food preparation that adds fat, sugar, or salt; skipping breakfast and/or lunch; grazing; or following fad diets is prevalent and associated with a poorer diet quality. MyPlate offers a helpful and customer-friendly tool to assist pediatricians counseling families on optimal eating plans for short- and long-term health.

Eating at Home

At home, much of what children and adolescents eat is under the control of their parents. Typically, parents shop for groceries and they control, to some extent, what food is available in the house. It has been demonstrated that modeling of healthful eating behavior by parents is a critical determinant of the food choices of children and adolescents. Counseling to improve diet should include guiding parents in using their influence to make healthier food choices available and attractive at home.

Regular family meals sitting at a table, as opposed to eating alone, in the living room, or watching television/screens, are associated with improved diet quality, perhaps because of increased opportunities for positive parenting during meals. Such an ideal situation is recommended but a challenge for many families who, with busy schedules and other stressors, are unable to provide such a setting. Another parenting challenge is to control the excess appetite of some children and adolescents. Encourage children to eat at a slower pace and to chew their food properly. Encourage conversation at the dinner table to prolong eating to 15 minutes. Offering vegetables while children are hungry at the beginning of the meal has been shown to increase vegetable consumption. Useful strategies, when the child is still hungry after a meal, include a 15- to 20-min pause (allow child to engage in another activity) before a second serving or offering foods that are insufficiently consumed, such as vegetables, whole grains, or fruits.

Eating at School

The National School Lunch Program and the School Breakfast Program provide low-cost meals to more than 5 billion children nationwide. Guidelines for meals are taken from the *Dietary Guidelines for Americans and the Dietary Reference, 2005*. Recommendations regarding the use of age-grade portion sizes, and amounts of vegetable and fruits, grains, and fats were included (Table 45-8). The training and equipment for school food service staff, school community engagement, parent education, and food industry involvement are among the necessary components. The year 2020 is the target year for achieving recommendations for sodium. In the meantime, while schools are working on implementing changes, parents should be encouraged to examine the weekly menu with their child and assist with their choices ahead of time. If children bring their lunch from home recommendations for what constitutes a healthy lunch should be provided by the Pediatrician. Parents can be directed to www.choosemyplate.org for healthy lunch ideas. In addition parties within classrooms should be limited to once a month.

Table 45-8 Revised National School Lunch Program and School Breakfast Program Recommendations

- Portion sizes of food are to be based on age-grade groups
- School lunches and breakfasts will have a minimum and maximum calorie level, maximum saturated fat content, and a maximum sodium content
- Foods must contain zero grams of trans fat per serving
- The inclusion of unsaturated vegetable oils is encouraged within calorie limits
- Vegetables and fruits are not interchangeable
- Vegetable offerings at lunch must include ½ cup equivalent of the following: dark green vegetables, bright orange vegetables, and legumes
- No more than half of fruit servings may be in the form of juice
- At least ½ of bread/grain offered must be whole grain
- Milk must be fat-free if flavored and either fat free or 1% if plain
- Students must select a fruit option at breakfast with their meal, and either a fruit or a vegetable at lunch for the meal to be reimbursable.

Adapted from IOM (Institute of Medicine): School meals: building blocks for healthy children. *Washington, DC, 2010, National Academies Press.*

Eating Out

The number of meals eaten outside the home or brought home from takeout restaurants has increased in all age groups of the U.S. population. The increased convenience of this meal pattern is undermined by the generally lower nutritional value of the meals, compared to home-cooked meals. Typically, meals consumed or purchased in fast-food or casual restaurants are of large portion size, are dense in calories, and contain large amounts of saturated fat, salt, and sugar, and low amounts of whole grains, fruits, and vegetables. Although still a problem currently, *trans* fat is slowing being phased out of most commercial restaurants. Although an increasing number of restaurants offer healthier alternatives, the vast majority of what is consumed at restaurants does not fit MyPlate.

With increasing age, an increasing number of meals and snacks are also consumed during peer social gatherings at friends' houses and parties. When a large part of a child's or adolescent's diet is consumed on these occasions, the diet quality can suffer, because food offerings are typically of low nutritional value. Parents and pediatricians need to guide teens in navigating these occasions while maintaining a healthful diet and enjoying meaningful social interactions. These occasions often are also opportunities for teens to consume alcohol; consequently, adult supervision is important.

NUTRITION ISSUES OF IMPORTANCE ACROSS PEDIATRIC AGES

Food Environment

Most families have some knowledge of nutrition and intend to provide their children with a healthful diet. The discrepancy between this fact and the actual quality of the diet consumed by U.S. children is often explained by challenges in the environment for families to make healthful food choices. Because the final food choice is made by individual children or their parents, interventions to improve diet have focused on individual knowledge and behavior changes, but have had limited success. A main determinant of food choice is taste, but other factors also influence these choices. One of the most useful conceptual frameworks for understanding the child's food environment in the context of obesity illustrates the variety of individual food and physical activity choices. Many of these determinants are not under the direct control of individual children or parents (Fig. 45-3). Understanding the context of food and lifestyle choices helps in understanding lack of changes or "poor compliance" and can decrease the frustration often experienced by the pediatricians who might "blame the victim" for behavior that is not entirely under their control.

Marketing and advertising of food to children is a particularly illustrative aspect of the food environment. Marketing includes strategies as diverse as shelf placements, association of cartoon characters with food products, coupons, and special offers or pricing, all of which influence food purchase choices. Television advertising is an important part of how children and adolescents hear about food, with an estimated 40,000 TV commercials per yr, seen by the average U.S. child, many of which are for food, as compared to the few hours of nutrition education they receive in school. Additional food advertisement increasingly occurs as brand placement in movies and TV shows, on websites, and even video games.

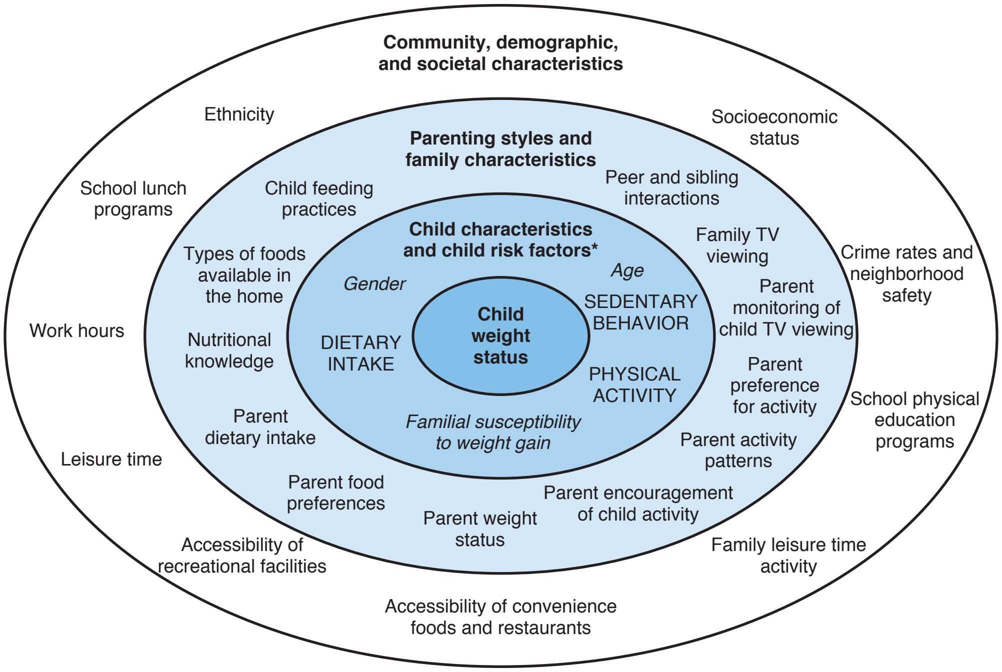

Figure 45-3 **A conceptual framework of the context of food and lifestyle choices.** Child risk factors (shown in uppercase lettering) refer to child behaviors associated with the development of overweight. Characteristics of the child (shown in italic lettering) interact with child risk factors and contextual factors to influence the development of overweight (i.e., moderator variables). *(From Davison KK, Birch LL: Childhood overweight: a contextual model and recommendations for future research,* Obes Rev *2:159–171, 2001. © 2001 The International Association for the Study of Obesity.)*

Using Food as Reward

It is a prevalent habit to use food as a reward or sometimes withdraw food as punishment. Most parents use this practice occasionally, and some use it almost systematically, starting at a young age. The practice is also commonly used in other settings where children spend time, such as daycare, school, or even athletic settings. Although it might be a good idea to limit some unhealthy but desirable food categories to special occasions, using food as a reward is problematic. Limiting access to some foods and making its access contingent on a particular accomplishment increases the desirability of that type of food. Conversely, encouraging the consumption of some foods renders them less desirable. Therefore, phrases such as "finish your vegetables, and you will get ice cream for dessert" can result in establishing unhealthy eating habits once the child has more autonomy in food choices. Parents should be counseled on such issues and encouraged to choose items other than food as reward, such as inexpensive toys or sporting equipment, family time, special family events, or collectable items. Similar types of behavior are also seen in schools and extra-curricular events. As opposed to rewarding or punishments of food (pizza/candy) daycare providers, teachers, and counselors should be encouraged to use alternative rewards such as minutes of free time, sitting in the teacher's chair, being the teacher helper, and homework-free nights.

Cultural Considerations in Nutrition and Feeding

Food choices, food preparation, eating patterns, and infant feeding practices all have very deep cultural roots. In fact, beliefs, attitudes, and practices surrounding food and eating are some of the most important components of cultural identity. Therefore, it is not surprising that in multicultural societies, great variability exists in the cultural characteristics of the diet. Even in a world where global marketing forces tend to reduce geographic differences in the types of food, or even brands, that are available, most families, especially during family meals at home, are still much influenced by their cultural background. Therefore, pediatricians should become familiar with the dietary characteristics of various cultures in their community, so that they can identify and address, in a nonjudgmental way and avoiding stereotypes, the potential nutritional issues related to the diet of their patients.

Vegetarianism

Vegetarianism is the practice of following a diet that excludes animal flesh foods, including beef, pork, poultry, fish, and shellfish. There are several variants of the diet, some of which also exclude eggs and/or some products produced from animal labor, such as dairy products and honey. There are many different variations in vegetarianism:

- Veganism: excludes all animal products. It may be part of a larger practice of abstaining from the use of animals products for any purpose.
- Ovovegetarianism: includes eggs but not dairy products.
- Lactovegetarianism: includes dairy products but excludes eggs.
- Lactoovovegetarianism: includes eggs and dairy products.
- Flexitarian: recent term referring to a vegetarian who will occasionally eat meat.

Another expression used for vegetarianism and veganism is "plant-based diets."

Other dietary practices commonly associated with vegetarianism include fruitarian diet (fruits, nuts, seeds, and other plant matter gathered without harm to the plant); Su vegetarian diet (a diet that excludes all animal products as well as onion, garlic, scallions, leeks, or shallots); a macrobiotic diet (whole grains and beans and, in some cases, fish); and raw vegan diet (fresh and uncooked fruits, nuts, seeds, and vegetables). The safety of these restrictive diets has not been studied in children. These diets can be very limited in macro- and micronutrients and are not recommended for children. Implementing vegetarian diets in teenage girls may be a sign of an eating disorder.

Vegetarianism is considered a healthful and viable diet; both the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) and the Dietitians of Canada have found that a properly planned and well-balanced vegetarian diet can satisfy the nutritional

goals for all stages of life. Compared with nonvegetarian diets, vegetarian diets have low levels of saturated fat, cholesterol, and animal protein, and relatively higher levels of complex carbohydrates, fiber, magnesium, potassium, folate, vitamins C and E, and phytochemicals. Vegetarians have a lower body mass index, cholesterol, and blood pressure, and are at decreased risk for cancer and ischemic heart disease.

Specific nutrients of concern in vegetarian diets include:

- **Iron:** Vegetarian diets have similar levels of iron compared to nonvegetarian diets, but the iron has lower bioavailability than iron from meat sources, and iron absorption may be inhibited by other dietary constituents, such as phytate (see Chapter 54). Iron stores are lower in vegetarians and vegans than in nonvegetarians; and iron deficiency is more common in vegetarian and vegan women and children. Foods rich in iron include iron-fortified cereals, black beans, cashews, kidney beans, lentils, oatmeal, raisins, black-eyed peas, soybeans, sunflower seeds, chickpeas, molasses, chocolate, and tempeh.
- **Vitamin B_{12}:** Plants are not a good source of B_{12} (see Chapter 49.7). Additional vitamin B_{12} can be obtained through dairy products and eggs; vegans need fortified foods or supplements. Breastfeeding by vegan mothers can place an infant at risk for vitamin B_{12} deficiency.
- **Fatty acids:** Vegetarians and vegans may be at risk for low levels of eicosapentaenoic acid (EPA) and DHA. The inclusion of sources of linolenic acid (precursor of EPA and DHA), such as walnuts, soy products, flaxseed, and canola oils, are recommended.
- **Calcium and vitamin D:** Without supplementation, vegan diets are low in calcium and vitamin D putting vegans at risk for impaired bone mineralization (see Chapter 51). *Vitamin D-OH levels should be monitored in vegans and supplemented for levels <30 dL.* Calcium sources include leafy greens (with low oxalate: broccoli, kale, or Chinese cabbage). Calcium and vitamin D are found in almond and soy milk, and fortified orange juice.
- **Zinc:** The bioavailability of zinc in plant sources tends to be low because of the presence of phytates and fiber that inhibit zinc absorption (see Chapter 54). Zinc is found in soy products, legumes, grains, cheese, and nuts.

Organic Foods

Parents may prefer organic foods to feed children secondary to concerns regarding chemical and hormonal treatment of animals and produce. The nutritional differences between organic and conventional foods may not be clinically relevant. Children consuming organic foods have lower or no detectable levels of pesticides in their urine compared to those consuming nonorganic foods. It remains unclear whether such a reduction in exposure to chemicals is clinically significant. Organic foods tend to have higher antioxidant levels and lower levels of cadmium. Similarly, despite concerns of parents, the amount of bovine growth hormone in conventional milk is thought to be neither significant nor biologically active in humans. Additionally, milk consumption from estrogen-treated cows does not result in endocrine disruptions in infants. However other chemicals in the environment, such as bisphenol-A (found in plastics), nitrates, endocrine disruptors, and phthalates, should be avoided. Organic certification of a food also suggests the food source is not from a genetically modified nutrient. Because the cost of these foods is generally higher than the cost of other foods, a prudent approach is to explain to families that the scientific basis for choosing organic foods is limited, but if it is their preference and they can afford the added cost, there is no reason not to eat organic foods.

Nutrition as Part of Complementary and Alternative Medicine, Functional Foods, Dietary Supplements, Vitamin Supplements, and Botanical and Herbal Products

The use of nutrition or nutritional supplements as complementary or alternative medicine is increasing, despite limited data on safety and efficacy, especially in children. Many parents assume that if a food or supplement is natural or organic, then there is no potential for risk and some that supplements are beneficial. However, adverse effects of some dietary supplements have been documented. It is difficult for pediatricians to compete against the aggressive marketing through multi-media sources of food supplements to families of healthy and chronically ill children. Additionally, pediatricians must compete against the word-of-mouth and advice from people without a scientific background and those with significant conflicts of interest. One reason to recommend caution to parents when it comes to dietary supplements, including botanical and herbal products, is that in the United States, unlike medications, these products are not evaluated for safety and efficacy before marketing and do not undergo the same level of quality control as medications. The potential for adverse effects or simply for inefficacy is therefore high (see Chapter 64).

Pediatricians are often asked by parents if their children need to receive a daily multivitamin. Unless the child follows a particular diet that may be poor in one or more nutrients for health, cultural, or religious reasons, or if the child has a chronic health condition that puts the child at risk for deficiency in 1 or more nutrients, multivitamins are not indicated. A diet that follows the guidelines of MyPlate contains sufficient nutrients to support healthy growth. Many children do not follow all the guidelines of MyPlate, and parents and pediatricians may be tempted to use multivitamin supplements just to make sure that nutrient deficiencies are avoided. Use of a daily multivitamin supplement can result in a false impression that the child's diet is complete and in decreased efforts to meet dietary recommendations with food rather than the intake of supplements (see Chapter 44) The average U.S. diet provides more than a sufficient amount of most nutrients, including most vitamins. Therefore, multivitamins should not be routinely recommended.

The Institute of Medicine recommends 600 IU of vitamin D per day in all children who drink less than 1,000 mL/day of vitamin D–fortified milk, representing the majority of U.S. children and adolescents. In some specific populations of children at risk for deficiency, supplements of vitamin B_{12}, iron, fat-soluble vitamins, or zinc may be considered.

Food Safety

Constantly keeping food safety issues in mind is an important aspect of feeding infants, children, and adolescents. In addition to choking hazards and food allergies, pediatricians and parents should be aware of food safety issues related to infectious agents and environmental contaminants. Food poisoning with bacteria, viruses, or their toxins are most common with raw or undercooked food, such as oysters, beef, and eggs, or cooked foods that have not been handled or stored properly. The specific bacteria and viruses involved in food poisoning are described in Chapter 340. Many chemical contaminants, such as heavy metals, pesticides, and organic compounds, are present in various foods, usually in small amounts. Because of concerns regarding their child's neurologic development and cancer risk, many questions arise from parents, especially after media coverage of isolated incidents. A recurring debate is the balance between the benefits of seafood for the growing brain and cardiovascular health and the risk of mercury contamination from consuming large predatory fish species. Pediatricians need to become familiar with reliable sources of information, such as the websites of the U.S. Environmental Protection Agency, the FDA, or the CDC. The Food Safety Modernization Act provides the FDA with authority to have stricter control over food production and distribution. The FDA can require that manufacturers develop food safety plans. A good source of information for patients and parents can be found at www.foodsafety.gov.

Nutritional Programming

Emerging epidemiologic evidence suggests that early nutrition starting during fetal development can have long-term impact on growth, and adult health. It is well established that undernutrition in early life can exert a long-term impact in terms of reduced adult height and academic achievements; other data, however, suggest that intrauterine growth restriction is associated with obesity and other adult cardiovascular risk factors. Rapid weight gain in infancy, either following intrauterine growth restriction or a period of malnutrition, is associated

with an increased risk for later obesity. The process that explains these changes has been termed "programming."

Preventive Nutrition Counseling in Pediatric Primary Care

An important part of the primary care well-child visit focuses on nutrition and growth because most families turn to pediatricians for guidance on child nutrition. Preventive nutrition is one of the cornerstones of preventive pediatrics and a critical aspect of anticipatory guidance. The first steps of nutrition counseling are nutritional status assessments, primarily done through growth monitoring and dietary intake assessment. Although dietary assessment is somewhat simple in infants who have a relatively monotonous diet, it is more challenging at older ages. The goals of dietary assessment in the primary care setting need to remain modest and include an idea of the eating patterns (time, location, and environment) and usual diet by asking the parent to describe the child's dietary intake on a typical day or in the last 24 hr. Pediatricians should encourage regularly scheduled meals and 1 or 2 snacks. Alternatively, a basic assessment of the child's consumption of vegetables, fruits, whole grains, low or nonfat dairy products, 100% fruit juice and sugar-sweetened beverages should be assessed. For more ambitious goals of dietary assessment, referral to a registered dietician with pediatric experience is recommended.

Once some understanding of the child's usual diet has been acquired, existing or anticipated nutritional problems should be addressed, such as diet quality, dietary habits, or portion size. For a few nutritional problems, a lack of knowledge can be addressed with nutrition education, but most pediatric preventive nutritional issues, such as overeating or poor food choices, are not the result of lack of parents' knowledge. Therefore, nutrition education alone is insufficient in these situations, and pediatricians need to acquire training in behavior-modification techniques or refer to specialists to assist their patients in engaging in healthy feeding and eating behaviors. The physical, cultural, and family environments in which the child lives should be kept in mind at all times, so that nutrition counseling is relevant and changes are feasible.

One important aspect of nutrition counseling is providing families with sources of additional information and behavioral change tools. Although some handouts are available from government agencies, the AAP, and other professional organizations for families without Internet access, an increasing number of families rely on the Internet to find nutrition information. Therefore, pediatricians need to become familiar with commonly used websites so that they can point families to reliable and unbiased sources of information. Perhaps the most useful websites for reliable and unbiased nutrition information for children are the USDA MyPlate website, the sites of the CDC, FDA, National Institutes of Health, and Institute of Medicine Food and Nutrition Board for government sources and the AAP, American Heart Association, and the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) for professional organization resources. Pediatricians should also be aware of sites that provide biased or even dangerous information, so that they can warn families accordingly. Examples include dieting sites, sites that openly promote dietary supplements or other food products, and the sites of "nonprofit" organizations that are mainly sponsored by food companies or that have other social or political agendas.

Food Assistance Programs in the USA

Several programs exist in the United States to ensure sufficient and high-quality nutrition for children of families who cannot always afford optimal nutrition. One of the most popular federal programs is the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). This program provides nutrition supplements to a large proportion of pregnant women, postpartum women, and children up to their 5th birthday. One of its strengths is that in order to qualify, families need to regularly visit a WIC nutritionist, who can be a useful resource for nutritional counseling. Other popular programs include school lunches, breakfasts, and after-school meals, as well as daycare and summer nutrition programs. Lower-income families are also eligible for the Supplemental Nutrition Assistance Program, formerly known as the Food Stamp Program. This program provides funds directly to families to purchase various food items in regular food stores.

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Chapter 46

Nutrition, Food Security, and Health

Ann Ashworth

MALNUTRITION AS THE INTERSECTION OF FOOD INSECURITY AND HEALTH INSECURITY

Undernutrition is usually an outcome of 3 factors, often in combination: household food supply, child-caring practices, and access to health and water/sanitation services. In famine and emergency settings, food shortage is the foremost factor, but in many countries with widespread undernutrition, food production or access to food might not be the most limiting factor. More important causes might be repeated childhood infections, especially diarrheal diseases linked with an unsafe environment and lack of exclusive breastfeeding, or inadequate complementary feeding practices, or the lack of time families have available for appropriate infant or maternal care. Figure 46-1 shows some of the many causal factors on the pathway to undernutrition and how they extend from household and community levels to national/international levels. Inequitable distribution of resources because of political, economic, and agricultural policies often denies families their right to adequate land, water, food, healthcare, education, and a safe environment, all of which can influence nutritional status.

Families with few economic resources who know how to care for their children and are enabled to do so can often use available food and health services to produce well-nourished children. If food resources and health services are not available in a community, or not utilized, or not accessible to some families, children might become undernourished. Undernutrition is not confined to low-income countries. It has been noted in chronically ill patients in neonatal and pediatric intensive care units in high-income countries and among patients with burns, HIV, tuberculosis, cystic fibrosis, chronic diarrhea syndromes, malignancies, bone marrow transplantation, and inborn errors of metabolism. Severe malnutrition has been reported in affluent communities in infants whose families believe in fad diets, and in infants with food allergies fed nutritionally inadequate foods such as rice "milk," which has a very low protein and micronutrient content (Fig. 46-2).

FOOD SECURITY

Food security exists "when all people, at all times, have access to sufficient, safe, nutritious food to maintain a healthy and active life." Four main dimensions of food security can be identified: **availability**, **access**, **utilization,** and **stability**. *Availability* refers to the supply of food (reflecting the level of food production, food stocks, and net trade). *Access* is at the household level, reflecting purchasing power, household food production, and food/cash transfers received through social safety net programs. The *utilization* dimension recognizes that even when a household has access to food it is not necessarily shared equitably within a household. *Stability* refers to being food secure at all times: Examples of situations that affect stability are the "lean seasons" before a harvest, natural disasters, political unrest, and rising food prices. To be food secure, all 4 dimensions must be met simultaneously.

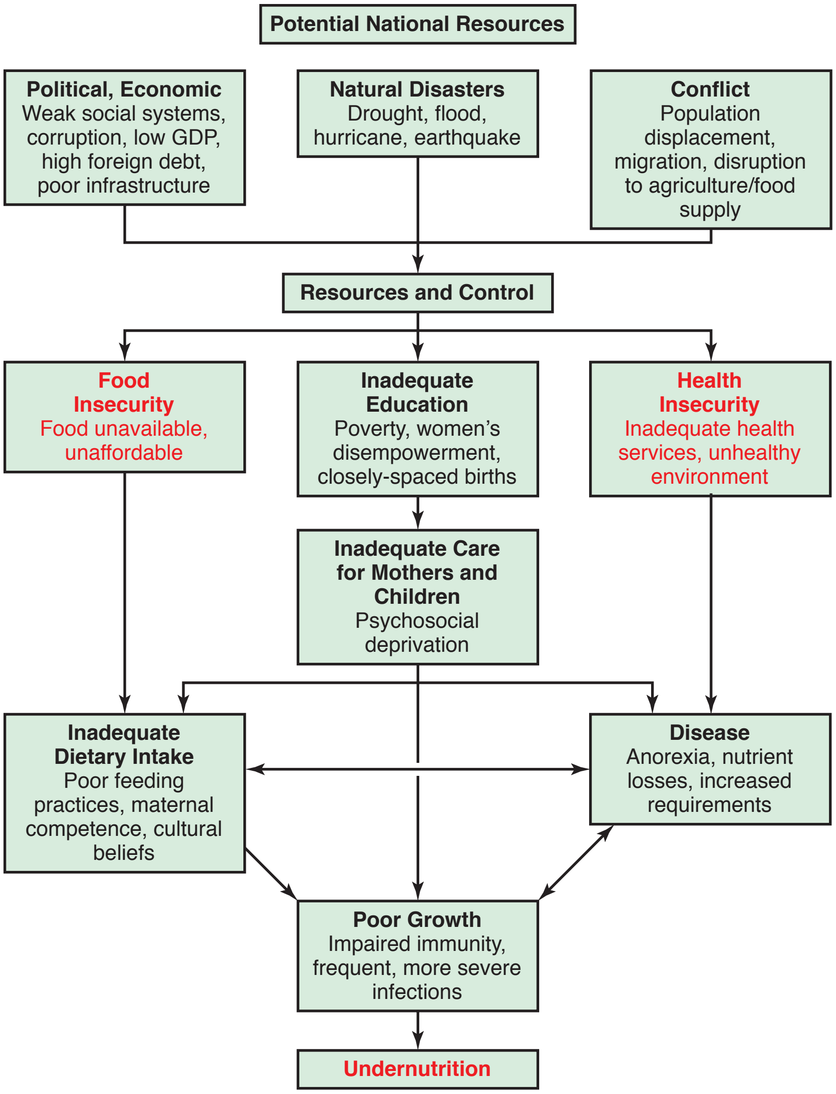

Figure 46-1 Basic, underlying, and immediate causes of undernutrition.

Measuring Food Insecurity

The most commonly used measurement of food insecurity is "undernourishment" (chronic hunger), and is the proportion of the population who are unable to meet daily energy requirements for light activities. It is an estimate calculated by the Food and Agriculture Organization (FAO) based on country-level Food Balance Sheets. It does not take nutrient adequacy into account, but has the advantage of being available for almost all countries annually (although with a time-lag) and assists in monitoring global trends. In addition, FAO measures food access by asking individuals about their experiences over the last 12 mo, such as whether they ran out of food, or skipped meals. The responses are graded from mild to severe food insecurity.

In 2011-2013, FAO estimated that about 842 million people, or 12% of the world's population, were undernourished, 98% of whom were in developing countries. The majority are rural poor subsisting on small plots of land or hired as laborers, and urban poor who lack the means to grow or buy food. Alongside the 0.84 billion people who are underfed, there are 1.5 billion who are overfed reflecting global inequalities, and the "double burden of malnutrition" in low- and middle-income countries.

Nutrition, Food Security, and Poverty

Household food security tracks income closely. With rising incomes, very poor households first increase their dietary energy intake to avert hunger. If incomes rise further there is a shift to more expensive staple foods and then to a more varied diet with a greater proportion of energy from animal sources, fruits and vegetables, fats and sugars, and less from cereals, roots and tubers. National economic growth tends to be accompanied by reductions in stunting, but economic growth can pass by the poor if they work in unaffected sectors, or are unable to take advantage of new opportunities because of lack of education, access to credit, or transportation, or if governments do not channel resources accruing from economic growth to healthcare, education, social protection, and other public services and infrastructure. There is good evidence that economic growth reduces poverty, but does not necessarily reduce undernutrition.

Food Security and Nutrition Targets

World leaders collectively agreed to 8 Millennium Development Goals (MDGs) in 2000. MDG 1 aimed to eradicate extreme poverty and hunger. The target to halve the proportion of people whose income is less than $1 per day was reached at the global level 5 yr ahead of the 2015 target. This was greatly helped by the progress made by China and India. Sub-Saharan Africa is unlikely to reach the target. The reductions in hunger are broadly consistent with those of poverty reduction, and rates of undernourishment in developing regions fell from 23.2% in 1990 to 14.3% in 2011-2013. Sub-Saharan Africa is the region least likely to achieve the target of halving undernourishment by 2015. The prevalence of underweight children (another MDG indicator of "hunger") fell from 29% in 1990 to 17% in 2012 for the

Figure 46-2 A 14 mo old girl with a "flaky paint" dermatitis. *(From Katz KA, Mahlberg MH, Honig PJ, et al: Rice nightmare: kwashiorkor in 2 Philadelphia-area infants fed Rice Dream beverage,* J Am Acad Dermatol *52(5 Suppl 1):S69–S72, 2005.)*

developing regions combined, but the rate of decline is thought insufficient to reach the global target by 2015. Rural children are almost twice as likely to be underweight as urban children, and the poorest quintile is almost 3 times as likely to be underweight as the richest quintile.

Sustainable Development Goals are expected to follow on from the MDGs. In addition, in 2012 the World Health Assembly agreed to 6 global nutrition targets to be reached by 2025, measured against a 2010 baseline, and the United Nations Secretary-General launched the Zero Hunger Challenge with 5 objectives that "would boost economic growth, reduce poverty and safeguard the environment" and "would foster peace and stability" (Table 46-1).

Table 46-1 Global Food Security and Nutrition Targets

ZERO HUNGER CHALLENGE OBJECTIVES	WORLD HEALTH ASSEMBLY GLOBAL NUTRITION TARGETS FOR 2025
• Access to an adequate and stable food supply for all • Elimination of stunting in children <2 yr and no malnutrition in pregnancy and early childhood • Sustainable food systems • Doubling of smallholder productivity and income, particularly for women • No loss or waste of food, and responsible consumption	• A 40% reduction in the number of stunted children <5 yr • A 50% reduction in anemia in women of reproductive age • A 30% reduction in low birthweight • No increase in childhood overweightness • Increase exclusive breastfeeding rates to at least 50% in the first 6 months • Reduce and maintain childhood wasting to less than 5%

Future Food Security

Between now and 2050 the world's population is expected to rise to around 9 billion, and an increase in food supply of 70-100% will be needed to feed this larger, more urban, and more affluent populace. Over this same period, the world's food supply is expected to diminish unless action is taken. Accelerating the decline in fertility rates and reducing overconsumption are basic, but difficult, actions to bridge the gap between increasing demand and diminishing supply. Equally challenging actions include limiting climate disruption, increasing the efficiency of food production, reducing waste, and reducing the demand for meat and dairy foods.

- *Limit climate disruption:* Drought, floods, and other extreme weather events are becoming more prevalent and destroy crops and livestock, often on a huge scale. Rising sea levels will lead to loss of productive land through inundation and salinization. Acidification of oceans will reduce marine harvests. Curbing greenhouse gas emissions is essential to minimize climate disruption, hence the aim to (a) cut fossil fuel use by at least half of present levels by 2050 so as to reduce CO_2 emissions and (b) change livestock husbandry and agronomic practices to reduce methane and nitrous oxide emissions.
- *Increase efficiency of food production*: Expanding the area of agricultural land to any large extent (e.g., by deforestation) is not a sustainable option because of adverse consequences on ecosystems and biodiversity, although some expansion of food production could be achieved by switching good quality land away from first-generation biofuels. For example, 40% of the U.S. corn harvest in 2010 went to biofuels. Efforts to increase the intensity of production need to be environmentally sustainable. These include optimizing yields by soil and water conservation, removal of technical and financial constraints faced by farmers, and breeding resource-efficient crops and livestock that are also climate-resilient and pest/disease-resistant.
- *Reduce waste*: Some 30-40% of food is wasted, either between harvesting and the market, or during retail, at home, and in the food service industry. Better transport and storage facilities in developing countries, less stringent sell-by dates, lower cosmetic standards for fruits and vegetables, and ending supersized portions would help reduce waste.
- *Change diets:* As wealth increases, so does the demand for processed foods, meat, dairy products, and fish. About one-third of global cereal production is fed to animals, so reducing consumption of meat from grain-fed livestock and increasing the proportion derived from the most efficient sources (pigs and poultry) would allow more people to be fed from the same amount of land.

UNDERNUTRITION

The greatest risk of undernutrition (underweight, stunting, wasting, and micronutrient deficiencies) occurs in the first 1000 days, from conception to 24 mo of age, and this early damage to growth and development can have adverse consequences in later life on health, intellectual ability, school achievement, work productivity, and earnings. Governments and agencies are therefore advised to focus interventions on this critical window of opportunity. For folate deficiency, which increases the risk of birth defects, this particular window of opportunity is before conception.

Measurement of Undernutrition

The term ***malnutrition*** encompasses both ends of the nutrition spectrum, from undernutrition to overweight. Many poor nutritional outcomes begin *in utero* and are manifest as low birthweight (LBW, <2,500 g). Preterm delivery and fetal growth restriction are the 2 main

Table 46-2 Classification of Undernutrition

CLASSIFICATION	INDEX	GRADING
Gomez (underweight)	90-75% of median weight-for-age	Grade 1 (mild)
	75-60%	Grade 2 (moderate)
	<60%	Grade 3 (severe)
Waterlow (wasting)	90-80% of median weight-for-height	Mild
	<70%	Severe
Waterlow (stunting)	95-90% of median height-for-age	Mild
	90-85%	Moderate
	<85%	Severe
WHO (wasting)	<–2 to >–3 SD weight-for-height	Moderate
	<–3	Severe
WHO (stunting)	<–2 to >–3 SD height-for-age	Moderate
	<–3	Severe
WHO (wasting) (for age group 6-59 mo)	115-125 mm mid-upper arm circumference	Moderate
	<115 mm	Severe

Figure 46-3 Measuring mid-upper arm circumference. *(Image courtesy of Nyani Quarmyne/Panos Pictures.)*

causes of LBW, with prematurity relatively more common in richer countries and fetal growth restriction relatively more common in poorer countries.

Nutritional status is often assessed in terms of anthropometry (Table 46-2). International standards of normal child growth under optimum conditions from birth to 5 yr have been established by the World Health Organization (WHO). To compile the standards, longitudinal data from birth to 24 mo of healthy, breastfed, term infants were combined with cross-sectional measurements of children ages 18-71 mo. The standards allow normalization of anthropometric measures in terms of z scores (standard deviation scores). A z-score is the child's height (weight) minus the median height (weight) for the age and sex of the child divided by the relevant standard deviation. The standards are applicable to all children everywhere, having been derived from a large multicountry study reflecting diverse ethnic backgrounds and cultural settings.

Height-for-age (or length-for-age for children <2 yr) is a measure of linear growth, and a deficit represents the cumulative impact of adverse events, usually in the first 1,000 days from conception, that result in *stunting,* or chronic malnutrition. A low height-for-age typically reflects socioeconomic disadvantage. A low **weight-for-height**, or *wasting*, usually indicates acute malnutrition. Conversely, a high weight-for-height indicates *overweight*. **Weight-for-age** is the most commonly used index of nutritional status, although a low value has limited clinical significance as it does not differentiate between wasting and stunting. Weight-for-age has the advantage of being somewhat easier to measure than indices that require height measurements. In humanitarian emergencies and some field settings, **mid-upper arm circumference** is used for screening wasted children (Fig. 46-3).

Body mass index (BMI) is calculated by dividing weight in kilograms by the square of height in meters. For children, BMI is age- and gender-specific. BMI-for-age can be used from birth to 20 yr and is a screening tool for thinness (<–2 SD), overweight (between +1 SD and +2 SD), and obesity (>+2 SD). To diagnose obesity, additional measures of adiposity are desirable as a high BMI can result from high muscularity, and not only from excess subcutaneous fat.

Micronutrient deficiencies are another dimension of undernutrition. Those of particular public health significance are vitamin A, iodine, iron, and zinc.

Vitamin A deficiency is caused by a low intake of retinol (in animal foods) or its carotenoid precursors, mainly beta-carotene (in orange-colored fruits and vegetables and dark green leaves) (see Chapter 48). The prevalence of clinical deficiency is assessed from symptoms and signs of xerophthalmia (principally night blindness and Bitot spots). Subclinical deficiency is defined as serum retinol concentration <0.70 µmol/L. Vitamin A deficiency is the leading cause of preventable blindness in children. It is also associated with a higher morbidity and mortality among young children.

Iodine deficiency is the main cause of preventable mental impairment (see Chapter 54). An enlarged thyroid (goiter) is a sign of deficiency. Severe deficiency in pregnancy causes fetal loss and permanent damage to the brain and central nervous system in surviving offspring (cretinism). It can be prevented by iodine supplementation before conception or during the first trimester of pregnancy. Postnatal iodine deficiency is associated with impaired mental function and growth retardation. The median urinary iodine concentration in children ages 6-12 yr is used to assess the prevalence of deficiency in the general population, and a median of <100 µg/L indicates insufficient iodine intake.

Iron-deficiency anemia is common in childhood either from low iron intakes or poor absorption, or as a result of illness or parasite infestation (see Chapter 54). Women also have relatively high rates of anemia as a result of menstrual blood loss, pregnancy, low iron intakes, poor absorption, and illness. Hemoglobin cutoffs to define anemia are 110 g/L for children 6-59 mo, 115 g/L for children 5-11 yr, and 120 g/L for children 12-14 yr. Cutoffs to define anemia for nonpregnant women are 120 g/L, 110 g/L for pregnant women, and 130 g/L for men.

Zinc deficiency increases the risk of morbidity and mortality from diarrhea, pneumonia, and possibly other infectious diseases (see Chapter 54). Zinc deficiency also has an adverse effect on linear growth. Deficiency at the population level is assessed from dietary zinc intakes.

Prevalence of Undernutrition

It is estimated that approximately 15% of births in low- and middle-income countries in 2010 were LBW. Rates of LBW are highest (26%) in southern Asia, and are twice those of sub-Saharan Africa. India accounts for approximately 40% of the world's low-weight births. Globally, in 2011 16% of children <5 yr of age were *underweight* (weight-for-age <–2 SD). The global prevalence of *stunting* (height-for-age <–2 SD) has declined from an estimated 40% to 26% over the last 20 yr, with the greatest reductions having taken place in Asia. Stunting prevalence is now highest in the African region (36% prevalence). *Wasting* (weight-for-height <–2 SD) affects 8% of children <5 yr, the prevalence having changed little over the past 2 decades. These figures represent 101 million underweight children, 165 million stunted children, and 52 million wasted children.

Asia carries 69% of the global burden of underweight children, 58% of the global burden of stunted children, and 70% of the global burden

of wasted children because of the combination of large population size and high prevalence. Africa carries most of the remaining global burden. For children <5 yr, the global prevalence is estimated to be 33% for *vitamin A deficiency*, 29% for *iodine deficiency*, 17% for *zinc deficiency*, and 18% for *iron-deficiency anemia*. Prevalence of micronutrient deficiencies tends to be highest in Africa. For pregnant women, the estimated prevalence of vitamin A deficiency is 15% and for iron-deficiency anemia 19%.

Rates of clinical deficiency of vitamin A in children <5 yr have been declining, probably as a result of high-dose vitamin A supplementation programs and measles vaccination (as measles leads to sizeable urinary loss of vitamin A), but subclinical deficiency remains widespread (more than 90 million children). Large-scale availability of iodized salt has reduced rates of iodine deficiency substantially, and iodized salt now reaches an estimated 70% of households. In contrast, progress in reducing rates of iron-deficiency anemia is slow, and rates remain largely static.

Consequences of Undernutrition

The most profound consequence of undernutrition is premature death (Table 46-3). Fetal growth restriction together with suboptimal breastfeeding in the first month of life contribute to 19% of all deaths in children <5 yr (1.3 million deaths/yr). When the effects of stunting, wasting and deficiencies of vitamin A and zinc are also considered, these 6 items jointly contribute to 45% of global child deaths (3.1 million deaths/yr), and many more are disabled or stunted for life. Anemia contributes to over one-quarter of maternal deaths.

The risk of child death from infectious diseases increases even with mild undernutrition, and as the severity of undernutrition increases, the risk increases exponentially (Table 46-4). Undernutrition impairs immune function and other host defenses, consequently childhood infections are more severe and longer lasting in undernourished children and more likely to be fatal compared with the same illnesses in well-nourished children. Also, infections can adversely affect nutritional status, and young children can quickly enter a cycle of repeated infections and ever-worsening malnutrition. Even for the survivors, physical and cognitive damage as a result of undernutrition can impact their future health and economic well-being. For girls, the cycle of undernutrition is passed on to the next generation when undernourished women give birth to LBW babies.

Fetal growth restriction and early childhood undernutrition also have consequences for adult chronic illness. LBW is associated with an increased risk of hypertension, stroke, and type 2 diabetes in adults. The increased risk is thought to reflect "fetal programming," a process by which fetal undernutrition leads to permanent changes in the structure and metabolism of organs and systems that manifest as disease in later life. The risk is exacerbated by low weight gain during the first 2 yr of life. The increased risk of adult chronic disease emanating from undernutrition in early life is a particular challenge to low-income countries with rapid economic growth.

Stunting before the age of 3 yr is associated with poorer motor and cognitive development and altered behavior in later years. The effect is

Table 46-3 Global Deaths in Children <5 yr Attributed to Nutritional Conditions

CONDITION	ATTRIBUTABLE DEATHS	% OF TOTAL DEATHS <5 YR
(a) Fetal growth restriction (<1 mo)	817,000	11.8
(b) Stunting (1-59 mo)	1,017,000	14.7
(c) Wasting (1-59 mo)	875,000	12.6
(d) Zinc deficiency (12-59 mo)	116,000	1.7
(e) Vitamin A deficiency (6-59 mo)	157,000	2.3
(f) Suboptimal breastfeeding (0-23 mo)	804,000	11.6
Joint effects of (a) + (f)	1,348,000	19.4
Joint effects of all 6 factors	3,097,000	44.7

From Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low- and middle-income countries, Lancet *382:427–451, 2013.*

Table 46-4 Hazard Ratios for All-Cause and Cause-Specific Deaths Associated with Stunting, Wasting, and Underweight in Children <5 yr

	DEATHS				
SD Score	**All**	**Pneumonia**	**Diarrhea**	**Measles**	**Other Infections**
Height/length-for-age					
<–3	5.5	6.4	6.3	6.0	3.0
–3 to <–2	2.3	2.2	2.4	2.8	1.9
–2 to <–1	1.5	1.6	1.7	1.3	0.9
≥–1	1.0	1.0	1.0	1.0	1.0
Weight-for-length					
<–3	11.6	9.7	12.3	9.6	11.2
–3 to <–2	3.4	4.7	3.4	2.6	2.7
–2 to <–1	1.6	1.9	1.6	1.0	1.7
≥–1	1.0	1.0	1.0	1.0	1.0
Weight-for-age					
<–3	9.4	10.1	11.6	7.7	8.3
–3 to <–2	2.6	3.1	2.9	3.1	1.6
–2 to <–1	1.5	1.9	1.7	1.0	1.5
≥–1	1.0	1.0	1.0	1.0	1.0

From Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low- and middle-income countries, Lancet *382:427–451, 2013.*

6-13 DQ (developmental quotient) points. Iodine and iron deficiencies also lead to loss of cognitive potential. Indications are that children living in areas of chronic iodine deficiency have an average reduction in IQ of 12-13.5 points compared with children in iodine-sufficient areas. Iron deficiency has a detrimental effect on the motor development of children <4 yr and on cognition of school-age children. The estimated deficit is 1.73 IQ points for each 10 g/L decrease in hemoglobin concentration.

Undernutrition can have substantial economic consequences for survivors and their families. The consequences can be quantified in 5 categories: increased costs of healthcare, either neonatal care for LBW babies or treatment of illness for infants and young children; productivity losses (and hence reduced earnings) associated with smaller stature and muscle mass; productivity losses from reduced cognitive ability and poorer school performance; increased costs of chronic diseases associated with fetal and early child malnutrition; and consequences of maternal undernutrition on future generations. The impact of nutrition on earnings appears to be independent of the effects of childhood deprivation.

Key Interventions

Interventions to address child undernutrition can be divided into those that address immediate causes (*nutrition-specific interventions*) and those that address underlying causes (*nutrition-sensitive interventions*) (Table 46-5). In the short-term, nutrition-specific interventions (e.g., salt iodization) can have substantial impacts even in the absence of economic growth, and micronutrient interventions (supplementation and fortification) are consistently ranked by economists of the Copenhagen Consensus Center as the most cost-effective investment. Increased attention is being given to nutrition-sensitive interventions as the best means of sustainably eliminating malnutrition, and to multisectoral policies that harness the synergism between the 2 types of intervention. Cross-sectoral linkages between agriculture, nutrition, and health are 1 example.

To reduce the adverse consequences of undernutrition on mortality, morbidity, and cognitive development, interventions must encompass both fetal and postnatal periods. Preventing LBW is essential, with emphasis on prevention of low maternal BMI and anemia, and in the longer term, prevention of low maternal stature. Other measures include smoking cessation, birth spacing, delaying pregnancy until after 18 yr of age, and intermittent preventive treatment of malaria. In the postnatal period, promotion and support of exclusive breastfeeding is a high priority. Although the Baby Friendly Hospital Initiative has a marked benefit on rates of exclusive breastfeeding in hospital, postnatal counseling from community workers or volunteers is needed to facilitate continuation of exclusive breastfeeding at home for 6 mo. Most studies show a lower risk of HIV transmission with exclusive breastfeeding than with mixed breastfeeding. The risk of transmission of HIV by breastfeeding is approximately 5-20% depending on duration, but can be reduced to <2% with antiretroviral drugs. Even without antiretroviral drugs, exclusively breastfed children of HIV-infected mothers in low-income countries have lower mortality than non-breastfed children, as the latter are at increased risk of death from diarrhea and pneumonia.

Interventions to improve infant feeding must be designed for the local setting and thus require careful formative research during their development. Messages should be few in number, feasible, and culturally appropriate. For complementary feeding, nutrient-rich, energy-dense mixtures of foods, and responsive feeding, are often emphasized. Where adequate complementary feeding is difficult to achieve and subclinical deficiencies are common, high-dose vitamin A supplementation every 6 mo in children <5 yr of age can reduce child mortality by 5-15% and zinc supplementation can reduce 1-4 yr mortality by 18%, diarrhea incidence by 13%, and pneumonia incidence by 19%. Monitoring of child growth provides an early alert to a nutrition or health problem but is only worthwhile if accompanied by good counseling and growth promotion activities. The impact of growth monitoring and promotion will be related to coverage, intensity of contact, health worker performance and communications skills, adequacy of resources, and the motivation and ability of families to follow agreed actions.

Table 46-5 Examples of Nutrition-Specific and Nutrition-Sensitive Interventions

NUTRITION-SPECIFIC INTERVENTIONS	NUTRITION-SENSITIVE INTERVENTIONS
• Promotion and support for exclusive breastfeeding for 6 mo, and continued breastfeeding for at least 2 yr • Promotion of adequate, timely, and safe complementary feeding from 6 mo • Increased micronutrient intake through dietary diversity • Micronutrient supplements for pregnant women (iron/folate) and young children (vitamin A, iron, zinc) in deficient areas • Zinc supplements to children during and after diarrhea (10-20 mg/day for 2 wk) • Prevention and treatment of severe acute malnutrition • Crop biofortification, food fortification, salt iodization • Reduced heavy physical activity in pregnancy	• Increased access to affordable, nutritious food; smallholder agriculture; credit and microfinance • Postharvest food processing and preservation • Vaccination against neonatal and childhood illness; access to healthcare • Improved water/sanitation and hygiene (e.g., handwashing with soap) • Education; women's empowerment; gender equality • Social protection (e.g., cash transfers) • Malaria prevention (vector control/bednets); intermittent preventive treatment during pregnancy and in children 3-59 mo • Birth spacing; delaying pregnancy until after 18 yr of age

Clinical Manifestations and Treatment of Undernutrition

Treatment of vitamin and mineral deficiencies is discussed in Chapters 48-54. Treatment of low birthweight and intrauterine growth restriction are discussed respectively in Chapter 97.

SEVERE ACUTE MALNUTRITION

Severe acute malnutrition is defined as severe wasting and/or bilateral edema.

Severe wasting is extreme thinness diagnosed by a weight-for-length (or height) below −3 SD of the WHO Child Growth Standards. In children ages 6-59 mo, a mid-upper arm circumference <115 mm also denotes extreme thinness: a color-banded tape (see Fig. 46-3) is a convenient way of screening children in need of treatment.

Bilateral edema is diagnosed by grasping both feet, placing a thumb on top of each, and pressing gently but firmly for 10 seconds. A pit (dent) remaining under each thumb indicates bilateral edema.

This definition of severe acute malnutrition distinguishes wasted/edematous children from those who are stunted, as the latter (although underweight) are not a priority for acute clinical care as their deficits in height and weight cannot be corrected in the short term. The previous name *protein-energy malnutrition* is avoided, as it oversimplifies the complex multideficiency etiology. Other terms are *marasmus* (severe wasting), *kwashiorkor* (characterized by edema), and *marasmic-kwashiorkor* (severe wasting + edema).

Children with severe acute malnutrition have had a diet insufficient in energy and nutrients relative to their needs. The magnitude of the deficits will differ depending on the duration of inadequacy, quantity and diversity of food consumed, presence of antinutrients (such as phytate), individual variation in requirements, and number and severity of coexisting infections and their duration. Infections can lead to profound nutrient deficits and imbalances: For example, amino acids are diverted to form acute-phase proteins and there are losses through diarrhea of potassium, magnesium, vitamin A, and zinc, and of glycine and taurine linked to small bowel bacterial overgrowth. Deficits can

also arise from increased nutrient utilization in response to noxae (e.g., cysteine and methionine to detoxify dietary cyanogens). Heterogeneity in the extent and nature of the deficits and imbalances, reflecting the diverse pathways to severe acute malnutrition, helps explain why affected children differ in their clinical presentation and degree of metabolic disturbance. Children who develop edematous malnutrition are more likely than nonedematous children to have been exposed to noxae that generate oxidative stress and/or to have greater deficits in free radical-scavenging antioxidants (glutathione, vitamins A, C, and E, and essential fatty acids) or cofactors (zinc, copper, selenium).

Clinical Manifestations of Severe Acute Malnutrition (Table 46-6)

Severe wasting (Fig. 46-4) is most visible on the thighs, buttocks, and upper arms, and over the ribs and scapulae where loss of fat and skeletal muscle is greatest. Wasting is preceded by failure to gain weight and then by weight loss. The skin loses turgor and becomes loose as subcutaneous tissues are broken down to provide energy. The face may retain a relatively normal appearance, but eventually becomes wasted and wizened. The eyes may be sunken from loss of retroorbital fat, and lachrymal and salivary glands may atrophy leading to lack of tears and a dry mouth. Weakened abdominal muscles and gas from bacterial overgrowth of the upper gut may lead to a distended abdomen. Severely wasted children are often fretful and irritable.

In *edematous malnutrition*, the edema is most likely to appear first in the feet and then in the lower legs. It can quickly develop into generalized edema affecting also the hands, arms, and face (Fig. 46-5). Skin changes commonly occur over the swollen limbs and include dark, crackled peeling patches (flaky paint dermatosis) with pale skin underneath that is easily infected. The hair is sparse and easily pulled out and may lose its curl. In dark-haired children, the hair may turn pale or reddish. The liver is often enlarged with fat. Children with edema are miserable and apathetic, and often refuse to eat.

Table 46-6 Clinical Signs of Malnutrition

SITE	SIGNS
Face	Moon face (kwashiorkor), simian facies (marasmus)
Eye	Dry eyes, pale conjunctiva, Bitot spots (vitamin A), periorbital edema
Mouth	Angular stomatitis, cheilitis, glossitis, spongy bleeding gums (vitamin C), parotid enlargement
Teeth	Enamel mottling, delayed eruption
Hair	Dull, sparse, brittle hair, hypopigmentation, flag sign (alternating bands of light and normal color), broomstick eyelashes, alopecia
Skin	Loose and wrinkled (marasmus), shiny and edematous (kwashiorkor), dry, follicular hyperkeratosis, patchy hyper- and hypopigmentation (crazy paving or flaky paint dermatoses), erosions, poor wound healing
Nails	Koilonychia, thin and soft nail plates, fissures, or ridges
Musculature	Muscle wasting, particularly buttocks and thighs; Chvostek or Trousseau sign (hypocalcemia)
Skeletal	Deformities, usually as a result of calcium, vitamin D, or vitamin C deficiencies
Abdomen	Distended: hepatomegaly with fatty liver; ascites may be present
Cardiovascular	Bradycardia, hypotension, reduced cardiac output, small vessel vasculopathy
Neurologic	Global developmental delay, loss of knee and ankle reflexes, impaired memory
Hematologic	Pallor, petechiae, bleeding diathesis
Behavior	Lethargic, apathetic, irritable on handling

From Grover Z, Ee LC: Protein energy malnutrition, Pediatr Clin N Am *56:1055–1068, 2009.*

Pathophysiology

When a child's intake is insufficient to meet daily needs, physiologic and metabolic changes take place in an orderly progression to conserve energy and prolong life. This process is called *reductive adaptation*. Fat stores are mobilized to provide energy. Later protein in muscle, skin, and the gastrointestinal tract is mobilized. Energy is conserved by reducing physical activity and growth, reducing basal metabolism and the functional reserve of organs and by reducing inflammatory and immune responses. These changes have important consequences:

- The liver makes glucose less readily, making the child more prone to hypoglycemia. It produces less albumin, transferrin, and other transport proteins. It is less able to cope with excess dietary protein and to excrete toxins.
- Heat production is less, making the child more vulnerable to hypothermia.
- The kidneys are less able to excrete excess fluid and sodium, and fluid easily accumulates in the circulation, increasing the risk of fluid overload.
- The heart is smaller and weaker and has a reduced output, and fluid overload readily leads to death from cardiac failure.
- Sodium builds up inside cells due to leaky cell membranes and reduced activity of the sodium/potassium pump, leading to excess body sodium, fluid retention, and edema.
- Potassium leaks out of cells and is excreted in urine, contributing to electrolyte imbalance, fluid retention, edema, and anorexia.
- Loss of muscle protein is accompanied by loss of potassium, magnesium, zinc, and copper.

Figure 46-4 Child with severe wasting.

- The gut produces less gastric acid and enzymes. Motility is reduced, and bacteria may colonize the stomach and small intestine, damaging the mucosa and deconjugating bile salts. Digestion and absorption are impaired.
- Cell replication and repair are reduced, increasing the risk of bacterial translocation through the gut mucosa.
- Immune function is impaired, especially cell-mediated immunity. The usual responses to infection may be absent, even in severe illness, increasing the risk of undiagnosed infection.
- Red cell mass is reduced, releasing iron which requires glucose and amino acids to be converted to ferritin, increasing the risk of hypoglycemia and amino acid imbalances. If conversion to ferritin is incomplete, unbound iron promotes pathogen growth and formation of free radicals.
- Micronutrient deficiencies limit the body's ability to deactivate free radicals, which cause cell damage. Edema and hair/skin changes are outward signs of cell damage.

When prescribing treatment it is essential to take these changes in function into account, otherwise organs and systems will be overwhelmed and death will rapidly ensue.

Figure 46-5 Child with generalized edema.

Principles of Treatment

Figure 46-6 shows the 10 steps of treatment, which are separated into 2 phases referred to as stabilization and rehabilitation. These steps apply to all clinical forms and all geographic locations, including North America and Europe. The aim of the stabilization phase is to repair cellular function, correct fluid and electrolyte imbalance, restore homeostasis, and prevent death from the interlinked triad of hypoglycemia, hypothermia, and infection. The aim of the rehabilitation phase is to restore wasted tissues (i.e., catch-up growth). It is essential that treatment proceeds in an ordered progression and that the metabolic machinery is repaired before any attempt is made to promote weight gain. Pushing ahead too quickly risks inducing the potentially fatal "refeeding syndrome."

Caregivers bring children to health facilities because of illness, rarely because of their malnutrition. A common mistake among healthcare providers is to focus on the illness and treat as for a well-nourished child. This approach ignores the deranged metabolism in malnourished children and can be fatal. Such children should be considered as severely malnourished with a complication, and treatment should follow the 10 steps. Two other potentially fatal mistakes are to treat edema with a diuretic and to give a high-protein diet in the early phase of treatment.

- ***Emergency treatment***: Table 46-7 summarizes the therapeutic directives for malnourished children with shock and other emergency conditions. Note that treatment of shock in these children is different (less rapid, smaller volume, different fluid) from treatment of shock in well-nourished children. This difference is because shock from dehydration and sepsis often coexist and are difficult to differentiate on clinical grounds. Thus one has to be guided by the response to treatment: children with dehydration respond to IV fluid whereas those with septic shock will not respond. Since severely malnourished children can quickly succumb to fluid overload, they must be monitored closely.
- ***Stabilization***: Table 46-8 summarizes the therapeutic directives for stabilization steps 1-7. Giving broad-spectrum antibiotics (Table 46-9) and feeding frequent small amounts of F75 (a specially formulated low-lactose milk with 75 kcal and 0.9 g protein per

	Stabilization		Rehabilitation
	Day 1–2	Day 3–7	Week 2–6
1. Prevent/treat hypoglycemia	→		
2. Prevent/treat hypothermia	→		
3. Treat/prevent dehydration	→		
4. Correct imbalance of electrolytes	———	———	——→
5. Treat infections	———	——→	
6. Correct deficiencies of micronutrients	—— no iron	———	with iron ——→
7. Start cautious feeding	———	——→	
8. Rebuild wasted tissue (catch-up growth)		——	——→
9. Provide loving care and play	———	———	——→
10. Prepare for follow-up		——	——→

Figure 46-6 The 10 steps of treatment for severe acute malnutrition and their approximate time frames.

Table 46-7 Emergency Treatment in Severe Malnutrition

CONDITION	IMMEDIATE ACTION
Shock • lethargic or unconscious and • cold hands Plus either: • slow capillary refill (longer than 3 sec) or • weak fast pulse	1. Give oxygen 2. Give sterile 10% glucose (5 mL/kg) by IV 3. Give IV fluid at 15 mL/kg over 1 hr, using: • Ringers lactate with 5% dextrose or • half-normal saline with 5% dextrose or • half-strength Darrow solution with 5% dextrose • if all of the above are unavailable, Ringer lactate 4. Measure and record pulse and respirations at the start and every 10 minutes If there are signs of improvement (pulse and respiration rates fall) repeat IV 15 mL/kg for 1 more hr. Then switch to oral or nasogastric rehydration with ReSoMal, 5-10 mL/kg in alternate hr (see Table 46-8 step 3) If there are no signs of improvement assume septic shock and: 1. Give maintenance fluid IV (4 mL/kg/hr) while waiting for blood 2. Order 10 mL/kg fresh whole blood and transfuse slowly over 3 hr. If signs of heart failure, give 5-7 mL/kg packed cells rather than whole blood 3. Give furosemide 1 mL/kg IV at the start of the transfusion
Hypoglycemia Blood glucose less than 3 mmol/L	See Table 46-8 step 1 for treatment
Severe dehydration	Do *not* give IV fluids except in shock See Table 46-8 step 3 for treatment
Very severe anemia Hb less than 4 g/dL	If very severe anemia (or Hb 4-6 g/dL AND respiratory distress): 1. Give whole blood 10 mL/kg slowly over 3 hr. If signs of heart failure, give 5-7 mL/kg packed cells rather than whole blood 2. Give furosemide 1 mL/kg IV at the start of the transfusion
Emergency eye care Corneal ulceration	If corneal ulceration: 1. Give vitamin A immediately (age <6 mo 50,000 IU, 6-12 mo 100,000 IU, >12 mo 200,000 IU) 2. Instill 1 drop atropine (1%) into affected eye to relax the eye and prevent the lens from pushing out

Table 46-8 Therapeutic Directives for Stabilization

STEP	PREVENTION	TREATMENT
1. Prevent/treat hypoglycemia blood glucose <3 mmol/L	Avoid long gaps without food and minimize need for glucose: 1. Feed immediately 2. Feed every 3 hr day and night (2 hr if ill) 3. Feed on time 4. Keep warm 5. Treat infections (they compete for glucose) *Note:* Hypoglycemia and hypothermia often coexist, and are signs of severe infection	If conscious: 1. 10% glucose (50 mL), or a feed (see step 7), or 1 teaspoon sugar under the tongue-whichever is quickest 2. Feed every 2 hr for at least the first day. Initially give ¼ of feed every 30 min 3. Keep warm 4. Start broad-spectrum antibiotics If unconscious: 1. Immediately give sterile 10% glucose (5 mL/kg) by IV 2. Feed every 2 hr for at least first day. Initially give ¼ of feed every 30 min. Use nasogastric (NG) tube if unable to drink 3. Keep warm. 4. Start broad-spectrum antibiotics
2. Prevent/treat hypothermia axillary <35°C (95°F); rectal <35.5°C (95.9°F)	Keep warm and dry and feed frequently 1. Avoid exposure 2. Dress warmly, including head and cover with blanket 3. Keep room hot; avoid draughts 4. Change wet clothes and bedding 5. Do not bathe if very ill 6. Feed frequently day and night 7. Treat infections	Actively rewarm 1. Feed 2. Skin-to-skin contact with carer ("kangaroo technique") or dress in warmed clothes, cover head, wrap in warmed blanket and provide indirect heat (e.g. heater; transwarmer mattress; incandescent lamp) 3. Monitor temperature hourly (or every 30 min if using heater) 4. Stop rewarming when rectal temperature is 36.5°C (97.7°F)
3. Prevent/treat dehydration	Replace stool losses 1. Give ReSoMal after each watery stool. ReSoMal (37.5 mmol Na/L) is a low-sodium rehydration solution for malnutrition	Do *not* give IV fluids unless the child is in shock 1. Give ReSoMal 5 mL/kg every 30 min for first 2 hr orally or NG tube 2. Then give 5-10 mL/kg in alternate hours for up to 10 hr. Amount depends on stool loss and eagerness to drink. Feed in the other alternate hour 3. Monitor hourly and stop if signs of overload develop (pulse rate increases by 25 beats/min and respiratory rate by 5 breaths/min; increasing edema; engorged jugular veins) 4. Stop when rehydrated (3 or more signs of hydration: less thirsty, passing urine, skin pinch less slow, eyes less sunken, moist mouth, tears, less lethargic, improved pulse and respiratory rate).

Continued

Table 46-8 Therapeutic Directives for Stabilization—cont'd

STEP	PREVENTION	TREATMENT
4. Correct electrolyte imbalance—deficit of potassium and magnesium, excess sodium		1. Give extra potassium (4 mmol/kg/day) and magnesium (0.6 mmol/kg/day) for at least 2 wk (see Table 46-12) *Note:* Potassium and magnesium are already added in Nutriset F75 and F100 packets
5. Prevent/treat infections	Minimize risk of cross-infection 1. Avoid overcrowding 2. Wash hands 3. Give measles vaccine to unimmunized children age >6 mo	Infections are often silent. Starting on the first day, give broad-spectrum antibiotics to all children. 1. For antibiotic choices/schedule see Table 46-9 2. Ensure all doses are given, and given on time 3. Cover skin lesions so they do not become infected *Note:* Avoid steroids as they depress immune function
6. Correct micronutrient deficiencies	*Note:* Folic acid, multivitamins, zinc, copper, and other trace minerals are already added in Nutriset F75 and F100 packets	Do *not* give iron in the stabilization phase 1. Give vitamin A on day 1 (under 6 mo 50,000 units; 6-12 mo 100,000 units; >12 mo 200,000 units) if child has any eye signs of vitamin A deficiency or has had recent measles. Repeat this dose on days 2 and 14 2. Folic acid 1 mg (5 mg on day 1) 3. Zinc (2 mg/kg/day) and copper (0.3 mg/kg/day).These are in the electrolyte/mineral solution and Combined Mineral Vitamin mix (CMV) and can be added to feeds and ReSoMal 4. Multivitamin syrup or CMV
7. Start cautious feeding		1. Give 8-12 small feeds of F75 to provide 130 mL/kg/day,100 kcal/kg/day and 1-1.5 g protein/kg/day 2. If gross edema, reduce volume to 100 ml/kg/day 3. Keep a 24-hr intake chart. Measure feeds carefully. Record leftovers 4. If child has poor appetite, coax and encourage to finish the feed. If unfinished, reoffer later. Use NG tube if eating 80% or less of the amount offered 5. If breastfed, encourage continued breastfeeding but also give F75 6. Transfer to F100 when appetite returns (usually within 1 wk) and edema has been lost or is reduced 7. Weigh daily and plot weight.

Table 46-9 Recommended Antibiotics*

	GIVE
If no complications	Amoxicillin oral 25 mg/kg twice daily for 5 days
If complications (shock, hypoglycemia, hypothermia, skin lesions, respiratory or urinary tract infections, or lethargy/sickly)	Gentamicin (7.5 mg/kg IV or IM) once daily for 7 days *and* Ampicillin (50 mg/kg IV or IM) every 6 hr for 2 days, then oral amoxicillin (25-40 mg/kg) every 8 hr for 5 days

*Local resistance patterns may require these to be adjusted: Ensure that there is Gram-negative cover.
If specific infections are identified, add appropriate antibiotics.
For persistent diarrhea/small bowel overgrowth, add metronidazole (7.5 mg/kg oral) every 8 hr for 7 days.

100 mL to which potassium, magnesium, and micronutrients are added), will reestablish metabolic control, treat edema, and restore appetite. The parenteral route should be avoided; children who lack appetite should be fed by nasogastric tube, as nutrients delivered within the gut lumen help in its repair. Table 46-10 gives recipes for preparing the special feeds, and their nutrient composition. Two recipes for F75 are shown: one requires no cooking, the other is cereal-based and has a lower osmolality, which may benefit children with persistent diarrhea. F75 is also available commercially in which maltodextrins replace some of the sugar and to which potassium, magnesium, minerals, and vitamins are already added.

Dehydration status is easily misdiagnosed in severely wasted children, as the usual signs (such as slow skin pinch, sunken eyes) may be present even without dehydration. Rehydration must therefore be closely monitored for signs of fluid overload. Serum electrolyte levels can be misleading because of sodium leaking from the blood into cells and potassium leaking out of cells. Keeping the intake of electrolytes and nutrients constant (see Table 46-9) allows systems to stabilize more quickly than adjusting intake in response to laboratory results.

Table 46-11 gives a recipe for the special rehydration solution used in severe malnutrition (ReSoMal). Therapeutic Combined Mineral Vitamin mix (CMV) contains electrolytes, minerals, and vitamins and is added to ReSoMal and feeds. If unavailable, potassium, magnesium, zinc, and copper can be added as an electrolyte/mineral stock solution (Table 46-12 provides a recipe) and a multivitamin supplement given separately.

- ***Rehabilitation***: The signals for entry to this phase are reduced/minimal edema and return of appetite.

A controlled transition over 3 days is recommended to prevent the "refeeding syndrome." After the transition,

Table 46-10 Recipes for Milk Formulas F75 and F100

	F75[b] (STARTER)	F75[c] (STARTER) (CEREAL-BASED)	F100[d] (CATCH-UP)
Dried skimmed milk (g)	25	25	80
Sugar (g)	100	70	50
Cereal flour (g)	—	35	—
Vegetable oil (g)	30	30	60
Electrolyte/mineral solution (mL)[a]	20	20	20
Water: make up to (mL)	1000	1000	1000
Content/100 mL			
Energy (kcal)	75	75	100
Protein (g)	0.9	1.1	2.9
Lactose (g)	1.3	1.3	4.2
Potassium (mmol)	4.0	4.2	6.3
Sodium (mmol)	0.6	0.6	1.9
Magnesium (mmol)	0.43	0.46	0.73
Zinc (mg)	2.0	2.0	2.3
Copper (mg)	0.25	0.25	0.25
% Energy from protein	5	6	12
% Energy from fat	32	32	53
Osmolality (mOsm/L)	413	334	419

Whisk at high speed to prevent oil from separating out.
[a]See Table 46-12 for recipe, or use commercially available therapeutic Combined Mineral Vitamin mix (CMV).
[b]A comparable F75 can be made from 35 g dried whole milk, 100 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL; or from 300 mL full cream cow's milk, 100 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL.
[c]This lower-osmolality formula may be helpful for children with dysentery or persistent diarrhea. Cook for 4 min.
[d]A comparable F100 can be made from 110 g dried whole milk, 50 g sugar, 30 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL; or from 880 mL full cream cow's milk, 75 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL.

Table 46-11 Recipe for Rehydration Solution for Malnutrition (ReSoMal)

INGREDIENT	AMOUNT
Water	2 L
WHO-ORS	One 1-L sachet*
Sucrose	50 g
Electrolyte/mineral solution†	mL

ReSoMal contains 37.5 mmol sodium and 40 mmol potassium/L
*Sachet contains 2.6 g sodium chloride, 2.9 g trisodium citrate, 1.5 g potassium chloride, 13.5 g glucose.
†See Table 46-12 for recipe, or use commercially available therapeutic Combined Mineral Vitamin mix (CMV).

Table 46-12 Recipe for Concentrated Electrolyte/Mineral Solution*

INGREDIENT	g	mol/20 mL
Potassium chloride: KCl	224.0	24 mmol
Tripotassium citrate	81.0	2 mmol
Magnesium chloride: $MgCl_2 . 6H_2O$	76.0	3 mmol
Zinc acetate: Zn acetate.$2H_2O$	8.2	300 μmol
Copper sulfate: $CuSO_4 . 5H_2O$	1.4	45 μmol
Water: make up to	2500 mL	

Add 20 mL when preparing 1 L of feed or ReSoMal.
*Make fresh each month. Use cooled boiled water.

unlimited amounts should be given of a high-energy, high-protein milk formula such as F100 (100 kcal and 3 g protein per 100 mL), or ready-to-use therapeutic food (RUTF), or family foods modified to have comparable energy and protein contents.

To make the transition, for 2 days replace F75 with an equal volume of F100 and then increase each successive feed by 10 mL until some feed remains uneaten (usually at around 200 mL/kg/day).

After the transition, give 150-220 kcal/kg/day and 4-6 g protein/kg/day and continue to give potassium, magnesium, and micronutrients. Add iron (3 mg/kg/day). If breastfed, encourage continued breastfeeding.

Children with severe malnutrition have developmental delays, so loving care, structured play, and sensory stimulation during and after treatment are essential to aid recovery of brain function.

Community-based treatment: Many children with severe acute malnutrition can be identified in their communities before medical complications arise. If these children have a good appetite and are clinically well, they can be rehabilitated at home through community-based therapeutic care, which has the added benefit of reducing their exposure to nosocomial infections and providing continuity of care after

recovery. It also reduces the time caregivers spend away from home and their opportunity costs, and can be cost-effective for health services.

Figure 46-7 shows the criteria for inpatient versus outpatient care. To maximize coverage and compliance, community-based therapeutic care has 4 main elements: community mobilization and sensitization; active case-finding; therapeutic care; and follow-up after discharge.

Community-based therapeutic care comprises steps 8-10, plus a broad-spectrum antibiotic (step 5). RUTF is usually provided, especially in times of food shortage. RUTF is specially designed for rehabilitating children with severe acute malnutrition at home. It is high in energy and protein and has electrolytes and micronutrients added. The most widely used RUTF is a thick paste that contains milk powder, peanuts, vegetable oil, and sugar. Pathogens cannot grow in it because of its low moisture content. Hospitalized children who have completed steps 1-7 and the transition can be transferred to community-based care for completion of their rehabilitation, thereby reducing their hospital stay to about 7-10 days.

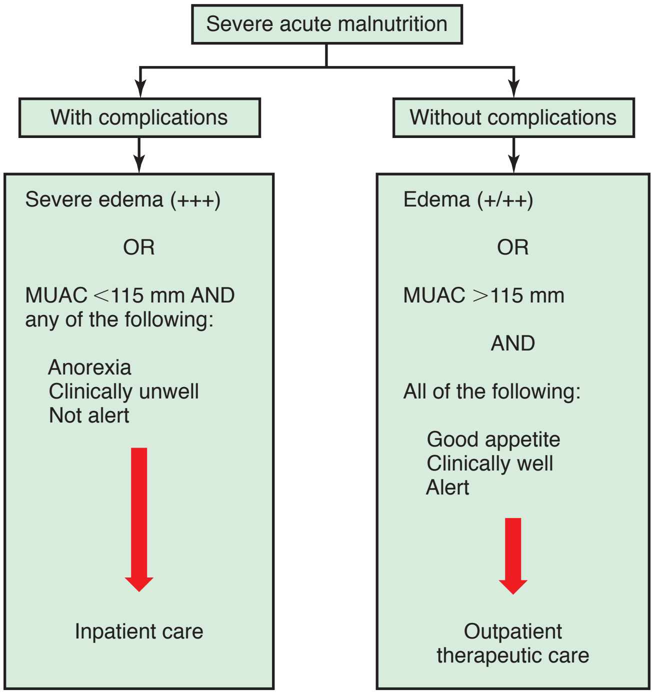

Figure 46-7 Flow diagram for inpatient and outpatient care in the child with severe acute malnutrition. MUAC, Mid upper arm circumference.

Bibliography is available at Expert Consult.

46.1 Refeeding Syndrome

Robert M. Kliegman

Refeeding syndrome can complicate the acute nutritional rehabilitation of children who are undernourished from any cause (Table 46-13). Refeeding syndrome is rare when the WHO recommendations for the treatment of malnutrition are followed (see Chapter 46); however, it may follow overly aggressive enteral or parenteral alimentation. Malnutrition usually has normal serum electrolytes but is associated with intracellular electrolyte depletion. When excessive carbohydrates are administered, the resultant increase in serum insulin levels may produce hypokalemia, hypophosphatemia, and hypomagnesemia. The hallmark of refeeding syndrome is the development of severe hypophosphatemia after the cellular uptake of phosphate during the 1st wk of starting to reefed. Serum phosphate levels of ≤0.5 mmol/L can produce weakness, rhabdomyolysis, neutrophil dysfunction, cardiorespiratory failure, arrhythmias, seizures, altered level of consciousness, or sudden death. Phosphate levels should be monitored during refeeding, and if they are low, phosphate should be administered during refeeding to treat severe hypophosphatemia (see Chapter 55.6).

Table 46-13 Clinical Signs and Symptoms of Refeeding Syndrome

HYPOPHOSPHATEMIA	HYPOKALEMIA	HYPOMAGNESEMIA	VITAMIN/THIAMINE DEFICIENCY	SODIUM RETENTION	HYPERGLYCEMIA
Cardiac	**Cardiac**	**Cardiac**	Encephalopathy	Fluid overload	**Cardiac**
Hypotension	Arrhythmias	Arrhythmias	Lactic acidosis	Pulmonary edema	Hypotension
Decreased stroke volume	**Respiratory**	**Neurologic**	Death	Cardiac compromise	**Respiratory**
Respiratory	Failure	Weakness			Hypercapnia
Impaired diaphragm contractility	**Neurologic**	Tremor			Failure
Dyspnea	Weakness	Tetany			**Other**
Respiratory failure	Paralysis	Seizures			Ketoacidosis
Neurologic	**Gastrointestinal**	Altered mental status			Coma
Paresthesia	Nausea	Coma			Dehydration
Weakness	Vomiting	**Gastrointestinal**			Impaired immune function
Confusion	Constipation	Nausea			
Disorientation	**Muscular**	Vomiting			
Lethargy	Rhabdomyolysis	Diarrhea			
Areflexic paralysis	Muscle necrosis	**Other**			
Seizures	**Other**	Refractory hypokalemia and hypocalcemia			
Coma	Death	Death			
Hematologic					
Leukocyte dysfunction					
Hemolysis					
Thrombocytopenia					
Other					
Death					

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Chapter **47**

Overweight and Obesity

Sheila Gahagan

Obesity is an important pediatric public health problem associated with risk of complications in childhood and increased morbidity and mortality throughout adult life.

EPIDEMIOLOGY

Obesity is a global public health problem, sparing only dramatically poor regions with chronic food scarcity such as sub-Saharan Africa and Haiti. In 2008, according to the World Health Organization, more than 1.4 billion persons ≥20 yr old were overweight or obese.

In the United States, 36% of adults are obese, and an additional 35% of adults are overweight. In children, the prevalence of obesity increased 300% over approximately 40 yr. The National Health and Nutrition Examination Survey, 2009-2010, found 32% of children, 2-19 yr old to be overweight or obese, and 17% in the obese range. Children's risk varies significantly by race/ethnicity. In 2009-2010, 24% of non-Hispanic Black, 21% of Hispanic, and >20% of American Indian/Alaskan Native children and adolescents were obese compared to 14% of white children. Across all racial groups, higher maternal education confers protection against childhood obesity.

Parental obesity correlates with a higher risk for obesity in their children. Prenatal factors including high preconceptual weight, gestational weight gain, high birth weight, and maternal smoking are associated with increased risk for later obesity. Paradoxically, intrauterine growth restriction with early infant catch-up growth is associated with the development of central adiposity and adult-onset cardiovascular risk. Breastfeeding is only modestly protective for obesity. Infants with high levels of negative reactivity (temperament) are at risk for obesity. Better self-regulation is protective.

BODY MASS INDEX

Obesity or increased adiposity is defined using the body mass index (BMI), which is an excellent proxy for more direct measurement of body fat. BMI = weight in kg/(height in meters)^2. Adults with a BMI ≥30 meet the criterion for obesity, and those with a BMI 25-30 fall in the overweight range. During childhood, levels of body fat change beginning with high adiposity during infancy. Body fat levels decrease for approximately 5.5 yr until the period called *adiposity rebound,* when body fat is typically at the lowest level. Adiposity then increases until early adulthood (Fig. 47-1). Consequently, obesity and overweight are defined using BMI percentiles; children >2 yr old with a BMI ≥95th percentile meet the criterion for obesity, and those with a BMI between the 85th and 95th percentiles fall in the overweight range.

ETIOLOGY

Humans have the capacity to store energy in adipose tissue, allowing improved survival in times of famine. Furthermore, humans innately prefer sweet and salty foods and reject bitter flavors. Many vegetables are bitter. These preferences probably reflect evolutionary adaptations to avoid consuming toxic plants. Nonetheless, repeated exposure to healthy foods promotes their acceptance and liking, especially in early life. Simplistically, obesity results from an imbalance of caloric intake and energy expenditure. Even incremental but sustained caloric excess results in excess adiposity. Individual adiposity is the result of a complex interplay among genetically determined body habitus, appetite, nutritional intake, physical activity, and energy expenditure. Environmental factors determine levels of available food, preferences for types of foods, levels of physical activity, and preferences for types of activities.

Environmental Changes

Over the last 4 decades, the food environment has changed dramatically. Changes in the food industry relate in part to social changes, as extended families have become more dispersed. Fewer families routinely prepare meals. Foods are increasingly prepared by a food industry, with high levels of calories, simple carbohydrates, and fat. The price of many foods has declined relative to the family budget. These changes, in combination with marketing pressure, have resulted in larger portion sizes and increased snacking between meals. The increased consumption of high-carbohydrate beverages, including sodas, sport drinks, fruit punch, and juice, adds to these factors.

One-third of U.S. children consume fast food daily. A typical fast food meal can contain 2000 kcal and 84 g of fat. Many children consume 4 servings of high-carbohydrate beverages per day, resulting in an additional 560 kcal of low nutritional value. Sweetened beverages have been linked to increased risk for obesity because children who drink high amounts of sugar do not consume less food. The dramatic increase in the use of high-fructose corn syrup to sweeten beverages and prepared foods is another important environmental change, leading to availability of inexpensive calories.

Since World War II, levels of physical activity in children and adults have declined. Changes in the built environment have resulted in more reliance on cars and decreased walking. Work is increasingly sedentary, and many sectors of society do not engage in physical activity during leisure time. For children, budgetary constraints and pressure for academic performance have led to less time devoted to physical education in schools. Perception of poor neighborhood safety is another factor that can lead to lower levels of physical activity when children are required to stay indoors. The advent of television, computers, and video games has resulted in opportunities for sedentary activities that do not burn calories.

Changes in another health behavior, sleep, might also contribute. Over the last 4 decades, children and adults have decreased the amount of time spent sleeping. Reasons for these changes may relate to increased time at work, increased time watching television, and a generally faster pace of life. Chronic partial sleep loss can increase risk for weight gain and obesity, with the impact possibly greater in children than in adults. In studies of young, healthy, lean men, short sleep duration was associated with decreased leptin levels and increased ghrelin levels, along with increased hunger and appetite. Sleep debt also results in decreased glucose tolerance and insulin sensitivity related to alterations in glucocorticoids and sympathetic activity. Some effects of sleep debt might relate to orexins, peptides synthesized in the lateral hypothalamus that can increase feeding, arousal, sympathetic activity, and/or neuropeptide Y activity.

Genetics

Genetic determinants also have a role in individual susceptibility to obesity (Table 47-1). Findings from genome-wide association studies explain a very small portion of interindividual variability in obesity. One important example, the *FTO* gene at 16q12, is associated with adiposity in childhood, probably explained by increased energy intake (Table 47-1). Monogenic forms of obesity have also been identified, including MC4R deficiency, associated with early-onset obesity and food-seeking behavior. In addition, there are genetic conditions associated with obesity, such as Prader-Willi syndrome, which results from absence of paternally expressed imprinted genes in the 15q11.2–q13 region. Prader-Willi syndrome is characterized by insatiable appetite and food seeking. Epigenetic environmental modification of genes may have a role in the development of obesity, especially during fetal and early life.

Endocrine and Neural Physiology

Monitoring of "stored fuels" and short-term control of food intake (appetite and satiety) occurs through neuroendocrine feedback loops linking adipose tissue, the gastrointestinal tract, and the central

2 to 20 years: Boys
Body mass index-for-age percentiles

NAME ______________________

RECORD # __________

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703

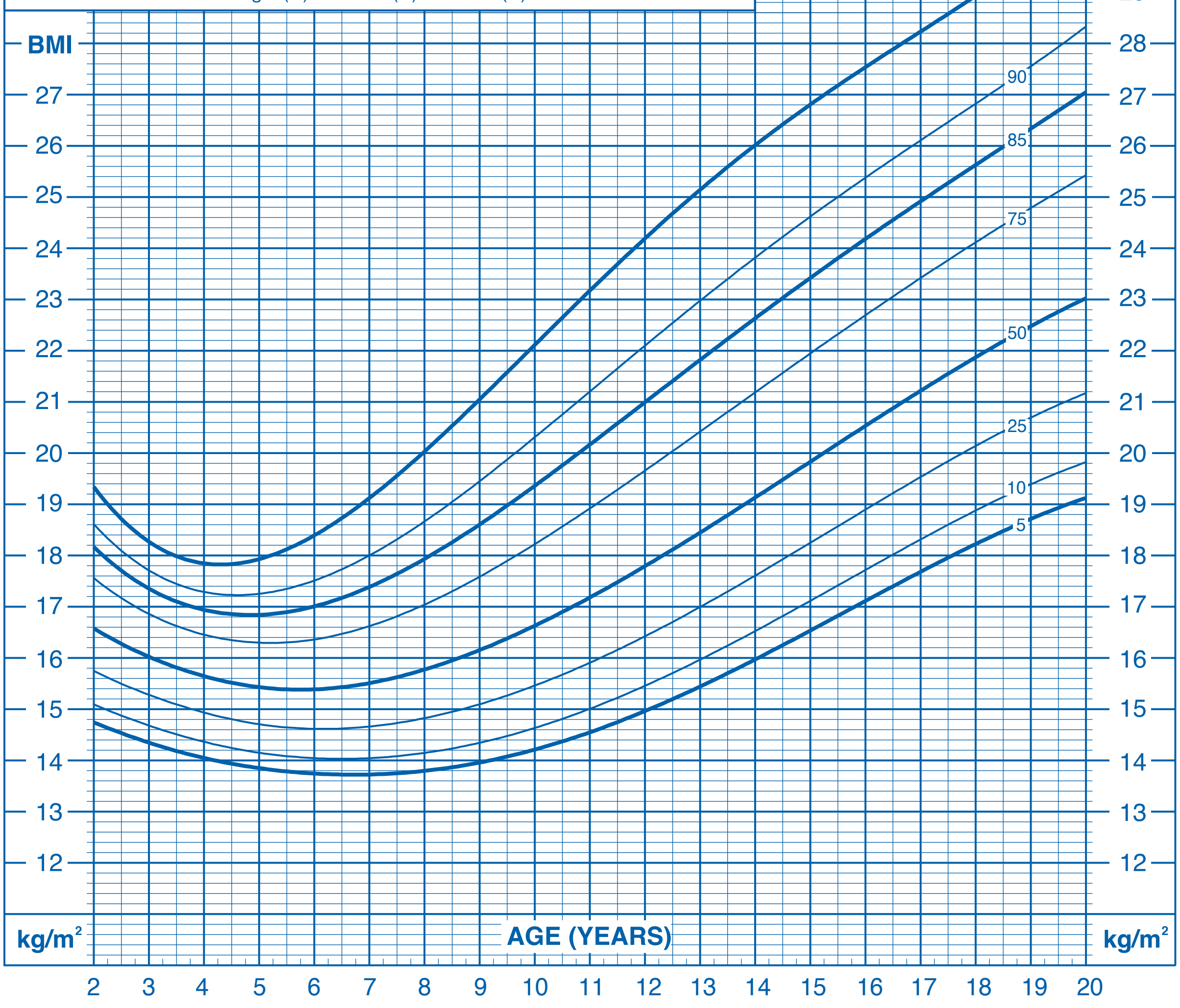

Published May 30, 2000 (modified 10/16/00).

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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A

Figure 47-1 Body mass index (BMI)-for-age profiles for boys and men *(A)* and girls and women *(B)*. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). See www.cdc.gov/growthcharts

2 to 20 years: Girls
Body mass index-for-age percentiles

NAME ______________________

RECORD # ____________

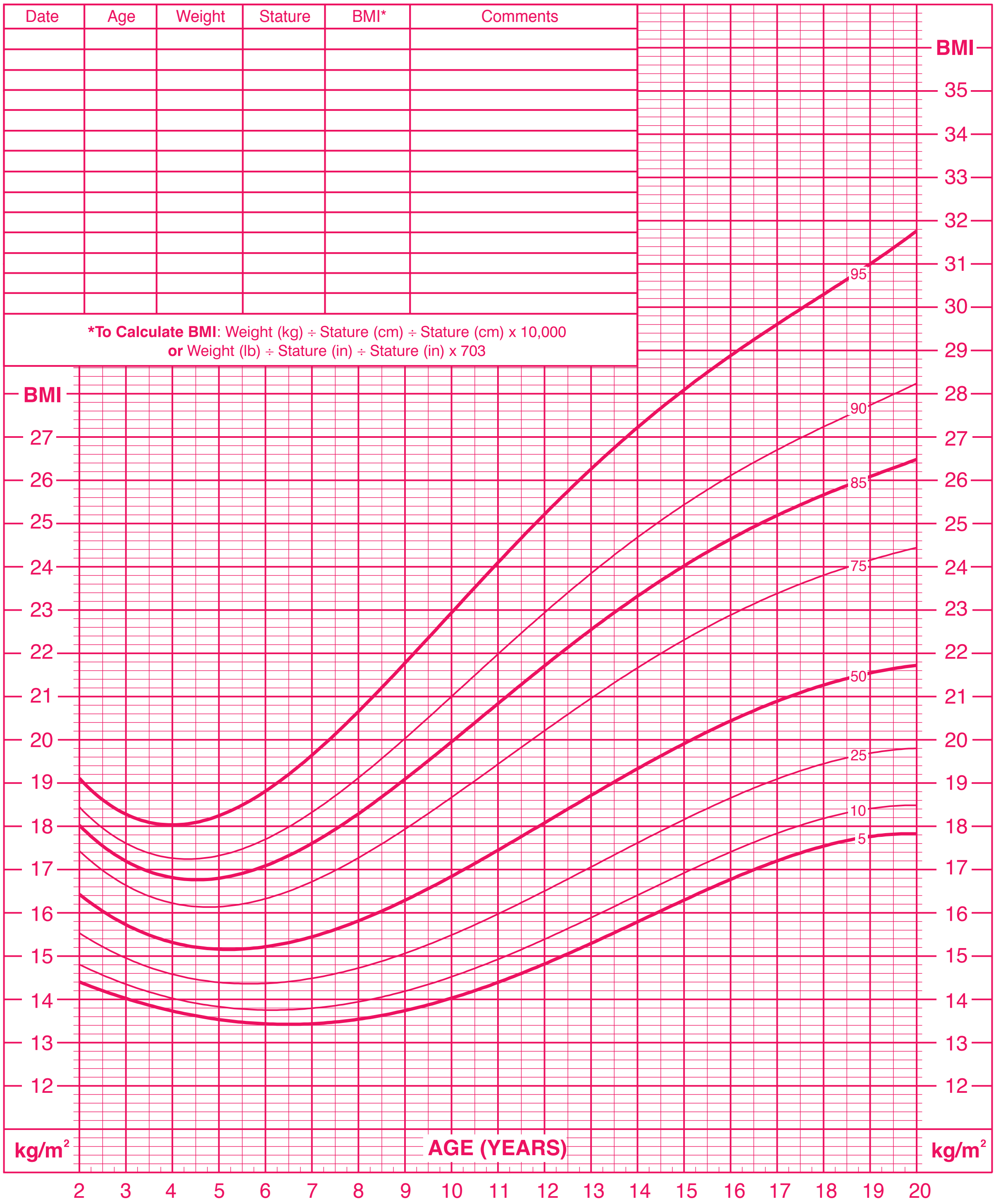

Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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B

Figure 47-1, cont'd

Table 47-1 Endocrine and Genetic Causes of Obesity

DISEASE	SYMPTOMS	LABORATORY
ENDOCRINE		
Cushing syndrome	Central obesity, hirsutism, moon face, hypertension	Dexamethasone suppression test
GH deficiency	Short stature, slow linear growth	Evoked GH response, IGF-1
Hyperinsulinism	Nesidioblastosis, pancreatic adenoma, hypoglycemia, Mauriac syndrome	Insulin level
Hypothyroidism	Short stature, weight gain, fatigue, constipation, cold intolerance, myxedema	TSH, FT_4
Pseudohypoparathyroidism	Short metacarpals, subcutaneous calcifications, dysmorphic facies, mental retardation, short stature, hypocalcemia, hyperphosphatemia	Urine cAMP after synthetic PTH infusion
GENETIC		
Alstrom syndrome	Cognitive impairment, retinitis pigmentosa, diabetes mellitus, hearing loss, hypogonadism, retinal degeneration	*ALMS1* gene
Bardet-Biedl syndrome	Retinitis pigmentosa, renal abnormalities, polydactyly, hypogonadism	*BBS1* gene
Biemond syndrome	Cognitive impairment, iris coloboma, hypogonadism, polydactyly	
Carpenter syndrome	Polydactyly, syndactyly, cranial synostosis, mental retardation	Mutations in the *RAB23* gene, located on chromosome 6 in humans
Cohen syndrome	Mid-childhood-onset obesity, short stature, prominent maxillary incisors, hypotonia, mental retardation, microcephaly, decreased visual activity	Mutations in the *VPS13B* gene (often called the *COH1* gene) at locus 8q22
Deletion 9q34	Early-onset obesity, mental retardation, brachycephaly, synophrys, prognathism, behavior and sleep disturbances	Deletion 9q34
Down syndrome	Short stature, dysmorphic facies, mental retardation	Trisomy 21
ENPP1 gene mutations	Insulin resistance, childhood obesity	Gene mutation on chromosome 6q
Fröhlich syndrome	Hypothalamic tumor	
FTO gene polymorphism	Dysregulation of orexigenic hormone acyl-ghrelin, poor postprandial appetite suppression	Homozygous for *FTO* AA allele
Leptin or leptin receptor gene deficiency	Early-onset severe obesity, infertility (hypogonadotropic hypogonadism)	Leptin
Melanocortin 4 receptor gene mutation	Early-onset severe obesity, increased linear growth, hyperphagia, hyperinsulinemia Most common known genetic cause of obesity Homozygous worse than heterozygous	*MC4R* mutation
Prader-Willi Syndrome	Neonatal hypotonia, slow infant growth, small hands and feet, mental retardation, hypogonadism, hyperphagia leading to severe obesity, paradoxically elevated ghrelin	Partial deletion of chromosome 15 or loss of paternally expressed genes
Proopiomelanocortin deficiency	Obesity, red hair, adrenal insufficiency, hyperproinsulinemia	Loss-of-function mutations of the *POMC* gene
Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD)	Often confused with congenital central hypoventilation syndrome (CCHS), presentation ≥1.5 yr with weight gain, hyperphagia, hypoventilation, cardiac arrest, central diabetes insipidus, hypothyroidism, growth hormone deficiency, pain insensitivity, hypothermia, precocious puberty, neural crest tumors	Unknown genes May be a paraneoplastic disorder
Turner syndrome	Ovarian dysgenesis, lymphedema, web neck, short stature, cognitive impairment	XO chromosome

cAMP, cyclic adenosine monophosphate; FT_4, free thyroxine; GH, growth hormone; IGF, insulin-like growth factor; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

nervous system (Fig. 47-2). Gastrointestinal hormones, including cholecystokinin, glucagon-like peptide-1, peptide YY, and vagal neuronal feedback promote satiety. Ghrelin stimulates appetite. Adipose tissue provides feedback regarding energy storage levels to the brain through hormonal release of adiponectin and leptin. These hormones act on the arcuate nucleus in the hypothalamus and on the solitary tract nucleus in the brainstem and, in turn, activate distinct neuronal networks. Adipocytes secrete adiponectin into the blood, with reduced levels in response to obesity and increased levels in response to fasting. Reduced adiponectin levels are associated with lower insulin sensitivity and adverse cardiovascular outcomes. Leptin is directly involved in satiety, as low leptin levels stimulate food intake and high leptin levels inhibit hunger in animal models and in healthy human volunteers. Adiposity correlates to serum leptin levels among children and adults, with the direction of effect remaining unclear.

Numerous neuropeptides in the brain, including peptide YY, agouti-related peptide, and orexin, appear to affect appetite stimulation, whereas melanocortins and α-melanocortin–stimulating hormone are involved in satiety. The neuroendocrine control of appetite and weight involves a negative-feedback system, balanced between short-term control of appetite and long-term control of adiposity (including leptin). Peptide YY reduces food intake via the vagal–brainstem–hypothalamic pathway. Developmental changes in peptide YY are evident as infants have higher levels of peptide YY than school-age children and adults. Obese children have lower fasting levels of peptide YY compared to adults. Weight loss may restore levels of peptide YY in children even though this does not happen in adults. In addition, patients homozygous for the *FTO* obesity risk allele demonstrate poor regulation of the orexigenic hormone acyl-ghrelin and have poor postprandial appetite suppression.

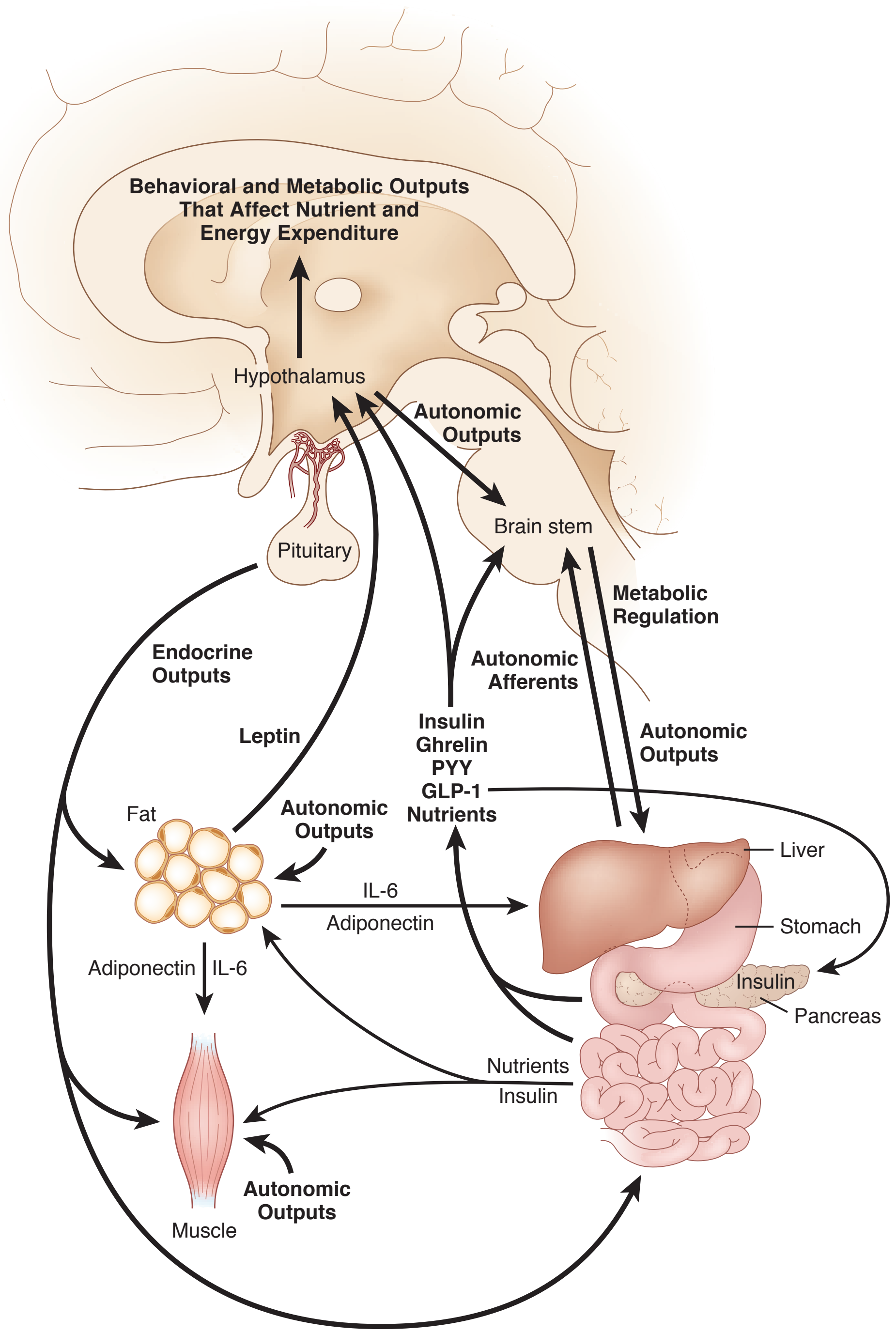

Figure 47-2 **Regulation of energy homeostasis by the brain–adipose tissue–intestinal axis.** Leptin stimulates hypothalamic anorexigenic and inhibits orexigenic neurons. Adiponectin stimulates hepatic, and muscle glucose utilization and increases insulin sensitivity, while interleukin-6 (IL-6) contributes to adipose tissue, muscle and hepatic insulin resistance. Peptide YY (PYY) inhibits orexigenic and glucagon-like peptide 1 (GLP-1) stimulates anorexigenic hypothalamic neurons. GLP-1 also augments glucose stimulated pancreatic insulin secretion and suppresses glucagon secretion. Insulin stimulates adipose tissue and muscle glucose uptake, enhances lipogenesis, suppresses hepatic glucose production, and has an inhibitory effect on the hypothalamic anorexigenic system. Ghrelin stimulates the orexigenic hypothalamic pathways. *(Modified from Melmed S, Polonsky KS, Larsen PR, Kronenberg HM:* Williams Textbook of Endocrinology*, ed 12, Philadelphia, 2011, Saunders.* Fig. 35-1.*)*

COMORBIDITIES

Complications of pediatric obesity occur during childhood and adolescence and persist into adulthood. An important reason to prevent and treat pediatric obesity is the increased risk for morbidity and mortality later in life. The Harvard Growth Study found that boys who were overweight during adolescence were twice as likely to die from cardiovascular disease as those who had normal weight. More immediate comorbidities include type 2 diabetes, hypertension, hyperlipidemia, and nonalcoholic fatty liver disease (Table 47-2). Insulin resistance increases with increasing adiposity and independently affects lipid metabolism and cardiovascular health. The metabolic syndrome (central obesity, hypertension, glucose intolerance, and hyperlipidemia) increases risk for cardiovascular morbidity and mortality. Nonalcoholic fatty liver disease (NAFLD) occurs in 10-25% of obese

Table 47-2 Obesity-Associated Comorbidities

DISEASE	POSSIBLE SYMPTOMS	LABORATORY CRITERIA
CARDIOVASCULAR		
Dyslipidemia	HDL <40, LDL >130, total cholesterol >200	Fasting total cholesterol, HDL, LDL, triglycerides
Hypertension	SBP >95% for sex, age, height	Serial testing, urinalysis, electrolytes, blood urea nitrogen, creatinine
ENDOCRINE		
Type 2 diabetes mellitus	Acanthosis nigrans, polyuria, polydipsia	Fasting blood glucose >110, hemoglobin A_{1c}, insulin level, C-peptide, oral glucose tolerance test
Metabolic syndrome	Central adiposity, insulin resistance, dyslipidemia, hypertension, glucose intolerance	Fasting glucose, LDL and HDL cholesterol
Polycystic ovary syndrome	Irregular menses, hirsutism, acne, insulin resistance, hyperandrogenemia	Pelvic ultrasound, free testosterone, LH, FSH
GASTROINTESTINAL		
Gallbladder disease	Abdominal pain, vomiting, jaundice	Ultrasound
Nonalcoholic fatty liver disease (NAFLD)	Hepatomegaly, abdominal pain, dependent edema, ↑ transaminases Can progress to fibrosis, cirrhosis	AST, ALT, ultrasound, CT, or MRI
NEUROLOGIC		
Pseudotumor cerebri	Headaches, vision changes, papilledema	Cerebrospinal fluid opening pressure, CT, MRI
Migraines	Hemicrania, headaches	None
ORTHOPEDIC		
Blount disease (tibia vara)	Severe bowing of tibia, knee pain, limp	Knee x-rays
Musculoskeletal problems	Back pain, joint pain, frequent strains or sprains, limp, hip pain, groin pain, leg bowing	X-rays
Slipped capital femoral epiphysis	Hip pain, knee pain, limp, decreased mobility of hip	Hip x-rays
PSYCHOLOGICAL		
Behavioral complications	Anxiety, depression, low self-esteem, disordered eating, signs of depression, worsening school performance, social isolation, problems with bullying or being bullied	Child Behavior Checklist, Children's Depression Inventory, Peds QL, Eating Disorder Inventory 2, subjective ratings of stress and depression, Behavior Assessment System for Children, Pediatric Symptom Checklist
PULMONARY		
Asthma	Shortness of breath, wheezing, coughing, exercise intolerance	Pulmonary function tests, peak flow
Obstructive sleep apnea	Snoring, apnea, restless sleep, behavioral problems	Polysomnography, hypoxia, electrolytes (respiratory acidosis with metabolic alkalosis)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; MRI, magnetic resonance imaging; Peds QL, Pediatric Quality of Life Inventory; SBP, systolic blood pressure.

adolescents. NAFLD is now the most common chronic liver disease in U.S. children and adolescents. It can present with advanced fibrosis or nonalcoholic steatohepatitis and may result in cirrhosis and hepatocellular carcinoma. Insulin resistance is commonly associated. Furthermore, NAFLD is independently associated with increased risk of cardiovascular disease.

Obesity may also be associated with chronic inflammation. Adiponectin, a peptide with antiinflammatory properties, occurs in reduced levels in obese patients as compared to insulin-sensitive, lean persons. Low adiponectin levels correlate with elevated levels of free fatty acids and plasma triglycerides as well as a high BMI, and high adiponectin levels correlate with peripheral insulin sensitivity. Adipocytes secrete peptides and cytokines into the circulation, and proinflammatory peptides such interleukin (IL)-6 and tumor necrosis factor-α (TNF-α) occur in higher levels in obese patients. Specifically, IL-6 stimulates production of C-reactive protein in the liver. C-reactive protein is a marker of inflammation and might link obesity, coronary disease, and subclinical inflammation.

Some complications of obesity are mechanical, including obstructive sleep apnea and orthopedic complications. Orthopedic complications include Blount disease and slipped femoral capital epiphysis (see Chapters 677, 678.4).

Mental health problems can coexist with obesity, with the possibility of bidirectional effects. These associations are modified by gender, ethnicity, and socioeconomic status. Self-esteem may be lower in obese adolescent girls compared to nonobese peers. Some studies have found an association between obesity and adolescent depression. There is considerable interest in the cooccurrence of eating disorders and obesity.

IDENTIFICATION

Overweight and obese children are often identified as part of routine medical care, and the child and family may be unaware that the child has increased adiposity. They may be unhappy with the medical provider for raising this issue and respond with denial or apparent lack of concern. It is often necessary to begin by helping the family understand the importance of healthy weight for current and future health, especially because intervention requires considerable effort by the child and the family. Forging a good therapeutic relationship is important, because obesity intervention requires a chronic disease management approach. Successful resolution of this problem necessitates considerable family and child effort over an extended period in order to change eating and activity behaviors.

EVALUATION

The evaluation of the overweight or obese child begins with examination of the growth chart for weight, height, and BMI trajectories; consideration of possible medical causes of obesity; and detailed

exploration of family eating, nutritional, and activity patterns. A complete pediatric history is used to uncover comorbid disorders. The family history focuses on the adiposity of other family members and the family history of obesity-associated disorders. The physical examination adds data that can lead to important diagnoses. Laboratory testing is guided by the need to identify comorbid conditions.

Examination of the growth chart reveals the severity, duration, and timing of obesity onset. Children who are overweight (BMI in the 85th-95th percentile) are less likely to have developed comorbid conditions than those who are obese (BMI ≥95th percentile). Those with a BMI ≥99th percentile are even more likely to have coexisting medical problems. Once obesity severity is determined, the BMI trajectory is examined to elucidate when the child became obese. Several periods during childhood are considered sensitive periods or times of increased risk for developing obesity, including infancy, adiposity rebound (when body fat is lowest at approximately age 5.5 yr), and adolescence. An abrupt change in BMI might signal the onset of a medical problem or a period of family or personal stress for the child. Examination of the weight trajectory can further expand understanding of how the problem developed. A young child might exhibit high weight and high height because linear growth can increase early in childhood if a child consumes excess energy. At some point, the weight percentile exceeds the height percentile and the child's BMI climbs into the obese range. Another example is a child whose weight rapidly increases when she reduces her activity level and consumes more meals away from home. Examination of the height trajectory can reveal endocrine problems, which often occur with slowing of linear growth.

Consideration of possible medical causes of obesity is essential, even though endocrine and genetic causes are rare (see Table 47-1). Growth hormone deficiency, hypothyroidism, and Cushing syndrome are examples of endocrine disorders that can lead to obesity. In general, these disorders manifest with slow linear growth. Because children who consume excessive amounts of calories tend to experience accelerated linear growth, short stature warrants further evaluation. Genetic disorders associated with obesity can have coexisting dysmorphic features, cognitive impairment, vision and hearing abnormalities, or short stature. In some children with congenital disorders such as myelodysplasia or muscular dystrophy, lower levels of physical activity can lead to secondary obesity. Some medications can cause excessive appetite and hyperphagia, resulting in obesity. Atypical antipsychotic medications often have this dramatic side effect. Rapid weight gain in a child or adolescent taking one of these medications might require a discontinuation of that medication. Poor linear growth and rapid changes in weight gain are indications for evaluation of possible medical causes.

Exploration of family eating and nutritional and activity patterns begins with a description of regular meal and snack times and family habits for walking, bicycle riding, active recreation, television, computer, and video game time. It is useful to request a 24-hr dietary recall with special attention to intake of fruits, vegetables, and water, as well as high-calorie foods and high-carbohydrate beverages. When possible, evaluation by a nutritionist is extremely helpful. This information will form the basis for incremental changes in eating behavior, caloric intake, and physical activity during the intervention.

Initial assessment of the overweight or obese child includes a complete review of bodily systems focusing on the possibility of comorbid conditions (see Table 47-2). Developmental delay and visual and hearing impairment can be associated with genetic disorders. Difficulty sleeping, snoring, or daytime sleepiness suggests the possibility of sleep apnea. Abdominal pain might suggest NAFLD. Symptoms of polyuria, nocturia, or polydipsia may be the result of type 2 diabetes. Hip or knee pain can be caused by secondary orthopedic problems, including Blount disease and slipped capital femoral epiphysis. Irregular menses may be associated with polycystic ovary syndrome. Acanthosis nigricans can suggest insulin resistance and type 2 diabetes (Fig. 47-3).

The family history begins with identifying other obese family members. Parental obesity is an important risk for child obesity. If all family members are obese, focusing the intervention on the entire family is reasonable. The child may be at increased risk for developing type 2 diabetes if a family history exists. Patients of African-American, Hispanic, or Native American heritage are also at increased risk for developing type 2 diabetes. Identification of a family history of hypertension, cardiovascular disease, or metabolic syndrome indicates increased risk for developing these obesity-associated conditions. If one helps the family to understand that childhood obesity increases risk for developing these chronic diseases, this educational intervention might serve as motivation to improve their nutrition and physical activity.

Figure 47-3 Acanthosis nigricans. *(From Gahagan S: Child and adolescent obesity,* Curr Probl Pediatr Adolesc Health Care *34:6–43, 2004.)*

Physical examination should be thorough, focusing on possible comorbid conditions (see Table 47-2). Careful screening for hypertension using an appropriately sized blood pressure cuff is important. Systematic examination of the skin can reveal acanthosis nigricans, suggesting insulin resistance, or hirsutism, suggesting polycystic ovary syndrome. Tanner staging can reveal premature adrenarche secondary to advanced sexual maturation in overweight and obese girls.

Laboratory testing for fasting plasma glucose, triglycerides, low-density lipoprotein and high-density lipoprotein cholesterol, and liver function tests are recommended as part of the initial evaluation for newly identified pediatric obesity (Table 47-3). Overweight children (BMI 85th-95th percentile) who have a family history of diabetes mellitus or signs of insulin resistance should also be evaluated with a fasting plasma glucose test. Other laboratory testing should be guided by history or physical examination findings.

INTERVENTION

There is evidence that some interventions result in modest but significant and sustained improvement in body mass. Based on behavior change theories, treatment includes specifying target behaviors, self-monitoring, goal setting, stimulus control, and promotion of self-efficacy and self-management skills. Behavior changes associated with improving BMI include drinking lower quantities of sugar-sweetened beverages, consuming higher-quality diets, increasing exercise, watching less TV, and self-weighing. Most successful interventions have been family based and take into account the child's developmental age. "Parent-only" treatment can be as effective as "parent–child" treatment. Because obesity is multifactorial, not all children and adolescents will respond to the same approach. For example, "loss-of-control" eating, associated with weight gain and obesity, predicts poor outcome in response to family-based treatment. Furthermore, clinical-treatment programs are expensive and not widely available. Therefore there is interest in novel approaches including Internet-based treatments and guided self-help.

It is important to begin with clear recommendations about appropriate caloric intake for the obese child (Table 47-4). Working with a dietitian is very helpful. Meals should be based on fruits, vegetables, whole grains, lean meat, fish, and poultry. Prepared foods should be chosen for their nutritional value, with attention to calories and fat. Foods that provide excessive calories and low nutritional value should be reserved for infrequent treats.

Weight-reduction diets in adults generally do not lead to sustained weight loss. Therefore, the focus should be on changes that can be maintained for life. Attention to eating patterns is helpful. Families should be encouraged to plan family meals, including breakfast. It is almost impossible for a child to make changes in nutritional intake and eating patterns if other family members do not make the same changes. Dietary needs also change developmentally, as adolescents require greatly increased calories during their growth spurts, and adults who lead inactive lives need fewer calories than active and growing children.

Table 47-3 Normal Laboratory Values for Recommended Tests

LABORATORY TEST	NORMAL VALUE
Glucose	<110 mg/dL
Insulin	<15 mU/L
Hemoglobin A_{1c}	<5.7%
AST (age 2-8 yr)	<58 U/L
AST (age 9-15 yr)	<46 U/L
AST (age 15-18 yr)	<35 U/L
ALT	<35 U/L
Total cholesterol	<170 mg/dL
LDL	<110 mg/dL
HDL	>45 mg/dL
Triglycerides (age 0-9 yr)	<75 mg/dL
Triglycerides (age 10-19 yr)	<90 mg/dL

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

From Children's Hospital of Wisconsin: The NEW (nutrition, exercise and weight management) kids program *(PDF file). http://www.chw.org/display/displayFile.asp?docid=33672&filename=/Groups/NEWKids/NewKidsReferral.PDF.*

Psychological strategies are helpful. The "traffic light" diet groups foods into those that can be consumed without any limitations (green), in moderation (yellow), or reserved for infrequent treats (red) (Table 47-5). The concrete categories are very helpful to children and families. This approach can be adapted to any ethnic group or regional cuisine. Motivational interviewing begins with assessing how ready the patient is to make important behavioral changes. The professional then engages the patient in developing a strategy to take the next step toward the ultimate goal of healthy nutritional intake. This method allows the professional to take the role of a coach, helping the child and family reach their goals. Other behavioral approaches include family rules about where food may be consumed; for example, "not in the bedroom."

Increasing physical activity without decreasing caloric intake is unlikely to result in weight loss. Nonetheless, it can increase aerobic fitness and decrease percent body fat even without weight loss. Therefore, increasing physical activity can decrease risk for cardiovascular disease, improve well-being, and contribute to weight loss. Increased physical activity can be accomplished by walking to school, engaging in physical activity during leisure time with family and friends, or enrolling in organized sports. Children are more likely to be active if their parents are active. Just as family meals are recommended, family physical activity is recommended.

Active pursuits can replace more sedentary activities. The American Academy of Pediatrics recommends that screen time be restricted to no more than 2 hr/day for children >2 yr old and that children <2 yr old not watch television. Television watching is often associated with eating, and many highly caloric food products are marketed directly to children during child-oriented television programs.

Pediatric providers should assist families to develop goals to change nutritional intake and physical activity. They can also provide the child and family with needed information. The family should not expect immediate lowering of BMI percentile related to behavioral changes but can instead count on a gradual decrease in the rate of BMI percentile increase until it stabilizes, followed by a gradual decrease in BMI percentile. Referral to multidisciplinary, comprehensive pediatric weight-management programs is ideal for obese children whenever possible.

There is no effective pharmacotherapy resulting in reversal of excess adiposity in children and adolescents. Available medications result in

Table 47-4 Recommended Caloric Intake Designated by Age and Gender

LIFE-STAGE GROUP	AGE (yr)	RELATIVELY SEDENTARY LEVEL OF ACTIVITY (kcal)	MODERATE LEVEL OF ACTIVITY (kcal)	ACTIVE (kcal)
Child	2-3	1,000	1,000-1,400	1,000-1,400
Female	4-8	1,200	1,400-1,600	1,400-1,800
	9-13	1,600	1,600-2,000	1,800-2,200
	14-18	1,800	2,000	2,400
Male	4-8	1,400	1,400-1,600	1,600-2,000
	9-13	1,800	1,800-2,200	2,000-2,600
	14-18	2,200	2,400-2,800	2,800-3,200

Adapted from U.S. Department of Agriculture: Dietary guidelines for Americans, *2005. http://www.health.gov/DIETARYGUIDELINES/dga2005/document/html/chapter2.htm.*

Table 47-5 Traffic Light Diet Plan

FEATURE	GREEN LIGHT FOODS	YELLOW LIGHT FOODS	RED LIGHT FOODS
Quality	Low-calorie, high-fiber, low-fat, nutrient-dense	Nutrient-dense, but higher in calories and fat	High in calories, sugar, and fat
Types of food	Fruits, vegetables	Lean meats, dairy, starches, grains	Fatty meats, sugar, sugar-sweetened beverages, fried foods
Quantity	Unlimited	Limited	Infrequent or avoided

modest weight loss or BMI improvement even when combined with behavioral interventions. Various classes of drugs are of interest, including those that decrease energy intake or act centrally as anorexiants, those that affect the availability of nutrients through intestinal or renal tubular reabsorption, and those that affect metabolism. The only U.S. Food and Drug Administration (FDA)-approved medication for obesity in children <16 yr old is orlistat, which decreases absorption of fat, resulting in modest weight loss. Complications include flatulence, oily stools, and spotting. This agent offers little benefit to severely obese adolescents. Because there are multiple redundant neural mechanisms that act to protect body weight, promoting weight loss is extremely difficult. For this reason, there is considerable interest in combining therapies that simultaneously target multiple weight-regulating pathways. One example, approved for adults, combines phentermine, a noradrenergic agent, with topiramate, a γ-aminobutyric acid (GABA)-ergic medication. This combination resulted in a mean 10.2-kg weight loss compared to 1.4 kg in the placebo group. Side effects are common and include dry mouth, constipation, paresthesias, insomnia, and cognitive dysfunction. Another promising example is the combination of amylin (decreases food intake and slows gastric emptying) with leptin (which has no anorexigenic effects when given alone). This combination requires injection and is in clinical trials in adults. Another FDA approved (for adults) drug is lorcaserin, a selective serotonin 2C receptor agonist. Establishing long-term safety and tolerability in children is a challenge as medications of interest have central nervous system effects or interfere with absorption of nutrients; teratologic effects must be considered for use in adolescent girls.

In some cases, it is reasonable to refer adolescents for evaluation for bariatric surgery. The American Pediatric Surgical Association Guidelines recommends that surgery be considered only in children with complete or near-complete skeletal maturity, a BMI ≥40, and a medical complication resulting from obesity, *after* they have failed 6 mo of a multidisciplinary weight management program. Surgical approaches include the Roux-en-Y and the adjustable gastric band. In obese adults, bariatric surgery reduces the risk of developing type 2 diabetes mellitus. In obese adult patients with existing type 2 diabetes, bariatric surgery improves the control of diabetes.

PREVENTION

Prevention of child and adolescent obesity is essential for public health in the United States and most other countries (Table 47-6 and 47-7). Efforts by pediatric providers can supplement national- and community-level public health programs. The National Institutes of Health and Centers for Disease Control and Prevention recommend a variety of initiatives to combat the current obesigenic environment, including promotion of breastfeeding, access to fruits and vegetables, walkable communities, and 60 min/day of activity for children. The U.S. Department of Agriculture sponsors programs promoting 5.5 cups of fruits and vegetables per day. Incentives for the food industry to promote consumption of healthier foods should be considered. Marketing of unhealthy foods to children has begun to be regulated. We expect to see changes in federal food programs including commodity foods, the Women, Infant, and Children Supplemental Food Program, and school-lunch programs to meet the needs of today's children.

Pediatric prevention efforts begin with careful monitoring of weight and BMI percentiles at healthcare maintenance visits. Attention to changes in BMI percentiles can alert the pediatric provider to increasing adiposity before the child becomes overweight or obese. All families should be counseled about healthy nutrition for their children because the current prevalence of overweight and obesity in adults is 65%. Therefore, approximately two-thirds of all children can be considered at risk for becoming overweight or obese at some time in their lives. Those who have an obese parent are at increased risk. Prevention efforts begin with promotion of exclusive breastfeeding for 6 mo and total breastfeeding for 12 mo. Introduction of infant foods at 6 mo should focus on cereals, fruits, and vegetables. Lean meats, poultry, and fish may be introduced later in the 1st year of life. Parents should be specifically counseled to avoid introducing highly sugared beverages and foods in the 1st year of life. Instead, they should expose their infants and young children to a rich variety of fruits, vegetables, grains, lean meats, poultry, and fish to facilitate acceptance of a diverse and healthy diet. Parenting matters, and authoritative parents are more likely to have children with a healthy weight than those who are authoritarian or permissive. Families who eat regularly scheduled meals together are less likely to have overweight or obese children. Child health professionals are able to address a child's nutritional status and to provide expertise in child growth and development.

Child health professionals can also promote physical activity during regular healthcare maintenance visits. Parents who spend some of their leisure time in physical activity promote healthy weight in their children. Beginning in infancy, parents should be cognizant of their child's developmental capability and need for physical activity. Because television, computer, and video game time can replace health-promoting physical activity, physicians should counsel parents to limit screen time for their children. Snacking during television watching should be discouraged. Parents can help their children to understand that television commercials intend to sell a product. Children can learn that their parents will help them by responsibly choosing healthy foods.

As obesity is determined by complex multifactorial conditions, prevention will take efforts at multiple levels of social organization. One example, EPODE (Ensemble Prévenons l'Obésité Des Enfants), is a multilevel prevention strategy, which began in France and has been adopted by more than 500 communities in 6 countries. The goal is for local environments, daycare centers, schools, recreational settings and families to adopt practices that promote healthy lifestyles for children from birth to 12 yr old. This initiative relies on 4 necessary components: political commitment to change, resources to support social marketing and changes, support services, evidence-based practices. All EPODE sites include monitoring and evaluation. Similar efforts are taking place in the United States. An example of a U.S. community effort is Shape Up Somerville, a citywide campaign to increase daily physical activity and healthy eating in Somerville, MA, which has been ongoing since 2002. This systems intervention focuses on school health curricula, healthier food in schools and restaurants, safe routes to school, walkable and bikeable streets and worksite wellness. Communitywide programs are important because neighborhood environmental factors (poverty) have been associated with obesity in its residents. Although these efforts have resulted in lower weight gain in older children and adolescents, there is considerable interest in focusing earlier in the life cycle. Beginning obesity prevention during pregnancy and engaging health systems, early childhood programs, and community systems to support healthier life cycles is an approach with tremendous promise.

Bibliography is available at Expert Consult.

Table 47-6	Proposed Suggestions for Preventing Obesity

PREGNANCY
Normalize body mass index before pregnancy.
Do not smoke.
Maintain moderate exercise as tolerated.
In gestational diabetics, provide meticulous glucose control.
Gestational weight gain within the Institute of Medicine (IOM) recommendations.

POSTPARTUM AND INFANCY
Breastfeeding: exclusive for 4-6 mo, continue with other foods for 12 mo.
Postpone the introduction of baby foods to 4-6 mo and juices to 12 mo.

FAMILIES
Eat meals as a family in a fixed place and time.
Do not skip meals, especially breakfast.
No television during meals.
Use small plates, and keep serving dishes away from the table.
Avoid unnecessary sweet or fatty foods and sugar-sweetened drinks.
Remove televisions from children's bedrooms; restrict times for television viewing and video games.
Do not use food as a reward.

SCHOOLS
Eliminate candy and cookie sales as fundraisers.
Review the contents of vending machines and replace with healthier choices; eliminate sodas.
Avoid financial support for sports teams from beverage and food industries.
Install water fountains and hydration stations.
Educate teachers, especially physical education and science faculty, about basic nutrition and the benefits of physical activity.
Educate children from preschool through high school on appropriate diet and lifestyle.
Mandate minimum standards for physical education, including 60 min of strenuous exercise 5 times weekly.
Encourage "the walking school bus": groups of children walking to school with adult supervision.

COMMUNITIES
Increase family-friendly exercise and safe play facilities for children of all ages.
Develop more mixed residential-commercial developments for walkable and bicyclable communities.
Discourage the use of elevators and moving walkways.
Provide information on how to shop and prepare healthier versions of culture-specific foods.

HEALTHCARE PROVIDERS
Explain the biologic and genetic contributions to obesity.
Give age-appropriate expectations for body weight in children.
Work toward classifying obesity as a disease to promote recognition, reimbursement for care, and willingness and ability to provide treatment.

INDUSTRY
Mandate age-appropriate nutrition labeling for products aimed at children (e.g., red light/green light foods, with portion sizes).
Encourage marketing of interactive video games in which children must exercise in order to play.
Use celebrity advertising directed at children for healthful foods to promote breakfast and regular meals.
Reduce portion size (drinks and meals).

GOVERNMENT AND REGULATORY AGENCIES
Classify childhood obesity as a legitimate disease.
Find novel ways to fund healthy lifestyle programs (e.g., with revenues from food and drink taxes).
Subsidize government-sponsored programs to promote the consumption of fresh fruits and vegetables.
Provide financial incentives to industry to develop more healthful products and to educate the consumer on product content.
Provide financial incentives to schools that initiate innovative physical activity and nutrition programs.
Allow tax deductions for the cost of weight loss and exercise programs.
Provide urban planners with funding to establish bicycle, jogging, and walking paths.
Ban advertising of fast foods, nonnutritious foods, and sugar-sweetened beverages directed at preschool children, and restrict advertising to school-age children.
Ban toys as gifts to children for purchasing fast foods.

Adapted from Speiser PW, Rudolf MCJ, Anhalt H, et al: Consensus statement: childhood obesity, J Clin Endocrinol Metab *90:1871–1887, 2005.*

Table 47-7	Anticipatory Guidance: Establishing Healthy Eating Habits in Children

Do not punish a child during mealtimes with regard to eating. The emotional atmosphere of a meal is very important. Interactions during meals should be pleasant and happy.
Do not use foods as rewards.
Parents, siblings, and peers should model healthy eating, tasting new foods, and eating a well-balanced meal.
Children should be exposed to a wide range of foods, tastes, and textures.
New foods should be offered multiple times. Repeated exposure leads to acceptance and liking.
Forcing a child to eat a certain food will decrease the child's preference for that food. Children's wariness of new foods is normal and should be expected. Offering a variety of foods with low-energy density helps children balance energy intake.
Parents should control what foods are in the home. Restricting access to foods in the home will increase rather than decrease a child's desire for that food.
Children tend to be more aware of satiety than adults, so allow children to respond to satiety, and stop eating. Do not force children to "clean their plate."

Adapted from Benton D: Role of parents in the determination of food preferences of children and the development of obesity, Int J Obes Relat Metab Disord *28:858–869, 2004. Copyright 2004. Reprinted by permission from Macmillan Publishers Ltd.*

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Chapter 48

Vitamin A Deficiencies and Excess

A. Catharine Ross and Libo Tan

OVERVIEW OF VITAMIN A

Vitamin A is a fat-soluble micronutrient that cannot be synthesized de novo by the mammalian body, thus it is an obligatory dietary factor. The term vitamin A is generally used to refer to a group of compounds that possess the biologic activity of *all-trans* retinol (Fig. 48-1). As a fat-soluble micronutrient, vitamin A is recognized as being essential for all vertebrates for normal vision, reproduction, cell and tissue differentiation, and functions of the immune system. Vitamin A plays critical roles in neonatal development. It is required for normal embryonic development, hematopoiesis, immune response, metabolism, and growth and differentiation of many types of cells.

Vitamin A can be obtained from the diet where its main form is as retinyl esters, such as retinyl palmitate, which are called preformed vitamin A. They are found primarily in certain foods of animal origin. Organ meats (especially liver, kidney) are very rich in vitamin A, while other meats, milk, and cheese contain moderate levels. Other sources of vitamin A include several provitamin A carotenoids, which are found naturally in many fruits and vegetables, especially yellow-orange vegetables (pumpkin, squash, sweet potato), and leafy green vegetables (chard, spinach, broccoli). One of the most abundant carotenoids is β-carotene. α-Carotene and β-cryptoxanthin also possess vitamin A activity at a lower bioactivity. In the body, these precursors are used for the synthesis of 2 essential metabolites of vitamin A. One is *all-trans* retinoic acid, the form of vitamin A required for cell differentiation and the regulation of gene transcription. It is the most bioactive form of vitamin A. The other is *11-cis* retinal, required for vision. It functions as the light-absorbing chromophore of the visual pigments rhodopsin and iodopsin.

METABOLISM OF VITAMIN A

Ingested retinyl esters must first be hydrolyzed in the intestinal lumen, a process that liberates unesterified retinol, for the absorption of vitamin A. Most of the retinol is then reesterified in the enterocytes. The absorption of preformed vitamin A is very efficient. Approximately 70-90% of dietary preformed vitamin A is absorbed as long as there is ~10 g or more fat in the meal. Chronic intestinal disorders or lipid malabsorption can result in vitamin A deficiency. Uncleaved provitamin-A carotenoids in the intestine are also incorporated into chylomicrons and delivered to various tissues. The estimated absorption efficiency of carotenoids is approximately 20-50%, and appears to be more variable among individuals than for preformed vitamin A. The efficiency of conversion of B-carotene to retinol is much lower than expected. The carotene cleavage enzyme β-carotene monooxygenase, present in the enterocyte, exhibits certain single nucleotide polymorphisms that reduce the efficiency of conversion of β-carotene to retinol.

Once retinol is esterified in the enterocyte, retinyl ester is then packaged into nascent chylomicrons, which are then secreted into the lymphatic vessels and transported via the circulation to the liver or to other tissues. When vitamin A status is adequate, most mammals, including humans, store most of their total body vitamin A in the liver, within stellate cells. When their vitamin A status is deficient, vitamin A stores can be mobilized; the released retinol can be used by extrahepatic tissues. Stored vitamin A is released from the liver into the circulation as retinol bound to its specific transport protein, retinol-binding protein (RBP), which binds to the thyroid hormone transport protein, transthyretin (TTR); this complex delivers retinol (as well as the thyroid hormone) to a large number of vitamin A target tissues. The major physiologic mediator of retinol uptake by cells in many tissues is Stra6, a widely expressed multitransmembrane domain protein that functions as a cell-surface receptor for retinol bound to RBP.

In target tissues, retinol is either esterified into retinyl esters for storage or oxidized into retinoic acid for function. In the eye, 11-*cis*-retinal is formed.

Vitamin A Status in Neonates

Neonates begin life with low levels of vitamin A, in plasma, liver, and extrahepatic tissues, compared with those in adults. Normal plasma levels of retinol are 20-50 μg/dL in infants, and increase gradually as children become older. Median serum retinol values are 1.19 μmol/L in both boys and girls ages 4-8 yr; 1.4 and 1.33 μmol/L in boys and

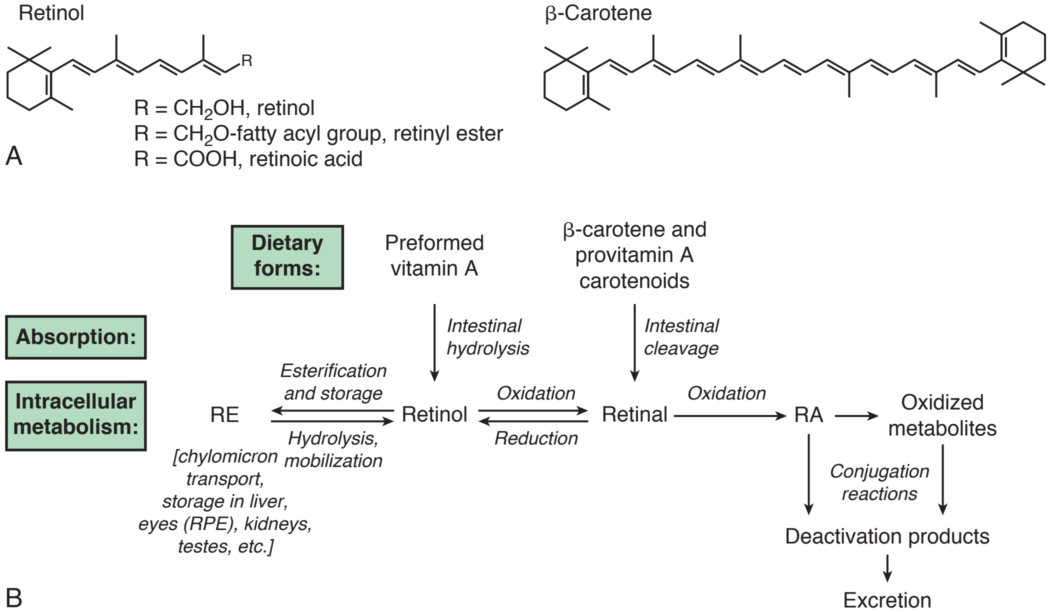

Figure 48-1 Vitamin A structures *(A)* and overview of vitamin A metabolism *(B)*.

girls, respectively, ages 9-13 yr; and 1.71 and 1.57 μmol/L in boys and girls, respectively, ages 14-18 yr (for conversion, 1 μmol/L = 28.6 μg/dL). Values of 1.96 and 1.85 μmol/L are found in 19-30 yr old adult men and women, respectively.

Retinol levels are even lower in neonates in developing countries where vitamin A intakes may be low and vitamin A deficiency is a common and significant nutritional problem. Lower vitamin A stores and plasma retinol concentrations are seen in low birthweight infants and in preterm newborns. Malnutrition, particularly protein nutrition, can cause vitamin A deficiency because of the impaired synthesis of RBP.

Inflammation as a Cause of Low Plasma Retinol

Inflammation is a cause of reduced levels of plasma retinol as a result of reduced synthesis of RBP and TTR. This condition may mimic a lack of vitamin A, but will not be corrected by supplementation. In U.S. adults, those with moderately elevated levels of C-reactive protein, indicative of mild inflammation, had lower average plasma retinol levels. The extent to which inflammation is a factor in low plasma retinol in children is uncertain but it is likely to be significant in acute infectious diseases such as measles, and possibly in chronic inflammatory conditions such as cystic fibrosis.

FUNCTIONS OF VITAMIN A AND MECHANISMS OF ACTION

Except for its role in vision, the pleiotropic actions of this micronutrient include many systemic functions that are mediated at the gene level by all-*trans*-retinoic acid (RA), which is a ligand for specific nuclear transcription factors, the retinoid receptors: RARs and RXRs. When an RAR is activated by the presence of RA, it combines with an RXR, and the resulting heterodimer binds to specific DNA sequences present in retinoid responsive genes (RAREs and RXREs, respectively) and therefore induce or repress the expression of a large number of genes. In this manner, vitamin A, via its active form, RA, regulates many genes that are involved in the fundamental biologic activities of cells, such as cell division, cell death, and cell differentiation. The term *retinoids* includes both natural and synthetic compounds with vitamin A activity and is most often used in the context of vitamin A action at the gene level. A large number of synthetic retinoids have been produced and some have gained clinical acceptance, such as in the treatment of skin disorders and certain cancers.

Retinoic acid is among the most important signaling molecules in vertebrate ontogenesis. It affects many physiologic processes, including reproduction, growth, embryonic and fetal development, and bone development, in addition to respiratory, gastrointestinal, hematopoietic, and immune functions. The role of vitamin A in immune function and host defense is particularly important in developing countries, where vitamin A supplementation or therapy reduces the morbidity and mortality rates of various diseases, such as measles (see Chapter 246).

Vitamin A plays a critical nongenomic role in vision. The human retina has 2 distinct photoreceptor systems: the rods, containing rhodopsin, which can detect low-intensity light, and the cones, containing iodopsin, which can detect different colors. The aldehyde form of vitamin A, retinal, is the prosthetic group on both visual proteins. The mechanism of vitamin A action in vision is based on the ability of the vitamin A molecule to photoisomerize (change shape when exposed to light). Thus, in the dark, low-intensity light isomerizes the rhodopsin prosthetic group, 11-*cis* retinal, to all-*trans*-retinal, generating an electrical signal that is transmitted via the optic nerve to the brain and results in visual sensation.

VITAMIN A DEFICIENCY

If the growing child has a well-balanced diet and obtains vitamin A from foods that are rich in vitamin A or provitamin-A (Table 48-1), the risk of vitamin A deficiency is small. However, even subclinical vitamin A deficiency can have serious consequences.

Deficiency states in developed countries are rare, except in some impoverished populations (see Chapter 46) or after mistakes in food preparation or with fad diets, but they are common in many developing countries and are often associated with global malnutrition (see Chapter 46). In the clinical setting, vitamin deficiencies can also occur as complications in children with various chronic disorders or diseases. Information obtained in the medical history related to dietary habits can be important in identifying the possibility of such nutritional problems. Except for vitamin A, toxicity from excess intake of vitamins is rare. Table 48-1 summarizes the food sources, functions, and deficiency and excess symptoms of the vitamins.

Clinical Manifestations of Vitamin A Deficiency

The most obvious symptoms of vitamin A deficiency are associated with the requirement of this vitamin for the maintenance of epithelial functions. In the intestines, a normal mucus-secreting epithelium (normal goblet cell function) is an effective barrier against pathogens that can cause diarrhea. Similarly, in the respiratory tract, a mucus-secreting epithelium is essential for the disposal of inhaled pathogens and toxicants. Characteristic changes as a result of vitamin A deficiency in the epithelia include a proliferation of basal cells, hyperkeratosis, and

Table 48-1 Vitamin A Characteristics

NAMES AND SYNONYMS	CHARACTERISTICS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	SOURCES
Retinol (vitamin A_1); 1 μg retinol = 3.3 IU vitamin A = 1 RAE Provitamins A: the plant pigments α-, β-, and γ-carotenes and cryptoxanthin have partial retinol activity: 12 μg β-carotene, or 24 μg other provitamin A carotenoids = 1 μg retinol	Fat-soluble; heat-stable; destroyed by oxidation, drying Bile necessary for absorption Stored in liver Protected by vitamin E	In vision, as retinal, for synthesis of the visual pigments rhodopsin and iodopsin In growth, reproduction, embryonic and fetal development, bone growth, immune and epithelial functions, via retinoic acid as a ligand for specific nuclear transcription factors, regulating genes involved in many fundamental cellular processes	Nyctalopia Photophobia, xerophthalmia, Bitot spots, conjunctivitis, keratomalacia leading to blindness Faulty epiphyseal bone formation Defective tooth enamel Keratinization of mucous membranes and skin Retarded growth Impaired resistance to infection, anemia, reproductive failure, fetal abnormalities	Anorexia, slow growth, drying and cracking of skin, enlargement of liver and spleen, swelling and pain of long bones, bone fragility, increased intracranial pressure, alopecia, carotenemia Fetal abnormalities	Liver, fish liver oils Dairy products, except skim milk Egg yolk, fortified margarine, fortified skim milk Carotenoids from plants: green vegetables, yellow fruits, and vegetables

RAE, retinol activity equivalent.

formation of stratified cornified squamous epithelium. Squamous metaplasia of the renal pelves, ureters, vaginal epithelium, and the pancreatic and salivary ducts can lead to increased infections in these areas. In the urinary bladder, loss of epithelial integrity can result in pyuria and hematuria. Epithelial changes in the skin caused by vitamin A deficiency are manifested as dry, scaly, hyperkeratotic patches, commonly on the arms, legs, shoulders, and buttocks. The combination of defective epithelial barriers to infection, low immune response, and lowered response to inflammatory stress, all because of insufficient vitamin A, can cause poor growth and serious health problems in children.

The most characteristic and specific signs of vitamin A deficiency are eye lesions, but they may be manifest rather late in the progression of vitamin A deficiency. Lesions caused by vitamin A deficiency develop insidiously and rarely occur before 2 yr of age. An early symptom is delayed adaptation to the dark, a result of reduced resynthesis of rhodopsin; later, when vitamin A deficiency is more advanced, it leads to **night blindness** as a consequence of the absence of retinal in the visual pigment, rhodopsin, of the retina. Photophobia is a common symptom. The pigment epithelium, the structural element of the retina, keratinizes. When the pigment epithelium degenerates, the rods and cones have no support and eventually break down, resulting in blindness.

As vitamin A deficiency progresses, the corneal and conjunctival epithelial tissues of the eye become severely altered; this change results from a lack of sufficient RA for normal epithelial cell morphology and function. The cornea protects the eye from the environment and is also important in light refraction. In early vitamin A deficiency, the cornea keratinizes, becomes opaque, is susceptible to infection, and forms dry, scaly layers of cells **(xerophthalmia).** The conjunctiva keratinizes and develops plaques (**Bitot spots** [Fig. 48-2]). In later stages, infection occurs, lymphocytes infiltrate, and the cornea becomes wrinkled; it degenerates irreversibly (keratomalacia and corneal ulceration), resulting in blindness. Advanced xerophthalmia (Fig. 48-3) and xerophthalmia with permanent damage to the eye (Fig. 48-4) may develop if untreated. These eye lesions are primarily diseases of the young and are a major cause of blindness in developing countries. Although rates of xerophthalmia have fallen, the number of affected children is still too high.

Other clinical signs of vitamin A deficiency include poor overall growth, diarrhea, susceptibility to infections, anemia, apathy, mental retardation, and increased intracranial pressure, with wide separation of the cranial bones at the sutures. There may be vision problems as a consequence of bone overgrowth causing pressure on the optic nerve.

Malnutrition, particularly protein deficiency, can cause vitamin A deficiency by the impaired synthesis of retinol transport protein. In developing countries, subclinical or clinical zinc deficiency can increase the risk of vitamin A deficiency. There is also some evidence of marginal zinc intakes in children in the United States.

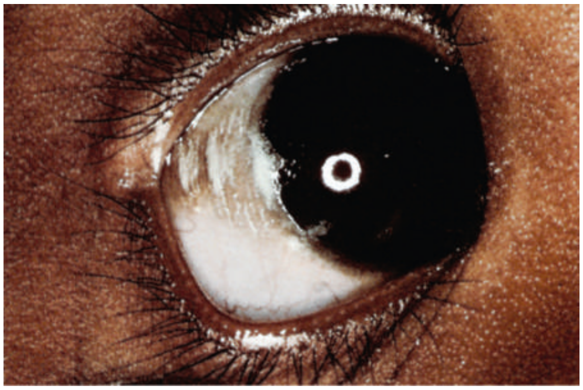

Figure 48-2 Bitot spots with hyperpigmentation seen in a 10 mo old Indonesian boy. *(From Oomen HAPC: Vitamin A deficiency, xerophthalmia and blindness,* Nutr Rev *6:161–166, 1974.)*

Diagnosis

Dark adaptation tests can be used to assess early-stage vitamin A deficiency. Although Bitot spots develop relatively early, those related to active vitamin A deficiency are usually confined to preschool-age children. Xerophthalmia is a very characteristic lesion of vitamin A deficiency. Caution must be exercised to exclude other, similar eye abnormalities from those associated with vitamin A deficiency. There are 3 useful indicators for detecting marginal vitamin A status, although they are mostly limited to research settings: conjunctival impression cytology, relative dose response, and modified relative dose response. A diet history can also be useful in suggesting or ruling out low intake as a cause. There is a relatively high prevalence of marginal vitamin A status among pregnant and lactating women. The plasma retinol level is not an accurate indicator of vitamin A status unless the deficiency is severe and liver stores are depleted, in which case low plasma retinol is likely to be evident. In children, plasma retinol values of <0.35 µmol/L are considered to be very deficient, 0.35-0.7 µmol/L are considered to be deficient, 0.7-1.05 µmol/L are considered to be marginal, and >1.05 µmol/L are considered to be adequate. It has long been thought that the liver vitamin A concentration must be 20 µg/g or higher to support a normal rate of secretion of retinol-RBP into plasma.

Epidemiology and Public Health Issues

Vitamin A deficiency and xerophthalmia still occur throughout much of the developing world and are linked to undernourishment and complicated by illness. Programs to provide periodic large doses of vitamin A have been instituted in many low-income countries in which vitamin

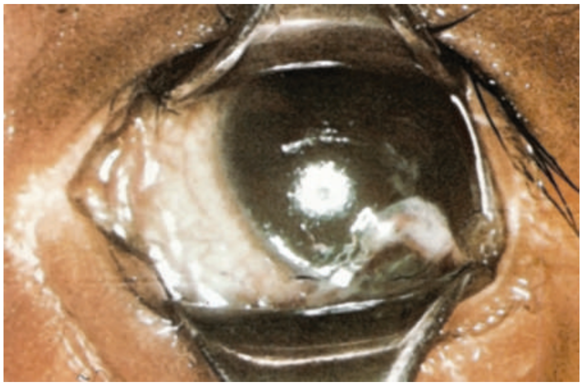

Figure 48-3 Advanced xerophthalmia with an opaque, dull cornea and some damage to the iris in a 1 yr old boy. *(From Oomen HAPC: Vitamin A deficiency, xerophthalmia and blindness,* Nutr Rev *6:161–166, 1974.)*

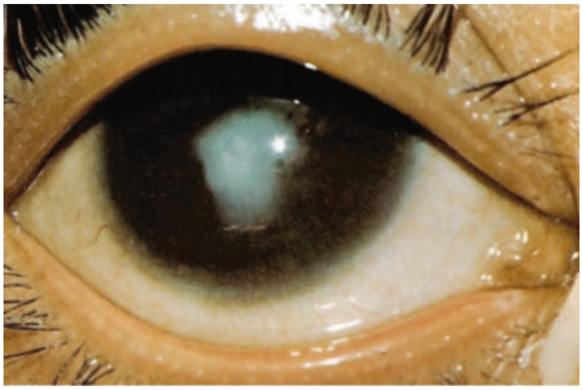

Figure 48-4 Recovery from xerophthalmia, showing a permanent eye lesion. *(From Bloch CE: Blindness and other disease arising from deficient nutrition [lack of fat soluble A factor],* Am J Dis Child *27:139, 1924.)*

Table 48-2 Dietary Reference Intakes for Vitamin A in Children

AGE RANGE	RECOMMENDED DIETARY ALLOWANCE (RDA) (μg retinol equivalents per day)	UPPER LEVEL (UL) (μg retinol equivalents per day)	COMMENTS
0-6 mo	400	600	The recommended intake for infants is an adequate intake, based on the amount of vitamin A normally present in breast milk
7-12 mo	500	600	
1-3 yr	300	600	The UL applies only to preformed vitamin A (retinol).
4-8 yr	400	900	
9-13 yr	600	1,700	
14-18 yr	900 male; 700 female	2,800	

A deficiency is still a public health problem. Vitamin A supplementation is considered part of the strategy of the World Health Organization's Millennium Development Goals to reduce <5 yr mortality. Other strategies being tested include improving the content of β-carotene in staple foods through plant breeding (biofortification).

Dietary Reference Intakes for the Healthy Population

Table 48-2 summarizes the dietary reference intakes for infants and children. Dietary reference intake values include the estimated average requirement, which is the mean biologic requirement for the nutrient in the population; the recommended dietary allowance (RDA), which is set to cover the needs of >97% of the population (thus the needs of many people are more than covered by the RDA); and the upper level (UL), an intake level above which risk of adverse effects may increase; the UL pertains only to chronic consumption of preformed vitamin A. The RDA is expressed as retinol activity equivalents (RAEs; 1 RAE = 1 μg all-*trans*-retinol; equivalents for provitamin-A in foods = 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin). From infancy to age 18 yr, the RDA increases as a consequence of increased body size, becoming higher for boys than girls during adolescence. During pregnancy, the RDA is 750-770 μg, and during lactation, the RDA is increased to 1,200-1,300 μg to ensure sufficient vitamin A content during breastfeeding.

It is noteworthy that, especially for young children, the UL is not far above the RDA, differing by only 2-fold in some age groups. This suggests that for children whose diet is good, care should be taken not to overuse dietary supplements containing preformed vitamin A and/or to avoid excessive consumption of foods that are rich in vitamin A, such as liver.

Vitamin A for Treatment of Deficiency

The safety and efficacy of vitamin A supplementation depend on the patient's state of health and the regimens of other treatments. A daily supplement of 1,500 μg of vitamin A is sufficient for treating latent vitamin A deficiency, after which intake an at RDA level should be the goal. In children without overt vitamin A deficiency, morbidity and mortality rates from viral infections, such as measles, have been reduced by administration of weekly doses equivalent to the RDA level of vitamin A, or higher doses of 30-60 mg of retinol (100,000-200,000 IU) given once or twice, under careful monitoring to avoid toxicity associated with excess vitamin A. Xerophthalmia is treated by giving 1,500 μg/kg body weight orally for 5 days followed by intramuscular injection of 7,500 μg of vitamin A in oil, until recovery.

Vitamin A is also used in preterm infants for improvement of respiratory function and prevention of the development of chronic lung disease. An analysis of 9 randomized controlled trials of vitamin A found that vitamin A appears to be beneficial in reducing death or oxygen requirement with no differences in neurodevelopmental outcomes.

HYPERVITAMINOSIS A

Chronic hypervitaminosis A results from excessive ingestion of preformed vitamin A (retinol or retinyl ester), generally for several weeks or months. The cause is often excessive use of vitamin A–containing supplements, or food faddism resulting in excessive intakes of organ meats. Toxicity can be induced in adults and children with chronic daily intakes of 15,000 μg and 6,000 μg, respectively. As there is no antidote for hypervitaminosis A, the prevention of this condition is most important. Symptoms may subside rapidly on withdrawal of the vitamin, but the rate of improvement depends on the amount of vitamin A that has built up in tissues. In extreme cases, hypervitaminosis A can be fatal. Signs of subacute or chronic toxicity can include headache; vomiting; anorexia; dry, itchy desquamating skin; seborrheic cutaneous lesions; fissuring at the corners of the mouth; alopecia and/or coarsening of the hair; bone abnormalities; swelling of the bones; enlargement of the liver and spleen; diplopia; increased intracranial pressure; irritability; stupor; limited motion; and dryness of the mucous membranes; desquamation of the palms and the soles of the feet. Radiographs may show hyperostosis affecting several long bones, especially in the middle of the shafts (Fig. 48-5). Serum levels of vitamin

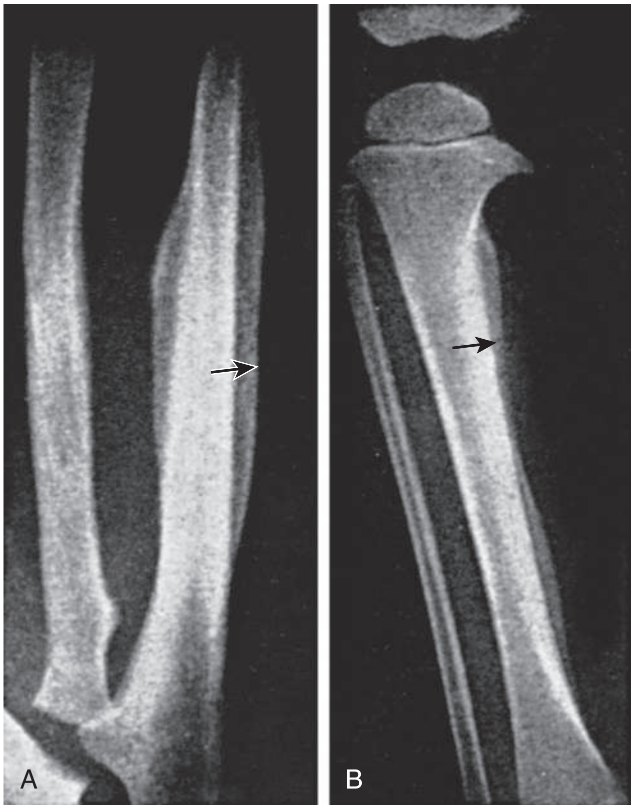

Figure 48-5 Hyperostosis of the ulna and tibia in an infant 21 mo of age, resulting from vitamin A positioning. *A,* Long, wavy cortical hyperostosis of the ulna (*arrow*). *B,* Long, wavy cortical hyperostosis of the right tibia (*arrow*), with a striking absence of metaphyseal changes. *(From Caffey J:* Pediatric x-ray diagnosis, *ed 5, Chicago, 1967, Year Book, p. 994.)*

A are elevated, mostly as retinyl ester contained in lipoproteins, which may contribute to membrane damage and symptoms, including release of liver enzymes into plasma. Hypercalcemia and/or liver cirrhosis may be present. Hypervitaminosis A is distinct from cortical hyperostosis (see Chapter 700).

In young children, toxicity is associated with vomiting and bulging fontanels. An affected child has anorexia, pruritus, and a lack of weight gain. Acute hypervitaminosis A, such as after consumption of a single large (30-60 mg dose) of vitamin A may include nausea, vomiting, and drowsiness; less-common symptoms include diplopia, papilledema, cranial nerve palsies, and other symptoms suggesting **pseudotumor cerebri.**

A syndrome of **severe congenital malformations** may occur in infants of mothers who have consumed therapeutic doses (0.5-1.5 mg/kg) of oral 13-*cis*-retinoic acid (e.g., Accutane), generally taken for the treatment of acne or cancer, during the 1st trimester of pregnancy. These malformations result in a high incidence (>20%) of spontaneous abortions and birth defects including characteristic craniofacial abnormalities. The U.S. Food and Drug Administration has increased the stringency of prescription of such drugs in women of childbearing age to attempt to reduce these birth defects.

Excessive intake of carotenoids is not associated with toxicity but can cause yellow coloration of the skin (carotenodermia) and serum (carotenemia) that disappears when intake is reduced. Children with liver disease, diabetes mellitus, or hypothyroidism are more susceptible. Food faddism including an excessive consumption of carotene-rich foods may be a cause of this condition.

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Chapter **49**

Vitamin B Complex Deficiencies and Excess

H.P.S. Sachdev and Dheeraj Shah

Vitamin B complex includes a number of water-soluble nutrients, including thiamine (B_1), riboflavin (B_2), niacin (B_3), pyridoxine (B_6), folate, cobalamin (B_{12}), biotin, and pantothenic acid. Choline and inositol are also considered part of the B complex and are important for normal body functions, but specific deficiency syndromes have not been attributed to a lack of these factors in the diet.

B-complex vitamins serve as coenzymes in many metabolic pathways that are functionally closely related. Consequently, a lack of one of the vitamins has the potential to interrupt a chain of chemical processes, including reactions that are dependent on other vitamins, and ultimately can produce diverse clinical manifestations. Because diets deficient in any one of the B-complex vitamins are often poor sources of other B vitamins, manifestations of several vitamin B deficiencies usually can be observed in the same person. It is therefore a general practice in a patient who has evidence of deficiency of a specific B vitamin to treat with the entire B-complex group of vitamins.

49.1 Thiamine (Vitamin B_1)

H.P.S. Sachdev and Dheeraj Shah

Thiamine diphosphate, the active form of thiamine, serves as a cofactor for several enzymes involved in carbohydrate catabolism such as pyruvate dehydrogenase, transketolase, and α-ketoglutarate. These enzymes also play a role in the hexose monophosphate shunt that generates nicotinamide adenine dinucleotide phosphate (NADP) and pentose for nucleic acid synthesis. Thiamine is also required for the synthesis of acetylcholine and γ-aminobutyric acid, which have important roles in nerve conduction. Thiamine is absorbed efficiently in the gastrointestinal (GI) tract, and may be deficient in persons with GI or liver disease. The requirement of thiamine is increased when carbohydrates are taken in large amounts and during periods of increased metabolism, such as fever, muscular activity, hyperthyroidism, pregnancy, and lactation. Alcohol affects various aspects of thiamine transport and uptake, contributing to the deficiency in alcoholics.

Pork (especially lean), fish, and poultry are good nonvegetarian **dietary sources** of thiamine. Main sources of thiamine for vegetarians are rice, oat, wheat, and legumes. Most ready-to-eat breakfast cereals are enriched with thiamine. Thiamine is water soluble and heat labile; most of the vitamin is lost when the rice is repeatedly washed and the cooking water is discarded. The breast milk of a well-nourished mother provides adequate thiamine; breastfed infants of thiamine-deficient mothers are at risk for deficiency. Thiamine antagonists (coffee, tea) and thiaminases (fermented fish) may contribute to thiamine deficiency. Most infants and older children consuming a balanced diet obtain an adequate intake of thiamine from food and do not require supplements.

DEFICIENCY

Deficiency of thiamine is associated with severely malnourished states, including malignancy and following surgery. The disorder (or spectrum of disorders) is classically associated with a diet consisting largely of polished rice (oriental beriberi); it can also arise if highly refined wheat flour forms a major part of the diet, in alcoholics, and in food faddists (occidental beriberi). Thiamine deficiency has often been reported from inhabitants of refugee camps consuming the polished rice–based monotonous diets. Low thiamine concentrations are also noted during critical illnesses.

Thiamine-responsive megaloblastic anemia (TRMA) syndrome is a rare autosomal recessive disorder characterized by megaloblastic anemia, diabetes mellitus, and sensorineural hearing loss, responding in varying degrees to thiamine treatment. The syndrome occurs because of mutations in the *SLC19A2* gene, encoding a thiamine transporter protein, leading to abnormal thiamine transportation and cellular vitamin deficiency. Thiamine and related vitamins may improve the outcome in children with Leigh encephalomyelopathy and type 1 diabetes mellitus.

Clinical Manifestations

Thiamine deficiency can develop within 2-3 mo of a deficient intake. Early symptoms of thiamine deficiency are nonspecific, such as fatigue, apathy, irritability, depression, drowsiness, poor mental concentration, anorexia, nausea, and abdominal discomfort. As the condition progresses, more-specific manifestations of **beriberi,** such as peripheral neuritis (manifesting as tingling, burning, paresthesias of the toes and feet), decreased deep tendon reflexes, loss of vibration sense, tenderness and cramping of the leg muscles, heart failure, and psychological disturbances, develop. Patients can have ptosis of the eyelids and atrophy of the optic nerve. Hoarseness or aphonia caused by paralysis of the laryngeal nerve is a characteristic sign. Muscle atrophy and tenderness of the nerve trunks are followed by ataxia, loss of coordination, and loss of deep sensation. Later signs include increased intracranial pressure, meningismus, and coma. The clinical picture of thiamine deficiency is usually divided into a dry (neuritic) type and a wet (cardiac) type. The disease is wet or dry depending on the amount of fluid that accumulates in the body as a result of factors such as cardiac and renal dysfunction, even though the exact cause for this edema is unknown. Many cases of thiamine deficiency show a mixture of both features and are more properly termed *thiamine deficiency with cardiopathy and peripheral neuropathy.*

The classic clinical triad of **Wernicke encephalopathy** (mental status changes, ocular signs, ataxia) is rarely reported in infants and

young children with severe deficiency secondary to malignancies or feeding of defective formula. An epidemic of life-threatening thiamine deficiency was seen in infants fed a defective soy-based formula that had undetectable thiamine levels. Manifestations included emesis, lethargy, restlessness, ophthalmoplegia, abdominal distention, developmental delay, failure to thrive, lactic acidosis, nystagmus, diarrhea, apnea, seizures, and auditory neuropathy.

Death from thiamine deficiency usually is secondary to cardiac involvement. The initial signs are cyanosis and dyspnea, but tachycardia, enlargement of the liver, loss of consciousness, and convulsions can develop rapidly. The heart, especially the right side, is enlarged. The electrocardiogram shows an increased Q-T interval, inverted T waves, and low voltage. These changes, as well as the cardiomegaly, rapidly revert to normal with treatment, but without prompt treatment, cardiac failure can develop rapidly and result in death. In fatal cases of beriberi, lesions are principally located in the heart, peripheral nerves, subcutaneous tissue, and serous cavities. The heart is dilated, and fatty degeneration of the myocardium is common. Generalized edema or edema of the legs, serous effusions, and venous engorgement are often present. Degeneration of myelin and axon cylinders of the peripheral nerves, with wallerian degeneration beginning in the distal locations, is also common, particularly in the lower extremities. Lesions in the brain include vascular dilation and hemorrhage.

Diagnosis

The diagnosis is often suspected on the basis of clinical setting and compatible symptoms. A high index of suspicion in children presenting with unexplained cardiac failure may sometimes be lifesaving. Objective biochemical tests of thiamine status include measurement of erythrocyte transketolase activity and the thiamine pyrophosphate effect. The biochemical diagnostic criteria of thiamine deficiency consist of low erythrocyte transketolase activity and high thiamine pyrophosphate effect (normal range: 0-14%). Urinary excretion of thiamine or its metabolites (thiazole or pyrimidine) after an oral loading dose of thiamine may also be measured to help identify the deficiency state. MRI changes of thiamine deficiency in infants are characterized by bilateral symmetric hyperintensities of the basal ganglia and frontal lobe, in addition to the lesions in the mammillary bodies, periaqueductal region, and thalami described in adults.

Prevention

A maternal diet containing sufficient amounts of thiamine prevents thiamine deficiency in breastfed infants, and infant formulas marketed in all developed countries provide recommended levels of intake. During complementary feeding, adequate thiamine intake can be achieved with a varied diet that includes meat and enriched or whole-grain cereals. When the staple cereal is polished rice, special efforts need to be made to include legumes and/or nuts in the ration. Thiamine and other vitamins can be retained in rice by **parboiling**, a process of steaming the rice in the husk before milling. Improvement in cooking techniques, such as not discarding the water used for cooking, minimal washing of grains, and reduction of cooking time helps to minimize the thiamine losses during the preparation of food. Thiamine supplementation should be ensured during total parenteral nutrition.

Treatment

In the absence of GI disturbances, oral administration of thiamine is effective. Children with cardiac failure, convulsions, or coma should be given 10 mg of thiamine intramuscularly or intravenously daily for the 1st wk. This treatment should then be followed by 3-5 mg of thiamine per day orally for at least 6 wk. The response is dramatic in infants and in those having predominantly cardiovascular manifestations, whereas the neurologic response is slow and often incomplete. Epilepsy, mental disability, and language and auditory problems of varying degree have been reported in survivors of severe infantile thiamine deficiency.

Patients with beriberi often have other B-complex vitamin deficiencies; therefore, all other B-complex vitamins should also be administered. Treatment of TRMA and other dependency states require higher dosages (100-200 mg/day). The anemia responds well to thiamine administration, and insulin for associated diabetes mellitus can also be discontinued in many cases of TRMA.

TOXICITY

There are no reports of adverse effects from consumption of excess thiamine by ingestion of food or supplements. A few isolated cases of pruritus and anaphylaxis have been reported in patients after parenteral administration of the vitamin.

Bibliography is available at Expert Consult.

49.2 Riboflavin (Vitamin B_2)

H.P.S. Sachdev and Dheeraj Shah

Riboflavin is part of the structure of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide, which participate in oxidation-reduction reactions in numerous metabolic pathways and in energy production via the mitochondrial respiratory chain. Riboflavin is stable to heat, but is destroyed by light. Milk, eggs, organ meats, legumes, and mushrooms are rich **dietary sources** of riboflavin. Most commercial cereals, flours, and breads are enriched with riboflavin.

DEFICIENCY

The causes of riboflavin deficiency are mainly related to malnourished and malabsorptive states, including GI infections. Treatment with some drugs, such as probenecid, phenothiazine, or oral contraceptives, can also cause the deficiency. The side chain of the vitamin is photochemically destroyed during phototherapy for hyperbilirubinemia, as it is involved in the photosensitized oxidation of bilirubin to more polar excretable compounds. Isolated **complex II deficiency**, a rare mitochondrial disease manifesting in infancy and childhood, responds favorably to riboflavin supplementation and thus can be termed a dependency state. **Brown-Vialetto-Van Laere syndrome** (BVVLS), a rare neurologic disorder characterized by progressive neurologic deterioration, hypotonia, sensorineural hearing loss, and pontobulbar palsy responds to treatment with high doses of riboflavin. Mutations in genes coding for riboflavin transporter proteins have been identified in children with BVVLS.

Clinical Manifestations

Clinical features of riboflavin deficiency include cheilosis, glossitis, keratitis, conjunctivitis, photophobia, lacrimation, corneal vascularization, and seborrheic dermatitis. Cheilosis begins with pallor at the angles of the mouth and progresses to thinning and maceration of the epithelium, leading to fissures extending radially into the skin (Fig. 49-1). In glossitis, the tongue becomes smooth, with loss of papillary structure (Fig. 49-2). Normochromic, normocytic anemia may also be seen because of the impaired erythropoiesis. A low riboflavin content of the maternal diet has been linked to congenital heart defects, but the evidence is weak.

Diagnosis

Most often, the diagnosis is based on the clinical features of angular cheilosis in a malnourished child, which responds promptly to riboflavin supplementation. A functional test of riboflavin status is done by measuring the activity of erythrocyte glutathione reductase (EGR), with and without the addition of FAD. An EGR activity coefficient (ratio of EGR activity with added FAD to EGR activity without FAD) of >1.4 is used as an indicator of deficiency. Urinary excretion of riboflavin <30 µg/24 hr also suggests low intakes.

Prevention

Table 49-1 lists the recommended daily allowance of riboflavin for infants, children, and adolescents. Adequate consumption of milk, milk products, and eggs prevents riboflavin deficiency. Fortification of

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Figure 49-1 Angular cheilosis with ulceration and crusting. *(Courtesy of National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India.)*

Figure 49-2 Glossitis as seen in riboflavin deficiency. *(From Zappe HA, Nuss S, Becker K, et al:* Riboflavin deficiency in Baltistan. http://www.rzuser.uni-heidelberg.de/%7Ecn6/baltista/ribofl_e.htm.*)*

Table 49-1 Water-Soluble Vitamins

NAMES AND SYNONYMS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	TREATMENT OF DEFICIENCY	CAUSES OF DEFICIENCY	DIETARY SOURCES	RDA* BY AGE
Thiamine (vitamin B_1)	Coenzyme in carbohydrate metabolism Nucleic acid synthesis Neurotransmitter synthesis	Neurologic (dry beriberi): irritability, peripheral neuritis, muscle tenderness, ataxia Cardiac (wet beriberi): tachycardia, edema, cardiomegaly, cardiac failure	3-5 mg/day PO thiamine for 6 wk	Polished rice–based diets Malabsorptive states Severe malnutrition Malignancies Alcoholism	Meat, especially pork; fish; liver Rice (unmilled), wheat germ; enriched cereals; legumes	0-6 mo: 0.2 mg/day 7-12 mo: 0.3 mg/day 1-3 yr: 0.5 mg/day 4-8 yr: 0.6 mg/day 9-13 yr: 0.9 mg/day 14-18 yr: Girls: 1.0 mg/day Boys: 1.2 mg/day
Riboflavin (vitamin B_2)	Constituent of flavoprotein enzymes important in oxidation-reduction reactions: amino acid, fatty acid, and carbohydrate metabolism and cellular respiration	Glossitis, photophobia, lacrimation, corneal vascularization, poor growth, cheilosis	3-10 mg/day PO riboflavin	Severe malnutrition Malabsorptive states Prolonged treatment with phenothiazines, probenecid, or OCPs	Milk, milk products, eggs, fortified cereals, green vegetables	0-6 mo: 0.3 mg/day 7-12 mo: 0.4 mg/day 1-3 yr: 0.5 mg/day 4-8 yr: 0.6 mg/day 9-13 yr: 0.9 mg/day 14-18 yr: Girls: 1.0 mg/day Boys: 1.3 mg/day
Niacin (vitamin B_3)	Constituent of NAD and NADP, important in respiratory chain, fatty acid synthesis, cell differentiation, and DNA processing	Pellagra manifesting as diarrhea, symmetric scaly dermatitis in sun-exposed areas, and neurologic symptoms of disorientation and delirium	50-300 mg/day PO niacin	Predominantly maize-based diets Anorexia nervosa Carcinoid syndrome	Meat, fish, poultry Cereals, legumes, green vegetables	0-6 mo: 2 mg/day 7-12 mo: 4 mg/day 1-3 yr: 6 mg/day 4-8 yr: 8 mg/day 9-13 yr: 12 mg/day 14-18 yr: Girls: 14 mg/day Boys: 16 mg/day
Pyridoxine (vitamin B_6)	Constituent of coenzymes for amino acid and glycogen metabolism, heme synthesis, steroid action, neurotransmitter synthesis	Irritability, convulsions, hypochromic anemia Failure to thrive Oxaluria	5-25 mg/day PO for deficiency states 100 mg IM or IV for pyridoxine-dependent seizures	Prolonged treatment with INH, penicillamine, OCPs	Fortified ready-to-eat cereals, meat, fish, poultry, liver, bananas, rice, potatoes	0-6 mo: 0.1 mg/day 7-12 mo: 0.3 mg/day 1-3 yr: 0.5 mg/day 4-8 yr: 0.6 mg/day 9-13 yr: 1.0 mg/day 14-18 yr: Girls: 1.2 mg/day Boys: 1.3 mg/day

Continued

Table 49-1 Water-Soluble Vitamins—cont'd

NAMES AND SYNONYMS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	TREATMENT OF DEFICIENCY	CAUSES OF DEFICIENCY	DIETARY SOURCES	RDA* BY AGE
Biotin	Cofactor for carboxylases, important in gluconeogenesis, fatty acid and amino acid metabolism	Scaly periorificial dermatitis, conjunctivitis, alopecia, lethargy, hypotonia, and withdrawn behavior	1-10 mg/day PO biotin	Consumption of raw eggs for prolonged periods Parenteral nutrition with infusates lacking biotin Valproate therapy	Liver, organ meats, fruits	0-6 mo: 5 µg/day 7-12 mo: 6 µg/day 1-3 yr: 8 µg/day 4-8 yr: 12 µg/day 9-13 yr: 20 µg/day 14-18 yr: 25 µg/day
Pantothenic acid (vitamin B_5)	Component of coenzyme A and acyl carrier protein involved in fatty acid metabolism	Experimentally produced deficiency in humans: irritability, fatigue, numbness, paresthesias (burning feet syndrome), muscle cramps		Isolated deficiency extremely rare in humans	Beef, organ meats, poultry, seafood, egg yolk Yeast, soybeans, mushrooms	0-6 mo: 1.7 mg/day 7-12 mo: 1.8 mg/day 1-3 yr: 2 mg/day 4-8 yr: 3 mg/day 9-13 yr: 4 mg/day 14-18 yr: 5 mg/day
Folic acid	Coenzymes in amino acid and nucleotide metabolism as an acceptor and donor of one-carbon units	Megaloblastic anemia Growth retardation, glossitis Neural tube defects in progeny	0.5-1 mg/day PO folic acid	Malnutrition Malabsorptive states Malignancies Hemolytic anemias Anticonvulsant therapy	Enriched cereals, beans, leafy vegetables, citrus fruits, papaya	0-6 mo: 65 µg/day 7-12 mo: 80 µg/day 1-3 yr: 150 µg/day 4-8 yr: 200 µg/day 9-13 yr: 300 µg/day 14-18 yr: 400 µg/day
Cobalamin (vitamin B_{12})	As deoxyadenosylcobalamin, acts as cofactor for lipid and carbohydrate metabolism As methylcobalamin, important for conversion of homocysteine to methionine and folic acid metabolism	Megaloblastic anemia, irritability, developmental delay, developmental regression, involuntary movements, hyperpigmentation	1,000 µg IM vitamin B_{12}	Vegan diets Malabsorptive states Crohn disease Intrinsic factor deficiency (pernicious anemia)	Organ meats, sea foods poultry, egg yolk, milk, fortified ready-to-eat cereals	0-6 mo: 0.4 µg/day 7-12 mo: 0.5 µg/day 1-3 yr: 0.9 µg/day 4-8 yr: 1.2 µg/day 9-13 yr: 1.8 µg/day 14-18 yr: 2.4 µg/day
Ascorbic acid (vitamin C)	Important for collagen synthesis, metabolism of cholesterol and neurotransmitters Antioxidant functions and nonheme iron absorption	Scurvy manifesting as irritability, tenderness and swelling of legs, bleeding gums, petechiae, ecchymoses, follicular hyperkeratosis, and poor wound healing	100-200 mg/day PO ascorbic acid for up to 3 mo	Predominantly milk-based (non–human milk) diets Severe malnutrition	Citrus fruits and fruit juices, peppers, berries, melons, tomatoes, cauliflower, leafy green vegetables	0-6 mo: 40 mg/day 7-12 mo: 50 mg/day 1-3 yr: 15 mg/day 4-8 yr: 25 mg/day 9-13 yr: 45 mg/day 14-18 yr: Girls: 65 mg/day Boys: 75 mg/day

*For healthy breastfed infants, the values represent adequate intakes, that is, the mean intake of apparently "normal" infants.
INH, isoniazid; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; OCP, oral contraceptive pill; RDA, recommended dietary allowance.
Source: Dietary Reference Intakes (DRIs): Recommended dietary allowances and adequate intakes, vitamins. *Food and Nutrition Board, Institute of Medicine, National Academies. Available from:* http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables.

cereal products is helpful for those who follow vegan diets or who are consuming inadequate amounts of milk products for other reasons.

Treatment

Treatment includes oral administration of 3-10 mg/day of riboflavin, often as an ingredient of a vitamin B–complex mix. The child should also be given a well-balanced diet, including milk and milk products.

TOXICITY

No adverse effects associated with riboflavin intakes from food or supplements have been reported, and the upper safe limit for consumption has not been established. Although the photosensitizing property of this vitamin raises the possibility for some potential risks, limited absorption in high-intake situations precludes such concerns.

Bibliography is available at Expert Consult.

49.3 Niacin (Vitamin B_3)

H.P.S. Sachdev and Dheeraj Shah

Niacin (nicotinamide or nicotinic acid) forms part of 2 cofactors, nicotinamide adenine dinucleotide and NADP, which are important in several biologic reactions, including the respiratory chain, fatty acid

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and steroid synthesis, cell differentiation, and DNA processing. Niacin is rapidly absorbed from the stomach and the intestines and can also be synthesized from tryptophan in the diet.

Major **dietary sources** of niacin are meat, fish, and poultry for non-vegetarians and cereals, legumes, and green leafy vegetables for vegetarians. Enriched and fortified cereal products and legumes also are major contributors to niacin intake. Milk and eggs contain little niacin but are good sources of tryptophan, which can be converted to nicotinamide adenine dinucleotide (60 mg tryptophan = 1 mg niacin).

DEFICIENCY

Pellagra, the classic niacin deficiency disease, occurs chiefly in populations where corn (maize), a poor source of tryptophan, is the major foodstuff. A severe dietary imbalance, such as in anorexia nervosa and in war or famine conditions, also can cause pellagra. Pellagra can also develop in conditions associated with disturbed tryptophan metabolism such as carcinoid syndrome and Hartnup disease.

Clinical Manifestations

The early symptoms of pellagra are vague: anorexia, lassitude, weakness, burning sensation, numbness, and dizziness. After a long period of deficiency, the classic triad of dermatitis, diarrhea, and dementia appears. **Dermatitis**, the most characteristic manifestation of pellagra, can develop suddenly or insidiously and may be initiated by irritants, including intense sunlight. The lesions first appear as symmetric areas of erythema on exposed surfaces, resembling sunburn, and might go unrecognized. The lesions are usually sharply demarcated from the surrounding healthy skin, and their distribution can change frequently. The lesions on the hands and feet often have the appearance of a glove or stocking (Fig. 49-3). Similar demarcations can also occur around the neck (Casal necklace) (Fig. 49-3). In some cases, vesicles and bullae develop (wet type). In others, there may be suppuration beneath the scaly, crusted epidermis; in still others, the swelling can disappear after a short time, followed by desquamation (Fig. 49-4). The healed parts of the skin might remain pigmented. The cutaneous lesions may be preceded by or accompanied by stomatitis, glossitis, vomiting, and/or diarrhea. Swelling and redness of the tip of the tongue and its lateral margins is often followed by intense redness, even ulceration, of the entire tongue and the papillae. Nervous symptoms include depression, disorientation, insomnia, and delirium.

The classic symptoms of pellagra usually are not well developed in infants and young children, but anorexia, irritability, anxiety, and apathy are common. Young patients might also have sore tongues and lips, and usually have dry and scaly skin. Diarrhea and constipation can alternate, and anemia can occur. Children who have pellagra often have evidence of other nutritional deficiency diseases.

Diagnosis

Because of lack of a good functional test to evaluate niacin status, the diagnosis of deficiency is usually made from the physical signs of glossitis, GI symptoms, and a symmetric dermatitis. Rapid clinical response to niacin is an important confirmatory test. A decrease in the concentration and/or a change in the proportion of the niacin metabolites N^1-methyl-nicotinamide and 2-pyridone in the urine provide biochemical evidence of deficiency and can be seen before the appearance of overt signs of deficiency. Histopathologic changes from the affected skin include dilated blood vessels without significant inflammatory infiltrates, ballooning of the keratinocytes, hyperkeratosis, and epidermal necrosis.

Prevention

Adequate intakes of niacin are easily met by consumption of a diet that consists of a variety of foods and includes meat, eggs, milk, and enriched or fortified cereal products. The dietary reference intake (DRI) is expressed in mg niacin equivalents (NE) in which 1 mg NE = 1 mg niacin or 60 mg tryptophan. An intake of 2 mg of niacin is considered adequate for infants 0-6 mo of age; and 4 mg is adequate for infants 7-12 mo of age. For older children, the recommended

Figure 49-3 Characteristic skin lesions of pellagra on hands and lesions on the neck (Casal necklace). *(Courtesy of Dr. J.D. MacLean, McGill Centre for Tropical Diseases, Montreal, Canada.)*

Figure 49-4 Clinical manifestations of niacin deficiency before *(A)* and after *(B)* therapy. *(From Weinsier RL, Morgan SL:* Fundamentals of clinical nutrition, *St. Louis, 1993, Mosby, p. 99.)*

intakes are 6 mg for 1-3 yr of age, 8 mg for 4-8 yr of age, 12 mg for 9-13 yr of age, and 14-16 mg for 14-18 yr of age.

Treatment

Children usually respond rapidly to treatment. A liberal and varied diet should be supplemented with 50-300 mg/day of niacin; in severe cases or in patients with poor intestinal absorption, 100 mg may be given intravenously. The diet should also be supplemented with other vitamins, especially other B-complex vitamins. Sun exposure should be avoided during the active phase of pellagra, and the skin lesions may be covered with soothing applications. Other coexisting nutrient deficiencies such as iron deficiency anemia should be treated. Even after successful treatment, the diet should continue to be monitored to prevent recurrence.

TOXICITY

There are no toxic effects associated with the intake of naturally occurring niacin in foods. Shortly after the ingestion of large doses of nicotinic acid taken as a supplement or a pharmacologic agent, a person often experiences a burning, tingling, and itching sensation as well as flushing on the face, arms, and chest. Large doses of niacin also can have nonspecific GI effects and can cause cholestatic jaundice or hepatotoxicity. Tolerable upper intake levels for children are approximately double the recommended dietary allowance.

Bibliography is available at Expert Consult.

49.4 Vitamin B_6 (Pyridoxine)

H.P.S. Sachdev and Dheeraj Shah

Vitamin B_6 includes a group of closely related compounds: pyridoxine, pyridoxal, pyridoxamine, and their phosphorylated derivatives. Pyridoxal 5′-phosphate (PLP) and, to a lesser extent, pyridoxamine phosphate function as coenzymes for many enzymes involved in amino acid metabolism, neurotransmitter synthesis, glycogen metabolism, and steroid action. If vitamin B_6 is lacking, glycine metabolism can lead to oxaluria. The major excretory product in the urine is 4-pyridoxic acid.

The vitamin B_6 content of human milk and infant formulas is adequate. Good **food sources** of the vitamin include fortified ready-to-eat cereals, meat, fish, poultry, liver, bananas, rice, and certain vegetables. Large losses of the vitamin can occur during high-temperature processing of foods or milling of cereals, whereas parboiling of rice prevents its loss.

DEFICIENCY

Because of the importance of vitamin B_6 in amino acid metabolism, high protein intakes can increase the requirement for the vitamin; the recommended daily allowances are sufficient to cover the expected range of protein intake in the population. The risk of deficiency is increased in persons taking medications that inhibit the activity of vitamin B_6 (isoniazid, penicillamine, corticosteroids, phenytoin, carbamazepine), in young women taking oral progesterone-estrogen contraceptives, and in patients receiving maintenance dialysis.

Clinical Manifestations

The deficiency symptoms seen in infants are listlessness, irritability, seizures, vomiting, and failure to thrive. Peripheral neuritis is a feature of deficiency in adults but is not usually seen in children. Electroencephalogram (EEG) abnormalities have been reported in infants as well as in young adult subjects in controlled depletion studies. Skin lesions include cheilosis, glossitis, and seborrheic dermatitis around the eyes, nose, and mouth. Microcytic anemia can occur in infants, but is not common. Oxaluria, oxalic acid bladder stones, hyperglycinemia, lymphopenia, decreased antibody formation, and infections also are associated with vitamin B_6 deficiency.

Several types of vitamin B_6 **dependence syndromes,** presumably resulting from errors in enzyme structure or function, respond to very large amounts of pyridoxine. These syndromes include pyridoxine-dependent epilepsy, a vitamin B_6–responsive anemia, xanthurenic aciduria, cystathioninuria, and homocystinuria (see Chapters 85, 456, and 601). Pyridoxine-dependent epilepsy involves mutations in the *ALDH7A1* gene causing deficiency of antiquitin, an enzyme involved in dehydrogenation of L-alpha-aminoadipic semialdehyde.

Diagnosis

The activity of the erythrocyte transaminases glutamic oxaloacetic transaminase and glutamic pyruvic transaminase is low in vitamin B_6 deficiency; tests measuring the activity of these enzymes before and after the addition of PLP may be useful as indicators of vitamin B_6 status. Abnormally high xanthurenic acid excretion after tryptophan ingestion also provides evidence of deficiency. Plasma PLP assays are being used more often, but factors other than deficiency can influence the results. Vitamin B_6 deficiency or dependence should be suspected in all infants with seizures. If more common causes of infantile seizures have been eliminated, 100 mg of pyridoxine can be injected, with EEG monitoring if possible. If the seizure stops, vitamin B_6 deficiency should be suspected. In older children, 100 mg of pyridoxine may be injected intramuscularly while the EEG is being recorded; a favorable response of the EEG suggests pyridoxine deficiency.

Prevention

Deficiency is unlikely in children consuming diets that meet their energy needs and contain a variety of foods. **Parboiling** of rice prevents the loss of vitamin B_6 from the grains. The DRIs for vitamin B_6 are 0.1 mg/day for infants up to 6 mo of age; 0.3 mg/day for ages 6 mo to 1 yr; 0.5 mg/day for ages 1-3 yr; 0.6 mg/day for ages 4-8 yr; 1.0 mg/day for ages 9-13 yr; and 1.2-1.3 mg/day for ages 14-18 yr. Infants whose mothers have received large doses of pyridoxine during pregnancy are at increased risk for seizures from pyridoxine dependence, and supplements during the 1st few weeks of life should be considered. Any child receiving a pyridoxine antagonist, such as isoniazid, should be carefully observed for neurologic manifestations; if these develop, vitamin B_6 should be administered or the dose of the antagonist should be decreased.

Treatment

Intramuscular or intravenous administration of 100 mg of pyridoxine is used to treat convulsions caused by vitamin B_6 deficiency. One dose should be sufficient if adequate dietary intake follows. For pyridoxine-dependent children, daily doses of 2-10 mg intramuscularly or 10-100 mg orally may be necessary.

TOXICITY

Adverse effects have not been associated with high intakes of vitamin B_6 from food sources. However, ataxia and sensory neuropathy have been reported with dosages as low as 100 mg/day in adults taking vitamin B_6 supplements for several months.

Bibliography is available at Expert Consult.

49.5 Biotin

H.P.S. Sachdev and Dheeraj Shah

Biotin functions as a cofactor for enzymes involved in carboxylation reactions within and outside mitochondria. These biotin-dependent carboxylases catalyze key reactions in gluconeogenesis, fatty acid metabolism, and amino acid catabolism.

There is limited information on the biotin content of foods; it is believed to be widely distributed, thus making a deficiency unlikely. Avidin found in raw egg whites acts as a biotin antagonist. Signs of biotin deficiency have been demonstrated in persons who consume large amounts of raw egg whites over long periods. Deficiency also has been described in infants and children receiving enteral and parenteral

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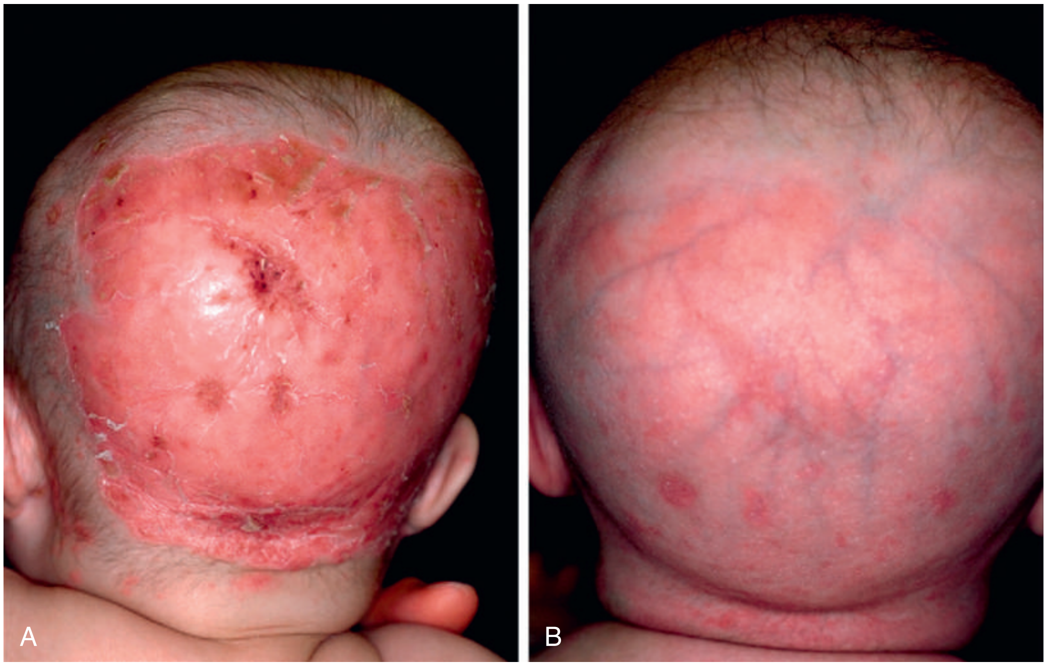

Figure 49-5 Scalp rash *(A)* Before treatment with biotin, *(B)* After 3 wk of biotin treatment. *(From Ito T, Nishie W, Fujita Y, et al: Infantile eczema caused by formula milk.* Lancet *381:1958, 2013.)*

nutrition formula that lack biotin. Treatment with valproic acid may result in a low biotinidase activity and/or biotin deficiency.

The clinical findings of biotin deficiency include scaly periorificial dermatitis, conjunctivitis, thinning of hair, and alopecia (Fig. 49-5). Central nervous system abnormalities seen with biotin deficiency are lethargy, hypotonia, seizures, ataxia, and withdrawn behavior. Biotin deficiency can be successfully treated using 1-10 mg of biotin orally daily. The adequate dietary intake values for biotin are 5 µg/day for ages 0-6 mo, 6 µg/day for ages 7-12 mo, 8 µg/day for ages 1-3 yr, 12 µg/day for ages 4-8 yr, 20 µg/day for ages 9-13 yr, and 25 µg/day for ages 14-18 yr. No toxic effects have been reported with very high doses.

Biotin responsive basal ganglia disease is a rare childhood neurologic disorder characterized by encephalopathy, seizures, and extrapyramidal manifestations. Chapter 85.6 describes conditions involving deficiencies in the enzymes holocarboxylase synthetase and biotinidase that respond to treatment with biotin.

Bibliography is available at Expert Consult.

49.6 Folate

H.P.S. Sachdev and Dheeraj Shah

Folate exists in a number of different chemical forms. Folic acid (pteroylglutamic acid) is the synthetic form used in fortified foods and supplements. Naturally occurring folates in foods retain the core chemical structure of pteroylglutamic acid but vary in their state of reduction, the single carbon moiety they bear, or the length of the glutamate chain. These polyglutamates are broken down and reduced in the small intestine to dihydro- and tetrahydrofolates, which are involved as coenzymes in amino acid and nucleotide metabolism as acceptors and donors of 1-carbon units. Folate is important for central nervous system development during embryogenesis.

Rice and cereals are rich **dietary sources** of folate, especially if enriched. Beans, leafy vegetables, and fruits such as oranges and papaya are good sources, too. The vitamin is readily absorbed from the small intestine and is broken down to monoglutamate derivatives by mucosal polyglutamate hydrolases. A high-affinity proton-coupled folate transporter (PCFT) seems to be essential for absorption of folate in intestine and in various cell types at low pH. The vitamin is also synthesized by the colonic bacteria, and the half-life of the vitamin is prolonged by enterohepatic recirculation.

DEFICIENCY

Because of its role in protein, DNA, and RNA synthesis, the risk of deficiency is increased during periods of rapid growth or increased cellular metabolism. Folate deficiency can result from poor nutrient content in diet, inadequate absorption (celiac disease, inflammatory bowel disease), increased requirement (sickle cell anemia, psoriasis, malignancies, periods of rapid growth as in infancy and adolescence), or inadequate utilization (long-term treatment with high-dose nonsteroidal antiinflammatory drugs; anticonvulsants such as phenytoin and phenobarbital; and methotrexate). Rare causes of deficiency are hereditary folate malabsorption, inborn errors of folate metabolism (methylene tetrahydrofolate reductase, methionine synthase reductase, and glutamate formiminotransferase deficiencies), and cerebral folate deficiency. A loss-of-function mutation in the gene coding for PCFT is the molecular basis for hereditary folate malabsorption. A high-affinity blocking autoantibody against the membrane-bound folate receptor in the choroid plexus preventing its transport across the blood–brain barrier is the likely cause of the infantile cerebral folate deficiency.

Clinical Manifestations

Folic acid deficiency results in megaloblastic anemia and hypersegmentation of neutrophils. Nonhematologic manifestations include glossitis, listlessness, and growth retardation not related to anemia. There is an association between low maternal folic acid status and neural tube defects, primarily spina bifida and anencephaly, and the role of periconceptional folic acid in their prevention is well established.

Hereditary folate malabsorption manifests at 1-3 mo of age with recurrent or chronic diarrhea, failure to thrive, oral ulcerations, neurologic deterioration, megaloblastic anemia, and opportunistic infections. Cerebral folate deficiency manifests at 4-6 mo of age with irritability, microcephaly, developmental delay, cerebellar ataxia, pyramidal tract signs, choreoathetosis, ballismus, seizures, and blindness as a result of optic atrophy. 5-Methyltetrahydrofolate levels are normal in serum and red blood cells (RBCs), but are markedly depressed in the cerebrospinal fluid.

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Diagnosis

The diagnosis of folic acid deficiency anemia is made in the presence of macrocytosis along with low folate levels in serum and/or RBCs. Normal serum folic acid levels are 5-20 ng/mL; with deficiency, serum folic acid levels are <3 ng/mL. Levels of RBC folate are a better indicator of chronic deficiency. The normal RBC folate level is 150-600 ng/mL of packed cells. The bone marrow is hypercellular because of erythroid hyperplasia, and megaloblastic changes are prominent. Large, abnormal neutrophilic forms (giant metamyelocytes) with cytoplasmic vacuolation also are seen.

Cerebral folate deficiency is associated with low levels of 5-methyltetrahydrofolate in the cerebrospinal fluid and normal folate levels in the plasma and RBCs. Mutations in the PCFT gene are demonstrated in the hereditary folate malabsorption.

Prevention

Breastfed infants have better folate nutrition than non–breastfed infants throughout infancy. Consumption of folate-rich foods and food-fortification programs are important to ensure adequate intake in children and in women of childbearing age. The DRIs for folate are 65 µg of dietary folate equivalents (DFE) for infants 0-6 mo of age and 80 µg of DFE for infants between 6 and 12 mo of age. (1 DFE = 1 µg food folate = 0.6 µg of folate from fortified food or as a supplement consumed with food = 0.5 µg of a supplement taken on an empty stomach.) For older children, the DRIs are 150 µg of DFE for ages 1-3 yr; 200 µg of DFE for ages 4-8 yr; 300 µg of DFE for ages 9-13 yr; and 400 µg of DFE for ages 14-18 yr. All women desirous of becoming pregnant should consume 400-800 µg folic acid daily; the dose is 4 mg/day in those having delivered a child with neural tube defect. To be effective, supplementation should be started at least 1 mo before conception, and continued through the first 2-3 mo of pregnancy. There may be a marginal benefit of periconceptional folate supplementation in prevention of autistic spectrum disorders. Providing iron and folic acid tablets for prevention of anemia in children and pregnant women is a routine strategy in at-risk populations. Mandatory fortification of cereal flours with folic acid coupled with health-education programs has been associated with a substantial reduction in incidence of neural tube defects in many countries.

Treatment

When the diagnosis of folate deficiency is established, folic acid may be administered orally or parenterally at 0.5-1.0 mg/day. Folic acid therapy should be continued for 3-4 wk or until a definite hematologic response has occurred. Maintenance therapy with 0.2 mg of folate is adequate. Prolonged treatment with oral folinic acid is required in cerebral folate deficiency, and the response may be incomplete. Treatment of hereditary folate malabsorption may be possible with intramuscular folinic acid; some patients may respond to high-dose oral folinic acid therapy.

TOXICITY

No adverse effects have been associated with consumption of the amounts of folate normally found in fortified foods. Excessive intake of folate supplements might obscure and potentially delay the diagnosis of vitamin B_{12} deficiency. Massive doses given by injection have the potential to cause neurotoxicity.

Bibliography is available at Expert Consult.

49.7 Vitamin B_{12} (Cobalamin)

H.P.S. Sachdev and Dheeraj Shah

Vitamin B_{12}, in the form of deoxyadenosylcobalamin, functions as a cofactor for isomerization of methylmalonyl-CoA to succinyl-CoA, an essential reaction in lipid and carbohydrate metabolism. Methylcobalamin is another circulating form of vitamin B_{12}, and is essential for methyl group transfer during the conversion of homocysteine to methionine. This reaction also requires a folic acid cofactor and is important for protein and nucleic acid biosynthesis. Vitamin B_{12} is important for hematopoiesis, central nervous system myelination, and mental and psychomotor development.

Dietary sources of vitamin B_{12} are almost exclusively from animal foods. Organ meats, muscle meats, sea foods (mollusks, oysters, fish), poultry, and egg yolk are rich sources. Fortified ready-to-eat cereals and milk and their products are the important sources of the vitamin for vegetarians. Human milk is an adequate source for breastfeeding infants if the maternal serum B_{12} levels are adequate. The vitamin is absorbed from ileum at alkaline pH after binding with intrinsic factor. Enterohepatic circulation, direct absorption, and synthesis by intestinal bacteria are additional mechanisms helping to maintain the vitamin B_{12} nutriture.

DEFICIENCY

Vitamin B_{12} deficiency because of inadequate dietary intake occurs primarily in persons consuming strict vegetarian or vegan diets. Prevalence of vitamin B_{12} deficiency is high in predominantly vegetarian or lactovegetarian populations. Breastfeeding infants of B_{12}-deficient mothers are also at risk for significant deficiency. Malabsorption of B_{12} occurs in celiac disease, ileal resections, Crohn disease, *Helicobacter pylori* infection, and autoimmune atrophic gastritis (pernicious anemia). Use of proton pump inhibitors and/or histamine 2 receptor antagonists may increase the risk of deficiency. Hereditary intrinsic factor deficiency and Imerslund-Gräsbeck disease are inborn errors of metabolism leading to vitamin B_{12} malabsorption. Mutations in the hereditary intrinsic factor gene cause hereditary intrinsic factor deficiency, whereas mutations in any of the 2 subunits (cubilin and amnionless) of the intrinsic factor receptor cause Imerslund-Gräsbeck disease.

Clinical Manifestations

The hematologic manifestations of vitamin B_{12} deficiency are similar to manifestations of folate deficiency and are discussed in Chapter 454.2. Irritability, hypotonia, developmental delay, developmental regression, and involuntary movements are the common neurologic symptoms in infants and children, whereas sensory deficits, paresthesias, and peripheral neuritis are seen in adults. Hyperpigmentation of the knuckles (Fig. 49-6) and palms is another common observation with B_{12} deficiency in children. Maternal B_{12} deficiency may also be an independent risk factor for fetal neural tube defects.

Figure 49-6 Hyperpigmentation of knuckles in an infant with vitamin B_{12} deficiency and megaloblastic anemia.

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Diagnosis

See Chapter 454.2.

Treatment

The hematologic symptoms respond promptly to parenteral administration of 250-1,000 µg vitamin B_{12}. Children with severe deficiency and those with neurologic symptoms need repeated doses; daily or alternate days in first week followed by weekly for the first 1-2 mo, and then monthly thereafter. Children having only hematologic presentation recover fully within 2-3 mo, whereas those with neurologic disease need at least 6 mo of therapy. Children with continuing malabsorptive state, and those having inborn errors of vitamin B_{12} malabsorption need lifelong treatment. Prolonged daily treatment with high dose (1,000-2,000 µg) oral vitamin B_{12} preparations has also been found to be equally effective in achieving hematologic and neurologic responses in the elderly, but the data are inadequate in children and young adults.

Prevention

The DRIs are 0.4 µg/day at age 0-6 mo, 0.5 µg/day at age 6-12 mo, 0.9 µg/day at age 1-3 yr, 1.2 µg/day at age 4-8 yr, 1.8 µg/day at age 9-13 yr, 2.4 µg/day at age 14-18 yr and in adults, 2.6 µg/day in pregnancy, and 2.8 µg/day in lactation. Pregnant and breastfeeding women should ensure an adequate consumption of animal products to prevent the deficiency in infants. Strict vegetarians, especially vegans, should ensure regular consumption of vitamin B_{12}. Food fortification with the vitamin helps to prevent deficiency in predominantly vegetarian populations.

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Chapter 50

Vitamin C (Ascorbic Acid)

Dheeraj Shah and H.P.S. Sachdev

Vitamin C is important for synthesis of collagen at the level of hydroxylation of lysine and proline in precollagen. It is also involved in neurotransmitter metabolism (conversion of dopamine to norepinephrine and tryptophan to serotonin), cholesterol metabolism (conversion of cholesterol to steroid hormones and bile acids), and the biosynthesis of carnitine. Vitamin C functions to maintain the iron and copper atoms, cofactors of the metalloenzymes, in a reduced (active) state. Vitamin C is an important antioxidant (electron donor) in the aqueous milieu of the body. Vitamin C enhances nonheme iron absorption, the transfer of iron from transferrin to ferritin, and the formation of tetrahydrofolic acid and thus can affect the cellular and immunologic functions of the hematopoietic system.

DIETARY NEEDS AND SOURCES

Humans depend on dietary sources for vitamin C. An adequate intake is 40 mg for age 0-6 mo and 50 mg for age 6-12 mo. For older children, the recommended dietary allowance is 15 mg for age 1-3 yr, 25 mg for age 4-8 yr, 45 mg for age 9-13 yr, and 65-75 mg for age 14-18 yr. The recommended dietary allowances during pregnancy and lactation are 85 mg/day and 120 mg/day, respectively. The requirement for vitamin C is increased during infectious and diarrheal diseases. Children exposed to smoking or environmental tobacco smoke also require increased amounts of foods rich in vitamin C. The best food sources of vitamin C are citrus fruits and fruit juices, peppers, berries, melons, tomatoes, cauliflower, and green leafy vegetables. Vitamin C is easily destroyed by prolonged storage, overcooking, and processing of foods.

Absorption of vitamin C occurs in the upper small intestine by an active process or by simple diffusion when large amounts are ingested. Vitamin C is not stored in the body but is taken up by all tissues; the highest levels are found in the pituitary and adrenal glands. The brain ascorbate content in the fetus and neonate is manyfold higher than the content in the adult brain, a finding probably related to its function in neurotransmitter synthesis.

When a mother's intake of vitamin C during pregnancy and lactation is adequate, the newborn will have adequate tissue levels of vitamin C related to active placental transfer, subsequently maintained by the vitamin C in breast milk or commercial infant formulas. Breast milk contains sufficient vitamin C to prevent deficiency throughout infancy. Infants consuming pasteurized or boiled animal milk are at significant risk of developing deficiency if the other sources of vitamin C are also lacking in the diet. Neonates whose feeding has been delayed because of clinical condition can also suffer from ascorbic acid deficiency. For patients on total parenteral nutrition, a parenteral dose of 80 mg/day is recommended for full-term infants and a parenteral dose of 25 mg/kg/day is recommended for preterm infants. Children who choose a limited diet or those on fad diets are at risk for vitamin C deficiency.

DEFICIENCY

A deficiency of vitamin C results in the clinical presentation of **scurvy**, the oldest nutritional deficiency disease to be recognized. Children fed predominantly heat-treated (ultrahigh-temperature or pasteurized) milk or unfortified formulas and not receiving fruits and fruit juices are at significant risk for symptomatic disease. In scurvy, there is defective formation of connective tissues and collagen in skin, cartilage, dentine, bone, and blood vessels, leading to their fragility. In the long bones, osteoid is not deposited by osteoblasts, cortex is thin, and the trabeculae become brittle and fracture easily.

Clinical Features

The early manifestations are irritability, loss of appetite, low-grade fever, musculoskeletal pain, and tenderness in the legs. These signs and symptoms are followed by leg swelling—most marked at the knees and the ankles—and **pseudoparalysis**. The infant might lie with the hips and knees semiflexed and the feet rotated outward. Subperiosteal hemorrhages in the lower limb bones sometimes acutely increase the swelling and pain, and the condition might mimic acute osteomyelitis or arthritis. A "rosary" at the costochondral junctions and depression of the sternum are other typical features (Fig. 50-1). The angulation of scorbutic beads is usually sharper than the angulation of a rachitic rosary. Gum changes are seen in older children after teeth have erupted and are manifested as bluish purple, spongy swellings of the mucous membrane, especially over the upper incisors (Fig. 50-2). Anemia, a common finding in infants and young children with scurvy, is related to impaired iron absorption and coexistent hematopoietic nutrient deficiencies including iron, vitamin B_{12}, and folate. Hemorrhagic

Figure 50-1 Scorbutic rosary. *(Courtesy of Dr J.D. MacLean, McGill Centre for Tropical Diseases, Montreal.)*

Figure 50-2 Gingival lesions in advanced scurvy. *(From* Nutrition, *ed 4, Kalamazoo, MI, 1980, The Upjohn Company, p. 80. Used with permission of Pfizer, Inc.)*

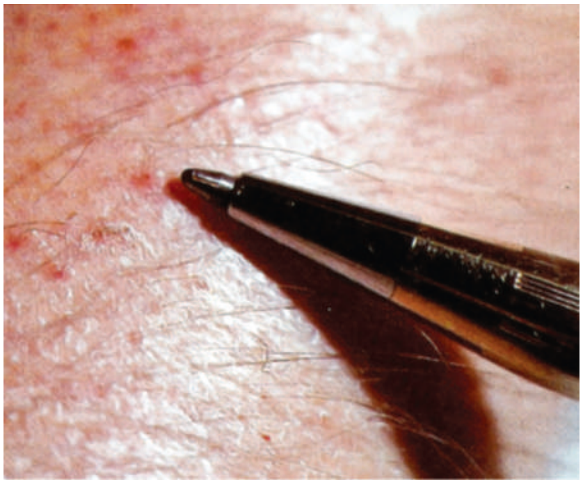

Figure 50-3 Perifollicular petechiae in scurvy. *(From Weinsier RL, Morgan SL:* Fundamentals of clinical nutrition, *St. Louis, 1993, Mosby, p. 85.)*

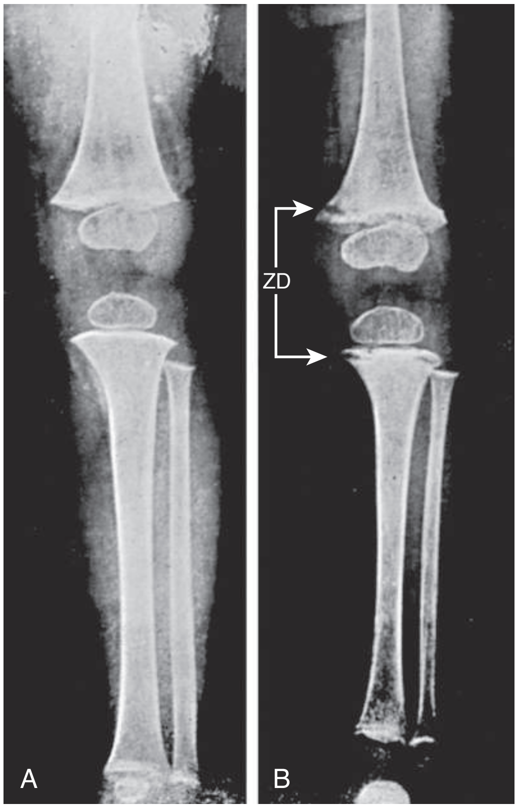

Figure 50-4 Radiographs of a leg. *A,* An early scurvy "white line" is visible on the ends of the shafts of the tibia and fibula; sclerotic rings (Wimberger sign) are shown around the epiphyses of the femur and tibia. *B,* More advanced scorbutic changes; zones of destruction (ZD) are evident in the femur and tibia. Pelkan spur is also seen at the cortical end.

manifestations of scurvy include petechiae, purpura, and ecchymoses at pressure points; epistaxis; gum bleeding; and the characteristic perifollicular hemorrhages (Fig. 50-3). Other manifestations are poor wound and fracture healing, hyperkeratosis of hair follicles, arthralgia, and muscle weakness.

Laboratory Findings and Diagnosis

The diagnosis of vitamin C deficiency is usually based on the characteristic clinical picture, the radiographic appearance of the long bones, and a history of poor vitamin C intake. The typical **radiographic changes** occur at the distal ends of the long bones and are particularly common at the knees. The shafts of the long bones have a ground-glass appearance because of trabecular atrophy. The cortex is thin and dense, giving the appearance of *pencil outlining* of the diaphysis and epiphysis. The *white line of Fränkel,* an irregular but thickened white line at the metaphysis, represents the zone of well-calcified cartilage. The epiphyseal centers of ossification also have a ground-glass appearance and are surrounded by a sclerotic ring (Fig. 50-4). The more specific but late radiologic feature of scurvy is a zone of rarefaction under the white line at the metaphysis. This zone of rarefaction *(Trümmerfeld zone),* a linear break in the bone that is proximal and parallel to the white line, represents area of debris of broken-down bone trabeculae and connective tissue. A *Pelkan spur* is a lateral prolongation of the white line and may be present at cortical ends. Epiphyseal separation can occur along the line of destruction, with either linear displacement or compression of the epiphysis against the shaft (Fig. 50-5). Subperiosteal hemorrhages are not visible using plain radiographs during the active phase of scurvy. However, during healing the elevated periosteum becomes calcified and radiopaque (Fig. 50-5), sometimes giving a dumbbell or club shape to the affected bone. MRI can demonstrate acute as well as healing subperiosteal hematomas along with periostitis, metaphyseal changes, and heterogeneous bone marrow signal intensity, even in absence of changes in plain radiographs. Gelatinous transformation of bone marrow, on aspiration, has been reported in children where the procedure was done on suspicion of a malignancy.

Biochemical tests are not very useful in the diagnosis of scurvy, because they do not reflect the tissue status. A plasma ascorbate concentration of <0.2 mg/dL usually is considered deficient. Leukocyte concentration of vitamin C is a better indicator of body stores, but this measurement is technically more difficult to perform. Leukocyte concentrations of $\leq 10\ \mu g/10^8$ white blood cells are considered deficient and indicate latent scurvy, even in the absence of clinical signs of deficiency. Saturation of the tissues with vitamin C can be estimated from the urinary excretion of the vitamin after a test dose of ascorbic acid. In healthy children, 80% of the test dose appears in the urine within 3-5 hr after parenteral administration. Generalized nonspecific aminoaciduria is common in scurvy, whereas plasma amino acid levels remain normal.

Differential Diagnosis

Scurvy is often misdiagnosed as arthritis, osteomyelitis, nonaccidental trauma (child abuse), or acrodynia. The early irritability and bone pain are sometimes attributed to nonspecific pains or other nutritional deficiencies. Copper deficiency results in a radiographic picture very

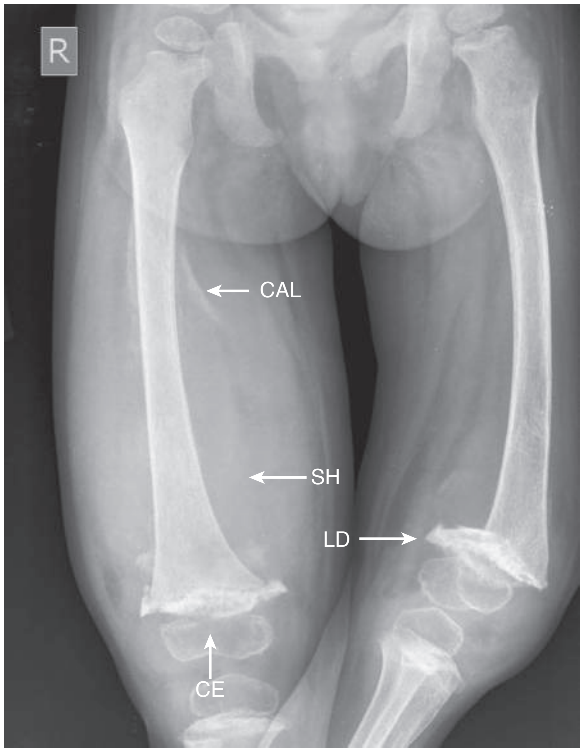

Figure 50-5 **Large subperiosteal hematoma (SH) with areas of calcification (CAL) is seen along the shaft of right femur of a child with advanced scurvy.** Epiphyseal separation is seen in both knees with linear displacement (LD) in left and compression (CE) against the shaft in right.

similar to that of scurvy. Henoch-Schönlein purpura, thrombocytopenic purpura, or leukemia is sometimes suspected in children presenting with hemorrhagic manifestations.

Treatment

Vitamin C supplements of 100-200 mg/day orally or parenterally ensure rapid and complete cure. The clinical improvement is seen within a week in most cases, but the treatment should be continued for up to 3 mo for complete recovery.

Prevention

Breastfeeding protects against vitamin C deficiency throughout infancy. In children consuming milk formula, fortification with vitamin C must be ensured. Children consuming heat-treated milk should consume adequate vitamin C–rich foods in infancy. Dietary or medicinal supplements are required in severely malnourished children, and chronic debilitating conditions such as malignancies and neurologic disorders.

TOXICITY

Daily intake of <2 g of vitamin C is generally without adverse effects in adults. Larger doses can cause gastrointestinal problems, such as abdominal pain and osmotic diarrhea. Megadoses of vitamin C should be avoided in patients with a history of urolithiasis or conditions related to excessive iron accumulation such as thalassemia and hemochromatosis. There is a paucity of data regarding vitamin C toxicity in children. The following values for tolerable upper intake levels are extrapolated from data for adults based on body weight differences: age 1-3 yr, 400 mg; age 4-8 yr, 650 mg; age 9-13 yr, 1,200 mg; and age 14-18 yr, 1,800 mg.

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Chapter 51

Rickets and Hypervitaminosis D

Larry A. Greenbaum

RICKETS

Bone consists of a protein matrix called *osteoid* and a mineral phase, principally composed of calcium and phosphate, mostly in the form of hydroxyapatite. Osteomalacia is present when there is inadequate mineralization of bone osteoid and occurs in children and adults. Rickets is a disease of growing bone that is caused by unmineralized matrix at the growth plates and occurs in children only before fusion of the epiphyses. Because growth plate cartilage and osteoid continue to expand but mineralization is inadequate, the growth plate thickens. There is also an increase in the circumference of the growth plate and the metaphysis, increasing bone width at the location of the growth plates and causing some of the classic clinical manifestations, such as widening of the wrists and ankles. There is a general softening of the bones that causes them to bend easily when subject to forces such as weight bearing or muscle pull. This softening leads to a variety of bone deformities.

Rickets is principally caused by vitamin D deficiency (Table 51-1) and was rampant in northern Europe and the United States during the early years of the 20th century. Although this problem was largely corrected through public health measures that provided children with adequate vitamin D, rickets remains a persistent problem in developed countries, with many cases still secondary to preventable nutritional vitamin D deficiency. It remains a significant problem in developing countries, and may be secondary to nutritional vitamin D deficiency and inadequate intake of calcium.

Etiology

There are many causes of rickets (Table 51-2), including vitamin D disorders, calcium deficiency, phosphorous deficiency, and distal renal tubular acidosis.

Clinical Manifestations

Most manifestations of rickets are a result of skeletal changes (Table 51-3). **Craniotabes** is a softening of the cranial bones and can be detected by applying pressure at the occiput or over the parietal bones. The sensation is similar to the feel of pressing into a ping-pong ball and then releasing. Craniotabes may also be secondary to osteogenesis imperfecta, hydrocephalus, and syphilis. It is a normal finding in many newborns, especially near the suture lines, but it typically disappears within a few months of birth. Widening of the costochondral junctions results in a **rachitic rosary**, which feels like the beads of a rosary as the examiner's fingers move along the costochondral junctions from rib to rib (Fig. 51-1). **Growth plate** widening is also responsible for the enlargement at the wrists and ankles. The horizontal depression along the lower anterior chest known as **Harrison groove** occurs from pulling of the softened ribs by the diaphragm during inspiration (Fig. 51-2). Softening of the ribs also impairs air movement and predisposes patients to atelectasis and pneumonia.

There is some variation in the clinical presentation of rickets based on the etiology. Changes in the lower extremities tend to be the dominant feature in X-linked hypophosphatemic rickets. Symptoms secondary to hypocalcemia occur only in those forms of rickets associated with decreased serum calcium (Table 51-4).

The chief complaint in a child with rickets is quite variable. Many children present because of skeletal deformities, whereas others have difficulty walking owing to a combination of deformity and weakness. Other common presenting complaints include failure to thrive and symptomatic hypocalcemia (see Chapter 572).

Table 51-1 Physical and Metabolic Properties and Food Sources of the Vitamins (D, E, and K)

NAMES AND SYNONYMS	CHARACTERISTICS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	SOURCES
VITAMIN D Vitamin D_3 (3-cholecalciferol), which is synthesized in the skin, and vitamin D_2 (from plants or yeast) are biologically equivalent; 1 μg = 40 IU vitamin D	Fat-soluble, stable to heat, acid alkali, and oxidation; bile necessary for absorption; hydroxylation in the liver and kidney necessary for biologic activity	Necessary for GI absorption of calcium; also increases absorption of phosphate; direct actions on bone, including mediating resorption	Rickets in growing children; osteomalacia; hypocalcemia can cause tetany and seizures	Hypercalcemia, which can cause emesis, anorexia, pancreatitis, hypertension, arrhythmias, CNS effects, polyuria, nephrolithiasis, renal failure	Exposure to sunlight (UV light); fish oils, fatty fish, egg yolks, and vitamin D–fortified formula, milk, cereals, bread
VITAMIN E Group of related compounds with similar biologic activities; α-tocopherol is the most potent and the most common form	Fat-soluble; readily oxidized by oxygen, iron, rancid fats; bile acids necessary for absorption	Antioxidant; protection of cell membranes from lipid peroxidation and formation of free radicals	Red cell hemolysis in premature infants; posterior column and cerebellar dysfunction; pigmentary retinopathy	Unknown	Vegetable oils, seeds, nuts, green leafy vegetables, margarine
VITAMIN K Group of naphthoquinones with similar biologic activities; K_1 (phylloquinone) from diet; K_2 (menaquinones) from intestinal bacteria	Natural compounds are fat-soluble; stable to heat and reducing agents; labile to oxidizing agent, strong acids, alkali, light; bile salts necessary for intestinal absorption	Vitamin K–dependent proteins include coagulation factors II, VII, IX, and X; proteins C, S, Z; matrix Gla protein, osteocalcin	Hemorrhagic manifestations; long-term bone and vascular health	Not established; analogs (no longer used) caused hemolytic anemia, jaundice, kernicterus, death	Green leafy vegetables, liver, certain legumes and plant oils; widely distributed

CNS, central nervous system; GI, gastrointestinal; UV, ultraviolet.

Table 51-2 Causes of Rickets

VITAMIN D DISORDERS
Nutritional vitamin D deficiency
Congenital vitamin D deficiency
Secondary vitamin D deficiency
Malabsorption
Increased degradation
Decreased liver 25-hydroxylase
Vitamin D–dependent rickets type 1 A and B
Vitamin D–dependent rickets type 2 A and B
Chronic kidney disease
CALCIUM DEFICIENCY
Low intake
Diet
Premature infants (rickets of prematurity)
Malabsorption
Primary disease
Dietary inhibitors of calcium absorption
PHOSPHORUS DEFICIENCY
Inadequate intake
Premature infants (rickets of prematurity)
Aluminum-containing antacids
RENAL LOSSES
X-linked hypophosphatemic rickets*
Autosomal dominant hypophosphatemic rickets*
Autosomal recessive hypophosphatemic rickets (1 and 2)*
Hereditary hypophosphatemic rickets with hypercalciuria
Overproduction of fibroblast growth factor-23
Tumor-induced rickets*
McCune-Albright syndrome*
Epidermal nevus syndrome*
Neurofibromatosis*
Fanconi syndrome
Dent disease
Distal renal tubular acidosis

*Disorders secondary to excess fibroblast growth factor-23.

Table 51-3 Clinical Features of Rickets

GENERAL
Failure to thrive
Listlessness
Protruding abdomen
Muscle weakness (especially proximal)
Fractures
HEAD
Craniotabes
Frontal bossing
Delayed fontanel closure
Delayed dentition; caries
Craniosynostosis
CHEST
Rachitic rosary
Harrison groove
Respiratory infections and atelectasis*
BACK
Scoliosis
Kyphosis
Lordosis
EXTREMITIES
Enlargement of wrists and ankles
Valgus or varus deformities
Windswept deformity (combination of valgus deformity of 1 leg with varus deformity of the other leg)
Anterior bowing of the tibia and femur
Coxa vara
Leg pain
HYPOCALCEMIC SYMPTOMS†
Tetany
Seizures
Stridor due to laryngeal spasm

*These features are most commonly associated with the vitamin D–deficiency disorders.
†These symptoms develop only in children with disorders that produce hypocalcemia (see Table 51-4).

Radiology

Rachitic changes are most easily visualized on posteroanterior radiographs of the wrist, although characteristic rachitic changes can be seen at other growth plates (Figs. 51-3 and 51-4). Decreased calcification leads to thickening of the growth plate. The edge of the metaphysis loses its sharp border, which is described as *fraying*. The edge of the metaphysis changes from a convex or flat surface to a more concave surface. This change to a concave surface is termed *cupping* and is most easily seen at the distal ends of the radius, ulna, and fibula. There is widening of the distal end of the metaphysis, corresponding to the clinical observation of thickened wrists and ankles, as well as the rachitic rosary. Other radiologic features include coarse trabeculation of the diaphysis and generalized rarefaction.

Diagnosis

Most cases of rickets are diagnosed based on the presence of classic radiographic abnormalities. The diagnosis is supported by physical examination findings (see Table 51-3) and a history and laboratory test results that are consistent with a specific etiology.

Figure 51-1 Rachitic rosary in a young infant.

Clinical Evaluation

Because the majority of children with rickets have a nutritional deficiency, the initial evaluation should focus on a dietary history, emphasizing intake of vitamin D and calcium. Most children in industrialized nations receive vitamin D from formula, fortified milk, or vitamin supplements. Along with the amount, the exact composition of the formula or milk is pertinent, because rickets has occurred in children given products that are called *milk* (e.g., soy milk) but are deficient in vitamin D and/or minerals.

Cutaneous synthesis mediated by sunlight exposure is an important source of vitamin D. It is important to ask about time spent outside, sunscreen use, and clothing, especially if there may be a cultural reason for increased covering of the skin. Because winter sunlight is ineffective at stimulating cutaneous synthesis of vitamin D, the season is an additional consideration. Children with increased skin pigmentation are at increased risk for vitamin D deficiency because of decreased cutaneous synthesis.

The presence of **maternal risk** factors for nutritional vitamin D deficiency, including diet and sun exposure, is an important consideration when a neonate or young infant has rachitic findings, especially if the infant is breastfed. Determining a child's intake of dairy products, the main dietary source of calcium, provides a general sense of calcium intake. High dietary fiber can interfere with calcium absorption.

The child's **medication** use is relevant, because certain medications, such as the anticonvulsants phenobarbital and phenytoin, increase degradation of vitamin D, and aluminum-containing antacids interfere with the absorption of phosphate.

Malabsorption of vitamin D is suggested by a history of liver or intestinal disease. Undiagnosed liver or intestinal disease should be suspected if the child has gastrointestinal (GI) symptoms, although occasionally rickets is the presenting complaint. Fat malabsorption is

Figure 51-2 Deformities in rickets showing curvature of the limbs, potbelly, and Harrison groove.

Table 51-4 Laboratory Findings in Various Disorders Causing Rickets

DISORDER	Ca	Pi	PTH	25-(OH)D	1,25-(OH)$_2$D	Alk Phos	URINE Ca	URINE Pi
Vitamin D deficiency	N, ↓	↓	↑	↓	↓, N, ↑	↑	↓	↑
Chronic kidney disease	N, ↓	↑	↑	N	↓	↑	N, ↓	↓
Dietary Pi deficiency	N	↓	N, ↓	N	↑	↑	↑	↓
Tumor-induced rickets	N	↓	N	N	RD	↑	↓	↑
Fanconi syndrome	N	↓	N	N	RD or ↑	↑	↓ or ↑	↑
Dietary Ca deficiency	N, ↓	↓	↑	N	↑	↑	↓	↑

↓, decreased; ↑, increased; ↑↑, extremely increased; 1,25-(OH)$_2$D, 1,25-dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; ADHR, autosomal dominant hypophosphatemic rickets; Alk Phos, alkaline phosphatase; ARHR, autosomal recessive hypophosphatemic rickets; Ca, calcium; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; N, normal; Pi, inorganic phosphorus; PTH, parathyroid hormone; RD, relatively decreased (because it should be increased given the concurrent hypophosphatemia); VDDR, vitamin D–dependent rickets; XLH, X-linked hypophosphatemic rickets.

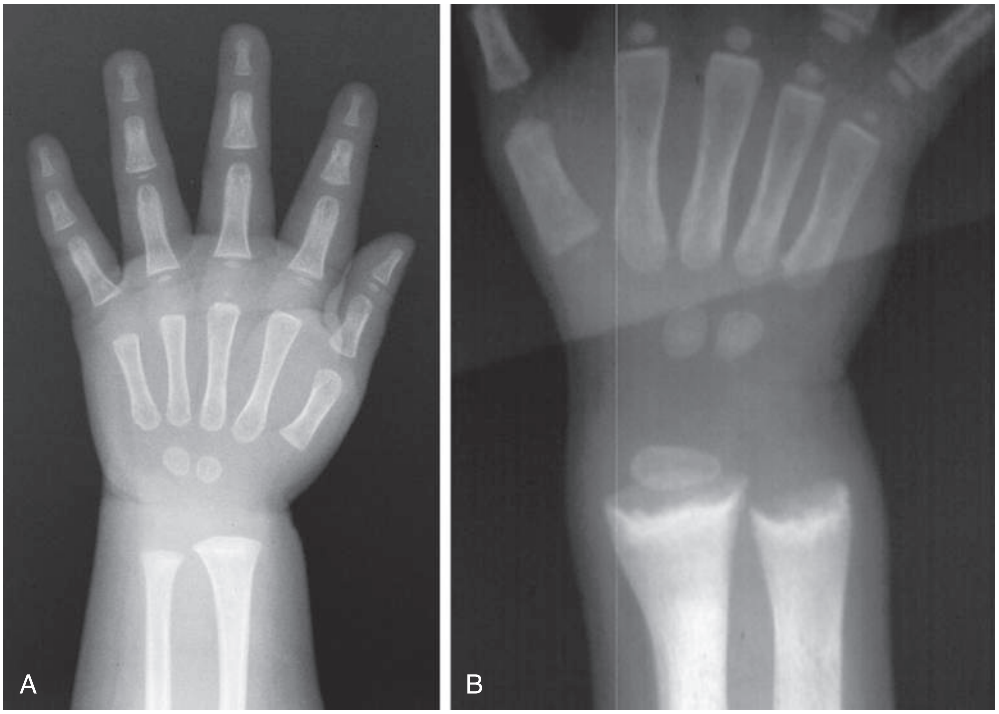

Figure 51-3 Wrist x-rays in a normal child *(A)* and in a child with rickets *(B)*. The child with rickets has metaphyseal fraying and cupping of the distal radius and ulna.

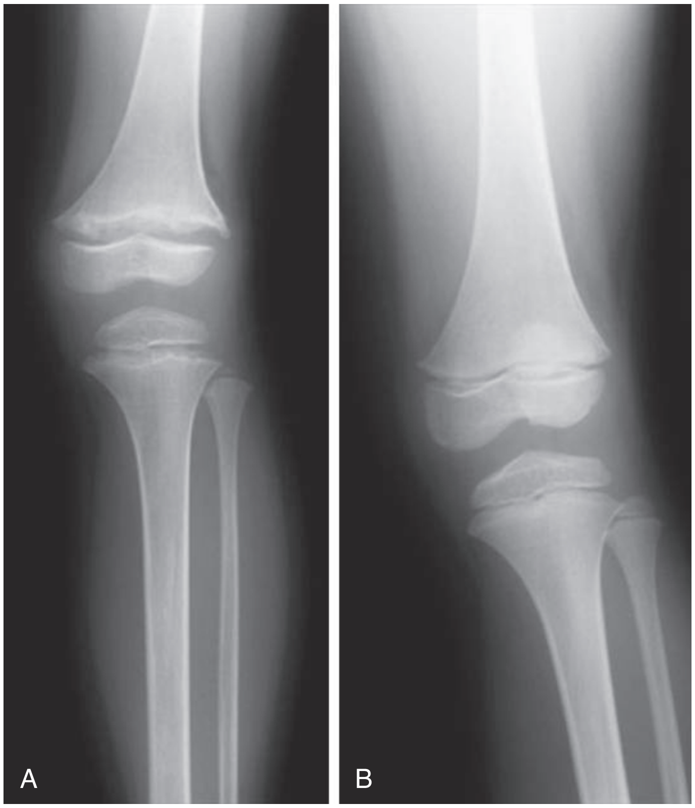

Figure 51-4 X-rays of the knees in a 7 yr old girl with distal renal tubular acidosis and rickets. *A*, At initial presentation, there is widening of the growth plate and metaphysical fraying. *B*, Dramatic improvement after 4 mo of therapy with alkali.

often associated with diarrhea or oily stools, and there may be signs or symptoms suggesting deficiencies of other fat-soluble vitamins (A, E, and K; see Chapters 48, 52, and 53).

A history of **renal disease** (proteinuria, hematuria, urinary tract infections) is an additional significant consideration, given the importance of chronic kidney disease as a cause of rickets. Polyuria can occur in children with chronic kidney disease or Fanconi syndrome.

Children with rickets might have a history of dental caries, poor growth, delayed walking, waddling gait, pneumonia, and hypocalcemic symptoms.

The family history is critical, given the large number of **genetic causes** of rickets, although most of these causes are rare. Along with bone disease, it is important to inquire about leg deformities, difficulties with walking, or unexplained short stature, because some parents may be unaware of their diagnosis. Undiagnosed disease in the mother is not unusual in X-linked hypophosphatemia. A history of a unexplained sibling death during infancy may be present in the child with cystinosis, the most common cause of Fanconi syndrome in children.

The physical examination focuses on detecting manifestations of rickets (see Table 51-3). It is important to observe the child's gait, auscultate the lungs to detect atelectasis or pneumonia, and plot the patient's growth. Alopecia suggests vitamin D–dependent rickets type 2.

The **initial laboratory** tests in a child with rickets should include serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D (1,25-D), creatinine, and electrolytes (see Tables 51-4 and 51-5 for interpretation). Urinalysis is useful for detecting the glycosuria and aminoaciduria (positive dipstick for protein) seen with Fanconi syndrome. Evaluation of urinary excretion of calcium (24 hr collection for calcium or calcium : creatinine ratio) is helpful if hereditary hypophosphatemic rickets with hypercalciuria or Fanconi syndrome is suspected. Direct measurement of other fat-soluble vitamins (A, E, and

Table 51-5 Biochemical Changes in Genetic Causes of Rickets

	SERUM BIOCHEMISTRY							URINE BIOCHEMISTRY		
	Phosphate	**Calcium**	**PTH**	**250HD**	**1,250H$_2$D**	**FGF23**	**Alk Phos**	**Phosphate**	**Calcium**	**OTHER FEATURES**
HYPOCALCEMIC VITAMIN D PATHWAY DEFECTS										
Vitamin D deficiency	Low	Variable	High	Low	Might be increased	NA	Increased	Increased	Low	Variable aminoaciduria
VDDR1B	Low	Low	High	Very low	Variable	NA	Increased	Increased	Low	250HD does not increase after vitamin D dosing
VDDR1A	Low	Low	High	Normal or high	Very low or ND	NA	Increased	Increased	Low	250HD does increase after vitamin D dosing
VDDR2A	Low	Low	High	Normal or high	High	NA	Increased	Increased	Low	—
VDDR2B	Low	Low	High	Normal or high	High	NA	Increased	Increased	Low	—
HYPOPHOSPHATEMIC RICKETS WITH RAISED FGF23										
XLH	Low	Normal	Normal or slightly high	Normal	Low	High	Increased	Increased	Variable	Urine calcium: creatinine used in monitoring therapy
ADHR	Low	Normal	Normal	Normal	Low	High	Increased	Increased	Variable	—
ARHR1	Low	Normal	Normal	Normal	Low	High	Increased	Increased	Variable	—
ARHR2	Low	Normal	Normal	Normal	Low	High	Increased	Increased	Variable	—
HYPOPHOSPHATEMIC RICKETS WITHOUT RAISED FGF23										
Dent's disease*	Low	Normal	Normal	Normal	Normal	Normal	Increased	Increased	High	Low molecular weight proteinuria
HHRH	Low	Normal	Normal	Normal	Normal	Normal	Increased	Increased	High	No loss of low molecular weight protein
αKlotho mutation	Low	Normal	Normal	Normal	Normal	Normal	Increased	Increased	Variable	—
OTHER INHERITED RACHITIC DISORDERS										
HPP (severe)	High	High	Low	Normal	Normal	Normal	Very low	Normal or high	High	Raised concentrations of mineralization inhibitors
HPP (mild)	Normal or high	Normal or high	Low or normal	Normal	Normal	Normal	Low	Normal	Variable	Raised concentrations of mineralization inhibitors

From Elder CJ, Bishop NJ: Rickets. Lancet 383:1665-1674, 2014.

PTH, parathyroid hormone; 250HD, calcidiol; 1,2SOH$_2$D, calcitriol; FGF23, fibroblast growth factor 23; Alk phos, alkaline phosphatase; NA, data not available; VDDR1B, vitamin D–dependent rickets due to defects in CYP2R1 encoding vitamin D 25-hydroxylase; VDDR1A, vitamin D–dependent rickets due to defects in CYP27BI encoding 25-hydroxyvitamin D-1alpha hydroxylase; ND, not detected; VDDR2A, vitamin D–dependent rickets due to defects in VDR encoding the vitamin D receptor; VDDR2B, vitamin D–dependent rickets due to defects in *HNRNPC* encoding hnRNPC1 and hnRNPC2; XLH, X-linked hypophosphatemic rickets due to mutations in *PHEX*; ADHR, autosomal dominant hypophosphatemic rickets due to mutations in *FGF23*; ARHR1, autosomal recessive hypophosphatemic rickets due to mutations in DMP1; ARHR2, autosomal recessive hypophosphatemic rickets due to mutations in *ENPP1*; HHRH, hereditary hypophosphatemic rickets with hypercalciuria due to mutations in *SLC34A3*; HPP, hypophosphatasia.

*Dent's disease is due to mutations in CLCN$_5$.

K) or indirect assessment of deficiency (prothrombin time for vitamin K deficiency) is appropriate if malabsorption is a consideration.

VITAMIN D DISORDERS

Vitamin D Physiology

Vitamin D can be synthesized in skin epithelial cells and therefore technically is not a vitamin. Cutaneous synthesis is normally the most important source of vitamin D and depends on the conversion of 7-dehydrochlesterol to vitamin D_3 (3-cholecalciferol) by ultraviolet B radiation from the sun. The efficiency of this process is decreased by melanin; hence, more sun exposure is necessary for vitamin D synthesis in people with increased skin pigmentation. Measures to decrease sun exposure, such as covering the skin with clothing or applying sunscreen, also decrease vitamin D synthesis. Children who spend less time outside have reduced vitamin D synthesis. The winter sun away from the equator is ineffective at mediating vitamin D synthesis.

There are few natural dietary sources of vitamin D. Fish liver oils have a high vitamin D content. Other good dietary sources include fatty fish and egg yolks. Most children in industrialized countries receive vitamin D via fortified foods, especially formula and milk (both of which contain 400 IU/L) and some breakfast cereals and breads. Supplemental vitamin D may be vitamin D_2 (which comes from plants or yeast) or vitamin D_3. Breast milk has a low vitamin D content, approximately 12-60 IU/L.

Vitamin D is transported bound to vitamin D–binding protein to the liver, where 25-hydroxlase converts vitamin D into 25-hydroxyvitamin D (25-D), the most abundant circulating form of vitamin D. Because there is little regulation of this liver hydroxylation step, measurement of 25-D is the standard method for determining a patient's vitamin D status. The final step in activation occurs in the kidney, where 1α-hydroxylase adds a second hydroxyl group, resulting in 1,25-D. The 1α-hydroxylase is upregulated by PTH and hypophosphatemia; hyperphosphatemia and 1,25-D inhibit this enzyme. Most 1,25-D circulates bound to vitamin D–binding protein.

1,25-D acts by binding to an intracellular receptor, and the complex affects gene expression by interacting with vitamin D–response elements. In the intestine, this binding results in a marked increase in calcium absorption, which is highly dependent on 1,25-D. There is also an increase in phosphorus absorption, but this effect is less significant because most dietary phosphorus absorption is vitamin D independent. 1,25-D also has direct effects on bone, including mediating resorption. 1,25-D directly suppresses PTH secretion by the parathyroid gland, thus completing a negative feedback loop. PTH secretion is also suppressed by the increase in serum calcium mediated by 1,25-D. 1,25-D inhibits its own synthesis in the kidney and increases the synthesis of inactive metabolites.

Nutritional Vitamin D Deficiency

Vitamin D deficiency remains the most common cause of rickets globally and is prevalent, even in industrialized countries. Because vitamin D can be obtained from dietary sources or from cutaneous synthesis, most patients in industrialized countries have a combination of risk factors that lead to vitamin D deficiency.

Etiology

Vitamin D deficiency most commonly occurs in infancy because of a combination of poor intake and inadequate cutaneous synthesis. Transplacental transport of vitamin D, mostly 25-D, typically provides enough vitamin D for the 1st 2 mo of life unless there is severe maternal vitamin D deficiency. Infants who receive formula receive adequate vitamin D, even without cutaneous synthesis. Because of the low vitamin D content of breast milk, breastfed infants rely on cutaneous synthesis or vitamin supplements. Cutaneous synthesis can be limited because of the ineffectiveness of the winter sun in stimulating vitamin D synthesis; avoidance of sunlight because of concerns about cancer, neighborhood safety, or cultural practices; and decreased cutaneous synthesis because of increased skin pigmentation.

The effect of skin pigmentation explains why most cases of nutritional rickets in the United States and northern Europe occur in breastfed children of African descent or other dark-pigmented populations. The additional impact of the winter sun is supported by the fact that such infants more commonly present in the late winter or spring. In some groups, complete covering of infants or the practice of not taking infants outside has a significant role, explaining the occurrence of rickets in infants living in areas of abundant sunshine, such as the Middle East. Because the mothers of some infants can have the same risk factors, decreased maternal vitamin D can also contribute, both by leading to reduced vitamin D content in breast milk and by lessening transplacental delivery of vitamin D. Rickets caused by vitamin D deficiency can also be secondary to unconventional dietary practices, such as vegan diets that use unfortified soy milk or rice milk.

Clinical Manifestations

The clinical features are typical of rickets (see Table 51-3), with a significant minority presenting with symptoms of hypocalcemia; prolonged laryngospasm is occasionally fatal. These children have an increased risk of pneumonia and muscle weakness leading to a delay in motor development.

Laboratory Findings

Tables 51-4 and 51-5 summarize the principal laboratory findings. Hypocalcemia is a variable finding as a result of the actions of the elevated PTH to increase the serum calcium concentration. The hypophosphatemia is caused by PTH-induced renal losses of phosphate, combined with a decrease in intestinal absorption.

The wide variation in 1,25-D levels (low, normal, or high) is secondary to the upregulation of renal 1α-hydroxylase caused by concomitant hypophosphatemia and hyperparathyroidism. Because serum levels of 1,25-D are much lower than the levels of 25-D, even with low levels of 25-D there is still often enough 25-D present to act as a precursor for 1,25-D synthesis in the presence of an upregulated 1α-hydroxylase. The level of 1,25-D is only low when there is severe vitamin D deficiency.

Some patients have a metabolic acidosis secondary to PTH-induced renal bicarbonate wasting. There may also be generalized aminoaciduria.

Diagnosis and Differential Diagnosis

The diagnosis of nutritional vitamin D deficiency is based on the combination of a history of poor vitamin D intake and risk factors for decreased cutaneous synthesis, radiographic changes consistent with rickets, and typical laboratory findings (see Tables 51-4 and 51-5). A normal PTH level almost never occurs with vitamin D deficiency and suggests a primary phosphate disorder.

Treatment

Children with nutritional vitamin D deficiency should receive vitamin D and adequate nutritional intake of calcium and phosphorus. There are 2 strategies for administration of vitamin D. With stoss therapy, 300,000-600,000 IU of vitamin D are administered orally or intramuscularly as 2-4 doses over 1 day. Because the doses are observed, stoss therapy is ideal in situations where adherence to therapy is questionable. The alternative is daily, high-dose vitamin D, with doses ranging from 2,000-5,000 IU/day over 4-6 wk. Either strategy should be followed by daily vitamin D intake of 400 IU/day if <1 yr old or 600 IU/day if >1 yr old. It is important to ensure that children receive adequate dietary calcium and phosphorus; this dietary intake is usually provided by milk, formula, and other dairy products.

Children who have symptomatic hypocalcemia might need intravenous calcium acutely, followed by oral calcium supplements, which typically can be tapered over 2-6 wk in children who receive adequate dietary calcium. Transient use of intravenous or oral 1,25-D (calcitriol) is often helpful in reversing hypocalcemia in the acute phase by providing active vitamin D during the delay as supplemental vitamin D is converted to active vitamin D. Calcitriol doses are typically 0.05 μg/kg/day. Intravenous calcium is initially given as an acute bolus for symptomatic hypocalcemia (20 mg/kg of calcium

chloride or 100 mg/kg of calcium gluconate). Some patients require a continuous intravenous calcium drip, titrated to maintain the desired serum calcium level. These patients should transition to enteral calcium, and most infants require approximately 1,000 mg of elemental calcium.

Prognosis

Most children have an excellent response to treatment, with radiologic healing occurring within a few months. Laboratory test results should also normalize rapidly. Many of the bone malformations improve dramatically, but children with severe disease can have permanent deformities and short stature. Rarely, patients benefit from orthopedic intervention for leg deformities, although this is generally not done until the metabolic bone disease has healed, there is clear evidence that the deformity will not self-resolve, and the deformity is causing functional problems.

Prevention

Most cases of nutritional rickets can be prevented by universal administration of 400 IU of vitamin D to infants who are breastfed. Older children should receive 600 IU/day. Vitamin D may be administered as a component of a multivitamin or as a vitamin D supplement.

Congenital Vitamin D Deficiency

Congenital rickets is quite rare in industrialized countries and occurs when there is severe maternal vitamin D deficiency during pregnancy. Maternal risk factors include poor dietary intake of vitamin D, lack of adequate sun exposure, and closely spaced pregnancies. These newborns can have symptomatic hypocalcemia, intrauterine growth retardation, and decreased bone ossification, along with classic rachitic changes. More subtle maternal vitamin D deficiency can have an adverse effect on neonatal bone density and birthweight, cause a defect in dental enamel, and predispose infants to neonatal hypocalcemic tetany. Treatment of congenital rickets includes vitamin D supplementation and adequate intake of calcium and phosphorus. Use of prenatal vitamins containing vitamin D prevents this entity.

Secondary Vitamin D Deficiency

Etiology

Along with inadequate intake, vitamin D deficiency can develop due to inadequate absorption, decreased hydroxylation in the liver, and increased degradation. Because vitamin D is fat-soluble, its absorption may be decreased in patients with a variety of liver and GI diseases, including cholestatic liver disease, defects in bile acid metabolism, cystic fibrosis and other causes of pancreatic dysfunction, celiac disease, and Crohn disease. Malabsorption of vitamin D can also occur with intestinal lymphangiectasia and after intestinal resection.

Severe liver disease, which is usually also associated with malabsorption, can cause a decrease in 25-D formation as a consequence of insufficient enzyme activity. Because of the large reserve of 25-hydroxlase activity in the liver, vitamin D deficiency as a result of liver disease usually requires a loss of >90% of liver function. A variety of medications increase the degradation of vitamin D by inducing the cytochrome P450 system. Rickets as a consequence of vitamin D deficiency can develop in children receiving anticonvulsants, such as phenobarbital or phenytoin, or antituberculosis medications, such as isoniazid or rifampin.

Treatment

Treatment of vitamin D deficiency attributable to malabsorption requires high doses of vitamin D. Because of its better absorption, 25-D (25-50 μg/day or 5-7 μg/kg/day) is superior to vitamin D_3. The dose is adjusted based on monitoring of serum levels of 25-D. Alternatively, patients may be treated with 1,25-D, which also is better absorbed in the presence of fat malabsorption, or with parenteral vitamin D. Children with rickets as a result of increased degradation of vitamin D by the cytochrome P450 system require the same acute therapy as indicated for nutritional deficiency (discussed earlier), followed by long-term administration of high doses of vitamin D (e.g., 1,000 IU/day), with dosing titrated based on serum levels of 25-D. Some patients require as much as 4,000 IU/day.

Vitamin D–Dependent Rickets, Type 1

Children with vitamin D–dependent rickets type 1, an autosomal recessive disorder, have mutations in the gene encoding renal 1α-hydroxylase, preventing conversion of 25-D into 1,25-D. These patients normally present during the 1st 2 yr of life and can have any of the classic features of rickets (see Table 51-3), including symptomatic hypocalcemia. They have normal levels of 25-D, but low levels of 1,25-D (see Table 51-5). Occasionally, 1,25-D levels are at the lower limit of normal, inappropriately low given the high PTH and low serum phosphorus levels, both of which should increase the activity of renal 1α-hydroxylase and cause elevated levels of 1,25-D. As in nutritional vitamin D deficiency, renal tubular dysfunction can cause a metabolic acidosis and generalized aminoaciduria.

Treatment

These patients respond to long-term treatment with 1,25-D (calcitriol). Initial doses are 0.25-2 μg/day, and lower doses are used once the rickets has healed. Especially during initial therapy, it is important to ensure adequate intake of calcium. The dose of calcitriol is adjusted to maintain a low-normal serum calcium level, a normal serum phosphorus level, and a high-normal serum PTH level. Targeting a low-normal calcium concentration and a high-normal PTH level avoids excessive dosing of calcitriol, which can cause hypercalciuria and nephrocalcinosis. Hence, patient monitoring includes periodic assessment of urinary calcium excretion, with a target of <4 mg/kg/day.

Vitamin D–Dependent Rickets, Type 2

Patients with vitamin D–dependent rickets type 2 have mutations in the gene encoding the vitamin D receptor, preventing a normal physiologic response to 1,25-D. Levels of 1,25-D are extremely elevated in this autosomal recessive disorder (see Table 51-4). Most patients present during infancy, although rickets in less severely affected patients might not be diagnosed until adulthood. Less-severe disease is associated with a partially functional vitamin D receptor. Approximately 50-70% of children have **alopecia**, which tends to be associated with a more severe form of the disease and can range from alopecia areata to alopecia totalis. Epidermal cysts are a less common manifestation.

Treatment

Some patients respond to extremely high doses of vitamin D_2, 25-D or 1,25-D, especially patients without alopecia. This response is due to a partially functional vitamin D receptor. All patients with this disorder should be given a 3-6 mo trial of high-dose vitamin D and oral calcium. The initial dose of 1,25-D should be 2 μg/day, but some patients require doses as high as 50-60 μg/day. Calcium doses are 1,000-3,000 mg/day. Patients who do not respond to high-dose vitamin D may be treated with long-term intravenous calcium, with possible transition to very high dose oral calcium supplements. Treatment of patients who do not respond to vitamin D is difficult.

Chronic Kidney Disease (See Chapter 535.2)

With chronic kidney disease, there is decreased activity of 1α-hydroxylase in the kidney, leading to diminished production of 1,25-D. In chronic kidney disease, unlike the other causes of vitamin D deficiency, patients have hyperphosphatemia as a result of decreased renal excretion (see Table 51-4).

Treatment

Therapy requires the use of a form of vitamin D that can act without 1-hydroxylation by the kidney (calcitriol), which both permits adequate absorption of calcium and directly suppresses the parathyroid gland. Because hyperphosphatemia is a stimulus for PTH secretion, normalization of the serum phosphorus level via a combination of dietary phosphorus restriction and the use of oral phosphate binders is as important as the use of activated vitamin D.

CALCIUM DEFICIENCY

Pathophysiology

Rickets secondary to inadequate dietary calcium is a significant problem in some countries in Africa, although there are cases in other regions of the world, including industrialized countries. Because breast milk and formula are excellent sources of calcium, this form of rickets develops after children have been weaned from breast milk or formula and is more likely to occur in children who are weaned early. Rickets develops because the diet has low calcium content, typically <200 mg/day. There is little intake of dairy products or other sources of calcium. In addition, because of reliance on grains and green leafy vegetables, the diet may be high in phytate, oxalate, and phosphate, which decrease absorption of dietary calcium. In industrialized countries, rickets caused by calcium deficiency can occur in children who consume an unconventional diet. Examples include children with milk allergy who have low dietary calcium and children who transition from formula or breast milk to juice, soda, or a calcium-poor soy drink, without an alternative source of dietary calcium.

This type of rickets can develop in children who receive intravenous nutrition without adequate calcium. Malabsorption of calcium can occur in celiac disease, intestinal abetalipoproteinemia, and after small bowel resection. There may be concurrent malabsorption of vitamin D.

Clinical Manifestations

Children have the classic signs and symptoms of rickets (see Table 51-3). Presentation can occur during infancy or early childhood, although some cases are diagnosed in teenagers. Because calcium deficiency occurs after the cessation of breastfeeding, it tends to occur later than the nutritional vitamin D deficiency that is associated with breastfeeding. In Nigeria, nutritional vitamin D deficiency is most common at 4-15 mo of age, whereas calcium-deficiency rickets typically occurs at 15-25 mo of age.

Diagnosis

Laboratory findings include increased levels of alkaline phosphatase, PTH, and 1,25-D (see Table 51-4). Calcium levels may be normal or low, although symptomatic hypocalcemia is uncommon. There is decreased urinary excretion of calcium, and serum phosphorus levels may be low as a result of renal wasting of phosphate from secondary hyperparathyroidism. In some children, there is coexisting nutritional vitamin D deficiency, with low 25-D levels.

Treatment

Treatment focuses on providing adequate calcium, typically as a dietary supplement (doses of 700 [1-3 yr age], 1,000 [4-8 yr age], 1,300 [9-18 yr age] mg/day of elemental calcium are effective). Vitamin D supplementation is necessary if there is concurrent vitamin D deficiency (discussed earlier). Prevention strategies include discouraging early cessation of breastfeeding and increasing dietary sources of calcium. In countries such as Kenya, where many children have diets high in cereal with negligible intake of cow's milk, school-based milk programs have been effective in reducing the prevalence of rickets.

PHOSPHOROUS DEFICIENCY

Inadequate Intake

With the exception of starvation or severe anorexia, it is almost impossible to have a diet that is deficient in phosphorus, because phosphorus is present in most foods. Decreased phosphorus absorption can occur in diseases associated with malabsorption (celiac disease, cystic fibrosis, cholestatic liver disease), but if rickets develops, the primary problem is usually malabsorption of vitamin D and/or calcium.

Isolated malabsorption of phosphorus occurs in patients with long-term use of aluminum-containing antacids. These compounds are very effective at chelating phosphate in the GI tract, leading to decreased absorption. This decreased absorption results in hypophosphatemia with secondary osteomalacia in adults and rickets in children. This entity responds to discontinuation of the antacid and short-term phosphorus supplementation.

Fibroblast Growth Factor-23

Fibroblast growth factor-23 (FGF-23) is a humoral mediator that decreases renal tubular reabsorption of phosphate and therefore decreases serum phosphorus. FGF-23, synthesized by osteocytes, also decreases the activity of renal 1α-hydroxylase, resulting in a decrease in the production of 1,25-D. Increased levels of FGF-23 cause many of the renal phosphate-wasting diseases (see Table 51-2).

X-Linked Hypophosphatemic Rickets

Among the genetic disorders causing rickets because of hypophosphatemia, X-linked hypophosphatemic rickets (XLH) is the most common, with a prevalence of 1/20,000. The defective gene is on the X chromosome, but female carriers are affected, so it is an X-linked dominant disorder.

Pathophysiology

The defective gene is called *PHEX* because it is a **PH**osphate-regulating gene with homology to **E**ndopeptidases on the **X** chromosome. The product of this gene appears to have an indirect role in inactivating FGF-23. Mutations in the *PHEX* gene lead to increased levels of FGF-23. Because the actions of FGF-23 include inhibition of phosphate reabsorption in the proximal tubule, phosphate excretion is increased. FGF-23 also inhibits renal 1α-hydroxylase, leading to decreased production of 1,25-D.

Clinical Manifestations

These patients have rickets, but abnormalities of the lower extremities and poor growth are the dominant features. Delayed dentition and tooth abscesses are also common. Some patients have hypophosphatemia and short stature without clinically evident bone disease.

Laboratory Findings

Patients have high renal excretion of phosphate, hypophosphatemia, and increased alkaline phosphatase; PTH and serum calcium levels are normal (see Table 51-4). Hypophosphatemia normally upregulates renal 1α-hydroxylase and should lead to an increase in 1,25-D, but these patients have low or inappropriately normal levels of 1,25-D.

Treatment

Patients respond well to a combination of oral phosphorus and 1,25-D (calcitriol). The daily need for phosphorus supplementation is 1-3 g of elemental phosphorus divided into 4-5 doses. Frequent dosing helps to prevent prolonged decrements in serum phosphorus because there is a rapid decline after each dose. In addition, frequent dosing decreases diarrhea, a complication of high-dose oral phosphorus. Calcitrol is administered 30-70 ng/kg/day divided into 2 doses.

Complications of treatment occur when there is not an adequate balance between phosphorus supplementation and calcitriol. Excess phosphorus, by decreasing enteral calcium absorption, leads to secondary hyperparathyroidism, with worsening of the bone lesions. In contrast, excess calcitriol causes hypercalciuria and nephrocalcinosis and can even cause hypercalcemia. Hence, laboratory monitoring of treatment includes serum calcium, phosphorus, alkaline phosphatase, PTH, and urinary calcium, as well as periodic renal ultrasounds to evaluate patients for nephrocalcinosis. Because of variation in the serum phosphorus level and the importance of avoiding excessive phosphorus dosing, normalization of alkaline phosphatase levels is a more useful method of assessing the therapeutic response than measuring serum phosphorus. For children with significant short stature, growth hormone is an effective option. Children with severe deformities might need osteotomies, but these procedures should be done only when treatment has led to resolution of the bone disease.

Prognosis

The response to therapy is usually good, although frequent dosing can lead to problems with compliance. Girls generally have less-severe disease than boys, probably because of the X-linked inheritance. Short stature can persist despite healing of the rickets. Adults generally do well with less-aggressive treatment, and some receive calcitriol alone.

Adults with bone pain or other symptoms improve with oral phosphorus supplementation and calcitriol.

Autosomal Dominant Hypophosphatemic Rickets

Autosomal dominant hypophosphatemic rickets (ADHR) is much less common than XLH. There is incomplete penetrance and variable age of onset. Patients with ADHR have a mutation in the gene encoding FGF-23 (*FGF23*). The mutation prevents degradation of FGF-23 by proteases, leading its level to increase. The actions of FGF-23 include decreased reabsorption of phosphate in the renal proximal tubule, which results in hypophosphatemia, and inhibition of the 1α-hydroxylase in the kidney, causing a decrease in 1,25-D synthesis.

In ADHR, as in XLH, abnormal laboratory findings are hypophosphatemia, an elevated alkaline phosphatase level, and a low or inappropriately normal 1,25-D level (see Table 51-4). Treatment is similar to the approach used in XLH.

Autosomal Recessive Hypophosphatemic Rickets

Autosomal recessive hypophosphatemic rickets (ARHR), type 1 is an extremely rare disorder caused by mutations in the gene encoding dentin matrix protein 1 (*DMP1*). ARHR, type 2 occurs in patients with mutations in the *ENPP1* gene. Mutations in *ENPP1* also cause generalized arterial calcification of infancy. Both types of ARHR are associated with elevated levels of FGF-23, leading to renal phosphate wasting, hypophosphatemia, and low or inappropriately normal levels of 1,25-D. Treatment is similar to the approach used in XLH, although monitoring for arterial calcification is prudent in patients with *ENPP1* mutations.

Hereditary Hypophosphatemic Rickets with Hypercalciuria

Hereditary hypophosphatemic rickets with hypercalciuria is a rare disorder that is mainly found in the Middle East.

Pathophysiology

This autosomal recessive disorder is caused by mutations in the gene for a sodium-phosphate cotransporter in the proximal tubule (*SLC34A3*). The renal phosphate leak causes hypophosphatemia, which then stimulates production of 1,25-D. The high level of 1,25-D increases intestinal absorption of calcium, suppressing PTH. Hypercalciuria ensues as a result of the high absorption of calcium and the low level of PTH, which normally decreases renal excretion of calcium.

Clinical Manifestations

The dominant symptoms are rachitic leg abnormalities (see Table 51-3), muscle weakness, and bone pain. Patients can have short stature, with a disproportionate decrease in the length of the lower extremities. The severity of the disease varies, and some family members have no evidence of rickets but have kidney stones secondary to hypercalciuria.

Laboratory Findings

Laboratory findings include hypophosphatemia, renal phosphate wasting, elevated serum alkaline phosphatase levels, and elevated 1,25-D levels. PTH levels are low (see Table 51-4).

Treatment

Therapy relies on oral phosphorus replacement (1-2.5 g/day of elemental phosphorus in 5 divided oral doses). Treatment of the hypophosphatemia decreases serum levels of 1,25-D and corrects the hypercalciuria. The response to therapy is usually excellent, with resolution of pain, weakness, and radiographic evidence of rickets.

Overproduction of FGF-23

Tumor-induced osteomalacia is more common in adults than in children, where it can produce classic rachitic findings. Most tumors are mesenchymal in origin and are usually benign, small, and located in bone. These tumors secrete FGF-23 and produce a biochemical phenotype that is similar to XLH, including urinary phosphate wasting, hypophosphatemia, elevated alkaline phosphatase levels, and low or inappropriately normal 1,25-D levels (see Table 51-4). Curative treatment is excision of the tumor. If the tumor cannot be removed, treatment is identical to that used for XLH.

Renal phosphate wasting leading to hypophosphatemia and rickets (or osteomalacia in adults) is a potential complication in **McCune-Albright syndrome,** an entity that includes the triad of polyostotic fibrous dysplasia, hyperpigmented macules, and polyendocrinopathy (see Chapter 563.6). Affected patients have inappropriately low levels of 1,25-D and elevated levels of alkaline phosphatase. The renal phosphate wasting and inhibition of 1,25-D synthesis are related to the polyostotic fibrous dysplasia. Patients have elevated levels of FGF-23, presumably produced by the dysplastic bone. Hypophosphatemic rickets can also occur in children with isolated polyostotic fibrous dysplasia. Although it is rarely possible, removal of the abnormal bone can cure this disorder in children with McCune-Albright syndrome. Most patients receive the same treatment as children with XLH. Bisphosphonate treatment decreases the pain and fracture risk associated with the bone lesions.

Rickets is an unusual complication of **epidermal nevus syndrome** (see Chapter 651). Patients have hypophosphatemic rickets due to renal phosphate wasting and also have an inappropriately normal or low level of 1,25-D as a consequence of excessive production of FGF-23. The timing of presentation with rickets varies from infancy to early adolescence. Resolution of hypophosphatemia and rickets has occurred after excision of the epidermal nevi in some patients, but not in others. In most cases, the skin lesions are too extensive to be removed, necessitating treatment with phosphorus supplementation and 1,25-D. Rickets caused by phosphate wasting is an extremely rare complication in children with **neurofibromatosis** (see Chapter 596.1).

Fanconi Syndrome

Fanconi syndrome is secondary to generalized dysfunction of the renal proximal tubule (see Chapter 529.1). There are renal losses of phosphate, amino acids, bicarbonate, glucose, urate, and other molecules that are normally reabsorbed in the proximal tubule. Some patients have partial dysfunction, with less generalized losses. The most clinically relevant consequences are hypophosphatemia caused by phosphate losses and proximal renal tubular acidosis caused by bicarbonate losses. Patients have rickets as a result of hypophosphatemia, with exacerbation from the chronic metabolic acidosis, which causes bone dissolution. Failure to thrive is a consequence of both rickets and renal tubular acidosis. Treatment is dictated by the etiology (see Chapter 529).

Dent Disease (See Chapter 531.3)

Dent disease is an X-linked disorder usually caused by mutations in the gene encoding a chloride channel that is expressed in the kidney (CLCN5). Some patients have mutations in the *OCRL 1* gene, which can also cause Lowe syndrome (see Chapter 530.1). Affected males have variable manifestations, including hematuria, nephrolithiasis, nephrocalcinosis, rickets, and chronic kidney disease. Almost all patients have low-molecular-weight proteinuria and hypercalciuria. Other, less universal abnormalities are aminoaciduria, glycosuria, hypophosphatemia, and hypokalemia. Rickets occurs in approximately 25% of patients, and it responds to oral phosphorus supplements. Some patients also need 1,25-D, but this treatment should be used cautiously because it can worsen the hypercalciuria.

RICKETS OF PREMATURITY (See Chapter 106)

Rickets in very-low-birthweight infants has become a significant problem, as the survival rate for this group of infants has increased.

Pathogenesis

The transfer of calcium and phosphorus from mother to fetus occurs throughout pregnancy, but 80% occurs during the 3rd trimester. Premature birth interrupts this process, with rickets developing when the

premature infant does not have an adequate supply of calcium and phosphorus to support mineralization of the growing skeleton.

Most cases of rickets of prematurity occur in infants with a birthweight <1,000 g. It is more likely to develop in infants with lower birthweight and younger gestational age. Rickets occurs because unsupplemented breast milk and standard infant formula do not contain enough calcium and phosphorus to supply the needs of the premature infant. Other risk factors include cholestatic jaundice, a complicated neonatal course, prolonged use of parenteral nutrition, the use of soy formula, and medications such as diuretics and corticosteroids.

Clinical Manifestations

Rickets of prematurity occurs 1-4 mo after birth. Infants can have nontraumatic fractures, especially of the legs, arms, and ribs. Most fractures are not suspected clinically. Because fractures and softening of the ribs lead to decreased chest compliance, some infants have respiratory distress due to atelectasis and poor ventilation. This rachitic respiratory distress usually develops >5 wk after birth, distinguishing it from the early-onset respiratory disease of premature infants. These infants have poor linear growth, with negative effects on growth persisting beyond 1 yr of age. An additional long-term effect is enamel hypoplasia. Poor bone mineralization can contribute to dolichocephaly. There may be classic rachitic findings, such as frontal bossing, rachitic rosary, craniotabes, and widened wrists and ankles (see Table 51-3). Most infants with rickets of prematurity have no clinical manifestations, and the diagnosis is based on radiographic and laboratory findings.

Laboratory Findings

Because of inadequate intake, the serum phosphorus level is low or low-normal in rickets of prematurity. The renal response is appropriate, with conservation of phosphate leading to a low urine phosphate level; the tubular reabsorption of phosphate is >95%. Most patients have normal levels of 25-D, unless there has been inadequate intake or poor absorption (discussed earlier). The hypophosphatemia stimulates renal 1α-hydroxylase, so levels of 1,25-D are high or high-normal. These high levels can contribute to bone demineralization, because 1,25-D stimulates bone resorption. Serum levels of calcium are low, normal, or high, and patients often have hypercalciuria. Elevated serum calcium levels and hypercalciuria are secondary to increased intestinal absorption and bone dissolution owing to elevation of 1,25-D levels and the inability to deposit calcium in bone because of an inadequate phosphorus supply. The hypercalciuria indicates that phosphorus is the limiting nutrient for bone mineralization, although increased provision of phosphorus alone often cannot correct the mineralization defect; increased calcium is also necessary. Hence, there is an inadequate supply of calcium and phosphorus, but the deficiency in phosphorus is greater.

Alkaline phosphatase levels are often elevated, but some affected infants have normal levels. In some instances, normal alkaline phosphatase levels may be secondary to resolution of the bone demineralization because of an adequate mineral supply despite the continued presence of radiologic changes, which take longer to resolve. However, alkaline phosphatase levels may be normal despite active disease. No single blood test is 100% sensitive for the diagnosis of rickets. The diagnosis should be suspected in infants with an alkaline phosphatase level that is >5-6 times the upper limit of normal for adults (unless there is concomitant liver disease) or a phosphorus level <5.6 mg/dL. The diagnosis is confirmed by radiologic evidence of rickets, which is best seen on films of the wrists and ankles. Films of the arms and legs might reveal fractures. The rachitic rosary may be visible on chest x-ray. Unfortunately, x-rays cannot show early demineralization of bone because changes are not evident until there is >20-30% reduction in the bone mineral content.

Diagnosis

Because many premature infants have no overt clinical manifestations of rickets, screening tests are recommended. These tests should include weekly measurements of calcium, phosphorus, and alkaline phosphatase. Periodic measurement of the serum bicarbonate concentration is also important, because metabolic acidosis causes dissolution of bone. At least 1 screening x-ray for rickets at 6-8 wk of age is appropriate in infants who are at high risk for rickets; additional films may be indicated in very high risk infants.

Prevention

Provision of adequate amounts of calcium, phosphorus, and vitamin D significantly decreases the risk of rickets of prematurity. Parenteral nutrition is often necessary initially in very premature infants. In the past, adequate parenteral calcium and phosphorus delivery was difficult because of limits secondary to insolubility of these ions when their concentrations were increased. Current amino acid preparations allow higher concentrations of calcium and phosphate, decreasing the risk of rickets. Early transition to enteral feedings is also helpful. These infants should receive either human milk fortified with calcium and phosphorus or preterm infant formula, which has higher concentrations of calcium and phosphorus than standard formula. Soy formula should be avoided because there is decreased bioavailability of calcium and phosphorus. Increased mineral feedings should continue until the infant weighs 3-3.5 kg. These infants should also receive approximately 400 IU/day of vitamin D via formula and vitamin supplements.

Treatment

Therapy for rickets of prematurity focuses on ensuring adequate delivery of calcium, phosphorus, and vitamin D. If mineral delivery has been good and there is no evidence of healing, then it is important to screen for vitamin D deficiency by measuring serum 25-D. Measurement of PTH, 1,25-D, and urinary calcium and phosphorus may be helpful in some cases.

DISTAL RENAL TUBULAR ACIDOSIS
(See Chapter 530)

Distal renal tubular acidosis usually manifests with failure to thrive. Patients have a metabolic acidosis with an inability to acidify the urine appropriately. Hypercalciuria and nephrocalcinosis are typically present. There are many possible etiologies, including autosomal recessive and autosomal dominant forms. Rickets is variable, and it responds to alkali therapy (see Fig. 51-4).

HYPERVITAMINOSIS D

Etiology

Hypervitaminosis D is secondary to excessive intake of vitamin D. It can occur with long-term high intake or with a substantial, acute ingestion (see Table 51-1). Most cases are secondary to misuse of prescribed or nonprescription vitamin D supplements, but other cases have been secondary to accidental overfortification of milk, contamination of table sugar, and inadvertent use of vitamin D supplements as cooking oil. The recommended upper limits for long-term vitamin D intake are 1,000 IU for children <1 year old and 2,000 IU for older children and adults. Hypervitaminosis D can also result from excessive intake of synthetic vitamin D analogs (25-D, 1,25-D). Vitamin D intoxication is never secondary to excessive exposure to sunlight, probably because ultraviolet irradiation can transform vitamin D_3 and its precursor into inactive metabolites.

Pathogenesis

Although vitamin D increases intestinal absorption of calcium, the dominant mechanism of the hypercalcemia is excessive bone resorption.

Clinical Manifestations

The signs and symptoms of vitamin D intoxication are secondary to hypercalcemia. GI manifestations include nausea, vomiting, poor feeding, constipation, abdominal pain, and pancreatitis. Possible cardiac findings are hypertension, decreased Q-T interval, and arrhythmias. The central nervous system effects of hypercalcemia include lethargy, hypotonia, confusion, disorientation, depression, psychosis, hallucinations, and coma. Hypercalcemia impairs renal concentrating

mechanisms, which can lead to polyuria, dehydration, and hypernatremia. Hypercalcemia can also lead to acute renal failure, nephrolithiasis, and nephrocalcinosis, which can result in chronic renal insufficiency. Deaths are usually associated with arrhythmias or dehydration.

Laboratory Findings

The classic findings in vitamin D intoxication are hypercalcemia and extremely elevated levels of 25-D (>150 ng/mL). Hyperphosphatemia is also common. PTH levels are appropriately decreased owing to hypercalcemia. Hypercalciuria is universally present and can lead to nephrocalcinosis, which is visible on renal ultrasound. Hypercalcemia and nephrocalcinosis can lead to renal insufficiency.

Surprisingly, levels of 1,25-D are usually normal. This may be a result of downregulation of renal 1α-hydroxylase by the combination of low PTH, hyperphosphatemia, and a direct effect of 1,25-D. There is evidence indicating that the level of free 1,25-D may be high, owing to displacement from vitamin D–binding proteins by 25-D. Nephrocalcinosis is often visible on ultrasound or CT scan. Anemia is sometimes present; the mechanism is unknown.

Diagnosis and Differential Diagnosis

The diagnosis is based on the presence of hypercalcemia and an elevated serum 25-D level, although children with excess intake of 1,25-D or another synthetic vitamin D preparation have normal levels of 25-D. With careful sleuthing, there is usually a history of excess intake of vitamin D, although in some situations (overfortification of milk by a dairy) the patient and family may be unaware.

The **differential diagnosis** of vitamin D intoxication focuses on other causes of hypercalcemia. **Hyperparathyroidism** produces hypophosphatemia, whereas vitamin D intoxication usually causes hyperphosphatemia. **Williams syndrome** is often suggested by phenotypic features and accompanying cardiac disease. **Idiopathic infantile hypercalcemia** occurs in children taking appropriate doses of vitamin D. **Subcutaneous fat necrosis** is a common cause of hypercalcemia in young infants; skin findings are usually present. The hypercalcemia of **familial benign hypocalciuric hypercalcemia** is mild, asymptomatic, and associated with hypocalciuria. Hypercalcemia of **malignancy** is an important consideration. High intake of calcium can also cause hypercalcemia, especially in the presence of renal insufficiency. Questioning about calcium intake should be part of the history in a patient with hypercalcemia. Occasionally, patients are intentionally taking high doses of calcium and vitamin D.

Treatment

The treatment of vitamin D intoxication focuses on control of hypercalcemia. Many patients with hypercalcemia are dehydrated as a result of polyuria from nephrogenic diabetes insipidus, poor oral intake, and vomiting. Rehydration lowers the serum calcium level via dilution and corrects prerenal azotemia. The resultant increased urine output increases urinary calcium excretion. Urinary calcium excretion is also increased by high urinary sodium excretion. The mainstay of the initial treatment is aggressive therapy with normal saline, often in conjunction with a loop diuretic to further increase calcium excretion.

Normal saline, with or without a loop diuretic, is often adequate for treating mild or moderate hypercalcemia. More significant hypercalcemia usually requires other therapies. Glucocorticoids decrease intestinal absorption of calcium by blocking the action of 1,25-D. There is also a decrease in the levels of 25-D and 1,25-D. The usual dosage of prednisone is 1-2 mg/kg/24 hr.

Calcitonin, which lowers calcium by inhibiting bone resorption, is a useful adjunct, but its effect is usually not dramatic. There is an excellent response to intravenous or oral bisphosphonates in vitamin D intoxication. Bisphosphonates inhibit bone resorption through their effects on osteoclasts. Hemodialysis using a low or 0 dialysate calcium can rapidly lower serum calcium in patients with severe hypercalcemia that is refractory to other measures.

Along with controlling hypercalcemia, it is imperative to eliminate the source of excess vitamin D. Additional sources of vitamin D such as multivitamins and fortified foods should be eliminated or reduced. Avoidance of sun exposure, including the use of sunscreen, is prudent. The patient should also restrict calcium intake.

Prognosis

Most children make a full recovery, but hypervitaminosis D may be fatal or can lead to chronic kidney disease. Because vitamin D is stored in fat, levels can remain elevated for months, necessitating regular monitoring of 25-D, serum calcium, and urine calcium.

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Chapter 52

Vitamin E Deficiency

Larry A. Greenbaum

Vitamin E is a fat-soluble vitamin and functions as an antioxidant, but its precise biochemical functions are not known. Vitamin E deficiency can cause hemolysis or neurologic manifestations and occurs in premature infants, in patients with malabsorption, and in an autosomal recessive disorder affecting vitamin E transport. Because of its role as an antioxidant, there is considerable research on the potential role of vitamin E supplementation in chronic illnesses.

PATHOGENESIS

The term *vitamin E* denotes a group of 8 compounds with similar structures and antioxidant activity. The most potent member of these compounds is α-tocopherol, which is also the main form in humans. The best dietary sources of vitamin E are vegetable oils, seeds, nuts, green leafy vegetables, and margarine (see Table 51-1).

The majority of vitamin E is located within cell membranes, where it prevents lipid peroxidation and the formation of free radicals. Other antioxidants, such as ascorbic acid, enhance the antioxidant activity of vitamin E. The importance of other functions of vitamin E is still being delineated.

Premature infants are particularly susceptible to vitamin E deficiency, because there is significant transfer of vitamin E during the last trimester of pregnancy. Vitamin E deficiency in premature infants causes thrombocytosis, edema, and hemolysis potentially causing anemia. The risk of symptomatic vitamin E deficiency was increased by the use of formulas for premature infants that had a high content of polyunsaturated fatty acids (PUFAs). These formulas led to a high content of PUFAs in red blood cell membranes, making them more susceptible to oxidative stress, which could be ameliorated by vitamin E. Oxidative stress was augmented by aggressive use of iron supplementation; iron increases the production of oxygen radicals. The incidence of hemolysis as a result of vitamin E deficiency in premature infants decreased secondary to the use of formulas with a lower content of PUFAs, less-aggressive use of iron, and provision of adequate vitamin E.

Because vitamin E is plentiful in common foods, primary dietary deficiency is rare except in premature infants and in severe, generalized malnutrition. Vitamin E deficiency does occur in children with fat malabsorption secondary to the need for bile acid for vitamin E absorption. Although symptomatic disease is most common in children with cholestatic liver disease, it can occur in patients with cystic fibrosis, celiac disease, short-bowel syndrome, or Crohn disease. The autosomal recessive disorder **abetalipoproteinemia** (see Chapter 86) causes fat malabsorption, and vitamin E deficiency is a common complication.

In **ataxia with isolated vitamin E deficiency** (AVED), a rare autosomal recessive disorder, there are mutations in the gene for α-tocopherol transfer protein (*TTPA*). Patients with this disorder are unable to incorporate vitamin E into lipoproteins before their release from the liver, leading to reduced serum levels of vitamin E. There is no associated fat malabsorption, and absorption of vitamin E from the intestine occurs normally.

CLINICAL MANIFESTATIONS

A severe, progressive neurologic disorder occurs in patients with prolonged vitamin E deficiency. Clinical manifestations do not appear until after 1 yr of age, even in children with cholestasis since birth. Patients may have cerebellar disease, posterior column dysfunction, and retinal disease. Loss of deep tendon reflexes is usually the initial finding. Subsequent manifestations include limb ataxia (intention tremor, dysdiadochokinesia), truncal ataxia (wide-based, unsteady gait), dysarthria, ophthalmoplegia (limited upward gaze), nystagmus, decreased proprioception (positive Romberg test), decreased vibratory sensation, and dysarthria. Some patients have pigmentary retinopathy. Visual field constriction can progress to blindness. Cognition and behavior can also be affected. Myopathy and cardiac arrhythmias are less-common findings.

In premature infants, hemolysis as a result of vitamin E deficiency typically develops during the 2nd mo of life. Edema may also be present.

LABORATORY FINDINGS

Serum vitamin E levels increase in the presence of high serum lipid levels, even when vitamin E deficiency is present. Hence, vitamin E status is best determined by measuring the ratio of vitamin E to serum lipids; a ratio <0.8 mg/g is abnormal in older children and adults; <0.6 mg/g is abnormal in infants <1 yr. Premature infants with hemolysis caused by vitamin E deficiency also often have elevated platelet counts.

Neurologic involvement can cause abnormal somatosensory evoked potentials and nerve conduction studies. Abnormalities on electroretinography can precede physical examination findings in patients with retinal involvement.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Premature infants with unexplained hemolytic anemia after the 1st mo of life, especially if thrombocytosis is present, either should be empirically treated with vitamin E or should have serum vitamin E and lipid levels measured. Children with neurologic findings and a disease that causes fat malabsorption should have their vitamin E status evaluated.

Because children with AVED do not have symptoms of malabsorption, a correct diagnosis requires a high index of suspicion. **Friedreich ataxia** has been misdiagnosed in some patients (see Chapter 597.1). Children with unexplained ataxia should be screened for vitamin E deficiency.

TREATMENT

For correction of deficiency in neonates, the dose of vitamin E is 25-50 units/day for 1 wk, followed by adequate dietary intake. Children with deficiency as a result of malabsorption should receive 1 unit/kg/day, with the dose adjusted based on levels; ongoing treatment is necessary. Children with AVED normalize their serum vitamin E levels with high doses of vitamin E and require ongoing treatment.

PROGNOSIS

The hemolytic anemia in infants resolves with correction of the vitamin E deficiency. Some neurologic manifestations of vitamin E deficiency may be reversible with early treatment, but many patients have little or no improvement. Importantly, treatment prevents progression.

PREVENTION

Premature infants should receive sufficient vitamin E via formula or breast milk fortifier and formula without a high content of PUFAs. Children at risk for vitamin E deficiency as a result of malabsorption should be screened for deficiency and given adequate vitamin E supplementation. Vitamin preparations with high content of all of the fat-soluble vitamins are available.

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Chapter 53

Vitamin K Deficiency

Larry A. Greenbaum

Vitamin K is necessary for the synthesis of clotting factors II, VII, IX, and X; deficiency of vitamin K can result in clinically significant bleeding. Vitamin K deficiency typically affects infants, who experience a transient deficiency related to inadequate intake, or patients of any age who have decreased vitamin K absorption. Mild vitamin K deficiency can affect long-term bone and vascular health (see Chapters 103.4 and 480).

PATHOGENESIS

Vitamin K is a group of compounds that have a common naphthoquinone ring structure. Phylloquinone, called *vitamin* K_1, is present in a variety of dietary sources, with green leafy vegetables, liver, and certain legumes and plant oils having the highest content. Vitamin K_1 is the form used to fortify foods and as a medication in the United States. Vitamin K_2 is a group of compounds called *menaquinones*, which are produced by intestinal bacteria. There is uncertainty regarding the relative importance of intestinally produced vitamin K_2. Menaquinones are also present in meat, especially liver, and cheese. A menaquinone is used pharmacologically in some countries.

Vitamin K is a cofactor for γ-glutamyl carboxylase, an enzyme that performs posttranslational carboxylation, converting glutamate residues in proteins to γ-carboxyglutamate (Gla). The Gla residues, by facilitating calcium binding, are necessary for protein function.

The classic Gla-containing proteins involved in blood coagulation that are decreased in vitamin K deficiency are factors II (prothrombin), VII, IX, and X. Vitamin K deficiency causes a decrease in proteins C and S, which inhibit blood coagulation, and protein Z, which also has a role in coagulation. All of these proteins are made only in the liver, except for protein S, a product of various tissues.

Gla-containing proteins are also involved in bone biology (e.g., osteocalcin and protein S) and vascular biology (matrix Gla protein and protein S). Based on the presence of reduced levels of Gla, these proteins appear more sensitive than the coagulation proteins to subtle vitamin K deficiency. There is evidence suggesting that mild vitamin K deficiency might have a deleterious effect on long-term bone strength and vascular health.

Because it is fat soluble, vitamin K requires the presence of bile salts for its absorption. Unlike other fat-soluble vitamins, there are limited body stores of vitamin K. In addition, there is high turnover of vitamin K, and the vitamin K–dependent clotting factors have a short half-life. Hence, symptomatic vitamin K deficiency can develop within weeks when there is inadequate supply because of low intake or malabsorption.

There are 3 forms of **vitamin K–deficiency bleeding** (VKDB) of the newborn (see Chapter 103.4). Early VKDB was formerly called *classic hemorrhagic disease of the newborn* and occurs at 1-14 days of age. Early VKDB is secondary to low stores of vitamin K at birth as a result of the poor transfer of vitamin K across the placenta and inadequate intake during the 1st few days of life. In addition, there is no intestinal synthesis of vitamin K_2 because the newborn gut is sterile. Early VKDB

occurs mostly in breastfed infants as a consequence of the low vitamin K content of breast milk (formula is fortified). Delayed feeding is an additional risk factor.

Late VKDB most commonly occurs at 2-12 wk of age, although cases can occur up to 6 mo after birth. Almost all cases are in breastfed infants because of the low vitamin K content of breast milk. An additional risk factor is occult malabsorption of vitamin K, as occurs in children with undiagnosed cystic fibrosis or cholestatic liver disease (e.g., biliary atresia, α_1-antitrypsin deficiency). Without vitamin K prophylaxis, the incidence is 4-10/100,000 newborns.

The third form of VKDB of the newborn occurs at birth or shortly thereafter. It is secondary to maternal intake of medications (warfarin, phenobarbital, phenytoin) that cross the placenta and interfere with vitamin K function.

VKDB as a result of fat malabsorption can occur in children of any age. Potential etiologies include cholestatic liver disease, pancreatic disease, and intestinal disorders (celiac sprue, inflammatory bowel disease, short-bowel syndrome). Prolonged diarrhea can cause vitamin K deficiency, especially in breastfed infants. Children with cystic fibrosis are most likely to have vitamin K deficiency if they have pancreatic insufficiency and liver disease.

Beyond infancy, low dietary intake by itself never causes vitamin K deficiency. However, the combination of poor intake and the use of broad-spectrum antibiotics that eliminate the intestine's vitamin K_2-producing bacteria can cause vitamin K deficiency. This scenario is especially common in the intensive care unit. Vitamin K deficiency can also occur in patients who receive total parenteral nutrition without vitamin K supplementation.

CLINICAL MANIFESTATIONS

In early VKDB, the most common sites of bleeding are the gastrointestinal (GI) tract, mucosal and cutaneous tissue, the umbilical stump, and the postcircumcision site; intracranial bleeding is less common. GI blood loss can be severe enough to require a transfusion. In contrast, the most common site of bleeding in late VKDB is intracranial, although cutaneous and GI bleeding may be the initial manifestation. Intracranial bleeding can cause convulsions, permanent neurologic sequelae, or death. In some cases of late VKDB, the presence of an underlying disorder may be suggested by jaundice or failure to thrive. Older children with vitamin K deficiency can present with bruising, mucocutaneous bleeding, or more serious bleeding.

LABORATORY FINDINGS

In patients with bleeding as a result of vitamin K deficiency, the prothrombin time (PT) is prolonged. The PT must be interpreted based on the patient's age, because it is normally prolonged in newborns (see Chapter 476). The partial thromboplastin time is usually prolonged, but it may be normal in early deficiency; factor VII has the shortest half-life of the coagulation factors and is the first to be affected by vitamin K deficiency, but isolated factor VII deficiency does not affect the partial thromboplastin time. The platelet count and fibrinogen level are normal.

When there is mild vitamin K deficiency, the PT is normal, but there are elevated levels of the undercarboxylated forms of the proteins that are normally carboxylated in the presence of vitamin K. These undercarboxylated proteins are called *proteins induced by vitamin K absence* (PIVKA). Measurement of undercarboxylated factor II (PIVKA-II) can be used to detect mild vitamin K deficiency. Determination of blood vitamin K levels is less useful because of significant variation based on recent dietary intake; levels do not always reflect tissue stores.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is established by the presence of a prolonged PT that corrects rapidly after administration of vitamin K, which stops the active bleeding. Other possible causes of bleeding and a prolonged PT include **disseminated intravascular coagulation** (DIC), liver failure, and rare hereditary deficiencies of clotting factors. DIC, which is most commonly secondary to sepsis, is associated with thrombocytopenia, low fibrinogen, and elevated D-dimers. Most patients with DIC have hemodynamic instability that does not correct with restoration of blood volume. Severe liver disease results in decreased production of clotting factors; the PT does not fully correct with administration of vitamin K. Children with a hereditary disorder have a deficiency in a specific clotting factor (I, II, V, VII, X).

Coumarin derivatives inhibit the action of vitamin K by preventing its recycling to an active form after it functions as a cofactor for γ-glutamyl carboxylase. Bleeding can occur with overdosage of the commonly used anticoagulant warfarin or with ingestion of rodent poison, which contains a coumarin derivative. High doses of salicylates also inhibit vitamin K regeneration, potentially leading to a prolonged PT and clinical bleeding.

TREATMENT

Infants with VKDB should receive 1 mg of parenteral vitamin K. The PT should decrease within 6 hr and normalize within 24 hr. For rapid correction in adolescents, the parenteral dose is 2.5-10 mg. In addition to vitamin K, a patient with severe, life-threatening bleeding should receive an infusion of fresh-frozen plasma, which corrects the coagulopathy rapidly. Children with vitamin K deficiency as a consequence of malabsorption require chronic administration of high doses of oral vitamin K (2.5 mg twice/wk to 5 mg/day). Parenteral vitamin K may be necessary if oral vitamin K is ineffective.

PREVENTION

Administration of either oral or parenteral vitamin K soon after birth prevents early VKDB of the newborn. In contrast, a single dose of oral vitamin K does not prevent a substantial number of cases of late VKDB. However, a single intramuscular injection of vitamin K (1 mg), the current practice in the United States, is almost universally effective, except in children with severe malabsorption. This increased efficacy of the intramuscular form is thought to be the result of a depot effect. Concerns about an association between parenteral vitamin K at birth and the later development of malignancy are unsubstantiated.

Discontinuing the offending medications before delivery can prevent VKDB attributable to maternal medications. If this is not possible, administration of vitamin K to the mother may be helpful. In addition, the neonate should receive parenteral vitamin K immediately after birth. If parenteral vitamin K does not correct the coagulopathy rapidly, then the child should receive fresh frozen plasma.

Children who are at high risk for malabsorption of vitamin K should receive supplemental vitamin K and periodic measurement of the PT.

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Chapter **54**

Micronutrient Mineral Deficiencies

Larry A. Greenbaum

Micronutrients include vitamins (see Chapters 48-53) and trace elements. By definition, a trace element is <0.01% of the body weight. Trace elements have a variety of essential functions (Table 54-1). With the exception of iron deficiency, trace element deficiency (see Table 54-1) is uncommon in developed countries, but some deficiencies (iodine, zinc, selenium) are important public health problems in a number of developing countries. Because of low nutritional requirements and plentiful supply, deficiencies of some of the trace elements are extremely rare in humans and typically occur in patients receiving

Table 54-1 Trace Elements

ELEMENT	PHYSIOLOGY	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	DIETARY SOURCES
Chromium	Potentiates the action of insulin	Impaired glucose tolerance, peripheral neuropathy, and encephalopathy	Unknown	Meat, grains, fruits, and vegetables
Copper	Absorbed via specific intestinal transporter Circulates bound to ceruloplasmin Enzyme cofactor (superoxide dismutase, cytochrome oxidase, and enzymes involved in iron metabolism and connective tissue formation)	Microcytic anemia, osteoporosis, neutropenia, neurologic symptoms, depigmentation of hair and skin	Acute: nausea, emesis, abdominal pain, coma, and hepatic necrosis Chronic toxicity (liver and brain injury) occurs in Wilson disease (see Chapter 357.2) and secondary to excess intake (see Chapter 357.3)	Vegetables, grains, nuts, liver, margarine, legumes, corn oil
Fluoride	Incorporated into bone	Dental caries (see Chapter 312)	Chronic: dental fluorosis (see Chapter 307)	Toothpaste, fluoridated water
Iodine	Component of thyroid hormone (see Chapter 564)	Hypothyroidism (see Chapters 566 and 568)	Hypothyroidism and goiter (see Chapters 566 and 568); maternal excess can cause congenital hypothyroidism and goiter (see Chapter 568.1)	Saltwater fish, iodized salt
Iron	Component of hemoglobin, myoglobin, cytochromes, and other enzymes	Anemia (see Chapter 456), decreased alertness, impaired learning	Acute (see Chapter 63): nausea, vomiting, diarrhea, abdominal pain, and hypotension Chronic excess usually secondary to hereditary disorders (see Chapters 463.9 and 357.4); causes organ dysfunction	Meat, fortified foods Deficiency can also result from blood loss (hookworm infestation, menorrhagia)
Manganese	Enzyme cofactor	Hypercholesterolemia, weight loss, decreased clotting proteins*	Neurologic manifestations, cholestatic jaundice	Nuts, meat, grains, tea
Molybdenum	Enzyme cofactor (xanthine oxidase and others)	Tachycardia, tachypnea, night blindness, irritability, coma*	Hyperuricemia and increased risk of gout	Legumes, grains, liver
Selenium	Enzyme cofactor (prevents oxidative damage)	Cardiomyopathy (Keshan disease), myopathy	Nausea, diarrhea, neurologic manifestations, nail and hair changes, garlic odor	Meat, seafood, whole grains, garlic
Zinc	Enzyme cofactor Constituent of zinc-finger proteins, which regulate gene transcription	Decreased growth, dermatitis of extremities and around orifices, impaired immunity, poor wound healing, hypogonadism, diarrhea Supplements beneficial in diarrhea and improve neurodevelopmental outcomes	Abdominal pain, diarrhea, vomiting Can worsen copper deficiency	Meat, shellfish, whole grains, legumes, cheese

*These deficiency states have been reported only in case reports associated with parenteral nutrition or highly unusual diets.

unusual diets or prolonged total parenteral nutrition without adequate delivery of a specific trace element. They can also occur in children with short bowel or malabsorption. Excess intake of trace elements (see Table 54-1) is uncommon, but it can result from environmental exposure or overuse of supplements.

For a number of reasons, children are especially susceptible to trace element deficiency. First, growth creates an increased demand for most trace elements. Second, some organs are more likely to sustain permanent damage because of trace element deficiency during childhood. The developing brain is particularly vulnerable to the consequences of certain deficiency states (iron, iodide). Similarly, adequate fluoride is most critical for dental health during childhood. Third, children, especially in the developing world, are more prone to gastrointestinal disorders that can cause trace element deficiencies because of malabsorption.

A normal diet provides adequate intake of most trace elements. However, the intake of certain trace elements varies significantly in different geographic locations. Iodide-containing food is plentiful near the ocean, but inland areas often have inadequate sources, leading to goiter and **hypothyroidism.** Iodine deficiency is not a problem in the United States because of the widespread use of iodized salt; however, symptomatic iodine deficiency (goiter and hypothyroidism) is common in many developing countries. Selenium content of the soil and consequently of food is also quite variable. Dietary selenium deficiency (associated with cardiomyopathy) occurs in certain locations, such as some parts of China.

The consequences of severe isolated trace mineral deficiency are illustrated in certain genetic disorders. The manifestations of **Menkes disease** (see Chapters 357.5 and 599) are caused by a mutation in the gene coding for a protein that facilitates intestinal copper absorption. This mutation results in severe copper deficiency; subcutaneous copper is an effective treatment. The recessive disorder **acrodermatitis enteropathica** (see Chapter 671) is secondary to malabsorption of zinc. These patients respond dramatically to zinc supplementation.

Children can have apparently asymptomatic deficiencies of certain trace elements but still benefit from supplementation. As an example, zinc is highly effective in treating children before or during diarrheal illnesses in the developing world.

Zinc deficiency is quite common in the developing world and is often associated with malnutrition or other micronutrient deficiencies (iron). Chronic zinc deficiency is associated with dwarfism, hypogonadism, dermatitis, and T-cell immunodeficiency. Diets rich in phytates bind zinc, impairing its absorption. Zinc supplementation in at-risk children reduces the incidence and severity of diarrhea, pneumonia, and possibly malaria. In developing countries, children who have diarrhea may benefit from zinc supplementation, especially if there is underlying malnutrition.

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Fluid and Electrolyte Disorders

PART VII

Chapter 55
Electrolyte and Acid-Base Disorders

55.1 Composition of Body Fluids

Larry A. Greenbaum

TOTAL BODY WATER

Total body water (TBW) as a percentage of body weight varies with age (Fig. 55-1). The fetus has very high TBW, which gradually decreases to approximately 75% of birthweight for a term infant. Premature infants have higher TBW than term infants. During the 1st yr of life, TBW decreases to approximately 60% of body weight and basically remains at this level until puberty. At puberty, the fat content of females increases more than that in males, who acquire more muscle mass than females. Because fat has very low water content and muscle has high water content, by the end of puberty TBW in males remains at 60%, but TBW in females decreases to approximately 50% of body weight. The high fat content in overweight children causes a decrease in TBW as a percentage of body weight. During dehydration, TBW decreases and, thus, is a smaller percentage of body weight.

FLUID COMPARTMENTS

TBW is divided between 2 main compartments: intracellular fluid (ICF) and extracellular fluid (ECF). In the fetus and newborn, the ECF volume is larger than the ICF volume (see Fig. 55-1). The normal postnatal diuresis causes an immediate decrease in the ECF volume. This is followed by continued expansion of the ICF volume, which results from cellular growth. By 1 yr of age, the ratio of the ICF volume to the ECF volume approaches adult levels. The ECF volume is approximately 20-25% of body weight, and the ICF volume is approximately 30-40% of body weight, close to twice the ECF volume (Fig. 55-2). With puberty, the increased muscle mass of males causes them to have a higher ICF volume than females. There is no significant difference in the ECF volume between postpubertal females and males.

The ECF is further divided into the plasma water and the interstitial fluid (see Fig. 55-2). The plasma water is 5% of body weight. The blood volume, given a hematocrit of 40%, is usually 8% of body weight, although it is higher in newborns and young infants; in premature newborns, it is approximately 10% of body weight. The volume of plasma water can be altered by pathologic conditions, including dehydration, anemia, polycythemia, heart failure, abnormal plasma osmolality, and hypoalbuminemia. The interstitial fluid, normally 15% of body weight, can increase dramatically in diseases associated with edema, such as heart failure, protein-losing enteropathy, liver failure, nephrotic syndrome, and sepsis. An increase in interstitial fluid also occurs in patients with ascites or pleural effusions.

There is a delicate equilibrium between the intravascular fluid and the interstitial fluid. The balance between hydrostatic and oncotic forces regulates the intravascular volume, which is critical for proper tissue perfusion. The intravascular fluid has a higher concentration of albumin than the interstitial fluid, and the consequent oncotic force draws water into the intravascular space. The maintenance of this gradient depends on the limited permeability of albumin across the capillaries. The hydrostatic pressure of the intravascular space, which is due to the pumping action of the heart, drives fluid out of the intravascular space. These forces favor movement into the interstitial space at the arterial ends of the capillaries. The decreased hydrostatic forces and increased oncotic forces, which result from the dilutional increase in albumin concentration, cause movement of fluid into the venous ends of the capillaries. Overall, there is usually a net movement of fluid out of the intravascular space to the interstitial space, but this fluid is returned to the circulation via the **lymphatics.** An imbalance in these forces may cause expansion of the interstitial volume at the expense of the intravascular volume. In children with hypoalbuminemia, the decreased oncotic pressure of the intravascular fluid contributes to the development of **edema.** Loss of fluid from the intravascular space may compromise the intravascular volume, placing the child at risk for inadequate blood flow to vital organs. This is especially likely in diseases in which capillary leak occurs because the loss of albumin from the intravascular space is associated with an increase in the albumin concentration in the interstitial space, further compromising the oncotic forces that normally maintain intravascular volume. In contrast, with **heart failure,** there is an increase in venous hydrostatic pressure from expansion of the intravascular volume, which is caused by impaired pumping by the heart, and the increase in venous pressure causes fluid to move from the intravascular space to the interstitial space. Expansion of the intravascular volume and increased intravascular pressure also cause the edema that occurs with acute glomerulonephritis.

ELECTROLYTE COMPOSITION

The composition of the solutes in the ICF and ECF are very different (Fig. 55-3). Sodium and chloride are the dominant cation and anion, respectively, in the ECF. The sodium and chloride concentrations in the ICF are much lower. Potassium is the most abundant cation in the ICF, and its concentration within the cells is approximately 30 times higher than in the ECF. Proteins, organic anions, and phosphate are the most plentiful anions in the ICF. The dissimilarity between the anions in the ICF and the ECF is largely determined by the presence of intracellular molecules that do not cross the cell membrane, the barrier separating the ECF and the ICF. In contrast, the difference in the distribution of cations—sodium and potassium—is a result of the activity of the Na^+,K^+-adenosine triphosphatase (ATPase) pump, which uses cellular energy to actively extrude sodium from cells and move potassium into cells. The chemical gradient between the intracellular potassium concentration and the extracellular potassium concentration creates the electrical gradient across the cell membrane. The concentration-dependent movement of potassium out of the cell makes the intracellular space negative relative to the extracellular space.

The difference in the electrolyte compositions of the ECF and the ICF has important ramifications in the evaluation and treatment of electrolyte disorders. The serum concentration of an electrolyte, which is measured clinically, does not always reflect the body content. This is because of the larger volume of the ICF compared with the ECF and the variation in electrolyte concentrations between these 2 compartments. The intracellular potassium concentration is much higher than the serum concentration. A shift of potassium from the intracellular space can maintain a normal or even an elevated serum potassium concentration, despite massive losses of potassium from the intracellular space. This is dramatically seen in diabetic ketoacidosis, in which a state of significant potassium depletion is often masked because of a transmembrane shift of potassium from the ICF to the ECF. For potassium and phosphorus, electrolytes with a high intracellular concentration, the serum level may not reflect total body content. Similarly, the serum calcium concentration does not predict the body content of calcium, which is largely in bone.

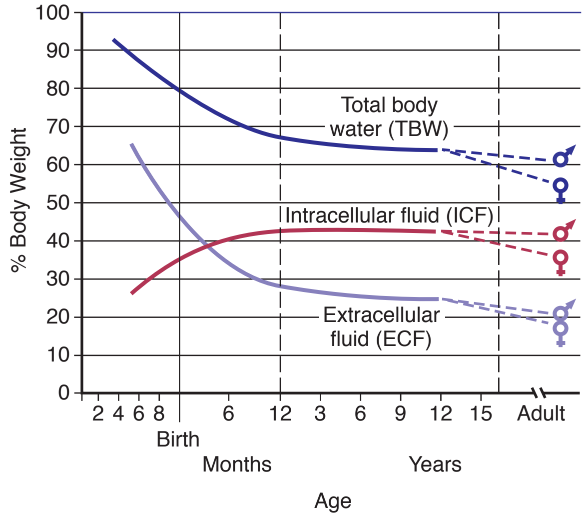

Figure 55-1 Total body water, intracellular fluid, and extracellular fluid as a percentage of body weight and a function of age. *(From Winters RW: Water and electrolyte regulation. In Winters RW, editor:* The body fluids in pediatrics, *Boston, 1973, Little, Brown.)*

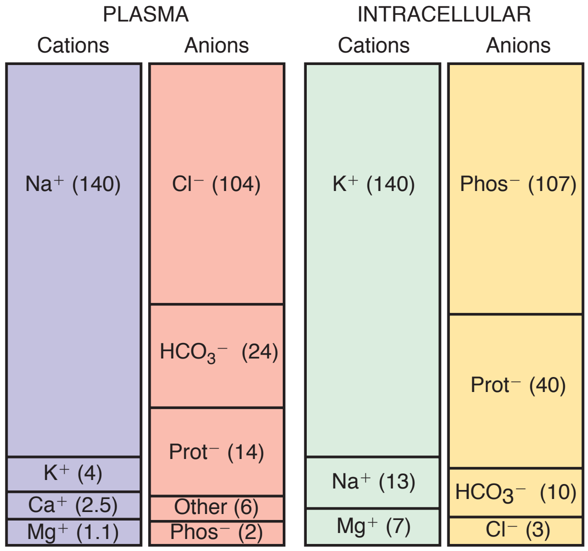

Figure 55-3 The concentrations of the major cations and anions in the intracellular space and the plasma, expressed in mEq/L.

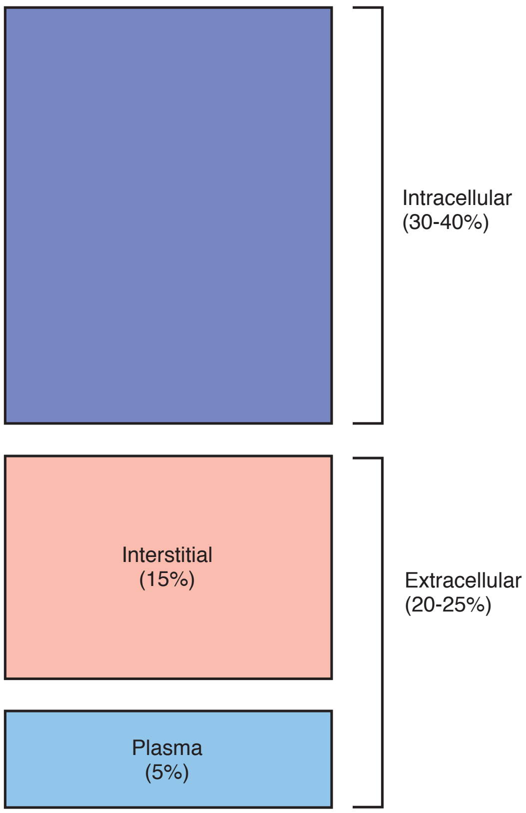

Figure 55-2 Compartments of total body water, expressed as percentages of body weight, in an older child or adult.

OSMOLALITY

The ICF and the ECF are in **osmotic equilibrium** because the cell membrane is permeable to water. If the osmolality in 1 compartment changes, then water movement leads to a rapid equalization of osmolality. This can lead to significant shifts of water between the intracellular space and the extracellular space. Clinically, the primary process is usually a change in the osmolality of the ECF, with a resultant shift of water into the ICF if the ECF osmolality decreases or a shift of water out of the ICF if the ECF osmolality increases. *The osmolality of the ECF can be determined, and it usually equals the ICF osmolality*. The plasma osmolality is normally 285-295 mOsm/kg, and it is measured by the degree of freezing point depression. The plasma osmolality can also be *estimated* by a calculation based on the following formula:

$$\text{Osmolality} = 2 \times [\text{Na}] + [\text{glucose}]/18 + [\text{BUN}]/2.8$$

Glucose and blood urea nitrogen (BUN) are measured in mg/dL. Division of these values by 18 and 2.8, respectively, as shown, converts the units into mmol/L. Multiplication of the sodium value by 2 accounts for its accompanying anions, principally chloride and bicarbonate. The calculated osmolality is usually slightly lower than the measured osmolality.

Glucose and urea normally contribute little to the plasma osmolality; multiplication of the sodium value by 2 provides an approximation of the osmolality. Urea is not confined to the extracellular space because it readily crosses the cell membrane and its intracellular concentration approximately equals its extracellular concentration. Whereas an elevated sodium concentration causes a shift of water from the intracellular space, with uremia, there is no osmolar gradient between the 2 compartments and, consequently, no movement of water. The only exception is during **hemodialysis,** when the decrease in extracellular urea is so rapid that the intracellular urea does not have time to equilibrate. This may lead to the **disequilibrium syndrome,** in which water shifts into brain cells, potentially causing severe symptoms. Ethanol, because it freely crosses cell membranes, is another ineffective osmole. The effective osmolality can be calculated as follows:

$$\text{Effective osmolality} = 2 \times [\text{Na}] + [\text{glucose}]/18$$

The effective osmolality (also called the tonicity) determines the osmotic force that is mediating the shift of water between the ECF and the ICF.

Hyperglycemia causes an increase in the plasma osmolality because it is not in equilibrium with the intracellular space. During hyperglycemia there is a shift of water from the intracellular space to the extracellular space. This is clinically important in children with hyperglycemia during diabetic ketoacidosis. The shift of water causes dilution of the sodium in the extracellular space, causing hyponatremia despite an elevated plasma osmolality. The magnitude of this effect can be calculated as follows:

$$[\text{Na}]_{\text{corrected}} = [\text{Na}]_{\text{measured}} + 1.6 \times ([\text{glucose}] - 100\ \text{mg/dL})/100$$

where $[Na]_{measured}$ = sodium concentration measured by the clinical laboratory and $[Na]_{corrected}$ = corrected sodium concentration (the

sodium concentration if the glucose concentration were normal and its accompanying water moved back into the cells). The $[Na]_{corrected}$ is the more reliable indicator of the patient's true ratio of total body sodium to TBW, the normal determinant of the sodium concentration.

Normally, the measured osmolality and the calculated osmolality are within 10 mOsm/kg. However, there are some clinical situations in which this does not occur. The presence of **unmeasured osmoles** causes the measured osmolality to be significantly elevated in comparison with the calculated osmolality. This difference is the **osmolal gap,** which is present when the measured osmolality exceeds the calculated osmolality by >10 mOsm/kg. Examples of unmeasured osmoles include ethanol, ethylene glycol, methanol, sucrose, sorbitol, and mannitol. These substances increase the measured osmolality but are not part of the equation for calculating osmolality. The presence of an osmolal gap is a clinical clue to the presence of unmeasured osmoles and may be diagnostically useful when there is clinical suspicion of poisoning with methanol or ethylene glycol.

Pseudohyponatremia is a second situation in which there is discordance between the measured osmolality and the calculated osmolality. Lipids and proteins are the solids of the serum. In patients with elevated serum lipids or proteins, the water content of the serum decreases because water is displaced by the larger amount of solids. Some instruments measure sodium concentration by determining the amount of sodium per liter of serum, including the solid component. When the solid component increases, there is a decrease in the sodium concentration per liter of serum, despite a normal concentration of sodium when based on the amount of sodium per liter of serum water. *It is the concentration of sodium in serum water that is physiologically relevant.* A similar problem occurs when using instruments that require dilution of the sample prior to measurement of sodium (indirect potentiometry). In both situations, the plasma osmolality is normal despite the presence of pseudohyponatremia, because the method for measuring osmolality is not appreciably influenced by the percentage of serum that is composed of lipids and proteins. Pseudohyponatremia is diagnosed by the finding of a normal measured plasma osmolality despite hyponatremia. This laboratory artifact does not occur if the sodium concentration in water is measured directly with an ion-specific electrode, such as occurs with the instruments used for measuring arterial blood gases. **Pseudohypernatremia** may occur in patients with very low levels of serum proteins via a similar mechanism.

When there are no unmeasured osmoles and pseudohyponatremia is not a concern, the calculated osmolality provides an accurate estimate of the plasma osmolality. Measurement of plasma osmolality is useful for detecting or monitoring unmeasured osmoles and confirming the presence of true hyponatremia. Whereas many children with high plasma osmolality are dehydrated—as seen with hypernatremic dehydration or diabetic ketoacidosis—high osmolality does not always equate with dehydration. A child with **salt poisoning** or **uremia** has an elevated plasma osmolality but may be volume overloaded. In many situations, it is best to focus on the components of the plasma osmolality and to analyze them individually to reach a correct clinical conclusion.

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55.2 Regulation of Osmolality and Volume

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The regulation of plasma *osmolality* and the intravascular *volume* is controlled by independent systems for water balance, which determines osmolality, and sodium balance, which determines volume status. Maintenance of normal osmolality depends on control of water balance. Control of volume status depends on regulation of sodium balance. When volume depletion is present, it takes precedence over regulation of osmolality, and retention of water contributes to the maintenance of intravascular volume.

REGULATION OF OSMOLALITY

The plasma osmolality is tightly regulated and maintained at 285-295 mOsm/kg. Modification of water intake and excretion maintains normal plasma osmolality. In the steady state, the combination of water intake and water produced by the body from oxidation balances water losses from the skin, lungs, urine, and gastrointestinal tract. Only water intake and urinary losses can be regulated.

Osmoreceptors in the hypothalamus sense the plasma osmolality (see Chapter 556). An elevated effective osmolality leads to secretion of antidiuretic hormone (ADH) by neurons in the supraoptic and paraventricular nuclei in the hypothalamus. The axons of these neurons terminate in the posterior pituitary. Circulating ADH binds to its V_2 receptors in the collecting duct cells of the kidney, and, via the generation of cyclic adenosine monophosphate, causes insertion of water channels (aquaporin-2) into the renal collecting ducts. This produces increased permeability to water, permitting resorption of water into the hypertonic renal medulla. The end result is that the urine concentration increases and water excretion decreases. Urinary water losses cannot be completely eliminated because there is obligatory excretion of urinary solutes, such as urea and sodium. The regulation of ADH secretion is tightly linked to plasma osmolality, responses being detectable with a 1% change in the osmolality. ADH secretion virtually disappears when the plasma osmolality is low, allowing excretion of maximally dilute urine. The consequent loss of **free water** (water without sodium) corrects the plasma osmolality. ADH secretion is not an all-or-nothing response; there is a graded adjustment as the osmolality changes.

Production of concentrated urine under the control of ADH requires a hypertonic renal medulla. The countercurrent multiplier, produced by the loop of Henle and the vasa recta, generates this hypertonicity. ADH stimulates sodium transport in the loop of Henle, helping to maintain this gradient when water retention is necessary.

Water intake is regulated by hypothalamic osmoreceptors, although these are different from the osmoreceptors that determine ADH secretion. These hypothalamic osmoreceptors, by linking to the cerebral cortex, stimulate thirst when the serum osmolality increases. Thirst occurs with a small increase in the serum osmolality.

Control of osmolality is subordinate to maintenance of an adequate intravascular volume. When volume depletion is present, both ADH secretion and thirst are stimulated, regardless of the plasma osmolality. The sensation of thirst requires moderate volume depletion but only a 1-2% change in the plasma osmolality. Although all of the mechanisms are not clear, angiotensin II, which is increased during volume depletion, is known to stimulate thirst. Baroreceptors, when sensing volume depletion, may also stimulate thirst.

A number of conditions can limit the kidney's ability to excrete adequate water to correct low plasma osmolality. In the **syndrome of inappropriate antidiuretic hormone (SIADH),** ADH continues to be produced despite a low plasma osmolality. In the presence of ADH, urinary dilution does not occur, and sufficient water is not excreted (see Chapters 55.3 and 559).

The glomerular filtration rate (GFR) affects the kidney's ability to eliminate water. With a decrease in the GFR, less water is delivered to the collecting duct, limiting the amount of water that can be excreted. The impairment in the GFR must be quite significant to limit the kidney's ability to respond to an excess of water.

The **minimum urine osmolality** is approximately 30-50 mOsm/kg. This places an upper limit on the kidney's ability to excrete water; sufficient solute must be present to permit water loss. Massive water intoxication may exceed this limit, whereas a lesser amount of water is necessary in the child with a diet that has very little solute. This is occasionally seen and can produce severe hyponatremia in children who receive little salt and have little urea production as a result of inadequate protein intake. Volume depletion is an extremely important cause of decreased water loss by the kidney despite a low plasma osmolality. This "appropriate" secretion of ADH occurs because volume depletion takes precedence over the osmolality in the regulation of ADH.

The normal response to increased plasma osmolality is conservation of water by the kidney. In **central diabetes insipidus,** this does not

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occur because of an absence of ADH secretion (see Chapters 55.3 and 558). Patients with **nephrogenic diabetes insipidus** have an inability to respond to ADH and produce dilute urine despite an increase in plasma osmolality (see Chapters 55.3 and 530).

The **maximum urine osmolality** is approximately 1,200 mOsm/kg. The obligatory solute losses dictate the minimum volume of urine that must be produced, even when maximally concentrated. Obligatory water losses increase in patients with high salt intake or high urea losses, as may occur after relief of a urinary obstruction or during recovery from acute tubular necrosis. An increase in urinary solute and, consequently, water losses occurs with an **osmotic diuresis,** which occurs classically from glycosuria in diabetes mellitus as well as iatrogenically after mannitol administration. There are developmental changes in the kidney's ability to concentrate the urine. The maximum urine osmolality in a newborn, especially a premature newborn, is less than that in an older infant or child. This limits the ability to conserve water and makes such a patient more vulnerable to hypernatremic dehydration. Very high fluid intake, as seen with **psychogenic polydipsia,** can dilute the high osmolality in the renal medulla, which is necessary for maximal urinary concentration. If fluid intake is restricted in patients with this condition, there may be some impairment in the kidney's ability to concentrate the urine, although this defect corrects after a few days without polydipsia. This may also occur during the initial treatment of central diabetes insipidus with desmopressin acetate; the renal medulla takes time to achieve its normal maximum osmolality. Loop diuretics, such as furosemide, by inhibiting sodium resorption in the ascending limb of the loop of Henle, decrease medullary hypertonicity, preventing excretion of maximally concentrated urine.

REGULATION OF VOLUME

An appropriate intravascular volume is critical for survival; both volume depletion and volume overload may cause significant morbidity and mortality. Because sodium is the principal extracellular cation and it is restricted to the ECF, adequate body sodium is necessary for maintenance of intravascular volume. The principal extracellular anion, chloride, is also necessary, but for simplicity, sodium balance is considered the main regulator of volume status because body content of sodium and that of chloride usually change proportionally, given the need for equal numbers of cations and anions. In some situations, chloride depletion is considered the dominant derangement causing volume depletion (metabolic alkalosis with volume depletion). In other situations, such as volume depletion with metabolic acidosis, sodium depletion may exceed chloride depletion.

The kidney determines sodium balance because there is little homeostatic control of sodium intake, even though salt craving does occasionally occur, typically in children with chronic renal salt loss. The kidney regulates sodium balance by altering the percentage of filtered sodium that is resorbed along the nephron. Normally, the kidney excretes <1% of the sodium filtered at the glomerulus. In the absence of disease, extrarenal losses and urinary output match intake, with the kidney having the capacity to adapt to large variations in sodium intake. When necessary, urinary sodium excretion can be reduced to virtually undetectable levels or increased dramatically.

Urinary sodium excretion is regulated by both intrarenal and extrarenal mechanisms. The most important determinant of renal sodium excretion is the volume status of the child; it is the effective intravascular volume that influences urinary sodium excretion. The effective intravascular volume is the volume status that is sensed by the body's regulatory mechanisms. Heart failure is a state of volume overload, but the effective intravascular volume is low because poor cardiac function prevents adequate perfusion of the kidneys and other organs. This fact explains the avid renal sodium retention that is often present in patients with heart failure.

Sodium resorption occurs throughout the nephron. Whereas the majority of filtered sodium is resorbed in the proximal tubule and the loop of Henle, the distal tubule and the collecting duct are the main sites for precise regulation of sodium balance. Approximately 65% of the filtered sodium is reclaimed in the proximal tubule, which is the major site for resorption of bicarbonate, glucose, phosphate, amino acids, and other substances that are filtered by the glomerulus. The transport of all these substances is linked to sodium resorption by cotransporters, or a sodium-hydrogen exchanger in the case of bicarbonate. This link is clinically important for bicarbonate and phosphate because their resorption parallels sodium resorption. In patients with **metabolic alkalosis and volume depletion**, correction of the metabolic alkalosis requires urinary loss of bicarbonate, but the volume depletion stimulates sodium and bicarbonate retention, preventing correction of the alkalosis. Volume expansion causes increased urinary losses of phosphate, even when there is phosphate depletion. Resorption of uric acid and urea occurs in the proximal tubule and increases when sodium retention increases. This arrangement accounts for the elevated uric acid and BUN measurements that often accompany dehydration, which is a stimulus for sodium retention in the proximal tubule. The cells of the proximal tubule are permeable to water; thus, water resorption in this segment parallels sodium resorption.

The loop of Henle is, in terms of absolute amount, the second most important site of sodium resorption along the nephron. The Na^+,K^+,$2Cl^-$ cotransporter on the luminal side of the membrane reclaims filtered sodium and chloride, whereas most of the potassium is recycled back into the lumen. This is the transporter that is inhibited by furosemide and other loop diuretics, which are highly effective at increasing sodium excretion. The ascending limb of the loop of Henle is not permeable to water, permitting sodium retention without water. ADH stimulates sodium retention in this segment; this arrangement helps create a more hypertonic medulla, which maximizes water conservation when ADH acts in the medullary collecting duct. Because loop diuretics inhibit sodium retention in this segment, their use causes a less hypertonic medulla, preventing excretion of maximally concentrated urine in the presence of ADH.

Sodium retention in the distal tubule is mediated by the thiazide-sensitive Na^+,Cl^- cotransporter. This segment of the nephron is relatively impermeable to water, and along with sodium and chloride retention, the distal tubule is important for delivery of fluid with a low sodium concentration to the collecting duct. This allows for excretion of water without sodium in patients who stop secreting ADH because of low plasma osmolality. Thiazide diuretics, by inhibiting sodium and chloride retention in this segment, prevent the excretion of water without electrolytes—partially explaining the severe hyponatremia that occasionally develops in patients receiving chronic thiazide diuretics.

The collecting duct, the final segment of the nephron, is important for the regulation of excretion of water, potassium, acid, and sodium. Even though the amount of sodium resorbed in this segment is less than in any other segment, this is the critical site for the regulation of sodium balance. Sodium resorption occurs via a sodium channel that is regulated by aldosterone. When these channels are open under the influence of aldosterone, almost all of the sodium can be resorbed. The uptake of sodium creates a negative charge in the lumen of the collecting duct, which facilitates the secretion of potassium and hydrogen ions. The potassium-sparing diuretics amiloride and triamterene block these sodium channels, and the inhibition of sodium uptake decreases potassium excretion. The potassium-sparing diuretic spironolactone blocks the binding of aldosterone to its receptor; thus, it indirectly decreases the activity of the sodium channels. The collecting duct is important for the regulation of water balance because it responds to ADH by inserting water channels that increase the permeability to water, and the hypertonicity of the renal medulla allows for maximal concentration of the urine.

The amount of sodium filtered at the glomerulus is directly proportional to the GFR. If sodium resorption in the nephron were constant, complete resorption of sodium with a small decrease in the GFR and significant renal sodium wasting with a small increase would result. This does not occur, however, because sodium resorption in the nephron is proportional to sodium delivery, a principle called **glomerular tubular balance.**

The **renin–angiotensin system** is an important regulator of renal sodium excretion. The juxtaglomerular apparatus produces renin in

response to decreased effective intravascular volume. Specific stimuli for renin release are decreased perfusion pressure in the afferent arteriole of the glomerulus, decreased delivery of sodium to the distal nephron, and β_1-adrenergic agonists, which increase in response to intravascular volume depletion. Renin, a proteolytic enzyme, cleaves angiotensinogen, producing angiotensin I. Angiotensin-converting enzyme converts angiotensin I into angiotensin II. The actions of angiotensin II include direct stimulation of the proximal tubule to increase sodium resorption and stimulation of the adrenal gland to increase aldosterone secretion. Through its actions in the distal nephron—specifically, the late distal convoluted tubule and the collecting duct—aldosterone increases sodium resorption. Aldosterone also stimulates potassium excretion, increasing urinary losses. Along with decreasing urinary loss of sodium, angiotensin II acts as a vasoconstrictor, which helps maintain adequate blood pressure in the presence of volume depletion.

Volume expansion stimulates the synthesis of atrial natriuretic peptide, which is produced by the atria in response to atrial wall distention. Along with increasing the GFR, atrial natriuretic peptide inhibits sodium resorption in the medullary portion of the collecting duct, facilitating an increase in urinary sodium excretion.

Volume overload occurs when sodium intake exceeds output. In children with kidney failure, there is an impaired ability to excrete sodium. This impairment tends to be proportional to the decrease in the GFR, although in some kidney diseases, such as renal dysplasia and juvenile nephronophthisis, damaged tubules cause significant sodium loss until the GFR is quite low. In general, as the GFR decreases, restriction of sodium intake becomes increasingly necessary. The GFR is low at birth, limiting a newborn's ability to excrete a sodium load. In other situations, there is a loss of the appropriate regulation of renal sodium excretion. This loss occurs in patients with excessive aldosterone, as is seen in primary hyperaldosteronism or renal artery stenosis, wherein excess renin production leads to high aldosterone levels. In acute glomerulonephritis, even without significantly reduced GFR, the normal intrarenal mechanisms that regulate sodium excretion malfunction, causing excessive renal retention of sodium and volume overload.

Renal retention of sodium occurs during volume depletion, but this appropriate response causes the severe excess in total body sodium that is present in heart failure, liver failure, nephrotic syndrome, and other causes of hypoalbuminemia. In these diseases, the effective intravascular volume is decreased, causing the kidney and the various regulatory systems to respond, leading to renal sodium retention and edema formation.

Volume depletion usually occurs when sodium losses exceed intake. The most common etiology in children is gastroenteritis. Excessive losses of sodium may also occur from the skin in children with burns, in sweat from patients with cystic fibrosis, or after vigorous exercise. Inadequate intake of sodium is uncommon except in neglect, in famine, or with an inappropriate choice of liquid diet in a child who cannot take solids. Urinary sodium wasting may occur in a range of renal diseases, from renal dysplasia to tubular disorders, such as Bartter syndrome. The neonate, especially if premature, has a mild impairment in the ability to conserve sodium. Iatrogenic renal sodium wasting takes place during diuretic therapy. Renal sodium loss occurs as a result of derangement in the normal regulatory systems. An absence of aldosterone, seen most commonly in children with **congenital adrenal hyperplasia** caused by 21-hydroxylase deficiency, causes sodium wasting (see Chapter 576).

Isolated disorders of water balance can affect volume status and sodium balance. Because the cell membrane is permeable to water, changes in TBW influence both the extracellular volume and the intracellular volume. In isolated water loss, as occurs in diabetes insipidus, the impact is greater on the intracellular space because of its higher volume compared with the extracellular space. This is why, in comparison with other types of dehydration, hypernatremic dehydration has less impact on plasma volume; most of the fluid loss comes from the intracellular space. Yet, significant water loss eventually affects intravascular volume and will stimulate renal sodium retention, even if total body sodium content is normal. Similarly, with acute water intoxication or SIADH, there is an excess of TBW, but most is in the intracellular space. However, there is some effect on the intravascular volume, which causes renal excretion of sodium. Children with SIADH or water intoxication have high urine sodium concentrations, despite hyponatremia. This finding reinforces the concept that there are independent control systems for water and sodium, yet the 2 systems interact when pathophysiologic processes dictate, and control of effective intravascular volume always takes precedence over control of osmolality.

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55.3 Sodium

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SODIUM METABOLISM

Body Content and Physiologic Function

Sodium is the dominant cation of the ECF (see Fig. 55-3), and it is the principal determinant of extracellular osmolality. Sodium is therefore necessary for the maintenance of intravascular volume. Less than 3% of sodium is intracellular. More than 40% of total body sodium is in bone; the remainder is in the interstitial and intravascular spaces. The low intracellular sodium concentration, approximately 10 mEq/L, is maintained by Na^+,K^+-ATPase, which exchanges intracellular sodium for extracellular potassium.

Intake

A child's diet determines the amount of sodium ingested—a predominantly cultural determination in older children. An occasional child has salt craving because of an underlying salt-wasting renal disease or adrenal insufficiency. Children in the United States tend to have very high sodium intakes because their diets include a large amount of "junk" food or fast food. Infants receive sodium from breast milk (≈7 mEq/L) and formula (7-13 mEq/L, for 20 calorie/oz formula).

Sodium is readily absorbed throughout the gastrointestinal tract. Mineralocorticoids increase sodium transport into the body, although this effect has limited clinical significance. The presence of glucose enhances sodium absorption owing to the presence of a cotransport system. This is the rationale for including sodium and glucose in oral rehydration solutions (see Chapter 340).

Excretion

Sodium excretion occurs in stool and sweat, but the kidney regulates sodium balance and is the principal site of sodium excretion. There is some sodium loss in stool, but it is minimal unless diarrhea is present. Normally, sweat has 5-40 mEq/L of sodium. Sweat sodium concentration is increased in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism. The higher sweat losses in these conditions may cause or contribute to sodium depletion.

Sodium is unique among electrolytes because water balance, not sodium balance, usually determines its concentration. When the sodium concentration increases, the resultant higher plasma osmolality causes increased thirst and increased secretion of ADH, which leads to renal conservation of water. Both of these mechanisms increase the water content of the body, and the sodium concentration returns to normal. During hyponatremia, the decrease in plasma osmolality stops ADH secretion, and consequent renal water excretion leads to an increase in the sodium concentration. Even though water balance is usually regulated by osmolality, volume depletion does stimulate thirst, ADH secretion, and renal conservation of water. Volume depletion takes precedence over osmolality; volume depletion stimulates ADH secretion, even if a patient has hyponatremia.

The excretion of sodium by the kidney is not regulated by the plasma osmolality. The patient's effective plasma volume determines the amount of sodium in the urine. This is mediated by a variety of regulatory systems, including the renin–angiotensin–aldosterone system and

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intrarenal mechanisms. In hyponatremia or hypernatremia, the underlying pathophysiology determines the amount of urinary sodium, not the serum sodium concentration.

HYPERNATREMIA

Hypernatremia is a sodium concentration >145 mEq/L, although it is sometimes defined as >150 mEq/L. Mild hypernatremia is fairly common in children, especially among infants with gastroenteritis. Hypernatremia in hospitalized patients may be iatrogenic—caused by inadequate water administration or, less often, by excessive sodium administration. Moderate or severe hypernatremia has significant morbidity, including the result of underlying disease, the effects of hypernatremia on the brain, and the risks of overly rapid correction.

Etiology and Pathophysiology

There are 3 basic mechanisms of hypernatremia (Table 55-1). Sodium intoxication is frequently iatrogenic in a hospital setting as a result of correction of metabolic acidosis with sodium bicarbonate. Baking soda, a putative home remedy for upset stomach, is another source of sodium bicarbonate; the hypernatremia is accompanied by a profound metabolic alkalosis. In hyperaldosteronism, there is renal retention of sodium and resultant hypertension; hypernatremia may not be present or is usually mild.

Table 55-1 Causes of Hypernatremia
EXCESSIVE SODIUM
Improperly mixed formula
Excess sodium bicarbonate
Ingestion of seawater or sodium chloride
Intentional salt poisoning (child abuse or Munchausen syndrome by proxy)
Intravenous hypertonic saline
Hyperaldosteronism
WATER DEFICIT
Nephrogenic diabetes insipidus
Acquired
X-linked (OMIM 304800)
Autosomal recessive (OMIM 222000)
Autosomal dominant (OMIM 125800)
Central diabetes insipidus
Acquired
Autosomal recessive (OMIM 125700)
Autosomal dominant (OMIM 125700)
Wolfram syndrome (OMIM 222300/598500)
Increased insensible losses
Premature infants
Radiant warmers
Phototherapy
Inadequate intake:
Ineffective breastfeeding
Child neglect or abuse
Adipsia (lack of thirst)
WATER AND SODIUM DEFICITS
Gastrointestinal losses
Diarrhea
Emesis/nasogastric suction
Osmotic cathartics (lactulose)
Cutaneous losses
Burns
Excessive sweating
Renal losses
Osmotic diuretics (mannitol)
Diabetes mellitus
Chronic kidney disease (dysplasia and obstructive uropathy)
Polyuric phase of acute tubular necrosis
Postobstructive diuresis

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

The classic causes of hypernatremia from a water deficit are **nephrogenic** and **central diabetes insipidus** (see Chapters 530 and 558). Hypernatremia develops in diabetes insipidus only if the patient does not have access to water or cannot drink adequately because of immaturity, neurologic impairment, emesis, or anorexia. Infants are at high risk because of their inability to control their own water intake. Central diabetes insipidus and the genetic forms of nephrogenic diabetes insipidus typically cause massive urinary water losses and very dilute urine. The water losses are less dramatic, and the urine often has the same osmolality as plasma when nephrogenic diabetes insipidus is secondary to intrinsic renal disease (obstructive uropathy, renal dysplasia, sickle cell disease).

The other causes of a water deficit are also secondary to an imbalance between losses and intake. Newborns, especially if premature, have high insensible water losses. Losses are further increased if the infant is placed under a radiant warmer or with the use of phototherapy for hyperbilirubinemia. The renal concentrating mechanisms are not optimal at birth, providing an additional source of water loss. Ineffective breastfeeding, often in a primiparous mother, can cause severe hypernatremic dehydration. Adipsia, the absence of thirst, is usually secondary to damage to the hypothalamus, such as from trauma, tumor, hydrocephalus, or histiocytosis. Primary adipsia is rare.

When hypernatremia occurs in conditions with deficits of sodium and water, the water deficit exceeds the sodium deficit. This occurs only if the patient is unable to ingest adequate water. Diarrhea results in depletion of both sodium and water. Because diarrhea is hypotonic—typical sodium concentration of 35-65 mEq/L—water losses exceed sodium losses, potentially leading to hypernatremia. Most children with gastroenteritis do not have hypernatremia because they drink enough hypotonic fluid to compensate for stool water losses (see Chapter 340). Fluids such as water, juice, and formula are more hypotonic than the stool losses, allowing correction of the water deficit and potentially even causing hyponatremia. Hypernatremia is most likely to occur in the child with diarrhea who has inadequate intake because of emesis, lack of access to water, or anorexia.

Osmotic agents, including mannitol and glucose in diabetes mellitus, cause excessive renal losses of water and sodium. Because the urine is hypotonic (sodium concentration of approximately 50 mEq/L) during an osmotic diuresis, water loss exceeds sodium loss and hypernatremia may occur if water intake is inadequate. Certain chronic kidney diseases, such as renal dysplasia and obstructive uropathy, are associated with tubular dysfunction, leading to excessive losses of water and sodium. Many children with such diseases have disproportionate water loss and are at risk for hypernatremic dehydration, especially if gastroenteritis supervenes. Similar mechanisms occur during the polyuric phase of acute tubular necrosis and after relief of urinary obstruction (postobstructive diuresis). Patients with either condition may have an osmotic diuresis from urinary losses of urea and an inability to conserve water because of tubular dysfunction.

Clinical Manifestations

Most children with hypernatremia are dehydrated and show the typical clinical signs and symptoms (see Chapter 57). Children with hypernatremic dehydration tend to have better preservation of intravascular volume because of the shift of water from the intracellular space to the extracellular space. This shift maintains blood pressure and urine output and allows hypernatremic infants to be less symptomatic initially and potentially to become more dehydrated before medical attention is sought. Breastfed infants with hypernatremia are often profoundly dehydrated, with failure to thrive. Probably because of intracellular water loss, the pinched abdominal skin of a dehydrated, hypernatremic infant has a "doughy" feel.

Hypernatremia, even without dehydration, causes central nervous system (CNS) symptoms that tend to parallel the degree of sodium elevation and the acuity of the increase. Patients are irritable, restless, weak, and lethargic. Some infants have a high-pitched cry and hyperpnea. Alert patients are very thirsty, even though nausea may be present. Hypernatremia may cause fever, although many patients have

an underlying process that contributes to the fever. Hypernatremia is associated with hyperglycemia and mild hypocalcemia; the mechanisms are unknown. Beyond the sequelae of dehydration, there is no clear direct effect of hypernatremia on other organs or tissues, except the brain.

Brain hemorrhage is the most devastating consequence of untreated hypernatremia. As the extracellular osmolality increases, water moves out of brain cells, leading to a decrease in brain volume. This decrease can result in tearing of intracerebral veins and bridging blood vessels as the brain moves away from the skull and the meninges. Patients may have subarachnoid, subdural, and parenchymal hemorrhages. Seizures and coma are possible sequelae of the hemorrhage, although seizures are more common during correction of hypernatremia. The cerebrospinal fluid protein is often elevated in infants with significant hypernatremia, probably owing to leakage from damaged blood vessels. Neonates, especially if premature, seem especially vulnerable to hypernatremia and excessive sodium intake. There is an association between rapid or hyperosmolar sodium bicarbonate administration and the development of intraventricular hemorrhages in neonates. Even though central pontine myelinolysis (CPM) is classically associated with overly rapid correction of hyponatremia, both CPM and extrapontine myelinolysis can occur in children with hypernatremia. Thrombotic complications occur in severe hypernatremic dehydration; they include stroke, dural sinus thrombosis, peripheral thrombosis, and renal vein thrombosis. This is secondary to dehydration and possibly hypercoagulability associated with hypernatremia.

Diagnosis

The etiology of hypernatremia is usually apparent from the history. Hypernatremia resulting from water loss occurs only if the patient does not have access to water or is unable to drink. In the absence of dehydration, it is important to ask about sodium intake. Children with excess sodium intake do not have signs of dehydration, unless another process is present. Severe sodium intoxication causes signs of volume overload, such as pulmonary edema and weight gain. **Salt poisoning** is associated with an elevated fractional excretion of sodium, whereas hypernatremic dehydration causes a low fractional excretion of sodium. In hyperaldosteronism, hypernatremia is usually mild or absent and is associated with edema, hypertension, hypokalemia, and metabolic alkalosis.

When there is isolated water loss, the signs of volume depletion are usually less severe initially because much of the loss is from the intracellular space. When pure water loss causes signs of dehydration, the hypernatremia and water deficit are usually severe. In the child with renal water loss, either central or nephrogenic diabetes insipidus, the urine is inappropriately dilute and urine volume is not low. The urine is maximally concentrated and urine volume is low if the losses are extrarenal or due to inadequate intake. With extrarenal causes of loss of water, the urine osmolality should be >1,000 mOsm/kg. When diabetes insipidus is suspected, the evaluation may include measurement of ADH and a water deprivation test, including a trial of desmopressin acetate (synthetic ADH analog) to differentiate between nephrogenic diabetes insipidus and central diabetes insipidus (see Chapters 530 and 558). A water-deprivation test is unnecessary if the patient has simultaneous documentation of hypernatremia and poorly concentrated urine (osmolality lower than that of plasma). In children with central diabetes insipidus, administration of desmopressin acetate increases the urine osmolality above the plasma osmolality, although maximum osmolality does not occur immediately because of the decreased osmolality of the renal medulla as a result of the chronic lack of ADH. In children with nephrogenic diabetes insipidus, there is no response to desmopressin acetate.

With combined sodium and water deficits, analysis of the urine differentiates between renal and nonrenal etiologies. When the losses are extrarenal, the kidney responds to volume depletion with low urine volume, concentrated urine, and sodium retention (urine sodium <20 mEq/L, fractional excretion of sodium <1%). With renal causes, the urine volume is not appropriately low, the urine is not maximally concentrated, and the urine sodium may be inappropriately elevated.

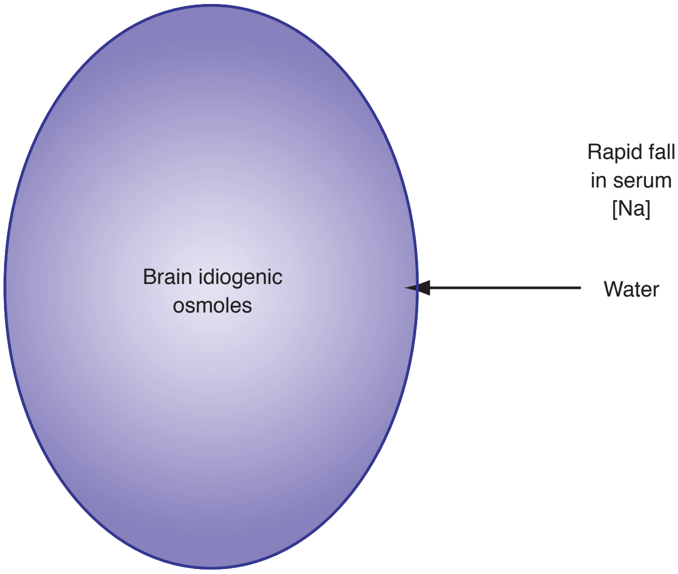

Figure 55-4 **Mechanism of brain edema during correction of hypernatremia.** A rapid decrease of the serum concentration during treatment of hypernatremia causes movement of water into brain cells, leading to cerebral edema. The presence of idiogenic osmoles in brain cells is responsible for the osmotic gradient.

Treatment

As hypernatremia develops, the brain generates **idiogenic osmoles** to increase the intracellular osmolality and prevent the loss of brain water. This mechanism is not instantaneous and is most prominent when hypernatremia has developed gradually. If the serum sodium concentration is lowered rapidly, there is movement of water from the serum into the brain cells to equalize the osmolality in the 2 compartments (Fig. 55-4). The resultant brain swelling manifests as seizures or coma.

Because of the associated dangers, hypernatremia should not be corrected rapidly. The goal is to decrease the serum sodium by <12 mEq/L every 24 hr, a rate of 0.5 mEq/L/hr. The most important component of correcting moderate or severe hypernatremia is frequent monitoring of the serum sodium value so that fluid therapy can be adjusted to provide adequate correction, neither too slow nor too fast. If a child has seizures as a result of brain edema secondary to rapid correction, administration of hypotonic fluid should be stopped. An infusion of 3% saline can acutely increase the serum sodium, reversing the cerebral edema.

In the child with hypernatremic dehydration, as in any child with dehydration, the **first priority is restoration of intravascular volume** with isotonic fluid (see Chapter 57). Normal saline is preferable to lactated Ringer solution because the lower sodium concentration of the latter can cause the serum sodium to decrease too rapidly, especially if multiple fluid boluses are given. Repeated boluses of normal saline (10-20 mL/kg) may be required to treat hypotension, tachycardia, and signs of poor perfusion (peripheral pulses, capillary refill time) (see Chapters 57 and 70).

The sodium concentration of the deficit replacement fluid, the rate of fluid administration, and the presence of continued water losses determine the rate of decrease of the sodium concentration. The following formula is often cited for calculating the water deficit:

$$\text{Water deficit} = \text{Body weight} \times 0.6(1\text{-}145)/[\text{current sodium}])$$

This calculation is equivalent to 3-4 mL of water per kg for each 1 mEq that the current sodium level exceeds 145 mEq. The utility of such formulas has never been proven in clinical practice. Most patients with hypernatremic dehydration do well with a fluid sodium concentration of approximately half-normal saline, but with a fluid rate that is only 20-30% greater than maintenance fluid. Use of this

concentration prevents excessive delivery of free water and too rapid a decrease in the serum sodium level. Patients with pure water loss may require a more hypotonic fluid (0.2 normal saline). Excessive water and sodium losses may also need to be replaced. If signs or symptoms of volume depletion develop, the patient receives additional boluses of isotonic saline. Monitoring of the rate of decrease of the serum sodium concentration permits adjustment in the rate and sodium concentration of the fluid that the patient is receiving, avoiding overly rapid correction of the hypernatremia (see Chapter 57 for additional details). Many patients with mild to moderate hypernatremic dehydration as a result of gastroenteritis can be managed with oral rehydration (see Chapter 340).

Acute, severe hypernatremia, usually secondary to sodium administration, can be corrected more rapidly because idiogenic osmoles have not had time to accumulate. This fact balances the high morbidity and mortality rates associated with hypernatremia with the dangers of overly rapid correction. When hypernatremia is severe and is caused by sodium intoxication, it may be impossible to administer enough water to correct the hypernatremia rapidly without worsening the volume overload. In this situation, dialysis allows for removal of the excess sodium, with the precise strategy dependent on the mode of dialysis. In less-severe cases, the addition of a loop diuretic increases the removal of excess sodium and water, decreasing the risk of volume overload. With sodium overload, hypernatremia is corrected with sodium-free intravenous fluid (5% dextrose in water).

Hyperglycemia from hypernatremia is not usually a problem and is not treated with insulin because the acute decrease in glucose may precipitate cerebral edema by lowering plasma osmolality. Rarely, the glucose concentration of intravenous fluids must be reduced (from 5% dextrose in water to 2.5% dextrose in water). The secondary hypocalcemia is treated as needed.

It is important to address the underlying cause of the hypernatremia, if possible. The child with central diabetes insipidus should receive desmopressin acetate. Because this treatment reduces renal excretion of water, excessive intake of water must consequently be avoided to prevent both overly rapid correction of the hypernatremia and the development of hyponatremia. Over the long-term, reduced sodium intake and the use of medications can somewhat ameliorate the water losses in nephrogenic diabetes insipidus (see Chapter 530). The daily water intake of a child who is receiving tube feeding may need to be increased to compensate for high losses. The patient with significant ongoing losses, such as through diarrhea, may need supplemental water and electrolytes (see Chapter 56). Sodium intake is reduced if it contributed to the hypernatremia.

HYPONATREMIA

Hyponatremia, a very common electrolyte abnormality in hospitalized patients, is a serum sodium level <135 mEq/L. Both total body sodium and TBW determine the serum sodium concentration. Hyponatremia exists when the ratio of water to sodium is increased. This condition can occur with low, normal, or high levels of body sodium. Similarly, body water can be low, normal, or high.

Etiology and Pathophysiology

Table 55-2 lists the causes of hyponatremia. Pseudohyponatremia is a laboratory artifact that is present when the plasma contains very high concentrations of protein (multiple myeloma, intravenous immunoglobulin infusion) or lipid (hypertriglyceridemia, hypercholesterolemia). It does not occur when a direct ion-selective electrode determines the sodium concentration in undiluted plasma, a technique that is used by arterial blood gas analyzers or point-of-care instruments. In true hyponatremia, the measured osmolality is low, whereas it is normal in pseudohyponatremia. Hyperosmolality, as may occur with hyperglycemia, causes a low serum sodium concentration because water moves down its osmotic gradient from the intracellular space into the extracellular space, diluting the sodium concentration. However, because the manifestations of hyponatremia are a result of the low plasma osmolality, patients with hyponatremia resulting from hyperosmolality do not have symptoms of hyponatremia. When the etiology of the hyperosmolality resolves, such as hyperglycemia in diabetes mellitus, water moves back into the cells and the sodium concentration rises to its "true" value. Mannitol or sucrose, a component of intravenous immunoglobulin preparations, may cause hyponatremia because of hyperosmolality.

Classification of hyponatremia is based on the patient's volume status. In **hypovolemic hyponatremia,** the child has lost sodium from the body. The water balance may be positive or negative, but sodium loss has been higher than water loss. The pathogenesis of the

Table 55-2 Causes of Hyponatremia
PSEUDOHYPONATREMIA
Hyperlipidemia
Hyperproteinemia
HYPEROSMOLALITY
Hyperglycemia
Iatrogenic (mannitol, sucrose, glycine)
HYPOVOLEMIC HYPONATREMIA
EXTRARENAL LOSSES
Gastrointestinal (emesis, diarrhea)
Skin (sweating or burns)
Third space losses (bowel obstruction, peritonitis, sepsis)
RENAL LOSSES
Thiazide or loop diuretics
Osmotic diuresis
Postobstructive diuresis
Polyuric phase of acute tubular necrosis
Juvenile nephronophthisis (OMIM 256100/606966/602088/604387/611498)
Autosomal recessive polycystic kidney disease (OMIM 263200)
Tubulointerstitial nephritis
Obstructive uropathy
Cerebral salt wasting
Proximal (type II) renal tubular acidosis (OMIM 604278)*
Lack of aldosterone effect (high serum potassium):
Absence of aldosterone (e.g., 21-hydroxylase deficiency [OMIM 201910])
Pseudohypoaldosteronism type I (OMIM 264350/177735)
Urinary tract obstruction and/or infection
EUVOLEMIC HYPONATREMIA
Syndrome of inappropriate antidiuretic hormone secretion
Nephrogenic syndrome of inappropriate antidiuresis (OMIM 304800)
Desmopressin acetate
Glucocorticoid deficiency
Hypothyroidism
Water intoxication:
Iatrogenic (excess hypotonic intravenous fluids)
Feeding infants excessive water products
Swimming lessons
Tap water enema
Child abuse
Psychogenic polydipsia
Diluted formula
Beer potomania
Exercise-induced hyponatremia
HYPERVOLEMIC HYPONATREMIA
Heart failure
Cirrhosis
Nephrotic syndrome
Acute, chronic kidney injury
Capillary leak caused by sepsis
Hypoalbuminemia caused by gastrointestinal disease (protein-losing enteropathy)

*Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

hyponatremia is usually a combination of sodium loss and water retention to compensate for the volume depletion. The patient has a pathologic increase in fluid loss, and this fluid contains sodium. Most fluid that is lost has a lower sodium concentration than that of plasma. Viral diarrhea fluid has, on average, a sodium concentration of 50 mEq/L. Replacing diarrhea fluid, which has a sodium concentration of 50 mEq/L, with formula, which has only approximately 10 mEq/L of sodium, reduces the sodium concentration. Intravascular volume depletion interferes with renal water excretion, the body's usual mechanism for preventing hyponatremia. The volume depletion stimulates ADH synthesis, resulting in renal water retention. Volume depletion also decreases the GFR and enhances water resorption in the proximal tubule, thereby reducing water delivery to the collecting duct.

Diarrhea as a result of gastroenteritis is the most common cause of **hypovolemic hyponatremia** in children. Emesis causes hyponatremia if the patient takes in hypotonic fluid, either intravenously or enterally, despite the emesis. Most patients with emesis have either a normal sodium concentration or hypernatremia. Burns may cause massive losses of isotonic fluid and resultant volume depletion. Hyponatremia develops if the patient receives hypotonic fluid. Losses of sodium from sweat are especially high in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism, although high losses can occur simply in a hot climate. Third-space losses are isotonic and can cause significant volume depletion, leading to ADH production and water retention, which can cause hyponatremia if the patient receives hypotonic fluid. In diseases that cause volume depletion through extrarenal sodium loss, the urine sodium level should be low (<10 mEq/L) as part of the renal response to maintain the intravascular volume. The only exceptions are diseases that cause both extrarenal and renal sodium losses: adrenal insufficiency and pseudohypoaldosteronism.

Renal sodium loss may occur in a variety of situations. In some situations, the urine sodium concentration is >140 mEq/L; thus, hyponatremia may occur without any fluid intake. In many cases, the urine sodium level is less than the serum concentration; thus, the intake of hypotonic fluid is necessary for hyponatremia to develop. In diseases associated with urinary sodium loss, the urine sodium level is >20 mEq/L despite volume depletion. This may not be true if the urinary sodium loss is no longer occurring, as is frequently the case if diuretics are discontinued. Because loop diuretics prevent generation of a maximally hypertonic renal medulla, the patient can neither maximally dilute nor concentrate the urine. The inability to maximally retain water provides some protection against severe hyponatremia. The patient receiving thiazide diuretics can concentrate the urine and is at higher risk for severe hyponatremia. Osmotic agents, such as glucose during diabetic ketoacidosis, cause loss of both water and sodium. Urea accumulates during renal failure and then acts as an osmotic diuretic after relief of urinary tract obstruction and during the polyuric phase of acute tubular necrosis. Transient tubular damage in these conditions further impairs sodium conservation. The serum sodium concentration in these conditions depends on the sodium concentration of the fluid used to replace the losses. Hyponatremia develops when the fluid is hypotonic relative to the urinary losses.

Renal salt wasting occurs in hereditary kidney diseases, such as juvenile nephronophthisis and autosomal recessive polycystic kidney disease. Obstructive uropathy, most commonly a consequence of posterior urethral valves, produces salt wasting, but patients with the disease may also have hypernatremia as a result of impaired ability to concentrate urine and high water loss. Acquired tubulointerstitial nephritis, usually secondary to either medications or infections, may cause salt wasting, along with other evidence of tubular dysfunction. CNS injury may produce cerebral salt wasting, which is theoretically caused by the production of a natriuretic peptide that causes renal salt wasting. In type II renal tubular acidosis (RTA), usually associated with Fanconi syndrome (see Chapter 529.1), there is increased excretion of sodium and bicarbonate in the urine. Patients with Fanconi syndrome also have glycosuria, aminoaciduria, and hypophosphatemia because of renal phosphate wasting.

Aldosterone is necessary for renal sodium retention and for the excretion of potassium and acid. In congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, the block of aldosterone production results in hyponatremia, hyperkalemia, and metabolic acidosis. In pseudohypoaldosteronism, aldosterone levels are elevated, but there is no response because of either a defective sodium channel or a deficiency of aldosterone receptors. A lack of tubular response to aldosterone may occur in children with urinary tract obstruction, especially during an acute urinary tract infection.

In **hypervolemic hyponatremia,** there is an excess of TBW and sodium, although the increase in water is greater than the increase in sodium. In most of the conditions that cause hypervolemic hyponatremia, there is a decrease in the effective blood volume, resulting from third space fluid loss, vasodilation, or poor cardiac output. The regulatory systems sense a decrease in effective blood volume and attempt to retain water and sodium to correct the problem. ADH causes renal water retention, and the kidney, under the influence of aldosterone and other intrarenal mechanisms, retains sodium. The patient's sodium concentration decreases because water intake exceeds sodium intake and ADH prevents the normal loss of excess water.

In these disorders, there is a low urine sodium concentration (<10 mEq/L) and an excess of both TBW and sodium. The only exception is in patients with renal failure and hyponatremia. These patients have an expanded intravascular volume, and hyponatremia can therefore appropriately suppress ADH production. Water cannot be excreted because very little urine is being made. Serum sodium is diluted through ingestion of water. Because of renal dysfunction, the urine sodium concentration may be elevated, but urine volume is so low that urine sodium excretion has not kept up with sodium intake, leading to sodium overload. The urine sodium concentration in renal failure varies. In patients with acute glomerulonephritis, because it does not affect the tubules, the urine sodium level is usually low, whereas in patients with acute tubular necrosis, it is elevated because of tubular dysfunction.

Patients with hyponatremia and no evidence of volume overload or volume depletion have **euvolemic hyponatremia.** These patients typically have an excess of TBW and a slight decrease in total body sodium. Some of these patients have an increase in weight, implying that they are volume-overloaded. Nevertheless, from a clinical standpoint, they usually appear normal or have subtle signs of fluid overload.

In SIADH, the secretion of ADH is not inhibited by either low serum osmolality or expanded intravascular volume (see Chapter 559). The result is that the child with SIADH is unable to excrete water. This results in dilution of the serum sodium and hyponatremia. The expansion of the extracellular volume as a result of the retained water causes a mild increase in intravascular volume. The kidney increases sodium excretion in an effort to decrease intravascular volume to normal; thus, the patient has a mild decrease in body sodium. SIADH most commonly occurs with disorders of the CNS (infection, hemorrhage, trauma, tumor, thrombosis), but lung disease (infection, asthma, positive pressure ventilation) and malignant tumors (producing ADH) are other potential causes. A variety of medications may cause SIADH, including recreational use of 3,4-methylenedioxymethylamphetamine (MDMA, or "Ecstasy"), opiates, antiepileptic drugs (carbamazepine, oxcarbazepine, valproate), tricyclic antidepressants, vincristine, Cytoxan, and selective serotonin reuptake inhibitors. The diagnosis of SIADH is one of exclusion, because other causes of hyponatremia must be eliminated (Table 55-3). Because SIADH is a state of intravascular volume expansion, low serum uric acid and BUN levels are supportive of the diagnosis.

A rare gain-of-function mutation in the renal ADH receptor causes **nephrogenic syndrome of inappropriate antidiuresis.** Patients with this X-linked disorder appear to have SIADH but have undetectable levels of ADH.

Hyponatremia in hospitalized patients is frequently caused by inappropriate production of ADH and administration of hypotonic intravenous fluids. Causes of inappropriate ADH production include stress, medications such as narcotics or anesthetics, nausea, and respiratory illness. The synthetic analog of ADH, desmopressin acetate, causes

Table 55-3	Diagnostic Criteria for Syndrome of Inappropriate Antidiuretic Hormone Secretion
Absence of:	
Renal, adrenal, or thyroid insufficiency	
Heart failure, nephrotic syndrome, or cirrhosis	
Diuretic ingestion	
Dehydration	
Urine osmolality >100 mOsm/kg (usually > plasma)	
Serum osmolality <280 mOsm/kg and serum sodium <135 mEq/L	
Urine sodium >30 mEq/L	
Reversal of "sodium wasting" and correction of hyponatremia with water restriction	

water retention and may cause hyponatremia if fluid intake is not appropriately limited. The main uses of desmopressin acetate in children are for the management of central diabetes insipidus and of nocturnal enuresis.

Excess water ingestion can produce hyponatremia. In these cases, the sodium concentration decreases as a result of dilution. This decrease suppresses ADH secretion, and there is a marked water diuresis by the kidney. Hyponatremia develops only because the intake of water exceeds the kidney's ability to eliminate water. This condition is more likely to occur in infants because their lower GFR limits their ability to excrete water.

Hyponatremia may develop in infants <6 mo of age when caregivers offer water to their infant as a supplement, during hot weather, or when they run out of formula. Hyponatremia may result in transient seizures, hypothermia, and poor tone. With cessation of water intake, the hyponatremia rapidly corrects. Infants <6 mo of age should not be given water to drink; infants between 6 and 12 mo of age should not receive more than 1-2 ounces. If the infant appears thirsty, the parent should offer formula or breastfeed the child.

In some situations, the water intoxication causes acute hyponatremia and is a consequence of a massive acute water load. Examples of causes of this water load include infant swimming lessons, inappropriate use of hypotonic intravenous fluids, water enemas, and forced water intake as a form of child abuse. Chronic hyponatremia occurs in children who receive water, but limited sodium and protein. The minimum urine osmolality is approximately 50 mOsm/kg, the kidney can excrete 1 L of water only if there is enough solute ingested to produce 50 mOsm for urinary excretion. Because sodium and urea (a breakdown product of protein) are the principal urinary solutes, a lack of intake of sodium and protein prevents adequate water excretion. This occurs with the use of diluted formula or other inappropriate diets. Subsistence on beer, a poor source of sodium and protein, causes hyponatremia because of the inability to excrete the high water load ("beer potomania"). **Exercise-induced hyponatremia**, reported commonly during marathons, is caused by excessive water intake, salt losses from sweat, and secretion of ADH.

The pathogenesis of the hyponatremia in glucocorticoid deficiency is multifactorial, and includes increased ADH secretion. In hypothyroidism, there is an inappropriate retention of water by the kidney, but the precise mechanisms are not clearly elucidated.

Clinical Manifestations

Hyponatremia causes a decrease in the osmolality of the extracellular space. Because the intracellular space then has a higher osmolality, water moves from the extracellular space to the intracellular space to maintain osmotic equilibrium. The increase in intracellular water causes cells to swell. Although cell swelling is not problematic in most tissues, it is dangerous for the brain, which is confined by the skull. As brain cells swell, there is an increase in intracranial pressure, which impairs cerebral blood flow. Acute, severe hyponatremia can cause brainstem herniation and apnea; respiratory support is often necessary. Brain cell swelling is responsible for most of the symptoms of hyponatremia. Neurologic symptoms of hyponatremia include anorexia, nausea, emesis, malaise, lethargy, confusion, agitation, headache, seizures, coma, and decreased reflexes. Patients may have hypothermia and Cheyne-Stokes respirations. Hyponatremia can cause muscle cramps and weakness; rhabdomyolysis can occur with water intoxication.

The symptoms of hyponatremia are mostly a result of the decrease in extracellular osmolality and the resulting movement of water down its osmotic gradient into the intracellular space. Brain swelling can be significantly obviated if the hyponatremia develops gradually, because brain cells adapt to the decreased extracellular osmolality by reducing intracellular osmolality. This reduction is achieved by extrusion of the main intracellular ions (potassium and chloride) and a variety of small organic molecules. This process explains why the range of symptoms in hyponatremia is related to both the serum sodium level and its rate of decrease. A patient with chronic hyponatremia may have only subtle neurologic abnormalities with a serum sodium level of 110 mEq/L, but another patient may have seizures because of an acute decline in serum sodium level from 140 to 125 mEq/L.

Diagnosis

The history usually points to a likely etiology of the hyponatremia. Most patients with hyponatremia have a history of volume depletion. Diarrhea and diuretic use are very common causes of hyponatremia in children. A history of polyuria, perhaps with enuresis, and/or salt craving is present in children with primary kidney diseases or absence of aldosterone effect. Children may have signs or symptoms suggesting a diagnosis of hypothyroidism or adrenal insufficiency (see Chapters 565 and 575). Brain injury raises the possibility of SIADH or cerebral salt wasting, with the caveat that SIADH is much more likely. Liver disease, nephrotic syndrome, renal failure, or congestive heart failure may be acute or chronic. The history should include a review of the patient's intake, both intravenous and enteral, with careful attention to the amounts of water, sodium, and protein.

The traditional first step in the diagnostic process is determination of the plasma osmolality. This is done because some patients with a low serum sodium value do not have low osmolality. The clinical effects of hyponatremia are secondary to the associated low osmolality. Without a low osmolality, there is no movement of water into the intracellular space.

A patient with hyponatremia can have a low, normal, or high osmolality. A normal osmolality in combination with hyponatremia occurs in pseudohyponatremia. Children with elevation of serum glucose concentration or of another effective osmole (mannitol) have a high plasma osmolality and hyponatremia. The presence of a low osmolality indicates "true" hyponatremia. Patients with low osmolality are at risk for neurologic symptoms and require further evaluation to determine the etiology of the hyponatremia.

In some situations, true hyponatremia is present despite a normal or elevated plasma osmolality. The presence of an ineffective osmole, most commonly urea, increases the plasma osmolality, but because the osmole has the same concentration in the intracellular space, it does not cause fluid to move into the extracellular space. There is no dilution of the serum sodium by water, and the sodium concentration remains unchanged if the ineffective osmole is eliminated. Most importantly, the ineffective osmole does not protect the brain from edema caused by hyponatremia. Hence, a patient may have symptoms of hyponatremia despite having a normal or increased osmolality because of uremia.

In patients with true hyponatremia, the next step in the diagnostic process is to clinically evaluate the volume status. Patients with hyponatremia can be hypovolemic, hypervolemic, or euvolemic. The diagnosis of volume depletion relies on the usual findings with dehydration (see Chapter 57), although subtle volume depletion may not be clinically apparent. In a patient with subtle volume depletion, a fluid bolus results in a decrease in the urine osmolality and an increase in the serum sodium concentration. Children with hypervolemia are **edematous** on physical examination. They may have ascites, pulmonary edema, pleural effusion, or hypertension.

Hypovolemic hyponatremia can have renal or nonrenal causes. The urine sodium concentration is very useful in differentiating between renal and nonrenal causes. When the losses are nonrenal and the kidney is working properly, there is renal retention of sodium, a normal homeostatic response to volume depletion. Thus, the urinary sodium concentration is low, typically <10 mEq/L, although sodium conservation in neonates is less avid. When the kidney is the cause of the sodium loss, the urine sodium concentration is >20 mEq/L, reflecting the defect in renal sodium retention. The interpretation of the urine sodium level is challenging with diuretic therapy because it is high when diuretics are being used but low after the diuretic effect is gone. This becomes an issue only when diuretic use is surreptitious. The urine sodium concentration is not useful if a metabolic alkalosis is present; the urine chloride concentration must be used instead (see Chapter 55.7).

Differentiating among the nonrenal causes of hypovolemic hyponatremia is usually facilitated by the history. Although the renal causes are more challenging to distinguish, a high serum potassium concentration is associated with disorders in which the sodium wasting is caused by absence of or ineffectiveness of aldosterone.

In the patient with hypervolemic hyponatremia, the urine sodium concentration is a helpful parameter. It is usually <10 mEq/L, except in the patient with renal failure.

Treatment

The management of hyponatremia is based on the pathophysiology of the specific etiology. The management of all causes requires judicious monitoring and avoidance of an overly quick normalization of the serum sodium concentration. A patient with severe symptoms (seizures), no matter the etiology, should be given a bolus of hypertonic saline to produce a small, rapid increase in serum sodium. Hypoxia worsens cerebral edema, and hyponatremia may cause hypoxia. Hence, pulse oximetry should be monitored, and hypoxia aggressively corrected.

With all causes of hyponatremia, it is important to avoid "overly rapid" correction. The reason is that rapid correction of hyponatremia may cause CPM. This syndrome, which occurs within several days of rapid correction of hyponatremia, produces neurologic symptoms, including confusion, agitation, flaccid or spastic quadriparesis, and death. There are usually characteristic pathologic and radiologic changes in the brain, especially in the pons, but extrapontine lesions are quite common and may cause additional symptoms. Despite severe symptoms, full recovery does occur in some patients.

CPM is more common in patients who are treated for chronic hyponatremia than in those treated for acute hyponatremia. Presumably, this difference is based on the adaptation of brain cells to the hyponatremia. The reduced intracellular osmolality that is an adaptive mechanism for chronic hyponatremia makes brain cells susceptible to dehydration during rapid correction of the hyponatremia, and this may be the mechanism of CPM. Even though CPM is rare in pediatric patients, it is advisable to avoid correcting the serum sodium concentration by >12 mEq/L/24 hr or >18 mEq/L/48 hr. Desmopressin is a potential option if the serum sodium level is increasing too rapidly. This guideline does not apply to acute hyponatremia, as may occur with water intoxication, because the hyponatremia is more often symptomatic and there has not been time for the adaptive decrease in brain osmolality to occur. The consequences of brain edema in acute hyponatremia exceed the small risk of CPM.

Patients with hyponatremia can have severe neurologic symptoms, such as seizures and coma. The seizures associated with hyponatremia generally are poorly responsive to anticonvulsants. The child with hyponatremia and severe symptoms needs to receive treatment that will quickly reduce cerebral edema. This goal is best accomplished by increasing the extracellular osmolality so that water moves down its osmolar gradient from the intracellular space to the extracellular space.

Intravenous hypertonic saline rapidly increases serum sodium, and the effect on serum osmolality leads to a decrease in brain edema. Each mL/kg of 3% sodium chloride increases the serum sodium by approximately 1 mEq/L. A child with active symptoms often improves after receiving 4-6 mL/kg of 3% sodium chloride.

The child with **hypovolemic hyponatremia** has a deficiency in sodium and may have a deficiency in water. The cornerstone of therapy is to replace the sodium deficit and any water deficit that is present. The first step in treating any dehydrated patient is to restore the intravascular volume with isotonic saline. Ultimately, complete restoration of intravascular volume suppresses ADH production, thereby permitting excretion of the excess water. Chapter 57 discusses the management of hyponatremic dehydration.

The management of **hypervolemic hyponatremia** is difficult. Patients with this disorder have an excess of both water and sodium. Administration of sodium leads to worsening volume overload and edema. In addition, the patients are retaining water and sodium because of their ineffective intravascular volume or renal insufficiency. The cornerstone of therapy is water and sodium restriction, because the patients have volume overload. Diuretics may help by causing excretion of both sodium and water. Vasopressin antagonists, by blocking the action of ADH and causing a water diuresis, are effective in correcting the hypervolemic hyponatremia caused by heart failure or cirrhosis.

Some patients with low albumin resulting from nephrotic syndrome have a better response to diuretics after an infusion of 25% albumin; the sodium concentration often normalizes as a result of expansion of the intravascular volume. A child with heart failure may have an increase in renal water and sodium excretion if there is an improvement in cardiac output. This improvement will "turn off" the regulatory hormones that are causing renal water (ADH) and sodium (aldosterone) retention. The patient with renal failure cannot respond to any of these therapies except fluid restriction. Insensible fluid losses eventually result in an increase in the sodium concentration as long as insensible and urinary losses are greater than intake. A more definitive approach in children with renal failure is to perform dialysis, which removes water and sodium.

In isovolumic hyponatremia, there is usually an excess of water and a mild sodium deficit. Therapy is directed at eliminating the excess water. The child with acute excessive water intake loses water in the urine because ADH production is turned off as a result of the low plasma osmolality. Children may correct their hyponatremia spontaneously over 3-6 hr. For acute, symptomatic hyponatremia as a result of water intoxication, hypertonic saline may be needed to reverse cerebral edema. For chronic hyponatremia from poor solute intake, the child needs to receive an appropriate formula, and excess water intake should be eliminated.

Children with iatrogenic hyponatremia caused by the administration of hypotonic intravenous fluids should receive 3% saline if they are symptomatic. Subsequent management is dictated by the patient's volume status. The hypovolemic child should receive isotonic intravenous fluids. The child with nonphysiologic stimuli for ADH production should undergo fluid restriction. Prevention of this iatrogenic complication requires judicious use of intravenous fluids (see Chapter 56).

Specific hormone replacement is the cornerstone of therapy for the hyponatremia of hypothyroidism or cortisol deficiency. Correction of the underlying defect permits appropriate elimination of the excess water.

SIADH is a condition of excess water, with limited ability of the kidney to excrete water. The mainstay of its therapy is fluid restriction. Furosemide is effective in the patient with SIADH and severe hyponatremia. Even in a patient with SIADH, furosemide causes an increase in water and sodium excretion. The loss of sodium is somewhat counterproductive, but this sodium can be replaced with hypertonic saline. Because the patient has a net loss of water and the urinary losses of sodium have been replaced, there is an increase in the sodium concentration, but no significant increase in blood pressure. Vasopressin antagonists (conivaptan, lixivaptan, tolvaptan), which block the action of ADH and cause a water diuresis, are effective at correcting euvolemic hyponatremia, but overly rapid correction is a potential complication.

Treatment of chronic SIADH is challenging. Fluid restriction in children is difficult for nutritional and behavioral reasons. Other

options are long-term furosemide therapy with sodium supplementation, an oral vasopressin antagonist (tolvaptan), or oral urea.

Bibliography is available at Expert Consult.

55.4 Potassium

Larry A. Greenbaum

POTASSIUM METABOLISM

Body Content and Physiologic Function

The intracellular concentration of potassium, approximately 150 mEq/L, is much higher than the plasma concentration (see Fig. 55-3). The majority of body potassium is contained in muscle. As muscle mass increases, there is an increase in body potassium. There is thus an increase in body potassium during puberty, and it is more significant in males. The majority of extracellular potassium is in bone; <1% of total body potassium is in plasma.

Because most potassium is intracellular, the plasma concentration does not always reflect the total body potassium content. A variety of conditions alter the distribution of potassium between the intracellular and extracellular compartments. The Na^+,K^+-ATPase maintains the high intracellular potassium concentration by pumping sodium out of the cell and potassium into the cell. This activity balances the normal leak of potassium out of cells via potassium channels that is driven by the favorable chemical gradient. Insulin increases potassium movement into cells by activating the Na^+,K^+-ATPase. Hyperkalemia stimulates insulin secretion, which helps mitigate the hyperkalemia. Acid–base status affects potassium distribution, probably via potassium channels and the Na^+,K^+-ATPase. A decrease in pH drives potassium extracellularly; an increase in pH has the opposite effect. β-Adrenergic agonists stimulate the Na^+,K^+-ATPase, increasing cellular uptake of potassium. This increase is protective, in that hyperkalemia stimulates adrenal release of catecholamines. α-Adrenergic agonists and exercise cause a net movement of potassium out of the intracellular space. An increase in plasma osmolality, as with mannitol infusion, leads to water movement out of the cells, and potassium follows as a result of solvent drag. The serum potassium concentration increases by approximately 0.6 mEq/L with each 10-mOsm rise in plasma osmolality.

The high intracellular concentration of potassium, the principal intracellular cation, is maintained via the Na^+,K^+-ATPase. The resulting chemical gradient is used to produce the resting membrane potential of cells. Potassium is necessary for the electrical responsiveness of nerve and muscle cells and for the contractility of cardiac, skeletal, and smooth muscle. The changes in membrane polarization that occur during muscle contraction or nerve conduction make these cells susceptible to changes in serum potassium levels. The ratio of intracellular to extracellular potassium determines the threshold for a cell to generate an action potential and the rate of cellular repolarization. The intracellular potassium concentration affects cellular enzymes. Potassium is necessary for maintaining cell volume because of its important contribution to intracellular osmolality.

Intake

Potassium is plentiful in food. Dietary consumption varies considerably, even though 1-2 mEq/kg is the recommended intake. The intestines normally absorb approximately 90% of ingested potassium. Most absorption occurs in the small intestine, whereas the colon exchanges body potassium for luminal sodium. Regulation of intestinal losses normally has a minimal role in maintaining potassium homeostasis, although renal failure, aldosterone, and glucocorticoids increase colonic secretion of potassium. The increase in intestinal losses in the setting of renal failure and hyperkalemia, which stimulates aldosterone production, is clinically significant, helping to protect against hyperkalemia.

Excretion

There is some loss of potassium in sweat, but it is normally minimal. The colon has the ability to eliminate some potassium. In addition, after an acute potassium load, much of the potassium, >40%, moves intracellularly, through the actions of epinephrine and insulin, which are produced in response to hyperkalemia. This process provides transient protection from hyperkalemia, but most ingested potassium is eventually excreted in the urine. The kidneys principally regulate long-term potassium balance, and they alter excretion in response to a variety of signals. Potassium is freely filtered at the glomerulus, but 90% is resorbed before the distal tubule and collecting duct, the principal sites of potassium regulation. The distal tubule and the collecting duct have the ability to absorb and secrete potassium. It is the amount of tubular secretion that regulates the amount of potassium that appears in the urine. The plasma potassium concentration directly influences secretion in the distal nephron. As the potassium concentration increases, secretion increases.

The principal hormone regulating potassium secretion is aldosterone, which is released by the adrenal cortex in response to increased plasma potassium. Its main site of action is the cortical collecting duct, where aldosterone stimulates sodium movement from the tubule into the cells. This movement creates a negative charge in the tubular lumen, facilitating potassium excretion. In addition, the increased intracellular sodium stimulates the basolateral Na^+,K^+-ATPase, causing more potassium to move into the cells lining the cortical collecting duct. Glucocorticoids, ADH, a high urinary flow rate, and high sodium delivery to the distal nephron also increase urinary potassium excretion. Potassium excretion is decreased by insulin, catecholamines, and urinary ammonia. Whereas ADH increases potassium secretion, it also causes water resorption, decreasing urinary flow. The net effect is that ADH has little overall impact on potassium balance. Alkalosis causes potassium to move into cells, including the cells lining the collecting duct. This movement increases potassium secretion, and because acidosis has the opposite effect, it decreases potassium secretion.

The kidney can dramatically vary potassium excretion in response to changes in intake. Normally, approximately 10-15% of the filtered load is excreted. In an adult, excretion of potassium can vary from 5-1,000 mEq/day.

HYPERKALEMIA

Hyperkalemia—because of the potential for lethal arrhythmias—is one of the most alarming electrolyte abnormalities.

Etiology and Pathophysiology

Three basic mechanisms cause hyperkalemia (Table 55-4). In the individual patient, the etiology is sometimes multifactorial.

Spurious hyperkalemia or pseudohyperkalemia is very common in children because of the difficulties in obtaining blood specimens. This laboratory result is usually caused by hemolysis during a heelstick or phlebotomy, but it can be the result of prolonged tourniquet application or fist clenching, either of which causes local potassium release from muscle.

The serum potassium level is normally 0.4 mEq/L higher than the plasma value, secondary to potassium release from cells during clot formation. This phenomenon is exaggerated with thrombocytosis because of potassium release from platelets. For every 100,000/m^3 increase in the platelet count, the serum potassium level rises by approximately 0.15 mEq/L. This phenomenon also occurs with the marked white blood cell count elevations sometimes seen with leukemia. Elevated white blood cell counts, typically >200,000/m^3, can cause a dramatic elevation in the serum potassium concentration. Analysis of a plasma sample usually provides an accurate result. It is important to analyze the sample promptly to avoid potassium release from cells, which occurs if the sample is stored in the cold, or cellular uptake of potassium and spurious hypokalemia, which occurs with storage of the sample at room temperature. Occasionally, heparin causes lysis of leukemic cells and a false elevation of the plasma sample; a blood gas syringe has less heparin and may provide a more accurate reading than a standard tube. There are rare genetic disorders causing leakage of potassium from red cells that may causes familial pseudohyperkalemia.

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Table 55-4 Causes of Hyperkalemia

SPURIOUS LABORATORY VALUE
Hemolysis
Tissue ischemia during blood drawing
Thrombocytosis
Leukocytosis
Familial pseudohyperkalemia (OMIM 609153/611184/612126)
INCREASED INTAKE
Intravenous or oral
Blood transfusions
TRANSCELLULAR SHIFTS
Acidosis
Rhabdomyolysis
Tumor lysis syndrome
Tissue necrosis
Hemolysis/hematomas/gastrointestinal bleeding
Succinylcholine
Digitalis intoxication
Fluoride intoxication
β-Adrenergic blockers
Exercise
Hyperosmolality
Insulin deficiency
Malignant hyperthermia (OMIM 145600/601887)
Hyperkalemic periodic paralysis (OMIM 170500)
DECREASED EXCRETION
Renal failure
Primary adrenal disease:
Acquired Addison disease
21-Hydroxylase deficiency (OMIM 201910)
3β-Hydroxysteroid dehydrogenase deficiency (OMIM 201810)
Lipoid congenital adrenal hyperplasia (OMIM 201710)
Adrenal hypoplasia congenita (OMIM 300200)
Aldosterone synthase deficiency (OMIM 203400/610600)
Adrenoleukodystrophy (OMIM 300100)
Hyporeninemic hypoaldosteronism:
Urinary tract obstruction
Sickle cell disease (OMIM 603903)
Kidney transplant
Lupus nephritis
Renal tubular disease:
Pseudohypoaldosteronism type I (OMIM 264350/177735)
Pseudohypoaldosteronism type II (OMIM 145260)
Bartter syndrome, type 2 (OMIM 241200)
Urinary tract obstruction
Kidney transplant
Medications:
Angiotensin-converting enzyme inhibitors
Angiotensin II blockers
Potassium-sparing diuretics
Calcineurin inhibitors
Nonsteroidal antiinflammatory drugs
Trimethoprim
Heparin
Drospirenone (in some oral contraceptives)

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Because of the kidney's ability to excrete potassium, it is unusual for excessive intake, by itself, to cause hyperkalemia. This condition can occur in a patient who is receiving large quantities of intravenous or oral potassium for excessive losses that are no longer present. Frequent or rapid blood transfusions can acutely increase the potassium level because of the potassium content of blood, which is variably elevated. Increased intake may precipitate hyperkalemia if there is an underlying defect in potassium excretion.

The intracellular space has a very high potassium concentration, so a shift of potassium from the intracellular space to the extracellular space can have a significant effect on the plasma potassium level. This shift occurs with metabolic acidosis, but the effect is minimal with an organic acid (lactic acidosis, ketoacidosis). A respiratory acidosis has less impact than a metabolic acidosis. Cell destruction, as seen with rhabdomyolysis, tumor lysis syndrome, tissue necrosis, or hemolysis, releases potassium into the extracellular milieu. The potassium released from red blood cells in internal bleeding, such as hematomas, is resorbed and enters the extracellular space.

Normal doses of succinylcholine or β-blockers and fluoride or digitalis intoxication all cause a shift of potassium out of the intracellular compartment. Succinylcholine should not be used during anesthesia in patients at risk for hyperkalemia. β-Blockers prevent the normal cellular uptake of potassium mediated by binding of β-agonists to the β_2-adrenergic receptors. Potassium release from muscle cells occurs during exercise, and levels can increase by 1-2 mEq/L with high activity. With an increased plasma osmolality, water moves from the intracellular space and potassium follows. This process occurs with hyperglycemia, although in nondiabetic patients, the resultant increase in insulin causes potassium to move intracellularly. In diabetic ketoacidosis, the absence of insulin causes potassium to leave the intracellular space, and the problem is compounded by the hyperosmolality. The effect of hyperosmolality causes a transcellular shift of potassium into the extracellular space after mannitol or hypertonic saline infusions. **Malignant hyperthermia,** which is triggered by some inhaled anesthetics, causes muscle release of potassium (see Chapter 611.2). **Hyperkalemic periodic paralysis** is an autosomal dominant disorder caused by a mutated sodium channel. It results in episodic cellular release of potassium and attacks of paralysis (see Chapter 611.1).

The kidneys excrete most of the daily potassium intake, so a decrease in kidney function can cause hyperkalemia. Newborn infants in general, and especially premature infants, have decreased kidney function at birth and thus are at increased risk for hyperkalemia despite an absence of intrinsic renal disease. Neonates also have decreased expression of potassium channels, further limiting potassium excretion.

A wide range of primary **adrenal disorders,** both hereditary and acquired, can cause decreased production of aldosterone, with secondary hyperkalemia (see Chapters 575 and 576). Patients with these disorders typically have metabolic acidosis and salt wasting with hyponatremia. Children with more subtle adrenal insufficiency may have electrolyte problems only during acute illnesses. The most common form of **congenital adrenal hyperplasia,** 21-hydroxylase deficiency, typically manifests in male infants as hyperkalemia, metabolic acidosis, hyponatremia, and volume depletion. Females with this disorder usually are diagnosed as newborns because of their ambiguous genitalia; treatment prevents the development of electrolyte problems.

Renin, via angiotensin II, stimulates aldosterone production. A deficiency in renin, a result of kidney damage, can lead to decreased aldosterone production. Hyporeninemia occurs in many kidney diseases, with some of the more common pediatric causes listed in Table 55-4. These patients typically have hyperkalemia and a metabolic acidosis, without hyponatremia. Some of these patients have impaired renal function, partially accounting for the hyperkalemia, but the impairment in potassium excretion is more extreme than expected for the degree of renal insufficiency.

A variety of **renal tubular disorders** impair renal excretion of potassium. Children with **pseudohypoaldosteronism type 1** have hyperkalemia, metabolic acidosis, and salt wasting leading to hyponatremia and volume depletion; aldosterone values are elevated. In the autosomal recessive variant, there is a defect in the renal sodium channel that is normally activated by aldosterone. Patients with this variant have severe symptoms, beginning in infancy. Patients with the autosomal dominant form have a defect in the aldosterone receptor, and the disease is milder, often remitting in adulthood. **Pseudohypoaldosteronism type 2 (familial hyperkalemic hypertension),** also called **Gordon syndrome,** is an autosomal dominant disorder characterized by hypertension caused by salt retention and impaired excretion of potassium and acid, leading to hyperkalemia and metabolic acidosis. Activating mutations in either WNK1 or WNK4, both serine-threonine kinases located in the distal nephron, cause Gordon syndrome. In the **Bartter syndrome** caused by

mutations in the potassium channel ROMK (type 2 Bartter syndrome), there can be transient hyperkalemia in neonates, but hypokalemia subsequently develops (see Chapter 531).

Acquired renal tubular dysfunction, with an impaired ability to excrete potassium, occurs in a number of conditions. These disorders, all characterized by tubulointerstitial disease, are often associated with impaired acid secretion and a secondary metabolic acidosis. In some affected children, the metabolic acidosis is the dominant feature, although a high potassium intake may unmask the defect in potassium handling. The tubular dysfunction can cause renal salt wasting, potentially leading to hyponatremia. Because of the tubulointerstitial damage, these conditions may also cause hyperkalemia as a result of hyporeninemic hypoaldosteronism.

The risk of hyperkalemia resulting from medications is greatest in patients with underlying renal insufficiency. The predominant mechanism of medication-induced hyperkalemia is impaired renal excretion, although angiotensin-converting enzyme inhibitors may worsen hyperkalemia in anuric patients, probably by inhibiting gastrointestinal potassium loss, which is normally upregulated in renal insufficiency. The hyperkalemia caused by trimethoprim generally occurs only at the very high doses used to treat *Pneumocystis jiroveci* pneumonia in patients with AIDS. Potassium-sparing diuretics may easily cause hyperkalemia, especially because they are often used in patients who are receiving oral potassium supplements. Oral contraceptives containing drospirenone, which blocks the action of aldosterone, may cause hyperkalemia and should not be used in patients with decreased renal function.

Clinical Manifestations

The most important effects of hyperkalemia are a result of the role of potassium in membrane polarization. The cardiac conduction system is usually the dominant concern. Changes in the electrocardiogram (ECG) begin with peaking of the T waves. This is followed, as the potassium level increases, by ST-segment depression, an increased PR interval, flattening of the P wave, and widening of the QRS complex. This process can eventually progress to ventricular fibrillation. Asystole may also occur. Some patients have paresthesias, fasciculations, weakness, and even an ascending paralysis, but cardiac toxicity usually precedes these clinical symptoms, emphasizing the danger of assuming that an absence of symptoms implies an absence of danger. Chronic hyperkalemia is generally better tolerated than acute hyperkalemia.

DIAGNOSIS

The etiology of hyperkalemia is often readily apparent. Spurious hyperkalemia is very common in children, so obtaining a second potassium measurement is often appropriate. If there is a significant elevation of the white blood cell or platelet count, the second measurement should be performed on a plasma sample that is evaluated promptly. The history should initially focus on potassium intake, risk factors for transcellular shifts of potassium, medications that cause hyperkalemia, and the presence of signs of renal insufficiency, such as oliguria and edema. Initial **laboratory evaluation** should include creatinine, BUN, and assessment of the acid–base status. Many etiologies of hyperkalemia cause a metabolic acidosis; a metabolic acidosis worsens hyperkalemia through the transcellular shift of potassium out of cells. Renal insufficiency is a common cause of the combination of metabolic acidosis and hyperkalemia. This association is also seen in diseases associated with aldosterone insufficiency or aldosterone resistance. Children with absence of or ineffective aldosterone often have hyponatremia and volume depletion because of salt wasting. Genetic diseases, such as congenital adrenal hyperplasia and pseudohypoaldosteronism, usually manifest in infancy and should be strongly considered in the infant with hyperkalemia and metabolic acidosis, especially if hyponatremia is present. It is important to consider the various etiologies of a transcellular shift of potassium. In some of these disorders, the potassium level continues to increase, despite the elimination of all potassium intake, especially when there is concurrent renal insufficiency. This increase is potentially seen in tumor lysis syndrome, hemolysis, rhabdomyolysis, and other causes of cell death. All of these entities can cause concomitant hyperphosphatemia and hyperuricemia. Rhabdomyolysis produces an elevated creatinine phosphokinase (CPK) value and hypocalcemia, whereas children with hemolysis have hemoglobinuria and a decreasing hematocrit. For the child with diabetes, an elevated blood glucose value suggests a transcellular shift of potassium.

Treatment

The plasma potassium level, the ECG, and the risk of the problem worsening determine the aggressiveness of the therapeutic approach. High serum potassium levels and the presence of ECG changes require vigorous treatment. An additional source of concern is the patient in whom plasma potassium levels are rising despite minimal intake. This situation can happen if there is cellular release of potassium (tumor lysis syndrome), especially in the setting of diminished excretion (renal failure).

The first action in a child with a concerning elevation of plasma potassium is to stop all sources of additional potassium (oral, intravenous). Washed red blood cells can be used for patients who require blood transfusions. If the potassium level is >6.5 mEq/L, an ECG should be obtained to help assess the urgency of the situation. Peak T waves are the first sign of hyperkalemia followed by a prolonged PR interval and, when most severe, a prolonged QRS complex. Life-threatening ventricular arrhythmias may also develop. The treatment of hyperkalemia has 2 basic goals: (a) to stabilize the heart to prevent life-threatening arrhythmias and (b) to remove potassium from the body. The treatments that acutely prevent arrhythmias all have the advantage of working quickly (within minutes) but do not remove potassium from the body. *Calcium stabilizes the cell membrane of heart cells, preventing arrhythmias.* It is given intravenously over a few minutes, and its action is almost immediate. Calcium should be given over 30 min in a patient who is receiving digitalis, because otherwise the calcium may cause arrhythmias. Bicarbonate causes potassium to move intracellularly, lowering the plasma potassium level. It is most efficacious in a patient with a metabolic acidosis. Insulin causes potassium to move intracellularly but must be given with glucose to avoid hypoglycemia. The combination of insulin and glucose works within 30 min. Nebulized albuterol, by stimulation of β_1-receptors, leads to rapid intracellular movement of potassium. This has the advantage of not requiring an intravenous route of administration, allowing it to be given concurrently with the other measures.

It is critical to begin measures that remove potassium from the body. In patients who are not anuric, a loop diuretic increases renal excretion of potassium. A high dose may be required in a patient with significant renal insufficiency. Sodium polystyrene sulfonate (Kayexalate) is an exchange resin that is given either rectally or orally. Sodium in the resin is exchanged for body potassium, and the potassium-containing resin is then excreted from the body. Some patients require dialysis for acute potassium removal. Dialysis is often necessary if the patient has either severe renal failure or an especially high rate of endogenous potassium release, as is sometimes present with tumor lysis syndrome or rhabdomyolysis. Hemodialysis rapidly lowers plasma potassium levels. Peritoneal dialysis is not nearly as quick or reliable, but it is usually adequate as long as the acute problem can be managed with medications and the endogenous release of potassium is not high.

Long-term management of hyperkalemia includes reducing intake via dietary changes and eliminating or reducing medications that cause hyperkalemia (see Chapter 535). Some patients require medications to increase potassium excretion, such as sodium polystyrene sulfonate and loop or thiazide diuretics. Some infants with chronic renal failure may need to start dialysis to allow adequate caloric intake without hyperkalemia. It is unusual for an older child to require dialysis principally to control chronic hyperkalemia. The disorders that are caused by a deficiency in aldosterone respond to replacement therapy with fludrocortisone.

HYPOKALEMIA

Hypokalemia is common in children, with most cases related to gastroenteritis.

Etiology and Pathophysiology

There are 4 basic mechanisms of hypokalemia (Table 55-5). Spurious hypokalemia occurs in patients with leukemia and very elevated white blood cell counts if plasma for analysis is left at room temperature, permitting the white blood cells to take up potassium from the plasma. With a transcellular shift, there is no change in total body potassium, although there may be concomitant potassium depletion resulting from other factors. Decreased intake, extrarenal losses, and renal losses are all associated with total body potassium depletion.

Because the intracellular potassium concentration is much higher than the plasma level, a significant amount of potassium can move into cells without markedly changing the intracellular potassium concentration. Alkalemia is one of the more common causes of a transcellular shift. The effect is much greater with a metabolic alkalosis than with a respiratory alkalosis. The impact of exogenous insulin on potassium movement into the cells is substantial in patients with diabetic ketoacidosis. Endogenous insulin may be the cause when a patient is given a bolus of glucose. Both endogenous (epinephrine in stress) and exogenous (albuterol) β-adrenergic agonists stimulate cellular uptake of potassium. Theophylline overdose, barium intoxication, administration of cesium chloride (a homeopathic cancer remedy), and toluene intoxication from paint or glue sniffing can cause a transcellular shift hypokalemia, often with severe clinical manifestations. Children with **hypokalemic periodic paralysis,** a rare autosomal dominant disorder, have acute cellular uptake of potassium (see Chapter 611). **Thyrotoxic periodic paralysis,** which is more common in Asians, is an unusual initial manifestation of hyperthyroidism. Affected patients have dramatic hypokalemia as a result of a transcellular shift of potassium. Hypokalemia can occur during refeeding syndrome (see Chapter 338.8).

Inadequate potassium intake occurs in **anorexia nervosa;** accompanying bulimia and laxative or diuretic abuse exacerbates the potassium deficiency. Sweat losses of potassium can be significant during vigorous exercise in a hot climate. Associated volume depletion and hyperaldosteronism increase renal losses of potassium (discussed later). Diarrheal fluid has a high concentration of potassium, and hypokalemia as a result of diarrhea is usually associated with a metabolic acidosis resulting from stool losses of bicarbonate. In contrast, a normal acid–base balance or a mild metabolic alkalosis is seen with laxative abuse. Intake of sodium polystyrene sulfonate or ingestion of clay because of pica increases stool losses of potassium.

Urinary potassium wasting may be accompanied by a metabolic acidosis (proximal or distal RTA). In diabetic ketoacidosis, although it is often associated with normal plasma potassium caused by transcellular shifts, there is significant total body potassium depletion from urinary losses because of the osmotic diuresis, and the potassium level may decrease dramatically with insulin therapy (see Chapter 589). Both the polyuric phase of acute tubular necrosis and postobstructive diuresis cause transient, highly variable potassium wasting and may be associated with a metabolic acidosis. Tubular damage, which occurs either directly from medications or secondary to interstitial nephritis, is often accompanied by other tubular losses of nutrients, including magnesium, sodium, and water. Such tubular damage may cause a secondary RTA with a metabolic acidosis. Isolated magnesium deficiency causes renal potassium wasting. Penicillin is an anion that is excreted in the urine, resulting in increased potassium excretion because the penicillin anion must be accompanied by a cation. Hypokalemia from penicillin therapy occurs only with the sodium salt of penicillin, not with the potassium salt.

Urinary potassium wasting is often accompanied by a metabolic alkalosis. This condition is usually associated with increased aldosterone, which increases urinary potassium and acid losses, contributing to the hypokalemia and the metabolic alkalosis. Other mechanisms often contribute to both the potassium losses and the metabolic alkalosis. With emesis or nasogastric suction, there is gastric loss of potassium, but this is fairly minimal, given the low potassium content of gastric fluid (≈10 mEq/L). More important is the gastric loss of hydrochloric acid (HCl), leading to a metabolic alkalosis and a state of volume depletion. The kidney compensates for the metabolic alkalosis by excreting bicarbonate in the urine, but there is obligate loss of potassium and sodium with the bicarbonate. The volume depletion raises aldosterone levels, further increasing urinary potassium losses and preventing correction of the metabolic alkalosis and hypokalemia until the volume depletion is corrected. Urinary chloride is low as a response to the volume depletion. Because the volume depletion is secondary to chloride loss, this is a state of chloride deficiency. There

Table 55-5 Causes of Hypokalemia
SPURIOUS
High white blood cell count
TRANSCELLULAR SHIFTS
Alkalemia
Insulin
α-Adrenergic agonists
Drugs/toxins (theophylline, barium, toluene, cesium chloride, hydroxychloroquine)
Hypokalemic periodic paralysis (OMIM 170400)
Thyrotoxic period paralysis
Refeeding syndrome
DECREASED INTAKE
Anorexia nervosa
EXTRARENAL LOSSES
Diarrhea
Laxative abuse
Sweating
Sodium polystyrene sulfonate (Kayexalate) or clay ingestion
RENAL LOSSES
With metabolic acidosis
Distal rental tubular acidosis (OMIM 179800/602722/267300)
Proximal renal tubular acidosis (OMIM 604278)*
Ureterosigmoidostomy
Diabetic ketoacidosis
Without specific acid–base disturbance
Tubular toxins: amphotericin, cisplatin, aminoglycosides
Interstitial nephritis
Diuretic phase of acute tubular necrosis
Postobstructive diuresis
Hypomagnesemia
High urine anions (e.g., penicillin or penicillin derivatives)
With metabolic alkalosis
Low urine chloride
Emesis or nasogastric suction
Chloride-losing diarrhea (OMIM 214700)
Cystic fibrosis (OMIM 219700)
Low-chloride formula
Posthypercapnia
Previous loop or thiazide diuretic use
High urine chloride and normal blood pressure
Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 607364/602522/241200/601678)
Autosomal dominant hypoparathyroidism (OMIM 146200)
EAST syndrome (OMIM 612780)
Loop and thiazide diuretics
High urine chloride and high blood pressure
Adrenal adenoma or hyperplasia
Glucocorticoid-remediable aldosteronism (OMIM 103900)
Renovascular disease
Renin-secreting tumor
17β-Hydroxylase deficiency (OMIM 202110)
11β-Hydroxylase deficiency (OMIM 202010)
Cushing syndrome
11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
Licorice ingestion
Liddle syndrome (OMIM 177200)

*Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.

EAST, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

were cases of chloride deficiency resulting from infant formula deficient in chloride, which caused a metabolic alkalosis with hypokalemia and low urine chloride levels. Current infant formula is not deficient in chloride. A similar mechanism occurs in cystic fibrosis because of chloride loss in sweat. In **congenital chloride-losing diarrhea**, an autosomal recessive disorder, there is high stool loss of chloride, leading to metabolic alkalosis, an unusual sequela of diarrhea. Because of stool potassium losses, chloride deficiency, and metabolic alkalosis, patients with this disorder have hypokalemia. During respiratory acidosis, there is renal compensation, with retention of bicarbonate and excretion of chloride. After the respiratory acidosis is corrected, the patients have chloride deficiency and posthypercapnic alkalosis with secondary hypokalemia. Patients with chloride deficiency, metabolic alkalosis, and hypokalemia have a urinary chloride level of <10 mEq/L. Loop and thiazide diuretics lead to hypokalemia, metabolic alkalosis, and chloride deficiency. During treatment, these patients have high urine chloride levels resulting from the effect of the diuretic. However, after the diuretics are discontinued, there is residual chloride deficiency, the urinary chloride level is appropriately low, and neither the hypokalemia nor the alkalosis resolves until the chloride deficiency is corrected.

The combination of metabolic alkalosis, hypokalemia, a high urine chloride level, and normal blood pressure is characteristic of **Bartter syndrome, Gitelman syndrome,** and **current diuretic use.** Patients with any of these conditions have high urinary losses of potassium and chloride, despite a state of relative volume depletion with secondary hyperaldosteronism. Bartter and Gitelman syndromes are autosomal recessive disorders caused by defects in tubular transporters (see Chapter 531). Bartter syndrome is usually associated with hypercalciuria, and often with nephrocalcinosis, whereas children with Gitelman syndrome have low urinary calcium losses but hypomagnesemia as a consequence of urinary magnesium losses. Some patients with Bartter syndrome have hypomagnesemia.

Some patients with hypoparathyroidism and hypocalcemia caused by an activating mutation of the calcium-sensing receptor (autosomal dominant hypoparathyroidism) have hypokalemia, hypomagnesemia, and metabolic alkalosis. The reason is that activation of the calcium-sensing receptor in the loop of Henle impairs tubular resorption of sodium and chloride, causing volume depletion and secondary hyperaldosteronism. **EAST syndrome,** an autosomal recessive disorder caused by mutations in the gene for a potassium channel present in the kidney, inner ear, and brain, consists of epilepsy, ataxia, sensorineural hearing loss, and tubulopathy (hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria).

In the presence of high aldosterone levels, there is urinary loss of potassium, hypokalemia, metabolic alkalosis, and an elevated urinary chloride level. Also, renal retention of sodium leads to hypertension. Primary hyperaldosteronism caused by adenoma or hyperplasia is much less common in children than in adults (see Chapter 578). Glucocorticoid-remediable aldosteronism, an autosomal dominant disorder that leads to high levels of aldosterone, is often diagnosed in childhood, although hypokalemia is not always present.

Increased aldosterone levels may be secondary to increased renin production. Renal artery stenosis leads to hypertension from increased renin and secondary hyperaldosteronism. The increased aldosterone can cause hypokalemia and metabolic alkalosis, although most patients have normal electrolyte levels. Renin-producing tumors, which are extremely rare, can cause hypokalemia.

A variety of disorders cause hypertension and hypokalemia without increased aldosterone levels. Some are a result of increased levels of mineralocorticoids other than aldosterone. Such increases occur in 2 forms of **congenital adrenal hyperplasia** (see Chapter 576). In 11β-hydroxylase deficiency, which is associated with virilization, the value of 11-deoxycorticosterone is elevated, causing variable hypertension and hypokalemia. A similar mechanism, increased 11-deoxycorticosterone, occurs in 17α-hydroxylase deficiency, but patients with this disorder are more uniformly hypertensive and hypokalemic, and they have a defect in sex hormone production. Cushing syndrome, frequently associated with hypertension, less commonly causes metabolic alkalosis and hypokalemia. This is secondary to the mineralocorticoid activity of cortisol. In 11β-hydroxysteroid dehydrogenase deficiency, an autosomal recessive disorder, the enzymatic defect prevents the conversion of cortisol to cortisone in the kidney. Because cortisol binds to and activates the aldosterone receptor, children with this deficiency have all the features of excessive mineralocorticoids, including hypertension, hypokalemia, and metabolic alkalosis. Patients with this disorder, which is also called apparent mineralocorticoid excess, respond to spironolactone therapy, which blocks the mineralocorticoid receptor. An acquired form of 11β-hydroxysteroid dehydrogenase deficiency occurs from the ingestion of substances that inhibit this enzyme. A classic example is glycyrrhizic acid, which is found in natural licorice. **Liddle syndrome** is an autosomal dominant disorder that results from an activating mutation of the distal nephron sodium channel that is normally upregulated by aldosterone. Patients have the characteristics of hyperaldosteronism—hypertension, hypokalemia, and alkalosis—but low serum aldosterone levels. These patients respond to the potassium-sparing diuretics (triamterene and amiloride) that inhibit this sodium channel (see Chapter 531.3).

Clinical Manifestations

The heart and skeletal muscle are especially vulnerable to hypokalemia. ECG changes include a flattened T wave, a depressed ST segment, and the appearance of a U wave, which is located between the T wave (if still visible) and the P wave. Ventricular fibrillation and torsades de pointes may occur, although usually only in the context of underlying heart disease. Hypokalemia makes the heart especially susceptible to digitalis-induced arrhythmias, such as supraventricular tachycardia, ventricular tachycardia, and heart block (see Chapter 435).

The clinical consequences of hypokalemia in skeletal muscle include muscle weakness and cramps. Paralysis is a possible complication, generally only at potassium levels <2.5 mEq/L. It usually starts in the legs and moves to the arms. Respiratory paralysis may require mechanical ventilation. Some patients have rhabdomyolysis; the risk increases with exercise. Hypokalemia slows gastrointestinal motility. This effect manifests as constipation; with potassium levels <2.5 mEq/L, an ileus may occur. Hypokalemia impairs bladder function, potentially leading to urinary retention.

Hypokalemia causes **polyuria** and **polydipsia** by impairing urinary concentrating ability, which produces nephrogenic diabetes insipidus. Hypokalemia stimulates renal ammonia production, an effect that is clinically significant if hepatic failure is present, because the liver cannot metabolize the ammonia. Consequently, hypokalemia may worsen hepatic encephalopathy. Chronic hypokalemia may cause kidney damage, including interstitial nephritis and renal cysts.

Diagnosis

Most causes of hypokalemia are readily apparent from the history. It is important to review the child's diet, gastrointestinal losses, and medications. Both emesis and diuretic use can be surreptitious. The presence of hypertension suggests excess mineralocorticoids. Concomitant electrolyte abnormalities are useful clues. The combination of hypokalemia and metabolic acidosis is characteristic of diarrhea and of distal and proximal RTA. A concurrent metabolic alkalosis is characteristic of emesis or nasogastric losses, aldosterone excess, use of diuretics, and Bartter and Gitelman syndromes. Figure 55-5 shows an approach to persistent hypokalemia.

If a clear etiology is not apparent, the measurement of urinary potassium distinguishes between renal and extrarenal losses. The kidneys should conserve potassium in the presence of extrarenal losses. Urinary potassium losses can be assessed with a 24 hr urine collection, a spot potassium : creatinine ratio, a fractional excretion of potassium, or calculation of the transtubular potassium gradient (TTKG), which is the most widely used approach in children:

$$\text{TTKG} = [K]_{urine}/[K]_{plasma} \times (\text{plasma osmolality/urine osmolality})$$

where $[K]_{urine}$ = urine potassium concentration and $[K]_{plasma}$ = plasma potassium concentration.

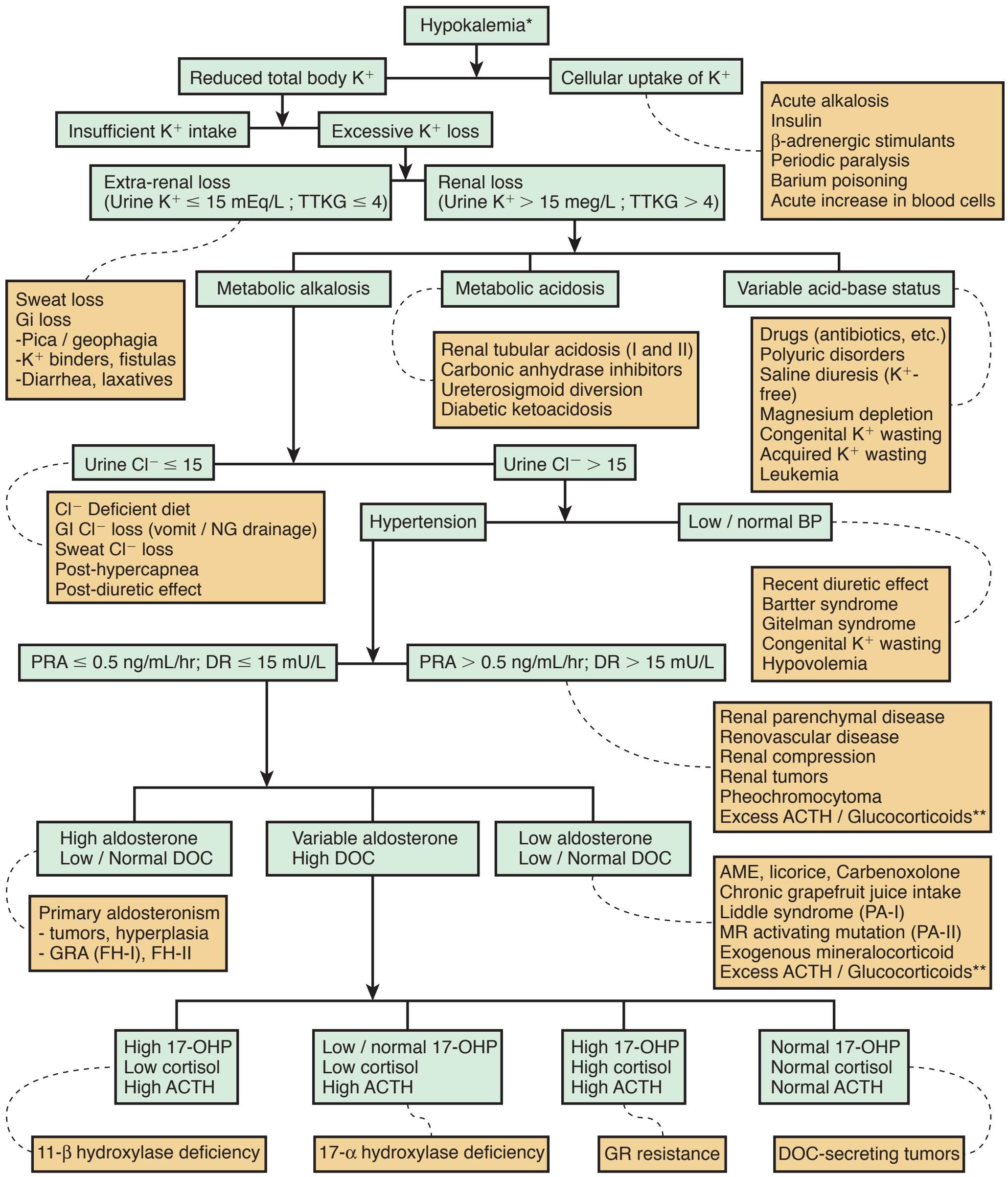

Figure 55-5 Diagnostic algorithm to evaluate persistent hypokalemia. *Spurious hypokalemia must be excluded. **Hypokalemia is uncommon in uncomplicated edematous disorders and in conditions associated with excessive glucocorticosteroids. Conditions associated with high circulating levels of glucocorticosteroids often have normal renin activity. 17-OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; AME, apparent mineralocorticoid excess; BP, blood pressure; Cl^-, chloride; DOC, 11-deoxycorticosterone; DR, direct renin assay; GI, gastrointestinal; FH-II, familial hyperaldosteronism type II; GR, glucocorticoid receptor; GRA (FH-I), glucocorticoid remediable aldosteronism (familial hyperaldosteronism type I); K^+, potassium; MR, mineralocorticoid receptor; PA-I, pseudoaldosteronism type I; PA-II, pseudoaldosteronism type II; PRA, plasma renin activity; TTKG, transtubular potassium gradient. *(From Shoemaker LR, Eaton BV, Buchino JJ: A three-year-old with persistent hypokalemia, J Pediatr 151:696–699, 2007.)*

The urine osmolality must be greater than the serum osmolality for the result of this calculation to be valid. A TTKG >4 in the presence of hypokalemia suggests excessive urinary losses of potassium. The urinary potassium excretion value can be misleading if the stimulus for renal loss, such as a diuretic, is no longer present.

Treatment

Factors that influence the treatment of hypokalemia include the potassium level, clinical symptoms, renal function, the presence of transcellular shifts of potassium, ongoing losses, and the patient's ability to tolerate oral potassium. Severe, symptomatic hypokalemia requires aggressive treatment. Supplementation is more cautious if renal function is decreased because of the kidney's limited ability to excrete excessive potassium. The plasma potassium level does not always provide an accurate estimation of the total body potassium deficit because there may be shifts of potassium from the intracellular space to the plasma. Clinically, such shifts occur most commonly with metabolic acidosis and the insulin deficiency of diabetic ketoacidosis; the plasma potassium measurement underestimates the degree of total body potassium depletion. When these problems are corrected, potassium moves into the intracellular space, so more potassium supplementation is required to correct the hypokalemia. Likewise, the presence of a transcellular shift of potassium into the cells indicates that the total body potassium depletion is less severe. In an isolated transcellular shift, as occurs in hypokalemic periodic paralysis, potassium supplementation should be used cautiously,

given the risk of hyperkalemia when the transcellular shift resolves. This caution is especially required in thyrotoxic periodic paralysis, which responds dramatically to propranolol, with correction of weakness and hypokalemia. Patients who have ongoing losses of potassium need correction of the deficit and replacement of the ongoing losses.

Because of the risk of hyperkalemia, intravenous potassium should be used very cautiously. Oral potassium is safer, albeit not as rapid in urgent situations. Liquid preparations are bitter tasting; microencapsulated or wax matrix formulations are less irritating than tablets to the gastric mucosa (oral dose: 2-4 mEq/kg/day with a maximum of 120-240 mEq/day in divided doses). The dose of intravenous potassium is 0.5-1.0 mEq/kg, usually given over 1 hr. The adult maximum dose is 40 mEq. Conservative dosing is generally preferred. Potassium chloride is the usual choice for supplementation, although the presence of concurrent electrolyte abnormalities may dictate other options. Patients with acidosis and hypokalemia can receive potassium acetate or potassium citrate. If hypophosphatemia is present, then some of the potassium deficit can be replaced with potassium phosphate. It is sometimes possible to decrease ongoing losses of potassium. For patients with excessive urinary losses, potassium-sparing diuretics are effective, but they need to be used cautiously in patients with renal insufficiency. If hypokalemia, metabolic alkalosis, and volume depletion are present (with gastric losses), then restoration of intravascular volume with adequate sodium chloride will decrease urinary potassium losses. Correction of concurrent hypomagnesemia is important because hypomagnesemia may cause hypokalemia. Disease-specific therapy is effective in many of the genetic tubular disorders.

Bibliography is available at Expert Consult.

55.5 Magnesium

Larry A. Greenbaum

MAGNESIUM METABOLISM

Body Content and Physiologic Function

Magnesium is the fourth most common cation in the body and the third most common intracellular cation (see Fig. 55-3). Between 50% and 60% of body magnesium is in bone, where it serves as a reservoir because 30% is exchangeable, allowing movement to the extracellular space. Most intracellular magnesium is bound to proteins; only approximately 25% is exchangeable. Because cells with higher metabolic rates have higher magnesium concentrations, most intracellular magnesium is present in muscle and liver.

The normal plasma magnesium concentration is 1.5-2.3 mg/dL (1.2-1.9 mEq/L; 0.62-0.94 mmol/L), with some variation among clinical laboratories. Infants have slightly higher plasma magnesium concentrations than older children and adults. Only 1% of body magnesium is extracellular (60% ionized; 15% complexed; 25% protein bound). In the United States, serum magnesium is reported as mg/dL (Table 55-6).

Table 55-6 Conversion Factors for Calcium, Magnesium, and Phosphorus

	UNIT	CONVERSION FACTOR	UNIT
Calcium	mg/dL	0.25	mmol/L
	mEq/L	0.5	mmol/L
	mg/dL	0.5	mEq/L
Magnesium	mg/dL	0.411	mmol/L
	mEq/L	0.5	mmol/L
	mg/dL	0.822	mEq/L
Phosphorus	mg/dL	0.32	mmol/L

Values in the left-column unit are converted into the right-column unit via multiplying by the conversion factor (e.g., calcium of 10 mg/dL × 0.25 = 2.5 mmol/L). Division of the right-column unit by the conversion factor converts to the units of the left-column unit.

Magnesium is a necessary cofactor for hundreds of enzymes. It is important for membrane stabilization and nerve conduction. Adenosine triphosphate (ATP) and guanosine triphosphate need associated magnesium when they are used by adenosine triphosphatases, cyclases, and kinases.

Intake

Between 30% and 50% of dietary magnesium is absorbed. Good dietary sources include green vegetables, cereals, nuts, meats, and hard water, although many foods contain magnesium. Human milk contains approximately 35 mg/L of magnesium; formula contains 40-70 mg/L. The small intestine is the major site of magnesium absorption, but the regulation of magnesium absorption is poorly understood. There is passive absorption, which permits high absorption in the presence of excessive intake. It probably occurs via a paracellular mechanism. Absorption is diminished in the presence of substances that complex with magnesium (free fatty acids, fiber, phytate, phosphate, oxalate); increased intestinal motility and calcium also decrease magnesium absorption. Vitamin D and parathyroid hormone (PTH) may enhance absorption, although this effect is limited. Intestinal absorption does increase when intake is decreased, possibly via a saturable active transport system. If there is no oral intake of magnesium, obligatory secretory losses prevent the complete elimination of intestinal losses.

Excretion

Renal excretion is the principal regulator of magnesium balance. There is no defined hormonal regulatory system, although PTH may increase tubular resorption. Approximately 15% of resorption occurs in the proximal tubule, and 70% in the thick ascending limb (TAL) of the loop of Henle. Proximal resorption may be higher in neonates. High serum magnesium levels inhibit resorption in the TAL, suggesting that active transport is involved. Approximately 5-10% of filtered magnesium is resorbed in the distal tubule. Hypomagnesemia increases absorption in the TAL and the distal tubule.

HYPOMAGNESEMIA

Hypomagnesemia is relatively common in hospitalized patients, although most cases are asymptomatic. Detection requires a high index of suspicion because magnesium is not measured in most basic metabolic panels.

Etiology and Pathophysiology

Gastrointestinal and renal losses are the major causes of hypomagnesemia (Table 55-7). Diarrheal fluid contains up to 200 mg/L of magnesium; gastric contents have only approximately 15 mg/L, but high losses can cause depletion. Steatorrhea causes magnesium loss as a result of the formation of magnesium-lipid salts; restriction of dietary fat can decrease losses.

Hypomagnesemia with secondary hypocalcemia, a rare autosomal recessive disorder, is caused by decreased intestinal absorption of magnesium and renal magnesium wasting. Patients with this disorder have mutations in a gene (*TRPM6*) that is expressed in intestine and kidney. TRPM6 codes for a transient receptor potential cation channel. The patients have seizures, tetany, tremor, or restlessness at 2-8 wk of life as a result of severe hypomagnesemia (0.2-0.8 mg/dL) and secondary hypocalcemia.

Renal losses may occur because of medications that are direct tubular toxins. Amphotericin frequently causes significant magnesium wasting and is typically associated with other tubular defects (especially potassium wasting). Cisplatin produces dramatic renal magnesium losses. Diuretics affect tubular handling of magnesium. Loop diuretics cause a mild increase in magnesium excretion, and thiazide diuretics have even less effect. Chronic use of proton pump inhibitors may cause hypomagnesemia. Potassium-sparing diuretics reduce magnesium losses. Osmotic agents, such as mannitol, glucose in diabetes

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Table 55-7 Causes of Hypomagnesemia

GASTROINTESTINAL DISORDERS
Diarrhea
Nasogastric suction or emesis
Inflammatory bowel disease
Celiac disease
Cystic fibrosis
Intestinal lymphangiectasia
Small bowel resection or bypass
Pancreatitis
Protein-calorie malnutrition
Hypomagnesemia with secondary hypocalcemia (OMIM 602014)*
RENAL DISORDERS
Medications
Amphotericin
Cisplatin
Cyclosporin
Loop diuretics
Mannitol
Pentamidine
Proton pump inhibitors
Aminoglycosides
Thiazide diuretics
Epidermal growth factor receptor inhibitors
Diabetes
Acute tubular necrosis (recovery phase)
Postobstructive nephropathy
Chronic kidney diseases
Interstitial nephritis
Glomerulonephritis
Post–renal transplantation
Hypercalcemia
Intravenous fluids
Primary aldosteronism
Genetic diseases
Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 607364/601678)
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (OMIM 248250)
Familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement (OMIM 248190)
Autosomal recessive renal magnesium wasting with normocalciuria (OMIM 611718)
Renal cysts and diabetes syndrome (OMIM 137920)
Autosomal dominant hypomagnesemia (OMIM 160120/613882/154020)
EAST syndrome (OMIM 612780)
Autosomal dominant hypoparathyroidism (OMIM 146200)
Mitochondrial disorders (OMIM 500005)
MISCELLANEOUS CAUSES
Poor intake
Hungry bone syndrome
Insulin administration
Pancreatitis
Intrauterine growth retardation
Infants of diabetic mothers
Exchange transfusion

*This disorder is also associated with renal magnesium wasting.
EAST, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

mellitus, and urea in the recovery phase of acute tubular necrosis, increase urinary magnesium losses. Epidermal growth factor receptor inhibitors cause renal magnesium wasting. Intravenous fluid, by expanding the intravascular volume, decreases renal resorption of sodium and water, thereby impairing magnesium resorption. Hypercalcemia inhibits magnesium resorption in the loop of Henle, although this inhibition does not occur in hypercalcemia caused by familial hypercalcemic hypocalciuria or lithium.

A number of rare genetic diseases cause renal magnesium loss. **Gitelman and Bartter syndromes,** both autosomal recessive disorders, are the most common entities (see Chapter 531). Gitelman syndrome, which is caused by a defect in the thiazide-sensitive Na^+-Cl^- cotransporter in the distal tubule, is usually associated with hypomagnesemia. Hypomagnesemia occurs in a minority of patients with Bartter syndrome, which can be caused by mutations in multiple genes that are necessary for sodium and chloride reabsorption in the loop of Henle. In both disorders, there is hypokalemic metabolic alkalosis. Typically, hypomagnesemia is not severe and is asymptomatic, although tetany as a result of hypomagnesemia occasionally occurs.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (Michelis-Castrillo syndrome), an autosomal recessive disorder, is caused by mutations in the gene for claudin 16 (paracellin-1), which is located in the tight junctions of the TAL of the loop of Henle. Patients with the disease have severe renal wasting of magnesium and calcium with secondary hypomagnesemia and nephrocalcinosis; serum calcium levels are normal. Chronic renal failure frequently occurs during childhood. Other features include kidney stones, urinary tract infections, hematuria, increased PTH levels, tetany, seizures, incomplete distal RTA, hyperuricemia, polyuria, and polydipsia. Patients with **familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement** have mutations in the gene for claudin 19.

Autosomal recessive renal magnesium wasting with normocalciuria is caused by mutations in the epidermal growth factor gene. Clinical manifestations include seizures, mild to moderate psychomotor retardation, and brisk tendon reflexes.

Autosomal dominant renal magnesium wasting is caused by mutations in a number of different genes. A dominant-negative mutation in the gene encoding the Na^+,K^+-adenosine triphosphatase γ subunit is associated with hypomagnesemia, increased urinary magnesium losses, hypocalciuria, and normocalcemia. Patients may present with seizures; most are asymptomatic, despite serum magnesium levels of 0.8-1.5 mg/dL. Mutations in *CNNM2*, which encodes a protein that mediates magnesium-sensitive sodium currents, cause isolated hypomagnesemia. A mutation in *KCNA1*, a gene that encodes a potassium channel, also causes an autosomal dominant form of hypomagnesemia; symptoms may be severe.

Renal cysts and diabetes syndrome, which is caused by mutations in the gene for hepatocyte nuclear factor-1β, is associated with hypomagnesemia, despite the frequent presence of renal insufficiency. The hypomagnesemia is usually mild but may cause symptomatic hypocalcemia. **EAST syndrome** is caused by mutations in a potassium channel, and patients with this autosomal recessive disorder have hypokalemia, metabolic alkalosis, and hypomagnesemia. **Autosomal dominant hypoparathyroidism** is caused by an activating mutation in the calcium-sensing receptor, which also senses magnesium levels in the kidney (see Chapter 571). The mutated receptor inappropriately perceives that magnesium and calcium levels are elevated, leading to urinary wasting of both cations. Hypomagnesemia, if present, is usually mild. A mutation in a mitochondrially encoded transfer RNA is associated with hypomagnesemia, hypertension, and hypercholesterolemia. Hypomagnesemia is occasionally present in children with other mitochondrial disorders.

Poor intake is an unusual cause of hypomagnesemia, although it can be seen in children who are hospitalized and receive only intravenous fluids without magnesium. In **hungry bone syndrome,** which most frequently occurs after parathyroidectomy in patients with hyperparathyroidism, magnesium moves into bone as a result of accelerated bone formation. These patients usually have hypocalcemia and hypophosphatemia via the same mechanism. A similar mechanism can occur during the **refeeding phase of protein-calorie malnutrition** in children, with high magnesium use during cell growth depleting the patient's limited reserves. Insulin therapy stimulates uptake of magnesium by cells, and in diabetic ketoacidosis, in which total body magnesium is low because of osmotic losses, hypomagnesemia frequently occurs. In **pancreatitis,** there is saponification of magnesium and calcium in necrotic fat, causing both hypomagnesemia and hypocalcemia.

Transient hypomagnesemia in newborns, which is sometimes idiopathic, is more commonly seen in infants of diabetic mothers, presumably as a result of maternal depletion from osmotic losses. Other maternal diseases that cause magnesium losses predispose infants to hypomagnesemia. Hypomagnesemia is more common in infants with intrauterine growth restriction. Hypomagnesemia may develop in newborn infants who require exchange transfusions because of magnesium removal by the citrate in banked blood.

Clinical Manifestations

Hypomagnesemia causes secondary hypocalcemia by impairing the release of PTH by the parathyroid gland and through blunting of the tissue response to PTH. Thus, hypomagnesemia is part of the differential diagnosis of hypocalcemia (see Chapter 571). It usually occurs only at magnesium levels <0.7 mg/dL. The dominant manifestations of hypomagnesemia are caused by hypocalcemia: tetany, presence of Chvostek and Trousseau signs, and seizures. However, with severe hypomagnesemia, these same signs and symptoms may be present despite normocalcemia. Persistent hypocalcemia caused by hypomagnesemia is a rare cause of rickets.

Many causes of hypomagnesemia also result in hypokalemia. Hypomagnesemia may produce renal potassium wasting and hypokalemia that corrects only with magnesium therapy. ECG changes with hypomagnesemia include flattening of the T wave and lengthening of the ST segment. Arrhythmias may occur, almost always in the setting of underlying heart disease.

Diagnosis

The etiology of hypomagnesemia is often readily apparent from the clinical situation. The child should be assessed for gastrointestinal disease, adequate intake, and kidney disease, with close attention paid to medications that may cause renal magnesium wasting. When the diagnosis is uncertain, an evaluation of urinary magnesium losses distinguishes between renal and nonrenal causes. The fractional excretion of magnesium (FE_{Mg}) is calculated via the following formula:

$$FE_{Mg} = (U_{Mg} \times P_{Cr})/([0.7 \times P_{Mg}] \times U_{Cr}) \times 100$$

where U_{Mg} is urinary magnesium concentration, P_{Cr} is plasma creatinine concentration, P_{Mg} is plasma magnesium concentration, and U_{Cr} is urinary magnesium concentration. The plasma magnesium concentration is multiplied by 0.7 because approximately 30% is bound to albumin and not filtered at the glomerulus.

The FE_{Mg} does not vary with age, but it does change according to the serum magnesium concentration. The FE_{Mg} ranges from 1-8% in children with normal magnesium levels. In the presence of hypomagnesemia as a result of extrarenal causes, it should be low because of renal conservation, typically <2%. The FE_{Mg} is inappropriately elevated in the setting of renal magnesium wasting; values are usually >4% and frequently are >10%. The measurement should not be made during a magnesium infusion, because the acute increase in serum magnesium increases urinary magnesium. Other approaches for evaluating urinary magnesium losses include calculation of 24 hr urinary magnesium losses and of the ratio of urine magnesium : urine creatinine, both of which vary with age.

The genetic causes of renal magnesium loss are distinguished on the basis of the measurement of other serum and urinary electrolytes. Children with Gitelman and Bartter syndromes have hypokalemia and metabolic alkalosis.

Treatment

Severe hypomagnesemia is treated with parenteral magnesium. Magnesium sulfate is given at a dose of 25-50 mg/kg (0.05-0.1 mL/kg of a 50% solution; 2.5-5.0 mg/kg of elemental magnesium). It is administered as a slow intravenous infusion, although it may be given intramuscularly in neonates. The rate of intravenous infusion should be slowed if a patient experiences diaphoresis, flushing, or a warm sensation. The dose is often repeated every 6 hr (every 8-12 hr in neonates), for a total of 2-3 doses, before the plasma magnesium concentration is rechecked. Lower doses are used in children with renal insufficiency.

Long-term therapy is usually given orally. Preparations include magnesium gluconate (5.4 mg elemental magnesium/100 mg), magnesium oxide (60 mg elemental magnesium/100 mg), and magnesium sulfate (10 mg elemental magnesium/100 mg). There are sustained-released preparations, such as Slow-Mag (60 mg elemental magnesium/tablet) and Mag-Tab SR (84 mg elemental magnesium/tablet). Oral magnesium dosing should be divided to decrease cathartic side effects. Alternatives to oral magnesium are intramuscular injections and nighttime nasogastric infusion, both designed to minimize diarrhea. Magnesium supplementation must be used cautiously in the context of renal insufficiency.

HYPERMAGNESEMIA

Clinically significant hypermagnesemia is almost always secondary to excessive intake. It is unusual, except in neonates born to mothers who are receiving intravenous magnesium for preeclampsia or eclampsia (see Chapter 106).

Etiology and Pathophysiology

There is no feedback mechanism to prevent magnesium absorption from the gastrointestinal tract. Magnesium is present in high amounts in certain laxatives, enemas, cathartics used to treat drug overdoses, and antacids. It is also usually present in total parenteral nutrition, and neonates may receive high amounts transplacentally if maternal levels are elevated. Usually the kidneys excrete excessive magnesium, but this ability is diminished in patients with chronic renal failure. In addition, neonates and young infants are vulnerable to excessive magnesium ingestion because of their reduced GFR. Most pediatric cases not related to maternal hypermagnesemia occur in infants as a result of excessive use of antacids or laxatives. Mild hypermagnesemia may occur in chronic renal failure, familial hypocalciuric hypercalcemia, diabetic ketoacidosis, lithium ingestion, milk-alkali syndrome, and tumor lysis syndrome. The hypermagnesemia in diabetic ketoacidosis occurs despite significant intracellular magnesium depletion as a result of urinary losses; hypomagnesemia often occurs after insulin treatment.

Clinical Manifestations

Symptoms usually do not appear until the plasma magnesium level is >4.5 mg/dL. Hypermagnesemia inhibits acetylcholine release at the neuromuscular junction, producing hypotonia, hyporeflexia, and weakness; paralysis occurs at high concentrations. The neuromuscular effects may be exacerbated by aminoglycoside antibiotics. Direct CNS depression causes lethargy and sleepiness; infants have a poor suck. Elevated magnesium values are associated with hypotension because of vascular dilation, which also causes flushing. Hypotension can be profound at higher concentrations from a direct effect on cardiac function. ECG changes include prolonged PR, QRS, and QT intervals. Severe hypermagnesemia (>15 mg/dL) causes complete heart block and cardiac arrest. Other manifestations of hypermagnesemia include nausea, vomiting, and hypocalcemia.

Diagnosis

Except for the case of the neonate with transplacental exposure, a high index of suspicion and a good history are necessary to make the diagnosis of hypermagnesemia. Prevention is essential; magnesium-containing compounds should be used judiciously in children with renal insufficiency.

Treatment

Most patients with normal renal function rapidly clear excess magnesium. Intravenous hydration and loop diuretics can accelerate this process. In severe cases, especially in patients with underlying renal insufficiency, dialysis may be necessary. Hemodialysis works faster than peritoneal dialysis. Exchange transfusion is another option in newborn infants. Supportive care includes monitoring of cardiorespiratory status, provision of fluids, monitoring of electrolyte levels, and

the use of pressors for hypotension. In acute emergencies, especially in the context of severe neurologic or cardiac manifestations, 100 mg/kg of intravenous calcium gluconate is transiently effective.

Bibliography is available at Expert Consult.

55.6 Phosphorus

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Approximately 65% of plasma phosphorus is in phospholipids, but these compounds are insoluble in acid and are not measured by clinical laboratories. It is the phosphorus content of plasma phosphate that is determined. The result is reported as either phosphate or phosphorus, although even when the term phosphate is used, it is actually the phosphorus concentration that is measured and reported. The result is that the terms phosphate and phosphorus are often used interchangeably. The term *phosphorus* is preferred when one is referring to the plasma concentration. Conversion from the units used in the United States (mg/dL) to mmol/L is straightforward (see Table 55-6).

PHOSPHORUS METABOLISM

Body Content and Physiologic Function

Most phosphorus is in bone or is intracellular, with <1% in plasma. At a physiologic pH, there are monovalent and divalent forms of phosphate because the pK of these forms is 6.8. Approximately 80% is divalent, and the remainder is monovalent at a pH of 7.4. A small percentage of plasma phosphate, approximately 15%, is protein bound. The remainder can be filtered by the glomerulus, with most existing as free phosphate and a small percentage complexed with calcium, magnesium, or sodium. Phosphate is the most plentiful intracellular anion, although the majority is part of a larger compound (ATP).

More than that of any other electrolyte, the phosphorus concentration varies with age (Table 55-8). The teleologic explanation for the high concentration during childhood is the need for phosphorus to facilitate growth. There is diurnal variation in the plasma phosphorus concentration, with the peak during sleep.

Phosphorus, as a component of ATP and other trinucleotides, is critical for cellular energy metabolism. It is necessary for cell signaling and nucleic acid synthesis, and it is a component of cell membranes and other structures. Along with calcium, phosphorus is necessary for skeletal mineralization. There is a significant need for a net positive phosphorus balance during growth, with the growing skeleton especially vulnerable to deficiency.

Intake

Phosphorus is readily available in food. Milk and milk products are the best sources of phosphorus; high concentrations are present in meat and fish. Vegetables have more phosphorus than fruits and grains. Gastrointestinal absorption of phosphorus is fairly proportional to intake, with approximately 65% of intake being absorbed, including a small amount that is secreted. Absorption, almost exclusively in the small intestine, occurs via a paracellular diffusive process and a vitamin D–regulated transcellular pathway. However, the impact of the change in phosphorus absorption caused by vitamin D is relatively small compared with the effect of variations in phosphorus intake.

Table 55-8 Serum Phosphorus Levels During Childhood

AGE	PHOSPHORUS LEVEL (mg/dL)
0-5 day	4.8-8.2
1-3 yr	3.8-6.5
4-11 yr	3.7-5.6
12-15 yr	2.9-5.4
16-19 yr	2.7-4.7

Excretion

Despite the wide variation in phosphorus absorption dictated by oral intake, excretion matches intake, except for the needs for growth. The kidney regulates phosphorus balance, which is determined by intrarenal mechanisms and hormonal actions on the nephron.

Approximately 90% of plasma phosphate is filtered at the glomerulus, although there is some variation based on plasma phosphate and calcium concentrations. There is no significant secretion of phosphate along the nephron. Resorption of phosphate occurs mostly in the proximal tubule, although a small amount can be resorbed in the distal tubule. Normally, approximately 85% of the filtered load is resorbed. A sodium-phosphate cotransporter mediates the uptake of phosphate into the cells of the proximal tubule.

The dietary phosphorus determines the amount of phosphate resorbed by the nephron. There are both acute and chronic changes in phosphate resorption that are based on intake. Many of these changes appear to be mediated by intrarenal mechanisms that are independent of regulatory hormones. Fibroblast growth factor-23 (FGF-23) inhibits renal resorption of phosphorus in the proximal tubule, and its level increases in the setting of hyperphosphatemia. FGF-23 also inhibits synthesis of calcitriol in the kidney by decreasing 1α-hydroxylase activity.

PTH, which is secreted in response to a low plasma calcium level, decreases resorption of phosphate, increasing the urinary phosphate level. This process appears to have a minimal effect during normal physiologic variation in PTH levels. However, it does have an impact in the setting of pathologic changes in PTH synthesis.

Low plasma phosphorus stimulates the 1α-hydroxylase in the kidney that converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (calcitriol). Calcitriol increases intestinal absorption of phosphorus and is necessary for maximal renal resorption of phosphate. The effect of a change in calcitriol on urinary phosphate is significant only when the level of calcitriol was initially low, arguing against a role for calcitriol in nonpathologic conditions.

HYPOPHOSPHATEMIA

Because of the wide variation in normal plasma phosphorus levels, the definition of hypophosphatemia is age-dependent (see Table 55-8). The normal range reported by a laboratory may be based on adult normal values and, therefore, may be misleading in children. A serum phosphorus level of 3 mg/dL, a normal value in an adult, indicates clinically significant hypophosphatemia in an infant.

The plasma phosphorus level does not always reflect the total body stores because only 1% of phosphorus is extracellular. Thus, a child may have significant phosphorus deficiency despite a normal plasma phosphorus concentration. This situation is especially common in conditions in which there is a shift of phosphorus from the intracellular space.

Etiology and Pathophysiology

A variety of mechanisms cause hypophosphatemia (Table 55-9). A transcellular shift of phosphorus into cells occurs with processes that stimulate cellular usage of phosphorus (glycolysis). Usually, this shift causes only a minor, transient decrease in plasma phosphorus, but if intracellular phosphorus deficiency is present, the plasma phosphorus level can decrease significantly, producing symptoms of acute hypophosphatemia. Glucose infusion stimulates insulin release, leading to entry of glucose and phosphorus into the cells. Phosphorus is then used during glycolysis and other metabolic processes. A similar phenomenon can occur during the treatment of diabetic ketoacidosis, and patients with this disorder are typically phosphorus-depleted owing to urinary phosphorus losses. **Refeeding** of patients with protein-calorie malnutrition causes anabolism, which leads to significant cellular demand for phosphorus. The increased phosphorus uptake for incorporation into newly synthesized compounds containing phosphorus leads to hypophosphatemia, which can be severe and symptomatic. Refeeding hypophosphatemia occurs frequently during treatment of severe anorexia nervosa. It can occur during treatment of children with malnutrition from any cause, such as cystic fibrosis, Crohn

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Table 55-9 Causes of Hypophosphatemia

TRANSCELLULAR SHIFTS
Glucose infusion
Insulin
Refeeding
Total parenteral nutrition
Respiratory alkalosis
Tumor growth
Bone marrow transplantation
Hungry bone syndrome
DECREASED INTAKE
Nutritional
Premature infants
Low phosphorus formula
Antacids and other phosphate binders
RENAL LOSSES
Hyperparathyroidism
Parathyroid hormone–related peptide
X-linked hypophosphatemic rickets (OMIM 307800)
Overproduction of fibroblast growth factor-23
Tumor-induced rickets
McCune-Albright syndrome
Epidermal nevus syndrome
Neurofibromatosis
Autosomal dominant hypophosphatemic rickets (OMIM 193100)
Autosomal recessive hypophosphatemic rickets (OMIM 241520)
Fanconi syndrome
Dent disease (OMIM 300009/300555)
Hypophosphatemic rickets with hypercalciuria (OMIM 241530)
Hypophosphatemic nephrolithiasis/osteoporosis type 1 (OMIM 612286)
Hypophosphatemic nephrolithiasis/osteoporosis type 2 (OMIM 612287)
Volume expansion and intravenous fluids
Metabolic acidosis
Diuretics
Glycosuria
Glucocorticoids
Kidney transplantation
MULTIFACTORIAL
Vitamin D deficiency
Vitamin D–dependent rickets type 1 (OMIM 264700)
Vitamin D–dependent rickets type 2 (OMIM 277440)
Alcoholism
Sepsis
Dialysis

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

disease, burns, neglect, chronic infection, or famine. Hypophosphatemia usually occurs within the 1st 5 days of refeeding and is prevented by a gradual increase in nutrition with appropriate phosphorus supplementation. Total parenteral nutrition without adequate phosphorus can cause hypophosphatemia.

Phosphorus moves into the intracellular space during a respiratory alkalosis and during recovery from a respiratory acidosis. An acute decrease in the carbon dioxide concentration, by raising the intracellular pH, stimulates glycolysis, leading to intracellular use of phosphorus and hypophosphatemia. Because a metabolic alkalosis has less effect on the intracellular pH (carbon dioxide diffuses across cell membranes much faster than bicarbonate), there is minimal transcellular phosphorus movement with a metabolic alkalosis.

Tumors that grow rapidly, such as those associated with leukemia and lymphoma, may use large amounts of phosphorus, leading to hypophosphatemia. A similar phenomenon may occur during the hematopoietic reconstitution that follows bone marrow transplantation. In **hungry bone syndrome,** there is avid bone uptake of phosphorus, along with calcium and magnesium, which can produce plasma deficiency of all 3 ions. Hungry bone syndrome is most common after parathyroidectomy for hyperparathyroidism because the stimulus for bone dissolution is acutely removed, but bone synthesis continues.

Nutritional phosphorus deficiency is unusual because most foods contain phosphorus. However, infants are especially susceptible because of their high demand for phosphorus to support growth, especially of the skeleton. Very-low-birthweight infants have particularly rapid skeletal growth, and phosphorus deficiency and rickets may develop if they are fed human milk or formula for term infants. There is also a relative deficiency of calcium. The provision of additional calcium and phosphorus, using breast milk fortifier or special premature infant formula, prevents this complication. Phosphorus deficiency, sometimes with concomitant calcium and vitamin D deficiencies, occurs in infants who are not given enough milk or who receive a milk substitute that is nutritionally inadequate.

Antacids containing aluminum hydroxide, such as Maalox and Mylanta, bind dietary phosphorus and secreted phosphorus, preventing absorption. This process can cause phosphorus deficiency and rickets in growing children. A similar mechanism causes hypophosphatemia in patients who are overtreated for hyperphosphatemia with phosphorus binders. In children with kidney failure, the addition of dialysis to phosphorus binders increases the risk of iatrogenic hypophosphatemia in these normally hyperphosphatemic patients. This complication, which is more common in infants, can worsen renal osteodystrophy.

Excessive renal losses of phosphorus occur in a variety of inherited and acquired disorders. Because PTH inhibits the resorption of phosphorus in the proximal tubule, **hyperparathyroidism** causes hypophosphatemia (see Chapter 573). The dominant clinical manifestation, however, is hypercalcemia, and the hypophosphatemia is usually asymptomatic. The phosphorus level in hyperparathyroidism is not extremely low, and there is no continued loss of phosphorus because a new steady state is achieved at the lower plasma phosphorus level. Renal excretion, therefore, does not exceed intake over the long-term. There are occasional malignancies that produce PTH-related peptide, which has the same actions as PTH and causes hypophosphatemia and hypercalcemia.

A variety of diseases cause renal phosphate wasting, hypophosphatemia, and rickets resulting from excess FGF-23 (see Chapter 51). These disorders include **X-linked hypophosphatemic rickets, tumor-induced osteomalacia**, **autosomal dominant hypophosphatemic rickets,** and **autosomal recessive hypophosphatemic rickets**. Heterozygous mutations in a phosphate transporter or a regulator of proximal tubule phosphate transport cause hypophosphatemia, osteoporosis, and nephrolithiasis (**hypophosphatemic nephrolithiasis/osteoporosis type 1 or 2**).

Fanconi syndrome is a generalized defect in the proximal tubule leading to urinary wasting of bicarbonate, phosphorus, amino acids, uric acid, and glucose (see Chapter 529). The clinical sequelae are a result of the metabolic acidosis and hypophosphatemia. In children, an underlying genetic disease, most commonly cystinosis, often causes Fanconi syndrome, but it can be secondary to a variety of toxins and acquired diseases. Some patients have incomplete Fanconi syndrome, and phosphorus wasting may be one of the manifestations.

Dent disease, an X-linked disorder, can cause renal phosphorus wasting and hypophosphatemia, although the latter is not present in most cases. Other possible manifestations of Dent disease include tubular proteinuria, hypercalciuria, nephrolithiasis, rickets, and chronic renal failure. Dent disease may be secondary to mutations in a gene that encodes a chloride channel or the OCRL1 gene, which may also cause Lowe syndrome (see Chapter 529.1). **Hypophosphatemic rickets with hypercalciuria** is a rare disorder, principally described in kindreds from the Middle East. Mutations in a sodium-phosphate cotransporter cause hypophosphatemia in this disorder, and complications may include nephrolithiasis and osteoporosis; the disorder is autosomal dominant.

Metabolic acidosis inhibits resorption of phosphorus in the proximal tubule. In addition, metabolic acidosis causes a transcellular shift of phosphorus out of cells because of intracellular catabolism. This

released phosphorus is subsequently lost in the urine, leading to significant phosphorus depletion, even though the plasma phosphorus level may be normal. This classically occurs in diabetic ketoacidosis in which renal phosphorus loss is further increased by the osmotic diuresis. With correction of the metabolic acidosis and the administration of insulin, both of which cause a transcellular movement of phosphorus into the cells, there is a marked decrease in the plasma phosphorus level.

Volume expansion from any cause, such as hyperaldosteronism or SIADH, inhibits resorption of phosphorus in the proximal tubule. This effect also occurs with high rates of intravenous fluids. Thiazide and loop diuretics can increase renal phosphorus excretion, but the increase is seldom clinically significant. Glycosuria and glucocorticoids inhibit renal conservation of phosphorus. Hypophosphatemia is common after kidney transplantation as a result of urinary phosphorus losses. Possible explanations include preexisting secondary hyperparathyroidism from chronic renal failure, glucocorticoid therapy, and upregulation of FGF-23 before transplantation. The hypophosphatemia usually resolves in a few months.

Both acquired and genetic causes of **vitamin D deficiency** are associated with hypophosphatemia (see Chapter 51). The pathogenesis is multifactorial. Vitamin D deficiency, by impairing intestinal calcium absorption, causes secondary hyperparathyroidism that leads to increased urinary phosphorus wasting. An absence of vitamin D decreases intestinal absorption of phosphorus and directly decreases renal resorption of phosphorus. The dominant clinical manifestation is rickets, although some patients have muscle weakness that may be related to phosphorus deficiency.

Alcoholism is the most common cause of severe hypophosphatemia in adults. Fortunately, many of the risk factors that predispose adult alcoholics to hypophosphatemia are not usually present in adolescents (malnutrition, antacid abuse, recurrent episodes of diabetic ketoacidosis). Hypophosphatemia often occurs in sepsis, but the mechanism is not clear. Aggressive, protracted hemodialysis, as might be used for the treatment of methanol or ethylene glycol ingestion, can cause hypophosphatemia.

Clinical Manifestations

There are acute and chronic manifestations of hypophosphatemia. Rickets occurs in children with long-term phosphorus deficiency. The clinical features of rickets are described in Chapter 51.

Severe hypophosphatemia, typically at levels <1.0-1.5 mg/dL, may affect every organ in the body because phosphorus has a critical role in maintaining adequate cellular energy. Phosphorus is a component of ATP and is necessary for glycolysis. With inadequate phosphorus, red blood cell 2,3-diphosphoglycerate levels decrease, impairing release of oxygen to the tissues. Severe hypophosphatemia can cause hemolysis and dysfunction of white blood cells. Chronic hypophosphatemia causes proximal muscle weakness and atrophy. In the intensive care unit, phosphorus deficiency may slow weaning from mechanical ventilation or cause acute respiratory failure. **Rhabdomyolysis** is the most common complication of acute hypophosphatemia, usually in the setting of an acute transcellular shift of phosphorus into cells in a child with chronic phosphorus depletion (anorexia nervosa). The rhabdomyolysis is actually somewhat protective, in that there is cellular release of phosphorus. Other manifestations of severe hypophosphatemia include cardiac dysfunction and neurologic symptoms, such as tremor, paresthesia, ataxia, seizures, delirium, and coma.

Diagnosis

The history and basic laboratory evaluation often suggest the etiology of hypophosphatemia. The history should investigate nutrition, medications, and familial disease. Hypophosphatemia and rickets in an otherwise healthy young child suggests a genetic defect in renal phosphorus conservation, Fanconi syndrome, inappropriate use of antacids, poor nutrition, vitamin D deficiency, or a genetic defect in vitamin D metabolism. The patient with Fanconi syndrome usually has metabolic acidosis, glycosuria, aminoaciduria, and a low plasma uric acid level. Measurement of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, calcium, and PTH differentiates among the various vitamin D deficiency disorders and primary renal phosphate wasting (see Chapter 51). Hyperparathyroidism is easily distinguished by the presence of elevated plasma PTH and calcium values.

Treatment

The plasma phosphorus level, the presence of symptoms, the likelihood of chronic depletion, and the presence of ongoing losses dictate the approach to therapy. Mild hypophosphatemia does not require treatment unless the clinical situation suggests that chronic phosphorus depletion is present or that losses are ongoing. Oral phosphorus can cause diarrhea, so the doses should be divided. Intravenous therapy is effective in patients who have severe deficiency or who cannot tolerate oral medications. Intravenous phosphorus is available as either sodium phosphate or potassium phosphate, with the choice usually based on the patient's plasma potassium level. Starting doses are 0.08-0.16 mmol/kg over 6 hr. The oral preparations of phosphorus are available with various ratios of sodium and potassium. This is an important consideration because some patients may not tolerate the potassium load, whereas supplemental potassium may be helpful in some diseases, such as Fanconi syndrome and malnutrition. Oral maintenance dosages are 2-3 mmol/kg/day in divided doses.

Increasing dietary phosphorus is the only intervention needed in infants with inadequate intake. Other patients may also benefit from increased dietary phosphorus, usually from dairy products. Phosphorus-binding antacids should be discontinued in patients with hypophosphatemia. Certain diseases require specific therapy (see Chapter 51).

HYPERPHOSPHATEMIA

Etiology and Pathophysiology

Renal insufficiency is the most common cause of hyperphosphatemia, with the severity proportional to the degree of kidney impairment (see Chapter 535). This occurs because gastrointestinal absorption of the large dietary intake of phosphorus is unregulated, and the kidneys normally excrete this phosphorus. As renal function deteriorates, increased excretion of phosphorus is able to compensate. When kidney function is <30% of normal, hyperphosphatemia usually develops, although the time of its development may vary considerably according to dietary phosphorus absorption. Many of the other causes of hyperphosphatemia are more likely to develop in the setting of renal insufficiency (Table 55-10).

Cellular content of phosphorus is high relative to plasma phosphorus, and cell lysis can release substantial phosphorus. This is the etiology of hyperphosphatemia in **tumor lysis syndrome, rhabdomyolysis,** and **acute hemolysis.** These disorders cause concomitant potassium

Table 55-10	Causes of Hyperphosphatemia
TRANSCELLULAR SHIFTS	
Tumor lysis syndrome	
Rhabdomyolysis	
Acute hemolysis	
Diabetic ketoacidosis and lactic acidosis	
INCREASED INTAKE	
Enemas and laxatives	
Cow's milk in infants	
Treatment of hypophosphatemia	
Vitamin D intoxication	
DECREASED EXCRETION	
Renal failure	
Hypoparathyroidism or pseudohypoparathyroidism (OMIM 146200/603233/103580/241410/203330)	
Acromegaly	
Hyperthyroidism	
Tumoral calcinosis with hyperphosphatemia (OMIM 211900)	

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

release and the risk of hyperkalemia. Additional features of tumor lysis and rhabdomyolysis are hyperuricemia and hypocalcemia, whereas indirect hyperbilirubinemia and elevated lactate dehydrogenase values are often present with hemolysis. An elevated CPK level is suggestive of rhabdomyolysis. During lactic acidosis or diabetic ketoacidosis, usage of phosphorus by cells decreases, and phosphorus shifts into the extracellular space. This problem reverses when the underlying problem is corrected, and especially with diabetic ketoacidosis, patients subsequently become hypophosphatemic as a result of previous renal phosphorus loss.

Excessive intake of phosphorus is especially dangerous in children with renal insufficiency. Neonates are at risk because renal function is normally reduced during the 1st few months of life. In addition, they may erroneously be given doses of phosphorus that are meant for an older child or adult. In infants fed cow's milk, which has higher phosphorus content than breast milk or formula, hyperphosphatemia may develop. **Fleet Enema** has a high amount of phosphorus that can be absorbed, especially in the patient with an ileus. Infants and children with Hirschsprung disease are especially vulnerable. There is often associated hypernatremia owing to sodium absorption and water loss from diarrhea. Sodium phosphorus laxatives may cause hyperphosphatemia if the dose is excessive or if renal insufficiency is present. Hyperphosphatemia occurs in children who receive overly aggressive treatment for hypophosphatemia. Vitamin D intoxication causes excessive gastrointestinal absorption of both calcium and phosphorus, and the suppression of PTH by hypercalcemia decreases renal phosphorus excretion.

The absence of PTH in **hypoparathyroidism** or PTH responsiveness in **pseudohypoparathyroidism** causes hyperphosphatemia because of increased resorption of phosphorus in the proximal tubule of the kidney (see Chapters 571 and 572). The associated hypocalcemia is responsible for the clinical symptoms. The hyperphosphatemia in hyperthyroidism or acromegaly is usually minor. It is secondary to increased resorption of phosphorus in the proximal tubule from the actions of thyroxine or growth hormone. Excessive thyroxine can also cause bone resorption, which may contribute to the hyperphosphatemia and cause hypercalcemia. Patients with **familial tumoral calcinosis,** a rare autosomal recessive disorder, have hyperphosphatemia as a result of decreased renal phosphate excretion and heterotopic calcifications. The disease may be secondary to mutations in the genes for a glycosyltransferase, the phosphatonin FGF-23, or the gene for Klotho, which encodes the coreceptor for FGF-23.

Clinical Manifestations

The principal clinical consequences of hyperphosphatemia are hypocalcemia and systemic calcification. The hypocalcemia is probably due to tissue deposition of calcium-phosphorus salt, inhibition of 1,25-dihydroxyvitamin D production, and decreased bone resorption. Symptomatic hypocalcemia is most likely to occur when the phosphorus level increases rapidly or when diseases predisposing to hypocalcemia are present (chronic renal failure, rhabdomyolysis). Systemic calcification occurs because the solubility of phosphorus and calcium in the plasma is exceeded. This is believed to happen when plasma calcium × plasma phosphorus, both measured in mg/dL, is >70. Clinically, this condition is often apparent in the conjunctiva, where it manifests as a foreign-body feeling, erythema, and injection. More ominous manifestations are hypoxia from pulmonary calcification and renal failure from nephrocalcinosis.

Diagnosis

Plasma creatinine and BUN levels should be assessed in any patient with hyperphosphatemia. The history should focus on intake of phosphorus and the presence of chronic diseases that may cause hyperphosphatemia. Measurement of potassium, uric acid, calcium, lactate dehydrogenase, bilirubin, hemoglobin, and CPK may be indicated if rhabdomyolysis, tumor lysis, or hemolysis is suspected. With mild hyperphosphatemia and significant hypocalcemia, measurement of the serum PTH level distinguishes between hypoparathyroidism and pseudohypoparathyroidism.

Treatment

The treatment of acute hyperphosphatemia depends on its severity and etiology. Mild hyperphosphatemia in a patient with reasonable renal function spontaneously resolves; the resolution can be accelerated by dietary phosphorus restriction. If kidney function is not impaired, then intravenous fluids can enhance renal phosphorus excretion. For more significant hyperphosphatemia or a situation such as tumor lysis or rhabdomyolysis, in which endogenous phosphorus generation is likely to continue, addition of an oral phosphorus binder prevents absorption of dietary phosphorus and can remove phosphorus from the body by binding what is normally secreted and absorbed by the gastrointestinal tract. Phosphorus binders are most effective when given with food. Binders containing aluminum hydroxide are especially efficient, but calcium carbonate is an effective alternative and may be preferred if there is a need to treat concomitant hypocalcemia. Preservation of renal function, for example with high urine flow in rhabdomyolysis or tumor lysis, is an important adjunct because it will permit continued excretion of phosphorus. If the hyperphosphatemia is not responding to conservative management, especially if renal insufficiency is supervening, then dialysis may be necessary to increase phosphorus removal.

Dietary phosphorus restriction is necessary for diseases causing chronic hyperphosphatemia. However, such diets are often difficult to follow, given the abundance of phosphorus in a variety of foods. Dietary restriction is often sufficient in conditions such as hypoparathyroidism and mild renal insufficiency. For more problematic hyperphosphatemia, such as with moderate renal insufficiency and end-stage renal disease, phosphorus binders are usually necessary. They include calcium carbonate, calcium acetate, sevelamer, and lanthanum. Aluminum-containing phosphorus binders are no longer used in chronic renal insufficiency because of the risk of aluminum toxicity. Dialysis directly removes phosphorus from the blood in patients with end-stage renal disease, but it is only an adjunct to dietary restriction and phosphorus binders, in that elimination of phosphorus by dialysis is not efficient enough to keep up with normal dietary intake.

Bibliography is available at Expert Consult.

55.7 Acid–Base Balance

Larry A. Greenbaum

ACID–BASE PHYSIOLOGY

Introduction and Terminology

Chronic, mild derangements in acid–base status may interfere with normal growth and development, whereas acute, severe changes in pH can be fatal. Control of acid–base balance depends on the kidneys, the lungs, and intracellular and extracellular buffers.

A normal pH is 7.35-7.45. There is an inverse relationship between the pH and the hydrogen ion concentration. At a pH of 7.40, the hydrogen ion concentration is 40 nmol/L. A normal serum sodium concentration, 140 mEq/L, is 1 million times higher. Maintaining a normal pH is necessary because hydrogen ions are highly reactive and are especially likely to combine with proteins, altering their function.

An **acid** is a substance that releases ("donates") a hydrogen ion (H^+). A base is a substance that accepts a hydrogen ion. An acid (HA) can dissociate into a hydrogen ion and a conjugate base (A^-), as follows:

$$HA \leftrightarrow H^+ + A^-$$

A strong acid is highly dissociated, so in this reaction, there is little HA. A weak acid is poorly dissociated; not all of the hydrogen ions are released from HA. A^- acts as a base when the reaction moves to the left. These reactions are in equilibrium. When HA is added to the system, there is dissociation of some HA until the concentrations of H^+ and A^- increase enough that a new equilibrium is reached. Addition of hydrogen ions causes a decrease in A^- and an increase in HA. Addition of A^- causes a decrease in hydrogen ions and an increase in HA.

Buffers are substances that attenuate the change in pH that occurs when acids or bases are added to the body. Given the extremely low

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concentration of hydrogen ions in the body at physiologic pH, without buffers a small amount of hydrogen ions could cause a dramatic decline in the pH. Buffers prevent the decrease in pH by binding the added hydrogen ions, as follows:

$$A^- + H^+ \rightarrow HA$$

The increase in hydrogen ion concentration drives this reaction to the right. Similarly, when base is added to the body, buffers prevent the pH from increasing by releasing hydrogen ions, as follows:

$$HA \rightarrow A^- + H^+$$

The best buffers are weak acids and bases. This is because a buffer works best when it is 50% dissociated (half HA and half A^-). The pH at which a buffer is 50% dissociated is its pK (ionization constant of acid). The best physiologic buffers have a pK close to 7.40. The concentration of a buffer and its pK determine the buffer's effectiveness (buffering capacity). When the pH is lower than the pK of a buffer, there is more HA than A^-. When the pH is higher than the pK, there is more A^- than HA.

Physiologic Buffers

The bicarbonate and nonbicarbonate buffers protect the body against major changes in pH. The **bicarbonate buffer system** is routinely monitored clinically. The bicarbonate buffer system is based on the relationship between carbon dioxide (CO_2) and bicarbonate (HCO_3^-):

$$CO_2 + H_2O \leftrightarrow H^+ + HCO_3^-$$

Carbon dioxide acts as an acid in that, after combining with water, it releases a hydrogen ion; bicarbonate acts as its conjugate base in that it accepts a hydrogen ion. The pK of this reaction is 6.1. The Henderson-Hasselbalch equation expresses the relationship among pH, pK, and the concentrations of an acid and its conjugate base. This relationship is valid for any buffer. The Henderson-Hasselbalch equation for bicarbonate and carbon dioxide is as follows:

$$pH = 6.1 + \log[HCO_3^-]/[CO_2]$$

The Henderson-Hasselbalch equation for the bicarbonate buffer system has 3 variables: pH, $[HCO_3^-]$, and $[CO_2]$. Thus, if any 2 of these variables are known, it is possible to calculate the third. When one is using the Henderson-Hasselbalch equation, it is important that carbon dioxide and bicarbonate have the same units. Carbon dioxide is reported clinically as mm Hg and must be multiplied by its solubility constant, 0.03 mmol/L/mm Hg, before the Henderson-Hasselbalch equation can be used. Mathematical manipulation of the Henderson-Hasselbalch equation produces the following relationship:

$$[H^+] = 24 \times P_{CO_2}/(HCO_3^-)$$

At a normal hydrogen ion concentration of 40 nmol (pH 7.40), the partial pressure of carbon dioxide (P_{CO_2}), which is expressed as mm Hg in this equation, is 40 when the bicarbonate concentration is 24 mEq/L. This equation emphasizes that the hydrogen ion concentration, and hence pH, can be determined by the ratio of P_{CO_2} and the bicarbonate concentration.

The bicarbonate buffer system is very effective as a result of the high concentration of bicarbonate in the body (24 mEq/L) and the fact that it is an open system. The remaining body buffers are in a closed system. The bicarbonate buffer system is an open system because the lungs increase carbon dioxide excretion when the blood carbon dioxide concentration increases. When acid is added to the body, the following reaction occurs:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

In a closed system, the CO_2 would increase. The higher CO_2 concentration would lead to an increase in the reverse reaction:

$$CO_2 + H_2O \rightarrow H^+ + HCO_3^-$$

This would increase the concentration of hydrogen ions, limiting the buffering capacity of bicarbonate. However, because the lungs excrete the excess carbon dioxide, the reverse reaction does not increase; this fact enhances the buffering capacity of bicarbonate. The same principle holds with the addition of base, because the lungs decrease carbon dioxide excretion and prevent the level of carbon dioxide from falling. The lack of change in carbon dioxide concentration dramatically increases the buffering capacity of bicarbonate.

The **nonbicarbonate buffers** include proteins, phosphate, and bone. Protein buffers consist of extracellular proteins, mostly albumin and intracellular proteins, including hemoglobin. Proteins are effective buffers, largely because of the presence of the amino acid histidine, which has a side chain that can bind or release hydrogen ions. The pK of histidine varies slightly, depending on its position in the protein molecule, but its average pK is approximately 6.5. This is close enough to a normal pH (7.4) to make histidine an effective buffer. Hemoglobin and albumin have 34 and 16 histidine molecules, respectively.

Phosphate can bind up to 3 hydrogen molecules, so it can exist as PO_4^{3-}, HPO_4^{2-}, $H_2PO_4^{1-}$, or H_3PO_4. However, at a physiologic pH, most phosphate exists as either HPO_4^{2-} or $H_2PO_4^{1-}$. $H_2PO_4^{1-}$ is an acid, and HPO_4^{2-} is its conjugate base:

$$H_2PO_4^{1-} \leftrightarrow H^+ + HPO_4^{2-}$$

The pK of this reaction is 6.8, making phosphate an effective buffer. The concentration of phosphate in the extracellular space is relatively low, limiting the overall buffering capacity of phosphate; it is less important than albumin. However, phosphate is found at a much higher concentration in the urine, where it is an important buffer. In the intracellular space, most phosphate is covalently bound to organic molecules (ATP), but it still serves as an effective buffer.

Bone is an important buffer. Bone is basic—it is composed of compounds such as sodium bicarbonate and calcium carbonate—and thus, dissolution of bone releases base. This release can buffer an acid load, although at the expense of bone density, if it occurs over an extended period. In contrast, bone formation, by consuming base, helps buffer excess base.

Clinically, we measure the extracellular pH, but it is the intracellular pH that affects cell function. Measurement of the intracellular pH is unnecessary because changes in the intracellular pH parallel the changes in the extracellular pH. However, the change in the intracellular pH tends to be less than the change in the extracellular pH because of the greater buffering capacity in the intracellular space.

NORMAL ACID–BASE BALANCE

The lungs and kidneys maintain a normal acid–base balance. Carbon dioxide generated during normal metabolism is a weak acid. The lungs prevent an increase in the P_{CO_2} in the blood by excreting the CO_2 that the body produces. CO_2 production varies according to the body's metabolic needs, increasing with physical activity. The rapid pulmonary response to changes in the CO_2 concentration occurs via central sensing of the P_{CO_2} and a subsequent increase or decrease in ventilation to maintain a normal P_{CO_2} (35-45 mm Hg). An increase in ventilation decreases the P_{CO_2}, and a decrease in ventilation increases the P_{CO_2}.

The kidneys excrete endogenous acid. An adult normally produces approximately 1-2 mEq/kg/24 hr of hydrogen ions. Children normally produce 2-3 mEq/kg/24 hr of hydrogen ions. The 3 principal sources of hydrogen ions are dietary protein metabolism, incomplete metabolism of carbohydrates and fat, and stool losses of bicarbonate. Because metabolism of protein generates hydrogen ions, endogenous acid production varies with protein intake. The complete oxidation of carbohydrates or fats to carbon dioxide and water does not generate hydrogen ions; the lungs remove the carbon dioxide. However, incomplete metabolism of carbohydrates or fats produces hydrogen ions. Incomplete glucose metabolism can produce lactic acid, and incomplete triglyceride metabolism can produce keto acids, such as β-hydroxybutyric acid and acetoacetic acid. There is always some baseline incomplete metabolism that contributes to endogenous acid production. This factor increases in pathologic conditions, such as lactic acidosis and diabetic ketoacidosis. Stool loss of bicarbonate is the third major source of endogenous acid production. The stomach secretes hydrogen ions,

but most of the remainder of the gastrointestinal tract secretes bicarbonate, and the net effect is a loss of bicarbonate from the body. To secrete bicarbonate, the cells of the intestine produce hydrogen ions that are released into the bloodstream. For each bicarbonate molecule lost in the stool, the body gains 1 hydrogen ion. This source of endogenous acid production is normally minimal but may increase dramatically in a patient with diarrhea.

The hydrogen ions formed from endogenous acid production are neutralized by bicarbonate, potentially causing the bicarbonate concentration to decrease. The kidneys regenerate this bicarbonate by secreting hydrogen ions. The lungs cannot regenerate bicarbonate, even though loss of carbon dioxide lowers the hydrogen ion concentration, as shown in the following reaction:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

A decrease in CO_2 concentration causes the reaction to move to the right, which decreases the hydrogen ion concentration, but it also lowers the bicarbonate concentration. During a metabolic acidosis, hyperventilation can lower the CO_2 concentration, decrease the hydrogen ion concentration, and thus increase the pH. The underlying metabolic acidosis is still present. Similarly, the kidneys cannot correct an abnormally high CO_2 concentration, as shown in the following reaction:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

An increase in the bicarbonate concentration also causes the reaction to move to the right, which increases the CO_2 concentration while simultaneously decreasing the hydrogen ion concentration. During a respiratory acidosis, increased renal generation of bicarbonate can decrease the hydrogen ion concentration and increase the pH, but cannot repair the respiratory acidosis. Both the lungs and the kidneys can affect the hydrogen ion concentration and hence the pH. However, only the lungs can regulate the CO_2 concentration, and only the kidneys can regulate the bicarbonate concentration.

Renal Mechanisms

The kidneys regulate the serum bicarbonate concentration by modifying acid excretion in the urine. This requires a 2-step process. First, the renal tubules resorb the bicarbonate that is filtered at the glomerulus. Second, there is tubular secretion of hydrogen ions. The urinary excretion of hydrogen ions generates bicarbonate that neutralizes endogenous acid production. The tubular actions necessary for renal acid excretion occur throughout the nephron (Fig. 55-6).

The resorption of filtered bicarbonate is a necessary first step in renal regulation of the acid–base balance. A normal adult has a GFR of approximately 180 L/24 hr. This fluid enters the Bowman space with a bicarbonate concentration that is essentially identical to the plasma concentration, normally 24 mEq/L. Multiplying 180 L by 24 mEq/L indicates that >4,000 mEq of bicarbonate enters the Bowman space each day. This bicarbonate, if not reclaimed along the nephron, would be lost in the urine and would cause a profound metabolic acidosis.

The proximal tubule reclaims approximately 85% of the filtered bicarbonate (Fig. 55-7). The final 15% is reclaimed beyond the proximal tubule, mostly in the ascending limb of the loop of Henle. Bicarbonate molecules are not transported from the tubular fluid into the cells of the proximal tubule. Rather, hydrogen ions are secreted into the tubular fluid, leading to conversion of filtered bicarbonate into CO_2 and water. The secretion of hydrogen ions by the cells of the proximal tubule is coupled to generation of intracellular bicarbonate, which is transported across the basolateral membrane of the proximal tubule cell and enters the capillaries. The bicarbonate produced in the cell replaces the bicarbonate filtered at the glomerulus.

Increased bicarbonate resorption by the cells of the proximal tubule—the result of increased hydrogen ion secretion—occurs in a variety of clinical situations. Volume depletion increases bicarbonate resorption. This is partially mediated by activation of the renin–angiotensin system; angiotensin II increases bicarbonate resorption. Increased bicarbonate resorption in the proximal tubule is one of the mechanisms that accounts for the metabolic alkalosis that may occur in some patients with volume depletion. Other stimuli that increase bicarbonate resorption include hypokalemia and an increased P_{CO_2}. This partially explains the observations that hypokalemia causes a metabolic alkalosis and that a respiratory acidosis leads to a compensatory increase in serum bicarbonate concentration.

Stimuli that decrease bicarbonate resorption in the proximal tubule may cause a decrease in the serum bicarbonate concentration. A decrease in the P_{CO_2} (respiratory alkalosis) decreases proximal tubule bicarbonate resorption, partially mediating the decrease in serum bicarbonate concentration that compensates for a respiratory alkalosis.

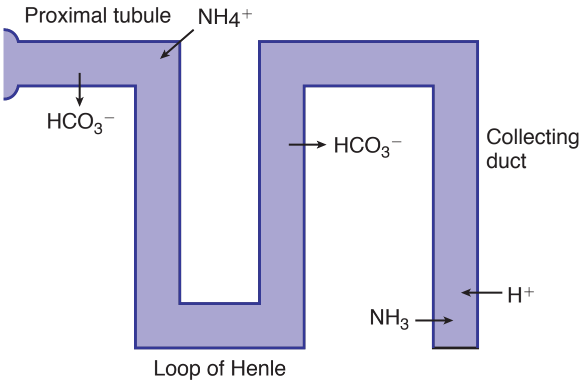

Figure 55-6 Tubular sites involved in acid–base balance. The proximal tubule is the site where most filtered bicarbonate is reclaimed, even though other sites along the nephron, especially the thick ascending limb of the loop of Henle, resorb some of the filtered bicarbonate. The collecting duct is the principal location for the hydrogen ion secretion that acidifies the urine. The proximal tubule generates the ammonia that serves as a urinary buffer in the collecting duct.

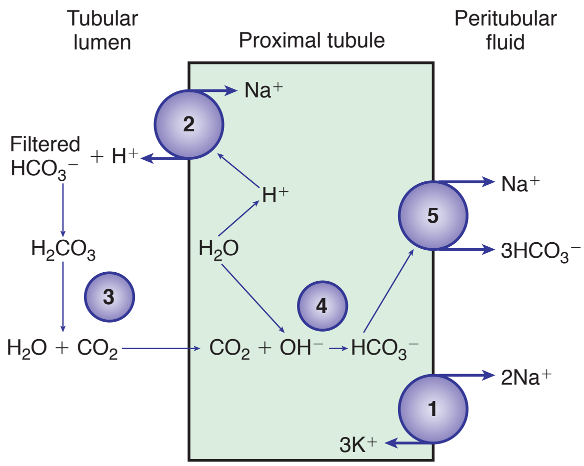

Figure 55-7 Resorption of filtered bicarbonate in the proximal tubule. The Na^+,K^+-ATPase *(1)* excretes sodium across the basolateral cell membrane, maintaining a low intracellular sodium concentration. The low intracellular sodium concentration provides the energy for the Na^+,H^+ antiporter *(2)*, which exchanges sodium from the tubular lumen for intracellular hydrogen ions. The hydrogen ions that are secreted into the tubular lumen then combine with filtered bicarbonate to generate carbonic acid. CO_2 and water are produced from carbonic acid (H_2CO_3). This reaction is catalyzed by luminal carbonic anhydrase *(3)*. CO_2 diffuses into the cell and combines with OH^- ions to generate bicarbonate. This reaction is catalyzed by an intracellular carbonic anhydrase *(4)*. The dissociation of water generates an OH^- ion and an H^+ ion. The Na^+,H^+ antiporter *(2)* secretes the hydrogen ions. Bicarbonate ions cross the basolateral membrane and enter the blood via the $3HCO_3^-/1Na^+$ cotransporter *(5)*. The energy for the $3HCO_3^-/1Na^+$ cotransporter comes from the negatively charged cell interior, which makes it electrically favorable to transport a net negative charge (i.e., 3 bicarbonates and only 1 sodium) out of the cell.

PTH decreases proximal tubule bicarbonate resorption; hyperparathyroidism may cause a mild metabolic acidosis. A variety of medications and diseases cause a metabolic acidosis by impairing bicarbonate resorption in the proximal tubule. Examples are the medication acetazolamide, which directly inhibits carbonic anhydrase, and the many disorders that cause proximal RTA (see Chapter 329).

After reclaiming filtered bicarbonate, the kidneys perform the second step in renal acid–base handling, the excretion of the acid created by endogenous acid production. Excretion of acid occurs mostly in the collecting duct, with a small role for the distal tubule.

Along with secretion of hydrogen ions by the tubular cells lining the collecting duct, adequate excretion of endogenous acid requires the presence of urinary buffers. The hydrogen pumps in the collecting duct cannot lower the urine pH below 4.5. The hydrogen ion concentration at pH 4.5 is <0.04 mEq/L; it would require >25 L of water with a pH of 4.5 to excrete 1 mEq of hydrogen ions. A 10-kg child, with an endogenous acid production of 20 mEq of hydrogen ions each day, would need to have a daily urinary output of >500 L without the presence of urinary buffers. As in the blood, buffers in the urine attenuate the decrease in pH that occurs with the addition of hydrogen ions. The 2 principal urinary buffers are phosphate and ammonia.

Urinary phosphate is proportional to dietary intake. Whereas most of the phosphate filtered at the glomerulus is resorbed in the proximal tubule, the urinary phosphate concentration is usually much greater than the serum phosphate concentration. This arrangement allows phosphate to serve as an effective buffer via the following reaction:

$$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^{1-}$$

The pK of this reaction is 6.8, making phosphate an effective buffer as the urinary pH decreases from 7.0 to 5.0 within the collecting duct. Although phosphate is an effective buffer, its buffering capacity is limited by its concentration; there is no mechanism for increasing urinary phosphate excretion in response to changes in acid–base status.

In contrast, ammonia production can be modified, allowing for regulation of acid excretion. The buffering capacity of ammonia is based on the reaction of ammonia with hydrogen ions to form ammonium:

$$NH_3 + H^+ \rightarrow NH_4^+$$

The cells of the proximal tubule are the source of the excreted ammonia, mostly through metabolism of glutamine via the following reactions:

$$\text{Glutamine} \rightarrow NH_4^+ + \text{glutamate}^-$$

$$\text{Glutamine}^- \rightarrow NH_4^+ + \alpha\text{-ketoglutarate}^{2-}$$

The metabolism of glutamine generates 2 ammonium ions. In addition, the metabolism of α-ketoglutarate generates 2 bicarbonate molecules. The ammonium ions are secreted into the lumen of the proximal tubule, whereas the bicarbonate molecules exit the proximal tubule cells via the basolateral $Na^+,3HCO_3^-$ cotransporter (see Fig. 55-6). This arrangement would seem to accomplish the goal of excreting hydrogen ions (as NH_4^+) and regenerating bicarbonate molecules. However, the ammonium ions secreted in the proximal tubule do not remain within the tubular lumen. Cells of the TAL of the loop of Henle resorb the ammonium ions. The result is that there is a high medullary interstitial concentration of ammonia, but the tubular fluid entering the collecting duct does not have significant amounts of ammonium ions. Moreover, the hydrogen ions that were secreted with ammonia, as ammonium ions, in the proximal tubule enter the bloodstream, canceling the effect of the bicarbonate generated in the proximal tubule. The excretion of ammonium ions, and hence of hydrogen ions, depends on the cells of the collecting duct.

The cells of the collecting duct secrete hydrogen ions and regenerate bicarbonate, which is returned to the bloodstream (Fig. 55-8). This bicarbonate neutralizes endogenous acid production. Phosphate and ammonia buffer the hydrogen ions secreted by the collecting duct. Ammonia is an effective buffer because of the high concentrations in the medullary interstitium and because the cells of the collecting duct are permeable to ammonia but not to ammonium. As ammonia

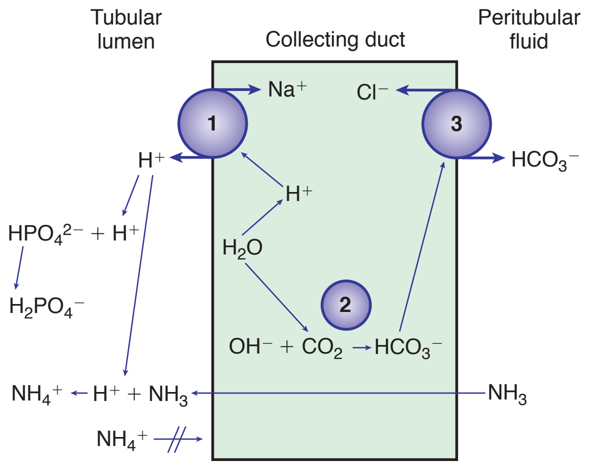

Figure 55-8 **Secretion of hydrogen ions in the collecting duct.** The dissociation of water generates an OH^- ion and an H^+ ion. The H^+-ATPase *(1)* secretes hydrogen ions into the tubular lumen. Bicarbonate is formed when an OH^- ion combines with CO_2 in a reaction mediated by carbonic anhydrase *(2)*. Bicarbonate ions cross the basolateral membrane and enter the blood via the HCO_3^-/Cl^- exchanger *(3)*. The hydrogen ions in the tubular lumen are buffered by phosphate and ammonia (NH_3). NH_3 can diffuse from the peritubular fluid into the tubular lumen, but ammonium (NH_4^+) cannot pass through the cells of the collecting duct.

diffuses into the lumen of the collecting duct, the low urine pH causes almost all of the ammonia to be converted into ammonium. This process maintains a low luminal ammonia concentration. Because the luminal pH is lower than the pH in the medullary interstitium, there is a higher concentration of ammonia within the medullary interstitium than in the tubular lumen, favoring movement of ammonia into the tubular lumen. Even though the concentration of ammonium in the tubular lumen is higher than in the interstitium, the cells of the collecting duct are impermeable to ammonium, preventing back-diffusion of ammonium out of the tubular lumen and permitting ammonia to be an effective buffer. The kidneys adjust hydrogen ion excretion according to physiologic needs. There is variation in endogenous acid production, largely a result of diet and pathophysiologic stresses, such as diarrheal losses of bicarbonate, which increase the need for acid excretion. Hydrogen excretion is increased by upregulation of hydrogen ion secretion in the collecting duct, causing the pH of the urine to decrease. This response is fairly prompt, occurring within hours of an acid load, but it is limited by the buffering capacity of the urine; the hydrogen pumps in the collecting duct cannot lower the pH to <4.5. A more significant increase in acid excretion requires upregulation of ammonia production by the proximal tubule so that more ammonia is available to serve as a buffer in the tubular lumen of the collecting duct. This response to a low serum pH reaches its maximum within 5-6 days; ammonia excretion can increase approximately 10-fold over the baseline value.

Acid excretion by the collecting duct increases in a number of different clinical situations. The extracellular pH is the most important regulator of renal acid excretion. A decrease in the extracellular pH from either a respiratory or a metabolic acidosis causes an increase in renal acid excretion. Aldosterone stimulates hydrogen ion excretion in the collecting duct, causing an increase in the serum bicarbonate concentration. This explains the metabolic alkalosis that occurs with primary hyperaldosteronism or secondary hyperaldosteronism caused by volume depletion. Hypokalemia increases acid secretion, by both stimulating ammonia production in the proximal tubule and increasing hydrogen ion secretion in the collecting duct. Hypokalemia therefore tends to produce a metabolic alkalosis. Hyperkalemia has the opposite effects, which may cause a metabolic acidosis.

In patients with an increased pH, the kidney has 2 principal mechanisms for correcting the problem. First, less bicarbonate is resorbed in the proximal tubule, leading to an increase in urinary bicarbonate

losses. Second, in a limited number of specialized cells, the process for secretion of hydrogen ions by the collecting duct (see Fig. 55-8) can be reversed, leading to secretion of bicarbonate into the tubular lumen and secretion of hydrogen ions into the peritubular fluid, where they enter the bloodstream.

CLINICAL ASSESSMENT OF ACID–BASE DISORDERS

The following equation, a rearrangement of the Henderson-Hasselbalch equation, emphasizes the relationship among the PCO_2, the bicarbonate concentration, and the hydrogen ion concentration:

$$[H^+] = 24 \times PCO_2/[HCO_3^-]$$

An increase in the PCO_2 or a decrease in the bicarbonate concentration increases the hydrogen ion concentration; the pH decreases. A decrease in the PCO_2 or an increase in the bicarbonate concentration decreases the hydrogen ion concentration; the pH increases.

Terminology

Acidemia is a pH below normal (<7.35), and **alkalemia** is a pH above normal (>7.45). An acidosis is a pathologic process that causes an increase in the hydrogen ion concentration, and an alkalosis is a pathologic process that causes a decrease in the hydrogen ion concentration. Whereas acidemia is always accompanied by an acidosis, a patient can have an acidosis and a low, normal, or high pH. For example, a patient may have a mild metabolic acidosis but a simultaneous, severe respiratory alkalosis; the net result may be alkalemia. Acidemia and alkalemia indicate the pH abnormality; acidosis and alkalosis indicate the pathologic process that is taking place.

A **simple acid–base disorder** is a single primary disturbance. During a simple metabolic disorder, there is respiratory compensation. With a metabolic acidosis, the decrease in the pH increases the ventilatory drive, causing a decrease in the PCO_2. The decrease in the CO_2 concentration leads to an increase in the pH. This appropriate respiratory compensation is expected with a primary metabolic acidosis. Despite the decrease in the CO_2 concentration, appropriate respiratory compensation is not a respiratory alkalosis, even though it is sometimes erroneously called a compensatory respiratory alkalosis. A low PCO_2 can be either the result of a primary respiratory alkalosis or of an appropriate respiratory compensation for a metabolic acidosis. Appropriate respiratory compensation also occurs with a primary metabolic alkalosis, although in this case the CO_2 concentration increases to attenuate the increase in the pH. The respiratory compensation for a metabolic process happens quickly and is complete within 12-24 hr; it cannot overcompensate for or normalize the pH.

During a primary respiratory process, there is metabolic compensation, mediated by the kidneys. The kidneys respond to a respiratory acidosis by increasing hydrogen ion excretion, thereby increasing bicarbonate generation and raising the serum bicarbonate concentration. The kidneys increase bicarbonate excretion to compensate for a respiratory alkalosis; the serum bicarbonate concentration decreases. Unlike respiratory compensation, which occurs rapidly, it takes 3-4 days for the kidneys to complete appropriate metabolic compensation. There is, however, a small and rapid compensatory change in the bicarbonate concentration during a primary respiratory process. The expected appropriate metabolic compensation for a respiratory disorder depends on whether the process is acute or chronic.

A **mixed acid–base disorder** is present when there is more than 1 primary acid–base disturbance. An infant with bronchopulmonary dysplasia may have a respiratory acidosis from chronic lung disease and a metabolic alkalosis from the furosemide used to treat the chronic lung disease. More dramatically, a child with pneumonia and sepsis may have severe acidemia as a result of a combined metabolic acidosis caused by lactic acid and respiratory acidosis caused by ventilatory failure.

There are formulas for calculating the appropriate metabolic or respiratory compensation for the 6 primary simple acid–base disorders (Table 55-11). The appropriate compensation is expected in a simple disorder; it is not optional. If a patient does not have the appropriate compensation, then a mixed acid–base disorder is present. A patient has a primary metabolic acidosis with a serum bicarbonate concentration of 10 mEq/L. The expected respiratory compensation is a CO_2 concentration of 23 mm Hg ± 2 (1.5 × 10 + 8 ± 2 = 23 ± 2; Table 55-11). If the patient's CO_2 concentration is >25 mm Hg, a concurrent respiratory acidosis is present; the CO_2 concentration is higher than expected. A patient may have a respiratory acidosis despite a CO_2 level below the "normal" value of 35-45 mm Hg. In this example, a CO_2 concentration <21 mm Hg indicates a concurrent respiratory alkalosis; the CO_2 concentration is lower than expected.

Table 55-11 Appropriate Compensation During Simple Acid–Base Disorders

DISORDER	EXPECTED COMPENSATION
Metabolic acidosis	$PCO_2 = 1.5 \times [HCO_3^-] + 8 \pm 2$
Metabolic alkalosis	PCO_2 increases by 7 mm Hg for each 10 mEq/L increase in serum $[HCO_3^-]$
RESPIRATORY ACIDOSIS	
Acute	$[HCO_3^-]$ increases by 1 for each 10 mm Hg increase in PCO_2
Chronic	$[HCO_3^-]$ increases by 3.5 for each 10 mm Hg increase in PCO_2
RESPIRATORY ALKALOSIS	
Acute	$[HCO_3^-]$ falls by 2 for each 10 mm Hg decrease in PCO_2
Chronic	$[HCO_3^-]$ falls by 4 for each 10 mm Hg decrease in PCO_2

Table 55-12 Normal Values of Arterial Blood Gases

pH	7.35-7.45
$[HCO_3^-]$	20-28 mEq/L
PCO_2	35-45 mm Hg

Diagnosis

A systematic evaluation of an arterial blood gas sample, combined with the clinical history, can usually explain the patient's acid–base disturbance. Assessment of an arterial blood gas sample requires knowledge of normal values (Table 55-12). In most cases, this is accomplished via a 3-step process (Fig. 55-9):

- Determine whether acidemia or alkalemia is present.
- Determine a cause of the acidemia or alkalemia.
- Determine whether a mixed disorder is present.

Most patients with an acid–base disturbance have an abnormal pH, although there are 2 exceptions. The first exception is in the patient with a mixed disorder, wherein the 2 processes have opposite effects on pH (a metabolic acidosis and a respiratory alkalosis) and cause changes in the hydrogen ion concentration that are comparable in magnitude, albeit opposite. The second exception is in the patient with a simple chronic respiratory alkalosis; in some instances, the appropriate metabolic compensation is enough to normalize the pH. In both of these situations, the presence of an acid–base disturbance is deduced because of the abnormal CO_2 and/or bicarbonate levels. Determining the acid–base disturbance in these situations requires proceeding to the third step of this process.

The second step requires inspection of the serum bicarbonate and CO_2 concentrations to determine a cause of the abnormal pH (see Fig. 55-9). In most cases, there is only 1 obvious explanation for the abnormal pH. In some mixed disorders, however, there may be 2 possibilities (a high PCO_2 and a low $[HCO_3^-]$ in a patient with acidemia). In such cases, the patient has 2 causes for abnormal pH (a metabolic acidosis and a respiratory acidosis, in this instance), and it is unnecessary to proceed to the third step.

The third step requires determining whether the patient's compensation is appropriate. It is assumed that the primary disorder

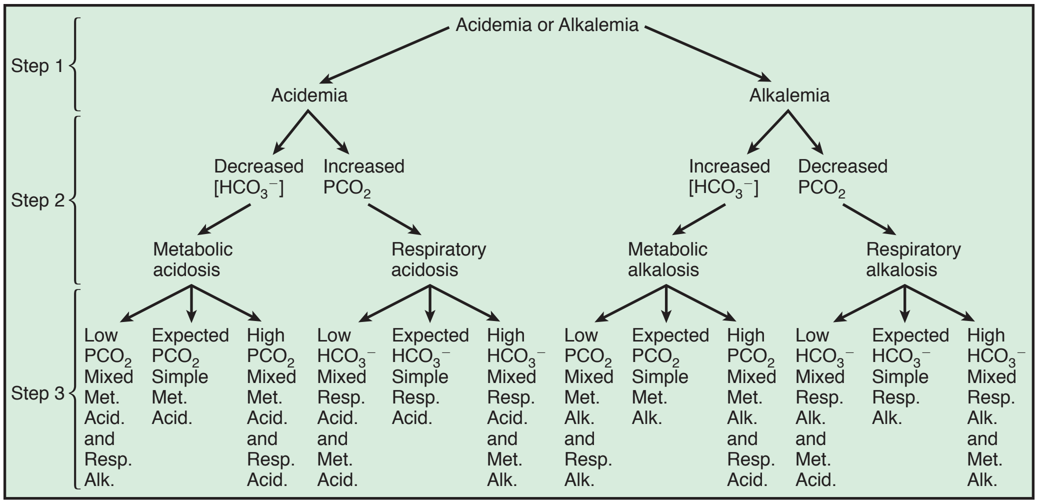

Figure 55-9 **Three-step process for interpreting acid–base disturbances.** In step 1, determine whether the pH is low (acidemia) or high (alkalemia). In step 2, establish an explanation for the acidemia or alkalemia. In step 3, calculate the expected compensation (see Table 55-11) and determine whether a mixed disturbance is present. Met. Acid., metabolic acidosis; Met. Alk., metabolic alkalosis; Resp. Acid., respiratory acidosis; Resp. Alk., respiratory alkalosis.

was diagnosed in the second step, and the expected compensation is calculated (see Table 55-11). If the compensation is appropriate, then a simple acid–base disorder is present. If the compensation is not appropriate, then a mixed disorder is present. The identity of the second disorder is determined by deciding whether the compensation is too little or too much compared with what was expected (see Fig. 55-9).

The history is always useful in evaluating and diagnosing patients with acid–base disturbances. It is especially helpful in a respiratory process. The expected metabolic compensation for a respiratory process changes according to whether the process is acute or chronic, which can be deduced only from the history. The metabolic compensation for an acute respiratory acidosis is less than that for a chronic respiratory acidosis. In a patient with a respiratory acidosis, a small increase in the bicarbonate concentration would be consistent with a simple acute respiratory acidosis or a mixed disorder (a chronic respiratory acidosis and a metabolic acidosis). Only the history can differentiate among the possibilities. Knowledge of the length of the respiratory process and the presence or absence of a risk factor for a metabolic acidosis (diarrhea) allows the correct conclusion to be reached.

METABOLIC ACIDOSIS

Metabolic acidosis occurs frequently in hospitalized children; diarrhea is the most common etiology. For a patient with an unknown medical problem, the presence of a metabolic acidosis is often helpful diagnostically, because it suggests a relatively narrow differential diagnosis.

Patients with a metabolic acidosis have a low serum bicarbonate concentration, although not every patient with a low serum bicarbonate concentration has a metabolic acidosis. The exception is the patient with a respiratory alkalosis, which causes a decrease in the serum bicarbonate concentration as part of appropriate renal compensation. In a patient with an isolated metabolic acidosis, there is a predictable decrease in the blood CO_2 concentration, as follows:

$$P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$$

A mixed acid–base disturbance is present if the respiratory compensation is not appropriate. If the P_{CO_2} is greater than predicted, then the patient has a concurrent respiratory acidosis. A lower P_{CO_2} than predicted indicates a concurrent respiratory alkalosis or, less commonly, an isolated respiratory alkalosis. Because the appropriate respiratory compensation for a metabolic acidosis **never normalizes** the patient's pH, the presence of a normal pH and a low bicarbonate concentration occurs only if some degree of respiratory alkalosis is present. In this situation, distinguishing an isolated chronic respiratory alkalosis from a mixed metabolic acidosis and acute respiratory alkalosis may be possible only clinically. In contrast, the combination of a low serum pH and a low bicarbonate concentration occurs only if a metabolic acidosis is present.

Etiology and Pathophysiology

There are many causes of a metabolic acidosis (Table 55-13), which occur via 3 basic mechanisms:

- Loss of bicarbonate from the body
- Impaired ability to excrete acid by the kidney
- Addition of acid to the body (exogenous or endogenous)

Diarrhea, the most common cause of metabolic acidosis in children, causes a loss of bicarbonate from the body. The amount of bicarbonate lost in the stool depends on the volume of diarrhea and the bicarbonate concentration of the stool, which tends to increase with more severe diarrhea. The kidneys attempt to balance the losses by increasing acid secretion, but metabolic acidosis occurs when this compensation is inadequate. Diarrhea often causes volume depletion as a result of losses of sodium and water, potentially exacerbating the acidosis by causing shock and a lactic acidosis. In addition, diarrheal losses of potassium lead to hypokalemia. Moreover, the volume depletion causes increased production of aldosterone. This increase stimulates renal retention of sodium, helping to maintain intravascular volume, but also leads to increased urinary losses of potassium, exacerbating the hypokalemia.

There are 3 forms of RTA: distal (type I), proximal (type II), and hyperkalemic (type IV) (see Chapter 529). In distal RTA, children may have accompanying hypokalemia, hypercalciuria, nephrolithiasis, and nephrocalcinosis. Failure to thrive because of chronic metabolic acidosis is the most common presenting complaint. Patients with distal RTA cannot acidify their urine and, thus, have a urine pH >5.5 despite a metabolic acidosis.

Proximal RTA is rarely present in isolation. In most patients, proximal RTA is part of Fanconi syndrome, a generalized dysfunction of the proximal tubule. The dysfunction leads to glycosuria, aminoaciduria, and excessive urinary losses of phosphate and uric acid. The presence of a low serum uric acid level, glycosuria, and aminoaciduria is helpful diagnostically. Chronic hypophosphatemia leads to rickets in children (see Chapter 51). Rickets and/or failure to thrive may be the presenting complaint. The ability to acidify the urine is intact in proximal RTA; thus, untreated patients have a urine pH <5.5. However, bicarbonate therapy increases bicarbonate losses in the urine, and the urine pH increases.

In hyperkalemic RTA, renal excretion of acid and potassium is impaired. Hyperkalemic RTA is the result of either an absence of

Table 55-13 Causes of Metabolic Acidosis
NORMAL ANION GAP
Diarrhea
Renal tubular acidosis (RTA):
Distal (type I) RTA (OMIM 179800/602722/267300)*
Proximal (type II) RTA (OMIM 604278)†
Hyperkalemic (type IV) RTA (OMIM 201910/264350/177735/145260)‡
Urinary tract diversions
Posthypocapnia
Ammonium chloride intake
INCREASED ANION GAP
Lactic acidosis
Tissue hypoxia
Shock
Hypoxemia
Severe anemia
Liver failure
Malignancy
Intestinal bacterial overgrowth
Inborn errors of metabolism
Medications
Nucleoside reverse transcriptase inhibitors
Metformin
Propofol
Ketoacidosis
Diabetic ketoacidosis
Starvation ketoacidosis
Alcoholic ketoacidosis
Kidney failure
Poisoning
Ethylene glycol
Methanol
Salicylate
Toluene
Paraldehyde

*Along with these genetic disorders, distal RTA may be secondary to renal disease or medications.
†Most cases of proximal RTA are not caused by this primary genetic disorder. Proximal RTA is usually part of Fanconi syndrome, which has multiple etiologies.
‡Hyperkalemic RTA can be secondary to a genetic disorder (some of the more common are listed) or other etiologies.
OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

aldosterone or an inability of the kidney to respond to aldosterone. In severe aldosterone deficiency, as occurs with congenital adrenal hyperplasia because of 21α-hydroxylase deficiency, the hyperkalemia and metabolic acidosis are accompanied by hyponatremia and volume depletion from renal salt wasting. Incomplete aldosterone deficiency causes less-severe electrolyte disturbances; children may have isolated hyperkalemic RTA, hyperkalemia without acidosis, or isolated hyponatremia. Patients may have aldosterone deficiency caused by decreased renin production by the kidney; renin normally stimulates aldosterone synthesis. Children with hyporeninemic hypoaldosteronism usually have either isolated hyperkalemia or hyperkalemic RTA. The manifestations of aldosterone resistance depend on the severity of the resistance. In the autosomal recessive form of pseudohypoaldosteronism type I, which is the result of an absence of the sodium channel that normally responds to aldosterone, there is often severe salt wasting and hyponatremia. In contrast, the aldosterone resistance in kidney transplant recipients usually produces either isolated hyperkalemia or hyperkalemic RTA; hyponatremia is unusual. Similarly, the medications that cause hyperkalemic RTA do not cause hyponatremia. Pseudohypoaldosteronism type II, an autosomal recessive disorder also known as **Gordon syndrome,** is a unique cause of hyperkalemic RTA because the genetic defect causes volume expansion and hypertension.

Children with **abnormal urinary tracts,** usually secondary to congenital malformations, may require diversion of urine through intestinal segments. Ureterosigmoidostomy, anastomosis of a ureter to the sigmoid colon, almost always produces a metabolic acidosis and hypokalemia. Consequently, ileal conduits are now the more commonly used procedure, although there is still a risk of a metabolic acidosis.

The **appropriate metabolic compensation for a chronic respiratory alkalosis** is a decrease in renal acid excretion. The resultant decrease in the serum bicarbonate concentration lessens the alkalemia caused by the respiratory alkalosis. If the respiratory alkalosis resolves quickly, the patient continues to have a decreased serum bicarbonate concentration, causing acidemia as the result of a metabolic acidosis. This resolves over 1-2 days via increased acid excretion by the kidneys.

Lactic acidosis most commonly occurs when inadequate oxygen delivery to the tissues leads to anaerobic metabolism and excess production of lactic acid. Lactic acidosis may be secondary to shock, severe anemia, or hypoxemia. When the underlying cause of the lactic acidosis is alleviated, the liver is able to metabolize the accumulated lactate into bicarbonate, correcting the metabolic acidosis. There is normally some tissue production of lactate that is metabolized by the liver. In children with severe liver dysfunction, impairment of lactate metabolism may produce a lactic acidosis. Rarely, a metabolically active malignancy grows so fast that its blood supply becomes inadequate, with resultant anaerobic metabolism and lactic acidosis. Patients who have short bowel syndrome resulting from small bowel resection can have bacterial overgrowth. In these patients, excessive bacterial metabolism of glucose into D-lactic acid can cause a lactic acidosis. Lactic acidosis occurs in a variety of inborn errors of metabolism, especially those affecting mitochondrial oxidation (see Chapter 87.4). Finally, medications can cause lactic acidosis. Nucleoside reverse transcriptase inhibitors that are used to treat HIV infection inhibit mitochondrial replication; lactic acidosis is a rare complication, although elevated serum lactate concentrations without acidosis are quite common. Metformin, commonly used for treating type 2 diabetes mellitus, is most likely to cause a lactic acidosis in patients with renal insufficiency. High dosages and prolonged use of propofol can cause lactic acidosis. Propylene glycol is a diluent in a variety of oral and intravenous medications; excessive intake causes a lactic acidosis, principally from accumulation of D-lactic acid.

In **insulin-dependent diabetes mellitus,** inadequate insulin leads to hyperglycemia and diabetic ketoacidosis (see Chapter 589). Production of acetoacetic acid and β-hydroxybutyric acid causes the metabolic acidosis. Administration of insulin corrects the underlying metabolic problem and permits conversion of acetoacetate and β-hydroxybutyrate into bicarbonate, which helps correct the metabolic acidosis. However, in some patients, urinary losses of acetoacetate and β-hydroxybutyrate may be substantial, preventing rapid regeneration of bicarbonate. In these patients, full correction of the metabolic acidosis requires renal regeneration of bicarbonate, a slower process. The hyperglycemia causes an osmotic diuresis, usually producing volume depletion, along with substantial losses of potassium, sodium, and phosphate.

In **starvation ketoacidosis,** the lack of glucose leads to keto acid production, which, in turn, can produce a metabolic acidosis, although it is usually mild as a result of increased acid secretion by the kidney. In alcoholic ketoacidosis, which is much less common in children than in adults, the acidosis usually follows a combination of an alcoholic binge with vomiting and poor intake of food. The acidosis is potentially more severe than with isolated starvation, and the blood glucose level may be low, normal, or high. Hypoglycemia and acidosis also suggest an inborn error of metabolism.

Renal failure causes a metabolic acidosis because of the need for the kidneys to excrete the acid produced by normal metabolism. With mild or moderate renal insufficiency, the remaining nephrons are usually able to compensate by increasing acid excretion. When the GFR is <20-30% of normal, the compensation is inadequate and a metabolic acidosis develops. In some children, especially those with chronic renal failure because of tubular damage, the acidosis develops at a higher GFR because of a concurrent defect in acid secretion by the distal tubule (distal RTA).

A variety of **toxic ingestions** (see Chapter 63) can cause a metabolic acidosis. **Salicylate** intoxication is now much less common because aspirin is no longer recommended for fever control in children. Acute

salicylate intoxication occurs after a large overdose. Chronic salicylate intoxication is possible with gradual buildup of the drug. Especially in adults, respiratory alkalosis may be the dominant acid–base disturbance. In children, the metabolic acidosis is usually the more significant finding. Other symptoms of salicylate intoxication are fever, seizures, lethargy, and coma. Hyperventilation may be particularly marked. Tinnitus, vertigo, and hearing impairment are more likely with chronic salicylate intoxication.

Ethylene glycol, a component of antifreeze, is converted in the liver to glyoxylic and oxalic acids, causing a severe metabolic acidosis. Excessive oxalate excretion causes calcium oxalate crystals to appear in the urine, and calcium oxalate precipitation in the kidney tubules can cause renal failure. The toxicity of methanol ingestion also depends on liver metabolism; formic acid is the toxic end product that causes the metabolic acidosis and other sequelae, which include damage to the optic nerve and CNS. Symptoms may include nausea, emesis, visual impairment, and altered mental status. Toluene inhalation and paraldehyde ingestion are other potential causes of a metabolic acidosis.

Many **inborn errors of metabolism** cause a metabolic acidosis (see Chapters 84-87). The metabolic acidosis may be the result of excessive production of keto acids, lactic acid, and/or other organic anions. Some patients have accompanying hypoglycemia or hyperammonemia. In most patients, the acidosis occurs episodically, only during acute decompensations, which may be precipitated by ingestion of specific dietary substrates, the stress of a mild illness, or poor compliance with dietary or medical therapy. In a few inborn errors of metabolism, patients have a chronic metabolic acidosis.

Clinical Manifestations

The underlying disorder usually produces most of the signs and symptoms in children with a mild or moderate metabolic acidosis. The clinical manifestations of the acidosis are related to the degree of acidemia; patients with appropriate respiratory compensation and less severe acidemia have fewer manifestations than those with a concomitant respiratory acidosis. At a serum pH <7.2, there may be impaired cardiac contractility and an increased risk of arrhythmias, especially if underlying heart disease or other predisposing electrolyte disorders are present. With acidemia, there may be a decrease in the cardiovascular response to catecholamines, potentially exacerbating hypotension in children with volume depletion or shock. Acidemia causes vasoconstriction of the pulmonary vasculature, which is especially problematic in newborn infants with persistent pulmonary hypertension (see Chapter 101.7).

The normal respiratory response to metabolic acidosis—compensatory hyperventilation—may be subtle with mild metabolic acidosis, but it causes discernible increased respiratory effort with worsening acidemia. The acute metabolic effects of acidemia include insulin resistance, increased protein degradation, and reduced ATP synthesis. Chronic metabolic acidosis causes failure to thrive in children. Acidemia causes potassium to move from the intracellular space to the extracellular space, thereby increasing the serum potassium concentration. Severe acidemia impairs brain metabolism, eventually resulting in lethargy and coma.

Diagnosis

The etiology of a metabolic acidosis is often apparent from the history and physical examination. Acutely, diarrhea and shock are common causes of a metabolic acidosis. Shock, which causes a lactic acidosis, is usually apparent on physical examination and can be secondary to dehydration, acute blood loss, sepsis, or heart disease. Failure to thrive suggests a chronic metabolic acidosis, as happens with renal insufficiency or RTA. New onset of polyuria occurs in children with undiagnosed diabetes mellitus and diabetic ketoacidosis. Metabolic acidosis with seizures and/or a depressed sensorium, especially in an infant, warrants consideration of an inborn error of metabolism. Meningitis and sepsis with lactic acidosis are more common explanations for metabolic acidosis with neurologic signs and symptoms. Identification of a toxic ingestion such as of ethylene glycol or methanol is especially important because of the potentially excellent response to specific therapy. A variety of medications can cause a metabolic acidosis; they may be prescribed or accidentally ingested. Hepatomegaly and metabolic acidosis may occur in children with sepsis, congenital or acquired heart disease, hepatic failure, or inborn errors of metabolism.

Basic laboratory tests in a child with a metabolic acidosis should include measurements of BUN, serum creatinine, serum glucose, urinalysis, and serum electrolytes. Elevated BUN and creatinine values are present in renal insufficiency, whereas an elevated BUN : creatinine ratio (>20 : 1) supports a diagnosis of prerenal azotemia and the possibility of poor perfusion with lactic acidosis. Metabolic acidosis, hyperglycemia, glycosuria, and ketonuria support a diagnosis of diabetic ketoacidosis. Starvation causes ketosis, but the metabolic acidosis, if present, is usually mild (HCO_3^- >18). In most children with ketosis from poor intake and metabolic acidosis there is a concomitant disorder, such as gastroenteritis with diarrhea, that explains the metabolic acidosis. Alternatively, metabolic acidosis with or without ketosis occurs in inborn errors of metabolism; patients with these disorders may have hyperglycemia, normoglycemia, or hypoglycemia. Adrenal insufficiency may cause metabolic acidosis and hypoglycemia. Metabolic acidosis with hypoglycemia also occurs with liver failure. Metabolic acidosis, normoglycemia, and glycosuria occur in children when type II RTA is part of Fanconi syndrome; the defect in resorption of glucose by the proximal tubule of the kidney causes the glycosuria.

The serum potassium level is often abnormal in children with a metabolic acidosis. Even though a metabolic acidosis causes potassium to move from the intracellular space to the extracellular space, many patients with a metabolic acidosis have a low serum potassium level owing to excessive body losses of potassium. With diarrhea, there are high stool losses of potassium and often secondary renal losses of potassium, whereas in type I or type II RTA, there are increased urinary losses of potassium. In diabetic ketoacidosis, urinary losses of potassium are high, but the shift of potassium out of cells because of a lack of insulin and metabolic acidosis is especially significant. Consequently, the initial serum potassium level can be low, normal, or high, even though total body potassium is almost always decreased. The serum potassium level is usually increased in patients with acidosis due to renal insufficiency; urinary potassium excretion is impaired. The combination of metabolic acidosis, hyperkalemia, and hyponatremia occurs in patients with severe aldosterone deficiency (adrenogenital syndrome) or aldosterone resistance. Patients with less severe, type IV RTA often have only hyperkalemia and metabolic acidosis. Very ill children with metabolic acidosis may have an elevated serum potassium value as a result of a combination of renal insufficiency, tissue breakdown, and a shift of potassium from the intracellular space to the extracellular space secondary to the metabolic acidosis.

The **plasma anion gap** is useful for evaluating patients with a metabolic acidosis. It divides patients into 2 diagnostic groups, those with normal anion gap and those with increased anion gap. The following formula determines the anion gap:

$$\text{Anion gap} = [Na^+] - [Cl^-] - [HCO_3^-]$$

A normal anion gap is 4-11, although there is variation among laboratories. The number of serum anions must equal the number of serum cations to maintain electrical neutrality (Fig. 55-10). The anion gap is the difference between the measured cation (sodium) and the measured anions (chloride + bicarbonate). The anion gap is also the difference between the unmeasured cations (potassium, magnesium, calcium) and the unmeasured anions (albumin, phosphate, urate, sulfate). An increased anion gap occurs when there is an increase in unmeasured anions. With a lactic acidosis, there is endogenous production of lactic acid, which is composed of positively charged hydrogen ions and negatively charged lactate anions. The hydrogen ions are largely buffered by serum bicarbonate, resulting in a decrease in the bicarbonate concentration. The hydrogen ions that are not buffered by bicarbonate cause the serum pH to decrease. The lactate anions remain, causing the increase in the anion gap.

An increase in unmeasured anions, along with hydrogen ion generation, is present in all causes of an increased gap metabolic acidosis (see Table 55-13). In diabetic ketoacidosis, the keto acids β-hydroxybutyrate

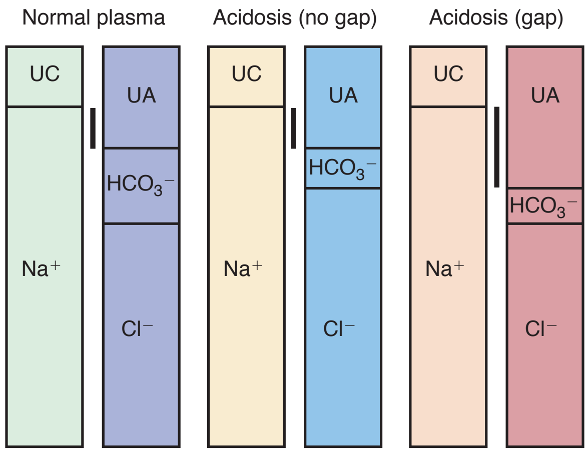

Figure 55-10 The anion gap, which is the difference between the sodium concentration and the combined concentrations of chloride and bicarbonate *(vertical lines)*. In both a gap and a nongap metabolic acidosis, there is a decrease in the bicarbonate concentration. There is an increase in unmeasured anions (UA) in patients with a gap metabolic acidosis. In a nongap metabolic acidosis, there is an increase in the serum chloride concentration. UC, unmeasured cations.

and acetoacetate are the unmeasured anions. In renal failure, there is retention of unmeasured anions, including phosphate, urate, and sulfate. The increase in unmeasured anions in renal failure is usually less than the decrease in the bicarbonate concentration. Renal failure is thus a mix of an increased gap and a normal gap metabolic acidosis. The normal gap metabolic acidosis is especially prominent in children with renal failure as a result of tubular damage, as occurs with renal dysplasia or obstructive uropathy, because these patients have a concurrent RTA. The unmeasured anions in toxic ingestions vary: formate in methanol intoxication, glycolate in ethylene glycol intoxication, and lactate and keto acids in salicylate intoxication. In inborn errors of metabolism, the unmeasured anions depend on the specific etiology and may include keto acids, lactate, and other organic anions. In a few inborn errors of metabolism, the acidosis occurs without generation of unmeasured anions; thus, the anion gap is normal.

A **normal anion gap** metabolic acidosis occurs when there is a decrease in the bicarbonate concentration without an increase in the unmeasured anions. With diarrhea, there is a loss of bicarbonate in the stool, causing a decrease in the serum pH and bicarbonate concentration; the serum chloride concentration increases to maintain electrical neutrality (see Fig. 55-10). Hyperchloremic metabolic acidosis is an alternative term for a normal anion gap metabolic acidosis. Calculation of the anion gap is more precise than using the chloride concentration to differentiate between a normal and an increased gap metabolic acidosis, in that the anion gap directly determines the presence of unmeasured anions. Electrical neutrality dictates that the chloride concentration increases or decreases according to the serum sodium concentration, making the chloride concentration a less reliable predictor of unmeasured anions than the more direct measure, calculation of the anion gap.

Approximately 11 mEq of the anion gap is normally secondary to albumin. A 1 g/dL decrease in the albumin concentration decreases the anion gap by roughly 2.5 mEq/L. Similarly, an increase in unmeasured cations, such as calcium, potassium, and magnesium, decreases the anion gap. Conversely, a decrease in unmeasured cations is a very unusual cause of an increased anion gap. Because of these variables, the broad range of a normal anion gap, and other variables, the presence of a normal or an increased anion gap is not always reliable in differentiating among the causes of a metabolic acidosis, especially when the metabolic acidosis is mild. In some patients there is more than 1 explanation for the metabolic acidosis, such as the child with diarrhea and lactic acidosis as a result of poor perfusion. The anion gap should not be interpreted in dogmatic isolation; consideration of other laboratory abnormalities and the clinical history improves its diagnostic utility.

Treatment

The most effective therapeutic approach for patients with a metabolic acidosis is repair of the underlying disorder, if possible. The administration of insulin in diabetic ketoacidosis and the restoration of adequate perfusion with intravenous fluids in lactic acidosis because of hypovolemia or shock eventually result in normalization of the acid–base balance. In other diseases, the use of bicarbonate therapy is indicated because the underlying disorder is irreparable. Children with metabolic acidosis caused by RTA or chronic renal failure require long-term base therapy. Patients with acute renal failure and metabolic acidosis need base therapy until their kidneys' ability to excrete hydrogen normalizes. In other disorders, the cause of the metabolic acidosis eventually resolves, but base therapy is necessary during the acute illness. In salicylate poisoning, alkali administration increases renal clearance of salicylate and decreases the amount of salicylate in brain cells. Short-term base therapy is often necessary in other poisonings (ethylene glycol, methanol) and inborn errors of metabolism (pyruvate carboxylase deficiency, propionic acidemia). Some inborn errors of metabolism require long-term base therapy.

The use of base therapy in diabetic ketoacidosis and lactic acidosis is controversial; there is little evidence that it improves patient outcome, and it has a variety of potential side effects. The risks of giving sodium bicarbonate include the possibility of causing hypernatremia or volume overload. Furthermore, the patient may have overcorrection of the metabolic acidosis once the underlying disorder resolves, because metabolism of lactate or keto acids generates bicarbonate. The rapid change from acidemia to alkalemia can cause a variety of problems, including hypokalemia and hypophosphatemia. Bicarbonate therapy increases the generation of CO_2, which can accumulate in patients with respiratory failure. Because CO_2 readily diffuses into cells, the administration of bicarbonate can lower the intracellular pH, potentially worsening cell function. Base therapy is usually reserved for children with severe acute lactic acidosis and severe diabetic ketoacidosis.

Oral base therapy is given to children with chronic metabolic acidosis. Sodium bicarbonate tablets are available for older children. Younger children generally take citrate solutions; the liver generates bicarbonate from citrate. Citrate solutions are available as sodium citrate, potassium citrate, and a 1 : 1 mix of sodium citrate and potassium citrate. The patient's potassium needs dictate the choice. Children with type I or type II RTA may have hypokalemia and may benefit from potassium supplements, whereas most children with chronic renal failure cannot tolerate additional potassium.

Oral or intravenous base can be used in acute metabolic acidosis; intravenous therapy is generally used when a rapid response is necessary. Sodium bicarbonate may be given as a bolus, usually at a dose of 1 mEq/kg, in an emergency situation. Another approach is to add sodium bicarbonate or sodium acetate to the patient's intravenous fluids, remembering to remove an equal amount of sodium chloride from the solution to avoid giving an excessive sodium load. Careful monitoring is mandatory so that the dose of base can be titrated appropriately. Tris-hydroxymethyl aminomethane (THAM) is an option in patients with a metabolic acidosis and a respiratory acidosis, because it neutralizes acids without releasing CO_2. THAM also diffuses into cells and therefore provides intracellular buffering.

Hemodialysis is another option for correcting a metabolic acidosis, and it is an appropriate choice in patients with renal insufficiency, especially if significant uremia or hyperkalemia is also present. Hemodialysis is advantageous for correcting the metabolic acidosis caused by methanol or ethylene glycol intoxication, because hemodialysis removes the offending toxin. In addition, these patients often have a severe metabolic acidosis that does not respond easily to intravenous bicarbonate therapy. Peritoneal dialysis is another option for correcting the metabolic acidosis due to renal insufficiency, although, because it relies on lactate as the source of base, it may not correct the metabolic acidosis in patients with concomitant renal failure and lactic acidosis.

Many causes of metabolic acidosis require specific therapy. Administration of a glucocorticoid and a mineralocorticoid is necessary in patients with adrenal insufficiency. Patients with diabetic ketoacidosis require insulin therapy, whereas patients with lactic acidosis respond to measures that alleviate tissue hypoxia. Along with correction of acidosis, patients with methanol or ethylene glycol ingestion should receive an agent that prevents the breakdown of the toxic substance to its toxic metabolites. Fomepizole has supplanted ethanol as the treatment of choice. These agents work by inhibiting alcohol dehydrogenase, the enzyme that performs the first step in the metabolism of ethylene glycol or methanol. There are a variety of disease-specific therapies for patients with a metabolic acidosis resulting from an inborn error of metabolism.

METABOLIC ALKALOSIS

Metabolic alkalosis in children is most commonly secondary to emesis or diuretic use. The serum bicarbonate concentration is increased with a metabolic alkalosis, although a respiratory acidosis also leads to a compensatory elevation of the serum bicarbonate concentration. With a simple metabolic alkalosis, however, the pH is elevated; alkalemia is present. Patients with a respiratory acidosis are acidemic. A metabolic alkalosis, by decreasing ventilation, causes appropriate respiratory compensation. P_{CO_2} increases by 7 mm Hg for each 10 mEq/L increase in the serum bicarbonate concentration. Appropriate respiratory compensation never exceeds a P_{CO_2} of 55-60 mm Hg. The patient has a concurrent respiratory alkalosis if the P_{CO_2} is lower than the expected compensation. A greater-than-expected P_{CO_2} occurs with a concurrent respiratory acidosis.

Table 55-14 Causes of Metabolic Alkalosis
CHLORIDE-RESPONSIVE (URINARY CHLORIDE <15 MEQ/L)
Gastric losses
Emesis
Nasogastric suction
Diuretics (loop or thiazide)
Chloride-losing diarrhea (OMIM 214700)
Chloride-deficient formula
Cystic fibrosis (OMIM 219700)
Post-hypercapnia
CHLORIDE-RESISTANT (URINARY CHLORIDE >20 MEQ/L)
High blood pressure
Adrenal adenoma or hyperplasia
Glucocorticoid-remediable aldosteronism (OMIM 103900)
Renovascular disease
Renin-secreting tumor
17β-Hydroxylase deficiency (OMIM 202110)
11β-Hydroxylase deficiency (OMIM 202010)
Cushing syndrome
11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
Licorice ingestion
Liddle syndrome (OMIM 177200)
Normal blood pressure
Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 607364/602522/241200/601678)
Autosomal dominant hypoparathyroidism (OMIM 146200)
EAST syndrome (OMIM 612780)
Base administration

EAST, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Etiology and Pathophysiology

The kidneys normally respond promptly to a metabolic alkalosis by increasing base excretion. Two processes are therefore usually present to produce a metabolic alkalosis. The first process is the generation of the metabolic alkalosis, which requires the addition of base to the body. The second process is the maintenance of the metabolic alkalosis, which requires impairment in the kidney's ability to excrete base.

The etiologies of a metabolic alkalosis are divided into 2 categories on the basis of urinary chloride level (Table 55-14). The alkalosis in patients with a **low urinary chloride** level is maintained by **volume depletion;** thus, volume repletion is necessary for correction of the alkalosis. The volume depletion in these patients is caused by losses of sodium and potassium, but the loss of chloride is usually greater than the losses of sodium and potassium combined. Because chloride losses are the dominant cause of the volume depletion, these patients require chloride to correct the volume depletion and metabolic alkalosis; they are said to have **chloride-responsive metabolic alkalosis.** In contrast, the alkalosis in a patient with an elevated urinary chloride concentration does not respond to volume repletion and so is termed **chloride-resistant metabolic alkalosis.**

Emesis or nasogastric suction results in **loss of gastric fluid,** which has a high content of HCl. Generation of hydrogen ions by the gastric mucosa causes simultaneous release of bicarbonate into the bloodstream. Normally, the hydrogen ions in gastric fluid are reclaimed in the small intestine (by neutralizing secreted bicarbonate). Thus, there is no net loss of acid. With loss of gastric fluid, this does not occur, and a metabolic alkalosis develops. This period is the generation phase of the metabolic alkalosis.

The maintenance phase of the metabolic alkalosis from gastric losses is due to the volume depletion ("chloride depletion" from gastric loss of HCl). Volume depletion interferes with urinary loss of bicarbonate, the normal renal response to a metabolic alkalosis. During volume depletion, several mechanisms prevent renal bicarbonate loss. First, there is a reduction in the GFR, so less bicarbonate is filtered. Second, volume depletion increases resorption of sodium and bicarbonate in the proximal tubule, limiting the amount of bicarbonate that can be excreted in the urine. This effect is mediated by angiotensin II and by adrenergic stimulation of the kidney, which are both increased in response to volume depletion. Third, the increase in aldosterone during volume depletion increases bicarbonate resorption and hydrogen ion secretion in the collecting duct.

In addition to volume depletion, gastric losses are usually associated with hypokalemia as a result of both gastric loss of potassium and, most importantly, increased urinary potassium losses. The increased urinary losses of potassium are mediated by aldosterone, through volume depletion, and by the increase in intracellular potassium secondary to the metabolic alkalosis, which causes potassium to move into the cells of the kidney, causing increased potassium excretion. Hypokalemia contributes to the maintenance of the metabolic alkalosis by decreasing bicarbonate loss. Hypokalemia increases hydrogen ion secretion in the distal nephron and stimulates ammonia production in the proximal tubule. Ammonia production enhances renal excretion of hydrogen ions.

A metabolic alkalosis can develop in patients receiving **loop** or **thiazide diuretics.** Diuretic use leads to volume depletion, which increases angiotensin II, aldosterone, and adrenergic stimulation of the kidney. Diuretics increase the delivery of sodium to the distal nephron, further enhancing acid excretion. Moreover, these diuretics cause hypokalemia, which increases acid excretion by the kidney. The increase in renal acid excretion generates the metabolic alkalosis, and the decrease in bicarbonate loss maintains it. In addition, patients who are receiving diuretics have a "contraction alkalosis." Diuretic use causes fluid loss without bicarbonate; thus, the remaining body bicarbonate is contained in a smaller total body fluid compartment. The bicarbonate concentration increases, helping to generate the metabolic alkalosis.

Diuretics are often used in patients with edema, such as those with nephrotic syndrome, heart failure, or liver failure. In many of these patients, metabolic alkalosis resulting from diuretic use develops despite the continued presence of edema. This is because the effective intravascular volume is low, and it is the effective intravascular volume that stimulates the compensatory mechanisms that cause and maintain a metabolic alkalosis. Many of these patients have a decreased effective intravascular volume before they begin diuretic therapy, increasing the likelihood of diuretic-induced metabolic alkalosis.

Diuretic use increases chloride excretion in the urine. Consequently, while a patient is receiving diuretics, the urine chloride level is typically

high (>20 mEq/L). After the diuretic effect has worn off, the urinary chloride level is low (<15 mEq/L) owing to appropriate renal chloride retention in response to volume depletion. Thus, categorization of diuretics on the basis of urinary chloride level depends on the timing of the measurement. However, the metabolic alkalosis from diuretics is clearly chloride responsive; it is corrected after adequate volume repletion. This is the rationale for including this process among the chloride-responsive causes of a metabolic alkalosis.

Most patients with diarrhea have a metabolic acidosis as a result of stool losses of bicarbonate. In **chloride-losing diarrhea,** an autosomal recessive disorder, there is a defect in the normal intestinal exchange of bicarbonate for chloride, causing excessive stool losses of chloride (see Chapter 338). In addition, stool losses of hydrogen ions and potassium cause metabolic alkalosis and hypokalemia, both of which are exacerbated by increased renal hydrogen and potassium losses from volume depletion. Treatment is with oral supplements of potassium and sodium chloride. Use of a gastric proton pump inhibitor, by decreasing gastric HCl production, reduces both the volume of diarrhea and the need for electrolyte supplementation.

An infant formula with extremely low chloride content has led to chloride deficiency and volume depletion. The infants fed this formula, which is no longer available, had a metabolic alkalosis and hypokalemia. **Cystic fibrosis** can rarely cause metabolic alkalosis, hypokalemia, and hyponatremia because of excessive losses of sodium chloride in sweat (see Chapter 403). The volume depletion causes the metabolic alkalosis and hypokalemia through increased urinary losses, whereas the hyponatremia, a less-common finding, is secondary to sodium loss combined with renal water conservation in an effort to protect the intravascular volume ("appropriate" ADH production).

A **posthypercapnic metabolic alkalosis** occurs after the correction of a chronic respiratory acidosis. This is typically seen in patients with chronic lung disease who are started on mechanical ventilation. During chronic respiratory acidosis, appropriate renal compensation leads to an increase in the serum bicarbonate concentration. This elevated bicarbonate concentration, because it is still present after acute correction of the respiratory acidosis, causes a metabolic alkalosis. The metabolic alkalosis persists because the patient with a chronic respiratory acidosis is intravascularly depleted because of the chloride loss that occurred during the initial metabolic compensation for the primary respiratory acidosis. In addition, many children with a chronic respiratory acidosis receive diuretics, which further decrease the intravascular volume. The metabolic alkalosis responds to correction of the intravascular volume deficit.

The **chloride-resistant** causes of metabolic alkalosis can be subdivided according to blood pressure status. Patients with **hypertension** either have increased aldosterone levels or act as if they do. Aldosterone levels are elevated in children with adrenal adenomas or hyperplasia. Aldosterone causes renal retention of sodium, with resultant hypertension. Metabolic alkalosis and hypokalemia result from aldosterone-mediated renal excretion of hydrogen ions and potassium. The urinary chloride level is not low because these patients are volume-overloaded, not volume-depleted. The volume expansion and hypertension allow normal excretion of sodium and chloride despite the presence of aldosterone. This is known as the mineralocorticoid escape phenomenon.

In **glucocorticoid-remediable aldosteronism,** an autosomal dominant disorder, there is excess production of aldosterone owing to the presence of an aldosterone synthase gene that is regulated by adrenocorticotropic hormone (ACTH) (see Chapter 576.8). Glucocorticoids effectively treat this disorder by inhibiting ACTH production by the pituitary, downregulating the inappropriate aldosterone production. Renovascular disease and renin-secreting tumors both cause excessive renin, leading to an increase in aldosterone, although hypokalemia and metabolic alkalosis are less-common findings than hypertension. In 2 forms of **congenital adrenal hyperplasia,** 11β-hydroxylase deficiency and 17α-hydroxylase deficiency, there is excessive production of the mineralocorticoid 11-deoxycorticosterone (see Chapters 576.2 and 576.4). Hypertension, hypokalemia, and metabolic alkalosis are more likely in 17α-hydroxylase deficiency than in 11β-hydroxylase deficiency. These disorders respond to glucocorticoids because the excess production of 11-deoxycorticosterone is under the control of ACTH.

Cushing syndrome frequently causes hypertension. Cortisol has some mineralocorticoid activity, and high levels can produce hypokalemia and metabolic alkalosis in patients with Cushing syndrome.

Cortisol can bind to the mineralocorticoid receptors in the kidney and function as a mineralocorticoid. This binding normally does not occur because 11β-hydroxysteroid dehydrogenase in the kidney converts cortisol to cortisone, which does not bind to the mineralocorticoid receptor. In 11β-hydroxysteroid dehydrogenase deficiency, also called **apparent mineralocorticoid excess,** cortisol is not converted in the kidney to cortisone. Cortisol is therefore available to bind to the mineralocorticoid receptor in the kidney and act as a mineralocorticoid. Patients with this deficiency, despite low levels of aldosterone, are hypertensive and hypokalemic, and they have a metabolic alkalosis. The same phenomenon can occur with excessive intake of natural licorice, a component of which, glycyrrhizic acid, inhibits 11β-hydroxysteroid dehydrogenase. The autosomal dominant disorder **Liddle syndrome** is secondary to an activating mutation of the sodium channel in the distal nephron (see Chapter 531.3). Upregulation of this sodium channel is one of the principal actions of aldosterone. Because this sodium channel is continuously open, children with Liddle syndrome have the features of hyperaldosteronism, including hypertension, hypokalemia, and metabolic alkalosis, but low serum levels of aldosterone.

Bartter syndrome and **Gitelman syndrome** are autosomal recessive disorders associated with **normal blood pressure,** elevations of urinary chloride, metabolic alkalosis, and hypokalemia (see Chapter 531). In Bartter syndrome, patients have a defect in sodium and chloride resorption in the loop of Henle. This leads to excessive urinary losses of sodium and chloride, and as in patients receiving loop diuretics, volume depletion and secondary hyperaldosteronism occur, causing hypokalemia and metabolic alkalosis. Gitelman syndrome is usually milder than Bartter syndrome. Patients have renal sodium and chloride wasting with volume depletion due mutations in the gene encoding the thiazide-sensitive sodium-chloride transporter in the distal tubule. As in patients receiving a thiazide diuretic, affected patients have volume depletion and secondary hyperaldosteronism with hypokalemia and metabolic alkalosis. Children with Gitelman syndrome have hypocalciuria and hypomagnesemia. Some patients with autosomal dominant hypoparathyroidism have hypokalemia and metabolic alkalosis due to impaired sodium and chloride resorption in the loop of Henle. **EAST syndrome** causes hypokalemia, metabolic alkalosis and hypomagnesemia.

Excessive base intake can cause a metabolic alkalosis. Affected patients do not have a low urine chloride level, unless there is associated volume depletion. In the absence of volume depletion, excess base is rapidly corrected via renal excretion of bicarbonate. Rarely, massive base intake can cause a metabolic alkalosis by overwhelming the kidney's ability to excrete bicarbonate. This may occur in infants who are given baking soda as a "home remedy" for colic or stomach upset. Each teaspoon of baking soda has 42 mEq of sodium bicarbonate. Infants have increased vulnerability because of a lower GFR, limiting the rate of compensatory renal bicarbonate excretion. A metabolic alkalosis may also occur in patients who receive a large amount of sodium bicarbonate during cardiopulmonary resuscitation. Blood products are anticoagulated with citrate, which is converted into bicarbonate by the liver. Patients who receive large amounts of blood products may have a metabolic alkalosis. Iatrogenic metabolic alkalosis can occur as a result of acetate in total parenteral nutrition. Aggressive use of bicarbonate therapy in a child with a lactic acidosis or diabetic ketoacidosis may cause a metabolic alkalosis. This event is especially likely in a patient in whom the underlying cause of the lactic acidosis is successfully corrected (restoration of intravascular volume in a patient with severe dehydration). Once the cause of the lactic acidosis resolves, lactate can be converted by the liver into bicarbonate, which when combined with infused bicarbonate can create a metabolic alkalosis. A similar phenomenon can occur in a child with diabetic ketoacidosis

because the administration of insulin allows keto acids to be metabolized, producing bicarbonate. However, this phenomenon rarely occurs because of judicious use of bicarbonate therapy in diabetic ketoacidosis and because there are usually significant pretreatment losses of keto acids in the urine, preventing massive regeneration of bicarbonate. Base administration is most likely to cause a metabolic alkalosis in patients who have an impaired ability to excrete bicarbonate in the urine. This impairment occurs in patients with concurrent volume depletion or renal insufficiency.

Clinical Manifestations

The symptoms in patients with a metabolic alkalosis are often related to the underlying disease and associated electrolyte disturbances. Children with chloride-responsive causes of metabolic alkalosis often have symptoms related to volume depletion, such as thirst and lethargy. In contrast, children with chloride-unresponsive causes may have symptoms related to hypertension.

Alkalemia causes potassium to shift into the intracellular space, producing a decrease in the extracellular potassium concentration. Alkalemia leads to increased urinary losses of potassium. Increased potassium losses are present in many of the conditions that cause a metabolic alkalosis. Therefore, most patients with a metabolic alkalosis have hypokalemia, and their symptoms may be related to the hypokalemia (see Chapter 55.4).

The symptoms of a metabolic alkalosis are caused by the associated alkalemia. The magnitude of the alkalemia is related to the severity of the metabolic alkalosis and the presence of concurrent respiratory acid–base disturbances. During alkalemia, the ionized calcium concentration decreases as a result of increased binding of calcium to albumin. The decrease in the ionized calcium concentration may cause symptoms of **tetany** (carpopedal spasm).

Arrhythmias are a potential complication of a metabolic alkalosis, and the risk for arrhythmia increases if there is concomitant hypokalemia. Alkalemia increases the risk of digoxin toxicity, and antiarrhythmic medications are less effective in the presence of alkalemia. In addition, alkalemia may decrease cardiac output. A metabolic alkalosis causes a compensatory increase in the P_{CO_2} by decreasing ventilation. In patients with underlying lung disease, the decrease in ventilatory drive can cause hypoxia. In patients with normal lungs, the hypoventilation seen in severe metabolic alkalosis can cause hypoxia.

Diagnosis

Measurement of the urinary chloride concentration is the most helpful test in differentiating among the causes of a metabolic alkalosis. The urine chloride level is low in patients with a metabolic alkalosis resulting from volume depletion, unless there is a defect in renal handling of chloride. The urine chloride level is superior to the urine sodium level in assessment of volume status in patients with a metabolic alkalosis, because the normal renal response to a metabolic alkalosis is to excrete bicarbonate. Because bicarbonate is negatively charged, it can be excreted only with a cation, usually sodium and potassium. Hence, a patient with a metabolic alkalosis may excrete sodium in the urine despite the presence of volume depletion, which normally causes avid sodium retention. *The urine chloride level is usually a good indicator of volume status, and it differentiates among the chloride-resistant and chloride-responsive causes of a metabolic alkalosis.*

Diuretics and gastric losses are the most common causes of metabolic alkalosis and are usually readily apparent from the patient history. Occasionally, metabolic alkalosis, usually with hypokalemia, may be a clue to the presence of bulimia or surreptitious diuretic use (see Chapter 28). Patients with bulimia have a low urine chloride level, indicating that they have volume depletion as a result of an extrarenal etiology, but there is no alternative explanation for their volume depletion. Surreptitious diuretic use may be diagnosed by obtaining a urine toxicology screen for diuretics. The urine chloride level is increased while a patient is using diuretics but is low when the patient stops taking them. Rarely, children with mild Bartter syndrome or Gitelman syndrome are misdiagnosed as having bulimia or abusing diuretics. The urine chloride value is always elevated in Bartter syndrome and Gitelman syndrome, and the urine toxicology screen for diuretics has a negative result. Metabolic alkalosis with hypokalemia is occasionally the initial manifestation of cystic fibrosis. An elevated sweat chloride finding is diagnostic.

Patients with a metabolic alkalosis and a high urinary chloride level are subdivided according to blood pressure status. Children with normal blood pressure may have Bartter syndrome or Gitelman syndrome. Excess base administration is another diagnostic possibility, but it is usually apparent from the history. In patients with sodium bicarbonate ingestion (baking soda), which may be unreported by the parent, the metabolic alkalosis usually occurs with significant hypernatremia. In addition, unless volume depletion is superimposed, the metabolic alkalosis from base ingestion resolves itself once the source of base is eliminated.

Measuring serum concentrations of renin and aldosterone differentiates children with a metabolic alkalosis, a high urinary chloride level, and elevated blood pressure. Both renin and aldosterone are elevated in children with either renovascular disease or a renin-secreting tumor. Aldosterone is high and renin is low in patients with adrenal adenomas or hyperplasia and glucocorticoid-remediable aldosteronism. Renin and aldosterone are low in children with Cushing syndrome, Liddle syndrome, licorice ingestion, 17α-hydroxylase deficiency, 11β-hydroxylase deficiency, and 11β-hydroxysteroid dehydrogenase deficiency. An elevated 24 hr urine cortisol value is diagnostic of Cushing syndrome, which is suspected from the presence of the other classic features of this disease (see Chapter 577). Elevations of 11-deoxycorticosterone values are seen in 17α-hydroxylase deficiency and 11β-hydroxylase deficiency.

Treatment

The approach to treatment of metabolic alkalosis depends on the severity of the alkalosis and the underlying etiology. In children with a mild metabolic alkalosis ($[HCO_3^-] < 32$), intervention is often unnecessary, although this depends on the specific circumstances. In a child with congenital heart disease who is receiving a stable dose of a loop diuretic, a mild alkalosis does not require treatment. In contrast, intervention may be appropriate in a child with a worsening mild metabolic alkalosis because of nasogastric suction. The presence of a concurrent respiratory acid–base disturbance also influences therapeutic decision making. A patient with a concurrent respiratory acidosis should have some increase in bicarbonate owing to metabolic compensation; thus, the severity of the pH elevation is more important than the bicarbonate concentration. In contrast, a patient with a respiratory alkalosis and a metabolic alkalosis is at risk for severe alkalemia; treatment may be indicated, even if the increase in bicarbonate value is only mild.

Intervention is usually necessary in children with moderate or severe metabolic alkalosis. The most effective approach is to address the underlying etiology. In some children, nasogastric suction may be decreased or discontinued. Alternatively, the addition of a gastric proton pump inhibitor reduces gastric secretion and losses of HCl. Diuretics are an important cause of metabolic alkalosis, and if a change is tolerated, they should be eliminated or the dose reduced. Adequate potassium supplementation or the addition of a potassium-sparing diuretic is also helpful in a child with a metabolic alkalosis from diuretics. Potassium-sparing diuretics not only decrease renal potassium losses but, by blocking the action of aldosterone, also decrease hydrogen ion secretion in the distal nephron, increasing urinary bicarbonate excretion. Many children cannot tolerate discontinuation of diuretic therapy; thus, potassium supplementation and potassium-sparing diuretics are the principal therapeutic approach. Arginine HCl may also be used to treat chloride-responsive metabolic acidosis if sodium or potassium salts are not appropriate. Arginine HCl may raise the serum potassium levels during administration. Rarely, in cases of severe metabolic alkalosis, acetazolamide is an option. A carbonic anhydrase inhibitor, acetazolamide decreases resorption of bicarbonate in the proximal tubule, causing significant bicarbonate loss in the urine. The patient receiving this drug must be monitored closely,

because acetazolamide produces major losses of potassium in the urine and increases fluid losses, potentially necessitating a reduction in dosage of other diuretics.

Most children with a metabolic alkalosis have one of the chloride-responsive etiologies. In these situations, administration of sufficient sodium chloride and potassium chloride to correct the volume deficit and the potassium deficit is necessary to correct the metabolic alkalosis. This approach may not be an option in the child who has volume depletion due to diuretics, because volume repletion may be contraindicated. Adequate replacement of gastric losses of sodium and potassium in a child with a nasogastric tube can minimize or prevent the development of the metabolic alkalosis. With adequate intravascular volume and a normal serum potassium concentration, the kidney is able to excrete the excess bicarbonate within a couple of days.

In children with the chloride-resistant causes of a metabolic alkalosis that are associated with hypertension, volume repletion is contraindicated because it would exacerbate the hypertension and would not repair the metabolic alkalosis. Ideally, treatment focuses on eliminating the excess aldosterone effect. Adrenal adenomas can be resected, licorice intake can be eliminated, and renovascular disease can be repaired. Glucocorticoid-remediable aldosteronism, 17α-hydroxylase deficiency, and 11β-hydroxylase deficiency respond to the administration of glucocorticoids. The mineralocorticoid effect of cortisol in 11β-hydroxysteroid dehydrogenase deficiency can be decreased with the use of spironolactone, which blocks the mineralocorticoid receptor. In contrast, the metabolic alkalosis in children with Liddle syndrome does not respond to spironolactone; however, either triamterene or amiloride is effective therapy because both agents block the sodium channel that is constitutively active in Liddle syndrome.

In children with Bartter syndrome and Gitelman syndrome, therapy includes oral potassium supplementation and potassium-sparing diuretics. Children with Gitelman syndrome often require magnesium supplementation, whereas children with severe Bartter syndrome often benefit from indomethacin.

RESPIRATORY ACIDOSIS

A respiratory acidosis is an inappropriate increase in blood CO_2 (P_{CO_2}). Carbon dioxide is a byproduct of metabolism, and it is removed from the body by the lungs. During a respiratory acidosis, there is a decrease in the effectiveness of CO_2 removal by the lungs. A respiratory acidosis is secondary to either pulmonary disease, such as severe bronchiolitis, or nonpulmonary disease, such as a narcotic overdose. Even though body production of CO_2 can vary, normal lungs are able to accommodate this variation; excess production of CO_2 is not an isolated cause of a respiratory acidosis. With impairment of alveolar ventilation, the rate of body production of CO_2 may affect the severity of the respiratory acidosis, but this is usually not a significant factor.

A respiratory acidosis causes a decrease in the blood pH, but there is normally a metabolic response that partially compensates, minimizing the severity of the acidemia. The acute metabolic response to a respiratory alkalosis occurs within minutes. The metabolic compensation for an acute respiratory acidosis is secondary to titration of acid by nonbicarbonate buffers. This buffering of hydrogen ions causes a predictable increase in the serum bicarbonate concentration: Plasma bicarbonate increases by 1 for each 10 mm Hg increase in the P_{CO_2} (acute compensation).

With a chronic respiratory acidosis, there is more significant metabolic compensation and, thus, less severe acidemia than in an acute respiratory acidosis with the same increase in P_{CO_2}. During a chronic respiratory acidosis, the kidneys increase acid excretion. This response occurs over 3-4 days and causes a predictable increase in the serum bicarbonate concentration: Plasma bicarbonate increases by 3.5 for each 10 mm Hg increase in the P_{CO_2} (chronic compensation).

The increase of serum bicarbonate concentration during a chronic respiratory acidosis is associated with a decrease in body chloride. After acute correction of a chronic respiratory acidosis, the plasma bicarbonate continues to be increased, and the patient has a metabolic alkalosis. Because of the chloride deficit, this is a chloride-responsive metabolic alkalosis; it corrects once the patient's chloride deficit is replaced.

A mixed disorder is present if the metabolic compensation is inappropriate. A higher-than-expected bicarbonate value occurs in the setting of a concurrent metabolic alkalosis, and a lower-than-expected bicarbonate value occurs in the setting of a concurrent metabolic acidosis. Evaluating whether compensation is appropriate during a respiratory acidosis requires clinical knowledge of the acuity of the process, because the expected compensation is different, depending on whether the process is acute or chronic.

The P_{CO_2} cannot be interpreted in isolation to determine whether a patient has a respiratory acidosis. A respiratory acidosis is always present if a patient has acidemia and an elevated P_{CO_2}. However, an elevated P_{CO_2} also occurs as appropriate respiratory compensation for a simple metabolic alkalosis. The patient is alkalemic; this is not a respiratory acidosis. During a mixed disturbance, a patient can have a respiratory acidosis and a normal or even low P_{CO_2}. This condition may occur in a patient with a metabolic acidosis; a respiratory acidosis is present if the patient does not have appropriate respiratory compensation (the P_{CO_2} is higher than expected from the severity of the metabolic acidosis).

Etiology and Pathophysiology

The causes of a respiratory acidosis are either pulmonary or nonpulmonary (Table 55-15). CNS disorders can decrease the activity of the central respiratory center, reducing ventilatory drive. A variety of medications and illicit drugs suppress the respiratory center. The signals from the respiratory center need to be transmitted to the respiratory muscles via the nervous system. Respiratory muscle failure can be secondary to disruption of the signal from the CNS in the spinal cord, the phrenic nerve, or the neuromuscular junction. Disorders directly affecting the muscles of respiration can prevent adequate ventilation, causing a respiratory acidosis.

Mild or moderate lung disease often causes a respiratory alkalosis as a result of hyperventilation secondary to hypoxia or stimulation of lung mechanoreceptors or chemoreceptors. Only more severe lung disease causes a respiratory acidosis. Upper airway diseases, by impairing air entry into the lungs, may decrease ventilation, producing a respiratory acidosis.

Increased production of CO_2 is never the sole cause of a respiratory acidosis, but it can increase the severity of the disease in a patient with decreased ventilation of CO_2. Increased production of CO_2 occurs in patients with fever, hyperthyroidism, excess caloric intake, and high levels of physical activity. Increased respiratory muscle work also increases CO_2 production.

Clinical Manifestations

Patients with a respiratory acidosis are often tachypneic in an effort to correct the inadequate ventilation. Exceptions include patients with a respiratory acidosis resulting from CNS depression and patients who are on the verge of complete respiratory failure secondary to fatigue of the respiratory muscles.

The symptoms of respiratory acidosis are related to the severity of the hypercarbia. Acute respiratory acidosis is usually more symptomatic than chronic respiratory acidosis. Symptoms are also increased by concurrent hypoxia or metabolic acidosis. In a patient breathing room air, hypoxia is always present if a respiratory acidosis is present. The potential CNS manifestations of respiratory acidosis include anxiety, dizziness, headache, confusion, asterixis, myoclonic jerks, hallucinations, psychosis, coma, and seizures.

Acidemia, no matter the etiology, affects the cardiovascular system. An arterial pH <7.2 impairs cardiac contractility and the normal response to catecholamines, in both the heart and the peripheral vasculature. Hypercapnia causes vasodilation, most dramatically in the cerebral vasculature, but hypercapnia produces vasoconstriction of the pulmonary circulation. Respiratory acidosis increases the risk of cardiac arrhythmias, especially in a child with underlying cardiac disease.

Table 55-15 Causes of Respiratory Acidosis

CENTRAL NERVOUS SYSTEM DEPRESSION
Encephalitis
Head trauma
Brain tumor
Central sleep apnea
Primary pulmonary hypoventilation (Ondine curse)
Stroke
Hypoxic brain damage
Obesity-hypoventilation (Pickwickian syndrome)
Increased intracranial pressure
Medications
Narcotics
Barbiturates
Anesthesia
Benzodiazepines
Propofol
Alcohols
DISORDERS OF THE SPINAL CORD, PERIPHERAL NERVES, OR NEUROMUSCULAR JUNCTION
Diaphragmatic paralysis
Guillain-Barré syndrome
Poliomyelitis
Spinal muscular atrophies
Tick paralysis
Botulism
Myasthenia
Multiple sclerosis
Spinal cord injury
Medications
Vecuronium
Aminoglycosides
Organophosphates (pesticides)
RESPIRATORY MUSCLE WEAKNESS
Muscular dystrophy
Hypothyroidism
Malnutrition
Hypokalemia
Hypophosphatemia
Medications
Succinylcholine
Corticosteroids
PULMONARY DISEASE
Pneumonia
Pneumothorax
Asthma
Bronchiolitis
Pulmonary edema
Pulmonary hemorrhage
Acute respiratory distress syndrome
Neonatal respiratory distress syndrome
Cystic fibrosis
Bronchopulmonary dysplasia
Hypoplastic lungs
Meconium aspiration
Pulmonary thromboembolus
Interstitial fibrosis
UPPER AIRWAY DISEASE
Aspiration
Laryngospasm
Angioedema
Obstructive sleep apnea
Tonsillar hypertrophy
Vocal cord paralysis
Extrinsic tumor
Extrinsic or intrinsic hemangioma
MISCELLANEOUS
Flail chest
Cardiac arrest
Kyphoscoliosis
Decreased diaphragmatic movement due to ascites or peritoneal dialysis

Diagnosis

The history and physical findings often point to a clear etiology. For the obtunded patient with poor respiratory effort, evaluation of the CNS is often indicated. This may include imaging studies (CT or MRI) and, potentially, a lumbar puncture for cerebrospinal fluid analysis. A toxicology screen for illicit drugs may also be appropriate. A response to naloxone is both diagnostic and therapeutic. In many of the diseases affecting the respiratory muscles, there is evidence of weakness in other muscles. Stridor is a clue that the child may have upper airway disease. Along with a physical examination, a chest radiograph is often helpful in diagnosing pulmonary disease.

In many patients, respiratory acidosis may be multifactorial. A child with bronchopulmonary dysplasia, an intrinsic lung disease, may worsen because of respiratory muscle dysfunction caused by severe hypokalemia resulting from long-term diuretic therapy. Conversely, a child with muscular dystrophy, a muscle disease, may worsen because of aspiration pneumonia.

For a patient with respiratory acidosis, calculation of the gradient between the alveolar oxygen concentration and the arterial oxygen concentration, the A-a O_2 gradient, is useful for distinguishing between poor respiratory effort and intrinsic lung disease. The A-a O_2 gradient is increased if the hypoxemia is caused by intrinsic lung disease (see Chapter 373).

Treatment

Respiratory acidosis is best managed by treatment of the underlying etiology. In some instances, the response is very rapid, such as after the administration of naloxone to a patient with a narcotic overdose. In contrast, in the child with pneumonia, a number of days of antibiotic therapy may be required before the respiratory status improves. In many children with a chronic respiratory acidosis, there is no curative therapy, although an acute respiratory illness superimposed on a chronic respiratory condition is usually reversible.

All patients with an acute respiratory acidosis are hypoxic, and therefore need to receive supplemental oxygen. Mechanical ventilation is necessary in some children with a respiratory acidosis. Children with a significant respiratory acidosis caused by a CNS disease usually require mechanical ventilation because such a disorder is unlikely to respond quickly to therapy. In addition, hypercarbia causes cerebral vasodilation, and the increase in intracranial pressure can be dangerous in a child with an underlying CNS disease. Readily reversible CNS depression, such as from a narcotic overdose, may not require mechanical ventilation. Decisions on mechanical ventilation for other patients depend on a number of factors. Patients with severe hypercarbia—P_{CO_2} >75 mm Hg—usually require mechanical ventilation (see Chapter 71). The threshold for intubation is lower if there is concomitant metabolic acidosis, a slowly responsive underlying disease, or hypoxia that responds poorly to oxygen, or if the patient appears to be tiring and respiratory arrest seems likely.

In patients with a chronic respiratory acidosis, the respiratory drive is often less responsive to hypercarbia and more responsive to hypoxia. Hence, with chronic respiratory acidosis, excessive use of oxygen can blunt the respiratory drive and therefore increase the P_{CO_2}. In these patients, oxygen must be used cautiously.

When possible, it is best to avoid mechanical ventilation in a patient with a chronic respiratory acidosis because extubation is often difficult. However, an acute illness may necessitate mechanical ventilation in a child with a chronic respiratory acidosis. When intubation is necessary, the P_{CO_2} should be lowered only to the patient's normal baseline, and this should be done gradually. These patients normally have an elevated serum bicarbonate concentration as a result of metabolic compensation for their respiratory acidosis. A rapid lowering of the P_{CO_2} can cause a severe metabolic alkalosis, potentially leading to complications, including cardiac arrhythmias, decreased cardiac output, and decreased cerebral blood flow. In addition, prolonged mechanical ventilation at a normal P_{CO_2} causes the metabolic compensation to resolve. When the patient is subsequently extubated, the patient will no longer benefit from metabolic compensation, causing a more severe acidemia because of the respiratory acidosis.

RESPIRATORY ALKALOSIS

A respiratory alkalosis is an inappropriate reduction in the blood CO_2 concentration. This is usually secondary to hyperventilation, initially causing removal of CO_2 to surpass production. Eventually, a new steady state is achieved, with removal equaling production, albeit at a lower CO_2 tension (P_{CO_2}). A respiratory alkalosis that is not the result of hyperventilation may occur in children receiving extracorporeal membrane oxygenation or hemodialysis, with CO_2 lost directly from the blood in the extracorporeal circuit.

With a simple respiratory alkalosis, the pH increases but there is a normal metabolic response that attenuates some of the change in the blood pH. A metabolic response to an acute respiratory alkalosis occurs within minutes, mediated by hydrogen ion release from nonbicarbonate buffers. The metabolic response to an acute respiratory alkalosis is predictable: Plasma bicarbonate falls by 2 for each 10 mm Hg decrease in the P_{CO_2} (acute compensation).

A chronic respiratory alkalosis leads to more significant metabolic compensation because of the actions of the kidneys, which decrease acid secretion, producing a decrease in the serum bicarbonate concentration. Both the proximal and distal tubules decrease acid secretion. Metabolic compensation for a respiratory alkalosis develops gradually and takes 2-3 days to produce the full effect: Plasma bicarbonate falls by 4 for each 10 mm Hg decrease in the P_{CO_2} (chronic compensation).

A chronic respiratory alkalosis is the only acid–base disturbance wherein appropriate compensation may normalize the pH, albeit >7.4.

A mixed disorder is present if the metabolic compensation is inappropriate. A higher than expected bicarbonate level occurs in the setting of a concurrent metabolic alkalosis, and a lower than expected bicarbonate level occurs in the setting of a concurrent metabolic acidosis. Evaluating whether compensation is appropriate during a respiratory alkalosis requires clinical knowledge of the acuity of the process, because the expected compensation differs according to whether the process is acute or chronic.

A low P_{CO_2} value does not always indicate a respiratory alkalosis. The P_{CO_2} also decreases as part of the appropriate respiratory compensation for a metabolic acidosis; this is not a respiratory alkalosis. A metabolic acidosis is the dominant acid–base disturbance in a patient with acidemia and a low P_{CO_2}, even though there could still be a concurrent respiratory alkalosis. In contrast, a respiratory alkalosis is always present in a patient with alkalemia and a low P_{CO_2}. Even a normal P_{CO_2} value may be consistent with a respiratory alkalosis in a patient with a metabolic alkalosis because an elevated P_{CO_2} is expected as part of appropriate respiratory compensation for the metabolic alkalosis.

Table 55-16 Causes of Respiratory Alkalosis
HYPOXEMIA OR TISSUE HYPOXIA
Pneumonia
Pulmonary edema
Cyanotic heart disease
Congestive heart failure
Asthma
Severe anemia
High altitude
Laryngospasm
Aspiration
Carbon monoxide poisoning
Pulmonary embolism
Interstitial lung disease
Hypotension
LUNG RECEPTOR STIMULATION
Pneumonia
Pulmonary edema
Asthma
Pulmonary embolism
Hemothorax
Pneumothorax
Respiratory distress syndrome (adult or infant)
CENTRAL STIMULATION
Central nervous system disease
Subarachnoid hemorrhage
Encephalitis or meningitis
Trauma
Brain tumor
Stroke
Fever
Pain
Anxiety (panic attack)
Psychogenic hyperventilation or anxiety
Liver failure
Sepsis
Pregnancy
Mechanical ventilation
Hyperammonemia
Extracorporeal membrane oxygenation or hemodialysis
Medications
Salicylate intoxication
Theophylline
Progesterone
Exogenous catecholamines
Caffeine

Etiology and Pathophysiology

A variety of stimuli can increase the ventilatory drive and cause a respiratory alkalosis (Table 55-16). Arterial hypoxemia or tissue hypoxia stimulates peripheral chemoreceptors to signal the central respiratory center in the medulla to increase ventilation. The resultant greater respiratory effort increases the oxygen content of the blood but depresses the P_{CO_2}. The effect of hypoxemia on ventilation begins when the oxygen saturation decreases to approximately 90% (P_{O_2} = 60 mm Hg), and hyperventilation increases as hypoxemia worsens. Acute hypoxia is a more potent stimulus for hyperventilation than chronic hypoxia; thus, chronic hypoxia, as occurs in cyanotic heart disease, causes a much-less-severe respiratory alkalosis than an equivalent degree of acute hypoxia. There are many causes of hypoxemia or tissue hypoxia, including primary lung disease, severe anemia, and carbon monoxide poisoning.

The lungs contain chemoreceptors and mechanoreceptors that respond to irritants and stretching and send signals to the respiratory center to increase ventilation. Aspiration or pneumonia may stimulate the chemoreceptors, whereas pulmonary edema may stimulate the mechanoreceptors. Most of the diseases that activate these receptors may also cause hypoxemia and can, therefore, potentially lead to hyperventilation via 2 mechanisms. Patients with primary lung disease may initially have a respiratory alkalosis, but worsening of the disease, combined with respiratory muscle fatigue, often causes respiratory failure and the development of a respiratory acidosis.

Hyperventilation in the absence of lung disease occurs with direct stimulation of the central respiratory center. This occurs with CNS diseases, such as meningitis, hemorrhage, and trauma. Central hyperventilation due to lesions, such as infarcts or tumors near the central respiratory center in the midbrain, increases the rate and depth of the respiratory effort. This respiratory pattern portends a poor prognosis because these midbrain lesions are frequently fatal. Systemic processes may cause centrally mediated hyperventilation. Although the exact mechanisms are not clear, liver disease causes a respiratory alkalosis that is usually proportional to the degree of liver failure. Pregnancy causes a chronic respiratory alkalosis, probably mediated by progesterone acting on the respiratory centers. Salicylates, although often causing a concurrent metabolic acidosis, directly stimulate the respiratory center to produce a respiratory alkalosis. The respiratory alkalosis during sepsis is probably due to cytokine release.

Hyperventilation may be secondary to an underlying disease that causes pain, stress, or anxiety. In psychogenic hyperventilation or in panic attacks, there is no disease process accounting for the hyperventilation. This disorder may occur in a child who has had an emotionally stressful experience. Alternatively, it may be part of a panic disorder,

especially if there are repeated episodes of hyperventilation. In such a patient, the symptoms of acute alkalemia increase anxiety, potentially perpetuating the hyperventilation.

A respiratory alkalosis is quite common in children receiving mechanical ventilation because the respiratory center is not controlling ventilation. In addition, these children may have a decreased metabolic rate and hence less CO_2 production because of sedation and paralytic medications. Normally, decreased CO_2 production and the resultant hypocapnia decrease ventilation, but this physiologic response cannot occur in a child who cannot reduce ventilatory effort.

Clinical Manifestations

The disease process that is causing the respiratory alkalosis is usually more concerning than the clinical manifestations of the respiratory alkalosis. Chronic respiratory alkalosis is usually asymptomatic because metabolic compensation decreases the magnitude of the alkalemia.

Acute respiratory alkalosis may cause chest tightness, palpitations, lightheadedness, circumoral numbness, and paresthesias of the extremities. Less-common manifestations include tetany, seizures, muscle cramps, and syncope. The lightheadedness and syncope are probably a result of the reduction in cerebral blood flow that is caused by hypocapnia. The reduction in cerebral blood flow is the rationale for using hyperventilation to treat children with increased intracranial pressure. The paresthesias, tetany, and seizures may be partially related to the reduction in ionized calcium that occurs because alkalemia causes more calcium to bind to albumin. A respiratory alkalosis also causes a mild reduction in the serum potassium level. Patients with psychogenic hyperventilation tend to be most symptomatic as a result of the respiratory alkalosis, and these symptoms, along with a sensation of breathlessness, exacerbate the hyperventilation.

Diagnosis

In many patients, hyperventilation producing a respiratory alkalosis is not clinically detectable, even with careful observation of the patient's respiratory effort. Metabolic compensation for a respiratory alkalosis causes a low serum bicarbonate concentration. When hyperventilation is not appreciated and only serum electrolytes are evaluated, there is often a presumptive diagnosis of a metabolic acidosis. If a respiratory alkalosis is suspected, only a blood gas determination can make the diagnosis.

Hyperventilation does not always indicate a primary respiratory disorder. In some patients, the hyperventilation is appropriate respiratory compensation for a metabolic acidosis. With a primary metabolic acidosis, acidemia is present and the serum bicarbonate level is usually quite low if there is clinically detectable hyperventilation. In contrast, the serum bicarbonate level never goes below 17 mEq/L as part of the metabolic compensation for acute respiratory alkalosis, and simple acute respiratory alkalosis causes alkalemia.

The etiology of a respiratory alkalosis is often apparent from the physical examination or history, and it may consist of lung disease, neurologic disease, or cyanotic heart disease. Hypoxemia is a common cause of hyperventilation, and it is important to diagnose because it suggests a significant underlying disease that requires expeditious treatment. Hypoxemia may be detected on physical examination (cyanosis) or by pulse oximetry. However, normal pulse oximetry values do not completely eliminate hypoxemia as the etiology of the hyperventilation. There are 2 reasons why pulse oximetry is not adequate for eliminating hypoxemia as a cause of a respiratory alkalosis. First, pulse oximetry is not very sensitive at detecting a mildly low arterial partial pressure of oxygen (pO_2). Second, the hyperventilation during a respiratory alkalosis causes the pO_2 to increase, possibly to a level that is not identified as abnormal by pulse oximetry. Only an arterial blood gas measurement can completely eliminate hypoxia as an explanation for a respiratory alkalosis. Along with hypoxemia, it is important to consider processes that cause **tissue hypoxia without necessarily causing hypoxemia**. Examples are carbon monoxide poisoning, severe anemia, and heart failure.

Lung disease without hypoxemia may cause hyperventilation. Although lung disease is often apparent by history or physical examination, a chest radiograph may detect more subtle disease. The patient with a pulmonary embolism may have benign chest radiograph findings, normal pO_2, and isolated respiratory alkalosis, although hypoxia may eventually occur. Diagnosis of a pulmonary embolism requires a high index of suspicion and should be considered in children without another explanation for respiratory alkalosis, especially if risk factors are present, such as prolonged bed rest and a hypercoagulable state (e.g., nephrotic syndrome or lupus anticoagulant).

Treatment

There is seldom a need for specific treatment of respiratory alkalosis. Rather, treatment focuses on the underlying disease. Mechanical ventilator settings are adjusted to correct iatrogenic respiratory alkalosis, unless the hyperventilation has a therapeutic purpose (e.g., treatment of increased intracranial pressure).

For the patient with hyperventilation secondary to anxiety, efforts should be undertaken to reassure the child, usually enlisting the parents. Along with reassurance, patients with psychogenic hyperventilation may benefit from benzodiazepines. During an acute episode of psychogenic hyperventilation, rebreathing into a paper bag increases the patient's Pco_2. Using a paper bag, instead of a plastic bag, allows adequate oxygenation but permits the CO_2 concentration in the bag to increase. The resultant increase in the patient's Pco_2 decreases the symptoms of the respiratory alkalosis that tend to perpetuate the hyperventilation. Rebreathing should be performed only once other causes of hyperventilation have been eliminated; pulse oximetry during the rebreathing is prudent.

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Chapter 56

Maintenance and Replacement Therapy

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Maintenance intravenous fluids are used in a child who cannot be fed enterally. Along with maintenance fluids, children may require concurrent **replacement fluids** if they have continued excessive losses, such as may occur with drainage from a nasogastric (NG) tube or with high urine output because of nephrogenic diabetes insipidus. If dehydration is present, the patient also needs to receive **deficit** replacement (see Chapter 57). A child awaiting surgery may need only maintenance fluids, whereas a child with diarrheal dehydration needs maintenance and deficit therapy and also may require replacement fluids if significant diarrhea continues.

MAINTENANCE THERAPY

Children normally have large variations in their daily intake of water and electrolytes. The only exceptions are patients who receive fixed dietary regimens orally, via a gastric tube, or as intravenous total parenteral nutrition (TPN). Healthy children can tolerate significant variations in intake because of the many homeostatic mechanisms that can adjust absorption and excretion of water and electrolytes (see Chapter 55). The calculated water and electrolyte needs that form the basis of maintenance therapy are not absolute requirements. Rather, these calculations provide reasonable guidelines for a starting point to estimate intravenous therapy. Children do not need to be started on intravenous fluids simply because their intake is being monitored in a hospital and they are not taking "maintenance fluids" orally, unless there is a pathologic process present that necessitates high fluid intake.

Table 56-1	Goals of Maintenance Fluids
Prevent dehydration Prevent electrolyte disorders Prevent ketoacidosis Prevent protein degradation	

Maintenance fluids are most commonly necessary in preoperative and postoperative surgical patients; many nonsurgical patients also require maintenance fluids. It is important to recognize when it is necessary to begin maintenance fluids. A normal teenager who is given nothing by mouth (NPO) overnight for a morning procedure does not require maintenance fluids because a healthy adolescent can easily tolerate 12 or 18 hr without oral intake. In contrast, a 6 mo old child waiting for surgery should begin receiving intravenous fluids within 8 hr of the last feeding. Infants become dehydrated more quickly than older patients. A child with obligatory high urine output from nephrogenic diabetes insipidus should begin receiving intravenous fluids soon after being classified as NPO.

Maintenance fluids are composed of a solution of water, glucose, sodium, and potassium. This solution has the advantages of simplicity, long shelf life, low cost, and compatibility with peripheral intravenous administration. Such a solution accomplishes the major objectives of maintenance fluids (Table 56-1). Patients lose water, sodium, and potassium in their urine and stool; water is also lost from the skin and lungs. Maintenance fluids replace these losses, thereby avoiding the development of dehydration and deficiency of sodium or potassium.

The glucose in maintenance fluids provides approximately 20% of the normal caloric needs of the patient, prevents the development of starvation ketoacidosis, and diminishes the protein degradation that would occur if the patient received no calories. Glucose also provides added osmoles, thus avoiding the administration of hypotonic fluids that may cause hemolysis.

Maintenance fluids do not provide adequate calories, protein, fat, minerals, or vitamins. This fact is typically not problematic for a patient receiving intravenous fluids for a few days. A patient receiving maintenance intravenous fluids is receiving inadequate calories and will lose 0.5-1% of weight each day. It is imperative that patients not remain on maintenance therapy indefinitely; TPN should be used for children who cannot be fed enterally for more than a few days, especially patients with underlying malnutrition.

Prototypical maintenance fluid therapy does not provide electrolytes such as calcium, phosphorus, magnesium, and bicarbonate. For most patients, this lack is not problematic for a few days, although there are patients who will not tolerate this omission, usually because of excessive losses. A child with renal tubular acidosis wastes bicarbonate in urine. Such a patient will rapidly become acidemic unless bicarbonate (or acetate) is added to the maintenance fluids. It is important to remember the limitations of maintenance fluid therapy.

MAINTENANCE WATER

Water is a crucial component of maintenance fluid therapy because of the obligatory daily water losses. These losses are both measurable (urine, stool) and not measurable (insensible losses from the skin and lungs). Failure to replace these losses leads to a child who is thirsty, uncomfortable, and, ultimately, dehydrated.

The goal of maintenance water is to provide enough water to replace these losses. Although urinary losses are approximately 60% of the total, the normal kidney has the ability to markedly modify water losses, with daily urine volume potentially varying by more than a factor of 20. Maintenance water is designed to provide enough water so that the kidney does not need to significantly dilute or concentrate the urine. It also provides a margin of safety, so that normal homeostatic mechanisms can adjust urinary water losses to prevent overhydration and dehydration. This adaptability obviates the need for absolute precision in determining water requirements. This fact is important, given the absence of absolute accuracy in the formulas for calculation of water needs. Table 56-2 provides a system for calculating maintenance water on the basis of the patient's weight and emphasizes the high water needs of smaller, less-mature patients. This approach is reliable, although calculations based on weight do overestimate the water needs of an overweight child, in whom it is better to base the calculations on the lean body weight, which can be estimated by using the 50th percentile of body weight for the child's height. It is also important to remember that there is an upper limit of 2.4 L/24 hr in adult-sized patients. Intravenous fluids are written as an hourly rate. The formulas in Table 56-3 enable rapid calculation of the rate of maintenance fluids.

Table 56-2 Body Weight Method for Calculating Daily Maintenance Fluid Volume

BODY WEIGHT	FLUID PER DAY
0-10 kg	100 mL/kg
11-20 kg	1,000 mL + 50 mL/kg for each kg >10 kg
>20 kg	1,500 mL + 20 mL/kg for each kg >20 kg*

*The maximum total fluid per day is normally 2,400 mL.

Table 56-3	Hourly Maintenance Water Rate
For body weight of 0-10 kg: 4 mL/kg/hr For body weight of 10-20 kg: 40 mL/hr + 2 mL/kg/hr × (wt − 10 kg) For body weight of >20 kg: 60 mL/hr + 1 mL/kg/hr × (wt − 20 kg)*	

*The maximum fluid rate is normally 100 mL/hr.

Table 56-4 Composition of Intravenous Solutions

FLUID	[Na]	[Cl⁻]	[K⁺]	[Ca²⁺]	[LACTATE−]
Normal saline (0.9% NaCl)	154	154	—	—	—
Half-normal saline (0.45% NaCl)	77	77	—	—	—
0.2 normal saline (0.2% NaCl)	34	34	—	—	—
Ringer lactate	130	109	4	3	28

INTRAVENOUS SOLUTIONS

The components of the commonly available solutions are shown in Table 56-4. Normal saline (NS) and Ringer lactate (LR) are isotonic solutions; they have approximately the same tonicity as plasma. Isotonic fluids without glucose are used for the acute correction of intravascular volume depletion (see Chapter 57). *The usual choices for maintenance fluid therapy in children are half-normal saline (1/2 NS) and NS.* These solutions are available with 5% dextrose (D5) or without dextrose. In addition, they are available with 20 mEq/L of potassium chloride, 10 mEq/L of potassium chloride, or no potassium. A hospital pharmacy can also prepare custom-made solutions with different concentrations of sodium or potassium. In addition, other electrolytes, such as calcium, magnesium, phosphate, acetate, and bicarbonate, can be added to intravenous solutions. Custom-made solutions take time to prepare and are much more expensive than commercial solutions. The use of custom-made solutions is necessary only for patients who have underlying disorders that cause significant electrolyte imbalances. The use of commercial solutions saves time and expense.

A normal plasma osmolality is 285-295 mOsm/kg. Infusing an intravenous solution peripherally with a much lower osmolality can cause water to move into red blood cells, leading to hemolysis. Thus, intravenous fluids are generally designed to have an osmolality that is either close to 285 or greater (fluids with moderately higher osmolality do not cause problems). Thus, 0.2NS (osmolality = 68) should not be

administered peripherally, but D5 0.2NS (osmolality = 346) or D5 ½ NS + 20 mEq/L KCl (osmolality = 472) can be administered.

There is controversy about the appropriate sodium content of maintenance fluids, considering the observation that hypotonic fluids may cause hyponatremia, which may have serious sequelae. Hypotonic fluids seem more physiologic given the low sodium content of breast milk and formula. However, hospitalized children often have impaired water excretion, either as a result of volume depletion or of nonosmotic stimuli for antidiuretic hormone (ADH) production (respiratory disease, central nervous system disease, stress, pain, nausea, medications such as narcotics). Hypotonic fluids increase the risk of hyponatremia; *0.2NS is no longer recommended as a standard maintenance fluid and its use is restricted at many hospitals.*

GLUCOSE

Maintenance fluids usually contain D5, which provides 17 calories/100 mL and nearly 20% of the daily caloric needs. This level is enough to prevent ketone production and helps minimize protein degradation, but the child will lose weight on this regimen. The weight loss is the principal reason why a patient needs to be started on TPN after a few days of maintenance fluids if enteral feedings are still not possible. Maintenance fluids are also lacking in such crucial nutrients as protein, fat, vitamins, and minerals.

SELECTION OF MAINTENANCE FLUIDS

D5 ½NS + 20 mEq/L KCl is recommended in the child who is NPO and does not have volume depletion or risk factors for nonosmotic ADH production. Children with volume depletion, baseline hyponatremia, or at risk for nonosmotic ADH production (lung infections such as bronchiolitis or pneumonia; central nervous system infection) should receive D5 NS + 20 mEq/L KCl. Surgical patients typically receive isotonic fluids (NS, LR) during surgery and in the recovery room for 6-8 hr postoperatively; the rate is typically approximately two-thirds of the calculated maintenance rate, with dextrose added if clinically indicated. Subsequent maintenance fluids should be D5 NS or LR, with addition of 10-20 mEq/L of KCl based on the serum potassium and the clinical setting. Electrolytes should be measured at least daily in all children receiving more than 50% of maintenance fluids intravenously unless the child is receiving prolonged intravenous fluids (TPN).

These guidelines assume that there is no disease process present that would require an adjustment in either the volume or the electrolyte composition of maintenance fluids. Neonates, and especially premature infants, are outside of the scope of these guidelines given their unique physiology. Children with renal insufficiency may be hyperkalemic or unable to excrete potassium and may not tolerate 10 or 20 mEq/L of potassium. Patients with persistent ADH production because of an underlying disease process (syndrome of inappropriate ADH secretion, congestive heart failure, nephrotic syndrome, liver disease) should receive less than maintenance fluids. Children with meningitis are fluid restricted unless intravascular volume depletion is present (see Chapter 603.1). Treatment is individualized, and careful monitoring is critical.

In children with complicated pathophysiologic derangements, it may be necessary to empirically adjust the electrolyte composition and rate of maintenance fluids on the basis of electrolyte measurements and assessment of fluid balance. **In all children, it is critical to carefully monitor weight, urine output, and electrolytes to identify overhydration or underhydration, hyponatremia, and other electrolyte disturbances, and to then adjust the rate or composition of the intravenous solution accordingly.**

VARIATIONS IN MAINTENANCE WATER AND ELECTROLYTES

The calculation of maintenance water is based on standard assumptions regarding water losses. There are patients, however, in whom these assumptions are incorrect. To identify such situations, it is helpful to understand the source and magnitude of normal water losses. Table 56-5 lists the 3 sources of normal water loss.

Table 56-5 Sources of Water Loss

Urine: 60%
Insensible losses: ≈35% (skin and lungs)
Stool: 5%

Table 56-6 Adjustments in Maintenance Water

SOURCE	CAUSES OF INCREASED WATER NEEDS	CAUSES OF DECREASED WATER NEEDS
Skin	Radiant warmer Phototherapy Fever Sweat Burns	Incubator (premature infant)
Lungs	Tachypnea Tracheostomy	Humidified ventilator
Gastrointestinal tract	Diarrhea Emesis Nasogastric suction	—
Renal	Polyuria	Oliguria/anuria
Miscellaneous	Surgical drain Third spacing	Hypothyroidism

Urine is the most important contributor to normal water loss. Insensible losses represent approximately one-third of total maintenance water (40% in infants and closer to 25% in adolescents and adults). Insensible losses are composed of evaporative losses from the skin and lungs that cannot be quantitated. The evaporative losses from the skin do not include sweat, which would be considered an additional (sensible) source of water loss. Stool normally represents a minor source of water loss.

Maintenance water and electrolyte needs may be increased or decreased, depending on the clinical situation. This may be obvious, in the case of the infant with profuse diarrhea, or subtle, in the case of the patient who has decreased insensible losses while receiving mechanical ventilation. It is helpful to consider the sources of normal water and electrolyte losses and to determine whether any of these sources is being modified in a specific patient. It is then necessary to adjust maintenance water and electrolyte calculations.

Table 56-6 lists a variety of clinical situations that modify normal water and electrolyte losses. The skin can be a source of very significant water loss, particularly in neonates, especially premature infants, who are under radiant warmers or are receiving phototherapy. Very-low-birthweight infants can have insensible losses of 100-200 mL/kg/24 hr. Burns can result in massive losses of water and electrolytes, and there are specific guidelines for fluid management in children with burns (see Chapter 75). Sweat losses of water and electrolytes, especially in a warm climate, can also be significant. Children with cystic fibrosis have increased sodium losses from the skin. Some children with pseudohypoaldosteronism also have increased cutaneous salt losses.

Fever increases evaporative losses from the skin. These losses are somewhat predictable, leading to a 10-15% increase in maintenance water needs for each 1°C (1.8°F) increase in temperature above 38°C (100.4°F). These guidelines are for a patient with a persistent fever; a 1 hr fever spike does not cause an appreciable increase in water needs.

Tachypnea or a tracheostomy increases evaporative losses from the lungs. A humidified ventilator causes a decrease in insensible losses from the lungs and can even lead to water absorption via the lungs; a ventilated patient has a decrease in maintenance water requirements. It may be difficult to quantify the changes that take place in the individual patient in these situations.

REPLACEMENT FLUIDS

The gastrointestinal (GI) tract is potentially a source of considerable water loss. GI water losses are accompanied by electrolytes and thus may cause disturbances in intravascular volume and electrolyte concentrations. GI losses are often associated with loss of potassium, leading to hypokalemia. Because of the high bicarbonate concentration in stool, children with diarrhea usually have a metabolic acidosis, which may be accentuated if volume depletion causes hypoperfusion and a concurrent lactic acidosis. Emesis or losses from an NG tube can cause a metabolic alkalosis (see Chapter 55).

In the absence of vomiting, diarrhea, or NG drainage, GI losses of water and electrolytes are usually quite small. All GI losses are considered excessive, and the increase in the water requirement is equal to the volume of fluid losses. Because GI water and electrolyte losses can be precisely measured, it is possible to use an appropriate replacement solution.

It is impossible to predict the losses for the next 24 hr; it is better to replace excessive GI losses as they occur. The child should receive an appropriate maintenance fluid that does not consider the GI losses. The losses should then be replaced after they occur, with use of a solution with a similar electrolyte concentration as the GI fluid. The losses are usually replaced every 1-6 hr, depending on the rate of loss, with very rapid losses being replaced more frequently.

Diarrhea is a common cause of fluid loss in children. It can cause dehydration and electrolyte disorders. In the unusual patient with significant diarrhea and a limited ability to take oral fluid, it is important to have a plan for replacing excessive stool losses. The volume of stool should be measured, and an equal volume of replacement solution should be given. Data are available on the average electrolyte composition of diarrhea in children (Table 56-7). With use of this information, it is possible to design an appropriate replacement solution. The solution shown in Table 56-7 replaces stool losses of sodium, potassium, chloride, and bicarbonate. Each 1 mL of stool should be replaced by 1 mL of this solution. The average electrolyte composition of diarrhea is just an average, and there may be considerable variation. It is therefore advisable to consider measuring the electrolyte composition of a patient's diarrhea if the amount is especially excessive or if the patient's serum electrolyte levels are problematic.

Loss of gastric fluid, via either emesis or NG suction, is also likely to cause dehydration, in that most patients with either condition have impaired oral intake of fluids. Electrolyte disturbances, particularly hypokalemia and metabolic alkalosis, are also common. These complications can be avoided by judicious use of a replacement solution. The composition of gastric fluid shown in Table 56-8 is the basis for designing a replacement solution.

Patients with gastric losses frequently have hypokalemia, although the potassium concentration of gastric fluid is relatively low. The associated urinary loss of potassium is an important cause of hypokalemia in this situation (see Chapter 55). These patients may need additional potassium either in their maintenance fluids or in their replacement fluids to compensate for prior or ongoing urinary losses. Restoration of the patient's intravascular volume, by decreasing aldosterone synthesis, lessens the urinary potassium losses.

Urine output is normally the largest cause of water loss. Diseases such as renal failure and syndrome of inappropriate ADH secretion can lead to a decrease in urine volume. The patient with oliguria or anuria has a decreased need for water and electrolytes; continuation of maintenance fluids produces fluid overload. In contrast, postobstructive diuresis, the polyuric phase of acute tubular necrosis, diabetes mellitus, and diabetes insipidus increase urine production. To prevent dehydration, the patient must receive more than standard maintenance fluids when urine output is excessive. The electrolyte losses in patients with polyuria are variable. In diabetes insipidus, the urine electrolyte concentration is usually low, whereas children with diseases such as juvenile nephronophthisis and obstructive uropathy usually have increased losses of both water and sodium.

The approach to decreased or increased urine output is similar (Table 56-9). The patient receives fluids at a rate to replace insensible losses. This is accomplished by a rate of fluid administration that is 25-40% of the normal maintenance rate, depending on the patient's age. Replacing insensible losses in the anuric child will theoretically maintain an even fluid balance, with the caveat that 25-40% of the normal maintenance rate is only an estimate of insensible losses. In the individual patient, this rate is adjusted on the basis of monitoring of the patient's weight and volume status. Most children with renal insufficiency receive little or no potassium because the kidney is the principal site of potassium excretion.

For the oliguric child, it is important to add a urine replacement solution to prevent dehydration. This issue is especially important in the patient with acute renal failure, in whom output may increase slowly, potentially leading to volume depletion and worsening of renal failure if the patient remains on only insensible fluids. A replacement solution of D5 ½NS is usually appropriate initially, although its composition may have to be adjusted if urine output increases significantly.

Most children with polyuria (except in diabetes mellitus; (see Chapter 589) should be started on replacement of insensible fluid plus urine losses. This approach avoids the need to attempt to calculate the volume of urine output that is "normal" so that the patient can be given replacement fluid for the excess. In these patients, urine output is, by definition, excessive, and it is important to measure the sodium and potassium concentrations of the urine to help in formulating the urine replacement solution.

Surgical drains and chest tubes can produce measurable fluid output. These fluid losses should be replaced when they are significant. They can be measured and replaced with an appropriate replacement solution. Third space losses, which manifest as edema and ascites, are due to a shift of fluid from the intravascular space into the interstitial space. Although these losses cannot be quantitated easily, third space losses can be large and may lead to intravascular volume depletion, despite

Table 56-7	Replacement Fluid for Diarrhea
AVERAGE COMPOSITION OF DIARRHEA	
Sodium: 55 mEq/L	
Potassium: 25 mEq/L	
Bicarbonate: 15 mEq/L	
APPROACH TO REPLACEMENT OF ONGOING LOSSES	
Solution: D5 ½NS + 30 mEq/L sodium bicarbonate + 20 mEq/L KCl	
Replace stool mL/mL every 1-6 hr	

Table 56-8	Replacement Fluid for Emesis or Nasogastric Losses
AVERAGE COMPOSITION OF GASTRIC FLUID	
Sodium: 60 mEq/L	
Potassium: 10 mEq/L	
Chloride: 90 mEq/L	
APPROACH TO REPLACEMENT OF ONGOING LOSSES	
Solution: normal saline + 10 mEq/L KCl	
Replace output mL/mL every 1-6 hr	

Table 56-9	Adjusting Fluid Therapy for Altered Renal Output
OLIGURIA/ANURIA	
Replacement of insensible fluid losses (25-40% of maintenance) with D5 ½NS	
Replace urine output mL/mL with D5 ½NS ± KCl	
POLYURIA	
Replacement of insensible fluid losses (25-40% of maintenance) with D5 ½NS ± KCl	
Measure urine electrolytes	
Replace urine output mL/mL with solution based on measured urine electrolytes	

the patient's weight gain. Replacement of third space fluid is empirical but should be anticipated in patients who are at risk, such as children who have burns or abdominal surgery. Third space losses and chest tube output are isotonic; thus, they usually require replacement with an isotonic fluid, such as NS or LR. Adjustments in the amount of replacement fluid for third space losses are based on continuing assessment of the patient's intravascular volume status. Protein losses from chest tube drainage can be significant, occasionally necessitating that 5% albumin be used as a replacement solution.

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Chapter 57

Deficit Therapy

Larry A. Greenbaum

Dehydration, most often caused by gastroenteritis, is a common problem in children. Most cases can be managed with oral rehydration (see Chapter 340). **Even children with mild to moderate hyponatremic or hypernatremic dehydration can be managed with oral rehydration.**

CLINICAL MANIFESTATIONS

The first step in caring for the child with dehydration is to assess the degree of dehydration (Table 57-1), which dictates both the urgency of the situation and the volume of fluid needed for rehydration. The infant with mild dehydration (3-5% of body weight dehydrated) has few clinical signs or symptoms. The infant may be thirsty; the alert parent may notice a decline in urine output. The history is most helpful. The infant with moderate dehydration has clear physical signs and symptoms. Intravascular space depletion is evident from an increased heart rate and reduced urine output. This patient needs fairly prompt intervention. The infant with severe dehydration is gravely ill. The decrease in blood pressure indicates that vital organs may be receiving inadequate perfusion. Immediate and aggressive intervention is necessary. If possible, the child with severe dehydration should initially receive intravenous therapy. For older children and adults, mild, moderate, or severe dehydration represents a lower percentage of body weight lost. This difference occurs because water accounts for a higher percentage of body weight in infants (see Chapter 55).

Clinical assessment of dehydration is only an estimate; thus, the patient must be continually reevaluated during therapy. The degree of dehydration is underestimated in hypernatremic dehydration because the movement of water from the intracellular space to the extracellular space helps preserve the intravascular volume.

Table 57-1	Clinical Evaluation of Dehydration
Mild dehydration (<5% in an infant; <3% in an older child or adult): Normal or increased pulse; decreased urine output; thirsty; normal physical findings	
Moderate dehydration (5-10% in an infant; 3-6% in an older child or adult): Tachycardia; little or no urine output; irritable/lethargic; sunken eyes and fontanel; decreased tears; dry mucous membranes; mild delay in elasticity (skin turgor); delayed capillary refill (>1.5 sec); cool and pale	
Severe dehydration (>10% in an infant; >6% in an older child or adult): Peripheral pulses either rapid and weak or absent; decreased blood pressure; no urine output; very sunken eyes and fontanel; no tears; parched mucous membranes; delayed elasticity (poor skin turgor); very delayed capillary refill (>3 sec); cold and mottled; limp, depressed consciousness	

The history usually suggests the etiology of the dehydration and may predict whether the patient will have a normal sodium concentration (isotonic dehydration), hyponatremic dehydration, or hypernatremic dehydration. The neonate with dehydration due to poor intake of breast milk often has hypernatremic dehydration. Hypernatremic dehydration is likely in any child with losses of hypotonic fluid and poor water intake, such as may occur with diarrhea, and poor oral intake because of anorexia or emesis. Hyponatremic dehydration occurs in the child with diarrhea who is taking in large quantities of low-salt fluid, such as water or formula.

Some children with dehydration are appropriately thirsty, but in others the lack of intake is part of the pathophysiology of the dehydration. Even though decreased urine output is present in most children with dehydration, good urine output may be deceptively present if a child has an underlying renal defect, such as diabetes insipidus or a salt-wasting nephropathy, or in infants with hypernatremic dehydration.

Physical examination findings are usually proportional to the degree of dehydration. Parents may be helpful in assessment of the child for the presence of sunken eyes, because this finding may be subtle. Pinching and gently twisting the skin of the abdominal or thoracic wall detects tenting of the skin (turgor, elasticity). Tented skin remains in a pinched position rather than springing quickly back to normal. It is difficult to properly assess tenting of the skin in premature infants or severely malnourished children. Activation of the sympathetic nervous system causes tachycardia in children with intravascular volume depletion; diaphoresis may also be present. Postural changes in blood pressure are often helpful for evaluating and assessing the response to therapy in children with dehydration. Tachypnea in children with dehydration may be present secondary to a metabolic acidosis from stool losses of bicarbonate or due to lactic acidosis from shock (see Chapter 70).

LABORATORY FINDINGS

Several laboratory findings are useful for evaluating the child with dehydration. The serum sodium concentration determines the type of dehydration. Metabolic acidosis may be a result of stool bicarbonate losses in children with diarrhea, secondary renal insufficiency, or lactic acidosis from shock. The anion gap is useful for differentiating among the various causes of a metabolic acidosis (see Chapter 55). Emesis or nasogastric losses usually cause a metabolic alkalosis. The serum potassium concentration may be low as a result of diarrheal losses. In children with dehydration as a result of emesis, gastric potassium losses, metabolic alkalosis, and urinary potassium losses all contribute to hypokalemia. Metabolic acidosis, which causes a shift of potassium out of cells, and renal insufficiency may lead to hyperkalemia. A combination of mechanisms may be present; thus, it may be difficult to predict the child's acid–base status or serum potassium level from the history alone.

The blood urea nitrogen (BUN) value and serum creatinine concentration are useful in assessing the child with dehydration. Volume depletion without parenchymal renal injury may cause a disproportionate increase in the BUN with little or no change in the creatinine concentration. This condition is secondary to increased passive resorption of urea in the proximal tubule as a result of appropriate renal conservation of sodium and water. The increase in the BUN with moderate or severe dehydration may be absent or blunted in the child with poor protein intake, because urea production depends on protein degradation. The BUN may be disproportionately increased in the child with increased urea production, as occurs with a gastrointestinal bleed or with the use of glucocorticoids, which increase catabolism. A significant elevation of the creatinine concentration suggests renal insufficiency, although a small, transient increase can occur with dehydration. **Acute tubular necrosis** (acute kidney injury) (see Chapter 535) because of volume depletion is the most common etiology of renal insufficiency in a child with volume depletion, but occasionally the child may have previously undetected chronic renal insufficiency or an alternative explanation for the acute renal failure. Renal vein thrombosis is a well-described sequela of severe dehydration in infants;

possible findings include thrombocytopenia and hematuria (see Chapter 519.7).

Hemoconcentration from dehydration causes increases in hematocrit, hemoglobin, and serum proteins. These values normalize with rehydration. A normal hemoglobin concentration during acute dehydration may mask an underlying anemia. A decreased albumin level in a dehydrated patient suggests a chronic disease, such as malnutrition, nephrotic syndrome, or liver disease, or an acute process, such as capillary leak. An acute or chronic protein-losing enteropathy may also cause a low serum albumin concentration.

CALCULATION OF THE FLUID DEFICIT

Determining the fluid deficit necessitates clinical determination of the percentage of dehydration and multiplication of this percentage by the patient's weight; a child who weighs 10 kg and is 10% dehydrated has a fluid deficit of 1 L.

APPROACH TO SEVERE DEHYDRATION

The child with dehydration needs acute intervention to ensure that there is adequate tissue perfusion. This resuscitation phase requires rapid restoration of the circulating intravascular volume and treatment of shock with an isotonic solution, such as normal saline (NS) or Ringer lactate (LR) (see Chapter 70). The child is given a fluid bolus, usually 20 mL/kg of the isotonic fluid, over approximately 20 min. The child with severe dehydration may require multiple fluid boluses and may need to receive the boluses as fast as possible. In a child with a known or probable metabolic alkalosis (the child with isolated vomiting), LR should not be used because the lactate would worsen the alkalosis.

Colloids, such as blood, 5% albumin, and plasma, are rarely needed for fluid boluses. A crystalloid solution (NS or LR) is satisfactory, with both less infectious risk and lower cost. Blood is obviously indicated in the child with significant anemia or acute blood loss. Plasma is useful for children with a coagulopathy. The child with hypoalbuminemia may benefit from 5% albumin, although there is evidence that albumin infusions increase mortality in adults. The volume and the infusion rate for colloids are generally modified compared with crystalloids (see Chapters 473).

The initial resuscitation and rehydration phase is complete when the child has an adequate intravascular volume. Typically, the child shows clinical improvement, including a lower heart rate, normalization of blood pressure, improved perfusion, better urine output, and a more alert affect.

With adequate intravascular volume, it is appropriate to plan the fluid therapy for the next 24 hr. A general approach is outlined in Table 57-2, with the caveat that there are many different approaches to correcting dehydration. In isonatremic or hyponatremic dehydration, the entire fluid deficit is corrected over 24 hr; a slower approach is used for hypernatremic dehydration (discussed later). The volume of isotonic fluids that the patient has received is subtracted from this total. The remaining fluid volume is then administered over 24 hr. The potassium concentration may need to be decreased or, less commonly, increased, depending on the clinical situation. Potassium is not usually included in the intravenous fluids until the patient voids and normal renal function is documented via measurement of BUN and creatinine. Children with significant ongoing losses need to receive an appropriate replacement solution (see Chapter 56).

Table 57-2 Fluid Management of Dehydration

Fluid Management of Dehydration
Restore intravascular volume:
Normal saline: 20 mL/kg over 20 min
Repeat as needed
Calculate 24-hr fluid needs: maintenance + deficit volume
Subtract isotonic fluid already administered from 24 hr fluid needs
Administer remaining volume over 24 hr using 5% dextrose NS + 20 mEq/L KCl
Replace ongoing losses as they occur

MONITORING AND ADJUSTING THERAPY

The formulation of a plan for correcting a child's dehydration is only the beginning of management. **All calculations in fluid therapy are only approximations.** This statement is especially true for the assessment of percentage dehydration. It is equally important to monitor the patient during treatment and to modify therapy on the basis of the clinical situation. Table 57-3 lists the cornerstones of patient monitoring. The patient's vital signs are useful indicators of intravascular volume status. The child with decreased blood pressure and an increased heart rate will probably benefit from a fluid bolus. Central venous pressure is an excellent indicator of fluid status in the critically ill child with shock.

The patient's intake and output are critically important in the dehydrated child. The child who, after 8 hr of therapy, has more output than input because of continuing diarrhea needs to be started on a replacement solution. See the guidelines in Chapter 56 for selecting an appropriate replacement solution. Urine output is useful for evaluating the success of therapy. Good urine output indicates that rehydration has been successful.

Signs of dehydration on physical examination suggest the need for continued rehydration. Signs of fluid overload, such as edema and pulmonary congestion, are present in the child who is overhydrated. An accurate daily weight measurement is critical for the management of the dehydrated child. There should be a gain in weight during successful therapy.

Measurement of serum electrolyte levels at least daily is appropriate for any child who is receiving intravenous rehydration. Such a child is at risk for sodium, potassium, and acid–base disorders. It is always important to look at trends. For instance, a sodium value of 144 mEq/L is normal; but if the sodium concentration was 136 mEq/L 12 hr earlier, then there is a distinct risk that the child will be hypernatremic in 12 or 24 hr. It is advisable to be proactive in adjusting fluid therapy.

Both hypokalemia and hyperkalemia are potentially serious (see Chapter 55). Because dehydration can be associated with acute renal failure and hyperkalemia, potassium is withheld from intravenous fluids until the patient has voided. The potassium concentration in the patient's intravenous fluids is not rigidly prescribed. Rather, the patient's serum potassium level and underlying renal function are used to modify potassium delivery. The patient with an elevated creatinine value and a potassium level of 5 mEq/L does not receive any potassium until the serum potassium level decreases. Conversely, the patient with a potassium level of 2.5 mEq/L may require additional potassium.

Metabolic acidosis can be quite severe in dehydrated children. Although normal kidneys eventually correct this problem, a child with renal dysfunction may be unable to correct a metabolic acidosis, and a portion of the patient's intravenous sodium chloride may have to be replaced with sodium bicarbonate or sodium acetate.

The serum potassium level is modified by the patient's acid–base status. Acidosis increases serum potassium by causing intracellular potassium to move into the extracellular space. Thus, as acidosis is corrected, the potassium concentration decreases. Again, it is best to anticipate this problem and to monitor the serum potassium concentration and adjust potassium administration appropriately.

Table 57-3 Monitoring Therapy

Monitoring Therapy
Vital signs:
Pulse
Blood pressure
Intake and output:
Fluid balance
Urine output
Physical examination:
Weight
Clinical signs of depletion or overload
Electrolytes

HYPONATREMIC DEHYDRATION

The pathogenesis of hyponatremic dehydration usually involves a combination of sodium and water loss and water retention to compensate for the volume depletion. The patient has a pathologic increase in fluid loss, and the lost fluid contains sodium. Most fluid that is lost has a lower sodium concentration, so patients with only fluid loss would have hypernatremia. Diarrhea has, on average, a sodium concentration of 50 mEq/L. Replacing diarrheal fluid with water, which has almost no sodium, causes a reduction in the serum sodium concentration. The volume depletion stimulates synthesis of antidiuretic hormone, resulting in reduced renal water excretion. Hence, the body's usual mechanism for preventing hyponatremia, renal water excretion, is blocked. The risk of hyponatremia is further increased if the volume depletion is a result of loss of fluid with a higher sodium concentration, as may occur with renal salt wasting, third space losses, or diarrhea with high sodium content (cholera).

The initial goal in treating hyponatremia is correction of intravascular volume depletion with isotonic fluid (NS or LR). An overly rapid (>12 mEq/L over the first 24 hr) or overcorrection in the serum sodium concentration (>135 mEq/L) is associated with an increased risk of **central pontine myelinolysis** (see Chapter 55). Most patients with hyponatremic dehydration do well with the same basic strategy that is outlined in Table 57-2. Again, potassium delivery is adjusted according to the initial serum potassium level and the patient's renal function. Potassium is not given until the patient voids.

The patient's sodium concentration is monitored closely to ensure appropriate correction, and the sodium concentration of the fluid is adjusted accordingly. Patients with ongoing losses require an appropriate replacement solution (see Chapter 56). Patients with neurologic symptoms (seizures) as a result of hyponatremia need to receive an acute infusion of hypertonic (3%) saline to increase the serum sodium concentration rapidly (see Chapter 55).

HYPERNATREMIC DEHYDRATION

Hypernatremic dehydration is the most dangerous form of dehydration because of complications of hypernatremia and of therapy. Hypernatremia can cause serious neurologic damage, including central nervous system hemorrhages and thrombosis. This damage appears to be secondary to the movement of water from the brain cells into the hypertonic extracellular fluid, causing brain cell shrinkage and tearing blood vessels within the brain (see Chapter 55).

The movement of water from the intracellular space to the extracellular space during hypernatremic dehydration partially protects the intravascular volume. Unfortunately, because the initial manifestations are milder, children with hypernatremic dehydration are often brought for medical attention with more profound dehydration.

Children with hypernatremic dehydration are often lethargic, and they may be irritable when touched. Hypernatremia may cause fever, hypertonicity, and hyperreflexia. More severe neurologic symptoms may develop if cerebral bleeding or thrombosis occurs.

Overly rapid treatment of hypernatremic dehydration may cause significant morbidity and mortality. Idiogenic osmoles are generated within the brain during the development of hypernatremia. These idiogenic osmoles increase the osmolality within the cells of the brain, providing protection against brain cell shrinkage caused by movement of water out of the cells and into the hypertonic extracellular fluid. They dissipate slowly during the correction of hypernatremia. With overly rapid lowering of the extracellular osmolality during the correction of hypernatremia, an osmotic gradient may be created that causes water movement from the extracellular space into the cells of the brain, producing cerebral edema. Symptoms of the resultant cerebral edema can range from seizures to brain herniation and death.

To minimize the risk of cerebral edema during the correction of hypernatremic dehydration, the serum sodium concentration should not decrease by >12 mEq/L every 24 hr. The deficits in severe hypernatremic dehydration may need to be corrected over 2-4 days (Table 57-4).

The initial resuscitation of hypernatremic dehydration requires restoration of the intravascular volume with NS. *LR should not be used because it is more hypotonic than NS and may cause too rapid a decrease in the serum sodium concentration, especially if multiple fluid boluses are necessary.*

Table 57-4 Treatment of Hypernatremic Dehydration

Restore intravascular volume:
Normal saline: 20 mL/kg over 20 min (repeat until intravascular volume restored)
Determine time for correction on basis of initial sodium concentration:
[Na] 145-157 mEq/L: 24 hr
[Na] 158-170 mEq/L: 48 hr
[Na] 171-183 mEq/L: 72 hr
[Na] 184-196 mEq/L: 84 hr
Administer fluid at constant rate over time for correction:
Typical fluid: 5% dextrose + half-normal saline (with 20 mEq/L KCl unless contraindicated)
Typical rate: 1.25-1.5 times maintenance
Follow serum sodium concentration
Adjust fluid on basis of clinical status and serum sodium concentration:
Signs of volume depletion: administer normal saline (20 mL/kg)
Sodium decreases too rapidly; either:
Increase sodium concentration of intravenous fluid
Decrease rate of intravenous fluid
Sodium decreases too slowly; either:
Decrease sodium concentration of intravenous fluid
Increase rate of intravenous fluid
Replace ongoing losses as they occur

To avoid cerebral edema during correction of hypernatremic dehydration, the fluid deficit is corrected slowly. The rate of correction depends on the initial sodium concentration (see Table 57-4). There is no general agreement on the choice or the rate of fluid for correcting hypernatremic dehydration. The choice and the rate of fluid administration are not nearly as important as vigilant monitoring of the serum sodium concentration and adjustment of the therapy according to the result (see Table 57-4). The rate of decrease of the serum sodium concentration is roughly related to the "free water" delivery, although there is considerable variation between patients. Free water is water without sodium. NS contains no free water, half-NS (½NS) is 50% free water, and water is 100% free water. Smaller patients, to achieve the same decrease in the sodium concentration, tend to need higher amounts of free water delivery per kilogram because of higher insensible fluid losses. Five percent dextrose (D5) with ½NS is usually an appropriate starting solution for a patient with hypernatremic dehydration. Some patients, especially infants with ongoing **high insensible water losses**, may need to receive D5 0.2NS, which should be used with great caution and constant monitoring. Others require D5 NS. A child with dehydration as a result of pure free water loss, as usually occurs with diabetes insipidus, usually needs a more hypotonic fluid than a child with depletion of both sodium and water due to diarrhea.

Adjustment in the sodium concentration of the intravenous fluid is the most common approach to modifying the rate of decrease in the serum concentration (see Table 57-4). For difficult-to-manage patients with severe hypernatremia, having 2 intravenous solutions (e.g., D5 ½ NS and D5 NS, both with the same concentration of potassium) at the bedside can facilitate this approach by allowing for rapid adjustments of the rates of the 2 fluids. If the serum sodium concentration decreases too rapidly, the rate of D5 NS can be increased and the rate of D5 ½ NS can be decreased by the same amount. Adjustment in the total rate of fluid delivery is another approach to modifying free water delivery. For example, if the serum sodium concentration is decreasing too slowly, the rate of the intravenous fluid can be increased, thereby increasing the delivery of free water. There is limited flexibility in modifying the rate of the intravenous fluid because patients generally should receive 1.25-1.5 times the normal maintenance fluid rate. Nevertheless, in some situations, it can be a helpful adjustment.

Because increasing the rate of the intravenous fluid increases the rate of decline of the sodium concentration, signs of volume depletion are

treated with additional isotonic fluid boluses. The serum potassium concentration and the level of renal function dictate the potassium concentration of the intravenous fluid; potassium is withheld until the patient voids. Patients with hypernatremic dehydration need an appropriate replacement solution if they have ongoing, excessive losses (see Chapter 56).

Seizures are the most common manifestation of **cerebral edema** from an overly rapid decrease of the serum sodium concentration during correction of hypernatremic dehydration. Signs of increased intracranial pressure or impending herniation may develop quite rapidly (see Chapter 68). Acutely, increasing the serum concentration via an infusion of 3% sodium chloride can reverse the cerebral edema. Each 1 mL/kg of 3% sodium chloride increases the serum sodium concentration by approximately 1 mEq/L. An infusion of 4 mL/kg often results in resolution of the symptoms. This strategy is similar to that used for treating symptomatic hyponatremia (see Chapter 55).

In patients with severe hypernatremia, oral fluids must be used cautiously. Infant formula, because of its low sodium concentration, has a high free water content, and especially if added to intravenous therapy, it may contribute to a rapid decrease in the serum sodium concentration. Less hypotonic fluid, such as an oral rehydration solution, may be more appropriate initially (see Chapter 340). If oral intake is allowed, its contribution to free water delivery must be taken into account, and adjustment in the intravenous fluid is usually appropriate. Judicious monitoring of the serum sodium concentration is critical.

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Chapter 58

Fluid and Electrolyte Treatment of Specific Disorders

ACUTE DIARRHEA

See Chapter 340.

PYLORIC STENOSIS

See Chapter 329.1.

PERIOPERATIVE FLUIDS

See Chapter 61.

Pediatric Drug Therapy

PART VIII

Chapter 59

Pediatric Pharmacogenetics, Pharmacogenomics, and Pharmacoproteomics

Kathleen A. Neville and J. Steven Leeder

The role of genetic factors in drug disposition and response, **pharmacogenetics**, has resulted in many examples of how variations in human genes can lead to interindividual differences in pharmacokinetics and drug response at the level of individual patients. Pharmacogenetic variability contributes to the broad range of drug responses observed in children at any given age or developmental stage; it is expected that children will benefit from the promise of **personalized medicine**—identifying the right drug for the right patient at the right time (Fig. 59-1). Numerous maturational processes occur from birth through adolescence such that utilization of information resulting from the Human Gene Project and related initiatives must take into account the changing patterns of gene expression that occur over development to improve pharmacotherapeutics in children.

PHARMACOGENETICS, PHARMACOGENOMICS, AND THE CONCEPT OF PERSONALIZED MEDICINE

The terms *pharmacogenomics* and *pharmacogenetics* tend to be used interchangeably, and precise, consensus definitions are often difficult to determine. **Pharmacogenetics** classically is defined as the study or clinical testing of genetic variations that give rise to interindividual differences in the response to drugs. The earliest examples of pharmacogenetic traits include specific adverse drug reactions, such as unusually prolonged respiratory muscle paralysis caused by succinylcholine, hemolysis associated with antimalarial therapy, and isoniazid-induced neurotoxicity, all of which are a consequence of inherited variations in enzyme activity. The importance of pharmacogenetic differences has become better understood and is exemplified by the fact that the half-lives of several drugs are more similar in monozygotic twins than in dizygotic twins. However, it is important to note that in addition to pharmacogenetic differences, environmental factors (diet, smoking status, concomitant drug or toxicant exposure), physiologic variables (age, sex, disease, pregnancy), and patient compliance all contribute to variations in drug metabolism and response. Likewise, ethnicity is another potential genetic determinant of drug variability. For example, Chinese patients who are HLA-B*1502–positive and white patients who are positive for HLA-A*3101 have an increased risk of carbamazepine-induced Stevens-Johnson syndrome; white patients who are HLA-B*5701–positive have an increased risk of hypersensitivity to abacavir (Table 59-1).

Pharmacogenomics represents the marriage of pharmacology and genomics, and can be defined as the broader application of genome-wide technologies and strategies to identify both disease processes that represent new targets for drug development and factors predictive of efficacy and risk of adverse drug reactions.

Pharmacokinetics describes temporal aspects of what the body does to a drug. It is often studied in conjunction with **pharmacodynamics**, which explores what a drug does to the body (see Chapter 60). The **pharmacokinetic** properties of a drug are determined by the genes that control the drug's disposition in the body (absorption, distribution, metabolism, excretion). Drug metabolizing enzymes and drug transporters play a particularly important role in this process (Table 59-2), and the functional consequences of genetic variations in many drug metabolizing enzymes have been described between subjects of both similar and different ethnic groups. The most common clinical manifestation of pharmacogenetic variability in drug biotransformation is an increased risk of concentration-dependent toxicity as a result of reduced clearance and consequent drug accumulation. On the other hand, rapid metabolism can lead to accumulation of a toxic metabolite, as has been reported for the hepatic conversion of codeine to morphine in 4 children ages 2-5 yr who received codeine for pain after tonsillectomy and adenoidectomy. This variant pharmacokinetics resulted in 3 deaths and 1 near-death from respiratory depression. As a result of these concerns, physicians are reminded to prescribe any drug at the lowest effective dose, for the shortest time, and only on an as-needed basis.

An equally important manifestation of this variability is lack of efficacy resulting from variations in metabolism of prodrugs. The pharmacogenetics of drug receptors and other target proteins involved in signal transduction or disease pathogenesis can also be expected to contribute significantly to interindividual variability in drug disposition and response.

Therapeutic drug monitoring programs recognize that all patients are unique and that the serum concentration-time data for an individual patient theoretically can be used to optimize pharmacotherapy. These programs have been the earliest application of personalized medicine; however, routine therapeutic drug monitoring does not necessarily translate to improved patient outcome in all situations.

The concept of **personalized medicine** is based on the premise that the wealth of information accompanying the application of genomic technologies to patient-related problems will allow for (1) stratification of patient populations according to their response to a particular medication (e.g., lack of drug efficacy or excessive toxicity), and (2) stratification of diseases into specific subtypes that are categorized according to genomic criteria and by response to particular treatments.

DEFINITION OF PHARMACOGENETIC TERMS

Genetic polymorphisms (variations) result when copies of a specific gene present within a population do not have identical nucleotide sequences. The term **allele** refers to one of a series of alternative DNA sequences for a particular gene. In humans, there are 2 copies of every gene. An individual's genotype for a given gene is determined by the set of alleles that the individual possesses. The most common form of genetic variation involves a single base change at a given location, referred to as a **single-nucleotide polymorphism (SNP)** (see Chapter 81). At the other end of the spectrum are **copy number variations,** which refer to the deletion or duplication of identical or near identical DNA sequences that may be thousands to millions of bases in size. Copy number variations occur less frequently than SNPs, but may constitute 0.5-1% of an individual's genome, and thereby contribute significantly to phenotypic variation. **Haplotypes** are collections of SNPs and other allelic variations that are located close to each other and when inherited together these create a catalog of haplotypes, or **HapMap.** When the alleles at a particular gene locus on both chromosomes are identical, a **homozygous** state exists, whereas the term **heterozygous** refers to the situation in which different alleles are present at the same gene locus. The term **genotype** refers to an individual's

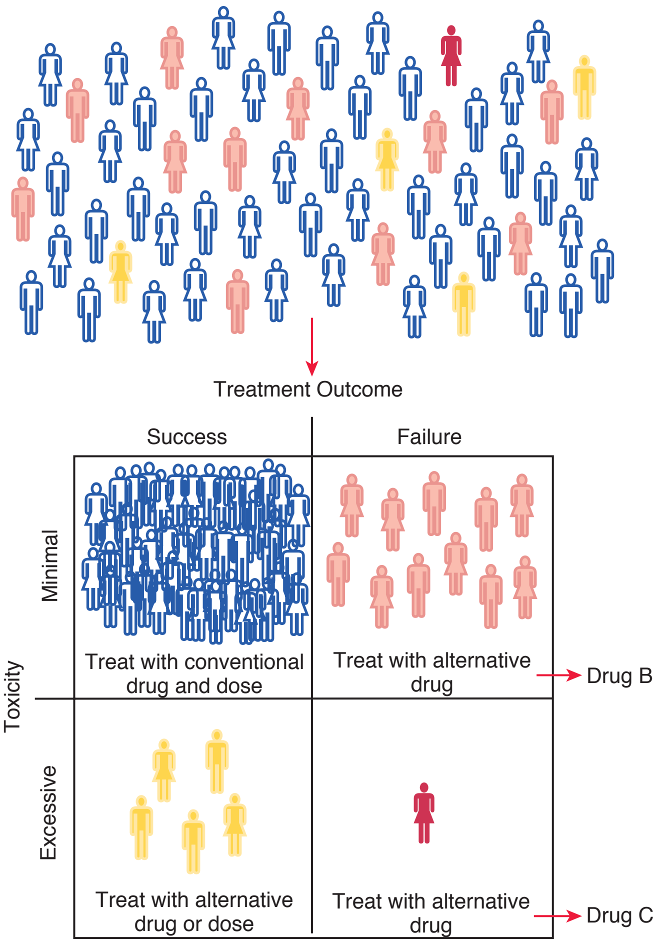

Figure 59-1 The promise of genomic medicine to human health and disease. The goal of personalized medicine will be achieved by identifying subgroups of patients who will respond favorably to a given drug with a minimum of side effects, as well as those who will not respond or who will show excessive toxicity with standard doses. A further benefit of pharmacogenomics will be the ability to select the most appropriate alternative drug for patients who cannot be treated successfully with conventional drugs and doses. *(Adapted from Yaffe SJ, Aranda JV:* Neonatal and pediatric pharmacology*, ed 3, Philadelphia, 2004, Lippincott Williams & Wilkins.)*

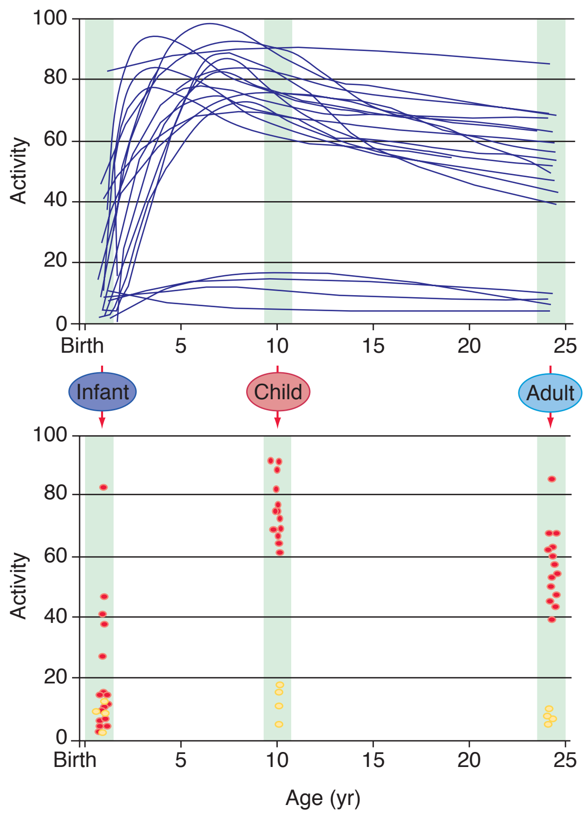

Figure 59-2 Developmental phenotypes. Variability in developmental changes in gene expression and functional enzyme activity are superimposed on pharmacogenetic determinants. The *top panel* shows the developmental profile of a theoretical drug-metabolizing enzyme over a 25 yr span in 20 subjects. At maturity (adults), allelic variation within the coding region of the gene gives rise to 2 distinct phenotypes, high activity in 92% of the population ("extensive metabolizers"; *red circles*) and low activity in 8% of the population ("poor metabolizers"; *yellow circles*). However, there is also interindividual variability in the rate at which functional activity is acquired after birth. For example, the 2 phenotypes may not be readily distinguishable in newborn infants immediately after birth. Furthermore, there may be discrete periods during childhood in which the genotype-phenotype relationship may differ from that observed in adults (e.g., developmental stages at which enzyme activity appears to be greater in children than in adults). *(Adapted from Leeder JS: Translating pharmacogenetics and pharmacogenomics into drug development for clinical pediatric and beyond.* Drug Discov Today *9:567–573, 2004.)*

genetic constitution, whereas the observable characteristics or physical manifestations constitute the **phenotype,** which is the net consequence of genetic and environmental effects (see Chapters 77-80). Pharmacogenetics focuses on the phenotypic consequences of allelic variation in single genes. **Pharmacogenetic polymorphisms** are monogenic traits that are functionally relevant to drug disposition and action and are caused by the presence (within 1 population) of more than 1 allele (at the same gene locus) and more than 1 phenotype with regard to drug interaction with the organism. The key elements of pharmacogenetic polymorphisms are heritability, the involvement of a single gene locus, functional relevance, and the fact that distinct phenotypes are observed within the population only after drug challenge.

DEVELOPMENTAL OR PEDIATRIC PHARMACOGENETICS AND PHARMACOGENOMICS

Our current understanding of pharmacogenetic principles involves enzymes responsible for drug **biotransformation.** Individuals are classified as being "fast," "rapid," or "extensive" metabolizers at one end of the spectrum, and "slow" or "poor" metabolizers at the other end of the continuum. This may or may not also include an "intermediate" metabolizer group, depending on the particular enzyme. With regard to biotransformation, children are more complex than adults as fetuses and newborns may be phenotypically "slow" or "poor" metabolizers for certain drug-metabolizing pathways because of their stage of development, and may acquire a phenotype consistent with their genotype at some point later in the developmental process as they mature. Examples of drug-metabolizing pathways that are significantly affected by ontogeny include glucuronidation and some of the cytochrome P450 (CYP) activities (see Chapters 60, 96, and 97). It is also apparent that not all infants acquire drug metabolism activity at the same rate. This is attributable to interactions between genetics and environmental factors. Interindividual variability in the trajectory (i.e., rate and extent) of acquired drug biotransformation capacity may be considered a **developmental phenotype** (Fig. 59-2), and it helps to explain the considerable variability in some CYP activities observed immediately after birth.

Pharmacogenetic, Pharmacogenomic, and Pharmacoproteomic and Metabolomic Tools

Several genotyping platforms are approved by the Food and Drug Administration and are beginning to enter the clinical arena. The Roche AmpliChip CYP450 Test was the first such device to receive FDA

Table 59-1 Examples of Effects of Gene Polymorphisms on Drug Response

GENE	ENZYME/TARGET	DRUG	CLINICAL RESPONSE
BCHE	Butyrylcholinesterase	Succinylcholine	Prolonged paralysis
CYP2C9	Cytochrome P450 2C9	Warfarin	Individuals having one or more reduced function alleles require lower doses of warfarin for optimal anticoagulation, especially initial anticoagulant control
CYP2C19	Cytochrome P450 2C19	Clopidogrel	Individuals having one or more loss-of-function alleles have reduced capacity to form the pharmacologically active metabolite of clopidogrel and reduced antiplatelet effect
CYP2D6	Cytochrome P450 2D6	Codeine	Poor metabolizers—individuals with 2 loss-of-function alleles—do not metabolize codeine to morphine and thus experience no analgesic effect; ultrarapid metabolizers (3 or more functional alleles) may experience morphine toxicity
G6PD	Glucose-6-phosphate dehydrogenase	Primaquine (others)	Hemolysis
*HLA-A*3101*	Human leukocyte antigen A31	Carbamazepine	Carriers of the *HLA-A*3101* allele have an increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis from carbamazepine
*HLA-B*1502*	Human leukocyte antigen B15	Allopurinol	Han Chinese carriers of the *HLA-B*1502* allele have an increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis from carbamazepine
*HLA-B*5701*	Human leukocyte antigen B57	Abacavir Flucloxacillin	Carriers of the *HLA-B*5701* allele have an increased risk of hypersensitivity reactions to abacavir and abacavir- and flucloxacillin-induced liver injury
*HLA-B*5801*	Human leukocyte antigen B58	Allopurinol	Carriers of the *HLA-B*5801* allele have an increased risk of severe cutaneous adverse reactions to allopurinol, including hypersensitivity reactions, Stevens-Johnson syndrome, and toxic epidermal necrolysis
NAT2	*N*-acetyltransferase 2	Isoniazid, hydralazine	Individuals homozygous for "slow acetylation" polymorphisms are more susceptible to isoniazid toxicity, or hydralazine-induced systemic lupus erythematosus
SLCO1B1	Organic anion transporting protein (OATP) 1B1	Simvastatin	Carriers of the *SLCO1B1*5* allele are at increased risk for musculoskeletal side effects from simvastatin
TPMT	Thiopurine *S*-methyltransferase	Azathioprine 6-Mercaptopurine	Individuals homozygous for an inactivating mutation have severe toxicity if treated with standard doses of azathioprine or 6-mercaptopurine; rapid metabolism causes undertreatment
UGT1A1	Uridine diphospho-glucuronosyltransferase 1A1	Irinotecan	The *UGT1A1*28* allele is associated with decreased glucuronidation of SN-38, the active metabolite of irinotecan, and increased risk of neutropenia
VKORC1	Vitamin K oxidoreductase complex 1	Warfarin	Individuals with a haplotype associated with reduced expression of the VKORC1 protein, the therapeutic target of warfarin, require lower doses of the drug for stable anticoagulation

approval, and many additional products have become available (https://www.pharmgkb.org/views/viewGeneticTests.action). In general, applications are limited to 1 or 2 genes, such as *CYP2C9* and *VKORC1* genotyping to guide warfarin therapy or genotyping of *UGT1A1* to reduce the risk of irinotecan toxicity. A more comprehensive chip that covers >90% of the absorption, distribution, metabolism, and excretion markers as defined by the PharmaADME group (http://pharmaadme.org) is available for drug development and research purposes, and the National Institute of General Medical Sciences–sponsored Pharmacogenomics Research Network has developed a list of high-priority genes of interest (http://pgrn.org/download/attachments/131165/PGRN-seq%20Gene%20List%2010-15-12%20Scherer%20Genes.pdf?version=1&modificationDate=1350681059000&api=v2).

In contrast to pharmacogenetic studies that typically target single genes, pharmacogenomic analyses are considerably broader in scope and focus on complex and highly variable drug-related phenotypes with targeting of many genes. Genomewide genotyping technologies have progressed beyond "SNP chips" to evaluate genetic variation at more than 1 million sites throughout an individual genome for SNP and copy number variation analyses to include massively parallel "next-generation sequencing" technologies. Genomewide association studies have been conducted in several pediatric settings, acute lymphoblastic leukemia, and pediatric inflammatory bowel disease. One goal of this type of study is to identify novel genes involved in disease pathogenesis that can lead to new therapeutic targets. Genomewide association studies are also being applied to identify genetic associations with response to drugs, such as warfarin and clopidogrel, and risk for drug-induced toxicity, including statin-induced myopathy and flucloxacillin hepatotoxicity. The "Manhattan plot," a form of data presentation for genomewide association studies, is common in many medical journals (Fig. 59-3*A*). Next-generation sequencing is being applied to rapidly diagnose mendelian disorders and pathologies thought to have a genetic origin when all other diagnostic approaches have been exhausted.

Investigating differential gene expression before and after drug exposure has the potential to correlate gene expression with variable drug responses and possibly uncover the mechanisms of tissue-specific drug toxicities. These types of studies use **microarray technology** or RNA-Seq (based on next-generation sequencing technologies) to monitor global changes in expression of thousands of genes (the **transcriptome**) simultaneously. The underlying hypothesis of these global

Table 59-2 Some Important Relationships Between Drugs and Cytochrome P450 (CYP) Enzymes* and P-Glycoprotein (P-gp) Transporter

ENZYME	DRUG SUBSTRATES	INHIBITORS	INDUCERS
CYP1A2	Caffeine, clomipramine (*Anafranil*[†]), clozapine (*Clozaril*[†]), theophylline	Cimetidine (*Tagamet*[†]) Fluvoxamine (*Luvox*[†]) Ciprofloxacin (*Cipro*)	Omeprazole (*Prilosec*[†]) Tobacco
CYP2C9	Diclofenac (*Voltaren*[†]), ibuprofen (*Motrin*[†]), piroxicam (*Feldene*[†]), losartan (*Cozaar*), irbesartan (*Avapro*), celecoxib (*Celebrex*), tolbutamide (*Orinase*[†]), warfarin (*Coumadin*[†]), phenytoin (*Dilantin*)	Fluconazole (*Diflucan*) Fluvastatin (*Lescol*) Amiodarone (*Cordarone*) Zafirlukast (*Accolate*)	Rifampin (*Rifadin*[†])
CYP2C19	Omeprazole, Lansoprazole (*Prevacid*), pantoprazole (*Protonix*), (*S*)-mephenytoin, (*S*)-citalopram (*Lexapro*); nelfinavir (*Viracept*), diazepam (*Valium*[†]), voriconazole (*Vfend*)	Cimetidine Fluvoxamine	Rifampin
CYP2D6	**CNS-active agents:** Atomoxetine (*Strattera*), amitriptyline (*Elavil*[†]), desipramine (*Norpramin*[†]), imipramine (*Tofranil*[†]), paroxetine (*Paxil*), haloperidol (*Haldol*[†]), risperidone (*Risperdal*), thioridazine (*Mellaril*[†])	Fluoxetine (*Prozac*[†]) Paroxetine (*Paxil*)	
	Antiarrhythmic agents: Mexiletine (*Mexitil*), propafenone (*Rythmol*)	Amiodarone (*Cordarone*[†]) Quinidine (*Quinidex*[†])	
	β Blockers: Propranolol (*Inderal*[†]), metoprolol (*Lopressor*[†]), timolol (*Blocadren*[†])	Terbinafine	
	Narcotics: Codeine, dextromethorphan, hydrocodone (*Vicodin*[†])		
	Others: Tamoxifen (*Nolvadex*)	Cimetidine Ritonavir	
CYP3A4	**Calcium channel blockers:** Diltiazem (*Cardizem*[†]), felodipine (*Plendil*), nimodipine (*Nimotop*), nifedipine (*Adalat*[†]), nisoldipine (*Sular*), nitrendipine, verapamil (*Calan*[†]) **Immunosuppressive agents:** Cyclosporine (*Sandimmune*, *Neoral*[†]), tacrolimus (*Prograf*)	Amiodarone	Barbiturates Carbamazepine (*Tegretol*[†]) Phenytoin (*Dilantin*[†]) Efavirenz (*Sustiva*)
	Steroids: Budesonide (*Pulmicort*), cortisol, 17β-estradiol, progesterone, testosterone	Fluconazole Ketoconazole (*Nizoral*[†]) Itraconazole (*Sporanox*)	Nevirapine (*Viramune*)
	Macrolide antibiotics: Clarithromycin (*Biaxin*), erythromycin (*Erythrocin*[†]), troleandomycin (*TAO*)	Clarithromycin Erythromycin Troleandomycin	
	Anticancer agents: Cyclophosphamide (*Cytoxan*[†]), gefitinib (*Iressa*), ifosfamide (*Ifex*), tamoxifen, vincristine (*Oncovin*[†]), vinblastine (*Velban*[†]) **Benzodiazepines:** Alprazolam (*Xanax*[†]), midazolam *Versed*[†]), triazolam (*Halcion*[†]) **Opioids:** Alfentanil (*Alfenta*[†]), fentanyl (*Sublimaze*[†]), sufentanil (*Sufenta*[†]) **HMG-CoA reductase inhibitors:** Lovastatin (*Mevacor*[†], simvastatin (*Zocor*), atorvastatin (*Lipitor*)	Imatinib	Rifampin Ritonavir[‡] St. John's wort
	HIV protease inhibitors: Indinavir (*Crixivan*), nelfinavir, ritonavir (*Norvir*), saquinavir (*Invirase, Fortovase*), amprenavir (*Agenerase*) **Others:** Quinidine (*Quinidex*[†]), sildenafil (*Viagra*), eletriptan (*Relpax*), ziprasidone (*Geodon*)	Ritonavir[‡] Indinavir Grapefruit juice Nefazodone (*Serzone*)	
P-gp	Aldosterone, amprenavir, atorvastatin, cyclosporine, dexamethasone (*Decadron*[†]), digoxin (*Lanoxin*[†]), diltiazem, domperidone (*Motilium*), doxorubicin (*Adriamycin*[†]), erythromycin, etoposide (*VePesid*), fexofenadine (*Allegra*), hydrocortisone, indinavir, ivermectin (*Stromectol*), lovastatin loperamide (*Imodium*[†]), nelfinavir, ondansetron (*Zofran*), paclitaxel (*Taxol*), quinidine, saquinavir, simvastatin, verapamil, vinblastine, vincristine	Amiodarone Carvedilol (*Coreg*) Clarithromycin Cyclosporine Erythromycin Itraconazole Ketoconazole Quinidine Ritonavir[‡] Tamoxifen Verapamil	Amprenavir Clotrimazole (*Mycelex*[†]) Phenothiazine Rifampin Ritonavir[‡] St. John's wort

*http://www.drug-interactions.com.
[†]Also available generically.
[‡]Can be both an inhibitor and an inducer.
CNS, central nervous system; HMG-CoA, β-hydroxy-β-methylglutaryl–coenzyme A.
From Drug interactions. Med Lett *2003;45(1158):47.*

gene profiling studies is that the measured signal intensity for each gene transcript represents its relative expression level; RNA-Seq allows absolute quantitation of gene expression, as well as detection of alternative splicing events. Gene expression profiling data are used to improve disease classification and risk stratification, and are utilized commonly in oncology. This approach was used to address treatment resistance in acute lymphoblastic leukemia, and has provided clinically relevant insights into the mechanistic basis of drug resistance and the genomic basis of interindividual variability in drug response. Subsets of transcripts, or gene expression "signatures," are being investigated as potential prognostic indicators for identifying patients at risk for treatment failure (Fig. 59-3*B*).

Proteomic studies use many different techniques to detect, quantify, and identify proteins in a sample **(expression proteomics),** and to

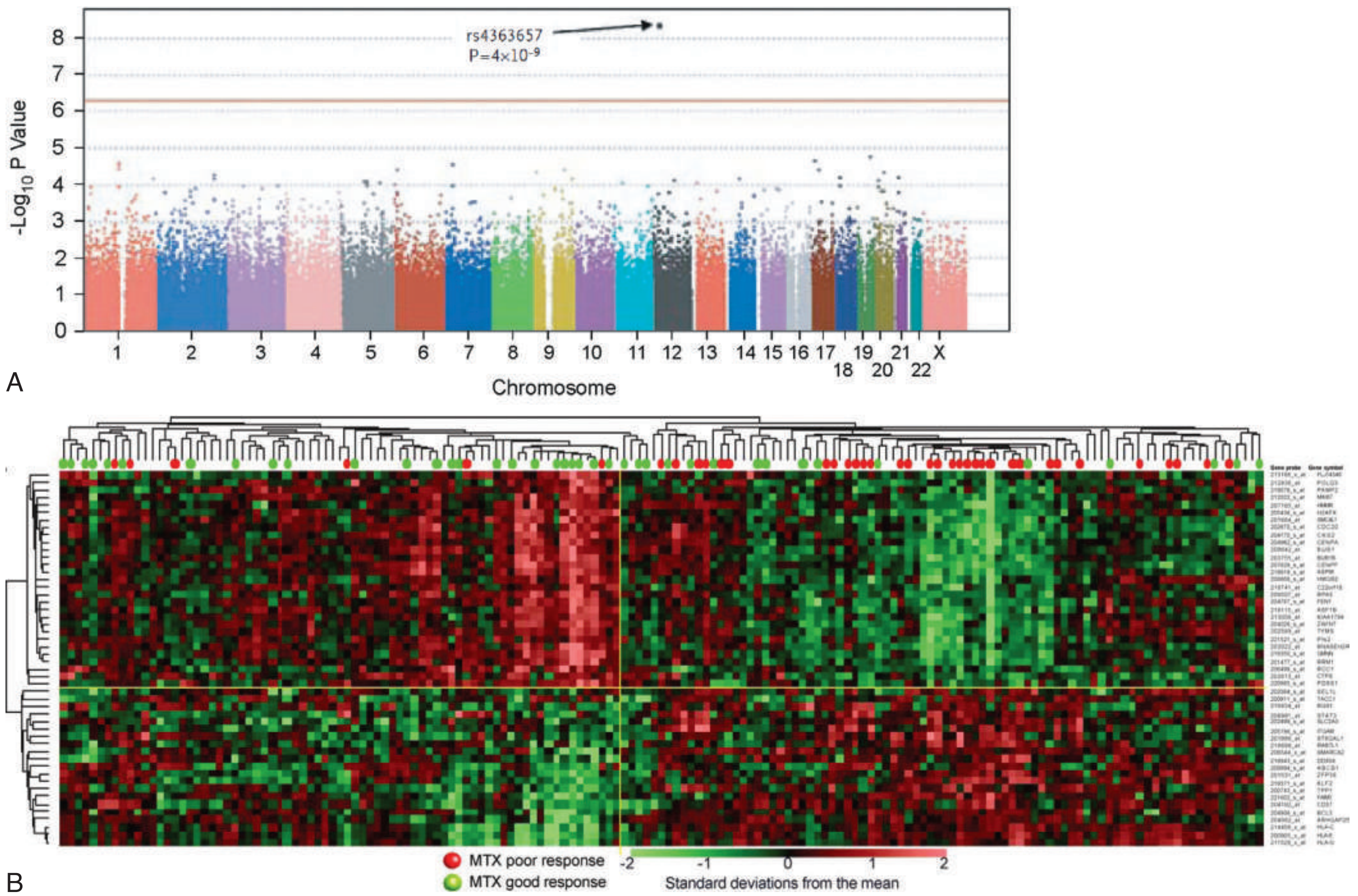

Figure 59-3 Presentations of pharmacogenomic data. **A,** Manhattan Plot from a genomewide association study. The Manhattan plot derives its name from the similarity of such a plot to the Manhattan skyline, and presents the genomewide significance of several hundred thousand SNPs distributed throughout the genome with the trait or phenotype of interest. In this example, each SNP included on the "chip" is plotted along the *x*-axis according to its chromosomal coordinate, with each color representing an individual chromosome from chromosome 1 to the X chromosome. The *y*-axis represents the inverse $\log_{10}$ of the *p* value for the association—the higher the value on the *y*-axis, the smaller the *p* value. A value of "15" corresponds to a *p* value of 10^{-15}. SNPs exceeding a particular threshold are subject to further verification and validation. **B,** "Heat map" constructed from gene expression data. In a heat map, the level of expression of many genes as obtained from microarray analysis is presented as a 2-dimensional matrix of values. Each column represents an individual patient and each row is an individual RNA transcript designated by the gene name. The level of gene expression is indicated by the color of each rectangle on a continuum from high expression *(red)* to low expression *(green).* In this example, ALL patients are clustered by their response to methotrexate, with patients responding to the drug having markedly different patterns of gene expression compared to nonresponders. One goal of personalized medicine is to use genomic information, like microarray data, to identify signatures of drug response (or risk of drug toxicity), to select the most appropriate drug among available options for each patient. *(**A** reprinted with permission from Search Collaborative Group. SLCO1B1 variants and statin-induced myopathy—a genome-wide study.* N Engl J Med *359:789–799, 2008;* ***B*** *from Sorich MJ, Pottier N, Pei D, Yang W, Kager L, et al. In vivo response to methotrexate forecasts outcome of acute lymphoblastic leukemia and has a distinct gene expression profile.* PLoS Med *5(4): e83, 2008.)*

characterize protein function in terms of activity and protein–protein or protein–nucleic acid interactions **(functional proteomics)**. Two-dimensional electrophoresis coupled with mass spectral detection is the mainstay of expression proteomics. Protein "spots" of interest are "picked," digested with a proteolytic enzyme such as trypsin, and identified by mass spectrometry. The data generated are compared with theoretically derived peptide mass databases for protein identification.

Metabolomics and metabonomics utilize sophisticated analytical platforms, such as nuclear magnetic resonance spectroscopy and liquid or gas chromatography coupled with mass spectral detection, to measure the concentrations of all small molecules present in a sample. **Metabolomics** refers to the study of the complete set of low-molecular-weight molecules (metabolites) present in a living system (cell, tissue, organ or organism) at a particular developmental or pathological state. **Metabonomics** is defined as the study of how the metabolic profile of biological systems changes in response to alterations because of pathophysiologic stimuli, toxic exposures, dietary changes, etc. **Pharmacometabonomics** has been defined as "the prediction of the outcome, efficacy or toxicity, of a drug or xenobiotic intervention in an individual based on a mathematical model of preintervention metabolite signatures." In the future, integrating metabolomics with pharmacogenomics and transcriptomics will result in a more "systems-based" understanding of cellular processes, especially in the context of drug efficacy and toxicity.

DEVELOPMENTAL PHARMACOGENETICS OF DRUG BIOTRANSFORMATION: APPLICATIONS TO PEDIATRIC DRUG THERAPY PRACTICE

The major consequence of pharmacogenetic polymorphisms in drug metabolizing enzymes is concentration-dependent toxicity caused by impaired drug clearance. In certain cases, reduced conversion of prodrug to therapeutically active compounds is also of clinical importance (see Table 59-2). Chemical modification of drugs via biotransformation reactions generally results in termination of biologic activity through decreased affinity for receptors or other cellular targets as well as more rapid elimination from the body. The process of drug biotransformation can be very complex, but is characterized by 3 important features. First is the concept of broad **substrate specificity**—a single

isozyme may metabolize a large variety of chemically diverse compounds. Second, many different enzymes may be involved in the biotransformation of a single drug (**enzyme multiplicity**). Finally, a given drug may undergo several different types of reactions. One example of this **product multiplicity** occurs with racemic warfarin, where at least 7 different hydroxylated metabolites are produced by different CYP isoforms.

Drug biotransformation reactions are conveniently classified into 2 main types, phase I and phase II reactions, which occur sequentially and serve to terminate biologic activity and enhance elimination (see Chapter 60). Phase I reactions introduce or reveal (via oxidation, reduction, or hydrolysis) a functional group within the substrate drug molecule that serves as a site for a phase II conjugation reaction. Phase II reactions involve conjugation with endogenous substrates, such as acetate, glucuronic acid, glutathione, glycine, and sulfate. These reactions further increase the polarity of an intermediate metabolite, make the compound more water soluble and thereby enhance its renal excretion. Interindividual variability in drug biotransformation activity (for both phase I and phase II reactions) is a consequence of the complex interplay among genetic (genotype, sex, race or ethnic background) and environmental (diet, disease, concurrent medication, other xenobiotic exposure) factors. The pathway and rate of a given compound's biotransformation is a function of each individual's unique phenotype with respect to the forms and amounts of drug-metabolizing enzymes expressed.

The **CYP** enzymes are quantitatively the most important of the **phase I enzymes**. These heme-containing proteins catalyze the metabolism of many lipophilic endogenous substances (i.e., steroids, fatty acids, fat-soluble vitamins, prostaglandins, leukotrienes, and thromboxanes) as well as exogenous compounds, including a multitude of drugs and environment toxins. CYP nomenclature is based on evolutionary considerations and uses the root symbol *CYP* for *cytochrome P450.* CYP enzymes that share at least 40% homology are grouped into families denoted by an Arabic number after the *CYP* root. Subfamilies, designated by a letter, appear to represent clusters of highly related genes. Members of the human CYP2 family, for example, have >67% amino acid sequence homology. Individual P450s in a subfamily are numbered sequentially (e.g., CYP3A4, CYP3A5). CYP enzymes that have been identified as being important in human drug metabolism are predominantly found in the CYP1, CYP2, and CYP3 gene families. Importantly, enzyme activity may be induced or inhibited by various agents (see Table 59-2).

For most CYP enzymes, genotype–phenotype relationships are influenced by development in that fetal expression is limited (with the exception of CYP3A7) and functional activity is acquired postnatally in isoform-specific patterns.

Phase II enzymes include arylamine *N*-acetyltransferases (NAT1, NAT2), glucuronosyltransferases (UGTs), epoxide hydrolase, glutathione *S*-transferases, sulfotransferases, and methyltransferases (catechol *O*-methyltransferase, thiopurine *S*-methyltransferase, several *N*-methyltransferases). Like the CYPs, UGTs, sulfotransferases, and glutathione *S*-transferases are gene families with multiple individual isoforms, each having its own preferred substrates, mode of regulation, and tissue-specific pattern of expression.

Clearance of some compounds appears to be greater in children relative to adults and the correlation between genotype and phenotype in neonatal life through adolescence may be overridden by these developmental phenomena.

CYP2D6

The *CYP2D6* gene locus is highly polymorphic, with more than 100 allelic variants identified to date (http://www.cypalleles.ki.se/cyp2d6.htm; see Table 59-2). Individual alleles are designated by the gene name *(CYP2D6)* followed by an asterisk, and an Arabic number. By convention, *CYP2D6*1* designates the fully functional wild-type allele. Allelic variants are the consequence of point mutations, single base-pair deletions or additions, gene rearrangements, or deletion of the entire gene, resulting in a reduction or complete loss of activity. Inheritance of 2 recessive loss-of-function alleles results in the **poor-metabolizer phenotype,** which is found in approximately 5-10% of white subjects and approximately 1-2% of Asian subjects. In white subjects, the *3, *4, *5, and *6 alleles are the most common loss-of-function alleles and account for approximately 98% of poor-metabolizer phenotypes. In contrast, CYP2D6 activity on a population basis tends to be lower in Asian and African-American populations because of a lower frequency of nonfunctional alleles (*3, *4, *5, and *6) and a relatively high frequency of population-selective alleles that are associated with decreased activity relative to the wild-type *CYP2D6*1* allele. The *CYP2D6*10* allele occurs at a frequency of approximately 50% in Asians, whereas *CYP2D6*17* and *CYP2D6*29* occur at relatively high frequencies in subjects of black African origin.

CYP2D6 is involved in the biotransformation of more than 40 therapeutic entities, including several β-receptor antagonists, antiarrhythmics, antidepressants, antipsychotics, and morphine derivatives (for an updated list, see http://static.medicine.iupui.edu/divisions/clinpharm/content/p450_Table_Oct_11_2009.pdf; see Table 59-2). CYP2D6 substrates commonly encountered in pediatrics include selective serotonin inhibitors (SSRIs; fluoxetine, paroxetine, sertraline), risperidone, atomoxetine, promethazine, tramadol, and codeine. Furthermore, nonprescription cold remedies such as dextromethorphan, diphenhydramine and chlorpheniramine are also CYP2D6 substrates. An analysis of CYP2D6 ontogeny in vitro that utilized a relatively large number of samples revealed that CYP2D6 protein and activity remain relatively constant after 1 wk of age up to 18 yr. Similarly, results from an in vivo longitudinal phenotyping study involving more than 100 infants over the 1st year of life demonstrated considerable interindividual variability in CYP2D6 activity, but no relationship between CYP2D6 activity and postnatal age between 2 wk and 12 mo of age. Furthermore, a cross-sectional study involving 586 children reported that the distribution of CYP2D6 phenotypes in children was comparable to that observed in adults by at least 10 yr of age. Thus, both available in vitro and in vivo data, albeit based on phenotype data rather than information on drug clearance from pharmacokinetic studies, imply that genetic variation is more important than developmental factors as a determinant of CYP2D6 variability in children.

One consequence of CYP2D6 developmental pharmacogenetics may be the syndrome of irritability, tachypnea, tremors, jitteriness, increased muscle tone, and temperature instability in neonates born to mothers receiving SSRIs during pregnancy. Controversy currently exists as to whether these symptoms reflect a neonatal withdrawal (hyposerotonergic) state or represent manifestations of serotonin toxicity analogous to the hyperserotonergic state associated with the SSRI-induced serotonin syndrome in adults (see Chapter 106.1). Delayed expression of CYP2D6 (and CYP3A4) in the 1st few wk of life is consistent with a hyperserotonergic state caused by delayed clearance of paroxetine and fluoxetine (CYP2D6) or sertraline (CYP3A4) in neonates exposed to these compounds during pregnancy. Furthermore, decreases in plasma SSRI concentrations and resolution of symptoms would be expected with increasing postnatal age and maturation of these pathways. Given that treatment of a "withdrawal" reaction may include administration of an SSRI, there is considerable potential for increased toxicity in affected neonates. Resolution of the question whether symptoms are caused by withdrawal vs a hyperserotonergic state is essential for appropriate management of SSRI-induced neonatal adaptation syndromes. Until further data are available, it is prudent to consider newborns and infants younger than 28 days of age as CYP2D6 genotypic poor metabolizers.

In older children, drug accumulation and resultant concentration-dependent toxicities in CYP2D6 genotypic poor metabolizers should be anticipated in the same way that they are in adults because of the risk of significant morbidity and mortality. Although a fluoxetine-related death has been reported in a 9 yr old child with a CYP2D6 poor metabolizer genotype, experience with paroxetine indicates that the risk of drug accumulation may also occur, under certain conditions, in individuals at the opposite end of the activity spectrum. The pharmacokinetics of paroxetine and nefazodone, both CYP2D6 substrates, correlate with the CYP2D6 phenotype in children and adolescents

7-17 yr of age. However, chronic dosing of paroxetine may lead to greater-than-anticipated drug accumulation in children classified as CYP2D6 extensive metabolizers. In depressed children and adolescents, as well as in adults, there is a disproportionate increase in peak concentrations and area under the serum concentration–time curves at higher dose levels. However, nonlinearity is more prominent in patients who are CYP2D6 extensive metabolizers, especially those with gene duplications and 3 or more functional alleles. The largest decreases in paroxetine clearance observed with ascending doses are seen in patients who have the greatest clearance at the initial dose level (10 mg/day) and are predicted to have the greatest CYP2D6 activity based on CYP2D6 genotype. This seemingly paradoxical effect is best explained in the context of data from in vitro studies. One proposed mechanism involves oxidation of paroxetine within the CYP2D6 active site to form a reactive intermediate that is associated with irreversible modification of the CYP2D6 protein in or near the active site. In theory, the greater the initial CYP2D6 activity, the greater the burden of reactive metabolite burden that is formed and thereby an increased loss of CYP2D6 catalytic activity. As a consequence, as the paroxetine dose is increased in patients with higher initial drug clearance, the risk of excessive drug accumulation increases disproportionately.

Theoretically, younger children may experience decreased efficacy or therapeutic failure with drugs such as codeine and tramadol that are dependent on functional CYP2D6 activity for conversion to the pharmacologically active species. CYP2D6 catalyzes the *O*-demethylation of inactive codeine to active morphine. Infants and children appear capable of converting codeine to morphine and achieving morphine : codeine ratios comparable to those of adults. However, in one study, morphine and its metabolites were not detected in 36% of children receiving codeine, making the level of analgesia from codeine unreliable in the studied pediatric population. Interestingly, in this study levels of morphine and its metabolites were not related to CYP2D6 phenotype. Finally, ultrarapid CYP2D6 metabolism of codeine may result in opiate intoxication, including maternal ultrarapid metabolism of codeine, which can result in high serum and breast milk concentrations of morphine and may have adverse effects in the breastfed neonate.

CYP2C9

Although several clinically useful compounds are substrates for CYP2C9 (http://static.medicine.iupui.edu/divisions/clinpharm/content/p450_Table_Oct_11_2009.pdf; see Table 59-2), the effects of allelic variation are most profound for drugs with a narrow therapeutic index, such as phenytoin, warfarin, and tolbutamide. In vitro studies show a progressive increase in CYP2C9 expression from 1-2% of mature levels in the 1st trimester to approximately 30% at term. Considerable variability (approximately 35-fold) in expression is apparent over the 1st 5 mo of life, with approximately one-half of the samples studied exhibiting values equivalent to those observed in adults. One interpretation of these data is that there is broad interindividual variability in the rate at which CYP2C9 expression is acquired after birth, and in general, the ontogeny of CYP2C9 activity in vivo, as inferred from pharmacokinetic studies of phenytoin in newborns, is consistent with the in vitro results. The apparent half-life of phenytoin is prolonged (approximately 75 hr) in preterm infants, but decreases to approximately 20 hr in term newborns. By 2 wk of age, the half-life has further declined to 8 hr. Concentration-dependent (saturable) metabolism of phenytoin, reflecting the functional acquisition of CYP2C9 activity, does not appear until approximately 10 days of age. The maximal velocity of phenytoin metabolism is reported to decrease from an average of 14 mg/kg/day in infants to 8 mg/kg/day in adolescents, which may reflect changes in the ratio of liver mass to total body mass observed over this period of development, as has been observed for warfarin.

At least 56 allelic variants of *CYP2C9* have been reported, but not all have been evaluated for their functional consequences. The *CYP2C9*2* allele is associated with approximately 5.5-fold decreased intrinsic clearance for *S*-warfarin relative to the wild-type enzyme. Allelic variations resulting in amino acid changes within the enzyme active site, such as the *CYP2C9*3, CYP2C9*4,* and *CYP2C9*5* alleles, are associated with activities that are approximately 5% of the wild-type protein. Approximately one-third of the white population carries a variant *CYP2C9* allele (*2 and *3 alleles, most commonly), whereas the *2 and *3 alleles are virtually nonexistent in African-American, Chinese, Japanese, and Korean populations. In contrast, the *5 allele has been detected in African-Americans, but not in white subjects. The risk of bleeding complications in patients treated with warfarin and with concentration-dependent toxicity in patients treated with phenytoin is most pronounced for individuals with a *CYP2C9*3/*3* genotype.

Compared to adults, the pharmacogenetics of warfarin dosing has not been studied as extensively in children. In adults, genetic variation in CYP2C9 and the warfarin target,VKORC1, as well as patient age, sex and weight, can account for 50-60% of the variation in warfarin dose requirements. A large fraction of the source of variation is still unknown, but it may be at least partially attributed to interactions with other drugs and foods. Studies in children demonstrate that the contribution of *VCKORC1* and *CYP2C9* genotypes to variability in warfarin dose to achieve a stable international normalized ratio is quite variable, ranging from <5% to approximately 30%, and in each study the contribution of age, or a developmental variable that correlates with age (e.g., height or weight) accounts for the largest amount of variability. The factors contributing to differences between children and adults, and especially among the published pediatric studies, are not clear at this time.

CYP2C19

In vitro, CYP2C19 protein and catalytic activity can be detected at levels representing 12-15% of mature values by 8 wk of gestation and remain essentially unchanged throughout gestation and at birth. Over the 1st 5 mo of postnatal age, CYP2C19 activity increases linearly. Adult levels are achieved by 10 yr of age, although variability in expression is estimated to be approximately 21-fold between 5 mo and 10 yr of age. The major source of this variability is likely pharmacogenetic in nature. The CYP2C19 poor-metabolizer phenotype (also known as *mephenytoin hydroxylase deficiency*) is present in 3-5% of the white population and 20-25% of Asians. Although 25 variant alleles have been reported to date, the 2 most common variant alleles, *CYP2C19*2* and *CYP2C19*3,* result from single base substitutions that introduce premature stop codons and, consequently, truncated polypeptide chains that possess no functional activity. Despite consistent increases in CYP2C19 activity observed in vitro over the 1st 5 mo of life, the results of an in vivo phenotyping study with omeprazole in Mexican children revealed a broad range of activity and implied that 17% of infants younger than 4 mo of age could be classified as poor metabolizers (no poor metabolizers were detected beyond that point). In contrast, 20% of children 3-9 mo old were classified as ultrarapid metabolizers compared with 6% of infants 1-3 mo of age. Similarly, a series of studies investigating pantoprazole pharmacokinetics in newborns, children and adolescents has revealed that the apparent oral clearance of pantoprazole is independent of *CYP2C19* genotype in the 1st 2-3 mo after birth, but poor metabolizers can be distinguished from extensive metabolizers after 4-6 mo of age. The pharmacokinetic parameters of omeprazole are comparable to those observed in adults are achieved by 2 yr of age.

CYP2C19 also plays an important role in the metabolism of lansoprazole. In Japanese adults treated with lansoprazole, amoxicillin, and clarithromycin for *Helicobacter pylori* infection, the eradication rate for CYP2C19 poor metabolizers (97.8%) and heterozygous extensive metabolizers (1 functional *CYP2C19* allele; 92.1%) was significantly greater than that observed in homozygous extensive metabolizers (72.7%). Of the 35 patients in whom initial treatment did not eradicate *H. pylori,* 34 had at least 1 functional *CYP2C19* allele and eradication could be achieved with higher lansoprazole doses in almost all cases. Given that the frequency of the functional *CYP2C19*1* allele is considerably greater in white subjects (approximately 0.84 [84%]) compared with Japanese subjects (approximately 0.55 [55%]), eradication failure can be expected to occur more frequently in whites. Because

proton pump inhibitors are widely used in children, pharmacogenetic as well as developmental considerations should guide pediatric dosing strategies.

CYP3A4, CYP3A5, and CYP3A7

The CYP3A subfamily consists of 4 members in humans (CYPs 3A4, 3A5, 3A7, and 3A43) and is quantitatively the most important group of CYP enzymes in terms of human hepatic drug biotransformation. These isoforms catalyze the oxidation of many different therapeutic entities, several of which are of potential importance to pediatric practice (for an updated list, see http://static.medicine.iupui.edu/divisions/clinpharm/content/p450_Table_Oct_11_2009.pdf; see Table 59-2). CYP3A7 is the predominant CYP isoform in fetal liver and can be detected in embryonic liver as early as 50-60 days' gestation. CYP3A4, the major CYP3A isoform in adults, is essentially absent in fetal liver, but increases gradually throughout childhood. Over the 1st 6 mo of life, CYP3A7 expression exceeds that of CYP3A4, although its catalytic activity toward most CYP3A substrates is rather limited compared with that of CYP3A4. CYP3A4 is also abundantly expressed in intestine, where it contributes significantly to the first-pass metabolism of orally administered drugs which are substrates (i.e., midazolam). CYP3A5 is polymorphically expressed and is present in approximately 25% of adult liver samples studied in vitro.

Several methods have been proposed to measure CYP3A activity. Using these various phenotyping probes, CYP3A4 activity has been reported to vary widely (up to 50-fold) among individuals, but the population distributions of activity are essentially unimodal and evidence for polymorphic activity has been elusive. Although 24 allelic variants have been identified to date (http://www.cypalleles.ki.se/cyp3a4.htm), most occur relatively infrequently and do not appear to be of clinical importance. Of interest to pediatrics is the *CYP3A4*1B* allele present in the *CYP3A4* promoter region. The clinical significance of this allelic variant appears limited with respect to drug biotransformation activity, despite being associated with 2-fold increased activity over the wild-type *CYP3A4*1* allele in in vitro assays. Although there does not appear to be an association between the *CYP3A4*1B* allele and age of menarche, a significant relationship does exist between the number of *CYP3A4*1B* alleles and the age at onset of puberty, as defined by Tanner breast score. In one study, 90% of 9 yr old girls with a *CYP3A4*1B/*1B* genotype had a Tanner breast score of ≥2 compared with 56% of *CYP3A4*1A/*1B* heterozygotes and 40% of girls homozygous for the *CYP3A4*1A* allele. Because CYP3A4 plays an important role in testosterone catabolism, the authors of the latter study proposed that the estradiol : testosterone ratio may be shifted toward higher values in the presence of the *CYP3A4*1B* allele and trigger the hormonal cascade that accompanies puberty. Intestinal CYP3A4 activity is inhibited by grapefruit juice and may result in higher levels of the many drugs metabolized by this enzyme; very large quantities of grapefruit juice may also inhibit the hepatic CYP3A4.

The *CYP3A4*22* allele has received attention due to its association with reduced clearance of statins in adults as well as immunosuppressants, such as cyclosporine and tacrolimus, in children and adults. Improved response to inhaled fluticasone has also been reported in asthmatic children who are carriers of the *CYP3A4*22* allele.

Polymorphic *CYP3A5* expression is largely the result of a SNP in intron 3 that creates a cryptic splice site and gives rise to messenger RNA splice variants that retain part of intron 3 with a premature stop codon. The truncated messenger RNA transcripts associated with this allele, *CYP3A5*3,* cannot be translated into a functional protein. Individuals with at least 1 wild-type *CYP3A5*1* allele express functional CYP3A5 protein, whereas those homozygous for *CYP3A5*3 (CYP3A5*3/*3)* do not express appreciable amounts of functional protein. Approximately 60% of African-Americans show functional hepatic CYP3A5 activity compared with only 33% of European Americans. Clinically important consequences of *CYP3A5* allelic variation have been reported in children. In pediatric heart transplant patients with a *CYP3A5*1/*3* genotype, tacrolimus concentrations were approximately 50% of those observed in patients with *CYP3A5*3/*3* genotypes, when corrected for dose, 3 mo, 6 mo, and 12 mo after transplant. Thus, larger doses of tacrolimus are required in patients with functional CYP3A5 protein to achieve comparable blood levels and to minimize the risk of rejection.

Glucuronosyltransferases

The UGT gene superfamily catalyzes the conjugation (with glucuronic acid) of several drugs used clinically in pediatrics, including morphine, acetaminophen, nonsteroidal antiinflammatory drugs, and benzodiazepines. The effect of development on glucuronidation capacity has been well described and is illustrated by hyperbilirubinemia, **gray baby syndrome** (the cardiovascular collapse associated with high doses of chloramphenicol in newborns), and the 3.5-fold increase in morphine clearance observed in premature neonates at 24-39 wk postconceptional age. As with the CYPs, there are multiple UGT isoforms, and the acquisition of functional UGT activity appears to be isoform- and substrate-specific.

UGT1A1 is the major UGT gene product responsible for bilirubin glucuronidation, and more than 100 genetic alterations have been reported (Table 59-3), most of which are rare and are more properly considered mutations rather than gene polymorphisms (see Chapters 102 and 357.1). Inheritance of 2 defective alleles is associated with reduced bilirubin-conjugating activity and gives rise to clinical conditions, such as Crigler-Najjar syndrome and Gilbert syndrome. More frequently occurring polymorphisms involve a dinucleotide (TA) repeat in the atypical TATA box of the *UGT1A1* promoter. The wild-type *UGT1A1*1* allele has 6 repeats (TA_6), and the TA_5 *(UGT1A1*33)*, TA_7 *(UGT1A1*28)*, and TA_8 *(UGT1A1*34)* variants are all associated with reduced activity. *UGT1A1*28,* the most frequent variant, is a contributory factor to prolonged neonatal jaundice. This variant is also associated with impaired glucuronidation and thus toxicity of the active metabolite, SN-38, of the chemotherapeutic agent irinotecan. Allelic variations in *UGT1A7* and *UGT1A9* are also associated with irinotecan toxicity in adults with colorectal cancer.

The consequences of allelic variation in the *UGT2B* family are less certain. The predominant routes of morphine elimination include biotransformation to the pharmacologically active 6-glucuronide and the inactive 3-glucuronide. 6-Glucuronide formation is almost exclusively catalyzed by UGT2B7, whereas several UGTs in the UGT1A subfamily and UGT2B7 both contribute to 3-glucuronide formation. Increased 6-glucuronide : morphine ratios have been reported in individuals homozygous for the SNPs constituting the *UGT2B7*2* allele. Although individuals genotyped as *UGT2B7*2/*2* may produce higher than anticipated concentrations of pharmacologically active morphine and its metabolites, prospective pharmacogenetic studies addressing phenotype-genotype correlations and the consequences of morphine analgesia have had conflicting results.

Arylamine *N*-Acetyltransferases

One of the earliest discovered and most widely recognized genetic polymorphisms is the NAT2 polymorphism. Approximately 50% of whites and African-Americans in North America are phenotypically slow metabolizers, placing a substantial number of individuals at increased risk for the development of adverse drug effects, such as sulfasalazine-induced hemolysis, hydrazine or arylamine-induced peripheral neuropathy, procainamide- or isoniazid-induced systemic lupus erythematosus, and Stevens-Johnson syndrome or toxic epidermal necrolysis associated with sulfonamide administration. NAT2 function is inherited in an autosomal dominant fashion, with the inheritance of 2 "slow" alleles required for expression of the slow-metabolizer phenotype. The relative proportion of rapid and slow metabolizers varies considerably with ethnic or geographic origin. The percentage of slow acetylators among Canadian Eskimos is 5%, but it approaches 90% in some Mediterranean populations.

In vivo, with the use of caffeine as a phenotyping probe, all infants 0-55 days of age appear to be phenotypically slow acetylators, whereas 50% and 62% of infants 122-224 and 225-342 days of age, respectively, can be characterized as fast acetylators. Several independent studies indicate that maturation of the NAT2 phenotype occurs during the 1st 4 yr of life. Phenotype-genotype discordance is likely to be most

Table 59-3 Internet Resources for Pharmacogenetics and Pharmacogenomics*

INTRODUCTION TO PHARMACOGENOMICS	
http://www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-molecular-medicine/current-topics/pharmacogenomics.shtml	
http://ghr.nlm.nih.gov/handbook/genomicresearch/pharmacogenomics	
http://learn.genetics.utah.edu/content/pharma/	
http://pgrn.org/display/pgrnwebsite/PGRN+Home	
http://www.pharmgkb.org/	
PHARMACOGENETICS: ALLELIC VARIANTS OF DRUG METABOLIZING ENZYMES	
CYP2C9	http://www.cypalleles.ki.se/cyp2c9.htm
CYP2C19	http://www.cypalleles.ki.se/cyp2c19.htm
CYP2D6	http://www.cypalleles.ki.se/cyp2d6.htm
CYP3A4	http://www.cypalleles.ki.se/cyp3a4.htm
CyP3A5	http://www.cypalleles.ki.se/cyp3a5.htm
UGTs	http://www.pharmacogenomics.pha.ulaval.ca/cms/ugt_alleles/
NAT1 and NAT2	http://nat.mbg.duth.gr/
PHARMACOGENETICS: SUBSTRATES OF DRUG METABOLIZING ENZYMES	
http://static.medicine.iupui.edu/divisions/clinpharm/content/p450_Table_Oct_11_2009.pdf	
PHARMACOGENETICS-BASED DOSING GUIDELINES	
Dosing guidelines incorporating pharmacogenetic data developed by the Clinical Pharmacogenetics Implementation Consortium are available on the National Guidelines Clearinghouse website a publicly accessible resource for evidence-based clinical guidelines sponsored by the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health Services:	
CYP2D6, CYP2C19, and tricyclic antidepressants	http://www.guideline.gov/content.aspx?id=43954
CYP2D6 and codeine	http://www.guideline.gov/content.aspx?id=39534
TPMT and thiopurines	http://www.guideline.gov/content.aspx?id=43955
HLA-B and allopurinol	http://www.guideline.gov/content.aspx?id=39536
HLA-B and abacavir	http://www.guideline.gov/content.aspx?id=39535
SLCO1B1 and simvastatin	http://www.guideline.gov/content.aspx?id=39537

*All sites were accessible on November 30, 2014.
HLA, human leukocyte antigen; TMPT, thiopurine methyltransferase.

apparent in the 1st 2-4 mo of life, and drugs that are highly dependent on NAT2 function for their elimination should be used with caution.

Thiopurine *S*-Methyltransferase

Thiopurine *S*-methyltransferase (TPMT) is a cytosolic enzyme that catalyses the *S*-methylation of aromatic and heterocyclic sulfur-containing compounds, such as 6-mercaptopurine (6MP), azathioprine, and 6-thioguanine, used in the treatment of acute lymphoblastic leukemia (ALL), inflammatory bowel disease, juvenile arthritis, and for the prevention of renal allograft rejection. To exert its cytotoxic effects, 6MP requires metabolism to thioguanine nucleotides by a multistep process that is initiated by hypoxanthine guanine phosphoribosyl transferase. TPMT prevents thioguanine nucleotide production by methylating 6MP (Fig. 59-4*A*). TPMT activity is usually measured in erythrocytes, with activity in erythrocytes reflecting that which is found in other tissues, including liver and leukemic blasts. Although approximately 89% of whites and African-Americans have high TPMT activity and 11% have intermediate activity, 1 in 300 individuals inherit TPMT deficiency as an autosomal recessive trait (Fig. 59-4*B*). In newborn infants, peripheral blood TPMT activity is reported to be 50% greater than in race-matched adults and shows a distribution of activity that is consistent with the polymorphism characterized in adults. There are no data currently to indicate how long this higher activity is maintained, although TPMT activities were comparable to previously reported adult values in a population of Korean schoolchildren age 7-9 yr. In patients with intermediate or low activity, more drug is shunted toward production of cytotoxic thioguanine nucleotides. TPMT can also methylate 6-thioinosine 5′-monophosphate to generate a methylated metabolite that is capable of inhibiting de novo purine synthesis (Fig. 59-4*C*). Three mutations have been identified in the TPMT gene (*2, *3A, *3C), which account for 98% of white subjects with low activity. These mutations encode proteins that undergo rapid proteolysis resulting in low enzyme activity.

*TPMT*3A* is the most common mutant allele and is characterized by 2 nucleotide transition mutations, G460A and A719G, that lead to 2 amino acid substitutions, Ala154Thr and Tyr240Cys (see Fig. 59-4*D*). Although the *3A allele only has a frequency of 0.03% in the general population, it represents 55% of all mutant alleles. Either mutation alone results in loss of functional activity through the production of unstable proteins that are subject to accelerated proteolytic degradation. Less-frequent allelic variants involve SNPs that produce amino acid substitutions in the coding region and defective intron–exon splicing. A polymorphic locus has been identified in the promoter region of the *TPMT* gene involving 4-8 repeats of a specific nucleotide sequence in tandem. Although these repeats appear to modulate TPMT activity when expressed in vitro, their role in regulating activity in vivo has not been clearly established.

The relatively few patients with low to absent TPMT activity (0.3%) are at increased risk for **severe myelosuppression** if treated with routine doses of thiopurines; thus, they require a 10-15–fold reduction in dose to minimize this risk. Furthermore, if not dosed properly, patients may be at increased risk for relapse as a result of inadequate or absent treatment with thiopurines. Given the expanding use of 6MP and azathioprine in pediatrics to treat inflammatory bowel disease and juvenile arthritis and to prevent renal allograft rejection, TPMT pharmacogenetics is not a trivial matter.

Introduction of the TPMT phenotype or genotype determination into pediatric practice will lead to safer, more efficacious treatment in pediatric patient groups. Although the majority of research has been conducted in patients with acute lymphoblastic leukemia, the observation that patients classified as having intermediate TPMT activity are more likely to be intolerant of 6MP or azathioprine and likely will require more frequent dosage reductions in response to drug-induced myelosuppression is equally applicable to other pediatric patient groups (i.e., patients with Crohn disease) treated with this family of drugs.

PHARMACOGENETICS OF DRUG TRANSPORTERS

There are several major types of membrane transporters, including organic anion transporter (OAT), organic anion transporting polypeptides (OATPs), organic cation transporting proteins (OCTs), and the adenosine triphosphate–binding cassette (ABC) transporters, such as P-glycoprotein and the multidrug-resistant proteins (MRPs).

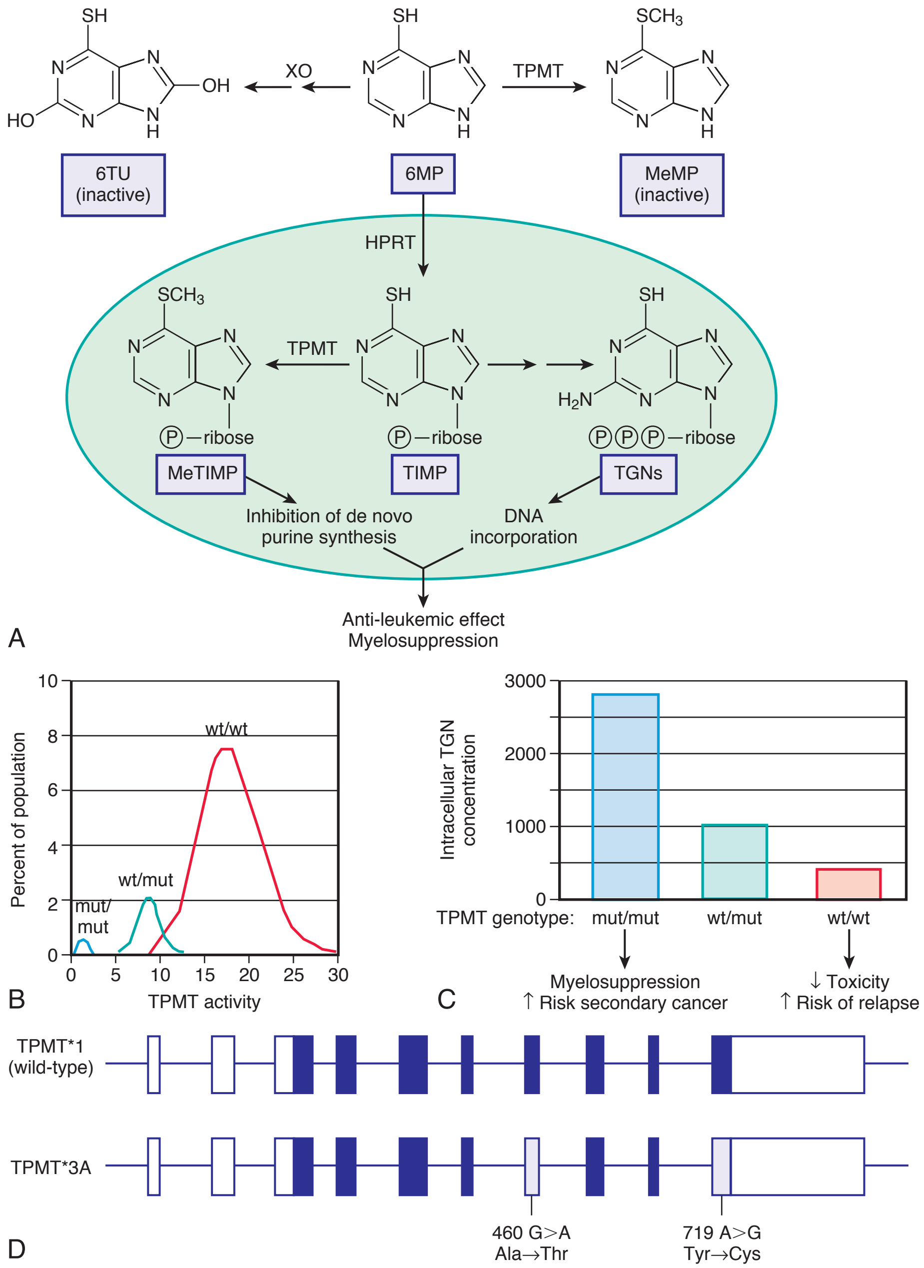

Figure 59-4 Thiopurine *S*-methyltransferase (TPMT) polymorphism. **A,** 6-Mercaptopurine (6MP) undergoes metabolism to thioguanine nucleotides (TGNs) to exert its cytotoxic effects. TPMT and xanthine oxidase reduce the amount of 6MP available for the bioactivation pathway to TGNs. TPMT can also methylate 6-thioinosine 5′-monophosphate (TIMP) to generate a methylated compound capable of inhibiting de novo purine synthesis. **B,** Distribution of TPMT activity in humans. Of the population, 89% has high activity, whereas 11% has intermediate activity. Approximately 1 in 300 individuals homozygous for 2 loss-of-function alleles has very low activity. **C,** Correlation between the TPMT genotype and intracellular TGN concentrations. In TPMT poor metabolizers, more 6MP is available to go down the bioactivation pathway to form TGNs; this situation is associated with an increased risk of myelosuppression. **D,** The most common variant TPMT allele is the result of 2 mutations that give rise to an unstable protein product that undergoes proteolytic degradation. *HPRT,* 6-thiomethylinosine 5-monophosphate; *MeMP,* 6-methylmercaptopurine; *MeTIMP,* hypoxanthine-guanine phosphoribosyl transferase; *mut,* mutant; *6TU,* 6-thiouric acid; *wt,* wild type. *(Modified with permission from Relling MV, Dervieux T: Pharmacogenetics and cancer therapy.* Nat Rev Cancer *11:99–108, 2001; copyright 2001, Macmillan Magazines Ltd.)*

Membrane transporters are heavily involved in drug disposition and actively transport substrate drugs between organs and tissues. Drug transporters are expressed at numerous epithelial barriers, such as intestinal epithelial cells, hepatocytes, renal tubular cells, and at the blood–brain barrier (Fig. 59-5). Transporters often are also determinants of drug resistance, and many drugs work by affecting the function of transporters. As such, polymorphisms in the genes encoding these proteins may have a significant effect on the absorption, distribution, metabolism, and excretion as well as the pharmacodynamic effect of a wide variety of compounds.

The Adenosine Triphosphate–Binding Cassette Superfamily

The ABC transporters belong to the largest known transporter gene family and translocate a variety of substrates, including chemotherapy agents. ABC multidrug transporter expression is implicated in tumor cell resistance to anticancer therapy, altered disposition of chemotherapy drugs, and toxic side effects associated with chemotherapy. More recently, the genetic heterogeneity of a number of the ABC transporter genes has been described. Apart from having at least 1 adenosine triphosphate (ATP)-binding domain, these transporters are

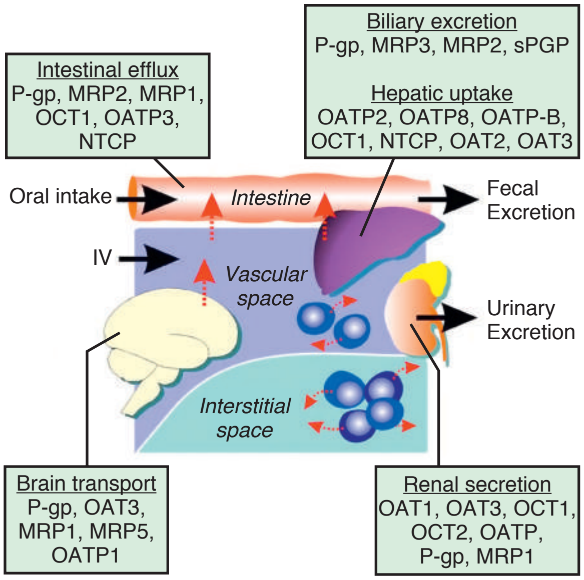

Figure 59-5 Schematic of important transport proteins and their known locations in humans. Spheres correspond to drug molecules. *(Reprinted with permission from American Pharmacists Association. Ritschel WA, Kearns GL, editors.* Handbook of basic pharmacokinetics including clinical applications, *ed 7, Washington, DC, 2009, American Pharmacists Association, p. 45.)*

characterized by a signature sequence of amino acid residues within the ATP-binding domain. In humans, the ABC transporters function as efflux pumps, which, together with detoxification enzymes, constitute a complex integrated "chemoimmunologic defense" system against drugs and other foreign chemicals. A variety of epithelial barriers, including the kidney, liver, and blood–brain barrier, have abundant expression of ABC transporters, such as P-glycoprotein (P-gp; also known as *MDR1*), and MRPs 1, 2, and 3. Powered by ATP, these transporters actively extrude substrates from the respective cell and organ.

Studies conducted in children need to also consider the ontogeny of P-gp expression. Based on studies utilizing human lymphocytes, it appears that P-gp activity is high at birth, decreases between the ages of 0 and 6 mo, and stabilizes between 6 mo and 2 yr of age. In contrast, P-gp can be detected in human neural stem/progenitor cells and decreases with differentiation. Furthermore, P-gp has been proposed as an endothelial marker for development of the blood–brain barrier, and expression increases with postnatal age as the blood–brain barrier matures. Thus, the developmental patterns of P-gp expression likely are tissue-specific, but data are very limited in this regard. Nevertheless, it is likely that expression of P-gp at a young age in gut and liver represents a protective mechanism in which both endogenous and exogenous toxins are efficiently excreted from the body. However, developmental patterns of expression in tissues of drug response, such as lymphocytes and tumors, may also affect the efficacy of intracellular drugs. For example, polymorphisms in the gene have been shown to be predictive of the ability to wean steroids after heart transplantation, as well as the susceptibility to and clinical outcome of treatment for pediatric ALL. On the other hand, immaturity of P-gp expression in the developing blood–brain barrier may contribute to discrete periods of increased susceptibility to drug toxicity in the central nervous system. However, for most other drugs, including immunosuppressants and protease inhibitors, studies investigating the effect of *ABCB1* polymorphisms in drug disposition and response have yielded conflicting results. In one study investigating the relationship between *ABCB1* genotype and cyclosporine pharmacokinetics, an effect of genotype on oral availability was only apparent in children older than 8 yr of age.

Organic Anion Transporting Polypeptides

OATPs in the solute carrier OAT (SLCO) represent a family of glycoprotein transporters with 12 transmembrane spanning domains, and are expressed in various epithelial cells. There are 11 OATPs in humans, some of which are ubiquitously expressed and others whose expression is restricted to specific tissues. Typical substrates include bile salts, hormones and their conjugates, toxins, and various drugs. The solute carrier, human OATP1A2 (OATP-A, OATP1, and OATP), is highly expressed in the intestine, kidney, cholangiocytes and the blood–brain barrier and may be important in the absorption, distribution, and excretion of a broad array of clinically important drugs. Several nonsynonymous polymorphisms have been identified in the gene encoding OATP1A2, SLCO1A2 (SLC21A3), with some of these variants demonstrating functional changes in the transport of OATP1A2 substrates.

OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3) are liver-specific transporters and promote the cellular uptake of endogenous substrates, such as bilirubin, bile acids, dehydroepiandrosterone-sulfate and leukotriene C_4, as well as various drugs, including several statins, methotrexate, and enalapril. Allelic variation in OATP1B1 (specifically, the *SLCO1B1*5* allele) results in reduced clearance and increased systemic exposure of several statin drugs (atorvastatin, pravastatin, and simvastatin), and is associated with an increased risk of musculoskeletal side effects from simvastatin. The ontogeny of OATP1B1 has not been extensively studied in children, but the results of a small pharmacogenetic study conducted in children with familial hypercholesterolemia and pediatric cardiac transplant patients revealed an association between *SLCO1B1*5* and pravastatin concentrations that was the opposite to that observed in adults. Several studies confirm that the 2 SNPs determining the most common *SLCO1B1* haplotypes (**1a, *1b, *5,* and **15*), rs4149056 and rs2306283, are associated with decreased clearance of high-dose methotrexate in children with ALL. Genotyping for *SLCO1B1* may be helpful in identifying patients at increased risk of toxicity due to reduced clearance/increased accumulation of methotrexate, but prospective studies have not yet been conducted.

Organic Cation Transporters

OCTs in the SCL22A subfamily are primarily expressed on the basolateral membrane of polarized epithelia, and mediate the renal secretion of small organic cations. Originally, OCT1 (also known as SLC22A1) was thought to be primarily expressed in liver, but recent studies localized its expression to the apical side of proximal and distal renal tubules. OCT2 (SLC22A2) is predominantly expressed on the basolateral surface of proximal renal tubules. In adults, allelic variation in OCT1 and OCT2 is associated with increased renal clearance of metformin. The role of genetic variation of OCT1 and OCT2 has not been studied in children, but developmental factors appear to be operative. For example, neonates possess very limited ability to eliminate organic cations, but this function increases rapidly during the 1st few mo of life, and when standardized for body weight or surface area, it tends to exceed adult levels during the toddler stage.

PHARMACOGENETICS OF DRUG RESPONSE: POLYMORPHISMS IN DRUG RECEPTORS, ION CHANNELS, AND OTHER DRUG TARGETS DURING GROWTH AND DEVELOPMENT

Receptors are the targets for drugs and endogenous transmitters because of their inherent molecular recognition sites. Drugs and transmitters bind to the receptor to produce a pharmacologic effect. Variability in the receptor protein or the ion channel may determine the magnitude of the pharmacologic response. For example, polymorphisms of the β_2-adrenergic receptor gene *(ADRB2)* are associated with variable responses to bronchodilator drugs.

Drug responses are seldom monogenic events because multiple genes are involved in both drug binding to the pharmacologic target and the subsequent downstream signal transduction events that ultimately collectively manifest as a therapeutic effect. Although genotypes at a particular locus may show a statistically significant effect on the outcome of interest, they may account for only a relatively small amount of the overall population variability for that outcome. For example, a particular group of SNPs in the corticotropin-releasing hormone receptor 1 *(CRHR1)* gene is associated with a statistically

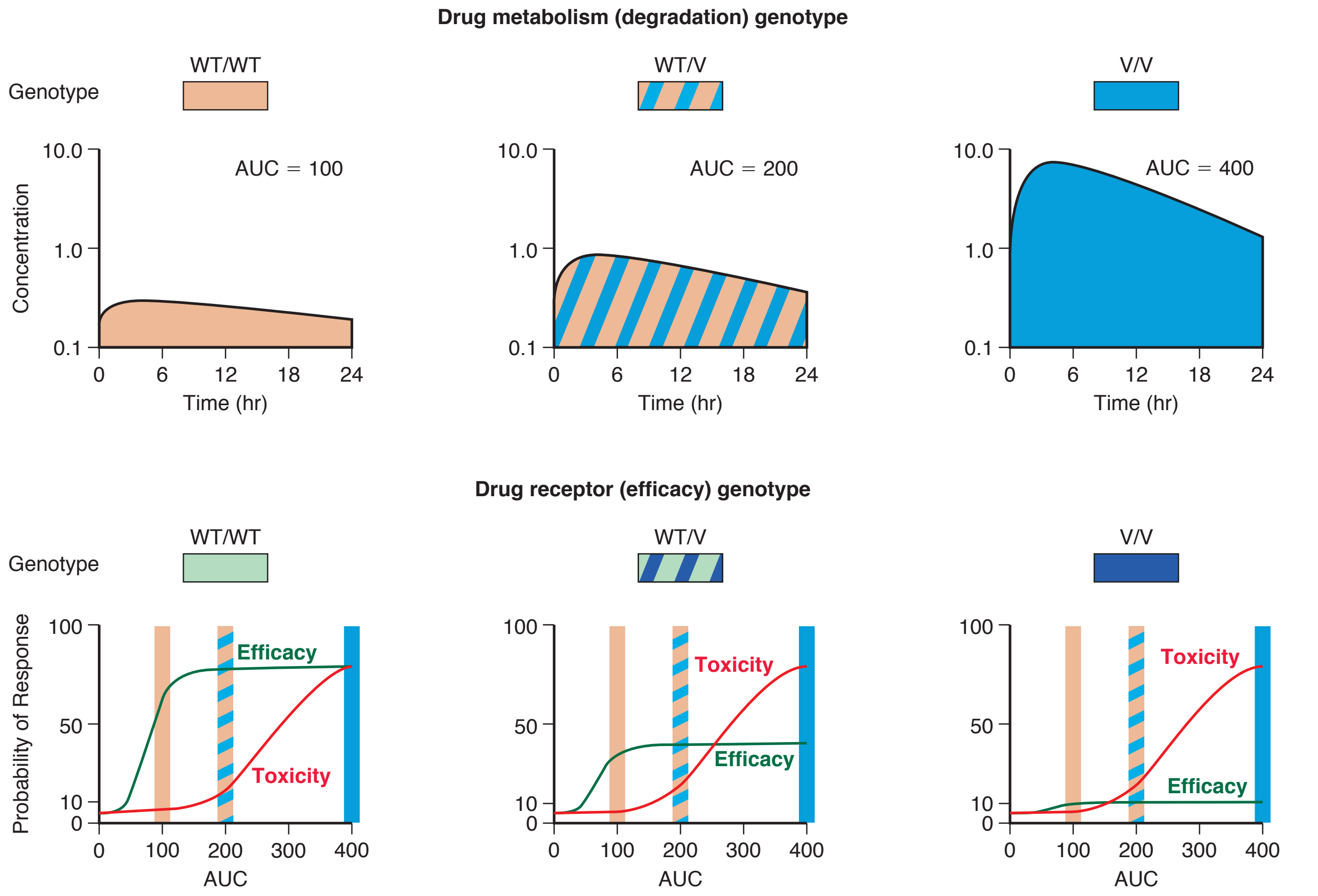

Polygenic drug response

Metabolism genotype		Receptor genotype	Probability of Response		Therapeutic Index	Individual risk : benefit assessment		
			Efficacy	Toxicity		Benefit	vs	risk
	+		65%	5%	13.0	Benefit	>>>>	Risk
	+		32%	5%	6.0	Benefit	>>>	Risk
	+		10%	5%	2.0	Benefit	>	Risk
	+		75%	15%	5.0	Benefit	>>	Risk
	+		40%	15%	2.7	Benefit	>	Risk
	+		10%	15%	0.7	Risk	>	Benefit
	+		80%	80%	1.0	Benefit	≈	Risk
	+		40%	80%	0.5	Risk	>>	Benefit
	+		10%	80%	0.1	Risk	>>>>	Benefit

Figure 59-6 **Polygenic determinants of drug response.** The potential effects of 2 genetic polymorphisms are illustrated. In each panel, there is a profile for subjects who have 2 wild-type alleles (WT/WT), those who are heterozygous for 1 wild-type and 1 variant (V) allele (WT/V), and those who have 2 variant alleles (V/V) for the depicted gene. The *top panel* illustrates a potential polymorphism involving a drug-metabolizing enzyme where variant alleles result in decreased drug metabolism and greater exposure (as shown by the increasing area under the concentration-time curve [AUC]). The *second panel* illustrates a potential polymorphism involving a drug receptor and depicts variant alleles which result in decreased receptor sensitivity. Note that for each receptor type, there are 3 possibilities for drug exposure. At the bottom is a table that shows the 9 resulting combinations of drug-metabolism and drug-receptor genotypes and the corresponding drug-response phenotypes calculated from data shown in the second panel. These phenotypes allow for calculation of a therapeutic index (i.e., efficacy : toxicity, in this example these range from 13 [65%:5%] to 0.1 [10%:80%]), which results in the ability to perform an individualized risk : benefit assessment. *(Adapted from Evans WE, McLeod HL: Pharmacogenomics—drug disposition, drug targets, and side effects.* N Engl J Med *348:538–549, 2003.)*

significant improvement in forced expiratory volume in 1 sec, but accounts for only 6% of the overall variability in response to inhaled corticosteroids (see Chapter 144). A series of subsequent studies has determined that allelic variation in several genes in the steroid pathway contributes to overall response to this form of therapy.

The listing and classification of receptors is a major initiative of the International Union of Pharmacology. The list of receptors and voltage-gated ion channels is available on the International Union of Pharmacology website (http://www.guidetopharmacology.org/).

CURRENT AND FUTURE APPLICATIONS FOR PHARMACOGENETICS AND PHARMACOGENOMICS IN PEDIATRICS

Progress being made in the treatment of ALL provides an outstanding example of how the application of pharmacogenomic principles can improve pediatric drug therapy (see Chapter 495). Despite improved understanding of the genetic determinants of drug response, however, many complexities remain to be resolved. Patients with ALL who have 1 wild-type allele and intermediate TPMT activity tend to have a better response to 6MP therapy than patients with 2 wild-type alleles and full activity. Reduced TPMT activity also places patients at risk for irradiation-induced secondary brain tumors and etoposide-induced acute myeloid leukemias. Pharmacogenetic polymorphisms of several additional genes also have the potential to influence successful treatment of ALL. Multiple genetic and treatment-related factors interact to create patient subgroups with varying degrees of risk, and these represent an opportunity for pharmacogenomic approaches to identify subgroups of patients who will benefit from specific treatment regimens and those who will be at risk for short- and long-term toxicities (Fig. 59-6).

The 20% of patients with ALL who do not respond to chemotherapy represent an additional challenge for pharmacogenomic research. Gene expression (microarray) studies in ALL blasts are able to discriminate among phenotypic subtypes and identify some individuals who are at risk for treatment failure. An analysis of acute treatment-induced changes in the gene response of ALL blasts obtained 1 day after the initiation of 6MP and methotrexate as single agents or in combinations of high-dose or low-dose methotrexate and 6MP showed several important insights into the cellular response to these treatments. Changes in gene expression were treatment-specific and could accurately discriminate among the 4 treatments. ALL cells of different molecular subtypes shared common cellular responses to treatment, suggesting that it may be possible to personalize treatment strategies in ALL.

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Chapter 60

Principles of Drug Therapy

Jennifer A. Lowry, Bridgette L. Jones, Tracy L. Sandritter, and Gregory L. Kearns

The clinical pharmacology of a given drug reflects a multifaceted set of properties that pertain to its disposition and action, and the response (e.g., adverse effects, therapeutic effects, and therapeutic outcome) to their administration/use. The 3 most important facets of the clinical pharmacology of a drug are its pharmacokinetics, pharmacodynamics, and the role of genetic variability as it may impact drug disposition or action (i.e., pharmacogenomics) (see Chapter 59).

Pharmacokinetics describes the movement of a drug throughout the body and the concentrations (or amounts) of a drug that reach a given body space and/or tissue and its residence time therein. Pharmacokinetics of a drug are conceptualized by considering those characteristics which collectively, are the determinants of the dose–concentration–effect relationship; namely, absorption, distribution, metabolism and excretion. **Pharmacodynamics** describes the relationship between drug dose or drug concentration and response. The response may be desirable *(effectiveness)* or untoward *(toxicity)*. Although in clinical practice the response to drugs in different patient populations is often described by a standard dosing or concentration range, response is best conceptualized along a continuum where the relationship between dose and response(s) are not linear. **Pharmacogenetics** is the study of how variant forms of human genes contribute to interindividual variability in either drug disposition (e.g., variant alleles of gene controlling the expression of a drug transporter) and/or response (e.g., variant alleles altering the drug–receptor interaction). The finding that drug responses can be influenced by the patient's genetic profile has offered great hope for realizing individualized pharmacotherapy when the relationship between genotype and phenotype (either disease and/or drug response) is predictive of drug response (see Chapter 59). In the developing child, it is apparent ontogeny that has the potential of modulating drug response through altering both pharmacokinetics and pharmacodynamics.

GENERAL PHARMACOKINETIC AND PHARMACODYNAMIC PRINCIPLES

Drug effect is produced only when an exposure (both amount and duration) occurs that is sufficient to produce a drug–receptor interaction capable of modulating the cellular milieu and inducing a biologic response. Thus, exposure–response relationships for a given drug represent an interface between pharmacokinetics and pharmacodynamics that can be simply conceptualized by consideration of 2 profiles: (1) plasma concentration vs effect (Fig. 60-1) and (2) plasma concentration vs time (Fig. 60-2).

The relationship between drug concentration and effect for most drugs is not linear (see Fig. 60-1). At a drug concentration of zero, the effect from the drug is generally zero or not perceptible (E_0). Following drug administration and/or with dose escalation, the concentration increases as does the effect; first in an apparent linear fashion (at low drug concentrations) followed by a nonlinear increase in effect to an asymptotic point in the relationship where a maximal effect (E_{max}) is attained that does not perceptibly change with further increases in

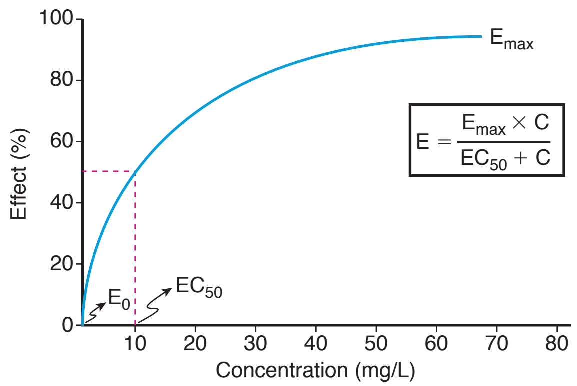

Figure 60-1 **Plasma concentration vs effect curve.** The percent effect is measured as a function of increasing drug concentration in the plasma. The dose at which no effect is seen in the population is E_0. The dose of a drug required to produce a specified effect in 50% of the population is abbreviated as EC_{50}. The concentration associated with the maximal effect that can be produced by a drug is abbreviated as E_{max}. *(From Abdel-Rahman SM, Kearns GL. The pharmacokinetic-pharmacodynamic interface: determinants of anti-infective drug action and efficacy in pediatrics. In Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL, editors,* Textbook of pediatric infectious disease, *ed 6, Philadelphia, 2009, WB Saunders, pp. 3156–3178, reproduced with permission.)*

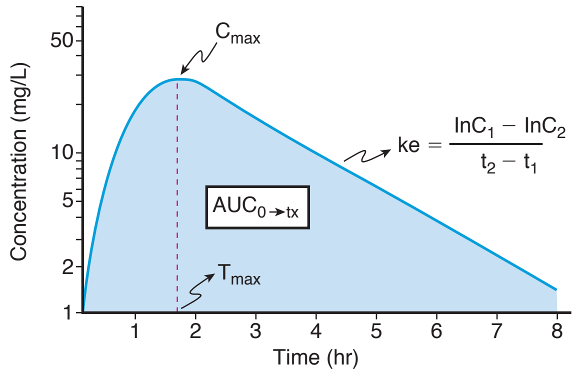

Figure 60-2 Semilogarithmic plot of the plasma concentration vs time curve for a hypothetical drug following extravascular administration. The area under the plasma level-time curve (AUC) is a concentration and time-dependent measure of systemic drug exposure. After administration, the drug is absorbed and reaches the maximal concentration (C_{max}) at its peak time (T_{max}). Following completion of drug absorption and distribution, plasma drug concentrations decline in an apparent monoexponential fashion whereby the slope of the apparent elimination phase represents the apparent elimination rate constant (ke). *(From Abdel-Rahman SM, Kearns GL. The pharmacokinetic-pharmacodynamic interface: determinants of anti-infective drug action and efficacy in pediatrics. In Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL, editors,* Textbook of pediatric infectious disease, *ed 6, Philadelphia, 2009, WB Saunders, pp. 3156–3178, reproduced with permission.)*

drug concentration. The point in the concentration–effect relationship where the observed effect represents 50% of the E_{max} is defined as EC_{50}, a common pharmacodynamic term used to compare concentration–effect relationships between patients (or research subjects) and between drugs that may be in a given drug class. In practice, E_{max} can be derived either from visual interpolation of the concentration–effect profile or via mathematical curve fitting of the relationship.

Because it is rarely possible to measure drug concentrations at or near the receptor, it is necessary to utilize a surrogate measurement to assess exposure–response relationships. In most instances, this surrogate is represented by the plasma drug concentration vs time curve. For drugs whose pharmacokinetic properties are best described by 1st-order (as opposed to zero-order or mixed-order) processes, a semilogarithmic plot of plasma drug concentration vs time data for an agent given by an extravascular route of administration (e.g., intramuscular, subcutaneous, intracisternal, peroral, transmucosal, transdermal, rectal) produces a pattern similar to that illustrated by Figure 60-2. The ascending portion of this curve represents a time during which the liberation of a drug from its formulation, dissolution of the drug in a biologic fluid (e.g., gastric or intestinal fluid, interstitial fluid; a prerequisite for absorption) and absorption of a drug are rate-limiting relative to its elimination. After the time (T_{max}) where maximal plasma concentrations (C_{max}) are observed, the plasma concentration decreases as metabolism and elimination become rate limiting; the terminal portion of this segment of the plasma concentration vs time curve being representative of drug elimination from the body. Finally, the area under the plasma concentration vs time curve (AUC), a concentration- and time-dependent parameter reflective of the degree of systemic exposure from a given drug dose, can be determined by integrating the plasma concentration data over time. By being able to characterize the pharmacokinetics of a specific drug, the clinician can use the data to individualize dosing regimens for patients who by virtue of development and/or disease, must have adjustments to either the dose and/or dosing interval so as to enable the production of the degree of systemic exposure associated with desired pharmacologic effects. For drugs where a therapeutic plasma concentration range and/or "target" systemic exposure (i.e., AUC) is known, a priori knowledge of pharmacokinetic parameters for a given population or patient within a population can facilitate the selection of a drug dosing regimen. When linked with information regarding the pharmacodynamic behavior of a drug and the status of the patient (e.g., age, organ function, disease state, concomitant medications), the application of pharmacokinetics affords the practitioner the ability to exercise some real degree of adaptive control over therapeutic decision making by enabling the selection of a drug and dosing regimen that has the greatest likelihood of producing both efficacy and safety.

THE IMPACT OF ONTOGENY ON DRUG DISPOSITION

Development represents a continuum of biologic events that enable adaptation, somatic growth, neurobehavioral maturation and eventually reproduction. The impact of development on the pharmacokinetics of a given drug is determined, to a great degree, by age-related changes in body composition and the acquisition of function in organs and organ systems, which are important in determining drug metabolism and excretion. Even though it is often convenient to classify pediatric patients on the basis of postnatal age for the provision of drug therapy (e.g., neonate 0-1 mo of age; infant 1-24 mo of age; children 2-12 yr of age; and adolescents 12-18 yr of age), it is important to recognize that the changes in physiology are not linearly related to age and may not correspond to these age-defined breakpoints. In fact, the most dramatic changes in drug disposition occur during the 1st 18 mo of life where the acquisition of organ function is most dynamic. Additionally, it is important to note that the pharmacokinetics of a given drug may be altered in pediatric patients consequent to intrinsic (e.g., gender, genotype, ethnicity, inherited diseases) or extrinsic (e.g., acquired disease states, xenobiotic exposure, diet, variability in therapeutic adherence) factors that may occur during the 1st 2 decades of life.

During development, certain stages of life profoundly influence drug response and disposition. Dramatic pharmacokinetic, pharmacodynamic, and psychosocial changes occur as preterm infants mature toward term, as infants mature through the 1st few years of life, and as children reach puberty and adolescence (Fig. 60-3). It is most useful to conceptualize the impact of ontogeny on drug disposition by considering its specific facets, namely, drug absorption, distribution, metabolism, and excretion, as well as ontogeny's impact on drug action (pharmacodynamics).

Drug Absorption

Absorption usually occurs via passive diffusion, but active transport or facilitated diffusion also may be necessary for drug entry into cells. Several physiologic factors affect this process, 1 or more of which may be altered in the face of certain disease states (e.g., inflammatory bowel disease, diarrhea) and, consequently, produce changes in drug bioavailability. The rate and extent of absorption can be significantly affected as a consequence of a child's normal growth and development.

Peroral Absorption

The most important factors that influence drug absorption from the gastrointestinal tract are related to the physiology of the stomach, intestine, and biliary tract (see Fig. 60-3C and Table 60-1). The rate and extent of peroral absorption of drugs depends primarily on the pH-dependent passive diffusion and motility of the stomach and intestinal tract as both of these factors will influence transit time of the drug. Gastric pH changes significantly throughout development with the highest (alkaline) values occurring during the neonatal period. In the fully mature neonate, the gastric pH ranges from 6-8 at birth and drops to 2-3 within a few hours of birth. However, after the 1st 24 hr of life, the gastric pH drifts upward because of the immaturity of the parietal cells. As the parietal cells mature, the gastric acid secretory capacity increases (pH decreases) over the 1st few months of life to reach consistent adult levels by 3-7 yr of age. As a result, the peroral bioavailability of acid-labile drugs, such as penicillin or ampicillin, is increased. In contrast, the absorption of weak organic acids (e.g., phenobarbital and phenytoin) is relatively decreased, a condition which may necessitate the administration of larger doses in the very young to achieve therapeutic plasma levels.

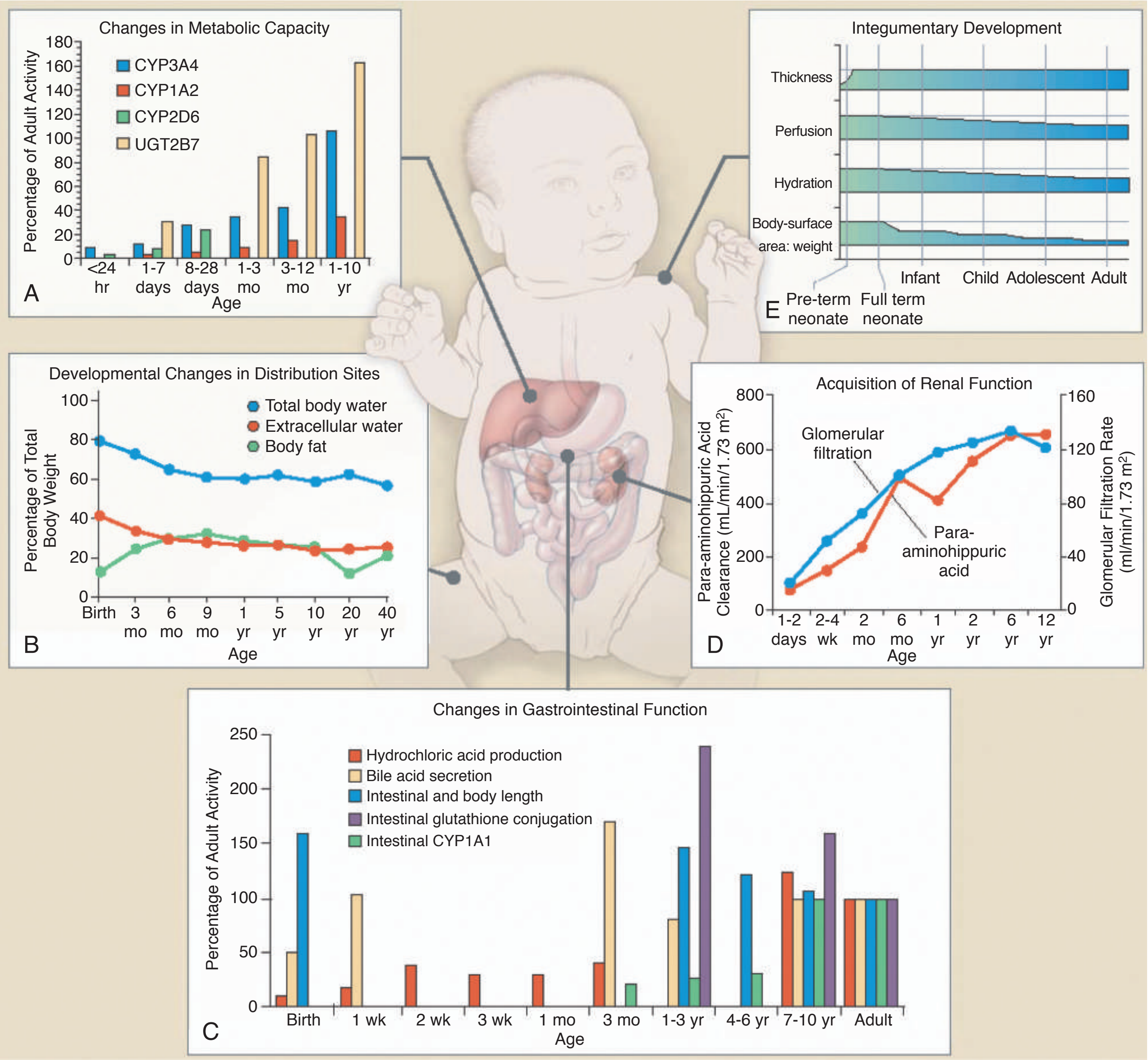

Figure 60-3 Developmental changes in physiologic factors that influence drug disposition in infants, children, and adolescents. Physiologic changes in multiple organ systems during development are responsible for age-related differences in drug disposition. **A**, As this graph shows, the activity of many cytochrome P450 (CYP) isoforms and a single glucuronosyltransferase (UGT) isoform is markedly diminished during the 1st 2 mo of life. In addition, the acquisition of adult activity over time is enzyme- and isoform-specific. **B,** This chart shows age-dependent changes in body composition that influence the apparent volume of distribution of drugs. Infants in the 1st 6 mo of life have markedly expanded total-body water and extracellular water, expressed as a percentage of total-body weight, as compared with older infants and adults. **C,** This graph summarizes the age-dependent changes in both the structure and function of the gastrointestinal tract. As with hepatic drug-metabolizing enzymes **(A)**, the activity of CYP1A1 in the intestine is low during early life. **D,** This chart shows the effect of postnatal development on the processes of active tubular secretion–represented by the clearance of paraaminohippuric acid and the glomerular filtration rate, both of which approximate adult activity by 6-12 mo of age. **E,** This graph shows age dependence in the thickness, extent of perfusion, and extent of hydration of the skin and the relative size of the skin-surface area (reflected by the ratio of body surface area to body weight). Although skin thickness is similar in infants and adults, the extent of perfusion and hydration diminishes from infancy to adulthood. *(From Kearns GL, Abdel-Rahman SM, Alander SW, et al, Developmental pharmacology—drug disposition, action, therapy in infants and children.* N Engl J Med *349:1157–1167, 2003. Reproduced with permission.)*

Gastric emptying time is prolonged throughout infancy and childhood consequent to reduced motility which may retard drug passage into the intestine where the majority of absorption takes place. Gastric emptying rates reach or exceed adult values by 6-8 mo of life. As such, intestinal motility is important for the rate of drug absorption and, like other factors, is dependent on the age of the child. Consequently, the rate of absorption of drugs with limited water solubility (e.g., phenytoin, carbamazepine) can be dramatically altered consequent to changes in gastrointestinal motility. In older infants and young children, more rapid rates of intestinal drug transit can reduce the bioavailability for some drugs (e.g., phenytoin) and/or drug formulations (e.g., sustained-release) by reducing their residency time at the absorption surfaces in the small intestine.

Lastly, neonates, particularly premature neonates, have a reduced bile acid pool and biliary function resulting in a decreased ability to solubilize and absorb lipophilic drugs. Even though biliary function

Table 60-1 Developmental Alteration in Intestinal Drug Absorption

PHYSIOLOGIC ALTERATION	NEONATE	INFANTS	CHILDREN
Gastric pH	>5	4-2	Normal (2-3)
Gastric emptying time	Irregular	Increased	Slightly increased
Intestinal motility	Reduced	Increased	Slightly increased
Intestinal surface area	Reduced	Near adult	Adult pattern
Microbial colonization	Reduced	Near adult	Adult pattern
Biliary function	Immature	Near adult	Adult pattern

Direction of alteration given relative to expected normal adult pattern.
Data from Morselli PL. Development of physiological variables important for drug kinetics. In: Morselli PL, Pippenger CE, Penry JK, editors. Antiepileptic drug therapy in pediatrics. *New York, 1983, Raven Press, pp. 1–12.*

develops in the 1st few months of life, it may be difficult for the neonate and young infant to absorb fat-soluble vitamins as low concentrations of bile acids are necessary for their absorption.

Extravascular Drug Absorption

With a bioavailability of 100%, intravenous drug administration is assumed to be the most dependable and accurate route for drug delivery. Absorption of drugs from tissues and organs (e.g., intramuscular, transdermal, and rectal) can also be affected by development (Table 60-2). Intramuscular blood flow changes with age, which can result in variable and unpredictable absorption. Reduced muscular blood flow in the 1st few days of life, the relative inefficiency of muscular contractions (useful in dispersing an IM drug dose), and an increased percentage of water per unit of muscle mass may delay the rate and/or extent of drugs given intramuscularly to the neonate. Muscular blood flow increases into infancy and, consequently, the bioavailability of drugs given by the IM route is comparable to that seen in children and adolescents.

In contrast, mucosal permeability (rectal and buccal) in the neonate is increased and thus, may result in enhanced absorption by this route. Transdermal drug absorption in the neonate and very young infant is increased as the result of a more hydrated stratum corneum (see Fig. 60-3*E*). In addition, the ratio of body surface area to body weight is greater in infants and children compared to adults. Collectively, these developmental differences may predispose the child to increased exposure and risk for toxicity for drugs/chemicals placed on the skin (e.g., silver sulfadiazine, topical corticosteroids, benzocaine, diphenhydramine) with higher likelihood of occurrence during the 1st 12 mo of life.

Normal developmental differences in drug absorption from most all extravascular routes of administration can influence the dose-plasma concentration relationship in a manner sufficient to alter pharmacodynamics. It should be recognized that the presence of disease states which influence a physiologic barrier for drug absorption and/or the time that a drug spends at a given site of absorption can further influence drug bioavailability and effect.

Drug Distribution

Drug distribution is influenced by a variety of drug-specific physiochemical factors (e.g., molecular size and weight, apparent partition coefficient, pK_a), the presence of drug transporters, blood/tissue protein binding, blood and tissue pH and perfusion. However, age-related changes to drug distribution are primarily related to developmental changes in body composition and the quantity of plasma proteins capable of drug binding. Age-dependent changes in the relative sizes of body water (total body water [TBW], extracellular water) and fat compartments may alter the apparent volume of distribution (VD) for a given drug. The absolute amounts and distribution of body water and fat depend on a child's age and nutritional status. As well, certain disease states (e.g., ascites, dehydration, burn injuries, disruption of the integument involving large surface area) can influence body water compartment sizes and thereby, further impact the VD for certain drugs.

Table 60-2 Influence of Ontogeny on Drug Absorption

PHYSIOLOGIC ALTERATION	NEONATE	INFANTS	CHILDREN
Oral absorption	Erratic	Increased	Near adult
Intramuscular absorption	Variable	Increased	Near adult
Percutaneous absorption	Increased	Increased	Near adult
Rectal absorption	Very efficient	Efficient	Near adult

Direction of alteration given relative to expected normal adult pattern.
Data from Morselli PL. Development of physiological variables important for drug kinetics. In: Morselli PL, Pippenger CE, Penry JK, editors. Antiepileptic drug therapy in pediatrics. *New York, 1983, Raven Press, pp. 1–12.*

Newborns have a much higher proportion of body mass in the form of water (~75% TBW) than older infants and children (see Fig. 60-3*B*). As well, the percent of extracellular water changes (decreases) from the newborn stage (approximately 45%) into adulthood (approximately 20-30%). In fact, the increase of TBW in the neonate is attributable to extracellular water. The reduction in TBW is rapid in the 1st year of life with adult values (approximately 55%) achieved by approximately 12 yr of age. In contrast, the percentage of intracellular water as a function of body mass remains stable from the 1st months of life through adulthood. The impact of developmental changes in body water spaces are exemplified by drugs such as the aminoglycoside antibiotics; compounds that distribute predominantly throughout the extracellular fluid space and have a higher VD (0.4-0.7 L/kg) in neonates and infants as compared to adults (0.2-0.3 L/kg).

Body fat percentage and composition increase during normal development. The body fat percentage in a neonate is approximately 16% (57% water and 35% lipid). Despite the relatively low body fat content in the neonate, it is important to note that the lipid content in the developing central nervous system (CNS) is high, which has implications for the distribution of lipophilic drugs and their CNS effects (e.g., propranolol) during this time period. The body fat percentage tends to increase up to approximately 10 yr of age and then changes composition with respect to puberty and sex to approach adult body fat composition (26% water and 71% lipid). In addition, a sex difference exists as the child ages into adolescence. The total body fat in males is reduced by 50% between 10 and 20 yr of life as compared to females in whom the reduction is approximately 25%.

Albumin, total proteins, and total globulins (e.g., α_1-acid glycoprotein) are the most important circulating proteins responsible for drug binding in plasma. The absolute concentration of these proteins is influenced by age, nutrition, and disease (Table 60-3). The concentrations of most all circulating plasma proteins are reduced in the neonate and young infant (approximately 80% of adult) and reach adult values by 1 year of age. A similar pattern of maturation is observed with α_1-acid glycoprotein (an acute-phase reactant capable of binding basic drugs) where neonatal plasma concentrations are approximately 3 times lower than in maternal plasma and attain adult values by approximately 1 year of age.

The extent of drug binding to proteins in the plasma may influence distribution characteristics. Only free, unbound drug can be distributed from the vascular space into other body fluids and, ultimately, to tissues where drug–receptor interaction occurs. Drug protein binding depends on a number of age-related variables, which can include the absolute amount of proteins and their available binding sites; the conformational structure of the binding protein (e.g., reduced binding of

Table 60-3 Factors Influencing Drug Binding in Pediatrics

PHYSIOLOGIC ALTERATION	NEONATE	INFANTS	CHILDREN
Plasma albumin	Reduced	Near adult	Near adult
Fetal albumin	Present	Absent	Absent
Total proteins	Reduced	Decreased	Near adult
Total globulins	Reduced	Decreased	Near adult
Serum bilirubin	Increased	Normal	Adult pattern
Serum free fatty acids	Increased	Normal	Adult pattern

Direction of alteration given relative to expected normal adult pattern.
Data from Morselli PL. Development of physiological variables important for drug kinetics. In: Morselli PL, Pippenger CE, Penry JK, editors. Antiepileptic drug therapy in pediatrics. *New York, 1983, Raven Press, pp. 1–12.*

Table 60-4 Impact of Development on Drug Metabolism

PHYSIOLOGIC ALTERATION	NEONATE	INFANTS	CHILDREN
Cytochrome P450 activity	Reduced	Increased	Slightly increased
Phase II enzyme activity	Reduced	Increased	Near adult
Blood esterase activity	Reduced	Normal (by 1 yr)	Adult pattern
Presystemic enzyme activity	Reduced	Increased	Near adult

Direction of alteration given relative to expected normal adult pattern.
Data from Morselli PL. Development of physiological variables important for drug kinetics. In: Morselli PL, Pippenger CE, Penry JK, editors. Antiepileptic drug therapy in pediatrics. *New York, 1983, Raven Press, pp. 1–12.*

acidic drugs to glycated albumin in patients with poorly controlled diabetes mellitus); the affinity constant of the drug for the protein; the influence of pathophysiologic conditions that either reduce circulating protein concentrations (e.g., ascites, major burn injury, chronic malnutrition, hepatic failure) or alter their structure (e.g., diabetes, uremia); and the presence of either endogenous or exogenous substances, which may compete for protein binding.

Developmentally associated changes in drug binding can occur as a consequence of altered protein concentrations and/or binding affinity. For example, circulating fetal albumin in the neonate has significantly reduced binding affinity for acid drugs such as phenytoin, which is extensively (94-98%) bound to albumin in adults as compared to 80-85% in the neonate. The resultant 6-8–fold difference in the free fraction can result in CNS adverse effects in the neonate when total plasma phenytoin concentrations are within the generally accepted "therapeutic range" (10-20 mg/L). The importance of reduced drug-binding capacity of albumin in the neonate is exemplified by interactions between endogenous ligands (e.g., bilirubin, free fatty acids) and drugs with greater binding affinity (e.g., the ability of sulfonamides to produce kernicterus).

Drug transporters, such as P-glycoprotein, MDR1, and MDR2 (multidrug resistance 1 or 2), can influence drug distribution. These drug transporters can markedly influence the extent to which drugs cross membranes in the body and whether drugs can penetrate or are secreted from the target sites (inside cancer cells or microorganisms, or crossing the blood–brain barrier). Thus, drug resistance to cancer chemotherapy, antibiotics, or epilepsy may be conferred by these drug transport proteins and their effect on drug distribution. While there are limited data on the ontogeny of drug transport proteins, available information demonstrates their presence as early as 22 wk gestation and low levels in the neonatal period which appear to rapidly increase to adult values by 1-2 yr of age.

Drug Metabolism

Metabolism reflects the biotransformation of an endogenous or exogenous molecule by 1 or more enzymes to moieties that are more hydrophilic and thus, can be more easily eliminated by excretion, secretion or exhalation. Although metabolism of a drug generally reduces its ability to produce a pharmacologic action, it can result in metabolites that have significant potency, thereby contributing to the overall pharmacodynamic profile of a drug (e.g., biotransformation of the tricyclic antidepressant amitriptyline to nortriptyline; cefotaxime to desacetylcefotaxime; theophylline to caffeine) or in some instances, can produce significant toxicity (e.g., biotransformation of codeine to morphine). In the case of prodrugs (e.g., zidovudine, enalapril, fosphenytoin) or some drug salts/esters (e.g., cefuroxime axetil, clindamycin phosphate), biotransformation is required to produce a pharmacologically active moiety. Finally, for some drugs, cellular injury and associated adverse reactions are the result of drug metabolism (e.g., acetaminophen hepatotoxicity, Stevens-Johnson syndrome associated with sulfamethoxazole).

The primary organ responsible for drug metabolism is the liver, although the kidney, small intestine, lung, adrenals, blood (phosphatases, esterases) and skin can also biotransform certain compounds. Drug metabolism occurs primarily in the endoplasmic reticula of cells via 2 general classes of enzymatic processes: **phase I,** or nonsynthetic, and **phase II,** or synthetic, reactions. Phase I reactions include oxidation, reduction, hydrolysis, and hydroxylation reactions, whereas phase II reactions primarily involve conjugation with an endogenous ligand (e.g., glycine, glucuronide, glutathione or sulfate). As illustrated by Figure 60-3*A*, many drug metabolizing enzymes demonstrate an ontogenic profile with generally low activity present at birth and maturation over a period of months to years (Table 60-4).

Even though there are many enzymes that are capable of catalyzing the biotransformation of drugs and xenobiotics, the quantitatively most important are represented by the cytochromes P450 (CYPs), a supergene family with at least 16 primary enzymes. The specific CYP isoforms responsible for the majority of human drug metabolism are represented by CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. These enzymes represent the products of genes that in some instances, are polymorphically expressed with allelic variants producing enzymes generally resulting in either no or reduced catalytic activity (a notable exception being the *17 allele of CYP2C19 which conveys increased activity) (see Chapter 59). At birth, the concentration of drug-oxidizing enzymes in fetal liver (corrected for liver weight) appears similar to that in adult liver. However, the activity of these oxidizing enzyme systems is reduced, which results in slow clearance (and prolonged elimination) of many drugs that are substrates for them (e.g., phenytoin, caffeine, diazepam, and many others). Postnatally, the hepatic CYPs appear to mature at different rates. Within hours after birth, CYP2E1 activity increases rapidly with CYP2D6 being detectable soon thereafter. CYP2C (CYP2C9 and CYP2C19) and CYP3A4 are present within the 1st mo of life, and a few months later, CYP1A2. CYP3A4 activity in young infants may exceed that observed in adults as reflected by the clearance of drugs that are substrates for this enzyme (e.g., cyclosporine, tacrolimus).

Compared to phase I drug-metabolizing enzymes, the impact of development on the activity of phase II enzymes (acetylation, glucuronidation, sulfation) is not characterized as well. Generally speaking, phase II enzyme activity is decreased in the newborn and increases into childhood. For example, conjugation of compounds metabolized by isoforms of glucuronosyltransferase (UGT; e.g., morphine, bilirubin, and chloramphenicol) is reduced at birth but can exceed adult values by 3-4 yr of age. Also, the ontogeny of UGT expression is isoform specific. Newborns and infants primarily metabolize the commonly used analgesic acetaminophen by sulfate conjugation whereas the UGT isoforms responsible for its glucuronidation (UGT1A1 and UGT1A9) have markedly reduced activity. As children age, the

glucuronide conjugate becomes predominant in the metabolism of therapeutic doses of acetaminophen. In contrast, the glucuronidation of morphine (a UGT2B7 substrate) can be detected as early as 24 wk gestation.

The activity of certain hydrolytic enzymes, including blood esterases, is also reduced during the neonatal period. The reduced activity of these plasma esterases in the newborn may account for the delayed metabolism (prolonged effect) of local anesthetics in the neonate. In addition, this may account for the prolonged effect that cocaine has on the fetus with prenatal exposures. Adult esterase activity is achieved by 10-12 mo of age.

The development of presystemic clearance or "1st-pass" metabolism is unclear given the involvement of multiple enzymes and transporters in the small intestine, many of which have patterns of developmental expression that may be more or less concordant. However, given that the activity of almost all drug metabolizing enzymes is markedly reduced in the neonate, the bioavailability of drugs given by the peroral route that may be subjected to significant presystemic clearance in older children and adults would appear to be markedly increased during the 1st days to weeks of life. It is important for the clinician to recognize that estimates of bioavailability for a host of drugs available in reference texts and therapeutic compendia are most often derived from studies conducted in young adults. Consequently, this information may not be predictive of the rate and/or extent of peroral drug absorption in a neonate or infant.

Finally, with regard to the impact of development on drug metabolism, it must be recognized that most therapeutic drugs are polyfunctional substrates for a host of enzymes and/or transporters. It is the isoform specific ontogenic profile (see Fig. 60-3) that must be considered in the context of deducing how development per se can affect the metabolic portion of drug clearance. True developmental dependence of drug clearance (CL) must also consider the role of pharmacogenetic constitution on the activity of enzymes/transporters (see Chapter 59) and the impact of ontogeny on the nonmetabolic routes (e.g., renal drug excretion, salivary and biliary drug excretion, pulmonary drug excretion) that contribute to the overall drug clearance (i.e., Total CL = $CL_{hepatic} + CL_{renal} + CL_{nonrenal}$).

Renal Drug Elimination

The kidney is the primary organ responsible for the excretion of drugs and their metabolites. The development of renal function begins during early fetal development and is complete by early childhood (see Fig. 60-3*D*; Table 60-5). Total renal drug clearance *(CL_{renal})* can be conceptualized by considering the following equation:

$$CL_{renal} = (GFR + ATS) - ATR$$

where glomerular filtration rate *(GFR)*, active tubular secretion *(ATS)*, and active tubular reabsorption *(ATR)* of drugs can contribute to overall clearance. As is true for hepatic drug metabolism, only free (unbound) drug and/or metabolite can be filtered by a normal glomerulus and/or either secreted or reabsorbed via a renal tubular transport proteins.

Renal clearance is limited in the newborn by both anatomical and functional immaturity of the nephron unit. In both the term and preterm neonate, GFR averages 2-4 mL/min/1.73 m^2 at birth. During the 1st few days of life, a drop in renal vascular resistance occurs which results in a net increase in renal blood flow and a re-distribution of intrarenal blood flow from a predominantly medullary to a cortical distribution. All of these changes are associated with a commensurate increase in GFR. In term neonates, GFR increases rapidly over the 1st few months of life and approaches adult values by 10-12 mo of life (see Fig. 60-3*D*). The rate of GFR acquisition is blunted in preterm neonates consequent to continued nephrogenesis, which occurs in the early postnatal period. In young children between 2 and 5 yr of age, GFR may exceed adult values, especially during periods of increased metabolic demand (e.g., during a fever).

In addition, there is a relative glomerular/tubular imbalance because of a more advanced maturation of glomerular function. Such an imbalance may persist up to 6 mo of age and may account for the observed decrease in the ATS of drugs commonly used in neonates and young infants (e.g., β-lactam antibiotics). Finally, there is some evidence that ATR is reduced in neonates and that it appears to mature at a slower rate than the GFR.

Altered renal drug clearance in the newborn and infants result in the different dosing recommendations commonly seen in pediatrics. The aminoglycoside antibiotic gentamicin provides an illustrative example. In adolescents and young adults with normal values for GFR (85-130 mL/min/1.73 m^2), the recommended dosing interval for the drug is 8 hr. In young children who may have a GFR >130 mL/min/1.73 m^2, a gentamicin dosing interval of every 6 hr may be necessary in selected patients who have serious infections that require maintaining steady-state peak and trough plasma concentrations near the upper boundary of the recommended therapeutic range. In contrast, to maintain "therapeutic" gentamicin plasma concentrations in neonates during the 1st few weeks of life, a dosing interval of 18-24 hr is required.

The impact of developmental differences in GFR on the elimination characteristics of a given drug can be assessed by estimating the apparent elimination rate constant (Kel) for a drug by using the following equation:

$$\text{Kel (in reduced renal function)} = Kel_{normal} \cdot \{[(GFR_{observed}/GFR_{normal}) - 1] \cdot Fel\} + 1$$

where the *Fel* represents the fraction of the drug excreted unchanged in an adult with normal renal function, $GFR_{observed}$ is the value calculated (from creatinine clearance or an age-appropriate estimation equation) for the patient (in mL/min/1.73 m^2), GFR_{normal} is the average value considered for a healthy adult (i.e., 120 mL/min/1.73 m^2) and Kel_{normal} is estimated from the average elimination $T_{1/2}$ (terminal half-life) for a drug taken from the medical literature using the following equation:

$$Kel_{normal}\,[hr^{-1}] = 0.693/T_{1/2 normal}\,[hr]$$

Table 60-5 Impact of Development on Renal Drug Elimination

PHYSIOLOGIC ALTERATION	NEONATE	INFANTS	CHILDREN
Glomerular filtration	Reduced	Normal (by 1 year)	Adult pattern
Active tubular secretion	Reduced	Near normal	Adult pattern
Active tubular reabsorption	Reduced	Near normal	Adult pattern
Active drug excretion	Reduced	Near normal	Adult pattern
Passive drug excretion	Reduced	Increased	Adult pattern
Excretion of basic drugs	Increased	Increased	Near normal

Direction of alteration given relative to expected normal adult pattern.

Data from Morselli PL. Development of physiological variables important for drug kinetics. In: Morselli PL, Pippenger CE, Penry JK, editors. Antiepileptic drug therapy in pediatrics. *New York, 1983, Raven Press, pp. 1–12.*

Likewise, the elimination $T_{1/2}$ for a drug in patients with reduced renal function can be estimated as follows:

$T_{1/2}$ (in reduced renal function) = 0.693/Kel (in reduced function)

An estimate of the drug elimination $T_{1/2}$ in patients with reduced renal function with knowledge of the desired interdose excursion in steady-state plasma concentrations can provide an ability to determine the desired drug dosing interval.

Impact of Ontogeny on Pharmacodynamics

Although, it is generally accepted that developmental differences in drug action exist, there is little evidence of true age-related pharmacodynamic variation among children of differing age groups and adults. Drug action is typically mediated by interaction of a small molecule with 1 or more receptors, which may be located either on or in a cell. Drug effect is mediated at the receptor by 4 main biochemical mechanisms involved in cell signaling. Binding of the receptors on the cell surface or within the cell activate downstream pathways that mediate a specific cellular action. Some receptors act as enzymes whereby, upon ligand binding, the enzyme phosphorylates downstream effector proteins, thereby activating or inhibiting a cellular signal. Guanosine triphosphate–binding regulatory protein, also known as G-protein–coupled receptors, are known targets for many drugs. Upon ligand binding, guanosine triphosphate binds to and activates the G-protein, in turn allowing it to activate second messenger regulatory proteins in the cell, again mediating cellular signaling. Other receptors mediate their actions through ion channels whereby, upon ligand binding, the cell's membrane potential or ionic composition is altered allowing cellular activation or inhibition. Lastly, some receptors act as transcription factors that, when bound by a ligand, transcription of specific genes within the cell are activated. Drug action is concentration dependent with onset and offset generally associated with appearance and disappearance, respectively, of the drug at the receptor(s) in an amount that is sufficient to initiate the cascade of biologic effects that terminate in drug action (see Fig. 60-1). The minimum effective concentration of a drug is that observed with the immediate onset of effect, whereas the duration of action is predicated upon the maintenance of drug concentrations at the receptor within a range that is associated with the desirable pharmacologic action(s). Receptor binding by a drug may have varying consequences. Drugs that are **agonists** bind to and activate the receptor, directly or indirectly achieving the desired effect. An agonist binding to a receptor results in the same biologic effect as binding of the endogenous ligand. **Partial agonist** binding results in activation of the receptor but maximal effect is not achieved even in the presence of receptor saturation. **Antagonists** bind to a receptor preventing binding of other molecules thereby preventing activation of the receptor.

Age-related pharmacokinetic variation resulting in altered drug disposition may result in less or more drug being available at the receptor(s) consequent to whether drug clearance is decreased or increased relative to values in adults. The resultant alteration in the dose–concentration profile may result in an attenuated (ineffective) or exaggerated (toxicity) response in children, which is especially relevant for drugs with a narrow therapeutic index (Fig. 60-4). Thus, in some circumstances, apparent developmental differences in drug response/effect may be simply explained on pharmacokinetic basis.

There is evidence supporting developmental differences in receptor number, density, distribution, function, and ligand affinity for some drugs. As there are limited data from humans, much of what is known has been derived from animal studies. In the CNS, unique developmental aspects of drug–receptor interaction affect therapeutic efficacy of both analgesic and sedative drugs in neonates. For example, the number of γ-aminobutyric acid receptors, which mediates inhibitory signal transduction in the CNS, is reduced in newborns compared to adults. Functional differences have also been observed between neonatal and adult brain upon γ-aminobutyric acid receptor activation. These changes may explain observed differences in dosing of drugs such as midazolam in infants, and in part may explain seizures experienced by infants upon benzodiazepine exposure. Another example

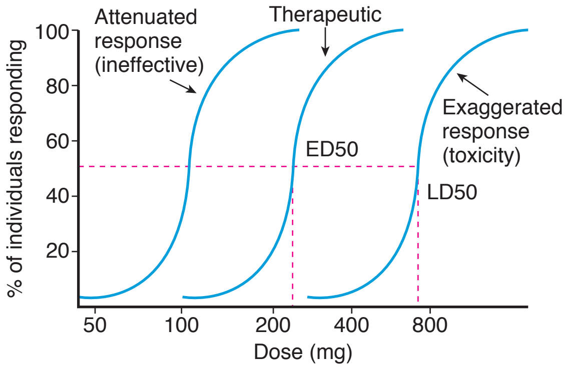

Figure 60-4 **Quantal dose–effect curve.** Age-related pharmacokinetic variation may result in alterations in drug concentration at the receptor resulting in ineffective, therapeutic, or toxic results. LD_{50} represents the dose at which 50% of the population is lethal. The ratio of the LD_{50} to the ED_{50} is an indication of the therapeutic index, which is a reflection of drug potency relative to its concentration.

in the CNS is illustrated by the μ-opioid receptor whereby receptor number is reduced in newborns and receptor distribution also differs between newborns and adults.

For the clinician, the consideration of age-dependent differences in pharmacodynamics is particularly relevant when they are associated with adverse drug reactions (e.g., higher incidence of valproic acid-associated hepatotoxicity in young infants; greater frequency of paradoxical CNS reactions to diphenhydramine in infants; weight gain associated with use of atypical antipsychotic drugs in adolescents) or when drugs have a narrow therapeutic index. This latter situation is exemplified by the immunomodulatory agent cyclosporine and the anticoagulant warfarin. In children younger than 1 yr old, the mean concentration of cyclosporine required to inhibit monocyte proliferation and the expression of the inflammatory cytokine interleukin-2 is less than required in older children. The age-associated pharmacodynamics of warfarin observed in children with congenital heart disease is, to a great degree, associated with developmental differences in serum concentrations of vitamin-K dependent coagulation factors (II, VII, IX, X) between children and adults. Developmental differences in drug action have also been observed between prepubertal children and adults with regard to warfarin action. Prepubertal children compared to adults exhibit a more profound response, demonstrated by lower protein C concentration, prothrombin fragments 1 and 2, and greater rise in international normalized ratio, to comparable doses of warfarin. Thus, when age-dependent pharmacodynamics of a given drug are evident, the use of simple allometric approaches for "scaling" the pediatric dose from the usual adult dose may not produce the desired pharmacologic effects.

Surrogate End Points

The assessment of pharmacodynamics in human infants and children has been hampered historically by a relative inability to use invasive methods for the direct assessment of drug effect. As a result, surrogate end points and biomarkers have been explored and, in some cases, have been successfully used to evaluate the impact of ontogeny on pharmacodynamics.

Biomarkers and surrogate end points (markers) are ideally simple, reliable, inexpensive, and easily obtainable measures of a biologic response or disease phenotype that can be used to facilitate either clinical research or patient care. **Biomarkers** have been defined by the U.S. National Institutes of Health as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." A **surrogate end point** is defined "as a biomarker that is intended to substitute for a specific clinical end point. A surrogate end point is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or

other scientific evidence." Reliable surrogate end points predict a specific physiologic event(s) (e.g., intraesophageal pH to assess gastroesophageal reflux), which may be utilized diagnostically, prognostically, or in predicting a specific drug response (therapeutic, subtherapeutic, or adverse) or potentially, the impact of ontogeny on pharmacodynamics. Specific examples of surrogate end points used in pediatric pharmacology include measurement of esophageal pH to assess the action of prokinetic or acid-modifying drugs, use of gastric scintigraphy and stable isotope-labeled compounds (e.g., ^{13}C-acetate, ^{13}C-octanoic acid) to assess gastric emptying rate, and pulmonary function tests (e.g., forced expiratory volume at 1 sec) to evaluate the effect(s) of drugs on pulmonary function in patients with conditions such as asthma and cystic fibrosis. Examples of biomarkers that have been used in pediatric studies to assess drug disposition or effect include hemoglobin A_{1C} plasma concentration (to assess efficacy of peroral hypoglycemic agents); urinary leukotriene concentrations (to assess effects of nonsteroidal antiinflammatory drugs); minimal inhibitory and minimal bacteriocidal concentrations of drugs to selected antiinfective agents; and the use of selective genotyping tests (e.g., projection of therapeutic warfarin dose requirement by use of *CYP2C9* [gene controlling expression of the enzyme primarily responsible for warfarin metabolism] and *VKORC1* [gene controlling expression of enzyme primarily involved in regulating warfarin effects on vitamin K dependent clotting factors] genotyping.

Additional Considerations in Pediatric Therapeutics

The use of adult-dose modification for pediatric dose prediction is based on the association between body size/composition and the physiologic determinants of drug disposition across the spectrum of age. Although these approaches may have some potential clinical utility in children older than 8 yr of age and in adolescents whose organ function and body composition approximates that of young adults, their utility is severely limited in neonates, infants, and children younger than 2 yr of age in whom ontogeny produces dramatic differences in drug disposition. This is especially problematic for therapeutic drugs whose doses cannot be easily individualized using patient-specific pharmacokinetic data obtained from therapeutic drug monitoring.

More than 20 different approaches for initial selection of a drug dose for pediatric patients have been described. The majority of these utilize either total body weight (BW) or body surface area (BSA) as surrogates, which reflect the developmental changes of either body composition or organ function that collectively are the major determinants of drug disposition. Dose selection based on BW or BSA will generally produce similar relationships between drug dose and resultant plasma concentration, except for those drugs whose apparent VD corresponds to the extracellular fluid pool (i.e., VD < 0.3 L/kg) for which a BSA-based approach is preferable. In contrast, for drugs whose apparent VD exceeds the extracellular fluid space (i.e., VD ≥ 0.3 L/kg), a BW-based approach for dose selection is preferable, which is the most frequently used method in pediatrics. When the pediatric dose for a given drug is not known, these principles can be used to best approximate a proper dose for the initiation of treatment as is illustrated by the following equations:

$$\text{Child dose (if VD} < 0.3\text{ L/kg)} = (\text{child BSA in m}^2/1.73\text{ m}^2) * \text{adult dose}$$

$$\text{Infant dose (if VD} \geq 0.3\text{ L/kg)} = (\text{infant BW in kg}/70\text{ kg}) * \text{adult dose}$$

It should be noted that this approach assumes that the child's weight, height, and body composition are age appropriate and normal, and that the "reference" normal adult has a BW and BSA of 70 kg and 1.73 m^2, respectively. It is useful only for selection of dose size and does not offer information regarding dosing interval because the equations contain no specific variable that describes potential age-associated differences in drug clearance.

In neonates and young infants with developmental immaturity in either GFR and/or ATS, it is often necessary to adjust the "normal" dosing interval (i.e., that used for older infants and children who have attained developmental competence of renal function) for drugs with significant (i.e., >50%) renal elimination so as to prevent excessive drug accumulation (and possible associated toxicity) with administration of multiple doses. To accomplish this therapeutic goal, it is necessary to estimate the apparent $T_{1/2}$ of the drug.

Drug-Level Monitoring

Drug response (either therapeutic or toxic) occurs only as a consequence of drug exposure. Clinically, systemic drug exposure is most commonly evaluated through assessing the plasma drug concentration; a surrogate measurement for a drug reaching its pharmacologic receptor(s).

In the patient, drug-level monitoring can be used to facilitate 2 approaches for evaluating the dose–concentration–effect relationship; therapeutic drug monitoring and pharmacokinetic-based dose individualization (clinical pharmacokinetics). **Therapeutic drug monitoring** largely entails a retrospective, reactive approach whereby drug concentrations in plasma (primarily) or other biologic fluids are measured at some point during either a constant rate intravenous infusion or during a dosing interval for drugs given by intermittent dosing schedules. These levels are then compared with those that are "desired" for a given drug based on published information and used to adjust the dose/dosing regimen in a quasi-empiric fashion. In using a therapeutic drug-monitoring approach, it should be recognized that for many drugs that are therapeutically monitored in the clinical setting (e.g., aminoglycoside antibiotics, vancomycin, phenytoin, phenobarbital, cyclosporine, tacrolimus, mycophenolate mofetil, selected antiretroviral drugs, acyclovir), "desired" plasma concentrations are generally determined from studies in adult patients in whom drug disposition and disease states may be quite different from those in infants and children.

In contrast to therapeutic drug monitoring, **clinical pharmacokinetics** represents a prospective, proactive approach where plasma drug concentrations are used to estimate pharmacokinetic parameters (e.g., apparent Kel, elimination $T_{1/2}$, apparent VD, total plasma clearance, AUC) which are then used to calculate a dosing regimen required to attain a desired level of systemic exposure (e.g., AUC, steady-state peak and/or trough plasma drug concentrations) that would portend a desired pharmacologic response. Of these 2 approaches, the use of drug-level data for performing clinical pharmacokinetics provides the most optimal approach for individualizing dose/dosing regimen and maintaining some adaptive control over the dose-concentration- effect relationship. This approach is particularly useful for patients who by virtue of their age and/or disease states, may have "abnormal" pharmacokinetics. Approaches used to enable the performance of clinical pharmacokinetics include the manual use of established formulas for calculating pharmacokinetic parameters (generally using a simple 1 compartment open model consequent to the few number of plasma drug-level observations obtained in the context of clinical patient care) or computer-based algorithms (e.g., Bayesian estimation, population-based pharmacokinetic approaches).

Common to both of the aforementioned approaches is the need to accurately assess plasma drug concentrations in a given patient. Figure 60-5 represents a hypothetical general steady-state plasma concentration vs time profile for a drug given by an extravascular route. It is provided to illustrate the following general principles that should be recognized and/or followed when plasma drug-level monitoring is used in patients as a "tool" to individualize drug treatment:

- When a drug reaches a pharmacokinetic steady state (a period corresponding to 5 times the apparent elimination $T_{1/2}$ for a given drug), both the excursion between the peak (C_{max}) and trough (C_{min}) plasma concentration and the AUC are identical between dose intervals provided that (1) the dose is not changed; (2) an exact dose-to-dose interval is maintained for drug administration; and (3) the route or rate of drug administration between dosing intervals has not changed.
- Steady-state plasma drug concentrations provide the best surrogate for assessing exposure–response relationships for a given drug. When used to support clinical pharmacokinetic approaches for dose regimen design, they provide the most accurate estimation of patient-specific pharmacokinetic parameters. Plasma

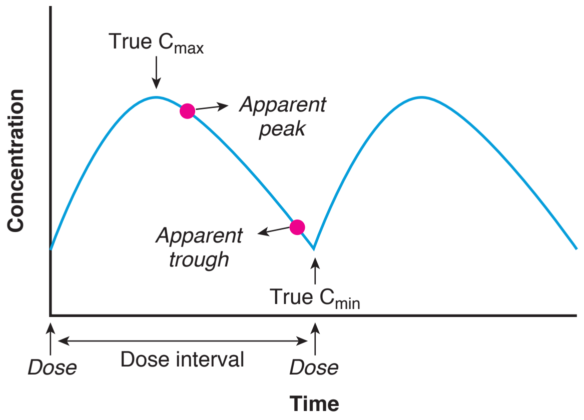

Figure 60-5 **Plasma concentration vs time profile for a hypothetical drug at steady state.** When dose size, route of administration, time of administration, and dosing interval remain constant, the resultant true peak (C_{max}) and trough (C_{min}) plasma concentrations and AUC from dose to dose are identical. Apparent values for C_{max} and C_{min} are denoted to illustrate the potential difference from true values that can result when the actual times for obtaining samples for either therapeutic drug monitoring or clinical pharmacokinetic applications are not realized.

concentrations assessed before the attainment of steady state can be useful for evaluating exaggerated drug response or predicting eventual steady-state drug levels/exposure.

To reliably interpret any drug plasma concentration, it is imperative that the clinician know and consider (1) the expected pharmacokinetic profile for a given drug (e.g., time after dosing required for completion of drug absorption (for extravascularly administered drugs) and distribution); (2) the exact time that the drug was administered; (3) for drugs given by intravenous infusion, the total duration of infusion (including time required to flush the dose from the intravenous tubing); (4) pertinent limitations of the analytical method used to measure the plasma drug level (e.g., range of linearity, potential for analytical interference from concomitant drugs); (5) the method used to obtain the blood specimen(s) used for plasma level determination (e.g., venous puncture vs cutaneous puncture; use of a vascular catheter that was different from the catheter used for drug administration); (6) whether the blood specimen was adequate for accurate drug level measurement (e.g., sufficient volume, presence or absence of hemolysis or lipemia); and (7) the *exact* time that the blood specimens were obtained in relationship to the time of drug administration and the drug dosing interval. This last point is illustrated by Figure 60-5, which denotes the "true" peak (C_{max}) and trough (C_{min}) plasma concentrations in relationship to apparent values; a situation that frequently occurs when "peak" and "trough" blood levels are ordered and nursing/phlebotomy procedures allow some period of leeway as to when they can be obtained. When such a discrepancy is realized and the exact timing of the samples relative to dose administration is known, corrections can be made to insure that pharmacokinetic parameters estimated from the data are accurate. If such a discrepancy is not realized, errant parameter estimation and dose regimen calculation/determination may result, thereby compromising either the safety or efficacy of drug treatment.

Drug Formulation and Administration

One of the more unique challenges in pediatric therapeutics is the **drug formulation** itself. Despite the increasing sensitivity for the need to study drugs in children before they are used in children and to have available "pediatric-friendly" formulations, many drug products that are formulated only for use in adults are routinely given to pediatric patients. Their use can result in inaccurate dosing (e.g., administration of a fixed dose to children with widely varying body weights), loss of desired performance characteristics of the formulation (e.g., crushing a sustained-release tablet or cutting a transdermal patch) and the exposure of infants and children to excipients (e.g., binding agents, preservatives) in amounts capable of producing adverse effects.

Peroral Drug Administration

One of the principal determinants of peroral drug administration in children is the ability to actually get the drug into the body. Peroral formulations are often expelled by children because of poor taste and texture. This is a significant issue, especially when considering that taste sensation differs as a consequence of development and on an interindividual basis. Solid formulations, such as tablets and capsules, are not easily administered to the majority of infants and children owing to their inability to easily and safely swallow them. For example, incomplete development of swallowing coordination may result in choking or aspiration when solid formulations are given to infants and small children. Finally, solid peroral formulations limit the ability for dose titration and dosing flexibility. Drug developers in the United States and abroad are working to address this limitation by the development of new techniques suitable for both oral and peroral drug administration that encompass both products (e.g., dispersible peroral tablets, oral films, titratable granules, oral melts) and drug administration devices (e.g., dosing straws, graduated cylinders for peroral granules).

With regard to dosing accuracy with peroral formulations, liquids (e.g., drops, solutions, syrups, suspensions, elixirs) are preferred for infants and young children. The utility of these formulations is often limited by palatability when taste-masking of the active ingredient(s) cannot be effectively achieved. In the case of suspension formulations, improper reconstitution and/or resuspension prior to dose administration can introduce problems related to accuracy of dosing. Other potential limitations of peroral liquid drug formulations (including those that may be extemporaneously compounded by the pharmacist from drug powder or from solid peroral dosage forms of a given drug) include potential problems related to drug stability, contamination (chemical or bacterial), portability and for some products, the need for them to be refrigerated so as to insure drug stability.

Administration of liquid medications can be associated with risk if the device for administering the medication is not appropriate (e.g., use of a kitchen teaspoon as opposed to a 5.0 mL dosing spoon) or used improperly when measuring a dose that is appropriate for the patient's age or weight. The low cost and convenience of hypodermic syringes has prompted many physicians and pharmacists to dispense them with liquid medications in order to improve accuracy. Although this approach is seemingly associated with greater accuracy in dosing, parents/caregivers can have difficulty in reading the graduations on a syringe and, also, the plastic caps on the plungers of syringes can produce a choking hazard for infants and young children. All of these problems can be obviated by education of parents/caregivers on how to reliably use special syringes for peroral dosing that pharmacists should dispense with every liquid drug formulation.

Parenteral Drug Administration

In contrast to adults where vascular access is relatively easy to obtain, difficulties are often present in the infant and young child. These are often produced by the smaller diameter of peripheral vessels (relative to the size of the intravenous cannula), developmentally associated differences in body composition (e.g., body fat distribution) and the use of topical anesthetic agents, some of which can produce venous constriction. The small peripheral blood vessels in infants and young children can also limit the volume and rate of intravenous drug administration because of issues of capacity and, in the instance of drugs capable of producing venous irritation, infusion-related discomfort.

An underappreciated issue that can complicate parenteral drug administration to infants occurs when the concentration of a given drug formulation does not enable accurate measurement of dose. Errors consequent to improper dilution of adult formulations necessary to ensure appropriate osmolarity and volume for IV administration (the most common resulting in a 10-fold overdose) are not uncommon. For example, morphine, a drug commonly used in neonates, infants, and children, is commonly available in a 2 mg/mL

concentration. A usual 0.1 mg/kg morphine dose for a 1 kg infant using this formulation would require a nurse or pharmacist to accurately withdraw 0.05 mL and administer it into a length of IV tubing with a dead space volume that may exceed that of the dose by approximately 100-fold. In this situation, accuracy of dose and infusion time can be significantly compromised. Although underdosing is often a serious problem when attempting to administer very small volumes, overdoses also occur, owing to inaccurate extemporaneous dilutions. Moreover, attempts to compensate for the volumes present within the IV tubing further predispose the patient to receive an incorrect, possibly unsafe, dose. Whenever such concentrated drug formulations are the only source for use, appropriate alteration of the stock parenteral solution should be performed and manufactured by the pharmacy department. As well, many errors can be avoided by the use of standard dilutions that all practitioners are aware of and using standardized approaches for IV drug administration that minimize complications associated with unrealized drug dilution and errant infusion times (e.g., pediatric syringe pumps attached to low-volume tubing).

Although used rather infrequently, IM drug administration offers a route of administration for many drugs in those instances where venous access is not immediately available or when a therapeutic drug regimen involves use of a single or limited number of doses. Although appealing with respect to immediacy, this route of administration can be associated with problems (e.g., muscle and/or nerve damage, sterile abscess formation, variable rate of drug absorption consequent to developmental differences in vascular perfusion of muscle beds), especially in the neonate and small infant. Finally, the decision to utilize the IM route must take into consideration the physicochemical properties (e.g., pH, osmolarity, solubility) of the drug formulation and/or any diluent used to prepare it.

Other Routes for Drug Administration

Neonates, infants, children, and adolescents with certain pulmonary conditions (e.g., reactive airway disease, viral-induced bronchiolitis, asthma, cystic fibrosis) frequently receive drugs (e.g., corticosteroids, β-adrenergic agonists, antimicrobial agents, mucolytic drugs) via inhalation. The pulmonary surface area in pediatric patients of all ages is a very effective, easily traversable barrier for drug absorption. Rate-limiting factors for pulmonary drug absorption include physicochemical factors associated with the drug and delivery system (e.g., particle size, diffusion coefficient, chemical stability of drug molecule in the lung) and physical factors that influence intrapulmonary drug deposition (e.g., active vs passive drug delivery to the tracheobronchial tree, respiratory minute volume, internal airway diameter); many of which are developmentally determined. For drugs formulated for delivery using a metered-dose inhaler (either drug powder or suspended particles using a carrier gas), developmental factors (e.g., incoordination of device actuation with inhalation, inability to follow instructions for clearing of airway, and passive inhalation with actuation of delivery device) either prevent their use (such as in infants and small children) or limit the bioavailability of the drug to be administered. In these instances, specific devices (e.g., masks, spacer chambers) and/or methods of delivery (e.g., continuous aerosolization via mask) can be used to improve the efficiency of drug delivery and, thereby, drug efficacy.

In pediatric patients, percutaneous drug administration is generally reserved for agents intended to produce a local effect within the dermis. Development has an impact on the barrier of the skin that, if not recognized and controlled for, can produce situations in which systemic toxicity can result (see "Drug Absorption" above). Similar therapeutic challenges occur when transmucosal routes (e.g., buccal, sublingual, rectal) are used for drug administration. Specifically, unpredictable systemic bioavailability may complicate treatment consequent to variability in the rate and/or extent of drug absorption. Finally, direct intraosseous drug administration via puncture of the tibia is occasionally used in infants and small children for administration of drugs and crystalloid fluids given acutely during resuscitation efforts. It is particularly useful when vascular access sufficient for drug administration cannot be immediately accomplished as the onset of action by this route is comparable with that seen after IV administration.

Adherence and Compliance

Beyond proper individualization of drug dose based on developmental considerations, the influence of concomitant disease/treatment and the selection of the proper drug formulation, the success of drug treatment in a pediatric patient is inextricably linked to the successful administration of the drug. Physical and cognitive immaturity makes the infant and the child a dependent creature in almost all respects, including those related to therapeutic drug administration. Until a child reaches an age at which they can physically self-administer a drug in an accurate, proficient fashion and can mentally assume responsibility for this task (generally from 7-14 yr of age, depending on the individual child), compliance with a drug regimen becomes the responsibility of an adult. In a hospital environment, compliance is ensured through the actions of physicians, nurses, and pharmacists who, collectively through an integrated system of medical care, assume this responsibility. Upon discharge, the responsibility is transferred to parents/guardians or other adult caregivers in an environment that is generally nonmedical. At this juncture, therapeutic compliance morphs into adherence as defined by the potential for conflicting demands (e.g., multiple adult caregivers; different external environments such as home, daycare, school; parents tending to the needs of multiple children) to introduce variability (anticipated and unpredictable) in drug administration. Whether treatment is for a self-limiting (e.g., antibiotic administration) or chronic (e.g., asthma, diabetes) condition, challenges to therapeutic adherence have the potential to serve as primary determinants of drug safety and efficacy in infants and young children.

In contrast to the period encompassing infancy and childhood, adolescence poses its own unique challenges to therapeutic adherence. During this period, psychosocial maturation almost always lags behind physical maturation. Development of cognitive and physical skills in most adolescents enables them to self-administer a prescribed medication in a proper manner with little to no supervision. However, psychodynamic issues experienced by a substantial number of adolescents (e.g., complete understanding of the ramifications of undertreatment, disease progression, and/or roles of disease prevention, and/or health maintenance; perceptions of immortality and the associated lack of need for treatment; disorganized patterns of thinking capable of confounding treatment schedules; defiant/oppositional behavior toward authority figures) can often precipitate therapeutic failure, through either undertreatment or overtreatment, the latter occasionally leading to drug toxicity. Unfortunately, the only maneuver that can be used to facilitate therapeutic compliance and adherence in the pediatric patient is the combination of vigilance (on behalf of all caregivers) and repetitive education coupled with positive reinforcement (e.g., the use of motivational interviewing techniques). When children reach the age of assent (i.e., generally by 7 yr of age in children who have normal neurobehavioral development), they have the beginning level of cognitive ability sufficient to engender understanding about their medical condition(s) and how effective treatment can be used to improve their life. Through diligent efforts placed toward patient education and reeducation, older children and adolescents can assume a level of responsibility for active partnership in their overall medical management, one that will mature as educational efforts, driven by a shared desire for an optimal outcome, are regularly made. The pediatrician's role in fostering this is paramount given their understanding of development and the regular patient–parent interactions that occur from birth through adolescence.

Drug–Drug Interactions

Pharmacokinetic and/or pharmacodynamic properties of drugs may be altered when 2 or more drugs are coadministered to a patient (refer to Table 60-6). Even though many interactions occur at the level of drug metabolism, they may also occur at the level of drug absorption (e.g., inhibition of intestinal CYP3A4 activity by grapefruit juice or St. John's wort and consequent reduction in presystemic clearance of

Table 60-6 Mechanism-Based Drug Interaction Table

PHARMACODYNAMIC	EXAMPLE DRUG COMBINATION	RESULT
Additive	a. Fentanyl and midazolam b. Class 1A antiarrhythmic with erythromycin c. Vancomycin plus aminoglycoside	Use of multiple medications with similar side effect profiles can lead to additive effects such as increased sedation (a), increased QT prolongation (b), and increased potential for nephrotoxicity (c)
Synergy	Penicillin plus aminoglycoside	Improved bactericidal efficacy against some Gram-positive organisms. Use of penicillin inhibits bacterial cell wall synthesis which for some Gram-positive organisms can improve the intracellular penetration of the aminoglycoside, which inhibits bacterial cell protein synthesis by binding to 30S and 50S ribosomal subunits
Antagonism	Opiate plus naloxone	Competitive receptor antagonism: Decreased efficacy of opiate medications, improvement in respiratory effort
PHARMACOKINETIC		
Absorption	*Inhibition of MDR1:* Amiodarone and digoxin	Increased digoxin concentration, digoxin toxicity (↓ digoxin 50%)
	Complex formation: Quinolone and tetracycline antibiotics with divalent/trivalent cations (e.g.; Ca^{2+}, Mg^{2+}, Fe^{3+}, Al^{3+})	Decreased antibiotic absorption
	Mycophenolate mofetil plus antacids	Decreased absorption of mycophenolate mofetil
	Pharmaceutical preparations: Ceftriaxone with IV fluids containing calcium	Crystalline deposits in lungs/kidneys of neonates
Distribution	Ceftriaxone + endogenous bilirubin	Displacement of bilirubin from albumin binding site, increased risk kernicterus in neonates
	NSAID plus warfarin	Displacement of warfarin from albumin binding site with consequent exaggerated anticoagulant response
Metabolism	*Induction:* Rifampin plus antiretrovirals	Decreased serum concentration of antiretroviral because of induced CYP metabolism
	Inhibition: Azole antifungals plus CYP3A4 substrates	↑ Drug levels because of inhibition of CYP3A4-mediated metabolism resulting in drug toxicity
Elimination	Penicillin plus probenecid	Decreased tubular secretion of penicillin resulting in increased serum concentrations
	Methotrexate plus aspirin	Inhibition of renal tubular secretion of methotrexate resulting increased methotrexate concentration

This table is not meant to be an all-inclusive list of drug–drug interactions. Care should be taken when prescribing all medications, and the potential of interactions should be considered. The practitioner is encouraged to assess the possibility of all interactions when prescribing medications.

NSAID, nonsteroidal antiinflammatory drug.

Modified from Rizack M, Hillman C: The Medical Letter handbook of adverse drug interactions. *New Rochelle, NY, 1989, The Medical Letter.*

CYP3A4 substrates), distribution (e.g., displacement of warfarin plasma protein binding by ibuprofen with consequent increased hemorrhagic risk), or elimination (e.g., inhibition of ATS of β-lactam antibiotics by probenecid). Drug–drug interactions may also occur at the level of the receptor (via competitive antagonism), many of which are intentional and produce therapeutic benefit in pediatric patients (e.g., antihistamine reversal of histamine effects, naloxone reversal of opiate adverse effects).

Drug–drug interactions that occur at the level of drug metabolism can be somewhat predictable based on a priori knowledge of a given drug's biotransformation profile. Although such information can be derived from the primary literature, it may not be immediately translated into a useful clinical context consequent to limitations associated with in vitro to in vivo extrapolation, which can include (1) use of animal models for characterizing metabolism; (2) extrapolating enzyme kinetics derived from pooled human liver microsomes or recombinant human drug-metabolizing enzymes to estimates of in vivo drug clearance; (3) extrapolating in vitro data obtained from fully competent (i.e., adult activity) hepatic microsomes to estimates of clearance in patients who may have developmental and/or disease-associated compromise in enzyme activity; (4) inaccurate accounting for pharmacogenetic variation in drug-metabolizing activity (i.e., constitutive activity); (5) the contribution of multiple different drug-metabolizing enzymes in the overall biotransformation of a given drug (i.e., a polyfunctional drug substrate); and (6) the potential role of enzyme induction or inhibition in vivo that is not reflected from conditions used for in vitro metabolism studies.

Despite these limitations, information pertaining to drug–substrate interaction can be useful in ascertaining the direction (e.g., enzyme inhibition → reduced clearance → higher plasma drug concentration → enhanced effect as compared to enzyme induction → increased clearance → reduced plasma drug concentration → diminished effect) of a drug–drug interaction. Although multiple sources describing specific drug–drug interactions exist (e.g., primary and secondary literature, drug product labeling), the information may not be complete or updated. In examining multiple information sources pertaining to this topic, the authors found a data compilation from Indiana University (http://medicine.iupui.edu/clinpharm/ddis/) to be the most complete and clinically useful. Utilizing primary literature should be assessed when information is not available in online sources.

Drug interactions may also occur at a pharmaceutical level as a result of a physicochemical incompatibility of two medications when combined. Such interactions generally alter the chemical structure of 1 or both constituents, thereby rendering them inactive and potentially dangerous (e.g., intravenous infusion of a crystalline precipitate or unstable suspension). For example, ceftriaxone should be avoided in infants younger than 28 days of age if they are receiving or are expected to receive intravenous calcium-containing products because of reports of neonatal deaths resulting from crystalline deposits in the lungs and kidneys. Alternatively, 2 drugs simultaneously administered perorally may form a complex that can inhibit drug absorption (e.g., coadministration of doxycycline with a food or drugs containing divalent cations).

Nonprescription preparations, herbal supplements, and certain foods also have the potential to produce interactions with drugs. These are often quite challenging for the clinician, especially for alternative therapies, in that their composition (or potency) may not be completely discernable from the product labels and because the disposition of many natural products has not been studied in either children or adults. Many patients and their parents also do not consider alternative

therapies (including nutraceuticals) to be "medicines" (and, consequently, will not disclose their use during a routine medication history) but to be safe "nutritional supplements" despite absent regulation for their testing. Consequently, a patient visit should begin with a thorough medication history that includes discussions of which nonprescription medications and herbal products are being used and their regularity of use. This allows the clinician to identify the primary ingredients contained in these products and query their potential for producing clinically significant drug–drug interactions. This can be efficiently accomplished through available web-based search engines (e.g., Natural Medicines Comprehensive Database, http://naturaldatabase.therapeuticresearch.com/home.aspx).

One of the most daunting challenges for the clinician is not to determine whether a drug–drug or drug–food interaction may be present, but if it will be of sufficient magnitude so as to be clinically significant. Extensive databases of reported and/or potential (e.g., theoretical mechanism- or metabolism-based) drug interactions exist and are widely available via the Internet (e.g., http://www.medscape.com/druginfo/druginterchecker; http://www.drugs.com/; http://www.umm.edu/adam/drug_checker.htm), some of which provide some assessment as to their potential significance. Many computer-based proprietary information systems used by hospital and community pharmacies are routinely used to screen a patient's medication profile (generally restricted to prescribed drugs) against new prescriptions to evaluate the potential for drug–drug interactions.

The provision of individualized, optimal drug therapy requires that the clinician make an assessment of potential drug–drug interactions and their significance. This requires knowledge of the interaction, the patient's condition, concomitant treatments (prescriptions, nonprescription drugs, alternative medicines), the impact of development on the dose– concentration–response relationship and a consideration of the risk-vs-benefit profile of the drug being prescribed. The clinician must be cognizant that if the clinician treats a potential drug–drug interaction as an absolute contraindication to drug use, it is possible that an alternative drug choice could produce a treatment associated with either less benefit or greater risk. Although many drugs have the potential to cause drug interactions, not all those documented may be clinically relevant for a given patient. *For patients with complex histories who require treatment with multiple medications, consultation with a clinical pharmacologist or pharmacist can help provide guidance on drug–drug interactions and their potential to impact therapy.*

Adverse Drug Reactions

Adverse drug reactions (ADRs) have been defined by the World Health Organization as "a response to a drug that is noxious and unintended, and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function." There are 2 traditional pharmacologic classifications of ADRs: type A and type B. Type A reactions are dose dependent, predictable, and account for 85-90% of all ADRs. These are often considered as "side effects" to medications. Type B reactions are not dose dependent, are unpredictable and account for approximately 10-15% of all adverse reactions. These are generally considered to represent hypersensitivity (i.e., allergic) reactions whereas some can have a nonimmune basis. Historically, such standardized definitions describing adverse events have not been routinely utilized. Furthermore, patients sometimes misinterpret some side effects as allergies (e.g., diarrhea with amoxicillin/clavulanate) and this may be perpetuated through the patient's medical record, thus potentially restricting a useful and necessary medication.

In the pediatric population, ADRs are common occurrences that produce a major burden to patients and the healthcare system. Studies concerning ADRs in pediatric patients suggest the following: (1) approximately 9% of all pediatric patients admitted to the hospital experience an ADR during their treatment; (2) the apparent incidence of ADRs in children in outpatient clinics is approximately 1.5%; (3) ADRs have been reported as being responsible for >2% of pediatric admissions to children's hospitals; and (4) approximately 40% of ADRs occurring in hospitalized children are potentially life-threatening. In considering these "statistics" it should be recognized that the true incidence of ADRs in children is not known as a consequence of generalized underreporting by healthcare providers (physicians, nurses, pharmacists), parents/caregivers, and patients (who may not recognize signs/symptoms and/or be unable to report them), and in many countries (including the United States), the lack of a standardized surveillance and real-time reporting system. As a consequence, estimation of their incidence relies upon spontaneous, volunteer reporting systems that lack uniformity and critical evaluation and do not provide both numerator and denominator data necessary to determine true incidence of a specific ADR in a specific subpopulation of patients.

Despite the limitations associated with determining the incidence of ADRs in children, it is estimated that their occurrence in patients 0-4 yr of age (3.8%) is more than double that seen at any other time throughout childhood and adolescence. The reasons for this are not currently known but may involve developmental differences in pharmacokinetics and/or pharmacodynamics (i.e., altered dose–concentration–effect relationship), age-associated differences in physiologic "systems" that modulate drug and/or metabolite-mediated cellular injury (e.g., the immune system) and/or the therapeutic use of drugs known to have a relatively high incidence of producing ADRs (e.g., delayed hypersensitivity reactions associated with β-lactam antibiotics). Also, it is important to recognize that infants can experience ADRs from drugs that are not administered to them therapeutically, but from incidental drug exposure (e.g., transplacental drug passage, breastfeeding). Examples include neonatal abstinence syndrome associated with maternal opiate use, production of a hyperserotonergic state in neonates born to mothers who received selective serotonin reuptake inhibitors during and through pregnancy, and opiate toxicity in breastfed infants whose mothers were taking codeine for pain management. In these instances, drug accumulation occurring because of reduced activity of drug-metabolizing enzymes associated with development, and, potentially, pharmacogenetically determined phenotypic changes that, in concert, can produce a level of systemic drug exposure sufficient to produce exaggerated drug response or frank toxicity.

There are also specific ADRs that occur at a much greater frequency in infants and children as compared to adults. Examples include aspirin-associated Reye syndrome, cefaclor-associated serum sickness-like reactions, lamotrigine-induced cutaneous toxicity, and in infants younger than 2 yr of age, valproic acid–induced hepatotoxicity. It is not clear whether the age predilection for these specific ADRs is associated with developmental differences in drug biotransformation related to both metabolite formation and detoxification or, alternatively, has a pharmacogenetic basis. Finally, it should be recognized that children, like adults, do experience hypersensitivity reactions to drugs. Examples include reactions to anticonvulsant drugs (e.g., phenytoin, carbamazepine, phenobarbital), sulfonamides (e.g., sulfamethoxazole, sulfasalazine), minocycline, cefaclor, and abacavir. These specific ADRs are not characteristic of type I (i.e., immediate) hypersensitivity reactions (e.g., true penicillin allergy) or anaphylactoid reactions; rather, they represent delayed hypersensitivity reactions that are classified as idiosyncratic with respect to their origin. A relatively common constellation of symptoms (fever, rash, and lymphadenopathy) suggests that abnormal activation/regulation of the immune system is a predominant component of their pathogenesis. Data from in vitro studies of sulfamethoxazole hypersensitivity also support this assertion. A requisite role for metabolic bioactivation (for anticonvulsants, sulfamethoxazole, and cefaclor) and, possibly, genetic factors, such as allelic variants in HLA-B (e.g., HLA-B*5701 and HLA-B*1502 associated with hypersensitivity reactions to abacavir and carbamazepine) appear also to be involved in their etiology.

PERSONALIZED MEDICINE

See also Chapter 59.

The general concept of personalized medicine involves the application of genomic information to predicting a disease, disease severity, and therapeutic response. This "new vision of medicine" has been described as the 3 Ps: predictive, personalized, and preventive. However, in children, ontogeny should also be considering when

discussing personalizing therapeutic treatments. Thus, the aim of pediatric personalized medicine is to uniquely combine genetic variation with developmental stage to provide a tailored approach to either drug avoidance (in the case of predicted, significant risk of an ADR) or treatment.

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Chapter 61

Anesthesia, Perioperative Care, and Sedation

Randall C. Wetzel

The primary purpose of general anesthesia is to suppress the conscious perception of, and physiologic response to, noxious stimuli and to render the patient unconscious. Potent drugs are used to blunt physiologic responses to what would otherwise be life-threatening trauma (surgery). Intraoperatively, the anesthesiologist is responsible for providing analgesia as well as physiologic and metabolic stability (Table 61-1). This responsibility is facilitated by obtaining an adequate preanesthesia history (Table 61-2). Although anesthetic risk has greatly decreased, the increased risk of morbidity and mortality in the perioperative period demands the utmost vigilance. The risk is even higher in certain disease states (Table 61-3).

GENERAL ANESTHESIA

Analgesia

Providing analgesia for procedures both in and out of the operating room is a major responsibility and functions within a spectrum of care (Table 61-4). Techniques exist to provide profound pain relief during operative procedures for all patients, including the most critically ill infants. Blunting the physiologic responses to painful stimuli inhibits the stress response and its multiple deleterious physiologic and metabolic consequences. The response to painful and stressful stimuli is a potent stimulus of the **systemic inflammatory response syndrome,** which leads to increased catabolism, physiologic instability, and increased mortality (see Chapter 70). Appropriate use of medication, such as fentanyl anesthesia in neonates, reduces the incidence of postoperative bradycardia, hypotension, acidosis, interventricular hemorrhage, coagulation abnormalities, hypoglycemia, and death.

Hypnosis and Amnesia

The blunting of both consciousness **(hypnosis)** and conscious recall **(amnesia)** is a crucial feature of pediatric anesthesia care. Awareness of painful, anxiety-provoking, and stressful conditions for children is

Table 61-1	Goals of Anesthesia
Analgesia	
Amnesia and a decreased level of consciousness	
Akinesia–absence of movement in response to painful stimuli	
Physiologic support and homeostatic management throughout the perioperative process	
Vigilance	

Table 61-2 The Preanesthetic History

Child's previous anesthetic and surgical procedures:
- Review the anesthetic record for information about the mask and endotracheal tube size; the type and size of laryngoscope used; difficulties with mask ventilation or intubation; prolonged emergence (awakening) from anesthesia; postoperative vomiting, postoperative agitation and disordered postoperative behavior in the days following anesthesia/surgery. In addition, a history of hyperthermia or acidosis in the child or family member should be sought.

Perinatal problems (especially for infants):
- Need for prolonged hospitalization
- Need for supplemental oxygen or intubation and ventilation
- History of apnea and bradycardia
- History of cardiovascular compromise

Other major illnesses and hospitalizations

Family history of anesthetic complications, malignant hyperthermia, or pseudocholinesterase deficiency

Respiratory problems:
- Long-term exposure to environmental tobacco smoke
- Obstructive apnea, breathing irregularities, or cyanosis (especially in infants younger than 6 mo of age)
- History of snoring or an obstructive breathing pattern
- Recent upper respiratory tract infection
- Recurrent respiratory infections
- Previous laryngotracheitis (croup) or laryngomalacia
- Asthma or wheezing during respiratory infections
- Airway abnormalities, facial anomalies, mucopolysaccharidosis

Cardiac problems:
- Murmur or history of congenital heart disease—ask for details
- Dysrhythmia
- Exercise intolerance
- Syncope
- Cyanosis

Gastrointestinal problems:
- Reflux and vomiting
- Feeding difficulties
- Failure to thrive
- Liver disease

Exposure to exanthems or potentially infectious pathogens

Neurologic problems:
- Seizures
- Developmental delay
- Neuromuscular diseases
- Increased intracranial pressure

Hematologic problems:
- Anemia
- Bleeding diathesis
- Tumor
- Immunocompromise
- Prior blood transfusions and reactions

Renal problems:
- Renal insufficiency, oliguria, anuria
- Fluid and electrolyte abnormalities

Psychosocial considerations:
- Posttraumatic stress
- Drug abuse, use of cigarettes or alcohol
- Physical or sexual abuse
- Family dysfunction
- Previous traumatic medical or surgical experience
- Psychosis, anxiety, depression

Gynecologic considerations:
- Sexual history (sexually transmitted infections)
- Possibility of pregnancy

Current medications:
- Prior administration of corticosteroids

Allergies:
- Drugs
- Iodine
- Latex products
- Surgical tape
- Food (especially soya and egg albumin)

Dental condition (loose or cracked teeth)

When and what the child last ate (especially in emergency procedures)

Table 61-3 Specific Pediatric Diseases and Their Anesthetic Implications

DISEASE	IMPLICATIONS
RESPIRATORY SYSTEM	
Asthma	Intraoperative bronchospasm that may be severe and even fatal Preoperative control is essential Pneumothorax or atelectasis Optimal preoperative medical management is essential; preoperative steroids may be required
Difficult airway	Special equipment and personnel may be required Should be anticipated in children with dysmorphic features or acute airway obstruction, as in epiglottitis or laryngotracheobronchitis or with an airway foreign body Patients with Down syndrome may require evaluation of the atlantooccipital joint Patients with storage diseases may be at high risk
Bronchopulmonary dysplasia	Barotrauma with positive pressure ventilation Oxygen toxicity, pneumothorax a risk
Cystic fibrosis	Airway reactivity, bronchorrhea, increased intraoperative pulmonary shunt and hypoxia Risk of pneumothorax, pulmonary hemorrhage Atelectasis, risk of prolonged postoperative ventilation Patient should be assessed for cor pulmonale
Sleep apnea	Pulmonary hypertension and cor pulmonale must be excluded Careful postoperative observation for obstruction required
CARDIAC	Need for antibiotic prophylaxis for bacterial endocarditis Use of air filters; careful purging of air from the intravenous equipment Physician must understand the effects of various anesthetics on the hemodynamics of specific lesions Preload optimization and avoidance of hyperviscous states in cyanotic patients Possible need for preoperative evaluation of myocardial function and pulmonary vascular resistance Provide information about pacemaker function and ventricular device function
HEMATOLOGIC	
Sickle cell disease	Possible need for simple or exchange transfusion based on preoperative hemoglobin concentration and percentage of hemoglobin S Importance of avoiding acidosis, hypoxemia, hypothermia, dehydration, and hyperviscosity states
Oncology	Pulmonary evaluation of patients who have received bleomycin, *bis*-chloroethyl-nitrosourea, chloroethyl-cyclohexyl-nitrosourea, methotrexate, or radiation to the chest Avoidance of high oxygen concentration Cardiac evaluation of patients who have received anthracyclines; risk of severe myocardial depression with volatile agents Potential for coagulopathy
RHEUMATOLOGIC	Limited mobility of the temporomandibular joint, cervical spine, arytenoid cartilages Careful preoperative evaluation required Possible difficult airway
GASTROINTESTINAL	
Esophageal, gastric	Potential for reflux and aspiration
Liver	High overall morbidity and mortality in patients with hepatic dysfunction Altered metabolism of many anesthetic drugs Potential for coagulopathy and uncontrollable intraoperative bleeding
RENAL	Altered electrolyte and acid–base status Altered clearance of many anesthetic drugs Need for preoperative dialysis in selected cases Succinylcholine to be used with extreme caution and only when the serum potassium level has recently been shown to be normal
NEUROLOGIC	
Seizure disorder	Avoidance of anesthetics that may lower the seizure threshold Optimal control ascertained preoperatively Preoperative serum anticonvulsant measurements
Increased intracranial pressure	Avoidance of agents that increase cerebral blood flow Avoidance of hypercarbia
Neuromuscular disease	Avoidance of depolarizing relaxants; at risk for hyperkalemia Patient may be at risk for malignant hyperthermia
Developmental delay	Patient may be uncooperative during induction and emergence
Psychiatric	Monoamine oxidase inhibitor (or cocaine) may interact with meperidine, resulting in hyperthermia and seizures Selective serotonin reuptake inhibitors may induce or inhibit various hepatic enzymes that may alter anesthetic drug clearance Illicit drugs may have adverse effects on cardiorespiratory homeostasis and may potentiate the action of anesthetics
ENDOCRINE	
Diabetes	Greatest risk is unrecognized intraoperative hypoglycemia; if insulin is administered, intraoperative blood glucose level monitoring needed; glucose and insulin must be provided, with adjustment for fasting condition and surgical stress
SKIN	
Burns	Difficult airway Risk of rhabdomyolysis and hyperkalemia from succinylcholine following burns for many months Fluid shifts Bleeding Coagulopathy
IMMUNOLOGIC	Retroviral drugs may inhibit benzodiazepine clearance Immunodeficiency requires careful infection control practices Cytomegalovirus-negative blood products, irradiation, or leukofiltration may be required
METABOLIC	Careful assessment of glucose homeostasis in infants

Table 61-4 Definitions of Anesthesia Care

MONITORED ANESTHESIA CARE A specific anesthesia service in which an anesthesiologist has been requested to participate in the care of a patient undergoing a diagnostic or therapeutic procedure. Monitored anesthesia care includes all aspects of anesthesia care: a preprocedure assessment, intraprocedure care, and postprocedure anesthesia management. During monitored anesthesia care, the anesthesiologist or a member of the anesthesia care team provides a number of specific services, which may include some or all of, but are not limited to, the following: • Discussing anesthesia care with the family and child, obtaining consent, allaying anxiety and answering questions—family centered anesthesia care. • Monitoring of vital signs, maintenance of the patient's airway, and continual evaluation of vital functions. • Diagnosing and treating clinical problems that occur during the procedure. • Administering sedatives, analgesics, hypnotics, anesthetic agents, or other medications as necessary to ensure patient safety and comfort. • Providing other medical services as needed to accomplish the safe completion of the procedure. Anesthesia care often includes the administration of medications for which the loss of normal protective reflexes or loss of consciousness is likely. *Monitored anesthesia care* refers to those clinical situations in which the patient remains able to protect the airway for the majority of the procedure. If the patient is rendered unconscious and/or loses normal protective reflexes for an extended period, this is considered a general anesthetic.
LIGHT SEDATION Administration of anxiolysis and/or analgesia that obtunds consciousness but does not obtund normal protective reflexes (cough, gag, swallow, hemodynamic reflexes), or spontaneous ventilation.
DEEP SEDATION Sedation that obtunds consciousness and normal protective reflexes or possesses a significant risk of blunting normal protective reflexes (cough, gag, swallow, hemodynamic reflexes), hemodynamic and respiratory insufficiency may occur.
GENERAL ANESTHESIA Administration of hypnosis, sedation, and analgesia that results in the loss of normal protective reflexes.
REGIONAL ANESTHESIA Induction of neural blockade (either central, neuraxial, epidural, or spinal; or peripheral nerve block, e.g., digital nerve block, brachial plexus block), which provides analgesia and is associated with regional motor blockade. Consciousness is not obtunded. Special expertise is required. Frequently, in children, anxiolysis and sedation are also necessary for this technique to be successful. Regional anesthesia (e.g., caudal epidural blockade) is used to supplement general anesthesia and provide postoperative analgesia.
LOCAL ANESTHESIA Provision of analgesia by local infiltration of an appropriate anesthetic agent. Does not require the presence or involvement of an anesthesiologist, although an anesthesiologist may provide local anesthesia services.
NO ANESTHESIOLOGIST An anesthesiologist will not be involved in the care of the child in any way.

just as deleterious, physically and psychologically, as the painful procedures themselves. Management is aimed at blunting the fear and emotional response during surgery, painful procedures (bone marrow aspiration, lumbar punctures), or nonpainful but anxiety-provoking procedures (MRI, CT). Many drugs provide anxiolysis, blunting of recall, and amnesia for such events (Table 61-5). Obtundation of consciousness may accompany the provision of analgesia. Hypnotic and sedative agents can induce altered consciousness without producing any analgesia; *analgesia* and *obtunded consciousness* are not synonymous. It is also possible to provide analgesia (local, spinal, or epidural analgesia) without obtunding consciousness.

Sedation describes a medically induced state that is on a continuum between the fully alert, awake state and general anesthesia (see Table 61-4). In addition to inducing unconsciousness and amnesia, general anesthesia obtunds or ablates critical physiologic reflexes; the most important are **airway-protective reflexes:** coughing, gagging, and swallowing. Cardiorespiratory reflexes are also obtunded with general anesthesia; respiratory depression and hemodynamic compromise may occur and may be profound. As sedation deepens toward general anesthesia, loss of airway patency, loss of airway-protective reflexes, and loss of cardiovascular stability occur. *Light (minimal) sedation* is anxiolysis without loss of these reflexes or airway patency. *Deep sedation* occurs when these reflexes are obtunded or lost (see Table 61-4). **Adequate sedation in children may be accompanied by the actual or potential loss of vital reflexes**. It is mandatory that those providing sedation for a child be able to detect the transition into deep sedation and general anesthesia and be prepared to manage the child's airway and circulation, and provide CPR if required.

Akinesia (Immobility or Muscular Relaxation)

Akinesia is the absence of movement. It is necessary to ensure safe and adequate operative conditions and to provide ideal conditions for advanced and meticulous surgery. Akinesia is often produced with muscle relaxants (see Table 61-5). These agents facilitate respiratory management in the perioperative period and in critically ill patients. The absence of movement is neither the absence of pain nor the presence of amnesia. **Whenever neuromuscular blocking agents are used, analgesia and sedation must be provided.**

Physiologic Support

The need for anesthesia increases the need to monitor and support physiologic integrity and homeostasis. Sedation and anesthesia have significant and potentially life-threatening physiologic consequences (see Tables 61-4 and 61-5). Maintenance of adequate cardiorespiratory function, fluid management, electrolyte control, thermoregulation, and concern for all aspects of the child's health are critical during anesthesia.

Vigilance

Constant, critical attention by physicians who understand the demands of the surgical procedure, as well as the changes in physiologic status and their implications, is mandatory to provide safe perioperative care

Table 61-5 Selected Drugs Used in Anesthesia

DRUG	USES AND IMPLICATIONS
MUSCLE RELAXANTS	
Succinylcholine	Used to facilitate endotracheal intubation and maintain muscle relaxation in emergency situations; now virtually never given routinely A depolarizing neuromuscular blocking agent with rapid onset and offset properties Associated with the development of malignant hyperthermia in susceptible patients Degraded by plasma cholinesterase, which may be deficient in some individuals; such a deficiency may result in prolonged effect Fasciculations may be associated with immediate increases in intracranial and intraocular pressures as well as postoperative muscle pain
Vecuronium, rocuronium, mivacurium, *cis*-atracurium, all aminosteroids	Nondepolarizing neuromuscular blockers Have less-rapid onset than succinylcholine but are longer-acting Prolonged ICU use may lead to profound muscle weakness Vecuronium and rocuronium are metabolized by the liver and excreted in bile; they are the most commonly used neuromuscular blocking agents *cis*-Atracurium is metabolized by plasma cholinesterase and therefore may be of benefit in patients with hepatic or renal disease
HYPNOTICS	
Propofol	Rapidly acting hypnotic; amnestic, but not analgesic, a general anesthetic agent Like pentothal, may cause hypotension Causes respiratory depression May increase the seizure threshold Great utility in titrated doses for sedation and with local anesthetic and short-acting opioid for outpatient procedures May suppress nausea Associated with the often fatal propofol infusion syndrome when used in prolonged intravenous infusion (>24 hr) and therefore not used for ICU sedation in children
Etomidate	Cardiovascular stability on induction with no increase in intracranial pressure Inhibits corticosteroid synthesis and increases ICU mortality Associated with myoclonus, potential difficulty with assisted ventilation, and pain on injection
Ketamine	Hypnotic analgesic and amnestic Causes sialorrhea and should be coadministered with an antisialagogue, such as atropine or glycopyrrolate May be associated with laryngospasm Causes endogenous catecholamine release, tachycardia, and bronchodilation Increases intracranial and intraocular pressures Decreases the seizure threshold
SEDATIVE–ANXIOLYTICS	
Benzodiazepines	Produce sedation, anxiolysis, or hypnosis, depending on the dose May produce antegrade, but not retrograde, amnesia All agents raise the seizure threshold, are metabolized by the liver, and depress respiration, especially when administered with opioids Frequently administered as premedications Diazepam may be painful on injection and has active metabolites Midazolam can be administered by various routes and has a short half-life Lorazepam has no active metabolites Sedation effected by all benzodiazepines may be reversed by flumazenil, but respiratory depression may not be reliably reversed
Dexmedetomidine	Produces anxiolysis, sedation, sympatholysis, by α_2-receptor stimulation centrally; has mild analgesic properties Side effects include hypotension and bradycardia Commonly used for procedural and ICU sedation Continuous infusion for ICU sedation; currently limited to 24 hr
ANALGESIC–SEDATIVES	
Opioids	Gold standard for providing analgesia All cause respiratory depression Morphine and, to a lesser extent, hydromorphone may cause histamine release The synthetic opioids fentanyl, sufentanil, and short-acting alfentanil may have a greater propensity to cause chest wall rigidity when administered rapidly or in high doses and are also associated with the rapid development of tolerance; these 3 drugs have particular utility in cardiac surgery because of the hemodynamic stability associated with their use Remifentanil is an ultra–short-acting synthetic opioid that is metabolized by plasma cholinesterase; it may have particular utility when deep sedation and analgesia are required along with the ability to assess neurologic status intermittently
INHALATIONAL AGENTS	
Nitrous oxide	Causes amnesia and mild analgesia at low concentrations Danger of hypoxic mixture if the oxygen concentration is not monitored and preventive safety mechanisms are not in place
Potent vapors, sevoflurane, desflurane, isoflurane	"Complete anesthetics"—they induce a state of hypnosis, analgesia, and amnesia All are myocardial depressants, and some are vasodilators May trigger malignant hyperthermia in susceptible individuals Sevoflurane is almost universally used for inhalation induction of anesthesia in children All are bronchodilators at equipotent concentrations Isoflurane, and especially desflurane are associated with a higher incidence of laryngospasm, when used for anesthetic induction, than sevoflurane

for all children. Careful attention to a child's preoperative condition is mandatory for minimizing the risk during perioperative care (see Tables 61-3 and 61-4).

INDUCTION OF GENERAL ANESTHESIA

The goal of induction of general anesthesia is to rapidly achieve surgical anesthesia by using IV or, more commonly in children, inhalational induction agents. In children who are too young to tolerate the establishment of vascular access before the induction of anesthesia, it is routine to induce anesthesia by mask inhalation of volatile anesthetics. In the operating room, a child is often accompanied by the parents (parental presence during induction [PPI]) and placed on the operating room table. Before the induction of anesthesia, monitors are usually applied to the child. These include a pulse oximeter, electrocardiogram electrodes, and a blood pressure cuff. The child is then cautiously introduced to the face mask, which contains a high gas flow (5-7 L/min of oxygen), frequently mixed with nitrous oxide. Inhalation of nitrous oxide and oxygen for 60-90 sec induces a state of euphoria. The airway responses to inhalational anesthetics are now blunted, and sevoflurane can be introduced into the inhaled gas mixture. This leads to unconsciousness within 30-60 sec while the child continues to breathe spontaneously.

The child is now "asleep," and the parents can be asked to leave. An IV line is then started, and comprehensive intraoperative monitoring initiated. Surgical anesthesia can be maintained by spontaneous ventilation with a mask; this is safe only when the airway is secure and patent, the stomach is empty, and the child is older than 6 mo of age. Procedures longer than 1 hr are not usually performed with mask inhalational anesthesia. If these conditions are not met, if the surgeon needs to approach the airway, or if muscular paralysis is required, then the airway must be secured with endotracheal intubation. Although endotracheal intubation can be performed under deep inhalational anesthesia with respiratory depression and obtunded cough and gag reflexes, the depth of anesthesia required to ablate airway reflexes is very close to the level that induces hemodynamic instability. Therefore, muscle relaxation with IV, nondepolarizing muscle relaxants is induced to facilitate endotracheal intubation. *Succinylcholine is rarely, if ever, used*. After paralysis is induced, direct laryngoscopy and airway intubation can be performed. Correct endotracheal tube placement is confirmed by direct laryngoscopy, end-tidal CO_2 measurement, endotracheal tube fogging, and the finding of bilaterally equal breath sounds during positive-pressure ventilation. If necessary, fiberoptic airway endoscopy and chest radiograph, in addition to these measures, can be used to confirm correct endotracheal tube placement.

After endotracheal intubation, spontaneous ventilation may be permitted, if muscle relaxants are not used or have worn off; it is routine to provide controlled mechanical ventilation. When the child is completely anesthetized, positioned for surgery, and hemodynamically stable, and maintenance anesthesia is achieved, the surgery can begin.

Inhalational Anesthetics

General anesthesia may be induced and maintained by either inhalation or the IV route. The inhalational anesthetics used in children include sevoflurane, isoflurane, and desflurane. Although halothane is the prototypical pediatric inhalational anesthetic agent, it has been replaced by sevoflurane and is no longer used in the United States.

The *minimal alveolar concentration* (MAC) of an inhalational anesthetic is the alveolar concentration (expressed as percent at 1 atmosphere) that provides sufficient depth of anesthesia for surgery in 50% of patients. For potent inhalational agents, the alveolar concentration of an anesthetic reflects the arterial concentration of anesthetic in the blood perfusing the brain. Thus, the MAC is an indication of anesthetic potency and is analogous to the ED_{50} (effective dose in 50% of recipients) of a drug. MAC is age-dependent, is lower in premature infants than in full-term infants, and decreases from term through infancy to preadolescence. In adolescence, MAC again increases, falling thereafter. Inhalational anesthetic agents are poorly soluble in blood but rapidly equilibrate between alveolar gas and blood.

Respiratory Effects

The advantages of inhalational anesthesia are rapid onset, rapid offset, convenient route of delivery and excretion (respiratory), and the ability to provide profound analgesia and amnesia. Inhalational anesthetics are all airway irritants and, in low doses, can cause laryngospasm. All inhalational anesthetics depress ventilation in a dose-dependent manner. Thus, expired CO_2 and $Paco_2$ (arterial partial pressure of carbon dioxide) increase in spontaneously breathing children. In addition, anesthesia also decreases end-expiratory lung volume. Small lung volumes result in a decrease in lung compliance, increases in total pulmonary resistance, work of breathing, and intrapulmonary arteriovenous shunting, and a restrictive lung defect. Inhalational anesthetics also shift the CO_2 response curve to the right, thus decreasing, but not ablating, the increase in minute ventilation with increasing $Paco_2$.

Inhalational anesthetics, which may induce apnea and hypoxia in premature infants and newborns, are less frequently used in premature infants and children. In neonates and young infants, general anesthesia always necessitates endotracheal intubation and controlled mechanical ventilation. In older children, spontaneous breathing through a mask or a laryngeal mask airway without controlled ventilation is possible for shorter operations. The decreased end-expiratory lung volume and increased work of breathing always necessitate higher inspired oxygen tension.

Cardiovascular Effects

Cardiovascular effects of inhalational anesthesia include depressed cardiac output and peripheral vasodilation; hypotension is frequent. *This is accentuated in hypovolemic patients*. This hypotensive effect is more pronounced in neonates than in older children and adults. Inhalational anesthetics also decrease baroreceptor and heart rate responses. Inhalational anesthesia blunts the hypoxic pulmonary vasomotor response in the pulmonary circulation, an effect that may contribute to hypoxemia.

The net effect of inhalational anesthesia is decreased oxygen delivery. Perioperatively, catabolism is enhanced and oxygen demand is increased; there may be a profound imbalance between oxygen demand and oxygen delivery. Development of a metabolic acidosis intraoperatively may reflect this imbalance. Because the cardiovascular depressant effects of inhalational anesthesia are greater in premature and newborn infants, these agents are of limited use in such patients.

All inhalational anesthetic agents cause *cerebrovasodilation*. Sevoflurane is a more potent cerebrovasodilator than isoflurane. Thus, in children with elevated intracranial pressure, impaired cerebral perfusion, or head trauma, and in premature neonates at risk for intraventricular hemorrhage, inhalational anesthetics should be used with extreme caution. Although inhalational anesthetics decrease cerebral oxygen consumption, they may disproportionately decrease blood flow, thus worsening oxygen delivery.

Specific Anesthetics

Sevoflurane

Sevoflurane is the most commonly used inhalational anesthetic in children for both induction and maintenance of general anesthesia. It is not a significant airway irritant and leads to smoother induction than isoflurane. Emergence from sevoflurane anesthesia is quite rapid; there is a significant amount of **emergence delirium**, especially if pain has been inadequately controlled or induction was stormy and preoperative anxiety high. This effect can be blunted by pretreatment with midazolam and adequate use of opioids, although the latter delay recovery from anesthesia. Metabolism of sevoflurane yields free fluoride, which may cause renal damage; consequently, the FDA has restricted the use of sevoflurane to <2 MAC hr, preferably with fresh gas flow rates >2 L/min.

Isoflurane

Isoflurane maintains cardiac output and cerebral perfusion more effectively than sevoflurane. Isoflurane is pungent and a significant airway irritant, with an unacceptably high incidence of complications, such as laryngospasm during induction. Emergence from anesthesia with

isoflurane is quite smooth, but slower than for sevoflurane. Cerebral blood flow is only minimally affected, and cerebral oxygen delivery is maintained. Because isoflurane is not a suitable induction agent, induction with sevoflurane or with an intravenous agent, and maintenance with isoflurane is a common pediatric anesthesia practice.

Desflurane

A potent airway irritant, desflurane causes coughing, breath holding, and laryngospasm during induction and therefore is unsuitable for induction. It is frequently used for maintenance of anesthesia, and emergence from desflurane anesthesia is rapid.

Nitrous Oxide

Nitrous oxide is a tasteless, colorless, odorless gas with potent analgesic properties. It induces a state of euphoria (hence its nickname, "laughing gas"). The MAC of nitrous oxide is >100; consequently, it is not suitable as a sole agent to maintain anesthesia. Nevertheless, nitrous oxide has few complications and produces little or no hemodynamic or respiratory depression. Commonly, during maintenance of general anesthesia, the inhalational gas mixture is 70% nitrous oxide and 30% oxygen, with the addition of an inhalational anesthetic or potentiation of analgesia with an opioid or a hypnotic agent. The deleterious effects of nitrous oxide are increased postoperative nausea and vomiting and, with long-term use (days), bone marrow suppression. Although there is no evidence of harmful sequelae of the use of nitrous oxide for routine anesthesia, its use has decreased because of the greater incidence of nausea and vomiting associated with it. Nitrous oxide is a potent analgesic that is safely used in a mixture of 50% nitrous oxide and oxygen (Entonox) in obstetrics and in emergency departments to provide analgesia. Although this combination appears to be safe, it potentiates the respiratory depressive effects of opioids, and its use, in combination with any other sedative, hypnotic, or opioid agent, requires very close monitoring because it may produce general anesthesia.

Intravenous Anesthetic Agents

Anesthesia can be both induced and maintained with either intermittent boluses or continuous infusions of IV anesthetic agents. Intravenous anesthetics include barbiturates, opioids, benzodiazepines, and miscellaneous drugs, such as propofol and ketamine. Intravenous anesthetic agents can induce anesthesia more rapidly than inhalational anesthetics, with fewer complications. Vascular access is required, so unless IV access has already been obtained, inhalation induction is the preferred route. For children arriving in the operating room with vascular access, IV induction should be routine, because it rapidly takes the child from the awake state to the anesthetized state with less psychologic and cardiorespiratory compromise than occurs with inhalational induction. All IV agents affect cardiorespiratory function. The 1 exception to this may be ketamine, which, in lower doses, releases catecholamines, which maintain cardiac function and blood pressure.

Propofol

Propofol is the most commonly used IV induction agent in pediatric anesthesiology and has a rapid onset. In doses of 2-3 mg/kg, propofol induces both respiratory depression and hypotension. Propofol can sometimes burn and itch on injection. It is formulated in 10% soy emulsion with egg emulsifiers, so is contraindicated in patients with soy or egg allergy. After induction of anesthesia, propofol is also a useful agent for maintaining hypnosis and amnesia, and can be used as a sole anesthetic agent for nonpainful procedures, such as radiation therapy, MRI, and CT studies. Combined with opioids, it provides excellent, brief anesthesia for painful procedures, such as lumbar puncture and bone marrow aspiration. Propofol is a general anesthetic agent that obtunds airway reflexes, respiration, and hemodynamic function; it should not be considered a "sedation agent." Although hemodynamic stability, and even spontaneous respirations, can be maintained with cautious propofol sedation, its use for prolonged sedation over several hours to days in children younger than 12 yr is associated with hemodynamic collapse, bradycardia, metabolic acidosis, cardiac failure, rhabdomyolysis, hyperlipidemia, profound shock, and death (**propofol infusion syndrome**). Its use for prolonged sedation (>12 hr) in the critical care setting in children is contraindicated.

Barbiturates

The most commonly used barbiturate for IV induction is sodium thiopental, although it is now rarely used. Although loss of consciousness is rapid, barbiturates do not provide analgesia. Thiopental depresses respiration, induces apnea, and can cause hypotension in the hypovolemic patient. Induction with 3-5 mg/kg of thiopental usually produces 5-10 min of unconsciousness within seconds. After IV induction with sodium thiopental, maintenance anesthesia can be established using benzodiazepines, IV opioids, or inhalational anesthetics.

Pentobarbital is commonly used for sedation in children. It is an IV drug that induces loss of consciousness. It is also a potent respiratory depressant, particularly when used in conjunction with opioids and benzodiazepines. Pentobarbital has a very prolonged effect. It is not an analgesic agent, and painful procedures cannot be performed with pentobarbital sedation without supplemental analgesia. Pentobarbital sedation that is deep enough for anxiolysis and nonpainful procedures generally results in prolonged sleep. Its potency and long duration of action make it difficult to titrate. It is not an ideal drug for sedation for short or painful procedures.

Sodium methohexital (Brevital) is another IV induction agent. It is similar to sodium thiopental and has a similar spectrum of respiratory depression.

Etomidate

Etomidate is an imidazole derivative used for the induction of anesthesia, frequently in emergency situations. Its action is not as rapid as that of propofol. The lack of cardiovascular depression has led to the use of etomidate in patients with hemodynamic compromise, cardiac disease, and septic shock. Unfortunately, by inhibition of 11β-hydroxylase, this agent depresses synthesis of both mineralocorticoids and glucocorticoids for up to 72 hr following a single induction dose. Etomidate increases mortality when used as a sedative in ICUs (for which it is now contraindicated) and when used in patients who receive merely an induction dose. Adrenal suppression by etomidate further complicates the management of the very patients with hemodynamic compromise in whom the agent has been indicated. The decision to continue use of this agent must weigh the serious risks against the short-term benefit of hemodynamic stability during anesthesia induction and sedation.

Ketamine

Ketamine rapidly induces general anesthesia that lasts for 15-30 min when given at 1-3 mg/kg IV. It has few side effects and can maintain adequate blood pressure and cardiac output. Ketamine is also effective when given intramuscularly, subcutaneously, nasally, or orally; the dose must be increased for these alternative routes. Ketamine dissociates the connections between the cortex and limbic system *(dissociative anesthesia)* by its inhibition of *N*-methyl-D-aspartate receptors, producing a unique anesthetic state. Ketamine is not only a hypnotic agent, providing obtundation and loss of consciousness, but also an analgesic agent, and can act as a sole IV agent to provide general anesthesia. With low doses of this agent, airway reflexes and spontaneous ventilation may be maintained; at higher doses, loss of airway reflexes, apnea, and respiratory depression occur. It is unwise to rely on ketamine to prevent aspiration of gastric contents during deep sedation. Intravenous ketamine is a useful general anesthetic agent for short procedures.

Ketamine produces disturbing postanesthetic dreams and hallucinations. These can occur at the time of emergence from anesthesia and for several weeks. In adults, the incidence of this effect is 30-50%; in prepubertal children, it may be 5-10%. Premedication with a benzodiazepine, such as midazolam, greatly reduces these sequelae; a benzodiazepine is routinely given to children receiving ketamine anesthesia. The other side effect of ketamine is that it is a potent secretagogue, enhancing oral and bronchial secretions. A drying agent, such as atropine or glycopyrrolate, is administered before the administration of ketamine.

A bronchial smooth muscle relaxant (bronchodilator), ketamine is a useful agent for sedating asthmatic patients and others in the ICU. Ketamine has been reported to increase intracranial pressure and therefore is not indicated in patients at risk for elevated intracranial pressure. Ketamine can increase myocardial oxygen demand and should be used cautiously in patients with impaired myocardial oxygen delivery or cardiac outflow tract obstruction.

Opioids

Opioids are superb analgesic agents, providing analgesia for painful procedures and postprocedural pain (see Chapter 62). Large doses of morphine (0.5-2 mg/kg), combined with nitrous oxide, provide adequate analgesia for painful procedures and surgery. Opioids suppress the CO_2 response, can induce apnea, and are respiratory depressants. Morphine is often associated with hypotension and bronchospasm from histamine release; it is used with caution in children with asthma. Morphine is a long-acting agent, and an equivalent dose per kilogram gives much higher blood levels in neonates than in older children, with plasma concentrations approximating 3 times those in adults. This reason for this difference is the longer elimination half-life (14 hr) in children than in adults (2 hr). Because of the prolonged activity and hemodynamic instability induced by morphine, the fentanyl class of synthetic opioids has replaced it.

Fentanyl is an effective agent to provide pain relief, analgesia, and sedation for painful procedures, with a shorter duration of action and a more stable hemodynamic profile than morphine. In equal analgesic doses, all opioids are equally potent respiratory depressants. Other anesthetic agents potentiate this respiratory depression, whether they are inhalational anesthetics or IV barbiturates or benzodiazepines.

Fentanyl use at 30-50 μg/kg obtunds the hemodynamic response to surgery and provides stable operating conditions. Effective analgesia and anesthesia can be provided with IV fentanyl in a 2-3 μg/kg bolus followed by a 1-3 μg/kg/hr continuous infusion. Hemodynamic effects can be blunted and recall totally obtunded with use of a nitrous-narcotic anesthetic technique, although muscle tone may remain high and spontaneous movements can occur. Nitrous-narcotic anesthetics usually are supplemented with a nondepolarizing muscle relaxant during maintenance anesthesia. If the patient will be extubated and resume spontaneous ventilation, reversal of the muscle relaxant is necessary.

Other synthetic opioids (sufentanil, alfentanil, remifentanil) are available, but fentanyl is the most commonly used opioid. Both sufentanil and alfentanil have been used for cardiac anesthesia; their potency is different from that of fentanyl. Alfentanil appears to cause an increased incidence of muscle rigidity, convulsions, and prolonged respiratory depression compared with fentanyl, and is not used in children.

Remifentanil has very rapid onset and offset of action. In doses of 0.25 μg/kg/min, surgical anesthesia can be maintained with this agent. Its short half-life and rapid offset are advantageous for rapid emergence from anesthesia. Unfortunately, its rapid offset of action also leads to postprocedural and postoperative pain and requires analgesic supplementation, frequently with an opioid, which removes the advantage of anesthesia with a short-acting opioid. Remifentanil may have a role in providing rapidly deepening anesthesia for particularly painful events or rapidly inducing analgesia. It is also used intraoperatively by continuous infusion to maintain anesthesia. It is a potent respiratory depressant and provides no postprocedural analgesia, features that limit its use.

Benzodiazepines

Benzodiazepines induce hypnosis, anxiolysis, sedation, and amnesia, and have anticonvulsant activity. In larger doses, they cause respiratory depression and apnea; they are synergistic with opioids and barbiturates in their respiratory depressant effects. Benzodiazepines are γ-aminobutyric acid agonists.

The most commonly used benzodiazepine in pediatric anesthesia is midazolam. Short acting and water soluble, it can be injected intravenously without pain. It is a potent hypnotic–anxiolytic–anticonvulsant and is approximately 4 times more potent than diazepam. In anxiolytic doses, midazolam (0.15 mg/kg) has no effect on respiratory rate, heart rate, or blood pressure, and provides excellent preoperative sedation that is frequently accompanied by amnesia. It can be administered orally, nasally, rectally, intravenously, or intramuscularly. Use of oral midazolam at a dose of 0.5-1.0 mg/kg, mixed in sweet, flavored syrup, induces anxiolysis in approximately 90% of children. This agent has no hemodynamic, oxygenation, or respiratory depressant effects at this dose level, but when midazolam is used as a sole agent, children may frequently lose their balance and head control, may have blurred vision, and, rarely, may become dysphoric. A child sedated with midazolam should not be left unattended and is not safe walking. Most children rapidly accept an inhalational anesthetic mask after oral midazolam premedication. The widespread use of preoperative oral midazolam has decreased the practice of PPI to calm younger children.

Dexmedetomidine

Dexmedetomidine is an IV agent that obtunds consciousness through central α_2-receptor stimulation, much like clonidine. It appears to cause no respiratory depression and produces anxiolysis, sedation, and mild analgesia. It is a sympatholytic, and its side effects include hypotension and bradycardia. Dexmedetomidine is commonly used for sedation in ICU patients as well as for procedures; it is being explored as an adjuvant for general anesthesia, especially in cardiac patients.

Complications During Induction of Anesthesia

The period between full wakefulness, with the child in control of airway reflexes, and general anesthesia, with total loss of control, is fraught with difficulty. During induction, laryngospasm, bronchospasm, vomiting, pulmonary aspiration of gastric contents, and subsequent aspiration pneumonitis pose a constant threat although they rarely occur. Concern about vomiting and aspiration dictates the use of preanesthetic fasting (NPO [nothing by mouth]) guidelines and indicates rapid sequence anesthetic induction.

Laryngospasm is the most common complication. During induction of anesthesia, especially with inhalational anesthetics, a period of excitement may occur. This period is associated with heightened airway reflexes, which can lead to coughing, gagging, laryngospasm, and bronchospasm. Laryngospasm is reflex closure of the larynx, which makes it impossible for the child to breathe or for assisted ventilation to be used. The child may make violent inspiratory efforts against a closed glottis, generating significantly negative intrathoracic pressure. This may affect cardiovascular function and cause postobstructive pulmonary edema. Laryngospasm can be prolonged, and hypoxia may ensue. Laryngospasm occurs in up to 2% of all anesthetic inductions in children younger than 9 yr and is half as common in older patients. Laryngospasm occurs twice as frequently in children with active or recent upper respiratory tract infection (URI). A history of passive smoking from environmental (parental) tobacco smoke increases the likelihood of laryngospasm 10-fold, and even more if the smoker is the child's mother.

Laryngospasm can be relieved during induction of anesthesia by increasing the anesthetic dosage, either intravenously or through inhalation (although with the glottis closed, further administration of inhalational anesthesia is not possible). Muscle relaxation relieves laryngospasm, and in an acute situation, this situation may be an indication for succinylcholine. Constant positive airway pressure administered by someone skilled in airway management to ensure patency of the soft tissues of the oropharynx may be beneficial in alleviating laryngospasm. Laryngospasm may also occur during emergence from anesthesia, because a state of excitement is again traversed between deep anesthesia and wakefulness.

Bronchospasm can occur during induction, either in response to histamine release as a result of many of the anesthetic agents or as part of a hyperexcitable stage. Endotracheal intubation may also induce bronchospasm during induction. Bronchospasm during induction is particularly common in children with asthma. Bronchospasm secondary to intubation in a patient with reactive airway disease can be severe, may be associated with life-threatening hypoxemia, and may make it

impossible to ventilate the child. The use of histamine-releasing anesthetic agents has been associated with total airway obstruction, respiratory failure, and cardiac arrest. Environmental tobacco smoke is a risk factor.

Other pulmonary problems with induction of anesthesia include massive atelectasis with hypoxemia, impaired ventilation and perfusion, blunted hypoxic pulmonary vasoconstriction, and increased airway secretions with decreased bronchociliary function. **Hypersecretion** is prevented by the routine use of antisialagogues, such as atropine. The newer inhalation agents are less-potent secretagogues, and the use of atropine premedication is much less common, but is probably indicated if ketamine is used.

Hemodynamic complications upon anesthesia induction include **hypotension,** which can be profound in hypovolemic patients; decreased myocardial function, which can be severe in patients with compromised cardiac function; and tachycardia and cardiac dysrhythmias. Inhalational anesthetics sensitize the myocardium to circulating catecholamines, and induction and excitement are associated with a hypercatecholaminergic state.

Parental Presence During Induction of Anesthesia

Parents may expect to be with their child during the induction of anesthesia. Removing a terrified child from the comforting arms of a parent is stressful for the child, the parent, and the caregivers. If this parental separation cannot be achieved comfortably with preoperative psychoprophylaxis and behavioral modification, including education and desensitization to the operative environment, or with pharmacologic aids, such as preoperative medications including benzodiazepine and barbiturates, then there may be a need to defer parent–child separation until general anesthesia is induced. Preoperative medication with oral benzodiazepine more frequently provides calm, smooth induction conditions than PPI without pharmacologic preparation. Although the use of PPI in the hands of a confident, competent anesthesia practitioner can replace the need for preoperative medication, it does not reliably predict smooth induction. PPI appears to decrease neither emergence phenomena nor the incidence of postoperative behavioral changes, and it does not appear to add an advantage for the child over that provided by preoperative sedative medication, such as with oral midazolam.

MAINTENANCE OF ANESTHESIA

Maintenance of anesthesia is the period between induction and emergence. The child should be asleep, unaware of pain, unresponsive with either motion or hemodynamic responses to painful stimuli, and homeostatically supported. The child is comatose, without airway-protective reflexes and with suppression or absence of respiration, and has received drugs that suppress hemodynamic adaptive responses. The child is also exposed to surgical trauma, and there may be blood loss and significant fluid shifts (third spacing), decreased intravascular volume, and hypothermia.

Anesthesia is usually maintained with or without nitrous oxide, an inhalational anesthetic such as isoflurane or sevoflurane, and an opioid for intraoperative analgesia, potentiation and deepening of anesthesia, and postoperative analgesia. A benzodiazepine is added either during premedication or intraoperatively to supplement hypnosis and amnesia. A nondepolarizing muscle relaxant (vecuronium or rocuronium) completes the pharmacologic maintenance of anesthesia. Agents can be given by continuous inhalational anesthesia or by continuous or bolus IV infusion.

During maintenance, the child may breathe spontaneously through an anesthetic mask or endotracheal tube or may be mechanically ventilated. All general anesthetic agents decrease end-expiratory lung volume, which is generally lower than functional residual capacity, with increases in pulmonary closing capacity and intrapulmonary shunt. Hypoxia would occur without supplemental oxygenation. These effects are compounded by respiratory depressant effects and the depressed CO_2 response curve. Therefore, it is generally considered that use of anesthetics for longer than 1 hr requires endotracheal intubation and positive-pressure ventilation. For long procedures, spontaneous breathing through a mask is possible; in smaller children, in whom the surgical field and the airway may be close together, the need to maintain a patent airway necessitates endotracheal intubation.

Muscle relaxation to facilitate endotracheal intubation was once accomplished with succinylcholine. This agent has a high-risk profile, however, and is associated with postoperative pain (muscle spasms); hyperkalemia; elevated intracranial, intraocular, and intragastric pressures; malignant hyperthermia; and myoglobinuria and renal damage. Succinylcholine is now rarely used, except to provide rapid relief of laryngospasm. Intubation of the airway is facilitated with a nondepolarizing, short-acting muscle relaxant. Rocuronium is the drug most commonly used for intubation. For procedures that last longer than 40 min, vecuronium and alcuronium are suitable to induce muscle relaxation for intubation. After intubation of the airway, the decision must be made whether to maintain muscle relaxation to facilitate surgery or to allow the child to resume spontaneous respiration. Prolonged use of a nondepolarizing muscle relaxant is common practice but may contribute to postoperative respiratory compromise if it is not fully reversed with appropriate agents.

Reversal of neuromuscular blockade is standard anesthetic practice. Effects of nondepolarizing muscle relaxants are reversed by increasing the concentration of acetylcholine with neostigmine (acetylcholine esterase inhibitor) and either atropine or glycopyrrolate to prevent the vagal effects. With the virtual abandonment of succinylcholine, only nondepolarizing muscle relaxants are routinely used for intubation. The termination of their action depends on metabolism and elution away from the neuromuscular junction. This process, even for the shortest-acting muscle relaxants (rocuronium), can take several minutes. An intubating dose of rocuronium to rapidly induce paralysis in emergency situations may not spontaneously reverse for 20 min or longer (compared with ≈3 min for succinylcholine). If the airway cannot be secured, disaster may follow in the child who is unable to breathe spontaneously and in whom blockade cannot be reversed.

Thermoregulation is critical during anesthesia. The absence of movement and the inhibition of shivering lead to difficulty in thermogenesis. All the contributors to heat loss—convection, radiation, evaporation, and conduction—occur during anesthesia. Humidification and warming of inspired air are required. Additional warming devices are commonly used, such as rewarming blankets. General anesthetic agents increase the interthreshold range (the minimal temperature change that will lead to sympathetic response, generally 0.3°C [0.5°F]). Although temperature sensing may remain normal, an autonomic response to hypothermia is not triggered. Anesthetic agents cause vasoparesis, which further impairs thermoregulation and increases heat loss. In newborns, inhalational anesthetics inhibit nonshivering thermogenesis from brown fat, putting them at higher risk for hypothermia.

Fluid Maintenance During Surgery and Anesthesia

Patients who are unconscious and immobile have lost venous pump mechanisms and have peripheral venous pooling. Anesthetic agents cause vasodilation, and anesthetized patients have relative hypovolemia. Intravascular volume expansion is frequently required after the induction of anesthesia to maintain adequate perfusion, tissue oxygenation, urine output, and blood pressure. Volume expansion is most commonly provided by isotonic salt-containing solutions (normal saline, lactated Ringer solution). Autonomic responses may be increased as part of the surgical stress response, with vasoconstriction and intravascular volume contraction caused by diuresis, intravascular volume loss from hemorrhage, evaporation (insensible loss, increased during surgery), and third space (interstitial space) fluid losses resulting from the inflammatory response. Abnormalities in the distribution of renal blood flow and secretion of antidiuretic hormone further complicate the regulation of intravascular volume.

The concern about **hypoglycemia** as a result of preoperative fasting led to the recommendation that infants and small children receive

Table 61-6	Intraoperative Pediatric Fluid Replacement
4 mL/kg/hr	1-10 kg
2 mL/kg/hr	10-20 kg
1 mL/kg/hr	per kg >20 kg
Example: a 22-kg child requires: (4 × 10) + (2 × 10) + (1 × 2) = 62 mL/hr	

isotonic solutions with 5% glucose. The occurrence of hyperglycemia and potential neurologic injury during cardiopulmonary bypass, or during neurosurgery and other situations in which central nervous system injury can occur, however, along with the recognition that hypoglycemia is rare in nonneonates, has called into question the routine use of glucose-containing solutions. In neonates, glucose monitoring during and after anesthesia is indicated. In older children with normal nutritional status, isotonic salt solutions without additional glucose are adequate. In children who are receiving parenteral alimentation with a solution containing a high glucose concentration (>10%), continuation of the glucose concentration should be ensured to avoid rebound hypoglycemia, which would occur if the high-glucose solution was stopped.

Intraoperative fluid maintenance includes (1) current maintenance fluids and replacement of usual deficits during the NPO period; (2) replacement of third space losses; and (3) replacement of extraordinary losses (hemorrhage). Infants should receive glucose-containing isotonic fluids, such as 5% dextrose in water with either 0.25 normal saline or isotonic crystalloid solutions. Table 61-6 is a guideline for determining fluid deficits and maintenance requirements in the operating room. Fluid deficits should be replaced over the 1st 2 or 3 hr of intraoperative management. Deficits are generally calculated as the number of hours of NPO status multiplied by the hourly maintenance rate for the child. Half of this deficit is replaced during the 1st hr and half during each of the subsequent 2 hr. If hypotension or tachycardia occurs or persists in the early stages of anesthesia, more rapid replacement of the fluid deficit is indicated. The deficit is replaced with isotonic crystalloid solutions.

Third space losses are replaced with isotonic salt solutions. For large operations, such as abdominal or thoracic procedures, during which there may be a large amount of evaporative loss as well as a significant amount of third space loss, 8-10 mL/kg per hr of surgery is generally given as IV fluid replacement. For smaller operations, such as herniorrhaphy, pyloromyotomy, and minor procedures, fluid replacement at 3-5 mL/kg/hr is indicated for third space losses. Even when surgery involves the extremities and third space losses are minor, it is wise to give an additional 1-2 mL/kg/hr to replace them.

A crystalloid solution is indicated for blood loss, at 3 mL per mL of blood lost. This formula could be reduced somewhat if blood is replaced on an mL-per-mL basis with packed red blood cells or whole blood equivalent. The use of albumin or other suitable colloid, such as fresh-frozen plasma in neonatal surgery, also decreases the amount of crystalloid replacement needed for blood loss. During maintenance anesthesia, if large-volume transfusions are required, warming the blood and crystalloid solutions avoids hypothermia. With major surgery and the resultant systemic inflammatory response syndrome, capillary integrity is lost and third space losses are common. Failure to replace this third space loss and restore intravascular volume leads to hypotension, shock, acidemia, and renal failure, and further stimulates the systemic inflammatory response syndrome.

RECOVERY FROM ANESTHESIA

Recovery from anesthesia includes emergence and postoperative recovery from surgery and anesthetics. **Emergence** describes the time and the physiologic response to decreasing depth of anesthesia during return to consciousness. During emergence, patients experience decreased anesthetic effect, increased stress responses, physiologic and psychologic responses to painful stimuli, excitement, and anxiety. Conscious realization of pain may lead to physiologic responses during emergence. Normal physiologic functions, such as spontaneous ventilation, resume and hemodynamic function improves. After routine elective procedures, the child should be fully conscious before leaving the operating room, with intact airway reflexes, the ability to follow simple commands, the effects of muscle relaxants reversed, and airway patency maintained. If the child is going to the ICU, or if for surgical reasons the decision is made to leave the child intubated, analgesia and sedation should be maintained, along with mechanical ventilation, in the postoperative period. Ideally, emergence should be as brief as possible, with maintenance of analgesia and anxiolysis and restoration of cardiorespiratory function. Inhalational anesthetic agents leave the system rapidly during ventilation, and muscle relaxants can be reversed; however, the effects of opioids, benzodiazepines, and IV hypnotic agents may be prolonged.

During emergence, the decision must be made whether to reverse the effects of muscle relaxants. The effects of long-acting, nondepolarizing muscle relaxants (vecuronium and pancuronium) are invariably reversed. If the child appears to be weak or to have respiratory depression in the postoperative phase, prolonged neuromuscular blockade should be considered.

POSTANESTHESIA CARE UNIT

In the postanesthesia care unit (PACU), the child is observed until there is adequate recovery from anesthesia and sedation. Parents should be permitted to comfort their children in the PACU. Achievement of spontaneous breathing, adequate arterial saturation (>95%), and hemodynamic stability are key recovery end points. The child should be arousable, responsive, and oriented before discharge from the PACU. The amount of time spent in the PACU depends on whether the child is being discharged to an inpatient nursing unit, to an ICU, to a postrecovery area, or directly home. Discharge from the PACU depends on the child's overall functional status—not merely the physiologic end points, but also the behavioral end points as well as the adequate provision of analgesia and control of postoperative nausea and vomiting. There are several scoring systems (Table 61-7) for determining whether a child is ready to be discharged from the PACU.

Complications in the Postanesthesia Care Unit

Respiratory Depression

Prolonged emergence from anesthesia and respiratory depression can be caused by opioids or inadequate antagonism of neuromuscular blocking agents. Pain can cause significant hypoventilation, especially after thoracic or abdominal surgery. Delayed emergence from anesthesia can occur as a result of retention of inhaled anesthetic agents worsened by hypoventilation. Hypothermia, especially in neonates, delays metabolism and excretion of anesthetics and also aggravates neuromuscular blockade. If respiratory depression is profound, then maintenance of the airway may require an oral airway. If the depression is severe, endotracheal intubation and mechanical ventilation are indicated.

Only in rare cases, in which **opioid suppression** is suspected, is reversal of the effects of opioid with naloxone indicated. Opioid reversal with naloxone reverses not only the respiratory depression but also the analgesia. A somnolent child with respiratory depression may become excited, agitated in severe pain, uncontrollable, and/or hypertensive after naloxone. Opioid reversal necessitates bedside attention by the physician to monitor the child's behavioral, hemodynamic, and respiratory status. *Naloxone is shorter-acting than most opioid analgesics.*

Atelectasis is another respiratory complication occurring in the 1st 48 hr after anesthesia. Although atelectasis suggests an inhaled foreign body, it is most likely caused by secretions and decreased respiratory effort secondary to pain. Microatelectasis may lead to postoperative infections. Aspiration pneumonia is another postoperative complication.

Postoperative stridor occurs in up to 2% of all pediatric patients. The use of uncuffed, atraumatic, nonirritant endotracheal tubes has decreased the incidence of airway trauma. The use of appropriately sized endotracheal tubes and assurance of an air leak <30 cm H_2O

Table 61-7 Recovery Scores

ALDRETE RECOVERY SCORE	>9 REQUIRED FOR DISCHARGE
ACTIVITY—VOLUNTARILY OR ON COMMAND	
Moves 4 extremities	2
Moves 2 extremities	1
No motion	0
BREATHING	
Deep breath, cough, cry	2
Dyspnea or shallow breathing	1
Apnea	0
BLOOD PRESSURE	
Within 20% of preanesthetic value	2
Within 20–50% of preanesthetic value	1
>50% outside preanesthetic value	0
COLOR	
Pink	2
Pale, blotchy, dusky	1
Cyanotic	0
CONSCIOUSNESS	
Fully aware, responds	2
Arouses to stimulus	1
Unresponsive	0
STEWARD RECOVERY SCORE	**6 REQUIRED FOR DISCHARGE**
ACTIVITY	
Moves limbs purposefully	2
Nonpurposeful movement	1
Still	0
CONSCIOUSNESS	
Awake	2
Responsive	1
Unresponsive	0
AIRWAY	
Coughing on command or crying	2
Maintaining patent airway	1
Requires airway maintenance	0

pressure further decreases the risk of airway trauma. A history of stridor increases the likelihood of postoperative complications. Stridor may be severe enough after extubation to require reintubation. Retractions and respiratory distress in the postoperative period should suggest this complication, and stridor or wheezing should confirm the diagnosis. Racemic epinephrine aerosols are effective therapy; their use requires prolonged observation because of the potential for recurrence of the airway obstruction. Stridor in infants suggests the need for overnight observation.

Hemodynamic instability is much less common in the PACU. Volume expansion may be required to maintain adequate blood pressure, peripheral perfusion, and urine output. Requirement for excessive volume replacement (>30 mL/kg) to maintain blood pressure, perfusion, and urine output in the postoperative period is an indication of shock and occult bleeding, and it necessitates surgical consultation.

Emergence delirium is noted in <3% of children and is more common in those 3-9 yr old. In the immediate hour after surgery, children may become extremely restless, combative, and disoriented, and may be screaming, inconsolably crying, or poorly communicative. These children pose a danger to themselves. This phenomenon is more common when barbiturates are used as part of premedication or induction and inhalational anesthetics or ketamine forms part of the maintenance anesthetic. Although disorientation is common in the postanesthetic stage, erratic, delirious behavior requires attention, with gentle restraint, a quiet environment, and comforting. Potential postoperative complications, such as hypoglycemia and hypoxemia, should be ruled out. Occasionally, it is necessary to sedate the child with benzodiazepines, although these agents prolong postanesthesia recovery time and when they wear off, emergence delirium may recur.

Awareness During Anesthesia

A primary goal of anesthesiology is obtunding consciousness to ablate awareness during procedures and recall afterward. In adults, certain anesthetic techniques are associated with an unacceptably high incidence of recall during anesthesia. Awareness and recall of events during a surgical procedure can be unpleasant and terrifying; the long-term sequelae of such recall in children are unknown. Continuous monitoring of cerebral electroencephalographic function by monitoring of the bispectral index has been recommended. Unfortunately, data in children do not confirm the efficacy of bispectral index monitoring as a means of determining anesthetic depth, and this fact, combined with the absence of meaningful data on intraoperative awareness and recall in infants and children, does not currently support the routine use of bispectral index monitoring.

Postoperative Nausea and Vomiting

After general anesthesia, 40-50% of children may experience nausea and vomiting. More than 80% of all high-risk children receiving inhalational anesthesia experience postoperative nausea and vomiting (PONV). It may occur in the immediate postoperative period, within the 1st 1-2 hr, or several hours after surgery and anesthesia. The etiology may be related to the stress and trauma of surgery combined with the emetic effects of anesthetic agents. Pain is an important cause of nausea and vomiting. Opioid analgesics also induce nausea and vomiting. Preoperative fasting does not decrease the incidence of nausea and vomiting. Indeed, hydration and glucose supplementation appear to be important factors in decreasing PONV. The use of analgesic agents other than opioids (acetaminophen, ketorolac) and regional or local anesthesia is associated with decreased PONV.

This complication prolongs recovery room times, requires significant nursing attention, and increases the use of potent antiemetic agents (ondansetron, other serotonin antagonists). Ondansetron is very efficacious as a prophylactic and in the treatment of PONV. Ondansetron and other serotonin antagonists are recommended for high-risk patients (strabismus surgery) or for actual treatment of PONV. They are contraindicated in children taking serotonin reuptake inhibitors for migraine headaches. Metoclopramide is useful prophylactically. Droperidol (which has an FDA-required black box label warning) must be used with caution because of the rare occurrence of prolonged QT interval and ventricular arrhythmias associated with its use.

Thermoregulation and Malignant Hyperthermia

For patients in the PACU, thermoregulation remains abnormal for several hours. Shivering is common in the postoperative state, and a feeling of extreme cold is common. Warm blankets are very comforting and seem to decrease shivering. **Hypothermia,** especially in neonates, leads to hypotension, bradycardia, acidosis, apnea, and prolongation of the effect of opioids and neuromuscular blocking agents. Although hypothermia has deleterious effects, rewarming must be done cautiously to avoid burning and cutaneous hyperthermia. **Hyperthermia,** with temperatures in excess of 39°C (102.2°F), is of concern in the postoperative period. If it occurs within hours of the use of an inhalational anesthetic, especially if succinylcholine was used, malignant hyperthermia must be suspected.

Malignant hyperthermia is an acute hypermetabolic syndrome that is triggered by inhalational anesthetic agents and succinylcholine. It resembles neuroleptic malignant syndrome. The onset of malignant hyperthermia may be acute, and its course may be fulminant and rapidly fatal. This condition, albeit rare (approximately 1 in 60,000 pediatric patients given anesthesia) is a constant concern. The disease is familial, and a family history of death or a febrile reaction during anesthesia should alert the anesthesiologist to its potential. Its clinical course is characterized by rapid onset of fever, acidosis, hypercarbia, and increased expired CO_2. High fever (38.5-46.0°C [101.3-114.8°F],

rising 1°C [1.8°F] every 5 min), muscle rigidity, metabolic acidosis, and hemodynamic collapse can occur. Death ensues from shock and cardiac dysrhythmias with ventricular fibrillation that is unresponsive to treatment. The mortality rate for malignant hyperthermia was once >70%. Aggressive therapy, including discontinuation of all inhalational anesthetic administration, correction of the metabolic acidosis, and treatment with the muscle relaxant sodium dantrolene, has reduced the mortality rate to <5%. Dantrolene and a kit containing supplies necessary to treat malignant hyperthermia should be present at every site where pediatric anesthesia is provided.

Malignant hyperthermia is probably genetically heterogeneous, with more than 10 genes contributing to susceptibility. Genetic mutations in the ryanodine receptor (the calcium channel of the sarcoplasmic reticulum) have been reported in 20-40% of humans with malignant hyperthermia. **Certain myopathies** are associated with the risk of malignant hyperthermia; these include Duchenne muscular dystrophy, Noonan phenotype, and, in children with a history of ptosis, squint, scoliosis, and muscle cramping. It is wise to avoid the use of succinylcholine in children with myopathies.

Malignant hyperthermia appears to occur from a massive triggering of excitation contraction coupling, sarcolemmal calcium release, and propagation of contraction by a complex biochemical process. The prolonged ischemic contraction leads to myolysis, with release of myoglobin, very high serum creatine phosphokinase levels, and renal failure secondary to myoglobinuria. Malignant hyperthermia generally occurs within the 1st 2 hr of anesthesia, but (rarely) can occur up to 24 hr later.

Certain phenomena are clues to the risk of malignant hyperthermia. The occurrence of masseter spasm during induction, with rigid clenching of the masseter muscles and an inability to open the mouth, may presage full-blown disease. Acute myoglobinuria associated with a malignant hyperthermia triggering agent is another clue. The child may not be hypermetabolic or febrile, but may have dark urine and high serum creatine phosphokinase levels, with the risk of myoglobin-induced renal tubular damage. The finding of dark urine after administration of an anesthetic requires investigation for malignant hyperthermia. An elevated creatine phosphokinase value and heme-positive urine in the absence of red blood cells in the urine indicate a need for renal protection with mannitol and alkaline diuresis.

Rapid therapy is essential. All known triggering agents must be stopped. Intravenous administration of dantrolene sodium (2.5 mg/kg IV as an initial dose) is begun as soon as possible. The need for repeated doses is indicated by the persistence of muscle rigidity, acidosis, and tachycardia, up to a maximum dose of 10 mg/kg. Once the symptoms are controlled, the patient should be observed for at least 24 hr after the laboratory values have returned to normal, because relapse can occur.

Prevention of malignant hyperthermia in susceptible patients requires the avoidance of triggering agents, which include inhalational anesthetics. Most anesthesiology departments are capable of delivering general anesthetics using anesthesia machines from which all traces of anesthetic vapors have been removed. Intravenous anesthesia and a nitrous-opioid technique are safe. Dantrolene prophylaxis is not recommended because the disease is rapidly treatable and because the drug causes respiratory depression and muscle weakness. For a child in whom malignant hyperthermia is suspected, the malignant hyperthermia hotline, 1-800-MHHYPER (1-800-644-9737), should be used to notify the Malignant Hyperthermia Association of the United States (MHAUS). The Malignant Hyperthermia Association registers susceptible patients and provides diagnostic and therapeutic information. Preanesthesia susceptibility testing includes genetic analysis of the ryanodine receptor gene, muscle biopsies, in vitro contraction studies, and, possibly, measurement of muscle CO_2 production in response to intramuscular caffeine.

Postoperative Apnea

Apnea within the 1st 48 hr after surgery and anesthesia in premature infants is common; both central apnea and obstructive apnea (mixed apnea) may occur. The use of respiratory depressants may impair respiratory control in neonates. Apnea is also a recognized stress response in neonates, and inadequate anesthesia is associated with increased apnea and respiratory complications.

The risk of postoperative apnea in premature neonates is inversely proportional to postconceptual age at the time of surgery. This risk is minimal by the time premature infants have reached the postconceptual age of 60 wk. Apnea is most common within the 1st 12 hr after surgery; postanesthetic apnea has been reported in premature infants up to 48 hr later. The incidence of apnea in full-term infants is debatable and has not been clearly demonstrated. It is generally agreed that general anesthesia should be avoided, except for emergency surgery, in full-term children younger than 44 wk postconceptual age. If surgery is required within the 1st mo of life, overnight observation and monitoring are indicated. Theophyllines decrease the incidence of postoperative apnea; they do not ablate it and therefore are not routinely used. The safest course is to monitor premature infants younger than 60 wk postconceptual age and full-term infants younger than 1 mo for at least 24 hr after anesthesia.

PREANESTHETIC EVALUATION

Most previously healthy children require minimal preoperative assessment. The American Society of Anesthesiologists (ASA) classification system for anesthetic care is the American Society of Anesthesiologists Physical Status classification (Table 61-8).

For American Society of Anesthesiologists Physical Status 1 patients, a brief history, notation of medical allergies, and a physical examination focusing on the airway, lungs, and cardiac function are sufficient. For all children who are being assessed for anesthesia risk, a family history should be obtained, for reactions to anesthetics, for drug allergies, and for sudden intraoperative death or hyperthermia after surgery, which may indicate a risk of malignant hyperthermia. In previously anesthetized children, questions should be asked regarding intraoperative anesthetic complications. The history should focus on determining whether the child is at risk for anesthetic or surgical stress as well as cardiorespiratory disease and airway compromise.

Recent URIs should be noted. A URI is an upper respiratory illness associated with fever, mucopurulent green or yellow nasal discharge, productive cough, injected sclerae, and increased mucous secretions. Clear rhinorrhea is generally not a concern. URIs can increase airway reactivity for up to 6 wk in both normal children and children with a history of reactive airway disease. URIs can also increase the risk of laryngospasm and bronchospasm, reduce mucociliary clearance, and raise the risk of intraoperative atelectasis and hypoxemia. It is generally recommended to avoid general anesthesia for elective procedures for 4-6 wk after a URI. In patients with chronic sinusitis and nasal polyps, infection should be thoroughly treated before elective anesthesia.

Acute, fatal bronchospasm can occur during induction of anesthesia and endotracheal intubation for routine, minor surgery in children with asthma. Those children at particular risk for anesthetic complications with asthma are those who were (1) admitted to the hospital within the previous year for their asthma, (2) seen in an emergency department in the last 6 mo, (3) admitted to an ICU, or (4) treated with

Table 61-8	American Society of Anesthesiology Physical Status Classification
Class 1: Healthy patient, no systemic disease	
Class 2: Mild systemic disease with no functional limitations (mild chronic renal failure, iron deficiency anemia, mild asthma)	
Class 3: Severe systemic disease with functional limitations (hypertension, poorly controlled asthma or diabetes, congenital heart disease, cystic fibrosis)	
Class 4: Severe systemic disease that is a constant threat to life (critically and/or acutely ill patients with major systemic disease)	
Class 5: Moribund patients not expected to survive 24 hr, with or without surgery	
Additional classification: "E"—emergency surgery	

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parenteral systemic steroids. The child should be free of wheezing for at least several days before surgery, even if this necessitates an increase in β-agonist dosage and the addition of steroids. Preoperative steroids are indicated for all children with asthma who are receiving asthma therapy or who have received such therapy within the last year. Prednisone, 1 mg/kg given 24 and 12 hr before surgery, significantly decreases airway reactivity perioperatively. Active wheezing is an indication for canceling elective surgery. If wheezing cannot be controlled on an outpatient basis with β-agonists, steroids, and other asthma therapy, then hospital admission of the child for more aggressive therapy before surgery is indicated.

Bronchopulmonary dysplasia also poses significant intraoperative risks. The same applies to cystic fibrosis and other chronic lung diseases. Every effort should be made to ensure that children with such disorders achieve the best possible respiratory status before surgery. Infections should be treated and reactive airways optimally treated without evidence of wheezing.

Airway Evaluation

Because the induction of anesthesia is associated with loss of spontaneous ventilation and airway reflexes, predicting the inability to bag-and-mask ventilate or endotracheally intubate a child before anesthesia is critical. The anesthesiologist must be told if the child has congenital anomalies that affect the airway (Table 61-9). Such anomalies include micrognathia syndromes, macroglossia syndromes, and some thoracic anomalies. Congenital anomalies associated with airway compromise should be diagnosed preoperatively. Conditions that impair mouth opening (temporomandibular joint disease) should be noted. A history of wheezing or stridor may indicate postoperative airway complications and difficult intraoperative airway management.

Mediastinal Masses

Children with anterior mediastinal masses, such as lymphomas and primary mediastinal tumors, are at serious risk for airway compromise, cardiac tamponade, and vascular obstruction. Induction of general anesthesia and even mild sedation can lead rapidly to total loss of the airway, with inability to ventilate the child and cardiovascular collapse. These patients often present in a semiemergency fashion, with the need for both a tissue diagnosis of the mass before treatment is initiated and a surgically placed central venous line.

Significant compression of vital structures can occur with seemingly mild symptoms. Tachypnea, orthopnea, wheezing, and sleep disturbances or avoidance of prone or supine positions are significant indications of serious risk. Pericardial tamponade or superior vena cava syndromes are more concerning findings. A CT scan showing >50% compression of the airway at the carina is an indication to prohibit general anesthesia and provide only mild sedation. Echocardiographic or CT evidence of pericardial tamponade, right ventricular compression, or compression of the pulmonary artery suggests severe risk.

Table 61-9 Difficult Airway Syndromes
Achondroplasia
Airway tumors, hemangiomas
Apert syndrome
Beckwith-Wiedemann syndrome
Choanal atresia
Cornelia de Lange syndrome
Cystic hygroma/teratoma
DiGeorge syndrome
Fractured mandible
Goldenhar syndrome
Juvenile rheumatoid arthritis
Mucopolysaccharidosis
Pierre Robin syndrome
Smith-Lemli-Opitz syndrome
Treacher-Collins syndrome
Trisomy 21
Turner syndrome

Biopsy with the child under local anesthesia may be indicated. If anesthesia is required, cardiopulmonary bypass should be considered, in case it becomes impossible to ventilate the child during surgery. In high-risk children, consideration should be given to initiating treatment with steroids, radiation therapy, and chemotherapy before obtaining a tissue diagnosis.

Down Syndrome

Children with Down syndrome are occasionally behaviorally difficult and are especially fearful of medical caregivers (see Chapter 81). Their cardiac anomalies, macroglossia, and upper airway obstruction can be challenging. Children with Down syndrome have atlantoaxial instability due to odontoid hypoplasia and joint laxity (see Chapter 680.3). In younger children, extension of the neck, routinely used to maintain and intubate the airway, may lead to cervical dislocation and spinal cord trauma. Some anesthesiologists recommend extension and flexion lateral neck films to detect instability before anesthesia. In children with Down syndrome, it is wise to exercise caution in stabilizing the cervical spine and also to avoid cervical flexion and extension.

Cardiovascular System

Because of the depressant effects of anesthetics and the increased metabolic demands of surgery, any compromise of myocardial function should be clearly delineated preoperatively. A preoperative electrocardiogram, an echocardiogram, and a cardiology consultation are indicated for children with a history of heart disease. An intracardiac shunt will affect oxygenation status intraoperatively. Because of the significant effect on the oxygen supply-and-demand relationship caused by general anesthesia and surgical stress, obstructive lesions, such as a valvular stenosis, must also be clearly defined. A history of cardiac dysrhythmias should be clearly understood, because inhalational anesthetics are dysrhythmogenic.

In neonates, ductus arteriosus, myocardial compromise, pulmonary edema, or congenital heart disease can significantly complicate oxygen delivery during anesthesia. Accurate diagnosis of cardiac murmurs in neonates is essential. Any preoperative cardiovascular compromise will be worsened intraoperatively and can catastrophically complicate the perioperative course.

Anemia should be diagnosed and corrected preoperatively if possible. A hematocrit value >30% is generally acceptable for routine elective anesthesia. If there are reasons to expect significant blood loss or prolonged convalescence, anemia should be corrected preoperatively. In the emergency setting, transfusion may be required. Although lower hematocrit values can be tolerated in unstressed children, the significant threat to oxygen delivery posed by anesthesia and surgery, especially if blood loss is expected, requires maintenance of an adequate hemoglobin concentration perioperatively.

Evidence of coagulopathy should be sought. Easy bruising, the use of aspirin, and familial bleeding disorders should be discussed. Intraoperative hemorrhagic bleeding can be difficult to control; massive perioperative blood transfusions have significant risk of morbidity and mortality. Preoperative correction of coagulopathic disorders is indicated. In neonates, assurance of vitamin K prophylaxis and adequate coagulation status is critical before any significant surgery. In neonates and critically ill children, adequacy of platelet count and, where indicated, coagulation factors, prothrombin time, and partial thromboplastin time should be assured.

Neurobehavioral Considerations

Seizures, significant neurologic impairment, altered level of consciousness, respiratory airway compromise secondary to neurologic disease, and neuromuscular disease should be sought and evaluated. Anticonvulsant drug metabolism is often altered perioperatively, and this change may affect anticonvulsant drug levels. Anticonvulsants may also complicate anesthetic management. Maintenance of appropriate anticonvulsant therapy postoperatively is important to avoid new seizures. Cerebrospinal fluid secretion is increased during surgery and general anesthesia. This fact is significant in patients in whom elevated intracranial pressure is suspected and in children with ventriculoperitoneal

shunts. In infants or older children with ventriculoperitoneal shunts, shunt patency and function should be assured before surgery.

Illness and the need for surgery or painful medical procedures are psychologically traumatic events for children and their families. Children are also remarkably adept at sensing stressful signals from their parents and caregivers. Many children who require anesthesia may have significant levels of fear and anxiety. Most children undergoing surgery have new-onset negative behavioral changes in the postoperative period, such as maladaptive behavioral responses that include generalized anxiety, enuresis, enhanced separation anxiety, temper tantrums, nighttime crying, and fear of strangers, doctors, and hospitals. Approximately 20% show these negative behavioral adaptations for 6 mo after surgery. Sleep quality is also altered postoperatively, resulting in further behavioral compromise.

The risk factors for postoperative behavioral changes include preoperative or induction anxiety and behaviors indicating extreme stress, as well as emergence excitation. The type of surgery may be important, with tonsillectomy and genitourinary surgery having a high incidence of postoperative behavioral changes, whereas simple procedures (tympanostomy tubes) seem to be associated with fewer changes. Another risk factor is recurrent procedures, such as anesthesia for laser surgery, strabismus surgery, or repeated eye examinations, which lead to difficult behavioral changes and have a significant effect on family dynamics.

Preoperative psychologic preparation programs decrease the incidence of postoperative behavioral changes, which last for up to 1 mo. PPI does not improve postoperative behavior. Oral midazolam (0.5 mg/kg) may decrease negative behavioral changes after surgery. Midazolam has the benefit of providing not only rapid-onset anxiolysis in 10-20 min but also very effective and rapid (10 min) amnesia.

Preoperative Preparation

The child should be in the best possible nutritional state, and nutritional supplementation, even hyperalimentation in chronically ill children, may be worthwhile.

Preoperative Fasting

Aspiration of gastric contents is a perioperative disaster and, if superimposed on lung disease, may be rapidly fatal. Aspiration may lead to laryngospasm and bronchospasm, with hypoxemia and hypoxic ischemic encephalopathy. It may also produce intraoperative atelectasis and postoperative pneumonia. It is vital to ensure that the stomach is as empty as possible before the induction of anesthesia. Acid aspiration is less likely with an empty stomach. Table 61-10 lists preoperative fasting (NPO status) guidelines.

Clear, sweet liquids (Pedialyte, 5% dextrose in water) facilitate gastric emptying, help avoid hypoglycemia, and can be given up to 2 hr before anesthesia in any child. For older infants and children, a fasting period of 4 hr for liquids provides optimal safety and minimal discomfort. Solids must be avoided for at least 8 hr before surgery. Because surgery is frequently scheduled in the morning, and for ease and clarity of understanding, the general guideline is no consumption of solids after midnight. Many conditions delay gastric emptying, and prolonged periods of fasting may be required in the presence of stress, anxiety, illness, trauma, gross obesity, or biliary atresia, or in children with delayed gastric emptying for other reasons.

Table 61-10 Guidelines for Preoperative Fasting ("2-4-6-8 Rule")*

TIME BEFORE SURGERY (hr)	ORAL INTAKE
2	Clear, sweet liquids
4	Breast milk
6	Infant formula, fruit juices, gelatin
8	Solid food

*These are general guidelines and may differ among hospitals.

The Full Stomach

Because of the serious complications of aspiration of gastric contents, it is desirable to secure the airway as rapidly as possible after obtundation in patients at risk for having a full stomach. Gastric emptying may be delayed for up to 96 hr after an acute episode of trauma or surgical illness. Under these circumstances, induction of general anesthesia and endotracheal intubation are performed in a rapid sequence (**rapid sequence induction**; see Chapter 67).

The risks of rapid sequence induction include the possibility that if the airway cannot be intubated, the child is paralyzed without a protected airway and ventilation may be hazardous or impossible. Rapid sequence induction should be performed by those who can definitely achieve endotracheal intubation quickly. It should be avoided in patients with a history of failed oral endotracheal intubation or with any of the many syndromes (micrognathia) associated with difficult intubation. Under these circumstances, bronchoscopic awake intubation may be indicated.

Before rapid sequence anesthesia induction, the child should be preoxygenated by breathing 100% oxygen for 2 min to give an extra margin of safety if intubation is difficult. The child should not receive assisted ventilation either before or after the administration of drugs because this may lead to increased gastric air and actually increase the likelihood of vomiting, regurgitation, and aspiration.

One common regimen for rapid sequence induction includes the administration of 1.5-3 mg/kg of propofol concurrently with either 0.9-1.2 mg/kg of rocuronium or 1.5 mg/kg of vecuronium. Immediately after the administration of sedation and muscle relaxants, the Sellick maneuver (cricoid pressure) should be performed by applying firm pressure in a posterior direction against the cricoid cartilage. This displaces the cricoid cartilage into the esophagus, forming an artificial sphincter to prevent reflux of the gastroesophageal contents. Cricoid pressure should be maintained until correct placement of the endotracheal tube is verified by direct visualization, fogging of the tube, and, in all circumstances, positive end-tidal CO_2.

POSTOPERATIVE PAIN MANAGEMENT

Continuation of analgesia and anxiolysis should follow surgery or painful procedures (see Chapter 62). Complete freedom from pain is not possible. Preoperative education about the surgery and a pain management plan, development of skills designed to decrease anticipatory anxiety, and active participation in treatment planning can be helpful for some children and families. Adjunctive therapy, such as virtual reality, hypnosis, pet therapy, and play therapy, also can decrease the need for potent analgesics postoperatively.

The combination of opioid and nonopioid analgesic agents and an understanding of the benefits and risks provide the foundation of pain management. A judicious combination of nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, intravenous acetaminophen, opioids, and regional analgesia has a role in postoperative pain management. Repeated evaluation is as important as the modality of pain management. Continuous and repetitive small doses of analgesia around the clock are more effective at reducing pain than occasional prn dosing intervals.

Patient-controlled analgesia (PCA), nurse-controlled analgesia, and parent-controlled analgesia are all used postoperatively (see Chapter 62). PCA provides continuous pain treatment and self-medication (vs intermittent or prn pain control) as well as control and comfort in an otherwise personally uncontrolled circumstance. PCA provides both a background low-dose infusion rate of a continuous opioid and the opportunity to supplement analgesia with bolus doses as needed. The practitioner can determine the continuous infusion rate, the bolus dose, the lockout interval, and the number of boluses per unit time that the patient may receive. PCA relies on the theory that patients cannot or will not overdose themselves because somnolence will decrease repeated self-administration. In young children, the use of the *pain button* (for pain relief) may be more difficult to ensure; children as young as 5 yr old have been able to use PCA successfully. In older children and adolescents, PCA should be a standard modality of postoperative pain management.

Regional Anesthesia

Regional anesthesia is the use of anesthetics to block the conduction of afferent neural impulses to the central nervous system. These can be local analgesic techniques, peripheral nerve blocks, nerve plexus blocks, or epidural and subarachnoid (spinal) nerve blocks. They may be administered either through a single injection (single shot) or through continuous infusion, as is common with epidural and occasionally subarachnoid blocks. They may be used for intraoperative anesthesia and postoperative analgesia, and they have the potential to decrease intraoperative analgesia and anesthetic use, as well as to provide postoperative pain management. Increased use of regional indwelling catheters to deliver continuous analgesia has shortened recovery times and hospital stays in children.

Analgesia at the site of need, without central cardiorespiratory depressant effects, can be valuable. Local anesthesia, with injection of lidocaine or bupivacaine into the affected area, can provide procedural analgesia that lasts for several hours. Infiltration of the wound site and the edges of an incision decreases postoperative pain in the initial hours after surgery. This can be performed by the surgeon at the conclusion of surgery and may supplement postoperative analgesia.

Epidural analgesia is common in pediatric practice. The epidural space lies between the dura and the pia and arachnoid membranes, an area through which all nerve roots pass. Bathing these nerve roots in local anesthetics inhibits conduction of pain impulses centrally. A single dose of epidural anesthetic may provide hours of pain relief, and a continuous infusion may provide effective pain relief for hours to days. The epidural injection of opioids can provide analgesia for 12-24 hr and is a potential supplement to postoperative analgesia.

A lumbar epidural injection is placed in the lumbar area to provide analgesia for labor and for surgery below the thorax. Caudal epidural analgesia is placed through the sacral hiatus, inferior to the distal end of the spinal cord. This is the site most commonly used for regional anesthesia and analgesia in children and is efficacious for the provision of pelvic and lower limb anesthesia as well as beneficial in orthopedic and urologic surgery. A continuous infusion of bupivacaine is the most common means of providing postoperative epidural pain relief; it may be mixed with an opioid (fentanyl or preservative-free morphine). It is also possible to provide epidural PCA with a continuous infusion pump and the ability of the patient to self-medicate with bolus prn dosing. Epidural analgesia can also provide pain relief in patients with chronic pain or pain caused by advanced malignant conditions.

The most serious complications of neuraxial anesthesia include cephalad spread of blockade with respiratory depression, paralysis of respiratory muscles, and, in extreme cases, brainstem analgesia and depression. The most common complications of neuraxial analgesia include mild discomfort; a paresthesia-like feeling of numbness and tingling; pruritus, which, if opioids are used, can be quite distressing; and occasional nausea and vomiting. Infection and epidural hematoma are extremely rare. Neuraxial opioids, especially when administered intrathecally, can cause respiratory depression; their use requires postoperative monitoring. The use of neuraxial opioids often requires treatment with antipruritic as well as antiemetic drugs.

Bibliography is available at Expert Consult.

61.1 Sedation and Procedural Pain

Randall C. Wetzel

The same drugs that induce general anesthesia are often used to provide sedation (see Table 61-5). Sedation care requires a presedation evaluation, intraprocedural monitoring, and postsedation recovery, analogous to the provision of anesthesia. Sedation is on the continuum between wakefulness and general anesthesia (see Table 61-4). The term **conscious sedation** refers to a condition in which a patient is sleepy, comfortable, and cooperative but maintains airway-protective and ventilatory reflexes. Unfortunately, for most children, this level of sedation provides little or no analgesia, and both psychologic and physiologic responses to painful stimuli persist. Sedation that is sufficient to obtund painful responses is most likely deep sedation. **Deep sedation** is a state of unarousability to voice and is accompanied by suppression of reflex responses. Management of sedated children requires vigilance and knowledge to ensure their safety and is governed by the same guidelines as anesthesia care (Table 61-11). A dose of sedative medication that causes minimal sedation in one subject may produce complete unconsciousness and apnea in another. Careful attention to guidelines for appropriate monitoring and management of sedation in children is imperative. For threatening and nonpainful procedures, anxiolysis or light sedation is frequently sufficient. For painful procedures (e.g., bone marrow aspiration, insertion of percutaneous IV catheter lines, lumbar punctures), the combination of sedation with analgesia that is required in children produces deep sedation.

Table 61-11 Systematic Approach to Sedation in Children
Thorough medical history, anticipating underlying medical problems that predispose the patient to sedation problems
Careful physical examination focused on the cardiorespiratory system and airway
Appropriate fasting
Informed consent
Pediatric drug dosing (mg/kg)
Appropriately sized equipment
A separate, dedicated observer to monitor sedated patients who may have airway compromise (induced or preexisting)
Documentation of vital signs and condition on a time-based record
Emergency backup system, "code" team, and "crash cart"
Fully equipped and staffed recovery area
Discharge criteria documenting recovery from sedation

Many specialists provide sedation and anesthesia care for children. The use of anesthetic agents is not limited to anesthesiologists, but a hospital's department of anesthesiology provides expertise in developing and managing systems of anesthesia care, including sedation. With the widespread use of the deceptively safe general anesthetic agent propofol to provide sedation, hospitals, pediatricians, and other care providers must ensure that credentialing, oversight, quality assurance, and protocols for administration of anesthetic agents provide safe care. Involvement of anesthesiologists in organizing services, training other practitioners, overseeing safety, systems, and quality, and remaining involved in the delivery of such care is sound practice. The elements of a safe system to provide procedural sedation for children are as follows:

- Defining the required knowledge set
- Defining the required skill set
- Determining the appropriate requisite training
- Ensuring adequate understanding of the drugs and their effects (desired and undesired) and interactions
- Credentialing providers
- Ensuring ongoing maintenance of skills
- Reviewing the practice
- Ensuring that the sites where anesthesia care is provided meet recognized standards
- Last but not least, overseeing a process of continuous quality improvement

Sedation with chloral hydrate (not approved by the FDA in the United States or the European Medicines Agency in the European Union), pentobarbital, or benzodiazepines is often adequate for nonpainful procedures. Nevertheless, there can be a high failure rate as well as complications by using this method, such as prolonged sedation (hours to overnight), ataxia, nausea and vomiting, desaturation, and the occasional need for rapid intervention. The temptation to add opioids and deepen sedation increases the risk of complications. The use of dexmedetomidine for procedural sedation is safe; recovery time can be prolonged, and success can be variable. The quickest way to ensure safely reversible sedation is with potent anesthetic agents.

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The ultra–short-acting anesthetics (propofol, methohexital, remifentanil) provide effective procedural sedation, but their use carries a higher likelihood of inadvertent oversedation and induction of general anesthesia. These anesthetics offer efficient and rapidly reversible procedural sedation. However, their use requires the presence of an anesthesiologist and/or specially trained, experienced, and qualified physicians.

Bibliography is available at Expert Consult.

61.2 Anesthetic Neurotoxicity

Randall C. Wetzel

There is compelling experimental evidence that anesthesia-induced neurodegeneration with developmental impairment occurs in neonatal animals. Pediatric anesthesiologists have become deeply concerned by the demonstration of anesthetic-induced apoptotic neuronal cell death, central nervous system neurodegenerative changes, and their effects on the developing brain. These studies demonstrate both histopathologic changes and developmental defects from both inhalational and IV anesthetics, including isoflurane, ketamine, benzodiazepines, and propofol given to newborn animals. Combinations of drugs may cause more injury. Existing nonclinical data implicate both *N*-methyl-D-aspartate and γ-aminobutyric acid pathways in apoptosis and cell death in neonates.

The studies reporting these results were performed in animals (largely rodents), and great controversy exists concerning dose, duration of treatment, species differences, and experimental design. Although there is cause for concern and further study, alternatives to general anesthesia for many procedures in infants do not exist. Perhaps regional anesthetic techniques and narcotic-based anesthetics will be increasingly used. Interestingly, dexmedetomidine appears to block the neurotoxic effects of other anesthetics. There is insufficient current data for suggesting the safety of one anesthetic approach over another. The potential for this neurotoxicity must be balanced against the necessity of providing adequate anesthesia for neonates.

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Chapter 62

Pediatric Pain Management

Lonnie K. Zeltzer, Elliot J. Krane, and Tonya M. Palermo

Pain is both a sensory and an emotional experience that, when unrecognized and undertreated, extracts a significant physiologic, biochemical, and psychologic toll. Many disease processes and most interventional procedures in pediatrics are associated with pain.

DEFINITION AND CATEGORIES OF PAIN

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." The important elements of this definition to be emphasized are (1) pain encompasses both peripheral physiologic and central cognitive/emotional components and (2) pain may or may not be associated with ongoing tissue damage—pain may exist in the absence of demonstrable somatic pathology, and may rather be the acquired or genetic consequence of abnormalities of peripheral neural signaling, central modulation, or brain processing of peripheral sensations or nociception.

Table 62-1 specifies important pain categories commonly treated (somatic, visceral, and neuropathic) and defines the elements and characteristics of nociception, the peripheral physiologic aspect of pain perception (Fig. 62-1). *Nociception* refers to how specialized fibers (largely, but not exclusively, the small unmyelinated A-delta and C fibers) in the peripheral nervous system transmit nerve impulses (usually transmitting signals originating from peripheral mechano- and chemoreceptors) through synapses in the spinal cord's dorsal horn through (but not exclusively through) the spinothalamic tracts to the brain's higher centers, where nociception is converted to pain, with all of its cognitive and emotional ramifications.

THE ASSESSMENT AND MEASUREMENT OF PAIN IN CHILDREN

Whenever feasible, the physician should ask the patient about the character, location, quality, duration, frequency, and intensity of the pain. Some children may not report pain because of fears (often well-founded) of talking to strangers, disappointing or bothering others, receiving an injection if they report pain, returning to the hospital if they admit to pain, and other negative possible reactions. For infants and nonverbal children, their parents, pediatricians, nurses, and other caregivers are constantly challenged to interpret whether the children's distressed behaviors represent pain, fear, hunger, or a range of other perceptions or emotions. Therapeutic trials of comfort measures (cuddling, feeding) and analgesic medications may be helpful in clarifying the triggers of the behaviors.

Behavior and physiologic signs are useful, but they can be misleading. A toddler may scream and grimace during an ear examination because of fear rather than pain. Conversely, children with inadequately relieved persistent pain from cancer, sickle cell disease, trauma, or surgery may withdraw from their surroundings and appear very quiet, leading observers to conclude falsely that they are comfortable or sedated. In these situations, increased dosing of analgesics may make the child become more, not less, interactive and alert. Similarly, neonates and young infants may close their eyes, furrow their brows, and clench their fists in response to pain. Adequate analgesia is often associated with eye opening and increased involvement in the surroundings. A child who is experiencing significant chronic pain may play normally as a way to distract attention away from pain. This coping behavior is sometimes misinterpreted as evidence of the child's "faking" or exaggerating pain at other times.

Age-Specific and Developmentally Specific Measures

Because infants, young children, and nonverbal children cannot express the quantity of pain they experience, several pain scales have been devised in an attempt to quantify pain in these populations (Fig. 62-2; Table 62-2).

The Newborn and Infant

There are several behavioral distress scales for the infant and young child, mostly emphasizing the patient's facial expressions, crying, and body movement. Facial expression measures appear most useful and specific in neonates. Autonomic and vital signs can indicate pain, but because they are nonspecific, they may reflect other processes, including fever, hypoxemia, and cardiac or renal dysfunction.

The Older Child

Children ages 3-7 yr become increasingly articulate in describing the intensity, location, and quality of pain. Pain is occasionally referred to adjacent areas; referral of hip pain to the leg or knee is common in this age range. Self-report measures for children this age include using drawings, pictures of faces, or graded color intensities. Children age 8 yr and older can usually use verbal numerical rating scales or visual analog pain scales accurately (see Fig. 62-2). Verbal numerical ratings are preferred and considered the gold standard; valid and reliable ratings can be obtained from children 8 yr and older. The Numerical

Rating Scale consists of numbers from 0-10, in which 0 represents no pain and 10 represents very severe pain. There is debate about the label for the highest pain rating, but the current agreement is *not* to use the term "worst pain possible," because children can always imagine a greater pain. In the United States, regularly documented pain assessments are required for hospitalized children and children attending outpatient hospital clinics and emergency departments. Pain scores do not always correlate with changes in heart rate or blood pressure.

The Cognitively Impaired Child

Measuring pain in cognitively impaired children remains a challenge. Understanding pain expression and experience in this population is important, because behaviors may be misinterpreted as indicating that cognitively impaired children are more insensitive to pain than cognitively competent children. Children with trisomy 21 may express pain less precisely and more slowly than the general population. Pain in children with autism spectrum disorders may be difficult to assess because these children may be both *hyposensitive* and *hypersensitive* to many different types of sensory stimuli, and they may have limited communication abilities. Although self-reports of pain can be elicited from some children who are cognitively impaired, observational measures have better validation among these children. The Noncommunicating Child's Pain Checklist—Postoperative Version is recommended for children up to 18 yr. Maladaptive behaviors and reduction in functions may also indicate pain. Children with severe cognitive impairments frequently experience pain.

A CONCEPTUAL FRAMEWORK FOR THE TREATMENT OF PEDIATRIC PAIN

A number of models have been developed to understand the various factors that influence children's pain. Many of these theories focus on factors that explain the interindividual variability in pain perception, and the chronicity and impairment experienced with pain. Central to these models are interrelationships among biologic, cognitive, affective, and social factors that influence children's pain and disability, commonly referred to as biopsychosocial models of pain. Biologic factors include the child's physical health, central nervous system factors (pain processing), sex, pubertal status, and genetic factors.

Table 62-1 Pain Categories and Characteristics

PAIN CATEGORY	DEFINITION AND EXAMPLES	CHARACTERISTICS
Somatic	Pain resulting from injury to or inflammation of tissues (skin, muscle, tendons, bone, joints, fascia, vasculature, etc.) *Examples:* burns, lacerations, fractures, infections, inflammatory conditions	*In skin and superficial structures:* sharp; pulsatile; well-localized *In deep somatic structures:* dull; aching; pulsatile; not well-localized
Visceral	Pain resulting from injury to or inflammation of viscera *Examples:* angina, hepatitic distention, bowel distention or hypermobility, pancreatitis	Aching and cramping; nonpulsatile; poorly localized (e.g., appendiceal pain perceived around umbilicus) or referred to distant locations (e.g., angina perceived in shoulder)
Neuropathic	Pain resulting from injury to, inflammation of, or dysfunction of the peripheral or central nervous systems. *Examples:* complex regional pain syndrome, phantom limb pain, Guillain-Barré syndrome, sciatica	Spontaneous; burning; lancinating or shooting; dysesthesias (pins and needles, electrical sensations); hyperalgesia (amplification of noxious stimuli); hyperpathia (widespread pain in response to a discrete noxious stimulus); allodynia (pain in response to nonpainful stimulation); pain may be perceived distal or proximal to site of injury, usually corresponding to innervation pathways (e.g., sciatica)

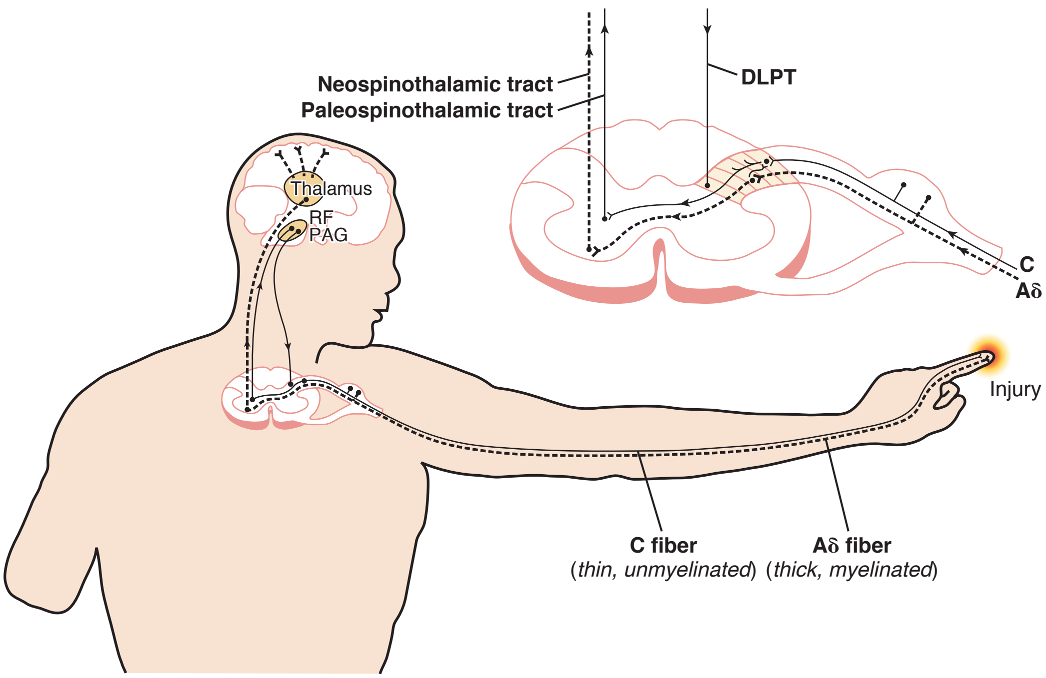

Figure 62-1 The typical neural pathways of nociception, also showing higher projection of nociception to the cortex, where the sensation of nociception is translated to the conscious and emotional phenomenon of pain. *DLPT,* dorsolateral pontine tegmentum; *PAG,* periaqueductal gray; *RF,* reticular formation.

Behavioral Indicators

Facial grimacing: The Neonatal Facial Coding System* uses several facial actions that may be indicators of pain. Pain is characterized by a bulging brow with tight creases in between; tightly closed eyelids; a deeply furrowed nasolabial groove; a horizontal, wide opened mouth; and a taut tongue that may be quivering along with the chin.

Crying: May be an indicator of pain.

Activity: Withdrawal or immobilization of a limb may be an indicator of pain.

Response to comfort measures: Feeding, swaddling, holding, and ensuring that the infant is neither wet nor cold may help to discriminate between pain and other conditions.

Physiologic indicators: Alterations in heart rate, blood pressure, SpO_2, respiratory rate, or alterations in pattern of respiration may be nonspecific indicators of pain.

Multidimensional Instrument

FLACC[†] Scoring System: May be used in preverbal, mechanically ventilated, or cognitively impaired patients; it is an acronym that includes five indicators, each scored as a 0, 1, or 2 that forms a ten-point composite scale with a range from "0" (no pain) to "10" (worst pain).

FLACC: Score each category between 0 and 2. The total score may be any number from 0 to 10.

Score:	0	1	2
Face	No expression	Occational action	Frequent action
Legs	Normal	Restless or tense	Kicking, legs withdrawn
Activity	Quiet	Shifting or tense	Rigid, arched, jerking
Cry	None	Moan, whimper	Steady crying, screaming, sobbing, or frequent complaints
Consolability	Content	Consolable	Inconsolable

Self-Report of Pain

Categorical description: Toddlers or young children are asked to say if they are having "a little bit," a "middle amount," or "a lot" of pain.

Faces Scales[‡]: Children who do not have an appreciation of ordinal numbering are asked to rate their pain based upon cartoons depicting facial indicators of distress.

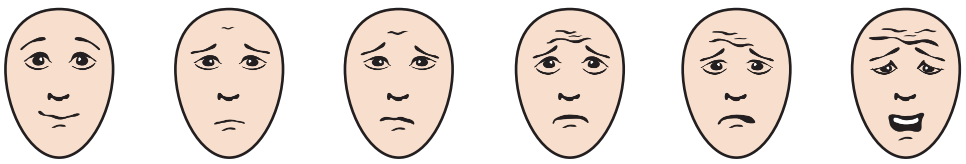

0 2 4 6 8 10

NRS[§]: Older children and teenagers are asked to rate their pain on a scale of "0" (no pain) to "10" (worst pain).

VAS[§]: Children or teenagers are asked to move an indicator along a mechanical slide to depict the level of pain; the clinician reads a number along a 10-cm indicator on the back to determine the numeric score.

Figure 62-2 Clinically useful pain assessment tools. *(Adapted from Burg FD, Ingelfinger JR, Polin RA, et al, editors:* Current pediatric therapy, *ed 18, Philadelphia, 2006, WB Saunders, p. 16; and Hicks CL, von Baeyer CL, Spafford P, et al: The Faces Pain Scale—revised: toward a common metric in pediatric pain measurement,* Pain *93:173–183, 2001.)*

Individual child cognitive and affective factors related to perception of pain are anxiety, fear, negative affect, pain behaviors, and functional disability, whereas social factors include such areas as culture, socioeconomic status, school environment, social and peer interactions, and parental and family factors.

A framework that considers the interplay of biologic, psychologic, and social factors is useful for understanding pediatric pain and to guide pain assessment and the delivery of both pharmacologic and nonpharmacologic interventions for pain management. Many simple interventions designed to promote relaxation and patient control can be expected to work synergistically with pain medications for optimal relief of pain and related distress. Moreover, psychologic interventions are often coupled with physical therapy interventions to assist in the management of disabling chronic pain.

Pharmacologic Treatment of Pain

Developmental Pharmacology

The pharmacokinetics and pharmacodynamics of analgesics vary with age; drug responses in infants and young children differ from those in older children and adults. The elimination half-life of most analgesics is prolonged in neonates and young infants because of their immature hepatic enzyme systems and glomerular filtration. Clearance of

Table 62-2 Pain Measurement Tools

NAME	FEATURES	AGE RANGE	ADVANTAGES	VALIDATION AND USES	LIMITATIONS
Visual Analog Scale (VAS)	Horizontal 10-cm line; subject marks a spot on the line between anchors of "no pain" (or neutral face) and "most pain imaginable" (or sad face)	6-8 yr and older	Good psychometric properties; validated for research purposes	Acute pain Surgical pain Chronic pain	Cannot be used in younger children or in those with cognitive limitations Requires language skills and numerical processing; upper anchor of "most pain" requires an experiential reference point that is lacking in many children
Likert Scale	Integers from 0-10, inclusive, corresponding to a range from no pain to most pain	6-8 yr and older	Good psychometric properties; validated for research purposes	Acute pain Surgical pain Chronic pain	Same as for VAS
Faces Scales (e.g., FACES-R, Wong-Baker, Oucher, Bieri, McGrath scales)	Subjects rate their pain by identifying with line drawings of faces or photos of children	4 yr and older	Can be used at younger ages than VAS and Likert	Acute pain Surgical pain	Choice of "no pain" face affects responses (neutral vs smiling); not culturally universal
Behavioral or combined behavioral-physiologic scales (e.g., FLACC, N-PASS, CHEOPS, OPS, FACS, NIPS)	Scoring of observed behaviors (e.g., facial expression, limb movement) ± heart rate and blood pressure	Some work for any ages; some work for specific age groups, including preterm infants	May be used in both infants and nonverbal children	FLACC, N-PASS: Acute pain Surgical pain	Nonspecific; overrates pain in toddlers and preschool children; underrates persistent pain; some measures are convenient, but others require videotaping and complex processing; vital sign changes unrelated to pain can occur and may affect total score
Autonomic measures (e.g., heart rate, blood pressure, heart rate spectral analyses)	Scores changes in heart rate, blood pressure, or measures of heart rate variability (e.g., "vagal tone")	All ages	Can be used at all ages; useful for patients receiving mechanical ventilation		Nonspecific; vital sign changes unrelated to pain may occur, and may artifactually increase or decrease score
Hormonal-metabolic measures	Plasma or salivary sampling of "stress" hormones (e.g., cortisol, epinephrine)	All ages	Can be used at all ages		Nonspecific; changes unrelated to pain can occur; inconvenient; cannot provide "real-time" information; standard normal values not available for every age bracket

analgesics may also be variable in young infants and children. Renal blood flow, glomerular filtration, and tubular secretion increase dramatically in the 1st few weeks, approaching adult values by 3-5 mo of age. Renal clearance of analgesics is often greater in toddlers and preschool-age children than in adults, whereas in premature infants clearance is reduced. Age-related differences in body composition and protein binding also exist. Total-body water as a fraction of body weight is greater in neonates than in children or adults. Tissues with high perfusion, such as the brain and heart, account for a larger proportion of body mass in neonates than do other tissues, such as muscle and fat. Because of decreased serum concentrations of albumin and α_1-acid glycoprotein, neonates have reduced protein binding of some drugs, resulting in higher amounts of free, unbound, pharmacologically active drug.

Acetaminophen, Aspirin, Nonsteroidal Antiinflammatory, and Coxib Drugs

Acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) have replaced aspirin as the most commonly used antipyretics and oral, nonopioid analgesics (Table 62-3).

Acetaminophen, a generally safe, nonopioid analgesic and antipyretic, has the advantage of intravenous, rectal, and oral routes of administration. Acetaminophen is not associated with the gastrointestinal or antiplatelet effects of aspirin and NSAIDs, making it a particularly useful drug in patients with cancer. Unlike aspirin and NSAIDs, acetaminophen has only mild antiinflammatory action.

Acetaminophen toxicity can result from either a large single dose or cumulative, excessive dosing over days or weeks (see Chapters 63 and 363). A single, massive overdose overwhelms the normal glucuronidation and sulfation metabolic pathways in the liver, whereas long-term overdosing exhausts supplies of the sulfhydryl donor glutathione, leading to alternative cytochrome P450–catalyzed oxidative metabolism and the production of the hepatotoxic metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI). Toxicity manifests as fulminant hepatic necrosis and failure in infants, children, and adults. Drug biotransformation processes are immature in neonates, very active in young children, and somewhat less active in adults. Young children are more resistant to acetaminophen-induced hepatotoxicity than are adults as a result of metabolism differences: Sulfation predominates over glucuronidation in young children, leading to a reduction in *N*-acetyl-*p*-benzoquinone imine production.

Aspirin is indicated for certain rheumatologic conditions and for inhibition of platelet adhesiveness, as in the treatment of Kawasaki disease. Concerns about Reye syndrome have resulted in a substantial decline in pediatric aspirin use (see Chapter 357).

The **NSAIDs** are used widely to treat pain and fever in children. NSAIDs are nonselective cyclooxygenase (COX) inhibitors (coxibs), that is, drugs that nonselectively block the activity of both COX-1

Table 62-3 Commonly Used Nonopioid Medications

MEDICATION	DOSAGE	COMMENT(S)
Acetaminophen	10-15 mg/kg PO q4h 10 mg/kg IV q4h 15 mg/kg IV q6h 10 mg/kg IV q6h (<2 yr) 20-30 mg/kg/PR q4h 40 mg/kg/PR q6-8h Maximum daily dosing: 90 mg/kg/24 hr (children) 60 mg/kg/24 hr (<2 yr) 30-45 mg/kg/24 hr (neonates)	Little antiinflammatory action; no antiplatelet or adverse gastric effects; overdosing can produce fulminant hepatic failure
Aspirin	10-15 mg/kg PO q4h Maximum daily dosing: 120 mg/kg/24 hr (children)	Antiinflammatory; prolonged antiplatelet effects; may cause gastritis; associated with Reye syndrome
Ibuprofen	8-10 mg/kg PO q6h	Antiinflammatory; transient antiplatelet effects; may cause gastritis; extensive pediatric safety experience
Naprosyn	5-7 mg/kg PO q8-12h	Antiinflammatory; transient antiplatelet effects; may cause gastritis; more prolonged duration than that of ibuprofen
Ketorolac	Loading dose 0.5 mg/kg, then 0.25-0.3 mg/kg IV q6h to a maximum of 5 days; maximum dose 30 mg loading with maximum dosing of 15 mg q6h	Antiinflammatory; reversible antiplatelet effects; may cause gastritis; useful for short-term situations in which oral dosing is not feasible
Celecoxib	3-6 mg/kg PO q12-24h	Antiinflammatory; no antiplatelet or gastric effects; cross-reactivity with sulfa allergies
Choline magnesium salicylate	10-20 mg/kg PO q8-12h	Weak antiinflammatory; lower risk of bleeding and gastritis than with conventional NSAIDs
Nortriptyline, amitriptyline, desipramine	0.1-0.5 mg/kg PO qhs	For neuropathic pain; facilitates sleep; may enhance opioid effect; may be useful in sickle cell pain; risk of dysrhythmia in prolonged QTc syndrome; may cause fatal dysrhythmia in overdose; FDA says agents may enhance suicidal ideation
Gabapentin	100 mg bid or tid titrated to up to 3,600 mg/24 hr	For neuropathic pain; associated with sedation, dizziness, ataxia, headache, and behavioral changes
Quetiapine, risperidone, chlorpromazine, haloperidol	Quetiapine: 6.25 or 12.5 mg PO qd (hs); may use q6h prn acute agitation with pain. Escalate dose to 25 mg/dose if needed. Risperidone: useful for PDD spectrum or tic disorder and chronic pain; 0.25-1 mg (in 0.25-mg increments) qd or bid; see PDR for other dosing.	Useful when arousal is amplifying pain; often used when patient first starting SSRI and then weaned after at least 2 wk; check for normal QTc before initiating; side effects include extrapyramidal reactions (diphenhydramine may be used to treat) and sedation; in high doses, can lower the seizure threshold
Fluoxetine	10-20 mg PO qd (usually in morning)	SSRI for children with anxiety disorders in which arousal amplifies sensory signaling; useful in PDD spectrum disorders in very low doses; best to use in conjunction with psychiatric evaluation
Sucrose solution via pacifier or gloved finger	*Preterm infants (gestational age):* 28 wk: 0.2 mL swabbed into mouth 28-32 wk: 0.2-2 mL, depending on suck/swallow >32 wk: 2 mL *Term infants:* 1.5-2 mL PO over 2 min	Allow 2 min before starting procedure; analgesia may last up to 8 min; the dose may be repeated once

FDA, U.S. Food and Drug Administration; IV, intravenous(ly): NSAIDs, nonsteroidal antiinflammatory drugs; PDD, pervasive developmental disorder; PDR, *Physicians' Desk Reference;* PR, per rectum; QTc, corrected QT interval on an electrocardiogram; SSRI, selective serotonin reuptake inhibitor.

(found in gastric mucosa and platelets) and COX-2 (active in inflammatory pathways and cortical renal blood flow regulation) enzymes that synthesize prostaglandins. In children with juvenile idiopathic arthritis, ibuprofen and aspirin are equally effective, but ibuprofen is associated with fewer side effects and better drug adherence. NSAIDs and coxibs used adjunctively in surgical patients reduce opioid requirements (and, therefore, opioid side effects) by as much as 35-40%. Although NSAIDs can be useful postoperatively, they should be used as an adjunct to, not as a substitute for, opioids in patients with moderate to severe pain.

Ketorolac, an IV or intranasal NSAID, is useful in treating moderate to severe acute pain in patients who are unable or unwilling to swallow oral NSAIDs. Intravenous ibuprofen is approved in the United States for the management of pain and fever for 5 days or fewer, although there is no pediatric indication in the package labeling. In Europe, IV ibuprofen is used to treat pediatric pain.

Adverse effects of NSAIDs are uncommon, but they may be serious when they occur. They include inhibition of bone growth and healing; gastritis with pain and bleeding; decreased renal blood flow that may reduce glomerular filtration and enhance sodium reabsorption, in some cases leading to tubular necrosis; hepatic dysfunction and liver failure; inhibition of platelet function; and an increased incidence of cardiovascular events in patients predisposed to stroke and myocardial infarction. Although the overall incidence of bleeding is very low, gastric bleeding is the most common cause of mortality related to this class of analgesics.

NSAIDs should not be used in the child with a bleeding diathesis or at risk for bleeding or when surgical hemostasis is a concern, such as after tonsillectomy. The drug class is usually avoided in the setting of bone healing, except perhaps in the 1st few days following surgery.

Renal injury from short-term use of ibuprofen in euvolemic children is quite rare; the risk is increased by hypovolemia or cardiac

dysfunction. The safety of both ibuprofen and acetaminophen for short-term use is well established (see Table 62-3).

Coxib drugs available in the United States are limited to oral celecoxib, whereas in Europe and elsewhere parenteral parecoxib and oral rofecoxib are available (parecoxib was not approved for use in the United States, while rofecoxib was approved and withdrawn from the market because of concern of enhancement of the risk of heart attacks and stroke, which was subsequently found to be associated with all the coxibs and NSAID drugs as well). The coxib drugs are selective COX-2 enzyme inhibitors; therefore they are effective antiinflammatory and analgesic molecules that generally do not result in platelet inhibition and bleeding or in gastric inflammation or ulceration, findings that may be seen with the nonselective COX inhibitors in the NSAID class. However, coxib drugs do inhibit regulation of cortical renal blood flow, and therefore carry the same risk of renal dysfunction and acute tubular necrosis. Celecoxib is therefore an appropriate primary or adjunctive analgesic to use in children following surgery, children with gastric mucosal pathology, or oncology patients in whom concern for hemostasis contraindicates conventional NSAIDs.

Opioids

Opioids are analgesic substances either derived from the opium poppy (opiates) or synthesized to have a similar chemical structure and mechanism of action (opioids). The older, pejorative term narcotics should not be used for these agents, because it connotes criminality and lacks pharmacologic descriptive specificity. Opioids are administered for moderate and severe pain, such as acute postoperative pain, sickle cell crisis pain, and cancer pain. Opioids can be administered by the oral, rectal, oral transmucosal, transdermal, intranasal, IV, epidural, intrathecal, subcutaneous, or intramuscular route. Historically, infants and young children have been underdosed with opioids for fear of significant respiratory side effects. In contrast, the use of opioids for moderate-to-severe noncancer pain does not have the evidence base that their use in cancer-associated pain does. There is concern for the potential for unwarranted use of opioids to increase the incidence of side effects. With proper understanding of the pharmacokinetic and pharmacodynamics of opioids, children can receive effective relief of pain and suffering with a good margin of safety (Tables 62-4 to 62-7).

Opioids act by mimicking the actions of endogenous opioid peptides, binding to receptors in the brain, brainstem, spinal cord, and peripheral nervous system, and thus leading to inhibition of nociception. Opioids have dose-dependent respiratory depressant effects, and they blunt ventilatory responses to hypoxia and hypercarbia. These respiratory depressant effects can be increased with coadministration of other sedating drugs, such as benzodiazepines or barbiturates. What was once thought to represent infants' particular sensitivity to the opioids' respiratory depressant effects we now understand to be a result of infants' lower metabolic clearance of opioids and higher blood levels with frequent dosing.

Optimal use of opioids requires proactive and anticipatory management of side effects (see Table 62-6). Common side effects include constipation, nausea, vomiting, urinary retention, and pruritus. The most common, troubling, but treatable side effect is constipation. Stool softeners and stimulant laxatives should be administered to most patients receiving opioids for more than a few days. Constipation also remains a problem with long-term opioid administration. A peripherally acting opiate μ-receptor antagonist, methylnaltrexone, promptly and effectively reverses opioid-induced constipation in patients with chronic pain who are receiving opioids daily. In addition lubiprostone, an epithelial chloride channel agent, has been approved for the treatment of opioid-induced constipation in adults with chronic noncancer pain. The side effect of nausea typically subsides with long-term dosing, but it may require treatment with antiemetics, such as a phenothiazine, butyrophenones, antihistamines, or a serotonin receptor antagonist such as ondansetron or granisetron. Pruritus and other complications during patient-controlled analgesia (PCA) with opioids may be effectively managed by low-dose IV naloxone (see Table 62-6).

One of the potent barriers to effective management of pain with opioids is the unrealistic fear of addiction held by many prescribing

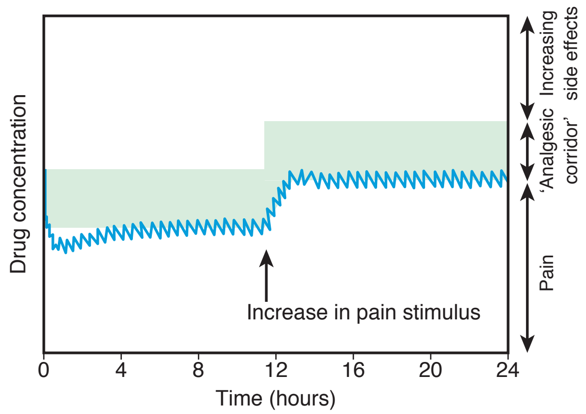

Figure 62-3 Patient-controlled analgesia is more likely to keep blood concentrations of opioid within the "analgesic corridor" and allows rapid titration if there is an increase in pain stimulus requiring higher blood levels of opioid to maintain the analgesia. *(From Burg FD, Ingelfinger JR, Polin RA, et al, editors:* Current pediatric therapy, *ed 18. Philadelphia, 2006, WB Saunders, p. 16.)*

pediatricians and parents. Pediatricians should understand the phenomena of tolerance, dependence, withdrawal, and addiction (see Table 62-5) and should know that the rational short- or long-term use of opioids in children does not lead to a predilection or risk of addiction in a child not otherwise at risk by virtue of genetic background and social milieu. It is important for pediatricians to realize that even patients with recognized substance-abuse diagnoses are entitled to effective analgesic management, which often includes the use of opioids. When there are legitimate concerns about addiction in a patient, then safe, effective opioid pain management is often best managed by specialists in pain management and/or addiction medicine.

There is no longer a reason to administer opioids by intramuscular injection. Continuous IV infusion of opioids is an effective option that permits more constant plasma concentrations and clinical effects than intermittent IV bolus dosing, without the pain associated with intramuscular injection. The most common approach in pediatric centers is to administer a low-dose basal opioid infusion, while permitting patients to use a patient-controlled analgesia (PCA) device to titrate the dosage above the infusion (see Chapter 61; Fig. 62-3). Compared with children given intermittent intramuscular morphine, children using PCA reported better pain scores. PCA has several other advantages: (1) dosing can be adjusted to account for individual pharmacokinetic and pharmacodynamic variation and for changing pain intensity during the day; (2) psychologically, the patient is more in control, actively coping with the pain; (3) overall opioid consumption is lower; (4) fewer side effects occur; and (5) patient satisfaction is generally much higher. Children as young as 5-6 yr can effectively use PCA. The device can be activated by parents or nurses—the latter practice known as PCA-by-proxy; PCA-by-proxy produces analgesia in a safe, effective manner for children who cannot activate the PCA demand button themselves because they are too young or intellectually or physically impaired. PCA overdoses occur when well-meaning, inadequately instructed parents pushed the PCA button in medically complicated situations with or without the use of PCA-by-proxy, highlighting the need for patient and family education, the use of protocols, and adequate nursing supervision.

Local Anesthetics

Local anesthetics are widely used in children for topical application, cutaneous infiltration, peripheral nerve block, epidural neuraxial blocks, intrathecal infusions, and IV infusions (see Chapter 61; Table 62-8). Local anesthetics can be used with excellent safety and effectiveness. Local anesthetics interfere with neural transmission by blocking sodium channels. Excessive systemic dosing can cause seizures, central nervous system (CNS) depression, and by cardiac and arteriolar sodium channel blockade hypotension, arrhythmias, cardiac

Table 62-4 Pediatric Dosage Guidelines for Opioid Analgesics

DRUG	EQUIANALGESIC DOSES		PARENTERAL DOSING (WEIGHT)		IV:PO DOSE RATIO	ORAL DOSING (WEIGHT)		COMMENTS
	IV	ORAL	<50 kg	>50 kg		<50 kg	>50 kg	
Fentanyl	10 µg	100 µg	0.5-1 µg/kg q1-2h 0.5-1.5 µg/kg/hr	0.5-1 µg/kg q1-2h 0.5-1.5 µg/kg/hr	Oral transmucosal: 1:10 Transdermal: 1:1	Oral transmucosal: 10 µg/kg Transdermal: 12.5-50 µg/hr	Transdermal patches available; patch reaches steady state at 24 hr and should be changed q72h	70-100 times as potent as morphine with rapid onset and shorter duration With high doses and rapid administration, can cause chest-wall rigidity Useful for short procedures; transdermal form should be used only in opioid-tolerant patients with chronic pain
Hydrocodone	N/A	1.5 mg	N/A	N/A	N/A	0.15 mg/kg	10 mg	Weak opioid; only available in form with acetaminophen
Hydromorphone	0.2 mg	0.6 mg	0.01 mg q2-4h 0.002 mg/kg/hr	0.01 mg q2-4h 0.002 mg/kg/hr	1:3	0.04-0.08 mg/kg q3-4h	2-4 mg q3-4h	5× the potency of morphine; no histamine release and fewer adverse events than morphine
Meperidine	10 mg	30 mg	0.5 mg/kg q2-4h	0.5 mg/kg q2-4h	1:4	2-3 mg/kg q3-4h	100-150 mg q3-4h	Primary use in low doses is for treatment of rigors and shivering after anesthesia or with amphotericin or blood products Not appropriate for repeated dosing
Methadone	1 mg	2 mg	0.1 mg/kg q8-24h	0.1 mg/kg q8-24h	1:2	0.2 mg/kg q8-12h PO; available as liquid or tablet	2.5 mg tid	Duration 12-24 hr; useful in certain types of chronic pain; requires additional vigilance, because it will accumulate over 72 hr and produce delayed sedation When patients who are tolerant to opioids are switched to methadone, they show incomplete cross-tolerance and improved efficacy; because it is associated with prolonged QTc, monitoring is needed for children on high and extended dosing
Morphine	1 mg	3 mg	0.05 mg/kg q2-4h 0.01-0.03 mg/kg/hr	*Bolus:* 5-8 mg q2-4h	1:3	Immediate release: 0.3 mg/kg q3-4h Sustained release: 20-35 kg: 10-15 mg q8-12h 35-50 kg: 15-30 mg q8-12h	Immediate release: 15-20 mg q3-4h Sustained release: 30-90 mg q8-12h	Potent opioid for moderate/severe pain; may cause histamine release Sustained-release form must be swallowed whole; if crushed, becomes immediate-acting, leading to acute overdose
Oxycodone	N/A	3 mg	N/A	N/A	N/A	0.1-0.2 mg q3-4h; available in liquid (1 mg/mL)	Immediate release: 5-10 mg q4h Sustained release: 10-120 mg q8-12h	Strong opioid only available as an oral agent in North America; more potent than and preferable to hydrocodone Sustained-release form must be swallowed whole; if crushed, becomes immediate-acting, leading to acute overdose

N/A, not available.

Table 62-5 Practical Aspects of Prescribing Opioids

- Morphine, hydromorphone, or fentanyl is regarded as first choice for severe pain.
- Dosing should be titrated and individualized. There is no "right" dose for everyone.
- The right dose is the dose that relieves pain with a good margin of safety.
- Dosing should be more cautious in infants, in patients with coexisting diseases that increase risk or impair drug clearance, and with concomitant administration of sedatives.
- Anticipate and treat peripheral side effects, including constipation, nausea, and itching.
- Give doses at sufficient frequency to prevent the return of severe pain before the next dose.
- Use a drug delivery method, such as patient-controlled anesthesia or continuous infusions that avoid the need for "prn" decision making.
- With opioid dosing for more than 1 wk, taper gradually to avoid abstinence syndrome.
- When converting between parenteral and oral opioid doses, use appropriate potency ratios (see Table 62-4).
- *Tolerance* refers to decreasing drug effect with continued administration of a drug. Over time a patient will need higher dosing to achieve the same clinical effect; however, tolerance to sedation and respiratory depression develop more rapidly than tolerance to analgesia. Thus, with higher doses, patients do not experience oversedation or respiratory depression.
- *Dependence* refers to the need for continued drug dosing to prevent abstinence syndrome when a drug is abruptly discontinued or its dose reduced. Abstinence syndrome is characterized by irritability, agitation, autonomic arousal, nasal congestion, piloerection, diarrhea and/or jitteriness, and yawning; it is produced by administration of potent opioids for >5-7 days.
- *Addiction,* a psychiatric pathology, refers to psychologic craving, compulsive drug-seeking behavior, and drug use despite medical harm. Addiction has strong genetic determinants. Opioid therapy does not lead to addiction in nonsusceptible individuals, nor does opioid underdosing prevent addiction; it may in fact increase drug-seeking behavior for relief of pain (such as watching the clock), referred to as "pseudoaddiction."

Table 62-6 Management of Opioid-Induced Adverse Effects

Respiratory depression	*Naloxone:* 0.01-0.02 mg/kg up to a full reversal dose of 0.1 mg/kg. May be given IV, IM, subcutaneously (SC), or via endotracheal tube (ET). The full reversal dose should initially be used for apnea in opioid-naïve patients. In opioid-tolerant patients, a reduced dose should be given and titrated up slowly to treat symptoms but prevent acute withdrawal. Ventilation may need to be supported during this process. Dose may be repeated every 2 min to a total of 10 mg. Adult maximum dose is 2 mg/dose. Give with caution to patients who are receiving long-term opioid therapy, as it may precipitate acute withdrawal. Duration of effect is 1-4 hr; therefore, close observation for renarcotization is essential.
Excessive sedation without evidence of respiratory depression	*Methylphenidate**: 0.3 mg/kg per dose PO (typically 10-20 mg/dose to a teenager) before breakfast and lunch. Do not administer to patients receiving clonidine, because dysrhythmias may develop. *Dextroamphetamine*: 2.5-10 mg on awakening and at noon. Not for use in young children or in patients with cardiovascular disease or hypertension. *Modafinil:* Pediatric dose not established. May be useful in selected patients. Typical adult dose: 50-200 mg/day. Change opioid or decrease the dose.
Nausea and vomiting	*Metoclopramide*†*:* 0.15 mg/kg IV up to 10 mg/dose q6-12h for 24 hr. *Trimethobenzamide:* PO or rectally (PR) if weight <15 kg, 100 mg q6h; if >15 kg, 200 mg q6h. (Note: Suppository contains benzocaine 2%.) Not for use in newborn infants or premature infants. 5-HT_3 blockers: *Ondansetron:* 0.15 mg/kg up to 8 mg IV q6-8h not to exceed 32 mg/day (also available as a sublingual tablet). *Granisetron:* 10-20 μg/kg IV q12-24h. *Prochlorperazine** (Compazine): >2 yr or >20 kg, 0.1 mg/kg per dose q8h IM or PO up to 10 mg/dose. Change opioid.
Pruritus	*Hydroxyzine*: 0.5 mg/kg PO q6h. *Nalbuphine:* 0.1 mg/kg IV q6h for pruritus caused by intraaxial opioids, especially fentanyl. Administer slowly over 15-20 min. May cause acute reversal of systemic μ-receptor effects and leave κ-agonism intact. *Naloxone:* 0.003-0.1 mg/kg/hr IV infusion (titrate up to decrease pruritus and reduce infusion if pain increases). *Ondansetron:* 0.05-0.1 mg/kg IV or PO q8h. *Cyproheptadine*†*:* 0.1-0.2 mg/kg PO q8-12h. Maximum dose 12 mg. Change opioid.
Constipation	Encourage water consumption, high-fiber diet, and vegetable roughage. *Bulk laxatives:* Metamucil, Maltsupex. *Lubricants:* Mineral oil 15-30 mL PO qd as needed (not for use in infants because of aspiration risk). *Surfactants:* Sodium docusate (Colace): <3 yr: 10 mg PO q8h 3-6 yr: 15 mg PO q8h 6-12 yr: 50 mg PO q8h >12 yr: 100 mg PO q8h *Stimulants:* Bisacodyl suppository (Dulcolax): <2 yr: 5 mg PR qhs >2 yr: 10 mg PR qhs *Senna syrup* (218 mg/5 mL): >3 yr, 5 mL qhs. *Enema:* Fleet's hypertonic phosphate enema (older children; risk of hyperphosphatemia). *Electrolytic/osmotic:* Milk of magnesia; for severe impaction: polyethylene glycol (GoLYTELY, MiraLAX).
Urinary retention	Straight catheterization, indwelling catheter.

*Avoid in patients taking monoamine oxidase inhibitors.
†May be associated with extrapyramidal side effects, which may be more commonly seen in children than in adults.
Modified from Burg FD, Ingelfinger JR, Polin RA, et al, editors: Current pediatric therapy, *ed 18, Philadelphia, 2006, WB Saunders, p. 16.*

Table 62-7 Equianalgesic Doses and Half-Lives ($T_{1/2\beta}$) of Some Commonly Used Opioids

OPIOID	IM/IV DOSE (mg)	ORAL DOSE (mg)	$T_{1/2\beta}$ (hr)
Morphine	10	30	2-3
Meperidine	100	400	3-4
Oxycodone	15	20-30	2-3
Fentanyl	0.15-0.2	—	3-5
Alfentanil	0.75-1.5	—	1-2
Sufentanil	0.02	—	2-3
Diamorphine	5	60	0.5*
Methadone	10	10-15	15-40
Hydromorphone	1.5	7.5	3-4
Tramadol†	100	100	5-7
Buprenorphine	0.4	0.8 (sublingual)	3-5
Pentazocine	60	150	3-5
Nalbuphine	10-20	—	2-4
Butorphanol	2	—	2-3

NOTES:
- Published reports vary in the suggested doses considered to be equianalgesic to morphine. Therefore, titration to clinical response in each patient is necessary.
- Suggested doses are the results of single-dose studies only. Therefore, use of the data to calculate total daily dose requirements and repeated or continuous doses may not be appropriate.
- There may be incomplete cross-tolerance between these drugs. In patients who have been receiving 1 opioid for a prolonged period, it is usually necessary to use a dose lower than the expected equianalgesic dose when changing to another opioid, and to titrate to effect.

*Rapidly hydrolyzed to morphine.
†Only part of its analgesic action results from action on μ opioid receptors.
Modified from Macintyre PE, Ready LB: Acute pain management: a practical guide, *ed 2, Philadelphia, 2001, WB Saunders, p. 19.*

Table 62-8 Classes of Local Anesthetic Drugs

Amides are metabolized in the liver and the elimination half-lives vary from about 1.5-3.5 hr	Lidocaine (lignocaine) Bupivacaine Prilocaine Dibucaine (cinchocaine) Mepivacaine Etidocaine Ropivacaine
Esters are metabolized in plasma (and to a lesser extent the liver) by pseudocholinesterases; thus their half-lives in the circulation are shorter than those of amides	Procaine Chloroprocaine Cocaine Tetracaine (amethocaine) Benzocaine

Modified from Macintyre PE, Ready LB: Acute pain management: a practical guide, *ed 2, Philadelphia, 2001, WB Saunders, p. 19.*

depression, and cardiovascular collapse. Unlike opioids, local anesthetics therefore require a strict maximum dosing schedule. Pediatricians should be aware of the need to calculate these doses and adhere to guidelines.

Topical local anesthetic preparations do not generally result in measurable systemic blood levels, and can reduce pain in diverse circumstances: suturing of lacerations, placement of peripheral IV catheters, lumbar punctures, and accessing of indwelling central venous ports. The application of tetracaine, epinephrine, and cocaine (TAC) results in good anesthesia for suturing wounds, but TAC should not be used on mucous membranes. Combinations of tetracaine with phenylephrine and lidocaine-epinephrine-tetracaine are equally as effective as TAC, eliminating the need to use a controlled substance (cocaine). EMLA, a topical eutectic mixture of lidocaine and prilocaine used to anesthetize intact skin, is commonly applied for venipuncture, lumbar puncture, and other needle procedures. EMLA is generally safe for use in neonates, but it is associated with prilocaine-induced methemoglobinemia. In circumcision, EMLA is more effective than placebo in providing analgesia, but probably less effective than ring block of the penis. EMLA should be used cautiously for circumcision, because its use may cause redness and blistering on the penis. A small area should be tested for hypersensitivity before EMLA is more widely applied. Lidocaine cream, 5%, has replaced EMLA in many pediatric centers. Lidocaine is the most commonly used local anesthetic for cutaneous infiltration. Maximum safe doses of lidocaine are 5 mg/kg without epinephrine and 7 mg/kg with epinephrine. Although concentrated solutions (2%) are commonly available from hospital pharmacies, more dilute solutions such as 0.25% and 0.5% are as equally as effective as 1-2% solutions. The diluted solutions cause less burning discomfort on injection and permit use of larger volumes without achieving toxic doses. In the surgical setting, cutaneous infiltration is more often performed with bupivacaine 0.25% or ropivacaine 0.2% because of the much longer duration of effect. The maximum dose of these long-acting amide anesthetics is 2-3 mg/kg.

Table 62-9 Examples of Neuropathic Pain Syndromes

PERIPHERAL NERVOUS SYSTEM FOCAL AND MULTIFOCAL LESIONS Postherpetic neuralgia Cranial neuralgias (such as trigeminal neuralgia, glossopharyngeal neuralgia) Diabetic mononeuropathy Nerve entrapment syndromes Plexopathy from malignancy or irradiation Phantom limb pain Posttraumatic neuralgia (such as nerve root compression or after thoracotomy) Ischemic neuropathy
PERIPHERAL NERVOUS SYSTEM GENERALIZED POLYNEUROPATHIES *Metabolic/nutritional:* Diabetes mellitus, pellagra, beriberi, multiple nutritional deficiency, hypothyroidism *Toxic:* Alcohol-, platinum-, or taxane-based chemotherapy, isoniazid, antiretroviral drugs *Infective/autoimmune:* HIV, acute inflammatory polyneuropathy (Guillain-Barré syndrome), neuroborreliosis (Bannwarth syndrome) *Hereditary:* Fabry disease *Malignancy:* Carcinomatosis *Others:* Idiopathic small fiber neuropathy
CENTRAL NERVOUS SYSTEM LESIONS Spinal cord injury Prolapsed disc Stroke (brain infarction, spinal infarction) Multiple sclerosis Surgical lesions (such as rhizotomy, cordotomy) Complex neuropathic disorders Complex regional pain syndrome types I and II

Modified from Freynhagen R, Bennett MI: Diagnosis and management of neuropathic pain, BMJ *339:b3002, 2009.*

Neuropathic pain may respond well to the local application of a lidocaine topical patch (Lidoderm) for 12 hr per day (Table 62-9). *Peripheral neuropathic* pain also may respond to IV lidocaine infusions, which may be used in hospital settings for refractory pain, complex regional pain syndromes, and pain associated with malignancies or the therapy of malignancies, such as oral mucositis following bone marrow transplantation. In these instances, 1-2 mg/kg/hr should be administered, and the infusion titrated to achieve a blood lidocaine level in the 2-5 μg/mL range, with use of twice-daily therapeutic blood monitoring. Table 62-10 lists approaches to *central neuropathic pain*.

Table 62-10 Treatment Recommendations for Central Neuropathic Pain Adapted from Current Evidence-Based Literature

MEDICATION CLASS/DRUG	RECOMMENDED STAGE OF TREATMENT
ANTIDEPRESSANTS	
Tricyclics (amitriptyline, nortriptyline)	1st or 2nd
Serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine)	1st or 2nd
ANTICONVULSANTS	
Pregabalin	1st or 2nd
Gabapentin	1st or 2nd
Lamotrigine	2nd or 3rd (in pain after stroke)
Valproate	3rd
OPIOIDS*	
Levorphanol	
MISCELLANEOUS	
Cannabinoids	2nd (in multiple sclerosis)
Mexiletine	3rd

*2nd or 3rd (no specification).
From Freynhagen R, Bennett MI: Diagnosis and management of neuropathic pain, BMJ 339:b3002, 2009.

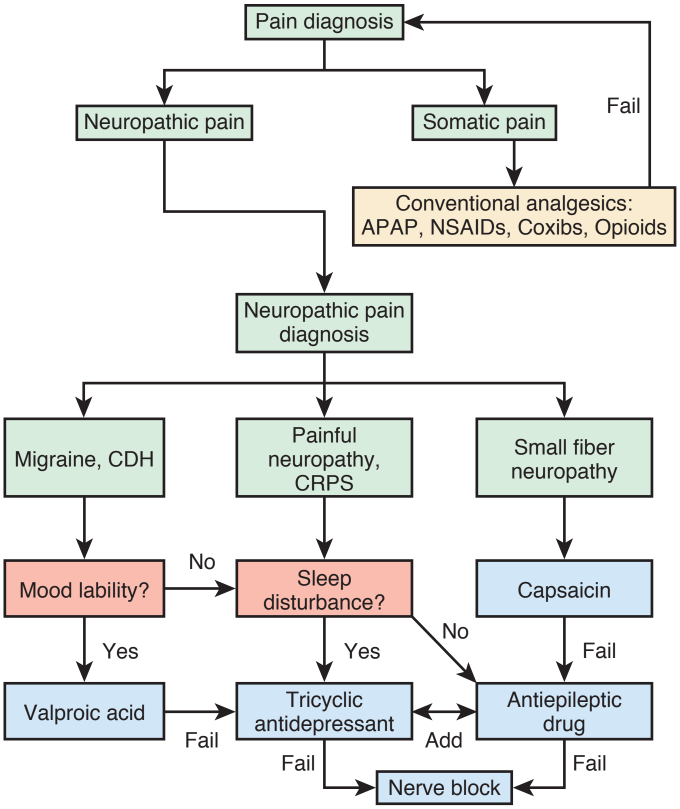

Figure 62-4 A decision tree for the selection of conventional and nonconventional analgesics. *APAP*, acetaminophen; *CDH*, chronic daily headaches; *CRPS*, complex regional pain syndromes; *NSAIDs*, nonsteroidal antiinflammatory drugs.

UNCONVENTIONAL MEDICATIONS IN PEDIATRIC PAIN

Unconventional analgesic medication refers to a wide number of drugs that were developed for other indications but that have been found to have analgesic properties. These drugs include some antidepressants, antiepileptic drugs (AEDs), and neurotropic drugs.

The unconventional analgesics are generally used to manage neuropathic pain conditions, migraine disorders, fibromyalgia syndrome, and some forms of functional chronic abdominal pain syndromes, but they are generally not used to manage surgical, somatic, or musculoskeletal pain. Figure 62-4 presents a decision-making tree that will help the physician select the appropriate analgesic category for various types of pain. The AED gabapentin confers analgesia as well as opioid-sparing benefits following major surgery in adults and in one well-conducted clinical trial in adolescents following spine surgery.

Although several unconventional analgesics have been approved by the FDA for analgesic uses, none has been specifically approved for use in youth with chronic pain. Thus, these drugs should be used with caution, with a focus on mitigating pain to allow a child to participate effectively in therapies and return to normal activity as soon as possible. The use of psychotropic medications should be guided by the principles applied to pharmacologic treatment of any symptom or disease. Target symptoms should be identified, and medication side effects monitored. To determine dosing regimens, the physician should consider the child's weight and the effects that medical condition and other medications, such as psychotropic drugs, may have on the child's metabolism. When available, therapeutic blood-level monitoring should be performed. Side effects should be addressed in detail with both parent and child, and specific instructions given for responding to possible adverse events. It may be necessary to directly address concerns about addiction, dependence, and tolerance in order to decrease treatment-related anxiety and improve medication adherence.

Antidepressant Medications

Antidepressant medications are useful in adults with chronic pain, including neuropathic pain, headaches, and rheumatoid arthritis, independent of their effects on depressive disorders. Antidepressants' analgesic properties inhibit norepinephrine reuptake in the CNS. In children, because clinical trials have been limited, the practitioner should use antidepressants cautiously to treat chronic pain or associated depressive or anxiety symptoms. The FDA issued a "black box warning," its strongest warning, to inform the public of a small but significant increase in suicidal thoughts and attempts in children and adolescents receiving antidepressants. A meta-analysis of studies involving children and adolescents receiving antidepressants indicated that no suicides had been completed. The pediatrician should address this issue with parents of patients being treated with antidepressants and should develop monitoring plans consistent with current FDA recommendations.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs), which have been studied most in children with chronic pain, are effective in pain relief for symptoms including neuropathic pain, functional abdominal pain, and migraine. The efficacy of TCAs may be based on inhibition of the neurochemical pathways involved in norepinephrine and serotonin reuptake and their interference with other neurochemicals involved in the perception or neural conduction of pain. Because sedation is the most common side effect of TCAs, these medications are also effective in treating the sleep disorders that frequently accompany pediatric pain. Biotransformation of TCAs is extensive in healthy children, so the child should be started on a bedtime dose, which may be able to then be titrated to a daily divided dose, with the larger dose given at bedtime. However, TCAs typically are administered only at bedtime. Pain symptoms usually remit at lower doses than those recommended or required for the treatment of mood disorders. Most children and adolescents do not require more than 0.25-0.5 mg/kg of amitriptyline or nortriptyline once a day at bedtime.

Attention should also be paid to hepatic microsomal enzyme metabolism, because CYP2D6 inhibitors, such as cimetidine and quinidine, can increase levels of TCAs. Anticholinergic side effects, which are remarkably uncommon in children in comparison with adults, often remit over time. Constipation, orthostatic hypotension, and

dental caries from dry mouth should be addressed by emphasizing the importance of hydration and oral hygiene. Other side effects include weight gain, mild bone marrow suppression, and liver dysfunction. Some practitioners recommend monitoring complete blood count and liver function values at baseline and periodically during therapy. TCA blood levels can be obtained as well, but pursuit of therapeutic blood monitoring generally should be decided on an individual basis, particularly if adherence, overdose, or sudden changes in mental status are an issue.

All TCAs inhibit cardiac conduction pathways and prolong the QT interval. Sudden cardiac death is reported in children taking TCAs, principally desipramine, probably related to QTc prolongation. There is no general agreement for monitoring the electrophysiologic effects of these drugs, but it is prudent to obtain a careful personal and family history focusing on cardiac arrhythmias, heart disease, and syncope before the initiation of treatment. If personal or family history is positive for any of these conditions, a baseline electrocardiogram should be obtained, with care taken to ensure that the QTc is <445 msec. We recommend that if the dose of amitriptyline or nortriptyline is increased beyond 0.25-0.5 mg/kg/day, an electrocardiogram should be performed for each dosing increase. With TCAs as with other antidepressants, physical dependence and a known discontinuation syndrome can occur. The discontinuation syndrome includes agitation, sleep disturbances, appetite changes, and gastrointestinal symptoms. These medications should be tapered slowly to assist in distinguishing among symptoms that indicate rebound, withdrawal, or the need for continuing the medication.

Serotonin and Serotonin-Norepinephrine Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have minimal efficacy in the treatment of a variety of pain syndromes in adults. SSRIs are very useful when symptoms of depression or anxiety disorders are present and cannot be addressed adequately by nonpharmacologic means. Although many SSRIs are used in practice with children, only fluoxetine has been approved by the FDA for use in children and adolescents. SSRIs have a significantly milder side-effect profile than do TCAs (most side effects of both are transient), and they have no anticholinergic side effects. Chief side effects include gastrointestinal symptoms, headaches, agitation, insomnia, sexual dysfunction, and anxiety. Rarely, hyponatremia, or the syndrome of inappropriate antidiuretic hormone secretion, may occur. Interactions with other medications that have serotonergic effects (tramadol, trazodone, tryptophan, and triptan migraine medication) may also occur. When these medications are used in combination, there is increased likelihood that a life-threatening **serotonergic syndrome** may occur, with associated symptoms of myoclonus, hyperreflexia, autonomic instability, muscle rigidity, and delirium. There is also a **discontinuation syndrome** associated with shorter-acting SSRIs (paroxetine), which includes dizziness, lethargy, paresthesias, irritability, and vivid dreams. Dosages of medications should be tapered slowly over several weeks.

The selective serotonin-norepinephrine reuptake inhibitors duloxetine and venlafaxine demonstrate significant efficacy with chronic neuropathic and other pain syndromes because they inhibit both serotonin and norepinephrine reuptake, and they may directly block associated pain receptors as well. Venlafaxine has no pain indication labeling, but duloxetine is FDA approved for managing neuropathic pain (diabetic neuropathy) and fibromyalgia syndrome.

Because both SSRIs and selective serotonin-norepinephrine reuptake inhibitors have fewer anticholinergic side effects than TCAs, adherence to them is better than in psychiatric populations taking TCAs. Side effects of both types of drugs include gastrointestinal symptoms, hyperhidrosis, dizziness, and agitation, but these effects generally wane over time. Hypertension and orthostatic hypotension may occur; in addition, the patient's blood pressure should be closely followed, and appropriate hydration should be stressed. Note that whereas appetite stimulation and weight gain are associated with all TCAs, duloxetine is often associated with weight loss, frequently a desirable side effect, especially in weight-conscious adolescent females.

Antiepileptic Drugs

Traditional anticonvulsants, such as carbamazepine and valproic acid, are believed to relieve chronic pain by blocking sodium (valproate and the gabapentinoids) or calcium channels (carbamazepine and oxcarbazepine) at the cellular neuronal level, thereby suppressing spontaneous electrical activity and restoring the normal threshold to depolarization of hypersensitive nociceptive neurons, without affecting normal nerve conduction. These medications are particularly useful in patients with mood disorders and neuropathic pain. In adults, the FDA has approved carbamazepine for trigeminal neuralgia and valproate for migraine prophylaxis, and pregabalin is approved in adults for neuropathic pain complicating diabetes, zoster, and for management of fibromyalgia. Anticonvulsant medications generally have gastrointestinal side effects in addition to sedation, anemia, ataxia, rash, and hepatotoxicity. Carbamazepine and oxcarbazepine are associated with an increased incidence of Stevens-Johnson syndrome. Liver function values and a complete blood count should be obtained at start of therapy (baseline) and monitored with use of both these agents. These medications have narrow therapeutic windows and may have extreme variability in therapeutic blood medication levels, as well as multiple drug–drug interactions; also, they may produce liver disease and renal impairment. Drug levels should be measured with each dose increase and periodically thereafter. Carbamazepine, in particular, causes autoinduction of hepatic microsomal enzymes, which can further complicate obtaining a therapeutic medication level. Frequent pregnancy tests are useful in menstruating female adolescents taking valproate, because severe neural tube defects are associated with this medication.

Less-toxic AEDs have supplanted the use of valproate and carbamazepine in patients with pain. These agents have their own, sometimes troubling side effect profiles, but they are far less toxic than their predecessors and they do not require monitoring of liver function, bone marrow function, or therapeutic blood levels. They are also far less lethal in accidental or deliberate overdose.

Gabapentin, the most widely prescribed AED for the management of pain disorders, demonstrates efficacy in treating children with chronic pain, particularly neuropathic pain, and is playing an increasing role in the management of routine surgical pain. Gabapentin has proven effective in treating chronic headache disorders, and many neuropathic pain syndromes including complex regional pain syndromes, chemotherapy induced neuropathy, postherpetic neuralgia, and diabetic neuropathy in both children and adults. This agent has a relatively benign side-effect profile and few drug interactions. Side effects include somnolence, dizziness, and ataxia. Children occasionally demonstrate side effects not reported in adults—severe impulsive or oppositional behavior, agitation, and, occasionally, depression. These side effects do not seem to be dose related.

A molecularly similar AED, **pregabalin**, works by mechanisms similar to those of gabapentin but appears to have a better side-effect profile. Because it undergoes virtually no hepatic metabolism, pregabalin has no significant drug–drug interactions, a concern in patients with chronic pain, who frequently take multiple medications—for both the pain and the underlying medical condition associated with the pain.

Topiramate also demonstrates greater success than traditional anticonvulsants in treating trigeminal neuralgia in adults and in migraine prophylaxis. Topiramate therapy results more frequently in cognitive dysfunction and short-term memory loss compared with gabapentin or pregabalin, and these neurocognitive effects are particularly problematic for school-age children. The pediatrician should also be aware that in female adolescents, topiramate is associated with weight loss, whereas other anticonvulsants are typically associated with significant weight gain.

Benzodiazepines

Children and adolescents with chronic pain may have comorbid psychologic conditions such as depressed mood, sleep disturbances, or anxiety disorders, including generalized anxiety disorder, separation anxiety, posttraumatic stress disorder, and panic attacks. Pervasive developmental disorders are also common in this population.

Psychologic factors can affect a youth's ability to cope with a pain disorder; a conditioned response to pain may be to feel out of control and to lead to increases in anxiety and pain. Conversely, the feeling of helplessness can sensitize the child to increasing amounts of pain, leading the child to perseverate on the pain, think catastrophically, and feel hopeless. Changes in children's normal routines, with a negative impact on participation in valued activities, may further promote hopelessness, resulting in increased pain experiences and development of a depressive disorder.

Benzodiazepines are anxiolytic medications that also have muscle relaxant effects. They are particularly appropriate in acute situations as valuable adjuncts to the management of pain in the hospital setting, because they inhibit painful muscle spasms in surgical patients, but more importantly because they suppress the anxiety that virtually every hospitalized child experiences, anxiety that interferes with restorative sleep and amplifies the child's perception of pain. Benzodiazepines are useful to calm children with anxiety and anticipatory anxiety about planned, painful procedures.

Because dependence, tolerance, and withdrawal may occur with prolonged use, benzodiazepines are generally not recommended for the routine management of *chronic pain*. In concert with psychotherapy, they help control anxiety symptoms that amplify the perception of pain. Infrequently, benzodiazepines may cause behavioral disinhibition, psychosis-like behaviors, or, in large doses, respiratory depression. When dosing these medications, the pediatrician should consider that many benzodiazepines are metabolized by the cytochrome P450 microsomal enzyme system. This issue may be less significant with lorazepam and oxazepam, which undergo 1st-pass hepatic conjugation. Side effects common to benzodiazepines include sedation, ataxia, anemia, increased bronchial secretions, and depressed mood. If a benzodiazepine is administered for more than several consecutive days, the dosage should be slowly tapered over 2 or more weeks; if therapy is abruptly discontinued, autonomic instability, delirium, seizures, and profound insomnia may occur. There are data that suggest that the use of benzodiazepines during hospitalization for serious disease, such as organ transplantation, might increase the risk of development of posttraumatic stress disorder.

Antipsychotics and Major Sedatives

Low doses of antipsychotic medications are often used to address more-severe anxiety and agitation sometimes associated with chronic pain. The use of these medications is controversial because the associated adverse events may be severe. Typical antipsychotics, including thioridazine (Mellaril), haloperidol (Haldol), and chlorpromazine (Thorazine), are associated with a decrease in seizure threshold, agranulocytosis, weight gain, cardiac conduction disturbances, tardive dyskinesia, orthostatic hypotension, hepatic dysfunction, and life-threatening laryngeal dystonia. These side effects are generally less severe with atypical antipsychotics. Because they may still occur, the pediatrician should obtain a baseline electrocardiogram, liver function values, and complete blood count. If the pediatrician is using typical antipsychotics, an inventory of movement disturbances, such as the Abnormal Involuntary Movement Scale test, should be performed at baseline and at every follow-up visit, because movement disorders can worsen with abrupt withdrawal of medications or can become irreversible.

Atypical antipsychotics are generally associated with less-severe side–effect profiles, particularly with regard to side effects such as dyskinesias and dystonias. Use of olanzapine (Zyprexa), which is particularly helpful with insomnia and severe anxiety, requires assessing and monitoring blood levels of glucose, cholesterol, and triglyceride; olanzapine's side effects may include diabetes, hypercholesterolemia, or significant weight gain. The anticholinergic side effects associated with quetiapine (Seroquel) warrant frequent monitoring of blood pressure. Risperidone at doses >6 mg may cause side effects similar to those of typical antipsychotics. Clozapine (Clozaril), which causes increased incidence of life-threatening agranulocytosis, should generally be avoided as a treatment for children and adolescents with chronic pain. Aripiprazole (Abilify) has been used for severe anxiety and/or for treatment-resistant depression. All antipsychotics are associated with the rare, but potentially lethal **neuroleptic malignant syndrome**, which includes severe autonomic instability, muscular rigidity, hyperthermia, catatonia, and altered mental status.

Nonpharmacologic Treatment of Pain

Numerous psychologic and physical treatments for relieving pain, fear, and anxiety as well as enhancing functioning have been a mainstay of pediatric pain treatment and have excellent safety profiles and proven effectiveness. In the area of acute and procedural pain, nonpharmacologic strategies have long been used to help reduce distress in children undergoing medical procedures and surgery. Many of the behavioral methods aim to help children shift attention from pain and alter pain perception (e.g., distraction, hypnosis, imagery). In the treatment of chronic pain, cognitive-behavioral therapies (CBTs) are the most implemented nonpharmacologic treatment. CBT was developed with the goal of modifying social/environmental and behavioral factors that may exacerbate the child's experience of pain and pain-related disability. There are now several decades of research available on CBTs for pediatric chronic pain. Meta-analyses of randomized controlled trials of CBT interventions have found large positive effects of psychologic intervention on pain reduction in children with headache, abdominal pain, and fibromyalgia. Effective strategies include cognitive-behavioral skills training, parent training, relaxation therapy, and biofeedback. The relative or comparative effectiveness of different interventions has been examined in studies of headache and abdominal pain in children. Biofeedback and relaxation therapies have been found to have superior effects to pharmacologic treatments in reducing headache pain in children and adolescents. Similarly, for recurrent abdominal pain, positive effects for CBT were found relative to pharmaceutical, botanical, and dietary interventions (which had very weak evidence).

Nonpharmacologic treatments of pain may be generalized to other treatment needs. A child with cancer who learns self-hypnosis to reduce distress from lumbar punctures may successfully apply this skill to other stressful medical and nonmedical situations. When deciding how to incorporate nonpharmacologic techniques to treat pain, the practitioner should: (1) pay attention to the patient's environment, optimal positioning, and physical comfort; (2) seek to integrate nonpharmacologic techniques with appropriate analgesics; (3) give children (and family members) developmentally and situationally appropriate information as to what to expect, given the child's medical condition, procedures, and treatments; (4) include patients and their families in decision making to ensure an appropriate treatment choice and to optimize adherence to treatment protocols; and (5) above all, develop a **communication plan** among the different therapists, typically with the pediatrician as the case manager, so that the messages to the child and parent are consistent and the modes of therapy are organized into an **integrative team approach**.

Cognitive-behavioral strategies refer to techniques that teach children how to manage pain by learning new ways to think about the pain and to change behaviors associated with the pain. This includes strategies aimed at enhancing children's confidence and self-efficacy, decreasing fear of pain, and promoting exposure to previously avoided activities. In addition, pain coping skills may shift the child's attentional focus away from pain and painful stimuli. Behavioral strategies focused on modifying contingencies in the child's environment (such as parental responses to pain behaviors) may influence pain expression, leading to changes in how children behave or respond to pain. Strategies may also be aimed specifically at modifying individual and family coping (e.g., difficulties in social relationships, psychosocial distress).

Parent and family education and/or psychotherapy, particularly cognitive-behavioral family approaches, have been shown to be effective for treating chronic pain. Parents can learn to cope with their own distress and to understand pain mechanisms and appropriate treatment of pain. Key strategies include teaching parents to alter family patterns that may inadvertently exacerbate pain through developing behavior plans. Parents are taught to create plans for the child to manage the child's own symptoms and increase independent functioning. Often, all adult caregivers (e.g., parents and teachers) need

guidance on developing a behavioral incentive plan to help the child return to school, gradually increase attendance, and receive tutoring, after a prolonged, pain-related absence.

Other Psychologic or Psychiatric Treatment

In addition to pain, there may be other psychologic disorders (e.g., anxiety disorders, major depression) that should be identified and addressed either as part of or separate from the pain management plan. Individual psychotherapy or psychiatric intervention may be warranted to adequately treat a comorbid disorder.

Relaxation techniques promote muscle relaxation and reduction of anxiety, which often accompanies and increases pain. Controlled breathing and progressive muscle relaxation are commonly used relaxation techniques for preschool-age and older children. Asking the child to focus on the breath and pretend to be blowing up a big balloon, while pursing the lips and exhaling slowly may help induce controlled breathing.

Distraction helps a child of any age shift attention away from pain and onto other activities. Common attention sustainers in the environment include bubbles, music, video games, television, the telephone, conversation, school, and play. Asking children to tell stories, or asking parents to read to the child, and even mutual story-telling can be helpful distracters. Being involved with social, school, physical, or other activities helps the child in chronic pain to regain function.

Hypnotherapy helps a child focus on an imaginative experience that is comforting, safe, fun, or intriguing. Hypnotherapy captures the child's attention, alters his sensory experiences, reduces distress, reframes pain experiences, creates time distortions, helps the child dissociate from the pain, and enhances feelings of mastery and self-control. Children with chronic pain can use metaphor, for example, imagining they have overcome something feared because of pain in real life. As the child increases mastery of imagined experiences, the enhanced sense of control can be used during actual pain rehabilitation. Hypnotherapy is best for children of school age or older.

Biofeedback involves controlled breathing, relaxation, or hypnotic techniques with a mechanical device that provides visual or auditory feedback to the child when the desired action is approximated. Common targets of actions include muscle tension, peripheral skin temperature through peripheral vasodilation, and anal control through rectal muscle contraction and relaxation. Biofeedback also enhances the child's sense of mastery and control, especially for the child who needs more "proof" of change than that generated through hypnotherapy alone.

Iyengar yoga was developed to achieve balance in mind, body, and spirit. This form of therapeutic yoga is especially effective for treating chronic pain; improving mood, energy, and sleep; and reducing anxiety. Iyengar yoga involves a series of asanas (body poses) oriented to the specific medical condition or symptoms. It uses props, such as blankets, bolsters, blocks, and belts, to support the body while the patient assumes more healing poses. Yoga promotes a sense of energy, relaxation, strength, balance, and flexibility and, over time, enhances a sense of mastery and control. In more advanced yoga, the child may learn certain types of breathing (pranayama) for added benefit. Mostly, through this form of yoga, the child learns mindfulness or being present and in the moment. By focusing on body and breath, the child can develop strategies to avoid ruminating about the past or worrying about the future.

Massage therapy involves the therapist's touching and applying varied degrees of pressure on the child's muscles. This massage is very useful for children with chronic pain and especially helpful for those with myofascial pain. There are several types of massage, including craniosacral therapy. For young children, it can be helpful to have parents learn and perform brief massage on their children before bedtime.

Physical therapy can be especially useful for children with chronic, musculoskeletal pain and for those deconditioned from inactivity. Exercise appears to specifically benefit muscle functioning, circulation, and posture, also improving body image, body mechanics, sleep, and mood. The physical therapist and the child can develop a graded exercise plan for enhancing the child's overall function.

Acupuncture involves the placement of needles at specific acupuncture points along a meridian, or energy field, after a diagnosis of excess or deficienct energy in that meridian as the primary cause of the pain is made by the acupuncturist. Acupuncture is a feasible, popular part of a pain management plan for children with chronic pain. Acupuncture alleviates chronic nausea, fatigue, and several chronic pain states, including migraine and chronic daily headaches, abdominal pain, and myofascial pain. Acupuncture also has efficacy in adults with myofascial pain, primary dysmenorrhea, sickle cell crisis pain, and sore throat pain. The acupuncturist must relate well to children so that the experience is not traumatic, because added stress would undo the benefits gained.

Transcutaneous electrical nerve stimulation (TENS) is the use of a battery-operated tool worn on the body to send electrical impulses into the body at certain frequencies set by the machine. TENS is believed to be quite safe and can be tried for many forms of localized pain. Children often find TENS helpful and effective.

Music and art therapy can be especially helpful for young and nonverbal children who would otherwise have trouble with traditional talk psychotherapies. Also, many creative children can more easily express fears and negative emotions through creative expression and, with the therapist's help, learn about themselves in the process.

Dance, movement, pet therapies, and aromatherapy have also been used and may be very helpful but have not been well studied in children for pain control.

Invasive Interventions in Treating Pain

Interventional neuraxial and peripheral nerve blocks provide intraoperative anesthesia, postoperative analgesia (see Chapter 61), treatment of acute pain (e.g., long bone fracture and the pain of acute pancreatitis), and contribute to the management of chronic pain (e.g., headaches, abdominal pain, complex regional pain syndromes [CRPS], and cancer pain). Even though interventional procedures are typically rarely used in nonmalignant chronic pain in children, they are described here so that the pediatrician will understand the different types of procedures that are more commonly carried out in adults and rarely described in pediatric texts.

Regional anesthesia provides several benefits: (1) it is an alternative to or augmentation of opioid-based pain control, thereby minimizing the opioid side effects of nausea, vomiting, somnolence, respiratory depression, pruritus, constipation, and physical dependence; (2) it generally provides better quality pain relief because it interrupts nociceptive pathways and more profoundly inhibits endocrine stress responses; (3) it results in earlier ambulation in recovering surgical patients; (4) it helps prevent atelectasis in the setting of severe chest pain; and (5) it usually results in earlier discharge from the hospital. Theoretically, the interruption of nociceptive pathways in the periphery by regional anesthetics will prevent, or reverse the process of amplification of pain signals induced by nociception (CNS wind-up, glial cell activation, etc.). For postoperative pain, effective regional anesthesia and good analgesia reduce the risks of acute pain transitioning into chronic pain.

Regional anesthesia is considered safe and effective if performed by trained staff with the proper equipment. Most nerve blocks are performed by an anesthesiologist or pain management physician; a few are easily performed by a nonanesthesiologist with appropriate training.

Head and Neck Blocks

Primary pain syndromes of the head, such as trigeminal neuralgia, are distinctly unusual in the pediatric population, and few surgical procedures in the head and neck are amenable to regional anesthesia. Pain following tonsillectomies is not amenable to nerve blockade, and neurosurgical incisional pain is usually mitigated by local infiltration of local anesthetic into the wound margins by the surgeon. Headache disorders, very common in the pediatric age group, often respond well to block of the greater and lesser occipital nerves, which provide sensation to much of the cranial structures, from the anterior hairline to the cervical region. The greater occipital nerve can be blocked adjacent to the occipital artery, which can usually be identified at the occipital

ridge midway between the occipital prominence and the mastoid process by palpation, Doppler sound amplification, or visually by ultrasound. The lesser occipital nerves emerge from deeper layers midway between the greater occipital nerve and the mastoid process, where subcutaneous infiltration is effective.

Upper-Extremity Blocks

The brachial plexus block controls pain during surgical procedures or other lesions of the upper extremities. This block also protects the extremity from movement, reduces arterial spasm, and blocks sympathetic outflow to the upper extremity. The brachial plexus, responsible for cutaneous and motor innervation of the upper extremity, is an arrangement of nerve fibers originating from spinal nerves C5 through C8 and T1, extending from the neck into the axilla, arm, and hand. The brachial plexus innervates the entire upper limb, except for the trapezius muscle and an area of skin near the axilla. If pain is located proximal to the elbow, the brachial plexus may be blocked above the clavicle (roots and trunks); if the pain is located distal to the elbow, the brachial plexus may be blocked below it (cords and nerves). The block may be given as a single injection with a long-acting anesthetic (bupivacaine or ropivacaine, sometimes augmented with clonidine or dexamethasone to prolong block duration and intensity) to provide up to 12 hr of analgesia, or given via a catheter (to infuse local anesthetic) attached to a pump that can provide continuous analgesia over days or even weeks.

Anesthesiologists frequently use an IV regional block (or Bier block) with a local anesthetic in combination with a vasodilator such as phentolamine and an NSAID (typically ketorolac) to manage the pain of CRPS. The technique requires placement of an IV cannula into the distal part of the affected extremity, exsanguination of the extremity by elevating and wrapping it in an elastic (Esmarch) bandage, and application of a double pneumatic tourniquet, which is then inflated. Local anesthetic with additives as indicated is then injected into the IV cannula, filling the exsanguinated vasculature. The tourniquet must remain inflated for at least 30 min to allow fixation of local anesthetic to tissues, which reduces peak blood concentration and toxicity upon tourniquet deflation. Although the anesthetic effect is limited to the time of tourniquet inflation, analgesia for pain disorders usually persists for days, weeks, or months after the block.

Trunk and Abdominal Visceral Blocks

Trunk blocks provide somatic and visceral analgesia and anesthesia for pain or surgery of the thorax and abdominal area. Sympathetic, motor, and sensory blockade may be obtained. These blocks are often used in combination to provide optimal relief. Intercostal and paravertebral blocks may be beneficial in those patients for whom an epidural injection or catheter is contraindicated, for example, in the patient with a coagulopathy. Respiratory function is maintained, and the side effects of opioid therapy are eliminated.

The intercostal, paravertebral, rectus sheath, and transverse abdominal plane blocks are the most useful ones for pediatric chest and abdominal pain. The celiac plexus block is most useful for visceral pain caused by malignant cancer or pancreatitis. A pediatrician may perform an intercostal block, but the other blocks are best performed by an experienced anesthesiologist or pain physician.

The intercostal block is used to block the intercostal nerves, the anterior rami of the thoracic nerves from T1 to T11. These nerves lie inferior and posterior to each rib, and between the inner and innermost intercostal muscles, with their corresponding vein and artery, where they can be blocked, generally posterior to the posterior axillary line. Ultrasound imaging of the intercostal nerves helps avoid injury to intercostal vessels or insertion of the needle through the pleura, which results in pneumothorax.

The paravertebral block, an alternative to intercostal nerve block or epidural analgesia, is useful for pain associated with thoracotomy or with unilateral abdominal surgery, such as nephrectomy or splenectomy. Essentially this block results in multiple intercostal blocks with a single injection. The thoracic paravertebral space, lateral to the vertebral column, contains the sympathetic chain, rami communicantes, and dorsal and ventral roots of the spinal nerves. Because it is a continuous space, local anesthetic injection will provide sensory, motor, and sympathetic blockade to several dermatomes. The paravertebral block may be performed as a single injection, or, for a very prolonged effect, as a continuous infusion over several days or weeks via a catheter inserted in the paravertebral space. This block is best performed by an anesthesiologist or interventional pain physician.

Ilioinguinal and iliohypogastric nerve blocks are indicated for surgery for inguinal hernia repair, hydrocele, or orchiopexy repair as well as for chronic pain subsequent to these procedures. The first lumbar nerve divides into the iliohypogastric and ilioinguinal nerves, which emerge from the lateral border of the psoas major muscle. The iliohypogastric nerve supplies the suprapubic area as it pierces the transversus abdominis muscle and runs deep to the internal oblique muscle. The ilioinguinal nerve supplies the upper medial thigh and superior inguinal region as it also pierces the transversus abdominis muscle and runs across the inguinal canal. Ultrasound guidance has made this nerve block nearly always successful.

The **celiac plexus block** is indicated for surgery or pain of the pancreas and upper abdominal viscera. The celiac plexus, located on each side of the L1 vertebral body, contains 1-5 ganglia. The aorta lies posterior, the pancreas anterior, and the inferior vena cava lateral to these nerves. The celiac plexus receives sympathetic fibers from the greater, lesser, and least splanchnic nerves, as well as from parasympathetic fibers from the vagus nerve. Autonomic fibers from the liver, gallbladder, pancreas, stomach, spleen, kidneys, intestines, and adrenal glands originate from the celiac plexus. This block requires CT guidance or fluoroscopy to provide direct visualization of the appropriate landmarks and to confirm correct needle placement. The close proximity of structures such as the aorta and vena cava make this a technical procedure best performed by an anesthesiologist, interventional pain physician, or radiologist.

Lower-Extremity Blocks

Lumbar plexus and sciatic nerve blocks provide pain control for painful conditions or surgical procedures of the lower extremities, with the benefit of providing analgesia to only 1 extremity while preserving motor and sensory function of the other. Unlike with some caudal or lumbar epidural blocks, the patient may still bear weight on the affected leg. The lumbosacral plexus is an arrangement of nerve fibers originating from spinal nerves L2-L4, and S1-S3. The lumbar plexus arises from L2-L4 and divides into the lateral femoral cutaneous, femoral, and obturator nerves. These nerves supply the muscles and sensation of the upper leg, with a sensory branch of the femoral nerve extending below the knee to innervate the medial aspect of the foreleg, ankle, and foot (saphenous nerve). The sacral plexus arises from L4-S3 and divides into the major branches of the sciatic, tibial, and common peroneal nerves. These nerves, in turn, supply the posterior thigh, lower leg, and foot. Unlike brachial plexus blocks, whose targets are accessible, blockade of the entire lower extremity requires more than 1 injection because the lumbosacral sheath is not accessible. Separate injections are necessary for the posterior (sciatic) and anterior (lumbar plexus) branches; the injections can be performed at any of several levels during the course of the nerve, as is clinically expedient. The lumbar plexus can be blocked in the back, resulting in analgesia of the femoral, lateral femoral cutaneous, and obturator nerves. Alternatively, any of these 3 nerves can be individually anesthetized, depending on the location of the pain. Similarly, the sciatic nerve can be anesthetized proximally as it emerges from the pelvis or more distally in the posterior thigh, or its major branches (the tibial and peroneal nerves) can be individually anesthetized. These nerve blocks are generally best performed by an anesthesiologist, interventional pain physician, or radiologist.

Sympathetic Blocks

Sympathetic blocks were once thought to be useful in the diagnosis and treatment of sympathetically mediated pain, CRPS, and other neuropathic pain conditions, but more recently large meta-analyses have shown their utility to be small. The peripheral sympathetic trunk is formed by the branches of the thoracic and lumbar spinal segments,

and it extends from the base of the skull to the coccyx. The sympathetic chain, which consists of separate ganglia containing nerves and autonomic fibers with separate plexuses, can be differentially blocked. These separate plexuses include the stellate ganglion in the lower neck and upper thorax, the celiac plexus in the abdomen, the second lumbar plexus for the lower extremities, and the ganglion impar for the pelvis. When blocks of these plexuses are performed, sympathectomy is obtained without attendant motor or sensory anesthesia.

The **stellate ganglion block** is indicated for pain in the face or upper extremity as well as for CRPS, phantom limb pain, amputation stump pain, or circulatory insufficiency of the upper extremities. The stellate ganglion arises from spinal nerves C7-T1 and lies anterior to the 1st rib. It contains ganglionic fibers to the head and upper extremities. Structures in close proximity include the subclavian and vertebral arteries anteriorly, the recurrent laryngeal nerve, and the phrenic nerve. The Chassaignac tubercle, the transverse process of the C6 vertebral body superior to the stellate ganglion, is a useful and easily palpable landmark for the block, but radiographic or ultrasound imaging is more typically used than surface anatomy and palpation.

The lumbar sympathetic block addresses pain in the lower extremity, CRPS, phantom limb pain, amputation stump pain, and pain from circulatory insufficiency. The lumbar sympathetic chain contains ganglionic fibers to the pelvis and lower extremities. It lies along the anterolateral surface of the lumbar vertebral bodies and is most often injected between the L2 and L4 vertebral bodies.

The analgesia produced by peripheral sympathetic blocks usually outlives the duration of the local anesthetic, often persisting for weeks or indefinitely. If analgesia is transient, the blocks may be performed with catheter insertion for continuous local anesthesia of the sympathetic chain over a period of days or weeks. Because precise radiographically guided placement of the needle and/or catheter is required for safety and success, sympathetic blocks are generally best performed by an anesthesiologist, interventional pain physician, or interventional radiologist.

Epidural Anesthesia (Thoracic, Lumbar, and Caudal)

Epidural anesthesia and analgesia are indicated for pain below the clavicles, management of CRPS, cancer pain unresponsive to systemic opioids, and pain limited by opioid side effects.

The 3 layers of the spinal meninges—the dura mater (outer), the arachnoid mater (middle), and the pia mater (inner)—envelop the spinal neural tissue. The subarachnoid space contains cerebrospinal fluid between the arachnoid mater and pia mater. The epidural space extends from the foramen magnum to the sacral hiatus. The epidural space, which contains fat, lymphatics, blood vessels, and the spinal nerves as they leave the spinal cord, separates the dura mater from the periosteum of the surrounding vertebral bodies. In children, the fat in the epidural space is not as dense as in adults, predisposing to greater spread of the local anesthetic from the site of injection.

Epidural local anesthetics block both sensory and sympathetic fibers, and if the local anesthetic is of sufficient concentration, they also block motor fibers. Mild hypotension may occur, although it is unusual in children younger than 8 yr. Epidural local anesthetics high in the thoracic spine may also anesthetize the sympathetic nerves to the heart (the cardiac accelerator fibers), producing bradycardia. In addition to using local anesthetics, it is routine to use opioids and α-agonists in the epidural space. These agents have their primary site of action in the spinal cord, to which they diffuse from their epidural depot. Side effects of epidural opioid administration include delayed respiratory depression, particularly when hydrophilic opioids such as morphine are used. The risk of this effect requires that children receiving epidural opioids by intermittent injection or continuous infusion be monitored by continuous pulse oximetry and nursing observation, particularly during the 1st 24 hr of therapy or after significant dose escalations. Respiratory depression occurring after the 1st 24 hr of epidural opioid administration is distinctly unusual.

Epidural clonidine, an α_2-agonist with μ-opioid analgesic properties, is associated with minimal risk and side effects. Although product labeling indicates use only in children with severe cancer pain, it is commonly used for routine postoperative pain as well as pain syndromes such as CRPS. Mild sedation is the most common side effect of epidural clonidine, and it is not associated with respiratory depression.

Because performing epidural blockade is technical and may result in spinal cord injury, it is best done by an anesthesiologist or pain physician skilled in the technique.

INTRATHECAL ANALGESIA

Intrathecal catheters infused with opioids, clonidine, ziconotide, and local anesthetics are occasionally applicable in pediatric patients suffering from intractable pain from cancer or other conditions. Typically, intrathecal catheters are attached to an implanted electronic pump containing a drug reservoir sufficient for several months of dosing. The technique is technical and best performed by an experienced pain management physician.

NERVE ABLATION AND DESTRUCTION

In infrequent pediatric cases, pain remains refractory in spite of maximal reliance upon oral and IV medications and nerve blockade. In these instances, temporary (ablation) or permanent (lytic) destruction of 1 or more nerves may be performed. These situations are rather extraordinary in children, and the techniques should be carefully weighed against the consideration of inducing permanent nerve destruction in a growing child with decades of life ahead. On the other hand, when pain is severe in life-limiting disease processes, the long-term considerations are less concerning, and these techniques should be discussed with a pain management specialist skilled in their performance.

CONSIDERATIONS FOR SPECIAL PEDIATRIC POPULATIONS

Pain Perception and Effects of Pain on Newborns and Infants

There are a number of sources of pain in the newborn period. These include acute pain (diagnostic and therapeutic procedures, minor surgery, monitoring), continuous pain (pain from thermal/chemical burns, postsurgical and inflammatory pain), and chronic or disease-related pain (repeated heelsticks, indwelling catheters, necrotizing enterocolitis, nerve injury, chronic conditions, thrombophlebitis). The most common sources of pain in healthy infants are acute procedures, such as heel lances, operations, and, in boys, circumcision.

In premature infants in the neonatal intensive care unit (NICU), there are many procedures performed. In the 1st wk of life, approximately 94% of preterm infants younger than 28 wk of gestational age are ventilated. Other procedures are heelsticks (the most commonly performed) and airway suctioning. Only a few of these procedures are preceded by any type of analgesia. Repeated handling and acute pain episodes sensitize the neonate to increased reactivity and stress responses to subsequent procedures they undergo as neonates or children. Typical stress responses include increases in heart rate, respiratory rate, blood pressure, and intracranial pressure. Cardiac vagal tone, transcutaneous oxygen saturation, carbon dioxide levels, and peripheral blood flow are decreased. Autonomic signs include changes in skin color, vomiting, gagging, hiccupping, diaphoresis, dilated pupils, and palmar and forehead sweating.

To assess pain in the newborn, it is critical to observe the infant for facial expression, body movements, crying, and any other atypical functional behaviors. The observer must consider the context in which the behavior is experienced. The infant's state (agitated, alert, asleep) and gestational and post-gestational ages also affect behavioral stress responses.

Untreated pain in the newborn has serious short-term and longer-term consequences. There has been a shift in most NICUs to more liberal use of opioids. Nonetheless, morphine, the traditional gold standard of analgesia for acute pain, may not be very effective and may have adverse long-term consequences. No differences have been found in the incidence of severe intraventricular hemorrhage or in the mortality rate when infants receiving morphine are compared with the

placebo group, and there are no changes in assessed pain from tracheal suctioning in ventilated infants receiving morphine compared with those receiving a placebo infusion. Morphine may not alleviate acute pain in ventilated preterm neonates, although there are few data on the effects of morphine and fentanyl in nonventilated newborns. The lack of opioid effects for acute pain in neonates may be due to an immaturity of opioid receptors; acute pain may cause the uncoupling of μ opioid receptors in the forebrain. Repetitive acute pain may create central neural changes in the newborn that may have long-term consequences for later pain vulnerability, cognitive effects, and opioid tolerance. There are both anatomic and behavioral manifestations of the adverse effects of neonatal stress, including pain, on brain development. Most neonatologists use opioids in painful situations. Sucrose and pacifiers are also being used in the NICU. The effects of sucrose (sweet taste) are believed to be opioid-mediated because they are reversed with naloxone; stress and pain relief are integrated through the endogenous opioid system. Sucrose, with or without a pacifier, may be effective for acute pain and stress control. Other nonpharmacologic strategies for stress and pain control include infant care by an individual primary nurse, tactile-kinesthetic stimuli (massage), "kangaroo care," and soothing sensorial saturation.

Children with Cancer Pain

The World Health Organization proposed an analgesic therapy model for cancer pain known as the *analgesic ladder* (Table 62-11). Designed to guide therapy in the Third World, this ladder consists of a hierarchy of oral pharmacologic interventions intended to treat pain of increasing magnitude. The hierarchy ignores modalities such as the use of nonconventional analgesics and interventional pain procedures, which are within the capability of physicians to prescribe in developed countries. Nevertheless, because oral medications are simple and efficacious, especially for home use, the ladder presents a framework for rationally using them before applying other drugs and techniques of drug administration.

Oral medications are the 1st line of analgesic treatment. Because NSAIDs affect platelet adhesiveness, they are typically not used. Opioid therapy is the preferred approach for moderate or severe pain. Nonopioid analgesics are used for mild pain, a weak opioid is added for moderate pain, and strong opioids are administered for more severe pain. Adjuvant analgesics can be added, and side effects and comorbid symptoms are actively managed. Determining the type and sources of the pain will help develop an effective analgesic plan. Certain treatments, such as the chemotherapeutic agent vincristine, are associated with neuropathic pain. Such pain might require anticonvulsants or TCAs. Organ-stretching pain from tumor growth within an organ might require strong opioids and/or radiation therapy if the tumor is radiosensitive. Organ obstruction, such as intestinal obstruction, should be diagnosed to relieve or bypass the obstruction.

It is important to consider both pharmacologic and nonpharmacologic strategies (e.g., cognitive-behavioral treatment, family and parent support) to treat pain in children with cancer.

Table 62-11	World Health Organization Analgesic Ladder for Cancer Pain
STEP 1 Patients who present with mild to moderate pain should be treated with a nonopioid.	
STEP 2 Patients who present with moderate to severe pain or for whom the step 1 regimen fails should be treated with an oral opioid for moderate pain combined with a nonopioid analgesic.	
STEP 3 Patients who present with very severe pain or for whom the step 2 regimen fails should be treated with an opioid used for severe pain, with or without a nonopioid analgesic.	

Children with Pain Associated with Advanced Disease

Patients with advanced diseases, including cancer, AIDS, neurodegenerative disorders, and cystic fibrosis, need palliative care approaches that focus on optimal quality of life. Nonpharmacologic and pharmacologic means of management of pain and other distressing symptoms are palliative care's key components. It should be highlighted here that "palliative care" should be offered to all children with serious diseases, whether or not the diseases are potentially curable and whether or not long life expectancy is predicted. Examples include young children diagnosed with acute lymphoblastic leukemia (>90% posttreatment life expectancy) and children undergoing organ transplantation. Palliative care in pediatrics is meant to connote treatment that focuses on symptom reduction, quality of life, and good family and clinical team communication. It is not just reserved for patients in hospice care or those at the end of life. Differences among these conditions that relate to the progression of underlying illness, associated distressing symptoms, and common emotional responses should shape individual treatment plans (see Chapter 43). For end-of-life care, more than 90% of children and adolescents with cancer can be made comfortable by standard escalation of opioids according to the World Health Organization protocol. A small subgroup (5%) has enormous opioid dose escalation to >100 times the standard morphine or other opiate infusion rate. In most of these cases, there is spread of solid tumors to the spinal cord, roots, or plexus, and signs of neuropathic pain are evident. Methadone given orally is often used in palliative care, not just end of life care, because of its long half-life and its targeting of both opioid and *N*-methyl-D-aspartate receptors. The type of pain experienced by the patient (neuropathic, myofascial) should determine the need for adjunctive agents. Complementary measures, such as massage, hypnotherapy, and/or spiritual care, should also be considered in palliative care. Although the oral route of opioid administration should be encouraged, especially to facilitate care at home if possible, some children are unable to take oral opioids. Transdermal and sublingual routes, as well an intravenous infusion with a PCA, are likely next choices. Small, portable infusion pumps are convenient for home use. If venous access is limited, a useful alternative is to administer opioids (especially morphine or hydromorphone, but not methadone or meperidine) through continuous subcutaneous infusion, with or without a bolus option. A small (e.g., 22-gauge) cannula is placed under the skin and secured on the thorax, abdomen, or thigh. Sites may be changed every 3-7 days, as needed. As noted, alternative routes for opioids include the transdermal and oral transmucosal routes. These latter routes are preferred over IV and subcutaneous drug delivery when the patient is being treated at home.

Examples of Chronic and Recurrent Pain Syndromes

Chronic pain is defined as recurrent or persistent pain lasting longer than the normal tissue healing time, approximately 3-6 mo. Children may experience pain related to injury (e.g., burns) or a chronic or underlying disease process (e.g., cancer, arthritis); pain can also be the chronic condition itself (e.g., CRPS, fibromyalgia, functional abdominal pain). During childhood, abdominal, musculoskeletal, and headache pain are the most frequently occurring conditions. However, definitions of chronic pain do not take into account standard criteria for assessing particular pain symptoms or for evaluating the intensity or impact of pain, and therefore include individuals with varying symptoms and experiences. Consequently, in epidemiologic surveys, prevalence estimates vary widely. Overall prevalence rates for different childhood pains range from 4-88%. For example, an average of 13.5-31.8% of adolescents in a community sample reported having weekly abdominal, headache, or musculoskeletal pains. Most epidemiologic studies report prevalence and do not report the severity or impact of the pain. Research indicates that only a subset of children and adolescents with chronic pain (approximately 5%) experience moderate-severe disability, and this likely better represents the estimated population for whom help is needed to treat pain and associated problems.

COMPLEX REGIONAL PAIN SYNDROMES

Neuropathic pain is caused by abnormal excitability in the peripheral or CNS that may persist after an injury heals or inflammation subsides. The pain, which can be acute or chronic, is described as burning or stabbing and may be associated with cutaneous hypersensitivity (allodynia), distortion of sensation (dysesthesia), and amplification of noxious sensations (hyperalgesia and hyperpathia). Neuropathic pain conditions may be responsible for >35% of referrals to chronic pain clinics, conditions that commonly include posttraumatic and postsurgical peripheral nerve injuries, phantom pain after amputation, pain after spinal cord injury, and pain caused by metabolic neuropathies. Neuropathic pain typically responds poorly to opioids. In adults, evidence suggests the efficacy of TCAs (nortriptyline, amitriptyline) and anticonvulsants (gabapentin, pregabalin) for treatment of neuropathic pain (see Tables 62-9 and 62-10).

CRPS type 1, formerly known as reflex sympathetic dystrophy, is well-described in the pediatric population. CRPS type 1 is a syndrome of neuropathic pain that typically follows an antecedent and usually minor injury to an extremity without identifiable nerve injury. The syndrome of CRPS type 1 includes severe spontaneous neuropathic pain, hyperpathia, hyperalgesia, severe cutaneous allodynia to touch and cold, changes in blood flow (typically extremity cyanosis), and sweating. In more advanced cases, symptoms include dystrophic changes of the hair, nails, and skin, immobility of the extremity (dystonia), and muscle atrophy. In the most advanced cases, symptoms include ankylosis of the joints of the extremity. Specific causal factors in CRPS type 1 in both children and adults remain elusive, although coincidental events may be noted. **CRPS type 2**, formerly referred to as causalgia, is less common.

The syndromes of CRPS type 2 and CRPS type 1 are virtually identical, except that the former is associated with a well-defined peripheral nerve injury. Treatment of CRPS in children has been extrapolated from that in adults, with some low-level evidence for efficacy of physical therapy, cognitive-behavioral therapy, nerve blocks, TCAs, gabapentin, and some other related drugs. All experts in pediatric pain management agree on the value of aggressive physical therapy. Some centers provide aggressive therapy without the use of pharmacologic agents or interventional nerve blocks; unfortunately, recurrent episodes may be seen in up to 50% of patients. Physical therapy can be extraordinarily painful for children to endure; it is tolerated only by the most stoic and motivated patients. If children have difficulty enduring the pain, there is a well-established role for using pharmacologic agents with or without peripheral or central neuraxial nerve blocks to render the affected limb sufficiently analgesic so that physical therapy can be tolerated. Pharmacologic interventions include the use of AEDs such as gabapentin and/or TCAs such as amitriptyline (see Fig. 62-4). Although there is clear evidence of a peripheral inflammatory component of CRPS, with release of cytokines and other inflammatory mediators from the peripheral nervous system in the affected limb, the use of antiinflammatory agents has been disappointing. Commonly used nerve block techniques include sympathetic nerve blocks, IV regional anesthetics, epidural analgesia, and peripheral nerve blocks. In extreme and refractory cases, more invasive strategies have been reported, including surgical sympathectomy and spinal cord stimulation. Although an array of treatments have some benefit, the mainstay of treatment remains physical therapy emphasizing desensitization, strengthening, and functional improvement. Additionally, pharmacologic agents and psychologic and complementary therapies are important components of a treatment plan. Invasive techniques, although not curative, are valuable if they permit the performance of frequent and aggressive physical therapy that cannot be carried out otherwise. Some children with CRPS become so easily sensitized that persistent and bothersome pain may develop at the site of the invasive procedure. A good biopsychosocial evaluation will help determine the orientation of the treatment components. At this time, there are insufficient data to indicate the superior value of interventional blocks, such as epidural anesthesia delivery, in children with CRPS type I, over physical and psychologic interventions, with or without pharmacological support.

MYOFASCIAL PAIN DISORDERS AND FIBROMYALGIA

Myofascial pain disorders are associated with tender points in the affected muscles as well as with muscle spasms (tight muscles). Treatment is targeted at relaxing the affected muscles through physical therapy, Iyengar yoga, massage, and/or acupuncture. Rarely are pharmacologic muscle relaxants helpful other than for creating tiredness at night for sleep. Dry needling or injections of local anesthetic into the tender points has been advocated, but the data do not support this as a standard treatment. Similarly, although botulinum toxin injections may be used, no data support this practice in children. Often poor body postures, repetitive use of a part of the body not used to that movement, or carrying heavy backpacks initiates pain. When it becomes widespread with multiple tender points, the diagnosis may be made of juvenile fibromyalgia, which may or may not continue to subsequently become adult fibromyalgia. Likely there are different subtypes of widespread pain syndromes, and physical therapy is a key component of treatment. Psychologic interventions may play an important role to assist the child in resuming normal activities and to manage any psychologic comorbidities. Any pain rehabilitation plan should enhance return to full function. Because there is a high incidence of chronic pain in parents of children presenting with a chronic pain condition, especially fibromyalgia, attention to parent and family factors is important. Parent training may entail teaching the parent to model more appropriate pain coping behaviors and to recognize the child's independent attempts to manage pain and function adaptively. Parents may also need referrals to obtain appropriate pain management for their own pain condition.

The drugs pregabalin and duloxetine have both been approved for management of fibromyalgia in adults in the United States, but there are no clinical studies confirming their effectiveness in children and adolescents.

ERYTHROMELALGIA

Erythromelalgia in children is generally primary, whereas in adults it may be either primary or secondary to malignancy or other hematologic disorders such as polycythemia vera. Patients with this disorder exhibit red, warm, hyperperfused distal limbs. The disorder is usually bilateral, and it may involve either or both the hands and feet. Patients perceive burning pain and typically seek relief by immersing the affected extremities in ice water, sometimes so often and for so long so that skin pathology results. Primary erythromelalgia has recently been shown to be caused by a genetic mutation in the gene for the NaV1.7 neuronal sodium channel on peripheral C nociceptive fibers, resulting in their spontaneous depolarization, and thus continuous burning pain. The most common mutation identified is in the *SCN9A* gene, although there are several mutations that affect the NaV1.7 channel. Interestingly, another mutation in the NaV1.7 channel results in a rare but devastating genetic condition, the congenital indifference to pain.

It is easy to distinguish erythromelalgia (or related syndromes) from CRPS. The limb afflicted with CRPS is typically cold and cyanotic, the disease is typically unilateral, and children with CRPS have cold allodynia, making immersion in cold water exquisitely painful; in erythromelalgia, ice water immersion is analgesic, the condition is bilateral and symmetrical, and associated with hyperperfusion of the distal extremity. The evaluation of hyperperfused limbs with burning pain should include genetic testing for Fabry disease and screening for hematologic malignancies, with diagnosis of primary erythromelalgia being one of exclusion. There are presently few clinical laboratories that are certified to perform the DNA analysis required to identify the common NaV1.7 mutations.

The definitive treatment of Fabry disease includes enzyme replacement as disease-modifying treatment and administration of neuropathic pain medications, such as gabapentin, although the success of antineuropathic pain drugs in small-fiber neuropathies has not been impressive. The treatment of erythromelalgia is far more problematic. Antineuropathic pain medications, such as AEDs and TCAs are typically prescribed but rarely helpful (see Fig. 62-4). Although one might predict that sodium channel–blocking AEDs might be effective in this

sodium channelopathy, oxcarbazepine has not proven to be a particularly effective modality. The pain responds well to regional anesthetic nerve blocks, but it returns immediately when the effects of the nerve block resolve. In contrast, in other neuropathic syndromes, the analgesia usually (and inexplicably) persists well after the resolution of the pharmacologic nerve block. Aspirin and even nitroprusside infusions are reported to be of benefit with secondary erythromelalgia, but they are not reported to be helpful in children with primary erythromelalgia. There are case reports in adults and clinical experience in children suggesting that periodic treatment with high-dose capsaicin cream is effective in alleviating the burning pain and disability of erythromelalgia. Capsaicin (essence of chili pepper) cream is a vanilloid receptor (TRPV1) agonist that depletes small-fiber peripheral nerve endings of the neurotransmitter substance P, which is an important neurotransmitter in the generation and transmission of nociceptive impulses. Once depleted, these nerve endings are no longer capable of generating spontaneous pain until the receptors regenerate, a process that takes many months.

OTHER CHRONIC PAIN CONDITIONS IN CHILDREN

It should be noted that there are a variety of genetic and other medical/surgical conditions that are often associated with chronic pain. Examples include Fabry disease, Chiari/syringomyelia, juvenile idiopathic arthritis, mitochondrial disorders, degenerative neurologic diseases, cerebral palsy, autism spectrum disorders, intestinal pseudoobstruction, inflammatory bowel disease, chronic migraine and chronic daily headaches, irritable bowel disease, and others. In many cases, treating the underlying disease, such as enzyme replacement in Fabry disease and in other lysosomal disorders, will reduce what otherwise might be progression of symptoms, but may not totally reduce pain and suffering, and other modalities will be needed. Finally, pain that persists and is not well treated can lead to central sensitization and widespread pain, such as seen in children with one pain source who develop fibromyalgia.

MANAGING COMPLEX CHRONIC PAIN PROBLEMS

Some patients with chronic pain have a prolonged course of evaluation in attempts to find what is expected as the singular "cause" of the pain, and thus also undergo many failed treatments. Parents worry that the doctors have not yet discovered the cause that may be serious and life-threatening, and children often feel not believed, that they are faking their pain, or are "crazy." There may be no identifiable or diagnosable condition and families may seek opinions from multiple treatment facilities in an attempt to find help for their suffering child. In fact, in many cases what may have begun as an acute injury or infectious event may result for some children into a chronic pain syndrome, with changes in the neurobiology of the pain signaling system.

In the context of disabling chronic pain, it is very important for the pediatrician to (1) avoid overmedication because this can exacerbate associated disability, (2) maintain an open mind and reassess the diagnosis if the clinical presentation changes, and (3) understand and communicate to the family that pain has a biologic basis (likely related to neural signaling and neurotransmitter dysregulation), and the pain is naturally distressing to the child and family. All patients and families should receive a simple explanation of pain physiology that helps them understand the importance of (1) functional rehabilitation to normalize pain signaling, (2) the low risk of causing further injury with systematic increases in normal functioning, and (3) the likely failure of treatment if pain is managed as if it were acute. Because it is counterintuitive for most people to move a part of the body that hurts, many patients with chronic pain have atrophy or contractures of a painful extremity from disuse. Additionally, associated increases in worry and anxiety may exacerbate pain and leave the body even more vulnerable to further illness, injury, and disability. Pain can have a significant impact on many areas of normal functioning and routine for children, and school absenteeism and related consequences of missed schooling are often significant problems. Appropriate assessment and evaluation of the child with chronic pain and the child's family is the critical first step necessary in developing a treatment plan.

Interdisciplinary pediatric pain programs have become the standard of care for treating complex chronic pain problems in youth. In recognition of the severity and complexity of pain and disability for some children, different settings and treatment delivery models for providing pain care have been explored. One option is inpatient and day hospital treatment programs. They often address barriers to access to outpatient treatment and coordination of care. In addition, they provide an intensive treatment option for children who do not make adequate progress in outpatient treatment or who are severely disabled by pain. Early programs developed in the 1990s focused on treatment of CRPS through intensive inpatient rehabilitation and exercise-based treatment programs. Later developing programs expanded to other clinical populations and expanded the treatment focus to incorporate a range of rehabilitation and psychologic therapies delivered both individually and in groups. The typical length of inpatient admissions for children with chronic pain in such programs is 3-4 wk and there is emerging evidence to suggest benefit from these programs.

Another intervention delivery option is remote management, referring to pain interventions utilized outside of the clinic/hospital setting to reach children in their homes or communities. Interventions are typically delivered using some form of technology, such as the Internet, or may rely on other media such as telephone counseling or use of written self-help materials. Most typically, remote management of pain includes monitoring, counseling, and/or delivery of behavioral and CBT interventions. Internet interventions have received the most research attention to date with published examples for several different pediatric chronic pain conditions with promising findings for pain reduction. Telemedicine, while in widespread use clinically for many pediatric health conditions, has not yet been formally evaluated in pediatric pain. Within any community, the pediatrician will need to locate appropriate referral sources for patients with complex chronic pain.

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Chapter 63

Poisoning

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Poisoning is now the number 1 cause of injury death in the United States, even surpassing that from motor vehicle collisions. The majority of these deaths are unintentional (i.e., not suicide). In adolescents, poisoning is the third leading cause of injury-related death. Of the more than 2 million human poisoning exposures reported annually to the National Poison Data Systems of the American Association of Poison Control Centers, approximately 50% occur in children younger than 6 yr old. Almost all of these exposures are unintentional and reflect the propensity for young children to put virtually anything in their mouths. Fortunately, children younger than 6 yr account for <2% of all poisoning fatalities reported to National Poison Data Systems.

More than 90% of toxic exposures in children occur in the home, and most involve only a single substance. Ingestion accounts for the vast majority of exposures, with a minority occurring via the dermal, inhalational, and ophthalmic routes. Approximately 50% of cases involve nondrug substances, such as cosmetics, personal care items, cleaning solutions, plants, and foreign bodies. Pharmaceutical preparations account for the remainder of exposures, and analgesics, topical preparations, cough and cold products, and vitamins are the most commonly reported categories.

The majority of poisoning exposures in children younger than 6 yr can be managed without direct medical intervention (beyond a call to

Table 63-1 Common Agents Potentially Toxic to Young Children (<6 yr) in Small Doses*

SUBSTANCE	TOXICITY
Aliphatic hydrocarbons (e.g., gasoline, kerosene, lamp oil)	Acute lung injury
Antimalarials (chloroquine, quinine)	Seizures, dysrhythmias
Benzocaine	Methemoglobinemia
β Blockers (lipid-soluble β blockers [e.g., propranolol] are more toxic than water-soluble β blockers [e.g., atenolol])	Bradycardia, hypotension
Calcium channel blockers	Bradycardia, hypotension, hyperglycemia
Camphor	Seizures
Caustics (pH <2 or >12)	Airway, esophageal and gastric burns
Clonidine	Lethargy, bradycardia, hypotension
Diphenoxylate and atropine (Lomotil)	CNS depression, respiratory depression
Hypoglycemics, oral (sulfonylureas and meglitinides)	Hypoglycemia, seizures
Laundry detergent packets (pods)	Airway issues, respiratory distress, altered mental status
Lindane	Seizures
Monoamine oxidase inhibitors	Hypertension followed by delayed cardiovascular collapse
Methyl salicylate	Tachypnea, metabolic acidosis, seizures
Opioids (especially methadone, buprenorphine)	CNS depression, respiratory depression
Organophosphate pesticides	Cholinergic crisis
Phenothiazines (especially chlorpromazine, thioridazine)	Seizures, dysrhythmias
Theophylline	Seizures, dysrhythmias
Tricyclic antidepressants	CNS depression, seizures, dysrhythmias, hypotension

*"Small dose" typically implies 1 or 2 pills or 5 mL.
CNS, central nervous system.

the regional poison control center), either because the product involved is not inherently toxic or the quantity of the material involved is not sufficient to produce clinically relevant toxic effects. However, a number of substances are potentially highly toxic to toddlers in small doses (Table 63-1). In 2012, carbon monoxide and analgesics (acetaminophen and salicylate) were the leading causes of poison-related fatalities in young children (<6 yr). In addition, prescription opioids, antidepressants, cardiovascular drugs, and aliphatic hydrocarbons were significant causes of mortality.

Poison prevention education should be an integral part of all well-child visits, starting at the 6 mo visit. Counseling parents and other caregivers about potential poisoning risks, how to poison-proof a child's environment, and what to do if an ingestion or exposure occurs diminishes the likelihood of serious morbidity or mortality. Poison prevention education materials are available from the American Academy of Pediatrics and regional poison control centers. A network of poison control centers exists in the United States, and anyone at any time can contact a regional poison center by calling this toll-free number: **1-800-222-1222**. Parents should be encouraged to share this number with grandparents, relatives, babysitters, and any other caregivers.

Product safety measures, poison prevention education, early recognition of exposures, and around-the-clock access to regionally based poison control centers all contribute to the favorable outcomes in young children. Poisoning exposures in children 6-12 yr old are much less common, involving only approximately 6% of all reported pediatric exposures. A second peak in pediatric exposures occurs in adolescence. Exposures in the adolescent age group are primarily intentional (suicide or abuse or misuse of substances) and thus often result in more severe toxicity (see Chapter 114). Families should be informed and given anticipatory guidance that nonprescription and prescription medications, and even household products (e.g., inhalants), are common sources of adolescent exposures. Adolescents (ages 13-19 yr) accounted for 45 of the 73 poison-related pediatric deaths in 2012 reported to National Poison Data System (4% of all fatalities called in to poison centers). Pediatricians should be aware of the signs of drug abuse or suicidal ideation in this population and should aggressively intervene (see Chapter 114).

PREVENTION

Deaths caused by unintentional poisoning among younger children have decreased dramatically over the past 2 decades, particularly among children younger than 5 yr of age. In 1970, when the Poison Packaging Prevention Act was passed, 226 poisoning deaths of children younger than age 5 yr occurred compared with only 21 in 2012. Poisoning prevention demonstrates the effectiveness of passive strategies, including the use of child-resistant packaging and limited doses per container. Difficulty using child-resistant containers by adults is an important cause of poisoning in young children today; in 18.5% of households in which poisoning occurred in children younger than 5 yr of age, the child-resistant closure was replaced, and 65% of the packaging used did not work properly. Nearly 20% of ingestions occur from drugs owned by grandparents, a group that has difficulty using traditional child-resistant containers.

Even though there has been success in preventing poisoning in young children, there has been a remarkable rise in poison-related death over the past 20 yr in the adolescent population. This has mirrored the ever-increasing rate of opioid prescriptions written by healthcare providers.

APPROACH TO THE POISONED PATIENT

The initial approach to the patient with a witnessed or suspected poisoning should be no different than that in any other sick child, starting with stabilization and rapid assessment of the airway, breathing, circulation, and mental status (see Chapter 67). In any patient with altered mental status, a serum dextrose concentration should be obtained early and naloxone administration should be considered. A targeted history and physical examination serves as the foundation for a thoughtful differential diagnosis, which can then be further refined through laboratory testing and other diagnostic studies.

INITIAL EVALUATION

History

Obtaining an accurate problem-oriented history is of paramount importance. Intentional poisonings (suicide attempts; abuse or misuse) are typically more severe than unintentional, exploratory ingestions. In patients without a witnessed exposure, historical features such as age of the child (toddler or adolescent), acute onset of symptoms without prodrome, sudden alteration of mental status, multiple system organ dysfunction, or high levels of household stress should suggest a possible diagnosis of poisoning.

Description of the Exposure

For household and workplace products, names (brand, generic, chemical) and specific ingredients, along with their concentrations, can often

be obtained from the labels. Poison control center specialists can also help to identify possible ingredients and review the potential toxicities of each component. In cases of suspected ingestion, poison center specialists can help identify pills based on markings, shape, and color. If referred to the hospital for evaluation, parents should be instructed to bring the products, pills, and/or containers with them to assist with identifying and quantifying the exposure. If a child is found with an unknown pill in the child's mouth, the history must include a list of all medications in the child's environment (including medications that grandparents, parents, siblings, caregivers, or other visitors might have brought into the house). In the case of an unknown exposure, clarifying where the child was found (e.g., garage, kitchen, laundry room, bathroom, backyard, workplace) can help to generate a list of potential toxins.

Next, it is important to clarify the timing of the ingestion and to obtain some estimate of how much of the substance was ingested. It is better to overestimate the amount ingested to prepare for the worst-case scenario. Counting pills or measuring the remaining volume of a liquid ingested can sometimes be useful in generating estimates. For inhalational, ocular, or dermal exposures, the concentration of the agent and the length of contact time with the material should be determined if possible.

Symptoms

Obtaining a description of symptoms experienced after ingestion, including their timing of onset relative to the time of ingestion and their progression, can generate a list of potential toxins and to predict the severity of the ingestion. Coupled with physical exam findings, reported symptoms assist practitioners in identifying *toxidromes* or recognized poisoning syndromes suggestive of poisoning from specific substances or classes of substances (Tables 63-2, 63-3, and 63-4).

Past Medical History

Underlying diseases can make a child more susceptible to the effects of a toxin. Concurrent drug therapy can also increase susceptibility because certain drugs may interact with the toxin. Pregnancy is a common precipitating factor in adolescents' suicide attempts and can influence both evaluation of the patient and subsequent treatment. A history of psychiatric illness can make patients more prone to substance abuse, misuse, intentional ingestions, and polypharmacy complications. A developmental history is important to ensure that the history provided is appropriate for the child's developmental stage (e.g., a report of a 6 mo old picking up a large container of laundry detergent and drinking it should raise a red flag).

Social History

Understanding the child's social environment helps to identify potential sources of exposures (caregivers, visitors, grandparents, recent parties or social gatherings) and environmental stressors (new baby, parent's illness, financial stress) that might have contributed to the ingestion. Unfortunately, some poisonings occur in the setting of serious neglect or intentional abuse.

Physical Examination

A targeted physical exam is important to identifying the potential toxin and assessing the severity of the exposure. Initial efforts should be directed toward assessing and stabilizing the airway, breathing, circulation, and mental status. Once one has ensured that the airway is secure and the patient is stable from a cardiopulmonary standpoint, a more extensive physical exam can help to identify characteristics of specific toxins or classes of toxins.

In the poisoned patient, the key features of the physical exam are the vital signs, mental status, pupils (size, reactivity) nystagmus, skin, bowel sounds, and odors. These findings might suggest a toxidrome that can guide the differential diagnosis and initial management.

Laboratory Evaluation

For select intoxications (e.g., salicylates, some anticonvulsants, acetaminophen, iron, digoxin, methanol, lithium, ethylene glycol, carbon monoxide, lead), quantitative blood concentrations are integral to confirming the diagnosis and formulating a treatment plan. For most exposures, quantitative measurement is not readily available and is not likely to alter management. All intoxicant levels must be interpreted in conjunction with the history. For instance, a methanol level of 20 mg/dL 1 hr after ingestion may well be nontoxic, whereas a similar level 24 hr after ingestion implies a patient with significant poisoning. In general, patients with multiple or chronic exposures to a drug or other chemical will be more symptomatic at lower drug levels than those with a single exposure.

Both urine drug-of-abuse screens and the more comprehensive drug screens vary widely in their ability to detect toxins and generally add little information to the clinical assessment, particularly if the agent is known and the patient's symptoms are consistent with that agent. If a drug screen is ordered, it is important to know that the components screened for, and the lower limits of detection, vary from laboratory to laboratory. In addition, the interpretation of most drug screens is hampered by false-positive and false-negative results; standard urine opiate screens will not be positive after exposure to a synthetic opioid (e.g., methadone, buprenorphine, fentanyl). The urine drug-of-abuse screen is typically of limited utility when it comes to medical clearance, but does serve a useful function for psychiatrists in their evaluation of the adolescent patient. Apart from its psychiatric usefulness, urine drug-of-abuse screens are potentially helpful in patients with altered mental status of unknown etiology, persistent, unexplained tachycardia, acute myocardial ischemia or stroke at a young age, and in the assessment of a neglected or abused child. Consultation with a medical toxicologist can be helpful in interpreting drug screens and ordering specific drug levels or metabolites that can aid in patient management.

In the case of a neglected or allegedly abused child, a positive toxicology screen can add substantial weight to a claim of abuse or neglect. In these cases and any case with medicolegal implications, any positive screen *must* be confirmed with gas chromatography/mass spectroscopy, which is considered the gold standard measurement for legal purposes.

Acetaminophen is a widely available medication and a commonly detected coingestant with the potential for severe toxicity. There is an effective antidote to acetaminophen poisoning that is time-dependent. Given that patients might initially be asymptomatic and might not report acetaminophen as a coingestant, an acetaminophen level should be checked in all patients who present after an intentional exposure or ingestion. A basic chemistry panel (electrolytes, renal function, glucose) is necessary for all poisoned or potentially poisoned patients. Any patient with acidosis (a low serum bicarbonate level on the serum chemistry panel), must have an anion gap calculated because of the more specific differential diagnoses associated with an elevated anion gap metabolic acidosis. Patients with a known overdose of acetaminophen should have their liver transaminases assessed, as well as an INR (international normalized ratio). A serum creatine kinase level is indicated on any patient with a prolonged "down time" as rhabdomyolysis can result from laying supine on a hard surface without movement for just a few hours. Serum osmolality is only helpful as a surrogate marker for a toxic alcohol exposure if a serum concentration of the alcohol cannot be obtained in a reasonable time frame. A urine pregnancy test is, of course, mandatory for all adolescent female patients. Based on the clinical presentation and the presumed poison, additional lab tests may also be helpful (Table 63-5).

Additional Diagnostic Testing

An electrocardiogram (ECG) is a quick and noninvasive bedside test that can yield important clues to diagnosis and prognosis. Toxicologists pay particular attention to the ECG intervals (Table 63-6). A widened QRS interval, putting the patient at risk for monomorphic ventricular tachycardia, suggests blockade of fast sodium channels, and may be seen after ingestion of tricyclic antidepressants, diphenhydramine, and cocaine, among others. A widened QTc interval suggests effects at the potassium rectifier channels and portends a risk of torsades de pointes (polymorphic ventricular tachycardia).

Table 63-2 Selected Historical and Physical Findings in Poisoning

SIGN	TOXIN
ODOR	
Bitter almonds	Cyanide
Acetone	Isopropyl alcohol, methanol, paraldehyde, salicylates
Alcohol	Ethanol
Wintergreen	Methyl salicylate
Garlic	Arsenic, thallium, organophosphates, selenium
OCULAR SIGNS	
Miosis	Opioids (except propoxyphene, meperidine, and pentazocine), organophosphates and other cholinergics, clonidine, phenothiazines, sedative–hypnotics, olanzapine
Mydriasis	Anticholinergics (e.g., antihistamines, TCAs, atropine), sympathomimetics (cocaine, amphetamines, PCP) postanoxic encephalopathy, opiate withdrawal
Nystagmus	Anticonvulsants, sedative–hypnotics, alcohols, PCP, ketamine, dextromethorphan
Lacrimation	Organophosphates, irritant gas or vapors
Retinal hyperemia	Methanol
CUTANEOUS SIGNS	
Diaphoresis	Cholinergics (organophosphates), sympathomimetics, withdrawal syndromes
Alopecia	Thallium, arsenic
Erythema	Boric acid, elemental mercury, cyanide, carbon monoxide, disulfiram, scombroid, anticholinergics, vancomycin
Cyanosis (unresponsive to oxygen)	Methemoglobinemia (e.g., benzocaine, dapsone, nitrites, phenazopyridine), amiodarone, silver
ORAL SIGNS	
Salivation	Organophosphates, salicylates, corrosives, ketamine, PCP, strychnine
Oral burns	Corrosives, oxalate-containing plants
Gum lines	Lead, mercury, arsenic, bismuth
GASTROINTESTINAL SIGNS	
Diarrhea	Antimicrobials, arsenic, iron, boric acid, cholinergics, colchicine, opioid withdrawal
Hematemesis	Arsenic, iron, caustics, NSAIDs, salicylates
Constipation	Lead
CARDIAC SIGNS	
Tachycardia	Sympathomimetics, anticholinergics, antidepressants, antipsychotics, methylxanthines (theophylline, caffeine), salicylates, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), withdrawal (ethanol, sedatives, clonidine, opioids), serotonin syndrome, neuroleptic malignant syndrome
Bradycardia	β Blockers, calcium channel blockers, digoxin, clonidine, organophosphates, opioids, sedative–hypnotics
Hypertension	Sympathomimetics, anticholinergics, monoamine oxidase inhibitors, serotonin syndrome, neuroleptic malignant syndrome, clonidine withdrawal
Hypotension	β Blockers, calcium channel blockers, cyclic antidepressants, iron, antipsychotics, barbiturates, clonidine, opioids, arsenic, amatoxin mushrooms, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), snake envenomation
RESPIRATORY SIGNS	
Depressed respirations	Opioids, sedative-hypnotics, alcohol, clonidine, barbiturates
Tachypnea	Salicylates, sympathomimetics, caffeine, metabolic acidosis, carbon monoxide, hydrocarbon aspiration
CENTRAL NERVOUS SYSTEM SIGNS	
Ataxia	Alcohols, anticonvulsants, sedative–hypnotics, lithium, dextromethorphan, carbon monoxide, inhalants
Coma	Opioids, sedative–hypnotics, anticonvulsants, antidepressants, antipsychotics, ethanol, anticholinergics, clonidine, GHB, alcohols, salicylates, barbiturates
Seizures	Sympathomimetics, anticholinergics, antidepressants (especially TCAs, bupropion, venlafaxine), cholinergics (organophosphates), isoniazid, camphor, lindane, salicylates, lead, nicotine, tramadol, water hemlock, withdrawal
Delirium/psychosis	Sympathomimetics, anticholinergics, LSD, PCP, hallucinogens, lithium, dextromethorphan, steroids, withdrawal
Peripheral neuropathy	Lead, arsenic, mercury, organophosphates

GHB, γ-hydroxybutyrate; LSD, lysergic acid diethylamide; NSAID, nonsteroidal antiinflammatory drug; PCP, phencyclidine; TCA, tricyclic antidepressant.

Chest x-ray may reveal signs of pneumonitis (e.g., hydrocarbon aspiration), noncardiogenic pulmonary edema (e.g., salicylate toxicity), or a foreign body. Abdominal x-ray is most helpful in screening for the presence of lead paint chips or other foreign bodies. It may detect a bezoar, demonstrate radiopaque tablets, or reveal drug packets in a body packer. Upper endoscopy may be useful for prognosis after significant caustic ingestions. Further diagnostic testing is based on the differential diagnosis and pattern of presentation.

PRINCIPLES OF MANAGEMENT

The principles of management of the poisoned patient are supportive care, antidotes, decontamination, and enhanced elimination. Few patients meet criteria for all of these interventions, though clinicians should consider each option in every poisoned patient so as not to miss a potentially lifesaving therapy. Antidotes are available for relatively few poisons (Table 63-7), thus emphasizing the importance of meticulous supportive care and close clinical monitoring.

Poison control center staff are specifically trained to provide expertise in the management of poisoning exposures. Parents should be instructed to call the poison control center (**1-800-222-1222**) for any concerning exposure. Poison specialists can assist parents in assessing the potential toxicity and severity of the exposure; they can further determine which children can be safely monitored at home and which children should be referred to the emergency department for further

Table 63-3 Recognizable Poison Syndromes ("Toxidromes")

TOXIDROME	SIGNS: VITAL SIGNS	MENTAL STATUS	PUPILS	SKIN	BOWEL SOUNDS	OTHER	POSSIBLE TOXINS
Sympathomimetic	Hypertension, tachycardia, hyperthermia	Agitation, psychosis, delirium, violence	Dilated	Diaphoretic	Normal to increased		Amphetamines, cocaine, PCP, bath salts (cathinones), ADHD medication
Anticholinergic	Hypertension, tachycardia, hyperthermia	Agitated, delirium, coma, seizures	Dilated	Dry, hot	Diminished	Ileus urinary retention	Antihistamines, tricyclic antidepressants, atropine, jimson weed
Cholinergic	Bradycardia BP and temp typically normal	Confusion, coma, fasciculations	Small	Diaphoretic	Hyperactive	Diarrhea, urination, bronchorrhea, bronchospasm, emesis, lacrimation, salivation	Organophosphates (insecticides, nerve agents), carbamates (physostigmine, neostigmine, pyridostigmine) Alzheimer medications, myasthenia treatments
Opioids	Respiratory depression bradycardia, hypotension, hypothermia	Depression, coma, euphoria	Pinpoint	Normal	Normal to decreased		Methadone, buprenorphine, morphine, oxycodone, heroin, etc.
Sedative–hypnotics	Respiratory depression, HR normal to decreased, BP normal to decreased, temp normal to decreased	Somnolence, coma	Small or normal	Normal	Normal		Barbiturates, benzodiazepines, ethanol
Serotonin syndrome (similar findings with neuroleptic malignant syndrome)	Hyperthermia, tachycardia, hypertension or hypotension (autonomic instability)	Agitation, confusion, coma	Dilated	Diaphoretic	Increased	Neuromuscular hyperexcitability: clonus, hyperreflexia (lower extremities > upper extremities)	SSRIs, lithium, MAOIs, linezolid, tramadol, meperidine, dextromethorphan
Salicylates	Tachypnea, hyperpnea, tachycardia, hyperthermia	Agitation, confusion, coma	Normal	Diaphoretic	Normal	Nausea, vomiting, tinnitus, ABG with primary respiratory alkalosis and primary metabolic acidosis; tinnitus or difficulty hearing	Aspirin and aspirin-containing products, methyl-salicylate
Withdrawal (sedative–hypnotic)	Tachycardia, tachypnea, hyperthermia	Agitation, tremor, seizure, hallucinosis, delirium tremens	Dilated	Diaphoretic	Increased		Lack of access to ethanol, benzodiazepines, barbiturates, GHB, or excessive use of flumazenil
Withdrawal (opioid)	Tachycardia	Restlessness, anxiety	Dilated	diaphoretic	Hyperactive	Nausea, vomiting, diarrhea	Lack of access to opioids or excessive use of naloxone

ABG, arterial blood gas; ADHD, attention-deficit/hyperactivity disorder; BP, blood pressure; GHB, γ-hydroxybutyrate; HR, heart rate; MAOI, monoamine oxidase inhibitor; PCP, phencyclidine; SSRI, selective serotonin reuptake inhibitor; temp, temperature.

Table 63-4 Mini-Toxidromes

TOXIDROMES	SYMPTOMS AND SIGNS	EXAMPLES
α_1 Antagonists	CNS depression, tachycardia, miosis	Chlorpromazine, quetiapine, clozapine, olanzapine, risperidone
α_2 Agonist	CNS depression, bradycardia, hypertension (early), hypotension (late), miosis	Clonidine, oxymetazoline, tetrahydrozoline, tizanidine
Clonus/myoclonus	CNS depression, myoclonic jerks, clonus, hyperreflexia	Carisoprodol, lithium, serotonergic agents, bismuth, organic lead, organic mercury
Sodium channel blockers	CNS toxicity, wide QRS	Cyclic antidepressants and structurally related agents, propoxyphene, quinidine/quinine, amantadine, antihistamines, bupropion, cocaine
Potassium channel blockers	CNS toxicity, long QT	Butyrophenones, methadone, phenothiazines, ziprasidone

CNS, central nervous system.
From Ruha AM, Levine M: Central nervous system toxicity. Emerg Med Clin North Am *32(1):205–221, 2014, Table 2, p. 208.*

Table 63-5 Screening Laboratory Clues in Toxicologic Diagnosis

ANION GAP METABOLIC ACIDOSIS (MNEMONIC = MUDPILES CAT) **M**ethanol, metformin **U**remia **D**iabetic ketoacidosis **P**ropylene glycol **I**soniazid, iron, massive ibuprofen **L**actic acidosis **E**thylene glycol **S**alicylates **C**ellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide) **A**lcoholic ketoacidosis **T**ylenol
ELEVATED OSMOLAR GAP Alcohols: ethanol, isopropyl, methanol, ethylene glycol
HYPOGLYCEMIA (MNEMONIC = HOBBIES) **H**ypoglycemics, oral: sulfonylureas, meglitinides **O**ther: quinine, unripe ackee fruit **B**eta **B**lockers **I**nsulin **E**thanol **S**alicylates (late)
HYPERGLYCEMIA Salicylates (early) Calcium channel blockers Caffeine
HYPOCALCEMIA Ethylene glycol Fluoride
RHABDOMYOLYSIS Neuroleptic malignant syndrome, serotonin syndrome Statins Mushrooms (*Tricholoma equestre*) Any toxin causing prolonged immobilization (e.g., opioids, antipsychotics) or excessive muscle activity or seizures (e.g., sympathomimetics)
RADIOPAQUE SUBSTANCE ON KUB (MNEMONIC = CHIPPED) **C**hloral hydrate, calcium carbonate **H**eavy metals (lead, zinc, barium, arsenic, lithium, bismuth) **I**ron **P**henothiazines **P**lay-Doh, potassium chloride **E**nteric-coated pills **D**ental amalgam, drug packets

KUB, kidney-ureter-bladder radiograph.

Table 63-6 Electrocardiographic Findings in Poisoning

PR INTERVAL PROLONGATION Digoxin Lithium
QRS PROLONGATION Tricyclic antidepressants Diphenhydramine Carbamazepine Cardiac glycosides Chloroquine, hydroxychloroquine Cocaine Lamotrigine Quinidine, quinine, procainamide, disopyramide Phenothiazines Propoxyphene Propranolol Bupropion, venlafaxine (rare)
QTc PROLONGATION* Amiodarone Antipsychotics (typical and atypical) Arsenic Cisapride Citalopram and other SSRIs Clarithromycin, erythromycin Disopyramide, dofetilide, ibutilide Fluconazole, ketoconazole, itraconazole Methadone Pentamidine Phenothiazines Sotalol

*This is a select list of important toxins, other medications are also associated with QTc prolongation.
SSRI, selective serotonin reuptake inhibitor.

evaluation and care. Ninety percent of all exposures in children younger than 6 yr of age called into poison centers are managed at home. The American Academy of Clinical Toxicology has generated consensus statements for out-of-hospital management of common ingestions (e.g., acetaminophen, iron, calcium channel blockers) that serve to guide poison center recommendations regarding whom to refer to an emergency department. Up to a third of calls to poison centers involve hospitalized patients.

SUPPORTIVE CARE

Careful attention is paid first to the "ABCs" of airway, breathing and circulation; there should be a low threshold to aggressively manage the airway of a poisoned patient because of the patient's propensity to

Table 63-7 Common Antidotes for Poisoning

POISON	ANTIDOTE	DOSAGE	ROUTE	ADVERSE EFFECTS, WARNINGS, COMMENTS
Acetaminophen	*N*-Acetylcysteine (Mucomyst)	140 mg/kg loading, followed by 70 mg/kg q4h	PO	Vomiting (patient-tailored regimens are the norm)
	N-Acetylcysteine (Acetadote)	150 mg/kg over 1 hr, followed by 50 mg/kg over 4 hr, followed by 100 mg/kg over 16 hr	IV	Anaphylactoid reactions (most commonly seen with loading dose) (Higher doses of the infusion are often recommended depending upon the acetaminophen level and the degree of injury)
Anticholinergics	Physostigmine	0.02 mg/kg over 5 min; may repeat q5-10min to 2 mg max	IV/IM	Bradycardia, seizures, bronchospasm *Note:* Do not use if conduction delays on ECG
Benzodiazepines	Flumazenil	0.2 mg over 30 sec; if response is inadequate, repeat q1min to 1 mg max	IV	Agitation, seizures; **do not use for unknown ingestions**
β Blockers	Glucagon	0.15 mg/kg bolus followed by infusion of 0.05-0.15 mg/kg/hr	IV	Hyperglycemia, vomiting
Calcium channel blockers	Insulin	1 unit/kg bolus followed by infusion of 0.5-1 unit/kg/hr	IV	Hypoglycemia Follow serum potassium and glucose closely
	Calcium salts	Dose depends on the specific calcium salt	IV	
Carbon monoxide	Oxygen	100% F_{IO_2} via non–rebreather mask (or ET if intubated)	Inhalational	Some patients may benefit from hyperbaric oxygen (see text)
Cyanide	Cyanide kit:			
	Amyl nitrate	1 crushable ampule; inhale 30 sec of each min	Inhalation	Methemoglobinemia
	Sodium nitrate	0.33 mL/kg of 3% solution if hemoglobin level is not known; otherwise, based on tables with product	IV	Methemoglobinemia Hypotension
	Sodium thiosulfate	1.6 mL/kg of 25% solution; may be repeated q30-60min to max of 50 mL	IV	If inducing methemoglobinemia is contraindicated; consider only using the thiosulfate component of the kit
	Hydroxocobalamin (Cyanokit)	70 mg/kg (adults: 5 g) given over 15 min	IV	Flushing/erythema, nausea, rash, chromaturia, hypertension, headache
Digitalis	Digoxin-specific Fab antibodies (Digibind; DigiFab)	1 vial binds 0.6 mg of digitalis glycoside; #vials = digitalis level × weight in kg/100	IV	Allergic reactions (rare), return of condition being treated with digitalis glycoside
Ethylene glycol, methanol	Fomepizole	15 mg/kg load; 10 mg/kg q12h × 4 doses; 15 mg/kg q12h until EG level is <20 mg/dL	IV	Infuse slowly over 30 min; If fomepizole is not available, can treat with oral ethanol (80 proof)
Iron	Deferoxamine	Infusion of 5-15 mg/kg/hr (max: 6 g/24 hr)	IV	Hypotension (minimized by avoiding rapid infusion rates)
Isoniazid (INH)	Pyridoxine	Empirical dosing: 70 mg/kg (max dose = 5 g) If ingested dose is known: 1 g per gram of INH	IV	May also be used for *Gyromitra* mushroom ingestions
Lead and other heavy metals (e.g., arsenic, inorganic mercury)	BAL (dimercaprol)	3-5 mg/kg/dose q4hr, for the 1st day; subsequent dosing depends on the toxin	Deep IM	Local injection site pain and sterile abscess, vomiting, fever, salivation, nephrotoxicity *Caution:* prepared in peanut oil; contraindicated in patients with peanut allergy
	Calcium disodium EDTA	35-50 mg/kg/day × 5 days; may be given as a continuous infusion or 2 divided doses/day	IV	Vomiting, fever, hypertension, arthralgias, allergic reactions, local inflammation, nephrotoxicity (maintain adequate hydration, follow UA and renal function)
	Dimercaptosuccinic acid (succimer, DMSA, Chemet)	10 mg/kg/dose q8h × 5 days, then 10 mg/kg q12h × 14 days	PO	Vomiting, hepatic transaminase elevation, rash

Continued

Table 63-7 Common Antidotes for Poisoning—cont'd

POISON	ANTIDOTE	DOSAGE	ROUTE	ADVERSE EFFECTS, WARNINGS, COMMENTS
Methemoglobinemia	Methylene blue, 1% solution	0.1-0.2 mL/kg (1-2 mg/kg) over 5-10 min; may be repeated q30-60min	IV	Vomiting, headache, dizziness, blue discoloration of urine
Opioids	Naloxone	0.01-0.1 mg/kg; adolescents/adults: 0.04-2 mg, repeated as needed; may give continuous infusion	IV	Acute withdrawal symptoms if given to addicted patients May also be useful for clonidine ingestions (inconsistent response)
Organophosphates	Atropine Pralidoxime (2-PAM)	0.05-0.1 mg/kg repeated q5-10min as needed 25-50 mg/kg over 5-10 min (max: 200 mg/min); can be repeated after 1-2 hr, then q10-12hr as needed	IV/ET IV/IM	Tachycardia, dry mouth, blurred vision, urinary retention Nausea, dizziness, headache, tachycardia, muscle rigidity, bronchospasm (rapid administration)
Salicylates	Sodium bicarbonate	Bolus 1-2 mEq/kg followed by a continuous infusion	IV	Follow potassium closely and replete as necessary Goal urine pH 7.5-8.0
Sulfonylureas	Octreotide and dextrose	1-2 μg/kg/dose (adults 50-100 μg) q6-8hr	IV/SC	
Tricyclic antidepressants	Sodium bicarbonate	Bolus 1-2 mEq/kg; repeated bolus dosing as needed to keep QRS <110 msec	IV	Indications: QRS widening (≥110 ms), hemodynamic instability; follow potassium

BAL, British antilewisite; DMSA, dimercaptosuccinic acid; ECG, electrocardiogram; FIO2, fraction of inspired oxygen; EDTA, ethylenediaminetetraacetic acid; EG, ethylene glycol; ET, endotracheal tube; max, maximum; UA, urinalysis.

quickly become comatose. In fact, endotracheal intubation is often the only significant intervention needed in many poisoned patients, especially those poisoned with neuroleptics. An important caveat is with the tachypneic patient with a clear lung exam and normal oxygen saturation. This should alert the clinician to the likelihood that the patient is compensating for an acidemia. Paralyzing such a patient and underventilating them might prove fatal. If intubation is absolutely necessary for airway protection or a tiring patient, a good rule of thumb is to match the ventilatory settings to the patient's preintubation minute ventilation.

In the hypotensive patient, it should be remembered that these patients often are not hypovolemic, but are poisoned; aggressive fluid resuscitation may lead to fluid overload. If hypotension persists after 1 or 2 standard boluses of crystalloid, infusion of a direct-acting vasopressor, such as norepinephrine or epinephrine, is preferred. Dysrhythmias are managed in the standard fashion apart from those caused by agents that block the fast sodium channels of the heart for which sodium bicarbonate therapy is utilized.

Seizures are primarily managed with agents that potentiate the γ-aminobutyric acid complex, such as benzodiazepines or barbiturates. Creatinine kinase levels should be drawn on any patient found unconscious. The goal of supportive therapy is to support the patient's vital functions until the patient can eliminate the toxin.

Antidotes

Antidotes are available for relatively few toxins (see Tables 63-7 and 63-8), but early and appropriate use of an antidote is a key element in managing the poisoned patient.

Decontamination

The majority of poisonings in children are from ingestion, although exposures can also occur via inhalational, dermal, and ocular routes. The goal of decontamination is to minimize absorption of the toxic substance. The specific method employed depends on the properties of the toxin itself and the route of exposure. Regardless of the decontamination method used, the efficacy of the intervention decreases with increasing time since exposure. *Decontamination should not be routinely employed for every poisoned patient.* Instead, careful decisions regarding the utility of decontamination should be made for each patient and should include consideration of the toxicity and pharmacologic properties of the exposure, the route of the exposure, the time since the exposure, and the risks vs the benefits of the decontamination method.

Table 63-8 Additional Antidotes

ANTIDOTES	TOXIN OR POISON
Latrodectus antivenin	Black widow spider
Botulinum antitoxin	Botulinum toxin
Insulin and glucose	Calcium channel antagonists
Diphenhydramine and/or benztropine	Dystonic reactions
Calcium salts	Fluoride, calcium channel blockers
Protamine	Heparin
Folinic acid	Methotrexate, trimethoprim, pyrimethamine
Crotalidae-specific Fab antibodies	Rattlesnake envenomation
Sodium bicarbonate	Sodium channel blockade (tricyclic antidepressants, type 1 antiarrhythmics)

Dermal and ocular decontamination begin with removal of any contaminated clothing and particulate matter, followed by flushing of the affected area with tepid water or normal saline. Treating clinicians should wear proper protective gear when performing irrigation. Flushing for a minimum of 10-20 minutes is recommended for most exposures, although some chemicals (e.g., alkaline corrosives) require much longer periods of flushing. Dermal decontamination, especially after exposure to adherent or lipophilic (e.g., organophosphates) agents, should include thorough cleansing with soap and water. Water should *not* be used for decontamination after exposure to highly reactive agents, such as elemental sodium, phosphorus, calcium oxide, and titanium tetrachloride. After an inhalational

exposure, decontamination involves moving the patient to fresh air and administering supplemental oxygen if indicated.

Gastrointestinal (GI) decontamination is a controversial topic among medical toxicologists. *GI decontamination strategies are most likely to be effective in the 1st hour after an acute ingestion*. GI absorption may be delayed after ingestion of agents that slow GI motility (anticholinergic medications, opioids), massive pill ingestions, sustained-release preparations, and ingestions of agents that can form pharmacologic bezoars (e.g., enteric-coated salicylates). GI decontamination at more than 1 hr after ingestion may be considered in patients who ingest toxic substances with these properties. Even rapid institution of GI decontamination with activated charcoal will, at best, bind only approximately 30% of the ingested substance. GI decontamination should never supplant excellent supportive care and should not be employed in an unstable or persistently vomiting patient. Described methods of GI decontamination include induced emesis with ipecac, gastric lavage, cathartics, activated charcoal, and whole-bowel irrigation (WBI). Of these, only activated charcoal and WBI are likely to be of clinical benefit.

Syrup of Ipecac

Syrup of ipecac contains 2 emetic alkaloids that work in both the central nervous system (CNS) and locally in the GI tract to produce vomiting. In the 1960s, the American Academy of Pediatrics lobbied for nonprescription availability of ipecac and in the 1980s recommended that ipecac be given to parents at the 6 mo well-child check, coupled with a discussion about poison prevention strategies. Since then, studies have failed to document a significant clinical impact from the use of ipecac and have documented multiple adverse events from its use. After a review of the evidence and assessment of the risks and benefits of ipecac use, the American Academy of Pediatrics, the American Academy of Clinical Toxicology, and the American Association of Poison Control Centers have all published statements in favor of **abandoning the use of ipecac.**

Gastric Lavage

Gastric lavage involves placing a tube into the stomach to aspirate contents, followed by flushing with aliquots of fluid, usually water or normal saline. Although gastric lavage was used routinely for many years, objective data do not document or support clinically relevant efficacy. This is particularly true in children, in whom only small-bore tubes can be used. Lavage is time-consuming and painful, and can induce bradycardia via a vagal response to tube placement. It can delay administration of more definitive treatment (activated charcoal), and under the best circumstances only removes a fraction of gastric contents. *Thus, in most clinical scenarios, the use of gastric lavage is no longer recommended.*

Single-Dose Activated Charcoal

Activated charcoal is thought to be a potentially useful method of GI decontamination, although clinical data to support this claim is limited. Charcoal is "activated" via heating to extreme temperatures, creating an extensive network of pores that provides a very large adsorptive surface area. Many, but not all, toxins are adsorbed onto its surface, thus preventing absorption from the GI tract. *Charcoal is most likely to be effective when given within 1 hr of ingestion.* Charged molecules (i.e., heavy metals, lithium, iron) and liquids do not bind well to activated charcoal (Table 63-9). Charcoal administration should also be avoided after ingestion of a caustic substance, because the presence of charcoal can impede subsequent endoscopic evaluation. A repeat dose of activated charcoal may be warranted in the cases of ingestion of an extended release product or, more commonly, with a significant salicylate poisoning as a result of its delayed and erratic absorption pattern.

The dose of activated charcoal is 1 g/kg in children or 50-100 g in adolescents and adults. Before administering charcoal, one *must* ensure that the patient's airway is intact or protected and that the patient has a benign abdominal exam. In the awake, uncooperative adolescent or child who refuses to drink the activated charcoal, there is relatively little utility and potential morbidity associated with forcing activated charcoal down a nasogastric tube, and such practice should be avoided. Approximately 20% of children vomit after receiving a dose of charcoal, emphasizing the importance of an intact airway and avoiding administration of charcoal after ingestion of substances that are particularly toxic when aspirated (e.g., hydrocarbons). If charcoal is given through a gastric tube in an intubated patient, placement of the tube should be carefully confirmed before activated charcoal is given because instillation of charcoal directly into the lungs can have disastrous effects. Constipation is another common side effect of activated charcoal, and in rare cases, bowel perforation has been reported.

In young children, practitioners may attempt to improve palatability by adding flavorings (chocolate or cherry syrup) or giving the mixture over ice cream. Cathartics (sorbitol, magnesium sulfate, magnesium citrate) have been used in conjunction with activated charcoal to prevent constipation and accelerate evacuation of the charcoal–toxin complex. There are no data demonstrating their value and there are numerous reports of adverse effects from cathartics. Cathartics should be used with care in young children and should never be used in multiple doses because of the risk of dehydration and electrolyte imbalance.

Table 63-9	Substances Poorly Adsorbed By Activated Charcoal
Alcohols	
Caustics: alkalis and acids	
Cyanide	
Heavy metals (e.g., lead)	
Hydrocarbons	
Iron	
Lithium	

Whole-Bowel Irrigation

WBI involves instilling large volumes (35 mL/kg/hr in children or 1-2 L/hr in adolescents) of a polyethylene glycol electrolyte solution (e.g., GoLYTELY) to "wash out" the entire GI tract. This technique may have some success after the ingestion of slowly absorbed substances (sustained-release preparations), substances not well adsorbed by charcoal (e.g., lithium, iron), transdermal patches, and drug packets. WBI can be combined with the use of activated charcoal, if appropriate (cocaine or heroin body packers). In children, WBI is of greatest utility in decontaminating the gut of a child whose abdominal X-ray demonstrates multiple lead paint chips. Careful attention should be paid to assessment of the airway and abdominal exam before initiating WBI, which should never be given to a patient without bowel sounds or with signs of obstruction or ileus, or without a protected airway. Given the rate of administration and volume needed to flush the system, WBI is typically administered via a nasogastric tube. WBI is continued until the rectal effluent is clear. Complications of WBI include vomiting, abdominal pain, and abdominal distention. Bezoar formation might respond to WBI but may also require endoscopy or surgery.

Enhanced Elimination

Enhancing excretion is only useful for a few toxins; in these cases, enhancing elimination is a potentially lifesaving intervention that results in improved clearance of a poison that has already been absorbed.

Urinary Alkalinization

A charged molecule, being polar and hydrophilic, does not easily cross a fat membrane. Such is the mechanism by which alkalinizing the urine enhances the elimination of some drugs that are weak acids by forming charged particles that are "trapped" within the renal tubules and thus excreted. Urinary alkalinization is accomplished via a continuous infusion of sodium bicarbonate–containing intravenous fluids, with a goal urine pH of 7.5-8. Alkalinization of the urine is most useful in managing salicylate and methotrexate toxicity.

Serum pH should be closely monitored because a serum pH of >7.55 is potentially dangerous to cellular functions. Other complications of

urinary alkalinization include electrolyte derangements, such as hypokalemia and hypocalcemia. This method of enhanced elimination is contraindicated in patients who are unable to tolerate the large volumes of fluid needed to achieve alkalinization, including patients with heart failure, kidney failure, pulmonary edema, or cerebral edema.

Hemodialysis

Few drugs or toxins are removed by dialysis in amounts sufficient to justify the risks and difficulty of dialysis. Toxins that are amenable to dialysis have the following properties: low volume of distribution (<1 L/kg), low molecular weight, low degree of protein binding, and high degree of water solubility. Examples of toxins for which dialysis may be useful include methanol, ethylene glycol, salicylates, theophylline, bromide, lithium, and, potentially, valproic acid. In addition to enhancing the elimination of the toxin itself, hemodialysis can also be useful to correct severe electrolyte disturbances and acid–base derangements resulting from the ingestion (e.g., metformin-associated lactic acidosis).

Multiple-Dose Activated Charcoal

Whereas single-dose activated charcoal is used as a method of decontamination, multiple doses of activated charcoal (MDACs) can help to enhance the elimination of some toxins. MDAC is typically given as 0.5 g/kg every 4-6 hr (for ≤24 hr) and continued until there is significant clinical improvement, including satisfactory decline of serum drug concentrations. MDACs enhance elimination via 2 proposed mechanisms: interruption of enterohepatic recirculation and "GI dialysis," which uses the intestinal mucosa as the dialysis membrane and pulls toxins from the bloodstream back into the intraluminal space, where they are adsorbed to the charcoal. The American Academy of Clinical Toxicology/European Association of Poisons Centres and Clinical Toxicologists position statement recommends MDAC in managing significant ingestions of carbamazepine, dapsone, phenobarbital, quinine, and theophylline. As with single-dose activated charcoal, contraindications to use of MDAC include an unprotected airway and a concerning abdominal exam (e.g., ileus, distention, peritoneal signs); thus the airway and abdominal exam *should be assessed before each dose.* A cathartic (e.g., sorbitol) may be given with the first dose, but it should not be used with subsequent doses owing to the risk of dehydration and electrolyte derangements. Although MDAC reduces the serum level of an intoxicant quicker than without MDAC, it has not been shown to have a significant impact on outcome.

Intralipid Emulsion Therapy

A potentially life-saving intervention of infusing Intralipid emulsions is a means of sequestering fat-soluble drugs and decreasing their impact at target organs. Initial experience regarding this intervention has been developed by anesthesiologists as a reversal agent for asystole resulting from inadvertent intravenous injection of bupivacaine. There are dozens of case reports published demonstrating the dramatic and rapid recovery of premorbid poisoned patients given a dose of Intralipid. Using the same 20% Intralipid used for total parenteral nutrition, a bolus dose of 1.5 mL/kg is given over 3 min, followed by an infusion of 0.25 mL/kg/min until recovery or a total of 10 mL/kg has been infused. Lipophilic drugs (LogP >2) are potentially bound by Intralipid emulsions, including calcium channel blockers (verapamil and diltiazem) and tricyclic antidepressants.

SELECTED COMPOUNDS COMMONLY INVOLVED IN PEDIATRIC POISONINGS

Herbal medicines (see Chapter 64), drugs of abuse (see Chapter 114), and environmental health hazards (see Chapters 718-725) are covered elsewhere.

Pharmaceuticals

Analgesics

Acetaminophen. Acetaminophen (APAP) is the most widely used analgesic and antipyretic in pediatrics, available in multiple formulations, strengths, and combinations. Consequently, APAP is commonly available in the home, where it can be unintentionally ingested by young children, taken in an intentional overdose by adolescents and adults, or inappropriately dosed in all ages. APAP toxicity remains the most common cause of acute liver failure in the United States, and is the number 1 cause of intentional poisoning death in the United States.

Pathophysiology. APAP toxicity results from the formation of a highly reactive intermediate metabolite, *N*-acetyl-*p*-benzoquinone imine. In therapeutic use, only a small percentage of a dose (approximately 5%) is metabolized by the hepatic cytochrome P450 enzyme CYP2E1 to *N*-acetyl-*p*-benzoquinone imine, which is then immediately conjugated with glutathione to form a nontoxic mercapturic acid conjugate. In overdose, glutathione stores are overwhelmed, and free *N*-acetyl-*p*-benzoquinone imine is able to combine with hepatic macromolecules to produce hepatocellular necrosis. The single acute toxic dose of APAP is generally considered to be >200 mg/kg in children and >7.5-10 g in adolescents and adults. Repeated administration of APAP at supratherapeutic doses (>90 mg/kg/day for consecutive days) can lead to hepatic injury or failure in some children, especially in the setting of fever, dehydration, poor nutrition, and other conditions that serve to reduce glutathione stores.

Any child with a history of acute ingestion of >200 mg/kg (unusual in children younger than 6 yr old) or with an acute intentional ingestion of any amount should be referred to a healthcare facility for clinical assessment and measurement of a serum APAP level.

Clinical and Laboratory Manifestations. Classically, 4 general stages of APAP toxicity have been described (Table 63-10). The initial signs are nonspecific (i.e., nausea and vomiting) and may not be present. Thus, the diagnosis of APAP toxicity cannot be based on clinical symptoms alone, but instead requires consideration of the combination of the patient's history, symptoms, and laboratory findings.

If a toxic ingestion is suspected, a serum APAP level should be measured 4 hr after the reported time of ingestion. For patients who present to medical care more than 4 hr after ingestion, a stat APAP level should be obtained. *APAP levels obtained <4 hr after ingestion, unless "nondetectable," are difficult to interpret and cannot be used to estimate the potential for toxicity.* Other important baseline labs include hepatic transaminases, renal function tests, and coagulation parameters.

Treatment. When considering the treatment of a patient poisoned or potentially poisoned with APAP, and after assessment of the ABCs, it is helpful to place the patient into one of the following 4 categories.

1. ***Prophylactic:*** By definition, these patients have a normal aspartate aminotransferase (AST). If the APAP level is known and the ingestion is within 24 hr of the level being drawn, then treatment

Table 63-10 Classic Stages in the Clinical Course of Acetaminophen Toxicity

STAGE	TIME AFTER INGESTION	CHARACTERISTICS
I	0.5-24 hr	Anorexia, vomiting, malaise Labs typically normal, except for acetaminophen level
II	24-48 hr	Resolution of earlier symptoms; right upper quadrant abdominal pain and tenderness; elevated hepatic transaminases (aspartate aminotransferase > alanine aminotransferase), INR
III	3-5 days	Peak transaminase elevations; development of liver failure, multi organ-system failure, death *or* recovery begins
IV	4 days-2 wk	Resolution of liver function abnormalities Clinical recovery precedes histologic recovery

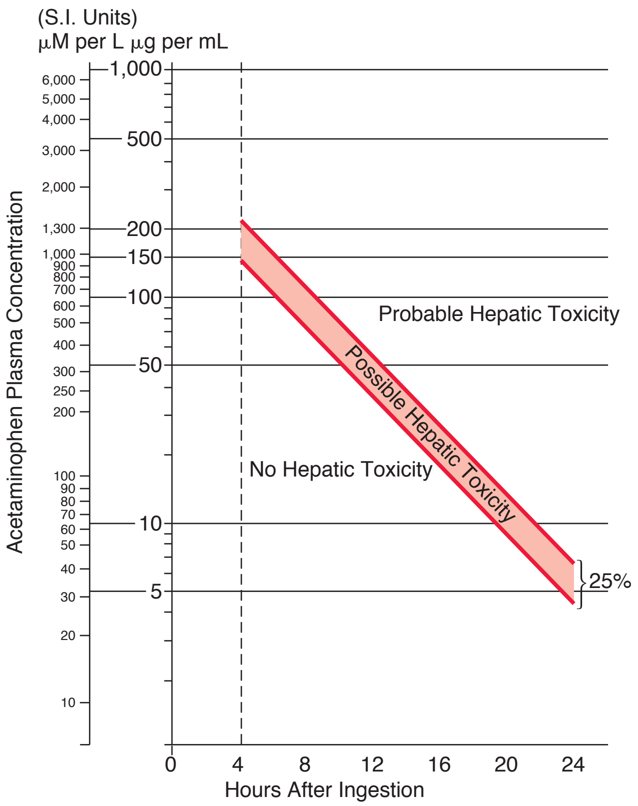

Figure 63-1 **Rumack-Matthew nomogram for acetaminophen poisoning, a semilogarithmic plot of plasma acetaminophen concentrations vs time.** Cautions for the use of this chart: The time coordinates refer to time after ingestion, serum concentrations obtained before 4 hr are not interpretable, and the graph should be used only in relation to a single acute ingestion with a known time of ingestion. This nomogram is not useful for chronic exposures or unknown time of ingestion and should be used with caution in the setting of coingestants that that slow gastrointestinal motility. The *lower solid line* is typically used in the United States to define toxicity and direct treatment, whereas the *upper line* is generally used in Europe. *(From Rumack BH, Hess AJ, editors:* Poisindex, *Denver, 1995, Micromedex. Adapted from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity,* Pediatrics *55:871–876, 1975.)*

decisions are based on where the level falls on the Rumack-Matthew nomogram (Fig. 63-1). Any patient with a serum APAP level in the possible or probable hepatotoxicity range per the nomogram should be treated with *N*-acetylcysteine (NAC). This nomogram is only intended for use in patients who present within 24 hr of a single *acute* APAP ingestion with a known time of ingestion. If treatment is recommended, they should receive either oral Mucomyst or IV Acetadote for 24 or 21 hr, respectively. Repeat AST and APAP concentration drawn toward the end of that interval should be obtained. If the AST is normal and the APAP becomes nondetectable, then treatment may be discontinued. If the AST becomes elevated, then the patient moves into the next category of treatment (injury). If APAP is still present, treatment should be continued until the level is nondetectable. In the case of a patient with a documented APAP level, normal AST, and an unknown time of ingestion, treatment should ensue until the level is nondetectable, with normal transaminases.

The importance of instituting therapy with either IV or oral NAC no later than 8 hr from the time of ingestion cannot be overemphasized. No patient, no matter the size of the ingestion, who receives NAC within 8 hr of overdose should die from liver failure. The further out from the 8 hr mark the initiation of therapy is delayed, the greater the risk of acute liver failure. Any patient presenting close to that 8 hr mark or beyond it after an APAP overdose should be empirically started on NAC pending lab results.

2. ***Hepatic Injury:*** These patients are exhibiting evidence of hepatocellular necrosis, manifested first as elevated liver transaminases (AST rises first, then the alanine aminotransferase), followed by a rise in the INR. Any patient in this category requires therapy with NAC (IV or oral). When to discontinue therapy in the clinically well patient remains controversial, but in general, the transaminases and INR have peaked and fallen significantly "toward" normal (they do not need to be normal). Most patients' liver enzymes will peak 3 or 4 days after their ingestion.
3. ***Acute Liver Failure:*** The King's College criteria are used to determine which patients should be referred for consideration of liver transplant. These criteria include acidemia (serum pH <7.3) after adequate fluid resuscitation, coagulopathy (INR >6), renal dysfunction (creatinine >3.4 mg/dL), and grade III or IV hepatic encephalopathy (see Chapter 364). A serum lactic acid >3 mmol/L (after IV fluids) adds to both the sensitivity and specificity of the criteria to predict death without liver transplant. The degree of transaminase elevation does not factor in to this decision making process.
4. ***Repeated Supratherapeutic Ingestion:*** APAP is particularly prone to unintentional overdose through the ingestion of multiple medications containing the drug or simply because people assume it to be safe at any dose. Ingestion of amounts significantly greater than the recommended daily dose for several days or more puts one at risk for liver injury. Because the Rumack-Matthew nomogram is not helpful in this scenario, a conservative approach is in order. In the asymptomatic patient, if the AST is normal and the APAP is <10 μg/mL, then no therapy is indicated. A normal AST and an elevated APAP warrants NAC dosing for at least long enough for the drug to metabolize while the AST remains normal. An elevated AST puts the patient in the "hepatic injury" category described above. A patient presenting with symptoms (i.e., right upper quadrant pain, vomiting, jaundice) should be empirically started on NAC pending lab results.

NAC is available in oral and intravenous forms, and both are equally efficacious (see Table 63-7 for the dosing regimens of the oral vs IV form). The intravenous form is used in patients with intractable vomiting, those with evidence of hepatic failure, and pregnant patients. Oral NAC has an unpleasant taste and smell, and can be mixed in soft drink or fruit juice or given via nasogastric tube to improve tolerability of the oral regimen. Administration of IV NAC (as a standard 3% solution to avoid administering excess free water, typically in 5% dextrose), especially the initial loading dose, is associated in some patients with the development of anaphylactoid reactions (non–immunoglobulin E mediated). These reactions are typically managed by stopping the infusion; treating with diphenhydramine, albuterol, and/or epinephrine as indicated; and restarting the infusion at a slower rate once symptoms have resolved. IV NAC is also associated with mild elevation in measured INR (range: 1.2-1.5). IV dosing does, however, deliver less drug to the liver compared with the oral regimen. As a result, many toxicologists now recommend higher doses of the IV formulation in patients with large overdoses.

Transaminases, synthetic function, and renal function should be followed daily while the patient is being treated with NAC. Patients with worsening hepatic function or clinical status might benefit from more frequent lab monitoring. A patient-tailored approach is the norm for when to stop NAC therapy, for deciding whom to refer for transplantation evaluation, and often for the dose of IV NAC in patients with either very high APAP levels or signs of significant injury. Consultation with the regional poison center and medical toxicologist can help streamline the care of these patients, ultimately shortening their length of stay with potentially improved outcomes.

Salicylates. The incidence of salicylate poisoning in young children has declined dramatically since APAP and ibuprofen replaced aspirin as the most commonly used analgesics and antipyretics in

pediatrics. However, salicylates remain widely available, not only in aspirin-containing products but also in antidiarrheal medications, topical agents (e.g., keratolytics, sports creams), oil of wintergreen, and some herbal products. Oil of wintergreen contains 5 g of salicylate in 1 teaspoon (5 mL), meaning ingestion of very small volumes of this product has the potential to cause severe toxicity.

Pathophysiology. Salicylates lead to toxicity by interacting with a wide array of physiologic processes, including direct stimulation of the respiratory center, uncoupling of oxidative phosphorylation, inhibition of the tricarboxylic acid cycle, and stimulation of glycolysis and gluconeogenesis. The acute toxic dose of salicylates is generally considered to be >150 mg/kg. More significant toxicity is seen after ingestions of >300 mg/kg, and severe, potentially fatal, toxicity is described after ingestions of >500 mg/kg.

Clinical and Laboratory Manifestations. Salicylate ingestions are classified as acute or chronic, and acute toxicity is far more common in pediatric patients. Early signs of acute salicylism include nausea, vomiting, diaphoresis, and tinnitus. Moderate salicylate toxicity can manifest as tachypnea and hyperpnea, tachycardia, and altered mental status. The tachycardia results in large part from marked insensible losses from vomiting, tachypnea, diaphoresis, and uncoupling of oxidative phosphorylation. Thus, careful attention should be paid to volume status and early volume resuscitation in the significantly poisoned patient. Signs of severe salicylate toxicity include hyperthermia, coma, and seizures. Chronic salicylism can have a more insidious presentation, and patients can show marked toxicity at significantly lower salicylate levels than in acute toxicity.

Classically, lab values from a patient poisoned with salicylates reveal a primary respiratory alkalosis and a primary, elevated anion gap, metabolic acidosis. Early in the course of acute salicylism, respiratory alkalosis dominates. As the respiratory stimulation diminishes, the patient will move toward the metabolic acidosis. Hyperglycemia (early) and hypoglycemia (late) have been described. Abnormal coagulation studies and acute kidney injury may be seen but are not common.

Serial serum salicylate levels should be closely monitored (every 2-3 hr initially) until they are consistently down trending. Salicylate absorption in overdose is often unpredictable and erratic, especially with an enteric coated product, and levels can rapidly increase into the highly toxic range, even many hours after the ingestion. The Done nomogram is of poor value and should not be used. Serum and urine pH and electrolytes should be followed closely. An APAP level should be checked in any patient who intentionally overdoses on salicylates, because APAP is a common coingestant and because people often confuse or combine their nonprescription analgesic medications. Salicylate toxicity can cause a noncardiogenic pulmonary edema, especially in chronic overdose; consequently, a chest x-ray is recommended in any patient in respiratory distress.

Treatment. For the patient who presents soon after an acute ingestion, initial treatment should include gastric decontamination with activated charcoal. Salicylate pills occasionally form concretions called bezoars, which should be suspected if serum salicylate concentrations continue to rise many hours after ingestion or are persistently elevated in spite of appropriate management. Gastric decontamination is typically not useful after chronic exposure.

Initial therapy focuses on aggressive volume resuscitation and prompt initiation of sodium bicarbonate therapy in the symptomatic patient, even before obtaining serum salicylate levels. Therapeutic salicylate levels are 10-20 mg/dL, and levels >30 mg/dL warrant treatment.

The primary mode of therapy for salicylate toxicity is **urinary alkalinization**. Urinary alkalinization enhances the elimination of salicylates by converting salicylate to its ionized form, "trapping" it in the renal tubules, and thus enhancing elimination. In addition, maintaining an alkalemic serum pH decreases CNS penetration of salicylates because charged particles are less able to cross the blood–brain barrier. Alkalinization is achieved by administration of a sodium bicarbonate infusion at approximately 2 times maintenance fluid rates. *The goals of therapy include a urine pH of 7.5-8, a serum pH of 7.45-7.55, and decreasing serum salicylate levels.* In general, in the presence of an acidosis, an aspirin-poisoned patient's status can be directly related to the patient's serum pH. The lower the pH, the greater the relative amount of salicylate in the uncharged/nonpolar form and the greater the penetration of the blood–brain barrier by the drug. Careful attention should also be paid to serial potassium levels, because hypokalemia impairs alkalinization of the urine; potassium is often added to the bicarbonate drip. Repeat doses of charcoal may be beneficial because of the often delayed and erratic absorption of aspirin. Parenteral glucose should be provided to any salicylate poisoned patients with altered mental status as they may have CNS hypoglycemia not noted in a peripheral serum glucose test.

In cases of severe toxicity, hemodialysis may be required. Indications for dialysis include severe acid–base abnormalities (specifically severe acidosis and acidemia), a rising salicylate level despite adequate decontamination and properly alkalinized urine, pulmonary edema, cerebral edema, seizures, and renal failure. Serum salicylate concentrations should always be interpreted along with the clinical status of the patient; on their own they are not a clear indicator of the need for dialysis.

Ibuprofen and Other Nonsteroidal Antiinflammatory Drugs. Ibuprofen and other nonsteroidal antiinflammatory drugs (NSAIDs) are often involved in unintentional and intentional overdoses owing to their widespread availability and common use as analgesics and antipyretics. Fortunately, serious effects after NSAID overdose are rare owing to their wide therapeutic index.

Pathophysiology. NSAIDs inhibit prostaglandin synthesis by reversibly inhibiting the activity of cyclooxygenase (COX), the primary enzyme responsible for the biosynthesis of prostaglandins. In therapeutic use, side effects include GI irritation, reduced renal blood flow, and platelet dysfunction. In an attempt to minimize these side effects, NSAID analogs have been developed that are more specific for the inducible form of COX (the COX-2 isoform) than the constitutive form, COX-1. However, overdose of the more selective COX-2 inhibitors (e.g., celecoxib [Celebrex]) is treated the same as overdose of nonspecific COX inhibitors (e.g., ibuprofen) because at higher doses, COX-2–selective agents lose their COX inhibitory selectivity.

Ibuprofen, the primary NSAID used in pediatrics, is well tolerated, even in overdose. In children, acute doses of <200 mg/kg rarely cause toxicity, but ingestions of >400 mg/kg can produce more serious effects, including altered mental status and metabolic acidosis.

Clinical and Laboratory Manifestations. Symptoms usually develop within 4-6 hr of ingestion and resolve within 24 hr. If toxicity does develop, it is typically manifested as nausea, vomiting, and abdominal pain. Although GI bleeding and ulcers have been described with chronic use, they are rare in the setting of acute ingestion. After massive ingestions, patients can develop marked CNS depression, anion gap metabolic acidosis, renal insufficiency, and (rarely) respiratory depression. Seizures have also been described, especially after overdose of mefenamic acid. Specific drug levels are not readily available nor do they inform management decisions. Renal function studies, acid–base balance, complete blood count, and coagulation parameters should be monitored after very large ingestions. Coingestants, especially APAP, should be ruled out after any intentional ingestion.

Treatment. Supportive care, including use of antiemetics and acid blockade as indicated, is the primary therapy for NSAID toxicity. Decontamination with activated charcoal should be considered if a patient presents within 1-2 hr of a potentially toxic ingestion. There is no specific antidote for this class of drugs. Given the high degree of protein binding and excretion pattern of NSAIDs, none of the modalities used to enhance elimination are particularly useful in managing these overdoses. Unlike in patients with salicylate toxicity, urinary alkalinization is not helpful for NSAID toxicity. Patients who develop significant clinical signs of toxicity should be admitted to the hospital for ongoing supportive care and monitoring. Patients who remain asymptomatic for 4-6 hr after ingestion may be considered medically cleared.

Oral Opioids. Opioids are a commonly abused class of medications (see Chapter 114), both in their IV and oral forms. Two specific

oral opioids, buprenorphine and methadone, merit particular mention because of potential life-threatening toxicity in toddlers with ingestion of even 1 pill. Both agents are used in managing opioid dependence, although buprenorphine is the drug of choice. Methadone is also widely used in the treatment of chronic pain, meaning multiday prescriptions can be filled. Both drugs are readily available for illicit purchase and potential abuse. Both drugs are of great potential toxicity to a toddler, especially buprenorphine, owing to its long half-life and high potency.

Pathophysiology. Methadone is a lipophilic synthetic opioid with potent agonist effects at μ-opioid receptors, leading to both its desired analgesic effects and undesired side effects, including sedation, respiratory depression, and impaired GI motility. Methadone is thought to cause QTc interval prolongation via interactions with the human ether-a-go-go–related gene (hERG)-encoded potassium rectifier channel. Methadone has an average half-life of >25 hr, which may be extended to >50 hr in overdose.

Suboxone is a combination of buprenorphine, a potent opioid with partial agonism at μ-opioid receptors and weak antagonism at κ-opioid receptors, and naloxone. Naloxone has poor oral bioavailability but is included in the formulation to discourage diversion for intravenous use, during which it can precipitate withdrawal. Suboxone is formulated for buccal or sublingual administration; consequently, toddlers can absorb significant amounts of drug even by sucking on a tablet. Buprenorphine has an average half-life of 37 hr.

Clinical and Laboratory Manifestations. In children, methadone and buprenorphine ingestions can manifest with the classic opioid toxidrome of respiratory depression, sedation, and miosis. Signs of more-severe toxicity can include bradycardia, hypotension, and hypothermia. Even in therapeutic use, methadone is associated with a prolonged QTc interval and risk of torsades de pointes. Accordingly, an ECG should be part of the initial evaluation after ingestion of methadone or any unknown opioid. Neither drug is detected on routine urine opiate screens, although some centers have added a separate urine methadone screen. Levels of both drugs can be measured, although this is rarely done clinically and is seldom helpful in the acute setting. An exception may be in the cases involving concerns about neglect or abuse, at which point urine for gas chromatography/mass spectroscopy, the legal gold standard, should be sent to confirm and document the presence of the drug.

Treatment. Patients with significant respiratory depression or CNS depression should be treated with the opioid antidote, naloxone (see Table 63-7). In pediatric patients who are not chronically on opioids, the full reversal dose of 0.1 mg/kg (max: 2 mg/dose) should be used. In contrast, opioid-dependent patients should be treated with smaller initial doses (0.01 mg/kg), which can then be repeated as needed to achieve the desired clinical response, hopefully avoiding abrupt induction of withdrawal. Because the half-lives of methadone and buprenorphine are far longer than that of naloxone, patients can require multiple doses of naloxone. These patients may benefit from a continuous infusion of naloxone, typically started at two-thirds of the reversal dose/hr and titrated to maintain an adequate respiratory rate and level of consciousness. Patients who have ingested methadone should be placed on a cardiac monitor and have serial ECGs to monitor for the development of a prolonged QTc interval. If a patient does develop a prolonged QTc, management includes close cardiac monitoring, repletion of electrolytes (potassium, calcium, and magnesium), and having magnesium and a defibrillator readily available should the patient develop torsades de pointes.

Given the potential for clinically significant and prolonged toxicity, any toddler who has ingested methadone, even if asymptomatic, should be admitted to the hospital for at least 24 hr of monitoring. Some experts advocate a similar approach to management of buprenorphine ingestions, even in the asymptomatic patient. As we gain more experience with pediatric buprenorphine exposures, some patients who remain absolutely asymptomatic for 6-8 hr after ingestion and *have a stable social setting* may be candidates for earlier discharge. In the meantime, these cases should be discussed with a poison control center or medical toxicologist before determining disposition.

Cardiovascular Medications

β-Adrenergic Receptor Blockers. β Blockers competitively inhibit the action of catecholamines at the β receptor. Therapeutically, β blockers are used for a variety of conditions, including hypertension, coronary artery disease, tachydysrhythmias, anxiety disorders, migraines, essential tremor, and hyperthyroidism. Because of its lipophilicity and blockade of fast sodium channels, propranolol is considered to be the most toxic member of the β-blocker class. Overdoses of water-soluble β blockers (e.g., atenolol) are associated with milder symptoms.

Pathophysiology. In overdose, β blockers decrease chronotropy and inotropy in addition to slowing conduction through atrioventricular nodal tissue. Clinically, these effects are manifested as bradycardia, hypotension, and heart block. Patients with reactive airways disease can experience bronchospasm as a result of blockade of β_2-mediated bronchodilation. β_2 Blockers interfere with glycogenolysis and gluconeogenesis, which can sometimes lead to hypoglycemia, especially in patients with poor glycogen stores (e.g., toddlers).

Clinical and Laboratory Manifestations. Toxicity typically develops within 6 hr of ingestion, although it may be delayed after ingestion of sotalol or sustained-release preparations. The most common features of severe poisoning are bradycardia and hypotension. Lipophilic agents, including propranolol, can enter the CNS and cause altered mental status, coma, and seizures. Overdose of β blockers with membrane-stabilizing properties (e.g., propranolol) can cause QRS interval widening and ventricular dysrhythmias.

Evaluation after β-blocker overdose should include an ECG, frequent reassessments of hemodynamic status, and blood glucose. Serum levels of β blockers are not readily available for routine clinical use and are not useful in management of the poisoned patient.

Treatment. In addition to supportive care and GI decontamination as indicated, glucagon is the antidote of choice for β-blocker toxicity (see Table 63-7). Glucagon stimulates adenyl cyclase and increases levels of cyclic adenosine monophosphate independent of the β receptor. Glucagon is typically given as a bolus and, if this is effective, followed by a continuous infusion. In practice, however, glucagon is often only marginally effective, limited by its proemetic effects, especially at the doses typically required. Other potentially useful interventions include calcium, vasopressors, and high-dose insulin. Seizures are managed with benzodiazepines, and QRS widening should be treated with sodium bicarbonate. Children who ingest 1 or 2 water-soluble β blockers are unlikely to develop toxicity and can typically be discharged to home if they remain asymptomatic over a 6-hr observation period. Children who ingest sustained-release products, highly lipid-soluble agents, and sotalol can require longer periods of observation before safe discharge. Any symptomatic child should be admitted for ongoing monitoring and directed therapy.

Calcium Channel Blockers. Calcium channel blockers (CCBs) are used for a variety of therapeutic indications and have the potential to cause severe toxicity, even after exploratory ingestions. Specific agents include verapamil, diltiazem, and the dihydropyridines (e.g., amlodipine, nifedipine). Of these, diltiazem and verapamil are the most dangerous in overdose.

Pathophysiology. CCBs antagonize L-type calcium channels, inhibiting calcium influx into myocardial and vascular smooth muscle cells. Verapamil works primarily by slowing inotropy and chronotropy, and has no effect on systemic vascular resistance (SVR). Diltiazem has effects both on the heart and the peripheral vasculature. The dihydropyridines exclusively diminish SVR. Verapamil and diltiazem can significantly diminish myocardial contractility and conduction, with diltiazem also lowering SVR. By contrast, dihydropyridines will drop the SVR, leading to vasodilation and reflex tachycardia (though this receptor selectivity may be lost after a large overdose). Because the same L-type calcium channels blocked by CCBs are also on the pancreatic islet cells, it is the norm for any patient significantly poisoned with a CCB to be hyperglycemic.

Clinical and Laboratory Manifestations. The onset of symptoms typically is soon after ingestion, although it may be delayed with ingestions of sustained-release products. Overdoses of CCBs lead

to hypotension, accompanied by bradycardia, normal heart rate, or even tachycardia, depending on the agent. One unique characteristic of CCB overdose is that patients can exhibit profound hypotension with preserved consciousness.

Initial evaluation should include an ECG, continuous and careful hemodynamic monitoring, and rapid measurement of serum glucose levels. Both the absolute degree of hyperglycemia and the percentage increase in serum glucose have been correlated with the severity of CCB toxicity in adults. The development of hyperglycemia can even precede the development of hemodynamic instability. Blood levels of CCBs are not readily available and are not useful in guiding therapy.

Treatment. Once initial supportive care has been instituted, GI decontamination should begin with activated charcoal as appropriate. WBI may be beneficial in a stable patient after ingestion of a sustained-release product. Calcium channel blockade in the smooth muscles of the GI tract can lead to greatly diminished motility; thus, any form of GI decontamination should be undertaken with careful attention to serial abdominal exams.

Calcium salts, administered either through a peripheral IV as calcium gluconate, or via a central line as calcium chloride, help to overcome blocked calcium channels. *High-dose insulin euglycemia therapy is considered the antidote of choice for CCB toxicity.* An initial bolus of 1 unit/kg of regular insulin is followed by an infusion at 0.5-1 unit/kg/hr (see Table 63-6). The main mechanism of high-dose insulin euglycemia is to improve the metabolic efficiency of a poisoned heart that is in need of carbohydrates for energy (instead of the usual free fatty acids), but has minimal circulating insulin. Blood glucose levels should be closely monitored, and supplemental glucose may be given to maintain euglycemia, although this is rarely necessary in the severely poisoned patient. Additional therapies include judicious IV fluid boluses and vasopressors (often in very high doses). Cardiac pacing is rarely of value. Lipid emulsion therapy (discussed earlier), is a potentially life-saving intervention especially for patients poisoned with the more lipid soluble CCBs, verapamil and diltiazem. In extreme cases, an intraaortic balloon pump or extracorporeal membrane oxygenation are potential rescue devices. Given the potential for profound and sometimes delayed toxicity in toddlers after ingestion of 1 or 2 CCB tablets, hospital admission and 24 hr of monitoring for all of these patients is strongly recommended.

Clonidine. Although originally intended for use as an antihypertensive, clonidine prescriptions in the pediatric population have increased markedly, owing to its reported efficacy in the management of attention-deficit/hyperactivity disorder, tic disorders, and other behavioral disorders. With this increased use has come a significant increase in pediatric ingestions and therapeutic misadventures. Clonidine is available in pill and transdermal patch forms.

Pathophysiology. Clonidine, along with the closely related agent guanfacine, is a centrally acting α_2-agonist with a very narrow therapeutic index. Agonism at central α_2 receptors decreases sympathetic outflow, producing lethargy, bradycardia, hypotension, and apnea. Toxicity can develop after ingestion of as little as 1 pill or after sucking on or swallowing a discarded transdermal patch. Even a "used" transdermal patch might contain as much as one-third to one-half of the original amount of drug.

Clinical and Laboratory Manifestations. The most common clinical manifestations of clonidine toxicity include lethargy, miosis, and bradycardia. Hypotension, respiratory depression, and apnea may be seen in severe cases. Very early after ingestion, patients may be hypertensive in the setting of agonism at peripheral α receptors and resulting vasoconstriction. Symptoms develop relatively soon after ingestion and typically resolve within 24 hr. Serum clonidine concentrations are not readily available and are of no clinical value in the acute setting. Though signs of clinical toxicity are common after clonidine overdose, death from clonidine alone is extremely unusual.

Treatment. Given the potential for significant toxicity, most young children warrant referral to a healthcare facility for evaluation after unintentional ingestions of clonidine. Gastric decontamination is usually of little value, owing to the small quantities ingested and the rapid onset of serious symptoms. Aggressive supportive care is imperative and is the cornerstone of management. Naloxone, often in high doses, has shown variable efficacy in treating clonidine toxicity. Other potentially useful therapies include atropine, IV fluid boluses, and vasopressors. Symptomatic children should be admitted to the hospital for close cardiovascular and neurologic monitoring. It should also be noted, that in a patient chronically on clonidine or guanfacine, rapid discontinuation of the drug, or even missing 1 or 2 doses, could lead to potentially dangerous elevations in blood pressure.

Digoxin. Digoxin is a cardiac glycoside extracted from the leaves of *Digitalis lanata*. Other natural sources of cardiac glycosides include *Digitalis purpura* (foxglove), *Nerium oleander* (oleander), *Convallaria majalis* (lily of the valley), Siberian ginseng, and the *Bufo marinus* toad. Therapeutically, digoxin is used in the management of heart failure and some supraventricular tachydysrhythmias. Acute overdose can occur in the setting of dosing errors (especially in younger children), unintentional or intentional medication ingestion, or exposure to plant material containing digitalis glycosides. Regarding exposure to such plants, toxicity is unusual unless the poison is concentrated in the form of a tea. Chronic toxicity can result from alteration of the digoxin dose, alteration in digoxin clearance as a result of renal impairment, or drug interactions.

Pathophysiology. Digoxin blocks the Na^+, K^+-ATPase (adenosine triphosphatase) pump, leading to intracellular loss of K^+ and gain of Na^+ and Ca^{2+}. This resulting rise in Ca^{2+} available to the contractile myocardium improves inotropy. An increase in myocardial automaticity leads to subsequent atrial, nodal, and ventricular ectopy. Digoxin also affects nodal conduction, leading to a prolonged refractory period, decreased sinus node firing, and slowed conduction through the atrioventricular node. Impaired Na-K exchange results in dangerously high levels of serum potassium. Overall, digoxin overdose manifests as a combination of slowed or blocked conduction and increased ectopy.

Clinical and Laboratory Manifestations. Nausea and vomiting are common initial symptoms of acute digoxin toxicity, manifesting within 6 hr of overdose. Cardiovascular manifestations include bradycardia, heart block, and a wide variety of dysrhythmias. CNS manifestations consist of lethargy, confusion, and weakness. Chronic toxicity is more insidious and manifests with GI symptoms, altered mental status, and visual disturbances.

Initial assessment should include an ECG, serum digoxin level, serum potassium, and kidney function tests. The serum digoxin level should be assessed at least 6 hr after ingestion and carefully interpreted in the setting of clinical symptoms because the digoxin level alone does not entirely reflect the severity of intoxication. In acute ingestions, serum potassium is an independent marker of morbidity and mortality, with levels >5.5 mEq/L predicting poor outcomes. In chronic toxicity, serum potassium is less useful as a prognostic marker and may be altered due to concomitant use of diuretics.

Digoxin has a very narrow therapeutic index. Therapeutic plasma digoxin concentrations are 0.5-2.0 ng/mL; a level >2 ng/mL is considered toxic and a level >6 ng/mL is considered potentially fatal (in chronic poisonings). Numerous drug interactions affect plasma digoxin concentrations. Medications known to increase serum digoxin concentrations include the macrolides, erythromycin and clarithromycin, spironolactone, verapamil, amiodarone, and itraconazole.

Treatment. Initial treatment includes good general supportive care and gastric decontamination with activated charcoal if the ingestion was recent. An antidote for digoxin, digoxin-specific Fab antibody fragments (Digibind or DigiFab) is available (see Table 63-7). Fab fragments bind free digoxin in both the intravascular and the interstitial spaces to form a pharmacologically inactive complex that is subsequently renally eliminated. Indications for Fab fragments include life-threatening dysrhythmias, K^+ value >5-5.5 mEq/L, serum digoxin level >15 ng/mL at any time or >10 ng/mL 6 hr after ingestion, ingestion >4 mg in children or >10 mg in adults, clinically significant hypotension or other cardiovascular instability, altered mental status, and renal failure. Atropine is potentially useful in managing symptomatic bradycardia. Although dogma states that patients on digoxin with severe hyperkalemia and QRS widening on the ECG should not receive calcium salts, this has not been supported in the literature. Once

stabilized, consultation with a cardiologist is recommended in the management of patients chronically on digoxin, because administration of Fab fragments can lead to recurrence of the patient's underlying dysrhythmias or dysfunction.

Iron. Historically, iron was a common cause of childhood poisoning deaths. However, preventive measures such as childproof packaging have significantly decreased the rates of serious iron toxicity in young children. Iron-containing products remain widely available, with the most potentially toxic being adult iron preparations and prenatal vitamins. The severity of an exposure is related to the amount of *elemental iron* ingested. Ferrous sulfate contains 20% elemental iron, ferrous gluconate 12%, and ferrous fumarate 33%. Multivitamin preparations and children's vitamins rarely contain enough elemental iron to cause significant toxicity.

Pathophysiology. Iron is directly corrosive to the GI mucosa, leading to hematemesis, melena, ulceration, infarction, and potential perforation. Early iron-induced hypotension is caused by massive volume losses, increased permeability of capillary membranes, and venodilation mediated by free iron. Iron accumulates in tissues, including the Kupffer cells of the liver and myocardial cells, leading to hepatotoxicity, coagulopathy, and cardiac dysfunction. Metabolic acidosis develops in the setting of hypotension, hypovolemia, and iron's direct interference with oxidative phosphorylation and the Krebs cycle. Pediatric patients who ingest >40 mg/kg of elemental iron should be referred to medical care for evaluation, although moderate to severe toxicity is typically seen with ingestions of >60 mg/kg.

Clinical and Laboratory Manifestations. Iron toxicity is classically described in 4, often overlapping, stages. The initial stage, 30 min to 6 hr after ingestion, consists of profuse vomiting and diarrhea (often bloody), abdominal pain, and significant volume losses leading to potential hypovolemic shock. Patients who do not develop GI symptoms within 6 hr of ingestion are unlikely to develop serious toxicity. The 2nd stage, 6-24 hr after ingestion, is often referred to as the "quiescent phase," as GI symptoms typically have resolved. However, careful clinical exam can reveal subtle signs of hypoperfusion, including tachycardia, pallor, and fatigue. During the 3rd stage, occurring 12-36 hr after ingestion, patients develop multisystem organ failure, shock, hepatic and cardiac dysfunction, acute lung injury or acute respiratory distress syndrome (ARDS), and profound metabolic acidosis. Death occurs most commonly during this stage. In patients who survive, the 4th stage (4-6 wk after ingestion) is marked by formation of strictures and signs of GI obstruction.

Symptomatic patients and patients with a large exposure by history should have serum iron levels drawn 4-6 hr after ingestion. Serum iron concentrations of <500 µg/dL 4-8 hr after ingestion suggest a low risk of significant toxicity, whereas concentrations of >500 µg/dL indicate that significant toxicity is likely. Additional lab evaluation in the ill patient should include arterial blood gas, complete blood count, serum glucose level, liver function tests, and coagulation parameters. Careful attention should be paid to ongoing monitoring of the patient's hemodynamic status. An abdominal x-ray might reveal the presence of iron tablets, though not all formulations of iron are radiopaque.

Treatment. Close clinical monitoring, combined with aggressive supportive and symptomatic care, is essential to the management of iron poisoning. Activated charcoal does not adsorb iron, and WBI remains the decontamination strategy of choice. Deferoxamine, a specific chelator of iron, is the antidote for moderate to severe iron intoxication (see Table 63-7). Indications for deferoxamine treatment include a serum iron concentration of >500 µg/dL or moderate to severe symptoms of toxicity, regardless of serum iron concentration. Deferoxamine is preferably given via continuous IV infusion at a rate of 15 mg/kg/hr. Hypotension is a common side effect of deferoxamine infusion and is managed by slowing the rate of the infusion and administering fluids and/or vasopressors as needed. Prolonged deferoxamine infusion (>24 hr) has been associated with pulmonary toxicity (ARDS) and *Yersinia* sepsis. The deferoxamine–iron complex can color the urine reddish ("vin rosé"), although this is an unreliable indicator of iron excretion. Clear end points for deferoxamine chelation are not well defined, but therapy is typically continued until clinical symptoms resolve. Consultation with a poison control center or medical toxicologist can yield guidelines for discontinuing deferoxamine.

Oral Hypoglycemics

Oral medications used in the management of type 2 diabetes include sulfonylureas, biguanides (e.g., metformin), thiazolidinediones, and meglitinides. Of these, only the sulfonylureas and meglitinides have the potential to cause profound hypoglycemia in both diabetic and nondiabetic patients. These classes of medications are widely prescribed and thus readily available for both unintentional and intentional exposures. In toddlers, ingestion of a single sulfonylurea tablet can lead to significant toxicity.

Pathophysiology. Sulfonylureas work primarily by enhancing endogenous insulin secretion. In binding to the sulfonylurea receptor, these drugs induce closure of potassium channels, leading to membrane depolarization, opening of calcium channels, and stimulation of calcium-mediated insulin release. Even in therapeutic use, the duration of hypoglycemic action can last up to 24 hr.

Clinical and Laboratory Manifestations. Hypoglycemia and symptoms associated with hypoglycemia are the primary clinical manifestations of sulfonylurea toxicity. These signs and symptoms can include diaphoresis, tachycardia, lethargy, irritability, coma, seizures, and even focal neurologic findings. As with other hyperinsulinemic states, sulfonylurea overdoses are associated with a nonketotic hypoglycemia. In the majority of cases, hypoglycemia develops within 6 hr of ingestion but can be delayed up to 16-18 hr after ingestion. Toddlers are particularly susceptible to hypoglycemia during an overnight fast.

Treatment. Patients with symptomatic hypoglycemia should be promptly treated with dextrose. In patients with mild symptoms, oral dextrose may be sufficient. However, patients with severe symptoms or profound hypoglycemia should be treated with a bolus of IV dextrose. Continuous dextrose infusions and repeated IV dextrose boluses should be avoided if possible, because this can stimulate further insulin release and lead to recurrent and prolonged hypoglycemia. Instead, the preferred antidote for symptomatic sulfonylurea toxicity is octreotide (see Table 63-7). Octreotide is a somatostatin analog that works via inhibiting insulin release. Octreotide is given IV or SC, typically in doses of 1-2 µg/kg (50-100 µg in adults) every 6-8 hr.

Given the potential for significant hypoglycemia, toddlers with witnessed or suspected sulfonylurea ingestions should be admitted to the hospital for monitoring and serial glucose measurements, at least for 12 hr, including an overnight fast. Patients of any age who develop hypoglycemia are also candidates for admission given the prolonged duration of hypoglycemic activity. Prophylactic IV dextrose infusions are not recommended because they can mask the symptoms of toxicity and stimulate further insulin secretion. Patients who require IV dextrose and/or octreotide should be monitored until they can demonstrate euglycemia for at least 8 hr off of all therapy.

With the increasing numbers of adolescents with type 2 diabetes, pediatricians should be familiar with the toxic effects of metformin as well. Although this agent does not cause hypoglycemia, its association with lactic acidosis is well documented (Metformin Associated Lactic Acidosis–MALA). This state typically arises after a large overdose in which the agent interferes with the liver's ability to clear lactic acid. Dangerously high serum lactate levels can result, leading to hemodynamic instability. Hemodialysis is usually the best option for patients with severe metformin-associated lactic acidosis.

Psychiatric Medications: Antidepressants

Selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline, paroxetine, citalopram) are the most commonly prescribed class of antidepressants. This trend results in large part from their wide therapeutic index and more favorable side-effect profile when compared to older agents such as tricyclic antidepressants (TCAs; amitriptyline, clomipramine, desipramine, doxepin, nortriptyline, imipramine) and monoamine oxidase inhibitors. Newer agents include the serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine) and other atypical antidepressants (e.g., bupropion).

Tricyclic Antidepressants. Although TCAs are now prescribed less commonly for depression, they remain in use for a variety of other conditions, including chronic pain syndromes, enuresis, attention-deficit/hyperactivity disorder, and obsessive compulsive disorder. TCAs can cause significant toxicity in children, even with ingestion of 1 or 2 pills (10-20 mg/kg).

Pathophysiology. TCAs achieve their desired antidepressant effects primarily via blockade of norepinephrine and serotonin reuptake. TCAs have complex interactions with other receptor types. Antagonism at muscarinic acetylcholine receptors leads to clinical features of the anticholinergic toxidrome. Antagonism at peripheral α-receptors leads to hypotension and syncope. Key to the toxicity of TCAs is their ability to block fast sodium channels, leading to impaired cardiac conduction and arrhythmias.

Clinical and Laboratory Manifestations. Cardiovascular and CNS symptoms dominate the clinical presentation of TCA toxicity. Symptoms typically develop within 1-2 hr of ingestion, and serious toxicity usually manifests within 6 hr of ingestion. Patients can have an extremely rapid progression from mild symptoms to life-threatening dysrhythmias. Patients often develop features of the anticholinergic toxidrome, including delirium, mydriasis, dry mucous membranes, tachycardia, hyperthermia, urinary retention, and slow GI motility. CNS toxicity can include lethargy, coma, myoclonic jerks, and seizures. Sinus tachycardia is the most common cardiovascular manifestation of toxicity; however, patients can develop widening of the QRS complex, premature ventricular contractions, and ventricular arrhythmias. Refractory hypotension is a poor prognostic indicator and is the most common cause of death in TCA overdose.

An ECG is a readily available bedside test that can help determine the diagnosis and prognosis of the TCA-poisoned patient (Fig. 63-2). A QRS duration of >100 msec identifies patients who are at risk for seizures and cardiac arrhythmias. An R wave in lead aVR of ≥3 mm is also an independent predictor of toxicity. Both of these ECG parameters are superior to measured serum TCA concentrations in identifying patients at risk for serious toxicity, and obtaining levels is rarely helpful in management of the acutely ill patient.

Treatment. Initial attention should be directed to supporting vital functions, including airway and ventilation support as needed. Gastric decontamination can be accomplished with activated charcoal in appropriate patients. Treating clinicians should obtain an ECG as soon as possible and follow serial ECGs to monitor for progression of toxicity.

Four primary effects seen at the bedside, along with their treatment recommendations, are listed here:

1. ***Altered mental status:*** TCA-poisoned patients can become deeply comatose relatively quickly, so careful and prompt attention to the airway and placement of an endotracheal tube is of paramount importance. The airway should be secured prior to any GI decontamination efforts.
2. ***Widened QRS on the ECG:*** TCAs (along with other agents such as diphenhydramine, cocaine, etc) will block the fast sodium channels on the myocardial cells, slowing the upstroke of the QRS complex. Because the effect on sodium channels is greatest within the 1st 6 hr, frequent ECGs (i.e., every 20-30 min) during this time frame are important. As the QRS approaches 160 msec, the chance of the patient developing monomorphic ventricular tachycardia rises to 30%. Sodium, usually in the form of sodium bicarbonate, is the antidote of choice. *Indications for sodium bicarbonate include a QRS duration ≥110 msec, ventricular dysrhythmias, and hypotension.* Multiple bolus doses of sodium bicarbonate, 1-2 mEq/kg each, may be needed to narrow the QRS to <110 msec. Some authors prefer to then place the patient on an infusion of sodium bicarbonate, but this may not be necessary if careful attention is paid to the QRS after the initial doses and repeat bolus dosing is provided as needed during those 1st 6-12 hr. Hypertonic (3%) saline and/or lipid emulsion therapy may be beneficial in refractory cases.
3. ***Hypotension:*** A direct acting vasopressor, such as norepinephrine or epinephrine, is the agent of choice. Boluses of intravenous crystalloid fluids should be used with caution to prevent fluid overload.
4. ***Seizures:*** Likely a result of the anticholinergic effects of TCAs, seizures are relatively common, typically brief, and should be treated with agents the work on the γ-aminobutyric acid receptor complex in the brain. Benzodiazepines are the agent of choice.

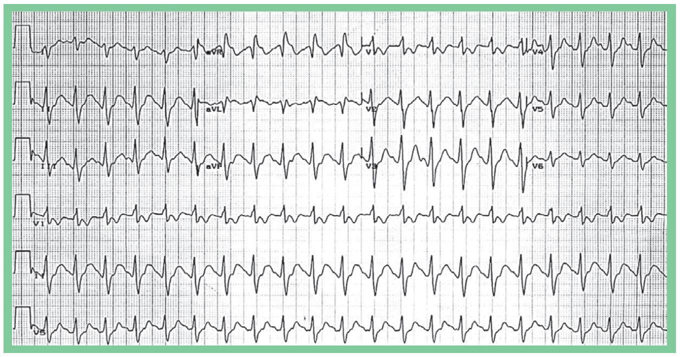

Figure 63-2 Electrocardiographic findings in tricyclic antidepressant toxicity. Note the tachycardia, widened QRS interval (144 msec), and prominent R wave in lead aVR. These findings are consistent with blockade of fast sodium channels.

Asymptomatic children should receive appropriate decontamination and be observed with continuous cardiac monitoring and serial ECGs for at least 6 hr. If any manifestations of toxicity develop, the child should be admitted to a monitored setting. Children who remain completely asymptomatic with normal serial ECGs may be candidates for discharge after 6 hr of close observation.

Selective Serotonin Reuptake Inhibitors. In overdose, SSRIs are considerably less toxic than TCAs. SSRIs are unlikely to cause significant toxicity in exploratory ingestions. Some data suggest that initiating SSRI therapy is associated with an increased risk of suicidal ideation and behavior (see Chapter 21).

Pathophysiology. SSRIs selectively block the reuptake of serotonin in the CNS. In contrast to TCAs and atypical antidepressants, SSRIs do not directly interact with other receptor types.

Clinical and Laboratory Manifestations. In overdose, the principal manifestations of toxicity are sedation and tachycardia. Cardiac conduction abnormalities (primarily QTc prolongation) and seizures have been described in significant overdoses, especially after ingestions of citalopram. An ECG should be part of the initial assessment after SSRI ingestion. Serum creatine kinase levels are almost always elevated in a patient with clinically significant serotonin syndrome.

Although development of the **serotonin syndrome** is seen more often after therapeutic use or overdose of several serotonergic agents in combination, it has also been described in ingestions of SSRIs alone (Table 63-11). Clinically, serotonin syndrome describes a spectrum of altered mental status, autonomic instability, fever, and neuromuscular hyperactivity (hyperreflexia, tremors, clonus in the lower extremities more than the upper extremities). One or all of these signs may be present to varying degrees.

Treatment. Initial management includes a careful assessment for signs and symptoms of serotonin syndrome and an ECG. Most patients simply require supportive care and observation until their mental status improves and tachycardia, if present, resolves. Management of serotonin syndrome is directed by the severity of symptoms; possible therapeutic interventions include benzodiazepines in mild cases and intubation, sedation, and paralysis in patients with severe manifestations (e.g., significant hyperthermia). Because agonism at the 5-HT_{2A} serotonin receptor is thought to be primarily responsible for the development of serotonin syndrome, use of the $5HT_{2A}$ receptor antagonist cyproheptadine is also beneficial. Cyproheptadine is only available in an oral form.

Atypical Antidepressants. The class known as atypical antidepressants includes agents such as venlafaxine and duloxetine (serotonin and norepinephrine reuptake inhibitors), bupropion (dopamine, norepinephrine, and some serotonin reuptake blockade), and

Table 63-11 Drugs Associated with the Serotonin Syndrome

DRUG TYPE	DRUGS
Selective serotonin reuptake inhibitors	Sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram
Antidepressant drugs	Trazodone, nefazodone, buspirone, clomipramine, venlafaxine
Monoamine oxidase inhibitors	Phenelzine, moclobemide, clorgyline, isocarboxazid
Anticonvulsants	Valproate
Analgesics	Meperidine, fentanyl, tramadol, pentazocine
Antiemetic agents	Ondansetron, granisetron, metoclopramide
Antimigraine drugs	Sumatriptan
Bariatric medications	Sibutramine
Antibiotics	Linezolid (a monoamine oxidase inhibitor), ritonavir (through inhibition of cytochrome P450 enzyme isoform 3A4)
Nonprescription cough and cold remedies	Dextromethorphan
Drugs of abuse	Methylenedioxymethamphetamine (MDMA, or "ecstasy"), lysergic acid diethylamide (LSD), 5-methoxydiisopropyltryptamine ("foxy methoxy"), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)
Dietary supplements and herbal products	Tryptophan, *Hypericum perforatum* (St. John's wort), *Panax ginseng* (ginseng)
Other	Lithium

From Boyer EW, Shannon M: The serotonin syndrome, N Engl J Med *352:1112–1120, 2005.*

trazodone (serotonin reuptake blockade and peripheral α-receptor antagonism). The variable receptor affinities of these agents lead to some distinctions in their clinical manifestations and management.

Clinical and Laboratory Manifestations. In overdose, venlafaxine and other serotonin and norepinephrine reuptake inhibitors are associated with cardiac conduction defects, including QRS and QTc prolongation, and seizures. Bupropion is one of the most common etiologies of toxicant-induced seizures in the United States. After ingestion of sustained or extended-release preparations, seizures can occur as late as 18-20 hr after ingestion. In addition, bupropion can cause tachycardia, agitation, and QRS and QTc prolongation. The structure of bupropion contains an amphetamine moiety, which can cause a false-positive result on the urine amphetamine screen. In addition to sedation and signs of serotonin excess, trazodone overdose may be associated with hypotension from blockade of peripheral α-receptors.

Treatment. Management is directed to clinical signs and symptoms. QRS interval prolongation may be treated with IV sodium bicarbonate as described in detail earlier. Seizures are often brief and self-limited, but they can be treated with benzodiazepines if necessary. Trazodone-associated hypotension typically responds to fluids, though it can require vasopressors in extreme cases. Because of the potential for delayed seizures, patients who ingest a sustained-release preparation of bupropion should be admitted to a monitored setting for at least 20-24 hr of observation.

Monoamine Oxidase Inhibitors. Monoamine oxidase inhibitors are now rarely used therapeutically; however, they remain important agents to know about given their potential for serious and delayed toxicity. Ingestions of as little as 1 or 2 pills (6 mg/kg) are associated with toxicity in children. Clinical manifestations initially include hypertension, hyperthermia, tachycardia, muscle rigidity, and seizures followed up to 24 hr later by hemodynamic instability and cardiovascular collapse. *Any child who ingests a monoamine oxidase inhibitor should be admitted to a monitored setting for at least 24 hr, regardless of symptoms.* Management includes blood pressure control, cooling and benzodiazepines for hyperthermia, serial monitoring of creatine kinase and renal function, and fluid and vasopressor therapy for hemodynamic instability.

Psychiatric Medications: Antipsychotics

Clinicians are increasingly prescribing antipsychotic medications in the pediatric population. Antipsychotic medications are commonly classified as either typical or atypical. In general, typical agents are associated with more side effects and toxicity than the atypical agents.

Pathophysiology. Typical or traditional antipsychotics (i.e., haloperidol, droperidol, thioridazine, chlorpromazine, and fluphenazine) are characterized by their antagonism at D_2 dopamine receptors. In therapeutic use, these agents are associated with extrapyramidal symptoms, tardive dyskinesia, and development of the neuroleptic malignant syndrome (NMS). The atypical agents (i.e., aripiprazole, clozapine, quetiapine, risperidone, ziprasidone) were developed with less dopamine (D_2-receptor) antagonism in efforts to avoid these side effects and improve their efficacy in managing the "negative" symptoms of schizophrenia. Instead, these agents have complex and varied interactions with multiple receptor types, including α-receptors, serotonin receptors, muscarinic acetylcholine receptors, and histamine receptors.

Clinical and Laboratory Manifestations. Typical antipsychotic toxicity commonly includes sedation, tachycardia, and prolongation of the QTc interval. Patients can present with acute dystonia, akathisia, and NMS, although these are seen less commonly in acute overdoses than in therapeutic use. The phenothiazines (e.g., thioridazine) can cause widening of the QRS interval owing to blockade of fast sodium channels. Clinically, NMS can be difficult to distinguish from serotonin syndrome.

Although the presentation of atypical antipsychotic toxicity can vary based on the receptor affinities of the specific agent, sedation, tachycardia, and QTc prolongation are common. Peripheral α-receptor blockade (e.g., with quetiapine) is associated with hypotension. In therapeutic use, clozapine is associated with agranulocytosis.

Diagnostic testing should include an ECG. Patients with hyperthermia or muscle rigidity should have a serum creatine kinase level sent to monitor for possible rhabdomyolysis. Antipsychotic levels are not readily available and are not helpful in managing acute poisoning.

Management. Initial management involves assessing and supporting vital functions. In some patients, CNS depression may be so profound as to require intubation for airway control. Acute dystonia is treated with diphenhydramine, benztropine, and sometimes benzodiazepines. Management of NMS includes conscientious supportive care, IV fluids, cooling, benzodiazepines, and bromocriptine or dantrolene in severe cases. QTc prolongation is managed with repletion of electrolytes (especially calcium, magnesium, and potassium), continuous cardiac monitoring, overdrive pacing, IV magnesium sulfate and/or defibrillation if the patient develops torsades de pointes. Seizures typically are well controlled with benzodiazepines. Hypotension usually responds to boluses of IV fluids, though vasopressor therapy is necessary in some cases.

Household Products

Caustics

Caustics include acids and alkalis as well as a few common oxidizing agents (see Chapter 327). Strong acids and alkalis can produce severe injury even in small-volume ingestions.

Pathophysiology. Alkalis produce a liquefaction necrosis, allowing further tissue penetration of the toxin and setting the stage for possible perforation. Acids produce a coagulative necrosis, which limits further tissue penetration, though perforation can still occur. The severity of the corrosive injury depends on the pH and

concentration of the product as well as the length of contact time with the product. Agents with a pH of <2 or >12 are most likely to produce significant injury.

Clinical Manifestations. Ingestion of caustic materials can produce injury to the oral mucosa, esophagus, and stomach. Patients can have significant esophageal injury even in the absence of visible oral burns. Symptoms include pain, drooling, vomiting, abdominal pain, and difficulty swallowing or refusal to swallow. Laryngeal injury can manifest as stridor and respiratory distress, necessitating intubation. In the most severe cases, patients can present in shock after perforation of a hollow viscus. Circumferential burns of the esophagus are likely to cause strictures when they heal, which can require repeated dilation or surgical correction and long-term follow-up for neoplastic changes in adulthood (see Chapter 327.2). Caustics on the skin or in the eye can cause significant tissue damage.

Treatment. Initial treatment of caustic exposures includes thorough removal of the product from the skin or eye by flushing with water. Emesis and lavage are contraindicated. Activated charcoal should not be used because it does not bind these agents and can predispose the patient to vomiting and subsequent aspiration. Stridor or other signs of respiratory distress should alert the provider to the need for a thorough evaluation of the airway for potential intubation or surgical airway management. Endoscopy can be performed within 12-24 hr of ingestion for prognostic and diagnostic purposes in symptomatic patients or those in whom injury is suspected on the basis of history and known characteristics of the ingested product. Endoscopy is contraindicated in any patient with signs of peritonitis. The use of corticosteroids or prophylactic antibiotics is not beneficial.

Cholinesterase-Inhibiting Insecticides

The most commonly used insecticides are organophosphates and carbamates; both are inhibitors of cholinesterase enzymes (acetylcholinesterase, pseudocholinesterase, and erythrocyte acetylcholinesterase). Most pediatric poisonings occur as the result of unintentional exposure to insecticides in and around the home or farm. The class of chemical warfare weapons known as "nerve agents" are also organophosphate compounds with a similar mechanism of action, but much greater potency.

Pathophysiology. Organophosphates and carbamates produce toxicity by binding to and inhibiting acetylcholinesterase, preventing the degradation of acetylcholine and resulting in its accumulation at nerve synapses. If left untreated, organophosphates form an irreversible bond to acetylcholinesterase, permanently inactivating the enzyme. This process, called *aging*, occurs over a variable time period depending on the characteristics of the specific organophosphate. Afterwards, a period of weeks to months is required to regenerate inactivated enzymes. In contrast, carbamates form a temporary bond to the enzymes, typically allowing reactivation of acetylcholinesterase within 24 hr.

Clinical and Laboratory Manifestations. Clinical manifestations of organophosphate and carbamate toxicity relate to the accumulation of acetylcholine at peripheral nicotinic and muscarinic synapses and in the CNS. Symptoms of carbamate toxicity are usually less severe than those seen with organophosphates. A commonly used mnemonic for the symptoms of cholinergic excess at muscarinic receptors is ***DUMBBELS***, which stands for *d*iarrhea/defecation, *u*rination, *m*iosis, *b*ronchorrhea/*b*ronchospasm, *b*radycardia, *e*mesis, *l*acrimation, and *s*alivation. Nicotinic signs and symptoms include muscle weakness, fasciculation, tremors, hypoventilation (diaphragm weakness), hypertension, tachycardia, and dysrhythmias. Severe manifestations include coma, seizures, shock, arrhythmias, and respiratory failure.

Diagnosis of poisoning is based primarily on history and physical exam findings. Red blood cell cholinesterase and pseudocholinesterase activity levels can be measured in the laboratory. These are only helpful when compared to the patient's known baseline. As such, these assessments are typically limited to farm workers undergoing ongoing occupational surveillance.

Treatment. Basic decontamination should be performed, including washing all exposed skin with soap and water and immediately removing all exposed clothing. Activated charcoal is unlikely to be of benefit as these are liquids that are rapidly absorbed. Basic supportive care should be provided, including fluid and electrolyte replacement and intubation and ventilation if necessary. The use of succinylcholine for rapid sequence intubation should be avoided as this paralytic is metabolized by the same cholinesterase enzymes now poisoned, leading to prolonged paralysis.

Two antidotes are useful in treating cholinesterase inhibitor poisoning: atropine and pralidoxime (see Table 63-7). Atropine, which antagonizes the muscarinic acetylcholine receptor, is useful for both organophosphate and carbamate intoxication. Often, large doses of atropine must be administered by intermittent bolus or via continuous infusion to control symptoms. Atropine dosing is primarily targeted to drying the respiratory secretions. Pralidoxime breaks the bond between the organophosphate and the enzyme, reactivating acetylcholinesterase. Pralidoxime is only effective if it is used before the bond ages and becomes permanent. Pralidoxime is not necessary for carbamate poisonings because the bond between the insecticide and the enzyme degrades spontaneously.

Without treatment, symptoms of organophosphate poisoning can persist for weeks, requiring continuous supportive care. Even with treatment, some patients develop a delayed polyneuropathy and a range of chronic neuropsychiatric symptoms.

Hydrocarbons

Hydrocarbons include a wide array of chemical substances found in thousands of commercial products. Specific characteristics of each product determine whether exposure will produce systemic toxicity, local toxicity, both, or neither. Nevertheless, aspiration of even small amounts of certain hydrocarbons can lead to serious, potentially life-threatening toxicity.

Pathophysiology. The most important manifestation of hydrocarbon toxicity is aspiration pneumonitis via inactivation of the type II pneumocytes and resulting surfactant deficiency (see Chapter 397). Aspiration usually occurs during coughing and gagging at the time of ingestion or vomiting after the attempted ingestion of an aliphatic hydrocarbon. The propensity of a hydrocarbon to cause aspiration pneumonitis is inversely proportional to its viscosity, and directly proportional to its volatility. Compounds with low viscosity and high volatility, such as mineral spirits, naphtha, kerosene, gasoline, and lamp oil, spread rapidly across surfaces and cover large areas of the lungs when aspirated. Only small quantities (<1 mL) of such chemicals need be aspirated to produce significant injury. Pneumonitis does not result from dermal absorption of hydrocarbons or from ingestion in the absence of aspiration. Gasoline and kerosene are poorly absorbed, but they often cause considerable irritation of the GI mucosa as they pass through the intestines.

Certain hydrocarbons have unique toxicities and can cause symptoms after ingestion, inhalation, or dermal exposures. Several chlorinated solvents, most notably carbon tetrachloride, can produce hepatic toxicity. Methylene chloride, found in some paint removers, is metabolized to carbon monoxide. Benzene is known to cause cancer, most commonly acute myelogenous leukemia, after long-term exposure. Nitrobenzene, aniline, and related compounds can produce methemoglobinemia. A number of volatile hydrocarbons, including toluene, propellants, refrigerants, and volatile nitrites, are commonly abused by inhalation. Some of these substances, principally the halogenated hydrocarbons (which contain a chlorine, bromine, or fluorine), can sensitize the myocardium to the effects of endogenous catecholamines. This can result in dysrhythmias and "sudden sniffing death." Chronic abuse of these agents can lead to cerebral atrophy, neuropsychologic changes, peripheral neuropathy, and kidney disease (see Chapter 114).

Clinical and Laboratory Manifestations. Transient, mild CNS depression is common after hydrocarbon ingestion or inhalation. Aspiration is characterized by coughing, which usually is the first clinical finding. Chest radiographs may initially be normal, but they often show abnormalities within 6 hr of exposure in patients who have aspirated. Respiratory symptoms can remain mild or progress rapidly to ARDS and respiratory failure. Fever and leukocytosis are common accompanying signs in patients with pneumonitis and don't necessarily

imply bacterial superinfection. Chest radiographs can remain abnormal long after the patient is clinically normal. Pneumatoceles can appear on the chest radiograph 2-3 wk after exposure.

After inhalational exposures to halogenated hydrocarbons, patients can present with ventricular dysrhythmias, often refractory to conventional management. Recurrent inhalation of the aromatic hydrocarbon toluene can lead to a type IV renal tubular acidosis.

Treatment. Emesis and lavage are contraindicated given the risk of aspiration. Activated charcoal is not useful because it does not bind the common hydrocarbons and can also induce vomiting. If hydrocarbon-induced pneumonitis develops, respiratory treatment is supportive (see Chapter 397). Neither corticosteroids nor prophylactic antibiotics have shown any clear benefit. Standard mechanical ventilation, high-frequency ventilation, and extracorporeal membrane oxygenation have all been used to manage the respiratory failure and ARDS associated with severe hydrocarbon-induced pneumonitis.

Patients with dysrhythmias in the setting of halogenated hydrocarbon inhalation should be treated with β blockers (usually esmolol) to block the effects of endogenous catecholamines on the sensitized myocardium.

Toxic Alcohols

Methanol is commonly found in windshield washer fluids, deicers, paint removers, fuel additives, liquid fuel canisters, and industrial solvents. *Ethylene glycol* is commonly found in antifreeze. Unintentional ingestion is the most common exposure in children, and small-volume ingestions of concentrated products can theoretically cause toxicity. The pathophysiology, acid–base derangements, and treatment of both chemicals are similar, although they differ in their primary end-organ toxicity. In both cases, the metabolites of the parent compounds are responsible for the serious clinical effects that can follow exposure.

Isopropyl alcohol (rubbing alcohol, hand sanitizers) causes intoxication similar to that associated with ethanol but can also cause a hemorrhagic gastritis and myocardial depression in massive ingestions. Unlike ethylene glycol and methanol, isopropyl alcohol is metabolized to a ketone and does not cause a metabolic acidosis. Management is similar to that of ethanol ingestions (see Chapter 114) and is not further discussed here.

Methanol.

Pathophysiology. Methanol is oxidized in the liver by alcohol dehydrogenase to formaldehyde, which is further oxidized to formic acid by aldehyde dehydrogenase. Toxicity is caused primarily by formic acid, which inhibits mitochondrial respiration.

Clinical and Laboratory Manifestations. Drowsiness, mild inebriation, nausea, and vomiting develop early after ingestion. The onset of serious effects, including profound metabolic acidosis and visual disturbances, is often delayed for up to 12-24 hr as the parent methanol is undergoing metabolism to its toxic metabolites. This metabolism is further slowed if ethanol has also been ingested, since the liver will preferentially metabolize ethanol. Visual disturbances include blurred or cloudy vision, constricted visual fields, decreased acuity, and the "feeling of being in a snowstorm" appear only after acidosis is well established. These visual defects may be reversible if treated early, but untreated they can lead to permanent blindness. On exam, dilated pupils, retinal edema, and optic disc hyperemia may be noted. Initially, patients have an elevated osmolar gap and then develop an anion gap metabolic acidosis as the parent compound is metabolized to formic acid.

In young children, determining if a significant exposure has occurred is usually difficult based on history. Methanol blood levels are available at some laboratories and should be sent after a concerning exposure. If methanol blood levels are not readily available, estimation of an osmolar gap may be used as a surrogate marker, but a normal osmolar gap does not rule out ingestion of any alcohol. Serum osmolality is measured by the freezing point depression method and compared with a calculated serum osmolarity.

Treatment. Treatment is as discussed for ethylene glycol toxicity.

Ethylene Glycol.

Pathophysiology. Ethylene glycol is oxidized by alcohol dehydrogenase in the liver to glycoaldehyde, which is further converted to glycolic acid by aldehyde dehydrogenase. Glycolic acid is responsible for the metabolic acidosis, and is further metabolized to glyoxylic and then to oxalic acid. Oxalic acid combines with serum and tissue calcium, forming calcium oxalate crystals that deposit throughout the body, especially in the renal parenchyma, leading to acute tubular necrosis.

Clinical and Laboratory Manifestations. Early symptoms include nausea, vomiting, CNS depression, and inebriation. Delayed manifestations include an anion gap metabolic acidosis, hypocalcemia, and acute kidney injury. Even later, patients can develop cranial nerve palsies.

Both ethylene glycol and methanol are capable of producing profound, life threatening metabolic acidosis and acidemia, with measured serum bicarbonates that may even be nondetectable. The onset of the acidosis is delayed up to 4-12 hr after ethylene glycol ingestion, and may be delayed further with any concomitant ingestion of ethanol. Ethylene glycol blood concentrations are technically difficult to perform and are available only at some larger reference laboratories. In the absence of readily available ethylene glycol concentrations, calculation of the osmolar gap may be helpful as a surrogate marker.

Examination of the urine with a Wood lamp is neither sensitive nor specific for ethylene glycol ingestion. The earliest sign on a urinalysis of ethylene glycol poisoning is usually hematuria. Calcium oxalate crystals can be seen on urine microscopy but might not be evident early after exposure. Electrolytes (including calcium), acid–base status, kidney function, and ECG should be closely monitored in poisoned patients.

Treatment. Because methanol and ethylene glycol are rapidly absorbed, gastric decontamination is generally not of value. The classic antidote for methanol and ethylene glycol poisoning was ethanol, a preferential substrate for alcohol dehydrogenase, thus preventing the metabolism of parent compounds to toxic metabolites. *Fomepizole* (see Table 63-7), a potent competitive inhibitor of alcohol dehydrogenase, has almost entirely replaced the use of ethanol owing to its ease of administration, lack of CNS and metabolic effects, and overall excellent patient tolerability profile. As with all poisons, a serum concentration must be interpreted along with the time removed from exposure. A patient with a methanol level of 20 mg/dL 24 hr after exposure had a much larger dose than a patient with the same level only 1 hr after ingestion. Indications for fomepizole include ethylene glycol or methanol level >20 mg/dL, history of potentially toxic ingestion (e.g., any intentional overdose), or history of ingestion with evidence of acidosis. There are few disadvantages to giving the initial dose of fomepizole to patients with a concerning history of ingestion or lab findings, and given the dosing schedule of fomepizole (every 12 hr), this strategy buys the clinician time to confirm or exclude the diagnosis before giving a second dose. Adjunctive therapy includes folate (methanol toxicity), pyridoxine (ethylene glycol toxicity) and sodium bicarbonate infusions for both (if acidemic). If a child has had an unintentional exposure and a level of the alcohol cannot be obtained, a reasonable approach is to follow serum chemistries every 4 hr until the child is 12 hr removed from the exposure. If the bicarbonate level on the chemistry panel does not fall in that time frame, then a toxic exposure is unlikely (assuming no ethanol is present).

Hemodialysis effectively removes ethylene glycol, methanol, and their metabolites (except calcium oxalate) and corrects acid–base and electrolyte disturbances. Fomepizole should be given both before and immediately after dialysis. Indications for dialysis include a methanol level of >50 mg/dL, acidosis, severe electrolyte disturbances, and renal failure. However, in the absence of acidosis and kidney failure, even massive ethylene glycol ingestions have been managed without dialysis. Methanol is another story, because its elimination in the setting of alcohol dehydrogenase inhibition is very prolonged, thus often warranting dialysis to remove the parent compound. Therapy (fomepizole and/or dialysis) should be continued until ethylene glycol and methanol levels are <20 mg/dL. While the visual effects from

methanol poisoning are usually permanent, the kidney injury from ethylene glycol injury is not. Patients requiring hemodialysis after ethylene glycol poisoning will almost always recover complete renal function within 2-6 wk. Consultation with a poison control center, medical toxicologist, and nephrologist may be helpful in managing toxic alcohol ingestions.

Plants

Exposure to plants, both inside the home and outside in backyards and fields, is one of the most common causes of unintentional poisoning in children. Fortunately, the majority of ingestions of plant parts (leaves, seeds, flowers) result in either no toxicity or mild, self-limiting effects. However, ingestion of certain plants (Table 63-12 outlines some of the most toxic plants) can lead to serious toxicity.

The potential toxicity of a particular plant is highly variable, depending on the part of the plant involved (flowers are generally less toxic than the root or seed), the time of year, growing conditions, and the route of exposure. Assessment of the potential severity after an exposure is also complicated by the difficulty in properly identifying the plant. Many plants are known by several common names, which can vary among communities. Poison control centers have access to professionals who can assist in properly identifying plants. They also are well versed in the common poisonous plants in their service area and the seasons when they are more abundant. For these reasons, consultation with the local poison control center may be very helpful in the management of these ingestions.

For potentially toxic plant ingestions, consider decontamination with activated charcoal in patients who present within 1-2 hr of ingestion; otherwise, treatment is primarily supportive and based on symptoms. The most common manifestation of toxicity after plant ingestion is GI upset, which can be managed with antiemetics and fluid and electrolyte support. Table 63-12 outlines management strategies for a few specific toxicities.

Toxic Gases

Carbon Monoxide

Although many industrial and naturally occurring gases pose a health risk by inhalation, the most common gas involved in pediatric exposures is carbon monoxide (CO). CO is a colorless, odorless gas produced during the combustion of any carbon-containing fuel. The less efficient the combustion, the greater the amount of CO produced. Wood-burning stoves, kerosene heaters, old furnaces or hot water heaters and automobiles are a few of the potential sources of CO, as is any closed space fire.

Pathophysiology. CO binds to hemoglobin with an affinity >200 times that of oxygen, forming carboxyhemoglobin (HbCO). In doing so, CO displaces oxygen and creates a conformational change in hemoglobin that impairs the delivery of oxygen to the tissues, leading to tissue hypoxia. HbCO levels are not well correlated with clinical signs of toxicity, likely because CO interacts with multiple proteins in addition to hemoglobin. CO binds to cytochrome oxidase, disrupting cellular respiration. CO displaces nitric oxide (NO) from proteins, allowing NO to bind with free radicals to form the toxic metabolite peroxynitrite. NO is also a potent vasodilator, in part responsible for clinical symptoms including headache, syncope, and hypotension.

Clinical and Laboratory Manifestations. Early symptoms are nonspecific and include headache, malaise, nausea, and vomiting. These symptoms are often misdiagnosed as indicating flu or food poisoning. At higher exposure levels, patients can develop mental status changes, confusion, ataxia, syncope, tachycardia, and tachypnea. Severe poisoning is manifested by coma, seizures, myocardial ischemia, acidosis, cardiovascular collapse, and potentially death. On exam, patients might have cherry-red skin. Emergency department evaluation should include an arterial or venous blood gas with HbCO determined by co-oximetry, and creatine kinase in severely poisoned patients, and an ECG in any patient with cardiac symptoms.

Treatment. In addition to general supportive care, treatment requires the administration of 100% oxygen to enhance elimination of CO. In ambient air, the average half-life of HbCO is 4-6 hr. This is dramatically reduced to 60-90 min by providing 100% oxygen at normal atmospheric pressures via a non-rebreather facemask. Severely poisoned patients might benefit from *hyperbaric oxygen (HBO),* which decreases the half-life of HbCO to 20-30 minutes. Though the clinical benefits and referral guidelines for HBO therapy remain controversial, commonly cited indications include syncope, coma, seizure, altered mental status, acute coronary syndrome, HbCO level >25%, abnormal cerebellar examination, and pregnancy. Consultation with a poison control center, medical toxicologist, or HBO facility can assist clinicians in determining which patients could benefit from HBO therapy. Sequelae of CO poisoning include persistent and delayed cognitive and cerebellar effects. HBO advocates believe that the risk of such sequelae is minimized through the delivery of 100% oxygen at 3 atmospheres of pressure. Patients are typically treated with oxygen, via either non-rebreather or a hyperbaric chamber, for between 6 and 24 hr. Prevention of CO poisoning should involve educational initiatives and the use of home CO detectors.

Hydrogen Cyanide

Pathophysiology. Cyanide inhibits cytochrome oxidase, part of the electron transport chain, interrupting cellular respiration and leading to profound tissue hypoxia. Patients may be exposed to hydrogen cyanide gas in the workplace (manufacturing of synthetic fibers, nitriles, and plastics) or via smoke inhalation in a fire.

Clinical and Laboratory Manifestations. Onset of symptoms is rapid after a significant exposure. Clinical manifestations of toxicity include headache, agitation and confusion, sudden loss of consciousness, tachycardia, cardiac dysrhythmias, and metabolic acidosis. Cyanide levels can be measured in whole blood, but they are not readily available at most institutions. A severe lactic acidosis (lactate >10 mmol/L) in fire victims suggests cyanide toxicity. Impaired oxygen extraction by tissues is implied by elevated mixed venous oxygen saturation, another laboratory finding suggesting cyanide toxicity.

Treatment. Treatment includes removal from the source of exposure, rapid administration of high concentrations of oxygen, and antidotal therapy. The cyanide antidote kit includes nitrites (amyl nitrite and sodium nitrite) used to produce methemoglobin, which then reacts with cyanide to form cyanomethemoglobin (see Table 63-7). The third part of the kit is sodium thiosulfate, given to hasten the metabolism of cyanomethemoglobin to hemoglobin and the less-toxic thiocyanate. In patients for whom induction of methemoglobinemia could produce more risk than benefit, the sodium thiosulfate component of the kit may be given alone. The FDA has approved *hydroxocobalamin* (a form of vitamin B_{12}) for use in known or suspected cyanide poisoning. This antidote reacts with cyanide to form the nontoxic cyanocobalamin, which is then excreted in urine. Side effects of hydroxocobalamin include red discoloration of the skin and urine, transient hypertension, and interference with colorimetric lab assays. *Overall, the safety profile of hydroxocobalamin appears superior to that of the cyanide antidote kit; thus this is now the preferred antidote for cyanide poisoning.*

Some Miscellaneous Toxic Agents Found in the Home

Single-Use Detergent Sacs

Commonly known as laundry "pods" for clothing, these products look like candy to many children. When bitten into, a relatively large dose of concentrated detergent is expelled under pressure onto the child's posterior pharynx and vocal cords. This can lead to stridor and other signs of respiratory distress. Occasionally, and for unknown reasons, these children may also develop altered mental status. Supportive care with attention to any airway and breathing issues is warranted. Admission to the hospital is often indicated. It should be noted, that these are not considered caustic ingestions. The pH of these products is in the neutral zone. As such, upper GI endoscopy is rarely indicated. Curiously, laundry detergent drank from a bottle is rarely of significant concern.

Table 63-12 Commonly Ingested Plants with Significant Toxic Potential

PLANT	SYMPTOMS	MANAGEMENT
Autumn crocus (*Colchicum autumnale*)	Vomiting Diarrhea Initial leukocytosis followed by bone marrow failure Multisystem organ failure	Activated charcoal decontamination Aggressive fluid resuscitation and supportive care
Belladonna alkaloids: jimson weed (*Datura stramonium*) Belladonna ("deadly nightshade"; *Atropa belladonna*)	Anticholinergic toxidrome Seizures	Supportive care, benzodiazepines Consider physostigmine if patient is a threat to self or others; only use if no conduction delays on ECG
Cardiac glycoside–containing plants (foxglove, lily of the valley, oleander, yellow oleander, etc)	Nausea Vomiting Bradycardia Dysrhythmias (AV block, ventricular ectopy) Hyperkalemia	Digoxin-specific Fab fragments
Jequirity bean and other abrin-containing species (e.g., rosary pea, precatory bean)	Oral pain Vomiting Diarrhea Shock Hemolysis Renal failure	Supportive care, including aggressive volume resuscitation and correction of electrolyte abnormalities
Monkshood (*Aconitum* species)	Numbness and tingling of lips/tongue Vomiting Bradycardia	Atropine for bradycardia Supportive care
Oxalate-containing plants: *Philodendron, Dieffenbachia, Colocasia* ("elephant ear")	Local tissue injury Oral pain Vomiting	Supportive care, pain control
Poison hemlock *(Conium maculatum)*	Vomiting Agitation followed by CNS depression Paralysis Respiratory failure	Supportive care
Pokeweed	Hemorrhagic gastroenteritis Burning of mouth and throat	Supportive care
Rhododendron	Vomiting Diarrhea Bradycardia	Atropine for symptomatic bradycardia Supportive care
Tobacco	Vomiting Agitation Diaphoresis Fasciculations Seizures	Supportive care
Water hemlock (*Cicuta* species)	Abdominal pain Vomiting Delirium Seizures	Supportive care, including benzodiazepines for seizures
Yew (*Taxus* species)	GI symptoms QRS widening Hypotension CV collapse	Supportive care Atropine for bradycardia Sodium bicarbonate does not appear to be effective

AV, atrioventricular; CNS, central nervous system; CV, cardiovascular; ECG, electrocardiogram; Fab, fragment, antigen binding; GI, gastrointestinal.

Electric Dishwasher Detergent

Especially when in the form of crystals, these products are highly alkaline (pH >13) and exposure via ingestion can lead to significant burns to the vocal cords and GI tract. Admission for upper GI endoscopy is usually indicated.

Magnets

Most foreign body ingestions are allowed to pass through the GI tract once they are known to have passed into the stomach. However, ingestion of 2 or more magnets (unless they are very weak refrigerator style magnets) cause concern for bowel obstruction and/or perforation. Admission for attempted retrieval via endoscopy or clearance via WBI is to be considered.

Batteries

Any disk or button style battery lodged in the esophagus or airway should be considered a true emergency warranting immediate referral to an endoscopist for removal. These batteries can cause necrosis of the tissues to which they are lodged via continued electrical discharge and/or leaking of their contents (the former is likely the primary method of injury). Mucosal contact for even 2 hr might induce necrosis. Once past the lower esophageal sphincter, button or even larger batteries (e.g., AA, AAA size) can usually be allowed to pass through the GI tract with close follow up.

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Chapter 64

Complementary Therapies and Integrative Medicine

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Integrative medicine focuses on promoting physical, mental, emotional, spiritual, social, educational, and occupational well-being in the context of a medical home in a healthy family and community. The foundations of integrative medicine are health-promoting practices including optimal nutrition and dietary supplements to avoid deficiencies; avoiding intake of addictive substances such as nicotine and illicit drugs; physical activity, adequate sleep, a healthy environment, and supportive social relationships. Evidence-based complementary therapies such as herbal remedies and other dietary supplements, massage, chiropractic, and other forms of bodywork, yoga, tai chi, meditation practices, hypnosis, guided imagery, biofeedback, and acupuncture may also be used. Although prayer and healing rituals are sometimes included under the rubric of complementary and integrative therapies, they are not covered in this chapter.

Not including multivitamins and mineral supplements (such as iron and calcium), the estimated prevalence of complementary and alternative medicine use in the United States by youth younger than 18 yr of age in 2007 was 8.7 million; the most common therapies included natural products, chiropractic, and deep breathing. Use of complementary therapies is most common among youth with chronic, incurable, or recurrent conditions such as asthma, autism, cancer, depression, and pain. For example, complementary therapies were used by 42-71% of pediatric patients in a 2013 study of specialty outpatient clinics in Canada; the therapies most commonly used by these patients were dietary supplements. Side effects were uncommon and most were minor.

Table 64-1 Most Commonly Used Dietary Supplements in Pediatrics

PRODUCT	USES
VITAMINS	
B_2 (riboflavin)	Migraine headache prophylaxis
B_6 (pyridoxine)	Pyridoxine-dependent epilepsy; neuropathy; nausea associated with pregnancy
B_9 (folate)	Prevention of neural tube defects
D	Prevention of rickets; treatment of deficiencies
Multivitamins	General health promotion, ADHD
MINERALS	
Iodine (salt)	Prevent goiter and mental retardation
Iron	Prevent and treat iron deficiency
Magnesium	Constipation, asthma, migraine prevention
Zinc	Diarrhea in nutrient-poor populations
HERBS	
Aloe vera	Mild burns
Chamomile	Mild sedative, dyspepsia
Echinacea	Prevention of upper respiratory infections
Ginger	Nausea
Lavender (aromatherapy)	Mild sedative
Peppermint	Irritable bowel syndrome
Tea tree oil	Anti-bacterial (acne remedies), pediculicide (lice)
OTHER	
Melatonin	Insomnia
Omega-3 fatty acids (fish oil)	ADHD, allergies, inflammation, anxiety and mood disorders
Probiotics	Antibiotic-associated diarrhea; *Clostridium difficile*–associated diarrhea; constipation; irritable bowel syndrome; pouchitis; inflammatory bowel disorders

ADHD, attention-deficit/hyperactivity disorder.

DIETARY SUPPLEMENTS

Under the 1994 Dietary Supplement Health and Education Act, a dietary supplement is a product taken by mouth that contains a *dietary ingredient* intended to supplement the diet. These may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements are the most commonly used complementary therapies for children and adolescents (Table 64-1). Some uses are common and recommended, such as vitamin D supplements for breastfed infants and probiotics to prevent *Clostridium difficile*–associated diarrhea, whereas other uses are more controversial, such as using herbal products to treat otitis media.

In the United States, dietary supplements do not undergo the same stringent evaluation and postmarketing surveillance as prescription medications. Although they may not claim to prevent or treat specific medical conditions, product labels may make *structure–function* claims. For example, a label may claim that a product *promotes a healthy immune system*, but it may not claim to cure the common cold.

According to the 2007 National Health Interview Survey, 37% of children in the United States used dietary supplements, with the majority using multivitamin and mineral products (31%) exclusively. Use of dietary supplements is most common among children whose families have higher income and education and whose parents use them; among older children; and among those suffering from chronic conditions.

Despite this widespread use, many patients and their parents who use dietary supplements do not talk with their physician about their use. Several guidelines have called for more complete dietary supplement history taking by healthcare professionals. The Joint Commission recommends that clinicians routinely ask patients about their use of dietary supplements and include this information as part of the medication reconciliation process.

DIETARY SUPPLEMENT SAFETY

Dietary supplements may have safety issues in children, though toxicity is much less common with nonprescription dietary supplements than with prescription medications. Toxicity depends on dose, use of cotherapies, and the underlying medical condition of the child. Modern use of a dietary supplement (e.g., ephedra for weight loss) may not reflect its traditional use (e.g., ephedra as a component of a traditional Chinese medicine tea in small doses to improve allergic or respiratory symptoms). Moreover, herbs that are apparently safe for most adults may be more hazardous in specific conditions (e.g., newborns, patients with impaired renal or hepatic function), under special circumstances (e.g., after organ transplantation or other surgery), or when combined with prescription medications. Some natural products are toxic in and of themselves (Table 64-2). Acute hepatic toxicity and death can result from ingestion of even small amounts of *Amanita* mushrooms. Even when a product is safe when used correctly, it can cause mild or severe toxicity when used incorrectly. Although peppermint is a commonly used and usually benign gastrointestinal spasmolytic included in after-dinner mints, it can exacerbate gastroesophageal reflux. Probiotics are generally safe when taken orally, but in an immune-compromised patient in an ICU setting, they may (rarely) cause sepsis.

Table 64-2 Potentially Toxic Herbs

HERB	TOXIC CONSTITUENTS	TYPICAL USES	POTENTIAL ACUTE ADVERSE EFFECTS	HOW TO TREAT OVERDOSE
Aconitum (monkshood, wolfsbane)	**Diester alkaloids:** Hypaconitine and aconitine (aconitine increases permeability for sodium ions and slows down repolarization, leading to paralysis of the nerve)	Facial neuralgia and sciatica Headache and migraines Rheumatic pain, arthritis, gout Pericarditis sicca	Nausea, vomiting, hypersalivation **CNS:** Paresthesias, muscular weakness, dizziness, ataxia, seizures, coma **Cardiac:** Bradycardia, hypotension, rhythm disorders	Supportive care Dioxin-specific antibodies, unless history excludes cardiac glycosides Do not give ipecac Activated charcoal and gastric emptying might help Avoid type 1 antiarrhythmics
Artemisia absinthium (wormwood)	**Thujone and isothujone:** Neurotoxins	Anorexia Dyspeptic conditions Liver and gallbladder disorders	**Mental status changes:** Restlessness, vertigo, tremors, agitation, seizures, headache Vomiting; stomach and intestinal cramps Rhabdomyolysis and renal failure	Supportive care Benzodiazepines
Atropa belladonna (deadly nightshade) of atropine)	**Alkaloids:** Hyoscyamine (the L-isomer)	Gastrointestinal symptoms Cardiac insufficiency and arrhythmia Asthma	**Anticholinergic reaction:** Tachycardia, hyperthermia, mydriasis, urine and feces retention, restlessness Nervous system and respiratory depression	Gastric lavage Physostigmine given in consultation with a poison specialist External cooling if temperature is >38.9°C (102°F) Benzodiazepines Hydration
Ayurvedic herbal remedies	Contaminated with lead, mercury, or arsenic	Traditional medicine from India; many purposes	Acute or chronic heavy metal toxicity	Depends on heavy metal
Digitalis purpurea (foxglove)	**Cardioactive glycosides:** Purpurea glycoside, digitoxin	Ulcers, boils, headaches, abscesses, paralysis, cardiac insufficiency	Nausea and vomiting, headache, loss of appetite Cardiac rhythm disorders **CNS:** Stupor, confusion, visual disorders, depression, psychosis, hallucinations	Supportive care Gastric lavage Activated charcoal Treatment of symptoms
Ephedra sinica (ma huang) Common names: Miner's tea, Mexican tea, Desert herb	**Alkaloids:** Ephedrine, pseudoephedrine (stimulates sympathomimetic receptors and the CNS)	Decongestant for upper respiratory infection Asthma Weight loss Stimulant	**Cardiac:** Hypertension, cardiomyopathy, myocardial infarction, arrhythmias **CNS:** Dizziness, restlessness, headaches, anxiety, hallucinations, tremors, seizures, psychosis, strokes Nausea and vomiting Contraindicated in diabetes or hypertension, angle-closure glaucoma, anxiety, prostate adenoma, thyroid disease, pheochromocytoma	Activated charcoal Benzodiazepine for seizures and sedation Vasodilators for hypertension Lidocaine and β blockers for arrhythmias External cooling if temperature is >38.9°C (102°F) Hydration therapy
Illicium anisatum (Japanese star anise tea)	Anisatins; block γ-aminobutyric acid	Colic in Latino and Caribbean populations	Seizures, tonic postures, myoclonus, hyperexcitability, irritability	Recovery with supportive care within 48 hr
Lobelia inflata (lobelia)	**Piperidine alkaloid:** L-Lobeline (stimulates nicotinic receptors)	Expectorant Asthma Spasmolytic Emetic To induce mental clarity and a feeling of well-being	**Gastrointestinal:** Nausea and vomiting, abdominal pain, diarrhea **CNS:** Anxiety, headache, dizziness, tremors, seizures, paresthesias, euphoria **Cardiac:** Arrhythmias, bradycardia, transient increase in blood pressure, decreased respiratory rate In overdose, lobeline can cause hypotension. Diaphoresis, muscle fasciculations and weakness, tremors, respiratory depression Dermatitis	Supportive care Gastric emptying Activated charcoal Benzodiazepines

Continued

Table 64-2 Potentially Toxic Herbs—cont'd

HERB	TOXIC CONSTITUENTS	TYPICAL USES	POTENTIAL ACUTE ADVERSE EFFECTS	HOW TO TREAT OVERDOSE
Longdan xieganwan	Aristolochic acid	Enhance health	Renal interstitial fibrosis End-stage renal failure Renal cell carcinoma	Supportive care
Mentha pulegium (pennyroyal)	Pennyroyal oil has a hepatotoxic effect Acute poisoning is not found with proper administration of the designated therapeutic use of pennyroyal leaf; however, the drug is not recommended owing to hepatotoxicity	Insect repellent Respiratory illness Digestive disorders Emmenagogue Abortifacient Wound treatment Gout	Uterine contractions **Gastrointestinal:** Nausea, vomiting, abdominal pain, hepatitis **Neurotoxin:** Delirium, dizziness, convulsions, seizures, paralysis, encephalopathy, coma Renal failure and hypertension Shock and disseminated intravascular coagulation Contraindicated in pregnancy	Supportive care *N*-Acetylcysteine
Pausinystalia yohimbe (yohimbe)	Indole alkaloids **Yohimbe:** α_2-Adrenoreceptor antagonist	Sexual disorders Exhaustion Improve muscle function	**Adverse reactions:** Dizziness, headache, anxiety, hypertension, indigestion, rash, insomnia, tachycardia, tremor, vomiting, hallucinations, nervousness, paresthesias, hypothermia, salivation, mydriasis, diarrhea, palpations, tachycardia Contraindicated in kidney and liver disease	Gastric emptying Activated charcoal Antiarrhythmics Hydration
Phytolacca americana (pokeweed, American nightshade)	Triterpene saponins (irritate mucous membranes) Lectins (toxic)	Antiinflammatory Arthritis Cancer Emetic and cathartic Rheumatism	Dizziness, somnolence, nausea, vomiting, diarrhea, tachycardia, hemorrhagic gastritis, hypotension, lymphocytosis, headache, respiratory depression, seizures	Hydration therapy, electrolyte correction, gastric emptying Activated charcoal Electrolyte replacement Emesis should not be induced if patient is experiencing symptoms of overdose
Stramonium folium (jimsonweed)	**Alkaloids:** Hyoscyamine (the L-isomer of atropine)	Asthma and cough Diseases of the autonomic nervous system	In high doses, leads to restlessness, mania, hallucinations, delirium **Overdose:** Tachycardia, mydriasis, flushing, dry mouth, decreased sweating, miction, constipation	Supportive care Gastric lavage Decreasing temperature Physostigmine Benzodiazepines
Viscum album (mistletoe)	Alkaloids Viscotoxins *(Viscum album)* cause hypotension, bradycardia, and arterial vasoconstriction Lectins	Antineoplastic adjuvant Antihypertensive Nervous disorders: calmative agent Rheumatism Antispasmodic	Fever, headaches, nausea, vomiting, diarrhea, bradycardia, angina, change in blood pressure, seizures, confusion, hallucination, allergic reactions, miosis, mydriasis, chills, coma 2 reported deaths in the last 35 yr; most ingestions lead to mild reactions	Supportive therapy Data inconclusive for inducing emesis Activated charcoal

CNS, central nervous system.

Although there are good manufacturing practices for dietary supplements in the United States, dietary supplement labels might not accurately reflect the contents or concentrations of ingredients. Because of natural variability, variations of 10-1,000–fold have been reported for several popular herbs, even across lots produced by the same manufacturer. Herbal products may be unintentionally contaminated with pesticides, microbial agents or products, or the wrong herb that was misidentified during harvesting. Products from developing countries (e.g., Ayurvedic products from South Asia) might contain toxic levels of mercury, cadmium, arsenic, or lead, either from unintentional contamination during manufacturing or from intentional additions by producers who believe that these metals have therapeutic value. Approximately 30-40% of Asian patent medicines include potent pharmaceuticals, such as analgesics, antibiotics, hypoglycemic agents, or corticosteroids; typically, the labels for these products are not written in English and do not note the inclusion of pharmaceutical agents. Even conventional mineral supplements, such as calcium, have been contaminated with lead or had significant problems with product variability.

Many families use supplements concurrently with medications, posing hazards of interactions (Table 64-3). St. John's wort induces CYP3A4 activity of the P450 enzyme system and thus can enhance elimination of most drugs, including digoxin, cyclosporine, protease inhibitors, oral contraceptives, and numerous antibiotics, leading to

Table 64-3 The HDS–Drug Interactions with Major Severity* (Other Than St. John's Wort)

HDS	DRUGS	POTENTIAL CONSEQUENCES/ REACTIONS†
5-Hydroxytryptophan	Fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine	↑Risk of serotonin syndrome
Acacia	Amoxicillin	↓Absorption of amoxicillin
Alfalfa	Warfarin	↓The effect of warfarin
Aloe vera	Digoxin	↑Digoxin toxicity
American ginseng	Warfarin	↓The effect of warfarin
Arginine	Enalapril, nitroglycerin	↑Hypotensive effects
	Spironolactone	↑Risk of hyperkalemia
Bitter orange	Phenelzine	↑Risk of hypertensive crisis
Cowhage	Methyldopa	↑Hypotensive effects
Danshen	Aspirin, ticlopidine, warfarin	↑Risk of bleeding
	Digoxin	↑Digoxin toxicity
Digitalis	Bendroflumethiazide, chlorothiazide, chlorthalidone, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, polythiazide, trichlormethiazide	↑Digoxin toxicity
	Digoxin	↑Digoxin toxicity
Dong quai	Aspirin, heparin, ticlopidine, warfarin	↑Risk of bleeding
Evening primrose	Warfarin	↑Risk of bleeding
Garlic	Ritonavir	↓The effect of ritonavir
	Saquinavir	↓The effect of saquinavir
	Warfarin	↑Risk of bleeding
Ginkgo	Aspirin, cilostazol, clopidogrel, dipyridamole, heparin, ibuprofen, naproxen, ticlopidine, warfarin	↑Risk of bleeding
	Risperidone	↑Risk of risperidone adverse effects
	Trazodone	Excessive sedation and potential coma
Glucosamine	Warfarin	↑Risk of bleeding
Green tea	Ephedrine	↑Risk of stimulatory adverse effects
Guarana	Ephedrine	↑Risk of stimulatory adverse effects
Hawthorn	Digoxin	↑Digoxin toxicity
Henbane	Chlorpheniramine, clemastine, dimenhydrinate, diphenhydramine, doxylamine, promethazine	↑Risk of anticholinergic side effects
Kava	Alprazolam, chlordiazepoxide, clonazepam, diazepam, estazolam, flurazepam, lorazepam, midazolam, morphine, oxazepam, phenobarbital, quazepam, temazepam, triazolam	↑Central nervous system depression
	Droperidol	↑Central nervous system depression
Licorice	Warfarin	↑Risk of bleeding
L-Tryptophan	Citalopram, duloxetine, fluoxetine, fluvoxamine, isocarboxazid, paroxetine, phenelzine, selegiline, sertraline, sibutramine, tranylcypromine, venlafaxine	↑Risk of serotonin syndrome
	Zolpidem	↑Zolpidem-induced side effect
Melatonin	Zolpidem	↑Sedative effects
N-Acetylcysteine	Nitroglycerin	Severe hypotension, intolerable headaches
Niacin	Atorvastatin, cerivastatin, lovastatin, rosuvastatin, simvastatin	↑Risk of myopathy or rhabdomyolysis
PABA	Dapsone, Sulfamethoxazole	↓Antibacterial effect
Pleurisy root	Digoxin	↑Digoxin toxicity
Potassium	Amiloride, benazepril, captopril, enalapril, fosinopril, indomethacin, lisinopril, moexipril, quinapril, ramipril, spironolactone, trandolapril, triamterene	↑Risk of hyperkalemia
Red yeast rice	Cyclosporine	↑Creatine phosphokinase values
S-Adenosylmethionine	Clomipramine	↑Risk of serotonin syndrome
Scotch broom	Haloperidol	↑The potential toxicity
	Phenelzine	↑Risk of hypertensive crisis
Valerian	Alprazolam, phenobarbital	↑Central nervous system depression

Continued

Table 64-3 The HDS–Drug Interactions with Major Severity* (Other Than St. John's Wort—cont'd

HDS	DRUGS	POTENTIAL CONSEQUENCES/ REACTIONS†
Vitamin A	Acitretin, bexarotene, etretinate, isotretinoin, tretinoin	↑Risk of vitamin A toxicity
Vitamin B_6	Altretamine	↓Response to altretamine
Vitamin E	Dicumarol	↑Risk of bleeding
Vitamin K	Warfarin	↓Effect of warfarin
Willow	Diclofenac, ibuprofen, naproxen, ticlopidine, warfarin	↑Risk of bleeding

*Any HDS–drug interactions with severity rated as contraindicated or major in either database of MicroMedex or NMCD were included in this table.
†Potential consequences or reactions were documented according to either aforementioned database with severity rating as major or contraindicated.
↓, Decreasing; ↑, increasing; HDS, herb and dietary supplements; PABA, para-aminobenzoic acid.
Adapted from Tsai HH, Lin HW, Pickard AS, et al: Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review. Int J Clin Pract *66:1056–1078, 2012, Table 4, p. 1065.*

Table 64-4 Common Folk Medicines By Cultural Origin

NAME	CONTENTS	POTENTIAL TOXICITY
HISPANIC		
Siete jarabes	Almond, castor oil, tolu, wild cherry licorice, cocillana, honey	GI upset, catharsis, electrolyte disturbances
Agua maravilla	Witch hazel, ethanol	Ethanol toxicity
Jarabe maguey	Maguey (Agave spp)	GI upset
Alcanfor	Camphor	Camphor toxicity
Azarcon	Lead	Lead intoxication
Greta	Lead	Lead intoxication
Azogue	Elemental mercury	Mercury intoxication
Ipecacuanha	Ipecac	Vomiting, myopathy
SOUTHEAST ASIAN		
Paylooah	Lead	Lead intoxication
INDIAN AND AYURVEDIC		
Surma	Lead	Lead intoxication
Deshi Dawa	Lead	Lead intoxication

GI, gastrointestinal.
From Kingston RL, Foley C. Herbal, traditional, and alternative medicines. In Shannon MW, Borron SW, Burns MJ, editors. Haddad and Winchester's clinical management of poisoning and drug overdose, *ed 4, Philadelphia, 2007, WB Saunders, Table 68-3.*

subtherapeutic serum levels. In contrast, St. John's wort may *enhance* the risk of the serotonin syndrome in patients on selective serotonin reuptake inhibitor agents, increase the sedation of opioids, increase the photosensitivity reactions of certain drugs, and increase the toxicity of propofol and sevoflurane.

Many folk medicine are named based on their natural language (Tables 64-4 and 64-5), which must be taken into consideration when treating specific ethnic populations.

DIETARY SUPPLEMENT EFFICACY

Evidence about the effectiveness of dietary supplements to prevent or treat pediatric problems is mixed, depending on the product used and condition treated. Some herbal products may be helpful adjunctive treatments for common childhood problems; some herbs have proved helpful for colic (fennel and the combination of chamomile, fennel, vervain, licorice, and balm mint), nausea (ginger), irritable bowel syndrome (peppermint), and diarrhea (probiotics).

MASSAGE AND CHIROPRACTIC

Massage is commonly provided at home by parents and by professional massage therapists, physical therapists, and nurses in clinical settings. Infant massage is routinely provided in many neonatal intensive care units to promote growth and development in preterm infants. Massage also has been demonstrated to be beneficial for pediatric patients suffering from asthma, insomnia, colic, cystic fibrosis, and juvenile ideopathic arthritis. Massage therapy is generally safe. Professional massage practice is regulated by state governments; more than 40 states license massage therapists, and 3 offer statewide independent certification.

More than 50,000 chiropractors are licensed in the United States, including licensure in all 50 states. Chiropractic care is covered by most major insurers. Up to 14% of all chiropractic visits are for pediatric patients, not including care provided by chiropractors working for athletic departments or professional teams. While chiropractic care may be useful for treating minor musculoskeletal injuries, parents need to be cautioned not to rely on chiropractic as the primary treatment for serious conditions, such as neurologic deficits, cancer or autism; data suggest that severe complications are possible.

MIND–BODY THERAPIES

Mind–body therapies such as slow, deep breathing, meditation, guided imagery, biofeedback, hypnosis, tai chi, and yoga, are the second most commonly used group of complementary therapies in pediatrics. These practices can be learned informally through books, YouTube videos, CDs, DVDs, smart phone applications, or classes, or in therapeutic sessions with health professionals, such as psychologists and social workers (Table 64-6). Substantial research suggests that such practices can aid in reducing anxiety, insomnia, and stress-related conditions including migraine headaches and functional abdominal pain. They can also help patients struggling with chronic pain.

Table 64-5 Spanish-English Botanical Name Translation Chart

SPANISH NAME	ENGLISH NAME	BOTANICAL NAME
Ajo	Garlic	*Allium sativum*
Cebolla	Onion	*Allium cepa*
Cenela	Cinnamon	*Cinnamomum aromaticum*
Clavo	Cloves	*Eugenia aromatica*
Comino	Cumin	*Cuminum cyminum*
Epasote or herba Sancti Mariae	Wormseed	*Chenopodium anthelminticum*
Estafiate	Wormwood	*Artemisia absinthium*
Eucalipto	Eucalyptus	*Eucalyptus globulus*
Granada	Pomegranate	*Punica granatum*
Jengibre	Ginger	*Zingiber officinale*
Limon	Lemon	*Citrus limon*
Manzanilla	Chamomile	*Anthemis nobilis* or *Chamomilla recutita* or *Matricaria chamomilla*
Oregano	Oregano	*Origanum vulgare*
Pelos de elote	Corn silk	*Zea mays*
Savila	Aloe vera	*Aloe vera*
Tomillo	Thyme	*Thymus vulgaris*
Una de gato	Cat's claw	*Uncaria tomentosa*
Valeriana	Valerian	*Valeriana officinalis*
Yerba buena	Spearmint	*Mentha spicata*

Table 64-6 Commonly Used Mind–Body Practices in Pediatrics

PRACTICE	USES
Biofeedback	Preventing migraine headaches; reducing stress and anxiety; encopresis/constipation treatment; treatment of stress incontinence; neurofeedback is experimental for ADHD
Deep breathing	Relaxation; stress management
Guided imagery	Stress management, anxiety, pain relief
Hypnosis	Correcting habit disorders; preventing headaches; managing pain
Meditation	Stress management, improving concentration
Tai chi	Improved balance, coordination, concentration, discipline
Yoga	Improved balance, coordination, concentration

ACUPUNCTURE

Modern acupuncture incorporates treatment traditions from China, Japan, Korea, France, and other countries. In the United States, acupuncturists are licensed to practice in 43 states, and acupuncture services are offered by more than 30% of North American academic pediatric pain treatment programs. The technique that has undergone most scientific study involves penetrating the skin with thin, solid, metallic needles manipulated by hand or by electrical stimulation. Variants include rubbing (shiatsu), heat (moxibustion), lasers, magnets, pressure (acupressure), or electrical currents.

Although most pediatric patients are averse to needles, patients who suffer from severe chronic pain or nausea may be amenable to trying acupuncture and often report that it is helpful. Acupuncture can offer significant benefits in the treatment of recurrent headache, anxiety, back and other types of pain, depression, and nausea. As with any therapy involving needles, infections and bleeding can occur, but more serious complications, such as pneumothorax, occur in <1 in 30,000 treatments.

Bibliography is available at Expert Consult.

Internet Resources

American Academy of Pediatrics Section on Integrative Medicine: http://www2.aap.org/sections/chim/default.cfm
Consortium of Academic Health Centers for Integrative Medicine: http://www.imconsortium.org/
National Institutes of Health's National Center for Complementary and Integrative Medicine: http://nccam.nih.gov
Natural Medicines Comprehensive Database (requires subscription): http://www.naturaldatabase.com
Natural Standard (requires subscription): http://www.naturalstandard.com
US Department of Defense Total Force Fitness: http://hprc-online.org/total-force-fitness

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The Acutely Ill Child

PART IX

Chapter 65

Evaluation of the Sick Child in the Office and Clinic

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Acutely ill children pose a challenge to a busy pediatrician's office. Illnesses can span the spectrum from simple viral infections to life-threatening emergencies. Pediatricians need to distinguish between patients who can be managed with close outpatient follow-up and those that need to be stabilized and transported to a higher level of care. Although patients of all ages can present with similar symptoms, the etiology of the illness can be age-dependent. The initial approach must focus on the general evaluation and stabilization of the acutely ill infant and child.

HISTORY

A thorough history is paramount to arriving at the correct diagnosis. Obtaining an accurate history from young patients is challenging, and parents often provide the most important information. On the basis of the chief complaint(s), the pediatrician must ask open-ended questions that help distinguish between common and potentially life-threatening entities. Common complaints leading to acute care visits for potential emergencies include **fever**, **altered mental status**, **vomiting**, **respiratory distress**, and **abdominal pain**.

Fever is the most common reason for a sick child visit. Most fevers are the result of self-limited viral infections. However, pediatricians need to be aware of the age-dependent potential for serious bacterial infections (e.g., urinary tract infections, sepsis, meningitis, pneumonia, dysentery, osteoarticular infection). During the first 2-3 mo of life, the neonate is at risk for sepsis caused by pathogens that are uncommon in older children. These organisms include group B streptococcus, *Escherichia coli, Listeria monocytogenes,* and herpes simplex virus. In neonates, the history must include maternal obstetric information and the patient's birth history. Risk factors for sepsis include maternal group B streptococcus colonization, prematurity, chorioamnionitis, and prolonged rupture of membranes. If there is a maternal history of sexually transmitted infections during the pregnancy, the differential diagnosis must be expanded to include those pathogens. Septic infants can present with lethargy, poor feeding, grunting respirations, and cool or mottled extremities, in addition to fever (or hypothermia). Infants with fever, irritability, and a bulging fontanel should be evaluated for meningitis. As the infant matures beyond 3 mo of age, the bacterial pathogens that usually cause bacteremia, sepsis, and meningitis are *Streptococcus pneumoniae, Haemophilus influenzae* type b, and *Neisseria meningitidis.* Urosepsis secondary to an *E. coli* urinary tract infection also needs to be considered. Immunization against some serotypes of *S. pneumoniae* has markedly reduced the occurrence of occult bacteremia and serious infections caused by that organism, as has immunization against *H. influenzae* type b. These remain potential concerns in those children not fully immunized against these pathogens. Other ailments that manifest with fever include septic arthritis and osteomyelitis, juvenile idiopathic arthritis, and Kawasaki disease. Children with a septic joint generally present with only 1 joint that is painful and often have pseudoparalysis of that joint. In contrast, patients with juvenile rheumatoid arthritis may present with pain, stiffness, swelling, and warmth of several joints. The diagnosis of Kawasaki disease should be considered if the patient meets the diagnostic criteria for this illness although some patients may have an atypical or incomplete presentation (see Chapter 166).

For patients presenting with **altered mental status**, the pediatrician should inquire about the presence of other symptoms, such as fever or headache. Screening questions should be asked regarding feeding changes, medications in the household, or the possibility of trauma. Parents will often describe a febrile child as "lethargic," but further questioning will reveal a tired-appearing child who interacts appropriately when the child has defervesced. Febrile patients need to be differentiated from the lethargic patient who presents with sepsis or meningitis. Infants with meningitis or sepsis may have a history of irritability, inconsolability, poor feeding, grunting respirations, seizures, decreased urine output, and/or color changes such as pallor, mottling, or cyanosis. Patients with poisonings or inborn errors of metabolism can also present with lethargy, poor feeding, unusual odors, seizures, and/or vomiting. Nonaccidental trauma should always be considered in a lethargic infant. Older children may present with altered mental status as a result of meningitis/encephalitis, trauma, or ingestions. Children with meningitis may have a history of fever and complaints of neck pain; other associated symptoms can include rash, headache, photophobia and/or vomiting. Children with ingestions can present with other abnormal neurologic symptoms such as ataxia, slurred speech, seizures, or characteristic constellations of vital sign changes and other physical findings (toxidromes).

Vomiting is a very common complaint of intestinal, other abdominal (e.g., pancreas, liver) or nongastrointestinal (e.g., hyperammonemia, increased intracranial pressure, poisoning) origin and may be a nonspecific sign of systemic illness. Questions to ask include about the presence of bilious or bloody emesis, abdominal distention, weight changes, presence of diarrhea, obstipation or hematochezia, history of trauma, and presence of headache. Although common causes of vomiting are gastroesophageal reflux and viral gastroenteritis, the pediatrician needs to be aware of other serious causes. In the infant, bilious emesis and abdominal distention and/or pain are worrisome for obstruction, as may be seen with malrotation with midgut volvulus or Hirschsprung disease. It is important to consider extraabdominal causes of vomiting in the neonate, including hydrocephalus, incarcerated hernia, inborn errors of metabolism, and nonaccidental trauma. Markedly increasing head circumference or a bulging fontanel can be the result of congenital hydrocephalus or can signal the presence of subdural hematomas from nonaccidental trauma. An infant who appears immediately hungry after projectile vomiting suggests a differential diagnosis of pyloric stenosis. In an older child, the differential diagnosis includes intussusception, incarcerated hernia, diabetic ketoacidosis, appendicitis, poisonings, and trauma. Patients with intussusception may present with vomiting and colicky abdominal pain. A history of increased urination in the presence of vomiting may herald the diagnosis of diabetes mellitus. Patients with headache and vomiting raise a concern for increased intracranial pressure and should be questioned about neurologic changes, meningismus, and fever.

Parents can interpret different symptoms as **respiratory distress**. Tachypnea secondary to fever is often a source of parental anxiety. Parents of newborn infants are sometimes alarmed by the presence of periodic breathing. Normal variations in respiratory patterns must be distinguished from true respiratory distress. Parents need to be questioned regarding associated symptoms such as fever, limitation of neck movement, drooling, choking, and the presence of stridor or wheezing.

A history of apnea or cyanosis warrants further investigation. Although wheezing is often secondary to bronchospasm, it can also be caused by cardiac disease or congenital anomalies such as vascular rings. Infants with congenital heart defects may be tachypneic but may lack any signs of respiratory distress as a compensatory mechanism for shock or metabolic acidosis. Parents often confuse and interpret stridor as wheezing, and care should be taken to differentiate the two. Stridor is most commonly caused by croup. However, anatomic abnormalities such as laryngeal webs, laryngomalacia, subglottic stenosis, and paralyzed vocal cords also cause stridor. Toddlers who present with wheezing or stridor after a coughing or choking episode should be evaluated for a foreign body aspiration. In toxic-appearing children with stridor, the pediatrician should consider epiglottitis, bacterial tracheitis, or a rapidly expanding retropharyngeal abscess. The incidence of epiglottitis has markedly declined with the advent of the *H. influenzae* type b (Hib) vaccine, but remains a possibility in the unimmunized or partially immunized patient. Children with retropharyngeal abscesses may also present with drooling and limitation of neck movement (especially hyperextension) after a recent upper respiratory infection or penetrating mouth injury.

Abdominal pain is another frequent complaint. Often this symptom is caused by a minor illness such as constipation, functional abdominal pain, urinary tract infection, or gastroenteritis. Parents should be questioned about associated symptoms including stooling patterns, abdominal distention, fever, urinary symptoms, and vomiting. In neonates, a tender abdomen is concerning for the presence of a small bowel obstruction; these infants tend to appear ill. There may be a history of vomiting and decreased or no stooling. Pediatricians should be wary of neonates with abdominal tenderness and bloody stools, as 10% of cases of necrotizing enterocolitis occur in term infants. Infants with milk protein intolerance can also present with bloody stools, but these infants are well-appearing and do not have abdominal tenderness. In older patients, the differential diagnosis for a potential emergency with abdominal pain expands to include intussusception and appendicitis. Patients with intussusception can present in a variety of ways, ranging from having episodes of colicky abdominal pain, but otherwise well in between episodes, to being lethargic or in shock. The diagnosis of appendicitis in the child younger than 3 yr is extremely difficult because children in this age group do not localize their pain well. Often the diagnosis is made after the appendix has ruptured.

The child's **past medical history** also needs to be obtained. It is important to be aware of any underlying chronic problems that might predispose the child to recurring infections or a serious acute illness. The child with sickle cell anemia is at increased risk for bacteremia, as well as painful vasoocclusive crisis. A careful review of systems can help in identifying the nature of the acute illness, as well as any complications needing intervention, such as dehydration accompanying an otherwise minor viral illness.

PHYSICAL EXAM

Observation is important in the evaluation of the acutely ill child. Most observational data that the pediatrician gathers during an acute illness should focus on assessing the child's response to stimuli. Do they awaken easily with a stimulus? Do they smile and interact with the examiner? Can the crying child be consoled by the parents' comforting? Assessing responses to stimuli requires knowledge of normal responses for different age groups, the manner in which those normal responses are elicited, and to what degree a response might be impaired. Thus, the pediatrician must be both clinically and developmentally oriented.

During the **physical examination**, the pediatrician seeks evidence of illness. The portions of the physical examination that require the child to be most cooperative are completed first. Initially, it is best to seat the child on the parent's lap; the older child may be seated on the examination table. It is also important to assess the child's willingness to move and ease of movement. It is reassuring to see the child moving about on the parent's lap with ease and without discomfort. Vital signs are often overlooked but are invaluable in assessing ill children. The degree of fever, the presence of tachycardia out of proportion to the fever, and the presence of tachypnea and hypotension all suggest a serious infection. The respiratory evaluation includes determining respiratory rate, the presence or absence of hypoxia by pulse oximetry, and noting any evidence of inspiratory stridor, expiratory wheezing, grunting, coughing, or increased work of breathing (e.g., retractions, nasal flaring, belly breathing). Because acute infections in children are most often caused by viral infections, the presence of nasal discharge may be noted. It is possible at this time to assess the skin for rashes. Frequently, viral infections cause an exanthem and many of these eruptions are diagnostic (e.g., the reticulated rash and "slapped-cheek" appearance of parvovirus infections or the typical appearance of hand-foot-and-mouth disease caused by coxsackieviruses). The skin examination may also yield evidence of more serious infections (bacterial cellulitis or petechiae and purpura associated with bacteremia). Cutaneous perfusion should be assessed by warmth and capillary refill time. When the child is seated and is least perturbed, an assessment of the fontanel can be completed; the examiner can determine whether the fontanel is depressed, flat, or bulging.

During this initial portion of the physical examination, when the child is most comfortable, the heart and lungs are auscultated. In the acutely febrile child, because of the relatively frequent occurrence of respiratory illnesses, it is important to assess adequacy of air entry into the lungs, equality of breath sounds, and evidence of adventitial breath sounds, especially wheezes, rales, and rhonchi. The coarse sound of air moving through a congested nasal passage is frequently transmitted to the lungs. The examiner can become attuned to these coarse sounds by placing the stethoscope near the child's nose and then compensating for this sound as the chest is auscultated. The cardiac examination is next; findings such as pericardial friction rub, loud murmurs, and distant heart sounds may indicate an infectious process involving the heart. The eyes are examined to identify features that might indicate an infectious process. Often, viral infections result in a watery discharge or redness of the bulbar conjunctivae. Bacterial infection, if superficial, results in purulent drainage; if the infection is more deep-seated, tenderness, swelling, and redness of the tissues surrounding the eye are present, as well as proptosis, reduced visual acuity, and altered extraocular movement. The extremities may then be evaluated not only for ease of movement but also for the possibility of swelling, heat, or tenderness; such abnormalities may indicate focal infections.

The components of the physical examination that are more bothersome to the child are completed last. This is best done with the patient on the examination table. Initially, the neck is examined to assess for areas of swelling, redness, or tenderness, as may be seen in cervical adenitis. Resistance to neck movement should prompt evaluation for signs of meningeal irritation (i.e., Kernig and Brudzinski signs) or a retropharyngeal abscess. During examination of the abdomen, the diaper is removed. The abdomen is inspected for distention. Auscultation is performed to assess adequacy of bowel sounds, followed by palpation. The child often fusses as the abdomen is auscultated and palpated. Every attempt should be made to quiet the child; if this is not possible, increased fussing as the abdomen is palpated may indicate tenderness, especially if this finding is reproducible. In addition to focal tenderness, palpation may elicit involuntary guarding or rebound tenderness (including tenderness to percussion); these findings indicate peritoneal irritation, as is seen in appendicitis. The inguinal area and genitals are then sequentially examined. The child is then placed in the prone position, and abnormalities of the back are sought. The spine and costovertebral angle areas are percussed to elicit any tenderness; such a finding may be indicative of vertebral osteomyelitis or diskitis and pyelonephritis, respectively.

Examining the ears and throat completes the physical examination. These are usually the most bothersome parts of the examination for the child, and parents frequently can be helpful in minimizing head movement. During the oropharyngeal examination, it is important to document the presence of enanthemas; these may be seen in many infectious processes, such as hand-foot-and-mouth disease caused by coxsackievirus. This portion of the examination is also important in documenting inflammation or exudates on the tonsils, which may be viral or bacterial.

Repeating portions of the assessment may be indicated. If the child cried continuously during the initial clinical evaluation, the examiner may not be certain whether the crying was caused by the high fever, stranger anxiety, or pain, or is indicative of a serious or localizing illness. Constant crying also makes portions of the physical examination, such as auscultation of the chest, more difficult. Before a repeat assessment is performed, efforts to make the child as comfortable as possible are indicated.

Febrile children can appear very ill, initially appearing listless, tachycardic, and tachypneic. These patients should receive antipyretic medications and be reassessed once they have defervesced. In the majority of children with uncomplicated viral illnesses, the vital signs normalize. Persistence of abnormal vital signs should prompt the clinician to further investigate the source of fever. Continued tachycardia and poor perfusion may be secondary to myocarditis. Tachypnea may be the sole symptom in patients with pneumonia, especially in children whose chief complaint is abdominal pain due to lower lobe pneumonia. Persistent irritability suggests meningitis/encephalitis.

RISK FACTORS

The sensitivity of the carefully performed clinical assessment, observation, history, and physical examination for the presence of serious illness is approximately 90%. If a serious illness is suspected, other data should be sought to improve this sensitivity level. Important supplemental data are age, body temperature, and the results of screening laboratory tests as indicated. Febrile children in the first 3 mo of life have yet to achieve immunologic maturity and therefore are more susceptible to severe infections. Thus, the febrile infant is at greater risk for serious bacterial infection than the child beyond 3 mo of age and warrants careful evaluation. Data from the era before widespread immunization for *H. influenzae* type b and pneumococcus suggest the risk of bacteremia in infants increases as the magnitude of fever increases; it is unclear how this applies today.

Screening laboratory tests may be helpful in identifying the febrile child at increased risk for selected serious illnesses. Practice guidelines from the prevaccine era suggested that white blood cell count might be useful in establishing a higher risk of bacteremia. Because the incidence of occult pneumococcal bacteremia in febrile children has declined significantly as a result of the introduction of conjugated pneumococcal vaccine, the utility of white blood cell count in otherwise healthy febrile young children older than 2-3 mo of age is questionable. Urinalysis and urine culture must always be considered when the source of fever is not apparent, especially in the highest-risk groups: females and uncircumcised males younger than 2 yr of age and all boys younger than 1 yr of age. The presence of leukocyte esterase, >5 white blood cells/high-power field on a spun urine specimen, or bacteria detected by Gram stain on an unspun urine specimen suggests urinary tract infection, but the sensitivity of these indicators is, on average, only 75-85%; urine culture is the definitive test. Procalcitonin, C-reactive protein, and interleukin-6 are being investigated as potential biomarkers of differentiating serious bacterial illness from benign viral disease in children.

MANAGEMENT

Most patients who present to the pediatrician's office with an acute illness will not require resuscitation. However, the pediatrician needs to be prepared to evaluate and begin resuscitation for the seriously ill or unstable child. The pediatrician's office should be stocked with appropriate equipment necessary to stabilize an acutely ill child. Maintenance of that equipment and ongoing training of the office staff in use of the equipment and procedures is required (see Chapter 66). The evaluation must begin with assessment of the ABCs—airway, breathing, and circulation. When assessing the airway, chest rise should be evaluated, and evidence of increased work of breathing sought. The examiner should ensure that the trachea is midline. If the airway is patent and no signs of airway obstruction are present, the patient is allowed to assume a position of comfort. If the child shows signs of airway obstruction, repositioning of the head with the chin-lift maneuver may alleviate the obstruction. An oral or nasal airway may be necessary in patients in whom airway patency cannot be maintained. These devices are not well-tolerated in conscious patients and may induce gagging or vomiting, and instead are most often utilized to facilitate effective bag-valve-mask ventilation. Once airway patency has been established, the adequacy of breathing should be evaluated. Slow respiratory rates or cyanosis may signal respiratory failure. If the airway is patent but the child's respiratory effort is inadequate, positive pressure ventilation via bag-valve-mask should be initiated. Oxygen should be administered to all seriously ill or hypoxic children via nasal cannula or face mask. Auscultation of the lung fields should assess for air entry, symmetry of breath sounds, and presence of adventitious breath sounds such as crackles or wheezes. Bronchodilator therapy can be initiated to alleviate bronchospasm. Racemic epinephrine is indicated for stridor at rest in a patient with croup. Once airway and breathing have been addressed, circulation must be evaluated. This involves assessment of cardiac output. Symptoms of shock include tachycardia, cool extremities, delayed capillary refill time, mottled or pale skin, and effortless tachypnea. *Hypotension is a late finding in shock and indicates significant decompensation has already taken place.* Vascular access is necessary for volume resuscitation in patients with impaired circulation, and an intraosseous line should be considered early on if there is any difficulty in vascular access for a patient requiring resuscitation. Once an intervention is performed, the clinician must reassess the patient.

If the febrile child is older than 3 mo and appears well, if the history or physical examination does not suggest a serious illness, the child may be followed expectantly. This profile applies to most children with acute febrile illnesses. If, on the other hand, the child appears ill, or the history or physical examination suggests a serious infection, definitive laboratory tests appropriate for those findings are indicated (chest x-ray for a child with grunting). If advanced imaging is required (ultrasound or CT scan for suspected appendicitis), it may be prudent to defer such testing to pediatric specialty care if the decision has already been made to transport the child to a higher level of care. The area of greatest controversy is whether laboratory studies are needed in a febrile child who appears well and has no abnormalities on history and physical examination, but who is younger than 3 mo or whose temperature is high. Many would agree that a sepsis work-up is indicated in the febrile child younger than 1 mo and possibly in the febrile child who is as old as 3 mo.

DISPOSITION

The majority of children evaluated in the office for an acute illness can be managed on an outpatient basis. These patients should have reassuring physical examinations, stable vital signs, and adequate follow-up. A mildly dehydrated patient can be discharged to home for a trial of oral rehydration. Patients with a respiratory illness who are exhibiting signs of mild respiratory distress may be monitored at home with a repeat examination scheduled for the next day. Depending on the child's status, the comfort of the parents, and the relationship of the family with the physician, telephone follow-up may be all that is necessary.

If the physician feels comfortable in following as an outpatient the child in whom no specific diagnosis has been established, a follow-up examination may yield the diagnosis. During the initial visit, or from one visit to the next during the acute illness, the change in symptoms or in the findings on physical examination over time may provide important diagnostic clues. For the child in whom a diagnosis has already been established and who does not require hospitalization, follow-up by telephone or an office visit should be used to monitor the course of the illness and to further educate and support the parents.

However, if it is deemed that the child needs a higher level of care, it is the pediatrician's responsibility to decide what method of transfer is appropriate. Physicians may be reluctant to call for help because of a misperception that 911 services should be activated only for full-blown resuscitations. Emergency Medical Services (EMS) transport should be initiated for any child who is physiologically unstable (e.g., with severe respiratory distress, hypoxia, signs of shock, or altered mental status). If the family's ability to comply promptly with

recommendation for emergency department evaluation is in question, that patient should also be transported by EMS. Some physicians and families may defer calling EMS because of the perception that a parent can get to the hospital faster by private car. Although rapidity of transport should be considered, the need for further interventions during transport and the risk of clinical decompensation are other important factors in the decision to activate EMS. Ultimately, the legal responsibility for choosing an appropriate level of transport for a patient lies with the referring physician, until responsibility of care is officially transferred to another medical provider.

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Chapter 66

Emergency Medical Services for Children

Joseph L. Wright and Steven E. Krug

The overwhelming majority of the 30 million children who present annually for emergency care in the United States are seen at community hospital emergency departments (EDs). Visits to children's hospital EDs account for just 11% of initial emergency care encounters. This distribution suggests that the greatest opportunity to optimize care for acutely ill or injured pediatric patients, on a population basis, occurs broadly as part of a systems-based approach to emergency services, an approach that incorporates the unique needs of children at every level. Conceptually, emergency medical services for children are characterized by an integrated, continuum of care model (Fig. 66-1). The model is designed such that patient care flows seamlessly from the primary care medical home through transport and on to hospital-based definitive care. It includes the following 5 principal domains of activity:

1. Prevention, primary and secondary
2. Out-of-hospital care, both emergency response and prehospital transport
3. Hospital-based care: ED and inpatient
4. Interfacility transport, as necessary, for definitive or subspecialty care (see Chapter 66.1)
5. Rehabilitation.

Figure 66-1 **The emergency medical services for children (EMSC) continuum of care.** Seriously ill and injured children interface with a large number of healthcare personnel as they move through the EMSC system.

The federal Emergency Medical Services for Children (EMSC) program of the Health Resources and Services Administration's Maternal and Child Health Bureau has stewarded improvements in the care of children in the context of the continuum of care model. The programmatic mission of the EMSC program is as follows:

- To ensure state-of-the-art emergency medical care for the ill or injured child and adolescent.
- To ensure that pediatric services are well integrated into an emergency medical services system and backed by optimal resources.
- To ensure that the entire spectrum of emergency services—including primary prevention of illness and injury, acute care, and rehabilitation—is provided to infants, children, adolescents, and young adults.

EMSC funding to states and U.S. territories has created a national framework upon which necessary advances in education, advocacy, and research are taking place. EMSC grantees, constituents, and stakeholders as well as professional organizations such as the American Academy of Pediatrics are collaboratively engaged in implementation activities and projects that address the pediatric-specific recommendations stemming from the Institute of Medicine (IOM) report *The Future of Emergency Care in the United States Health System*.

THE PRIMARY CARE PHYSICIAN AND OFFICE PREPAREDNESS

The primary care physician (PCP) has multiple important roles in the emergency medical services system. Through anticipatory guidance, the PCP can help shape the attitudes, knowledge, and behaviors of parent and child, with the primary goal of preventing acute medical events, such as injury and status asthmaticus. The point of care initiation for many acute problems is often the PCP office. From the standpoint of personnel, equipment, training, and protocols, the PCP office setting must be adequately prepared to initially manage acute and emergency exacerbations of common pediatric conditions, such as respiratory distress and seizures. Furthermore, on rare occasion, the PCP office environment may be confronted with a child in clinical extremis who requires resuscitative intervention and stabilization. It is, therefore, incumbent upon the PCP not only to ensure access to emergency medical services (EMS), that is, 911 system activation, but also to ensure that there is adequate, onsite psychomotor skill preparation to deal with such an emergency. Office preparedness requires training and continuing education for staff members, protocols for emergency intervention, ready availability of appropriate resuscitation drugs and equipment, and knowledge of local EMS resources and ED capabilities.

Staff Training and Continuing Education

It is a reasonable expectation that all office staff, including receptionists and medical assistants, be trained in cardiopulmonary resuscitation (CPR) and that their certification be maintained on an annual basis. Nurses and physicians should also have training in a systematic approach to pediatric resuscitation. Core knowledge may be obtained through standardized courses in advanced life support (ALS) offered by national medical associations and professional organizations. Frequent recertification is important for knowledge retention and skill maintenance. Examples are the Pediatric Advanced Life Support (PALS) and Pediatric Emergency Assessment, Recognition and Stabilization (PEARS) courses sponsored by the American Heart Association, the Advanced Pediatric Life Support (APLS) course sponsored by the American Academy of Pediatrics (AAP) and the American

College of Emergency Physicians (ACEP), and the Emergency Nurses Pediatric Course (ENPC) sponsored by the Emergency Nurses Association (ENA).

Protocols

Standardized protocols for telephone triage of seriously ill or injured children are essential. When a child's status is in question and prehospital care is available, ambulance transport in the care of trained personnel is always preferable to transport by privately owned vehicle. This obviates the potentially serious medical consequences of relying on unskilled and distraught parents without the ability to provide even basic life support (BLS) measures to an unstable child during transport to an ED. Practitioners can work with their local pediatric emergency care resource center (e.g., children's hospital or academic department of pediatrics) to develop and maintain written protocols for office-based management of a range of conditions, including anaphylaxis, cardiopulmonary arrest, head trauma, ingestions, shock, status asthmaticus, status epilepticus, and upper airway obstruction. Regular practice using mock code scenarios improves office-based practitioner confidence and self-efficacy in managing these problems.

Resuscitation Equipment

Availability of necessary equipment is a vital part of an emergency response. Every physician's office should have essential resuscitation equipment and medications packaged in a pediatric resuscitation cart or kit (Table 66-1). This cart or kit should be checked on a regular basis and kept in an accessible location known to all office staff. Outdated medications, a laryngoscope with a failed light source, or an empty oxygen tank represents a potential catastrophe in a resuscitation scenario. Such an incident can be easily avoided if an equipment checklist and maintenance schedule are implemented. A pediatric kit that includes posters, laminated cards, or a color-coded length-based resuscitation tape specifying emergency drug doses and equipment size is invaluable in avoiding critical therapeutic errors during resuscitation.

To facilitate emergency response when a child needs rapid intervention in the office, all personnel should have designated roles. Organizing a "code team" within the office ensures that necessary equipment is made available to the physician in charge, that an appropriate medical record detailing all interventions and the child's response is generated, and that the 911 call for EMS response or a transport team is made in a timely fashion.

Transport

Once the child has been stabilized, a decision must be made on how to transport a child to a facility capable of providing definitive care. If a child has required airway or cardiovascular support, has altered mental status or unstable vital signs, or has significant potential to deteriorate en route, it is not appropriate to send the child via privately owned vehicle, regardless of proximity to a hospital. Even when an ambulance is called, it is the PCP's responsibility to initiate essential life support measures and to attempt to stabilize the child before transport.

In metropolitan centers with numerous public and private ambulance agencies, the PCP must be knowledgeable about the level of service that is provided by each. The availability of BLS versus ALS services, the configuration of the transport team, and pediatric expertise vary markedly among agencies and across jurisdictions. BLS services provide basic support of airway, breathing, and circulation, whereas ALS units are capable of providing resuscitation drugs and procedural interventions as well. Some communities may have only BLS services available, whereas others may have a 2-tiered system, providing both BLS and ALS. It may be appropriate to consider medical air transport when definitive or specialized care is not available within an immediate community or when ground transport times are prolonged. In that case, initial transport via ground to an appropriate helicopter landing zone or a local hospital for interval stabilization may be undertaken, pending arrival of the air transport team. Independent of whether a child is to be transported by air or ground, copies of the pertinent medical records and any radiologic studies or laboratory results should be sent with the patient, and a call made to the physicians at the receiving facility to alert them to the referral and any treatments administered. Such notification is not merely a courtesy; direct physician-to-physician communication is essential to ensure adequate transmission of patient care information, to allow

Table 66-1 Recommended Drugs and Equipment for Pediatric Office Emergencies

	PRIORITY
DRUGS	
Oxygen	E
Albuterol for inhalation	E
Epinephrine (1 : 1,000)	E
Activated charcoal	S
Antibiotics	S
Anticonvulsants (diazepam/lorazepam)	S
Corticosteroids (parenteral/oral)	S
Dextrose (25%)	S
Diphenhydramine (parenteral, 50 mg/mL)	S
Epinephrine (1 : 10,000)	S
Atropine sulfate (0.1 mg/mL)	S
Naloxone (0.4 mg/mL)	S
Sodium bicarbonate (4.2%)	S
INTRAVENOUS FLUIDS	
Normal saline (NS) or lactated Ringer solution (500-mL bags)	S
5% dextrose, 0.45 NS (500-mL bags)	S
EQUIPMENT FOR AIRWAY MANAGEMENT	
Oxygen and delivery system	E
Bag-valve-mask (450-mL and 1,000-mL)	E
Clear oxygen masks, breather and non-rebreather, with reservoirs (infant, child, adult)	E
Suction device, tonsil tip, bulb syringe	E
Nebulizer (or metered-dose inhaler with spacer/mask)	E
Oropharyngeal airways (sizes 00-5)	E
Pulse oximeter	E
Nasopharyngeal airways (sizes 12-30F)	S
Magill forceps (pediatric, adult)	S
Suction catheters (sizes 5-16F and Yankauer suction tip)	S
Nasogastric tubes (sizes 6-14F)	S
Laryngoscope handle (pediatric, adult) with extra batteries, bulbs	S
Laryngoscope blades (straight 0-2; curved 2-3)	S
Endotracheal tubes (uncuffed 2.5-5.5; cuffed 6.0-8.0)	S
Stylets (pediatric, adult)	S
Esophageal intubation detector or end-tidal carbon dioxide detector	S
EQUIPMENT FOR VASCULAR ACCESS AND FLUID MANAGEMENT	
Butterfly needles (19-25 gauge)	S
Catheter-over-needle device (14-24 gauge)	S
Arm boards, tape, tourniquet	S
Intraosseous needles (16-, 18-gauge)	S
Intravenous tubing, micro-drip	S
MISCELLANEOUS EQUIPMENT AND SUPPLIES	
Color-coded tape or preprinted drug doses	E
Cardiac arrest board/backboard	E
Sphygmomanometer (infant, child, adult, thigh cuffs)	E
Splints, sterile dressings	E
Automated external defibrillator with pediatric capabilities	S
Spot glucose test	S
Stiff neck collars (small/large)	S
Heating source (overhead warmer/infrared lamp)	S

E, essential; S, strongly suggested.

From American Academy of Pediatrics, Committee on Pediatric Emergency Medicine; Frush K: Policy statement-preparation for emergencies in the offices of pediatricians and pediatric primary care providers, Pediatrics *120:200-212, 2007. Reaffirmed* Pediatrics *128:e748, 2011.*

mobilization of necessary resources in the ED, and to redirect the transport if the emergency physician believes that the child would be more optimally treated at a facility with specialized services.

PEDIATRIC PREHOSPITAL CARE

Prehospital care refers to emergency assistance rendered by trained emergency medical personnel before a child reaches a treating medical facility. The goals of prehospital care are to further minimize systemic insult or injury through a series of well-defined and appropriate interventions and to embrace principles that ensure patient safety. Most communities in the United States have a formalized EMS system; the organizational structure and nature of emergency medical response depend greatly on local demographics and population base. EMS may be provided by volunteers or career professionals working in a fire-based or independent “third service” response system. Key points to recognize in negotiation of the juncture between the community physician and the local EMS system include access to the system, provider capability, and destination determination.

Access to the EMS System

Virtually all Americans have access to the 911 telephone service that provides direct access to a dispatcher who coordinates police, fire, and EMS responses. Some communities have an enhanced 911 system, in which the location of the caller is automatically provided to the dispatcher, permitting emergency response even if the caller, such as a young child, cannot give an address. The extent of medical training for these dispatchers varies among communities, as do the protocols by which they assign an emergency response level (BLS vs ALS). In some smaller communities, no coordinated dispatch exists, and emergency medical calls are handled by the local law enforcement agency.

When activating the 911 system, the physician must make clear to the dispatcher the nature of the medical emergency and the condition of the child. In many communities, emergency medical dispatchers are trained to ask a series of questions per protocol that determines the appropriate level of provider to be sent.

Provider Capability

There are many levels of training for prehospital EMS providers, ranging from individuals capable of providing only first aid to those trained and licensed to provide ALS. All EMS personnel, whether basic emergency medical technicians (EMTs) or paramedics, receive training in pediatric emergencies; however, pediatric cases actually constitute roughly 10% of all EMS transports.

First responders may be law enforcement officers or firefighters, who are dispatched to provide emergency medical assistance, or bystanders. Public safety personnel have a minimum of 40 hr of training in first aid and CPR. Their role is to provide rapid response and stabilization pending the arrival of more highly trained personnel. In some smaller communities, this may be the only prehospital emergency medical response available.

In the United States, the bulk of emergency medical response is provided by EMTs, who may be volunteers or paid professionals. Basic EMTs may staff an ambulance after undergoing a training program of approximately 100 hr. They are licensed to provide BLS services but may receive further training in some jurisdictions to expand their scope of practice to include intravenous catheter placement and fluid administration, management of airway adjuncts, and the use of an automated external defibrillator.

Paramedics, or EMT-Ps, represent the highest level of EMT response, with medical training and supervised field experience of approximately 1,000 hr. Paramedic skills include advanced airway management, including endotracheal intubation; placement of peripheral, central, or intraosseous lines; intravenous administration of drugs; administration of nebulized aerosols; needle thoracostomy; and cardioversion and defibrillation. These professionals provide ALS services, functioning out of an ambulance equipped as a mobile intensive care unit. In a joint policy statement entitled *Equipment for Ground Ambulances*, the AAP, the ACEP, the American College of Surgeons Committee on Trauma, EMSC, the ENA, the National Association of EMS Physicians, and the National Association of EMS Officials have published guideline standards for essential ambulance equipment, medications, and supplies necessary to provide BLS and ALS care across the age spectrum. This essential equipment list represents one of the reference standards that the federal EMSC program has adopted as a performance measure for state-level operational readiness to care for children in an EMS system.

Both basic EMTs and paramedics function under the delegated licensing authority of a supervisory EMS medical director. This physician oversight of prehospital practice is broadly characterized under the umbrella term *medical control*. **Direct, or online, medical control** refers to medical direction either at the scene or in real time via voice or video transmission. **Indirect, or offline, medical control** refers to the administering of medical direction prior to and after the provision of care. Offline activities, such as provider education and training, protocol development, and medical leadership of quality assurance/quality improvement programs, represent areas in need of greater pediatric input. As a measure of the degree to which EMSC permanence is being established in state EMS systems, the federal EMSC program has required demonstration of participation in online and offline medical direction activities for pediatric patients and the seating of an EMSC advisory committee at the state level. These advisory bodies are well positioned to support EMS agencies in their pediatric readiness as well as provide a forum for the active engagement of pediatric care experts at a system level.

Destination Determination

The destination to which a pediatric patient is transported may be defined by parental preference, provider preference, or jurisdictional protocol, which is typically predicated on field assessment of anatomic and physiologic criteria and, in the case of trauma, mechanism of injury. In communities served by an organized trauma or regionalized EMS system that incorporates pediatric designation based on objectively verified hospital capabilities, seriously ill or injured children may be triaged by protocol to the highest-level center reachable within a reasonable amount of time. The mantra is to deliver the child to the **“right care in the right time,”** even if it requires bypassing closer hospitals. An exception is the child in full arrest, for whom expeditious transport to the nearest facility is always warranted. In 2012, modification of the Centers for Disease Control and Prevention’s national field trauma triage guidelines included a refinement of age-specific vital sign assessment criteria to more accurately reflect the unique physiologic response to injury in children. The Centers for Disease Control and Prevention guidelines are a valuable resource for pediatricians involved in EMS medical direction and are accessible as a multipurpose toolkit, including an educational webinar and downloadable mobile application, at http://www.cdc.gov/fieldtriage.

Regionalization in the context of EMS is defined as a geographically organized system of services that ensures access to care at a level appropriate to patient needs while maintaining efficient use of available resources. This system concept is especially germane in the care of children, given the relative scarcity of facilities capable of managing the full range and scope of pediatric conditions (Fig. 66-2). Regionalized systems of care coordinated with emergency medical dispatch, field triage, and EMS transport have demonstrated efficacy in improving outcomes for pediatric trauma patients, especially for younger children and for children with isolated head injury. Emerging evidence also suggests a similar benefit conferred to children in shock identified in the field who are preferentially transported to hospital EDs with documented pediatric ALS capability. The existence of statewide or regional standardized systems that formally recognize hospitals able to stabilize and/or manage pediatric medical emergencies is another federal EMSC performance measure against which operational capacity to provide optimal pediatric emergency care in this country is currently being judged.

In communities that do not have a hospital with the equipment and personnel resources to provide definitive pediatric inpatient care, interfacility transport of a child to a regional center should be undertaken after initial stabilization (see Chapter 66.1). When interfacility

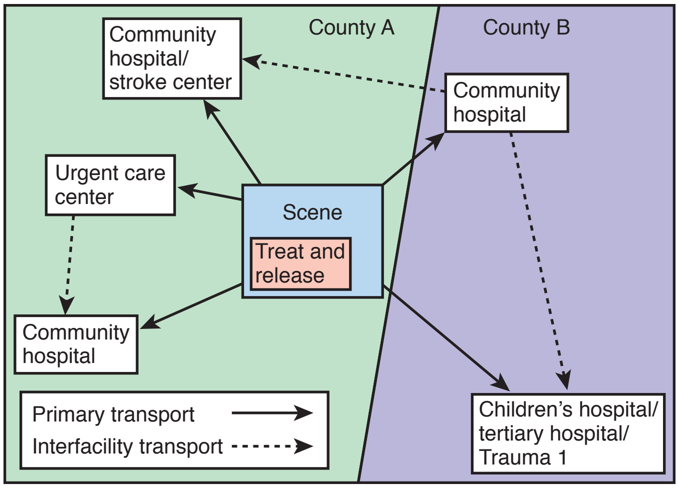

Figure 66-2 Transport options within a coordinated, regionalized emergency medical services system model. The objective is to ensure access to definitive care at a level appropriate to meet patient needs. *Solid arrows,* primary transport; *dotted arrows,* interfacility transport. *(Adapted from Institute of Medicine, Committee on the Future of Emergency Care in the U.S. Health System:* Hospital-based emergency care: at the breaking point, *Washington, DC, 2006, National Academies Press.)*

transport is to be undertaken, indications for transfer, parental consent for transfer, and acceptance of the patient by the receiving physician must all be clearly documented in the medical record.

THE EMERGENCY DEPARTMENT

The ability of hospital EDs to respond to the emergency care of children varies and depends on a number of factors in addition to availability of equipment and supplies. Training, awareness, and experience of the staff as well as access to pediatricians and medical and surgical subspecialists also play a key role. The majority of children who require emergency care are evaluated in community hospitals by physicians, nurses, and other healthcare providers with variable degrees of pediatric training and experience. Although children account for 25-30% of all ED visits, only a fraction of these encounters represent true emergencies. Because the volume of critical pediatric cases is low, emergency physicians and nurses working in community hospitals often have limited opportunity to reinforce their knowledge and skills in the assessment of ill or injured children and in pediatric resuscitation. General pediatricians from the community may be consulted when a seriously ill or injured child presents to the ED, and they should have a structured approach to the initial evaluation and treatment of an unstable child of any age, regardless of the underlying diagnosis. Early recognition of life-threatening abnormalities in oxygenation, ventilation, perfusion, and central nervous system function and rapid intervention to correct those abnormalities are key to successful resuscitation and stabilization of the pediatric patient.

In its report *The Future of Emergency Care in the U.S. Health System*, the IOM strongly recommended that hospitals and EMS systems appoint qualified coordinators for pediatric emergency care, a recommendation consistent with pediatric emergency readiness guidelines advocated by the AAP and ACEP. Only 18% of EDs in the United States currently appoint a physician coordinator, and 12% appoint a nursing coordinator for pediatric emergency care. EDs that do appoint these positions tend to be more prepared as measured by compliance with nationally published guidelines on the care of children in the ED.

Minimum standards must be met by community EDs to ensure that children receive the best emergency care possible. Updated guidelines for the care of children in the ED have been published, reaffirmed and are endorsed by the AAP, the ACEP, and the ENA. These guidelines provide current information on policies, procedures, protocols, quality assurance methods, and equipment and supplies considered essential for managing pediatric emergencies. Specific recommendations on equipment, supplies, and medications for the ED are listed and updates are available on the AAP website. Table 66-2 lists sample policies, procedures, and protocols specifically addressing the needs of children in the ED.

The way in which the family supports the child during a crisis and, consequently, how the family is supported in the ED when caring for the child are critical to patient recovery, family satisfaction, and

Table 66-2 Guidelines for Pediatric-Specific Policies, Procedures, and Protocols for the Emergency Department
Illness and injury triage
Pediatric patient assessment and reassessment
Documentation of pediatric vital signs, abnormal vital signs, and actions to be taken for abnormal vital signs
Immunization assessment and management of the underimmunized patient
Sedation and analgesia for procedures, including medical imaging
Consent (including situations in which a parent is not immediately available)
Social and mental health issues
Physical or chemical restraint of patients
Child maltreatment (physical and sexual abuse, sexual assault, and neglect) mandated reporting criteria, requirements, and processes
Death of the child in the emergency department
Do-not-resuscitate orders
Family-centered care, including: 1. Involving families in patient care decision-making and in medication safety processes. 2. Family presence during all aspects of emergency care, including resuscitation. 3. Education of the patient, family, and regular caregivers. 4. Discharge planning and instruction. 5. Bereavement counseling.
Communication with patient's medical home or primary healthcare provider
Medical imaging policies that address age- or weight-appropriate dosing for children receiving studies that impart ionizing radiation, consistent with ALARA (as low as reasonably achievable) principles
All-hazard disaster preparedness plan that addresses the following pediatric issues: a. Availability of medications, vaccines, equipment, and appropriately trained providers for children in disasters. b. Pediatric surge capacity for both injured and noninjured children. c. Decontamination, isolation, and quarantine of families and children of all ages. d. A plan that minimizes parent-child separation and includes system tracking of pediatric patients, allowing for the timely reunification of separated children with their families. e. Access to specific medical and mental health therapies, as well as social services, for children in the event of a disaster. f. Disaster drills, which should include a pediatric mass casualty incident at least every 2 yr. g. Care of children with special healthcare needs. h. A plan that includes evacuation of pediatric units and pediatric specialty units.

Data from American Academy of Pediatrics Committee on Pediatric Emergency Medicine; American College of Emergency Physicians Pediatric Committee; Emergency Nurses Association Pediatric Committee: Joint policy statement—guidelines for care of children in the emergency department, Pediatrics *124:1233-1243, 2009. Reaffirmed* Pediatrics *132:e281, 2013.*

the mitigation of posttraumatic stress. Commitment to patient- and family-centered care in the ED ensures that the patient and family experience guides the practice of culturally sensitive care and promotes patient dignity, comfort, and autonomy. In the ED setting, particular issues, such as family presence, deserve specific attention. Surveys of parents have indicated that most want to be with their child during invasive procedures and even during resuscitation. Allowing their presence has been shown to reduce parental and patient anxiety and does not interfere with procedure performance. Patient- and family-centered care is also associated with improved care quality and patient safety.

EMERGING ISSUES IN EMSC

Of the pediatric-specific recommendations promulgated by the IOM in its widely publicized 2006 report on the future of emergency care, 3 have emerged as especially important for EMSC. The first deals directly with increased federal funding for the EMSC program, which supports more than 80 grantees with an established presence in 49 states, 5 U.S. territories, the District of Columbia, and the freely associated states of Micronesia, Palau, and the Marshall Islands. The grant awards cover 5 distinct funding categories ranging from basic science and clinical investigation to public sector capacity-building programs to national technical assistance centers to multicenter trials conducted within a large research network. Through the diversity of activity generated within the program, and in collaboration with stakeholders, the EMSC program affords synergistic opportunity to further the progress realized in the program's first 30 yr of existence. A tumultuous appropriations history not-with-standing, including several years of budget elimination, Congressional reauthorization, due in 2014, and will ensure stability for the EMSC program at least in the near term.

In addition to EMSC resource support, the IOM also recommended that (a) federal agencies in partnership with state and regional planning bodies and emergency care provider organizations convene a panel with multidisciplinary expertise to develop strategies for addressing pediatric needs in the event of a disaster, and (b) the U.S. Department of Health and Human Services conduct a study to examine the gaps and opportunities in emergency care research, including pediatric emergency care, and recommend a strategy for the optimal organization and funding of the research effort. Both of these recommendations have generated activity of significant import to the emergency care community, EMSC specifically, and warrant mention.

Disaster Preparedness

Children constitute approximately 30% of the population; in a catastrophic event, natural or human-made, several unique factors place children at disproportionate, increased risk. During the day large groups of children are typically cohorted, separate from their families, in schools and daycare centers where mass casualties can easily occur and reunification is challenging. Furthermore, in the event of a biologic or chemical attack, unique anatomic, developmental, and physiologic features make children especially vulnerable to absorption and/or inhalation of toxic agents. Following the broad pediatric impact of the devastating Gulf Coast hurricanes Katrina and Rita in the mid-2000s, Congress established the National Commission on Children and Disasters. The Commission's mandate was to conduct a comprehensive study to examine and assess the needs of children as they relate to preparation for, mitigation of, response to, and recovery from all hazards, including major disasters and emergencies. The findings and recommendations of the Commission's 2010 report to the President and to Congress have established a broad framework for ongoing preparedness efforts related not only to child physical health, but also, importantly, to behavioral and emotional well-being. In addition, pertinent resources related to pediatric-focused areas of concerns such as evacuation, separation-reunification, sheltering, countermeasures, surge capacity and triage are being monitored and chronicled under the PEDPrepared Disaster Clearinghouse at the EMSC National Resource Center website, http://www.emscnrc.org/pedprepared.

Bibliography is available at Expert Consult.

66.1 Interfacility Transport of the Seriously Ill or Injured Pediatric Patient

*Elizabeth A. Edgerton and Bruce L. Klein**

Patients often seek treatment at facilities that lack sufficient expertise to treat their conditions, necessitating transfer to more appropriate specialty centers. This is especially pronounced in pediatrics. EMS providers or parents usually take children to local EDs first, where their conditions and physiologic stabilities are assessed. Although bringing a child directly to the local ED may be proper logistically, local EDs can be less than ideal for pediatric emergencies. Children account for 27% of all ED visits but only 6% of EDs have all the necessary supplies for pediatric emergencies. Also, general EDs are less likely to have pediatric expertise or policies in place for the care of children. Outcomes for critically ill children treated in pediatric intensive care units (PICUs) are better than for those treated in adult ICUs. When pediatric critical care is required, transport to a regional PICU is indicated. In addition, often the type of subspecialty care needed (e.g., pediatric orthopedics) is available only at the pediatric center.

Pediatric transport medicine consists of the interfacility transfer of infants, children, and adolescents from community facilities to pediatric centers that can provide the needed level of expertise. Transport is performed by professionals proficient in pediatric transport on specially age-equipped ground, rotorcraft, or fixed-wing ambulances. Pediatric transport medicine is a multidisciplinary field comprising pediatric critical care and pediatric emergency medicine physicians (and, sometimes for very young infants, neonatologists); nurses, respiratory therapists, and paramedics with advanced training for pediatric transport; and communications specialists. The goal is to deliver quality pediatric care to the region's children, while optimizing the use of regional resources. For the individual child, the aim is to stabilize and, when appropriate, begin treating as soon as possible—that is, at the local ED and during transport, well before arrival at the referral center.

The AAP Section on Transport Medicine, the Association of Air Medical Services, the Federal Aviation Administration (FAA), and others have published recommendations regarding transport programs. Models for pediatric transport services vary depending on the needs and available resources in a geographic region, but all should have certain basic components: a network of community hospitals and regional pediatric centers; an established communications and dispatch system that easily facilitates transfer to the pediatric center; ground and/or air ambulances; medical and nursing leadership from pediatric critical care or pediatric emergency medicine (or neonatology); experienced pediatric medical control physicians (MCPs); a multidisciplinary team of pediatric transport professionals specially trained to provide the appropriate level of care required during transport; operational and clinical policies and procedures that guarantee safe, state-of-the-art, and timely pediatric critical care transport; and a database for quality and performance assessment.

COMMUNICATIONS AND DISPATCH CENTER

Communications are one of the most vital components of a regional transport system. Treating a critically ill or injured child is an uncommon event for most community physicians. Therefore, they need to know *whom*, *how*, and *when* to call for assistance in the stabilization and transfer of a pediatric patient. The communications and dispatch center provides a single telephone number for such calls.

The communications and dispatch center coordinates communications among the outlying facility, receiving unit, MCP, transport team, and others. This center may be part of a hospital unit (e.g., ED, PICU), self-contained in a single institution (e.g., Emergency Communications and Information Center), or based offsite as a freestanding center coordinating communications and dispatch for multiple transport programs.

Staffing varies depending on the type of center. On-duty nurses or physicians may receive calls at unit-based models with low volumes.

*Adapted initially from Dr. Lorry R. Frankel's chapter in the 18th edition of this book.

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In contrast, dedicated communications specialists usually staff self-contained or freestanding centers, which tend to be busier. The communications specialist has numerous responsibilities, including answering the referring physician's call promptly; documenting essential patient demographic information; arranging for immediate consultation with the MCP; dispatching the transport team to the referring facility expeditiously; updating the referring facility with any changes in the arrival time; and coordinating medical control and other necessary transport-related calls. The transport team must be equipped with a cellular telephone or radio for immediate contact with the receiving and referring facilities.

MEDICAL CONTROL PHYSICIAN

The MCP is involved in the clinical care and safe transport of the patient from the time of referral through arrival at the receiving hospital unit. The MCP's oversight increases once the transport team arrives at the referring facility. The MCP should have expertise in pediatric critical care or pediatric emergency medicine (or sometimes neonatology). Besides having the knowledge required to stabilize a critically ill or injured child, the MCP must be familiar with the transport environment; the transport team members' capabilities; the program's policies and procedures; and the region's geography, medical resources, and regulations regarding interhospital transport. The MCP must possess good interpersonal and communication skills and must be able to maintain collegiality with the referring hospital's staff during a potentially difficult and stressful situation.

Once a transport call is received, the MCP must be immediately available to confer with the referring physician. Although the MCP may have other responsibilities, these transport responsibilities take priority in order to avoid undue delays when transferring a critically ill child. Often the MCP recommends further testing or therapeutic interventions that can be delivered by the referring hospital before the transport team arrives. The MCP may seek additional guidance from other specialists, as necessary. Because the child's condition may change rapidly, the MCP must remain ready to give additional advice. All conversations and recommendations regarding the care of the patient should be documented. Some centers record these conversations.

After discussion with the referring physician—and, when warranted, with the transport staff—the MCP determines the best team composition and vehicle for transport. The MCP usually does not accompany the team but remains available, by phone or radio, to supervise care.

TRANSPORT TEAM

Transport team composition varies among programs—and sometimes within an individual program. The team's composition is based on a variety of factors, including the severity of the child's illness or injury; the distance to the referring facility; the team members' advanced practice abilities; the referrer's (reasonable or unreasonable) insistence that a physician be present; the program's historical professional makeup; and the region's staffing regulations. The team should be composed of physicians, nurses, respiratory therapists, and/or paramedics who have expertise in pediatric critical care or pediatric emergency medicine (or neonatology in some cases), as well as advanced education and training in those cognitive and procedural areas important for pediatric critical care transport. There is a lower incidence of transport-related morbidity for critically ill and injured children transported by pediatric specialty teams than for those transported by generalist teams.

Various scoring systems have been developed to predict the need for a physician during transport. It seems that a team member's training, experience, and skill in treating critically ill patients are more important considerations than that team member's professional degree. Team members must understand basic pediatric pathophysiology and collectively must be able to assess and monitor a critically ill or injured child; manage the airway and provide respiratory support; obtain vascular access; perform point-of-care testing; and administer those medications commonly used in pediatric critical care transport. They must be familiar with the physiologic alterations as well as practical difficulties of the transport environment and, importantly, must be comfortable working in an out-of-hospital setting. Physicians are less often deployed on transport teams in part because of the advanced training that other healthcare professionals on the transport team receive.

The transport team should have a designated team leader who, in addition to the team leader's many other responsibilities, interacts with the MCP during the transport. Once the team arrives at the referring facility, the team should reassess the child's condition, review all of the pertinent diagnostic studies and therapies, and discuss the situation with the referring staff and parents. If the patient's condition has changed significantly, the team leader may need to contact the MCP for additional advice. Otherwise, the team leader should generally notify the MCP before starting to bring the child to the receiving facility. Any care delivered by the team during transport should be documented, and copies of all medical records—including laboratory data, radiographs, and scans—should accompany the child to the pediatric center. The receiving unit must be updated prior to arrival so it can finalize preparations for the patient.

GROUND VERSUS AIR AMBULANCE

Transport options include ground, rotorcraft, and fixed-wing ambulances. Vehicle selection depends on the child's emergency needs; transport team's capabilities; any out-of-ordinary staffing or equipment requirements (e.g., for extracorporeal membrane oxygenation, inhaled nitric oxide or heliox); referring facility's abilities; distance; terrain; traffic patterns; ground or air ambulance availability; helicopter landing pad or airport access; weather conditions; and expense.

The transport vehicle must be equipped with electrical power, oxygen, and suction and must have sufficient space for the equipment and supplies that the team brings along—stretcher or isolette, monitor, ventilator, oxygen tank(s), medication pack(s), infusion pumps, and more. Compared with helicopters, ambulances are more spacious and able to carry more weight, so they can accommodate larger teams and more equipment. Another advantage of ground ambulance transport is the ability to stop en route if the patient's condition deteriorates; this feature greatly facilitates the performance of certain interventions, such as intubation.

An airplane may be able to fly to an area when distance (>150 miles), altitude, or weather precludes helicopter use. However, the use of an airplane necessitates several ambulance transfers, with their attendant delays and potential complications. There also are delays when the plane must fly from a remote base to the program's jurisdiction.

TRANSPORT PHYSIOLOGY

When possible, the transport team tries to provide the same care during transport as the patient would receive in the specialty center. This can be difficult, though, because of limitations in personnel, equipment, and space, as well as other environmental challenges.

The team and child are subjected to variable intensities of background noise and vibration while traveling in the vehicle cabin. Noise can impair the team's ability to auscultate breath sounds, heart sounds, and blood pressure, another reason for monitoring vital signs mechanically and relying on other assessment modalities, such as the level of mentation, skin color, and capillary refill. To mitigate noise, the helicopter crew and patient should wear helmets or headphones (or another wearable noise attenuator such as MiniMuffs [Natus Medical Incorporated, San Carlos, CA]). Motion and vibration can lead to increased metabolic rate, shortness of breath, and fatigue in the patient, as well as motion sickness in the patient and staff.

On fixed- or certain rotary-wing transports, the patient may suffer adverse physiologic effects from altitude. With increasing altitude, the barometric (atmospheric) pressure decreases and gases expand. As the barometric pressure drops and gas expands, the partial pressures of ambient oxygen (PO_2) and, consequently, arterial oxygen (PaO_2) decrease. For example, at 8,000 feet—an elevation at which unpressurized airplanes may fly, as well as the effective cabin altitude for many pressurized airplanes flying at 35,000 to 40,000 feet—the barometric pressure, PO_2, PaO_2, and arterial oxygen saturation fall to 565 mm Hg, 118 mm Hg, 61 mm Hg, and 93%, respectively. (In comparison, the barometric pressure, PO_2, PaO_2, and arterial oxygen saturation are

760 mm Hg, 159 mm Hg, 95 mm Hg, and 100% at sea level.) Although healthy individuals usually tolerate these changes well, patients with respiratory insufficiency, significant blood loss, or shock may decompensate and should receive supplemental oxygen.

Gases expand 10-15% at the few thousand feet at which helicopters typically fly, and approximately 30% at 8,000 feet. Gases within the body itself also expand as the altitude increases. Gas expansion must be appreciated during transport via air of a patient with a pneumocephalus, pneumothorax, bowel obstruction, or another condition involving entrapped gas. Prior to transport, a pneumothorax should be decompressed, and a nasogastric tube inserted for ileus.

SAFETY

Safety is of paramount importance and mandates constant vigilance by everyone involved. Accident rates for pediatric air and ground transport are estimated at approximately 1/1,000 transports. The team should routinely attend pilot briefs, as well as perform safety inspections of the vehicles and equipment, aided by checklists. When in doubt, the MCP should solicit input from the staff about whether to transport via air or ground ambulance or to employ lights and sirens, decisions that cannot be taken lightly. The pilot's or driver's judgment as to the safety of proceeding during inclement weather or with a mechanical problem must not be overruled.

Organizations, such as the FAA and the National Transportation Safety Board, play a role in ensuring safe interfacility transport. The Commission on Accreditation of Medical Transport Systems (CAMTS) is an independent, peer review organization that was established in 1990 in response to the number of air medical accidents in the 1980s. CAMTS, through voluntary participation, audits and accredits fixed-wing, rotary-wing, and ground interfacility medical transport services.

FAMILY-CENTERED CARE

Family-centered care represents a philosophy that respects the important role that family members play in a child's care. It recognizes family members and healthcare providers as partners in caring for the child. Family presence during transport is beneficial because it provides support to children in stressful situations and assists healthcare providers in delivering care to patients with complex and/or chronic medical problems.

As care is transitioned from the referring hospital, it is the transport team's responsibility to maintain family-centered care. The team meets with family members to explain the transport process, obtain consent, and discuss anticipated management. When possible, the transport team should attempt to accommodate a family member's presence onboard. However, the family member and child may need to be separated when the child is critically ill and rapid transport is essential, or if there is space or weight limitations in the air or ground ambulance. In these situations, it is important that family members have a clear understanding of how the child will be cared for during the separation.

REFERRING HOSPITAL RESPONSIBILITIES

Transfer of a patient to another facility requires written documentation by the referring physician of the need and reasons for transfer, including a statement that the risks and benefits, as well as any alternatives, have been discussed with the parents. The parent's informed consent to the transfer should be obtained.

Federal law under the Emergency Medical Treatment and Active Labor Act (EMTALA), part of the Consolidated Omnibus Budget Reconciliation Act (COBRA), imposes specific requirements that a patient presenting to an ED be given a medical screening examination without regard to ability to pay. If upon examination an emergency medical condition is found, the hospital is required to stabilize the patient or to transfer the patient to another facility if unable to stabilize the patient or if requested by the patient. The primary requirement is that the referring physician must certify that the medical risks of transfer are outweighed by its potential benefits. The receiving hospital must agree to accept the patient and have the space and staff to provide the necessary treatment. The transferring hospital is responsible for arranging for the transfer and ensuring that it is performed by qualified medical personnel with appropriate equipment. It must send copies of the patient's medical records and test results, even those that become available after the transfer is complete.

Some referring hospitals have entered into transfer agreements with specialty centers in the interests of facilitating the smooth and safe transfer of the pediatric patient. Having prepared forms for all of the above purposes also aids in the transfer process.

Each hospital needs to review its facility's guidelines, and if established guidelines do not exist the EMSC, in partnership with the Emergency Nurses Association and the Society of Trauma Nurses, has developed the "Inter Facility Transfer Tool Kit for the Pediatric Patient" (available at www.pediatricreadiness.org). This tool kit includes the essentials for comprehensively and safely transferring the pediatric patient to the most appropriate level of care in a timely manner.

EDUCATIONAL OUTREACH

Besides safe and rapid transport, regional pediatric transport programs (and their specialty centers) have an obligation to provide educational opportunities to community healthcare providers so that these providers can acquire the necessary skills to evaluate and stabilize a critically ill or injured child until the transport team arrives. These learning activities may include transport case reviews; lectures on pediatric acute care topics; resuscitation programs such as the PALS course, APLS course, and S.T.A.B.L.E. (sugar and safe care, temperature, airway, blood pressure, lab work, emotional support) program; and rotations through the specialty center's pediatric ED and PICU. These activities also help cement relationships with the referring facility's staff.

Bibliography is available at Expert Consult.

66.2 Outcomes and Risk Adjustment

Evaline A. Alessandrini

Health services research has documented wide variation in the likelihood that patients receive quality, evidence-based healthcare, and this can negatively impact the health of children and youth. The complexities of delivering high-quality healthcare are magnified in the ED. Patients are in crisis, EDs are often overcrowded, patient–physician relationships are based on brief interactions, and the variety of complaints and diagnoses is immense.

OUTCOME MEASURES IN EMERGENCY MEDICAL SERVICES FOR CHILDREN

Emergency Care for Children: Growing Pains, one report of the 2007 IOM series on the future of emergency care, recommends that pediatric emergency medical systems specifically support the development of national standards for emergency care performance measurement. The Donabedian structure–process–outcome model has set the framework for most contemporary quality measurement and improvement activities. Structural elements provide indirect quality-of-care measures related to a physical setting and resources. Process indicators provide a measure of the quality of care and services by evaluating the method or process by which care is delivered, including both technical and interpersonal components. Outcome elements describe valued results related to lengthening life, relieving pain, reducing disabilities, and satisfying the consumer.

Defining relevant outcomes for pediatric emergency care is difficult. A true "outcome-based" approach describes observable measures such as mortality, risk of organ system failure, and disability. An alternative approach is a "resource-based" outcome measure definition related to the level of care required. Children who are more ill, in general, require more resources. Thus, resource use across groups of patients reflects relative severity of illness in the groups. Examples of resource-based outcomes include need for hospital admission (ED disposition), ED

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Table 66-3	Stakeholder-Endorsed Outcome Measures for Pediatric Emergency Care

- Overall patient satisfaction with ED visit—nurses
- Overall patient satisfaction with ED visit—physicians
- Parent/caregiver understanding of ED discharge instructions
- ED length of stay for patients <18 yr of age
- Percentage of patients <18 yr of age left without being seen (LWBS)
- Effective pediatric procedural sedation
- Acute fracture patients with documented reduction in pain within 90 min of ED arrival
- Improvement in asthma severity score for patients with acute exacerbations
- ED revisit within 48 hr resulting in admission
- Medication error rates
- Global sentinel never events
- Unplanned return visit within 72 hr for the same/related asthma exacerbation
- Failure to achieve seizure control within 30 min of ED arrival
- Return visits within 48 hr resulting in admission for all urgent and emergency patients

Table 66-4	Elements of the PRISA II Score

- Age <90 days
- Minor injury
- Abdominal pain in an adolescent
- Immunodeficiency
- Indwelling medical device
- Controller asthma medication
- Referral status
- Temperature
- Decreased mental status
- Low systolic blood pressure (<70 neonates and infants; <83 children; <100 adolescents)
- High diastolic blood pressure (>59 neonates and infants; >70 children; >90 adolescents)
- Low serum bicarbonate value (<20 mEq/L)
- High potassium value (>4.9 mEq/L)
- High blood urea nitrogen value (>80 mg/dL)
- High white blood cell count (>20,000/mm^3)
- Oxygen therapy other than during inhaled bronchodilator treatments
- Low bicarbonate and high potassium values

Table 66-5	Elements of the RePEAT Score

- Age
- Chief complaint
- Triage category
- Current use of prescription medications
- Arrival via EMS (ground/air)
- Heart rate
- Respiratory rate
- Temperature

length of stay, costs, and diagnostic and therapeutic interventions performed in the ED. Table 66-3 provides a list of outcome measures for pediatric emergency care developed by EMSC stakeholders during 2 separate consensus meetings.

RISK ADJUSTMENT

Measuring outcomes offers opportunities for EDs and other components of the healthcare system to make effective improvements over time, benchmark, and compare their end results with those of other institutions. Meaningful comparisons between EDs or within an ED over time generally require risk adjustment, which accounts for patient-related attributes such as age, or for preexisting conditions associated with the outcome of interest. Risk-adjustment "levels the playing field," so that comparison of outcomes is as fair and meaningful as possible. Because children present to EDs with illnesses of varying acuity, ranging from rashes and colds to cardiac arrest, there is an inextricable linkage of severity to outcomes. Severity typifies the concept of "risk"—the higher the severity, the higher the risk of a given outcome. Without risk adjustment, EDs with sicker patients may appear to have worse outcomes.

A large number of instruments have been developed to adjust for severity or risk in clinical research and quality improvement activities. The commonly used PRISM (Pediatric Risk of Mortality) score is not well-suited for EMSC, given the extremely low rate of mortality. Several disease-specific acuity scoring systems are available for use in EMSC. The majority of these are intended for use in trauma patients, including the Injury Severity Score, Trauma Score, and Pediatric Trauma Score.

RISK ADJUSTMENT TOOLS IN EMSC

The choice of a risk-adjustment tool depends on several factors, including the population under study, the setting, and the outcomes of interest. Two risk-adjustment tools have been developed specifically for pediatric emergency medicine, the second-generation Pediatric Risk of Admission (PRISA II) score and the Revised Pediatric Emergency Assessment Tool (RePEAT).

Pediatric Risk of Admission II

PRISA II uses components of acute and chronic medical history and physiology to determine the probability of hospitalization. The outcome measure of interest is mandatory hospital admission (admissions utilizing therapies best delivered on an inpatient basis). Table 66-4 lists the patient-related attributes contributing to the PRISA II risk-adjustment score. Analytic models including the PRISA II score have good calibration (how well the probabilities predicted from the model correlated with the observed outcomes in the population) and discrimination (the ability to categorize subjects correctly into the categories of interest) with respect to mandatory hospital admission. Construct validity of the PRISA score was demonstrated by measuring the rates of the secondary outcomes: mandatory admission, PICU admission, and mortality. As the probability of hospital admission rose, the proportion of patients with these increasing care requirements also increased. This finding strongly supports the use of the PRISA II score as a valid measure of severity of illness. In addition, PRISA II was used to demonstrate racial/ethnic differences in severity-adjusted hospitalization rates, and also demonstrated that teaching hospitals had higher than expected severity-adjusted admission rates in comparison with nonteaching hospitals.

Revised Pediatric Emergency Assessment Tool

The RePEAT uses a limited set of data collected at the time of triage to model severity of illness as reflected by the level of care provided in the ED. This tool was developed to predict the level of care provided—routine assessment (clinical examination only ± nonprescription medicine), specific ED care (ED diagnostics and/or therapeutics), or hospital admission—with the implicit assumption that patients with a higher level of care have a higher severity of illness. Table 66-5 lists the patient-related attributes contributing to the RePEAT risk-adjustment score. As with the PRISA II score, analytic models including the RePEAT score have good calibration and discrimination with respect to predicting ED care and hospital admission. Furthermore, analytic models that compare costs and ED length of stay between EDs are improved by adjustment for severity of illness using the RePEAT score. These results demonstrate that RePEAT is a reasonable marker of severity of illness and that inclusion of this severity index substantially improves the ability to compare outcomes between EDs.

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66.3 Principles Applicable to the Developing World

Jennifer I. Chapman and David M. Walker

International pediatric emergency medicine is an emerging academic field whose practitioners are committed to international collaboration aimed at improving the quality of care for children outside their national borders (Table 66-6).

Many models currently exist for the delivery of emergency care. The **triage officer** model is one in which a practitioner who works in an ED briefly provides intake for all patients and calls specialists to provide definitive care depending on the nature of the presenting complaint. The **multiple physician** model describes a scenario in which patients are divided by their chief complaints into medical, surgical, and pediatric groups. The field of emergency medicine provides a specialist skilled in the recognition, stabilization, and definitive treatment of a wide variety of acute illnesses and injuries. This approach to managing an emergency center is more efficient, relies less heavily on specialist availability, and requires fewer highly trained practitioners to operate. Children and adolescents constitute a subpopulation of emergency patients that deserves special attention because of pediatric-specific conditions, unique anatomy and physiology, developmental staging, and parental interactions.

The maturity of pediatric emergency medicine (PEM) in any given area depends on the healthcare priorities and resources of that geographic or physical setting. The places in which emergency care takes place range from the community (for those with no access to organized medical care) to state-of-the-art pediatric EDs in populated centers. The scope ranges from care of the individual patient to the management of populations of children involved in large-scale disasters. Barriers to quality care are different in each situation and in each part of the world, with the implication for the astute international PEM practitioner that solutions must be targeted to the local context of healthcare within a given environment.

Table 66-6 Pediatric Emergency Medicine (PEM) Professional Organizations

Organization	Country
Pediatric Emergency Medicine Society of Australia and New Zealand (PEMS) Website: www.pems-aunz.org	Australia, New Zealand
PEM Section, Canadian Association of Emergency Physicians (CAEP)	Canada
PEM Section, Canadian Paediatric Society (CPS) Website: www.cps.ca/en/sections/section/emergency-medicine	Canada
Groupe Francophone de Réanimation et Urgences Pédiatriques (GFRUP) Website: www.gfrup.com	France
Society for Trauma and Emergency Pediatrics (STEP) Website: stepindia.org.in	India
Pediatric Emergency Medicine Israel (PEMI) Website: www.pemi.org.il	Israel
La Società Italiana di Medicina Emergenza ed Urgenza Pediatrica (SIMEUP) Website: www.simeup.com	Italy
La Asociación Nacional Mexicana de Urgencias/Emergencias Pediátricas (ANMUEP) Website: www.anmuep.org	Mexico
Sociedad Española de Urgencias de Pediatria (SEUP) Website: www.seup.org	Spain
Pediatric Emergency Medicine Switzerland (PEMS) Website: www.pems.ch	Switzerland
Çocuk Acil Tıp ve Yoğun Bakım Derneği (Society of Pediatric Emergency and Intensive Care Medicine) Website: www.cayd.org.tr	Turkey
PEM Section, European Society for Emergency Medicine (EuSEM) Website: www.eusem.org/sectionpaediatric/	Europe
Association of Paediatric Emergency Medicine (APEM) Website: www.apem.me.uk	UK
PEM Interest Group, Society for Academic Emergency Medicine (SAEM) Website: http://community.saem.org/saem/communities/viewcommunities/groupdetails?CommunityKey=3dc973c2-35fd-42c2-9dcf-99e69a20d206	USA
Section on Emergency Medicine, American Academy of Pediatrics (AAP) Website: www.aap.org/sections/pem	USA
PEM Section, American College of Emergency Physicians (ACEP) Website: www.acep.org/pediatricsection	USA

EMSC AND THE CONTINUUM OF CARE MODEL

EMSC is a U.S. federal initiative designed to reduce child and youth disability and death as a result of severe illness or injury. The EMSC program has developed an operational framework for conceptualizing a systems approach to emergency care for children, known as the *continuum of care model*. The model specifically refers to the seamless care of ill and injured children from the community and medical home through to definitive care and return to the community. It has the following 5 principal components:

1. Prevention
2. Out-of-hospital care, both emergency response and prehospital transport
3. Hospital-based care: emergency center and inpatient unit
4. Interfacility transport, as necessary, for definitive or subspecialty care (see Chapter 66.1)
5. Rehabilitation

This framework can also be applied to discussion of emergency care for children on an global level. With medical infrastructures that may not be consistent or well-organized, or that have been weakened by civil strife, natural disasters, and economic loss, the focus of child health in the developing world has been on prevention and acute care.

APPLYING THE CONTINUUM OF CARE MODEL TO THE DEVELOPING WORLD

Prevention

Infectious Diseases

International child health has focused mainly on reducing preventable childhood illnesses, primarily through immunizations. Enormous advances have been realized in measles, neonatal tetanus, and polio reduction; wild-type smallpox was eradicated in 1978. Although there are advocates for providing primary care interventions (e.g., vaccinations) in the ED, the role of the PEM practitioner in this area of prevention has been limited.

Injuries

Injuries are a leading cause of childhood morbidity and mortality. Unintentional injuries constitute 90% of injury mortality to children ages 5-19 yr and are the cause of 9% of the world's mortality. Intentional injuries, an underrecognized and underreported phenomenon primarily for cultural reasons, make a smaller but significant contribution. Unintentional injuries cause more than 2,000 childhood deaths daily or 950,000 annually worldwide. The burden of these deaths is borne disproportionately by children in middle- and lower-income

countries, where more than 95% of all injury deaths occur. For each of these deaths, many more children are permanently disabled and an even larger number are treated and released without permanent sequelae.

The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) have outlined several proven injury prevention strategies of which child health practitioners in the global community must be aware. The top 3 causes of injury mortality are traffic-related injuries, burns, and drowning. There are 7 specific effective strategies for reducing **road traffic injuries:** a minimum drinking age, appropriate child restraints and seatbelts, helmets for motorcycle and bicycle riders, reduced vehicle speeds around schools and residential areas, running lights on motorcycles, graduated licensing for drivers, and separation of different types of road users. There is insufficient evidence to demonstrate that school-based programs on drunk driving, increased pedestrian visibility, or designated driver programs are effective. Although these strategies have been proven effective, the data are based on research from the United States and may not be generalizable to other countries. It may be difficult to reduce vehicle speeds around schools when there is insufficient infrastructure for street signs. Alternatively, lack of separation of car and bus traffic from bicyclists and pedestrians contributes to unsafe and dangerous road conditions. This is more of a problem in lower- and middle-income countries, where bicycles and motorized 2-wheel vehicles are used to carry children as well as goods, while the drivers negotiate among rapidly moving vehicles. With rising income, these countries have seen increases in both the number of cars and the number of 2-wheeled vehicles, with a corresponding increase in the number of related injuries.

For reducing **drowning deaths**, strategies that have proven effective focus on creating barriers between children and water hazards, such as covering wells, buckets, and other standing sources of water, and placing high fences around pools (see Chapter 74). **Burns** have been addressed by advocating for installation of smoke detectors and lowering the temperature of water from water heaters (see Chapter 75).

For the PEM practitioner, involvement in prevention depends largely on the local epidemiology of injuries and the factors contributing to those injuries. Involvement can include parental and patient education or activism to change local practices through laws and new community standards. Additionally, work can be done with groups of practitioners or healthcare centers to increase capacity to care for injured children. One can also work on a larger scale on projects initiated by a group such as the WHO, UNICEF, or Safe Kids Worldwide, to develop and evaluate intervention strategies that target specific preventable injuries.

Out-of-Hospital Care

Out-of-hospital care comprises access to emergency services, prehospital care, and interfacility transport of patients. Morbidity and mortality arise from delayed or limited access to emergency care, lack of prehospital care, transport without proper monitoring or trained personnel, or delayed transport to a higher level of care. Safe transport of seriously ill children is a neglected global health issue. An emergency response system must address the following links in the patient's care: a communication system with prompt activation of EMS, the correct assessment and initial treatment of the patient, and the rapid transport to definitive care.

Access to Care

When a child is injured or ill, a parent or caretaker must be able to access help and activate EMS. Many countries around the world have dedicated emergency numbers to rapidly dispatch medical, police, or fire services. The simple "112" emergency number has been adopted and is being phased in throughout the European Union member states, to be used to access medical, fire and police services in addition to secondary regional emergency access numbers. The universal U.S. emergency number system 911 today covers the large majority of the country (98%) and has enhanced features of automatically linking the phone number to an address. However, there remain limitations to universal access resulting from absence of phones in some households, unclear addresses in rural areas, and insufficient reach of the emergency system. In low- and middle-income countries, no such universal emergency numbers have been established, requiring access by direct dialing to an ambulance, if such private services exist. In most low- and middle-income countries, the family must bring the ill or injured child to the health facility for stabilization and treatment. For this to occur, families must overcome financial and geographic barriers, which can result in delayed presentation for care. This delay predictably increases the acuity of the illness or injury and associated complications, and decreases the likelihood of full recovery and survival.

Prehospital Care

In regions with maturing EMS systems, there must be adequately trained personnel to stabilize and transport the child to a medical facility. The quality and level of training of such prehospital personnel vary tremendously among countries and within regions of the same country. In urban areas, there is a greater concentration of medical care and therefore a greater opportunity to have strong prehospital training. In most of Asia and sub-Saharan Africa, trained personnel are used primarily to transfer patients between health facilities, and not from the initial site of illness or injury. In most high-income countries, EMS are dispatched to the patient.

A different approach to prehospital work is exemplified by the French EMS, called Service d'Aide Médicale Urgente (SAMU). In this system, a physician is integral to the prehospital team. A physician, typically an emergency medicine specialist in larger areas, will review every call for acuity and can dispatch a physician-led team by ambulance to go to the patient's home to assess, stabilize, and initiate treatment. This Franco-German system is used in other countries, including many in Latin America and Europe. There are no clear data on the cost-effectiveness and patient outcomes associated with delivery of patients to the nearest facility versus bringing hospital resources to the patient. Some research suggests, however, that it is difficult for ambulance-based physicians to maintain their field skills given the relatively low frequency of high-acuity or high-complexity cases.

Around the world, the effort to establish standardized approaches to prehospital care exists primarily in the form of courses to educate EMS and hospital personnel in the emergency management of patients. For trauma care, the WHO manuals *Prehospital Trauma Care Systems* and *Guidelines for Essential Trauma Care* both focus on guidelines for prehospital and trauma care systems that are affordable and sustainable. The AAP course Pediatric Education for Prehospital Professionals is a dynamic, modularized teaching tool designed to provide specific pediatric prehospital education that can be adapted to any EMS system. Table 66-7 lists additional prehospital resources.

Although most middle- and high-income countries have a system of trained EMS workers, low-income countries lack this advanced tier of emergency care. In these countries, commercial drivers, volunteers, and willing bystanders provide the first line of care. Training a cadre of first responders can rely on existing networks of aid or can be drawn from specific populations, such as students, soldiers, or public servants. Training needs to emphasize basic lifesaving and limb-saving interventions, including how to stop bleeding and support breathing, access advanced care, and splint broken limbs. In Ghana, for example, 335 taxi drivers participated in a first-aid course that relied heavily on demonstration and practice rather than knowledge transfer through didactic sessions. Taxi drivers were selected because they already provided much of the transport for injured patients, either voluntarily or for pay by the family. Two years after the course, external evaluators favorably rated the quality of their care in comparison with that of a group of untrained drivers. In rural areas, such first responders become vital in providing emergency interventions when more definitive care is distant. Thus, a system of trained first responders forms the foundation of an effective prehospital system.

Methods of Transport

In many low-income countries, there is no means of transport other than the family's motorized or other type of transport. Health centers may only have 1 vehicle for transport to a higher-level facility. This

Table 66-7	Pediatric Emergency Medicine (PEM) Resources
Prehospital	Advanced Medical Life Support (AMLS) Newest course developed by the National Association of Emergency Medical Technicians (NAEMT) to provide more clinical teaching and reasoning around emergent medical problems. Course is open to physicians, nurses EMTs and paramedics. Website: www.naemt.org/education/amls/amls.aspx
	Prehospital Trauma Life Support Available in 33 countries, PHTLS is the leading continuing education program for prehospital emergency trauma care. Website: www.phtls.org
	International Trauma Life Support Training course for prehospital trauma care. Website: www.itrauma.org
	The Sphere Project Downloadable modules on disaster preparedness. Website: www.sphereproject.org
	Pediatric Education for Prehospital Professionals (PEPP) Curriculum designed specifically to teach prehospital professionals how to assess and manage ill or injured children. Website: www.peppsite.org
	Pocket Book of Hospital Care for Children A publication of WHO providing guidelines for the management of common illnesses with limited resources. Incorporates both the Emergency Triage Assessment and Treatment (ETAT) and Integrated Management of Childhood Illness (IMCI) guidelines. Website: www.who.int/maternal_child_adolescent/documents/9241546700/en/index.html
Hospital care	Where There Is No Doctor: A Village Health Handbook Healthcare manual for health workers, clinicians, and others involved in primary healthcare delivery and health promotion programs around the world. Available for purchase or as a free download. Website: www.hesperian.org
	CHILDisaster Network Registry for those with education and experience in humanitarian emergencies to volunteer their time when needed in time of a disaster. Website: www.aap.org/disaster
Humanitarian emergencies	Management of Complex Humanitarian Emergencies: Focus on Children and Families Training course offered by the Children in Disasters Project, sponsored by the Rainbow Center for Global Child Health (RCGCH) in Cleveland, OH. Held in early June annually.
	Manual for the Health Care of Children in Humanitarian Emergencies Publication of WHO that provides comprehensive guidance on child care in emergencies; includes information on care of traumatic injuries and mental health emergencies. Website: www.who.int/child_adolescent_health/documents/9789241596879/en/index.html
	PEMdatabase.org A website devoted to pediatric emergency medicine. Contains links to conferences, evidence-based medicine reviews, research networks, and professional organizations. Website: www.pemdatatbase.org
Access to academic publications relevant to PEM	HINARI Access to Research Initiative Program established by WHO and others to enable developing countries to gain access to one of the world's largest collections of biomedical and health literature. Website: www.who.int/hinari/en
	ACEP Ambassador Program Provides the names of U.S.-boarded emergency medicine physicians who can provide advice and information on issues pertaining to the progress and status of emergency medicine in their assigned countries. Website: www.acep.org/content.aspx?id=25138
Involvement	International emergency medicine section, American College of Emergency Physicians This group maintains a list of international organizations and clinical opportunities, many of which involve emergency care of children. Website: http://www.acep.org/_InternationalSection/International-Emergency-Medicine-Related-Resources/
	Section of International Child Health, American Academy of Pediatrics Lists of non-U.S. clinical opportunities, many of which involve emergency care. Website: http://www2.aap.org/sections/ich/working_overseas.htm
	U.S. Agency for International Development (USAID) Government agency providing U.S. economic and humanitarian assistance worldwide. Website: www.usaid.gov
	WHO Publication catalog, media resources, health articles, and current health news. Website: www.who.int/topics/child_health/en
Health organizations involved in international PEM activities	UNICEF Organization dedicated to providing lifesaving assistance to children affected by disasters and to protecting their rights in any circumstances. Website: www.unicef.org
	Safe Kids Worldwide The first and only international nonprofit organization dedicated solely to preventing unintentional childhood injury. Website: www.safekids.org

vehicle may also be used for outreach primary care services, such as offering immunizations and collecting drugs and equipment from a central supply location, and, sometimes, improperly for personal reasons by local officials or politicians. In large cities, taxis and auto rickshaws are frequently used because they are rapidly available and well disseminated within cities. Where there are organized prehospital systems, different types of vehicles are adapted for emergency transportation, from fully equipped ambulances to basic transport with trained personnel. The WHO recommends identifying transport vehicles in advance, choosing vehicles that can be repaired and maintained locally, and equipping the vehicles according to recognized standards. Therefore the provision of available and appropriately staffed and equipped transport vehicles is crucial to the realization of recommended emergency care plans.

Hospital-Based Care

Once a child has reached a medical facility for the care of an injury or illness, adequate emergency services must be available. In many countries, the ED serves only as a triage area where patients are distinguished by their likely disease process and directed for admission to the corresponding unit within the hospital. Strengthening emergency services includes seeing the ED as a unit where definitive treatment can be provided to the ill and injured child. Critically ill children must receive not only prompt care but also correct care. Such expedience and accuracy are ensured by implementation of an effective triage system, moving the sickest patients to immediate care and standardizing the initial care of emergency conditions.

Triage

Children requiring emergency care frequently are not promptly recognized. Too often, children presenting to EDs are treated on a first-come first-served basis, in an approach that creates long waiting times for critically ill children, a contributor to unnecessary mortality. Medical facilities need to adopt an efficient and effective triage system in order to rapidly respond to the needs of patients and to assign the appropriate amount of resources. To this end, WHO has developed a course entitled Emergency Triage Assessment and Treatment (ETAT). This course teaches health practitioners to triage patients on arrival as having emergency, priority, or nonurgent signs and to provide emergency treatment for life-threatening conditions. ETAT emphasizes the evaluation of a patient's ABCD status to identify emergency situations—the patency of the airway (A), the quality of breathing (B), the quality of circulation and presence of coma or convulsions (C), and the presence of severe dehydration (D).

One of the benefits of the ETAT guidelines is that they can be adapted to centers with limited resources and are applicable to areas with high morbidity and mortality from meningitis, dehydration, malaria, respiratory illness, and malnutrition. Another benefit is that the care algorithms are based on limited diagnostic studies, that is, hemoglobin measurement, blood smear for malaria, and bedside blood glucose testing. Widely accepted triage assessment guidelines are teachable to emergency care staff, and their adoption can provide better organization within a healthcare center. At the Queen Elizabeth Central Hospital in Blantyre, Malawi, for example, the institution of triage and rapid treatment in its emergency care center led to a 50% decrease in the mortality of children within 24 hr of presentation to the hospital, with a further 50% decrease as implementation and practice of triaging patients have continued.

Beyond triage, education on overall emergency center organization is a low-resource intervention that can obviate some of the obstacles to quality care delivery. Additionally, the arrangement of short-stay areas (hydration and infusion rooms) can lessen the burden on inpatient units.

Pediatric-Specific Emergency Centers

Descriptions on the development of pediatric-specific emergency centers are insufficient. Anecdotally, most countries have developed at least 1 pediatric-capable center, usually as part of an academic medical center. The emergency services in these centers are variable, but certainly can be a starting point from which to build overall improvement in pediatric emergency care.

Practitioners

Throughout the world, nurses, paramedics, and nonspecialist physicians provide most of the care to acutely ill or injured children. The majority of sick children attend local clinics or district or central hospitals, where financial and human resources are not always matched to the potential acuity of presenting patient complaints. Nominal supervision is provided to staff attending these patients. Pediatric EDs located in tertiary hospitals are often staffed by training physicians with little or no supervision from faculty, who themselves may have limited exposure to or training in PEM. General hospitals lack dedicated pediatric staff; guidelines as to which patients should be moved to a higher level of care are often not standardized and depend on local influences and/or cultural beliefs about health and illness.

Clinical Guidelines

The Integrated Management of Childhood Illnesses (IMCI) guidelines were developed by the WHO and UNICEF to provide assistance in the initial triage and management of the presenting signs and symptoms of the major killers of the under–5 yr population in first-level health facilities (e.g., clinics, health centers, and outpatient departments of hospitals). The flow charts within each chapter of the IMCI manuals allow easy accessibility to materials that can enhance education and outreach to less experienced health workers.

Evaluations in various countries of the implementation of IMCI guidelines have shown improvements in health worker performance and quality of care as well as decreases in delay in treatment and mortality of under–5 yr children. These guidelines also dramatically reduce the cost of healthcare. The WHO website provides all the necessary implementation tools, including course manuals and evaluation tools.

Trauma

Morbidity and mortality from trauma is one of the most prevalent problems for children worldwide. Trauma care presents the challenge of sequential, often simple, interventions that must be performed in a timely manner to limit the severity of the outcome. However, with lack of specific training, signs and symptoms of pediatric trauma may go unrecognized or may be underappreciated. Trauma courses such as Advanced Trauma Life Support are educational tools that can be disseminated to improve the quality of care at emergency centers worldwide. For low-resource settings, the WHO has developed the Integrated Management for Emergency and Essential Surgical Care toolkit, which provides clear directions and reasoning for the initial care of injured patients. Not expressly addressed in the Advanced Trauma Life Support course is specific concern about child abuse as the cause of trauma. This is an area of pediatric care that many countries do not yet address in their medical training, their law enforcement, or their judicial systems. The epidemiologic need for reliable trauma registries is great, as is the need to identify personnel with trauma management skill sets and dedicated trauma centers to serve as higher-level referral sites.

Equipment

Pediatric emergency textbooks, pediatric and emergency medicine professional organizations, WHO, and nongovernmental and governmental health organizations have all published pediatric emergency equipment guidelines, for a variety of settings in which acutely ill and injured children would present. Although these equipment guidelines may represent minimum supplies to treat the widest variety of pediatric emergencies, the roles of substitution and improvisation often provide for equivalent function of recommended supplies.

Inpatient Services

After the initial stabilization, children requiring ongoing care are admitted to the hospital. The quality of inpatient services varies greatly depending on institutional and provider experience, comfort with pediatric conditions, and the resources available to treat them. The WHO has produced the *Pocket Book of Hospital Care for Children,*

which is based on IMCI guidelines and focuses on inpatient management of high-morbidity/high-mortality illnesses common in developing countries.

HUMANITARIAN DISASTERS

Children are a vulnerable population who experience disproportionate suffering during humanitarian emergencies, either natural (earthquakes, tsunamis, hurricanes, floods, and droughts) or manmade (armed conflicts, terrorist attacks). The under–5 yr population is especially susceptible to infectious diseases, malnutrition, and trauma following disasters. The Rainbow Center for Global Child Health at the Case Western Reserve University School of Medicine offers a training course, Management of Humanitarian Emergencies: Focus on Children and Families, that concentrates on the needs of children in disasters. The intent of the Center is to educate and train health professionals, relief workers, and policymakers to recognize and address the unique needs of children affected by manmade and natural disasters worldwide. The AAP also maintains a CHILDisaster Network, which acts as an electronic database of child health professionals with education and experience in humanitarian emergencies. Nongovernmental organizations can access the database to solicit practitioners to aid in disaster response.

The WHO's *Manual for the Health Care of Children in Humanitarian Emergencies* is based on IMCI guidelines and addresses the emergency care of children in disaster situations in which hospital facilities and resources are not immediately available. It goes beyond the IMCI guidelines by discussing initial assessment and management of trauma, burns, and poisonings. Preexisting IMCI guidelines assumed a functioning health system that facilitated the referral of children, which may not be available in all emergency situations. This manual also includes the initial management of severe conditions, such as injuries, burns, neonatal illness, and psychosocial problems, which are considered high priority in acute care settings.

Exchange and Dissemination of Information

The WHO established the HINARI (Health InterNetwork Access to Research Initiative) program to allow free or reduced-cost access to more than 6,200 journal publications. This Internet access is made available to the 108 countries with gross national income per capita less than $3,500. For middle-income countries not meeting the financial eligibility, Internet access continues to be a barrier, and resources may be limited to out-of-date textbooks and journals.

Another valuable tool is the website Pemdatabase.org. This nonproprietary site was started as an online resource for PEM practitioners. It contains links to PEM abstracts and articles, evidence-based reviews, pediatric resuscitation websites, relevant journals, as well as PEM conferences and professional organizations.

Bibliography is available at Expert Consult.

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Chapter 67

Pediatric Emergencies and Resuscitation

Mary E. Hartman and Ira M. Cheifetz

Injuries are the leading cause of death in American children and young adults and are responsible for more childhood deaths than all other causes combined (see Chapter 5.1). Children are particularly vulnerable to injury for a number of reasons, including their small size, relative physical uncoordination, and limited ability to predict or understand danger. In addition, the immaturity of their developing bones, ligaments, and muscles; their thin body walls; and their relatively large heads, compared with total body surface area, make young children susceptible to serious or fatal injury from falls and collisions.

Most injuries in childhood are unintentional, and many are preventable. Motor vehicle–related injuries are the most common cause of unintentional injury and death for U.S. children, many of which are related to speeding, aggressive driving, failure to use proper passenger restraints, and/or alcohol. Consistent use of bicycle helmets could reduce the severity of head injuries, the leading cause of death when a bicyclist is struck by a car, by more than 80%. Four-sided fencing around swimming pools and use of flotation devices for every passenger in a boat could greatly reduce the risk of drowning, the second leading cause of accidental death in children younger than 5 yr and the third major cause of death in adolescents. Serious injuries can become fatal when appropriate medical care is delayed.

Rapid, effective bystander cardiopulmonary resuscitation (CPR) for children is associated with survival rates as high as 70%, with good neurologic outcome. However, bystander CPR is still provided for less than 50% of children who experience cardiac arrest outside medical settings. This has led to long-term survival rates of <40%, with many survivors suffering a poor neurologic outcome.

APPROACH TO THE EMERGENCY EVALUATION OF A CHILD

The first response to a pediatric emergency of any cause is a systematic, rapid **general assessment** of the scene and the child to identify immediate threats to the child, care providers, or others. If an emergency is identified, the emergency response system (emergency medical services [EMS]) should be activated immediately. Care providers should then proceed through **primary**, **secondary**, and **tertiary assessments** as allowed by the child's condition, safety of the scene, and resources available. This standardized approach provides organization to what might otherwise be a confusing or chaotic situation and reinforces an organized thought process for care providers. If, at any point in these assessments, the caregiver identifies a life-threatening problem, the assessment is halted and lifesaving interventions are begun. Further assessment and intervention should be delayed until other caregivers arrive or the condition is successfully treated.

General Assessment

Upon arrival at the scene of a compromised child, a caregiver's first task is a quick survey of the scene itself. Is the rescuer or child in imminent danger because of circumstances at the scene (fire, high-voltage electricity)? If so, can the child be safely extricated to a safe location for assessment and treatment? Can the child be safely moved with the appropriate precautions (i.e., cervical spine protection), if indicated? A rescuer is expected to proceed only if these safety conditions have been met.

Once the caregiver and patient's safety has been ensured, the caregiver performs **a rapid visual survey** of the child, assessing the child's **general appearance and cardiopulmonary function**. This action should be very quick (only a few seconds) and should include assessment of (1) general appearance (determining color, tone, alertness, and responsiveness); (2) adequacy of breathing (distinguishing between normal, comfortable respirations and respiratory distress or apnea); and (3) adequacy of circulation (identifying cyanosis, pallor, or mottling). A child found unresponsive from an *unwitnessed* collapse should be approached with a gentle touch and the verbal question, "Are you OK?" If there is no response, the caregiver should immediately shout for help and send someone to both activate the emergency response system (EMS) and locate an automated external defibrillator (AED) (Fig. 67-1). The provider should then determine whether the child is breathing and, if not, provide 2 rescue breaths as described later under "Recognition and Treatment of Respiratory Distress and Failure." If the child is adequately breathing, then the circulation is quickly assessed. Any child with a heart rate below 60 beats/min or without a pulse requires immediate CPR, as described under

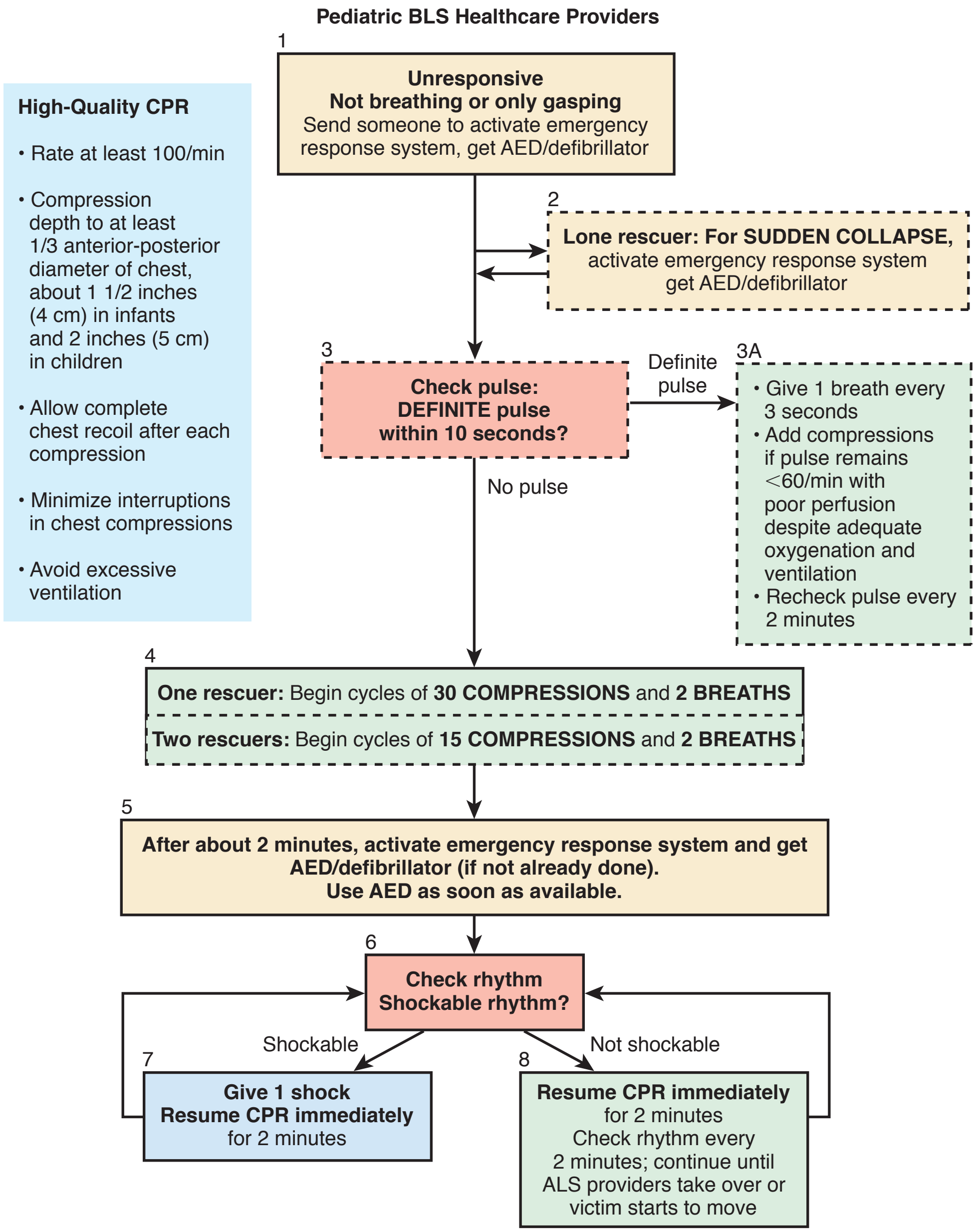

Note: The boxes bordered with dashed lines are performed by healthcare providers and not by rescuers

Figure 67-1 **Pediatric basic life support algorithm.** AED, automated external defibrillator; ALS, advanced life support; CPR, cardiopulmonary resuscitation. *(From Berg MD, Schexnayder SM, Chameides L, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 13,* Circulation *122[Suppl 3]:S862–S875, 2010, Fig. 3, p. S866.)*

"Recognition and Management of Cardiac Arrest." If the caregiver *witnesses* the sudden collapse of a child, the caregiver should have a higher suspicion for a sudden cardiac event. In this case, rapid deployment of an AED is of paramount importance. The provider should very briefly delay care of the child to activate EMS and locate the nearest AED.

Primary Assessment

Once the emergency response system has been activated and the child is determined not to need CPR, the caregiver should proceed with a primary assessment that includes a **brief, hands-on assessment of cardiopulmonary and neurologic function and stability**. This assessment includes a limited physical exam, evaluation of vital signs, and measurement of pulse oximetry if possible. Again, a standardized approach is best. The American Heart Association, in its Pediatric Advanced Life Support (PALS) curriculum, supports the structured format of **Airway, Breathing, Circulation, Disability, Exposure (ABCDE)**. The goal of the primary assessment is to obtain a focused, systems-based assessment of the child's injuries or abnormalities, so that resuscitative efforts can be directed to these areas; if the caregiver identifies a life-threatening abnormality, further evaluation is postponed until appropriate corrective action has been taken.

The exam and vital sign data can be interpreted only if the caregiver has a thorough understanding of normal values. In pediatrics, normal respiratory rate, heart rate, and blood pressure have age-specific norms (Table 67-1). These ranges can be difficult to remember, especially if used infrequently. However, several standard principals apply: (1) no child's respiratory rate should be >60 breaths/min for a sustained period; (2) normal heart rate is roughly 2-3 times normal respiratory rate for age; and (3) a simple guide for pediatric blood pressure is that

Table 67-1 Normal Vital Signs According to Age

AGE	HEART RATE (beats/min)	BLOOD PRESSURE (mm Hg)	RESPIRATORY RATE (breaths/min)
Premature	120-170*	55-75/35-45†	40-70‡
0-3 mo	100-150*	65-85/45-55	35-55
3-6 mo	90-120	70-90/50-65	30-45
6-12 mo	80-120	80-100/55-65	25-40
1-3 yr	70-110	90-105/55-70	20-30
3-6 yr	65-110	95-110/60-75	20-25
6-12 yr	60-95	100-120/60-75	14-22
12+ yr	55-85	110-135/65-85	12-18

*In sleep, infant heart rates may drop significantly lower, but if perfusion is maintained, no intervention is required.
†A blood pressure cuff should cover approximately two-thirds of the arm; too small a cuff yields spuriously high pressure readings, and too large a cuff yields spuriously low pressure readings.
‡Many premature infants require mechanical ventilatory support, making their spontaneous respiratory rate less relevant.

the lower limit of systolic blood pressure should be ≥60 mm Hg for neonates; ≥70 mm Hg for 1 mo-1 yr olds; ≥70 mm Hg + (2 × age) for 1-10 yr olds; and ≥90 mm Hg for any child older than 10 yr.

Airway and Breathing

The most common precipitating event for cardiac instability in infants and children is respiratory insufficiency. Therefore, rapid assessment of respiratory failure and immediate restoration of adequate ventilation and oxygenation remain the first priority in the resuscitation of a child. Using a systematic approach, the caregiver should first assess whether the child's airway is patent and maintainable. A healthy, patent airway is open and unobstructed, allowing normal respiration without noise or effort. A maintainable airway is one that is either already patent or can be made patent with a simple maneuver. To assess airway patency, the provider should look for breathing movements in the child's chest and abdomen, listen for breath sounds, and feel the movement of air at the child's mouth and nose. Abnormal breathing sounds (i.e., snoring or stridor), increased work of breathing, and apnea are all findings potentially consistent with airway obstruction. If there is evidence of airway obstruction, then maneuvers to relieve the obstruction should be instituted before the caregiver proceeds to evaluate the child's breathing (see under "Recognition and Treatment of Respiratory Distress and Failure").

Assessment of breathing includes evaluation of the child's respiratory rate, respiratory effort, abnormal sounds, and pulse oximetry. Normal breathing appears comfortable, is quiet, and occurs at an age-appropriate rate. Abnormal respiratory rates include apnea and rates that are either too slow (bradypnea) or too fast (tachypnea). **Bradypnea and irregular respiratory patterns require urgent attention, as they are often signs of impending respiratory failure and apnea.** Signs of increased respiratory effort include nasal flaring, grunting, chest or neck muscle retractions, head bobbing, and "seesaw" respirations. Hemoglobin oxygen desaturation, as measured by pulse oximetry, often accompanies parenchymal lung disease apnea or airway obstruction. However, providers should keep in mind that adequate perfusion is required to produce a reliable oxygen saturation measurement. A child with low oxygen saturation is a child in distress. Central cyanosis is a sign of severe hypoxia and indicates an emergent need for oxygen supplementation and respiratory support.

Circulation

Cardiovascular function is assessed by evaluation of skin color and temperature, heart rate, heart rhythm, pulses, capillary refill time, and blood pressure. In nonhospital settings, much of the important information can be obtained without measuring the blood pressure; lack of blood pressure data should not prevent the provider for determining adequacy of circulation or implementing a lifesaving response. Mottling, pallor, delayed capillary refill, cyanosis, poor pulses, and cool extremities are all signs of diminished perfusion and compromised cardiac output. Tachycardia is the earliest and most reliable sign of shock, but is itself fairly nonspecific and should be correlated with other components of the exam, such as weakness, threadiness, and absence of pulses. An age-specific approach to pulse assessment will yield best results.

Table 67-2 AVPU Neurologic Assessment

A	The child is awake, alert, and interactive with parents and care providers
V	The child responds only if the care provider or parents call the child's name or speak loudly
P	The child responds only to painful stimuli, such as pinching the nail bed of a toe or finger
U	The child is unresponsive to all stimuli

From Ralston M, Hazinski MF, Zaritsky AL, et al, editors: Pediatric advanced life support course guide and PALS provider manual: provider manual, *Dallas, 2007, American Heart Association.*

Table 67-3 Glasgow Coma Scale

EYE OPENING (TOTAL POSSIBLE POINTS 4)			
Spontaneous	4		
To voice	3		
To pain	2		
None	1		
VERBAL RESPONSE (TOTAL POSSIBLE POINTS 5)			
OLDER CHILDREN		**INFANTS AND YOUNG CHILDREN**	
Oriented	5	Appropriate words; smiles, fixes, and follows	5
Confused	4	Consolable crying	4
Inappropriate	3	Persistently irritable	3
Incomprehensible	2	Restless, agitated	2
None	1	None	1
MOTOR RESPONSE (TOTAL POSSIBLE POINTS 6)			
Obeys	6		
Localizes pain	5		
Withdraws	4		
Flexion	3		
Extension	2		
None	1		

Adapted and modified from Teasdale G, Jennett B: Assessment of coma and impaired consciousness: a practical scale, Lancet *2:81–84, 1974.*

Disability

In the setting of a pediatric emergency, *disability* refers to a child's neurologic function in terms of the level of consciousness and cortical function. Standard evaluation of a child's neurologic condition can be done quickly with an assessment of pupillary response to light (if one is available) and use of either of the standard scores used in pediatrics: the Alert, Verbal, Pain, Unresponsive (AVPU) Pediatric Response Scale and the Glasgow Coma Scale (GCS) (Tables 67-2, 67-3, and 68-1). The causes of decreased level of consciousness in children are numerous and include conditions as diverse as respiratory failure with hypoxia or hypercarbia, hypoglycemia, poisonings or drug overdose, trauma, seizures, infection, and shock. **Most commonly, an ill or injured child has an altered level of consciousness because of respiratory compromise, circulatory compromise, or both**. Any child with a depressed

level of consciousness should be immediately assessed for abnormalities in cardiorespiratory status.

The Alert, Verbal, Pain, Unresponsive Pediatric Response Scale. The AVPU scoring system is used to determine both a child's level of consciousness and cerebral cortex function. Unlike the GCS (see later), the AVPU scale is not developmentally dependent—a child does not have to understand spoken language or follow commands, merely respond to a stimulus. The child is scored according to the amount of stimulus required to get a response, from alert (no stimulus, the child is already awake and interactive) to unresponsive (child does not respond to any stimulus) (see Table 67-2).

The Glasgow Coma Scale. Although the GCS has not been validated as a prognostic scoring system for infants and young children as it has been in adults, it is commonly used in the assessment of pediatric patients with an altered level of consciousness. The GCS is the most widely used method of evaluating a child's neurologic function and has 3 components. Individual scores for eye opening, verbal response, and motor response are added together, with a maximum of 15 points (see Table 67-3). Patients with a GCS score ≤8 require aggressive management, including stabilization of the airway and breathing with endotracheal intubation and mechanical ventilation, respectively, and, if indicated, placement of an intracranial pressure monitoring device. The Full Outline of Unresponsiveness (FOUR) score is another useful assessment and monitoring tool (see Table 68-1).

Exposure

Exposure is the final component of the pediatric primary assessment. This component of the exam is reached only after the child's airway, breathing, and circulation have been assessed and determined to be stable or have been stabilized through simple interventions. In this setting, *exposure* stands for the dual responsibility of the provider to both expose the child to assess for previously unidentified injures and consider prolonged exposure in a cold environment as a possible cause of hypothermia and cardiopulmonary instability. The provider should undress the child (as is feasible and reasonable) to perform a focused physical exam, assessing for burns, bruising, bleeding, joint laxity, and fractures. If possible, the provider should assess the child's temperature. All maneuvers should be performed with careful maintenance of cervical spine precautions.

Secondary Assessment

For care providers in community or outpatient settings, transfer of care of a child to emergency or hospital personnel may occur before a full secondary assessment is possible. However, before the child is removed from the scene and separated from witnesses or family, a brief history should be obtained for medical providers at the accepting facility. **The components of a secondary assessment include a focused history and focused physical exam.**

The history should be targeted to information that could explain cardiorespiratory or neurologic dysfunction and should take the form of a **SAMPLE history (Signs/symptoms, Allergies, Medications, Past medical history, timing of Last meal, and Events leading to this situation)**. Medical personnel not engaged in resuscitative efforts can be dispatched to elicit history from witnesses or relatives. The physical exam during the secondary assessment is a thorough head-to-toe exam, although the severity of the child's illness or injury could necessitate curtailing portions of the exam or postponing nonessential elements until a later time.

Tertiary Assessment

The tertiary assessment occurs in a hospital setting, where ancillary laboratory and radiographic assessments contribute to a thorough understanding of the child's condition. A basic blood chemistry profile, complete blood count, liver function tests, coagulation studies, and arterial blood gas analyses give fairly broad (but somewhat nonspecific) estimates of renal function, acid–base balance, cardiorespiratory function, and presence or absence of shock. Chest radiographs can be useful to evaluate both the heart and lungs, although more detailed estimates of heart function and cardiac output can be made with echocardiography. Arterial and central venous catheters can be placed to monitor arterial and central venous pressure (see under "Vascular Access").

RECOGNITION AND TREATMENT OF RESPIRATORY DISTRESS AND FAILURE

The goals of initial management of respiratory distress or failure are to rapidly stabilize the child's airway and breathing and to identify the cause of the problem so that further therapeutic efforts can be appropriately directed.

Airway Obstruction

Children <5 yr old are particularly susceptible to foreign-body aspiration and choking. Liquids are the most common cause of choking in infants, whereas small objects and food (e.g., grapes, nuts, hot dogs, candies) are the most common source of foreign bodies in the airways of toddlers and older children. A history consistent with foreign-body aspiration is considered diagnostic. Any child in the proper setting with the sudden onset of choking, stridor, or wheezing has foreign-body aspiration until proven otherwise.

Airway obstruction is treated with a sequential approach, starting with the head-tilt/chin-lift maneuver to open and support the airway, followed by inspection for a foreign body, and finger-sweep clearance or suctioning if one is visualized (Fig. 67-2). Blind suctioning or finger sweeps of the mouth **are not recommended**. A nasopharyngeal airway or oropharyngeal airway can be inserted for airway support, if indicated. A conscious child suspected of having a partial foreign-body obstruction should be permitted to cough spontaneously until coughing is no longer effective, respiratory distress and stridor increase, or the child becomes unconscious.

If the child becomes unconscious, the child should be gently placed on the ground, supine. The provider should then open the airway with the head-tilt/chin-lift maneuver and attempt mouth-to-mouth ventilation (Figs. 67-3 and 67-4). If ventilation is unsuccessful, the airway is repositioned, and ventilation attempted again. If there is still no chest rise, attempts to remove a foreign body are indicated. In an infant <1 yr old, a combination of 5 back blows and 5 chest thrusts is administered

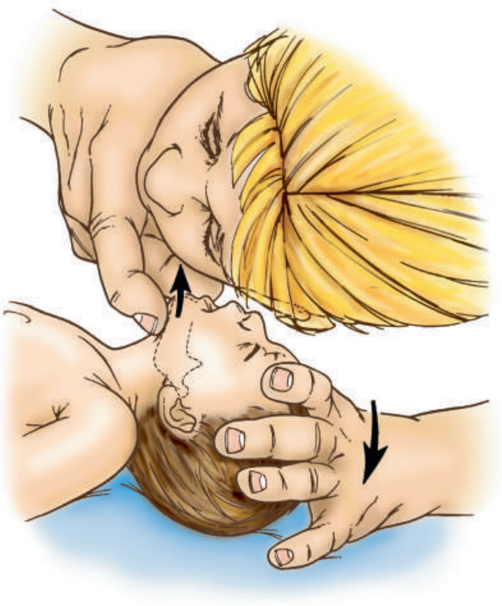

Figure 67-2 Opening the airway with the head-tilt/chin-lift maneuver. One hand is used to tilt the head, extending the neck. The index finger of the rescuer's other hand lifts the mandible outward by lifting the chin. Head-tilt should not be performed if a cervical spine injury is suspected. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

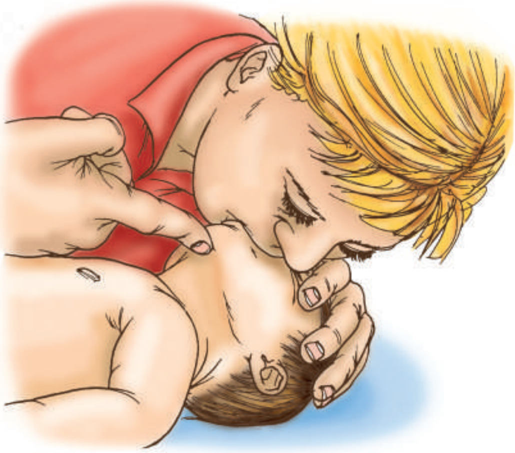

Figure 67-3 Rescue breathing in an infant. The rescuer's mouth covers the infant's nose and mouth, creating a seal. One hand performs the head-tilt while the other hand lifts the infant's jaw. Avoid head-tilt if the infant has sustained head or neck trauma. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

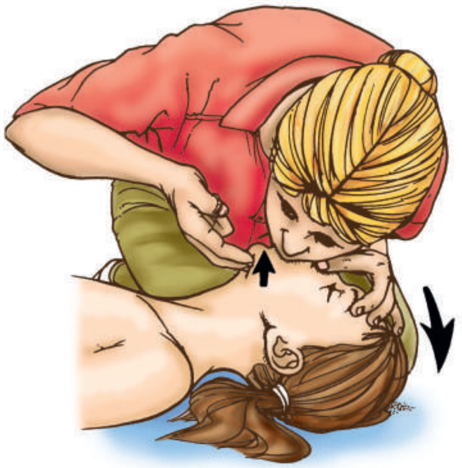

Figure 67-4 Rescue breathing in a child. The rescuer's mouth covers the child's mouth, creating a mouth-to-mouth seal. One hand maintains the head-tilt; the thumb and forefinger of the same hand are used to pinch the child's nose. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

(Fig. 67-5). After each cycle of back blows and chest thrusts, the child's mouth should be visually inspected for the presence of the foreign body. If identified within finger's reach, it should be removed with a gentle finger sweep. If no foreign body is visual, ventilation is again attempted. If this is unsuccessful, the head is repositioned, and ventilation attempted again. If there is no chest rise, the series of back blows and chest thrusts is repeated.

For a conscious child >1 yr old, providers should give a series of 5 abdominal thrusts (Heimlich maneuver) with the child standing or sitting (Fig. 67-6); this should occur with the child lying down if unconscious (Fig. 67-7). After the abdominal thrusts, the airway is examined for a foreign body, which should be removed if visualized. If no foreign body is seen, the head is repositioned, and ventilation attempted. If it is unsuccessful, the head is repositioned and ventilation is attempted again. If these efforts are unsuccessful, the Heimlich sequence is repeated.

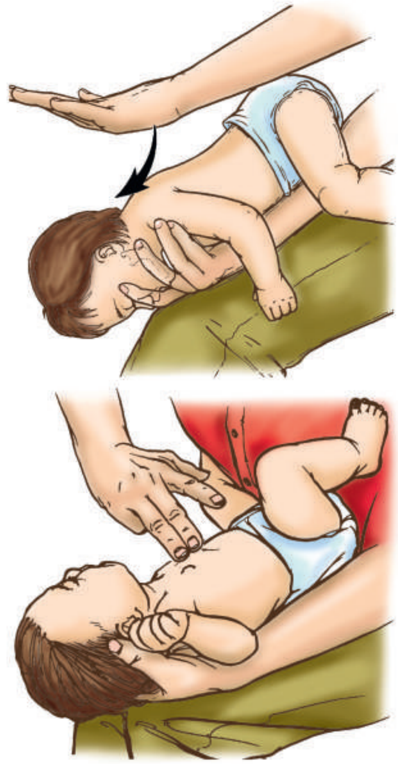

Figure 67-5 Back blows *(top)* and chest thrusts *(bottom)* to relieve foreign-body airway obstruction in the infant. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

Figure 67-6 Abdominal thrusts with the victim standing or sitting (conscious). *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

Figure 67-7 Abdominal thrusts with victim lying (conscious or unconscious). *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

Airway Narrowing

Airway obstruction can also be caused by airway narrowing, in both the upper and lower airways. *Upper airway obstruction* refers to narrowing of the extrathoracic portion of the airway, including the oropharynx, larynx, and trachea. In the upper airways, narrowing is most often caused by airway edema (croup or anaphylaxis). Lower airway disease affects all intrathoracic airways, notably the bronchi and bronchioles. In the lower airways, bronchiolitis and acute asthma exacerbations are the major contributors to intrathoracic airway obstruction in children, causing airway narrowing through a combination of airway swelling, mucus production, and circumferential smooth muscle constriction of smaller airways.

Airway support for these processes is dictated by both the underlying condition and the clinical severity of the problem. In cases of mild upper airway obstruction, the child has minimally elevated work of breathing (evidenced by tachypnea and few to mild retractions). Stridor, if present at all, should be audible with only coughing or activity. Children with these findings can be supported with nebulized cool mist and supplemental oxygen as needed. In cases with moderate obstruction, in which the child has a higher work of breathing and more pronounced stridor, nebulized racemic epinephrine and oral or intravenous (IV) dexamethasone can be added. Children with severe upper airway obstruction have marked retractions, prominent stridor, and decreased air entry on auscultation of the lung fields. Most children with significant airway obstruction are also hypoxic, and many appear dyspneic and agitated. A child in severe distress needs to be closely observed, as the signs of impending respiratory failure may be initially confused with improvement. Stridor becomes quieter and retractions less prominent when a child's respiratory effort begins to diminish. The child in respiratory failure can be distinguished from one who is improving by evidence of poor air movement on auscultation and lethargy or decreased level of consciousness from hypercarbia, hypoxia, or both. When anaphylaxis is suspected as the cause for upper airway edema, providers should administer an intramuscular or IV dose of epinephrine as needed (see Chapter 149). No matter the cause, any child in impending respiratory failure should be prepared for endotracheal intubation and respiratory support.

In cases of lower airway obstruction, therapies are targeted to both relieving the obstruction and reducing the child's work of breathing. Inhaled bronchodilators, such as albuterol, augmented by oral or IV corticosteroids, remain the mainstay of therapy in settings of mild to moderate acute distress caused by lower airway obstruction. Children with more significant obstruction appear dyspneic, with tachypnea, retractions, and easily audible wheezing. In these cases, the addition of an anticholinergic agent, such as nebulized ipratropium bromide, or a smooth muscle relaxant, such as magnesium sulfate, may provide further relief, although the evidence for these measures remains controversial (see Chapter 144). Supplemental oxygen and IV fluid hydration can also be useful adjuncts. As in cases of upper airway obstruction, impending respiratory failure in children with lower airway obstruction can be insidious. When diagnosed early in a school-age child who is cooperative, respiratory failure can be averted through judicious use of noninvasive support, with continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or heliox (combined helium-oxygen therapy). Endotracheal intubation should be performed only by skilled providers, preferably in a hospital setting, because there is a high risk of respiratory and circulatory compromise in patients with lower airway obstruction during the procedure.

Parenchymal Lung Disease

Parenchymal lung disease includes a heterogeneous list of conditions, such as pneumonia, acute respiratory distress syndrome, pneumonitis, bronchiolitis, bronchopulmonary dysplasia, cystic fibrosis, and pulmonary edema. The commonalities of these conditions are their effects on the small airways and alveoli, including inflammation and exudation leading to consolidation of lung tissue, decreased gas exchange, and increased work of breathing. Clinical management of these conditions includes specific treatment as indicated (i.e., antibiotics for bacterial pneumonia) and supportive care in the form of supplemental oxygen, noninvasive respiratory support (with CPAP or BiPAP), or invasive mechanical ventilation.

Advanced Airway Management Techniques

Bag-Valve-Mask Positive Pressure Ventilation

Rescue breathing with a bag-valve-mask apparatus can be as effective as endotracheal intubation and safer when the provider is inexperienced with intubation. Bag-valve-mask ventilation itself requires training to ensure that the provider is competent to select the correct mask size, open the child's airway, form a tight seal between the mask and the child's face, deliver effective ventilation, and assess the effectiveness of the ventilation. An appropriately sized mask is one that fits over the child's mouth and nose but does not extend below the chin or over the eyes (Fig. 67-8). An adequate seal is best achieved via a combination "C–E" grip on the mask, in which the thumb and index finger form the letter "C" on top of the mask, pressing the mask downward onto the child's face, and the remaining 3 fingers form an "E" grip under the child's mandible, holding the jaw forward and extending the head up toward the mask. Using this method, the care provider can secure the mask to the child's face with 1 hand and use the other hand to compress the ventilation bag (Fig. 67-9).

The provider may have to move the head and neck through a range of positions to find the one that best maintains airway patency and allows maximal ventilation. In infants and young children, optimal ventilation is often provided when the child's head is in the neutral "sniffing" position without hyperextension of the head (Fig. 67-10). Poor chest rise and persistently low oxygen saturation values indicate inadequate ventilation. In this setting, the care provider should recheck the mask's seal on the child's face, reposition the child's head, and consider suctioning the airway if indicated. If these maneuvers do not restore ventilation, then the provider should consider endotracheal intubation.

Endotracheal Intubation

A child requires intubation when at least 1 of these conditions exists: (1) the child is unable to maintain airway patency or protect the airway against aspiration (as occurs in settings of neurologic compromise); (2) the child is failing to maintain adequate oxygenation; (3) the child is failing to control blood carbon dioxide levels and maintain safe

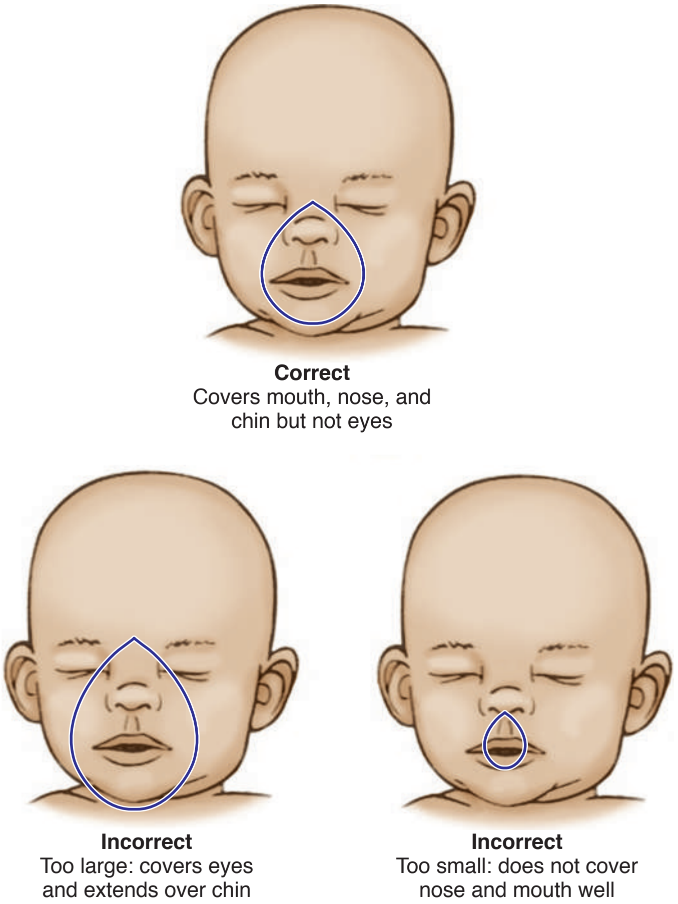

Figure 67-8 **Appropriate sizing technique for pediatric bag-valve-mask apparatus.** *(From American Academy of Pediatrics and the American Heart Association; Kattwinkel J (ed):* Textbook of Neonatal Resuscitation, *ed 6. Elk Grove, IL: American Academy of Pediatrics, 2011. Fig 3-17.)*

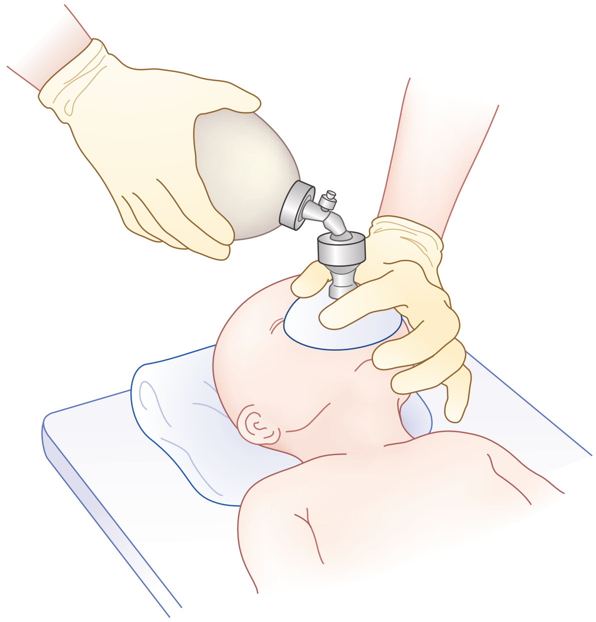

Figure 67-9 "C–E" grip to secure bag-valve-mask to a child's face with appropriate seal.

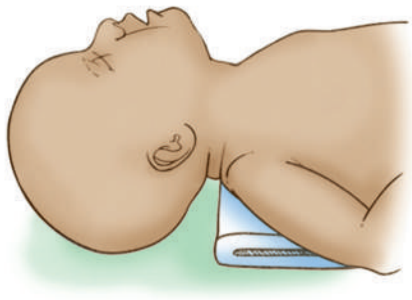

Figure 67-10 **Appropriate head position for bag-valve-mask ventilation.** *(From American Academy of Pediatrics and the American Heart Association; Kattwinkel J (ed):* Textbook of Neonatal Resuscitation, *ed 6. Elk Grove, IL: American Academy of Pediatrics, 2011. Fig 3-19.)*

acid–base balance; (4) sedation and/or paralysis is required for a procedure; and (5) care providers anticipate a deteriorating course that will eventually lead to any of the first 4 conditions. There are few *absolute contraindications* to tracheal intubation, but experts generally agree that in settings of known complete airway obstruction, endotracheal intubation should be avoided, and emergency cricothyroidotomy performed instead. Another important consideration is to ensure that caregivers provide appropriate cervical spine protection during the intubation procedure when neck or spinal cord injury is suspected.

The most important phase of the intubation procedure is the preprocedure preparation, when the provider ensures all the equipment and staff needed for safe intubation are present and functioning. An easy pneumonic for this is **SOAP MM**: suction (Yankauer suction catheter attached to wall suction); oxygen (both preoxygenation of the patient and devices needed to deliver oxygen, such as a bag-valve-mask device); airway (appropriately sized endotracheal tube and laryngoscope); people (all those needed during and immediately after the procedure, such as respiratory therapists and nurses); monitor (to monitor the child's oxygen saturation, heart rate, and blood pressure); and medications (to sedate the child and allow the provider to control the airway). A simple formula for selecting the appropriately sized endotracheal tube (ET) is as follows:

$$\text{Uncuffed ET size (in mm)} = \left(\frac{\text{age in years}}{4}\right) + 4$$

Analgesia is recommended to reduce metabolic stress, discomfort, and anxiety during intubation. Pretreatment with a sedative, an analgesic, and possibly a muscle relaxant is recommended unless the situation is an emergency (i.e., apnea, asystole, unresponsiveness) and the administration of drugs would cause an unacceptable delay.

Because many intubations in critically ill children are emergency procedures, caregivers should be prepared for rapid sequence intubation (RSI) (Fig. 67-11; Table 67-4). The goals of RSI are to induce anesthesia and paralysis and to complete intubation quickly. This approach minimizes elevations of intracranial pressure and blood pressure that may accompany intubation in awake or lightly sedated patients. Because the stomach generally cannot be emptied before RSI, the Sellick maneuver (downward pressure on the cricoid cartilage to compress the esophagus against the vertebral column) should be used to prevent aspiration of gastric contents.

Once the patient is intubated, proper ET placement should be assessed by auscultation of breath sounds, evidence of symmetric chest rise, and analysis of exhaled carbon dioxide (CO_2) by a colorimetric device placed within the respiratory tubing near the ET or a device that directly measures carbon dioxide elimination (i.e., capnogram or capnograph). Chest radiography is necessary to confirm appropriate tube position.

RECOGNITION AND MANAGEMENT OF SHOCK

In simple terms, shock occurs when oxygen and nutrient delivery to the tissues is inadequate to meet metabolic demands (see Chapter 70).

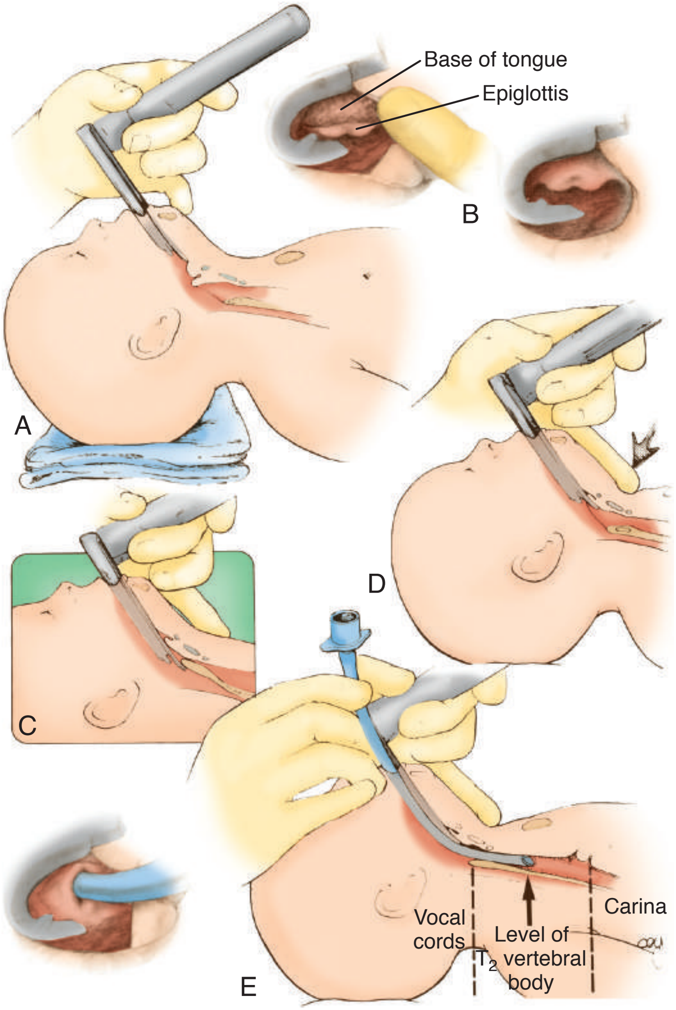

Figure 67-11 *A-E,* Intubation technique. *(From Fleisher G, Ludwig S:* Textbook of pediatric emergency medicine, *Baltimore, 1983, Williams & Wilkins, p. 1250.)*

The definition of shock does not include hypotension, and it is important for care providers to understand that **shock does not begin when blood pressure drops; it merely worsens and becomes more difficult to treat once blood pressure is abnormal.**

Early *compensated* shock, whereby oxygen delivery is mostly preserved through compensatory mechanisms, is defined by the presence of normal blood pressure. When compensatory mechanisms fail, the shock progresses to *decompensated* shock, which is defined by hypotension and organ dysfunction. In *irreversible* shock, organ failure progresses and death ensues.

Shock is also often described according to the underlying pathophysiology, which dictates the appropriate therapeutic response. *Hypovolemic shock* is the most common type of shock in children worldwide, usually related to fluid losses from severe diarrhea. Hemorrhage is a cause of hypovolemic shock after trauma or intestinal hemorrhage. When hypovolemia occurs as a result of third spacing of intravascular fluids into the extravascular compartment, the shock is described as *distributive shock*. The most common causes of distributive shock are sepsis and burn injuries, in which release of inflammatory cytokines causes massive capillary leak of fluid and proteins, leading to low oncotic pressure and intravascular volume. In settings of profound myocardial dysfunction, a child has tissue hypoperfusion from *cardiogenic shock*. The most common causes of cardiogenic shock are congenital heart disease, myocarditis, and cardiomyopathies. *Obstructive shock* occurs when cardiac output is lowered by obstruction of blood flow to the body, as occurs when a ductus arteriosus closes in a child with ductus-dependent systemic blood flow in pericardial tamponade, tension pneumothorax, or massive pulmonary embolism.

The evaluation of a child in shock should proceed as described in the preceding sections on primary, secondary, and tertiary assessments. If the child presents in a hospital setting, providers should obtain central venous and arterial access to permit a more thorough laboratory assessment of all organ systems, including studies of renal and liver function, acid–base balance and presence of lactic acidosis, hypoxemia and/or hypercapnia, and evidence of coagulopathy or disseminated intravascular coagulation. Chest radiography and more sophisticated assessments, such as echocardiography, may also be useful. Respiratory and cardiovascular support should be provided as indicated.

The treatment of shock focuses on the modifiable determinants of oxygen delivery while reducing the imbalance between oxygen demand and supply. A multipronged approach is recommended; it consists of optimizing the oxygen content of the blood, improving the volume and distribution of cardiac output, correcting metabolic derangements, and reducing oxygen demand. Blood oxygen content is maximized when hemoglobin values are normal and 100% of available hemoglobin is saturated with oxygen. Transfusion should be considered in the presence of hemorrhagic or distributive shock, in which crystalloid volume resuscitation has led to hemodilution and anemia. High oxygen saturations may be achieved by simple maneuvers such as oxygen administration via nasal cannula or face mask, but supportive measures that provide positive pressure, such as CPAP, BiPAP, or even mechanical ventilation, may be necessary. Therapies to increase cardiac output should be selected on the basis of underlying pathophysiology. For hypovolemic and distributive shock, aggressive volume resuscitation, guided by arterial and central venous pressures, is the mainstay of therapy. In obstructive shock, relief of the obstruction is critical. The ductus arteriosus can often be reopened with prostaglandin administration, and tamponade physiology can be relieved with appropriate drain placement, as described under "Nonvascular Emergency Procedures."

RECOGNITION OF BRADYARRHYTHMIAS AND TACHYARRHYTHMIAS

In the advanced life support setting, arrhythmias are most usefully classified according to the observed heart rate (slow or fast) and its effect on perfusion (adequate or poor). If, in the primary survey, a caregiver finds a child with an abnormal heart rate plus poor perfusion and/or altered mental status, then the rhythm is inadequate no matter its rate. In those settings, the child is diagnosed with shock, and further evaluation is halted until appropriate resuscitation has been initiated.

Bradyarrhythmias

By definition, a child is *bradycardic* when the heart rate is slower than the normal range for age (see Table 67-1). Sinus bradycardia can be a harmless incidental finding in an otherwise healthy person and is not commonly associated with cardiac compromise. A relative bradycardia occurs when the heart rate is too slow for a child's activity level or metabolic needs. A clinically significant bradycardia occurs when the heart rate is slow and there are signs of systemic hypoperfusion (i.e., pallor, altered mental status, hypotension, acidosis). Symptomatic bradycardia occurs most often in the setting of hypoxia but can also be caused by hypoglycemia, hypocalcemia, other electrolyte abnormalities, and intracranial hypertension. Bradyarrhythmias are often the most common prearrest rhythms in young children.

Initial management of symptomatic bradycardia includes support or opening of the airway and confirming or establishing adequate oxygenation and ventilation (Fig. 67-12). After the child's breathing has been secured, the child should be reassessed for continued bradycardia and poor perfusion. If cardiac compromise was solely the result of respiratory insufficiency, support of the child's airway and breathing may have been sufficient to restore normal hemodynamics. If respiratory support does not correct the perfusion abnormalities, then further care is based on the quality of perfusion and the degree of

Table 67-4 Rapid Sequence Intubation

STEP	PROCEDURE	COMMENT/EXPLANATION
1	Obtain a brief history and perform an assessment	Rule out drug allergies; examine the airway anatomy (e.g., micrognathia, cleft palate)
2	Assemble equipment, medications, etc.	See lists below
3	Preoxygenate the patient	With bag/mask, nasal cannula, hood or blow-by
4	Premedicate the patient with lidocaine, atropine	Lidocaine minimizes the ICP rise with intubation and can be applied topically to the airway mucosa for local anesthesia Atropine helps blunt the bradycardia associated with upper airway manipulation and reduces airway secretions
5	Induce sedation and analgesia	Sedatives: *Thiopental* (2-5 mg/kg): Very rapid onset; can cause hypotension *Diazepam* (0.1 mg/kg): Onset 2-5 min; elimination in 30-60 min or more *Ketamine* (2 mg/kg): Onset 1-2 min; elimination in 30-40 min. May cause hallucinations if used alone; causes higher ICP, mucous secretions, increased vital signs, and bronchodilation Analgesics: *Fentanyl* (3-10 μg/kg, may repeat 3-4×): Rapid administration risks "tight chest" response, with no effective ventilation. Effects wear off in 20-30 min *Morphine* (0.05-0.1 mg/kg dose): May last 30-60 min; may lead to hypotension in hypovolemic patients
6	Pretreat with nondepolarizing paralytic agent	Small dose of a nondepolarizing paralytic agent (see below), with intent of diminishing the depolarizing effect of succinylcholine, which is administered next
7	Administer muscle relaxants	Succinylcholine dose is 1-2 mg/kg; causes initial contraction of muscles, then relaxation. This depolarization can, however, raise ICP and blood pressure. Onset of paralysis in 30-40 sec; duration is 5-10 min Increased use of pretreatment with a nondepolarizing muscle relaxant, especially rocuronium (1 mg/kg), which has a very rapid onset and short duration. Other nondepolarizing agents include vecuronium and pancuronium, both dosed at 0.1 mg/kg
8	Perform a Sellick maneuver	Pressure on the cricoid cartilage, to occlude the esophagus and prevent regurgitation or aspiration
9	Perform endotracheal intubation	ET: Select the proper size for the age and weight of the child Laryngoscope blades: A variety of Miller and the Macintosh blades Patient supine; the neck is extended moderately to the "sniffing" position
10	Secure the tube and verify the position with a roentgenogram	ET secured with tape to the cheeks and upper lip or to an adhesive patch applied to the skin near the mouth
11	Begin mechanical ventilation	Verify tube placement before ventilating with positive pressure; if an ET tube is in one bronchus, barotraumas may occur

ET, endotracheal tube; ICP, intracranial pressure.

bradycardia. **A heart rate less than 60 beats/min with poor perfusion is an indication to begin chest compressions.** If the bradycardia persists, vascular access should be obtained; resuscitative epinephrine should be administered, and it should be repeated every 3-5 min for persistent symptomatic bradycardia. If increased vagal tone (e.g., in the setting of head injury with raised intracranial pressure) or primary atrioventricular block is suspected, atropine can also be given. For cases of refractory bradycardia, cardiac pacing should be considered. During the resuscitation of a child with bradycardia, providers should assess and treat factors known to cause bradycardia, referred to collectively as the **6 Hs** (hypoxia, hypovolemia, hydrogen ions [acidosis], hypokalemia or hyperkalemia, hypoglycemia, hypothermia), and **5 Ts** (toxins, tamponade, tension pneumothorax, thrombosis [in either the pulmonary or cardiac circulations], and trauma [causing hypovolemia, intracranial hypertension, cardiac compromise or tamponade]) (Table 67-5).

Tachyarrhythmias

Tachyarrhythmias represent a variety of rhythm disturbances of both atrial and ventricular origin (see Chapter 435). Sinus tachycardia is a normal physiologic response to the body's need for increased cardiac output or oxygen delivery, as occurs with fever, exercise, or stress. It can also occur in more pathologic states, such as hypovolemia, anemia, pain, anxiety, and metabolic stress. Tachyarrhythmias that do not originate in the sinus node are often categorized as narrow complex rhythms (those originating in the atrium, such as atrial flutter or supraventricular tachycardia [SVT]) and wide complex rhythms (those rhythms of ventricular origin, such as ventricular tachycardia).

The initial management of tachycardia includes confirmation that the child has an adequate airway and life-sustaining breathing and circulation (Fig. 67-13). For children with persistent symptoms, further treatment is based on whether the QRS complex of the electrocardiogram (ECG) is narrow (≤0.09 sec) or wide (>0.09 sec). For narrow complex tachycardia, providers must distinguish between sinus tachycardia and SVT. In sinus tachycardia, (a) the history and onset are consistent with a known cause of tachycardia, such as fever or dehydration and (b) P waves are consistently present, are of normal morphology, and occur at a rate that varies somewhat. In SVT, (a) onset is often abrupt without prodrome and (b) P waves are absent or polymorphic, and when present, their rate is often fairly steady at or above 220 beats/min. For children with SVT and good perfusion, vagal maneuvers can be attempted. In cases in which SVT is associated with poor perfusion, providers should rapidly move to convert the child's heart rhythm back to sinus rhythm. If the child already has IV access, then adenosine can be given via IV with rapid "push." Adenosine has an extremely short half-life, so a proximal IV is best, and the adenosine should be set up with a 3-way stopcock so it can be given and immediately flushed into the circulation. If the child does not have IV access, or adenosine does

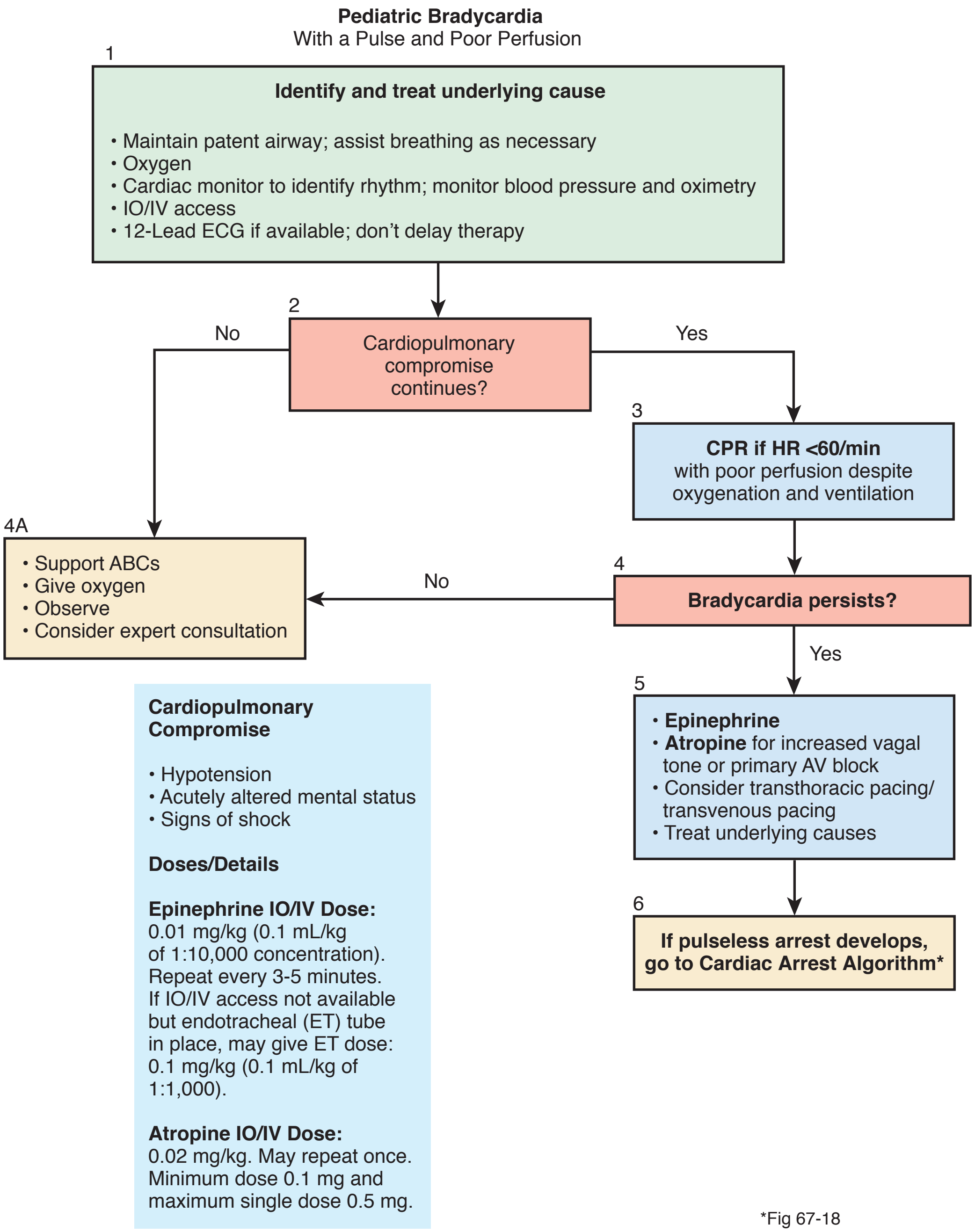

Figure 67-12 Pediatric advanced life support bradycardia algorithm. ABCs, airway, breathing, and circulation; AV, atrioventricular (conductor); ECG, electrocardiogram; HR, heart rate. *(From Kleinman ME, Chameides L, Schexnayder SM, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 14,* Circulation *122[Suppl 3]:S876–S908, 2010, Fig. 2, p. S887.)*

not successfully convert the heart rhythm back to sinus rhythm, then **synchronized cardioversion**, using 0.5-1.0 joule/kg, should be performed. In cases of wide complex tachycardia, providers should move immediately to cardioversion and increase the dose to 2 joules/kg if 1 joule/kg is not effective. As with cases of bradycardia, providers should review the 6 Hs and 5 Ts to identify factors that might be contributing to the tachycardia (see Table 67-5).

RECOGNITION AND MANAGEMENT OF CARDIAC ARREST

Cardiac arrest occurs when the heart fails as an effective pump and blood flow ceases. Outwardly, the patient in cardiac arrest presents as unresponsive and apneic with no palpable pulse. Internally, the cessation of nutrient flow causes progressive tissue ischemia and organ dysfunction. If not rapidly reversed, cardiac arrest leads to progressive deterioration in brain and heart function such that resuscitation and recovery are no longer possible.

Pediatric cardiac arrest is rarely caused by a sudden coronary event or arrhythmia. Instead, cardiac arrest in children is most often the end result of progressive asphyxia, caused by tissue hypoxia, acidosis, and nutrient depletion at the end stages of respiratory deterioration, shock, or heart failure. Therefore, **the most important treatment of cardiac arrest is anticipation and preventive: Intervening when a child manifests respiratory distress or early stages of shock can prevent deterioration to full-blown arrest**. When sudden cardiac arrest does occur, it is most often associated with an arrhythmia, specifically ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). In sudden events such as these, the key to successful resuscitation is early

Table 67-5 Potentially Treatable Conditions Associated with Cardiac Arrest

CONDITION	COMMON CLINICAL SETTINGS	CORRECTIVE ACTIONS
Acidosis	Preexisting acidosis, diabetes, diarrhea, drugs and toxins, prolonged resuscitation, renal disease, and shock	Reassess the adequacy of cardiopulmonary resuscitation, oxygenation, and ventilation; reconfirm endotracheal tube placement Hyperventilate Consider intravenous bicarbonate if pH <7.2 after above actions have been taken
Cardiac tamponade	Hemorrhagic diathesis, cancer, pericarditis, trauma, after cardiac surgery, and after myocardial infarction	Administer fluids; obtain bedside echocardiogram, if available Perform pericardiocentesis; immediate surgical intervention is appropriate if pericardiocentesis is unhelpful but cardiac tamponade is known or highly suspected
Hypothermia	Alcohol abuse, burns, central nervous system disease, debilitated patient, drowning, drugs and toxins, endocrine disease, history of exposure, homelessness, extensive skin disease, spinal cord disease, and trauma	If hypothermia is severe (temperature <30°C [86°F]), limit initial shocks for ventricular fibrillation or pulseless ventricular tachycardia to 3; initiate active internal rewarming and cardiopulmonary support If hypothermia is moderate (temperature 30-34°C [86-93.2°F]), proceed with resuscitation (space medications at longer intervals than usual), passively rewarm child, and actively rewarm truncal body areas
Hypovolemia, hemorrhage, anemia	Major burns, diabetes, gastrointestinal losses, hemorrhage, hemorrhagic diathesis, cancer, pregnancy, shock, and trauma	Administer fluids Transfuse packed red blood cells if hemorrhage or profound anemia is present Thoracotomy is appropriate when a patient has cardiac arrest from penetrating trauma and a cardiac rhythm and the duration of cardiopulmonary resuscitation before thoracotomy is <10 min
Hypoxia	Consider in all patients with cardiac arrest	Reassess the technical quality of cardiopulmonary resuscitation, oxygenation, and ventilation; reconfirm endotracheal tube placement
Hypomagnesemia	Alcohol abuse, burns, diabetic ketoacidosis, severe diarrhea, diuretics, and drugs (e.g., cisplatin, cyclosporine, pentamidine)	Administer 1-2 g magnesium sulfate IV over 2 min
Poisoning	Alcohol abuse, bizarre or puzzling behavioral or metabolic presentation, classic toxicologic syndrome, occupational or industrial exposure, and psychiatric disease	Consult a toxicologist for emergency advice on resuscitation and definitive care, including an appropriate antidote Prolonged resuscitation efforts may be appropriate; immediate cardiopulmonary bypass should be considered, if available
Hyperkalemia	Metabolic acidosis, excessive administration of potassium, drugs and toxins, vigorous exercise, hemolysis, renal disease, rhabdomyolysis, tumor lysis syndrome, and clinically significant tissue injury	If hyperkalemia is identified or strongly suspected, treat* with all of the following: 10% calcium chloride (5-10 mL by slow IV push; do not use if hyperkalemia is secondary to digitalis poisoning), glucose and insulin (50 mL of 50% dextrose in water and 10 units of regular insulin IV), sodium bicarbonate (50 mmol IV; most effective if concomitant metabolic acidosis is present), and albuterol (15-20 mg nebulized or 0.5 mg by IV infusion)
Hypokalemia	Alcohol abuse, diabetes, use of diuretics, drugs and toxins, profound gastrointestinal losses, hypomagnesemia	If profound hypokalemia (<2.0-2.5 mmol of potassium) is accompanied by cardiac arrest, initiate urgent IV replacement (2 mmol/min IV for 10-15 mmol)*; then reassess
Pulmonary embolism	Hospitalized patient, recent surgical procedure, peripartum, known risk factors for venous thromboembolism, history of venous thromboembolism, or prearrest presentation consistent with a diagnosis of acute pulmonary embolism	Administer fluids; augment with vasopressors as necessary Confirm the diagnosis, if possible; consider immediate cardiopulmonary bypass to maintain patient's viability Consider definitive care (e.g., thrombolytic therapy, embolectomy by interventional radiology or surgery)
Tension pneumothorax	Placement of a central catheter, mechanical ventilation, pulmonary disease (including asthma, chronic obstructive pulmonary disease, and necrotizing pneumonia), thoracentesis, and trauma	Needle decompression, followed by chest tube insertion

*Adult dose. Adjust for size of child. See Table 67-6.

From Eisenbery MS, Mengert TJ: Cardiac resuscitation, N Engl J Med *344:1304–1313, 2001.*

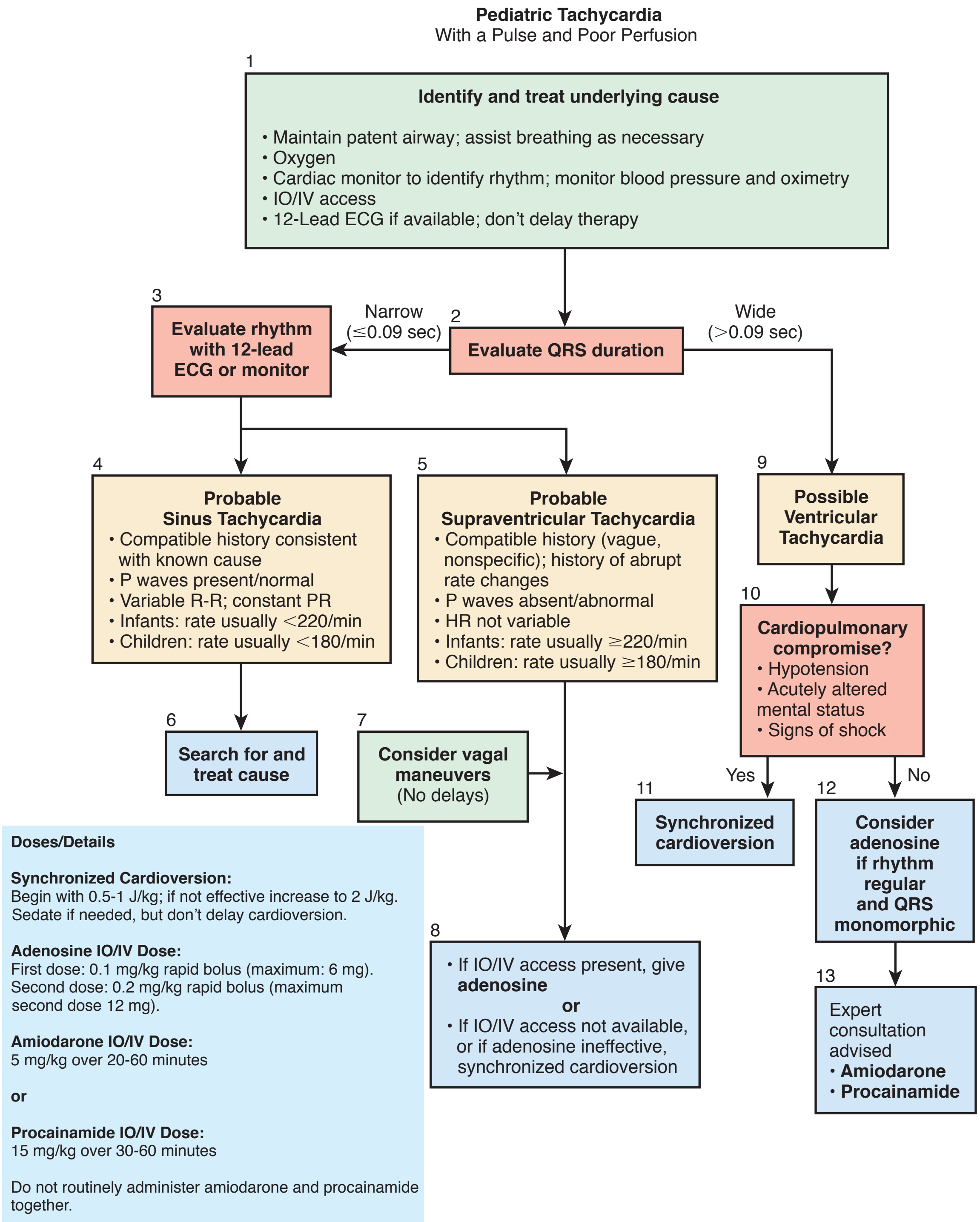

Figure 67-13 **Pediatric advanced life support tachycardia algorithm.** AV, atrioventricular (conductor); ECG, electrocardiogram; HR, heart rate. *(From Kleinman ME, Chameides L, Schexnayder SM, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 14,* Circulation *122[Suppl 3]:S876–S908, 2010, Fig. 3, p. S888.)*

recognition of the arrhythmia and prompt treatment with high-quality CPR and defibrillation.

The principle behind high-quality CPR is that adequate chest compressions—those that circulate blood around the body with a good pulse pressure—are the most important component of CPR. The caregiver providing chest compressions should ***push hard, push fast, allow for complete chest recoil, and minimize interruptions.*** Ideally, chest compressions should be interrupted only for ventilation, a rhythm check, or delivery of a defibrillating shock.

Cardiac arrest is recognized from general and primary survey findings consistent with a pale or cyanotic child who is unresponsive, apneic, and pulseless. Even experienced providers have a relatively high error rate when asked to determine presence or absence of pulse in a child. Therefore, any child found unresponsive and apneic can be presumed to be in cardiac arrest, and a rescuer should respond accordingly. **A lone rescuer for an *unwitnessed* pediatric cardiac arrest in an outpatient setting should treat the arrest as asphyxial in nature and should immediately initiate CPR.** The rescuer should perform

Figure 67-14 Combined jaw-thrust/spine stabilization maneuver for the pediatric trauma victim. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

initial rescue breaths and 2 min of chest compressions and ventilations before leaving the child to activate the emergency response system. For an in-hospital arrest, the provider should call for help and send someone else to activate the emergency response system while beginning CPR. **A lone rescuer in an outpatient setting who *witnesses* a child's sudden collapse should treat the arrest as a primary arrhythmia, should immediately activate the EMS system, and should obtain an AED.** Upon returning to the child, the rescuer should confirm pulselessness, turn on the AED, place the leads on the child's chest, and follow the defibrillator's voice commands.

The initial step in CPR for a child of any age is to restore ventilation and oxygenation as quickly as possible. Upon confirmation of unresponsiveness, apnea, and pulselessness, the provider should open the airway with a head-tilt/chin-lift maneuver (or jaw-thrust if cervical spine trauma is suspected) and provide 2 initial rescue breaths (Fig. 67-14). These breaths are deep and slow, lasting approximately 1 sec per breath. The breaths are adequate if they cause the chest to rise and fall and improve the child's color. If the breaths appear inadequate, the child should be repositioned, and the breaths delivered again. If the breaths remain ineffective, the provider should assess the child for foreign body aspiration. After 2 effective rescue breaths, the child's pulse should be assessed. If the child has a pulse but remains apneic (or with ineffective breathing), then the rescuer should continue to provide assisted ventilation at an age-appropriate rate. Infants and children ≤8 yr old should receive rescue breathing at a rate of roughly 15-20 breaths/min, or roughly 1 breath every 3-5 sec. Children >8 yr old should receive 10-12 breaths/min, or 1 breath every 5-6 sec.

If the child remains pulseless, chest compressions should be initiated. Chest compressions in infants <1 yr old may be performed by placing 2 thumbs on the midsternum with the hands encircling the thorax or by placing 2 fingers over the midsternum and compressing (Figs. 67-15 and 67-16). For children >1 yr old, the care provider should perform chest compressions over the lower half of the sternum with the heel of 1 hand, or with 2 hands as used for adult resuscitation (Fig. 67-17). In all cases, care should be taken to avoid compression of the xiphoid and the ribs. When feasible, a cardiac resuscitation board should be placed under the child's back to maximize the efficiency of compressions. When a lone rescuer provides CPR, the universal ratio of 30 compressions to 2 ventilations is used. Pediatric patients in cardiac arrest are thought to have the best chance of survival if more frequent ventilation is offered. Therefore, the ratio should be lowered to 15 compressions to 2 ventilations for children ≤8 yr old as soon as a second care provider is available. In the outpatient setting, resuscitation effort should pause periodically to allow the provider to make an assessment of the possible return of spontaneous heart rate, pulse, and respirations. The goal of CPR is to reestablish spontaneous circulation

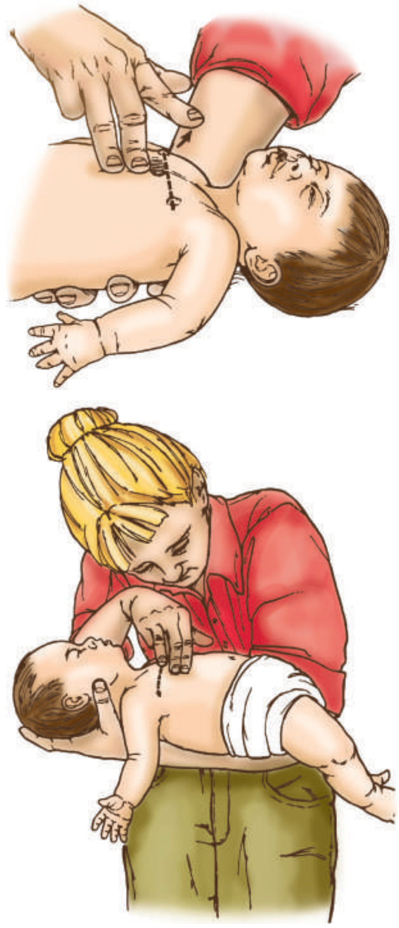

Figure 67-15 Cardiac compressions. *Top,* The infant is supine on the palm of the rescuer's hand. *Bottom,* Performing CPR while carrying an infant or small child. Note that the head is kept level with the torso. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

at a level that is compatible with survival. If resuscitative efforts do not succeed in reestablishing life-sustaining breathing and circulation, the medical team must decide whether continued efforts are warranted or whether the resuscitation should be stopped. If EMS care is en route, bringing the potential for further escalation in care such as endotracheal intubation, vascular access, and medications, CPR should be continued as long as possible or deemed reasonable by the rescuers.

In the in-hospital setting, the ECG should dictate further resuscitative efforts. For children without a pulse and in asystole or electromechanical dissociation (pulseless electrical activity), providers should continue rescue breathing and CPR, obtain vascular access, and give emergency IV epinephrine (Fig. 67-18). For continued asystole or pulseless electrical activity, epinephrine can be repeated every 3-5 min. Patient history, physical exam findings, and laboratory evaluation should be used to elicit correctable causes of arrest (such as the 6 Hs and 5 Ts) (see Table 67-5). CPR should be continued after epinephrine administration, to circulate the drug through the body. After 5 cycles of CPR, providers should reassess the child for the presence of a pulse or a change in the ECG rhythm that would necessitate a different response.

For those children with pulseless VT or VF, emergency defibrillation is indicated (see Fig. 67-18). Providers should apply the pads to the child's bare chest and back and follow the verbal instructions given by the AED. For younger children, a defibrillator (if available) set to the dose of 2 joules/kg should be used. Ideally, the AED used in a child

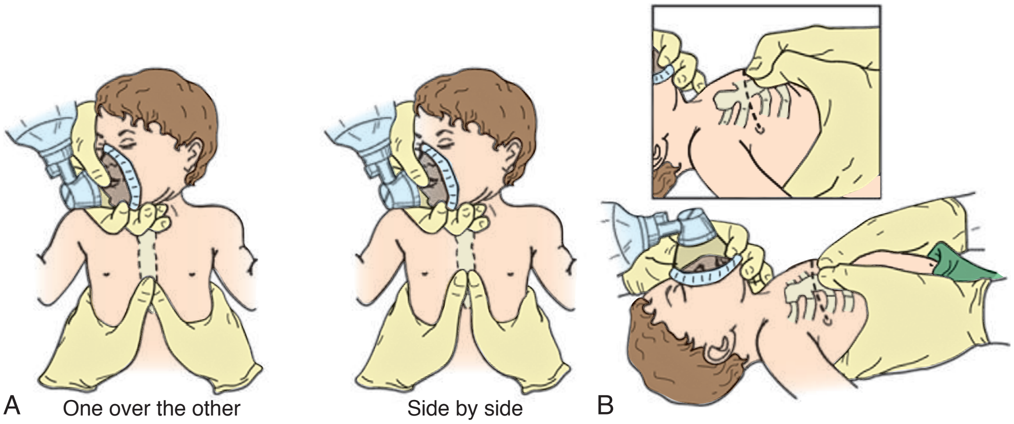

Figure 67-16 **Thumb method of chest compressions.** *A*, Infant receiving chest compressions with thumb 1 fingerbreadth below the nipple line and hands encircling chest. *B*, Hand position for chest encirclement technique for external chest compressions in neonates. Thumbs are side by side over the lower third of the sternum. In the small newborn, thumbs may need to be superimposed *(inset)*. Gloves should be worn during resuscitation. *(From Fleisher GR, Ludwig S, editors:* Textbook of pediatric emergency medicine, *Philadelphia, 2010, Wolters Kluwer/Lippincott Williams & Wilkins Health, Fig. 2.2.)*

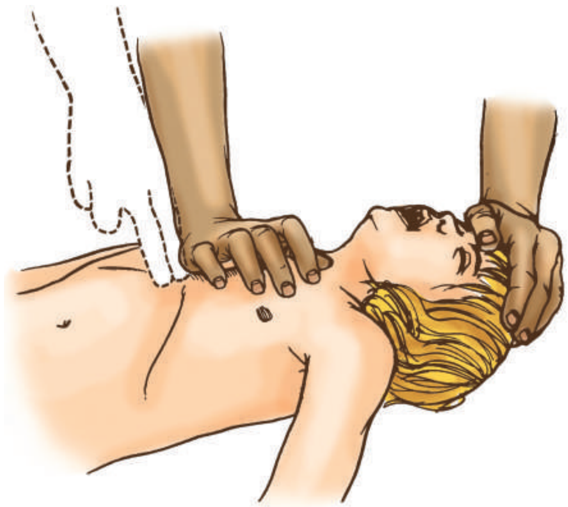

Figure 67-17 **Locating the hand position for chest compression in a child.** Note that the rescuer's other hand is used to maintain the head position to facilitate ventilation. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

≤8 yr of age should be equipped with an attenuated adult dose or should be designed for children; if neither device is available, a standard adult AED should be used. CPR should be immediately restarted after defibrillation. Emergency dose epinephrine can also be administered with another 5 cycles of CPR to ensure its circulation throughout the child's body. If the ECG rhythm continues to show VF or VT, defibrillation can be alternated with epinephrine. For refractory VF or VT, an IV antiarrhythmic, such as amiodarone or lidocaine, can be given (Tables 67-6 and 67-7).

New approaches to CPR in adults have highlighted the potential value of bystander chest compression alone in the initial resuscitation in a community setting. In addition, the combination of vasopressin, methylprednisolone, and epinephrine during an in-hospital cardiac arrest followed by hydrocortisone during the postresuscitation shock period has resulted in a better outcome than patients treated with epinephrine alone. Whether these observations are applicable to young children, who often have different etiologies for cardiopulmonary arrest, has not been determined.

Traditionally, continuing CPR >20 min in children with in-hospital cardiac arrest has been considered futile. With current practice for CPR, survival for in-hospital cardiac arrest is approximately 40% for CPR duration <15 min compared with approximately 12% for CPR lasting >35 min. Survivors had a favorable neurologic outcome in 70% with a CPR duration <15 min compared with 60% for those requiring resuscitation for >35 min.

VASCULAR ACCESS

Venous Access

Veins suitable for cannulation are numerous, but there is considerable anatomic variation from patient to patient. In the upper extremities, the median antecubital vein, located in the antecubital fossa, is often the largest and easiest to access (Fig. 67-19). Many veins on the dorsum of the hand are also suitable for cannulation because they are often large and easily located on the flat surface of the dorsum of the hand, and their cannulation is well tolerated. The cephalic vein is usually cannulated at the wrist, along the forearm, or at the elbow. The median vein of the forearm is also suitable because it lies along a flat surface of the forearm. In the lower extremity, the great saphenous vein, located just anterior to the medial malleolus, is accessible in most patients. The dorsum of the foot usually has a large vein in the midline, passing across the ankle joint, but catheters are difficult to maintain in this vein because dorsiflexion tends to dislodge them. A second large vein on the lateral side of the foot, running in the horizontal plane, usually 1-2 cm dorsal to the lower margin of the foot, is preferable (Fig. 67-20). The most notable scalp veins are the superficial temporal (just anterior to the ear) and posterior auricular (just behind the ear).

Deeper and larger central veins can provide more reliable, larger-bore access for medications, nutritive solutions, and blood sampling than peripheral venous lines. They may be reached by percutaneous cannulation or surgical exposure. In infants and young children, the femoral vein is often the easiest to access and cannulate, but the internal jugular and subclavian veins may also be used (Figs. 67-21 and 67-22). Because of its proximity to the median nerve, the brachial vein is not often recommended for cannulation.

Intraosseous Access

Intraosseous (IO) needles (for intramedullary venous plexus access) are special rigid, large-bore needles that resemble those used for bone marrow aspiration. IO cannulation is recommended for patients for whom IV access proves difficult or unattainable, even in older children. If venous access is not available within 1 min in a child with cardiopulmonary arrest, an IO needle should be placed in the anterior proximal tibia (with care taken to avoid traversing the epiphyseal plate). The needle should penetrate the anterior layer of compact bone, and its tip

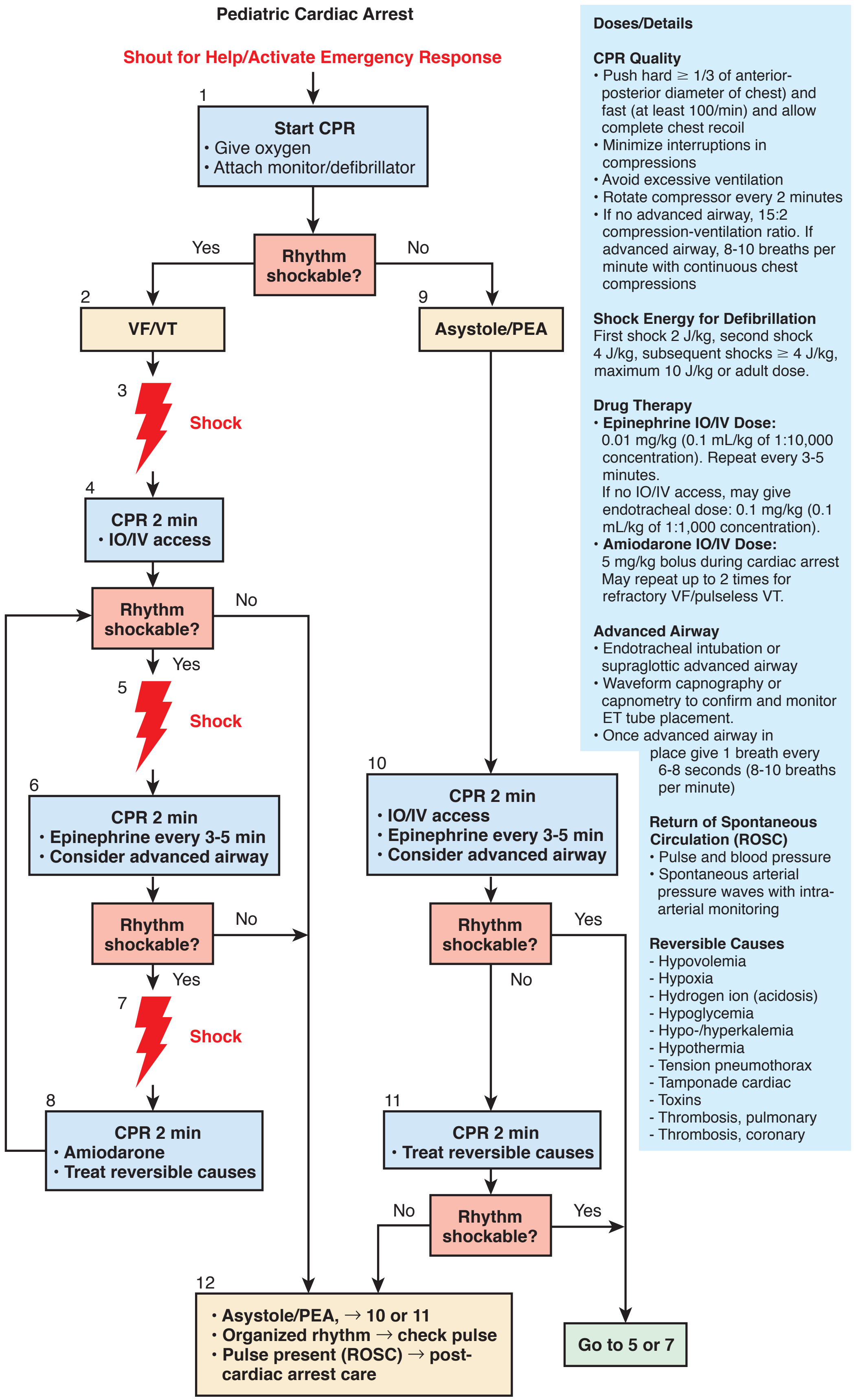

Figure 67-18 Pediatric advanced life support pulseless arrest algorithm. *(From Kleinman ME, Chameides L, Schexnayder SM, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 14, Circulation 122[Suppl 3]: S876–S908, 2010, Fig. 1, p. S885.)*

Table 67-6 Medications for Pediatric Resuscitation and Arrhythmias

MEDICATION	DOSE	REMARKS
Adenosine	0.1 mg/kg (maximum 6 mg) Repeat: 0.2 mg/kg (maximum 12 mg)	Monitor ECG Rapid IV/IO bolus
Amiodarone	5 mg/kg IV/IO; repeat up to 15 mg/kg Maximum: 300 mg	Monitor ECG and blood pressure Adjust administration rate to urgency (give more slowly when perfusing rhythm is present) Use caution when administering with other drugs that prolong QT interval (consider expert consultation)
Atropine	0.02 mg/kg IV/IO 0.03 mg/kg ET* Repeat once if needed Minimum dose: 0.1 mg Minimum single dose: Child, 0.5 mg Adolescent, 1 mg	Higher doses may be used with organophosphate poisoning
Calcium chloride (10%)	20 mg/kg IV/IO (0.2 mL/kg)	Slowly Adult dose: 5-10 mL
Epinephrine	0.01 mg/kg (0.1 mL/kg 1 : 10,000) IV/IO 0.1 mg/kg (0.1 mL/kg 1 : 1,000) ET* Maximum dose: 1 mg IV/IO; 10 mg ET	May repeat q 3-5 min
Glucose	0.5-1 g/kg IV/IO	D10W: 5-10 mL/kg D25W: 2-4 mL/kg D50W: 1-2 mL/kg
Lidocaine	Bolus: 1 mg/kg IV/IO Maximum dose: 100 mg Infusion: 20-50 μg/kg/min ET*: 2-3 mg	
Magnesium sulfate	25-50 mg/kg IV/IO over 10-20 min; faster in torsades de pointes Maximum dose: 2g	
Naloxone	<5 yr or ≤20 kg: 0.1 mg/kg IV/IO/ET* ≥5 yr or >20 kg: 2 mg IV/IO/ET*	Use lower doses to reverse respiratory depression associated with therapeutic opioid use (1-15 μg/kg)
Procainamide	15 mg/kg IV/IO over 30-60 min Adult dose: 20 mg/min IV infusion up to total maximum dose of 17 mg/kg	Monitor EGG and blood pressure Use caution when administering with other drugs that prolong QT interval (consider expert consultation)
Sodium bicarbonate	1 mEq/kg/dose IV/IO slowly	After adequate ventilation

*Flush with 5 mL of normal saline and follow with 5 ventilations.
ECG, electrocardiogram; ET, endotracheal tube; IO, intraosseous; IV, intravenous.
From ECC Committee, Subcommittees and Task Forces of the American Heart Association: 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, Circulation *112:IV1–203, 2005.*

Table 67-7 Medications to Maintain Cardiac Output and for Postresuscitation Stabilization*

MEDICATION	DOSE RANGE	COMMENT
Inamrinone	0.75-1 mg/kg IV/IO over 5 min; may repeat 2x; then: 2-20 μg/kg/min	Inodilator
Dobutamine	2-20 μg/kg/min IV/IO	Inotrope; vasodilator
Dopamine	2-20 μg/kg/min IV/IO in low doses; pressor in higher doses	Inotrope; chronotrope; renal and splanchnic vasodilator
Epinephrine	0.1-1 μg/kg/min IV/IO	Inotrope; chronotrope; vasodilator in low doses; vasopressor in higher doses
Milrinone	50-75 μg/kg IV/IO over 10-60 min then 0.5-0.75 μg/kg/min	Inodilator
Norepinephrine	0.1-2 μg/kg/min	Inotrope; vasopressor
Sodium nitroprusside	1-8 μg/kg/min	Vasodilator; prepare only in D5W

*Alternative formula for calculating an infusion: Infusion rate (mL/hr) = [weight (kg) × dose (μg/kg/min) × 60 (min/hr)]/concentration μg/mL).
D5W, 5% dextrose in water; IO, intraosseous; IV, intravenous.
From ECC Committee, Subcommittees and Task Forces of the American Heart Association: 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, Circulation *112:IV1–IV203, 2005.*

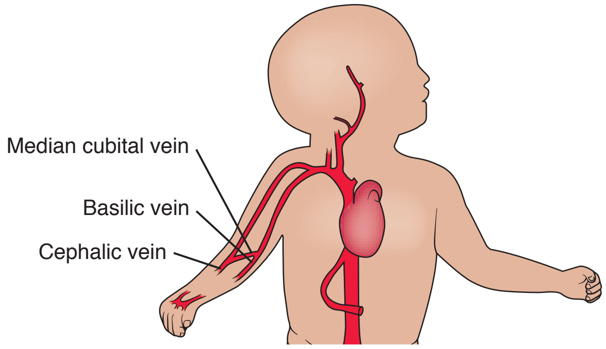

Figure 67-19 Veins of the upper extremity. *(From Roberts JR, Hedges JR, editors:* Clinical procedures in emergency medicine, *ed 4, Philadelphia, 2004, Saunders.)*

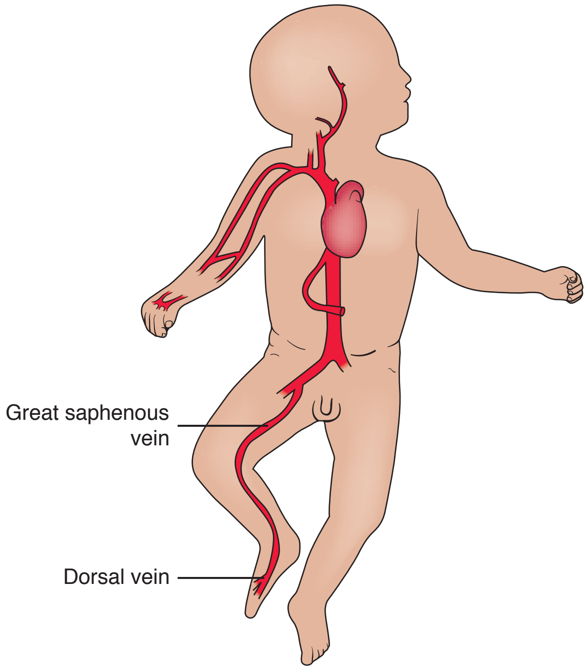

Figure 67-20 Veins of the lower extremity. *(From Roberts JR, Hedges JR, editors:* Clinical procedures in emergency medicine, *ed 4, Philadelphia, 2004, Saunders.)*

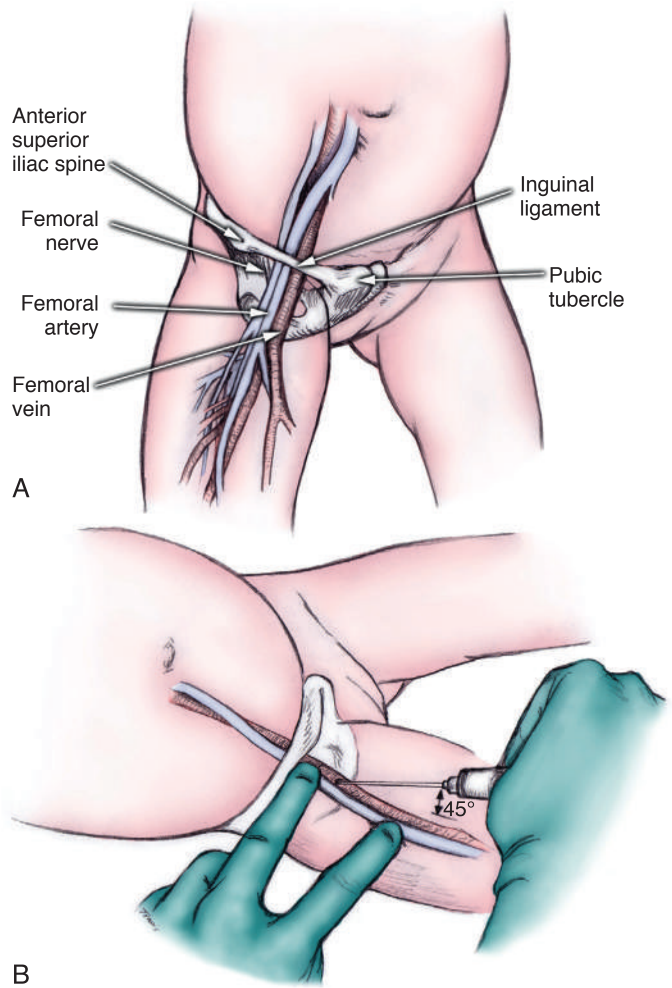

Figure 67-21 Femoral vein approach. Remember the mnemonic NAVEL for nerve, artery, vein, empty space, and lymphatics. *(From Putigna F, Solenberger R:* Central venous access. http://emedicine.medscape.com/article/940865-overview.*)*

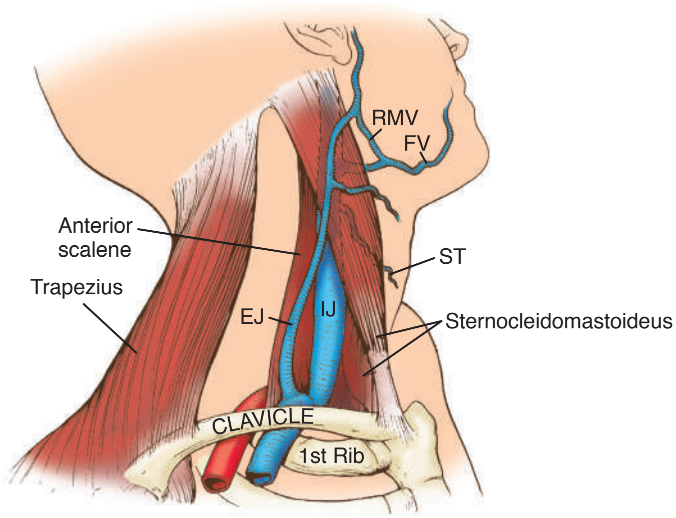

Figure 67-22 Internal and external jugular veins. EJ, external jugular vein; FV, facial vein; IJ, internal jugular vein; RMV, retromandibular vein; ST, superior thyroid vein. The 2 heads of the sternocleidomastoideus are indicated by the *lines*. *(From Mathers LW, Smith DW, Frankel L: Anatomic considerations in placement of central venous catheters,* Clin Anat *5:89, 1992. Reprinted by permission of Wiley-Liss.)*

advanced into the spongy interior of the bone (Fig. 67-23). Commercially available IO kits frequently include drills that obviate the complications of needle placement associated with manual placement. Any and all medications, blood products, and fluids may be administered through the IO route, including all medications required for emergency resuscitation. Complications are uncommon, but may include osteomyelitis with prolonged infusions and tibial fracture.

Arterial Access

Arterial access is indicated when care providers need frequent blood sampling, particularly to assess adequacy of oxygenation, ventilation, or acid–base balance, and/or continuous blood pressure monitoring. The radial artery, the most commonly cannulated artery, lies on the lateral side of the anterior wrist, just medial to the styloid process of the radius (Fig. 67-24). The ulnar artery, just lateral to the tendon of the flexor carpi ulnaris, is used less often because of its proximity to the ulnar nerve. Useful sites in the lower extremity, particularly in neonates and infants, are the dorsalis pedis artery, on the dorsum of the foot between the tendons of the tibialis anterior and the extensor hallucis longus, and the posterior tibial artery, posterior to the medial

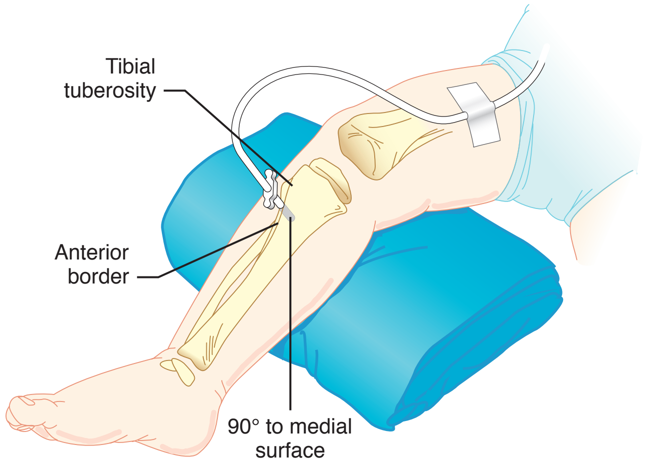

Figure 67-23 Intraosseous cannulation technique. *(From Zwass MS, Gregory GA: Pediatric and neonatal intensive care. In Miller RD, Eriksson LI, Fleisher LA, et al, editors:* Miller's anesthesia, *ed 7, Philadelphia, 2009, Churchill Livingstone, Fig. 84-1.)*

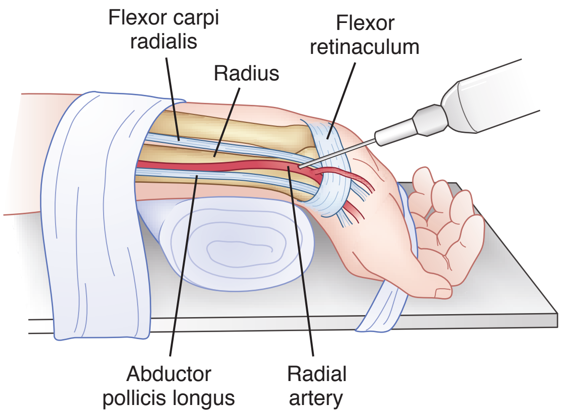

Figure 67-24 Radial artery anatomy and cannulation.

malleolus. Arterial catheters require special care for insertion and subsequent management because the blood flow to tissue can be compromised and considerable hemorrhage can occur if an arterial catheter is dislodged.

NONVASCULAR EMERGENCY PROCEDURES

Thoracentesis and Chest Tube Placement

Thoracentesis is the placement of a needle or catheter into the pleural space to evacuate fluid, blood, or air. Most insertions are performed in one of the intercostal spaces between the 4th and 9th ribs in the plane of the midaxillary line. After appropriate systemic and local anesthesia/sedation is performed as clinically indicated, a skin incision is made, and dissection through the chest wall is accomplished in layers with use of blunt dissection techniques. The needle (and later, the chest tube) that enters the pleural space should penetrate the intercostal space by passing over the superior edge of the lower rib, because there are larger vessels along the inferior edge of the rib. Ideally, the chest tube should lie anterior in the pleural space for air accumulation, and posterior for fluid accumulation. A radiograph must be obtained to verify chest tube placement and evacuation of the pleural space.

Pericardiocentesis

When fluid, blood, or gas accumulates in the pericardial sac, a danger is that the heart will be compressed and will not be able to fill and empty with normal volumes of blood, leading to diminished cardiac output. The cardinal signs of such a restrictive pericardial effusion are tachycardia, hypotension, and decreasing oxygen saturation. Pericardiocentesis includes needle aspiration of the pericardial sac, often followed by the placement of a catheter for continuous drainage. As for thoracentesis, chest radiography should be done to confirm catheter location as well as to evaluate for presence of any complications, such as pneumothorax or hemothorax.

POSTRESUSCITATION CARE

After successful resuscitation, close observation in an intensive care unit, where the child can receive ongoing multiorgan system assessments and support, is critical. Optimal postresuscitation care includes ongoing support of cardiovascular and respiratory system function as needed and the identification and treatment of other organ system dysfunction that may have contributed to (or resulted from) the child's cardiopulmonary instability. Good postresuscitation intensive care also includes supportive services for the child's parents, siblings, family, and friends.

Induced hypothermia (32-34°C [89.6-91.4°F] for ≈48 hr) may improve survival and neurologic function in adult and pediatric survivors of CPR. This is a controversial treatment that has inconsistently proven beneficial in comatose adult survivors of cardiac arrest. Randomized clinical trials in children are in progress. *Furthermore, hyperthermia must be avoided.* Hypoxic-ischemic encephalopathy with subsequent development of seizures, intellectual impairment, and spasticity, is a serious and common complication of cardiac arrest. *In addition hyperglycemia and hypoglycemia should be avoided.*

Postresuscitation management generally has 2 phases, similar to earlier, emergency resuscitative care. First, the providers must assess the child's airway and breathing and must support oxygenation and ventilation as indicated. If the child has ongoing respiratory failure and has been supported with bag-valve-mask ventilation until this time, the providers should now move forward with intubation. Once the child is intubated, mechanical ventilation must be established, and respiratory assessments performed, such as chest radiography and arterial blood gas sampling and analysis. The child's circulatory system must also be assessed and supported as needed. Continuous arterial blood pressure monitoring can help the provider determine the need for, and response to, inotropic and chronotropic medications (see Table 67-7). Once the ABCs have been managed, providers can move on to full organ system assessments. A systematic approach that employs a full physical exam and laboratory evaluation to reveal the child's respiratory, cardiovascular, neurologic, gastrointestinal, renal, and hematologic system function should be used.

Communication with the family is an essential element of postresuscitation care. The family should be thoroughly briefed on the elements of the resuscitation performed, the child's condition, and ongoing medical concerns, uncertainties, or issues by the *most senior provider available*. This provider should be available to answer the family's questions, clarify information, and provide comfort. Other support staff, such as social workers and chaplains, should be contacted, as the family wishes, to provide additional support and comfort. For situations in which the resuscitation is ongoing and the child is not expected to survive, the American Academy of Pediatrics recommends that the provider make every effort possible to have the family present at the bedside if they wish. Family presence during CPR or other emergency resuscitative efforts, even if the child dies, is associated with a more positive medical experience than if they are excluded. In cases in which the child is critically ill but stable, the family should be brought to the bedside as soon as the healthcare team deems it safe and appropriate.

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Chapter 68

Neurologic Emergencies and Stabilization

Patrick M. Kochanek and Michael J. Bell

NEUROCRITICAL CARE PRINCIPLES

The brain has high metabolic demands, which are further increased during growth and development. Preservation of nutrient supply to the brain is the mainstay of care for children with evolving brain injuries. *Intracranial dynamics* describes the physics of the interactions of the contents—brain parenchyma, blood (arterial, venous, capillary) and cerebrospinal fluid (CSF)—within the cranium. Normally, brain parenchyma accounts for up to 85% of the contents of the cranial vault, and the remaining portion is divided between CSF and blood. The brain resides in a relatively rigid cranial vault, and cranial compliance decreases with age as the skull ossification centers gradually replace cartilage with bone. The **intracranial pressure (ICP)** is derived from the volume of its components and the bony compliance. The **perfusion pressure** of the brain (cerebral perfusion pressure [CPP]) is equal to the pressure of blood entering the cranium (mean arterial pressure) minus the ICP, in most cases.

Increases in intracranial volume can result from swelling, masses, or increases in blood and CSF volumes. As these volumes increase, compensatory mechanisms decrease ICP by (a) decreasing CSF volume (CSF is displaced into the spinal canal or absorbed by arachnoid villi), (b) decreasing cerebral blood volume (venous blood return to the thorax is augmented), and/or (c) increasing cranial volume (sutures pathologically expand or bone is remodeled). Once compensatory mechanisms are exhausted (the increase in cranial volume is too large), small increases in volume lead to large increases in ICP or intracranial hypertension (Fig. 68-1). As ICP continues to increase, brain ischemia can occur as CPP falls. Further increases in ICP can ultimately displace the brain downward into the foramen magnum—a process called **cerebral herniation,** which can become irreversible in minutes and may lead to severe disability or death; Figure 68-2 notes other sites of brain herniation.

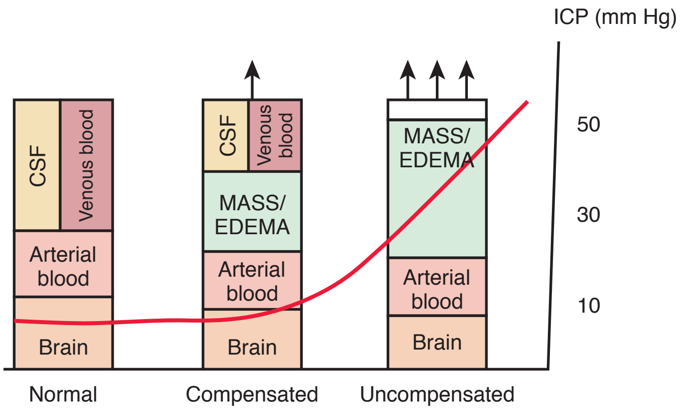

Figure 68-1 The Munro-Kellie doctrine describes intracranial dynamics in the setting of an expanding mass lesion (i.e., hemorrhage, tumor) or brain edema. In the normal state, the brain parenchyma, arterial blood, CSF, and venous blood occupy the cranial vault at a low pressure, generally <10 mm Hg. With an expanding mass lesion or brain edema, initially there is a compensated state as a result of reduced CSF and venous blood volumes, and ICP remains low. Further expansion of the lesion, however, leads to an uncompensated state when compensatory mechanisms are exhausted and intracranial hypertension results. See text for details.

Oxygen and glucose are required by brain cells for normal functioning, and these nutrients must be constantly supplied by cerebral blood flow (CBF). Normally, CBF is constant over a wide range of blood pressures (blood pressure autoregulation of CBF) via actions mainly within the cerebral arterioles. Cerebral arterioles are maximally dilated at lower blood pressures and maximally constricted at higher pressures so that CBF does not vary during normal fluctuations (Fig. 68-3). Acid–base balance of the CSF (often reflected by acute changes in arterial partial pressure of carbon dioxide [$Paco_2$]), body/brain temperature, glucose utilization, and other vasoactive mediators (i.e., adenosine, nitric oxide) can also affect the cerebral vasculature.

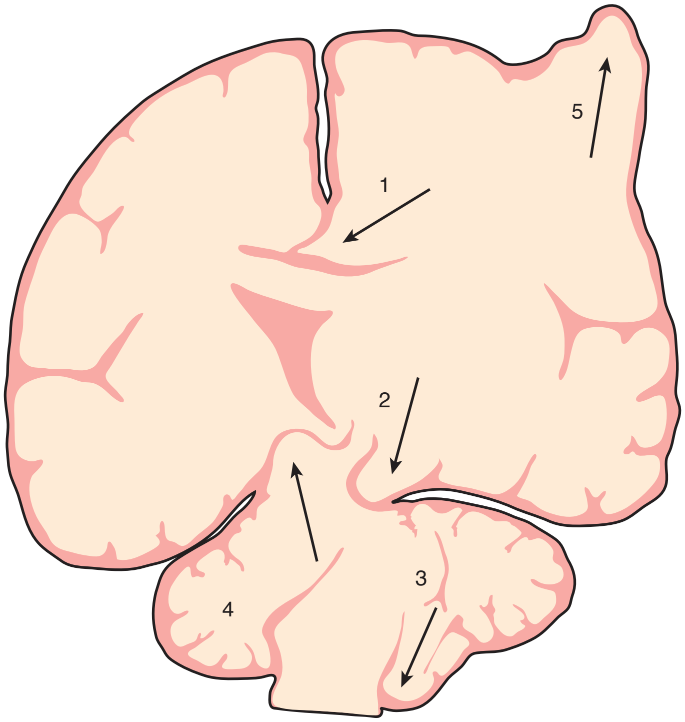

Figure 68-2 Different forms of brain herniation. *1,* Cingulate. *2,* Uncal. *3,* Cerebellar tonsillar. *4,* Upward cerebellar. *5,* Transcalvarial. *(From Fishman RA:* Cerebrospinal fluid in diseases of the nervous system, *Philadelphia, 1980, Saunders.)*

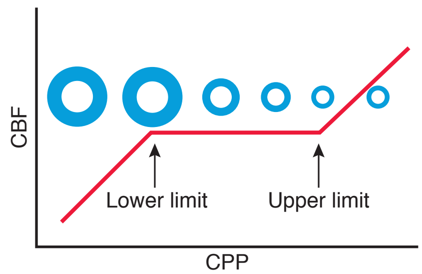

Figure 68-3 Schematic of the relationship between CBF and CPP. The diameter of a representative cerebral arteriole is also shown across the center of the *y* axis to facilitate understanding of the vascular response across CPP that underlies blood pressure autoregulation of CBF. CPP is generally defined as the mean arterial pressure (MAP) minus the ICP. At normal values for ICP, this generally represents MAP. Thus, normally, CBF is kept constant between the lower limit and upper limit of autoregulation; in normal adults, these values are ≈50 mm Hg and 150 mm Hg, respectively. In children, the upper limit of autoregulation is likely proportionally lower than the adult value relative to normal MAP for age. However, according to the work of Vavilala et al. (2003), lower limit values are surprisingly similar in infants and older children. Thus, infants and young children may have less reserve for adequate CPP. See text for details.

Knowledge of these concepts is instrumental to preventing secondary brain injury. Increases in CSF pH that occur because of inadvertent hyperventilation (decreased $Paco_2$) can produce cerebral ischemia. Hyperthermia-mediated increases in cerebral metabolic demands may damage vulnerable brain regions after injury. Hypoglycemia can produce neuronal death when CBF fails to compensate. Prolonged seizures can lead to permanent injuries if hypoxemia occurs from loss of airway control.

Attention to detail and constant reassessment are paramount in managing children with critical neurologic insults. Among the most valuable tools for serial, objective assessments of neurologic condition is the Glasgow Coma Scale (GCS) (see Table 67-3 in Chapter 67). Originally developed to assess level of consciousness after traumatic brain injury (TBI) in adults, the GCS is also valuable in pediatrics. Modifications to the GCS have been made for nonverbal children and are available for infants and toddlers (see Table 67-3 in Chapter 67). Serial assessments of the GCS score along with a focused neurologic examination are invaluable to detection of injuries before permanent damage occurs in the vulnerable brain.

The FOUR (full outline of unresponsiveness) score (Table 68-1) is a modification of the GCS, which eliminates the verbal response but adds two functional assessments of the brain stem (pupil, corneal, cough reflexes, and respiratory patterns).

The most-studied monitoring device in clinical practice is the **ICP monitor**. Monitoring is accomplished by a catheter inserted either into the cerebral ventricle (externalized ventricular drain) or into brain parenchyma (parenchymal transducer). ICP-directed therapies are standard of care in TBI and are used in other conditions, such as intracranial hemorrhage, Reye syndrome, and some cases of encephalopathy, meningitis, and encephalitis. Other devices being used include catheters that measure brain tissue oxygen concentration, external probes that noninvasively assess brain oxygenation by absorbance of near-infrared light (near-infrared spectroscopy), monitors of brain electrical activity (continuous electroencephalography [EEG] or somatosensory, visual, or auditory evoked potentials), and CBF monitors (transcranial Doppler, xenon CT, perfusion MRI, or tissue probes). In the current severe TBI guidelines, brain tissue oxygen concentration monitoring received level III support and thus, may be considered.

TRAUMATIC BRAIN INJURY

Etiology

Mechanisms of TBI include motor vehicle crashes, falls, assaults, and abusive head trauma. Most TBIs in children are from closed-head injuries.

Epidemiology

TBI is an important pediatric public health problem, with approximately 37,000 cases resulting in the death of more than 7,000 children annually in the United States.

Pathology

Epidural, subdural, and parenchymal intracranial hemorrhages can result. Injury to gray or white matter is also commonly seen and includes focal cerebral contusions, diffuse cerebral swelling, axonal injury, and injury to the cerebellum or brainstem. Patients with severe TBI often have multiple findings; diffuse and potentially delayed cerebral swelling is common.

Pathogenesis

TBI results in primary and secondary injury. Primary injury from the impact produces irreversible tissue disruption. In contrast, 2 types of secondary injury are targets of neurointensive care. First, some of the ultimate damage seen in the injured brain evolves over hours or days, and the underlying mechanisms involved (edema, apoptosis, and secondary axotomy) are therapeutic targets. Second, the injured brain is vulnerable to additional insults because injury disrupts normal autoregulatory defense mechanisms; disruption of autoregulation of CBF can lead to ischemia from hypotension that would otherwise be tolerated by the uninjured brain.

Table 68-1 Commonly Used Coma Scores

GLASGOW COMA SCALE	FULL OUTLINE OF UNRESPONSIVENESS (FOUR) SCORE
Eye Opening 1 = does not open eyes 2 = opens eyes in response to noxious stimuli 3 = opens eyes in response to voice 4 = opens eyes spontaneously	*Eye Response* 4 = eyelids open or opened, tracking, or blinking to command 3 = eyelids open but not tracking 2 = eyelids closed but open to loud voice 1 = eyelids closed but open to pain 0 = eyelids remain closed with pain
Verbal Output 1 = makes no sounds 2 = makes incomprehensible sounds 3 = utters inappropriate words 4 = confused and disoriented 5 = speaks normally and oriented	*Motor Response* 4 = thumbs-up, fist, or peace sign 3 = localizing to pain 2 = flexion response to pain 1 = extension response to pain 0 = no response to pain or generalized myoclonus status
Motor Response (Best) 1 = makes no movements 2 = extension to painful stimuli 3 = abnormal flexion to painful stimuli 4 = flexion/withdrawal to painful stimuli 5 = localized to painful stimuli 6 = obeys commands	*Brainstem Reflexes* 4 = pupil and corneal reflexes present 3 = one pupil wide and fixed 2 = pupil or corneal reflexes absent 1 = pupil and corneal reflexes absent 0 = absent pupil, corneal, and cough reflex
	Respiration 4 = not intubated, regular breathing pattern 3 = not intubated, Cheyne-Stokes breathing pattern 2 = not intubated, irregular breathing 1 = breathes above ventilatory rate 0 = breathes at ventilator rate or apnea

From Edlow JA, Rabinstein A, Traub SJ, Wijdicks EFM: Diagnosis of reversible causes of coma. Lancet 384:2064-2076, 2014.

Clinical Manifestations

The hallmark of **severe TBI** is coma (**GCS score 3-8**). Often, coma is seen immediately after the injury and is sustained. In some cases, such as with an epidural hematoma, a child may be alert on presentation but may deteriorate after a period of hours. A similar picture can be seen in children with diffuse swelling, in whom a *talk-and-die* scenario has been described. Clinicians should also not be lulled into underappreciating the potential for deterioration of a child with **moderate TBI** (**GCS score 9-12**) with a significant contusion, because progressive swelling can potentially lead to devastating complications. In the comatose child with severe TBI, the second key clinical manifestation is the development of intracranial hypertension. The development of increased ICP with impending herniation may be heralded by new-onset or worsening headache, depressed level of consciousness, vital sign changes (hypertension, bradycardia, irregular respirations), and signs of 6th (lateral rectus palsy) or 3rd (anisocoria [dilated pupil], ptosis, down-and-out position of globe as a result of rectus muscle palsies) cranial nerve compression. Increased ICP is managed with continuous ICP monitoring, as well as monitoring for clinical signs of increased ICP or impending herniation. The development of brain swelling is progressive. Significantly raised ICP (>20 mm Hg) can occur early after severe TBI, but peak ICP generally is seen at 48-72 hr.

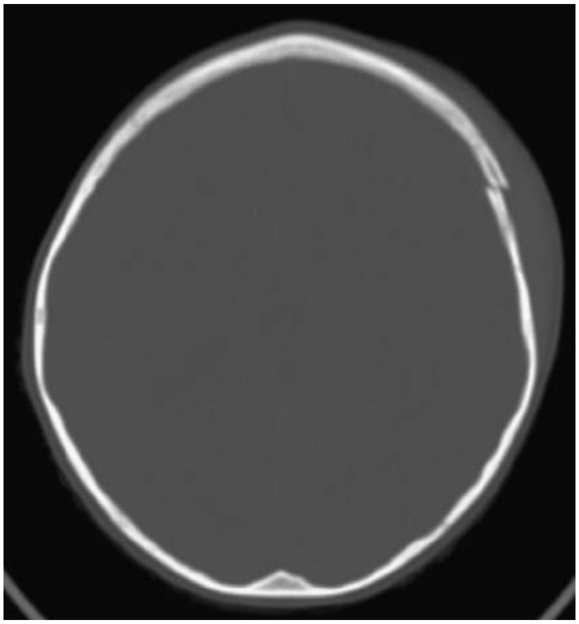

Figure 68-4 Mildly displaced skull fracture seen on CT imaging (bone window view) in a 4 yr old who fell and hit her head on a curb.

Figure 68-5 Left frontal epidural hematoma observed on CT imaging in a 12 yr old child who fell off his bike onto concrete surface.

Need for ICP-directed therapy may persist for longer than a week. A few children have coma without increased ICP, resulting from axonal injury or brainstem injury. *In addition to head trauma, it is critical to identify potential cervical spine injury.*

Laboratory Findings

Cranial CT should be obtained immediately after resuscitation and cardiopulmonary stabilization (Figs. 68-4 to 68-10). In some cases, magnetic resonance imaging can be diagnostic (Fig. 68-11). Generally, other laboratory findings are normal in isolated TBI, although occasionally coagulopathy or the development of the syndrome of inappropriate antidiuretic hormone secretion or, rarely, cerebral salt wasting is seen. In the setting of TBI with polytrauma, other injuries can result in laboratory abnormalities, and a full trauma survey is important in all patients with severe TBI (see Chapter 72).

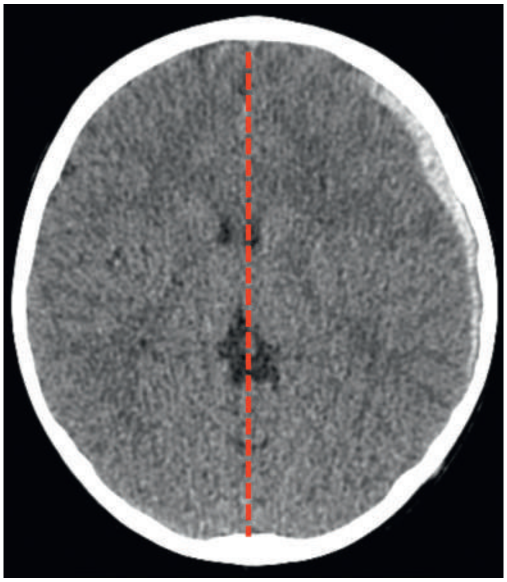

Figure 68-6 Left subdural hematoma observed on CT imaging in a 10 yr old child after a motor vehicle accident. Note, there is effacement of the left lateral ventricle and midline shift noted (see *dotted line* for midline reference).

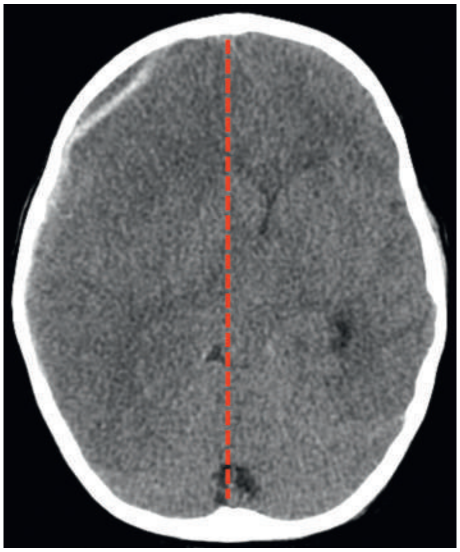

Figure 68-7 Hyperacute right frontal subdural hematoma observed on CT imaging in a 5 yr old after a motor vehicle accident. Note that the hyperacute aspect of the subdural hematoma is dark on CT imaging in the early stage after injury. Also, note that there is marked midline shift of intracranial contents, as both lateral ventricles are displaced into the left side of the skull.

Diagnosis and Differential Diagnosis

In severe TBI, the diagnosis is generally obvious from the history and clinical presentation. Occasionally, TBI severity can be overestimated because of concurrent alcohol or drug intoxication. The diagnosis of TBI can be problematic in cases of abusive head trauma or following an anoxic event such as drowning or smoke inhalation.

Treatment

Infants and children with severe or moderate TBI (GCS score 3-8 or 9-12, respectively) receive intensive care unit (ICU) monitoring. Evidence-based guidelines for management of severe TBI have been published (Fig. 68-12). This approach to ICP-directed therapy is also reasonable for other conditions in which ICP is monitored. Care involves a multidisciplinary team comprising pediatric caregivers from

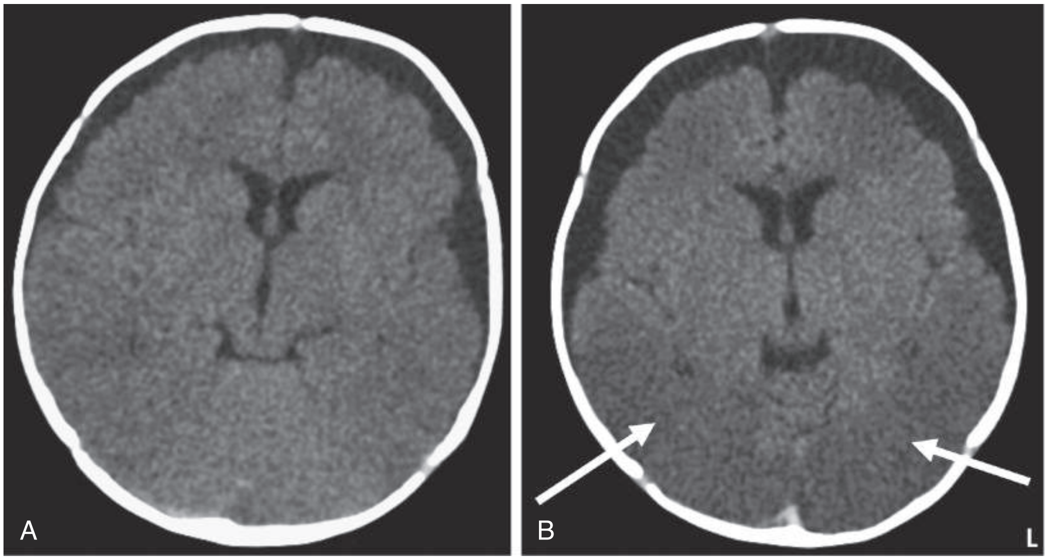

Figure 68-8 In a 3 mo old child who suffered from abusive head trauma, initial CT imaging *(A)* demonstrates chronic subdural hematoma bilaterally. Three days after hospitalization *(B)*, the subdural hematomas are slightly larger but infarctions are noted in the posterior areas of brain parenchyma (see *arrows*).

Figure 68-9 In a 16 yr old who fell off of his dirt bike, CT imaging demonstrates intraparenchymal hemorrhage and significant surrounding edema (*arrow*).

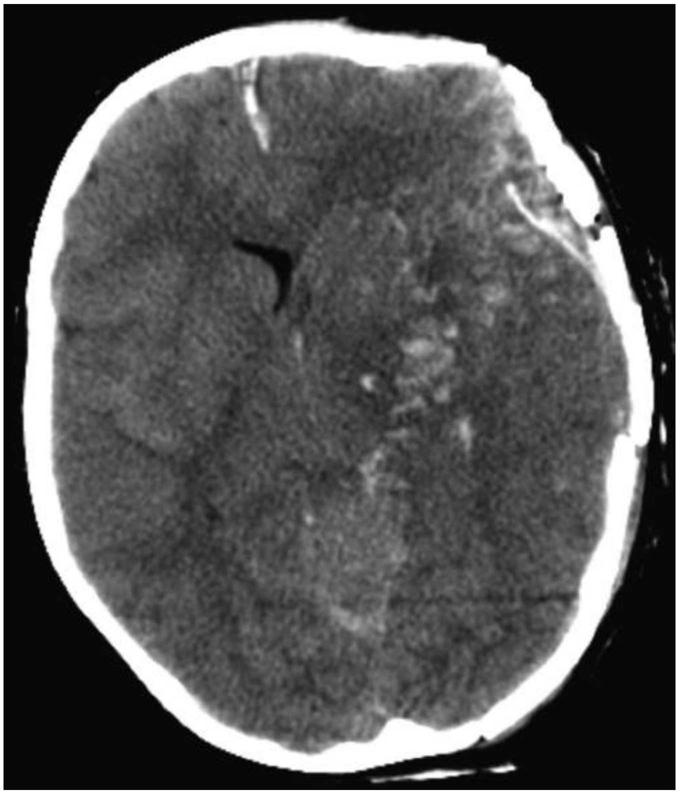

Figure 68-10 An 11 yr old child was hit in the head by a horse, and CT imaging demonstrates multiple, comminuted skull fractures with fragments of bone within the brain parenchyma, multifocal areas of intraparenchymal hemorrhage, and obliteration of the left lateral ventricle.

neurologic surgery, critical care medicine, surgery, and rehabilitation, and is directed at preventing secondary insults and managing raised ICP. Initial stabilization of infants and children with severe TBI includes rapid sequence tracheal intubation with spine precautions along with maintenance of normal extracerebral hemodynamics, including blood gas values (partial pressure arterial oxygen, $Paco_2$), mean arterial pressure, and temperature. Intravenous fluid boluses may be required to treat hypotension. Euvolemia is the target, and hypotonic fluids should be rigorously avoided; normal saline is the fluid of choice. Pressors may be needed as guided by monitoring of central venous pressure, with avoidance of both fluid overload and exacerbation of brain edema. A trauma survey should be performed. Once stabilized, the patient should be taken for CT scanning to rule out the need for emergency neurosurgical intervention. If surgery is not

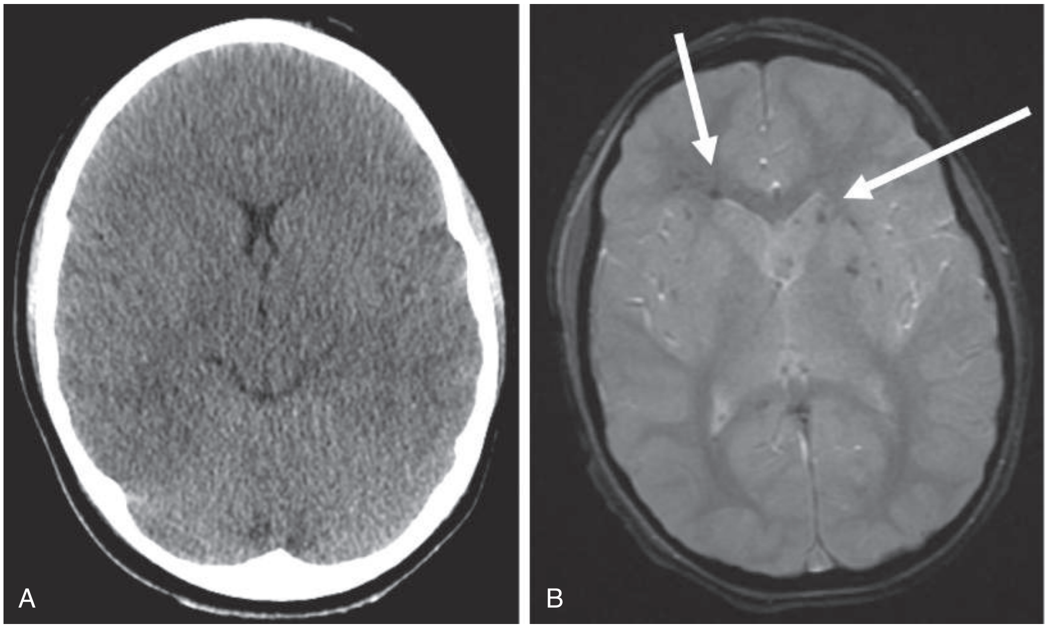

Figure 68-11 In a 6 yr old child who was hit by a car while riding his bike, initial CT imaging demonstrates no obvious abnormality (*A*). However, immediate MRI demonstrates multiple areas of punctate hemorrhages (lucencies) consistent with diffuse axonal injury (*B, arrows*).

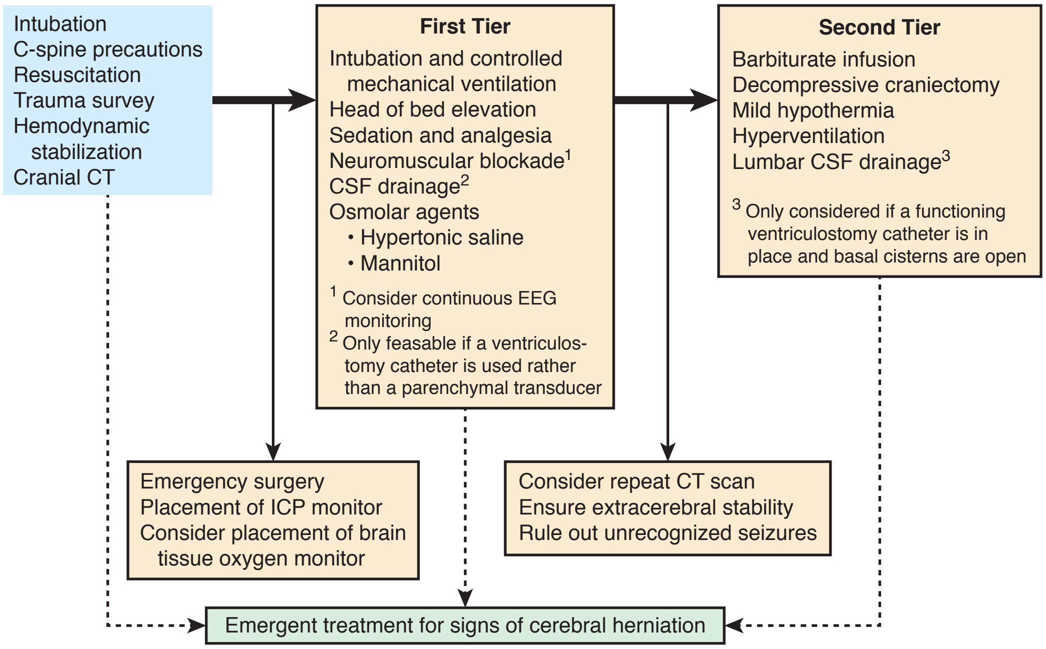

Figure 68-12 Schematic outlining the approach to management of a child with severe TBI. It is based on the 2012 guidelines for the management of severe TBI, along with minor modifications from later literature. The ICP and CPP targets are discussed in the text. This schematic is specifically presented for severe TBI, for which the experience with ICP-directed therapy is greatest. Nevertheless, the general approach provided here is relevant to the management of intracranial hypertension in other conditions for which evidence-based data on ICP monitoring and ICP-directed therapy are lacking. Please see text for details.

required, an ICP monitor should be inserted to guide the treatment of intracranial hypertension. Serial assessment of brain edema on CT scan can also help guide management.

During stabilization or at any time during the treatment course, patients can present with signs and symptoms of cerebral **herniation** (pupillary dilation, systemic hypertension, bradycardia, extensor posturing). Because herniation and its devastating consequences can sometimes be reversed if promptly addressed, it should be treated as a medical emergency, with use of hyperventilation with a fraction of inspired oxygen of 1.0, and intubating doses of either thiopental or pentobarbital and either mannitol (0.25-1.0 g/kg IV) or hypertonic saline (3% solution, 5-10 mL/kg IV).

ICP should be maintained <20 mm Hg; age-dependent CPP targets are ≈50 mm Hg for children 2-6 yr of age; 55 mm Hg for those 7-10 yr of age; and 65 mm Hg for those 11-16 yr of age. First-tier therapy includes elevation of the head of the bed, ensuring midline positioning of the head, controlled mechanical ventilation, and sedation and analgesia (i.e., benzodiazepines and narcotics). If neuromuscular blockade is needed, it may be desirable to monitor EEG continuously because *status epilepticus* can occur; this complication will not be recognized

in a paralyzed patient and is associated with raised ICP and unfavorable outcome. If a ventricular rather than parenchymal catheter is used to monitor ICP, therapeutic CSF drainage is available and can be provided either continuously (often targeting an ICP >5 mm Hg) or intermittently in response to ICP spikes, generally 20 mm Hg. Other first-tier therapies include the osmolar agents mannitol (0.25-1.0 g/kg IV over 20 min), given in response to ICP spikes >20 mm Hg or with a fixed (q4-6h) dosing interval, and hypertonic saline (often given as a continuous infusion of 3% saline at 0.1-1.0 mL/kg/hr). Choice of osmolar agent depends on the preference of the treating center. These 2 agents can be used concurrently. It is recommended to avoid serum osmolality >320 mOsm/L. A Foley urinary catheter should be placed to monitor urine output.

If ICP remains refractory to treatment, careful reassessment of the patient is needed to rule out unrecognized hypercarbia, hypoxemia, fever, hypotension, hypoglycemia, pain, and seizures. Repeat imaging should be considered to rule out a surgical lesion. Guidelines-based second-tier therapies for refractory raised ICP are available, but evidence favoring a given second-tier therapy is limited. In some centers, decompressive craniectomy is used. Others use a pentobarbital infusion, with a loading dose of 5-10 mg/kg over 30 min followed by 5 mg/kg every hour for 3 doses and then maintenance with an infusion of 1 mg/kg/hr. Careful blood pressure monitoring is required because of the possibility of drug-induced hypotension and the frequent need for support with fluids and/or pressors. Mild hypothermia (32-34°C [89.6-93.2°F]) to control refractory ICP can be induced and maintained by means of surface cooling. Sedation and neuromuscular blockade are used to prevent shivering, and rewarming should be slow, no faster than 1°C (1.8°F) every 4-6 hr. Hypotension should be prevented during rewarming. Refractory raised ICP can also be treated with hyperventilation ($Paco_2$ = 25-30 mm Hg). Other second-tier therapies (e.g., lumbar CSF drainage) are options.

Supportive Care

Euvolemia should be maintained, and isotonic fluids are recommended until resolution of intracranial hypertension. The syndrome of inappropriate antidiuretic hormone secretion and salt wasting can develop and are important to differentiate, because management of the former is fluid restriction and that of the latter is sodium replacement. Severe hyperglycemia (blood glucose level >200 mg/dL) should be avoided and treated. The blood glucose level should be monitored frequently. Early nutrition with enteral feedings is advocated. Corticosteroids should generally not be used unless adrenal insufficiency is documented. Tracheal suctioning can exacerbate raised ICP. Timing of the use of sedation around suctioning events and/or use of tracheal or IV lidocaine can be helpful. Seizures are common after severe acute TBI. Early posttraumatic seizures (within 1 wk) will complicate management of TBI and are often difficult to treat. Anticonvulsant prophylaxis with fosphenytoin, carbamazepine, or levetiracetam is a common treatment option. Late posttraumatic seizures (≥7 days after TBI) and, if recurrent, late posttraumatic epilepsy are not prevented by prophylactic anticonvulsants, whereas early posttraumatic seizures are prevented by initiating anticonvulsants soon after TBI. Antifibrinolytic agents (tranexamic acid) reduce hemorrhage size as well as the development of new focal ischemic cerebral lesions, and improve survival in adults with severe traumatic brain injury.

Prognosis

Mortality rates for children with severe TBI who reach the pediatric ICU range between 10% and 30%. Ability to control ICP is related to patient survival, and the extent of cranial and systemic injuries correlates with quality of life. Motor and cognitive sequelae resulting from severe TBI generally benefit from rehabilitation to minimize long-term disabilities. Recovery from TBI may take months to achieve. Physical therapy, and in some centers methylphenidate, helps with motor and behavioral recovery. Pituitary insufficiency may be an uncommon but significant complication of severe TBI.

Bibliography is available at Expert Consult.

68.1 Brain Death

K. Jane Lee

Brain death is the irreversible cessation of all functions of the entire brain, including the brainstem. It is also known as the determination of death using neurologic criteria. Although brain death is legally accepted in the United States as the equivalent of death from the irreversible cessation of circulatory and respiratory functions, it can be difficult to understand and is not universally accepted.

EPIDEMIOLOGY

In children, brain death most commonly develops following TBI (including brain injury from nonaccidental trauma) or asphyxial injury. Pathogenesis is multifactorial, with the end result being irreversible loss of brain and brainstem function.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Guidelines for the determination of brain death in children were first published in 1987 by a Special Task Force to the American Academy of Pediatrics. These were revised for the first time in 2011 by a combined group from the Society of Critical Care Medicine, the American Academy of Pediatrics, and the Child Neurology Society.

Brain death is primarily a clinical diagnosis. Although ancillary tests such as EEG and CBF studies are sometimes used to assist in making the diagnosis, repeated clinical examination is the standard for diagnosis. The 3 key components of clinical brain death diagnosis are demonstrations of coexisting **irreversible coma with a known cause**, **absence of brainstem reflexes**, and **apnea**.

Before a determination of brain death may be made, it is of utmost importance that the cause of the coma be determined through the use of historical, radiologic, and laboratory data to rule out a reversible condition. Potentially reversible causes of coma include metabolic disorders; toxins; sedative drugs; paralytic agents; hypothermia; hypoxia; hypotension/shock; recent cardiopulmonary resuscitation; hypoglycemia/hyperglycemia; hyponatremia/hypernatremia; hypercalcemia; hypermagnesemia; nonconvulsive status epilepticus; hypothyroidism; hypocortisolism; hypercarbia; liver or renal failure; sepsis; meningitis; encephalitis; subarachnoid hemorrhage; and surgically remediable brainstem lesions. Confounding factors must be corrected prior to initiation of brain death assessment.

Coma

The state of **coma** requires that the patient be unresponsive, even to noxious stimuli. Any purposeful motor response, such as localization, does not constitute coma. Likewise, any posturing (decerebrate or decorticate) is not consistent with coma, and therefore not consistent with brain death. The presence of spinal cord reflexes—even complex reflexes—does not preclude the diagnosis of brain death.

Brainstem Reflexes

Brainstem reflexes must be absent. Table 68-2 lists the brainstem reflexes to be tested, the brainstem location of each reflex, and the result of each test that is consistent with a diagnosis of brain death.

Apnea

Apnea is the absence of respiratory effort in response to an adequate stimulus. A partial pressure of carbon dioxide (pCO_2) value ≥60 mm Hg *and* >20 mm Hg above baseline is considered sufficient. Apnea is clinically confirmed through the apnea test. Because the apnea test has the potential to destabilize the patient, this test is performed only if the first 2 criteria for brain death (irreversible coma and absence of brainstem reflexes) are already confirmed.

The **apnea test** assesses the function of the medulla in driving ventilation. It is performed by first ensuring appropriate hemodynamics and temperature and the absence of apnea-producing drug effects or significant metabolic derangements. The patient is then preoxygenated with 100% oxygen for approximately 10 minutes and ventilation is adjusted to achieve a pCO_2 of approximately 40 mm Hg. A baseline

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Table 68-2 Brainstem Reflex Testing to Determine Brain Death

BRAINSTEM REFLEX	AREA TESTED	HOW TO PERFORM THE EXAM	EXPLANATION OF RESULTS
Pupillary light reflex	CN II and III, midbrain	Shine a light into the eyes while closely observing pupillary size	Midposition (4-6 mm) or fully dilated pupils that are not reactive to light are consistent with brain death. Pinpoint pupils, even if nonreactive, suggest intact function of the Edinger-Westphal nucleus in the midbrain and are therefore not consistent with brain death.
Oculocephalic reflex (doll's-eyes reflex)	CN III, VI, and VIII, midbrain, pons	Manually rotate the patient's head side to side and closely watch the position of the eyes. Should not be performed in a patient with a cervical spine injury.	In an intact patient, the eyes remain fixed on a distant spot, as if maintaining eye contact with that spot. In an exam consistent with brain death, the eyes move in concert with the patient's head movement.
Corneal reflex	CN III, V, and VII, pons	Touch the patient's cornea with a cotton swab.	In the intact patient, the touch results in eyelid closure, and the eye may rotate upward. In an exam consistent with brain death, there is no response.
Oculovestibular reflex	CN III, IV, VI, and VIII, pons, midbrain	Irrigate the tympanic membrane with iced water or saline and look for eye movement.	Absence of eye movement is consistent with brain death.
Gag and cough reflex	CN IX and X, medulla	Touch the posterior pharynx with a tongue depressor or a cotton-tipped swab to stimulate a gag. Advance a suction catheter through the endotracheal tube to the carina to stimulate a cough.	Absence of both a cough and a gag is consistent with brain death.

CN, cranial nerve.

blood gas result documents the starting values. During the test, oxygenation can be maintained with 100% oxygen via a T-piece attached to the endotracheal tube or via a resuscitation bag such as a Mapleson device. Throughout the test, the child's hemodynamics and oxygen saturation are monitored while the physician observes for respiratory efforts. A blood gas sample is obtained approximately 10 min into the test and every 5 min thereafter until the target pCO_2 is surpassed; ventilatory support is resumed at that time. If at any point during the test the patient becomes hypoxic or hypotensive, the test is aborted and ventilatory support is resumed. Absence of respiratory efforts with a pCO_2 ≥60 mm Hg and >20 mm Hg above baseline is consistent with brain death.

OBSERVATION PERIODS

To establish the diagnosis of brain death, the findings must remain consistent for 2 examinations separated by an observation period. Recommended observation periods are 24 hr for neonates from 37 wk gestation to term infants 30 days old, and 12 hr for infants and children older than 30 days. An observation period of 24-48 hr prior to initiation of brain death assessment is recommended following CPR or severe acute brain injury.

ANCILLARY STUDIES

Ancillary studies are not required for the diagnosis of brain death unless the clinical examination including the apnea test cannot be safely or reliably completed. Examples include cervical spinal cord injury, presence of high-therapeutic or supratherapeutic levels of sedative medications, or hemodynamic instability or desaturation during an apnea test. Ancillary studies may also be used to shorten the recommended observation period. In this case, 2 complete clinical examinations, including apnea test, should be completed and documented along with the ancillary study.

The 2 most commonly used ancillary tests are EEG and radionuclide CBF studies. A valid **EEG** to support suspected brain death must be performed according to accepted technical requirements, under conditions of normothermia and appropriate hemodynamics, and in the absence of drug levels sufficient to suppress the EEG response. An EEG that demonstrates **electrocerebral silence** over a 30 min recording time under these conditions supports the diagnosis of brain death. Advantages of this study are its wide availability and low risk. Disadvantages include potential confounders, such as artifact in the tracing and the presence of suppressing levels of drugs such as barbiturates.

A **radionuclide CBF study** consists of intravenous injection of a radiopharmaceutical agent followed by imaging of the brain to look for cerebral uptake. Like EEG, nuclear medicine scans are widely available and low risk. Unlike EEG, these studies are not affected by drug levels. A study that shows absence of uptake in the brain demonstrates absence of CBF and is supportive of brain death. Four-vessel intracranial contrast angiography was previously used as the definitive ancillary test, but practical technical difficulties and risks have led to the use of nuclear medicine scans instead.

Interpretation of both EEG and radionuclide CBF studies should be done by appropriately trained and qualified individuals. If the studies show electrical activity or presence of CBF, brain death cannot be declared. A 24 hr waiting period is recommended prior to repeating the clinical examination or ancillary study.

DOCUMENTATION

Documentation is an important aspect of diagnosing brain death. Complete documentation should include statements of the following:

1. Etiology and irreversibility of the coma.
2. Absence of confounding factors: hypothermia, hypotension, hypoxia, significant metabolic derangement, significant drug levels.
3. Absence of motor response to noxious stimulation.
4. Absence of brainstem reflexes: pupillary light reflex, oculocephalic/oculovestibular reflex, corneal reflex, cough and gag reflex.
5. Absence of respiratory effort in response to an adequate stimulus; blood gas values should be documented at the beginning and end of the apnea test.

SUPPORTIVE CARE

Following a diagnosis of brain death, supportive care may continue for hours to days as the family makes decisions about potential organ donation and comes to terms with the diagnosis. A diagnosis of brain death may not be accepted by the family for personal, religious, or

cultural reasons. It is important for care providers to be patient and supportive of the family dealing with this difficult situation.

OBJECTIONS TO THE IDEA OF BRAIN DEATH

Although the concept of brain death is widely accepted and very useful in facilitating organ transplantation, it is not accepted by all. Several countries do not recognize brain death, and some individuals, both medical personnel and laypeople, object to the idea of brain death.

It has been pointed out that some patients who meet brain death criteria continue to show evidence of integrative functioning, such as control over free-water homeostasis (absence of diabetes insipidus), control of temperature regulation, capacity for growth and wound healing, and variability of heart rate and blood pressure in response to stimulus. Along with scientific arguments, there are also philosophical arguments about what constitutes death and whether a person who lacks function of the brain, but not of the body, is truly dead.

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Chapter 69

Syncope

George F. Van Hare

Syncope is defined as a sudden transient loss of consciousness with inability to maintain postural tone. The most common cause of syncope in the normal pediatric population is **neurocardiogenic syncope**, also known as vasovagal syncope (Table 69-1). Although this type of syncope is very common in adolescence and has an excellent prognosis, other causes for loss of consciousness are more dangerous, thus syncope may be the first sign of more serious conditions (Table 69-2). Indeed, the occurrence of syncope may well be the pediatrician's best opportunity to diagnose a life-threatening condition before the patient subsequently succumbs. The task of the clinician, therefore, is not only to counsel the family and the patient concerning the common form, but also to rule out a number of important life-threatening cardiac problems.

EPIDEMIOLOGY

Most syncope presents during adolescence, typically between 11 and 13 yr of age. The incidence is somewhat higher in girls than in boys. Approximately 25% of all young adults will have experienced at least 1 episode of neurocardiogenic syncope.

MECHANISMS

Syncope by whatever mechanism is caused by a lack of adequate cerebral blood flow with loss of consciousness and inability to see remain upright. The mechanisms underlying neurocardiogenic syncope are not completely understood but seem to involve some trigger event that leads to vasodilation, venous pooling in the lower part of the body exacerbated by prolonged standing, decreased cardiac filling with compensatory sinus tachycardia and sympathetic nervous system activity, and, finally, activation of cardiac C fibers leading to reflex bradycardia. The typical event is triggered by a variety of factors, such as disgust, the site of blood, other emotional reactions, particular smells, or simply prolonged standing (see Table 69-1). Most patients display a mixed picture with both blood pressure and heart rate changes. Prior to syncope, the blood pressure declines and the heart rate increases, and with loss of consciousness there is often significant bradycardia. Other patients display a principally vasopressor response with a drop in blood pressure as the most important feature. Still others primarily have a cardioinhibitory response in which sudden profound bradycardia or asystole occurs with little or no change in blood pressure prior to the event. Making the distinction between these various patterns leading

Table 69-1 Noncardiac Causes of Syncope
Reflex vasodepressor syncope
Neurocardiogenic (vasovagal)
Emotion (seeing blood)
Pain (needle phobia)
Miscellaneous situational reflex
Tussive
Sneeze
Exercise/post exercise
Swallowing
Stretching
Defecation
Micturition
Valsalva (increased intrathoracic pressure)
Breath holding spells
Systemic illness
Hypoglycemia
Anemia
Infection
Hypovolemia, dehydration
Adrenal insufficiency
Narcolepsy/cataplexy
Pulmonary embolism
Ruptured ectopic pregnancy
Central nervous system
Seizure (atonic, absence, myoclonic-astatic)
Stroke/transient ischemic attack
Subarachnoid hemorrhage
Dysautonomia
Basilar artery migraine
Drug effects
β-Blocking agents
Vasodilating agents
Opiates
Sedatives
Drugs prolonging QT interval
Diuretics
Anticonvulsant agents
Antihistamines
Antidepressant agents
Anxiolytic agents
Drugs of abuse
Insulin, oral hypoglycemic agents
Carbon monoxide
Other etiologies
Carotid sinus sensitivity
Subclavian steal
Panic attack/anxiety
Conversion disorder

Table 69-2 Life-Threatening Cardiac Causes of Syncope
Long QT syndromes (congenital and drug induced)
Cardiomyopathies
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Arrhythmogenic right ventricular dysplasia
Brugada syndrome
Catecholminergic polymorphic ventricular tachycardia
Myocarditis
Wolff-Parkinson-White syndrome
Coronary artery anomalies
Late postoperative arrhythmias
Congenital or acquired complete atrioventricular block
Aortic, mitral, or pulmonic valve stenosis
Primary pulmonary hypertension
Eisenmenger syndrome
Dissecting aortic aneurysm (Marfan syndrome)
Cardiac tumor

to syncope is important for treatment considerations. In any case, with loss of consciousness and the assumption of supine posture, venous return and atrial filling dramatically increases and adequate blood pressure returns quickly.

Primary cardiac causes of syncope (see Table 69-2) include arrhythmias (see Chapter 435) such as **long QT syndrome**, **Wolff-Parkinson-White syndrome** (particularly with atrial fibrillation), ventricular tachycardia, and occasionally supraventricular tachycardia. Ventricular tachycardia may be associated with **hypertrophic cardiomyopathy**, repaired **congenital heart disease**, or a genetic cause such as **catecholaminergic polymorphous ventricular tachycardia**. Other arrhythmias that may lead to syncope are bradyarrhythmias such as **sinus node dysfunction** and high-grade 2nd or 3rd degree atrioventricular (AV) block. Patients with **congenital complete AV** block may present with syncope. Syncope may also be caused by cardiac obstructive lesions, such as **critical aortic stenosis,** or coronary artery anomalies, such as an **aberrant left coronary artery arising from the right sinus of Valsalva**. Finally, patients with **primary pulmonary hypertension** or **Eisenmenger syndrome** may experience syncope. In all of the obstructive forms of syncope, exercise increases the likelihood of an episode as the obstruction interferes with the ability of the heart to increased cardiac output in response to exercise.

Noncardiac causes of loss of consciousness include epilepsy, but may also include basilar artery migraine, hysterical syncope, and pseudo-seizures (see Table 69-1). Occasionally patients with narcolepsy may present as syncope. Hypoglycemia and hyperventilation may also present with syncope.

EVALUATION

The most important goal in the evaluation of the new patient with syncope is to diagnose life-threatening causes of syncope so that these causes can be managed. Many patients presenting with sudden cardiac arrest caused by conditions such as long QT syndrome will have previously experienced an episode of syncope, and so the presentation with syncope is an opportunity to prevent sudden death.

The most important tool in evaluation is a careful history. The patient with neurocardiogenic syncope will be able to describe the circumstances of the event and specific prodromal symptoms. Typically, the patient will have been standing for a period of time, often on a hot day, or has gotten up suddenly from sleep or resting in a supine position. Occurrence in the shower is common, presumably caused by standing and vasodilation caused by hot water. For boys, the occurrence while urinating while standing is sometimes reported. The occurrence of syncope in girls while sitting or standing and having their hair brushed is common. Typical prodromal symptoms prior to syncope include lightheadedness, dizziness, nausea, sweating, and feeling hot or cold. Patients may report visual field changes and "rushing" in their ears. Witnesses will usually note extreme pallor or a gray color change. Injury to the patient as a result of the episode of syncope is unusual in common syncope, as the patient usually has adequate prodromal symptoms to avoid injury. Loss of consciousness is generally transient once the patient becomes supine; the loss of consciousness resolves rapidly (seconds to minutes), and there is no clear postevent state of sleepiness. Often, patients will describe other episodes with similar prodromal symptoms which did not lead to complete loss of consciousness but were aborted, often because the patient was able to assume recumbent posture. Some patients have a few tonic–clonic movements while unconscious, which resolve within seconds, and do not signify a seizure disorder.

The characteristics of cardiac syncope not due to neurocardiogenic mechanisms are generally quite different. A number of "red flags" can be identified that should lead the clinician to be suspicious that the mechanism is a life-threatening cardiac cause rather than simple fainting (Table 69-3). The occurrence during exercise suggests an arrhythmia or coronary obstruction. Injury as a result of an episode of syncope suggests sudden occurrence with a lack of adequate prodromal symptoms, and suggests an arrhythmia. The occurrence of syncope while recumbent would be quite unusual in a patient with neurocardiogenic syncope and therefore raises the possibility of a cardiac or neurologic cause. Occasionally, a patient with syncope caused by a tachyarrhythmia will report the sensation of a racing heart prior to the event, but this is actually unusual.

Table 69-3	"Red Flags" in the Evaluation of Patients with Syncope
Syncope with activity or exercise or supine	
Syncope not associated with prolonged standing	
Syncope precipitated by loud noise or extreme emotion	
Absence of presyncope or lightheadedness	
Family history of syncope, drowning, sudden death, familial ventricular arrhythmia syndromes*, cardiomyopathy	
Syncope requiring CPR	
Injury with syncope	
Anemia	
Other cardiac symptoms	
Chest pain	
Dyspnea	
Palpitations	
History of cardiac surgery	
History of Kawasaki disease	
Implanted pacemaker	
Abnormal physical examination	
Murmur	
Gallop rhythm	
Loud and single second heart sound	
Systolic click	
Increased apical impulse (tachycardia)	
Irregular rhythm	
Hypo- or hypertension	
Clubbing	
Cyanosis	

*Long Qt syndrome, Brugada syndrome, catecholamine polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia.

A careful family history is essential in evaluation of syncope. Specifically, if there are first-degree relatives with inherited syndromes, such as a long QT syndrome or hypertrophic cardiomyopathy, this should lead to more specific evaluation of the patient. Also, if there are relatives who have died suddenly in young age without a clear and convincing cause, inherited cardiac arrhythmias or cardiomyopathies should also be suspected.

Patients with a history of heart disease, especially cardiac repair, may have causes that are specific to their repair. Sinus node dysfunction is common after the Senning or Mustard procedure for transposition of the great vessels. Ventricular tachycardia may be seen following repair of tetralogy of Fallot. A patient with a history of septal defect repair should be evaluated for the late occurrence of AV block, and patients with an implanted pacemaker should be evaluated for pacemaker lead failure.

The physical examination may also offer clues (see Table 69-3). Patients with hypertrophic cardiomyopathy may have a prominent cardiac impulse and/or an ejection murmur, as will patients with aortic stenosis. The patient with primary pulmonary hypertension will have a loud and single second heart sound and may also have an ejection click and the murmur of pulmonary insufficiency. Scars from prior cardiac surgery and pacemaker implantation would be evident.

All patients presenting with a first episode of syncope should have an electrocardiogram obtained, looking primarily for QT interval prolongation, preexcitation, ventricular hypertrophy, T-wave abnormalities, and conduction abnormalities. Other tests that may be needed depending on the results of the initial evaluation may include echocardiography, cardiac MRI, or 24-hr Holter monitoring. In patients for whom there is a strong suspicion of a paroxysmal arrhythmia, an implantable loop recorder may be the most effective means of diagnosis.

Tilt-table testing was originally developed by the military and was applied to the general population of otherwise normal individuals who have experienced syncope. While patients with neurocardiogenic syncope often will experience an episode during the tilt-table test, the test is poorly reproducible and neither particularly sensitive nor

specific. The use of tilt-table testing for the otherwise normal adolescent with simple fainting is discouraged. Some pediatric cardiologists still employ the test in severely affected individuals who are not responding to standard therapy, as a way of planning more aggressive therapy.

Additional tests to look for anemia, hypoglycemia, drugs of abuse, and other etiologies noted in Table 69-1 will be determined by the history and physical exam.

TREATMENT

Most patients with neurocardiogenic syncope will experience eventual resolution by adulthood; many even get better spontaneously within a few months or years. Many therapies have been employed for this condition, but it is difficult to determine which ones are truly effective because of the lack of randomized prospective studies. Nonetheless, initial salt and water supplementation is commonly recommended, particularly in those who have a low-salt diet or who have limited their fluid intake. A reasonable second step is treatment with fludrocortisone, a mineralocorticoid that promotes sodium and water retention with potassium loss. In patients who have a prominent low-blood-pressure response, the α-agonist midodrine may be useful. Both midodrine and fludrocortisone should be managed with careful monitoring of the supine blood pressure, as they may lead to supine hypertension. Some have advocated the use of β blockers such as, pindolol, which offers some advantages because of its intrinsic sympathomimetic activity; randomized prospective trials have not supported the effectiveness of beta blockers. Occasionally, the use of selective serotonin reuptake inhibitors is effective in certain patients. Occasional patients who present with profound bradycardia or asystole can be helped by implantation of a dual-chamber transvenous pacemaker with programmed hysteresis (rapid pacing in response to a sudden drop in heart rate).

The most important therapeutic step is educational. Once the young patient is aware of the importance of the prodromal symptoms, they can take appropriate steps to change position and not attempt to remain standing. In many, this is all that is necessary to adequately manage their symptoms.

Bibliography is available at Expert Consult.

69.1 Disorders of Orthostatic Intolerance

George F. Van Hare

Postural orthostatic tachycardia syndrome (POTS) is a female-predominant condition in which the patient experiences an impressive and symptomatic elevation in heart rate on standing. This orthostatic intolerance disorder manifests with presyncopal symptoms, lightheadedness, dizziness, palpitations, leg weakness and tremulousness on standing. An orthostatic heart rate of >120 beats/min and a rise in heart rate of ≥30 beats/min with 5 min of standing suggest the diagnosis. *This should not be confused with neurocardiogenic syncope*. Patients with POTS often also complain of other symptoms, such as fatigue, chest pain, headaches, abdominal pain, bloating, nausea, emesis, sleep disturbances, and fatigue. There is an overlap with patients with POTS and chronic fatigue syndrome or functional gastrointestinal disorders. Many patients are evaluated in dysautonomia programs and may have evidence of a **small fiber polyneuropathy**. Treatment of POTS is symptomatic and often not particularly successful. The use of β blockers may be effective; some physicians have advised increase physical activity through cardiac rehabilitation.

Juvenile-onset widespread pain syndromes associated with a small fiber polyneuropathy (dysautonomia) have associated gastrointestinal, cardiovascular, fatigue, headache symptoms as well as erythromelalgia. Steroids or intravenous immunoglobulin has been used to treat this disorder.

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Chapter 70

Shock

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Shock is an acute process characterized by the body's inability to deliver adequate oxygen to meet the metabolic demands of vital organs and tissues. Insufficient oxygen at the tissue level is unable to support normal aerobic cellular metabolism, resulting in a shift to less-efficient anaerobic metabolism. As shock progresses, increases in tissue oxygen extraction are unable to compensate for this deficiency in oxygen delivery, leading to progressive clinical deterioration and lactic acidosis. If inadequate tissue perfusion persists, adverse vascular, inflammatory, metabolic, cellular, endocrine, and systemic responses worsen physiologic instability.

Compensation for inadequate oxygen delivery involves a complex set of responses that attempt to preserve oxygenation of the vital organs (i.e., brain, heart, kidneys, liver) at the expense of other organs (i.e., skin, gastrointestinal tract, muscles). Of importance, the brain is especially sensitive to periods of poor oxygen supply, given its lack of capacity for anaerobic metabolism. Initially, shock is often well compensated, but it may rapidly progress to an uncompensated state requiring more aggressive therapies to achieve clinical recovery or improvement. The combination of a continued presence of an inciting trigger and the body's exaggerated and potentially harmful neurohumoral, inflammatory, and cellular responses leads to the progression of shock. Irrespective of the underlying cause of shock, the specific pattern of response, pathophysiology, clinical manifestations, and treatments may vary significantly, depending on the specific etiology (which may be unknown), the clinical circumstances, and an individual patient's biologic response to the shock state. Untreated shock causes irreversible tissue and organ injury (i.e., irreversible shock) and, ultimately, death.

EPIDEMIOLOGY

Shock occurs in approximately 2% of all hospitalized infants, children, and adults in developed countries, and the mortality rate varies substantially depending on the etiology and clinical circumstances. Most patients who do not survive, do not die in the acute hypotensive phase of shock, but rather as a result of associated complications and **multiple organ dysfunction syndrome (MODS).** MODS is defined as any alteration of organ function that requires medical support for maintenance, and the presence of MODS in patients with shock substantially increases the probability of death. In pediatrics, educational efforts and the utilization of standardized management guidelines that emphasize early recognition and intervention along with the rapid transfer of critically ill patients to a pediatric intensive care unit have led to decreases in the mortality rate for shock (Fig. 70-1).

DEFINITION

Shock classification systems generally define 5 major types of shock: hypovolemic, cardiogenic, distributive, obstructive, and septic (Table 70-1). **Hypovolemic shock,** the most common cause of shock in children worldwide, is most frequently caused by diarrhea, vomiting, or hemorrhage. **Cardiogenic shock** is seen in patients with either congenital heart disease (before or after surgery, including heart transplantation) or with congenital or acquired cardiomyopathies, including acute myocarditis. **Obstructive shock** stems from any lesion that creates a mechanical barrier that impedes adequate cardiac output, which include pericardial tamponade, tension pneumothorax, pulmonary embolism, and ductus-dependent congenital heart lesions. **Distributive shock** is caused by inadequate vasomotor tone, which leads to capillary leak and maldistribution of fluid into the interstitium. **Septic shock** is often discussed synonymously with distributive shock, but the septic process usually involves a more complex interaction of distributive, hypovolemic, and cardiogenic shock.

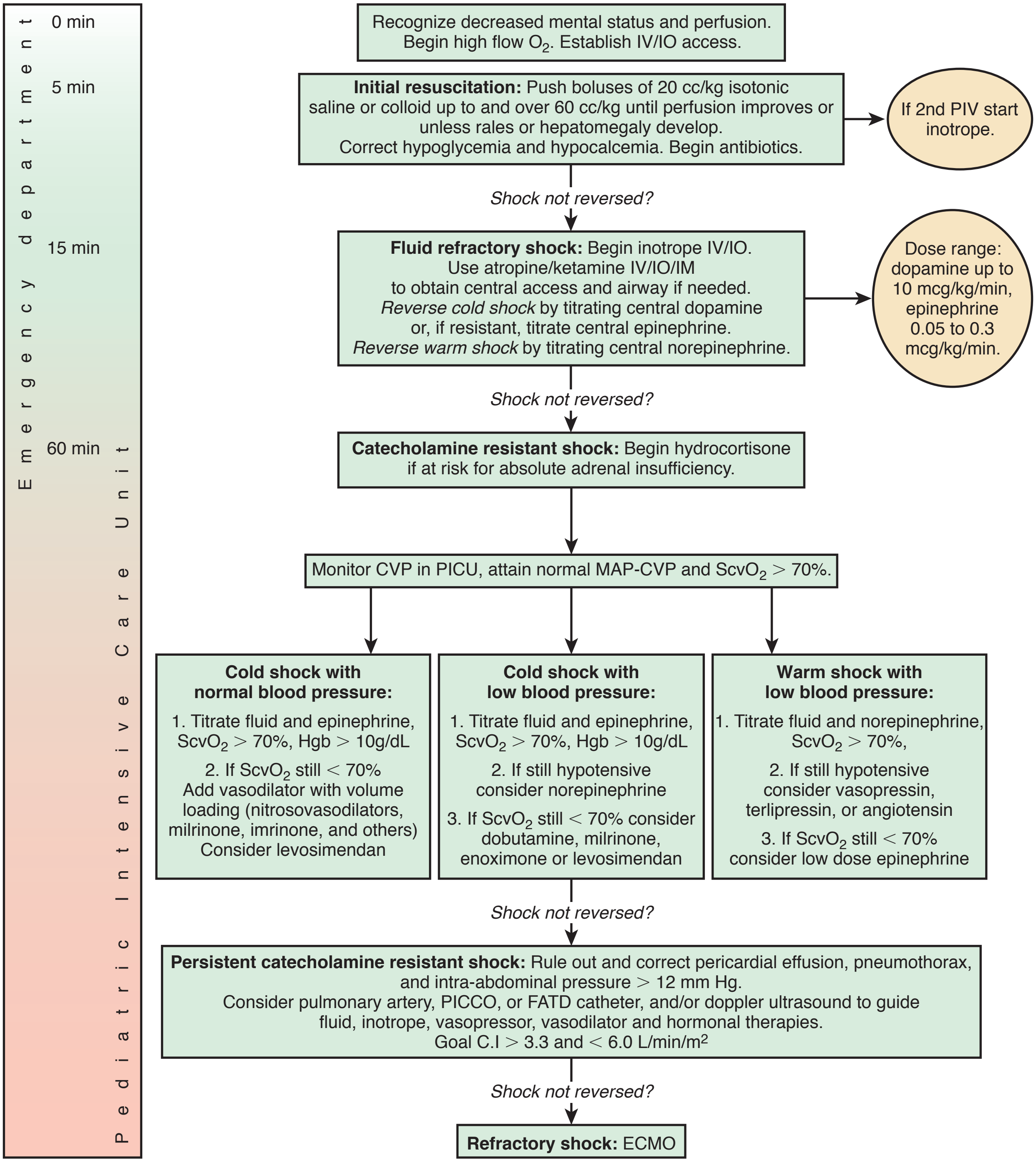

Figure 70-1 **Algorithm for time-sensitive, goal-directed, stepwise management of hemodynamic support in infants and children.** CI, cardiac index; CRRT, continuous renal replacement therapy; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; FATD, femoral arterial thermodilution; Hgb, hemoglobin; IM, intramuscular; IO, intraosseous; IV, intravenous; MAP, mean arterial pressure; PICCO, pulse contour cardiac output. *(From Brierly J, Carcillo JA, Choong K, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine,* Crit Care Med *37:666-688, 2009. Copyright 2009, Society of Critical Care Medicine and Lippincott Williams & Wilkins.)*

PATHOPHYSIOLOGY

An initial insult triggers shock, leading to inadequate oxygen delivery to organs and tissues. Compensatory mechanisms attempt to maintain blood pressure by increasing cardiac output and systemic vascular resistance (SVR). The body also attempts to optimize oxygen delivery to the tissues by increasing oxygen extraction and redistributing blood flow to the brain, heart, and kidneys at the expense of the skin and gastrointestinal tract. These responses lead to an initial state of **compensated shock,** in which blood pressure is maintained. If treatment is not initiated or is inadequate during this period, **decompensated shock** develops, with hypotension and tissue damage that may lead to **multisystem organ dysfunction** and ultimately death (Fig. 70-2, Tables 70-2 and 70-3).

In the early phases of shock, multiple compensatory physiologic mechanisms act to maintain blood pressure and preserve tissue perfusion and oxygen delivery. Cardiovascular effects include increases in heart rate, stroke volume, and vascular smooth muscle tone, which are regulated through sympathetic nervous system activation and

Table 70-1 Types of Shock

HYPOVOLEMIC	CARDIOGENIC	DISTRIBUTIVE	SEPTIC	OBSTRUCTIVE
Decreased preload secondary to internal or external losses	Cardiac pump failure secondary to poor myocardial function	Abnormalities of vasomotor tone from loss of venous and arterial capacitance	Encompasses multiple forms of shock Hypovolemic: third spacing of fluids into the extracellular, interstitial space Distributive: early shock with decreased afterload Cardiogenic: depression of myocardial function by endotoxins	Decreased cardiac output secondary to direct impediment to right- or left-heart outflow or restriction of all cardiac chambers
POTENTIAL ETIOLOGIES				
Blood loss: hemorrhage; Plasma loss: burns, nephrotic syndrome; Water/electrolyte loss: vomiting, diarrhea	Congenital heart disease Cardiomyopathies: infectious or acquired, dilated or restrictive Ischemia Arrhythmias	Anaphylaxis Neurologic: loss of sympathetic vascular tone secondary to spinal cord or brainstem injury Drugs	Bacterial Viral Fungal (immunocompromised patients are at increased risk)	Tension pneumothorax Pericardial tamponade Pulmonary embolism Anterior mediastinal masses Critical coarctation of the aorta

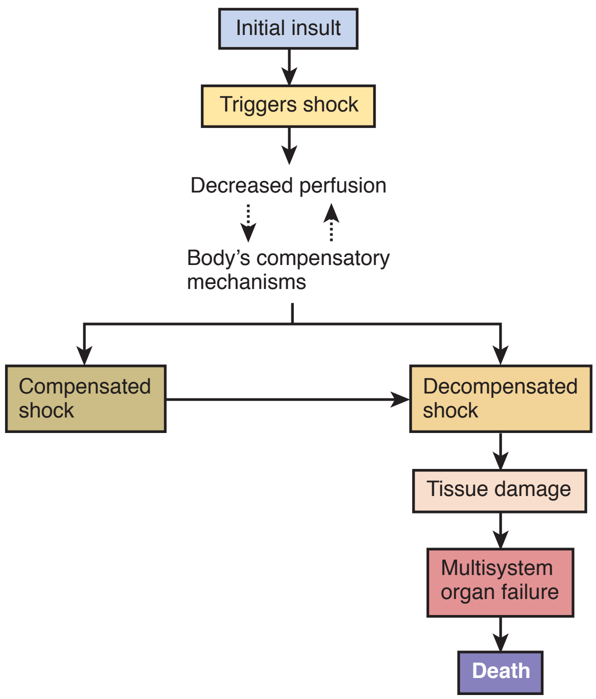

Figure 70-2 Algorithm for decompensated shock.

neurohormonal responses. Respiratory compensation involves greater CO_2 elimination in response to the metabolic acidosis and increased CO_2 production from poor tissue perfusion. Renal excretion of hydrogen ions and retention of bicarbonate also increase in an effort to maintain normal body pH (see Chapter 55.7). Maintenance of intravascular volume is facilitated via sodium regulation through the renin–angiotensin–aldosterone and atrial natriuretic factor axes, cortisol and catecholamine synthesis and release, and antidiuretic hormone secretion. Despite these compensatory mechanisms, the underlying shock and host response lead to vascular endothelial cell injury and significant leakage of intravascular fluids into the interstitial extracellular space.

Another important aspect of the initial pathophysiology of shock is the impact on cardiac output. All forms of shock affect cardiac output via several mechanisms, with changes in heart rate, preload, afterload, and myocardial contractility occurring separately or in combination (Table 70-4). **Hypovolemic shock** is characterized primarily by fluid loss and decreased preload. Tachycardia and an increase in SVR are the initial compensatory responses to maintain cardiac output and systemic blood pressure. Without adequate volume replacement, hypotension develops, followed by tissue ischemia and further clinical deterioration. When there is preexisting low plasma oncotic pressure (caused by nephrotic syndrome, malnutrition, hepatic dysfunction, acute severe burns, etc.), even further volume loss and exacerbation of shock may occur because of endothelial breakdown and worsening capillary leak.

In contrast, the underlying pathophysiologic mechanism leading to **distributive shock** is a state of abnormal vasodilation and decreased SVR. Sepsis, hypoxia, poisonings, anaphylaxis, spinal cord injury, or mitochondrial dysfunction can cause vasodilatory shock (Fig. 70-3). The lowering of SVR is accompanied initially by a maldistribution of blood flow away from vital organs and a compensatory increase in cardiac output. This process leads to significant decreases in both preload and afterload. Therapies for distributive shock must address both of these problems simultaneously.

Cardiogenic shock may be seen in patients with myocarditis, cardiomyopathy, congenital heart disease, or arrhythmias, or following cardiac surgery (see Chapter 434). In these instances, myocardial contractility is affected, leading to systolic and/or diastolic dysfunction. The later phases of all forms of shock frequently have a negative impact on the myocardium, leading to development of a cardiogenic component to the shock state.

Septic shock is often a unique combination of distributive, hypovolemic, and cardiogenic shock. Hypovolemia from intravascular fluid losses occurs through capillary leak. Cardiogenic shock results from the myocardial-depressant effects of sepsis, and distributive shock is the result of decreased SVR. The degree to which a patient exhibits each of these responses varies, but there are frequently alterations in preload, afterload, and myocardial contractility.

In septic shock, it is important to distinguish between the inciting infection and the host inflammatory response. Normally, host immunity prevents the development of sepsis via activation of the reticular endothelial system along with the cellular and humoral immune systems. This host immune response produces an inflammatory cascade of toxic mediators, including hormones, cytokines, and enzymes. If this inflammatory cascade is uncontrolled, derangement of the microcirculatory system leads to subsequent organ and cellular dysfunction.

The **systemic inflammatory response syndrome** (**SIRS**) is an inflammatory cascade that is initiated by the host response to an

Table 70-2 Criteria for Organ Dysfunction

ORGAN SYSTEM	CRITERIA FOR DYSFUNCTION
Cardiovascular	Despite administration of isotonic intravenous fluid bolus ≥60 mL/kg in 1 hr: decrease in BP (hypotension) systolic BP <90 mm Hg, mean arterial pressure <70 mm Hg, <5th percentile for age, or systolic BP <2 SD below normal for age *or* Need for vasoactive drug to maintain BP in normal range (dopamine >5 µg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) *or* Two of the following: Unexplained metabolic acidosis: base deficit >5.0 mEq/L Increased arterial lactate: >1 mmol/Liter or >2× upper limit of normal Oliguria: urine output <0.5 mL/kg/hr Prolonged capillary refill: >5 sec Core to peripheral temperature gap >3°C (5.4°F)
Respiratory	PaO_2/FIO_2 ratio <300 in absence of cyanotic heart disease or preexisting lung disease *or* $PaCO_2$ >65 torr or 20 mm Hg over baseline $PaCO_2$ *or* Need for >50% FIO_2 to maintain saturation ≥92% *or* Need for nonelective invasive or noninvasive mechanical ventilation
Neurologic	GCS score ≤11 *or* Acute change in mental status with a decrease in GCS score ≥3 points from abnormal baseline
Hematologic	Platelet count <100,000/mm^3 or a decline of 50% in the platelet count from the highest value recorded over the last 3 days (for patients with chronic hematologic or oncologic disorders) *or* INR >1.5 *or* Activated prothrombin time >60 sec
Renal	Serum creatinine >0.5 mg/dL, ≥2× upper limit of normal for age, or 2-fold increase in baseline creatinine value
Hepatic	Total bilirubin ≥4 mg/dL (not applicable for newborn) Alanine transaminase level 2× upper limit of normal for age

BP, blood pressure; FIO_2, fraction of inspired oxygen; GCS, Glasgow Coma Scale; INR, international normalized ratio; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, partial pressure arterial oxygen.

infectious or noninfectious trigger (Table 70-5). This inflammatory cascade is triggered when the host defense system does not adequately recognize and/or clear the triggering event. The inflammatory cascade initiated by shock can lead to hypovolemia, cardiac and vascular failure, acute respiratory distress syndrome (ARDS), insulin resistance, decreased cytochrome P450 activity (decreased steroid synthesis), coagulopathy, and unresolved or secondary infection. Tumor necrosis factor (TNF) and other inflammatory mediators increase vascular permeability, causing diffuse capillary leak, decreased vascular tone, and an imbalance between perfusion and metabolic demands of the tissues. TNF and interleukin (IL)-1 stimulate the release of proinflammatory and antiinflammatory mediators, causing fever and vasodilation. Proinflammatory mediators include IL-6, IL-12, interferon-γ, and macrophage migration inhibitory factor; antiinflammatory cytokines include IL-10, transforming growth factor-β, and IL-4. Arachidonic acid metabolites lead to the development of fever, tachypnea, ventilation–perfusion abnormalities, and lactic acidosis. Nitric oxide, released from the endothelium or inflammatory cells, is a major contributor to hypotension. Myocardial depression is caused directly by myocardial-depressant factors, TNF, and some interleukins, and further depressed via depleted catecholamines, increased β-endorphin, and production of myocardial nitric oxide.

The inflammatory cascade (Fig. 70-4) is initiated by toxins or superantigens via macrophage binding or lymphocyte activation. The vascular endothelium is both a target of tissue injury and a source

Table 70-4 Pathophysiology of Shock

EXTRACORPOREAL FLUID LOSS Hypovolemic shock may be a result of direct blood loss through hemorrhage or abnormal loss of body fluids (diarrhea, vomiting, burns, diabetes mellitus or insipidus, nephrosis)
LOWERING PLASMA ONCOTIC FORCES Hypovolemic shock may also result from hypoproteinemia (liver injury, or as a progressive complication of increased capillary permeability)
ABNORMAL VASODILATION Distributive shock (neurogenic, anaphylaxis, or septic shock) occurs when there is loss of vascular tone—venous, arterial, or both (sympathetic blockade, local substances affecting permeability, acidosis, drug effects, spinal cord transection)
INCREASED VASCULAR PERMEABILITY Sepsis may change the capillary permeability in the absence of any change in capillary hydrostatic pressure (endotoxins from sepsis, excess histamine release in anaphylaxis)
CARDIAC DYSFUNCTION Peripheral hypoperfusion may result from any condition that affects the heart's ability to pump blood efficiently (ischemia, acidosis, drugs, constrictive pericarditis, pancreatitis, sepsis)

Table 70-3 Signs of Decreased Perfusion

ORGAN SYSTEM	↓ PERFUSION	↓↓ PERFUSION	↓↓↓ PERFUSION
Central nervous system	—	Restless, apathetic, anxious	Agitated/confused, stuporous, coma
Respiration	—	↑ Ventilation	↑↑ Ventilation
Metabolism	—	Compensated metabolic acidemia	Uncompensated metabolic acidemia
Gut	—	↓ Motility	Ileus
Kidney	↓ Urine volume ↑ Urinary specific gravity	Oliguria (<0.5 mL/kg/hr)	Oliguria/anuria
Skin	Delayed capillary refill	Cool extremities	Mottled, cyanotic, cold extremities
Cardiovascular system	↑ Heart rate	↑↑ Heart rate ↓ Peripheral pulses	↑↑ Heart rate ↓ Blood pressure, central pulses only

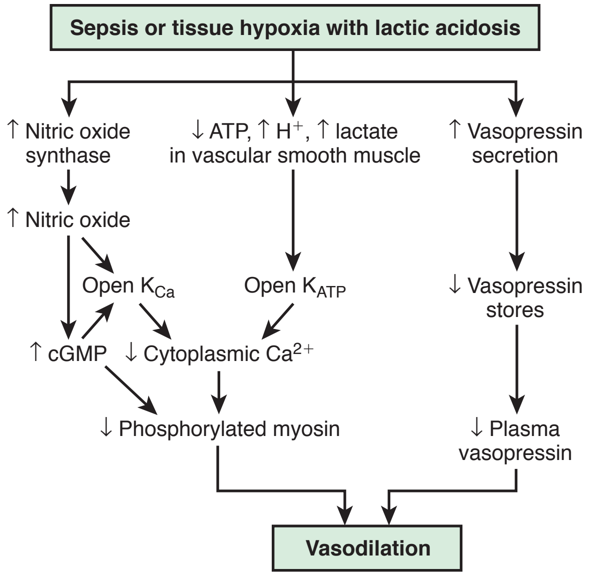

Figure 70-3 **Mechanisms of vasodilatory shock.** Septic shock and states of prolonged shock causing tissue hypoxia with lactic acidosis increase nitric oxide synthesis, activate the adenosine triphosphate (ATP)–sensitive and calcium-regulated potassium channels (K_{ATP} and K_{Ca}, respectively) in vascular smooth muscle, and lead to depletion of vasopressin. cGMP, cyclic guanosine monophosphate. *(From Landry DW, Oliver JA: The pathogenesis of vasodilatory shock,* N Engl J Med *345:588-595, 2001.)*

of mediators that may cause further injury. Biochemical responses include the production of arachidonic acid metabolites, release of myocardial depressant factors, release of endogenous opiates, activation of the complement system, as well as the production and release of many other mediators, which may be either proinflammatory or antiinflammatory. The balance between these mediator groups for an individual patient contributes to the progression of disease and affects the chance for survival.

CLINICAL MANIFESTATIONS

Table 70-1 shows a classification system for shock. Categorization is important, but there may be significant overlap among these groups, especially in septic shock. The clinical presentation of shock depends in part on the underlying etiology, but if unrecognized and untreated, all forms of shock follow a common and untoward progression of clinical signs and pathophysiologic changes that may ultimately lead to irreversible organ injury and death (see Fig. 70-2).

Shock may initially manifest as only tachycardia, with or without tachypnea. Progression leads to decreased urine output, poor peripheral perfusion, respiratory distress or failure, alteration of mental status, and low blood pressure (see Table 70-3). A significant misconception is that shock occurs only with low blood pressure; hypotension is often a late finding and is not a criterion for the diagnosis of shock because of a complex set of compensatory mechanisms attempting to preserve blood pressure. Hypotension reflects an advanced state of decompensated shock and is associated with increased morbidity and mortality.

Hypovolemic shock often manifests initially as orthostatic hypotension and is associated with dry mucous membranes, dry axillae, poor skin turgor, and decreased urine output. Depending on the degree of dehydration, the patient with hypovolemic shock may present with either normal or slightly cool distal extremities, and pulses may be normal, decreased, or absent depending on disease severity. The presenting signs of **cardiogenic shock** are tachypnea, cool extremities, delayed capillary filling time, poor peripheral and/or central pulses, declining mental status, and decreased urine output, caused by the combination of decreased cardiac output and compensatory peripheral

Table 70-5	Differential Diagnosis of Systemic Inflammatory Response Syndrome

INFECTION
Bacteremia or meningitis (*Streptococcus pneumoniae, Haemophilus influenzae* type b, *Neisseria meningitidis,* group A streptococcus, *Staphylococcus aureus*)
Viral illness (influenza, enteroviruses, hemorrhagic fever group, herpes simplex virus, respiratory syncytial virus, cytomegalovirus, Epstein-Barr virus)
Encephalitis (arboviruses, enteroviruses, herpes simplex virus)
Rickettsiae (Rocky Mountain spotted fever, *Ehrlichia,* Q fever)
Syphilis
Vaccine reaction (pertussis, influenza, measles)
Toxin-mediated reaction (toxic shock, staphylococcal scalded skin syndrome)

CARDIOPULMONARY
Pneumonia (bacteria, virus, mycobacteria, fungi, allergic reaction)
Pulmonary emboli
Heart failure
Arrhythmia
Pericarditis
Myocarditis

METABOLIC-ENDOCRINE
Adrenal insufficiency (adrenogenital syndrome, Addison disease, corticosteroid withdrawal)
Electrolyte disturbances (hyponatremia or hypernatremia; hypocalcemia or hypercalcemia)
Diabetes insipidus
Diabetes mellitus
Inborn errors of metabolism (organic acidosis, urea cycle, carnitine deficiency, mitochondrial disorders)
Hypoglycemia
Reye syndrome

GASTROINTESTINAL
Gastroenteritis with dehydration
Volvulus
Intussusception
Appendicitis
Peritonitis (spontaneous, associated with perforation or peritoneal dialysis)
Necrotizing enterocolitis
Hepatitis
Hemorrhage
Pancreatitis

HEMATOLOGIC
Anemia (sickle cell disease, blood loss, nutritional)
Methemoglobinemia
Splenic sequestration crisis
Leukemia or lymphoma
Hemophagocytic syndromes

NEUROLOGIC
Intoxication (drugs, carbon monoxide, intentional or accidental overdose)
Intracranial hemorrhage
Infant botulism
Trauma (child abuse, accidental)
Guillain-Barré syndrome
Myasthenia gravis

OTHER
Anaphylaxis (food, drug, insect sting)
Hemolytic-uremic syndrome
Kawasaki disease
Erythema multiforme
Hemorrhagic shock–encephalopathy syndrome
Poisoning
Toxic envenomation
Macrophage activation syndrome

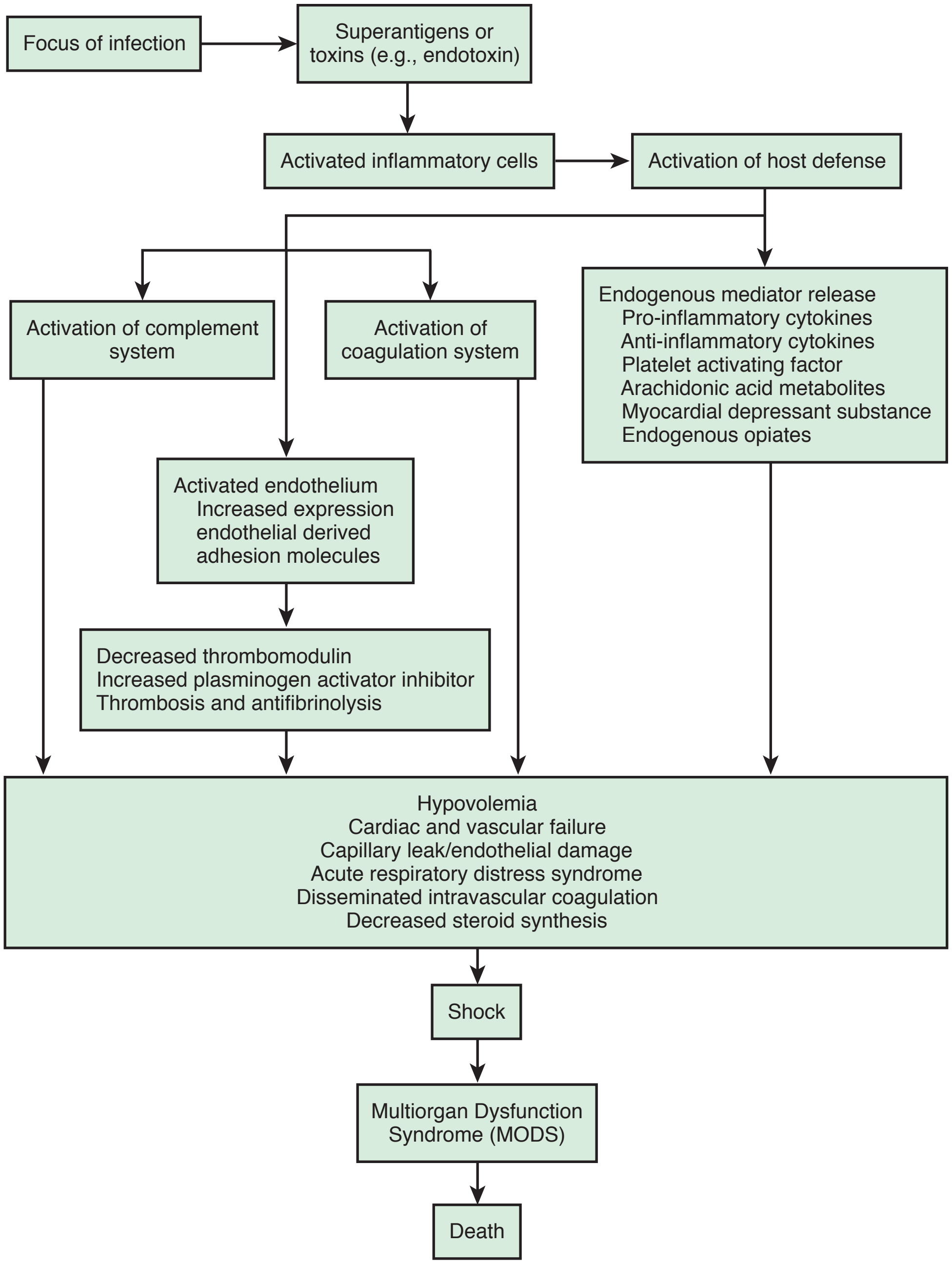

Figure 70-4 Hypothetical pathophysiology of the septic process.

vasoconstriction (see Chapter 442.1). **Obstructive shock** often also manifests as inadequate cardiac output because of a physical restriction of forward blood flow, and the acute presentation may quickly progress to cardiac arrest. **Distributive shock** manifests initially as peripheral vasodilation and increased but inadequate cardiac output.

Regardless of etiology, uncompensated shock, with hypotension, high SVR, decreased cardiac output, respiratory failure, obtundation, and oliguria, occurs late in the progression of disease. Table 70-6 lists the hemodynamic findings in various shock states. Additional clinical findings in shock include cutaneous lesions such as petechiae, diffuse erythema, ecchymoses, ecthyma gangrenosum, and peripheral gangrene. Jaundice can be present either as a sign of infection or as a result of **MODS**.

Sepsis is defined as **SIRS** resulting from a suspected or proven infectious etiology. The clinical spectrum of sepsis begins when a systemic (e.g., bacteremia, rickettsial disease, fungemia, viremia) or localized (e.g., meningitis, pneumonia, pyelonephritis) infection progresses from sepsis to **severe sepsis** (the presence of sepsis combined with organ dysfunction). Further deterioration leads to **septic shock** (severe sepsis plus the persistence of hypoperfusion or hypotension despite adequate fluid resuscitation or a requirement for vasoactive agents), **MODS**, and possibly death (Table 70-7). This is a complex spectrum of clinical problems that is a leading cause of mortality in children worldwide. This mortality can be mitigated and outcomes improved with early recognition and treatment.

Although **septic shock** is primarily distributive in nature, multiple other elements of pathophysiology are represented in this disease process. The initial signs and symptoms of sepsis include alterations in temperature regulation (hyperthermia or hypothermia), tachycardia, and tachypnea. In the early stages (hyperdynamic phase, low SVR, or "warm" shock), cardiac output increases in an attempt to maintain adequate oxygen delivery and meet the greater metabolic demands of the organs and tissues. As septic shock progresses, cardiac output falls in response to the effects of numerous inflammatory mediators, leading to a compensatory elevation in SVR and the development of "cold" shock.

Table 70-6 Hemodynamic Variables in Different Shock States

TYPE OF SHOCK	CARDIAC OUTPUT	SYSTEMIC VASCULAR RESISTANCE	MEAN ARTERIAL PRESSURE	CAPILLARY WEDGE PRESSURE	CENTRAL VENOUS PRESSURE
Hypovolemic	↓	↑	↔ or ↓	↓↓↓	↓↓↓
Cardiogenic*					
Systolic	↓↓	↑↑↑	↔ or ↓	↑↑	↑↑
Diastolic	↔	↑↑	↔	↑↑	↑
Obstructive	↓	↑	↔ or ↓	↑↑†	↑↑†
Distributive	↑↑	↓↓↓	↔ or ↓	↔ or ↓	↔ or ↓
Septic					
Early	↑↑↑	↓↓↓	↔ or ↓‡	↓	↓
Late	↓↓	↓↓	↓↓	↑	↑ or ↔

*Systolic or diastolic dysfunction.
†Wedge pressure, central venous pressure, and pulmonary artery diastolic pressures are equal.
‡Wide pulse pressure.

Table 70-7 International Consensus Definitions for Pediatric Sepsis

Infection	Suspected or proven infection or a clinical syndrome associated with high probability of infection
SIRS	Two of 4 criteria, 1 of which must be abnormal temperature or abnormal leukocyte count: 1. Core temperature >38.5°C (101.3°F) or <36°C (96.8°F) (rectal, bladder, oral, or central catheter) 2. Tachycardia: Mean heart rate >2 SD above normal for age in absence of external stimuli, chronic drugs or painful stimuli *or* Unexplained persistent elevation over 0.5-4 hr *or* In children <1 yr old, persistent bradycardia over 0.5 hr (mean heart rate <10th percentile for age in absence of vagal stimuli, β-blocker drugs, or congenital heart disease) 3. Respiratory rate >2 SD above normal for age or acute need for mechanical ventilation not related to neuromuscular disease or general anesthesia 4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy) or >10% immature neutrophils
Sepsis	SIRS plus a suspected or proven infection
Severe sepsis	Sepsis plus 1 of the following: 1. Cardiovascular organ dysfunction, defined as: • Despite >40 mL/kg of isotonic intravenous fluid in 1 hr: • Hypotension <5th percentile for age or systolic blood pressure <2 SD below normal for age *or* • Need for vasoactive drug to maintain blood pressure *or* • 2 of the following: • Unexplained metabolic acidosis: base deficit >5 mEq/L • Increased arterial lactate: >2 times upper limit of normal • Oliguria: urine output <0.5 mL/kg/hr • Prolonged capillary refill: >5 sec • Core to peripheral temperature gap >3°C (5.4°F) 2. ARDS as defined by the presence of a PaO_2/FIO_2 ratio ≤300 mm Hg, bilateral infiltrates on chest radiograph, and no evidence of left heart failure or Sepsis plus 2 or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic)
Septic shock	Sepsis plus cardiovascular organ dysfunction as defined above
MODS	Presence of altered organ function such that homeostasis cannot be maintained without medical intervention

FIO_2, fraction of inspired oxygen; PaO_2, partial pressure arterial oxygen.

DIAGNOSIS

Shock is a clinical diagnosis based on a thorough history and physical examination (see Tables 70-2 and 70-3). Of note, septic shock has a specific consensus conference definition (see Table 70-7). In cases of suspected septic shock, an infectious etiology should be sought through culture of clinically appropriate specimens and prompt initiation of empiric antimicrobial therapy based on patient age, underlying disease, and geographic location, recognizing that time is necessary for incubation of cultures, and results often are not positive. Additional evidence for identifying an infectious etiology as the cause of SIRS includes physical examination findings, imaging, presence of white blood cells in normally sterile body fluids, and suggestive rashes such as petechiae and purpura. Affected children should be admitted to an intensive care unit or other highly monitored environment, as indicated by clinical status and the resources of the medical facility. These patients necessitate continuous monitoring, with a combination of

noninvasive (pulse oximetry, capnography, near infra-red spectroscopy) and invasive (central venous pressure, arterial blood pressure) techniques as clinically indicated.

LABORATORY FINDINGS

Laboratory findings often include evidence of hematologic abnormalities and electrolyte disturbances. Hematologic abnormalities may include thrombocytopenia, prolonged prothrombin and partial thromboplastin times, reduced serum fibrinogen level, elevations of fibrin split products, and anemia. Elevated neutrophil counts and increased immature forms (i.e., bands, myelocytes, promyelocytes), vacuolation of neutrophils, toxic granulations, and Döhle bodies can be seen with infection. Neutropenia or leukopenia may be an ominous sign of overwhelming sepsis.

Glucose dysregulation, a common stress response, may manifest as hyperglycemia or hypoglycemia. Other electrolyte abnormalities are hypocalcemia, hypoalbuminemia, and metabolic acidosis. Renal and/or hepatic function may also be abnormal. Patients with ARDS or pneumonia have impairment of oxygenation (decreased partial pressure arterial oxygen [Pao_2]) as well as of ventilation (increased arterial partial pressure of carbon dioxide [$Paco_2$]) in the later stages of lung injury (see Chapter 71).

The hallmark of uncompensated shock is an imbalance between oxygen delivery (Do_2) and oxygen consumption (Vo_2). Oxygen delivery normally exceeds oxygen consumption threefold. The oxygen extraction ratio is approximately 25%, thus producing a normal **mixed venous oxygen saturation** (SVo_2) of 75-80%. A falling SVo_2 value, as measured by cooximetry, reflects an increasing oxygen extraction ratio and documents a decrease in oxygen delivery relative to consumption. This increase in oxygen extraction by the end-organs is an attempt to maintain adequate oxygen delivery at the cellular level. This state is manifested clinically by increased lactic acid production (high anion gap, metabolic acidosis) caused by anaerobic metabolism and the compensatory increase in tissue oxygen extraction. The gold standard measurement of SVo_2 is from a pulmonary arterial catheter, but measurements from this location are often not clinically feasible. Sites such as the right ventricle, right atrium, superior vena cava ($SVco_2$), or inferior vena cava are often used as for surrogate measures of mixed venous blood to follow the adequacy of oxygen delivery and effectiveness of therapeutic interventions. *Elevated blood lactate levels reflect poor tissue oxygen delivery noted in all forms of shock.*

TREATMENT

Initial Management

Early recognition and prompt intervention are extremely important in the management of all forms of shock (Tables 70-8 to 70-12). **(The vital sign targets and dose recommendations in Tables 70-9 to 70-11 should be adjusted to pediatric-size patients).** Baseline mortality is much lower in pediatric shock than in adult shock, and further improvements in mortality are associated with early interventions (see Fig. 70-1). The initial assessment and treatment of the pediatric shock patient should include stabilization of airway, breathing, and circulation as established by the American Heart Association's pediatric advanced life support and neonatal advanced life support guidelines (see Chapter 67). Depending on the severity of shock, further airway intervention, including intubation and mechanical ventilation, may be necessary to lessen the work of breathing and decrease the body's overall metabolic demands.

Given the predominance of sepsis and hypovolemia as the most common causes of shock in the pediatric population, most therapeutic regimens are based on guidelines established in these settings. Immediately following establishment of intravenous (IV) or intraosseous

Table 70-8 Goal-Directed Therapy of Organ System Dysfunction in Shock

SYSTEM	DISORDERS	GOALS	THERAPIES
Respiratory	Acute respiratory distress syndrome Respiratory muscle fatigue Central apnea	Prevent/treat: hypoxia and respiratory acidosis Prevent barotrauma Decrease work of breathing	Oxygen Noninvasive ventilation Early endotracheal intubation and mechanical ventilation Positive end-expiratory pressure (PEEP) Permissive hypercapnia High-frequency ventilation Extracorporeal membrane oxygenation (ECMO)
Renal	Prerenal failure Renal failure	Prevent/treat: hypovolemia, hypervolemia, hyperkalemia, metabolic acidosis, hypernatremia/hyponatremia, and hypertension Monitor serum electrolytes	Judicious fluid resuscitation Establishment of normal urine output and blood pressure for age Furosemide (Lasix) Dialysis, ultrafiltration, hemofiltration
Hematologic	Coagulopathy (disseminated intravascular coagulation) Thrombosis	Prevent/treat: bleeding Prevent/treat: abnormal clotting	Vitamin K Fresh-frozen plasma Platelets Heparinization
Gastrointestinal	Stress ulcers Ileus Bacterial translocation	Prevent/treat: gastric bleeding Avoid aspiration, abdominal distention Avoid mucosal atrophy	Histamine H_2-receptor–blocking agents or proton pump inhibitors Nasogastric tube Early enteral feedings
Endocrine	Adrenal insufficiency, primary or secondary to chronic steroid therapy	Prevent/treat: adrenal crisis	Stress-dose steroids in patients previously given steroids Physiologic dose for presumed primary insufficiency in sepsis
Metabolic	Metabolic acidosis	Correct etiology Normalize pH	Treatment of hypovolemia (fluids), poor cardiac function (fluids, inotropic agents) Improvement of renal acid excretion Low-dose (0.5-2.0 mEq/kg) sodium bicarbonate if the patient is not showing response, pH <7.1, and ventilation (CO_2 elimination) is adequate

Table 70-9 Recommendations: Initial Resuscitation and Infection Issues—Adults

INITIAL RESUSCITATION

1. Protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L). Goals during the 1st 6 hr of resuscitation:
   (a) Central venous pressure 8-12 mm Hg
   (b) Mean arterial pressure (MAP) ≥65 mm Hg
   (c) Urine output ≥0.5 mL kg^{-1} hr
   (d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively
2. In patients with elevated lactate levels, targeting resuscitation to normalize lactate as rapidly as possible.

SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT

1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy.
2. Hospital-based performance improvement efforts in severe sepsis.

DIAGNOSIS

1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (>45 min) in the start of antimicrobial(s). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 hr) inserted.
2. Use of the 1,3 β-D-glucan assay, mannan and antimannan antibody assays, if available and invasive candidiasis is in differential diagnosis of cause of infection.
3. Imaging studies performed promptly to confirm a potential source of infection.

ANTIMICROBIAL THERAPY

1\. Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock and severe sepsis without septic shock as the goal of therapy.
2a. Initial empiric antiinfective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis.
2b. Antimicrobial regimen should be reassessed daily for potential deescalation.
3\. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection.
4a. Combination empirical therapy for neutropenic patients with severe sepsis and for patients with difficult to treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp.
For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum β-lactam and either an aminoglycoside or a fluoroquinolone is for *Pseudomonas aeruginosa* bacteremia. A combination of beta-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections.
4b. Empiric combination therapy should not be administered for more than 3-5 days. Deescalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known.
5\. Duration of therapy typically 7-10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *Staphylococcus aureus*; some fungal and viral infections or immunologic deficiencies, including neutropenia.
6\. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin.
7\. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause.

SOURCE CONTROL

1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the 1st 12 hr after the diagnosis is made, if feasible.
2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred.
3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (e.g., percutaneous rather than surgical drainage of an abscess).
4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established.

INFECTION PREVENTION

1a. Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; this infection control measure can then be instituted in healthcare settings and regions where this methodology is found to be effective.
1b. Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 41(2):580-637, 2013, Table 5, p. 589.

access, aggressive, early goal-directed therapy should be initiated unless there are significant concerns for cardiogenic shock as an underlying pathophysiology. Rapid IV administration of 20 mL/kg isotonic fluid should be initiated in an attempt to reverse the shock state. This bolus should be repeated quickly up to 60-80 mL/kg; it is not unusual for severely affected patients to require this volume within the 1st hr of treatment.

Rapid fluid resuscitation totaling 60-80 mL/kg or more is associated with improved survival without an increased incidence of pulmonary edema. Fluid resuscitation in increments of 20 mL/kg should be titrated to normalize heart rate (according to age-based heart rates), urine output (to 1 mL/kg/hr), capillary refill time (to <2 sec), and mental status. Fluid resuscitation may sometimes require as much as 200 mL/kg or greater. It must be stressed that hypotension is often a late and ominous finding, and normalization of blood pressure alone is not a reliable endpoint for assessing the effectiveness of resuscitation. Although the type of fluid (crystalloid vs. colloid) is an area of ongoing debate, fluid resuscitation (usually crystalloid) in the 1st hr is unquestionably essential to survival in septic shock, regardless of the fluid type administered.

In one study conducted in Kenya and Tanzania, routine bolus fluid resuscitation of severely ill, febrile children with poor perfusion was unexpectedly associated with a higher mortality than children receiving nonbolus intravenous infusions. The children in this study had a

Table 70-10 Surviving Sepsis Campaign Care Bundles

To be completed within 3 hr:
1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

To completed within 6 hr:
5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg
6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   Measure central venous pressure (CVP)*
   Measure central venous oxygen saturation ($ScvO_2$)*
7. Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $ScvO_2$ of ≥70%, and normalization of lactate.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med *41(2):580-637, 2013, Fig. 1, p. 591.*

high incidence of malaria, severe anemia, hypoxia, and coma; most were thought to have bacterial infections. There were no children with dengue shock syndrome or hypovolemia secondary to gastroenteritis. The World Health Organization's definition of shock that requires fluid boluses (cold hands, capillary refill >3 sec, fast and weak pulses) was not present in all patients; only 6% had hypotension. This study raises issues about bolus fluid resuscitation in resource poor areas, particularly in children with a high prevalence of malaria and anemia.

If shock remains refractory following 60-80 mL/kg of volume resuscitation, vasopressor therapy (norepinephrine, or epinephrine) should be instituted while additional fluids are administered. Current guidelines recommend administration of these vasoactive agents via peripheral intravenous lines, with very close monitoring of the peripheral intravenous sites while central venous access is being obtained based on data demonstrating that delay in the initiation of inotropes in shock is associated with increased mortality

Additional Early Considerations

In **septic shock** specifically, early administration of broad-spectrum antimicrobial agents is associated with a reduction in mortality. The choice of antimicrobial agents depends on the predisposing risk factors and the clinical situation. Bacterial resistance patterns in the community and/or hospital should be considered in the selection of optimal antimicrobial therapy. Neonates should be treated with ampicillin

Table 70-11 Recommendations: Hemodynamic Support and Adjunctive Therapy—Adults

FLUID THERAPY OF SEVERE SEPSIS
1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock.
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock.
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids.
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients.
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables.

VASOPRESSORS
1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg.
2. Norepinephrine as the first choice vasopressor.
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure.
4. Vasopressin 0.03 units/min can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage.
5. Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/min should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) NE is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low, or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve MAP target.
8. Low-dose dopamine should not be used for renal protection.
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available.

INOTROPIC THERAPY
1. A trial of dobutamine infusion up to 20 μg/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP.
2. Not using a strategy to increase cardiac index to predetermined supranormal levels.

CORTICOSTEROIDS
1. Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day.
2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone.
3. In treated patients, hydrocortisone tapered when vasopressors are no longer required.
4. Corticosteroids should not be administered for the treatment of sepsis in the absence of shock.
5. When hydrocortisone is given, use continuous flow.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med *41(2):580-637, 2013, Table 6, p. 596.*

Table 70-12 Recommendations: Special Considerations in Pediatrics

INITIAL RESUSCITATION
1. For respiratory distress and hypoxemia start with face mask oxygen or if needed and available, high flow nasal cannula oxygen or nasopharyngeal CPAP (NP CPAP). For improved circulation, peripheral intravenous access or intraosseous access can be used for fluid resuscitation and inotrope infusion when a central line is not available. If mechanical ventilation is required then cardiovascular instability during intubation is less likely after appropriate cardiovascular resuscitation.
2. Initial therapeutic end points of resuscitation of septic shock: capillary refill of ≤2 sec, normal blood pressure for age, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 mL kg^{-1} hr^{-1}, and normal mental status. $ScvO_2$ saturation ≥70% and cardiac index between 3.3 and 6.0 L/min/m^2 should be targeted thereafter.
3. Follow American College of Critical Care Medicine-Pediatric Life Support (ACCM-PALS) guidelines for the management of septic shock.
4. Evaluate for and reverse pneumothorax, pericardial tamponade, or endocrine emergencies in patients with refractory shock.

ANTIBIOTICS AND SOURCE CONTROL
1. Empiric antibiotics should be administered within 1 hr of the identification of severe sepsis. Blood cultures should be obtained before administering antibiotics when possible but this should not delay administration of antibiotics. The empiric drug choice should be changed as epidemic and endemic ecologies dictate (e.g., H1N1, methicillin-resistant *Staphylococcus aureus* [MRSA], chloroquine-resistant malaria, penicillin-resistant pneumococci, recent ICU stay, neutropenia).
2. Clindamycin and antitoxin therapies for toxic shock syndromes with refractory hypotension.
3. Early and aggressive source control.
4. *Clostridium difficile* colitis should be treated with enteral antibiotics if tolerated. Oral vancomycin is preferred for severe disease.

FLUID RESUSCITATION
1. In the industrialized world with access to inotropes and mechanical ventilation, initial resuscitation of hypovolemic shock begins with infusion of isotonic crystalloids or albumin with boluses of up to 20 mL/kg crystalloids (or albumin equivalent) over 5-10 minutes, titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses, and level of consciousness without inducing hepatomegaly or rales. If hepatomegaly or rales exist then inotropic support should be implemented, not fluid resuscitation. In nonhypotensive children with severe hemolytic anemia (severe malaria or sickle cell crises), blood transfusion is considered superior to crystalloid or albumin bolus.

INOTROPES/VASOPRESSORS/VASODILATORS
1. Begin peripheral inotropic support until central venous access can be attained in children who are not responsive to fluid resuscitation.
2. Patients with low cardiac output and elevated systemic vascular resistance states with normal blood pressure should be given vasodilator therapies in addition to inotropes.

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)
1. Consider ECMO for refractory pediatric septic shock and respiratory failure.

CORTICOSTEROIDS
1. Timely hydrocortisone therapy in children with fluid refractory, catecholamine resistant shock and suspected or proven absolute (classic) adrenal insufficiency.

PROTEIN C AND ACTIVATED PROTEIN CONCENTRATE
No recommendation as no longer available.

BLOOD PRODUCTS AND PLASMA THERAPIES
1. Similar hemoglobin targets in children as in adults. During resuscitation of low superior vena cava oxygen saturation shock (<70 %), hemoglobin levels of 10 g/dL are targeted. After stabilization and recovery from shock and hypoxemia, a lower target (>7.0 g/dL) can be considered reasonable.
2. Similar platelet transfusion targets in children as in adults.
3. Use plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura.

MECHANICAL VENTILATION
1. Lung-protective strategies during mechanical ventilation.

SEDATION/ANALGESIA/DRUG TOXICITIES
1. We recommend use of sedation with a sedation goal in critically ill mechanically ventilated patients with sepsis.
2. Monitor drug toxicity labs because drug metabolism is reduced during severe sepsis, putting children at greater risk of adverse drug-related events.

GLYCEMIC CONTROL
1. Control hyperglycemia using a similar target as in adults (≤180 mg/dL). Glucose infusion should accompany insulin therapy in newborns and children because some hyperglycemic children make no insulin whereas others are insulin resistant.

DIURETICS AND RENAL REPLACEMENT THERAPY
1. Use diuretics to reverse fluid overload when shock has resolved, and if unsuccessful then continuous venovenous hemofiltration (CVVH) or intermittent dialysis to prevent >10% total body weight fluid overload.

DEEP VEIN THROMBOSIS (DVT) PROPHYLAXIS
No recommendation on the use of DVT prophylaxis in prepubertal children with severe sepsis.

STRESS ULCER (SU) PROPHYLAXIS
No recommendation on the use of SU prophylaxis in prepubertal children with severe sepsis

NUTRITION
1. Enteral nutrition given to children who can be fed enterally, and parenteral feeding in those who cannot (grade 2C).

CPAP, continuous positive airway pressure.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med *41(2):580-637, 2013, Table 9, p. 614.*

plus cefotaxime and/or gentamicin. Acyclovir should be added if herpes simplex virus is suspected clinically. In infants and children, community-acquired infections with *Neisseria meningitidis* can initially be treated empirically with a 3rd-generation cephalosporin (ceftriaxone or cefotaxime). *Haemophilus influenzae* infections can be treated empirically with a 3rd-generation cephalosporin (ceftriaxone or cefotaxime). The prevalence of resistant *Streptococcus pneumoniae* requires the addition of vancomycin. Suspicion of community- or hospital-acquired, methicillin-resistant *Staphylococcus aureus* infection warrants coverage with vancomycin, depending on local resistance patterns. If an intraabdominal process is suspected, anaerobic coverage should be included with an agent such as metronidazole, clindamycin, or piperacillin-tazobactam.

Nosocomial sepsis should generally be treated with at least a 3rd- or 4th-generation cephalosporin or a penicillin with an extended Gram-negative spectrum (e.g., piperacillin-tazobactam). An aminoglycoside should be added as the clinical situation warrants. Vancomycin should be added to the regimen if the patient has an indwelling medical device (see Chapter 179), Gram-positive cocci are isolated from the blood, methicillin-resistant *S. aureus* infection is suspected, or as empiric coverage for *S. pneumoniae* in a patient with meningitis. Empirical coverage for fungal infections should be considered for selected immunocompromised patients (see Chapter 178). It should be noted that these are broad, generalized recommendations that must be tailored to the individual clinical scenario and to the local resistance patterns of the community and/or hospital.

Distributive shock that is not secondary to sepsis is caused by a primary abnormality in vascular tone. Cardiac output in affected patients is usually maintained and may initially be supranormal. These patients may benefit temporarily from volume resuscitation, but the early initiation of a vasoconstrictive agent to increase SVR is an important element of clinical care. Patients with spinal cord injury and spinal shock may benefit from either phenylephrine or vasopressin to increase SVR, and epinephrine is the treatment of choice for patients with anaphylaxis (Table 70-13). Epinephrine has peripheral α-adrenergic as well as inotropic effects that may improve the myocardial depression seen with anaphylaxis and its associated inflammatory response (see Chapter 149).

Patients with **cardiogenic shock** have poor cardiac output secondary to systolic and/or diastolic myocardial depression, often with a compensatory elevation in SVR. These patients may show poor response to fluid resuscitation and may decompensate quickly when fluids are administered. Smaller boluses of fluid (5-10 mL/kg) should be given in cardiogenic shock to replace deficits and maintain preload. In any patient with shock whose clinical status deteriorates with fluid resuscitation, a cardiogenic etiology should be considered, and further administration of intravenous fluids should be provided judiciously. Early initiation of myocardial support with epinephrine or dopamine to improve cardiac output is important in this context and early consideration should be given to administration of inodilator, such as milrinone.

Despite adequate cardiac output with the support of inotropic agents, a high SVR with poor peripheral perfusion and acidosis may persist in cardiogenic shock. Therefore, if not already started, milrinone therapy may improve systolic function and decrease SVR without causing a significant increase in heart rate. Furthermore, this agent has the added benefit of enhancing diastolic relaxation. Dobutamine or other vasodilating agents, such as nitroprusside, may also be considered in this setting (Table 70-14). Titration of these agents should target clinical end points, including increased urine output, improved peripheral perfusion, resolution of acidosis, and normalization of mental status. Even though they may be beneficial in other forms of shock, agents that improve blood pressure by increasing SVR, such as norepinephrine and vasopressin, should generally be avoided in patients with cardiogenic shock. These agents may cause further decompensation and potentially precipitate cardiac arrest as a result of the increased afterload and additional work imposed on the myocardium. The combination of inotropic and vasoactive agents must be tailored to the pathophysiology of the individual patient with close and frequent reassessment of the patient's cardiovascular status.

For patients with **obstructive shock**, fluid resuscitation may be briefly temporizing in maintaining cardiac output, but the primary insult must be immediately addressed. Examples of lifesaving therapeutic interventions for such patients are pericardiocentesis for pericardial effusion, pleurocentesis or chest tube placement for pneumothorax, thrombectomy/thrombolysis for pulmonary embolism, and the initiation of a prostaglandin infusion for ductus-dependent cardiac lesions. There is often a "last-drop" phenomenon associated with some obstructive lesions, in that small additional amounts of intravascular volume depletion may lead to a rapid deterioration, including cardiac arrest, if the obstructive lesion is not corrected.

Regardless of the etiology of shock, metabolic status should be meticulously maintained (see Table 70-8). Electrolyte levels should be monitored closely and corrected as needed. Hypoglycemia is common and should be promptly treated. Neonates and infants in particular may have profound glucose dysregulation in association with shock. Glucose levels should be checked routinely and treated appropriately, especially early in the course of illness. Hypocalcemia, which may contribute to myocardial dysfunction, should be treated with a goal of normalizing the ionized calcium concentration. There is no evidence that supranormal calcium levels benefit the myocardium, and hypercalcemia may actually be associated with increased myocardial toxicity.

Adrenal function is another important consideration in shock, and hydrocortisone replacement may be beneficial. Up to 50% of critically ill patients may have absolute or relative adrenal insufficiency. Patients at risk for adrenal insufficiency include those with congenial adrenal hypoplasia, abnormalities of the hypothalamic-pituitary axis, and

Table 70-13 Cardiovascular Drug Treatment of Shock

DRUG	EFFECT(S)	DOSING RANGE	COMMENT(S)
Dopamine	↑ Cardiac contractility Significant peripheral vasoconstriction at >10 µg/kg/min	3-20 µg/kg/min	↑ Risk of arrhythmias at high doses
Epinephrine	↑ Heart rate and ↑ cardiac contractility Potent vasoconstrictor	0.05-3.0 µg/kg/min	May ↓ renal perfusion at high doses ↑ Myocardial O_2 consumption Risk of arrhythmia at high doses
Dobutamine	↑ Cardiac contractility Peripheral vasodilator	1-10 µg/kg/min	—
Norepinephrine	Potent vasoconstriction No significant effect on cardiac contractility	0.05-1.5 µg/kg/min	↑ Blood pressure secondary to ↑ systemic vascular resistance ↑ Left ventricular afterload
Phenylephrine	Potent vasoconstriction	0.5-2.0 µg/kg/min	Can cause sudden hypertension ↑ O_2 consumption

Table 70-14	Vasodilators/Afterload Reducers		
DRUG	**EFFECT(S)**	**DOSING RANGE**	**COMMENT(S)**
Nitroprusside	Vasodilator (mainly arterial)	0.5-4.0 µg/kg/min	Rapid effect Risk of cyanide toxicity with prolonged use (>96 hr)
Nitroglycerin	Vasodilator (mainly venous)	1-20 µg/kg/min	Rapid effect Risk of increased intracranial pressure
Prostaglandin E_1	Vasodilator Maintains an open ductus arteriosus in the newborn with ductal-dependent congenital heart disease	0.01-0.2 µg/kg/min	Can lead to hypotension Risk of apnea
Milrinone	Increased cardiac contractility Improves cardiac diastolic function Peripheral vasodilation	Load 50 µg/kg over 15 min 0.5-1.0 µg/kg/min	Phosphodiesterase inhibitor—slows cyclic adenosine monophosphate breakdown

recent therapy with corticosteroids (including patients with asthma, rheumatic diseases, malignancies, and inflammatory bowel disease). These patients are at high risk for adrenal dysfunction and should receive stress doses of hydrocortisone. Steroids may also be considered in patients with shock that is unresponsive to fluid resuscitation and catecholamines. While there may be a subset of pediatric septic shock patients that benefit from treatment with hydrocortisone, currently available pediatric data do not demonstrate an overall survival benefit in patients with shock treated with hydrocortisone. Determination of baseline cortisol levels prior to steroid administration may be beneficial in guiding therapy, although this idea remains controversial.

Considerations for Continued Therapy

After the 1st hr of therapy and attempts at early reversal of shock, focus on goal-directed endpoints should continue in an intensive care setting (see Fig. 70-1 and Table 70-8). Clinical endpoints serve as global markers for organ perfusion and oxygenation. Laboratory parameters such as SVo_2 (or $ScvO_2$), serum lactate concentration, cardiac index, and hemoglobin serve as adjunctive measures of tissue oxygen delivery. Hemoglobin should be maintained at 10 g/dL, SVo_2 (or $ScvO_2$) >70%, and cardiac index at 3.3-6.0 L/min/m^2 to optimize oxygen delivery in the acute phase of shock. It is important to note that cardiac index is rarely monitored in the clinical setting owing to the limited use of pulmonary artery catheters and the lack of accurate noninvasive cardiac output monitors for infants and children. Blood lactate levels and calculation of base deficit from arterial blood gas values are very useful markers for the adequacy of oxygen delivery. These traditional markers are all indicators of global oxygen utilization and delivery, and there is increasing interest in measures of local tissue oxygenation including near infra-red spectroscopy of the cerebrum, flank, or abdomen.

Respiratory support should be used as clinically appropriate. When shock leads to ARDS requiring mechanical ventilation, lung-protective strategies to keep plateau pressure below 30 cm H_2O and maintain tidal volume at 6 mL/kg have been shown to improve mortality in adult patients (see Chapter 71). These data are extrapolated to pediatric patients because of the lack of definitive pediatric studies in this area. Additionally, after the initial shock state has been reversed, data demonstrate that judicious fluid administration, renal replacement therapy, and fluid removal may also be useful in children with anuria or oliguria and fluid overload (see Chapter 535). Other interventions include correction of coagulopathy with fresh frozen plasma or cryoprecipitate and platelet transfusions as necessary, especially in the presence of active bleeding.

If shock remains refractory despite maximal therapeutic interventions, mechanical support with **extracorporeal membrane oxygenation** or a **ventricular assist device** may be indicated. Extracorporeal membrane oxygenation may be lifesaving in cases of refractory shock regardless of underlying etiology. Similarly, a ventricular assist device may be indicated for refractory cardiogenic shock in the setting of cardiomyopathy or recent cardiac surgery. Systemic anticoagulation, which is required while patients are receiving mechanical support, may be difficult, given the significant coagulopathy often encountered in refractory shock, especially when the underlying etiology is sepsis. Mechanical support in refractory shock poses substantial risks but can improve survival in specific populations of patients.

PROGNOSIS

In septic shock, mortality rates are as low as 3% in previously healthy children and 6-9% in children with chronic illness (compared with 25-30% in adults). With early recognition and therapy, the mortality rate for pediatric shock continues to improve, but shock and MODS remain one of the leading causes of death in infants and children. The risk of death involves a complex interaction of factors, including the underlying etiology, presence of chronic illness, host immune response, and timing of recognition and therapy.

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Chapter 71

Respiratory Distress and Failure

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The term **respiratory distress** is often used to indicate signs and symptoms of abnormal respiratory pattern. A child with nasal flaring, tachypnea, chest wall retractions, stridor, grunting, dyspnea, and wheezing is often judged as having respiratory distress. The magnitude of these findings is used to judge the clinical severity of respiratory distress. Although nasal flaring is a nonspecific sign, the other signs are useful in localizing the site of pathology (see Chapters 373 and 374). Respiratory failure is defined as inability of the lungs to provide sufficient oxygen (hypoxic respiratory failure) or remove carbon dioxide (ventilatory failure) to meet metabolic demands. Whereas respiratory

Table 71-1 Typical Localizing Signs for Pulmonary Pathology

SITE OF PATHOLOGY	RESPIRATORY RATE	RETRACTIONS	AUDIBLE SOUNDS
Extrathoracic airway	↑	↑↑↑↑	Stridor
Intrathoracic extrapulmonary	↑	↑↑	Wheezing
Intrathoracic intrapulmonary	↑↑	↑↑	Wheezing
Alveolar interstitial	↑↑↑	↑↑↑	Grunting

distress is a clinical impression, the diagnosis of **respiratory failure** indicates inadequacy of oxygenation or ventilation, or both. Respiratory distress can occur in patients without respiratory disease, and respiratory failure can occur in patients without respiratory distress.

RESPIRATORY DISTRESS

A careful physical examination must be performed when managing a child in respiratory distress. Nasal flaring is an extremely important sign of distress, especially in infants. It is indicative of discomfort, pain, fatigue, or breathing difficulty. The state of responsiveness is another crucial sign. Lethargy, disinterest in surroundings, and poor cry are suggestive of exhaustion, hypercarbia, and impending respiratory failure. Abnormalities of the rate and depth of respirations can occur with both pulmonary and nonpulmonary causes of respiratory distress. In diseases of decreased lung compliance, such as pneumonia and pulmonary edema, respirations are characteristically rapid and shallow (decreased tidal volume). In obstructive airway diseases, such as asthma and laryngotracheitis, respirations are deep (increased tidal volume) but less rapid. Rapid and deep respirations without other respiratory signs should alert the physician to the possibility of nonrespiratory causes of respiratory distress, such as response to metabolic acidosis (diabetic ketoacidosis, renal tubular acidosis) or stimulation of the respiratory center (encephalitis, ingestion of central nervous system [CNS] stimulants). Chest wall, suprasternal, and subcostal retractions are manifestations of increased inspiratory effort, weak chest wall, or both. Inspiratory stridor indicates airway obstruction above the thoracic inlet, whereas expiratory wheezing results from airway obstruction below the thoracic inlet. Grunting is most commonly heard in diseases with decreased functional residual capacity (e.g., pneumonia, pulmonary edema) and peripheral airway obstruction (e.g., bronchiolitis).

Respiratory Disease Manifesting as Respiratory Distress

Clinical examination is important in localizing the site of pathology (see Chapter 373). Extrathoracic airway obstruction occurs anywhere above the thoracic inlet. Inspiratory stridor, suprasternal, chest wall, and subcostal retractions, and prolongation of inspiration are hallmarks of extrathoracic airway obstruction. By comparison, features of intrathoracic airway obstruction are prolongation of expiration and expiratory wheezing. Typical manifestations of alveolar interstitial pathology are rapid, shallow respirations, chest wall retractions, and grunting. The site of pathology can be localized and the differential diagnosis established on the basis of the clinical signs and symptoms (Tables 71-1 and 71-2).

Respiratory Distress without Respiratory Disease

Although respiratory distress most commonly results from diseases of lungs, airways, and chest wall, pathology in other organ systems can manifest as "respiratory distress" and lead to misdiagnosis and inappropriate management (Table 71-3). Respiratory distress resulting from heart failure or diabetic ketoacidosis may be misdiagnosed as asthma and improperly treated with albuterol, resulting in worsened hemodynamic state or ketoacidosis. Careful history and physical examination provide essential clues in avoiding misdiagnosis.

Table 71-2 Examples of Anatomic Sites of Lesions Causing Respiratory Failure

LUNG	RESPIRATORY PUMP
CENTRAL AIRWAY OBSTRUCTION Choanal atresia Tonsilloadenoidal hypertrophy Retropharyngeal/peritonsillar abscess Laryngomalacia Epiglottitis Vocal cord paralysis Laryngotracheitis Subglottic stenosis Vascular ring/pulmonary sling Mediastinal mass Foreign-body aspiration Obstructive sleep apnea	THORACIC CAGE Kyphoscoliosis Diaphragmatic hernia Flail chest Eventration of diaphragm Asphyxiating thoracic dystrophy Prune-belly syndrome Dermatomyositis Abdominal distention
PERIPHERAL AIRWAY OBSTRUCTION Asthma Bronchiolitis Foreign-body aspiration Aspiration pneumonia Cystic fibrosis α_1-Antitrypsin deficiency	BRAINSTEM Arnold-Chiari malformation Central hypoventilation syndrome CNS depressants Trauma Increased intracranial pressure CNS infections
ALVEOLAR-INTERSTITIAL DISEASE Lobar pneumonia Acute respiratory distress syndrome/hyaline membrane disease Interstitial pneumonia Hydrocarbon pneumonia Pulmonary hemorrhage/hemosiderosis	SPINAL CORD Trauma Transverse myelitis Spinal muscular atrophy Poliomyelitis Tumor/abscess
	NEUROMUSCULAR Phrenic nerve injury Birth trauma Infant botulism Guillain-Barré syndrome Muscular dystrophy Myasthenia gravis Organophosphate poisoning

Cardiovascular Disease Manifesting as Respiratory Distress

A child with cardiovascular pathology may present with respiratory distress caused by 2 mechanisms: (1) decreased lung compliance and (2) cardiogenic shock (Table 71-4). Diseases that result in an increased pulmonary arterial blood flow (e.g., left-to-right shunts) or increased pulmonary venous pressure (e.g., left ventricular dysfunction from hypertension or myocarditis, obstructed total anomalous pulmonary

Table 71-3 Nonpulmonary Causes of Respiratory Distress

	EXAMPLE(S)	MECHANISM(S)
Cardiovascular	Left-to-right shunt Congestive heart failure Cardiogenic shock	↑ Pulmonary blood/water content Metabolic acidosis Baroreceptor stimulation
Central nervous system	Increased intracranial pressure Encephalitis Neurogenic pulmonary edema Toxic encephalopathy	Stimulation of brainstem respiratory centers
Metabolic	Diabetic ketoacidosis Organic acidemia Hyperammonemia	Stimulation of central and peripheral chemoreceptors
Renal	Renal tubular acidosis Hypertension	Stimulation of central and peripheral chemoreceptors Left ventricular dysfunction → increased pulmonary blood/water content
Sepsis	Toxic shock syndrome Meningococcemia	Cytokine stimulation of respiratory centers Baroreceptor stimulation from shock Metabolic acidosis

Table 71-4 Cardiovascular Pathology Manifesting as Respiratory Distress

I. DECREASED LUNG COMPLIANCE
  A. Left-to-Right Shunts
    1. Ventricular septal defect, atrial septal defect, patent ductus arteriosus, atrioventricular canal, truncus arteriosus
    2. Cerebral or hepatic arteriovenous fistula
  B. Ventricular Failure
    1. Left-heart obstructive lesions
      a) aortic stenosis
      b) coarctation of the aorta
      c) mitral stenosis
      d) interrupted aortic arch
      e) hypoplastic left heart syndrome
    2. Myocardial infarction
      a) anomalous left coronary artery arising from the pulmonary artery
    3. Hypertension
      a) acute glomerulonephritis
    4. Inflammatory/Infectious
      a) myocarditis
      b) pericardial effusion
    5. Idiopathic
      a) dilated cardiomyopathy
      b) hypertrophic obstructive cardiomyopathy
  C. Pulmonary Venous Obstruction
    1. Total anomalous pulmonary venous return with obstruction
    2. Cor triatriatum

II. SHOCK RESULTING IN METABOLIC ACIDOSIS
  A. Left-Heart Obstructive Lesions
  B. Acute Ventricular Failure
    1. Myocarditis, myocardial infarction

venous return) cause an increase in pulmonary capillary pressure and transudation of fluid into the pulmonary interstitium and alveoli. The increased pulmonary blood and water content leads to decreased lung compliance and results in rapid shallow respirations.

It is important to recognize that interstitial lung edema can not only manifest as alveolar fluid, but as small airway obstruction as well. Wheezing as a sign of congestive cardiac disease is common in infants and young children and should be recognized. Patients with cardiac lesions that result in a low cardiac output state, such as obstructive lesions of left side of the heart and acquired or congenital cardiomyopathy, often present in a state of shock with decreased tissue perfusion and metabolic acidosis. Such children demonstrate respiratory distress because of stimulation of chemoreceptors by metabolic acidosis and stimulation of baroreceptors by decreased blood pressure. The likelihood of a particular cardiovascular illness manifesting as respiratory distress depends on age at presentation (Table 71-5).

Neurologic Disease Manifesting as Respiratory Distress

CNS dysfunction can lead to alterations in respiratory patterns. Increased intracranial pressure (ICP) may manifest as respiratory distress. Early rise in ICP results in stimulation of respiratory centers, leading to increases in the rate (tachypnea) and depth (hyperpnea) of respiration. The resultant decrease in Pa_{CO_2} and elevation of cerebrospinal fluid pH lead to cerebral vasoconstriction and amelioration of intracranial hypertension. Cerebral hemispheric and midbrain lesions often result in hyperpnea as well as tachypnea. In such situations, blood gas measurements typically show respiratory alkalosis without hypoxemia. Pathology affecting the pons and medulla manifests as irregular breathing patterns such as apneustic breathing (prolonged inspiration with brief expiratory periods), Cheyne-Stokes breathing (alternate periods of rapid and slow breathing), and irregular, ineffective breathing or apnea. Level of consciousness is most often impaired when abnormal breathing pattern from a brainstem disorder is present. Along with respiratory changes, other manifestations of CNS dysfunction and increased ICP may be present, such as focal neurologic signs, pupillary changes, hypertension, and bradycardia (see Chapter 63). Occasionally, severe CNS dysfunction can result in **neurogenic pulmonary edema** and respiratory distress, which may be a result of excessive sympathetic discharge resulting in increased pulmonary venous hydrostatic pressure as well as increased pulmonary capillary

Table 71-5 Typical Chronology of Heart Disease Presentation in Children

AGE	MECHANISM	DISEASE
Newborn (1-10 days)	↑ Arteriovenous pressure difference	Arteriovenous fistula (brain, liver)
	Ductal closure	Single ventricle lesions or severe ventricular outflow obstruction
	Independent pulmonary and systemic blood flow	Transposition of the great arteries
	Pulmonary venous obstruction	Total anomalous pulmonary venous return (TAPVR)
Young Infant (1-6 mo)	↓ Pulmonary vascular resistance	Left-to-right shunt
	↓ Pulmonary artery pressure	Anomalous left coronary artery to the pulmonary artery
Any Age	Rate disturbance	Tachy- or bradyarrhythmias
	Infection	Myocarditis, pericarditis
	Abnormal cardiac myocytes	Cardiomyopathy
	Excess afterload	hypertension

permeability. **Central neurogenic hyperventilation** is characteristically observed in CNS involvement by illnesses such as urea cycle defects and encephalitis. **Bradycardia and apnea** may be caused by CNS-depressant medications, poisoning, prolonged hypoxia, trauma, or infection (see Table 71-2).

Toxic-Metabolic States Manifesting as Respiratory Distress

Direct stimulation of respiratory centers resulting in respiratory alkalosis is encountered in certain intoxications, such as those involving salicylates and theophylline. Similarly, intoxication with general CNS stimulants, such as cocaine and amphetamines may manifest as increased respirations. Presence of endogenous and exogenous toxins, such as organic acidemias, ingestion of methanol and ethylene glycol, and late stages of salicylism, cause metabolic acidosis and compensatory hyperventilation, which can manifest as respiratory distress. Blood gas measurements show decreased pH and compensatory hypocarbia with normal oxygenation. Metabolic disorders causing hyperammonemia, on the other hand, cause respiratory alkalosis (decreased $Paco_2$ with increased pH) because ammonia is a stimulant of respiratory centers.

Other Nonpulmonary Entities Manifesting as Respiratory Distress

Sepsis and septic shock may manifest as respiratory distress by causing acute respiratory distress syndrome (ARDS), hypovolemic stimulation of baroreceptors, stimulation of respiratory centers by cytokines, and lactic acidosis. Other indirect causes of lung injury include systemic inflammatory conditions, trauma, transfusion-related acute lung injury, and pancreatitis. Similarly, renal disease may manifest as respiratory distress by causing metabolic acidosis (e.g., renal tubular acidosis or renal failure) or hypertensive left ventricular failure and fluid overload.

RESPIRATORY FAILURE

Respiratory failure occurs when oxygenation and ventilation are insufficient to meet the metabolic demands of the body. Respiratory failure may result from an abnormality in (1) lung and airways, (2) chest wall and muscles of respiration, or (3) central and peripheral chemoreceptors. Clinical manifestations depend largely on the site of pathology (Table 71-6). Although respiratory failure is traditionally defined as respiratory dysfunction resulting in Pao_2 <60 torr with breathing of room air and $Paco_2$ >50 torr resulting in acidosis, the patient's general state, respiratory effort, and potential for impending exhaustion are more important indicators than blood gas values.

Acute lung injury due to pneumonia, sepsis, aspiration, drowning, embolism, trauma, smoke inhalation, or drug overdose may lead to the **ARDS** (Tables 71-7 and 71-8; Fig. 71-1).

Pathophysiology of Respiratory Failure

Respiratory failure can be classified into (1) hypoxic respiratory failure (failure of oxygenation) and (2) hypercarbic respiratory failure (failure of ventilation). Systemic venous (pulmonary arterial) blood is arterialized after equilibration with alveolar gas in the pulmonary capillaries and is carried back to the heart by pulmonary veins. The arterial gas is influenced by the composition of inspired gas, and the effectiveness of alveolar ventilation, pulmonary capillary perfusion, and diffusion capacity of the alveolar capillary membrane. Abnormality at any of these steps can result in respiratory failure. Hypoxic respiratory failure results from intrapulmonary shunting and venous admixture or insufficient diffusion of oxygen from alveoli into pulmonary capillaries. This can be

Table 71-6 Typical Clinical Manifestations of Respiratory Failure

SITE OF PATHOLOGY	SYMPTOM
Lung and Airways	Nasal flaring, retractions, tachypnea, wheezing stridor, grunting
Chest wall and muscles of respiration	Nasal flaring, tachypnea, paradoxical respirations
Respiratory control	Shallow or slow respirations, abnormal respiratory patterns, apnea

Table 71-7 Simplified Consensus Definition of Acute Lung Injury

- Acute onset (<7 days)
- Severe hypoxemia (PaO_2/FIO_2 <300 for acute lung injury, or <200 for acute respiratory distress syndrome)
- Diffuse bilateral pulmonary infiltrates on frontal radiograph consistent with pulmonary edema (these can be patchy and asymmetric, and pleural effusions can be present)
- Absence of left atrial hypertension (pulmonary artery wedge pressure <18 mm Hg if measured)

From Wheeler AP, Bernard GR: Acute lung injury and the acute respiratory distress syndrome: a clinical review, Lancet 369:1553–1564, 2007.

Table 71-8 New Berlin Definition of ARDS in Infancy and Early Childhood

	BERLIN DEFINITION CRITERIA	SUITABILITY IN INFANTS
Timing	Within 1 wk of a known clinical insult or new or worsening respiratory symptoms	Acute time frame is specified
Chest X-rays or tomography scan	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules. (Illustrative clinical cases and chest X-rays have been provided)	Including illustrative radiographs is important, because ARDS appearance may be different in children and in adults
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema, if no ARDS risk factors are present	Echocardiography widely used, whereas Swan-Ganz catheters are rarely used in early childhood. Including risk factors in the ARDS definition is important, because they may be different in children and in adults
Oxygenation*		
Mild	200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H_2O†	Noninvasive CPAP is widely used in early childhood. PEEP threshold (5 cm H_2O) is a value commonly used during early childhood
Moderate	100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O	
Severe	PaO_2/FIO_2 < 100 mm Hg with PEEP ≥ 5 cm H_2O	

*If altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2 × (barometric pressure/760)].
†This may be delivered noninvasively in the mild acute respiratory distress syndrome group.
CPAP, continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

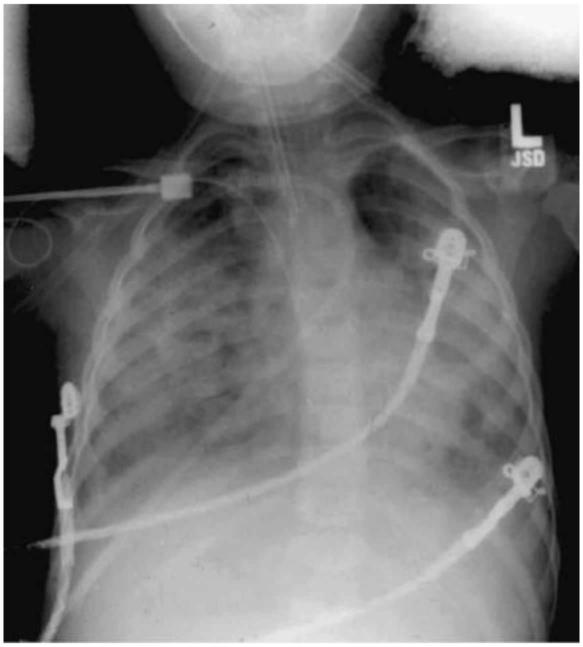

Figure 71-1 Frontal portal chest radiograph showing diffuse bilateral infiltrates consistent with acute lung injury. *(From Wheeler AP, Bernard GR: Acute lung injury and the acute respiratory distress syndrome: a clinical review*, Lancet *369:1553–1564, 2007.)*

caused by conditions such as small airway obstruction, increased barrier to diffusion (such as interstitial edema or fibrosis), or in conditions where alveoli are collapsed or filled with fluid (e.g., ARDS, pneumonia, atelectasis, or pulmonary edema). In most cases, hypoxic respiratory failure is associated with a decreased functional residual capacity, and can be managed by recruitment with positive pressure ventilation. Hypercarbic respiratory failure is caused by decreased minute alveolar ventilation (tidal volume multiplied by respiratory rate). This can occur from centrally-mediated disorders of respiratory drive, increased dead space ventilation, or obstructive airway disease. The two entities may coexist as a combined failure of oxygenation and ventilation.

Ventilation–Perfusion Mismatch, Venous Admixture, Intrapulmonary Shunt

For exchange of O_2 and CO_2 to occur, alveolar gas must be exposed to blood in pulmonary capillaries. Both ventilation and perfusion are lower in nondependent areas of the lung and higher in dependent areas of the lung. The difference in perfusion ($\dot{Q}$) is greater than the difference in ventilation ($\dot{V}$). Perfusion in excess of ventilation results in incomplete "arterialization" of systemic venous (pulmonary arterial) blood and is referred to as *venous admixture*. Perfusion of unventilated areas is referred to as *intrapulmonary shunting* of systemic venous blood to systemic arterial circulation. Conversely, ventilation that is in excess of perfusion is "wasted"; that is, it does not contribute to gas exchange and is referred to as *dead space ventilation*. Dead space ventilation results in return of greater amounts of atmospheric gas which has not participated in gas exchange and has negligible CO_2 to the atmosphere during exhalation. The end result is a decrease in mixed expired P_{CO_2} (P_{ECO_2}) and an increase in the Pa_{CO_2}-P_{ECO_2} gradient. The fraction of tidal volume that occupies dead space (V_D/V_T) is calculated as follows:

$$[(Pa_{CO_2} - P_{ECO_2}) \div Pa_{CO_2}]$$

Normal V_D/V_T is around 0.33. V_D/V_T increases in states that result in decreased pulmonary perfusion, such as pulmonary hypertension, hypovolemia, and decreased cardiac output. Venous admixture and intrapulmonary shunting predominantly affect oxygenation, resulting in a P_{AO_2}-Pa_{O_2} (A-aO_2) gradient without elevation in Pa_{CO_2}. This is caused by the greater ventilation of perfused areas, which is sufficient to normalize Pa_{CO_2} but not Pa_{O_2} because of their respective dissociation curves (see Chapter 365). The relative straight-line relationship of hemoglobin-CO_2 dissociation allows for averaging of P_{CO_2} from hyperventilated and hypoventilated areas. Because the association between oxygen tension and hemoglobin saturation plateaus with increasing Pa_{O_2}, the decreased hemoglobin-O_2 saturation in poorly ventilated areas cannot be compensated for by well-ventilated areas where hemoglobin-O_2 saturation has already reached near-maximum. This results in decreased arterial oxyhemoglobin saturation (Sa_{O_2}) and Pa_{O_2}. Elevation of Pa_{CO_2} in such situations is indicative of coincident alveolar hypoventilation. Examples of diseases leading to venous admixture include asthma and aspiration pneumonia, and those of intrapulmonary shunt include lobar pneumonia and ARDS.

Diffusion

Even if ventilation and perfusion are matched, gas exchange requires diffusion across the interstitial space between alveoli and pulmonary capillaries. Under normal conditions, there is sufficient time for the pulmonary capillary blood to equilibrate with alveolar gas across the interstitial space. When the interstitial space is filled with inflammatory cells or fluid, diffusion is impaired. Because the diffusion capacity of CO_2 is 20 times greater than that of O_2, diffusion defects manifest as hypoxemia rather than hypercarbia. Even with the administration of 100% oxygen, P_{AO_2} increases to around 660 torr from 100 torr at sea level, and the concentration gradient for diffusion of O_2 is increased by only 6.6 times. Therefore, with diffusion defects, lethal hypoxemia will set in before clinically significant CO_2 retention results. In fact, in such situations P_{CO_2} is often decreased because of the hyperventilation that accompanies hypoxemia. Presence of hypercarbia in diseases that impair diffusion is indicative of alveolar hypoventilation from coexisting airway obstruction, exhaustion, or CNS depression. Examples of disease that impair diffusion are interstitial pneumonia, ARDS, scleroderma, and pulmonary lymphangiectasia.

MONITORING A CHILD IN RESPIRATORY DISTRESS AND RESPIRATORY FAILURE

Clinical Examination

It cannot be overemphasized that clinical observation is the most important component of monitoring. The presence and magnitude of abnormal clinical findings, their progression with time, and their temporal relation to therapeutic interventions serve as guides to diagnosis and management (see Chapter 373). As much as possible, the child with respiratory distress or failure should be observed in the position of greatest comfort and in the least threatening environment.

Pulse oximetry is the most commonly utilized technique to monitor oxygenation. Noninvasive and safe, it is the standard of care in bedside monitoring of children during transport, procedural sedation, surgery, and critical illness. It indirectly measures arterial hemoglobin-O_2 saturation by differentiating oxyhemoglobin from deoxygenated hemoglobin using their respective light absorption at wavelengths of 660 nm (red) and 940 nm (infrared). A pulsatile circulation is required to enable detection of oxygenated blood entering the capillary bed. Percentage of oxyhemoglobin is reported as Sa_{O_2}; however, the correct description is oxyhemoglobin saturation as measured by pulse oximetry (Sp_{O_2}). This is because Sp_{O_2} may not reflect Sa_{O_2} in certain situations. It is important to be familiar with the hemoglobin-O_2 dissociation curve (see Chapter 373) in order to estimate Pa_{O_2} at a given oxyhemoglobin saturation. Because of the shape of the hemoglobin-O_2 dissociation curve, changes in Pa_{O_2} above 70 torr are not readily identified by pulse oximetry. Also, at the same Pa_{O_2} level, there may be a significant change in Sp_{O_2} at a different blood pH value. In most situations, an Sp_{O_2} value greater than 95% is a reasonable goal, especially in emergency situations. There are exceptions, such as in patients with single ventricle cardiac lesions, in whom the pulmonary and systemic circulations are receiving blood flow from the same ventricle (e.g., after Norwood procedure for hypoplastic left heart syndrome), or with large left-to-right shunts (e.g., ventricular septal defect and patent ductus arteriosus). In these types of pathophysiologic situations, a lower Sp_{O_2}

is desired to avoid excessive blood flow to the lungs and pulmonary edema from the pulmonary vasodilatory effects of oxygen, and, in the patient with a single ventricle, diverting blood flow away from the systemic circulation. Because most commercially available pulse oximeters recognize all types of hemoglobin as either oxyhemoglobin or deoxygenated hemoglobin, they provide inaccurate information in the presence of carboxyhemoglobin and methemoglobin. In carbon monoxide poisoning, carboxyhemoglobin absorbs light in the same (red) wavelength as oxyhemoglobin, leading to overestimation of oxygen saturation. Methemoglobin absorbs light in both the oxygenated and deoxygenated wavelengths, which can cause either an overestimation or underestimation of oxygen saturation. Data suggests that increasing methemoglobin concentrations tend to drive Spo_2 toward 85%, no matter the actual percent of oxyhemoglobin. At lower methemoglobin levels, the pulse oximetry reading is falsely low, whereas high levels lead to a falsely high pulse oximetry reading. Newer pulse oximeters may have the ability to distinguish dyshemoglobinemias and to prevent false readings, but these are not currently in widespread use. It should be recognized that dangerous levels of hypercarbia may exist in patients with ventilatory failure, who have satisfactory Spo_2 if they are receiving supplemental oxygen. Pulse oximetry should not be the only monitoring method in patients with primary ventilatory failure, such as neuromuscular weakness and CNS depression. It is also unreliable in patients with poor perfusion and poor pulsatile flow to the extremities. Despite these limitations, pulse oximetry is a noninvasive, easily applicable, and effective means of evaluating the percentage of oxyhemoglobin in most patients.

Capnography (end-tidal CO_2 measurement) is helpful in determining the effectiveness of ventilation and pulmonary circulation. This method is especially useful for monitoring the level of ventilation in intubated patients. Diseases resulting in increased dead space or decreased pulmonary blood flow lead to decreases in end-tidal CO_2 and an overestimation of the adequacy of ventilation.

Blood Gas Abnormalities in Respiratory Distress and Respiratory Failure

Arterial blood gas analysis offers valuable assistance in diagnosis, monitoring, and management of a child in respiratory distress and failure. Because of technical difficulties in obtaining an arterial sample in children, a capillary blood gas (CBG) sample is most often obtained in emergency situations. A properly “arterialized” CBG sample obtained by warming the digit and obtaining free flowing blood is acceptable. The blood sample needs to be processed without delay. CBG provides a good estimate of $Paco_2$ and arterial pH, but less so for Pao_2. In patients who mainly require monitoring of their ventilation (especially those whose oxygenation is being monitored with pulse oximetry) a venous blood gas sample provides reliable estimate of arterial pH and Pco_2 values, provided tissue perfusion is reasonably adequate. Venous Pco_2 is approximately 6 torr higher and pH approximately 0.03 lower than the arterial values. Venous Po_2 has a poor correlation with Pao_2. Mixed venous O_2 saturation obtained from a central venous catheter in the right atrium is an excellent marker of the balance between oxygen delivery and oxygen consumption. In patients with a constant arterial O_2 content and O_2 consumption, mixed venous O_2 saturation offers valuable information regarding cardiac output.

Blood gas analysis is important not only for determining the adequacy of oxygenation and ventilation but also for determining site of the respiratory pathology and planning treatment (see Chapter 373). Briefly, in presence of pure alveolar hypoventilation (such as airway obstruction above the carina, decreased CO_2 responsiveness and neuromuscular weakness), the blood gas will show respiratory acidosis with an elevated Pco_2 but a relative sparing of oxygenation. $\dot{V}/\dot{Q}$ mismatch (peripheral airway obstruction, bronchopneumonia) will be reflected in increasing hypoxemia and variable levels of Pco_2 (low, normal, high) depending on severity of disease. Intrapulmonary right to left shunting and diffusion defects (alveolar-interstitial diseases such as pulmonary edema, ARDS) will be associated with a large A-ao_2 gradient and hypoxemia with relative sparing of CO_2 elimination unless there is coincident fatigue or CNS depression.

Acid–Base Abnormalities in a Child with Respiratory Distress and Respiratory Failure

It is crucial to analyze the magnitude and appropriateness of changes in pH, Pco_2 and bicarbonate (HCO_3^-) as they provide useful clues to the underlying pathophysiology and presence of more than one disorder. To do so, it is useful to assume baseline values of pH 7.40, Pco_2 40 torr, and HCO_3^- 24 mEq/L. Newborns have lower renal threshold for bicarbonate and therefore have slightly different baseline values of pH 7.38, Pco_2 35 torr and HCO_3^- 20 mEq/L.

Metabolic Acidosis with Respiratory Compensation

Patients with metabolic acidosis have decreased pH resulting from decreased serum bicarbonate. Chemoreceptor stimulation results in hyperventilation and respiratory compensation which may clinically manifest as respiratory distress. It should be recognized that a normal compensation does not completely correct the pH but rather minimizes a change in pH that would otherwise occur without compensation. The adequacy of respiratory compensation is judged by the extent of the decline in $Paco_2$ in response to the decline in HCO_3^- or pH. A normal compensation for metabolic acidosis results in a fall in Pco_2 by 1.2 torr for every 1 mEq/L fall in HCO_3^- The most commonly used method to analyze the adequacy of respiratory compensation is the Winter’s formula: $Paco_2 = (HCO_3^- \times 1.5) + 8 \pm 2$. A quick method is to look at the last 2 digits of pH (provided it is not below 7.10) which should be within 2 torr of Pco_2. For example, pH 7.27, Pco_2 26 torr, and bicarbonate 12 mEq/L represents metabolic acidosis with a normal respiratory compensation response. On the other hand, pH 7.15, Pco_2 30 torr, and HCO_3^- 10 mEq/L constitutes metabolic acidosis with inadequate respiratory compensation. The reasons for inadequate compensation include decreased CO_2 responsiveness (e.g. narcotic poisoning, cerebral edema), abnormalities of lungs and airways, or neuromuscular weakness. A decrease in $Paco_2$ that is greater than what could be expected as a normal compensatory response to metabolic acidosis is indicative of a mixed disorder. For example, a pH 7.20, Pco_2 15 torr, and HCO_3^- 7.5 mEq/L represents metabolic acidosis with a concomitant respiratory alkalosis because the decline in Pco_2 is greater than what can be expected as normal compensation. Combination of metabolic acidosis and respiratory alkalosis is often encountered in serious conditions such as cardiogenic shock (anxiety, stimulation of baroreceptors), sepsis, or toxic-metabolic states (salicylates, organic academia).

Respiratory Acidosis with Metabolic Compensation

Patients with respiratory acidosis have decreased pH as a result of elevated $Paco_2$. An acute increase in Pco_2 of 10 torr results in a decrease in pH by 0.08. Thus, a child with severe status asthmaticus and a $Paco_2$ of 60 torr will have blood pH of around 7.24. Chronically elevated (greater than 3-5 days) $Paco_2$ is accompanied by renal compensation and increase in serum bicarbonate limiting the fall in pH to 0.03 for every 10 torr rise in $Paco_2$. Thus an infant with bronchopulmonary dysplasia who has a basal $Paco_2$ of 60 torr will have blood pH around 7.34. These findings are helpful in distinguishing acute vs. chronic changes in $Paco_2$. Also, for a given level of CO_2 accumulation, a decrease in pH that is greater than expected is indicative of concomitant metabolic acidosis and a decline in pH that is less than expected is due to accompanying metabolic alkalosis.

Assessment of Oxygenation and Ventilation Deficits

For standardizing management, following clinical progress, and determining prognosis for patients with defects in oxygenation or ventilation, various indicators have been proposed. Each one has its strengths and limitations:

A-ao_2 gradient: Calculated by subtracting arterial Po_2 from alveolar Po_2 ($PAo_2 - Pao_2$). For the comparison to be valid, it must be at the same Fio_2.

Pao_2/Fio_2 ratio is calculated by dividing arterial Po_2 by Fio_2. In hypoxic respiratory failure, a Pao_2/Fio_2 value <300 is consistent with acute lung injury, and a value <200 is consistent with ARDS.

Although the intent is to measure $\dot{V}/\dot{Q}$ mismatch, intrapulmonary shunt, and diffusion defect, the status of alveolar hypoventilation could have a significant impact on PaO_2/FIO_2.

PaO_2/PAO_2 is determined by dividing arterial PO_2 by alveolar PO_2. The level of alveolar ventilation is accounted for in the calculation of PAO_2. Therefore, PaO_2/PAO_2 is more indicative of $\dot{V}/\dot{Q}$ mismatch and alveolar capillary integrity.

Oxygenation index (OI) is aimed at standardizing oxygenation to the level of therapeutic interventions such as mean airway pressure (MAP) and FIO_2, which are directed toward improving oxygenation. None of the previously mentioned indicators of oxygenation account for the degree of positive pressure respiratory support. OI is calculated as follows:

$$OI = \left(MAP \times \%\, O_2\ inspired\right) \div PaO_2$$

The limitation of OI is that level of ventilation is not accounted for in the assessment.

Ventilation index (VI) is aimed at standardizing alveolar ventilation to the level of therapeutic interventions (such as peak inspiratory pressure [PIP] and ventilator rate) directed toward lowering $PaCO_2$. VI is calculated as follows:

$$VI = \left[Ventilator\ Rate \times (PIP - PEEP) \times PaCO_2\right] \div 1000$$

MANAGEMENT

The goal of management for respiratory distress and respiratory failure is to ensure a patent airway and provide necessary support for adequate oxygenation of the blood and removal of CO_2. Compared with hypercapnia, hypoxemia is a life-threatening condition; therefore, initial therapy for respiratory failure should be aimed at ensuring adequate oxygenation.

Oxygen Administration

Supplemental oxygen administration is the least invasive and most easily tolerated therapy for hypoxemic respiratory failure. *Nasal cannula* oxygen provides low levels of oxygen supplementation and is easy to administer. Oxygen is humidified in a bubble humidifier and delivered via nasal prongs inserted in to the nares. In children, a flow rate <5 L/min is most often used because of increasing nasal irritation with higher rates. A common formula for an estimation of the FIO_2 during use of a nasal cannula in older children and adults is as follows:

$$FIO_2\%\, O_2\ \text{delivered} = 21\% + \left[\left(\text{nasal cannula flow (L/min)} \times 3\right)\right]$$

The typical FIO_2 value using this method is between 23% and 40%, although the FIO_2 varies according to the size of the child, the respiratory rate, and the volume of air moved with each breath. In a young child, because typical nasal cannula flows are a greater percentage of total minute ventilation, significantly higher FIO_2 may be provided. Alternately, a *simple mask* may be employed, which consists of a mask with open side ports and a valveless oxygen source. Variable amounts of room air are entrained through the ports and around the side of the mask, depending on the fit, size, and minute volume of the child. Oxygen flow rates vary from 5-10 L/min, yielding typical FIO_2 values between 0.30 and 0.65. If more precise delivery of oxygen is desired, other mask devices should be used.

A *Venturi mask* delivers preset fractions of oxygen through a mask and reservoir system by entraining precise amounts of room air into the reservoir with high-flow oxygen. The amount of room air entrainment and subsequent FIO_2 are determined by the adapter at the end of each mask reservoir. The adapter can be chosen to provide between 30% and 50% oxygen concentrations. Oxygen flow rates of 5-10 L/min are recommended to achieve desired FIO_2 and to prevent rebreathing. *Partial rebreather* and *nonrebreather* masks use a reservoir bag attached to a mask to provide higher fractions of oxygen. Partial rebreather masks have 2 open exhalation ports and contain a valveless oxygen reservoir bag. Some exhaled gas can mix with reservoir gas during exhalation, although most exits the mask via the exhalation ports. Through these ports, room air is also entrained during inspiration. A partial rebreather mask can provide up to 0.6 FIO_2 as long as oxygen flow is adequate to keep the bag from collapsing (typically 10-15 L/min). As with nasal cannulas, smaller children with smaller tidal volumes entrain less room air, and their FIO_2 values will be higher. Nonrebreather masks include 2 one-way valves, 1 between the oxygen reservoir bag and the mask and 1 on 1 of the 2 exhalation ports. This arrangement minimizes mixing of exhaled and fresh gas and entrainment of room air during inspiration. The second exhalation port has no valve, a safeguard to allow some room air to enter the mask in the event of disconnection from the oxygen source. A nonrebreather mask can provide up to 0.95 FIO_2. The use of a nonrebreather mask in conjunction with an oxygen blender allows delivery of fractions of oxygen between 0.50 and 0.95. When supplemental oxygen alone is inadequate to improve oxygenation, or when ventilation problems coexist, additional therapies may be necessary.

Airway Adjuncts

Maintenance of a patent airway is a critical step in maintaining adequate oxygenation and ventilation. Artificial pharyngeal airways may be useful in patients with oropharyngeal or nasopharyngeal airway obstruction and in those with neuromuscular weakness in whom native extrathoracic airway resistance contributes to respiratory compromise. An *oropharyngeal airway* is a stiff plastic spacer with grooves along each side that can be placed in the mouth to run from the teeth along the tongue to its base just above the vallecula. The spacer prevents the tongue from opposing the posterior pharynx and occluding the airway. Because the tip sits at the base of the tongue, it is usually not tolerated by patients who are awake or whose gag reflex is strong. The *nasopharyngeal airway*, or nasal trumpet, is a flexible tube that can be inserted into the nose to run from the nasal opening along the top of the hard and soft palate with the tip ending in the hypopharynx. It is useful in bypassing obstruction from enlarged adenoids or from contact of the soft palate with the posterior nasopharynx. Because it is inserted past the adenoids, a nasopharyngeal airway should be used with caution in patients with bleeding tendencies.

Inhaled Gases

Helium-oxygen mixture (*heliox*) is useful in overcoming airway obstruction and improving ventilation. Helium is much less dense and slightly more viscous than nitrogen. When substituted for nitrogen, helium helps maintain laminar flow across an obstructed airway, decreases airway resistance, and improves ventilation. It is especially helpful in diseases of large airway obstruction in which turbulent airflow is more common, such as acute laryngotracheobronchitis, subglottic stenosis, and vascular ring. It is also used in patients with severe status asthmaticus. To be effective, helium should be administered in concentrations of at least 60%, so associated hypoxemia may limit its use in patients requiring more than 40% oxygen. *Nitric oxide (NO)* is a powerful inhaled pulmonary vasodilator. Its use may improve pulmonary blood flow and $\dot{V}/\dot{Q}$ mismatch in patients with diseases that elevate pulmonary vascular resistance, such as persistent pulmonary hypertension of the newborn, primary pulmonary hypertension, and secondary pulmonary hypertension as a result of chronic excess pulmonary blood flow (e.g., ventriculoseptal defect) or collagen vascular diseases. NO is administered in doses ranging from 5-20 parts per million. Although administration of NO to unintubated patients is possible, it is usually administered to patients receiving mechanical ventilation through endotracheal tubes, because of the need for precision in NO dosing.

Positive-Pressure Respiratory Support

Noninvasive positive-pressure respiratory support is useful in treating both hypoxemic and hypoventilatory respiratory failure. Positive airway pressure helps aerate partially atelectatic or filled alveoli, prevent alveolar collapse at end exhalation, and increase functional residual capacity (FRC). This improves pulmonary compliance and hypoxemia and decreases intrapulmonary shunt. In addition, positive pressure ventilation is useful in preventing collapse of extrathoracic airways by maintaining positive airway pressure during inspiration. Improving compliance and overcoming airway resistance also improves tidal volume and, therefore, ventilation. A **high-flow nasal cannula** delivers

gas flow at 4-16 L/min, providing significant continuous positive airway pressure (CPAP). The amount of CPAP provided is not quantifiable and varies with each patient, depending on the percentage of total inspiratory flow that is delivered from the cannula, airway anatomy, and degree of mouth breathing. In small children, the relative amount of CPAP for a given flow is usually greater than in older children, and may provide significant positive pressure. The F_{IO_2} can be adjusted by provision of gas flow through an oxygen blender. Another benefit of a high-flow nasal cannula system is the washout of CO_2 from the nasopharynx, which decreases rebreathing of CO_2 and dead space ventilation. For delivery of high-flow air or oxygen, adequate humidification is essential and is achieved with use of a separate heated humidification chamber. CPAP can also be provided through snugly fitting nasal prongs or a tight-fitting facial mask attached to a ventilator or other positive-pressure device. Noninvasive CPAP is most useful in diseases of mildly decreased lung compliance and low FRC, such as atelectasis and pneumonia. Diseases of extrathoracic airway obstruction in which extrathoracic negative airway pressures during inspiration lead to airway narrowing (e.g., laryngotracheitis, obstructive sleep apnea, postextubation airway edema) may also benefit from CPAP. Potential risks include nasal irritation, hyperinflation from excessive CPAP in smaller patients, and abdominal distention from swallowed air.

Bilevel positive airway pressure (BiPAP) machines provide positive airway pressure during exhalation and additional positive pressure during inspiration. A BiPAP device allows one to set an expiratory positive airway pressure and an inspiratory positive airway pressure. The additional positive pressure during inspiration helps augment tidal volume and improve alveolar ventilation in low compliance and obstructive lung disease. The inspiratory and expiratory pressures can be adjusted independently to suit individual needs and comfort. Because of the additional support during inspiration, patients with neuromuscular weakness in particular tend to benefit from BiPAP support. BiPAP may also be helpful in diseases of intrathoracic airway obstruction. During exhalation, expiratory positive airway pressure can decrease the effects of airway closure by raising intraluminal pressure and ameliorating intrathoracic airway collapse. During inspiration, inspiratory positive airway pressure can unload inspiratory muscles, and decrease work of breathing (Fig. 71-2).

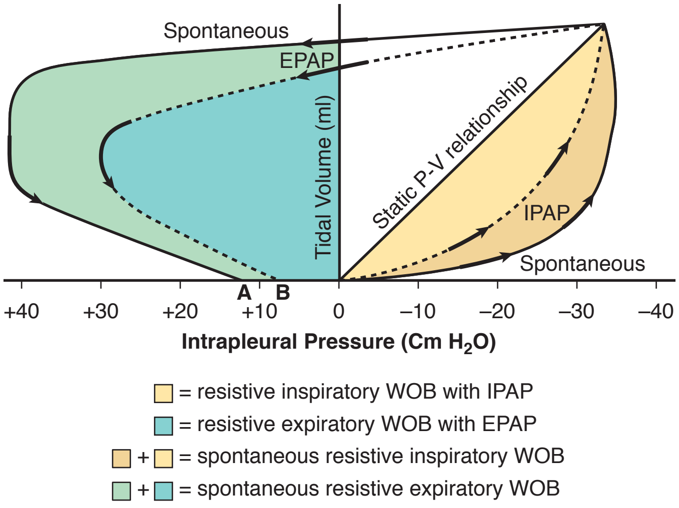

Figure 71-2 **Work of breathing (WOB) in status asthmaticus with and without noninvasive positive pressure ventilation.** In the expiratory limb of the respiratory cycle, the equal pressure point is displaced distally, causing airways to begin to close at a higher lung volume (increased closing capacity), leading to dynamic hyperinflation, and autopositive end-expiratory pressure (auto-PEEP) *(A)*. Application of expiratory positive airway pressure stents the airways, reducing intrathoracic airway collapse, dynamic hyperinflation, auto-PEEP *(B)*, and WOB. In the inspiratory limb, the patient needs to generate less negative pressure to initiate inspiration because of lower autopositive end-expiratory pressure. Inspiratory muscles are further unloaded by inspiratory positive airway pressure (IPAP) throughout inspiration for the given tidal volume. Both expiratory and inspiratory WOB are thus reduced by application of noninvasive positive pressure ventilation. *(From Sarnaik AA, Sarnaik AP: Noninvasive ventilation in pediatric status asthmaticus: Sound physiologic rationale but is it really safe, effective, and cost-efficient?* Pediatr Crit Care Med *13:484–485, 2012.)*

Endotracheal Intubation and Mechanical Ventilation

When hypoxemia or significant hypoventilation persists despite the interventions already described, tracheal intubation and mechanical ventilation are indicated. Additional indications for intubation include maintaining airway patency in patients who have the potential for airway compromise, such as those with actual or potential neurologic deterioration, and in patients with hemodynamic instability.

Proper monitoring is essential to ensuring a safe and successful tracheal intubation. Pulse oximetry, heart rate, and blood pressure monitoring are mandatory and should be forgone only in situations calling for emergency intubation. All necessary equipment, including bag-mask ventilation device, laryngoscope, tracheal tube with stylet, and suction equipment, must be available and working properly prior to initiation of intubation. The proper internal diameter (ID) for the tracheal tube can be estimated using the following formula:

$$ID = (Age\,[yr]/4) + 4$$

Table 71-9 provides average values for age, size, and depth of insertion for tracheal tubes. Preoxygenation of the patient with high fractions of inspired oxygen is essential and will allow maximum procedure time prior to the onset of hypoxemia.

Although intubation can be accomplished without sedation and pharmacologic paralysis in selected patients, the physiologic benefits of these measures to the patient as well as to the facilitation of the intubation usually far outweigh the risks; sedation and paralysis should be considered standard unless contraindicated. Administration of a sedative and analgesic followed by a paralytic agent is a common pharmacologic regimen for facilitating intubation. The particular type and dose of each agent often depends on the underlying disease and clinician preference. Table 71-10 lists commonly used agents. An alternative to this pharmacologic approach, especially when intubation is urgent or the patient is suspected of having a full stomach, increasing the risk of aspiration, is rapid sequence intubation (see Chapter 67).

Once adequate sedation and/or paralysis have been achieved, ventilation should be assisted with a bag-mask device. After optimal

Table 71-9 Average Size and Depth Dimensions for Tracheal Tubes

PATIENT AGE	INTERNAL DIAMETER (mm)	OROTRACHEAL DEPTH (cm)	NASOTRACHEAL DEPTH (cm)
Premature	2.0-3.0	8-9	9-10
Full-term neonate	3.0-3.5	10	11
6 mo	4.0	11	13
12-24 mo	4.5	13-14	16-17
4 yr	5.0	15	17-18
6 yr	5.5	17	19-20
8 yr	6.0	19	21-22
10 yr	6.5	20	22-23
12 yr	7.0	21	23-24
14 yr	7.5	22	24-25
Adult	8.0-9.0	23-25	25-28

Table 71-10 Medications Commonly Used for Intubation

	DRUG	DOSE	ONSET (min)	DURATION (min)	COMMENTS
Sedatives/anesthetics	Midazolam	0.1 mg/kg IV	3-5	60-120	Amnesia Respiratory depression
	Lorazepam	0.1 mg/kg IV	3-5	120-240	Amnesia Respiratory depression
	Ketamine	1-2 mg/kg IV 4-6 mg/kg IM	2-3	10-15	↑ HR, BP, and ICP Bronchodilation
	Propofol	1-3 mg/kg IV	0.5-2	10-15	↓ BP Apnea
	Thiopental	4-7 mg/kg IV	0.5-1	5-10	↓ BP Apnea
Analgesics	Fentanyl	2-5 µg/kg IV	3-5	30-90	Respiratory depression Chest wall rigidity
	Morphine	0.1 mg/kg IV	5-15	120-240	↓ BP Respiratory depression
Neuromuscular blocking agents	Vecuronium	0.1 mg/kg IV	2-3	30-75	↑ HR Renal elimination
	Rocuronium	0.6-1.2 mg/kg IV 1 mg/kg IM	5-15	15-60	↑ HR Renal elimination
	Cisatracurium	0.1 mg/kg IV	2-3	25-30	Histamine release Nonrenal elimination

BP, blood pressure; HR, heart rate; ICP, intracranial pressure; IM, intramuscularly; IV, intravenously.

preoxygenation, intubation can be performed. The clinician uses his/her dominant hand to open the patient's mouth and inserts the laryngoscope blade gently along the tongue to its base. The airway opening can be visualized by applying lift up and away from the clinician, along the axis of the laryngoscope handle. If a straight (Miller) laryngoscope blade is used, the epiglottis is lifted anteriorly by the tip of the blade to visualize the glottis. If a curved (Macintosh) blade is used, the tip should be advanced into the vallecula and then lifted to visualize the glottis. Secretions often obscure visualizations at this step and should be suctioned clear. Once clear visualization of the vocal cords is accomplished, the tube can be placed through the cords. Rapid confirmation of tube placement is essential and should be assessed by as many of the following steps as possible: Auscultation of both lung fields as well as the epigastrium for equal breath sounds and good air movement and evaluation of the abdomen for increasing distention should be performed. Adequate bilateral chest expansion and misting inside the tracheal tube with each breath are suggestive of proper tube placement. An increasing heart rate, if heart rate has decreased during the attempt, and a rising or normal pulse oximetry reading are suggestive of successful tube placement. Preoxygenation may significantly delay a drop in Spo_2 with improper tube placement, leading to a significant delay in its recognition. Confirmation of exhaled CO_2 is mandatory. It can be accomplished with use of a disposable colorimetric CO_2 detector or with capnography. In situations of very low pulmonary perfusion, such as cardiac arrest, exhaled CO_2 may not be detected. A chest radiograph should also be obtained to confirm proper placement of the tracheal tube, which should lie roughly halfway between the glottis and the carina (see Chapter 62).

Transient Manual Ventilation in the Immediate Preintubation and Postintubation Periods

Establishment of ventilation via bag and mask or bag and tracheal tube is required prior to transport of the patient to a setting of continued critical care. The technique of manual ventilation should take into account the underlying pathology. Ventilation of patients with diseases characterized by low FRC (pneumonia, pulmonary edema, ARDS, etc.) should include the application of positive end-expiratory pressure (PEEP) to prevent alveolar derecruitment. This can be accomplished with use of a PEEP valve on a self-inflating ventilation bag or by careful manipulation of exhaust gas using an anesthesia bag. Such diseases are also characterized by a short time constant and therefore are best managed with relatively small tidal volumes and high ventilation rates. Diseases characterized by airway obstruction have prolonged time constants and are therefore best managed with relatively slow rates and high tidal volumes.

Bibliography is available at Expert Consult.

71.1 Mechanical Ventilation

Ashok P. Sarnaik and Christopher Mastropietro

The decision to institute mechanical ventilation is based mainly on the need to assist lung function; supporting left ventricular performance and treating intracranial hypertension are additional indications. Although there are no absolute criteria for derangement of gas exchange, Pao_2 <60 torr while breathing >60% oxygen, $Paco_2$ >60 torr, and pH <7.25 are often reasons to initiate mechanical ventilation. Clinical impressions of fatigue and impending exhaustion are also indications for ventilatory support even in the presence of adequate gas exchange. Positive-pressure ventilation is a powerful means of decreasing left ventricular afterload, and it is used for this purpose in patients with cardiogenic shock resulting from left ventricular dysfunction. Mechanical ventilation is also used in patients whose respirations are unreliable (e.g., unconscious patients, those with neuromuscular dysfunction) and when deliberate hyperventilation is desired, such as in patients with intracranial hypertension.

Mechanical ventilation neither is intended to normalize gas exchange nor is a form of cure. The goals are to maintain sufficient oxygenation and ventilation to ensure tissue viability until the disease process has resolved and to minimize the inevitable complications of the therapeutic intervention itself. Pao_2, $Paco_2$, and pH levels are maintained in ranges that provide a safe environment for the patient while protecting the lungs from damage due to oxygen toxicity, pressure (barotrauma), tidal volume overdistention (volutrauma), atelectrauma, and cytokine release (biotrauma) (Figs. 71-3 and 71-4).

BASIC CONCEPTS OF VENTILATOR MANAGEMENT

Equation of Motion

A pressure gradient is required for air to move from one place to another (Fig. 71-5). During natural spontaneous ventilation, inspiration results from generation of negative intrapleural pressure from

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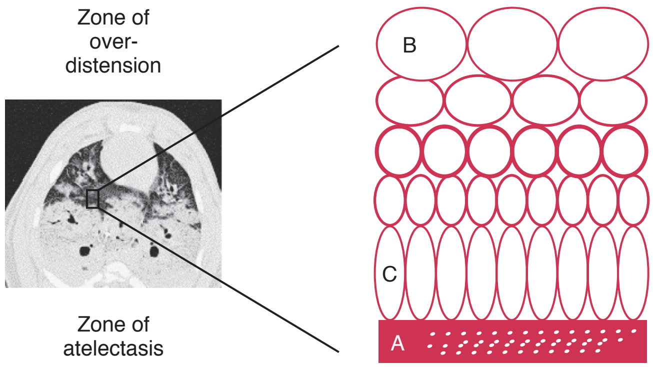

Figure 71-3 **Atelectrauma.** The interface between collapsed and consolidated lung *(A)* and overdistended lung units *(B)* is heterogeneous and unstable. Depending on ambient conditions, this region is prone to cyclic recruitment and derecruitment and localized asymmetric stretch of lung units *(C)* immediately apposed to regions of collapsed lung. *(From Pinhu L, Whitehead T, Evans T, et al: Ventilator-associated lung injury,* Lancet *361:332–340, 2003.)*

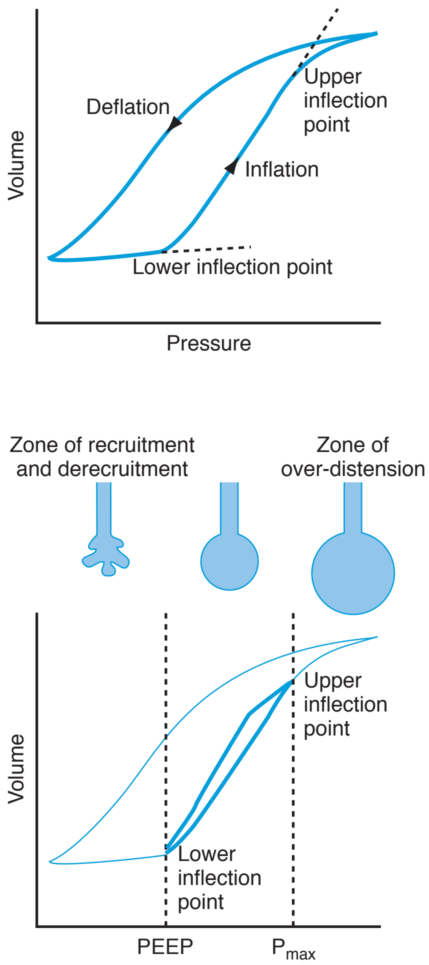

Figure 71-4 **Pulmonary pressure-volume relation in a patient with acute lung injury.** *Top,* The lower inflection point is typically 12-18 cm H_2O, and the upper inflection point 26-32 cm H_2O. *Bottom,* Specific protective ventilation strategies require that positive end-expiratory pressure is set just above the lower inflection point and the pressure limit (P_{max}) just below the upper inflection point. Hence the lung is ventilated in the safe zone between the zone of recruitment and derecruitment and the zone of overdistention, and both high-volume and low-volume injury are avoided. *(From Pinhu L, Whitehead T, Evans T, et al: Ventilator-associated lung injury,* Lancet *361:332–340, 2003.)*

1. Pressure gradient is required to move air from one place to another
2. Movement of air is opposed by flow-resistive and elastic properties of the system

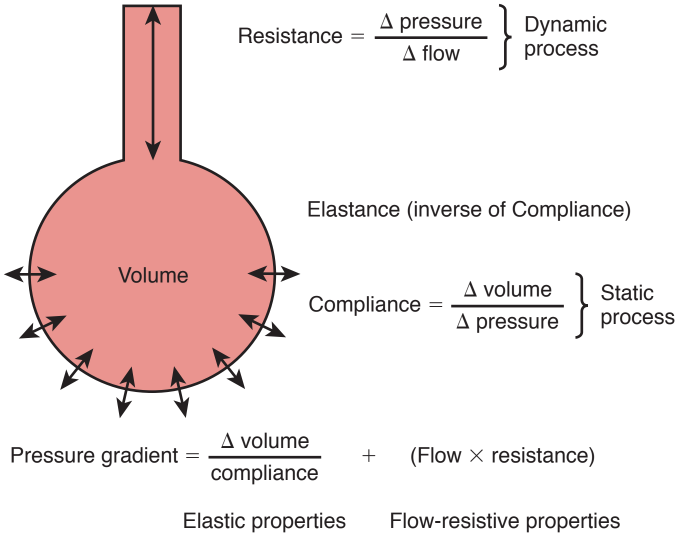

Figure 71-5 **Equation of motion.** A pressure gradient is required to move air from one place to another. In the lungs, the required pressure gradient must overcome the lung and chest wall elastance (static component) and the flow-resistive properties (dynamic component). The static component is increased in alveolar interstitial diseases and stiff chest wall, whereas the dynamic component is increased with airway obstruction.

contraction of the diaphragm and intercostal muscles, drawing air from the atmosphere across the airways into the alveoli. During mechanical ventilation, inspiration results from positive pressure created by compressed gases through the ventilator, which pushes air across the airways into alveoli. In both spontaneous and mechanical ventilation, exhalation results from alveolar pressure generated by the elastic recoil of the lung and the chest wall. Pressure necessary to move a given amount of air into the lung is determined by 2 factors: lung and chest wall elastance, and airway resistance. Figure 71-5 describes the relationship among pressure gradient, compliance, and resistance. *Elastance*—defined as the change in pressure (ΔP) divided by the change in volume (ΔV)—refers to the property of a substance to oppose deformation. It is opposite of *compliance* (ΔV ÷ ΔP), the property of a substance to allow distention or lengthening when subjected to pressure. Compliance (C) is therefore expressed as 1/elastance.

The pressure needed to overcome tissue elastance is measured in conditions in which there is no flow (at end-inspiration and end-expiration) and is therefore a reflection of static conditions in the lung. It is influenced by tidal volume and compliance (P = ΔV ÷ C). It is increased with high tidal volume and low compliance. This pressure gradient is used to calculate the static compliance of the respiratory system (C_{STAT}).

Resistance (R) refers to the opposition to generation of flow. It is measured as the amount of pressure needed to generate a unit of flow (ΔP ÷ ΔFlow). Pressure needed to overcome airway resistance is calculated as flow multiplied by resistance. Because this pressure is needed only when the flow is occurring through the airways, it is referred to as the *dynamic component*. Pressure to overcome flow-resistive properties is measured when there is maximum flow and is therefore under dynamic conditions. It is increased in conditions with greater airway resistance and flow rate. Flow rate depends on the time allowed for inspiration and expiration. At higher respiratory rates, there is less time available for each inspiration and expiration, necessitating higher flows; therefore higher pressure is required to overcome flow-resistive properties. The pressure gradient necessary to move air from one place to another is the sum of pressure needed to overcome the elastic and flow-resistive properties of the lung. This pressure gradient is taken into

account to calculate the dynamic compliance of the respiratory system (C_{DYN}). The difference in change in pressure between static conditions and dynamic conditions is attributable to airway resistance.

Functional Residual Capacity

Also see Chapter 373.

During inspiration, oxygen-enriched gas enters alveoli. During exhalation, oxygen continues to be removed by the pulmonary capillary circulation. *FRC* is the volume of gas left in the alveoli at the end of expiration. It is the only source of gas available for gas exchange during exhalation. In diseases with decreased FRC (e.g., ARDS, pulmonary edema), alveolar oxygen concentration declines sharply throughout expiration, resulting in hypoxemia. Two ventilator strategies commonly employed to improve oxygenation in such situations are the application of PEEP and increasing the inspiratory time (Tɪ) (Fig. 71-6). PEEP increases FRC, whereas a longer Tɪ allows longer exposure of pulmonary capillary blood to a higher concentration of O_2 during inspiration.

Time Constant

At the beginning of inspiration, the atmospheric pressure is higher than the pressure in the alveoli, resulting in movement of air into the

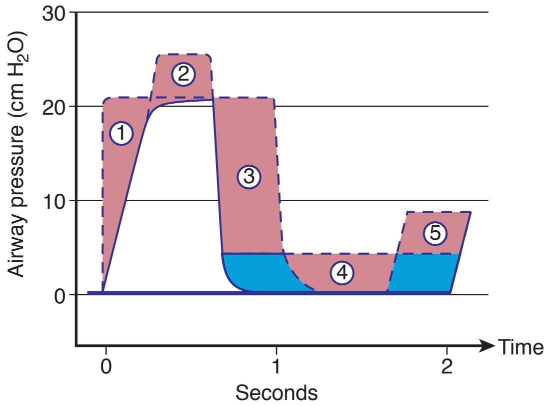

Figure 71-6 Five different ways to increase mean airway pressure: *(1)* Increase the respiratory flow rate, producing a square wave inspiratory pattern; *(2)* increase the peak inspiratory pressure; *(3)* reverse the inspiratory-expiratory ratio or prolong the inspiratory time without changing the rate; *(4)* increase positive end-expiratory pressure; and *(5)* increase the ventilatory rate by reducing the expiratory time without changing the inspiratory time. *(From Harris TR, Wood BR: Physiologic principles. In Goldsmith JP, Karotkin EH, editors:* Assisted ventilation of the neonate, *ed 3. Philadelphia, 1996, WB Saunders.)*

alveoli. During mechanical ventilation, the ventilator circuit serves as the patient's atmosphere. As alveoli expand with air, the alveolar pressure rises throughout inspiration until it equilibrates with the ventilator pressure, at which time airflow ceases. Expiration starts when the ventilator pressure falls below the alveolar pressure. Alveolar pressure decreases throughout expiration until it reaches the ventilator pressure, at which time no further egress of air from the alveoli occurs. If inspiration or expiration is terminated before pressure equilibration between alveoli and the ventilator is allowed to occur, alveolar expansion during inspiration or alveolar emptying during expiration is incomplete. Incomplete inspiration results in delivery of decreased tidal volume, whereas incomplete expiration is associated with air trapping and the presence of residual PEEP in the alveoli that is greater than the ventilator pressure, referred to as *auto-PEEP*. Some time is required for pressure equilibration to occur between alveoli and the atmosphere, which is reflected in the *time constant* (TC). It takes 3 TCs for 95%, and 5 TCs for 99%, of pressure equilibration to occur. The TC depends on compliance and resistance, and their relationship is depicted in Figure 71-7. TC is calculated as compliance multiplied by resistance ($C \times R$) and is measured in seconds.

Diseases with decreased compliance (increased elastance) are characterized by high elastic recoil pressure, which results in more rapid equilibration of alveolar and ventilator pressures, thereby decreasing TC. Diseases with increased airway resistance are associated with slower flow rates, require longer time for movement of air from one place to another, and therefore have increased TC. Airways expand during inspiration and narrow during expiration (see Chapter 373). Therefore, expiratory time constant (TCᴇ) is longer than inspiratory time constant (TCɪ). In intrathoracic airway obstruction (asthma, bronchiolitis, aspiration syndromes), airway narrowing is much more pronounced during expiration. Therefore, although both TCᴇ and TCɪ are prolonged in such diseases, TCᴇ is much more prolonged than TCɪ. Patients with such diseases therefore are best ventilated with slower rates, higher tidal volume, and longer expiratory time than inspiratory time. In diseases characterized by decreased compliance, both TCᴇ and TCɪ are short; however, the TCᴇ is closer to TCɪ than in normal lungs because of the stiffer alveoli recoil with greater force. Patients with these diseases are best ventilated with small Vᴛ to prevent ventilator-induced lung injury and with a relatively longer inspiratory time in each breath to improve oxygenation.

Critical Opening Pressure

Collapsed or atelectatic alveoli require a considerable amount of pressure to open. Once open, the alveoli require relatively less pressure for continued expansion. The process of opening atelectatic alveoli is called *recruitment*. In a normal lung, alveoli remain open at the end of expiration, and therefore the lung requires relatively less pressure to receive its tidal volume. In a disease process in which the alveoli

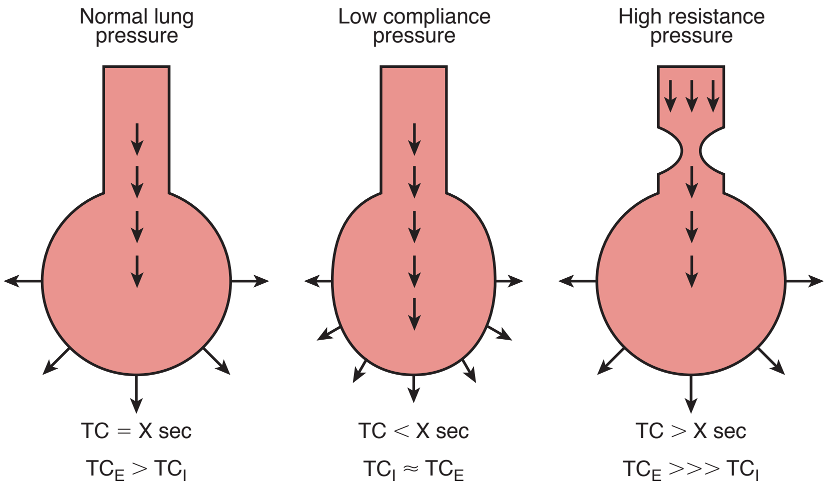

Figure 71-7 Time constant (TC). A certain amount of time is necessary for pressure equilibration (and therefore completion of delivery of gas) to occur between proximal airway and alveoli. TC, a reflection of time required for pressure equilibration, is a product of compliance and resistance. In diseases of decreased lung compliance, less time is needed for pressure equilibration to occur, whereas in diseases of increased airway resistance, more time is required. Expiratory TC is increased much more than inspiratory TC in obstructive airway diseases, because airway narrowing is exaggerated during expiration.

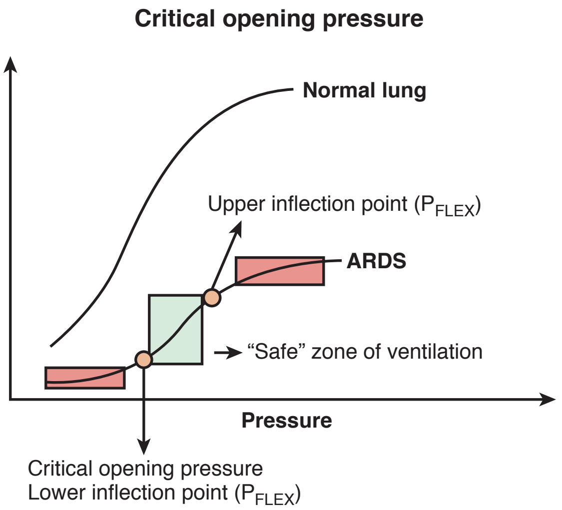

Figure 71-8 **Volume-pressure relationship in normal lung and in ARDS.** In ARDS, atelectatic alveoli require a considerable amount of pressure to open. Critical opening pressure, also referred to as lower P_{FLEX}, is the airway pressure above which further alveolar expansion occurs with relatively less pressure. Upper P_{FLEX} is the airway pressure above which further increase in pressure results in less alveolar expansion; this is the area of alveolar overdistention. Keeping tidal volume between upper and lower P_{FLEX} values is considered less injurious to the lung.

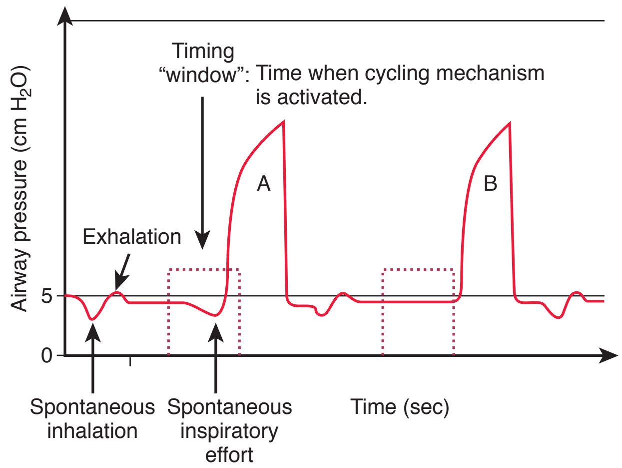

Figure 71-9 **Synchronized intermittent mandatory ventilation.** At set intervals, the ventilator's timing circuit becomes activated and a timing "window" appears *(dotted line area).* If the patient initiates a breath in the timing window, the ventilator delivers a mandatory breath. If no spontaneous effort occurs, the ventilator delivers a mandatory breath at a fixed time after the timing window. *(From Banner MJ, Gallagher TJ: Respiratory failure in the adult: ventilatory support. In Kirby RR, Smith RA, Desautels DA, editors:* Mechanical ventilation, *New York, 1985, Churchill Livingstone.)*

collapse at the end of expiration (e.g., ARDS), a substantial amount of pressure is required to open the alveoli during inspiration. This pressure causes ventilator-induced lung injury via 2 mechanisms: (1) barotrauma at the terminal airway–alveolar junction and (2) volutrauma as a result of overdistention of alveoli that are already open (see Figs. 71-3 and 71-4). Although a pulmonary parenchymal disease process is rarely uniform, and each of the millions of alveoli may have its own mechanical characteristics, a composite volume-pressure relationship could be conceptualized for the whole lung (Fig. 71-8).

In these situations, the lower and upper portions of the curve are relatively horizontal, and the middle portion is more vertical. At the beginning of inspiration, atelectatic alveoli are being recruited, requiring high pressure for a relatively small increase in volume. Once they are recruited, further increase in volume requires relatively less pressure. The pressure at which most alveoli are open is called *critical opening pressure*; this point is also referred to as the *lower inflection point* (lower P_{FLEX}). After the lower P_{FLEX}, greater volume can be delivered for relatively less pressure until the upper P_{FLEX} is reached, at which the volume-pressure curve again becomes relatively horizontal. The goal of mechanical ventilation in alveolar interstitial pathology is to deliver a tidal volume between the lower and upper inflection points, the so-called safe zone of ventilation. If V_T is delivered with a change in inflation pressure that includes the lower P_{FLEX}, alveoli are likely to open *and* close during every breath, a process termed *tidal recruitment* that is injurious to the lung, especially at the terminal airway–alveolar junction. If V_T is delivered with a change of pressure that includes the upper P_{FLEX}, overdistention of alveoli is likely to occur, resulting in volutrauma and barotrauma. Keeping tidal ventilation between the upper and lower P_{FLEX} values is accomplished by maintaining a level of PEEP to produce baseline alveolar recruitment and delivering a relatively small (6 mL/kg) V_T. Termed "open lung" strategy, this approach has proved to be beneficial in alveolar interstitial diseases such as ARDS.

PHASES OF MECHANICAL VENTILATION

The planning of a ventilatory strategy must consider the four phases of the respiratory cycle separately, taking into account these patient clinical characteristics: (1) initiation of respiration and a variable that is controlled, often referred to as *mode;* (2) inspiratory phase characteristics, which determine the duration of inspiration and how the pressure or volume is delivered; (3) termination of inspiration, often referred to as *cycle;* and (4) expiratory phase characteristics. Ideally, mechanical ventilation should not completely take over the work of breathing but, rather, should assist the patient's own respiratory effort. In the absence of the patient's effort, respiratory muscle deconditioning may occur, making weaning from mechanical ventilation more difficult.

Initiation of Inspiration and the Control Variable (Mode)

The initiation of inspiration may be set to occur at a predetermined rate and interval regardless of patient effort, or it could be timed in response to patient effort. Once inspiration is initiated, the ventilator breath either is controlled entirely by the ventilator (control mode) or supports the patient's inspiratory effort to a predetermined inspiratory volume or pressure target (support mode). Advances in technology allow for greater patient–ventilator synchrony to occur. The ventilator may be set to be "triggered" by the signal it receives as a result of patient effort. This may be in the form of lowering of either pressure (pressure trigger) or airflow (flow trigger) in the ventilator circuit generated by the patient's inspiratory effort. If no such signal is received because of lack of patient effort, the ventilator delivers a breath at an interval selected by the operator.

Control Modes

Intermittent Mandatory Ventilation Mode

In intermittent mandatory ventilation (IMV), the inspiration is initiated at a set frequency with a timing mechanism independent of patient effort. In between machine-delivered breaths, the patient can breathe spontaneously from a fresh source of gas. IMV allows for adjustment of ventilator support according to the patient's needs, making it useful in the weaning process. Lack of synchrony between machine-delivered breaths and patient efforts may result in ineffective ventilation and patient discomfort, especially when IMV is delivered at a high rate. In such cases, the patient may require sedation and pharmacologic paralysis for efficient delivery of tidal volume. To obviate this problem, *synchronized IMV (SIMV)* is used, whereby the machine-delivered breaths are triggered by the patient's inspiratory efforts (Fig. 71-9). In between the machine-delivered breaths, a fresh source of gas is available for spontaneous patient breaths. In the

absence of patient effort, the patient receives a backup rate much like in IMV mode. Even with SIMV, ventilator–patient asynchrony can occur, because VT, inflation pressure, and inspiratory time are determined by the ventilator alone.

Assist-Control Mode

In assist-control (AC) mode, each and every patient breath is triggered by pressure or flow generated by patient inspiratory effort and "assisted" with either preselected inspiratory pressure or volume. The rate of respirations is therefore determined by the patient's inherent rate. A backup total (patient and ventilator) obligatory rate is set to deliver a minimum number of breaths. On AC mode with a backup rate of 20 breaths/min, all of the breaths of a patient with an inherent respiratory rate of 15 breaths/min will be assisted by the ventilator, and the patient will receive 5 additional breaths/min. On the other hand, a patient with an inherent rate of 25 breaths/min will receive all 25 breaths assisted. Although useful in some patients, the AC mode cannot be used in the weaning process, which involves gradual decrease in ventilator support.

Control Variable

Once initiated, either the tidal volume or the pressure delivered by the machine can be controlled. The machine-delivered breath is thus referred to as either volume-controlled or pressure-controlled (Table 71-11).

With *volume-controlled ventilation* (VCV), machine-delivered volume is the primary control, and the inflation pressure generated depends on the respiratory system's compliance and resistance. Changes in respiratory system compliance and resistance are therefore easily detected from changes observed in inflation pressure. In *pressure-controlled ventilation* (PCV), the pressure change above the baseline is the primary control, and the tidal volume delivered to the lungs depends on the respiratory system's compliance and resistance. Changes in respiratory system compliance and resistance do not affect inflation pressure and may therefore go undetected unless the exhaled VT is monitored. VCV and PCV have their own advantages and disadvantages (see Table 71-11). Generally speaking, PCV is more efficient than VCV in terms of amount of tidal volume delivered for a given inflation pressure during ventilation of a lung that has nonuniform time constants, such as asthma. In VCV, relatively less-obstructed airways are likely to receive more of the machine-delivered volume throughout inspiration than relatively more-obstructed airways with longer time constants (Fig. 71-10*A*). This situation would result in uneven ventilation, higher PIP, and a decrease in dynamic compliance. In PCV, because of a constant inflation pressure that is held throughout inspiration, relatively less-obstructed lung units with shorter time constants would achieve pressure equilibration earlier during inspiration than the relatively more-obstructed areas. Thus, units with shorter TCs would attain their final volume earlier in inspiration, and those with longer TCs would continue to receive additional volume later in inspiration (Fig. 71-10*B*). This situation would result in more even distribution of inspired gas, delivery of more VT for the same inflation pressure, and improved dynamic compliance in comparison with VCV.

Pressure-regulated volume control (PRVC) combines the advantages of VCV and PCV. In this mode, the VT and TI are controlled as primary variables but the ventilator determines the amount of pressure needed to deliver the desired VT. Inflation pressure is thus adjusted to deliver the prescribed VT over the TI, depending on the patient's respiratory compliance and resistance.

Support Modes

Pressure-support ventilation (PSV) and *volume-support ventilation* (VSV) are designed to support the patient's spontaneous respirations. With PSV, initiation of inspiration is triggered by the patient's spontaneous breath, which is then "supported" by a rapid rise in ventilator pressure to a preselected level. The inspiration is continued until the inspiratory flow rate falls to a set level (generally 25% of peak flow rate) as the patient's lungs fill up. Thus, TI is controlled by the patient's own efforts. PSV can be combined with SIMV so that any breath above the SIMV rate is supported by PSV. Allowing the patient to control as much of the rate, VT, and inspiratory time as possible is considered a gentler form of mechanical ventilation than SIMV, in which the VT (or inflation pressure) and TI are preset. PSV as the sole source of mechanical ventilator support is often not adequate for patients with severe lung disease; however, it is especially useful in patients in the process of being weaned and in patients who require mechanical ventilation for relatively minor lung disease or for neuromuscular weakness. VSV is similar to PSV, in that all the spontaneous breaths are supported. In VSV, inspiratory pressure to support spontaneous breaths is adjusted to guarantee a preset VT. If there is a change in respiratory mechanics or patient effort, the inspiratory pressure to support the breath initiated by patient effort is automatically adjusted to deliver the set VT.

Inspiratory Phase Characteristics

TI, inspiratory flow waveform, and pressure rise time can be adjusted in the inspiratory phase to suit the patient's respiratory mechanics.

In PCV, the duration of TI is directly set in seconds. In VCV, the inspiratory time can be adjusted by adjusting the inspiratory flow (volume/time). The choice of TI value depends on the respiratory rate, which determines the total duration of each breath, and on the estimation of inspiratory and expiratory time constants. Decreasing the flow rate delivery increases TI, and vice versa. With an increase in TI, the pulmonary capillary blood is exposed to a higher level of alveolar P_{O_2} for a longer time. This is beneficial in diseases with decreased FRC, such as ARDS and pulmonary edema. An increase in TI also increases

Table 71-11 Characteristics of Pressure-Controlled and Volume-Controlled Methods of Ventilation

	PRESSURE-CONTROLLED VENTILATION	VOLUME-CONTROLLED VENTILATION
Control setting(s)	Inflation pressure Inspiratory time Rise time	VT Flow rate Inspiratory flow pattern (constant vs decelerating)
Machine-delivered volume	Depends on respiratory system compliance and resistance	Constant
Inflation pressure	Constant	Depends on respiratory system compliance and resistance
Endotracheal tube leak	Somewhat compensated	Leaked volume part of VT
Distribution of ventilation	More uniform in lungs with varying time constant units	Less uniform in lungs with varying time constant units
Patient comfort	Possibly compromised	Possibly enhanced
Weaning	Inflation pressure adjustment required to deliver desired VT	VT remains constant, inflation pressure automatically weaned

VT, tidal volume.

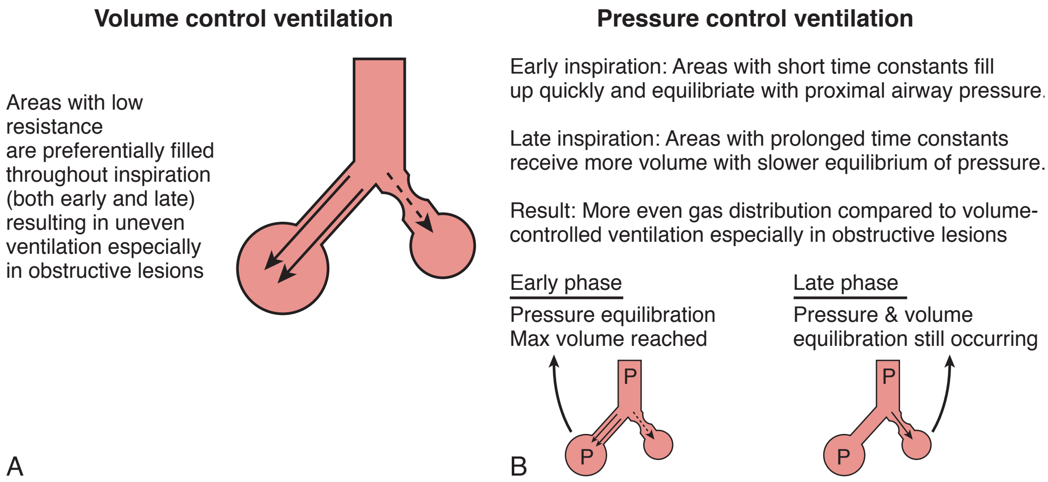

Figure 71-10 *A,* In VCV, VT is delivered to the less-obstructed areas throughout inspiration. Obstructed areas of the lung therefore receive a lower proportion of VT, resulting in uneven ventilation. *B,* In PCV, less-obstructed areas equilibrate with inflation pressure and therefore receive most of their VT early during inspiration. More-obstructed areas, with prolonged time constants, require longer time for pressure equilibration and therefore continue to receive a portion of their VT later during inspiration. The entire VT is more evenly distributed than with volume-cycled ventilation.

VT without increasing inflation pressure in PCV if inspiratory flow is still occurring at the end of expiration. It must be recognized that at a given ventilator rate, an increase in TI decreases expiratory time (TE). Therefore, any strategy that employs an increase in the inspiratory component of the respiratory cycle should ensure that the decreased TE is still sufficient for complete exhalation.

Inspiratory flow waveform can be adjusted in VCV mode as either a constant flow (square waveform) or a decelerating flow (descending ramp waveform). With a square waveform, flow is held constant throughout inspiration. In a descending ramp waveform, the flow is maximum at the start of inspiration and declines throughout its duration. It is debatable which flow pattern is better for a given disease. In PCV and PSV, the prescribed PIP is reached through delivery of airflow. The time required for the ventilator to reach PIP is reflected in the *pressure rise time,* which can be adjusted by control of flow at the beginning of the inspiratory phase. The inspiratory flow rise time is adjusted to provide comfort for a patient who is awake and also to prevent an extremely rapid rise in inspiratory pressure, which might result in barotrauma.

Termination of Inspiration (Cycle)

The two most commonly used inspiratory terminating mechanisms in control modes are time-cycled and volume-cycled. With a time-cycled mechanical breath, inspiration is terminated after a preselected TI has elapsed, whereas with volume-cycled breath, the inspiration ends after a preselected volume has been delivered by the machine into the ventilator circuit. A time-cycled breath is almost always pressure-limited, with the PIP held constant for the duration of inspiration. A volume-cycled breath can be pressure-limited as a safety mechanism to avoid barotrauma. The inspiration-terminating mechanism is set somewhat differently in support modes. In PSV, the inspiration is set to end after the inspiratory flow decreases below a certain percentage (usually 25%) of peak inspiratory flow. This happens when the patient no longer desires to receive additional VT. Such a breath can be termed *flow-cycled*. In volume support mode, inspiration is terminated when the patient has received the desired VT.

Expiratory Phase Maneuvers

The most useful expiratory phase maneuver is the application of PEEP, which is applied to both the control breath and the assisted breath. The most important clinical benefits of PEEP are to recruit atelectatic alveoli and to increase FRC in patients with alveolar–interstitial diseases and thereby improve oxygenation. There is growing recognition that even a brief disconnection from a ventilator, and therefore having zero end-expiratory pressure, can result in significant alveolar derecruitment and decline in oxygenation. In patients with obstructive lesions in which insufficient exhalation results in air trapping and auto-PEEP, extrinsic PEEP (that applied through a mechanical device) can prevent airway closure during expiration and improve ventilation. Other salutary effects of PEEP include redistribution of extravascular lung water away from gas-exchanging areas, improved ventilation–perfusion relationship, and stabilization of the chest wall. The effect of PEEP on lung compliance is variable, depending on the level of PEEP provided and the patient's pulmonary mechanics. By shifting the VT ventilation to a more favorable part of the pressure-volume curve, PEEP may recruit more alveoli, delay airway closure, and improve lung compliance. Excessive PEEP, on the other hand, may lead to overdistention of alveoli and reduced compliance. The effect of PEEP in individual patients can be ascertained by measuring exhaled VT and calculating dynamic compliance. Other deleterious effects of PEEP include decreased venous return, increased pulmonary vascular resistance, and decreased cardiac output.

ADDITIONAL VENTILATORY MODALITIES

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) improves oxygenation in cases of severe hypoxemic respiratory failure resulting from alveolar-interstitial disease. This modality applies a CPAP, designated $CPAP_{HIGH}$, to recruit and maintain FRC with brief intermittent release phases of $CPAP_{LOW}$ to allow alveolar gas to escape. $CPAP_{HIGH}$ is analogous to PIP, and $CPAP_{LOW}$ is similar to setting PEEP. In contrast to the patient receiving conventional mechanical ventilation, a patient receiving APRV spends the majority of time in the $CPAP_{HIGH}$ phase, which may last as long as 3-5 sec with a brief (0.3-0.5 sec) time in the $CPAP_{LOW}$ phase. These atypically long inspiratory times are tolerated because of a floating expiratory valve in the ventilator circuit that permits spontaneous breathing during $CPAP_{HIGH}$ phase. Therefore, even if $CPAP_{HIGH}$ phase can be considered inspiratory and $CPAP_{LOW}$ phase can be considered expiratory as far as the ventilator is concerned, the patient is able to breathe spontaneously during both of these phases. The longer ventilator inspiratory times recruit lung units, and the ability to breathe spontaneously during this phase allows distribution of gas flow to atelectatic lung regions. The outcome benefit of APRV in pediatric hypoxemic respiratory failure has not been proven.

High-Frequency Ventilation

Mechanical ventilation at supraphysiologic rates and low tidal volumes, known as high-frequency ventilation (HFV), improves gas

exchange in a selected group of patients who show no response to traditional ventilatory modalities. The mechanism of alveolar ventilation in HFV is very different from that in conventional ventilation, in that HFV is less dependent on VT and more dependent on asymmetric velocities and convective dispersion of inspired gas. Patients with severe persistent hypoxic failure are most likely to benefit from HFV. HFV is also helpful in patients with bronchopleural fistula and persistent air leaks. The main tenet of HFV is to recruit lung volume with a high MAP and produce smaller fluctuations in alveolar pressure during inspiration and expiration, thus maintaining a satisfactory FRC and reducing alveolar stretch. The 2 most investigated techniques of HFV are high-frequency oscillation (HFO) and high-frequency jet ventilation (HFJV).

The most commonly used HFV modality is HFO, which employs a mechanism to generate to-and-fro air movement. Additional air is dragged in (entrained) through a parallel circuit via a Venturi effect. Air is pushed in during inspiration and actively sucked out during expiration. The main determinants of oxygenation are FIO_2 and MAP, whereas ventilation is determined by changes in pressure (amplitude) from the MAP. Commonly used respiratory frequency varies from 5 Hz (300 breaths/min) in adults and older children, to 6-8 Hz (360-480 breaths/min) in young children, 8-10 Hz (480-600 breaths/min) in infants, and 10-12 Hz (600-720 breaths/min) in newborn and premature babies.

In HFJV, a high-frequency interrupter is interposed between a high-pressure gas source and a small cannula that is incorporated in the endotracheal tube (ET). The cannula propels tiny amounts of gas (jets) at high velocity and high frequency through the ET. An additional amount of gas is entrained from a parallel circuit. Unlike in HFO, expiration occurs passively in HFJV as a result of elastic recoil of the lung and the chest wall. PEEP is set through the parallel circuit by a conventional ventilator in line. Respiratory rate is generally set at 420 breaths/min. Major determinants of oxygenation are FIO_2 and PEEP, and the major determinant of ventilation is PIP.

CONVENTIONAL VENTILATOR SETTINGS

FIO_2

The shape of the hemoglobin–oxygen dissociation curve dictates that oxygen content in the blood is not linearly related to PaO_2. A PaO_2 value that results in an oxyhemoglobin saturation of 95% is reasonable in most situations, because a higher PaO_2 would cause minimal increase in arterial oxygen content, and a modest (≈10 torr) drop in PaO_2 would result in minimal decrease in oxyhemoglobin saturation. In most cases, a PaO_2 value of 70-75 torr is a reasonable goal. FIO_2 values that are higher than those necessary to attain oxyhemoglobin saturations of 95% expose the patient to unnecessary oxygen toxicity. Whenever possible, FIO_2 values should be decreased to a level ≤0.4 as long as oxyhemoglobin saturation remains 95% or above.

Mode

The choice of mode of ventilation depends on how much ventilator–patient interaction is desired and the disease entity that is being treated. SIMV or AC is chosen as the control mode, PCV, VCV, or PRVC is chosen as the variable that is to be controlled, and pressure support and volume support are the choices for support modes.

Tidal Volume and Rate

As previously discussed, alveolar ventilation, the chief determinant of $PaCO_2$, is calculated using VT, respiratory rate, and dead space volume. A change in VT results in a corresponding change in VA without affecting the dead space ventilation. A change in respiratory rate will affect the VA as well as the dead space ventilation. As mentioned earlier, the choice of VT and rate depends on the time constant. In a patient with relatively normal lungs, an age-appropriate ventilator rate and a VT of 7-10 mL/kg would be appropriate initial settings. Diseases associated with decreased time constants (decreased static compliance, e.g., ARDS, pneumonia, pulmonary edema) are best treated with small (6 mL/kg) VT and relatively rapid rates (25-40 breaths/min). Diseases associated with prolonged TCs (increased airway resistance, e.g., asthma, bronchiolitis) are best treated with relatively slow rates and higher (10-12 mL/kg) VT. In PCV, the delivered VT depends on the compliance and resistance of the patient's respiratory system and needs to be monitored to ensure the appropriate amount for a given situation. An inflation pressure of 15-25 cm H_2O is sufficient for most patients, but it may need adjustment, depending on the amount of exhaled VT observed. It should be emphasized that achieving a "normal" $PaCO_2$ value is not a goal of mechanical ventilation. Mild hypercapnia (permissive hypercapnia) should be acceptable, especially when one is attempting to limit injurious inflation pressures or VTs.

Inspiratory Time and Expiratory Time

Inspiratory time and expiratory time are adjusted by setting inspiratory flow rate in VCV and by setting the precise TI in PCV. Increasing the inspiratory time results in an increase in MAP, improvement in oxygenation in diseases with decreased FRC, and better distribution of VT in obstructive lung disease. Sufficient expiratory time must be provided to ensure adequate emptying of the alveoli.

Positive End-Expiratory Pressure

The best level of PEEP depends on the disease entity that is being treated, and it may change in the same patient from time to time. Decisions are often based on the PaO_2/FIO_2 ratio and the measurement of dynamic compliance.

PATIENT-VENTILATOR ASYNCHRONY

Patient–ventilator asynchrony occurs when the patient's respiratory pattern does not match that of the ventilator. This can occur during all phases of respiration. Adverse effects of patient- ventilator asynchrony include wasted effort, ineffective delivery of desired VT, excessive generation of intrathoracic pressure resulting in barotrauma and adverse effects on cardiac output, increased work of breathing, and patient discomfort. Although several mechanisms exist to facilitate patient–ventilator asynchrony, a certain amount of asynchrony is inevitable unless the patient is pharmacologically sedated and paralyzed.

Triggering the Ventilator

The patient must be able to trigger the ventilator without excessive effort. Ventilators can be pressure-triggered or flow-triggered. With pressure triggering, the inspiratory valve opens and flow is delivered when a set negative pressure is generated within the patient–ventilator circuit during both inspiration and expiration. The amount of pressure required to trigger an inspiration depends on the pressure trigger sensitivity. In flow triggering, the ventilator provides a base flow of gas through the ventilator–patient circuit. When a flow sensor on the expiratory limb of the patient–ventilator circuit detects a decrease in flow as a result of the patient's inspiratory effort, the inspiratory valve opens and a ventilator breath is delivered. The degree of change in flow required to trigger an inspiration depends on the flow trigger sensitivity. Flow triggering is considered to be more comfortable, primarily because the patient receives some flow prior to triggering the ventilator, in contrast to pressure triggering, in which no flow is provided until the ventilator breath is triggered. Increasing the trigger sensitivity by decreasing the change in either pressure or flow needed to trigger an inspiration decreases the work of breathing. However, reducing the required pressure or flow excessively could result in accidental triggering and unwanted breaths by turbulence caused by condensation in the ventilator circuit, ET leaks, or cardiac oscillations.

Selection of Appropriate Inspiratory Time

The duration of TI should match the patient's own inspiratory phase. If TI is too long, the patient's drive to exhale may begin before the ventilator breath has cycled off. When this occurs, exhalation occurs against inspiratory flow and a closed exhalation valve, resulting in increased work of breathing, excessive rise in intrathoracic pressure, and discomfort. If TI is too short, the patient may be still inhaling without respirator support. In general terms, TI is usually initiated at 0.5-0.7 sec for neonates, 0.8-1 sec in older children, and 1-1.2 sec for adolescents and adults. Adjustments need to be made through

individual patient observations and according to the type of lung disease present. In patients with severe lung disease (both obstructive and restrictive), unnatural TI and TE values may have to be selected, as discussed earlier. In such situations, adequate analgesia, sedation, and, in extreme cases, neuromuscular blockade may be needed.

Selection of Inspiratory Flow Pattern

In VCV, inappropriate flow may be another source of patient–ventilator dyssynchrony. After initiation of inspiration, if the set amount of flow is inadequate to meet patient demand, a state of "flow starvation" occurs, resulting in excessive work of breathing and discomfort. Such cases may require a decelerating inspiratory flow pattern, in which a higher flow is provided in the beginning of inspiration and less toward the end as the lungs fill up. On the other hand, such a pattern may be uncomfortable for a patient who desires more gradual alveolar filling. The selection of inspiratory flow pattern should be based on the individual patient's respiratory mechanics. In PCV and PSV, the inspiratory rise time determines the manner in which the airway pressure is raised and VT delivered. Considerations for choosing the appropriate rise time in PCV and PSV are similar to those for choosing the inspiratory flow pattern in VCV.

Use of Support Modes

As much as possible, a conscious patient should be allowed to have spontaneous breaths that are supported by either PSV or VSV. This approach minimizes the mandatory breaths generated by the ventilator that are beyond the patient's control to modulate. Therefore, continued assessments should be made to determine whether the patient is able to maintain ventilatory requirements more in support modes and less in control modes.

Use of Sedation and Pharmacologic Paralysis

Having a conscious but comfortable patient is a desirable goal during mechanical ventilation. Spontaneous breaths with good muscle tone and presence of cough are important for adequate clearance of tracheobronchial secretions. The patient's ability to indicate distress is also important in identifying and preventing potential injurious factors. In certain situations, management of patient–ventilator asynchrony assumes far greater importance when the asynchrony is causing unacceptable derangement of gas exchange and ventilator-induced lung injury. Both alveolar interstitial lung pathology and obstructive airway diseases may necessitate unnatural and uncomfortable settings for respiratory rate, TI, and inflation pressures. In such situations, deep sedation is often necessary. Benzodiazepines and opiates are the agents most commonly used for this purpose. In extreme situations, pharmacologic paralysis with a nondepolarizing agent, such as vecuronium, is required to abolish any patient effort and respiratory muscle tone. When pharmacologic paralysis is used, deep sedation must be ensured so that the patient does not sense pain and discomfort. Pharmacologic sedation and paralysis can ensure total control of the patient's ventilation by mechanical means and may result in lifesaving improvement in gas exchange with reduction in inflation pressures. However, long-term use of such agents may be associated with undesirable consequences and higher morbidity. The risk of inadequate tracheobronchial secretions and atelectasis is potentially greater. Long-term use of pharmacologic sedation may be associated with chemical dependency and withdrawal manifestations, and prolonged neuromuscular blockade is associated with neuromyopathy in critically ill patients. The benefits of sedation and pharmacologic paralysis therefore should be carefully balanced with the risks, and periodic assessments should be made to determine the need for their continuation.

Cardiopulmonary Interactions

Mechanical ventilation can have both salutary as well as adverse effects on cardiac performance. By decreasing oxygen consumption necessary for work of breathing, oxygen supply to vital organs is improved. Positive-pressure breathing decreases left ventricular afterload, thus enhancing stroke volume and cardiac output in patients with failing myocardium (e.g., myocarditis). On the other hand, the decreased systemic venous return may further compromise stroke volume in hypovolemic patients. Such patients will require intravascular fluid loading. Also an increase in pulmonary vascular resistance (PVR) as a result of positive intrathoracic pressure may result in further decompensation of a poorly performing right ventricle. PVR is at its lowest value at an optimum FRC. When FRC is too low or too high, PVR (and therefore the right ventricular afterload) is increased. Both desirable and undesirable effects of cardiopulmonary interactions may coexist and require ongoing assessment and necessary interventions.

MONITORING RESPIRATORY MECHANICS

Exhaled Tidal Volume

Exhaled tidal volume (VTE) is measured by a pneumotachometer in the ventilator circuit during exhalation. In VCV, part of the machine-delivered volume may leak out during inspiration and therefore never reach the patient. Measurement of VTE more accurately describes the VT that is contributing to the patient's alveolar ventilation. In PCV, the VTE depends on the patient's respiratory system compliance and resistance, and therefore offers valuable diagnostic clues. A decrease in VTE during PCV is indicative of either decrease in compliance or increase in resistance and is helpful in directing the clinician to appropriate investigation and management. An increase in VTE is indicative of improvement and may require weaning of inflation pressures to adjust the VTE.

Peak Inspiratory Pressure

In VCV and PRVC, the PIP is the secondary variable determined by the patient's respiratory system compliance and resistance. An increase in PIP in these modes is indicative of decreased compliance (e.g., atelectasis, pulmonary edema, pneumothorax) or increased resistance (e.g., bronchospasm, obstructed ET). During VCV and PRVC, decreasing the respiratory rate or prolonging the TI will result in a lower PIP in patients with prolonged time constants because more time will be available for alveoli to fill. In such patients, a decrease in PIP suggests increased compliance or decreased resistance of the respiratory system.

Respiratory System Dynamic Compliance and Static Compliance

The changes in PIP during VCV and PRVC, and in VTE during PCV, are determined by C_{DYN} of the respiratory system (lung and chest wall). Dynamic compliance is calculated as follows:

$$C_{DYN} = V_{TE} \div (PIP - PEEP)$$

It takes into account both the flow-resistive and the elastic properties of the respiratory system. Changes in C_{DYN} can be used to assess effects of different levels of PEEP as tidal ventilation is shifted along the slope of the volume-pressure curve (see Fig. 71-8). An increase in PEEP in alveolar-interstitial diseases (increased elastance), resulting in an increase in C_{DYN} suggests alveolar recruitment, whereas a decrease in C_{DYN} may indicate overdistention. Similarly, in obstructive diseases (increased resistance), adjustment in PEEP levels to ameliorate airway collapse during exhalation can be guided by monitoring C_{DYN}. To assess only the elastic recoil of the lung, measurement of C_{STAT} when there is no airflow is required. This measurement is performed by using an inspiratory hold maneuver with the patient under neuromuscular blockade and observing pressure-time and flow-time waveforms (Fig. 71-11). During this maneuver, inspiratory flow ceases while the expiratory valve continues to remain closed, thus allowing pressure to equilibrate throughout the ventilator circuit and the patient's lungs. This pressure, referred to as the *plateau pressure* (P_{plat}), is reflective of alveolar pressure. C_{STAT} is calculated as follows:

$$C_{STAT} = V_{TE} \div (P_{plat} - PEEP)$$

The difference between C_{DYN} and C_{STAT} is attributable to airway resistance. This difference is minimal in alveolar-interstitial diseases but substantial in airway obstruction.

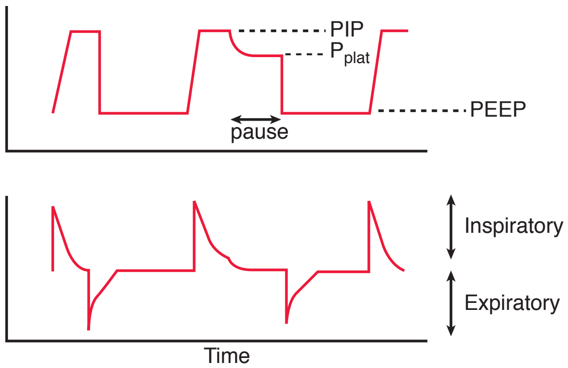

Figure 71-11 Alveolar pressure is best determined by measurement of plateau pressure (P_{plat}). Inspiration is paused for an extended period, and alveolar gas pressure is allowed to equilibrate with the ventilator circuit pressure. Airway pressure at the end of the inspiratory pause is P_{plat}. The difference between peak inspiratory pressure (PIP) and P_{plat} is to overcome flow-resistive properties of the lung, whereas P_{plat} reflects the pressure needed to overcome elastic properties of lung and chest wall.

Assessment of Auto-PEEP

Auto-PEEP is assessed with the use of an expiratory pause maneuver in which inspiration is delayed and alveolar pressure is allowed to equilibrate with the airway. In diseases with airway obstruction, insufficient alveolar emptying may occur if exhalation time is not adequate. The alveolar pressure in excess of the set PEEP at the completion of the expiratory pause is measured as auto-PEEP or intrinsic PEEP. Auto-PEEP can have adverse effects on ventilation and hemodynamic status. It can be managed by decreasing the respiratory rate or inspiratory time and thus allowing greater time for exhalation. Auto-PEEP may also be managed by increasing the set PEEP ("extrinsic" PEEP), thereby delaying airway closure during exhalation and improving alveolar emptying.

Assessment of Dead Space Ventilation

Positive pressure ventilation and application of PEEP may result in a decrease in venous return, cardiac output, and, therefore, also the pulmonary perfusion. Ventilation of poorly perfused alveoli results in dead space ventilation, which does not contribute to gas exchange. The dead space–V_T fraction can be calculated with the following equation:

$$V_D/V_T = (PaCO_2 - PECO_2) \div PaCO_2$$

Normal V_D/V_T is 0.33. Increased V_D/V_T is indicative of poorly perfused alveoli. Patients with increased V_D/V_T may require intravascular volume infusion or other means of augmenting the cardiac output to improve pulmonary perfusion. The V_D/V_T fraction is calculated and displayed by commercially available capnographs, which measure endotracheal P_{CO_2} continuously.

VENTILATOR-INDUCED LUNG INJURY

Like most medical therapies, mechanical ventilation can be harmful if appropriate principles are not followed. Lung volumes that are too high or too low should be avoided. In attempting to recruit and maintain FRC, the clinician must be careful not to overdistend alveoli. Excessive PIP and V_T can lead to unwelcome stress and strain on alveolar walls. This volutrauma and barotrauma can lead to disruption of tight junctions between alveolar epithelial and capillary endothelial cells, causing fluid and protein transudation in the alveoli. Inflammatory mediators and cytokines are released, exacerbating the injury and promoting exudative fluid formation. Decreased production and inactivation of surfactant result in atelectasis and further impairment of gas exchange. Evidence shows that in patients with severe acute hypoxemic respiratory failure, avoidance of $V_T \geq 10$ mL/kg and $P_{plat} \geq 30$ cm H_2O limits diffuse alveolar damage.

Insufficient PEEP is another important mechanism of ventilator-induced lung injury. Alveoli that are recruited during inspiration must remain open during expiration; if they do not, atelectrauma occurs, which is defined as undesirable shear stress on alveolar walls as they are opened and closed repeatedly. Therefore, the ideal PEEP for a patient should maximize the number of open alveoli and minimize the number of overdistended alveoli. Careful adjustments of PEEP may also permit the clinician to wean a patient from a high inspired oxygen concentration, another potential source of lung injury (oxytrauma). Though most patients receive an inspired oxygen concentration of 100% during endotracheal intubation and at the beginning of mechanical ventilation, increasing PEEP to recruit alveoli without overdistention should be quickly instituted to improve oxygenation and permit weaning of the F_{IO_2}. Although an F_{IO_2} value below which there is no risk of oxygen toxicity is unknown, most clinicians aim for a value <0.6.

Ventilator-Associated Pneumonia

The pathophysiology of ventilator-associated pneumonia (VAP) is multifactorial. Aspiration of oral and/or gastric secretions, colonization of ETs, and suppression of cough reflexes with sedation all play a role. New-onset fever and leukocytosis accompanied by demonstration of an infiltrative process by chest radiographs are consistent with a diagnosis of VAP. This complication can lead to worsened gas exchange, increased duration of ventilation, and even death. Elevation of the head of the bed to 30 degrees after initiation of mechanical ventilation and use of a protocol for oral decontamination during mechanical ventilation are two means of reducing the risk for VAP. The most effective strategy to minimize any of the aforementioned complications is regular assessment of extubation readiness and liberation from mechanical ventilation as soon as clinically possible.

Weaning

Weaning from mechanical ventilation should be considered as a patient's respiratory insufficiency begins to improve. Most pediatricians favor gradual weaning from ventilator support. With SIMV, the ventilator rate is slowly reduced, allowing the patient's spontaneous breaths (typically assisted with pressure or volume support) to assume a larger proportion of the minute ventilation. When the ventilator rate is low (<5 breaths/min) such that its contribution to minute ventilation is minimal, assessment of extubation readiness is performed. An alternative method of gradual weaning is transition to a pressure support mode of ventilation. In this mode, no ventilator rate is set, allowing all triggered breaths to be assisted with pressure support. The clinician reduces the pressure support slowly to a low value (<5-10 cm H_2O), at which point assessment of extubation readiness is performed. During either technique, weaning should be halted if tachypnea, increased work of breathing, hypoxemia, hypercapnia, acidosis, diaphoresis, tachycardia, or hypotension occurs.

The most objective means of assessing extubation readiness is a spontaneous breathing trial (SBT). Prior to performance of an SBT, a patient should be awake with intact airway reflexes, capable of handling oropharyngeal secretions, and with stable hemodynamic status. In addition, gas exchange should be adequate, defined as a Pa_{O_2} >60 mm Hg while receiving an F_{IO_2} <0.4 and PEEP ≤5 cm H_2O. If these criteria are present, a patient should be started on CPAP with minimal or no pressure support (≤5 cm H_2O). If this SBT is tolerated with no episodes of respiratory or cardiovascular decompensation, successful extubation is likely. Some neonates and small children cannot be calmed or consoled long enough to complete the SBT. In this situation, extubation readiness must be assessed on a low level of ventilator support. Data suggest that there is a low risk of extubation failure if the patient is comfortable and has stable hemodynamic status with adequate gas exchange and spontaneous V_T >6.5 mL/kg while receiving <20% of total minute ventilation from the ventilator. Certain patient populations are at increased risk for extubation failure, such as young infants, children mechanically ventilated for >7 days, and patients with chronic respiratory or neurologic conditions. These children often benefit from transition to a noninvasive form of positive pressure ventilation (e.g., high-flow nasal cannula, CPAP, or BiPAP)

delivered via nasal prongs or face mask to increase the odds of successful extubation. The likelihood of postextubation upper airway obstruction, the most common cause of extubation failure in children, cannot be predicted on the basis of an SBT result or bedside measurements of physiologic variables. Traumatic endotracheal intubation and subglottic swelling from the ET irritation, especially in patients who exhibit agitation while receiving mechanical ventilation, are common causes of airway narrowing after extubation. Administration of intravenous corticosteroids (dexamethasone 0.5 mg/kg every 6 hr for 4 doses prior to extubation) has been shown to minimize the incidence of postextubation airway obstruction. In patients in whom postextubation airway obstruction develops, the need for re-intubation may be obviated by administration of nebulized racemic epinephrine and heliox.

Bibliography is available at Expert Consult.

71.2 Long-Term Mechanical Ventilation

See Chapter 418.

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Chapter 72

Acute Care of the Victim of Multiple Trauma

Cindy Ganis Roskind, Peter S. Dayan, and Bruce L. Klein

EPIDEMIOLOGY

Injury is a leading cause of death and disability in children throughout the world (see Chapter 5.1). According to the World Health Organization report on child injury prevention, unintentional injuries are one of the leading causes of death in children younger than 20 yr and the leading cause of death in children between 10 and 20 yr of age in the world. Road traffic–related injuries, drowning, fire-related events, and falls rank among the top causes of death and disability in children. In Asia, injury accounts for more than 50% of deaths in children <18 yr, with drowning accounting for approximately half. In the United States, more than 12,000 children die each year secondary to unintentional injury, with motor vehicle–related injuries being the leading cause.

Deaths represent only a small fraction of the total trauma burden. Approximately 9.2 million children are treated in U.S. emergency departments (EDs) each year for injury, most commonly for falls. Many survivors of trauma have permanent or temporary functional limitations. Motor vehicle–related injuries and falls rank among the top 15 causes of disability-adjusted life years in children worldwide.

Trauma is frequently classified according to the number of significantly injured body parts (≥1), the severity of injury (mild, moderate, or severe), and the mechanism of injury (blunt or penetrating). In childhood, blunt trauma predominates, accounting for the majority of injuries. In adolescence, penetrating trauma increases in frequency, accounting for approximately 15% of injuries, and has a higher case fatality rate.

REGIONALIZATION AND TRAUMA TEAMS

Mortality and morbidity rates have decreased in geographic regions with comprehensive, coordinated trauma systems. Treatment at designated trauma centers is associated with decreased mortality. At the scene of injury, paramedics should administer necessary advanced life support and perform triage (Fig. 72-1; Tables 72-1 and 72-2). It is usually preferable to bypass local hospitals and rapidly transport a seriously injured child directly to a pediatric trauma center (or a trauma center with pediatric commitment). Children have lower mortality rates after severe blunt trauma when they are treated in designated pediatric trauma centers or in hospitals with pediatric intensive care units.

Table 72-1	Changes in 2011 Guidelines for Field Triage of Injured Patients Compared with 2006 Guidelines

Step One: Physiologic Criteria
- Changed GCS <14 to GCS ≤13
- Added "or need for ventilatory support" to respiratory criteria

Step Two: Anatomic Criteria
- Changed "all penetrating injuries to head, neck, torso and extremities proximal to elbow and knee" to "all penetrating injuries to head, neck, torso and extremities proximal to elbow or knee"
- Changed "flail chest" to "chest wall instability or deformity (e.g., flail chest)"
- Changed "crushed, degloved, or mangled extremity" to "crushed, degloved, mangled, or pulseless extremity"
- Changed "amputation proximal to wrist and ankle" to "amputation proximal to wrist or ankle"

Step Three: Mechanism-of-Injury Criteria
- Added "including roof" to intrusion criterion

Step Four: Special Considerations
- Added the following to older adult criteria
  - SBP <110 might represent shock after age 65 yr
  - Low-impact mechanisms (e.g., ground-level falls) might result in severe injury
- Added "patients with head injury are at high risk for rapid deterioration" to anticoagulation and bleeding disorders criterion
- Removed "end-stage renal disease requiring dialysis" and "time-sensitive extremity injury"

Transition Boxes
- Changed layout of the figure
- Modified specific language of the transition boxes

GCS, Glasgow Coma Scale; SBP, systolic blood pressure.

From Sasser SM, Hunt RC, Faul M, et al: Guidelines for field triage of injured patients: Recommendations of the National Expert Panel on Field Triage, 2011. MMWR Recomm Rep *61(RR-1):1-20, 2012 (Box 2, p. 8).*

Table 72-2	Children Requiring Pediatric Trauma Center Care

- Patients with serious injury to >1 organ or system
- Patients with 1-system injury who require critical care or monitoring in an intensive care unit
- Patients with signs of shock who require >1 transfusion
- Patients with fracture complicated by suspected neurovascular or compartment injury
- Patients with fracture of the axial skeleton
- Patients with ≥2 long-bone fractures
- Patients with potential replantation of an extremity
- Patients with suspected or actual spinal cord or column injury
- Patients with head injury with any 1 of the following:
  - Orbital or facial bone fracture
  - Cerebrospinal fluid leak
  - Altered state of consciousness
  - Changing neurologic signs
  - Open-head injury
  - Depressed skull fracture
  - Requiring intracranial pressure monitoring
  - Patients suspected of requiring ventilator support

Modified from Krug SE: The acutely ill or injured child. In Behrman RE, Kliegman RM, editors: Nelson essentials of pediatrics, *ed 4, Philadelphia, 2002, WB Saunders, p. 96.*

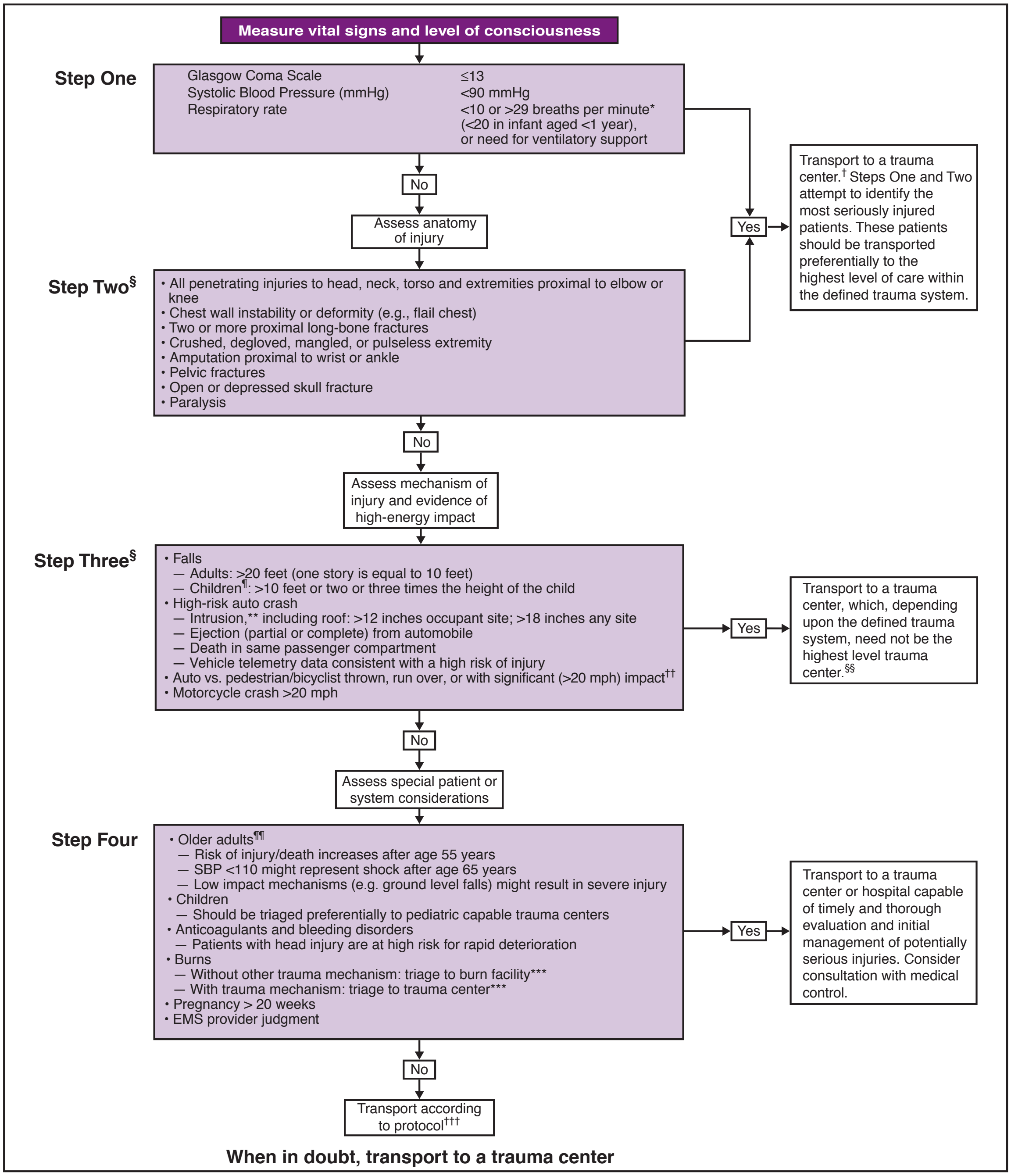

* The upper limit of respiratory rate in infants is >29 breaths per minute to maintain a higher level of overtriage for infants.

† Trauma centers are designated Level I-IV. A Level I center has the greatest amount of resources and personnel for care of the injured patient and provides regional leadership in education, research, and prevention programs. A Level II facility offers similar resources to a Level I facility, possibly differing only in continuous availability of certain subspecialties or sufficient prevention, education, and research activities for Level I designation; Level II facilities are not required to be resident or fellow education centers. A Level III center is capable of assessment, resuscitation, and emergency surgery, with severely injured patients being transferred to a Level I or II facility. A Level IV trauma center is capable of providing 24-hour physician coverage, resuscitation, and stabilization to injured patients before transfer to a facility that provides a higher level of trauma care.

§ Any injury noted in Step Two or mechanism identified in Step Three triggers a "yes" response.

¶ Age <15 years.

** Intrusion refers to interior compartment intrusion, as opposed to deformation which refers to exterior damage.

†† Includes pedestrians or bicyclists thrown or run over by a motor vehicle or those with estimated impact >20 mph with a motor vehicle.

§§ Local or regional protocols should be used to determine the most appropriate level of trauma center within the defined trauma system; need not be the highest-level trauma center.

¶¶ Age >55 years.

*** Patients with both burns and concomitant trauma for whom the burn injury poses the greatest risk for morbidity and mortality should be transferred to a burn center. If the nonburn trauma presents a greater immediate risk, the patient may be stabilized in a trauma center and then transferred to a burn center.

††† Patients who do not meet any of the triage criteria in Steps One through Four should be transported to the most appropriate medical facility as outlined in local EMS protocols.

Figure 72-1 Guidelines for Field Triage of Injured Patients—United States, 2011. *(From Guidelines for Field Triage of Injured Patients: recommendations of the National Expert Panel on Field Triage. MMWR 61:6, 2012.)*

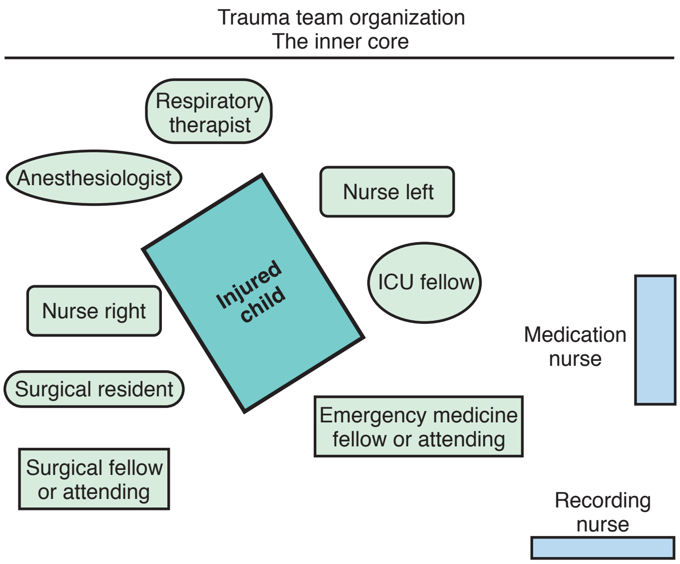

Figure 72-2 Members of the inner core of the trauma team at Children's National Medical Center (Washington, DC). Members of the outer core include a nursing administrator, a social worker, a radiology technician, a transport technician, and a security officer. ICU, intensive care unit.

Table 72-3 Pediatric Trauma Score

	CATEGORY		
Component	+2	+1	–1
Size	≥20 kg	10-12 kg	<10 kg
Airway	Normal	Maintainable	Unmaintainable
Systolic BP	≤90 mm Hg	90-50 mm Hg	<50 mm Hg
CNS	Awake	Obtunded/LOC	Coma/decerebrate
Open wound	None	Minor	Major/penetrating
Skeletal	None	Closed fracture	Open/multiple fractures
Sum total points			

Children with a Pediatric Trauma Score ≤6 are at increased risk of mortality as well as morbidity.

From Tepas JJ, Mollitt DL, Talbert JL, et al: The pediatric trauma score as a predictor of injury severity in the injured child. J Pediatr Surg *22:14–18, 1987, Table 1, p. 15.*

When the receiving ED is notified before the child's arrival, the trauma team should also be mobilized in advance. Each member has defined tasks. A senior surgeon (surgical coordinator) or, sometimes initially, an emergency physician leads the team. Team compositions vary somewhat from hospital to hospital; Figure 72-2 shows the model used at Children's National Medical Center (Washington, DC). Consultants, especially neurosurgeons and orthopedic surgeons, must be promptly available; the operating room staff should be alerted.

Physiologic status, anatomic locations, and/or mechanism of injury are used for field triage as well as to determine whether to activate the trauma team. More importance should be placed on physiologic compromise and less on mechanism of injury. Scoring scales such as the Abbreviated Injury Scale (AIS), Injury Severity Score (ISS), Pediatric Trauma Score (Table 72-3), and Revised Trauma Score use these parameters to predict patient outcome. The AIS and ISS are used together. First, the AIS is used to numerically score injuries—as 1 minor, 2 moderate, 3 serious, 4 severe, 5 critical, or 6 probably lethal—in each of 6 ISS body regions: head/neck, face, thorax, abdomen, extremity, and external. The ISS is the sum of the squares of the highest 3 AIS region scores.

PRIMARY SURVEY

During the primary survey, the physician quickly assesses and treats any life-threatening injuries. The principal causes of death shortly after trauma are airway obstruction, respiratory insufficiency, shock from hemorrhage, and central nervous system injury. The primary survey addresses the ABCDEs: Airway, Breathing, Circulation, neurologic Deficit, and Exposure of the patient and control of the Environment.

Airway/Cervical Spine

Optimizing oxygenation and ventilation, while protecting the cervical spine from potential further injury is of paramount importance. Initially, cervical spine injury should be suspected in any child sustaining multiple, blunt trauma. Children are at risk for such injuries because of their relatively large heads, which augment flexion–extension forces, and weak neck muscles, which predispose them to ligament injuries. To prevent additional spinal injury, the current standard is to immobilize the cervical (and thoracic and lumbar) spine in neutral position with a stiff collar, head blocks, tape or cloth placed across the forehead, torso, and thighs to restrain the child, and a rigid backboard.

Airway obstruction manifests as snoring, gurgling, hoarseness, stridor, and/or diminished breath sounds (even with apparently good respiratory effort). Children are more likely than adults to have airway obstruction because of their smaller oral and nasal cavities, proportionately larger tongues and greater amounts of tonsillar and adenoidal tissue, higher and more anterior glottic openings, and narrower larynxes and tracheas. Obstruction is common in patients with severe head injuries, owing in part to decreased muscle tone, which allows the tongue to fall posteriorly and occlude the airway. With trauma, obstruction can also result from fractures of the mandible or facial bones, secretions such as blood or vomitus, crush injuries of the larynx or trachea, or foreign body aspiration.

If it is necessary to open the airway, a jaw thrust **without head tilt** is recommended. This procedure minimizes cervical spine motion. In an unconscious child, an oropharyngeal airway can be inserted to prevent posterior displacement of the mandibular tissues. A semiconscious child will gag with an oropharyngeal airway but may tolerate a nasopharyngeal airway. *A nasopharyngeal airway is contraindicated when there is a possibility of a cribriform plate fracture*. If these maneuvers plus suctioning do not clear the airway, oral endotracheal intubation is indicated. When endotracheal intubation proves difficult, a laryngeal mask airway can be used as a temporary alternative. A laryngeal mask airway consists of a tube with an inflatable cuff that rests above the larynx and thus does not require placement of the tube into the trachea. Emergency cricothyrotomy is needed in <1% of trauma victims.

Breathing

The physician assesses breathing by counting the respiratory rate; visualizing chest wall motion for symmetry, expansion, and accessory muscle use; and auscultating breath sounds in both axillae. Continuous wave form capnography monitoring may also be used as an adjunct; however it is less reliable in patients with shock. In addition to looking visually for cyanosis, pulse oximetry is standard. If ventilation is inadequate, bag-valve-mask ventilation with 100% oxygen must be initiated immediately, followed by endotracheal intubation. End-expiratory carbon dioxide (CO_2) detectors help verify accurate tube placement.

Head trauma is the most common cause of respiratory insufficiency. An unconscious child with a severe head injury may have a variety of breathing abnormalities, including Cheyne-Stokes respirations, slow irregular breaths, and apnea.

Although less common than a pulmonary contusion, tension pneumothorax and massive hemothorax are immediately life-threatening (Tables 72-4 and 72-5). **Tension pneumothorax** occurs when air accumulates under pressure in the pleural space. The adjacent lung is compacted, the mediastinum is pushed toward the opposite hemithorax, and the heart, great vessels, and contralateral lung are compressed or

Table 72-4 Life-Threatening Chest Injuries

TENSION PNEUMOTHORAX
One-way valve leak from the lung parenchyma or tracheobronchial tree
Collapse with mediastinal and tracheal shift to the side opposite the leak
Compromises venous return and decreases ventilation of the other lung
Clinically, manifests as respiratory distress, unilateral absence of breath sounds, tracheal deviation, distended neck veins, tympany to percussion of the involved side, and cyanosis
Relieve first with needle aspiration, then with chest tube drainage
OPEN PNEUMOTHORAX (SUCKING CHEST WOUND)
Effect on ventilation depends on size
MAJOR FLAIL CHEST
Usually caused by blunt injury resulting in multiple rib fractures
Loss of bone stability of the thoracic cage
Major disruption of synchronous chest wall motion
Mechanical ventilation and positive end-expiratory pressure required
MASSIVE HEMOTHORAX
Must be drained with a large-bore tube
Initiate drainage only with concurrent vascular volume replacement
CARDIAC TAMPONADE
Beck Triad:
1. Decreased or muffled heart sounds
2. Distended neck veins from increased venous pressure
3. Hypotension with pulsus paradoxus (decreased pulse pressure during inspiration)
Must be drained

Modified from Krug SE: The acutely ill or injured child. In Behrman RE, Kliegman RM, editors: Nelson essentials of pediatrics, *ed 4, Philadelphia, 2002, WB Saunders, p. 97.*

kinked (see Chapter 411). Both ventilation and cardiac output are impaired. Characteristic findings include cyanosis, tachypnea, retractions, asymmetric chest rise, contralateral tracheal deviation, diminished breath sounds on the ipsilateral (more than contralateral) side, and signs of shock. Needle thoracentesis, followed by thoracostomy tube insertion, is diagnostic and lifesaving. **Hemothorax** results from injury to the intercostal vessels, lungs, heart, or great vessels. When ventilation is adequate, fluid resuscitation should begin before evacuation, because a large amount of blood may drain through the chest tube, resulting in shock.

Circulation

The most common type of shock in trauma is hypovolemic shock caused by hemorrhage. Signs of shock include tachycardia; weak pulse; delayed capillary refill; cool, mottled, pale skin; and altered mental status (see Chapter 70). Early in shock, blood pressure remains normal because of compensatory increases in heart rate and peripheral vascular resistance (Table 72-6). Some individuals can lose up to 30% of blood volume before blood pressure declines. *It is important to note that 25% of blood volume equals 20 mL/kg, which is only 200 mL in a 10 kg child.* Losses >40% of blood volume cause severe hypotension that, if prolonged, may become irreversible. Direct pressure should be applied to control external hemorrhage. Blind clamping of bleeding vessels, which risks damaging adjacent structures, is not advisable.

Cannulating a larger vein, such as an antecubital vein, is usually the quickest way to achieve intravenous access. A short, large-bore catheter offers less resistance to flow, allowing for more rapid fluid administration. Ideally, a second catheter should be placed within the first few minutes of resuscitation in a severely injured child. If intravenous access is crucial and not rapidly obtainable, an intraosseous catheter should be inserted; all medications and fluids can be administered intraosseously. Other alternatives are central venous access using the Seldinger technique (e.g., in the femoral vein) and, rarely, surgical

Table 72-5 Differential Diagnosis of Immediately Life-Threatening Cardiopulmonary Injuries

	TENSION PNEUMOTHORAX	MASSIVE HEMOTHORAX	CARDIAC TAMPONADE
Breath sounds	Ipsilaterally decreased more than contralaterally	Ipsilaterally decreased	Normal
Percussion note	Hyperresonant	Dull	Normal
Tracheal location	Contralaterally shifted	Midline or shifted	Midline
Neck veins	Distended	Flat	Distended
Heart tones	Normal	Normal	Muffled

Modified from Cooper A, Foltin GL: Thoracic trauma. In Barkin RM, editor: Pediatric emergency medicine, *ed 2, St. Louis, 1997, Mosby, p. 325.*

Table 72-6 Systemic Responses to Blood Loss in Pediatric Patients

SYSTEM	MILD BLOOD LOSS (<30%)	MODERATE BLOOD LOSS (30-45%)	SEVERE BLOOD LOSS (>45%)
Cardiovascular	Increased heart rate; weak, thready peripheral pulses; normal systolic blood pressure; normal pulse pressure	Markedly increased heart rate; weak, thready central pulses; peripheral pulses absent; low normal systolic blood pressure	Tachycardia followed by bradycardia; central pulses very weak or absent; peripheral pulses absent; hypotension; diastolic blood pressure may be undetectable
Central nervous system	Anxiety; irritability; confusion	Lethargy; dulled response to pain	Coma
Skin	Cool, mottled; capillary refill prolonged	Cyanotic; capillary refill markedly prolonged	Pale and cold
Urine output	Low to very low	Minimal	None

Adapted from American College of Surgeons Committee on Trauma: Advanced trauma life support for doctors: student course manual, *Chicago, 2008, American College of Surgeons, p. 234.*

cutdown (e.g., in the saphenous vein). Ultrasonography can facilitate central venous catheter placement.

Aggressive, intravenous fluid resuscitation is essential early in shock to prevent further deterioration. Isotonic crystalloid solution, such as lactated Ringer injection or normal saline (20 mL/kg), should be infused rapidly. No consensus exists to support the routine use of colloid or hypertonic saline solution for shock (see Chapter 70). When necessary, repeated crystalloid boluses should be given. Most children are stabilized with administration of crystalloid solution alone. However, if the patient remains in shock after boluses totaling 40-60 mL/kg of crystalloid, then 10-15 mL/kg of cross-matched, packed red blood cells should be transfused. Although less desirable, type-specific or O-negative cells can be substituted pending availability of cross-matched blood. When shock persists despite these measures, surgery to stop internal hemorrhage is usually indicated.

Neurologic Deficit

Neurologic status is briefly assessed by determining the level of consciousness and evaluating pupil size and reactivity. The level of consciousness can be classified using the mnemonic AVPU: Alert, responsive to Verbal commands, responsive to Painful stimuli, or Unresponsive.

Head injuries account for at least 75% of pediatric blunt trauma deaths. Primary direct cerebral injury occurs within seconds of the event and is irreversible. Secondary injury is caused by subsequent anoxia or ischemia. The goal is to minimize secondary injury by ensuring adequate oxygenation, ventilation, and perfusion, and maintaining normal intracranial pressure (ICP). A child with severe neurologic impairment—i.e., with a Glasgow Coma Scale (GCS; see Table 67-3 in Chapter 67) score of 8 or less—should be intubated.

Signs of increased ICP, including progressive neurologic deterioration and evidence of transtentorial herniation, must be treated immediately (see Chapter 68). Hyperventilation lowers $Paco_2$, resulting in cerebral vasoconstriction, reduced cerebral blood flow, and decreased ICP. Brief hyperventilation remains an immediate option for patients with acute increases in ICP. Prophylactic hyperventilation or vigorous or prolonged hyperventilation is not recommended, because the consequent vasoconstriction may excessively decrease cerebral perfusion and oxygenation. Mannitol lowers ICP and may improve survival. Because mannitol acts via osmotic diuresis, it can exacerbate hypovolemia and must be used cautiously. Hypertonic saline may be a useful agent for control of increased ICP in patients with severe head injury and may possibly decrease mortality when compared with mannitol. Neurosurgical consultation is mandatory. If signs of increased ICP persist, the neurosurgeon must decide whether to operate emergently.

Exposure and Environmental Control

All clothing should be cut away to reveal any injuries. Cutting is quickest and minimizes unnecessary patient movement.

Children often arrive mildly hypothermic because of their higher body surface area : mass ratios. They can be warmed with use of radiant heat as well as heated blankets and intravenous fluids.

SECONDARY SURVEY

During the secondary survey, the physician completes a detailed, head-to-toe physical examination.

Head Trauma

A GCS or Pediatric GCS score (see Table 67-3 in Chapter 67) should be assigned to every child with significant head trauma. This scale assesses eye opening and motor and verbal responses. In the Pediatric GCS, the verbal score is modified for age. The GCS helps categorize neurologic disability, and serial measurements identify improvement or deterioration over time. Patients with low scores 6-24 hr after injuries have poorer prognoses.

In the ED, CT scanning of the head without a contrast agent has become standard to determine the type of injury in patients with concerning findings. Diffuse cerebral injury with edema is a common and serious finding on CT scan in severely brain-injured children. Focal evacuable hemorrhagic lesions (e.g., epidural hematoma) occur less commonly but may require immediate neurosurgical intervention (Fig. 72-3).

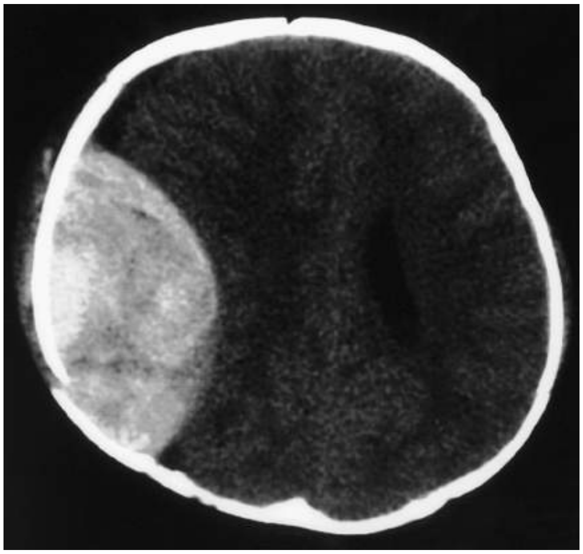

Figure 72-3 According to the history provided, the 7-month-old girl whose head CT scan is shown here did not wake up for her nightly feeding and began vomiting in the morning. The mother's boyfriend reported that the infant had fallen from a chair the previous day. The CT scan shows a large epidural hematoma on the right and marked shift of the midline from right to left. The right lateral ventricle is compressed as a result of the mass effect, and the left lateral ventricle is slightly prominent. The infant underwent emergency surgical evacuation of the epidural hematoma and recovered uneventfully. *(From O'Neill JA Jr:* Principles of pediatric surgery, *ed 2, St. Louis, 2003, Mosby, p. 191.)*

Monitoring of ICP should be strongly considered for children with severe brain injury, particularly for those with a GCS score of 8 or less and abnormal head CT findings (see Chapter 68). An advantage of an intraventricular catheter over an intraparenchymal device is that cerebrospinal fluid can be drained to treat acute increases in ICP. Hypoxia, hypercarbia, hypotension, and hyperthermia must be aggressively managed to prevent secondary brain injury. Cerebral perfusion pressure should be maintained >40 mm Hg at least (although some experts recommend an even higher minimum).

A child with a severe brain injury must be treated aggressively in the ED because it is very difficult to accurately predict long-term neurologic outcome. Compared with adults with similar injuries, children are thought to have better functional outcomes.

Cervical Spine Trauma

Cervical spine injuries occur in <3% of children with blunt trauma—with the risk being substantially higher in those with GCS scores ≤8—but they are associated with significant mortality and morbidity. Bony injuries occur mainly from C1 to C4 in children younger than 8 yr. In older children, they occur equally in the upper and lower cervical spine. The mortality rate is significantly higher in patients with upper cervical spine injuries. *Spinal cord injury without radiographic (vertebral body) abnormalities (SCIWORA) on plain films or CT may be present.* Patients with SCIWORA have neurologic symptoms, and spinal cord abnormalities are nearly always noted on MRI. Approximately 30% of all patients with cervical spine injuries have permanent neurologic deficits.

Evaluation begins with a detailed history and neurologic examination. Identifying the mechanism of injury helps in estimating the likelihood of a cervical spine injury. Both the patient and the paramedic should be asked whether any neurologic symptoms or signs, such as weakness or abnormal sensation, were present before arrival in the

Table 72-7 National Emergency X-Ray Utilization Study (NEXUS) to Rule Out Cervical Spine Injury Following Blunt Trauma

If none of the following are present, the patient is at very low risk for clinically significant cervical spine injury:
- Midline cervical tenderness
- Evidence of intoxication
- Altered level of alertness
- Focal neurologic deficit
- Distracting painful injury

Modified from Hoffman JR, Mower WR, Wolfson AB, et al: Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma, N Engl J Med *343:94-99, 2000, and Viccellio P, Simon H, Pressman BD, et al: A prospective multicenter study of cervical spine injury in children,* Pediatrics *108(2):e20, 2001.*

Table 72-8 Indications for Operation in Thoracic Trauma

THORACOTOMY IMMEDIATELY OR SHORTLY AFTER INJURY
- Massive continuing pneumothorax or large air leak from tracheobronchial injury (cannot expand lung and ventilate)
- Cardiac tamponade
- Open pneumothorax
- Esophageal injury
- Aortic or other vascular injury
- Acute rupture of the diaphragm

DELAYED THORACOTOMY
- Chronic rupture of the diaphragm
- Clotted hemothorax
- Persistent chylothorax
- Traumatic intracardiac defects
- Evacuation of large foreign bodies
- Chronic atelectasis from traumatic bronchial stenosis

Modified from O'Neill JA Jr: Principles of pediatric surgery, *ed 2, St. Louis, 2003, Mosby, p. 157.*

ED. In a child with neurologic symptoms and normal findings on cervical spine plain radiographs and CT scan, SCIWORA must be considered.

Whenever the history, physical examination, or mechanism of injury suggests a cervical spine injury, radiographs should be obtained after initial resuscitation. The National Emergency X-Radiography Utilization Study (NEXUS) cervical spine rule helps identify low-risk patients who may not require radiographs (Table 72-7). The standard series of plain radiographs includes lateral, anteroposterior, and odontoid views. Some centers use cervical spine CT as the primary diagnostic tool, particularly in patients with abnormal GCS scores and/or significant injury mechanisms, recognizing that CT is more sensitive in detecting bony injury than plain radiographs. CT is also helpful if an odontoid fracture is suspected, because young children typically do not cooperate enough to obtain an "open-mouth" (odontoid) radiographic view. Use of cervical spine CT scan must be balanced with the knowledge that CT exposes thyroid tissue to 90-200 times the amount of radiation from plain films. MRI is indicated in a child with suspected SCIWORA and may also be useful in the evaluation of children who remain obtunded.

Rapid diagnosis of spinal cord injury is essential. Initiating high-dose intravenous methylprednisolone within 8 hr of spinal cord injury has been shown to improve motor outcome and remains standard therapy.

Thoracic Trauma

Pulmonary contusions occur frequently in young children with blunt chest trauma. A child's chest wall is relatively pliable; therefore, less force is absorbed by the rib cage, and more is transmitted to the lungs. Respiratory distress may be noted initially or may develop during the first 24 hr after injury.

Rib fractures result from significant external force. They are noted in patients with more severe injuries and are associated with a higher mortality rate. Flail chest, which is caused by multiple rib fractures, is rare in children. Indications for operative management in thoracic trauma are listed in Table 72-8. Table 72-5 shows the differential diagnosis of immediately life-threatening cardiopulmonary injuries.

Abdominal Trauma

Liver and spleen contusions, hematomas, and lacerations account for the majority of intra-abdominal injuries from blunt trauma. The kidneys, pancreas, and duodenum are relatively spared because of their retroperitoneal location. Pancreatic and duodenal injuries are more common after a bicycle handlebar impact or a direct blow to the abdomen (Table 72-9).

Although a thorough examination for intraabdominal injuries is essential, achieving it often proves difficult. Misleading findings can result from gastric distention after crying or in an uncooperative toddler. Calm reassurance, distraction, and gentle, persistent palpation help with the examination. Important findings include distention, bruises, and tenderness. Specific symptoms and signs give insight into

Table 72-9 Frequency of Abdominal Organ Injury by Injury Mechanism

BLUNT		PENETRATING	
Organ	**%**	**Organ**	**%**
Spleen	30	Gastrointestinal tract	70
Liver	28	Liver	27
Kidneys	28	Blood vessels	19
Gastrointestinal tract	14	Kidneys	10
Bladder/urethra/ureters	4	Spleen	9
Pancreas	3	Bladder/urethra/ureters	8
Blood vessels	3	Pancreas	6

Modified from O'Neill JA Jr: Principles of pediatric surgery, *ed 2, St. Louis, 2003, Mosby, p. 159.*

the mechanism of injury and the potential for particular injuries. Pain in the left shoulder may signify splenic trauma. A lap belt mark across the abdomen suggests a bowel or mesentery injury. The presence of certain other injuries, such as lumbar spinal fractures and femur fractures, increases the likelihood of intraabdominal injury.

An abdominal CT scan with intravenous contrast medium enhancement rapidly identifies structural and functional abnormalities and is the preferred study in a stable child. It has excellent sensitivity and specificity for splenic (Fig. 72-4), hepatic (Fig. 72-5), and renal injuries, but is not as sensitive for diaphragmatic, pancreatic, or intestinal injuries. Small amounts of free fluid or air or a mesenteric hematoma may be the only sign of an intestinal injury. Administration of an oral contrast agent is not routinely recommended for all abdominal CT scans, but it sometimes aids in identifying an intestinal, especially a duodenal, injury.

Although *focused assessment with sonography in trauma (FAST)* examination helps detect hemoperitoneum, the variably low sensitivity of this test in children suggests that it should not be used to exclude intraabdominal injury in patients with a high pretest probability for injury. Serial FAST exams over time may be used by skilled ultrasonographers to rule out injury in need of intervention. FAST is most useful in patients who have blunt trauma and are hemodynamically unstable or patients who require operative intervention for nonabdominal injuries, because in these cases the performance of a CT scan may not be feasible.

Nonoperative treatment has become standard for hemodynamically stable children with splenic, hepatic, and renal injuries from blunt

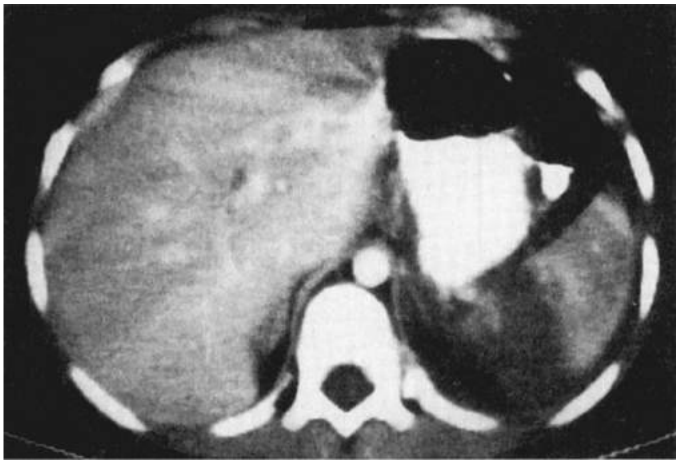

Figure 72-4 **CT scan with intravenous and gastrointestinal contrast enhancement shows an isolated splenic rupture that resulted from blunt trauma.** This injury responded to nonoperative management, as do most splenic injuries. *(From O'Neill JA Jr:* Principles of pediatric surgery, *ed 2, St. Louis, 2003, Mosby, p. 166.)*

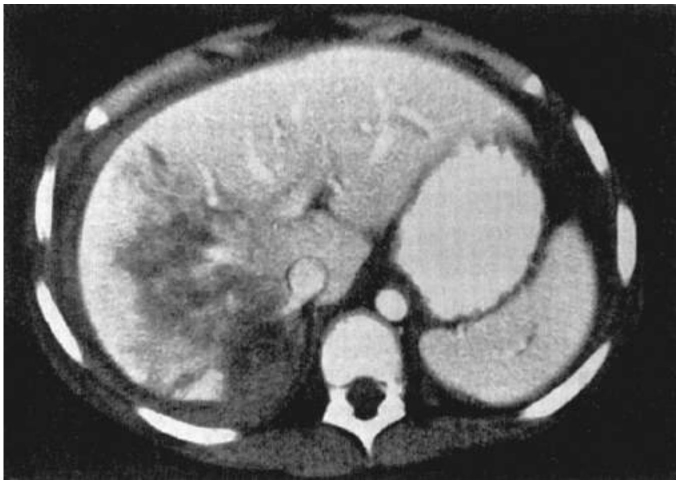

Figure 72-5 **CT scan performed after severe blunt injury of the abdomen shows a bursting injury of the liver.** The patient was stable, and no operative intervention was required. The decision to perform surgery should be based on the patient's physiologic stability. *(From O'Neill JA Jr:* Principles of pediatric surgery, *ed 2, St. Louis, 2003, Mosby, p. 168.)*

trauma. The majority of such children can be treated nonsurgically. In addition to avoiding perioperative complications, nonoperative treatment decreases the need for blood transfusions and shortens hospital stay. When laparotomy is indicated, splenic repair is preferable to splenectomy.

Pelvic Trauma

Pelvic fractures in children are much less common than in adults, occurring in approximately 4% of children with more severe blunt trauma. Pelvic fractures are typically caused by high forces (e.g., from high-speed motor vehicle crashes or pedestrian impacts) and are often associated with intraabdominal and/or vascular injuries. The pelvis itself forms a ring, and high-force impacts can lead to disruption of this ring. When the ring is disrupted in more than one location, such as the symphysis pubis and the sacroiliac joint, the ring can become unstable and displaced, potentially injuring large pelvic vessels and leading to massive blood loss. Catheter-directed embolization to control bleeding, performed by an interventional radiologist, may be required.

The pelvis should be assessed for stability by means of compression–distraction maneuvers. If instability is noted, immediate external fixation with a pelvis-stabilizing device or a sheet should be applied, and orthopedic consultation sought. A trauma patient with a potential pelvic fracture should receive an anteroposterior pelvic radiograph in the trauma bay, or a CT scan, if highly suspicious. Children without a high-risk clinical finding (i.e., GCS <14; abdominal pain or tenderness, pelvic tenderness, laceration, ecchymosis, or abrasion; positive urinalysis, or femur fracture) or a high-risk mechanism of injury (i.e., unrestrained motor vehicle collision, motor vehicle collision with ejection, motor vehicle collision rollover, auto vs. pedestrian, or auto vs. bicycle) are unlikely to have pelvic fractures, however.

Lower Genitourinary Trauma

The perineum should be inspected, and the stability of the bones of the pelvis assessed. Urethral injuries are more common in males. Findings suggestive of urethral injury include scrotal or labial ecchymoses, blood at the urethral meatus, gross hematuria, and a superiorly positioned prostate on rectal examination (in an adolescent male). Certain pelvic fractures also increase the risk for potential genitourinary injury. Any of these findings is a contraindication to urethral catheter insertion and warrants consultation with a urologist. Retrograde urethrocystogram and CT scan of the pelvis and abdomen are used to determine the extent of injury.

Extremity Trauma

Extremity fractures may initially be missed as clinicians attend to more life-threatening injuries. Thorough examination of the extremities is essential because extremity fractures are among the most frequently overlooked injuries in children with multiple trauma. All limbs should be inspected for deformity, swelling, and bruises; palpated for tenderness; and assessed for active and passive range of motion, sensory function, and perfusion.

Before radiographs are obtained, suspected fractures and dislocations should be immobilized, and an analgesic administered. Splinting a femur fracture helps alleviate pain and may decrease blood loss. An orthopedic surgeon should be consulted immediately to evaluate children with compartment syndrome, neurovascular compromise, open fracture, and most traumatic amputations.

Radiologic and Laboratory Evaluation

Some authorities recommend ordering multiple studies in the ED that include lateral cervical spine, anteroposterior chest, and anteroposterior pelvis radiographs; arterial blood gas analysis; serum lactate determinations; complete blood cell count; electrolyte measurements; blood glucose and blood urea nitrogen measurements; serum creatinine, amylase, and lipase determinations; liver function tests; prothrombin and partial thromboplastin time determinations; blood typing and cross-matching; and urinalysis. One benefit of standardizing the evaluation of patients with major trauma is that fewer decisions need to be made on an individual basis, possibly expediting ED management.

Some of these studies have prognostic importance. A large base deficit is associated with a higher mortality rate, and elevated lactate values correlate with poor prognosis.

There are limitations of standard tests. The lateral cervical spine radiograph can miss clinically significant injuries. Hemoglobin and hematocrit values provide baseline values in the ED, but they may not have yet equilibrated after a hemorrhage. Abnormal liver function test results or elevated serum amylase and lipase values may be noted in patients with significant abdominal trauma, but most patients with significant trauma to the abdomen already have clinical indications for CT scanning or surgery. The majority of previously healthy children have normal coagulation profiles; these may become abnormal after major head trauma. Although routine urinalysis or dipstick urine testing for blood has been recommended for children, other data suggest that this evaluation may be unnecessary in patients without gross hematuria, hypotension, or other associated abdominal injuries.

Table 72-10 Prediction Rule for Identification of Children at Very Low Risk of Clinically Important Brain Injuries After Head Trauma

Children <2 yr are at very low risk of clinically important traumatic brain injury if they have NONE of the following:	*Children 2-18 yr are at very low risk of clinically important traumatic brain injury if they have NONE of the following:*
Severe mechanism of injury History of LOC >5 seconds GCS ≤14 or other signs of altered mental status Not acting normally per parent Palpable skull fracture Occipital/parietal/temporal scalp hematoma	Severe mechanism of injury History of LOC History of vomiting GCS ≤14 or other signs of altered mental status Severe headache in the ED Signs of basilar skull fracture

Modified from Kuppermann N, Holmes JF, Dayan PS, et al: Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study, Lancet *374:1160–1170, 2009.*

Table 72-11 Prediction Rule for Identification of Children at Very Low Risk of Clinically Important Intraabdominal Injuries After Blunt Trauma

If none of the following are present, the patient is at low risk for clinically significant intraabdominal injury:
GCS <14
Vomiting
Evidence of thoracic wall trauma
Decreased breath sounds
Evidence of abdominal wall trauma or seatbelt sign
Abdominal pain
Abdominal tenderness

Modified from Holmes JF, Lillis K, Monroe D, et al: Identifying children at very low risk of clinically important blunt abdominal injuries, Ann Emerg Med *62(2): 107–116e2, 2013.*

Clinical prediction rules that combine patient history with physical exam findings have been developed to identify those at low risk of injury for whom specific radiographic and laboratory studies may not be necessary. The NEXUS C-spine rule is a sensitive, easily applicable rule that was validated for adults and children, although the younger population was smaller (see Table 72-7). Several clinical prediction rules have been developed to identify children at low risk of traumatic brain injury (Table 72-10). Another clinical prediction rule has been developed to identify children at very low risk of clinically-important intra-abdominal injuries following blunt trauma (Table 72-11). Although this rule has a negative predictive value of 99.9%, it needs to be externally validated before widespread implementation.

Psychological and Social Support

Serious multisystem trauma may result in significant long-term psychological and social difficulties for the child and family, particularly when there is a major head injury. Like adults, children are at risk for depressive symptoms and posttraumatic stress disorder. Caregivers face persistent stress and have been noted to have more psychological symptoms. Psychological and social support, during the resuscitation period and afterwards, is extremely important. Parents often prefer to be offered the choice to be present during resuscitations. A member of the resuscitation team should be made responsible for answering the family's questions and supporting them in the trauma room.

Bibliography is available at Expert Consult.

72.1 Care of Abrasions and Minor Lacerations

Joanna S. Cohen and Bruce L. Klein

LACERATIONS AND CUTS

Lacerations are tears of the skin caused by blunt or shearing forces. A cut (or a stab), in contrast, is an injury inflicted by a sharp object. Although distinguishing between the two can be important for forensic purposes, their evaluation and management are similar. In this chapter, lacerations include cuts and stabs.

Epidemiology

More than half of the 12 million wounds treated annually in U.S. EDs are lacerations. Approximately 30% occur in children younger than 18 yr. Approximately 2% of pediatric office visits are related to wound management.

Evaluation

The history should include the mechanism of injury, the amount of force, and the time the injury occurred. The mechanism helps determine whether there may be foreign material in the wound, which would increase the risk for infection. Particularly in children, it is essential to determine whether the injury was inflicted intentionally. If nonaccidental trauma is suspected, state or local child protective services agency should be notified. The type of force causing the laceration also influences the risk of infection, as a significant crush injury is more likely to become infected than a shearing one. Blunt injury, such as bumping the head, is a common cause of lacerations in children and is less likely to become infected. Theoretically, the amount of bacteria in the wound should increase exponentially with the time from injury to repair; however, the length of time that results in a clinically significant increase in wound infection is unclear. Older wounds may require delayed primary closure or healing by secondary intention. The patient or parent should be asked about any special host factors that may predispose to infection or impede healing, such as diabetes, malnutrition, obesity, and steroid therapy, as well as immunization status, with particular attention to tetanus administration.

On exam, the provider should note the size and depth of the wound, as well as any associated vascular, neurologic, tendon, or other tissue injury. The laceration's location also is important with regard to both the risk for infection and the cosmetic outcome. Compared with lacerations in adults, those in children occur more commonly on the face and scalp and less commonly on the upper extremities. Because the face and scalp are more vascular, wounds located there are less likely to become infected. Lacerations overlying joints are more likely to develop wider scars as a result of tension during healing.

Treatment

The goals of treatment are to establish hemostasis, minimize the risk of infection, restore skin and underlying tissue integrity, and produce the most functionally and cosmetically acceptable result possible. Complications of wounds, including infection, hypertrophic scar formation, and functional limitation occur in 8% of children.

Any significant bleeding must be controlled (with external pressure usually) before a thorough evaluation of the wound can occur. *If there is a skin flap, it should be returned to its original position before application of pressure.* A tourniquet may need to be applied if bleeding cannot be controlled with direct pressure. Clothing over the injury should be removed to minimize wound contamination. Jewelry encircling an injured extremity should be removed to prevent the jewelry from forming a constricting band when the extremity swells.

It is best to administer a local anesthetic early, before exploration and more meticulous cleansing of the wound. This anesthetic can be applied topically (e.g., lidocaine, epinephrine, and tetracaine gel) or infiltrated locally or as a regional nerve block (e.g., lidocaine or bupivacaine), depending on the location of the laceration and the complexity of the repair. Pain from lidocaine infusion can be reduced by buffering the lidocaine with sodium bicarbonate. Sometimes

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nonpharmacologic or additional pharmacologic methods of analgesia and anxiolysis are required for a young, frightened, or uncooperative child. The wound should be examined under proper light to enable identification of foreign bodies or damage to vessels, nerves, or tendons.

Many lacerations, especially heavily contaminated ones, benefit from irrigation, with either water or sterile saline, to reduce the risk of infection. It is important to recognize that many traumatic lacerations treated in the ED or office are only minimally contaminated, containing less than 10^2 bacterial colonies. In fact, in one of the few human studies on irrigation, irrigation did not decrease the infection rate of minimally contaminated scalp or facial lacerations in patients who presented to an ED within 6 hr of injury. Another concern is that higher-pressure irrigation may actually increase tissue damage, making the wound and adjacent tissue more susceptible to infection and delaying healing. These caveats notwithstanding, irrigation has benefits, although which technique to use—that is, which device, what size syringe, what size needle, which solution, how much volume, how much pressure—remains to be determined. These features may vary for different types of lacerations. In heavily contaminated wounds, the benefit of higher-pressure irrigation likely outweighs the harm of tissue damage. For heavily contaminated lacerations, a typical recommendation is to use a 35- to 65-mL syringe attached to a plastic splatter shield, or a 19-gauge needle if a splatter shield is unavailable, and to irrigate with approximately 100 mL of solution per centimeter of wound. Conversely, for relatively clean wounds, lower-pressure irrigation minimizes tissue damage, which may be more important for outcome than any decrease in bacterial clearance that may ensue. Debridement of devitalized tissue with higher-pressure irrigation, scrubbing, or surgical excision can also be necessary in certain cases, such as crush injuries.

Most lacerations seen in the pediatric ED or office should be closed primarily. Contraindications to primary closure (e.g., certain bite wounds) do exist (see Chapter 724). Although it is commonly accepted that the time from injury to repair should be as brief as possible to minimize the risk of infection, there is no universally accepted guideline as to what length of time is too long for primary wound closure. Also, this length of time varies for different types of lacerations. A prudent recommendation is that higher-risk wounds should be closed within 6 hr at most after the injury but that some low-risk wounds (e.g., clean facial lacerations) may be closed as late as 12-24 hr.

Many lacerations can be closed with simple, interrupted, 4-0, 5-0, or 6-0, nonabsorbable sutures. For lacerations under tension, horizontal or vertical mattress sutures, which provide added strength and may evert the wound edges better, can be used instead. For lacerations in cosmetically significant areas, a running intradermal stitch may produce a less conspicuous, more aesthetic scar than simple or mattress skin sutures, which can leave unattractive track marks. Deeper lacerations may need repair with an absorbable dermal and/or fascial layer. Other complex lacerations, such as those involving the ear, eyelid, nose, lip, tongue, genitalia, or fingertip, sometimes require more advanced techniques as well as subspecialty consultation.

Staples, topical skin adhesives, and surgical tape are acceptable alternatives to sutures, depending on the laceration's location and the healthcare provider's preference. Staples are particularly useful for lacerations of the scalp, where the appearance of the scar tends to be less important. Topical skin adhesives (octylcyanoacrylates or butylcyanoacrylates) are ideal for linear, relatively superficial lacerations with easily approximated edges that are not under tension. They are particularly good for lacerations located in areas where suture track marks are especially undesirable, or in situations where resources are constrained.

Maintaining a warm, moist, wound environment following repair accelerates wound healing without increasing the risk of infection. A topical antimicrobial ointment (e.g., bacitracin or a bacitracin, neomycin, and polymyxin B combination) and conventional gauze dressing provide such an environment and reduce the infection rate. Compared with conventional dressings, occlusive dressings (hydrocolloids, hydrogels, polyurethane films) may be better at accelerating healing, reducing infection, and decreasing pain but are more expensive. Occlusive dressings that adhere (hydrocolloids or polyurethane films) are impractical for lacerations with protruding sutures. If the laceration overlies or is near a joint, splinting helps limit mobility and can speed healing and minimize dehiscence.

For most routine lacerations evaluated in the ED or office that are repaired early and meticulously, prophylactic systemic antibiotics are unnecessary because they do not decrease the rate of infection. Antibiotic prophylaxis is or may be indicated for human and many animal bites, for open fractures and joints, and for grossly contaminated wounds, as well as for wounds in patients who are immunosuppressed or have prosthetic devices. Tetanus prophylaxis should be administered, if indicated, according to Centers for Disease Control and Prevention guidelines (see Chapter 211).

ABRASIONS

An *abrasion* is a scrape to the epidermis, and sometimes the dermis, that is usually caused by friction of the skin against a rough surface. "Road rash" is a colloquial term for abrasions that result from friction of the skin against pavement. Motor vehicle collisions with pedestrians and cycling accidents are common causes of road rash in children. Road rash can be extensive, involving multiple areas on the body. These abrasions also can be deep, and they often contain embedded debris. A "rug burn" is an abrasion sustained by sliding across a carpet. Some abrasions display specific patterns and are called *imprint abrasions*. Ligature marks are a type of imprint abrasion caused by a rope or cord that has been tied around a part of the body and has rubbed against the skin. These injuries should alert the clinician to the likelihood of nonaccidental (including self-inflicted) trauma.

Treatment

All abrasions should be cleansed thoroughly, and any debris or foreign material removed. If debris is not removed, abnormal skin pigmentation, known as post-traumatic tattooing, can occur and can be difficult to treat. A nonadherent occlusive dressing or a topical antibiotic and conventional dressing should be applied. Tetanus prophylaxis should be administered, if indicated (see Chapter 211). Large and/or deep abrasions that have not healed in a few weeks require consultation with a plastic surgeon for more advanced care.

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Chapter 73

Altitude-Associated Illness in Children (Acute Mountain Sickness)

Susan Niermeyer and Michael Yaron

High-altitude illness represents a spectrum of clinical entities with neurologic and pulmonary manifestations that overlap in their presentations and share common elements of pathophysiology. **Acute mountain sickness (AMS)** is the relatively benign and self-limited presentation, whereas **high-altitude pulmonary edema (HAPE)** and **high-altitude cerebral edema (HACE)** represent the potentially

life-threatening manifestations. Children are at risk of developing these conditions as they travel to high mountainous locations with their families pursuing outdoor recreation, tourism, or relocation to high-altitude communities.

In 1987, it was estimated that more than 1 million visitors of all ages travelled annually to the remote high mountain ranges of Asia, Africa, and South America, and approximately 35 million visitors travelled annually to high-altitude recreation areas in the western United States; today these numbers are likely to be underestimations. Given the large number of families travelling to high-altitude mountain locations worldwide and the potential for 25% of those travelling to even moderate altitudes to develop altitude-related symptoms, this has become a significant public health issue. Significant morbidity among children travelling with their families to high altitude locations warrants improved education of the populations at risk and the clinicians who care for them.

ETIOLOGY

Definitions

The altitude threshold where clinical illness may begin to occur is 1,500 meters (~4,900 ft). At this altitude a mild impairment in oxygen transport begins, yet altitude illness is relatively rare until higher elevations are reached. Children with underlying medical problems that impair oxygen transport may be predisposed to developing altitude illness at these lower levels. At moderate high altitude, 2,500-3,500 meters (~8,000-11,500 feet) arterial oxygen saturation (Sa_{O_2}) is generally well maintained; however, mild tissue hypoxia may occur as a result of low arterial oxygen partial pressure (Pa_{O_2}) and altitude illness becomes common after rapid ascent over 2,500 m. This is the altitude range that most people visit and the elevation of many popular ski resorts in the United States, thus the most common range to find the greatest number of altitude illness cases. Very high altitude, 3,500-5,500 meters (~11,500-18,000 feet) is associated with the most serious altitude illness, as Sa_{O_2} falls below 90%. Here saturations fall on the steep portion of the oxyhemoglobin dissociation curve, and marked desaturation may occur with relatively small increases in altitude. At these heights severe hypoxemia is seen with sleep, exercise and illness. HAPE and HACE are most common in this environment. *Extreme high altitude,* above 5,500 meters (~18,000 feet) generally results in severe altitude illness during acute ascent without supplemental oxygen. Acclimatization at intermediate altitudes is required to reach extreme altitudes. Complete acclimatization is not possible, and long visits in this range result in progressive deterioration.

Environmental Considerations

The partial pressure of oxygen (pO_2) in the atmosphere decreases logarithmically as geographic altitude rises, but oxygen remains a constant 20.93% of the barometric pressure. The degree of hypoxia is related to the geographic altitude and the local variability of barometric pressure. The shape of the earth is slightly flat at the poles and bulging at the equator. The atmospheric envelope that surrounds the earth has a similar shape; thus the barometric pressure and the relative altitude are lower at higher latitudes than at the equator. The atmospheric envelope also develops seasonal variations in its local thickness, resulting in barometric pressures that are lower and relative altitudes that are higher during the winter season. Local weather can also have a significant effect on barometric pressure from day to day. A strong low-pressure front can reduce the barometric pressure 10-20 mm Hg and result in a significant temporary increase (150-500 m) in relative altitude.

GENERAL EFFECTS OF HYPOBARIC HYPOXIA

Arterial oxygen saturation falls with increasing altitude, eventually triggering central chemoreceptor responses to produce hyperventilation in an attempt to normalize oxygen saturation; relative hypoventilation exacerbates the hypoxemia of high-altitude exposure. During sleep, periodic breathing associated with high-altitude exposure may result in periods of apnea, causing further arterial oxygen desaturation. Fluid homeostasis often shifts at altitude, resulting in a generalized fluid retention and redistribution into intracellular and interstitial spaces manifested by peripheral edema, decreased urinary output, and impaired gas exchange.

Acclimatization

Gradual ascents allowing for acclimatization over several weeks have allowed successful summiting of many of the world's highest peaks without supplemental oxygen. Without this gradual approach, rapid exposure to extreme altitude results in loss of consciousness and asphyxia in a matter of minutes. Children may acclimatize at least as well if not better than adults when comparing heart rate and arterial saturation of children 7-9 yr of age to their parents during a slow ascent.

Some of the responses to hypoxia are mediated at the molecular level by hypoxia inducible factor (HIF). This transcriptional activator orchestrates the expression of hundreds of genes in response to both acute and chronic hypoxic conditions. Acclimatization begins at the altitude that causes the oxygen saturation of arterial blood to fall below sea level values. Most healthy, unacclimatized visitors to high altitude will not experience a significant drop in oxygen saturation ($Sa_{O_2} < 90\%$) until they reach elevations above 8,000 feet. Children with preexisting conditions that reduce oxygen transport may have altitude intolerance and hypoxic stress at lower levels. Of particular importance are both acute and chronic cardiac and respiratory illnesses. An individual's inherent ability to acclimatize is also important. Some acclimatize easily without developing clinical symptoms, others may transiently develop AMS during acclimatization, and a few have marked reactions to altitude exposure, fail to acclimatize, and develop severe altitude illness. Previous successful acclimatization may be predictive of future responses for adults in similar conditions but may not be the case for children.

The most important response to acute hypoxia is an increase in minute ventilation. Peripheral chemoreceptors in the carotid bodies respond to hypoxia by signaling the respiratory control center in the medulla to increase ventilation. This decreases alveolar carbon dioxide partial pressure resulting in a corresponding increase of alveolar oxygen tension and arterial oxygenation. This increased ventilation known as the **hypoxic ventilatory response (HVR)**, varies in magnitude among individuals, may be genetically predetermined, and is related to the ability to acclimatize. A low HVR and relative hypoventilation are implicated in the pathogenesis of both AMS and HAPE, whereas a strong HVR enhances acclimatization. As ventilation increases, a respiratory alkalosis occurs, exerting negative feedback on central respiratory control, limiting further ventilation increase. The kidneys excrete bicarbonate in an effort to compensate for the alkalosis. As the pH normalizes, ventilation rises slowly, reaching a maximum after 4-7 days. *This process is enhanced by acetazolamide, which induces a bicarbonate diuresis.*

Increased sympathetic activity and catecholamine release on ascent result in elevation of heart rate, blood pressure, cardiac output, and venous tone. Except at extreme altitudes, acclimatization results in the resting heart rate gradually returning to near sea level values. *Resting relative tachycardia is evidence of poor acclimatization.*

Hematopoietic acclimatization consists of an increase in hemoglobin and the number of red blood cells and increase in 2,3-diphosphoglycerate. After acute ascent, an early increase of up to 15% occurs in hemoglobin concentration primarily from fluid shifting into the extravascular space. Acclimatization leads to an increase in plasma volume and total blood volume. Erythropoietin is secreted in a HIF-mediated response to hypoxemia within hours of ascent, stimulating the production of new red blood cells, which begin to appear in the circulation in 4 or 5 days. Hypoxemia also increase 2,3-diphosphoglycerate, resulting in a rightward shift of the oxyhemoglobin dissociation curve, favoring release of oxygen from the blood to the tissues. This is counteracted by the leftward shift of the oxyhemoglobin dissociation curve caused by the respiratory alkalosis from hyperventilation. The result is a net null change in the oxyhemoglobin curve and an increase in oxygen-hemoglobin binding in the lung, raising Sa_{O_2}. Climbers at extreme altitude respond with marked hyperventilation, alkalosis and leftward shift; this leftward shift favors oxygen loading in a hypoxic environment and increases Sa_{O_2}. Some

individuals with mutant hemoglobin and high oxygen-hemoglobin affinity have been found to acclimatize more efficiently at moderate altitudes than their normal counterparts.

ACUTE MOUNTAIN SICKNESS

Epidemiology and Risk Factors

The incidence of high-altitude illness depends on several variables including the rate of ascent, previous altitude exposure, and individual genetic susceptibility. Sleeping altitude, final altitude reached, and duration of stay at altitude are also clear risk factors for AMS development. AMS is very common with rapid ascent. Climbers around the world who ascend quickly (1 or 2 days) from sea level to altitudes of 14,000-20,000 feet have a very high incidence of AMS (27-83%). The rapid ascent profile associated with air travel to high altitude locations also results in high AMS attack rates. Trekkers who fly into the Khumbu region to explore the Mt. Everest area have a higher incidence of AMS (47%) compared with those who walk (23%). Skiers who visit resorts in the western United States from sea level generally fly or drive to the region but sleep at relatively moderate altitudes (6,300-9,700 ft). Among this population, AMS occurs in approximately 25%.

Children have the same incidence of AMS as adults. Individual (genetic) susceptibility for the development of AMS plays a significant role in risk assessment. Most individuals with previous histories of AMS after acute ascent are likely to experience similar symptoms with repeated visits to altitude. While anecdotal clinical experience supports this concept in children, limited data exist regarding recurrent AMS in children. Gender does not affect the incidence of AMS.

Pathophysiology

The symptoms of AMS develop several hours after arrival at high altitude, whereas the development of HAPE and HACE generally requires several days of altitude exposure. Because hypoxemia occurs within minutes of arrival, it cannot be the direct cause of high-altitude illness, but rather the initiating factor.

The clinical manifestations of AMS/HACE are primarily the result of central nervous system dysfunction caused by hemodynamic mechanical factors and biochemical mediators of permeability. The central nervous system (CNS) vasodilatory response to hypoxemia causes an increase in cerebral blood flow and volume. Significant elevation of brain volume is observed in moderate to severe AMS and HACE but has not been demonstrated in mild AMS. Hypoxic alteration of CNS vascular autoregulation and hypertension from exercise may increase pressure transmission to the brain's capillary beds resulting in transcapillary leakage and vasogenic edema. HIF-mediated vascular endothelial growth factor, the inducible form of nitric oxide synthase, reactive cytokines, and free radical formation may increase permeability. Both mechanical and biochemical activation of the trigeminovascular system have been proposed as the cause of high-altitude headache, the primary symptom of AMS. While vasogenic edema has been implicated in severe AMS and HACE, magnetic resonance imaging (MRI) reveals signal changes in subjects with and without clinical AMS.

Many of the responses to hypoxia and altitude exposure occur both in individuals who develop symptoms and those who remain free of AMS. To address the discrepancy in symptomatic illness, the "tight fit" hypothesis was proposed. This theory suggests that the development of AMS/HACE is the result of a lack of intracranial space to accommodate increasing volume from brain swelling and edema that develop at altitude. The adequacy of the intracranial and intraspinal space to buffer changes in brain and cerebrospinal fluid (CSF) volume is the central concept. Buffering occurs as the intracranial CSF is displaced via the foramen magnum into the space available in the spinal canal, followed by increased CSF absorption and decreased CSF production. Individuals with less CSF buffering capacity have less compliance and are hypothesized to become more symptomatic (develop AMS).

Diagnosis

In adults, the symptoms of mild AMS are similar to those of a viral syndrome, an ethanol "hangover," or simple physical exhaustion. To diagnose AMS, an adult must be in the setting of a recent gain in altitude, be at the new altitude for at least several hours, and report a headache *plus* at least 1 of the following symptoms: gastrointestinal upset (anorexia, nausea, or vomiting), general weakness or fatigue, dizziness or lightheadedness, or difficulty sleeping. These symptoms comprise the adult Lake Louise criteria for AMS. The headache may vary from mild to severe; anorexia plus nausea, with or without vomiting, are common. Sleep disturbance caused by periodic breathing is common in all visitors to high altitudes but is exacerbated in the setting of AMS. All the symptoms of AMS can range in severity from mild to incapacitating. Symptoms develop within a few hours after ascent and generally reach maximum severity between 24 and 48 hr, followed by gradual resolution. Most adults become symptom free by the 3rd or 4th day. The vague nature of this presentation has resulted in many misdiagnoses and morbidity among adults. In the setting of recent altitude exposure, these symptoms warrant a presumptive diagnosis of AMS and limitation of further ascent. There are no diagnostic physical signs in cases of mild AMS. Any evidence of CNS dysfunction, such as mild ataxia or altered mentation, is early evidence of HACE. Similarly, while dyspnea on exertion is universal at high altitudes, dyspnea at rest is an early indicator of HAPE.

Among infants and older preverbal children (up to 3 yr of age), AMS is diagnosed using nonverbal criteria. In this age range, AMS is manifested by increased fussiness, decreased playfulness, decreased appetite, and sleep disturbance. In most cases of AMS in very young children, all of these symptoms are present. Fussiness is defined as a state of irritability that is not easily explained by a cause, such as tiredness, wet diaper, hunger, teething, or pain from an injury. Fussy behavior may include crying, restlessness or muscular tension. Decreased playfulness may be profound. Alterations of appetite may progress to frank vomiting. Sleep disturbance can manifest with either increased or decreased sleep when compared to normal patterns. Most often decreased sleep and the inability to nap are noted.

The diagnosis of AMS in older children with early language skills (ages 4-11 yr) may be made with cautious use of the adult Lake Louise criteria. The language used in this adult questionnaire may be too complex and may underestimate AMS if not understood by the child. This is particularly true for questions regarding headache (the key symptom of AMS) and gastrointestinal symptoms. An age-appropriate modified Lake Louise Score for 4-11 yr old children has been proposed and used in the research setting (Fig. 73-1). Evaluating for the presence of headache can be accomplished by asking if the "head hurts" or by using a visual "faces" pain scale. Gastrointestinal symptoms are evaluated by asking children if they are "hungry" rather than trying to evaluate their appetite.

Many of the symptoms manifested by AMS in children may also result from the disruption of normal routine with travel. A change in environment, sleeping accommodation, or eating options can result in a fussy child. The threshold scores for AMS diagnostic criteria are modified to account for these baseline variations. Parents can easily learn to recognize AMS in preverbal children using the Children's Lake Louise Score to alert them to the constellation of alterations in fussiness (headache equivalent), appetite, playfulness and sleep in their young child (see Fig. 73-1). Educating parents to recognize the symptoms of AMS in themselves is also important as an ill parent can indirectly compromise a child's safety.

Other acute illnesses can mimic AMS in young children. It must be emphasized that altered mental status, neurologic abnormalities, breathing difficulty or cyanosis are not part of uncomplicated AMS. **Any of these signs warrant immediate medical attention.** If serious bacterial illness, a surgical condition, or another problem meriting specific intervention is suspected in a child, descent to lower altitude is recommended to eliminate the confounding variable of altitude illness.

Periodic Breathing

Periodic breathing at altitude is common at all ages during sleep, resulting in brief repeated episodes of oxyhemoglobin desaturation. Prepubertal children (9-12 yr old) have similar night-time oxygen

AMOUNT OF UNEXPLAINED FUSSINESS

0 1 2 3 4 5 6

No Fussiness — Intermittent Fussiness — Constant Fussiness When Awake

INTENSITY OF FUSSINESS

0 1 2 3 4 5 6

No Fussiness — Moderate Fussiness — Severe Fussiness When Awake

FUSSINESS SCORE (**FS**) = Amount + Intensity

RATE HOW WELL YOUR CHILD HAS **EATEN** TODAY (**E**)

0—Normal
1—Slightly less than normal
2—Much less than normal
3—Vomiting or not eating

RATE HOW **PLAYFUL** YOUR CHILD IS TODAY (**P**)

0—Normal
1—Playing slightly less
2—Playing much less than normal
3—Not playing

RATE ABILITY OF YOUR CHILD TO **SLEEP** TODAY (**S**)

0—Normal
1—Slightly less or more than normal
2—Much less or more than normal
3—Not able to sleep

CLLS = FS + E + P + S

The CLLS must be $\geq$7 with both the FS $\geq$4 and E+P+S $\geq$3 to confirm acute mountain sickness.

Figure 73-1 Children's Lake Louise Score. Fussiness is defined as a state of irritability that is not easily explained by a cause, such as tiredness, hunger, teething or pain from an injury. Fussy behavior may include crying, restlessness, or muscular tension. Please rate your child's typical fussy behavior *during the last 24 hr* without the benefit of your intervention.

desaturations as their parents; they have somewhat more stable breathing patterns with less periodicity. While periodic breathing is not a sign of AMS, the exacerbation of hypoxia during sleep plays a role in AMS development. Newborn infants normally have periodicity in their respiratory pattern, and this periodicity is increased by high-altitude exposure and sleep. Oxygen saturations of awake neonates who are born in Colorado at 3,100 m range from 88-91%. During sleep with increased periodic breathing, oxygen saturation may drop to 81% during the 1st wk of life. The amount and magnitude of respiratory periodicity decreases as the child matures and saturation during sleep increases to 86% after 2 mo. A stable mature pattern is usually reached by 6 mo of age. Preterm babies may demonstrate marked periodicity with prolonged desaturation as a result of their immaturity. Acute ascent with a child born preterm is best delayed until maturity, when normal pulmonary function and respiratory drive can be demonstrated. Parents of normal young babies may become distressed as they note marked periodic breathing patterns in their child after ascent to moderate altitude. Clinicians can reassure parents that this is generally not a precursor of true apnea; however, desaturation can occur with periodic breathing in sleep, especially at higher altitudes.

Management

The management of AMS must include strict adherence to the principle that further ascent to a higher sleeping altitude is contraindicated after the symptoms of altitude illness occur. Halting ascent or activity to allow further acclimatization may reverse the symptoms; however; the ascent exacerbates the underlying pathologic processes and may lead to disastrous results. Stopping further ascent and waiting for acclimatization treats most AMS in 1-4 days. Mild cases of AMS may be treated without descent if monitoring by a reliable caregiver is available. In addition to rest, symptomatic therapy includes analgesics and antiemetics. AMS that becomes worse or does not respond to maintenance of altitude, rest, and pharmacologic intervention mandates descent. Descent (500-1,000 m) is effective treatment for all forms of altitude illness and should be tailored to the individual response. *The presence of neurologic abnormalities (ataxia or altered mentation) or evidence of pulmonary edema (dyspnea at rest) mandates descent because these signs indicate a progression of AMS to severe altitude illness.*

Supplemental oxygen administration relieves AMS symptoms, including small amounts (1-2 L/min) given during sleep. In the wilderness, oxygen tanks are impractically heavy and are usually unavailable in adequate amounts; therefore, oxygen therapy is usually reserved for the more serious manifestations of high-altitude illness. In resort settings, oxygen may be readily available for use in the hotel or condominium, but use in children is often difficult. Hyperbaric therapy that simulates descent is also effective.

Treatment of headache and nausea can be beneficial during the course of mild AMS, and in many cases this may be all that is necessary. Ibuprofen and acetaminophen are useful for the treatment of high-altitude headache; evidence supports this conservative approach in children as well. For nausea and vomiting, ondansetron oral dissolving tablets may be used.

Acetazolamide is a carbonic anhydrase inhibitor that induces a renal bicarbonate diuresis, causing a metabolic acidosis that increases ventilation and arterial oxygenation. This respiratory stimulation improves sleep when the hypoxemia caused by periodic breathing is eradicated by acetazolamide. Acetazolamide accelerates acclimatization and, if

Table 73-1 Medications for Treatment of Altitude-Associated Illness in Children (No Studies in Children for High-Altitude Indications)

MEDICATION	CLASSIFICATION	INDICATION	DOSE AND ROUTE	ADVERSE EFFECTS
Acetazolamide	Carbonic anhydrase inhibitor	AMS prevention*	2.5 mg/kg PO every 12 hours; maximum 125 mg/dose	Collateral effects include paresthesias and taste alteration
		AMS treatment	2.5 mg/kg PO every 12 hours; maximum 250 mg/dose	
Dexamethasone	Steroid	AMS prevention†		Risk of adverse effects precludes prophylactic use
		AMS HACE treatment‡	0.15 mg/kg PO/IM/IV every 6 hr; maximum 4 mg/dose	Hypertension, gastrointestinal hemorrhage, pancreatitis, growth inhibition
Nifedipine	Calcium-channel blocker	HAPE treatment (small children)§	0.5 mg/kg PO every 4-8 hr; maximum 20 mg/dose	Hypotension
		HAPE treatment (>60 kg)§	30 mg SR PO every 12 hr or 20 mg SR PO every 8 hours	
		Reentry HAPE prevention	Same dose as HAPE treatment	
Sildenafil	Phosphodiesterase-5 inhibitor	HAPE¶	0.5 mg/kg/dose PO every 4-8 hr; maximum 50 mg/dose every 8 hr	FDA warning against chronic use in children

*AMS prophylaxis is not routinely recommended in children. It is indicated when rapid ascent profile is unavoidable or previous altitude illness in child about to undergo similar ascent profile. Doses as low as 1.25 mg/kg every 12 hr have been successful in some children.

†Use not warranted due to risk of adverse effects. Use slow graded ascent or acetazolamide.

‡Oxygen and descent are the treatment of choice for severe AMS. If acetazolamide is not tolerated dexamethasone may be used. Oxygen, descent, and dexamethasone should be used in HACE.

§In emergency settings where oxygen and descent are not an option, then nifedipine is indicated.

¶In emergency settings where oxygen and descent are not an option, if nifedipine is not well tolerated, then sildenafil may provide an alternative.

given early in the development of AMS, rapidly resolves symptoms. The dose for children is 2.5 mg/kg/dose given twice daily to a maximum of 250 mg/dose (Table 73-1). Treatment for 48 hr is usually adequate for resolution of symptoms.

The most common adverse reactions to acetazolamide in adults include paresthesias, polyuria, and taste alterations. Less common reactions include nausea, drowsiness, tinnitus, transient myopia, and, rarely, rash. Acetazolamide is a nonantibiotic sulfa compound that carries a low risk of cross-reactivity for individuals with an allergy to sulfa antibiotics. A history of anaphylaxis or severe skin reactions to any sulfa-containing medication contraindicates the use of acetazolamide. Acetazolamide should be avoided in breastfeeding mothers and pregnant women.

Dexamethasone is an effective alternative treatment for AMS in adults. Although dexamethasone can resolve the symptoms of AMS, it does not play a role in acclimatization and symptoms may recur when the treatment is withdrawn. Adverse reactions to dexamethasone of concern in the pediatric population are pancreatitis, pseudotumor cerebri, and interference with normal growth. While these reactions are generally seen with prolonged use, dexamethasone should be avoided in children for prophylaxis and used for treatment only in extreme situations where alternatives such as descent or oxygen therapy are unavailable. The dosage of dexamethasone is 0.15 mg/kg/dose orally every 6 hr to a maximum of 4 mg per dose.

Prevention

Individuals who have a known susceptibility to the development of AMS and those for whom slow ascent is impractical may consider prophylactic medication. *Acetazolamide remains the compound of choice for AMS prophylaxis.* Numerous studies have demonstrated its effectiveness in adults, and 125 mg twice daily starting 24 hr before ascent and continuing for the first 2 days at high altitude is recommended. The recommended dosage of acetazolamide for AMS prophylaxis for children is 2.5 mg/kg/dose orally up to 125 mg total given twice daily. Ibuprofen when compared to acetazolamide is equally efficacious in preventing headache in adults. Dexamethasone also prevents AMS. However the potential adverse effects in children preclude its use for prophylaxis in this age group. Recommendations for hyperhydration are frequently given in the lay literature, yet no evidence supports this advice. Drinking excessive amounts of free water may lead to hyponatremia and possibly complicate altitude illness.

HIGH ALTITUDE CEREBRAL EDEMA

Epidemiology and Risk Factors

HACE is rare in children, but it is rapidly fatal if unrecognized. Generally seen in adults with prolonged stays above 3,000 m, HACE is usually associated with concurrent AMS or HAPE, but can occur on its own.

Pathophysiology

HACE is regarded as the extreme expression of the same pathophysiology underlying AMS. In patients with HACE, MRI studies reveal white matter changes consistent with vasogenic edema that correlate with symptoms; evidence of cytotoxic edema has also been described.

Diagnosis

HACE is differentiated from severe AMS by the presence of neurologic signs. Most common are ataxia and altered mental status including confusion, progressive decrease in responsiveness, and eventually coma. Less common are focal cranial nerve palsies, motor and sensory deficits, and seizures. CT imaging is consistent with edema and increased intracranial pressure. MRI shows a high T2 signal in the white matter, specifically in the splenium of the corpus callosum, with diffusion-weighted technique.

Management

Descent remains the most effective treatment for HACE. Supplemental oxygen, if available, is useful especially if descent is not possible or delayed. Portable hyperbaric treatment is beneficial but its use should not delay descent if feasible. Dexamethasone should be administered at a dose of 0.15 mg/kg per dose given orally every 6 hr. The few mild cases of HACE reported in children have recovered with dexamethasone and descent.

HIGH ALTITUDE PULMONARY EDEMA

Epidemiology and Risk Factors

HAPE is a *noncardiogenic pulmonary edema* characterized by extravasation of intravascular fluid into the extravascular space of the lung.

HAPE generally occurs in the setting of recent ascent, most often at altitudes above 2,500 m, but in some cases at altitudes as low as 1,740 m. Among children, HAPE occurs in 2 distinct settings. **Type I HAPE** (or simply HAPE) occurs in a child who resides at low altitude who travels to high altitude. **Type II HAPE** (also termed reentry HAPE or reascent HAPE) affects children who reside at high altitude but become ill on their return home after descent to lower altitudes. HAPE may also occur in children who develop acute respiratory illnesses that exacerbate hypoxia at high altitude. Fatal outcomes of HAPE in children have been reported. Most mild and moderate cases resolve without difficulty, however if unrecognized and untreated, rapid progression to death can occur, especially when infection or cardiac conditions complicate the illness.

The incidence of HAPE is highly variable, as it depends not only on the altitude attained, but also the speed of ascent and prior history of HAPE. HAPE is significantly less common than AMS and its incidence in children resident at low altitude appears to parallel that among low-altitude-resident adults. HAPE affects male and female children more equally than adults, among whom the observed male predominance appears due to strenuous sport activities and military assignments. The occurrence and even the pathophysiology of HAPE may vary by population and genetic background. Individuals of Tibetan ancestry, resident on the Himalayan plateau and having minimal admixture with other populations, represent the extreme of adaptation to high altitude and rarely experience HAPE. Other native populations residing at high altitude, such as Andeans, do not appear to be protected from HAPE, and certain populations may have genetic polymorphisms associated with pulmonary edema. A number of conditions may predispose a child to HAPE (Table 73-2). Preexisting viral respiratory infections have been linked to HAPE, especially in children. Cardiorespiratory conditions associated with pulmonary hypertension, such as atrial and ventricular septal defects, pulmonary vein stenosis, congenital absence of a pulmonary artery, and obstructive sleep apnea also predispose to HAPE. Down syndrome is also a risk factor for HAPE development, as are previously repaired congenital heart defects and the presence of hypoplastic lungs. Undiagnosed structural cardiopulmonary abnormalities may result in severe hypoxia and/or altitude illness once ascent occurs.

Table 73-2 Conditions Associated with Increased Risk of HAPE

Condition
Environmental
Ascent above 2,500 m
Rapid rate of ascent (generally >1,000 m per day)
Cold exposure
Cardiac
Anomalies causing increased pulmonary blood flow or increased pulmonary arterial pressure
Ventricular septal defect, atrial septal defect, patent foramen ovale, patent ductus arteriosus
Anomalous pulmonary venous return or pulmonary vein stenosis
Unilateral absent pulmonary artery or isolated pulmonary artery of ductal origin
Coarctation of the aorta
Congestive heart failure
Pulmonary
Chronic lung disease
Bronchopulmonary dysplasia
Pulmonary hypoplasia
Supplemental oxygen requirement at sea level
Pulmonary hypertension
Perinatal respiratory distress
Persistent pulmonary hypertension of the newborn
Perinatal asphyxia or depression
Sleep apnea
Infectious
Upper respiratory tract infection
Bronchitis/bronchiolitis
Pneumonitis
Otitis media
Pharmacologic
Any medication causing central nervous system and respiratory depression
Alcohol
Sympathomimetics
Systemic
Down syndrome (trisomy 21)
History of premature birth or low birthweight

Physiology

Alveolar hypoxia results in vasoconstriction of pulmonary arterioles just proximal to the alveolar capillary bed. Hypoxic pulmonary vasoconstriction is a normal physiologic response to optimize ventilation/perfusion ($\dot{V}/\dot{Q}$) matching by redistributing regional pulmonary blood flow to areas of highest ventilation, thereby optimizing arterial oxygenation. Under conditions that result in widespread alveolar hypoxia, extensive pulmonary vasoconstriction will lead to significant elevations in pulmonary arterial pressure; uneven pulmonary vasoconstriction can result in localized overperfusion, increased capillary pressures, distention, and leakage in the remaining vessels. This explains the patchy and heterogeneous edema that is classically observed in HAPE. The combination of pulmonary hypertension and uneven pulmonary vasoconstriction appears to be necessary in the pathogenesis of HAPE. Children and adolescents acutely exposed to high-altitude hypoxia demonstrated pulmonary hypertension, with increases in pulmonary artery pressure inversely related to age. Once the vascular leak occurs and alveolar fluid accumulates, a defect in transepithelial sodium transport impairs the clearance of alveolar fluid and contributes to HAPE.

Diagnosis

The diagnosis of HAPE is based on clinical findings and their evolution in the context of recent ascent from lower elevation. There is no single diagnostic test or constellation of laboratory findings. Symptoms commonly develop within 24-96 hr, and onset of symptoms often occurs during the first or second night at altitude when hypoxia may be exacerbated during sleep. HAPE generally is not observed beyond 5 days after ascent to altitude (unless additional ascent occurs) because pulmonary vascular remodeling and acclimatization have taken place. The minimum criteria to diagnose HAPE include: recent exposure to altitude, dyspnea at rest, radiographic evidence of alveolar infiltrates, and near-complete resolution of both clinical and radiographic signs within 48 hr after descent or institution of oxygen therapy. Portable ultrasound has been shown useful to diagnose HAPE through the finding of "comet tails," artifacts created by microreflections of the ultrasound beam within interlobular septae thickened by interstitial and/or alveolar edema.

The symptoms of AMS and HAPE show considerable overlap, and AMS may precede the development of HAPE in approximately half of patients. Frequently patients first exhibit general malaise that may progress to more specific signs of dyspnea at rest, then cardiopulmonary distress. Young children may show agitation and general debility. Older children may complain of headache, and children of all ages frequently experience nausea and vomiting. Cough is a common pulmonary sign. Dyspnea at rest, orthopnea, cyanosis, tachycardia, and chest pain herald worsening compromise, which may advance within hours to production of pink-tinged sputum.

Findings on physical exam frequently are less severe than a patient's chest radiograph and the hypoxemia on pulse oximetry would predict. Children often appear pale, with or without visible cyanosis. Low-grade fever (<38.5°C [101.3°F]) is common and respiratory rate is generally increased. Auscultation typically reveals rales, usually greater in the right lung than the left on presentation. The radiographic pattern of pulmonary edema can be highly variable, from patchy and peripheral to more homogeneous in severe cases (Fig. 73-2). Often, the right lung shows more radiographic changes of edema than the left. Cardiomegaly is an uncommon finding, but peribronchial and perivascular cuffing are frequent, as well as enlargement of the pulmonary artery

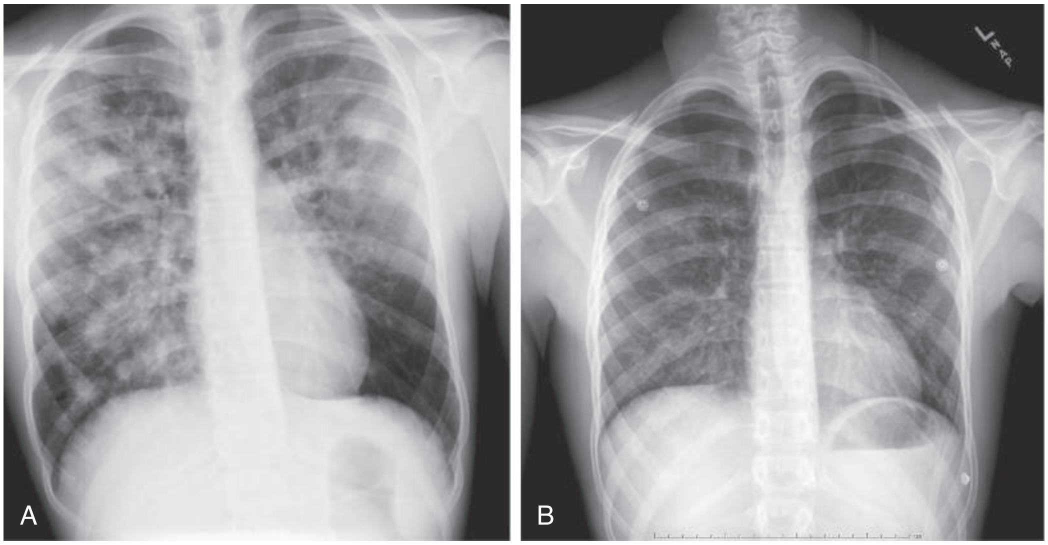

Figure 73-2 AMS and HAPE. A healthy 15 yr old male flew from Buffalo, NY, to Denver, CO, and immediately drove with his school group from the airport to a ski resort at 9,300 feet in the Rocky Mountains. The following day he felt dizzy and complained of headache. Symptoms of headache and dizziness continued along with emesis daily for 2 days. A snowboarding coach brought the patient to the local emergency facility the next day because of dyspnea, cough, headache, emesis, and fatigue. Pulse oximetry showed an arterial saturation of 51%. Chest x-ray showed diffuse pulmonary edema *(A)*. The patient was transported to Denver (5,280 feet) by ambulance with 15 L/min oxygen via a nonrebreathing mask. Saturations improved with descent and were 94% on arrival at the Children's Hospital Colorado emergency department. Breath sounds remained coarse and the patient was tachycardic and tachypneic. Oxygen flow was weaned to 1 L/min shortly after admission. Two days after presentation, lung exam was improved, without crackles. Repeat chest x-ray showed clearing of edema pattern *(B)*. The patient maintained adequate saturations without supplemental oxygen and was discharged. *(Courtesy of the Department of Radiology, Children's Hospital of Colorado.)*

silhouette and dilation of more peripheral pulmonary arteries. Significant arterial oxygen desaturation, as measured by pulse oximetry, is a consistent finding, with saturations frequently below 75%. A complete blood count often reveals a leukocytosis with a left shift of the granulocyte series.

The **differential diagnosis** of HAPE includes pneumonia, bronchitis/bronchiolitis, asthma, and other forms of cardiogenic and noncardiogenic pulmonary edema as well as pulmonary embolism. HAPE is most frequently misdiagnosed as pneumonia or a viral respiratory illness, especially when suspicion of altitude-associated pathology is not appropriately high. The presenting signs of cough, dyspnea, and orthopnea, follow by sputum production can easily be misinterpreted as pneumonia, an impression that is reinforced by the frequent accompaniment of low-grade fever. Respiratory viral infections increase the risk of developing HAPE, which may lead to further confusion in diagnosis.

Complications of HAPE in children often relate to underlying, sometimes undiagnosed, cardiopulmonary pathology or coexisting viral infections which potentiate the severity of pulmonary edema and pulmonary hypertension. Acute altitude exposure in such circumstances may lead to severe presentations that progress rapidly to extreme hypoxemia or cardiac failure and death. Children with trisomy 21, with or without structural cardiac anomalies, show increased susceptibility to HAPE and rapid symptom progression. Neonatal respiratory distress with pulmonary hypertension has been linked to exaggerated hypoxic pulmonary vasoreactivity in early adulthood and thereby a theoretical predisposition to HAPE. Other conditions related to pulmonary overcirculation (atrial and ventricular septal defects, patent foramen ovale, patent ductus arteriosus) small cross-sectional area of the pulmonary vascular bed (unilateral absent pulmonary artery, pulmonary hypoplasia), obstruction to pulmonary venous return (total anomalous pulmonary venous return, pulmonary vein stenosis), or left-sided obstruction (coarctation of the aorta) potentiate HAPE. Inflammatory processes, such as viral infection, predispose to HAPE and may worsen hypoxemia. Infection with respiratory syncytial virus, in particular, may trigger severe pulmonary hypertension.

Management

Descent with supplemental oxygen is the treatment of choice for HAPE in children. When feasible, or in the absence of medical care, rapid descent of at least 500-1,000 m usually results in rapid recovery. As with all altitude illness the magnitude of the descent is tailored to the resolution of symptoms. Oxygen and bed rest without descent can be safe and effective treatment for mild HAPE in children where careful medical observation is available. Mild HAPE in children and young adults at 3,750 m has been treated with bed rest alone, although clinical recovery may be slower compared to treatment with supplemental oxygen.

Supplemental oxygen at altitude is administered at 2-6 L/min by nasal cannula for 48-72 hr to maintain an arterial oxygen saturation of at least 90%. Increasing oxygen saturation above 90% does not result in further reduction in pulmonary artery pressure and does not accelerate edema resolution in adults. Oxygen flow can be weaned with improvement in symptoms and saturations; at flow rates below 2-4 L/min, children may be sufficiently stable and comfortable to continue treatment at home under the monitoring of family. Instructions to avoid physical exertion and exposure to cold should be given to reduce exposure to factors known to elevate pulmonary artery pressure. Most children experience complete resolution of mild HAPE within 24-72 hr of oxygen therapy when treated at altitude of symptom onset.

Pharmacotherapy for pediatric HAPE is rarely needed since oxygen and descent are so effective. In emergency situations without the options of supplemental oxygen or descent, pharmacotherapy is indicated. Nifedipine has been well studied for the treatment of adult HAPE. Extrapolated dosing for children is 0.5 mg/kg/dose given orally every 4-8 hr and titrated to response (maximum 10 mg/dose). Liquid-filled capsules of nifedipine (10 mg/0.34 mL) can be punctured to obtain doses for children less than 20 kg; sustained-release formulations cannot be broken to obtain reliable smaller doses. Patients should be monitored for hypotension during nifedipine administration. Phosphodiesterase type 5 inhibitors have been studied for HAPE prevention in adults. Although sildenafil and tadalafil have shown effectiveness in adults, there is concern around use of this class of agents in young children after the U.S. Food and Drug Administration warning against the use of sildenafil for pediatric pulmonary hypertension

between 1 and 17 yr of age because of an apparent increase in mortality during long-term therapy. Alveolar fluid clearance is upregulated by β-adrenergic agonists and inhaled β-agonists may successfully prevent and treat HAPE.

SPECIAL CONSIDERATIONS

Reentry HAPE

Children residing at high altitude may also experience HAPE of the type termed reentry or reascent HAPE. Reentry HAPE occurs upon reascent to the altitude of residence after a sojourn to low altitude. Although stays at low altitude as short as 24 hr may be sufficient to trigger reentry HAPE, most cases occur after several days at lower altitude. Children between 4 and 18 yr of age are much more likely to develop reentry HAPE than adults.

Reentry HAPE has a significant probability of recurrence and may justify pharmacologic prophylaxis to prevent the accumulated burden of morbidity. Acetazolamide has been used empirically based on its blunting of hypoxic pulmonary vasoconstriction in adults and the potential risk of hypotension and reflex tachycardia with nifedipine. The β_2-adrenergic agonist salmeterol has also been shown effective as prophylaxis in adults. Nifedipine may be a reasonable prophylactic option in older children and adolescents with histories of multiple episodes of HAPE.

Symptomatic High-Altitude Pulmonary Hypertension

Infants and young children resident at high altitude may also experience symptomatic high-altitude pulmonary hypertension, also termed **subacute infantile mountain sickness**. All infants, regardless of altitude of gestation and birth have thickened and muscularized interlobular and intralobular pulmonary arteries and pulmonary artery pressure that are initially near systemic. While muscular regression and fall in pulmonary artery pressure occur rapidly at sea level, infants permanently residing at high altitude demonstrate slowed regression of these characteristics through infancy and even childhood. Certain infants become symptomatic with exaggerated hypoxemia and signs of subacute pulmonary hypertension; these signs correlate with pathologic findings of right ventricular hypertrophy and dilation, increased muscularization of the pulmonary arterial bed and eventual right-sided congestive heart failure. Treatment may require relocation to a lower altitude.

Travel With Young Infants

Newborn infants retain some of the circulatory characteristics of recent fetal life, and these can pose a unique risk for altitude exposure. The fetal circulation has high pulmonary resistance, low pulmonary blood flow and both intra- and extra-cardiac shunts that optimize oxygenation via the placenta instead of the fetal lungs. After birth, a transition begins that closes fetal shunts and establishes normal pulmonary circulation and oxygen transport. **Exposure to marked hypoxia can result in reversion to fetal shunting patterns despite the absence of a placenta.** Normal infants at sea level complete these changes in 4-6 wk, though for infants born at moderate or high altitude, changes may last 3 mo or longer. Travel to high altitude with young infants is generally safe after 4-6 wk when circulatory changes have occurred, breastfeeding is established, and congenital abnormalities may have been detected.

Air travel with young infants frequently raises questions about the effects of exposure to hypobaric hypoxia, as the pressurization of aircraft cabins may vary up to an altitude equivalent of 8,500 feet (approximately 2,600 m). Transoceanic flights are generally not long enough to trigger AMS or HAPE; infants may experience transient desaturation with feedings during flight and likely experience discomfort because of dry air, and stress caused by noise and vibration. Former preterm infants without chronic lung disease who have attained 3 mo corrected gestational age do not appear to experience greater hypoxia during air travel than term infants; infants with more significant lung disease merit hypoxic challenge or provision for supplemental oxygen in flight.

Sickle Trait/Disease

Children with sickle cell disease or sickle trait should avoid travel to altitude, as hypoxemia may trigger sickling and painful crises, including splenic crises. Up to 20% of pediatric patients with sickle cell and sickle-thalassemia disease may experience a vasoocclusive crisis at moderate altitude or in pressurized aircraft. Oxygen is advised for air travelers with known sickle cell disease. Although the majority of children with sickle trait remain asymptomatic, children can experience splenic ischemia or infarction, with severe left upper quadrant pain. Splenic infarction may be more common in nonblack patients (often of Mediterranean origin) with sickle trait.

PREVENTION

A comprehensive approach to travel to high altitude with children should focus on 3 phases: planning the ascent and assessment of risk, recognition and management of altitude-associated illness, and follow-up of any illness relative to future travel or diagnostic testing necessary.

Planning for travel to high altitude with children should consider rate of ascent, formulation of an emergency plan for communication and evacuation, and availability of medical care at the high-altitude destination. Slow ascent with time for acclimatization is the best prevention for all forms of altitude illness. Ideally, the first night should be spent at an altitude no higher than 2,800 m and then 2-3 nights should be spent at 2,500-3,000 m, with a subsequent increase (to a new sleeping altitude) of not more than 500 m each night. One extra night of acclimatization (at the same sleeping altitude) should be taken for every 1,000 m gained. Rapid ascent by air may be avoidable through alternate routes or alternate means of transportation. Difficult descent situations (where further ascent may be necessary before descent is possible) should be avoided with children. The availability of medical care and evacuation from altitude will influence the degree of personal preparation necessary. Widespread coverage by cellular and satellite phone service may give a false sense of security in remote regions where both terrain and weather can limit the arrival of definitive help.

Medical risk assessment encompasses consideration of age, previous altitude-associated illness, and possible predisposing circumstances to altitude illness. Very young infants (younger than 4-6 wk) may not have completed the postnatal circulatory transition and may be more vulnerable to altitude-associated desaturation with periodic breathing, right-to-left shunting across the foramen ovale, and hypoxic pulmonary vasoconstriction. Infants who required supplemental oxygen during the neonatal period, especially for pulmonary hypertension, may be at risk for hypoxemia with prolonged altitude exposure. History and physical exam are useful to identify conditions predisposing to HAPE, including recent viral infections, cardiac malformations, or obstructive sleep apnea. Low-risk children should not need medications for prophylaxis and should use gradual ascent to prevent illness.

Prompt recognition of altitude-associated illness requires awareness of the context in which illness occurs and familiarity with the signs and symptoms. Parents are generally adept at recognizing deviation from baseline behavior of their children. Clinicians should emphasize to parents that breathing difficulty, cyanosis, cough productive of pink-tinged sputum, altered mental status, or neurologic abnormalities are *not* part of uncomplicated AMS, but instead are serious signs of potential HAPE or HACE that deserve immediate medical attention.

Descent is the mainstay of therapy for all forms of altitude-associated illness in children. When descent is not feasible or illness is mild, other therapeutic options may be chosen. Severe altitude illness or death can be avoided in children by adherence to 3 general principles:

1. Recognition of the early signs of altitude illness and willingness by adult caregivers to acknowledge them.
2. No further ascent, especially to sleep at a higher altitude, when experiencing even minor symptoms/signs of altitude illness.
3. Immediate descent if signs/symptoms worsen while resting/receiving treatment at the altitude of onset.

Uncomplicated AMS with full resolution of symptoms upon descent or treatment does not require diagnostic work-up, but may prompt discussion of slower ascent, specific plans for treatment, or even

prophylaxis for future travel. Signs of HAPE or severe hypoxemia in a child disproportionate to the altitude reached should prompt further diagnostic evaluation, including consideration of echocardiography. Underlying cardiac conditions may not be apparent on physical examination at low altitude; cardiac echocardiography or catheterization under conditions of controlled hypoxia or hypoxic exercise may be necessary. Families of HAPE-susceptible children should be advised to avoid travel during or shortly after viral infection.

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Chapter 74

Drowning and Submersion Injury

Derya Caglar and Linda Quan

Drowning is one of the leading causes of childhood morbidity and mortality in the world. Prevention is the most important step to reducing the impact of drowning injury, followed by early initiation of cardiopulmonary resuscitation (CPR) at the scene.

ETIOLOGY

Children are at risk of drowning when they are exposed to a water hazard in their environment. The World Congress of Drowning definition of drowning is: "Drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid." The term *drowning* does not imply the final outcome—death or survival; the outcome should be denoted as fatal or nonfatal drowning. Use of this terminology should improve consistency in reporting and research; the use of confusing descriptive terms such as "near," "wet," "dry," "secondary," "silent," "passive," and "active" should be abandoned. The injury following a drowning event is hypoxia.

EPIDEMIOLOGY

From 2005-2009, an average of 3,880 people per year were victims of fatal drowning and an estimated 5,789 persons were treated in U.S. hospital emergency departments (EDs) for nonfatal drowning. Compared with other types of injuries, drowning has one of the highest case fatality rates. Highest drowning death rates were seen in children ages 1-4 yr and 15-19 yr (2.55 and 1.29/100,000, respectively). In children, drowning is second only to motor vehicle injury as a leading cause of death from unintentional injury in the United States. Pediatric hospitalization rates associated with drowning ranged from 4.7 to 2.4 per 100,000 between 1993 and 2008. Rates of fatal drowning hospitalization declined from 0.5 to 0.3 deaths per 100,000 during the same period. Morbidity following nonfatal drowning is poorly studied.

The risk of drowning and the circumstances leading to it vary by age (Fig. 74-1). Drowning risk also relates to other host factors including male gender, alcohol use, a history of seizures, swimming lessons. Environmental risk factors include exposure to water and varying supervision. These factors are embedded in the context of geography, climate, socioeconomic status, and culture.

Children Younger Than 1 Year of Age

Most (71%) drowning deaths in children younger than 1 yr occur in the bathtub, when an infant is left alone or with an older sibling. Infant tub seats or rings may exacerbate the risk by giving caregivers a false sense of security that the child is safe in the tub. The next major risk to this age group is the large (5-gallon) household bucket, implicated in 16% of infant drowning deaths. These buckets are approximately 30 cm tall and designed to not tip over when half full. The average 9-mo-old child tends to be top-heavy, so can easily fall head first into a half-full bucket, become stuck, and drown within minutes.

Children 1-4 Years of Age

Drowning rates are consistently highest in 1-4 yr old children, likely because of their curious, but unaware, nature, coupled with the rapid progression of their physical capabilities. U.S. rates are highest in the southern regions, in some areas as high as 7.62/100,000, which approaches rates seen in developing countries. A common factor in many of these deaths is a lapse in adult supervision, often <5 min. Most U.S. drownings occur in residential swimming pools. Usually, the child is in the child's own home and the caregiver does not expect the child to be anywhere near the pool.

In rural areas, children in this age group often drown in irrigation ditches or nearby ponds and rivers. The circumstances are similar to those noted previously, in a body of water that is near the house. Drowning is one of the leading causes of farm injury–related deaths in children.

School-age Children

School-age children are at increased risk of drowning in natural bodies of water such as lakes, ponds, rivers, and canals. Although swimming pools account for the majority of nonfatal drownings, open water accounts for a higher death rate from this age group on through adolescence. Unlike for preschool children, swimming or boating activities are important factors in drowning injuries in school-aged children.

Adolescents

The second major peak in drowning death rates occurs in older adolescents, age 15-19 yr. Almost 70% drown in natural freshwater. In this age group particularly, striking disparities in drowning deaths exist in gender and race. Males account for 80% of fatal drownings. The drowning rates for adolescent males are nearly 10 times higher than those for adolescent females. The gender disparity may likely be related to males' greater risk-taking behavior, greater alcohol use, less perception about risks associated with drowning, as well as greater belief in their swimming ability than females. In 2009, as in previous years, drowning rates for black males age 15-19 yr were nearly double those for white males of the same age. Racial differences are only partially explained by socioeconomic status; other cultural factors contribute. Black children are more likely to drown in unguarded public or apartment pools, whereas white children are more likely to drown in private residential pools. Hispanic and foreign-born children have lower rates of drowning than their white counterparts. Differences in exposure to swimming lessons, cultural attitudes, and fears about swimming, as well as experience around water, may contribute to drowning risk.

Underlying Conditions

Several underlying medical conditions are associated with drowning at all ages. A number of studies have found an increased risk, up to 19-fold, in individuals with epilepsy. Drowning risk for children with seizures is greatest in bathtubs and swimming pools. Cardiac etiologies, including arrhythmias, myocarditis, and prolonged QT syndromes have been found in some children who die suddenly in the water (see Chapters 435.5), particularly in those with a family history of syncope, cardiac arrest, prior drowning, or QT prolongation. Some children with long QT syndrome are misdiagnosed as having seizures.

Drowning may also be an intentional injury. A history of the event that changes or is inconsistent with the child's developmental stage is the key to recognition of intentional drowning. Physical examination and other physical injuries rarely provide clues. Child abuse is more often recognized in bathtub-related drownings. Suicide usually occurs in lone swimmers in open water.

Alcohol Use

The use of alcohol and drugs greatly increases the risk of drowning. Of teenagers and adults who die, 30-40% have positive blood alcohol

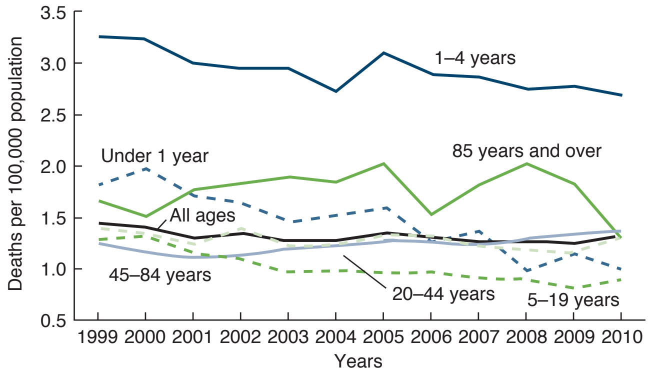

Figure 74-1 Death rates from unintentional drowning, by age group: United States, 1999-2010. A total of 46,419 deaths from unintentional drowning occurred in the United States from 1999 through 2010, an average of 3,868 deaths per year. Source: CDC/NCHS, National Vital Statistics System, Mortality. *(From Xu JQ: Unintentional drowning deaths in the United States, 1999-2010. NCHS Data Brief 149. Hyattsville, MD: National Center for Health Statistics, 2014.)*

levels. Alcohol can impair judgment, leading to riskier behavior, decreased balance and coordination, and blunted ability to self-rescue. Furthermore, an intoxicated adult may provide less-effective supervision of children around water.

Sports and Recreation

Most drowning deaths in the United States occur during recreational activities. Drowning is the leading cause of noncardiac sports-related deaths. Surveys confirm that alcohol use is common during water recreation, as is not using a personal flotation device (PFD) during boating activities. In 2012, the United States Coast Guard reported that almost 90% of those who drowned in boating accidents in the United States were not wearing a PFD.

Global Impact of Drowning

Drowning injury is a significant problem for children worldwide, with the vast majority (96%) of fatalities occurring in low and middle income countries in Asia. Given the relative size of the pediatric population in many of these countries, drowning is one of the leading causes of death globally. A recent UNICEF study estimated that approximately 77,000 children in this region alone died from drowning between 2004 and 2008. This number vastly underestimates the global drowning rate, as many drowning deaths in this region go unreported, with 64-100% of immediate fatalities going unrecognized. In addition, these data exclude any cases of drowning as the result of intentional harm or assault, accidents of watercraft or water transport, and drowning related to forces of nature/cataclysmic storms, which usually claim large numbers of lives per incident; thus true numbers of fatal drownings are likely much higher.

Some patterns of pediatric drowning are similar in all countries. By most accounts, the highest rates are seen in males and in children 1-4 yr old.

Whereas bathtubs and places of recreation (i.e., pools, spas) are significant locations for drowning in U.S. children, these are virtually unreported locations for drownings in developing countries. Instead, the predominant locations are near or around the home, involving bodies of water used for activities of daily living. These include water-collecting systems, ponds, ditches, creeks, and watering holes. In tropical areas, death rates increase during monsoon season, when ditches and holes rapidly fill with rain, and are highest during daylight hours, when caregivers are busy with daily chores.

Drowning during natural disasters such as storms and floods is important in all areas of the world. The largest numbers of reported flood-related deaths occur in developing nations; most are drownings that occur during the storm surge. In the United States and much of Europe, advances in weather monitoring and warning systems have reduced such deaths. U.S. flooding incidents, including hurricanes Katrina and Sandy, showed that drowning caused the most deaths, particularly when people became trapped in their vehicles, were unable or refused to evacuate homes, or attempted to rescue others.

PATHOPHYSIOLOGY

Drowning victims drown silently and do not signal distress or call for help. Vocalization is precluded by efforts to achieve maximal lung volume to keep the head above the water or by aspiration leading to laryngospasm. Young children can struggle for only 10-20 sec and adolescents for 30-60 sec before final submersion. A swimmer in distress is vertical in the water, pumping the arms up and down. This splashing or efforts to breathe are often misconstrued by nearby persons as merely “playing” in the water until the victim sinks.

Anoxic–Ischemic Injury

After experimental submersion, a conscious animal initially panics, trying to surface. During this stage, small amounts of water enter the hypopharynx, triggering laryngospasm. There is a progressive decrease in arterial blood oxygen saturation (Sao_2), and the animal soon loses consciousness from hypoxia. Profound hypoxia and medullary depression lead to terminal apnea. At the same time, the cardiovascular response leads to progressively decreasing cardiac output and oxygen delivery to other organs. By 3-4 min, myocardial hypoxia leads to abrupt circulatory failure. Ineffective cardiac contractions with electrical activity may occur briefly, without effective perfusion (pulseless electrical activity). With early initiation of CPR, spontaneous circulation may initially be successfully restored. The extent of the global hypoxic–ischemic injury determines the final outcome and becomes more evident over subsequent hours.

With modern intensive care, the cardiorespiratory effects of resuscitated drowning victims are usually manageable and are less often the cause of death than irreversible hypoxic–ischemic central nervous system (CNS) injury (see Chapter 68). CNS injury is the most common cause of mortality and long-term morbidity. Although the duration of anoxia before irreversible CNS injury begins is uncertain, it is probably on the order of 3-5 min. Ninety percent of victims with reported submersions of less than 5 min survive and appear normal at hospital discharge.

Several hours after cardiopulmonary arrest, cerebral edema may occur, although the mechanism is not entirely clear. Severe cerebral edema can elevate intracranial pressure (ICP), contributing to further ischemia; intracranial hypertension is an ominous sign of profound CNS damage.

All other organs and tissues may exhibit signs of hypoxic–ischemic injury. In the lung, damage to the pulmonary vascular endothelium can lead to acute respiratory distress syndrome (see Chapter 71). Aspiration may also compound pulmonary injury. Myocardial dysfunction (so-called stunning), arterial hypotension, decreased cardiac output, arrhythmias, and cardiac infarction may also occur. Acute kidney injury, cortical necrosis, and renal failure are common complications of major hypoxic–ischemic events (see Chapter 535.1). Vascular endothelial injury may initiate disseminated intravascular coagulation, hemolysis, and thrombocytopenia. Many factors contribute to gastrointestinal damage; bloody diarrhea with mucosal sloughing may be seen and often portends a fatal injury. Serum levels of hepatic transaminases and pancreatic enzymes are often acutely increased. Violation of normal mucosal protective barriers predisposes the victim to bacteremia and sepsis.

Pulmonary Injury

Pulmonary aspiration (see Chapter 397) occurs in a majority of drowning victims, but the amount of aspirated fluid is usually small. Aspirated water does not obstruct airways and is readily moved into the

pulmonary circulation with positive pressure ventilation. It can wash out surfactant and cause alveolar instability, ventilation-perfusion mismatch, and intrapulmonary shunting. In humans, aspiration of small amounts (1-3 mL/kg) can lead to marked hypoxemia and a 10-40% reduction in lung compliance. The composition of aspirated material can affect the patient's clinical course: Gastric contents, pathogenic organisms, toxic chemicals, and other foreign matter can injure the lung or cause airway obstruction. Clinical management is not significantly different in saltwater and freshwater aspirations, because most victims do not aspirate enough fluid volume to make a clinical difference. A few children may have massive aspiration, increasing the likelihood of severe pulmonary dysfunction.

Cold Water Injury

Drowning should be differentiated from **cold water immersion** injuries, in which the victim remains afloat, keeping the head above water without respiratory impairment in cold waters. The definition of cold water varies from less than 15-20°C (59-68°F).

Heat loss through conduction and convection is more efficient in water than in air. Children are at increased risk for hypothermia because of their relatively high ratio of body surface area to mass, decreased subcutaneous fat, and limited thermogenic capacity. Hypothermia can develop as a result of prolonged surface contact with cold water during immersion, while the airway is above water, or with submersion. Body temperature may also continue to fall as a result of cold air, wet clothes, hypoxia, and hospital transport. Hypothermia in pediatric drowning victims may be observed even after drowning in relatively warm water and in warm climates.

Immersion in cold water has immediate respiratory and cardiovascular effects. Victims experience **cold water shock**, a dynamic series of cardiorespiratory physiologic responses that can cause drowning. In adults, immersion in icy water results in intense involuntary reflex hyperventilation and to a decrease in breath-holding ability to <10 sec, which leads to fluid aspiration. Severe bradycardia, the diving reflex, occurs in adults but is transient and rapidly followed by supraventricular and ectopic tachycardia and hypertension. There is no evidence that the diving reflex has any protective effect.

Even after surviving the chaotic minutes of cold water shock, after an additional 5-10 min of cold water immersion, the victim can become incapacitated. Cooling of large and small muscles disables the victim's ability to grab hold, swim or perform other self-rescue maneuvers. Depending on water and air temperature, insulation, body surface area, thermogenic capacity, physical condition, swimming efforts, or high water flow rates, heat loss with continued immersion can significantly decrease core temperature to hypothermic levels within 30-60 min.

The symptoms and severity of hypothermia are categorized based on body temperature. The victim with mild hypothermia has a temperature of 34-36°C (93.2-96.8°F) with intact thermogenic mechanisms (shivering and nonshivering thermogenesis, vasoconstriction) and active movements. Compensatory mechanisms usually attempt to restore normothermia at body temperatures >32°C (89.6°F). Lower core temperatures lead to impaired cognition, coordination, and muscle strength and with it, less ability to self-rescue. Thermoregulation may fail and spontaneous rewarming will not occur. With moderate hypothermia (30 to <34°C [86 to <93.2°F]), loss of consciousness leads to water aspiration. Progressive bradycardia, impaired myocardial contractility, and loss of vasomotor tone contribute to inadequate perfusion, hypotension, and possible shock. At body temperatures <28°C (82.4°F), extreme bradycardia is usually present with decreases in cardiac output, and the propensity for spontaneous ventricular fibrillation or asystole is high. Central respiratory center depression with moderate to severe hypothermia results in hypoventilation and eventual apnea. A deep coma, with fixed and dilated pupils and absence of reflexes at very low body temperatures (<25-29°C [77-84.2°F]), may give the false appearance of death.

The brain can cool to a neuroprotective level if the cooling process is quick and cardiac output lasts long enough for sufficient heat loss to occur prior to the onset of severe hypoxia. However, if submersion leading to drowning occurs prior to development of a neuroprotective level of hypothermia, severe anoxia devastates tissue organs. The theoretical benefits, implications, and consequences of hypothermia in drowning victims are areas of controversy. Known adverse effects are associated with hypothermia, and these must be balanced against the potential benefits observed in experimental data. One should clearly differentiate among (a) controlled hypothermia, such as that used in the operating room before the onset of hypoxia or ischemia, (b) accidental hypothermia, such as occurs in drowning, which is uncontrolled and variable, with onset during or shortly after hypoxia–ischemia, and (c) therapeutic hypothermia, involving the purposeful and controlled lowering and maintenance of body (or brain) temperature at some time after a hypoxic–ischemic event.

In drowning victims with uncontrolled accidental hypothermia associated with icy water submersion, there are a few case reports of good neurologic recovery after prolonged (10-150 min) cardiopulmonary arrest. Almost all of these rare survivors have been in freezing water (<5°C [41°F]) and had core body temperatures <30°C (86°F), often much lower. Presumably, very rapid and sufficiently deep hypothermia developed in these fortunate survivors before irreversible hypoxic–ischemic injury occurred.

Most often hypothermia is a poor prognostic sign, and a neuroprotective effect has not been demonstrated. In King County, Washington, where the water is cold but rarely icy, 92% of drowning survivors with good neurologic outcomes had initial body temperatures ≥34°C (93.2°F), whereas 61% of those who died or had severe neurologic injury had temperatures <34°C (93.2°F). In another study of comatose drowning patients admitted to pediatric intensive care units (PICUs), 65% of hypothermic patients (body temperature <35°C [95°F]) died, compared with a 27% observed mortality rate in nonhypothermic victims. Similarly, in Finland (where the median water temperature was 16°C [60.9°F]) and in the United States, a beneficial effect of drowning-associated hypothermia was not seen in pediatric submersion victims; submersion duration <10 min was most strongly related to good outcome, not water temperature.

MANAGEMENT

The clinical course and outcome for a submersion victim are primarily determined by the duration of submersion, the speed of the rescue, and the effectiveness of resuscitative efforts. Two groups may be identified on the basis of responsiveness at the scene. The first group consists of children who require minimal resuscitation at the scene and quickly regain spontaneous respiration and consciousness. They have good outcomes and minimal complications. These victims should be transported from the scene to the ED for further evaluation and observation.

The second group comprises children in cardiac arrest who require aggressive or prolonged resuscitation and have a high risk of multiorgan system complications, major neurologic morbidity, or death. Compared with cardiac arrest from other causes, cardiac arrest from drowning has a higher survival rate.

Initial management of drowning victims requires coordinated and experienced prehospital care following the ABCs (airway, breathing, circulation) of emergency resuscitation (see Chapter 67). Cardiopulmonary resuscitation of drowning victims must include providing ventilation. Children with severe hypoxic injury and symptoms often remain comatose and lack brainstem reflexes despite the restoration of oxygenation and circulation. Subsequent ED and PICU care often involve advanced life support strategies and management of multiorgan dysfunction.

Initial Evaluation and Resuscitation

See Chapter 67.

Once a submersion has occurred, immediate institution of CPR efforts at the scene is imperative. The goal is to reverse the anoxia from submersion and limit secondary hypoxic injury after submersion. Every minute that passes without the reestablishment of adequate

breathing and circulation dramatically decreases the possibility of a good outcome. When safe for the victim and the rescuer, institution of in-water resuscitation for nonbreathing victims by trained personnel may improve the likelihood of survival. Victims usually need to be extricated from the water as quickly as possible so that effective CPR can be provided. Common themes in children who have good recovery are a short duration of event and initiation of CPR as soon as possible, prior to arrival of emergency medical services.

Initial resuscitation must focus on rapidly restoring oxygenation, ventilation, and adequate circulation. The airway should be clear of vomitus and foreign material, which may cause obstruction or aspiration. **Abdominal thrusts should not be used** for fluid removal, because many victims have a distended abdomen from swallowed water; abdominal thrusts may increase the risk of regurgitation and aspiration. In cases of suspected airway foreign body, chest compressions or back blows are preferable maneuvers.

The cervical spine should be protected in anyone with potential traumatic neck injury (see Chapters 68 and 72). Cervical spine injury is a rare concomitant injury in drowning; only approximately 0.5% of submersion victims have cervical spine injuries. History of the event and victim age guide suspicion of cervical spine injury. Drowning victims with cervical spine injury are usually preteens or teenagers whose drowning event involved diving, a motorized vehicle crash, a fall from a height, a water sport accident, child abuse, or other clinical signs of serious traumatic injury. In such cases, the neck should be maintained in a neutral position and protected with a well-fitting cervical collar. Patients rescued from unknown circumstances may also warrant cervical spine precautions. In low-impact submersions, spinal injuries are exceedingly rare, and routine spinal immobilization is not warranted.

If the victim has ineffective respiration or apnea, ventilatory support must be initiated immediately (see Chapter 67). Mouth-to-mouth or mouth-to-nose breathing by trained bystanders often restores spontaneous ventilation. As soon as it is available, supplemental oxygen should be administered to all victims. Positive-pressure bag-mask ventilation with 100% inspired oxygen should be instituted in patients with respiratory insufficiency. If apnea, cyanosis, hypoventilation, or labored respiration persists, trained personnel should perform endotracheal tube intubation as soon as possible. Intubation is also indicated to protect the airway in patients with depressed mental status or hemodynamic instability. Hypoxia must be corrected rapidly to optimize the chance of recovery.

Concurrent with securing of airway control, oxygenation, and ventilation, the child's cardiovascular status must be evaluated and treated according to the usual resuscitation guidelines and protocols. Heart rate and rhythm, blood pressure, temperature, and end-organ perfusion require urgent assessment. CPR should be instituted immediately in pulseless, bradycardic, or severely hypotensive victims. Continuous monitoring of the electrocardiogram (ECG) allows appropriate diagnosis and treatment of arrhythmias. Slow capillary refill, cool extremities, and altered mental status are potential indicators of shock (see Chapter 70).

Recognition and treatment of hypothermia are the unique aspects of cardiac resuscitation in the drowning victim (Table 74-1). Core temperature must be evaluated, especially in children, because moderate to severe hypothermia can depress myocardial function and cause arrhythmias. Wet clothing should be removed to prevent ongoing heat losses, however, in the hemodynamically stable patient, rewarming should be initiated in the controlled environment of the receiving ED or PICU. Unstable patients (i.e. arrhythmias) should be warmed to 34°C (93.2°F), taking care not to overheat. Trials are investigating if therapeutic hypothermia might be helpful or if avoiding hyperthermia is actually the key element to long-term neurologic survival.

Often, IV fluids and cardioactive medications are required to improve circulation and perfusion. Vascular access should be established as quickly as possible for the administration of fluids or pressors. Intraosseous catheter placement is a potentially lifesaving vascular access technique that avoids the delay usually associated with multiple attempts to establish IV access in critically ill children. Epinephrine is usually the initial drug of choice in victims with bradyasystolic cardiopulmonary arrest (the IV dose is 0.01 mg/kg of 1 : 10,000 solution given q3-5min as needed). Epinephrine can be given intratracheally (endotracheal tube dose is 0.1-0.2 mg/kg of 1 : 1,000 solution) if no IV access is available. An intravascular bolus of lactated Ringer solution or 0.9% normal saline (10-20 mL/kg) is often used to augment preload; repeated doses may be necessary. Hypotonic or glucose-containing solutions should not be used for intravascular volume administration of drowning victims.

Hospital-Based Evaluation and Treatment

Most pediatric drowning victims should be observed for at least 6-8 hr, even if they are asymptomatic on presentation to the ED. At a minimum, serial monitoring of vital signs (respiratory rate, heart rate, blood pressure, and temperature) and of oxygenation by pulse oximetry, repeated pulmonary examination, and neurologic assessment should be performed in all drowning victims. Other studies may also be warranted, depending on the specific circumstances (possible abuse or neglect, traumatic injuries, or suspected intoxication). Almost half of asymptomatic or minimally symptomatic alert children (those who do not require advanced life support in the prehospital setting or who have an initial ED Glasgow Coma Scale [GCS] score of ≥13) experience some level of respiratory distress or hypoxemia progressing to pulmonary edema, usually during the 1st 4-8 hr after submersion. Most alert children with early respiratory symptoms respond to oxygen and, despite abnormal initial radiographs, become asymptomatic with a return of normal room air Sa_{O_2} and pulmonary examination by 4-6 hr. Subsequent delayed respiratory deterioration is extremely unlikely in such children. Selected low-risk patients who are alert and asymptomatic with normal physical findings and oxygenation levels may be considered for discharge after 6-8 hr of observation, as long as appropriate follow-up can be ensured.

Cardiorespiratory Management

For children who are not in cardiac arrest, the level of respiratory support should be appropriate to the patient's condition and is a continuation of prehospital management. Frequent assessments are required to ensure that adequate oxygenation, ventilation, and airway control are maintained (see Chapter 71). *Hypercapnia should generally be avoided in potentially brain-injured children.* Patients with actual or potential hypoventilation or markedly elevated work of breathing should receive mechanical ventilation to avoid hypercapnia and decrease the energy expenditures of labored respiration.

Measures to stabilize cardiovascular status should also continue. Conditions contributing to myocardial insufficiency include hypoxic–ischemic injury, ongoing hypoxia, hypothermia, acidosis, high airway pressures during mechanical ventilation, alterations of intravascular volume, and electrolyte disorders. Heart failure, shock, arrhythmias, or cardiac arrest may occur. Continuous ECG monitoring is mandatory for recognition and treatment of arrhythmias (see Chapter 435).

The provision of adequate oxygenation and ventilation is a prerequisite to improving myocardial function. Fluid resuscitation and inotropic agents are often necessary to improve heart function and restore tissue perfusion (see Chapter 67). Increasing preload with IV fluids may be beneficial through improvements in stroke volume and cardiac output. Overzealous fluid administration, especially in the presence of poor myocardial function, can worsen pulmonary edema.

For patients with persistent cardiopulmonary arrest on arrival in the ED after *non–icy water* drowning, the decision to withhold or stop resuscitative efforts can be addressed by review of the history and the response to treatment. Because there are reports of good outcome following ongoing CPR in the ED, most drowning victims should be treated aggressively upon presentation. However, for children who do not show ready response to aggressive resuscitative efforts, the need for prolonged ongoing CPR after non–icy water submersion almost invariably predicts death or persistent vegetative state. Consequently, in most cases, discontinuation of CPR in the ED is probably warranted

Table 74-1 Approach to Drowning-Prevention Strategies

	HOME	RECREATION	NEIGHBORHOOD
Water hazards	Swimming pools Ponds Bathtubs Large buckets	Playing in water- swimming, wading Playing near water Being on water—boating	Irrigation ditches Watering holes Water drainage
Common risks	Lapse in supervision Unexpected toddler exposure Delayed discovery of child Reliance on water wings or pool toys Reliance on sibling or bath seat for bathing supervision	Lapse in supervision Change in weather Unfamiliarity with or change(s) in water conditions: • Steep drop-off • Current/tide • Low temperature Alcohol use Peer pressure	Lapse in supervision, particularly when caregiver is socializing Risky behavior when with peers
Prevention strategies	Recognize hazards and risks Provide constant adult supervision around water Install 4-sided, isolation fencing of pools Install rescue equipment and phone at poolside Learn swimming and water survival skills Avoid bath, instead shower, if a child/teen with seizure disorder Learn first aid and CPR	Provide constant adult supervision Swim in lifeguarded areas Know when and how to wear U.S. Coast Guard–approved PFDs Avoid alcohol and other drugs Learn swimming and water survival skills Teach children about water safety Be aware of current weather and water conditions Learn first aid and CPR	Identify hazardous bodies of water Prevent access to water with barriers Provide fenced-in "safe area" for water recreation Provide lifeguarded swim sites Provide access to low cost swim/water survival lessons

for victims of non–icy water submersion who do not respond to resuscitation within 25-30 min. Final decisions regarding whether and when to discontinue resuscitative efforts must be individualized, with the understanding that the possibility of good outcome is generally very low with protracted resuscitation efforts.

Neurologic Management

Drowning victims who present to the hospital awake and alert usually have normal neurologic outcomes. In comatose victims, irreversible CNS injury is highly likely. The most critical and effective neurologic intensive care measures after drowning are rapid restoration and maintenance of adequate oxygenation, ventilation, and perfusion. Core body temperature and glucose management may also be important modulators of neurologic injury after hypoxia–ischemia.

Comatose drowning patients are at risk for intracranial hypertension. There is little evidence that ICP monitoring and therapy to reduce intracranial hypertension improve outcomes for drowning victims. Patients with elevated ICP usually have poor outcomes—either death or persistent vegetative state. Children with normal ICP can also have poor outcomes, although less frequently. Conventional neurologic intensive care therapies, such as fluid restriction, hyperventilation, and administration of muscle relaxants, osmotic agents, diuretics, barbiturates, and steroids, have not been shown to benefit the drowning victim, either individually or in combination. There is some evidence that these therapies may reduce overall mortality but increase the number of survivors with severe neurologic morbidity.

Electroencephalographic monitoring has only limited value in the management of drowning victims and is generally not recommended, except to detect seizures or as an adjunct in the clinical evaluation of brain death (see Chapter 68.1). Seizures should be treated if possible, although they tend to be very refractory. There is no evidence that treatment of seizures after drowning improves outcome. Fosphenytoin or phenytoin (loading dose of 10-20 mg of phenytoin equivalents/kg, followed by maintenance dosing with 5-8 mg of phenytoin equivalents/kg/day in 2-3 divided doses; levels should be monitored) may be considered as an anticonvulsant; it may have some neuroprotective effects and may mitigate neurogenic pulmonary edema. Benzodiazepines, barbiturates, and other anticonvulsants may also have some role in seizure therapy.

With optimal management, many initially comatose children can have impressive neurologic improvement, but usually do so within the 1st 24-72 hr. Unfortunately, almost half of deeply comatose drowning victims admitted to the PICU die of their hypoxic brain injury or survive with severe neurologic damage. Many children become brain dead. Deeply comatose drowning victims who do not show substantial improvement on neurologic examination after 24-72 hr and whose coma cannot be otherwise explained should be seriously considered for limitation or withdrawal of support.

Other Management Issues

A few drowning victims may have traumatic injury (see Chapter 72), especially if their drowning event involved participation in high energy water sports such as personal watercraft, boating, diving, or surfing. A high index of suspicion for such injury is required. Spinal precautions should be maintained in victims with altered mental status and suspected traumatic injury. Significant anemia suggests trauma and internal hemorrhage.

Hypoxic–ischemic injury can have multiple systemic effects, although protracted organ dysfunction is uncommon in the absence of severe CNS injury. Hyperglycemia is associated with a poor outcome in pediatric drowning victims. Its etiology is unclear but it is possibly a stress response.

Manifestations of acute kidney injury may be seen after hypoxic–ischemic injury (see Chapter 535). Diuretics, fluid restriction, and dialysis are occasionally needed to treat fluid overload or electrolyte disturbances; renal function usually normalizes in survivors. Rhabdomyolysis after drowning has been reported.

Profuse bloody diarrhea and mucosal sloughing usually portend a grim prognosis; conservative management includes bowel rest, nasogastric suction, and gastric pH neutralization. Nutritional support for most drowning victims is usually not difficult, because the majority of children either die or recover quickly and resume a normal diet within a few days; enteral tube feeding or parenteral nutrition is occasionally indicated in children who do not recover quickly.

Hyperthermia after drowning or other types of brain injury may increase the risk of mortality and exacerbate hypoxic–ischemic CNS damage. Almost half of drowning victims have a fever during the 1st 48 hr after submersion. Hyperthermia is usually not caused by

infection and resolves without antibiotics in approximately 80% of patients. Generally, prophylactic antibiotics are not recommended. However, there is general consensus that fever or hyperthermia (core body temperature >37.5°C [99.5°F]) in comatose drowning victims resuscitated from cardiac arrest should be prevented at all times in the acute recovery period (at least the 1st 24-48 hr).

Psychiatric and psychosocial sequelae in the family of a pediatric drowning victim are common. Grief, guilt, and anger are common among family members, including siblings. Divorce rates of up to 80% within a few years of the injury have been reported, and parents often report difficulties with employment or substance abuse. Friends and family may blame the parents for the event. Professional counseling, pastoral care, or social work referral should be initiated for drowning victims and their families.

Hypothermia Management

Attention to core body temperature starts in the field and continues during transport and in the hospital. The goal is to prevent or treat moderate or severe hypothermia. Damp clothing should be removed from all drowning victims. Rewarming measures are generally categorized as passive, active external, or active internal (see Chapter 76). Passive rewarming measures can be applied in the prehospital or hospital setting; they include the provision of dry blankets, a warm environment, and protection from further heat loss. They should be instituted as soon as possible for hypothermic drowning victims who have not had a cardiac arrest.

Full CPR with chest compressions is indicated for hypothermic victims if no pulse can be found or if narrow complex QRS activity is absent on ECG (see Chapters 67 and 76). When core body temperature is <30°C (86°F), resuscitative efforts should proceed according to the current American Heart Association guidelines for CPR, but IV medications may be given at a lower frequency in moderate hypothermia because of decreased drug clearance. When ventricular fibrillation is present in severely hypothermic victims (core temperature <30°C [86°F]), defibrillation should be initiated but may not be effective until the core temperature is ≥30°C (86°F), at which time successful defibrillation may be more likely.

Significant controversy surrounds the discontinuation of prolonged resuscitative efforts in hypothermic drowning victims. Body temperature should be taken into account before resuscitative efforts are terminated. Other considerations include whether the victim may have been immersed prior to submerged, whether water was icy or the cooling was very rapid with fast-flowing cold water. Victims with profound hypothermia may appear clinically dead, but full neurologic recovery is possible, although rare. Attempts at lifesaving resuscitation should not be withheld on the basis of initial clinical presentation unless the victim is obviously dead (dependent lividity or rigor mortis). Rewarming efforts should usually be continued until the temperature is 32-34°C (89.6-93.2°F); if the victim continues to have no effective cardiac rhythm and remains unresponsive to aggressive CPR, then resuscitative efforts may be discontinued.

Complete rewarming is not indicated for all arrest victims before resuscitative efforts are abandoned. Discontinuing resuscitation in victims of non–icy water submersion who remain asystolic despite 30 min of CPR is probably warranted. Physicians must use their individual clinical judgment about deciding to stop resuscitative efforts, taking into account the unique circumstances of each incident.

Once a drowning victim has undergone successful CPR after a cardiac arrest, temperature management should be carefully considered, and body temperature should be continuously monitored. In victims in whom resuscitation duration was brief and who are awake soon after resuscitation, attempts to restore and maintain normothermia are warranted. Careful monitoring is necessary to prevent unrecognized worsening hypothermia, which can have untoward consequences.

For drowning victims who remain comatose after successful CPR, more contentious issues include rewarming of hypothermic victims and controlled application of therapeutic hypothermia. Although there is no evidence basis or consensus of opinion, many investigators cautiously recommend that hypothermic drowning victims who remain unresponsive because of hypoxic–ischemic encephalopathy after restoration of adequate spontaneous circulation should not be actively rewarmed to normal body temperatures. Active rewarming should be limited to victims with core body temperatures <32°C (89.6°F), but temperatures 32-37.5°C (89.6-99.5°F) should be allowed without further rewarming efforts.

More controversial is the induction of therapeutic hypothermia in drowning victims who remain comatose because of hypoxic-ischemic encephalopathy after CPR for cardiac arrest. The 2002 World Congress on Drowning recommended that hypothermia (32-34°C [89.6-93.2°F]) be instituted as soon as possible after resuscitation and sustained for 12-24 hr. They recommended that patients be intubated, mechanically ventilated, and treated with sedatives and/or analgesics (with or without neuromuscular blocking agents) as necessary to prevent shivering and maintain hypothermia then gradually rewarmed.

However, a specific recommendation for therapeutic hypothermia, especially in children, is not yet generally accepted. The Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (2002) did not recommend therapeutic hypothermia in drowned children resuscitated after cardiopulmonary arrest, citing insufficient evidence and older studies demonstrating a potential deleterious effect in pediatric drowning victims. Several subsequent studies evaluating extracorporeal membrane circulation, rewarming, and therapeutic hypothermia in pediatric and adult drowned patients have shown no significant improvement in neurologic outcome or mortality rates.

PROGNOSIS

The outcomes for drowning victims are remarkably bimodal: The great majority of victims either have a good outcome (intact or mild neurologic sequelae) or a bad outcome (severe neurologic sequelae, persistent vegetative state or death), with very few exhibiting intermediate neurologic injury at hospital discharge. Subsequent evaluation of good outcome survivors may identify significant persistent cognitive deficits. Of hospitalized pediatric drowning victims, 15% die and as many as 20% survive with severe permanent neurologic damage.

Strong predictors of outcome are based on the incident and response to treatment at the scene. Intact survival or mild neurologic impairment has been seen in 91% of children with submersion duration <5 min and in 87% with resuscitation duration <10 min. Children with normal sinus rhythm, reactive pupils, or neurologic responsiveness at the scene virtually always had good outcomes (99%). Poor outcome is highly likely in patients with deep coma, apnea, absence of papillary responses, and hyperglycemia in the ED, with submersion durations >10 min, and with failure of response to CPR given for 25 min. In one comprehensive case series, all children with *resuscitation durations* >25 min either died or had severe neurologic morbidity, and all victims with *submersion durations* >25 min died. Long-term health-related quality of life and school performance in subjects who had received either bystander or emergency medical service personnel initiated CPR was high if their submersion duration was <10 mins. Higher morbidity, mortality, and lower quality of life was reported in those patients with >10 mins submersion durations. In several studies of pediatric drowning, submersion duration was the best predictor of outcome and water temperature was not. However, there are rare case reports of intact recovery following non–icy water drowning with longer submersion or resuscitation duration.

The GCS score has some limited utility in predicting recovery. Children with a score ≥6 on hospital admission generally have a good outcome, whereas those with a score ≤5 have a much higher probability of poor neurologic outcome. Occasionally, children with a GCS score of 3 or 4 in the ED have complete recovery. Improvement in the GCS score during the first several hours of hospitalization may indicate a better prognosis. Overall, early GCS assessments fail to adequately

distinguish children who will survive intact from those with major neurologic injury.

Neurologic examination and progression during the 1st 24-72 hr are the best prognosticators of long-term CNS outcome. Children who regain consciousness within 48-72 hr, even after prolonged resuscitation, are unlikely to have serious neurologic sequelae. In a small series of comatose victims of non–icy water submersion, all survivors with a good outcome had spontaneous purposeful movements and normal brainstem function within 24 hr; good recovery did not occur in any child with abnormal brainstem function or absence of purposeful movements at 24 hr. In another small series of drowning victims who remained unconscious >24 hr and survived for at least 1 yr, 73% remained in a persistent vegetative state and the rest had severe neurologic impairment, had many complications and a high mortality rate: 45% died during the study's 1-yr follow-up period.

In a large retrospective series of 274 pediatric drowning victims, of those with an initial GCS score of 3 in the ED, only 14% survived intact. Almost all, 95%, of victims who demonstrated purposeful neurologic function within 48 hr survived intact and 100% of those whose first purposeful neurologic response occurred within 6 hr survived intact. Laboratory and technologic methods to improve prognostication have not yet proved superior to neurologic examination. Serial neurologic evaluations after CPR should be performed over the ensuing 48-72 hr, with consideration given to limitation or withdrawal of support in patients who do not have significant neurologic recovery, even though this may occur before absolute prognostic certainty is achieved.

PREVENTION

The most effective way to decrease the injury burden of drowning is prevention. Drowning is a multifaceted problem, but several evidence based preventive strategies are effective. The pediatrician has a prime opportunity to identify and inform families at risk of these strategies through anticipatory guidance. In 2010, the American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention revised its policy statement on the prevention of drowning to advocate for more anticipatory guidance regarding the appropriate supervision of children, access to swim lessons, the presence of lifeguards, barriers to swimming pools, and use of PFDs. A family-centered approach to anticipatory guidance for water safety helps explore and identify the water hazards that each family is exposed to in their environment. The practitioner can then discuss the best tools and strategies for prevention that are relevant for the particular family. It is important to identify the risks both in and around the home and in other locations they may frequent, often when vacationing, such as vacation or relatives' homes. For some families the focus may be on bathtubs and bucket safety; for others, home pools or hot tubs may be the major hazards. If the family recreates near or on open water, they also need to learn about safety around boats and open water. In a rural environment, water collection systems and natural bodies of water may pose great risk.

Parents must build layers of water protection around their children. Table 74-1 provides an approach to the hazards and preventive strategies relevant to the most common sources of water involved in childhood drowning. A common preventive strategy for exposure to all water types and all ages is ensuring appropriate supervision. Pediatricians should define for parents what constitutes appropriate supervision at the various developmental levels of childhood. Many parents either underestimate the importance of adequate supervision or are simply unaware of the risks associated with water. Even parents who say that constant supervision is necessary will often admit to brief lapses while their child is alone near water. Parents also overestimate the abilities of older siblings; many bathtub drownings occur when an infant or toddler is left with a child younger than 5 yr.

Supervision of infants and young children means that a responsible adult should be with the child every moment. The caregiver must be alert, must not be consuming alcohol or other drugs or socializing, and must be attentive and focused entirely on watching the child. Even a brief moment of inattention, such as to answer a phone, get a drink, or hold a conversation, can have tragic consequences. If the child does not swim, "touch supervision" is required, meaning that the caregiver should be within arm's reach at all times. Adolescents require active adult supervision and avoidance of alcohol or drug use during water activities. Learning to swim offers another layer of protection. Children may start swim lessons at an early age that are developmentally appropriate and aimed at the individual child's readiness and skill level. Swim lessons are beneficial and to provide some level of protection to young children. A study from Bangladesh, where drowning accounts for 20% of all deaths in children ages 1-4 yr, showed that swim lessons and water safety curricula are cost-effective and led to a decrease in mortality from drowning. As with any other water safety intervention, parents need to know that swimming lessons and acquisition of swim skills cannot be solely relied on to prevent drowning. No child can be "drown-proof." A supervising caretaker should be aware of where and how to get help and know how to safely rescue a child in trouble. Because only those trained in water rescue can safely attempt it, families should be encouraged to swim in designated areas only when and where a lifeguard is on duty.

Children and adolescents should never swim alone regardless of their swimming abilities. Even as they become more independent and participate in recreational activities without their parents, they should be encouraged to seek areas that are watched by lifeguards. Lifeguards rescue more than 100,000 Americans each year from drowning, and probably prevent millions more drownings through verbal warnings and prompt interventions when needed. It is important to emphasize that even if the child is considered a strong swimmer, the ability to swim in a pool does not translate to being safe in open water, where water temperature, currents, and underwater obstacles can present additional and unfamiliar challenges. For swimmers, supervision by lifeguards reduces drowning risk, because lifeguards monitor risk behaviors and are trained in the difficult and potentially dangerous task of rescuing drowning victims.

Two of the preventive strategies listed in Table 74-1 deserve special mention. The most vigorously evaluated and effective drowning intervention applies to swimming pools. Isolation fencing that completely surrounds a pool, with a secure, self-locking gate, reduces the risk of drowning. Guidelines for appropriate fencing, provided by the U.S. Consumer Product Safety Commission, are very specific; they were developed through testing of active toddlers in a gymnastics program on their ability to climb barriers of different materials and heights and recent studies show them to be effective in preventing drowning in young children. In families who have a pool on their property, caregivers often erroneously believe that if a child falls into the water there will be a loud noise or splash to alert them. Sadly, these events are usually silent, delaying timely rescue. This finding highlights the need for a fence that actually separates the pool from the house, not just surrounds the entire property. The use of U.S. Coast Guard–approved lifejackets or PFDs should be advised with all families spending time around open water, not just those who consider themselves boaters. This issue is also particularly important for families who will participate in aquatic activities on a vacation. A PFD should be chosen with respect to the weight of the child and the proposed activity. Young children should wear PFDs that will float their head up. Parents should be urged to wear PFDs, too, as their use is associated with greater use by their children. Toys such as water wings and "floaties" should not be relied upon as drowning prevention measures.

Effective preventive efforts must also consider cultural practices. Different ethnic groups may have certain attitudes, beliefs, dress, or other customs that may affect their water safety. The higher drowning risk of minority children needs to be addressed by community-based prevention programs.

In addition to anticipatory guidance, pediatricians can play an active role in drowning prevention by participating in advocacy efforts to

improve legislation for pool fencing, PFD use, and alcohol consumption in various water activities. Several counties in the United States, Australia, and New Zealand have laws requiring isolation fencing for pools. Their effectiveness has been limited by a lack of enforcement. Similarly, all states have boating-under-the-influence laws but, similarly, rarely enforce them. Furthermore, efforts at the community level may be needed to ensure the availability of swimming lessons for underserved populations and lifeguarded swim areas.

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Chapter 75

Burn Injuries

Alia Y. Antoon and Mary K. Donovan

Burns are a leading cause of unintentional injury in children, second only to motor vehicle crashes. There has been a decline in the incidence of burn injury requiring medical care that has coincided with a stronger focus on burn treatment and prevention, increased fire and burn prevention education, greater availability of regional treatment centers, widespread use of smoke detectors, greater regulation of consumer products and occupational safety, and societal changes such as reductions in smoking and alcohol abuse.

EPIDEMIOLOGY

Approximately 2 million people in the United States require medical care for burn injuries each year. Approximately 50% of these patients are younger than age 5 yr, with an average age of 32 mo. The principal cause of the burn is scald; one of the causes of scald burn is heating liquids in the microwave. The leading cause of burn in children 5-14 yr of age is flame injury. In children ages 5-10 yr, this is usually a result of match play, whereas, for older children, it is usually a result of gasoline ignition. Fires are a major cause of mortality in children, accounting for up to 34% of fatal injuries in those younger than age 16 yr. Scald burns account for 85% of total injuries and are most prevalent in children younger than 4 yr. Although the incidence of hot water scalding has been reduced by legislation requiring new water heaters to be preset at 48.9°C (120°F), scald injury remains the leading cause of hospitalization for burns. Steam inhalation used as a home remedy to treat respiratory infections is another potential cause of burns. Flame burns account for 13%; the remaining are electrical and chemical burns. Clothing ignition events have declined since passage of the Federal Flammable Fabric Act requiring sleepwear to be flame-retardant; however, the U.S. Consumer Product Safety Commission has voted to relax the existing children's sleepwear flammability standard. Polyester is the fabric most resistant to ignition by small flame source. Polyester does burn deeply as it melts, but it self-extinguishes when the flame source is removed. Cotton, on the other hand, continues to burn after the flame source has been removed resulting in large deep burns. Polyester melts downward, sparing the face and respiratory tract; cotton burns upward toward the face. Pellet stove, glass front stoves, and flat top stoves are becoming frequent sources of hand burns in children. Approximately 18% of burns are the result of child abuse (usually scalds), making it important to assess the pattern and site of injury and their consistency with the patient history (see Chapter 40). Friction burns from treadmills are also a problem. Hands are the most commonly injured sites, with deep 2nd-degree friction injury sometimes associated with fractures of the fingers. Anoxia, not the actual burn, is a major cause of morbidity and mortality in house fires.

Review of the history usually shows a common pattern: scald burns to the side of the face, neck, and arm if liquid is pulled from a table or stove; burns in the pant leg area if clothing ignites; burns in a splash pattern from cooking; and burns on the palm of the hand from contact with a hot stove. However, "glove or stocking" burns of the hands and feet, single-area deep burns on the trunk, buttocks, or back, and small, full-thickness burns (cigarette burns) in young children should raise the suspicion of child abuse (see Chapter 40).

Burn care involves a range of activities: prevention, acute care and resuscitation, wound management, pain relief, reconstruction, rehabilitation, and psychosocial adjustment. Children with massive burns require early and appropriate psychological and social support as well as resuscitation. Surgical debridement, wound closure, and rehabilitative efforts should be instituted concurrently to promote optimal rehabilitation. Aggressive surgical removal of devitalized tissue, infection control, and judicious use of antibiotics, as well as early nutrition and cautious use of intubation and mechanical ventilation, are necessary to maximize survival. Children who have sustained burn injuries differ in appearance from their peers, necessitating supportive efforts for reentry to school and social and sporting activities.

PREVENTION

The aim of burn prevention is a continuing reduction in the number of serious burn injuries (Table 75-1). Effective first aid and triage can decrease both the extent (area) and the severity (depth) of injuries. The use of flame-retardant clothing and smoke detectors, control of hot water temperature (thermostat settings) to 48.9°C (120°F) within buildings, and prohibition of cigarette smoking have been partially successful in reducing the incidence of burn injuries. Treatment of children with significant burn injuries in dedicated burn centers facilitates medically effective care, improves survival, and leads to greater cost efficiency. Survival of at least 80% of patients with burns of 90% of the body surface area (BSA) is possible; the overall survival rate of children with burns of all sizes is 99%. Death is more likely in children with irreversible anoxic brain injury sustained at the time of the burn. It is well-known that burns occur in predictable patterns. Seasonal pattern sources include:

Winter

- Glass front fireplaces/pellet stoves and radiators increase hand burns
- Treadmill injuries as more people exercise inside—child imitates adults or young child touches belt

Summer

- Fireworks, sparkler—temperatures reach 537.8°C (1000°F)
- Burn contact with hot grill; hand/feet burn from hot embers
- Lawnmowers

Spring/Fall

- Burning leaves
- Gasoline burns
- Tap water scalds are essentially preventable through a combination of behavioral and environmental changes

Pediatricians can play a major role in preventing the most common burns by educating parents and healthcare providers. Simple, effective, efficient, and cost-effective preventive measures include the use of appropriate clothing and smoke detectors, and the planning of routes for emergency exit from the home. The National Fire Protection Association (NFPA) recommends replacing smoke detector batteries annually and the smoke detector alarm every 10 yr (or earlier, if indicated on the device). Child neglect and abuse must be seriously considered when the history of the injury and the distribution of the burn do not match.

ACUTE CARE, RESUSCITATION, AND ASSESSMENT

Indications for Admission

Burns covering >10% of total BSA, burns associated with smoke inhalation, burns resulting from high-tension (voltage) electrical injuries,

Table 75-1 Burn Prophylaxis

PREVENT FIRES Install and use smoke detectors Control the hot water thermostat—in public buildings, the maximum water temperature should be 48.9°C (120°F) Keep fire, matches, and lighters out of the reach of children Avoid cigarette smoking, especially in bed Do not leave lit candles unattended Use flame retardant–treated clothing Use caution when cooking, especially with oil Keep cloth items off heaters
PREVENT INJURY Roll, but do not run, if clothing catches fire; wrap in a blanket Practice escape procedures Crawl beneath smoke if a fire occurs indoors Use educational materials*

*National Fire Protection Association pamphlets and videos.

Table 75-2 Indications for Hospitalization for Burns

Burns affecting >10% of BSA Burns >10-20% of BSA in adolescent/adult 3rd-Degree burns Electrical burns caused by high-tension wires or lightening Chemical burns Inhalation injury, regardless of the amount of BSA burned Inadequate home or social environment Suspected child abuse or neglect Burns to the face, hands, feet, perineum, genitals, or major joints Burns in patients with preexisting medical conditions that may complicate the acute recovery phase Associated injuries (fractures) Pregnancy

and burns associated with suspected child abuse or neglect should be treated as emergencies, and the child hospitalized (Table 75-2). Small 1st- and 2nd-degree burns of the hands, feet, face, perineum, and joint surfaces also require admission if close follow-up care is difficult to provide. Children who have been in enclosed-space fires and those who have face and neck burns should be hospitalized for at least 24 hr for observation for signs of central nervous system (CNS) effects of anoxia from carbon monoxide poisoning and pulmonary effects from smoke inhalation.

First Aid Measures

Acute care should include the following measures:

1. Extinguish flames by rolling the child on the ground; cover the child with a blanket, coat, or carpet.
2. After determining that the airway is patent, remove smoldering clothing or clothing saturated with hot liquid. Jewelry, particularly rings and bracelets, should be removed or cut away to prevent constriction and vascular compromise during the edema phase in the 1st 24-72 hr after burn injury.
3. In cases of chemical injury, brush off any remaining chemical, if powdered or solid; then use copious irrigation or wash the affected area with water. Call the local poison control center for the neutralizing agent to treat a chemical ingestion.
4. Cover the burned area with clean, dry sheeting and apply cold (not iced) wet compresses to small injuries. Significant large-burn injury (>15% of BSA) decreases body temperature control and contraindicates the use of cold compresses.
5. If the burn is caused by hot tar, use mineral oil to remove the tar.
6. Administer analgesic medications.

Table 75-3 Acute Treatment of Burns

First aid, including washing of wounds and removal of devitalized tissue Fluid resuscitation Provision of energy requirements Control of pain Prevention of infection—early excision and grafting Prevention of excessive metabolic expenditures Control of bacterial wound flora Use of biologic and synthetic dressings to close the wound

Emergency Care

Life-support measures are as follows (Table 75-3):

1. Rapidly review the cardiovascular and pulmonary status and document pre-existing or physiologic lesions (asthma, congenital heart disease, renal or hepatic disease).
2. Ensure and maintain an adequate airway and provide humidified oxygen by mask or endotracheal intubation (Fig. 75-1). The latter may be needed in children who have facial burns or a burn sustained in an enclosed space, before facial or laryngeal edema becomes evident. If hypoxia or carbon monoxide poisoning is suspected, 100% oxygen should be used (see Chapters 67 and 71).
3. Children with burns >15% of BSA require intravenous (IV) fluid resuscitation to maintain adequate perfusion. In an emergency situation if IV access is unattainable, an intraosseous line should be placed. When inserting central lines to provide high-volume fluid, special attention should be paid to use a very-small-caliber catheter in small children to avoid injury to the vascular lining, which may predispose to formation of clots. All inhalation injuries, regardless of the extent of BSA burn, require venous access to control fluid intake. All high-tension and electrical injuries require venous access to ensure forced alkaline diuresis in case of muscle injury to avoid myoglobinuric renal damage. Lactated Ringer solution, 10-20 mL/kg/hr (normal saline may be used if lactated Ringer solution is not available), is initially infused until proper fluid replacement can be calculated. Consultation with a specialized burn unit should be made to coordinate fluid therapy, the type of fluid, the preferred formula for calculation, and preferences for the use of colloid agents, particularly if transfer to a burn center is anticipated.
4. Evaluate the child for associated injuries, which are common in patients with a history of high-tension electrical burn, especially if there has also been a fall from a height. Injuries to the spine, bones, and thoracic or intraabdominal organs may occur (see Chapter 72). Cervical spine precautions should be observed until this injury is ruled out. There is a very high risk of cardiac abnormalities, including ventricular tachycardia and ventricular fibrillation, resulting from conductivity of the high electric voltage. Cardiopulmonary resuscitation should be instituted promptly at the scene, and cardiac monitoring should be started upon the patient's arrival at the emergency department (see Chapter 67).
5. Children with burns of >15% of BSA should not receive oral fluids (initially), because gastric distention may develop. These children require insertion of a nasogastric tube in the emergency department to prevent aspiration.
6. A Foley catheter should be inserted to monitor urine output in all children who require IV fluid resuscitation.
7. All wounds should be wrapped with sterile dressings until a decision is made about whether to treat the patient on an outpatient basis or refer the patient to an appropriate facility for treatment.
8. A carbon monoxide measurement (carboxyhemoglobin [HbCO]) should be obtained for fire victims, and 100% oxygen administered until the result is known.

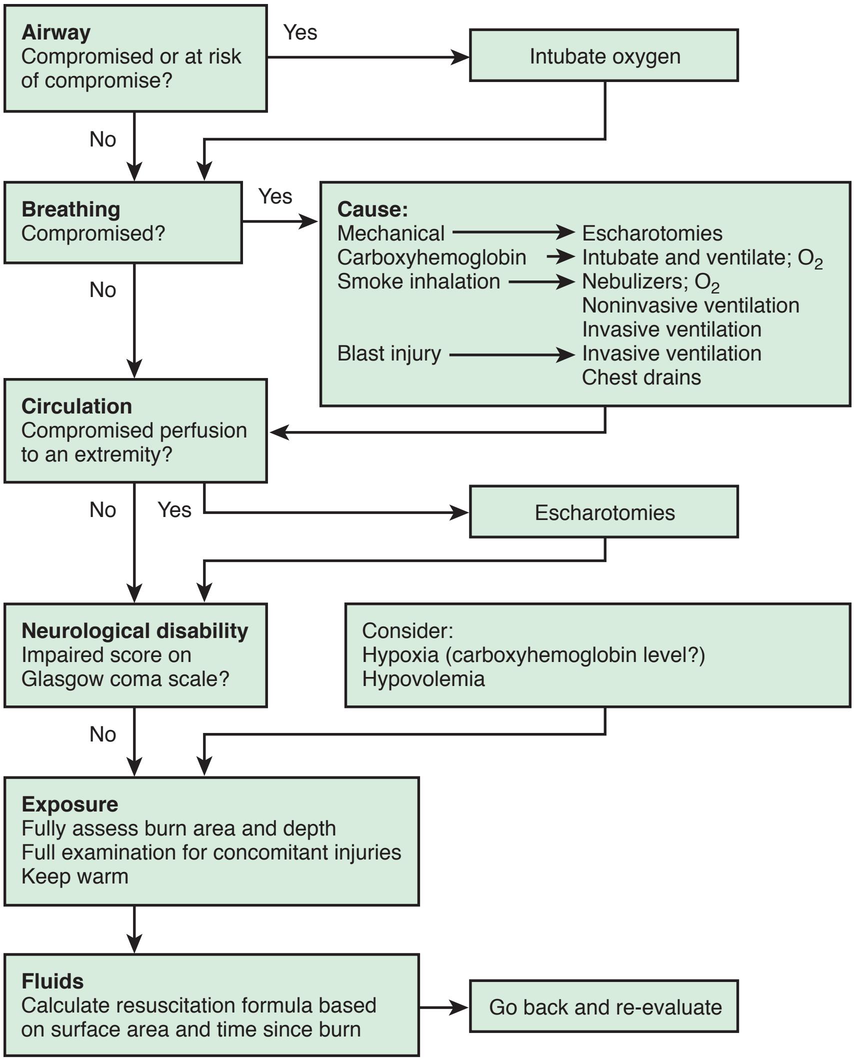

Figure 75-1 Algorithm for the primary survey of a major burn injury. O_2, oxygen. *(From Hettiaratchy S, Papini R: Initial management of a major burn I: overview.* BMJ *328:1555-1557, 2004.)*

9. Review child immunization, burns under 10% BSA do not require tetanus prevention, burns over 10% need tetanus immunization; use diphtheria, tetanus toxoids and acellular pertussis (DTaP) for tetanus prophylaxis for ages <11 yr, and tetanus, diphtheria and pertussis (TdaP) for ages >11 yr (see Chapter 211).

Classification of Burns

Proper triage and treatment of burn injury require assessment of the extent and depth of the injury (Table 75-4 and Fig. 75-2). **First-degree burns** involve only the epidermis and are characterized by swelling, erythema, and pain (similar to mild sunburn). Tissue damage is usually minimal, and there is no blistering. Pain resolves in 48-72 hr; in a small percentage of patients, the damaged epithelium peels off, leaving no residual scars.

A **2nd-degree burn** involves injury to the entire epidermis and a variable portion of the dermal layer (vesicle and blister formation are characteristic). A **superficial** 2nd-degree burn is extremely painful because a large number of remaining viable nerve endings are exposed. Superficial 2nd-degree burns heal in 7-14 days as the epithelium regenerates in the absence of infection. Midlevel to deep 2nd-degree burns also heal spontaneously if wounds are kept clean and infection-free. Pain is less than in more superficial burns because fewer nerve endings remain viable. Fluid losses and metabolic effects of deep dermal (2nd-degree) burns are essentially the same as those of 3rd-degree burns.

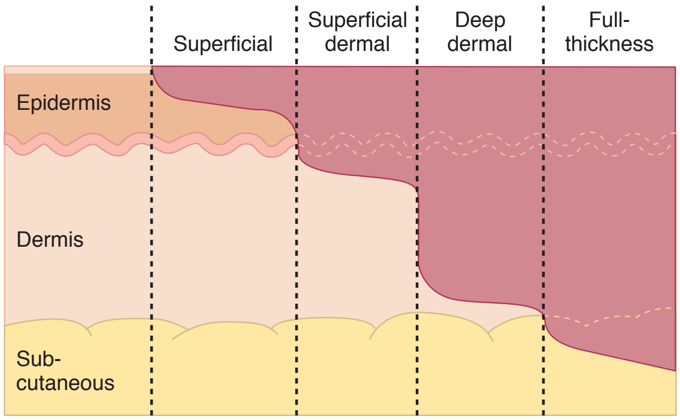

Figure 75-2 Diagram of the different burn depths. *(From Hettiaratchy S, Papini R: Initial management of a major burn II: assessment and resuscitation,* BMJ *329:101-103, 2004.)*

Full-thickness, or 3rd-degree, burns involve destruction of the entire epidermis and dermis, leaving no residual epidermal cells to repopulate the damaged area. The wound cannot epithelialize and can heal only by wound contraction or skin grafting. The absence of painful sensation and capillary filling demonstrates the loss of nerve

Table 75-4 Categories of Burn Depth

	1ST-DEGREE BURN	2ND-DEGREE, OR PARTIAL-THICKNESS, BURN	3RD-DEGREE, OR FULL-THICKNESS, BURN
Surface appearance	Dry, no blisters Minimal or no edema Erythematous Blanches, bleeds	Moist blebs, blisters Underlying tissue is mottled pink and white, with fair capillary refill Bleeds	Dry, leathery eschar Mixed white, waxy, khaki, mahogany, soot-stained No blanching or bleeding
Pain	Very painful	Very painful	Insensate
Histologic depth	Epidermal layers only	Epidermis, papillary, and reticular layers of dermis May include domes of subcutaneous layers	Down to and may include fat, subcutaneous tissue, fascia, muscle, and bone
Healing time	2-5 days with no scarring	Superficial: 5-21 days with no grafting Deep partial: 21-35 days with no infection; if infected, converts to full-thickness burn	Large areas require grafting, but small areas may heal from the edges after wks

and capillary elements. The use of Doppler scanner has become a valuable adjunct tool in burn depth assessment and burn healing potential.

Estimation of Body Surface Area for a Burn

Appropriate burn charts for different childhood age groups should be used to accurately estimate the extent of BSA burned. The volume of fluid needed in resuscitation is calculated from the estimation of the extent and depth of burn surface. Mortality and morbidity also depend on the extent and depth of the burn. The variable growth rate of the head and extremities throughout childhood makes it necessary to use BSA charts, such as that modified by Lund and Brower or the chart used at the Shriners Hospital for Children in Boston (Fig. 75-3). The **rule of nines** used in adults may be used only in children older than 14 yr or as a very rough estimate to institute therapy before transfer to a burn center. In small burns, <10% of BSA, the **rule of palm** may be used, especially in outpatient settings: The area from the wrist crease to the finger crease (the palm) in the child equals 1% of the child's BSA.

TREATMENT

Outpatient Management of Minor Burns

A patient with 1st- and 2nd-degree burns of <10% of BSA may be treated on an outpatient basis unless family support is judged inadequate or there are issues of child neglect or abuse. These outpatients do not require a tetanus booster (unless not fully immunized) or prophylactic penicillin therapy. Blisters should be left intact and dressed with bacitracin or silver sulfadiazine cream (Silvadene). Dressings should be changed once daily, after the wound is washed with lukewarm water to remove any cream left from the previous application. Very small wounds, especially those on the face, may be treated with bacitracin ointment and left open. Debridement of the devitalized skin is indicated when the blisters rupture. A variety of wound dressings/wound membranes are available (e.g., AQUACEL Ag dressing [ConvaTec USA, Skillman, NJ] in a soft felt-like material impregnated with silver ion) may be applied to 2nd-degree burns and wrapped with a dry sterile dressing; similar wound membranes provide pain control, prevention of wound desiccation, and reduction in wound colonization (Table 75-5). These dressings are usually kept on for 7-10 days but are checked twice a week.

Burns to the palm with large blisters usually heal beneath the blisters; they should receive close follow-up on an outpatient basis. The great majority of superficial burns heal in 10-20 days. Deep 2nd-degree burns take longer to heal and may benefit from enzymatic debridement ointment application (collagenase ointment) applied daily on the wound, which aids in the removal of the dead tissue. These ointments should not be applied to the face to avoid the risk of getting them into the eyes.

The depth of scald injuries is difficult to assess early; conservative treatment is appropriate initially, with the depth of the area involved

Table 75-5 Partial Listing of Some Commonly Used Wound Membranes—Selected Characteristics

MEMBRANE	CHARACTERISTIC(S)
Porcine xenograft	Adheres to coagulum Excellent pain control
Biobrane	Bilaminate Fibrovascular in growth into inner layer
Acticoat	Nonadherent dressing that delivers silver
AQUACEL-Ag	Absorptive hydrofiber that delivers silver
Various semipermeable membranes	Provide vapor and bacterial barrier
Various hydrocolloid dressings	Provide vapor and bacterial barrier Absorb exudates
Various impregnated gauzes	Provide barrier while allowing drainage

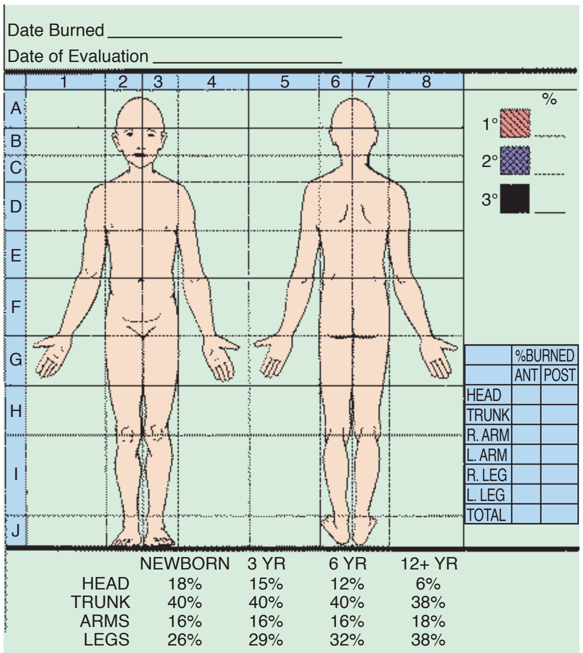

Figure 75-3 **Chart to determine the developmentally related percentage of BSA affected by a burn injury.** ANT, anterior; POST, posterior; R., right; L., left. *(Courtesy of Shriners Hospital for Crippled Children, Burn Institute, Boston Unit.)*

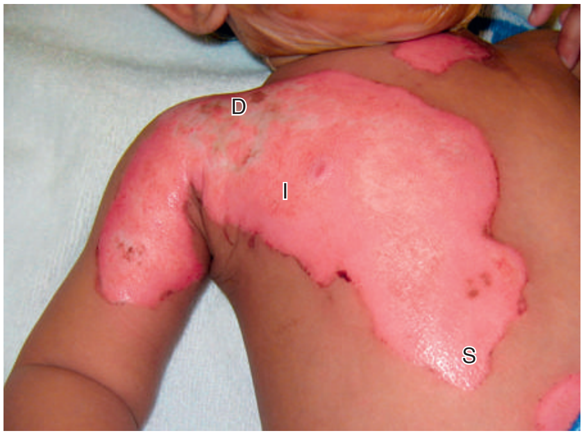

Figure 75-4 Tea scald over the chest and shoulder of a child showing heterogeneity of burn depth. D, deep; I, intermediate; S, superficial. *(From Enoch S, Roshan A, Shah M: Emergency and early management of burns and scalds,* BMJ *338:937-941, 2009.)*

determined before grafting is attempted (Fig. 75-4). This approach obviates the risk of anesthesia and unnecessary grafting.

Fluid Resuscitation

Fluid resuscitation should begin soon after the injury has occurred, in the emergency department before transferring to a burn center. For most children, the Parkland formula is an appropriate starting guideline for fluid resuscitation (4 mL lactated Ringer solution/kg/% BSA burned). Half of the fluid is given over the 1st 8 hr, calculated from the time of onset of injury; the remaining fluid is given at an even rate over the next 16 hr. The rate of infusion is adjusted according to the patient's response to therapy. Pulse and blood pressure should return to normal, and an adequate urine output (>1 mL/kg/hr in children; 0.5-1.0 mL/kg/hr in adolescents) should be accomplished by varying the IV infusion rate. Vital signs, acid–base balance, and mental status reflect the adequacy of resuscitation. Because of interstitial edema and sequestration of fluid in muscle cells, patients may gain up to 20% over baseline (preburn) body weight. Patients with burns of 30% of BSA require a large venous access (central venous line) to deliver the fluid required over the critical 1st 24 hr. Patients with burns of >60% of BSA may require a multilumen central venous catheter; these patients are best cared for in a specialized burn unit. In addition to fluid resuscitation, children should receive standard maintenance fluids (see Chapter 56).

During the 2nd 24 hr after the burn, patients begin to reabsorb edema fluid and to experience diuresis. Half of the 1st day's fluid requirement is infused as lactated Ringer solution in 5% dextrose. Children younger than 5 yr may require the addition of 5% dextrose in the 1st 24 hr of resuscitation. Controversy exists as to whether colloid should be provided in the early period of burn resuscitation. One preference is to use colloid replacement concurrently if the burn is >85% of total BSA. Colloid is usually instituted 8-24 hr after the burn injury. In children younger than 12 mo, sodium tolerance is limited; the volume and sodium concentration of the resuscitation solution should be decreased if the urinary sodium level is rising. The adequacy of resuscitation should be constantly assessed by means of vital signs as well as urine output, blood gas, hematocrit, and serum protein measurements. Some patients require arterial and central venous lines, particularly those undergoing multiple excision and grafting procedures, as needed, for monitoring and replacement purposes. Central venous pressure monitoring may be indicated to assess circulation in patients with hemodynamic or cardiopulmonary instability. Femoral vein cannulation is a safe access for fluid resuscitation, especially in infants and children. Burn patients who require frequent blood gas monitoring benefit from radial or femoral arterial catheterization.

Oral supplementation may start as early as 48 hr after burn. Milk formula, artificial feedings, homogenized milk, or soy-based products can be given by bolus or constant infusion through a nasogastric or small bowel feeding tube. As oral fluids are tolerated, IV fluids are decreased proportionately in an effort to keep the total fluid intake constant, particularly if pulmonary dysfunction is present.

A 5% albumin infusion may be used to maintain the serum albumin levels at a desired 2 g/dL. The following rates are effective: for burns of 30-50% of total BSA, 0.3 mL of 5% albumin/kg/% BSA burn is infused over 24 hr; for burns of 50-70% of total BSA, 0.4 mL/kg/% BSA burn is infused over 24 hr; and for burns of 70-100% of total BSA, 0.5 mL/kg/% BSA burn is infused over 24 hr. Infusion of packed red blood cells is recommended if the hematocrit falls to <24% (hemoglobin = 8 g/dL). Some authorities recommend treatment for hematocrit <30% or hemoglobin <10 g/dL in patients with systemic infection, hemoglobinopathy, cardiopulmonary disease, anticipated (or ongoing) blood loss, and if repeated excision and grafting of full-thickness burns are needed. Fresh-frozen plasma is indicated if clinical and laboratory assessment shows a deficiency of clotting factors, a prothrombin level >1.5 times control, or a partial thromboplastin time >1.2 times control in children who are bleeding or are scheduled for an invasive procedure or a grafting procedure that could result in an estimated blood loss of more than half of blood volume. Fresh-frozen plasma may be used for volume resuscitation within 72 hr of injury in patients younger than 2 yr with burns over 20% of BSA and associated inhalation injury.

Sodium supplementation may be required for children with burns of >20% of BSA if 0.5% silver nitrate solution is used as the topical antibacterial burn dressing. Sodium losses with silver nitrate therapy are regularly as high as 350 mmol/m^2 burn surface area. Oral sodium chloride supplement of 4 g/m^2 burn area/24 hr is usually well tolerated, divided into 4-6 equal doses to avoid osmotic diarrhea. The aim is to maintain serum sodium levels >130 mEq/L and urinary sodium concentration >30 mEq/L. Young children under 5 yr of age are especially susceptible to hyponatremic and cerebral edema. IV potassium supplementation is supplied to maintain a serum potassium level >3 mEq/dL. Potassium losses may be significantly increased when 0.5% silver nitrate solution is used as the topical antibacterial agent or when aminoglycoside, diuretic, or amphotericin therapy is required.

Prevention of Infection and Surgical Management of the Burn Wound

Controversy exists over the prophylactic use of penicillin for all patients hospitalized with acute burn injury and the periodic replacement of central venous catheters to prevent infection. In some units, a 5-day course of penicillin therapy is used for all patients with acute burns; standard-dose crystalline penicillin is given orally or intravenously in 4 divided doses. Erythromycin may be used as an alternative in penicillin-allergic children. Other units have discontinued prophylactic use of penicillin therapy without an increase in the infection rate. Similarly, there is conflicting evidence as to whether relocation of the IV catheter every 48-72 hr decreases or increases the incidence of catheter-related sepsis. Some recommend that the central venous catheter be replaced and relocated every 5-7 days, even if the site is not inflamed and there is no suspicion of catheter-related sepsis.

Mortality related to burn injury is associated not with the toxic effect of thermally injured skin, but with the metabolic and bacterial consequences of a large open wound, reduction of the patient's host resistance, and malnutrition. These abnormalities set the stage for life-threatening bacterial infection originating from the burn wound. Wound treatment and prevention of wound infection also promote early healing and improve aesthetic and functional outcomes. Topical treatment of the burn wound with 0.5% silver nitrate solution, silver sulfadiazine cream, or mafenide acetate (Sulfamylon) cream or topical solution at a concentration of 2.5-5% to be used for wounds with multidrug–resistant bacteria aims at prevention of infection (Table 75-6). These 3 agents have tissue-penetrating capacity. Regardless of the choice of topical antimicrobial agent, it is essential that all 3rd-degree burn tissue be fully excised before bacterial colonization occurs and that the area is grafted as early as possible to prevent deep wound sepsis. Children with a burn of >30% of BSA should be housed in a bacteria-controlled nursing unit to prevent cross-contamination

Table 75-6 Topical Agents Used for Burns

AGENT	EFFECTIVENESS	EASE OF USE
Silvadene cream (silver sulfadiazine)	Good penetration	Changed once daily Residue *must* be washed off with each dressing change
Mafenide acetate cream* (Sulfamylon cream)	Broad spectrum, including *Pseudomonas* Rapid and deep wound penetration	Closed dressings Changed twice daily Residue *must* be washed off with each dressing changed
0.5% Silver nitrate solution	Bacteriostatic Broad spectrum, including some fungi Superficial penetration	Closed bulky dressing soaked every 2 hr and changed once daily
AQUACEL Ag	Dressing impregnated with silver	Applied directly to 2nd-degree burn; occlusive dressing kept for 10 days

*Mafenide acetate solution at concentrations of 2.5% or 5% for use on heavily colonized multidrug–resistant organisms to be used for 5 days only.

and to provide a temperature- and humidity-controlled environment to minimize hypermetabolism.

Deep 2nd-degree burns of >10% of BSA benefit from early excision and grafting. To improve outcome, sequential excision and grafting of 3rd-degree and deep 2nd-degree burns is required in children with large burns. Prompt excision with immediate wound closure is achieved with autografts, which are often meshed to increase the efficiency of coverings. Alternatives for wound closure, such as allografts, xenografts, and Integra (Integra LifeSciences, York, PA) and other synthetic skin coverings (bilaminate membrane composed of a porous lattice of crosslinked chondroitin-6-sulfate engineered to induce neovascularization as it is biodegraded), may be important for wound coverage in patients with extensive injury to limit fluid, electrolyte, and protein losses and to reduce pain and minimize temperature loss. Epidermal cultured cells (autologous keratinocytes) are a costly alternative and are not always successful. An experienced burn team can safely perform early-stage or total excision while burn fluid resuscitation continues. Important keys to success are: (1) accurate preoperative and intraoperative determination of burn depth, (2) the choice of excision area and appropriate timing, (3) control of intraoperative blood loss, (4) specific instrumentation,(5) the choice and use of perioperative antibiotics, and (6) the type of wound coverage chosen. This process can accomplish early wound coverage without the use of recombinant human growth hormone.

Nutritional Support

Supporting the increased energy requirements of a patient with a burn is a high priority. The burn injury produces a hypermetabolic response characterized by both protein and fat catabolism. Depending on the time lapse since the burn, children with a burn of 40% of total BSA require basal energy expenditure (oxygen consumption) approximately 50-100% higher than predicted for their age. Early excision and grafting can decrease the energy requirement. Pain, anxiety, and immobilization increase the physiologic demands. Additional energy expenditure is caused by cold stress if environmental humidity and temperature are not controlled; this is especially true in young infants, in whom the large surface area : mass ratio allows proportionately greater heat loss than in adolescents and adults. Providing environmental temperatures of 28-33°C (82.4-91.4°F), adequate covering during transport and liberal use of analgesics and anxiolytics can decrease caloric demands. Special units to control ambient temperature and humidity may be necessary for children with large surface area burns. Appropriate sleep intervals are necessary and should be part of the regimen. Sepsis increases metabolic rates, and early enteral nutrition, initially with high-carbohydrate, high-protein caloric support (1,800 cal/m^2/24 hr maintenance plus 2,200 cal/m^2 of burn/24 hr) reduces metabolic stress.

The objective of caloric supplementation programs is to maintain body weight and minimize weight loss by meeting metabolic demands. This reduces the loss of lean body mass. Calories are provided at approximately 1.5 times the basal metabolic rate, with 3-4 g/kg of protein/day. The focus of nutritional therapy is to support and compensate for the metabolic needs. Multivitamins, particularly the B vitamin group, vitamin C, vitamin A, and zinc, are also necessary.

Alimentation should be started as soon as is practical, both enterally and parenterally, to meet all of the caloric needs and keep the gastrointestinal tract active and intact after the resuscitative phase. Patients with burns of >40% of total BSA need a flexible nasogastric or small bowel feeding tube to facilitate continuous delivery of calories without the risk of aspiration. To decrease the risk of infectious complications, parenteral nutrition is discontinued as soon as is practical, after delivery of sufficient enteral calories are established. Continuous gastrointestinal feeding is essential, even if feeding is interrupted, causing frequent visits to the operating room, until full grafting takes place. The use of anabolic agents (growth hormone, oxandrolone, low-dose insulin) or anticatabolic agents (propranolol) remains controversial, although β-blocking agents may reduce metabolic stress. Burn centers caring for large burns (>50% BSA, 3rd-degree) in patients who might be malnourished have used the anabolic steroid oxandrolone, at a dose of 0.1-0.2 mg/kg/day given orally, to promote better protein synthesis while the nutritional support by nasogastric feeding and IV hyperalimentation continues.

Topical Therapy

Topical therapy is widely used and is effective against most burn wound pathogens (see Table 75-6). A number of topical agents are used: 0.5% silver nitrate solution, sulfacetamide acetate cream or solution, silver sulfadiazine cream, and Accuzyme ointment or AQUACEL Ag+. Accuzyme is an enzymatic debridement agent and may cause a stinging feeling for 15 min after application. Preferences vary among burn units. Each topical agent has advantages and disadvantages in application, comfort, and bacteriostatic spectrum. Mafenide acetate is a very effective broad-spectrum agent with the ability to diffuse through the burn eschar; it is the treatment of choice for injury to cartilaginous surface, such as the ear; mafenide acetate solution at a concentration of 5% is useful for the treatment of burn wounds that are heavily colonized with multidrug–resistant bacteria (use should be limited to 5 days). The carbonic anhydrase inhibition activity of mafenide acetate may cause acid–base imbalance if large surface areas are treated, and adverse reactions to the sulfur-containing agents may produce transient leukopenia. This latter reaction is mostly noted with the use of silver sulfadiazine cream when applied over large surface areas in children younger than 5 yr of age. This phenomenon is transient, self-limiting, and reversible. No sulfa-containing agent should be used if the child has a history of sulfa allergies.

Inhalational Injury

Inhalational injury is serious in the infant and child, particularly if preexisting pulmonary conditions are present (see Chapter 71). Inhalation injury should be suspected in a patient confined to a closed space (building), with a history of an explosion or a decreased level of consciousness, or with evidence of carbon deposits in the oropharynx or nose, singed facial hair and carbonaceous sputum. Mortality estimates vary, depending on the criteria for diagnosis, but are 45-60% in adults; exact figures are not available in children. Evaluation aims at early identification of inhalation airway injuries. These may occur from (1) direct heat (greater problems with steam burns), (2) acute asphyxia, (3) carbon monoxide poisoning, and (4) toxic fumes, including cyanides from combustible plastics. Sulfur and nitrogen oxides and alkalis

formed during the combustion of synthetic fabrics produce corrosive chemicals that may erode mucosa and cause significant tissue sloughing. Exposure to smoke may cause degradation of surfactant and decrease its production, resulting in atelectasis. Inhalation injury and burn injury are synergistic, and the combined effect can increase morbidity and mortality.

The pulmonary complications of burns and inhalation can be divided into 3 syndromes that have distinct clinical manifestations and temporal patterns:

1. Early complications include carbon monoxide poisoning, airway obstruction, and pulmonary edema.
2. The acute respiratory distress syndrome usually becomes clinically evident later, at 24-48 hr, although it can occur even later (see Chapter 71).
3. Late complications (days to weeks) include pneumonia and pulmonary emboli.

Inhalation injury should be assessed from the evidence of obvious injury (swelling or carbonaceous material in the nasal passages), wheezing, crackles or poor air entry, and laboratory determinations of (HbCO) and arterial blood gases.

Treatment is initially focused on establishing and maintaining a patent airway through prompt and early nasotracheal or orotracheal intubation and adequate ventilation and oxygenation. Wheezing is common, and β-agonist aerosols or inhaled corticosteroids are useful. Aggressive pulmonary toilet and chest physiotherapy are necessary in patients with prolonged nasotracheal intubation or in the rare patient with a tracheotomy. An endotracheal tube can be maintained for months without the need for tracheostomy. If tracheotomy must be performed, it should be delayed until burns at and near the site have healed, and then it should be performed electively, with the child under anesthesia and the use of optimal tracheal positioning and hemostasis. In children with inhalation injury or burns of the face and neck, upper airway obstruction can develop rapidly; endotracheal intubation becomes a lifesaving intervention. Extubation should be delayed until the patient meets the accepted criteria for maintaining the airway.

Signs of CNS injury from hypoxemia caused by asphyxia or carbon monoxide poisoning vary from irritability to depression. Carbon monoxide poisoning may be mild (<20% HbCO), with slight dyspnea, headache, nausea, and decreased visual acuity and higher cerebral functions; moderate (20-40% HbCO), with irritability, agitation, nausea, dimness of vision, impaired judgment, and rapid fatigue; or severe (40-60% HbCO), producing confusion, hallucination, ataxia, collapse, acidosis, and coma. Measurement of HbCO is important for diagnosis and treatment. The PaO_2 value may be normal and the HbCO saturation values misleading because HbCO is not detected by the usual tests of oxygen saturation. Carbon monoxide poisoning is assumed until the tests are performed, and it is treated with 100% oxygen. Significant carbon monoxide poisoning requires hyperbaric oxygen therapy (see Chapter 63).

Patients with severe inhalation injury or with other causes of respiratory deterioration that lead to acute respiratory distress syndrome who do not improve with conventional pressure-controlled ventilation (progressive oxygenation failure, as manifested by oxygen saturation <90% while receiving FIO_2 of 0.9-1.0 and positive end-expiratory pressure of at least 12.5 cm H_2O) may benefit from high-frequency ventilation or nitric oxide inhalation treatment. Nitric oxide usually is administered through the ventilator at 5 parts per million (ppm) and increased to 30 ppm. This method of therapy reduces the need for extracorporeal membrane oxygenation.

Pain Relief and Psychologic Adjustment

See Chapter 62.

It is important to provide adequate analgesia, anxiolytics, and psychologic support to reduce early metabolic stress, decrease the potential for posttraumatic stress syndrome, and allow future stabilization as well as physical and psychologic rehabilitation. Patients and family members require team support to work through the grieving process and accept long-term changes in appearance.

Children with burn injury show frequent and wide fluctuations in pain intensity. Appreciation of pain depends on the depth of the burn; the stage of healing; the patient's age and stage of emotional development and cognition; the experience and efficiency of the treating team; the use of analgesics and other drugs; the patient's pain threshold; and interpersonal and cultural factors. From the onset of treatment, **preemptive pain control** during dressing changes is of paramount importance. The use of a variety of nonpharmacologic interventions as well as pharmacologic agents must be reviewed throughout the treatment period. Opiate analgesia, prescribed in an adequate dose and timed to cover dressing changes, is essential to comfort management. A supportive person who is consistently present and "knows" the patient profile can integrate and encourage patient participation in burn care. The problem of undermedication is most prevalent in adolescents, in whom fear of drug dependence may inappropriately influence treatment. A related problem is that the child's specific pain experience may be misinterpreted; for anxious patients, those who are confused and alone, or those with preexisting emotional disorders, even small wounds may illicit intense pain. Anxiolytic medication added to the analgesic is usually helpful and has more than a synergistic effect. Equal attention is necessary to decrease stress in the intubated patient. Other modalities of pain and anxiety relief (relaxation techniques) can decrease the physiologic stress response. Oral morphine sulfate (immediate release) is recommended at a consistent schedule at a dose of 0.3-0.6 mg/kg every 4-6 hr initially and until wound cover is accomplished. Morphine sulfate IV bolus at a dose of 0.05-0.1 mg/kg maximum of 2-5 mg every 2 hr is administered. Morphine sulfate rectal suppositories may be useful at a dose of 0.3-0.6 mg/kg every 4 hr when oral administration is not possible. The use of codeine preparation should be limited to children older than age 6 yr because of the "ultrarapid metabolizers" of codeine into morphine. For anxiety, lorazepam is given on a consistent schedule, 0.05-0.1 mg/kg/dose every 6-8 hr. To control pain during a procedure (dressing change or debridement), oral morphine at a dose of 0.3-0.6 mg/kg is given 1-2 hr before the procedure and this is supplemented by a morphine IV bolus at a dose of 0.05-0.1 mg/kg given immediately before the procedure. Lorazepam at a dose of 0.04 mg/kg is given orally or intravenously, if necessary, for anxiety before the procedure. Midazolam (Versed) is also very useful for conscious sedation given at a dose of 0.01-0.02 mg/kg for nonintubated patients and 0.05-0.1 mg/kg for intubated patients, as an intravenous infusion or bolus, and may be repeated in 10 min. During the process of weaning from analgesics, the dose of oral opiates is reduced by 25% over 1-3 days, sometimes with the addition of acetaminophen as opiates are tapered. Antianxiety medications are tapered by reducing the dose of benzodiazepines at 25-50% per dose daily over 1-3 days.

For ventilated patients, pain control is accomplished by using morphine sulfate intermittently as an IV bolus at a dose of 0.05-0.1 mg/kg every 2 hr. Doses may need to be increased gradually, and some children may need continuous infusion; a starting dose of 0.05 mg/kg/hr given as an infusion is increased gradually as the need of the child changes. Naloxone is rarely needed but should be immediately available to reverse the effect of morphine, if necessary; if needed for an airway crisis, it should be given in a dose of 0.1 mg/kg up to a total of 2 mg, either intramuscularly or intravenously. For patients undergoing assisted respiration who require treatment of anxiety, midazolam is used as an intermittent IV bolus (0.04 mg/kg given by slow push every 4-6 hr) or as a continuous infusion. For intubated patients, opiates do not need to be discontinued during the process of weaning from the ventilator. Benzodiazepine should be reduced to approximately half the dose over 24-72 hr before extubation; too-rapid weaning from a benzodiazepine can lead to seizures.

There is a growing use of psychotropic medication in the care of children with burns, including prescription of selective serotonin reuptake inhibitors as antidepressants, the use of haloperidol as a neuroleptic in the critical care setting, and the treatment of posttraumatic stress disorder with benzodiazepines. Conscious sedation utilizing ketamine or propofol may be used for major dressing changes.

Reconstruction and Rehabilitation

To ensure maximum cosmetic and functional outcome, occupational and physical therapy must begin on the day of admission, continue throughout hospitalization, and, for some patients, continue after discharge. Physical rehabilitation involves body and limb positioning, splinting, exercises (active and passive movement), assistance with activities of daily living, and gradual ambulation. These measures maintain adequate joint and muscle activity with as normal a range of movement as possible after healing or reconstruction. Pressure therapy is necessary to reduce hypertrophic scar formation; a variety of prefabricated and custom-made garments are available for use in different body areas for prevention of hypertrophic scarring. These custom-made garments deliver consistent pressure on scarred areas; they shorten the time of scar maturation and decrease the thickness of the scar, the redness, and the associated itching. Continued adjustments to scarred areas (scar release, grafting, rearrangement) and multiple minor cosmetic surgical procedures are necessary to optimize long-term function and improve appearance. Replacement of areas of alopecia and scarring has been achieved with the use of tissue expander techniques. The use of ultrapulse laser for reduction of scarring is an adjunct in scar management.

School Reentry and Long-Term Outcome

It is best for the child to return to school immediately after discharge. Occasionally, a child may need to attend a few half-days (because of rehabilitation needs). It is important for the child to return to the child's normal routine of attending school and being with peers. Planning for a return to home and school often requires a *school reentry program* that is individualized to each child's needs. For a school-age child, planning for the return to school occurs simultaneously with planning for discharge. The hospital schoolteacher contacts the local school and plans the program with the school faculty, nurses, social workers, recreational/child-life therapists, and rehabilitation therapists. This team should work with students and staff to ease anxiety, answer questions, and provide information. Burns and scars evoke fears in those who are not familiar with this type of injury and can result in a tendency to withdraw from or reject the burned child. A school reentry program should be appropriate to a child's development and changing educational needs.

Major advances have made it possible to save the lives of children with massive burns; whereas some children have had lingering physical difficulties, most have a satisfactory quality of life. The comprehensive burn care that includes experienced multidisciplinary aftercare plays an important role in recovery. Table 75-7 lists the long-term complications of burns.

Table 75-7 Common Long-Term Disabilities in Patients with Burn Injuries

DISABILITIES AFFECTING THE SKIN AND SOFT TISSUE
Hypertrophic scars
Susceptibility to minor trauma
Dry skin
Contractures
Itching and neuropathic pain
Alopecia
Chronic open wounds
Skin cancers
ORTHOPEDIC DISABILITIES
Amputations
Contractures
Heterotopic ossification
Temporary reduction in bone density
METABOLIC DISABILITIES
Heat sensitivity
Obesity
PSYCHIATRIC AND NEUROLOGIC DISABILITIES
Sleep disorders
Adjustment disorders
Posttraumatic stress syndrome
Depression
Body image issues
Neuropathy and neuropathic pain
Long-term neurologic effects of carbon monoxide poisoning
Anoxic brain injury
LONG-TERM COMPLICATIONS OF CRITICAL CARE
Deep-vein thrombosis, venous insufficiency, or varicose veins
Tracheal stenosis, vocal cord disorders, or swallowing disorders
Renal or adrenal dysfunction
Hepatobiliary or pancreatic disease
Cardiovascular disease
Reactive airway disease or bronchial polyposis
PREEXISTING DISABILITIES THAT CONTRIBUTED TO THE INJURIES
Risk-taking behavior
Untreated or poorly treated psychiatric disorder

Modified from Sheridan RL, Schultz JT, Ryan CM, et al: Case records of the Massachusetts General Hospital: weekly clinicopathological exercises: case 6-2004: a 35-year-old woman with extensive, deep burns from a nightclub fire, N Engl J Med *350:810-821, 2004.*

SPECIAL SITUATIONS

Electrical Burns

There are 3 types of electrical burns. **Minor electrical burns** usually occur as a result of biting on an extension cord. These injuries produce localized burns to the mouth, which usually involve the portions of the upper and lower lips that come in contact with the extension cord. The injury may involve or spare the corners of the mouth. Because these are nonconductive injuries (do not extend beyond the site of injury), hospital admission is not necessary and care is focused on the area of the injury visible in the mouth, it is low voltage, does not cause entry or exit wounds, or cardiac issues. Treatment with topical antibiotic creams is sufficient until the patient is seen in a burn unit outpatient department or by a plastic surgeon.

A more serious category of electrical burn is the **high-tension electrical wire burn**, for which children must be admitted for observation, regardless of the extent of the surface area burn. Deep muscle injury is typical and cannot be readily assessed initially. These injuries result from high voltage (>1,000 V) and occur particularly at high-voltage installations, such as electric power stations or railroads; children climb an electric pole and touch an electric box out of curiosity or accidentally touch a high-tension electric wire. Such injuries have a mortality rate of 3-15% for children who arrive at the hospital for treatment. Survivors have a high rate of morbidity, including major limb amputations. Points of entry of current through the skin and the exit site show characteristic features consistent with current density and heat. The majority of entrance wounds involve the upper extremity, with small exit wounds in the lower extremity. The electrical path, from entrance to exit, takes the shortest distance between the 2 points and may produce injury in any organ or tissue in the path of the current. Multiple exit wounds in some patients attest to the possibility of several electrical pathways in the body, placing virtually any structure in the body at risk (Table 75-8). Damage to the abdominal viscera, thoracic structures, and the nervous system (confusion, coma, paralysis) in areas remote from obvious extremity injury occurs and must be sought, particularly in injuries with multiple current pathways or those in which the victim falls from a high pole. Sometimes an **ignition** occurs and results in concurrent flame burn and clothing fire. Cardiac abnormalities, manifested as ventricular fibrillation or cardiac arrest, are common; patients with high-tension electrical injury need an initial electrocardiogram and cardiac monitoring until they are stable and have been fully assessed. Higher-risk patients have abnormal electrocardiographic findings and a history of loss of consciousness. Renal damage from deep muscle necrosis and subsequent myoglobinuria is another complication; such patients need forced alkaline diuresis to minimize renal damage. Soft-tissue (muscle) injury of an extremity may produce a compartment syndrome. Aggressive removal of all dead

Table 75-8 Electrical Injury: Clinical Considerations

	CLINICAL MANIFESTATIONS	MANAGEMENT
General	—	Extricate the patient; perform ABCs of resuscitation; immobilize the spine History: voltage, type of current Complete blood count with platelets, electrolytes, blood urea nitrogen (BUN), creatinine, glucose
Cardiac	Dysrhythmias: asystole, ventricular fibrillation, sinus tachycardia, sinus bradycardia, premature atrial contractions, premature ventricular contractions, conduction defects, atrial fibrillation, ST-T wave changes	Treat dysrhythmias Cardiac monitor, electrocardiogram, and radiographs with suspected thoracic injury Creatinine phosphokinase with isoenzyme measurements if indicated
Pulmonary	Respiratory arrest, acute respiratory distress, aspiration syndrome	Protect and maintain the airway Mechanical ventilation if indicated, chest radiograph, arterial blood gas levels
Renal	Acute renal failure, myoglobinuria	Provide aggressive fluid management unless a central nervous system injury is present Maintain adequate urine output, >1 mL/kg/hr Consider central venous or pulmonary artery pressure monitoring Measure urine myoglobin; perform urinalysis; measure BUN, creatinine
Neurologic	Immediate: loss of consciousness, motor paralysis, visual disturbances, amnesia, agitation; intracranial hematoma Secondary: pain, paraplegia, brachial plexus injury, syndrome of inappropriate antidiuretic hormone secretion, autonomic disturbances, cerebral edema Delayed: paralysis, seizures, headache, peripheral neuropathy	Treat seizures Provide fluid restriction if indicated Consider spine radiographs, especially cervical CT scan of the brain if indicated
Cutaneous/oral	Oral commissure burns, tongue and dental injuries; skin burns resulting from ignition of clothes, entrance and exit burns, and arc burns Electrical burns to the mouth could include oral commissures and lips, low voltage electrical burns secondary to high conductivity of saliva	Search for the entrance/exit wound Treat cutaneous burns; determine the tetanus status Obtain a plastic surgery of ear, nose, and throat consultation if needed No entry or exit wounds, no cardiac involvement. All injuries are localized management is observation till eschar slough off and granulation tissue fills in. Obtain plastic surgeon evaluation after first healing had occurred usually with scar formation.
Abdominal	Viscus perforation and solid organ damage; ileus; abdominal injury rare without visible abdominal burns	Place a nasogastric tube if the patient has airway compromise or ileus Obtain serum glutamate oxaloacetate transaminase or aspartate aminotransferase, serum glutamate-pyruvic transaminase, alanine aminotransferase, amylase, BUN, and creatinine measurements and, CT scans as indicated
Musculoskeletal	Compartment syndrome from subcutaneous necrosis limb edema and deep burns Long bone fractures, spine injuries	Monitor the patient for possible compartment syndrome Obtain radiographs and orthopedic/general surgery consultations as indicated
Ocular	Visual changes, optic neuritis, cataracts, extraocular muscle paresis	Obtain an ophthalmology consultation as indicated

Modified from Hall ML, Sills RM: Electrical and lightning injuries. In Barkin RM, editor: Pediatric emergency medicine, *St. Louis, 1997, Mosby, p. 484.*

and devitalized tissue, even with the risk of functional loss, remains the key to effective management of the electrically damaged extremity. Early debridement facilitates early closure of the wound. Damaged major vessels must be isolated and buried in a viable muscle to prevent exposure. Survival depends on immediate intensive care, whereas a functional result depends on long-term care and delayed reconstructive surgery.

Lightning burns occur when a high-voltage current directly strikes a person (most dangerous) or when the current strikes the ground or an adjacent (in-contact) object. A step voltage burn is observed when lightning strikes the ground and travels up one leg and down the other (the path of least resistance). Lightning burns depend on the current path, the type of clothing worn, the presence of metal, and cutaneous moisture. Entry, exit, and path lesions are possible; the prognosis is poorest for lesions of the head or legs. Internal organ injury along the path is common and does not relate to the severity of the cutaneous burn. Linear burns, usually 1st- or 2nd-degree, are in the locations where sweat is present. Feathering or an arborescent pattern is characteristic of lightning injury. Lightning may ignite clothing or produce serious cutaneous burns from heated metal in the clothing. Internal complications of lightning burns include cardiac arrest caused by asystole, transient hypertension, premature ventricular contractions, ventricular fibrillation, and myocardial ischemia. Most severe cardiac complications resolve if the patient is supported with cardiopulmonary resuscitation (see Chapter 67). CNS complications include cerebral edema, hemorrhage, seizures, mood changes, depression, and paralysis of the lower extremities. Rhabdomyolysis and myoglobinuria (with possible renal failure) also occur. Ocular manifestations include vitreous hemorrhage, iridocyclitis, retinal tearing or retinal detachment.

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Useful Links

www.ameriburn.org.
www.cpsc.gov.
www.safekids.org.

Chapter 76

Cold Injuries

Alia Y. Antoon and Mary K. Donovan

The involvement of children and youth in snowmobiling, mountain climbing, winter hiking, and skiing places them at risk for cold injury. Cold injury may produce either local tissue damage, with the injury pattern depending on exposure to damp cold (frostnip, immersion foot, or trench foot), dry cold (which leads to local frostbite), or generalized systemic effects (hypothermia).

PATHOPHYSIOLOGY

Ice crystals may form between or within cells, interfering with the sodium pump, and may lead to rupture of cell membranes. Further damage may result from clumping of red blood cells or platelets, causing microembolism or thrombosis. Blood may be shunted away from an affected area by secondary neurovascular responses to the cold injury; this shunting often further damages an injured part while improving perfusion of other tissues. The spectrum of injury ranges from mild to severe and reflects the result of structural and functional disturbance in small blood vessels, nerves, and skin.

ETIOLOGY

Body heat may be lost by conduction (wet clothing, contact with metal or other solid conducting objects), convection (wind chill), evaporation, or radiation. Susceptibility to cold injury may be increased by dehydration, alcohol or drug use, impaired consciousness, exhaustion, hunger, anemia, impaired circulation as a consequence of cardiovascular disease, and sepsis; it is also greater in very young or older persons. Certain medications may contribute to hypothermia, while others may display reduced metabolism or clearance during hypothermia (Table 76-1).

Hypothermia occurs when the body can no longer sustain normal core temperature by physiologic mechanisms, such as vasoconstriction, shivering, muscle contraction, and nonshivering thermogenesis. When shivering ceases, the body is unable to maintain its core temperature; when the body core temperature falls to <35°C (95°F), the syndrome of hypothermia occurs. Wind chill, wet or inadequate clothing, and other factors increase local injury and may cause dangerous hypothermia, even in the presence of an ambient temperature that is not <17-20°C (50-60°F).

CLINICAL MANIFESTATIONS

Frostnip

Frostnip results in the presence of firm, cold, white areas on the face, ears, or extremities. Blistering and peeling may occur over the next 24-72 hr, occasionally leaving mildly increased hypersensitivity to cold for some days or weeks. Treatment consists of warming the area with an unaffected hand or a warm object before the lesion reaches a stage of stinging or aching and before numbness supervenes. Rewarming in a water bath (40-42.2°C [104-108°F]) is effective.

Table 76-1 Drugs Displaying Reduced Metabolism or Clearance in Hypothermia

Atropine	Procaine
Digoxin	Propranolol
Fentanyl	Sulfanilamide (AVC cream)
Gentamicin	Succinylcholine
Lidocaine	D-Tubocurarine
Phenobarbital	

Modified from Bope ET, Kellerman RD, editors, Conn's current therapy 2014, Philadelphia, 2014, Elsevier/Saunders, Box 3, p. 1135.

Immersion Foot (Trench Foot)

Immersion foot occurs in cold weather when the feet remain in damp or wet, poorly ventilated boots. The feet become cold, numb, pale, edematous, and clammy. Tissue maceration and infection are likely, and prolonged autonomic disturbance is common. This autonomic disturbance leads to increased sweating, pain, and hypersensitivity to temperature changes, which may persist for years. Treatment includes drying the foot, gentle rewarming and nonsteroidal antiinflammatory drugs for pain. Prevention consists of using well-fitting, insulated, waterproof, nonconstricting footwear. Once damage has occurred, patients must choose clothing and footwear that are more appropriate, dry, and well-fitting. The disturbance in skin integrity is managed by keeping the affected area dry and well-ventilated and by preventing or treating infection. Only supportive measures are possible for control of autonomic symptoms.

Frostbite

With frostbite, initial stinging or aching of the skin progresses to cold, hard, white anesthetic and numb areas. Clear or hemorrhagic vesicles may develop over the exposed areas. On rewarming, the area becomes blotchy, itchy, and often red, swollen, and painful. The injury spectrum ranges from complete normality to extensive tissue damage, even gangrene, if early relief is not obtained.

Treatment consists of warming the damaged area. It is important not to cause further damage by attempting to rub the area with ice or snow. The area may be warmed against an unaffected hand, the abdomen, or an axilla during transfer of the patient to a facility where more rapid warming with a warm (not hot) water bath is possible. If the skin becomes painful and swelling occurs, antiinflammatory agents are helpful and an analgesic agent is necessary. Freeze and rethaw cycles are most likely to cause permanent tissue injury, and it may be necessary to delay definitive warming and apply only mild measures if the patient is required to walk on the damaged feet en route to definitive treatment. In the hospital, the affected area should be immersed in warm water (approximately 42°C [107.6°F]), with care taken not to burn the anesthetized skin. Broken vesicles may be debrided, but intact vesicles should be left alone. Vasodilating agents, such as prazosin and phenoxybenzamine, may be helpful. Use of anticoagulants (heparin, dextran) has had equivocal results; results of chemical and surgical sympathectomy have also been equivocal. Oxygen is of help only at high altitudes. Meticulous local care, prevention of infection, and keeping the rewarmed area dry, open, and sterile provide optimal results. Recovery can be complete, and prolonged observation with conservative therapy is justified before any excision or amputation of tissue is considered. Analgesia and maintenance of good nutrition are necessary throughout the prolonged waiting period.

Hypothermia

Hypothermia may occur in winter sports when injury, equipment failure, or exhaustion decreases the level of exertion, particularly if sufficient attention is not paid to wind chill. Immersion in frozen bodies of water and wet wind chill rapidly produce hypothermia. As the core temperature of the body falls, insidious onset of extreme lethargy, fatigue, incoordination, and apathy occurs, followed by mental confusion, clumsiness, irritability, hallucinations, and finally, bradycardia. A number of medical conditions, such as cardiac disease, diabetes mellitus, hypoglycemia, sepsis, β-blocking agent overdose, and substance abuse, may need to be considered in a differential diagnosis. The decrease in rectal temperature to <34°C (93°F) is the most helpful diagnostic feature. Hypothermia associated with drowning is discussed in Chapter 74.

Prevention is a high priority. Of extreme importance for those who participate in winter sports is wearing layers of warm clothing, gloves, socks within insulated boots that do not impede circulation, and a warm head covering, as well as application of adequate waterproofing and protection against the wind. Thirty percent of heat loss for infants occurs from the head. Ample food and fluid must be provided during exercise. Those who participate in sports should be alert to the presence of cold or numbing of body parts, particularly the nose, ears, and

extremities, and they should review methods to produce local warming and know to seek shelter if they detect symptoms of local cold injury. Application of petrolatum (Vaseline) to the nose and ears gives certain protection against frostbite.

Treatment at the scene aims at prevention of further heat loss and early transport to adequate shelter (Table 76-2). Dry clothing should be provided as soon as practical, and transport should be undertaken if the victim has a pulse. If no pulse is detected at the initial review, cardiopulmonary resuscitation is indicated (see Chapter 67; Fig. 76-1). During transfer, jarring and sudden motion should be avoided because these occurrences may cause ventricular arrhythmia. It is often difficult to attain a normal sinus rhythm during hypothermia.

If the patient is conscious, mild muscle activity should be encouraged, and a warm drink offered. If the patient is unconscious, external warming should be undertaken initially with use of blankets and a sleeping bag; wrapping the patient in blankets or sleeping bag with a warm companion may increase the efficiency of warming. On arrival at a treatment center while a warming bath of 45-48°C (113-118°F) water is prepared, the patient should be warmed through inhalation of warm, moist air or oxygen or with heating pads or thermal blankets. Monitoring of serum chemistry values and an electrocardiogram are

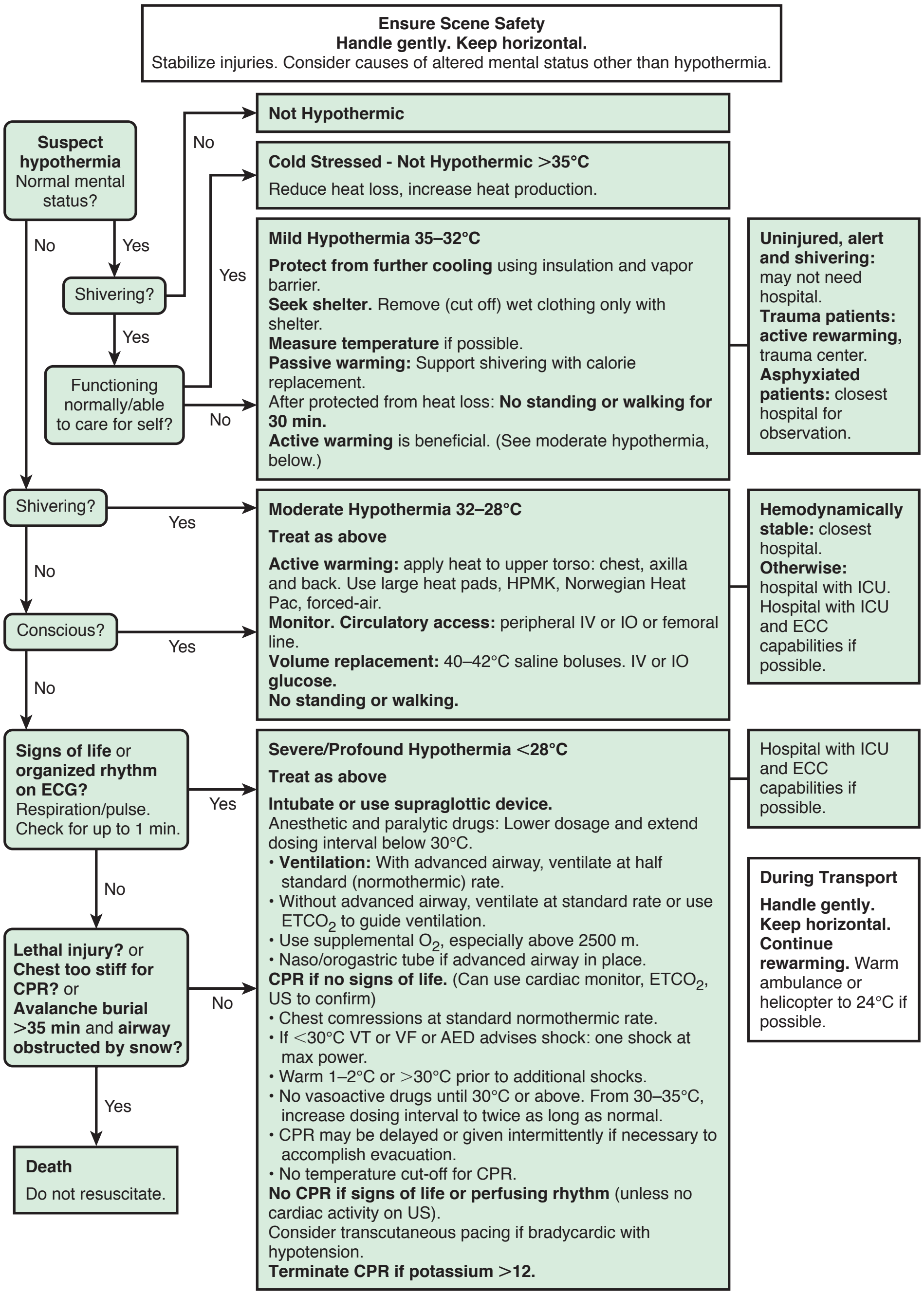

Figure 76-1 Recommendations for out-of-hospital evaluation and treatment of accidental hypothermia. ECG, electrocardiogram; CPR, cardiopulmonary resuscitation; HPMK, Hypothermia Prevention Management Kit; IV, intravenous; IO, intraosseous; ETCO2, end-tidal carbon dioxide; VT, ventricular tachycardia; VF, ventricular fibrillation; AED, automatic external defibrillator; US, ultrasound; ICU, intensive care unit; ECC, extracorporeal circulation. *(From Zafren K, Giesbrecht GG, Danzl DF, et al: Wilderness Medical Society Practice Guidelines for the Out-of-Hospital Evaluation and Treatment of Accidental Hypothermia: 2014 Update,* Wilderness Environ Med *25:S66–S85, 2014. Fig 2.)*

Table 76-2 Management of Hypothermia

HISTORY AND PHYSICAL
Gentle handling of the patient to prevent arrhythmias
ABCDE: cardiopulmonary resuscitation for ventricular fibrillation and asystole
Underlying disease diagnosis and treatment
Vital signs, pulse oximetry, electrocardiogram
Wet or cold clothing removed and patient placed in warm environment
LABORATORY TESTS
Arterial blood gas analysis corrected for temperature
Electrolytes, BUN creatinine, Ca, Mg, P
CBC with differential, PT/PTT, fibrinogen
Glucose, amylase/lipase
LFT
Additional labs, if appropriate, such as toxicology screen
PASSIVE REWARMING
≥32°C (89.6°F) in patients who are capable of spontaneous thermogenesis
ACTIVE REWARMING
<32°C (89.6°F), cardiovascular instability, patients at risk for developing hypothermia
Close monitoring for core-temperature afterdrop
Acute: external and/or core rewarming
Chronic (<32°C [89.6°F] for longer than 24 hr): core rewarming
Extracorporeal membrane oxygenation
Availability of rapid deployment

ABCDE, *a*irway and possibly *a*ntibiotics, *b*reathing, *c*irculation, *d*isability or neurologic and possible *d*extrose, *e*xtracorporeal support if all else fails; BUN, blood urea nitrogen; Ca, calcium; CDC, complete blood count; LFT liver function test; Mg, magnesium; P, phosphorus; PT, prothrombin time; PTT, partial thromboplastin time.

From Burg FD, Ingelfinger JR, Polin RA, Gershon AA (eds): Current pediatric therapy, *ed 18, Philadelphia, 2006, Saunders/Elsevier, Table 4, p. 174.*

necessary until the core temperature rises to >35°C (95°F) and can be stabilized. Control of fluid balance, pH, blood pressure, and oxygen concentration is necessary in the early phases of the warming period and resuscitation. In severe hypothermia, there may be a combined respiratory and metabolic acidosis. Hypothermia may falsely elevate pH; nonetheless, most authorities recommend warming the arterial blood gas specimen to 37°C (98.6°F) before analysis and regarding the result as one from a normothermic patient. In patients with marked abnormalities, warming measures, such as gastric or colonic irrigation with warm saline or peritoneal dialysis, may be considered, but the effectiveness of these measures in treating hypothermia is unknown. In accidental deep hypothermia (core temperature 28°C [82.4°F]) with circulatory arrest, rewarming with cardiopulmonary bypass may be lifesaving for previously healthy young individuals. If rewarming is not successful despite appropriate measures, one should suspect infection, drug overdose, endocrine disorders, or a futile resuscitation.

Chilblain (Pernio)

Chilblain (pernio) is a form of cold injury in which erythematous, vesicular, or ulcerative lesions occur. The lesions are presumed to be of vascular or vasoconstrictive origin. They are often itchy, may be painful, and result in swelling and scabbing. The lesions are most often found on the ears, the tips of the fingers and toes, and exposed areas of the legs. The lesions last for 1-2 wk but may persist for longer. Treatment consists of prophylaxis: avoiding prolonged chilling and protecting potentially susceptible areas with a cap, gloves, and stockings. Prazosin and phenoxybenzamine may be helpful in improving circulation if this is a recurrent problem. For significant itching, local corticosteroid preparations may be helpful.

COLD-INDUCED FAT NECROSIS (PANNICULITIS)

A common, usually benign injury, cold-induced fat necrosis occurs upon exposure to cold air, snow, or ice and manifests in exposed (or, less often, covered) surfaces as red (or, less often, purple to blue) macular, papular, or nodular lesions. Treatment is with nonsteroidal antiinflammatory agents. The lesions may last 10 days to 3 wk (see Chapter 660) but may persist for longer. There is a possibility of severe coagulopathy associated with poor outcome in some of the severe cold injuries, thus meriting anticoagulation therapy.

Bibliography is available at Expert Consult.

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Human Genetics

PART X

Chapter 77

Integration of Genetics Into Pediatric Practice

Brendan Lee

Genetic testing involves analyzing genetic material to obtain information related to a person's health status using chromosomal (cytogenetic) analysis (see Chapter 81) or DNA-based testing.

DIAGNOSTIC TESTING

Diagnostic genetic testing helps explain a set of signs and/or symptoms of a disease. The list of disorders for which specific genetic tests is available is extensive. The website http://www.ncbi.nlm.nih.gov/gtr/ provides a database of available tests that is provider driven and so claims are not validated by the site's host, the National Institutes of Health.

Single-gene disorders can be tested by at least 3 different approaches: linkage analysis, array comparative genomic hybridization (aCGH), and direct mutation (DNA sequence-based) analysis, usually by DNA sequencing (Table 77-1). Linkage analysis is used if the responsible gene is mapped but not yet identified, or if it is impractical to find specific mutations, usually because of the large size and larger number of different mutations in some genes. aCGH can be used to detect large multigene deletions or duplications (**copy number variations**). In addition, with increasing resolution, single gene or smaller intragenic deletions or duplications can be detected by aCGH. *Direct DNA mutation analysis is preferred and is possible with the availability of the complete human genome sequence.* An emerging feature is the increasing recognition of oligogenic disease where more than 1 disease gene contributes to a complex phenotype. The ability to sequence hundreds to thousands of genes at once has provided insight into this added layer of complexity in disease pathogenesis.

Linkage testing involves tracking a genetic trait through a family using closely linked polymorphic markers as a surrogate for the trait (Fig. 77-1). It requires testing an extended family and is vulnerable to several pitfalls, such as genetic recombination, genetic heterogeneity, and incorrect diagnosis in the proband. **Genetic recombination** occurs between any pair of loci, the frequency being proportional to the distance between them. This problem can be ameliorated by using very closely linked markers and, if possible, using markers that flank the specific gene. **Genetic heterogeneity** can be problematic for a linkage-based test if there are multiple distinct genomic loci that can cause the same phenotype, resulting in the risk that the locus tested for is not the one responsible for disease in the family. **Incorrect diagnosis** in the proband also leads to tracking the wrong gene. Linkage testing remains useful for several genetic conditions, though it is increasingly being superseded by the availability of direct DNA sequencing. It is critically important that genetic counseling be provided to the family to explain the complexities of interpretation of test results.

aCGH (see Chapter 81) can detect copy number variation in a patient's DNA by comparing it to a standard control DNA. In so doing, it provides a level of genetic resolution between what is available with DNA sequencing and what is available with chromosome analysis. Whereas earlier technologies could only identify large deletions or duplications that might encompass multiple genes, aCGH can resolve deletions or duplications of several kilobases within 1 gene. In theory, this approach can detect deletion and duplication mutations that would be missed by either chromosome analysis or direct mutation testing by DNA sequencing. However, because the specific resolution and coverage of different aCGH platforms can vary tremendously for different gene regions, the sensitivity for detecting deletions and duplications can vary for different diseases and laboratories.

Direct DNA-based mutation testing avoids the pitfalls of linkage testing by detecting the specific gene mutation (i.e., sequence change). The specific approach used is customized to the biology of the gene being tested. In some disorders, 1 or a few distinct mutations occur in all affected individuals. This is the case in sickle cell anemia, in which the same single base substitution occurs in everyone with the disorder. In other conditions, there may be many possible mutations that account for the disorder in different individuals. Cystic fibrosis is an example: more than 1,000 distinct mutations have been found in the *CFTR* gene. Mutation analysis is challenging because no single technique can detect all possible mutations. However, with the completion of the human genome sequence and high-throughput DNA sequencing technology, the approach of choice is to directly sequence DNA that is generated by **polymerase chain reaction** amplification of DNA isolated from peripheral blood white blood cells. The limitation of this approach is that only DNA that is amplified is sequenced, and usually this is restricted to the *coding* or *exonic* regions of a gene. Because mutations sometimes occur in the *noncoding intronic* regions, failure to detect a mutation does not exclude the diagnosis. In addition, genes in a deleted region will not be deleted. Although DNA sequencing can be highly specific, it is not completely sensitive because of practical limitations of what is commercially available. This is, however, rapidly changing because of technologic advances.

The most useful development in clinical DNA diagnosis is application of **next-generation sequencing** technology to testing panels of genes that target disease symptoms (e.g., low bone mass, ataxia) or the **whole exome (whole exome sequencing [WES])**. Here, advances in sequencing methodology have allowed for massively parallel sequencing of hundreds of genes of all of the gene coding sequences (approximately 20,000 genes) from single sample. The challenge is not so much the generation of DNA sequence, but the interpretation of enormous genetic variation within a single sample. Direct sequencing of tens to hundreds of genes in next generation sequencing panels offer a potentially higher sensitivity as the "depth" of read is higher without complicating high discovery rate of **variants of unknown sequences (VUS)**. WES also offers the potential for identifying new disease-gene associations as well as phenotypes caused by more than one disease gene (i.e., oligogenic phenotypes). An important ethical consideration is the reporting of incidental findings, whether medically or nonmedically actionable in a patient; WES may identify mutations that cause aminoglycoside sensitive hearing loss. This would be medically actionable. At the same time, the discovery of apolipoprotein E variants in a child that increase Alzheimer disease risk susceptibility may not. Hence, counseling for patients undergoing WES is important so that only wanted results are reported back to the patient. Guidelines are currently evolving for reporting of incidental findings for WES by the American College of Medical Genetics (www.acmg.net). Practice varies among institutions and recommendations vary among international genetic organizations about the approach for revealing incidental findings to patients. Many leave the choice up to the patient/family about revealing incidental findings from WES/whole genome sequencing. Most require revealing to the patient/family significant diseases

Table 77-1 Approaches for Genetic Testing

TYPE OF MUTATION TESTING	RESOLUTION	ADVANTAGES	DISADVANTAGES	SAMPLE REQUIREMENTS
Linkage	Depends on location of polymorphic markers near putative disease gene	Possible when specific disease-causing genetic mutation is not identifiable or found	Can give only diagnostic probability based on likelihood of genetic recombination between presumed DNA mutation and polymorphic markers	Requires multiple family members with documented mendelian pattern of inheritance within family
aCGH	Several kilobases to several hundreds of kilobases	Able to detect small deletion or duplications within 1 or more genes	Can miss small deletions or insertions depending on resolution of the array used	Single patient sample sufficient, though having sample from biological parents can help with interpretation
Direct DNA-based testing (e.g., DNA sequencing)	Single base-pair changes	High specificity if previously described deleterious mutation is found	Can miss deletion or duplication of a segment of gene	Single patient sample sufficient, though having sample from biological parents can help with interpretation

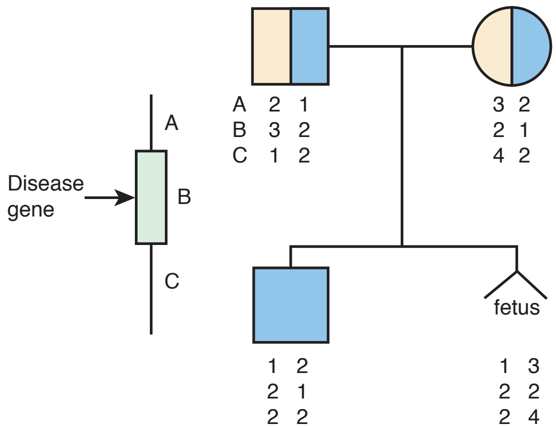

Figure 77-1 **Use of linkage analysis in prenatal diagnosis of an autosomal recessive disorder.** Both parents are carriers, and they have 1 affected son. The numbers below the symbols indicate alleles at 3 polymorphic loci: A, B, and C. Locus B resides within the disease gene. The affected son inherited the 1-2-2 chromosome from his father and the 2-1-2 chromosome from his mother. The fetus has inherited the same chromosome from the father, but the 3-2-4 chromosome from the mother and therefore is most likely to be a carrier.

(actionable) with a specific and successful treatment/prevention strategy (Table 77-2).

Genetic testing is interpreted in light of 3 factors: analytical validity, clinical validity, and clinical utility. **Analytical validity** is test accuracy: Does the test correctly detect the presence or absence of mutation? Most genetic tests have a very high analytical validity, assuming that human error, such as sample mix-up, has not occurred. Such errors are possible, and unlike most medical tests, a genetic test is unlikely to be repeated, because it is assumed that the result will not change over time. Therefore, human errors can go undetected for long periods of time.

Clinical validity is the degree to which the test correctly predicts presence or absence of disease. False-positive and false-negative test results can occur. **False-positive results** are more likely for predictive tests than for diagnostic tests. An important contributing factor is **nonpenetrance:** An individual with an at-risk genotype might not clinically express the condition. Another factor is the finding of a genetic variant of unknown significance. Detection of a base sequence variation in an affected patient does not prove that it is the cause of the patient's disorder. In exomic sequencing, there may be more than 30,000 VUS; in whole genome sequencing there may be more than 3,000,000 VUS. Various lines of evidence are used to establish

Table 77-2 Variants That Are Incidental Findings Are Assigned to 1 of 4 Categories

Childhood onset	Medically actionable*
Childhood onset	Not medically actionable†
Adult onset	Medically actionable*
Adult onset	Not medically actionable†

*"Medically actionable" refers to a variant in a gene in which knowledge of the particular variant will affect medical decision making such as initiation of a treatment, family planning, etc.

†"Not medically actionable" refers to variants that increase the individual's risk for a disease in which no treatment is proven to significantly change medical decision making.

From Bick D, Dimmock D: Whole exome and whole genome sequencing. Curr Opin Pediatr 23:594–600, 2011, Table 2, p. 597.

pathogenicity. These include finding the variant only in affected individuals, inferring that the variant alters the function of the gene product, determining whether the amino acid altered by the mutation is conserved in evolution, and determining whether the mutation segregates with disease in the family. In some cases, it is possible to be sure whether the variant is pathogenic or incidental. In spite of all of these approaches, it might still be impossible to definitively assign causality with 100% confidence.

False-negative results reflect an inability to detect a mutation in an affected patient. This occurs principally in disorders where genetic heterogeneity—**allelic** (different mutations occur in one causative gene) heterogeneity or **locus** (more than one gene can cause a disease) heterogeneity—is the rule. It is difficult to detect all possible mutations within a gene, because mutations can be varied in location within the gene and in the type of mutation. Direct sequencing may miss gene deletions or rearrangements, and mutations may be found within noncoding sequences such as introns or the promoter; a negative DNA test does not necessarily exclude a diagnosis.

Clinical utility is the degree to which the results of a test guide clinical management. For genetic testing, clinical utility includes establishing a diagnosis that obviates the need for additional workup or guiding surveillance or treatment. Test results may also be used as a basis for genetic counseling. For some disorders, genetic testing is possible but the test results do not add to the clinical assessment. If the diagnosis and genetic implications are already clear, it might not be necessary to pursue genetic testing.

PREDICTIVE TESTING

Predictive genetic testing involves performing a test in a person who is at risk for developing a genetic disorder **(presymptomatic),** usually on the basis of family history, yet who does not manifest signs or

symptoms. This is usually done for disorders that display age-dependent penetrance; the likelihood of manifesting signs and symptoms increases with age, as in cancer or Huntington disease.

A major caution with predictive testing is that the presence of a gene mutation does not necessarily mean that the disease will develop. Many of the disorders with age-dependent penetrance display *incomplete penetrance*. A person who inherits a mutation might never develop signs of the disorder. There is concern that a positive DNA test could result in stigmatization of the person and might not provide information that will guide medical management. Stigmatization might include psychological stress, but it could also include discrimination, including denial of health, life, or disability insurance, or employment (see Chapter 78).

It is generally agreed that predictive genetic tests should be performed for children if the results of the test will benefit the medical management of the child. Otherwise, the test should be deferred until the child has an understanding of the risks and benefits of testing and can provide informed consent. Individual states offer varying degrees of protection from discrimination on the basis of genetic testing. A major milestone in the prevention of genetic discrimination was the passage of the Genetic Information Nondiscrimination Act (GINA) in 2008, which is a federal law that prohibits discrimination in health coverage or employment based on genetic information; it does not protect against refusal of life insurance.

PREDISPOSITIONAL TESTING

It is expected that genetic tests will become available that will predict risk of disease. Common disorders are multifactorial in etiology; there may be many different genes that contribute to risk of any specific condition (see Chapter 82). Most of the genetic variants that have been found to correlate with risk of a common disease add small increments of relative risk, probably in most cases too little to guide management. It is possible that further discovery of genes that contribute to common disorders will reveal examples of variants that convey more significant levels of risk. It is also possible that testing several genes together will provide more information about risk than any individual gene variant would confer. The rationale for predispositional testing is that the results would lead to strategies aimed at risk reduction as part of a *personalized approach* to healthcare maintenance. This might include avoidance of environmental exposures that would increase risk of disease (cigarette smoking and α_1-antitrypsin deficiency), medical surveillance (familial breast cancer and mammography), or, in some cases, pharmacologic (statins and hypercholesteremia) treatment. The value of predispositional testing will need to be critically appraised through outcomes studies as these tests are developed.

PHARMACOGENETIC TESTING

Polymorphisms in drug metabolism genes can result in distinctive patterns of drug absorption, metabolism, excretion, or effectiveness (see Chapters 59 and 82). Knowledge of individual genotypes will guide pharmacologic therapy, allowing customization of choice of drug and dosage to avoid toxicity and provide a therapeutic response. An example of this is testing for polymorphisms within the methylenetetrahydrofolate reductase (*MTHFR*) gene for susceptibility of potentially increased toxicity to methotrexate antimetabolite therapy for treatment of acute lymphoblastic leukemia.

77.1 Genetic Counseling

Brendan Lee

Genetic counseling is a communication process in which the genetic contribution to health is explained, along with specific risks of transmission of a trait and options to manage the condition and its inheritance (Table 77-3). The counselor is expected to present information in a neutral, nondirective manner and to provide support to the individual and family to cope with decisions that are made.

Table 77-3 Indications for Genetic Counseling
Advanced parental age
• Maternal age ≥35 yr
• Paternal age ≥50 yr
Previous child with or family history of
• Congenital abnormality
• Dysmorphology
• Intellectual disability
• Isolated birth defect
• Metabolic disorder
• Chromosome abnormality
• Single-gene disorder
Adult-onset genetic disease (presymptomatic testing)
• Cancer
• Huntington disease
Consanguinity
Teratogen exposure (occupational, abuse)
Repeated pregnancy loss or infertility
Pregnancy screening abnormality
• Maternal serum α-fetoprotein
• Maternal triple or quad screen or variant of this test
• Fetal ultrasonography
• Fetal karyotype
Heterozygote screening based on ethnic risk
• Sickle cell anemia
• Tay-Sachs, Canavan, and Gaucher diseases
• Thalassemias
Follow-up to abnormal neonatal genetic testing
Prior to whole genome or exome sequencing
Prior to preimplantation genetic testing

Genetic counseling has evolved from a model of care that was developed in the context of prenatal diagnosis and pediatrics (see Table 77-3). For prenatal diagnosis, the task is to assess risk of a couple having a child with a genetic condition and to advise the couple about options to manage that risk, including reproductive options such as artificial insemination and prenatal or preimplantation genetic diagnosis. In pediatrics, the task is to establish a diagnosis in a child, provide longitudinal care for the child, and advise the parents about risk of recurrence as well as options to deal with that risk.

The genetic counseling role has expanded, particularly with advances in understanding the genetics of adult-onset or common disorders. Genetic counseling has a major role in risk assessment for cancer, especially breast and ovarian cancer or colon cancer, for which well-defined genetic tests are available to assess risk to an individual.

TALKING TO FAMILIES

The type of information provided to a family depends on the urgency of the situation, the need to make decisions, and the need to collect additional information. There are 4 situations in which genetic counseling is particularly important.

The first is the **prenatal diagnosis** of a congenital anomaly or genetic disease. The need for information is urgent because a family must often decide whether to continue or to terminate a pregnancy. Risks to the mother must also be considered. The second type of situation occurs when a child is born with a life-threatening congenital anomaly or genetic disease. Decisions must be made immediately with regard to how much support should be provided for the child and whether certain types of therapy should be attempted. The third situation arises later in life when a diagnosis with a genetic implication is made; a couple is planning a family and there is a family history of a genetic problem, including whether one member of a couple carries a translocation or is a carrier of an abnormal gene for an autosomal recessive or X-linked disorder; an adolescent or young adult has a family history of an adult-onset genetic disorder (Huntington disease, breast cancer); unusual features are present and a diagnosis is wanting or not possible; and there is suspected exposure to a toxic substance or teratogen. It is often necessary to have several meetings with a family in this third situation. Urgency is not as much of an issue as being sure that they have

as much information and as many options as are available. The fourth situation is counselling prior to genome sequencing where the family is given options of what they want reported back to them (actionable, nonactionable incidental findings vs. a specific diagnosis).

GENETIC COUNSELING

Providing accurate information to families requires:

- Taking a careful family history and constructing a pedigree that lists the patient's relatives (including abortions, stillbirths, deceased persons) with their sex, age, and state of health, up to and including 3rd-degree relatives.
- Gathering information from hospital records about the affected individual and, in some cases, about other family members.
- Documenting prenatal, pregnancy, and delivery histories.
- Reviewing the latest available medical, laboratory, and genetic information concerning the disorder.
- Performing a careful physical examination of the affected individual (photographs, measurements) and of apparently unaffected individuals in the family.
- Establishing or confirming the diagnosis by the diagnostic tests available.
- Giving the family information about support groups.
- Providing new information to the family as it becomes available (a mechanism for updating needs to be established).

Counseling sessions must include the specific condition, knowledge of the diagnosis of the particular condition, the natural history of the condition, the genetic aspects of the condition and the risk of recurrence, prenatal diagnosis and prevention, therapies and referral, support groups, and nondirective counseling.

Specific Condition or Conditions

If a specific diagnosis is made and confirmed, that should be discussed with the family and information should be provided in writing. However, often the disorder fits into a spectrum (e.g., one of many types of arthrogryposis) or the diagnosis is clinical rather than laboratory based. In those situations, the family needs to understand the limits of present knowledge and that additional research will probably lead to better information in the future.

Knowledge of the Diagnosis of the Particular Condition

Although it is not always possible to make an exact diagnosis, having a diagnosis as accurate as possible is important. Estimates of recurrence risk for various family members depend on an accurate diagnosis. When a specific diagnosis cannot be made (as in many cases of multiple congenital anomalies), the various possibilities in the differential diagnosis should be discussed with the family and empirical information should be provided. If specific diagnostic tests are available, they should be discussed. Often, empirical recurrence risks can be given even without a specific laboratory-based diagnosis. At the same time, even negative laboratory testing can further modify this risk.

Natural History of the Condition

It is very important to discuss the natural history of the specific genetic disorder in the family. Affected persons and their families have questions regarding the prognosis and potential therapy that can be answered only with knowledge of the natural history. If there are other possible diagnoses, their natural history may also be discussed. If the disorder is associated with a spectrum of clinical outcomes or complications, the worst and best scenarios, as well as treatment and referral to the appropriate specialist, should be addressed.

Genetic Aspects of the Condition and Recurrence Risk

The genetic aspects and risk of recurrence are important because all family members need to be aware of their reproductive choices. The genetics of the disorder can be explained with visual aids (e.g., diagrams of chromosomes). It is important to provide accurate occurrence and recurrence risks for various members of the family, including unaffected individuals. If a definite diagnosis cannot be made, it is necessary to use empirical recurrence risks. Counseling should give patients the necessary information to understand the various options and let the patients make their own informed decisions regarding pregnancy, adoption, artificial insemination, prenatal diagnosis, screening, carrier detection, and termination of pregnancy. It may be necessary to have more than 1 counseling session.

Prenatal Diagnosis and Prevention

Many different methods of prenatal diagnosis are available, depending on the specific genetic disorder (see Chapter 96). The use of ultrasonography allows prenatal diagnosis of anatomic abnormalities such as congenital heart defects. Amniocentesis and chorionic villus sampling are used to obtain fetal tissue for analysis of chromosomal abnormalities, biochemical disorders, and DNA studies. Maternal blood or serum sampling is used for some types of screening. Fetal cells can be retrieved from the umbilical cord or from maternal blood (free fetal DNA) for testing, although mothers might harbor cells from all previous pregnancies.

Therapies and Referral

A number of genetic disorders require the care of a specialist. Girls with Turner syndrome usually need to be evaluated by an endocrinologist. Prevention of known complications is a priority. The psychological adjustment of the family might require specific intervention. When to discuss the diagnosis of a chronic disease with the patient is always a difficult decision. The decision to do so should always involve the parents and an assessment of the maturity and capacity of the child or adolescent.

Alternative medicines or nontraditional therapies are often brought to attention by parents after exhaustive Internet searches. Such treatments should not necessarily be dismissed out of hand because the physician and counselor should serve as an important resource for helping parents navigate the maze of nonstandard treatments. Instead, the relative merits of treatments should be framed in the context of cost and benefit, scientific rationale, evidence from controlled and/or observational studies, the placebo effect, safety of the treatment, and the gaps in our own scientific knowledge base.

Support Groups

A large number of community lay support groups have been formed to provide information and to fund research on specific genetic and nongenetic conditions. An important part of genetic counseling is to give information about these groups to patients and to suggest a contact person for the families. Many groups have established websites with very helpful information; it is important to stress to families that their individual disease course will be unique.

Follow-up

Families should be encouraged to continue to ask questions and keep up with new information about the specific disorder. New developments often influence the diagnosis and therapy of specific genetic disorders. Lay support groups are a good source of new information.

Nondirective Counseling

Genetic counseling is usually nondirective; choices about reproduction are left to the family to decide what is right for them. The role of the counselor (physician, genetic counselor, nurse, medical geneticist) is to provide information in understandable terms and outline the range of options available.

77.2 Management and Treatment of Genetic Disorders

Brendan Lee

Genetic conditions are often chronic disorders; few are amenable to curative therapies. Nevertheless, many management options are

available. All patients and families should be provided information about the disorder, genetic counseling, anticipatory guidance, and appropriate medical surveillance. Surgical management is available for many conditions that are associated with congenital anomalies or predisposition to tumors.

Resources for patients include the National Organization of Rare Disorders (www.rarediseases.org), the Genetic Alliance (www.geneticalliance.org), the National Library of Medicine (www.nlm.nih.gov/medlineplus/geneticdisorders.html), and a large number of disease-specific websites. A current listing of federally and privately funded clinical trials, including many for genetic diseases, is available at www.*ClinicalTrials.gov*.

Specific medical therapies for genetic disorders can be classified into physiologic and replacement therapies. Much effort is currently focused in developing gene and cell therapies.

PHYSIOLOGIC THERAPIES

Physiologic therapies attempt to ameliorate the phenotype of a genetic disorder by modifying the physiology of the affected individual. The underlying defect itself is not altered by treatment. Physiologic therapies are used in the treatment of **inborn errors of metabolism** (see Chapter 84). These include dietary manipulation, such as avoiding phenylalanine by persons with phenylketonuria; coenzyme supplementation for some patients with methylmalonic acidemia and mitochondrial diseases; stimulation of alternative pathways to excrete ammonia for those with urea cycle disorders; bisphosphonate treatment for those with osteogenesis imperfecta to reduce bone fractures; and avoiding cigarette smoking by persons with α_1-antitrypsin deficiency. Physiologic treatments can be highly effective, but they usually need to be maintained for a lifetime because they do not affect the underlying genetic disorder. Many of these treatments are most effective when begun early in life before irreversible damage has occurred. This is the rationale for comprehensive newborn screening for inborn errors of metabolism.

Many physiologic therapies use small-molecule pharmaceuticals (e.g., to remove ammonia in those with urea cycle disorders). Pharmacologic treatments directly target a defective cellular pathway that is altered by an abnormal or a missing gene product. However, there are relatively few such therapies. One example is the development of imatinib, a small molecule tyrosine kinase inhibitor developed specifically to target the biologic pathway altered in chronic myelogenous leukemia (CML). CML is usually associated with a chromosome 9;22 translocation (the Philadelphia chromosome) that creates a fusion of the BCR protein and the *Abl* oncogene. Imatinib is a small molecule that blocks the adenosine triphosphate binding in the fusion protein; it is highly effective in treatment of CML and several other malignancies. Other examples include large-molecule biologics such as “humanized” monoclonal antibodies.

REPLACEMENT THERAPIES

Replacement therapies include replacement of a missing metabolite, an enzyme, an organ, or even a specific gene.

Enzyme Replacement

Enzyme replacement therapy is a component of the treatment of cystic fibrosis to manage intestinal malabsorption. Pancreatic enzymes are easily administered orally, because they must be delivered to the gastrointestinal tract.

Enzyme replacement strategies are effective for some lysosomal storage disorders. Enzymes are targeted for the lysosome by modification with mannose-6-phosphate, which binds to a specific receptor. This receptor is also present on the cell surface, so lysosomal enzymes with exposed mannose-6-phosphate residues can be infused into the blood and are taken into cells and transported to lysosomes. Enzyme replacement therapies are available for Gaucher disease and Fabry disease, some mucopolysaccharidoses (I, II, VI), Niemann-Pick disease type C, and Pompe disease.

One complication of enzyme replacement therapy is antibody response to the enzyme. The magnitude of this response is not always predictable and varies depending on the enzyme preparation and the disease. In most cases, the patient’s antibody response does not affect the treatment’s efficacy (e.g., in Gaucher disease), but in other situations it may be a significant hurdle (e.g., in Pompe disease).

Transplantation

Cell and organ transplantation are potentially effective approaches to replacement of a defective gene. Aside from transplantation to replace damaged tissues, transplantation of stem cells, liver, or bone marrow is also used for several diseases, mainly inborn errors of metabolism, and hematologic or immunologic disorders. A successful transplant is essentially curative, though there may be significant risks and side effects (see Chapters 135-139). Cell and tissue transplantation are effective in many clinical scenarios, but there is always short-term morbidity, often associated with either surgical (liver) or preparative (bone marrow) regimens, and long-term morbidity related to chronic immunosuppression and graft failure. Bone marrow transplantation is the best example of stem cell therapy, but much effort is focused on identifying, characterizing, expanding, and using other tissue stem cells for regenerative therapies.

Alternatively, research has focused on replacing a defective gene (gene therapy). In theory, if we can target the specific tissue that has a deficiency in the gene or gene product, this can offer a less invasive means of achieving a cure of a genetic disorder. Ultimately, gene therapy depends on the unique interaction of the disease pathophysiology, which is specific to the patient, and the gene delivery vehicle.

Gene-transfer vehicles include viral and nonviral approaches. Most human clinical trials have used viral vectors because of their efficiency of tissue transduction. In some diseases, such as X-linked and adenosine deaminase-deficient severe combined immunodeficiency, clinical gene therapy is a viable and effective option (see Chapter 126.1). Preliminary results suggest that gene therapy (intraocular delivery) may be effective for Leber congenital amaurosis.

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Chapter 78

The Genetic Approach in Pediatric Medicine

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Since the completion of the Human Genome Project, we have seen an unprecedented expansion in our understanding of how human health is impacted by variations in genomic sequence and epigenetic, non-sequence-based, changes that affect gene expression. This period has also seen the development and implementation of new clinical tests that have made it easier for physicians to detect such changes. In addition, this period has seen a dramatic increase in the availability of information about the genetic aspects of pediatric diseases, particularly on the Internet (Table 78-1).

THE BURDEN OF GENETIC DISORDERS IN CHILDHOOD

Medical problems associated with genetic disorders can appear at any age with the most obvious and serious problems typically manifesting in childhood. It has been estimated that 53/1,000 children and young adults can be expected to have diseases with an important genetic component. If congenital anomalies are included, the rate increases to 79/1,000. In 1978, it was estimated that just over half of admissions to

Table 78-1 Useful Internet Genetic Reference Sites

RESOURCE	WEB ADDRESS
National Center for Biotechnology Information. A general reference maintained by the National Library of Medicine.	www.ncbi.nlm.nih.gov
Online Mendelian Inheritance in Man. A useful resource for clinicians containing information on all known mendelian disorders and more than 12,000 genes. Information focuses on the relationship between phenotype and genotype.	www.ncbi.nlm.nih.gov/omim
Genetic Testing Registry. A resource that provides information on individual genes, genetic tests, clinical laboratories, and medical conditions. This resource also provides access to GeneReviews, a collection of expert-authored reviews on a variety of genetic disorders.	www.ncbi.nlm.nih.gov/gtr/
Genetics Home Reference. A resource that provides consumer-friendly information about the effects of genetic variations on human health.	www.ghr.nlm.nih.gov
National Human Genome Research Institute. A resource for information about human genetics and ethical issues.	www.genome.gov
Human Gene Mutation Database. A searchable index of all described mutations in human genes with phenotypes and references.	www.hgmd.cf.ac.uk
DECIPHER. A database designed to aid physicians in determining the potential consequences of chromosomal deletions and duplications.	http://decipher.sanger.ac.uk
Database of Genomic Variants. A database of chromosomal alterations seen in normal controls.	http://dgv.tcag.ca/dgv/app/home
Gene Letter. An online magazine of genetics.	www.geneletter.com
American Society of Human Genetics	www.ashg.org
American College of Medical Genetics	www.acmg.net

pediatric hospitals were for a genetically determined condition. By 1996, owing to changes in healthcare delivery and a greater understanding of the genetic basis of many disorders, that percentage rose to 71% in 1 large pediatric hospital in the United States, and 96% of chronic disorders leading to admission had an obvious genetic component or were influenced by genetic susceptibility. Major categories of genetic disorders include single-gene, genomic, chromosomal, and multifactorial conditions.

Individually, **single-gene disorders** are rare, but collectively they represent an important contribution to childhood disease. The hallmark of a single-gene disorder is that the phenotype is overwhelmingly determined by changes that affect an individual gene. The phenotypes associated with single-gene disorders can vary from one patient to another based on the severity of the change affecting the gene and additional modifications caused by genetic, environmental, and/or stochastic factors. This feature of genetic disease is termed **variable expressivity**. Common single-gene disorders include sickle cell anemia and cystic fibrosis.

Single-gene disorders tend to occur when changes in a gene have a profound effect on the quantity of the gene product produced—either too much or too little—or the function of the gene product—either a loss of function or a harmful gain of function. Single-gene disorders can be caused by de novo changes that are not found in the unaffected parents of the affected individual or they may be caused by inherited changes. When a single-gene disorder is known to be caused by changes in only 1 gene or a small number of individual genes, searching for deleterious changes is most often performed by directly sequencing that gene and, in some cases, looking for small deletions and/or duplications. When multiple genes can potentially cause a particular disorder, it is sometimes more efficient and cost effective to screen large numbers of disease causing genes using a disease-specific panel that takes advantage of next generation sequencing technology than to screen genes individually. When such panels are not available, or when the diagnosis is in question, physicians may consider screening the protein coding regions of all genes by **whole exome sequencing** on a clinical basis. Indeed in many circumstances, whole exome sequencing is less expensive than sequencing multiple individual genes. In the future, whole genome sequencing—in which an individual's entire genome is sequenced—may become a valid clinical option as the cost of such tests fall and our ability to interpret the clinical consequences of thousands of changes that are identified in such tests improves.

The risk of having a child with a particular single gene disorder can vary from one population to another. In some cases this is the result of a **founder effect,** in which a specific change affecting a disease-causing gene becomes relatively common in a population derived from a small number of founders. This high frequency is maintained when there is relatively little interbreeding with persons outside of that population because of social, religious, or physical barriers. This is the case for Tay-Sachs disease in Ashkenazi Jews and French Canadians. Other changes may be subject to positive selection when found in the heterozygous carrier state. In this case, carriers of a genetic change (heterozygotes) have a survival advantage over noncarriers. This can occur even when individuals who inherit 2 copies of the change (homozygotes) have severe medical problems. This type of positive selection is evident among individuals in sub-Saharan Africa who carry a hemoglobin mutation that confers relative resistance to malaria but causes sickle cell anemia in homozygotes.

Genomic disorders are a group of diseases caused by alterations in the genome, including deletions (copy number loss), duplications (copy number gain), inversions (altered orientation of a genomic region) and chromosomal rearrangements (altered location of a genomic region). **Contiguous gene disorders** are caused by changes that affect two or more genes that contribute to the clinical phenotype and are located near each other on a chromosome. DiGeorge syndrome, which is caused by deletions of genes located on chromosome 22q11, is a common example. Some genomic disorders are associated with distinctive phenotypes whose pattern can be recognized clinically. Other genomic disorders do not have a distinctive pattern of anomalies, but can cause developmental delay, cognitive impairment, structural birth defects, abnormal growth patterns and changes in physical appearance. Fluorescent in situ hybridization (FISH) can provide information about the copy number and location of a specific genomic region. Array-based copy number detection assays can be used to screen for chromosomal deletions (large and small) and duplication across the genome but do not provide information about the orientation or location of genomic regions. A chromosome analyses (karyotyping) can detect relatively large chromosomal deletions and duplications and can also be useful in identifying inversions and chromosomal rearrangements even when they are copy-number neutral

changes that do not result in a deletion or duplication of genomic material.

Deletions, duplications, and chromosomal rearrangements that affect whole chromosomes, or large portions of a chromosome, are commonly referred to as **chromosomal disorders.** One of the most common chromosomal disorders is Down syndrome, which is most commonly associated with the presence of an extra copy, or **trisomy,** of an entire chromosome 21. When all or a part of a chromosome is missing, the disorder is referred to as **monosomy**. Translocations are a type of chromosomal rearrangement in which a genomic region from 1 chromosome is transferred to a different location on the same chromosome or on a nonhomologous chromosome. Translocations can be balanced, meaning that no genetic material has been lost or gained, or they can be unbalanced, in which case some genetic material has been deleted or duplicated. Chromosomal disorders can often be identified on a chromosome analysis (karyotype) or by FISH. Evidence of a chromosomal disorder may also be revealed by an array-based copy number detection assays if genetic material has been gained or lost.

In some cases, only a portion of cells that make up a person's body are affected by the single gene defect, the genomic disorder or the chromosomal defect. This is referred to as **mosaicism** and indicates that the individual's body is made up of 2 or more distinct cell populations.

Polygenic disorders are caused by the cumulative effects of changes or variations in more than 1 gene. Multifactorial disorders are caused by the cumulative effects of changes or variations in multiple genes and/or the combined effects of both genetic and environmental factors. Spina bifida and isolated cleft lip or palate are common birth defects that display multifactorial inheritance patterns. Multifactorial inheritance is seen in many common pediatric disorders, such as asthma and diabetes mellitus. These traits can cluster in families but do not have a mendelian pattern of inheritance (see Chapter 80). In most cases, the genetic changes or variations that are contributing to a particular case are unknown and genetic counseling is based on empirical data.

THE CHANGING PARADIGM OF GENETICS IN MEDICINE

Genetic testing is increasingly available for a wide variety of both rare and relatively common genetic disorders. Genetic testing is commonly used in pediatric medicine to resolve uncertainty regarding the underlying etiology of a child's medical problems and provides a basis for improved genetic counseling and possibly specific therapy. Even in cases where a specific treatment is not available, identifying a genetic cause can aid physicians in providing individuals and family with accurate prognostic and recurrence risk information and usually helps to relieve unfounded feelings of guilt and/or stem the tide of misdirected blame.

Genetic tests will ultimately come to underlie a high proportion of medical decisions and will be seamlessly incorporated into routine medical care. Although most genetic testing is presently aimed at identifying or confirming a diagnosis, in the future, genetic testing may find wider application as a means of determining if an individual is predisposed to develop a particular disease. Another area in which genetic testing could make a significant impact is on individualized drug treatment. It has long been known that genetic variation in the enzymes involved in drug metabolism underlies differences in the therapeutic effect and toxicity of some drugs. As the genetic changes that underlie these variations are identified, new genetic tests may be developed that will allow physicians to tailor treatments based on individual variations in drug metabolism, responsiveness, and susceptibility to toxicity (see Chapter 59). It is likely that the expansion of such testing will depend, at least in part, on the extent to which such testing can be linked to strategies to prevent disease or improve outcome (see Chapter 77). If such links can be made, it could usher in a new era of personalized medical treatment.

Long-standing and highly successful carrier screening programs have existed for disorders such as Tay-Sachs disease and many other rare single-gene disorders that are prevalent in specific populations. Couples are commonly offered screening for a variety of conditions, in part based on ancestry (Tay-Sachs disease, hemoglobinopathies, cystic fibrosis). Couples found to be at increased risk for such disorders can be offered prepregnancy or prenatal testing aimed at detecting specific disease causing mutations.

Prenatal screening is routinely offered for chromosomal disorders such as trisomy 13, trisomy 18, and Down syndrome. An increasing number of pregnancies affected by these and other genetic disorders are being recognized by noninvasive screening tests of maternal serum in the first and second trimesters and by fetal ultrasound. When genetic disorders are suspected, chorionic villus sampling at 10-12 wk of gestation or by amniocentesis at 16-18 wk of gestation can provide material for genetic testing. Approaches to noninvasive prenatal diagnosis by sampling of cell-free fetal DNA or fetal cells in maternal blood are also becoming available. When a couple is at risk for a specific genetic defect, **preimplantation genetic diagnosis** can sometimes be used to select unaffected early embryos, which are then implanted as part of an in vitro fertilization procedure.

Although prenatally obtained genetic material can be used to identify single-gene disorders, genomic disorders, and chromosomal anomalies, the information obtained on any pregnancy depends on the tests that are ordered. It is important that physicians select the most appropriate prenatal tests and that couples understand both the limitations of these tests and that no amount of genetic testing can guarantee the birth of a healthy child.

Specific treatments are not available for the majority of genetic disorders. However, there are some important exceptions. Inborn errors of metabolism were the first genetic disorders to be recognized, and many are amenable to treatment by dietary manipulation (see Chapter 84). These conditions result from genetically determined deficiency of specific enzymes, leading to the buildup of toxic substrates and/or deficiency of critical end products.

Individual metabolic disorders tend to be very rare, but their combined impact on the pediatric population is significant. Tandem mass spectrometry has made it relatively inexpensive to screen for a large number of these disorders in the newborn period. Use of this technology not only dramatically increases the number of metabolic disorders identified within a population but also allows treatment to be initiated at a much earlier stage in development (see Chapters 77 and 84).

Another area where progress has been made regarding genetic therapies has been in the treatment of lysosomal storage disorders. These are a group of metabolic diseases caused by defects in lysosomal function. Lysosomes are cellular organelles that contain specific digestive enzymes. Some of these disorders that were lethal or associated with intractable chronic illness can now be treated using specially modified enzymes that are administered by intravenous infusion. These enzymes are then taken up by cells and incorporated into lysosomes. Conditions such as Gaucher disease and Fabry disease are routinely treated using **enzyme replacement,** and similar therapies are being developed for other lysosomal disorders.

Therapeutic advances are also being made in the treatment of nonmetabolic genetic disorders. Improvements in surgical techniques and intensive care medicine are extending the survival of children with life-threatening birth defects like congenital diaphragmatic hernia and severe cardiac defects. In many cases, the life expectancy of children with debilitating genetic disorders is also increasing. A good example is the increasing life expectancy of individuals with cystic fibrosis, largely owing to improvements in antibiotic therapy as well as the management of chronic pulmonary disease and malabsorption. A major consequence of these advances is that an increasing percentage of affected patients is surviving into adulthood, creating a need to transition care from pediatric to adult providers.

Gene-replacement therapies have long been anticipated. However, it has proved difficult to develop safe and effective approaches for inserting genes into diseased tissues in a way that allows physiologically meaningful levels of gene expression to be maintained over long periods. Stem cell-based therapies have also been touted as a potential treatment for a number of intractable disorders, but clear evidence that such therapies are effective has yet to materialize.

ETHICS ISSUES

Like all medical care, genetic testing, diagnosis, and treatment should be performed confidentially. Nothing is as personal as one's genetic information, and all efforts should be made to avoid any stigma for the patient. Many people fear that results of genetic testing will put them, or their child, at risk for genetic discrimination. Genetic discrimination occurs when people are treated unfairly because of a difference in their DNA that suggests that they have a genetic disorder or are at an increased risk of developing a certain disease. In the United States, the Genetic Information Nondiscrimination Act of 2008 protects individuals from genetic discrimination at the hands of health insurers and employers, but does not extend protection against discrimination from providers of life, disability, or long-term care insurance.

Like all medical decision-making, the decisions about genetic testing should be based on a careful evaluation of the potential benefits and risks. In the pediatric setting, these decisions may be more difficult because physicians and parents are often called on to make decisions for a child who cannot directly participate in discussions about the testing. Molecular diagnostic tests are often used to diagnose malformation syndromes, cognitive delay, or other disabilities wherein there is a clear benefit to the child. In other cases, such as genetic testing for susceptibility to adult-onset diseases, it is appropriate to wait until the child or adolescent is mature enough to weigh the pros and cons and make his or her own decisions about genetic testing.

Policies regarding genetic testing of children have been developed collaboratively by the American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG; *Pediatrics* 131[3]:620-622, 2013). These recommendations are outlined here:

1. Decisions about whether to offer genetic testing and screening should be driven by the best interest of the child.
2. Genetic testing is best offered in the context of genetic counseling. Genetic counseling can be performed by clinical geneticists, genetic counselors, or any other health care provider with appropriate training and expertise. The AAP and ACMG support the expansion of educational opportunities in human genomics and genetics for medical students, residents, and practicing pediatric primary care providers.

Diagnostic Testing

3. In a child with symptoms of a genetic condition, the rationale for genetic testing is similar to that of other medical diagnostic evaluations. Parents or guardians should be informed about the risks and benefits of testing, and their permission should be obtained. Ideally, and when appropriate, the assent of the child should be obtained.
4. When performed for therapeutic purposes, pharmacogenetic testing of children is acceptable, with permission of parents or guardians and, when appropriate, the child's assent. If a pharmacogenetic test result carries implications beyond drug targeting or dose-responsiveness, the broader implications should be discussed before testing.

Newborn Screening

5. The AAP and ACMG support the mandatory offering of newborn screening for all children. After education and counseling about the substantial benefits of newborn screening, its remote risks, and the next steps in the event of a positive screening result, parents should have the option of refusing the procedure, and an informed refusal should be respected.

Carrier Testing

6. The AAP and ACMG do not support routine carrier testing in minors when such testing does not provide health benefits in childhood. The AAP and ACMG advise against school-based testing or screening programs, because the school environment is unlikely to be conducive to voluntary participation, thoughtful consent, privacy, confidentiality, or appropriate counseling about test results.
7. For pregnant adolescents or for adolescents considering reproduction, genetic testing and screening should be offered as clinically indicated, and the risks and benefits should be explained clearly.

Predictive Genetic Testing

8. Parents or guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood-onset conditions. Ideally, the assent of the child should be obtained.
9. Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality. An exception might be made for families for whom diagnostic uncertainty poses a significant psychosocial burden, particularly when an adolescent and his or her parents concur in their interest in predictive testing.
10. For ethical and legal reasons, healthcare providers should be cautious about providing predictive genetic testing to minors without the involvement of their parents or guardians, even if a minor is mature. Results of such tests may have significant medical, psychological, and social implications, not only for the minor but also for other family members.

Histocompatibility Testing

11. Tissue compatibility testing of minors of all ages is permissible to benefit immediate family members but should be conducted only after thorough exploration of the psychosocial, emotional, and physical implications of the minor serving as a potential stem cell donor. A donor advocate or similar mechanism should be in place from the outset to avert coercion and safeguard the interests of the child.

Adoption

12. The rationale for genetic testing of children in biological families should apply for adopted children and children awaiting placement for adoption. If a child has a known genetic risk, prospective adoptive parents must be made aware of this possibility. In rare cases, it may be in a child's best interest to undergo predictive genetic testing for a known risk before adoption to ensure the child's placement with a family capable of and willing to accept the child's potential medical and developmental challenges. In the absence of such indications, genetic testing should not be performed as a condition of adoption.

Disclosure

13. At the time of genetic testing, parents or guardians should be encouraged to inform their child of the test results at an appropriate age. Parents or guardians should be advised that, under most circumstances, a request by a mature adolescent for test results should be honored.
14. Results from genetic testing of a child may have implications for the parents and other family members. Healthcare providers have an obligation to inform parents and the child, when appropriate, about these potential implications. healthcare providers should encourage patients and families to share this information and offer to help explain the results to the extended family or refer them for genetic counseling.
15. Misattributed paternity, use of donor gametes, adoption, or other questions about family relationships may be uncovered "incidentally" whenever genetic testing is performed, particularly when testing multiple family members. This risk should be discussed, and a plan about disclosure or nondisclosure should be in place before testing.

Direct-to-Consumer Testing

16. The AAP and ACMG strongly discourage the use of direct-to-consumer and home-kit genetic testing of children because of the lack of oversight on test content, accuracy, and interpretation.

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Chapter 79

The Human Genome

Daryl A. Scott and Brendan Lee

The Human Genome Project, culminated in the sequencing of the human genome and greatly expanded our ability to study human genes and to explore the roles of genes in both rare and common disorders. Over time, it has also become apparent that the genome includes far more than a coded store of information to produce proteins.

The human genome has approximately 25,000 genes that encode the wide variety of proteins found in the human body. Reproductive or germline cells contain 1 copy (N) of this genetic complement and are **haploid,** whereas somatic (nongermline) cells contain 2 complete copies (2N) and are **diploid.** Genes are organized into long segments of DNA, which, during cell division, are compacted into intricate structures together with proteins to form chromosomes. Each somatic cell has 46 chromosomes: 22 pairs of autosomes, or nonsex chromosomes, and 1 pair of sex chromosomes (XY in a male, XX in a female). Germ cells (ova or sperm) contain 22 autosomes and 1 sex chromosome, for a total of 23. At fertilization, the full diploid chromosome complement of 46 is again realized in the embryo.

Most of the genetic material is contained in the cell's nucleus. The mitochondria (the cell's energy-producing organelles) contain their own unique genome. The **mitochondrial chromosome** consists of a double-stranded circular piece of DNA, which contains 16,568 base pairs (bp) of DNA and is present in multiple copies per cell. The proteins that occupy the mitochondria are produced either in the mitochondria, using information contained in the mitochondrial genome, or are produced outside of the mitochondria, using information contained in the nuclear genome and transported into the organelle. Sperm do not usually contribute mitochondria to the developing embryo, so all mitochondria are maternally derived and a child's mitochondrial genetic makeup derives exclusively from the child's biological mother.

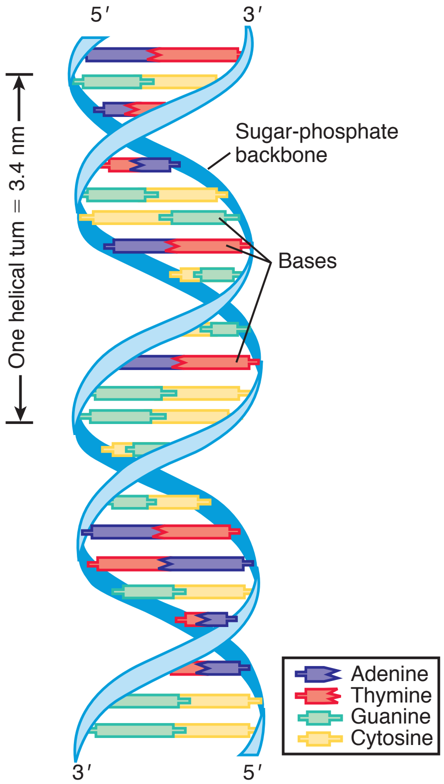

Figure 79-1 DNA double helix, with sugar-phosphate backbone and nitrogenous bases. *(From Jorde LB, Carey JC, Bamshad MJ, et al, editors:* Medical genetics, *ed 2, St. Louis, 1999, Mosby, p. 8.)*

FUNDAMENTALS OF MOLECULAR GENETICS

The central tenet of molecular genetics is that information encoded in DNA, predominantly located in the cell nucleus, is transcribed into messenger RNA (mRNA), which is then transported to the cytoplasm, where it is translated into protein. A gene is a unit that includes a regulatory region and a coding region that stores information corresponding to the sequence of amino acids in a specific protein.

DNA consists of a pair of chains of a sugar-phosphate backbone linked by pyrimidine and purine bases to form a **double helix** (Fig. 79-1). The sugar in DNA is deoxyribose. The pyrimidines are cytosine (C) and thymine (T); the purines are guanine (G) and adenine (A). The bases are linked by hydrogen bonds such that A always pairs with T and G with C. Each strand of the double helix has polarity, with a free phosphate at one end (5′) and an unbonded hydroxyl on the sugar at the other end (3′). The 2 strands are oriented in opposite polarity in the double helix.

The replication of DNA follows the pairing of bases in the parent DNA strand. The original 2 strands unwind by breaking the hydrogen bonds between base pairs. Free nucleotides, consisting of a base attached to a sugar-phosphate, form new hydrogen bonds with their complementary bases on the parent strand; new phosphodiester bonds are created by the enzyme **DNA polymerase.** Replication of chromosomes begins simultaneously at multiple sites, forming replication bubbles that expand bidirectionally until the entire DNA molecule (chromosome) is replicated. Errors in DNA replication, or mutations induced by environmental mutagens such as irradiation or chemicals, are detected and potentially corrected by DNA repair systems.

A prototypical gene consists of a regulatory region, segments called **exons** that encode the amino acid sequence of a protein, and intervening segments called **introns** (Fig. 79-2). **Transcription** starts at the promoter region and continues through the entire length of the gene to form mRNA. The introns are removed and the exons spliced together to form a mature message, which is exported to the cytoplasm. There the mRNA is bound to ribosomes and translated into protein.

Transcription is initiated by attachment of RNA polymerase to the promoter site upstream of the beginning of the coding sequence. Specific proteins bind to the region to either repress or activate transcription by opening up the chromatin, which is a complex of DNA and histone proteins. It is the action of these regulatory proteins **(transcription factors)** that determines, in large part, when a gene is turned on or off. Some genes are also turned on and off by methylation of cytosine bases that are adjacent to guanines (CpG [cytosine-phosphate-guanine] bases). Methylation is an example of an **epigenetic** change, meaning a change that can affect gene expression, and possibly the characteristics of a cell or organism, but that does not involve a change in the underlying genetic sequence. Gene regulation is flexible and responsive, with genes being turned on or off during development and in response to internal and external environmental conditions and stimuli.

Transcription proceeds through the full length of the gene, synthesizing mRNA in a 5′ to 3′ direction. RNA, like DNA, is a sugar-phosphate chain with pyrimidines and purines. In RNA, the sugar is ribose and uracil replaces the thymine found in DNA. The RNA reads off 1 strand of DNA to copy a complementary RNA sequence. A "cap" consisting of 7-methylguanosine is added to the 5′ end of the RNA in a 5′-5′ bond and, for most transcripts, several hundred adenine bases are enzymatically added to the 3′ end after transcription.

mRNA **processing** occurs in the nucleus and consists of excision of the introns and splicing together of the exons. Specific sequences at the start and end of introns mark the sites where the splicing machinery will act on the transcript. In some cases, there may be tissue-specific

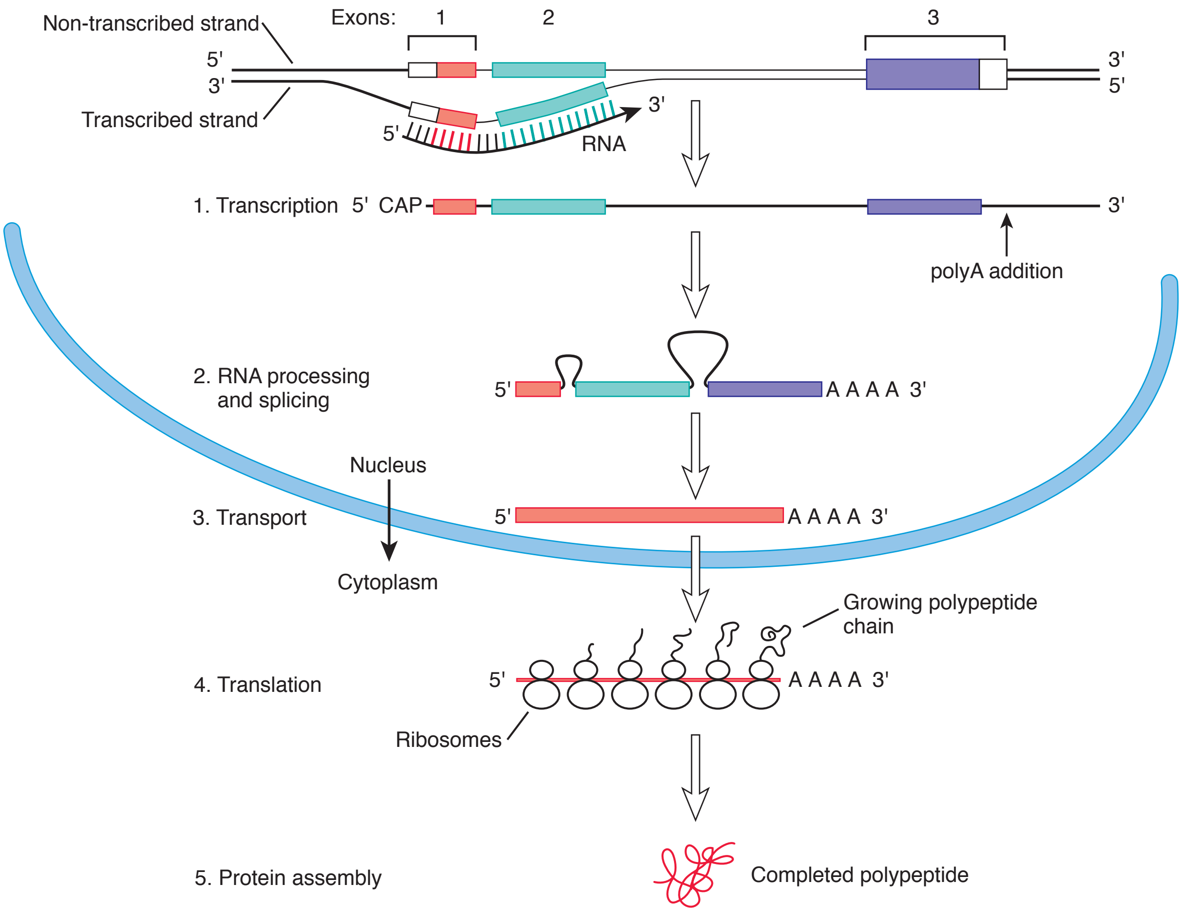

Figure 79-2 **Flow of information from DNA to RNA to protein for a hypothetical gene with three exons and two introns.** Within the exons, blue indicates the coding sequences. Steps include transcription, RNA processing and splicing, RNA transport from the nucleus to the cytoplasm, and translation. *(From Nussbaum RL, McInnis RR, Willard HF, Hamosh A, editors:* Thompson & Thompson genetics in medicine, *ed 7, Philadelphia, 2007, Saunders/Elsevier,* Fig 3.5, *p. 31.)*

patterns to splicing, so that the same primary transcript can produce multiple distinct proteins.

The processed transcript is next exported to the cytoplasm, where it binds to ribosomes, which are complexes of protein and RNA. The genetic code is then read in triplets of bases, each triplet corresponding with a specific amino acid or providing a signal that terminates **translation.** The triplet codons are recognized by transfer RNAs that include complementary anticodons and bind the corresponding amino acid, delivering it to the growing peptide. A new amino acid is enzymatically attached to the peptide; each time an amino acid is added, the ribosome moves one triplet codon step along the mRNA. Eventually a stop codon is reached, at which point translation ends and the peptide is released. In some proteins, there are **posttranslational modifications,** such as attachment of sugars (glycosylation); the protein is then delivered to its destination within or outside the cell by trafficking mechanisms that recognize portions of the peptide.

An emerging layer of complexity and genetic regulation is that of noncoding RNAs. This refers to RNAs that are transcribed from DNA but are not translated into proteins. Noncoding RNAs function in mediating splicing and the processing of coding RNAs in the nucleus and the translation of coding RNAs in ribosomes. The roles of large noncoding RNAs (>200 bp) and short noncoding RNAs (<200 bp) extend beyond these processes to impact a diverse set of biologic functions including regulation of gene expression. For example, microRNAs (miRNAs) are a class of small RNAs that control gene expression in the cell by directly targeting specific sets of coding RNAs by direct RNA–RNA binding. This RNA–RNA interaction can lead to degradation of the target coding RNA or inhibition of translation of the protein specified by that coding RNA. miRNAs, in general, target and regulate several hundred mRNAs.

GENETIC VARIATION

The process of producing protein from a gene is subject to disruption at multiple levels owing to alterations in the coding sequence (Fig. 79-3). Changes in the regulatory region can lead to altered gene expression, including increased or decreased rates of transcription, failure of gene activation, or activation of the gene at inappropriate times or in inappropriate cells. Changes in the coding sequence can lead to **substitution** of one amino acid for another **(missense mutation** or **nonsynonymous)** or creation of a stop codon in the place of an amino acid codon. Overall, missense or nonsense mutations are the most common (~56% of mutations); small deletions or insertions represent approximately 24% of mutations (Table 79-1). Some single-base changes do not affect the amino acid (silent or wobble mutation or synonymous), because there may be several triplet codons that correspond with a single amino acid. Amino acid substitutions can have a profound effect on protein function if the chemical properties of the substituted amino acid are markedly different from the usual one. Other substitutions can have a subtle or no effect on protein function, particularly if the substituted amino acid is chemically similar to the original one.

Genetic changes can also include **insertions** or **deletions.** Insertions or deletions of a nonintegral multiple of 3 bases into the coding sequence leads to a **frameshift,** altering the grouping of bases into triplets. This leads to translation of an incorrect amino acid sequence and often a premature stop to translation. Insertion or deletion of an

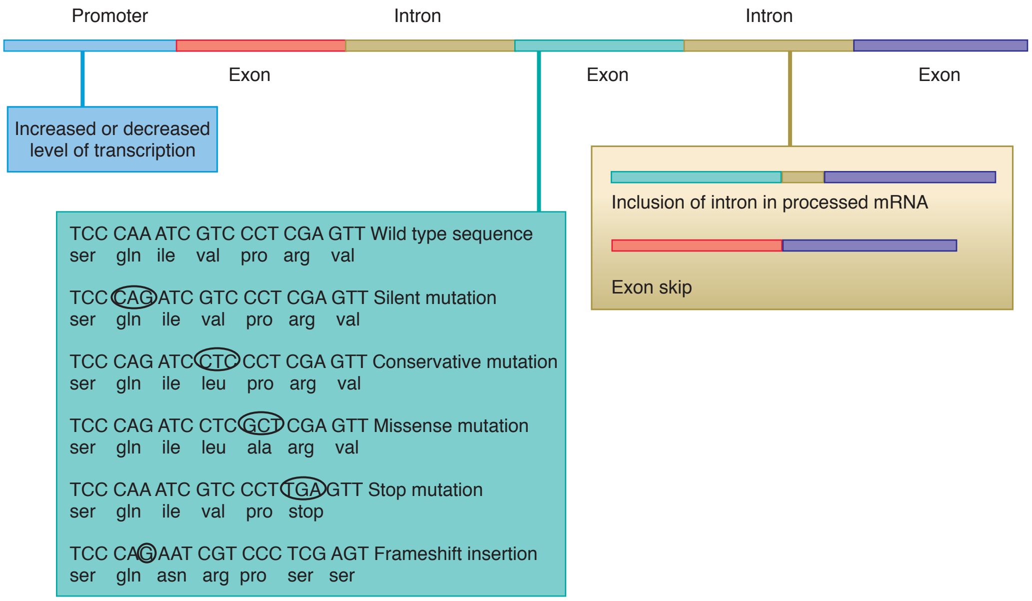

Figure 79-3 **Various types of intragenic mutations.** Promoter mutations alter rate of transcription or disrupt gene regulation. Base changes within exons can have various effects, as shown. Mutations within introns can lead to inclusion of some intronic sequence in the final processed mRNA, or it can lead to exon skipping.

Table 79-1 Main Classes, Groups, and Types of Mutation and Effects on Protein Product

CLASS	GROUP	TYPE	EFFECT ON PROTEIN PRODUCT
Substitution	Synonymous	Silent*	Same amino acid
	Nonsynonymous	Missense*	Altered amino acid—may affect protein function or stability
		Nonsense*	Stop codon—loss of function or expression from degradation of mRNA
		Splice site	Aberrant splicing—exon skipping or intron retention
		Promoter	Altered gene expression
Deletion	Multiple of 3 (codon)		In-frame deletion of 1 or more amino acid(s)—may affect protein function or stability
	Not multiple of 3	Frameshift	Likely to result in premature termination with loss of function or expression
	Large deletion	Partial gene deletion	May result in premature termination with loss of function or expression
		Whole gene deletion	Loss of expression
Insertion	Multiple of 3 (codon)		In-frame insertion of 1 or more amino acid(s)—may affect protein function or stability
	Not multiple of 3	Frameshift	Likely to result in premature termination with loss of function or expression
	Large insertion	Partial gene duplication	May result in premature termination with loss of function or expression
		Whole gene duplication	May have an effect because of increased gene dosage
	Expansion of trinucleotide repeat	Dynamic mutation	Altered gene expression or altered protein stability or function

*Some have been shown to cause aberrant splicing.
From Turnpenny P, Ellard S (Editors): Emery's elements of medical genetics, *ed 14, Philadelphia, 2012, Elsevier/Churchill Livingstone, Table 2.2, p. 23.*

integral multiple of 3 bases into the coding sequence will insert or delete a corresponding number of amino acids from the protein leading to in-frame alterations that maintain the amino acid sequence outside of the deleted or duplicated amino acids. Larger-scale insertions or deletions can disrupt a coding sequence or result in complete deletion of an entire gene or group of genes.

Mutations usually can be classified as causing a loss of function or a gain of function. **Loss-of-function mutations** cause a reduction in the level of protein function as a result of decreased expression or production of a protein that does not work as efficiently. In some cases, loss of protein function from one gene is sufficient to cause disease. **Haploinsufficiency** describes the situation in which maintenance of a normal phenotype requires the proteins produced by both copies of a gene, and a 50% decrease in gene function results in an abnormal phenotype. Hence, haploinsufficient phenotypes are, by definition, dominantly inherited. Loss-of-function mutations can also have a dominant negative effect when the abnormal protein product actively interferes with the function of the normal protein product. Both of these situations lead to diseases inherited in a dominant fashion (see Chapter 80). In other cases, loss-of-function mutation must be present in both copies of a gene before an abnormal phenotype results. This situation typically results in diseases inherited in a recessive fashion (see Chapter 80).

Gain-of-function mutations typically cause dominantly inherited diseases. These mutations can result in production of a protein molecule with an increased ability to perform a normal function or they

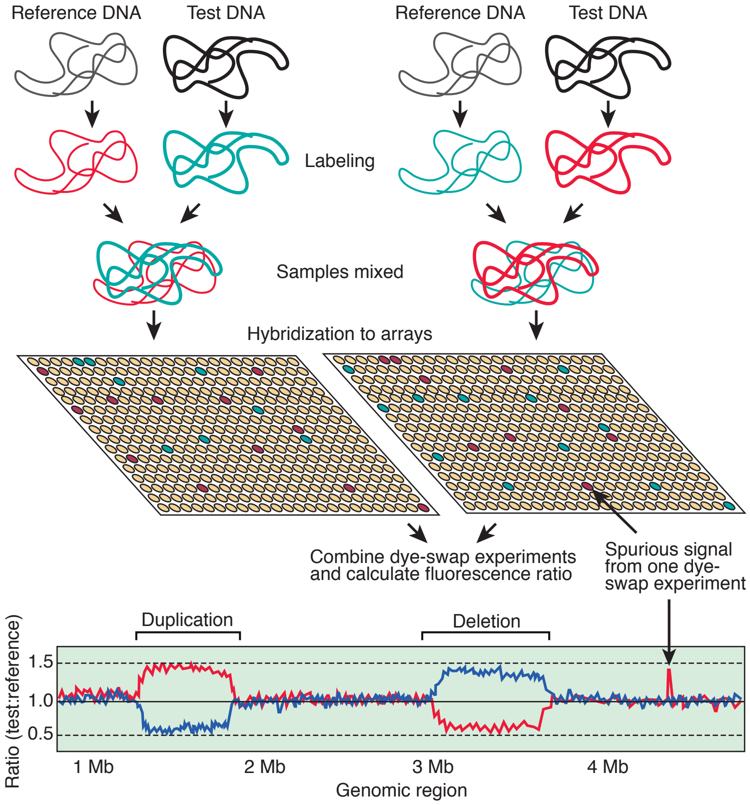

Figure 79-4 **Array comparative genomic hybridization.** Test and reference DNA samples are differentially labeled, mixed, and passed over a target array of probes (e.g., bacterial artificial chromosome clones or oligonucleotides) containing DNA fragments from across the whole human genome. The experiment is often repeated with reversal of the test and reference dyes to detect dye effects or identify spurious signals. DNA samples hybridize with their corresponding probe, and the ratio of fluorescence from each probe (test:reference) is used to detect regions that vary in copy number between the test and the reference sample (*red line:* original hybridization; *blue line:* dye-swapped hybridization). Equal copy number for both the test and reference DNA is identified by equal binding, resulting in a ratio of 1:1. Duplication in a genomic region of the test sample is identified by an increased ratio, and a deletion is identified by a decreased ratio, but a deletion in the test sample is indistinguishable from a duplication in the reference sample. These ratios are usually converted to log2 scale for further analysis. *(Adapted from Feuk L, Carson AR, Scherer SW: Structural variation in the human genome,* Nat Rev Genet *7:85–97, 2006, with permission from* Nature Reviews Genetics.*)*

can confer a novel property on the protein. The gain-of-function mutation in **achondroplasia,** the most common of the disproportionate, short-limbed short stature disorders, exemplifies the enhanced function of a normal protein. Achondroplasia results from a mutation in the fibroblast growth factor receptor 3 gene (*FGFR3*), which leads to activation of the receptor, even in the absence of fibroblast growth factor. In **sickle cell disease,** an amino acid is substituted into the hemoglobin molecule that has little effect on the ability of the protein to transport oxygen. However, sickle hemoglobin chains have a novel property. Unlike normal hemoglobin, sickle hemoglobin chains aggregate under conditions of deoxygenation, forming fibers that deform the red cells.

Other gain-of-function mutations result in overexpression or inappropriate expression of a gene product. Many cancer-causing genes **(oncogenes)** are normal regulators of cellular proliferation during development. However, expression of these genes in adult life and/or in cells in which they usually are not expressed can result in neoplasia.

In some cases, changes in gene expression are caused by changes in the number of copies of a gene that are present in the genome (Fig. 79-4). Although some **copy number variations** are common and do not appear to cause or predispose to disease, others are clearly disease causing. Charcot-Marie-Tooth disease type 1A, the most common inherited form of chronic peripheral neuropathy of childhood, is caused by duplications of the gene for peripheral myelin protein 22, resulting in overexpression as a consequence of the existence of 3 active copies of this gene. Deletions of this same gene leaving only 1 active copy are responsible for a different disorder, hereditary neuropathy with liability to pressure palsies.

Deletions and duplications can vary in their extent and can involve several genes, even when they are not visible on a traditional chromosome analysis. Such changes are commonly called **microdeletions** and **microduplications.** When deletion or duplication of 2 or more genes in the same chromosomal region each play a role in the resulting clinical features, the condition can also be referred to as a **contiguous gene disorder**.

In some cases the recognition of a specific constellation of features leads the clinician to suspect a specific microdeletion or microduplication syndrome. Examples of such disorders include Smith-Magenis, DiGeorge, and Williams syndromes. In other cases, the clinician may be alerted to this possibility by an unusually diverse array of clinical features in one patient or the presence of unusual features in a person with a known condition. Owing to the close physical proximity of a series of genes, different deletions involving the short arm of the X chromosome can produce individuals with various combinations of ichthyosis, Kallmann syndrome, ocular albinism, intellectual disability, chondrodysplasia punctata, and short stature.

DNA rearrangements can also take place in somatic cells-meaning cells that do not go on to produce ova or sperm. Rearrangements that occur in lymphoid cells are required for the formation of functional immunoglobulin in B cells and antigen-recognizing receptors on T cells. Large segments of DNA, which code for the variable and the constant regions of either immunoglobulin or the T-cell receptor, are physically joined at a specific stage in the development of an immunocompetent lymphocyte. These rearrangements take place during development of the lymphoid cell lineage in humans and result in the extensive diversity of immunoglobulin and T-cell receptor molecules. It is as a result of this postgermline DNA rearrangement that no 2 individuals, not even identical twins, are really identical, because mature lymphocytes from each will have undergone random DNA rearrangements at these loci.

Studies of the human genome sequence reveal that any 2 individuals differ in about 1 base in 1,000. Some of these differences are silent; some result in changes that explain phenotypic differences (hair or eye color, physical appearance); some have medical significance, causing single-gene disorders such as sickle cell anemia or explaining susceptibility to common pediatric disorders such as asthma. Genetic variants in a single gene that occur at a frequency of >1% in a population are often referred to as **polymorphisms.** These variations may be silent or subtle or have significant phenotypic effects.

GENOTYPE-PHENOTYPE CORRELATIONS IN GENETIC DISEASE

The term **genotype** is used to signify the internally coded, heritable information of an individual and can also be used to refer to which particular alternative version **(allele)** of a gene is present at a specific location **(locus)** on a chromosome. A **phenotype** is the observed structural, biochemical, and physiologic characteristics of an individual, determined by the genotype, and can also refer to the observed structural and functional effects of a mutant allele at a specific locus. Many mutations result in predictable phenotypes. In these cases, physicians can predict clinical outcomes and plan appropriate treatment strategies based on a patient's genotype.

The **long QT syndrome** exemplifies a disorder with predictable associations between a patient's genotype and his or her phenotype (see Chapter 435.5). Long QT syndrome is genetically heterogeneous, meaning that mutations in several different genes can cause the same disorder. The risk for cardiac events (syncope, aborted cardiac arrest, or sudden death) is higher with long QT syndrome mutations involving the *KCNQ1* gene (63%) or the *KCNH2* gene (46%) than among subjects with mutations in the *SCN5A* gene (18%). In addition, those with mutations involving *KCNQ1* experience most of their episodes during exercise and rarely during rest or sleep. In contrast, individuals with mutations in *KCNH2* and *SCN5A* are more likely to have episodes during sleep or rest, and rarely during exercise. Therefore, mutations in specific genes (genotype) are correlated with specific manifestations (phenotype) of long QT syndrome. These types of relationships are commonly referred to as *genotype–phenotype correlations.*

Mutations in the fibrillin-1 gene associated with **Marfan syndrome** represent another example of predictable genotype–phenotype correlations (see Chapter 702). Marfan syndrome is characterized by the combination of skeletal, ocular, and aortic manifestations, with the most devastating outcome being aortic root dissection and sudden death. Sixty-five exons make up the fibrillin-1 gene, and mutations have been found in almost all of these exons. The location of the mutation within the gene (genotype) might play a significant role in determining the severity of the condition (phenotype). Neonatal Marfan syndrome is caused by mutations in exons 24-27 and in exons 31 and 32, whereas milder forms are caused by mutations in exons 59-65 and in exons 37 and 41.

Genotype–phenotype correlations have also been observed in some complications of **cystic fibrosis** (CF; see Chapter 403). Although pulmonary disease is the major cause of morbidity and mortality, CF is a multisystem disorder that affects not only the epithelia of the respiratory tract but also the exocrine pancreas, intestine, male genital tract, hepatobiliary system, and exocrine sweat glands. CF is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene. More than 1,600 different mutations have been identified. The most common is a deletion of 3 nucleotides that removes the amino acid phenylalanine (F) at the 508th position on the protein (ΔF508 mutation), which accounts for approximately 70% of all CF mutations and is associated with severe disease. The best genotype–phenotype correlations in CF are seen in the context of pancreatic function, with most common mutations being classified as either pancreatic sufficient or pancreatic insufficient. Persons with pancreatic sufficiency usually have either 1 or 2 pancreatic-sufficient alleles, indicating that pancreatic-sufficient alleles are dominant. In contrast, the genotype–phenotype correlation in pulmonary disease is much weaker, and persons with identical genotypes have wide variations in the severity of their pulmonary disease. This finding may be accounted for in part by genetic modifiers or environmental factors.

There are many disorders in which the effects of mutations on phenotype can be modified by changes in the other allele of the same gene, by changes in specific **modifier genes,** and/or variations in a number of unspecified genes **(genetic background).** When sickle cell anemia is coinherited with the gene for hereditary persistence of fetal hemoglobin, the sickle cell phenotypic expression is less severe. Modifier genes in CF can influence the development of congenital meconium ileus, or colonization with *Pseudomonas aeruginosa.* Modifier genes can also affect the manifestations of Hirschsprung disease, neurofibromatosis type 2, craniosynostosis, and congenital adrenal hyperplasia. The combination of genetic mutations producing glucose-6-phosphate dehydrogenase deficiency and longer versions of the TATAA element in the uridine diphosphate–glucuronosyltransferase gene promoter exacerbates neonatal physiologic hyperbilirubinemia.

HUMAN GENOME PROJECT

A rudimentary genetic map can be made using genetic linkage, which is based on the principle that alleles at 2 genetic loci that are located near each other segregate together in a family unless they are separated by genetic **recombination.** The frequency of recombination between the loci can be used to estimate the physical distance between points. Some of the first maps of the human genome were linkage maps based on a set of polymorphic genetic loci located along the entire human genome. Linkage analysis is still used to map the location of genetic changes responsible for phenotypic traits and genetic disorders that are inherited in a mendelian fashion.

In contrast to linkage maps, which are based on recombination frequencies, physical maps rely on overlapping DNA fragments to determine the location of loci with respect to one another. Several strategies can be used to create physical maps of a chromosomal region. In one strategy, segments of the region of interest with lengths from hundreds or thousands to a few million base pairs are isolated and placed in microorganisms such as bacteria or yeast. Common regions contained in different organism can then be identified and this information can be used to piece together a map composed of overlapping DNA pieces, each contained in a different microorganism. The pieces contained in each organism can then be sequenced to obtain the DNA sequence of the entire region. An alternative strategy involves breaking the entire genome into random fragments, sequencing the fragments, and then using a computer to order the fragments based on overlapping segments. This whole genome approach in combination with new next-generation sequencing technologies has resulted in a dramatic reduction in the cost of sequencing an individual's entire genome.

Analysis of the human genome has produced some surprising results. The number of genes is still not known precisely but appears to be around 25,000. This is fewer than had been expected and in the same range as many simpler organisms. The number of protein products encoded by the genome is greater than the number of genes. This is a result of the presence of alternative promoter regions, alternative splicing, and posttranslational modifications, which can allow a single gene to encode a number of protein products.

It is also apparent that most of the human genome does not encode protein, with <5% being transcribed and translated, though a much larger percentage may be transcribed without translation. Many transcribed sequences are not translated but represent genes that encode RNAs that serve a regulatory role. A large fraction of the genome consists of repeated sequences that are interspersed among the genes. Some of these are transposable genetic elements that can move from place to place in the genome. Others are static elements that were expanded and dispersed in the past during human evolution. Other repeated sequences might play a structural role. There are also regions of genomic duplications. Such duplications are substrate for evolution, allowing genetic motifs to be copied and modified to serve new roles in the cell. Duplications can also play a role in chromosomal rearrangement, permitting nonhomologous chromosome segments to pair during meiosis and exchange material. This is another source of evolutionary change and a potential source of chromosomal instability leading to congenital anomalies or cancer. Low copy repeats also play an important role in causing genomic disorders. When low copy repeats flank unique genomic segments, these regions can be duplicated or deleted through a process known as *nonallelic homologous recombination.*

Availability of the entire human genomic sequence permits the study of large groups of genes, looking for patterns of gene expression or genome alteration. Microarrays permit the expression of thousands of genes to be analyzed on a small glass chip. Increasingly, studies of gene expression are being performed using next generation sequencing

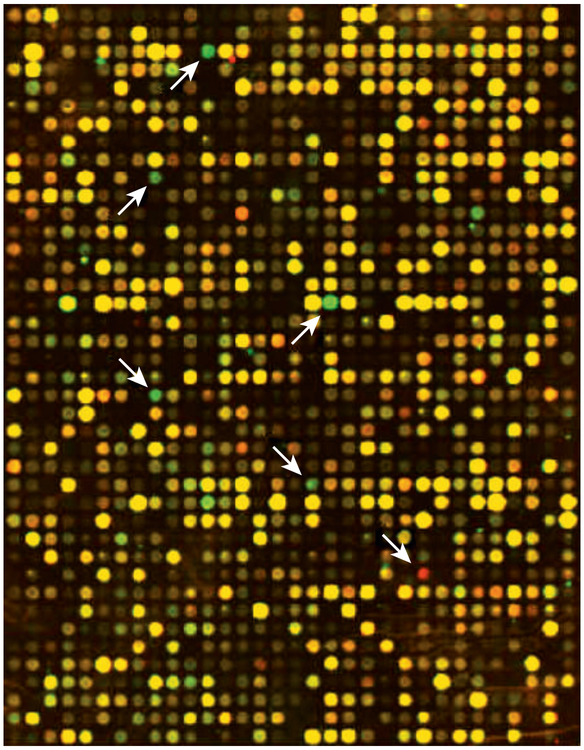

Figure 79-5 Microarray containing 36,000 oligonucleotides. The microarray was exposed to RNA from normal fibroblasts (labeled in *red*; see *arrows*) and fibroblasts from a patient with Niemann-Pick disease, type C (labeled *green*). Arrows point to regions in which there was a strong hybridization signal with either normal or disease RNA. This microarray was used to search for genes that are highly expressed in the fibroblasts of patients. *(From Jorde LB, Carey JC, Bamshad MJ, et al, editors:* Medical genetics, *ed 3, St. Louis, 2006, Mosby, p. 116.)*

techniques to obtain information about all of the RNA transcripts in a tissue sample. In some cases the patterns of gene expression provide signatures for particular disease states, such as cancer, or change in response to therapy (Fig. 79-5).

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Chapter 80

Patterns of Genetic Transmission

Daryl A. Scott and Brendan Lee

FAMILY HISTORY AND PEDIGREE NOTATION

The family history remains the most important screening tool for pediatricians in identifying a patient's risk for developing a wide range of diseases, from multifactorial conditions, such as diabetes and attention-deficit disorder, to single-gene disorders such as sickle cell anemia and cystic fibrosis. Through a detailed family history the physician can often ascertain the mode of genetic transmission and the risks to family members. Because not all familial clustering of disease is caused by genetic factors, a family history can also identify common environmental and behavioral factors that influence the occurrence of disease. The main goal of the family history is to identify genetic susceptibility, and the cornerstone of the family history is a systematic and standardized pedigree.

A **pedigree** provides a graphic depiction of a family's structure and medical history. It is important when taking a pedigree to be systematic and use standard symbols and configurations (Figs. 80-1 to 80-4) so that anyone can read and understand the information. In the pediatric setting, the **proband** is typically the child or adolescent who is being evaluated. The proband is designated in the pedigree by an arrow.

A 3 to 4–generation pedigree should be obtained for every new patient as an initial screen for genetic disorders segregating within the family. The pedigree can provide clues to the inheritance pattern of these disorders and can aid the clinician in determining the risk to the proband and other family members. The closer the relationship of the proband to the person in the family with the genetic disorder, the greater is the shared genetic complement. **First-degree** relatives, such as a parent, full sibling, or child, share ½ their genetic information on average; first cousins share ⅛. Sometimes the person providing the family history may mention a distant relative who is affected with a genetic disorder. In such cases a more extensive pedigree may be needed to identify the risk to other family members. For example, a history of a distant maternally related cousin with mental retardation caused by fragile X syndrome can still place a male proband at an elevated risk for this disorder.

MENDELIAN INHERITANCE

There are 3 classic forms of genetic inheritance: **autosomal dominant, autosomal recessive,** and **X-linked.** These are referred to as *mendelian inheritance forms,* after Gregor Mendel, the 19th-century monk whose experiments led to the laws of **segregation of characteristics, dominance,** and **independent assortment.** These remain the foundation of single-gene inheritance.

Autosomal Dominant Inheritance

Autosomal dominant inheritance is determined by the presence of 1 abnormal gene on 1 of the autosomes (chromosomes 1-22). Autosomal genes exist in pairs, with each parent contributing 1 copy. In an autosomal dominant trait, a change in 1 of the paired genes has an effect on the phenotype; this can refer to physical manifestations, behavioral characteristics, or differences detectable only through laboratory tests, even though the other copy of the gene is functioning correctly.

The pedigree for an autosomal dominant disorder (Fig. 80-5) demonstrates certain characteristics. The disorder is transmitted in a vertical (parent-to-child) pattern and can appear in multiple generations. This is illustrated by individual I.1 (see Fig. 80-5) passing on the changed gene to II.2 and II.5. An affected individual has a 50% (1 in 2) chance of passing on the deleterious gene in *each* pregnancy and, therefore, of having a child affected by the disorder. This is referred to as the **recurrence risk** for the disorder. Unaffected individuals (family members who do not manifest the trait) do not pass the disorder to their children. Males and females are equally affected. Although not a characteristic per se, the finding of male-to-male transmission essentially confirms autosomal dominant inheritance. Vertical transmission can also be seen with X-linked traits. However, because a father passes on his Y chromosome to a son, male-to-male transmission cannot be seen with an X-linked trait. Therefore, male-to-male transmission eliminates X-linked inheritance as a possible explanation. Although male-to-male transmission can occur with Y-linked genes as well, there are very few Y-linked disorders compared with thousands having the autosomal dominant inheritance pattern.

Although parent-to-child transmission is a characteristic of autosomal dominant inheritance, for many patients with an autosomal dominant disorder there is no history of an affected family member. There are several possible reasons: First, the patient may represent a **new mutation** that occurred in the DNA of the egg or sperm that came together to form that individual. Second, many autosomal dominant conditions demonstrate **incomplete penetrance,** meaning that not all individuals who carry the mutation have phenotypic manifestations. In a pedigree this can appear as a **skipped generation,** in which an

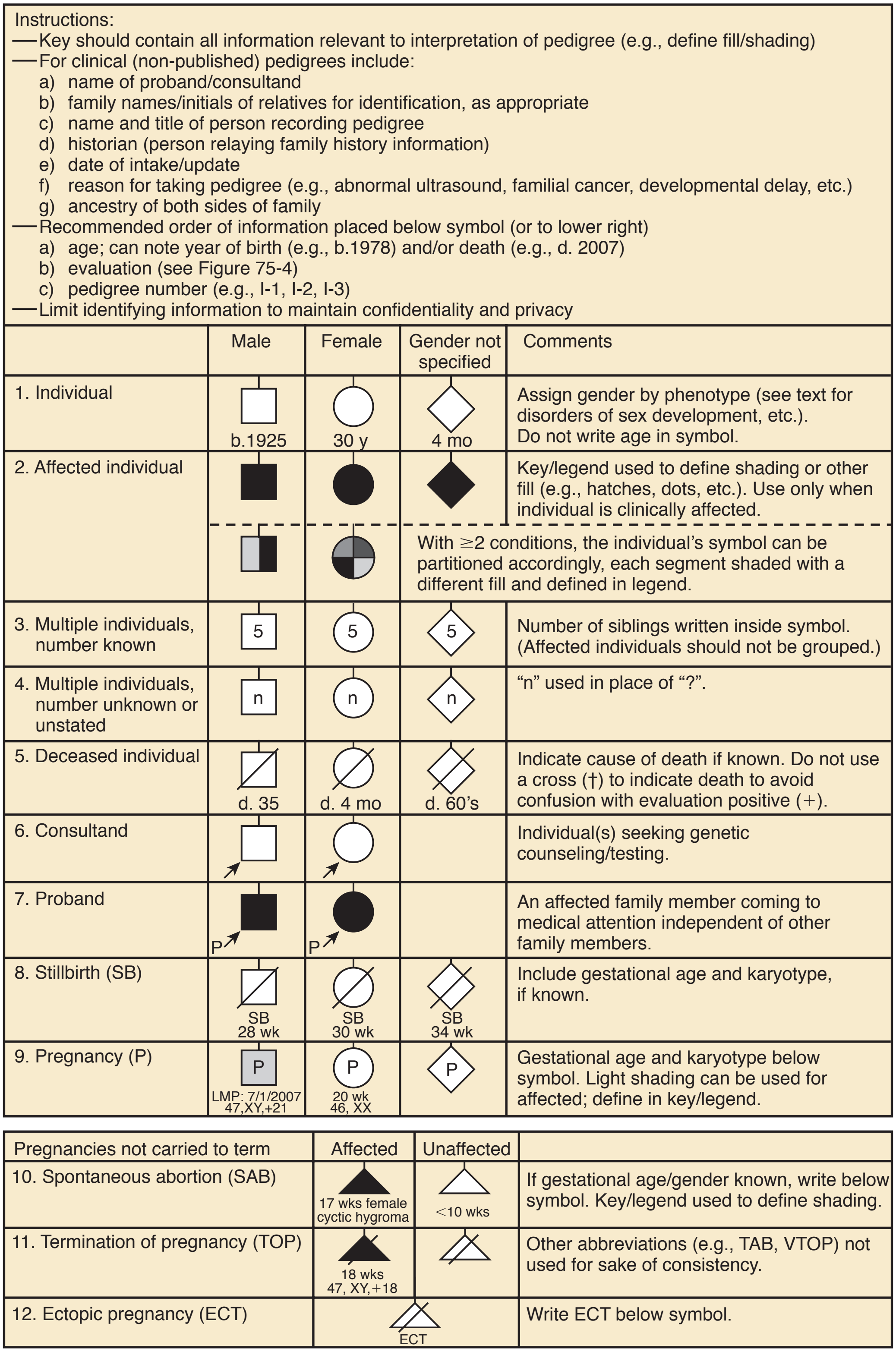

Figure 80-1 Common pedigree symbols, definitions, and abbreviations. *(From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors,* J Genet Couns *17:424–433, 2008.)*

unaffected individual links 2 affected persons (Fig. 80-6). There are many potential reasons that a disorder exhibits incomplete penetrance, including the effect of modifier genes, environmental factors, gender, and age. Third, individuals with the same autosomal dominant mutation can manifest the disorder to different degrees. This is termed **variable expression** and is a characteristic of many autosomal dominant disorders. Fourth, some spontaneous genetic mutations occur not in the egg or sperm that forms a child, but rather in a cell in the developing embryo. Such events are referred to as **somatic mutations,** and because not all cells are affected, the change is said to be *mosaic.* The

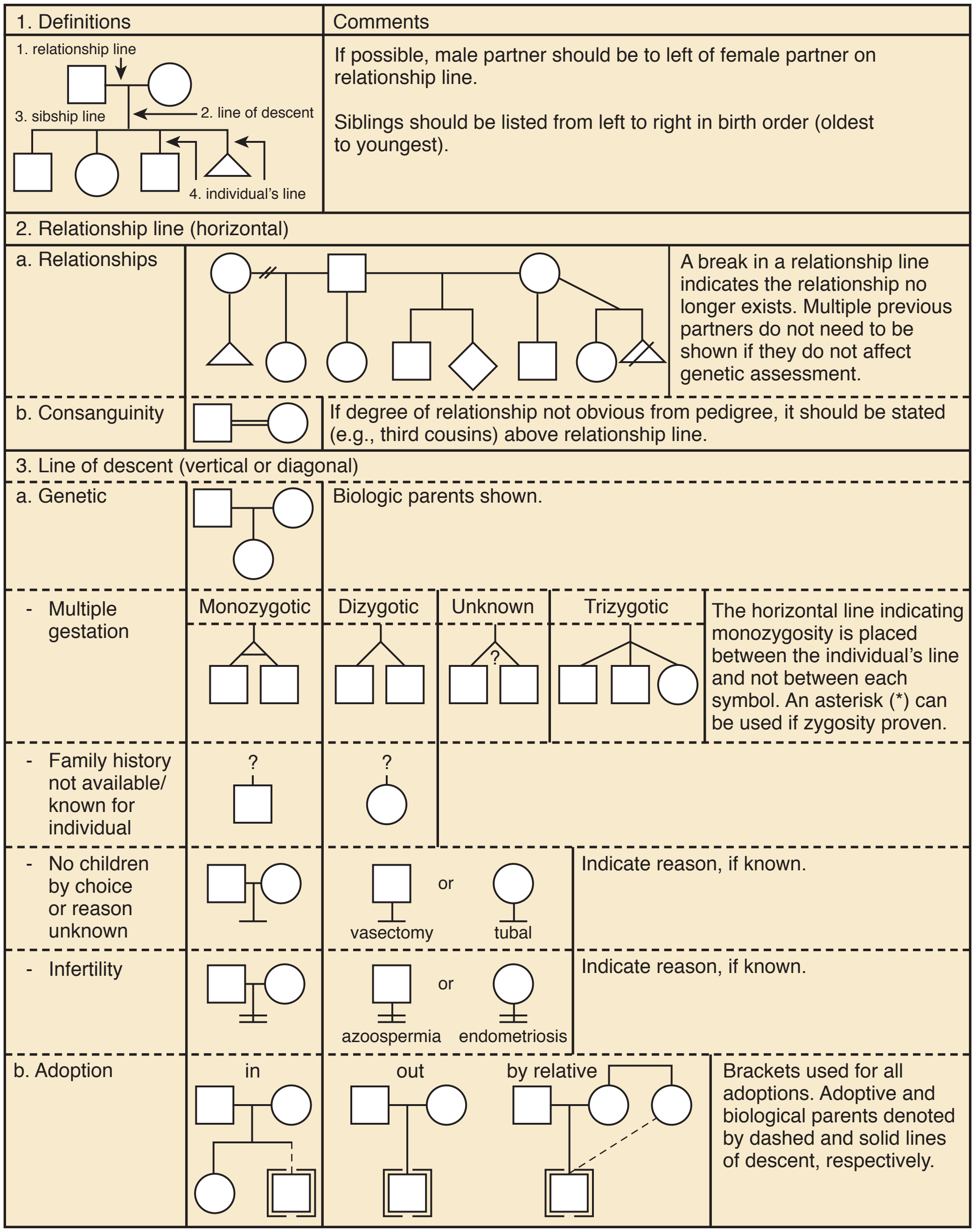

Figure 80-2 Pedigree line definitions. *(From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors, J Genet Couns 17:424–433, 2008.)*

resulting phenotype caused by a somatic mutation can be varied, but it is usually milder than if all cells contain the mutation. In **germline mosaicism,** the mutation occurs in cells that populate the germline that produce eggs or sperm. A germline mosaic might not have any manifestations of the disorder but might produce multiple eggs or sperm that carry the mutation.

Autosomal Recessive Inheritance

Autosomal recessive inheritance involves mutations in both copies of a gene. Examples of autosomal recessive diseases are cystic fibrosis and sickle cell disease. Characteristics of autosomal recessive traits (Fig. 80-7) include **horizontal transmission,** the observation of multiple affected members of a kindred in the same generation, but no affected family members in other generations; recurrence risk of 25% for parents with a previous affected child; males and females being equally affected, although some traits exhibit different expression in males and females and increased incidence, particularly for rare traits, in the offspring of consanguineous parents. **Consanguinity** refers to the existence of a relationship by a common ancestor and increases the chance that both parents carry a gene affected by an identical mutation that they inherited. Consanguinity between parents of a child with a suspected genetic disorder implies (but does not prove) autosomal recessive inheritance. Although consanguineous unions are uncommon in Western society, in other parts of the world (southern India, Japan, and the Middle East) they are common; the incidence may be as high as 50%. The risk of a genetic disorder for the offspring of a first-cousin marriage (6-8%) is about double the risk in the general population (3-4%).

Every individual probably has several rare, harmful, recessive mutations. Because most mutations carried in the general population occur

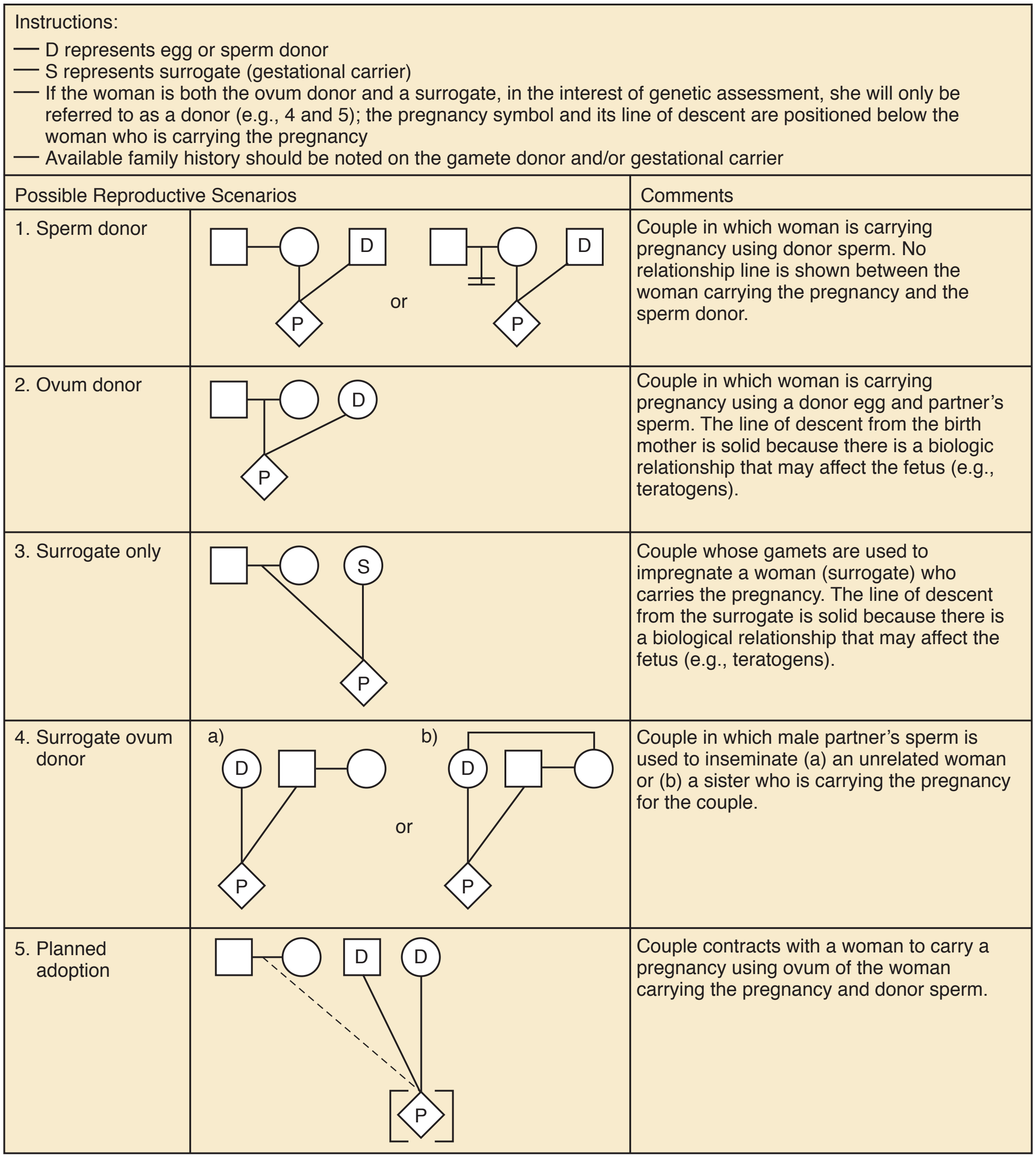

Figure 80-3 Assisted reproductive technology symbols and definitions. *(From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors,* J Genet Couns *17:424–433, 2008.)*

at a very low frequency, it does not make economic sense to screen the entire population in order to identify the small number of persons who carry these mutations. As a result, these mutations typically remain undetected unless an affected child is born to a couple who both carry mutations affecting the same gene.

However, in some genetic isolates (small populations separated by geography, religion, culture, or language) certain rare recessive mutations are far more common than in the general population. Even though there may be no known consanguinity, couples from these genetic isolates have a greater chance of sharing mutant alleles inherited from a common ancestor. Screening programs have been developed among some such groups to detect persons who carry common disease-causing mutations and therefore are at increased risk for having affected children. For example, a variety of autosomal recessive conditions are more common among Ashkenazi Jews than in the general population. Couples of Ashkenazi Jewish ancestry should be offered prenatal or preconception screening for Gaucher disease type 1 (carrier rate 1:14), cystic fibrosis (1:25), Tay-Sachs disease (1:25), familial dysautonomia (1:30), Canavan disease (1:40), glycogen storage disease type 1A (1:71), maple syrup urine disease (1:81), Fanconi anemia type C (1:89), Niemann-Pick disease type A (1:90), Bloom syndrome (1:100), mucolipidosis IV (1:120), and possibly neonatal familial hyperinsulinemic hypoglycemia.

The prevalence of carriers of certain autosomal recessive genes in some larger populations is unusually high. In such cases, heterozygote advantage is postulated. For example, the carrier frequencies of sickle cell disease in the African population and of cystic fibrosis in the northern European population are much higher than would be expected from new mutations. It is possible that heterozygous carriers have had an advantage in terms of survival and reproduction over

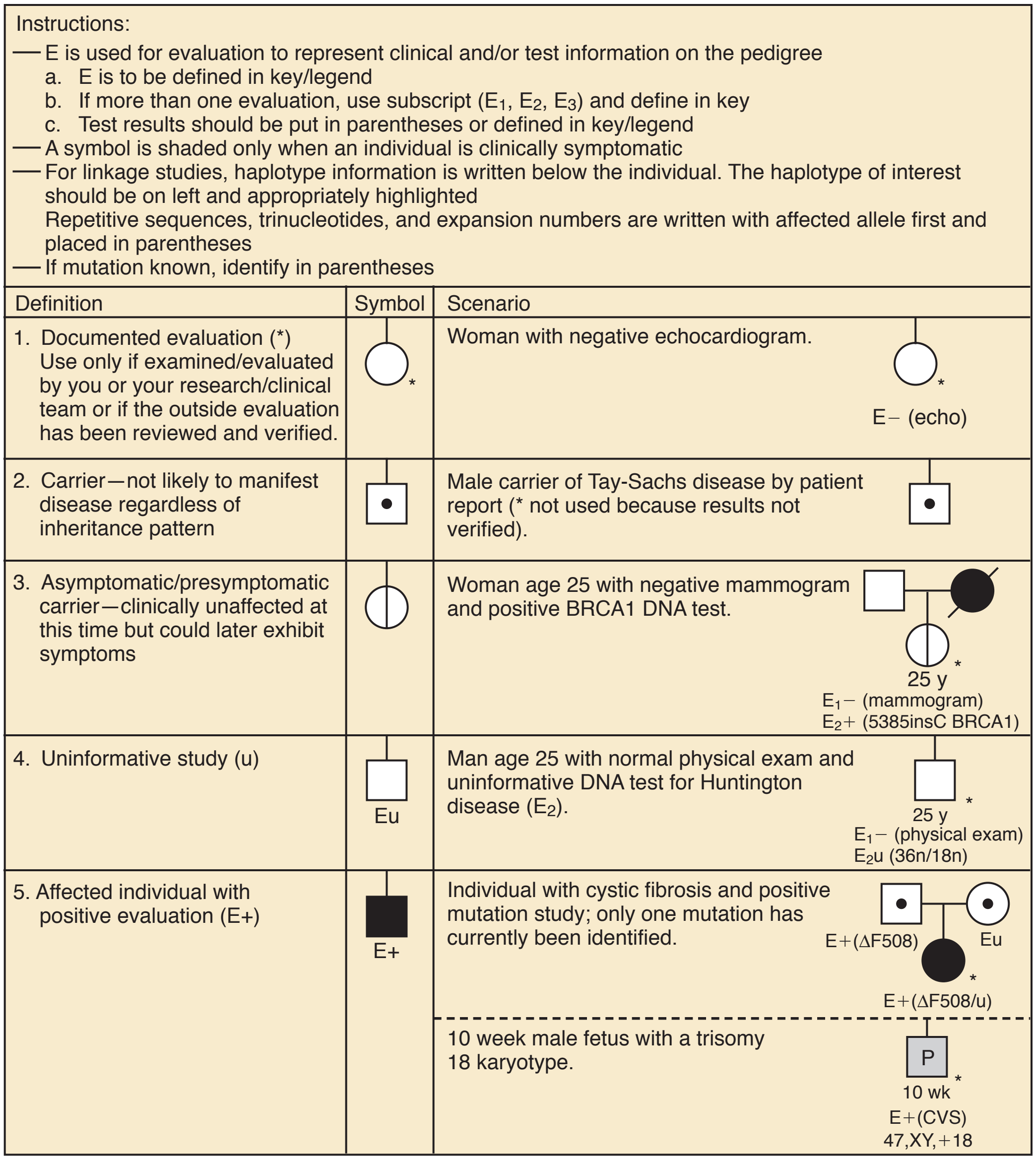

Figure 80-4 **Pedigree symbols of genetic evaluation and testing information.** *(From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors, J Genet Couns 17:424–433, 2008.)*

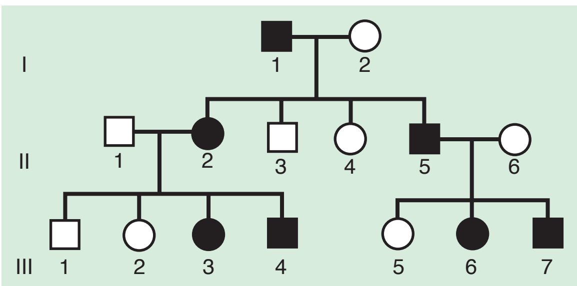

Figure 80-5 **Autosomal dominant pedigree.** Pedigree showing typical inheritance of a form of achondroplasia *(FGFR3)* inherited as an autosomal dominant trait. *Black,* affected patients.

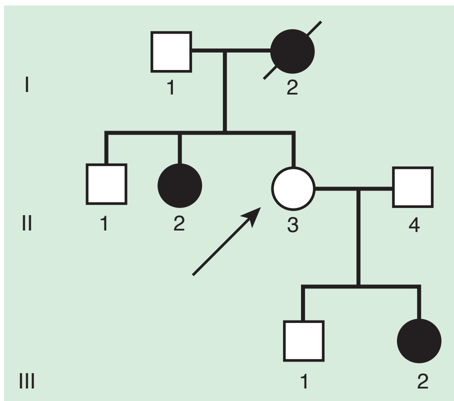

Figure 80-6 **Incomplete penetrance.** This family segregates a familial cancer syndrome, familial adenomatous polyposis. Individual II.3 is an obligate carrier, but there are no findings to suggest the disorder. This disorder is nonpenetrant in this individual.

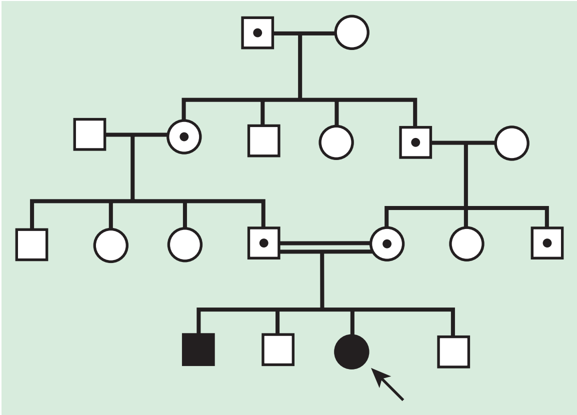

Figure 80-7 Autosomal recessive pedigree with parental consanguinity. *Central dot,* carriers; *black,* affected patients.

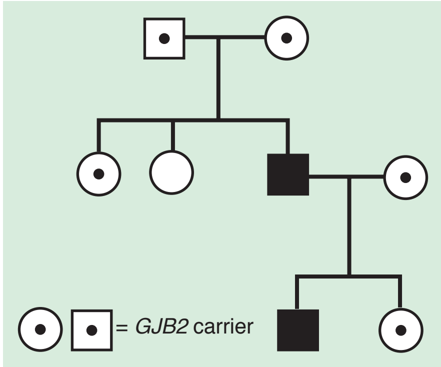

Figure 80-8 Pseudodominant inheritance. *Black,* affected (deaf); *central dot* shows carrier who is asymptomatic (unaffected).

noncarriers. In sickle cell disease, the carrier state might confer some resistance to malaria; in cystic fibrosis, the carrier state has been postulated to confer resistance to cholera or enteropathogenic *Escherichia coli* infections. Population-based carrier screening for cystic fibrosis is recommended for persons of northern European and Ashkenazi Jewish ancestry; population-based screening for sickle cell disease is recommended for persons of African ancestry.

If the frequency of an autosomal recessive disease is known, the frequency of the heterozygote or carrier state can be calculated from the **Hardy-Weinberg formula:**

$$p^2 + 2pq + q^2 = 1$$

where *p* is the frequency of one of a pair of alleles and *q* is the frequency of the other. For example, if the frequency of cystic fibrosis among white Americans is 1 in 2,500 (p^2), then the frequency of the heterozygote (2pq) can be calculated: If $p^2 = 1/2{,}500$, then $p = 1/50$ and $q = 49/50$; $2pq = 2 \times (1/50) \times (49/50) = 98/2500$ or 3.92%.

Pseudodominant Inheritance

Pseudodominant inheritance refers to the observation of apparent dominant (parent to child) transmission of a known autosomal recessive disorder (Fig. 80-8). This occurs when a homozygous affected individual has a partner who is a heterozygous carrier, and it is most likely to occur for relatively common traits, such as sickle cell anemia or nonsyndromic autosomal recessive hearing loss because of mutations in *GJB2*, the gene that encodes Connexin 26.

X-Linked Inheritance

Characteristics of X-linked inheritance (Fig. 80-9) include the following:

- Males are more commonly and more severely affected than females.
- Female carriers are generally unaffected, or if affected, they are affected more mildly than males.
- Female carriers have a 25% risk for having an affected son, a 25% risk for a carrier daughter, and a 50% chance of having a child that does not inherit the mutated X-linked gene.
- Affected males have carrier daughters and unaffected sons because they pass their X chromosome to all of their daughters and their Y chromosome to all of their sons. Male-to-male transmission excludes X-linkage but is seen with autosomal dominant and Y-linked inheritance.

A female occasionally exhibits signs of an X-linked trait similarly to a male. This occurs rarely owing to homozygosity for an X-linked trait or the presence of a sex chromosome abnormality (45,X or 46,XY female) or skewed or nonrandom X-inactivation. **X chromosome inactivation** occurs early in development and involves random and irreversible inactivation of most genes on one X chromosome in female

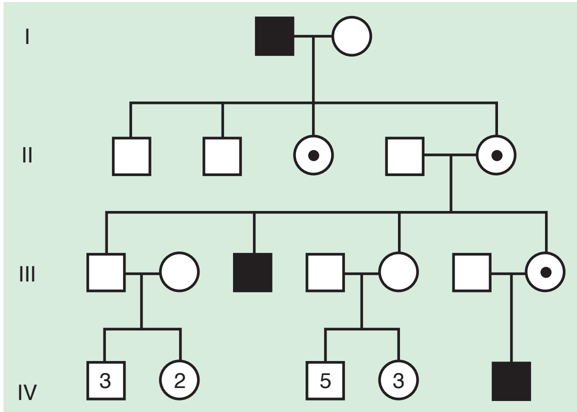

Figure 80-9 Pedigree demonstrating X-linked recessive inheritance.

cells (Fig. 80-10). In some cases, a preponderance of cells inactivates the same X chromosome, resulting in phenotypic expression of an X-linked mutation if it resides on the active chromosome. This can occur owing to chance, selection against cells that have inactivated the X chromosome carrying the normal gene, or X chromosome abnormalities that result in inactivation of the X chromosome carrying the normal gene.

Some X-linked disorders are inherited in an **X-linked dominant** fashion in which female carriers typically manifest abnormal findings. An affected man will have only affected daughters and unaffected sons, and half of the offspring of an affected woman will be affected (Fig. 80-11). Some X-linked dominant conditions are lethal in a high percentage of males. An example is incontinentia pigmenti (see Chapter 596.7). The pedigree shows only affected females and an overall ratio of 2 : 1 females to males with an increased number of miscarriages (Fig. 80-12).

Y-LINKED INHERITANCE

There are few Y-linked traits. These demonstrate *only* male-to-male transmission, and only males are affected (Fig. 80-13). Most Y-linked genes are related to male sex determination and reproduction and are associated with infertility. Therefore, it is rare to see familial transmission of a Y-linked disorder. However, advances in assisted reproductive technologies might make it possible to have familial transmission of male infertility.

Of special note are the pseudoautosomal regions on the Y chromosome that have homology that is shared by both Xp and Yp. Very few genes reside in this region. One of the few is *SHOX*. Heterozygous *SHOX* mutations cause **Leri-Weil dyschondrosteosis,** a rare skeletal dysplasia that involves bilateral bowing of the forearms with

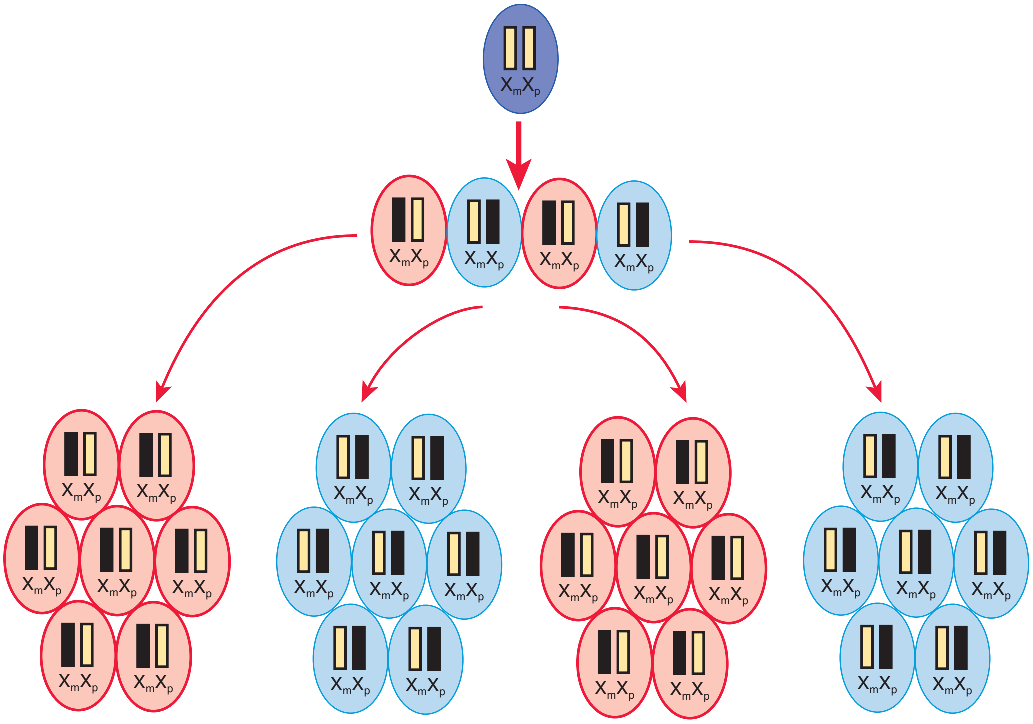

Figure 80-10 X-inactivation. *Black* marks the active X chromosome. Color of the cell represents its active X chromosome is paternally (X_p, *blue*) or maternally (X_m, *pink*) derived.

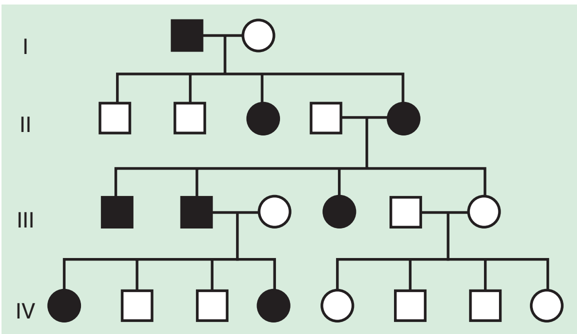

Figure 80-11 Pedigree pattern demonstrating X-linked dominant inheritance. Note there is no father-to-son transmission in this situation, and hemizygosity (i.e., X-linked gene in a male) is not lethal. In some X-linked dominant conditions, X-linked males have a more severe phenotype and might not survive. In that case, only females manifest the disease (see Fig. 80-12).

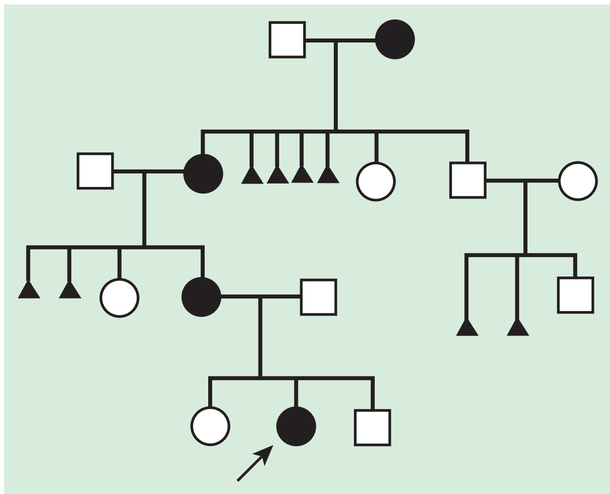

Figure 80-12 Pedigree of an X-linked dominant disorder with male lethality, such as incontinentia pigmenti.

dislocations of the ulna at the wrist and generalized short stature. Homozygous mutations cause the much more severe **Langer mesomelic dwarfism.**

DIGENIC INHERITANCE

Digenic inheritance explains the occurrence of **retinitis pigmentosa** (RP) in children of parents who each carry a mutation in a different RP-associated gene. Both parents have normal vision, as would be expected, but their offspring who are **double heterozygotes**—having inherited both mutations—develop RP. Digenic pedigrees (Fig. 80-14) can exhibit characteristics of both autosomal dominant (vertical transmission) and autosomal recessive inheritance (1 in 4 recurrence risk). For example, a couple in which the 2 unaffected partners are carriers for mutation in 2 different RP-associated genes that show digenic inheritance have a 1 in 4 risk of having an affected child similar to what is seen in autosomal recessive inheritance. However, their affected

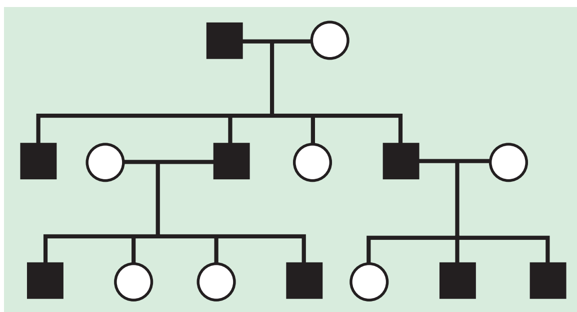

Figure 80-13 Y-linked inheritance. *Black,* affected patient.

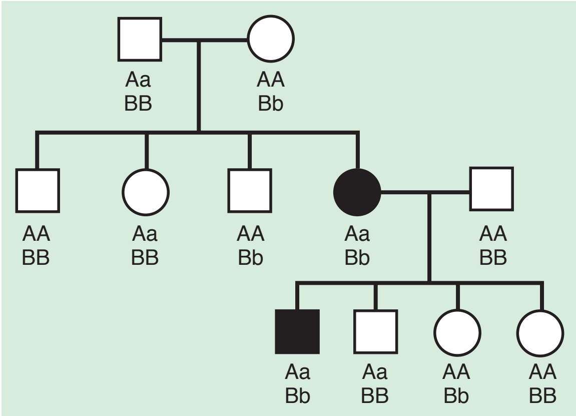

Figure 80-14 Digenic pedigree. Here, the disease alleles are *a* and *b* and they reside on distinct genetic loci or genes. For a person to have the disease, heterozygosity for mutant alleles in both genes (A/a;B/b) is required.

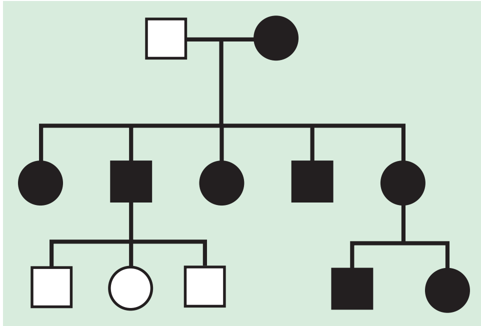

Figure 80-15 Pedigree of a mitochondrial disorder, exhibiting maternal inheritance. *Black,* affected patient.

children, and affected children in subsequent generations, have a 1 in 4 risk of transmitting both mutations to their offspring, who would be affected (vertical transmission).

PSEUDOGENETIC INHERITANCE AND FAMILIAL CLUSTERING

Sometimes nongenetic reasons for the occurrence of a particular disease in multiple family members can produce a pattern that mimics genetic transmission. These nongenetic factors can include identifiable environmental factors, teratogenic exposures, or as yet undetermined and/or undefined factors. Examples of identifiable factors might include multiple siblings in a family having asthma as a result of exposure to cigarette smoke from their parents or having failure to thrive, developmental delay, and unusual facial appearance caused by exposure to alcohol during pregnancy.

In some cases the disease is sufficiently common in the general population that some familial clustering occurs simply by chance. Breast cancer affects 11% of all women, and it is possible that several women in a family will develop breast cancer even in the absence of a genetic predisposition. However, hereditary breast cancer associated with mutations in *BRCA1* and *BRCA2* should be suspected in any individual who has a personal history of breast cancer with onset before age 50 yr, early-onset breast and ovarian cancer at any age, bilateral or multifocal breast cancer, a family history of breast cancer or breast and ovarian cancer consistent with autosomal dominant inheritance, and/or a personal or family history of male breast cancer.

NONTRADITIONAL INHERITANCE

Some genetic disorders are inherited in a manner that does not follow classical Mendelian patterns. Nontraditional inheritance includes mitochondrial disorders, triplet repeat expansion diseases, and imprinting defects.

Mitochondrial Inheritance

An individual's mitochondrial genome is entirely derived from the mother because sperm contain few mitochondria, which are typically shed upon fertilization. It follows that mitochondrial disorders exhibit maternal inheritance. A woman with a mitochondrial genetic disorder can have affected offspring of either sex, but an affected father cannot pass on the disease to his offspring (Fig. 80-15). Mitochondrial DNA mutations are often deletions or point mutations; overall, 1:400 people has a maternally inherited pathogenic mitochondrial DNA mutation.

In individual families, mitochondrial inheritance may be difficult to distinguish from autosomal dominant or X-linked inheritance, but in many cases, paying close attention to the sex of the transmitting and nontransmitting parents can suggest a mitochondrial basis (Table 80-1).

The mitochondria are the cell's suppliers of energy, and it is not surprising that the organs that are most affected by the presence of abnormal mitochondria are those that have the greatest energy requirements, such as the brain, muscle, heart, and liver (see Chapters 87.4, 361, 598.2, and 611.4). Common manifestations include developmental delay, seizures, cardiac dysfunction, decreased muscle strength and tone, and hearing and vision problems. Examples of mitochondrial disorders include **MELAS** (*m*yopathy, *e*ncephalopathy, *l*actic *a*cidosis, and *s*trokelike episodes), **MERRF** (*m*yoclonic *e*pilepsy associated with *r*agged *r*ed *f*ibers), and **Kearns-Sayre syndrome** (ophthalmoplegia, pigmentary retinopathy, and cardiomyopathy) (see Chapter 598.2 and 611.4).

Mitochondrial diseases can be highly variable in clinical manifestation. This is partly because cells can contain multiple mitochondria, each bearing several copies of the mitochondrial genome. Thus, a cell can have a mixture of normal and abnormal mitochondrial genomes, which is referred to as **heteroplasmy.** Unequal segregation of mitochondria carrying normal and abnormal genomes and replicative advantage can result in varying degrees of heteroplasmy in the cells of an affected individual, including the individual ova of an affected female. Because of this, a mother may be asymptomatic and yet have children who are severely affected. The level of heteroplasmy at which disease symptoms typically appear can also vary based on the type of mitochondrial mutation. Detection of mitochondrial genome mutations can require sampling of the affected tissue for DNA analysis; testing for mitochondrial DNA mutations may in some tissues, such as blood, be inadequate because the mutation may be found primarily in affected tissues such as muscle.

Triplet Repeat Expansion Disorders

Triplet repeat expansion disorders are distinguished by the special dynamic nature of the disease-causing mutation. Triplet repeat expansion disorders include fragile X syndrome, myotonic dystrophy, Huntington disease, spinocerebellar ataxias, and several others (Table 80-2). These disorders are caused by expansion in the number of 3-bp repeats. The **fragile X gene,** *FMR1,* normally has 5-40 CGG triplets. An error in replication can result in expansion of that number to a level in the gray zone between 41 and 58 repeats, or to a level referred to as **premutation,** which comprises 59-200 repeats. Some male carriers of the premutation develop fragile X–associated tremor/ataxia syndrome (FXTAS) as adults, and female carriers of the premutation are at risk for fragile X-associated primary ovarian insufficiency (*FXPOI*). Persons with a premutation are also at risk for having the gene expand further in subsequent meiosis, hence crossing into the range of full mutation in offspring. In fragile X, the threshold for clinical diagnosis is above 200 repeats. With this number of repeats, the *FMR1* gene becomes hypermethylated, and protein production is lost.

Some triplet expansions associated with other genes can cause disease through a mechanism other than decreased protein production. In **Huntington disease,** the expansion causes the gene product

Table 80-1 Representative Examples of Disorders Caused by Mutations in Mitochondrial DNA and Their Inheritance

DISEASE	PHENOTYPE	MOST FREQUENT MUTATION IN MTDNA MOLECULE	HOMOPLASMY VS. HETEROPLASMY	INHERITANCE
Leber hereditary optic neuropathy	Rapid optic nerve death, leading to blindness in young adult life	Substitution Arg340His in *ND1* gene of complex I of electron transport chain; other complex I missense mutations	Homoplasmic (usually)	Maternal
NARP, Leigh disease	Neuropathy, ataxia, retinitis pigmentosa, developmental delay, mental retardation, lactic acidemia	Point mutations in ATPase subunit 6 gene	Heteroplasmic	Maternal
MELAS	Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; may manifest only as diabetes mellitus	Point mutation in $tRNA^{Leu}$	Heteroplasmic	Maternal
MERRF	Myoclonic epilepsy, ragged red fibers in muscle, ataxia, sensorineural deafness	Point mutation in $tRNA^{Lys}$	Heteroplasmic	Maternal
Deafness	Progressive sensorineural deafness, often induced by aminoglycoside antibiotics	A1555G mutation in 12S rRNA	Homoplasmic	Maternal
	Nonsyndromic sensorineural deafness	A7445G mutation in 12S rRNA	Homoplasmic	Maternal
Chronic progressive external ophthalmoplegia (CPEO)	Progressive weakness of extraocular muscles	The common MELAS point mutation in $tRNA^{Lys}$; large deletions similar to KSS	Heteroplasmic	Maternal if point mutations
Pearson syndrome	Pancreatic insufficiency, pancytopenia, lactic acidosis	Large deletions	Heteroplasmic	Sporadic, somatic mutations
Kearns-Sayre syndrome (KSS)	PEO of early onset with heart block, retinal pigmentation	5 kb large deletion	Heteroplasmic	Sporadic, somatic mutations

mtDNA, Mitochondrial DNA; rRNA, ribosomal RNA; tRNA, transfer RNA.
From Nussbaum RL, McInnes RR, Willard HF, editors: Thompson & Thompson genetics in medicine, *ed 6, Philadelphia, 2001, WB Saunders, p. 246.*

Table 80-2 Diseases Associated with Polynucleotide Repeat Expansions

DISEASE	DESCRIPTION	REPEAT SEQUENCE	NORMAL RANGE	ABNORMAL RANGE	PARENT IN WHOM EXPANSION USUALLY OCCURS	LOCATION OF EXPANSION
CATEGORY 1						
Huntington disease	Loss of motor control, dementia, affective disorder	CAG	6-34	36-100 or more	More often through father	Exon
Spinal and bulbar muscular atrophy	Adult-onset motor-neuron disease associated with androgen insensitivity	CAG	11-34	40-62	More often through father	Exon
Spinocerebellar ataxia type 1	Progressive ataxia, dysarthria, dysmetria	CAG	6-39	41-81	More often through father	Exon
Spinocerebellar ataxia type 2	Progressive ataxia, dysarthria	CAG	15-29	35-59	—	Exon
Spinocerebellar ataxia type 3 (Machado-Joseph disease)	Dystonia, distal muscular atrophy, ataxia, external ophthalmoplegia	CAG	13-36	68-79	More often through father	Exon
Spinocerebellar ataxia type 6	Progressive ataxia, dysarthria, nystagmus	CAG	4-16	21-27	—	Exon
Spinocerebellar ataxia type 7	Progressive ataxia, dysarthria, retinal degeneration	CAG	7-35	38-200	More often through father	—
Spinocerebellar ataxia type 17	Progressive ataxia, dementia, bradykinesia, dysmetria	CAG	29-42	47-55	—	Exon
Dentatorubral-pallidoluysian atrophy/Haw River syndrome	Cerebellar atrophy, ataxia, myoclonic epilepsy, choreoathetosis, dementia	CAG	7-25	49-88	More often through father	Exon

Continued

Table 80-2 Diseases Associated with Polynucleotide Repeat Expansions—cont'd

DISEASE	DESCRIPTION	REPEAT SEQUENCE	NORMAL RANGE	ABNORMAL RANGE	PARENT IN WHOM EXPANSION USUALLY OCCURS	LOCATION OF EXPANSION
CATEGORY 2						
Pseudoachondroplasia, multiple epiphyseal dysplasia	Short stature, joint laxity, degenerative joint disease	GAC	5	6-7	—	Exon
Oculopharyngeal muscular dystrophy	Proximal limb weakness, dysphagia, ptosis	GCG	6	7-13	—	Exon
Cleidocranial dysplasia	Short stature, open skull sutures with bulging calvaria, clavicular hypoplasia, shortened fingers, dental anomalies	GCG, GCT, GCA	17	27 (expansion observed in 1 family)	—	Exon
Synpolydactyly	Polydactyly and syndactyly	GCG, GCT, GCA	15	22-25	—	Exon
CATEGORY 3						
Myotonic dystrophy (DM1; chromosome 19)	Muscle loss, cardiac arrhythmia, cataracts, frontal balding	CTG	5-37	100 to several thousand	Either parent, but expansion to congenital form through mother	3′ untranslated region
Myotonic dystrophy (DM2; chromosome 3)	Muscle loss, cardiac arrhythmia, cataracts, frontal balding	CCTG	<75	75-11,000	—	3′ untranslated region
Friedreich ataxia	Progressive limb ataxia, dysarthria, hypertrophic cardiomyopathy, pyramidal weakness in legs	GAA	7-2	200-900 or more	Autosomal recessive inheritance, so disease alleles are inherited from both parents	Intron
Fragile X syndrome (FRAXA)	Mental retardation, large ears and jaws, macroorchidism in males	CGG	6-52	200-2,000 or more	Exclusively through mother	5′ untranslated region
Fragile site (FRAXE)	Mild mental retardation	GCC	6-35	>200	More often through mother	5′ untranslated region
Spinocerebellar ataxia type 8	Adult-onset ataxia, dysarthria, nystagmus	CTG	16-37	107-127	More often through mother	3′ untranslated region
Spinocerebellar ataxia type 10	Ataxia and seizures	ATTCT	12-16	800-4,500	More often through father	Intron
Spinocerebellar ataxia type 12	Ataxia, eye movement disorders; variable age at onset	CAG	7-28	66-78	—	5′ untranslated region
Progressive myoclonic epilepsy type 1	Juvenile-onset convulsions, myoclonus, dementia	12-bp repeat motif	2-3	30-75	Autosomal recessive inheritance, so transmitted by both parents	5′ untranslated region

From Jorde LB, Carey JC, Bamshad MJ, et al: Medical genetics, ed 3, St. Louis, 2006, Mosby, p. 82.

to have a new, toxic effect on the neurons of the basal ganglia. For most triplet-repeat disorders, there is a clinical correlation to the size of the expansion, with a greater expansion causing more severe symptoms and/or earlier age of onset for the disease. The observation of increasing severity of disease and early age at onset in subsequent generations is termed **genetic anticipation** and is a defining characteristic of many triplet-repeat expansion disorders (Fig. 80-16).

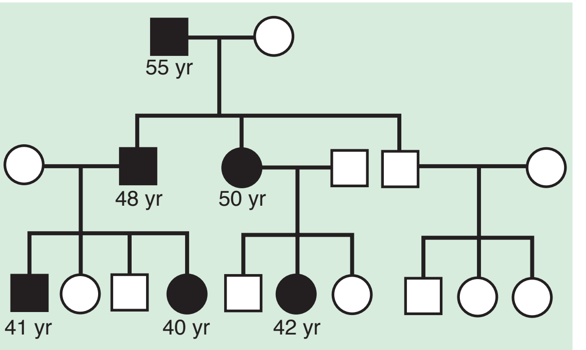

Figure 80-16 Myotonic dystrophy pedigree illustrating anticipation. In this case, the age at onset for family members affected with an autosomal dominant disease is lower in more recent generations. *Black,* affected patients.

Genetic Imprinting

The 2 copies of most autosomal genes are functionally equivalent. However, in some cases only 1 copy of a gene is transcribed and the other copy is silenced. This gene silencing is typically associated with methylation of DNA, which is an **epigenetic modification**, meaning it does not change the nucleotide sequence of the DNA (Fig. 80-17). In **imprinting**, gene expression depends on the parent of origin of the chromosome (see Chapter 81.8). Imprinting disorders result from an imbalance of active copies of a given gene, which can occur for several reasons. **Prader-Willi** and **Angelman syndromes**, two distinct disorders associated with developmental impairment, are illustrative. Both

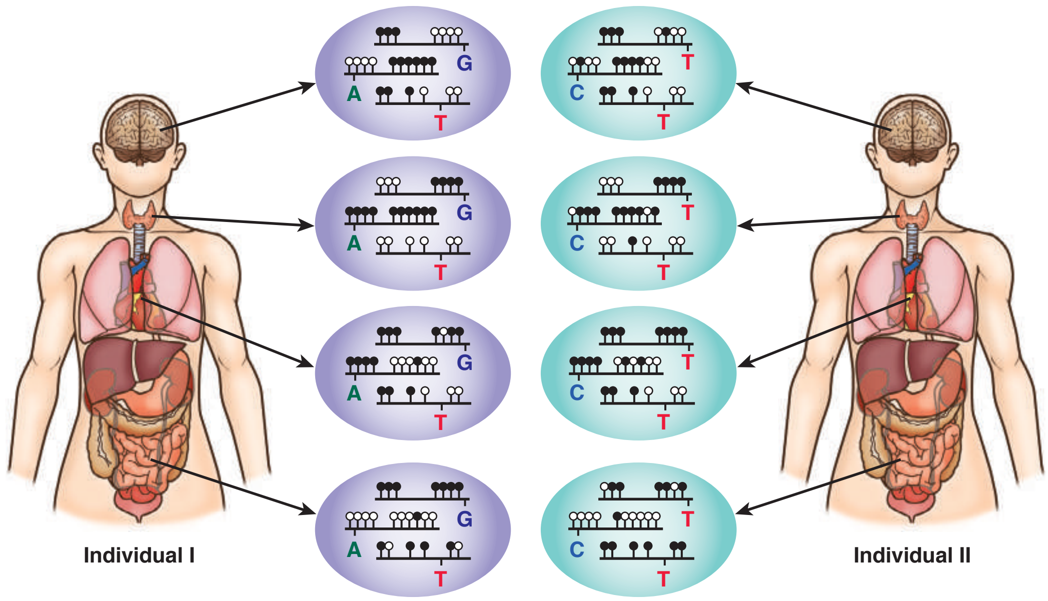

Figure 80-17 Tissue-specific DNA methylation and epigenetic heterogeneity among individuals. A subset of the DNA methylation patterns within a cell is characteristic of that cell type. Cell type–specific and tissue-specific DNA methylation are illustrated by organ-to-organ variations in the clusters of methylated CpGs within the same individual. Despite overall consistency in tissue-specific DNA methylation patterns, variations in these patterns exist among different individuals. Methylated CpGs are indicated by a *filled circle* and unmethylated CpGs by an *open circle*. SNPs are indicated by the corresponding base. *(Redrawn from Brena RM, Huang THM, Plass C: Toward a human epigenome*, Nat Genet *38:1359–1360, 2006.)*

can be caused by microdeletions of chromosome 15q11-12. The microdeletion in Prader-Willi syndrome is always on the paternally derived chromosome 15, whereas in Angelman syndrome it is on the maternal copy. *UBE3A* is the gene responsible for Angelman syndrome. The paternal copy of *UBE3A* is transcriptionally silenced in the brain and the maternal copy continues to be transcribed. If an individual has a maternal deletion, an insufficient amount of *UBE3A* protein is produced in the brain, resulting in the neurologic deficits seen in Angelman syndrome.

Uniparental disomy (UPD), the rare occurrence of a child inheriting both copies of a chromosome from the same parent, is another genetic mechanism that can cause Prader-Willi and Angelman syndromes. Inheriting both chromosomes 15 from the mother is functionally the same as deletion of the paternal 15q12 and results in Prader-Willi syndrome. Approximately 30% of cases of Prader-Willi syndrome is caused by paternal UPD15, whereas maternal UPD15 accounts for only 3% of Angelman syndrome (see Chapter 81.8).

A mutation in an imprinted gene is another cause. Mutations in *UBEA3* account for almost 11% of patients with Angelman syndrome and also result in familial transmission. The most uncommon cause is a mutation in the imprinting center, which results in an inability to correctly imprint the *UBE3A*. In a woman, the inability to reset the imprinting on her paternally inherited chromosome 15 imprint results in a 50% risk of passing on an incorrectly methylated copy of *UBE3A* to a child who would then develop Angelman syndrome.

Beside 15q12, other imprinted regions of clinical interest include the short arm of chromosome 11, where the genes for Beckwith-Wiedemann syndrome and nesidioblastosis map, and the long arm of chromosome 7 with maternal UPD of 7q, which has been associated with some cases of idiopathic short stature and Russell-Silver syndrome.

Imprinting of a gene can occur during gametogenesis or early embryonic development (reprogramming). Genes can become inactive or active by various mechanisms including DNA methylation or demethylation or histone acetylation or deacetylation, with different patterns of (de)methylation noted on paternal or maternal imprintable chromosome regions. Some genes demonstrate tissue-specific imprinting (see Fig. 80-17). Several studies suggest that there may be a small but significantly increased incidence of imprinting disorders, specifically Beckwith-Wiedemann and Angelman syndrome, associated with assisted reproductive technologies such as in vitro fertilization and intracytoplasmic sperm injection. However, the overall incidence of these disorders in children conceived using assisted reproductive technologies is likely to be <1%.

MULTIFACTORIAL AND POLYGENIC INHERITANCE

Multifactorial inheritance refers to traits that are caused by a combination of inherited, environmental, and stochastic factors (Fig. 80-18). Multifactorial traits differ from polygenic inheritance, which refers to traits that result from the additive effects of multiple genes. Multifactorial traits segregate within families but do not exhibit a consistent or recognizable inheritance pattern. Characteristics include the following:

- There is a similar rate of recurrence among all 1st-degree relatives (parents, siblings, offspring of the affected child). It is unusual to find a substantial increase in risk for relatives related more distantly than 2nd degree to the index case.
- The risk of recurrence is related to the incidence of the disease.
- Some disorders have a sex predilection, as indicated by an unequal male : female incidence. Pyloric stenosis, for example, is more common in males, whereas congenital dislocation of the hips is more common in females. Where there is an altered sex ratio, the risk is higher for the relatives of an index case whose gender is less commonly affected than relatives of an index case of the more commonly affected gender. For example, the risk to the son of an affected female with infantile pyloric stenosis is 18%, compared with the 5% risk for the son of an affected male. An affected female presumably has a greater genetic susceptibility, which she can then pass on to her offspring.
- The likelihood that both identical twins will be affected with the same malformation is less than 100% but much greater than the chance that both members of a nonidentical twin pair will be affected. This is in contrast with the pattern seen in mendelian

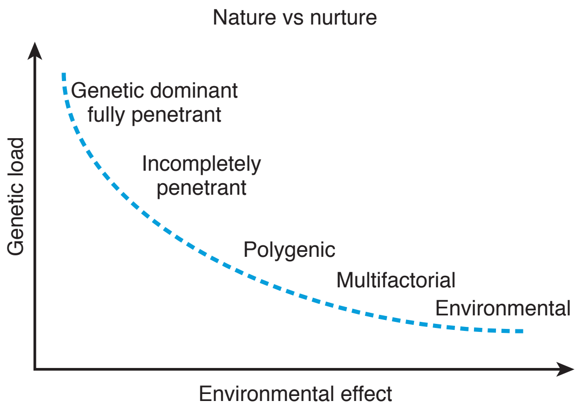

Figure 80-18 **The progressive decrease in the genetic load contributing to the development of a disease creates a smooth transition in the distribution of illnesses on an etiologic diagram.** In theory, no diseases are completely free from the influence of both genetic and environmental factors. *(From Bomprezzi R, Kovanen PE, Martin R: New approaches to investigating heterogeneity in complex traits,* J Med Genet *40:553–559, 2003. Reproduced with permission from the BMJ Publishing Group.)*

inheritance, in which identical twins almost always share fully penetrant genetic disorders.

- The risk of recurrence is increased when multiple family members are affected. A simple example is that the risk of recurrence for unilateral cleft lip and palate is 4% for a couple with 1 affected child and increases to 9% with 2 affected children. It is sometimes difficult to distinguish between a multifactorial and mendelian etiology in families with multiple affected individuals.
- The risk of recurrence may be greater when the disorder is more severe. For example, an infant who has long-segment Hirschsprung disease has a greater chance of having an affected sibling than the infant who has short-segment Hirschsprung disease.

There are 2 types of multifactorial traits. One exhibits continuous variation, with "normal" individuals falling within a statistical range—often defined as having a value 2 SDs above and/or below the mean—and "abnormals" falling outside that range. Examples include such traits as intelligence, blood pressure, height, and head circumference. For many of these traits, offspring values can be estimated based on a modified average of their parental values, with nutritional and environmental factors playing an important role.

With other multifactorial traits, the distinction between normal and abnormal is based on the presence or absence of a particular trait. Examples include pyloric stenosis, neural tube defects, congenital heart defects, and cleft lip and cleft palate. Such traits follow a threshold model (see Fig. 80-15). A distribution of liability because of genetic and nongenetic factors is postulated in the population. Individuals who exceed a threshold liability develop the trait, and those below the threshold do not.

The balance between genetic and environmental factors is demonstrated by **neural tube defects.** Genetic factors are implicated by the increased recurrence risk for parents of an affected child compared with the general population, yet the recurrence risk is about 3%, less than what would be expected if the trait was caused by a single, fully penetrant mutation. The role of nongenetic environmental factors can be seen in the fact that the recurrence risk can be lowered by up to 87% if the mother-to-be takes 4 mg of folic acid per day starting 3 mo before conception.

Many adult-onset diseases behave as if they are caused by multifactorial inheritance. Diabetes, coronary artery disease, and schizophrenia are examples.

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Chapter 81

Cytogenetics

Carlos A. Bacino and Brendan Lee

Clinical cytogenetics is the study of chromosomes: their structure, function, inheritance, and abnormalities. Chromosome abnormalities are very common and occur in approximately 1-2% of live births, 5% of stillbirths, and 50% of early fetal losses in the 1st trimester of pregnancy (Table 81-1). Chromosome abnormalities are more common among persons with intellectual disability and they play a significant role in the development of some neoplasias.

Chromosome analyses are indicated in persons presenting with multiple congenital anomalies, dysmorphic features, and/or intellectual disability. The specific indications for studies include advanced maternal age (>35 yr) or multiple abnormalities on fetal ultrasound (prenatal testing), multiple congenital anomalies, unexplained growth restriction in the fetus or postnatal problems in growth and development, ambiguous genitalia, unexplained intellectual disability with or without associated anatomic abnormalities, primary amenorrhea or infertility, recurrent miscarriages (≥3) or prior history of stillbirths and neonatal deaths, a 1st-degree relative with a known or suspected structural chromosome abnormality, clinical findings consistent with a known anomaly, some malignancies, and chromosome breakage syndromes (e.g., Bloom syndrome, Fanconi anemia).

Table 81-1 Incidence of Chromosomal Abnormalities in Newborn Surveys

TYPE OF ABNORMALITY	NUMBER	APPROXIMATE INCIDENCE
SEX CHROMOSOME ANEUPLOIDY		
Males (43,612 newborns)		
47,XXY	45	1/1,000
47,XYY	45	1/1,000
Other X or Y aneuploidy	32	1/1,350
Total	**122**	**1/360 male births**
Females (24,547 newborns)		
45,X	6	1/4,000
47,XXX	27	1/900
Other X aneuploidy	9	1/2,700
Total	**42**	**1/580 female births**
AUTOSOMAL ANEUPLOIDY (68,159 NEWBORNS)		
Trisomy 21	82	1/830
Trisomy 18	9	1/7,500
Trisomy 13	3	1/22,700
Other aneuploidy	2	1/34,000
Total	**96**	**1/700 live births**
STRUCTURAL ABNORMALITIES (68,159 NEWBORNS)		
Balanced rearrangements		
Robertsonian	62	1/1,100
Other	77	1/885
Unbalanced rearrangements		
Robertsonian	5	1/13,600
Other	38	1/1,800
Total	**182**	**1/375 live births**
All Chromosome Abnormalities	442	1/154 live births

Data from Hsu LYF: Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In Milunsky A, editor: Genetic disorders and the fetus, *ed 4, Baltimore, 1998, Johns Hopkins University Press, pp. 179-248.*

81.1 Methods of Chromosome Analysis

Carlos A. Bacino and Brendan Lee

Cytogenetic studies are usually performed on peripheral blood lymphocytes, although cultured fibroblasts may also be used. Prenatal (fetal) chromosome studies are performed with cells obtained from the amniotic fluid, chorionic villus tissue, and fetal blood or, in the case of preimplantation diagnosis, by analysis of a blastomere. Cytogenetic studies of bone marrow have an important role in tumor surveillance, particularly among patients with leukemia. These are useful to determine induction of remission and success of therapy or, in some cases, the occurrence of relapses.

Chromosome anomalies include abnormalities of number and structure and are the result of errors during cell division. There are 2 types of cell division: mitosis, which occurs in most somatic cells, and meiosis, which is limited to the germ cells. In **mitosis,** 2 genetically identical daughter cells are produced from a single parent cell. DNA duplication has already occurred during **interphase** in the S phase of the cell cycle (DNA synthesis). Therefore, at the beginning of mitosis the chromosomes consist of 2 double DNA strands joined together at the centromere known as *sister chromatids.* Mitosis can be divided into 4 stages: **prophase**, **metaphase**, **anaphase**, and **telophase**. Prophase is characterized by condensation of the DNA. Also during prophase, the nuclear membrane and the nucleolus disappear and the mitotic spindle forms. In metaphase, the chromosomes are maximally compacted and are clearly visible as distinct structures. The chromosomes align at the center of the cell and spindle fibers connect to the centromere of each chromosome and extend to centrioles at the 2 poles of the mitotic figure. In anaphase, the chromosomes divide along their longitudinal axes to form 2 daughter chromatids, which then migrate to opposite poles of the cell. Telophase is characterized by formation of 2 new nuclear membranes and nucleoli, duplication of the centrioles, and cytoplasmic cleavage to form the 2 daughter cells.

Meiosis begins in the female oocyte during fetal life and is completed years to decades later. In males, it begins in a particular spermatogonial cell sometime between adolescence and adult life and is completed in a few days. Meiosis is preceded by DNA replication so that at the outset each of the 46 chromosomes consists of 2 chromatids. In meiosis, a **diploid cell** (2n = 46 chromosomes) divides to form **haploid cells** (n = 23 chromosomes). Meiosis consists of 2 major rounds of cell division. In meiosis I, each of the homologous chromosomes pair precisely so that **genetic recombination,** involving exchange between 2 DNA strands **(crossing over),** can occur. This results in a reshuffling of the genetic information on the recombined chromosomes and allows further genetic diversity. Each daughter cell then receives 1 of each of the 23 homologous chromosomes. In oogenesis, 1 of the daughter cells receives most of the cytoplasm and becomes the egg, whereas the other smaller cell becomes the first polar body. Meiosis II is similar to a mitotic division but without a preceding round of DNA duplication (replication). Each of the 23 chromosomes divides longitudinally, and the homologous chromatids migrate to opposite poles of the cell. This produces 4 spermatogonia in males, or an egg cell and a second polar body in females, each with a haploid (n = 23) set of chromosomes. Consequently, meiosis fulfills 2 crucial roles: It reduces the chromosome number from diploid (46) to haploid (23) so that upon fertilization a diploid number is restored, and it allows genetic recombination.

Two errors of cell division commonly occur during meiosis or mitosis, and either can result in an abnormal number of chromosomes. The first is **nondisjunction,** in which 2 chromosomes fail to separate during meiosis and thus migrate together into 1 of the new cells, producing 1 cell with 2 copies of the chromosome and another with no copy. The second is **anaphase lag,** in which a chromatid or chromosome is lost during mitosis because it fails to move quickly enough during anaphase to become incorporated into 1 of the new daughter cells (Fig. 81-1).

For chromosome analysis, cells are cultured (for varying periods depending on cell type), with or without stimulation, and then artificially arrested in mitosis during metaphase (or prometaphase), later on subjected to a hypotonic solution to allow disruption of the nuclear cell membrane and proper dispersion of the chromosomes for analysis, fixed, banded, and finally stained. The most commonly used banding and staining method is the GTG banding (G-bands trypsin Giemsa), also known as G banding, which produces a unique combination of dark (G-positive) and light (G-negative) bands that permits recognition of all individual 23 chromosome pairs for analysis.

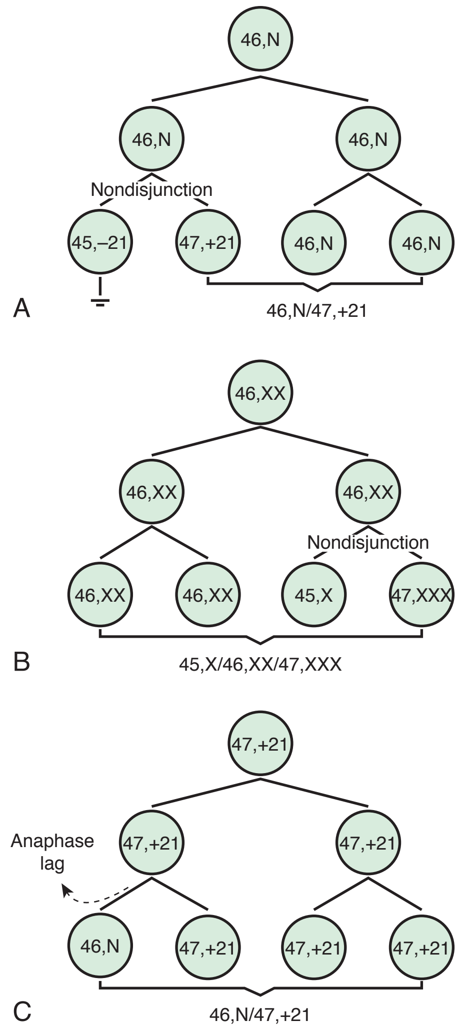

Figure 81-1 Generation of mosaicism. *A,* Postzygotic nondisjunction in an initially normal conceptus. In this example, 1 cell line (monosomic 21) is subsequently lost, with the final karyotype 46,N/47,+21. *B,* Postzygotic nondisjunction in an initially 46,XX conceptus, resulting in 45,X/46,XX/47,XXX mosaicism. *C,* Postzygotic anaphase lag in an initially 47,+21 conceptus. *(From Gardner RJM, Sutherland GR.* Chromosome abnormalities and genetic counseling, *ed 3 New York, 2003, Oxford University Press, p. 33, Figure 43.1. By permission of Oxford University Press, Inc.,* www.oup.com.*)*

Other banding techniques, such as Q-banding using quinacrine, reverse banding (R-banding) using acridine orange, and C-banding (constitutive heterochromatin) using barium hydroxide, are available for use in certain circumstances but are losing ground to molecular technologies. Metaphase chromosome spreads are first evaluated microscopically, and then their images are photographed or captured by a video camera and stored on a computer to be later analyzed. Humans have 46 chromosomes or 23 pairs, which are classified as autosomes for chromosomes 1 to 22, and the sex chromosomes, often referred as sex complement: XX for females and XY for males. The homologous chromosomes from a metaphase spread can then be paired and arranged systematically to assemble a karyotype according to well-defined standard conventions like those established by International

System for Human Cytogenetic Nomenclature (ISCN), with chromosome 1 being the largest and 22 the smallest. According to nomenclature, the description of the karyotype includes the total number of chromosomes followed by the sex chromosome constitution. A normal karyotype is 46,XX for females and 46,XY for males (Fig. 81-2). Abnormalities are noted after the sex chromosome complement.

Although the internationally accepted system for human chromosome classification relies largely on the length and banding pattern of each chromosome, the position of the centromere relative to the ends of the chromosome also is a useful distinguishing feature (Fig. 81-3). The centromere divides the chromosome in 2, with the short arm designated as the **p arm** and the long arm designated as the **q arm**. A plus or minus sign before the number of a chromosome indicates that there is an extra or missing chromosome, respectively. Table 81-2 lists some of the abbreviations used for the descriptions of chromosomes and their abnormalities. A metaphase chromosome spread usually shows 450-550 bands. Prophase and prometaphase chromosomes are longer, are less condensed, and often show 550-850 bands. High-resolution analysis is useful for detecting subtle chromosome abnormalities that might otherwise go unrecognized.

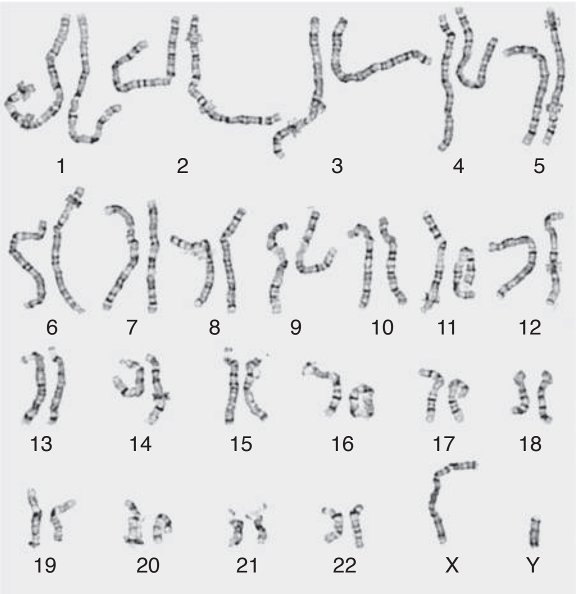

Figure 81-2 **Karyotype of a normal male at the 550-600 band level.** The longer the chromosomes are captured at metaphase or sometimes prometaphase, the more bands that can be visualized.

Molecular techniques such as fluorescence in situ hybridization (FISH) and array comparative genomic hybridization studies (conventional CGH and array CGH [aCGH]) have filled a significant void for the diagnosing cryptic chromosomal abnormalities. These techniques identify subtle abnormalities that are often below the resolution of standard cytogenetic studies. **FISH** is used to identify the presence, absence, or rearrangement of *specific* DNA segments and is performed with gene- or region-specific DNA probes. Several FISH probes are used in the clinical setting: unique sequence or single-copy probes, repetitive-sequence probes (alpha satellites in the pericentromeric regions), and multiple-copy probes (chromosome specific or painting) (Fig. 81-4*A* and *B*). FISH involves using a unique known DNA sequence or probe labeled with a fluorescent dye that is complementary to the studied region of disease interest. The labeled probe is exposed to the DNA on a microscope slide, typically metaphase or interphase chromosomal DNA. When the probe pairs with its complementary DNA sequence, it can be then visualized by fluorescence microscopy (Fig. 81-5). In metaphase chromosome spreads, the exact chromosomal

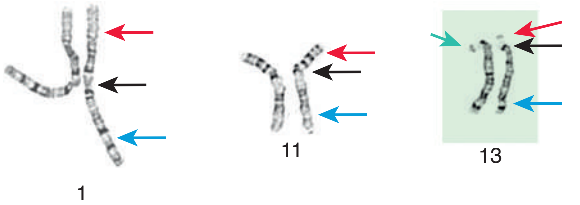

Figure 81-3 **Example of different chromosome types according to the position of the centromere.** On the *left* is a chromosome 1 pair with the centromere equidistant from the short and long arm (also known as metacentric). In the center is a chromosome 11 pair that is submetacentric. On the right is a chromosome 13 pair that is an example of an acrocentric chromosome. Acrocentric chromosomes contain a very small short arm, stalks, and satellite DNA. The *black arrow* indicates the position of the centromere. The *blue arrow* shows the long arm of a chromosome. The *red arrow* shows the short arm of a chromosome. The *green arrow* highlights the satellite region, which is made of DNA repeats. The *light area* between the short arm and the satellite is known as the stalk.

Table 81-2 Some Abbreviations Used for Description of Chromosomes and Their Abnormalities

ABBREVIATION	MEANING	EXAMPLE	CONDITION
XX	Female	46,XX	Normal female karyotype
XY	Male	46,XY	Normal male karyotype
[##]	Number [#] of cells	46,XY[12]/47,XXY[10]	Number of cells in each clone, typically inside brackets Mosaicism in Klinefelter syndrome with 12 normal cells and 10 cells with an extra X chromosome
cen	Centromere		
del	Deletion	46,XY,del(5p)	Male with deletion of chromosome 5 short arm
der	Derivative	46,XX,der(2),t(2p127q13)	Female with a structurally rearranged chromosome 2 that resulted from a translocation between chromosomes 2 and 7
dup	Duplication	46,XY,dup(15)(q11-13)	Male with interstitial duplication in the long arm of chromosome 15 in the Prader-Willi/Angelman syndrome region
ins	Insertion	46,XY,ins(3)(p13q21q26)	Male with an insertion within chromosome 3 A piece between q21q26 has reinserted on p13
inv	Inversion	46,XY,inv(2)(p21q31)	Male with pericentric inversion of chromosome 2 with breakpoints at bands p21 and q31

Table 81-2 Some Abbreviations Used for Description of Chromosomes and Their Abnormalities—cont'd

ABBREVIATION	MEANING	EXAMPLE	CONDITION
ish	Metaphase FISH	46,XX.ish del(7)(q11.23q11.23)	Female with deletion in the Williams syndrome region detected by in situ hybridization
nuc ish	Interphase FISH	nuc ish(DXZ1 × 3)	Interphase in situ hybridization showing 3 signals for the X chromosome centromeric region
mar	Marker	47,XY,+mar	Male with extra, unidentified chromosome material
mos	Mosaic	mos 45,X[14]/46,XX[16]	Turner syndrome mosaicism (analysis of 30 cells showed that 14 cells were 45,X and 16 cells were 46,XX)
p	Short arm	46,XY,del(5)(p12)	Male with a deletion on the short arm of chromosome 5, band p12 (short nomenclature)
q	Long arm	46,XY,del(5)(q14)	Male with a deletion on the long arm of chromosome 5, band 14
r	Ring chromosome	46,X,r(X)(p21q27)	Female with 1 normal X chromosome and a ring X chromosome
t	Translocation	t(2;8)(q33;q24.1)	The interchange of material between chromosomes 2 and 8 with breakpoints at bands 2q33 and 8q24.1
ter	Terminal	46,XY,del(5)(p12-pter)	Male with a deletion of chromosome 5 between p12 and the end of the short arm (long nomenclature)
/	Slash	45,X/46,XY	Separate lines or clones Mosaicism for monosomy X and a male cell line
+	Gain of	47,XX,+21	Female with trisomy 21
–	Loss of	45,XY,–21	Male with monosomy 21

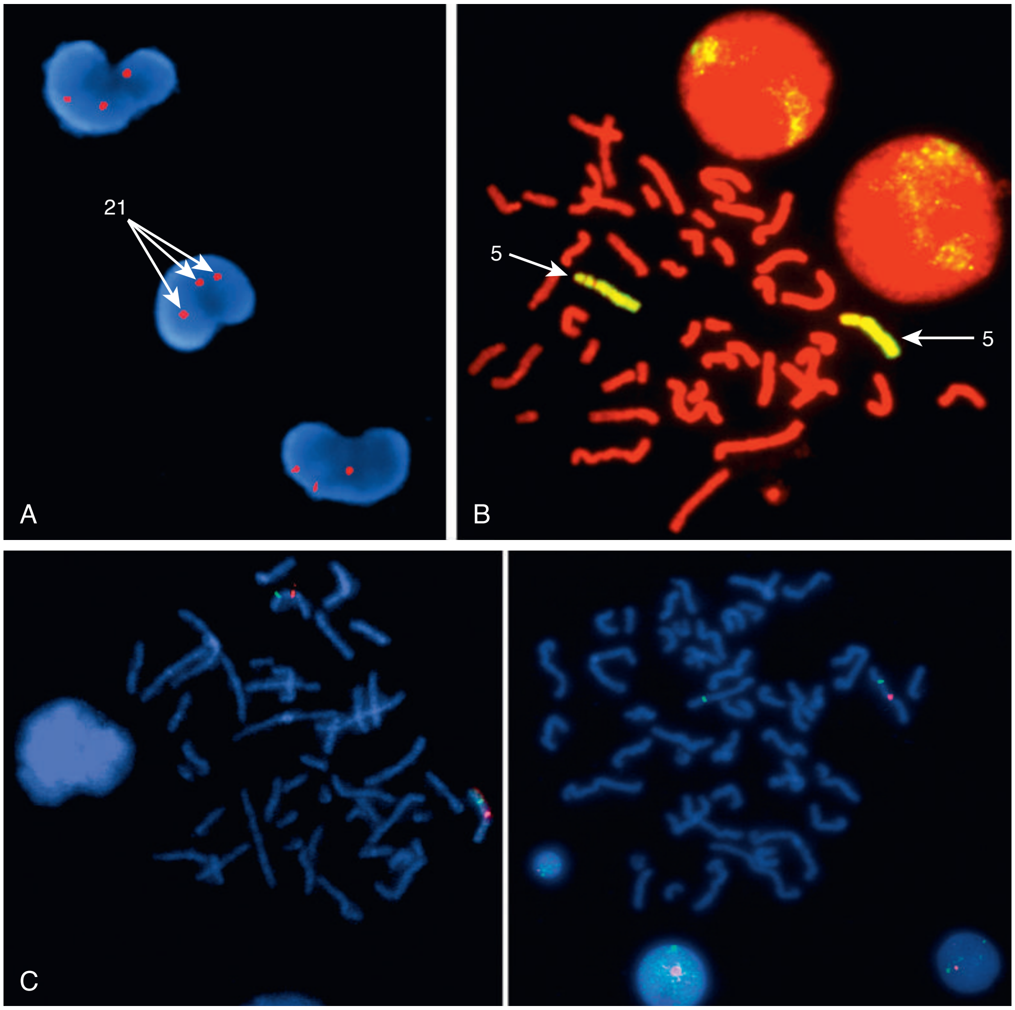

Figure 81-4 *A,* FISH analysis of interphase peripheral blood cells from a patient with Down syndrome using a chromosome 21-specific probe. The 3 red signals mark the presence of 3 chromosomes 21. *B,* FISH analysis of a metaphase chromosome spread from a clinically normal individual using a whole-chromosome paint specific for chromosome 5. Both chromosomes 5 are completely labeled *(yellow)* along their entire length. *C,* FISH on metaphase cells using a unique sequence probe that hybridizes to the elastin gene on chromosome 7q11.23, inside the Williams syndrome critical region. The elastin probe is labeled in *red*, and a control probe on chromosome 7 is labeled in *green*. The left image shows normal hybridization to chromosome 7, with 2 signals for the elastin region and 2 for the control probe. The right image shows a normal chromosome on the right with control and elastin signals, and a deleted chromosome 7 on the *left*, evidenced by a single signal for the control probe. This image corresponds to a patient with a Williams syndrome region deletion.

Continued

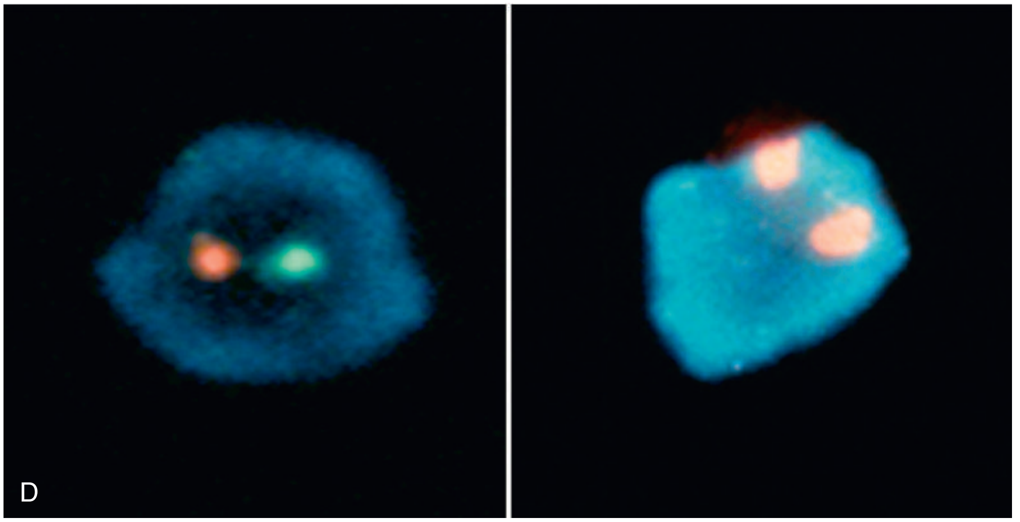

Figure 81-4, cont'd *D,* FISH in interphase cells using DNA probes that hybridize to repetitive α-satellite sequences in the pericentromeric region for the sex chromosomes. *Left,* interphase cells with 2 signals, 1 labeled in *red* for the X chromosome and *green* for the Y chromosome, consistent with a normal male chromosome complement. *Right,* interphase cell showing 2 *red* signals for the X chromosome, compatible with a normal female chromosome complement.

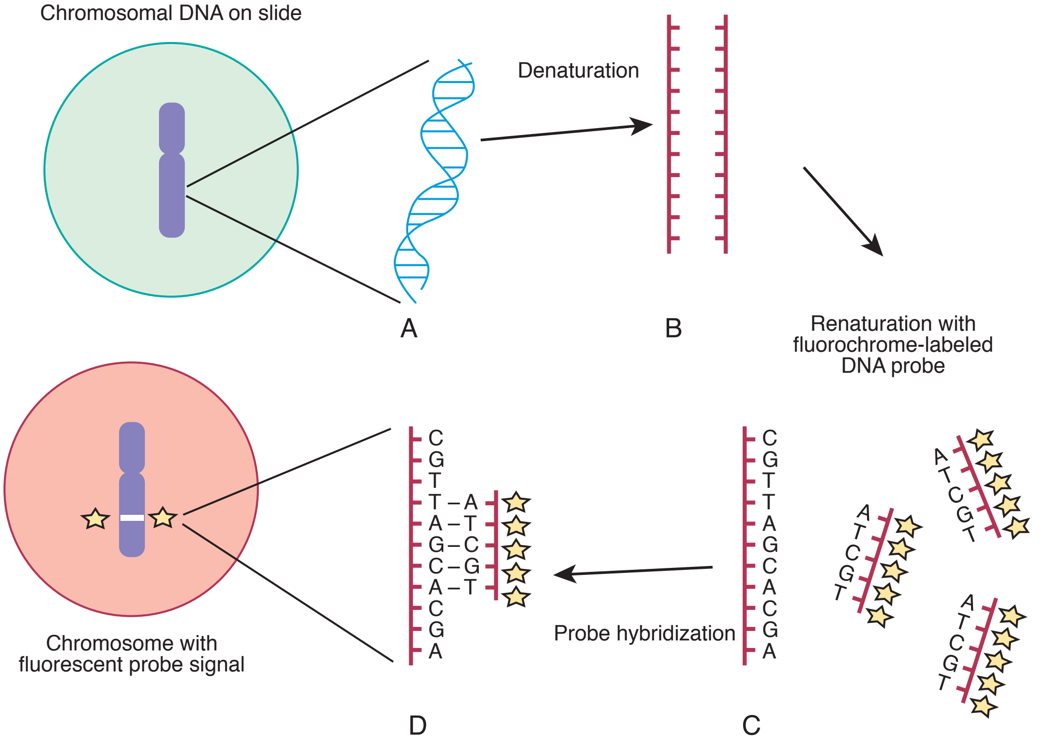

Figure 81-5 FISH involves denaturation of double-stranded DNA as present in metaphase chromosomes or interphase nuclei on cytogenetic slide preparations *(A)* into single-stranded DNA *(B).* The slide-bound (in situ) DNA is then renatured or reannealed in the presence of excess copies of a single-stranded, fluorochrome-labeled DNA base-pair sequence or probe *(C).* The probe anneals or "hybridizes" to sites of complementary DNA sequence *(D)* within the chromosomal genome. Probe signal is visualized and imaged on the chromosome by fluorescent microscopy. *(From Lin RL, Cherry AM, Bangs CD, et al: FISHing for answers: the use of molecular cytogenetic techniques in adolescent medicine practice. In Hyme HE, Greydanus D, editors:* Genetic disorders in adolescents: state of the art reviews. Adolescent medicine, *Philadelphia, 2002, Hanley and Belfus, pp. 305–313.)*

location of each probe copy can be documented and often the *number of copies* (deletions, duplications) of the DNA sequence as well. When the interrogated segments (as in genomic duplications) are close together, only interphase cells can accurately determine the presence of 2 or more copies or signals since in metaphase cells, some duplications might falsely appear as a single signal.

With high-resolution chromosome analysis it is very difficult to recognize deletions of <5 million bp (5 Mbp); FISH can reliably detect deletions as small as 50-200 kb of DNA. This has allowed the clinical characterization of a number of *microdeletion syndromes*. Other probes hybridize to repetitive sequences located to the pericentromeric regions. Pericentromeric probes are still widely used for the rapid identification of certain trisomies in interphase cells of blood smears, or even in the rapid analysis of prenatal samples from cells obtained through amniocentesis. Such probes are available for chromosomes 13, 18, and 21 and for the sex pair X and Y (see Fig. 81-4*C* and *D*). With regards to the detection of genomic disorders, FISH is no longer the first line of testing, and its role has also mostly changed to the confirmation of microarray findings.

Spectral karyotyping and **multicolor FISH** are similar molecular cytogenetic techniques that use 24 different chromosome painting probes and 5 fluorochromes to simultaneously visualize every chromosome in a metaphase spread. Each of the 24 different chromosome paints is labeled with a different combination of the 5 fluorescent dyes, which emit at different wavelengths. Each of the 22 autosomes and the X and Y chromosomes has its own unique spectrum of wavelengths of fluorescence. Special filters, cameras, and image-processing software are required to identify each chromosome. Spectral karyotyping and multicolor FISH are especially useful for identifying the complex chromosome rearrangements found in many tumors. This technique requires very special and costly equipment and is being displaced by comparative aCGH.

CGH is a molecular-based technique that involves differentially labeling the patient's DNA with a fluorescent dye (green) and a normal reference DNA with another fluorescent dye (red; Fig. 81-6). Equal amounts of the 2-label DNA samples are mixed and then used as a painting probe for FISH with normal metaphase chromosomes. The ratio of green : red fluorescence is measured along each chromosome. Regions of amplification of the patient's DNA display an excess of green fluorescence, and regions of loss show excess red fluorescence. If the patient's and the control DNA are equally represented, the green : red ratio is 1 : 1 and the chromosomes appear yellow.

A modified version of this technology, aCGH, uses DNA spotted onto a slide or **microarray** grid. In this case, instead of metaphase

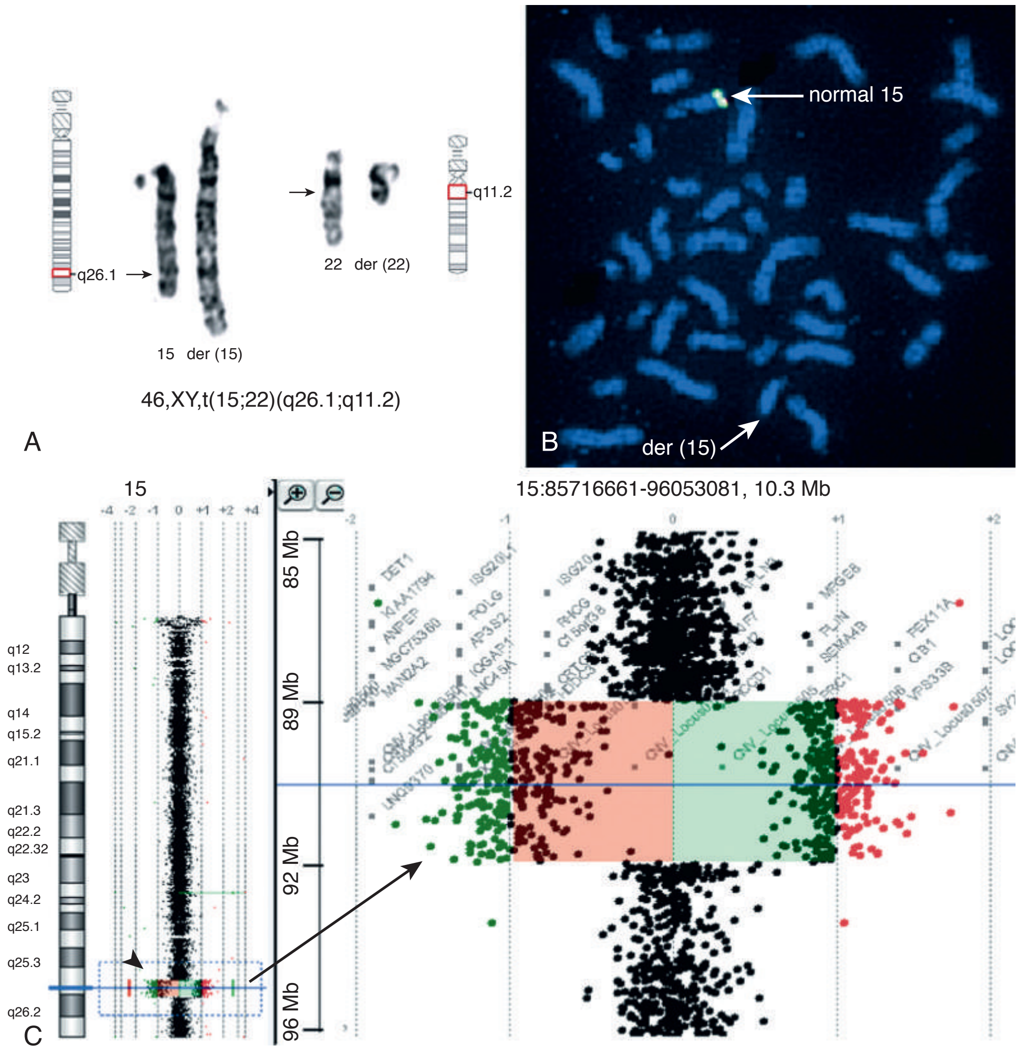

Figure 81-6 An example of a cryptic microdeletion at a translocation breakpoint of an apparently balanced translocation in a patient with DD and growth defect. *A*, Partial karyotype shows t(15;22)(q26.1;q11.2). *B*, FISH with clones 2O19 *(green)* and 354M14 *(red)* at 15q26.1; *arrows* indicate signals only present on the normal chromosome 15, suggesting a deletion on the der(15). *C*, Two-color aCGH with dye swap with 244 K oligo probes; *arrowhead* indicates a 3.3-Mbp deletion at chromosome 15q26.1-q26.2, *arrow* points to the close-up view of the deletion. *(From Li MM, Andersson HC: Clinical application of microarray-based molecular cytogenetics: an emerging new era of genomic medicine,* J Pediatr *155:311-317, 2009, with permission of the authors and publisher.)*

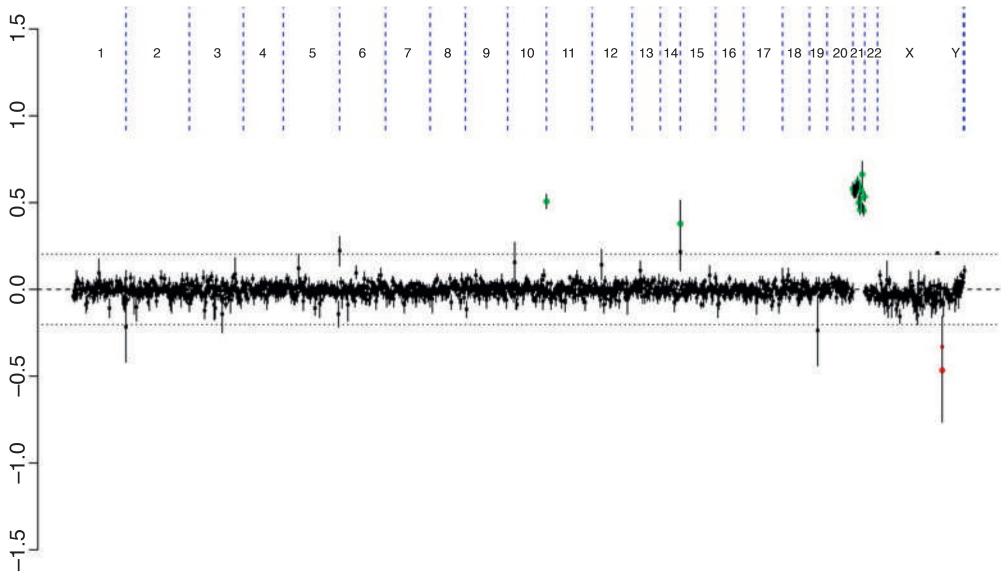

Figure 81-7 aCGH in a female patient with Down syndrome. Each *black dot* represents a piece of DNA segment specific for different chromosome location. Most of the dots displayed between the 0.0 and 0.2 axis are considered within normal range. Exceptions are often a result of polymorphic variations. A group of dots colored in *green* clusters on chromosome 21 and above 0.5. Those represent a *gain* in copy number of DNA segments for chromosome 21 as seen in Down syndrome and consistent with trisomy 21.

chromosomes, segments of DNA are represented by oligonucleotides (short DNA segments) distributed in a microarray that resembles the chromosomes in a metaphase. The detection is currently possible at the single exon resolution level depending on the arrays employed.

There are many advantages of aCGH. It can test all critical disease-causing regions in the genome at once; FISH requires the clinical knowledge and tests only 1 area at a time. aCGH can detect duplications and deletions not currently recognized as recurrent disease-causing regions probed by FISH. aCGH can detect single and contiguous gene deletion syndromes. aCGH does not always require cell culture to generate sufficient DNA, something that may be important in the context of prenatal testing because of timing. There are disadvantages to aCGH: It does not detect balanced translocations, inversions, or very low-levels of mosaicism.

There are different types of aCGH; some of them are more targeted while others have whole-genome coverage. **Targeted aCGH** is an effective and efficient technique for detecting clinically known cryptic chromosomal aberrations, which are typically associated with known disease phenotypes; many of these arrays have expanded detection to areas potentially susceptible to recurring deletion or duplication. **Whole-genome arrays** target the entire genome. The advantage of this latter technique is that it allows better and denser coverage of the entire genome in evenly spaced portions; its disadvantage is that interpretation of deletions or duplications may be difficult if it involves areas not previously known to be involved in disease. There is a new type of array being used in the clinical setting and that is the so-called single nucleotide polymorphism (SNP) array. SNPs are polymorphic variations between 2 nucleotides and when analyzed in massive parallel fashion, they can provide very valuable clinical information. Several million SNPs normally occur in the human genome. SNP arrays can help with the detection of uniparental disomies as well as consanguinity. Many arrays currently used in clinical practice combine the use of oligonucleotides for the detection of copy number variations in conjunction with SNPs.

There are many **copy number variations** causing deletion or duplication in the human genome. Thus, most detected genetic abnormalities, unless associated with very well-known clinical phenotypes, require *parental investigations* because a detected copy number variation that is inherited might turn out to be an incidental polymorphic variant. A de novo abnormality (i.e., one found only in the child and not the parents) is often more significant if it is associated with an abnormal phenotype found only in the child and if it involves genes with important functions. aCGH is a very valuable technology alone or when combined with FISH and conventional chromosome studies (Fig. 81-7).

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81.2 Down Syndrome and Other Abnormalities of Chromosome Number

Brendan Lee

ANEUPLOIDY AND POLYPLOIDY

Human cells contain a multiple of 23 chromosomes (n = 23). A haploid cell (n) has 23 chromosomes (typically in the ovum or sperm). If a cell's chromosomes are an exact multiple of 23 (46, 69, 92 in humans), those cells are referred to as euploid. **Polyploid** cells are euploid cells with more than the normal **diploid** number of 46 (2n) chromosomes: 3n, 4n. Polyploid conceptions are usually not viable, but the presence of mosaicism with a karyotypically normal line can allow survival. Mosaicism is an abnormality defined as the presence of 2 or more cell lines in a single individual. Polyploidy is a common abnormality seen in 1st-trimester pregnancy losses. **Triploid cells** are those with 3 haploid sets of chromosomes (3n) and are only viable in a mosaic form. Triploid infants can be liveborn but do not survive long. Triploidy is often the result of fertilization of an egg by 2 sperm (dispermy). Failure of 1 of the meiotic divisions, resulting in a diploid egg or sperm, can also result in triploidy. The phenotype of a triploid conception depends on the origin of the extra chromosome set. If the extra set is of **paternal** origin, it results in a partial hydatidiform mole with poor embryonic development, but triploid conceptions that have an extra set of **maternal** chromosomes results in severe embryonic retardation with a small fibrotic placenta that is typically spontaneously aborted.

Abnormal cells that do not contain a multiple of haploid number of chromosomes are termed **aneuploid** cells. Aneuploidy is the most common and clinically significant type of human chromosome abnormality, occurring in at least 3-4% of all clinically recognized pregnancies. **Monosomies** occur when only 1, instead of the normal 2, of a given chromosome is present in an otherwise diploid cell. In humans,

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most autosomal monosomies appear to be lethal early in development, and survival is possible in **mosaic forms** or by means of chromosome rescue (restoration of the normal number by duplication of single monosomic chromosome). An exception to this rule is monosomy for the X chromosome (45,X), seen in Turner syndrome; it has been estimated that the majority of 45,X conceptuses are lost early in pregnancy for as yet unexplained reasons.

The most common cause of aneuploidy is **nondisjunction,** the failure of chromosomes to disjoin normally during meiosis (see Fig. 81-1). Nondisjunction can occur during meiosis I or II or during mitosis. After meiotic nondisjunction, the resulting gamete either lacks a chromosome or has 2 copies instead of 1 normal copy, resulting in a monosomic or trisomic zygote, respectively.

Trisomy is characterized by the presence of 3 chromosomes, instead of the normal 2, of any particular chromosome. Trisomy is the most common form of aneuploidy. Trisomy can occur in all cells or it may be mosaic. Most individuals with trisomy exhibit a consistent and specific phenotype depending on the chromosome involved.

FISH is a technique that can be used for rapid diagnosis in the prenatal detection of common fetal aneuploidies including chromosomes 13, 18, and 21, as well as sex chromosomes (see Fig. 81-4*C* and *D*). The most common numerical abnormalities in liveborn children include trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome), and sex chromosomal aneuploidies: Turner syndrome (usually 45,X), Klinefelter syndrome (47,XXY), 47,XXX, and 47,XYY, By far the most common type of trisomy in liveborn infants is trisomy 21 (47,XX,+21 or 47,XY,+21) (see Table 81-1). Trisomy 18 and trisomy 13 are relatively less common and are associated with a characteristic set of congenital anomalies and severe intellectual disability (Table 81-3). The occurrence of trisomy 21 and other trisomies increases with advanced maternal age (≥35 yr). Owing to this increased risk, women who are ≥35 yr at the time of delivery should be offered genetic counseling and prenatal diagnosis (including serum screening, ultrasonography, and amniocentesis or chorionic villus sampling; see Chapter 96).

DOWN SYNDROME

Trisomy 21 is the most common genetic cause of moderate intellectual disability. The incidence of Down syndrome in live births is approximately 1 in 733; the incidence at conception is more than twice that rate; the difference is accounted by early pregnancy losses. In addition to cognitive impairment, Down syndrome is associated with congenital anomalies and characteristic dysmorphic features (Figs. 81-8 and 81-9; Table 81-4). Although there is variability in the clinical features, the constellation of phenotypic features is fairly consistent and permits clinical recognition of trisomy 21. Affected individuals are more prone to congenital heart defects (50%) such as atrioventricular septal defects, ventricular septal defects, isolated secundum atrial septal defects,

Table 81-3 Chromosomal Trisomies and Their Clinical Findings

SYNDROME	INCIDENCE	CLINICAL MANIFESTATIONS
Trisomy 13, Patau syndrome	1/10,000 births	Cleft lip often midline; flexed fingers with postaxial polydactyly; ocular hypotelorism, bulbous nose; low-set, malformed ears; microcephaly; cerebral malformation, especially holoprosencephaly; microphthalmia, cardiac malformations; scalp defects; hypoplastic or absent ribs; visceral and genital anomalies Early lethality in most cases, with a median survival of 7 days; ~91% die by 1 year. Survivors have significant neurodevelopmental delay
Trisomy 18, Edwards syndrome	1/6,000 births	Low birthweight, closed fists with index finger overlapping the 3rd digit and the 5th digit overlapping the 4th, narrow hips with limited abduction, short sternum, rocker-bottom feet, microcephaly, prominent occiput, micrognathia, cardiac and renal malformations, and intellectual disability ~92% of children die in the first year; with full support ~25% may survive 1 yr. Survivors have significant neurodevelopmental delay
Trisomy 8, mosaicism	1/20,000 births	Long face, high prominent forehead, wide upturned nose, thick everted lower lip, microretrognathia, low-set ears, high arched, sometimes cleft, palate; osteoarticular anomalies common (camptodactyly of 2nd to 5th digits, small patella); deep plantar and palmar creases; moderate intellectual disability

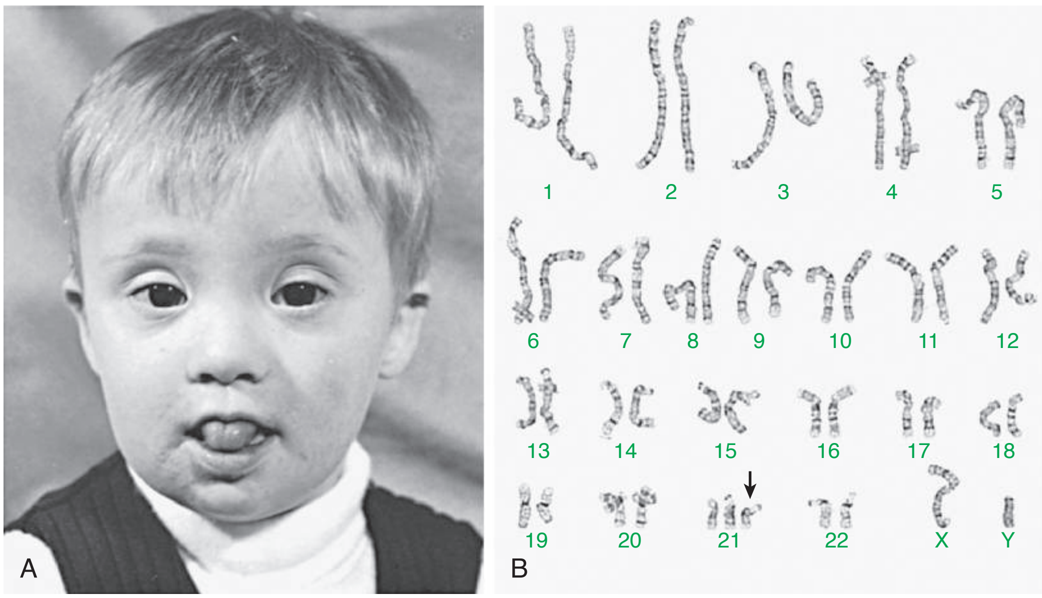

Figure 81-8 *A*, Face of a child with Down syndrome. *B*, Karyotype of a male with trisomy 21 as seen in Down syndrome. This karyotype reveals 47 chromosomes instead of 46, with an extra chromosome in pair 21.

Figure 81-9 Prehensile foot in a 1 mo old child with Down syndrome. *(From Wiedemann HR, Kunze J, Dibbern H:* Atlas of clinical syndromes: a visual guide to diagnosis, *ed 3, St. Louis, 1989, Mosby.)*

patent ductus arteriosus, and tetralogy of Fallot. Congenital and acquired gastrointestinal anomalies and hypothyroidism are common (Table 81-5). Other abnormalities include megakaryoblastic leukemia, immune dysfunction, diabetes mellitus, and problems with hearing and vision (Table 81-5). Alzheimer disease–like dementia is a known complication that occurs as early as the 4th decade and has an incidence 2-3 times higher than sporadic Alzheimer disease. Most males with Down syndrome are sterile, but some females have been able to reproduce, with a 50% chance of having trisomy 21 pregnancies. Two genes (*DYRK1A, DSCR1*) in the putative critical region of chromosome 21 may be targets for therapy.

Developmental delay is universal (Tables 81-6 and 81-7; Fig. 81-10). Cognitive impairment does not uniformly affect all areas of development. Social development is relatively spared, but children with Down syndrome have considerable difficulty using expressive language. Understanding these individual developmental strengths will maximize the educational process for children with Down syndrome. Persons with Down syndrome often benefit from programs aimed at stimulation, development, and education. These programs are most effective in addressing social skills that often appear advanced for the intellectual delay. Children with Down syndrome also benefit from anticipatory guidance, which establishes the protocol for screening, evaluation, and care for patients with genetic syndromes and chronic disorders (Table 81-8). Up to 15% of children with Down syndrome have misalignment of cervical vertebra C1, which places them at risk for spinal cord injury with neck hyperextension or extreme flexion. Special Olympics recommends sports participation and training but requires x-ray examination (full extension and flexion views) of the neck prior to participation in sports that may result in hyperextension or radical flexion or pressure on the neck or upper spine; sports include diving starts in swimming, butterfly stroke, diving, pentathlon, high jump, equestrian sports, gymnastics, football, soccer, alpine skinning, and warm up exercises placing stress on the head and neck. If atlantoaxial instability is diagnosed, Special Olympics will permit participation if the parents or guardians request so and only after obtaining written certification from a physician and acknowledgment of the risks by the parent or guardian.

The majority of children with Down syndrome do not have behavior problems. It is estimated that psychiatric comorbidity is 18-38% in this population. These estimates are higher than in unaffected children, but they are lower than in children with similar levels of intellectual disability from other etiologies. All maladaptive behaviors in persons with Down syndrome are thought to be inherently linked to cognitive impairment. Common behavioral difficulties that occur in children with Down syndrome include inattentiveness, stubbornness, and a need for routine and sameness. Aggression and self-injurious behavior are less common in this population. All of these behaviors can respond to educational or pharmacologic interventions.

The life expectancy for children with Down syndrome is reduced and is approximately 50-55 yr. Little prospective information about the secondary medical problems of adults with Down syndrome is known. Retrospective studies have shown premature aging and an increased risk of Alzheimer disease in adults with Down syndrome. These studies have also shown unexpected negative associations between Down syndrome and other medical comorbidities. Persons with Down syndrome have fewer than expected deaths caused by solid tumors and ischemic heart disease. This same study reported increased risk of adult deaths due to congenital heart disease, seizures, and leukemia. In one large study, leukemias accounted for 60% of all cancers in people with Down

Table 81-4	Clinical Features of Down Syndrome in the Neonatal Period
CENTRAL NERVOUS SYSTEM	
Hypotonia*	
Developmental delay	
Poor Moro reflex*	
CRANIOFACIAL	
Brachycephaly with flat occiput	
Flat face*	
Upward slanted palpebral fissures*	
Epicanthal folds	
Speckled irises (Brushfield spots)	
Three fontanels	
Delayed fontanel closure	
Frontal sinus and midfacial hypoplasia	
Mild microcephaly	
Short hard palate	
Small nose, flat nasal bridge	
Protruding tongue, open mouth	
Small dysplastic ears*	
CARDIOVASCULAR	
Endocardial Cushing defects	
Ventricular septal defect	
Atrial septal defect	
Patent ductus arteriosus	
Aberrant subclavian artery	
Pulmonary hypertension	
MUSCULOSKELETAL	
Joint hyperflexibility*	
Short neck, redundant skin*	
Short metacarpals and phalanges	
Short 5th digit with clinodactyly*	
Single transverse palmar creases*	
Wide gap between 1st and 2nd toes	
Pelvic dysplasia*	
Short sternum	
Two sternal manubrium ossification centers	
GASTROINTESTINAL	
Duodenal atresia	
Annular pancreas	
Tracheoesophageal fistula	
Hirschsprung disease	
Imperforate anus	
Neonatal cholestasis	
CUTANEOUS	
Cutis marmorata	

*Hall's criteria to aid in diagnosis.

Table 81-5 Additional Features of Down Syndrome That Can Develop or Become Symptomatic with Time

NEUROPSYCHIATRIC Developmental delay Seizures Autism spectrum disorders Behavioral disorders (disruptive) Depression Alzheimer disease
SENSORY Congenital or acquired hearing loss Serous otitis media Refractive errors (myopia) Congenital or acquired cataracts Nystagmus Strabismus Glaucoma Blocked tear ducts
CARDIOPULMONARY Acquired mitral, tricuspid, or aortic valve regurgitation Endocarditis Obstructive sleep apnea
MUSCULOSKELETAL Atlantoaxial instability Hip dysplasia Slipped capital femoral epiphyses Avascular hip necrosis Recurrent joint dislocations (shoulder, knee, elbow, thumb)
ENDOCRINE Congenital or acquired hypothyroidism Diabetes mellitus Infertility Obesity Hyperthyroidism
HEMATOLOGIC Transient myeloproliferative syndrome Acute lymphocytic leukemia Acute myelogenous leukemia
GASTROINTESTINAL Celiac disease Delayed tooth eruption Respiratory Obstructed sleep apnea Frequent infections (sinusitis, nasopharyngitis, pneumonia)
CUTANEOUS Hyperkeratosis Seborrhea Xerosis Perigenital folliculitis

syndrome and 97% of all cancers in children with Down syndrome. There was decreased risk of solid tumors in all age groups, including neuroblastomas and nephroblastomas in children with Down syndrome and epithelial tumors in adults with Down syndrome.

Most adults with Down syndrome are able to perform activities of daily living. However, most adults with Down syndrome have difficulty with complex financial, legal, or medical decisions. In most circumstances, a conservator is appointed for the adult with Down syndrome.

The risk of having a child with trisomy 21 is highest in women who conceive at >35 yr of age. Even though younger women have a lower risk, they represent half of all mothers with babies with Down syndrome because of their higher overall birth rate. *All women should be offered screening for Down syndrome* in their 2nd trimester by means of 4 maternal serum tests (free β-human chorionic gonadotropin [β-hCG], unconjugated estriol, inhibin, and α-fetoprotein). This is

Table 81-6 Developmental Milestones

Milestone	CHILDREN WITH DOWN SYNDROME Average (mo)	CHILDREN WITH DOWN SYNDROME Range (mo)	UNAFFECTED CHILDREN Average (mo)	UNAFFECTED CHILDREN Range (mo)
Smiling	2	1.5-3	1	1.5-3
Rolling over	6	2-12	5	2-10
Sitting	9	6-18	7	5-9
Crawling	11	7-21	8	6-11
Creeping	13	8-25	10	7-13
Standing	10	10-32	11	8-16
Walking	20	12-45	13	8-18
Talking, words	14	9-30	10	6-14
Talking, sentences	24	18-46	21	14-32

From Levine MD, Carey WB, Crocker AC, editors: Developmental-behavioral pediatrics, *ed 2, Philadelphia, 1992, Saunders.*

Table 81-7 Self-Help Skills

Skill	DOWN SYNDROME CHILDREN Average (mo)	DOWN SYNDROME CHILDREN Range (mo)	UNAFFECTED CHILDREN Average (mo)	UNAFFECTED CHILDREN Range (mo)
EATING				
Finger feeding	12	8-28	8	6-16
Using spoon/fork	20	12-40	13	8-20
TOILET TRAINING				
Bladder	48	20-95	32	18-60
Bowel	42	28-90	29	16-48
DRESSING				
Undressing	40	29-72	32	22-42
Putting clothes on	58	38-98	47	34-58

From Levine MD, Carey WB, Crocker AC, editors: Developmental-behavioral pediatrics, *ed 2, Philadelphia, 1992, Saunders.*

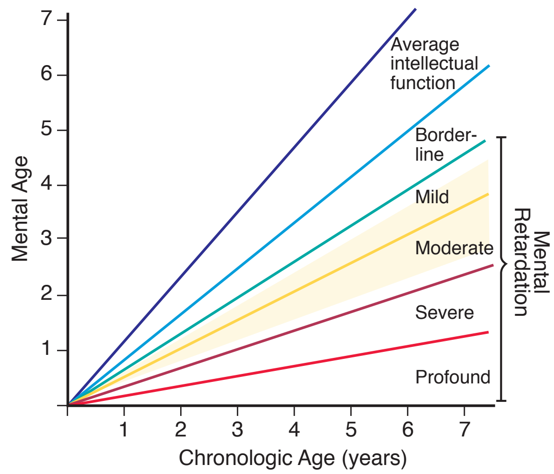

Figure 81-10 The area shaded in yellow denotes the range of intellectual function of the majority of children with Down syndrome. *(From Levine MD, Carey WB, Crocker AC, editors:* Developmental-behavioral pediatrics, *ed 2, Philadelphia, 1992, WB Saunders, p. 226.)*

Table 81-8 Health Supervision for Children with Down Syndrome

CONDITION	TIME TO SCREEN	COMMENT
Congenital heart disease	Birth; by pediatric cardiologist Young adult for acquired valve disease	50% risk of congenital heart disease; increased risk for pulmonary hypertension
Strabismus, cataracts, nystagmus	Birth or by 6 mo; by pediatric ophthalmologist **Check vision annually**	Cataracts occur in 15%, refractive errors in 50%
Hearing impairment or loss	Birth or by 3 mo with auditory brainstem response or otoacoustic emission testing; check hearing q6mo up to 3 yr if tympanic membrane is not visualized; **annually thereafter**	Risk for congenital hearing loss plus 50-70% risk of serous otitis media
Constipation	Birth	Increased risk for Hirschsprung disease
Celiac disease	At 2 yr or with symptoms	Screen with IgA and tissue transglutaminase antibodies
Hematologic disease	At birth and in adolescence or if symptoms develop	Increased risk for neonatal polycythemia (18%), leukemoid reaction, leukemia (<1%)
Hypothyroidism	Birth; repeat at 6-12 mo and **annually**	Congenital (1%) and acquired (5%)
Growth and development	At each visit Use Down syndrome growth curves	Discuss school placement options Proper diet to avoid obesity
Obstructive sleep apnea	Start at ~1 yr and at each visit	Monitor for snoring, restless sleep
Atlantoaxial subluxation or instability (incidence 10-30%)	At each visit by history and physical exam Radiographs at 3-5 yr or when planning to participate in contact sports Radiographs indicated wherever neurologic symptoms are present even if transient (neck pain, torticollis, gait disturbances, weakness) Many are asymptomatic	Special Olympics recommendations are to screen for high-risk sports, e.g., diving, swimming, contact sports
Gynecologic care	Adolescent girls	Menstruation and contraception issues
Recurrent infections	When present	Check IgG subclass and IgA levels
Psychiatric, behavioral disorders	At each visit	Depression, anxiety, obsessive-compulsive disorder, schizophrenia seem in 10-17% Autism spectrum disorder in 5-10% Early-onset Alzheimer disease

IgA, immunoglobulin A; IgG, immunoglobulin G.

Data from Committee on Genetics: Health supervision for children with Down syndrome, Pediatrics *107:442-449, 2001; and Baum RA, Spader M, Nash PL, et al: Primary care of children and adolescents with Down syndrome: an update,* Curr Probl Pediatr Adolesc Health Care *38:235–268, 2008.*

known as the *quad screen;* it can detect up to 80% of Down syndrome pregnancies compared to 70% in the triple screen. Both tests have a 5% false-positive rate. There is a method of screening during the 1st trimester using fetal nuchal translucency (NT) thickness that can be done alone or in conjunction with maternal serum β-hCG and pregnancy-associated plasma protein-A (PAPP-A). In the 1st trimester, NT alone can detect ≤70% of Down syndrome pregnancies, but with β-hCG and PAPP-A, the detection goes up to 87%. If both 1st and 2nd trimester screens are combined using NT and biochemical profiles (integrated screen), the detection rate goes up to 95%. If only 1st trimester quad screening is done, maternal serum α-fetoprotein (which is decreased in affected pregnancies) is recommended as a 2nd trimester follow-up.

Detection of cell free fetal DNA in maternal plasma is also diagnostic. The noninvasive detection of fetal trisomy 21 by analyzing cell-free fetal DNA in maternal serum is an important advance in prenatal diagnosis of Down syndrome. Next-generation DNA sequencing has reduced the cost of this procedure, which has a high degree of accuracy (98% detection rate) and applicability. The prenatal screens are also useful for other trisomies, although the detection rates may be different from those given for Down syndrome.

In approximately 95% of the cases of Down syndrome there are 3 copies of chromosome 21. The origin of the supernumerary chromosome 21 is maternal in 97% of the cases as a result of errors in meiosis. The majority of these occur in maternal meiosis I (90%). Approximately 1% of persons with trisomy 21 are mosaics, with some cells having 46 chromosomes, and another 4% have a **translocation** that involves chromosome 21. The majority of translocations in Down syndrome are fusions at the centromere between chromosomes 13, 14, 15, 21, and 22 known as *Robertsonian translocations.* The translocations can be de novo or inherited. Very rarely is Down syndrome diagnosed in a patient with only a part of the long arm of chromosome 21 in triplicate **(partial trisomy).** Isochromosomes and ring chromosomes are other rarer causes of trisomy 21. Down syndrome patients without a visible chromosome abnormality are the least common. It is not possible to distinguish the phenotypes of persons with full trisomy 21 and those with a translocation. Representative genes on chromosome 21 and their potential effects on development are noted in Table 81-9. Patients who are mosaic tend to have a milder phenotype.

Chromosome analysis is indicated in every person suspected of having Down syndrome. If a translocation is identified, parental chromosome studies must be performed to determine whether one of the parents is a translocation carrier, which carries a high recurrence risk for having another affected child. That parent might also have other family members at risk. Translocation (21;21) carriers have a 100% recurrence risk for a chromosomally abnormal child, and other Robertsonian translocations, such as t(14;21), have a 5-7% recurrence risk when transmitted by females. Genomic dosage imbalance contributes through direct and indirect pathways to the Down syndrome phenotype and its phenotypic variation.

Tables 81-10 and 81-11 provide more information on other aneuploidies and partial autosomal aneuploidies (Figs. 81-11 to 81-14).

Bibliography is available at Expert Consult.

Table 81-9 Genes Localized to Chromosome 21 That Possibly Affect Brain Development, Neuronal Loss, and Alzheimer Type Neuropathology

SYMBOL	NAME	POSSIBLE EFFECT IN DOWN SYNDROME	FUNCTION
SIM2	Single-minded homolog 2	Brain development	Required for synchronized cell division and establishment of proper cell lineage
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	Brain development	Expressed during neuroblast proliferation Believed important homolog in regulating cell-cycle kinetics during cell division
GART	Phosphoribosylglycinamide formyltransferase Phosphoribosylglycinamide synthetase Phosphoribosylaminoimidazole synthetase	Brain development	Expressed during prenatal development of the cerebellum
PCP4	Purkinje cell protein 4	Brain development	Function unknown but found exclusively in the brain and most abundantly in the cerebellum
DSCAM	Down syndrome cell adhesion molecule	Brain development and possible candidate gene for congenital heart disease	Expressed in all molecule regions of the brain and believed to have a role in axonal outgrowth during development of the nervous system
GRIK1	Glutamate receptor, ionotropic kainite1	Neuronal loss	Function unknown, found in the cortex in fetal and early postnatal life and in adult primates, most concentrated in pyramidal cells in the cortex
APP	Amyloid beta (A4) precursor protein (protease nexin-II, Alzheimer disease)	Alzheimer type neuropathy	Seems to be involved in plasticity, neurite outgrowth, and neuroprotection
S100B	S100 calcium binding protein β (neural)	Alzheimer type neuropathy	Stimulates glial formation
SOD1	Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis, adult)	Accelerated aging?	Scavenges free superoxide molecules in the cell and might accelerate aging by producing hydrogen peroxide and oxygen

Table 81-10 Other Rare Aneuploidies and Partial Autosomal Aneuploidies

DISORDER	KARYOTYPE	CLINICAL MANIFESTATIONS
Trisomy 8	47,XX/XY,+8	Growth and mental deficiency are variable The majority of patients are mosaics Deep palmar and plantar furrows are characteristic
Trisomy 9	47,XX/XY,+9	The majority of patients are mosaics Clinical features include craniofacial (high forehead, microphthalmia, low-set malformed ears, bulbous nose) and skeletal (joint contractures) malformations and heart defects (60%)
Trisomy 16	47,XX/XY,+16	The most commonly observed autosomal aneuploidy in spontaneous abortion; the recurrence risk is negligible
Tetrasomy 12p	46,XX[12]/46,XX, +i(12p)[8] (mosaicism for an isochromosome 12p)	Known as Pallister-Killian syndrome. Sparse anterior scalp hair, eyebrows, and eyelashes, prominent forehead, chubby cheeks, long philtrum with thin upper lip and cupid-bow configuration, polydactyly, and streaks of hyper- and hypopigmentation

Table 81-11 Findings That May Be Present in Trisomy 13 and Trisomy 18

TRISOMY 13	TRISOMY 18
HEAD AND FACE	
Scalp defects (e.g., cutis aplasia) Microphthalmia, corneal abnormalities Cleft lip and palate in 60%-80% of cases Microcephaly Microphthalmia Sloping forehead Holoprosencephaly (arhinencephaly) Capillary hemangiomas Deafness	Small and premature appearance Tight palpebral fissures Narrow nose and hypoplastic nasal alae Narrow bifrontal diameter Prominent occiput Micrognathia Cleft lip or palate Microcephaly
CHEST	
Congenital heart disease (e.g., VSD, PDA, and ASD) in 80% of cases Thin posterior ribs (missing ribs)	Congenital heart disease (e.g., VSD, PDA, ASD) Short sternum, small nipples

Continued

Table 81-11 Findings That May Be Present in Trisomy 13 and Trisomy 18—cont'd

TRISOMY 13	TRISOMY 18
EXTREMITIES	
Overlapping of fingers and toes (clinodactyly) Polydactyly Hypoplastic nails, hyperconvex nails	Limited hip abduction Clinodactyly and overlapping fingers; index over 3rd, 5th over 4th; closed fist Rocker-bottom feet Hypoplastic nails
GENERAL	
Severe developmental delays and prenatal and postnatal growth restriction Renal abnormalities Only 5% live >6 mo	Severe developmental delays and prenatal and postnatal growth restriction Premature birth, polyhydramnios Inguinal or abdominal hernias Only 5% live >1 yr

ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.
From Behrman RE, Kliegman RM: Nelson essentials of pediatrics, *ed 4, Philadelphia, 2002, WB Saunders, p. 142.*

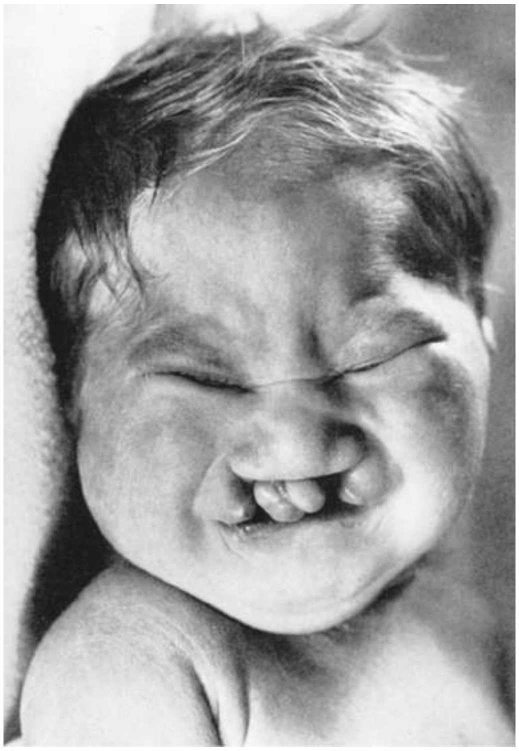

Figure 81-11 Facial appearance of a child with trisomy 13. *(From Wiedemann HR, Kunze J, Dibbern H:* Atlas of clinical syndromes: a visual guide to diagnosis, *ed 3, St. Louis, 1989, Mosby.)*

Figure 81-12 Trisomy 18: overlapping fingers and hypoplastic nails. *(From Wiedemann HR, Kunze J, Dibbern H:* Atlas of clinical syndromes: a visual guide to diagnosis, *ed 3, St. Louis, 1989, Mosby.)*

Figure 81-13 Trisomy 18: rocker-bottom feet (protruding calcanei). *(From Wiedemann HR, Kunze J, Dibbern H:* Atlas of clinical syndromes: a visual guide to diagnosis, *ed 3, St. Louis, 1989, Mosby.)*

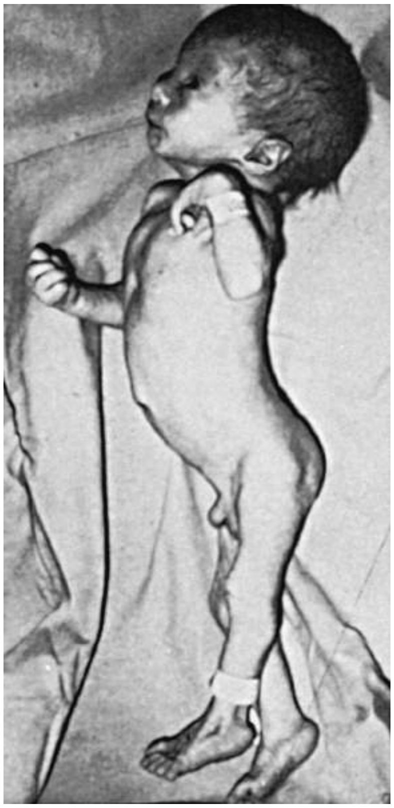

Figure 81-14 Male infant with trisomy 18 at age 4 days. Note prominent occiput, micrognathia, low-set ears, short sternum, narrow pelvis, prominent calcaneus, and flexion abnormalities of the fingers.

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81.3 Abnormalities of Chromosome Structure

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TRANSLOCATIONS

Translocations, which involve the transfer of material from 1 chromosome to another, occur with a frequency of 1 in 500 liveborn human infants. They may be inherited from a carrier parent or appear de novo, with no other affected family member. Translocations are commonly reciprocal or Robertsonian, involving 2 chromosomes (Fig. 81-15).

Reciprocal translocations are the result of breaks in nonhomologous chromosomes, with reciprocal exchange of the broken segments. Carriers of a reciprocal translocation are usually phenotypically normal but are at an increased risk for miscarriage caused by transmission of unbalanced reciprocal translocations and for bearing chromosomally abnormal offspring. Unbalanced translocations are the result of abnormalities in the segregation or crossover of the translocation carrier chromosomes in the germ cells.

Robertsonian translocations involve 2 acrocentric chromosomes (chromosomes 13, 14, 15, 21, and 22) that fuse near the centromeric region with a subsequent loss of the short arms. Because the short arms of all 5 pairs of acrocentric chromosomes have multiple copies of genes for ribosomal RNA, loss of the short arm of 2 acrocentric chromosomes has no deleterious effect. The resulting karyotype has only 45 chromosomes, including the translocated chromosome that is made up of the long arms of the 2 fused chromosomes. Carriers of Robertsonian translocations are usually phenotypically normal.

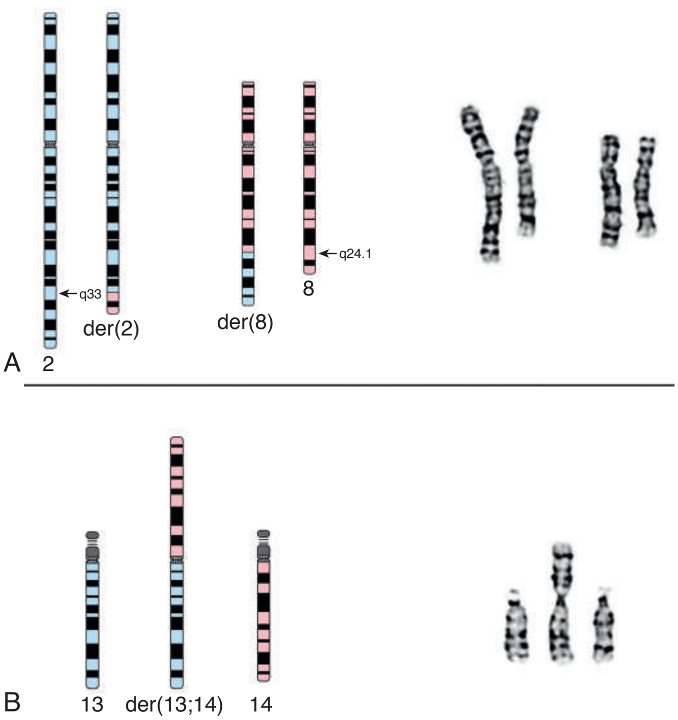

Figure 81-15 *A,* Schematic diagram *(left)* and partial G-banded karyotype *(right)* of a reciprocal translocation between chromosome 2 *(blue)* and chromosome 8 *(pink)*. The breakpoints are on the long *(q)* arm of both chromosomes at bands 2q33 and 8q24.1, with the reciprocal exchange of material between the derivative *(der)* chromosomes 2 and 8. This translocation is balanced, with no net gain or loss of material. The nomenclature for this exchange is t(2;8)(q33:q24.1). *B,* Schematic diagram *(left)* and partial G-banded karyotype *(right)* of a Robertsonian translocation between chromosomes 13 *(blue)* and 14 *(pink)*. The breakpoints are at the centromere (band q10) of both chromosomes, with fusion of the long arms into a single derivative chromosome and loss of the short *(p)* arm material. The nomenclature for this exchange is der(13;14)(q10;q10).

However, they are at increased risk for miscarriage and unbalanced translocations in phenotypically abnormal offspring.

In some rare instances, translocations can involve 3 or more chromosomes, as seen in complex rearrangements. Another, less common type is the insertional translocation. Insertional translocations result from a piece of chromosome material that breaks away and later is reinserted inside the same chromosome at a different site or inserted in another chromosome.

INVERSIONS

An inversion requires that a single chromosome break at 2 points; the broken piece is then inverted and joined into the same chromosome. Inversions occur in 1 in 100 live births. There are 2 types of inversions: pericentric and paracentric. In **pericentric inversions,** the breaks are in the 2 opposite arms of the chromosome and include the centromere. They are usually discovered because they change the position of the centromere. The breaks in **paracentric inversions** occur in only 1 arm. Carriers of inversions are usually phenotypically normal, but they are at increased risk for miscarriages, typically in paracentric inversions, and chromosomally abnormal offspring in pericentric inversions.

DELETIONS AND DUPLICATIONS

Deletions involve loss of chromosome material and, depending on their location, they can be classified as **terminal** (at the ends of chromosomes) or **interstitial** (within the arms of a chromosome). They may be isolated or they may occur along with a duplication of another chromosome segment. The latter typically occurs in unbalanced reciprocal chromosomal translocation secondary to abnormal crossover or segregation in a translocation or inversion carrier.

A carrier of a deletion is monosomic for the genetic information of the missing segment. Deletions are usually associated with intellectual disability and malformations. The most commonly observed deletions in routine chromosome preparations include 1p–, 4p–, 5p–, 9p–, 11p–, 13q–, 18p–, 18q–, and 21q– (Table 81-12 and Fig. 81-16), all distal or terminal deletions of the short or the long arms of chromosomes. Deletions may be observed in routine chromosome preparations, and deletions and translocations larger than 5-10 Mbp are usually visible microscopically.

High-resolution banding techniques, FISH, and molecular studies like aCGH can reveal deletions that are too small to be seen in ordinary or routine chromosome spreads (see Fig. 81-7). **Microdeletions** involve loss of small chromosome regions, the largest of which are detectable only with prophase chromosome studies and/or molecular methods. For submicroscopic deletions, the missing piece can only be detected using molecular methodologies such as DNA-based studies like aCGH or FISH. The presence of extra genetic material from the same chromosome is referred to as **duplication.** Duplications can also be sporadic or result from abnormal segregation in translocation or inversion carriers.

Microdeletions and microduplications usually involve regions that include several genes, so that the affected individuals can have a distinctive phenotype depending on the number of genes involved. When such a deletion involves more than a single gene, the condition is referred to as a **contiguous gene deletion syndrome** (Table 81-13). With the advent of clinically available aCGH, a large number of duplications, most of them microduplications, have been uncovered. Most of those **microduplication syndromes** are the reciprocal duplications of the known deletions or microdeletion counterparts and have distinctive clinical features (Table 81-14).

Subtelomeric regions are often involved in chromosome rearrangements that cannot be visualized using routine cytogenetics. Telomeres, which are the distal ends of the chromosomes, are gene-rich regions. The distal structure of the telomeres is essentially common to all chromosomes, but proximal to those, there are unique regions known as subtelomeres, which typically involved in deletions and most other chromosome rearrangements. Small subtelomeric deletions, duplications, or rearrangements (translocations, inversions) may be relatively common in nonspecific intellectual disability with minor anomalies. Subtelomeric rearrangements have been found in 3-7% of children

Table 81-12 Common Deletions and Their Clinical Manifestations

DELETION	CLINICAL ABNORMALITIES
4p–	Wolf-Hirschhorn syndrome. The main features are a typical “Greek helmet” facies secondary to ocular hypertelorism, prominent glabella, and frontal bossing; microcephaly, dolichocephaly, hypoplasia of the orbits, ptosis, strabismus, nystagmus, bilateral epicanthic folds, cleft lip and palate, beaked nose with prominent bridge, hypospadias, cardiac malformations, and intellectual disability.
5p–	Cri-du-chat syndrome. The main features are hypotonia, short stature, characteristic shrill cry in the first few weeks of life (cat-like cry), microcephaly with protruding metopic suture, hypertelorism, bilateral epicanthic folds, high arched palate, wide and flat nasal bridge, and intellectual disability.
9p–	The main features are craniofacial dysmorphology with trigonocephaly, slanted palpebral fissures, discrete exophthalmos secondary to supraorbital hypoplasia, arched eyebrows, flat and wide nasal bridge, short neck with low hairline, genital anomalies, long fingers and toes with extra flexion creases, cardiac malformations, and intellectual disability.
13q–	The main features are low birthweight, failure to thrive, microcephaly, and severe intellectual disability. Facial features include high wide nasal bridge, hypertelorism, ptosis, micrognathia. Ocular malformations are common (retinoblastoma). The hands have hypoplastic or absent thumbs and syndactyly.
18p–	A few patients (15%) are severely affected and have cephalic and ocular malformations: holoprosencephaly, cleft lip and palate, ptosis, epicanthal folds, and varying degrees of intellectual disability. Most (80%) have only minor malformations and mild intellectual disability.
18q–	Growth deficiency, hypotonia with “frog-like” position with the legs flexed, externally rotated, and in hyperabduction. The face is characteristic with depressed midface and apparent protrusion of the mandible, deep-set eyes, short upper lip, everted lower lip (“carp-like” mouth); antihelix of the ears is very prominent; varying degrees of intellectual disability and belligerent personality. Myelination abnormalities in the central nervous system.

Table 81-13 Microdeletion and Contiguous Gene Syndromes and Their Clinical Manifestations

DELETION	SYNDROME	CLINICAL MANIFESTATIONS
1p36	1p deletion	Growth restriction, dysmorphic features with midface hypoplasia, straight thin eyebrows, pointy chin, sensorineural hearing loss, progressive cardiomyopathy, hypothyroidism, seizures, intellectual disability
5q35	Sotos (50% are deletions of *NSD1* gene in Asians but only 6% in whites)	Overgrowth, macrocephaly, prominent forehead, prominence of extraaxial fluid spaces on brain imaging, large hands and feet, hypotonia, clumsiness, mental disabilities
6p25	Axenfeld-Rieger	Axenfeld-Rieger malformation, hearing loss, congenital heart defects, dental anomalies, developmental delays, facial dysmorphism
7q11.23	Williams	Round face with full cheeks and lips, long philtrum, stellate pattern in iris, strabismus, supravalvular aortic stenosis and other cardiac malformations, varying degrees of intellectual disability, friendly personality
8p11	8p11	Kallmann syndrome 2 (hypogonadotropic hypogonadism and anosmia), spherocytosis (deletions of ankyrin 1), multiple congenital anomalies, intellectual disability
8q24.1-q24.13	Langer-Giedion or trichorhinophalangeal type II	Sparse hair, multiple cone-shaped epiphyses, multiple cartilaginous exostoses, bulbous nasal tip, thickened alar cartilage, upturned nares, prominent philtrum, large protruding ears, mild intellectual disability
9q22	Gorlin	Multiple basal cell carcinomas, odontogenic keratocysts, palmoplantar pits, calcification falx cerebri
9q34	9q34 deletion	Distinct face with synophrys, anteverted nares, tented upper lip, protruding tongue, midface hypoplasia, conotruncal heart defects, intellectual disability
10p12-p13	DiGeorge 2	Many of the DiGeorge 1 and velocardiofacial 1 features (conotruncal defects, immunodeficiency, hypoparathyroidism, dysmorphic features)
11p11.2	Potocki-Shaffer	Multiple exostoses, parietal foramina, craniosynostosis, facial dysmorphism, syndactyly, intellectual disability
11p13	WAGR	Hypernephroma (Wilms tumor), aniridia, male genital hypoplasia of varying degrees, gonadoblastoma, long face, upward slanting palpebral fissures, ptosis, beaked nose, low-set poorly formed auricles, intellectual disability
11q24.1-11qter	Jacobsen	Growth restriction, intellectual disability, cardiac and digit anomalies, thrombocytopenia
15q11-q13 (paternal)	Prader-Willi	Severe hypotonia and feeding difficulties at birth, voracious appetite and obesity in infancy, short stature (responsive to growth hormone), small hands and feet, hypogonadism, intellectual disability

Table 81-13 Microdeletion and Contiguous Gene Syndromes and Their Clinical Manifestations—cont'd

DELETION	SYNDROME	CLINICAL MANIFESTATIONS
15q11-q13 (maternal)	Angelman	Hypotonia, feeding difficulties, gastroesophageal reflux, fair hair and skin, midface hypoplasia, prognathism, seizures, tremors, ataxia, sleep disturbances, inappropriate laughter, poor or absent speech, severe intellectual disability
16p13.3	Rubinstein-Taybi	Microcephaly, ptosis, beaked nose with low-lying philtrum, broad thumbs and large toes, intellectual disability
17p11.2	Smith-Magenis	Brachycephaly, midfacial hypoplasia, prognathism, myopia, cleft palate, short stature, severe behavioral problems, intellectual disability
17p13.3	Miller-Dieker	Microcephaly, lissencephaly, pachygyria, narrow forehead, hypoplastic male external genitals, growth restriction, seizures, profound intellectual disability
20p12	Alagille syndrome	Bile duct paucity with cholestasis; heart defects, particularly pulmonary artery stenosis; ocular abnormalities (posterior embryotoxon); skeletal defects such as butterfly vertebrae; long nose
22q11.2	Velocardiofacial-DiGeorge syndrome	Conotruncal cardiac anomalies, cleft palate, velopharyngeal incompetence, hypoplasia or agenesis of the thymus and parathyroid glands, hypocalcemia, hypoplasia of auricle, learning disabilities, psychiatric disorders
22q13.3 deletion		Hypotonia, developmental delay, normal or accelerated growth, severe expressive language deficits, autistic behavior
Xp21.2-p21.3		Duchenne muscular dystrophy, retinitis pigmentosa, adrenal hypoplasia, intellectual disability, glycerol kinase deficiency
Xp22.2-p22.3		Ichthyosis, Kallmann syndrome, intellectual disability, chondrodysplasia punctata
Xp22.3	Microphthalmia with linear defects (MLS)	Microphthalmia, linear skin defects, poikiloderma, congenital heart defects, seizures, intellectual disability

Table 81-14 Microduplications and Their Clinical Manifestations

DUPLICATION CHROMOSOME REGION	DISEASE REGION	CLINICAL FEATURES
1q21.1		Macrocephaly, DD, learning disabilities
3q29		Mild to moderate MR, microcephaly
7q11.23	Williams syndrome	DD and severe expressive language disorder, autistic features, subtle dysmorphisms
15q13.3	Prader-Willi/Angelman syndrome region	DD, MR, autistic features in duplications of maternal origin
15q24		Growth restriction, DD, microcephaly, digital anomalies, hypospadias, connective tissue abnormalities
16p11.2		FTT, severe DD, short stature, GH deficiency, dysmorphic features
17p11.2	Potocki-Lupski syndrome	Hypotonia, cardiovascular anomalies, FTT, DD, verbal apraxia, autism, anxiety
17q21.31		Severe DD, microcephaly, short and broad digits, dysmorphic features
22q11.2	Velocardiofacial-DiGeorge syndrome	Cardiovascular defects, velopharyngeal insufficiency
Xq28	*MECP2* gene region (Rett syndrome)	In males: infantile hypotonia, immune deficiency, dysmorphic features, DD, speech delay, autistic behavior, regression in childhood

DD, developmental delay; ID, intellectual disability; FTT, failure to thrive; GH, growth hormone; MR, mental retardation.

with moderate to mild intellectual disability and 0.5% of children with mild intellectual disability.

Clinical features (>30%) include short stature, microcephaly, hypertelorism, nose and ear abnormalities, and cryptorchidism. This group is also characterized by a family history of intellectual disability and an increased likelihood of restricted growth beginning in the prenatal period. Telomere mutations have also been associated with dyskeratosis congenita and other aplastic anemia syndromes as well as pulmonary or hepatic fibrosis. Both the subtelomeric rearrangements and the microdeletion and microduplication syndromes are typically diagnosed by molecular techniques like aCGH, FISH, and multiple ligation-dependent primer amplification. Recent studies show that aCGH can detect 14-18% of abnormalities in patients who are previously known to have normal chromosome studies.

INSERTIONS

Insertions occur when a piece of a chromosome broken at 2 points is incorporated into a break in another part of a chromosome. A total of 3 breakpoints are then required, and they can occur between 2 or within 1 chromosome. A form of nonreciprocal translocation, insertions are rare. Insertion carriers are at risk of having offspring with deletions or duplications of the inserted segment.

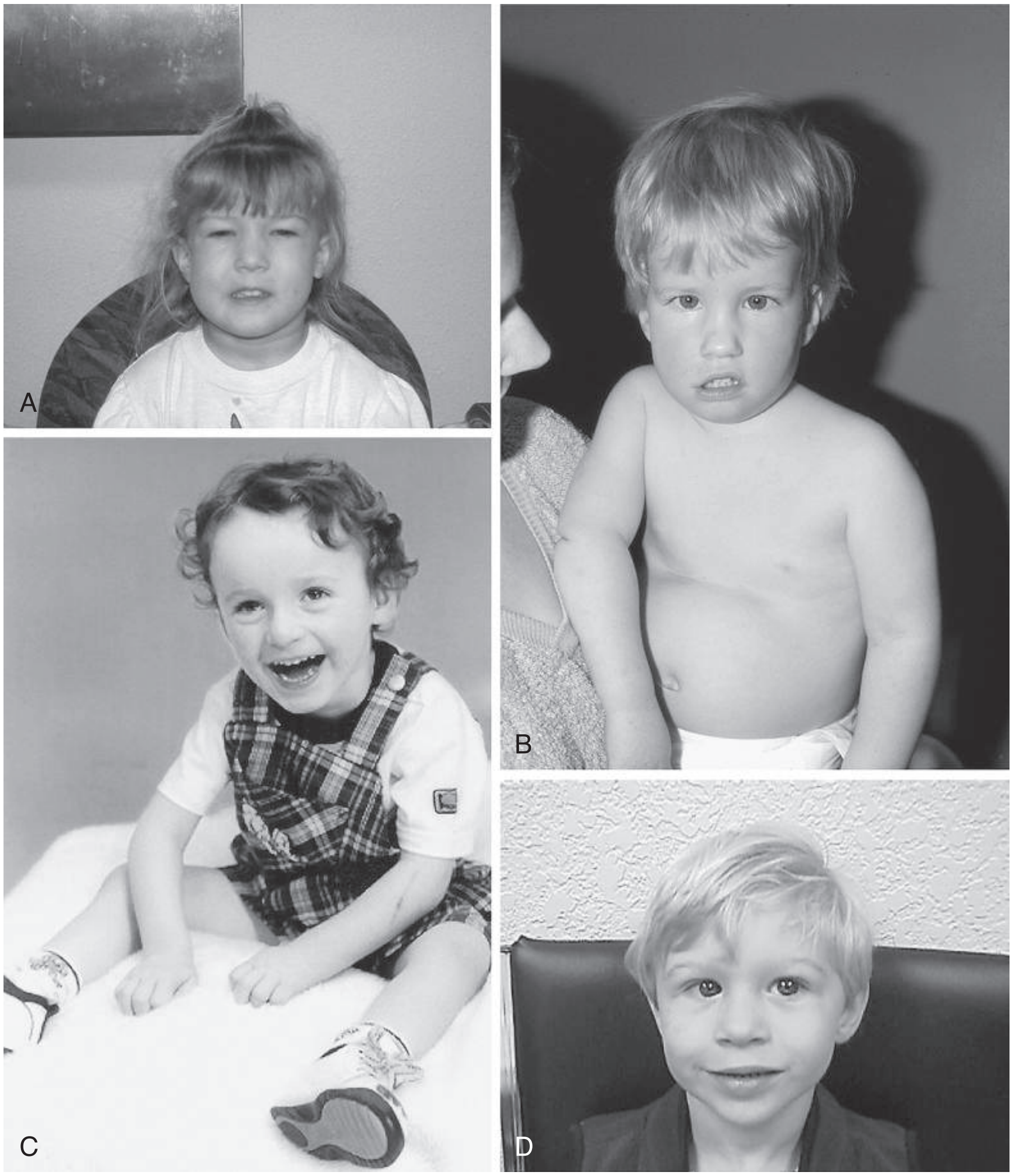

Figure 81-16 *A*, Child with velocardiofacial syndrome (deletion 22q11.2). *B*, Child with Prader-Willi syndrome (deletion 15q11-13). *C*, Child with Angelman syndrome (deletion 15q11-13). *D*, Child with Williams syndrome (deletion 7q11.23). *(From Lin RL, Cherry AM, Bangs CD, et al: FISHing for answers: the use of molecular cytogenetic techniques in adolescent medicine practice. In Hyme HE, Greydanus D, editors:* Genetic disorders in adolescents: state of the art reviews. Adolescent medicine, *Philadelphia, 2002, Hanley and Belfus, pp. 305–313.)*

ISOCHROMOSOMES

Isochromosomes consist of 2 copies of the same chromosome arm joined through a single centromere and forming mirror images of one another. The most commonly reported autosomal isochromosomes tend to involve chromosomes with small arms. Some of the more common chromosome arms involved in this formation include 5p, 8p, 9p, 12p, 18p, and 18q. There is also a common isochromosome abnormality seen in long arm of the X chromosome, and associated with Turner syndrome. Individuals who have 1 isochromosome within 46 chromosomes are monosomic for genes in the lost short arm and trisomic for the genes present in the long arm of the X chromosome.

MARKER AND RING CHROMOSOMES

Marker chromosomes are rare and are usually chromosome fragments that are too small to be identified by conventional cytogenetics; they usually occur in addition to the normal 46 chromosomes. Most are sporadic (70%); mosaicism is often (50%) noted because of the mitotic instability of the marker chromosome. The incidence in newborn infants is 1 in 3,300, and the incidence in persons with intellectual disability is 1 in 300. The associated phenotype ranges from normal to severely abnormal depending on the amount of chromosome material and number of genes associated with the fragment.

Ring chromosomes, which are found for all human chromosomes, are rare. A ring chromosome is formed when both ends of a chromosome are deleted and the ends are then joined to form a ring. Depending on the amount of chromosome material that is lacking or in excess (if the ring is in addition to the normal chromosomes), a patient with a ring chromosome can appear normal or nearly normal or can have intellectual disability and multiple congenital anomalies.

Marker and ring chromosomes can be found in the cells of solid tumors of children the cells of whose organs do not contain this additional chromosomal material.

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81.4 Sex Chromosome Aneuploidy

Carlos A. Bacino and Brendan Lee

About 1 in 400 males and 1 in 650 females have some form of sex chromosome abnormality. Considered together, sex chromosome abnormalities are the most common chromosome abnormalities seen in liveborn infants, children, and adults. Sex chromosome abnormalities can be either structural or numerical and can be present in all cells or in a mosaic form. Those affected with these abnormalities might have few or no physical or developmental problems (Table 81-15).

TURNER SYNDROME

Turner syndrome is a condition characterized by complete or partial monosomy of the X chromosome and defined by a combination of phenotypic features (Table 81-16). Half of the patients with Turner syndrome have a 45,X chromosome complement. The other half exhibits mosaicism and varied structural abnormalities of the X or Y chromosome. Maternal age is not a predisposing factor for children with 45,X. Turner syndrome occurs in approximately 1 in 5,000 female live births. In 75% of patients, the lost sex chromosome is of paternal origin (whether an X or a Y). 45,X is one of the chromosome abnormalities most often associated with spontaneous abortion. It has been estimated that 95-99% of 45,X conceptions are miscarried.

Clinical findings in the newborns can include small size for gestational age, webbing of the neck, protruding ears, and lymphedema of the hands and feet, although many newborns are phenotypically normal (Fig. 81-17). Older children and adults have short stature and exhibit variable dysmorphic features. Congenital heart defects (40%) and structural renal anomalies (60%) are common. The most common heart defects are bicuspid aortic valves, coarctation of the aorta, aortic stenosis, and mitral valve prolapse. The gonads are generally streaks of fibrous tissue **(gonadal dysgenesis).** There is primary amenorrhea and lack of secondary sex characters. These children should receive regular endocrinologic testing (see Chapter 586). Most patients tend to be of normal intelligence, but intellectual disability is seen in up to 6% of affected children. They are also at increased risk for behavioral problems and deficiencies in spatial and motor perception. Guidelines for health supervision for children with Turner syndrome are published by the American Academy of Pediatrics and include pubertal induction, as well as treatment with growth hormone and oxandrolone.

Patients with **45,X/46,XY mosaicism,** can have Turner syndrome, although this form of mosaicism can also be associated with male pseudohermaphroditism, male or female genitalia in association with

Table 81-15 Sex Chromosome Abnormalities

DISORDER	KARYOTYPE	APPROXIMATE INCIDENCE
Klinefelter syndrome	47,XXY 48,XXXY Other (48,XXYY; 49,XXXYY; mosaics)	1/575-1/1,000 males 1/50,000-1/80,000 male births
XYY syndrome	47,XYY	1/800-1,000 males
Other X or Y chromosome abnormalities		1/1,500 males
XX males	46,XX	1/20,000 males
Turner syndrome	45,X Variants and mosaics	1/2,500-1/5,000 females
Trisomy X	47,XXX 48,XXXX and 49,XXXXX	1/1,000 females Rare
Other X chromosome abnormalities		1/3,000 females
XY females	46,XY	1/20,000 females

Table 81-16 Signs Associated with Turner Syndrome

Short stature
Congenital lymphedema
Horseshoe kidneys
Patella dislocation
Increased carrying angle of elbow (cubitus valgus)
Madelung deformity (chondrodysplasia of distal radial epiphysis)
Congenital hip dislocation
Scoliosis
Widespread nipples
Shield chest
Redundant nuchal skin (in utero cystic hygroma)
Low posterior hairline
Coarctation of aorta
Bicuspid aortic valve
Cardiac conduction abnormalities
Hypoplastic left-heart syndrome and other left-heart abnormalities
Gonadal dysgenesis (infertility, primary amenorrhea)
Gonadoblastoma (increased risk if Y chromosome material is present)
Learning disabilities (nonverbal perceptual motor and visuospatial skills) (in 70%)
Developmental delay (in 10%)
Social awkwardness
Hypothyroidism (acquired in 15-30%)
Type 2 diabetes mellitus (insulin resistance)
Strabismus
Cataracts
Red-green color blindness (as in males)
Recurrent otitis media
Sensorineural hearing loss
Inflammatory bowel disease
Celiac disease (increased incidence)

Figure 81-17 Redundant nuchal skin *(A)* and puffiness of the hands *(B)* and feet *(C)* in Turner syndrome. *(From Sybert VP, McCauley E: Turner's syndrome,* N Engl J Med *351:1227–1238, 2004. Copyright © 2004 Massachusetts Medical Society.)*

mixed gonadal dysgenesis, or a normal male phenotype. This variant is estimated to represent approximately 6% of patients with mosaic Turner syndrome. Some of the patients with Turner syndrome phenotype and a Y cell line exhibit masculinization. Phenotypic females with 45,X/46,XY mosaicism have a 15-30% risk of developing **gonadoblastoma.** The risk for the patients with a male phenotype and external testes is not so high, but tumor surveillance is nevertheless recommended. The American Academy of Pediatrics has recommended the use of FISH analysis to look for Y-chromosome mosaicism in all 45,X patients. If Y chromosome material is identified, laparoscopic gonadectomy is recommended.

Noonan syndrome shares many clinical features with Turner syndrome (old name was pseudo-Turner syndrome), although it is an autosomal dominant disorder resulting from mutations in several genes that are involved in the RAS-MAPK (mitogen-activated protein kinase) pathway. The most common of these is *PTPN11* (50%), which encodes a protein-tyrosine phosphatase (SHP-2) on chromosome 12q24.1. Other genes include *SOS1* in 10-13%, *RAF1* in 3-17%, *KRAS* <5%, *BRAF* <2%, and *MAP2K* <2%. Overlapping phenotypes are seen in LEOPARD (lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, deafness) syndrome, cardiofaciocutaneous syndrome, and Costello syndrome; these are Noonan-related disorders. Features common to Noonan syndrome include short stature, low posterior hairline, shield chest, congenital heart disease, and a short or webbed neck (Table 81-17). In contrast to Turner syndrome, Noonan syndrome affects both sexes and has a different pattern of congenital heart disease, typically involving right-sided lesions.

KLINEFELTER SYNDROME

Persons with Klinefelter syndrome are phenotypically male; this syndrome is the most common cause of hypogonadism and infertility in males and the most common sex chromosome aneuploidy in humans (see Chapter 583). Eighty percent of children with Klinefelter syndrome have a male karyotype with an extra chromosome X-47,XXY; the remaining 20% have multiple sex chromosome aneuploidies (48,XXXY; 48,XXYY; 49,XXXXY), mosaicism (46,XY/47,XXY), or structurally abnormal X chromosomes. The greater the aneuploidy, the more severe the mental impairment and dysmorphism. Early studies showed that the birth prevalence is approximately 1 in 1,000 males. The current prevalence of 47,XXY appears to have increased to approximately 1 in 580 liveborn boys; the reasons for this are still unknown. Errors in paternal nondisjunction in meiosis I account for half of the cases.

Puberty occurs at the normal age, but the testes remain small. Patients develop secondary sex characters late; 50% develop gynecomastia. They have taller stature. Because many patients with Klinefelter syndrome are phenotypically normal until puberty, the syndrome often goes undiagnosed until they reach adulthood, when their infertility aids in their clinical identification. Patients with 46,XY/47,XXY have a better prognosis for testicular function. Their intelligence shows variability and ranges from above to below average. Persons with Klinefelter syndrome can show behavioral problems, learning disabilities, and deficits in language. Problems with self-esteem are often the case with adolescents and adults. Substance abuse, depression, and anxiety have been reported in adolescents with Klinefelter syndrome. Those who have higher X chromosome counts show impaired cognition. It has been estimated that each additional X chromosome reduces the IQ by 10-15 points, when comparing these persons with their normal siblings. The main effect is seen in language skills and social domains.

47,XYY

The incidence of 47,XYY is approximately 1 in 800-1,000 males, with many cases remaining undiagnosed, because most affected individuals have a normal appearance and normal fertility. The extra Y is the result of nondisjunction at paternal meiosis II. Those with this abnormality have normal intelligence but are at risk for learning disabilities. Behavioral abnormalities including hyperactive behavior, pervasive developmental disorder, and aggressive behavior have been reported. Early reports that assigned stigmata of criminality to this disorder have long been disproved.

Bibliography is available at Expert Consult.

Table 81-17 Signs Associated with Noonan Syndrome
Short stature
Failure to thrive (use Noonan growth curve)
Tall forehead
Epicanthal folds
Ptosis
Blue-green irises
Hypertelorism
Low nasal bridge, upturned nose
Downward-slanting palpebral fissures
Myopia
Nystagmus
Low-set auricles
Dental malocclusion
Low posterior hairline
Short webbed neck (excessive nuchal skin), cystic hygroma
Shield chest
Pectus carinatum superiorly
Scoliosis
Pigmented villonodular synovitis (polyarticular)
Cubitus valgus
Pulmonary valve stenosis (dysplastic valve)
Hypertrophic cardiomyopathy
Atrial septal defect, ventricular septal defect
Lymphedema
Nevi, lentigines, café-au-lait spots
Cryptorchidism
Small penis
Delayed puberty
Bleeding disorders, including thrombocytopenia and factor deficiencies
Leukemia, myeloproliferative disorders, other malignancies
Cognitive delay (*KRAS* mutation)

81.5 Fragile Chromosome Sites

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Fragile sites are regions of chromosomes that show a tendency for separation, breakage, or attenuation under particular growth conditions. They appear as a gap in the staining. At least 120 chromosomal loci, many of them heritable, have been identified as fragile sites in the human genome (see Table 80-2).

One fragile site that has clinical significance is the one on the distal long arm of chromosome Xq27.3 associated with the **fragile X syndrome.** Fragile X accounts for 3% of males with intellectual disability. There is another fragile site on the X chromosome (FRAXE on Xq28) that has also been implicated in mild intellectual disability. The FRA11B (11q23.3) breakpoints are associated with Jacobsen syndrome (condition caused by deletion of the distal long arm of chromosome 11). Fragile sites can also play a role in tumorigenesis. CGG repeat expansion silences the gene producing fragile X mental retardation protein (FMRP) that regulates the translation of multiple mRNAs to specific proteins, thus affecting synaptic function. FMRP deficiency upregulates the metabotropic glutamate receptor (mGluR) 5 pathway. FMRP deficiency also alters the expression of matrix metalloproteinase (MMP) 9.

The main **clinical manifestations** of fragile X syndrome in affected males are intellectual disability, autistic behavior, macroorchidism, hyperextensible finger joints, and characteristic facial features (Table 81-18). The macroorchidism may not be evident until puberty. The facial features, which include a long face, large ears, and a prominent square jaw, become more obvious with age. Females affected with

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Table 81-18 Clinical Features of Full and Premutation *FMR1* Alleles

Disorder	PHENOTYPE Cognitive or Behavioral	Clinical and Imaging Signs	Onset	Penetrance
FULL MUTATION				
FXS	Developmental delay: mean IQ = 42 in M; IQ is higher if significant residual FMRP is produced (e.g., females and mosaic males or unmethylated full mutations) Autism 20-30% ADHD 80% Anxiety 70-100%	Hypothalamic dysfunction: macroorchidism, 40%* Facial features, 60%,* large cupped ears, elongated face, high arched palate Connective tissue abnormalities: mitral valve prolapse, scoliosis, joint laxity, flat feet Others: seizures (20%), recurrent otitis media (60%), strabismus (8-30%)	Neonate	M 100%
PREMUTATION				
Female reproductive symptoms		POF (<40 yr) Early menopause (<45 yr)	Adult-/child hood	F 20%† F 30%†
FXTAS	Cognitive decline, dementia, apathy, disinhibition, irritability, depression	Gait ataxia, intention tremor, Parkinsonism, neuropathy, autonomic dysfunction	>50 yr	M 33%‡ F unknown
Neurodevelopmental disorder	ADHD, autism, or developmental delay	Mild features of FXS	Childhood	8% (1/13)*

*Frequency of those signs in prepubertal boys; {1/3} of boys with FXS are without classic facial features. Macroorchidism is present in 90% of men.
†Maximum penetrance reported for allele size approximately 80-90 CGG repeats.
‡Penetrance is correlated with age and repeat size.
ADHD, attention-deficit/hyperactivity disorder; F, female; FXS, fragile-X syndrome; M, male; POF, premature ovarian failure.
From Jacquemont S, Hagerman RJ, Hagerman PJ, et al: Fragile-X syndrome and fragile X-associated tremor/ataxia syndrome: two faces of FMRI, Lancet Neurol *6:45–55, 2007, Table 1.*

Table 81-19 Therapy for *FMR1* Related Disorders

DISORDER	SYMPTOM	THERAPY AND INTERVENTIONS	FUTURE POTENTIAL THERAPY
FULL MUTATION			
FXS*	ADHD	Stimulants	mGluR5 antagonists
	Anxiety, hyperarousal, aggressive outbursts	SSRIs, atypical antipsychotics, occupational therapy, behavioral therapy, counseling	mGluR5 antagonists
	Seizures	Carbamazepine, valproic acid	mGluR5 antagonists
	Cognitive deficit	Occupational therapy, speech therapy, special education support	mGluR5 antagonists
PREMUTATION			
POF	Premature ovarian failure	Reproductive counseling, egg donation Hormone replacement therapy	Cryopreservation of ovarian tissue
FXTAS†	Intention tremor	β-Blockers	
	Parkinsonism	Carbidopa/levodopa	
	Cognitive decline, dementia	Acetylcholinesterase inhibitors	
	Anxiety, apathy, disinhibition, irritability, depression	Venlafaxine, SSRIs	
	Neuropathic pain	Gabapentin	

*These data are based on a survey in 2 large referral centers. Drugs for anxiety were more frequently prescribed than those for neurologic signs.
†There have been no controlled studies to assess drugs for FXTAS. These data were collected through a questionnaire study (n = 56).
ADHD, attention-deficit/hyperactivity disorder; FXS, fragile-X syndrome; FXTAS, fragile X-associated tremor/ataxia syndrome; POF, premature ovarian failure; SSRI, selective serotonin reuptake inhibitor.
From Jacquemont S, Hagerman RJ, Hagerman PJ, et al: Fragile-X syndrome and fragile X-associated tremor/ataxia syndrome: two faces of FMRI, Lancet Neurol *2006:45–55, 2007, Table 2.*

fragile X show varying degrees of intellectual disability and/or learning disabilities. Diagnosis of fragile X is possible by DNA testing that shows an expansion of a triplet DNA repeat inside the *FMR1* gene on the X chromosome larger than 200 repeats. The expansion involves an area of the gene that contains a variable number of trinucleotide (CGG) repeats. The larger the triplet repeat expansion, the more significant the intellectual disability. In cases where the expansion is large, females can also manifest different degrees of intellectual disability. Males with premutation triple repeat expansions (50-200 repeats), have been found to have an adult, late onset progressive neurodegenerative disorder known as **fragile X-associated tremor/ataxia syndrome**. Therapy of the diverse neuropsychiatric manifestations associated with fragile X syndrome is noted in Table 81-19. Inhibitors of the mGluR (overexpressed in fragile X) are undergoing clinical trials. In preliminary trials, minocycline (lowers MMP9) has resulted in short term improvements in anxiety, mood, and the clinical Global Impression Scale.

Bibliography is available at Expert Consult.

81.6 Mosaicism

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Mosaicism describes an individual or tissue that contains ≥2 different cell lines typically derived from a single zygote and the result of mitotic nondisjunction (see Fig. 81-1). Study of placental tissue from chorionic

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villus samples collected at or before the 10th wk of gestation has shown that 2% or more of all conceptions are mosaic for a chromosome abnormality. With the exception of chromosomes 13, 18, and 21, complete autosomal trisomies are usually nonviable; the presence of a normal cell line might allow these other trisomic conceptions to survive to term. Depending on the point at which the new cell line arises during early embryogenesis, mosaicism may be present in some tissues but not in others. Germline mosaicism, which refers to the presence of mosaicism in the germ cells of the gonad, may be associated with an increased risk for recurrence of an affected child whether the germ cells are affected with a chromosomal abnormality or specific gene mutation.

PALLISTER-KILLIAN SYNDROME

Pallister-Killian syndrome is characterized by coarse facies (prominent full cheeks), abnormal ear lobes, localized alopecia, pigmentary skin anomalies, diaphragmatic hernia, cardiovascular anomalies, supernumerary nipples, seizures, and profound intellectual disability. The syndrome is due to mosaicism for an isochromosome 12p. The presence of the isochromosome 12p in cells gives 4 functional copies for the short arm of chromosome 12 in the affected cells. The isochromosome 12p is preferentially cultured from fibroblasts that can be readily obtained from a skin punch biopsy and is seldom present in lymphocytes. The abnormalities seen in affected persons probably reflect the presence of abnormal cells during early embryogenesis.

HYPOMELANOSIS OF ITO

Hypomelanosis of Ito is characterized by unilateral or bilateral macular hypo- or hyperpigmented whorls, streaks, and patches (see Chapter 653). Sometimes these pigmentary defects follow the lines of Blaschko. Hair and tooth anomalies are common. Abnormalities of the eyes, musculoskeletal system (growth asymmetry, syndactyly, polydactyly, clinodactyly), and central nervous system (microcephaly, seizures, intellectual disability) may also be present. Patients with hypomelanosis of Ito might have 2 genetically distinct cell lines. The mosaic chromosome anomalies that have been observed involve both autosomes and sex chromosomes and have been demonstrated in about 50% of patients. The mosaicism might not be visible in lymphocyte-derived chromosome studies; it is more likely to be found when chromosomes are analyzed from skin fibroblasts. The distinct cell lines might not always be due to observable chromosomal anomalies but might result from single gene mutations or other mechanisms.

81.7 Chromosome Instability Syndromes

Carlos A. Bacino and Brendan Lee

Chromosome instability syndromes, formerly known as chromosome breakage syndromes, are characterized by an increased risk of malignancy and specific phenotypes. They display autosomal recessive inheritance and have an increased frequency of chromosome breakage and/or rearrangement, either spontaneous or induced. They result from specific defects in DNA repair, cell cycle control, and apoptosis. The resulting chromosomal instability leads to the increased risk of developing neoplasms. The classic chromosome instability syndromes are Fanconi anemia, ataxia telangiectasia, Nijmegen syndrome, ICF (immunodeficiency, centromere instability, and facial anomalies) syndrome, Roberts syndrome, Werner syndrome, and Bloom syndrome.

81.8 Uniparental Disomy and Imprinting

Carlos A. Bacino and Brendan Lee

UNIPARENTAL DISOMY

Uniparental disomy (UPD) occurs when both chromosomes of a pair or areas from 1 chromosome in any individual have been inherited from a single parent. UPD can be of 2 types: uniparental isodisomy or uniparental heterodisomy. **Uniparental isodisomy** means that both chromosomes or chromosomal regions are identical (typically the result of monosomy rescue by duplication). **Uniparental heterodisomy** means that the 2 chromosomes are different members of a pair, both of which were still inherited from 1 parent. This results from a trisomy that is later reduced to disomy, leaving 2 copies from 1 parent. The phenotypical result of UPD varies according to the chromosome involved, the parent who contributed the chromosomes, and whether it is isodisomy or heterodisomy. Three types of phenotypic effects are seen in UPD: those related to imprinted genes (i.e., the absence of a gene that is normally expressed only when inherited from a parent of a specific sex), those related to the uncovering of autosomal recessive disorders, and those related to a vestigial aneuploidy producing mosaicism (see Chapter 80).

In uniparental isodisomy, both chromosomes or regions (and thus the genes) in the pair are identical. This is particularly important when the parent is a carrier of an autosomal recessive disorder. If the offspring of a carrier parent has UPD with isodisomy for a chromosome that carries an abnormal gene, the abnormal gene will be present in 2 copies and the phenotype will be that of the autosomal recessive disorder; the child has an autosomal recessive disorder even though only 1 parent is a carrier of that recessive disorder. It is estimated that all human beings carry approximately 20 abnormal autosomal recessive genes. Some autosomal recessive disorders like spinal muscular atrophy, cystic fibrosis, cartilage-hair hypoplasia, α- and β-thalassemias, and Bloom syndrome have been reported in cases of UPD. The possibility of uniparental isodisomy should also be considered when a person is affected with >1 recessive disorder because the abnormal genes for both disorders could be carried on the same isodisomic chromosome. Uniparental isodisomy is a *rare* cause of recessively inherited disorders. Uniparental isodisomies can also be detected by SNP microarrays.

Maternal UPD involving chromosomes 2, 7, 14, and 15 and **paternal UPD** involving chromosomes 6, 11, 15, and 20 are associated with phenotypic abnormalities of growth and behavior. UPD of maternal chromosome 7 is associated with a phenotype similar to Russell-Silver syndrome with intrauterine growth restriction. These phenotypic effects may be related to imprinting (see under Imprinting, below) (Fig. 81-18).

UPD for chromosome 15 is seen in some cases of Prader-Willi syndrome and Angelman syndrome. In **Prader-Willi syndrome**, approximately 25-29% of cases have maternal UPD (missing the paternal chromosome 15). In **Angelman syndrome**, paternal UPD of chromosome 15 is rarer and is observed in approximately 5% of the cases (missing the maternal chromosome 15). The phenotype for Prader-Willi syndrome (Fig. 81-19) and Angelman syndrome in cases of UPD is thought to result from the lack of the functional contribution from a particular parent of chromosome 15. In Prader-Willi syndrome the paternal contribution is missing, and the maternal contribution is missing in Angelman syndrome. Prader-Willi may be due to paternal deficiency of HB11-85 snoRNAs (small nucleolar RNAs). These findings suggest that there are differences in function of certain regions of chromosome 15, depending on whether it is inherited from the mother or from the father.

UPD most commonly arises when a pregnancy starts off as a **trisomic conception followed by trisomy rescue.** Because most trisomies are lethal, the fetus can only survive if a cell line loses 1 of the extra chromosomes to revert to the disomic state. One-third of the time, the disomic cell line is uniparental. This is the typical mechanism for Prader-Willi syndrome, and it is often associated with advanced maternal age. The embryo starts off as trisomy 15 secondary to maternal meiosis I nondisjunction, followed by random loss of the paternal chromosome. In this case, the disomic cell line becomes the more viable one and outgrows the trisomic cell line. When mosaic trisomy is found at prenatal diagnosis, care should be taken to determine whether UPD has resulted and whether the chromosome involved is one of the disomies known to be associated with phenotypic abnormalities. There must always be concern that some residual cells that are trisomic are present in some tissues, leading to malformations or

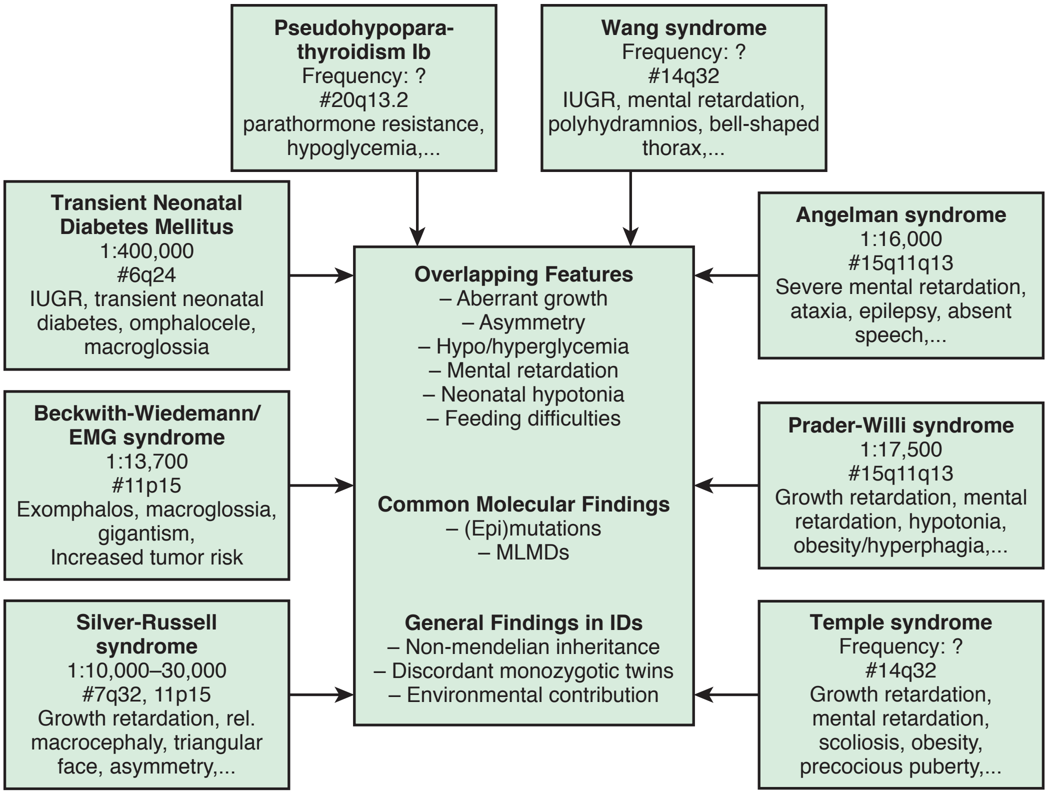

Figure 81-18 Overview of the common clinical and molecular findings in the 8 known imprinting disorders, including specific features, frequencies, and major chromosomal localization. *#6q24*, chromosome 6q24; *EMG*, exomphalos-macroglossia-gigantism; *IUGR*, intrauterine growth restriction. *(From Eggermann T, Elbracht M, Schröder C, et al: Congenital imprinting disorders: a novel mechanism linking seemingly unrelated disorders.* J Pediatr *163:1202-1207, 2013, Fig. 2, p. 1204).*

dysfunction. The presence of aggregates of trisomic cells might account for the spectrum of abnormalities seen in persons with UPD.

IMPRINTING

Traditional genetics has for many years suggested that most genes are equally expressed when inherited from maternal versus paternal lineages. The only exception to this rule were genes on the X chromosome that are subject to inactivation, and the immunoglobulin genes subject to allelic exclusion, a phenomenon that results in monoallelic expression of a particular immunoglobulin chain by switching on and off expression of parental alleles. Genomic imprinting occurs when the phenotypic expression of a gene depends on the parent of origin for certain genes or in some cases entire chromosome regions. Whether the genetic material is expressed or not depends on the sex of the parent from whom it was derived. Genomic imprinting can be suspected in some cases on the basis of a pedigree. In these pedigrees, the disease is always transmitted from 1 sex and could be passed on silently for several generations by the opposite sex (Figs. 81-20 and 81-21). Imprinting probably occurs in many different parts of the human genome and is thought to be particularly important in gene expression related to development, growth, cancer, and even behavior; over 60 genes have been classified as imprintable. Imprinting disorders may arise from UPD, deletions or duplications, epigenetic aberrant methylation patterns, or point mutations in a specific gene.

A classic example of imprinting disorder is seen in Prader-Willi syndrome and Angelman syndrome, 2 very different clinical conditions. These syndromes are usually associated with deletion of the same region in the proximal long arm of chromosome 15. A deletion on the paternally derived chromosome causes Prader-Willi syndrome, in which the maternally derived copy is still intact but some of the imprinted genes within this region normally remain silent. In contrast, a maternal deletion of the same region causes Angelman syndrome, leaving intact the paternal copy that in this case has genes that are also normally silent. In other situations, UPD can lead to the same diagnosis. Maternal UPD for chromosome 15 results in Prader-Willi syndrome due to lack of the paternal chromosome 15 contribution. In contrast, in Angelman syndrome, the UPD is always paternal, with no maternal contribution (Table 81-20). Many other disorders are associated with this type of parent of origin effect, as in some cases of Beckwith-Wiedemann syndrome, Russell-Silver syndrome, and neonatal diabetes.

Table 81-20 Molecular Mechanisms Causing Prader-Willi and Angelman Syndromes

	PRADER-WILLI SYNDROME	ANGELMAN SYNDROME
15q11-q13 deletion	~70% (paternal)	~70% (maternal)
Uniparental disomy	~30% (maternal)	~5% (paternal)
Single-gene mutation	None detected	E6-AP ubiquitin-protein ligase (10% of total but seen only in familial cases)
Imprinting center mutation	5%	5%
Unidentified	<1%	10-15%

Data from Nicholls RD, Knepper JL: Genome organization, function and imprinting in Prader-Willi and Angelman syndromes. Annu Rev Genomics Hum Genet *2:153-175, 2001; and Horsthemke B, Buiting K: Imprinting defects on human chromosome 15.* Cytogenet Genome Res *113:292–299, 2006.*

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Figure 81-19 *A* and *B*, Individual showing morbid obesity with facial features as shown. *C*, Upper extremities are notable for small hands relative to body size. *D*, External genitalia after laparoscopic orchiopexy at 13 mo. Parental informed consent, as approved by the Baylor College of Medicine Institutional Review Board, was obtained to publish the photographs. *(From Sahoo T, del Gaudio D, German JR, et al: Prader-Willi phenotype caused by paternal deficiency for the HBII-85 C/D box small nucleolar RNA cluster,* Nat Genet *40:719–721, 2008.)*

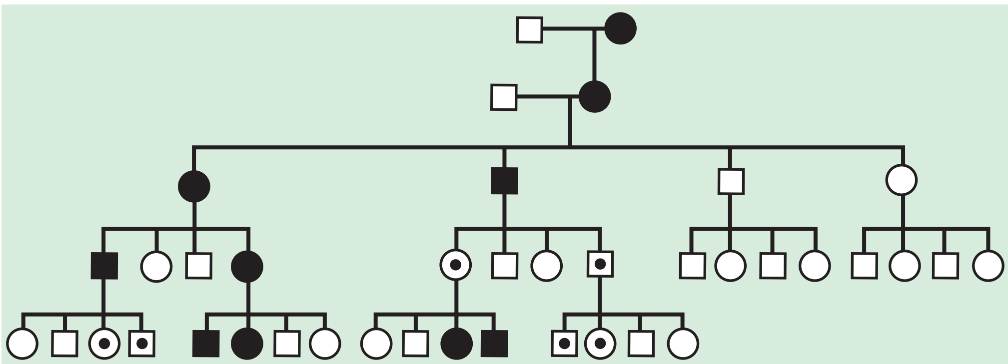

Figure 81-20 **In this hypothetical pedigree suggestive of imprinting, phenotypic effects occur only when the mutated gene is transmitted from the mother, but not when it is transmitted from the father, that is, maternal deficiency.** Equal numbers of males and females can be affected and not affected phenotypically in each generation. A nonmanifesting transmitter gives a clue to the sex of the parent who passes the expressed genetic information; that is, in maternal deficiency disorders (also termed paternal imprinting), there are "skipped" nonmanifesting females. This is theoretical, because in most clinical scenarios of maternal deficiency, such as Angelman syndrome, affected persons do not reproduce.

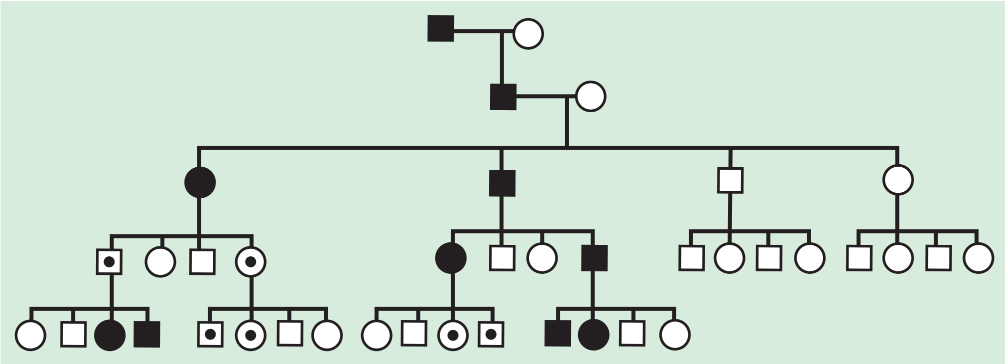

Figure 81-21 **In theoretical pedigrees suggestive of paternal deficiency (maternal imprinting), phenotypic effects occur only when the mutated gene is transmitted from the father, but not when transmitted from the mother.** Equal numbers of males and females can be affected and not affected phenotypically in each generation. In a theoretical situation, a nonmanifesting transmitter gives a clue to the sex of the parent who passes on the expressed genetic information; that is, in paternal deficiency (also known as maternal imprinting), there are "skipped" nonmanifesting males. In real-life clinical instances of Prader-Willi syndrome, affected persons do not reproduce.

Chapter 82

Genetics of Common Disorders

John W. Belmont and Brendan Lee

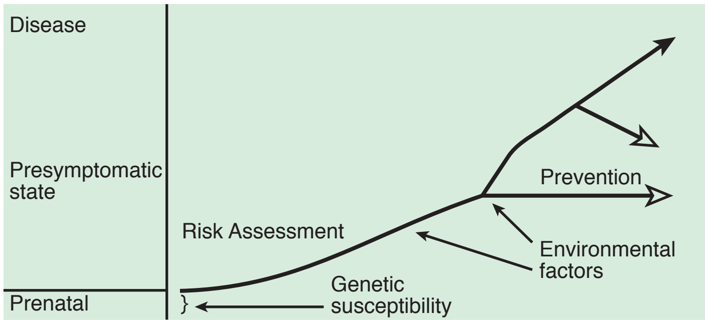

Figure 82-1 Model for the influence of genetics on health. Everyone inherits some genetic liability for disease risk, but for multifactorial disorders this is insufficient to produce disease on its own. Over time, exposure to environmental factors leads from a presymptomatic to a disease state. Identifying the genes responsible for risk can lead to prevention strategies or treatments.

Genetic studies are useful in diagnosing and treating rare pediatric conditions, often alleviating suffering, extending life, and, in the case of neonatal metabolic and presymptomatic screening, preventing injury before symptoms develop. Genetic studies can also contribute to the understanding of more common diseases, such as asthma and diabetes. An understanding of the complex and potentially multiple pathways leading to disease is crucial for the development of new therapies and prevention strategies.

Common pediatric diseases are often multifactorial, and the combination of many genes and environmental factors triggers a complex sequence of events leading to disease. Each individual has variations in his or her set of genes; the cumulative effect of the individual's gene variants with each other and with the environment influence susceptibility to disease, response to various medications, and susceptibility to specific drug toxicities. The complexity of the combination of contributing factors increases the challenge of finding genetic variants that cause disease. Genetic tools include the completed human genome sequence, public databases of genetic variants, and the human haplotype map. In addition to public genetic databases, dramatic reduction in the cost of genotyping and DNA sequencing has allowed very large numbers of genetic variants to be efficiently tested in large numbers of patients. Most of these studies focus on common variants (those with frequencies >5%). New technologies for DNA sequencing are already allowing whole exome sequencing in many individuals at very low cost. This technology is being used to investigate the role of rare coding sequence variants in common diseases. The incorporation of these tools into large, well-designed population studies is the field of **genetic epidemiology.** Many new methods for analyzing genetic data have been developed, stimulating a renaissance in applied population genetics. So far, these methods of investigation have been used less extensively in pediatric diseases than in adult-onset conditions. This is a consequence of the relative lack of large-scale DNA sample sets for many common diseases of children.

We can now project that in the near future it will become routine to carry out "genomic profiling" by one technique or another for individual children. These methods will find clinical utility in decision algorithms for disease screening and initiation of treatment, drug selection, and targeted preventive strategies. The results will be of an unprecedented complexity, so that physicians and parents will increasingly rely on the coupling of genetic data to clinical decision support tools linked to the electronic health record.

82.1 Major Genetic Approaches to the Study of Common Pediatric Disorders

John W. Belmont and Brendan Lee

Figure 82-1 shows a model for the genetic contribution to health. Genetic variation that can have an impact on disease susceptibility is present in every person. Sometimes single-gene mutations cause a condition, as is the case for cystic fibrosis or sickle cell anemia. But other kinds of genetic variations can contribute much less strongly to the emergence of specific medical conditions, and the effect can depend upon exposure to certain environmental factors. One goal in medical genetics is to identify genes that contribute to disease in the hope of preventing the occurrence of disease, either by avoiding inciting environmental factors or by instituting interventions that reduce risk. For persons who cross the threshold of disease, the goal is to better understand the pathogenesis in the hope that this will suggest better approaches to treatment. Common genetic variation can also influence response to medications and the risk of toxicities of various medications and environmental toxins.

Complex traits may be inherently difficult to study if there are problems with the precision of clinical diagnosis. This is particularly true of neurobehavioral traits. A starting point in the genetic analysis of a complex trait is to obtain evidence in support of a genetic contribution and to estimate the relative strength of genetic and environmental factors. Complex traits typically exhibit familial clustering, but are not transmitted in a regular pattern like autosomal dominant or recessive inheritance. Complex traits often show variation among different ethnic or racial groups, possibly reflecting the differences in gene variants among these groups.

Assessing the potential genetic contribution begins by determining whether the trait is seen among related individuals more often than in the general population. A common measure of **familiality** is the first-degree relative risk (usually designated by the symbol λ_s), which is equal to the ratio of the prevalence rate in siblings and/or parents to the prevalence rate in the general population. For example, the λ_s for type 1 diabetes is about 15. The relative strength of genetic and nongenetic risk factors can be estimated by variance components analysis, and the **heritability** of a trait is the estimate of the fraction of the total variance contributed by genetic factors (Fig. 82-2).

It is not uncommon for a minority of cases of common diseases like diabetes to be caused by single-gene mutations (mendelian inheritance), chromosomal disorders, and other genomic disorders. These less-common causes of the disease can often provide important insight into the most important molecular pathways involved. Chromosomal regions with genes that might contribute to disease susceptibility could theoretically be located with **linkage mapping,** which locates regions of DNA that are inherited in families with the specific disease. But practically, this has turned out to be quite difficult for most complex traits either because of a dearth of families or because the effect of individual genetic loci is weak.

Phenotypic variance		Genetic variance		Environmental variance		Measurement variance
V_P	=	V_G	+	V_E	+	V_M

$$h^2 = V_G / V_P$$

Heritability

Figure 82-2 Heritability concept. The phenotypic variance of a particular trait can be partitioned between the contributions of the genetic variance, the environmental variance, and the measurement variance. This is usually empirically determined. Heritability is defined by the proportion of the phenotypic variance that is accounted for by the genetic variance. One can estimate the heritability from correlation of a quantitative trait between relatives.

Genetic **association studies** are more powerful in identifying common gene variants (>5% in the population) that confer increased risk of disease, but they fail if the disease-causing gene variants are relatively rare. Detection of the modest effect of each variant and interactions with environmental factors requires well-powered studies that often include thousands of subjects. A number of parallel approaches for analyzing the aggregate effects of rare variants in genes have also been developed. Such rare variant association methods also seem to require large sample sizes because the gene effects have also proven to be relatively weak.

Linkage mapping and association studies require markers along the DNA that can be ascertained, or **genotyped,** with large-scale, high-throughput laboratory techniques. Markers that are typically used are in the forms of microsatellites and **single-nucleotide polymorphisms** (SNPs; Fig. 82-3). Although humans all have the same genetic material, each person's genome is slightly different. A sample of the same region of genome from 50 people will reveal that approximately 1 in every 200 bases varies from the more common form. Although most SNPs lack any obvious function, a few alter the amino acid sequence of the protein or affect regulation of gene expression. Some of these functional alterations directly affect susceptibility to disease. A complex clinical **phenotype** can be defined by the presence or absence of a disease as a **dichotomous trait**, or by selection of a clinically meaningful variable such as serum glucose in type 2 diabetes, which is a continuous or **quantitative trait**.

Although it might not be possible to define subgroups of patients in advance based on common disease mechanisms, the more uniform the phenotype, the more likely that a genetic study will be successful. **Locus heterogeneity** refers to the situation in which a trait results from the independent action of more than 1 gene. **Allelic heterogeneity** indicates that more than 1 variant in a particular gene can contribute to disease risk. The development of a trait or disease from a nongenetic mechanism results in a **phenocopy**. These 3 factors often contribute to the difficulty in identifying individual disease susceptibility genes because they reduce the effective size of the study population.

A person bearing any variant or **allele** (inherited unit, DNA segment, or chromosome) in a gene has a certain probability of being affected with a specific gene variant-associated disease. This is called the

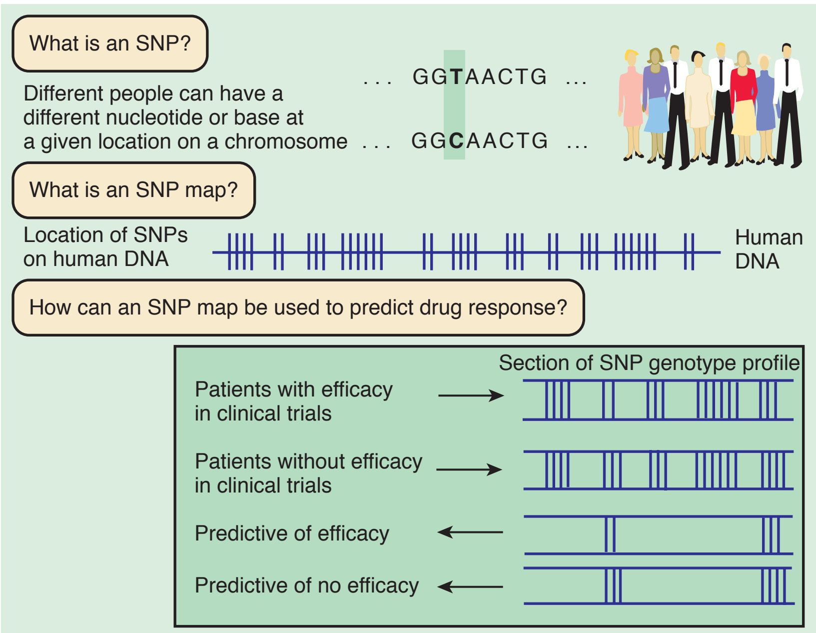

Figure 82-3 Different combinations of SNPs are found in different individuals. The locations of these SNPs can be pinpointed on maps of human genes. Subsequently, they can be used to create profiles that are associated with difference in response to a drug, such as efficacy and nonefficacy. *(Adapted from Roses A: Pharmacogenetics and the practice of medicine,* Nature *405:857-865, 2000. Copyright 2000. Reprinted by permission of Macmillan Publishers Ltd.)*

penetrance. Some diseases manifest signs only later in life (age-related penetrance), which could lead to misclassifying children who actually have the disease-producing gene as unaffected. Single-gene disorders are typically caused by mutations with relatively high penetrance, but some common variants have very low penetrance because their overall contribution to the disease is small. Many such common variants can contribute to disease risk for a complex trait. For example, normal human height is influenced by more than 400 genes.

Ideally, important environmental exposures should be measured and accounted for in a population because there may be a dependent interaction between the environmental factor and specific genetic variant. An example is the likely requirement for a viral infection preceding onset of type 1 diabetes. Although **gene X environment interactions** are strongly suspected to play an important role in common diseases, it is difficult to identify and measure them. Very large studies with uniform collection of information about environmental exposures are rare. New methods, such as genome-wide analysis of DNA methylation, may show evidence of environmental effects—so-called **developmental programming**. This information might be used to discover and validate gene-environment interactions.

LINKAGE MAPPING

Linkage studies were used in the past to isolate genes that cause rare genetic syndromes; modified methods have been used to identify chromosomal regions linked to more common diseases. Linkage studies involve tagging segments of a person's genome with markers that allow identification of segments that have been inherited through the family along with disease. The markers are typically **microsatellites** or **SNPs** that define and help to distinguish which type of an allele any person carries. The type of an allele is referred to as a **genotype.** Linkage analyses of common diseases have shown inconsistent results. Factors such as heterogeneity, pleiotropy, variable expressivity, and reduced penetrance, in addition to variability in environmental exposures, weaken the power of linkage studies in complex traits.

GENETIC ASSOCIATION

For multifactorial common diseases, association analyses may be used to identify causally important genes. There are two types of association study: **direct association,** in which the causal variant itself is tested to see whether its presence correlates with disease, and **indirect association,** in which markers that are physically close to the biologically important variant are used as proxies. The correlation of markers with other genetic variants in a small region of the genome is called **linkage disequilibrium**. Indirect association is enabled by the construction of a detailed genetic map in 3 reference populations (Europeans, Asians, West Africans) through the International HapMap Project. SNPs that tag most of the genome have been identified and can be genotyped at low cost using specially designed microarrays.

Three basic study designs are used for association testing: a case-control design, in which the frequency of an allele in the affected group is compared with the unaffected group; a family-based control design, in which parents or siblings of an affected individual are used as the controls; and a cohort design, in which large numbers of subjects are ascertained and then followed for the onset of any number of diseases. The cohort analysis is very expensive and there are few true cohort studies.

Family-based control study designs are somewhat attractive for pediatric diseases because it is usually possible to enroll parents. These studies solve a major problem in testing for association because the parents are perfectly matched for genetic background. When parents are collected, the statistical test used for these studies is called the **transmission disequilibrium test** (TDT). TDT compares the transmitted genotype with the inferred nontransmitted genotype. The success of all association analysis depends on the design of a well-powered study, with enough subjects, and an accurately measured trait to avoid phenotypical misclassification. In large, population-based studies, confounding by ethnicity or **population stratification** could distort results. Some genetic variants are more common in people from a particular ethnic group, which could cause an apparent association of a variant with a disease, when the disease rate happens to be higher in that group. This association would not be a true association between an allele and a disease, because the association would be confounded by genetic background. The family-based tests using the TDT are immune to population stratification. However, TDT and related study designs are inherently less efficient than case-control studies. Newer methods for measuring subtle mismatching between cases and controls using many thousands of markers routinely genotyped in genome-wide association studies allow this effect to be accounted for.

Association studies should be a powerful tool to find genetic variation that confers risk to an individual; the effect of any one genetic variant will be a very small contribution to the complex disease pathway. Genetic variants have been found that implicate a novel gene in a process, motivating more in-depth research into systems that will affect disease outcome. Associations such as the *ApoE4* variant with an increased risk of Alzheimer disease are noted by many studies. Many published association results are not reproducible; insufficient power and stratification might account for the inconsistencies. As of early 2014, more than 6000 disease associations for more than 600 medically important traits have been discovered and replicated in large studies.

New low-cost methods for sequencing the complete exomes and genomes of individuals will soon allow a more comprehensive evaluation of the full range of genetic variants involved in common diseases. The goal of the $1000 genome once seemed distant but may be achieved very soon. Rare genetic variants, including small insertions or deletions, could turn out to be extremely important in explaining the impact of genetic factors in important pediatric diseases such as autism, cardiovascular malformations, and other birth defects. Common traits such as obesity, diabetes, and autoimmune diseases might also be affected by rare variants. In common severe disorders like intellectual disability and complex heart malformations, de novo mutations (i.e., mutations not present in either parent) are likely to play an important role.

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Chapter 83

Genetic Approaches to Rare and Undiagnosed Diseases

William A. Gahl, David R. Adams, Thomas C. Markello, Neal F. Boerkoel, and Cynthia J. Tifft

Rare and novel disorders often present in childhood and represent a diagnostic challenge that can be addressed using advanced genetic techniques.

SCOPE OF GENETIC DISEASE

An estimated 7000 rare disorders are recognized, and the existence of approximately 23,000 human genes suggests that many more genetic diseases will be discovered in the future. These genetic diseases comprise a set of maladies amenable to a variety of diagnostic approaches. Knowledge about the human genome creates a new opportunity to diagnose extremely rare disorders and discover new diseases. One

approach was taken by the National Institutes of Health (NIH) Undiagnosed Diseases Program (UDP).

Potential reasons patients may remain undiagnosed despite intensive prior investigation include:

- The genetic mutation had not previously been associated with the disease phenotype
- There is allelic heterogeneity (same gene but different mutation producing a different phenotype)
- There is locus heterogeneity (different genes producing similar phenotype)
- Presentation of monosymptomology or unusual features of a polysymptomatic or rare disease

The 3,000 patient applications to the UDP have involved collaboration between the referring healthcare team and the NIH group. Prior investigations are recounted in a summary letter from the referring clinician and documented with medical records that include photos, videos, imaging and histologic slides of biopsy material. Specialty consultants review the records and the UDP directors determine the next steps. The patients who are accepted come to the Clinical Center for a week-long inpatient admission. Approximately half of the patients with undiagnosed diseases have neurological disease; cardiovascular, rheumatology, immunology, and pulmonary problems are also frequent. Approximately 40% of accepted patients are children, among whom unknown multiple congenital anomalies and neurologic disorders are common.

CLINICAL EVALUATION

The term undiagnosed refers to patients who remain without a definitive diagnosis after an extensive workup. This occurs in part because every individual has a unique genetic and environmental background, and diseases express themselves in an unlimited number of ways. Undiagnosed conditions include those that have never been seen by the diagnostician, unusual presentations of otherwise recognizable conditions, and combinations of conditions that obfuscate each other's identities. A thorough clinical investigation allows the clinician to broaden the differential diagnosis through research, consultation, clinical testing and consideration of atypical presentations of previously known diseases. Extensive phenotyping, imaging, and other tests provide better documentation of the presentation and make the case available for association with future newly discovered diseases, genetic variants, and patient cohorts.

A complete history anchors the data, and includes prenatal and neonatal findings, developmental milestones, growth pattern, onset and progression of symptoms and signs, precipitating influences, response to medications, and a pedigree to determine which family members are affected. Pertinent physical findings include dysmorphisms, organomegaly, neurologic impairment, bone involvement, and dermatologic findings. Because many rare and novel disorders are multisystemic, consultants play a critical role in every diagnostic evaluation. Typical studies performed to address possible diagnoses are listed in Table 83-1. The evaluation of a pediatric neurology case involves even more extensive studies (Table 83-2).

An inpatient admission allows for close interaction among experts in different fields, informs the workup of complex cases, and often leads to a focus on the discovery of a new disease. In that situation, other family members need to be evaluated to definitively ascertain whether they are affected with the disorder under consideration.

AVAILABLE COMMERCIAL LABORATORY GENETIC STUDIES

Once phenotyping is complete, a differential list of genetic disorders can be compiled. Laboratory molecular testing is available for an increasingly large spectrum of molecular disorders. In many cases, several related diseases are included in a panel of molecular tests. Examples include X-linked cognitive impairment, hereditary spastic paraplegia, spastic paraplegia and gait, spinocerebellar ataxias, dystonias, and mitochondrial disorders. Some of these individual tests and panels are expensive, and added together they may exceed the cost of exome sequencing.

Table 83-1 Initial Studies to Generate New Diagnostic Hypotheses

TEST(S)	RELATED DISORDERS/ DISORDER GROUPS
Electrolytes, lactate, pyruvate	Energy metabolism defects, including mitochondrial disorders
Plasma amino acids	Renal disorders, amino acid disorders
Urine organic acids	Renal disorders, organic acid disorders, energy metabolism disorders, vitamin deficiencies
Aldolase, creatine phosphokinase	Muscle disorders
Carnitine (free, total, acyl, panel)	Fatty acid oxidation disorders, carnitine metabolism disorders
Cerebrospinal fluid (CSF) analysis	Neurotransmitter disorders, inborn errors of metabolism, select disorders that may present only in the CSF
Brain MRI/magnetic resonance spectroscopy	Structural clues to disorders affecting central nervous system
Mass spectrometry to detect *N*- and *O*-linked proteoglycan abnormalities	Congenital disorders of glycosylation
Lysosomal enzyme testing	Lysosomal storage diseases
White cell and skin electron microscopy	Lysosomal storage diseases; neuronal lipofuscinoses
Pathologic evaluation of affected tissues with special stains, DNA hybridization	Any
Echo-/electrocardiogram	Cardiac defects
Nerve conduction velocity/ electromyogram	Neurologic defects
Fibroblast cell line	Any
Single-nucleotide polymorphism/exome/ genome/karyotype	Any
Erythrocyte sedimentation rate, C-reactive protein	Inflammatory disorders

SINGLE-NUCLEOTIDE POLYMORPHISM ARRAYS

There are 2 technologies that are cost-effective for medical uses and can examine the entire genome with resolution at the level of a single base pair. These are single-nucleotide polymorphism (SNP) arrays (microarrays or chips) and next-generation sequencing. The human genome's 3.2 billion bases include many that are polymorphic. Polymorphisms are bases that are not the usual one at a defined position and yet occur with a frequency of >1% within a given population. For any 2 individuals who are not closely related, there are approximately 2.5×10^6 SNPs that vary between them (and between each individual and the canonical human reference), or about 1 polymorphism for every 1,000 bases in the genome on average. Within a single ethnic population there is about 1 common SNP per 3,000-7,000 bases, where common means a greater than 10% chance that any 1 patient will be polymorphic (heterozygous) at that position. A few hundred thousand to a few million of these common SNPs can be included on a DNA hybridization array and examined simultaneously in a single laboratory test. This technique produces genome-wide results that reveal copy number variations; mosaicism is also revealed, as are regions of

Table 83-2 Diagnostic Evaluation of the Neurologically Impaired Child

CONSULTATIONS
Genetics/genetic counseling
Neurology
Endocrinology
Immunology
Rheumatology
Dermatology
Cardiology
Neuropsychology
Nutrition
Rehabilitative medicine
  Physical therapy
  Occupational therapy
  Speech therapy
	ADDITIONAL TESTING IF CLINICALLY INDICATED
	Electron microscopy of white blood cell buffy coat for inclusion bodies
	Electron microscopy of skin biopsy for evidence of storage
	Stool for ova and parasites, occult blood, fecal fat, or fecal calprotectin
	Autoimmune antibodies
	Vaccine response titers
	C3/C4
	Quantitative immunoglobulins
	T-cell subsets
	Conjunctival or salivary gland biopsy

PROCEDURES Swallow study for aspiration Abdominal ultrasound (hepatosplenomegaly) Skeletal survey (dysostosis) Bone density scan (nonambulatory or growth-failure patients) Bone age Electroencephalogram Muscle biopsy for electron transport chain function and histology Nerve biopsy	**RESEARCH SPECIMENS** Cerebrospinal fluid Serum Plasma Skin biopsy for fibroblasts and/or melanocytes Isolated DNA/RNA Urine
LABORATORY EVALUATIONS Complete blood count with differential and peripheral smear Comprehensive metabolic panel Prothrombin time/partial thromboplastin time (for anesthesia sedation) Thyroid-stimulating hormone, thyroxine Vitamins A, E, 1,25-dihydroxyvitamin D Lactate/pyruvate Ammonia Amino acids (plasma and urine) Organic acids (urine) Acylcarnitine profile Total and free carnitine Lysosomal enzyme analysis in leukocytes and/or fibroblasts White blood cell coenzyme Q Purines and pyrimidines (urine) α-Glucosidase (plasma and urine) Peroxisomal panel Oxysterols Methylmalonic acid and homocystine (plasma) Copper/ceruloplasmin Vitamins A and E Transferrin isoelectric focusing *N*- and *O*-glycans (plasma) Oligosaccharides and free glycans (urine) Glycosaminoglycans (urine)	**STUDIES UNDER SEDATION** 3T MRI/magnetic resonance spectroscopy of brain (and spine if indicated) Skin biopsy Ophthalmologic exam Brainstem auditory evoked response Electroretinogram Lumbar puncture for biopterin, neopterin, neurotransmitters, folate, and inflammatory markers Dental exam Large blood draws Catheterization for urine Any part of the physical exam difficult to do in an awake child, including dysmorphology measurements and genital and rectal exam Electromyography and nerve conduction studies

identity by descent. These results are very useful in complementing the next-generation sequencing results. One example of this is the use of the SNP deletion regions to denote where to look for a point mutation in the next-generation sequence of the child (to detect the compound heterozygous recessive pairing of a deletion with a point mutation).

EXOME SEQUENCING

Technical advances have allowed for massive DNA sequencing at a reasonable price, making it feasible to determine the sequence of the coding regions of almost all of the human genes. Because this involves 1.7% of the 3.2 billion bases in the human genome, **exome sequences** comprise approximately 60,000,000 bases. These satisfactorily cover 80-85% of the known genes, and are determined by sequencing short "reads" (DNA fragments) and aligning them to a composite reference sequence of the human genome. In part because of SNP interference with hybridization, ambiguities in alignment, and chemistry error rates, the average exome has about 20,000 bases (0.03%) that differ from the "reference" sequence and from any other single, unrelated human sequence of the same ethnic group. Most of these variants are inconsequential polymorphisms. The problem is that each of the 20,000 variants of unknown significance is a **potential** disease-causing variant, yet only 1 is ***the*** disease-causing mutation for a monogenic disorder (with perhaps 2 or 3 additional loci modifying severity). The task of the clinician is to reduce the credible variants from 20,000 to a manageable number, such as 5.

This process involves using "filters," or programs that eliminate false-positive variants without eliminating the true variants. The single best filter uses the exome sequencing (ES) of nuclear family members (i.e., parents and siblings), but only if their true affected or unaffected status is certain. If, for example, an unaffected sibling's gene has 2 variants on opposite alleles that are the same as those of the affected proband, then those variants can be eliminated as causing the proband's disease. This emphasizes the importance of collecting family DNA and obtaining a very careful evaluation of family members. In general, having the proband, both parents and a sibling provides sufficient power to reduce the candidate variants to a reasonable number for all mendelian inheritance models, assuming complete penetrance.

As an example, if autosomal recessive inheritance is postulated, then the ES analysis should require mutations on both alleles of the proband, with 1 of the 2 mutations present in 1 parent and the other

mutation present in the other parent. Affected sibs must have both mutations, and unaffected sibs must have either 1 or none. Software programs have succeeded using a homozygous recessive model, and for significantly deleterious variants, using a compound heterozygous recessive model.

Base changes that result in amino acid changes (missense mutations) are evaluated by programs that gauge the pathogenicity of the change. This involves estimates of how tightly the base is conserved over evolution, whether the amino acid changes charge, size, or conformation, and, sometimes, where in the protein the amino acid change resides. Analyzing how changes in the genetic code influence protein function remains an inexact science, but approximations have been used with some success. Software programs, including PolyPhen-2, SIFT, and MutationTaster, rate the pathogenicity of amino acid changes. In addition, evolutionary consistency of a base can be evidence of deleteriousness of a change in that base, even if it is not involved in an amino acid change (promoter binding domains, methylation sites). Finally, some filters compare variants to databases that list changes considered to be benign (database of single-nucleotide polymorphisms), known to cause diseases other than those under investigation, or simply found frequently in many random genomes (1000 Genomes). These databases can be very helpful, but they are not entirely reliable because their entries have not been curated in all cases to a medically useful level of confidence.

The analysis of exome sequences is advancing rapidly, based upon the development of new filters and larger, better, and more informative databases. However, several key points need to be considered when employing genome-scale sequencing for clinical diagnostics.

Positive predictive value gives the likelihood that a positive test is a true positive. This is higher in a population in which a disease is frequent and lower in a population where the disease is rare. A person being tested with ES will show no clinical signs or symptoms of most of the genetic diseases for which the ES tests. Therefore, many apparently positive findings will be false positives. This manifests as the frequent occurrence of DNA variations in genes that are associated with phenotypes that do not match the person being tested. Such variants are difficult to interpret.

Individual versus family studies are relevant, as family data allow for variants to be substantially filtered. This advantage must be weighed against the financial costs of studying families versus individuals. Furthermore, family studies are useless if an affected person is called unaffected or *vice versa*. *Therefore, phenotyping family members is critical*. For later-onset conditions, younger siblings may not be suitable for inclusion in an exome study unless their affected status can be determined unambiguously.

Data revisiting policies must be addressed. Genome-scale sequencing generates data for many genes beside those involved in the current diagnostic effort. The sequencing data are of potential use in the future care of the patient. Even though some mutated genes are not reported because they are not currently associated with any medical condition, future advances may implicate such a gene in a human disease. The person ordering the exome study should be aware of the data reuse policy of the testing facility. In the current testing environment, time-limited data reuse and/or reuse fees are increasingly common.

Early discussion with a genetic specialist is critical. Genetic counseling should be sought before an exome study is sent rather than after the results become available. Proper consent for exome studies is an involved process, including information about disease risk factors, unrelated medical conditions, carrier states and cancer susceptibility. Consented individuals should be given the opportunity to consider which types of results they would like to have returned.

Anticipating findings that are difficult to use clinically is an important part of counseling. The problem of variants of unknown significance is well known for any type of genetic testing. Genome-scale sequencing amplifies this problem to include a wide variety of results that are difficult to use for medical decision making. Depending on the breadth of analysis and the resulting clinical report, different numbers of such findings will be returned to the ordering physician. Discussing such variants with families can be difficult; counseling families about the likelihood of receiving this type of result before testing is performed can help the family to cope when the report is returned (see Chapter 77).

When used as a gene panel, ES rules *in* but does not rule *out*. An exome study is a cost-effective way to test many genes at one time. However, there can be variation in coverage of any given exon among exome datasets. Therefore, even though exome studies are a powerful tool for variant discovery, they are not always sufficient to exclude variants in a panel of genes. With careful analysis involving laboratory validation on many similarly processed individuals, the exome coverage of any given gene can be assessed. However, commercial/clinical testing facilities may be unwilling to perform such an analysis when a large set of genes needs to be considered. Therefore, there is still a role for the use of a gene panel when the index of suspicion is high for a disorder caused by 1 of a large group of genes. Cerebellar ataxia and hereditary spastic paraparesis are examples.

Providing information to the testing facility improves the chances of a diagnosis. ES interpretation will benefit substantially from the incorporation of accurate and detailed clinical information about the presenting phenotype. The more clinical information that is provided to the testing lab, the more specific and useful the clinical report will be.

GENE FUNCTION STUDIES

Despite filtering for frequency and predicted deleteriousness, a variant identified by genomic sequencing cannot be interpreted as the cause of an individual's disease unless it has been previously demonstrated to cause a disease with a similar phenotype. To prove causality, medical genetics relies upon association (the recurrence of mutations within a gene among individuals with a similar phenotype). For rare diseases, there may be too few affected patients to demonstrate a statistically-significant association. In this setting, other evidence will be required to connect a specific genetic variant with an isolated phenotype. One approach is to accumulate additional diagnostic data about the patient that can be used to prioritize genetic variants (phenotype ontologies, metabolomics, glycomics, proteomics, and lipidomics). A second approach is to develop models that recapitulate the disease in question, such as mice, zebrafish, fruit flies, yeast, and cultured cells. Third, the variant in question can be linked to a biologic process or pathway that is known to cause a similar phenotype when disturbed. Finally, standardized and correlated phenotypic and genomic data are deposited into a database to identify other individuals with a similar phenotype and mutations in the same gene.

Physicians may apply their past biases to a group of variants that could be disease causing, but this is often misleading. A standardized computational approach would be preferable. For example, the Human Phenotype Ontology will standardize the description of a disease and, because the descriptors have been mapped to other human diseases and to mutant model organisms, will identify possible candidate genes and genetic networks for causing the disease. Similarly, untargeted laboratory screening tests provide an unbiased survey of patient cellular biology and physiology and a more informed prioritization of variants causing the patient's disease.

The ultimate proof of causality is to ameliorate the disease process by correcting the genetic defect, and this can sometimes be demonstrated in a model system that recapitulates the human disease. If model systems fail to identify the genetic cause of an individual's disease, one must search for other patients with a similar phenotype and mutations in the same gene. This can be accomplished using public databases that are interpreted using strict statistical and biologic standards.

PEDIATRIC ISSUES

During its first 4 yr, the UDP at NIH received 500 pediatric applications. In >10% of cases, more than 1 family member, usually a sibling, was similarly affected. There were 2 peaks in the age distribution of the children: 1 at 4-5 yr, reflecting patients with congenital disorders, and 1 at 16-18 yr representing disorders with symptom onset at early school age. The majority of applicants had been on a diagnostic odyssey for more than 5 yr. Of the 200 pediatric cases accepted, 175 were

evaluated to date and 25% received a diagnosis. Of the diagnoses, half were obtained using conventional diagnostic methods, including clinical suspicion with molecular confirmation, biochemical testing with molecular confirmation, or radiographic interpretation. In the remainder of cases the diagnosis was arrived at using SNP analysis and next-generation sequencing; all of these were rare diseases.

Pediatric medical records require attention to what has and what has not been completed previously. The electronic medical record is an important tool for medical practice, but *copy forward* functions can perpetuate errors, such as reports of normal testing when in fact the test was recommended or ordered but cancelled. Repetitive copying also fosters sloppiness in critical thinking, failure to take an adequate history, and missing the nuances of symptom progression. *A history and physical examination should be performed anew and all prior testing results confirmed via copies of original laboratory reports.*

Prolonged and painful procedures should be performed under sedation, but the risks associated with sedation must be weighed against the value of the information and samples to be obtained (see Table 83-2).

CONSIDERATIONS FOR FAMILIES OF UNDIAGNOSED CHILDREN

When a child comes to a genetics clinic for evaluation the parents want to know:

- What does my child have? (diagnosis)
- Why did it happen? (etiology/inheritance)
- What will happen in the future? (natural history)
- Is there a treatment? (therapy)
- Could the same thing happen to other family members? (recurrence risk)

The answers to all of these questions require an accurate diagnosis. The lack of a diagnosis also makes both the family and the physician uncomfortable, raises suspicion among relatives and acquaintances, and creates feelings of guilt about not having worked hard enough to find a diagnosis. As a consequence, families consult more and more specialists, and are often frustrated with the lack of coordination among providers. It is helpful for the family to save copies of every test and every visit from each institution and compile them in a binder for travel among institutions. A 2-3 page narrative summarizing the child's history, medications, list of healthcare providers with contact information, main medical issues, level of functioning on well days and sick days, and interventions that worked in the past, can be invaluable in an emergency room setting. An electronic copy is easily updated. Parents can always be the best advocates for their child, particularly an undiagnosed child.

Recommendations to parents of an undiagnosed child are similar to those that apply to any child with chronic illness:

- Keep copies of all records, electronic and otherwise, and organize them routinely, especially copies of original reports from "send-out" labs.
- Carry an updated emergency letter.
- Establish a medical home even if you obtain many second opinions.
- Find a physiatrist (rehabilitation medicine physician) to coordinate rehabilitative care.
- Be aggressive with the school system about services using, a legal advocate if necessary.
- Explore parent support groups for unknown disorders (Syndromes Without a Name, National Organization for Rare Disorders).
- Periodically check with providers (especially geneticists) for new diagnoses reported in the medical literature.
- Carve out time for yourselves as caregivers by engaging extended family members or respite care services.
- Work at supporting and being attentive to well children in the family.
- For the very sick dying child, consider an autopsy as a final attempt to establish a diagnosis especially when there is a possibility of future pregnancies.

THE DIAGNOSTIC SPECTRUM

The extent of determining the diagnosis varies considerably, from that of recognizing a clinical entity, to a largely molecular diagnosis, or to one in which the entire pathogenesis is known. In addition to known disorders, SNP and ES analyses may also identify variants in genes that are candidates for causing a new disease.

One example of a diagnosis involves 2 brothers whose parents were first cousins. The brothers had an early-onset spastic ataxia-neuropathy syndrome, with lower-extremity spasticity, peripheral neuropathy, ptosis, oculomotor apraxia, dystonia, cerebellar atrophy, and progressive myoclonic epilepsy. A homozygous missense mutation (c.1847G>A; p.Y616C) in *AFG3L2*, which encodes a subunit of a mitochondrial protease, was identified by ES. The AFG3L2 protein can bind to another AFG3L2 molecule or to paraplegin. UDP collaborators in Germany used a yeast model system to demonstrate that the patients' mutation affects the specific amino acid involved in the formation of both of these complexes. As a result, the brothers exhibited the signs and symptoms of a known AFG3L2 defect, autosomal dominant spinocerebellar ataxia type 28 (SCA28), and a known paraplegin defect, hereditary spastic paraplegia type 7 (SPG7). Other features of a mitochondrial disorder (oculomotor apraxia, extrapyramidal dysfunction, myoclonic epilepsy) were also present. The 2 brothers represent the first such cases in the world, and expand the phenotype of AFG3L2 disease.

A second example involves 2 siblings ages 5 and 10 yr with hypotonia, developmental delays, facial dysmorphisms, hearing loss, nystagmus, seizures, and atrophy on brain MRI. In this case, the leading clue was biochemical in nature, and genetic analysis confirmed the diagnosis. Urine thin-layer chromatography for oligosaccharides identified a strong band determined by mass spectrometry to consist of a tetrasaccharide containing 3 glucoses and one mannose. This suggested a defect of glucosidase I, the first enzyme involved in endoplasmic reticulum trimming of *N*-linked glycoproteins from a high-mannose to a complex form. Mutation analysis confirmed compound heterozygous mutations in the glucosidase I gene, establishing the diagnosis of congenital disorder of glycosylation IIb; the 2 siblings were the second and third patients in the world with this disorder.

The genetic analysis of rare and undiagnosed diseases has also yielded a variety of unique phenotypes that very likely represent new diseases. When variants in multiple genes are candidates for causing such a disorder, functional studies are required to demonstrate causality. This was successfully accomplished for a new disorder of vascular calcification identified and elucidated through the UDP at the NIH and found to be caused by a genetic deficiency of CD73, an enzyme on the surface of vascular cells that converts adenosine monophosphate to adenosine and inorganic phosphate.

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Metabolic Disorders

PART XI

Chapter 84
An Approach to Inborn Errors of Metabolism

Iraj Rezvani and Geoffrey A. Rezvani

Many childhood conditions are caused by single-gene mutations that encode specific proteins. These mutations can result in the alteration of primary protein structure or the amount of protein synthesized. The function of a protein, whether it is an enzyme, receptor, transport vehicle, membrane component, or structural element, may be compromised or abolished. These hereditary biochemical disorders are termed **inborn errors of metabolism** or **inherited metabolic disorders.**

Most mutations are clinically inconsequential and represent polymorphic differences that set individuals apart *(genetic polymorphism).* Some mutations produce disease states that range from very mild to lethal. Severe forms of these disorders usually become clinically apparent in the newborn period or shortly thereafter.

COMMON CHARACTERISTICS OF GENETIC DISORDERS OF METABOLISM

Although the manifestations of genetic metabolic disorders are quite variable, the following features are shared among most of these conditions:

1. The affected infant is normal at birth and becomes symptomatic later on in life. This differentiates these infants from those who appear sick at birth as a result of birth trauma, intrauterine insults, chromosomal abnormalities, or other genetic diseases.
2. The nature of the mutation that causes the dysfunction of the gene usually varies from family to family. This results in variation in severity of the phenotype in different families. An exception to this is found when a specific mutation has been preserved in an ethnic group primarily from inbreeding (the founder effect). An example is maple syrup urine disease in Old Order Mennonites in the United States (mainly in Lancaster County, PA), in whom all the affected infants have the same mutation and hence the same phenotype (see Chapter 85.6).
3. Mutations causing severe malfunction of the gene or its product result in clinical manifestations shortly after birth. In general, the earlier the appearance of clinical symptoms, the more severe the disease.
4. The majority of conditions are inherited as autosomal recessive traits. Therefore, a history of consanguinity in the parents or of an unexplained death of a family member in the neonatal period may raise the question of an inherited metabolic disease in the sick infant.
5. Most genetic metabolic conditions can be controlled successfully by some form of therapy, and a few can be potentially cured by the use of bone marrow or liver transplants. These patients can have a normal life if diagnosed and treated early, before irreversible damage to organs, especially to the brain, occurs. This underlines the importance of early diagnosis, which can be achieved through mass screening of all newborn infants.

MASS SCREENING OF NEWBORN INFANTS

Common characteristics of genetic metabolic conditions and the significance of early diagnosis make a strong argument for screening all newborn infants for the presence of these conditions. During the past half-century, methods have been developed to screen all infants inexpensively with accurate and fast-yielding results. Tandem mass spectrometry is the latest technical advance in the field. This method requires a few drops of blood to be placed on a filter paper and mailed to a central laboratory for assay. A large number of genetic conditions can be identified by this method when complemented by a few equally efficient assays for other specific disorders (Tables 84-1 and 84-2). Severe forms of some of these diseases may cause clinical manifestations before the results of the newborn screening become available. It should also be noted that these methods may identify mild forms of inherited metabolic conditions, some of which may never cause clinical manifestations in the lifetime of the individual. Potential psychosocial implications of such findings can be drastic and deserve serious consideration. An example of this is 3-methylcrotonyl-coenzyme A carboxylase deficiency, which has been identified with unexpectedly high frequency in screening programs using tandem mass spectrometry. The majority of these children have remained asymptomatic (see Chapter 85.6).

CLINICAL MANIFESTATIONS OF GENETIC METABOLIC DISEASES

Physicians and other healthcare providers who care for children should familiarize themselves with early manifestations of genetic metabolic disorders, because (1) severe forms of some of these conditions may cause symptoms before the results of screening studies become available, and (2) the current screening methods, although quite extensive, identify a small number of all inherited metabolic conditions. In the newborn period, the clinical findings are usually nonspecific and similar to those seen in infants with sepsis. A genetic disorder of metabolism should be considered in the differential diagnosis of a severely ill newborn infant, and special studies should be undertaken if the index of suspicion is high (Fig. 84-1).

Signs and symptoms such as lethargy, poor feeding, convulsions, and vomiting may develop as early as a few hours after birth. Occasionally, vomiting may be severe enough to suggest the diagnosis of pyloric stenosis, which is usually not present, although it may occur simultaneously in such infants. Lethargy, poor feeding, convulsions, and coma also may be seen in infants with hypoglycemia (see Chapters 92 and 107) or hypocalcemia (see Chapters 51 and 571). Measurements of blood concentrations of glucose and calcium and response to intravenous injection of glucose or calcium usually establish these diagnoses. Some of these disorders have a high incidence in specific population groups. Tyrosinemia type 1 is more common among French-Canadians of Quebec than in the general population. Therefore, knowledge of the ethnic background of the patient may be helpful in diagnosis. *Physical examination* usually reveals nonspecific findings; most signs are related to the central nervous system. Hepatomegaly is a common finding in a variety of inborn errors of metabolism. Occasionally, a peculiar odor may offer an invaluable aid to the diagnosis (Table 84-3). A physician caring for a sick infant should smell the patient and the patient's excretions; for example, patients with maple syrup urine disease have the unmistakable odor of maple syrup in their urine and on their bodies.

Occasionally, the onset of a genetic metabolic condition may occur months or years after birth. These children usually have mutations that render the gene partially nonfunctional. *Clinical manifestations,* such as intellectual disability, motor deficits, developmental regression, convulsions, myopathy, recurrent emesis, and cardiomyopathy, in a child beyond the neonatal period should raise the possibility of an inherited

Table 84-1 Disorders Recommended By the American College of Medical Genetics Task Force for Inclusion in Newborn Screening ("Primary Disorders")*

DISORDERS OF ORGANIC ACID METABOLISM
Isovaleric acidemia
Glutaric aciduria type I
3-Hydroxy-3-methylglutaric aciduria
Multiple carboxylase deficiency
Methylmalonic acidemia, mutase deficiency form
3-Methylcrotonyl-CoA carboxylase deficiency
Methylmalonic acidemia, cblA and cblB forms
Propionic acidemia
β-Ketothiolase deficiency
DISORDERS OF FATTY ACID METABOLISM
Medium-chain acyl-CoA dehydrogenase deficiency
Very-long-chain acyl-CoA dehydrogenase deficiency
Long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency
Carnitine uptake defect
DISORDERS OF AMINO ACID METABOLISM
Phenylketonuria
Maple syrup urine disease
Homocystinuria
Citrullinemia
Argininosuccinic acidemia
Tyrosinemia type I
HEMOGLOBINOPATHIES
Sickle cell anemia (hemoglobin S)
Hemoglobin S-β-thalassemia
Hemoglobin SC disease
OTHER DISORDERS
Congenital hypothyroidism
Biotinidase deficiency
Congenital adrenal hyperplasia
Galactosemia
Hearing deficiency
Cystic fibrosis

*At this time, there is state-to-state variation in newborn screening; a list of the disorders that are screened for by each state is available at http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/nbsdisorders.pdf.

cblA, Cobalamin A defect; cblB, cobalamin B defect; CoA, coenzyme A.

Table 84-2 Secondary Conditions Recommended By American College of Medical Genetics* Task Force for Inclusion in Newborn Screening

ORGANIC ACID METABOLISM DISORDERS
Methylmalonic acidemia, cblC and cblD forms
2-Methyl-3-hydroxybutyric aciduria
Isobutyryl-CoA dehydrogenase deficiency
2-Methylbutyryl-CoA dehydrogenase deficiency
3-Methylglutaconic aciduria
Malonic acidemia
FATTY ACID OXIDATION DISORDERS
Medium-/short-chain 3-OH acyl-CoA dehydrogenase deficiency
Short-chain acyl-CoA dehydrogenase deficiency
Medium-chain ketoacyl-CoA thiolase deficiency
Glutaric acidemia type 2
Carnitine palmitoyltransferase I deficiency
Carnitine palmitoyltransferase II deficiency
Carnitine acylcarnitine translocase deficiency
Dienoyl-CoA reductase deficiency
AMINO ACID METABOLISM DISORDERS
Hyperphenylalaninemia, benign (not phenylketonuria)
Tyrosinemia type II
Tyrosinemia type III
Defects of biopterin cofactor biosynthesis
Defects of biopterin cofactor regeneration
Argininemia
Hypermethioninemia
Citrullinemia type II
HEMOGLOBINOPATHICS
Hemoglobin variants (including hemoglobin E)
OTHERS
Galactose epimerase deficiency
Galactokinase deficiency

*The American College of Medical Genetics task force recommended reporting 25 disorders ("secondary targets") in addition to the primary disorders that can be detected through screening but that do not meet the criteria for primary disorders.

cblC, Cobalamin C defect; cblD, cobalamin D defect; CoA, coenzyme A.

Table 84-3 Inborn Errors of Amino Acid Metabolism Associated with Peculiar Odor

INBORN ERROR OF METABOLISM	URINE ODOR
Glutaric acidemia (type II)	Sweaty feet, acrid
Hawkinsinuria	Swimming pool
3-Hydroxy-3-methylglutaric aciduria	Cat urine
Isovaleric acidemia	Sweaty feet, acrid
Maple syrup urine disease	Maple syrup
Hypermethioninemia	Boiled cabbage
Multiple carboxylase deficiency	Tomcat urine
Oasthouse urine disease	Hops-like
Phenylketonuria	Mousey or musty
Trimethylaminuria	Rotting fish
Tyrosinemia	Boiled cabbage, rancid butter

metabolic disease. There may be an episodic or intermittent pattern, with episodes of acute clinical manifestations separated by periods of seemingly disease-free states. The episodes are usually triggered by stress or a nonspecific catabolic insult such as an infection. The child may die during one of these acute attacks. A genetic disorder of metabolism should be considered in any child with 1 or more of the following manifestations: unexplained intellectual disability, developmental delay or regression, motor deficits or adventitious movements (e.g., dystonia, choreoathetosis), convulsions, unusual odor (particularly during an acute illness); intermittent episodes of unexplained vomiting, acidosis, mental deterioration, psychotic behavior or coma; hepatomegaly; renal stones; muscle weakness; or cardiomyopathy. For example, urea cycle defects may present with confusion, behavioral disturbances, catatonia, hallucinations, psychosis, or depression. Catatonia may also be seen in disorders of folate metabolism, porphyria, Wilson disease, and some storage diseases. Severe seizures may be noted in molybdenum cofactor deficiency, biotinidase deficiency, neuronal ceroid lipofuscinosis, nonketolic hyperglycinemia, or creatine deficiency.

Diagnosis usually requires a variety of specific *laboratory studies.* Measurements of serum concentrations of ammonia, bicarbonate, and pH are often very helpful initially in differentiating major causes of genetic metabolic disorders (see Fig. 84-1). Elevation of blood ammonia is usually caused by defects of urea cycle enzymes. Infants with elevated blood ammonia levels from urea cycle defects commonly have normal serum pH and bicarbonate values; without measurement of blood ammonia, they may remain undiagnosed and succumb to their disease. Elevation of serum ammonia is also observed in some infants with certain organic acidemias. These infants are severely acidotic because of accumulation of organic acids in body fluids.

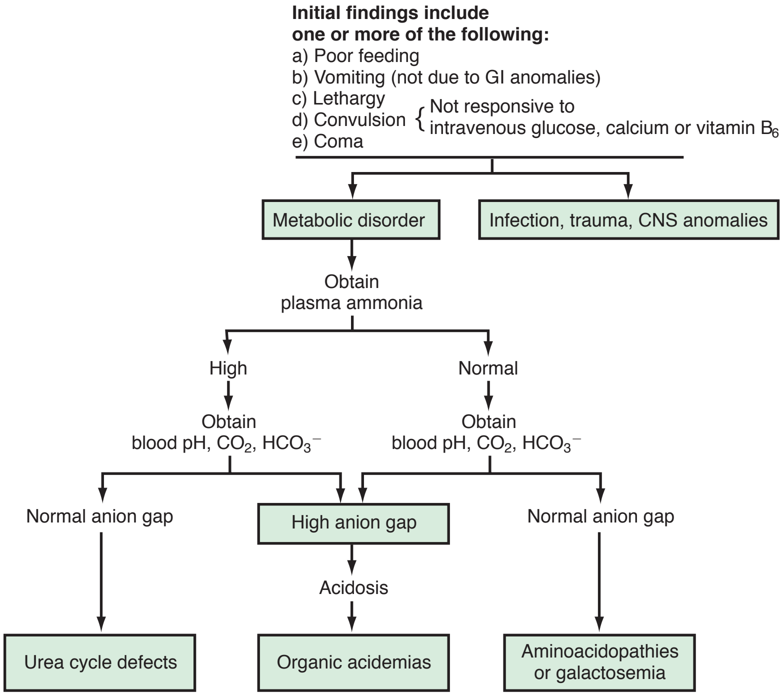

Figure 84-1 **Initial clinical approach to a full term newborn infant with a suspected genetic metabolic disorder.** This schema is a guide to the elucidation of some of the metabolic disorders in newborn infants. Although some exceptions to this schema exist, it is appropriate for most cases.

When blood ammonia, pH, and bicarbonate values are normal, other aminoacidopathies (such as hyperglycinemia) or galactosemia should be considered; galactosemic infants may also manifest cataracts, hepatomegaly, ascites, and jaundice.

TREATMENT

The majority of patients with genetic disorders of metabolism respond to 1 or all of the following treatments:

1. Special diets play an important role in the treatment of affected children. Dietary changes should be tailored to the pathophysiology of the condition and vary greatly among disorders.
2. Peritoneal dialysis or hemodialysis for expeditious removal of accumulated noxious compounds. This is a very effective modality for treatment of the acute phase of the condition.
3. Administration of the deficient metabolite.
4. Administration of the cofactor or coenzyme to maximize the residual enzyme activity.
5. Activation of alternate pathways to reduce the noxious compounds accumulated because of the genetic mutation.
6. Administration of the deficient enzyme.
7. Bone marrow transplantation.
8. Liver transplantation.

The bone marrow and liver transplantation modalities have the potential to cure the metabolic abnormalities. Replacement of the mutant gene with a normal one (gene therapy) is still in the experimental phase.

Treatment of genetic disorders of metabolism is complex and requires medical and technical expertise. The therapeutic regimen often needs to be tailored to the individual patient because of large phenotypic variations in the severity of the disease, even within a single family. Providing education and support for the family is the key to successful long-term therapy. Even in patients with hopeless prognoses every effort should be made to establish correct diagnoses premortem as the autopsy results are often noncontributory to the diagnosis. Effective treatment is best achieved by a team of specialists (physician metabolic genetics specialist, nutritionist, geneticist, neurologist, and psychologist) in a major medical center.

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Chapter 85

Defects in Metabolism of Amino Acids

85.1 Phenylalanine

Iraj Rezvani and Can H. Ficicioglu

Phenylalanine is an essential amino acid. Dietary phenylalanine not utilized for protein synthesis is normally degraded by way of the tyrosine pathway (Fig. 85-1). Deficiency of the enzyme phenylalanine hydroxylase (PAH) or of its cofactor tetrahydrobiopterin (BH_4) causes accumulation of phenylalanine in body fluids and in the brain.

Hyperphenylalaninemia depends on the degree of enzyme deficiency and may vary from very high plasma concentrations (>20 mg/dL or >1,200 µmole/L, **classic phenylketonuria**) to mildly elevated levels (2-10 mg/dL or 120-600 µmole/L, **mild hyperphenylalaninemia**). In affected infants with plasma concentrations >20 mg/dL, excess phenylalanine is metabolized to phenylketones (phenylpyruvate and phenylacetate; see Fig. 85-1) that are excreted in the urine, giving rise to the term *phenylketonuria* (PKU). These metabolites have no role in pathogenesis of central nervous system (CNS) damage in patients with PKU; their presence in the body fluids simply signifies the severity of the condition. The term **hyperphenylalaninemia** implies lower plasma levels (<20 mg/dL) of phenylalanine. The brain is the main organ affected by hyperphenylalaninemia. The CNS damage in affected patients is caused by the elevated concentration of phenylalanine in brain tissue. The high blood levels of phenylalanine in PKU saturate the transport system across the blood–brain barrier causing inhibition of the cerebral uptake of other large neutral amino acids such as tyrosine and tryptophan. The exact mechanism of damage caused by elevated levels of intracerebral phenylalanine remains elusive. There have been a few adults with classic PKU and normal intelligence who have

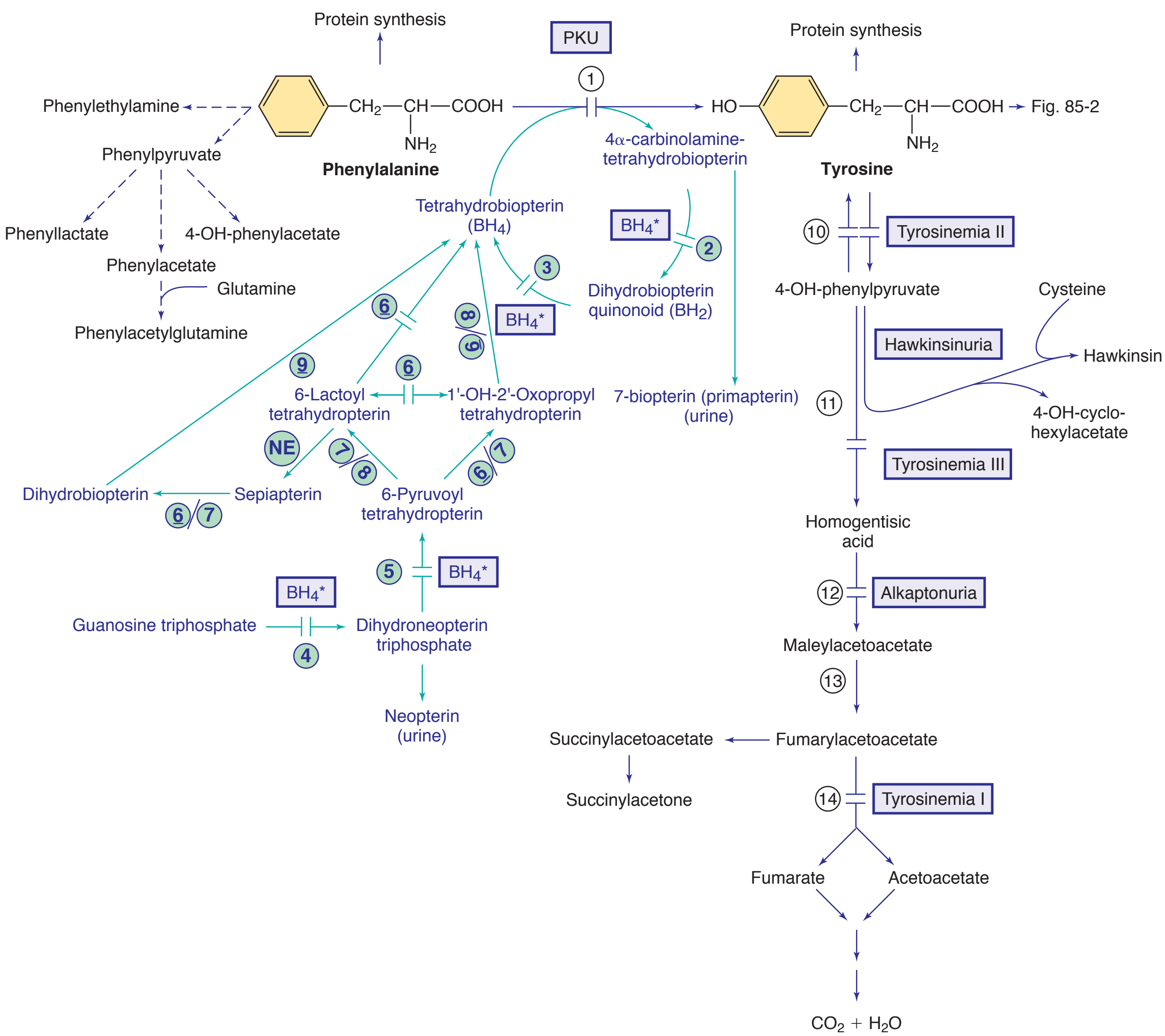

Figure 85-1 Pathways of phenylalanine and tyrosine metabolism. Enzyme defects causing genetic conditions are depicted as horizontal bars crossing the reaction arrow(s). Pathways for synthesis of cofactor BH_4 are shown in purple. PKU* refers to defects of BH_4 metabolism that affect the phenylalanine, tyrosine, and tryptophan hydroxylases (see Figs. 85-2 and 85-5). **Enzymes:** *(1)* Phenylalanine hydroxylase, *(2)* pterin-carbinolamine dehydratase, *(3)* dihydrobiopterin reductase, *(4)* guanosine triphosphate (GTP) cyclohydrolase, *(5)* 6-pyruvoyltetrahydropterin synthase, *(6)* sepiapterin reductase, *(7)* carbonyl reductase, *(8)* aldolase reductase, *(9)* dihydrofolate reductase, *(10)* tyrosine aminotransferase, *(11)* 4-hydroxyphenylpyruvate dioxygenase, *(12)* homogentisic acid dioxygenase, *(13)* maleylacetoacetate isomerase, *(14)* fumarylacetoacetate hydrolase, *(NE)* nonenzymatic.

never been treated with a phenylalanine-restricted diet. Phenylalanine content of the brain in these individuals was found to be close to that of normal subjects when studied by magnetic resonance spectroscopy (MRS).

CLASSIC PHENYLKETONURIA

Severe hyperphenylalaninemia (plasma phenylalanine levels >20 mg/dL), if untreated, invariably results in the development of signs and symptoms of classic PKU, except in rare unpredictable cases (see above).

Clinical Manifestations

The affected infant is normal at birth. Profound intellectual disability develops gradually if the infant remains untreated. Cognitive delay may not be evident for the first few months. In untreated patients, 50-70% will have an IQ below 35, and 88-90% will have an IQ below 65. Only 2-5% of untreated patients will have normal intelligence. Many patients require institutional care if the condition remains untreated. Vomiting, sometimes severe enough to be misdiagnosed as pyloric stenosis, may be an early symptom. Older untreated children become hyperactive with autistic behaviors, including purposeless hand movements, rhythmic rocking, and athetosis.

The infants are lighter in their complexion than unaffected siblings. Some may have a seborrheic or eczematoid rash, which is usually mild and disappears as the child grows older. These children have an unpleasant odor of phenylacetic acid, which has been described as musty or mousey. Neurologic signs include seizures (approximately 25%), spasticity, hyperreflexia, and tremors; more than 50% have electroencephalographic abnormalities. Microcephaly, prominent maxillae with widely spaced teeth, enamel hypoplasia, and growth retardation are other common findings in untreated children. The clinical manifestations of classic PKU are rarely seen in those countries in which neonatal screening programs for the detection of PKU are in effect.

Nonphenylketonuria Hyperphenylalaninemias (Milder Forms of Hyperphenylalaninemia)

In any screening program for PKU, a group of infants is identified in whom initial plasma concentrations of phenylalanine are above normal (i.e., >2 mg/dL or 120 µmole/L) but <20 mg/dL (1,200 µmole/L). These infants do not excrete phenylketones. Patients with non-PKU

hyperphenylalaninemia may still require dietary therapy, depending on their untreated plasma phenylalanine level. Attempts have been made to classify these patients in different subgroups depending on the degree of hyperphenylalaninemia, but such a practice has little clinical or therapeutic advantage. The possibility of deficiency of BH_4 should be investigated in all infants with the milder forms of hyperphenylalaninemia (see below).

Diagnosis

Because of the gradual and nonspecific nature of early clinical symptoms such as vomiting, developmental delay, or eczematoid rash, hyperphenylalaninemia is usually diagnosed through newborn screening in all developed countries. In infants with positive screening results, diagnosis should be confirmed by quantitative measurement of plasma phenylalanine concentration. Identification and measurement of phenylketones in the urine has no place in any screening program. In countries and places where such programs are not in effect, identification of phenylketones in the urine by ferric chloride may offer a simple test for diagnosis of infants with developmental and neurologic abnormalities. Once the diagnosis of hyperphenylalaninemia is established, additional studies for BH_4 metabolism should be performed to rule out BH_4 deficiency as the cause of hyperphenylalaninemia (see below).

Neonatal Screening for Hyperphenylalaninemia

Effective and relatively inexpensive methods for mass screening of newborn infants have been developed and are used in the United States and several other countries. A few drops of blood, which are placed on a filter paper and mailed to a central laboratory, are used for assay. The bacterial inhibition assay of Guthrie, which was the first method used for this purpose, has been replaced by more precise and quantitative methods (fluorometric and tandem mass spectrometry). The method of choice is tandem mass spectrometry, which identifies all forms of hyperphenylalaninemia with a low false-positive rate and excellent accuracy and precision. The addition of the phenylalanine : tyrosine molar ratio has further reduced the number of false-positive results. Diagnosis must be confirmed by measurement of plasma phenylalanine concentration. Blood phenylalanine in affected infants with PKU may rise to diagnostic levels as early as 4 hr after birth, even in the absence of protein feeding. It is recommended that the blood for screening be obtained in the first 24-48 hr of life after feeding protein to reduce the possibility of false-negative results, especially in the milder forms of the condition.

Treatment

The mainstay of treatment of PKU is a low–phenylalanine diet. The general consensus is to start diet treatment immediately in patients with blood phenylalanine levels above 10 mg/dL (600 µmole/L). Most physicians also advocate phenylalanine-restricted diet in patients with mild hyperphenylalaninemia whose levels are persistently above 6 mg/dL (360 µmole/L). It is generally accepted that infants with persistent (more than a few days) plasma levels of phenylalanine ≥6 mg/dL (360 µmole/L) should be treated with a phenylalanine-restricted diet similar to that for classic PKU. The goal of therapy is to reduce phenylalanine levels in the plasma and brain. Formulas free of or low in phenylalanine are commercially available. The diet should be started as soon as the diagnosis is established. Because phenylalanine is not synthesized endogenously, small amounts of phenylalanine should be added to the diet to prevent *phenylalanine deficiency*. Dietary deficiency of this amino acid is manifested by lethargy, failure to thrive, anorexia, anemia, rashes, diarrhea, and even death; moreover, tyrosine becomes an essential amino acid in this disorder and its adequate intake must be ensured. Special food items low in phenylalanine are commercially available for dietary treatment of affected children and adults.

There is no firm consensus concerning optimal level of blood phenylalanine in affected patients either across different countries or among treatment centers in the United States. In 2001, the National Institutes of Health Consensus Development Panel recommended that plasma phenylalanine levels be maintained between 2 and 6 mg/dL in neonates through 12 yr of age and between 2 and 15 mg/dL in older individuals. Given that brain development continues in adolescence and even in adulthood, maintenance of lower plasma phenylalanine levels (2-10 mg/dL) has been strongly encouraged even after 12 yr of age. The duration of diet therapy is also controversial. Discontinuation of therapy, even in adulthood, may cause deterioration of IQ and cognitive performance. The current recommendation from the 2001 National Institutes of Health Consensus Development Panel is that all patients be kept on a phenylalanine-restricted diet for life. Lifelong adherence to a low phenylalanine diet is extremely difficult. Patients, who maintain good control as children but discontinue the phenylalanine-restricted diet as teenagers or adults, may experience significant difficulties with executive function concentration, emotional liability, and depression. Executive dysfunction may also occur in early treated children in spite of diet treatment.

Given the difficulty of maintaining a strict low-phenylalanine diet, there are continuing attempts to find other modalities for treatment of these patients. Administration of large neutral amino acids (LNAAs) is another approach to diet therapy. LNAAs (tyrosine, tryptophan, arginine, leucine, isoleucine, valine, methionine, histidine, lysine, threonine and phenylalanine) share the same transporter protein (LNAA type 1, LAT-1) for transit through the intestinal cell membrane and blood–brain barrier. Binding of LNAA to the transporter protein is a competitive process. The rationale for use of LNAA is that these molecules compete with phenylalanine for transport across the blood–brain barrier; therefore, large concentrations of other LNAAs in the intestinal lumen and in the blood reduce the uptake of phenylalanine into bloodstream and the brain. Clinical trials to establish the efficacy of this treatment are lacking at this time. Oral administration of BH_4, the cofactor for PAH, may result in reduction of plasma levels of phenylalanine in some patients with PAH deficiency. Plasma levels of phenylalanine in these patients may decrease enough to allow for considerable modification of their dietary restriction. In very rare cases, the diet may be discontinued because the phenylalanine levels remain under 6 mg/dL. The response to BH_4 cannot be predicted consistently on the basis of genotype, especially in compound heterozygous patients. Sapropterin dihydrochloride (Kuvan), a synthetic form of BH_4, which acts as a cofactor in patients with residual PAH activity, is approved by the FDA to reduce phenylalanine levels in PKU. At a dose of 10 mg/kg/day, it reduces phenylalanine levels in up to 40% of patients. Preliminary trials with recombinant phenylalanine ammonia lyase have been encouraging and demonstrated reduced blood levels of phenylalanine during treatment.

Low mineral bone density and osteopenia have been reported in affected individuals of all ages. Although inadequate intake of natural proteins seems to be the major culprit, the exact pathogenesis of this sequela remains unclear.

Long-term care of patients with PKU is best achieved by a team of experienced professionals (metabolic specialist, nutritionist, and psychologist) in a regional treatment center.

Pregnancy in Women with Hyperphenylalaninemia (Maternal Phenylketonuria)

Pregnant women with hyperphenylalaninemia who are not on a phenylalanine-restricted diet have a very high risk of having offspring with intellectual disability, microcephaly, growth retardation, congenital malformations, and congenital heart disease. These complications are directly correlated with elevated maternal blood phenylalanine levels during pregnancy. Prospective mothers who have been treated for hyperphenylalaninemia should be maintained on a phenylalanine-restricted diet before and during pregnancy; the best observed outcomes occur when strict control of maternal blood phenylalanine concentration is instituted before pregnancy or by 8 wk of gestation at the latest. The currently recommended phenylalanine concentrations are between 2 and 6 mg/dL (120-360 µmol/L) throughout the pregnancy. All women with hyperphenylalaninemia who are of childbearing age should be counseled properly as to the risk of the just described congenital anomalies in their offspring.

HYPERPHENYLALANINEMIA CAUSED BY DEFICIENCY OF THE COFACTOR TETRAHYDROBIOPTERIN

In 1-3% of infants with hyperphenylalaninemia, the defect resides in 1 of the enzymes necessary for production or recycling of the cofactor BH_4 (see Fig. 85-1). If these infants are misdiagnosed as having PKU, they may deteriorate neurologically despite adequate control of plasma phenylalanine. BH_4 is synthesized from guanosine triphosphate (GTP) through several enzymatic reactions (see Fig. 85-1). In addition to acting as a cofactor for PAH, BH_4 is also a cofactor for tyrosine hydroxylase and tryptophan hydroxylase, which are involved in the biosynthesis of dopamine (Fig. 85-2) and serotonin (see Fig. 85-5), respectively. Therefore, patients with hyperphenylalaninemia as a result of BH_4 deficiency also manifest neurologic findings related to deficiencies of the neurotransmitters dopamine and serotonin. Four enzyme deficiencies leading to defective BH_4 formation cause hyperphenylalaninemia with concomitant deficiencies of dopamine and serotonin. These include autosomal recessive GTP cyclohydrolase deficiency, pterin-carbinolamine dehydratase deficiency, dihydropteridine reductase deficiency, and 6-pyruvoyltetrahydropterin synthase deficiency. More than half of the reported patients have had a deficiency of 6-pyruvoyltetrahydropterin synthase. Autosomal dominant forms of GTP deficiency and sepiapterin reductase deficiency result in deficiencies of neurotransmitters without hyperphenylalaninemia (see Chapter 85.11 and Fig. 85-1).

Clinical Manifestations

Infants with cofactor deficiency are identified during screening programs for PKU because of evidence of hyperphenylalaninemia. Plasma phenylalanine levels may be as high as those in classic PKU or in the range of milder forms of hyperphenylalaninemia. However, the clinical manifestations of the neurotransmitter disorders differ greatly from those of PKU. Neurologic symptoms of the neurotransmitter disorders often manifest in the first few months of life and include extrapyramidal signs (choreoathetotic or dystonic limb movements, axial and truncal hypotonia, hypokinesia), feeding difficulties, and autonomic abnormalities. Intellectual disability, seizures, hypersalivation, and swallowing difficulties are also seen. The symptoms are usually progressive and often have a marked diurnal fluctuation. Prognosis and outcome strongly depend on the age at which the diagnosis is made and treatment is introduced, but also on the specific nature of the mutation and resulting enzyme defect.

Diagnosis

Despite the low incidence of BH_4 defects, all newborns with hyperphenylalaninemia detected through newborn screening should be screened for BH_4 defects.

BH_4 deficiency and the responsible enzyme defect may be diagnosed by the following studies:

1. Measurement of neopterin (oxidative product of dihydroneopterin triphosphate) and biopterin (oxidative product of dihydrobiopterin and BH_4) in body fluids, especially urine (see Fig. 85-1). In patients with GTP cyclohydrolase deficiency, urinary excretion of both neopterin and biopterin is very low. In patients with 6-pyruvoyltetrahydropterin synthase deficiency, there is a marked elevation of neopterin excretion and a concomitant decrease in biopterin excretion. In patients with dihydropteridine reductase deficiency, neopterin is normal, but biopterin is very high. Excretion of biopterin increases in this enzyme deficiency because the quinonoid dihydrobiopterin cannot be recycled back to BH_4. Patients with pterin-carbinolamine dehydratase deficiency excrete 7-biopterin (an unusual isomer of biopterin) in their urine. In addition, examination of cerebrospinal fluid (CSF) reveals decreased levels of dopamine, serotonin, and their metabolites in all patients with BH_4 deficiency (see Chapter 85.11).
2. BH_4 loading test. An oral dose of BH_4 (20 mg/kg) normalizes plasma phenylalanine and phenylalanine : tyrosine ratio in patients with BH_4 deficiency within 4-8 hr. The blood phenylalanine should be elevated (>400 µmole/L) to enable interpretation of the results. This may be achieved by discontinuing diet therapy for 2 days before the test or by administering a loading dose of phenylalanine (100 mg/kg) 3 hr before the test. In BH_4-responsive PKU caused by PAH deficiency, blood phenylalanine levels may decrease during the BH_4 loading test, but increase later even with BH_4 supplementation. Patients who demonstrate phenylalanine levels within normal range over at least a week without a phenylalanine-restricted diet can be continued on BH_4 supplementation as the sole treatment for the hyperphenylalaninemia. However, it is imperative that plasma

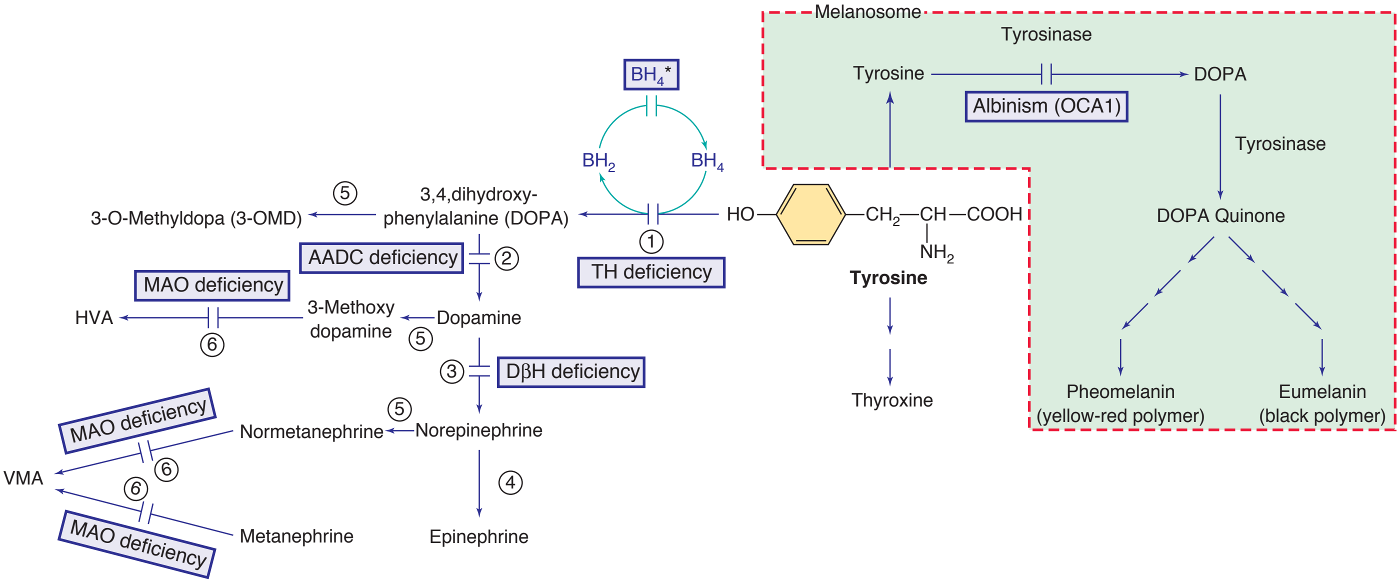

Figure 85-2 Other pathways involving tyrosine metabolism. PKU* indicates hyperphenylalaninemia caused by tetrahydrobiopterin (BH_4) deficiency (see Fig. 85-1). HVA, homovanillic acid; VMA, vanillylmandelic acid. **Enzymes:** *(1)* Tyrosine hydroxylase (TH), *(2)* aromatic L-amino acid decarboxylase (AADC), *(3)* dopamine β-hydroxylase (DβH), *(4)* phenylethanolamine-*N*-methyltransferase (PNMT), *(5)* catechol *O*-methyltransferase (COMT), *(6)* monoamine oxidase (MAO).

phenylalanine levels be monitored prospectively to ensure that phenylalanine levels remain within the normal range.
3. Enzyme assay. The activity of dihydropteridine reductase can be measured in the dry blood spots on the filter paper used for screening purposes. 6-Pyruvoyltetrahydropterin synthase activity can be measured in the liver, kidneys, and erythrocytes. Carbinolamine dehydratase activity can be measured in the liver and kidneys. GTP cyclohydrolase activity can be measured in the liver and in cytokine (interferon-γ) stimulated mononuclear cells or fibroblasts (the enzyme activity is normally very low in unstimulated cells).
4. Genetic test. Mutation analysis and deletion/duplication studies are clinically available for all these enzyme defects and help to confirm the diagnosis.

Treatment

The goals of therapy are to correct hyperphenylalaninemia and to restore neurotransmitter deficiencies in the CNS. The control of hyperphenylalaninemia is important in patients with cofactor deficiency, because high levels of phenylalanine cause intellectual disability and also interfere with the transport of neurotransmitter precursors (tyrosine, tryptophan) into the brain. Plasma phenylalanine should be maintained as close to normal as possible (<6 mg/dL). This can be achieved by oral supplementation of BH_4 (5-20 mg/kg/day). Sapropterin dihydrochloride (Kuvan), a synthetic form of BH_4, is commercially available, although it is expensive.

Lifelong supplementation with **neurotransmitter precursors** such as L-dopa and 5-hydroxytryptophan, along with carbidopa to inhibit degradation of L-dopa before it enters the CNS, is necessary in most of these patients even when treatment with BH_4 normalizes plasma levels of phenylalanine. BH_4 does not readily enter the brain to restore neurotransmitter production. To minimize untoward side effects (especially L-dopa–induced dyskinesia), the treatment should be started with low doses of L-dopa/carbidopa and 5-hydroxytryptophan, and should be adjusted based on response to therapy and clinical improvement for each individual patient. Supplementation with folinic acid is also recommended in patients with dihydropteridine reductase deficiency. Unfortunately, attempting to normalize neurotransmitter levels using neurotransmitter precursors usually does not fully resolve the neurologic symptoms as a result of the inability to attain normal levels of BH_4 in the brain. Patients often demonstrate intellectual disability, fluctuating abnormalities of tone, eye movement abnormalities, poor balance and coordination, decreased ability to ambulate, and seizures in spite of supplementation with neurotransmitter precursors.

Hyperprolactinemia occurs in patients with BH_4 deficiency and may be the result of hypothalamic dopamine deficiency. Measurement of serum prolactin levels may be a convenient method for monitoring adequacy of neurotransmitter replacement in affected patients.

Some drugs, such as trimethoprim sulfamethoxazole, methotrexate, and other antileukemic agents, are known to inhibit dihydropteridine reductase enzyme activity and should be used with great caution in patients with BH_4 deficiency.

Genetics and Prevalence

All defects causing hyperphenylalaninemia are inherited as autosomal recessive traits. The prevalence of PKU in the United States is estimated at 1 in 14,000 to 1 in 20,000 live births. The prevalence of non-PKU hyperphenylalaninemia is estimated at 1 in 50,000 live births. The condition is more common in whites and Native Americans and less prevalent in African-Americans, Hispanics, and Asians.

The gene for PAH is located on chromosome 12q23.2 and many disease-causing mutations have been identified in different families. The majority of patients are compound heterozygotes for 2 different mutant alleles. The gene for 6-pyruvoyl tetrahydropterin synthase *(PTS)*, the most common cause of BH_4 deficiency, resides on chromosome 11q23.1, the gene for dihydropteridine reductase *(QDPR)* is located on chromosome 4p15.2, and those of carbinolamine dehydratase *(PCBD1)* and GTP cyclohydrolase *(GCH1)* are on 10q22.1 and 14q22.2, respectively. Many disease-causing mutations of these genes have been identified. Prenatal diagnosis is possible using specific genetic probes in cells obtained from biopsy of the chorionic villi.

TETRAHYDROBIOPTERIN DEFECTS WITHOUT HYPERPHENYLALANINEMIA

See Chapter 85.11.

Bibliography is available at Expert Consult.

85.2 Tyrosine

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Tyrosine is derived from ingested proteins or is synthesized endogenously from phenylalanine. It is used for protein synthesis and is a precursor of dopamine, norepinephrine, epinephrine, melanin, and thyroxine. Excess tyrosine is metabolized to carbon dioxide and water (see Fig. 85-1). Hereditary causes of hypertyrosinemia include deficiencies of tyrosine aminotransferase, 4-hydroxyphenylpyruvate dioxygenase (4-HPPD), and fumarylacetoacetate hydrolase. *Acquired hypertyrosinemia* may occur in severe hepatocellular dysfunction (liver failure), scurvy (vitamin C is the cofactor for 4-HPPD), and hyperthyroidism. Hypertyrosinemia is common in blood samples obtained soon after eating and in premature infants.

TYROSINEMIA TYPE I (TYROSINOSIS, HEREDITARY TYROSINEMIA, HEPATORENAL TYROSINEMIA)

This severe disease of the liver, kidney, and peripheral nerves is caused by a deficiency of the enzyme fumarylacetoacetate hydrolase. Organ damage is believed to result from accumulation of metabolites of tyrosine degradation, especially fumarylacetoacetate and succinylacetone.

Clinical Manifestations and Natural History

Untreated, the affected infant appears normal at birth and typically presents between 2 and 6 mo of age but rarely may become symptomatic in the 1st mo or appear healthy beyond the 1st yr of life. The earlier the presentation, the poorer the prognosis. The 1 yr mortality of untreated children, which is approximately 60% in infants who develop symptoms before 2 mo of age, decreases to 4% in infants who become symptomatic after 6 mo of age.

An acute **hepatic crisis** commonly heralds the onset of the disease and is usually precipitated by an intercurrent illness that produces a catabolic state. Fever, irritability, vomiting, hemorrhage, hepatomegaly, jaundice, elevated levels of serum transaminases, and hypoglycemia are common. An odor resembling boiled cabbage may be present, resulting from increased methionine metabolites. Most hepatic crises resolve spontaneously, but may progress to liver failure and death. Between the crises, varying degrees of failure to thrive, hepatomegaly, and coagulation abnormalities often persist. Cirrhosis and eventually hepatocellular carcinoma occur with increasing age. Carcinoma is unusual before 2 yr of age.

Episodes of acute **peripheral neuropathy** resembling acute porphyria occur in approximately 40% of affected children. These crises, often triggered by a minor infection, are characterized by severe pain, often in the legs, associated with extensor hypertonia of the neck and trunk, vomiting, paralytic ileus, and, occasionally, self-induced injuries of the tongue or buccal mucosa. Marked weakness and paralysis occur in about 30% of episodes, which may lead to respiratory failure requiring mechanical ventilation. Crises typically last 1-7 days but recuperation from paralytic crises can require weeks to months.

Renal involvement is manifested as a Fanconi-like syndrome with hyperphosphaturia, hypophosphatemia, normal anion gap metabolic acidosis, and vitamin D–resistant rickets. Nephromegaly and nephrocalcinosis may be present on ultrasound examination. Glomerular failure may occur in adolescents and older patients.

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Hypertrophic cardiomyopathy and hyperinsulinism are seen in some infants.

Laboratory Findings

The presence of elevated levels of succinylacetone in serum and urine is diagnostic for tyrosinemia type I (see Fig. 85-1). In untreated patients, the blood level of α-fetoprotein is increased, often markedly, and liver-synthesized coagulation factors are decreased in most patients; serum levels of transaminases are often increased, with marked increases being possible during acute hepatic episodes. Serum concentration of bilirubin is usually normal but can be increased with liver failure. Increased levels of α-fetoprotein are present in the cord blood of affected infants, indicating intrauterine liver damage. Plasma tyrosine levels are usually elevated at diagnosis but this is a nonspecific finding and is dependent on dietary intake. Plasma levels of other amino acids, particularly methionine, may also be elevated in patients with liver damage. Hyperphosphaturia, hypophosphatemia, and generalized aminoaciduria may occur. The urinary level of 5-aminolevulinic acid is elevated because of inhibition of 5-aminolevulinic hydratase by succinylacetone.

Diagnosis is usually established by demonstration of elevated levels of succinylacetone in urine or blood. Neonatal screening for hypertyrosinemia detects only a minority of patients with tyrosinemia type I. Succinylacetone, which is now assayed by some neonatal screening programs, has higher sensitivity and specificity than tyrosine and is the preferred metabolite for screening. Tyrosinemia type I should be differentiated from other causes of hepatitis and hepatic failure in infants, including galactosemia, hereditary fructose intolerance, neonatal iron storage disease, giant cell hepatitis, and citrullinemia type II (see Chapter 85.12).

Treatment and Outcome

A diet low in phenylalanine and tyrosine can slow but does not halt the progression of the condition. The **treatment of choice** is nitisinone, which inhibits tyrosine degradation at 4-HPPD (see Fig. 85-1). This treatment prevents acute hepatic and neurologic crises. Although nitisinone stops or greatly slows disease progression, some pretreatment liver damage is not reversible. Therefore, patients must be followed for development of cirrhosis or **hepatocellular carcinoma**. On imaging, the presence of even a single liver nodule usually indicates underlying cirrhosis. Most liver nodules in tyrosinemic patients are benign but current imaging techniques do not accurately distinguish all malignant nodules. Liver transplantation is an effective therapy for tyrosinemia type I and alleviates the risk of hepatocellular carcinoma. The impact of nitisinone treatment on the need for liver transplantation is still under study but the greatest effect is in patients treated early, such as children detected by neonatal screening, prior to the development of clinical symptoms. In early-treated patients, nitisinone has greatly reduced the need for liver transplantation. At any age, nitisinone treatment eliminates the occurrence of acute episodes of liver failure and neurologic crises although they are at risk for impaired cognitive function. Because nitisinone treatment causes an increase in plasma tyrosine level, a diet restricted in tyrosine and phenylalanine is prescribed. Rarely, nitisinone-treated patients develop corneal crystals, presumably of tyrosine, which are reversible by strict dietary compliance. This finding, combined with observations of developmental delay in some patients with tyrosinemia type II who chronically have elevated tyrosine levels, suggest that a diet low in phenylalanine and tyrosine should be continued in patients treated with nitisinone. The dietary treatment of patients with tyrosine and phenylalanine restriction necessitates surveillance to ensure adequate intakes of other nutrients and amino acids.

Genetics and Prevalence

Tyrosinemia type I is inherited as an autosomal recessive trait. The gene for fumarylacetoacetate hydrolase (*FAH*) maps to chromosome 15q 25.1 and; numerous disease-causing mutations of the gene have been reported. DNA analysis is useful for molecular prenatal diagnosis if the familial mutations are known and for carrier testing in groups at risk for specific mutations such as French-Canadians from the Saguenay-Lac Saint-Jean region of Quebec. The prevalence of the condition is estimated to be 1 in 1,846 live births in the Saguenay-Lac Saint-Jean region and approximately 1 in 100,000 live births worldwide. But tyrosinemia type I is panethnic; lack of French-Canadian or Scandinavian ancestry does not exclude the diagnosis. Prenatal diagnosis is typically performed by measurement of succinylacetone in amniotic fluid, or if the familial mutations are known, by DNA analysis of amniocytes or of chorionic villi.

TYROSINEMIA TYPE II (RICHNER-HANHART SYNDROME, OCULOCUTANEOUS TYROSINEMIA)

This rare autosomal recessive disorder is caused by deficiency of tyrosine aminotransferase and results in palmar and plantar hyperkeratosis, herpetiform corneal ulcers, and intellectual disability (see Fig. 85-1). **Ocular manifestations,** which may occur as early as 6 mo of age, include excessive tearing, redness, pain, and photophobia. Corneal lesions are presumed to be because of tyrosine deposition. In contrast to herpetic ulcers, corneal lesions in tyrosinemia type II stain poorly with fluorescein and often are bilateral. **Skin lesions**, which may develop later in life, include painful, nonpruritic hyperkeratotic plaques on the soles, palms, and fingertips. Intellectual disability, which occurs in approximately 50% of patients, is usually mild to moderate.

The principal **laboratory finding** in untreated patients is marked hypertyrosinemia (20-50 mg/dL; 1,100-2,750 µmole/L). Surprisingly, 4-hydroxyphenylpyruvic acid and its metabolites are also elevated in urine despite being downstream from the metabolic block (see Fig. 85-1). This is hypothesized to occur via the action of other transaminases in the presence of high tyrosine concentrations, producing 4-hydroxyphenylpyruvic acid in cellular compartments like the mitochondrion in which it cannot be further degraded. In contrast to tyrosinemia type I, liver and kidney function are normal, as are serum concentrations of other amino acids and succinylacetone. Tyrosinemia type II is caused by *TAT* gene mutations, causing deficiency of cytosolic tyrosine aminotransferase activity in liver.

Diagnosis of type II tyrosinemia is established by assay of plasma tyrosine concentration in patients with suggestive findings. Molecular diagnosis is possible. Assay of liver tyrosine aminotransferase activity requires a liver biopsy and is rarely indicated.

Treatment with a diet low in tyrosine and phenylalanine improves the biochemical abnormalities and can normalize the skin and eye. The claim that intellectual disability may be prevented by early diet therapy is reasonable and is consistent with some case reports. The gene for tyrosine aminotransferase (*TAT)* maps to chromosome 16q22.2 and several disease-causing mutations have been identified. About half of reported cases are of Italian descent.

TYROSINEMIA TYPE III (PRIMARY DEFICIENCY OF 4-HYDROXYPHENYLPYRUVATE DIOXYGENASE [4-HPPD])

Only a few cases have been reported; most were detected by amino acid chromatography performed for various neurologic findings. Age at presentation has been from 1-17 mo. Developmental delay, seizures, intermittent ataxia, and self-destructive behavior are reported; a causal link to 4-HPPD deficiency is not formally established. Liver and renal abnormalities are absent. Asymptomatic infants with 4-HPPD deficiency have been identified by neonatal screening for hypertyrosinemia.

The **diagnosis** is suspected in children with sustained moderate increases in plasma levels of tyrosine (typically 350-700 µmole/L on a normal diet) and the presence of 4-hydroxyphenylpyruvic acid and its metabolites 4-hydroxyphenyllactic and 4-hydroxyphenylacetic acids in urine. Diagnosis may be refined by demonstrating the presence of mutations in the gene (*HPD*) for 4-HPPD on chromosome 12q24.31, or rarely, by demonstrating a low activity of 4-HPPD enzyme; the latter requires a liver biopsy and is not usually indicated.

Given the possible association with neurologic abnormalities, dietary reduction of plasma tyrosine levels is prudent. It is also logical

to attempt a trial of vitamin C, the cofactor for 4-HPPD. The condition is inherited as an autosomal recessive trait.

HAWKINSINURIA

Certain missense mutations in the gene for 4-HPPD result in an abnormal enzyme activity. The mutant enzyme, incapable of normally oxidizing 4-hydroxyphenylpyruvate to homogentisic acid, forms an intermediate that reacts with cysteine to form the unusual organic acid hawkinsin ([2-L-cystein-*S*-yl-1,4-dihydroxycyclohex-5-en-1-yl]acetic acid, named after the first affected family, Fig. 85.1); secondary glutathione deficiency may occur. Hawkinsinuria is inherited as an autosomal dominant trait and a few specific causal missense mutations have been identified. The same mutation, a substitution of threonine for the normal alanine codon at position 33 of the 4-HPPD gene, has been identified in unrelated patients with hawkinsinuria. The condition is, perhaps, more prevalent than once realized.

Individuals with this disorder are symptomatic only during infancy. The symptoms usually appear in the first few months of life; commonly after weaning from breastfeeding and with the introduction of a high-protein diet. Severe metabolic acidosis, ketosis, failure to thrive, mild hepatomegaly, and an unusual odor (described as like that of a swimming pool) are reported manifestations of this disorder. Mental development is usually normal.

Symptomatic infants and asymptomatic affected children and adults excrete hawkinsin, 4-hydroxyphenylpyruvic acid, and its metabolites (4-hydroxyphenyllactic and 4-hydroxyphenylacetic acids), 4-hydroxycyclohexylacetic acid and 5-oxoproline (owing to secondary glutathione deficiency) in their urine. The plasma tyrosine level, which is moderately elevated in the symptomatic infants, may become normal in the asymptomatic affected individuals. **Treatment** consists of a low-protein diet during infancy. Breastfeeding is encouraged. A trial with large doses of vitamin C (up to 1,000 mg/24 hr) is also recommended. The mutant enzyme is susceptible to inhibition by nitisinone; clinical studies showing the efficacy of this agent in symptomatic infants are lacking at this time, and the indications for its use are not known.

TRANSIENT TYROSINEMIA OF THE NEWBORN

In a small number of newborn infants, plasma tyrosine may be as high as 60 mg/dL (3,300 µmole/L) during the 1st 2 wk of life. Most affected infants are premature and are receiving high-protein diets. Transient tyrosinemia is felt to result from delayed maturation of 4-HPPD (see Fig. 85-1). Lethargy, poor feeding, and decreased motor activity are noted in some patients. Most are asymptomatic and are identified by a high blood phenylalanine or tyrosine level on routine screening. Laboratory findings include marked elevation of plasma tyrosine with a moderate increase in plasma phenylalanine. The finding of hypertyrosinemia differentiates this condition from PKU. 4-Hydroxyphenylpyruvic acid and its metabolites (see above) are present in the urine. Hypertyrosinemia usually resolves spontaneously in the 1st mo of life. It can be corrected promptly by reducing dietary protein to below 2 g/kg/24 hr and by administering vitamin C (200-400 mg/24 hr). Mild intellectual deficits have been reported in some infants who had this condition, but the causal relationship to hypertyrosinemia is not conclusively established.

ALKAPTONURIA

This rare (with an incidence of approximately 1 in 250,000 live births) autosomal recessive disorder is caused by a deficiency of homogentisic acid oxidase (homogentisate 1,2-dioxigenase). In alkaptonuria, large amounts of homogentisic acid are formed (see Fig. 85-1), which are excreted in urine or deposited in tissues.

The main **clinical manifestations** of alkaptonuria consist of ochronosis and arthritis in adulthood. The only sign in children is a blackening of the urine on standing, caused by oxidation and polymerization of homogentisic acid. A history of gray- or black-stained diapers should suggest the diagnosis. This sign may never be noted; hence, diagnosis is often delayed until adulthood. *Ochronosis,* which is seen clinically as dark spots on the sclera or ear cartilage, results from the accumulation of the black polymer of homogentisic acid. *Arthritis* is another result of this deposition and can be disabling with advancing age. It involves the large joints (spine, hip, and knee) and is usually more severe in males. Like rheumatoid arthritis, the alkaptonuric arthritis has acute exacerbations, but the radiologic findings are typical of osteoarthritis, with characteristic narrowing of the joint spaces and calcification of the intervertebral discs. High incidence of heart disease (mitral and aortic valvulitis, calcification of the heart valves, and myocardial infarction) has been noted.

The **diagnosis** is confirmed by finding massive excretion of homogentisic acid on urine organic acid testing. Tyrosine levels are normal. The enzyme is expressed only in the liver and kidneys.

Treatment of the arthritis is symptomatic. Nitisinone efficiently reduces homogentisic acid production in alkaptonuria. If presymptomatic individuals are detected, treatment with nitisinone, combined with a phenylalanine- and tyrosine-restricted diet, seems reasonable, although no experience is available regarding long-term efficacy.

The gene for homogentisic acid oxidase *(HGD)* maps to chromosome 3q13.3. Several disease-causing mutations have been identified. Alkaptonuria is commonest in the Dominican Republic and Slovakia.

TYROSINE HYDROXYLASE DEFICIENCY

See Chapter 85.11.

ALBINISM (See also Chapters 622 and 653)

Albinism is caused by deficiency of melanin, the main pigment of the skin and eye (Table 85-1). Melanin is synthesized by melanocytes from tyrosine in a membrane-bound intracellular organelle, the melanosome. Melanocytes originate from the embryonic neural crest and migrate to the skin, eyes (choroid and iris), hair follicles, and inner ear. The melanin in the eye is confined to the iris stromal and retinal pigment epithelia, whereas in skin and hair follicles, it is secreted into the epidermis and hair shaft. Albinism can be caused by deficiencies of melanin synthesis, by some hereditary defects of melanosomes, or by disorders of melanocyte migration. Neither the biosynthetic pathway of melanin nor many facets of melanocyte cell biology are completely elucidated (see Fig. 85-2). The end products are 2 pigments: *pheomelanin,* which is a yellow-red pigment, and *eumelanin,* a brown-black pigment.

Table 85-1 Classification of Major Causes of Albinism

TYPE	GENE	CHROMOSOME
OCULOCUTANEOUS ALBINISM (OCA)		
OCA1 (tyrosinase deficient)	*TYR*	11q14-q21
OCA1A (severe deficiency)	*TYR*	11q14-q21
OCA1B (mild deficiency)*	*TYR*	11q14-q21
OCA2 (tyrosinase positive)†	*OCA2*	15q12-q13
OCA3 (Rufous, red OCA)	*TYRP1*‡	9p23
OCA4	*SLC45A2*	5p13.3
Hermansky-Pudlak syndrome	*HPS1-9*	Different chromosomes
Chédiak-Higashi syndrome	*LYST*	1q42.1
OCULAR ALBINISM (OA)		
OA1 (Nettleship-Falls type)	*OA*	Xp22.3
LOCALIZED ALBINISM		
Piebaldism	*KIT*	4q12
Waardenburg syndrome (WS1-WS4)	See text	See text

*This includes Amish, minimal pigment, yellow albinism, and platinum and temperature-sensitive variants.
†Includes brown OCA.
‡Tyrosinase-related protein 1.

Clinically, primary albinism can be generalized or localized. Primary generalized albinism can be either ocular or oculocutaneous. Some syndromes feature albinism in association with platelet, immunological, or neurological dysfunction.

In generalized oculocutaneous albinism, hypopigmentation can be either complete or partial. Individuals with complete albinism do not develop either generalized (tanning) or localized (pigmented nevi) skin pigmentation.

The diagnosis of albinism is usually evident, but for some white children whose families are particularly light-skinned, normal variation may be a diagnostic consideration. Unlike patients with albinism, normal fair-skinned children progressively develop pigmentation with age, do not exhibit the eye manifestations of albinism, and have pigmentary development similar to other family members. The clinical diagnosis of oculocutaneous albinism, as opposed to other types of cutaneous hypopigmentation, requires the presence of characteristic eye findings.

The ocular manifestations of albinism include hypopigmentation of iris and retina with foveal hypoplasia along with, reduced visual acuity, refractive errors, nystagmus, alternating strabismus, and a red reflex (diffuse reddish hue of the iris produced during ophthalmoscopic or slit-lamp examination of the eye). There is also an abnormality in routing of the optic fibers at the chiasm. Unlike normally in pigmented individuals, in patients with albinism the majority of the nerve fibers from the temporal side of the retina cross to the contralateral hemisphere of the brain. This results in lack of biocular (stereoscopic) vision and depth perception, and in repeated switching of vision from eye to eye, causing alternating strabismus. This abnormality also causes a characteristic pattern of visual-evoked potentials. These findings are highly specific for albinism and can be used to formally establish the clinical diagnosis. Regular ophthalmologic follow-up is recommended for patients with oculocutaneous albinism; correction of refractive errors can maximize visual function. Normally the alternating strabismus does not result in amblyopia and does not require surgery.

Patients with albinism should be counseled to avoid UV radiation by wearing protective long-sleeved clothing and by using sunscreens with a sun protection factor rating above 30. All forms of oculocutaneous albinism are autosomal recessive traits.

Melanin is also present in the cochlea. Albino individuals may be more susceptible to ototoxic agents such as gentamicin.

Many clinical forms of albinism have been identified. Some of the seemingly distinct clinical forms are caused by different mutations of the same gene. Several genes located on different chromosomes are involved in melanogenesis (see Table 85-1). Attempts to differentiate types of albinism based on the mode of inheritance, tyrosinase activity, or the extent of hypopigmentation have failed to yield a comprehensive classification. The following classification is based on the distribution of albinism in the body and the type of mutated gene.

Mutation detection is clinically available for most albinism genes (see Table 85-1). Molecular diagnosis is of little use therapeutically in isolated albinism but can be helpful for precise genetic counseling of families.

Oculocutaneous (Generalized) Albinism

Lack of pigment is generalized, affecting skin, hair, and eyes. At least 4 genetically distinct forms of oculocutaneous albinism (OCA) have been identified: OCA_1, OCA_2, OCA_3, and OCA_4. The lack of pigment is complete in patients with OCA_1 A; the other types may not be clinically distinguishable from one another. All affected individuals have ocular manifestations of albinism (see above). All forms are inherited as autosomal recessive traits.

OCA_1 (Tyrosinase-Deficient Albinism)

The defect in these patients resides in the tyrosinase gene, *TYR*, located on chromosome 11q14.3. Many mutant alleles have been identified. Most affected individuals are genetic compounds, heterozygous for 2 different mutant alleles. A clinical clue to the diagnosis of OCA_1 is complete lack of pigment at birth. The condition can be subdivided to OCA_1 A and OCA_1 B, based on enzyme activity and difference in clinical manifestations as a function of age.

OCA_1 A (Tyrosinase-Negative OCA)

In these individuals, who have the most severe form of OCA, both *TYR* alleles have mutations that completely inactivate tyrosinase. Clinically, lack of pigment in the skin (milky white), hair (white hair), and eyes (red gray irides) is evident at birth and remains unchanged throughout life. They do not tan and do not develop pigmented nevi or freckles.

OCA_1 B

These patients have *TYR* gene mutations that preserve some residual activity. Clinically they completely lack pigment at birth, but with age become light blond with light blue or hazel eyes. They develop pigmented nevi and freckles and they may tan. OCA_1 B patients, depending on the degree of pigmentation, were once subdivided into different groups and thought to be genetically distinct.

OCA_2 (Tyrosinase-Positive OCA)

This is the most common form of generalized OCA, particularly in African blacks. Clinically, the phenotype is highly variable; most patients demonstrate some pigmentation of the skin and eyes at birth and continue to accumulate pigment throughout their lives. The hair is yellow at birth and may darken with age. They have pigmented nevi and freckles and some may tan. They may be clinically indistinguishable from OCA_1 B. Individuals with OCA_2, however, have normal tyrosinase activity in hair bulbs. The defect is in the *OCA_2* gene which is homologous to the *p* (pink-eyed dilution) gene in the mouse. This gene produces the P protein, a melanosome membrane protein. Patients with forms of Prader-Willi and Angelman syndromes caused by microdeletion of chromosome 15q12 that includes the *OCA_2* gene have mild pigmentary deficiency (see Chapter 81.8).

OCA_3 (Rufous Albinism)

This form has been identified only in Africans, African-Americans, and natives of New Guinea. Patients have reddish hair and reddish brown skin as adults. The skin color is peculiar to this form. In the young, the coloration may resemble that of OCA_2. Patients with OCA_3 can make pheomelanin but not eumelanin. The mutation is in the tyrosinase-related protein 1 (*TYRP1*) gene (located on chromosome 9p23), the function of which is not well-understood.

OCA_4

Similar manifestations to OCA_2 (both in the skin and the eyes) have been observed in patients (mostly from Japan) with mutations in the *SLC45A2* (previously called *MATP*) gene located on chromosome 5p13.2.

Ocular Albinism

Ocular albinism (OA) is limited to the eye. All the eye findings of albinism (see above) are present. Most cases are X-linked (OA_1).

Ocular Albinism 1 (Nettleship-Falls Type)

Only the hemizygous male has the complete manifestation. Segments of abnormal retinal pigmentation may be present in heterozygous females. An X-linked OA with late-onset sensorineural deafness has also been reported. The diagnosis of ocular albinism 1 (OA_1) is evident in males with the features of albinism in the eye, normal skin pigmentation, and a positive family history suggestive of an X-linked recessive transmission. Mild hypopigmentation of the skin (compared to unaffected siblings) may be present. It is a nonprogressive disorder and the eye findings, in fact, often improve with age. In patients who are the first of their families to be affected, electron microscopic demonstration of characteristic mega melanosomes in skin biopsies or hair root specimens is useful, as is mutation analysis of the *OA_1* gene on chromosome Xp22.2.

Syndromic Forms of Generalized Albinism

Hermansky-Pudlak Syndrome

This group of autosomal recessive disorders is caused by mutations of 1 of 9 different genes located on different chromosomes, *HPS1* to *HPS9*. Hermansky-Pudlak syndrome is suspected in patients with albinism and a bleeding diathesis. Disease subtype can be established with molecular studies.

The *HPS* genes are necessary for normal structure and function of lysosome-derived organelles, including melanosomes and platelet dense bodies. Patients have a tyrosinase-positive OCA of variable severity associated with platelet dysfunction (owing to the absence of platelet dense bodies). A ceroid-like material accumulates in tissues. Hermansky-Pudlak syndrome is most prevalent in 2 regions of Puerto Rico (type 1 in the northwest and type 3 in the central regions as a result of different founder effects). The cutaneous and ocular symptoms of albinism are present. Patients can develop epistaxis, postsurgical bleeding, or abundant menses. Bleeding time is prolonged but platelet count is normal. Major complications are progressive pulmonary fibrosis in young adults and Crohn-like inflammatory bowel disease in adolescents and young adults. Kidney failure and cardiomyopathy are reported. Neutropenia is described in HPS type 2. Treatment is symptomatic.

Chédiak-Higashi Syndrome

Patients with this rare autosomal recessive condition (see Chapter 130) have OCA of variable severity and susceptibility to infection. Bacterial infections of skin and upper respiratory tract are common. Giant peroxidase-positive lysosomal granules can be seen in granulocytes in a blood smear. Patients have a reduced number of melanosomes, which are abnormally large (macromelanosomes). The bleeding tendency is typically mild. The major, life-threatening complication is macrophage activation with hemophagocytic lymphohistiocytosis, manifested by fever, lymphadenopathy, hepatosplenomegaly, cytopenias, and elevated plasma ferritin level. Patients surviving childhood may develop cerebellar atrophy, peripheral neuropathy, and cognitive delay. Mutations in the *LYST* gene on chromosome 1q are the only known cause of this syndrome.

Hypopigmentation is a feature of other syndromes, some with abnormalities of lysosomal biogenesis or melanosome biology, such as *Griscelli syndrome* (silver-gray hair, pigmentary dilution of skin, and melanosomal clumping in hair shafts and the center of melanocytes, with intellectual disability or macrophage activation with hemophagocytosis in different subtypes), *Vici syndrome* (combined immunodeficiency, intellectual disability, agenesis of the corpus callosum, cataracts, and cleft lip and palate), and MAPBP interacting protein deficiency (short stature, recurrent infections, neutropenia).

Localized Albinism

Localized albinism refers to localized patches of hypopigmentation of skin and hair, which may be evident at birth or develop with time. These conditions are caused by abnormal migration of melanocytes during embryonic development.

Piebaldism

Piebaldism is an autosomal dominant inherited condition in which the individual is usually born with a white forelock. The underlying skin is depigmented and devoid of melanocytes. In addition, there are usually white macules on the face, trunk, and extremities. Mutations in the *KIT* gene have been shown in affected patients.

Waardenburg Syndrome

In this syndrome, a white forelock is associated with lateral displacement of inner canthi of the eyes, broad nasal bridge, heterochromia of irides, and sensorineural deafness. This condition is inherited as an autosomal dominant trait. Four major types of this syndrome have been identified. Patients with type 1 (WS1, the most common form) have all the above clinical findings including lateral displacement of inner canthi. The condition is caused by mutation (>90%) or deletion of the *PAX3* gene. Patients with type 2 (WS2) have all the clinical findings of WS1 except the lateral displacement of inner canthi. Genetically, this is a heterogeneous condition caused by mutations in different genes located on different chromosomes. Patients with type 3 (WS3) have all the findings seen in individuals with WS1 plus hypoplasia and contractures of the upper limbs. It is caused by heterozygous or homozygous mutations of *PAX3* gene. Type 4 (WS4), associated with Hirschsprung disease, is heterogeneous; mutations in different genes (*EDN3, EDNRB,* or *SOX10*) have been identified in different patients.

Other causes of localized hypopigmentation are discussed in other chapters (e.g., hypomelanosis of Ito, see Chapters 81 and 653; and vitiligo, see Chapter 653).

Bibliography is available at Expert Consult.

85.3 Methionine

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The usual pathway for catabolism of methionine, an essential amino acid, produces *S*-adenosylmethionine, which serves as a methyl group donor for methylation of a variety of compounds in the body, and cysteine, which is formed through a series of reactions collectively called trans-sulfuration (Fig. 85-3).

HOMOCYSTINURIA (HOMOCYSTINEMIA)

Normally, most homocysteine, an intermediate compound of methionine degradation, is remethylated to methionine. This methionine-sparing reaction is catalyzed by the enzyme methionine synthase, which requires a metabolite of folic acid (5-methyltetrahydrofolate) as a methyl donor and a metabolite of vitamin B_{12} (methylcobalamin), as well as *S*-adenosylcobalamin, as cofactors (see Fig. 85-3). Only approximately 20% of total homocysteine (and its dimer homocystine) is in free form in the plasma of normal individuals. The rest is bound to proteins as mixed disulfides. Three major forms of homocystinemia and homocystinuria have been identified.

Homocystinuria Caused by Cystathionine β-Synthase Deficiency (Classic Homocystinuria)

This is the most common inborn error of methionine metabolism. Approximately 40% of affected patients respond to high doses of vitamin B_6 and usually have milder clinical manifestations than those who are unresponsive to vitamin B_6 therapy. These patients possess some residual enzyme activity.

Infants with this disorder are normal at birth. **Clinical manifestations** during infancy are nonspecific and may include failure to thrive and developmental delay. The diagnosis is usually made after 3 yr of age, when subluxation of the ocular lens **(ectopia lentis)** occurs. This causes severe myopia and iridodonesis (quivering of the iris). Astigmatism, glaucoma, staphyloma, cataracts, retinal detachment, and optic atrophy may develop later in life. Progressive **intellectual disability** is common. Normal intelligence has been reported. In an international survey of more than 600 patients, IQ scores ranged from 10-135. Higher IQ scores are seen in vitamin B_6–responsive patients. **Psychiatric and behavioral disorders** have been observed in more than 50% of affected patients. Convulsions occur in approximately 20% of patients. Affected individuals with homocystinuria manifest **skeletal abnormalities** resembling those of Marfan syndrome (see Chapter 702); they are usually tall and thin, with elongated limbs and arachnodactyly. Scoliosis, pectus excavatum or carinatum, genu valgum, pes cavus, high-arched palate, and crowding of the teeth are commonly seen. These children usually have fair complexions, blue eyes, and a peculiar malar flush. Generalized osteoporosis, especially of the spine, is the main roentgenographic finding. **Thromboembolic episodes** involving both large and small vessels, especially those of the brain, are common and may occur at any age. Optic atrophy, paralysis, cor pulmonale, and severe hypertension (from renal infarcts) are among the serious consequences of thromboembolism, which is caused by

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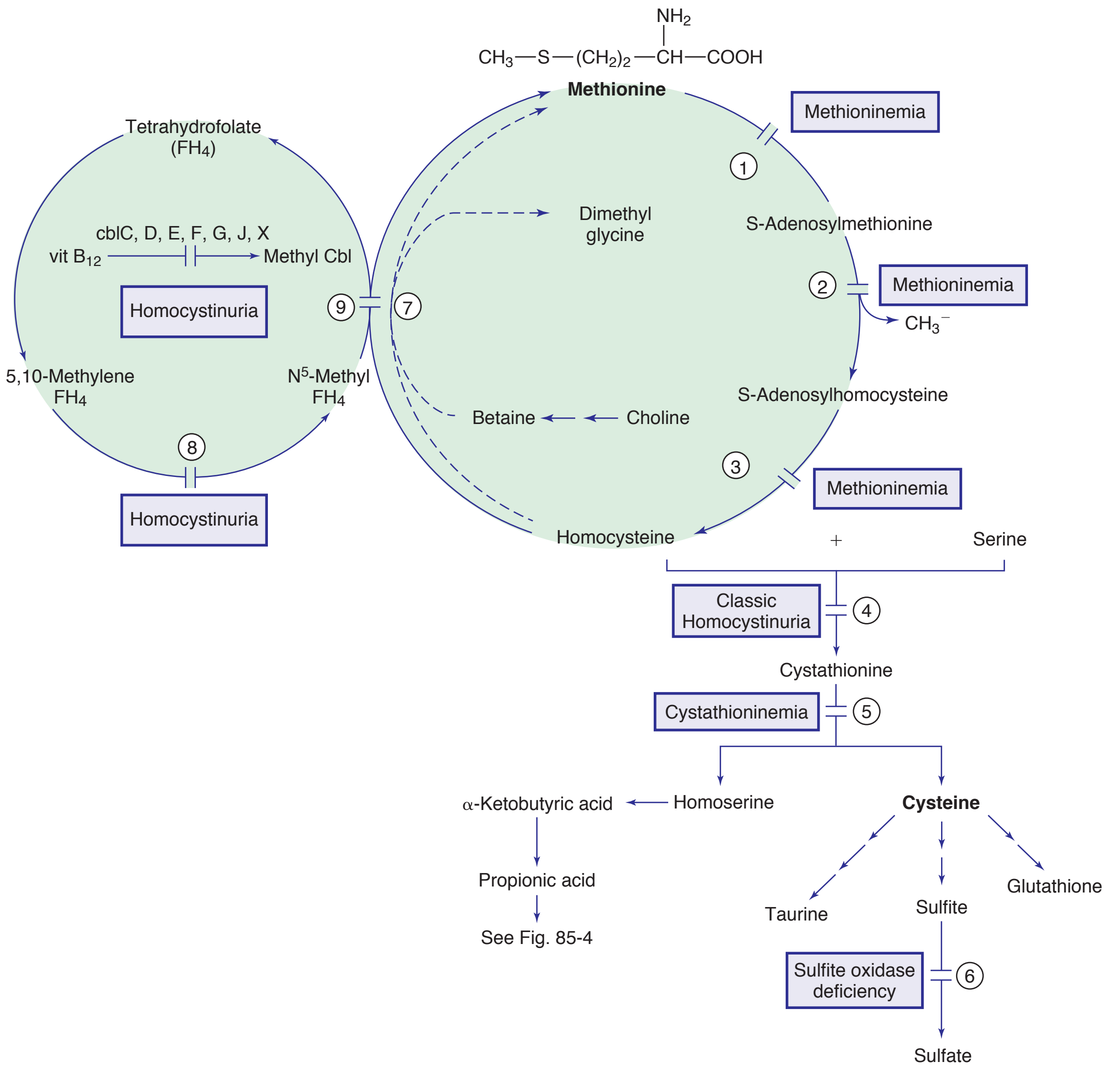

Figure 85-3 Pathways in the metabolism of sulfur-containing amino acids. **Enzymes:** *(1)* Methionine adenosyltransferase (MAT I/III), *(2)* glycine-N-methyltransferase, *(3)* adenosylhomocysteine hydrolase, *(4)* cystathionine synthase, *(5)* cystathionase, *(6)* sulfite oxidase, *(7)* betaine homocysteine methyltransferase, *(8)* methylene tetrahydrofolate reductase, *(9)* Methionine synthase (cblG).

changes in the vascular walls and increased platelet adhesiveness secondary to elevated homocystine levels. The risk of thromboembolism increases after surgical procedures. Spontaneous pneumothorax and acute pancreatitis are rare complications.

Elevations of both methionine and homocystine (or homocysteine) in body fluids are the diagnostic **laboratory findings**. Freshly voided urine should be tested for homocystine because this compound is unstable and may disappear as the urine is stored. Cystine is low or absent in plasma. The diagnosis may be established by assay of the enzyme in liver biopsy specimens, cultured fibroblasts, or phytohemagglutinin-stimulated lymphocytes or by DNA analysis.

Treatment with high doses of vitamin B_6 (200-1,000 mg/24 hr) causes dramatic improvement in most patients who are responsive to this therapy. The degree of response to vitamin B_6 treatment may be different in different families. Some patients may not respond because of folate depletion; a patient should not be considered unresponsive to vitamin B_6 until folic acid (1-5 mg/24 hr) has been added to the treatment regimen. Restriction of methionine intake in conjunction with cysteine supplementation is recommended for patients who are unresponsive to vitamin B_6. The need for dietary restriction and its extent remains controversial in patients with vitamin B_6–responsive form. In some patients with this form, addition of betaine may obviate the need for any dietary restriction. Betaine (trimethylglycine, 6-9 g/24 hr for adults or 200-250 mg/kg/day for children) lowers homocysteine levels in body fluids by remethylating homocysteine to methionine (see Fig. 85-3); this may result in further elevation of plasma methionine levels. This treatment has produced clinical improvement (preventing vascular events) in patients who are unresponsive to vitamin B_6 therapy. Cerebral edema has occurred in a patient with vitamin B_6–nonresponsive homocystinuria and dietary noncompliance during betaine therapy. Administration of large doses of vitamin C (1 g/day) has improved endothelial function; long-term clinical efficacy is not known.

More than 100 pregnancies in women with the classic form of homocystinuria have been reported with favorable outcomes for both mothers and infants. The majority of infants were full-term and normal. Postpartum thromboembolic events occurred in a few mothers. All but 1 of the 38 affected male patients has had normal offspring.

The screening of newborn infants for classic homocystinuria has been performed worldwide and a prevalence of 1 in 200,000 to 1 in 350,000 live births has been estimated. The condition seems more common in New South Wales, Australia (1 in 60,000 live births), and Ireland. Early treatment of patients identified by the screening process has produced favorable results. The mean IQ of 16 patients with vitamin B_6–unresponsive form treated in early infancy was 94 ± 4. Dislocation of the lens seemed to be prevented in some patients.

Homocystinuria is inherited as an autosomal recessive trait. The gene for cystathionine β-synthase *(CBS)* is located on chromosome 21q22.3. Prenatal diagnosis is feasible by performing an enzyme assay of cultured amniotic cells or chorionic villi or by DNA analysis. Many disease-causing mutations (>150) have been identified in different families. The majority of affected patients are compound heterozygotes for 2 different alleles. Heterozygous carriers are usually asymptomatic; thromboembolic events and coronary heart disease are more common in these individuals than in the normal population.

Homocystinuria Caused by Defects in Methylcobalamin Formation

Methylcobalamin is the cofactor for the enzyme methionine synthase, which catalyzes remethylation of homocysteine to methionine. There are at least 7 distinct defects in the intracellular metabolism of cobalamin that may interfere with the formation of methylcobalamin. To better understand the metabolism of cobalamin, see methylmalonic acidemia (Fig. 85-4; see Chapter 85.6 and Fig. 85-3). The 7 defects are designated as *cbl*C, *cbl*D (including *cbl*D variant 1), *cbl*E *(methionine synthase reductase)*, *cbl*G *(methionine synthase)*, and *cbl*F, *cbl*J, and *cbl*X. Patients with *cbl*C, *cbl*D (not including those with *cbl*D variant 1 or variant 2), *cbl*F, *cblJ*, and *cblX* defects have methylmalonic acidemia in addition to homocystinuria, because formation of both adenosylcobalamin and methylcobalamin is impaired (See Chapter 85.6 for further information about these defects.).

Patients with *cbl*E, *cbl*G, and *cbl*D variant 1 defects are unable to form methylcobalamin and develop homocystinuria without methylmalonic acidemia (see Fig. 85-4); fewer than 40 patients are known with each of these diseases.

The **clinical manifestations** are similar in patients with all of these defects. Vomiting, poor feeding, failure to thrive, lethargy, hypotonia, seizures, and developmental delay may occur in the first few months of life. One patient with the *cbl*G defect was not symptomatic (except for mild developmental delay) until she was 21 yr old when she developed difficulty in walking and numbness of the hands. **Laboratory findings** include megaloblastic anemia, homocystinuria, and hypomethioninemia. The presence of megaloblastic anemia differentiates these defects from homocystinuria due to methylenetetrahydrofolate reductase deficiency (see below). The absence of hypermethioninemia differentiates both of these conditions from cystathionine β-synthase deficiency (see above). Renal artery thrombosis, hemolytic uremic syndrome, pulmonary hypertension and optic nerve atrophy have been reported in some patients with these defects.

Diagnosis is established by complementation studies performed in cultured fibroblasts. Prenatal diagnosis has been accomplished by studies in amniotic cell cultures. These conditions (*cbl*E, *cbl*G, and *cbl*D variant 1) are inherited as autosomal recessive traits. The gene for *cbl*E is *MTRR*, encoding methionine synthase reductase (located on chromosome 5p15.3-p15.2) and the gene for *cbl*G is *MTR*, encoding methionine synthase (located on chromosome 1q43); *cbl*D variant 1 is caused by mutations affecting the C-terminal of the *MMADHC* gene (located on chromosome 2q23.2). Several disease-causing mutations, including a common missense mutation (P1173L) in the *MTR* gene, have been described.

Treatment with vitamin B_{12} in the form of hydroxycobalamin (1-2 mg/24 hr) is used to correct the clinical and biochemical findings. Results vary among both diseases and sibships.

Defects causing both homocystinuria and methylmalonic acidemias are discussed in Chapter 85.6.

Homocystinuria Caused by Deficiency of Methylenetetrahydrofolate Reductase

This enzyme reduces 5,10-methylenetetrahydrofolate to form 5-methyltetrahydrofolate, which provides the methyl group needed for remethylation of homocysteine to methionine (see Fig. 85-3).

The severity of the enzyme defect and the clinical manifestations varies considerably in different families. **Clinical findings** vary from apnea, seizure, microcephaly, coma, and death to developmental delay, ataxia, and motor abnormalities or even psychiatric manifestations. Premature vascular disease or peripheral neuropathy has been reported as the only manifestation of this enzyme deficiency in some patients. Adults with severe enzyme deficiency may even be completely asymptomatic. Exposure to the anesthetic nitrous oxide (which inhibits methionine synthase) in patients with methylenetetrahydrofolate reductase (MTHFR) deficiency may result in neurologic deterioration and death.

Laboratory findings include moderate homocystinemia and homocystinuria. The methionine concentration is low or low normal. This finding differentiates this condition from classic homocystinuria caused by cystathionine β-synthase deficiency. Absence of megaloblastic anemia distinguishes this condition from homocystinuria caused by methylcobalamin formation (see above). Thromboembolism of vessels has also been observed in these patients. Diagnosis may be confirmed by the enzyme assay in cultured fibroblasts or leukocytes or by finding causal mutation in the *MTHR* gene.

A number of polymorphisms have been described in the *MTHR* gene. Two of these (677C → T and 1298A → C) may affect levels of plasma total homocysteine and have been studied as possible risk factors for a wide variety of medical conditions, ranging from birth defects to vascular disease and even cancer, Alzheimer disease, and death from leukemia. To date, the best data support a role for 677C → T polymorphism as a risk factor for neural tube defects. Although a clinical test for this polymorphism is widely available, its predictive value in any given individual has yet to be determined.

Treatment of severe MTHFR deficiency with a combination of folic acid, vitamin B_6, vitamin B_{12}, methionine supplementation, and betaine has been tried. Of these, early treatment with betaine seems to have the most beneficial effect.

The condition is inherited as an autosomal recessive trait; the gene for the enzyme has been located on chromosome 1p36.3 and many disease-causing mutations have been reported in the *MTHFR* gene. Prenatal diagnosis can be offered by measuring MTHFR enzyme activity in cultured chorionic villus cells or amniocytes, by linkage analysis in informative families, or by DNA analysis of the mutation.

HYPERMETHIONINEMIA

Primary (Genetic) Hypermethioninemia

Elevation of plasma level of methionine occurs in the following genetic conditions:

1. **Classic homocystinuria (see above).**
2. **Hepatic methionine adenosyltransferase (MAT I/MAT III) deficiency:** This enzyme, which has 2 isoforms, MAT I (tetrameric) and MAT III (dimeric), is encoded by a single gene *(MAT 1A)* and is involved in the first step of methionine catabolism (see Fig. 85-3). Another structurally similar enzyme, MAT II, is encoded by a different gene (*MAT 2A* on chromosome 2p11.2) and is expressed predominately in nonhepatic tissues (kidney, brain, lymphocytes). Deficiency of MAT I/MAT III causes hypermethioninemia without homocystinuria. The majority of these patients have been diagnosed in the neonatal period through screening for homocystinuria. Most affected individuals have residual enzyme activity and remain asymptomatic throughout life despite persistent hypermethioninemia. Some complain of an unusual offensive odor to their breath (boiled cabbage). A few patients with complete enzyme deficiency have had neurologic abnormalities related to demyelination (intellectual disability, dystonia, dyspraxia).

   Laboratory studies reveal markedly elevated levels of plasma methionine with a low level of *S*-adenosylmethionine and normal concentrations of *S*-adenosylhomocysteine and homocysteine. These findings differentiate this condition from other causes of hypermethioninemia.

   No uniformly accepted therapeutic regimen has yet emerged. Diets low in methionine result in lowering of plasma methionine, but the advisability of such diets has been questioned since lowering of the plasma methionine level causes further lowering of *S*-adenosylmethionine in the body.

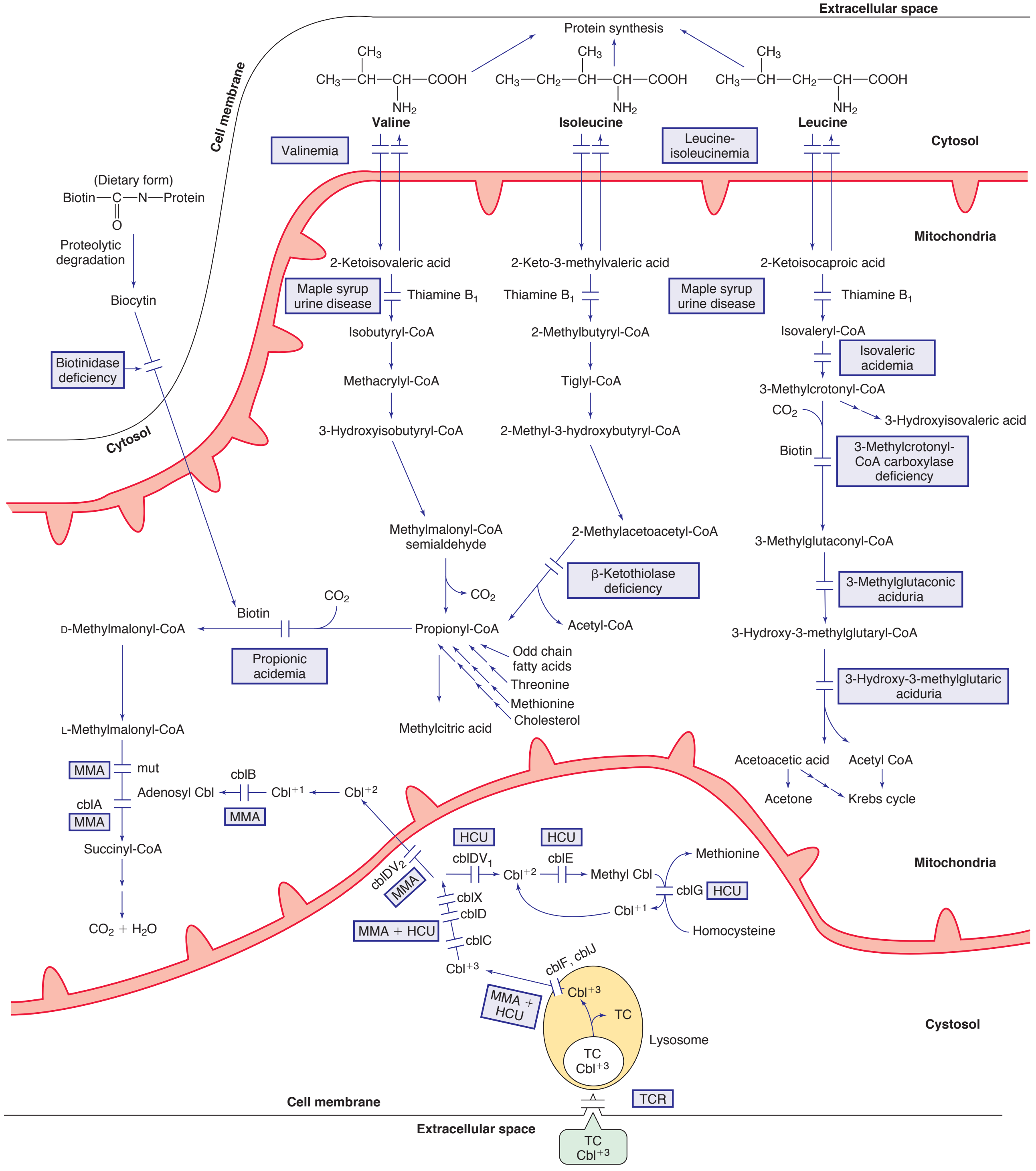

Figure 85-4 Pathways in the metabolism of the branched-chain amino acids, biotin, and vitamin B_{12} (cobalamin). Adenosyl Cbl, adenosylcobalamin; Cbl, cobalamin; cbl, defect in metabolism of cobalamin; cblDV1, cblD variant 1; cblDV2, cblD variant 2; HCU, homocystinuria; Methyl Cbl, methylcobalamin; MMA, methylmalonic acidemia; MUT, mutase; OHCbl, hydroxycobalamin; TC, transcobalamin; TCR, transcobalamin receptor. See text for the name of the enzymes.

Supplementation with *S*-adenosylmethionine in conjunction with a low methionine diet seems prudent, but no large clinical experience is yet available. Normal pregnancies producing normal offspring have been reported in mothers with MAT (MAT IA) deficiency. The condition is inherited as an autosomal recessive trait. The gene for hepatic MAT is on chromosome 10q22 and several disease-causing mutations have been identified.

3. **Glycine *N*-methyltransferase deficiency:** Although there are many methyltransferases present in the body, glycine *N*-methyltransferase is the critical one for catabolism of *S*-adenosylmethionine to *S*-adenosylhomocysteine (see Fig. 85-3). Three patients with deficiency of this enzyme have been reported to date. Clinically, patients were asymptomatic except for mild hepatomegaly and elevated serum levels of transaminases. Other laboratory findings included hypermethioninemia and very high

levels of serum *S*-adenosylmethionine. No specific treatment has yet been identified. The condition seems to be inherited as an autosomal recessive trait; the gene for the enzyme *(GNMT)* is on chromosome 6p21.1.

4. **Adenosylhomocysteine hydrolase deficiency:** Deficiency of this enzyme (see Fig. 85-3) has been reported in 6 patients from 5 different families. Psychomotor retardation and severe hypotonia were common clinical findings in affected individuals. Laboratory studies included elevated levels of serum creatine kinase, hypoalbuminemia (causing fetal hydrops in 1 family), hypoprothrombinemia and markedly elevated levels of serum *S*-adenosylhomocysteine with moderate elevations of plasma methionine and *S*-adenosylmethionine. Marked elevation in *S*-adenosylhomocysteine has been thought to cause inhibition of methyltransferases, including those involved in synthesis of creatine (see Fig. 85-10) and choline, resulting in their deficiencies. MRI of the brain showed delayed myelination of the white matter. Treatment with a low methionine diet in conjunction with creatine and phosphatidylcholine shows encouraging results in some patients.
5. **Tyrosinemia type I** (see Chapter 85.2).
6. **Citrin deficiency** (see Chapter 85.12).

Acquired (Nongenetic) Hypermethioninemia

Hypermethioninemia occurs in premature and some full-term infants receiving high-protein diets, in whom it may represent delayed maturation of the enzyme MAT. Lowering the protein intake usually resolves the abnormality. It is also commonly found in patients with various forms of liver disease.

CYSTATHIONINEMIA (CYSTATHIONINURIA)

Secondary cystathioninuria occurs in patients with vitamin B_6 or B_{12} deficiency, liver disease (particularly damage caused by galactosemia), thyrotoxicosis, hepatoblastoma, neuroblastoma, ganglioblastoma, or defects in remethylation of homocysteine.

Cystathionase deficiency results in massive cystathioninuria and mild to moderate cystathioninemia; cystathionine is not normally detectable in blood. Deficiency of this enzyme is inherited as an autosomal recessive trait and its prevalence is estimated to be about 1 in 14,000 live births. Affected subjects with a wide variety of clinical manifestations have been reported. Lack of a consistent clinical picture and the presence of cystathioninuria in a number of individuals free of clinical findings suggest that cystathionase deficiency may be of no clinical significance. A majority of reported cases are responsive to oral administration of large doses of vitamin B_6 (≥100 mg/24 hr). When cystathioninuria is discovered in a patient, vitamin B_6 treatment seems indicated, but its beneficial effect has not been established. The gene encoding for cystathionase (*CTH*) is located on chromosome16 1p31.1

Bibliography is available at Expert Consult.

85.4 Cysteine/Cystine

Iraj Rezvani

Cysteine is a sulfur-containing nonessential amino acid that is synthesized from methionine (see Fig. 85-3). In the presence of oxygen, 2 molecules of cysteine are oxidized to form cystine. The most common genetic disorders of cysteine/cystine metabolism are cystinuria (see Chapter 547) and cystinosis (see Chapter 529.3).

Sulfite Oxidase Deficiency (Molybdenum Cofactor Deficiency)

At the last step in cysteine metabolism, sulfite is oxidized to sulfate by sulfite oxidase, and the sulfate is excreted in the urine (see Fig. 85-3). This enzyme requires a molybdenum-pterin complex named molybdenum cofactor. This cofactor is also necessary for the function of 2 other enzymes in humans: xanthine dehydrogenase (which oxidizes xanthine and hypoxanthine to uric acid) and aldehyde oxidase (involved in oxidizing a number of natural compounds and drugs). Three enzymes, encoded by 3 different genes (*MOCS1*, *MOCS2,* and *GPHN*) are involved in the synthesis of the cofactor. The genes for these enzymes are mapped to chromosomes 6p21.2, 5q11.2, and 14q23.3, respectively. Deficiency of any of the 3 enzymes causes cofactor deficiency with identical phenotype. Most patients, who were originally diagnosed as having sulfite oxidase deficiency, have been proven to have molybdenum cofactor deficiency. Both conditions are inherited as autosomal recessive traits. The gene for sulfite oxidase (*SUOX*) is on chromosome 12q13.2.

The enzyme and or the cofactor deficiencies produce identical **clinical manifestations**. Refusal to feed, vomiting, severe intractable seizures (tonic, clonic, myoclonic), cortical atrophy with subcortical multicystic lesions, and severe developmental delay may develop within a few weeks after birth. Bilateral dislocation of ocular lenses is a common finding in patients who survive the neonatal period. The intractable seizures seen in this condition are, in large part, a consequence of secondary vitamin B_6 dependency. The accumulation of sulfites in body fluids in this condition causes the inhibition of antiquitin enzyme which is necessary for conversion of α-aminoadipic semialdehyde to α-aminoadipic acid; the resultant accumulation of α-aminoadipic semialdehyde and its cyclic form P6C causes the inactivation of pyridoxal-5-phosphate (active form of vitamin B_6) and, hence, the vitamin B_6–dependent epilepsy (see also Chapter 85.14).

These children excrete large amounts of sulfite, thiosulfate, *S*-sulfocysteine, xanthine, and hypoxanthine in their urine. Urinary and serum levels of uric acid and urinary concentration of sulfate are diminished. Fresh urine should be used for screening purposes and for quantitative measurements of sulfite, because oxidation of sulfite to sulfate at room temperature may produce false-negative results. Increased concentrations of α-aminoadipic semialdehyde and its cyclic form, P6C, and pipecolic acid are present in the CSF, plasma, and urine.

Diagnosis is confirmed by measurement of sulfite oxidase and molybdenum cofactor in fibroblasts and liver biopsies, respectively or by DNA studies. Prenatal diagnosis is possible by performing an assay of sulfite oxidase activity in cultured amniotic cells, in samples of chorionic villi or by DNA studies.

No effective **treatment** is available; large doses of vitamin B_6 (5-100 mg/kg) result in dramatic alleviation of seizures but do not seem to alter the devastating neurologic outcome. Most children die in the 1st 2 yr of life. One patient had an initial response to cyclic pyranopterin monophosphate (cPMP). The prevalence of these deficiencies in the general population is not known.

Bibliography is available at Expert Consult.

85.5 Tryptophan

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Tryptophan is an essential amino acid and a precursor for nicotinic acid (niacin) and serotonin (Fig. 85-5). The genetic disorders of metabolism of serotonin, one of the major neurotransmitters, are discussed in Chapter 85.11.

HARTNUP DISORDER

In this autosomal recessive disorder, named after the first affected family, there is a defect in the transport of monoamino-monocarboxylic amino acids (neutral amino acids), including tryptophan, by the intestinal mucosa and renal tubules. The transporter protein for these amino acids (B0AT1) is encoded by the *SLC6A19* gene located on chromosome 5p15.33. Two chemically close transcription factors, angiotensin-converting enzyme (ACE2) in the intestine and renal tubules, and collectrin in the renal tubules, are required for expression of B0AT1 transporter protein by the *SLC6A19* gene. The mutated gene in patients with Hartnup disorder, unable to interact with the above

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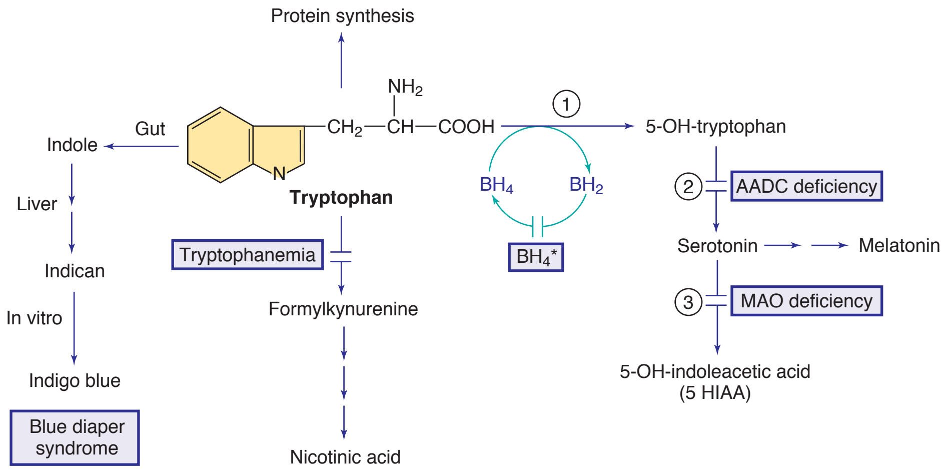

Figure 85-5 Pathways in the metabolism of tryptophan. PKU* indicates hyperphenylalaninemia caused by tetrahydrobiopterin deficiency (see Fig. 85-1). **Enzymes:** *(1)* Tryptophan hydroxylase, *(2)* aromatic L-amino acid decarboxylase (AADC), *(3)* monoamine oxidase (MAO).

transcription factors, results in deficiency of B0AT1 protein either in the intestine or in the renal tubules or in both. This explains the absence of renal or intestinal transport defect seen in some affected families. Decreased intestinal absorption of tryptophan in conjunction with its increased renal loss is believed to cause reduced availability of tryptophan for niacin synthesis in affected individuals. Most children with Hartnup defect remain asymptomatic. The major clinical manifestation in the rare symptomatic patient is cutaneous photosensitivity. The skin becomes rough and red after moderate exposure to the sun, and with greater exposure, a pellagra-like rash may develop. The rash may be pruritic, and a chronic eczema may develop. The skin changes have been reported in affected infants as young as 10 days of age. Some patients may have intermittent ataxia manifested as an unsteady, wide-based gait. The ataxia may last a few days and usually recovers spontaneously. Mental development is usually normal. Two individuals in the original kindred were cognitively impaired. Episodic psychiatric manifestations such as irritability, emotional instability, depression, and suicidal tendencies, have been observed; these changes are usually associated with bouts of ataxia. Short stature and atrophic glossitis are seen in some patients.

Most children diagnosed with Hartnup disorder by neonatal screening have remained asymptomatic. This indicates that other factors are also involved in pathogenesis of the clinical condition.

The main **laboratory finding** is aminoaciduria, which is restricted to neutral amino acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, histidine). Urinary excretion of proline, hydroxyproline, and arginine remains normal. This finding differentiates Hartnup disorder from other causes of generalized aminoaciduria, such as Fanconi syndrome. Plasma concentrations of neutral amino acids are usually normal. This seemingly unexpected finding occurs because these amino acids are absorbed as dipeptides and the transport system for small peptides is intact in Hartnup disorder. The indole derivatives (especially indican) may be found in large amounts in some patients, owing to bacterial breakdown of unabsorbed tryptophan in the intestines.

Diagnosis is established by the striking intermittent nature of symptoms and the previously described urinary findings.

Treatment with nicotinic acid or nicotinamide (50-300 mg/24 hr) and a high-protein diet results in a favorable response in symptomatic patients. Because of the intermittent nature of the clinical manifestations, the efficacy of these treatments is difficult to evaluate. The prevalence of the disorder is estimated to be 1 in 20,000 to 1 in 30,000 live births. Normal outcome both for mother and fetus is reported in affected pregnant women.

Bibliography is available at Expert Consult.

85.6 Valine, Leucine, Isoleucine, and Related Organic Acidemias

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The early steps in the degradation of these 3 essential amino acids, the **branched-chain amino acids**, are similar (see Fig. 85-4). The intermediate metabolites are all organic acids, and deficiency of any of the degradative enzymes, except for the transaminases, causes acidosis; in such instances, the organic acids proximal to the enzymatic block accumulate in body fluids and are excreted in the urine. These disorders commonly cause metabolic acidosis, which usually occurs in the first few days of life. Although most of the clinical findings are nonspecific, some manifestations may provide important clues to the nature of the enzyme deficiency. Figure 85-6 presents an approach to infants suspected of having an organic acidemia. Definitive diagnosis is usually established by identifying and measuring specific organic acids in body fluids (blood, urine), by the enzyme assay, and by identification of the mutant gene.

Organic acidemias are not limited to defects in the catabolic pathways of branched-chain amino acids. Disorders causing accumulation of other organic acids include those derived from lysine (see Chapter 85.14), those associated with lactic acid (see Chapter 87), and dicarboxylic acidemias associated with defective fatty acid degradation (see Chapter 86.1).

MAPLE SYRUP URINE DISEASE

Decarboxylation of leucine, isoleucine, and valine is accomplished by a complex enzyme system (branched-chain α-ketoacid dehydrogenase [BCKDH]) using thiamine (vitamin B_1) pyrophosphate as a coenzyme. This mitochondrial enzyme consists of 4 subunits: $E_{1\alpha}$, $E_{1\beta}$, E_2, and E_3. The E_3 subunit is shared with 2 other dehydrogenases in the body, namely pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. Deficiency of any of these subunits causes maple syrup urine disease (MSUD) (see Fig. 85-4), named after the sweet odor of maple syrup found in body fluids, especially urine. Clinical conditions caused by defects in $E_{1\alpha}$, $E_{1\beta}$, E_2 and E_3 are designated as MSUD type IA, type IB, type 2, and type 3 respectively. This classification, however, is not very helpful clinically because the severity of clinical manifestations does not correlate with or correspond specifically to any single type. An affected infant with type 1A defect can have clinical manifestations ranging from relatively mild to very severe. A more useful classification, based on clinical findings and response to thiamine administration, has identified 5 phenotypes of MSUD as follows:

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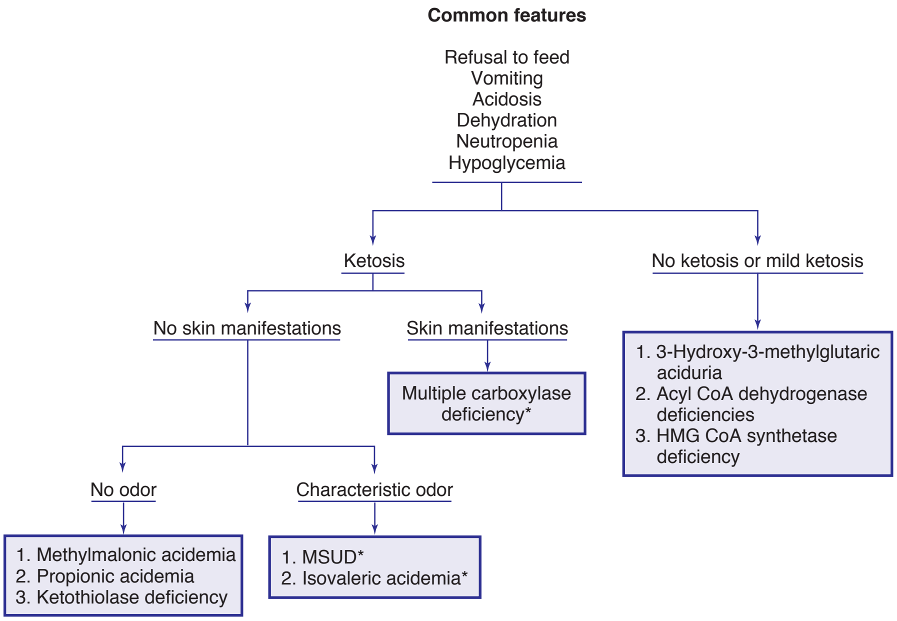

Figure 85-6 Clinical approach to infants with organic acidemia. *Asterisks* indicate disorders in which patients have a characteristic odor (see text and Table 85-2). MSUD, maple syrup urine disease.

Classic Maple Syrup Urine Disease

This form has the most severe clinical manifestations. Affected infants who are normal at birth develop poor feeding and vomiting in the 1st wk of life; lethargy and coma may ensue within a few days. Physical examination reveals hypertonicity and muscular rigidity with severe opisthotonos. Periods of hypertonicity may alternate with bouts of flaccidity manifested as repetitive movements of the extremities (boxing and bicycling). Neurologic findings are often mistakenly thought to be caused by generalized sepsis and meningitis. Cerebral edema may be present; convulsions occur in most infants, and hypoglycemia is common. In contrast to most hypoglycemic states, correction of the blood glucose concentration does not improve the clinical condition. Aside from the serum glucose, routine laboratory findings are usually unremarkable, except for varying degrees of metabolic acidosis. Death usually occurs in untreated patients in the first few weeks or months of life.

Diagnosis is often suspected because of the peculiar odor of maple syrup found in urine, sweat, and cerumen (see Fig. 85-6). It is usually confirmed by amino acid analysis showing marked elevations in plasma levels of leucine, isoleucine, valine, and alloisoleucine (a stereoisomer of isoleucine not normally found in blood) and depression of alanine. Leucine levels are usually higher than those of the other 3 amino acids. Urine contains high levels of leucine, isoleucine, and valine and their respective ketoacids. These ketoacids may be detected qualitatively by adding a few drops of 2,4-dinitrophenylhydrazine reagent (0.1% in 0.1N HCl) to the urine; a yellow precipitate of 2,4-dinitrophenylhydrazone, is formed in a positive test. Neuroimaging during the acute state may show cerebral edema, which is most prominent in the cerebellum, dorsal brainstem, cerebral peduncle, and internal capsule. After recovery from the acute state and with advancing age, hypomyelination and cerebral atrophy may be seen in neuroimaging of the brain. The enzyme activity can be measured in leukocytes and cultured fibroblasts.

Treatment of the acute state is aimed at hydration and rapid removal of the branched-chain amino acids and their metabolites from the tissues and body fluids. Because renal clearance of these compounds is poor, hydration alone may not produce a rapid improvement. Peritoneal dialysis or, preferably, hemodialysis is the most effective mode of therapy in critically ill infants and should be instituted promptly; significant decreases in plasma levels of leucine, isoleucine, and valine are usually seen within 24 hr of institution of treatment. Sufficient calories and nutrients should be provided intravenously or orally as soon as possible so as to reverse the patient's catabolic state. Cerebral edema, if present, may need to be treated with mannitol, diuretics (e.g., furosemide), or hypertonic saline.

Treatment after recovery from the acute state requires a diet low in branched-chain amino acids. Synthetic formulas devoid of leucine, isoleucine, and valine are available commercially. Because these amino acids cannot be synthesized endogenously, small amounts of them should be added to the diet; the amount should be titrated carefully by performing frequent analyses of the plasma amino acids. A clinical condition resembling **acrodermatitis enteropathica** (see Chapter 671) occurs in affected infants whose plasma isoleucine concentration becomes very low; addition of isoleucine to the diet causes a rapid and complete recovery. Patients with MSUD should remain on the diet for the rest of their lives. Liver transplantation has been performed in a number of patients with classic MSUD with promising results. These children have been able to tolerate a normal diet.

The long-term prognosis of affected children remains guarded. Severe ketoacidosis, cerebral edema, and death may occur during any stressful situation such as infection or surgery, especially in mid-childhood. Cognitive and other neurologic deficits are common sequelae.

Intermediate (Mild) Maple Syrup Urine Disease

In this form, affected children develop milder disease after the neonatal period. **Clinical manifestations** are insidious and limited to the CNS. Patients have mild to moderate intellectual disability (usually after 5 mo of age) with or without seizures. They have the odor of maple syrup and excrete moderate amounts of the branched-chain amino acids and their ketoacid derivatives in the urine. Plasma concentrations of leucine, isoleucine, and valine are moderately increased whereas those of lactate and pyruvate are normal. These children are commonly diagnosed during an intercurrent illness when signs and symptoms of classic MSUD may occur. The dehydrogenase activity is 3-40% of normal. Because patients with thiamine-responsive MSUD usually have manifestations similar to those seen in the mild form, a trial of thiamine therapy is recommended. Diet therapy, similar to that of classic MSUD, is needed.

Intermittent Maple Syrup Urine Disease

In this form of MSUD, seemingly normal children develop vomiting, odor of maple syrup, ataxia, lethargy, and coma during any stress or catabolic state such as infection or surgery. During these attacks, laboratory findings are indistinguishable from those of the classic form, and death may occur. **Treatment** of the acute attack of intermittent

MSUD is similar to that of the classic form. After recovery, although a normal diet is tolerated, a diet low in branched-chain amino acids is recommended. Activity of the dehydrogenase in patients with the intermittent form is higher than in the classic form and may reach 40% of the normal activity.

Thiamine-Responsive Maple Syrup Urine Disease

Some children with mild or intermediate forms of MSUD who are treated with high doses of thiamine have dramatic clinical and biochemical improvement. Although some respond to treatment with thiamine at 10 mg/24 hr, others may require as much as 200 mg/24 hr for at least 3 wk before a favorable response is observed. These patients also require diets deficient in branched-chain amino acids. The enzymatic activity in these patients is 30-40% of normal.

Maple Syrup Urine Disease Caused by a Deficiency of E_3 Subunit (Maple Syrup Urine Disease Type 3)

This is a very rare disorder. Patients develop lactic acidosis in addition to signs and symptoms similar to those of intermediate MSUD because the E_3 subunit is also a component of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. Progressive neurologic impairment manifested by hypotonia and developmental delay occurs after 2 mo of age. Abnormal movements progress to ataxia. Death may occur in early childhood.

Laboratory findings include persistent lactic acidosis with high levels of plasma lactate, pyruvate, and alanine. Plasma concentrations of branched-chain amino acids are moderately increased. Patients excrete large amounts of lactate, pyruvate, α-glutarate, and the 3 branched-chain ketoacids in their urine.

No effective **treatment** is available. Dietary restrictions of branched-chain amino acids and treatment with high doses of thiamine, biotin, and lipoic acid have been ineffective.

Genetics and Prevalence of Maple Syrup Urine Disease

All forms of MSUD are inherited as an autosomal recessive trait. The gene for each subunit resides on different chromosomes. The gene for $E_{1\alpha}$ (*BCKDHA*) is on chromosome 19q13.1-q13.2; that for $E_{1\beta}$ (*BCKDHB*) is on chromosome 6q14.1; the gene for E_2 (*DBT*) is on chromosome 1p21.2; and that for E_3 (*DLD*) is on chromosome 7q31.1. Many different disease-causing mutations (>160) have been identified in patients with different forms of MSUD. A given clinical phenotype is caused by a variety of genotypes; as an example, patients from different pedigrees with the classic form of MSUD have been shown to have mutations in genes for $E_{1\alpha}$, $E_{1\beta}$, or E_2 subunits. The exception is the thiamine-responsive MSUD that is shown to be caused by mutations in the E_2 gene in all reported cases to date. Most patients are compound heterozygotes inheriting 2 different mutant alleles. Mutations in genes for $E_{1\alpha}$ (45%) and $E_{1\beta}$ (35%) account for approximately 80% of cases.

The prevalence is estimated at 1 in 185,000 live births. The classic form of MSUD is more prevalent in the Old Order Mennonites in the United States, with estimated prevalence of 1 in 380 live births. Affected patients in this population are homozygous for a specific mutation (c.1312T>A) in the $E_{1\alpha}$ subunit gene.

Early detection of MSUD is feasible by mass screening of newborn infants. In most cases (especially those with classic form of MSUD), however, the infant may be quite sick by the time the results of the screening becomes available (see Chapter 84). Prenatal diagnosis has been accomplished by enzyme assay of the cultured amniocytes, cultured chorionic villus tissue, or direct assay of samples of the chorionic villi and by identification of the mutant gene.

Several successful pregnancies have occurred in women with different forms of MSUD. No ill effects have been observed in the offspring of these patients. Episodes of metabolic decompensation have occurred in the mothers during pregnancy and the postpartum period.

ISOVALERIC ACIDEMIA

This condition is caused by the deficiency of the enzyme isovaleryl CoA dehydrogenase (see Fig. 85-4). Clinically, two forms of the condition are recognized in symptomatic patients: the acute form and the chronic intermittent form.

Clinical manifestations in the *acute form* include vomiting and severe acidosis in the first 2 wk of life. Lethargy, convulsions, and coma may ensue, and death may occur if proper therapy is not initiated. The vomiting may be severe enough to suggest pyloric stenosis. The characteristic odor of "sweaty feet" may be present (in body sweat and cerumen, but not in the urine; see Fig. 85-6). Infants who survive this acute episode will go on to have the chronic intermittent form later in life. In the *chronic intermittent form of the disease,* the first clinical manifestations (vomiting, lethargy, acidosis or coma) may not appear until the child is a few months or a few years old. In both forms, acute episodes of metabolic decompensations may occur during a catabolic state such as an infection. Acute episodes may be mistaken for diabetic ketoacidosis. With worldwide application of newborn screening technology (see Chapter 84) it is now becoming clear that the clinical spectrum in affected patients can range from completely asymptomatic to the acute form. Older siblings of symptomatic newborn infants have been reported with identical genotype and biochemical abnormalities but without any clinical manifestations.

Laboratory findings during the acute attacks include ketoacidosis, neutropenia, thrombocytopenia, and occasionally pancytopenia. Hypocalcemia, hyperglycemia, and moderate to severe hyperammonemia may be present in some patients. Increases in plasma ammonia may suggest a defect in the urea cycle (see Chapter 85.12). In urea cycle defects, the infant is not acidotic (see Fig. 85-6).

Diagnosis is established by demonstrating marked elevations of isovaleric acid and its metabolites (isovalerylglycine, 3-hydroxyisovaleric acid) in body fluids, especially urine. The main compound in plasma is isovalerylcarnitine, which can be measured even in a few drops of dried blood on a filter paper. Diagnosis can be confirmed by measurement of the enzyme activity in cultured skin fibroblasts or by the identification of the mutant gene.

Treatment of the acute attack is aimed at hydration, reversal of the catabolic state (by providing adequate calories orally or intravenously), correction of metabolic acidosis (by infusing sodium bicarbonate), and removal of the excess isovaleric acid. Because isovalerylglycine has a high urinary clearance, administration of glycine (250 mg/kg/24 hr) is recommended to enhance formation of isovalerylglycine. L-Carnitine (100 mg/kg/24 hr orally) also increases removal of isovaleric acid by forming isovalerylcarnitine, which is excreted in the urine. In patients with significant hyperammonemia (blood ammonia >200 µM), measures that reduce blood ammonia should be employed (see Chapter 85.12). Exchange transfusion and peritoneal dialysis may be needed if the previously described measures fail to induce significant clinical and biochemical improvement. After recovery from the acute attack, the patient should receive a low-protein diet (1.0-1.5 g/kg/24 hr) and should be given glycine and carnitine supplements. Pancreatitis (acute or recurrent forms) has been reported in survivors. Normal development can be achieved with early and proper treatment.

Prenatal diagnosis may be accomplished by measuring isovalerylglycine in amniotic fluid, by enzyme assay in cultured amniocytes, or by identification of the mutant gene. Successful pregnancy with favorable outcomes both for the mother and the infant has been reported. Mass screening of newborn infants for detection of this condition is in use in the United States and other countries (see Chapter 84). Isovaleric acidemia is inherited as an autosomal recessive trait. The gene (*IVD*) has been mapped to chromosome 15q15.1 and many disease-causing mutations have been identified. The prevalence of the condition is estimated from 1 in 62,500 (in parts of Germany) to 1 in 250,000 live births (in the United States).

MULTIPLE CARBOXYLASE DEFICIENCIES (DEFECTS IN UTILIZATION OF BIOTIN)

Biotin is a water-soluble vitamin that is a cofactor for all 4 carboxylase enzymes in humans: pyruvate carboxylase, acetyl CoA carboxylase,

propionyl CoA carboxylase, and 3-methylcrotonyl CoA carboxylase. The latter 2 are involved in the metabolic pathways of leucine, isoleucine, and valine (see Fig. 85-4).

Dietary biotin is bound to proteins; free biotin is generated in the intestine by the action of digestive enzymes, by intestinal bacteria, and perhaps by biotinidase. The latter enzyme, which is found in serum and most tissues in the body, is also essential for the recycling of biotin in the body by releasing it from the apoenzymes (carboxylases; see Fig. 85-4). Free biotin must form a covalent peptide bond with the apoprotein of the 4 carboxylases to form the activated enzyme (holocarboxylase). This binding is catalyzed by holocarboxylase synthetase. Deficiencies in this enzyme activity or in biotinidase result in malfunction of all the carboxylases and in organic acidemia.

Holocarboxylase Synthetase Deficiency (Multiple Carboxylase Deficiency Neonatal or Early Form)

Infants with this rare autosomal recessive disorder become symptomatic in the first few weeks of life. Symptoms may appear as early as a few hours after birth to 21 mo of age. **Clinically,** the affected infants who seem normal at birth develop breathing difficulties (tachypnea and apnea) shortly after birth. Feeding problems, vomiting, and hypotonia are also commonly present. If the condition remains untreated, generalized erythematous rash with exfoliation and alopecia (partial or total), failure to thrive, irritability, seizures, lethargy, and even coma may occur. Developmental delay is common. Immune deficiency manifests with susceptibility to infection. The urine may have a peculiar odor, which has been described as similar to tomcat urine. The rash, when present, differentiates this condition from other organic acidemias (see Fig. 85-6).

Laboratory findings include metabolic acidosis, ketosis, hyperammonemia, and the presence of a variety of organic acids (lactic acid, propionic acid, 3-methylcrotonic acid, 3-methylcrotonylglycine, tiglylglycine, methylcitrate, and 3-hydroxyisovaleric acid) in body fluids. Diagnosis is confirmed by the enzyme assay in lymphocytes or cultured fibroblasts or by identification of the mutant gene. Most mutations cause the enzyme to have an increased K_m (Michaelis-Menten dissociation constant) for biotin; the enzyme activity in such patients can be restored by the administration of large doses of biotin.

Treatment with biotin (10 mg/day orally) usually results in an improvement in clinical manifestations and may normalize the biochemical abnormalities. Early diagnosis and treatment are critical to prevent irreversible neurologic damage. In some patients, however, complete resolution may not be achieved even with large doses (up to 80 mg/day) of biotin.

The gene for holocarboxylase synthetase (*HLCS*) is located on chromosome 21q22.1 and many disease-causing mutations have been identified in different families. Prenatal diagnosis has been accomplished by assaying enzyme activity in cultured amniotic cells and by measurement of intermediate metabolites (3-hydroxyisovalerate and methylcitrate) in amniotic fluid or by DNA analysis. Pregnant mothers who had previous offspring with holocarboxylase synthetase deficiency have been treated with biotin late in pregnancy. Affected infants were normal at birth, but the efficacy of the treatment as related to the outcome remains unclear.

Biotinidase Deficiency (Multiple Carboxylase Deficiency—Juvenile or Late Form)

The absence of biotinidase results in biotin deficiency. Infants with this deficiency may develop **clinical manifestations** similar to those seen in infants with holocarboxylase synthetase deficiency but, unlike the latter, symptoms may appear later when the child is several months or years old; symptoms may develop as early as 1 wk of age. Therefore, the term "late form" does not apply to all cases and can be misleading. The delay is presumably because of the presence of sufficient free biotin derived from the mother or the diet. Clinical manifestations are mostly confined to skin and the nervous system. Atopic or seborrheic dermatitis, candidiasis, alopecia, ataxia, seizures (usually myoclonic type), hypotonia, developmental delay, optic atrophy, sensorineural hearing loss, and immunodeficiency (from T-cell abnormalities) may occur. A small number of children with intractable seborrheic dermatitis and partial (15-30% activity) deficiency of the enzyme, in whom the dermatitis resolved with biotin therapy, have been reported; these children were otherwise asymptomatic. Asymptomatic children and adults with this enzyme deficiency have been identified in screening programs. Most of these individuals have been shown to have partial deficiency of the enzyme activity. With the advent of mass screening of newborn infants and early identification and treatment of the affected patients, the clinical disease is predicted to become extinct.

Laboratory findings and the pattern of organic acids in body fluids resemble those associated with holocarboxylase synthetase deficiency (see above). Diagnosis can be established by measurement of the enzyme activity in the serum or by the identification of the mutant gene.

Treatment with free biotin (5-20 mg/24 hr) results in a dramatic clinical and biochemical response. Treatment with biotin is also suggested for individuals with partial biotinidase deficiency.

The prevalence of this autosomal recessive trait is estimated at 1 in 60,000 live births. The gene for biotinidase (*BTD*) is located on chromosome 3p25.1 and many disease-causing mutations (approximately 150) have been identified in different families. Prenatal diagnosis is possible by the measurement of the enzyme activity in the amniotic cells or by identification of the mutant gene.

Multiple Carboxylase Deficiency Because of Dietary Biotin Deficiency

Acquired deficiency of biotin may occur in infants receiving total parenteral nutrition without added biotin, in patients receiving prolonged anticonvulsant drugs (phenytoin, primidone, carbamazepine) or in children with short bowel syndrome or chronic diarrhea who are receiving formulas low in biotin. Excessive ingestion of raw eggs may also cause biotin deficiency because the protein avidin in egg white binds biotin and makes it unavailable for absorption. Infants with biotin deficiency may develop dermatitis, alopecia, and candidal skin infections.

ISOLATED 3-METHYLCROTONYL COENZYME A (CoA) CARBOXYLASE DEFICIENCY

This enzyme is 1 of 4 carboxylase enzymes in the body that require biotin as a cofactor (see Fig. 85-4). An isolated deficiency of this enzyme must be differentiated from disorders of biotin metabolism (multiple carboxylase deficiency), which causes diminished activity of all 4 carboxylases (see above). 3-Methylcrotonyl CoA carboxylase is a heteromeric enzyme consisting of α (biotin containing) and β subunits.

Clinical manifestations are highly variable, ranging from fatal neonatal onset (seizures, hypotonia, acidosis) to completely asymptomatic adults (including mothers of affected newborn infants). In the severe form of the condition, the affected infant who has been seemingly normal develops an acute episode of vomiting, hypotonia, lethargy, and convulsions after a minor infection. The onset is usually between 3 wk and 3 yr of age. Death may occur during the acute episode.

Laboratory findings during acute episodes include mild to moderate acidosis, ketosis, severe hypoglycemia, hyperammonemia, and elevated serum levels of liver transaminases. Large amounts of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine are found in the urine. Urinary excretion of 3-methylcrotonic acid is not usually increased in this condition because the accumulated 3-methylcrotonyl CoA is converted to 3-hydroxyisovaleric acid. Severe secondary carnitine deficiency is common. The condition should be differentiated biochemically from multiple carboxylase deficiency (see above) in which lactic acid and metabolites of propionic acid are present in body fluids in addition to 3-hydroxyisovaleric acid. Diagnosis may be confirmed by measurement of the enzyme activity in cultured fibroblasts or by DNA analysis. Documentation of normal activities of other carboxylases is necessary for definitive diagnosis.

Treatment of acute episodes is similar to that of isovaleric acidemia (see above). Hydration and measures to correct metabolic acidosis and hypoglycemia (by infusing sodium bicarbonate and glucose) should be instituted promptly. Administration of L-carnitine and glycine is also recommended. These patients are unresponsive to biotin therapy. Patients who, in earlier reports, were found to be biotin-responsive were most probably suffering from multiple carboxylase deficiency as a result of biotinidase deficiency (see above). Long-term treatment includes a diet restricted in leucine in conjunction with the oral administration of L-carnitine (75-100 mg/kg/24 hr) and the prevention of catabolic states. Normal growth and development are expected in these patients.

The condition is inherited as an autosomal recessive trait. The gene for α subunit (*MCC1*) is located on chromosome 3q27.1 and that for the β subunit (*MCC2*) is mapped to chromosome 5q13.2. Mutation in either of these genes may result in the deficiency of the enzyme activity. Similar phenotype may be caused by different genotype. Several disease-causing mutations in either gene have been identified in different families. Newborn screening programs using tandem mass spectrometry have identified an unexpectedly high number of infants with 3-methylcrotonyl CoA carboxylase deficiency (1 : 50,000). Only a small number (<10%) of the affected infants become symptomatic; none of the symptoms reported so far could be clearly attributed to the degree of enzyme deficiency. These findings have questioned the advisability of including this condition in the routine newborn screening programs because the psychologic and financial burdens may outweigh the potential benefits.

3-METHYLGLUTACONIC ACIDURIA

Six inherited conditions are known to be associated with excessive excretion of 3-methylglutaconic acid in the urine. Deficiency of the enzyme 3-methylglutaconyl CoA hydratase (see Fig. 85-4) has been documented in only 1 condition (type I). In the other 5 conditions, the enzyme activity is normal despite a modest 3-methylglutaconic aciduria. The reason for increased urinary excretion of 3-methyglutaconic acid in these conditions is not completely understood; although these conditions are caused by mutations in different genes, the gene products are all critical for normal mitochondrial function. Only 3-methyglutaconic acidurias—types I, II, and III—are discussed here because the clinical pictures of types IV and V (dilated cardiomyopathy with ataxia) are not well delineated.

3-Methylglutaconic Aciduria Type I (3-Methylglutaconyl Coenzyme A Hydratase Deficiency)

See Figure 85-4.

Two main clinical forms of the condition have been described. In the childhood form, nonspecific neurodevelopmental findings such as speech delay or regression, choreoathetoid movements, optic atrophy, and mild psychomotor delay may be present. Metabolic acidosis may occur during a catabolic state. In the adulthood form, affected individuals remain asymptomatic until the 2nd or 3rd decades of life, when a clinical picture of slowly progressing leukoencephalopathy with optic atrophy, dysarthria, ataxia, spasticity, and dementia occurs. MRI of brain typically shows white matter abnormalities that may precede appearance of clinical symptoms by years. Asymptomatic affected children and adults have also been reported. Patients excrete large amounts of 3-methylglutaconic acid and moderate amounts of 3-hydroxyisovaleric and 3-methylglutaric acids in urine. Deficiency of 3-methylglutaconyl CoA hydratase has been shown in cultured fibroblasts and lymphoblasts. **Treatment** with a low leucine diet seems to be indicated even in asymptomatic affected individuals. Beneficial effects of this therapy on the clinical course of the disease remain to be determined. Administration of L-carnitine has resulted in clinical improvement in 1 patient. The condition is inherited as an autosomal recessive trait; the gene for the hydratase enzyme (*AUH*) is mapped to chromosome 9q22.3.

3-Methylglutaconic Aciduria Type II (X-Linked Cardiomyopathy, Neutropenia, Growth Retardation, and 3-Methylglutaconic Aciduria with Normal 3-Methylglutaconyl Coenzyme A Hydratase, Barth Syndrome)

This X-linked mitochondrial condition is caused by deficiency of tafazzin, a mitochondrial protein (enzyme), encoded by *TAZ* gene. This enzyme is necessary for processing of immature cardiolipin into the mature form (cardiolipin remodeling). Cardiolipin, a mitochondrial phospholipid, is critical for the integrity of inner mitochondrial membrane. **Clinical manifestations** of this condition, which usually occur in the first year of life in a male infant, include dilated cardiomyopathy (manifested as respiratory distress and heart failure), hypotonia, growth retardation, hypoglycemia, and moderate to severe cyclic neutropenia. The onset of clinical manifestations may be as late as 49 yr of age, but most affected individuals become symptomatic by adolescence. If patients survive infancy, relative improvement may occur with advancing age. Cognitive development is usually normal despite delayed motor function.

Laboratory findings include mild to moderate increases in urinary excretion of 3-methylglutaconic, 3-methylglutaric, and 2-ethylhydracrylic acids. Unlike 3-methylglutaconic aciduria type I, urinary excretion of 3-hydroxyisovaleric acid is not elevated. The activity of the enzyme 3-methylglutaconyl CoA hydratase is normal. Cyclic neutropenia is a common finding. Lactic acidosis, hypoglycemia, low serum cholesterol concentration and abnormal mitochondrial ultrastructure have been shown in some patients. Total cardiolipin and subclasses of cardiolipin are very low in skin fibroblast cultures from these patients. This finding may be useful for establishing the diagnosis.

The condition is inherited as an X-linked recessive trait. The gene (*TAZ*) has been mapped to chromosome Xq28 and several disease-causing mutations have been identified. The modest 3-methylglutaconic aciduria seen in this condition is thought to be related to the defect in mitochondrial membrane causing the leakage of this organic acid. No effective treatment is available. Older surviving patients may benefit from cardiac transplantation. There are reasons to believe that the condition is perhaps more common than realized; most affected patients remain undiagnosed or misdiagnosed as having viral cardiomyopathy.

3-Methylglutaconic Aciduria Type III (Costeff Optic Atrophy Syndrome)

Clinical manifestations in these patients include early onset optic atrophy and later development of choreoathetoid movements, spasticity, ataxia, dysarthria, and mild developmental delay. All reported patients except 1 were Iraqi Jews living in Israel. These patients excrete moderate amounts of 3-methylglutaconic and 3-methylglutaric acids. Activity of the enzyme 3-methylglutaconyl CoA hydratase is normal. The reason for the increased excretion of these organic acids remains unclear. The condition is inherited as an autosomal recessive trait. The gene for this condition (*OPA3*) is mapped to chromosome 19q13.2-q13.3. Mutation of this gene is believed to cause mitochondrial dysfunction. No effective treatment is available.

β-KETOTHIOLASE (3-OXOTHIOLASE) DEFICIENCY (MITOCHONDRIAL ACETOACETYL COENZYME A THIOLASE [T_2] DEFICIENCY)

This reversible mitochondrial enzyme is involved in final steps of catabolism of isoleucine and also in oxidation of fatty acids. It cleaves 2-methylacetoacetyl CoA to propionyl-CoA plus acetyl-CoA in isoleucine catabolic pathway (see Fig. 85-4). In the fatty acid oxidation pathway, the enzyme generates 2 moles of acetyl-CoA from 1 mole of acetoacetyl-CoA (Fig. 85-7). The same enzyme synthesizes 2-methyacetoacetate-CoA and acetoacetyl-CoA in the reverse direction (Fig. 85-7).

Clinical manifestations are quite variable, ranging from an asymptomatic course in an adult to severe episodes of acidosis starting in the

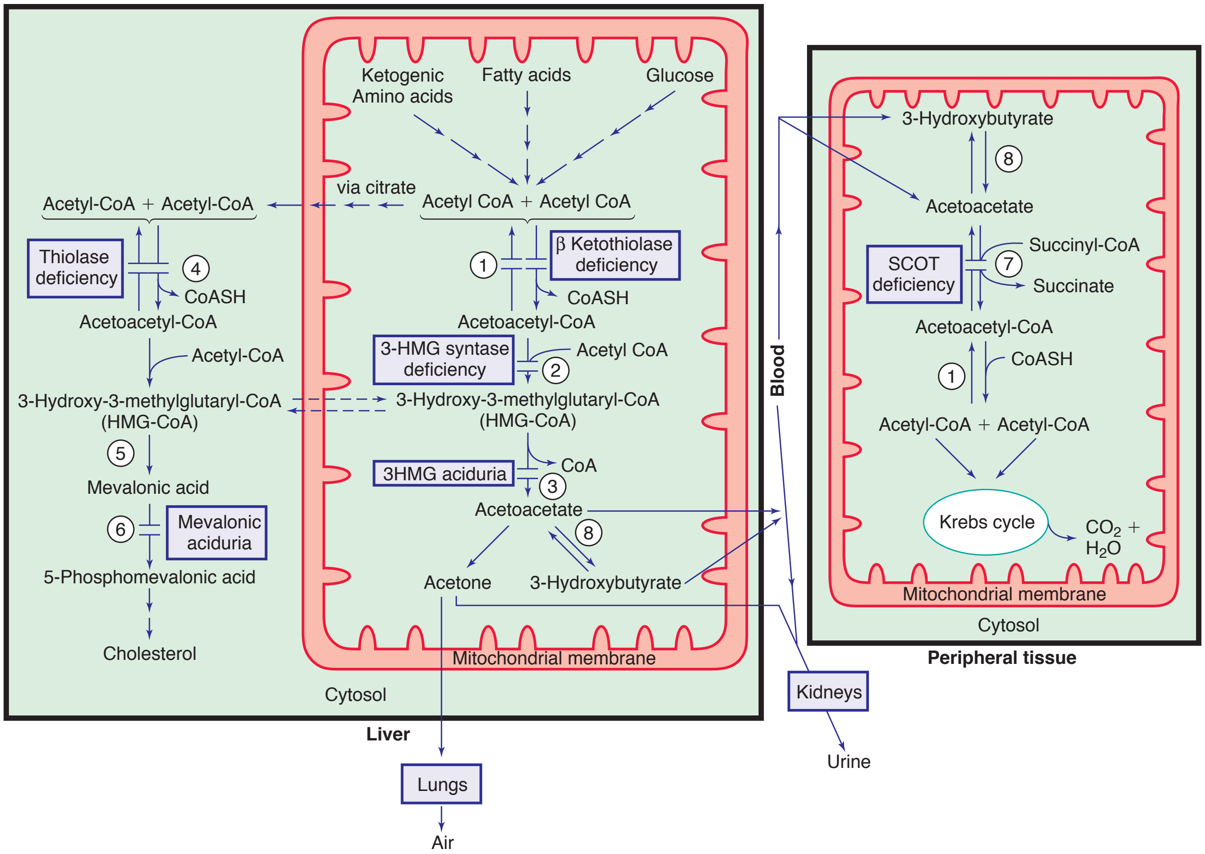

Figure 85-7 Formation (liver) and metabolism (peripheral tissues) of ketone bodies and cholesterol synthesis. **Enzymes:** *(1)* Mitochondrial acetoacetyl CoA thiolase, *(2)* HMG-CoA synthase, *(3)* HMG-CoA lyase, *(4)* cytosolic acetoacetyl CoA thiolase, *(5)* HMG-CoA reductase, *(6)* mevalonic kinase, *(7)* succinyl CoA:3-ketoacid CoA transferase (SCOT), *(8)* 3-hydroxybutyrate dehydrogenase.

1st yr of life. Typically, these children have intermittent episodes of unexplained ketosis and acidosis. These episodes usually occur after an intercurrent infection and respond quickly to intravenous fluids and bicarbonate therapy. Mild to moderate hyperammonemia may also be present during attacks. Both hypoglycemia and hyperglycemia have been reported in isolated cases. The child may be completely asymptomatic between episodes and may tolerate a normal protein diet well. Cognitive development is normal in most children. The episodes may be misdiagnosed as salicylate poisoning because of the similarity of the clinical findings and the interference of elevated blood levels of acetoacetate with the colorimetric assay for salicylate.

Laboratory findings during the acute attack include acidosis, ketosis, and hyperammonemia. The urine contains large amounts of 2-methylacetoacetate and its decarboxylated products butanone, 2-methyl-3-hydroxybutyrate, and tiglylglycine. Lower concentrations of these urinary metabolites persist during the seemingly well periods. Mass screening of newborn infants may yield false-negative results in affected infants who are well at the time of blood sampling. Mild hyperglycinemia may also be present. The clinical and biochemical findings should be differentiated from those seen with propionic and methylmalonic acidemias (see later). Diagnosis may be established by assay of the enzyme in leukocytes or cultured fibroblasts, or identification of the mutant gene.

Treatment of acute episodes includes hydration and infusion of bicarbonate to correct the acidosis; a 10% glucose solution with the appropriate electrolytes and intravenous lipids may be used to minimize the catabolic state. Restriction of protein intake (1-2 g/kg/24 hr) is recommended for long-term therapy. Oral L-carnitine (50-100 mg/kg/24 hr) is also recommended to prevent possible secondary carnitine deficiency. Long-term prognosis for achieving normal life seems very favorable. Three reported patients graduated from high school and 1 has attended college. All patients continued to have abnormal metabolites in body fluids. Successful pregnancy with normal outcomes for both mother and infant has been reported.

The pathogenesis of ketosis in this condition is not adequately explained because, in this enzyme deficiency, one expects impaired ketone formation (see Fig. 85-7). It is postulated that excess acetoacetyl CoA produced from other sources is used as a substrate for 3-hydroxy-3-methylglutaryl (HMG) CoA synthesis in the liver.

This condition is inherited as an autosomal recessive trait and may be more prevalent than has been appreciated. It is most prevalent in Tunisia. The gene (*ACAT1*) for this enzyme (T_2) is located on chromosome 11q22.3.

CYTOSOLIC ACETOACETYL COENZYME A THIOLASE DEFICIENCY

This enzyme catalyzes the cytosolic production of acetoacetyl CoA from 2 moles of acetyl CoA (see Fig. 85-7). Cytosolic acetoacetyl CoA is the precursor of hepatic cholesterol synthesis. Cytosolic acetoacetyl CoA thiolase is a completely different enzyme from mitochondrial thiolase (see above and Fig. 85-4). Clinical manifestations in patients with this very rare enzyme deficiency are similar to those in patients with mevalonic acidemia (see below). Severe progressive developmental delay, hypotonia, and choreoathetoid movements develop in the first few months of life. Laboratory findings are nonspecific; elevated levels of lactate, pyruvate, acetoacetate, and 3-hydroxybutyrate may be found in blood and urine. One patient had normal levels of acetoacetate and 3-hydroxybutyrate. Diagnosis can be established by demonstrating a deficiency in cytosolic thiolase activity in liver biopsy or in cultured fibroblasts or by DNA analysis. No effective treatment is available. The gene (*ACAT2*) for this condition is mapped to chromosome 6q25.3.

MITOCHONDRIAL 3-HYDROXY-3-METHYLGLUTARYL COENZYME A SYNTHASE DEFICIENCY

This enzyme catalyzes synthesis of 3-hydroxy-3-methylglutaryl (HMG)-CoA from acetoacetyl CoA in the mitochondria. This is a critical step in ketone body synthesis in the liver (see Fig. 85-7). A few patients with deficiency of this enzyme have been reported. All patients have had similar presentations and outcomes. Signs and symptoms of acute hypoglycemia have occurred after an acute illness (gastroenteritis). Age at presentation has ranged from 18 mo to 6 yr. All children were asymptomatic before the episodes and remained normal after the recovery (except for mild hepatomegaly with fatty infiltration). None of the patients has had a second episode, perhaps as a result of preventive measures to avoid prolonged fasting during ensuing intercurrent illnesses. Hepatomegaly was a consistent physical finding in all patients. Laboratory findings included hypoglycemia, acidosis with mild or no ketosis, elevation of liver function tests, and massive dicarboxylic aciduria. The clinical and laboratory findings may be confused with those of patients with defects in fatty acid metabolism (see Chapter 86.1). In contrast to the latter, blood concentrations of acylcarnitine conjugates are normal in patients with HMG-CoA synthase deficiency. Fasting of these patients has produced the abovementioned clinical and biochemical abnormalities.

Treatment consisted of provision of adequate calories and avoidance of prolonged periods of fasting. No dietary protein restriction was needed.

The condition is inherited as an autosomal recessive trait. The gene (*HMGCS2*) for this enzyme is located on chromosome 1p13-p12 and several disease-causing mutations have been identified. The condition should be considered in any child with fasting hypoglycemia and is perhaps more common than appreciated.

3-HYDROXY-3-METHYLGLUTARIC ACIDURIA

This condition is a result of a deficiency of HMG-CoA lyase (see Fig. 85-4). This enzyme catalyzes the conversion of HMG-CoA to acetoacetate and is a rate-limiting enzyme for ketogenesis (see Fig. 85-7). **Clinically,** more than 60% of patients become symptomatic between 3 and 11 mo of age (infantile form), whereas approximately 30% develop symptoms in the first few days of life (neonatal form). One child remained asymptomatic until 15 yr of age (childhood form). Episodes of vomiting, severe hypoglycemia, hypotonia, acidosis with mild or no ketosis, and dehydration may rapidly lead to lethargy, ataxia, and coma. These episodes often occur during a catabolic state such as fasting or an intercurrent infection. Hepatomegaly is common. These manifestations may be mistaken for Reye syndrome or medium-chain acyl-CoA dehydrogenase deficiency. Patients are usually clinically asymptomatic between the attacks; 1 patient died of acute cardiomyopathy at age 7 mo during a febrile illness. Development is usually normal, but intellectual disability and seizures with abnormalities of white matter (shown by MRI) have been observed in patients with prolonged episodes of hypoglycemia.

Laboratory findings include hypoglycemia, moderate to severe hyperammonemia, and acidosis. There is mild or no ketosis (see Fig. 85-7). Urinary excretion of 3-hydroxy-3-methylglutaric acid and other proximal intermediate metabolites of leucine catabolism (3-methylglutaconic acid and 3-hydroxyisovaleric acid) is markedly increased causing the urine to smell like cat urine. These organic acids are excreted in the urine as carnitine conjugates, resulting in secondary carnitine deficiency. Glutaric and adipic acids may also be increased in urine during acute attacks. **Diagnosis** may be confirmed by enzyme assay in cultured fibroblasts, leukocytes, or liver specimens or by identification of the mutant gene. Prenatal diagnosis is possible by the assay of the enzyme in cultured amniocytes or a chorionic villus biopsy or by DNA analysis.

Treatment of acute episodes includes hydration, infusion of glucose to control hypoglycemia, provision of adequate calories, and administration of bicarbonate to correct acidosis. Hyperammonemia should be treated promptly (see Chapter 85.12). Exchange transfusion and peritoneal dialysis may be required in patients with severe hyperammonemia. Restriction of protein and fat intake is recommended for long-term management. Oral administration of L-carnitine (50-100 mg/kg/24 hr) prevents secondary carnitine deficiency. Prolonged fasting should be avoided. One child died after routine immunization. The condition is inherited as an autosomal recessive trait. The gene (*HNGCL*) for HMG-CoA lyase resides on chromosome 1p36.11 and several disease-causing mutations have been identified in different families. The gene defect appears to be more common in the Arabic population, especially in Saudi Arabia.

SUCCINYL COENZYME A:3-KETOACID COENZYME A TRANSFERASE (SCOT) DEFICIENCY

This enzyme is necessary for the metabolism of ketone bodies (acetoacetate and 3-hydroxybutyrate) in peripheral tissues (see Fig. 85-7). A deficiency of this enzyme results in the underutilization and accumulation of ketone bodies and ketoacidosis. Only a few patients with succinyl coenzyme A:3-ketoacid coenzyme A transferase deficiency have been reported to date; the condition may not be rare because many cases are, perhaps, undiagnosed.

The **presentation** is an acute episode of unexplained severe ketoacidosis in an infant who had been growing and developing normally. About half of the patients become symptomatic in the 1st wk of life, and all become symptomatic before 2 yr of age. The acute episode is often precipitated by an intercurrent infection or a catabolic state. Death may occur during these episodes. A chronic subclinical ketosis usually persists between the attacks. Development is usually normal.

Laboratory findings during the acute episode are nonspecific and include metabolic acidosis and ketonuria with high levels of acetoacetate and 3-hydroxybutyrate in blood and urine. No other organic acids are found in the blood or in the urine. Blood glucose levels are usually normal, but hypoglycemia has been reported in 2 affected newborn infants with severe ketoacidosis. Plasma amino acids are usually normal. **Diagnosis** can be established by demonstrating a deficiency of enzyme activity in cultured fibroblasts or by DNA analysis.

Treatment of acute episodes consists of hydration, correction of acidosis, and the provision of a diet adequate in calories. Long-term treatment with a high-carbohydrate diet and avoidance of catabolic states is recommended. *This condition should be considered in any infant with unexplained bouts of ketoacidosis.* The condition is inherited as an autosomal recessive trait. The gene (*OXCT1*) for this enzyme is located on chromosome 5p13, and several disease-causing mutations have been found in different families.

MEVALONIC ACIDURIA

Mevalonic acid, an intermediate metabolite of cholesterol synthesis, is converted to 5-phosphomevalonic acid by the action of the enzyme mevalonate kinase (MVK) (see Fig. 85-7). Based on clinical manifestations and degree of enzyme deficiency, 2 forms of this condition have been recognized.

Mevalonic Aciduria, Severe Form

Clinical manifestations include intellectual disability, failure to thrive, growth retardation, hypotonia, ataxia, hepatosplenomegaly, cataracts, and facial dysmorphism (dolichocephaly, frontal bossing, low-set ears, downward slanting of the eyes, and long eyelashes). Recurrent crises, characterized by fever, vomiting, diarrhea, arthralgia, edema, lymphadenopathy, further enlargement of liver and spleen, and morbilliform rash have been observed in all patients. These episodes last 4-5 days and recur up to 25 times/yr. Death may occur during these crises.

Laboratory findings include marked elevation of mevalonic acid in urine; the concentration may be as high as 56,000 µmole/mole of creatinine (normal: <0.3). Plasma levels of mevalonic acid are also greatly increased (as high as 54 µmole/dL; normal: <0.004). This is the only abnormal organic acid found in these patients. The level of mevalonic acid tends to correlate with the severity of the condition and increases during crises. Serum cholesterol concentration is normal or mildly decreased. Serum concentration of creatine kinase is markedly increased. Sedimentation rate and serum leukotriene-4 are increased

during the crises. Serial examination of the brain by MRI reveals progressive atrophy of the cerebellum.

Diagnosis may be confirmed by assay of MVK activity in lymphocytes or in cultured fibroblasts or by DNA analysis. The enzyme activity in this form of the condition is below the detection level. No effective therapy is available. **Treatment** with high doses of prednisone (2 mg/kg/24 hr) causes improvement of the acute crises. The condition is inherited as an autosomal recessive trait. Prenatal diagnosis is possible by measurement of mevalonic acid in the amniotic fluid, by assay of the enzyme activity in cultured amniocytes or chorionic villus samples or by demonstration of the mutant gene. The gene (*MVK*) for the enzyme is on chromosome 12q24.

Periodic Fever with Hyperimmunoglobulinemia D (Mevalonic Aciduria, Mild Form)

See Chapter 163.

Some mutations of mevalonic kinase gene *(MVK)* cause mild deficiencies of the enzyme and produce the clinical picture of periodic fever with hyperimmunoglobulinemia D. These patients have periodic bouts of fever associated with abdominal pain, vomiting, diarrhea, arthralgia, arthritis, hepatosplenomegaly, lymphadenopathy, and morbilliform rash (even petechiae and purpura), which usually start before 1 yr of age. The attacks can be produced by vaccination, minor trauma, or stress; usually occur every 1-2 mo; and last 2-7 days. Patients are free of symptoms between acute attacks. The diagnostic laboratory finding is elevation of serum immunoglobulin D (IgD); IgA is also elevated in 80% of patients. During acute attacks, leukocytosis, increased C-reactive protein, and mild mevalonic aciduria may be present. High concentrations of serum IgD differentiate this condition from familial Mediterranean fever.

Treatment

See Chapter 163.

PROPIONIC ACIDEMIA (PROPIONYL COENZYME A CARBOXYLASE DEFICIENCY)

Propionic acid is an intermediate metabolite of isoleucine, valine, threonine, methionine, odd-chain fatty acids, and cholesterol catabolism. It is normally carboxylated to methylmalonic acid by the mitochondrial enzyme propionyl CoA carboxylase, which requires biotin as a cofactor (see Fig. 85-4). The enzyme is composed of 2 nonidentical subunits, α and β. Biotin is bound to the α subunit.

Clinical findings are nonspecific. In the severe form of the condition, patients develop symptoms in the first few days or weeks of life. Poor feeding, vomiting, hypotonia, lethargy, dehydration, and clinical signs of severe ketoacidosis progress rapidly to coma and death. Seizures occur in approximately 30% of affected infants. If an infant survives the first attack, similar episodes may occur during an intercurrent infection or constipation or after ingestion of a high-protein diet. Moderate to severe intellectual disability and neurologic manifestations reflective of extrapyramidal (dystonia, choreoathetosis, tremor), and pyramidal (paraplegia) dysfunction are common sequelae in the older survivors. Neuroimaging shows these abnormalities, which usually occur after an episode of metabolic decompensation, to be a result of damage to the basal ganglia, especially to the globus pallidus. This phenomenon has been referred to in the literature as **metabolic stroke**. This is the main cause of neurologic sequelae seen in the surviving affected children.

In the milder forms, the older infant may have intellectual disability without acute attacks of ketosis. Some affected children may have episodes of unexplained severe ketoacidosis separated by periods of seemingly normal health. Mass screening of newborn infants has identified milder forms of the condition; a few of these infants were completely asymptomatic at diagnosis. The severity of clinical manifestations may also be variable within a family; in 1 kindred, a brother was diagnosed at 5 yr of age whereas his 13 yr old sister, with the same level of enzyme deficiency, was asymptomatic.

Laboratory findings during the acute attack include severe metabolic acidosis with a large anion gap, ketosis, neutropenia, thrombocytopenia, and hypoglycemia. Moderate to severe hyperammonemia is common; plasma ammonia concentrations usually correlate with the severity of the disease. In contrast to other causes of hyperammonemia, plasma concentration of glutamine is within normal limits or even decreased. Presence of severe metabolic acidosis differentiates propionic academia from hyperammonemic states caused by urea cycle defects. Measurement of plasma ammonia is especially helpful in planning therapeutic strategy during episodes of exacerbation in a patient whose diagnosis has been established. Pathogenesis of hyperammonemia is not well understood. Glycine concentration is elevated in all body fluids (blood, urine, and spinal fluid) in almost all patients. This is the result of inhibition of glycine cleavage enzyme (Fig. 85-8) in the liver. Glycine elevation has also been observed in patients with methylmalonic acidemia. These disorders were collectively referred to as *ketotic hyperglycinemia* in the past before the specific enzyme deficiencies were elucidated. A decrease in plasma levels of branched-chain amino acids (leucine, isoleucine, valine) is a common finding. Mild to moderate increase in blood concentrations of lactate and lysine may also be present in these patients. Concentrations of propionic acid and methylcitric acid (presumably made by the condensation of propionyl CoA with oxaloacetic acid) are markedly elevated in the plasma and urine of infants with propionic acidemia. 3-Hydroxypropionic acid, propionylglycine, and other intermediate metabolites of isoleucine catabolism, such as tiglic acid, tiglylglycine, and 2-methyloacetoacetic acid, are also found in urine. Moderate elevations in blood levels of ammonia, glycine, and previously mentioned organic acids usually persist between the acute attacks. CT scan and MRI of the brain may reveal cerebral atrophy, demyelination, and abnormalities in the globus pallidus and basal ganglia as the evidence of a metabolic stroke in this condition (see above).

The **diagnosis** of propionic acidemia should be differentiated from multiple carboxylase deficiencies (see above and Fig. 85-6). Infants with the latter condition may have skin manifestations and excrete large amounts of lactic acid, 3-methylcrotonic acid, and 3-hydroxyisovaleric acid in addition to propionic acid. The presence of hyperammonemia may suggest a genetic defect in the urea cycle enzymes. Infants with defects in the urea cycle are usually not acidotic (see Fig. 85-1) and have elevated levels of plasma glutamine. Definitive diagnosis of propionic acidemia can be established by measuring the enzyme activity in leukocytes or cultured fibroblasts or by DNA analysis.

Treatment of acute attacks includes hydration, correction of acidosis, and amelioration of the catabolic state by provision of adequate calories through parenteral hyperalimentation. Minimal amounts of protein (0.25 g/kg/24 hr), preferably as a protein deficient in propionate precursors, should be provided in the hyperalimentation fluid very early in the course of treatment. To curtail the possible production of propionic acid by intestinal bacteria, sterilization of the intestinal tract flora by antibiotics (oral neomycin, or metronidazole) should be promptly initiated. Constipation should also be treated. Patients with propionic acidemia may develop carnitine deficiency, presumably as a result of urinary loss of propionylcarnitine formed from the accumulated organic acid. Administration of L-carnitine (50-100 mg/kg/24 hr orally or 10 mg/kg/24 hr intravenously) normalizes fatty acid oxidation and improves acidosis. In patients with concomitant hyperammonemia, measures to reduce blood ammonia should be employed (see Chapter 85.12). Very ill patients with severe acidosis and hyperammonemia require peritoneal dialysis or hemodialysis to remove ammonia and other toxic compounds rapidly and efficiently. Although no infant with true propionic acidemia has been found to be responsive to biotin, this compound should be administered (10 mg/24 hr orally) to all infants during the first attack and until the diagnosis is established.

Long-term treatment consists of a low-protein diet (1.0-1.5 g/kg/24 hr) and administration of L-carnitine (50-100 mg/kg/24 hr orally). Synthetic proteins deficient in propionate precursors (isoleucine, valine, methionine, and threonine) may be used to increase the amount of dietary protein (to 1.5-2.0 g/kg/24 hr) while causing minimal change in propionate production. Excessive supplementation with these proteins may cause a deficiency of the essential amino acids,

especially isoleucine (which may cause a condition resembling acrodermatitis enteropathica; see see Chapter 671). To avoid this problem, natural proteins should comprise most of the dietary protein (50-75%). Some patients may require chronic alkaline therapy to correct chronic acidosis. The concentration of ammonia in the blood usually normalizes between attacks, and chronic treatment of hyperammonemia is not usually needed. Catabolic states that may trigger acute attacks (infections, constipation) should be treated promptly and aggressively. Close monitoring of blood pH, amino acids, urinary content of propionate and its metabolites, and growth parameters is necessary to ensure the proper balance of the diet and the success of therapy.

Long-term prognosis is guarded. Death may occur during an acute attack. Normal psychomotor development is possible, especially in the mild forms identified through screening programs; most children identified clinically manifest some degree of permanent neurodevelopmental deficit such as tremor, dystonia, chorea, and pyramidal signs despite adequate therapy. These neurologic findings may be sequelae of a metabolic stroke occurring during an acute decompensation (see above). Cardiomyopathy with potential progression to heart failure and death may develop in older affected children despite adequate metabolic control. Acute pancreatitis has also been reported in these patients.

Prenatal diagnosis is achieved by measuring the enzyme activity in cultured amniotic cells or in samples of uncultured chorionic villi, by measurement of methylcitrate in amniotic fluid, or by identification of the mutant gene.

The condition is inherited as an autosomal recessive trait and can be identified by mass screening of newborns with a worldwide prevalence of 1:50,000 to 1:100,000 live births. It is more prevalent in Saudi Arabia (1:2,000 to 1:5,000 live births). The gene for the α subunit (*PCCA*) is located on chromosome 13q32 and that of the β subunit (*PCCB*) is mapped to the chromosome 3q21-q22. Mutations in either gene can cause the condition. Many mutations in either gene have been identified in different patients. Pregnancy with normal outcome has been reported in affected females.

METHYLMALONIC ACIDEMIA

Methylmalonic acid, a structural isomer of succinic acid, is usually derived from propionic acid as part of the catabolic pathways of isoleucine, valine, threonine, methionine, cholesterol, and odd-chain fatty acids. Two enzymes are involved in the conversion of D-methylmalonic acid to succinic acid: methylmalonyl CoA racemase, which forms the L isomer; and methylmalonyl CoA mutase, which converts the L-methylmalonic acid to succinic acid (see Fig. 85-4). The latter enzyme requires adenosylcobalamin, a metabolite of vitamin B_{12}, as a coenzyme. Deficiency of either the mutase or its coenzyme causes the accumulation of methylmalonic acid and its precursors in body fluids. A deficiency of the racemase can be associated with mild elevations of methylmalonic acid, but the clinical consequence of racemase deficiency is not known.

At least 2 forms of mutase apoenzyme deficiencies have been identified. These are designated mut^0, meaning no detectable enzyme activity, and mut^-, indicating residual, although abnormal, mutase activity. The majority of reported patients with methylmalonic acidemia have a deficiency of the mutase apoenzyme (mut^0 or mut^-). These patients are not responsive to vitamin B_{12} therapy. In the remaining patients with methylmalonic acidemia, the defect resides in the formation of adenosylcobalamin.

Defects in Metabolism of Vitamin B_{12} (Cobalamin)

Dietary vitamin B_{12} requires intrinsic factor, a glycoprotein secreted by the gastric parietal cells, for absorption in the terminal ileum. It is transported in the blood by haptocorrin and transcobalamin. The transcobalamin–cobalamin complex (TC-Cbl) is recognized by a specific receptor on the cell membrane and enters the cell by endocytosis. TC-Cbl is hydrolyzed in the lysosome, and free cobalamin is released into the cytosol (see Fig. 85-4). In the cytoplasm, cobalamin binds to the MMACHC protein (see *cbl*C later), which reduces the cobalt of the molecule from 3 valences (cob[III]alamin) to 2 (cob[II]alamin) before it enters the mitochondria, where it reacts with adenosine triphosphate and an unknown reductase to form adenosylcobalamin (coenzyme for methylmalonyl CoA mutase). Alternatively, partially reduced cobalamin in the cytosol may interact with methionine synthase and methionine synthase reductase to form methylcobalamin (coenzyme for methionine synthase; see Fig. 85-3). The MMADHC protein (see *cbl*D) appears to play a role in determining whether cobalamin enters the mitochondria or remains in the cytoplasm.

Uptake of TC-Cbl by cells is impaired in individuals with mutations affecting transcobalamin receptor which is located on the cell surface. Individuals homozygous for mutations at the *CD320* gene, which encodes the transcobalamin receptor, have elevations of serum methylmalonic acid, which can be detected by newborn screening using tandem mass spectroscopy, but it is not clear whether there is a clinical phenotype associated with this disorder.

Nine different defects in the intracellular metabolism of cobalamin have been identified. These are designated *cbl*A through *cbl*G, *cbl*J, and *cbl*X (*cbl* stands for a defect in any step of cobalamin metabolism). The *cbl*A, *cbl*B, and *cbl*D variant 2 defects cause methylmalonic acidemia alone. In patients with *cbl*C, classic *cbl*D, *cbl*F, *cbl*J, and *cbl*X defects, synthesis of both adenosylcobalamin and methylcobalamin is impaired, causing homocystinuria in addition to methylmalonic acidemia. The *cbl*D variant 1, *cbl*E, and the *cbl*G defects affect only the synthesis of methylcobalamin, resulting in homocystinuria without methylmalonic aciduria, but usually with megaloblastic anemia (see Chapter 85.3).

Clinical manifestations of patients with methylmalonic acidemia caused by mut^0, mut^-, *cbl*A, *cbl*B, and *cblD* variant 2 are similar. There are wide variations in clinical presentation, ranging from very sick newborn infants to asymptomatic adults, regardless of the nature of the enzymatic defect or the biochemical abnormalities. In severe forms, lethargy, feeding problems, vomiting, tachypnea (from acidosis), and hypotonia may develop in the first few days of life and may progress to coma and death if untreated. Infants who survive the first attack may go on to develop similar acute metabolic episodes during a catabolic state (such as infection) or after ingestion of a high-protein diet. Between the acute attacks, the patient commonly continues to exhibit hypotonia and feeding problems with failure to thrive. In milder forms, patients may present later in life with hypotonia, failure to thrive, and developmental delay. Asymptomatic patients with typical biochemical abnormalities of methylmalonic acidemia are also reported. It is important to note that mental development and IQ of patients with methylmalonic acidemia may remain within the normal range despite repeated acute attacks and regardless of the nature of the enzyme deficiency. In a study of patients with different forms of the condition, developmental delay was noted in 47%. One adolescent girl with a mut^- deficiency had an IQ of 129.

The episodic nature of the condition and its biochemical abnormalities may be confused with those of ethylene glycol (antifreeze) ingestion. The peak of propionate in a blood sample from an infant with methylmalonic acidemia has been mistaken for ethylene glycol when the sample was assayed by gas chromatography without mass spectrometry.

Laboratory findings include ketosis, acidosis, anemia, neutropenia, thrombocytopenia, hyperglycinemia, hyperammonemia, hypoglycemia, and the presence of large quantities of methylmalonic acid in body fluids (see Fig. 85-6). Propionic acid and its metabolites 3-hydroxypropionate and methylcitrate are also found in the urine. Hyperammonemia may suggest the presence of genetic defects in the urea cycle enzymes; patients with defects in urea cycle enzymes are not acidotic (see Fig. 85-12). The reason for hyperammonemia is not well understood.

Diagnosis can be confirmed by measuring propionate incorporation and performing complementation analysis in cultured fibroblasts, by measuring the specific activity of the mutase enzyme in biopsies or cell extracts or by identifying the mutations in the causal gene.

Treatment of acute attacks is similar to that of attacks in patients with propionic acidemia (see above), except that large doses (1 mg/24 hr) of vitamin B_{12} are used instead of biotin. Long-term treatment consists of administration of a low-protein diet (1.0-1.5 g/

kg/24 hr), L-carnitine (50-100 mg/kg/24 hr orally), and vitamin B_{12} (1 mg/24 hr for patients with defects in vitamin B_{12} metabolism; the dose can be decreased depending on the clinical response). The protein composition of the diet is similar to that prescribed for patients with propionic acidemia. Chronic alkaline therapy is usually required to correct chronic acidosis, especially during infancy and early childhood. Blood levels of ammonia usually normalize between the attacks, and chronic treatment of hyperammonemia is rarely needed. Stressful situations that may trigger acute attacks (such as infection) should be treated promptly.

Inadequate oral intake secondary to poor appetite is a common and bothersome complication in long-term management of these patients. Consequently, enteral feeding (through a nasogastric tube or gastrostomy) should be considered early in the course of the treatment. Close monitoring of blood pH, amino acid levels, blood and urinary concentrations of methylmalonate, and growth parameters is necessary to ensure proper balance in the diet and the success of therapy. Glutathione deficiency, responsive to high doses of ascorbate, has been described. Liver, kidney, and combined liver and kidney transplantations have been attempted in a small number of affected patients. Liver transplantation reduced but did not eliminate the metabolic abnormalities and did not prevent the occurrence of metabolic stroke. Kidney transplantation alone restored the renal function but caused only minor improvement in the methylmalonic acidemia.

Prognosis depends on the severity of symptoms and the occurrence of complications (see below). In general, patients with complete deficiency of mutase apoenzyme (*mut*^{0}) have the least-favorable prognosis and those with *mut*$^-$ and *cbl*A defects have a better outcome than those with *cbl*B.

Complications have been noted in survivors. Metabolic strokes (see above) have been reported in a few patients during an acute episode of metabolic decompensation. These patients have survived with major extrapyramidal (tremor, dystonia) and pyramidal (paraplegia) sequelae.

Chronic renal failure necessitating renal transplant has been reported in a number of older patients with the condition. This complication has been observed in all genetic forms of the condition. **Tubulointerstitial nephritis** has been documented in some of these patients and is thought to be the major cause of renal failure. The pathogenesis remains unclear.

Acute and recurrent pancreatitis has been reported in affected patients as young as 13 mo of age. This complication may account for a fair number of hospitalizations of these children.

The prevalence of all forms of methylmalonic aciduria is estimated to be in the range of 1 in 48,000 live births. All defects causing isolated methylmalonic acidemia are inherited as autosomal recessive traits. Successful mass screening of newborn infants has been achieved by the tandem mass spectrometry method. The gene for the mutase (*MUT*) is on the short arm of chromosome 6p12.3; over 220 different mutations have been identified in the *MUT* gene, including a number of ethnic-specific mutations. Neonates with methylmalonic acidemia and severe diabetes owing to the absence of β cells, who have paternal uniparental isodisomy of chromosome 6, have been reported. Mutations in the genes for *cbl*A (*MMAA,* on chromosome 4q31-q31.2), *cbl*B (*MMAB,* on chromosome 12q24), and all forms of *cbl*D (*MMADHC,* on chromosome 2q23.2) have been identified in affected patients. The previously described *cbl*H group is identical to *cbl*D variant 2.

Successful pregnancy with normal outcomes for both the mother and the baby has been reported.

COMBINED METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA (*cbl*C, *cbl*D, *cbl*F, *cbl*J, AND *cbl*X DEFECTS)

More than 550 patients with methylmalonic acidemia and homocystinuria because of *cbl*C have been reported. Indeed, with the advent of expanded newborn screening, it has become evident that *cbl*C may be as common as mutase deficiency. The other disorders are much rarer: 17 patients with *cbl*D, 15 with *cbl*F, 3 with *cbl*J, and 12 with *cbl*X have been identified to date (see Figs. 85-3 and 85-4). Neurologic findings are prominent in patients with *cbl*C and *cbl*D defects. Most patients with the *cbl*C defect present in the first year of life because of failure to thrive, lethargy, poor feeding, intellectual disability, and seizures. Intrauterine growth restriction and microcephaly may precede postnatal manifestations in some affected infants. Late-onset patients with sudden development of dementia and myelopathy have been reported, even with presentation in adulthood. Megaloblastic anemia is a common finding in patients with *cbl*C defect. Mild to moderate increases in concentrations of methylmalonic acid and homocysteine are found in body fluids. Unlike patients with classic homocystinuria, plasma levels of methionine are low to normal in these defects. Neither hyperammonemia nor hyperglycinemia are found in these patients. Like *cblC* patients, males with *cbl*X have elevations of both homocysteine and methylmalonic acid, but tend to have milder elevations of these metabolites. Clinically, patients with *cbl*X resemble those with *cbl*C but have more severe neurologic findings.

The **clinical findings** in the *cbl*F defect are quite variable; the first 2 patients had poor feeding, growth and developmental delay, and persistent stomatitis manifesting in the 1st 3 wk of life. One patient was not diagnosed until age 10 yr and had findings suggestive of rheumatoid arthritis, a pigmented skin abnormality, and encephalopathy. Vitamin B_{12} malabsorption has been noted in patients with *cbl*F defect. Clinical manifestations of *cbl*J are identical to those of *cbl*F.

Experience with **treatment** of patients with *cbl*C, *cbl*D, *cbl*F, *cblJ* and *cbl*X defects is limited. Large doses of hydroxycobalamin (1-2 mg/24 hr) in conjunction with betaine (6-9 g/24 hr) seem to produce biochemical improvement with variable clinical effect. Unexplained severe hemolytic anemia, hemolytic uremic syndrome, hydrocephalus, and congestive heart failure have been major complications in patients with *cbl*C defect.

The *cbl*C disorder is caused by mutations in the *MMACHC* gene located on chromosome 1p34.1. Approximately 75 different mutations have been identified, including a number of common mutations, and ones that are more common in specific ethnic groups. The *cbl*D disorder is caused by mutations in the *MMADHC* gene on chromosome 2q23.2. Mutations resulting in *cbl*D variant 1 (causing only homocystinuria) affect the C-terminal domain of the gene product; those resulting in *cbl*D variant 2 (causing only methylmalonic aciduria) affect the N terminus. Patients with classical form of *cbl*D, with both homocystinuria and methylmalonic, have mutations resulting in decreased protein expression. The *cbl*F disorder is caused by mutations in the *LMBRD1* gene (on chromosome 6q13) encoding a lysosomal membrane protein. The *cbl*J disorder is a phenocopy of *cbl*F and is associated with mutations in the *ABCD4* gene (on chromosome 14q24.3), encoding an adenosine triphosphate–binding cassette protein localized to the lysosomal membrane. Mutations in either *LMBRD1* or *ABCD4* genes result in failure of release of cobalamin from lysosomes. The *cbl*X disorder is caused by mutations in the *HCFC1* gene on the X chromosome, which encodes a DNA-binding protein that appears to be required for expression of the *MMACHC* gene.

Patients with *cbl*D variant 1, *cbl*E, and *cbl*G defects do not have methylmalonic acidemia (see Chapter 85.3).

Bibliography is available at Expert Consult.

85.7 Glycine

Iraj Rezvani

Glycine is a nonessential amino acid synthesized mainly from serine and threonine. Structurally, it is the simplest amino acid. It is involved in many reactions in the body, especially in the nervous system where it functions as a neurotransmitter (excitatory in the cortex, inhibitory in the brainstem and the spinal cord; see Chapter 85.11). Its main catabolic pathway requires the complex glycine cleavage enzyme to cleave the first carbon of glycine and convert it to carbon dioxide (see Fig. 85-8). The glycine cleavage protein, a mitochondrial multienzyme, is composed of 4 proteins: P protein (glycine decarboxylase), H protein, T protein, and L protein, which are encoded by 4 different genes.

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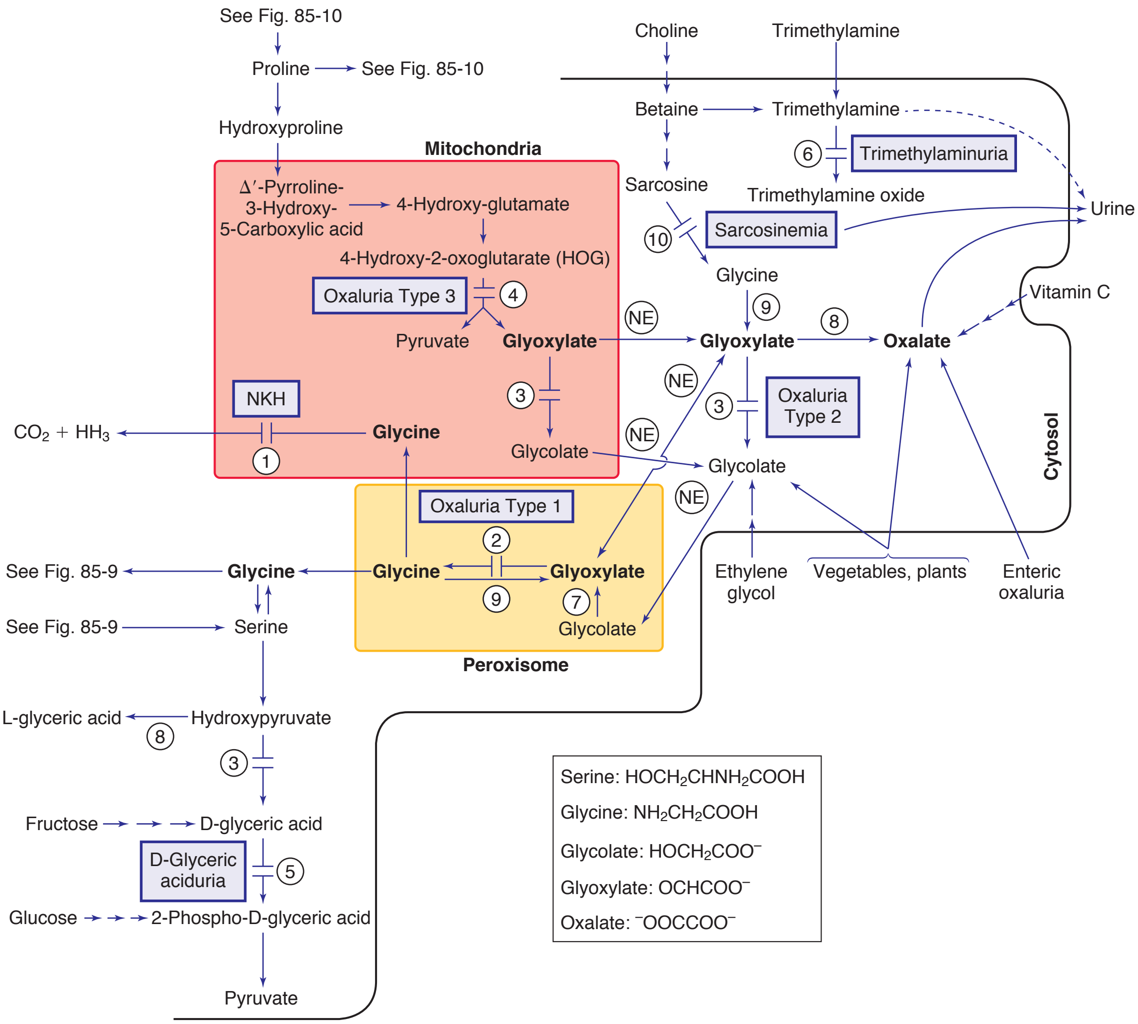

Figure 85-8 **Pathways in the metabolism of glycine and glyoxylic acid.** FH_4, tetrahydrofolate; (NE), nonenzymatic; NKH, nonketotic hyperglycinemia. **Enzymes:** *(1)* Glycine cleavage enzyme, *(2)* alanine: glyoxylate aminotransferase, *(3)* Glyoxylic reductase/hydroxypyruvate reductase (GR/HRP), *(4)* hydroxyoxoglutarate aldolase (HOGA), *(5)* glycerate kinase, *(6)* trimethylamine oxidase, *(7)* glycolate oxidase (D-amino acid oxidase), *(8)* lactate dehydrogenase, *(9)* glycine oxidase, *(10)* sarcosine dehydrogenase.

HYPOGLYCINEMIA

Defects in the biosynthetic pathway of serine (see Chapter 85.8) cause deficiency of glycine in addition to that of serine in body fluids, especially in the CSF. Isolated primary deficiency of glycine has not been reported.

HYPERGLYCINEMIA

Elevated levels of glycine in body fluids occur in propionic acidemia and methylmalonic acidemia that are collectively referred to as ketotic hyperglycinemia because of coexistence of acidosis and ketosis. The pathogenesis of hyperglycinemia in these disorders is not fully understood, but inhibition of the glycine cleavage enzyme system by the various organic acids has been shown to occur in some of the patients. The term **nonketotic hyperglycinemia** (NKH) is reserved for the clinical condition caused by the genetic deficiency of the glycine cleavage enzyme system (see Fig. 85-8). In this condition, hyperglycinemia is present without ketosis.

NONKETOTIC HYPERGLYCINEMIA, GLYCINE ENCEPHALOPATHY

Four forms of this condition have been identified: neonatal, infantile, late onset, and transient.

Neonatal Hyperglycemia

This is the most common form of NKH. **Clinical manifestations** develop in the first few days of life (between 6 hr and 8 days after birth). Poor feeding, failure to suck, lethargy, and profound hypotonia may progress rapidly to a deep coma, apnea, and death. Convulsions, especially myoclonic seizures and hiccups, are common.

Laboratory findings reveal moderate to severe hyperglycinemia (as high as 8 times normal) and hyperglycinuria. The unequivocal elevation of glycine concentration in the spinal fluid (15-30 times normal) and the high ratio of glycine concentration in spinal fluid to that in plasma (a value >0.08) are diagnostic of NKH. Serum pH is normal; plasma serine levels are usually low.

Approximately 30% of affected infants die despite supportive therapy. Those who survive develop profound psychomotor retardation and intractable seizure disorders (myoclonic and/or grand mal seizures). Hydrocephalus, requiring shunting, and pulmonary hypertension have been noted in some survivors.

Infantile Nonketotic Hyperglycinemia

These previously normal infants develop **signs and symptoms** of neonatal NKH (see above) after 6 mo of age. Seizures are the common presenting signs. This condition appears to be a milder form of

neonatal hyperglycinemia; infants usually survive and intellectual disability is not as profound as in the neonatal form.

Laboratory findings in these patients are identical to those seen in the neonatal form.

Late-Onset Nonketotic Hyperglycinemia, Mild Episodic Form

Progressive spastic diplegia, optic atrophy, and choreoathetotic movements are the main **clinical manifestations**. Age of onset has been between 2 and 33 yr. Symptoms of delirium, chorea, and vertical gaze palsy may occur episodically in some patients during an intercurrent infection. Mental development is usually normal, but mild cognitive impairment has been reported in some patients. Seizures have been reported in only 1 patient.

Laboratory findings are similar to but not as pronounced as in the neonatal form.

Transient Nonketotic Hyperglycinemia

Most **clinical and laboratory manifestations** of this form are indistinguishable from those of the neonatal form. By 2-8 wk of age, however, the elevated glycine levels in plasma and CSF normalize and a complete clinical recovery may occur. Most of these patients develop normally with no neurologic sequelae, but intellectual disability has been noted in some. The etiology of this condition is not known, but it is believed to be a consequence of immaturity of the enzyme system.

All forms of NKH should be differentiated from ketotic hyperglycinemia, D-glyceric aciduria (see below), and ingestion of valproic acid. The latter compound causes a moderate increase in blood and urinary concentrations of glycine. Repeat assays after discontinuation of the drug should establish the diagnosis.

Diagnosis can be established by assay of the enzyme in liver or brain specimens or by identification of the mutation. Enzyme activity in the neonatal form is close to zero, whereas in the other forms, some residual activity is present. In most patients with the neonatal form, the enzyme defect resides in the P protein; defects in the T protein account for the rest. The enzyme assay in 3 patients with the infantile and late-onset forms has revealed 2 patients with a defect in the T protein and 1 with a defect in the H protein.

No effective **treatment** is known. Exchange transfusion, dietary restriction of glycine, and administration of sodium benzoate or folate have not altered the neurologic outcome. Drugs that counteract the effect of glycine on neuronal cells, such as strychnine, diazepam, and dextromethorphan, have shown some beneficial effects only in patients with the mild forms of the condition.

NKH is inherited as an autosomal recessive trait. The prevalence is not known, but high frequency of the disorder has been noted in northern Finland (1 in 12,000 live births). The newborn screening method using tandem mass spectrometry may not identify affected infants. The gene for P protein (*GLDC*) is on chromosome 9p24.1. The gene for H protein (*GCSH*) is mapped to chromosome 16q23.2 and that for T protein (*AMT*) is on chromosome 3p21.31. The L protein gene (*DLD*) is on chromosome 7q31.7. Several disease-causing mutations have been identified. Prenatal diagnosis has been accomplished by performing an assay of the enzyme activity in chorionic villous biopsy specimens or by identification of the mutant gene.

SARCOSINEMIA

Increased concentrations of sarcosine (*N*-methylglycine) are observed in both blood and urine, but no consistent clinical picture has been attributed to this metabolic defect. This is a recessively inherited metabolic condition caused by a defect in sarcosine dehydrogenase, the enzyme that converts sarcosine to glycine (see Fig. 85-8). The gene for this enzyme (*SARDH*) is on chromosome 9q34.2.

D-GLYCERIC ACIDURIA

D-Glyceric acid is an intermediate metabolite of serine and fructose metabolism. This rare condition is caused by deficiency of glycerate kinase enzyme (see Fig. 85-8). **Clinical manifestations** are highly variable. In the severe form of the condition, signs and symptoms of encephalopathy (hypotonia, seizures, and mental and motor deficits) with laboratory findings of hyperglycinemia and hyperglycinuria are suggestive of NKH. These patients have elevated levels of D-glyceric acid in all body fluids and excrete large quantities of D-glyceric acid in urine. This compound is not normally detectable in urine. Mild forms of the condition with mild speech delay or even normal development have also been reported.

No effective therapy is available. Restriction of fructose reduced the incidence of seizures in 1 patient. The gene for glycerate kinase *(GLYCTK)* is on chromosome 3p21.1.

TRIMETHYLAMINURIA

Trimethylamine is normally produced in the intestine from the breakdown of dietary choline and trimethylamine oxide by bacteria. Egg yolk and liver are the main sources of choline, and fish is the major source of trimethylamine oxide. Trimethylamine is absorbed and oxidized in the liver by trimethylamine oxidase (flavin-containing monooxygenases) to trimethylamine oxide, which is odorless and excreted in the urine (see Fig. 85-8). Deficiency of this enzyme results in massive excretion of trimethylamine in urine. There is a foul body odor that resembles that of a rotten fish, which may have significant social and psychosocial ramifications. Transient symptomatic trimethylaminuria can occur in normal individuals following ingestion of large quantities of the abovementioned foods. Restriction of fish, eggs, liver, and other sources of choline (such as nuts and grains) in the diet significantly reduces the odor. **Treatment** with short courses of oral metronidazole, neomycin, or lactulose cause temporary reduction in the body odor. The gene for trimethylamine oxidase *(FMO3)* has been mapped to chromosome 1q24.3.

HYPEROXALURIA AND OXALOSIS

Normally, oxalic acid is derived mostly from oxidation of glyoxylic acid and, to a lesser degree, from oxidation of ascorbic acid (see Fig. 85-8). Glyoxylic acid is formed from oxidation of glycolic acid and glycine in the peroxisomes, and catabolism of hydroxyproline in the mitochondria (Figs. 85-8 and 85-9). Vegetables and foods containing oxalic acid, such as spinach and rhubarb, are the main *exogenous* sources of glycolic and oxalic acids; most of glyoxylic and oxalic acids are produced endogenously. Normally, a major portion of glyoxylate produced in the body is shuttled to peroxisomes where it is converted to glycine by the action of the enzyme alanine-glyoxylate aminotransferase. Deficiency of this enzyme causes hyperoxaluria type 1. Most of the remaining glyoxylate in the cytosol is reduced to glycolate by the action of the enzyme glyoxylate reductase/hydroxypyruvate reductase. Deficiency of this enzyme causes hyperoxaluria type 2. These 2 pathways protect the body from excessive production of oxalic acid (see Fig. 85-8). Any glyoxylate that cannot be disposed of through these pathways is readily converted to oxalic acid by the action of the enzyme lactate dehydrogenase (LDH). Oxalic acid cannot be further metabolized in humans and is excreted in the urine as oxalates. Calcium oxalate is relatively insoluble in water and precipitates in tissues (kidneys and joints) if its concentration increases in the body.

Secondary hyperoxaluria has been observed in pyridoxine deficiency (cofactor for alanine-glyoxylate aminotransferase; see Fig. 85-8), in patients with inflammatory bowel disease, extensive resection of small bowel, or jejunoileal bypass *(enteric hyperoxaluria)*, after ingestion of ethylene glycol or high doses of vitamin C, and after administration of the anesthetic agent methoxyflurane (which oxidizes directly to oxalic acid). Acute, fatal hyperoxaluria may develop after ingestion of plants with high oxalic acid content such as sorrel or intentional ingestion of oxalic acid. Precipitation of calcium oxalate in tissues causes hypocalcemia, liver necrosis, renal failure, cardiac arrhythmia, and death. The lethal dose of oxalic acid is estimated to be between 5 and 30 g.

Primary hyperoxaluria is a genetic disorder in which large amounts of oxalates accumulate in the body. Three types of primary hyperoxaluria have been identified to date. The term **oxalosis** refers to deposition of calcium oxalate in parenchymal tissues.

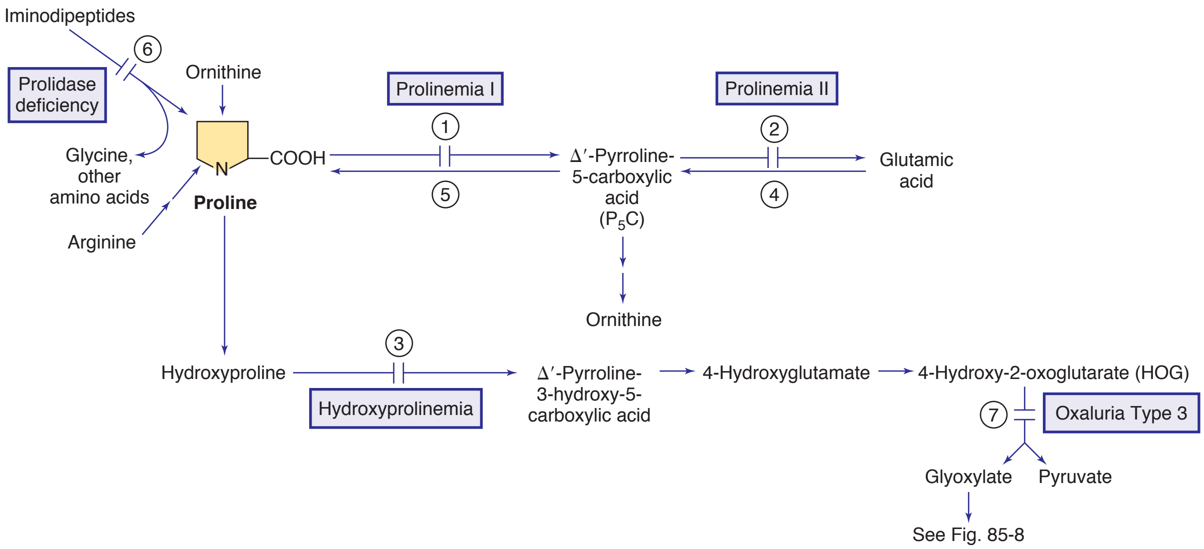

Figure 85-9 Pathways in the metabolism of proline. **Enzymes:** *(1)* Proline oxidase (dehydrogenase), *(2)* Δ^1-pyrroline-5-carboxylic acid (P5C) dehydrogenase, *(3)* hydroxyproline oxidase, *(4)* Δ^1-pyrroline-5-carboxylic acid (P5C) synthase, *(5)* Δ^1-pyrroline-5-carboxylic acid (P5C) reductase, *(6)* prolidase, *(7)* 4-hydroxyoxoglutarate aldolase (HOGA).

Primary Hyperoxaluria Type 1

This rare condition is the most common form of primary hyperoxaluria. It is caused by deficiency of the peroxisomal enzyme alanine-glyoxylate aminotransferase, which is expressed only in the liver peroxisomes and requires pyridoxine (vitamin B_6) as its cofactor. In the absence of this enzyme, glyoxylic acid, which cannot be converted to glycine, is transferred to the cytosol, where it is oxidized to oxalic acid (see above and Fig. 85-8).

There is a wide variation in the age of presentation (4 mo to 25 yr). The majority of patients become symptomatic in late childhood or early adolescence. In 19% of cases, symptoms develop before 1 yr of age (neonatal oxaluria). The initial **clinical manifestations** are related to renal stones and nephrocalcinosis. Renal colic and asymptomatic hematuria lead to a gradual deterioration of renal function, manifested by growth retardation and uremia. Most patients die before 20 yr of age from renal failure if the disorder is left untreated. Acute arthritis is a rare manifestation and may be misdiagnosed as gout because uric acid is usually elevated in patients with type 1 hyperoxaluria. Late forms of the disease presenting during adulthood have also been reported. Crystalline retinopathy and optic neuropathy causing visual loss have occurred in a few patients.

A marked increase in urinary excretion of oxalate (normal excretion 10-50 mg/24 hr) is the most important **laboratory finding**. The presence of oxalate crystals in urinary sediment is rarely helpful for diagnosis because such crystals are often seen in normal individuals. Urinary excretion of glycolic acid and glyoxylic acid is increased in most patients but not in all. **Diagnosis** can be confirmed by performing an assay of the enzyme in liver specimens or by identification of the mutant gene.

Treatment has been largely unsuccessful. In some patients (especially those whose condition is a result of mistargeting of the enzyme to the mitochondria; see below) administration of large doses of pyridoxine reduces urinary excretion of oxalate. Renal transplantation in patients with renal failure has not improved the outcome in most cases, because oxalosis has recurred in the transplanted kidney. Combined liver and kidney transplants have resulted in a significant decrease in plasma and urinary oxalate, and this may be the most effective treatment of this disorder, particularly in children.

The condition is inherited as an autosomal recessive trait. The gene for this enzyme *(AGXT)* is mapped to chromosome 2q37.3. Several mutations of the gene have been described in patients with this condition. The most common mutation results in the mistargeting of the enzyme to the mitochondria instead of the peroxisomes. The in vitro enzyme activity in these patients may reach the level found in obligate heterozygotes. In vivo function remains defective, however. Approximately 30% of patients with hyperoxaluria type 1 are estimated to have this defect.

Prenatal diagnosis has been achieved by the measurement of fetal hepatic enzyme activity obtained by needle biopsy or by DNA analysis of chorionic villous samples.

Primary Hyperoxaluria Type 2 (L-Glyceric Aciduria)

This rare condition is caused by a deficiency of D-glycerate dehydrogenase glyoxylate reductase/hydroxypyruvate reductase enzyme complex (see Fig. 85-8). A deficiency in the activity of this enzyme results in an accumulation of 2 intermediate metabolites, hydroxypyruvate (the ketoacid of serine) and glyoxylic acid. Both these compounds are further metabolized by LDH to L-glyceric acid and oxalic acid, respectively. Approximately 30% of reported patients are from the Saulteaux-Ojibway Indians of Manitoba.

These patients are indistinguishable from those with hyperoxaluria type 1. Renal stones presenting with renal colic and hematuria may develop before age 2 yr. Renal failure is less common in this condition than in hyperoxaluria type 1; the urine contains large amounts of L-glyceric acid in addition to high levels of oxalate. L-Glyceric acid is not normally present in urine. Urinary excretion of glycolic acid and glyoxylic acid is not increased. The presence of L-glyceric acid without increased levels of glycolic and glyoxylic acids in urine differentiate this type from type1 hyperoxaluria. **Diagnosis** can be confirmed by the enzyme assay in liver biopsy or by the identification of the mutant gene. The gene *(GRHPR)* is mapped to chromosome 9p13.2.

No effective **therapy** is available. As with the hyperoxaluria type 1 renal transplant does offer a cure because of recurrence of oxalosis in the transplanted kidney; no experience with kidney-liver transplantation is available at this time.

Primary Hyperoxaluria Type 3

Approximately 5% of patients with primary hyperoxaluria have neither type 1 nor type 2 hyperoxaluria. Genetic studies reveal mutations in the gene for 4-hydroxy-2-oxoglutarate aldolase enzyme. This mitochondrial enzyme catalyzes the final step in metabolic pathway of hydroxyproline generating pyruvate and glyoxylate from 4-hydroxy-2-oxoglutarate (HOG; see Figs. 85-8 and 85-9). In vitro studies show inhibition of glyoxylate reductase/hydroxypyruvate reductase enzyme activity by high concentration of HOG (the compound that

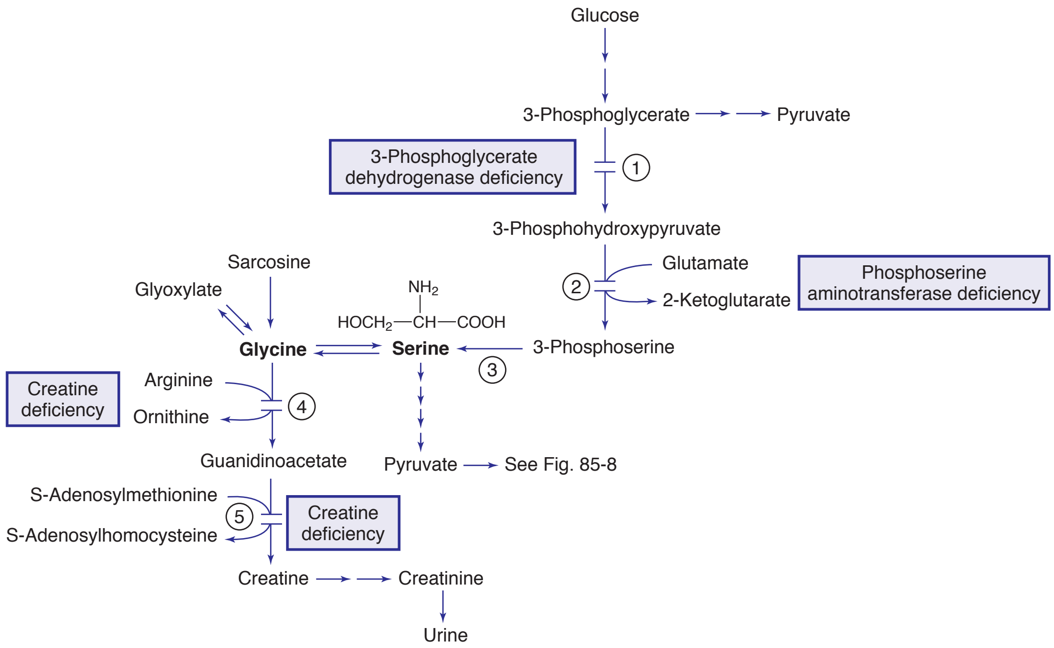

Figure 85-10 Pathways for the synthesis of serine and creatine. **Enzymes:** *(1)* 3-Phosphoglycerate dehydrogenase, *(2)* phosphoserine aminotransferase, *(3)* phosphoserine phosphatase, *(4)* arginine:glycine amidinotransferase (AGAT). *(5)* guanidinoacetate methyltransferase (GAMT).

accumulates in patients with hyperoxaluria type 3). This inhibition results in a biochemical phenotype similar to hyperoxaluria type 2 (see Fig. 85-8). It is also possible that the accumulated HOG is transferred into the cytosol and cleaved to form pyruvate and glyoxylate by the action of one of the cytosolic aldolases.

All probands in this cohort presented with calcium oxalate kidney stones in early childhood but asymptomatic older siblings were also identified. Renal function has remained normal in all patients. Increased levels of HOG have been found in urine, serum and liver biopsy samples of these patients. The gene for the enzyme *(HOGA1)* has been mapped to chromosome 10q24.2 and several different mutations have been identified in different families. The condition may be more common than type 2 hyperoxaluria.

Creatine Deficiency

Creatine is synthesized mainly in the liver, pancreas, and kidneys and to a lesser degree in the brain from arginine and glycine (Fig. 85-10) and is transported to muscles and the brain, where there is high activity of the enzyme creatine kinase. Phosphorylation and dephosphorylation of creatine in conjunction with adenosine triphosphate and diphosphate provide high-energy phosphate transfer reactions in these organs. Creatine is nonenzymatically metabolized to creatinine at a constant daily rate and is excreted in the urine. Three genetic conditions are known to cause creatine deficiency in the brain and other tissues. Two are because of deficiency of the enzymes involved in the biosynthesis of creatine. These enzymes are arginine:glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT; Fig. 85-10). Both conditions respond well to creatine supplementation. The third condition, an X-linked inherited defect, is caused by deficiency of the creatinine transporter (CRTR) protein and is not responsive to creatine administration.

Clinical manifestations of the 3 defects, which are similar, relate to the brain and muscles, and may appear in the first few weeks or months of life. Developmental delay, intellectual disability, speech delay, psychiatric symptoms (autistic behavior, hallucination), hypotonia, ataxia, and seizures are common findings. Dystonic movements are seen in severe GAMT deficiency.

Laboratory findings include decreased creatine and creatinine in blood and urine in patients with AGAT and GAMT defects. The urinary ratio of creatine to creatinine is increased in patients with a CRTR defect. Marked elevations of guanidinoacetate in blood, urine, and especially in spinal fluid (CSF), are diagnostic of GAMT defects. In contrast, low levels of guanidinoacetate are found in body fluids in the AGAT defect. Absence of creatine and creatine phosphate (in all 3 defects) and high levels of guanidinoacetate (in the GAMT defect) can be demonstrated in the brain by magnetic resonance spectroscopy (MRS). MRI of the brain shows signal hyperintensity in the globus pallidus. **Diagnosis** of AGAT or GAMT defects may be confirmed by measurement of the enzyme in the liver, cultured fibroblasts, or stimulated lymphoblasts or by the identification of the mutant gene DNA analysis of the gene. Diagnosis of CRTR is confirmed by DNA analysis or creatine uptake by fibroblasts.

Treatment with creatine monohydrate (350 mg-2 g/kg/day) orally results in a dramatic improvement in muscle tone and overall mental development and normalizes MRI and electroencephalographic findings in patients with AGAT and GAMT defects. It is believed that early treatment may assure normal development. No therapy is available for the CRTR defect; administration of creatine and its precursors (arginine and glycine) has failed to change the clinical course of the condition in affected patients. AGAT and GAMT defects are inherited as autosomal recessive traits. The gene for AGAT *(GATM)* is on chromosome 15q21.1 and that for GAMT *(GAMT)* is on chromosome 19p13.3. CRTR is an X-linked trait and the gene (*SLC6A8*) is on Xq28. CRTR defect is the most common cause of creatine deficiency, accounting for up to 1% of males with intellectual disability of unknown cause. AGAT defect is very rare (only 7 patients reported to date). Creatine deficiency must be considered in any patient with concomitant brain and muscle dysfunction, as treatment can produce a dramatic response in some cases.

Bibliography is available at Expert Consult.

85.8 Serine

Iraj Rezvani

Serine is a nonessential amino acid supplied through dietary sources and through its endogenous synthesis, mainly from glucose and glycine (see Fig. 85-10). The endogenous production of serine comprises an

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important portion of the daily requirement of this amino acid, especially in the synaptic junctions where it functions as a neurotransmitter (see Chapter 85.11). Consequently, deficiency of any of the enzymes involved in the biosynthesis of serine causes neurologic manifestations. Affected patients respond favorably to oral supplementation with serine and glycine provided that the treatment is initiated very early in life. Figure 85-8 shows the metabolic pathway for synthesis and catabolism of serine.

3-PHOSPHOGLYCERATE DEHYDROGENASE DEFICIENCY

Deficiency of this enzyme causes deficiencies of serine and glycine in the body. Three forms of the condition have been recognized: infantile, juvenile, and adult forms. In the infantile form, which is the most common phenotype, the **clinical manifestations** appear typically in utero with microcephaly and intrauterine growth retardation. In 1 infant who was normocephalic at birth, the head failed to grow normally postnatally. Feeding problems, failure to thrive, vomiting, irritability, intractable seizures, severe developmental delay, and hypertonia progressing into spastic tetraplegia are common findings that develop shortly after birth. Nystagmus, cataracts, hypogonadism, and megaloblastic anemia have been observed in some affected infants.

Laboratory findings include low levels of serine and glycine in plasma and very low levels of serine and glycine in CSF. No abnormal organic acid metabolite is found in the urine. MRI of the brain shows cerebral atrophy with enlarged ventricles, significant attenuation of white matter and impaired myelination.

The juvenile form of the condition has been reported in 2 siblings who presented at 5 and 9 yr of age with mild intellectual disability and absence seizures. Head size and MRI of the brain were normal.

Only 1 adult patient with congenital cataracts and intellectual disability has been reported. This patient developed progressive polyneuropathy resembling Charcot-Marie-Tooth disease type 2.

Diagnosis can be confirmed by measurement of the enzyme activity in cultured fibroblasts and by DNA analysis.

Treatment with high doses of serine (500-700 mg/kg/24 hr, orally) alone or in conjunction with glycine (200-300 mg/kg/24 hr) normalizes the serine levels in the blood and CSF. This treatment produces significant improvement in all clinical findings except for the psychomotor retardation; seizure activity subsides within a few days of therapy and may be halted completely. Microcephaly improves in young affected infants. There is evidence to indicate that psychomotor retardation may be prevented if the treatment starts in the first few days of life or, even better, in utero.

The condition is inherited as an autosomal recessive trait. The gene for 3-phosphoglycerate dehydrogenase enzyme (*PHGDH*) has been mapped to chromosome 1p12 and a few disease-producing mutations have been identified in different families. Prenatal diagnosis has been achieved by DNA analysis in a family with previously affected offspring; administration of serine to the mother corrected the microcephaly in the affected fetus as evidenced by ultrasound imaging. Treatment with supplemental serine has continued postnatally; the patient remains normal neurologically at 12 yr of age. The favorable response of this condition to a simple treatment makes this diagnosis an important consideration in any child with microcephaly and neurologic defects such as psychomotor delay or a seizure disorder. Measurements of serine and glycine in the CSF are critical for diagnosis because mild decreases of these amino acids in the plasma can be easily overlooked.

PHOSPHOSERINE AMINOTRANSFERASE DEFICIENCY

This enzyme catalyzes conversion of 3-phosphohydroxypyruvate to 3-phosphoserine (see Fig. 85-10). Deficiency of this enzyme has been reported in 2 siblings from an English family. Poor feeding, cyanotic episodes, and jerky movements developed shortly after birth in the first affected infant and progressed to intractable seizures by 9 wk of age. The infant was microcephalic. Electroencephalography (EEG) was consistent with multifocal seizures. Neuroimaging showed generalized cerebral and cerebellar atrophies. **Laboratory studies** were all within normal limits except for a mild decrease in plasma levels of serine and glycine with pronounced deficiencies of these 2 amino acids in the CSF. **Treatment** with serine (500 mg/kg/day) and glycine (200 mg/kg/day) was started at 11 wk of age but resulted in only marginal clinical improvement; the child died at 7 mo of age. The younger affected sibling, who was treated with serine and glycine within a few hours after birth, remained asymptomatic at 3 yr of age.

The condition is inherited as an autosomal recessive trait and the gene for the enzyme (PSAT1) is mapped to chromosome 9q21.2. Based on this single report one can assume that this is a treatable genetic condition with a favorable outcome if the treatment is initiated early in life.

Bibliography is available at Expert Consult.

85.9 Proline

Iraj Rezvani

Proline is a nonessential amino acid synthesized endogenously from glutamic acid, ornithine, and arginine (see Fig. 85-9). Proline and hydroxyproline are found in high concentrations in collagen. Neither of these amino acids is normally found in urine in the free form except in early infancy. Excretion of proline and hydroxyproline as iminopeptides (dipeptides and tripeptides containing proline or hydroxyproline) reflects collagen turnover and is increased in disorders of accelerated collagen turnover, such as rickets or hyperparathyroidism. Proline is also found at synaptic junctions and functions as a neurotransmitter (see Chapter 85.11). The catabolic pathway of proline/hydroxyproline produces glyoxylic acid which can be further metabolized to glycine or oxalic acid (see Fig. 85-8).

HYPERPROLINEMIA

Two types of primary hyperprolinemia have been described.

Hyperprolinemia Type I

This rare autosomal recessive condition is caused by deficiency of proline oxidase (proline dehydrogenase; see Fig. 85-9). Clinical manifestations are variable; some affected individuals are asymptomatic but patients with severe psychomotor retardation and seizures have been reported. Schizophrenia is a common finding in these patients. The gene for proline oxidase *(PRODH)* is located on chromosome 22q11.2 and several disease-causing mutations have been identified. Microdeletions involving this region of chromosome 22 cause velocardiofacial (DiGeorge, Shprintzen) syndrome; approximately 50% of patients with this syndrome have been reported to have hyperprolinemia type I. Therefore, all patients with hyperprolinemia type I should be screened (by fluorescence in situ hybridization analysis) for presence of DiGeorge syndrome.

Laboratory studies reveal high concentrations of proline in plasma, urine, and in the CSF. Approximately 30% of obligate heterozygous individuals (parents, siblings) also have hyperprolinemia. Increased urinary excretion of hydroxyproline and glycine is also present; this is from saturation of the shared tubular reabsorption mechanism by massive prolinuria.

No effective **treatment** has yet emerged. Restriction of dietary proline causes modest improvement in plasma proline with no proven clinical benefit.

Hyperprolinemia Type II

This is a rare autosomal recessive condition caused by the deficiency of pyrroline-carboxylic acid dehydrogenase (aldehyde dehydrogenase 4 [ALDH4]; see Fig. 85-9). Psychomotor retardation (modest to severe) and seizures (usually precipitated by an intercurrent infection) have been reported in most affected children, but asymptomatic patients have also been reported.

Laboratory studies reveal increased concentrations of proline and Δ^1-pyrroline-5-carboxylic acid (P5C) in blood, urine, and the CSF.

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Increased excretion of xanthurenic acid also has been reported in this condition. The presence of P5C differentiates this condition from hyperprolinemia type I (see above). Increased levels of P5C in body fluids, especially in the CNS, cause inactivation of vitamin B_6 and generate a state of vitamin B_6 dependency (see Chapter 85.14). Vitamin B_6 dependency is perhaps the main cause of seizures and neurologic findings in this condition and may explain the variability in clinical manifestations in different patients. **Treatment** with high doses of vitamin B_6 in conjunction with a diet low in proline is recommended but the experience remains very limited because of paucity of patients. The gene for P5C dehydrogenase (ALDH4) is on chromosome 1p36.13.

PROLIDASE DEFICIENCY

During collagen degradation, imidodipeptides (dipeptides containing proline such as glycylproline) are released and are normally cleaved by tissue prolidase. This enzyme requires manganese for its proper activity. Deficiency of prolidase, which is inherited as an autosomal recessive trait, results in the accumulation of imidodipeptides in body fluids.

The **clinical manifestations** of this rare condition and the age at onset are quite variable (19 mo to 19 yr) and include recurrent, painful skin ulcers, which are typically on hands and legs. Other skin lesions that may precede ulcers by several years may include scaly erythematous maculopapular rash, purpura, and telangiectasia. Most ulcers become infected. Healing of the ulcers may take 4-7 mo. Mild to severe cognitive and motor deficits and susceptibility to infections are also present in most patients (recurrent otitis media, sinusitis, respiratory infection, splenomegaly). Infection is the cause of death. Some patients may have craniofacial abnormalities such as ptosis, ocular proptosis, hypertelorism, small beaked nose and prominent cranial sutures. Asymptomatic cases have also been reported. Development of systemic lupus erythematosus has been noted in affected children of 1 family; young patients with systemic lupus erythematosus should be screened for prolidase deficiency. High levels of urinary excretion of imidodipeptides are diagnostic. Enzyme assay may be performed in erythrocytes or cultured skin fibroblasts.

Oral supplementation with proline, ascorbic acid, and manganese, and the topical use of proline and glycine, result in an improvement in leg ulcers. These treatments have not been found to be consistently effective in all patients.

The gene for prolidase enzyme *(PEPD)* has been mapped to chromosome 19q13.11 and several disease-causing mutations have been identified in different families.

Bibliography is available at Expert Consult.

85.10 Glutamic Acid

Iraj Rezvani

Glutamic acid and its aminated derivative glutamine have a wide range of functions in the body. One of the major products of glutamic acid is glutathione (γ-glutamyl cysteinylglycine). This ubiquitous tripeptide, with its function as the major antioxidant in the body, is synthesized and degraded through a complex cycle called the γ-glutamyl cycle (Fig. 85-11). Because of its free sulfhydryl (-SH) group and its abundance in the cell, glutathione protects other sulfhydryl-containing compounds (such as enzymes and CoA) from oxidation. It is also involved in the detoxification of peroxides, including hydrogen peroxide, and in keeping the intracellular milieu in a reduced state. The common consequences of glutathione deficiency are hemolysis and hemolytic anemia. In addition, glutathione participates in amino acid transport

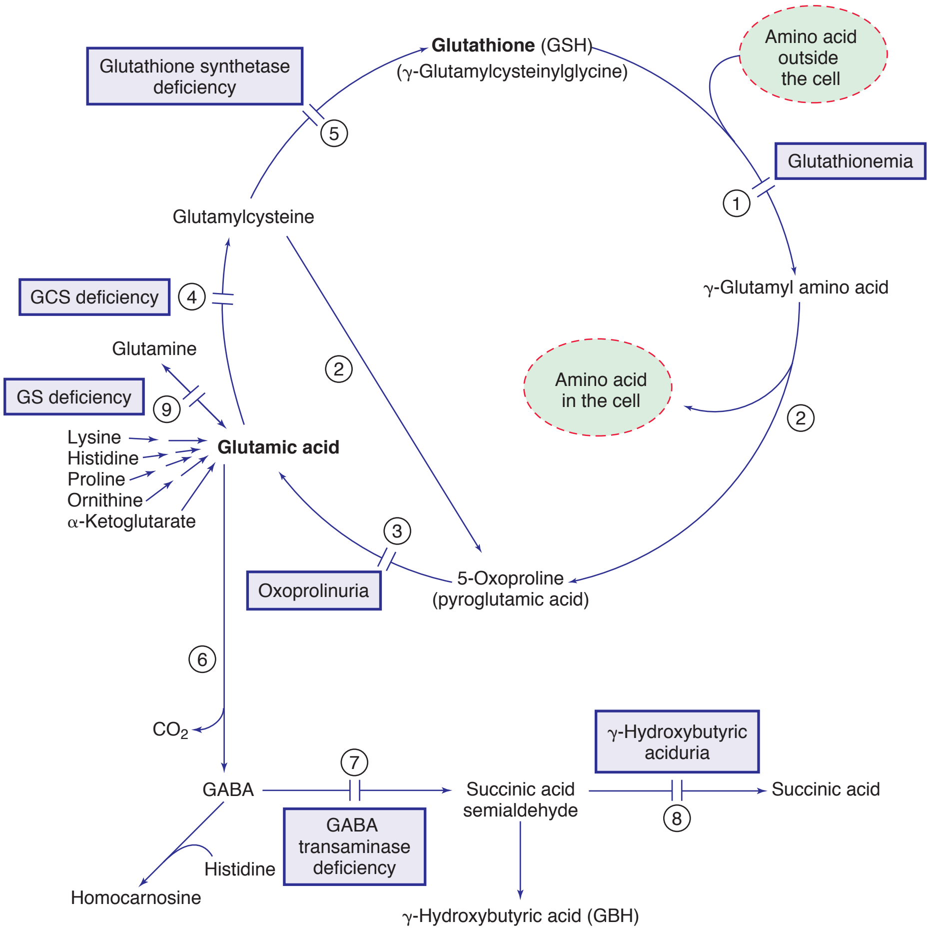

Figure 85-11 The γ-glutamyl cycle. Defects of the glutathione synthesis and degradation are noted. **Enzymes:** *(1)* γ-Glutamyl transpeptidase, *(2)* γ-glutamyl cyclotransferase, *(3)* 5-oxoprolinase, *(4)* γ-glutamyl-cysteine synthetase, *(5)* glutathione synthetase, *(6)* glutamic acid decarboxylase, *(7)* γ-aminobutyric acid (GABA) transaminase, *(8)* succinic semialdehyde dehydrogenase, *(9)* glutamine synthase.

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across the cell membrane through the γ-glutamyl cycle. Glutamic acid is also the precursor of γ-aminobutyric acid (GABA), a major neurotransmitter in the nervous system (see Chapter 85.11).

GLUTATHIONE SYNTHETASE DEFICIENCY

See Figure 85-11.

Three forms of this rare condition have been reported. In the **severe form**, which is a result of generalized deficiency of the enzyme, severe acidosis and massive 5-oxoprolinuria are the rule. In the **mild form**, in which the enzyme deficiency causes glutathione deficiency only in erythrocytes, neither 5-oxoprolinuria nor acidosis has been observed. A **moderate form** has also been observed in which the hemolytic anemia is associated with variable degrees of acidosis and 5-oxoprolinuria. In all forms, patients have hemolytic anemia secondary to glutathione deficiency.

Glutathione Synthetase Deficiency, Severe Form (Pyroglutamic Acidemia, Severe 5-Oxoprolinuria) and Moderate Form

Affected newborn infants with this rare condition usually develop acute symptoms of metabolic acidosis, jaundice, and mild to moderate hemolytic anemia in the first few days of life. Chronic acidosis continues after recovery. Similar episodes of life-threatening acidosis may occur during an infection such as gastroenteritis or after a surgical procedure. Progressive neurologic damage, manifested by intellectual disability, spastic tetraparesis, ataxia, tremor, dysarthria, and seizures, develops with age. Susceptibility to infection, presumably as a consequence of granulocyte dysfunction, is observed in some patients. Patients with the moderate form of the condition have milder acidosis and less 5-oxoprolinuria than is seen in the severe form, with no neurologic manifestations.

Laboratory findings include metabolic acidosis, mild to moderate degrees of hemolytic anemia, and 5-oxoprolinuria. High concentrations of 5-oxoproline are also found in blood. The urinary and blood levels of 5-oxoproline is less pronounced in patients with moderate form of the condition. The glutathione content of erythrocytes is markedly decreased. Increased synthesis of 5-oxoproline in this disorder is believed to be a result of the conversion of γ-glutamylcysteine to 5-oxoproline by the enzyme γ-glutamyl cyclotransferase (see Fig. 85-11). γ-Glutamylcysteine production increases greatly because the normal inhibitory effect of glutathione on the γ-glutamylcysteine synthetase enzyme is removed. A deficiency of glutathione synthetase has been demonstrated in a variety of cells including erythrocytes.

Treatment of acute attack includes hydration, correction of acidosis (by infusion of sodium bicarbonate), and measures to correct anemia and hyperbilirubinemia. Chronic administration of alkali is usually needed indefinitely. Administration of large doses of vitamins C and E has been recommended. Drugs and oxidants that are known to cause hemolysis and stressful catabolic states should be avoided. Oral administration of glutathione analogs has been tried with variable success.

Prenatal diagnosis can be achieved by the measurement of 5-oxoproline in amniotic fluid, by enzyme analysis in cultured amniocytes or chronic villous samples, or by DNA analysis of the gene. Successful pregnancy in an affected female (moderate form), with favorable outcomes for both mother and infant, has been reported.

Glutathione Synthetase Deficiency, Mild Form

This form has been reported in only a few patients. Mild to moderate hemolytic anemia has been the only **clinical finding** in these patients. Splenomegaly has been reported in some patients. Cognitive development is normal; metabolic acidosis and increased concentrations of 5-oxoproline do not occur. Similar to other types of glutathione synthase deficiency, this form is caused by mutations in the gene that encodes the enzyme. These mutations, however, decrease the half-life of the enzyme, which causes an increased rate of protein turnover without affecting its catalytic function. The expedited rate of enzyme turnover caused by these mutations is of no consequence for tissues with protein synthetic capability. However, inability of mature erythrocytes to synthesize protein, results in glutathione deficiency in the erythrocytes. **Treatment** is that of hemolytic anemia and avoidance of drugs and oxidants that can trigger the hemolytic process.

All forms of the condition are inherited as an autosomal recessive trait. The gene for this enzyme *(GSSD)* is located on chromosome 20q11.2. Several disease-causing mutations have been identified in different families.

5-Oxoprolinase Deficiency (5-Oxoprolinuria)

The main cause of massive 5-oxoprolinuria is glutathione synthetase deficiency (see above). Moderate 5-oxoprolinuria has been found in a variety of metabolic and acquired conditions, such as in patients with severe burns, Stevens-Johnson syndrome, homocystinuria, urea cycle defects, and tyrosinemia type I.

A few individuals with moderate 5-oxoprolinuria (4-10 g/day) as a result of 5-oxoprolinase (see Fig. 85-11) deficiency have been identified. No specific **clinical picture** has yet emerged; completely asymptomatic affected individuals have also been identified. It is, therefore, not clear whether 5-oxoprolinase deficiency is of any clinical consequence. No **treatment** has been recommended. The gene for the enzyme *(OPLAH)* is on chromosome 8q24.3.

γ-Glutamylcysteine Synthetase Deficiency

Only a few patients with this enzyme deficiency have been reported. The most consistent **clinical manifestation** has been mild chronic hemolytic anemia. Acute attacks of hemolysis have occurred after exposure to sulfonamides. Peripheral neuropathy and progressive spinocerebellar degeneration have been noted in 2 siblings in adulthood. **Laboratory findings** of chronic hemolytic anemia were present in all patients. Generalized aminoaciduria is also present because the γ-glutamyl cycle is involved in amino acid transport in cells (see Fig. 85-11). **Treatment** is that of hemolytic anemia and avoidance of drugs and oxidants that may trigger the hemolytic process. The condition is inherited as an autosomal recessive trait; the gene *(GCLC)* is mapped to chromosome 6p12.1.

GLUTATHIONEMIA (γ-GLUTAMYL TRANSPEPTIDASE DEFICIENCY)

This enzyme is present in any cell that has secretory or absorptive functions. It is especially abundant in the kidneys, pancreas, intestines, and liver. The enzyme is also present in the bile. Measurement of this enzyme in the blood is commonly performed to evaluate liver and bile duct diseases.

Deficiency of this enzyme causes elevation in glutathione concentrations in body fluids, but the cellular levels remain normal (see Fig. 85-11). Because only a few patients with enzyme deficiency have been reported, the scope of **clinical manifestations** has not yet been defined. Mild to moderate intellectual disability and severe behavioral problems were observed in 3 patients. One of the 2 sisters with this condition had normal intelligence as an adult, however, and the other had Prader-Willi syndrome.

Laboratory findings include marked elevations in urinary concentrations of glutathione (up to 1 g/day), γ-glutamylcysteine, and cysteine. None of the reported patients has had generalized aminoaciduria, a finding that would have been expected to occur in this enzyme deficiency (see Fig. 85-11).

Diagnosis can be confirmed by measurement of the enzyme activity in leukocytes or cultured skin fibroblasts. No effective **treatment** is available.

The condition is inherited as an autosomal recessive trait. The enzyme GGT (γ-glutamyl transpeptidase) is a complex protein and is encoded by at least 7 genes.

GENETIC DISORDERS OF METABOLISM OF γ-AMINOBUTYRIC ACID

See also Chapter 85.11.

Congenital Glutamine Deficiency

Glutamine is synthesized endogenously from glutamate and ammonia by a ubiquitous enzyme, glutamine synthetase (see Fig. 85-11).

Glutamine is known to be involved in several important functions, including detoxification of ammonia. Deficiency of this enzyme, resulting in glutamine deficiency, has been reported in 3 infants from 3 unrelated families. All affected infants manifested multiorgan involvement including significant brain malformations (abnormal gyrations, hypomyelination), facial abnormalities (broad nasal root, low-set ears) hypotonia and seizures at birth. Two of the patients died from multiorgan failure (respiratory and heart failure) in the neonatal period; 1 child was alive at 3 yr of age with severe developmental delay. Glutamine was absent in plasma, urine, and CSF, but plasma levels of glutamic acid were normal. Genetic defects of this enzyme underline the critical role of glutamine in embryogenesis especially in normal brain development. The condition is inherited as an autosomal recessive trait; the gene for glutamine synthetase *(GLUL)* is mapped to chromosome 1q25.3

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85.11 Genetic Disorders of Neurotransmitters

Iraj Rezvani and K. Michael Gibson

Neurotransmitters are chemical substances released from the axonal end of excited neurons at the synaptic junctions; they mediate initiation and amplification or inhibition of neural impulses. A number of amino acids and their metabolites comprise the bulk of neurotransmitters. Mutations in genes responsible for the synthesis or degradation of these substances may cause conditions that usually manifest neurologic and/or psychiatric abnormalities (Table 85-2). In the past, children affected by disorders of neurotransmitters have been given diagnoses such as cerebral palsy, seizure disorder, parkinsonism, dystonia, or autism. Diagnosis, in most cases, requires specialized laboratory studies of the **CSF,** because some of the neurotransmitters generated in the CNS (dopamine and serotonin) do not cross the blood–brain barrier and their abnormal concentrations are not detected in the serum or urine. An ever-growing number of these conditions are being identified; diseases that were once thought to be very rare are now diagnosed with increasing frequency.

TYROSINE HYDROXYLASE DEFICIENCY (INFANTILE PARKINSONISM, AUTOSOMAL RECESSIVE DOPA-RESPONSIVE DYSTONIA, SEGAWA SYNDROME, AUTOSOMAL RECESSIVE FORM)

Tyrosine hydroxylase catalyzes the formation of L-dopa from tyrosine. Deficiency of this enzyme, reported in several children, results in deficiencies of dopamine and norepinephrine (see Fig. 85-2). The clinical picture resembles that of autosomal dominant dystonia caused by GTP cyclohydrolase deficiency (see below); the clinical spectrum of the condition is still being elucidated.

Clinical manifestations range from mild to very severe. In general, 2 phenotypes have been recognized. In the mild form (dopa-responsive dystonia or type A), symptoms of unilateral limb dystonia causing gait incoordination and postural tremor occur in childhood and worsen with age if the condition remains untreated. Diurnal variation of symptoms (worse at the end of the day) may be present. Cognitive development is usually normal. In the severe form of the condition (infantile parkinsonism, infantile encephalopathy or type B), the clinical manifestations occur at birth or shortly thereafter. These include microcephaly, developmental delay, involuntary movements of the limbs with spasticity, dystonia, ptosis, expressionless face, oculogyric crises (upward rolling-eye movements) and autonomic dysfunction (temperature instability, excessive sweating, hypoglycemia, salivation, tremor, gastrointestinal reflux, constipation). Brisk reflexes, myoclonus, athetosis and distal chorea may be present. This form usually does not respond to treatment with L-dopa.

Laboratory findings include reduced levels of dopamine and its metabolite homovanillic acid (HVA), and normal concentrations of BH_4, neopterin, and 5-hydroxyindoleacetic acid (5-HIAA, a metabolite of serotonin) in the CSF. Serum prolactin levels are usually elevated. These findings are not diagnostic of the condition; diagnosis should be established by gene study.

Treatment with L-dopa/carbidopa results in significant clinical improvement in most patients, but is invariably associated with L-dopa induced dyskinesias. To minimize the side effects of therapy, the treatment should be started with a low dose and increased very slowly if needed. Other therapeutic interventions include anticholinergics, serotonergic agents and monoamine oxidase (MAO) B inhibitors, including amantadine, biperiden, and selegiline. Bilateral subthalamic nucleus deep brain stimulation has shown clinical efficacy in 1 case. The gene for tyrosine hydroxylase (TH) is located on chromosome 11p15.5; it is inherited as an autosomal-recessive trait.

Table 85-2 Genetic Disorders of Neurotransmitters in Children

TRANSMITTER	SYNTHESIS DEFECTS	DEGRADATION DEFECTS
MONOAMINES		
Dopamine	TH deficiency	MAO deficiency
Serotonin and dopamine	AADC deficiency	MAO deficiency
	BH_4 deficiency	
	With hyperphe	
	Without hyperphe	
Norepinephrine	DβH deficiency	MAO deficiency
GABA	?	GABA transaminase deficiency
		GHB aciduria
Histamine	HDC deficiency	?
TRANSPORTER PROTEINS		
Dopamine transporter	DAT deficiency	?
Vesicular monoamine transporter	VMAT2 deficiency	?
AMINO ACIDS		
Proline	?	Hyperprolinemia
Serine	3-PGD, PSAT deficiencies	?
Glycine	3-PDG, PSAT deficiencies	NKH

AADC, aromatic L-amino acid decarboxylase; BH_4, tetrahydrobiopterin; DAT, dopamine transporter; DβH, dopamine β-hydroxylase; GABA, γ-aminobutyric acid; GHB, γ-hydroxybutyric; HDC, histidine decarboxylase; hyperphe, hyperphenylalaninemia; MAO, monoamine oxidase; NKH, nonketotic hyperglycinemia; 3-PGD, 3-phosphoglycerate dehydrogenase; PSAT, phosphoserine aminotransferase; TH, tyrosine hydroxylase; VMAT2, vesicular monoamine transporter 2.

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Aromatic L-Amino Acid Decarboxylase Deficiency

Aromatic L-amino acid decarboxylase (AADC) catalyzes the decarboxylation of both 5-hydroxytryptophan (to form serotonin, see Fig. 85-5) and L-dopa (to generate dopamine, see Fig. 85-2). **Clinical manifestations** are related to underproduction of dopamine and serotonin. Poor feeding, lethargy, hypotension, hypothermia, eye rolling (oculogyric crises), and ptosis have been observed in affected neonates. Clinical findings in infants and older children include developmental delay, truncal hypotonia with hypertonia of limbs, oculogyric crises, extrapyramidal movements (choreoathetosis, dystonia, myoclonus), and autonomic abnormalities (sweating, salivation, irritability, temperature instability, hypotension). Symptoms often have a diurnal variation becoming worse by the end of the day.

Laboratory findings include decreased concentrations of dopamine and serotonin and their metabolites (HVA, 5-HIAA, vanillylmandelic acid [VMA] and norepinephrine), and increased levels of 5-hydroxytryptophan, L-dopa and its metabolite (3-*O*-methyldopa) in body fluids, especially in CSF. Elevated serum concentrations of prolactin (a result of dopamine deficiency) have also been observed. MRI of the brain reveals cerebral atrophy with degenerative changes in the white matter. A urine screening program, focused on 3-*O*-methyldopa and VMA, has demonstrated diagnostic promise in high-prevalence populations.

Treatment with neurotransmitter precursors has produced limited clinical improvement. Dopamine and serotonin have no therapeutic value because of their inability to cross the blood–brain barrier. Dopamine agonists (L-dopa/carbidopa, bromocriptine), MAO inhibitors (tranylcypromine), serotonergic agents and high doses of pyridoxine (cofactor for AADC enzyme) have been tried. No treatment of choice has yet emerged. Pyridoxine supplementation in patients harboring the S250F variant may be beneficial. Preimplantation genetic diagnosis after in vitro fertilization has been achieved in the high-prevalence Taiwanese population. The gene encoding AADC (*DDC*) is on chromosome 7p12.1. The condition is inherited as an autosomal recessive trait; several disease-causing mutations have been reported in different families.

TETRAHYDROBIOPTERIN DEFICIENCY

See Chapter 85.1.

BH_4 is the cofactor for PAH (see Fig. 85-1), tyrosine hydroxylase (see Fig. 85-2), tryptophan hydroxylase (see Fig. 85-5), and nitric oxide synthase. It is synthesized from GTP in many tissues (see Fig. 85-1). Deficiencies of enzymes involved in the biosynthesis of BH_4 result in inadequate production of this cofactor which causes deficiencies of monoamine neurotransmitters with or without concomitant hyperphenylalaninemia.

Tetrahydrobiopterin Deficiency with Hyperphenylalaninemia

See Chapter 85.1.

Tetrahydrobiopterin Deficiency Without Hyperphenylalaninemia

Hereditary Progressive Dystonia, Autosomal Dominant Dopa-Responsive Dystonia, Segawa Syndrome, Autosomal Dominant Form

See also Chapter 597.3.

This form of dystonia is caused by GTP cyclohydrolase I deficiency. It is inherited as an autosomal dominant trait and is more common in females than males (4 : 1).

Clinical manifestations usually start in early childhood with tremor and dystonia of the lower limbs (toe gait), which may spread to all extremities within a few years. Torticollis, dystonia of the arms, and poor coordination may precede dystonia of the lower limbs. Early development is generally normal. Symptoms have an impressive diurnal variation, becoming worse by the end of the day and improving with sleep. Autonomic instability is not uncommon. Parkinsonism may also be present or develop with advancing age. Late presentation in adult life has also been reported, associated with action dystonia (writer's cramp), torticollis or generalized rigid hypertonia with tremor but without postural dystonia. Additionally, limited data on adults suggest symptoms related to serotonin deficiency (sleep disturbance, cognitive impairment and impulsivity).

Laboratory findings show reduced levels of BH_4 and neopterin in the CSF without hyperphenylalaninemia. Dopamine and its metabolite (HVA) may also be reduced in CSF. The serotonergic pathway is less affected by this enzyme deficiency; thus, concentrations of serotonin and its metabolites are usually normal. Plasma phenylalanine is normal but an oral phenylalanine loading test (100 mg/kg) produces an abnormally high plasma phenylalanine level with an elevated phenylalanine/tyrosine ratio. The ratio, obtained at the 2nd and 3rd hr postload, in combination with urine neopterin level, has optimal diagnostic specificity and sensitivity. The existence of asymptomatic carriers indicates that other factors or genes may play a role in pathogenesis. The asymptomatic carrier may be identified by the phenylalanine loading test (see above).

Diagnosis may be confirmed by reduced levels of BH_4 and neopterin in CSF, through measurement of the enzyme activity, and via molecular genetic analysis (see Chapter 85.1). Clinically, the condition should be differentiated from other causes of dystonias and childhood parkinsonism, especially tyrosine hydroxylase, sepiapterin reductase, and aromatic amino acid decarboxylase deficiencies.

Treatment with L-dopa/carbidopa usually produces dramatic clinical improvement. Oral administration of BH_4 is also effective but is rarely used. The gene for GTP cyclohydroxylase I (*GCH1*) is located on chromosome 14q22.2.

Sepiapterin Reductase Deficiency

Sepiapterin reductase is involved in conversion of 6-pyruvoyl-tetrahydropterin to BH_4, and also participates in the salvage pathway of BH_4 synthesis (see Fig. 85-1). Sepiapterin reductase deficiency results in accumulation of 6-lactoyl-tetrahydropterin, which is converted to sepiapterin nonenzymatically. The majority of sepiapterin is metabolized to BH_4 through the salvage pathway in peripheral tissues (see Fig. 85-1), but because of the low activity of dihydrofolate reductase in brain, the amount of BH_4 remains insufficient for proper synthesis of dopamine and serotonin. This explains the absence of hyperphenylalaninemia, as well as an explanation for the often delayed diagnosis. Sepiapterin reductase deficiency may also be underdiagnosed as highly specialized CSF assays are required.

Clinical manifestations usually appear within a few months of life. Cardinal manifestations include paroxysmal stiffening, oculogyric crises, and hypotonia. Additional findings include motor and language delays, weakness, limb hypertonia, dystonia, hyperreflexia, and early onset parkinsonism. The symptoms usually have a diurnal variation. Misdiagnosis as cerebral palsy is common.

Diagnosis is established by measurement of CSF neurotransmitters and pterin metabolites which reveal decreased dopamine, HVA, norepinephrine, 5-HIAA and marked elevations of sepiapterin and dihydrobiopterin. The serum concentration of prolactin is elevated. The phenylalanine loading test (see above) may have diagnostic utility. Diagnosis may be confirmed by enzyme assay in fibroblasts or via molecular genetic analysis.

Treatment with slowly increasing doses of L-dopa/carbidopa and 5-hydroxytryptophan usually produces dramatic clinical improvement.

The condition is inherited as an autosomal recessive trait; the gene (SPR) for the enzyme is located on chromosome 2p13.2.

DOPAMINE β-HYDROXYLASE DEFICIENCY

See Figure 85-2.

This rare condition has been reported in only a few adult subjects with profound deficits of cardiovascular autonomic regulation resulting in predisposition to orthostatic hypotension. Past histories reveal ptosis, hypotension, hypothermia, hypoglycemia and nasal stuffiness in the neonatal and childhood periods. Presyncopal symptomatology includes dizziness, blurred vision, dyspnea, nuchal discomfort and chest pain; olfactory function remains relatively intact.

Laboratory findings include absence of norepinephrine and epinephrine and their metabolites with elevated levels of dopamine and its metabolite (HVA) in plasma, CSF, and urine. Elevated plasma dopamine may be pathognomonic for this disease. MRI of the brain shows decreased brain volume, consistent with the neurotrophic role of norepinephrine. **Treatment** with 3,4-dihydroxyphenylserine, which is converted to norepinephrine directly in vivo by the action of AADC, leads to significant improvement in orthostatic hypotension and normalizes noradrenaline and its metabolites. The condition is inherited as an autosomal recessive trait; the gene *(DBH)* for the enzyme resides on chromosome 9q34.2.

MONOAMINE OXIDASE (MAO) DEFICIENCY

There are 2 MAO isoenzymes: MAO A and MAO B. Both enzymes catalyze oxidative deamination of most biogenic amines in the body, including serotonin (see Fig. 85-5), norepinephrine, epinephrine, and dopamine (see Fig. 85-2). The genes for both isoenzymes are on the X chromosome (A, Xp11.3; B, Xp11.23). Male patients with MAO A deficiency manifest borderline intellectual deficiency and impaired impulse control. MAO B deficiency is found in patients with Norrie disease (see Chapter 622). Patients with isolated MAO B deficiency exhibit normal clinical characteristics and behavior. Combined MAO A and B deficiency causes severe intellectual disability and behavioral problems, associated with more extreme laboratory abnormalities (4-6–fold serotonin elevation in physiologic fluids, elevated *O*-methylated amine metabolites, and reduced deamination products [VMA, HVA]). A de novo microdeletion in Xp11.3 has been reported twice; the microdeletion in 1 male infant manifested with severe intellectual disability and episodic hypotonia. Dietary intervention (low tyramine, phenylethylamine and dopa/dopamine intake) did not improve the patients' blood serotonin levels.

γ-AMINOBUTYRIC ACID (GABA)

GABA is the main inhibitory neurotransmitter, which is synthesized in the synapses through decarboxylation of glutamic acid by glutamic acid decarboxylase (GAD). The same pathway is responsible for production of GABA in other organs, especially the kidneys and the β cells of the pancreas. GAD enzyme requires pyridoxine (vitamin B_6) as cofactor. Two GAD enzymes (GAD_{65} and GAD_{67}) have been identified. GAD_{67} is the main enzyme in the brain and GAD_{65} is the major enzyme in the β cells. Antibodies against GAD_{65} and GAD_{67} are the major markers for type1 diabetes and **stiff-person syndrome**, respectively. Deficiency of neither form of the enzyme has been reported in humans. GABA is catabolized to succinic acid by 2 enzymes, GABA transaminase and succinic semialdehyde dehydrogenase (SSADH) (see Fig. 85-11).

γ-Aminobutyric Acid Transaminase Deficiency

See Figure 85-11.

Clinical manifestations in the 2 index infant siblings included severe psychomotor retardation, hypotonia, hyperreflexia, lethargy, refractory seizures, and increased linear growth. Increased concentrations of GABA and β-alanine were found in CSF. Evidence of leukodystrophy was noted in the postmortem examination of the brain. A third case showed severe psychomotor retardation, recurrent episodic lethargy and intractable seizures with comparable CSF metabolite abnormalities to those of the index probands. GABA transaminase deficiency is demonstrated in brain and lymphocytes. No effective **treatment** has been identified. Intervention with vitamin B_6, the cofactor for the enzyme, was without therapeutic benefit. The gene *(ABAT)*, maps to chromosome 16p13.2; the condition is inherited as an autosomal recessive trait.

Succinic Semialdehyde Dehydrogenase Deficiency (γ-Hydroxybutyric Aciduria)

SSADH deficiency is the most common genetic disorder of neurotransmitters (see Fig. 85-11). Clinical manifestations, which usually begin in early infancy, include intellectual disability with disproportionate deficit in expressive language, hypotonia and ataxia; seizures occur in approximately 50% of patients. A diagnosis of **autism spectrum** disorder occurs disproportionately. Neuropsychiatric morbidity (especially oppositional defiance, obsession-compulsion, and hyperactivity) can be disabling, especially in adolescents and adults. Abnormal EEG findings include background slowing and generalized spike-wave paroxysms, with variable lateralization in hemispheric onset and voltage predominance. Photosensitivity and electrographic status epilepticus of sleep have been reported in combination with difficulties in sleep maintenance and excessive daytime somnolence. MRI of the brain shows an increased T2-weighted hyperintensity involving the globus pallidi, cerebellar dentate nuclei, and subthalamic nuclei, usually in a bilaterally symmetrical distribution.

The biochemical hallmark, γ-hydroxybutyric acid (GHB), is elevated in physiologic fluids (CSF, plasma, urine) in all patients. Increased concentrations of GABA are also found in CSF. Heightened diagnostic suspicion evolves through documentation of elevated urinary γ-hydroxybutyric acid, and confirmation is achieved by molecular genetic testing.

Treatment remains elusive; vigabatrin (GABA-transaminase inhibitor) has been employed empirically, with mixed outcomes, and there is concern with its use as it further elevates CNS GABA in an already hyper-GABAergic disorder. Additionally, vigabatrin leads to constriction of the visual field and long-term use is contraindicated. Magnesium valproate has shown efficacy for behavioral problems and seizure control in a single case.

The gene for SSADH *(ALDH5A1)* is located on chromosome 6p22, and inheritance follows an autosomal-recessive pattern. Prenatal diagnosis has been achieved by measurement of GHB in the amniotic fluid, assay of the enzyme activity in the amniocytes or in biopsy specimens of chorionic villi or by DNA analysis.

DEFECTS IN NEUROTRANSMITTERS TRANSPORTER PROTEINS

More than 20 different proteins are involved in transporting different neurotransmitters across the neuronal membranes. The main function of most of these transporters is to remove the excess neurotransmitters from the synaptic junction (cleft) back into the presynaptic neurons (reuptake). This recycling process not only regulates the precise effect of neurotransmitters at the synaptic junction but also resupplies the presynaptic neurons with neurotransmitters for future use. A few transporter proteins are involved in shuttling neurotransmitters from the neuronal cytoplasm across the membrane of synaptic vesicles for storage (vesicular transporters). Upon neuronal stimulation, these vesicles release a bolus of neurotransmitters via exocytosis. As expected, mutations in transporter proteins interfere with the proper reuptake and storage of neurotransmitters and may result in clinical manifestations similar to those seen in deficiencies of neurotransmitters metabolism themselves. Two conditions caused by mutations of neurotransmitter protein transporters have been described.

Dopamine Transporter Protein Deficiency

This transporter protein is involved in reuptake of dopamine by the presynaptic neurons, and its deficiency causes depletion of dopamine, and hence a dopamine deficiency state. Dopamine transporter protein (DAT) is encoded by *SLC6A3* gene on chromosome 5p15.33. Mutation of this gene has been reported in 3 children from 2 unrelated consanguineous families. These children presented with **symptoms** of infantile parkinsonism-dystonia syndrome. Symptoms of irritability and feeding difficulties started shortly after birth and progressed to hypotonia, lack of head control, parkinsonism, dystonia and global developmental delay by early infancy. Two of the patients were misdiagnosed as having cerebral palsy. MRI of the brain showed no abnormalities.

Examination of the CSF revealed marked elevation of HVA and normal level of 5-HIAAs. The urinary level of HVA, as well as the serum concentration of prolactin, were increased. Diagnosis was established by demonstrating the loss of function mutation in the *SLC6A3* gene. No effective treatment has been identified. **Treatment** with L-dopa/carbidopa did not result in any improvements in clinical or biochemical parameters.

Dopamine–Serotonin Vesicular Transporter Disease (Vesicular Monoamine Transporter Deficiency)

This autosomal recessive condition, described in 8 children from a consanguineous Saudi Arabian family is caused by a mutation in the *SLC18A2* gene. This gene encodes the vesicular monoamine transporter 2 (*VMAT2*), which is involved in transporting dopamine and serotonin from the cytoplasm into the synaptic storage vesicles located in the axonal terminals of the presynaptic neurons. Affected children manifested symptoms consistent with deficiencies of dopamine (hypotonia progressing into dystonia, parkinsonism, oculogyric crises), serotonin (sleep and psychiatric disturbances), and norepinephrine-epinephrine (excessive sweating, tremors, temperature instability, postural hypotension and ptosis). Symptoms started at 4 mo of age with hypotonia, lack of head control, inconsolable crying and oculogyric crises. Cognitive development was initially normal but deteriorated with age. No diurnal variation of the symptoms was noted. EEG, MRI, and MRS of the brain, as well as concentrations of all neurotransmitters and their metabolites in the CSF, were within normal limits. Urinary concentrations of 5-HIAA and HVA were moderately increased, whereas those of norepinephrine and epinephrine were decreased.

The phenotype resembles that seen in AADC and BH_4 deficiencies (see above). Proper diagnosis requires mutation analysis of the *SLC18A2* gene (located on chromosome 10q25.3). **Treatment** with L-dopa/carbidopa caused exacerbation of symptoms, whereas treatment with pramipexole, a dopamine receptor agonist, resulted in a favorable clinical response.

HISTIDINE DECARBOXYLASE DEFICIENCY

Decarboxylation of histidine by histidine decarboxylase produces histamine, which functions as a neurotransmitter in the brain. Deficiency of this enzyme (expressed mainly in the posterior hypothalamus) results in deficiency of histamine in the CNS, and in 1 family caused an autosomal dominant form of Tourette syndrome (see Chapter 85.13).

HYPERPROLINEMIA

Psychomotor retardation and seizures are common findings in most patients with hyperprolinemia type I and type II. Patients with type I hyperprolinemia also have an increased risk of developing schizophrenia. The contribution of increased concentration of proline to the pathogenesis of these conditions, however, remains unclear. The neurologic abnormalities observed in hyperprolinemia type II are mainly because of development of vitamin B_6 dependency in this condition (see Chapter 85.9).

3-PHOSPHOGLYCERATE DEHYDROGENASE DEFICIENCY

See Chapter 85.8.

PHOSPHOSERINE AMINOTRANSFERASE DEFICIENCY

See Chapter 85.8.

NONKETOTIC HYPERGLYCINEMIA

See Chapter 85.7.

Bibliography is available at Expert Consult.

85.12 Urea Cycle and Hyperammonemia (Arginine, Citrulline, Ornithine)

Iraj Rezvani and Marc Yudkoff

Catabolism of amino acids results in the production of free ammonia, which, in high concentration, is toxic to the CNS. Mammals detoxify ammonia to urea through a series of reactions known as the urea cycle (Fig. 85-12), which is composed of 5 enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), and arginase. A 6th enzyme, *N*-acetylglutamate (NAG) synthetase, catalyzes synthesis of NAG, which is an obligatory activator (effector) of the CPS enzyme. Individual deficiencies of these enzymes have been observed and, with an overall estimated prevalence of 1 in 35,000 live births, they are the most common genetic causes of hyperammonemia in infants.

GENETIC CAUSES OF HYPERAMMONEMIA

Hyperammonemia, sometimes severe, occurs in inborn errors of metabolism other than the urea cycle defects (Table 85-3). The pathogenesis for hyperammonemia in some of these conditions is not fully understood, although it is probable that the accumulation of a toxic metabolite–usually an organic acid–compromises function of the urea cycle.

CLINICAL MANIFESTATIONS OF HYPERAMMONEMIA

In the **neonatal period**, *symptoms and signs* are mostly related to brain dysfunction and are similar regardless of the cause of the hyperammonemia. The affected infant is normal at birth but becomes symptomatic following the introduction of dietary protein. Refusal to eat, vomiting, tachypnea, and lethargy can quickly progress to a deep coma. Convulsions are common. Physical examination may reveal hepatomegaly in addition to obtundation. Hyperammonemia can trigger increased intracranial pressure that may be manifested by a bulging fontanelle and dilated pupils.

In **infants and older children** acute hyperammonemia is manifested by vomiting and neurologic abnormalities such as ataxia, mental confusion, agitation, irritability, and combativeness. These manifestations may alternate with periods of lethargy and somnolence that ultimately progress to coma.

Routine **laboratory studies** show no specific findings when hyperammonemia is caused by defects of the urea cycle enzymes. Blood urea nitrogen is usually low in these patients; serum pH is usually normal or mildly elevated. There may be mild increases in serum transaminases (alanine aminotransferase, aspartate aminotransferase) because ammonia can cause swelling of hepatic mitochondria. In some patients with severe OTC deficiency, criteria may be met for acute liver failure, as patients with severe OTC-related liver injury may have moderate hyperammonemia (100-400 µmol/L). In infants with organic acidemias, hyperammonemia is commonly associated with severe acidosis as well as ketonuria. Newborn infants with hyperammonemia are often misdiagnosed as having sepsis; they may succumb without a correct diagnosis. Neuroimaging with CT scanning may reveal cerebral edema. Autopsy is usually unremarkable. It is imperative to measure plasma ammonia levels in any ill infant whose clinical manifestations cannot be explained by an obvious infection.

DIAGNOSIS

The main criterion for diagnosis is hyperammonemia. Each clinical laboratory should establish its own normal values for blood ammonia. Normal newborn values are higher than those of the older child or adult. Levels as high as 100 µmole/L occur in healthy term infants and as high as 150 µmole/L in premature infants. An ill infant usually manifests a blood ammonia level >200 µmole/L. Figure 85-13 illustrates an approach to the differential diagnosis of hyperammonemia in the newborn infant. Careful inspection of individual plasma amino acids commonly reveals abnormalities that may help the diagnosis. In patients with deficiencies of either CPS, OTC, or NAG synthetase, frequent findings include elevations in plasma glutamine and alanine with concurrent decrements in citrulline and arginine. These disorders cannot be differentiated from one another by the plasma amino acid levels alone. A marked increase in urinary orotic acid in patients with OTC deficiency differentiates this defect from CPS deficiency. Differentiation between the CPS deficiency and the NAG synthetase deficiency may require an assay of the respective enzymes or sequencing of the relevant genes. Clinical improvement occurring after oral administration of carbamylglutamate, however, may suggest

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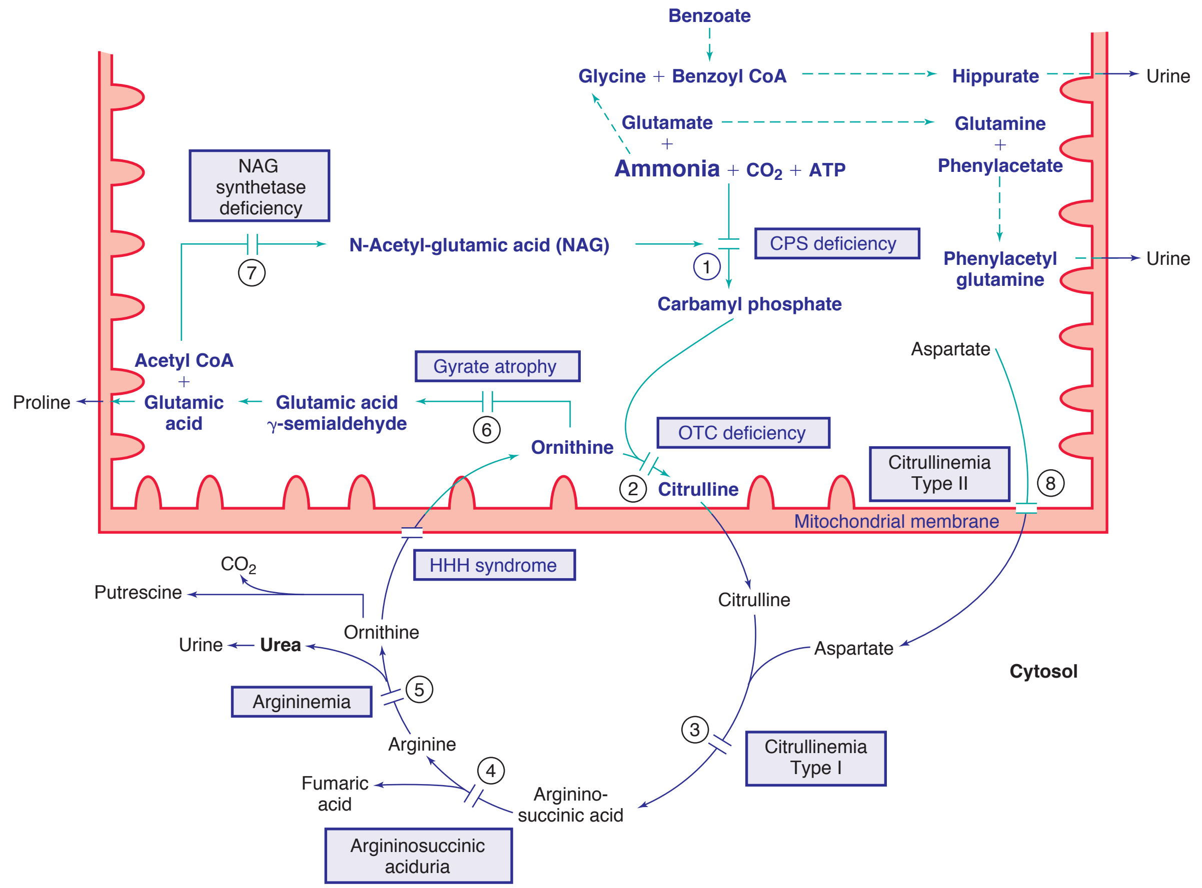

Figure 85-12 **Urea cycle: pathways for ammonia disposal and ornithine metabolism.** Reactions occurring in the mitochondria are depicted in *purple.* Reactions shown with *interrupted arrows* are the alternate pathways for the disposal of ammonia. **Enzymes:** *(1)* Carbamyl phosphate synthetase (CPS), *(2)* ornithine transcarbamylase (OTC), *(3)* argininosuccinic acid synthetase (AS), *(4)* argininosuccinic acid lyase (AL), *(5)* arginase, *(6)* ornithine 5-aminotransferase, *(7)* *N*-acetylglutamate (NAG) synthetase, *(8)* citrin. HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia.

Table 85-3 Inborn Errors of Metabolism Causing Hyperammonemia

Deficiencies of the urea cycle enzymes
Carbamyl phosphate synthetase
Ornithine transcarbamylase
Argininosuccinate synthetase
Argininosuccinate lyase
Arginase *N*-acetylglutamate synthetase
Organic acidemias
Propionic acidemia
Methylmalonic acidemia
Isovaleric acidemia
β-Ketothiolase deficiency
Multiple carboxylase deficiencies
Medium-chain fatty acid acyl-coenzyme A dehydrogenase deficiency
Glutaric acidemia type I
3-Hydroxy-3-methylglutaric aciduria
Lysinuric protein intolerance
Hyperammonemia-hyperornithinemia-homocitrullinemia syndrome
Transient hyperammonemia of the newborn
Congenital hyperinsulinism with hyperammonemia

NAG synthetase deficiency. Patients with a deficiency of ASS, ASL, or arginase have marked increases in the plasma levels of citrulline, argininosuccinic acid, or arginine, respectively. Indeed, the combination of hyperammonemia and marked hypercitrullinemia or argininosuccinic acidemia is virtually pathognomonic for these disorders. Children with urea cycle defects often self-select a low-protein, high-carbohydrate diet, especially those with late-onset disease or symptomatic females with OTC deficiency.

Mass screening of newborn infants identifies patients with ASS, ASL, and arginase deficiencies.

TREATMENT OF ACUTE HYPERAMMONEMIA

Clinical outcome depends mainly on the severity and the duration of hyperammonemia. Serious neurologic sequelae are likely in newborns with severe elevations in blood ammonia (>300 µmole/L) for more than 12 hr. Thus, acute hyperammonemia should be treated promptly and vigorously. The goal of therapy is to lower the concentration of ammonia. This is accomplished in 2 ways: (a) removal of ammonia from the body in a form other than urea and (b) minimizing endogenous protein breakdown and favoring endogenous protein synthesis by providing adequate calories and essential amino acids (Table 85-4). Fluid, electrolytes, glucose (5-15%), and lipids (1-2 g/kg/24 hr) should be infused intravenously together with minimal amounts of protein (0.25 g/kg/24 hr), preferably including essential amino acids. Oral feeding with a low-protein formula (0.5-1.0 g/kg/24 hr) through a nasogastric tube should be started as soon as sufficient improvement in the clinical condition is seen.

Because the kidneys clear ammonia poorly, its removal from the body must be expedited by formation of compounds with a high renal clearance. An important advance in the treatment of hyperammonemia has been the introduction of acylation therapy by using an exogenous organic acid which is acylated endogenously with nonessential amino acids to form a nontoxic compound with high renal clearances. The main organic acids used for this purpose are sodium salts of benzoic acid and phenylacetic acid. Benzoate forms hippurate with endogenous glycine in the liver (see Fig. 85-12). Each mole of benzoate

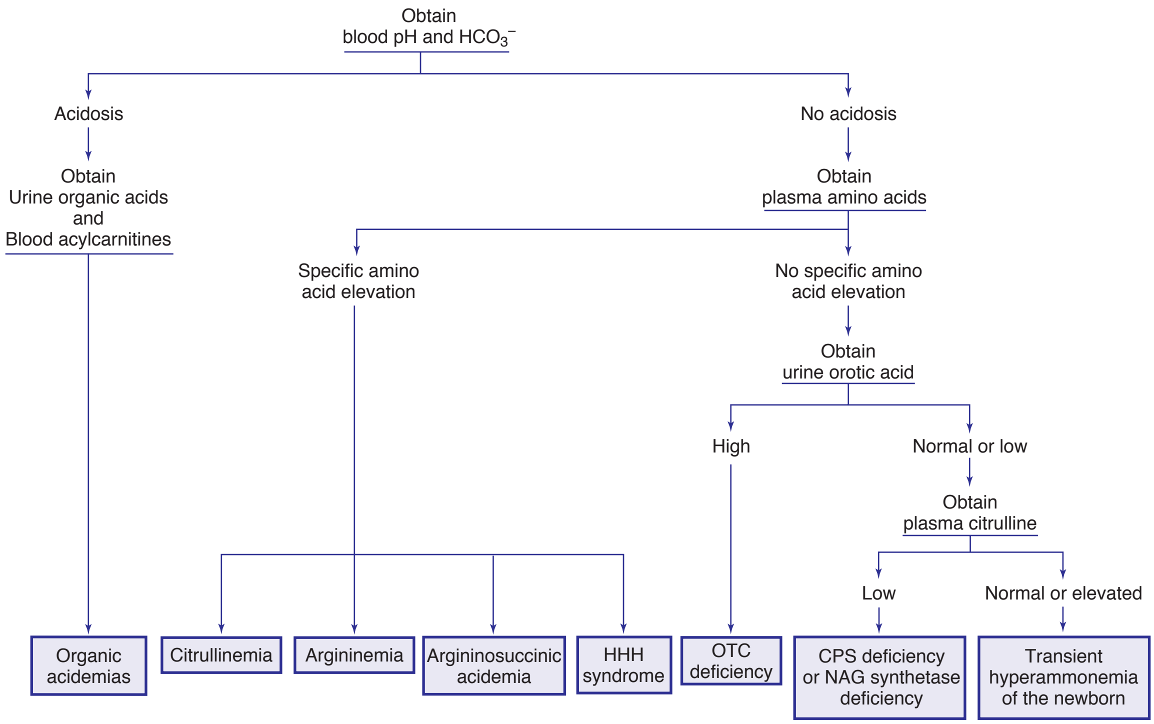

Figure 85-13 **Clinical approach to a newborn infant with symptomatic hyperammonemia.** CPS, carbamyl phosphate synthetase; HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia; NAG, *N*-acetylglutamate; OTC, ornithine transcarbamylase.

Table 85-4 Treatment of Acute Hyperammonemia in an Infant

1. Provide adequate calories, fluid, and electrolytes intravenously (10% glucose, NaCl* and intravenous lipids 1 g/kg/24 hr). Add minimal amounts of protein preferably as a mixture of essential amino acids (0.25 g/kg/24 hr) during the 1st 24 hr of therapy.
2. Give priming doses of the following compounds:
   (To be added to 20 mL/kg of 10% glucose and infused within 1-2 hr)
   - Sodium benzoate 250 mg/kg†
   - Sodium phenylacetate 250 mg/kg†
   - Arginine hydrochloride 200-600 mg/kg as a 10% solution
3. Continue infusion of sodium benzoate† (250-500 mg/kg/24 hr), sodium phenylacetate† (250-500 mg/kg/24 hr), and arginine (200-600 mg/kg/24 hr‡) following the above priming doses. These compounds should be added to the daily intravenous fluid.
4. Initiate peritoneal dialysis or hemodialysis if above treatment fails to produce an appreciable decrease in plasma ammonia.

*The concentration of sodium chloride should be calculated to be 0.45-0.9% including the amount of the sodium in the drugs.
†Sodium from these drugs should be included as part of the daily sodium requirement.
‡The higher dose is recommended in the treatment of patients with citrullinemia and argininosuccinic aciduria. Arginine is not recommended in patients with arginase deficiency and in those whose hyperammonemia is secondary to organic acidemia.

removes 1 mole of ammonia as glycine. Phenylacetate conjugates with glutamine to form phenylacetylglutamine, which is readily excreted in the urine. One mole of phenylacetate removes 2 moles of ammonia as glutamine from the body (see Fig. 85-12). A combined formulation of benzoate and phenylacetate (Ammonul) is commercially available for intravenous use.

Another valuable therapeutic adjunct is intravenous infusion of arginine, which is effective in all patients (except those with arginase deficiency). Arginine administration supplies the urea cycle with ornithine and NAG (see Fig. 85-12). In patients with citrullinemia, 1 mole of arginine reacts with 1 mole of ammonia (as carbamyl phosphate) to form citrulline. In patients with argininosuccinic acidemia, 2 moles of ammonia (as carbamyl phosphate and aspartate) react with arginine to form argininosuccinic acid. Citrulline and argininosuccinate are less toxic than ammonia and more readily excreted by the kidneys. In patients with CPS or OTC deficiency, arginine administration is indicated because this amino acid is not produced in sufficient amounts to enable endogenous protein synthesis. Patients with OTC deficiency benefit from supplementation with citrulline (200 mg/kg/24 hr) because 1 mole of citrulline reacts with 1 mole of ammonia (as aspartic acid) to form arginine. Administration of arginine or citrulline is **contraindicated** in patients with arginase deficiency, a rare condition in which the presenting clinical picture is one of spastic diplegia rather than hyperammonemia (see below). Arginine therapy is of no benefit if hyperammonemia is secondary to an organic acidemia. In a newborn infant with an initial episode of hyperammonemia, arginine should be used until the diagnosis is established.

Benzoate, phenylacetate, and arginine may be administered together for maximal therapeutic effect. A priming dose of these compounds is followed by continuous infusion until recovery from the acute state occurs (see Table 85-4). Both benzoate and phenylacetate are usually supplied as concentrated solutions and should be properly diluted (1-2% solution) for intravenous use. The recommended therapeutic doses of both compounds deliver a substantial amount of sodium to the patient; this amount should be included in calculation of the daily sodium requirement. Benzoate and phenylacetate (or the combined formulation, Ammonul) should be used with caution in newborn infants with hyperbilirubinemia because they may displace bilirubin from albumin; however, there are no documented cases of kernicterus (see Chapter 102.4) reported in neonates with hyperammonemia who have received such therapies. In infants at risk, it is advisable to reduce bilirubin to a safe level before administering benzoate or phenylacetate.

If the foregoing therapies fail within hours to produce any appreciable change in the blood ammonia level, peritoneal dialysis or, preferably, hemodialysis should be used. Exchange transfusion has little effect on reducing total body ammonia; it should be used only if dialysis cannot be employed promptly or when the patient is a newborn infant with hyperbilirubinemia (see above). Hemodialysis dramatically lowers blood ammonia within a few hours, but if it is unavailable or technically

unfeasible, peritoneal dialysis may be used as an alternative. When hyperammonemia is caused by an organic acidemia, peritoneal dialysis effectively removes both the offending organic acid and ammonia.

Oral administration of neomycin limits growth of intestinal bacteria that can produce ammonia. However, this modality is of limited use in patients (such as affected neonates) in whom reduction of hyperammonemia is an urgent priority. Oral lactulose acidifies the intestinal lumen, thereby reducing the diffusion of ammonia across the intestinal epithelium. This agent is of limited applicability in newborns in whom the risks of acidemia and dehydration are high.

There has been interest in the use of cooling as a therapeutic adjunct in newborn infants with metabolic encephalopathies like that caused by hyperammonemia. Clinical studies are in progress to evaluate the efficacy of this approach. There may be considerable lag between the normalization of ammonia and an improvement in the neurologic status of the patient. Several days may be needed before the infant becomes fully alert.

Long-Term Therapy

Once the infant is alert, therapy should be tailored to the underlying cause of the hyperammonemia. In general, all patients, regardless of the enzymatic defect, require some degree of protein restriction (1-2 g/kg/24 hr). In patients with defects in the urea cycle, chronic administration of benzoate (250-500 mg/kg/24 hr), phenylacetate (250-500 mg/kg/24 hr), and arginine (200-400 mg/kg/24 hr) or citrulline (in patients with OTC deficiency, 200-400 mg/kg/24 hr) is effective in maintaining blood ammonia levels within the normal range. Arginine and citrulline are contraindicated in patients with argininemia. Phenylbutyrate may be used in place of phenylacetate, because the patient and the family may not accept the latter owing to its offensive odor. A commercial preparation of the compound is available for oral use (Buphenyl). A significant innovation is the introduction of glycerol phenylbutyrate. This compound, unlike Buphenyl, is not a sodium salt and avoids the consequent coadministration of large amounts of sodium. It is approved for children ≥2 yr but is not yet approved for use in newborns. Benzoate and phenylacetate may lower carnitine levels, but clinical signs of carnitine deficiency or benefit from carnitine supplementation have not yet been demonstrated.

These compounds have been used during pregnancy without obvious teratogenic effect. However, experience is still quite limited and appropriate caution should be exercised.

Growth parameters, especially head circumference, and nutritional indices (blood albumin, prealbumin, pH, electrolytes, amino acids, zinc, selenium) should be followed closely. Long-term care of these patients is best achieved by a team of experienced professionals (pediatrician, nutritionist, child neurologist, metabolic geneticist). Skin lesions resembling **acrodermatitis enteropathica** (see Chapter 671) have been noted in a few patients with different types of urea cycle defects, presumably from deficiency of essential amino acids, especially arginine, caused by overzealous dietary protein restriction. Catabolic states (infections, fasting) that may trigger hyperammonemia should be avoided. They must be treated vigorously should they occur. It is important that all children with urea cycle defects avoid valproic acid (Depakote) because this drug elevates blood ammonia even in healthy subjects. In patients with CPS, OTC, and ASS deficiencies, acute hyperammonemic attacks may be precipitated by valproate administration.

CARBAMYL PHOSPHATE SYNTHETASE AND *N*-ACETYLGLUTAMATE SYNTHETASE DEFICIENCIES

See Figures 85-12 and 85-13.

Deficiencies of these 2 enzymes produce similar **clinical and biochemical manifestations**. There is a wide variation in severity of symptoms and in the age at presentation. In near complete enzymatic deficiency, symptoms appear during the first few days or even hours of life with signs and symptoms of hyperammonemia (refusal to eat, vomiting, lethargy, convulsion, and coma). Increased intracranial pressure is frequent. Late forms (as late as 32 yr of age) may present as an acute bout of hyperammonemia (lethargy, headache, seizures, psychosis) in a seemingly normal individual. Coma and death may occur during these episodes (a previously asymptomatic 26 yr old female died from hyperammonemia during childbirth). Diagnostic confusion with migraine is frequent. Intermediate forms with intellectual disability and chronic subclinical hyperammonemia interspersed with bouts of acute hyperammonemia have also been observed.

Laboratory findings include hyperammonemia. The plasma aminogram commonly shows a marked increase of glutamine and alanine with relatively low levels of citrulline and arginine. These are nondiagnostic changes that occur in hyperammonemia of diverse cause. Urinary orotic acid is usually low or may be absent (see Fig. 85-13).

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition is outlined above (see Table 85-4). Patients with NAG synthetase deficiency benefit from oral administration of carbamylglutamate. It is therefore important to differentiate between CPS and NAG synthetase deficiencies by gene sequencing. Deficiency of NAG synthetase is rare in North America.

CPS and NAG synthetase deficiencies are inherited as an autosomal recessive trait; the CPS enzyme is normally present in liver and intestine. The gene *(CPS1)* is mapped to chromosome 2q34; several disease-causing mutations have been found in different families. The prevalence of the condition is not known. The gene for NAG synthetase *(NAGS)* is located on chromosome 17q21.31. Neither of these conditions is identified by the mass screening of the newborn infants.

ORNITHINE TRANSCARBAMYLASE DEFICIENCY

See Figures 85-12 and 85-13.

In this X-linked partially dominant disorder, the hemizygous males are more severely affected than heterozygous females. The heterozygous females may have a mild form of the disease, but the majority (approximately 75%) is asymptomatic, although investigations indicate subtle neurologic defects even in women without a frank history of hyperammonemia. This is the most common form of all the urea cycle disorders, comprising approximately 40% of cases.

Clinical manifestations in a male newborn are usually those of severe hyperammonemia (see above) occurring in the first few days of life. Milder forms of the condition are commonly seen in heterozygous females and in some affected males. **Mild** forms characteristically have episodic manifestations, which may occur at any age (usually after infancy). Episodes of hyperammonemia (manifested by vomiting and neurologic abnormalities such as ataxia, mental confusion, agitation, combativeness and frank psychosis) are separated by periods of wellness. These episodes usually occur after ingestion of a high-protein diet or as a result of a catabolic state such as infection. Hyperammonemic coma, cerebral edema, and death may occur during one of these attacks. Cognitive development may proceed normally. Mild to moderate intellectual disability, however, is common. Gallstones have been seen in the survivors; the mechanism remains unclear.

The major **laboratory finding** during the acute attack is hyperammonemia accompanied by marked elevations of plasma concentrations of glutamine and alanine with low levels of citrulline and arginine. The blood level of urea is usually low. A marked increase in the urinary excretion of orotic acid differentiates this condition from CPS deficiency (see Fig. 85-13). Orotate may precipitate in urine as a pink-colored gravel or stones. In the mild form, these laboratory abnormalities may revert to normal between attacks. This form should be differentiated from all the episodic conditions of childhood. In particular, patients with lysinuric protein intolerance (see Chapter 85.14) may demonstrate some features of OTC deficiency, but the former can be differentiated by increased urinary excretion of lysine, ornithine, and arginine and elevated blood concentrations of citrulline.

The **diagnosis** is most conveniently confirmed by identification of the mutant gene, for which several commercial laboratories offer sequencing. As many as 20% of affected patients demonstrate a normal sequence, perhaps because the mutation involves an intron or a leader peptide. For these cases enzyme assay in a liver biopsy may be indicated. Prenatal diagnosis is feasible by analysis of DNA in amniocytes or chorionic villous samples. An oral protein load, which increases

plasma ammonia and urinary orotic acid levels, may identify asymptomatic heterozygous female carriers. A marked increase in urinary excretion of orotidine after an allopurinol loading test also detects obligate female carriers. Mild cerebral dysfunction may be present in asymptomatic female carriers. The importance of a detailed family history should be emphasized. A history of migraine or protein aversion is common in maternal female relatives of the proband. Indeed, careful scrutiny of the family history may reveal a pattern of unexplained deaths in male newborns in the maternal lineage.

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are outlined above. Citrulline is used in place of arginine in patients with OTC deficiency. Liver transplantation is a successful treatment for patients with OTC deficiency. It even has been performed during infancy.

The gene for OTC has been mapped to the X chromosome (Xp21.1). Many disease-causing mutations (>300) have been identified. The degree of enzyme deficiency and the genotype determine severity of the phenotype in most cases. Mothers of affected infants are expected to be carriers of the mutant gene unless a de novo mutation has occurred. A mother who gave birth to 2 affected male offspring was found to have a normal genotype, suggesting gonadal mosaicism in the mother. This condition is not identified by the mass screening of newborn infants.

ARGININOSUCCINATE SYNTHETASE (ASS) DEFICIENCY (CITRULLINEMIA)

See Figures 85-12 and 85-13.

Two clinically and genetically distinct forms of citrullinemia have been identified. The classic form (type I) is caused by the deficiency of the ASS enzyme. The adult form (type II) is caused by the deficiency of a mitochondrial transport protein named citrin.

Citrullinemia Type I (Classic Citrullinemia)

This condition is caused by the deficiency of ASS (see Fig. 85-12) and has variable **clinical manifestations** depending on the degree of the enzyme deficiency. Two major forms of the condition have been identified. The **severe or neonatal form**, which is most common, appears in the first few days of life with signs and symptoms of hyperammonemia (see above). In the **subacute or mild form**, clinical findings such as failure to thrive, frequent vomiting, developmental delay, and dry, brittle hair appear gradually after 1 yr of age. Acute hyperammonemia, triggered by an intercurrent catabolic state, may bring the diagnosis to light.

Laboratory findings are similar to those found in patients with OTC deficiency except that the plasma citrulline concentration is markedly elevated (50-100 times normal) (Fig. 85-13). Urinary excretion of orotic acid is moderately increased; crystalluria as a result of precipitation of orotates may also occur. The **diagnosis** is confirmed by assay of enzyme activity in cultured fibroblasts or by DNA analysis. Prenatal diagnosis is feasible with enzyme assay in cultured amniotic cells or by DNA analysis of cells obtained from chorionic villous biopsy.

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are outlined earlier in this chapter and in Table 85-3. Plasma concentration of citrulline remains elevated at all times and may increase further after administration of arginine. Although prognosis is poor for symptomatic neonates, patients with the mild disease usually do well on a protein-restricted diet in conjunction with sodium benzoate, phenylbutyrate, and arginine therapy. Mild to moderate cognitive impairment is a common sequela, even in a well-treated patient.

Citrullinemia is inherited as an autosomal recessive trait. The gene *(ASS 1)* is located on chromosome 9q34.11. Several disease-causing mutations have been identified in different families. The majority of patients are compound heterozygotes for 2 different alleles. The prevalence of the condition is not known. The recent introduction of neonatal screening for urea cycle defects has disclosed affected patients who are ostensibly asymptomatic, even with ingestion of a regular diet. Long-term follow-up is needed to be certain that these individuals do not sustain neurologic sequelae.

Citrullinemia Resulting From Citrin Deficiency (Citrullinemia Type II)

Citrin (aspartate-glutamate carrier protein) is a mitochondrial transporter encoded by a gene *(SLC25A13)* located on chromosome 7q21.3. One this protein's functions is to transport aspartate from mitochondria into cytoplasm; aspartate is required for converting citrulline to argininosuccinic acid (see Fig. 85-12). If aspartate is unavailable to the cytoplasmic component of the urea cycle, urea will not be formed at a normal rate and citrulline will accumulate. ASS activity is deficient in the liver of these patients, but no mutation in the gene for ASS has been found. It is postulated that citrin deficiency or its mutated gene interferes with translation of messenger RNA for ASS enzyme in the liver. Mutation in the gene for citrin produces 2 distinct clinical entities. The condition initially was reported almost exclusively in Japan but a few non-Japanese patients have been identified. Two clinical forms of citrin deficiency have been described.

Neonatal Intrahepatic Cholestasis (Citrullinemia Type II—Neonatal Form)

Clinical and laboratory manifestations, which usually start before 1 yr of age, include cholestatic jaundice with mild to moderate direct (conjugated) hyperbilirubinemia, marked hypoproteinemia, clotting dysfunction (increased prothrombin time and partial thromboplastin time), and increased serum GGTP and alkaline phosphatase activities; liver transaminases are usually normal. Plasma concentrations of ammonia and citrulline are usually normal, but moderate elevations are reported. There may be increases in plasma concentrations of methionine, tyrosine, alanine, and threonine. Elevated levels of serum galactose have been found even though the enzymes of galactose metabolism are normal. The reason for hypergalactosemia is not known. Marked elevation in the serum level of α-fetoprotein is also present. These findings resemble those of tyrosinemia type I, but unlike the latter condition, urinary excretion of succinylacetone is not elevated (see Chapter 85.2). Liver biopsy shows fatty infiltration, cholestasis with dilated canaliculi, and a moderate degree of fibrosis. The condition is usually self-limiting and the majority of infants recover spontaneously by 1 yr of age with only supportive and symptomatic treatment. Hyperammonemia and hypercitrullinemia, if present, should be treated with a low-protein diet and other appropriate measures (see above). Hepatic failure requiring liver transplantation has occurred in a few cases. Although the condition is commonly seen in Japan, the diagnosis should be considered in any case of unexplained neonatal hepatitis with cholestasis. Data on the long-term prognosis and the natural history of the condition are limited; development into the adult form of the condition (see below) after several years of seemingly asymptomatic hiatus has been observed.

Citrullinemia Type II, Adult Form (Adult-Onset Citrullinemia, Citrullinemia Type II—Mild Form)

This form starts suddenly in a previously normal individual and manifests with neuropsychiatric symptoms such as disorientation, delirium, delusion, aberrant behavior, tremors, and frank psychosis. Moderate degrees of hyperammonemia and hypercitrullinemia are present. The age at onset is usually between 20 and 40 yr (range: 11-85 yr). Patients who recover from the first episode may have recurrent attacks and most will die within a few years of diagnosis, mainly from cerebral edema. Pancreatitis, hyperlipidemia, and hepatoma are major complications among the survivors. Medical **treatment** has been mostly ineffective for prevention of future attacks. Indeed, some have speculated that the administration of large amounts of glucose might even prove deleterious, as the citrin transporter is important to the glycolytic pathway. Liver transplantation is the most effective therapy.

Several disease-causing mutations of the gene have been identified in affected Japanese families. The pathogenesis of citrullinemia type II (neonatal and adult forms) remains enigmatic. Although the frequency of homozygosity is relatively high in Japan (1 : 20,000 people), the clinical condition has a frequency of only 1 : 100,000 people. This indicates that a substantial number of homozygous individuals remain asymptomatic. Only a few non-Japanese patients have been identified.

ARGININOSUCCINATE LYASE DEFICIENCY (ARGININOSUCCINIC ACIDURIA)

See Figures 85-12 and 85-13.

The severity of the **clinical and biochemical manifestations** varies considerably. In the **neonatal form**, signs and symptoms of severe hyperammonemia (see above) develop in the first few days of life and mortality is high. Infants who survive the initial acute episode pursue a **subacute or late form** that is characterized by intellectual disability, failure to thrive, and hepatomegaly. A common finding is dry and brittle hair (trichorrhexis nodosa). Gallstones have been seen in some survivors. Acute attacks of severe hyperammonemia may occur during a catabolic state.

Laboratory findings include hyperammonemia, moderate elevations in liver enzymes, nonspecific increases in plasma levels of glutamine and alanine, a moderate increase in plasma levels of citrulline (less than that seen in citrullinemia), and marked increase in the concentration of argininosuccinic acid in plasma, urine and spinal fluid (see Fig. 85-13). The levels in the spinal fluid are usually higher than those in plasma. The enzyme is normally present in erythrocytes, the liver and cultured fibroblasts. Prenatal diagnosis is possible by measurement of the enzyme activity in cultured amniotic cells or by identification of the mutant gene. Argininosuccinic acid is also elevated in the amniotic fluid of affected fetuses.

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are outlined earlier in this chapter. Intellectual disability, persistent hepatomegaly with mild increases in liver enzymes, and bleeding tendencies as a result of abnormal clotting factors are common sequelae. This deficiency is inherited as an autosomal recessive trait with a prevalence of about 1 in 70,000 live births. The gene *(ASL)* is located on chromosome 7q11.21. Early detection is achieved through mass screening of newborn infants.

ARGINASE DEFICIENCY (HYPERARGININEMIA)

See Figures 85-12 and 85-13.

This defect is inherited as an autosomal recessive trait. There are 2 genetically distinct arginases in humans. One is cytosolic (ARG1) and is expressed in the liver and erythrocytes, and the other (ARG2) is found in renal and brain mitochondria. The gene for ARG1, the enzyme that is deficient in patients with arginase deficiency, is mapped to chromosome 6q23.2. The role of the mitochondrial enzyme is not well understood; its activity increases in patients with argininemia but has no protective effect. Several disease-causing mutations have been identified in different families.

Clinical manifestations of this rare condition are quite different from those of other urea cycle enzyme defects. The onset is insidious; the infant usually remains asymptomatic in the first few months or years of life. A **progressive spastic diplegia** with scissoring of the lower extremities, choreoathetotic movements, and loss of developmental milestones in a previously normal infant may suggest a degenerative disease of the CNS. Some children were treated for years as cases of cerebral palsy before their arginase deficiency was confirmed. Intellectual disability is progressive; seizures are common, but episodes of severe hyperammonemia are not usually seen. Hepatomegaly may be present. The acute neonatal form with intractable seizures, cerebral edema, and death has also been reported.

Laboratory findings include marked elevations of arginine in plasma and CSF (see Fig. 85-13). Urinary orotic acid is increased. Plasma ammonia levels may be normal or mildly elevated. Urinary excretion of arginine, lysine, cystine, and ornithine is usually increased, but normal levels have also been noted. Therefore, determination of amino acids in plasma is a critical step in the diagnosis of argininemia. The guanidino compounds (α-keto-guanidinovaleric acid and α-keto-argininic acid) are markedly increased in urine. The **diagnosis** is confirmed by assaying arginase activity in erythrocytes or by the identification of the mutant gene.

Treatment consists of a low-protein diet devoid of arginine. The composition of the diet and the daily intake of protein should be monitored by frequent plasma amino acid determinations. Sodium benzoate (250-375 mg/kg/24 hr) is also effective in controlling hyperammonemia and lowering plasma arginine levels. Intellectual disability is a common sequela of the condition. One patient developed type 1 diabetes at age 9 yr while his argininemia was under good control. Liver transplantation has produced promising results but no experience with long term outcome is available. Early detection is feasible through mass screening of newborn infants.

TRANSIENT HYPERAMMONEMIA OF THE NEWBORN

See Figure 85-13.

The blood concentration of ammonia in full-term infants may be as high as 100 µmole/L, or 2-3 times greater than that of the older child or adult. In premature infants, the upper limit of normal for blood ammonia may be as high as 150 µmole/L. Blood levels approximate the adult normal values after a few weeks of life. These infants are asymptomatic, and follow-up studies up to 18 mo of age have not revealed any significant neurologic deficits.

Severe transient hyperammonemia is observed in some newborn infants. The majority of affected infants are premature and have mild respiratory distress syndrome. Hyperammonemic coma may develop within 2-3 days of life, and the infant may succumb to the disease if treatment is not started immediately. **Laboratory studies** reveal marked hyperammonemia (plasma ammonia as high as 4,000 µmole/L) with moderate increases in plasma levels of glutamine and alanine. Plasma concentrations of urea cycle intermediate amino acids are usually normal except for citrulline, which may be moderately elevated. The cause of the disorder is unknown. Urea cycle enzyme activities are normal. **Treatment** of hyperammonemia should be initiated promptly and continued vigorously (see above). Recovery without sequelae is common, and hyperammonemia does not recur even with a normal protein diet.

ORNITHINE

Ornithine, a key intermediate of the urea cycle, is not incorporated into natural proteins. Rather, it is generated in the cytosol from arginine and must be transported into mitochondria, where it is a substrate for the OTC reaction, which forms citrulline. Excess ornithine is catabolized by 2 enzymes, ornithine 5-aminotransferase, which is a mitochondrial enzyme and converts ornithine to a proline precursor, and ornithine decarboxylase, which resides in the cytosol and converts ornithine to putrescine (see Fig. 85-12). Two genetic disorders feature hyperornithinemia: gyrate atrophy of the retina and hyperammonemia-hyperornithinemia-homocitrullinemia syndrome.

Gyrate Atrophy of the Retina and Choroid

This is a rare, autosomal recessive disorder caused by a deficiency of ornithine 5-aminotransferase (see Fig. 85-12). Approximately 30% of the reported cases are from Finland. **Clinical manifestations** are limited to the eyes and include night blindness, myopia, loss of peripheral vision, and posterior subcapsular cataracts. These eye changes start between 5 and 10 yr of age and progress to complete blindness by the 4th decade of life. Atrophic lesions in the retina resemble cerebral gyri. These patients usually have normal intelligence and a 10-20–fold increase in plasma levels of ornithine (400-1,400 µmole/L). They have neither hyperammonemia nor increases in plasma concentrations of any other amino acids; plasma levels of glutamate, glutamine, lysine, creatine, and creatinine are moderately decreased. Some patients respond partially to high doses of pyridoxine. An arginine-restricted diet in conjunction with supplemental lysine, proline, and creatine has been successful in reducing plasma ornithine concentration and has produced some clinical improvement. The gene for ornithine 5-aminotransferase *(OAT)* is mapped to chromosome 10q26.13. Many (at least 60) disease-causing mutations have been identified in different families.

HYPERAMMONEMIA-HYPERORNITHINEMIA-HOMOCITRULLINEMIA SYNDROME

In this rare autosomal recessive disorder, the defect is in the transport system of ornithine from the cytosol into the mitochondria, resulting in accumulation of ornithine in the cytosol and a deficiency of this

amino acid in mitochondria. The former causes hyperornithinemia and the latter results in disruption of the urea cycle and hyperammonemia (see Fig. 85-12). Homocitrulline is presumably formed from the reaction of mitochondrial carbamyl phosphate with lysine, which can become a substrate for the OTC reaction when ornithine is deficient. **Clinical manifestations** of hyperammonemia may develop shortly after birth or may be delayed until adulthood. Acute episodes of hyperammonemia manifest as refusal to feed, vomiting, and lethargy; coma may occur during infancy. Progressive neurologic signs, such as lower limb weakness, increased deep tendon reflexes, spasticity, clonus, seizures, and varying degrees of psychomotor retardation may develop if the condition remains undiagnosed. No clinical ocular findings have been observed in these patients.

Laboratory findings reveal marked increases in plasma levels of ornithine and homocitrulline in addition to hyperammonemia (see Fig. 85-13). Acute episodes of hyperammonemia should be treated promptly (see above). Restriction of protein intake improves hyperammonemia. Oral supplementation with ornithine and arginine (or citrulline) has produced clinical improvement in some patients. The gene for this disorder *(SLC25A15)* is located on chromosome 13q14.11.

Bibliography is available at Expert Consult.

85.13 Histidine

Iraj Rezvani

Histidine is an essential amino acid only during infancy. Its biosynthetic pathway in older children and adults is poorly understood. Histidine is degraded through the urocanic acid pathway to glutamic acid. Several genetic biochemical aberrations involving the degradative pathway of histidine have been reported, but none has any clinical consequence.

Decarboxylation of histidine by histidine decarboxylase produces histamine. Deficiency of this enzyme is the cause of familial form of **Tourette syndrome** (see Chapter 85.11).

Bibliography is available at Expert Consult.

85.14 Lysine

Iraj Rezvani

Lysine is catabolized through 2 pathways. In the first pathway, lysine is condensed with α-ketoglutaric acid to form saccharopine. Saccharopine is then catabolized to α-aminoadipic acid semialdehyde and glutamic acid. These first 2 steps are catalyzed by α-aminoadipic semialdehyde synthase, which has 2 activities: lysine-ketoglutarate reductase, and saccharopine dehydrogenase (see Fig. 85-14). In the second pathway, lysine is first transaminated and then condensed to its cyclic forms, pipecolic acid and piperidine-6-carboxylic acid (P6C). The latter compound (P6C) and its linear form, α-aminoadipic acid semialdehyde, are oxidized to α-aminoadipic acid by the enzyme antiquitin. This is the major pathway for D-lysine in the body and for the L-lysine in the brain (see Fig. 85-14).

Hyperlysinemia, *α-aminoadipic acidemia*, and *α-ketoadipic acidemia* are 3 biochemical conditions that are caused by inborn errors of metabolism of lysine. Individuals with these conditions are usually asymptomatic.

PYRIDOXINE (VITAMIN B_6)-DEPENDENT EPILEPSY

Pyridoxal 5′-phosphate, the active form of pyridoxine, is the cofactor for many enzymes including those involved in the metabolism of neurotransmitters. Intracellular deficiency of pyridoxal 5′-phosphate in the brain may result in a seizure disorder that is refractory to common anticonvulsant agents but is responsive to high doses of pyridoxine. This pyridoxine-dependent epilepsy is seen in the following genetic metabolic conditions:

Antiquitin (α-Aminoadipic Semialdehyde Dehydrogenase) Deficiency

This is the most common cause of pyridoxine-dependent epilepsy. Deficiency of antiquitin results in accumulation of P6C in brain tissue (see Fig. 85-14); P6C reacts with pyridoxal 5′-phosphate and renders it inactive. Large doses of pyridoxine are, therefore, needed to overcome this inactivation.

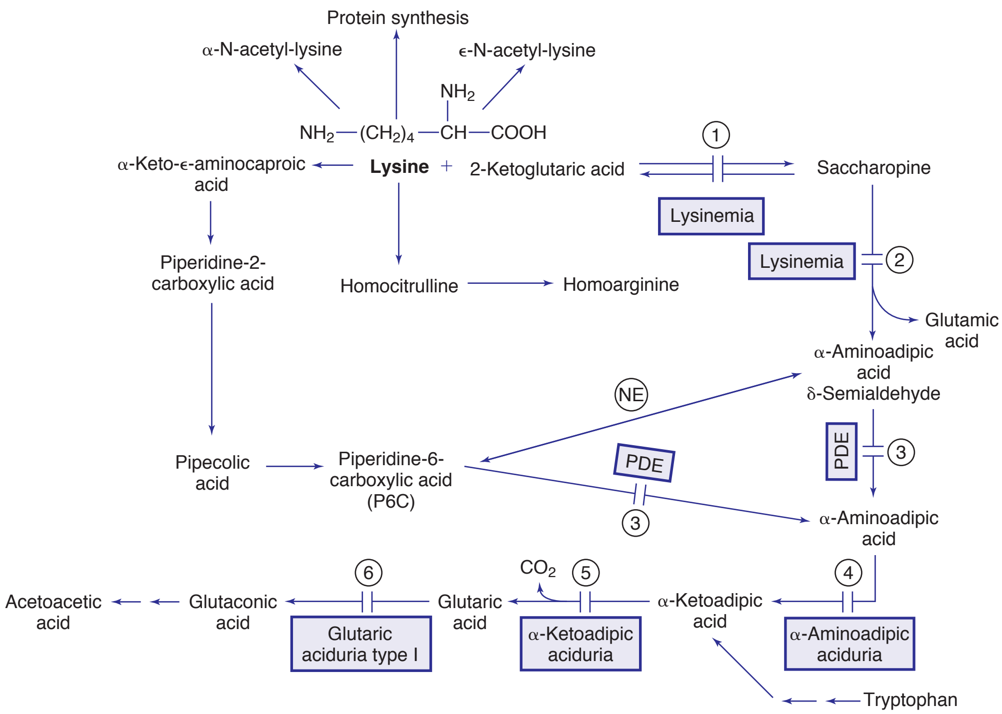

Figure 85-14 Pathways in the metabolism of lysine. **Enzymes:** *(1)* Lysine ketoglutarate reductase, *(2)* saccharopine dehydrogenase, *(3)* α-aminoadipic semialdehyde/piperidine-6-carboxylic acid (P6C) dehydrogenase (antiquitin), *(4)* α-aminoadipic acid transferase, *(5)* α-ketoadipic acid dehydrogenase, *(6)* glutaryl-CoA-dehydrogenase. NE, nonenzymatic; PDE, pyridoxine-dependent epilepsy.

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Sulfite Oxidase Deficiency (Molybdenum Cofactor Deficiency)

In this rare condition (see Chapter 85.4), accumulation of sulfites causes inhibition of enzymatic activity of antiquitin and accumulation of P6C, which, in turn, causes inactivation of pyridoxal-5′-phospate and vitamin B_6 dependency.

Hyperprolinemia Type II

In this condition, accumulation of P5C in brain tissue causes inactivation of pyridoxal-5′-phosphate and hence pyridoxine dependency (see Chapter 85.9 and Fig. 85-9).

Hypophosphatasia

Pyridoxal-5′-phosphate is the main circulating form of pyridoxine. Alkaline phosphatase is required for dephosphorylation of pyridoxal-5′-phosphate to generate free pyridoxine which is the only form of vitamin B_6 that can cross the blood–brain barrier and enter the brain cells. Pyridoxine is rephosphorylated intracellularly to form pyridoxal-5′-phosphate. In the infantile form of hypophosphatasia, pyridoxal-5′-phosphate cannot be dephosphorylated to free pyridoxine because of marked deficiency of tissue nonspecific alkaline phosphatase. This results in deficiency of pyridoxine in the brain and pyridoxine-dependent epilepsy (see Chapters 593 and 705).

The main **clinical manifestation** of pyridoxine-dependent epilepsy caused by antiquitin deficiency is generalized seizures, which usually occur in the first few hours of life and are unresponsive to conventional anticonvulsant therapies. Some mothers of affected fetuses report abnormal intrauterine fluttering movements. The seizures are usually tonic-clonic in nature but can be almost any type. Other manifestations such as dystonia, respiratory distress, and abdominal distention with vomiting, hepatomegaly, hypoglycemia and hypothermia may be present. Late-onset forms of the condition (as late as 5 yr of age) have been reported. Consequently, a trial with vitamin B_6 is recommended in any infant with intractable convulsions (see Chapters 593.4 and 593.6).

Laboratory studies reveal increased concentrations of α-aminoadipic semialdehyde and pipecolic acid in the CSF, plasma, and urine. EEG shows abnormalities corresponding to the type of seizures; these changes usually normalize after treatment. Neuroimaging may be normal but cerebellar and cerebral atrophy, periventricular hyperintensity, intracerebral hemorrhage, and hydrocephalus may be present.

Treatment with large doses of vitamin B_6 (50-100 mg/kg) usually results in a dramatic improvement of both seizures and the EEG abnormalities. The dependency and hence the therapy are lifelong. The therapeutic benefit of a lysine-restricted diet remains to be determined. Learning problems and speech delay are common sequelae. The condition is inherited as an autosomal recessive trait; the gene for antiquitin *(ALDH7A1)* is on chromosome 5q31.

GLUTARIC ACIDURIA TYPE I

Glutaric acid is an intermediate in the degradation of lysine (see Fig. 85-14), hydroxylysine, and tryptophan. Glutaric aciduria type I, a disorder caused by a deficiency of glutaryl CoA dehydrogenase, should be differentiated from glutaric aciduria type II, a distinct clinical and biochemical disorder caused by defects in the electron transport system (see Chapter 86.1).

Clinical Manifestations

Affected infants with glutaric aciduria type I may develop normally up to 2 yr of life; macrocephaly is a common finding in these infants and precedes onset of neurologic manifestations. Some affected infants may also show subtle neurologic symptoms, such as hypotonia, irritability, and feeding problems, during this seemingly asymptomatic period. The onset of the condition is usually heralded by acute encephalopathic findings such as loss of normal developmental milestones (head control, sitting), choreoathetosis, seizures, generalized rigidity, opisthotonos, and dystonia. These symptoms may occur suddenly in a seemingly normal infant after a minor infection. Recovery from the first attack usually occurs slowly, but some residual neurologic abnormalities, especially dystonia and extrapyramidal movements may persist. Additional acute attacks resembling the first one usually occur during episodes of intercurrent infections or catabolic states. In some patients, these signs and symptoms may develop gradually in the first few years of life; hypotonia and choreoathetosis may gradually progress into rigidity and dystonia (“insidious form”). Acute episodes of metabolic decompensation with vomiting, ketosis, seizures, and coma also occur in this form after infection or other catabolic states. Death usually occurs in the 1st decade of life during one of these episodes. The affected infants are prone to development of subdural hematoma and retinal hemorrhage following minor falls and head traumas. This may be misdiagnosed as child abuse. The intellectual abilities usually remain relatively normal in most patients.

Laboratory Findings

During acute episodes, mild to moderate metabolic acidosis and ketosis may occur. Hypoglycemia, hyperammonemia, and elevations of serum transaminases are seen in some patients. High concentrations of glutaric acid are usually found in urine, blood, and CSF. 3-Hydroxyglutaric acid may also be present in the urine. Plasma concentrations of amino acids are usually within normal limits. Laboratory findings may be unremarkable between attacks. Severely affected children without glutaric aciduria have also been reported (“low excretors”). In some of these patients, the glutaric acid is elevated only in the spinal fluid. In any child with progressive dystonia and dyskinesia, activity of the enzyme glutaryl CoA dehydrogenase should be measured in leukocytes or cultured fibroblasts as urinary glutaric acid may not be elevated in those patients who are the “low excretors.” Neuroimaging of the brain may reveal macrocephaly, increased extraaxial (particularly frontal) fluid, striatal lesions, dilated lateral ventricles, cortical atrophy (mainly in frontotemporal region), and fibrosis.

Treatment

A low-protein diet (especially a diet restricted in lysine and tryptophan) and high doses (200-300 mg/24 hr) of riboflavin (the coenzyme for glutaryl CoA dehydrogenase) and L-carnitine (50-100 mg/kg/24 hr orally) produce a dramatic decrease in the levels of glutaric acid in body fluids, but their effects on the clinical outcome have been variable. Early diagnosis (through newborn screening) with prevention and aggressive treatment of intercurrent catabolic states (infections) are shown to minimize striatal insults and assure a more favorable prognosis. The addition of a GABA analog (baclofen) and valproic acid to the therapeutic regimen produces improvement in some affected children.

The condition is inherited as an autosomal recessive trait. The prevalence is estimated at 1 : 100,000 live births worldwide. The condition is more prevalent in some ethnic populations (Canadian Oji-Cree Indians, Irish travelers, black South Africans, Swedes, and the Old Order Amish population in the United States). The gene for glutaryl CoA dehydrogenase *(GCDH)* is located on chromosome 19p13.2 and many disease-causing mutations have been reported in different families. A single mutation *(A421V)* accounts for all the patients from the Lancaster County (Pennsylvania) Old Order Amish community.

Prenatal diagnosis may be accomplished by demonstrating increased concentrations of glutaric acid in amniotic fluid, by the assay of the enzyme activity in amniocytes or chorionic villous samples, or by identification of the mutant gene.

LYSINURIC PROTEIN INTOLERANCE (FAMILIAL PROTEIN INTOLERANCE)

This rare autosomal recessive disorder is caused by a defect in the transport of the cationic amino acids lysine, ornithine, and arginine in both intestine and kidneys. Unlike patients with cystinuria, urinary excretion of cystine is not increased in these patients. Deficiency of the transporter protein in this condition causes multisystem manifestations, which start initially with gastrointestinal symptoms. Refusal to feed, nausea, aversion to protein, vomiting, and mild diarrhea, which may result in failure to thrive, wasting, and hypotonia, start shortly

after birth. Breastfed infants usually remain asymptomatic until shortly after weaning. This may be because of the low protein content of breast milk. Episodes of hyperammonemia may occur after ingestion of a high-protein diet. Mild to moderate hepatosplenomegaly, osteoporosis, sparse brittle hair, thin extremities with moderate centripetal adiposity, and growth retardation are common physical findings in patients whose condition has remained undiagnosed. Mental development is usually normal, but moderate intellectual disability has been observed in 20% of patients.

Progressive **interstitial pneumonitis with bouts of acute exacerbation commonly occurs in these patients.** This usually progresses to severe **alveolar proteinosis**. **Clinical manifestations** include progressive exertional dyspnea, fatigue, cough, diminished breath sound, and inspiratory rales; cyanosis may develop in older patients. Some patients have remained undiagnosed until the appearance of pulmonary manifestations. Radiographic evidence of pulmonary fibrosis has been observed in up to 65% of patients without clinical manifestations of pulmonary involvement.

Renal involvement is manifested initially by proteinuria, hematuria, and elevation of serum creatinine, which may progress to end-stage renal failure. Renal tubular involvement with findings compatible with Fanconi syndrome may also be present. Renal biopsy reveals pathologic findings consistent with glomerulonephritis and tubulointerstitial nephritis. Hematologic findings of anemia, leukopenia, and thrombocytopenia may also be present. A condition resembling hemophagocytic lymphohistiocytosis/macrophage activation syndrome has also been reported. Immunologic abnormalities (impaired lymphocyte function, abnormalities in immune globulins, hypocomplementemia), hypercholesterolemia, hypertriglyceridemia, and acute pancreatitis have also been reported in these patients.

Laboratory findings may reveal hyperammonemia and an elevated concentration of urinary orotic acid, which develop after protein feeding. Plasma concentrations of lysine, arginine, and ornithine are usually mildly decreased, but urinary levels of these amino acids, especially lysine, are greatly increased. The pathogenesis of hyperammonemia is not well understood. All enzymes of the urea cycle are normal. Hyperammonemia may be related to disruption of the urea cycle secondary to deficiency of arginine and ornithine. However, in patients with cystinuria who also have defects in the transport of lysine, arginine, and ornithine in both intestine and kidneys, hyperammonemia is not observed. Plasma concentrations of alanine, glutamine, serine, glycine, proline, and citrulline are usually increased. Anemia, increased serum levels of ferritin, LDH, and thyroxine-binding globulin, have also been observed in these patients. This condition should be differentiated from hyperammonemia caused by urea cycle defects (see Chapter 85.12), especially in heterozygous females with OTC deficiency. Increased urinary excretion of lysine, ornithine, and arginine and elevated blood levels of citrulline are not seen in patients with OTC deficiency.

The transport defect in this condition resides in the basolateral (antiluminal) membrane of enterocytes and renal tubular epithelia. This explains the observation that cationic amino acids are unable to cross these cells even when administered as dipeptides. Lysine in the form of dipeptide crosses the luminal membrane of the enterocytes but hydrolyzes to free lysine molecules in the cytoplasm. Free lysine, unable to cross the basolateral membrane of the cells, diffuses back into the lumen.

Treatment with a low-protein diet (1.0-1.5 g/kg/24 hr) supplemented with citrulline (100 mg/kg/day) has produced biochemical and clinical improvements. Episodes of hyperammonemia should be treated promptly (see Chapter 85.12). Supplementation with lysine is not useful because it is poorly absorbed and tends to produce diarrhea and abdominal pain. Diet therapy has no effect in prevention or amelioration of the multisystem manifestations. Treatment with high doses of prednisone has been effective in the management of acute pulmonary complications in some patients. Bronchopulmonary lavage is the treatment of choice for patients with alveolar proteinosis. The condition is most prevalent in Finland and Japan where the prevalence is 1 : 60,000 and 1 : 57,000 live births, respectively.

The gene for lysinuric protein intolerance *(SLC7A7)* is mapped to chromosome 14q11.2, and several disease-causing mutations have been identified in different families. Pregnancies in affected mothers have been complicated by anemia, thrombocytopenia, toxemia, and bleeding, but offspring have been normal.

Bibliography is available at Expert Consult.

85.15 Aspartic Acid (Canavan Disease)

Kimberlee M. Matalon and Reuben K. Matalon

N-Acetylaspartic acid, a derivative of aspartic acid, is synthesized in the brain and is found in a high concentration similar to glutamic acid. The exact function of *N*-acetylaspartic acid is unknown, but it may serve as a reservoir for acetate, which is needed for myelin synthesis. Aspartoacylase, cleaves the *N*-acetyl group from *N*-acetylaspartic acid. Deficiency of aspartoacylase, leads to Canavan disease, a severe **leukodystrophy**, characterized by excessive excretion of *N*-acetylaspartic acid and spongy degeneration of the white matter of the brain. Canavan disease is an autosomal recessive disorder and is more prevalent in individuals of Ashkenazi Jewish descent than in other ethnic groups. Aspartoacylase deficiency can be determined in skin fibroblasts, but the diagnosis is easy to ascertain by increased excretion of *N*-acetylaspartic acid in the urine. The gene for Canavan disease has been cloned, and mutations can be measured in patients, family members, and at-risk populations.

ETIOLOGY AND PATHOLOGY

The deficiency of the enzyme aspartoacylase leads to the accumulation of *N*-acetylaspartic acid in the brain, especially in white matter, and massive urinary excretion of this compound. Excessive amounts of *N*-acetylaspartic acid are also present in the blood and CSF. Brain biopsies of patients with Canavan disease show spongy degeneration of the myelin fibers, astrocytic swelling, and elongated mitochondria. There is striking vacuolization and astrocytic swelling in white matter. Electron microscopy reveals distorted mitochondria. As the disease progresses, the ventricles enlarge, owing to cerebral atrophy.

CLINICAL MANIFESTATIONS

The severity of Canavan disease covers a wide spectrum. Infants usually appear normal at birth and may not manifest symptoms of the disease until 3-6 mo of age, when they develop **progressive macrocephaly**, severe hypotonia, persistent head lag, and delayed milestones. As the disease progresses, there is spasticity, joint stiffness, and contractures. Optic atrophy and seizures develop. Feeding difficulties, poor weight gain, and gastroesophageal reflux may occur in the 1st yr of life; swallowing deteriorates, and nasogastric feeding or permanent gastrostomy may be required. Most patients die in the 1st decade of life; with improved nursing care, they may survive through the second decade.

ATYPICAL CANAVAN DISEASE

Juvenile or mildly affected patients with Canavan disease usually present with mild developmental delay, although 1 patient also had a large head and retinitis pigmentosa. These children have moderately increased urinary excretion of *N*-acetylaspartic acid, which suggests Canavan disease. Brain MRI demonstrates increased signal intensity in the basal ganglia rather than global white matter disease, sometimes leading to confusion with mitochondrial disease.

Diagnosis

In a typical patient with Canavan disease, CT scan and MRI reveal diffuse white matter degeneration, primarily in the cerebral hemispheres, with less involvement of the cerebellum and brainstem (Fig. 85-15). Repeated evaluations may be required. MRS performed at the time MRI is done can show the high peak of *N*-acetylaspartic acid, suggesting Canavan disease. The definitive diagnosis can be established by finding elevated amounts of *N*-acetylaspartic acid in the urine or

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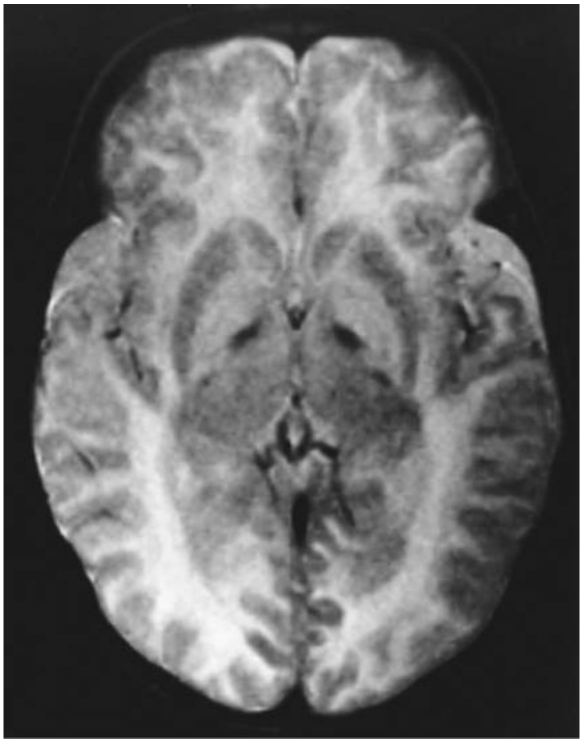

Figure 85-15 Axial T-weighted MRI of a 2 yr old patient with **Canavan disease.** Extensive thickening of the white matter is seen.

blood. A deficiency of aspartoacylase can be found in cultured skin fibroblasts. The biochemical method is the preferred choice for diagnosis. *N*-acetylaspartic acid is found only in trace amounts (24 ± 16 µmol/mmol creatinine) in the urine of unaffected individuals, whereas in patients with Canavan disease its concentration is in the range of 1,440 ± 873 µmol/mmol creatinine. High levels of *N*-acetylaspartic acid can also be detected in plasma, CSF, and brain tissue. The activity of aspartoacylase in the fibroblasts of obligate carriers is less than or equal to half of the activity found in normal individuals. The differential diagnosis of Canavan disease should include Alexander disease, which is another leukodystrophy associated with macrocephaly. Alexander disease is caused by a defect in the synthesis of glial fibrillary acidic protein and the diagnosis can be ruled out by molecular diagnosis on blood lymphocytes.

There are 2 mutations leading to Canavan disease predominant in the Ashkenazi Jewish population. The first is an amino acid substitution (E285A) in which glutamic acid is substituted for alanine. This mutation is the most frequent and encompasses 83% of 100 mutant alleles examined in Ashkenazi Jewish patients. The second common mutation is a change from tyrosine to a nonsense mutation, leading to a stop in the coding sequence (Y231X). This mutation accounts for 13% of the 100 mutant alleles. In the non-Jewish population, more diverse mutations have been observed, and the 2 mutations common in Jewish people are rare. A different mutation (A305E), the substitution of alanine for glutamic acid, accounts for 40% of 62 mutant alleles in non-Jewish patients. More than 50 mutations are described in the non-Jewish population. With Canavan disease, it is important to obtain a molecular diagnosis because this will lead to accurate counseling and prenatal guidance for the family. If the mutations are not known, prenatal diagnosis relies on the level of *N*-acetylaspartic acid in the amniotic fluid. In Ashkenazi Jewish patients, the carrier frequency can be as high as 1:36, which is close to that of Tay-Sachs disease. Carrier screening for Canavan disease is available for Jewish individuals. Genotype phenotype correlation and aspartoacylase expression show that expression studies may aid in understanding the disease.

Patients with juvenile or mild forms of Canavan disease have been compound heterozygotes with a mild mutation on one allele and a severe mutation on the other mutation. Mild mutations include p.Tyr288Cys and p.Arg71His.

Treatment and Prevention

No specific treatment is available. Feeding problems and seizures should be treated on an individual basis. Genetic counseling, carrier testing, and prenatal diagnosis are the only methods of prevention. Gene therapy attempts in children with Canavan disease have shown lack of long-term adverse events, some decrease in the brain elevation of *N*-acetylaspartic acid, improved seizure frequency, and stabilization of overall clinical status. There are ongoing trials of glycerol-triacetate as a supplement for acetate deficiency.

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Chapter 86

Defects in Metabolism of Lipids

86.1 Disorders of Mitochondrial Fatty Acid β-Oxidation

Charles A. Stanley and Michael J. Bennett

Mitochondrial β-oxidation of fatty acids is an essential energy-producing pathway. It is a particularly important pathway during prolonged periods of starvation, and during periods of reduced caloric intake because of gastrointestinal illness or increased energy expenditure during febrile illness. Under these conditions, the body switches from using predominantly carbohydrate to predominantly fat as its major fuel. Fatty acids are also important fuels for exercising skeletal muscle and are the preferred substrate for the heart. In these tissues, fatty acids are completely oxidized to carbon dioxide and water. The end products of hepatic fatty acid oxidation are the ketone bodies β-hydroxybutyrate and acetoacetate. These cannot be oxidized by the liver but are exported to and serve as important fuels in peripheral tissues, particularly the brain, which can partially substitute ketone bodies for glucose during periods of fasting.

Genetic defects have been identified in nearly all of the known steps in the fatty acid oxidation pathway; all are recessively inherited (Table 86-1).

Clinical manifestations characteristically involve those tissues with a high β-oxidation flux, including liver, skeletal, and cardiac muscle. The most common presentation is an acute episode of life-threatening coma and hypoglycemia induced by a period of fasting because of defective hepatic ketogenesis. Other manifestations may include chronic cardiomyopathy and muscle weakness or exercise-induced acute rhabdomyolysis. The fatty acid oxidation defects can often be asymptomatic during periods when there is no fasting stress. Acutely presenting disease may be misdiagnosed as **Reye syndrome** or, if fatal, as **sudden unexpected infant death**. Fatty acid oxidation disorders are easily overlooked because the only specific clue to the diagnosis may be the finding of inappropriately low concentrations of urinary ketones in an infant who has hypoglycemia. Genetic defects in ketone body utilization may also be overlooked because ketosis is an expected finding with fasting hypoglycemia. In some circumstances, clinical manifestations appear to arise from toxic effects of fatty acid metabolites rather than inadequate energy production. These include disorders (long chain 3-hydroxyacyl dehydrogenase

Table 86-1 Mitochondrial Fatty Acid Oxidation Disorders—Clinical and Biochemical Features

ENZYME DEFICIENCY	GENE	CLINICAL PHENOTYPE	LABORATORY FINDINGS
Carnitine transporter	*OCTN2 SLC22A5*	Cardiomyopathy, skeletal myopathy, liver disease, sudden death, endocardial fibroelastosis, prenatal and newborn screening diagnosis reported	↓ Total and free carnitine, normal acylcarnitines, acylglycine, and organic acids
Long-chain fatty acid transporter	*FATP1-6*	Rare, acute liver failure in childhood requiring liver transplantation	Reduced intracellular C_{14}-C_{18} fatty acids, reduced fatty acid oxidation
Carnitine palmitoyl transferase-I	*CPT-IA*	Liver failure, renal tubulopathy, and sudden death. Prenatal and newborn screening diagnosis reported, maternal preeclampsia, HELLP syndrome association described in a few patients	Normal or ↑ free carnitine, normal acylcarnitines, acylglycine, and organic acids
Carnitine acylcarnitine translocase	*CACT SLC25A20*	Chronic progressive liver failure, persistent ↑ NH_3, hypertrophic cardiomyopathy. Newborn screening diagnosis reported	Normal or ↓ free carnitine, abnormal acylcarnitine profile
Carnitine palmitoyl transferase-II	*CPT-II*	Early and late onset types. Liver failure, encephalopathy, skeletal myopathy, cardiomyopathy, renal cystic changes, newborn screening diagnosis reported. Adult form with acute rhabdomyolysis, myoglobinuria	Normal or ↓ free carnitine, abnormal acylcarnitine profile
Short-chain acyl-CoA dehydrogenase	*SCAD ACADS*	Clinical phenotype is unclear. Many individuals appear to be normal. Others have a variety of inconsistent signs and symptoms. Subset may have severe manifestations of unclear relationship to biochemical defects. Newborn screening diagnosis reported; significance being questioned	Normal or ↓ free carnitine, elevated urine ethylmalonic acid, inconsistently abnormal acylcarnitine profile
Medium-chain acyl-CoA dehydrogenase	*MCAD ACADM*	Hypoglycemia, hepatic encephalopathy, sudden death. Newborn screening diagnosis possible, maternal preeclampsia, HELLP syndrome association described rarely	Normal or ↓ free carnitine, ↑ plasma acylglycine, plasma C_6-C_{10} free fatty acids, ↑ C_8-C_{10} acyl-carnitine
Very long-chain acyl-CoA dehydrogenase	*VLCAD ACADVL*	Dilated cardiomyopathy, arrhythmias, hypoglycemia, and hepatic steatosis. Late-onset, stress-induced rhabdomyolysis, episodic myopathy. Prenatal and newborn screening diagnosis possible.	Normal or ↓ free carnitine, ↑ plasma $C_{14:1}$, C_{14} acylcarnitine, ↑ plasma C_{10}-C_{16} free fatty acids
ETF dehydrogenase*	*ETF-DH*	Nonketotic fasting hypoglycemia, congenital anomalies, milder forms of liver disease, cardiomyopathy, and skeletal myopathy. Newborn screening diagnosis reported	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ acylcarnitine, urine organic acid and acylglycines
ETF-α*	*α-ETF*	Nonketotic fasting hypoglycemia, congenital anomalies, liver disease, cardiomyopathy, and skeletal myopathy also described. Newborn screening diagnosis reported	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ acylcarnitine, urine organic acid and acylglycines
ETF-β*	*β-ETF*	Fasting hypoglycemia, congenital anomalies, liver disease, cardiomyopathy, and skeletal myopathy also described. Newborn screening diagnosis reported	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ acylcarnitine, urine organic acid and acylglycines
Short-chain L-3-hydroxyacyl-CoA dehydrogenase	*SCHAD HADH*	Hyperinsulinemic hypoglycemia, cardiomyopathy, myopathy. Newborn screening diagnosis reported	Normal or ↓ free carnitine, elevated free fatty acids, inconsistently abnormal urine organic acid, ↑3-OH glutarate. ↑ plasma C_4-OH acylcarnitine
Long-chain L-3-hydroxyacyl-CoA dehydrogenase	*LCHAD HADH-A*	Newborn screening diagnosis reported, maternal preeclampsia, HELLP syndrome, and AFLP association described frequently. See also MTP below for clinical manifestations	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ free fatty acids, ↑ C_{16}-OH and C_{18}-OH carnitines
MTP	*HADH-A, HADH-B*	Severe cardiac and skeletal myopathy, hypoglycemia, acidosis, hyper NH_3, sudden death, elevated liver enzymes, retinopathy. Maternal preeclampsia, HELLP syndrome, and AFLP association described frequently	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ free fatty acids, ↑ C_{16}-OH and C_{18}-OH carnitines
Long-chain 3-ketoacyl-CoA thiolase	*LKAT HADH-B*	Severe neonatal presentation, hypoglycemia, acidosis, ↑ creatine kinase, cardiomyopathy, neuropathy, and early death	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ free fatty acids, ↑ 2-*trans*, 4-*cis*-decadienoylcarnitine
2,4-Dienoyl-CoA reductase	*DECR1*	Only 1 patient described, hypotonia in the newborn, mainly severe skeletal myopathy and respiratory failure. Hypoglycemia rare	Normal or ↓ free carnitine, ↑ acyl:free carnitine ratio, normal urine organic acids and acylglycines

Continued

Table 86-1 Mitochondrial Fatty Acid Oxidation Disorders—Clinical and Biochemical Features—cont'd

ENZYME DEFICIENCY	GENE	CLINICAL PHENOTYPE	LABORATORY FINDINGS
HMG CoA synthetase	*HMGCS2*	Hypoketosis and hypoglycemia, rarely myopathy	Elevated total plasma fatty acids, enzyme studies in biopsied liver may be diagnostic, genetic testing is preferred
HMG CoA lyase	*HMGCL*	Hypoketosis and hypoglycemia, rarely myopathy	Normal free carnitine, ↑ C_5-OH, and methylglutaryl-carnitine, enzymes studies in fibroblasts may be diagnostic

*Also known as glutaric acidemia type II or multiple acyl-CoA dehydrogenase deficiency (MADD).

AFLP, acute fatty liver of pregnancy; CoA, coenzyme A; ETF, electron transport flavoprotein; HELLP, hemolysis, elevated liver enzymes, low platelets; MTP, mitochondrial trifunctional protein; NH_3, ammonia.

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[LCHAD], carnitine palmitoyltransferase-1A [CPT-IA], mitochondrial trifunctional protein [MTP; also known as TFP] deficiencies) in which the presence of a homozygous affected fetus increases the risk of a life-threatening illness in the heterozygote mother, resulting in acute fatty liver of pregnancy or **preeclampsia with HELLP** (hemolysis, elevated liver enzymes, low platelets) syndrome. Malformations of the brain and kidneys have been described in severe electron transfer flavoprotein (ETF), ETF dehydrogenase (ETF-DH), and carnitine palmitoyltransferase-2 (CPT-II) deficiencies that might reflect in utero toxicity of fatty acid metabolites or a developmental role for these enzymes. Progressive retinal degeneration, peripheral neuropathy, and chronic progressive liver disease have been identified in LCHAD and MTP deficiency. Newborn screening programs using tandem mass spectrometry detect characteristic acylcarnitines seen in many of these disorders and permit presymptomatic diagnosis. Screening programs have provided evidence to demonstrate that all the fatty acid oxidation disorders combined are among the most common inborn errors of metabolism.

Figures 86-1 and 86-2 outline the steps involved in the oxidation of a typical long-chain fatty acid. In the *carnitine cycle*, fatty acids are transported across the barrier of the inner mitochondrial membrane as acylcarnitine esters. Within the mitochondria, successive turns of the 4-step β-*oxidation cycle* convert the coenzyme A (CoA)-activated fatty acid to acetyl-CoA units. Two to 3 different chain-length specific isoenzymes are needed for each of these β-oxidation steps to accommodate the different-sized fatty acyl-CoA species. The electron transfer pathway carries electrons generated in the first β-oxidation step (acyl-CoA dehydrogenase) to the *electron transport chain* at the level of coenzyme Q for adenosine triphosphate production, while electrons generated from the third step (3-hydroxyacyl-CoA dehydrogenase) enter the *electron transport chain* at the level of complex 1. Most of the acetyl-CoA generated from hepatic β-oxidation flows through the *pathway of ketogenesis* to form β-hydroxybutyrate and acetoacetate.

DEFECTS IN THE β-OXIDATION CYCLE

Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common fatty acid oxidation disorder. The disorder shows a strong founder effect; most patients have a northwestern European ancestry, and the majority of patients are homozygous for a single common missense mutation, an A-G transition at complementary DNA position 985 that changes a lysine to glutamic acid at residue 329 (K329E).

Clinical Manifestations

Previously undiagnosed affected patients usually present in the first 3 mo-5 yr of life with episodes of acute illness triggered by prolonged fasting (longer than 12-16 hr). Signs and symptoms include vomiting and lethargy, which rapidly progress to coma or seizures and cardiorespiratory collapse. Sudden unexpected infant death may occur. The liver may be slightly enlarged with fat deposition. Attacks are rare until the infant is beyond the first few months of life, presumably because of more frequent feedings at a younger age. Affected older infants are at higher risk of illness as they begin to fast through the night or are exposed to fasting stress during an intercurrent childhood illness. Presentation in the first days of life with neonatal hypoglycemia has been reported in newborns that were fasted inadvertently. Diagnosis of MCAD has occasionally been documented in previously healthy teenage and adult individuals, indicating that even patients who have been asymptomatic in infancy are still at risk for metabolic decompensation if exposed to sufficient periods of fasting. An unknown number may remain asymptomatic. Prior to routine newborn screening testing, as many as 25% of MCAD deficient cases died or suffered severe brain damage from their first episode. Most patients are now diagnosed in the newborn period by blood spot acylcarnitine screening, allowing the initiation of early treatment and prevention of many of the severe signs and symptoms.

Laboratory Findings

During acute episodes, hypoglycemia is usually present. Plasma and urinary ketone concentrations are inappropriately low (**hypoketotic hypoglycemia**). Because of the hypoketonemia, there is little or no metabolic acidosis, which is expected to be present in many children with hypoglycemia. Tests of liver function are abnormal, with elevations of liver enzymes (alanine aminotransferase, aspartate aminotransferase), elevated blood ammonia, and prolonged prothrombin and partial thromboplastin times. Liver biopsy at times of acute illness shows microvesicular or macrovesicular steatosis from triglyceride accumulation. During fasting stress or at times of acute illness, urinary organic acid profiles by gas chromatography/mass spectrometry show inappropriately low concentrations of ketones and elevated levels of medium-chain dicarboxylic acids (adipic, suberic, and sebacic acids) that derive from microsomal and peroxisomal omega oxidation of accumulated medium-chain fatty acids. Plasma and tissue concentrations of total carnitine are reduced to 25-50% of normal, and the fraction of total esterified carnitine is increased. This pattern of **secondary carnitine deficiency** is seen in most fatty acid oxidation defects and reflects competition between increased acylcarnitine levels and free carnitine for transport at the plasma membrane. Significant exceptions to this rule are the plasma membrane carnitine transporter, CPT-IA and β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) synthase deficiencies that do not manifest secondary carnitine deficiency.

Diagnostic metabolite patterns include increased plasma $C_{8:0}$, $C_{10:0}$, and $C_{10:1}$ acylcarnitine species and increased urinary acylglycines including hexanoyl-propionyl, suberyl-propionyl, and 3-phenylpropionyl glycines. Newborn screening programs using tandem mass spectrometry, which almost all babies born in the United States receive, can diagnose presymptomatic MCAD deficiency based on the detection of the abnormal acylcarnitines in filter paper blood spots. In many cases, the diagnosis can be confirmed by finding the common A985G mutation. A second common variant, T199C, has been detected in infants with

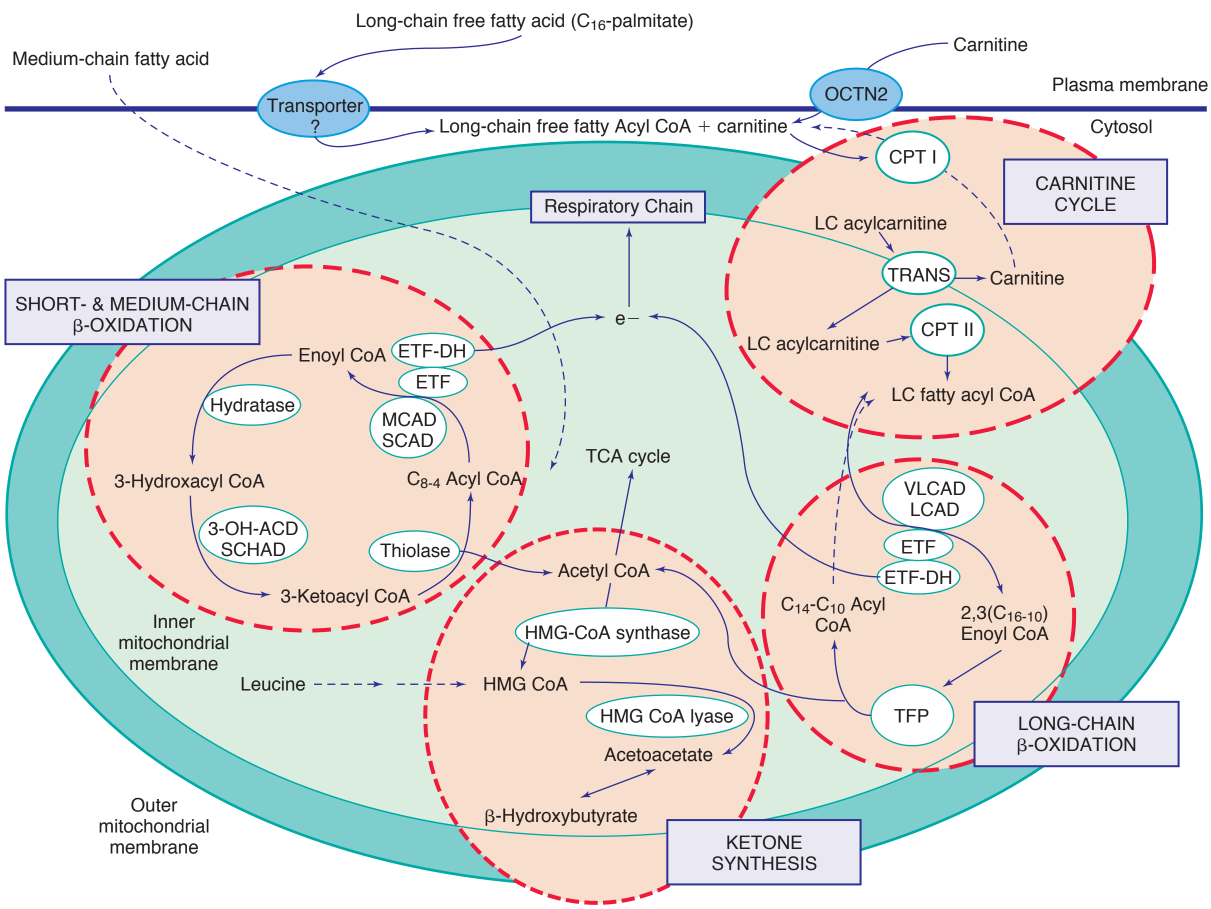

Figure 86-1 **Mitochondrial fatty acid oxidation.** Carnitine enters the cell through the action of the organic cation/carnitine transporter (OCTN2). Palmitate, a typical 16-carbon long-chain fatty acid, is transported across the plasma membrane and can be activated to form a long-chain (LC) fatty acyl coenzyme A (CoA). It then enters into the carnitine cycle, where it is transesterified by carnitine palmitoyltransferase-I (CPT-I), translocated across the inner mitochondrial membrane by carnitine/acylcarnitine translocase (TRANS), and then reconverted into a long-chain fatty acyl-CoA by carnitine palmitoyltransferase-II (CPT-II) to undergo β-oxidation. Very-long-chain acyl-CoA dehydrogenase (VLCAD/LCAD) leads to the production of (C_{16}-C_{10}) 2,3 enoyl CoA. Mitochondrial trifunctional protein (MTP) contains the activities of enoyl CoA hydratase (hydratase), 3-OH-hydroxyacyl-CoA dehydrogenase (3-OH-ACD), and β-ketothiolase (thiolase). Acetyl-CoA, reduced form of flavin adenine dinucleotide (FADH), and reduced form of nicotinamide adenine dinucleotide (NADH) are produced. Medium- and short-chain fatty acids (C8-4) can enter the mitochondrial matrix independent of the carnitine cycle. Medium-chain acyl-CoA dehydrogenase (MCAD), short-chain acyl-CoA dehydrogenase (SCAD), and short-chain hydroxy acyl-CoA dehydrogenase (SCHAD) are required. Acetyl-CoA can then enter the Krebs (TCA) cycle. Electrons are transported from FADH to the respiratory chain via the electron transfer flavoprotein (ETF) and the electron transfer flavoprotein dehydrogenase (ETF-DH). NADH enters the electron transport chain through complex I. In liver, acetyl-CoA can be converted into hydroxymethylglutaryl (HMG) CoA by β-hydroxy-β-methylglutaryl-CoA synthase (HMG CoA synthase) and then the ketone body acetoacetate by the action of β-hydroxy-β-methylglutaryl-CoA lyase (HMG-CoA lyase).

characteristic acylcarnitines in newborn screening tests. Interestingly, this allele has not been seen to date in symptomatic MCAD patients; it may represent a milder mutation.

Treatment

Acute illnesses should be promptly treated with intravenous fluids containing 10% dextrose to treat or prevent hypoglycemia and to suppress lipolysis as rapidly as possible (see Chapter 92). Chronic therapy consists of avoiding fasting. This usually requires simply adjusting the diet to ensure that overnight fasting periods are limited to <10-12 hr. Restricting dietary fat or treatment with carnitine is controversial. The necessity for active therapeutic intervention for individuals with the T199C variant has not yet been established.

Prognosis

Up to 25% of unrecognized patients may die during their first attack of illness. There is frequently a history of a previous sibling death that is presumed to be from an unrecognized MCAD deficiency. Some patients may suffer permanent brain injury during an attack of profound hypoglycemia. The prognosis for survivors without brain damage is excellent because progressive cognitive impairment or cardiomyopathy does not occur in MCAD deficiency. Muscle pain and reduced exercise tolerance may become evident with increasing age. Fasting tolerance improves with age and the risk of illness decreases. Because as many as 35% of affected patients have never had an episode, testing of siblings of affected patients is important to detect asymptomatic family members.

Very-Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is the second most commonly diagnosed disorder of fatty acid oxidation. It was originally termed long-chain acyl-CoA dehydrogenase deficiency before the existence of the inner mitochondrial membrane-bound VLCAD was known. *All patients previously diagnosed as having long-chain acyl-CoA dehydrogenase deficiency have VLCAD gene defects.* Patients with VLCAD deficiency have no ability to oxidize physiologic long-chain fatty acids and are usually more severely affected than those with MCAD deficiency who have a milder oxidative defect. VLCAD deficiency presents earlier in infancy and has more chronic problems

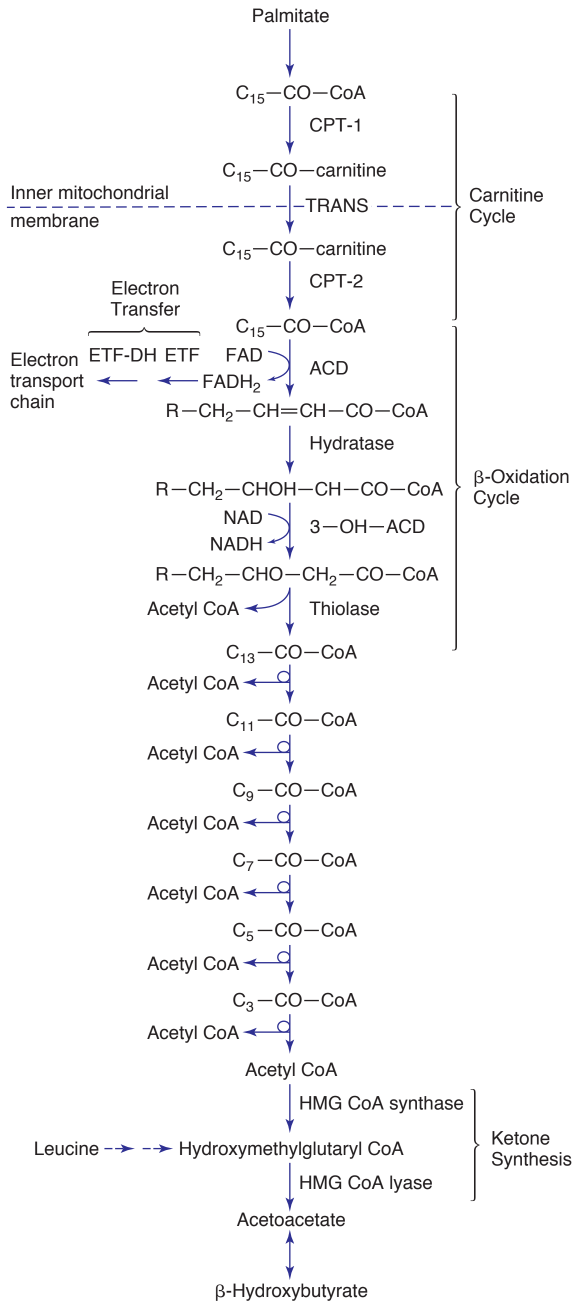

Figure 86-2 Pathway of mitochondrial oxidation of palmitate, a typical 16-carbon long-chain fatty acid. Enzyme steps include carnitine palmitoyltransferase (CPT) 1 and 2, carnitine/acylcarnitine translocase (TRANS), electron transfer flavoprotein (ETF), ETF dehydrogenase (ETF-DH), acyl-CoA dehydrogenase (ACD), enoyl CoA hydratase (hydratase), 3-hydroxy-acyl-CoA dehydrogenase (3-OH-ACD), β-ketothiolase (thiolase), β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) synthase, and lyase.

with muscle weakness or episodes of muscle pain and rhabdomyolysis. Cardiomyopathy may be present during acute attacks provoked by fasting. The left ventricle may be hypertrophic or dilated and show poor contractility on echocardiography. Sudden unexpected death has occurred in several patients, but most who survived the initial episode showed improvement, including normalization of cardiac function. Other physical and routine laboratory features are similar to those of MCAD deficiency, including secondary carnitine deficiency. The urinary organic acid profile shows a nonketotic dicarboxylic aciduria with increased levels of $C_{6\text{-}12}$ dicarboxylic acids. Diagnosis may be suggested by an abnormal acylcarnitine profile with plasma or blood spot $C_{14:0,\ 14:1,\ 14:2}$ acylcarnitine species; however, the specific diagnosis requires mutational analysis of the VLCAD gene. Treatment is based primarily on avoidance of fasts for longer than 10-12 hr. Continuous intragastric feeding is useful in some patients.

Short-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

A small number of patients with 2 clear null mutations in the short-chain acyl-CoA dehydrogenase (SCAD) gene have been described with variable phenotype. Most individuals classified as being SCAD deficient have polymorphic DNA changes in the SCAD gene; for example, 2 common polymorphisms are G185S and R147W, which are homozygously present in 7% of the population. Some investigators argue that these may be susceptibility changes, which require a second, as yet unknown, genetic mutation to express a clinical phenotype; while others believe that SCAD deficiency is a harmless biochemical condition. This autosomal recessive disorder presents with neonatal hypoglycemia and may have normal levels of ketone bodies. The diagnosis is indicated by elevated levels of butyrylcarnitine (C4-carnitine) on newborn blood spots or plasma and increased excretion of urinary ethylmalonic acid and butyrylglycine. These metabolic abnormalities are most pronounced in patients with null mutations and variably present in patients who are homozygous for the common polymorphisms.

The necessity for treatment in SCAD deficiency has not yet been established. It has been proposed that long-term evaluation of asymptomatic individuals is necessary to determine whether this is or is not a real disease. Although most individuals with SCAD deficiency remain asymptomatic throughout life, it has been proposed that there is a subset of individuals with SCAD deficiency with severe manifestations, including dysmorphic facial features, feeding difficulties/failure to thrive, metabolic acidosis, ketotic hypoglycemia, lethargy, developmental delay, seizures, hypotonia, dystonia, and myopathy.

Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase/Mitochondrial Trifunctional Protein Deficiency

The LCHAD enzyme is part of a MTP, which also contains 2 other steps in β-oxidation: long-chain enoyl CoA hydratase and long-chain β-ketothiolase. It is a heterooctameric protein composed of 4 α and 4 β chains that derive from distinct contiguous genes with a common promoter region. In some patients, only the LCHAD activity of the MTP is affected (LCHAD deficiency), whereas others have deficiencies of all 3 activities (MTP deficiency).

Clinical manifestations include attacks of acute hypoketotic hypoglycemia similar to MCAD deficiency; patients often show evidence of more severe disease, including cardiomyopathy, muscle cramps and weakness, and abnormal liver function (cholestasis). Toxic effects of fatty acid metabolites may produce pigmented retinopathy leading to blindness, progressive liver failure, peripheral neuropathy, and rhabdomyolysis. Life-threatening obstetric complications, acute fatty liver of pregnancy, and **HELLP** syndrome are observed in heterozygous mothers carrying homozygotic fetuses affected with LCHAD/MTP deficiency. Sudden unexpected infant death may occur. The diagnosis is indicated by elevated levels of blood spot or plasma 3-hydroxy acylcarnitines of chain lengths C_{16}-C_{18}. Urinary organic acid profile in patients may show increases in levels of 3-hydroxydicarboxylic acids of chain lengths C_6-C_{14}. Secondary carnitine deficiency is common. A common mutation in the α subunit, E474Q, is seen in more than 60% of LCHAD-deficient patients. This mutation in the fetus is especially associated with the obstetric complications, but other mutations in either subunit may also be linked to maternal illness.

Treatment is similar to that for MCAD or VLCAD deficiency; that is, avoiding fasting stress. Some investigators have suggested that dietary supplements with medium-chain triglyceride oil to bypass the defect in long-chain fatty acid oxidation and docosahexaenoic acid (for protection against the retinal changes) may be useful. Liver transplantation has been attempted in cases with severe liver failure, but does

not ameliorate the metabolic abnormalities or prevent the myopathic or retinal complications.

Short-Chain 3-Hydroxyacyl-Coenzyme A Dehydrogenase Deficiency

Only 12 patients with proven mutations of short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD) have been reported, although a few additional unpublished cases are known to the authors. Most cases with recessive mutations of the SCHAD gene have presented with episodes of hypoketotic hypoglycemia that was caused by hyperinsulinism. In contrast to patients with other forms of fatty acid oxidation disorders, these cases required specific therapy with diazoxide for hyperinsulinism to avoid recurrent hypoglycemia. A single case with compound heterozygous mutations presented with fulminant hepatic failure at age 10 mo. The SCHAD protein has a nonenzymatic function (moonlighting) in which it directly interacts with glutamate dehydrogenase (GDH) to inhibit its activity. In the absence of an SCHAD protein, this inhibition is removed leading to upregulation of GDH enzyme activity, a recognized cause of hyperinsulinism usually caused by activating mutations of the GDH gene. This severe deficiency of SCHAD protein often presents predominantly as protein sensitive hypoglycemia rather than as fasting hypoglycemia. It appears that if a SCHAD protein is present the inhibition of GDH is maintained even when there is no SCHAD enzyme activity; these patients may present with a more traditional fatty acid oxidation defect. Specific metabolic markers for SCHAD deficiency include elevated plasma C4-hydroxy acylcarnitine and urine 3-hydroxyglutaric acid.

Treatment of SCHAD deficient patients with hyperinsulinism is with diazoxide. There is insufficient experience with the non-hyperinsulinemic form of SCHAD deficiency at present to recommend treatment modalities, but prevention of fasting seems advisable, which is similar to other fatty acid oxidation disorders.

DEFECTS IN THE CARNITINE CYCLE

Plasma Membrane Carnitine Transport Defect (Primary Carnitine Deficiency)

Primary carnitine deficiency is the only genetic defect in which carnitine deficiency is the cause, rather than the consequence, of impaired fatty acid oxidation. The most common presentation is progressive **cardiomyopathy** with or without **skeletal muscle weakness** beginning at 1-4 yr of age. A smaller number of patients may present with fasting hypoketotic hypoglycemia in the 1st yr of life before the cardiomyopathy becomes symptomatic. The underlying defect involves the plasma membrane sodium gradient-dependent carnitine transporter that is present in heart, muscle, and kidney. This transporter is responsible both for maintaining intracellular carnitine concentrations 20-50–fold higher than plasma concentrations and for renal conservation of carnitine.

Diagnosis of the carnitine transporter defect is aided by the fact that patients have extremely reduced carnitine levels in plasma and muscle (1-2% of normal). Heterozygote parents have plasma carnitine levels approximately 50% of normal. Fasting ketogenesis may be normal because liver carnitine transport is normal, but it may become impaired if dietary carnitine intake is interrupted. The fasting urinary organic acid profile may show a hypoketotic dicarboxylic aciduria pattern if hepatic fatty acid oxidation is impaired, but it is otherwise unremarkable. The defect in carnitine transport can be demonstrated clinically by the severe reduction in renal carnitine threshold or by in vitro assay of carnitine uptake using cultured fibroblasts or lymphoblasts. Mutations in the organic cation/carnitine transporter *(OCTN2)* underlie this disorder. Treatment with pharmacologic doses of oral carnitine (100-200 mg/kg/day) is highly effective in correcting the cardiomyopathy and muscle weakness, as well as any impairment in fasting ketogenesis. Muscle total carnitine concentrations remain <5% of normal on treatment.

Carnitine Palmitoyltransferase-IA Deficiency

Several dozen infants and children have been described with a deficiency of the liver and kidney carnitine palmitoyltransferase-I (CPT-I) isozyme (CPT-IA). Clinical manifestations include fasting hypoketotic hypoglycemia, occasionally with markedly abnormal liver function tests and, rarely, with renal tubular acidosis. The heart and skeletal muscle are not involved because the muscle isozyme is unaffected. Fasting urinary organic acid profile sometimes shows a hypoketotic C_6-C_{12} dicarboxylic aciduria but may be normal. Plasma acylcarnitine analysis demonstrates mostly free carnitine with very little acylated carnitine. This observation has been used to establish CPT-IA diagnosis on newborn screening by tandem mass spectrometry. CPT-IA deficiency is the only fatty acid oxidation disorder in which plasma total carnitine levels are elevated often to 150-200% of normal. This may be explained by the fact that the inhibitory effects of long-chain acylcarnitines on the renal tubular carnitine transporter are absent in CPT-IA deficiency. The enzyme defect can be demonstrated in cultured fibroblasts or lymphoblasts. CPT-IA deficiency in the fetus has been associated with acute fatty liver of pregnancy in the mother in a single case report. A common variant in the CPT-IA gene has been identified in individuals of Inuit background in the United States and First Nations tribes in Canada and Greenland. The variant is detected by a positive newborn acylcarnitine screen; enzyme activity is reduced by 80% and regulation by malonyl-CoA is lost. It has not been established if this is a pathologic DNA variant or an adaptation to ancient Inuit and First Nations high-fat diets. This variant is associated with an increased risk for sudden infant death syndrome. Treatment for the severe form of CPT-IA deficiency is similar to that for MCAD deficiency with avoidance of situations where fasting ketogenesis is necessary.

Carnitine:Acylcarnitine Translocase Deficiency

This defect of the inner mitochondrial membrane carrier protein for fatty acylcarnitines blocks the entry of long-chain fatty acids into the mitochondria for oxidation. The clinical phenotype of this disorder is characterized by a severe and generalized impairment of fatty acid oxidation. Most newborn patients present with attacks of fasting-induced hypoglycemia, hyperammonemia, and cardiorespiratory collapse. All symptomatic newborns have had evidence of cardiomyopathy and muscle weakness. Several patients with a partial translocase deficiency and milder disease without cardiac involvement have also been identified. No distinctive urinary or plasma organic acids are noted, although increased levels of plasma long-chain acylcarnitines of chain lengths C_{16}-C_{18} are reported. Diagnosis can be confirmed using genetic analysis. Functional carnitine:acylcarnitine translocase activity can be measured in cultured fibroblasts or lymphoblasts. Treatment is similar to that of other long-chain fatty acid oxidation disorders.

Carnitine Palmitoyltransferase-II Deficiency

Three forms of CPT-II deficiency have been described. The **severe neonatal lethal** presentation of this disorder is associated with a profound enzyme deficiency, and early death has been reported in several newborns with dysplastic kidneys, cerebral malformations, and mild facial anomalies. A milder, second defect, is associated with an **adult presentation** of episodic rhabdomyolysis. The first episode usually does not occur until late childhood or early adulthood. Attacks may be precipitated by prolonged exercise. There is aching muscle pain and myoglobinuria that may be severe enough to cause renal failure. Serum levels of creatine kinase are elevated to 5,000-100,000 units/L. Fasting hypoglycemia has not been described, but fasting may contribute to attacks of myoglobinuria. Muscle biopsy shows increased deposition of neutral fat. The myopathic presentation of CPT-II deficiency is associated with a common mutation S113L. This mutation produces a heat-labile protein that is unstable to increased muscle temperature during exercise resulting in the myopathic presentation. The **third intermediate** form of CPT-II deficiency presents in infancy/early childhood with fasting-induced hepatic failure, cardiomyopathy, and skeletal myopathy with hypoketotic hypoglycemia, but does not have the severe developmental changes seen in the neonatal lethal presentation. This pattern is similar to that seen in VLCAD deficiency and management is identical.

Diagnosis of all forms of CPT-II deficiency can be made by a combination of molecular analysis and demonstrating deficient enzyme activity in muscle or other tissues and in cultured fibroblasts.

DEFECTS IN THE ELECTRON TRANSFER PATHWAY

Electron Transfer Flavoprotein and Electron Transfer Flavoprotein Dehydrogenase Deficiencies (Glutaric Acidemia Type 2, Multiple Acyl-Coenzyme A Dehydrogenation Defects)

ETF and ETF-DH function to transfer electrons into the mitochondrial electron transport chain from dehydrogenation reactions catalyzed by VLCAD, MCAD, and SCAD, as well as by glutaryl-CoA dehydrogenase and 4 enzymes involved in branched-chain amino acid oxidation. Deficiencies of ETF or ETF-DH produce illness that combines the features of impaired fatty acid oxidation and impaired oxidation of several amino acids. Complete deficiencies of either protein are associated with severe illness in the newborn period, characterized by acidosis, hypoketotic hypoglycemia, coma, hypotonia, cardiomyopathy, and an unusual odor of sweaty feet caused by isovaleryl-CoA dehydrogenase inhibition. Some affected neonates have had facial dysmorphism and polycystic kidneys similar to that seen in severe CPT-II deficiency, which suggests that toxic effects of accumulated metabolites may occur in utero.

Diagnosis can be made from the urinary organic acid profile, which shows abnormalities corresponding to blocks in oxidation of fatty acids (ethylmalonate and C_6-C_{10} dicarboxylic acids), lysine (glutarate), and branched-chain amino acids (isovaleryl-, isobutyryl-, and α-methylbutyryl-glycine) and by molecular testing. Most severely affected infants do not survive the neonatal period.

Partial deficiencies of ETF and ETF-DH produce a disorder that may mimic MCAD deficiency or other milder fatty acid oxidation defects. These patients have attacks of fasting hypoketotic coma. The urinary organic acid profile reveals primarily elevations of dicarboxylic acids and ethylmalonate, derived from short-chain fatty acid intermediates. Secondary carnitine deficiency is present. Some patients with mild forms of ETF/ETF-DH deficiency benefit from treatment with high doses of riboflavin, which is a cofactor for the pathway of electron transfer.

DEFECTS IN KETONE SYNTHESIS PATHWAY

β-Hydroxy-β-Methylglutaryl-Coenzyme A Synthase Deficiency

See Chapter 85.6.

HMG-CoA synthase is the rate-limiting step in the conversion of acetyl-CoA derived from fatty acid β-oxidation in the liver to ketones. Several patients with this defect have recently been identified. The presentation is one of fasting **hypoketotic hypoglycemia** without evidence of impaired cardiac or skeletal muscle function. Urinary organic acid profile showed only a hypoketotic dicarboxylic aciduria. Plasma and tissue carnitine levels are normal, in contrast to all the other disorders of fatty acid oxidation. A separate synthase enzyme, present in cytosol for cholesterol biosynthesis, is not affected. The HMG-CoA synthase defect is expressed only in the liver and cannot be demonstrated in cultured fibroblasts. The gene has been cloned, and mutations in the affected patients have been characterized. Avoiding fasting is usually a successful treatment.

β-Hydroxy-β-Methylglutaryl-Coenzyme A Lyase Deficiency

See Chapter 85.6.

DEFECTS IN KETONE BODY UTILIZATION

The ketone bodies, β-hydroxybutyrate and acetoacetate, are the end products of hepatic fatty acid oxidation and are important metabolic fuels for the brain during fasting. Two defects in utilization of ketones in brain and other peripheral tissues present as episodes of **hyperketotic** coma, with or without hypoglycemia.

Succinyl-Coenzyme A:3-Ketoacid-Coenzyme A Transferase Deficiency

See Chapter 85.6.

Several patients with succinyl-CoA:3-ketoacid-CoA transferase (SCOT) deficiency have been reported. The characteristic presentation is an infant with recurrent episodes of severe ketoacidosis induced by fasting. Plasma acylcarnitine and urine organic acid abnormalities do not distinguish SCOT deficiency from other causes of ketoacidosis. Treatment of episodes requires infusion of glucose and large amounts of bicarbonate until metabolically stable. Patients usually exhibit inappropriate hyperketonemia even between episodes of illness. SCOT is responsible for activating acetoacetate in peripheral tissues using succinyl CoA as a donor to form acetoacetyl-CoA. Deficient enzyme activity can be demonstrated in brain, muscle, and fibroblasts from affected patients. The gene has been cloned, and numerous mutations have been characterized.

β-Ketothiolase Deficiency

See Chapter 85.6.

Bibliography is available at Expert Consult.

86.2 Disorders of Very Long Chain Fatty Acids

Gerald V. Raymond

PEROXISOMAL DISORDERS

The peroxisomal diseases are genetically determined disorders caused either by the failure to form or maintain the peroxisome or by a defect in the function of a single protein that is normally located in this organelle. These disorders cause serious disability in childhood and occur more frequently and present a wider range of phenotype than has been recognized in the past.

Etiology

Peroxisomal disorders are subdivided into 2 major categories (Table 86-2).

In category A, the **peroxisomal biogenesis disorders (PBDs)**, the basic defect is the failure to import 1 or more proteins into the organelle. In category B, **defects affect a single peroxisomal protein**. The peroxisome is present in all cells except mature erythrocytes and is a subcellular organelle surrounded by a single membrane; more than 50

Table 86-2 Classification of Peroxisomal Disorders

A: DISORDERS OF PEROXISOME IMPORT
A1: Zellweger syndrome
A2: Neonatal adrenoleukodystrophy
A3: Infantile Refsum disease
A4: Rhizomelic chondrodysplasia punctata
B: DEFECTS OF SINGLE PEROXISOMAL ENZYME
B1: X-linked adrenoleukodystrophy
B2: Acyl-CoA oxidase deficiency
B3: Bifunctional enzyme deficiency
B4: Peroxisomal thiolase deficiency
B5: Classic Refsum disease
B6: 2-Methylacyl-CoA racemase deficiency
B7: DHAP acyltransferase deficiency
B8: Alkyl-DHAP synthase deficiency
B9: Mevalonic aciduria
B10: Glutaric aciduria type III
B11: Hyperoxaluria type I
B12: Acatalasemia

CoA, coenzyme A; DHAP, dihydroxyacetone phosphate.

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peroxisomal enzymes are identified. Some enzymes are involved in the production and decomposition of hydrogen peroxide; others are concerned with lipid and amino acid metabolism. Most peroxisomal enzymes are first synthesized in their mature form on free polyribosomes and enter the cytoplasm. Proteins that are destined for the peroxisome contain specific peroxisome targeting sequences (PTSs). Most peroxisomal matrix proteins contain PTS1, a 3-amino acid sequence at the carboxyl terminus. PTS2 is an aminoterminal sequence that is critical for the import of enzymes involved in plasmalogen and branched-chain fatty acid metabolism. Import of proteins involves a complex series of reactions that involves at least 23 distinct proteins. These proteins, referred to as peroxins, are encoded by *PEX* genes.

Epidemiology

Except for X-linked adrenoleukodystrophy (ALD), all the peroxisomal disorders in Table 86-2 are **autosomal recessive traits**. ALD is the most common peroxisomal disorder, with an estimated incidence of 1 in 17,000 live births. The combined incidence of the other peroxisomal disorders is estimated to be 1 in 50,000 live births.

Pathology

Absence or reduction in the number of peroxisomes is pathognomonic for disorders of peroxisome biogenesis. In most disorders, there are membranous sacs that contain peroxisomal integral membrane proteins, which lack the normal complement of matrix proteins; these are peroxisome "ghosts." Pathologic changes are observed in most organs and include profound and characteristic defects in neuronal migration; micronodular cirrhosis of the liver; renal cysts; chondrodysplasia punctata; sensorineural hearing loss; retinopathy; congenital heart disease; and dysmorphic features.

Pathogenesis

It is likely that all pathologic changes are secondary to the peroxisome defect. Multiple peroxisomal enzymes fail to function in the PBDs (Table 86-3). The enzymes that are diminished or absent are synthesized but are degraded abnormally fast because they may be unprotected outside of the peroxisome. It is not clear how defective peroxisome functions lead to the widespread pathologic manifestations.

Mutations in 12 different *PEX* genes have been identified in PBDs. The pattern and severity of pathologic features vary with the nature of the import defects and the degree to which import is impaired. These gene defects lead to disorders that were named before their relationship to the peroxisome was recognized, namely, Zellweger syndrome, neonatal ALD, infantile Refsum disease, and rhizomelic chondrodysplasia punctata (RCDP). The first 3 disorders are considered to form a clinical continuum, with Zellweger syndrome the most severe, infantile Refsum disease the least severe, and neonatal ALD intermediate. They can be caused by mutations in any of the 11 genes involved in peroxisome assembly. The specific gene defects cannot be distinguished on the basis of clinical features. The clinical severity varies with the degree to which protein import is impaired. Mutations that abolish import completely are often associated with the Zellweger syndrome phenotype, whereas a missense mutation, in which some degree of import function is retained, leads to the somewhat milder phenotypes. A defect in *PEX7,* which involves the import of proteins that utilize PTS2, is associated with RCDP. *PEX7* defects that leave import partially intact are associated with milder phenotypes, some of which resemble classic Refsum disease.

The genetic disorders that involve single peroxisomal enzymes usually have clinical manifestations that are more restricted and relate to the single biochemical defect. The primary adrenal insufficiency of ALD is caused by accumulation of very-long-chain fatty acids (VLCFAs) in the adrenal cortex, and the peripheral neuropathy in Refsum disease is caused by the accumulation of phytanic acid in Schwann cells and myelin.

Table 86-3	Abnormal Laboratory Findings Common to Disorders of Peroxisome Biogenesis
Peroxisomes absent to reduced in number	
Catalase in cytosol	
Deficient synthesis and reduced tissue levels of plasmalogens	
Defective oxidation and abnormal accumulation of very-long-chain fatty acids	
Deficient oxidation and age-dependent accumulation of phytanic acid	
Defects in certain steps of bile acid formation and accumulation of bile acid intermediates	
Defects in oxidation and accumulation of L-pipecolic acid	
Increased urinary excretion of dicarboxylic acids	

Peroxisomal Biogenesis Disorders with Milder or Atypical Phenotypes

Newborn infants with **Zellweger syndrome** show striking and consistent recognizable abnormalities. Of central diagnostic importance are the typical facial appearance (high forehead, unslanting palpebral fissures, hypoplastic supraorbital ridges, and epicanthal folds; Fig. 86-3), severe weakness and hypotonia, neonatal seizures, and eye abnormalities. Because of the hypotonia and craniofacial appearance, Down syndrome may be suspected. Infants with Zellweger syndrome rarely live more than a few months. More than 90% show postnatal growth failure. Table 86-4 lists the main clinical abnormalities.

Patients with **neonatal ALD** show fewer, less-prominent craniofacial features. Neonatal seizures occur frequently. Some degree of psychomotor developmental delay is present; function remains in the severely or profoundly retarded range, and development may regress after 3-5 yr of age, probably from a progressive leukodystrophy. Hepatomegaly, impaired liver function, pigmentary degeneration of the retina, and severely impaired hearing are invariably present. Adrenocortical function is usually impaired and may require adrenal hormone replacement. Chondrodysplasia punctata and renal cysts are absent.

Figure 86-3 **Four patients with Zellweger cerebrohepatorenal syndrome.** Note the high forehead, epicanthal folds, and hypoplasia of supraorbital ridges and midface. *(Courtesy of Hans Zellweger, MD.)*

Table 86-4 Main Clinical Abnormalities in Zellweger Syndrome

ABNORMAL FEATURE	Cases in Which the Feature Was Present NO.	%
High forehead	58	97
Flat occiput	13	81
Large fontanelle(s), wide sutures	55	96
Shallow orbital ridges	33	100
Low/broad nasal bridge	23	100
Epicanthus	33	92
High arched palate	35	95
External ear deformity	39	97
Micrognathia	18	100
Redundant skin fold of neck	13	100
Brushfield spots	5	83
Cataract/cloudy cornea	30	86
Glaucoma	7	58
Abnormal retinal pigmentation	6	40
Optic disc pallor	17	74
Severe hypotonia	94	99
Abnormal Moro response	26	100
Hyporeflexia or areflexia	56	98
Poor sucking	74	96
Gavage feeding	26	100
Epileptic seizures	56	92
Psychomotor retardation	45	100
Impaired hearing	9	40
Nystagmus	30	81

From Heymans HAS: Cerebro-hepato-renal (Zellweger) syndrome: clinical and biochemical consequences of peroxisomal dysfunctions. *Thesis, University of Amsterdam, 1984.*

Patients with **infantile Refsum disease** have survived to adulthood. They are able to walk, although gait may be ataxic and broad based. Cognitive function is in the severely impaired range. All have sensorineural hearing loss and pigmentary degeneration of the retina. They have moderately dysmorphic features that may include epicanthal folds, a flat bridge of the nose, and low-set ears. Early hypotonia and hepatomegaly with impaired function are common. Levels of plasma cholesterol and high- and low-density lipoprotein are often moderately reduced. Chondrodysplasia punctata and renal cortical cysts are absent. Postmortem study in infantile Refsum disease reveals micronodular liver cirrhosis and small hypoplastic adrenals. The brain shows no malformations, except for severe hypoplasia of the cerebellar granule layer and ectopic locations of the Purkinje cells in the molecular layer. The mode of inheritance is autosomal recessive.

Some patients with PBDs have milder and atypical phenotypes. They may present with peripheral neuropathy or with retinopathy, impaired vision, or cataracts in childhood, adolescence, or adulthood and have been diagnosed to have **Charcot-Marie-Tooth** disease or **Usher syndrome**. Some patients have survived to the 5th decade. Defects in *PEX7,* which most commonly lead to the RCDP phenotype, may also lead to a milder phenotype with clinical manifestations similar to those of classical Refsum disease (phytanoyl-CoA hydroxylase deficiency).

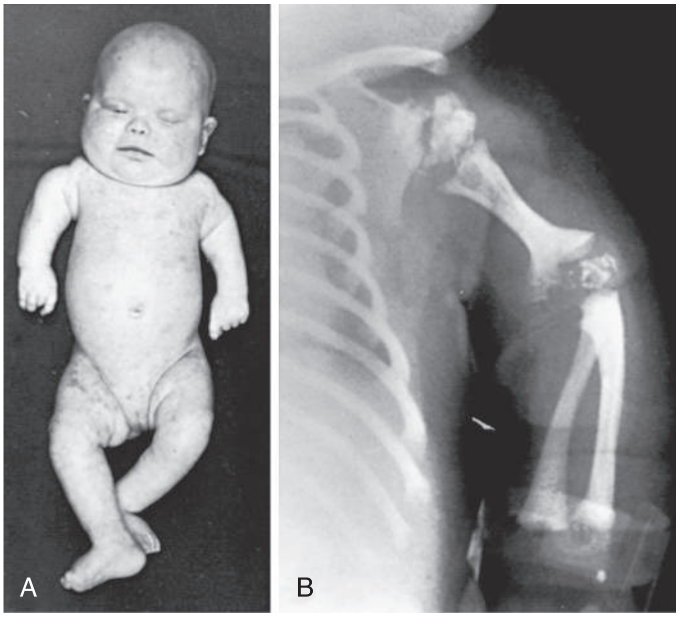

Figure 86-4 **A,** Newborn infant with rhizomelic chondrodysplasia punctata. Note the severe shortening of the proximal limbs, the depressed bridge of the nose, hypertelorism, and widespread scaling skin lesions. **B,** Note the marked shortening of the humerus and epiphyseal stippling at the shoulder and elbow joints. *(Courtesy of John P. Dorst, MD.)*

Rhizomelic Chondrodysplasia Punctata

RCDP is characterized by the presence of stippled foci of calcification within the hyaline cartilage and is associated with dwarfing, cataracts (72%), and multiple malformations caused by contractures. Vertebral bodies have a coronal cleft filled by cartilage that is a result of an embryonic arrest. Disproportionate short stature affects the proximal parts of the extremities (Fig. 86-4*A*). Radiologic abnormalities consist of shortening of the proximal limb bones, metaphyseal cupping, and disturbed ossification (Fig. 86-4*B*). Height, weight, and head circumference are less than the 3rd percentile, and these children have a severe intellectual disability. Skin changes such as those observed in ichthyosiform erythroderma are present in approximately 25% of patients.

Isolated Defects of Peroxisomal Fatty Acid Oxidation

The disorders labeled B1 through B3 (see Table 86-2) each involve 1 of 3 enzymes involved in peroxisomal fatty acid oxidation. Their clinical manifestations resemble those of the Zellweger spectrum disorder continuum; they can be distinguished from disorders of peroxisome biogenesis only by laboratory tests. Defects of bifunctional enzyme are common and are found in approximately 15% of patients with the Zellweger spectrum disorder. Patients with isolated acyl-CoA oxidase deficiency have a somewhat milder phenotype that resembles and come to attention because of the development of a childhood leukodystrophy.

Isolated Defects of Plasmalogen Synthesis

Plasmalogens are lipids in which the first carbon of glycerol is linked to an alcohol rather than a fatty acid. They are synthesized through a complex series of reactions, the first 2 steps of which are catalyzed by the peroxisomal enzymes dihydroxyacetone phosphate alkyl transferase and synthase. Deficiency of either of these enzymes (B4 and B5 in Table 86-2) leads to a phenotype that is clinically indistinguishable from the peroxisomal import disorder RCDP. This latter disorder is caused by a defect in *PEX7,* the receptor for PTS2. It shares the severe deficiency of plasmalogens with disorders B4 and B5 but, in addition, has defects of phytanic oxidation. The fact that disorders B4 and B5 are associated with the full phenotype of RCDP suggests that a deficiency of plasmalogens is sufficient to produce it.

Classic Refsum Disease

The defective enzyme (phytanoyl-CoA oxidase) is localized to the peroxisome. The manifestation of classic adult Refsum disease includes impaired vision from retinitis pigmentosa, ichthyosis, peripheral neuropathy, ataxia, and, occasionally, cardiac arrhythmias. In contrast to infantile Refsum disease, cognitive function is normal and there are no congenital malformations. Classic Refsum disease often does not manifest until young adulthood, but visual disturbances such as night blindness, ichthyosis, and peripheral neuropathy may already be present in childhood and adolescence. Early diagnosis is important because institution of a phytanic acid-restricted diet can reverse the peripheral neuropathy and prevent the progression of the visual and central nervous system manifestations. The classic Refsum disease phenotype may also be caused by defects in *PEX7*.

2-Methylacyl-Coenzyme A Racemase Deficiency

This disorder is caused by an enzyme defect that leads to the accumulation of the branched-chain fatty acids (phytanic and pristanic acid) and bile acids. Patients present with adult-type peripheral neuropathy and may also have pigmentary degeneration of the retina.

Laboratory Findings

Laboratory tests for peroxisomal disorders can be viewed at 3 levels of complexity.

Level 1: Does the Patient Have a Peroxisomal Disorder?

This can be resolved by noninvasive tests that are generally available (see Table 86-4). *Measurement of plasma VLCFA is the most commonly used assay*. Whereas plasma VLCFA levels are elevated in many patients with peroxisomal disorders, this is not always the case. The most important exception is RCDP, in which VLCFA levels are normal, but plasma phytanic acid levels are increased and red blood cell plasmalogen levels are reduced. In some other peroxisomal disorders, the biochemical abnormalities are still more restricted. Therefore, a panel of tests is recommended and includes plasma levels of VLCFA and phytanic, pristanic, and pipecolic acids and red blood cell levels of plasmalogens. Tandem mass spectrometry techniques also permit convenient quantitation of bile acids in plasma and urine. This panel of tests can be performed on 2 mL samples of venous blood and permits detection of most peroxisomal disorders. Furthermore, normal results make the presence of the typical peroxisomal disorder unlikely.

Level 2: What Is the Precise Nature of the Peroxisomal Disorder?

Table 86-5 lists the main biochemical abnormalities in the various peroxisomal disorders. When combined with the clinical presentation, the panel of level 1 tests (see above) is often sufficient to identify the precise nature of the defect. Marked reduction of erythrocyte plasmalogen levels combined with elevated plasma phytanic acid permits precise diagnosis in a patient with the clinical features of RCDP. Classic Refsum disease can be diagnosed by demonstration of increased plasma phytanic acid combined with normal or reduced levels of pristanic acid levels, while in D-bifunctional enzyme deficiency and 2-methylacyl-CoA racemase deficiency, the levels of pristanic and phytanic acid are both increased. Precise identification of some peroxisomal disorders may require more extensive studies in cultured skin fibroblasts. This may be required for the differentiation of PBDs from defects in bifunctional enzyme. In PBDs, the patient's peroxisomes are absent and catalase is in the soluble fraction, whereas in bifunctional enzyme defect, peroxisomes are present and catalase is in the particulate fraction. Fibroblast studies are required to identify the nature of the molecular defect in PBDs. Whether such specialized studies are clinically warranted depends on individual circumstances. Precise definition of the defect in a proband may improve the precision of prenatal diagnosis in at-risk pregnancies, and it is required for carrier detection. It is also of value in setting prognosis.

Level 3: What Is the Molecular Defect?

Definition of the molecular defect in the proband, which is now offered in several laboratories, is essential for carrier detection and speeds prenatal diagnosis. Characterization of the mutation may be of prognostic value in patients with *PEX1* defects. This defect is present in approximately 60% of PBD patients, and about half of the *PEX1* defects have the G843D allele, which is associated with a significantly milder phenotype than is found in other mutations.

Diagnosis

There are several noninvasive laboratory tests that permit precise and early diagnosis of peroxisomal disorders (see Table 86-4). The challenge in PBDs is to differentiate them from the large variety of other conditions that can cause hypotonia, seizures, failure to thrive, or dysmorphic features. Experienced clinicians can readily recognize classic Zellweger syndrome by its clinical manifestations. However, more mildly affected PBD patients often do not show the full clinical spectrum of disease and may be identifiable only by laboratory assays. Clinical features that serve as indications for these diagnostic assays include severe intellectual disability; weakness and hypotonia; dysmorphic features; neonatal seizures; retinopathy, glaucoma, or cataracts; hearing deficits; enlarged liver and impaired liver function; and chondrodysplasia punctata. The presence of 1 or more of these abnormalities increases the likelihood of this diagnosis. Atypical milder forms presenting as peripheral neuropathy have also been described.

Some patients with the isolated defects of peroxisomal fatty acid oxidation (group B) resemble those with group A disorders and can be detected by the demonstration of abnormally high levels of VLCFAs.

Patients with RCDP must be distinguished from patients with other causes of chondrodysplasia punctata. In addition to warfarin embryopathy and Zellweger syndrome, these disorders include the milder autosomal dominant form of chondrodysplasia punctata (Conradi-Hünermann syndrome), which is characterized by longer survival, absence of severe limb shortening, and usually intact intellect; an X-linked dominant form; and an X-linked recessive form associated with a deletion of the terminal portion of the short arm of the X chromosome. RCDP is suspected clinically because of the shortness of limbs, psychomotor retardation, and ichthyosis. The most decisive laboratory test is the demonstration of abnormally low plasmalogen levels in red blood cells and an impaired capacity to synthesize plasmalogens in cultured skin fibroblasts. These biochemical defects are not present in other types of chondrodysplasia punctata. Chondrodysplasia punctata may also be associated with a defect of 3β-hydroxysteroid-Δ^8,Δ^7-isomerase, an enzyme involved in biosynthesis of cholesterol.

Complications

Patients with Zellweger cerebrohepatorenal syndrome have multiple disabilities involving muscle tone, swallowing, cardiac abnormalities, liver disease, and seizures. These conditions are treated symptomatically, but the prognosis is poor, and most patients succumb in the first year of life. Patients with RCDP may develop quadriparesis owing to compression at the base of the brain.

Treatment

The most effective therapy is the dietary treatment of classic Refsum disease with a phytanic acid-restricted diet.

For patients with the somewhat milder variants of the peroxisome import disorders, success has been achieved with multidisciplinary early intervention, including physical and occupational therapy, hearing aids or cochlear implants, alternative communication, nutrition, and support for the parents. Although most patients continue to function in the severely delayed range, some make significant gains in self-help skills, and several are in stable condition in their teens or even early 20s.

Attempts to mitigate some of the secondary biochemical abnormalities include the oral administration of docosahexaenoic acid. The levels of this substance are greatly reduced in patients with disorders of peroxisome biogenesis and this therapy normalizes the plasma levels of

Table 86-5 Peroxisomal Disorders That Involve Fatty Acid Oxidation: Diagnostic Assays

DISEASE	ASSAY		FINDING
Zellweger syndrome Neonatal adrenoleukodystrophy Infantile Refsum disease	Plasma	VLCFA	Increased
		Phytanic acid	Age-dependent increase
		Pristanic acid	Age-dependent increase
		Pipecolic acid	Increased
		Bile acid	Increased, abnormal pattern
	RBCs	Plasmalogen levels	Variably decreased
	Fibroblasts	VLCFA levels	Increased
		VLCFA oxidation	Decreased
		Plasmalogen synthesis	Decreased
		Phytanic, pristanic oxidation	Decreased
		Catalase localization	Cytosolic
		Immunocytochemistry	Peroxisomes absent
		Complementation	Complementation between infantile Refsum disease and other peroxisomal disorder (except Zellweger) flibroblasts
		DNA	*PEX* gene mutations
Rhizomelic chondrodysplasia punctata	Plasma	Phytanic acid	Increased
		VLCFA	Normal
	RBCs	Plasmalogen levels	Decreased
	Fibroblasts	Plasmalogen synthesis	Decreased
		Phytanic acid oxidation	Decreased
		DNA	*PEX7* defect
X-linked ALD hemizygote	Plasma	VLCFA	Increased
	Fibroblasts	VLCFA levels	Increased
		VLCFA oxidation	Decreased
		ALDP immunoreactivity	Absent in 70%
		DNA	*ABCD1* mutation
X-linked ALD heterozygote	Plasma	VLCFA	Variable increase in 85% of heterozygotes
	Fibroblasts	VLCFA levels	Variable increase in 90% of heterozygotes
		ALDP immunoreactivity	Variable decrease
		DNA	*ABCD1* mutation
Bifunctional enzyme defect	Plasma	VLCFA	Increased
		Phytanic acid	Increased
		Pristanic acid	Increased
		Bile acids	Increased, abnormal pattern
	Fibroblasts	VLCFA levels	Increased
		Pristanic acid oxidation	Decreased
		Catalase localization	Peroxisomal
		Enzyme	D-bifunctional protein deficiency
Acyl-CoA oxidase deficiency	Plasma	VLCFA	Increased
	Fibroblasts	VLCFA levels	Increased
		VLCFA oxidation	Decreased
		Enzyme	Acyl-CoA oxidase defect
2-Methylacyl-CoA racemase deficiency	Plasma	Pristanic acid	Increased
		Bile acids	Increased, abnormal pattern
	Fibroblasts	Pristanic acid oxidation	Decreased
		Enzyme	2-Methylacyl-CoA oxidase defect
Classic Refsum disease	Plasma	Phytanic acid	Increased
		Pristanic acid	Decreased
	Fibroblasts	Enzyme	Phytanoyl-CoA deficiency

ALD, adrenoleukodystrophy; ALDP, adrenoleukodystrophy protein; CoA, coenzyme A; RBC, red blood cell; VLCFA, very-long-chain fatty acid.

this substance. Although there were anecdotal reports of clinical improvement, a randomized placebo-controlled study failed to find benefit.

Genetic Counseling

All the peroxisomal disorders, except hyperoxaluria type 1, can be diagnosed prenatally in the 1st or 2nd trimester. The tests are similar to those described for postnatal diagnosis (see Table 86-5) and use chorionic villus sampling or amniocytes. Because of the 25% recurrence risk, couples with an affected child must be advised about the availability of prenatal diagnosis. Heterozygotes can be identified in ALD and in those disorders in which the molecular defect has been identified.

ADRENOLEUKODYSTROPHY (X-LINKED)

ALD is a genetically determined disorder associated with the accumulation of saturated VLCFAs and a progressive dysfunction of the adrenal cortex and central and peripheral nervous system white matter.

Etiology

The key biochemical abnormality is the tissue accumulation of saturated VLCFAs, with a carbon chain length of 24 or more. Excess hexacosanoic acid ($C_{26:0}$) is the most striking and characteristic feature. This accumulation of fatty acids is caused by genetically deficient peroxisomal degradation of fatty acid. The gene that is defective *(ABCD1)* codes for a peroxisomal membrane protein (ALDP, the ALD protein). Most families have a mutation that is "private" (unique to that kindred)

and these are updated on the website, http://x-ald.nl. The mechanism by which the ALDP defect leads to VLCFA accumulation appears to be a disruption of transport of saturated fatty acids into the peroxisome with resultant continued elongation of progressively longer fatty acids.

Epidemiology

The minimum incidence of ALD in males is 1 in 21,000, and the combined incidence of ALD males and heterozygous females in the general population is estimated to be 1 in 17,000. All races are affected. The various phenotypes often occur in members of the same kindred.

Pathology

Characteristic lamellar cytoplasmic inclusions can be demonstrated with the electron microscope in adrenocortical cells, testicular Leydig cells, and nervous system macrophages. These inclusions probably consist of cholesterol esterified with VLCFA. They are most prominent in cells of the zona fasciculata of the adrenal cortex, which at first are distended with lipid and later atrophy.

The nervous system can display 2 types of lesions. In the severe childhood cerebral form and in the rapidly progressive adult forms, demyelination is associated with an inflammatory response manifested by the accumulation of perivascular lymphocytes that is most intense in the parietooccipital region. In the slowly progressive adult form, **adrenomyeloneuropathy**, the main finding is a distal axonopathy that affects the long tracts in the spinal cord. The inflammatory response is mild or absent.

Pathogenesis

The adrenal dysfunction is probably a direct consequence of the accumulation of VLCFAs. The cells in the zona fasciculata are distended with abnormal lipids. Cholesterol esterified with VLCFA is relatively resistant to adrenocorticotropic hormone (ACTH)-stimulated cholesterol ester hydrolases, and this limits the capacity to convert cholesterol to active steroids. In addition, $C_{26:0}$ excess increases the viscosity of the plasma membrane and this may interfere with receptor and other cellular functions.

There is no correlation between the neurologic phenotype and the nature of the mutation or the severity of the biochemical defect as assessed by plasma levels of VLCFAs or between the degree of adrenal involvement and nervous system involvement. The severity of the illness and rate of progression correlate with the intensity of the inflammatory response. The inflammatory response may be cytokine mediated and may involve an autoimmune response triggered in an unknown way by the excess of VLCFAs. Mitochondrial damage and oxidative stress also contribute. Approximately half of the patients do not experience the inflammatory response; this difference is not understood.

Clinical Manifestations

There are 5 relatively distinct phenotypes, 3 of which are present in childhood with symptoms and signs. In all the phenotypes, development is usually normal in the first 3-4 yr of life.

In the **childhood cerebral form** of ALD, symptoms are first noted most commonly between the ages of 4 and 8 yr. The most common initial manifestations are hyperactivity, which is often mistaken for an attention deficit disorder, and worsening school performance in a child who had previously been a good student. **Auditory discrimination** is often impaired, although tone perception is preserved. This may be evidenced by difficulty in using the telephone and greatly impaired performance on intelligence tests in items that are presented verbally. Spatial orientation is often impaired. Other initial symptoms are disturbances of vision, ataxia, poor handwriting, seizures, and strabismus. Visual disturbances are often caused by involvement of the cerebral cortex, which leads to variable and seemingly inconsistent visual capacity. **Seizures** occur in nearly all patients and may represent the first manifestation of the disease. Some patients present with increased intracranial pressure or with unilateral mass lesions. Impaired cortisol response to ACTH stimulation is present in 85% of patients, and mild hyperpigmentation is noted. In most patients with this phenotype, adrenal dysfunction is recognized only after the condition is diagnosed because of the cerebral symptoms. Cerebral childhood ALD tends to progress rapidly with increasing spasticity and paralysis, visual and hearing loss, and loss of ability to speak or swallow. The mean interval between the first neurologic symptom and an apparently vegetative state is 1.9 yr. Patients may continue in this apparently vegetative state for 10 yr or more.

Adolescent ALD designates patients who experience neurologic symptoms between the ages of 10 and 21 yr. The manifestations resemble those of childhood cerebral ALD except that progression is slower. Approximately 10% of patients present acutely with status epilepticus, adrenal crisis, acute encephalopathy, or coma.

Adrenomyeloneuropathy first manifests in late adolescence or adulthood as a progressive paraparesis caused by long tract degeneration in the spinal cord. Approximately half of the patients also have involvement of the cerebral white matter.

The **"Addison only"** phenotype is an important condition. Of male patients with Addison disease, 25% may have the biochemical defect of ALD. Many of these patients have intact neurologic systems, whereas others have subtle neurologic signs. Many acquire adrenomyeloneuropathy in adulthood.

The term "asymptomatic ALD" is applied to persons who have the biochemical defect of ALD but are free of neurologic or endocrinal disturbances. Nearly all persons with the gene defect eventually become neurologically symptomatic.

Approximately 50% of female heterozygotes acquire a syndrome that resembles adrenomyeloneuropathy but is milder and of later onset. Adrenal insufficiency and cerebral disease are rare.

Cases of typical ALD have occurred in relatives of those with adrenomyeloneuropathy. One of the most difficult problems in the management of X-linked ALD is the common observation that affected individuals in the same family may have quite different clinical courses. For example, in 1 family, 1 affected boy had severe classic ALD culminating in death by age 10 yr; another affected male (a brother) had late-onset adrenomyeloneuropathy, and a third had no symptoms at all.

Laboratory and Radiographic Findings

The most specific and important laboratory finding is the demonstration of abnormally high levels of VLCFA in plasma, red blood cells, or cultured skin fibroblasts. The test should be performed in a laboratory that has experience with this specialized procedure. Positive results are obtained in all male patients with ALD and in approximately 85% of female carriers of ALD. Mutation analysis is the most reliable method for the identification of carriers.

Neuroimaging

Patients with childhood cerebral or adolescent ALD show cerebral white matter lesions that are characteristic with respect to location and attenuation patterns on MRI. In 80% of patients, the lesions are symmetric and involve the periventricular white matter in the posterior parietal and occipital lobes. Approximately 50% show a garland of accumulated contrast material adjacent and anterior to the posterior hypodense lesions (Fig. 86-5*A*). This zone corresponds to the zones of intense perivascular lymphocytic infiltration where the blood–brain barrier breaks down. In 12% of patients, the initial lesions are frontal. Unilateral lesions that produce a mass effect suggestive of a brain tumor may occur. MRI provides a clearer delineation of normal and abnormal white matter than does CT (Fig. 86-5*B*).

Impaired Adrenal Function

More than 85% of patients with the childhood form of ALD have elevated levels of ACTH in plasma and a subnormal rise of cortisol levels in plasma following intravenous injection of 250 µg of ACTH (Cortrosyn).

Diagnosis and Differential Diagnosis

The earliest manifestations of childhood cerebral ALD are difficult to distinguish from the more common attention-deficit disorders or

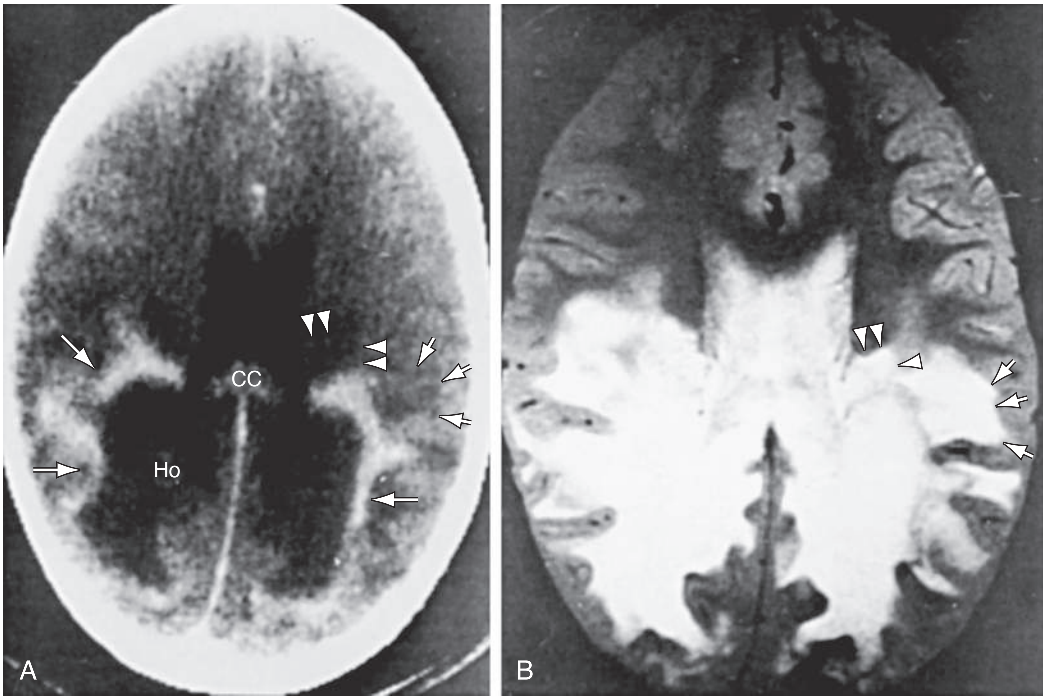

Figure 86-5 **A,** Contrast-enhanced CT abnormalities in adrenoleukodystrophy with typical parietooccipital location, showing symmetric bilateral hypodense inactive zones (Ho). The enhancing active periphery zone of hypodensity is demarcated by *arrows*. Compare the anterior zone of hypodensity *(arrowheads)* with that on the MRI in **B.** CC, corpus callosum. **B,** MRI of the same pattern and area shown by CT. MRI T2-weighted image shows a high-intensity signal of the abnormally bright parietooccipital white matter. Subcortical involvement is better identified on MRI. Separation of active zones may be better appreciated by CT, because both inactive and active zones are seen at high-signal areas on MRI. It is assumed, however, that such major distinctions afforded by CT will also be demonstrable when IV enhancement (paramagnetic enhancement) becomes readily available. Note the hypodense involvement of CT (*arrowheads* and *arrows* in **A**) compared with the well-resolved lesions on MRI in **B.** *(From Kumar AJ, Rosenbaum WE, Naidu S, et al: Adrenoleukodystrophy: corresponding MR imaging with CT,* Radiology *165:497–504, 1987.)*

learning disabilities. Rapid progression, signs of dementia, or difficulty in auditory discrimination suggest ALD. Even in early stages, CT or MRI may show strikingly abnormal changes. Other leukodystrophies or multiple sclerosis may mimic these radiographic findings, although early ALD has more of a predilection for the posterior brain than its mimics. Definitive diagnosis depends on demonstration of VLCFA excess, which occurs only in ALD and the other peroxisomal disorders.

Cerebral forms of ALD may present as increased intracranial pressure and unilateral mass lesions. These have been misdiagnosed as gliomas, even after brain biopsy, and several patients have received radiotherapy before the correct diagnosis was made. Measurement of VLCFA in plasma or brain biopsy specimens is the most reliable differentiating test.

Adolescent or adult cerebral ALD can be confused with **psychiatric disorders**, dementing disorders, or epilepsy. The first clue to the diagnosis of ALD may be the demonstration of white matter lesions by neuroimaging; assays of VLCFA are confirmatory.

ALD cannot be distinguished clinically from other forms of Addison disease; it is recommended that assays of VLCFA levels be performed in all male patients with Addison disease. ALD patients do not usually have antibodies to adrenal tissue in their plasma.

Complications

An avoidable complication is the occurrence of adrenal insufficiency. The most difficult neurologic problems are those related to bed rest, contracture, coma, and swallowing disturbances. Other complications involve behavioral disturbances and injuries associated with defects of spatial orientation, impaired vision and hearing, and seizures.

Treatment

Corticosteroid replacement for adrenal insufficiency or adrenocortical hypofunction is effective. It may be lifesaving and increase general strength and well-being, but it does not alter the course of the neurologic disability.

Bone Marrow Transplantation

Bone marrow transplantation (BMT) benefits patients who show early evidence of the inflammatory demyelination that is characteristic of the rapidly progressive neurologic disability in boys and adolescents with the cerebral ALD phenotype. BMT is a high-risk procedure, and patients must be selected with great care. The mechanism of the beneficial effect is incompletely understood. Bone marrow-derived cells do express ALDP, the protein that is deficient in ALD; approximately 50% of brain microglial cells are bone marrow derived. The favorable effect may be caused by modification of the brain inflammatory response. Five to 10 yr follow-up of boys and adolescents who had early cerebral involvement has shown stabilization. On the other hand, BMT has not shown favorable effects in patients who already had severe brain involvement and may accelerate disease progression under these circumstances. The nonverbal IQ has been found to be of predictive value, and transplant is not recommended in patients with performance IQ significantly below 80. Unfortunately, in more than half the patients who are diagnosed because of neurologic symptoms, the illness is so advanced at the time of diagnosis that they are not candidates for transplant.

Consideration of BMT is most relevant in neurologically asymptomatic or mildly involved patients. Screening at-risk relatives of symptomatic patients identifies these patients most frequently. Screening by measurement of plasma VLCFA levels in patients with Addison disease may also identify candidates for BMT. Because of its risk (10-20% mortality) and the fact that up to 50% of untreated patients with ALD do not develop inflammatory brain demyelination, transplant is not recommended in patients who are free of demonstrable brain involvement. The MRI is also of key importance for the crucial decision of whether transplant should be performed. MRI abnormalities precede

clinically evident neurologic or neuropsychologic abnormalities. The brain MRI should be monitored at 6 mo intervals in neurologically asymptomatic boys and adolescents between the ages of 3 and 15 yr. If the MRI is normal, BMT is not indicated. If brain MRI abnormalities develop, the patient should be evaluated at 3 mo intervals to determine if the abnormality is progressive, in combination with careful neurologic and neuropsychologic evaluation; and if early progressive involvement is confirmed, transplant should be considered. Magnetic resonance spectroscopy improves the capacity to determine whether the brain involvement is progressive. It is not known whether BMT has a favorable effect on the noninflammatory spinal cord involvement in adults with the adrenomyeloneuropathy phenotype.

Lorenzo's Oil Therapy

The administration of Lorenzo's oil to asymptomatic boys in an open study reduced the risk of developing the childhood cerebral phenotype by a factor of 2 or more. Lorenzo's oil (4 : 1 mixture of glyceryl trioleate and glyceryl trierucate) combined with a dietary regimen is under investigation for neurologically asymptomatic boys who have a normal brain MRI and are younger than 8 yr old. It has been determined that it must be supervised carefully. Adrenal function and brain MRI must be monitored. Patients who develop progressive MRI abnormalities are evaluated for hematopoietic stem cell transplant when changes are still in an early phase. Lorenzo's oil has not been shown to alter disease progression in patients who already have cerebral involvement.

Supportive Therapy

The progressive behavioral and neurologic disturbances associated with the childhood form of ALD are extremely difficult for the family. ALD patients require the establishment of a comprehensive management program and partnership among the family, physician, visiting nursing staff, school authorities, and counselors. In addition, parent support groups (e.g., United Leukodystrophy Foundation) are often helpful. Communication with school authorities is important because under the provisions of Public Law 94-142, children with ALD qualify for special services as "other health impaired" or "multihandicapped." Depending on the rate of progression of the disease, special needs might range from relatively low-level resource services within a regular school program to home- and hospital-based teaching programs for children who are not mobile.

Management challenges vary with the stage of the illness. The early stages are characterized by subtle changes in affect, behavior, and attention span. Counseling and communication with school authorities are of prime importance. Changes in the sleep–wake cycle can be benefited by the judicious use at night of medications for sleep.

As the leukodystrophy progresses, the modulation of muscle tone and support of bulbar muscular function are major concerns. Baclofen in gradually increasing doses (5 mg twice a day to 25 mg 4 times a day) is an effective pharmacologic agent for the treatment of acute episodic painful muscle spasms. Other agents may also be used, with care being taken to monitor the occurrence of side effects and drug interactions. As the leukodystrophy progresses, bulbar muscular control is lost. Although initially this can be managed by changing the diet to soft and pureed foods, most patients eventually require a gastrostomy tube. At least 30% of patients have focal or generalized seizures that usually readily respond to standard anticonvulsant medications.

Genetic Counseling and Prevention

Genetic counseling and primary and secondary prevention of ALD are of crucial importance. Extended family screening should be offered to all at-risk relatives of symptomatic patients; one program led to the identification of more than 250 asymptomatic affected males and 1,200 women heterozygous for ALD. The plasma assay permits reliable identification of affected males in whom plasma VLCFA levels are increased already on the day of birth. Identification of asymptomatic males permits institution of steroid replacement therapy when appropriate and prevents the occurrence of adrenal crisis, which may be fatal. Monitoring of brain MRI also permits identification of patients who are candidates for BMT at a stage when this procedure has the greatest chance of success. Plasma VLCFA assay is recommended in all male patients with Addison disease. ALD has been shown to be the cause of adrenal insufficiency in more than 25% of boys with Addison disease of unknown cause. Identification of women heterozygous for ALD is more difficult than that of affected males. Plasma VLCFA levels are normal in 15-20% of heterozygous women, and failure to note this has led to serious errors in genetic counseling. DNA analysis permits accurate identification of carriers, provided that the mutation has been defined in a family member, and is the procedure recommended for the identification of heterozygous women.

Prenatal diagnosis of affected male fetuses can be achieved by measurement of VLCFA levels in cultured amniocytes or chorionic villus cells and by mutation analysis. Whenever a new patient with ALD is identified, a detailed pedigree should be constructed and efforts should be made to identify all at-risk female carriers and affected males. These investigations should be accompanied by careful and sympathetic attention to social, emotional, and ethical issues during counseling.

Bibliography is available at Expert Consult.

86.3 Disorders of Lipoprotein Metabolism and Transport

William A. Neal and Collin C. John

EPIDEMIOLOGY OF BLOOD LIPIDS AND CARDIOVASCULAR DISEASE

The Seven Countries Study of geographic, social class, and ethnic differences in coronary heart disease (CHD) around the world found strong associations between average intake of saturated fats, plasma cholesterol, and mortality from CHD. Of all common chronic diseases, none is so clearly influenced by both environmental and genetic factors as CHD. This multifactorial disorder is strongly associated with increasing age and male gender, though it is increasingly apparent that heart disease is underrecognized in women. Tobacco use confers a 2-fold higher lifetime risk. Sedentary activity and high intake of saturated fats leading to adiposity increase risk through differences in the plasma levels of lipoproteins that are atherogenic. Family history is a reflection of the combined influence of lifestyle and genetic predisposition to early heart disease. Risk of premature heart disease associated with positive family history is 1.7 times higher than in families with no such history.

The pathogenesis of atherosclerosis begins during childhood. The Johns Hopkins Precursors Study demonstrated that white male medical students with blood cholesterol levels in the lowest quartile showed only a 10% incidence of CHD 3 decades later, whereas those in the highest quartile had a 40% incidence. The Pathobiological Determinants of Atherosclerosis in Youth Study demonstrated a significant relationship between the weight of the abdominal fat pad and the extent of atherosclerosis found at autopsy on subjects 15-34 yr of age. The Bogalusa Heart Study of more than 3,000 black and white children and adolescents has provided the most comprehensive longitudinal data relating the presence and severity of CHD risk factors with semi-quantifiable severity of atherosclerosis. Coronary atherosclerosis was present in 8.5% of military autopsies performed following combat or unintentional injuries.

The "fetal origins hypothesis" is based on the observation that infants born with low birthweight have a higher incidence of heart disease as adults. Epidemiologic studies support the idea that prenatal and early postnatal conditions may affect adult health status. Children who are large for gestational age at birth and exposed to an intrauterine environment of either diabetes or maternal obesity are at increased risk of eventually developing the "metabolic syndrome" (insulin resistance, type II diabetes, obesity, CHD). Breastfeeding preterm infants confers a long-term cardioprotective benefit 13-16 yr later. Those adolescents who were breastfed as infants had lower C-reactive protein

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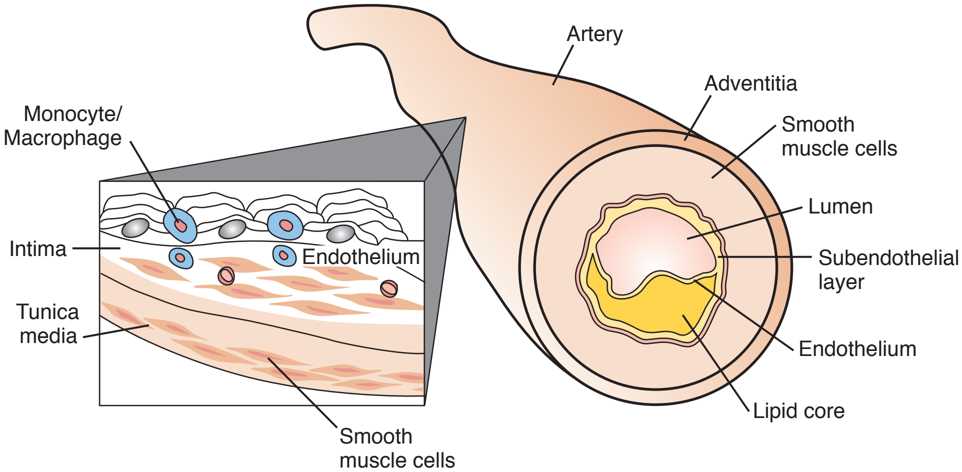

Figure 86-6 The early stage of development of atherosclerosis begins with penetration of the intimal lining of the vessel by inflammatory cells. Deposition of lipid within the subendothelial lining of the arterial wall eventually leads to disruption of smooth muscle cells to form an atheromatous lipid core that impinges on the lumen. Chronic inflammation leads to plaque instability, setting the stage for plaque rupture and complete occlusion of the vessel lumen by clot formation.

concentrations and a 14% lower low-density lipoprotein (LDL):high-density lipoprotein (HDL) ratio compared to those fed infant formulas. The impact of early nutrition and other lifestyle variables on gene expression, known as epigenetics, is an important mechanism by which adult metabolism and body composition may be determined.

In addition, secondary causes of hyperlipidemia may be the result of drugs (cyclosporine, steroids, isotretinoin, protease inhibitors, alcohol, thiazide diuretics, β-blocking agents, valproate) or various diseases (nephrotic syndrome, hypothyroidism, Cushing syndrome, anorexia nervosa, obstructive jaundice).

BLOOD LIPIDS AND ATHEROGENESIS

Numerous epidemiologic studies demonstrate the association of hypercholesterolemia, referring to elevated total blood cholesterol, with atherosclerotic disease. The ability to measure subcomponents within classes of lipid particles, as well as markers of inflammation, have further elucidated the process of atherogenesis and plaque rupture leading to acute coronary syndromes. Atherosclerosis affects primarily the coronary arteries but may also involve the aorta, arteries of the lower extremities, and carotid arteries.

The early stage of development of atherosclerosis is thought to begin with vascular endothelial dysfunction and intima-media thickness, which has been shown to occur in preadolescent children with risk factors such as obesity or familial hypercholesterolemia. The complex process of penetration of the intimal lining of the vessel may be a consequence of a variety of insults, including the presence of highly toxic oxidized LDL particles. Lymphocytes and monocytes penetrate the damaged endothelial lining, where they become macrophages laden with LDL lipids and then become foam cells. Such accumulation is counterbalanced by HDL particles capable of removing lipid deposits from the vessel wall. Fundamental to plaque formation is an inflammatory process (elevated C-reactive protein) involving macrophages and the arterial wall. The deposition of lipid within the subendothelial lining of the arterial wall appears macroscopically as fatty streaks, which may to some degree be reversible. A later stage of plaque development involves disruption of arterial smooth muscle cells stimulated by the release of tissue cytokines and growth factors. The atheroma is composed of a core of fatty substance separated from the lumen by collagen and smooth muscle (Fig. 86-6). Growth of the atherosclerotic plaque may result in ischemia of the tissue supplied by the artery. Chronic inflammation within the atheroma, results in plaque instability and subsequent rupture. Platelet adherence leads to clot formation at the site of rupture, resulting in myocardial infarction or a cerebrovascular event.

PLASMA LIPOPROTEIN METABOLISM AND TRANSPORT

Abnormalities of lipoprotein metabolism are associated with diabetes mellitus and premature atherosclerosis. Lipoproteins are soluble complexes of lipids and proteins that effect transport of fat absorbed from the diet, or synthesis by the liver and adipose tissues, for utilization and storage. Dietary fat is transported from the small intestine as chylomicrons. Lipids synthesized by the liver as very-low-density lipoproteins (VLDLs) are catabolized to intermediate-density lipoproteins (IDLs) and LDLs. HDLs are fundamentally involved in VLDL and chylomicron metabolism and cholesterol transport. Nonesterified free fatty acids are metabolically active lipids derived from lipolysis of triglycerides stored in adipose tissue bound to albumin for circulation in the plasma (Fig. 86-7).

Lipoproteins consist of a central core of triglycerides and cholesteryl esters surrounded by phospholipids, cholesterol, and proteins (Fig. 86-8). The density of the several classes of lipoproteins is inversely proportional to the ratio of lipid to protein (Fig. 86-9). Lipoproteins consist of a central core of triglycerides and cholesteryl esters surrounded by phospholipids, cholesterol, and proteins.

Constituent proteins are known as apolipoproteins (Table 86-6). They are responsible for a variety of metabolic functions in addition to their structural role, including cofactors or inhibitors of enzymatic pathways, and mediators of lipoprotein binding to cell surface receptors. ApoA is the major apolipoprotein (Apo) of HDL. ApoB is present in LDL, VLDL, IDL, and chylomicrons. ApoB-100 is derived from the liver, whereas apoB-48 comes from the small intestine. ApoC-I, C-II, and C-III are small peptides important in triglyceride metabolism. Loss of function and disruptive mutations of the *APOC3* gene are associated with low levels of triglycerides and a reduced risk of ischemic CHD. Likewise, apoE, which is present in VLDL, HDL, chylomicrons, and chylomicron remnants, plays an important role in the clearance of triglycerides.

Transport of Exogenous (Dietary) Lipids

All dietary fat with the exception of medium-chain triglycerides is efficiently carried into the circulation by way of lymphatic drainage from the intestinal mucosa. Triglyceride and cholesteryl esters combine with apoA and apoB-48 in the intestinal mucosa to form chylomicrons, which are carried into the peripheral circulation via the lymphatic system. HDL particles contribute apoC-II to the chylomicrons, required for the activation of lipoprotein lipase (LPL) within the capillary endothelium of adipose, heart, and skeletal muscle tissue. Free fatty acids are oxidized, esterified for storage as

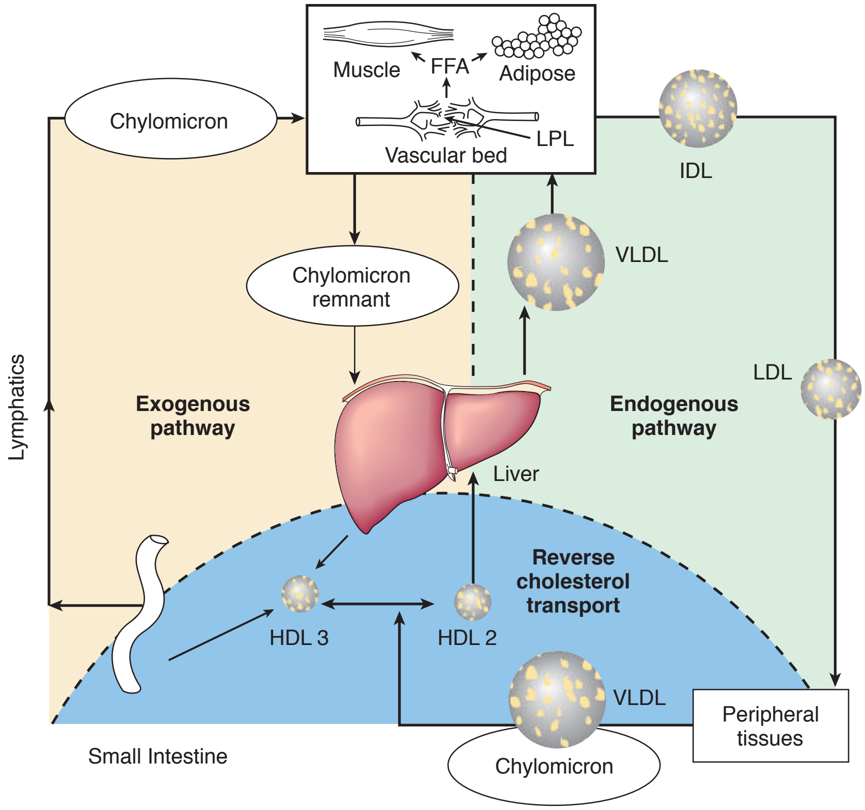

Figure 86-7 The exogenous, endogenous, and reverse cholesterol pathways. The exogenous pathway transports dietary fat from the small intestine as chylomicrons to the periphery and the liver. The endogenous pathway denotes the secretion of very-low-density lipoprotein (VLDL) from the liver and its catabolism to intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL). Triglycerides are hydrolyzed from the VLDL particle by the action of lipoprotein lipase (LPL) in the vascular bed, yielding free fatty acids (FFAs) for utilization and storage in muscle and adipose tissue. High-density lipoprotein (HDL) metabolism is responsible for the transport of excess cholesterol from the peripheral tissues back to the liver for excretion in the bile. Nascent HDL-3 particles derived from the liver and small intestine are esterified to more mature HDL-2 particles by enzyme-mediated movement of chylomicron and VLDL into the HDL core, which is removed from the circulation by endocytosis.

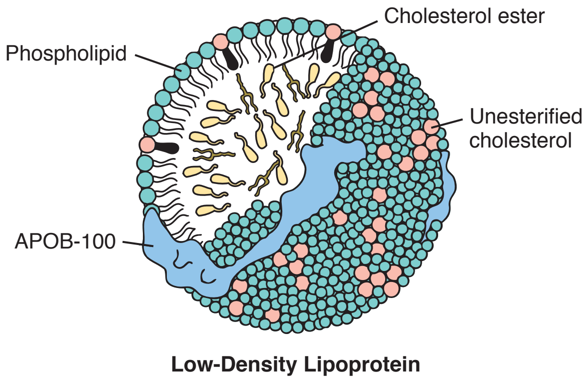

Figure 86-8 Schematic of low-density lipoprotein. Lipoprotein consists of a central core of cholesteryl esters, surrounded by phospholipids, cholesterol, and protein.

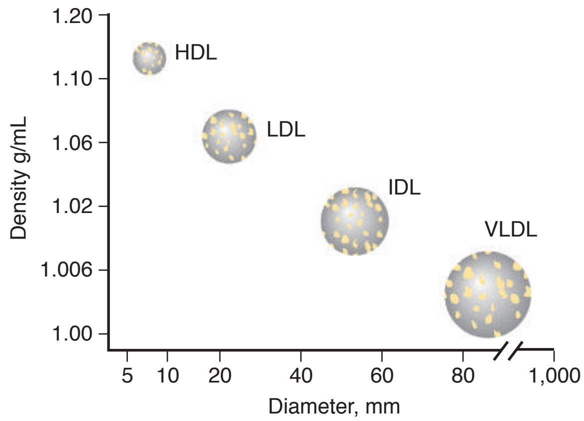

Figure 86-9 The density of the several classes of lipoprotein is inversely proportional to the ratio of lipid to protein. As lipid is less dense than protein, the more lipid contained in the particle increases its size and decreases its density. *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *IDL,* intermediate density lipoprotein; *VLDL,* very-low-density lipoprotein.

triglycerides, or released into the circulation bound to albumin for transport to the liver. After hydrolysis of the triglyceride core from the chylomicron, apoC particles are recirculated back to HDL. The subsequent contribution of apoE from HDL to the remnant chylomicron facilitates binding of the particle to hepatic LDL receptors (LDL-R). Within the hepatocyte, the chylomicron remnant may be incorporated into membranes, resecreted as lipoprotein back into the circulation, or secreted as bile acids. Normally, all dietary fat is disposed of within 8 hr after the last meal, an exception being individuals with a disorder of chylomicron metabolism. Postprandial hyperlipidemia is a risk factor for atherosclerosis. Abnormal transport of chylomicrons and their remnants may result in their absorption into the blood vessel wall as foam cells, caused by the ingestion of cholesteryl esters by macrophages, the earliest stage in the development of fatty streaks.

Transport of Endogenous Lipids from the Liver

The formation and secretion of VLDL from the liver and its catabolism to IDL and LDL particles describe the endogenous lipoprotein pathway. Fatty acids used in the hepatic formation of VLDL are derived primarily by uptake from the circulation. VLDL appears to be transported from the liver as rapidly as it is synthesized, and it consists of triglycerides, cholesteryl esters, phospholipids, and apoB-100. Nascent particles of VLDL secreted into the circulation combine with apoC and apoE. The size of the VLDL particle is determined by the amount of triglyceride present, progressively shrinking in size as triglyceride is hydrolyzed by the action of LPL, yielding free fatty acids for utilization

Table 86-6 Characteristics of the Major Lipoproteins

LIPOPROTEIN	SOURCE	SIZE (nm)	DENSITY (g/mL)	Composition %		
				PROTEIN	LIPID	APOLIPOPROTEINS
Chylomicrons	Intestine	80-1,200	<0.95	1-2	98-99	C-I, C-II, C-III, E, A-I, A-II, A-IV, B-48
Chylomicron remnants	Chylomicrons	40-150	<1.0006	6-8	92-94	B-48, E
VLDL	Liver, intestine	30-80	0.95-1.006	7-10	90-93	B-100, C-I, C-II, C-III
IDL	VLDL	25-35	1.006-1.019	11	89	B-100, E
LDL	VLDL	18-25	1.019-1.063	21	79	B-100
HDL	Liver, intestine VLDL, Chylomicrons	5-20	1.125-1.210	32-57	43-68	A-I, A-II, A-IV C-I, C-II, C-III D, E

HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

or storage in muscle and adipose tissue. Hydrolysis of approximately 80% of the triglyceride present in VLDL particles produces IDL particles containing an equal amount of cholesterol and triglyceride. The remaining remnant IDL is converted to LDL for delivery to peripheral tissues or to the liver. ApoE is attached to the remnant IDL particle to allow binding to the cell and subsequent incorporation into the lysosome. Individuals with deficiency of either apoE2 or hepatic triglyceride lipase accumulate IDL in the plasma.

LDL particles account for approximately 70% of the plasma cholesterol in normal individuals. LDL receptors are present on the surfaces of nearly all cells. Most LDL is taken up by the liver, and the rest is transported to peripheral tissues such as the adrenal glands and gonads for steroid synthesis. Dyslipidemia is greatly influenced by LDL-R activity. The efficiency with which VLDL is converted into LDL is also important in lipid homeostasis.

High-Density Lipoprotein and Reverse Cholesterol Transport

As hepatic secretion of lipid particles into the bile is the only mechanism by which cholesterol can be removed from the body, transport of excess cholesterol from the peripheral cells is a vitally important function of HDL. HDL is heavily laden with apoA-I containing lipoproteins, which is nonatherogenic in contrast to B lipoproteins. Cholesterol-poor nascent HDL particles secreted by the liver and small intestine are esterified to more mature HDL-2 particles by the action of the enzyme lecithin-cholesterol acyltransferase (LCAT), which facilitates movement of chylomicrons and VLDL into the HDL core. HDL-2 may transfer cholesteryl esters back to apoB lipoproteins mediated by cholesteryl ester transfer protein (CETP), or the cholesterol-rich particle may be removed from the plasma by endocytosis, completing reverse cholesterol transport. Low HDL may be genetic (deficiency of apoA-I) or secondary to increased plasma triglyceride.

LCAT deficiency results in diminished maturation of HDL particles, affecting their ability to do reverse cholesterol transport. This reduces its protective effect on atherosclerosis. There are rare reports, however, of less-than-expected severity of atherosclerosis despite low HDL secondary to LCAT deficiency, suggesting that the relationship may, for unknown reasons, be variable.

HYPERLIPOPROTEINEMIAS

Hypercholesterolemia

See Table 86-7.

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a monogenic autosomal codominant disorder characterized by strikingly elevated LDL cholesterol, premature cardiovascular disease (CVD), and tendon xanthomas. In the past, FH referred to defects of LDL receptor activity. However, genetic studies have broadened our understanding of the etiology of this lipoprotein abnormality to include defects in the genes for ApoB, as well as proprotein convertase subtilisin/kexin type 9. Severe hypercholesterolemia predisposing to premature CHD may be caused by other genetic abnormalities yet to be discovered. Of the nearly 800 mutations described, some result in failure of synthesis of the LDL receptor (receptor negative) and others cause defective binding or release at the lipoprotein-receptor interface. Receptor negative mutations result in more severe phenotypes than receptor defective mutations.

Homozygous Familial Hypercholesterolemia

FH homozygotes inherit 2 abnormal LDL receptor genes, resulting in markedly elevated plasma cholesterol levels ranging between 500 and 1,200 mg/dL. Triglyceride levels are normal to mildly elevated, and HDL levels may be slightly decreased. The condition occurs in 1 in 1,000,000 persons. Receptor-negative patients have <2% normal LDL receptor activity, whereas those who are receptor-defective may have as much as 25% normal activity and a better prognosis.

The prognosis is poor regardless of the specific LDL receptor aberration. Severe atherosclerosis involving the aortic root and coronary arteries is present by early to mid-childhood. These children usually present with xanthomas, which may cause thickening of the Achilles tendon or extensor tendons of the hands, or cutaneous lesions on the hands, elbows, knees, or buttocks (Figs. 86-10, 86-11, and 86-12). Corneal arcus may be present. Family history is informative because premature heart disease is strongly prevalent among relatives of both parents. The diagnosis may be confirmed by measuring LDL receptor activity in cultured skin fibroblasts. Phenotypic expression of the disease may also be assessed by measuring receptor activity on the surface of lymphocytes by using cell sorting techniques.

Untreated homozygous patients rarely survive to adulthood. Symptoms of coronary insufficiency may occur; sudden death is common. LDL apheresis to selectively remove LDL particles from the circulation is recommended for many children as it slows the progression of atherosclerosis. Liver transplantation is also successful in decreasing LDL cholesterol levels, but complications related to immunosuppression are common. HMG-CoA reductase inhibitors may be modestly effective depending on the specific class of LDL receptor defect present. Combination therapy with ezetimibe, selectively blocking cholesterol adsorption in the gut, usually results in further decline in LDL levels; it has largely replaced the use of bile acid sequestrants. Early clinical trials using microsomal triglyceride transfer protein inhibition with lomitapide resulted in a significant reduction in all apoB lipoproteins, including LDL, but hepatic fat deposition as a side effect limits consideration of this pharmacologic approach at this time. Mipomersen, an antisense oligonucleotide that binds to the sequence that encodes apolipoprotein B, reduces the synthesis of apoB and thus also VLDL and LDL; LDL cholesterol levels may decline approximately 25% with this treatment. Adverse effects include flu-like symptoms, hepatic steatosis, and cirrhosis.

Table 86-7 Hyperlipoproteinemias

DISORDER	LIPOPROTEINS ELEVATED	CLINICAL FINDINGS	GENETICS	ESTIMATED INCIDENCE
Familial hypercholesterolemia	LDL	Tendon xanthomas, CHD	AD	1 in 500
Familial defective ApoB-100	LDL	Tendon xanthomas, CHD	AD	1 in 1,000
Autosomal recessive hypercholesterolemia	LDL	Tendon xanthomas, CHD	AR	<1 in 1,000,000
Sitosterolemia	LDL	Tendon xanthomas, CHD	AR	<1 in 1,000,000
Polygenic hypercholesterolemia	LDL	CHD		1 in 30?
Familial combined hyperlipidemia	LDL, TG	CHD	AD	1 in 200
Familial dysbetalipoproteinemia	LDL, TG	Tuberoeruptive xanthomas, peripheral vascular disease	AD	1 in 10,000
Familial chylomicronemia (Frederickson type I)	TG$\uparrow\uparrow$	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	1 in 1,000,000
Familial hypertriglyceridemia (Frederickson type IV)	TG$\uparrow$	±CHD	AD	1 in 500
Familial hypertriglyceridemia (Frederickson type V)	TG$\uparrow\uparrow$	Xanthomas ± CHD	AD	
Familial hepatic lipase deficiency	VLDL	CHD	AR	<1 in 1,000,000

AD, autosomal dominant; AR, autosomal recessive; CHD, coronary heart disease; LDL, low-density lipoproteins, TG, triglycerides; VLDL, very-low-density lipoproteins.

Figure 86-10 **Homozygous familial hypercholesterolemia.** Tendon xanthomas in a 5 yr old male with homozygous familial hypercholesterolemia noted at the knee **(A),** wrist **(B),** and Achilles **(C).** *(Modified from Macchiaiolo M, Gagliardi MG, Toscano A, et al: Homozygous familial hypercholesterolaemia.* Lancet *379:1330, 2012.)*

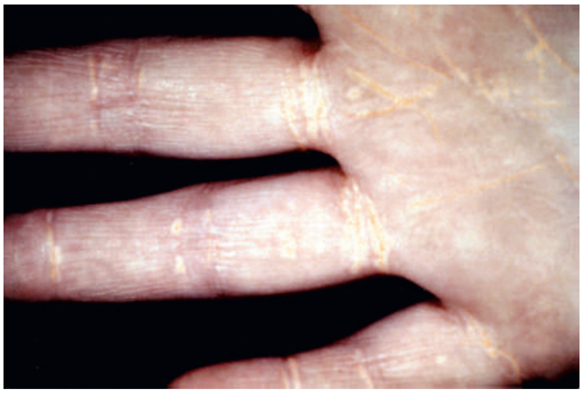

Figure 86-11 Striate palmar xanthomata. *(From Durrington P: Dyslipidaemia,* Lancet *362:717–731, 2003.)*

Figure 86-12 Eruptive xanthomata on extensor surface of forearm. *(From Durrington P: Dyslipidaemia,* Lancet *362:717–731, 2003.)*

Heterozygous Familial Hypercholesterolemia

Heterozygous FH is one of the most common single-gene mutations associated with acute coronary syndromes and atherosclerotic CHD in adults. Its prevalence is approximately 1 in 500 individuals worldwide, but the frequency may be as high as 1 in 250 in selected populations, such as French-Canadians, Afrikaners, and Christian Lebanese, as a result of the founder effect of unique new mutations.

Heart disease accounts for more than half of all deaths in Western society. The pathogenesis of CHD is both environmental and genetic, and the complex interrelationship between the 2 determines the phenotypic expression of disease. Chinese people with heterozygous FH living in China have a mean LDL cholesterol of 168 mg/dL, whereas immigrant Chinese with the disease living in Canada average 288 mg/dL. This dramatic disparity in lipoprotein levels between geographic locations is expected to narrow as dietary and physical activity practices in China approximate those of the industrialized West.

Because heterozygous FH is a codominant condition with nearly full penetrance, 50% of first-degree relatives of affected individuals will have the disease, as will 25% of 2nd-degree relatives. An estimated 10 million people have FH worldwide. Symptoms of CHD usually occur at the mean age of 45-48 yr in males, and a decade later in females. Genetic testing of individuals who fulfill clinical criteria for the diagnosis of heterozygous FH is positive approximately 80% of the time.

The World Health Organization has targeted FH for individualized intervention strategies because of its large effect on morbidity and mortality. A relatively small percentage of the population accounts for a disproportionately high share of the burden of CVD. The clinical expression of the disease is straightforward and treatment is effective.

One cannot overemphasize the importance of family history for suspecting the possibility of FH. Indeed, the whole basis for deciding which children should have blood cholesterol testing is determined by a family history of premature CHD and/or parental hypercholesterolemia. In fact, the risk of CHD in individuals with FH can be as high as 20 times greater than the general population.

Plasma levels of LDL cholesterol do not allow unequivocal diagnosis of FH heterozygotes, but values are generally twice normal for age because of 1 absent or dysfunctional allele. The U.S. MED-PED ("make early diagnosis–prevent early death") Program based in Utah has formulated diagnostic criteria. Similar criteria with minor variations exist in the United Kingdom and Holland. Within well-defined FH families, the diagnosis is reliably made according to LDL cutoff points. More stringent criteria are required to establish the diagnosis in previously undiagnosed families, requiring strong evidence of an autosomal inheritance pattern and higher LDL cutoff points. At a total cholesterol level of 310 mg/dL, only 4% of persons in the general population would have FH, whereas 95% of persons who were first-degree relatives of known cases would have the disease. The mathematical probability of FH, verified by molecular genetics, is derived from a U.S. population cohort and may not be applicable to other countries.

Very high cholesterol levels in children should prompt extensive screening of adult 1st- and 2nd-degree relatives ("reverse" cholesterol screening). A child younger than age 18 yr with total plasma cholesterol of 270 mg/dL and/or low-density lipoprotein-cholesterol (LDL-C) of 200 mg/dL has an 88% chance of having FH. *Formal clinical diagnosis of FH is based upon the presence of 2 or more family members having elevated LDL cholesterol levels greater than 220 mg/dL. It should be noted, however, that LDL-C level cutoff points vary with age* (Table 86-8). Conversely, criteria for diagnosing probable FH in a child whose first-degree relative has known FH require only modest elevation of total cholesterol to 220 mg/dL (LDL-C 155 mg/dL).

Treatment of children with FH should begin with a rather rigorous low-fat diet (see below). Diet alone is rarely sufficient for decreasing blood cholesterol levels to acceptable levels (LDL-C <130 mg/dL).

Ezetimibe blocks cholesterol adsorption in the gastrointestinal tract and has a low risk of side effects. Data suggest that ezetimibe will lower total cholesterol by 20-30 mg/dL. *HMG-CoA reductase inhibitors are the drug of choice for treatment of FH because of their remarkable effectiveness and acceptable risk profile.* There is sufficient clinical experience with this class of drugs in children to document that they are as effective in children as in adults, and the risks of elevated hepatic enzymes and myositis are no greater than in adults.

Familial Defective ApoB-100

Familial defective apoB-100 is an autosomal dominant condition that is indistinguishable from heterozygous FH. LDL cholesterol levels are increased, triglycerides are normal, adults often develop tendon

Table 86-8 Percentage of Youths Younger Than Age 18 Yr Expected to Have FH According to Cholesterol Levels and Closest Relative with FH

		Percentage With FH at That Level			
		Degree of Relative			
TOTAL CHOL (mg/dL)	LDL CHOL (mg/dL)	FIRST	SECOND	THIRD	GENERAL POPULATION
180	122	7.2	2.4	0.9	0.01
190	130	13.5	5.0	2.2	0.03
200	138	26.4	10.7	4.9	0.07
210	147	48.1	23.6	11.7	0.19
220	155	73.1	47.5	27.9	0.54
230	164	90.0	75.0	56.2	1.8
240	172	97.1	93.7	82.8	6.3
250	181	99.3	97.6	95.3	22.2
260	190	99.9	99.5	99.0	57.6
270	200	100.0	99.9	99.8	88.0
280	210	100.0	100.0	100.0	97.8
290	220	100.0	100.0	100.0	99.6
300	230	100.0	100.0	100.0	99.9
310	210	100.0	100.0	100.0	100.0

Chol, cholesterol; FH, familial hypercholesterolemia; LDL, low-density lipoprotein.

From Williams RR, Hunt SC, Schumacher MC, et al: Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics, Am J Cardiol *72:171–176, 1993.*

xanthomas, and premature CHD occurs. Familial defective apoB-100 is caused by mutation in the receptor binding region of apoB-100, the ligand of the LDL receptor, with an estimated frequency of 1 in 700 people in Western cultures. It is usually caused by substitution of glutamine for arginine in position 3500 in apoB-100, which results in reduced ability of the LDL receptor to bind LDL cholesterol, thus impairing its removal from the circulation. Specialized laboratory testing can distinguish familial defective apoB-100 from FH, but this is not necessary, except in research settings, because treatment is the same.

Autosomal Recessive Hypercholesterolemia

This rare condition, caused by a defect in LDL receptor–mediated endocytosis in the liver, clinically presents with severe hypercholesterolemia at levels intermediate between those found in homozygous and heterozygous FH. It is disproportionately present among Sardinians, and is modestly responsive to treatment with HMG-CoA reductase inhibitors.

Sitosterolemia

A rare autosomal recessive condition characterized by excessive intestinal adsorption of plant sterols, sitosterolemia is caused by mutations in the adenosine triphosphate-binding cassette transporter system, which is responsible for limiting adsorption of plant sterols in the small intestine and promotes biliary excretion of the small amounts adsorbed. Plasma cholesterol levels may be severely elevated, resulting in tendon xanthomas and premature atherosclerosis. Diagnosis can be confirmed by measuring elevated plasma sitosterol levels. Treatment with HMG-CoA reductase inhibitors is not effective, but cholesterol adsorption inhibitors, such as ezetimibe, and bile acid sequestrants are effective.

Polygenic Hypercholesterolemia

Primary elevation in LDL cholesterol among children and adults is most often polygenic; the small effects of many genes are impacted by environmental influences (diet). Plasma cholesterol levels are modestly elevated; triglyceride levels are normal. Polygenic hypercholesterolemia aggregates in families sharing a common lifestyle but does not follow predictable hereditary patterns found in single-gene lipoprotein defects. Treatment of children with polygenic hypercholesterolemia is directed toward adoption of a healthy lifestyle: reduced total and saturated fat consumption and at least 1 hr of physical activity daily. Cholesterol-lowering medication is rarely necessary.

Hypercholesterolemia with Hypertriglyceridemia

Familial Combined Hyperlipidemia

This is an autosomal dominant condition characterized by moderate elevation in plasma LDL cholesterol and triglycerides, and reduced plasma HDL cholesterol. It is the most common primary lipid disorder, occurring in approximately 1/200 people. Family history of premature heart disease is typically positive; the formal diagnosis requires that at least two first-degree relatives have evidence of one of three variants of dyslipidemia: (1) >90th percentile plasma LDL cholesterol; (2) >90th percentile LDL cholesterol and triglycerides; and (3) >90th percentile triglycerides. Individuals switch from one phenotype to another. Xanthomas are not a feature of familial combined hyperlipidemia (FCHL). Elevated plasma apoB levels with increased small dense LDL particles support the diagnosis.

Children and adults with FCHL have coexisting adiposity, hypertension, and hyperinsulinemia, suggesting the presence of the *metabolic syndrome.* Formal diagnosis in adults of this syndrome as defined by the National Cholesterol Education Program (NCEP)'s Adult Treatment Panel III identifies 6 major components: abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance with or without impaired glucose tolerance, evidence of vascular inflammation, and prothrombotic state. It is estimated that 30% of overweight adults fulfill criteria for the diagnosis of metabolic syndrome, including 65% of those with FCHL. Hispanics and South Asians from the Indian subcontinent are especially susceptible. There is no official definition of metabolic syndrome for children. Absolute cutoffs for diagnosis in children do not account for continuous variables in aging, sexual maturation, and race/ethnicity.

FCHL and type II diabetes share many features of the metabolic syndrome, suggesting that they are less distinct entities than originally conceptualized. Genetic association studies reveal evidence for a common genetic background. The resultant metabolic overlap is associated with ectopic fat accumulation and insulin resistance. The mechanisms associating visceral adiposity with the metabolic syndrome and type II diabetes are not fully understood. A plausible unifying principle is that obesity causes endoplasmic reticulum stress, leading to suppression of insulin receptor signaling and thus insulin resistance and heightened inflammatory response. How this relates to atherogenesis is unclear. It is assumed that hypercholesterolemia and, with less certainty, hypertriglyceridemia confer risk for CVD in patients with FCHL. When features of the metabolic syndrome are included in logistic models shared etiologic features such as increased visceral adiposity become apparent. Visceral adiposity increases with age and its importance in children as a risk factor for heart disease and diabetes is limited by the relative paucity of data. Although longitudinal measurement of waist circumference and the presence of intraabdominal fat as determined by MRI is being conducted in the research setting, body mass index (BMI) remains the surrogate for adiposity in the pediatric clinical setting.

The metabolic syndrome is a dramatic illustration of the interaction of genetics and the environment. Genetic susceptibility is essential as an explanation for premature heart disease in individuals with FCHL. Unhealthy lifestyle, poor diet, and physical inactivity contribute to obesity and attendant features of the metabolic syndrome.

The cornerstone of management is lifestyle modification. This includes a diet low in saturated fats, trans fats, and cholesterol, as well as reduced consumption of simple sugars. Increased dietary intake of fruits and vegetables is important, as is 1 hr of moderate physical activity daily. Compliance among children and their parents is often a problem, but small incremental steps are more likely to succeed than aggressive weight-loss strategies. It is very important that the child's caregivers participate in the process. Plasma triglyceride levels are usually quite responsive to dietary restriction, especially reduction in the amount of sweetened drinks consumed. Blood cholesterol levels may decrease by 10-15%, but if LDL cholesterol remains >160 mg/dL, drug therapy should be considered.

Familial Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)

Familial dysbetalipoproteinemia (FDBL) is caused by mutations in the gene for apoE, which when exposed to environmental influences such as high fat, high caloric diet, or excessive alcohol intake, results in a mixed type of hyperlipidemia. Patients tend to have elevated plasma cholesterol and triglycerides to a relatively similar degree. HDL cholesterol is typically normal in contrast to other causes of hypertriglyceridemia associated with low HDL. This rare disorder affects approximately 1 in 10,000 persons. ApoE mediates removal of chylomicron and VLDL remnants from the circulation by binding to hepatic surface receptors. The polymorphic *apoE* gene expresses in 3 isoforms: *apoE3, apoE2,* and *apoE4. E4* is the "normal" allele present in the majority of the population. The *apoE2* isoform has lower affinity for the LDL receptor and its frequency is approximately 7%. Approximately 1% of the population is homozygous for *apoE2/E2,* the most common mutation associated with FDBL, but only a minority expresses the disease. Expression requires precipitating illnesses such as diabetes, obesity, renal disease, or hypothyroidism. Individuals homozygous for *apoE4/E4* are at risk for late-onset Alzheimer disease and dementia from repeated sports-related head injuries.

Most patients with FDBL present in adulthood with distinctive xanthomas. Tuberoeruptive xanthomas resemble small grape-like clusters on the knees, buttocks, and elbows. Prominent orange-yellow discoloration of the creases of the hands (palmar xanthomas) is also typically present. Atherosclerosis, often presenting with peripheral vascular

disease, usually occurs in the 4th or 5th decade. Children may present with a less-distinctive rash and generally have precipitating illnesses.

The diagnosis of FDBL is established by lipoprotein electrophoresis, which demonstrates a broad beta band containing remnant lipoproteins. Direct measurement of VLDL by ultracentrifugation can be performed in specialized lipid laboratories. A VLDL : total triglyceride ratio >0.30 supports the diagnosis. *ApoE* genotyping for *apoE2* homozygosity can be performed, confirming the diagnosis in the presence of the distinctive physical findings. A negative result does not necessarily rule out the disease as other mutations in *apoE* may cause even more serious manifestations.

Pharmacologic treatment of FDBL is necessary to decrease the likelihood of symptomatic atherosclerosis in adults. HMG-CoA reductase inhibitors, nicotinic acid, and fibrates are all effective. FDBL is quite responsive to recommended dietary restriction.

Hypertriglyceridemias

The familial disorders of triglyceride-rich lipoproteins include both common and rare variants of the Frederickson classification system. These include chylomicronemia (type I), familial hypertriglyceridemia (type IV), and the more severe combined hypertriglyceridemia and chylomicronemia (type V). Hepatic lipase deficiency also results in a similar combined hyperlipidemia.

Familial Chylomicronemia (Type I Hyperlipidemia)

This rare single-gene defect, like FH, is caused by mutations affecting clearance of apoB-containing lipoproteins. Deficiency or absence of LPL or its cofactor apoC-II, which facilitates lipolysis by LPL, causes severe elevation of triglyceride rich plasma chylomicrons. HDL cholesterol levels are decreased. As clearance of these particles is markedly delayed, the plasma is noted to have a turbid appearance even after prolonged fasting (Fig. 86-13). Chylomicronemia caused by LPL deficiency is associated with modest elevation in triglycerides, whereas this is not the case when the cause is deficient or absent apoC-II. Both are autosomal recessive conditions with a frequency of approximately 1 in 1,000,000. The disease usually presents during childhood with acute pancreatitis. Eruptive xanthomas on the arms, knees, and buttocks may be present, and there may be hepatosplenomegaly. The diagnosis is established by assaying triglyceride lipolytic activity. Treatment of chylomicronemia is by vigorous dietary fat restriction supplemented by fat-soluble vitamins. Medium-chain triglycerides that are adsorbed into the portal venous system may augment total fat intake, and administration of fish oils may also be beneficial.

Figure 86-13 Milky plasma from patient with acute abdominal pain. *(From Durrington P: Dyslipidaemia,* Lancet *362:717–731, 2003.)*

Familial Hypertriglyceridemia (Type IV Hyperlipidemia)

Familial hypertriglyceridemia (FHTG) is an autosomal dominant disorder of unknown etiology that occurs in approximately 1 in 500 individuals. It is characterized by elevation of plasma triglycerides >90th percentile (250-1,000 mg/dL range), often accompanied by slight elevation in plasma cholesterol and low HDL. FHTG does not usually manifest until adulthood, although it is expressed in approximately 20% of affected children. In contrast to FCHL, FHTG is not thought to be highly atherogenic. It is most likely caused by defective breakdown of VLDL, or less often by overproduction of this class of lipoproteins.

The diagnosis should include the presence of at least one first-degree relative with hypertriglyceridemia. FHTG should be distinguished from FCHL and FDBL, as the latter require more vigorous treatment to prevent coronary or peripheral vascular disease. The differentiation is usually possible on clinical grounds, in that lower LDL cholesterol levels accompany FHTG, but measurement of normal apoB levels in FHTG may be helpful in ambiguous situations.

A more severe hypertriglyceridemia characterized by increased levels of chylomicrons as well as VLDL particles (Frederickson type V) may occasionally be encountered. Triglyceride levels are often >1,000 mg/dL. The disease is rarely seen in children. In contrast to chylomicronemia (Frederickson type I), LPL or apoC-II deficiency is not present. These patients often develop eruptive xanthomas in adulthood, whereas type IV hypertriglyceridemia individuals do not. Acute pancreatitis may be the presenting illness. As with other hypertriglyceridemias, excessive alcohol consumption and estrogen therapy can exacerbate the disease.

Secondary causes of transient hypertriglyceridemia should be ruled out before making a diagnosis of FHTG. A diet high in simple sugars and carbohydrates, or excessive alcohol consumption as well as estrogen therapy may exacerbate hypertriglyceridemia. Adolescents and adults should be questioned about excessive consumption of soda and other sweetened drinks, as it is common to encounter people who drink supersized drinks or multiple 12 oz cans of sweetened drinks daily. Cessation of this practice often results in dramatic fall in triglyceride levels as well as weight among those who are obese. HDL cholesterol levels will tend to rise as BMI stabilizes.

Pediatric diseases associated with hyperlipidemia include hypothyroidism, nephrotic syndrome, biliary atresia, glycogen storage disease, Niemann-Pick disease, Tay-Sachs disease, systemic lupus erythematosus, hepatitis, and anorexia nervosa (Table 86-9). Certain medications exacerbate hyperlipidemia, including isotretinoin (Accutane), thiazide diuretics, oral contraceptives, steroids, β blockers, immunosuppressants, and protease inhibitors used in the treatment of HIV.

Treatment of hypertriglyceridemia in children rarely requires medication unless levels >1,000 mg/dL persist after dietary restriction of fats, sugars, and carbohydrates, accompanied by increased physical activity. In such cases, the aim is to prevent episodes of pancreatitis. The common use of fibrates (fenofibric acid) and niacin in adults with hypertriglyceridemia is not recommended in children. HMG-CoA reductase inhibitors are reasonably effective in lowering triglyceride levels, and there is considerably more experience documenting the safety and efficacy of this class of lipid-lowering medications in children. In adults, prescription (Lovaza, Vascepa) and nonprescription fish oils have been approved by the FDA as adjuncts to diet in the treatment of severe hypertriglyceridemias.

Table 86-9	Secondary Causes of Hyperlipidemia
HYPERCHOLESTEROLEMIA	
Hypothyroidism	
Nephrotic syndrome	
Cholestasis	
Anorexia nervosa	
Drugs: progesterone, thiazides, Tegretol, cyclosporine	
HYPERTRIGLYCERIDEMIA	
Obesity	
Type II diabetes	
Alcohol	
Renal failure	
Sepsis	
Stress	
Cushing syndrome	
Pregnancy	
Hepatitis	
AIDS, protease inhibitors	
Drugs: anabolic steroids, β blockers, estrogen, thiazides	
REDUCED HIGH-DENSITY LIPOPROTEIN	
Smoking	
Obesity	
Type II diabetes	
Malnutrition	
Drugs: β Blockers, anabolic steroids	

Hepatic Lipase Deficiency

Hepatic lipase deficiency is a very rare autosomal recessive condition causing elevation in both plasma cholesterol and triglycerides. Hepatic lipase hydrolyzes triglycerides and phospholipids in VLDL remnants and IDL, preventing their conversion to LDL. HDL cholesterol levels tend to be increased rather than decreased, suggesting the diagnosis. Laboratory confirmation is established by measuring hepatic lipase activity in heparinized plasma.

Disorders of High-Density Lipoprotein Metabolism

Primary Hypoalphalipoproteinemia

Isolated low HDL cholesterol is a familial condition that often follows a pattern suggestive of autosomal dominant inheritance but may occur independent of family history. It is the most common disorder of HDL metabolism. It is defined as HDL cholesterol <10th percentile for gender and age with normal plasma triglycerides and LDL cholesterol. Whether it is associated with more rapid atherosclerosis is uncertain. It appears to be related to a reduction in apoA-I synthesis and increased catabolism of HDL. Secondary causes of low HDL cholesterol, such as the metabolic syndrome, and rare diseases such as LCAT deficiency and Tangier disease must be ruled out.

Familial Hyperalphalipoproteinemia

This is an unusual condition conferring deceased risk for CHD among family members. Plasma levels of HDL cholesterol exceed 80 mg/dL.

Familial Apolipoprotein A-I Deficiency

Mutations in the *apoA-I* gene may result in complete absence of plasma HDL. Nascent HDL is produced in the liver and small intestine. Free cholesterol from peripheral cells is esterified by LCAT, enabling formation of mature HDL particles. ApoA-I is required for normal enzymatic functioning of LCAT. The resultant accumulation of free cholesterol in the circulation eventually leads to corneal opacities, planar xanthomas, and premature atherosclerosis. Some patients, however, may have mutations of *apoA-I* that result in very rapid catabolism of the protein not associated with atherogenesis, despite HDL cholesterol levels in the 15-30 mg/dL range.

Tangier Disease

This is an autosomal codominant disease associated with levels of HDL cholesterol <5 mg/dL. It is caused by mutations in ABCA1, a protein that facilitates the binding of cellular cholesterol to apoA-I. This results in free cholesterol accumulation in the reticuloendothelial system manifested by tonsillar hypertrophy of a distinctive orange color and hepatosplenomegaly. Intermittent peripheral neuropathy may occur from cholesterol accumulation in Schwann cells. Diagnosis should be suspected in children with enlarged orange tonsils and extremely low HDL cholesterol levels.

Familial Lecithin–Cholesterol Acyltransferase Deficiency

Mutations affecting LCAT interfere with the esterification of cholesterol, thereby preventing formation of mature HDL particles. This is associated with rapid catabolism of apoA-I. Free circulating cholesterol in the plasma is greatly increased, which leads to corneal opacities and HDL cholesterol levels <10 mg/dL. Partial LCAT deficiency is known as “fish-eye” disease. Complete deficiency causes hemolytic anemia and progressive renal insufficiency early in adulthood. This rare disease is not thought to cause premature atherosclerosis. Laboratory confirmation is based on demonstration of decreased cholesterol esterification in the plasma.

Cholesteryl Ester Transfer Protein Deficiency

Mutations involving the *CETP* gene are localized to chromosome 16y21. CETP facilitates the transfer of lipoproteins from mature HDL to and from VLDL and chylomicron particles, thus ultimately regulating the rate of cholesterol transport to the liver for excretion in the bile. About half of mature HDL-2 particles are directly removed from the circulation by HDL receptors on the surface of the liver. The other half of cholesteryl esters in the core of HDL exchange with triglycerides in the core of apoB lipoproteins (VLDL, IDL, LDL) for transport to the liver. Homozygous deficiency of CETP has been observed in subsets of the Japanese population with extremely high HDL cholesterol levels (>150 mg/dL).

Conditions Associated with Low Cholesterol

Disorders of apoB-containing lipoproteins and intracellular cholesterol metabolism are associated with low plasma cholesterol.

Abetalipoproteinemia

This rare autosomal recessive disease is caused by mutations in the gene encoding microsomal triglyceride transfer protein necessary for the transfer of lipids to nascent chylomicrons in the small intestine and VLDL in the liver. This results in absence of chylomicrons, VLDL, LDL, and apoB, and very low levels of plasma cholesterol and triglycerides. Fat malabsorption, diarrhea, and failure to thrive present in early childhood. Spinocerebellar degeneration, secondary to vitamin E deficiency, manifests in loss of deep tendon reflexes progressing to ataxia and lower extremity spasticity by adulthood. Patients with abetalipoproteinemia also acquire a progressive pigmented retinopathy associated with decreased night and color vision and eventual blindness. The neurologic symptoms and retinopathy may be mistaken for Friedreich ataxia. Differentiation from Friedreich ataxia is suggested by the presence of malabsorption and acanthocytosis on peripheral blood smear in abetalipoproteinemia. Many of the clinical manifestations of the disease are a result of malabsorption of fat-soluble vitamins, such as vitamins E, A, and K. Early treatment with supplemental vitamins, especially E, may significantly slow the development of neurologic sequelae. Vitamin E is normally transported from the small intestine to the liver by chylomicrons, where it is dependent on the endogenous VLDL pathway for delivery into the circulation and peripheral tissues. Parents of children with abetalipoproteinemia have normal blood lipid and apoB levels.

Familial Hypobetalipoproteinemia

Familial homozygous hypobetalipoproteinemia is associated with symptoms very similar to those of abetalipoproteinemia, but the inheritance pattern is autosomal codominant. The disease is caused by mutations in the gene encoding apoB-100 synthesis. It is distinguishable from abetalipoproteinemia in that heterozygous parents of probands

Table 86-10 Major Clinical Characteristics of Smith-Lemli-Opitz Syndrome: Frequent Anomalies (>50% of Patients)

CRANIOFACIAL
Microcephaly
Blepharoptosis
Anteverted nares
Retromicrognathia
Low-set, posteriorly rotated ears
Midline cleft palate
Broad maxillary alveolar ridges
Cataracts (<50%)
SKELETAL ANOMALIES
Syndactyly of toes II/III
Postaxial polydactyly (<50%)
Equinovarus deformity (<50%)
GENITAL ANOMALIES
Hypospadias
Cryptorchidism
Sexual ambiguity (<50%)
DEVELOPMENT
Pre- and postnatal growth retardation
Feeding problems
Mental retardation
Behavioral abnormalities

From Haas D, Kelley RI, Hoffmann GF: Inherited disorders of cholesterol biosynthesis, Neuropediatrics *32:113–122, 2001.*

Table 86-11 Characteristic Malformations of Internal Organs in Severely Affected Smith-Lemli-Opitz Patients

CENTRAL NERVOUS SYSTEM
Frontal lobe hypoplasia
Enlarged ventricles
Agenesis of corpus callosum
Cerebellar hypoplasia
Holoprosencephaly
CARDIOVASCULAR
Atrioventricular canal
Secundum atrial septal defect
Patent ductus arteriosus
Membranous ventricular septal defect
URINARY TRACT
Renal hypoplasia or aplasia
Renal cortical cysts
Hydronephrosis
Ureteral duplication
GASTROINTESTINAL
Hirschsprung disease
Pyloric stenosis
Refractory dysmotility
Cholestatic and noncholestatic progressive liver disease
PULMONARY
Pulmonary hypoplasia
Abnormal lobation
ENDOCRINE
Adrenal insufficiency

From Haas D, Kelley RI, Hoffmann GF: Inherited disorders of cholesterol biosynthesis, Neuropediatrics *32:113–122, 2001.*

have plasma LDL cholesterol and apoB levels less than half normal. There are no symptoms or sequelae associated with the heterozygous condition.

The selective inability to secrete apoB-48 from the small intestine results in a condition resembling abetalipoproteinemia or homozygous hypobetalipoproteinemia. Sometimes referred to as Anderson disease, the failure of chylomicron absorption causes steatorrhea and fat-soluble vitamin deficiency. The blood level of apoB-100, derived from normal hepatocyte secretion, is normal in this condition.

Smith-Lemli-Opitz Syndrome

Patients with Smith-Lemli-Opitz syndrome (SLOS) often have multiple congenital anomalies and developmental delay caused by low plasma cholesterol and accumulated precursors (Tables 86-10 and 86-11). Family pedigree analysis has revealed its autosomal recessive inheritance pattern. Mutations in the *DHCR7* (7-dehydrocholesterol-Δ7 reductase) gene result in deficiency of the microsomal enzyme DHCR7, which is necessary to complete the final step in cholesterol synthesis. It is not known why defects in cholesterol synthesis result in congenital malformations, but as cholesterol is a major component of myelin and a contributor to signal transduction in the developing nervous system, neurodevelopment is severely impaired. The incidence of SLOS is estimated to be 1 in 20,000-60,000 births among whites, with a somewhat higher frequency in Hispanics and lower incidence in individuals of African descent.

Spontaneous abortion of SLOS fetuses may occur. Type II SLOS often leads to death by the end of the neonatal period. Survival is unlikely when the plasma cholesterol level is <20 mg/dL. Laboratory measurement should be performed by gas chromatography, as standard techniques for lipoprotein assay include measurement of cholesterol precursors, which may yield a false-positive result. Milder cases may not present until late childhood. Phenotypic variance ranges from microcephaly, cardiac and brain malformation, and multiorgan system failure to only subtle dysmorphic features and mild developmental delay. Treatment includes supplemental dietary cholesterol (egg yolk) and HMG-CoA reductase inhibition to prevent the synthesis of toxic precursors proximal to the enzymatic block.

Disorders of Intracellular Cholesterol Metabolism

Cerebrotendinous Xanthomatosis

This autosomal recessive disorder presents clinically in late adolescence with tendon xanthomas, cataracts, and progressive neurodegeneration. It is caused by tissue accumulation of bile acid intermediates shunted into cholestanol resulting from mutations in the gene for sterol 27-hydroxylase. This enzyme is necessary for normal mitochondrial synthesis of bile acids in the liver. Early treatment with chenodeoxycholic acid reduces cholesterol levels and prevents the development of symptoms.

Wolman Disease and Cholesterol Ester Storage Disease

These autosomal recessive disorders are caused by lack of lysosomal acid lipase. After LDL cholesterol is incorporated into the cell by endocytosis, it is delivered to lysosomes where it is hydrolyzed by lysosomal lipase. Failure of hydrolysis because of complete absence of the enzyme causes accumulation of cholesteryl esters within the cells. Hepatosplenomegaly, steatorrhea, and failure to thrive occur during early infancy, leading to death by the age of 1 yr. In cholesterol ester storage disease, a less-severe form than Wolman disease, there is low but detectable acid lipase activity.

Niemann-Pick Disease Type C

This is a disorder of intracellular cholesterol transport characterized by accumulation of cholesterol and sphingomyelin in the central nervous and reticuloendothelial systems. Death from this autosomal recessive neurologic disease usually occurs by adolescence.

Lipoprotein Patterns in Children and Adolescents

Table 86-12, derived primarily from the Lipid Research Clinics Population Studies, shows the distribution of lipoprotein levels in American

Table 86-12 Plasma Cholesterol and Triglyceride Levels in Childhood and Adolescence: Means and Percentiles

	Total Triglyceride (mg/dL)					Total Cholesterol (mg/dL)					Low-Density Lipoprotein Cholesterol (mg/dL)					High-Density Lipoprotein Cholesterol (mg/dL)*				
	5TH	MEAN	75TH	90TH	95TH	5TH	MEAN	75TH	90TH	95TH	5TH	MEAN	75TH	90TH	95TH	5TH	10TH	25TH	MEAN	95TH
Cord	14	34	—	—	84	42	68	—	—	103	17	29	—	—	50	13	—	—	35	60
1-4 YR																				
Male	29	56	68	85	99	114	155	170	190	203	—	—	—	—	—	—	—	—	—	—
Female	34	64	74	95	112	112	156	173	188	200	—	—	—	—	—	—	—	—	—	—
5-9 YR																				
Male	28	52	58	70	85	125	155	168	183	189	63	93	103	117	129	38	42	49	56	74
Female	32	64	74	103	126	131	164	176	190	197	68	100	115	125	140	36	38	47	53	73
10-14 YR																				
Male	33	63	74	94	111	124	160	173	188	202	64	97	109	122	132	37	40	46	55	74
Female	39	72	85	104	120	125	160	171	191	205	68	97	110	126	136	37	40	45	52	70
15-19 YR																				
Male	38	78	88	125	143	118	153	168	183	191	62	94	109	123	130	30	34	39	46	63
Female	36	73	85	112	126	118	159	176	198	207	59	96	111	29	137	35	38	43	52	74

*Note that different percentiles are listed for HDL cholesterol.

Data for cord blood from Strong W: Atherosclerosis: its pediatric roots. In Kaplan N, Stamler J, editors: Prevention of coronary heart disease, *Philadelphia, 1983, WB Saunders. Data for children 1-4 yr from Tables 6, 7, 20, and 21, and all other data from Tables 24, 25, 32, 33, 36, and 37 in* Lipid research clinics population studies data book, *Vol. 1, "The prevalence study," NIH publication No. 80-1527. Washington, DC, 1980, National Institutes of Health.*

youth at various ages. Total plasma cholesterol rises rapidly from a mean of 68 mg/dL at birth to a level approximately twice that by the end of the neonatal period. A very gradual rise in total cholesterol level occurs until puberty, at which time the mean level reaches 160 mg/dL. Total cholesterol falls transiently during puberty, in males because of a small decrease in HDL cholesterol, and in females secondary to a slight fall in LDL cholesterol. Blood cholesterol levels track reasonably well as individuals age.

High blood cholesterol tends to aggregate in families, a reflection of genetic and environmental influences.

Acceptable total cholesterol among children and adolescents is <170 mg/dL; borderline is 170-199 mg/dL; and high >200 mg/dL. Acceptable LDL cholesterol is <110 mg/dL; borderline 110-129 mg/dL; and high >130 mg/dL. HDL cholesterol should be >40 mg/dL.

Blood Cholesterol Screening

Previous guidelines for cholesterol measurement in children utilized a *targeted approach*. This meant obtaining a fasting lipid panel in a select group of children between the ages of 2 and 10 yr who met at least 1 of the following criteria:

- Parents or grandparents have documented premature coronary artery disease (before the age of 55 yr if male and 65 yr if female)
- Parents have been found to have high blood concentration of cholesterol (>240 mg/dL)
- Family history is unobtainable, particularly those with other risk factors such as obesity, hypertension, smoking, and/or diabetes mellitus.

Reliance on family history of premature heart disease or known parental heart disease, or known parental hypercholesterolemia was considered by some to be too insensitive and difficult to apply. Data from a large cohort of 5th grade school children who had comprehensive screening of CVD risk factors conducted by the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project, which utilized a *universal screening* approach, found 36% of children with severe dyslipidemia did not fulfill criteria for the selective screening approach.

The American Academy of Pediatrics began recommending a universal screening approach for cholesterol screening to all children in 2011. They recommend a lipid profile to be checked for all children between the ages of 9 and 11 yr and then another between ages 17 and 21 yr as cholesterol levels may vary after puberty. However, if a child would have met the selective criteria from the previous guidelines, then screening can occur as early as age 2 yr. Of note, new data suggest that obtaining a nonfasting lipid profile can be just as useful in detecting severe genetic dyslipidemias as a fasting lipid profile, and thus, can be used as the first line of screening in children. Fasting lipid profiles may also be used depending on parental, child, and clinician preference, especially if there is concern for hypertriglyceridemia, as triglycerides are more affected by fasting status.

If a nonfasting lipid profile is used and reveals a non-HDL cholesterol (total cholesterol − HDL cholesterol) >145 mg/dL, then 2 separate **fasting** lipid profiles should be obtained at least 2 wk apart but within 3 mo of each other and the results averaged together to confirm the abnormality. If a fasting lipid profile is initially used and reveals an LDL-C ≥130 mg/dL, then another fasting lipid profile at least 2 wk apart but within 3 mo should be obtained and the results averaged together. In summary, children with suspected dyslipidemias should have results confirmed with 2 separate **fasting** lipid profiles.

Risk Assessment and Treatment of Hyperlipidemia

The NCEP recommends a population-based approach toward healthy lifestyle applicable to all children, and an individualized approach directed at those children at high risk (Fig. 86-14). The important focus on maintenance of a healthy lifestyle rather than aggressive weight reduction is recommended by the American Academy of Pediatrics.

All children with dyslipidemias are stratified according to the presence of "high-level" or "moderate-level" risk factors to determine their ultimate treatment. High-level risk factors are defined as the following: hypertension requiring drug therapy (blood pressure ≥99th percentile + 5 mm Hg), current cigarette smoker, BMI at the ≥ 97th percentile, presence of type I or type II diabetes mellitus, chronic kidney disease, postorthoptic heart transplant, and/or Kawasaki disease with current aneurysms. Moderate-level risk factors are defined as the following: hypertension that does not require drug therapy, BMI at the ≥95th percentile but <97th percentile, HDL cholesterol <40 mg/dL, Kawasaki disease with regressed coronary aneurysms, chronic inflammatory disease, HIV infection, and/or presence of nephrotic syndrome.

The initial treatment for dyslipidemia in a child always begins with a 6-mo trial of lifestyle modification, namely, changes in dietary and physical activity patterns. Being overweight confers special risk of CVD because of the strong association with the insulin resistance syndrome (metabolic syndrome). Although there is no standardized definition of metabolic syndrome defined for youth, it is likely that half of all severely obese children are insulin resistant. Data from the CARDIAC project noted that 49% of 5th grade children with the hyperpigmented rash, acanthosis nigricans, had 3 or more factors for the insulin resistance syndrome when using the definition classically used for adults, including evidence of insulin resistance, hypertension, HDL cholesterol <40 mg/dL, triglycerides >150 mg/dL, in addition to obesity.

The Cardiovascular Health Integrated Lifestyle Diet-1 (CHILD-1) diet is the first level of dietary change to be recommended for all children with dyslipidemias. The CHILD-1 diet is specially designed for children with risk factors for coronary artery disease and focuses on such things as limitation of dietary cholesterol to no more than 300 mg/day, limitation of sugary drink consumption, use of reduced fat/skim milk, avoiding foods high in *trans*-type fats, limitation of foods high in sodium, and encouraging consumption of foods high in fiber. Specific recommendations are dependent on the child's age.

The use of the Cardiovascular Health Integrated Lifestyle Diet-2 (CHILD-2) diet is recommended if the CHILD-1 diet alone is unsuccessful. Although similar in many aspects to the CHILD-1 diet, the CHILD-2 diet is geared toward a specific dyslipidemia type, where the CHILD-2 LDL diet is recommended for those children with elevated LDL levels and the CHILD-2 TG diet is recommended for those children presenting with elevated triglycerides. The basic recommendations of calorie consumption for the CHILD-2 diet are as follows: only 25% to 30% of calories from fat, less than or equal to 7% of calories from saturated fat about 10% of calories from monounsaturated fat, less than 200 mg/d of cholesterol. If the CHILD-2 LDL diet is recommended, the use of plant sterols and water-soluble fiber is emphasized. If the CHILD-2 TG diet is recommended, the increasing consumption of complex carbohydrates and omega-3 fatty acids is emphasized.

If followed, these dietary recommendations will provide adequate calories for optimal growth and development without promoting obesity. Compliance on the part of children and their caregivers is challenging in today's society. Children learn eating habits from their parents. Successful adoption of a healthier lifestyle is far more likely to occur if meals and snacks in the home are applicable to the entire family rather than an individual child. A regular time for meals together as a family is desirable. Grandparents and other nonparental caregivers sometimes need to be reminded not to indulge the child who is on a restricted diet. Additionally, the rise in obesity is prompting some school districts to restrict sweetened drink availability, and offer more nutritious cafeteria selections.

As mentioned, changes in physical activity habits are also an important part of the initial lifestyle modification. The National Association for Sport and Physical Education recommends that children should accumulate at least 60 minutes of age-appropriate physical activity on most days of the week. Extended periods (2 hr or more) of daytime inactivity are discouraged, as is more than 2 hr of television and other forms of screen time. Unfortunately, the continued rise in sedentary activity among our youth contributes to the increase in obesity nationwide, which in turn, leads to the increasing prevalence of other risk factors such as hypertension.

Pharmacologic Therapy. See Tables 86-13 and 86-14.

The use of pharmacotherapy to treat dyslipidemias in children has been advocated by the American Academy of Pediatrics since the

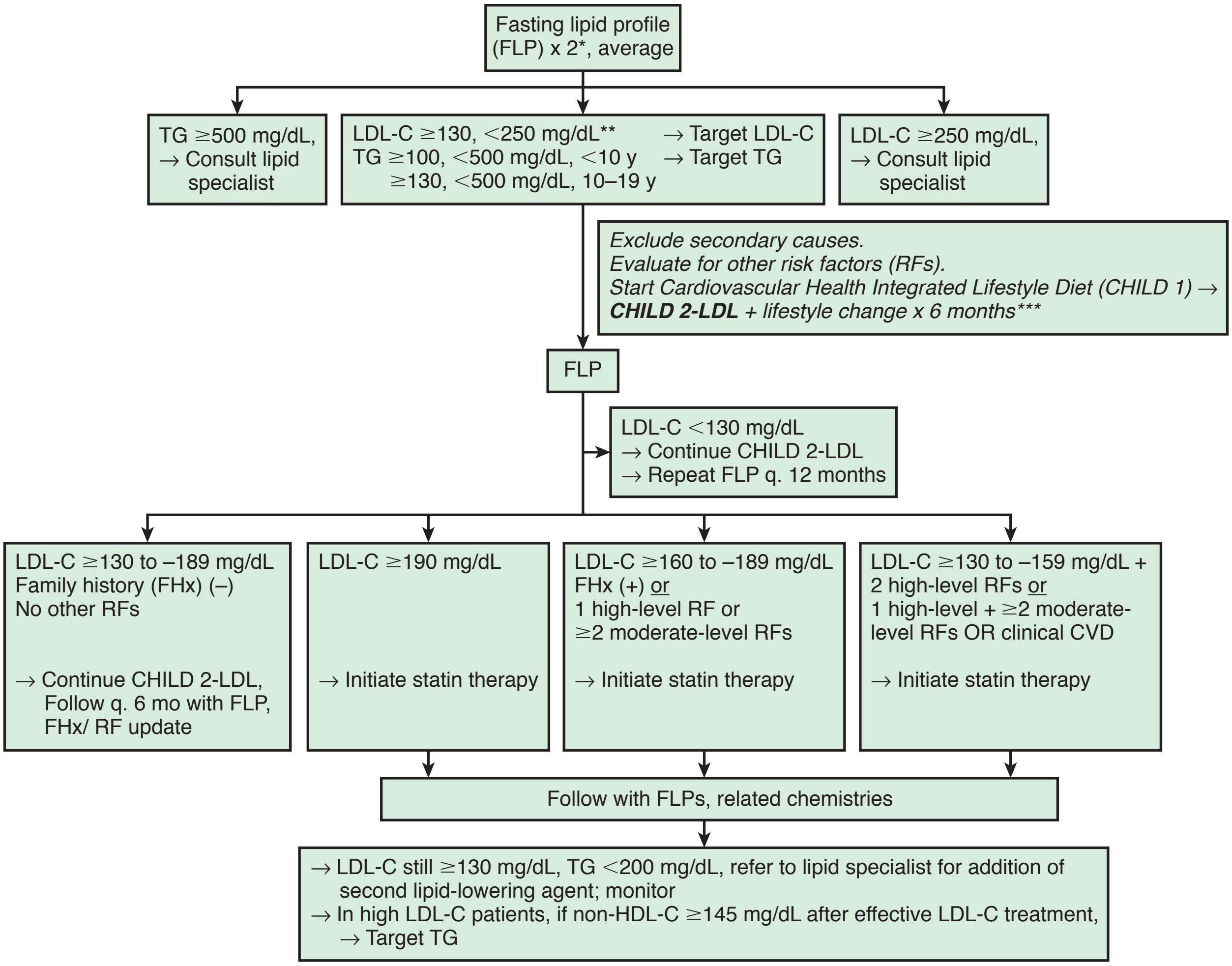

* Obtain FLPs at least 2 weeks but no more than 3 months apart.
** Use of drug therapy is limited to children ≥10 y with defined risk profiles.
*** In a child with LDL-C >190 mg/dL and other RFs, trial of CHILD 2 LDL diet may be abbreviated.

Figure 86-14 Algorithm of the evaluation, risk assessment, follow-up, and treatment of children based on low-density lipoprotein (LDL) cholesterol levels. *FLP*, fasting lipid profile; *TG*, triglycerides. *(From Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary report.* Pediatrics *128(Suppl 5):S213–S256, 2011, Fig. 9-1.)*

Table 86-13 Drugs Used for the Treatment of Hyperlipidemia

DRUG	MECHANISM OF ACTION	INDICATION	STARTING DOSE
HMG-CoA reductase inhibitors (statins)	↓ Cholesterol and VLDL synthesis ↑ Hepatic LDL receptors	Elevated LDL	5-80 mg qhs
Bile acid sequestrants: Cholestyramine Colestipol	↑ Bile and excretion	Elevated LDL	 4-32 g daily 5-40 g daily
Nicotinic acid	↓ Hepatic VLDL synthesis	Elevated LDL Elevated TG	100-2,000 mg tid
Fibric acid derivatives: Gemfibrozil	↑ LPL ↓ VLDL	Elevated TG	600 mg bid
Fish oils	↓ VLDL production	Elevated TG	3-10 g daily
Cholesterol absorption inhibitors: Ezetimibe	↓ Intestinal absorption cholesterol	Elevated LDL	10 mg daily

LDL, low-density lipoprotein; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very-low-density lipoprotein.

Table 86-14 Side Effects of Lipid-Lowering Drugs

DRUG AND SITE OR TYPE OF EFFECT	EFFECT
STATINS	
Skin	Rash
Nervous system	Loss of concentration, sleep disturbance, headache, peripheral neuropathy
Liver	Hepatitis, loss of appetite, weight loss, and increases in serum aminotransferases to 2-3 times the upper limit of the normal range
Gastrointestinal tract	Abdominal pain, nausea, diarrhea
Muscles	Muscle pain or weakness, myositis (usually with serum creatine kinase >1,000U/L), rhabdomyolysis with renal failure
Immune system	Lupus-like syndrome (lovastatin, simvastatin, or fluvastatin)
Protein binding	Diminished binding of warfarin (lovastatin, simvastatin, fluvastatin)
BILE ACID-BINDING RESINS	
Gastrointestinal tract	Abdominal fullness, nausea, gas, constipation, hemorrhoids, anal fissure, activation of diverticulitis, diminished absorption of vitamin D in children
Liver	Mild serum aminotransferase elevations, which can be exacerbated by concomitant treatment with a statin
Metabolic system	Increases in serum triglycerides of ≈10% (greater increases in patients with hypertriglyceridemia)
Electrolytes	Hyperchloremic acidosis in children and patients with renal failure (cholestyramine)
Drug interactions	Binding of warfarin, digoxin, thiazide diuretics, thyroxine, statins
NICOTINIC ACID	
Skin	Flushing, dry skin, pruritus, ichthyosis, acanthosis nigricans
Eyes	Conjunctivitis, cystoid macular edema, retinal detachment
Respiratory tract	Nasal stuffiness
Heart	Supraventricular arrhythmias
Gastrointestinal tract	Heartburn, loose bowel movements or diarrhea
Liver	Mild increase in serum aminotransferases, hepatitis with nausea and fatigue
Muscles	Myositis
Metabolic system	Hyperglycemia (incidence: ≈5% higher in patients with diabetes), increase of 10% in serum uric acid
FIBRATES	
Skin	Rash
Gastrointestinal tract	Stomach upset, abdominal pain (mainly gemfibrozil), cholesterol-saturated bile, increase of 1-2% in gallstone incidence
Genitourinary tract	Erectile dysfunction (mainly clofibrate)
Muscles	Myositis with impaired renal function
Plasma proteins	Interference with binding of warfarin, requiring reduction in the dose of warfarin by ≈30%
Liver	Increased serum aminotransferases

From Knopp RH: Drug treatment of lipid disorders, N Engl J Med *341:498–512, 1999.*

inception of screening and treatment guidelines from the NCEP in 1992. Although the treatment guidelines have been slightly modified by the American Academy of Pediatrics since that time, pharmacologic therapy with cholesterol-lowering medication still remains a cornerstone of therapy for children who fail to respond to a 6 mo period of rigorous lifestyle modification. Drug therapy should be considered when one of the following conditions are met, which are also shown in Figure 86-14:

- LDL cholesterol remains >190 mg/dL
- LDL cholesterol remains >160 mg/dL with presence of 1 high-level risk factor and/or at least 2 moderate-level risk factors
- LDL cholesterol remains >130 mg/dL with presence of at least 2 high-level risk factors, 1 high-level risk factor, **and** at least 2 moderate-level risk factors, or evidence of coronary artery disease

Considerable experience with drug therapy in children and adolescents with hyperlipidemia over the past 20 yr has expanded therapeutic options, improved compliance, and enhanced efficacy. In the past, the mainstay of drug therapy was bile acid sequestrants such as cholestyramine and colestipol because they were not systemically absorbed. Interruption of the enterohepatic circulation of bile acids promotes synthesis in the liver of new bile acids from cholesterol. Gastrointestinal side effects and taste resulted in less than desirable compliance, even when there were few viable options.

HMG-CoA reductase inhibitors, also known as "statins" are remarkably effective in lowering LDL cholesterol levels and reducing plaque inflammation, thereby reducing the likelihood of a sudden coronary event in an at-risk adult within weeks of starting the medication. As a class, they work by blocking the intrahepatic biosynthesis of cholesterol, thereby stimulating the production of more LDL receptors on the cell surface and facilitating the uptake of LDL cholesterol from the bloodstream. The NCEP Adult Treatment Panel advocates aggressive lowering of LDL to below 70 mg/dL in individuals with known coronary artery disease. This information is relevant because a child who fulfills criteria for consideration of cholesterol-lowering medication will almost always have inherited the condition from one of the child's parents. Not infrequently, when providing care for the child, questions come up about screening and treatment of parents or grandparents. Statins are equally effective in children, capable of lowering LDL-C levels by 50% when necessary. They are considered first-line therapy for children who meet criteria for pharmacologic therapy. They also will effect a modest reduction in triglycerides and an inconsistent increase in HDL cholesterol. Their side–effect profile, mainly liver dysfunction and rarely rhabdomyolysis with secondary renal failure, should be taken into consideration before prescribing the drug. However, there has been no evidence to date that complications are any more frequent in children than adults, and skeletal muscle discomfort seems to be somewhat less of a problem. Drug interactions may occur as well, so careful attention should be paid to a child's active prescriptions to avoid potentiation of the aforementioned side effects. Children should have liver enzymes monitored regularly, and creatine phosphokinase measured if muscle aches or weakness occurs. Liver enzymes may be allowed to rise 3-fold before discontinuing the drug. There is a suggested link between the use of statins and increased risk of developing type II diabetes mellitus in

adults, but these results have not been replicated in children. It should be reemphasized that children with modest elevations in cholesterol, such as that seen in polygenic hypercholesterolemia, are not, as a rule, candidates for statins because of their side–effect profile. Statins should be started at the lowest effective dose and allowed at least 8 wk to achieve their peak effect. If LDL levels are not at goal, which in children who are treated is generally established to be <130 mg, then the medication may be titrated upwards with careful monitoring of side effects.

Other cholesterol-lowering medications such as nicotinic acid and fibrates have been used far less often in children than bile acid sequestrants and statins. Nicotinic acid and fibrates have been used selectively in children with marked hypertriglyceridemia (>500 mg/dL) at risk for acute pancreatitis, though dietary restriction of complex sugars and carbohydrates will usually result in significant lowering of triglyceride levels. Current guidelines recommend treatment of LDL cholesterol as the initial priority and after LDL levels are at goal, then if triglycerides remain between 200 and 499 mg/dL and non-HDL cholesterol remains ≥145 mg/dL treatment, pharmacologic treatment to reduce triglyceride levels is indicated. Omega-3 fatty acid supplementation, available both over the counter and in prescription form, is a safe and useful treatment thought to reduce triglyceride levels by decreasing the hepatic synthesis of triglycerides.

Ezetimibe has proven to be useful in the pediatric population because of its efficacy and low side–effect profile. Ezetimibe reduces plasma LDL cholesterol by blocking sterol absorption in enterocytes. The drug is marketed as an adjunct to statins when adult subjects are not achieving sufficient blood lipid lowering with statins alone. Not surprisingly, large clinical trials of ezetimibe used as monotherapy in children have not been conducted because the potential market in the pediatric age group is small. Nevertheless, there are sufficient reports in the literature documenting the effectiveness of this medication without worrisome side effects that one can feel on relatively safe grounds recommending it instead of a statin when moderate hypercholesterolemia is encountered, or apprehension from parents makes using a statin difficult.

Bibliography is available at Expert Consult.

86.4 Lipidoses (Lysosomal Storage Disorders)

Margaret M. McGovern and Robert J. Desnick

The lysosomal lipid storage diseases are diverse disorders, each caused by an inherited deficiency of a specific lysosomal hydrolase leading to the intralysosomal accumulation of the enzyme's particular substrate (Tables 86-15 and 86-16). With the exception of Wolman disease and cholesterol ester storage disease, the lipid substrates share a common structure that includes a ceramide backbone (2-*N*-acylsphingosine) from which the various sphingolipids are derived by substitution of hexoses, phosphorylcholine, or 1 or more sialic acid residues on the terminal hydroxyl group of the ceramide molecule. The pathway of sphingolipid metabolism in nervous tissue (Fig. 86-15) and in visceral organs (Fig. 86-16) is known; each catabolic step, with the exception of the catabolism of lactosylceramide, has a genetically determined metabolic defect and a resultant disease. Because sphingolipids are essential components of all cell membranes, the inability to degrade these substances and their subsequent accumulation results in the physiologic and morphologic alterations and characteristic clinical manifestations of the lipid storage disorders (see Table 86-15). Progressive lysosomal accumulation of glycosphingolipids in the central nervous system leads to neurodegeneration, whereas storage in visceral cells can lead to organomegaly, skeletal abnormalities, pulmonary infiltration, and other manifestations. The storage of a substrate in a specific tissue is dependent on its normal distribution in the body.

Diagnostic assays for the identification of affected individuals rely on the measurement of the specific enzymatic activity in isolated leukocytes or cultured fibroblasts or lymphoblasts. Figure 86-17 shows an approach to differentiating these disorders. For most disorders, carrier identification and prenatal diagnosis are available; a specific diagnosis is essential to permit genetic counseling. Neonatal screening using dried blood spots and performing enzyme assays and mutational analysis for Gaucher, Pompe, Fabry, and Niemann-Pick diseases are undergoing pilot studies. The characterization of the genes that encode the specific enzymes required for sphingolipid metabolism permit the development of therapeutic options, such as recombinant enzyme replacement therapy, as well as the potential of cell or gene therapy. Identification of specific disease-causing mutations improves diagnosis, prenatal detection, and carrier identification. For several disorders (Gaucher, Fabry, and Niemann-Pick types A and B disease), it has been possible to make genotype–phenotype correlations that predict disease severity and allow more precise genetic counseling. Inheritance is autosomal recessive except for X-linked Fabry disease.

GM_1 GANGLIOSIDOSIS

GM_1 gangliosidosis most frequently presents in early infancy, but has been described in patients with juvenile and adult onset subtypes. Inherited as an autosomal recessive trait, each subtype results from a different gene mutation that leads to the deficient activity of β-galactosidase, a lysosomal enzyme encoded by a gene on chromosome 3 (3p21.33). Although the disorder is characterized by the pathologic accumulation of GM_1 gangliosides in the lysosomes of both neural and visceral cells, GM_1 ganglioside accumulation is most marked in the brain. In addition, keratan sulfate, a mucopolysaccharide, accumulates in liver and is excreted in the urine of patients with GM_1 gangliosidosis. The β-galactosidase gene has been isolated and sequenced; mutations causing the disease subtypes have been identified.

The clinical manifestations of the infantile form of GM_1 gangliosidosis may be evident in the newborn as hepatosplenomegaly, edema, and skin eruptions (**angiokeratoma**). It most frequently presents in the first 6 mo of life with developmental delay followed by progressive psychomotor retardation and the onset of tonic–clonic seizures. A typical facies is characterized by low-set ears, frontal bossing, a depressed nasal bridge, and an abnormally long philtrum. Up to 50% of patients have a **macular cherry-red spot**. Hepatosplenomegaly and skeletal abnormalities similar to those of the mucopolysaccharidoses, including anterior beaking of the vertebrae, enlargement of the sella turcica, and thickening of the calvarium, are present. By the end of the first year of life, most patients are blind and deaf, with severe neurologic impairment characterized by decerebrate rigidity. Death usually occurs by 3-4 yr of age. The juvenile-onset form of GM_1 gangliosidosis is clinically distinct, with a variable age at onset. Affected patients present primarily with neurologic symptoms including ataxia, dysarthria, intellectual disability, and spasticity. Deterioration is slow; patients may survive through the 4th decade of life. These patients lack the visceral involvement, facial abnormalities, and skeletal features seen in type 1 disease. Adult-onset patients have been described who present with gait and speech abnormalities, dystonia and mild skeletal abnormalities. There is no specific treatment for either form of GM_1 gangliosidosis.

The diagnosis of GM_1 gangliosidosis should be suspected in infants with typical clinical features and is confirmed by the demonstration of the deficiency of β-galactosidase activity in peripheral leukocytes. Other disorders that share some of the features of the GM_1 gangliosidoses include Hurler disease (mucopolysaccharidosis type I), I-cell disease, and Niemann-Pick disease (NPD) type A, which can each be distinguished by the demonstration of their specific enzymatic deficiencies. Carriers of the disorder are detected by the measurement of the enzymatic activity in peripheral leukocytes or by identifying the specific gene mutations; prenatal diagnosis is accomplished by determination of the enzymatic activity in cultured amniocytes or chorionic villi or identification of the specific disease-causing mutations. Currently only supportive therapy is available for patients with GM_1 gangliosidosis. However studies in mice with GM_1-gangliosidosis have demonstrated that orally administered *N*-octyl-4-epi-β-valienamine

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Table 86-15 Clinical Findings in Lysosomal Storage Diseases

NOMENCLATURE	ENZYME DEFECT	HYDROPS FETALIS	COARSE FACIAL FEATURES DYSOSTOSIS MULTIPLEX	HEPATOSPLENOMEGALY
MUCOLIPIDOSES				
Mucolipidoses II, I-cell disease	*N*-Acetylglucosaminylphosphotransferase	(+)	++	+
Mucolipidosis III, Pseudo-Hurler	*N*-Acetylglucosaminylphosphotransferase	–	+	(+)
Mucolipidosis IV	Unknown	–	–	+
SS				
Fabry disease	α-Galactosidase	–	–	–
Farber disease	Ceramidase	–	–	(+)
Galactosialidosis	β-Galactosidase and sialidase	(+)	++	++
GM_1 gangliosidosis	β-Galactosidase	(+)	++	+
GM_2 gangliosidosis (Tay-Sachs disease, Sandhoff disease)	β-Hexosaminidases A and B	–	–	(+)
Gaucher type I	Glucocerebrosidase	–	–	++
Gaucher type II	Glucocerebrosidase	(+)	–	++
Gaucher type III	Glucocerebrosidase	(+)	–	+
Niemann-Pick type A	Sphingomyelinase	(+)	–	++
Niemann-Pick type B	Sphingomyelinase	–	–	++
Metachromatic leukodystrophy	Arylsulfatase A	–	–	–
Krabbe disease	β-Galactocerebrosidase	–	–	–
LIPID STORAGE DISORDERS				
Niemann-Pick type C	Intracellular cholesterol transport	–	–	(+)
Wolman disease	Acid lipase	(+)	–	+
Ceroid lipofuscinosis, infantile (Santavuori-Haltia)	Palmitoyl-protein thioesterase (CLN1)	–	–	–
Ceroid lipofuscinosis, late infantile (Jansky-Bielschowsky)	Pepstatin-insensitive peptidase (CLN2); variants in Finland (CLN5), Turkey (CLN7), and Italy (CLN6)	–	–	–
Ceroid lipofuscinosis, juvenile (Spielmeyer-Vogt)	CLN3, membrane protein	–	–	–
Ceroid lipofuscinosis, adult (Kufs, Parry)	CLN4, probably heterogeneous	(+)	–	–
OLIGOSACCHARIDOSES				
Aspartylglucosaminuria	Aspartylglucosylaminase	–	+	(+)
Fucosidosis	α-Fucosidase	–	++	(+)
α-Mannosidosis	α-Mannosidase	–	++	+
β-Mannosidosis	β-Mannosidase	–	+	(+)
Schindler disease	α-*N*-Acetylgalactosaminidase	–	–	–
Sialidosis I	Sialidase	(+)	–	–
Sialidosis II	Sialidase	(+)	++	+

++, Prominent; +, often present; (+), inconstant or occurring later in the disease course; –, not present; GAG, glycosaminoglycans.

Modified from Hoffmann GF, Nyhan WL, Zschoke J, et al: Storage disorders in inherited metabolic diseases, *Philadelphia, 2002, Lippincott Williams & Wilkins, pp. 346–351.*

(NOEV),which stabilizes the mutant enzyme protein produced by affected animals, crossed the brain and improved neurologic deterioration suggesting that this approach may be useful to study in humans.

THE GM_2 GANGLIOSIDOSES

The GM_2 gangliosidoses include Tay-Sachs disease and Sandhoff disease; each results from the deficiency of β-hexosaminidase activity and the lysosomal accumulation of GM_2 gangliosides, particularly in the central nervous system. Both disorders have been classified into infantile-, juvenile-, and adult-onset forms based on the age at onset and clinical features. β-Hexosaminidase occurs as 2 isozymes: β-hexosaminidase A, which is composed of 1 α and 1 β subunit, and β-hexosaminidase B, which has 2 β subunits. β-Hexosaminidase A deficiency results from mutations in the α subunit and causes Tay-Sachs disease, whereas mutations in the β-subunit gene result in the deficiency of both β-hexosaminidases A and B and cause Sandhoff

CARDIAC INVOLVEMENT CARDIAC FAILURE	MENTAL DETERIORATION	MYOCLONUS	SPASTICITY	PERIPHERAL NEUROPATHY	CHERRY-RED SPOT	CORNEAL CLOUDING	ANGIOKERATOMATA
++	++	–	–	–	–	(+)	–
–	(+)	–	–	–	–	+	–
–	(+)	–	–	–	–	–	–
+	–	–	–	–	–	+	++
++	+	–	–	+	(+)	–	–
+	++	(+)	+	–	+	+	+
(+)	++	–	(+)	–	(+)	+	+
–	++	+	+	–	++	–	–
–	–	–	–	–	–	–	–
–	++	+	+	–	–	–	–
–	+	(+)	(+)	–	–	–	–
–	+	(+)	–	(+)	(++)	–	–
–	–	–	–	(+)	(+)	–	–
–	++	–	+	++	(+)	–	–
–	++	–	+	++	(+)	–	–
–	+	–	–	–	(+)	–	–
(+)	–	–	–	–	(+)	–	–
–	+	+	+	–	–	–	–
–	+	+	+	–	–	–	–
–	+	–	(+)	–	–	–	–
–	+	–	–	–	–	–	–
(+)	+	–	–	–	–	(+)	(+)
+	++	+	+	–	–	–	(+)
–	++	–	(+)	–	–	++	(+)
–	+	–	+	+	–	–	(+)
–	+	+	+	–	–	–	–
–	–	++	+	+	++	(+)	–
+	++	(+)	–	–	++	–	+

disease. Both are autosomal recessive traits, with Tay-Sachs disease being more frequent in the Ashkenazi Jewish population, where the carrier frequency is approximately 1 in 25.

More than 50 mutations have been identified; most are associated with the infantile forms of disease. Three mutations account for >98% of mutant alleles among Ashkenazi Jewish carriers of Tay-Sachs disease, including 1 allele associated with the adult-onset form. Mutations that cause the subacute or adult-onset forms result in enzyme proteins with residual enzymatic activities, the levels of which correlate with the severity of the disease.

Patients with the infantile form of Tay-Sachs disease have clinical manifestations in infancy including loss of motor skills, increased startle reaction, and macular pallor and **retinal cherry-red spots** (see Table 86-15). Affected infants usually develop normally until 4-5 mo of age when decreased eye contact and an exaggerated startle response to noise (**hyperacusis**) are noted. **Macrocephaly**, not associated with

Table 86-16 Symptoms Encountered in Patients with Lysosomal Storage Disorders

SYSTEM	MANIFESTATIONS
Neurologic	Hypotonia Floppy-infant syndrome Trismus Strabismus Opisthotonus Spasticity Seizures Peripheral neuropathy Developmental delay Irritability Extrapyramidal movement disorder Hydrocephalus
Respiratory	Congenital lobar emphysema Recurrent respiratory infections Hoarseness
Endocrine	Osteopenia Metabolic bone disease Secondary hyperparathyroidism Congenital adrenal hyperplasia
Cardiovascular	Cardiomegaly Congenital heart failure Arrhythmias Wolff-Parkinson-White syndrome Cardiomyopathy
Dysmorphology	
Head and neck	Macrocephaly Enlarged nuchal translucency Microstomia Micrognathia/microretrognathia Long philtrum
Limbs	Bilateral broad thumbs and toes Bilateral club feet
Oral	Macroglossia Molar hypoplasia Hypertrophic gums
Facial	Bilateral epicanthal inferior orbital creases Palpebral edema Hypertelorism Coarse facies Low-set ears
Gastrointestinal	Hepatosplenomegaly Neonatal cholestasis
Bones and joints	Lytic bone lesions Joint contractures Dysostosis multiplex Hyperphosphatasemia Vertebral breaking Broadening of tubular bones Punctuate epiphysis Craniosynostosis Painful joint swelling
Skin	Congenital ichthyosis Collodion infant Hypopigmentation Telangiectasias Extended Mongolian spots
Ocular	Corneal clouding Megalocornea Glaucoma Cherry-red spots Fundi hypopigmentation Bilateral cataracts
Hematologic	Anemia Thrombocytopenia
Hydrops fetalis	Nonimmune hydrops fetalis Congenital ascites

From Staretz-Chacham O, Lang TC, LaMarca ME, et al: Lysosomal storage disorders in the newborn, Pediatrics *123:1191–1207, 2009.*

hydrocephalus, may develop. In the 2nd yr of life, seizures develop which may be refractory to anticonvulsant therapy. Neurodegeneration is relentless, with death occurring by the age of 4 or 5 yr. The juvenile and later-onset forms initially present with ataxia and dysarthria and may not be associated with a macular cherry-red spot.

The clinical manifestations of **Sandhoff** disease are similar to those of Tay-Sachs disease. Infants with Sandhoff disease have hepatosplenomegaly, cardiac involvement, and mild bony abnormalities. The juvenile form of this disorder presents as ataxia, dysarthria, and mental deterioration, but without visceral enlargement or a macular cherry red spot. There is no treatment available for Tay-Sachs disease or Sandhoff disease, although experimental approaches are being evaluated.

The diagnosis of infantile Tay-Sachs disease and Sandhoff disease is usually suspected in an infant with neurologic features and a cherry-red spot. Definitive diagnosis is made by determination of β-hexosaminidase A and B activities in peripheral leukocytes. The 2 disorders are distinguished by the enzymatic assay, because in Tay-Sachs disease only the β-hexosaminidase A isozyme is deficient, whereas in Sandhoff disease both of the β-hexosaminidase A and B isozymes are deficient. At-risk pregnancies for both disorders can be prenatally diagnosed by determining the enzyme levels in fetal cells obtained by amniocentesis or chorionic villus sampling. Identification of carriers in families is also possible by β-hexosaminidases A and B determination. Indeed, for Tay-Sachs disease, carrier screening of all couples in which at least 1 member is of Ashkenazi Jewish descent is recommended before the initiation of pregnancy to identify couples at risk. These studies can be conducted by the determination of the level of β-hexosaminidase A activity in peripheral leukocytes or plasma. Molecular studies to identify the exact molecular defect in enzymatically identified carriers should also be performed to permit more specific identification of carriers in the family and to allow prenatal diagnosis in at-risk couples by both enzymatic and genotype determinations. The incidence of Tay-Sachs disease has been markedly reduced since the introduction of carrier screening programs in the Ashkenazi Jewish population. Newborn screening may be possible by measuring specific glycosphingolipid markers, or the relevant enzymatic activities in dried blood spots.

GAUCHER DISEASE

This disease is a multisystemic lipidosis characterized by hematologic abnormalities, organomegaly, and skeletal involvement, the latter usually manifesting as bone pain and pathologic fractures (see Table 86-15). It is one of the most common lysosomal storage diseases and the most prevalent genetic defect among Ashkenazi Jews. There are 3 clinical subtypes delineated by the absence or presence and progression of neurologic manifestations: type 1 or the adult, nonneuronopathic form; type 2, the infantile or acute neuronopathic form; and type 3, the juvenile or subacute neuronopathic form. All are autosomal recessive traits. Type 1, which accounts for 99% of cases, has a striking predilection for Ashkenazi Jews, with an incidence of approximately 1 in 1,000 live births and a carrier frequency of approximately 1 in 18 adults.

Gaucher disease results from the deficient activity of the lysosomal hydrolase, acid β-glucosidase, which is encoded by a gene located on chromosome 1q21-q31. The enzymatic defect results in the

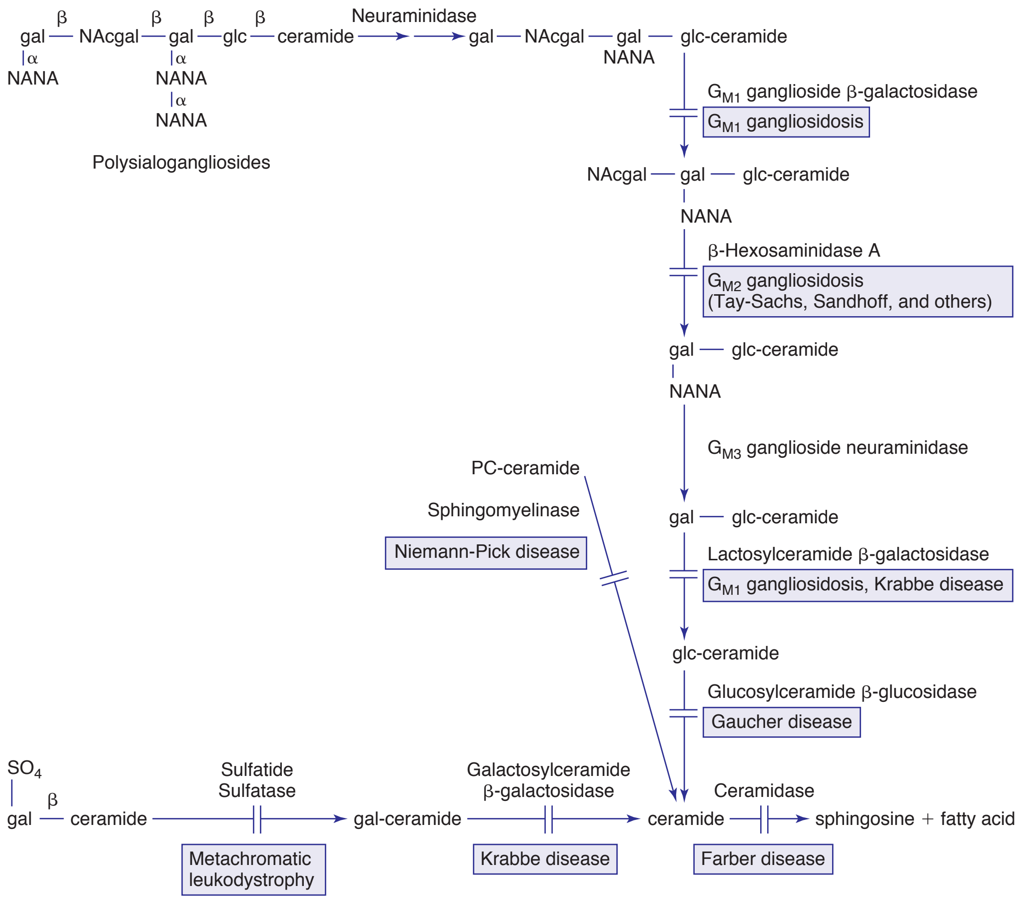

Figure 86-15 Pathways in the metabolism of sphingolipids found in nervous tissues. The name of the enzyme catalyzing each reaction is given with the name of the substrate that it hydrolyzes. Inborn errors are depicted as *bars* crossing the reaction *arrows,* and the name of the associated defect or defects is given in the nearest *box.* The gangliosides are named according to the nomenclature of Svennerholm. Anomeric configurations are given only at the largest starting compound. *Gal,* galactose; *glc,* glucose; *NAcgal, N*-acetylgalactosamine; *NANA, N*-acetylneuraminic acid; *PC,* phosphorylcholine.

accumulation of undegraded glycolipid substrates, particularly glucosylceramide, in cells of the reticuloendothelial system. This progressive deposition results in infiltration of the bone marrow, progressive hepatosplenomegaly, and skeletal complications. Four mutations—N370S, L444P, 84insG, and IVS2+2—account for approximately 95% of mutant alleles among Ashkenazi Jewish patients, permitting screening for this disorder in this population. Genotype–phenotype correlations have been noted, providing the molecular basis for the clinical heterogeneity seen in Gaucher disease type 1. Patients who are homozygous for the N370S mutation tend to have later onset, with a more indolent course than patients with 1 copy of N370S and another common allele.

Clinical manifestations of type 1 Gaucher disease have a variable age at onset, from early childhood to late adulthood, with most symptomatic patients presenting by adolescence. At presentation, patients may have bruising from thrombocytopenia, chronic fatigue secondary to anemia, hepatomegaly with or without elevated liver function test results, splenomegaly, and bone pain. Occasional patients have pulmonary involvement at the time of presentation. Patients presenting in the 1st decade frequently are not Jewish and have growth retardation and a more malignant course. Other patients may be discovered fortuitously during evaluation for other conditions or as part of routine examinations; these patients may have a milder or even a benign course. In symptomatic patients, splenomegaly is progressive and can become massive. Most patients develop radiologic evidence of skeletal involvement, including an Erlenmeyer flask deformity of the distal femur. Clinically apparent bony involvement, which occurs in most patients, can present as bone pain, a pseudoosteomyelitis pattern or pathologic fractures. Lytic lesions can develop in the long bones, including the femur, ribs, and pelvis; osteosclerosis may be evident at an early age. Bone crises with severe pain and swelling can occur. Bleeding secondary to thrombocytopenia may manifest as epistaxis or bruising and is frequently overlooked until other symptoms become apparent. With the exception of the severely growth-retarded child, who may experience developmental delay secondary to the effects of chronic disease, development and intelligence are normal.

The pathologic hallmark of Gaucher disease is the Gaucher cell in the reticuloendothelial system, particularly in the bone marrow (Fig. 86-18). These cells, which are 20-100 µm in diameter, have a characteristic wrinkled paper appearance resulting from the presence of intracytoplasmic substrate inclusions. The cytoplasm of the Gaucher cell reacts strongly positive with the periodic acid–Schiff stain. The presence of this cell in bone marrow and tissue specimens is highly suggestive of Gaucher disease, although it also may be found in patients with granulocytic leukemia and myeloma.

Gaucher disease type 2 is a rare form and does not have an ethnic predilection. It is characterized by a rapid neurodegenerative course with extensive visceral involvement and death within the first years of life. It presents in infancy with increased tone, strabismus, and organomegaly. Failure to thrive and stridor caused by laryngospasm are typical. After a several-year period of psychomotor regression, death typically occurs secondary to respiratory compromise. **Gaucher disease type 3** presents with clinical manifestations that are intermediate to those seen in types 1 and 2, with presentation in childhood

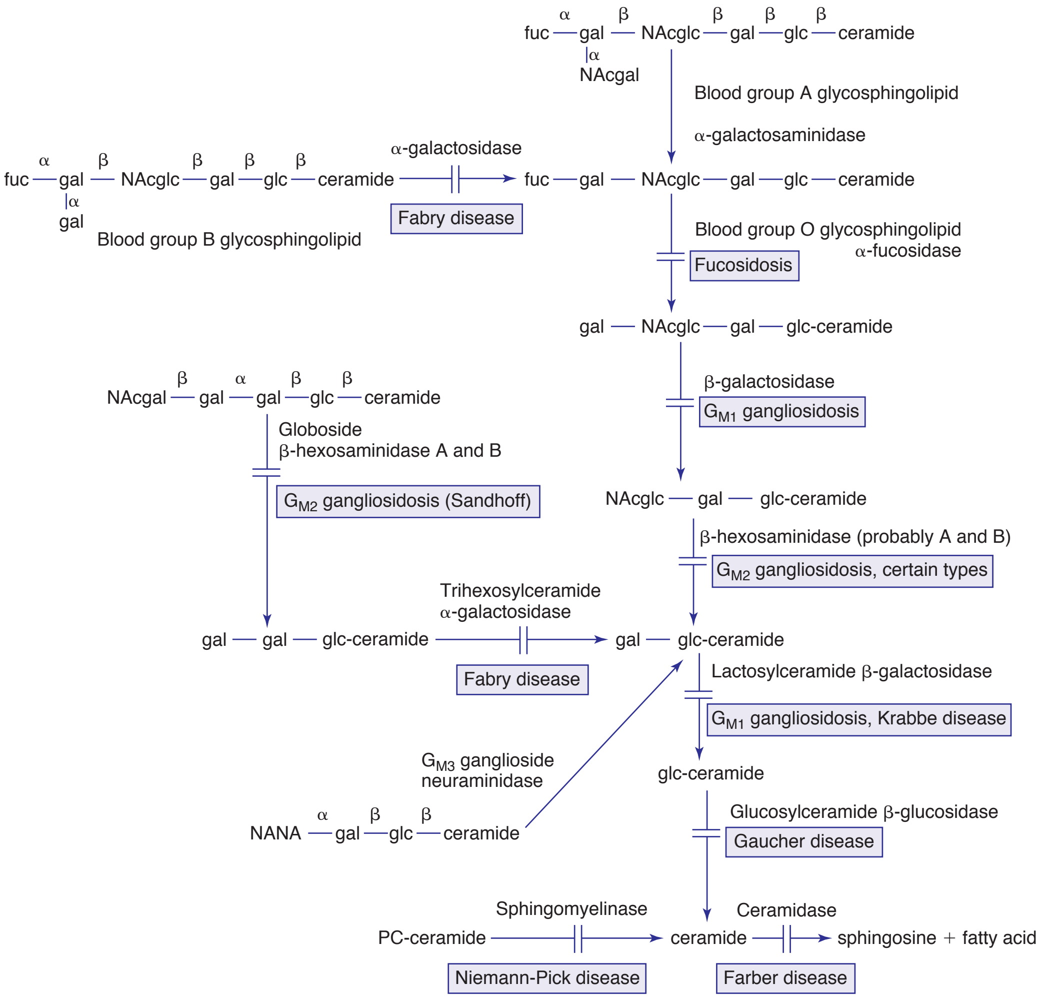

Figure 86-16 Pathways in the degradation of sphingolipids found in visceral organs and red or white blood cells. See also the legend for Figure 86-15. *Fuc,* fucose; *NAcglc, N*-acetylglucosamine.

and death by age 10-15 yr. It has a predilection for the Swedish Norrbottnian population, among whom the incidence is approximately 1 in 50,000. Neurologic involvement is present. Type 3 disease is further classified as types 3a and 3b based on the extent of neurologic involvement and whether there is progressive myotonia and dementia (type 3a) or isolated supranuclear gaze palsy (type 3b).

Gaucher disease should be considered in the differential diagnosis of patients with unexplained organomegaly, who bruise easily, have bone pain, or have a combination of these conditions. Bone marrow examination usually reveals the presence of Gaucher cells. All suspected diagnoses should be confirmed by determination of the acid β-glucosidase activity in isolated leukocytes or cultured fibroblasts, and by identification of their specific acid β-glucosidase gene mutations. In Ashkenazi Jewish individuals the identification of carriers can be achieved best by molecular testing for the common Ashkenazi mutations. Testing should be offered to all family members, keeping in mind that heterogeneity, even among members of the same kindred, can be so great that nonsymptomatic affected individuals may be diagnosed. Prenatal diagnosis is available by determination of enzyme activity and/or the specific family mutations in chorionic villi or cultured amniotic fluid cells.

Treatment of patients with Gaucher disease type 1 includes enzyme replacement therapy. The efficacy of enzyme replacement therapy with mannose-terminated recombinant human acid β-glucosidase has definitively been demonstrated. Most symptoms (organomegaly, hematologic indices, bone pain) are reversed by enzyme replacement therapy (60 IU/kg) administered by intravenous infusion every other week and the bone involvement can be stabilized or improved. Two additional enzyme preparations are approved by the FDA for the treatment of type 1 Gaucher disease, including velaglucerase alfa (VPRIV, Shire HGT), which is produced in human fibrosarcoma cells, and taliglucerase alfa (Uplyso, Protalix Biotherapeutics), which is produced in carrot cells.

Although enzyme replacement does not alter the neurologic progression of patients with Gaucher disease types 2 and 3, it has been used in selected patients as a palliative measure, particularly in type 3 patients with severe visceral involvement. Alternative treatments, including the use of oral substrate reduction agents designed to decrease the synthesis of glucosylceramide by chemical inhibition of glucosylceramide synthase (e.g., miglustat), also are available. A small number of patients have undergone bone marrow transplantation (BMT), which is curative but is associated with significant morbidity and mortality from the procedure, limiting the selection of appropriate candidates.

NIEMANN-PICK DISEASE

The original description of NPD was what is now known as **type A NPD**, a fatal disorder of infancy characterized by failure to thrive, hepatosplenomegaly, and a rapidly progressive neurodegenerative course that leads to death by 2-3 yr of age. **Type B** disease is a non-neuronopathic form observed in children and adults. **Type C** disease is a neuronopathic form that results from defective cholesterol transport. All subtypes are inherited as autosomal recessive traits and display variable clinical features (see Table 86-15).

NPD types A and B result from the deficient activity of acid sphingomyelinase, a lysosomal enzyme encoded by a gene on chromosome

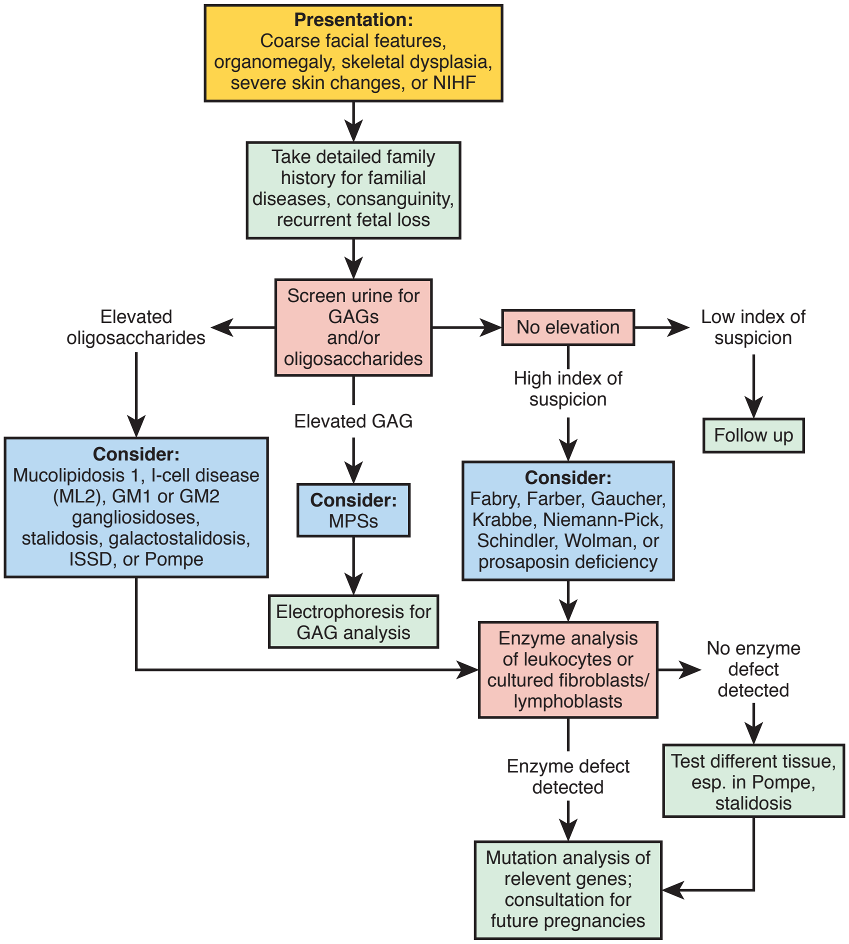

Figure 86-17 Algorithm of the clinical evaluation recommended for an infant with a suspected lysosomal storage disease. *GAGs,* glycosaminoglycans; *NIHF,* nonimmune hydrops fetalis. *(From Staretz-Chacham O, Lang TC, LaMarca ME, et al: Lysosomal storage disorders in the newborn,* Pediatrics *123:1191–1207, 2009.)*

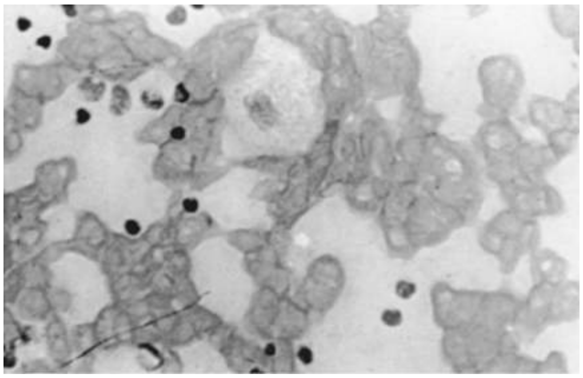

Figure 86-18 Cells from the spleen of a patient with Gaucher disease. A characteristic spleen cell is shown engorged with glucocerebroside.

11 (11p15.1-p15.4). The enzymatic defect results in the pathologic accumulation of sphingomyelin, a ceramide phospholipid, and other lipids in the monocyte–macrophage system, the primary pathologic site. The progressive deposition of sphingomyelin in the central nervous system results in the neurodegenerative course seen in type A, and in nonneural tissue in the systemic disease manifestations of type B, including progressive lung disease in some patients. A variety of mutations in the acid sphingomyelinase gene that cause types A and B NPD have been identified.

The clinical manifestations and course of type A NPD is uniform and is characterized by a normal appearance at birth. Hepatosplenomegaly, moderate lymphadenopathy, and psychomotor retardation are evident by 6 mo of age, followed by neurodevelopmental regression and death by 3 yr. With advancing age, the loss of motor function and the deterioration of intellectual capabilities are progressively debilitating; and in later stages, spasticity and rigidity are evident. Affected infants lose contact with their environment. In contrast to the stereotyped type A phenotype, the clinical presentation and course of patients with type B disease are more variable. Most are diagnosed in infancy or childhood when enlargement of the liver or spleen, or both, is detected during a routine physical examination. At diagnosis, type B NPD patients usually have evidence of mild pulmonary involvement, usually detected as a diffuse reticular or finely nodular infiltration on the chest radiograph. **Pulmonary symptoms** may present in adults. In most patients, hepatosplenomegaly is particularly prominent in childhood, but with increasing linear growth, the abdominal protuberance decreases and becomes less conspicuous. In mildly affected patients, the splenomegaly may not be noted until adulthood, and there may be minimal disease manifestations.

Severely affected patients may have liver involvement leading to life-threatening cirrhosis, portal hypertension, and ascites. Clinically significant pancytopenia caused by secondary **hypersplenism** may require partial or complete splenectomy; this should be avoided if possible because splenectomy frequently causes progression of pulmonary disease, which can be life-threatening. In general, type B patients do not have neurologic involvement and have a normal IQ. Some patients with type B disease have cherry-red maculae or haloes and subtle neurologic symptoms (peripheral neuropathy). In some type B patients, decreased pulmonary diffusion caused by alveolar infiltration becomes evident in late childhood or early adulthood and progresses with age.

Severely affected individuals may experience significant pulmonary compromise by 15-20 yr of age. Such patients have low PO_2 values and dyspnea on exertion. Life-threatening bronchopneumonias may occur, and cor pulmonale has been described.

Type C NPD patients often present with prolonged neonatal jaundice, appear normal for 1-2 yr, and then experience a slowly progressive and variable neurodegenerative course. Their hepatosplenomegaly is less severe than that of patients with types A or B NPD, and they may survive into adulthood. The underlying biochemical defect in type C patients is an abnormality in cholesterol transport, leading to the accumulation of sphingomyelin and cholesterol in their lysosomes and a secondary partial reduction in acid sphingomyelinase activity (see Chapter 86.3).

In type B NPD patients, splenomegaly is usually the first manifestation detected. The splenic enlargement is noted in early childhood; in very mild disease, the enlargement may be subtle and detection may be delayed until adolescence or adulthood. The presence of the characteristic NPD cells in bone marrow aspirates supports the diagnosis of type B NPD. Patients with type C NPD, however, also have extensive infiltration of NPD cells in the bone marrow and, thus, all suspected cases should be evaluated enzymatically to confirm the clinical diagnosis by measuring the acid sphingomyelinase activity level in peripheral leukocytes, cultured fibroblasts, or lymphoblasts, or a combination of these cells. Patients with types A and B NPD have markedly decreased levels (1-10%), whereas patients with type C NPD have normal or somewhat decreased acid sphingomyelinase activities. The enzymatic identification of NPD carriers is problematic. In families in which the specific molecular lesion has been identified, however, family members can be accurately tested for heterozygote status by DNA analysis. Prenatal diagnosis of types A and B NPD can be made reliably by the measurement of acid sphingomyelinase activity in cultured amniocytes or chorionic villi; molecular analysis of fetal cells to identify the specific acid sphingomyelinase mutations can provide the specific diagnosis or serve as a confirmatory test. The clinical diagnosis of type C NPD can be supported by the demonstration of filipin stain positivity in cultured fibroblasts and/or by identifying a specific mutation in the *NPC 1* or *2* gene.

Currently there is no specific treatment for NPD. Orthotopic liver transplantation in an infant with type A disease and cord blood transplantation in several type B NPD patients have been attempted with little or no success. BMT in a small number of type B NPD patients has been successful in reducing the spleen and liver volumes, the sphingomyelin content of the liver, the number of Niemann-Pick cells in the marrow, and radiologically detected infiltration of the lungs. In 1 patient, liver biopsies taken up to 33 mo posttransplantation showed only a moderate reduction in stored sphingomyelin. A phase I trial of enzyme replacement therapy for type B NPD has been completed which demonstrated elevated cytokine and bilirubin levels at the higher doses administered (0.6 and 1.0 mg/kg). The observed toxicity is presumably a result of the catabolism of the accumulated sphingomyelin to ceramide. Further clinical studies to evaluate effectiveness of this approach are planned. Clinical trials of miglustat (Actelion, Basel, Switzerland) have been performed and the drug has been approved in Europe for the treatment of type C disease. Treatment of type A disease by BMT has not been successful presumably because of the severe neurologic involvement.

FABRY DISEASE

This disease is an X-linked inborn error of glycosphingolipid metabolism caused by the absent or markedly deficient activity of α-galactosidase A (α-gal A). There are 2 major phenotypes. Affected males with the classic phenotype present in childhood with angiokeratomas (telangiectatic skin lesions), hypohidrosis, corneal and lenticular opacities, acroparesthesias, and with advancing age develop vascular disease of the kidney, heart, and/or brain (see Table 86-15). This classic phenotype is caused by the absent activity of the α-gal A and has an estimated prevalence of approximately 1 in 50,000 males. The later-onset phenotype occurs in affected males with residual α-gal A activity and presents in the 4th to 8th decades with cardiac disease and/or renal failure. This phenotype is more prevalent than the classic phenotype.

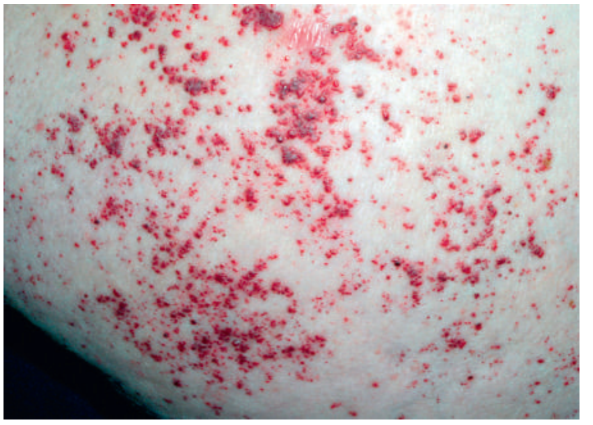

Figure 86-19 Typical angiokeratomas. Angiokeratomas are quite large and easily recognizable, but if only a few lesions exist or they are restricted only to the genitalia or umbilical regions, they can be easily missed. *(From Zarate VA, Hopkin RJ: Fabry's disease,* Lancet *372:1427, 2008.)*

Heterozygous females for the classic phenotype can be asymptomatic or as severely affected as the males, the variability a result of random X-inactivation. The enzyme deficiency results from mutations in the α-gal A gene located on the long arm of the X chromosome (Xq22). The enzymatic defect leads to the systemic accumulation of neutral glycosphingolipids, primarily globotriaosylceramide, particularly in the plasma and lysosomes of vascular endothelial and smooth muscle cells, cardiac myocytes, and renal podocytes. The progressive vascular glycosphingolipid deposition in classically affected males results in small vessel occlusion and ischemia, leading to the major disease manifestations. The complementary DNA and genomic sequences encoding α-gal A have been characterized and more than 500 different mutations in the α-gal A gene are responsible for this lysosomal storage disease.

The **angiokeratomas** usually occur in childhood and may lead to early diagnosis (Fig. 86-19). They increase in size and number with age and range from barely visible to several millimeters in diameter. The lesions are punctate, dark red to blue-black, and flat or slightly raised. They do not blanch with pressure, and the larger ones may show slight hyperkeratosis. Characteristically, the lesions are most dense between the umbilicus and knees, in the "bathing trunk area," but may occur anywhere, including the oral mucosa. The hips, thighs, buttocks, umbilicus, lower abdomen, scrotum, and glans penis are common sites, and there is a tendency toward symmetry. Variants without skin lesions have been described. Sweating is usually decreased or absent. Corneal opacities and characteristic lenticular lesions, observed under slit-lamp examination, are present in affected males, as well as in approximately 90% of heterozygotes from families with the classic phenotype. Conjunctival and retinal vascular tortuosity is common and results from the systemic vascular involvement.

Pain is the most debilitating symptom in childhood and adolescence. **Fabry crises,** lasting from minutes to several days, consist of agonizing, burning pain in the hands, feet, and proximal extremities and are usually associated with exercise, fatigue, fever, or a combination of these factors. These painful acroparesthesias usually become less frequent in the 3rd and 4th decades of life, although in some men, they may become more frequent and severe. Attacks of abdominal or flank pain may simulate appendicitis or renal colic.

The major morbid symptoms result from the progressive involvement of the vascular system. Early in the course of the classic phenotype, casts, red cells, and lipid inclusions with characteristic birefringent "Maltese crosses" appear in the urinary sediment. Proteinuria, isosthenuria, and gradual deterioration of renal function and development of azotemia occur in the 2nd through 4th decades in the classic phenotype and in the 4th to 8th decades in the later-onset form. Cardiovascular findings may include arrhythmias, left ventricular hypertrophy, angina, myocardial ischemia or infarction, and heart failure. Mitral insufficiency is the most common valvular lesion. Cerebrovascular

manifestations, including transient ischemic attacks and strokes, result from multifocal small vessel involvement. Other features may include chronic bronchitis and dyspnea, lymphedema of the legs without hypoproteinemia, episodic diarrhea, osteoporosis, retarded growth, and delayed puberty. Death most often results from renal failure or vascular disease of the heart or brain. Before hemodialysis or renal transplantation, the mean age at death for affected men was 40 yr. Patients with the later-onset phenotype with residual α-gal A activity have cardiac and/or renal disease. The cardiac manifestations include hypertrophy of the left ventricular wall and interventricular septum, and electrocardiographic abnormalities consistent with cardiomyopathy. Patients may progress to hypertrophic cardiomyopathy or myocardial infarction, or both.

The diagnosis in classically affected males is most readily made from the history of painful acroparesthesias, hypohidrosis, the presence of the characteristic skin lesions, and the observation of the corneal opacities and lenticular lesions. The disorder is often misdiagnosed as rheumatic fever, erythromelalgia, or neurosis. The skin lesions must be differentiated from the benign angiokeratomas of the scrotum (Fordyce disease) or from angiokeratoma circumscriptum. **Angiokeratomas** identical to those of Fabry disease have been reported in fucosidosis, aspartylglycosaminuria, late-onset GM_1 gangliosidosis, galactosialidosis, α-*N*-acetylgalactosaminidase deficiency, and sialidosis. Later-onset patients have been identified among patients on hemodialysis and among patients with hypertrophic cardiomyopathy or who have suffered cryptogenic strokes. Later-onset patients lack the early classic manifestations such as the angiokeratomas, acroparesthesias, hypohidrosis, and corneal opacities. The diagnosis of classic and later-onset patients is confirmed biochemically by the demonstration of markedly decreased α-gal A activity in plasma, isolated leukocytes, or cultured fibroblasts or lymphoblasts. The specific α-gal A mutation can be determined by gene sequencing.

Heterozygous females may have corneal opacities, isolated skin lesions, and intermediate activities of α-gal A in plasma or cells. Rare female heterozygotes may have manifestations as severe as those in affected males. Asymptomatic at-risk females in families affected by Fabry disease, however, should be optimally diagnosed by the direct analysis of their family's specific mutation. Prenatal detection of affected males can be accomplished by the demonstration of deficient α-gal A activity and/or the family's specific gene mutation in chorionic villi obtained in the 1st trimester or in cultured amniocytes obtained by amniocentesis in the 2nd trimester of pregnancy. Fabry disease can be detected by newborn screening and pilot studies have been conducted in Italy and Taiwan.

Treatment for Fabry disease may include the use of phenytoin and/or carbamazepine to decrease the frequency and severity of the chronic acroparesthesias and the periodic crises of excruciating pain. Renal transplantation and long-term hemodialysis are lifesaving procedures for patients with renal failure.

Enzyme replacement therapy for Fabry patients using recombinant human α-gal A preparations produced in Chinese hamster ovary cells (agalsidase beta, Fabrazyme, Genzyme Corporation) and in human fibrosarcoma cells (agalsidase alfa, Replagal, Shire HGT) has been developed. Both Fabrazyme and Replagal were approved by the European Medicines Agency in the European Union, but only Fabrazyme is approved by the FDA in the United States. The effectiveness of enzyme replacement therapy with Fabrazyme in stabilization of renal disease, regression of hypertrophic cardiomyopathy, reduction of pain, and improvement in quality of life has been demonstrated. Because most classically affected males produce no enzyme protein, these patients produce immunoglobulin G antibodies in response to the infused enzyme which can impact the effectiveness of substrate clearance. Treatment of classically affected males should begin in childhood.

FUCOSIDOSIS

This is a rare autosomal recessive disorder caused by the deficient activity of α-fucosidase and the accumulation of fucose-containing glycosphingolipids, glycoproteins, and oligosaccharides in the lysosomes of the liver, brain, and other organs (see Table 86-15). The α-fucosidase gene is on chromosome 1 (1p24), and specific mutations are known. Although the disorder is panethnic, most reported patients are from Italy and the United States. There is wide variability in the clinical phenotype, with the most severely affected patients presenting in the first year of life with developmental delay and somatic features similar to those of the mucopolysaccharidoses. These features include frontal bossing, hepatosplenomegaly, coarse facial features, and macroglossia. The central nervous system storage results in a relentless neurodegenerative course, with death in childhood. Patients with milder disease have angiokeratomas and longer survival. No specific therapy exists for the disorder, which can be diagnosed by the demonstration of deficient α-fucosidase activity in peripheral leukocytes or cultured fibroblasts. Carrier identification and prenatal diagnosis are possible by determination of the enzymatic activity or the specific family mutations.

SCHINDLER DISEASE

This is an autosomal recessive neurodegenerative disorder that results from the deficient activity of α-*N*-acetylgalactosaminidase and the accumulation of sialylated and asialoglycopeptides and oligosaccharides (see Table 86-15). The gene for the enzyme is located on chromosome 22 (22q11). The disease is clinically heterogeneous, and 2 major phenotypes have been identified. Type I disease is an infantile-onset neuroaxonal dystrophy. Affected infants have normal development for the first 9-15 mo of life followed by a rapid neurodegenerative course that results in severe psychomotor retardation, cortical blindness, and frequent myoclonic seizures. Type II disease is characterized by a variable age at onset, mild intellectual disability, and angiokeratomas. There is no specific therapy for either form of the disorder. The diagnosis is by demonstration of the enzymatic deficiency in leukocytes or cultured skin fibroblasts or specific gene mutations.

METACHROMATIC LEUKODYSTROPHY

This is an autosomal recessive white matter disease caused by a deficiency of arylsulfatase A (ASA), which is required for the hydrolysis of sulfated glycosphingolipids. Another form of metachromatic leukodystrophy (MLD) is caused by a deficiency of a sphingolipid activator protein (SAP1), which is required for the formation of the substrate–enzyme complex. The deficiency of this enzymatic activity results in the white matter storage of sulfated glycosphingolipids, which leads to demyelination and a neurodegenerative course. The *ASA* gene is on chromosome 22 (22q13.31qter); specific mutations tend to fall into 2 groups that correlate with disease severity.

The clinical manifestations of the late **infantile** form of MLD, which is most common, usually present between 12 and 18 mo of age as irritability, inability to walk, and hyperextension of the knee, causing genu recurvatum. The clinical progression of the disease relates to the pathologic involvement of both central and peripheral nervous system, giving a mixture of upper and lower motor neuron and cognitive and psychiatric signs. Deep tendon reflexes are diminished or absent. Gradual muscle wasting, weakness, and hypotonia become evident and lead to a debilitated state. As the disease progresses, nystagmus, myoclonic seizures, optic atrophy, and quadriparesis appear, with death in the 1st decade of life (see Table 86-15). The **juvenile** form of the disorder has a more indolent course with onset that may occur as late as 20 yr of age. This form of the disease presents with gait disturbances, mental deterioration, urinary incontinence, and emotional difficulties. The **adult** form, which presents after the 2nd decade, is similar to the juvenile form in its clinical manifestations, although emotional difficulties and psychosis are more prominent features. Dementia, seizures, diminished reflexes, and optic atrophy also occur in both the juvenile and adult forms. The pathologic hallmark of MLD is the deposition of metachromatic bodies, which stain strongly positive with periodic acid–Schiff and Alcian blue, in the white matter of the brain. Neuronal inclusions may be seen in the midbrain, pons, medulla, retina, and spinal cord; demyelination occurs in the peripheral nervous system. The diagnosis of MLD should be suspected in patients with the clinical features of leukodystrophy. Decreased nerve conduction velocities, increased cerebrospinal fluid protein, metachromatic deposits in sampled segments of sural nerve, and metachromatic granules in urinary

sediment are all suggestive of MLD. Confirmation of the diagnosis is based on the demonstration of the reduced activity of ASA in leukocytes or cultured skin fibroblasts. SAP deficiency is diagnosed by measuring the concentration of SAP1 in cultured fibroblasts using a specific antibody to the protein. The diagnosis, identification of carriers and prenatal diagnosis are available for both forms of the disorder by detection of the causative mutations in the ASA or SAP genes.

Unrelated donor umbilical cord blood transplantation has been undertaken in some pediatric patients with MLD. A longitudinal study of 6 patients with late-infantile onset and 14 with juvenile onset revealed that motor deficits present at the time of transplant did not improve and that neurologic symptoms continued to progress in those with late-infantile presentation. In contrast, in juvenile patients the brainstem auditory evoked responses, visual evoked potentials, electroencephalogram, and/or peripheral nerve conduction velocities stabilized or improved. Therefore consideration of umbilical cord blood transplantation for children with presymptomatic late-infantile MLD or minimally symptomatic juvenile MLD may be indicated.

MULTIPLE SULFATASE DEFICIENCY

This is an autosomal recessive disorder that results from the enzymatic deficiency of at least 9 sulfatases including arylsulfatases A, B, and C, and iduronate-2-sulfatase. The specific defect is an enzyme in the C-α-formylglycine generating system (the gene for which is located at 3p26), which introduces a common posttranslational modification in all of the affected sulfatases and explains the occurrence of these multiple enzyme defects. Because of the deficiency of these enzymes, sulfatides, mucopolysaccharides, steroid sulfates, and gangliosides accumulate in the cerebral cortex and visceral tissues, resulting in a clinical phenotype with features of a **leukodystrophy** as well as those of the **mucopolysaccharidoses**. Severe ichthyosis may also occur. Carrier testing and prenatal diagnosis by measurement of the enzymatic activities or the specific gene defects can be performed. There is no specific treatment for multiple sulfatase deficiency other than supportive care.

KRABBE DISEASE

This condition, also called globoid cell leukodystrophy, is an autosomal recessive fatal disorder of infancy. It results from the deficient activity of galactocerebrosidase and the white matter accumulation of galactosylceramide, which is normally found almost exclusively in the myelin sheath. Both peripheral and central myelin are affected, resulting in spasticity and cognitive impairment coupled with deceptively normal or even absent deep tendon reflexes. The galactocerebrosidase gene is on chromosome 14 (14q31), and specific disease-causing mutations are known. The **infantile** form of Krabbe disease is rapidly progressive and patients present in early infancy with irritability, seizures, and hypertonia (see Table 86-15). Optic atrophy is evident in the 1st yr of life, and mental development is severely impaired. As the disease progresses, optic atrophy and severe developmental delay become apparent; affected children exhibit opisthotonos and die before 3 yr of age. A **late infantile** form of Krabbe presents after the age of 2 yr. Affected individuals have a course similar to that of the early infantile form.

The diagnosis of Krabbe disease relies on the demonstration of the specific enzymatic deficiency in white blood cells or cultured skin fibroblasts. Causative gene mutations have been identified. Carrier identification and prenatal diagnosis are available. The development of methods to measure galactocerebrosidase activity on dried blood spots has led to the inclusion of Krabbe disease in the newborn screening programs of some states. Treatment of infants with Krabbe disease with umbilical cord blood cell transplantation has been reported in prenatally identified asymptomatic newborns and symptomatic infants. Transplanted infants appear to develop neurologic manifestations at a slower rate but succumb to a neurologic demise.

FARBER DISEASE

This is a rare autosomal recessive disorder that results from the deficiency of the lysosomal enzyme acid ceramidase and the accumulation of ceramide in various tissues, especially the joints. Symptoms can begin in the first year of life with painful joint swelling and nodule formation (Fig. 86-20), which is sometimes diagnosed as rheumatoid arthritis. As the disease progresses, nodule or granulomatous formation on the vocal cords can lead to hoarseness and breathing difficulties; failure to thrive is common. In some patients, moderate central nervous system dysfunction is present (see Table 86-15). Patients may die of recurrent pneumonias in their teens; there is currently no specific therapy. The diagnosis of this disorder should be suspected in patients who have nodule formation over the joints but no other findings of rheumatoid arthritis. In such patients, ceramidase activity should be determined in cultured skin fibroblasts or peripheral leukocytes. Various disease causing mutations have been identified in the acid ceramidase gene. Carrier detection and prenatal diagnosis are available.

Figure 86-20 Forearm of an 18 mo old girl with Farber disease. Note the painful joint swelling and the nodule formation. The infant was suspected of having rheumatoid arthritis.

WOLMAN DISEASE AND CHOLESTEROL ESTER STORAGE DISEASE

These are autosomal recessive lysosomal storage diseases that result from the deficiency of acid lipase and the accumulation of cholesterol esters and triglycerides in histiocytic foam cells of most visceral organs. The gene for lysosomal acid lipase is on chromosome 10 (10q24-q25). Wolman disease is the more severe clinical phenotype and is a fatal disorder of infancy. Clinical features become apparent in the first weeks of life and include failure to thrive, relentless vomiting, abdominal distention, steatorrhea, and hepatosplenomegaly (see Table 86-15). There usually is hyperlipidemia. Hepatic dysfunction and fibrosis may occur. **Calcification of the adrenal glands** occurs in about 50% of patients. Death usually occurs within the first 6 mo of life.

Cholesterol ester storage disease is a less-severe disorder that may not be diagnosed until adulthood. Hepatomegaly can be the only detectable abnormality, but affected individuals are at significant risk for premature cirrhosis and atherosclerosis. Adrenal calcification can occur in severe early onset patients.

Diagnosis and carrier identification are based on measuring acid lipase activity in peripheral leukocytes or cultured skin fibroblasts. Disease causing mutations have been identified in the acid ceramide gene. Prenatal diagnosis depends on measuring decreased enzyme levels or identifying specific mutations in cultured chorionic villi or amniocytes. There is no specific therapy available for either disorder. Although pharmacologic agents to suppress cholesterol synthesis, in combination with cholestyramine and diet modification, have been used in patients there is little to no clinical benefit. Enzyme

replacement therapy is currently being evaluated in clinical trials for both diseases (see Chapter 86.3).

Bibliography is available at Expert Consult.

86.5 Mucolipidoses

Margaret M. McGovern and Robert J. Desnick

I-cell disease (mucolipidosis II [ML-II]) and pseudo-Hurler polydystrophy (mucolipidosis III [ML-III]) are rare autosomal recessive disorders that share some clinical features with Hurler syndrome (see Chapter 88). These diseases result from the abnormal targeting of newly synthesized lysosomal enzymes that normally have phosphorylated mannose residues for binding to the mannose-6-phosphate receptors which transport the enzymes to the lysosomes. These mannose-6-phosphate residues are synthesized in a 2-step reaction that occurs in the Golgi apparatus and is mediated by 2 enzymatic activities. The enzyme that catalyzes the first step, the lysosomal enzyme *N*-acetylglucosamine-1-phosphotransferase, is defective in both ML-II and ML-III, which are allelic disorders resulting from mutations in the GlcNAc-phosphotransferase α/β-subunits precursor gene *(GNPTAB)*. This enzyme deficiency results in abnormal targeting of the lysosomal enzymes which are consequently secreted into the extracellular matrix. Because the lysosomal enzymes require the acidic environment of the lysosome to function, patients with this defect accumulate a variety of different substrates because of the intracellular deficiency of most lysosomal enzymes. The diagnosis of ML-II and ML-III can be made by the determination of the serum lysosomal enzymatic activities, which are markedly elevated, or by the demonstration of their reduced enzymatic activity levels in cultured skin fibroblasts. Direct measurement of the phosphotransferase activity is possible as well. Prenatal diagnosis is available for both disorders by measurement of lysosomal enzymatic activities in amniocytes or chorionic villus cells; carrier identification is available for both disorders by measurement of enzymatic activities using cultured skin fibroblasts or by mutation analysis of the causative gene. Neonatal screening by tandem mass spectroscopy may detect I-cell disease.

I-CELL DISEASE

This disorder, ML-II, shares many of the clinical manifestations of Hurler syndrome (see Chapter 88), although there is no mucopolysacchariduria and the presentation is earlier (see Table 86-15). Some patients have clinical features evident at birth, including coarse facial features, craniofacial abnormalities, restricted joint movement, and hypotonia. Nonimmune hydrops may be present in the fetus. The remainder of patients present in the first year with severe psychomotor retardation, coarse facial features, and skeletal manifestations that include kyphoscoliosis and a lumbar gibbus. Patients may also have congenital dislocation of the hips, inguinal hernias, and gingival hypertrophy. Progressive, severe psychomotor retardation leads to death in early childhood. No treatment is available.

PSEUDO-HURLER POLYDYSTROPHY

Pseudo-Hurler polydystrophy (ML-III) is a less-severe disorder than I-cell disease, with later onset and survival to adulthood reported. Affected children may present around the age of 4 or 5 yr with joint stiffness and short stature. Progressive destruction of the hip joints and moderate dysostosis multiplex are evident. Radiographic evidence of low iliac wings, flattening of the proximal femoral epiphyses with valgus deformity of the femoral head, and hypoplasia of the anterior third of the lumbar vertebrae are characteristic findings. Ophthalmic findings include corneal clouding, retinopathy, and astigmatism; visual complaints are uncommon (see Table 86-15). Some patients have learning disabilities or intellectual disability. Treatment, which should include orthopedic care, is symptomatic.

Bibliography is available at Expert Consult.

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Chapter 87

Defects in Metabolism of Carbohydrates

Priya S. Kishnani and Yuan-Tsong Chen

Carbohydrate synthesis and degradation provide the energy required for most metabolic processes. The important carbohydrates include 3 monosaccharides—glucose, galactose, and fructose—and a polysaccharide, glycogen. Figure 87-1 shows the relevant biochemical pathways of these carbohydrates. Glucose is the principal substrate of energy metabolism. A continuous source of glucose from dietary intake, gluconeogenesis, and glycogenolysis of glycogen maintains normal blood glucose levels. Metabolism of glucose generates adenosine triphosphate (ATP) via glycolysis (conversion of glucose or glycogen to pyruvate), mitochondrial oxidative phosphorylation (conversion of pyruvate to carbon dioxide and water), or both. Dietary sources of glucose come from ingesting polysaccharides, primarily starch and disaccharides, including lactose, maltose, and sucrose. Oral intake of glucose is intermittent and unreliable. Glucose made de novo from amino acids, primarily alanine (gluconeogenesis), contributes to maintaining the euglycemic state, but this process requires time. The breakdown of hepatic glycogen provides the rapid release of glucose, which maintains a constant blood glucose concentration. Glycogen is also the primary stored energy source in muscle, providing glucose for muscle activity during exercise. Galactose and fructose are monosaccharides that provide fuel for cellular metabolism; their role is less significant than that of glucose. Galactose is derived from lactose (galactose + glucose), which is found in milk and milk products. Galactose is an important energy source in infants, but it is first metabolized to glucose. Galactose (exogenous or endogenously synthesized from glucose) is also an important component of certain glycolipids, glycoproteins, and glycosaminoglycans. The dietary sources of fructose are sucrose (fructose + glucose, sorbitol) and fructose itself, which is found in fruits, vegetables, and honey.

Defects in glycogen metabolism typically cause an accumulation of glycogen in the tissues, hence the name **glycogen storage disease** (Table 87-1). Defects in gluconeogenesis or the glycolytic pathway, including galactose and fructose metabolism, do not result in an accumulation of glycogen (Table 87-1). The defects in pyruvate metabolism in the pathway of the conversion of pyruvate to carbon dioxide and water via mitochondrial oxidative phosphorylation are more often associated with **lactic acidosis** and some tissue glycogen accumulation.

87.1 Glycogen Storage Diseases

Priya S. Kishnani and Yuan-Tsong Chen

The disorders of glycogen metabolism, the glycogen storage diseases (GSDs), result from deficiencies of various enzymes or transport proteins in the pathways of glycogen metabolism (see Fig. 87-1). The glycogen found in these disorders is abnormal in quantity, quality, or both. GSDs are categorized by numeric type in accordance with the chronological order in which these enzymatic defects were identified. This numeric classification is still widely used, at least up to number VII. The GSDs can also be classified by organ involvement and clinical manifestations into liver and muscle glycogenoses (see Table 87-1).

There are more than 12 forms of glycogenoses. Glucose-6-phosphatase deficiency (type I), lysosomal acid α-glucosidase deficiency (type II), debrancher deficiency (type III), and liver phosphorylase kinase

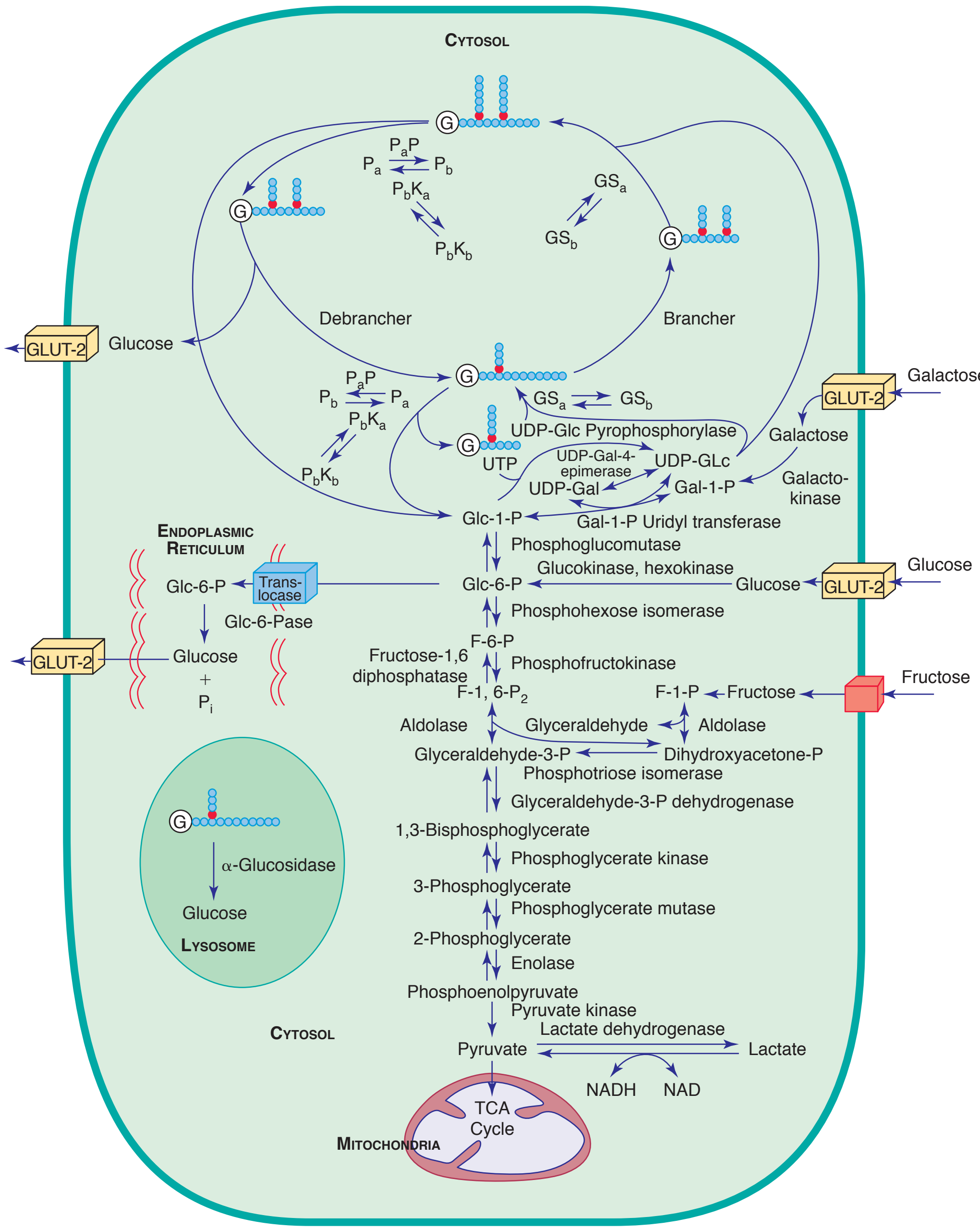

Figure 87-1 **Pathway related to glycogen storage diseases and galactose and fructose disorders.** *G*, glycogen, the primer for glycogen synthesis; *GLUT-2*, glucose transporter 2; *GSa*, active glycogen synthase; *GSb*, inactive glycogen synthase; *NAD/NADH*, nicotinamide-adenine dinucleotide; *Pa*, active phosphorylase; *PaP*, phosphorylase a phosphatase; *Pb*, inactive phosphorylase; *PbKa*, active phosphorylase b kinase; *PbKb*, inactive phosphorylase b kinase; *UDP*, uridine diphosphate. *(Modified from Beaudet AR: Glycogen storage disease. In Harrison TR, Isselbacher KJ, editors:* Harrison's principles of internal medicine, *ed 13, New York, 1994, McGraw-Hill. Reproduced with permission of The McGraw-Hill Companies.)*

deficiency (type IX) are the most common of those that typically present in early childhood; myophosphorylase deficiency (type V, McArdle disease) is the most common in adolescents and adults. The frequency of all forms of GSD is approximately 1 in 20,000 live births.

LIVER GLYCOGENOSES

The GSDs that principally affect the liver include glucose-6-phosphatase deficiency (type I), debranching enzyme deficiency (type III), branching enzyme deficiency (type IV), liver phosphorylase deficiency (type VI), phosphorylase kinase deficiency (type IX, formerly termed GSD VIa), glycogen synthase deficiency (type 0), and glucose transporter-2 defect. Because hepatic carbohydrate metabolism is responsible for plasma glucose homeostasis, this group of disorders typically causes fasting hypoglycemia and hepatomegaly. Some (types III, IV, IX) can be associated with liver cirrhosis. Other organs can also be involved and may manifest as renal dysfunction in type I, myopathy (skeletal and/or cardiomyopathy) in types III and IV, as well as in some rare forms of phosphorylase kinase deficiency, and neurologic involvement in types II (the brain, anterior horns cells), III (peripheral nerves), and IV (some patients can present with diffuse central and peripheral nervous system dysfunction).

Type I Glycogen Storage Disease (Glucose-6-Phosphatase or Translocase Deficiency, Von Gierke Disease)

Type I GSD is caused by the absence or deficiency of glucose-6-phosphatase activity in the liver, kidney, and intestinal mucosa. It can be divided into 2 subtypes: type Ia, in which the glucose-6-phosphatase

Table 87-1 Features of the Disorders of Carbohydrate Metabolism

DISORDERS	BASIC DEFECTS	CLINICAL PRESENTATION	COMMENTS
LIVER GLYCOGENOSES			
Type/Common Name			
Ia/Von Gierke	Glucose-6-phosphatase	Growth retardation, hepatomegaly, hypoglycemia; elevated blood lactate, cholesterol, triglyceride, and uric acid levels	Common, severe hypoglycemia
Ib	Glucose-6-phosphate translocase	Same as type Ia, with additional findings of neutropenia and impaired neutrophil function	10% of type Ia
IIIa/Cori or Forbes	Liver and muscle debrancher deficiency (amylo-1,6-glucosidase)	Childhood: hepatomegaly, growth retardation, muscle weakness, hypoglycemia, hyperlipidemia, elevated transaminase levels; liver symptoms can progress to liver failure later in life	Common, intermediate severity of hypoglycemia
IIIb	Liver debrancher deficiency; normal muscle enzyme activity	Liver symptoms same as in type IIIa; no muscle symptoms	15% of type III
IV/Andersen	Branching enzyme	Failure to thrive, hypotonia, hepatomegaly, splenomegaly, progressive cirrhosis (death usually before 5th yr), elevated transaminase levels	Rare neuromuscular variants exist
VI/Hers	Liver phosphorylase	Hepatomegaly, typically mild hypoglycemia, hyperlipidemia, and ketosis	Rare, typically benign glycogenosis; severe presentation also known
Phosphorylase kinase deficiency	Phosphorylase kinase	Hepatomegaly, mild hypoglycemia, hyperlipidemia, and ketosis	Common, typically a benign glycogenosis, severe progressive forms also present
Glycogen synthase deficiency	Glycogen synthase	Early morning drowsiness and fatigue, fasting hypoglycemia, and ketosis, no hepatomegaly	Decreased liver glycogen store
Fanconi-Bickel syndrome	Glucose transporter 2 (GLUT-2)	Failure to thrive, rickets, hepatorenomegaly, proximal renal tubular dysfunction, impaired glucose and galactose utilization	GLUT-2 expressed in liver, kidney, pancreas, and intestine
MUSCLE GLYCOGENOSES			
Type/Common Name			
II/Pompe infantile	Acid α-glucosidase (acid maltase)	Cardiomegaly, hypotonia, hepatomegaly; onset: birth to 6 mo	Common, cardiorespiratory failure leading to death by age 1-2 yr; minimal to no residual enzyme activity
II/Late-onset Pompe (juvenile and adult)	Acid α-glucosidase (acid maltase)	Myopathy, variable cardiomyopathy, respiratory insufficiency; onset: childhood to adulthood	Residual enzyme activity
Danon disease	Lysosome-associated membrane protein 2 (LAMP2)	Hypertrophic cardiomyopathy	Rare, X-linked
PRKAG2 deficiency	Adenosine monophosphate (AMP)-activated protein kinase γ	Hypertrophic cardiomyopathy	Autosomal dominant
V/McArdle	Myophosphorylase	Exercise intolerance, muscle cramps, increased fatigability	Common, male predominance
VII/Tarui	Phosphofructokinase	Exercise intolerance, muscle cramps, hemolytic anemia, myoglobinuria	Prevalent in Japanese and Ashkenazi Jews
Phosphoglycerate kinase deficiency	Phosphoglycerate kinase	As with type V	Rare, X-linked
Phosphoglycerate mutase deficiency	M subunit of phosphoglycerate mutase	As with type V	Rare, majority of patients are African-American
Lactate dehydrogenase deficiency	M subunit of lactate dehydrogenase	As with type V	Rare
GALACTOSE DISORDERS			
Galactosemia with transferase deficiency	Galactose-1-phosphate uridyltransferase	Vomiting, hepatomegaly, cataracts, aminoaciduria, failure to thrive	African-American patients tend to have milder symptoms
Galactokinase deficiency	Galactokinase	Cataracts	Benign
Generalized uridine diphosphate galactose-4-epimerase deficiency	Uridine diphosphate galactose-4-epimerase	Similar to transferase deficiency with additional findings of hypotonia and nerve deafness	A benign variant also exists
FRUCTOSE DISORDERS			
Essential fructosuria	Fructokinase	Urine reducing substance	Benign
	Fructose-1-phosphate aldolase	Acute: vomiting, sweating, lethargy	
Hereditary fructose intolerance		Chronic: failure to thrive, hepatic failure	Prognosis good with fructose restriction

Continued

Table 87-1 Features of the Disorders of Carbohydrate Metabolism—cont'd

DISORDERS	BASIC DEFECTS	CLINICAL PRESENTATION	COMMENTS
DISORDERS OF GLUCONEOGENESIS			
Fructose-1,6-diphosphatase deficiency	Fructose-1,6-diphosphatase	Episodic hypoglycemia, apnea, acidosis	Good prognosis, avoid fasting
Phosphoenolpyruvate carboxykinase deficiency	Phosphoenolpyruvate carboxykinase	Hypoglycemia, hepatomegaly, hypotonia, failure to thrive	Rare
DISORDERS OF PYRUVATE METABOLISM			
Pyruvate dehydrogenase complex defect	Pyruvate dehydrogenase	Severe fatal neonatal to mild late onset, lactic acidosis, psychomotor retardation, and failure to thrive	Most commonly caused by $E_{1\alpha}$ subunit, defect X-linked
Pyruvate carboxylase deficiency	Pyruvate carboxylase	Same as above	Rare, autosomal recessive
Respiratory chain defects (oxidative phosphorylation disease)	Complexes I-V, many mitochondrial DNA mutations	Heterogeneous with multisystem involvement	Mitochondrial inheritance
DISORDERS IN PENTOSE METABOLISM			
Pentosuria	L-Xylulose reductase	Urine-reducing substance	Benign
Transaldolase deficiency	Transaldolase	Liver cirrhosis and failure, cardiomyopathy	Autosomal recessive
Ribose-5-phosphate isomerase deficiency	Ribose-5-phosphate isomerase	Progressive leukoencephalopathy and peripheral neuropathy	

enzyme is defective; and type Ib, in which a translocase that transports glucose-6-phosphate across the microsomal membrane is defective. The defects in both type Ia and type Ib lead to inadequate hepatic conversion of glucose-6-phosphate to glucose through normal glycogenolysis and gluconeogenesis and make affected individuals susceptible to fasting hypoglycemia.

Type I GSD is an autosomal recessive disorder. The structural gene for glucose-6-phosphatase is located on chromosome 17q21; the gene for translocase is on chromosome 11q23. Common mutations responsible for the disease are known. Carrier detection and prenatal diagnosis are possible with the DNA-based diagnosis.

Clinical Manifestations

Patients with type I GSD may present in the neonatal period with hypoglycemia and lactic acidosis; they more commonly present at 3-4 mo of age with hepatomegaly, hypoglycemic seizures, or both. These children often have **doll-like faces** with fat cheeks, relatively thin extremities, short stature, and a protuberant abdomen that is a consequence of massive hepatomegaly; the kidneys are also enlarged, whereas the spleen and heart are normal.

The biochemical hallmarks of the disease are hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia. Hypoglycemia and lactic acidosis can develop after a short fast. Hyperuricemia is present in young children; gout rarely develops before puberty. Despite marked hepatomegaly, the liver transaminase levels are usually normal or only slightly elevated. Intermittent diarrhea may occur in GSD I. In patients with GSD Ib, the loss of mucosal barrier function as a result of inflammation, which is likely related to the disturbed neutrophil function, seems to be the main cause of diarrhea. Easy bruising and epistaxis are common and are associated with a prolonged bleeding time as a result of impaired platelet aggregation and adhesion.

The plasma may be "milky" in appearance as a result of a striking elevation of triglyceride levels. Cholesterol and phospholipids are also elevated, but less prominently. The lipid abnormality resembles type IV hyperlipidemia and is characterized by increased levels of very-low-density lipoprotein, low-density lipoprotein, and a unique apolipoprotein profile consisting of increased levels of apolipoproteins B, C, and E, with relatively normal or reduced levels of apolipoproteins A and D. The histologic appearance of the liver is characterized by a universal distention of hepatocytes by glycogen and fat. The lipid vacuoles are particularly large and prominent. There is little associated fibrosis.

All these findings apply to both type Ia and type Ib GSD, but **type Ib** has additional features of recurrent bacterial infections from **neutropenia** and impaired neutrophil function. Gut mucosa ulceration culminating in GSD enterocolitis is also common. Exceptional cases of type Ib without neutropenia and type Ia with neutropenia have been reported.

Although type I GSD affects mainly the liver, multiple organ systems are involved. Puberty is often delayed. Females can have ultrasound findings consistent with **polycystic ovaries;** other features of polycystic ovary syndrome (acne, hirsutism) are not seen. Nonetheless, fertility appears to be normal, as evidenced in several reports of successful pregnancy in women with GSD I. Increased bleeding during menstrual cycles, including life-threatening menorrhagia, has been noted and could be related to the impaired platelet aggregation. Symptoms of gout usually start around puberty from long-term hyperuricemia. Secondary to the lipid abnormalities, there is an increased risk of **pancreatitis.** The dyslipidemia, together with elevated erythrocyte aggregation, predisposes these patients to atherosclerosis. Premature atherosclerosis has not yet been clearly documented except for rare cases. Impaired platelet aggregation and increased antioxidative defense to prevent lipid peroxidation may function as a protective mechanism to help reduce the risk of atherosclerosis. Frequent fractures and radiographic evidence of **osteopenia** are common; bone mineral content is reduced even in prepubertal patients.

By the 2nd or 3rd decade of life, most patients with type I GSD exhibit **hepatic adenomas** that can hemorrhage and, in some cases, become malignant. **Pulmonary hypertension** has been seen in some long-term survivors of the disease. Iron refractory anemia and an increased prevalence of thyroid autoimmunity are also being recognized.

Renal disease is another complication, and most patients with type I GSD who are older than 20 yr of age have proteinuria. Many also have hypertension, renal stones, nephrocalcinosis, and altered creatinine clearance. Glomerular hyperfiltration, increased renal plasma flow, and microalbuminuria are often found in the early stages of renal dysfunction and can occur before the onset of proteinuria. In younger patients, hyperfiltration and hyperperfusion may be the only signs of renal abnormalities. With the advancement of renal disease, focal segmental glomerulosclerosis and interstitial fibrosis become evident. In some patients, renal function has deteriorated and progressed to failure, requiring dialysis and transplantation. Other renal

abnormalities include amyloidosis, a Fanconi-like syndrome, hypocitraturia, hypercalciuria, and a distal renal tubular acidification defect.

Diagnosis

The diagnosis of type I GSD is suspected on the basis of clinical presentation and the laboratory findings of hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia. Neutropenia is noted in GSD Ib patients, typically before 1 yr of age. It has also been noted in some cases of GSD Ia, especially those with the mutation p.G188A. Administration of glucagon or epinephrine results in little or no rise in blood glucose level, but the lactate level rises significantly. Before the glucose-6-phosphatase and glucose-6-phosphate translocase genes were cloned, a definitive diagnosis required a liver biopsy. Gene-based mutation analysis provides a noninvasive way to diagnose most patients with types Ia and Ib disease.

Treatment

Treatment is designed to maintain normal blood glucose levels and is achieved by continuous nasogastric infusion of glucose or oral administration of uncooked cornstarch. Nasogastric drip feeding can be introduced in early infancy from the time of diagnosis. It can consist of an elemental enteral formula or contain only glucose or a glucose polymer to provide sufficient glucose to maintain euglycemia during the night. Frequent feedings with high-carbohydrate content are given during the day.

Uncooked cornstarch acts as a slow-release form of glucose and can be introduced at a dose of 1.6 g/kg every 4 hr for children younger than 2 yr of age. The response of young children is variable. As the child grows older, the cornstarch regimen can be changed to every 6 hr at a dose of 1.6-2.5 g/kg of body weight. New starch products, which are currently being developed, are thought to be longer acting, better tolerated, and more palatable. A short-term double-blind crossover pilot study comparing uncooked, physically modified cornstarch to traditional cornstarch showed that the majority of GSD I patients treated with the new starch had better short-term metabolic control and longer duration of euglycemia, especially at night. However, more extensive studies replicating these results are necessary. Because fructose and galactose cannot be converted directly to glucose in GSD type I, these sugars are restricted in the diet. Sucrose (table sugar, cane sugar, other ingredients), fructose (fruit, juice, high fructose corn syrup), lactose (dairy foods), and sorbitol should be avoided or limited. As a result of these dietary restrictions, vitamins and minerals such as calcium and vitamin D may be deficient and supplementation is required to prevent nutritional deficiencies. Dietary therapy improves hyperuricemia, hyperlipidemia, and renal function, slowing the development of renal failure. This therapy fails, however, to normalize blood uric acid and lipid levels completely in some individuals, despite good metabolic control, especially after puberty. The control of hyperuricemia can be further augmented by the use of allopurinol, a xanthine oxidase inhibitor. The hyperlipidemia can be reduced with lipid-lowering drugs such as beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and fibrate (see Chapter 86). Microalbuminuria, an early indicator of renal dysfunction in type I disease, is treated with angiotensin-converting enzyme inhibitors. Citrate supplements can be beneficial for patients with hypocitraturia by preventing or ameliorating nephrocalcinosis and development of urinary calculi. Growth hormone should be used with extreme caution and limited to only those with a documented growth hormone deficiency. Even in those cases, there should be close monitoring of metabolic parameters and presence of adenomas.

In patients with type Ib GSD, granulocyte and granulocyte-macrophage colony-stimulating factors are successful in correcting the neutropenia, decreasing the number and severity of bacterial infections, and improving the chronic inflammatory bowel disease. The minimum effective dose should be used, as side effects are noted on these agents, including splenomegaly, hypersplenism, and bone pain.

Orthotopic liver transplantation is a potential cure of type I GSD. However, the inherent short- and long-term complications leave this as a treatment of last resort, usually for patients with liver malignancy, multiple liver adenomas, metabolic derangements refractory to medical management, and/or liver failure. Large adenomas (>2 cm) that are rapidly increasing in size and/or number may require partial hepatic resection. Smaller adenomas (<2 cm) can be treated with percutaneous ethanol injection or transcatheter arterial embolization. A challenge is the recurrence of liver adenomas with potential for malignant transformation in these patients, ultimately requiring a liver transplant.

Bone marrow transplantation has been reported to correct the neutropenia of type Ib GSD.

Before any surgical procedure, the bleeding status must be evaluated and good metabolic control established. Prolonged bleeding times can be normalized by the use of intensive intravenous glucose infusion for 24-48 hr before surgery. Use of 1-deamino-8-D-arginine vasopressin (DDAVP) can reduce bleeding complications. Lactated Ringer solution should be avoided because it contains lactate and no glucose. Glucose levels should be maintained in the normal range throughout surgery with the use of 10% dextrose. Overall, metabolic control is assessed by growth, improvement, and correction of the metabolic abnormalities such as elevated lactate, glucose, triglyceride, cholesterol, and uric acid levels.

Prognosis

Previously, many patients with type I GSD died at a young age, and the prognosis was guarded for those who survived. Long-term complications occur mostly in adults whose disease was not adequately treated during childhood. Early diagnosis and effective treatment have improved the outcome, although renal disease and formation of hepatic adenomas with potential risk for malignant transformation remain serious complications. The ability to identify transformation to hepatocellular carcinoma in the liver adenomas remains a challenge: α-fetoprotein and carcinoembryonic antigen levels often remain normal in the setting of hepatocellular carcinoma.

Type III Glycogen Storage Disease (Debrancher Deficiency, Limit Dextrinosis)

Type III GSD is caused by a deficiency of glycogen debranching enzyme activity. Debranching enzyme, together with phosphorylase, is responsible for complete degradation of glycogen. When debranching enzyme is defective, glycogen breakdown is incomplete and an abnormal glycogen with short outer branch chains and resembling limit dextrin accumulates. Deficiency of glycogen debranching enzyme causes hepatomegaly, hypoglycemia, short stature, variable skeletal myopathy, and variable cardiomyopathy. The disorder usually involves both liver and muscle and is termed type IIIa GSD. In approximately 15% of patients, the disease appears to involve only liver and is classified as type IIIb.

Type III glycogenosis is an autosomal recessive disease that has been reported in many different ethnic groups; the frequency is relatively high in Sephardic Jews from North Africa. The gene for debranching enzyme is located on chromosome 1p21. More than 40 different mutations are identified; 2 exon 3 mutations c.18_19delGA (previously described as c.17_18delAG) and p.Gln6X are specifically associated with glycogenosis IIIb. Carrier detection and prenatal diagnosis are possible using DNA-based linkage or mutation analysis.

Clinical Manifestations

During infancy and childhood, the disease may be indistinguishable from type I GSD, because hepatomegaly, hypoglycemia, hyperlipidemia, and growth retardation are common (Fig. 87-2). Splenomegaly may be present, but the kidneys are not enlarged. Hepatomegaly and hepatic symptoms in most patients with type III GSD improve with age; however, progressive liver cirrhosis and failure can occur. Hepatocellular carcinoma has also been reported, more typically in patients with progressive liver cirrhosis. The frequency of adenomas in individuals with GSD III is far less than in individuals with GSD I. Furthermore, the relationship of hepatic adenomas and malignancy in GSD III is unclear. α-Fetoprotein and carcinoembryonic antigen levels are not good predictors of the presence of hepatocellular adenomas or malignant transformation. A single case of malignant transformation

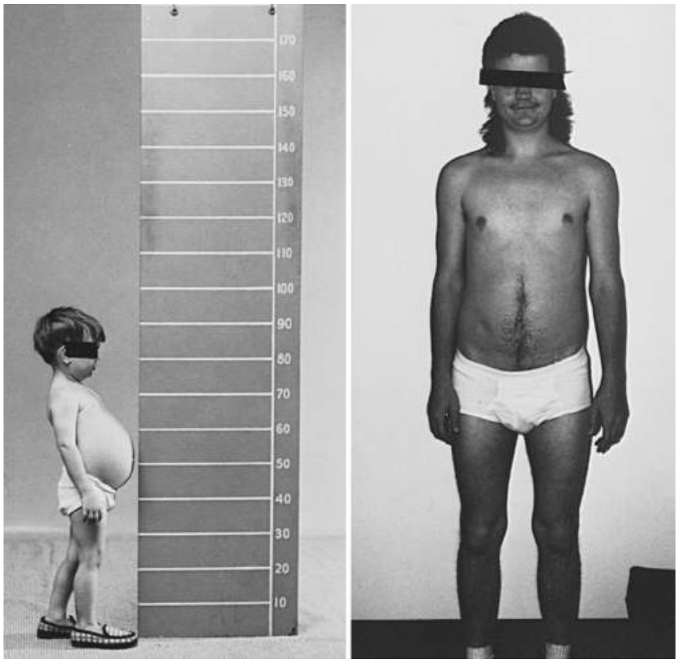

Figure 87-2 Growth and development in a patient with type IIIb glycogen storage disease. The patient has debrancher deficiency in liver but normal activity in muscle. As a child, he had hepatomegaly, hypoglycemia, and growth retardation. After puberty, he no longer had hepatomegaly or hypoglycemia, and his final adult height is normal. He had no muscle weakness or atrophy; this is in contrast to type IIIa patients, in whom a progressive myopathy is seen in adulthood.

at the site of adenomas has been noted. In patients with muscular involvement (type IIIa), muscle weakness can present in childhood but can become severe after the 3rd or 4th decade of life, as evidenced by slowly progressive weakness and wasting. Because patients with GSD III can have decreased bone density, they are at an increased risk of potential fracture. Myopathy does not follow any particular pattern of involvement; both proximal and distal muscles are involved. Electromyography reveals a widespread myopathy; nerve conduction studies are often abnormal. Ventricular hypertrophy is a frequent finding, but overt cardiac dysfunction is rare. Cardiac pathology has shown diffuse involvement of various cardiac structures including vacuolation of myocytes, atrioventricular conduction, and hyperplasia of smooth muscles. There have been some reports of life-threatening arrhythmia and need for heart transplant in some GSD III patients. Hepatic symptoms in some patients may be so mild that the diagnosis is not made until adulthood, when the patients show symptoms and signs of neuromuscular disease. The initial diagnosis has been confused with Charcot-Marie-Tooth disease. Polycystic ovaries are common; some patients can develop hirsutism, irregular menstrual cycles, and other features of polycystic ovarian syndrome. Fertility does not appear to be reduced; successful pregnancies in patients with GSD III have been reported.

Hypoglycemia and hyperlipidemia are common. In contrast to type I GSD, elevation of liver transaminase levels and fasting ketosis are prominent, but blood lactate and uric acid concentrations are usually normal. Serum creatine kinase levels can be useful to identify patients with muscle involvement; normal levels do not rule out muscle enzyme deficiency. The administration of glucagon 2 hr after a carbohydrate meal provokes a normal increase in blood glucose; after an overnight fast, glucagon may provoke no change in blood glucose level.

Diagnosis

The histologic appearance of the liver is characterized by a universal distention of hepatocytes by glycogen and the presence of fibrous septa. The fibrosis and the paucity of fat distinguish type III glycogenosis from type I. The fibrosis, which ranges from minimal periportal fibrosis to micronodular cirrhosis, appears in most cases to be nonprogressive. Overt cirrhosis has been seen in some patients with GSD III.

Patients with myopathy and liver symptoms have a generalized enzyme defect (type IIIa). The deficient enzyme activity can be demonstrated not only in liver and muscle, but also in other tissues such as heart, erythrocytes, and cultured fibroblasts. Patients with hepatic symptoms without clinical or laboratory evidence of myopathy have debranching enzyme deficiency only in the liver, with enzyme activity retained in the muscle (type IIIb). Definite diagnosis requires enzyme assay in liver, muscle, or both. Mutation analysis can provide a noninvasive method for diagnosis and subtype assignment in the majority of patients.

Treatment

Dietary management is less demanding than in type I GSD. Patients do not need to restrict dietary intake of fructose and galactose. If hypoglycemia is present, frequent meals high in carbohydrates with cornstarch supplements or nocturnal gastric drip feedings are usually effective. A high-protein diet during the daytime plus overnight protein enteral infusion is also effective in preventing hypoglycemia and preventing endogenous protein breakdown because protein can be used as a substrate for gluconeogenesis, a pathway that is intact in type III GSD. There is no satisfactory treatment for the progressive myopathy other than recommending a high-protein diet and an exercise program. Liver transplantation has been performed in GSD III patients with progressive cirrhosis and/or hepatic carcinoma. There are reports of cardiac transplant in GSD III patients with end stage cardiac disease.

Type IV Glycogen Storage Disease (Branching Enzyme Deficiency, Amylopectinosis, or Andersen Disease)

Deficiency of branching enzyme activity results in accumulation of an abnormal glycogen with poor solubility. The disease is referred to as type IV GSD or amylopectinosis because the abnormal glycogen has fewer branch points, more α 1-4 linked glucose units, and longer outer chains, resulting in a structure resembling amylopectin. Type IV GSD is an autosomal recessive disorder. The glycogen branching enzyme *(GBE)* gene is located on chromosome 3p21. More than 20 mutations responsible for type IV GSD have been identified, and their characterization in individual patients can be useful in predicting the clinical outcome. The nearly complete absence of GBE activity with null mutations has been associated with perinatal death and fatal neonatal hypotonia. Residual GBE enzyme activity of greater than 5% and at least 1 missense mutation are associated with a nonlethal phenotype and, in some situations, a lack of progressive liver disease.

Clinical Manifestations

This disorder is clinically variable. The most common and classic form is characterized by progressive cirrhosis of the liver and is manifested in the first 18 mo of life as hepatosplenomegaly and failure to thrive. The cirrhosis progresses to portal hypertension, ascites, esophageal varices, and liver failure that usually lead to death by 5 yr of age. Rare patients survive without progression of liver disease; these patients have a milder hepatic form and do not require a liver transplant.

A **neuromuscular** form of the disease has been reported with 4 main variants recognized based on age of presentation. The perinatal form presents as a fetal akinesia deformation sequence and death in the perinatal period. The congenital form presents at birth with severe hypotonia, muscle atrophy, and neuronal involvement with death in the neonatal period; some patients have cardiomyopathy. The childhood form presents primarily with myopathy or cardiomyopathy. The adult form presents with diffuse central and peripheral nervous system dysfunction accompanied by accumulation of polyglucosan material in the nervous system (**adult polyglucosan body disease**). For adult polyglucosan disease, a leukocyte or nerve biopsy is needed to establish the diagnosis as branching enzyme deficiency is limited to those tissues.

Diagnosis

Tissue deposition of amylopectin-like materials can be demonstrated in liver, heart, muscle, skin, intestine, brain, spinal cord, and peripheral nerve. The hepatic histologic findings are characterized by micronodular cirrhosis and faintly stained basophilic inclusions in the hepatocytes. The inclusions consist of coarsely clumped, stored material that is periodic acid–Schiff positive and partially resistant to diastase digestion. Electron microscopy shows, in addition to the conventional α and β glycogen particles, accumulation of the fibrillar aggregations that are typical of amylopectin. The distinct staining properties of the cytoplasmic inclusions, as well as electron microscopic findings, could be diagnostic. However, polysaccharides with histologic features reminiscent of type IV disease, but without enzymatic correlation, have been observed. The definitive diagnosis rests on the demonstration of the deficient branching enzyme activity in liver, muscle, cultured skin fibroblasts, or leukocytes, or on the identification of disease-causing mutations in the *GBE* gene. Prenatal diagnosis is possible by measuring the enzyme activity in cultured amniocytes, chorionic villi, or mutation analysis.

Treatment

There is no specific treatment for type IV GSD. Unlike patients with the other liver GSDs (I, III, VI, IX), those with GSD IV do not have hypoglycemia, which is only seen when there is overt liver cirrhosis. Liver transplantation has been performed for patients with progressive hepatic failure, but because it is a multisystem disorder involving many organ systems, the long-term success of liver transplantation is unknown. Individuals with significant diffuse reticuloendothelial involvement may have greater risk for morbidity and mortality, which may impact the success rate for liver transplants. Caution should be taken in selecting type IV patients for liver transplantation because these patients have variable phenotypes, which include a nonprogressive form of the liver disease and in some cases, extrahepatic manifestations of the disease.

Type VI Glycogen Storage Disease (Liver Phosphorylase Deficiency, Hers Disease)

There are few patients with documented liver phosphorylase deficiency. Such patients usually have a benign course and present with hepatomegaly and growth retardation in early childhood; however, some cases are more severe. Hypoglycemia, hyperlipidemia, and hyperketosis are of variable severity. Lactic acid and uric acid levels are normal. The heart and skeletal muscles are not involved. The hepatomegaly and growth retardation improve with age and usually disappear around puberty. Some patients with severe hepatomegaly, recurrent severe hypoglycemia, hyperketosis, and postprandial lactic acidosis have recently been reported. Treatment is symptomatic, as some patients require no specific treatment. A high-carbohydrate, high-protein diet and frequent feeding are effective in preventing hypoglycemia. Blood glucose and ketones should be monitored routinely, especially during periods of increased activity/illness.

GSD VI is an autosomal recessive disease. Diagnosis can be confirmed through molecular testing of the liver phosphorylase gene *(PYGL),* which is found on chromosome 14q21-22 and has 20 exons. Many mutations are known in this gene; a splice-site mutation in intron 13 has been identified in the Mennonite population. A liver biopsy showing elevated glycogen content and decreased hepatic phosphorylase enzyme activity can also be used to make a diagnosis.

Type IX Glycogen Storage Disease (Phosphorylase Kinase Deficiency)

This disorder represents a heterogeneous group of glycogenoses. Phosphorylase, the rate-limiting enzyme of glycogenolysis, is activated by a cascade of enzymatic reactions involving adenylate cyclase, cyclic adenosine monophosphate–dependent protein kinase (protein kinase A), and phosphorylase kinase. The latter enzyme has 4 subunits (α, β, γ, δ), each encoded by different genes on different chromosomes and differentially expressed in various tissues. This cascade of reactions is stimulated primarily by glucagon. Glycogenosis could be the result of any enzyme deficiency along this pathway; the most common is the deficiency of phosphorylase kinase. Phosphorylase kinase (PhK) deficiency varies clinically as a result of defects in the various genes encoding the four subunits of the protein. Mutations in the *PHKA1* gene causes muscle PhK deficiency; mutations in the *PHKA2* and *PHKG2* genes cause liver PhK deficiency; mutations in the *PHKB* gene cause PhK deficiency in liver and muscle. Mutations in the *PHKG1* gene have not been identified. Defects in subunits α, β, and γ are responsible for liver presentation. Liver PhK deficiency's physical features are usually recognizable within the first 2 yr of life and include short stature and abdominal distention from moderate to marked hepatomegaly. The clinical severity of liver PhK deficiency varies considerably. Hyperketotic hypoglycemia, if present, is usually mild but can be severe in some cases. Ketosis may occur even when glucose levels are normal. In some children, there may be mild delays in gross motor development and hypotonia. Liver fibrosis can occur and progress to cirrhosis in rare cases, particularly in patients with *PHKG2* mutations. Liver adenoma appears to be very rare. Cognitive and speech delays have been reported in a few individuals, but it is not clear whether these delays are caused by PhK deficiency or whether they are coincidental. Polycystic ovaries are common in females with liver PhK deficiency. Renal tubular acidosis has been reported in rare cases. Cardiac manifestations have not been reported. Unlike in GSD I, lactic acidosis, bleeding tendency, and loose bowel movements are not characteristic. Although growth is retarded during childhood, normal height and complete sexual development are eventually achieved. As with debrancher deficiency, abdominal distention and hepatomegaly usually decrease with age and may disappear by adolescence. Most adults with liver PhK deficiency are asymptomatic, although further long-term studies are needed to fully assess the impact of this disorder in adults. Phenotypic variability within each subtype is being uncovered with the availability of molecular testing. The incidence of all subtypes of PhK deficiency is approximately 1 : 100,000 live births.

X-Linked Liver Phosphorylase Kinase Deficiency

X-linked liver PhK deficiency is the most common form of liver glycogenoses. In addition to liver, enzyme activity can also be deficient in erythrocytes, leukocytes, and fibroblasts; it is normal in muscle. Typically, a 1-5 yr old male presents with growth retardation, an incidental finding of hepatomegaly, and a slight delay in motor development. Cholesterol, triglycerides, and liver enzymes are mildly elevated. Ketosis may occur after fasting. Lactate and uric acid levels are normal. Hypoglycemia is typically mild, if present, but can be severe. The response in blood glucose to glucagon is normal. Hepatomegaly and abnormal blood chemistries gradually improve and can normalize with age. Most adults achieve a normal final height and are usually asymptomatic despite a persistent PhK deficiency. In rare cases, liver fibrosis can occur and progress to cirrhosis. Liver histology shows glycogen-distended hepatocytes, steatosis, and potentially mild periportal fibrosis. The accumulated glycogen (β particles, rosette form) has a frayed or burst appearance and is less compact than the glycogen seen in type I or type III GSD. Fibrous septal formation and low-grade inflammatory changes may be present.

The structural gene for the common liver isoform of the PhK α subunit, *PHKA2,* is located on the X chromosome (αL at Xp22.2). Mutations in the *PHKA2* gene account for 75% of all PhK cases. X-linked liver PhK deficiency is further subdivided into 2 biochemical subtypes: XLG1, with measurable deficiency of PhK activity in both blood cells and liver, and XLG2, with normal in vitro PhK activity in blood cells and variable activity in liver. It is suspected that XLG2 may be caused by missense mutations that affect enzyme regulation, while nonsense mutations affecting the amount of protein result in XLG1.

Autosomal Liver and Muscle Phosphorylase Kinase Deficiency

PhK deficiency in liver and blood cells with an autosomal mode of inheritance has been reported. As with the X-linked form, hepatomegaly and growth retardation are the predominant symptoms in early

childhood. Some patients also exhibit muscle hypotonia. In a few cases where enzyme activity has been measured, reduced PhK activity has been demonstrated in muscle. Mutations causing milder autosomally transmitted liver and muscle PhK deficiency are found in the *PHKB* gene (chromosome 16q12-q13), which encodes the β subunit. Several nonsense mutations, a single-base insertion, a splice-site mutation, and a large intragenic mutation have been identified. In addition, a missense mutation was discovered in an atypical patient with normal blood cell PhK activity.

Autosomal Liver Phosphorylase Kinase Deficiency

This form of PhK deficiency is caused by mutations in the testis/liver isoform of the γ subunit gene (TL, *PHKG2*). In contrast to X-linked PhK deficiency, patients with mutations in the *PHKG2* gene typically have more severe phenotypes with recurrent hypoglycemia and often develop progressive liver cirrhosis. *PHKG2* maps to chromosome 16p12.1- p11.2; many disease-causing mutations are known for this gene.

Muscle-Specific Phosphorylase Kinase Deficiency

A few cases of PhK deficiency restricted to muscle are known. Patients, both male and female, present either with muscle cramps and myoglobinuria with exercise or with progressive muscle weakness and atrophy. PhK activity is decreased in muscle but normal in liver and blood cells. There is no hepatomegaly or cardiomegaly. The structural gene for the muscle-specific form α subunit (αM) is located at Xq12. Mutations of the gene have been found in some male patients with this disorder. The gene for muscle γ subunit (γM, *PHKG1*) is on chromosome 7p12. No mutations in this gene have been reported so far.

Phosphorylase Kinase Deficiency Limited to Heart

These patients present with **cardiomyopathy** in infancy and rapidly progress to heart failure and death. PhK deficiency is demonstrated in the heart with normal enzyme activity in skeletal muscle and liver. Studies have questioned the existence of cardiac-specific primary PhK deficiency. However, the disease presentation has now been linked to the γ2 subunit of adenosine monophosphate–activated protein kinase (see “Glycogen Storage Diseases Mimicking Hypertrophic Cardiomyopathy” below). The γ2 subunit is encoded by the *PRKAG2* gene.

Diagnosis

Definitive diagnosis of PhK deficiency requires demonstration of the enzymatic defect in affected tissues. PhK can be measured in leukocytes and erythrocytes, but because the enzyme has many isozymes, the diagnosis can be easily missed without studies of liver, muscle, or heart. Mutation analysis is necessary in many cases to determine the disease's subtype. Individuals with liver PhK deficiency also usually have elevated transaminases, mildly elevated triglycerides and cholesterol, normal uric acid and lactic acid concentrations, and normal glucagon responses.

The *PHKA2* gene encoding the α subunit is most commonly involved, followed by the *PHKB* gene encoding the β subunit, regardless of the presence of deficiency in erythrocytes. Mutations in the *PHKG2* gene underlying γ-subunit deficiency are typically associated with severe liver involvement with recurrent hypoglycemia and liver fibrosis.

Treatment

The treatment for liver PhK deficiency is symptomatic. It includes a high-carbohydrate, high-protein diet and frequent feedings to prevent hypoglycemia, although many patients require no specific treatment. Cornstarch can be administered with symptom-dependent dosage and timing (0.6-2.5 g/kg every 6 hr). Oral intake of glucose, if tolerated, should be used to treat hypoglycemia. If not, intravenous glucose should be given. Prognosis for the X-linked and certain autosomal forms is typically good, however, patients with mutations in the γ subunit typically have a more severe clinical course with progressive liver disease. There is no treatment for the fatal form of isolated cardiac PhK deficiency other than heart transplantation.

Glycogen Synthase Deficiency

Deficiency of hepatic glycogen synthase *(GYS2)* activity leads to a marked decrease of glycogen stored in the liver. The gene for GYS2 is located at 12p12.2. Several mutations of this gene have been identified in patients with GSD 0. The disease appears to be rare in humans, and in the true sense, this is not a type of GSD because the deficiency of the enzyme leads to decreased glycogen stores. Patients present in infancy with early morning (prebreakfast) drowsiness, pallor, emesis, and fatigue, and sometimes convulsions associated with hypoglycemia and hyperketonemia. Blood lactate and alanine levels are low, and there is no hyperlipidemia or hepatomegaly. Prolonged hyperglycemia, glycosuria, and elevation of lactate with normal insulin levels after administration of glucose or a meal suggest a possible diagnosis of deficiency of glycogen synthase. Definitive diagnosis requires a liver biopsy to measure the enzyme activity or identification of mutations in the liver glycogen synthase gene, located on chromosome 12p12.2. Treatment consists of frequent meals, rich in protein, and nighttime supplementation with uncooked cornstarch to prevent hypoglycemia and hyperketonemia. Most children with GSD 0 are cognitively and developmentally normal. Short stature and osteopenia are common features. The prognosis seems good for patients who survive to adulthood, including resolution of hypoglycemia, except during pregnancy.

Muscle Glycogen Synthase Deficiency

This GSD results from muscle glycogen synthase (glycogen synthase I, *GYS1*) deficiency. The gene for GYS1 has been localized to chromosome 19q13.3. The disease is extremely rare and was reported in 3 children of consanguineous parents of Syrian origin. Muscle biopsies showed lack of glycogen, predominantly oxidative fibers, and mitochondrial proliferation. Glucose tolerance was normal. Molecular study revealed a homozygous stop mutation (R462→ter) in the muscle glycogen synthase gene. The phenotype was variable in the 3 siblings and ranged from sudden cardiac arrest, muscle fatigability, hypertrophic cardiomyopathy, an abnormal heart rate, and hypotension while exercising, to mildly impaired cardiac function at rest.

Hepatic Glycogenosis with Renal Fanconi Syndrome (Fanconi-Bickel Syndrome)

This rare autosomal recessive disorder is caused by defects in the facilitative glucose transporter 2 (GLUT-2), which transports glucose in and out of hepatocytes, pancreatic β cells, and the basolateral membranes of intestinal and renal epithelial cells. The disease is characterized by proximal renal tubular dysfunction, impaired glucose and galactose utilization, and accumulation of glycogen in liver and kidney.

The affected child typically presents in the first year of life with failure to thrive, rickets, and a protuberant abdomen from hepatomegaly and nephromegaly. The disease may be confused with GSD type I because a Fanconi-like syndrome can also develop in type I disease patients. Adults commonly present with short stature, dwarfism, and excess fat in the abdomen and shoulders. Patients are more susceptible to fractures owing to early-onset generalized osteopenia. In addition, intestinal malabsorption and diarrhea may occur.

Laboratory findings include glucosuria, phosphaturia, generalized aminoaciduria, bicarbonate wasting, hypophosphatemia, increased serum alkaline phosphatase levels, and radiologic findings of rickets. Mild fasting hypoglycemia and hyperlipidemia may be present. Liver transaminase, plasma lactate, and uric acid levels are usually normal. Oral galactose or glucose tolerance tests show intolerance, which could be explained by the functional loss of GLUT-2 preventing liver uptake of these sugars. Tissue biopsy results show marked accumulation of glycogen in hepatocytes and proximal renal tubular cells, presumably owing to the altered glucose transport out of these organs. Diffuse glomerular mesangial expansion along with glomerular hyperfiltration and microalbuminuria similar to nephropathy in GSD Ia and diabetes have been reported.

Fanconi-Bickel syndrome is rare. Seventy percent of patients with a detectable GLUT-2 mutation have consanguineous parents. Most patients are homozygous for the disease-related mutations; some patients are compound heterozygotes. The majority of mutations detected thus far predict a premature termination of translation. The resulting loss of the C-terminal end of the GLUT-2 protein predicts a nonfunctioning glucose transporter with an inward-facing substrate-binding site.

There is no specific treatment. Symptom-dependent treatment with phosphate and bicarbonate can result in growth improvement. Symptomatic replacement of water, electrolytes, and vitamin D; restriction of galactose intake; and a diet similar to that used for diabetes mellitus presented in frequent and small meals with an adequate caloric intake may also improve growth.

MUSCLE GLYCOGENOSES

The role of glycogen in muscle is to provide substrates for the generation of ATP for muscle contraction. The muscle GSDs are broadly divided into 2 groups. The first group is characterized by hypertrophic cardiomyopathy, progressive skeletal muscle weakness and atrophy, or both, and includes deficiencies of acid α-glucosidase, a lysosomal glycogen degrading enzyme (type II GSD), lysosomal-associated membrane protein 2 (LAMP2), and adenosine monophosphate–activated protein kinase γ2 (PRKAG2). The second group comprises muscle energy disorders characterized by muscle pain, exercise intolerance, myoglobinuria, and susceptibility to fatigue. This group includes myophosphorylase deficiency (McArdle disease, type V) and deficiencies of phosphofructokinase (type VII), phosphoglycerate kinase, phosphoglycerate mutase, and lactate dehydrogenase. Some of these latter enzyme deficiencies can also be associated with compensated hemolysis, suggesting a more generalized defect in glucose metabolism.

Type II Glycogen Storage Disease (Lysosomal Acid α-1,4-Glucosidase Deficiency, Pompe Disease)

Pompe disease, also referred to as GSD type II or acid maltase deficiency, is caused by a deficiency of acid α-1,4-glucosidase (acid maltase), an enzyme responsible for the degradation of glycogen in lysosomes. This enzyme defect results in lysosomal glycogen accumulation in multiple tissues and cell types, with cardiac, skeletal, and smooth muscle cells being the most seriously affected. The disease is characterized by accumulation of glycogen in lysosomes, as opposed to its accumulation in cytoplasm in the other glycogenoses.

Pompe disease is an autosomal recessive disorder with an incidence of approximately 1 in 40,000 live births in whites and 1 in 18,000 live births in Han Chinese. The gene for acid α-glucosidase is on chromosome 17q25.2. Multiple pathogenic mutations have been identified that could be helpful in delineating the phenotypes. An example is a splice-site mutation (IVS1-13T→G; c.-32-13T>G), commonly seen in late-onset patients of white race.

Clinical Manifestations

The disorder encompasses a range of phenotypes, each including myopathy but differing in age at onset, organ involvement, and clinical severity. **Infantile Pompe disease** was uniformly lethal without enzyme replacement therapy with alglucosidase alfa. Affected infants present in the first few weeks to months of life with hypotonia, a generalized muscle weakness with a "floppy infant" appearance, neuropathic bulbar weakness, feeding difficulties, macroglossia, hepatomegaly, and a hypertrophic cardiomyopathy followed by death from cardiorespiratory failure or respiratory infection usually by 1 yr of age. **Late-onset Pompe disease (juvenile and adult-onset disease)** is characterized by a lack or absence of severe cardiac involvement and a less-severe short-term prognosis. Symptoms related to progressive dysfunction of skeletal muscles can start as early as 1 yr of age to as late as the 6th decade of life. The clinical picture is dominated by slowly progressive proximal muscle weakness with truncal involvement and greater involvement of the lower limbs than the upper limbs. The pelvic girdle, paraspinal muscles, and diaphragm are the muscle groups most seriously affected. Other symptoms may include lingual weakness, ptosis, and dilation of blood vessels such as the basilar artery and the ascending aorta. These patients often present with proximal or limb girdle muscle weakness. With disease progression, patients become confined to wheelchairs and require artificial ventilation. The initial symptoms in some patients may be respiratory insufficiency manifested by somnolence, morning headache, orthopnea, and exertional dyspnea, which eventually lead to sleep-disordered breathing and respiratory failure. Respiratory failure is the cause of significant morbidity and mortality in this form of the disease. Basilar artery aneurysms with rupture also contribute to mortality in some cases. The age of death varies from early childhood to late adulthood, depending on the rate of disease progression and the extent of respiratory muscle involvement. With the advent of enzyme replacement therapy, a new picture of the natural history is emerging for both infantile and late onset patients with Pompe disease.

Laboratory Findings

These include elevated levels of serum creatine kinase, aspartate aminotransferase, and lactate dehydrogenase. In the infantile form a chest x-ray showing massive cardiomegaly is frequently the first symptom detected. Electrocardiographic findings include a high-voltage QRS complex and a shortened PR interval. Echocardiography reveals thickening of both ventricles and/or the intraventricular septum and/or left ventricular outflow tract obstruction. Muscle biopsy shows the presence of vacuoles that stain positively for glycogen; acid phosphatase is increased, presumably from a compensatory increase of lysosomal enzymes. Electron microscopy reveals glycogen accumulation within the membranous sac and in the cytoplasm. Electromyography reveals myopathic features with excessive electrical irritability of muscle fibers and pseudomyotonic discharges. Serum creatine kinase is not always elevated in adult patients. Depending on the muscle sampled or tested, the muscle histologic appearance and electromyography may not be abnormal.

Some patients with infantile Pompe disease who had peripheral nerve biopsies demonstrated glycogen accumulation in the neurons and Schwann cells, too. Infantile Pompe disease may manifest both myopathic and neuropathic clinical signs. Generally, the former predominate.

Diagnosis

The confirmatory step for a diagnosis of Pompe disease is enzyme assay demonstrating deficient acid α-glucosidase or gene sequencing showing 2 pathogenic mutations in the *GAA* gene. The enzyme assay is usually done in dried blood spots, leukocytes, blood mononuclear cells, muscle, and cultured skin fibroblasts, using maltose, glycogen, or 4-methylumbelliferyl-α-D-glucopyranoside (4MUG) as a substrate. Deficiency is usually more severe in the infantile form than in the late-onset forms. The skin fibroblast assay is usually preferred to muscle biopsy because it is a less-invasive procedure with the advantage of maintaining a cell line for future use and providing information on residual enzyme activity. Blood-based assays, especially dried blood spots, have the advantage of a rapid turnaround time. A muscle biopsy can yield faster results and provide additional information about glycogen content and site of glycogen storage within and outside the lysosomes of muscle cells. A major limitation of a muscle biopsy in late-onset patients is the variable pathology and glycogen accumulation in different muscles and within muscle fibers; muscle histology and glycogen content can vary depending on the site of muscle biopsy. There is also a high risk from anesthesia in infantile patients. An electrocardiogram can be helpful in making the diagnosis in suspected cases of the infantile form and should be done for patients suspected of having Pompe disease before any procedure requiring anesthesia, including muscle biopsy, is performed. Urinary glucose tetrasaccharides are elevated in the urine of affected patients, and levels are extremely high in infantile patients. This biomarker is valuable for diagnosis and monitoring response to therapy in Pompe disease. Prenatal diagnosis using amniocytes or chorionic villi is available for the infantile form of the disease.

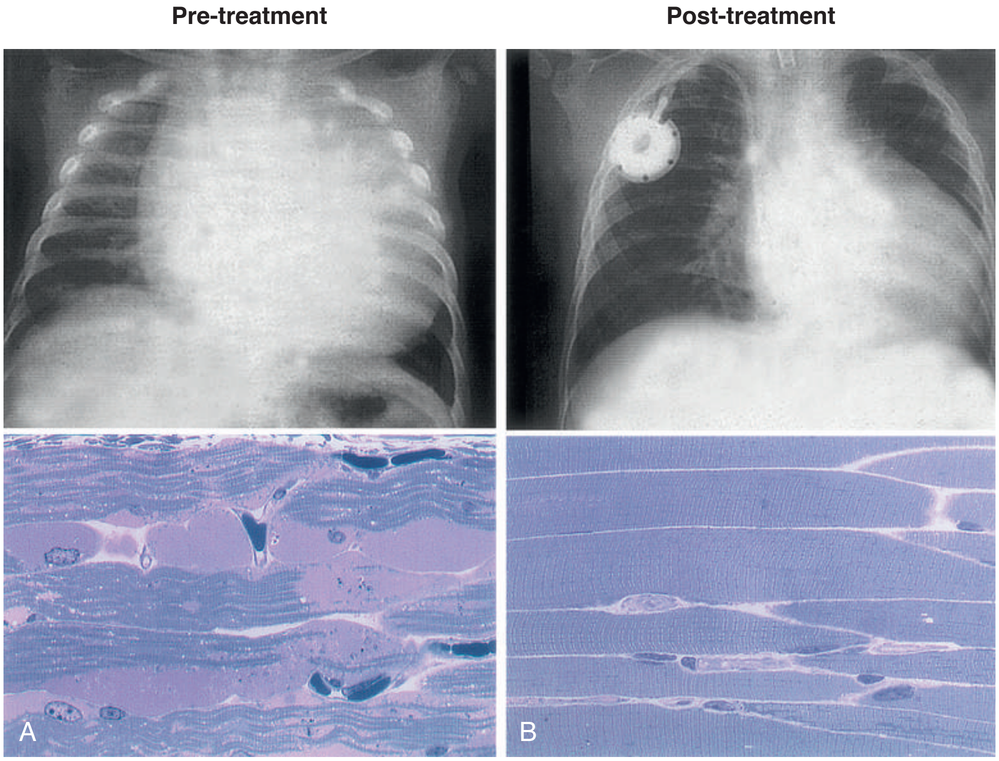

Figure 87-3 Chest x-ray and muscle histology findings of an infantile-onset Pompe disease patient before **(A)** and after **(B)** enzyme replacement therapy. Note the decrease in heart size and muscle glycogen with the therapy. *(Modified from Amalfitano A, Bengur AR, Morse RP, et al: Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial,* Genet Med *3:132–138, 2001.)*

Treatment

Treatment options were once limited to supportive or palliative care. Specific enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase (alglucosidase alfa, [Myozyme or Lumizyme]) is available for treatment of Pompe disease. Recombinant acid α-glucosidase is capable of preventing deterioration or reversing abnormal cardiac and skeletal muscle functions (Fig. 87-3). ERT should be initiated as soon as possible across the disease spectrum, especially for babies with the infantile form who are diagnosed via newborn screening, as the disease is very rapidly progressive. The dosage is 20 mg/kg given every 2 wk. A high-protein diet and exercise therapy may also be beneficial. Nocturnal ventilatory support, when indicated, should be used. It has been shown to improve the quality of life and is particularly beneficial during a period of respiratory decompensation. Early diagnosis and treatment are necessary for optimal outcomes in Pompe disease. Newborn screening using blood-based assays in Taiwan has resulted in early identification of Pompe cases and, as a result, has improved disease outcomes through the early initiation of ERT.

Glycogen Storage Diseases Mimicking Hypertrophic Cardiomyopathy

Deficiencies of LAMP2 (also called Danon disease) and PRKAG2 result in accumulation of glycogen in the heart and skeletal muscle. Danon disease is transmitted as an X-linked trait and PRKAG2 deficiency as an autosomal dominant trait. These patients present primarily as a hypertrophic cardiomyopathy, but can be distinguished from the usual causes of hypertrophic cardiomyopathy caused by defects in sarcomere protein genes by their electrophysiologic abnormalities, particularly ventricular preexcitation and conduction defects. The onset of cardiac symptoms, including chest pain, palpitation, syncope, and cardiac arrest, can occur between the ages of 8 and 15 yr for LAMP2 deficiency, younger than the average age of 33 yr for patients with PRKAG2 deficiency. However, there are several reports of patients with mutations in the PRKAG2 gene presenting early. These cases present in early infancy with severe hypertrophic cardiomyopathy and a rapidly fatal course. In the past, several of these cases were misdiagnosed as GSD IX as a result of secondary low PhK activity in the heart. The p.Arg531Gln and p.Arg384Thr mutations in the PRKAG2 gene are incompatible with life. Other mutations (p.Arg302Gln, p.Thr400Ans, p.Asn488Ile, and p.His487Tyr) associated with Wolff-Parkinson-White syndrome and adult-onset hypertrophic cardiomyopathy are less disruptive.

The prognosis for LAMP2 deficiency is poor with progressive end-stage heart failure early in adulthood. With the exception of the fatal infantile presentation, cardiomyopathy caused by PRKAG2 mutations is compatible with long-term survival, although some patients may necessitate the implantation of a pacemaker and aggressive control of arrhythmias.

Type V Glycogen Storage Disease (Muscle Phosphorylase Deficiency, McArdle Disease)

GSD V is caused by the deficiency of muscle phosphorylase activity. Lack of this enzyme limits muscle ATP generation by glycogenolysis, resulting in muscle glycogen accumulation, and is the prototype of muscle energy disorders. A deficiency of myophosphorylase impairs the cleavage of glucosyl molecules from the straight chain of glycogen.

Clinical Manifestations

Symptoms usually first develop in late childhood or in the 2nd decade of life. In general, clinical heterogeneity is uncommon, but cases suggesting otherwise have been documented. Studies have shown that McArdle disease can manifest in individuals as old as 74 yr of age, as well as in infancy, in a fatal, early-onset form characterized by hypotonia, generalized muscle weakness, and respiratory complication. Symptoms are generally characterized by exercise intolerance with muscle cramps and pain. Two types of activity tend to cause symptoms: brief exercise of great intensity, such as sprinting or carrying heavy loads; and less intense but sustained activity, such as climbing stairs or walking uphill. Moderate exercise, such as walking on level ground,

can be performed by most patients for long periods. Many patients experience a characteristic "second wind" phenomenon. If they slow down or pause briefly at the first appearance of muscle pain, they can resume exercise with more ease. As a result of the underlying myopathy, these patients may be at risk for statin-induced myopathy and rhabdomyolysis. While patients typically experience episodic muscle pain and cramping from exercise, 35% of patients with McArdle disease report permanent pain that has a serious impact on sleep and other activities. Studies also suggest that there may also be a link between GSD V and levels of cognitive impairment.

Approximately 50% of patients report burgundy-colored urine after exercise, which is the consequence of exercise-induced **myoglobinuria** secondary to **rhabdomyolysis.** Intense myoglobinuria after vigorous exercise may cause acute renal failure. In rare cases, electromyographic findings may suggest an inflammatory myopathy and the diagnosis can be confused with polymyositis.

The level of serum creatine kinase is usually elevated at rest and increases more after exercise. Exercise also increases the levels of blood ammonia, inosine, hypoxanthine, and uric acid. The latter abnormalities are attributed to accelerated recycling of muscle purine nucleotides owing to insufficient ATP production. Type V GSD is an autosomal recessive disorder. The gene for muscle phosphorylase *(PYGM)* has been mapped to chromosome 11q13.

Diagnosis

The standard diagnosis for GSD V includes a muscle biopsy to measure glycogen content as well as enzyme and mutation analysis. An ischemic exercise test offers a rapid diagnostic screening for patients with a metabolic myopathy. Lack of an increase in blood lactate levels and exaggerated blood ammonia elevations indicate muscle glycogenosis and suggest a defect in the conversion of muscle glycogen or glucose to lactate. The abnormal ischemic exercise response is not limited to type V GSD. Other muscle defects in glycogenolysis or glycolysis produce similar results (deficiencies of muscle phosphofructokinase, phosphoglycerate kinase, phosphoglycerate mutase, or lactate dehydrogenase).

Phosphorus MRI allows for the noninvasive evaluation of muscle metabolism. Patients with type V GSD have no decrease in intracellular pH and have excessive reduction in phosphocreatine in response to exercise. The diagnosis should be confirmed by enzymatic evaluation of muscle. A common nonsense mutation p.R49X in exon 1 is found in 90% of white patients, and a deletion of a single codon in exon 17 is found in 61% of Japanese patients. The p.R49X mutation represents 55% of alleles in Spanish patients, whereas the p.W797R mutation represents 14% and the p.G204S represents 9% of mutant alleles in the Spanish population. There seems to be an association between clinical severity of GSD V and the presence of the D allele of the angiotensin-converting enzyme insertion/deletion polymorphism. This may help explain the spectrum of phenotypic variability manifested in this disorder.

Treatment

Avoidance of strenuous exercise prevents the symptoms; however, regular and moderate exercise is recommended to improve exercise capacity. Glucose or sucrose given before exercise or injection of glucagon can markedly improve tolerance in these patients. A high-protein diet may increase muscle endurance and creatine supplement has been shown to improve muscle function in some patients. The clinical response to creatine is dose-dependent: muscle pain may increase on high doses of creatine supplementation. Vitamin B_6 supplementation reduces exercise intolerance and muscle cramps. Longevity is not generally affected.

Type VII Glycogen Storage Disease (Muscle Phosphofructokinase Deficiency, Tarui Disease)

Type VII GSD is caused by a deficiency of muscle phosphofructokinase, which catalyzes the ATP-dependent conversion of fructose-6-phosphate to fructose-1,6-diphosphate and is a key regulatory enzyme of glycolysis. Phosphofructokinase is composed of 3 isoenzyme subunits (M [muscle], L [liver], and P [platelet]) that are encoded by different genes and differentially expressed in tissues. Skeletal muscle contains only the M subunit, and red blood cells contain a hybrid of L and M forms. Type VII disease is caused by a defective M isoenzyme, which causes a complete enzyme defect in muscle and a partial defect in red blood cells.

Type VII GSD is an autosomal recessive disorder and is prevalent among Japanese people and Ashkenazi Jews. The gene for muscle phosphofructokinase is located on chromosome 12q13.3. A splicing defect and a nucleotide deletion in the muscle phosphofructokinase gene account for 95% of mutant alleles in Ashkenazi Jews. Diagnosis based on molecular testing is thus possible in this population.

Clinical Manifestations

Six features of type VII are distinctive: (1) Exercise intolerance, usually evident in childhood, is more severe than in type V disease and may be associated with nausea, vomiting, and severe muscle pain; vigorous exercise causes severe muscle cramps and myoglobinuria. (2) Compensated hemolysis occurs as evidenced by an increased level of serum bilirubin and an elevated reticulocyte count. (3) Hyperuricemia is common and exaggerated by muscle exercise to a greater degree than that observed in type V or III GSD. (4) An abnormal polysaccharide is present in muscle fibers; it is periodic acid–Schiff-positive but resistant to diastase digestion. (5) Exercise intolerance is particularly acute after meals that are rich in carbohydrates because glucose cannot be utilized in muscle and because glucose inhibits lipolysis, thereby depriving muscle of fatty acid and ketone substrates. In contrast, patients with type V disease can metabolize bloodborne glucose derived from either liver glycogenolysis or exogenous glucose; indeed, glucose infusion improves exercise tolerance in type V patients. (6) There is no spontaneous second-wind phenomenon because of the inability to metabolize blood glucose.

Other rare type VII variants occur. One variant presents in infancy with hypotonia and limb weakness and proceeds to a rapidly progressive myopathy that leads to death by 4 yr of age. There is a second variant that occurs in infancy and results in congenital myopathy and arthrogryposis with a fatal outcome. A third variant presents in infancy with hypotonia, mild developmental delay and seizures. An additional presentation is hereditary nonspherocytic hemolytic anemia. Although these patients do not experience muscle symptoms, it remains unclear whether these symptoms will develop later in life. One variant presents in adults and is characterized by a slowly progressive, fixed muscle weakness rather than cramps and myoglobinuria. It may also cause mitral valve thickening from glycogen buildup.

Diagnosis

To establish a diagnosis, a biochemical or histochemical demonstration of the enzymatic defect in the muscle is required. The absence of the M isoenzyme of phosphofructokinase can also be demonstrated in blood cells and fibroblasts.

Treatment

There is no specific treatment. Avoidance of strenuous exercise is advisable to prevent acute attacks of muscle cramps and myoglobinuria. Drugs such as statins should be avoided. Precautionary measures should be taken to avoid hyperthermia while undergoing anesthesia. Carbohydrate meals and glucose infusions have demonstrated worsening symptoms because of the body's inability to utilize glucose. The administered glucose tends to lower the levels of fatty acids in the blood, a primary source of muscle fuel. One case of a child with a severe infantile form of GSD VII, demonstrated that the initiation of a ketogenic diet resulted in significant clinical improvement.

Other Muscle Glycogenoses with Muscle Energy Impairment

Six additional defects in enzymes—phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase, fructose-1,6-bisphosphate aldolase A, muscle pyruvate kinase, and β-enolase in the pathway of the terminal glycolysis—cause symptoms and signs of muscle energy

impairment similar to those of types V and VII GSD. The failure of blood lactate to increase in response to exercise is a useful diagnostic test and can be used to differentiate muscle glycogenoses from disorders of lipid metabolism, such as carnitine palmitoyl transferase II deficiency and very long chain acyl-CoA dehydrogenase deficiency, which also cause muscle cramps and myoglobinuria. Muscle glycogen levels can be normal in the disorders affecting terminal glycolysis and assaying the muscle enzyme activity is needed to make a definite diagnosis. There is no specific treatment. Avoidance of strenuous exercise prevents acute attacks of muscle cramps and myoglobinuria. Avoidance of drugs such as statins, and malignant hyperthermia precautions for patients undergoing anesthesia should be followed.

Bibliography is available at Expert Consult.

87.2 Defects in Galactose Metabolism

Priya S. Kishnani and Yuan-Tsong Chen

Milk and dairy products contain lactose, the major dietary source of galactose. The metabolism of galactose produces fuel for cellular metabolism through its conversion to glucose-1-phosphate (see Table 87-1). Galactose also plays an important role in the formation of galactosides, which include glycoproteins, glycolipids, and glycosaminoglycans. Galactosemia denotes the elevated level of galactose in the blood and is found in 3 distinct inborn errors of galactose metabolism in 1 of the following enzymes: galactose-1-phosphate uridyl transferase, galactokinase, and uridine diphosphate galactose-4-epimerase. The term *galactosemia,* although adequate for the deficiencies in any of these disorders, generally designates the transferase deficiency.

GALACTOSE-1-PHOSPHATE URIDYL TRANSFERASE DEFICIENCY GALACTOSEMIA

Two forms of the deficiency exist: infants with complete or near complete deficiency of the enzyme (classic galactosemia) and those with partial transferase deficiency. **Classic galactosemia** is a serious disease with onset of symptoms typically by the second half of the 1st wk of life. The incidence is predicted to be 1 in 60,000 live births. The newborn infant receives high amounts of lactose (up to 40% in breast milk and certain formulas), which consists of equal parts of glucose and galactose. Without the transferase enzyme, the infant is unable to metabolize galactose-1-phosphate, the accumulation of which results in injury to kidney, liver, and brain. This injury may begin prenatally in the affected fetus by transplacental galactose derived from the diet of the heterozygous mother or by endogenous production of galactose in the fetus.

Clinical Manifestations

The diagnosis of uridyl transferase deficiency should be considered in newborn or young infants with any of the following features: jaundice, hepatomegaly, vomiting, hypoglycemia, seizures, lethargy, irritability, feeding difficulties, poor weight gain or failure to regain birth weight, aminoaciduria, nuclear cataracts, vitreous hemorrhage, hepatic failure, liver cirrhosis, ascites, splenomegaly, or intellectual disability. Symptoms are milder and improve when milk is temporarily withdrawn and replaced by intravenous or lactose-free nutrition. Patients with galactosemia are at increased risk for *Escherichia coli* neonatal sepsis; the onset of sepsis often precedes the diagnosis of galactosemia. Pseudotumor cerebri can occur and cause a bulging fontanel. Death from liver and kidney failure and sepsis may follow within days. When the diagnosis is not made at birth, damage to the liver (cirrhosis) and brain (intellectual disability) becomes increasingly severe and irreversible.

Partial transferase deficiency is generally asymptomatic. It is more frequent than classic galactosemia and is diagnosed in newborn screening because of moderately elevated blood galactose and/or low transferase activity. Galactosemia should be considered for the newborn or young infant who is not thriving or who has any of the preceding findings. Light and electron microscopy of hepatic tissue reveals fatty infiltration, the formation of pseudoacini, and eventual macronodular cirrhosis. These changes are consistent with a metabolic disease but do not indicate the precise enzymatic defect.

Diagnosis

The preliminary diagnosis of galactosemia is made by demonstrating a reducing substance in several urine specimens collected while the patient is receiving human milk, cow's milk, or any other formula containing lactose. The reducing substance found in urine by Clinitest (glucose, galactose, and others) can be identified by chromatography or by an enzymatic test specific for galactose. Galactosuria is present, provided the last milk feed does not date back more than a few hours and the child is not vomiting excessively. Clinistix urine test results are usually negative because the test materials rely on the action of glucose oxidase, which is specific for glucose and is nonreactive with galactose. Owing to a proximal renal tubular syndrome, the acutely ill baby may also excrete glucose together with amino acids. Because galactose is injurious to persons with galactosemia, diagnostic challenge tests dependent on administering galactose orally or intravenously should not be used. Direct enzyme assay using erythrocytes establishes the diagnosis. One needs to confirm that the patient did not receive a blood transfusion before the collection of the blood sample, as a diagnosis could be missed. A novel method utilizes nonradioactive UV and high-performance liquid chromatography to accurately detect levels of galactose-1-phosphate uridyl transferase in erythrocytes.

Genetics

Transferase deficiency is an autosomal recessive disorder. Based on newborn screening in the United States, the frequency of the disease is approximately 1 in 47,000 live births. There are several enzymatic variants of galactosemia. The *Duarte variant,* a single amino acid substitution (p.N314D), has diminished red cell enzyme activity (50% of normal), but usually no clinical significance. This variant is the most common, with a carrier frequency of 12% in the general population. Those who are heterozygous for the Duarte variant of galactosemia typically have 25% of normal galactose activity, few symptoms, elevated metabolites, and no need for intervention. Other similar variants expressing little enzyme activity typically require no intervention. Some African-American patients have milder symptoms despite the absence of measurable transferase activity in erythrocytes; these patients retain 10% enzyme activity in liver and intestinal mucosa, whereas most white patients have no detectable activity in any of these tissues. More than 230 identifiable mutations have been associated with transferase deficiency. In African-Americans, 62% of alleles are represented by the p.S135L mutation, a mutation that is responsible for a milder disease course. In the white population, 70% of alleles are represented by the p.Q188R and p.K285N missense mutations and are associated with severe disease. Carrier testing and prenatal diagnosis can be performed by direct enzyme analysis of amniocytes or chorionic villi; testing can also be DNA based.

Treatment and Prognosis

Because of newborn screening for galactosemia, patients are being identified and treated early. Various non–lactose-containing milk substitutes are available (casein hydrolysates, soybean-based formula). Elimination of galactose from the diet along with adequate calcium supplementation reverses growth failure and renal and hepatic dysfunction. Cataracts regress, and most patients have no impairment of vision. Early diagnosis and treatment have improved the prognosis of galactosemia; however, on long-term follow-up, patients still manifest ovarian failure with primary or secondary amenorrhea, decreased bone mineral density, developmental delay, and learning disabilities that increase in severity with age. **Hypergonadotrophic hypogonadism** is reported in 80% to more than 90% of female patients with classic galactosemia. Although most women with classic galactosemia are infertile when they reach childbearing age, a small number have given birth. Most patients manifest speech disorders, whereas a smaller number demonstrate poor growth and impaired motor function and balance (with or without overt ataxia). The relative control of

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galactose-1-phosphate levels does not always correlate with long-term outcome, leading to the belief that other factors, such as elevated galactitol, decreased uridine diphosphate galactose (a donor for galactolipids and proteins), and endogenous galactose production may be responsible.

GALACTOKINASE DEFICIENCY

The deficient enzyme is galactokinase, which normally catalyzes the phosphorylation of galactose. The principal metabolites accumulated are galactose and galactitol. Two genes are reported to encode galactokinase: *GK1* on chromosome 17q24 and *GK2* on chromosome 15. Cataracts are usually the sole manifestation of galactokinase deficiency; pseudotumor cerebri is a rare complication. The affected infant is otherwise asymptomatic. Heterozygote carriers may be at risk for presenile cataracts. Affected patients have an increased concentration of blood galactose levels, provided they have been fed a lactose-containing formula. The diagnosis is made by demonstrating an absence of galactokinase activity in erythrocytes or fibroblasts. Transferase activity is normal. Treatment is dietary restriction of galactose.

URIDINE DIPHOSPHATE GALACTOSE-4-EPIMERASE DEFICIENCY

The abnormally accumulated metabolites are similar to those in transferase deficiency; however, there is also an increase in cellular uridine diphosphate galactose. There are 2 distinct forms of epimerase deficiency. The first is a benign form discovered incidentally through neonatal screening programs. Affected persons are healthy and without problems; the enzyme deficiency is limited to leukocytes and erythrocytes. No treatment is required. The second form of epimerase deficiency is severe, and clinical manifestations resemble transferase deficiency, with the additional symptoms of hypotonia and nerve deafness. The enzyme deficiency is generalized, and clinical symptoms respond to restriction of dietary galactose. Although this form of galactosemia is rare, it must be considered in a symptomatic patient with measurable galactose-1-phosphate who has normal transferase activity. Diagnosis is confirmed by the assay of epimerase in erythrocytes.

Patients with the severe form of epimerase deficiency cannot synthesize galactose from glucose and are galactose-dependent. Because galactose is an essential component of many nervous system structural proteins, patients are placed on a galactose-restricted diet rather than a galactose-free diet.

Infants with the mild form of epimerase deficiency have not required treatment. It is advisable to follow urine specimens for reducing substances and exclude aminoaciduria within a few weeks of diagnosis while the infant is still on lactose-containing formula.

The gene for uridine diphosphate galactose-4-epimerase is located on chromosome 1 at 1p36. Carrier detection is possible by measurement of epimerase activity in the erythrocytes. Prenatal diagnosis for the severe form of epimerase deficiency, using an enzyme assay of cultured amniotic fluid cells, is possible.

Bibliography is available at Expert Consult.

87.3 Defects in Fructose Metabolism

Priya S. Kishnani and Yuan-Tsong Chen

Two inborn errors are known in the specialized pathway of fructose metabolism: benign or essential fructosuria and hereditary fructose intolerance (HFI). Fructose-1,6-bisphosphatase deficiency, although strictly speaking not a defect of the specialized fructose pathway, is discussed in Chapter 87.4.

DEFICIENCY OF FRUCTOKINASE (ESSENTIAL OR BENIGN FRUCTOSURIA)

Deficiency of fructokinase is not associated with any clinical manifestations. It is an accidental finding usually made because the asymptomatic patient's urine contains a reducing substance. No treatment is necessary and the prognosis is excellent. Inheritance is autosomal recessive with an incidence of 1 in 120,000 live births. The gene encoding fructokinase is located on chromosome 2p23.3.

Fructokinase catalyzes the first step of metabolism of dietary fructose: conversion of fructose to fructose-1-phosphate (see Fig. 87-1). Without this enzyme, ingested fructose is not metabolized. Its level is increased in the blood, and it is excreted in urine because there is practically no renal threshold for fructose. Clinitest results reveal the urinary-reducing substance, which can be identified as fructose by chromatography.

DEFICIENCY OF FRUCTOSE-1,6-BISPHOSPHATE ALDOLASE (ALDOLASE B, HEREDITARY FRUCTOSE INTOLERANCE)

Deficiency of fructose-1,6-bisphosphate aldolase is a severe condition of infants that appears with the ingestion of fructose-containing food and is caused by a deficiency of fructose aldolase B activity in the liver, kidney, and intestine. The enzyme catalyzes the hydrolysis of fructose-1,6-bisphosphate into triose phosphate and glyceraldehyde phosphate. The same enzyme also hydrolyzes fructose-1-phosphate. Deficiency of this enzyme activity causes a rapid accumulation of fructose-1-phosphate and initiates severe toxic symptoms when exposed to fructose.

Epidemiology and Genetics

The true incidence of HFI is unknown but may be as high as 1 in every 26,000 live births. The gene for aldolase B is on chromosome 9q22.3. At least 40 mutations causing HFI are known. A single missense mutation, a G→C transversion in exon 5 resulting in the normal alanine at position 149 being replaced by a proline, is the most common mutation identified in northern Europeans. This mutation, plus 2 other point mutations (p.A174D and p.N334K), account for 80-85% of HFI in Europe and the United States. Diagnosis of HFI can be made by direct DNA analysis and phosphorus magnetic resonance spectroscopy.

Clinical Manifestations

Patients with HFI are asymptomatic until fructose or sucrose (table sugar) is ingested (usually from fruit, fruit juice, or sweetened cereal). Symptoms may occur early in life, soon after birth if foods or formulas containing these sugars are introduced into the diet. Certain patients are very sensitive to fructose, whereas others can tolerate moderate intakes (up to 250 mg/kg/day). The average intake of fructose in Western societies is 1-2 g/kg/day. Early clinical manifestations resemble galactosemia and include jaundice, hepatomegaly, vomiting, lethargy, irritability, and convulsions. There may also be a higher incidence of celiac disease in HFI patients (>10%) than in the general population (1-3%). Laboratory findings include a prolonged clotting time, hypoalbuminemia, elevation of bilirubin and transaminase levels, and proximal tubular dysfunction. Acute fructose ingestion produces symptomatic hypoglycemia; the higher the intake, the more severe is the clinical picture. Chronic ingestion results in failure to thrive and hepatic disease. If the intake of the fructose persists, hypoglycemic episodes recur, and liver and kidney failure progress, eventually leading to death.

Diagnosis

Suspicion of the enzyme deficiency is fostered by the presence of a reducing substance in the urine during an episode. The fructose challenge, although an effective method of diagnosis, causes a rapid fall, first of serum phosphate and then of blood glucose, and a subsequent increase in uric acid and magnesium. Because of high risks to the patient who can become acutely ill after the oral tolerance test, it should not be performed. Definitive diagnosis is made by assay of fructaldolase B activity in the liver. Gene-based diagnosis is available for most patients with this disease; a common mutation (substitution of *Pro* for *Ala* at position 149) accounts for 53% of HFI alleles worldwide.

Treatment

Treatment consists of the complete elimination of all sources of sucrose, fructose, and sorbitol from the diet. It may be difficult because these

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sugars are widely used additives, found even in most medicinal preparations. With treatment, liver and kidney dysfunction improves, and catch-up in growth is common. Intellectual development is usually unimpaired. As the patient matures, symptoms become milder even after fructose ingestion; the long-term prognosis is good. Because of voluntary dietary avoidance of sucrose, affected patients have few dental caries.

Bibliography is available at Expert Consult.

87.4 Defects in Intermediary Carbohydrate Metabolism Associated with Lactic Acidosis

Priya S. Kishnani and Yuan-Tsong Chen

Lactic acidosis occurs with defects of carbohydrate metabolism that interfere with the conversion of pyruvate to glucose via the pathway of gluconeogenesis or to carbon dioxide and water via the mitochondrial enzymes of the Krebs cycle. Figure 87-4 depicts the relevant metabolic pathways. Type I GSD, fructose-1,6-diphosphatase deficiency, and phosphoenolpyruvate carboxylase deficiency are disorders of gluconeogenesis associated with lactic acidosis. Pyruvate dehydrogenase complex deficiency, respiratory chain defects, and pyruvate carboxylase deficiency are disorders in the pathway of pyruvate metabolism causing lactic acidosis. Lactic acidosis can also occur in defects of fatty acid oxidation, organic acidurias (see Chapters 85.6, 85.10, and 86.1), or biotin utilization diseases. These disorders are easily distinguishable by the presence of abnormal acylcarnitine profiles, amino acids in the blood, and unusual organic acids in the urine. Blood lactate, pyruvate, and acylcarnitine profiles and the presence of these unusual urine organic acids should be determined in infants and children with unexplained acidosis, especially if there is an increase of anion gap.

Lactic acidosis unrelated to an enzymatic defect occurs in hypoxemia. In this case, as well as in defects in the respiratory chain, the serum pyruvate concentration may remain normal (<1.0 mg/dL with an increased lactate: pyruvate ratio), whereas pyruvate is usually increased when lactic acidosis results from an enzymatic defect in gluconeogenesis or pyruvate dehydrogenase complex (both lactate and pyruvate are increased and the ratio is normal). Lactate and pyruvate should be measured in the same blood specimen and on multiple blood specimens obtained when the patient is symptomatic because lactic acidosis can be intermittent. Figure 87-5 is an algorithm for the differential diagnosis of lactic acidosis.

DISORDERS OF GLUCONEOGENESIS

Deficiency of Glucose-6-Phosphatase (Type I Glycogen Storage Disease)

Type I GSD is the only glycogenosis associated with significant lactic acidosis. The chronic metabolic acidosis predisposes these patients to osteopenia; after prolonged fasting, the acidosis associated with hypoglycemia is a life-threatening condition (see Chapter 87.1).

Fructose-1,6-Diphosphatase Deficiency

Fructose-1,6-diphosphatase deficiency impairs the formation of glucose from all gluconeogenic precursors, including dietary fructose. Hypoglycemia occurs when glycogen reserves are limited or exhausted. The clinical manifestations are characterized by life-threatening episodes of acidosis, hypoglycemia, hyperventilation, convulsions, and coma. In about half of the cases, the deficiency presents in the 1st wk of life. In infants and small children, episodes are triggered by febrile infections and gastroenteritis if oral food intake decreases. The frequency of the attacks decreases with age. Laboratory findings include low blood glucose, high lactate and uric acid levels, and metabolic acidosis. In contrast to HFI, there is usually no aversion to sweets; renal tubular and liver functions are normal.

The diagnosis is established by demonstrating an enzyme deficiency in either liver or intestinal biopsy. The enzyme defect can also be demonstrated in leukocytes in some cases. The gene coding for fructose-1,6-diphosphatase is located on chromosome 9q22; mutations are characterized, making carrier detection and prenatal diagnosis possible. Treatment of acute attacks consists of correction of hypoglycemia and acidosis by intravenous glucose infusion; the response is usually rapid. Avoidance of fasting, aggressive management of infections and restriction of fructose and sucrose from the diet can prevent further episodes. For long-term prevention of hypoglycemia, a slowly released carbohydrate such as cornstarch is useful. Patients who survive childhood develop normally.

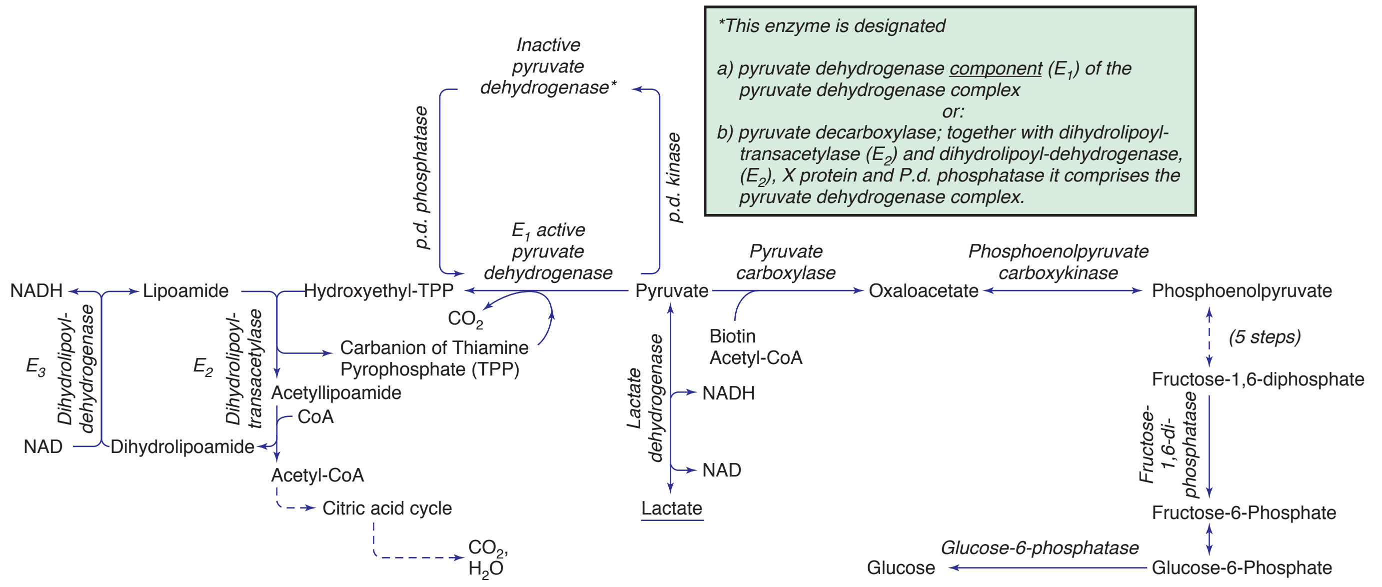

Figure 87-4 Enzymatic reactions of carbohydrate metabolism, deficiencies of which can give rise to lactic acidosis, pyruvate elevations, or hypoglycemia. The pyruvate dehydrogenase complex comprises, in addition to E_1, E_2, and E_3, an extra lipoate-containing protein (not shown), called protein X, and pyruvate dehydrogenase phosphatase.

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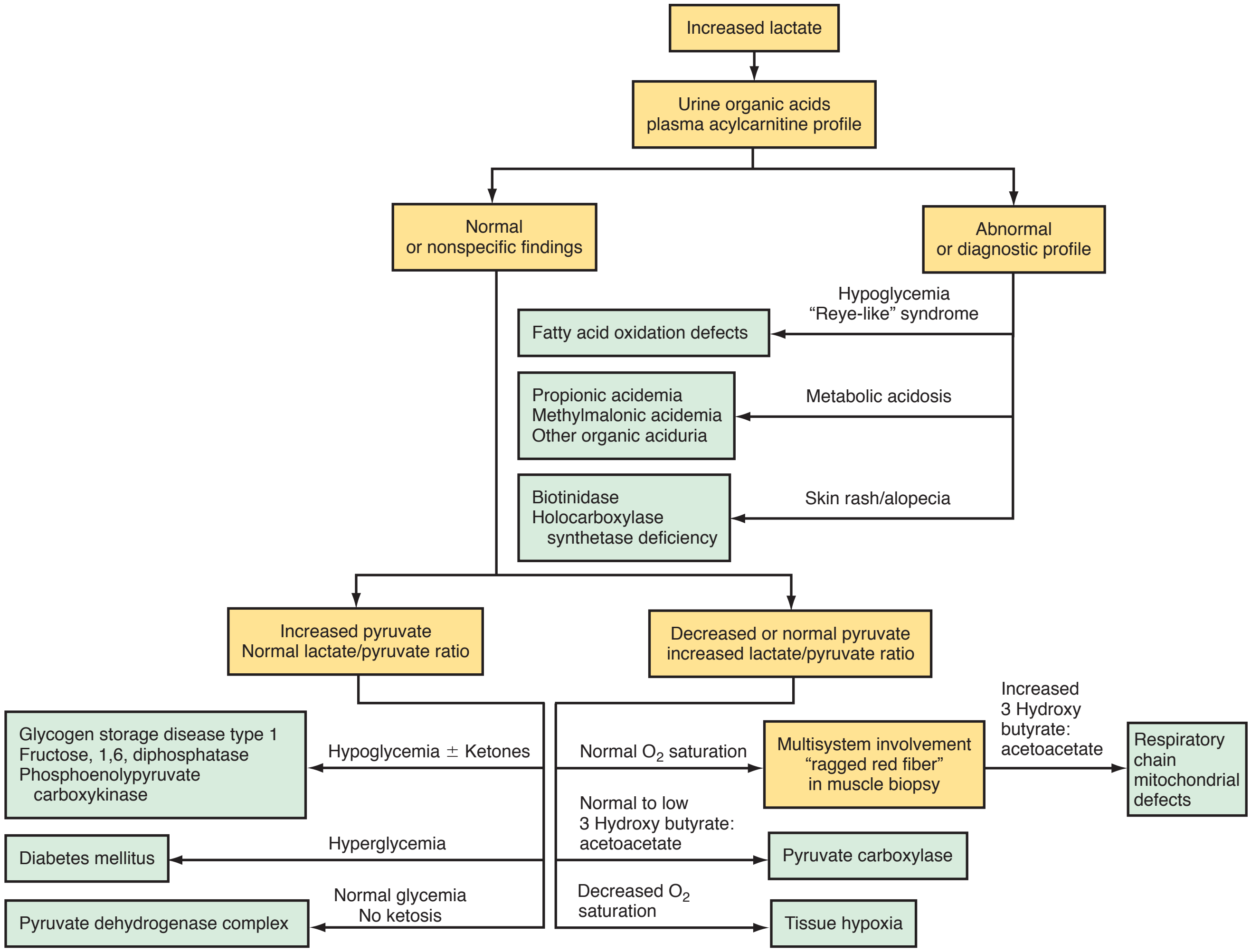

Figure 87-5 Algorithm of the differential diagnosis of lactic acidosis.

Phosphoenolpyruvate Carboxykinase Deficiency

Phosphoenolpyruvate carboxykinase (PEPCK) is a key enzyme in gluconeogenesis. It catalyzes the conversion of oxaloacetate to phosphoenolpyruvate (see Fig. 87-4). PEPCK deficiency is both a mitochondrial enzyme deficiency and a cytosolic enzyme deficiency, encoded by 2 distinct genes.

The disease has been reported in only a few cases. The clinical features are heterogeneous, with hypoglycemia, lactic acidemia, hepatomegaly, hypotonia, developmental delay, and failure to thrive as the major manifestations. There may be multisystem involvement, with neuromuscular deficits, hepatocellular damage, renal dysfunction, and cardiomyopathy. The diagnosis is based on the reduced activity of PEPCK in liver, fibroblasts, or lymphocytes. Fibroblasts and lymphocytes are not suitable for diagnosing the cytosolic form of PEPCK deficiency because these tissues possess only mitochondrial PEPCK. To avoid hypoglycemia, patients should be treated with slow-release carbohydrates such as cornstarch, and fasting should be avoided.

DISORDERS OF PYRUVATE METABOLISM

Pyruvate is formed from glucose and other monosaccharides, from lactate, and from alanine. It is metabolized through 4 main enzyme systems: lactate dehydrogenase, alanine aminotransferase, pyruvate carboxylase, and pyruvate dehydrogenase complex. Deficiency of the M subunit of lactate dehydrogenase causes exercise intolerance and myoglobinuria (see Chapter 87.1).

Pyruvate Dehydrogenase Complex Deficiency

After entering the mitochondria, pyruvate is converted into acetyl-CoA by the pyruvate dehydrogenase complex (PDHC), which catalyzes the oxidation of pyruvate to acetyl-CoA, which then enters the tricarboxylic acid cycle for ATP production. The complex comprises 5 components: E_1, an α-ketoacid decarboxylase; E_2, a dihydrolipoyl transacylase; E_3, a dihydrolipoyl dehydrogenase; protein X, an extra lipoate-containing protein; and pyruvate dehydrogenase phosphatase. The most common is a defect in the E_1 (see Fig. 87-4).

Deficiency of the PDHC is the most common of the disorders leading to lactic acidemia and central nervous system dysfunction. The central nervous system dysfunction occurs because the brain obtains its energy primarily from oxidation of glucose. Brain acetyl-CoA is synthesized nearly exclusively from pyruvate.

The E_1 defects are caused by mutations in the gene coding for E_1 α subunit, which is X-linked. Although X-linked, its deficiency is a problem in both males and females even though only 1 E_1 α allele in females carries a mutation.

Clinical Manifestations

The disease has a wide spectrum of presentations from the most severe neonatal presentation to a mild late-onset form. The **neonatal onset** is associated with lethal lactic acidosis, white matter cystic lesions, agenesis of the corpus callosum, and the most severe enzyme deficiency. **Infantile onset** can be lethal or associated with psychomotor delay and chronic lactic acidosis, cystic lesions in the brainstem and basal ganglia, and pathologic features resembling **Leigh disease** (see below).

Neurologic symptoms in PDHC can be categorized into 2 groups: the first, abnormal brain development seen in both males and females, and the second, brain lesions and epilepsy seen in male patients only. Older children, usually boys, may have less acidosis, have greater enzyme activity, and manifest ataxia with high-carbohydrate diets. Intelligence may be normal. Patients of all ages may have facial dysmorphology, features similar to those of fetal alcohol syndrome.

The E_2 and protein X-lipoate defects are rare and result in severe psychomotor retardation. The E_3 lipoamide dehydrogenase defect leads to deficient activity not only in the PDHC, but also in the α-ketoglutarate and branched-chain ketoacid dehydrogenase complexes. This deficiency is more common in the Ashkenazi Jewish population. Recent studies suggest that the reactive oxygen species generated by the mutations responsible for lipoamide dehydrogenase deficiency may in fact explain certain disease characteristics and suggest the utility of antioxidant therapy. Pyruvate dehydrogenase phosphatase deficiency has also been reported. These other PDHC defects have clinical manifestations within the variable spectrum associated with PDHC deficiency due to E_1 deficiency.

Treatment

The general prognosis is poor except in rare cases in which mutation is associated with altered affinity for thiamine pyrophosphate, which may respond to thiamine supplementation. Because carbohydrates can aggravate lactic acidosis, a ketogenic diet is recommended. The diet has been found to lower the blood lactate level; the long-term benefit to patient outcome is unclear. A potential treatment strategy is to maintain any residual PDHC in its active form by **dichloroacetate,** an inhibitor of E_1 kinase. Beneficial effects of controlling postprandial lactic acidosis in some patients have been shown. Young children with congenital acidosis generally tolerate oral dichloroacetate well, but continued exposure is associated with peripheral neuropathy, a condition that could be attributable to the drug or the disease.

Deficiency of Pyruvate Carboxylase

Pyruvate carboxylase is a mitochondrial, biotin-containing enzyme essential in the process of gluconeogenesis; it catalyzes the conversion of pyruvate to oxaloacetate. The enzyme is also essential for Krebs cycle function as a provider of oxaloacetate and is involved in lipogenesis and formation of nonessential amino acids. Clinical manifestations of this deficiency have varied from neonatal severe lactic acidosis accompanied by hyperammonemia, citrullinemia, and hyperlysinemia **(type B)** to late-onset mild to moderate lactic acidosis and developmental delay **(type A).** In both types, patients who survived usually had severe psychomotor retardation with seizures, spasticity, and microcephaly. Some patients have pathologic changes in the brainstem and basal ganglia that resemble **Leigh disease** (see below). The clinical severity appears to correlate with the level of the residual enzyme activity. A "benign" form of pyruvate carboxylase deficiency characterized by recurrent attacks of lactic acidosis and mild neurologic deficits has also been described (type C). Laboratory findings are characterized by elevated levels of blood lactate, pyruvate, alanine, and ketonuria. In the case of type B, blood ammonia, citrulline, and lysine levels are also elevated, which might suggest a primary defect of the urea cycle. The mechanism is likely caused by depletion of oxaloacetate, which leads to reduced levels of aspartate, a substrate for argininosuccinate synthase in the urea cycle (see Chapter 85.12). The gene for pyruvate carboxylase is located on chromosome 11q13.4-q13.5 and approximately 15 mutations have been identified.

Treatment consists of avoidance of fasting, and eating a carbohydrate meal before bedtime. During acute episodes of lactic acidosis, patients should receive continuous intravenous glucose. Aspartate and citrate supplements restore the metabolic abnormalities; whether this treatment can prevent the neurologic deficits is not known. Liver transplantation has been attempted; its benefit remains unknown. Diagnosis of pyruvate carboxylase deficiency is made by the measurement of enzyme activity in liver or cultured skin fibroblasts and must be differentiated from holocarboxylase synthase or biotinidase deficiency.

Deficiency of Pyruvate Carboxylase Secondary to Deficiency of Holocarboxylase Synthase or Biotinidase

Deficiency of either holocarboxylase synthase (HCS) or biotinidase, which are enzymes of biotin metabolism, result in multiple carboxylase deficiency (pyruvate carboxylase and other biotin-requiring carboxylases and metabolic reactions) and in clinical manifestations associated with the respective deficiencies, as well as rash, lactic acidosis, and alopecia (see Chapter 85.6). The course of HCS or biotinidase deficiency can be protracted, with intermittent exacerbation of chronic lactic acidosis, failure to thrive, seizures, and hypotonia leading to spasticity, lethargy, coma, and death. Auditory and optic nerve dysfunction can lead to deafness and blindness, respectively. Late-onset milder forms have also been reported. Laboratory findings include metabolic acidosis and abnormal organic acids in the urine. In HCS deficiency, biotin concentrations in plasma and urine are normal. Diagnosis can be made in skin fibroblasts or lymphocytes by assay for HCS activity, and in the case of biotinidase, in the serum by a screening blood spot.

Treatment consists of biotin supplementation, 5-20 mg/day, and is generally effective if treatment is started before the development of brain damage. Patients identified through newborn screening and treated with biotin have remained asymptomatic.

Both enzyme deficiencies are autosomal recessive traits. The incidence of HCS deficiency is approximately 1 in 87,000 live births. HCS and biotinidase are located on chromosome 21q22 and 3p25, respectively. Ethnic-specific mutations in the HCS gene have been identified. Two common mutations (del7/ins3 and p.R538C) in the biotinidase gene account for 52% of all mutant alleles in symptomatic patients with biotinidase deficiency.

Mitochondrial Respiratory Chain Defects (Oxidative Phosphorylation Disease)

The mitochondrial respiratory chain catalyzes the oxidation of fuel molecules and transfers the electrons to molecular oxygen with concomitant energy transduction into ATP (oxidative phosphorylation). The respiratory chain produces ATP from adenosine diphosphate and inorganic phosphate utilizing the energy from electrons transferred from nicotinamide adenine dinucleotide (NADH) or flavin adenine dinucleotide and includes 5 specific complexes (I: NADH–coenzyme Q reductase; II: succinate–coenzyme Q reductase; III: coenzyme QH_2 cytochrome C reductase; IV: cytochrome C oxidase; V: ATP synthase). Each complex is composed of 4-35 individual proteins and, with the exception of complex II (which is encoded solely by nuclear genes), is encoded by nuclear or mitochondrial DNA (inherited only from the mother by mitochondrial inheritance). Defects in any of these complexes or assembly systems produce chronic lactic acidosis presumably because of a change of the reduction-oxidation state with increased concentrations of NADH. In contrast to PDHC or pyruvate carboxylase deficiency, skeletal muscle and heart are usually involved in the respiratory chain disorders, and in muscle biopsy, "ragged red fibers" (indicating mitochondrial proliferation) are very suggestive when present (see Fig. 87-5). Because of the ubiquitous nature of oxidative phosphorylation, a defect of the mitochondrial respiratory chain accounts for a vast array of clinical manifestations and should be considered in patients in all age groups presenting with multisystem involvement. Some deficiencies resemble **Leigh disease** (see below), whereas others cause infantile myopathies such as **MELAS** (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), **MERRF** (myoclonic epilepsy and ragged red fibers), and **Kearns-Sayre syndrome** (external ophthalmoplegia, acidosis, retinal degeneration, heart block, myopathy, and high cerebrospinal fluid protein) (Table 87-2; Chapters 598.2 and 611.4). There is a higher incidence of psychiatric disorders in adults with a primary oxidative phosphorylation disease than in the general population. Diagnosis requires demonstration of abnormalities of oxidative phosphorylation enzyme complex activities in tissues or of mitochondrial DNA or a nuclear gene coding for mitochondrial functions, or both (Fig. 87-6). Muscle histology, including

Table 87-2 Clinical and Genetic Heterogeneity of Disorders Related to Mutations in Mitochondrial DNA*

SYMPTOMS, SIGNS, AND FINDINGS	Large Deletions in mtDNA			Mutation in Transfer RNA		Mutation in Ribosomal RNA	Mutation in Messenger RNA		
	KSS	PEO	PS	MERRF	MELAS	AID	NARP	MILS	LHON
CENTRAL NERVOUS SYSTEM									
Seizures	–	–	–	**+++**	+	–	–	+	–
Ataxia	+	–	–	+	+		+	±	–
Myoclonus	–	–	–	+	±	–	–	–	–
Psychomotor retardation	–	–	–	–	–	–	–	+	–
Psychomotor regression	+	–	–	±	+	–	–	–	–
Hemiparesis and hemianopia	–	–	–	–	**+++**	–	–	–	–
Cortical blindness	–	–	–	–	+	–	–	–	–
Migraine-like headaches	–	–	–	–	+	–	–	–	–
Dystonia	–	–	–	–	+	–	–	+	±
PERIPHERAL NERVOUS SYSTEM									
Peripheral neuropathy	±	–	–	±	±	–	**+**	–	–
MUSCLE									
Weakness and exercise intolerance	+	**+++**	–	+	+	–	+	+	–
Ophthalmoplegia	+	+	±	–	–	–	–	–	–
Ptosis		+	–	–	–	–	–	–	–
EYE									
Pigmentary retinopathy	**+**	–	–	–	–	–	**+**	±	–
Optic atrophy	–	–	–	–	–	–	±	±	
BLOOD									
Sideroblastic anemia	±	–	**+**	–	–	–	–	–	–
ENDOCRINE SYSTEM									
Diabetes mellitus	±	–	–	–	±	–	–	–	–
Short stature	+	–	–	+	+	–	–	–	–
Hypoparathyroidism	±	–	–	–	–	–	–	–	–
HEART									
Conduction disorder	**+**	**–**	–	–	±	–	–	–	±
Cardiomyopathy	±	–	–	–	±	**+**	–	±	–
GASTROINTESTINAL SYSTEM									
Exocrine pancreatic dysfunction	±	–	**+**	–	–	–	–	–	–
Intestinal pseudoobstruction	–	–	–	–	+	–	–	–	–
EAR, NOSE, AND THROAT									
Sensorineural hearing loss	±	–	–	+	+	**+**	±	–	–
KIDNEY									
Fanconi syndrome		–	**±**	–	**±**	–	–	–	–
LABORATORY FINDINGS									
Lactic acidosis	+	±	+	+	+	±	±	±	–
Ragged-red fibers on muscle biopsy	+	+	±	+	+	–	–	–	–
MODE OF INHERITANCE									
Maternal	–	–	–	+	+	–	+	+	+
Sporadic	+	+	+	–	–	–	–	–	–

*Characteristic constellations of symptoms and signs are bolded.

+, Presence of a symptom, sign, or finding; –, absence of a symptom, sign, or finding; ±, possible presence of a symptom, sign, or finding; AID, aminoglycoside-induced deafness; KSS, Kearns-Sayre syndrome; LHON, Leber's hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibers; MILS, maternally inherited Leigh syndrome; mtDNA, mitochondrial DNA; NARP, neuropathy, ataxia, and retinitis pigmentosa; PEO, progressive external ophthalmoplegia; PS, Pearson syndrome.

From DiMauro S, Schon EA: Mitochondrial respiratory-chain diseases, N Engl J Med *348:2656–2668, 2003.*

electron microscopy can detect ragged red fibers and other abnormalities typical of mitochondrial myopathies. Analysis of oxidative phosphorylation complexes I-IV from intact mitochondria isolated from fresh skeletal muscle is the most sensitive assay for mitochondrial disorders; however, electron transport chain testing of flash-frozen muscle provides an alternative approach when fresh muscle testing is not available. Next-generation sequencing of mitochondrial DNA and panels of nuclear genes provides a noninvasive alternative to diagnosis, albeit with lower sensitivity. Specific criteria may assist in making a diagnosis (Table 87-3). Table 87-4 lists clues to the diagnosis of mitochondrial diseases.

Treatment remains largely symptomatic and does not significantly alter the outcome of disease. Some patients appear to respond to cofactor supplements, typically coenzyme Q_{10} ± L-carnitine at pharmacologic doses. The addition of creatine monohydrate and α-lipoic acid supplementation may add a significant benefit.

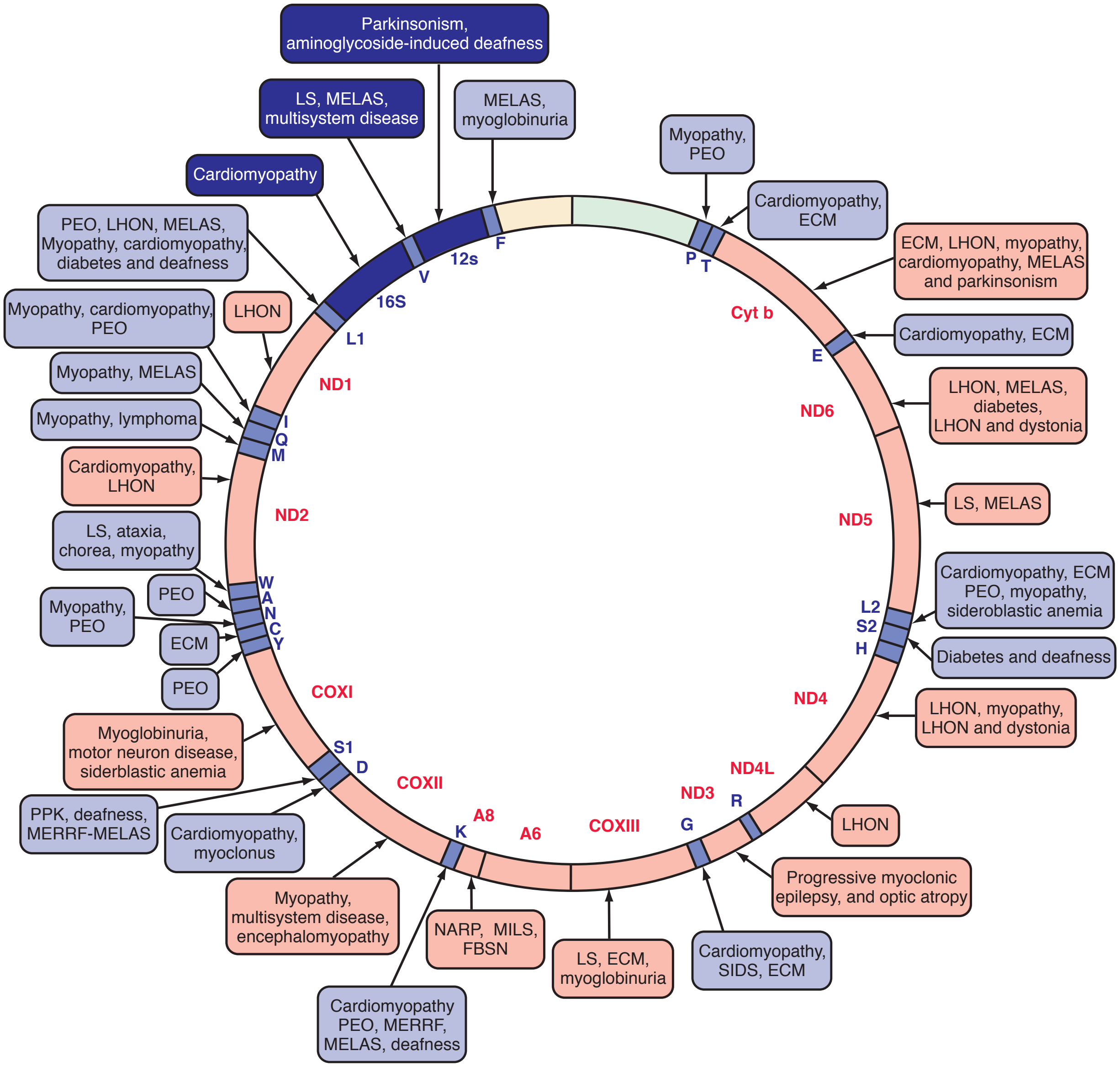

Figure 87-6 **Mutations in the human mitochondrial genome that are known to cause disease.** Disorders that are frequently or prominently associated with mutations in a particular gene are shown in *bold.* Diseases caused by mutations that impair mitochondrial protein synthesis are shown in *blue*. Diseases caused by mutations in protein-coding genes are shown in *red. ECM,* encephalomyopathy; *FBSN,* familial bilateral striatal necrosis; *LHON,* Leber hereditary optic neuropathy; *LS,* Leigh syndrome; *MELAS,* mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; *MERRF,* myoclonic epilepsy with ragged-red fibers; *MILS,* maternally inherited Leigh syndrome; *NARP,* neuropathy, ataxia, and retinitis pigmentosa; *PEO,* progressive external ophthalmoplegia; *PPK,* palmoplantar keratoderma; *SIDS,* sudden infant death syndrome. *(From DiMauro S, Schon EA: Mitochondrial respiratory-chain diseases,* N Engl J Med *348:2656–2668, 2003. Copyright 2003 Massachusetts Medical Society. All rights reserved.)*

Leigh Disease (Subacute Necrotizing Encephalomyelopathy)

Leigh disease is a heterogenous neurologic disease that remains a neuropathologic description characterized by demyelination, gliosis, necrosis, relative neuronal sparing, and capillary proliferation in specific brain regions. In decreasing order of severity, the affected areas are the basal ganglia, brainstem cerebellum, and cerebral cortex (see Chapter 598). The classic presentation is of an infant who presents with central hypotonia, developmental regression or arrest, and signs of brainstem or basal ganglia involvement. The clinical presentation is highly variable. Diagnosis is usually confirmed by radiologic or pathologic evidence of symmetric lesions affecting the basal ganglia, brainstem, and subthalamic nuclei. Patients with Leigh disease have defects in several enzyme complexes. Dysfunction in cytochrome C oxidase (complex IV) is the most commonly reported defect, followed by NADH-coenzyme Q reductase (complex I), PDHC, and pyruvate carboxylase. Mutations in the nuclear *SURF1* gene, which encodes a factor involved in the biogenesis of cytochrome C oxidase and mitochondrial DNA mutations in the adenosine triphosphatase 6 coding region, are common molecular findings in patients with Leigh disease. Patients with Leigh disease frequently present with developmental delay, seizures, altered consciousness, failure to thrive, pericardial effusion, and dilated cardiomyopathy. The prognosis for Leigh syndrome is poor. In a study of 14 cases, there were 7 fatalities before the age of 1.5 yr.

Lactic acidosis, hypoglycemia, and encephalopathy have also been reported in patients with thiamine transporter deficiency and with pyridoxine-dependent epilepsy. Both disorders should improve by the provision of thiamine and pyridoxine, respectively.

Bibliography is available at Expert Consult.

Table 87-3 Modified Walker Criteria Applied to Children Referred for Evaluation of Mitochondrial Disease

	MAJOR CRITERIA	MINOR CRITERIA
Clinical	Clinically complete RC encephalomyopathy* or a mitochondrial cytopathy defined as fulfilling 3 criteria†	Symptoms compatible with an RC defect‡
Histology	>2% RRF in skeletal muscle	Smaller numbers of RRF, SSAM, or widespread electron microscopy abnormalities of mitochondria
Enzymology	Cytochrome c oxidase–negative fibers or residual activity of an RC complex <20% in a tissue; <30% in a cell line, or <30% in 2 or more tissues	Antibody-based demonstration of an RC defect or residual activity of an RC complex 20-30% in a tissue, 30-40% in a cell line, or 30-40% in 2 or more tissues
Functional	Fibroblast ATP synthesis rates >3 SD below mean	Fibroblast ATP synthesis rates 2-3 SD below mean, or fibroblasts unable to grow in galactose media
Molecular	Nuclear or mtDNA mutation of undisputed pathogenicity	Nuclear or mtDNA mutation of probable pathogenicity
Metabolic		One or more metabolic indicators of impaired metabolic function

*Leigh disease, Alpers disease, lethal infantile mitochondrial disease, Pearson syndrome, Kearns-Sayre syndrome, MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), MERRF (myoclonic epilepsy associated with ragged red fibers), NARP (neuropathy, ataxia and retinitis pigmentosa), MNGIE (mitochondrial neurogastrointestinal encephalomyopathy), and LHON (Leber hereditary optic neuropathy).

†(1) Unexplained combination of multisystemic symptoms that is essentially pathognomonic for an RC disorder, (2) a progressive clinical course with episodes of exacerbation or a family history strongly indicative of an mtDNA mutation, and (3) other possible metabolic or nonmetabolic disorders have been excluded by appropriate testing.

‡Added pediatric features: stillbirth associated with a paucity of intrauterine movement, neonatal death or collapse, movement disorder, severe failure to thrive, neonatal hypotonia, and neonatal hypertonia as minor clinical criteria.

ATP, adenosine triphosphate; mtDNA, mitochondrial DNA; RC, respiratory chain; RRF, ragged red fibers; SSAM, subsarcolemmal accumulation of mitochondria.

From Scaglia F, Towbin JA, Craigen WJ, et al: Clinical spectrum, morbidity and mortality in 113 pediatric patients with mitochondrial disease, Pediatrics *114:925–931, 2004.*

Table 87-4 Clues to the Diagnosis of Mitochondrial Disease

NEUROLOGIC
Cerebral stroke-like lesions in a nonvascular pattern
Basal ganglia disease
Encephalopathy: recurrent or with low/moderate dosing of valproate
Neurodegeneration
Epilepsia partialis continua
Myoclonus
Ataxia
MRI findings consistent with Leigh disease
Characteristic MRS peaks
Lactate peak at 1.3 ppm TE (time to echo) at 35 and 135
Succinate peak at 2.4 ppm
CARDIOVASCULAR
Hypertrophic cardiomyopathy with rhythm disturbance
Unexplained heart block in a child
Cardiomyopathy with lactic acidosis (>5 mM)
Dilated cardiomyopathy with muscle weakness
Wolff-Parkinson-White arrhythmia
OPHTHALMOLOGIC
Retinal degeneration with signs of night blindness, color vision deficits, decreased visual acuity, or pigmentary retinopathy
Ophthalmoplegia/paresis
Fluctuating, dysconjugate eye movements
Ptosis
Sudden- or insidious-onset optic neuropathy/atrophy
GASTROENTEROLOGIC
Unexplained or valproate-induced liver failure
Severe dysmotility
Pseudoobstructive episodes
OTHER
A newborn, infant, or young child with unexplained hypotonia, weakness, failure to thrive, and a metabolic acidosis (particularly lactic acidosis)
Exercise intolerance that is not in proportion to weakness
Hypersensitivity to general anesthesia
Episodes of acute rhabdomyolysis

From Haas RH, Parikh S, Falk MJ, et al: Mitochondrial disease: a practical approach for primary care physicians, Pediatrics *120:1326–1333, 2007, Table 1, p. 1327.*

87.5 Defects in Pentose Metabolism

Priya S. Kishnani and Yuan-Tsong Chen

Approximately 90% of glucose metabolism in the body is via the glycolytic pathway, with the remaining 10% via the hexose monophosphate pathway. The hexose monophosphate shunt leads to formation of pentoses, as well as providing NADH. One of the metabolites is ribose-5-phosphate, which is used in the biosynthesis of ribonucleotides and deoxyribonucleotides. Through the transketolase and transaldolase reactions, the pentose phosphates can be converted back to fructose-6-phosphate and glucose-6-phosphate.

ESSENTIAL PENTOSURIA

Essential pentosuria is a benign disorder encountered principally in Ashkenazi Jews and is an autosomal recessive trait. The urine contains L-xylulose, which is excreted in increased amounts because of a block in the conversion of L-xylulose to xylitol as a result of xylitol dehydrogenase deficiency. The condition is usually discovered accidentally in a urine test for reducing substances; no treatment is required.

Transaldolase Deficiency

Few patients have reported symptoms that include liver cirrhosis, hepatosplenomegaly, severe neonatal hepatopathy, and cardiomyopathy. Biochemical abnormalities revealed elevated levels of arabitol, ribitol, and erythritol in the urine. Most recently, erythronic acid has been identified by urine nuclear magnetic resonance spectroscopy as another hallmark metabolite. Enzyme assay in the lymphoblasts and fibroblasts demonstrated low transaldolase activity, which was confirmed by mutations in the transaldolase gene. In addition, measurement of transaldolase activity in fibroblasts, lymphoblasts, or liver tissue, as well as assessing urinary concentrations of polyols also can be used to confirm the diagnosis.

Ribose-5-Phosphate Isomerase Deficiency

Only 1 case of this disorder has been reported. The affected male had psychomotor delay from early in life and developed epilepsy at 4 yr of age. Thereafter, a slow neurologic regression developed, with prominent cerebellar ataxia, some spasticity, optic atrophy, and a mild sensorimotor neuropathy. MRI of the brain at ages 11 yr and 14 yr showed

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extensive abnormalities of the cerebral white matter. Proton magnetic resonance spectroscopy (MRS) of the brain revealed elevated levels of ribitol and D-arabitol. These pentitols were also increased in urine and plasma similar to the patient found in transaldolase deficiency. Enzyme assays in cultured fibroblasts showed deficient ribose-5-phosphate isomerase activity, which was confirmed by a molecular study. These results combined with a study of ribose-5-phosphate isomerase–deficient mice converged to demonstrate that the specific genetic pairing of a null allele with an allele coding for a form of the enzyme that is only partly active, allowing for cell-type-dependent expression deficits, is a contributing factor to the rarity of the disease. Ribose-5-phosphate isomerase deficiency may represent an example of a single-gene disease that appears seldom because of its complex molecular etiology.

Bibliography is available at Expert Consult.

87.6 Disorders of Glycoprotein Degradation and Structure

Margaret M. McGovern and Robert J. Desnick

The disorders of glycoprotein degradation and structure include several lysosomal storage diseases that result from defects in glycoprotein degradation, and the congenital disorders of glycosylation (CDGs), which are pathophysiologically unrelated. Glycoproteins are macromolecules that are composed of oligosaccharide chains linked to a peptide backbone. They are synthesized by 2 pathways: the glycosyltransferase pathway, which synthesizes oligosaccharides linked *O*-glycosidically to serine or threonine residues; and the dolichol, lipid-linked pathway, which synthesizes oligosaccharides linked *N*-glycosidically to asparagine.

The glycoprotein lysosomal storage diseases result from the deficiency of the enzymes that normally participate in the degradation of oligosaccharides and include sialidosis, galactosialidosis, aspartylglucosaminuria, and α-mannosidosis. In some instances, the underlying abnormality that leads to glycoprotein accumulation also results in abnormal degradation of other classes of macromolecules that contain similar oligosaccharide linkages, such as certain glycolipids and proteoglycans. In these instances, the underlying enzymatic deficiency results in the accumulation of both glycoproteins and glycolipids. The classification of these types of disorders as lipidoses or glycoproteinoses is dependent on the nature of the predominantly stored substance. In general, the glycoprotein disorders are characterized by autosomal recessive inheritance and a progressive disease course with clinical features that resemble those seen in the mucopolysaccharidoses.

SIALIDOSIS AND GALACTOSIALIDOSIS

Sialidosis is an autosomal recessive disorder that results from the primary deficiency of neuraminidase because of mutations in the gene that encodes this protein, which is located on chromosome 10. In contrast, galactosialidosis is caused by the deficiency of 2 lysosomal enzymes—neuraminidase and β-galactosidase. The loss of these enzymatic activities results from mutations in a gene located on chromosome 20 that encodes protective protein/cathepsin A, which functions to stabilize these enzymatic activities. Neuraminidase normally cleaves terminal sialyl linkages of several oligosaccharides and glycoproteins. Its deficiency results in the accumulation of oligosaccharides, and the urinary excretion of sialic acid terminal oligosaccharides and sialylglycopeptides. Examination of tissues from affected individuals reveals pathologic storage of substrate in many tissues including liver, bone marrow, and brain.

The clinical phenotype associated with neuraminidase deficiency is variable and includes type I sialidosis which usually presents in the 2nd decade of life with myoclonus and the presence of a cherry-red spot. These patients typically come to attention secondary to gait disturbances, myoclonus, or visual complaints. In contrast, type II sialidosis occurs as congenital, infantile, and juvenile forms. The congenital and infantile forms result from isolated neuraminidase deficiency, whereas the juvenile form results from both neuraminidase and β-galactosidase deficiency. The congenital type II disease is characterized by hydrops fetalis, neonatal ascites, hepatosplenomegaly, stippling of the epiphyses, periosteal cloaking, and stillbirth or death in infancy. The type II infantile form presents in the 1st yr of life with dysostosis multiplex, moderate intellectual disability, visceromegaly, corneal clouding, cherry red spot, and seizures. The juvenile type II form of sialidosis, which is sometimes designated *galactosialidosis,* has a variable age of onset ranging from infancy to adulthood. In infancy, the phenotype is similar to that of GM_1 gangliosidosis, with edema, ascites, skeletal dysplasia, and cherry-red spot. Patients with later-onset disease have dysostosis multiplex, visceromegaly, mental retardation, dysmorphism, corneal clouding, progressive neurologic deterioration, and bilateral cherry red spots. No specific therapy exists for any form of the disease, although studies in animal models have demonstrated improvement in the phenotype after bone marrow transplantation. The diagnosis of sialidosis and galactosialidosis is achieved by the demonstration of the specific enzymatic deficiency. Prenatal diagnosis using cultured amniotic cells is also possible.

ASPARTYLGLUCOSAMINURIA

This is a rare autosomal recessive lysosomal storage disorder, except in Finland, where the carrier frequency is estimated at 1 in 36 adults. The disorder results from the deficient activity of aspartylglycosaminidase and the subsequent accumulation of aspartylglycosamine, particularly in the liver, spleen, and thyroid. The gene for the enzyme has been localized to the long arm of chromosome 4 and the complementary DNA has been cloned and sequenced. In the Finnish population, a single mutation in the gene *(C163S)* accounts for most mutant alleles, whereas outside of Finland, a large number of private mutations have been described. Affected individuals with aspartylglucosaminuria typically present in the 1st yr of life with recurrent infections, diarrhea, and hernias. Coarsening of the facies and short stature usually develop later. Other features include joint laxity, macroglossia, hoarse voice, crystal-like lens opacities, hypotonia, and spasticity. Psychomotor development is usually near normal until the age of 5 yr when a decline is noted. Behavioral abnormalities are typical and IQ values in affected adults are usually <40. Survival to adulthood is common, with most early deaths attributable to pneumonia or other pulmonary causes. Definitive diagnosis requires measurement of the enzyme in peripheral blood leukocytes. Molecular diagnosis by analysis of DNA for the C163S mutation is possible for Finnish patients. Several patients have undergone allogeneic bone marrow transplants with some reports of stabilization of the neurologic phenotype, but this approach has not been proven effective and no specific treatment is available. Prenatal diagnosis by the determination of the level of aspartylglycosaminidase in cultured amniocytes or chorionic villi has been reported.

α-MANNOSIDOSIS

This autosomal recessive disorder results from the deficient activity of α-mannosidase and the accumulation of mannose-rich compounds. The gene encoding the enzyme has been localized to chromosome 19p13.2-q12, although the complementary DNA has not been cloned. Affected patients with this disorder display clinical heterogeneity. There is a severe infantile form, or type I disease, and a milder juvenile variant, type II disease. All patients have psychomotor retardation, facial coarsening, and dysostosis multiplex. The infantile form of the disorder, however, is characterized by more rapid cognitive deterioration, with death occurring between the ages of 3 and 10 yr. Patients with the infantile form also have more severe skeletal involvement and hepatosplenomegaly. The juvenile disorder is characterized by onset of symptoms in early childhood or adolescence with milder somatic features and survival to adulthood. Hearing loss, destructive synovitis, pancytopenia, and spastic paraplegia have been reported in type II patients. No specific therapy exists for the disorder. The diagnosis is made by the demonstration of the deficiency of α-mannosidase activity in white blood cells or cultured fibroblasts, and prenatal diagnosis has also been achieved.

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Table 87-5 Congenital Disorders of Glycosylation: Disorders According to the New Nomenclature

	CLINICAL FEATURES	DIAGNOSTIC APPROACH
DEFECTS OF PROTEIN *N*-GLYCOSYLATION		
PMM2-CDG (CDG-Ia) MPI-CDG (CDG-Ib) ALG6-CDG (CDG-Ic) ALG3-CDG (CDG-Id) ALG12-CDG (CDG-Ig) ALG8-CDG (CDG-Ih) ALG2-CDG (CDG-Ii) DPAGT1-CDG (CDG-Ij) ALG1-CDG (CDG-Ik) ALG9-CDG (CDG-Il) RFT1-CDG (CDG-In) ALG11-CDG (CDG-Ip) TUSC3-CDG MAGT1-CDG MGAT2-CDG (CDG-IIa) GCS1-CDG (CDG-IIb)	Dysmorphic facial features, abnormal lipid distribution, strabismus, protein-losing enteropathy, frequent vomiting, failure to thrive, short stature, cardiomyopathy, pericardial fluid collection, proteinuria, hepatomegaly, liver cirrhosis, hypotonia, ataxia, speech delay, mental retardation, seizures, cataract, retinitis pigmentosa, visual loss, peripheral neuropathy, hypothyreosis, thrombosis, bleeding anomalies, osteoporosis, recurrent infections, thrombocytopenia	Screening by TIEF, confirming type I or type II pattern. In type I, measurement of PMM and PMI enzyme activity in leukocytes or fibroblasts. In case of normal results of PMM/PMI, lipid-linked oligosaccharides analysis in fibroblasts. In type II, mass spectrometry of isolated serum N-glycans or serum apoC-III isoelectrophoresis. Based on the findings, choose appropriate genetic testing. Normal TIEF results* necessitate direct mutation analysis
DEFECTS OF PROTEIN *O*-GLYCOSYLATION		
EXT1/EXT2-CDG B4GALT7-CDG GALNT3-CDG SLC35D1-CDG POMT1/POMT2-CDG POMGNT1-CDG SCDO3-CDG B3GALTL-CDG	Multiple exostosis; short stature/joint laxity/progeria; familial tumoral calcinosis; skeletal dysplasia; muscle dystrophy; brain developmental defect; spondylocostal dysostosis; congenital eye anomalies/cataract	Syndromic presentation and organ-specific expression of the disease necessitates a genetic approach; upon suspicion perform direct mutation analysis
DEFECTS OF GLYCOSPHINGOLIPID AND GPI-ANCHOR GLYCOSYLATION		
SIAT9-CDG PIGM-CDG PIGV-CDG	Epilepsy; hepatomegaly/portal vein thrombosis; hyperphosphatasia, mental retardation	Mutation analysis. Expression analysis of glycosylphosphatidylinositol-linked proteins (e.g., CD59 or CD24) on hematopoietic cells
DEFECTS OF MULTIPLE GLYCOSYLATION AND OTHER PATHWAYS		
DPM1-CDG (CDG-Ie) DPM3-CDG (CDG-Io) MPDU1-CDG (CDG-If) GNE-CDG B4GALT1-CDG (CDG-IId) SLC35A1-CDG (CDG-IIf) SLC35C1-CDG (CDG-IIc) DK1-CDG (CDG-Im) SRD5A3-CDG (CDG-Iq) COG-CDG (COG1, COG4, COG5, COG6, COG7, COG 8) ATP6VOA2-CDG SEC23B-CDG	Dysmorphic facial features, strabismus; cardiomyopathy, muscle dystrophy; hepatomegaly; recurrent infections; thrombosis/bleeding anomalies; hypotonia, mental retardation, seizures; cardiomyopathy; ichthyosis, ataxia, visual loss; skeletal dysplasia; hyperthermia, adducted thumbs; failure to thrive; cutis laxa; HEMPAS	Screening by TIEF, confirming type I or type II pattern. In type II pattern, additional apo-C III isoelectric focusing. In patients with normal TIEF, if there is a syndromic presentation upon suspicion perform direct mutation analysis. In patients with muscle dystrophy perform dystroglycan staining in muscle biopsy, in a syndromic presentation upon suspicion direct mutation analysis

Previous congenital disorders of glycosylation nomenclature are in parentheses.
*Normal TIEF results can be due to young age or also in GCS1-CDG, SLC35C1-CDG and SLC35A1-CDG.
Apo, apolipoprotein; GPI, glycophosphatidylinositol; HEMPAS, hereditary erythroblastic multinuclearity with a positive acidified serum; PMI, phosphomannoisomerase; PMM, phosphomannomutase; TIEF, transferrin isoelectric focusing.
From Theodore M, Morava E: Congenital disorders of glycosylation: sweet news. Curr Opin Pediatr *23(6):581–587, 2011.*

CONGENITAL DISORDERS OF GLYCOSYLATION

These are a heterogenous group of autosomal recessive disorders that result from defective protein and lipid glycosylation. The protein glycosylation disorders result from defects of *N*-glycosylation, combined *N*- and *O*-glycosylation, the dolichol pathway and the conserved oligomeric Golgi complex. The more recently discovered lipid-glycosylation disorders include defects of ganglioside synthesis (GM_3 synthase deficiency) and the glycophosphatidylinositol anchor system. In addition, there are patients with glycosylation defects for which the molecular and biochemical bases are not yet known.

To date, more than 30 CDG subtypes have been identified (Table 87-5). In general, most CDG disorders are multisystemic and present with variable involvement of the central nervous system (most often hypotonia and ataxia), abnormal fat distribution, ocular movement defects, coagulation abnormalities, gastrointestinal symptoms including protein-losing enteropathy, retinitis pigmentosa, hormonal abnormalities, and, in some cases, dysmorphic features. CDG type Ia, which results from mutations in the gene that encodes phosphomannomutase, is the most common form. The most consistent clinical features of this disorder include variable degrees of psychomotor retardation, subcutaneous fat pads and inverted nipples. Frequent neurologic findings in infancy include cerebellar atrophy (Fig. 87-7), hypotonia, weakness, hyperreflexia, and strokelike episodes (Table 87-6).

In childhood, ataxia, muscle atrophy, decreased deep tendon reflexes, toe walking, and continued stroke-like episodes are observed. The latter events may be related to coagulopathies characterized by reduced antithrombin III and proteins C and S, in conjunction with abnormal levels of factors VIII, IX, XI, and XIII, which together increase risk for bleeding and thrombosis. Growth failure, liver dysfunction, retinal

Table 87-6 Characteristics of Representative Congenital Disorders of Glycosylation

NAME	DEFECT	DYSMORPHOLOGY	NEUROLOGIC SIGNS	GASTROINTESTINAL SIGNS	OTHER SIGNS
CDG-Ia	Phosphomannomutase 2	Fat maldistribution: narrow waist, fat in axilla, groin, buttock High nasal bridge Prominent jaw Large ears Inverted nipples	Hypotonia Hyporeflexia Strabismus Ataxia: olivopontocerebellar atrophy or hypoplasia Mental retardation (IQ 40-60) Stroke-like episodes Hemorrhagic cerebral infarcts Polyneuropathy Muscle wasting Scoliosis Spinal stenosis Kyphosis Pigmentary retinal degeneration Contractures Seizures	Poor feeding, failure to thrive Carnitine deficiency Diarrhea Liver failure	Cardiomyopathy Pericardial effusions Nephrotic syndrome Renal tubulopathy Severe infections Hypogonadism Absent puberty TBG deficiency ↓ Levels of: antithrombin III, α_1-acid glycoprotein, α_1-antitrypsin, ferritin, ceruloplasmin, proteins C + S, factor XI, complement C1, C3a, C4a
CDG-Ib	Phosphomannose isomerase	None	Normal development	Protein-losing enteropathy Failure to thrive Chronic intractable diarrhea Hepatic fibrosis Hyperinsulinemic hypoglycemia Vomiting	Coagulopathy ↓ Proteins C, S, antithrombin III
CDG-Ic	Glucosyltransferase	None	Similar to CDG-Ia but milder Mild cerebellar hypoplasia Seizures		Frequent infections Coagulopathy Failure to thrive Recurrent eyelid edema Pigmentary retinal degeneration
CDGId	Mannosyltransferase	High-arched palate	Microcephaly Seizures (severe) Developmental delay CNS atrophy	Failure to thrive	Coagulopathy
CDG-Ie	Dolichol-phosphate-mannose synthetase Failure to thrive	High-arched palate Down-slanting palpebral fissures Hemangiomas Short arms Small hands Dysplastic nails	Microcephaly Hypotonia Developmental delay Seizures (severe) Cortical blindness Hyperreflexia Delayed myelination	Failure to thrive	↑ CPK
CDG-IIa	*N*-acetyl-glucosaminyl-transferase II	Facial dysmorphology	Stereotypic hand movements Seizures Developmental delay No neuropathy or cerebellar hypoplasia	Failure to thrive	Coagulopathy
CDG-IIb	Glucosidase I	Facial dysmorphology	Hypotonia Retardation Seizures	Hepatomegaly	Coagulopathy
CDG-IIc	GDP-fucose transporter I	Facial dysmorphology	Developmental delay Hypotonia	Failure to thrive	Recurrent infections with leukocytosis
CDG-x or CDG-Ix	Unknown	Like CDG-Ia Microcephaly	Hypotonia Seizures Cerebellar hypoplasia Developmental delay	Intractable diarrhea Failure to thrive	Nonimmune hydrops Cataracts Thrombocytopenia Renal tubulopathy Distal bone demineralization
CDG-Ih	Glucosyltransferase 2	Facial dysmorphology	Seizures Hypotonia Developmental delay	Chronic diarrhea Protein-losing enteropathy Chronic liver disease	Coagulopathy Renal microcysts Nephrotic syndrome
CDG-X variant	Unknown	None	None	Asymptomatic cryptogenic Chronic liver disease	Coagulopathy

Table 87-6	Characteristics of Representative Congenital Disorders of Glycosylation—cont'd				
NAME	**DEFECT**	**DYSMORPHOLOGY**	**NEUROLOGIC SIGNS**	**GASTROINTESTINAL SIGNS**	**OTHER SIGNS**
CDG-IIX	Unknown	None	Developmental delay Hypotonia Cerebral atrophy	Chronic diarrhea Liver cirrhosis	Recurrent infections
CDG-XIV	Phosphoglucomutase 1 (previously a glycogenosis)	Bifid uvula	Muscle weakness Rhabdomyolysis	Hepatomegaly Elevated liver enzymes	Dilated cardiomyopathy Malignant hyperthermia Growth retardation Hypoglycemia May respond to galactose supplementation

CDG, congenital disorders of glycosylation; CNS, central nervous system; CPK, creatine phosphokinase; GDP, guanosine diphosphate; TBG, thyroid-binding globulin.

Figure 87-7 Sagittal T2-weighted MR image shows severe spinal cord compression with myelopathy *(white arrow)*, together with cerebellar atrophy *(black arrow)*, and cortical atrophy of the parietal lobe *(red arrow)*. *(From Schade van Westrum SM, Nederkoorn PJ, Schuurman PR, et al: Skeletal dysplasia and myelopathy in congenital disorder of glycosylation type 1A,* J Pediatr *148:115–117, 2006, Fig. 1.)*

degeneration, and skeletal abnormalities have also been described. The skeletal features can include contractures, kyphoscoliosis, and pectus carinatum, all of which may be secondary to the neurologic effects of the disorder. Pericardial effusion in older patients and hypertrophic obstructive cardiomyopathy in the infant also may occur.

Among the other types, few have distinctive phenotypes. These include CDG-Ib, which is characterized by protein-losing enteropathy and normal neurologic function; CDG-If, which includes ichthyosis and growth retardation; and CDG-IIf, in which macrothrombocytopenia is present.

Diagnostic testing for CDG types that result from defects of *N*-glycosylation begins with isoelectric focusing of *N*-glycosylated serum transferring. For some types further confirmation of the diagnosis by enzymatic analysis in fibroblasts or leukocytes and/or mutation analysis of the relevant gene is available. Although prenatal diagnosis by analysis of transferrin has been attempted, it has not proven reliable. Treatment of these disorders is symptomatic, except for CDG-Ib, which responds to oral mannose (100-150 mg/kg/day every 4-6 hr).

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Chapter 88

Mucopolysaccharidoses

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Mucopolysaccharidoses are hereditary, progressive diseases caused by mutations of genes coding for lysosomal enzymes needed to degrade glycosaminoglycans (acid mucopolysaccharides). Glycosaminoglycans (GAGs) are long-chain complex carbohydrates composed of uronic acids, amino sugars, and neutral sugars. The major GAGs are chondroitin-4-sulfate, chondroitin-6-sulfate, heparan sulfate, dermatan sulfate, keratan sulfate, and hyaluronan. These substances are synthesized and, with the exception of hyaluronan, linked to proteins to form proteoglycans, major constituents of the ground substance of connective tissue, of nuclear and cell membranes. Degradation of proteoglycans starts with the proteolytic removal of the protein core followed by the stepwise degradation of the glycosaminoglycan moiety. Failure of this degradation because of absent or grossly reduced activity of mutated lysosomal enzymes results in the intralysosomal accumulation of glycosaminoglycan fragments (Fig. 88-1). Distended lysosomes accumulate in the cell, interfere with cell function and lead to characteristic pattern of clinical, radiologic, and biochemical abnormalities (Table 88-1, Fig. 88-2). Within this pattern, specific diseases can be recognized which evolve from the intracellular accumulation of different degradation products (Table 88-2). As a general rule, the impaired degradation of heparan sulfate is more closely associated with intellectual disability, and the impaired degradation of dermatan sulfate, chondroitin sulfates, and keratan sulfate with mesenchymal abnormalities. Variable expression within a given entity results from allelic mutations and varying residual activity of mutated enzymes. For instance, allelic mutations of the gene encoding L-iduronidase may result in severe Hurler disease with early death or in mild Scheie disease manifesting only with limited joint mobility, mild skeletal abnormalities and corneal opacities. Mucopolysaccharidoses are autosomal recessive disorders with the exception of Hunter disease, which is X-linked recessive. Their overall frequency is between 3.5 in 100,000 births and 4.5 in 100,000 births. The most common subtype is MPS-III, followed by MPS-I and MPS-II.

CLINICAL ENTITIES

Mucopolysaccharidosis I

Mucopolysaccharidosis (MPS)-I is caused by mutations of the *IDUA* gene on chromosome 4p16.3 encoding α-L-iduronidase. Mutation analysis has revealed 2 major alleles, W402X and Q70X, account for more than half the MPS-I alleles in the white population. The

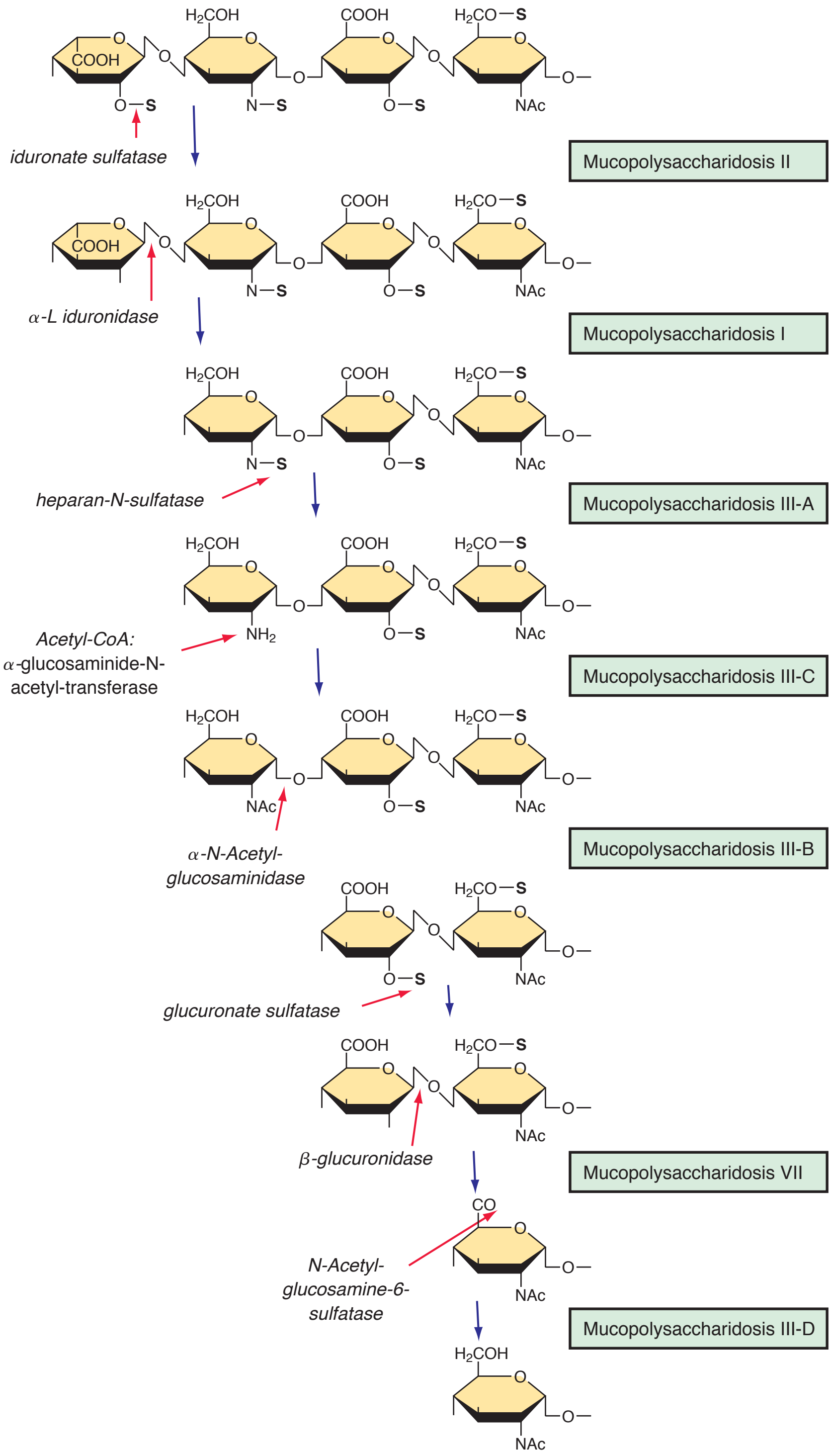

Figure 88-1 Degradation of heparan sulfate and mucopolysaccharidoses resulting from the deficiency of individual enzymes. Some of these enzymes are also involved in the degradation of other glycosaminoglycans (not shown).

mutations introduce stop codons with ensuing absence of functional enzyme (null alleles) and in homozygosity or compound heterozygosity give rise to Hurler disease. Other mutations occur in only 1 or a few individuals.

Deficiency of α-L-iduronidase results in a wide range of clinical involvement from severe Hurler disease to mild Scheie disease, which are ends of a broad clinical spectrum. Homozygous nonsense mutations result in severe forms of MPS-I, whereas missense mutations are more likely to preserve some residual enzyme activity associated with a milder form of the disease.

Hurler Disease

This form of MPS-I (MPS-IH) is a severe, progressive disorder with multiple organ and tissue involvement that results in premature death, usually by 10 yr of age. An infant with Hurler syndrome appears normal at birth, but inguinal herniae are often present. Diagnosis is usually made between 6 and 24 mo with evidence of hepatosplenomegaly, coarse facial features, corneal clouding, large tongue, prominent forehead, joint stiffness, short stature, and skeletal dysplasia. Acute cardiomyopathy has been found in some infants younger than 1 yr of age. Most patients have recurrent upper respiratory tract and

ear infections, noisy breathing, and persistent copious nasal discharge. Valvular heart disease with incompetence notably of the mitral and aortic valves regularly develops and narrowing of the coronary arteries occurs. Obstructive airway disease, notably during sleep, may necessitate tracheotomy. Obstructive airway disease, respiratory infection, and cardiac complications are the common causes of death.

Most children with Hurler syndrome acquire only limited language skills because of developmental delay, combined conductive and neurosensory hearing loss, and an enlarged tongue. Progressive ventricular enlargement with increased intracranial pressure caused by communicating hydrocephalus also occurs. Corneal clouding, glaucoma, and retinal degeneration are common. Radiographs show a characteristic skeletal dysplasia known as dysostosis multiplex (Figs. 88-3 and 88-4). The earliest radiographic signs are thick ribs and ovoid vertebral bodies. Skeletal abnormalities in addition to those shown in the figures include enlarged, coarsely trabeculated diaphyses of the long bones with irregular metaphyses and epiphyses. With progression of the disease macrocephaly develops with thickened calvarium, premature closure of lambdoid and sagittal sutures, shallow orbits, enlarged J-shaped sella, and abnormal spacing of teeth with dentigerous cyst.

Table 88-1 Recognition Pattern of Mucopolysaccharidoses

	Mucopolysaccharidosis Type						
MANIFESTATIONS	**I-H**	**I-S**	**II**	**III**	**IV**	**VI**	**VII**
Mental deficiency	+	−	±	+	−	−	±
Coarse facial features	+	(+)	+	+	−	+	±
Corneal clouding	+	+	−	−	(+)	+	±
Visceromegaly	+	(+)	+	(+)	−	+	+
Short stature	+	(+)	+	−	+	+	+
Joint contractures	+	+	+	−	−	+	+
Dysostosis multiplex	+	(+)	+	(+)	+	+	+
Leucocyte inclusions	+	(+)	+	+	−	+	+
Mucopolysacchariduria	+	+	+	+	+	+	+

I-H, Hurler disease; I-S, Scheie disease; II Hunter disease; III, Sanfilippo disease; IV, Morquio disease; VI, Maroteaux-Lamy disease; VII Sly disease.

Hurler-Scheie Disease

The clinical phenotype of MPS-IH/S is intermediate between Hurler and Scheie diseases and is characterized by progressive somatic involvement, including dysostosis multiplex with little or no intellectual dysfunction. The onset of symptoms is usually observed between 3 and 8 yr of age; survival to adulthood is common. Cardiac involvement and upper airway obstruction contribute to clinical morbidity. Some patients have spondylolisthesis, which may cause cord compression.

Scheie Disease

MPS-IS is a comparatively mild disorder characterized by joint stiffness, aortic valve disease, corneal clouding, and mild dysostosis multiplex. Onset of significant symptoms is usually after the age of 5 yr, with diagnosis made between 10 and 20 yr of age. Patients with Scheie disease have normal intelligence and stature but have significant joint and ocular involvement. A carpal tunnel syndrome often develops. Ophthalmic features include corneal clouding, glaucoma, and retinal degeneration. Obstructive airway disease, causing sleep apnea, develops in some patients, necessitating tracheotomy. Aortic valve disease is common and has required valve replacement in some patients.

Mucopolysaccharidosis II

Hunter disease, (MPS-II) is an X-linked disorder caused by the deficiency of iduronate 2-sulfatase (IDS). The gene encoding IDS is mapped to Xq28. Point mutations of the *IDS* gene have been detected in approximately 80% of patients with MPS-II. Major deletions or rearrangements of the *IDS* gene have been found in the rest, and these are usually associated with a more severe clinical phenotype. As an X-linked recessive disorder, Hunter disease manifests almost exclusively in males. However, it has been observed in females and this is

MPS-I MPS-II MPS-III MPS-IV MPS-VI

Figure 88-2 **Patients with various types of mucopolysaccharidoses.** MPS-I: Hurler disease, patient age 3 yr; MPS-II: Hunter disease, patient age 12 yr; MPS-III: Sanfilippo disease, patient age 4 yr; MPS-IV: Morquio disease, patient age 10 yr; MPS-VI: Maroteaux-Lamy disease, patient age 15 yr.

Table 88-2 Mucopolysaccharidoses: Clinical, Molecular, and Biochemical Aspects

MPS TYPE	EPONYM	INHERITANCE	GENE CHROMOSOME	MAIN CLINICAL FEATURES	DEFECTIVE ENZYME	ASSAY	MIM NUMBER
I-H	Pfaundler-Hurler	AR	*IDUA* 4p16.3	Severe Hurler phenotype, mental deficiency, corneal clouding, death usually before age 14 yr, Hurler phenotype, mental retardation, corneal clouding, death usually before age 14 yr	α-L-iduronidase	L,F,Ac,CV	252800 607014
I-S	Scheie	AR	*IDUA* 4p16.4	Stiff joints, corneal clouding, aortic valve disease, normal intelligence, survive to adulthood	α-L-iduronidase	L,F,Ac,CV	607016
I-HS	Hurler-Scheie	AR	*IDUA* 4p16.4	Phenotype intermediate between I-H and I-S	α-L-iduronidase	L,F,Ac,Cv	607015
II	Hunter	XLR	*IDS* Xq27.3-28	Severe course similar to I-H but clear corneae. Mild course: less pronounced features, later manifestation, survival to adulthood with mild or without mental deficiency	Iduronate sulfate sulfatase	S,F,Af,Ac,Cv	309900
III-A	Sanfilippo A	AR	*SGSH* 17q25.3	Behavioral problems, sleeping disorder, aggression, progressive dementia, mild dysmorphism, coarse hair, clear corneas; survival to adulthood possible	Heparan-S-sulfamidase	L,F,Ac,Cv	252900 605270
II-IB	Sanfilippo B	AR	*NAGLU* 17q21		*N*-Acetyl-α-D-glucosaminidase	S,F,Ac,Cv	252920
III-C	Sanfilippo C	AR	*HGSNAT* 8p11.21		Acetyl-CoA:α-glucosaminide *N*-acetyltransferase	F,Ac	252930
III-D	Sanfilippo D	AR	*GNS* 12q14		*N*-Acetylglucosamine-6-sulfatase	F,Ac	252940 607664
IV-A	Morquio A	AR	*GALNS* 16q24.3	Short-trunk dwarfism, fine corneal opacities, characteristic bone dysplasia; final height below 125 cm	*N*-Acetyl-galactosamine-6-sulfatase	L,F,Ac	253000
IV-B	Morquio B	AR	*GLB1* 3p21.33	Same as IV-A, but milder; adult height over 120 cm	β-Galactosidase	L,F,Ac,Cv	253010 230500
VI	Maroteaux-Lamy	AR	*ARSB* 5q11-q13	Hurler phenotype with marked corneal clouding but normal intelligence; mild, moderate and severe expression in different families	*N*-Acetyl-galactosamine-4-sulfatase (arylsulfatase B)	L,F,Ac	253200
VII	Sly	AR	*GUSB* 7q21.11	Varying from fetal hydrops to mild dysmorphism; dense inclusions in granulocytes	β-Glucuronidase	S,F,Ac,Cv	253220
IX	Hyaluronidase deficiency	AR	*HYAL1* 3p21.3	Periarticular masses, no Hurler phenotype H	Hyaluronidase 1	S	601492

Ac, cultured amniotic cells; Af, amniotic fluid; Cv, chorionic villi; F, cultured fibroblasts; L, leukocytes; MIM, Mendelian Inheritance in Man Catalogue; S, serum.

explained by skewed inactivation of the X-chromosome carrying the normal gene.

Marked molecular heterogeneity explains the wide clinical spectrum of Hunter disease. Patients with severe MPS-II have features similar to those of Hurler disease except for the lack of corneal clouding and the somewhat slower progression of somatic and central nervous system (CNS) deterioration. Coarse facial features, short stature, dysostosis multiplex, joint stiffness, and intellectual disability manifest between 2 and 4 yr of age. Grouped skin papules are present in some patients. Extensive mongolian spots present at birth have been observed in African and Asian patients and may be an early marker of the disease. Gastrointestinal storage may produce chronic diarrhea. Communicating hydrocephalus and spastic paraplegia may develop due to thickened meninges. In severely affected patients, extensive, slowly progressive neurologic involvement precedes death, which usually occurs between 10 and 15 yr of age.

Patients with the mild form can have a near-normal or normal life span, minimal CNS involvement and slow progression of somatic deterioration with preservation of cognitive function in adult life. Survival to ages 65 and 87 yr has been reported and some patients have had children. Somatic features are Hurler-like but milder with a greatly reduced rate of progression. Adult height may exceed 150 cm. Airway involvement, valvular cardiac disease, hearing impairment, carpal tunnel syndrome, and joint stiffness are common and can result in significant loss of function in both the mild and severe forms.

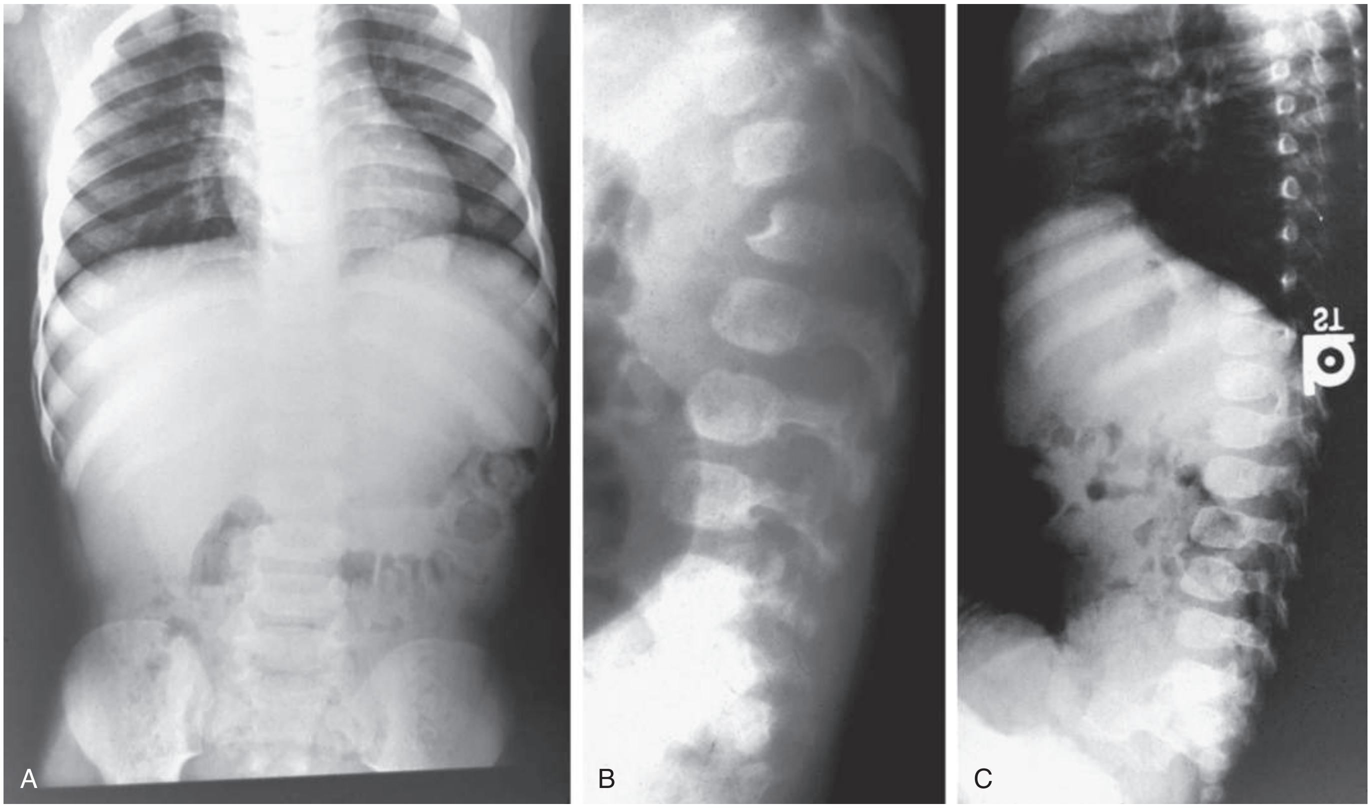

Figure 88-3 Dysostosis multiplex. **A,** Sanfilippo disease, patient age 4 yr: The ribs are wide. **B,** Sanfilippo disease, patient age 4 yr: immature, ovoid configuration of the vertebral bodies. **C,** Hurler disease, patient age 18 mo: anterosuperior hypoplasia of L-1 resulting in hook-shaped appearance.

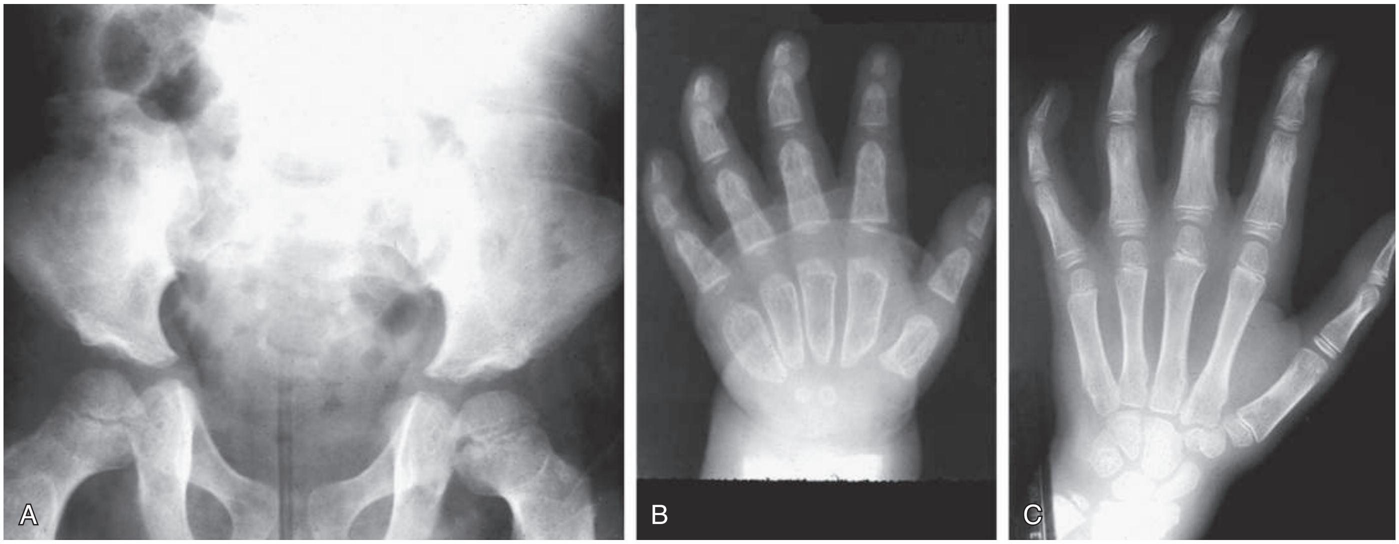

Figure 88-4 Dysostosis multiplex. **A,** MPS-IH, patient age 10 yr. The inferior portions of the ilia are hypoplastic with resulting iliac flare and shallow acetabular fossae. The femoral necks are in valgus position. **B,** MPS-IH, patient age 4 yr. Metacarpals and phalanges are abnormally short, wide and deformed with proximal pointing of the metacarpals and bullet-shaped phalanges. Bone trabeculation is coarse and the cortices are thin. **C,** MPS-IS, patient age 13 yr. The carpal bones are small leading to a V-shaped configuration of the digits. The short tubular bones are well modeled. Flexion of the middle and distal phalanges II-V is caused by joint contractures.

Mucopolysaccharidosis III

Sanfilippo disease makes up a genetically heterogeneous but clinically similar group of 4 recognized types. Each type is caused by a different enzyme deficiency involved in the degradation of heparan sulfate (see Fig. 88-1). Mutations have been found in all the MPS-III disorders for which the genes have been isolated.

Phenotypic variation exists in MPS-III patients, but to a lesser degree than in other MPS disorders. Patients with Sanfilippo disease are characterized by slowly progressive, severe CNS involvement with mild somatic disease. Such disproportionate involvement of the CNS is unique to MPS-III. Onset of clinical features usually occurs between 2 and 6 yr in a child who previously appeared normal. Presenting features include delayed development, hyperactivity with aggressive behavior, coarse hair, hirsutism, sleep disorders, and mild hepatosplenomegaly. Delays in diagnosis of MPS-III are common because of the mild physical features, hyperactivity, and slowly progressive neurologic disease. Severe neurologic deterioration occurs in most patients by 6-10 yr, accompanied by rapid deterioration of social and adaptive

skills. Severe behavior problems such as sleep disturbance, uncontrolled hyperactivity, temper tantrums, destructive behavior, and physical aggression are common. Profound developmental regression and behavior problems often occur in patients with normal physical strength, making management particularly difficult.

Mucopolysaccharidosis IV

Morquio disease (MPS-IV) is caused by a deficiency of *N*-acetylgalactosamine-6-sulfatase (MPS-IVA) or of β-galactosidase (MPS-IVB). Both result in the defective degradation of keratan sulfate. The gene encoding *N*-acetylgalactosamine-6-sulfatase is on chromosome 16q24.3 and the gene encoding β-galactosidase, *GLB1*, on chromosome 3p21.33. β-Galactosidase catalyzes hydrolysis of GM_1 ganglioside in addition to endohydrolysis of keratan sulfate, and most mutations of *GLB1* result in generalized gangliosidosis, a spectrum of neurodegenerative disorders associated with dysostosis multiplex. A W273L mutation of the *GLB1* gene, either in the homozygous state or as part of compound heterozygosity, commonly results in Morquio B disease.

Both types of Morquio disease are characterized by short-trunk dwarfism, fine corneal deposits, a skeletal dysplasia that is distinct from other mucopolysaccharidoses, and preservation of intelligence. MPS-IVA is usually more severe than MPS-IVB with adult heights of less than 125 cm in the former and more than 150 cm in the latter. However, there is considerable variability of expression in both subtypes. The appearance of genua valga, kyphosis, growth retardation with short trunk and neck, and waddling gait with a tendency to fall are early symptoms of MPS-IV. Extraskeletal manifestations include mild corneal clouding, small teeth with abnormally thin enamel, frequent caries formation and occasionally hepatomegaly and cardiac valvular lesions. Instability of the odontoid process and ligamentous laxity is regularly present and can result in life-threatening atlantoaxial instability and dislocation. Surgery to stabilize the upper cervical spine, usually by posterior spinal fusion, before the development of cervical myelopathy can be lifesaving.

Mucopolysaccharidosis VI

Maroteaux-Lamy disease is caused by mutations of the *ARSB* gene on chromosome 5q11-13 encoding *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B). It is characterized by severe to mild somatic involvement, as seen in MPS-I, but with preservation of intelligence. The somatic involvement of the severe form of MPS-IV is characterized by corneal clouding, coarse facial features, joint stiffness, valvular heart disease, communicating hydrocephalus, and dysostosis multiplex. In the severe form, growth can be normal for the first few years of life but seems to virtually stop after age 6-8 yr. The mild to intermediate forms of Maroteaux-Lamy disease can be easily confused with Scheie syndrome. Spinal cord compression from thickening of the dura in the upper cervical canal with resultant myelopathy is a frequent occurrence in patients with MPS-VI.

Mucopolysaccharidosis VII

Sly syndrome (MPS-VII) is caused by mutations of the *GUSB* gene located on chromosome 7q21.11. Mutations result in a deficiency of β-glucuronidase, intracellular storage of glycosaminoglycan fragments and a very wide range of clinical involvement. The most severe form presents as lethal nonimmune fetal hydrops and may be detected in utero by ultrasound. Some severely affected newborns survive for some months and have, or develop, signs of lysosomal storage including thick skin, visceromegaly, and dysostosis multiplex. Less-severe forms of MPS-VII present during the first years of life with features of MPS-I but slower progression. Corneal clouding varies. Patients with manifestation after 4 yr of life have skeletal abnormalities of dysostosis multiplex but normal intelligence and usually clear corneae. They may be found incidentally on the basis of a blood smear that shows coarse granulocytic inclusions.

Mucopolysaccharidosis IX

The disorder is caused by a mutation in the *HYAL1* gene on chromosome 3p21.2-21.2 encoding one of 3 hyaluronidases. Clinical findings in the only known patient, a 14-year old girl, were bilateral nodular soft-tissue periarticular masses, lysosomal storage of GAGs in histiocytes, mildly dysmorphic craniofacial features, short stature, normal joint movement and normal intelligence. Small erosions in both acetabula were the only radiographic findings.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical suspicion of a MPS justifies a skeletal survey. Radiographs of chest, spine, pelvis and hands may show early signs of dysostosis multiplex. The next diagnostic step is to assay the urinary excretion of GAG. Semiquantitative spot tests are quick and inexpensive but subject to both false-positive and false-negative results. Quantitative analysis of single GAG by various methods, or of oligosaccharides by tandem mass spectrometry, is preferable and reveals type-specific profiles. Morquio disease is often missed in urinary assays but can reliably be diagnosed in serum using monoclonal antibodies to keratan sulfate.

Any individual who is suspected of an MPS disorder based on clinical features, radiographic results, or urinary GAG screening tests should have a definitive diagnosis established by enzyme assay. Serum, leukocytes, or cultured fibroblasts are used as the tissue source for measuring lysosomal enzymes (see Table 88-2).

Prenatal diagnosis is available for all MPSs and is carried out on cultured cells from amniotic fluid or chorionic villus biopsy. Measurement of GAGs in amniotic fluid is unreliable. Carrier testing in Hunter syndrome, an X-linked disorder, requires analysis of *IDS* gene once the specific mutation or chromosome arrangement in the family under consideration is known. Prenatal molecular analysis must be offered in a male fetus of a proven female carrier of the *IDS* gene. His risk to be affected is 50%. It is very small, but not zero, in a female fetus as a result of skewed maternal X-chromosome inactivation. Molecular analysis in patients with other enzymatically proven mucopolysaccharidoses or in known carriers is costly and usually not required. MPSs I, II, and VI are candidates for neonatal blood spot screening by tandem mass spectrometry allowing early diagnosis and enzyme replacement therapy.

Mucolipidoses and oligosaccharidoses manifest with the same clinical and radiographic features as mucopolysaccharidoses. In these conditions the urinary excretion of GAGs is not elevated. Hurler-like facial features, joint contractures, dysostosis multiplex and elevated urinary GAG excretion differentiate the mucopolysaccharidoses from congenital disorders of glycosylation and other neurodegenerative and dwarfing conditions.

TREATMENT

Hematopoietic stem cell transplantation and enzyme replacement therapy are performed in specialized institutions (Table 88-3). Experimental forms of therapy include substrate reduction by flavonoids, gene silencing, read-through attempts and transplantation of autologous hematopoietic stem cells that have been genetically modified ex vivo to express the missing protein. Symptomatic measures are listed in Table 88-4.

Bone marrow transplantation from related or unrelated donors and **cord blood transplantation** have resulted in significant clinical improvement of somatic disease in MPSs I, II, and VI. Clinical effects are increased life expectancy, resolution or improvement of growth, hepatosplenomegaly, joint stiffness, facial appearance, pebbly skin changes in MPS-II, obstructive sleep apnea, heart disease, communicating hydrocephalus, and hearing loss. Enzyme activity in serum and urinary GAG excretion normalize. Transplantation does not significantly improve the neuropsychologic outcome of MPS patients with impaired cognition at the time of transplantation. This is true for MPSs IH, II, and III. However, patients with MPS-I who have undergone transplantation before 24 mo of age and with a baseline mental development index greater than 70 have improved long-term outcome. Early transplantation in MPS-II may have the same effect. Transplantation in MPS-VI stabilizes or improves cardiac manifestations, posture and joint mobility. Stem cell transplantation does not correct skeletal and ocular anomalies and they have to be treated with appropriate orthopedic and ophthalmologic procedures. Cord blood

Table 88-3 Therapies Aimed at Proximate Causes of Mucopolysaccharidoses

MPS TYPE	STEM CELL TRANSPLANTATION (SCT)	ENZYME REPLACEMENT	REMARKS
I	Yes	Aldurazyme	Transplantation before age 2 yr. Enzyme replacement before and after transplantation
II	Questionable	Elaprase	Lack of neurologic improvement after stem cell transplantation
III	No	No	Experimental: Substrate reduction by flavanoids
IVA	No	Preclinical	Recombinant GALNS trial in course
VI	Yes	Naglazyme	Sustained improvement
VII	Questionable	?	Single SCT attempt without neurologic improvement

GALNS, galactosamine(*N*-acetyl)-6-sulfate sulfatase.

Table 88-4 Symptomatic Management of Mucopolysaccharidoses

PROBLEM	PREDOMINANTLY IN	MANAGEMENT
NEUROLOGIC		
Hydrocephalus	MPS-I, -II, -VI, -VII	Funduscopy, CT scan
Chronic headaches	All	Ventriculoperitoneal shunting
Behavioral disturbance	MPS-III	Behavioral medication, sometimes CT scan, ventriculoperitoneal shunting
Disturbed sleep/wake circle	MPS-III	Melatonin
Seizures	MPS-I, -II, -III	Electroencephalogram, anticonvulsants
Odontoid hypoplasia	MPS-IV	Cervical MRI, upper cervical fusion
Spinal cord compression	All	Laminectomy, dural excision
OPHTHALMOLOGIC		
Corneal opacity	MPS-I, -VI, -VII	Corneal transplant
Glaucoma	MPS-I, -VI, -VII	Medication, surgery
Retinal degeneration	MPS-I, -II	Night light
EARS, AIRWAYS		
Recurrent otitis media	MPS-I, -II, -VI, -VII	Ventilating tubes
Impaired hearing	All except MPS-IV	Audiometry, hearing aids
Obstruction	All except MPS-III	Adenotomy, tonsillectomy, bronchodilator therapy, continuous positive airway pressure at night, laser excision of tracheal lesions, tracheotomy
CARDIAC		
Cardiac valve disease	MPS-I, -II, -VI, -VII	Endocarditis prevention, valve replacement
Coronary insufficiency	MPS-I, -II, -VI, -VII	Medical therapy
Arrhythmias	MPS-I, -II, -VI, -VII	Antiarrhythmic medication, pacemaker
ORAL, GASTROINTESTINAL		
Hypertrophic gums, poor teeth	MPS-I, -II, -VI, -VII	Dental care
Chronic diarrhea	MPS-II	Diet modification, loperamide
MUSCULOSKELETAL		
Joint stiffness	All except MPS-IV	Physical therapy
Weakness	All	Physical therapy, wheelchair
Gross long bone malalignment	All	Corrective osteotomies
Carpal tunnel syndrome	MPS-I, -II, -VI, -VII	Electromyography, surgical decompression
ANESTHESIA	All except MPS-III	Avoid atlantoaxial dislocation, use angulated video intubation laryngoscope and small endotracheal tubes

transplantation is the therapy of choice in children with MPS-IH, and possibly MPS-II, before the age of 2 yr, but transplantation-related death or primary graft failure, which occur in approximately one-third of the patients, must be weighed against other therapeutic options.

Enzyme replacement using recombinant α-L-iduronidase has been approved for patients with MPS-I. It reduces organomegaly and ameliorates rate of growth, joint mobility, reduces the number of episodes of sleep apnea and urinary GAG excretion. The enzyme does not cross the blood–brain barrier and does not prevent deterioration of cognition and other neurologic functions. Consequently, this therapy is reserved for patients with mild CNS involvement. To stabilize extraneural manifestations, it is also recommended in young patients before stem cell transplantation. Recombinant iduronate-2-sulfatase ameliorates the nonneurologic manifestations of Hunter disease, and recombinant *N*-acetylgalactosamine-4-sulfatase has been successfully tested in patients with MPS-VI.

Primary prevention through genetic counseling and tertiary prevention to avoid or arrest complications remain the mainstay of pediatric care. Multidisciplinary attention to respiratory and cardiovascular complications, hearing loss, carpal tunnel syndrome, spinal cord compression, hydrocephalus and other problems can greatly improve the quality of life for patients and their families (see Table 88-4). The progressive nature of clinical involvement in MPS patients dictates the need for specialized and coordinated evaluation.

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Chapter 89

Disorders of Purine and Pyrimidine Metabolism

James C. Harris

The inherited disorders of purine and pyrimidine metabolism cover a broad spectrum of illnesses with various presentations. These include hyperuricemia, acute renal failure, renal stones, gout, unexplained neurologic deficits (seizures, muscle weakness, choreoathetoid and dystonic movements), developmental disability, intellectual disability, compulsive self-injury and aggression, autistic-like behavior, unexplained anemia, failure to thrive, susceptibility to recurrent infection (immune deficiency), and deafness. When identified, all family members should be screened.

Purines and pyrimidines form the basis of nucleotides and nucleic acids (DNA and RNA) and so are involved in all biologic processes. Metabolically active nucleotides are formed from heterocyclic nitrogen-containing purine bases (guanine and adenine) and pyrimidine bases (cytosine, uridine, and thymine): all cells require a balanced supply of nucleotides for growth and survival. Purines provide the primary source of cellular energy through adenosine triphosphate (ATP) and the basic coenzymes (nicotinamide adenine dinucleotide and its reduced form) for metabolic regulation and play a major role in signal transduction (guanosine triphosphate [GTP], cyclic adenosine monophosphate, cyclic guanosine monophosphate). Figure 89-1 shows the early steps in the biosynthesis of the purine ring. Purines are primarily produced from endogenous sources, and in the usual circumstances dietary purines have a small role. The end product of purine metabolism in humans is uric acid (2,6,8-trioxypurine).

Uric acid is not a specific disease marker so the cause of its elevation must be determined. The serum level of uric acid present at any time depends on the size of the purine nucleotide pool which is derived from de novo purine synthesis, catabolism of tissue nucleic acids, and increased turnover of preformed purines. Uric acid is poorly soluble and must be excreted continuously to avoid toxic accumulation in the body. Its renal excretion involves the following components: (1) glomerular filtration, (2) reabsorption in the proximal convoluted tubule, (3) secretion near the terminus of the proximal tubule, and (4) limited reabsorption near these secretory sites. Thus, renal loss of uric acid is a result of renal tube excretion and is a function of serum uric acid concentration and non-specific transporters that remove uric acid. Because renal tubule excretion is greater in children than in adults, serum uric acid levels are a less reliable indicator of uric acid production in children than in adults, and, consequently, measurement of the level in urine may be required to determine excessive production. Clearance of a smaller portion of uric acid is via the gastrointestinal tract (biliary and intestinal secretion). Owing to poor solubility of uric acid under normal circumstances, uric acid is near the maximal tolerable limits, and small alterations in production or solubility or changes in secretion may lead to hyperuricemia and can result in precipitation in extremities such as fingers or toes, which defines clinical gout. In renal insufficiency, urate excretion is increased by residual nephrons and by the gastrointestinal tract. Increased production of uric acid is found in malignancy, Reye syndrome, Down syndrome, psoriasis, sickle cell anemia, cyanotic congenital heart disease, pancreatic enzyme replacement, glycogen storage disease types I, III, IV, and V, hereditary fructose intolerance, and acyl-coenzyme A dehydrogenase deficiency.

The metabolism of both purines and pyrimidines can be divided into biosynthetic, salvage and catabolic pathways. The first, the de novo pathway, involves a multistep biosynthesis of phosphorylated ring structures from precursors such as CO_2, glycine, and glutamine. Purine and pyrimidine nucleotides are produced from ribose-5-phosphate or carbamyl phosphate, respectively. The second, a single-step salvage pathway, recovers purine bases and pyrimidine nucleosides derived from either dietary intake or the catabolic pathway (Figs. 89-2 and 89-3). In the de novo pathway, the nucleosides guanosine, adenosine, cytidine, uridine, and thymidine are formed by the addition of ribose-1-phosphate to the purine bases guanine or adenine, and to the pyrimidine bases cytosine, uracil, and thymine respectively. The phosphorylation of these nucleosides produces monophosphate, diphosphate, and triphosphate nucleotides, as well as the deoxy-nucleotides that are utilized for DNA formation. Under usual circumstances, the salvage pathway predominates over the biosynthetic pathway, as nucleotide salvage saves energy for cells. Only a small fraction of the nucleotides turned over by the body each day are degraded and excreted. Synthesis of nucleotides is most active in tissues with high rates of cellular turnover, such as gut epithelium, skin, and bone marrow. The third pathway is catabolism. The end product of the catabolic pathway of the purines in humans is uric acid, whereas catabolism of pyrimidines produces citric acid cycle intermediates.

Inborn errors in the **synthesis** of **purine nucleotides** comprise the phosphoribosylpyrophosphate synthetase spectrum of disorders, including deficiency and superactivity, adenylosuccinate lyase deficiency, and 5-amino-4-imizolecarboxamide (AICA) riboside deficiency (AICA-ribosiduria). Disorders resulting from abnormalities in purine **catabolism** comprise muscle adenosine monophosphate (AMP) deaminase deficiency, adenosine deaminase deficiency, purine nucleoside phosphorylase deficiency, and xanthine oxidoreductase deficiency. Disorders resulting from the purine **salvage** pathway comprise hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency, and adenine phosphoribosyltransferase (APRT) deficiency.

The sole inborn error of **pyrimidine synthesis** is hereditary orotic aciduria (uridine monophosphate synthase deficiency). Disorders resulting from abnormalities in pyrimidine catabolism comprise dihydropyrimidine dehydrogenase (DPD) deficiency, dihydropyrimidinase (DPH) deficiency, and β-ureidopropionase deficiency, pyrimidine 5′-nucleotidase deficiency, and mitochondrial thymidine phosphorylase deficiency. A disorder resulting from the **pyrimidine salvage** is thymidine kinase 2 deficiency.

GOUT

Gout presents with hyperuricemia, uric acid nephrolithiasis, and acute inflammatory arthritis. Gouty arthritis is caused by monosodium urate crystal deposits that result in inflammation in joints and surrounding tissues. The presentation is most commonly monoarticular, typically in the metatarsophalangeal joint of the big toe. Tophi, deposits of monosodium urate crystals, may occur over points of insertion of tendons at the elbows, knees, and feet or over the helix of the ears. Primary gout ordinarily occurs in middle-aged men, results mainly from decreased renal excretion of uric acid, or purine overconsumption, or high intake of alcohol or fructose, or a combination of these factors. Gout occurs in any condition that leads to reduced clearance of uric acid: during therapy for malignancy or with dehydration, lactic acidosis, ketoacidosis, starvation, diuretic therapy, and renal failure. Excessive purine, alcohol, or fructose ingestion may increase uric acid levels. The biochemical etiology of gout is unknown for most of those affected, and it is considered to be a polygenic trait. Purine overproduction is a rare cause of primary gout, and is associated with several genetic disorders discussed below. Secondary gout is either the result of another disorder in which there is rapid tissue breakdown or cellular turnover leading to increased production or decreased excretion of uric acid, or the result of some types of drug treatment, for example diuretics cause plasma volume reduction and can precipitate a gouty attack.

Gout resulting from endogenous purine overproduction is associated with hereditary disorders of 3 different enzymes that result in

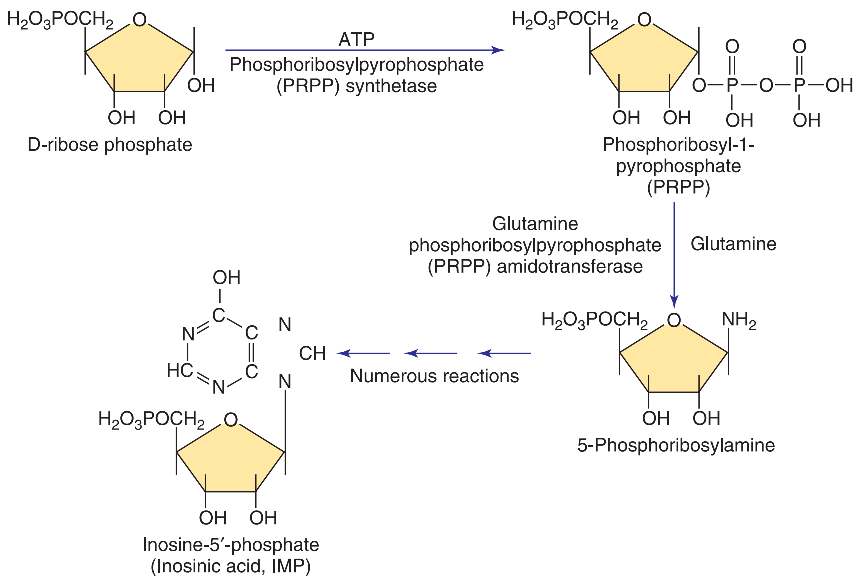

Figure 89-1 Early steps in the biosynthesis of the purine ring.

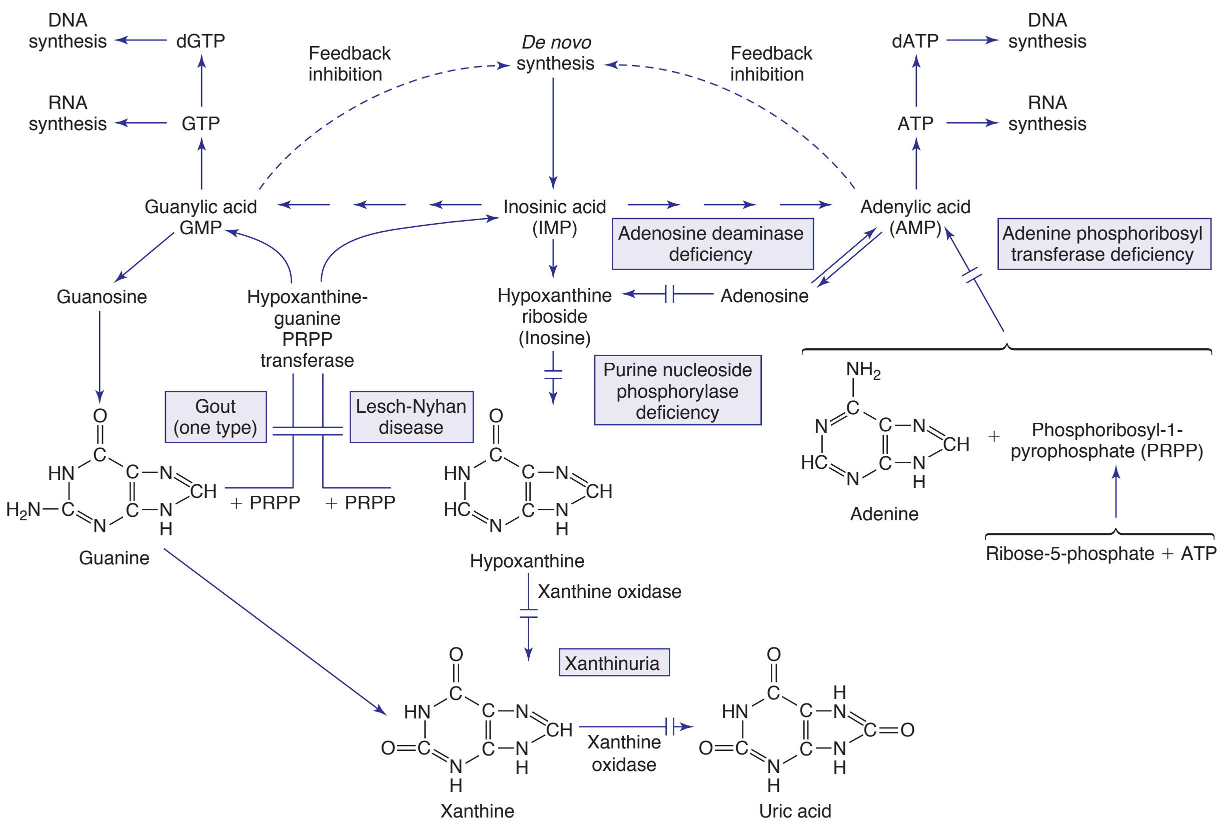

Figure 89-2 Pathways in purine metabolism and salvage.

hyperuricemia. These comprise the HPRT deficiency spectrum (ranging from severe deficiency or Lesch-Nyhan syndrome to partial HPRT deficiency), 2 forms of superactivity of PP-ribose-P synthetase, and glycogen storage disease type I (glucose-6-phosphatase deficiency; see Chapter 87.1). In the first two, the basis of hyperuricemia is purine nucleotide and uric acid overproduction, whereas in the third it is both excessive uric acid production and diminished renal excretion of urate. Glycogen storage disease types III, V, and VII are associated with exercise-induced hyperuricemia, the consequence of rapid ATP utilization and failure to regenerate it effectively during exercise (see Chapter 87.1).

Juvenile gout resulting from purine underexcretion is polygenic, consisting of the familial juvenile hyperuricemic nephropathy group of disorders. This includes medullary cystic kidney disease type 2, mapped to chromosome 16p11.2, which has been shown to result from uromodulin mutations; the term *uromodulin-associated kidney disease* has been proposed for them. Other genes classified as forms of familial juvenile hyperuricemic nephropathy include those for renin and hepatic nuclear factor-1β. Unlike the 3 inherited purine disorders that are X-linked and the recessively inherited glycogen storage disease, these are autosomal dominant conditions. Familial juvenile hyperuricemic nephropathy is associated with severe renal hypoexcretion of

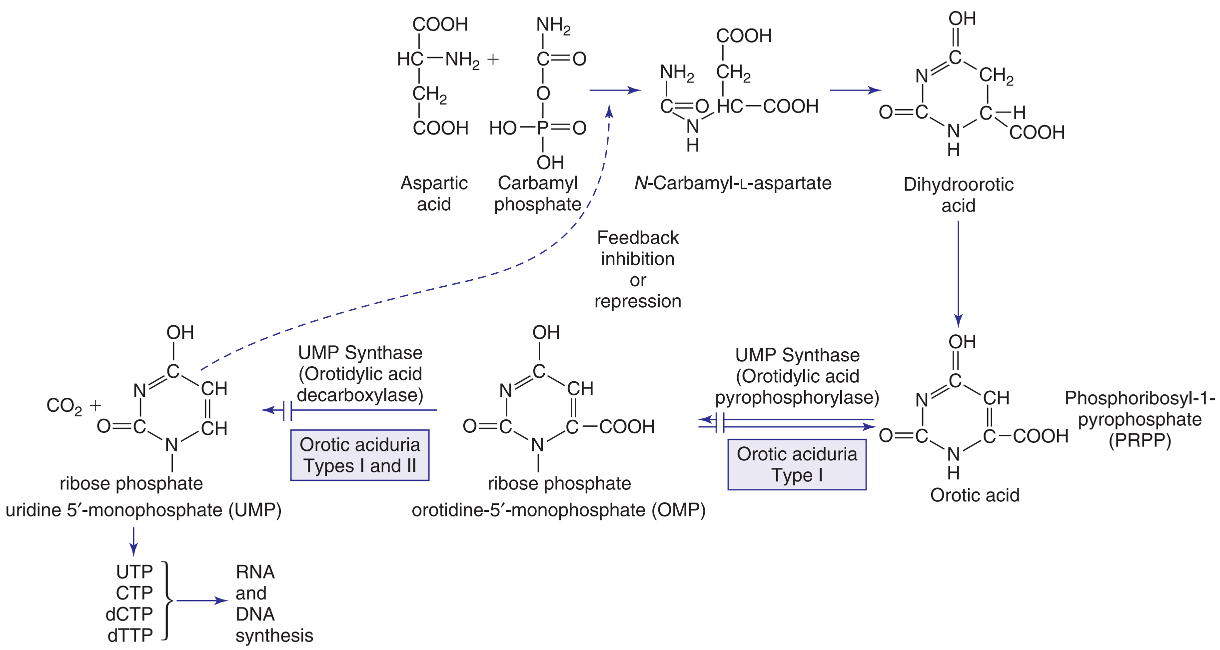

Figure 89-3 Pathways in pyrimidine biosynthesis.

uric acid. Although it most commonly presents from puberty up to the 3rd decade, it has been reported in infancy. It is characterized by early onset, hyperuricemia, gout, familial renal disease, and low urate clearance relative to glomerular filtration rate. It occurs in both males and females and is frequently associated with a rapid decline in renal function that may lead to death unless diagnosed and treated early. Once familial juvenile hyperuricemic nephropathy is recognized, presymptomatic detection is of critical importance to identify asymptomatic family members with hyperuricemia and to begin treatment, when indicated, to prevent nephropathy.

Genetics

Familial juvenile hyperuricemic nephropathy-2 (HNFJ2; 613092) is caused by mutation in the renin gene (*REN*; 179820) on chromosome 1q32. HNFJ3 (614227) has been mapped to chromosome 2p22.1-p21.

Treatment

Treatment of hyperuricemia involves the combination of allopurinol or febuxostat (xanthine oxidase inhibitors) to decrease uric acid production, probenecid to increase uric acid clearance in those with normal renal function, and increased fluid intake to reduce the concentration of uric acid. A low purine diet, weight reduction, and reduced alcohol and reduced fructose intake (as fructose both reduces urate clearance and accelerates ATP breakdown to uric acid) are recommended.

ABNORMALITIES IN PURINE SALVAGE

HPRT Deficiency

Lesch-Nyhan disease (LND) is a rare X-linked disorder of purine metabolism that results from HPRT deficiency. This enzyme is normally present in each cell in the body, but its highest concentration is in the brain, especially in the basal ganglia. Clinical manifestations include hyperuricemia, intellectual disability, dystonic movement disorder that may be accompanied by choreoathetosis and spasticity, dysarthric speech, and compulsive self-biting, usually beginning with the eruption of teeth.

There is a severity spectrum for the clinical presentations of HPRT deficiency. HPRT levels are related to the extent of motor symptoms, to the presence or absence of self-injury, and possibly to the level of cognitive function. Purine overproduction is present. The majority of individuals with classic LND have low or undetectable levels of the HPRT enzyme. Partial deficiency in HPRT **(Kelley-Seegmiller syndrome)** with more than 1.5-2.0% enzyme is associated with purine overproduction and variable neurologic dysfunction (neurologic HPRT deficiency). HPRT deficiency with activity levels >8% of normal still exhibit purine (and uric acid) overproduction but apparently normal cerebral functioning (HPRT-related hyperuricemia) although cognitive deficits may occur. Qualitatively similar cognitive deficit profiles have been reported in both LND and variant cases. Variants produced scores that are intermediate between those of patients with LND and normal controls on nearly every neuropsychological measure tested.

Genetics

The HPRT gene has been localized to the long arm of the X chromosome (q26-q27). The complete amino acid sequence for HPRT is known (approximately 44 kb; 9 exons). The disorder appears in males; occurrence in females is extremely rare and ascribed to nonrandom inactivation of the normal X chromosome. Absence of HPRT activity prevents the normal metabolism of hypoxanthine resulting in excessive uric acid production and manifestations of gout, necessitating specific drug treatment (allopurinol). Because of the enzyme deficiency, hypoxanthine accumulates in the cerebrospinal fluid, but uric acid does not; uric acid is not produced in the brain and does not cross the blood–brain barrier. The behavior disorder is not caused by hyperuricemia or excess hypoxanthine because patients with partial HPRT deficiency, the variants with hyperuricemia, do not self-injure and infants having isolated hyperuricemia from birth do not develop self-injurious behavior.

The prevalence of the classic LND has been estimated at 1 in 100,000 to 1 in 380,000 persons based on the number of known cases in the United States. The incidence of partial variants is not known. Those with the classic syndrome rarely survive the 3rd decade because of renal or respiratory compromise. The life span may be normal for patients with partial HPRT deficiency without severe renal involvement.

Pathology

No specific brain abnormality is documented after detailed histopathology and electron microscopy of affected brain regions. Magnetic resonance imaging has documented reductions in the volume of basal ganglia nuclei. Abnormalities in neurotransmitter metabolism have been identified in 3 autopsied cases. All 3 patients had very low HPRT levels (less than 1% in striatal tissue and 1-2% of control in thalamus cortex). There was a functional loss of 65-90% of the nigrostriatal and

mesolimbic dopamine terminals, although the cells of origin in the substantia nigra did not show dopamine reduction. The brain regions primarily involved were the caudate nucleus, putamen, and nucleus accumbens. It is proposed that the neurochemical changes may be linked to functional abnormalities, possibly resulting from a diminution of arborization or branching of dendrites rather than cell loss. A neurotransmitter abnormality is demonstrated by changes in cerebrospinal fluid neurotransmitters and their metabolites, and confirmed by positron emission tomography scans of dopamine function. Reductions in vivo in the presynaptic dopamine transporter have been documented in the caudate and putamen of 6 individuals.

The mechanism whereby HPRT leads to the neurologic and behavioral symptoms is unknown. However, both hypoxanthine and guanine metabolism are affected and GTP and adenosine have substantial effects on neural tissues. The functional link between purine nucleotides and the dopamine system is through salvage of guanine by HPRT to form GTP: this is essential for GTP cyclohydrolase activity, the first step in the synthesis of pterins and dopamine. Patients with inherited GTP cyclohydrolase deficiency show clinical features in common with LND. Dopamine reduction in brain is documented in HPRT-deficient strains of mutant mice. Dopamine binding to its receptor results in either an activation (D1 receptor) or an inhibition (D2 receptor) of adenylcyclase. Both receptor effects are mediated by G proteins (GTP-binding proteins) dependent on guanine diphosphate in the guanine diphosphate/GTP exchange for cellular activation. Dopamine and adenosine systems are also linked through the role of adenosine as a neuroprotective agent in preventing neurotoxicity. Adenosine derives from AMP which depends on hypoxanthine salvage in the brain by HPRT. Adenosine agonists mimic the biochemical and behavioral actions of dopamine antagonists, whereas adenosine receptor antagonists act as functional dopamine agonists. LND can thus be seen as arising ultimately from nucleotide depletion specifically in the brain, which relies upon the HPRT salvage pathway, leading to dopamine and adenosine depletions.

Clinical Manifestations

At birth, infants with LND have no apparent neurologic dysfunction. After several months, developmental delay, intellectual disability and neurologic signs become apparent. Before the age of 4 mo, hypotonia, recurrent vomiting, and difficulty with secretions may be noted. By approximately 8-12 mo, extrapyramidal signs appear, primarily dystonic movements. In some cases, spasticity may become apparent at this time; in some instances, it becomes apparent later in life.

Cognitive function is usually reported to be in the mild-to-moderate range of intellectual disability, although some individuals test in the low normal range. Because test scores may be influenced by difficulty in testing the subjects owing to their movement disorder and dysarthric speech, overall intelligence may be underestimated.

The age of onset of self-injury may be as early as 1 yr and occasionally as late as the teens. Self-injury occurs, although all sensory modalities, including pain, are intact. The self-injurious behavior usually begins with self-biting, although other patterns of self-injurious behavior emerge with time. Most characteristically, the fingers, mouth, and buccal mucosa are mutilated. Self-biting is intense and causes tissue damage and may result in the amputation of fingers and substantial loss of tissue around the lips. Extraction of primary teeth may be required. The biting pattern can be asymmetric, with preferential mutilation of the left or right side of the body. The type of behavior is different from that seen in other intellectual disability syndromes involving self-injury. Self-hitting and head-banging are the most common initial presentations in other syndromes. The intensity of the self-injurious behavior generally requires that the patient be restrained. When restraints are removed, the patient with LND may appear terrified, and stereotypically place a finger in the mouth. The patient may ask for restraints to prevent elbow movement; when the restraints are placed or replaced, he may appear relaxed and more good humored. Dysarthric speech may cause interpersonal communication problems; however, the higher-functioning children can express themselves fully and participate in verbal therapy.

The self-mutilation presents as a compulsive behavior that the child tries to control but frequently is unable to resist. Older individuals may enlist the help of others and notify them when they are comfortable enough to have restraints removed. In some instances, the behavior may lead to deliberate self-harm. The LND individual may also show compulsive aggression and inflict injury to others through pinching, grabbing, or hitting or by using verbal forms of aggression. Afterward he may apologize, stating that this behavior was out of his control. Other maladaptive behaviors include head- or limb-banging, eye-poking, and psychogenic vomiting.

Diagnosis

The presence of dystonia along with self-mutilation of the mouth and fingers suggests LND. With partial HPRT deficiency, recognition is linked to either hyperuricemia alone or hyperuricemia and a dystonic movement disorder. Serum levels of uric acid that exceed 4-5 mg uric acid/dL and a urine uric acid : creatinine ratio of ≥3-4 : 1 are highly suggestive of HPRT deficiency, particularly when associated with neurologic symptoms. The definitive diagnosis requires an analysis of the HPRT enzyme. This is assayed in an erythrocyte lysate. Individuals with classic LND have near 0% enzyme activity and those with partial variants show values between 1.5% and 60%. The intact cell HPRT assay in skin fibroblasts offers a good correlation between enzyme activity and the severity of the disease. Molecular techniques are used for gene sequencing and the identification of carriers.

Differential diagnosis includes other causes of infantile hypotonia and dystonia. Children with LND are often initially incorrectly diagnosed as having athetoid cerebral palsy. When a diagnosis of cerebral palsy is suspected in an infant with a normal prenatal, perinatal, and postnatal course, then LND should be considered. Partial HPRT deficiency may be associated with acute renal failure in infancy; therefore, clinical awareness of partial HPRT deficiency is of particular importance. The simplest test to exclude LND or partial deficiency is the urinary uric acid : creatinine ratio.

An understanding of the molecular disorder has led to effective drug treatment for uric acid accumulation and arthritic tophi, renal stones, and neuropathy. However, reduction in uric acid alone does not influence the neurologic and behavioral aspects of LND. Despite treatment from birth for uric acid elevation, behavioral and neurologic symptoms are unaffected. The most significant complications of LND are renal failure and self-mutilation.

Treatment

Medical management of this disorder focuses on the prevention of renal failure by pharmacologic treatment of hyperuricemia with high fluid intake along with alkalinization and allopurinol (or more febuxostat). A low purine diet and reduced fructose intake are desirable.

Allopurinol treatment must be monitored because urinary oxypurine excretion with all overproduction disorders is sensitive to allopurinol, resulting in an increased urine concentration of xanthine, which is extremely insoluble. Self-mutilation is reduced through behavior management, and the use of restraints or removal of teeth or both. Pharmacologic approaches to decrease anxiety and spasticity with medication have mixed results. Drug therapy focuses on symptomatic management of anticipatory anxiety, mood stabilization and reduction of self-injurious behavior. Although there is no standard drug treatment, diazepam may be helpful for anxiety symptoms, Risperdal for aggressive behavior and carbamazepine or gabapentin for mood stabilization. Each of these medications may reduce self-injurious behavior by helping to reduce anxiety and stabilize mood. *S*-adenosylmethionine (SAMe), which is thought to act by countering nucleotide depletion in the brain, has been reported to specifically reduce the rate of self-injury in some cases.

Bone marrow transplantation, based on the hypothesis that the central nervous system damage is produced by a circulating toxin, has been carried out in several patients. Several infant patients have died of complications of bone marrow transplantation. To date, there is no evidence that bone marrow transplantation is a beneficial treatment

approach; it remains an experimental and potentially dangerous therapy. Two patients received partial exchange transfusions every 2 mo for 3-4 yr. Erythrocyte HPRT activity was 10-70% of normal during this period, but no reduction of neurologic or behavioral symptoms was apparent. Successful preimplantation genetic diagnosis and in vitro fertilization for LND has been reported with the birth of an unaffected male infant.

Both the motivation for self-injury and its biologic basis must be addressed in treatment programs. Yet behavioral techniques alone, using operant conditioning approaches, have not proved to be an adequate general treatment. Although behavioral procedures have had some selective success in reducing self-injury, generalization outside the experimental setting limits this approach and patients under stress may revert to their previous self-injurious behavior. Behavioral approaches may also focus on reducing the self-injurious behavior through the treatment of phobic anxiety associated with being unrestrained. The most common techniques are systematic desensitization, extinction, and differential reinforcement of other (competing) behavior. Stress management has been recommended to assist patients to develop more effective coping mechanisms. Individuals with LND do not respond to contingent electric shock or similar aversive behavioral measures. An increase in self-injury may be observed when aversive methods are utilized.

Restraint (day and night) and dental procedures are common means to prevent self-injury. The time in restraints is linked to the age of onset of self-injury. Children with LND can participate in making decisions regarding restraints and the type of restraints. The time in restraints may potentially be reduced with systematic behavior treatment programs. Many patients have teeth extracted to prevent self-injury. Others use a protective mouth guard designed by a dentist. Most parents suggest that stress reduction and awareness of the patient's needs are the most effective in reducing self-injury. Positive behavioral techniques of reinforcing appropriate behavior are rated effective by almost half of the families.

Deep brain stimulation to the anteroventral internal globus pallidus is a procedure that has successfully treated self-injury and lessened dystonia in several case reports.

Adenine Phosphoribosyltransferase Deficiency (Dihydroxyadeninuria)

Adenine phosphoribosyltransferase (APRT), a purine salvage enzyme, catalyzes the synthesis of AMP from adenine and 5-phosphoribosyl-1-pyrophosphate (PP-ribose-P). The absence of this enzyme results in the cellular accumulation of adenine and its being oxidized as an alternative substrate by xanthine dehydrogenase to form 2,8-dihydroxyadenine, which is extremely insoluble. APRT deficiency is present from birth, becoming apparent as early as 5 mo and as late as the 7th decade.

Genetics

The disorder is an autosomal recessive trait with considerable clinical heterogeneity. The APRT gene is located on chromosome 16q (16q24.3) and encompasses 2.8 kb of genomic DNA.

Clinical Manifestations

Clinical manifestations include urinary calculus formation with crystalluria, urinary tract infections, hematuria, renal colic, dysuria and acute renal failure. The presence of brownish spots on the infant's diaper or of yellow-brown crystals in the urine is suggestive of the diagnosis. The 2,8-dihydroxyadenine is cleared efficiently by the kidneys and so does not accumulate in plasma, but precipitates readily in the renal lumen.

Laboratory

Urinary levels of adenine, 8-hydroxyadenine, and 2,8-dihydroxyadenine are elevated while plasma uric acid is normal. The deficiency may be complete (type I) or partial (type II); the partial deficiency is reported in Japan. The diagnosis is made based on the level of residual enzyme in erythrocyte lysates. The renal calculi, composed of 2,8-dihydroxyadenine, are radiolucent, soft, and easily crushed. These stones are not distinguishable from uric acid stones by routine tests but require high-performance liquid chromatography, UV, infrared, mass spectrometry, x-ray crystallography, or capillary electrophoresis for diagnosis, particularly to distinguish from stones in HPRT deficiency.

Treatment

Treatment includes high fluid intake, dietary purine restriction, and allopurinol, which inhibits the conversion of adenine to its metabolites, further 2,8-dihydroxyadenine excretion, and further stone formation. Alkalinization of the urine is to be avoided, because, unlike that of uric acid, the solubility of 2,8-dihydroxyadenine does not increase up to pH 9. Shockwave lithotripsy has been reported to be successful. The prognosis depends on renal function at the time of diagnosis. Early treatment is critical in the prevention of stones because severe renal insufficiency may accompany late recognition.

DISORDERS LINKED TO PURINE NUCLEOTIDE SYNTHESIS

Phosphoribosylpyrophosphate Synthetase Superactivity and Deficiency

Phosphoribosylpyrophosphate (PRPP) is a substrate involved in the synthesis of essentially all nucleotides and important in the regulation of the de novo pathways of purine and pyrimidine nucleotide synthesis. The synthetase enzyme (PRPS) produces PRPP from ribose-5-phosphate and ATP, as shown in Figures 89-1 and 89-2. PRPP is the first intermediary compound in the de novo synthesis of purine nucleotides that lead to the formation of inosine monophosphate, then to ATP and GTP.

Genetic disorders of this enzyme affect only the PRPS-1 isoform; PRPS-2 mutations have not been described. PRPS-1 disorders are all X-linked and are divided into "superactivity," which occurs as 2 phenotypes (infantile or early-childhood onset, and a milder form with late-juvenile or early-adult onset), and "deficiency," which is a spectrum disorder that is distinguished clinically according to severity as 3 disorders: Arts syndrome, Charcot-Marie-Tooth disease X-linked-5, and X-linked deafness-2 (DFN2).

Superactivity of the enzyme results in an increased generation of PRPP in dividing cells. Because PRPP aminotransferase, the first enzyme of the purine de novo pathway, is not physiologically saturated by PRPP, the synthesis of purine nucleotides increases, and, consequently, the production of uric acid is increased. PRPP synthetase superactivity is one of the few hereditary disorders in which there is enhancement of the activity of an enzyme. The infantile or early-childhood form of PRPS-1 superactivity has severe neurologic attributes accompanied by uric acid overproduction, whereas individuals with the late-juvenile or early-adult presentation are neurologically normal but still have uric acid overproduction.

Deficiency of PRPS-1 produces depleted purine nucleotide synthesis in tissues dependent upon PRPS-1, which includes brain as well as other neural tissues and lung.

Genetics

Three distinct complementary DNAs for PRPS have been cloned and sequenced. Two forms, PRPS-1 and PRPS-2, are X-linked to Xq22-q24 and Xp22.2-p.22.3 (escapes X inactivation), respectively, and are widely expressed; the third locus maps to human chromosome 7 and appears to be transcribed only in the testes. PRPS-1 defects are thus inherited as X-linked traits and present with varying degrees of severity. The late-onset form of superactivity arises from increased transcription of normal messenger RNA; the cause of this has not been discovered. The early-onset form of superactivity arises from mutations affecting allosteric regulation of the protein that controls feedback inhibition by inorganic phosphate and dinucleotides. At the same time, these mutations destabilize the protein, so that in slow or nonreplicating cells, such as neurons and red blood cells, the enzyme becomes inactive. In contrast, the deficiency phenotypes of PRPS-1 are produced by mutations directly affecting enzyme function, usually in the substrate

binding site. Even though the defect is X-linked it should be considered in a child or young adult of either sex with hyperuricemia and/or hyperuricosuria and normal HPRT activity in lysed red cells.

Clinical Manifestations

Clinical manifestations in affected hemizygous males with the early-onset form of superactivity include signs of uric acid overproduction that are apparent in infancy or early childhood and neurodevelopmental retardation and sensorineural deafness. Hypotonia, delays in motor milestones, ataxia, and autistic-like behavior have been described. Heterozygous female carriers may also develop gout and hearing impairment. The late-onset type is found in males who show only hyperuricemia and hyperuricosuria, but no neurologic signs. The mildest form of PRPS-1 deficiency manifests as progressive post-lingual hearing loss in X-linked deafness-2. More severe mutations constitute the Charcot-Marie-Tooth disease X-linked-5 phenotype, which includes peripheral neuronopathy, hearing impairment, and optic atrophy. The most severe PRPS-1 mutations occur in patients with Arts syndrome who also have central neuropathy and an impaired immune system. Females appear to be unaffected, but hemizygous males have usually not survived beyond the 1st decade, typically succumbing to lung disease. Therapy with *S*-adenosylmethionine has prolonged survival, although the neurologic deficits, including the deafness, do not appear to be responsive.

A mechanism for the neurologic symptoms is unknown but it can be hypothesized that nucleotide depletion is present in neural tissues including the brain. Abnormalities of hearing and vision are typical of PRPS-1 deficiency, where the absence of this enzyme presumably compromises these highly energy-dependent neural functions. The high transcript level of PRPS-1 in lung and bone marrow also suggests that its absence may be causal for the recurrent lung infections that characterize Arts syndrome.

Laboratory

For PRPS-1 "superactivity" (both juvenile and adult presentations), serum uric acid may be grossly raised and the urinary excretion of uric acid increased. For PRPS "deficiency," uric acid is normal, not low, probably because PRPS-2 provides the major uric acid forming activity in liver and other major organs. Diagnosis requires that PRPS-1 activity be measured in erythrocytes and cultured fibroblasts. The adult superactivity disorder must be differentiated from partial HPRT deficiency involving the salvage pathway, which also presents with mild or absent neurologic traits accompanied by hyperuricemia.

Treatment

Treatment of PRPS deficiency, specifically Arts syndrome, has involved mainly experimental therapy with *S*-adenosylmethionine, as a dietary supplement to correct the depletion of purines. Dietary purines are usually not absorbed into the body but are degraded to uric acid by the gut. *S*-adenosylmethionine supplementation (beginning at 20 mg/kg/day orally) has been effective in greatly reducing the acute hospitalization episodes of 2 brothers with Arts syndrome, over a period of 10 yr. Treatment of PRPS superactivity is aimed at controlling the hyperuricemia with allopurinol, which inhibits xanthine oxidase, the last enzyme of the purine catabolic pathway. Uric acid production is reduced and is replaced by hypoxanthine, which is more soluble, and xanthine. The initial dose of allopurinol is 10-20 mg/kg/24 hr in children and is adjusted to maintain normal uric acid levels in plasma. The risk of xanthine stone formation is similar to that described for LND. A low purine diet (one free of organ meats, dried beans, and sardines), high fluid intake, and alkalinization of the urine to establish a urinary pH of 6.0-6.5 is necessary. These measures control the hyperuricemia and urate nephropathy but do not affect the neurologic symptoms. There is no known treatment for the neurologic complications.

Adenylosuccinate Lyase Deficiency (Succinylpurinuria)

Adenylosuccinase lyase deficiency is an inherited deficiency of de novo purine synthesis in humans. adenylosuccinase lyase is an enzyme that catalyzes 2 pathways in de novo synthesis and purine nucleotide recycling. These are the conversion of succinylaminoimidazole carboxamide ribotide into aminoimidazole carboxamide ribotide (AICAR) in the de novo synthesis of purine nucleotides and the conversion of adenylosuccinate (S-AMP) into AMP, the second step in the conversion of inosine monophosphate (IMP) into AMP, in the purine nucleotide cycle. Adenylosuccinase lyase deficiency results in the accumulation in urine, cerebrospinal fluid, and to a smaller extent, in plasma, of succinylaminoimidazole carboxamide riboside and succinyladenosine (S-Ado), the dephosphorylated derivatives of succinylaminoimidazole carboxamide ribotide and S-AMP, respectively.

Genetics

This is an autosomal recessive disorder; the gene has been mapped to chromosome 22q13.1-q13.2 and approximately 20 gene mutations have been identified. Laboratory investigations show grossly raised succinylpurines in urine and cerebrospinal fluid, which are normally undetectable.

Clinical Manifestations

Clinical manifestations include varying degrees of psychomotor retardation, generally accompanied by a seizure disorder and/or autistic-like behaviors (poor eye contact and repetitive behaviors). Neonatal seizures and a severe infantile epileptic encephalopathy are often the first manifestations of this disorder. Others demonstrate moderate to severe intellectual disability sometimes associated with growth retardation and muscle hypotonia. One reported case, a girl, tested in the mild range of intellectual disability. The form with profound intellectual disability has been designated type I; the variant case with mild intellectual disability as type II. Other patients have an intermediate clinical symptom pattern with moderately delayed psychomotor development, seizures, stereotypies, and agitation.

Pathology

CT and MRI of the brain may show hypotrophy or hypoplasia of the cerebellum, particularly the vermis. It is proposed that rather than being caused by purine nucleotide depletion, the symptoms are from the neurotoxic effects of accumulating succinylpurines. The ratio of S-Ado : succinylaminoimidazole carboxamide riboside has been linked to phenotype severity, suggesting that succinylaminoimidazole carboxamide riboside is the more toxic compound and that S-Ado might be neuroprotective.

The laboratory diagnosis is based on the presence in urine and cerebrospinal fluid of succinylaminoimidazole carboxamide riboside and S-Ado, both normally undetectable.

Treatment

No successful treatment has been demonstrated for this disorder. *S*-adenosylmethionine supplementation therapy was tested for 6 mo for a baby diagnosed in the early postnatal period, but no amelioration of symptoms were noted, providing further evidence that the disorder arises from nucleotide toxicity rather than depletion. Prenatal diagnosis has been reported. Systematic screening is suggested in infants and children with unexplained psychomotor retardation, and/or seizures disorder.

Aminoimidazole Carboxamide Ribotide Transformylase/Inosine Monophosphate Cyclohydrolase Deficiency

AICA riboside is the dephosphorylated product of AICAR, also termed ZMP. Along with its di- and triphosphates, ZMP accumulates in red blood cells and fibrocytes in inherited deficiency of the bifunctional enzyme AICAR transformylase/IMP cyclohydrolase (ATIC), which catalyzes the conversion of AICAR to formyl-AICAR.

Genetics

This is an inborn error of purine biosynthesis caused by a mutation of the *ATIC* gene effecting AICAR transformylase activity. In a single

reported case AICAR transformylase was profoundly deficient, whereas the IMP cyclohydrolase level was 40% of normal.

Clinical Features

The disorder is described in a female infant with profound intellectual disability, epilepsy, dysmorphic features (prominent forehead and metopic suture, brachycephaly, wide mouth with thin upper lip, low-set ears, and prominent clitoris because of fused labia minora), and congenital blindness.

Laboratory

Urinary screening with the Bratton-Marshall test to detect AICA resulted in the identification of this disorder. The transformylase was found to be deficient in fibroblasts in this disorder, confirming diagnosis.

Treatment

No successful treatment is described.

DISORDERS RESULTING FROM ABNORMALITIES IN PURINE CATABOLISM

Myoadenylate Deaminase Deficiency (Muscle Adenosine Monophosphate Deaminase Deficiency)

Myoadenylate deaminase is a muscle-specific isoenzyme of AMP deaminase that is active in skeletal muscle. During exercise, the deamination of AMP leads to increased levels of IMP and ammonia in proportion to the work performed by the muscle. Two forms of myoadenylate deaminase deficiency are known: an inherited (primary) form that may be asymptomatic or associated with cramps or myalgia with exercise, and a secondary form that may be associated with other neuromuscular or rheumatologic disorders.

Clinical Manifestations

Clinical manifestations are most commonly isolated muscle weakness, fatigue, myalgias following moderate-to-vigorous exercise, or cramps. Myalgia may be associated with an increased serum creatine kinase level and detectable electromyelographic abnormalities. Muscle wasting or histologic changes on biopsy are absent. The age of onset may be as early 8 mo of life with approximately 25% of cases recognized between 2 and 12 yr of age. The enzyme defect has been identified in asymptomatic family members. Secondary forms of muscle AMP deaminase deficiency have been identified in Werdnig-Hoffmann disease, Kugelberg-Welander syndrome, polyneuropathies, and amyotrophic lateral sclerosis (see Chapter 612.2). The metabolic disorder involves the purine nucleotide cycle. As shown in Figure 89-2, the enzymes involved in this cycle are AMP deaminase, S-AMP synthetase, and S-AMP lyase. It is proposed that muscle dysfunction in AMP deaminase deficiency results from impaired energy production during muscle contraction. It is unclear how individuals may carry the deficit and be asymptomatic. In addition to muscle dysfunction, a mutation of liver AMP deaminase has been proposed as a cause of primary gout, leading to overproduction of uric acid.

Genetics

The inherited form of the disorder is an autosomal recessive trait. *AMP-D1,* the gene responsible for encoding muscle AMP deaminase, is located on the short arm of chromosome 1 (1p13-21). Population studies reveal that a mutant allele is found at high frequency in white populations, but alternative splicing of the gene can result in removal of the mutation and normal enzyme function. As a result, the disorder is usually screened by performing the forearm ischemic exercise test. The elevation of venous plasma ammonia following exercise that is seen in normal subjects is absent in AMP deaminase deficiency.

Laboratory

The final diagnosis is made by histochemical or biochemical assays of a muscle biopsy. The primary form is distinguished by the finding of enzyme levels below 2% with little or no immunoprecipitable enzyme. Affected individuals are advised to exercise with caution to prevent rhabdomyolysis and myoglobinuria.

Treatment

Although there are no documented fully effective treatments, it has been proposed that enhancing the rate of replenishment of the ATP pool might be beneficial. Using this rationale treatment with ribose (2-60 g/24 hr orally, in divided doses) or xylitol, that is converted to ribose, has been reported to improve endurance and muscle strength in some cases but is ineffective in others. Genetic approaches may be feasible in the future for inherited cases while treatment of the underlying condition is essential in secondary cases.

Adenosine Deaminase Deficiency

See Chapter 126.1.

Purine Nucleoside Phosphorylase Deficiency

See Chapter 126.2.

Xanthine Oxidoreductase Deficiency (Hereditary Xanthinuria/Molybdenum Cofactor Deficiency)

Xanthine oxidoreductase (XOR) is the catalytic enzyme in the final step of the purine catabolic pathway and oxidizes hypoxanthine to xanthine and xanthine to uric acid. Because XOR exists in 2 forms, xanthine dehydrogenase and xanthine oxidase, the deficiency is also referred to as xanthine dehydrogenase/xanthine oxidase deficiency. Xanthine, the immediate precursor of uric acid, is less soluble than uric acid in urine and deficiency of the enzyme results in xanthinuria. XOR deficiency may occur in isolated form (xanthinuria type 1), in a combined form involving XOR and aldehyde oxidase deficiencies (xanthinuria type II), or multiple deficiencies of XOR, aldehyde oxidase, and sulfite oxidase (molybdenum cofactor deficiency). All 3 forms result in an almost total replacement of uric acid by hypoxanthine and xanthine in urine, while plasma uric acid is very low or undetectable.

Patients with the isolated form can be asymptomatic or have mild symptoms; renal stones, often not visible on radiography, are a risk for renal damage and may appear at any age, when patients may present with loin pain or renal insufficiency. For type II xanthinuria the clinical presentation is similar to type I, but patients also have aldehyde oxidase deficiency, which has no known clinical attributes. Molybdenum cofactor deficiency arises from inherited deficiency of molybdenum cofactor synthase, which affects all 3 molybdoenzymes, and like isolated sulfite oxidase deficiency, it usually presents with neonatal feeding problems, neonatal seizures, increased or decreased muscle tone, ocular lens dislocation, severe intellectual disability, and death in early childhood. Milder cases have presented with lens dislocation only.

Genetics

The inheritance of all 3 types of xanthinuria is complex and autosomal recessive. Type I results from mutations in the human *XDH* gene located on chromosome 2p22. Type II xanthinuria arises from mutations in the molybdenum cofactor synthase gene located on chromosome 18q12.2; this encodes molybdenum cofactor sulfurase, which is essential for the activity of both XOR and aldehyde oxidase. Type III xanthinuria (XOR, aldehyde oxidase and sulfite oxidase deficiencies) can arise from functional mutations in any of 3 genes: *MOCS1* (encoding 2 enzymes for synthesis of the precursor via a bicistronic transcript), *MOCS2* (encoding molybdopterin synthase), or *GPHN* (encoding gephyrin), located at 6p21.2, 5q11.2, and 14q23.3, respectively.

Laboratory

Diagnosis is made initially by measuring plasma and/or urinary concentrations of uric acid. Plasma uric acid is very low or absent (<1 mg/dL). Urinary uric acid is reduced, being replaced by xanthine and hypoxanthine. Type II patients can be distinguished by the absence in urine of methyl-2-pyridone-carboxamide, the product of nicotinamide (niacin) breakdown by aldehyde oxidase. Alternately, type II patients

can be distinguished from type I by their inability to oxidize a test dose of allopurinol to oxypurinol, via aldehyde oxidase. Molybdenum cofactor deficiency is distinguished by an additional excessive urinary excretion of sulfite and other sulfur-containing metabolites such as sulfocysteine.

Enzyme assay of XOR is not usually offered because it requires jejunal or liver biopsy, as these are the only human tissues that contain appreciable amounts of the enzyme. Sulfite oxidase and the molybdenum cofactor synthase can be measured in liver and fibroblasts. Molecular genetic analysis can be used to confirm diagnosis by searching for functional mutations among the three groups of genes.

Treatment

Although isolated deficiency is generally benign, treatment with a diet of low purines and low fructose (which reduces ATP breakdown to xanthine) with increased fluid intake is recommended. Allopurinol is not recommended. The prognosis for molybdenum cofactor deficiency has previously been very poor, but trials of cyclic pyranopterin monophosphate are promising.

DISORDERS OF PYRIMIDINE METABOLISM

The pyrimidines are the building blocks of DNA and RNA and involved in the formation of active intermediates in carbohydrate and phospholipid metabolism (e.g., uridine diphosphate glucose, cytidine diphosphate choline), glucuronidation in detoxification processes (uridine diphosphate), and glycosylation of proteins and lipids.

The essential precursor for pyrimidine biosynthesis is carbamylphosphate, which is shared with the urea cycle. Consequently, proximal blockages of the urea cycle results in carbamyl-phosphate overflowing into the pyrimidine pathway. Pyrimidine synthesis differs from that of purines in that the single pyrimidine ring is first assembled to form orotic acid and then linked to ribose phosphate to form the central pyrimidine nucleotide uridine monophosphate (UMP). The pyrimidine bases, uracil and thymine, are catabolized in 4 steps, as shown in Figure 89-3. Eight disorders of pyrimidine metabolism are reviewed. Purine catabolism has an easily measurable end point in uric acid; however, there is no equivalent compound in pyrimidine catabolism. The first defect (hereditary orotic aciduria) is in the de novo synthetic pathway, 1 defect (thymidine kinase) is part of pyrimidine salvage, and the other disorders involve overactivity (in 1 syndrome) or defects in the pyrimidine degradation pathway. Pyrimidine disorders may present as anemia, neuropathologies, or multisystem mitochondrial disorders. The first 3 steps of the degradation pathways for thymine and uracil, respectively, make use of the same enzymes (DPD, DPH, and UP). These 3 steps result in the conversion of uracil into β-alanine. There is increasing evidence that pyrimidines play an important role in the regulation of the nervous system. Reduced production of the neurotransmitter function of β-alanine is hypothesized to produce clinical symptoms. Clinically, pyrimidine disorders may be overlooked because they are rare and their symptoms are not highly specific; however, they should be considered as possible causes of anemia and neurologic disease and are a contraindication for treatment of cancer patients with certain pyrimidine analogs.

Uridine Monophosphate Synthase Type 1 Deficiency (Hereditary Orotic Aciduria)

Hereditary orotic aciduria is a disorder of pyrimidine synthesis associated with deficient activity of the last 2 steps of the de novo pyrimidine synthetic pathway, orotate phosphoribosyltransferase, orotidine-5′-monophosphate decarboxylase (ODC). The activities of these 2 steps reside in separate domains of a bifunctional protein, UMP synthase. This catalyzes the 2-step conversion of orotic acid to UMP, via orotidine monophosphate. Hereditary orotic aciduria (UMP synthase deficiency) results in the excessive accumulation of orotic acid.

Genetics

UMP synthase deficiency is inherited as an autosomal recessive disorder, with both functional domains encoded on a single gene, UMPS, which is located on the long arm of chromosome 3 (3q13). Theoretically, random mutations in the gene should have equal chances of producing either orotate phosphoribosyltransferase or ODC deficiency, but there has been only a single case of ODC deficiency reported. Genetic metabolic defects that involve 4 of the 6 enzymes associated with the urea cycle may also result in orotic aciduria, secondary to PPRP depletion resulting from a substantial increased flux through the pyrimidine synthesis pathway.

Clinical

Clinically patients with hereditary orotic aciduria (UMPS type 1 deficiency) have a macrocytic hypochromic megaloblastic anemia that is unresponsive to the usual forms of therapy (iron, folic acid, and vitamin B_{12}), and may develop leukopenia. Onset is usually in first months of life. Untreated, this disorder can lead to developmental disability, intellectual disability, failure to thrive, cardiac disease, strabismus, crystalluria, and occasional ureteric obstruction. Renal function is generally normal. Heterozygotes may have mild orotic aciduria but are not otherwise affected. The clinical features are thought to be related to pyrimidine nucleotide depletion. Metabolites derived from several pharmacologic agents (5-azauridine, allopurinol) can produce secondary orotic aciduria and orotidinuria by specifically inhibiting the ODC step of UMP synthase. Orotic aciduria may also occur in association with parenteral nutrition, essential amino acid deficiency, and Reye syndrome.

Laboratory

The enzymatic defect may be demonstrated in liver, lymphoblasts, erythrocytes, leukocytes, and cultured skin fibroblasts. A carrier detection test is available, as is prenatal diagnosis, although the condition is treatable.

Treatment

The administration of uridine in doses of 50-300 mg/kg/day has been used in treatment leading to clinical improvement and reduction in orotic acid excretion. Lifelong treatment is required. Uracil is ineffective because, unlike purines, pyrimidine salvage occurs at the nucleoside (uridine) level. The long-term prognosis in uncomplicated cases is good; however, congenital malformations and other associated features may adversely affect outcome.

Dihydropyrimidine Dehydrogenase Deficiency (Thymine-Uraciluria, Pyrimidinuria)

DPD catalyzes the initial and rate-limiting step in the degradation of the pyrimidine bases uracil and thymine. DPD has been identified in most tissues, with the highest activity being in lymphocytes.

Genetics

DPD deficiency is an autosomal recessive disorder, with the *DPYD* gene mapping to chromosome 1p22, with at least 32 polymorphisms detected. It is estimated that the frequency of heterozygosity may be as high as 3%.

The clinical manifestations in children may include seizure disorder, intellectual disability and motor delay. Less frequent are growth retardation, microcephaly, autistic-like behavior, and ocular anomalies. Others do not show developmental abnormalities but may have milder neurological symptoms and language disorder. Unaffected cases have been reported, raising discussion about possible secondary gene effects. In most cases, there is an initial period of normal psychomotor development, followed by subsequent developmental delays. Symptoms may be linked to altered uracil, thymine, or β-alanine homeostasis. Because β-alanine is a structural analog of γ-aminobutyric acid and glycine, it has been proposed that it may affect inhibitory neurotransmission. DPD is the initial and rate-limiting enzyme in the inactivation of the neoplastic drug 5-fluorouracil, being responsible for 80% of its catabolism. Patients with partial DPD deficiency are at risk for developing a severe 5-fluorouracil-associated toxicity. In adult patients, neurotoxicity (headache, somnolence, visual illusions and memory impairment) linked to pyrimidinemia following 5-fluorouracil treatment for cancer is reported in previously healthy individuals.

Laboratory
DPD deficiency is characterized by a variable phenotype and diagnosed by the gross accumulation of thymine and uracil in urine (thymine-uraciluria), plasma and cerebrospinal fluid. Uric acid levels have been reported to be normal. Prenatal diagnosis has been reported.

Treatment
There is no established treatment for this disorder, however, patients with seizures do respond to anticonvulsant medications. DPYD*5 (rs1801159) and 1896 T > C (rs17376848) are potentially useful predictive markers of patients' responses to 5-FU chemotherapy.

Dihydropyrimidinase Deficiency (Dihydropyrimidinuria)
DPH is the second enzyme in the 3-step degradation pathway of uracil and thymine. DPH deficiency is characterized by increased urinary excretion of dihydrouracil and dihydrothymine (dihydropyrimidinuria), as well as uracil and thymine. Similar to DPD deficiency, there is a variable clinical phenotype.

Genetics
This is an autosomal recessive disorder, with the *DPYS* gene mapped to chromosome 8q22. In 1 study there was no significant difference in residual activity between mutations observed in symptomatic and asymptomatic individuals, again similar to DPD deficiency. Population prevalence in a Japanese sample was 0.1%.

Clinical
Clinical manifestations are similar to DPD deficiency, which is evidence that defects in these sequential steps produce a common disorder. Symptoms in 3 unrelated affected cases include seizures with dysmorphic features and developmental delay in 2 of these cases. However, 3 unrelated infant and 2 adult asymptomatic cases were identified in a screening program for pyrimidine degradation disorders in Japan and were asymptomatic despite the accumulation of pyrimidine degradation products in body fluids.

Laboratory
Organic acid screening may identify increased amounts of uracil and thymine in urine. Oral loading tests with uracil, dihydrouracil, thymine, and dihydrothymine have been used to detect carriers of the deficiency. In symptomatic cases, treatment with β-alanine has been attempted with equivocal results. A single case of increased sensitivity to 5-fluorouracil has been reported.

Deficiency of β-Ureidopropionase (*N*-Carbamyl-β-Amino Aciduria)
The pyrimidine bases uracil and thymine are degraded via the consecutive action of 3 enzymes to β-alanine and β-aminoisobutyric acid, respectively. The third enzyme in the pathway is ureidopropionase, and its deficiency leads to *N*-carbamyl-β-amino aciduria. 3-ureidopropionic acid (3-UPA) acts as endogenous neurotoxin via inhibition of mitochondrial energy metabolism resulting in the initiation of secondary, energy-dependent excitotoxic mechanisms.

Genetics
Fluorescence in situ hybridization localized the human β-ureidopropionase gene, *UPB1,* to 22q11.2.

Clinical
Clinical manifestations in a reported case include muscular hypotonia, dystonic movements, and severe developmental delay.

Laboratory
Neuropathology involves both gray and white matter. Ureidopropionase deficiency leads to pathologic accumulation of 3-UPA in body fluids. Urinary analysis in a reported case showed elevated levels of *N*-carbamyl-β-alanine and *N*-carbamyl-β-aminoisobutyric acid (ureidoisobutyric acid). The enzyme is expressed only in the liver and no activity of β-ureidopropionase is detected in a liver biopsy.

Treatment
There is no known treatment for ureidopropionase deficiency.

Pyrimidine 5′-Nucleotidase Deficiency
Erythrocyte maturation is accompanied by RNA degradation and the release of mononucleotides. Pyrimidine 5′-nucleotidase is the first degradative enzyme of the pyrimidine salvage cycle and catalyzes the hydrolysis of pyrimidine 5′-nucleotides to the corresponding nucleosides. Enzyme deficiency results in the accumulation of high levels of cytidine and uridine nucleotides in the erythrocytes that, in turn, results in hemolysis. Deficiency of pyrimidine 5′-nucleotidase may be at least in part compensated in vivo by other nucleotidases or perhaps other nucleotide metabolic pathways.

Genetics
This is an autosomal recessive disorder involving the gene *pyrimidine 5′-nucleotidase deficiency* on chromosome 7 (7p15). Affected pyrimidine 5′-nucleotidase deficiency patients clinically present with a defect restricted to erythrocytes that is characterized by nonspherocytic hemolytic anemia with basophilic stippling. Other characteristic features include splenomegaly, increased indirect bilirubin, and hemoglobinuria. Lead is a powerful inhibitor of pyrimidine 5′-nucleotidase and assessment of lead levels should be included whenever hemolytic anemia, pyrimidine 5′-nucleotidase deficiency, and basophilic stippling are found together.

Laboratory
Diagnosis requires assay of erythrocyte UMP hydrolysis to form uridine and inorganic phosphate. The enzyme defect should be suspected in patients with nonspherocytic hemolytic anemia with basophilic stippling. The anemia is usually moderate, and transfusions are rarely necessary.

Treatment
There is no specific treatment. Splenectomy has not proved to be an effective treatment. Lead-induced acquired pyrimidine 5′ nucleotidase deficiency is treatable, unlike the congenital deficiency.

OVERACTIVE CYTOSOLIC 5′-NUCLEOTIDASE (PYRIMIDINE NUCLEOTIDE DEPLETION)
Pyrimidine nucleotide depletion and overactive cytosolic 5′-nucleotidase, may lead to a neurodevelopmental disorder. Four unrelated patients showed 6-10–fold elevation in the activity of pyrimidine 5′-nucleotidase in fibroblasts with both purine and pyrimidine substrates. Investigation in cultured fibroblasts derived from these patients showed normal incorporation of purine bases into nucleotides but decreased incorporation of uridine and orotic acid.

Clinical
Clinical manifestations include developmental delay, seizures, ataxia, recurrent infections, severe language deficit, hyperactivity, short attention span, and aggressive behavior appearing within the first few years of life. Affected patients show electroencephalogram abnormalities. Metabolic testing is normal except for persistent hypouricosuria. It is proposed that increased catabolic activity and decreased pyrimidine salvage cause a deficiency of pyrimidine nucleotides.

Treatment
Treatment is with oral uridine based on compensating for the increased nucleotide catabolism. All reported patients treated with uridine showed improved speech and behavior, decreased seizure activity with discontinuation of seizure medications, and decreased frequency of infections.

Thymidine Phosphorylase Deficiency (Mitochondrial Neurogastrointestinal Encephalomyopathy)
Thymidine phosphorylase catalyzes the catabolism in mitochondria of thymidine to thymine. This enzyme is also known as "platelet-derived

endothelial cell growth factor" because of its angiogenic properties, or "gliostatin" indicating its inhibitory effects on glial cell proliferation. It has been implicated in mitochondrial nucleoside metabolism. Plasma thymidine level is increased more than 20-fold in patients compared to controls. Loss of function of thymidine phosphorylase causes mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), which is inherited as a single autosomal recessive disorder, causing mitochondrial DNA depletion and instability. In MNGIE, loss of thymidine phosphorylase activity causes toxic accumulations of the nucleosides thymidine and deoxyuridine that are incorporated by the mitochondrial pyrimidine salvage pathway and cause deoxynucleoside triphosphate pool imbalances.

Genetics

The *TYMP* gene encoding thymidine phosphorylase has been identified as the MNGIE gene and is mapped to chromosome 22q13.32-qter, but the protein is imported into mitochondria.

Clinical Manifestations

Clinical manifestations of MNGIE include ptosis, progressive external ophthalmoparesis, gastrointestinal dysmotility and malabsorption, cachexia, peripheral neuropathy, skeletal muscle myopathy and leukoencephalopathy.

Laboratory

Muscle biopsies typically reveal mitochondrial abnormalities. Screening is performed by detection of grossly raised thymidine and deoxyuridine in urine, which are normally absent. Confirmation of the diagnosis can made by assay of thymidine phosphorylase activity in peripheral leukocytes. Molecular genetic analysis will show functional mutations in the *TYMP* gene. Increased thymidine and/or deoxyuridine nucleotides may cause mitochondrial nucleotide pool imbalance resulting in mitochondrial DNA alterations, in particular DNA depletion.

Treatment

Supportive treatment is indicated. There is no established therapy for MNGIE; bone marrow transplantation has been performed on several patients but no improvement in symptoms or progression of the disease has been reported. Allogeneic hematopoietic stem cell transplantation to restore thymidine phosphorylase activity and eliminate toxic metabolites is a potential therapy for MNGIE.

THYMIDINE KINASE 2 DEFICIENCY

Thymidine kinase 2 (TK2) is a key enzyme for the pyrimidine salvage pathway to provide precursor nucleotide for mitochondrial DNA. TK2 deficiency causes tissue-specific depletion of mitochondrial DNA. TK2 normally phosphorylates thymidine and deoxycytidine.

Genetics

The TK2 gene is located on chromosome 16q 22; the deficiency is inherited in an autosomal recessive manner.

Clinical

Clinically, affected individuals with TK2 deficiency have severe myopathy and depletion of muscular mitochondrial DNA in infancy.

Treatment

No specific treatment is available. Supportive treatment is indicated.

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Chapter 90

Hutchinson-Gilford Progeria Syndrome

Leslie B. Gordon

Hutchinson-Gilford progeria syndrome (progeria) is a rare, fatal, autosomal dominant segmental premature aging disease. With an estimated incidence of 1 in 4,000,000 live births and prevalence of 1 in 18 million, there were a total of 350 children living with progeria in 2013 worldwide. There is no gender, ethnic, or regional bias. Progeria is caused by a single base mutation in *LMNA*, which results in the production of a mutant lamin A protein called progerin. Progerin is found in increased concentration in skin and the vascular wall of normal older compared to younger individuals, suggesting a role in normal aging. Children develop progressive atherosclerosis and die of heart attacks or strokes at a median age of 14.5 yr, most often between ages 5 and 20 yr.

CLINICAL MANIFESTATIONS

Children develop the appearance of accelerated aging. Physical appearance changes dramatically each year that the children age (Fig. 90-1).

Dermatologic Changes

Skin findings are often apparent as initial signs of progeria. These are variable in severity and include areas of discoloration, stippled pigmentation, tightened areas that can restrict movement, and areas of the trunk or legs where small (1-2 cm) soft, bulging skin is present. Although usually born with normal hair present, patients lose cranial hair within the first few years, and are left with soft, downy, sparse immature hair on the scalp, no eyebrows, and scant eye lashes.

Failure to Thrive

Children with progeria experience apparently normal fetal and early postnatal development. Within the first year of life, abnormalities in growth and body composition are readily apparent; severe failure to thrive ensues, heralding generalized lipoatrophy, with apparent wasting of limbs, circumoral cyanosis, and prominent veins around the scalp, neck, and trunk. The mean weight, which is normal at birth, decreases to below the third percentile for normal children despite adequate caloric intake for normal growth and normal resting energy expenditure. A retrospective data set of 35 children showed an average weight gain of only 0.44 kg/year, beginning at 24 mo of age and persisting throughout life. There is interpatient variation in weight gain, but the projected weight gain over time in an individual patient is constant, linear, and very predictable. Children with progeria reach a final height of approximately 1 m and weight of approximately 14 kg. Head circumference is normal. Weight deficit is more pronounced than height deficit and this, associated with the loss of subcutaneous fat, results in the emaciated appearance characteristic of children with progeria. Clinical problems caused by the lack of subcutaneous fat include insulin resistance, sensitivity to cold temperatures, and foot discomfort because of a lack of fat cushioning. Although overt diabetes is very unusual in progeria, approximately 30-40% of children suffer from insulin resistance.

Ocular Abnormalities

Tightened skin and a paucity of subcutaneous fat around the eyes causes most patients to sleep with eyelids partially open, resulting in corneal dryness and eye tearing. Patients can develop exposure keratopathy and/or corneal ulcers, which can disrupt sight. Artificial tears

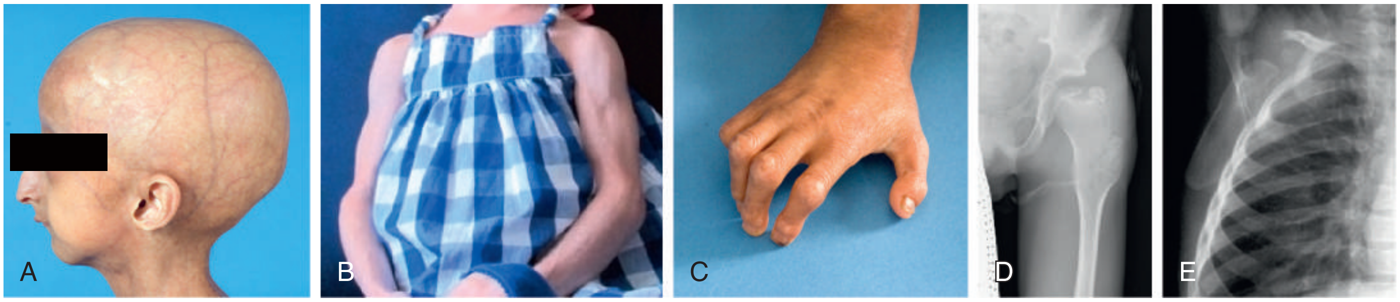

Figure 90-1 **A,** Profile of head and face of a child with progeria. Note the alopecia, beaked nose, and retrognathia. **B,** The arms of this child demonstrate absence of subcutaneous fat. **C,** Contractures in multiple joints including fingers, elbows, hips, knees, and ankles may be present at birth and/or in later years. **D,** Hip dysplasia is often progressive and may result in avascular necrosis, hip dislocation, and inability to bear weight. **E,** A pyriform chest structure and a small clavicle can lead to reducible shoulder dislocations. *(Photos courtesy of The Progeria Research Foundation and Boston Children's Hospital.)*

during the day and taping or covering the eyes at night are recommended. Some degree of photophobia is common.

Dental Abnormalities

Dentition is severely delayed in development and crowded due to micrognathia. Eruption may be delayed for many months, and primary teeth may persist for the duration of life. Secondary teeth are present, but may or may not erupt. They sometimes erupt on the lingual and palatal surfaces of the mandibular and maxillary alveolar ridges, rather than in place of the primary incisors. In some but not all cases, extracting primary teeth promotes movement of secondary teeth into place.

Bone and Cartilaginous Abnormalities

Aberrant development of bone structure and bone density represents a unique skeletal dysplasia which is not based in malnutrition. Acroosteolysis of the distal phalanges, distal clavicular resorption and thin, tapered ribs are early signs of progeria that appear as early as 3 mo of age. Facial disproportion, a narrowed nasal bridge and retrognathia make intubation extremely difficult, and fiberoptic intubation is recommended. A pyriform chest structure and a small clavicle can lead to reducible shoulder dislocations (Fig. 90-1*E*). Long bone remodeling of the femoral head–neck axis following knee and ankle contractures results in coxa valga, straightening of the femoral head-neck axis to >125 degrees. The bony pelvis is normal and these changes give rise to a "horse riding" stance. Hip dysplasia is often progressive and may result in avascular necrosis, hip dislocation, and inability to bear weight (Fig. 90-1*D*). Other long bone changes include flaring of the humeral and femoral metaphyses and constriction of the radial neck. Bone age is generally normal, with variable readings within a single radiograph. Growth plates are normal. Bone structure assessed by peripheral quantitative computed tomography of the radius demonstrates distinct and severe abnormalities in bone structural geometry and skeletal strength. Areal bone density Z scores by dual-energy X-ray absorptiometry are abnormally low, but improve after adjustment for height and age. Fracture rates in progeria are normal.

Joint contractures, a result of ligamentous and skin changes, limit range of motion. Contractures in multiple joints including fingers, elbows, hips, knees and ankles may be present at birth and/or in later years (Fig. 90-1*C*). Physical therapy is recommended routinely and throughout life to maximize joint function.

Hearing

Low tone conductive hearing loss is pervasive in progeria, and is indicative of a stiff tympanic membrane, and/or deficits in the middle ear bony and ligamentous structures. Overall, this does not affect ability to hear the usual spoken tones but preferential classroom seating is recommended.

Cardiovascular Disease

Death occurs primarily from myocardial infarction, and less often from strokes. Progeria is a primary vasculopathy, characterized by pervasive accelerated vascular stiffening, followed by large and small vessel occlusive disease as a result of atherosclerotic plaque formation, with valvular and cardiac insufficiency in later years. Hypertension, angina, cardiomegaly, metabolic syndrome, and heart failure are common end-stage events. Routine carotid ultrasound for plaque monitoring, carotid-femoral pulse wave velocity measures for vascular stiffening, and echocardiography are recommended.

Cerebrovascular Arteriopathy and Stroke

Cerebral infarction may occur while the child exhibits a normal electrocardiogram. The earliest incidence of stroke occurred at the age of 0.4 yr. More often they occur in the later yr. Radiographic evidence on MRI of infarction can be found in 60% of the patients, in whom half are clinically silent. Both large- and small-vessel disease is found; collateral vessel formation is extensive. Carotid artery occlusions are well documented, but infarction can occur in their absence. Propensity toward strokes and an underlying stiff vasculature make maintaining adequate blood pressure through hydration (i.e., habitually drinking well) a priority in progeria; special care should be taken when considering maintenance of consistent blood pressure during general anesthesia, airplane trips, and hot weather.

Normally Functioning Systems

Liver, kidney, thyroid, immune, gastrointestinal, and neurologic systems (other than stroke-related) remain intact. Intellect is normal for age.

Laboratory Findings

The most consistent laboratory findings are low serum leptin and insulin resistance. Platelet count is often moderately high. Lipid panels, blood chemistries, endocrine and coagulation and other tests are generally normal.

MOLECULAR PATHOGENESIS

Mutations in the *LMNA* gene cause progeria. The normal *LMNA/C* gene encodes the proteins lamins A and C, of which only lamin A is associated with human diseases. The lamin proteins are the principal proteins of the nuclear lamina, a complex molecular interface located between the inner membrane of the nuclear envelope and chromatin. The integrity of the lamina is central to many cellular functions, creating and maintaining structural integrity of the nuclear scaffold, DNA replication, RNA transcription, organization of the nucleus, nuclear pore assembly, chromatin function, cell cycling, and apoptosis.

Progeria is almost always a sporadic autosomal dominant disease. There is 1 proven case of mosaicism. Progeria is caused by the accelerated use of an alternative, internal splice site that results in the deletion of 150 base pairs in the 3' portion of exon 11 of the *LMNA* gene. In approximately 90% of cases, this results from a single C to T transition at nucleotide 1824 that is silent (Gly608Gly), but optimizes an internal splice site within exon 11. The remaining 10% of cases possess 1 of several single base mutations within the intron 11 splice donor site,

thus reducing specificity for this site and altering the splicing balance in favor of the internal splice. Subsequent to all of these mutations, translation followed by posttranslational processing of the altered messenger RNA produces progerin, a shortened abnormal lamin A protein with a 50-amino-acid deletion near its C-terminal end. An understanding of the posttranslational processing pathway and how it is altered to create progerin has led to a number of treatment prospects for the disease.

Both lamin A and progerin possess a farnesyl side group attached during posttranslational processing. This is a lipophilic moiety which facilitates intercalation of proteins into the inner nuclear membrane where most of the lamin and progerin functions are performed. For normal lamin A, loss of the farnesyl anchor releases prelamin from the nuclear membrane, rendering it soluble for autophagic degradation. However, progerin retains its farnesyl moiety. It remains anchored to the membrane, binding other proteins, causing blebbing of the nucleus, disrupting mitosis, and altering gene expression.

Disease in progeria is produced by a ***dominant negative*** mechanism; it is the action of progerin, not the diminution of lamin A that causes the disease phenotype. The severity of disease is determined in part by progerin levels, which are regulated by the particular mutation, tissue type, or other factors influencing use of the internal splice site.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Overall, the constellation of small body habitus, bone, hair, subcutaneous fat, and skin changes results in the marked physical resemblance among patients with progeria (Fig. 90-2). For this reason, clinical diagnosis can be achieved or excluded with relative confidence even at young ages, though there have been a few cases of low progerin-expressing patients with extremely mild signs. Clinical suspicion should be followed by *LMNA* genetic sequence testing. The disorders that resemble progeria are those grouped as the senile-like syndromes and include Wiedemann-Rautenstrauch syndrome, Werner syndrome, Cockayne syndrome, Rothmund-Thomson syndrome, restrictive dermopathy, and Nestor-Guillermo progeria syndrome (Table 90-1). Patients often fall under none of these diagnoses and represent ultrarare, unnamed progeroid laminopathies that carry either non–progerin-producing mutations in lamin or the lamin-associated enzyme Zmpste24, or progeroid syndromes without lamin mutations.

Figure 90-2 **Two unrelated children with progeria.** Note the physical resemblance of each to the other. *(Photo courtesy of The Progeria Research Foundation.)*

Table 90-1 Features of Hutchinson-Gilford Progeria Syndrome and Disorders That Resemble It

	HUTCHINSON-GILFORD PROGERIA SYNDROME	WIEDEMANN-RAUTENSTRAUCH SYNDROME	WERNER SYNDROME	COCKAYNE SYNDROME	ROTHMUND-THOMPSON SYNDROME	RESTRICTIVE DERMOPATHY
Causative gene	*LMNA*	Unknown	*WRN, LMNA*	*CSA, SP*	RecQL helicase gene w/8q24.3	LAMIN A/C mutations
Inheritance	Dominant	Recessive	Recessive	Recessive	Recessive	Recessive
Onset	Infancy	Newborn	Young Adult	Newborn	Infancy	Newborn
Hair loss	+Total	Scalp + patchy	Scalp + male pattern	–	+Diffuse	+Diffuse
Skin thinning	+	+	+	–	+	+
Subcutaneous fat loss	+	+	+	+	–	–
Skin calcification	–	–	+	–	–	–
Hyperkeratosis	–	–	+	–	+	–
Cataracts	–	–	+	+	+	–
Short stature	+	+	+	+	+	+
Coxa valga	+	–	–	–	–	–
Acroosteolysis	+	+	+	–	–	–
Mandibular dysplasia	+	+	–	–	–	+
Vasculopathy	+	–	+	+	–	–
Voice abnormality	+	–	+	–	–	–
Diabetes	–	+	+	–	–	–
Hypogonadism	+	–	+	+	+	–
Dental abnormality	+	+	+	+	+	+

Modified from Hegele RA: Drawing the line in progeria syndromes, Lancet 362;416–417, 2003.

PROGNOSIS, TREATMENT, AND PATIENT RESOURCES

Children with progeria develop a severe premature form of atherosclerosis. Prior to death, cardiac decline with left-sided hypertrophy, valvular insufficiency, and pulmonary edema develop; neurovascular decline with transient ischemic attack, strokes, and occasionally seizures can result in significant morbidity. Death occurs as a result of heart attack (~80%) and stroke (~20%), generally between age 5 and 20 yr, with a median life span of 14.5 yr.

No specific FDA-approved treatment for this condition exists. Growth hormone has resulted in increased rate of weight gain and overall size when administered at 0.05 mg/kg/day SC, but weight still remained well below that seen in normal children. Low-dose aspirin therapy is recommended at 2 mg/kg body weight per day, as an extension of what is known about decreasing cardiovascular risk in the general at-risk adult population. It is not known whether growth hormone or low-dose aspirin has any effect on morbidity or mortality.

The first potentially beneficial treatment prospect for progeria was published in 2011. Inhibiting posttranslational progerin farnesylation with a drug named lonafarnib was aimed at preventing this disease-causing protein from anchoring to the nuclear membrane where it carries out much of its damage. A prospective single-arm clinical trial was initiated with a cohort of 25 progeria patients between 3 and 16 yr of age, treated for a minimum of 2 yr (NCT00425607). Lonafarnib was well tolerated; the most common side effects were diarrhea, nausea, and loss of appetite, which generally improved with time. Subgroups of patients experienced increased rate of weight gain, decreased vascular stiffness measured via improved carotid-femoral wave velocity, and carotid artery echodensity, increased radial bone structural rigidity, improved sensorineural hearing, and early evidence of decreased headache, transient ischemic attack and stroke rates. Dermatologic, dental, joint contracture, insulin resistance, lipodystrophy, bone mineral density, and joint contractures were unaffected by drug treatment. The evidence for improved cardiovascular status in children with progeria is most encouraging. A study published in 2014 demonstrated increased estimated lifespan for children with progeria taking farnesylation inhibitors such as lonafarnib.

An ongoing clinical trial which adds pravastatin and zoledronate, 2 FDA-approved drugs, to the lonafarnib regimen is similarly aimed at inhibiting progerin farnesylation (NCT00916747).

The Progeria Foundation (www.progeriaresearch.org) maintains an international registry, diagnostics program, and complete patient care manual and coordinates clinical treatment trials.

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Chapter 91

The Porphyrias

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Porphyrias are metabolic diseases resulting from altered activities of specific enzymes of the heme biosynthetic pathway. These enzymes are most active in bone marrow and liver. Erythropoietic porphyrias, in which overproduction of heme pathway intermediates occurs primarily in bone marrow erythroid cells, usually present at birth or in early childhood with cutaneous photosensitivity, or in the case of congenital erythropoietic porphyria (CEP), even in utero as nonimmune hydrops. Erythropoietic protoporphyria (EPP) is the most common porphyria in children and of most interest to pediatricians. Most porphyrias are hepatic, with overproduction and initial accumulation of porphyrin precursors or porphyrins in the liver. Activation of hepatic porphyrias is very rare during childhood, reflecting the distinct hepatic regulatory mechanisms for heme biosynthesis that are influenced by pubertal development. Homozygous forms of the hepatic porphyrias may manifest clinically prior to puberty. Children who are heterozygous for inherited hepatic porphyrias may present with nonspecific and unrelated symptoms, and parents often request advice about long-term prognosis and express concerns about drugs that may exacerbate these conditions.

The DNA sequences and chromosomal locations are established for the human genes of the enzymes in this pathway, and multiple disease-related mutations have been found for each porphyria. The inherited porphyrias display autosomal dominant, recessive or X-linked inheritance. Although initial diagnosis of porphyria by biochemical methods remains essential, it is especially important to confirm the diagnosis by demonstrating a specific gene mutation(s).

THE HEME BIOSYNTHETIC PATHWAY

Heme is required for a variety of hemoproteins such as hemoglobin, myoglobin, respiratory cytochromes, and cytochrome P450 enzymes (CYPs). It is believed that the 8 enzymes in the pathway for heme biosynthesis are active in all tissues. Hemoglobin synthesis in erythroid precursor cells accounts for approximately 85% of daily heme synthesis in humans. Hepatocytes account for most of the rest, primarily for synthesis of CYPs, which are especially abundant in the liver endoplasmic reticulum, and turn over more rapidly than many other hemoproteins, such as the mitochondrial respiratory cytochromes. Pathway intermediates are the porphyrin precursors δ-aminolevulinic acid (ALA, also known as 5-aminolevulinic acid) and porphobilinogen (PBG), and porphyrins (mostly in their reduced forms, known as porphyrinogens) (Fig. 91-1). At least in humans, these intermediates do not accumulate in significant amounts under normal conditions or have important physiologic functions.

A deficiency of each enzyme in the pathway is associated with a specific porphyria (Table 91-1). The first enzyme, ALA synthase (ALAS), occurs in 2 forms. An erythroid specific form, termed ALAS2, is deficient in X-linked sideroblastic anemia, as a result of mutations of the *ALAS2* gene on chromosome Xp11.2. Gain of function mutations of *ALAS2* because of deletions in the last exon cause X-linked protoporphyria (XLP), a cutaneous porphyria which is phenotypically identical to EPP.

Regulation of heme synthesis differs in the 2 major heme-forming tissues. Liver heme biosynthesis is primary controlled by ALAS1. Synthesis of ALAS1 in liver is regulated by a "free" heme pool (see Fig. 91-1), which can be augmented by newly synthesized heme or by existing heme released from hemoproteins and destined for breakdown to biliverdin by heme oxygenase.

In the erythron, novel regulatory mechanisms allow for the production of the very large amounts of heme needed for hemoglobin synthesis. The response to stimuli for hemoglobin synthesis occurs during cell differentiation, leading to an increase in cell number. Also, unlike the liver, heme has a stimulatory role in hemoglobin formation, and the stimulation of heme synthesis in erythroid cells is accompanied by increases not only in ALAS2, but also by sequential induction of other heme biosynthetic enzymes. Separate erythroid-specific and nonerythroid or "housekeeping" transcripts are known for the first 4 enzymes in the pathway. The separate forms of ALAS are encoded by genes on different chromosomes, but for each of the other 3, erythroid and nonerythroid transcripts are transcribed by alternative promoters in the same gene. Heme also regulates the rate of its synthesis in erythroid cells by controlling the transport of iron into reticulocytes.

Intermediates of the heme biosynthetic pathway are efficiently converted to heme and, normally, only small amounts of the intermediates are excreted. Some may undergo chemical modifications before excretion. Whereas the porphyrin precursors ALA and PBG are colorless, nonfluorescent, and largely excreted unchanged in urine, PBG may degrade to colored products such as the brownish pigment called *porphobilin* or spontaneously polymerize to uroporphyrins. Porphyrins are red in color and display bright red fluorescence when exposed to long wavelength UV light. Porphyrinogens, which are colorless and nonfluorescent, are the reduced form of porphyrins, and when they

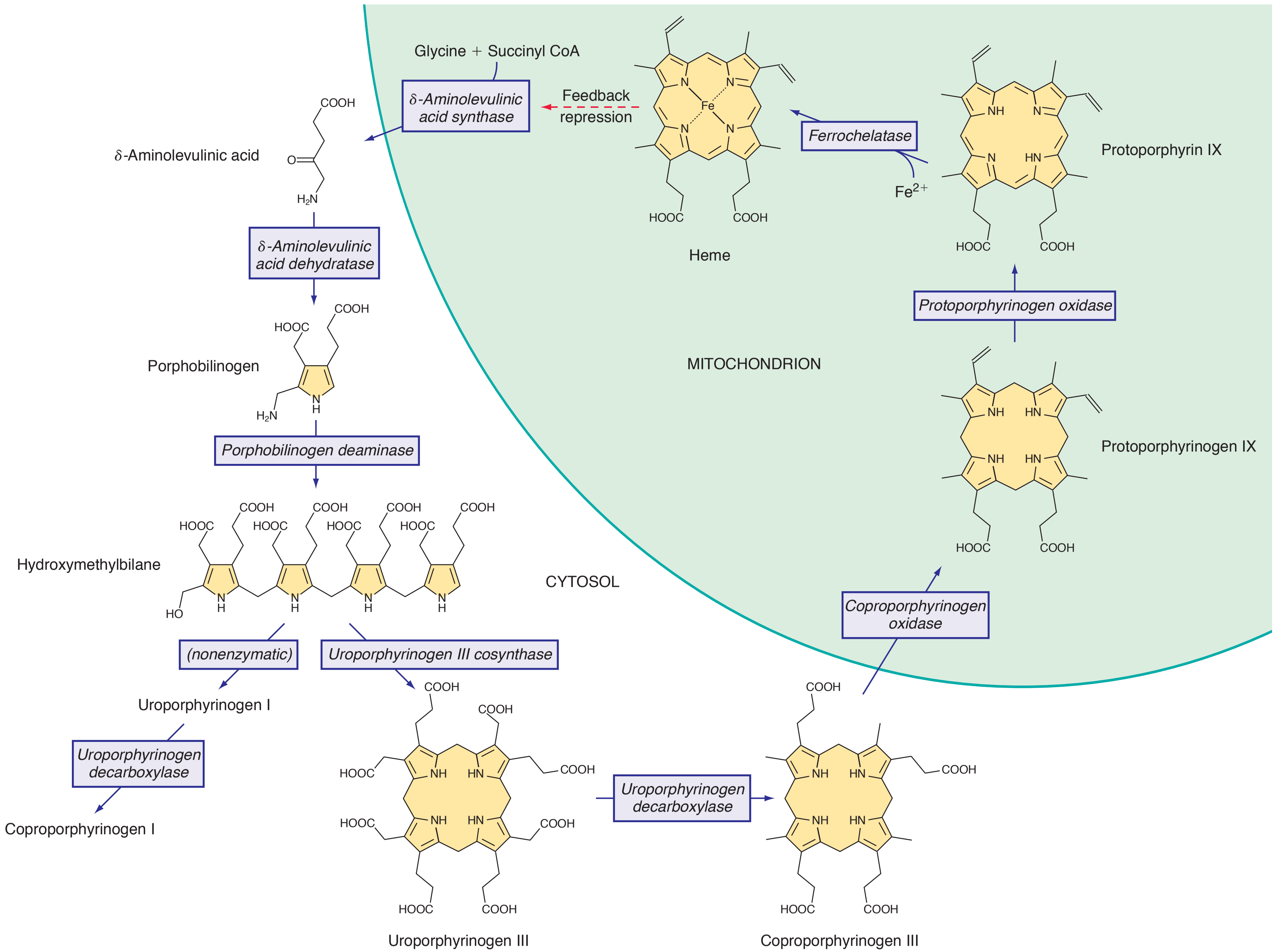

Figure 91-1 **Enzymes and intermediates of the heme biosynthetic pathway.** The pathway is regulated in the liver by the end product, heme, mainly by feedback repression *(dashed arrow).*

Table 91-1 The Human Porphyrias: Mutations, Time of Presentation, and Tissue- and Symptom-Based Classifications

				Classifications			
DISEASE (ABBREVIATION)	ENZYME (ABBREVIATION)	INHERITANCE	PRESENTATION	HEPATIC	ERYTHROPOIETIC	ACUTE/ NEUROLOGIC	CUTANEOUS
X-Linked protoporphyria (XLP)	*δ-Aminolevulinate synthase 2 (ALAS2)*	X-linked	Childhood		X		X
δ-Aminolevulinic acid dehydratase porphyria (ADP)	*δ-Aminolevulinic acid dehydratase (ALAD)*	Autosomal recessive	Mostly post puberty	X	X*	X	
Acute intermittent porphyria (AIP)	*Porphobilinogen deaminase (PBGD)*	Autosomal dominant	Post puberty	X		X	
Homozygous AIP		Homozygous dominant	Childhood	X	X	X	
Congenital erythropoietic porphyria (CEP)	*Uroporphyrinogen III synthase (UROS)*	Autosomal recessive	In utero or infancy		X		X
Porphyria cutanea tarda (PCT) type 1	*Uroporphyrinogen decarboxylase (UROD)*	Sporadic	Adults	X			X
PCT type 2†		Autosomal dominant	Adults	X			X
PCT type 3		Unknown	Adults	X			X
Hepatoerythropoietic porphyria (HEP)		Homozygous dominant	Childhood	X	X*		X
Hereditary coproporphyria (HCP)	*Coproporphyrinogen oxidase (CPOX)*	Autosomal dominant	Post puberty	X		X	X
Homozygous HCP		Homozygous dominant	Childhood	X	X	X	X
Variegate porphyria (VP)	*Protoporphyrinogen oxidase (PPOX)*	Autosomal dominant	Post puberty	X		X	X
Homozygous VP		Homozygous dominant	Childhood	X	X	X	X
Erythropoietic protoporphyria (EPP)	*Ferrochelatase (FECH)*	Autosomal recessive(most commonly heteroallelic with hypomorphic allele)	Childhood		X		X

*ADP and HEP are considered primarily hepatic porphyrias, but substantial increases in erythrocyte zinc protoporphyrin suggest an erythropoietic component.
†PCT is a result of inhibition of hepatic UROD. Autosomal dominant inheritance of a partial deficiency of UROD is a predisposing factor in cases defined as familial (type 2) PCT.

Table 91-2 The 3 Most Common Human Porphyrias and Their Major Features

	PRESENTING SYMPTOMS	EXACERBATING FACTORS	MOST IMPORTANT SCREENING TESTS	TREATMENT
Acute intermittent porphyria	Neurologic, adult onset	Drugs (mostly P450-inducers), progesterone, dietary restriction	Urinary porphobilinogen	Hemin, glucose
Porphyria cutanea tarda	Skin blistering and fragility (chronic), adult onset	Iron, alcohol, smoking, estrogens, hepatitis C, HIV, halogenated hydrocarbons	Plasma (or urine) porphyrins	Phlebotomy, low-dose hydroxychloroquine
Erythropoietic protoporphyria	Skin pain and swelling (mostly acute), childhood onset		Erythrocyte (or plasma) porphyrins	Beta-carotene

accumulate are readily autoxidized to the corresponding porphyrins when outside the cell. Only the type III isomers of uroporphyrinogen and coproporphyrinogen are converted to heme (see Fig. 91-1).

ALA and PBG are excreted in urine. Excretion of porphyrins and porphyrinogens in urine or bile is determined by the number of carboxyl groups. Those with many carboxyl groups, such as uroporphyrin (octacarboxyl porphyrin) and heptacarboxyl porphyrin, are water soluble and readily excreted in urine. Those with fewer carboxyl groups, such as protoporphyrin (dicarboxyl porphyrin), are not water soluble and are excreted in bile and feces. Coproporphyrin (tetracarboxyl porphyrin) is excreted partly in urine and partly in bile. Because coproporphyrin I is more readily excreted in bile than is coproporphyrin III, impaired hepatobiliary function may increase total urinary coproporphyrin excretion and the ratio of these isomers.

CLASSIFICATION AND DIAGNOSIS OF PORPHYRIAS

Two classification schemes reflect either the underlying pathophysiology or clinical features, and both are useful for diagnosis and treatment (see Table 91-1). In **hepatic** and **erythropoietic** porphyrias, the source of excess production of porphyrin precursors and porphyrins is the liver and bone marrow, respectively. **Acute porphyrias** cause neurologic symptoms that are associated with increases of 1 or both of the porphyrin precursors, ALA and PBG. In the **cutaneous porphyrias,** photosensitivity results from transport of porphyrins in blood from the liver or bone marrow to the skin. **Dual porphyria** refers to the very rare cases of porphyria with deficiencies of 2 different heme pathway enzymes.

It is notable that, porphyria cutanea tarda (PCT), acute intermittent porphyria (AIP) and EPP in that order the 3 most common porphyrias considering all age groups are very different in clinical presentation, precipitating factors, methods of diagnosis, and effective therapy (Table 91-2). Two of the 4 acute porphyrias, hereditary coproporphyria (HCP) and variegate porphyria (VP), can also cause lesions indistinguishable from PCT (see Table 91-1). CEP causes more severe blistering lesions, often with secondary infection and mutilation. EPP and XLP have the same phenotype and are distinct from the other cutaneous porphyrias in causing nonblistering photosensitivity that occurs acutely after sun exposure. EPP is also the most common porphyria to become manifest before puberty.

First-Line Laboratory Diagnostic Testing

A few sensitive and specific first-line laboratory tests should be obtained whenever symptoms or signs suggest the diagnosis of porphyria. If a first-line or screening test is significantly abnormal, more comprehensive testing should follow to establish the type of porphyria. Overuse of laboratory tests for screening can lead to unnecessary expense and even delay in diagnosis. In patients who present with a past diagnosis of porphyria, laboratory reports that were the basis for the original diagnosis must be reviewed, and if these were inadequate, further testing considered.

Acute porphyria should be suspected in patients with neurovisceral symptoms such as abdominal pain after puberty, when initial clinical evaluation does not suggest another cause, and *urinary porphyrin precursors (ALA and PBG)* and *total porphyrins* should be measured. Urinary PBG is virtually always increased during acute attacks of acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), and is not substantially increased in any other medical conditions. Therefore, this measurement is both sensitive and specific. A method for rapid, in-house testing for urinary PBG, such as the Trace PBG kit (Thermo Scientific, 1-800-640-0640), should be available in-house at all major medical facilities. Results from **spot** (**single void**) urine specimens are highly informative because very substantial increases are expected during acute attacks of porphyria. A 24 hr collection can unnecessarily delay diagnosis. The same spot urine specimen should be saved for quantitative determination of ALA and PBG to confirm the qualitative PBG result and total porphyrins. This will detect patients with ALA dehydratase porphyria (ADP) and some cases of HCP and VP, as urinary porphyrins may remain increased longer than porphyrin precursors in the latter disorders. Measurement of urinary porphyrins alone should be avoided for screening, because these are often increased in many disorders other than porphyrias, such as chronic liver disease, and misdiagnoses of porphyria can result from minimal increases in urinary porphyrins that have no diagnostic significance.

PBG is a colorless pyrrole that forms a violet pigment with Ehrlich reagent (*p*-dimethylaminobenzaldehyde). Other substances, principally urobilinogen, also react with Ehrlich aldehyde. A reliable quantitative method for both ALA and PBG, which uses small anion and cation exchange columns to separate interfering substances before adding Ehrlich reagent, has been available for many years. ALA is reacted to form a pyrrole, which is then also measured using Ehrlich reagent. The Trace PBG kit to detect increased PBG is based on this method.

Blistering Cutaneous Porphyrias

Blistering skin lesions caused by porphyria are virtually always accompanied by increases in *total plasma porphyrins.* A fluorometric method is preferred, because the porphyrins in plasma in VP are mostly covalently linked to plasma proteins and may be less readily detected by high-pressure liquid chromatography. The normal range for plasma porphyrins is somewhat increased in patients with end-stage renal disease. Urinary porphyrins are also increased in these porphyrias, but also in many other medical conditions.

Nonblistering Cutaneous Porphyria

Although a total plasma porphyrin determination will usually detect EPP and XLP, an erythrocyte protoporphyrin determination is more sensitive. Increases in erythrocyte protoporphyrin occur in many other conditions. Therefore, the diagnosis of EPP must be confirmed by showing a predominant increase in metal-free protoporphyrin rather than zinc protoporphyrin. In XLP, both free and zinc protoporphyrin can be elevated. Interpretation of laboratory reports can be misleading, because the term *free erythrocyte protoporphyrin* often refers to iron-free protoporphyrin (including zinc protoporphyrin) rather than metal-free protoporphyrin.

Second-Line Testing

More extensive testing is well justified when a first-line test is positive. A substantial increase in PBG may be caused by AIP, HCP, or VP. These acute porphyrias can be distinguished by measuring erythrocyte porphobilinogen deaminase (PBGD), urinary porphyrins (using the same spot urine sample), fecal porphyrins, and plasma porphyrins. The various porphyrias that cause blistering skin lesions are differentiated by measuring porphyrins in urine, feces, and plasma. Confirmation at the DNA level is important once the diagnosis is established by biochemical testing.

Testing for Subclinical Porphyria

It is often difficult to diagnose or “rule out” porphyria in patients who had suggestive symptoms months or years in the past, and in relatives of patients with acute porphyrias, because porphyrin precursors and porphyrins may be normal. More extensive testing and consultation with a specialist laboratory and physician may be needed. Before evaluating relatives, the diagnosis of porphyria should be firmly established in an index case, and the laboratory results reviewed to guide the choice of tests for the family members. The index case or another family member with confirmed porphyria should be retested if necessary. Identification of a disease-causing mutation in an index case greatly facilitates detection of additional gene carriers as biochemical tests in latent carriers may be normal.

δ-AMINOLEVULINIC ACID DEHYDRATASE PORPHYRIA

This porphyria is sometimes termed *Doss porphyria* after the investigator who described the first cases. The term *plumboporphyria* emphasizes the similarity of this condition to lead poisoning, but incorrectly implies that it is due to lead exposure.

Etiology

This porphyria results from a deficiency of δ-aminolevulinic acid dehydratase (ALAD), which is inherited as an autosomal recessive trait. Only 6 cases have been confirmed by mutation analysis. The prevalence of heterozygous ALAD deficiency was estimated to be <1% in Germany and approximately 2% in Sweden.

Pathology and Pathogenesis

ALAD catalyzes the condensation of 2 molecules of ALA to form the pyrrole PBG (see Fig. 91-1). The enzyme is subject to inhibition by a number of exogenous and endogenous chemicals. ALAD is the principal lead-binding protein in erythrocytes, and lead can displace the zinc atoms of the enzyme. Inhibition of erythrocyte ALAD activity is a sensitive index of lead exposure.

Eleven abnormal ALAD alleles, most with point mutations, have been identified, some expressing partial activity, such that heme synthesis is partially preserved. The amount of residual enzyme activity may predict the phenotypic severity of this disease. Immunochemical studies in 3 cases demonstrated nonfunctional enzyme protein that cross-reacted with anti-ALAD antibodies. Five of the 6 reported ADP cases inherited a different ALAD mutation from each parent. One reported patient with late-onset disease who was heterozygous for a mutant allele developed ADP associated with a myeloproliferative disorder and expansion of an affected clone of erythroid cells.

ADP is often classified as a hepatic porphyria, although the site of overproduction of ALA is not established. A patient with severe, early-onset disease underwent liver transplantation, without significant clinical or biochemical improvement, which might suggest that the excess intermediates did not originate in the liver. Excess urinary coproporphyrin III in ADP might originate from metabolism of ALA to porphyrinogens in a tissue other than the site of ALA overproduction. Administration of large doses of ALA to normal subjects also leads to substantial coproporphyrinuria. Increased erythrocyte protoporphyrin may, as in all other homozygous porphyrias, be explained by accumulation of earlier pathway intermediates in bone marrow erythroid cells during hemoglobin synthesis, followed by their transformation to protoporphyrin after hemoglobin synthesis is complete. Neurologic symptoms are attributed to neurotoxic effects of ALA, but this is unproven.

Clinical Manifestations

In most cases, symptoms resemble other acute porphyrias, including acute attacks of abdominal pain and neuropathy. Precipitating factors, such as exposure to harmful drugs, have not been evident in most cases. Four of the reported cases were adolescent males. A Swedish infant had more severe disease, with neurologic impairment and failure to thrive. A 63 yr old man in Belgium developed an acute motor polyneuropathy concurrently with a myeloproliferative disorder.

Laboratory Findings

Urinary ALA, coproporphyrin III, and erythrocyte zinc protoporphyrin are substantially increased. Urinary PBG is normal or slightly increased. Erythrocyte ALAD activity is markedly reduced and both parents should have approximately half-normal activity of this enzyme and normal urinary ALA.

Diagnosis and Differential Diagnosis

The 3 other acute porphyrias are characterized by substantial increases in both ALA and PBG. In contrast, ALA but not PBG is substantially increased in ADP. A marked deficiency of erythrocyte ALAD and half-normal activity in the parents support the diagnosis. Other causes of ALAD deficiency, such as **lead poisoning,** must be excluded. Succinylacetone accumulates in hereditary tyrosinemia type 1 and is structurally similar to ALA, inhibits ALAD, and can cause increased urinary excretion of ALA and clinical manifestations that resemble acute porphyria. Idiopathic acquired ALAD deficiency has been reported. Unlike lead poisoning, the deficient ALAD activity in ADP is not restored by the in vitro addition of sulfhydryl reagents such as dithiothreitol. Even if no other cause of ALAD deficiency is found, it is essential to confirm the diagnosis of ADP by molecular studies.

Treatment

Treatment experience is limited but is similar to other acute porphyrias. Glucose seems not very effective but may be tried for mild symptoms. Hemin therapy was apparently effective for acute attacks in adolescent male cases, and weekly infusions prevented attacks in 2 of these cases. Hemin was not effective either biochemically or clinically in the Swedish child with severe disease, and produced a biochemical response but no clinical improvement in the Belgian man with a late-onset form, who had a peripheral neuropathy but no acute attacks. Hemin is also effective in treating porphyria-like symptoms associated with hereditary tyrosinemia, and can significantly reduce urinary ALA and coproporphyrin in lead poisoning. Avoidance of drugs that are harmful in other acute porphyrias is advisable. Liver transplantation was not effective in the child with severe disease.

Prognosis

The outlook is generally good in typical cases, although recurrent attacks may occur. The course was unfavorable in the Swedish child with more severe disease, and is uncertain in adults with late-onset disease associated with myeloproliferative disorders.

Prevention and Genetic Counseling

Heterozygous parents should be aware that subsequent children are at risk for the disease, as in any autosomal recessive disorder. Prenatal diagnosis is possible, but has not been reported.

ACUTE INTERMITTENT PORPHYRIA

This disorder is also termed *pyrroloporphyria, Swedish porphyria,* and *intermittent acute porphyria* and is the most common type of acute porphyria in most countries.

Etiology

AIP results from the deficient activity of the housekeeping form of PBGD. This enzyme is also known as hydroxymethylbilane (HMB)

synthase; the prior term, uroporphyrinogen I synthase, is obsolete. PBGD catalyzes the deamination and head-to-tail condensation of 4 PBG molecules to form the linear tetrapyrrole, HMB (also known as preuroporphyrinogen; see Fig. 91-1). A unique dipyrromethane cofactor binds the pyrrole intermediates at the catalytic site until 6 pyrroles (including the dipyrrole cofactor) are assembled in a linear fashion, after which the tetrapyrrole HMB is released. The apo-deaminase generates the dipyrrole cofactor to form the holodeaminase, and this occurs more readily from HMB than from PBG. Indeed, high concentrations of PBG may inhibit formation of the holodeaminase. The product HMB can cyclize nonenzymatically to form nonphysiologic uroporphyrinogen I, but in the presence of the next enzyme in the pathway is more rapidly cyclized to form uroporphyrinogen III.

Erythroid and housekeeping forms of the enzyme are encoded by a single gene on human chromosome 11 (11q24.1→q24.2), which contains 15 exons. The 2 isoenzymes are both monomeric proteins and differ only slightly in molecular weight (approximately 40 and 42 kDa, respectively), and result from alternative splicing of 2 distinct messenger RNA (mRNA) transcripts arising from 2 promoters. The housekeeping promoter functions in all cell types, including erythroid cells.

The pattern of inheritance of AIP is autosomal dominant, with very rare homozygous cases that present in childhood. More than 380 *PBGD* mutations, including missense, nonsense, and splicing mutations, and insertions and deletions have been identified in AIP, and in many population groups, including blacks. Most mutations are found in only 1 or a few families. But because of founder effects, some are more common in certain geographic areas such as northern Sweden (W198X), Holland (R116W), Argentina (G116R), Nova Scotia (R173W), and Switzerland (W283X). De novo mutations may be found in approximately 3% of cases. *Chester porphyria* was initially described as a variant form of acute porphyria in a large English family but was found to be caused by a *PBGD* mutation. The nature of the *PBGD* mutation does not account for the severity of the clinical presentation, which varies markedly within families.

Most mutations lead to approximately half-normal activity of the housekeeping and erythroid isozymes and half-normal amounts of their respective enzyme proteins in all tissues of heterozygotes. In approximately 5% of unrelated AIP patients, the housekeeping isozyme is deficient, but the erythroid-specific isozyme is normal. Mutations causing this variant are usually found within exon 1 or its 5′ splice donor site or initiation of translation codon. Immunochemical methods can distinguish mutations that are cross-reactive immunologic material (CRIM)–positive (i.e., having excess CRIM relative to the mutant enzyme activity), whereas CRIM-negative mutations either do not synthesize a mutant enzyme protein, or the protein is not stable and not immunologically detectable using anti-PBGD antibodies. A child with homozygous AIP was found to have inherited a different CRIM-positive mutation from each parent.

Pathology and Pathogenesis

Induction of the rate-limiting hepatic enzyme ALAS1 is thought to underlie acute exacerbations of this and the other acute porphyrias. AIP remains latent (or asymptomatic) in the great majority of those who are heterozygous carriers of *PBGD* mutations, and this is almost always the case before puberty. In those with no history of acute symptoms, porphyrin precursor excretion is usually normal, suggesting that half-normal hepatic PBGD activity is sufficient and hepatic ALAS1 activity is not increased. Many nongenetic factors that lead to clinical expression of AIP, including certain drugs and steroid hormones, have the capacity to induce hepatic ALAS1 and CYPs. Under conditions in which heme synthesis is increased in the liver, half-normal PBGD activity may become limiting and ALA, PBG, and other heme pathway intermediates may accumulate. In addition, heme synthesis becomes impaired and heme-mediated repression of hepatic ALAS1 is less effective.

It is not proven, however, that hepatic PBGD remains constant at approximately 50% of normal activity during exacerbations and remission of AIP, as in erythrocytes. An early report suggested that the enzyme activity is considerably less than half-normal in the liver during an acute attack. Hepatic PBGD activity might be reduced further once AIP becomes activated if, as suggested, excess PBG interferes with assembly of the dipyrromethane cofactor for this enzyme. It also seems likely that currently unknown genetic factors play a contributing role in, for example, patients who continue to have attacks even when known precipitants are avoided.

The fact that AIP is almost always latent before puberty suggests that **endocrine factors,** and especially adult levels of steroid hormones, are important for clinical expression. Symptoms are more common in women suggesting a role for female hormones. Premenstrual attacks are probably the result of endogenous progesterone. Acute porphyrias are sometimes exacerbated by exogenous steroids, including oral contraceptive preparations containing progestins. Surprisingly, pregnancy is usually well tolerated, suggesting that beneficial metabolic changes may ameliorate the effects of high levels of progesterone.

Drugs that are unsafe in acute porphyrias (Table 91-3) include those having the capacity to induce hepatic ALAS1, which is closely associated with induction of CYPs. Some chemicals (e.g., griseofulvin) can increase heme turnover by promoting the destruction of specific CYPs to form an inhibitor (e.g., *N*-methyl protoporphyrin) of ferrochelatase (FECH, the final enzyme in the pathway). Sulfonamide antibiotics are harmful but apparently not inducers of hepatic heme synthesis. Ethanol and other alcohols are inducers of ALAS1 and some CYPs.

Nutritional factors, principally reduced intake of calories and carbohydrates, as may occur with illness or attempts to lose weight, can increase porphyrin precursor excretion and induce attacks of porphyria. Increased carbohydrate intake may ameliorate attacks. Hepatic ALAS1 is modulated by the peroxisome proliferator-activated receptor γ coactivator-1α, which is an important link between nutritional status and exacerbations of acute porphyria.

Other factors have been implicated. Chemicals in cigarette smoke, such as polycyclic aromatic hydrocarbons, can induce hepatic CYPs and heme synthesis. A survey of AIP patients found an association between smoking and repeated porphyric attacks. Attacks may result from metabolic stress and impaired nutrition associated with major illness, infection, or surgery.

The additive effect of multiple predisposing factors, including drugs, endogenous hormones, nutritional factors, and smoking, is suggested by clinical observations. Exposure to drugs and other precipitating factors is less likely to cause an attack in patients who have had no recent symptoms than in those with recent and frequent porphyric symptoms.

Neurologic Mechanisms

The mechanism of neural damage in acute porphyrias is poorly understood. The most favored hypothesis at present is that 1 or more heme precursors, or perhaps a derivative, are neurotoxic. Increased ALA in AIP, HCP, VP, ADP, plumbism, and hereditary tyrosinemia type 1, which have similar neurologic manifestations, suggests that this substance or a derivative may be neuropathic. Porphyrins derived from ALA after its uptake into cells may have toxic potential. ALA can also interact with γ-aminobutyric acid receptors. Severe AIP improves markedly after allogeneic liver transplantation, which supports the hypothesis that heme precursors from the liver cause the neurologic manifestations.

Epidemiology

AIP occurs in all races and is the most common acute porphyria, with a roughly estimated prevalence in most countries of approximately 5 in 100,000. In Sweden, prevalence was estimated to be 7.7 in 100,000, including latent cases with normal porphyrin precursors. A much higher prevalence of 60-100 in 100,000 in northern Sweden is the result of a founder effect. The combined prevalence of AIP and VP in Finland is approximately 3.4 in 100,000. A survey of chronic psychiatric patients in the United States using an erythrocyte PBGD determination found a high prevalence (210 in 100,000) of PBGD deficiency, but a study in Mexico found a similar prevalence in psychiatric patients and controls. Population screening by erythrocyte PBGD activity or DNA analysis revealed a prevalence of 200 heterozygotes per 100,000

Table 91-3 Drugs Regarded as Unsafe and Safe in Acute Porphyrias

UNSAFE	SAFE
Barbiturates	Narcotic analgesics
Sulfonamide antibiotics*	Aspirin
Meprobamate* (also mebutamate,* tybutamate*)	Acetaminophen
Carisoprodol*	Phenothiazines
Glutethimide*	Penicillin and derivatives
Methyprylon	Streptomycin
Ethchlorvynol*	Glucocorticoids
Mephenytoin	Bromides
Phenytoin*	Insulin
Succinimides	Atropine
Carbamazepine*	Cimetidine
Clonazepam‡	Ranitidine†
Primidone*	Acetaminophen (paracetamol)
Valproic acid*	Acetazolamide
Pyrazolones (aminopyrine, antipyrine)	Allopurinol
Griseofulvin*	Amiloride
Ergots	Bethanidine
Metoclopramide*‡	Bumetanide
Rifampin*	Cimetidine
Pyrazinamide*‡	Coumarins
Diclofenac*‡	Fluoxetine
Progesterone and synthetic progestins*	Gabapentin
Danazol*	Gentamicin
Alcohol	Guanethidine
Angiotensin-converting enzyme inhibitors (especially enalapril)‡	Ofloxacin
Calcium channel blockers (especially nifedipine)‡	Propranolol
Ketoconazole	Succinylcholine Tetracycline

This partial listing does not include all available information about drug safety in acute porphyrias. Other sources should be consulted for drugs not listed here.

*Porphyria has been listed as a contraindication, warning, precaution, or adverse effect in U.S. labeling for these drugs. Estrogens are also listed as harmful in porphyria, but have been implicated as harmful in acute porphyrias mostly based only on experience with estrogen-progestin combinations. Although estrogens can exacerbate PCT, there is little evidence they are harmful in the acute porphyrias.

†Porphyria has been listed as a precaution in U.S. labeling for this drug. However, this drug is regarded as safe by other sources.

‡These drugs have been classified as probably safe by some sources, but this is controversial and they should be avoided.

people in Finland, and 1 in approximately 1,675 (60 in 100,000 people) in France. Therefore, carriers of *PBGD* mutations that can cause AIP may be common.

Clinical Manifestations

Neurovisceral manifestations of acute porphyrias may appear any time after puberty, but rarely before. Very rare cases of homozygous AIP develop severe neurologic manifestations early in childhood.

In affected heterozygotes, acute attacks are characterized by a constellation of nonspecific symptoms, which may become severe and life-threatening. **Abdominal pain** occurs in 85-95% of cases, is usually severe, steady, and poorly localized, but sometimes cramping, and accompanied by signs of ileus, including abdominal distention and decreased bowel sounds. Nausea, vomiting, and constipation are common, but increased bowel sounds and diarrhea may occur. Bladder dysfunction may cause hesitancy and dysuria. **Tachycardia,** the most common physical sign, occurs in up to 80% of attacks. This is often accompanied by hypertension, restlessness, coarse or fine tremors, and excess sweating, which are attributed to sympathetic overactivity and increased catecholamines. Other common manifestations include mental symptoms; pain in the extremities, head, neck, or chest; muscle weakness; and sensory loss. Because all these manifestations are neurologic rather than inflammatory, there is little or no abdominal tenderness, fever, or leukocytosis.

Porphyric neuropathy is primarily motor and appears to result from axonal degeneration rather than demyelinization. Sensory involvement is indicated by pain in the extremities, which may be described as muscle or bone pain, and by numbness, paresthesias, and dysesthesias. Paresis may occur early in an attack, but is more often a late manifestation in an attack that is not recognized and adequately treated. Rarely, severe neuropathy develops when there is little or no abdominal pain. Motor weakness most commonly begins in the proximal muscles of the upper extremities and then progresses to the lower extremities and the periphery. It is usually symmetric, but occasionally asymmetric or focal. Initially, tendon reflexes may be little affected or hyperactive and become decreased or absent. Cranial nerves, most commonly X and VII, may be affected, and blindness from involvement of the optic nerves or occipital lobes has been reported. More common central nervous system manifestations include seizures, anxiety, insomnia, depression, disorientation, hallucinations, and paranoia. Seizures may result from hyponatremia, porphyria itself, or an unrelated cause. Chronic depression and other mental symptoms occur in some patients, but attribution to porphyria is often difficult.

Hyponatremia is common during acute attacks. Inappropriate antidiuretic hormone secretion is often the most likely mechanism, but salt depletion from excess renal sodium loss, gastrointestinal loss, and poor intake have been suggested as causes of hyponatremia in some patients. Unexplained reductions in total blood and red blood cell volumes are sometimes found, and increased antidiuretic hormone secretion might then be an appropriate physiologic response. Other electrolyte abnormalities may include hypomagnesemia and hypercalcemia.

The attack usually resolves within several days, unless treatment is delayed. Abdominal pain may resolve within a few hours and paresis within a few days. Even severe motor neuropathy can improve over months or several years, but may leave some residual weakness. Progression of neuropathy to respiratory and bulbar paralysis and death is uncommon with appropriate treatment and removal of harmful drugs. Sudden death may result from cardiac arrhythmia.

Laboratory Findings

Levels of ALA and PBG are substantially increased during acute attacks and these may decrease after an attack but usually remain increased unless the disease becomes asymptomatic for a prolonged period. A population-based study in Sweden indicated that symptoms suggestive of porphyria may occur in heterozygotes during childhood, in contrast to adults, even when urinary porphyria precursors are not elevated. This study lacked a comparison with the frequency of such nonspecific symptoms in a control group of children.

Porphyrins are also markedly increased, which accounts for reddish urine in AIP. These are predominantly uroporphyrins, which can form nonenzymatically from PBG. But because the increased urinary porphyrins in AIP are predominantly isomer III, their formation is likely to be largely enzymatic, which might occur if excess ALA produced in the liver enters cells in other tissues and is then converted to porphyrins via the heme biosynthetic pathway. Porphobilin, a degradation product of PBG, and dipyrrylmethenes appear to account for brownish

urinary discoloration. Total fecal porphyrins and plasma porphyrins are normal or slightly increased in AIP. Erythrocyte protoporphyrin may be somewhat increased in patients with manifest AIP.

Erythrocyte PBGD activity is approximately half-normal in most patients (70-80%) with AIP. The normal range is wide and overlaps with the range for AIP heterozygotes. As noted, some PBGD gene mutations cause the enzyme to be deficient only in nonerythroid tissues. PBGD activity is also highly dependent on erythrocyte age, and an increase in erythropoiesis from concurrent illness in an AIP patient may raise the activity into the normal range.

Diagnosis and Differential Diagnosis

An increased urinary PBG establishes that a patient has 1 of the 3 most common acute porphyrias (see Table 91-2). Measuring PBG in serum is preferred when there is coexistent severe renal disease, but is less sensitive when renal function is normal. Measurement of urinary ALA is less sensitive than PBG and also less specific, but will detect ADP, the fourth type of acute porphyria. Erythrocyte PBGD activity is decreased in most AIP patients and helps confirm the diagnosis in a patient with high PBG. A normal enzyme activity in erythrocytes does not exclude AIP.

Knowledge of the *PBGD* mutation in a family enables reliable identification of other gene carriers. PBGD deficiency can be documented in a fetus by finding a *PBGD* mutation in these cells.

Complications

AIP and other acute porphyrias are commonly associated with mild abnormalities in liver function tests. The risk of more advanced liver disease and hepatocellular carcinoma is also increased during adult life, perhaps 60-70–fold, even in asymptomatic individuals who have increased porphyrins or porphyrin precursors. Few patients who developed this neoplasm had increases in serum α-fetoprotein. Patients with acute porphyrias, especially older than age 50 yr must be screened at least yearly by ultrasound or an alternative imaging method.

The risk of chronic hypertension and impaired renal function, most often with evidence of interstitial nephritis, is increased in AIP. A nephrotoxic effect of ALA may contribute. This may progress to severe renal failure and require renal transplantation.

Increased serum thyroxin levels because of increased thyroxin-binding globulin occur in some AIP patients. Hypercholesterolemia and elevated low-density lipoprotein cholesterol appear to be less common in this disorder than previously thought.

Treatment

Hemin

Intravenous hemin, combined with symptomatic and supportive measures, is the treatment of choice for most acute attacks of porphyria. There is a favorable biochemical and clinical response to early treatment with hemin, but less rapid clinical improvement if treatment is delayed. It is no longer recommended that therapy with hemin for a severe attack be started only after an unsuccessful trial of intravenous glucose for several days. Mild attacks, without severe manifestations such as paresis and hyponatremia, may be treated initially with intravenous glucose. After intravenous administration, hemin binds to hemopexin and albumin in plasma and is taken up primarily in hepatocytes. Hemin then enters and augments the regulatory heme pool in hepatocytes, represses the synthesis of hepatic ALAS1, and dramatically reduces porphyrin precursor overproduction.

Hemin* is available for IV administration in the United States as a lyophilized hematin preparation (Panhematin, Recordati). Degradation products begin to form as soon as the lyophilized product is reconstituted with sterile water, and these are responsible for phlebitis at the site of infusion and a transient anticoagulant effect. Loss of venous access due to phlebitis is common after repeated administration. Stabilization of lyophilized hematin by reconstitution with 30% human albumin can prevent these adverse effects, and is recommended, especially if a peripheral vein is used for the infusion. Uncommon side effects of hemin include fever, aching, malaise, hemolysis, anaphylaxis, and circulatory collapse. Heme arginate, a more stable hemin preparation, is available in Europe and South Africa.

Hemin treatment should be instituted only after a diagnosis of acute porphyria has been initially confirmed by a marked increase in urinary PBG (determined most rapidly using a kit). When prior documentation of the diagnosis is available for review, it is not essential to confirm an increase in PBG with every recurrent attack, if other causes of the symptoms are excluded clinically. The standard regimen of hemin for treatment of acute porphyric attacks is 3-4 mg/kg daily for 4 days. Lower doses have less effect on porphyrin precursor excretion and probably less clinical benefit.

*Hemin is the generic name for all heme preparations used for intravenous administration. Hemin is also a chemical term that refers to the oxidized (ferric) form of heme (iron protoporphyrin IX), and is usually isolated as hemin chloride. In alkaline solution, the chloride is replaced by the hydroxyl ion, forming hydroxyheme, or hematin.

General and Supportive Measures

Drugs that may exacerbate porphyrias (see Table 91-3) should be discontinued whenever possible, and other precipitating factors identified. Hospitalization is warranted, except for mild attacks, for treatment of severe pain, nausea, and vomiting; for administration of hemin and fluids; and for monitoring vital capacity, nutritional status, neurologic function, and electrolytes. Pain usually requires a narcotic analgesic; there is low risk for addiction after recovery from the acute attack. Ondansetron or a phenothiazine such as chlorpromazine is needed for nausea, vomiting, anxiety, and restlessness. Chloral hydrate or low doses of short-acting benzodiazepines can be given for restlessness or insomnia. β-Adrenergic blocking agents may be useful during acute attacks to control tachycardia and hypertension, but may be hazardous in patients with hypovolemia and incipient cardiac failure.

Carbohydrate Loading

The effects of carbohydrates on repressing hepatic ALAS1 and reducing porphyrin precursor excretion are weak compared to those of hemin. Therefore, only mild attacks (mild pain, no paresis or hyponatremia) are treated with carbohydrate loading. Glucose polymer solutions by mouth are sometimes tolerated. At least 300 g of intravenous glucose, usually given as a 10% solution, has been recommended for adults hospitalized with attacks of porphyria. Amounts up to 500 g daily may be more effective, but large volumes may favor development of hyponatremia.

Other Therapies

Liver transplantation was effective in several patients with severe AIP. A group from the United Kingdom reported their experience with liver transplantation in 10 AIP patients with significantly impaired quality of life and recurrent attacks which were refractory to medical management. Patients had a complete biochemical and symptomatic resolution posttransplantation; 2 patients in this series, however, succumbed to multiorgan failure posttransplantation. Liver transplantation is a high-risk procedure and should be considered as a last resort in patients with severe recurrent attacks that are refractory to other treatment. Cimetidine, a well-known inhibitor of hepatic CYPs, can prevent experimental forms of porphyria induced by chemical agents that undergo activation by these enzymes, but these models are not highly relevant to human AIP. The drug's use is based on uncontrolled observations.

Seizures and Other Complications

Seizures caused by hyponatremia or other electrolyte imbalances may not require prolonged treatment with anticonvulsant drugs, most of which have at least some potential for exacerbating acute porphyrias. Bromides, gabapentin, and probably vigabatrin are safe. Clonazepam may be less harmful than phenytoin or barbiturates. Control of hypertension may help prevent chronic renal impairment, which can progress and require renal transplantation.

Safe and Unsafe Drugs

Patients often do well with avoidance of harmful drugs. Table 91-3 lists some drugs known or strongly suspected to be harmful or safe in the

acute porphyrias. More extensive listings are available on websites of the European Porphyria Network (www.porphyria-europe.com) and the American Porphyria Foundation (www.porphyriafoundation.com), but some listings are controversial. Information regarding safety is lacking for many drugs, especially for those recently introduced.

Exogenous progestins, usually in combination with estrogens, can induce attacks of porphyria. Estrogens are seldom reported to be harmful when given alone or in animal and hepatocyte culture systems. Synthetic steroids with an ethynyl substituent can cause a mechanism-based destruction of hepatic CYPs and should probably be avoided in patients with acute porphyria. Danazol is especially contraindicated.

Other Situations

Major surgery can be carried out safely in patients with acute porphyria, especially if barbiturates are avoided. Halothane has been recommended as an inhalation agent and propofol and midazolam as intravenous induction agents.

Pregnancy is usually well tolerated, which is surprising, because levels of progesterone, a potent inducer of hepatic ALAS1, are considerably increased during pregnancy. Some women do experience continuing attacks during pregnancy. This has sometimes been attributed to reduced caloric intake or metoclopramide, a drug sometimes used to treat hyperemesis gravidarum and considered harmful in acute porphyrias.

Diabetes mellitus and other endocrine conditions are not known to precipitate attacks of porphyria. In fact, the onset of diabetes mellitus and resulting high circulating glucose levels may decrease the frequency of attacks and lower porphyrin precursor levels in AIP.

Prognosis

The outlook for patients with acute porphyrias has improved markedly in the past several decades. In Finland, for example, 74% of patients with AIP or VP reported that they led normal lives, and <30% had recurrent attacks during several years of follow-up. In those presenting with acute symptoms, recurrent attacks were most likely within the next 1-3 yr. Moreover, only 6% of gene carriers who had never had attacks developed symptoms. The improved outlook may result from earlier detection, better treatment of acute attacks, and replacement of harmful drugs such as barbiturates and sulfonamides with safer drugs. Some patients continue to have recurrent attacks, chronic pain, and other symptoms even after avoiding known exacerbating factors.

Prevention

For prevention of attacks, it is important to identify multiple inciting factors and remove as many as possible. Drugs for concurrent medical conditions should be reviewed. Because dietary factors are often inapparent, consultation with a dietitian may be useful. A well-balanced diet that is somewhat high in carbohydrate (60-70% of total calories) and sufficient to maintain weight is recommended. There is little evidence that additional dietary carbohydrate helps further in preventing attacks, and it may lead to weight gain. Patients who wish to lose excess weight should do so gradually and when they are clinically stable. Rapid weight loss after bariatric surgery may exacerbate acute porphyrias. Iron deficiency, which can be detected by a low serum ferritin, should be corrected.

Gonadotropin-releasing hormone analogs, which reversibly suppress ovulation, can be dramatically effective for preventing frequently recurring luteal phase attacks, but baseline and continuing gynecologic evaluation and bone density measurements are important, and transdermal estrogen or a bisphosphonate may be added to prevent bone loss. Hemin administered once or twice weekly can prevent frequent, noncyclic attacks of porphyria in some patients.

Genetic Counseling

Children with a family history of porphyria are often seen by pediatricians for evaluation and counseling. Information and laboratory results from a relative with proven porphyria must be reviewed in order to guide testing of the child, which is different depending on the type of acute porphyria. A mutation identified in the index case can be sought in the child. If the child is found to have inherited the mutation, counseling to avoid potentially harmful drugs is appropriate. Counseling should also emphasize that the great majority of those who inherit a *PBGD* mutation never develop symptoms, and the prognosis of those who do is favorable. Therefore, a normal, healthy life is expected, especially with avoidance of harmful drugs and other factors and prompt recognition and treatment of symptoms should they occur. Given the favorable outlook for most mutation carriers, even during pregnancy, having children is not precluded, and prenatal diagnosis of acute porphyrias is less important than it is for many other inherited diseases.

CONGENITAL ERYTHROPOIETIC PORPHYRIA

Also termed *Günther disease,* this rare disease usually presents with photosensitivity shortly after birth or in utero as nonimmune hydrops.

Etiology

CEP is an autosomal recessive disease caused by a marked deficiency of uroporphyrinogen III synthase (UROS). Many *UROS* mutations have been identified among CEP families. Later-onset disease in adults is likely to be associated with myeloproliferative disorders and expansion of a clone of erythroblasts that carry a *UROS* mutation.

Pathology and Pathogenesis

UROS, which is markedly deficient in CEP, catalyzes inversion of pyrrole ring D of HMB (the pyrrole ring shown on the right end of the molecule in Fig. 91-1) and rapid cyclization of the linear tetrapyrrole to form uroporphyrinogen III. This enzyme is also termed *uroporphyrinogen III cosynthase.* The human enzyme is a monomer. The gene for the enzyme is found on chromosome 10q25.3→q26.3, and contains 10 exons. Erythroid and housekeeping transcripts are generated by alternative promoters but encode the same enzyme.

In CEP, HMB accumulates in erythroid cells during hemoglobin synthesis and cyclizes nonenzymatically to form uroporphyrinogen I, which is auto-oxidized to uroporphyrin I. Some of the uroporphyrinogen I that accumulates is metabolized to coproporphyrinogen I, which accumulates because it is not a substrate for coproporphyrinogen oxidase. Thus, both uroporphyrin I and coproporphyrin I accumulate in the bone marrow and are then found in circulating erythrocytes, plasma, urine, and feces.

A variety of *UROS* mutations have been identified in CEP, including missense and nonsense mutations, large and small deletions and insertions, splicing defects, and intronic branch point mutations. At least 4 mutations have been identified in the erythroid-specific promoter. Many patients inherited a different mutation from each parent, and most mutations have been detected in only 1 or a few families. An exception is a common mutation, C73R, which is at a mutational hotspot and was found in ≈33% of alleles. One child with CEP had a *GATA1* mutation, with no *UROS* mutation. The CEP phenotype may be modulated by gain of function *ALAS2* mutations, which were first identified as causing XLP.

Genotype–phenotype correlations have been based on the in vitro expression of various CEP mutations and the severity of associated phenotypic manifestations. The C73R allele, which is associated with a severe phenotype in homozygotes or in patients heteroallelic for C73R and another mutation expressing little residual activity, resulted in <1% of normal enzyme activity. Patients with the C73R allele and heteroallelic for other mutations expressing more residual activity have milder disease.

Hemolysis is a common feature of CEP. Excess porphyrins in circulating erythrocytes cause cell damage, perhaps by a phototoxic mechanism, leading to both intravascular hemolysis and increased splenic clearance of erythrocytes. Also important is ineffective erythropoiesis, with intramedullary destruction of porphyrin-laden erythroid cells and breakdown of heme. Expansion of the bone marrow as a result of erythroid hyperplasia may contribute to **bone loss.** Nutrient deficiencies sometimes cause erythroid hypoplasia. Despite the marked deficiency of UROS, heme production in the bone marrow is increased because of hemolysis and a compensatory increase in hemoglobin

Figure 91-2 Congenital erythropoietic porphyria. The diaper of an affected baby demonstrates the red color of urine. *(From Paller AS, Macini AJ:* Hurwitz clinical pediatric dermatology, *ed 3, Philadelphia, 2006, Elsevier Saunders, p. 517.)*

Figure 91-3 Congenital erythropoietic porphyria. Vesicles, bullae, and crusts on sun-exposed areas. *(From Paller AS, Macini AJ:* Hurwitz clinical pediatric dermatology, *ed 3, Philadelphia, 2006, Elsevier Saunders, p. 517.)*

Figure 91-4 Congenital erythropoietic porphyria. Brownish teeth that fluoresce under Wood lamp examination. *(From Paller AS, Macini AJ:* Hurwitz clinical pediatric dermatology, *ed 3, Philadelphia, 2006, Elsevier Saunders, p. 517.)*

production. This occurs, however, at the expense of marked accumulation of HMB, which is converted to porphyrinogens and porphyrins.

Clinical Manifestations

In severe cases, CEP can cause fetal loss, or be recognized in utero as intrauterine hemolytic anemia and **nonimmune hydrops fetalis.** CEP may be associated with neonatal hyperbilirubinemia, and **phototherapy may unintentionally induce severe photosensitivity and scarring.**

The most characteristic presentation is reddish urine or pink staining of diapers by urine or meconium shortly after birth (Fig. 91-2). With sun exposure, severe blistering lesions appear on exposed areas of skin on the face and hands, and have been termed *hydroa aestivale* because they are more severe with greater sunlight exposure during summer (Fig. 91-3). Vesicles and bullae, as well as friability, hypertrichosis, scarring, thickening, and areas of hypopigmentation and hyperpigmentation are very similar to those seen in PCT but usually much more severe. Infection and scarring sometimes cause loss of facial features and fingers and damage to the cornea, ears, and nails. Porphyrins are deposited in dentine and bone in utero. Reddish-brown teeth in normal light, an appearance termed **erythrodontia,** display reddish fluorescence under long-wave UV light (Fig. 91-4). Unaffected children born to a mother with CEP may have erythrodontia. Hemolysis and splenomegaly are common in CEP. Bone marrow compensation may be adequate, especially in milder cases. Patients with severe phenotypes, however, are often transfusion-dependent. Splenomegaly may contribute to the anemia and cause leukopenia and thrombocytopenia, which may be complicated by significant bleeding. Neuropathic symptoms are absent, and there is no sensitivity to drugs, hormones, and carbohydrate restriction. The liver may be damaged by iron overload or viral hepatitis acquired from blood transfusions.

Milder cases of CEP with onset of symptoms in adult life and without erythrodontia may mimic PCT. These late-onset cases are likely to be associated with myeloproliferative disorders, and expansion of a clone of cells carrying a *UROS* mutation.

Laboratory Findings

Urinary porphyrin excretion and circulating porphyrin levels in CEP are much higher than in almost all other porphyrias. Urinary porphyrin excretion can be as high as 50-100 mg daily, and consists mostly of uroporphyrin I and coproporphyrin I. ALA and PBG are normal. Fecal porphyrins are markedly increased, with a predominance of coproporphyrin I.

Marked increases in erythrocyte porphyrins in CEP consist mostly of uroporphyrin I and coproporphyrin I. These porphyrins are also increased in bone marrow, spleen, plasma, and, to a lesser extent, liver. The porphyrin pattern in erythrocytes is influenced by rates of erythropoiesis and erythroid maturation. A predominance of protoporphyrin has been noted in some CEP patients, and in 1 such patient, uroporphyrin and coproporphyrin increased when erythropoiesis was stimulated by blood removal.

Diagnosis and Differential Diagnosis

The diagnosis of CEP should be documented by full characterization of porphyrin patterns and identification of the underlying mutations. In later-onset cases, an underlying myeloproliferative disorder and a UROS somatic mutation should be suspected and studied in detail.

The clinical picture in hepatoerythropoietic porphyria (HEP) may be very similar, but the porphyrin patterns in urine and feces in HEP resemble PCT. A predominant increase in erythrocyte protoporphyrin is unusual in CEP but is characteristic of HEP, and rare homozygous cases of AIP, HCP, and VP. EPP is also distinguished by normal urinary porphyrins and by increases in erythrocyte metal-free protoporphyrin, whereas the increased protoporphyrin in other conditions is complexed with zinc.

CEP should be suspected as a cause of nonimmune hydrops or hemolytic anemia in utero. With recognition of the disease at this stage, intrauterine transfusion can be considered, and severe, scarring photosensitivity from phototherapy for hyperbilirubinemia avoided. Prenatal diagnosis is feasible by finding red-brown discoloration and increased porphyrins in amniotic fluid, and measuring porphyrins in fetal erythrocytes and plasma. UROS activity can be measured in cultured amniotic fluid cells, or *UROS* mutations identified in chorionic villi or cultured amniotic cells.

Treatment

Protection from sunlight exposure, minimizing skin trauma, and prompt treatment of any cutaneous infections are highly important in managing CEP. Sunscreen lotions and beta-carotene are sometimes beneficial. Transfusions to achieve a level of hemoglobin sufficient to suppress erythropoiesis significantly can be quite effective in reducing porphyrin levels and photosensitivity. Concurrent deferoxamine to reduce iron overload, and hydroxyurea to suppress erythropoiesis further may provide additional benefit. Splenectomy reduces hemolysis and transfusion requirements in some patients. Oral charcoal may increase fecal loss of porphyrins, but may contribute little in more severe cases. Intravenous hemin may be somewhat effective, but has not been extensively studied and seems unlikely to provide long-term benefit.

The most effective treatment is bone marrow or stem cell transplantation in early childhood, which has markedly reduced porphyrin levels and photosensitivity and increased long-term survival.

Prognosis

The outlook is favorable in milder cases and in patients with more severe disease especially after successful bone marrow or stem cell transplantation.

Prevention and Genetic Counseling

Genetic counseling is important for affected families, because CEP can be recognized before birth and a severe phenotype can often be predicted by identifying the nature of the UROS mutations.

PORPHYRIA CUTANEA TARDA

PCT is the most common and readily treated human porphyria (see Table 91-2). It occurs in mid or late adult life, and is rare in children. Previous terms include *symptomatic porphyria, PCT symptomatica,* and *idiosyncratic porphyria.* The underlying cause is a liver-specific, acquired deficiency of uroporphyrinogen decarboxylase (UROD) with contributions by several types of genetic and acquired factors. Heterozygous *UROD* mutations are found in familial PCT. HEP, the homozygous form of familial PCT, usually has a more severe presentation in childhood, resembling CEP clinically.

Etiology

PCT is caused by a reduction of hepatic UROD activity to 20% of normal activity or less. An inhibitor of hepatic UROD has been characterized as uroporphomethene, which is derived from partial oxidation of the enzyme substrate uroporphyrinogen. CYPs, such as CYP1A2, as well as iron, are involved in its formation (Fig. 91-5). Although enzyme activity is inhibited, the amount of hepatic enzyme protein measured immunochemically remains at its genetically determined level.

UROD catalyzes the decarboxylation of the 4 acetic acid side chains of uroporphyrinogen (an octacarboxyl porphyrinogen) to form

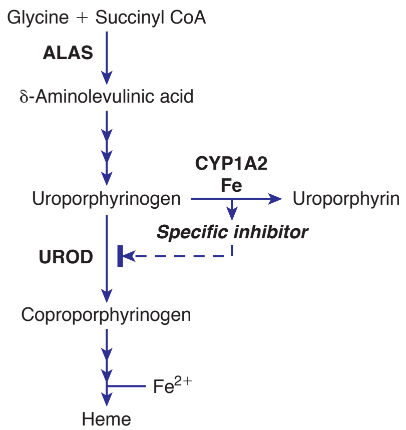

Figure 91-5 Formation of a specific inhibitor of uroporphyrinogen decarboxylase in the liver in porphyria cutanea tarda. ALAS, δ-aminolevulinic acid synthase; CYP1A2, cytochrome P450 1A2; UROD, uroporphyrinogen decarboxylase.

coproporphyrinogen (a tetracarboxyl porphyrinogen) (see Fig. 91-1). The enzyme reaction occurs in a sequential, clockwise fashion, with the intermediate formation of hepta-, hexa-, and pentacarboxyl porphyrinogens. Uroporphyrinogen III, as compared with other uroporphyrinogen isomers, is the preferred substrate. Human UROD is a dimer with the 2 active site clefts juxtaposed. The UROD gene is on chromosome 1p34 and contains 10 exons, with only 1 promoter. Therefore, the gene is transcribed as a single mRNA in all tissues.

The majority of PCT patients (i.e., ≈80%) have no *UROD* mutations and are said to have sporadic (type 1) disease. Some are heterozygous for *UROD* mutations and are said to have familial (type 2) PCT. Described mutations include missense, nonsense, and splice-site mutations, several small and large deletions, and small insertions, with only a few identified in more than 1 family. A few of these mutations may be located near the active site cleft, but most appear to involve regions with important structural roles. Being heterozygous for a *UROD* mutation is insufficient to cause PCT unless a UROD inhibitor is also generated. Because penetrance of the genetic trait is low, many patients with familial PCT have no family history of the disease.

Induction of hepatic ALAS1 is not a prominent feature in PCT, although alcohol may increase this enzyme slightly. Iron and estrogens are also not potent inducers of ALAS1 and drugs that are potent inducers of ALAS1 and CYPs are much less commonly implicated in PCT than in acute porphyrias.

Blistering skin lesions result from porphyrins that are released from the liver. Sunlight exposure leads to generation of reactive oxygen species in the skin, complement activation, and lysosomal damage.

Epidemiology

Differences in prevalence probably relate to geographic variations in susceptibility factors such as hepatitis C and ethanol use. The yearly incidence in the United Kingdom was estimated at 2-5 in 1,000,000 in the general population, and the prevalence in the United States and Czechoslovakia was estimated at approximately 1 in 25,000 and 1 in 5,000 in the general population, respectively. The disease was reported to be prevalent in the Bantus of South Africa in association with iron overload. PCT is more common in males, possible because of greater alcohol intake, and in women it is commonly associated with estrogen use.

A massive outbreak of PCT occurred in eastern Turkey in the 1950s. Wheat intended for planting and treated with hexachlorobenzene as a fungicide was consumed by many at a time of food shortage. Cases and small outbreaks of PCT after exposure to other chemicals including di- and trichlorophenols and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin) have been reported. The manifestations improved in most cases when the exposure was stopped. There are reported cases of delayed onset many years after chemical exposure.

Pathology and Pathogenesis

PCT is currently classified into 3 clinically similar types. Generation of a UROD inhibitor in the liver plays an important role in all 3 types. The 80% of patients with **type 1 (sporadic)** PCT have no UROD mutations, and UROD activity is normal in nonhepatic tissues such as erythrocytes. In **familial (type 2)** PCT, a heterozygous *UROD* mutation results in a partial (approximately 50%) deficiency of UROD in all tissues from birth, and the disease becomes active in some heterozygotes when other susceptibility factors are present and a UROD inhibitor is generated in the liver, reducing hepatic UROD activity to 20% of normal or less. HEP results from inheritance of a *UROD* mutation from each parent and typically cause severe photosensitivity resembling CEP starting in early childhood. Some compound heterozygotes have developed symptoms in childhood more typical of PCT. **Type 3** is rare, and describes PCT with normal erythrocyte UROD activity occurring in more than 1 family member. Another genetic basis, such as *HFE* mutations, may be identified in type 3.

CYPs, especially CYP1A2, can catalyze the oxidation of uroporphyrinogen to uroporphyrin. This uroporphyrinogen oxidase activity is

enhanced by iron, and leads to formation of a UROD inhibitor (see Fig. 91-5). CYP1a2 seems essential for development of uroporphyria in rodents, because experimental uroporphyria does not develop in *CYP1a2* knockout mice.

Susceptibility Factors

The following factors are implicated in the development of PCT, and these occur in various combinations in individual patients.

Iron

A normal or increased amount of iron in the liver is essential for developing PCT, and treatment by phlebotomy to reduce hepatic iron leads to remission. Serum ferritin levels are usually in the upper part of the normal range or moderately increased and liver histology commonly shows increased iron staining. Prevalence of the C282Y mutation of the *HFE* gene, which is the major cause of hemochromatosis in people of northern European ancestry, is increased in both type 1 and type 2 PCT, and approximately 10% of patients are C282Y homozygotes. In southern Europe, the H63D mutation is more commonly associated. PCT may develop in patients with secondary iron overload. Reduced hepatic expression of the hormone hepcidin occurs in hemochromatosis and also in PCT, regardless of *HFE* genotype, which may explain hepatic siderosis in this condition.

Hepatitis C

This viral infection is highly prevalent in PCT in most geographic locations; in the United States, for example, it is present in 56-74% of cases, which is similar to rates in southern Europe. Prevalence of hepatitis C in PCT is lower in northern Europe (<20%). Steatosis and oxidative stress in hepatitis C may favor iron-mediated generation of reactive oxygen species and a UROD inhibitor. Dysregulation of hepcidin occurs in hepatitis C and may lead to increased iron absorption.

HIV

Many reports suggest that HIV infection can contribute to the development of PCT, although less commonly than does hepatitis C.

Ethanol

The long-recognized association between alcohol and PCT may be explained by the generation of active oxygen species, which may cause oxidative damage, mitochondrial injury, depletion of reduced glutathione and other antioxidant defenses, increased production of endotoxin, and activation of Kupffer cells. Alcohol may contribute to iron overload by impairing hepcidin production.

Smoking and Cytochrome P450 Enzymes

Smoking has not been extensively studied as a susceptibility factor but is commonly associated with alcohol use in PCT. It may act to induce hepatic CYPs and oxidative stress. Hepatic CYPs are thought to be important in oxidizing uroporphyrinogen and generating a UROD inhibitor (see Fig. 91-5). Genetic polymorphisms of *CYP1A2* and *1A1* have been implicated in human PCT. The frequency of an inducible *CYP1A2* genotype was more common in PCT patients than in controls in several studies.

Antioxidant Status

Ascorbic acid deficiency contributes to uroporphyria in laboratory models and perhaps in human PCT. In 1 series, plasma ascorbate levels were substantially reduced in 84% of patients with PCT. Low levels of serum carotenoids were also described, further suggesting that oxidant stress in hepatocytes is important in PCT.

Estrogens

Use of estrogen-containing oral contraceptives or postmenopausal estrogen replacement is very commonly associated with PCT (type 1 or 2) in women. PCT sometimes occurs during pregnancy, although it is not clear whether the risk is increased.

Clinical Manifestations

Cutaneous Manifestations

PCT is readily recognized by blistering and crusted skin lesions on the backs of the hands, which are the most sun-exposed areas of the body, and somewhat less commonly on the forearms, face, ears, neck, legs, and feet. The fluid-filled vesicles commonly rupture and become crusted or denuded areas, heal slowly, and are subject to infection. The skin on the backs of the hands is characteristically friable, and minor trauma may cause blisters or denudation of skin. Small white plaques, termed milia, may precede or follow vesicle formation. Facial hypertrichosis and hyperpigmentation are also common. Severe scarring and thickening of sun-exposed skin may resemble scleroderma. Skin biopsy findings include subepidermal blistering and deposition of periodic acid–Schiff-positive material around blood vessels and fine fibrillar material at the dermoepithelial junction, which may relate to excessive skin fragility. Immunoglobulin G, other immunoglobulins, and complement are also deposited at the dermoepithelial junction and around dermal blood vessels. The skin lesions and histologic changes are not specific for PCT. The same findings occur in VP and HCP, and resemble those of CEP and HEP, but are usually less severe. PCT usually develops in mid or late adult life. Earlier onset may be seen in those with UROD or *HFE* mutations. Childhood onset is rare, and suggests heterozygosity or even compound heterozygosity for UROD mutations.

Liver Abnormalities

PCT is almost always associated with nonspecific liver abnormalities, especially increased serum transaminases and γ-glutamyltranspeptidase, even in the absence of heavy alcohol intake or hepatitis C. Most histologic findings, such as necrosis, inflammation, increased iron, and increased fat, are nonspecific. Specific findings include red fluorescence of liver tissue, and fluorescent, birefringent, needle-like inclusions presumably consisting of porphyrins. Electron microscopy shows these inclusions are in lysosomes, and paracrystalline inclusions are found in mitochondria. Distorted lobular architecture and cirrhosis are more common with long-standing disease.

The risk of developing hepatocellular carcinoma is increased, with reported incidences ranging from 4-47% in PCT. These tumors seldom contain large amounts of porphyrins.

Other Findings and Associations

Mild or moderate erythrocytosis in some adult patients is not well understood, but chronic lung disease from smoking may contribute. An earlier onset of symptoms may be noted in patients with genetic predisposing factors, such as an inherited partial deficiency of UROD or the C282Y/C282Y *HFE* genotype. Iron overload secondary to conditions such as myelofibrosis and end-stage renal disease may be associated with PCT. The disease can be especially severe in patients with end-stage renal disease, because the lack of urinary excretion leads to much higher concentrations of porphyrins in plasma, and the excess porphyrins are poorly dialyzable. PCT occurs more frequently in patients with systemic lupus erythematosus and other immunologic disorders than would have been expected by chance.

Laboratory Findings

Porphyrins accumulate in the liver mostly as the oxidized porphyrins rather than porphyrinogens in PCT, as indicated by the immediate red fluorescence observed in liver tissue. This develops over weeks or months before porphyrins appear in plasma and are transported to the skin, causing photosensitivity. In contrast to the acute hepatic porphyrias, only a very small increase in synthesis of heme pathway intermediates and little or no increase in hepatic ALAS1 are required to account for the excess porphyrins excreted in PCT.

Hepatic UROD deficiency leads to a complex pattern of excess porphyrins, which initially accumulate as porphyrinogens, and then undergo nonenzymatic oxidation to the corresponding porphyrins (uro-, hepta-, hexa-, and pentacarboxyl porphyrins, and isocoproporphyrins). Uroporphyrin and heptacarboxyl porphyrin predominate in

urine, with lesser amounts of coproporphyrin and penta- and hexacarboxyl porphyrin. A normally minor pathway is accentuated by UROD deficiency, whereby pentacarboxyl porphyrinogen is oxidized by coproporphyrinogen oxidase (CPOX; the next enzyme in the pathway), forming isocoproporphyrinogen, an atypical tetracarboxyl porphyrinogen. Relative to normal values, urinary porphyrins are increased to a greater extent than fecal porphyrins. However, the total amount of porphyrins excreted in feces in PCT exceeds that in urine, and total excretion of type III isomers (including isocoproporphyrins, which are mostly derived from the type III series) exceeds that of type I isomers. Perhaps because uroporphyrinogen III is the preferred substrate for UROD, more uroporphyrinogen I than III accumulates and is excreted in PCT. Hepta- and hexacarboxyl porphyrin are mostly isomer III; and pentacarboxyl porphyrin and coproporphyrin are approximately equal mixtures of isomers I and III.

Diagnosis and Differential Diagnosis

Plasma porphyrins are always increased in clinically manifest PCT, and a total plasma porphyrin determination is most useful for screening. A normal value rules out PCT and other porphyrias that produce blistering skin lesions. If increased, it is useful to determine the plasma fluorescence emission maximum at neutral pH, because a maximum near 619 nm is characteristic of PCT (as well as CEP and HCP) and, most important, excludes VP, which has a distinctly different fluorescence maximum. Increased urinary porphyrins, with a predominance of uroporphyrin and heptacarboxyl porphyrin, is confirmatory. Urine porphyrins are less useful for initial screening because nonspecific increases, especially of coproporphyrin, occur in liver disease and other medical conditions. Urinary ALA may be increased slightly, and PBG is normal.

Familial (type 2) can be distinguished from sporadic (type 1) PCT by finding decreased erythrocyte UROD activity (in type 2), or more reliably by finding a disease-related *UROD* mutation. Type 3 is distinguished from type 1 only by occurrence of PCT in a relative. Biochemical findings in HEP are similar to those in PCT, but with an additional marked increase in erythrocyte zinc protoporphyrin.

Pseudoporphyria (also known as pseudo-PCT) presents with skin lesions that closely resemble PCT, but without significant increases in plasma porphyrins. A photosensitizing drug such as a nonsteroidal antiinflammatory agent is sometimes implicated. Both PCT and pseudoporphyria may occur in patients with end-stage renal disease.

Complications

Cutaneous blisters may rupture and become infected, sometimes leading to cellulitis. In more-severe disease in patients with end-stage renal disease, repeated infections can be mutilating, as in CEP. Pseudoscleroderma, with scarring, contraction, and calcification of skin and subcutaneous tissue, is a rare complication. Other complications include advanced liver disease and hepatocellular carcinoma.

Treatment

Two specific and effective forms of treatment, namely phlebotomy or low-dose hydroxychloroquine, are available. Susceptibility factors should be removed when possible. The diagnosis of PCT must be firmly established, because conditions that produce identical cutaneous lesions do not respond to these treatments. Treatment can usually be started after demonstrating an increase in plasma total porphyrins and excluding VP by analysis of the fluorescence spectrum at neutral pH, while urine and fecal studies are still pending. Use of alcohol, estrogens (in women), and smoking should be stopped, and patients tested for hepatitis C, HIV, and *HFE* mutations. Some susceptibility factors and the degree of iron overload as assessed by the serum ferritin concentration, influence the choice of treatment.

Phlebotomy is considered standard therapy, and is effective both in children and adults with PCT because it reduces hepatic iron content. Treatment is guided by plasma (or serum) ferritin and porphyrin levels. Hemoglobin or hematocrit levels should be followed to prevent symptomatic anemia. For adults, a unit of blood (≈450 mL) is removed at about 2 wk intervals until a target serum ferritin near the lower limit of normal (≈15 ng/mL) is achieved. A total of 6-8 phlebotomies is often sufficient. After this, plasma porphyrin concentrations continue to fall from pretreatment levels (generally 10-25 µg/dL) to below the upper limit of normal (≈1 µg/dL), usually after several more weeks. This is followed by gradual clearing of skin lesions, sometimes including pseudoscleroderma. Liver function abnormalities may improve, and hepatic siderosis, needle-like inclusions, and red fluorescence of liver tissue will disappear. Although remission usually persists even if ferritin levels later return to normal, it is advisable to follow porphyrin levels and reinstitute phlebotomies if these begin to rise. Infusions of deferoxamine, an iron chelator, may be used when phlebotomy is contraindicated.

An alternative when phlebotomy is contraindicated or poorly tolerated is a low-dose regimen of hydroxychloroquine (or chloroquine). Normal doses of these 4-aminoquinoline antimalarials increase plasma and urinary porphyrin levels and increase photosensitivity in PCT, reflecting an outpouring of porphyrins from the liver. This is accompanied by acute hepatocellular damage, with fever, malaise, nausea, and increased serum transaminases, but is followed by complete remission of the porphyria. These adverse consequences of normal doses are largely avoided by a low-dose regimen (hydroxychloroquine 100 mg or chloroquine 125 mg, of a normal tablet, twice weekly), which can be continued until plasma or urine porphyrins are normalized. There is at least some risk of retinopathy, which may be lower with hydroxychloroquine. The mechanism of action of 4-aminoquinolines in PCT is not known but is quite specific, because these drugs are not useful in other porphyrias. Recent studies indicate that low-dose hydroxychloroquine is as safe and effective as phlebotomy in PCT.

In patients with PCT and hepatitis C, PCT should be treated first because this condition is more symptomatic and can be treated more quickly and effectively. Treatment of PCT by phlebotomy may not be possible once interferon-ribavirin treatment is complicated by anemia. Moreover, treatment of hepatitis C may be more effective after iron reduction.

PCT in patients with end-stage renal disease is often more severe and difficult to treat. However, erythropoietin administration can correct anemia, mobilize iron, and support phlebotomy in many cases. Improvement after renal transplantation may be partly from resumption of endogenous erythropoietic production.

Liver imaging and a serum α-fetoprotein determination may be advisable in all PCT patients, perhaps at 6-12 mo intervals, for early detection of hepatocellular carcinoma. Finding low-erythrocyte UROD activity or a *UROD* mutation identifies those with an underlying genetic predisposition, which does not alter treatment but is useful for genetic counseling.

Prognosis

PCT is the most readily treated form of porphyria, and complete remission is expected with treatment either by phlebotomy or low-dose hydroxychloroquine. There is little information on rates of recurrence and long-term outlook. Risk for hepatocellular carcinoma is increased, and some susceptibility factors such as hepatitis C can lead to complications even after PCT is in remission.

Prevention and Genetic Counseling

Patients with PCT may have concerns about risk to other family members. A heritable *UROD* mutation can usually be detected or excluded by measuring erythrocyte UROD activity, although DNA studies are more sensitive. Relatives of patients with *UROD* mutations have an increased risk for developing PCT, and may have increased motivation to avoid adverse behaviors such as ethanol and tobacco use and exposures to hepatitis C and HIV. Such counseling would be given to anyone, however. The finding of *HFE* mutations, and especially C282Y, should prompt screening of relatives, some of whom may be C282Y homozygotes and warrant lifelong monitoring of serum ferritin.

HEPATOERYTHROPOIETIC PORPHYRIA

HEP, which is the homozygous form of familial (type 2) PCT, resembles CEP clinically. Excess porphyrins originate mostly from liver, with

a pattern consistent with severe UROD deficiency. This rare disorder has no particular racial predominance.

Etiology
HEP is an autosomal recessive disorder, although most patients have inherited a different mutation from unrelated parents. In contrast to most mutations in familial (type 2) PCT, most causing HEP are associated with expression of some residual enzyme activity. At least 1 genotype is associated with the predominant excretion of pentacarboxyl porphyrin.

Pathology and Pathogenesis
Excess porphyrins originate primarily from the liver in HEP, although the substantial increase in erythrocyte zinc protoporphyrin indicates that the heme biosynthetic pathway is also impaired in bone marrow erythroid cells. Apparently, porphyrinogens accumulate in the marrow while hemoglobin synthesis is most active, and are metabolized to protoporphyrin after hemoglobin synthesis is complete. The cutaneous lesions are a result of photoactivation of porphyrins in skin, as in other cutaneous porphyrias.

Clinical Manifestations
Like CEP, this disease usually presents with blistering skin lesions, hypertrichosis, scarring, and red urine in infancy or childhood. Sclerodermoid skin changes are sometimes prominent. Unusually mild cases have been described. Concurrent conditions that affect liver function can alter disease severity. For example, the disease became manifest because of hepatitis A in a 2 yr old child, and then improved with recovery of liver function.

Laboratory Findings
Biochemical findings resemble those in PCT with accumulation and excretion of uroporphyrin, heptacarboxyl porphyrin, and isocoproporphyrin. But in addition, erythrocyte zinc protoporphyrin is substantially increased.

Diagnosis and Differential Diagnosis
HEP is distinguished from CEP by increases in both uroporphyrin and heptacarboxyl porphyrin, and isocoproporphyrins. In CEP, the excess erythrocyte porphyrins are predominantly uroporphyrin and coproporphyrin rather than protoporphyrin. Blistering skin lesions are unusual in EPP, the excess erythrocyte protoporphyrin in that disease is free and not complexed with zinc, and urinary porphyrins are normal.

Treatment and Prognosis
Avoiding sunlight exposure is most important in managing this disease, as in CEP. Oral charcoal was helpful in a severe case associated with dyserythropoiesis. Phlebotomy has shown little or no benefit. The outlook depends on the severity of the enzyme deficiency and may be favorable if sunlight can be avoided.

Prevention and Genetic Counseling
As part of genetic counseling in affected families, it is feasible to diagnose HEP in utero, either by analysis of porphyrins in amniotic fluid or DNA studies.

HEREDITARY COPROPORPHYRIA
This autosomal dominant hepatic porphyria is caused by a deficiency of CPOX. The disease presents with acute attacks, as in AIP. Cutaneous photosensitivity may occur, but much less commonly than in VP. Rare homozygous cases present in childhood.

Etiology
A partial (50%) deficiency in CPOX activity has been found in all cells studied from patients with HCP. A much more profound deficiency is found in homozygous cases. Human CPOX is a homodimer composed of 39 kDa subunits, and contains no metals or prosthetic groups. The enzyme requires molecular oxygen, and is localized in the mitochondrial intermembrane space. A single active site on the enzyme catalyzes the oxidative decarboxylation of 2 of the 4 propionic acid groups of coproporphyrinogen III to form the 2 vinyl groups at positions 2 and 4, on rings A and B, respectively, of protoporphyrinogen IX (see Fig. 91-1). Most of the intermediate tricarboxyl porphyrinogen, termed *harderoporphyrinogen,* is not released before undergoing the second decarboxylation to protoporphyrinogen IX. Coproporphyrinogen I is not a substrate for this enzyme.

The human *CPOX* gene contains 7 exons and is located on chromosome 3q12.1. A single promoter contains elements for both housekeeping and erythroid-specific expression. A variety of *CPOX* gene mutations have been described in HCP, with a predominance of missense mutations and no genotype-phenotype correlations. Harderoporphyria, an autosomal recessive biochemical variant form of HCP, is caused by *CPOX* mutations that impair substrate binding, leading to premature release of harderoporphyrinogen.

Epidemiology
HCP is less common than AIP and VP, but its prevalence has not been carefully estimated. There is no obvious racial predominance. Homozygous HCP is rare and presents during childhood. Harderoporphyria, a biochemically distinguishable variant of HCP, has been recognized in heteroallelic and homoallelic forms.

Pathology and Pathogenesis
Increased ALA and PBG during acute attacks of HCP may be explained by induction of ALAS1 and by the normally relatively low activity of PBGD in the liver. Hepatic ALAS1 is increased during acute attacks, but is normal when the disease is latent and porphyrin precursor excretion is normal. Because coproporphyrinogen III concentration in the liver is probably less than the K_m for CPOX, the reaction rate is likely to be determined in part by substrate concentration. The substrate coproporphyrinogen appears to be lost more readily from the liver cell than, for example, uroporphyrinogen, especially when heme synthesis is stimulated. Coproporphyrin and coproporphyrinogen are both transported into bile and excreted in urine, and do not appear to accumulate in the liver in HCP.

Clinical Manifestations
Symptoms are identical to those of AIP except that attacks are generally milder, and cutaneous lesions that resemble those in PCT develop occasionally. Severe motor neuropathy and respiratory paralysis can occur. Like other acute porphyrias, HCP is almost always latent before puberty, and symptoms are most common in adult women. Attacks are precipitated by the same factors that cause attacks in AIP, including fasting, oral contraceptive steroids, and hormone increases during the luteal phase of the menstrual cycle. Concomitant liver diseases may increase porphyrin retention and photosensitivity. The risk of hepatocellular carcinoma is increased, as in other acute porphyrias.

The clinical features of homozygous HCP or harderoporphyria, which begin in early childhood, may include jaundice, hemolytic anemia, hepatosplenomegaly, and skin photosensitivity. These symptoms are generally quite distinct from those seen in heterozygotes.

Laboratory Findings
The porphyrin precursors ALA and PBG are increased during acute attacks, but may decrease more rapidly than in AIP. Marked increases in coproporphyrin III in urine and feces are more persistent. In homozygous cases, porphyrin excretion may be more markedly increased and is accompanied by substantial increases in erythrocyte zinc protoporphyrin. Harderoporphyria is characterized by a marked increase in fecal excretion of harderoporphyrin (tricarboxyl porphyrin) as well as coproporphyrin. Plasma porphyrins are usually normal or only slightly increased.

Diagnosis and Differential Diagnosis
The diagnosis of HCP is readily established in patients with clinically manifest disease, although urinary ALA, PBG, and uroporphyrin may revert to normal more quickly than in AIP. Urinary coproporphyrin

III is increased. Urinary porphyrins, especially coproporphyrin, can be increased in many medical conditions such as liver disease, and small increases may not be clinically significant and lead to an incorrect diagnosis of HCP. Fecal porphyrins are mostly coproporphyrin (isomer III) in HCP, whereas in VP, coproporphyrin III and protoporphyrin are often increased approximately equally. Plasma porphyrins are usually normal in HCP and increased in VP.

The ratio of fecal coproporphyrin III to coproporphyrin I is especially sensitive for detecting latent heterozygotes (especially adults). Assays for CPOX, a mitochondrial enzyme, require cells such as lymphocytes and are not widely available. Identification of a *CPOX* mutation in an index case greatly facilitates screening family members.

Treatment and Prognosis

Acute attacks of HCP are treated as in AIP, which includes intravenous hemin and identifying and avoiding precipitating factors. Cholestyramine may be of some value for photosensitivity occurring with liver dysfunction. Phlebotomy and chloroquine are not effective. Gonadotropin-releasing hormone analogs can be effective for prevention of cyclic attacks. The prognosis is generally better than in AIP.

Prevention and Genetic Counseling

These are the same as in other acute porphyrias.

Variegate Porphyria

This hepatic porphyria is caused by a deficiency of protoporphyrinogen oxidase (PPOX), which is inherited as an autosomal dominant trait. The disorder is termed *variegate* because it can present with neurologic or cutaneous manifestations. Other terms have included *porphyria variegata, protocoproporphyria,* and *South African genetic porphyria.* Rare cases of homozygous VP are symptomatic in childhood.

Etiology

PPOX is approximately half normal in all cells studied in patients with VP. The enzyme is more markedly deficient in rare cases of homozygous VP, with approximately half-normal enzyme activity in parents.

Human PPOX is a homodimer that contains flavin adenine dinucleotide and is localized to the cytosolic side of the inner mitochondrial membrane. Membrane-binding domains may be docked onto human FECH, the next enzyme in the pathway, which is embedded in the opposite side of the membrane. PPOX catalyzes the oxidation of protoporphyrinogen IX to protoporphyrin IX by the removal of 6 hydrogen atoms (see Fig. 91-1). The enzyme requires molecular oxygen. The substrate is readily oxidized nonenzymatically to protoporphyrin under aerobic conditions, or if exported into the cytosol. PPOX is highly specific for protoporphyrinogen IX, and is inhibited by tetrapyrroles such as heme, biliverdin, and bilirubin and by certain herbicides that cause protoporphyrin to accumulate and induce phototoxicity in plants. Inhibition by bilirubin may account for decreased PPOX activity in Gilbert disease.

The human *PPOX* gene on chromosome 1q22-q23 consists of 1 noncoding and 12 coding exons. A single PPOX transcript is produced in a variety of tissues, but putative transcriptional element binding sequences may allow for erythroid-specific expression. Many *PPOX* mutations have been reported in VP families. A missense mutation, R59W, is prevalent in South Africa. No convincing genotype–phenotype correlations have been identified. Mutations in homozygous cases of VP are more likely to encode enzyme proteins with residual activity.

Epidemiology

VP is less common than AIP in most countries. The R59W mutation is highly prevalent in South African whites (3 in 1,000 in this population). This example of genetic drift or "founder effect" has been traced to a man or his wife who emigrated from Holland to South Africa in 1688. In Finland, the prevalence is 1.3 in 100,000 people and is about as common as AIP.

Pathology and Pathogenesis

Acute attacks develop in a minority (approximately 25%) of heterozygotes for PPOX deficiency, and are often attributable to drugs, steroids, and nutritional factors that play a role in other acute porphyrias. Protoporphyrinogen IX accumulates and undergoes autoxidation to protoporphyrin IX. Coproporphyrinogen III may accumulate as the result of a close functional association between PPOX in the inner mitochondrial membrane and CPOX in the intermembrane space. Liver porphyrin content is not increased. The increased porphyrin content in plasma consists of porphyrin–peptide conjugates, which may be formed from protoporphyrinogen. Increased ALA and PBG during acute attacks may be explained, as in HCP, by induction of ALAS1 by exacerbating factors, and by the normally relatively low activity of PBGD in liver. Furthermore, PBGD is inhibited by protoporphyrinogen, the substrate for PPOX.

Clinical Manifestations

Symptoms develop in some heterozygotes after puberty. Neurovisceral symptoms occurring as acute attacks are identical to AIP but are generally milder and less often fatal. Drugs, steroids, and nutritional alterations such as fasting, which are harmful in AIP, can also induce attacks of VP. Attacks occur equally in males and females, at least in South Africa. Cutaneous fragility, vesicles, bullae, hyperpigmentation, and hypertrichosis of sun-exposed areas are much more common than in HCP. They are likely to occur apart from and be more long lasting than the neurovisceral symptoms. Oral contraceptives can precipitate cutaneous manifestations. Acute attacks have become less common, and skin manifestations are more frequently the initial presentation; this may be due to earlier diagnosis and counseling. The risk of hepatocellular carcinoma is increased.

Symptoms of homozygous VP begin in infancy or childhood. These children generally have severe photosensitivity, neurologic symptoms, convulsions, developmental disturbances, and sometimes growth retardation, but do not have acute attacks.

Laboratory Findings

Urinary ALA, PBG, and uroporphyrin are increased during acute attacks but often less so than in AIP, and may be normal or only slightly increased during remission. Plasma porphyrins, urinary coproporphyrin III, and fecal coproporphyrin III and protoporphyrin are more persistently increased between attacks. Erythrocyte zinc protoporphyrin levels are markedly increased in homozygous VP, and may be modestly increased in heterozygous cases.

Diagnosis and Differential Diagnosis

VP is readily distinguished from AIP and HCP, which also present with acute attacks and increases in PBG. Plasma porphyrin analysis is especially useful, because the plasma porphyrins in VP are tightly protein bound, resulting in a characteristic fluorescence emission spectrum at neutral pH. Fecal porphyrins are increased, with approximately equal amounts of coproporphyrin III and protoporphyrin. Fluorometric detection of plasma porphyrins is more sensitive than stool porphyrin analysis in asymptomatic VP. PPOX assays using cells that contain mitochondria, such as lymphocytes, are sensitive for identifying asymptomatic carriers but are not widely available. Knowing the *PPOX* mutation in an index case enables the identification of relatives who carry the same mutation.

Treatment

Acute attacks are treated as in AIP. Hemin is beneficial for acute attacks but not for cutaneous symptoms. Light protection is important in patients with skin manifestations, using long-sleeved clothing, gloves, a broad-brimmed hat, and opaque sunscreen preparations. Exposure to short-wavelength UV light, which does not excite porphyrins, may increase skin pigmentation and provide some protection. Phlebotomy and chloroquine are not effective. Surprisingly, oral activated charcoal was reported to increase porphyrin levels and worsen skin manifestations.

Prognosis and Prevention

The outlook of patients with VP has improved, which may be attributed to improved treatment, earlier diagnosis, and detection of latent cases. Cyclic acute attacks in women can be prevented with a gonadotropin-releasing hormone analog, as in AIP. A diagnosis of VP or any other acute porphyria should not lead to difficulty obtaining insurance, because the prognosis is usually good once the diagnosis is established.

Genetic Counseling

This is the same as in other acute porphyrias.

ERYTHROPOIETIC PROTOPORPHYRIA

In this autosomal recessive disorder, protoporphyrin accumulates as the result of a marked deficiency of FECH, the last enzyme in the heme biosynthetic pathway, because of *FECH* mutations. EPP is sometimes termed *protoporphyria* or *erythrohepatic protoporphyria,* although the liver does not contribute substantially to production of excess protoporphyrin in uncomplicated cases. XLP is a genetically distinct form of porphyria that is less common than EPP but with the same phenotype, and is a result of gain of function *ALAS2* mutations.

Etiology

FECH, the enzyme that is deficient in EPP, catalyzes the final step in heme synthesis, which is insertion of ferrous iron (Fe^{2+}) into protoporphyrin IX (see Fig. 91-1). The enzyme is also termed *heme synthetase* or *protoheme ferrolyase.* The human enzyme is a dimer, and each homodimer contains a [2Fe-2S] cluster, which may have a role in bridging homodimers. FECH is found in the mitochondrial inner membrane where its active site faces the mitochondrial matrix. It may be associated with complex I of the mitochondrial electron transport chain, and the ferrous iron substrate may be produced upon nicotinamide adenine dinucleotide oxidation. FECH is specific for the reduced form of iron, but can utilize other metals such as Zn^{2+} and Co^{2+} and other dicarboxyl porphyrins. Accumulation of free protoporphyrin rather than zinc protoporphyrin in EPP indicates that formation of the latter is dependent on FECH activity in vivo.

The human *FECH* gene is located on chromosome 18q21.3, has a single promoter sequence, and contains 11 exons. Two mRNAs of 1.6 and 2.5 kb were described, which may be explained by the use of 2 alternative polyadenylation signals. The larger transcript is more abundant in murine erythroid cells, suggesting erythroid-specific regulation of FECH. A variety of *FECH* mutations have been reported in EPP, including missense, nonsense, and splicing mutations, small and large deletions, and an insertion.

The inheritance of 2 alleles associated with reduced FECH activity is required for disease expression. This is consistent with FECH activities as low as 15-25% of normal in EPP patients. In most patients, a disabling mutation on 1 *FECH* allele is combined with a common variant affecting the other allele. This common variant *FECH* allele (IVS3-48T > C) produces less-than-normal amounts of enzyme because it expresses an aberrantly spliced mRNA that is degraded by a nonsense-mediated RNA decay mechanism. The IVS3-48T > C *FECH* variant by itself does not cause disease, even when homozygous. In a few families, 2 severe *FECH* mutations have been found, without the IVS3-48T > C allele. EPP with autosomal recessive inheritance occurs naturally in cattle and in mouse models.

XLP is associated with gain-of-function deletions in the last exon of *ALAS2*. These lesions delete the last 10-20 amino acids of the ALAS2 polypeptide and apparently make the enzyme more stable. Free protoporphyrin predominates in erythrocytes in these cases, but because FECH activity is normal the proportion of zinc protoporphyrin is greater than in classic EPP. XLP accounts for approximately 2% of cases with the EPP phenotype in Europe and approximately 10% of cases in North America.

EPP is sometimes associated with myelodysplastic syndromes and expansion of a clone of hematopoietic cells with deletion of one *FECH* allele or other *FECH* mutations. In such cases, there is late onset of the disease.

Epidemiology

EPP is the most common porphyria to cause symptoms in children, but is often not diagnosed until adult life. Overall it is the third most common porphyria, although its prevalence is not precisely known (see Table 91-2). It is described mostly in white people, but occurs in other races. The IVS3-48T > C splice variant is common in whites and East Asians, but rare in Africans, which explains lower disease prevalence in populations of African origin.

Pathology and Pathogenesis

FECH is deficient in all tissues in EPP, but bone marrow reticulocytes are thought to be the primary source of the excess protoporphyrin, some of which enters plasma and circulates to the skin. Circulating erythrocytes are no longer synthesizing heme and hemoglobin, but they contain excess free protoporphyrin, which also contributes. In XLP caused by terminal deletions in exon 11 of ALAS2, all intermediates of the heme pathway are overproduced and ultimately accumulate in bone marrow erythroblasts as protoporphyrin. FECH is not deficient in the variant form, and this enzyme chelates some of the excess protoporphyrin with zinc. An aberrantly spliced mitoferrin transcript, which limits iron transport into mitochondria, has also been described in this condition. The liver functions as an excretory organ rather than a major source for excess protoporphyrin. But FECH deficiency in the skin and liver may be important, as tissue transplantation studies in mice suggest that skin photosensitivity and liver damage occur only when FECH is deficient in these tissues.

Patients with EPP and XLP are maximally sensitive to light in the 400 nm range, which corresponds to the so-called Soret band (the narrow peak absorption maximum that is characteristic for protoporphyrin and other porphyrins). Having absorbed light, porphyrins enter an excited energy state and release energy as fluorescence, singlet oxygen, and other reactive oxygen species. Tissue damage is accompanied by lipid peroxidation, oxidation of amino acids, crosslinking of proteins in cell membranes, and damage to capillary endothelial cells. Such damage may be mediated by photoactivation of the complement system and release of histamine, kinins, and chemotactic factors. Repeated acute damage leads to thickening of the vessel walls and perivascular deposits from accumulation of serum components. Deposition of amorphous material containing immunoglobulin, complement components, glycoproteins, acid glycosaminoglycans, and lipids around blood vessels occurs in the upper dermis.

There is little evidence for impaired erythropoiesis or hemolysis in EPP. However, mild anemia with microcytosis, hypochromia and reticulocytosis is common. Iron accumulation in erythroblasts and ring sideroblasts have been noted in bone marrow in some patients. Decreased transferrin saturation and low or low-normal serum ferritin suggest iron deficiency. Iron status should be carefully evaluated in EPP patients, keeping in mind that iron deficiency may lead to further increases in protoporphyrin and increase the risk for cholestasis. Oral iron supplements are often poorly absorbed in EPP, which is unexplained. Some patients report increased photosensitivity when given iron supplements, but whether this is from transient increases in porphyrins when iron deficiency is corrected and erythropoiesis increases is not known.

Liver damage that develops in a small proportion of EPP and XLP patients is attributed to excess protoporphyrin, which is cholestatic, insoluble in water and excreted only by hepatic uptake and biliary excretion. Some may be reabsorbed by the intestine and undergo enterohepatic circulation. With cholestasis the excess protoporphyrin that accumulates in the liver can form crystalline structures in hepatocytes, and impair mitochondrial function.

Clinical Manifestations

Symptoms of cutaneous photosensitivity begin in childhood, and consist of pain, redness, and itching occurring within minutes of sunlight exposure. Swelling may resemble angioneurotic edema, and *solar urticaria.* Symptoms are usually worse in the spring and summer. Petechiae and purpuric lesions may be seen, but blisters are usually absent. Chronic changes may include lichenification, leathery pseudovesicles,

labial grooving, and nail changes, but changes in pigmentation and pronounced scarring are unusual. Although physical findings in EPP and XLP may not be impressive, the symptoms significantly impair quality of life to a greater extent than in PCT and VP. An association between autosomal recessive EPP and seasonal palmar keratoderma is unexplained. Neuropathy develops only in some patients with severe hepatic decompensation.

Unless hepatic or other complications develop, protoporphyrin levels and symptoms of photosensitivity remain remarkably stable for many years in most patients. Factors that exacerbate hepatic porphyrias play little or no role in EPP or XLP. Mild, unexplained hypertriglyceridemia has been described. Erythrocyte protoporphyrin levels may decrease and sunlight tolerance may improve during pregnancy, which is unexplained.

Laboratory Findings

Protoporphyrin is substantially increased in circulating erythrocytes in EPP, and consists almost entirely of free protoporphyrin. In a variant form of EPP caused by ALAS2 exon 11 deletions, both zinc protoporphyrin and free protoporphyrin are increased, although the latter still predominates. Protoporphyrin is also increased in bone marrow, plasma, bile, and feces. Other porphyrins and porphyrin precursors are normal in uncomplicated EPP.

Diagnosis and Differential Diagnosis

A diagnosis of EPP is confirmed primarily by finding a substantially elevated concentration of erythrocyte protoporphyrin, which is predominantly metal-free and not complexed with zinc. In XLP, both free and zinc complexed protoporphyrins are elevated. Erythrocyte total protoporphyrin levels are on average higher in XLP more variable in EPP, possible reflecting differences in severity of the many reported *FECH* mutations. Erythrocyte zinc protoporphyrin concentration is increased in some homozygous porphyrias, iron deficiency, lead poisoning, anemia of chronic disease, hemolytic conditions, and many other erythrocytic disorders. Many assays for erythrocyte protoporphyrin or "free erythrocyte protoporphyrin" measure only zinc protoporphyrin (i.e., iron-free rather than metal-free protoporphyrin). Therefore, reports must be interpreted with care, and confirmation obtained from a laboratory that reliably fractionates metal-free and zinc protoporphyrin.

Plasma total porphyrin concentration is often less increased in EPP than in other cutaneous porphyrias, and may be normal. Great care must be taken to avoid light exposure during sample processing, because plasma porphyrins in EPP are particularly subject to photodegradation. Urinary porphyrin precursors and porphyrins are not increased.

Measurement of FECH activity requires cells containing mitochondria and is not widely available. A greater than expected proportion of zinc protoporphyrin (more than ~15% of the total) in erythrocytes is important in identifying XLP. DNA studies are increasingly important for confirming *FECH* or *ALAS2* mutations and for genetic counseling.

Life-threatening protoporphyric hepatopathy is heralded by increasingly abnormal liver function tests, increasing erythrocyte and plasma protoporphyrin levels, and worsening photosensitivity. Increases in urinary porphyrins, especially coproporphyrin, in this setting are attributable to liver dysfunction.

Complications

Biliary stones containing protoporphyrin are sometimes symptomatic and require cholecystectomy. Protoporphyric hepatopathy occurs in less than 5% of EPP patients, including children, and may be chronic or progress rapidly to death from liver failure. This liver disease is sometimes the major presenting feature of EPP. In XLP, liver disease may be more frequent and in 1 report of 8 families, 17% of patients had overt liver dysfunction. Protoporphyric hepatopathy can cause acute upper abdominal pain suggesting biliary obstruction, and unnecessary laparotomy to exclude this possibility can be detrimental. Concurrent conditions that impair liver function, such as viral hepatitis, alcohol intake, iron deficiency, fasting, or oral contraceptive steroids, may contribute. Liver histology shows marked deposition of protoporphyrin in liver cells and bile canaliculi. Patients with protoporphyric liver failure most often have *FECH* "null mutations" and the IVS3–48T>C hypoexpression allele, but some may have 2 severe mutant *FECH* alleles or XLP caused by *ALAS2* exon 11 deletions. The bone marrow is probably the major source of protoporphyrin, even in EPP patients with hepatic failure.

Treatment

Exposure to sunlight should be avoided, which is aided by wearing closely woven clothing. Oral beta-carotene leads to clinical improvement and greater tolerance to light in some patients, usually 1-3 mo after starting treatment. In most adults, doses of 120-180 mg daily will maintain serum carotene levels in the recommended range of 600-800 mg/dL, but doses up to 300 mg daily may be needed. Mild skin discoloration from carotenemia is expected. The recommended product is Lumitene, which was initially developed as a drug for treating this disease, rather than nutritional products that are less standardized. Beta-carotene may quench singlet oxygen or free radicals, but does not substantially alter circulating porphyrin levels. Better tolerance of sunlight may result in tanning, which provides additional protection. Oral cysteine may also quench excited oxygen species and was found to increase tolerance to sunlight in EPP.

Measures to darken the skin may also be helpful. This may be accomplished by narrow-band UV-B phototherapy or with topical products such as dihydroxyacetone and lawsone (naphthoquinone). Afamelanotide, a synthetic analog of melanocyte-stimulating hormone shows promise for increasing sunlight tolerance in EPP and XLP and is currently in Phase 3 trials in the United States. Caloric restriction and drugs or hormone preparations that impair hepatic excretory function should be avoided, and iron deficiency should be corrected if present. Vitamin D supplementation and hepatitides A and B vaccination are recommended.

Treatment of protoporphyric hepatopathy must be individualized and results are unpredictable. Ursodeoxycholic acid may be of some value in early stages. Cholestyramine or activated charcoal may interrupt the enterohepatic circulation of protoporphyrin, promote its fecal excretion, and reduce liver protoporphyrin content. Spontaneous resolution may occur, especially if another reversible cause of liver dysfunction, such as viral hepatitis or alcohol abuse, is contributing. In patients with severe hepatic decompensation, combined treatment with plasmapheresis, transfusion to suppress erythropoiesis, intravenous hemin to suppress erythroid and hepatic protoporphyrin production, ursodeoxycholic acid, vitamin E, and cholestyramine may be beneficial.

Motor neuropathy resembling that seen in acute porphyrias sometimes develops in EPP patients with liver disease before or after transfusion or liver transplantation and is sometimes reversible. Artificial lights, such as operating room lights during liver transplantation or other surgery, may cause severe photosensitivity, with extensive burns of the skin and peritoneum and photodamage of circulating erythrocytes.

With continued progression of liver disease, liver transplantation may be considered. Although liver disease may recur in the transplanted liver as a result of continued bone marrow production of excess protoporphyrin, outcomes are comparable to transplantation for other types of liver disease. Bone marrow transplantation should also be considered after liver transplantation if a suitable donor is available.

Prognosis

Typical EPP patients have lifelong photosensitivity but can otherwise expect normal longevity. Protoporphyric liver disease is often life-threatening; however, the incidence is low.

Prevention

Symptoms can be prevented by avoiding sunlight. Avoiding agents that may cause liver damage may help prevent liver complications.

Genetic Counseling

DNA studies to identify *FECH* mutations, the common IVS3–48T>C *FECH* hypoexpression allele, or ALAS2 exon 11 deletions are increasingly important for genetic counseling. EPP may improve during pregnancy. In classic EPP, DNA studies in both parents can predict the risk for EPP occurring in an offspring.

Dual Porphyria

Dual porphyria refers to patients with porphyria who have deficiencies of more than 1 enzyme of the heme biosynthetic pathway. An unusual pattern of porphyrin precursors and porphyrins may suggest the presence of 2 enzyme deficiencies. Mutations of 2 heme pathway enzymes have been documented in only 2 patients with porphyria. One presented with acute porphyria and had heterozygous mutations in both the *CPOX* and *ALAD* genes. The other had symptoms of AIP and PCT and was documented to have both *PBGD* and *UROD* mutations. In other reported cases, 1 or both enzyme deficiencies were based on enzyme measurements.

Porphyria Resulting from Tumors

Very rarely, hepatocellular tumors contain and presumably produce excess porphyrins, but such cases have not been studied carefully. Hepatocellular carcinomas complicating PCT and acute hepatic porphyrias usually are not described as containing large amounts of porphyrins. Erythropoietic porphyrias can develop late in life from clonal expansion of erythroid cells containing a specific enzyme deficiency in patients who have developed myelodysplastic or myeloproliferative syndromes.

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Chapter 92

Hypoglycemia

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Glucose has a central role in fuel economy and is a source of energy storage in the form of glycogen, fat, and protein (see Chapter 87). As an immediate source of energy, glucose provides 38 mol of adenosine triphosphate (ATP) per mole of glucose oxidized. Glucose is essential for energy metabolism in the brain where it is usually the preferred substrate and where its utilization accounts for nearly all of the brain's oxygen consumption. Cerebral glucose uptake occurs through a glucose transporter molecule or molecules that are not regulated by insulin. Cerebral transport of glucose is a Glut1, carrier-mediated, facilitated diffusion process that is dependent on blood glucose concentration. Hence, low concentrations of blood glucose result in cerebral glucopenia. Deficiency of brain glucose transporters can result in seizures because of low cerebral and cerebrospinal fluid (CSF) glucose concentrations (hypoglycorrhachia) despite normal blood glucose levels. To maintain the blood glucose concentration and prevent it from falling precipitously to levels that impair brain function, an elaborate regulatory system has evolved.

The defense against hypoglycemia is integrated by the autonomic nervous system and by hormones that act in concert to enhance glucose production through enzymatic modulation of glycogenolysis and gluconeogenesis, while simultaneously limiting peripheral glucose utilization which conserves glucose for cerebral metabolism. Hypoglycemia represents a defect in one or several of the complex interactions that normally integrate glucose homeostasis during feeding and fasting. This process is particularly important for neonates, in whom there is an abrupt transition from intrauterine life, characterized by dependence on transplacental glucose supply, to extrauterine life, characterized ultimately by the autonomous ability to maintain euglycemia. Because prematurity or placental insufficiency may limit tissue nutrient deposits, and genetic abnormalities in enzymes or hormones may become evident in the neonate, hypoglycemia is common in the neonatal period.

DEFINITION

In neonates, there is not always an obvious correlation between blood glucose concentration and the classic clinical manifestations of hypoglycemia. The absence of symptoms does not indicate that glucose concentration is normal and has not fallen to less than some optimal level for maintaining brain metabolism. There is evidence that hypoxemia and ischemia may potentiate the role of hypoglycemia in causing permanent brain damage. Consequently, the lower limit of accepted normality of the blood glucose level in newborn infants with associated illness that already impairs cerebral metabolism has not been determined (see Chapter 107). Out of concern for possible neurologic, intellectual, or psychologic sequelae in later life, most authorities recommend that any value of blood glucose <55 mg/dL in neonates be viewed with suspicion and vigorously treated. This is particularly applicable after the initial 2-3 hr of life, when glucose normally has reached its nadir; subsequently, blood glucose levels begin to rise and achieve values of 50 mg/dL or higher after 12-24 hr. By day 3 of life in normal full-term newborns, blood glucose averages approximately 60 mg/dL. In older infants and children, a whole blood glucose concentration of <55 mg/dL (10-15% higher for serum or plasma) represents hypoglycemia, because counterregulatory mechanisms are activated at these glucose concentrations.

SIGNIFICANCE AND SEQUELAE

Most of the endogenous hepatic glucose production in infants and young children, which occurs several hours after feeding and during fasting, can be accounted for by brain metabolism.

Because the brain grows most rapidly in the 1st yr of life and because the larger proportion of glucose turnover is used for brain metabolism, sustained or repetitive hypoglycemia in infants and children can retard brain development and function. Transient isolated and asymptomatic hypoglycemia of short duration does not appear to be associated with these severe sequelae. In the rapidly growing brain, glucose may also be a source of membrane lipids and, together with protein synthesis it can provide structural proteins and myelination that are important for normal brain maturation. Under conditions of severe and sustained hypoglycemia, these cerebral structural substrates may become degraded to energy-usable intermediates such as lactate, pyruvate, amino acids, and ketoacids, which can support brain metabolism at the expense of brain growth. The capacity of the newborn brain to take up and oxidize ketone bodies is about 5-fold greater than that of the adult brain. However, the capacity of the liver to produce ketone bodies is limited in the immediate newborn period, especially in the presence of hyperinsulinism, which acutely inhibits hepatic glucose output, lipolysis, and ketogenesis, thereby depriving the brain of any alternate fuel sources. Although the brain may metabolize ketones, these alternate fuels cannot completely replace glucose as an essential central nervous system (CNS) fuel. The deprivation of the brain's major energy source during hypoglycemia and the limited availability of alternate fuel sources during hyperinsulinism have predictable adverse consequences on brain metabolism and growth: decreased brain oxygen consumption and increased breakdown of endogenous structural components with destruction of functional membrane integrity.

The major long-term sequelae of severe, prolonged hypoglycemia are cognitive impairment, recurrent seizure activity, cerebral palsy and autonomic dysregulation. Subtle effects on personality are also possible but have not been clearly defined. Permanent neurologic sequelae are present in 25-50% of patients with severe recurrent symptomatic hypoglycemia who are younger than 6 mo of age. These sequelae may be reflected in pathologic changes characterized by reduced myelination in cerebral white matter and atrophy of the cerebral cortex, reflected in enlargement of the sulci and thinning of the gyri of the brain. These sequelae also are more likely when alternative fuel sources are limited,

as occurs with hyperinsulinism, when the episodes of hypoglycemia are repetitive or prolonged, or when they are compounded by hypoxia. There is no precise knowledge relating the duration or severity of hypoglycemia to subsequent neurologic development of children in a predictable manner. Although less common, hypoglycemia in older children may also produce long-term neurologic defects through neuronal death mediated, in part, by cerebral excitotoxins released during hypoglycemia.

SUBSTRATE, ENZYME, AND HORMONAL INTEGRATION OF GLUCOSE HOMEOSTASIS

In the Newborn

See Chapter 107.

Under nonstressed conditions, fetal glucose is derived entirely from the mother through placental transfer. Therefore, fetal glucose concentration usually reflects, but is slightly lower than, maternal glucose levels. Catecholamine release, which occurs with fetal stress such as hypoxia, mobilizes fetal glucose and free fatty acids (FFAs) through β-adrenergic mechanisms, reflecting β-adrenergic activity in fetal liver and adipose tissue. Catecholamines may also inhibit fetal insulin and stimulate glucagon release.

The acute interruption of maternal glucose transfer to the fetus at delivery imposes an immediate need to mobilize endogenous glucose. Three related events facilitate this transition: changes in hormones, changes in their receptors, and changes in key enzyme activity. There is a 3-5–fold abrupt increase in glucagon concentration within minutes to hours of birth. The level of insulin usually falls initially and remains in the basal range for several days without demonstrating the usual brisk response to physiologic stimuli such as glucose. A dramatic surge in spontaneous catecholamine secretion is also characteristic. Epinephrine can also augment growth hormone secretion by α-adrenergic mechanisms; growth hormone levels are elevated at birth. Acting in concert, these hormonal changes at birth mobilize glucose via glycogenolysis and gluconeogenesis, activate lipolysis, and promote ketogenesis. As a result of these processes, plasma glucose concentration stabilizes after a transient decrease immediately after birth, liver glycogen stores become rapidly depleted within hours of birth, and gluconeogenesis from alanine, a major gluconeogenic amino acid, can account for approximately 10% of glucose turnover in the human newborn infant by several hours of age. FFA concentrations also increase sharply in concert with the surges in glucagon and epinephrine, and are followed later by rises in ketone bodies. Glucose is thus partially spared for brain utilization while FFAs and ketones provide alternative fuel sources for muscle as well as essential gluconeogenic factors such as acetyl coenzyme A (CoA) and the reduced form of nicotinamide adenine dinucleotide from hepatic fatty acid oxidation, which is required to drive gluconeogenesis.

In the early postnatal period, responses of the endocrine pancreas favor glucagon secretion so that blood glucose concentration can be maintained. These adaptive changes in hormone secretion are paralleled by similarly striking adaptive changes in hormone receptors. Key enzymes involved in glucose production also change dramatically in the perinatal period. Thus, there is a rapid fall in glycogen synthase activity and a sharp rise in phosphorylase activity after delivery. Similarly, the amount of the rate-limiting enzyme for gluconeogenesis, phosphoenolpyruvate carboxykinase, rises dramatically after birth, activated in part by the surge in glucagon and the fall in insulin. This framework can explain several causes of neonatal hypoglycemia based on inappropriate changes in hormone secretion and unavailability of adequate reserves of substrates in the form of hepatic glycogen, muscle as a source of amino acids for gluconeogenesis, and lipid stores for the release of fatty acids. In addition, appropriate activities of key enzymes governing glucose homeostasis are required (see Fig. 87-1 in Chapter 87).

In Older Infants and Children

Hypoglycemia in older infants and children is analogous to that of adults, in whom glucose homeostasis is maintained by glycogenolysis in the immediate postfeeding period and by gluconeogenesis several hours after meals. The liver of a 10 kg child contains 20-25 g of glycogen, which is sufficient to meet normal glucose requirements of 4-6 mg/kg/min for only 6-12 hr. Beyond this period, hepatic gluconeogenesis must be activated. Both glycogenolysis and gluconeogenesis depend on the metabolic pathway summarized in Figure 87-1. Defects in glycogenolysis or gluconeogenesis may not be manifested in infants until the frequent feeding at 3-4 hr intervals ceases and infants sleep through the night, a situation usually present by 3-6 mo of age. The source of gluconeogenic precursors is derived primarily from muscle protein. The muscle bulk of infants and small children is substantially smaller relative to body mass than that of adults, whereas glucose requirements/unit of body mass are greater in children, so the ability to compensate for glucose deprivation by gluconeogenesis is more limited in infants and young children, as is the ability to withstand fasting for prolonged periods. The ability of muscle to generate alanine, the principal gluconeogenic amino acid, may also be limited. Thus, in normal young children, the blood glucose level falls after 24 hr of fasting, insulin concentrations fall appropriately to levels of <5-10 µU/mL, lipolysis and ketogenesis are activated, and ketones may appear in the urine.

The switch from glycogen synthesis during and immediately after meals to glycogen breakdown and later gluconeogenesis is governed by hormones, of which insulin is of central importance. Plasma insulin concentrations increase to peak levels of 5-10–fold greater than their baseline of approximately 5-10 µU/mL after meals, which serve to lower the blood glucose concentration through the activation of glycogen synthesis, enhancement of peripheral glucose uptake, and inhibition of glucose production. In addition, lipogenesis is stimulated, whereas lipolysis and ketogenesis are curtailed. During fasting, plasma insulin concentrations fall to ≤5-10 µU/mL, and together with the rise of counterregulatory hormones, this fall in insulin results in activation of gluconeogenic pathways (see Fig. 87-1). Fasting glucose concentrations are maintained through the activation of glycogenolysis and gluconeogenesis, inhibition of glycogen synthesis, and activation of lipolysis and ketogenesis. It should be emphasized that a plasma insulin concentration of >5 µU/mL, in association with a blood glucose concentration of ≤50-55 mg/dL (2.8-3.0 mM), is abnormal, indicating a **state** of excessive insulin action, here termed **hyperinsulinism,** because of failure of the mechanisms that normally result in suppression of insulin secretion during fasting or hypoglycemia.

The hypoglycemic effects of insulin are opposed by the actions of several hormones whose concentration in plasma increases as blood glucose falls. These **counterregulatory hormones**—glucagon, growth hormone, cortisol, and epinephrine—act in concert by increasing blood glucose concentrations via activating glycogenolytic enzymes (glucagon, epinephrine); inducing gluconeogenic enzymes (glucagon, cortisol); inhibiting glucose uptake by muscle (epinephrine, growth hormone, cortisol); mobilizing amino acids from muscle for gluconeogenesis (cortisol); activating lipolysis and thereby providing glycerol for gluconeogenesis and fatty acids for ketogenesis (epinephrine, cortisol, growth hormone, glucagon); and inhibiting insulin release and promoting growth hormone and glucagon secretion (epinephrine).

Congenital or acquired deficiency of any one of these hormones is uncommon but will result in hypoglycemia, which occurs when endogenous glucose production cannot be mobilized to meet energy needs in the postabsorptive state, that is, 8-12 hr after meals or during fasting. Concurrent deficiency of several hormones (**hypopituitarism**) may result in hypoglycemia that is more severe or appears earlier during fasting than that seen with isolated hormone deficiencies. Most of the causes of hypoglycemia in neonates, infants and children reflect inappropriate adaptation to fasting as a result of excess insulin action, or inadequate counter-regulatory hormone response primarily of cortisol and growth hormone, or enzymatic defects in the mechanisms for glycogen storage and release, or defects in gluconeogenesis.

CLINICAL MANIFESTATIONS

See Chapter 107.

Clinical features generally fall into 2 categories. The first includes symptoms associated with the activation of the autonomic nervous system and epinephrine release, usually seen with a rapid decline in blood glucose concentration (Table 92-1). The second category includes

Table 92-1	Manifestations of Hypoglycemia in Childhood

FEATURES ASSOCIATED WITH ACTIVATION OF AUTONOMIC NERVOUS SYSTEM AND EPINEPHRINE RELEASE*
Anxiety†
Perspiration†
Palpitation (tachycardia)†
Pallor‡
Tremulousness‡
Weakness
Hunger
Nausea
Emesis

FEATURES ASSOCIATED WITH CEREBRAL GLUCOPENIA
Headache†
Mental confusion†
Visual disturbances (↓ acuity, diplopia)†
Organic personality changes†
Inability to concentrate†
Dysarthria
Staring
Paresthesias
Dizziness
Amnesia
Ataxia, incoordination
Refusal to feed‡
Somnolence, lethargy‡
Seizures‡
Coma
Stroke, hemiplegia, aphasia
Decerebrate or decorticate posture

*Some of these features will be attenuated if the patient is receiving β-adrenergic blocking agents.
†Common.
‡Most common manifestations in the newborn.

symptoms caused by decreased cerebral glucose utilization (cerebral glycopenia), usually associated with a slow decline in blood glucose level or prolonged hypoglycemia (Table 92-1). Although these classic symptoms occur in older children, the symptoms of hypoglycemia in newborns and infants may be subtler and include cyanosis, apnea, hypothermia, hypotonia, poor feeding, lethargy, and seizures. Some of these symptoms may be so mild that they are missed. Occasionally, hypoglycemia may be asymptomatic in the immediate newborn period. Newborns with hyperinsulinism are often large for gestational age; older infants with hyperinsulinism may eat excessively because of chronic hypoglycemia and become obese. In childhood, hypoglycemia may present as behavior problems, inattention, ravenous appetite, or seizures. It may be misdiagnosed as epilepsy, inebriation, personality disorders, headache, hysteria, and developmental delay. A blood glucose determination should always be performed in sick neonates, who should be vigorously treated if concentrations are <50 mg/dL. At any age, hypoglycemia should be considered a cause of an initial episode of convulsions or a sudden deterioration in psychobehavioral functioning or level of consciousness.

Many neonates have asymptomatic (chemical) hypoglycemia. The incidence of symptomatic hypoglycemia is highest in small for gestational age infants (Fig. 92-1). The exact incidence of symptomatic hypoglycemia has been difficult to establish because many of the symptoms in neonates occur **together** with other conditions such as infections, especially sepsis and meningitis; CNS anomalies, hemorrhage, or edema; hypocalcemia and hypomagnesemia; asphyxia; drug withdrawal; apnea of prematurity; congenital heart disease; or polycythemia.

The onset of symptoms in neonates varies from a few hours to a week after birth. In approximate order of frequency, symptoms include jitteriness or tremors, apathy, episodes of cyanosis, convulsions, intermittent apneic spells or tachypnea, weak or high-pitched cry, limpness or lethargy, difficulty feeding, and eye rolling. Episodes of sweating, sudden pallor, hypothermia, and cardiac arrest and failure also occur.

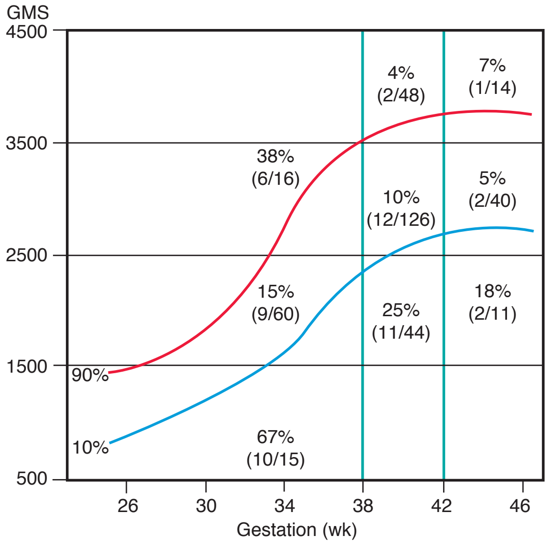

Figure 92-1 Incidence of hypoglycemia by birthweight, gestational age, and intrauterine growth. *(From Lubchenco LO, Bard H: Incidence of hypoglycemia in newborn infants classified by birthweight and gestational age,* Pediatrics *47:831–838, 1971.)*

Frequently, a clustering of episodic symptoms may be noted. Because these clinical manifestations may result from various causes, it is critical to measure serum glucose levels and determine whether symptoms disappear with the administration of sufficient glucose to raise the blood glucose to normal levels; if they do not, other diagnoses must be considered.

CLASSIFICATION OF HYPOGLYCEMIA IN INFANTS AND CHILDREN

Classification is based on knowledge of the control of glucose homeostasis in infants and children (Table 92-2).

Neonatal, Transient, Small for Gestational Age, and Premature Infants

See Chapter 107.

The estimated incidence of symptomatic hypoglycemia in newborns is 1-3 in 1,000 live births. This incidence is increased severalfold in certain high-risk neonatal groups (see Table 92-2 and Fig. 92-1). The premature and small for gestational age (SGA) infants are vulnerable to the development of hypoglycemia. The factors responsible for the high frequency of hypoglycemia in this group, as well as in other groups outlined in Table 92-2, are related to the inadequate stores of liver glycogen, muscle protein, and body fat needed to sustain the substrates required to meet energy needs. These infants are small by virtue of prematurity or impaired placental transfer of nutrients. Their enzyme systems for gluconeogenesis may not be fully developed. **Transient hyperinsulinism** responsive to diazoxide has also been reported as contributing to hypoglycemia in asphyxiated, SGA, and premature newborn infants. This form of hyperinsulinism associated with perinatal asphyxia, intrauterine growth restriction, maternal toxemia and other perinatal stressors, is probably the most common cause of hyperinsulinemic hypoglycemia in neonates and may be quite severe. In most cases, the condition resolves quickly, but it may persist to 7 mo of life or longer.

In contrast to deficiency of substrates or enzymes, the hormonal system appears to be functioning normally at birth in most low-risk neonates. Despite hypoglycemia, plasma concentrations of alanine, lactate, and pyruvate are higher, implying their diminished rate of utilization as substrates for gluconeogenesis. Infusion of alanine elicits further glucagon secretion but causes no significant rise in glucose. During the initial 24 hr of life, plasma concentrations of acetoacetate and β-hydroxybutyrate are lower in SGA infants than in full-term infants, implying diminished lipid stores, diminished fatty acid mobilization, impaired ketogenesis, or a combination of these

Table 92-2 Classification of Hypoglycemia in Infants and Children

NEONATAL TRANSITIONAL (ADAPTIVE) HYPOGLYCEMIA
Associated with Inadequate Substrate or Immature Enzyme Function in Otherwise Normal Neonates
Prematurity
Small for gestational age
Normal newborn
Transient Neonatal Hyperinsulinism
Infant of diabetic mother
Small for gestational age
Discordant twin
Birth asphyxia
Infant of toxemic mother

NEONATAL, INFANTILE, OR CHILDHOOD PERSISTENT HYPOGLYCEMIAS
Hyperinsulinism
Recessive K_{ATP} channel HI
Recessive HADH (hydroxyl acyl-CoA dehydrogenase) mutation HI
Recessive UCP2 (mitochondrial uncoupling protein 2) mutation HI
Focal K_{ATP} channel HI
Dominant K_{ATP} channel HI
Atypical congenital hyperinsulinemia (no mutations in *ABCC8* or *KCN11* genes)
Dominant glucokinase HI
Dominant glutamate dehydrogenase HI (hyperinsulinism/hyperammonemia syndrome)
Dominant mutations in HNF-4A and HNF-1A (hepatic nuclear factors 4α and 1α) HI with monogenic diabetes of youth later in life
Dominant mutation in SLC16A1(the pyruvate transporter)—exercise-induced hypoglycemia
Acquired islet adenoma
Beckwith-Wiedemann syndrome
Insulin administration (Munchausen syndrome by proxy)
Oral sulfonylurea drugs
Congenital disorders of glycosylation
Counterregulatory Hormone Deficiency
Panhypopituitarism
Isolated growth hormone deficiency
Adrenocorticotropic hormone deficiency
Addison disease
Epinephrine deficiency
Glycogenolysis and Gluconeogenesis Disorders
Glucose-6-phosphatase deficiency (GSD 1a)
Glucose-6-phosphate translocase deficiency (GSD 1b)
Amylo-1,6-glucosidase (debranching enzyme) deficiency (GSD 3)
Liver phosphorylase deficiency (GSD 6)
Phosphorylase kinase deficiency (GSD 9)
Glycogen synthetase deficiency (GSD 0)
Fructose-1,6-diphosphatase deficiency
Pyruvate carboxylase deficiency
Galactosemia
Hereditary fructose intolerance

Lipolysis Disorders
Fatty Acid Oxidation Disorders
Carnitine transporter deficiency (primary carnitine deficiency)
Carnitine palmitoyltransferase-1 deficiency
Carnitine translocase deficiency
Carnitine palmitoyltransferase-2 deficiency
Secondary carnitine deficiencies
Very-long-, long-, medium-, short-chain acyl-CoA dehydrogenase deficiency

OTHER ETIOLOGIES
Substrate-Limited
Ketotic hypoglycemia
Poisoning—drugs
Salicylates
Alcohol
Oral hypoglycemic agents
Insulin
Propranolol
Pentamidine
Quinine
Disopyramide
Ackee fruit (unripe)—hypoglycin
Vacor (rat poison)
Trimethoprim-sulfamethoxazole (with renal failure)
Liver Disease
Reye syndrome
Hepatitis
Cirrhosis
Hepatoma

AMINO ACID AND ORGANIC ACID DISORDERS
Maple syrup urine disease
Propionic acidemia
Methylmalonic acidemia
Tyrosinosis
Glutaric aciduria
3-Hydroxy-3-methylglutaric aciduria

SYSTEMIC DISORDERS
Sepsis
Carcinoma/sarcoma (secreting—insulin-like growth factor II)
Heart failure
Malnutrition
Malabsorption
Antiinsulin receptor antibodies
Antiinsulin antibodies
Neonatal hyperviscosity
Renal failure
Diarrhea
Burns
Shock
Postsurgical
Pseudohypoglycemia (leukocytosis, polycythemia)
Excessive insulin therapy of insulin-dependent diabetes mellitus
Factitious
Nissen fundoplication (dumping syndrome)
Falciparum malaria

GSD, glycogen storage disease; HI, hyperinsulinemia; K_{ATP}, regulated potassium channel.

conditions. Diminished lipid stores are most likely because fat (triglyceride) feeding of newborns results in a rise in the plasma levels of glucose, ketones such as β OH butyrate and FFA. For infants with perinatal asphyxia, and some SGA newborns who have transient hyperinsulinism, hypoglycemia and diminished concentrations of β OH butyrate and FFAs are the hallmark of hyperinsulinism.

The role of FFAs and their oxidation in stimulating neonatal gluconeogenesis is essential. The provision of FFAs as triglyceride feedings from formula or human milk together with gluconeogenic precursors may prevent the hypoglycemia that usually ensues after neonatal fasting. For these and other reasons, milk feedings are introduced early (at birth or within 2-4 hr) after delivery. In the hospital setting, when feeding is precluded by virtue of respiratory distress or when feedings alone cannot maintain blood glucose concentrations at levels >50 mg/dL, intravenous glucose at a rate that supplies 4-8 mg/kg/min should be started. Infants with transient neonatal hypoglycemia can usually maintain the blood glucose level spontaneously after 2-3 days of life, but some require longer periods of support. In these latter infants,

insulin values >5 μU/mL at the time of hypoglycemia should be treated with diazoxide.

Infants Born to Diabetic Mothers

See Chapter 107.1.

Of the transient hyperinsulinemic states, infants born to diabetic mothers are the most common. Gestational diabetes affects some 2% of pregnant women, and ≈1 in 1,000 pregnant women have insulin-dependent diabetes. At birth, infants born to these mothers may be large and plethoric, and their body stores of glycogen, protein, and fat are replete.

Hypoglycemia in infants of diabetic mothers is mostly related to hyperinsulinemia and partly related to diminished glucagon secretion. Hypertrophy and hyperplasia of the islets is present, as is a brisk, biphasic, and typically mature insulin response to glucose; this brisk insulin response is absent in normal infants. Infants born to diabetic mothers also have a subnormal surge in plasma glucagon immediately after birth, subnormal glucagon secretion in response to stimuli, and, initially, excessive sympathetic activity that may lead to adrenomedullary exhaustion as reflected by decreased urinary excretion of epinephrine. The normal plasma hormonal pattern of low insulin, high glucagon, and high catecholamines is reversed to a pattern of high insulin, low glucagon, and low epinephrine. As a consequence of this abnormal hormonal profile, endogenous glucose production is significantly inhibited compared with that in normal infants, thus predisposing them to hypoglycemia.

Mothers whose diabetes has been well controlled during pregnancy, labor, and delivery generally have infants near normal size who are less likely to develop neonatal hypoglycemia and other complications formerly considered typical of such infants (see Chapter 107.1). In supplying exogenous glucose to these hypoglycemic infants, it is important to avoid hyperglycemia that evokes a prompt exuberant insulin release, which may result in rebound hypoglycemia. When needed, glucose should be provided at continuous infusion rates of 4-8 mg/kg/min, but the appropriate dose for each patient must be individually adjusted. During labor and delivery, maternal hyperglycemia should be avoided because it results in fetal hyperglycemia, which predisposes to hypoglycemia when the glucose supply is interrupted at birth. Hypoglycemia persisting or occurring after 1 wk of life requires an evaluation for the causes listed in Table 92-2.

Infants born with **erythroblastosis fetalis** may also have hyperinsulinemia and share many physical features, such as large body size, with infants born to diabetic mothers. The cause of the hyperinsulinemia in infants with erythroblastosis is not clear.

PERSISTENT OR RECURRENT HYPOGLYCEMIA IN INFANTS AND CHILDREN

Hyperinsulinism

Most children with hyperinsulinism that causes hypoglycemia present in the neonatal period or later in infancy; hyperinsulinism is the most common cause of persistent hypoglycemia in early infancy. Infants who have hyperinsulinism may be macrosomic at birth, reflecting the anabolic effects of insulin in utero. There is no history or biochemical evidence of maternal diabetes. The onset of symptoms is from birth to 18 mo of age, but occasionally it only becomes evident in older children. Insulin concentrations are inappropriately elevated at the time of documented hypoglycemia; with nonhyperinsulinemic hypoglycemia, plasma insulin concentrations should be <5 μU/mL and no higher than 10 μU/mL. In affected infants, plasma insulin concentrations at the time of hypoglycemia are commonly >5-10 μU/mL. Some authorities set more stringent criteria, arguing that any value of insulin >2 μU/mL with hypoglycemia is abnormal. The insulin (μU/mL):glucose (mg/dL) ratio is commonly >0.4; plasma insulin-like growth factor binding protein-1 (IGFBP-1), β OH butyrate, and FFA levels are low with hyperinsulinism. Rare instances of activating mutations in the insulin receptor signaling pathway have been reported where the clinical and biochemical features are similar to states of excessive insulin secretion, yet insulin concentrations are low to the point of being undetectable. Hence, the preferred term is **hyperinsulinism**, to describe a state of increased insulin action. Macrosomic infants may present with hypoglycemia from the first days of life. Infants with lesser degrees of hyperinsulinism may manifest hypoglycemia only after the first few weeks to months, when the frequency of feedings has been decreased to permit the infant to sleep through the night, and hyperinsulinism prevents the mobilization of endogenous glucose. Increasing appetite and demands for feeding, wilting spells, jitteriness, and frank seizures are the most common presenting features. Additional clues include the rapid development of fasting hypoglycemia within 4-8 hr of food deprivation compared with other causes of hypoglycemia (Tables 92-3 and 92-4); the need for high rates of exogenous glucose infusion to prevent hypoglycemia, often at rates >10-15 mg/kg/min; the absence of ketonemia or acidosis; and elevated C-peptide or proinsulin levels at the time of hypoglycemia. The latter insulin-related products are absent in **factitious hypoglycemia** from exogenous administration of insulin as a form of child abuse (Munchausen by proxy syndrome; see Chapter 40.2). Hypoglycemia is invariably provoked by withholding feedings for several hours, permitting simultaneous measurement of glucose, insulin, ketones, and FFAs in the same sample at the time of clinically manifested hypoglycemia. This is termed the **critical sample.** The glycemic response to glucagon at the time of hypoglycemia reveals a brisk increment in glucose concentration of at least 40 mg/dL, which implies that glucose mobilization has been restrained by insulin but that glycogenolytic mechanisms are intact (Tables 92-5, 92-6, and 92-7).

The measurement of serum IGFBP-1 concentration may help diagnose hyperinsulinism. The secretion of IGFBP-1 is acutely inhibited by insulin action; IGFBP-1 concentrations are low during hyperinsulinism-induced hypoglycemia. In patients with spontaneous or fasting-induced hypoglycemia with a low insulin level (ketotic hypoglycemia, normal fasting), IGFBP-1 concentrations are significantly higher.

The differential diagnosis of endogenous hyperinsulinism includes **diffuse β-cell hyperplasia** or **focal β-cell microadenoma.**

The distinction between these 2 major entities is important because the former, if unresponsive to medical therapy, requires near total pancreatectomy, despite which hypoglycemia may persist or diabetes mellitus may ensue at some later time. Some affected infants may respond to sirolimus. By contrast, focal adenomas diagnosed

Table 92-3 Hypoglycemia in Infants and Children: Clinical and Laboratory Features

GROUP	AGE AT DIAGNOSIS (mo)	GLUCOSE* (mg/dL)	INSULIN (μU/mL)	FASTING TIME TO HYPOGLYCEMIA (hr)
HYPERINSULINEMIA (*N* = 12)				
Mean	7.4	23.1	22.4	2.1[†]
SEM	2.0	2.7	3.2	0.6
NONHYPERINSULINEMIA (*N* = 16)				
Mean	41.8	36.1	5.8	18.2
SEM	7.3	2.4	0.9	2.9

*In hypoglycemia caused by hyperinsulinism β OH butyrate and FFA are low compared with normal at same duration of fasting.
[†]Milder forms of hyperinsulinism may require up to 18 hr of fasting to provoke hypoglycemia.
SEM, standard error of mean.
Adapted from Antunes JD, Geffner ME, Lippe BM, et al: Childhood hypoglycemia: differentiating hyperinsulinemic from nonhyperinsulinemic causes, J Pediatr 116:105–108, 1990.

Table 92-4 Correlation of Clinical Features with Molecular Defects in Persistent Hyperinsulinemic Hypoglycemia in Infancy

TYPE	MACROSOMIA	HYPOGLYCEMIA/ HYPERINSULINEMIA	FAMILY HISTORY	MOLECULAR DEFECTS	ASSOCIATED CLINICAL, BIOCHEMICAL, OR MOLECULAR FEATURES	RESPONSE TO MEDICAL MANAGEMENT	RECOMMENDED SURGICAL APPROACH	PROGNOSIS
Sporadic	Present at birth	Moderate/severe in first days to weeks of life	Negative	? *SUR1*/K_{IR} 6.2 Mutations not always identified in diffuse hyperplasia	Loss of heterozygosity in microadenomatous tissue	Generally poor; may respond better to somatostatin than to diazoxide	Partial pancreatectomy if frozen section shows β-cell crowding with small nuclei—suggests microadenoma Subtotal >95% pancreatectomy if frozen section shows giant nuclei in β-cells—suggests diffuse hyperplasia	Excellent if focal adenoma is removed, thereby curing hypoglycemia and retaining sufficient pancreas to avoid diabetes Guarded if subtotal (>95%) pancreatectomy is performed because diabetes develops in, and hypoglycemia persists in
Autosomal recessive	Present at birth	Severe in first days to weeks of life	Positive	*SUR*/K_{IR} 6.2	Consanguinity a feature in some populations	Poor	Subtotal pancreatectomy	Guarded
Autosomal dominant	Unusual	Moderate onset usually post 6 mo of age	Positive	Glucokinase (activating) Some cases gene unknown	None	Very good to excellent	Surgery usually not required Partial pancreatectomy only if medical management fails	Excellent
Autosomal dominant	Unusual	Moderate onset usually post 6 mo of age	Positive	Glutamate dehydrogenase (activating)	Modest hyperammonemia	Very good to excellent	Surgery usually not required	Excellent
Beckwith-Wiedemann syndrome	Present at birth	Moderate, spontaneously resolves post 6 mo of age	Negative	Duplicating/ imprinting in chromosome 11p15.1	Macroglossia, omphalocele, hemihypertrophy	Good	Not recommended	Excellent for hypoglycemia; guarded for possible development of embryonal tumors (Wilms hepatoblastoma)
Congenital disorders of glycosylation	Not usual	Moderate/onset post 3 mo of age	Negative	Phosphomannose isomerase deficiency	Hepatomegaly, vomiting, intractable diarrhea	Good with mannose supplement	Not recommended	Fair

Table 92-5 Analysis of Critical Blood Sample During Hypoglycemia and 30 Minutes After Glucagon*

SUBSTRATES
Glucose
Free fatty acids
Ketones
Lactate
Uric acid
Ammonia
HORMONES
Insulin
Cortisol
Growth hormone
Thyroxine, thyroid-stimulating hormone
Insulin-like growth factor binding protein-1†

*Glucagon 50 μg/kg with maximum of 1 mg IV or IM.
†Measure once only before or after glucagon administration. Rise in glucose of ≥40 mg/dL after glucagon given at the time of hypoglycemia strongly suggests a hyperinsulinemic state with adequate hepatic glycogen stores and intact glycogenolytic enzymes. If ammonia is elevated to 100-200 μM, consider activating mutation of glutamate dehydrogenase.

Table 92-6 Criteria for Diagnosing Hyperinsulinism Based on "Critical" Samples (Drawn at a Time of Fasting Hypoglycemia: Plasma Glucose <50 mg/dL)

1. Hyperinsulinemia (plasma insulin >2 μU/mL)*
2. Hypofatty acidemia (plasma free fatty acids <1.5 mmol/L)
3. Hypoketonemia (plasma β-hydroxybutyrate: <2.0 mmol/L)
4. Inappropriate glycemic response to glucagon, 1 mg IV (change in glucose >40 mg/dL)

*Depends on sensitivity of insulin assay.
From Stanley CA, Thomson PS, Finegold DN, et al: Hypoglycemia in infants and neonates. In Sperling MA, editor: Pediatric endocrinology, *ed 2, Philadelphia, 2002, WB Saunders, pp. 135–159.*

Table 92-7 Diagnosis of Acute Hypoglycemia in Infants and Children

ACUTE SYMPTOMS PRESENT
1. Obtain blood sample before and 30 min after glucagon administration.
2. Obtain urine as soon as possible. Examine for ketones; if not present and hypoglycemia confirmed, suspect hyperinsulinemia or fatty acid oxidation defect; if present, suspect ketotic, hormone deficiency, inborn error of glycogen metabolism, or defective gluconeogenesis.
3. Measure glucose in the original blood sample. If hypoglycemia is confirmed, proceed with substrate-hormone measurement as in Table 92-5.
4. If glycemic increment after glucagon exceeds 40 mg/dL above basal, suspect hyperinsulinemia.
5. If insulin level at time of confirmed hypoglycemia is >5 μU/mL, suspect endogenous hyperinsulinemia; if >100 μU/mL, suspect factitious hyperinsulinemia (exogenous insulin injection). Admit to hospital for supervised fast.
6. If cortisol is <10 μg/dL or growth hormone is <5 ng/mL, or both, suspect adrenal insufficiency or pituitary disease, or both. Admit to hospital for hormonal testing and neuroimaging.

HISTORY SUGGESTIVE: ACUTE SYMPTOMS NOT PRESENT
1. Careful history for relation of symptoms to time and type of food intake, bearing in mind age of patient. Exclude possibility of alcohol or drug ingestion. Assess possibility of insulin injection, salt craving, growth velocity, intracranial pathology.
2. Careful examination for hepatomegaly (glycogen storage disease; defect in gluconeogenesis); pigmentation (adrenal failure); stature and neurologic status (pituitary disease).
3. Admit to hospital for provocative testing:
   a. 24 hr fast under careful observation; when symptoms provoked, proceed with steps 1-4 as when acute symptoms present.
   b. Pituitary–adrenal function using arginine-insulin stimulation test if indicated.
4. Consider molecular diagnostic test before liver biopsy for histologic and enzyme determinations.
5. Oral glucose tolerance test (1.75 g/kg; max 75 g) if reactive hypoglycemia suspected (dumping syndrome, etc.).

preoperatively or intraoperatively permit localized curative resection with subsequent normal glucose metabolism. Approximately 50% of the autosomal recessive or sporadic forms of neonatal/infantile hyperinsulinism are caused by focal microadenomas, which may be distinguished from the diffuse form by the pattern of insulin response to selective insulin secretagogues infused into an arterial branch supplying the pancreas, with sampling via the hepatic vein. However, these invasive and technically difficult procedures have been largely abandoned in favor of positron emission tomography using 18-fluoro-L-dopa. This technique can distinguish the diffuse form (uniform fluorescence throughout the pancreas) from the focal form (focal uptake of 18-fluoro-L-dopa and localized fluorescence) with an extremely high degree of reliability, success, specificity, and sensitivity (see Fig. 92-3 and below).

Insulin-secreting macroadenomas are rare in childhood and may be diagnosed preoperatively via CT or MRI. The plasma levels of insulin alone, however, cannot distinguish the aforementioned entities. The diffuse or microadenomatous forms of islet cell hyperplasia represent a variety of genetic defects responsible for abnormalities in the endocrine pancreas characterized by autonomous insulin secretion that is not appropriately reduced when blood glucose declines spontaneously or in response to provocative maneuvers such as fasting (see Tables 92-4, 92-7, and 92-8 and Fig. 92-2). Clinical, biochemical, and molecular genetic approaches now permit classification of congenital hyperinsulinism, formerly termed **nesidioblastosis,** into distinct entities. **Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)** may be inherited or sporadic, is severe, and is caused by mutations that affect the regulation of the potassium channel intimately involved in insulin secretion by the pancreatic β cell (Fig. 92-2). Normally, glucose entry into the β cell is enabled by the non–insulin-responsive glucose transporter GLUT-2. On entry, glucose is phosphorylated to glucose-6-phosphate by the enzyme glucokinase, enabling glucose metabolism to generate ATP. The rise in the molar ratio of ATP relative to adenosine diphosphate closes the ATP-sensitive potassium channel in the cell membrane (K_{ATP} channel). This channel is composed of 2 subunits, the K_{IR} 6.2 channel, part of the family of inward-rectifier potassium channels, and a regulatory component in intimate association with K_{IR} 6.2 known as the sulfonylurea receptor (SUR1). Together, K_{IR} 6.2 and SUR1 constitute the potassium-sensitive ATP channel K_{ATP}. Normally, the K_{ATP} is open, but with the rise in ATP and closure of the channel, potassium accumulates intracellularly, causing depolarization of the membrane, opening of voltage-gated calcium channels, influx of calcium into the cytoplasm, and secretion of insulin via exocytosis. The genes for both SUR1 and K_{IR} 6.2 are located close together on the short arm of chromosome 11, the site of the insulin gene. **Inactivating** mutations in the gene for SUR1 or, less often, K_{IR} 6.2 prevent the potassium channel from opening; it remains variably closed with constant depolarization and, therefore, constant inward flux of calcium; hence, insulin secretion is continuous and not governed by the glucose concentration. A milder autosomal dominant form of these defects is also reported. Likewise, an **activating** mutation in glucokinase or glutamate dehydrogenase enzyme activity results in closure of the potassium channel through overproduction of ATP which causes hyperinsulinism. Genetic defects in fatty acid metabolism, in the insulin transcription factor HNF-4α and HNF-1α, and in the uncoupling protein UCP-2 of the mitochondrial gene complex also have been involved in

Table 92-8 Clinical Manifestations and Differential Diagnosis in Childhood Hypoglycemia

				Serum		Effect of 24-36 hr Fast on Plasma					Glycemic Response to Glucagon		Glycemic Response to Infusion of	
Condition	Hypoglycemia	Urinary Ketones or Reducing Sugars	Hepatomegaly	LIPIDS	URIC ACID	GLUCOSE	INSULIN	KETONES	ALANINE	LACTATE	FED	FASTED	ALANINE	GLYCEROL
Normal	0	0	0	Normal	Normal	↓	↓	↑	↓	Normal	↑	↓		Not indicated
Hyperinsulinemia	Recurrent severe	0	0	Normal or ↑	Normal	↓↓	↑↑	↓↓	Normal	Normal	↑	↑		Not indicated
Ketotic hypoglycemia	Severe with missed meals	Ketonuria +++	0	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓		Not indicated
Fatty acid oxidation disorder	Severe with missed meals	Absent	0 to + Abnormal liver function test results	Abnormal	↑		Contraindicated				↑	↓		Not indicated
Hypopituitarism	Moderate with missed meals	Ketonuria ++		Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓	↑	↑
Adrenal insufficiency	Severe with missed meals	Ketonuria ++	0	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓	↑	↑
Enzyme deficiencies	Severe-constant	Ketonuria +++	+++	↑↑	↑↑	↓↓	↓	↑↑	↑↑	↑↑	0	0-↓↓	0	0
Glucose-6-phosphatase debrancher	Moderate with fasting	++	++	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	0-↓↓	↑	↑
Phosphorylase	Mild-moderate	Ketonuria ++	+	Normal	Normal	↓	↓	↑↑	↓↓	Normal	0-↑	0-↓↓	↑	↑
Fructose-1, 6-diphosphatase	Severe with fasting	Ketonuria +++	+++	↑↑	↑↑	↓↓	↓	↑↑	↑↑	↑↑	↑	0-↓↓	↓	↓
Galactosemia	After milk or milk products	0 Ketones;(s) +	+++	Normal	Normal	↓	↓	↑	↓	Normal	↑	0-↓↓	↑	↑
Fructose intolerance	After fructose	0 Ketones;(s) +	+++	Normal	Normal	↓	↓	↑	↓	Normal	↑	0-↓↓	↑	↑

Details of each condition are discussed in the text.
0, absence; ↑ or ↓ indicates respectively small increase or decrease; ↑↑ or ↓↓ indicates respectively large increase or decrease.

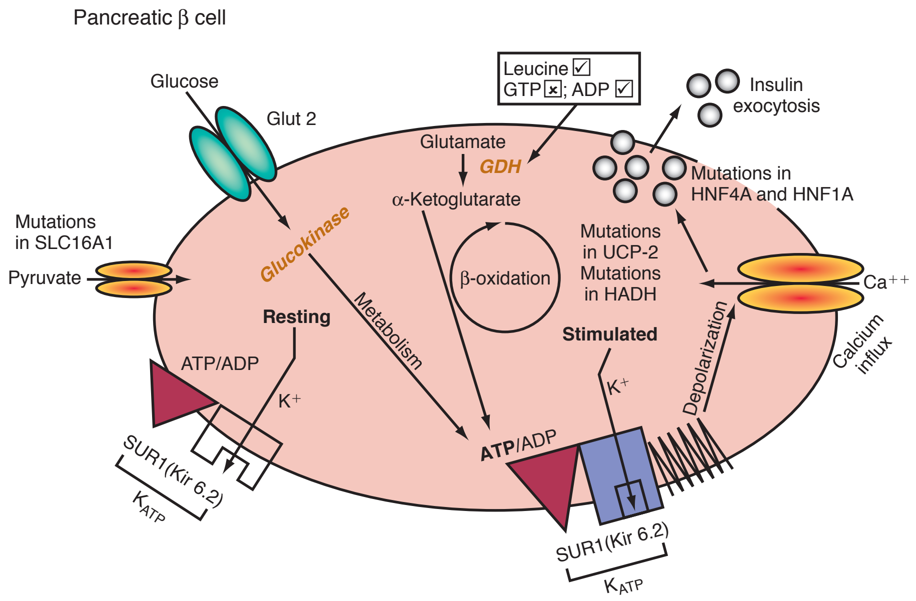

Figure 92-2 **Schematic of the pancreatic cell with some important steps in insulin secretion.** The membrane-spanning, adenosine triphosphate (ATP)-sensitive potassium (K^+) channel (K_{ATP}) consists of 2 subunits: the sulfonylurea receptor (SUR) and the inward rectifying K channel (K_{IR} 6.2). In the resting state, the ratio of ATP to adenosine diphosphate (ADP) maintains K_{ATP} in an open state, permitting efflux of intracellular K^+. When blood glucose concentration rises, its entry into the β cell is facilitated by the GLUT-2 glucose transporter, a process not regulated by insulin. Within the β cell, glucose is converted to glucose-6-phosphate by the enzyme glucokinase and then undergoes metabolism to generate energy. The resultant increase in ATP relative to ADP closes K_{ATP}, preventing efflux of K^+, and the rise of intracellular K^+ depolarizes the cell membrane and opens a calcium (Ca^{2+}) channel. The intracellular rise in Ca^{2+} triggers insulin secretion via exocytosis. Sulfonylureas trigger insulin secretion by reacting with their receptor (SUR) to close K_{ATP}; diazoxide inhibits this process, whereas somatostatin, or its analog octreotide, inhibits insulin secretion by interfering with calcium influx. Genetic mutations in SUR1 or K_{IR} 6.2 that prevent K_{ATP} from being open, tonically maintain inappropriate insulin secretion and are responsible for autosomal recessive forms of persistent hyperinsulinemic hypoglycemia of infancy (PHHI). One form of autosomal dominant PHHI is caused by an activating mutation in glucokinase. The amino acid leucine also triggers insulin secretion by closure of K_{ATP}. Metabolism of leucine is facilitated by the enzyme glutamate dehydrogenase (GDH), and overactivity of this enzyme in the pancreas leads to hyperinsulinemia with hypoglycemia, associated with hyperammonemia from overactivity of GDH in the liver. Mutations in the pyruvate channel SLC16A1 can cause ectopic expression in the β cell and permit pyruvate, accumulated during exercise, to induce insulin secretion and hence exercise-induced hypoglycemia. Mutations in the mitochondrial uncoupling protein 2 (UCP2) and hydroxyl acyl-CoA dehydrogenase (HADH) are associated with hyperinsulinism (HI) by mechanisms yet to be defined. Mutations in the transcription factors hepatic nuclear factors (HNF) 4α and 1α can be associated with neonatal macrosomia and HI, but progress to monogenic diabetes of youth (MODY) later in life. √, stimulation; GTP, guanosine triphosphate; X, inhibition.

hyperinsulinemic hypoglycemia. **Inactivating** mutations of the glucokinase gene or **activating** mutations of the ATP regulated potassium channel which prevent or limit closure of the channel, are responsible for inadequate insulin secretion and form the basis of some forms of maturity-onset diabetes of youth or of neonatal diabetes mellitus (see Chapter 589).

The familial forms of PHHI are more common in certain populations, notably Arabic and Ashkenazi Jewish communities, where it may reach an incidence of approximately 1 in 2,500, compared with the sporadic rates in the general population of approximately 1 in 50,000. These **autosomal recessive forms** of PHHI typically present in the immediate newborn period as macrosomic newborns with a weight frequently >4.0 kg and severe recurrent or persistent hypoglycemia manifesting in the initial hours or days of life. Glucose infusions as high as 15-20 mg/kg/min and frequent feedings fail to maintain euglycemia. Diazoxide, which acts by opening K_{ATP} channels (see Fig. 92-2) fails to control hypoglycemia adequately. Somatostatin (octreotide), which also opens K_{ATP} channels and inhibits calcium flux, may be partially effective in approximately 50% of patients (see Fig. 92-2). Calcium channel blocking agents have had inconsistent effects. Some affected infants have responded to sirolimus. When affected patients are unresponsive to these measures, pancreatectomy is strongly recommended to avoid the long-term neurologic sequelae of hypoglycemia. If surgery is undertaken, preoperative CT or MRI rarely reveals an isolated adenoma, which would then permit local resection. Intraoperative ultrasonography may identify a small impalpable adenoma, permitting local resection. Adenomas often present in late infancy or early childhood.

Distinguishing between **focal** and **diffuse** cases of **persistent hyperinsulinism** has been attempted in several ways. Preoperatively, transhepatic portal vein catheterization and selective pancreatic venous sampling to measure insulin may localize a focal lesion from the step-up in insulin concentration at a specific site. Selective catheterization of arterial branches supplying the pancreas, followed by infusion of a secretagogue such as calcium and portal vein sampling for insulin concentration (arterial stimulation-venous sampling) may localize a lesion. Both approaches are highly invasive, restricted to specialized centers, and not uniformly successful in distinguishing the focal from the diffuse forms, hence, these techniques are not recommended. 18F-labeled L-dopa combined with positron emission tomography scanning is a highly promising means to distinguish the focal from the diffuse lesions of hyperinsulinism unresponsive to medical management (Fig. 92-3). The "gold standard" remains intraoperative histologic characterization. Diffuse hyperinsulinism is characterized by large β cells with abnormally large nuclei, whereas focal adenomatous lesions display small and normal β cell nuclei. Although *SUR1* mutations are present in both types, the focal lesions arise by a random loss of a maternally imprinted growth-inhibitory gene on maternal chromosome 11p in association with paternal transmission of a mutated *SUR1* or K_{IR} 6.2 paternal chromosome 11p expressing the insulin-like growth factor 2 *(IGF2)* gene. Thus the focal form represents a double hit–loss of maternal repressor and transmission of a paternal mutation that contains a growth-promoting gene. Local excision of focal adenomatous islet cell hyperplasia results in a cure with little or no recurrence. For the diffuse form, near-total resection of 85-90% of the pancreas is recommended. The near-total pancreatectomy required for the diffuse

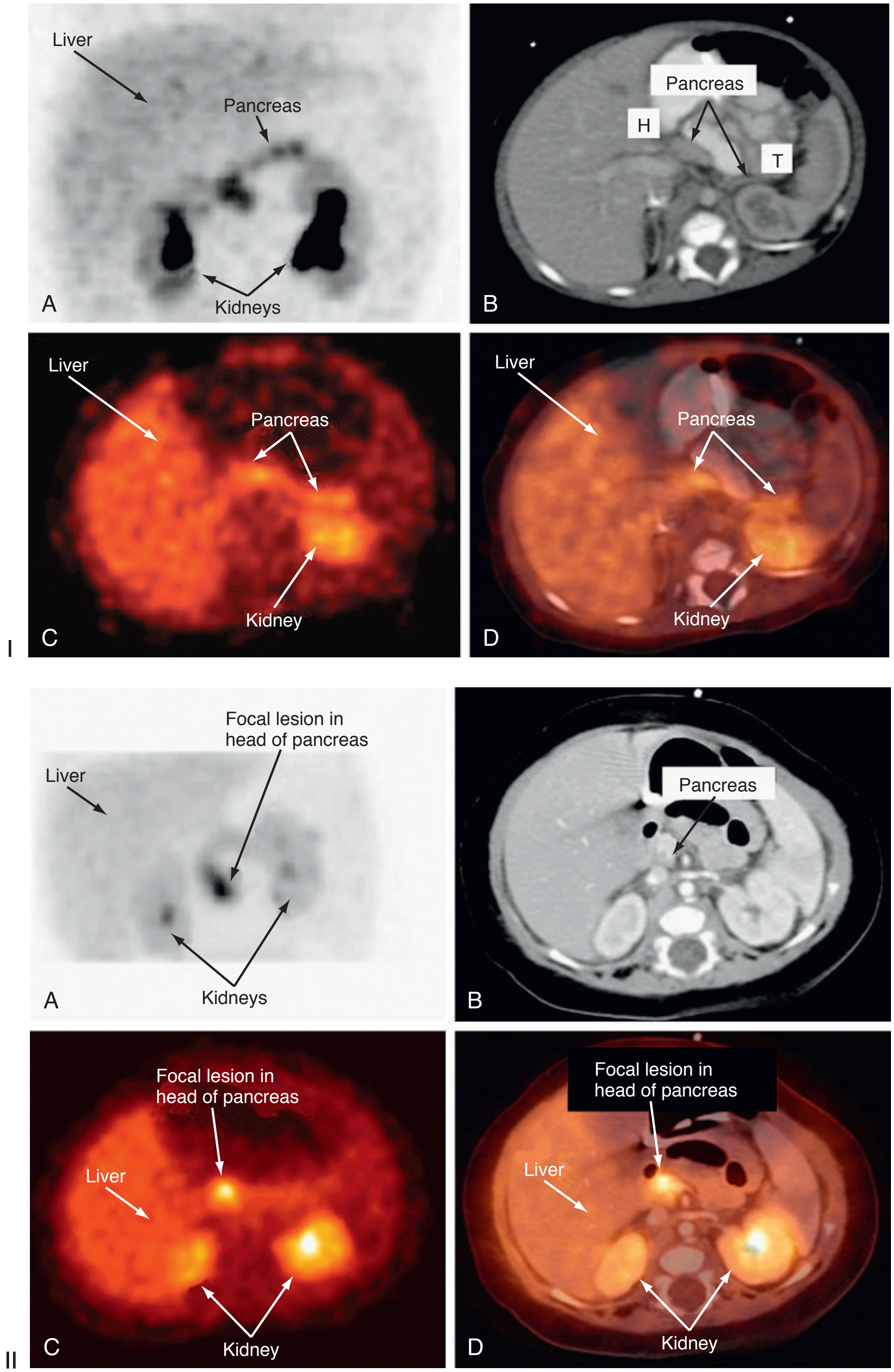

Figure 92-3 Congenital hyperinsulinism. **I** Panels (diffuse): [18F]-DOPA positron emission tomography (PET) of patient with diffuse form of congenital hyperinsulinism. **A,** Diffuse uptake of [18F]-DOPA is visualized throughout the pancreas. Transverse views show **(B)** normal pancreatic tissue on abdominal CT; **(C)** diffuse uptake of [18F]-DOPA in pancreas; and **(D)** confirmation of pancreatic uptake of [18F]-DOPA with coregistration. H, head of pancreas; T, tail of pancreas. **II** Panels (focal): [18F]-DOPA PET of patient with focal form of congenital hyperinsulinism. **A,** Discrete area of increased [18F]-DOPA uptake is visualized in the head of the pancreas. The intensity of this area is greater than that observed in the liver and neighboring normal pancreatic tissue. Transverse views show **(B)** normal pancreatic tissue on abdominal CT; **(C)** focal uptake of [18F]-DOPA in pancreatic head; and **(D)** confirmation of [18F]-DOPA uptake in the pancreatic head with coregistration. *(Courtesy of Dr. Olga Hardy, Children's Hospital of Philadelphia.)*

hyperplastic lesions is, however, often associated with persistent hypoglycemia with the later development of hyperglycemia or frank, insulin-requiring diabetes mellitus.

Further resection of the remaining pancreas may occasionally be necessary if hypoglycemia recurs and cannot be controlled by medical measures, such as the use of octreotide or diazoxide.

Experienced pediatric surgeons in medical centers equipped to provide the necessary preoperative and postoperative care, diagnostic evaluation, and management should perform surgery. In some patients who have been managed medically, hyperinsulinism and hypoglycemia regress over months. This is similar to what occurs in children with the hyperinsulinemic hypoglycemia seen in the epigenetic and genetic imprinting disorder **Beckwith-Wiedemann syndrome.**

If hypoglycemia first manifests between 3 and 6 mo of age or later, a therapeutic trial using medical approaches with diazoxide, octreotide, and frequent feedings can be attempted for up to 2-4 wk. Failure to maintain euglycemia without undesirable side effects from the drugs may prompt the need for surgery. Some success in suppressing insulin release and correcting hypoglycemia in patients with PHHI has been reported with the use of the long-acting somatostatin analog octreotide. Most cases of neonatal PHHI are sporadic; familial forms permit genetic counseling on the basis of anticipated autosomal recessive inheritance.

A second form of familial PHHI suggests **autosomal dominant inheritance.** The clinical features tend to be less severe, and onset of hypoglycemia is most likely, but not exclusively, to occur beyond the immediate newborn period and usually beyond the period of weaning at an average age at onset of about 1 yr. At birth, macrosomia is rarely observed, and response to diazoxide is almost uniform. The initial presentation may be delayed and rarely occur as late as 30 yr, unless provoked by fasting. The genetic basis for this autosomal dominant form has not been delineated; it is not always linked to K_{IR} 6.2/*SUR1*. The activating mutation in glucokinase is transmitted in an autosomal dominant manner. If a family history is present, genetic counseling for a 50% recurrence rate can be given for future offspring.

A third form of persistent PHHI is associated with **mild and asymptomatic hyperammonemia,** usually as a sporadic occurrence, although dominant inheritance occurs. Presentation is more like the autosomal dominant form than the autosomal recessive form. Diet and diazoxide control symptoms, but pancreatectomy may be necessary in some cases. The association of hyperinsulinism and hyperammonemia is caused by an inherited or de novo gain-of-function mutation in the enzyme glutamate dehydrogenase. The resulting increase in glutamate oxidation in the pancreatic β cell raises the ATP concentration and, hence, the ratio of ATP:adenosine diphosphate, which closes K_{ATP}, leading to membrane depolarization, calcium influx, and insulin secretion (see Fig. 92-2). In the liver, the excessive oxidation of glutamate to β-ketoglutarate may generate ammonia and divert glutamate from being processed to *N*-acetylglutamate, an essential cofactor for removal of ammonia through the urea cycle via activation of the enzyme carbamoyl phosphate synthetase. The hyperammonemia is mild, with concentrations of 100-200 μM/L, and produces no CNS symptoms or consequences, as seen in other hyperammonemic states. Leucine, a potent amino acid for stimulating insulin secretion and implicated in leucine-sensitive hypoglycemia, acts by allosterically stimulating glutamate dehydrogenase. Thus, **leucine-sensitive hypoglycemia** may be a form of the hyperinsulinemia–hyperammonemia syndrome or a potentiation of mild disorders of the K_{ATP} channel; it need not always be associated with a modest increase in serum ammonia.

Hypoglycemia associated with hyperinsulinemia is also seen in approximately 50% of patients with the **Beckwith-Wiedemann syndrome.** This syndrome is caused by an imprinting disorder (see Chapter 81) and characterized by omphalocele, gigantism, macroglossia, microcephaly, and visceromegaly (Fig. 92-4). Distinctive lateral earlobe fissures and facial nevus flammeus are present; hemihypertrophy occurs in many of these infants. Diffuse islet cell hyperplasia occurs in infants with hypoglycemia. The diagnostic and therapeutic approaches are the same as those discussed previously, although

Figure 92-4 Beckwith-Wiedemann syndrome. *(Courtesy of Dr. Michael Cohen, Dalhousie University, Halifax, Nova Scotia. From Jones KL:* Smith's recognizable patterns of human malformation, *ed 6, Philadelphia, 2006, WB Saunders.)*

microcephaly and slowing of brain development may occur independently of hypoglycemia. Patients with the Beckwith-Wiedemann syndrome may acquire tumors, including Wilms tumor, hepatoblastoma, adrenal carcinoma, gonadoblastoma, and rhabdomyosarcoma. This overgrowth syndrome is caused by mutations in the chromosome 11p15.5 region close to the genes for insulin, SUR1, K_{IR} 6.2, and IGF2. Duplications in this region and genetic imprinting from a defective or absent copy of the maternally derived gene are involved in the variable features and patterns of transmission. Hypoglycemia may resolve in weeks to months of medical therapy. Pancreatic resection may rarely be needed.

Hyperinsulinemic hypoglycemia in infancy is reported as a manifestation of one form of **congenital disorder of glycosylation**. Disorders of protein glycosylation usually present with neurologic symptoms but may also include liver dysfunction with hepatomegaly, intractable diarrhea, protein-losing enteropathy, and hypoglycemia (see Chapter 87.6). These disorders are often underdiagnosed. One entity associated with hyperinsulinemic hypoglycemia is caused by phosphomannose isomerase deficiency, and clinical improvement followed supplemental treatment with oral mannose at a dose of 0.17 g/kg 6 times per day.

After the first 12 mo of life, hyperinsulinemic states are uncommon until islet cell adenomas reappear as a cause after the patient is several years of age. Hyperinsulinemia as a result of **islet cell adenoma** should be considered in any child 5 yr or older who presents with hypoglycemia. Islet cell adenomas do not "light up" during scanning with L-dopa labeled with fluorine-18. An islet cell adenoma in a child should arouse suspicion of the possibility of **multiple endocrine neoplasia** type 1 (Wermer syndrome), which involves mutations in the menin gene and may be associated with hyperparathyroidism and with pituitary tumors. Tables 92-7 and 92-8 outline the diagnostic approach. Fasting for up to 24-36 hr usually provokes hypoglycemia; coexisting hyperinsulinemia confirms the diagnosis,

provided that factitious administration of insulin by the parents, a form of **Munchausen syndrome by proxy,** is excluded. Occasionally, provocative tests may be required. Exogenously administered insulin can be distinguished from endogenous insulin by simultaneous measurement of C-peptide concentration. If C-peptide levels are elevated, endogenous insulin secretion is responsible for the hypoglycemia; if C-peptide levels are low but insulin values are high, exogenous insulin has been administered, perhaps as a form of child abuse. Islet cell adenomas at this age are treated by surgical excision. Antibodies to insulin or the insulin receptor (**insulin mimetic action**) are also rarely associated with hypoglycemia. Activating mutations in the Akt2 signaling complex of the insulin receptor also can cause hyperinsulinism. Some **tumors** produce insulin-like growth factors, thereby provoking hypoglycemia by interacting with the insulin receptor. The astute clinician must also consider the possibility of deliberate or accidental ingestion of drugs such as a sulfonylurea or related compound that stimulates insulin secretion. In such cases, insulin and C-peptide concentrations in blood will be elevated. Inadvertent substitution of an insulin secretagogue by a dispensing error should be considered in those taking medications who suddenly develop documented hypoglycemia.

A rare form of hyperinsulinemic hypoglycemia has been reported after **exercise**. Whereas glucose and insulin remain unchanged in most people after moderate, short-term exercise, rare patients manifest severe hypoglycemia with hyperinsulinemia 15-50 min after the same standardized exercise. This form of exercise-induced hyperinsulinism is caused by an abnormal responsiveness of β-cell insulin release in response to pyruvate generated during exercise. The gene responsible for this syndrome, *SLC16A1,* regulates a transporter, MCT1R, that controls the entry of pyruvate into cells. Dominant mutations in *SLC16A1* that increase the ectopic expression of MCTR1 transporter in pancreatic β cells permit excessive entry of pyruvate into β cells and act to increase insulin secretion with resultant hypoglycemia during exercise.

Hypoglycemia with so-called nesidioblastosis has also rarely been reported after **bariatric surgery** for obesity. The mechanism for this form of hyperinsulinemic hypoglycemia remains to be defined.

Infants and children with **Nissen fundoplication,** a relatively common procedure used to ameliorate gastroesophageal reflux, frequently have an associated "dumping" syndrome with hypoglycemia. Characteristic features include significant hyperglycemia of 200 mg/dL and up to 500 mg/dL 30 min postprandially, and severe hypoglycemia (average 32 mg/dL in one series) 1.5-3.0 hr later. The early hyperglycemia phase is associated with brisk and excessive insulin release that causes the rebound hypoglycemia. A role for exaggerated GLP1 secretion has been proposed and glucagon responses have been reported to be inappropriately low in some cases. However, the physiologic mechanisms are not always clearly understood, and attempted treatments not always effective; **acarbose,** an inhibitor of glucose absorption, was reported to be successful in one small series.

Endocrine Deficiency

Hypoglycemia associated with endocrine deficiency is usually caused by adrenal insufficiency with or without associated growth hormone deficiency (see Chapters 557 and 575). In panhypopituitarism, isolated adrenocorticotropic hormone (ACTH) or growth hormone deficiency, or combined ACTH deficiency plus growth hormone deficiency, the incidence of hypoglycemia is as high as 20%. In the newborn period, hypoglycemia may be the presenting feature of hypopituitarism; in males, a microphallus may provide a clue to a coexisting deficiency of gonadotropin. Newborns with hypopituitarism often have a form of "hepatitis" associated with cholestatic jaundice and hypoglycemia. The combination of hypoglycemia and cholestatic jaundice requires exclusion of hypopituitarism as a cause, as the jaundice resolves with replacement treatment of growth hormone, cortisol, and thyroid as required. This constellation is often associated with the syndrome of **septooptic dysplasia.** When adrenal disease is severe, as in congenital adrenal hyperplasia caused by enzyme defects in cortisol synthesis, adrenal hemorrhage, or congenital hypoplasia of the adrenal glands, disturbances in serum electrolytes with hyponatremia and hyperkalemia or ambiguous genitals may provide diagnostic clues (see Chapter 576). In older children, failure of growth should suggest growth hormone deficiency. Hyperpigmentation or salt-craving may provide the clue to Addison disease with increased ACTH levels or adrenal unresponsiveness to ACTH owing to a defect in the adrenal receptor for ACTH, congenital adrenal hypoplasia, adrenoleukodystrophy, or the Allgrove triple A syndrome. The frequent association of Addison disease in childhood with hypoparathyroidism (hypocalcemia), chronic mucocutaneous candidiasis, and other endocrinopathies which constitute the autoimmune polyendocrinopathy syndrome type 1 should be considered. Adrenoleukodystrophy, and congenital adrenal hypoplasia are sex-linked conditions and should be considered in the differential diagnosis of primary Addison disease in male children (see Chapter 86.2).

Hypoglycemia in cortisol–growth hormone deficiency may be caused by decreased gluconeogenic enzymes with cortisol deficiency, increased glucose utilization because of a lack of the antagonistic effects of growth hormone on insulin action, or failure to supply endogenous gluconeogenic substrate in the form of alanine and lactate with compensatory breakdown of fat and generation of ketones. Deficiency of these hormones results in reduced gluconeogenic substrate, which resembles the syndrome of ketotic hypoglycemia. Investigation of a child with hypoglycemia, therefore, requires exclusion of ACTH-cortisol or growth hormone deficiency and, if diagnosed, its appropriate replacement with cortisol or growth hormone.

Epinephrine deficiency could theoretically be responsible for hypoglycemia. Urinary excretion of epinephrine has been diminished in some patients with spontaneous or insulin-induced hypoglycemia in whom absence of pallor and tachycardia was also noted, suggesting that failure of catecholamine release, as the result of a defect anywhere along the hypothalamic–autonomic–adrenomedullary axis, might be responsible for the hypoglycemia. This possibility has been challenged, owing to the rarity of hypoglycemia in patients with bilateral adrenalectomy, provided that they receive adequate glucocorticoid replacement, and because diminished epinephrine excretion is found in normal patients with repeated insulin-induced hypoglycemia. Many of the patients described as having hypoglycemia with failure of epinephrine excretion fit the criteria for ketotic hypoglycemia. Also, repetitive hypoglycemia leads to diminished cortisol plus epinephrine responses, as seen most commonly in insulin-treated diabetes mellitus and the syndrome of hypoglycemia unawareness, associated with autonomic failure.

Glucagon deficiency in infants or children may theoretically be associated with hypoglycemia but has never been documented.

Substrate Limited

Ketotic Hypoglycemia

Ketotic hypoglycemia is the **most common** form of *childhood* hypoglycemia. This condition usually presents between the ages of 18 mo and 5 yr and commonly remits spontaneously by the age of 8-9 yr. Hypoglycemic episodes typically occur during periods of intercurrent illness when food intake is limited. The classic history is of a child who eats poorly or completely avoids the evening meal, is difficult to arouse from sleep the following morning and hence eats poorly again, and may have a seizure or be comatose by mid-morning. Another common presentation occurs when parents sleep late and the affected child is unable to eat breakfast, thus prolonging the overnight fast.

At the time of documented hypoglycemia, there is associated ketonuria and ketonemia; plasma insulin concentrations are appropriately low, ≤5-10 μU/mL, thus excluding hyperinsulinemia. A ketogenic provocative diet, formerly used as a diagnostic test, is no longer used to establish the diagnosis because fasting alone provokes a hypoglycemic episode with ketonemia and ketonuria within 12-18 hr in susceptible individuals. Normal children of similar age can withstand fasting without hypoglycemia developing during the same period, although

even normal children may acquire these features by 36 hr of fasting.

Children with ketotic hypoglycemia have plasma alanine concentrations that are markedly reduced in the basal state after an overnight fast and decline even further with prolonged fasting. Alanine, produced in muscle, is a major gluconeogenic precursor. Alanine is the only amino acid that is significantly lower in these children, and infusions of alanine (250 mg/kg) produce a rapid rise in plasma glucose without causing significant changes in blood lactate or pyruvate levels, indicating that the entire gluconeogenic pathway from the level of pyruvate is intact, but that there is a deficiency of substrate. Glycogenolytic pathways are also intact because glucagon induces a normal glycemic response in affected children in the fed state. The levels of hormones that counter hypoglycemia are appropriately elevated, and insulin is appropriately low.

The etiology of ketotic hypoglycemia may be a defect in any of the complex steps involved in protein catabolism, oxidative deamination of amino acids, transamination, alanine synthesis, or alanine efflux from muscle. Children with ketotic hypoglycemia are frequently smaller than age-matched controls and often have a history of transient neonatal hypoglycemia. Any decrease in muscle mass may compromise the supply of gluconeogenic substrate at a time when glucose demands per unit of body weight are already relatively high, thus predisposing the patient to the rapid development of hypoglycemia, with ketosis representing the attempt to switch to an alternative fuel supply. Children with ketotic hypoglycemia may represent the low end of the spectrum of children's capacity to tolerate fasting. Similar relative intolerance to fasting is present in normal children, who cannot maintain blood glucose after 30-36 hr of fasting, compared with the adult's capacity for prolonged fasting. Although the defect may be present at birth, it may not be evident until the child is stressed by more prolonged periods of calorie restriction. Moreover, the spontaneous remission observed in children at age 8-9 yr might be explained by the increase in muscle bulk with its resultant increase in supply of endogenous substrate and the relative decrease in glucose requirement per unit of body mass with increasing age.

In anticipation of spontaneous resolution of this syndrome, treatment of ketotic hypoglycemia consists of frequent feedings of a high-protein, high-carbohydrate diet. During intercurrent illnesses, parents should be taught to test the child's urine for the presence of ketones, the appearance of which precedes hypoglycemia by several hours. In the presence of ketonuria, liquids of high carbohydrate content should be offered to the child. If these cannot be tolerated, the child should be treated with intravenous glucose administration in a hospital.

Branched-Chain Ketonuria (Maple Syrup Urine Disease)

See Chapter 85.6.

The hypoglycemic episodes were once attributed to high levels of leucine, but evidence indicates that interference with the production of alanine and its availability as a gluconeogenic substrate during calorie deprivation is responsible for hypoglycemia.

Glycogen Storage Disease

See Chapter 87.1.

Glucose-6-Phosphatase Deficiency (Type I Glycogen Storage Disease)

Affected children usually display a remarkable tolerance to their chronic hypoglycemia; blood glucose values in the range of 20-50 mg/dL are not associated with the classic symptoms of hypoglycemia, possibly reflecting the adaptation of the CNS to ketone bodies and lactate as alternative fuels. Hepatomegaly and poor growth are consistent physical features. Hypoglycemia is associated with acidosis (HCO_3 <18 mEq/L), increased β O-B and lactate; hyperuricemia also is frequent. Management is discussed in detail in Chapter 87.

Amylo-1,6-Glucosidase Deficiency (Debrancher Enzyme Deficiency; Type III Glycogen Storage Disease)

See Chapter 87.

Liver Phosphorylase Deficiency (Type VI Glycogen Storage Disease)

See Chapter 87.

Low hepatic phosphorylase activity may result from a defect in any of the steps of activation; a variety of defects have been described. Hepatomegaly, excessive deposition of glycogen in liver, growth retardation, and occasional symptomatic hypoglycemia occur. A diet high in protein and reduced in carbohydrate usually prevents hypoglycemia.

Glycogen Synthetase Deficiency

See Chapter 87.

The inability to synthesize glycogen is rare. There is hypoglycemia and hyperketonemia after fasting because glycogen reserves are markedly diminished or absent. After feeding, however, hyperglycemia with glucosuria may occur because of the inability to assimilate some of the glucose load into glycogen. During fasting hypoglycemia, levels of the counterregulatory hormones, including catecholamines, are appropriately elevated or normal, and insulin levels are appropriately low. The liver is not enlarged. Protein-rich feedings at frequent intervals result in dramatic clinical improvement, including growth velocity. This condition mimics the syndrome of ketotic hypoglycemia and should be considered in the differential diagnosis of that syndrome.

Disorders of Gluconeogenesis

Fructose-1,6-Diphosphatase Deficiency

See Chapter 87.3.

A deficiency of this enzyme results in a block of gluconeogenesis from all possible precursors below the level of fructose-1,6-diphosphate. Infusion of these gluconeogenic precursors results in lactic acidosis without a rise in glucose; acute hypoglycemia may be provoked by inhibition of glycogenolysis. Glycogenolysis remains intact, and glucagon elicits a normal glycemic response in the fed, but not in the fasted, state. Accordingly, affected individuals have hypoglycemia only during caloric deprivation, as in fasting, or during intercurrent illness. As long as glycogen stores remain normal, hypoglycemia does not develop. In affected families, there may be a history of siblings with known hepatomegaly who died in infancy with unexplained metabolic acidosis.

Defects in Fatty Acid Oxidation

See Chapter 86.

The important role of fatty acid oxidation in maintaining gluconeogenesis is underscored by examples of congenital or drug-induced defects in fatty acid metabolism that may be associated with fasting hypoglycemia.

Various congenital enzymatic deficiencies causing defective carnitine or fatty acid metabolism occur. A severe and relatively common form of fasting hypoglycemia with hepatomegaly, cardiomyopathy, and hypotonia occurs with long- and medium-chain fatty acid CoA dehydrogenase deficiency. Plasma carnitine levels are low, ketones are not present, but dicarboxylic aciduria is present in urine. Clinically, patients with **acyl-CoA dehydrogenase deficiency** present with a Reye-like syndrome (see Chapter 361), recurrent episodes of severe fasting hypoglycemic coma, and cardiorespiratory arrest (sudden infant death syndrome-like events). Severe hypoglycemia and metabolic acidosis without ketosis also occur in patients with multiple acyl-CoA dehydrogenase disorders. Hypotonia, seizures, and acrid odor are other clinical clues. Survival depends on whether the defects are severe or mild; diagnosis is established from studies of enzyme activity in liver biopsy tissue or in cultured fibroblasts from affected patients. Tandem mass spectrometry can be employed for blood samples, even those on filter paper, for screening of congenital inborn errors. Molecular diagnosis also is available for most entities. The frequency of this disorder

is at least 1 in 10,000-15,000 births. Avoidance of fasting and supplementation with carnitine may be lifesaving in these patients who generally present in infancy.

Interference with fatty acid metabolism also underlies the fasting hypoglycemia associated with Jamaican vomiting sickness, with atractyloside, and with the drug valproate. In **Jamaican vomiting sickness,** the unripe ackee fruit contains a water-soluble toxin, hypoglycin, which produces vomiting, CNS depression, and severe hypoglycemia. The hypoglycemic activity of hypoglycin derives from its inhibition of gluconeogenesis secondary to its interference with the acyl-CoA and carnitine metabolism essential for the oxidation of long-chain fatty acids. The disease is almost totally confined to Jamaica, where ackee forms a staple of the diet for the poor. The ripe ackee fruit no longer contains this toxin. *Atractyloside* is a reagent that inhibits oxidative phosphorylation in mitochondria by preventing the translocation of adenine nucleotides, such as ATP, across the mitochondrial membrane. Atractyloside is a perhydrophenanthrenic glycoside derived from *Atractylis gummifera.* This plant is found in the Mediterranean basin; ingestion of this "thistle" is associated with hypoglycemia and a syndrome similar to Jamaican vomiting sickness. The anticonvulsant drug **valproate** is associated with side effects, predominantly in young infants, which include a Reye-like syndrome, low serum carnitine levels, and the potential for fasting hypoglycemia. In all these conditions, hypoglycemia *is not associated with ketonuria.*

Acute Alcohol Intoxication

The liver metabolizes alcohol as a preferred fuel, and generation of reducing equivalents during the oxidation of ethanol alters the reduced form of nicotinamide adenine dinucleotide : nicotinamide adenine dinucleotide ratio, which is essential for certain gluconeogenic steps. As a result, gluconeogenesis is impaired and hypoglycemia may ensue if glycogen stores are depleted by starvation or by preexisting abnormalities in glycogen metabolism. In toddlers who have been unfed for some time, even the consumption of small quantities of alcohol can precipitate these events. The hypoglycemia promptly responds to intravenous glucose, which should always be considered in a child who presents initially with coma or seizure, after taking a blood sample to determine glucose concentration. The possibility of the child's ingesting alcoholic drinks must also be considered if there was a preceding adult evening party. A careful history allows the diagnosis to be made and may avoid needless and expensive hospitalization and investigation.

Salicylate Intoxication

See Chapter 63.

Both hyperglycemia and hypoglycemia occur in children with salicylate intoxication. Accelerated utilization of glucose, resulting from augmentation of insulin secretion by salicylates, and possible interference with gluconeogenesis may contribute to hypoglycemia. Infants are more susceptible than are older children. Monitoring of blood glucose levels with appropriate glucose infusion in the event of hypoglycemia should form part of the therapeutic approach to salicylate intoxication in childhood. Ketosis may occur.

Phosphoenolpyruvate Carboxykinase Deficiency

Deficiency of this rate-limiting gluconeogenic enzyme is associated with severe fasting hypoglycemia and variable onset after birth. Hypoglycemia may occur within 24 hr after birth, and defective gluconeogenesis from alanine can be documented in vivo. Liver, kidney, and myocardium demonstrate fatty infiltration, and atrophy of the optic nerve and visual cortex may occur. Hypoglycemia may be profound. Lactate and pyruvate levels in plasma have been normal, but a mild metabolic acidosis may be present. The fatty infiltration of various organs is caused by increased formation of acetyl-CoA, which becomes available for fatty acid synthesis. Diagnosis of this rare entity can be made with certainty only through appropriate enzymatic determinations in liver biopsy material or molecular diagnosis. Avoidance of periods of fasting through frequent feedings rich in carbohydrate should be helpful because glycogen synthesis and breakdown are intact.

Pyruvate Carboxylase Deficiency

See Chapter 87.

Other Enzyme Defects

Galactosemia (Galactose-1-Phosphate Uridyl Transferase Deficiency)

See Chapter 87.

Fructose Intolerance (Fructose-1-Phosphate Aldolase Deficiency)

See Chapter 87.

Acute hypoglycemia is caused by the inhibition by fructose-1-phosphate of glycogenolysis via the phosphorylase system and of gluconeogenesis at the level of fructose-1,6-diphosphate aldolase. Affected individuals usually learn spontaneously to eliminate fructose from their diet.

Defects in Glucose Transporters

Glut-1 Deficiency

Rarely infants with a seizure disorder are found to have low CSF glucose concentrations despite normal plasma glucose. Lactate concentrations in CSF are low, suggesting decreased glycolysis rather than bacterial infection, which causes low CSF glucose with high lactate. The erythrocyte glucose transporter is defective, suggesting a similar defect in the brain glucose transporter responsible for the clinical features. A ketogenic diet reduces the severity of seizures by supplying an alternate source of brain fuel that bypassed the defect in glucose transport.

Glut-2 Deficiency

Children with hepatomegaly, galactose intolerance, and renal tubular dysfunction **(Fanconi-Bickel syndrome)** have a deficiency of the GLUT-2 glucose transporter of plasma membranes. In addition to liver and kidney tubules, GLUT-2 is also expressed in pancreatic β cells. Hence, the clinical manifestations reflect impaired glucose release from liver and defective tubular reabsorption of glucose plus phosphaturia and aminoaciduria**.**

Systemic Disorders

Several systemic disorders are associated with hypoglycemia in infants and children. Neonatal sepsis is often associated with hypoglycemia, possibly as a result of diminished caloric intake with impaired gluconeogenesis. Similar mechanisms may apply to the hypoglycemia found in severely malnourished infants or those with severe malabsorption. Hyperviscosity with a central hematocrit of >65% is associated with hypoglycemia in at least 10-15% of affected infants. **Falciparum malaria** is associated with hyperinsulinemia and hypoglycemia. Heart and renal failure are also associated with hypoglycemia, but the mechanism is obscure.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Table 92-8 and Figure 92-5 list the pertinent clinical and biochemical findings in the common childhood disorders associated with hypoglycemia. A careful and detailed history is essential in every suspected or documented case of hypoglycemia (see Table 92-7). Specific points to be noted include age at onset, temporal relation to meals or caloric deprivation, and a family history of prior infants known to have had hypoglycemia or of unexplained infant deaths. In the 1st wk of life, the majority of infants have the transient form of neonatal hypoglycemia either as a result of prematurity/intrauterine growth restriction or by virtue of being born to diabetic mothers. The absence of a history of maternal diabetes, but the presence of macrosomia and the characteristic large plethoric appearance of an "infant of a diabetic mother" should arouse the possibility of hyperinsulinemic hypoglycemia of infancy, probably resulting from a K_{ATP} channel defect that is familial (autosomal recessive) or sporadic; decreased β OH butyrate, low FFAs, and plasma insulin concentrations >5-10 μU/mL in the presence of documented hypoglycemia confirm this diagnosis. The presence of

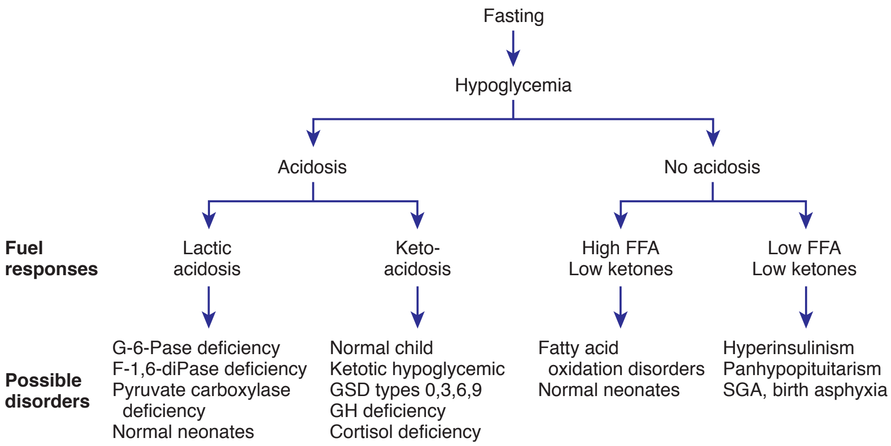

Figure 92-5 Algorithm for diagnosis of hypoglycemia based on fasting fuel responses. F1,6-diPase, fructose-1,6-diphosphatase; FFA, free fatty acid; G-6Pase, glucose-6-phosphatase; GH, growth hormone; GSD, glycogen storage disease; SGA, small for gestational age. *(From Kliegman RM, Greenbaum LA, Lye PS, editors:* Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier Saunders.)*

hepatomegaly should arouse suspicion of an enzyme deficiency such as glucose-6-phosphate in glycogen storage disease-1 or other glycogen storage diseases; if a non–glucose-reducing sugar is present in the urine (e.g., Clinitest positive but Clinistix negative), galactosemia is most likely. In males, the presence of a microphallus suggests the possibility of hypopituitarism, which also may be associated with cholestatic jaundice in both sexes; evidence of a midline facial defect such as cleft palate also suggests possible hypopituitarism as the cause of hypoglycemia via deficiency in growth hormone and/or cortisol. A high index of suspicion and awareness of hypoglycemia as the cause for unusual behavior of any "sick" newborn should prompt a **bedside glucose determination**. However, because glucose meters have an accuracy of only ±20%, any blood glucose value <60 mg/dL must be confirmed by a formal laboratory measurement that is performed without delay on a blood sample preserved in a tube that prevents glycolysis, which can cause spurious low values.

Past the newborn period, clues to the cause of persistent or recurrent hypoglycemia may be obtained through a careful history, physical examination, and initial laboratory findings. The temporal relation of the hypoglycemia to food intake may suggest that the defect is one of gluconeogenesis, if symptoms occur 6 hr or more after meals. If hypoglycemia occurs shortly after meals, hyperinsulinism should be suspected and confirmed or excluded via measurement of β OH butyrate, insulin, and FFA in a sample in which blood glucose is <50 mg/dL. The autosomal dominant forms of hyperinsulinemic hypoglycemia need to be considered, with measurement of glucose, insulin, and ammonia, and careful history for other affected family members of any age. Measurement of IGFBP-1 may be useful; it is low in states of hyperinsulinism and high in other forms of hypoglycemia. The presence of hepatomegaly suggests one of the enzyme deficiencies in glycogen breakdown or in gluconeogenesis, as outlined in Table 92-8. The absence of ketonemia or ketonuria at the time of initial presentation strongly suggests hyperinsulinism or a defect in fatty acid oxidation. In most other causes of hypoglycemia, with the exception of galactosemia and fructose intolerance, ketonemia and ketonuria are present at the time of fasting hypoglycemia. At the time of the hypoglycemia, serum should be obtained for determination of substrates especially β OH butyrate, lactate and FFA as well as hormones especially insulin, cortisol, ACTH, and growth hormone, followed by repeated measurement after an intramuscular or intravenous injection of glucagon, as outlined in Table 92-7. Table 92-8 summarizes the interpretation of the findings. Hypoglycemia with ketonuria in children between ages 18 mo and 5 yr is most likely to be ketotic hypoglycemia, especially if hepatomegaly is absent. The ingestion of a toxin, including alcohol or salicylate, can usually be excluded rapidly by the history. Inadvertent or deliberate drug ingestion and errors in dispensing medicines should also be considered. Munchhausen by proxy should be considered when parents or other caregivers have access to insulin or insulin secretagogues—high insulin concentrations in the sample with low concentrations of C-peptide confirm exogenous insulin administration. Deliberate or accidental ingestion of drugs that stimulate endogenous insulin secretion will result in both high insulin and C-peptide concentrations and may require specialized laboratory methods that identify the offending substance.

When the history is suggestive, but acute symptoms are not present, a 24 hr supervised fast can usually provoke hypoglycemia and resolve the question of hyperinsulinism or other conditions (see Table 92-8). Rarely, such a fast needs to be extended to 36 hr, but only in older children. Such a fast is contraindicated if a fatty acid oxidation defect is suspected; other approaches such as mass tandem spectrometry or molecular diagnosis, or both, should be considered. Because adrenal insufficiency may mimic ketotic hypoglycemia, plasma cortisol and ACTH levels should be determined at the time of documented hypoglycemia; increased buccal or skin pigmentation may provide the clue to primary adrenal insufficiency with elevated ACTH (melanocyte-stimulating hormone) activity. Short stature or a decrease in the growth rate may provide the clue to pituitary insufficiency involving growth hormone as well as ACTH. Definitive tests of pituitary–adrenal function, such as the arginine-insulin stimulation test for growth hormone insulin-like growth factor-1, IGFBP-1, and cortisol release, may be necessary.

In the presence of hepatomegaly and hypoglycemia, a presumptive diagnosis of the enzyme defect can often be made through the clinical manifestations, presence of hyperlipidemia, acidosis, hyperuricemia, response to glucagon in the fed and fasted states, and response to infusion of various appropriate precursors (see Tables 92-7 and 92-8). Table 92-8 summarizes these clinical findings and investigative approaches. Definitive diagnosis of the glycogen storage disease may require molecular diagnosis (see Chapter 87). Occasional patients with all the manifestations of glycogen storage disease are found to have normal enzyme activity. These definitive studies require special expertise available only in certain institutions.

TREATMENT

The prevention of hypoglycemia and its resultant effects on CNS development are critically important in the newborn period. For neonates with hyperinsulinism not associated with maternal diabetes, subtotal or focal pancreatectomy may be needed, unless hypoglycemia can be readily controlled with long-term diazoxide, somatostatin analogs (e.g., octreotide), or sirolimus.

Treatment of **acute symptomatic** neonatal or infant hypoglycemia includes intravenous administration of 2 mL/kg of 10% dextrose in water ($D_{10}W$), followed by a continuous infusion of glucose at 6-8 mg/kg/min, adjusting the rate to maintain blood glucose levels in the normal range. If hypoglycemic seizures are present, some recommend a 4 mL/kg bolus of $D_{10}W$.

Treatment of asymptomatic hyperglycemia in at risk infants usually includes enteral feedings rather than parenteral glucose. If symptoms develop or the hypoglycemia persists despite enteral feedings, intravenous glucose is indicated. Dextrose gel (40% at 400 mg/kg)

administered into the mouth may be an alternative to enteral feedings if breast milk or if formula is not available.

The management of **persistent** neonatal or infantile hypoglycemia includes increasing the rate of intravenous glucose infusion to 10-15 mg/kg/min or more, if needed. This may require a central venous or umbilical venous catheter to administer a hypertonic 15-25% glucose solution. If hyperinsulinism is present, it should be medically managed initially with diazoxide and then somatostatin analogs. If hypoglycemia is unresponsive to intravenous glucose plus diazoxide (maximal doses up to 15-20 mg/kg/day) and somatostatin analogs, surgery via partial or near-total pancreatectomy should be considered. Such surgery should be performed in centers with the requisite facilities, and trained staff experienced in the procedures. If possible, surgery should be preceded by [18F]-L-DOPA scanning to localize a lesion which can then provide guidance to the surgeon for curative resection before the operation is undertaken.

Oral diazoxide, 5-15 mg/kg/24 hr given in divided doses twice daily, may reverse hyperinsulinemic hypoglycemia but may also produce hirsutism, edema, nausea, hyperuricemia, electrolyte disturbances, advanced bone age, immunoglobulin G deficiency, and, rarely, hypotension with prolonged use. The long-acting somatostatin analog octreotide may be helpful in controlling hyperinsulinism causing hypoglycemia in patients with islet cell disorders, including genetic mutations in K_{ATP} channel and islet cell adenoma. Glucagon given by continuous IV infusion at 5 µg/kg/hr together with octreotide administered subcutaneously every 6-12 hr in doses of 20-50 µg/kg/day in neonates and young infants may maintain blood glucose, but generally these agents are used as a temporizing measure before surgery for partial or more complete pancreatectomy. Potential but unusual complications of octreotide include poor growth because of inhibition of growth hormone release, pain at the injection site, vomiting, diarrhea, and hepatic dysfunction (hepatitis, cholelithiasis), and necrotizing enterocolitis; tachyphylaxis to the drug's effects is more common. It may be particularly useful for the treatment of refractory hypoglycemia despite subtotal pancreatectomy. Total pancreatectomy is not optimal therapy, owing to the risks of surgery, permanent diabetes mellitus, and exocrine pancreatic insufficiency. Continued prolonged medical therapy without pancreatic resection if hypoglycemia is controllable is worthwhile, because over time some children have a spontaneous resolution of the hyperinsulinism-induced hypoglycemia. This should be balanced against the risk of hypoglycemia-induced CNS injury and the toxicity of drugs.

PROGNOSIS

The prognosis is good in asymptomatic neonates with hypoglycemia of short duration. Hypoglycemia recurs in 10-15% of infants after adequate treatment. Recurrence is more common if intravenous fluids are extravasated or discontinued too rapidly before oral feedings are well tolerated. Children who had transient neonatal hypoglycemia have an increased incidence of ketotic hypoglycemia later in life.

The prognosis for normal intellectual function must be guarded because prolonged, recurrent, and severe symptomatic hypoglycemia is associated with neurologic sequelae. Symptomatic infants with hypoglycemia, particularly low-birthweight infants, those with persistent hyperinsulinemic hypoglycemia, and severely hypoglycemic infants born to poorly controlled diabetic mothers, have a poorer prognosis for subsequent normal intellectual development than asymptomatic infants do.

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The Fetus and the Neonatal Infant

PART XII

Chapter 93

Overview of Mortality and Morbidity

Waldemar A. Carlo

The risk for mortality in fetuses and neonates is very high around the time of birth. The perinatal period is most often defined as the period from the 28th wk of gestation through the 7th day after birth. The neonatal period is defined as the 1st 28 days after birth and may be further subdivided into the very early (birth to <24 hr), early (birth to <7 days), and late neonatal periods (7 days to <28 days). Infancy is defined as the 1st yr after birth.

Perinatal mortality is influenced by prenatal, maternal, and fetal conditions and by circumstances surrounding delivery. Perinatal deaths are associated with intrauterine growth restriction (IUGR); conditions that predispose the fetus to asphyxia, such as placental insufficiency; severe congenital malformations; and overwhelming early-onset neonatal infections (Table 93-1). The major causes of neonatal mortality are prematurity/low birthweight (LBW) and congenital anomalies (Fig. 93-1). Mortality is highest during the 1st 24 hr after birth. Neonatal mortality (4.04/1,000 in 2011) accounts for about two-thirds of all infant deaths (deaths before 1 yr of age). Neonatal and postneonatal mortality rates in the United States have declined slightly in the last decade (Fig. 93-2). Factors related to the decline in mortality include improved obstetric and neonatal intensive care management with a significant reduction in birthweight-specific neonatal mortality (Fig. 93-3). Further reduction in neonatal mortality will depend on prevention of preterm delivery and LBW, prenatal diagnosis and early management of congenital anomalies, and effective diagnosis and treatment of diseases that result from adverse factors during pregnancy, labor, and/or delivery (see Table 93-1). In the United States each year, approximately 6 million pregnancies, 4 million live births, 19,000 neonatal deaths, and 28,000 infant deaths occur. Approximately 10% of births are to teenage women between the ages of 15 and 19 yr, a proportion that has been decreasing for approximately 50 yr (Fig. 93-4). Births to girls 10-14 yr of age, very young mothers who are at great social and medical risk, declined substantially over this period.

Infant mortality rates (deaths occurring from birth to 12 mo per 1,000 live births) vary by country; in 2010, rates were lowest in Hong Kong (1.7/1,000 births), moderate in the United States (6.1/1,000), and highest in developing, resource-poor countries (30-150/1,000). Medical, socioeconomic, and cultural factors influence perinatal and neonatal mortality. Preventive variables such as health education, prenatal care, nutrition, social support, risk identification, and obstetric care can effectively reduce perinatal, neonatal, and infant mortality. A number of reasons can explain in part the relatively higher infant mortality in the United States than in other countries. There is evidence of differential reporting of live births versus fetal deaths or stillbirths among countries. Many countries do not report as live births those of infants as mature as up to 27 wk if they die early after birth. The reporting of vital events in the United States is more complete than in many countries, including developed countries. This situation in part explains the larger proportion of LBW/preterm infants in the United States than in other countries. Increases in recorded preterm live births, especially of the most immature infants (<500 g body weight) in the United States, result in increases in both neonatal and infant mortality rates. Nonetheless, continuing healthcare disparities in part account for the higher infant mortality rate in the United States. Infants of African-American women continue to have a high infant mortality rate (12.76/1,000), which is more than twice the rates of infants of white (5.52/1,000) and Hispanic mothers (4.76/1,000 Central and South American vs. 7.29/1,000 Puerto Rican).

In the United States, approximately 50% of infant deaths in 2011 were a consequence of 4 conditions (classified according to the *International Classification of Diseases*, 10th revision): congenital malformations (20.1%), disorders relating to prematurity and unspecified LBW (16.9%), sudden infant death syndrome (8.2%), and newborns affected by maternal complications of pregnancy (6.3%). LBW (as a result of preterm delivery and/or IUGR) is a major determinant of both neonatal and infant mortality rates and, together with congenital anomalies (cardiac, central nervous system, respiratory), contributes significantly to childhood morbidity. In developing countries, LBW/prematurity, birth asphyxia, and infections are the major causes of infant deaths.

The LBW rate (infants weighing ≤2,500 g at birth each year) in the United States increased from 6.6% to 8.2% between 1981 and 2008, whereas the very-low birthweight (VLBW) rate (infants weighing ≤1,500 g at birth) increased from 1.1% to 1.46% of all births. In the past decade, LBW has increased among white infants, mainly because of a rise in the number of multiple births (often associated with assisted reproduction). Nonetheless, LBW and VLBW rates remain highest among black infants. Reasons for the racial disparity in LBW remain unclear. Despite advances in prenatal and obstetric care, racial disparity in birthweight persists, thus suggesting the need for novel prevention programs. Furthermore, although preterm LBW survival is better among black neonates, overall neonatal and infant mortality rates remain highest among blacks (Fig. 93-5), even for infants born to extremely low-risk mothers (married, age 20-34 yr, ≥13 yr of education, adequate prenatal care, no medical risk factors, no alcohol or tobacco use during pregnancy). A reduction in the racial disparity in mortality is an important public health issue reflected in *Healthy People 2020*, the U.S. national health objectives for the year 2020.

LBW is caused by preterm birth, IUGR, or both. The predominant cause of LBW in the United States is preterm birth, whereas in developing countries, the cause is more often IUGR. Although IUGR does not appear to further increase the risk of mortality in preterm infants, both morbidity and mortality are increased in term growth-restricted infants. VLBW infants are most often premature (<37 wk of gestation), although IUGR may also complicate their early delivery. Even though VLBW occurs in only 1-2% of all infants in the United States, their births represent a large proportion of the neonatal and infant mortality, as well as of infants with both short- and long-term complications, including neurodevelopmental handicaps. The etiology of preterm birth is complex, multifactorial, and not completely understood. Causes include maternal diseases such as severe preeclampsia requiring elective delivery, premature rupture of membranes, uterine abnormalities, placental bleeding (abruptio, previa), multiple-fetus gestation, drug misuse, maternal chronic illnesses, fetal distress, and infection. A complex interaction can be noted among infection, inflammation, and both preterm premature rupture of membranes and preterm birth. Infectious antecedents include maternal urinary tract infection, chorioamnionitis, bacterial vaginosis, and upper and lower genitourinary tract infection with a variety of agents (*Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis,* and group B streptococcus). Preconceptional dietary folate supplementation may effectively reduce the rate of spontaneous

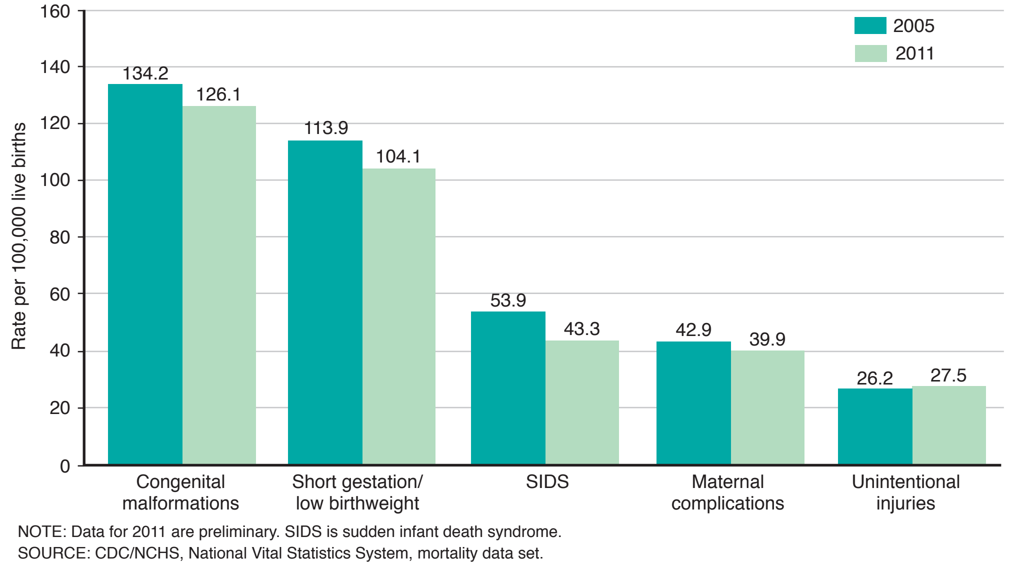

Figure 93-1 Infant mortality rates for the 5 leading causes of infant death in 2011: United States, 2005 and 2011. *(From CDC/NCHS, National Vital Statistics, mortality data set.* NCHS Data Brief, *No. 120, April 2013.)*

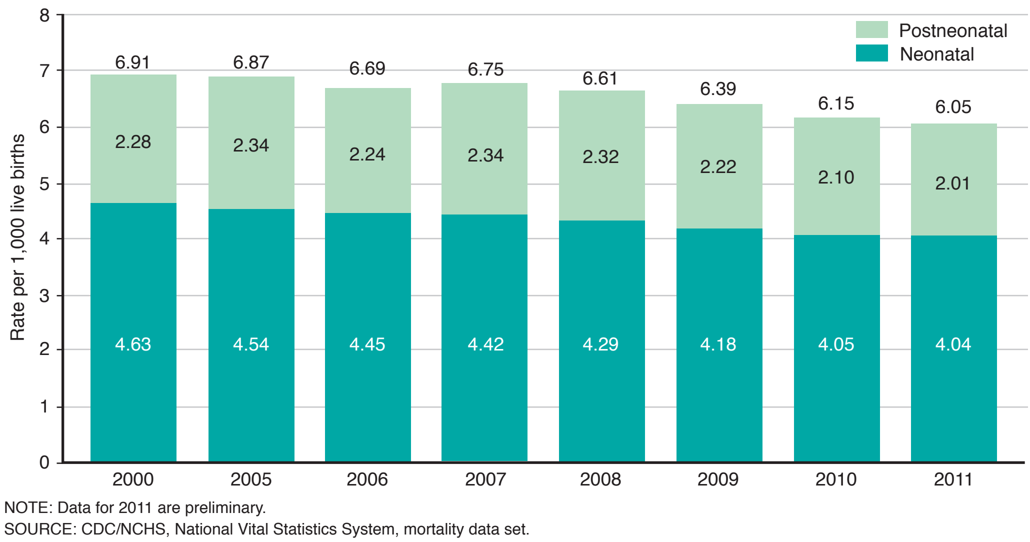

Figure 93-2 Infant, neonatal, and postneonatal mortality rates: United States, 2000 and 2005-2011. *(From CDC/NCHS, National Vital Statistics, mortality data set.* NCHS Data Brief, *No. 120, April 2013.)*

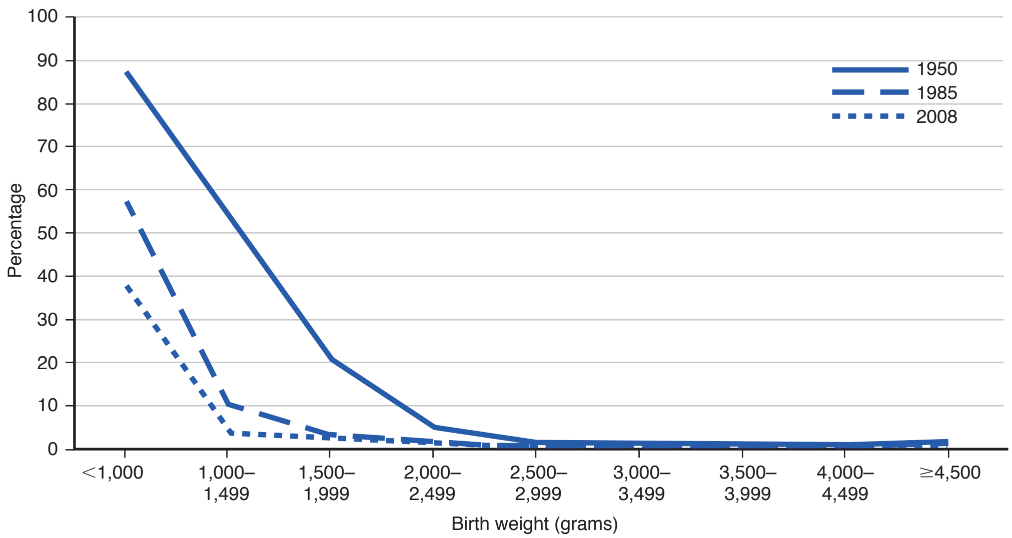

Figure 93-3 Birthweight-specific neonatal mortality—United States, 1950, 1985, and 2008. *(From Centers for Disease Control and Prevention: Grand rounds: public health approaches to reducing U.S. infant mortality.* MMWR Morb Mortal Wkly Rep *62(31):625–628, 2013, Fig. 3, p. 627.)*

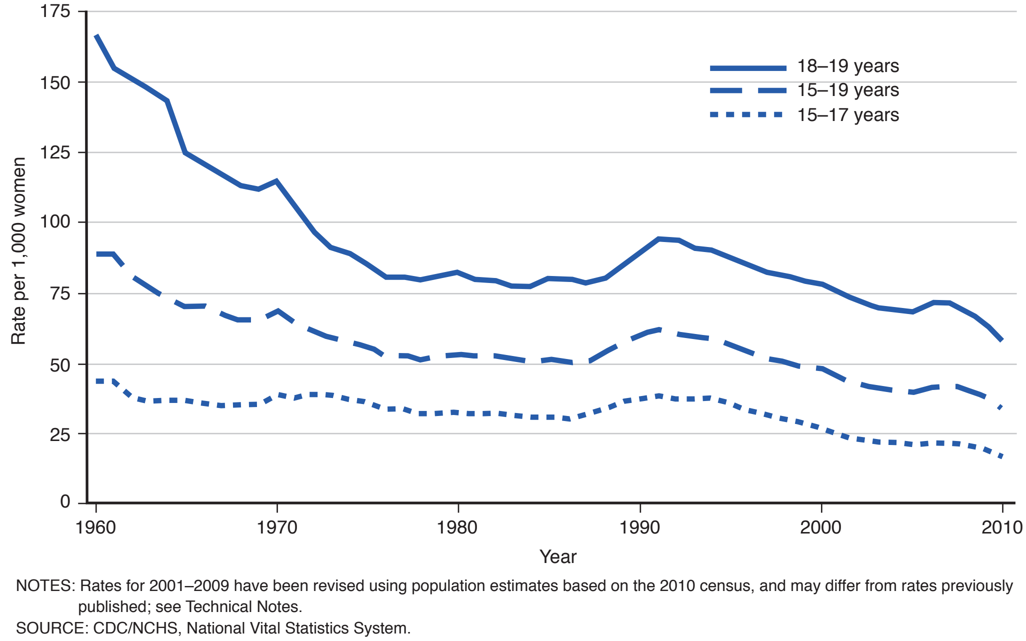

Figure 93-4 Birth rates for teenagers ages 15-19 yr, by age: United States, 1960-2010. *(From Martin JA, Hamilton BE, Ventura SJ, et al: Birth: final data for 2010.* Natl Vital Stat Rep *61(1):1–72, 2012, Fig. 3, p. 4.)*

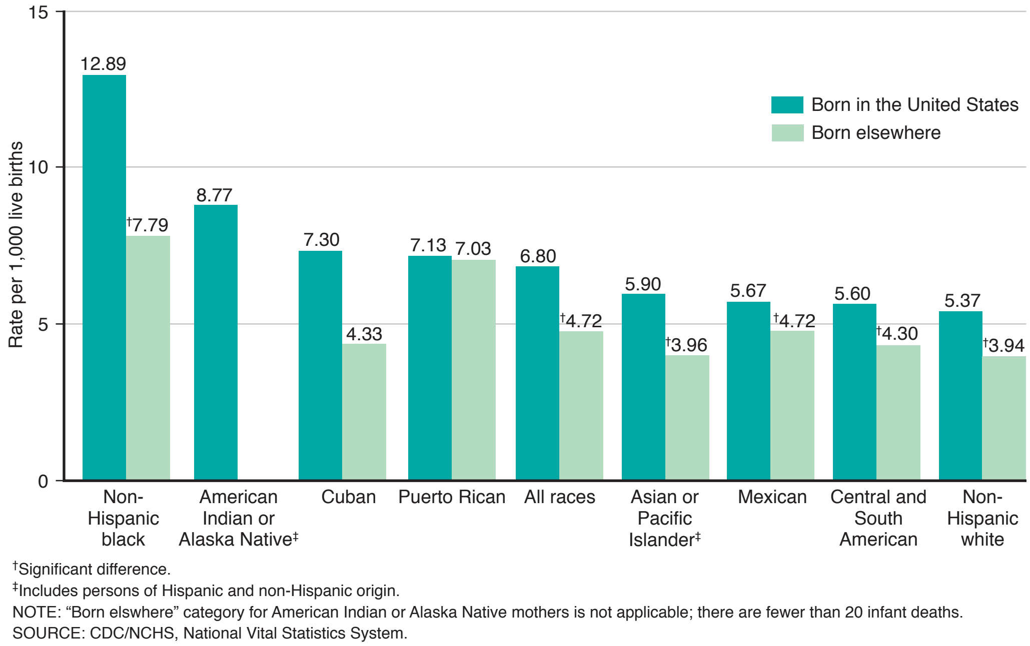

Figure 93-5 Infant mortality rates, by place of birth and by race and ethnicity of mother: United States, 2009. *(From Mathews TJ, MacDorman MF: Infant mortality statistics from the 2009 period linked birth/infant death data set.* Natl Vital Stat Rep *61(8):1–27, 2013.)*

preterm birth. In many cases, the cause of preterm delivery is unknown. The number of late preterm births (34-36 wk) has increased owing in part to elective deliveries; late preterm neonates are also at increased risk for morbidity and mortality. If possible, elective delivery should be delayed until ≥39 wk.

Although 99% of births occur in hospitals, only 80-85% of pregnant women receive ideal prenatal care in the 1st trimester. Many women who receive inadequate prenatal care are at risk for perinatal complications. Barriers to prenatal care include lack or insufficiency of money or insurance to pay for care; poor coordination of services, including language and cultural issues; and inadequate effective education about the importance of prenatal care. Successful and adequate provision of high-quality prenatal care requires competent healthcare professionals and coordination of services among physicians' offices, clinics, community hospitals, specially regionalized programs for high-risk mothers and infants, and tertiary care centers. Regional perinatal programs should provide continuing education and consultation in both the community and the referral center and transportation for pregnant women and newborn infants to appropriate hospitals; they should also include a regional hospital with facilities, equipment, and personnel for obstetric and neonatal intensive care (Table 93-2).

Fetal deaths slightly exceed neonatal deaths in their contribution to perinatal mortality. The fetal mortality rate in the United States has been declining steadily during the last 2 decades and decreased to 6.2/1000 in 2004. Obstetricians and maternal–fetal medicine subspecialists have a central role in reducing perinatal mortality and

morbidity. The overall decrease in fetal death has been from a reduction in late fetal deaths (≥28 wk). Intrapartum fetal deaths have declined more than antepartum fetal deaths, reflecting improvements in care during labor and delivery. It is important to emphasize the ability to predict the maturity and functional reserve of a fetus both before and during labor so that fetuses and infants at greatest risk can be identified as early as possible. The obstetrician and pediatrician must interact effectively to anticipate perinatal problems and take prompt preventive and therapeutic measures.

Causes of intrauterine fetal demise include obstetric conditions (preeclampsia, others), placental and umbilical cord abnormalities, genetic and syndromic disorders, intrauterine infections, fetal growth restriction, and preexisting maternal diseases. In approximately 40% of intrauterine fetal demise, there is no identifiable etiology.

Table 93-1	Major Causes of Perinatal and Neonatal Mortality
FETAL	
Placental insufficiency	
Intrauterine infection	
Severe congenital malformations (anomalies)	
Umbilical cord accident	
Abruptio placentae	
Hydrops fetalis	
PRETERM	
Severe immaturity	
Respiratory distress syndrome	
Intraventricular hemorrhage	
Congenital anomalies	
Infection	
Necrotizing enterocolitis	
Bronchopulmonary dysplasia (BPD)	
FULL TERM	
Congenital anomalies	
Birth asphyxia	
Trauma	
Infection	
Meconium aspiration pneumonia	
Persistent pulmonary hypertension (PPHN)	

Postneonatal mortality refers to deaths between 28 days and 1 yr of life. Historically, these infant deaths were a result of causes outside the neonatal period, such as sudden infant death syndrome, infections (respiratory, enteric), and trauma. With the advent of modern neonatal care, many VLBW and preterm infants who would have died in the 1st mo of life now survive the neonatal period only to succumb to the sequelae listed in Table 93-3. This delayed neonatal mortality is an important contributor to postneonatal mortality and explains its lack of decline during the last years.

Late preterm infants are at risk for hypothermia, hypoglycemia, respiratory distress, apnea, jaundice, feeding difficulties, dehydration, and suspected sepsis. They are also at risk of having rehospitalizations. Even term infants born at 37 and 38 wk by cesarean section are at increased risk for respiratory distress syndrome, transient tachypnea of the newborn, suspected sepsis, hypoglycemia, need for ventilatory support, and admission to the neonatal intensive care unit (Table 93-4).

For the most immature infants at the limit of viability (22-25 wk gestation), decision making about care is a complex process that involves the physician, other health professionals, and the family. The challenge for all premature infants is not only to improve survival, but also to reduce short-term complications and improve long-term neurodevelopmental outcome. Adverse neurodevelopmental sequelae include cerebral palsy, seizures, hydrocephalus requiring a shunt, blindness, deafness, and cognitive impairment. The risk of an adverse outcome increases with decreasing gestational age at birth. Higher birthweight, female gender, singleton birth, and antenatal steroids reduce the risk of neurodevelopment impairment or death. Early morbidity and prognostic variables that contribute to adverse neurodevelopmental outcomes include intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis requiring extensive bowel resection, neonatal infection, and bronchopulmonary dysplasia. Many studies have documented the impact of adverse social and family risk factors on poor outcome.

Table 93-2 Levels of In-Hospital Perinatal Care

MATERNAL	NEONATE
BASIC	
Monitor and care for low-risk patients	Resuscitation
	Stabilization
Triage for high risk for transfer	Well neonatal care
Detection and care of unanticipated labor problems	Nursery care
Emergency cesarean delivery within 30 min	Visitation
	General pediatrician staff (capable of neonatal resuscitation)
Blood bank, anesthesia, radiology, ultrasound, and laboratory support	
Care of postpartum problems	
Obstetrician, nurse, midwife staff	
SPECIAL CARE	
Basic services plus:	*Basic services plus:*
Care of high-risk pregnancies	Care of high-risk neonate with short-term problems
Triage, transfer of high-risk pregnancies (<32 wk, intrauterine growth retardation, preeclampsia, severe maternal medical illness)	Stabilization before transfer (<1,500 g, <32 wk, critically ill)
	Accept convalescing back (reverse) transfers
SUBSPECIALTY CARE	
Basic plus specialty care plus:	*Basic plus specialty care plus:*
Experienced perinatologist (24-hr coverage)	Experienced neonatologist (24-hr coverage)
Evaluation of high-risk therapies	Inborn plus transferred patients
Care for severe maternal medical or obstetric illnesses	Evaluation of high-risk therapies
	All pediatric medical, radiologic, and surgical subspecialties
High-risk fetal care (Rh disease, nonimmune hydrops, life-threatening anomalies)	Neonatal intensive care unit with operating room capabilities
	High-risk follow-up
Outcomes research	Outcomes research
Community education	Community education

From American Academy of Pediatrics, American College of Obstetricians and Gynecologists: Guidelines for perinatal care, *ed 5, Elk Grove Village, IL, 2002, American Academy of Pediatrics.*

Table 93-3 Morbidities and Sequelae of Perinatal and Neonatal Illness

MORBIDITIES	EXAMPLES
CENTRAL NERVOUS SYSTEM	
Spastic diplegic-quadriplegic cerebral palsy	Hypoxic–ischemic encephalopathy, periventricular leukomalacia, undetermined antenatal factors
Choreoathetotic cerebral palsy	Bilirubin encephalopathy (kernicterus)
Microcephaly	Hypoxic-ischemic encephalopathy, intrauterine infection (rubella, CMV)
Communicating hydrocephalus	Intraventricular hemorrhage, meningitis
Seizures	Hypoxic-ischemic encephalopathy, hypoglycemia
Encephalopathy	Congenital infections (rubella, CMV, HIV, toxoplasmosis)
Educational failure and/or mental retardation	Immaturity, hypoxia, hypoglycemia, cerebral palsy, intraventricular hemorrhage, low socioeconomic status
SENSATION—PERIPHERAL NERVES	
Reduced visual acuity (blindness)	Retinopathy of prematurity
Strabismus	Undetermined, prematurity
Hearing impairment (deafness)	Drug toxicity (furosemide, aminoglycosides), bilirubin encephalopathy, hypoxia ± hyperventilation
Poor speech	Immaturity, chronic illness, hypoxia, prolonged endotracheal intubation, hearing deficit
Paralysis–paresis	Birth trauma—brachial plexus, phrenic nerve, spinal cord
RESPIRATORY	
BPD	Oxygen toxicity, barotrauma
Subglottic stenosis	Endotracheal tube injury
Sudden infant death syndrome	Prematurity, BPD, infant of illicit drug user
Choanal stenosis, nasal septum destruction	Nasotracheal intubation
	Growth failure
CARDIOVASCULAR	
Cyanosis	Precorrective palliative care of congenital cyanotic heart disease, cor pulmonale from BPD, reactive airway
Heart failure	Precorrective palliative care of complex congenital heart disease, BPD, ventricular septal defect
GASTROINTESTINAL	
Short-gut syndrome	Necrotizing enterocolitis, gastroschisis, malrotation-volvulus, cystic fibrosis, intestinal atresia
Cholestatic liver disease (cirrhosis, hepatic failure)	Hyperalimentation toxicity, sepsis, short-gut syndrome
Failure to thrive	Short-gut syndrome, cholestasis, BPD, cerebral palsy, severe congenital heart disease
Inguinal hernia	Unknown
MISCELLANEOUS	
Cutaneous scars	Chest tube or intravenous catheter placement, hyperalimentation, subcutaneous infiltration, fetal puncture, intrauterine varicella, cutis aplasia
Absence of radial artery pulse	Frequent arterial puncture
Hypertension	Renal thrombi, repair of coarctation of aorta

BPD, bronchopulmonary dysplasia; CMV, cytomegalovirus.

Table 93-4 Incidence of Adverse Outcome According to Completed Week of Gestation at Delivery for Infants Born by Caesarean Section

OUTCOME	WK 37 (N = 934)	WK 38 (N = 3909)	WK 39 (N = 6512)	WK 40 (N = 1385)	WK 41 (N = 1385)	WK 42 (N = 113)
Respiratory distress syndrome	3.7	1.9	0.9	0.9	0.8	1.8
Transient tachypnea of the newborn	4.8	3.9	2.7	2.5	4.8	6.2
Admission to the neonatal intensive care unit	12.8	8.1	5.9	4.8	7.9	14.2
Suspected sepsis	6.6	3.9	2.4	2.6	3.6	10.6
Treated hypoglycemia	2.4	0.9	0.7	0.8	1.6	1.8
Ventilation	1.9	0.9	0.4	0.4	0.4	

From Tita AT, Landon MB, Spong CY, et al: Timing of elective repeat cesarean delivery at term and neonatal outcomes, N Engl J Med *360:111–120, 2009.*

High-risk infants must be monitored after discharge so that neurodevelopmental impairment is detected as early as possible and to ensure that children and families receive any interventions indicated and adequate support to optimize long-term outcome. At school age, former VLBW and preterm infants have poorer physical growth, cognitive function, and school performance. Although disadvantages may persist into adulthood, data now suggest that there may be cognitive improvement throughout childhood.

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Chapter 94

The Newborn Infant

Waldemar A. Carlo

See also Chapter 9.

The neonatal period is a highly vulnerable time for infants as they are completing many of the physiologic adjustments required for extrauterine existence. The high neonatal morbidity and mortality rates attest to the fragility of life during this period; of all deaths occurring in the 1st yr of life in the United States, two-thirds are in the neonatal period. The annual rate of deaths during the 1st yr is unequaled by the rate in any other period of life until the 7th decade.

94.1 History in Neonatal Pediatrics

Waldemar A. Carlo

The perinatal history should include the following information:

- Demographic and social data: socioeconomic status, age, race
- Past medical illnesses in the mother and family, including previous siblings: cardiopulmonary disorders, infectious diseases, genetic disorders, anemia, jaundice, diabetes mellitus
- Previous maternal reproductive problems: stillbirth, prematurity, blood group sensitization
- Events occurring in the present pregnancy: preterm labor, fetal assessments, vaginal bleeding, medications, acute illness, duration of rupture of membranes
- Description of the labor (duration, fetal presentation, fetal distress, fever) and delivery (cesarean section, anesthesia or sedation, use of forceps, Apgar scores, need for resuscitation)

94.2 Physical Examination of the Newborn Infant

Waldemar A. Carlo

Many physical and behavioral characteristics of a normal newborn infant are described in Chapters 9 and 590.

The **initial examination** of a newborn infant should be performed as soon as possible after delivery. Temperature, pulse, respiratory rate, color, signs of respiratory distress, tone, activity, and level of consciousness of infants should be monitored frequently until stabilization. For high-risk deliveries, this examination should take place in the delivery room and should focus on congenital anomalies, maturation and growth, and pathophysiologic problems that may interfere with normal cardiopulmonary and metabolic adaptation to extrauterine life. Congenital anomalies of varying degrees of severity may be present in 3-5% of infants. After a stable delivery room course, a second and more detailed examination should be performed within 24 hr of birth. If an infant remains in the hospital longer than 48 hr, a **discharge examination** should be performed within 24 hr of discharge. For a healthy infant, the mother should be present during this examination; even minor, seemingly insignificant anatomic variations may worry the parents and should be explained. The explanation must be careful and skillful so that otherwise unworried parents are not unduly alarmed. Infants should not be discharged from the hospital without a final examination because certain abnormalities, particularly cyanosis and heart murmurs, often appear or disappear in the immediate neonatal period; in addition, evidence of disease that has just been acquired may be noted. The pulse (normal: 120-160 beats/min), respiratory rate (normal: 30-60 breaths/min), temperature, weight, length, head circumference, and dimensions of any visible or palpable structural abnormality should be assessed. Blood pressure is determined if a neonate appears ill or has a heart murmur. Pulse oximetry should be performed to screen for critical congenital heart disease and is part of the routine screening for newborn infants. An oxygen saturation ≥95% test after 24 hr after birth in otherwise healthy appearing term infants has >99% sensitivity and specificity to rule out critical congenital heart disease. Neonates with oxygen saturations <95% should be referred for evaluation and possible echocardiogram (see Chapter 425).

Examining a newborn requires patience, gentleness, and procedural flexibility. Thus, if the infant is quiet and relaxed at the beginning of the examination, palpation of the abdomen or auscultation of the heart should be performed first, before other, more disturbing manipulations are attempted.

GENERAL APPEARANCE

Physical activity may be absent during normal sleep, or it may be decreased by the effects of illness or drugs; an infant may be either lying with the extremities motionless, to conserve energy for the effort of difficult breathing, or vigorously crying, with accompanying activity of the arms and legs. Both active and passive muscle tone and any unusual posture should be noted. Coarse, tremulous movements with ankle or jaw **myoclonus** are more common and less significant in newborn infants than at any other age. Such movements tend to occur when an infant is active, whereas convulsive twitching usually occurs in a quiet state. **Edema** may produce a superficial appearance of good nutrition. Pitting after applied pressure may or may not be noted, but the skin of the fingers and toes lacks the normal fine wrinkles when filled with fluid. Edema of the eyelids commonly results from irritation caused by the administration of silver nitrate. Generalized edema may occur with prematurity, hypoproteinemia secondary to severe erythroblastosis fetalis, nonimmune hydrops, congenital nephrosis, Hurler syndrome, and from unknown causes. Localized edema suggests a congenital malformation of the lymphatic system; when confined to one or more extremities of a female infant, it may be the initial sign of Turner syndrome (see Chapters 81 and 586).

SKIN

Vasomotor instability and peripheral circulatory sluggishness are revealed by deep redness or purple lividity in a crying infant, whose color may darken profoundly with closure of the glottis preceding a vigorous cry, and by harmless cyanosis (**acrocyanosis**) of the hands and feet, especially when they are cool. Mottling, another example of general circulatory instability, may be associated with serious illness or related to a transient fluctuation in skin temperature. An extraordinary division of the body from the forehead to the pubis into red and pale halves is known as **harlequin color change**, a transient and harmless condition. Significant **cyanosis** may be masked by the pallor of circulatory failure or anemia; alternatively, the relatively high hemoglobin content of the 1st few days and the thin skin may combine to produce an appearance of cyanosis at a higher Pa_{O_2} (partial pressure arterial oxygen) than in older children. Localized cyanosis is differentiated from ecchymosis by the momentary blanching pallor (with cyanosis) that occurs after pressure. The same maneuver also helps in demonstrating icterus. **Pallor** may be caused by anemia, asphyxia, shock, or edema. Early recognition of anemia may lead to a diagnosis of fetomaternal blood transfusion, erythroblastosis fetalis, subcapsular hematoma of the liver or spleen, subdural hemorrhage, or fetal–maternal or twin–twin transfusion. Without being anemic, postmature infants tend to have paler and thicker skin than term or premature infants. The ruddy appearance of plethora is seen with polycythemia.

The vernix and common transitory macular capillary hemangiomas of the eyelids and neck are described in Chapter 647. Cavernous

hemangiomas are deeper, blue masses that, if large, may trap platelets and produce disseminated intravascular coagulation or interfere with local organ function. Scattered petechiae may be seen on the presenting part (usually the scalp or face) after a difficult delivery. Slate-blue, well-demarcated areas of pigmentation called **Mongolian spots** are seen over the buttocks, back, and sometimes other parts of the body in more than 50% of black, Native American, and Asian infants, and occasionally in white infants. These benign patches have no known anthropologic significance despite their name; they tend to disappear within the 1st year. The vernix, skin, and especially the cord may be stained brownish yellow if the amniotic fluid has been colored by the passage of meconium during or before birth.

The skin of premature infants is thin and delicate and tends to be deep red; in extremely premature infants, the skin appears almost gelatinous and translucent. Fine, soft, immature hair called **lanugo** frequently covers the scalp and brow and may also cover the face of premature infants. Lanugo has usually been lost or replaced by vellus hair in term infants. **Tufts of hair** over the lumbosacral spine suggest an underlying abnormality, such as occult spina bifida, a sinus tract, or a tumor. The nails are rudimentary in very premature infants, but they may protrude beyond the fingertips in infants born past term. Postterm infants may have a peeling, parchment-like skin (Fig. 94-1), a severe degree of which may mimic ichthyosis congenita (see Chapter 658).

In many neonates, small, white papules on an erythematous base develop 1-3 days after birth. This benign rash, **erythema toxicum**, persists for as long as 1 wk, contains eosinophils, and is usually distributed on the face, trunk, and extremities (see Chapter 647). **Pustular melanosis**, a benign lesion seen predominantly in black neonates, contains neutrophils and is present at birth as a vesiculopustular eruption around the chin, neck, back, extremities, and palms or soles; it lasts 2-3 days. Both lesions need to be distinguished from more dangerous vesicular eruptions such as herpes simplex (see Chapter 252) and staphylococcal disease of the skin (see Chapter 181.1).

Amniotic bands may disrupt the skin, extremities (amputation, ring constriction, syndactyly), face (clefts), or trunk (abdominal or thoracic wall defects). Their cause is uncertain but may be related to amniotic membrane rupture or vascular compromise with fibrous band formation. Excessive skin fragility and extensibility with joint hypermobility suggest Ehlers-Danlos syndrome, Marfan syndrome, congenital contractural arachnodactyly, and other disorders of collagen synthesis.

Figure 94-1 **Infant with intrauterine growth retardation as a result of placental insufficiency.** Note the long, thin appearance with peeling, parchment-like dry skin, alert expression, meconium staining of the skin, and long nails. *(From Clifford S:* Advances in pediatrics, *vol 9, Chicago, 1962, Year Book.)*

SKULL

The head circumference of all infants should be plotted on a growth chart to rule out **microcephalus** and **megalencephaly**. The skull may be molded, particularly if the infant is the first-born and if the head has been engaged in the pelvic canal for a considerable time. The parietal bones tend to override the occipital and frontal bones. The head of an infant born by cesarean section or from a breech presentation is characterized by its roundness. The suture lines and the size and fullness of the anterior and posterior fontanels should be determined digitally by palpation. Premature fusion of sutures (**cranial synostosis**) is identified as a hard nonmovable ridge over the suture and an abnormally shaped skull. Great variation in the size of the **fontanels** exists at birth; if small, the anterior fontanel usually tends to enlarge during the first few mo after birth. The persistence of excessively large anterior (normal: 20 ± 10 mm) and posterior fontanels has been associated with several disorders (Table 94-1). Persistently small fontanels suggest microcephaly, craniosynostosis, congenital hyperthyroidism, or wormian bones; presence of a third fontanel suggests trisomy 21, but is seen in preterm infants. Soft areas (**craniotabes**) are occasionally found in the parietal bones at the vertex near the sagittal suture; they are more common in preterm infants and in infants who have been exposed to uterine compression. Although such soft areas are usually insignificant, their possible pathologic cause should be investigated if they persist. Soft areas in the occipital region suggest the irregular calcification and wormian bone formation associated with osteogenesis imperfecta, cleidocranial dysostosis, lacunar skull, cretinism, and, occasionally, Down syndrome. Transillumination of an abnormal skull in a dark room followed by ultrasound or magnetic resonance imaging will rule out hydranencephaly and hydrocephaly (see Chapter 591). An excessively large head (megalencephaly) suggests hydrocephaly, storage disease, achondroplasia, cerebral gigantism, neurocutaneous syndromes, or inborn errors of metabolism, or may be familial. The skull of a premature infant may suggest hydrocephaly because of the relatively larger brain growth in comparison with growth of other organs. Depression of the skull (indentation, fracture, ping pong ball deformity) is usually of prenatal onset and a result of prolonged focal

Table 94-1 Disorders Associated with a Large Anterior Fontanel
Achondroplasia
Apert syndrome
Athyrotic hypothyroidism
Cleidocranial dysostosis
Congenital rubella syndrome
Hallermann-Streiff syndrome
Hydrocephaly
Hypophosphatasia
Intrauterine growth restriction
Kenny syndrome
Osteogenesis imperfecta
Prematurity
Pyknodysostosis
Russell-Silver syndrome
Trisomies 13-, 18-, and 21
Vitamin D deficiency rickets

pressure by the bony pelvis. Atrophic or alopecic scalp areas may represent aplasia cutis congenita, which may be sporadic, or autosomal dominant, or associated with trisomy 13, chromosome 4 deletion, or Johanson-Blizzard syndrome. Deformational plagiocephaly may be the result of in utero positioning forces on the skull and manifests as an asymmetric skull and face with ear malalignment (see Chapter 592). It is associated with torticollis and vertex positioning.

FACE

The general appearance of the face should be noted with regard to dysmorphic features, such as epicanthal folds, widely or narrowly spaced eyes, microphthalmos, asymmetry, long philtrum, and low-set ears, which are often associated with congenital syndromes. The face may be asymmetric as a result of a 7th nerve palsy, hypoplasia of the depressor muscle at the angle of the mouth, or an abnormal fetal posture (see Chapter 108); when the jaw has been held against a shoulder or an extremity during the intrauterine period, the mandible may deviate strikingly from the midline. Symmetric facial palsy suggests absence or hypoplasia of the 7th nerve nucleus (**Möbius syndrome**).

Eyes

The eyes often open spontaneously if the infant is held up and tipped gently forward and backward. This maneuver, a result of labyrinthine and neck reflexes, is more successful for inspecting the eyes than is forcing the lids apart. Conjunctival and retinal hemorrhages are usually benign. Retinal hemorrhages are more common with vacuum- or forceps-assisted deliveries, than spontaneous vaginal delivery, and least common after cesarean section. They are usually bilateral, intraretinal, and in the posterior pole. They resolve in most infants by 2 wk of age (85%) and in all infants by 4 wk. **Pupillary reflexes** are present after 28-30 wk of gestation. The iris should be inspected for colobomas and heterochromia. A cornea >1 cm in diameter in a term infant (with photophobia and tearing) suggests congenital glaucoma and requires prompt ophthalmologic consultation. The presence of bilateral red reflexes suggests the absence of cataracts and intraocular pathology (see Chapters 619, 627-633). **Leukokoria** (white pupillary reflex) suggests cataracts, tumor, chorioretinitis, retinopathy of prematurity, or a persistent hyperplastic primary vitreous and warrants an immediate ophthalmologic consultation.

Ears

Deformities of the pinnae are occasionally seen. Unilateral or bilateral preauricular skin tags occur frequently; if pedunculated, they can be tightly ligated at the base, resulting in dry gangrene and sloughing. The tympanic membrane, easily seen otoscopically through the short and straight external auditory canal, normally appears dull gray.

Nose

The nose may be slightly obstructed by mucus accumulated in the narrow nostrils. The nares should be symmetric and patent. Dislocation of the nasal cartilage from the vomerian groove results in asymmetric nares. Anatomic obstruction of the nasal passages secondary to unilateral or bilateral choanal atresia results in respiratory distress.

Mouth

A normal mouth may rarely have precocious dentition, with natal (present at birth) or neonatal (eruption after birth) teeth in the lower incisor position or aberrantly placed; these teeth are shed before the deciduous ones erupt (see Chapter 307). Alternatively, such teeth occur in Ellis-van Creveld, Hallermann-Streiff, and other syndromes. Extraction is not usually indicated. Premature eruption of deciduous teeth is even more unusual. The soft and hard palate should be inspected and palpated for a complete or submucosal cleft, and the contour noted if the arch is excessively high or the uvula is bifid. On the hard palate on either side of the raphe, there may be temporary accumulations of epithelial cells called **Epstein pearls**. Retention cysts of similar appearance may also be seen on the gums. Both disappear spontaneously, usually within a few weeks of birth. Clusters of small white or yellow follicles or ulcers on erythematous bases may be found on the anterior tonsillar pillars, most frequently on the 2nd or 3rd day of life. Of unknown cause, they clear without treatment in 2-4 days.

Neonates do not have active salivation. The tongue appears relatively large; the frenulum may be short, but its shortness (**tongue-tied** or **ankyloglossia**) is rarely a reason for cutting it. If there are problems with feedings (breast or bottle) and the frenulum is short, frenulotomy (frenotomy) may be indicated. Frenotomy may reduce maternal nipple pain and improve breastfeeding scores more rapidly than no treatment, but over time neonates not treated with frenotomy also had successful feeding. The sublingual mucous membrane occasionally forms a prominent fold. The cheeks have fullness on both the buccal and the external aspects as a result of the accumulation of fat making up the sucking pads. These pads, as well as the labial tubercle on the upper lip (**sucking callus**), disappear when suckling ceases. A marble-sized buccal mass is usually caused by benign idiopathic fat necrosis.

The throat of a newborn infant is hard to see because of the low arch of the palate; it should be clearly viewed because posterior palatal or uvular clefts are easy to miss. The tonsils are small.

NECK

The neck appears relatively short. Abnormalities are not common but include goiter, cystic hygroma, branchial cleft rests, teratoma, hemangioma, and lesions of the sternocleidomastoid muscle that are presumably traumatic or due to a fixed positioning in utero that produces either a hematoma or fibrosis, respectively. Congenital **torticollis** causes the head to turn toward and the face to turn away from the affected side. Plagiocephaly, facial asymmetry, and hemihypoplasia may develop if it is untreated (see Chapter 592.1). Redundant skin or webbing in a female infant suggests intrauterine lymphedema and Turner syndrome (see Chapters 81 and 586). Both clavicles should be palpated for fractures.

CHEST

Breast hypertrophy is common, and milk may be present (but should not be expressed). Asymmetry, erythema, induration, and tenderness suggest mastitis or a breast abscess. Supernumerary nipples, inverted nipples, or widely spaced nipples with a shield-shaped chest may be seen; the last finding suggests Turner syndrome.

LUNGS

Much can be learned by observing breathing. Normal variations in rate and rhythm are characteristic and fluctuate according to the infant's physical activity, the state of wakefulness, or the presence of crying. Because fluctuations are rapid, the respiratory rate should be counted for a full minute with the infant in the resting state, preferably asleep. Under these circumstances, the usual rate for normal term infants is 30-60 breaths/min; in premature infants the rate is higher and fluctuates more widely. A rate consistently greater than 60 breaths/min during periods of regular breathing that persists for more than an hour after birth is an indication to rule out pulmonary, cardiac, or metabolic disease (acidosis) etiologies. Preterm infants may breathe with a Cheyne-Stokes rhythm, known as periodic respiration, or with complete irregularity. Irregular gasping, sometimes accompanied by spasmodic movements of the mouth and chin, strongly indicates serious impairment of the respiratory centers.

The breathing of newborn infants at rest is almost entirely diaphragmatic, so during inspiration, the soft front of the thorax is usually drawn inward while the abdomen protrudes. If the baby is quiet, relaxed, and with good color, this "paradoxic movement" does not necessarily signify insufficient ventilation. On the other hand, labored respiration with retractions is important evidence of respiratory distress syndrome, pneumonia, anomalies, or mechanical disturbance of the lungs. A weak persistent or intermittent groaning, whining cry, or **grunting** during expiration can signify potentially serious cardiopulmonary disease or sepsis and warrants immediate attention. When benign, the grunting resolves between 30 and 60 min after birth. Flaring of the alae nasi and retraction of the intercostal muscles and sternum are common signs of pulmonary pathology.

Normally, the breath sounds are bronchovesicular. Suspicion of pulmonary pathology because of diminished breath sounds, rhonchi, retractions, or cyanosis should always be verified with a chest radiograph.

HEART

Normal variation in the size and shape of the chest makes it difficult to estimate the size of the heart. The location of the heart should be determined to detect dextrocardia. Transitory murmurs usually represent a closing ductus arteriosus. Although congenital heart disease may not initially produce a murmur, a substantial portion of infants in whom persistent murmurs are detected during routine neonatal examination have underlying malformation. Evaluation of the heart by echocardiography is essential when the possibility of a significant lesion exists, particularly if oxygen saturations are below 95%.

The pulse is usually 110-140 beats/min at rest, but may vary normally from 90 beats/min in relaxed sleep to 180 beats/min during activity. The still higher rate of supraventricular tachycardia (>220 beats/min) may be determined better with a cardiac monitor or electrocardiogram than by auscultation. Preterm infants usually have a higher resting heart rate, up to about 160 beats/min, but may have a sudden onset of sinus bradycardia secondary to apnea. On both admission to and discharge from the nursery, the infant's pulses should be palpated in the upper and lower extremities to detect coarctation of the aorta.

Blood pressure measurements may be a valuable diagnostic aid in ill infants (see Chapter 425). The oscillometric method is the easiest and most accurate noninvasive method available. Continuous direct measurement of blood pressure with an umbilical artery catheter may be indicated in special circumstances for critically ill infants in an intensive care unit (Fig. 94-2).

ABDOMEN

The liver is usually palpable, sometimes as much as 2 cm below the rib margin. Less commonly, the tip of the spleen may be felt. The approximate size and location of each kidney can usually be determined on deep palpation. At no other period of life does the amount of air in the gastrointestinal tract vary so much, nor is it usually so great under normal circumstances. The intestinal tract is gasless at birth. Gas is swallowed soon after birth, and gas should normally be present in the rectum on roentgenogram by 24 hr of age. The abdominal wall is normally weak (especially in premature infants), and diastasis recti and umbilical hernias are common, particularly among black infants.

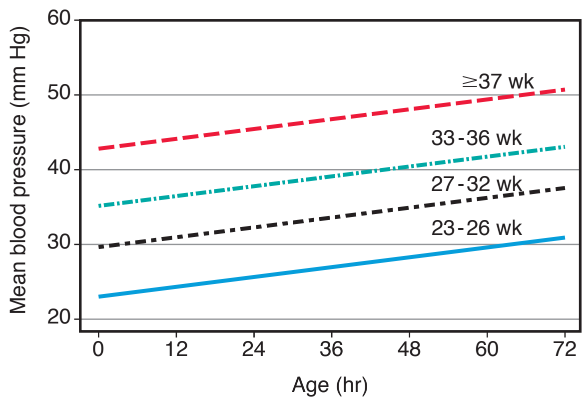

Figure 94-2 **Nomogram for mean blood pressure (BP) in neonates with gestational ages of 23-43 wk derived from continuous arterial BP measurements obtained from 103 infants admitted to the neonatal intensive care unit.** The graph shows the predicted mean BP of neonates of different gestational ages during the 1st 72 hr of life. Each line represents the lower limit of the 80% confidence interval (2-tail) of the mean BP for each gestational age group; 90% of infants for each gestational age group will be expected to have a mean BP value equal to or above the value indicated by the corresponding line, the lower limit of the confidence interval. *(From Nuntnarumit P, Yang W, Bada-Ellzey SB: Blood pressure measurements in the newborn,* Clin Perinatol *26:976–996, 1999.)*

Unusual masses should be investigated immediately with ultrasonography. Renal pathology is the cause of most neonatal abdominal masses. **Cystic abdominal masses** include hydronephrosis, multicystic-dysplastic kidneys, adrenal hemorrhage, hydrometrocolpos, intestinal duplication, and choledochal, ovarian, omental, or pancreatic cysts. **Solid masses** include neuroblastoma, congenital mesoblastic nephroma, hepatoblastoma, and teratoma. A solid flank mass may be caused by **renal vein thrombosis**, which becomes clinically apparent with hematuria, hypertension, and thrombocytopenia. Renal vein thrombosis in infants is associated with polycythemia, dehydration, maternal diabetes, asphyxia, sepsis, nephrosis, and hypercoagulable states such as antithrombin III and protein C deficiency.

Abdominal distention at birth or shortly afterward suggests either obstruction or perforation of the gastrointestinal tract, often as a result of meconium ileus; later distention suggests lower bowel obstruction, sepsis, or peritonitis. A scaphoid abdomen in a newborn suggests diaphragmatic hernia. Abdominal wall defects produce an omphalocele (see Chapter 105) when they occur through the umbilicus and gastroschisis when they occur lateral to the midline. Omphaloceles are associated with other anomalies and syndromes such as Beckwith-Wiedemann, conjoined twins, trisomy 18, meningomyelocele, and imperforate anus. **Omphalitis** is an acute local inflammation of the periumbilical tissue that may extend to the abdominal wall, the peritoneum, the umbilical vein or portal vessels, or the liver and may result in later portal hypertension. The umbilical cord should have 2 arteries and 1 vein. A single umbilical artery is associated with an increased risk for an occult renal anomaly.

GENITALS

The genitals and mammary glands normally respond to transplacentally acquired maternal hormones to produce enlargement and secretion of the breasts in both sexes and prominence of the genitals in females, often with considerable nonpurulent discharge. These transitory manifestations require no intervention.

An imperforate hymen or other causes of vaginal obstruction may result in **hydrometrocolpos** and a lower abdominal mass. A normal scrotum at term is relatively large; its size may be increased by the trauma of breech delivery or by a transitory hydrocele, which is distinguished from a hernia by palpation and transillumination. The testes should be in the scrotum or should be palpable in the canals in term infants. Black male infants usually have dark pigmentation of the scrotum before the rest of the skin assumes its permanent color. The scrotum may be ecchymotic from breech presentation or a retroperitoneal hemorrhage; it may contain meconium particles associated with meconium peritonitis.

The prepuce of a newborn infant is normally tight and adherent. Severe hypospadias or epispadias should always lead one to suspect either that abnormal sex chromosomes are present (see Chapter 81) or that the infant is actually a masculinized female with an enlarged clitoris, because this finding may be the first evidence of adrenogenital syndrome (see Chapter 576). Erection of the penis is common and has no significance. Urine is usually passed during or immediately after birth; a period without voiding may normally follow. Most neonates void by 12 hr, and approximately 95% of preterm and term infants void within 24 hr.

ANUS

Some passage of meconium usually occurs within the 1st 12 hr after birth; 99% of term infants and 95% of premature infants pass meconium within 48 hr of birth. Imperforate anus is not always visible and may require evidence obtained by gentle insertion of the examiner's little finger or a rectal tube. Radiographic study is required. Passage of meconium does not rule out an imperforate anus if a rectal–vaginal fistula is present. The dimple or irregularity in skinfold often normally

present in the sacrococcygeal midline may be mistaken for an actual or potential neurocutaneous sinus.

EXTREMITIES

During examination of the extremities, the effects of fetal posture (see Chapter 672) should be noted so that their cause and usual transitory nature can be explained to the mother. Such explanations are particularly important after breech presentations. A fracture or nerve injury associated with delivery can be detected more commonly by observation of the extremities in spontaneous or stimulated activity than by any other means. The hands and feet should be examined for polydactyly, syndactyly, and abnormal dermatoglyphic patterns such as a simian crease.

The hips of all infants should be examined with specific maneuvers to rule out congenital dislocation (see Chapter 678.1).

NEUROLOGIC EXAMINATION

See Chapters 9 and 590.

In utero neuromuscular diseases associated with limited fetal motion produce a constellation of signs and symptoms that are independent of the specific disease. Severe positional deformations and contractures produce arthrogryposis. Other manifestations of fetal neuromuscular disease include breech presentation, polyhydramnios, failure to breathe at birth, pulmonary hypoplasia, dislocated hips, undescended testes, thin ribs, and clubfoot. Many congenital disorders manifest as hypotonia, hypertonia, or seizures.

Bibliography is available at Expert Consult.

94.3 Routine Delivery Room and Initial Care

Waldemar A. Carlo

Low-risk infants may initially be placed on the mother's abdomen after delivery; clearing the mouth of secretions with gentle suction with a bulb syringe or soft catheter is indicated if there is an excessive (copious) amount of fluid in the mouth or nares. In resource-poor countries, gentle wiping of the face, nose, and mouth with a soft cloth may be equally effective as a bulb syringe. Nonetheless, spontaneously breathing neonates with no distress do not need any assisted method to clear their airway. Most healthy infants who appear to be in satisfactory condition should be given directly to their mothers for immediate bonding and nursing. Delayed clamping of the umbilical cord (~30 sec) has value in reducing the incidence of anemia in infancy. If respiratory distress is a concern, infants should be placed under warmers for observation.

The **Apgar score** is a practical method of systematically assessing newborn infants immediately after birth (Table 94-2). A low score may be the result of fetal distress but may also be caused by a number of factors, including prematurity and drugs given to the mother during labor (Table 94-3). The Apgar score was not designed to predict neurologic outcome. Indeed, the score is normal in most patients in whom cerebral palsy subsequently develops, and the incidence of cerebral palsy is low in infants with Apgar scores of 0-3 at 5 min (but higher than in infants with Apgar scores of 7-10). Low Apgar scores and umbilical artery blood pH predict neonatal death. An Apgar score of 0-3 at 5 min is uncommon but is a better predictor of neonatal death (in both term and preterm infants) than an umbilical artery pH ≤7.0; the presence of both variables increases the relative risk of neonatal mortality in term and preterm infants (Table 94-4). Infants who fail to initiate respiration should receive prompt resuscitation and close observation (see Chapter 100).

MAINTENANCE OF BODY HEAT

Newborn infants are at risk for heat loss and hypothermia for several reasons. Relative to body weight, the body surface area of a newborn infant is approximately 3 times that of an adult. Generation of body heat depends in large part on body weight, but heat loss depends on surface area. In low birthweight and preterm infants, the insulating layer of subcutaneous fat is thin. The estimated rate of heat loss in a newborn is approximately 4 times that of an adult. Under the usual delivery room conditions (20-25°C [68-77°F]), an infant's skin temperature falls approximately 0.3°C (0.54°F)/min and deep body temperature decreases approximately 0.1°C (0.18°F)/min during the period immediately after delivery; these rates generally result in a

Table 94-3 Factors Affecting the Apgar Score*

FALSE-POSITIVE (NO FETAL ACIDOSIS OR HYPOXIA; LOW APGAR SCORE)
Prematurity
Analgesics, narcotics, sedatives
Magnesium sulfate
Acute cerebral trauma
Precipitous delivery
Congenital myopathy
Congenital neuropathy
Spinal cord trauma
Central nervous system anomaly
Lung anomaly (diaphragmatic hernia)
Airway obstruction (choanal atresia)
Congenital pneumonia and sepsis
Previous episodes of fetal asphyxia (recovered)
Hemorrhage-hypovolemia
FALSE-NEGATIVE (ACIDOSIS; NORMAL APGAR SCORE)
Maternal acidosis
High fetal catecholamine levels
Some full-term infants

*Regardless of the etiology, a low Apgar score because of fetal asphyxia, immaturity, central nervous system depression, or airway obstruction identifies an infant needing immediate resuscitation.

Table 94-2 Apgar Evaluation of Newborn Infants*

SIGN	0	1	2
Heart rate	Absent	Below 100	Over 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril (tested after oropharynx is clear)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink, extremities blue	Completely pink

*Sixty sec after complete birth of the infant (disregarding the cord and placenta), the 5 objective signs listed here are evaluated, and each is given a score of 0, 1, or 2. A total score of 10 indicates an infant in the best possible condition. An infant with a score of 0-3 requires immediate resuscitation.

Modified from Apgar V: A proposal for a new method of evaluation of the newborn infant, Curr Res Anesth Analg *32:260–267, 1953.*

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Table 94-4 Incidence of Neonatal Death in 132,228 Singleton Infants Born at Term (37th wk of Gestation or Later) in Relation to Apgar Scores at 5 Minutes of Age*

5-MIN APGAR SCORE	NO. OF LIVE BIRTHS	NO. NEONATAL DEATHS (PER 1,000 BIRTHS)	RELATIVE RISK (95% CI)
0-3	86	21 (244)	1,460 (835-2,555)
4-6	561	5 (9)	53 (20-140)
7-10	131,581	22 (0.2)	1

*Infants with 5-min Apgar scores of 7-10 served as the reference group.
CI, confidence interval.
From Casey BM, McIntire DD, Leveno KJ: The continuing value of the Apgar score for the assessment of newborn infants, N Engl J Med *344:467–471, 2001.*

cumulative loss of 2-3°C (3.6-5.4°F) in deep body temperature (corresponding to a heat loss of approximately 200 kcal/kg). The heat loss occurs by 4 mechanisms: (1) **convection** of heat energy to the cooler surrounding air, (2) **conduction** of heat to the colder materials touching the infant, (3) **heat radiation** from the infant to other nearby cooler objects, and (4) **evaporation** from skin and lungs.

Metabolic acidosis, hypoxemia, hypoglycemia, and increased renal excretion of water and solutes may develop in term infants exposed to cold after birth because of their effort to compensate for heat loss. Heat production is augmented by increasing the metabolic rate and oxygen consumption in part by releasing norepinephrine, which results in nonshivering thermo-genesis through oxidation of fat, particularly brown fat. In addition, muscular activity may increase. Hypoglycemic or hypoxic infants cannot increase their oxygen consumption when exposed to a cold environment, and their central temperature decreases. After labor and vaginal delivery, many newborn infants have mild to moderate metabolic acidosis, for which they may compensate by hyperventilating, a response that is more difficult for infants with central nervous system depression (asphyxia, drugs) and infants exposed to cold stress in the delivery room. Therefore, to reduce heat loss, it is desirable to ensure that infants are dried and either wrapped in blankets or placed with the mother or under radiant warmers. **Skin-to-skin contact** with the mother is the optimal method of maintaining temperature in the stable newborn. Because carrying out resuscitative measures on a covered infant or one enclosed in an incubator is difficult, a radiant heat source should be used to warm the baby during resuscitation.

ANTISEPTIC SKIN AND CORD CARE

Careful removal of the amniotic fluid and blood from the skin shortly after birth may reduce the risk of infection with bloodborne agents. Once a healthy infant's temperature has stabilized, the entire skin and cord should be cleansed with warm water or a mild nonmedicated soap solution and rinsed with water to reduce the incidence of skin and periumbilical colonization with pathogenic bacteria and subsequent infectious complications. To avoid heat loss, the infant is then dried and wrapped in clean blankets. To reduce colonization with *Staphylococcus aureus* and other pathogenic bacteria, the umbilical cord may be treated daily with a bactericidal or antimicrobial agents such as chlorhexidine, triple dye, or bacitracin. One application of triple dye followed by twice-daily alcohol swabbing (until the cord falls off) reduces colonization, exudates, and foul odor of the umbilicus in comparison with dry care (soap and water when soiled). On the rare occasion of *S. aureus* nursery epidemics, a single hexachlorophene bath may be used. Topical ointments should not be applied to preterm infants in neonatal intensive care units because this treatment increases the risk of bacterial sepsis. Routine or repeated total-body exposure to hexachlorophene may be neurotoxic, particularly in low-birthweight infants, and is thus contraindicated. Nursery personnel should use alcohol-based solutions or chlorhexidine or iodophor-containing antiseptic soaps for routine handwashing before caring for each infant. Rigid enforcement of hand-to-elbow washing for 2 min in the initial wash and 15-30 sec in subsequent washes is essential for staff and visitors entering the nursery.

OTHER MEASURES

The eyes of all infants, including those born by cesarean section, must be protected against gonococcal ophthalmia neonatorum by application of a 1-cm ribbon of erythromycin (0.5%) or tetracycline (1.0%) sterile ophthalmic ointments in each lower conjunctival sac. This procedure may be delayed during the initial short-alert period after birth to promote bonding, but once applied, drops should not be rinsed out (see Chapters 192 and 226.3). A 1% silver nitrate solution is an acceptable alternative, but leads to a transient chemical conjunctivitis in 10-20% of cases.

Although hemorrhage in newborn infants can be a result of factors other than vitamin K deficiency, an intramuscular injection of 0.5-1 mg of water-soluble vitamin K_1 (phytonadione) should be given to all infants shortly after birth to prevent hemorrhagic disease of the newborn (see Chapter 103.4). Oral vitamin K is not as effective as the parenteral dosage.

Hepatitis B immunization before discharge from the nursery is recommended for newborns with weight >2 kg irrespective of maternal hepatitis status.

Neonatal screening is available for various genetic, metabolic, hematologic, and endocrine disorders. All states in the United States have adopted the Advisory Committee on Heritable Disorders in Newborns and Children, although the specific tests performed vary by state based in part to disease prevalence, detection rates, and costs (see Chapter 84). The most commonly identified disorders (and their rates) include hypothyroidism (52/100,000 births), cystic fibrosis (30/100,000), hemoglobinopathies (26/100,000), medium-chain acyl–coenzyme A dehydrogenase deficiency (6/100,000), galactosemia (5/100,000), phenylketonuria (5/100,000), and adrenal hyperplasia (5/100,000). To be effective in the timely identification and prompt management of treatable diseases, screening programs must include not only high-quality laboratory tests but also follow-up of infants with abnormal test results; education, counseling, and psychologic support for families; and prompt referral of the identified neonate for accurate diagnosis and appropriate treatment.

Hearing impairment, a serious morbidity that affects speech and language development, may be severe in 2/1,000 births and overall affects 5/1,000 births. Universal screening of infants is recommended to ensure early detection of hearing loss and appropriate, timely intervention.

Universal screening with pulse oximetry provides early detection of ductal dependent cyanotic congenital heart disease (see Chapter 425).

Universal screening for hyperbilirubinemia should include risk assessment in all infants with measurement of serum or transcutaneous bilirubin levels before hospital discharge.

Universal screening for congenital hip dysplasia with physical examination with the Ortolani (sensation of the dislocated hip reducing) and Barlow (unstable hip dislocating from the acetabulum) tests is recommended but routine hip ultrasound is not indicated.

Routine measurement of the hematocrit or blood glucose value is not necessary in the absence of risk factors.

Bibliography is available at Expert Consult.

94.4 Nursery Care

Waldemar A. Carlo

Non–high-risk, healthy infants may be taken to the "regular" (normal) newborn nursery or may be placed in the mother's room if the hospital has rooming-in facilities.

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The bassinet, preferably of clear plastic to allow for easy visibility and care, should be cleaned frequently. All professional care should be given to the infant in the bassinet, including the physical examination, clothing changes, temperature taking, skin cleansing, and other procedures that, if performed elsewhere, would establish a common contact point and possibly provide a channel for cross infection. The clothing and bedding should be minimal, only enough needed for an infant's comfort; the nursery temperature should be kept at approximately 22-26°C (72-78°F). The infant's temperature should be taken by axillary measurement. Although the interval between temperature measurements depends on many circumstances, it need not be shorter than 4 hr during the 1st 2-3 days and 8 hr thereafter. Axillary temperatures of 36.5-37.4°C (97.7-99.3°F) are within normal limits. Weighing at birth and daily thereafter is sufficient. Healthy infants should be placed supine to reduce the risk of sudden infant death syndrome.

Vernix is spontaneously shed within 2-3 days, much of it adhering to the clothing, which should be completely changed daily. The diaper should be checked before and after feeding and when the baby cries; it should be changed when wet or soiled. The perineal area can be cleaned with baby wipes or with mild soap and warm water. Meconium or feces should be cleansed from the buttocks with sterile cotton moistened with sterile water. The foreskin of a male infant should not be retracted.

Infants should meet minimum criteria before hospital discharge (Table 94-5). Late preterm infants (34-36 wk) and infants with early discharge (<48 hr) or very early discharge (<24 hr) are at increased risk of rehospitalization. Early discharge requires careful ambulatory follow-up at home (by a visiting nurse) or in the office within 48 hr of discharge.

Table 94-5 Criteria for Discharge from the Normal Newborn Nursery*

Criteria
Uncomplicated antepartum, intrapartum, postpartum courses
Vaginal delivery
Singleton at 38-42 wk: appropriate for gestational age
Normal vital signs including respiratory rate <60 breaths/min; axillary temperature 36.1-37°C (97.0-98.6°F) in open crib
Physical examination reveals no abnormalities requiring continued hospitalization
Urination; stool × 1
At least 2 uneventful, successful feedings
No excessive bleeding 2 hr after circumcision
No jaundice within 24 hr of birth; if jaundice, appropriate management and follow-up are in place
Evidence of parental knowledge, ability, and confidence to care for the baby at home:
Feeding
Cord, skin, genital care
Recognition of illness (jaundice, poor feeding, lethargy, fever, etc.)
Infant safety (car seat, supine sleep position, etc.)
Availability of family and physician support (physician follow-up)
Laboratory evaluation:
Syphilis
Hepatitis B surface antigen and vaccination or appointment for vaccination
Coombs test and blood type if clinically indicated
Expanded metabolic screening: phenylketonuria, thyroid, galactosemia, sickle cell
Hearing screening
No social risks:
Substance abuse
History of child abuse
Domestic violence
Mental illness
Teen mother
Homelessness
Barriers to follow-up
Source of continuing medical care is identified

*It is not likely that all these criteria will be met before 48 hr of age.
Adapted from American Academy of Pediatrics, American College of Obstetricians and Gynecologists: Guidelines for perinatal care, *ed 7, Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

Bibliography is available at Expert Consult.

94.5 Parent–Infant Bonding

Waldemar A. Carlo

See also Chapter 9.

Normal infant development depends partly on a series of affectionate responses exchanged between a mother and her newborn infant that binds them psychologically and physiologically. This bonding is facilitated and reinforced by the emotional support of a loving family. The attachment process may be important in enabling some mothers to provide loving care during the neonatal period and subsequently during childhood. The power of this attachment is so great that it enables the mother and the father to make unusual sacrifices necessary for the day-to-day care of the infant, care night after night, giving feedings 24 hr a day, attending to crying, and so on. The sacrifices continue for many years as parents dedicate much of their lives to their children.

Parent–infant bonding is initiated before birth with the planning and confirmation of the pregnancy. Subsequently, there is a growing awareness of the baby as an individual, starting usually with the remarkably powerful event of "quickening" or sensation of fetal movements. After delivery and during the ensuing weeks, sensory (visual, auditory, olfactory) and physical contact between the mother and baby triggers various mutually rewarding and pleasurable interactions, such as the mother touching the infant's extremities and face with her fingertips and encompassing and gently massaging the infant's trunk with her hands. Touching an infant's cheek elicits responsive turning toward the mother's face or toward the breast with nuzzling and licking of the nipple, a powerful stimulus for prolactin secretion. An infant's initial quiet alert state provides the opportunity for eye-to-eye contact, which is particularly important in stimulating the loving and possessive feelings of many parents for their babies. An infant's crying elicits the maternal response of touching the infant and speaking in a soft, soothing, higher-toned voice. Initial contact between the mother and infant should take place in the delivery room, and opportunities for extended intimate contact and breastfeeding should be provided within the 1st hours after birth. Delayed or abnormal maternal–infant bonding, as occurs because of prematurity, infant or maternal illness, birth defects, or family stress, may harm infant development and maternal caretaking ability. Hospital routines should be designed to encourage parent–infant contact. Open nurseries, rooming-in arrangements, care by parents, and family-centered care increase the opportunities for better parent–infant interaction.

NURSERIES AND BREASTFEEDING

See Chapter 45 for full discussions of breastfeeding and formula feeding.

Ample evidence indicates that there are infant and maternal benefits to breastfeeding. Practices that encourage successful breastfeeding include antepartum education and encouragement, immediate postpartum mother–infant contact with suckling, rooming-in arrangements, demand feeding, inclusion of fathers in breastfeeding education, and support from experienced women. Nursing at first for least 5 min at each breast is reasonable, allows a baby to obtain most of the available breast contents, and provides effective stimulation for increasing the milk supply. Nursing episodes should then be extended according to the comfort and desire of the mother and infant. A confident and relaxed mother, supported by an encouraging home and hospital environment, is likely to nurse well. The Baby-Friendly Hospital Initiative, a global effort (sponsored by the World Health Organization and the United Nations Children's Fund) to promote breastfeeding, recommends 10 steps to successful breastfeeding (Table 94-6). Some hospital practices contribute to difficulties in breastfeeding by enforcing 4-hr feeding schedules, limiting nursing time, using only 1 breast at a

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feeding, washing nipples with substances other than water, delaying the first feeding, providing formula supplements, and using heavy intrapartum sedation.

DRUGS AND BREASTFEEDING

Maternal medications may affect the production and safety of breast milk (Table 94-7). Although most commonly used medications are safe, the safety of any new drug to be used while a woman is breastfeeding must be confirmed before the drug is initiated and/or breastfeeding is continued. Maternal sedatives may result in sedation of the infant. Maternal drugs that are weak acids, composed of large molecules, plasma bound, or poorly absorbed from the maternal or neonatal intestine are less likely to affect a neonate.

CONTRAINDICATIONS TO BREASTFEEDING

Medical contraindications to breastfeeding in the United States include infants with galactosemia, maple syrup urine disease, and phenylketonuria. Maternal conditions that contraindicate breastfeeding include infection with HIV, human T-cell lymphotropic virus types 1 and 2, active tuberculosis (until appropriately treated ≥2 wk and not considered contagious), herpes virus infection on breast, and maternal treatment with some radioactive compounds (Table 94-8).

Table 94-6 Ten Steps to Successful Breastfeeding

Every facility providing maternity services and care for newborn infants should accomplish the following:

1. Have a written breastfeeding policy that is routinely communicated to all healthcare staff.
2. Train all healthcare staff in the skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within a half hour of birth.
5. Show mothers how to breastfeed and how to maintain lactation even if they should be separated from their infants.
6. Give newborn infants no food or drink other than breast milk unless *medically* indicated.
7. Practice rooming-in (allow mothers and infants to remain together) 24 hr a day.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers (also called *dummies* or *soothers*) to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

From Protecting, promoting and supporting breastfeeding: the special role of maternity services. A joint WHO/UNICEF statement. *Geneva, 1989, World Health Organization.*

Table 94-7 Drugs and Breastfeeding

CONTRAINDICATED
- Amphetamines
- Antineoplastic agents
- Bromocriptine
- Chloramphenicol
- Clozapine
- Cocaine
- Cyclophosphamide
- Diethylstilbestrol
- Doxorubicin
- Ecstasy
- Ergots
- Gold salts
- Heroin
- Immunosuppressants
- Iodides
- Kava
- Lithium
- Methimazole
- Methamphetamine
- Phencyclidine (PCP)
- Radiopharmaceuticals
- Thiouracil
- Yohimbe

AVOID OR GIVE WITH CAUTION
- Alcohol
- Amiodarone
- Anthraquinones (laxatives)
- Aspirin (salicylates)
- Atropine
- β-Adrenergic blocking agents
- Benzodiazepines
- Birth control pills
- Bromides
- Buprenorphine/naltrexone
- Bupropion
- Calciferol
- Cascara
- Ciprofloxacin
- Codeine
- Dicumarol
- Dihydrotachysterol
- Domperidone
- Estrogens
- Hydrocodone
- Marijuana
- Metoclopramide
- Metronidazole
- Meperidine
- Oxycodone
- Phenobarbital*
- Primidone
- Psychotropic drugs
- Reserpine
- Salicylazosulfapyridine (sulfasalazine)

PROBABLY SAFE
- Acetaminophen
- Acyclovir
- Aldomet
- Anesthetics
- Antibiotics (not chloramphenicol)
- Antiepileptics
- Antihistamines*
- Antithyroid (not methimazole)
- Bishydroxycoumarin (dicumarol)
- Chlorpromazine*
- Cyclosporine
- Depo-Provera
- Digoxin
- Dilantin (phenytoin)
- Diuretics
- Fluoxetine
- Furosemide
- Haloperidol*
- Hydralazine
- Indomethacin, other nonsteroidal antiinflammatory drugs
- Low-molecular-weight heparins
- Metformin
- Methadone*
- Morphine
- Muscle relaxants
- Paroxetine
- Prednisone
- Propranolol
- Propylthiouracil
- Sedatives*
- Sertraline
- Theophylline
- Vitamins
- Warfarin

*Watch for sedation.

Table 94-8 Summary of Infectious Agents Detected in Milk and Newborn Disease

INFECTIOUS AGENT	DETECTED IN BREAST MILK?	BREAST MILK REPORTED AS CAUSE OF NEWBORN DISEASE?	MATERNAL INFECTION CONTRAINDICATION TO BREASTFEEDING?
BACTERIA			
Mastitis/*Staphylococcus aureus*	Yes	No	No, unless breast abscess present
Mycobacterium tuberculosis:			
Active disease	Yes	No	Yes, because of aerosol spread, or tuberculosis mastitis
Purified protein derivative skin test result positive, chest radiograph findings negative	No	No	No
Escherichia coli, other Gram-negative rods	Yes, stored	Yes, stored	—
Group B streptococci	Yes	Yes	No*
Listeria monocytogenes	Yes	Yes	No*
Coxiella burnetii	Yes	Yes	No*
Syphilis	No	No	No†

Continued

Table 94-8	Summary of Infectious Agents Detected in Milk and Newborn Disease—cont'd		
INFECTIOUS AGENT	**DETECTED IN BREAST MILK?**	**BREAST MILK REPORTED AS CAUSE OF NEWBORN DISEASE?**	**MATERNAL INFECTION CONTRAINDICATION TO BREASTFEEDING?**
VIRUSES			
HIV	Yes	Yes	Yes, developed countries
Cytomegalovirus:			
Term infant	Yes	Yes	No
Preterm infant	Yes	Yes	Evaluate on an individual basis
Hepatitis B virus	Yes, surface antigen	No	No, developed countries‡
Hepatitis C virus	Yes	No	No§
Hepatitis E virus	Yes	No	No
Human T-cell leukemia virus (HTLV)-1	Yes	Yes	Yes, developed countries
HTLV-2	Yes	?	Yes, developed countries
Herpes simplex virus	Yes	No/?yes	No, unless breast vesicles present
Rubella			
Wild type	Yes	Yes, rare	No
Vaccine	Yes	No	No
Varicella-zoster virus	Yes	No	No, cover active lesions¶
Epstein-Barr virus	Yes	No	No
Human herpesvirus (HHV)-6	No	No	No
HHV-7	Yes	No	No
West Nile virus	Possible	Possible	Unknown
PARASITES			
Toxoplasma gondii	Yes	Yes, 1 case	No

*Provided that the mother and child are taking appropriate antibiotics.
†Treat mother and child if active disease.
‡Immunize and immune globulin at birth.
§Provided that the mother is HIV-seronegative. Mothers should be counseled that breast milk transmission of hepatitis C virus has not been documented, but is theoretically possible.
¶Provide appropriate antivaricella therapy or prophylaxis to newborn.
Modified from Jones CA: Maternal transmission of infectious pathogens in breast milk, J Paediatr Child Health *37:576–582, 2001.*

Donor human milk, particularly purchased through the Internet, may be contaminated with potential pathogens. Contamination is much less of a concern with unpasteurized human milk obtained from a milk bank.

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Chapter 95
High-Risk Pregnancies

Waldemar A. Carlo and Namasivayam Ambalavanan

High-risk pregnancies are those that increase the likelihood of abortion, fetal death, preterm delivery, intrauterine growth restriction, poor cardiopulmonary or metabolic transitioning at birth, fetal or neonatal disease, congenital malformations, or mental retardation and other handicaps (Table 95-1; see Chapter 96). Some factors, such as ingestion of a teratogenic drug in the 1st trimester, are causally related to the risk; others, such as hydramnios, are associations that alert a physician to determine the etiology and avoid the inherent risks associated with excessive amniotic fluid. On the basis of their history, 10-20% of pregnant women can be identified as being at high risk; nearly half of all perinatal mortality and morbidity is associated with these high-risk pregnancies. Although assessing antepartum risk is important in reducing perinatal mortality and morbidity, some pregnancies become high risk only during labor and delivery; therefore, careful monitoring is critical throughout the intrapartum course.

Identifying high-risk pregnancies is important not only because it is the first step toward prevention but also because therapeutic steps may often be taken to reduce the risks to the fetus or neonate if the physician knows of the potential for difficulty.

GENETIC FACTORS

The occurrence of chromosomal abnormalities, congenital anomalies, inborn errors of metabolism, mental retardation, or any familial disease in blood relatives increases the risk of the same condition in the infant. Because many parents recognize only obvious clinical manifestations of genetically determined diseases, specific inquiry should be made about any disease affecting 1 or more blood relatives.

MATERNAL FACTORS

The lowest neonatal mortality rate occurs in infants of mothers who receive adequate prenatal care and who are 20-30 yr of age. Pregnancies in both teenagers and women older than 40 yr, particularly primiparous women, are at increased risk for intrauterine growth restriction, fetal distress, and intrauterine death. Advanced maternal age increases the risk of both chromosomal and nonchromosomal fetal malformations (Fig. 95-1).

Maternal illness (Table 95-2), multiple pregnancies (particularly those involving monochorionic twinning), infections (Table 95-3), and certain drugs (see Chapter 96) increase the risk for the fetus. The use of assisted reproductive technology (in vitro fertilization, intracytoplasmic sperm injection) increases the risk of perinatal mortality, infant morbidity, prematurity, low and very-low birthweight, and cerebral palsy, largely because of the increase in multiple-fetus pregnancies with such technology; the risks for birth defects are also increased, in part, because of epigenetic effects on gene expression.

Table 95-1 Factors Associated with High-Risk Pregnancy
ECONOMIC
Poverty
Unemployment
Uninsured, underinsured health insurance
Poor access to prenatal care
CULTURAL–BEHAVIORAL
Low educational status
Poor healthcare attitudes
No care or inadequate prenatal care
Cigarette, alcohol, illicit drug use
Age <20 or >40 yr
Unmarried
Short interpregnancy interval
Lack of support group (husband, family, religion)
Stress (physical, psychologic)
Black race
BIOLOGIC–GENETIC
Previous low birthweight or preterm infant
Low weight for height
Poor weight gain during pregnancy
Short stature
Poor nutrition
Consanguinity
Intergenerational effects
Low maternal birthweight
Hereditary diseases (inborn error of metabolism)
REPRODUCTIVE
Previous cesarean section
Previous infertility
Conception by reproductive technology
Prolonged gestation
Prolonged labor
Previous infant with cerebral palsy, mental retardation, birth trauma, congenital anomalies
Abnormal lie (breech)
Multiple gestations
Premature rupture of membranes
Infection (systemic, amniotic, extra-amniotic, cervical)
Preeclampsia or eclampsia
Uterine bleeding (abruptio placentae, placenta previa)
Parity (0 or >5 previous deliveries)
Uterine or cervical anomalies
Fetal disease
Abnormal fetal growth
Idiopathic premature labor
Iatrogenic prematurity
High or low levels of maternal serum α-fetoprotein
MEDICAL
Diabetes mellitus
Hypertension
Congenital heart disease
Autoimmune disease
Sickle cell anemia
Intercurrent surgery or trauma
Sexually transmitted infection
Maternal hypercoagulable states
Exposure to prescription medications
TORCH (*t*oxoplasmosis, *o*ther agents, *r*ubella, *c*ytomegalovirus, *h*erpes simplex) infection

Preterm birth is common in high-risk pregnancies (see Chapter 97). Factors associated with prematurity, noted in Table 95-1, include biologic markers such as cervical shortening, genital infection, fetal fibronectin in cervicovaginal secretions, serum α-fetoprotein, and preterm premature rupture of membranes (PROM). PROM occurs in 30-40% of preterm deliveries, and it is a leading identifiable cause of prematurity. Preterm delivery is often difficult to predict.

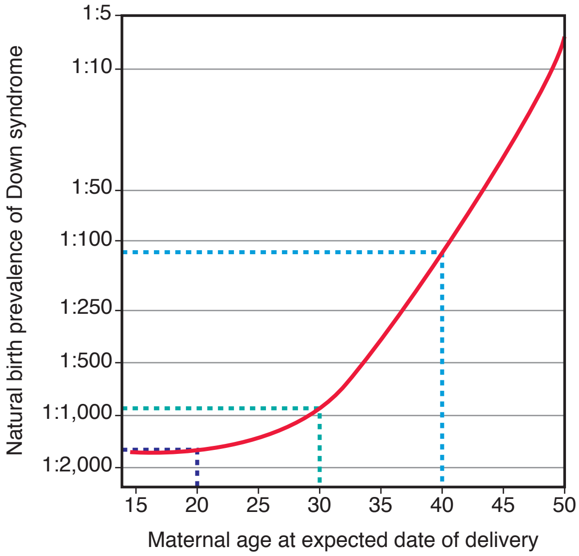

Figure 95-1 Natural birth prevalence of Down syndrome according to maternal age. *(From Wald NJ, Leck I:* Antenatal and neonatal screening, *ed 2, Oxford, 2000, Oxford University Press.)*

Polyhydramnios and **oligohydramnios** indicate high-risk pregnancies. Although the turnover rate of amniotic fluid is rapid, during normal pregnancy the amniotic fluid volume gradually increases at a rate of <10 mL/day until about the 34th wk of pregnancy, after which it slowly diminishes. Volumes vary widely in normal pregnancy; term volume may be 500-2,000 mL. A volume estimated at greater than 2,000 mL in the 3rd trimester constitutes polyhydramnios, and a volume estimated at <500 mL indicates oligohydramnios. Polyhydramnios complicates 1-3%, and oligohydramnios 1-5%, of pregnancies. The ultrasonographic criteria for these diagnoses are based on the amniotic fluid index, which is determined by measuring the vertical diameter of amniotic fluid pockets in four quadrants; an index >24 cm suggests polyhydramnios, whereas an index <5 cm suggests oligohydramnios.

Acute polyhydramnios is rare and is usually associated with preterm labor and delivery. **Chronic polyhydramnios** is diagnosed in the 3rd trimester from the discrepancy between uterine size and gestational age; it is occasionally not diagnosed until the patient has dysfunctional labor or an abnormally large amount of amniotic fluid is noted during delivery. Polyhydramnios is associated with preterm labor, abruptio placentae, multiple congenital anomalies, and fetal neuromuscular dysfunction or obstruction of the gastrointestinal tract that interferes with reabsorption of the amniotic fluid that is normally swallowed by the fetus (Table 95-4). Increased fetal urination or edema formation is also associated with excessive amniotic fluid volume. Ultrasound demonstrates the increased amniotic fluid surrounding the fetus and detects associated fetal anomalies, hydrops, pleural effusions, and ascites. In 60% of patients, no cause is identified. Symptomatic polyhydramnios may be managed by serial amniocenteses or by short-course maternal indomethacin if the problem is caused by excessive fetal urination. Treatment is indicated for acute maternal respiratory distress and threatened preterm labor or to provide time for the administration of corticosteroids to enhance fetal lung maturity.

Oligohydramnios is associated with congenital anomalies; intrauterine growth restriction; severe renal, bladder, or urethral anomalies; and drugs that interfere with fetal urination (see Table 95-4). Oligohydramnios becomes most evident after 20 wk of gestation, when fetal urination is the major source of amniotic fluid. Rupture of the membranes is the most common cause of oligohydramnios and must be ruled out if oligohydramnios is suspected, especially if a normal-sized

Table 95-2 Maternal Conditions Affecting the Fetus or Neonate

DISORDER	EFFECT(S)	MECHANISM(S)
Autoantibody against folate receptors	Neural tube defects	Blockage of cellular uptake of folate
Cervical neoplasia	Preterm premature rupture of membranes	Associated with loop electrosurgical excision procedure or cone therapy
Cholestasis	Preterm delivery, intrauterine fetal demise	Unknown, possibly hepatitis E
Cyanotic heart disease	Intrauterine growth restriction	Low fetal oxygen delivery
Diabetes mellitus:		
Mild	Large for gestational age, hypoglycemia	Fetal hyperglycemia—produces hyperinsulinemia; insulin promotes growth
Severe	Growth restriction	Vascular disease, placental insufficiency
Drug addiction	Intrauterine growth restriction, neonatal withdrawal	Direct drug effect plus poor diet
Endemic goiter	Hypothyroidism	Iodine deficiency
Graves disease	Transient neonatal thyrotoxicosis	Placental immunoglobulin passage of thyroid-stimulating antibody
Herpes gestationis (noninfectious)	Bullous rash, intrauterine fetal demise	Autoantibody similar to that in bullous pemphigoid
Hyperparathyroidism	Neonatal hypocalcemia	Maternal calcium crosses to fetus and suppresses fetal parathyroid gland
Hypertension	Intrauterine growth restriction, intrauterine fetal demise	Placental insufficiency, fetal hypoxia
Idiopathic thrombocytopenic purpura	Thrombocytopenia	Nonspecific maternal platelet antibodies cross placenta
Isoimmune neutropenia or thrombocytopenia	Neutropenia or thrombocytopenia	Specific antifetus neutrophil or platelet antibody crosses placenta after sensitization of mother
Malignant melanoma	Placental or fetal tumor	Metastasis
Myasthenia gravis	Transient neonatal myasthenia	Immunoglobulin to acetylcholine receptor crosses placenta
Myotonic dystrophy	Neonatal myotonic dystrophy, congenital contractures, respiratory insufficiency	Genetic anticipation
Obesity	Macrosomia, hypoglycemia	Unknown
Phenylketonuria	Microcephaly, retardation	Elevated fetal phenylalanine values
Poor nutrition	Intrauterine growth restriction, adult insulin resistance	Reduced fetal nutrients, nutritional programming
Preeclampsia, eclampsia	Intrauterine growth restriction, thrombocytopenia, neutropenia, fetal demise	Uteroplacental insufficiency, fetal hypoxia, vasoconstriction
Renal transplantation	Intrauterine growth restriction	Uteroplacental insufficiency
Rhesus or other blood group sensitization	Fetal anemia, hypoalbuminemia, hydrops, neonatal jaundice	Antibody crosses placenta and is directed to fetal cells with antigen
Sickle cell anemia	Preterm birth, intrauterine growth restriction, stillbirth	Maternal sickling producing fetal hypoxia
Systemic lupus erythematosus	Congenital heart block, rash, anemia, thrombocytopenia, neutropenia	Antibody directed to fetal heart, red and white blood cells, and platelets

bladder is seen on fetal ultrasound. Oligohydramnios causes fetal compression abnormalities such as fetal distress, clubfoot, spadelike hands, and a flattened nasal bridge. The most serious complication of chronic oligohydramnios is **pulmonary hypoplasia.** The risk of umbilical cord compression during labor and delivery is increased in pregnancies complicated by oligohydramnios and may be alleviated by saline amnioinfusion. Prophylactic intrapartum amnioinfusion reduces the need for cesarean section and improves Apgar scores.

Antenatal screening can be used to detect a number of disorders, including Down syndrome and other chromosomal abnormalities, neural tube defects and other structural anomalies, Tay-Sachs disease and other metabolic genetic diseases, hemoglobinopathies and other blood disorders, and cystic fibrosis. Screening methods include maternal blood tests, fetal ultrasound, and diagnostic tests on cells or fluid obtained by amniocentesis or chorionic villus sampling and by fetal blood or tissue sampling. Cell-free fetal DNA in maternal blood has higher sensitivity (>99%) and lower false-positive rates for trisomy 21 (Down syndrome) and other chromosomal abnormalities than a combination of maternal serum analytes and ultrasound.

Second-trimester screening (15-18 wk) of maternal serum α-fetoprotein (MSAFP) values is used to screen for open neural tube defects. Approximately 90% of affected pregnancies can be detected by an elevated MSAFP value. Gastroschisis, omphalocele, congenital nephrosis, twins, and other abnormal conditions can also be identified.

Table 95-3 Maternal Infections Affecting the Fetus or Newborn

INFECTION	MODE(S) OF TRANSMISSION	OUTCOME
BACTERIA		
Group B streptococcus	Ascending cervical	Sepsis, pneumonia
Escherichia coli	Ascending cervical	Sepsis, pneumonia
Listeria monocytogenes	Transplacental	Sepsis, pneumonia
Ureaplasma urealyticum	Ascending cervical	Pneumonia, meningitis
Mycoplasma hominis	Ascending cervical	Pneumonia
Chlamydia trachomatis	Vaginal passage	Conjunctivitis, pneumonia
Syphilis	Transplacental, vaginal passage	Congenital syphilis
Borrelia burgdorferi	Transplacental	Prematurity, fetal demise
Neisseria gonorrhoeae	Vaginal passage	Ophthalmia (conjunctivitis), sepsis, meningitis
Mycobacterium tuberculosis	Transplacental	Prematurity, fetal demise, congenital tuberculosis
Granulocytic ehrlichiosis	Transplacental	Sepsis
VIRUS		
Rubella	Transplacental	Congenital rubella
Cytomegalovirus	Transplacental, breast milk (rare)	Congenital cytomegalovirus or asymptomatic
HIV	Transplacental, vaginal passage, breast milk	Congenital acquired immunodeficiency syndrome
Hepatitis B	Vaginal passage, transplacental, breast milk	Neonatal hepatitis, chronic hepatitis B surface antigen carrier state
Hepatitis C	Transplacental	Uncommon, but neonatal hepatitis, chronic carrier state possible
Lymphocytic choriomeningitis	Transplacental	Fetal, neonatal death; hydrocephalus, chorioretinitis
Herpes simplex type 2 or 1	Transplacental	Congenital herpes simplex virus
	Vaginal passage, ascending	Neonatal encephalitis, disseminated viremia
Varicella-zoster	Transplacental:	
	Early	Congenital anomalies
	Late	Neonatal varicella
Parvovirus	Transplacental	Fetal anemia, hydrops
Coxsackie B	Fecal-oral	Myocarditis, meningitis, hepatitis
Poliomyelitis	Transplacental	Congenital poliomyelitis
Epstein-Barr	Transplacental	Anomalies(?)
Rubeola	Transplacental	Abortion, fetal measles
West Nile	Transplacental	Chorioretinitis, focal cerebral necrosis
Dengue virus	Transplacental	Thrombocytopenia, lymphocytosis
PARASITES		
Toxoplasmosis	Transplacental	Congenital toxoplasmosis or asymptomatic
Malaria	Transplacental	Abortion, prematurity, intrauterine growth restriction
Trypanosomiasis	Transplacental	Congenital Chagas disease
Hookworm	None	Maternal anemia, low birthweight
FUNGI		
Candida	Ascending, cervical	Sepsis, pneumonia, rash
PRION		
Creutzfeldt-Jakob disease	Transplacental, colostrum	Hypothetical route, no long-term data

Low MSAFP is associated with incorrect gestational age estimates, trisomy 18 or 21, and intrauterine growth restriction.

A pregnancy should be considered high risk when the uterus is inappropriately large or small. A uterus large for the estimated stage of gestation suggests the presence of multiple fetuses, hydramnios, or an excessively large infant; an inappropriately small infant suggests oligohydramnios or poor intrauterine growth. PROM more than 24 hr before delivery carries a risk of fetal infection; it also increases the risk of premature birth. PROM at term usually results in the onset of labor within 48 hr but poses a risk of chorioamnionitis and umbilical cord compression. With **PROM** before 37 wk, there is a longer latency until labor starts, and its occurrence has the added risks of cord prolapse, oligohydramnios, abruptio placentae, fetal malposition; also, if membrane rupture is present for >7 days in a fetus during the 2nd trimester, pulmonary hypoplasia, uterine-induced deformations, and extremity contractures can develop. Prolonged and difficult labor increases the risk for mechanical and hypoxic damage. A tumultuous short labor with a precipitous delivery increases the risk of birth asphyxia and intracranial hemorrhage. **Placental separation** at any time before delivery and abnormal implantation or compression of the cord increase the possibility of brain damage from fetal hypoxia; brown or muddy amniotic fluid suggests that meconium has been passed, possibly during an episode of fetal hypoxia.

Although the safety of any type of delivery depends on the skill of the obstetrician, additional hazards accompany particular methods and result from the circumstances that dictated them. The risk of **intracranial hemorrhage** is greater in infants delivered by vacuum extraction or forceps than in those born unassisted in spontaneous vaginal deliveries. Neonatal deaths after mid-forceps delivery, breech extraction, and version are likely to be related to traumatic intracranial injury.

Infants born by **cesarean section** present problems possibly related to the unfavorable obstetric circumstance that necessitated the operation. In normal term pregnancies without any indication of fetal distress, cesarean section delivery carries a greater risk than delivery through the birth canal. Controversy exists regarding the safest type of delivery for a nondistressed, viable immature fetus, especially in a breech presentation; cesarean section may involve less risk than the "stress" of labor and the potentially hypoxic effects of uterine contractions during vaginal delivery. Term infants in breech position (≈3-4% of term births) that do not assume vertex position after external cephalic version attempts may also benefit from cesarean section.

Table 95-4	Conditions Associated with Disorders of Amniotic Fluid Volume

OLIGOHYDRAMNIOS
Amniotic fluid leak/rupture of membranes
Intrauterine growth restriction
Fetal anomalies
Twin–twin transfusion (donor)
Renal agenesis (Potter syndrome)
Urethral atresia
Prune-belly syndrome
Pulmonary hypoplasia
Amnion nodosum
Indomethacin
Angiotensin-converting enzyme inhibitors or receptor antagonists
Intestinal pseudoobstruction

POLYHYDRAMNIOS
Congenital anomalies:
Anencephaly
Hydrocephaly
Tracheoesophageal fistula
Duodenal atresia
Spina bifida
Cleft lip or palate
Cystic adenomatoid lung malformation
Diaphragmatic hernia

Syndromes:
Achondroplasia
Klippel-Feil
Trisomy 18
Trisomy 21
TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex)
Hydrops fetalis
Multiple congenital anomalies

Other:
Diabetes mellitus
Twin–twin transfusion (recipient)
Fetal anemia
Fetal heart failure
Polyuric renal disease
Neuromuscular diseases
Nonimmune hydrops
Chylothorax
Teratoma
Idiopathic

Although transient tachypnea is the most frequently associated problem with cesarean section, respiratory distress syndrome and persistent pulmonary hypertension may develop, particularly in infants born by cesarean section to women who are not in labor, in those with uncertain dates, and in those born to diabetic mothers or after asphyxia. A trial of labor after a previous low segment cesarean section may have benefits and harms but there are limited data to make firm recommendations. In women with more than one previous cesarean section, there is an increased risk of uterine rupture. An elective cesarean section should be delayed until ≥39 wk of gestation. Earlier delivery increases the risk to the newborns.

Anesthesia and analgesia affect the fetus as well as the mother; severe maternal hypoxemia secondary to hypoventilation or hypotension resulting from epidural anesthesia may lead to severe fetal hypoxia and shock. Skilled use of medication avoids severe fetal narcosis while securing the benefits of gentle and unhurried delivery. Even skilled administration may result in a mildly depressed infant whose crying and breathing may be delayed 1-2 min and who may be somewhat inactive for several hours.

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Chapter 96

The Fetus

Waldemar A. Carlo and
Namasivayam Ambalavanan

The major emphasis in fetal medicine involves (1) assessment of fetal growth and maturity, (2) evaluation of fetal well-being or distress, (3) assessment of the effects of maternal disease on the fetus, (4) evaluation of the effects of drugs administered to the mother on the fetus, and (5) identification and treatment of fetal disease or anomalies. Some aspects of human fetal growth and development are summarized in Chapter 8.

96.1 Fetal Growth and Maturity

Waldemar A. Carlo and Namasivayam Ambalavanan

Ultrasonography of the fetus, a common obstetric procedure, is both safe and reasonably accurate. Indications for antenatal ultrasonography include estimation of gestational age (unknown dates, discrepancy between uterine size and dates or suspected growth restriction), assessment of amniotic fluid volume, estimation of fetal weight, determination of the location of the placenta and the number and position of fetuses, and identification of congenital anomalies.

Fetal growth can be assessed by ultrasonography as early as 6-8 wk. The most accurate assessment of gestational age is by 1st-trimester ultrasound measurement of crown–rump length. The biparietal diameter is used to assess gestational age beginning in the 2nd trimester. Through 30 wk the biparietal diameter accurately estimates gestation to within ± 10 days. Later in gestation, accuracy falls to ± 3 wk. Methods used to assess gestational age closer to term include measurement of abdominal circumference and femoral length. If a single ultrasound examination is performed, the most information can be obtained with a scan at 18-20 wk, when both gestational age and fetal anatomy can be evaluated. Serial scans may be useful in assessing fetal growth. Two patterns of fetal growth restriction have been identified: continuous fetal growth 2 SD below the mean for gestational age or a normal fetal growth curve that abruptly slows or flattens later in gestation (Fig. 96-1).

Fetal maturity and dating are usually assessed by history (last menstrual period), physical examination, auscultation of fetal heart sounds at 16-18 wk, maternal perception of fetal movements at 18-20 wk, fundal height, and ultrasound (growth). Lung maturation may be estimated by determining the surfactant content of amniotic fluid (see Chapter 101.3).

Bibliography is available at Expert Consult.

96.2 Fetal Distress

Waldemar A. Carlo and Namasivayam Ambalavanan

Fetal compromise may occur during the antepartum or intrapartum period; it may be asymptomatic in the antenatal period. Antepartum fetal surveillance is warranted for women at increased risk for fetal death, including those with a history of stillbirth, intrauterine growth restriction (IUGR), oligohydramnios or polyhydramnios, multiple gestation, rhesus sensitization, hypertensive disorders, diabetes mellitus or other chronic maternal disease, decreased fetal movement, and postterm pregnancy. The predominant cause of antepartum fetal distress is uteroplacental insufficiency, which may manifest clinically as IUGR, fetal hypoxia, increased vascular resistance in fetal blood vessels (Figs. 96-2 and 96-3), and, when severe, mixed respiratory and

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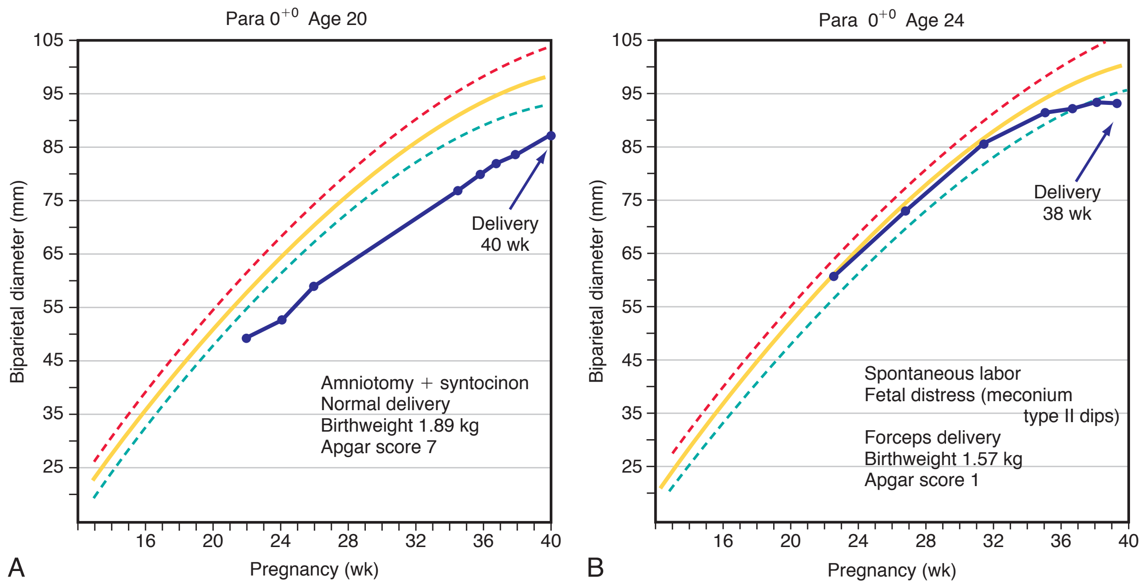

Figure 96-1 **A,** Example of a "low-profile" growth retardation pattern in an uneventful pregnancy and labor. The baby cried at 1 min and hypoglycemia did not develop. Birthweight was below the 5th percentile for gestational age. **B,** Example of a "late-flattening" growth retardation pattern. The mother had a typical history of preeclampsia, and the infant had intrapartum fetal distress, a low Apgar score, and postnatal hypoglycemia. Birthweight was below the 5th percentile for gestational age. *(From Campbell S: Fetal growth,* Clin Obstet Gynecol *1:41–65, 1974.)*

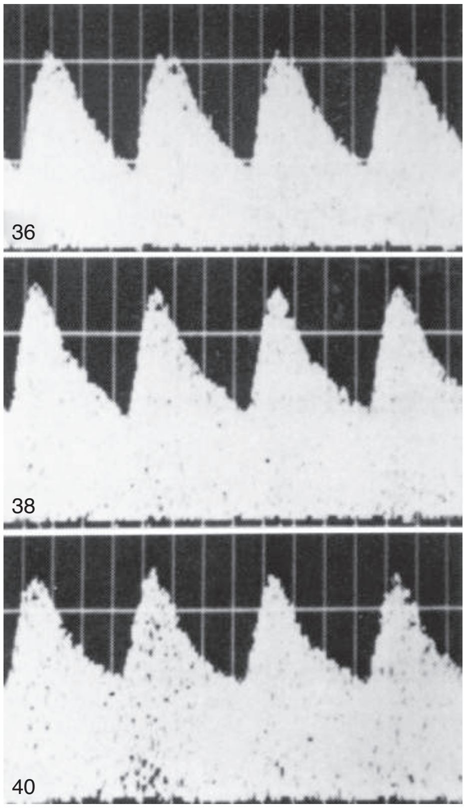

Figure 96-2 **Normal Doppler velocity in sequential studies of fetal umbilical artery flow velocity waveforms from one normal pregnancy.** Note the systolic peak flow with lower but constant heart flow during diastole. The systolic : diastolic ratio can be determined and, in normal pregnancies, is less than 3 after the 30th wk of gestation. The *numbers* indicate the weeks of gestation. *(From Trudinger B: Doppler ultrasound assessment of blood flow. In Creasy RK, Resnik R, editors:* Maternal-fetal medicine: principles and practice, *ed 5, Philadelphia, 2004, WB Saunders.)*

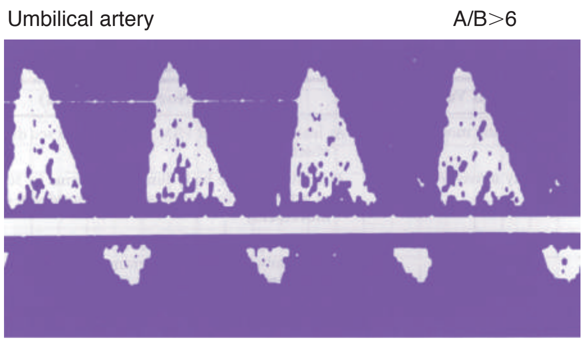

Figure 96-3 **Abnormal umbilical artery Doppler in which the diastolic component shows flow in a reverse direction.** This finding occurs in severe intrauterine hypoxia and intrauterine growth restriction. *(From Trudinger C: Doppler ultrasound assessment of blood flow. In Creasy RK, Resnik R, editors:* Maternal-fetal medicine: principles and practice, *ed 5, Philadelphia, 2004, WB Saunders.)*

metabolic (lactic) acidosis. The goals of antepartum fetal surveillance are to prevent intrauterine fetal demise, to prevent hypoxic brain injury, and to either prolong gestation in women at risk for preterm delivery when such prolongation is safe or deliver a fetus when it is in jeopardy. Table 96-1 lists methods for assessing fetal well-being.

The most commonly used noninvasive tests are the nonstress test (NST), the full and modified biophysical profile (BPP), and, less commonly, the contraction stress test (CST). The **NST** monitors the presence of fetal heart rate accelerations that follow fetal movement. A reactive (normal) NST result demonstrates 2 fetal heart rate accelerations of at least 15 beats/min lasting 15 sec. A nonreactive NST result suggests fetal compromise and requires further assessment with a CST or the BPP. A **CST** observes the fetal heart rate response to spontaneous, nipple-stimulated, or oxytocin-stimulated uterine contractions. Fetal compromise is suggested when the majority of contractions in 10 min are followed by late decelerations. A CST is relatively contraindicated in women with preterm premature rupture of membranes, a previous uterine scar from a classic cesarean section, multiple

Table 96-1 Fetal Diagnosis and Assessment

METHOD	COMMENT(S) AND INDICATION(S)
IMAGING	
Ultrasound (real-time)	Biometry (growth), anomaly (morphology) detection Biophysical profile Amniotic fluid volume, hydrops
Ultrasound (Doppler)	Velocimetry (blood flow velocity) Detection of increased vascular resistance secondary to fetal hypoxia
Embryoscopy	Early diagnosis of limb anomaly
Fetoscopy	Detection of facial, limb, cutaneous anomalies
MRI	Defining of lesions before fetal surgery
FLUID ANALYSIS	
Amniocentesis	Fetal maturity (L : S ratio), karyotype (cytogenetics), biochemical enzyme analysis, molecular genetic DNA diagnosis, bilirubin, or α-fetoprotein determination Bacterial culture, pathogen antigen, or genome detection
Cordocentesis (percutaneous umbilical blood sampling)	Detection of blood type, anemia, hemoglobinopathies, thrombocytopenia, acidosis, hypoxia, polycythemia, immunoglobulin M antibody response to infection Rapid karyotyping and molecular DNA genetic diagnosis Fetal therapy (see Table 96-5)
FETAL TISSUE ANALYSIS	
Chorionic villus biopsy	Karyotype, molecular DNA genetic analysis, enzyme assays
Skin biopsy	Hereditary skin disease*
Liver biopsy	Enzyme assay*
Circulating fetal DNA or cells in maternal blood or plasma	Molecular DNA genetic analysis including microarray analysis, chromosome number, specific gene testing, or genetic sequencing
MATERNAL SERUM α-FETOPROTEIN CONCENTRATION	
Elevated	Twins, neural tube defects (anencephaly, spina bifida), intestinal atresia, hepatitis, nephrosis, fetal demise, incorrect gestational age
Reduced	Trisomies, aneuploidy
MATERNAL CERVIX	
Fetal fibronectin	Indicates risk of preterm birth
Bacterial culture	Identifies risk of fetal infection (group B streptococcus, *Neisseria gonorrhoeae*)
Fluid	Determination of premature rupture of membranes
ANTEPARTUM BIOPHYSICAL MONITORING	
Nonstress test	Fetal distress; hypoxia
Contraction stress test	Fetal distress; hypoxia
Biophysical profile and modified biophysical profile	Fetal distress; hypoxia
Intrapartum fetal heart rate monitoring	See Fig. 96-4

*DNA genetic analysis on chorionic villus samples, amniocytes from amniocentesis, or fetal cells recovered from the maternal circulation may obviate the need for direct fetal tissue biopsy if the gene or genetic marker is available (e.g., the gene for Duchenne muscular dystrophy).
L : S, lecithin : sphingomyelin ratio.

gestations, incompetent cervix, and placenta previa. The goals of fetal monitoring are to prevent intrauterine fetal demise and hypoxic brain injury. Although the CST and NST have low false-negative rates, both have high false-positive rates. The full **BPP** assesses fetal breathing, body movement, tone, heart rate, and amniotic fluid volume, and it is used to improve the accurate and safe identification of fetal compromise (Table 96-2). A score of 2 is given for each observation present. A total score of 8-10 is reassuring; a score of 6 is equivocal, and retesting should be done in 12-24 hr; and a score of 4 or less warrants immediate evaluation and possible delivery. The BPP has good negative predictive value. The modified BPP consists of the combination of an ultrasound estimate of amniotic fluid volume (the amniotic fluid index) and the NST. When results of both are normal, fetal compromise is very unlikely. Signs of progressive compromise seen on Doppler ultrasonography include reduced, absent, or reversed diastolic waveform velocity in the fetal aorta or umbilical artery (see Fig. 96-3 and Table 96-1). High-risk fetuses often have combinations of abnormalities, such as oligohydramnios, reversed diastolic Doppler umbilical artery blood flow velocity, and a low BPP.

Fetal compromise *during labor* may be detected by monitoring the fetal heart rate, uterine pressure, and fetal scalp blood pH (Fig. 96-4). **Continuous fetal heart rate monitoring** detects abnormal cardiac patterns by instruments that compute the beat-to-beat fetal heart rate from a fetal electrocardiographic signal. Signals are derived from an electrode attached to the fetal presenting part, from an ultrasonic transducer placed on the maternal abdominal wall to detect continuous ultrasonic waves reflected from the contractions of the fetal heart, or from a phonotransducer placed on the mother's abdomen. Uterine contractions are simultaneously recorded from an amniotic fluid catheter and pressure transducer or from a tocotransducer applied to the maternal abdominal wall overlying the uterus. Fetal heart rate patterns show various characteristics, some of which suggest fetal compromise. The baseline fetal heart rate is the average rate between uterine contractions, which gradually decreases from approximately 155 beats/min in early pregnancy to approximately 135 beats/min at term; the normal range at term is 110-160 beats/min. **Tachycardia** (>160 beats/min) is associated with early fetal hypoxia, maternal fever, maternal hyperthyroidism, maternal β-sympathomimetic drug or atropine therapy, fetal anemia, infection, and some fetal arrhythmias. The last do not generally occur with congenital heart disease and may resolve spontaneously at birth. **Fetal bradycardia** (<110 beats/min) may be normal (e.g., 105-110 beats/min) but may occur with fetal hypoxia, placental transfer of local anesthetic agents and β-adrenergic blocking agents, and, occasionally, heart block with or without congenital heart disease.

Normally, the baseline fetal heart rate is variable. **Variability** is classified as follows: **absence of variability**, if an amplitude change is undetectable; **minimal variability** if amplitude range is ≤5 beats/min

Table 96-2 Biophysical Profile Scoring: Technique and Interpretation		
BIOPHYSICAL VARIABLE	**NORMAL SCORE (2)**	**ABNORMAL SCORE (0)**
Fetal breathing movements (FBMs)	At least 1 episode of FBM of at least 30 sec duration in 30 min observation	Absence of FBM or no episode ≥30 sec in 30 min
Gross body movement	At least 3 discrete body/limb movements in 30 min (episodes of active continuous movement considered a single movement)	2 or fewer episodes of body/limb movements in 30 min
Fetal tone	At least 1 episode of active extension with return to flexion of fetal limb(s) or trunk Opening and closing of hand considered evidence of normal tone	Either slow extension with return to partial flexion or movement of limb in full extension or absence of fetal movement with the hand held in complete or partial deflection
Reactive fetal heart rate (FHR)	At least 2 episodes of FHR acceleration of ≥15 beats/min and at least 15 sec in duration associated with fetal movement in 30 min	Less than 2 episodes of acceleration of FHR or acceleration of <15 beats/min in 30 min
Qualitative amniotic fluid (AF) volume*	At least 1 pocket of AF that measures at least 2 cm in 2 perpendicular planes	Either no AF pockets or a pocket <2 cm in 2 perpendicular planes

*Modification of the criteria for reduced amniotic fluid from less than 1 cm to less than 2 cm would seem reasonable. Ultrasound is used for biophysical assessment of the fetus.

From Creasy RK, Resnik R, Iams JD, editors: Maternal-fetal medicine: principles and practice, *ed 5, Philadelphia, 2004, Saunders.*

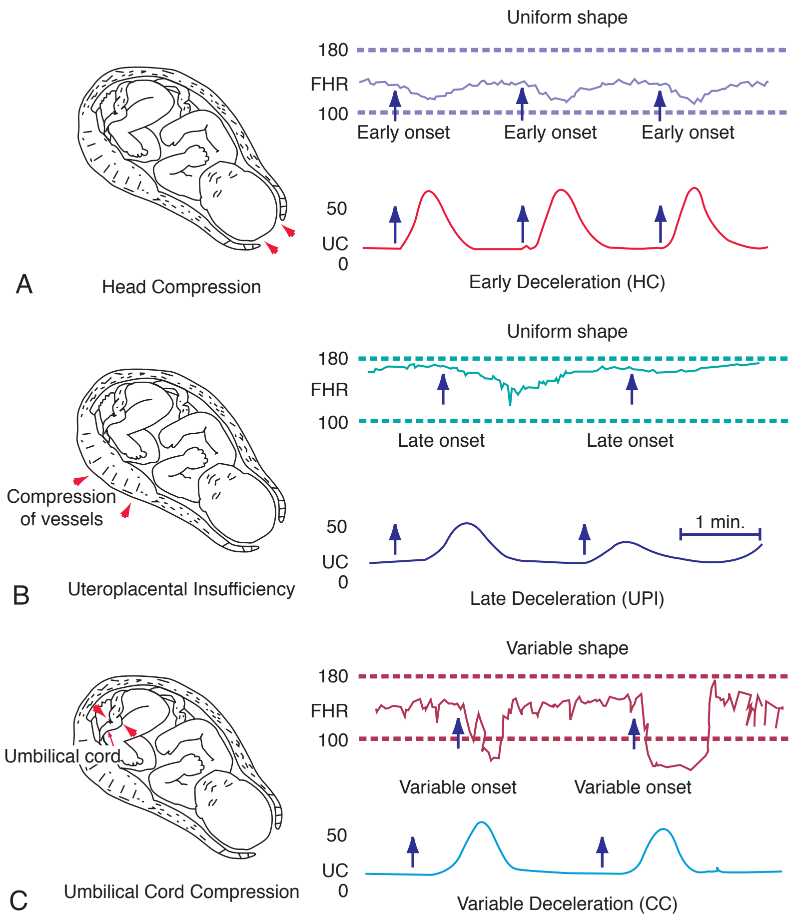

Figure 96-4 **Patterns of periodic fetal heart rate deceleration.** The tracing in **A** shows early deceleration occurring during the peak of uterine contractions as a result of pressure on the fetal head. **B,** Late deceleration caused by uteroplacental insufficiency. **C,** Variable deceleration as a result of umbilical cold compression. *Arrows* denote the time relationship between the onset of fetal heart rate changes and uterine contractions. *(From Hon EH:* An atlas of fetal heart rate patterns, *New Haven, CT, 1968, Harty Press.)*

(beats/min); **moderate variability** if amplitude range is 6-25 beats/min; **marked variability** if amplitude range is >25 beats/min. Variability may be decreased or lost with fetal hypoxemia or the placental transfer of drugs such as atropine, diazepam, promethazine, magnesium sulfate, and most sedative and narcotic agents. Prematurity, the sleep state, and fetal tachycardia may also diminish beat-to-beat variability.

Periodic accelerations or decelerations of the fetal heart rate in response to uterine contractions may also be monitored (see Fig. 96-4). An **acceleration** is an abrupt increase in fetal heart rate of ≥15 beats/

Table 96-3 Characteristics of Decelerations of the Fetal Heart Rate

LATE DECELERATION
- Visually apparent, usually symmetric *gradual* decrease and return of the fetal heart rate (FHR) associated with a uterine contraction.
- A *gradual* FHR decrease is defined as duration of ≥30 sec from the onset to the nadir of the FHR.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The deceleration is delayed in timing, with the nadir of the deceleration occurring after the peak of the contraction.
- In most cases, the onset, nadir, and recovery of the deceleration occur after the beginning, peak, and ending of the contraction, respectively.

EARLY DECELERATION
- Visually apparent, usually symmetric *gradual* decrease and return of the FHR associated with a uterine contraction.
- A *gradual* FHR decrease is defined as duration of ≥30 sec from the onset to the FHR nadir.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The nadir of the deceleration occurs at the same time as the peak of the contraction.
- In most cases, the onset, nadir, and recovery of the deceleration are coincident with the beginning, peak, and ending of the contraction, respectively.

VARIABLE DECELERATION
- Visually apparent, *abrupt* decrease in FHR.
- An *abrupt* FHR decrease is defined as duration <30 sec from the onset of the deceleration to the beginning of the FHR nadir of the deceleration.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The decrease in FHR is ≥15 beats/min, lasting ≥15 sec, and <2 min in duration.
- When variable decelerations are associated with uterine contractions, their onset, depth, and duration commonly vary with successive uterine contractions.

From Macones GA, Hankins GDV, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines, Obstet Gynecol *112:661–666, 2008.*

min in ≥15 sec. The presence of accelerations or moderate variability reliably predicts the absence of fetal metabolic acidemia. However, their absence does not reliably predict fetal acidemia or hypoxemia. **Early deceleration** associated with head compression is a repetitive pattern of gradual decrease and return of the fetal heart rate that is coincidental with the uterine contraction (Table 96-3). **Variable deceleration** (associated with cord compression) is characterized by variable shape, abrupt onset and occurrence with consecutive contractions, and return to baseline at or after the conclusion of the contraction. **Late deceleration,** associated with fetal hypoxemia, occurs repetitively after a uterine contraction is well established and persists into the interval following contractions. The late deceleration pattern is usually associated with maternal hypotension or excessive uterine activity, but it may be a response to any maternal, placental, umbilical cord, or fetal factor that limits effective oxygenation of the fetus. Reflex late decelerations with normal beat-to-beat variability are associated with chronic compensated fetal hypoxia, and they occur during uterine contractions that temporarily impede oxygen transport to the heart. Nonreflex late decelerations are more ominous and indicate severe hypoxic depression of myocardial function. Approximately 10-15% of term fetuses have terminal (just before delivery) fetal heart rate decelerations that are usually benign if they lasted <10 min prior to delivery. Neonates with longer terminal decelerations without recovery (persistent bradycardia) are associated with fetal acidosis and need neonatal ICU observation or treatment.

If late decelerations are unresponsive to oxygen supplementation, hydration, discontinuation of labor stimulation, and position changes, prompt delivery is indicated. A 3-tier system has been developed by a panel of experts for interpretation of fetal heart rate tracings (Table 96-4). **Category I tracings** are normal and are strongly predictive of normal fetal acid–base status at the time of the observation. **Category II tracings** are not predictive of abnormal fetal status, but there is insufficient evidence to categorize them as category I or III; further evaluation, surveillance, and reevaluation are indicated. **Category III tracings** are abnormal and predictive of abnormal fetal acid–base status at the time of observation. Category III tracings require prompt evaluation and efforts to expeditiously resolve the abnormal fetal heart rate as previously discussed for late decelerations.

Fetal scalp blood sampling during labor through a slightly dilated cervix may aid in confirming fetal distress suspected on the basis of variations in fetal heart rate or the presence of meconium in amniotic

Table 96-4 Three-Tier Fetal Heart Rate Interpretation System

CATEGORY I
Category I fetal heart rate (FHR) tracings include all of the following:
- Baseline rate: 110-160 beats per minute (beats/min)
- Baseline FHR variability: moderate
- Late or variable decelerations: absent
- Early decelerations: present or absent
- Accelerations: present or absent

CATEGORY II
Category II FHR tracings include all FHR tracings not categorized as category I or category III. Category II tracings may represent an appreciable fraction of those encountered in clinical care. Examples of category II FHR tracings include any of the following:

Baseline rate
- Bradycardia not accompanied by absence of baseline variability
- Tachycardia

Baseline FHR variability
- Minimal baseline variability
- Absence of baseline variability not accompanied by recurrent decelerations
- Marked baseline variability

Accelerations
- Absence of induced accelerations after fetal stimulation

Periodic or episodic decelerations
- Recurrent variable decelerations accompanied by minimal or moderate baseline variability
- Prolonged deceleration, ≥2 min but <10 min
- Recurrent late decelerations with moderate baseline variability
- Variable decelerations with other characteristics, such as slow return to baseline, "overshoots," and "shoulders"

CATEGORY III
Category III FHR tracings include either:
- Absence of baseline FHR variability and any of the following:
- Recurrent late decelerations
- Recurrent variable decelerations
- Bradycardia
- Sinusoidal pattern

From Macones GA, Hankins GDV, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines, Obstet Gynecol *112:661–666, 2008.*

fluid. The proper use of this technique may result in earlier delivery of depressed infants, who thus have a better chance of successful resuscitation, increased survival, and less morbidity. Alternatively, when continuous fetal heart rate monitoring or general clinical evaluation suggests that a fetus is at risk, a normal fetal scalp blood sample may help avert obstetric intervention.

Fetal scalp blood pH in normal labor decreases from approximately 7.33 early in labor to approximately 7.25 at the time of vaginal delivery; the base deficit is approximately 4-6 mEq/L. Changes in the buffer base may be particularly helpful in assessing fetal status, because they correspond to the accumulation of fetal lactic acid. A pH <7.25 suggests fetal distress, and a pH <7.20 is an indication for further assessment and intervention. Determination of the lactate concentration in fetal scalp blood is another tool for monitoring the condition of the fetus.

Umbilical cord blood samples obtained at the time of delivery are useful to document fetal acid–base status. Although the exact cord blood pH value that defines significant fetal acidemia is unknown, an umbilical artery pH <7.0 has been associated with greater need for resuscitation and a higher incidence of respiratory, gastrointestinal, cardiovascular, and neurologic complications. Nonetheless, in many cases, even when a low pH is detected, newborn infants are neurologically normal.

Intrapartum fetal pulse oximetry is another measure of fetal status. Even though initial data suggested that intrapartum fetal pulse oximetry could help identify fetuses with a nonreassuring status, a large randomized controlled trial showed that intrapartum fetal pulse oximetry does not lead to a reduction in cesarean section rates or improvement in the condition of newborns at birth.

Bibliography is available at Expert Consult.

96.3 Maternal Disease and the Fetus

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INFECTIOUS DISEASES

See Table 95-3.

Almost any maternal infection with severe systemic manifestations may result in miscarriage, stillbirth, or premature labor. Whether these results are a consequence of infection of the fetus or are secondary to maternal illness is not always clear. Maternal hyperthermia may be associated with an increased incidence of congenital anomalies, including neural tube defects (NTDs). Regardless of the severity of the maternal infection, certain agents frequently infect the fetus and have serious sequelae. Fetuses of mothers infected with these agents are often small for gestational age and sometimes microcephalic. Some infections, such as rubella, may also produce congenital malformations if they occur during the period of organogenesis. Intrauterine infection/chorioamnionitis may be an important risk factor for cerebral white matter injury and subsequent cerebral palsy. Infections that affect maternal nutrition (e.g., hookworm) may also result in IUGR.

NONINFECTIOUS DISEASES

See Table 95-2.

Maternal diabetes increases the risk for neonatal hypoglycemia, hypocalcemia, respiratory distress syndrome and other respiratory problems, polycythemia, macrosomia, myocardial dysfunction, jaundice, and congenital malformations (see Chapter 107.1). There is increased risk for incidence of uteroplacental insufficiency, polyhydramnios, and intrauterine death in poorly controlled diabetic mothers. **Eclampsia–preeclampsia** of pregnancy, **chronic hypertension**, and **chronic renal disease** can result in IUGR, prematurity, and intrauterine death, all probably caused by diminished uteroplacental perfusion. Uncontrolled maternal **hypothyroidism** or **hyperthyroidism** is responsible for relative infertility, spontaneous abortion, premature labor, and fetal death. Hypothyroidism in pregnant women (even if mild or asymptomatic) can adversely affect neurodevelopment of the child. Maternal **immunologic diseases** such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus, myasthenia gravis, and Graves disease, all of which are mediated by immunoglobulin G autoantibodies that can cross the placenta, frequently cause transient illness in the newborn. Maternal autoantibodies to the folate receptor are associated with NTDs, whereas maternal immunologic sensitization to paternal antigens may be associated with neonatal hemochromatosis. Untreated maternal **phenylketonuria** results in miscarriage, congenital cardiac malformations, and injury to the brain of a nonphenylketonuric heterozygotic fetus.

Bibliography is available at Expert Consult.

96.4 Maternal Medication and Toxin Exposure and the Fetus

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The use of medications or herbal remedies during pregnancy is potentially harmful to the fetus. Consumption of medications occurs during the majority of pregnancies. The average mother has taken 4 drugs other than vitamins or iron during pregnancy. Almost 40% of pregnant women receive a drug for which human safety during pregnancy has not been established (category C pregnancy risk; see later). Moreover, many women are exposed to potential reproductive toxins, such as occupational, environmental, or household chemicals, including solvents, pesticides, and hair products. The effects of drugs taken by the mother vary considerably, especially in relation to the time in pregnancy when they are taken and the fetal genotype for drug-metabolizing enzymes. Miscarriage or congenital malformations result from the maternal ingestion of teratogenic drugs during the period of organogenesis. Maternal medications taken later, particularly during the last few weeks of gestation or during labor, tend to affect the function of specific organs or enzyme systems, and they adversely affect the neonate rather than the fetus (Tables 96-5 and 96-6).

The effects of drugs may be evident immediately in the delivery room or later in the neonatal period, or they may be delayed even longer. The administration of diethylstilbestrol during pregnancy, for instance, increased the risk for vaginal adenocarcinoma in female offspring in the 2nd or 3rd decade of life.

Evidence has confirmed an interaction between genetic factors and susceptibility to certain drugs or environmental toxins. Phenytoin teratogenesis may be mediated by genetic differences in the enzymatic production of epoxide metabolites; specific genes may influence the adverse effects of benzene exposure during pregnancy. Polymorphisms of genes encoding enzymes that metabolize the polycyclic aromatic hydrocarbons in cigarette smoke influence the growth-restricting effects of smoking on the fetus.

Often the risk of controlling maternal disease must be balanced with the risk of possible complications in the fetus. The majority of women with epilepsy have normal fetuses. Nonetheless, several commonly used antiepileptic drugs are associated with congenital malformations. Infants exposed to valproic acid may have multiple anomalies, including NTDs, hypospadias, facial anomalies, cardiac anomalies, and limb defects. In addition, they have lower developmental index scores than unexposed infants and infants exposed to other commonly used antiepileptic drugs.

Methotrexate is used for medical termination of pregnancy; surviving exposed infants may be at higher risk for congenital anomalies, IUGR, hypotonia, and developmental delay.

Moderate or high alcohol intake (≥7 drinks per week or ≥3 drinks on multiple occasions) is a risk for fetal alcohol syndrome. The exposed fetuses are at risk for growth failure, central nervous system abnormalities, cognitive defects, and behavioral problems. Smoking during pregnancy is associated with IUGR and facial clefts.

In view of the limits of current knowledge about the fetal effects of maternal medication, drugs and herbal agents should not be prescribed

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during pregnancy without weighing of maternal need against the risk of fetal damage. All women should be specifically counseled to abstain from the use of alcohol, tobacco, and illicit drugs during pregnancy.

Bibliography is available at Expert Consult.

96.5 Teratogens

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When an infant or child has a congenital malformation or is developmentally delayed, the parents often wrongly blame themselves and attribute the child's problems to events that occurred during pregnancy. Because benign infections occur and several nonteratogenic drugs are often taken during many pregnancies, the pediatrician must evaluate the presumed viral infections and the drugs ingested to help parents understand their child's birth defect. The causes of approximately 40% of congenital malformations are unknown. Although only a relatively few agents are recognized to be teratogenic in humans (see Tables 96-5 and 96-6), new agents continue to be identified. Overall, only 10% of anomalies are due to recognizable teratogens (see Chapter 108). The time of exposure is usually during organogenesis at less than 60 days of gestation. Specific agents produce predictable lesions. Some agents have a dose or threshold effect; below the threshold, no alterations in growth, function, or structure occur. Genetic variables such as the presence of specific enzymes may metabolize a benign agent into a more toxic-teratogenic form (e.g., phenytoin conversion to its

Table 96-5 Agents Acting on Pregnant Women That May Adversely Affect the Structure or Function of the Fetus and Newborn

DRUG	EFFECT ON FETUS
Accutane (isotretinoin)	Facial-ear anomalies, heart disease, CNS anomalies
Alcohol	Congenital cardiac, CNS, limb anomalies; IUGR; developmental delay; attention deficits; autism
Aminopterin	Abortion, malformations
Amphetamines	Congenital heart disease, IUGR, withdrawal
Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists	Oligohydramnios, IUGR, renal failure, Potter-like syndrome
Azathioprine	Abortion
Busulfan (Myleran)	Stunted growth; corneal opacities; cleft palate; hypoplasia of ovaries, thyroid, and parathyroids
Carbamazepine	Spina bifida, possible neurodevelopmental delay
Carbimazole	Scalp defects, choanal atresia, esophageal atresia, developmental delay
Carbon monoxide	Cerebral atrophy, microcephaly, seizures
Chloroquine	Deafness
Chorionic villus sampling	Probably no effect, possibly limb reduction
Cigarette smoking	LBW for gestational age
Cocaine/crack	Microcephaly, LBW, IUGR, behavioral disturbances
Cyclophosphamide	Multiple malformations
Danazol	Virilization
17α-Ethinyl testosterone (Progestoral)	Masculinization of female fetus
Hyperthermia	Spina bifida
Infliximab	Possible increased risk of live vaccine associated disease in infant; neutropenia
Lithium	Ebstein anomaly, macrosomia
Lopinavir-ritonavir	Transient adrenal dysfunction
6-Mercaptopurine	Abortion
Methyl mercury	Minamata disease, microcephaly, deafness, blindness, mental retardation
Methyltestosterone	Masculinization of female fetus
Misoprostol	Arthrogryposis, cranial neuropathies (Möbius syndrome), equinovarus
Mycophenolate mofetil	Craniofacial, limb, cardiovascular, CNS anomalies
Norethindrone	Masculinization of female fetus
Penicillamine	Cutis laxa syndrome
Phenytoin	Congenital anomalies, IUGR, neuroblastoma, bleeding (vitamin K deficiency)
Polychlorinated biphenyls	Skin discoloration—thickening, desquamation, LBW, acne, developmental delay
Prednisone	Oral clefts

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Table 96-5 Agents Acting on Pregnant Women That May Adversely Affect the Structure or Function of the Fetus and Newborn—cont'd

DRUG	EFFECT ON FETUS
Progesterone	Masculinization of female fetus
Quinine	Abortion, thrombocytopenia, deafness
Selective serotonin reuptake inhibitors	Small increased risk of congenital anomalies, persistent pulmonary hypertension of newborn
Statins	IUGR, limb deficiencies, VACTERAL
Stilbestrol (diethylstilbestrol [DES])	Vaginal adenocarcinoma in adolescence
Streptomycin	Deafness
Tetracycline	Retarded skeletal growth, pigmentation of teeth, hypoplasia of enamel, cataract, limb malformations
Thalidomide	Phocomelia, deafness, other malformations
Toluene (solvent abuse)	Craniofacial abnormalities, prematurity, withdrawal symptoms, hypertonia
Topiramate	Cleft lip
Trimethadione and paramethadione	Abortion, multiple malformations, mental retardation
Valproate	CNS (spina bifida), facial and cardiac anomalies, limb defects, impaired neurologic function, autism spectrum disorder
Vitamin D	Supravalvular aortic stenosis, hypercalcemia
Warfarin (Coumadin)	Fetal bleeding and death, hypoplastic nasal structures

CNS, central nervous system; IUGR, intrauterine growth restriction; LBW, low birthweight. VACTERAL, vertebral, anal, cardiac, tracheoesophageal fistula, renal, arterial, limb.

Table 96-6 Agents Acting on Pregnant Women That May Adversely Affect the Newborn Infant*

Acebutolol—IUGR, hypotension, bradycardia
Acetazolamide—metabolic acidosis
Amiodarone—bradycardia, hypothyroidism
Anesthetic agents (volatile)—CNS depression
Adrenal corticosteroids—adrenocortical failure (rare)
Ammonium chloride—acidosis (clinically inapparent)
Aspirin—neonatal bleeding, prolonged gestation
Atenolol—IUGR, hypoglycemia
Baclofen—withdrawal
Blue cohosh herbal tea—neonatal heart failure
Bromides—rash, CNS depression, IUGR
Captopril, enalapril—transient anuric renal failure, oligohydramnios
Caudal-paracervical anesthesia with mepivacaine (accidental introduction of anesthetic into scalp of baby)—bradypnea, apnea, bradycardia, convulsions
Cholinergic agents (edrophonium, pyridostigmine)—transient muscle weakness
CNS depressants (narcotics, barbiturates, benzodiazepines) during labor—CNS depression, hypotonia
Cephalothin—positive direct Coombs test reaction
Dexamethasone—periventricular leukomalacia
Fluoxetine and other SSRIs—transient neonatal withdrawal, hypertonicity, minor anomalies, preterm birth, prolonged QT interval
Haloperidol—withdrawal
Hexamethonium bromide—paralytic ileus
Ibuprofen—oligohydramnios, pulmonary hypertension
Imipramine—withdrawal
Indomethacin—oliguria, oligohydramnios, intestinal perforation, pulmonary hypertension
Intravenous fluids during labor (e.g., salt-free solutions)—electrolyte disturbances, hyponatremia, hypoglycemia
Iodide (radioactive)—goiter
Iodides—goiter
Lead—reduced intellectual function
Magnesium sulfate—respiratory depression, meconium plug, hypotonia
Methimazole—goiter, hypothyroidism
Morphine and its derivatives (addiction)—withdrawal symptoms (poor feeding, vomiting, diarrhea, restlessness, yawning and stretching, dyspnea and cyanosis, fever and sweating, pallor, tremors, convulsions)
Naphthalene—hemolytic anemia (in G6PD-deficient infants)
Nitrofurantoin—hemolytic anemia (in G6PD-deficient infants)
Oxytocin—hyperbilirubinemia, hyponatremia
Phenobarbital—bleeding diathesis (vitamin K deficiency), possible long-term reduction in IQ, sedation
Primaquine—hemolytic anemia (in G6PD-deficient infants)
Propranolol—hypoglycemia, bradycardia, apnea

Continued

Table 96-6 Agents Acting on Pregnant Women That May Adversely Affect the Newborn Infant—cont'd

Propylthiouracil—goiter, hypothyroidism
Pyridoxine—seizures
Reserpine—drowsiness, nasal congestion, poor temperature stability
Sulfonamides—interfere with protein binding of bilirubin; kernicterus at low levels of serum bilirubin, hemolysis with G6PD deficiency
Sulfonylurea agents—refractory hypoglycemia
Sympathomimetic (tocolytic β-agonist) agents—tachycardia
Thiazides—neonatal thrombocytopenia (rare)
Tumor necrosis factor blocking agents—neutropenia
Valproate—developmental delay
Zolpidem (Ambien)—low birthweight

*See also Table 96-5.
CNS, central nervous system; G6PD, glucose-6-phosphate dehydrogenase; IUGR, intrauterine growth restriction; SSRI, selective serotonin reuptake inhibitor.

epoxide). In many circumstances, the same agent and dose may not consistently produce the lesion.

Reduced enzyme activity of the folate methylation pathway, particularly the formation of 5-methyltetrahydrofolate, may be responsible for neural tube or other birth defects. The common thermolabile mutation of 5,10-methylene tetrahydrofolate reductase may be one of the enzymes responsible. Folate supplementation for all pregnant women (by direct fortification of cereal grains, mandatory in the United States), and oral folic acid tablets taken during organogenesis may overcome this genetic enzyme defect, thus reducing the incidence of neural tube and perhaps other birth defects.

The U.S. Food and Drug Administration (FDA) classifies drugs into 5 pregnancy risk categories. **Category A** drugs pose no risk on the basis of evidence from controlled human studies. For **category B** drugs, either no risk has been shown in animal studies but no adequate studies in humans *or* some risk has been shown in animal studies but these results are not confirmed by human studies. For **category C** drugs, either definite risk has been shown in animal studies but no adequate human studies have been performed *or* no data is available from either animal or human studies. **Category D** includes drugs with some risk but with a benefit that may exceed that risk for the treated life-threatening condition, such as streptomycin for tuberculosis. **Category X** is for drugs that are contraindicated in pregnancy on the basis of animal and human evidence and for which the risk exceeds the benefits.

The specific mechanism of action is known or postulated for very few teratogens. Warfarin, an anticoagulant because it is a vitamin K antagonist, prevents the carboxylation of γ- carboxyglutamic acid, which is a component of osteocalcin and other vitamin K–dependent bone proteins. The teratogenic effect of warfarin on developing cartilage, especially nasal cartilage, appears to be avoided if the pregnant woman's anticoagulation treatment is switched from warfarin to heparin for the period between weeks 6 and 12 of gestation. Hypothyroidism in the fetus may be caused by the maternal ingestion of an excessive amount of iodides or propylthiouracil; each interferes with the conversion of inorganic to organic iodides. Phenytoin may be teratogenic because of the accumulation of a metabolite as a result of deficiency of epoxide hydrolase.

Recognition of teratogens offers the opportunity to prevent related birth defects. If a pregnant woman is informed of the potentially harmful effects of alcohol on her unborn infant, she may be motivated to avoid alcohol consumption during pregnancy. A woman with insulin-dependent diabetes mellitus may significantly decrease her risk for having a child with birth defects by achieving good control of her disease before conception.

Bibliography is available at Expert Consult.

96.6 Radiation

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See also Chapter 718.

Accidental exposure of a pregnant woman to radiation is a common cause for anxiety about whether her fetus will have genetic abnormalities or birth defects. It is unlikely that exposure to diagnostic radiation will cause gene mutations; no increase in genetic abnormalities has been identified in the offspring exposed as unborn fetuses to the atomic bomb explosions in Japan in 1945.

A more realistic concern is whether the exposed human fetus will show birth defects or a higher incidence of malignancy. The estimated radiation dose for most radiographs is less than 0.1 rad, and for most CT scans it is less than 5 rad. Imaging studies with high radiation exposure (such as CT scans) can be modified to ensure that radiation doses are kept as low as possible. Thus, single diagnostic studies do not result in radiation doses high enough to affect the embryo or fetus. Therapeutic abortion should not be recommended, given the low likelihood for high radiation exposure. Most of the evidence suggests that usual fetal radiation exposure does not increase the risk of childhood leukemia and other cancers. The limited data on human fetuses show that large doses of radiation (20-50 rad) may cause fetal death (the most sensitive period is the 3rd and 4th postconception wk) as well as microcephaly, severe mental retardation, and growth retardation (the most sensitive period is 4th to 15th wk). The available data suggest no harmful fetal effect of diagnostic MRI or ultrasonography.

Bibliography is available at Expert Consult.

96.7 Intrauterine Diagnosis of Fetal Disease

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See Table 96-1 and Chapter 96.2.

Diagnostic procedures are used to identify fetal diseases when abortion is being considered, when direct fetal treatment is possible, or when a decision is made to deliver a viable but premature infant to avoid intrauterine fetal demise. Fetal assessment is also indicated in a broader context when the family, medical, or reproductive history of the mother suggests the presence of a high-risk pregnancy or a high-risk fetus (see Chapters 95 and 96.3).

Various methods are used for identifying fetal disease (see Table 96-1). Fetal ultrasonographic imaging may detect fetal growth abnormalities (by biometric measurements of biparietal diameter, femoral length, or head or abdominal circumference) or fetal malformations (Fig. 96-5). Although 89% of fetuses whose biparietal diameter is 9.5 cm or more are at least in the 37th wk of gestation, the lungs of these fetuses may not be mature. Serial determinations of growth velocity and the head-to-abdomen circumference ratio enhance the ability to detect IUGR. Real-time ultrasonography may identify placental abnormalities (abruptio placentae, placenta previa) and fetal anomalies such as hydrocephalus, NTDs, duodenal atresia, diaphragmatic hernia, renal agenesis, bladder outlet obstruction, congenital heart disease, limb abnormalities, sacrococcygeal teratoma, cystic hygroma, omphalocele, gastroschisis, and hydrops (Table 96-7).

Real-time ultrasonography also facilitates performance of cordocentesis and the BPP by imaging fetal breathing, body movements, tone, and amniotic fluid volume (see Table 96-2). Doppler velocimetry

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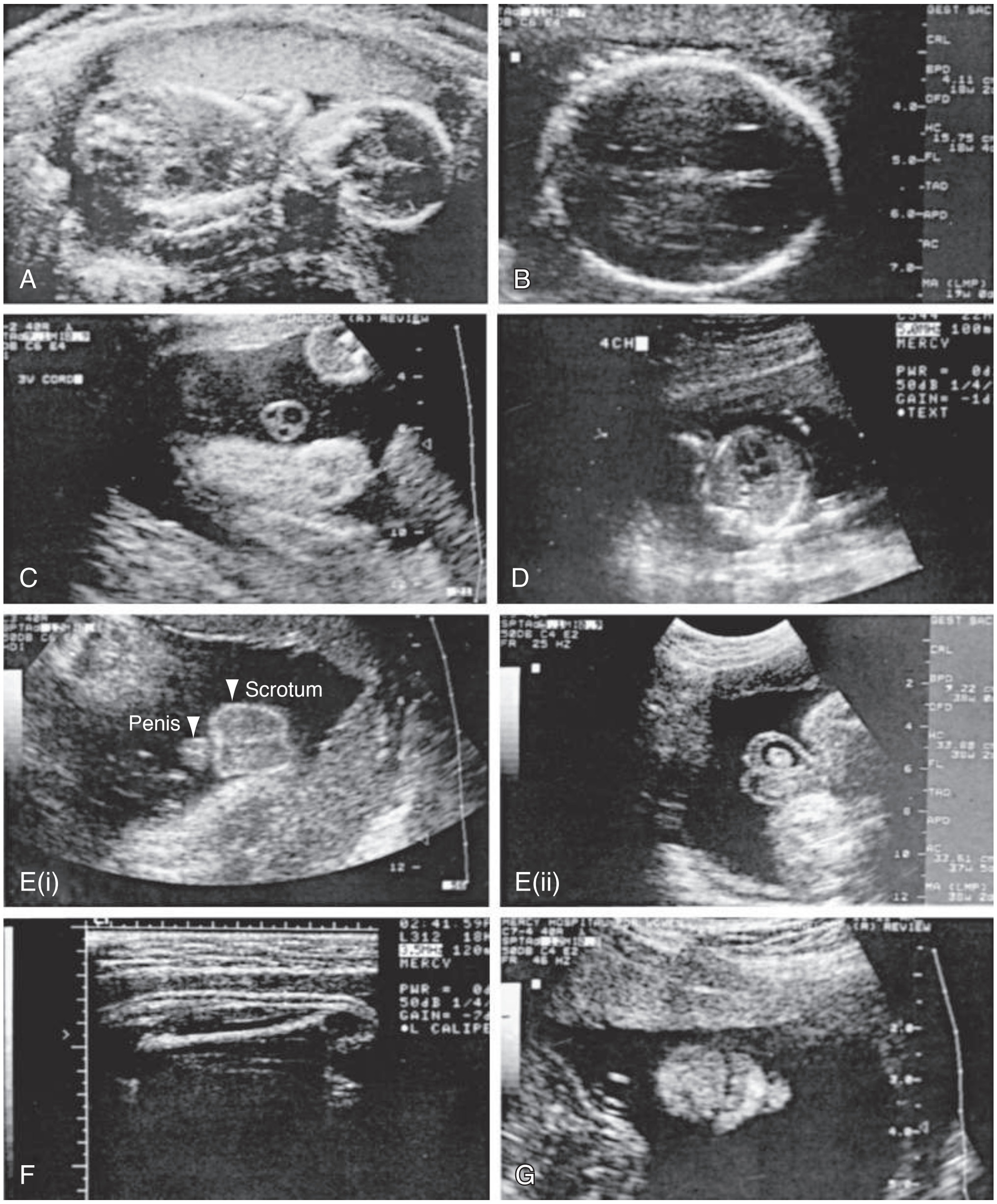

Figure 96-5 **Assessment of fetal anatomy.** **A,** Overall view of the uterus at 24 wk showing a longitudinal section of the fetus and an anterior placenta. **B,** Transverse section at the level of the lateral ventricle at 18 wk showing (*on the right*) prominent anterior horns of the lateral ventricles on either side of the midline echo of the falx. **C,** Cross-section of the umbilical cord showing that the lumen of the umbilical vein is much wider than that of the 2 umbilical arteries. **D,** Four-chambered view of the heart at 18 wk with equal-sized atria. **E(i),** Normal male genitals near term. **E(ii),** Hydrocele outlining a testicle within the scrotum projecting into a normal-size pocket of amniotic fluid at 38 wk. Approximately 2% of male infants after birth have clinical evidence of a hydrocele that is often bilateral, not to be confused with subcutaneous edema occurring during vaginal breech birth. **F,** Section of a thigh near term showing thick subcutaneous tissue (4.6 mm between markers) above the femur of a fetus with macrosomia. **G,** Fetal face viewed from below, showing (*from right to left*) the nose, alveolar margin, and chin at 20 wk. *(From Special investigative procedures. In Beischer NA, Mackay EV, Colditz PB, editors:* Obstetrics and the newborn, *ed 3, Philadelphia, 1997, WB Saunders.)*

assesses fetal arterial blood flow (vascular resistance) (see Figs. 96-2 and 96-3). Radiographic examination of the fetus has been replaced by real-time ultrasonography, MRI, and fetoscopy.

Amniocentesis, the transabdominal withdrawal of amniotic fluid during pregnancy for diagnostic purposes (see Table 96-1), is frequently performed to determine the timing of delivery of fetuses with erythroblastosis fetalis or the need for fetal transfusion. It is also done for genetic indications, usually between the 15th and 16th wk of gestation, with results available within 1-2 wk. The most common indication for genetic amniocentesis is advanced maternal age (the risk for chromosome abnormality at age 21 yr is 1:526, vs. 1:8 at age 49 yr). The amniotic fluid may be directly analyzed for amino acids, enzymes, hormones, and abnormal metabolic products, and amniotic fluid cells may be cultivated to permit detailed cytologic analysis for prenatal detection of chromosomal abnormalities and DNA-gene or enzymatic analysis for the detection of inborn metabolic errors. Analysis of amniotic fluid may also help in identifying NTDs (elevation of α-fetoprotein), adrenogenital syndrome (elevation of 17-ketosteroids and pregnanetriol), and thyroid dysfunction. Chorionic villus biopsy (transvaginal or transabdominal) performed in the 1st trimester also provides fetal cells but may pose a slightly increased risk for fetal loss and limb reduction defects. Fetal DNA in maternal plasma and fetal cells circulating in maternal blood are potential noninvasive sources of material for prenatal diagnosis. This technology may eliminate the need for amniocentesis or chorionic villus sampling.

Table 96-7 Significance of Fetal Ultrasonographic Anatomic Findings

PRENATAL OBSERVATION	DEFINITION	DIFFERENTIAL DIAGNOSIS	SIGNIFICANCE	POSTNATAL EVALUATION
Dilated cerebral ventricles	Ventriculomegaly ≥10 mm	Hydrocephalus Hydranencephalous Dandy-Walker cyst Agenesis of corpus callosum	Transient isolated ventriculomegaly is common and usually benign Persistent or progressive ventriculomegaly more worrisome Identify associated cranial and extracranial anomalies Bilateral ventriculomegaly increases risk of developmental delay Unilateral ventriculomegaly may be normal variant	Serial head US or CT Evaluate for extracranial anomalies
Choroid plexus cysts	Size ~10 mm: unilateral or bilateral 1-3% incidence	Abnormal karyotype (trisomy 18, 21) Aneuploidy risk 1 : 100 if isolated. ↑ Risk (1 : 3) with other anomalies. Risk ↑ if large, complex, or bilateral cysts or advanced maternal age	Often isolated, benign; resolves by 24-28 wk Fetus should be examined for other organ anomalies; then amniocentesis should be performed for karyotype	Head US or CT Examine for extracranial anomalies; karyotype if indicated
Nuchal pad thickening	≥6 mm at 15-20 wk	Cystic hygroma trisomy 21, 18 Turner syndrome (XO) Nonchromosomal syndromes Normal (~25%)	≈50% of affected fetuses have chromosome abnormalities Amniocentesis for karyotype needed	Evaluate for multiple organ malformations; karyotype if indicated
Dilated renal pelvis	Pyelectasis ≥5 to 10 mm 0.6-1% incidence	Uteropelvic junction obstruction Vesicoureteral reflux Posterior ureteral valves Entopic ureterocele Large-volume nonobstruction	Often "physiologic" and transient Reflux is common If dilation is >10 mm or associated with caliectasis, pathologic cause should be considered If large bladder present, posterior urethral valves and megacystics-megaduodenum syndrome should be considered	Repeat ultrasonography on day 5 and at 1 mo; voiding cystourethrogram, prophylactic antibiotics
Echogenic bowel	0.6% incidence	CF, meconium peritonitis, trisomy 21 or 18, other chromosomal abnormalities cytomegalovirus, toxoplasmosis, GI obstruction	Often normal (65%) 10% of affected fetuses have CF; 1.5% have aneuploidy	Sweat chloride and DNA testing Karyotype Surgery for obstruction Evaluation for TORCH (toxoplasmosis, other agents, rubella, CMV, herpes simplex) syndrome
Stomach appearance	Small or absent or with double bubble	Upper GI obstruction (esophageal atresia) Double bubble signifies duodenal atresia Abnormal karyotype Polyhydramnios Stomach in chest signifies diaphragmatic hernia	Must also consider neurologic disorders that reduce swallowing Over 30% with double bubble have trisomy 21	Chromosomes, kidney, ureter, and bladder radiograph if indicated, upper GI series, neurologic evaluation

CF, cystic fibrosis; CMV, cytomegalovirus; GI, gastrointestinal; US, ultrasound.

The best available chemical indices of fetal maturity are provided by determination of amniotic fluid creatinine and lecithin levels, which reflect the maturity of the fetal kidneys and lungs, respectively. Lecithin is produced in the lungs by type II alveolar cells and eventually reaches the amniotic fluid via the effluent from the trachea. Until the middle of the 3rd trimester, its concentration nearly equals that of sphingomyelin; thereafter, the sphingomyelin concentration remains constant in amniotic fluid while the lecithin concentration increases. By 35 wk, the lecithin : sphingomyelin (L : S) ratio averages about 2 : 1, indicative of lung maturity.

Earlier lung maturation may occur in the presence of severe premature separation of the placenta, premature rupture of the fetal membranes, narcotic addiction, or maternal hypertensive and renal vascular disease. A delay in pulmonary maturation may be associated with hydrops fetalis or maternal diabetes without vascular disease. The likelihood of hyaline membrane disease is greatly reduced with L : S ratios of 2 : 1 or more, although hypoxia, acidosis, and hypothermia may increase the risk despite this "mature" L : S ratio. Maternal and fetal blood have an L : S ratio of about 1 : 4; thus, contamination will not alter the significance of a ratio of 2 : 1 or more. Meconium contamination,

sample storage, and sample centrifugation may reduce the reliability of the L:S ratio.

Saturated phosphatidylcholine or phosphatidylglycerol concentrations in amniotic fluid may be more specific and sensitive predictors of pulmonary maturity, especially in high-risk pregnancies such as those occurring in women with diabetes (see Chapters 95 and 107.1).

Amniocentesis can be carried out with little discomfort to the mother, but even in experienced hands, the procedure entails some small risk, such as direct damage to the fetus, placental puncture and bleeding with secondary damage to the fetus, stimulation of uterine contraction and premature labor, amnionitis, and maternal sensitization to fetal blood. The earlier in gestation that amniotic puncture is done, the greater the risk to the fetus. Using ultrasound for placental and fetal localization can reduce the risk of complications. The procedure should be limited to cases in which the potential benefits of the findings will outweigh the risk.

Cordocentesis, or percutaneous umbilical blood sampling, is used to diagnose fetal hematologic abnormalities, genetic disorders, infections, and fetal acidosis (see Table 96-1). Under direct ultrasonographic visualization, a long needle is passed into the umbilical vein at its entrance to the placenta or fetal abdominal wall. Umbilical blood may be withdrawn to determine fetal hemoglobin, platelet concentration, lymphocyte DNA, the presence of infection, or $Pa{O_2}$, pH, $P{CO_2}$, and lactate levels.

Transfusion or administration of drugs can be performed through the umbilical vein (Table 96-8). Serum screening is offered to pregnant women at midgestation to evaluate the risk for Down syndrome (trisomy 21) and congenital malformations known to cause elevations of various markers, including abdominal wall and NTDs. A combination of these biochemical markers (including α-fetoprotein, inhibin A, estriol, pregnancy-associated plasma protein A, and β-HCG [human chorionic gonadotropin]) and ultrasound increases the positive

Table 96-8 Fetal Therapy

DISORDER	POSSIBLE TREATMENT
HEMATOLOGIC	
Anemia with hydrops (erythroblastosis fetalis)	Umbilical vein packed red blood cell transfusion
Thalassemia	Fetal stem cell transplantation
Isoimmune thrombocytopenia	Umbilical vein platelet transfusion, maternal IVIG
Autoimmune thrombocytopenia (ITP)	Maternal steroids and IVIG
Chronic granulomatous disease	Fetal stem cell transplantation
METABOLIC-ENDOCRINE	
Maternal phenylketonuria (PKU)	Phenylalanine restriction
Fetal galactosemia	Galactose-free diet (?)
Multiple carboxylase deficiency	Biotin if responsive
Methylmalonic acidemia	Vitamin B_{12} if responsive
21-Hydroxylase deficiency	Dexamethasone
Maternal diabetes mellitus	Tight insulin control during pregnancy, labor, and delivery
Fetal goiter	Maternal hyperthyroidism—maternal propylthiouracil Fetal hypothyroidism—intra-amniotic thyroxine
Bartter syndrome	Maternal indomethacin may prevent nephrocalcinosis and postnatal sodium losses
Neonatal iron storage disease (alloimmune)	Maternal IVIG
FETAL DISTRESS	
Hypoxia	Maternal oxygen, position
Intrauterine growth restriction	Maternal oxygen, position, improve macronutrients and micronutrients if deficient
Oligohydramnios, premature rupture of membranes with variable deceleration	Amnioinfusion (antepartum and intrapartum)
Polyhydramnios	Amnioreduction (serial), indomethacin (if from increased urine output) if indicated
Supraventricular tachycardia	Maternal digoxin,* flecainide, procainamide, amiodarone, quinidine
Lupus anticoagulant	Maternal aspirin, prednisone
Meconium-stained fluid	Amnioinfusion
Congenital heart block	Dexamethasone, pacemaker (with hydrops)
Premature labor	Magnesium sulfate, antibiotics sympathomimetics, indomethacin
RESPIRATORY	
Pulmonary immaturity	Betamethasone
Bilateral chylothorax—pleural effusions	Thoracentesis, pleuroamniotic shunt
CONGENITAL ABNORMALITIES[†]	
Neural tube defects	Folate, vitamins (prevention); fetal surgery[‡]
Posterior urethral valves, urethral atresia (lower urinary tract obstruction)	Percutaneous vesicoamniotic shunt
Cystic adenomatoid malformation (with hydrops)	Pleuroamniotic shunt or resection[‡]
Fetal neck masses	Secure an airway with EXIT procedure[‡]
INFECTIOUS DISEASE	
Group B streptococcus colonization	Ampicillin, penicillin
Chorioamnionitis	Antibiotics
Toxoplasmosis	Spiramycin, pyrimethamine, sulfadiazine, and folic acid
Syphilis	Penicillin
Tuberculosis	Antituberculosis drugs
Lyme disease	Penicillin, ceftriaxone
Parvovirus	Intrauterine red blood cell transfusion for hydrops, severe anemia
Chlamydia trachomatis	Erythromycin
HIV-AIDS	Maternal and neonatal antiretroviral therapy (see Chapter 276)
Cytomegalovirus	Ganciclovir by umbilical vein

Continued

Table 96-8 Fetal Therapy	
DISORDER	**POSSIBLE TREATMENT**
OTHER	
Nonimmune hydrops (anemia)	Umbilical vein packed red blood cell transfusion
Narcotic abstinence (withdrawal)	Maternal low-dose methadone
Severe combined immunodeficiency disease	Fetal stem cell transplantation
Sacrococcygeal teratoma (with hydrops)	In utero resection or catheter directed vessel obliteration
Twin-twin transfusion syndrome	Repeated amniocentesis, yttrium-aluminum-garnet (YAG) laser photocoagulation of shared vessels
Twin reversed arterial perfusion (TRAP) syndrome	Digoxin, indomethacin, cord occlusion
Multifetal gestation	Selective reduction
Neonatal hemochromatosis	Maternal IVIG

*Drug of choice (may require percutaneous umbilical cord sampling and umbilical vein administration if hydrops is present). Most drug therapy is given to the mother, with subsequent placental passage to the fetus.
†Detailed fetal ultrasonography is needed to detect other anomalies; karyotype is also indicated.
‡EXIT permits surgery and other procedures.
EXIT, ex utero intrapartum treatment; IVIG, intravenous immunoglobulin; (?), possible but not proved efficacy.

predictive value of these screening tests. Nonetheless fetal karyotyping by analysis of fetal DNA in maternal plasma is another accurate method to diagnose trisomy 21. Additionally, families with a known genetic syndrome may be offered prenatal genetic testing from amniotic fluid or amniocytes obtained via amniocentesis or chorionic villus sampling.

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96.8 Treatment and Prevention of Fetal Disease

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Management of a fetal disease depends on coordinated advances in diagnostic accuracy and knowledge of the disease's natural history; an understanding of fetal nutrition, pharmacology, immunology, and pathophysiology; the availability of specific active drugs that cross the placenta; and therapeutic procedures. Progress in providing specific treatments for accurately diagnosed diseases has improved with the advent of real-time ultrasonography and cordocentesis (see Tables 96-1 and 96-8).

The incidence of sensitization of Rh-negative women by Rh-positive fetuses has been reduced by prophylactic administration of Rh(D) immunoglobulin to mothers early in pregnancy and after each delivery or abortion, thus reducing the frequency of hemolytic disease in their subsequent offspring. Fetal erythroblastosis (see Chapter 103.2) may be accurately diagnosed by amniotic fluid analysis and treated with intrauterine intraperitoneal or, more often, intraumbilical vein transfusions of packed Rh-negative blood cells to maintain the fetus until it is mature enough to have a reasonable chance of survival.

Fetal hypoxia or distress may be diagnosed with moderate success. Treatment, however, remains limited to supplying the mother with high concentrations of oxygen, positioning the uterus to avoid vascular compression, and initiating operative delivery before severe fetal injury occurs.

Pharmacologic approaches to fetal immaturity (e.g., administration of steroids to the mother to accelerate fetal lung maturation and decrease the incidence of respiratory distress syndrome [Chapter 101.3] in prematurely delivered infants) are successful. Inhibiting labor with tocolytic agents is unfortunately not successful in most patients with premature labor. Management of definitively diagnosed fetal genetic disease or congenital anomalies consists of parental counseling or abortion; rarely, high-dose vitamin therapy for a responsive inborn error of metabolism (biotin-dependent disorders) or fetal transfusion (with red blood cells or platelets) may be indicated. Fetal surgery (see Table 96-8) remains an a largely experimental approach to therapy and is available only in a few highly specialized perinatal centers. The nature of the defect and its consequences, as well as ethical implications for the fetus and the parents, must be considered. In a randomized controlled trial, fetal surgery for myelomeningocele improved neurological function (mental and motor development) and decreased the need for shunts by 50% but increased the prematurity rate.

Folic acid supplementation decreases the incidence and recurrence of (NTDs). Because the neural tube closes within the 1st 28 days of conception, periconceptional supplementation is needed for prevention. It is recommended that women without a prior history of a NTD ingest 400 μg/day of folic acid throughout their reproductive years. Women with a history of a prior pregnancy complicated by an NTD or a 1st-degree relative with an NTD should have preconceptional counseling and should ingest 4 mg/day of supplemental folic acid beginning at least 1 mo before conception. Fortification of cereal grain flour with folic acid is established policy in the United States and some other countries. The optimal concentration of folic acid in enriched grains is somewhat controversial. The incidence of NTD in the United States and other countries has decreased significantly since these public health initiatives were implemented. Use of some antiepileptic drugs (valproate, carbamazepine) during pregnancy is associated with an increased risk of NTD. Women taking these medications should ingest 1-5 mg of folic acid/day in the preconception period.

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Chapter 97

The High-Risk Infant

Waldemar A. Carlo

Neonates at risk should be identified as early as possible prenatally or after birth to decrease neonatal morbidity and mortality (see Chapter 93). The term *high-risk infant* designates an infant who should be under close observation by experienced physicians and nurses. Table 97-1 lists the factors that define infants as being high risk. Approximately 10-20% of all births require special or neonatal intensive care. Usually needed for only a few days, such care may last from a few hours to several months. In some institutions, initial care for high-risk infants is provided in a special or transitional care nursery, often within the labor and delivery suite. This facility should be equipped and staffed like a neonatal intensive care area.

Examination of the fresh **placenta**, **cord**, and **membranes** may alert the physician to a newborn infant at high risk and may help confirm a diagnosis in a sick infant. **Fetal blood loss** may be indicated by

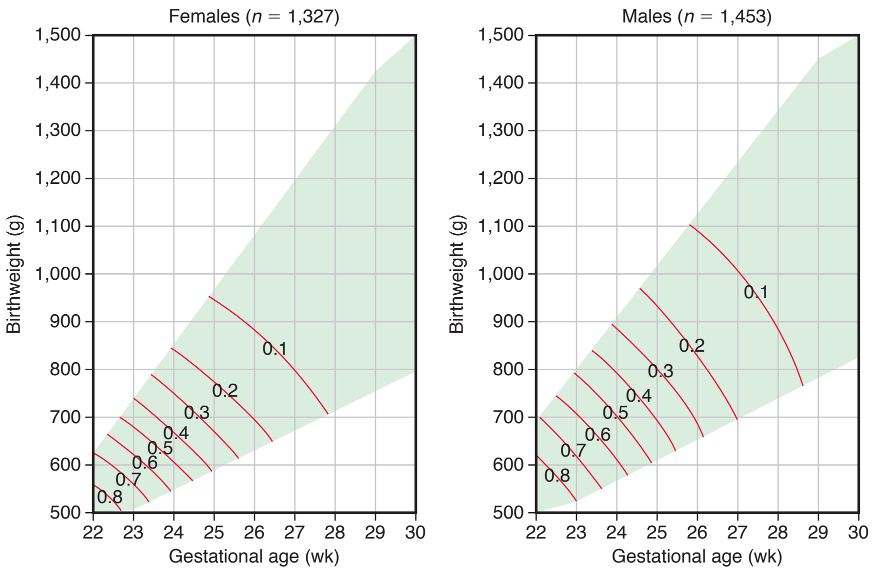

Figure 97-1 Estimated mortality risk by birthweight and gestational age based on singleton infants in National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers between January 1, 1995, and December 31, 1996. *(From Lemons JA, Bauer CR, Oh W, et al: Very low birthweight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996,* Pediatrics *107:E1, 2001; available at www.pediatrics.org.cgi/content/full/107/1/el.)*

Table 97-1 Factors That Define an Infant as Being High Risk

Factors That Define an Infant as Being High Risk
DEMOGRAPHIC SOCIAL FACTORS
Maternal age <16 or >40 yr
Illicit drug, alcohol, cigarette use
Poverty
Unmarried
Emotional or physical stress
PAST MEDICAL HISTORY
Genetic disorders
Diabetes mellitus
Hypertension
Asymptomatic bacteriuria
Rheumatologic illness (systemic lupus erythematosus)
Immune-mediated diseases (immunoglobulin G crossing placenta)
Long-term medication (see Tables 96-5 and 96-6 in Chapter 96)
PREVIOUS PREGNANCY
Intrauterine fetal demise
Neonatal death
Prematurity
Intrauterine growth restriction
Congenital malformation
Incompetent cervix
Blood group sensitization, neonatal jaundice
Neonatal thrombocytopenia
Hydrops
Inborn errors of metabolism
PRESENT PREGNANCY
Vaginal bleeding (abruptio placentae, placenta previa)
Sexually transmitted infections (colonization: herpes simplex, group B streptococcus, chlamydia, syphilis, hepatitis B, HIV)
Multiple gestation
Preeclampsia
Premature rupture of membranes
Short interpregnancy time
Poly-/oligohydramnios
Acute medical or surgical illness
Inadequate prenatal care
Familial or acquired hypercoagulable states
Abnormal fetal ultrasonographic findings
Treatment of infertility
LABOR AND DELIVERY
Premature labor (<37 wk)
Postdates pregnancy (≥42 wk)
Fetal distress
Immature lethicin : sphingomyelin ratio; absence of phosphatidylglycerol
Breech presentation
Meconium-stained fluid
Nuchal cord
Cesarean section
Forceps delivery
Apgar score <4 at 1 min
NEONATE
Birthweight <2,500 or >4,000 g
Birth <37 or ≥42 wk of gestation
Small or large for gestational age
Respiratory distress, cyanosis
Congenital malformation
Pallor, plethora, petechiae

placental pallor, retroplacental hematoma, and tears in the velamentous cords or chorionic blood vessels supplying the succenturiate lobes. Placental edema and secondary possible immunoglobulin G deficiency in a newborn may be associated with fetofetal transfusion syndrome, hydrops fetalis, congenital nephrosis, or hepatic disease. **Amnion nodosum** (granules on the amnion) and **oligohydramnios** are associated with pulmonary hypoplasia and renal agenesis, whereas small whitish nodules on the cord suggest a candidal infection. Short cords and noncoiled cords occur with chromosome abnormalities and omphalocele. True umbilical cord knots are seen in approximately 1% of births and are associated with a long cord, small fetal size, polyhydramnios, monoamniotic twinning, fetal demise, and low Apgar scores.

Chorioangiomas are associated with prematurity, abruptio placentae, polyhydramnios, and intrauterine growth restriction (IUGR). **Meconium staining** suggests in utero stress, and opacity of the fetal surface of the placenta suggests infection. Single umbilical arteries are associated with an increased incidence of congenital renal abnormalities and syndromes.

For many infants who are born prematurely, are small for gestational age (SGA), have significant perinatal asphyxia, are breech, or are born with life-threatening congenital anomalies, there are no previously identified risk factors. For any given duration of gestation, the lower the birthweight, the higher the neonatal mortality; for any given birthweight, the shorter the gestational duration, the higher the neonatal mortality (Fig. 97-1). The highest risk of neonatal and infant mortality occurs in infants who weigh <1,000 g at birth and whose gestation was <28 wk. The lowest risk of neonatal mortality occurs in infants with a birthweight of 3,000-4,000 g and a gestational age of 39-41 wk. As

birthweight increases from 400 to 3,000 g and gestational age increases from 23 to 39 wk, a logarithmic decrease in neonatal mortality occurs. In the United States, approximately 50% of all infant deaths occur in infants born after less than 27 wk of gestation or infants weighing less than 1,000 g. Neonatal mortality rates rise sharply for infants weighing more than 4,000 g at birth and for those whose gestational period is 42 wk or longer. Because neonatal mortality largely depends on birthweight and gestational age, Figure 97-1 can be used to help identify high-risk infants quickly. This analysis is based on total live births and therefore describes the mortality risk only at birth. Because most neonatal mortality occurs within the 1st hours and days after birth, the outlook improves dramatically with increasing postnatal survival. Prediction of death as well as neurodevelopmental impairment improves after birth and continues to improve over the first days and weeks after birth. The importance of gestational age, birth weight, and other perinatal factors for prediction of outcomes decline whereas the importance of respiratory illnesses and other morbidities increase.

97.1 Multiple-Gestation Pregnancies

Waldemar A. Carlo

INCIDENCE

The incidence of spontaneous twinning is highest among blacks and East Indians, followed by northern European whites, and is lowest in the Asian races. Specific rates are 1/56 in Belgium, 1/70 among American blacks, 1/86 in Italy, 1/88 among American whites, 1/130 in Greece, 1/150 in Japan, and 1/300 in China. Differences in the incidence of twins mainly involve fraternal (polyovular) dizygotic twins. Triplets are estimated to occur in 1 in 86^2 pregnancies and quadruplets in 1 in 86^3 pregnancies in the United States. The incidence of monozygotic twins (3-5/1,000) is unaffected by racial or familial factors. The incidence of twins detected by ultrasonography at 12 wk of gestation (3-5%) is much higher than that occurring later in pregnancy; the **vanishing twin syndrome** results in a singleton fetus. Although the incidence of spontaneous multifetal gestation has been stable over the years, the overall incidence of multifetal gestation is increasing as a result of treatment of infertility with ovarian stimulants (clomiphene, gonadotropins) and in vitro fertilization. Twins account for about 2.5% of births but approximately 15% of extremely low birthweight (ELBW, ≤1,000 g) infants.

ETIOLOGY

The occurrence of monovular twins appears to be independent of genetic influence. Polyovular pregnancies are more frequent beyond the second pregnancy, in older women, and in families with a history of polyovular twins. They may result from simultaneous maturation of multiple ovarian follicles, but follicles containing 2 ova have been described as a genetic trait leading to twin pregnancies. Twin-prone women have higher levels of gonadotropin. Polyovular pregnancies occur in many women treated for infertility.

Conjoined twins (Siamese twins—incidence 1/50,000) result from relatively late monovular separation. The prognosis for conjoined twins depends on the possibility of surgical separation, which, in turn, depends on the extent to which vital organs are shared. The site of connections varies: thoracoomphalopagus (28% of conjoined twins), thoracopagus (18%), omphalopagus (10%), craniopagus (6%), and incomplete duplication (10%). Difficult-to-separate conjoined twins have occasionally survived to adulthood. Most conjoined twins are female.

Superfecundation, or fertilization of an ovum by an insemination that takes place after 1 ovum has already been fertilized, and **superfetation,** or fertilization and subsequent development of an embryo when a fetus is already present in the uterus, have been proposed as uncommon explanations for differences in size and appearance of certain twins at birth.

A prenatal diagnosis of pregnancy with twins is suggested by a uterine size that is greater than that expected for gestational age, auscultation of 2 fetal hearts, and elevated maternal serum α-fetoprotein or human chorionic gonadotropin levels, and it is confirmed by ultrasonography.

MONOZYGOTIC VERSUS DIZYGOTIC TWINS

Identifying twins as monozygotic or dizygotic (monovular or polyovular) is useful in determining the relative influence of heredity and environment on human development and disease. Twins not of the same sex are dizygotic. In twins of the same sex, zygosity should be determined and recorded at birth through careful examination of the placenta. Detailed blood typing, gene analysis, or tissue (human leukocyte antigen) typing can also be used to determine zygosity. Monozygotic twins may have physical and cognitive differences because their in utero environment may have been different; differences may exist in the mitochondrial genome, in posttranslational gene product modification, and in the epigenetic modification of nuclear genes in response to environmental factors.

Examination of the Placenta

If the placentas are separate, they are always dichorionic (present in 75%), but the twins are not necessarily dizygotic, because initiation of monovular twinning at the first cell division or during the morula stage may result in 2 amnions, 2 chorions, and even 2 placentas. One-third of monozygotic twins are dichorionic and diamnionic.

An apparently single placenta may be present with either monovular or polyovular twins; yet inspection of a polyovular placenta usually reveals that each twin has a separate chorion that crosses the placenta between the attachments of the cords and two amnions. Separate or fused dichorionic placentas may be disproportionate in size. The fetus attached to the smaller placenta or the smaller portion of the placenta is usually smaller than its twin or is malformed. **Monochorionic twins** are usually diamnionic, and almost invariably, the placenta is a single mass.

Problems of twin gestation include polyhydramnios, hyperemesis gravidarum, preeclampsia, premature rupture of membranes, vasa previa, velamentous insertion of the umbilical cord, abnormal presentations (breech), and premature labor. **Monoamniotic twins** have a high fatality rate owing to obstruction of the circulation secondary to intertwining of the umbilical cords. Twins of widely discrepant size are usually monochorionic.

When compared with the first-born twin, the second twin is at increased risk for respiratory distress syndrome and asphyxia. Twins are at risk for IUGR, twin–twin transfusion, and congenital anomalies, which occur predominantly in monozygotic twins. Anomalies are a result of compression deformation of the uterus from crowding (hip dislocation), vascular communication with embolization (ileal atresia, porencephaly, cutis aplasia) or without embolization (acardiac twin), and unknown factors that cause twinning (conjoined twins, anencephaly, meningomyelocele).

Placental vascular anastomoses occur with high frequency only in monochorionic twins. In monochorionic placentas, the fetal vasculature is usually joined, sometimes in a very complex manner. The vascular anastomoses in monochorionic placentas may be artery to artery, vein to vein, or artery to vein. They are usually balanced so that neither twin suffers. Artery-to-artery communications cross over placental veins, and when anastomoses are present, blood can readily be stroked from one fetal vascular bed to the other. Vein-to-vein communications are similarly recognized but are less common. A combination of artery-to-artery and vein-to-vein anastomoses is associated with the condition of **acardiac fetus.** This rare lethal anomaly (1/35,000) is secondary to the **TRAP** (twin reversed arterial perfusion) **syndrome**. In utero neodynium : yttrium-aluminum-garnet (Nd : YAG) laser ablation of the anastomosis or cord occlusion can be used to treat heart failure in the surviving twin. In rare cases, 1 umbilical cord may arise from the other after leaving the placenta. In such cases, the twin attached to the secondary cord usually is malformed or dies in utero.

In the **fetal transfusion syndrome,** an artery from 1 twin acutely or chronically delivers blood that is drained into the vein of the other. The

Table 97-2 Characteristic Changes in Monochorionic Twins with Uncompensated Placental Arteriovenous Shunts

TWIN ON	
Arterial Side—Donor	**Venous Side—Recipient**
Prematurity	Prematurity
Oligohydramnios	Polyhydramnios
Small premature	Hydrops
Malnourished	Large premature
Pale	Well nourished
Anemic	Plethoric
Hypovolemia	Polycythemic
Hypoglycemia	Hypervolemic
Microcardia	Cardiac hypertrophy
Glomeruli small or normal	Myocardial dysfunction
Arterioles thin walled	Tricuspid valve regurgitation Right ventricular outflow obstruction Glomeruli large Arterioles thick walled

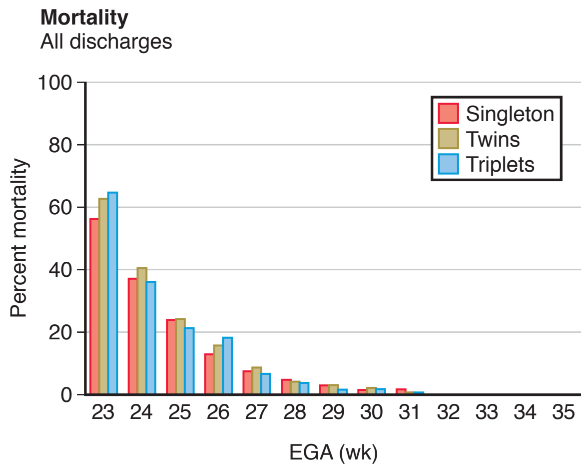

Figure 97-2 **Mortality, all discharges.** The neonatal mortality rate for all babies who died during the original hospitalization at each week of gestational age is given. The *bars on the left* represent singletons; the *middle bars* represent twins, and the *bars on the right* represent triplets. There are no differences among singleton births, twin births, and triplet births. EGA, estimated gestational age. *(From Garite TJ, Clark RH, Elliott JP, et al: Twins and triplets: the effect of plurality and growth on neonatal outcome compared with singleton infants,* Am J Obstet Gynecol *191:700–707, 2004.)*

latter becomes plethoric and large, and the former is anemic and small. Generally, with chronicity, 5 g/dL hemoglobin and 20% body weight differences can be noted in this syndrome. Maternal hydramnios in a twin pregnancy suggests fetal transfusion syndrome. Anticipating this possibility by preparing to transfuse the donor twin or bleed the recipient twin may be lifesaving. Death of the donor twin in utero may result in generalized fibrin thrombi in the smaller arterioles of the recipient twin, possibly as the result of transfusion of thromboplastin-rich blood from the macerating donor fetus. Disseminated intravascular coagulation may develop in the surviving twin. Table 97-2 lists the more frequent changes associated with a large uncompensated arteriovenous shunt from the placenta of 1 twin to that of the other. Treatment of this highly lethal problem includes maternal digoxin, aggressive amnioreduction for polyhydramnios, selective twin termination, and Nd : YAG laser or fetoscopic ablation of the anastomosis.

Postnatal Identification

The following physical criteria can be used to determine whether twins are monovular: (1) both must be of the same sex; (2) their features, including ears and teeth, must be obviously alike (but they need not resemble each other more than the lateral halves of one individual); (3) their hair must be identical in color, texture, natural curl, and distribution; (4) their eyes must be of the same color and shade; (5) their skin must be of the same texture and color (nevi may be differently apportioned and distributed); (6) their hands and feet must be of the same conformation and of similar size; and (7) their anthropometric values must show close agreement.

PROGNOSIS

Most twins are born prematurely, and maternal complications of pregnancy are more common than with single pregnancies. The risk for twins is most often associated with twin–twin transfusion, assisted reproductive technology, and early-onset discordant growth. Although monochorionic twins have a significantly higher perinatal mortality, there is no significant difference between the neonatal mortality rates of twin births and single births in comparable weight and gestational age groups (Fig. 97-2). Because most twins are premature, their overall mortality is higher than that of single-birth infants. The perinatal mortality of twins is about 4 times that of singletons. Monoamnionic twins have an increased likelihood of entangling the cords, which may lead to asphyxia. Theoretically, the second twin is more subject to anoxia than the first because the placenta may separate after birth of the first twin and before birth of the second. In addition, delivery of the second twin may be difficult because it may be in an abnormal presentation (breech, entangled), uterine tone may be decreased, or the cervix may begin to close after the first twin's birth. Triplet or higher-order births are associated with an increased risk of death or neurodevelopmental impairment when compared with ELBW singleton and twin infants.

The mortality for multiple gestations with 4 or more fetuses is excessively high for each fetus. Because of this poor prognosis, selective fetal reduction (with transabdominal intrathoracic fetal injection of KCl) to 2 or3 fetuses has been offered as a treatment option. Monozygotic twins have an increased risk of 1 twin dying in utero. The surviving twin has a greater risk for cerebral palsy and other neurodevelopmental sequelae.

The risk of multiple gestation pregnancies using assisted reproductive technologies may be reduced by elective single embryo transfers. In addition, elective delivery of twins at 37 wk reduces the complication rate for the fetuses and the mother. Furthermore, in twin pregnancies between 32 and 39 wk of gestation, planned vaginal delivery is preferred if the first twin is in the cephalic presentation.

TREATMENT

Prenatal diagnosis enables the obstetrician and pediatrician to anticipate the birth of infants who are at high risk because of twinning. Close observation is indicated during labor and in the immediate neonatal period so that prompt treatment of asphyxia or fetal transfusion syndrome can be initiated. The decision to perform an immediate blood transfusion in a severely anemic "donor twin" or to perform a partial exchange transfusion of a "recipient twin" must be based on clinical judgment.

Bibliography is available at Expert Consult.

97.2 Prematurity and Intrauterine Growth Restriction

Waldemar A. Carlo

DEFINITIONS

Traditionally, a delivery date is determined 280 days after the last menstrual period; however, only 4% deliver at 280 days and only 70%

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deliver within 10 days of the estimated delivery date. Human gestation length from ovulation to birth may be 268 days, with a range of 37 days.

Liveborn infants delivered before 37 wk from the 1st day of the last menstrual period are termed premature by the World Health Organization. Low birthweight (LBW; birthweight of 2,500 g or less) is a consequence of prematurity, poor intrauterine growth (IUGR, also referred to as SGA), or both.

The American College of Obstetrics and Gynecology redefines term into subgroups: early term (37 0/7 wk of gestation to 38 6/7 wk), full term (39 0/7–40 6/7 wk), and late term (41 0/7–41 6/7 wk). Early term was previously referred to as late preterm.

Prematurity and IUGR are associated with increased neonatal morbidity and mortality. Ideally, definitions of LBW for individual populations should be based on data that are as genetically and environmentally homogeneous as possible. As previously mentioned, Figure 97-1 presents variations in mortality based on birthweight, gestational age, and gender.

INCIDENCE

There is an increasing percentage of deaths in children <5 yr of age that occur in the neonatal period. More than 5% of deaths in children <5 yr of age occur within the 1st mo of life, with about half of the deaths attributable to prematurity. Approximately 8% of liveborn neonates in the United States weigh <2,500 g; the rate for blacks is almost twice that for whites. Over the past 2 decades, the LBW rate has increased primarily because of an increased number of preterm births registered as live births. Women whose first births are delivered before term are at increased risk for recurrent preterm delivery. Approximately 30% of LBW infants in the United States have IUGR and are born after 37 wk of gestation. At LBW rates >10%, the contribution of IUGR increases and that of prematurity decreases. In developing countries, approximately 70% of LBW infants have IUGR. Infants with IUGR have greater morbidity and mortality than do appropriately grown, gestational age–matched infants (see Fig. 97-1). Although U.S. infant mortality rates have fallen since 1971, the ethnic disparity between black infants and white or Hispanic infants remains unchanged. Black infants have higher neonatal mortality rates and comprise a larger percentage of low birthweight births in the United States.

The incidence of preterm births in the United States continues to rise (Figs. 97-3 and 97-4) and is partly a result of multiple gestation pregnancies and increased reporting as live births of the most immature babies.

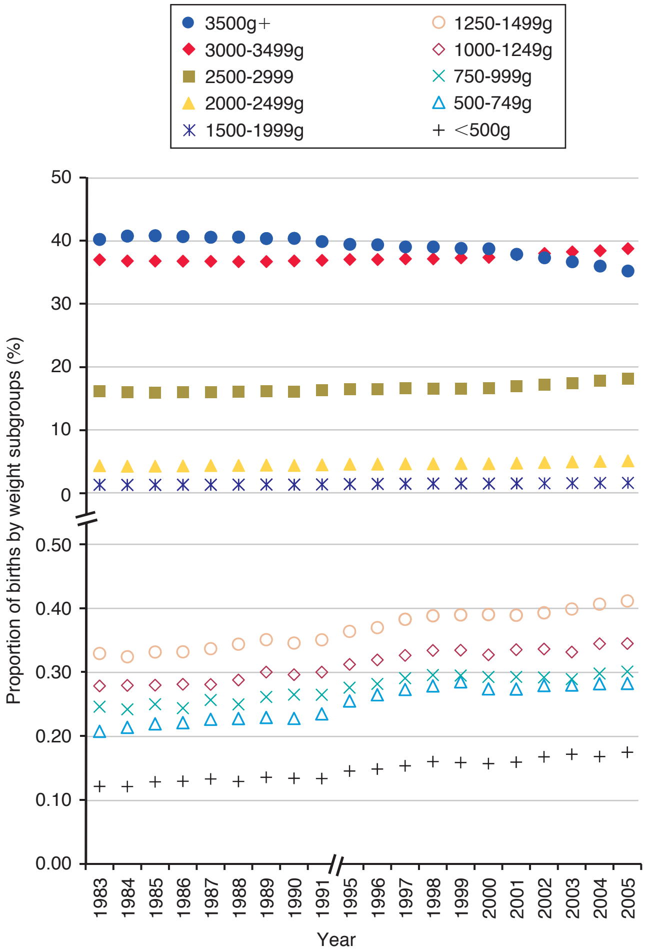

Figure 97-3 **Percentage contributions of infants in each very-low birthweight subgroup to total births for 1983-2005.** The contribution of infants in each very-low birthweight subgroup increased during the study period. *(From Lau C, Ambalavanan N, Chakraborty H, et al: Extremely low birth weight and infant mortality rates in the United States,* Pediatrics *131:855–860, 2013.)*

VERY LOW BIRTHWEIGHT INFANTS

Very-low birthweight (VLBW) infants weigh <1,500 g and are predominantly premature. In the United States in 2011, the VLBW rates were approximately 1.44% overall, 2.99% among blacks, and 1.14% among whites. The VLBW rate is an accurate predictor of the infant mortality rate. VLBW infants account for more than 50% of neonatal deaths and 50% of handicapped infants; their survival is directly related to birthweight, with approximately 20% of those between 500 and 600 g and >90% of those between 1,250 and 1,500 g surviving. The VLBW rate has remained unchanged for black Americans but has increased among whites, perhaps because of a rise in multiple births among whites. Perinatal care has improved the rate of survival of VLBW infants. When compared with term infants, VLBW neonates have a higher incidence of rehospitalization during the 1st yr of life for sequelae of prematurity, infections, neurologic complications, and psychosocial disorders.

FACTORS RELATED TO PREMATURE BIRTH AND LOW BIRTHWEIGHT

It is difficult to separate completely the factors associated with prematurity from those associated with IUGR (see Chapters 94 and 95). A strong positive correlation exists between both preterm birth and IUGR and low socioeconomic status. Families of low socioeconomic status have higher rates of maternal undernutrition, anemia, and illness; inadequate prenatal care; drug misuse; obstetric complications; and maternal history of reproductive inefficiency (abortions, stillbirths, premature or LBW infants). Other associated factors, such as single-parent families, teenage pregnancies, short interpregnancy interval, and mothers who have borne more than 4 previous children, are also encountered more frequently in such families. Systematic differences in fetal growth have also been described in association with maternal size, birth order, sibling weight, social class, maternal smoking, and other factors. The degree to which the variance in birthweight among various populations is caused by environmental (extrafetal) rather than genetic differences in growth potential is difficult to determine.

The etiology of preterm birth is multifactorial and involves a complex interaction between fetal, placental, uterine, and maternal factors (Table 97-3).

Premature birth of infants whose LBW is appropriate for their preterm gestational age is associated with medical conditions characterized by an inability of the uterus to retain the fetus, interference with the course of the pregnancy, premature rupture of the amniotic membranes or premature separation of the placenta, multifetal gestation, or an undetermined stimulus to effective uterine contractions before term.

Overt or asymptomatic bacterial infection (group B streptococci, *Listeria monocytogenes, Ureaplasma urealyticum, Mycoplasma hominis, Chlamydia, Trichomonas vaginalis, Gardnerella vaginalis, Bacteroides* spp.) of the amniotic fluid and membranes (chorioamnionitis) may initiate preterm labor. Bacterial products may stimulate the production

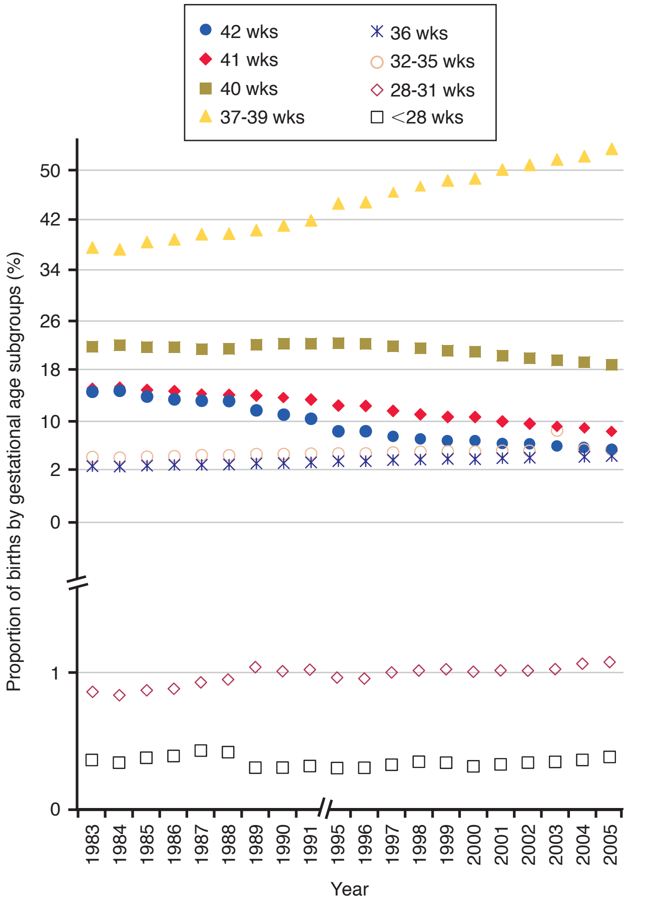

Figure 97-4 Percentage contributions of infants in gestational age subgroups to total births for 1983-2005. *(From Lau C, Ambalavanan N, Chakraborty H, et al: Extremely low birth weight and infant mortality rates in the United States,* Pediatrics *131:855–860, 2013.)*

of local inflammatory mediators (interleukin-6, prostaglandins), which may induce premature uterine contractions or a local inflammatory response with focal amniotic membrane rupture. Appropriate antibiotic therapy reduces the risk of fetal infection and may prolong gestation.

Most preterm births are "spontaneous" without an identifiable cause; genetic predisposition may increase the risk of prematurity. In one study, 6 genes were associated with prematurity. In addition, attempts at prevention of prematurity with hydroxyprogesterone caproate intramuscular injections or vaginal progesterone therapy, suggest a role for an endocrine–genetic relationship.

IUGR is associated with medical conditions that interfere with the circulation and efficiency of the placenta, with the development or growth of the fetus, or with the general health and nutrition of the mother (Table 97-4). Many factors are common to both prematurely born and LBW infants with IUGR. IUGR is associated with decreased insulin production or insulin (or insulin-like growth factor) action at the receptor level. Infants with insulin-like growth factor-1 receptor defects, pancreatic hypoplasia, or transient neonatal diabetes have IUGR. Genetic mutations affecting the glucose-sensing mechanisms of the pancreatic islet cells that result in decreased insulin release (loss of function of the glucose-sensing glucokinase gene) give rise to IUGR.

IUGR may be a normal fetal response to nutritional or oxygen deprivation. Therefore, the issue is not the IUGR but rather the ongoing risk of fetal malnutrition or hypoxia. Similarly, some preterm births signify a need for early delivery from a potentially disadvantageous intrauterine environment. IUGR is often classified as reduced growth that is symmetric (head circumference, length, and weight equally affected) or asymmetric (with relative sparing of head growth) (see Fig. 96-1 in Chapter 96). **Symmetric IUGR** often has an earlier onset and is associated with diseases that seriously affect fetal cell number, such as conditions with chromosomal, genetic, malformation, teratogenic, infectious, or severe maternal hypertensive etiologies. It is important to assess gestational age carefully in infants suspected to have symmetric IUGR because incorrect overestimation of gestational age may lead to the diagnosis of symmetric IUGR. **Asymmetric IUGR** is often of late onset, demonstrates preservation of Doppler waveform velocity to the carotid vessels, and is associated with poor maternal nutrition or with late onset or exacerbation of maternal vascular

Table 97-3	Identifiable Causes of Preterm Birth
FETAL Fetal distress Multiple gestation Erythroblastosis Nonimmune hydrops	
PLACENTAL Placental dysfunction Placenta previa Abruptio placentae	
UTERINE Bicornuate uterus Incompetent cervix (premature dilation)	
MATERNAL Preeclampsia Chronic medical illness (cyanotic heart disease, renal disease) Infection (*Listeria monocytogenes*, group B streptococcus, urinary tract infection, bacterial vaginosis, chorioamnionitis) Drug abuse (cocaine)	
OTHER Premature rupture of membranes Polyhydramnios Iatrogenic Trauma	

Table 97-4	Factors Often Associated with Intrauterine Growth Restriction
FETAL Chromosomal disorders Chronic fetal infections (cytomegalic inclusion disease, congenital rubella, syphilis) Congenital anomalies—syndrome complexes Irradiation Multiple gestation Pancreatic hypoplasia Insulin deficiency (production or action of insulin) Insulin-like growth factor type I deficiency	
PLACENTAL Decreased placental weight, cellularity, or both Decrease in surface area Villous placentitis (bacterial, viral, parasitic) Infarction Tumor (chorioangioma, hydatidiform mole) Placental separation Twin transfusion syndrome	
MATERNAL Toxemia Hypertension or renal disease, or both Hypoxemia (high altitude, cyanotic cardiac or pulmonary disease) Malnutrition (micronutrient or macronutrient deficiencies) Chronic illness Sickle cell anemia Drugs (narcotics, alcohol, cigarettes, cocaine, antimetabolites)	

disease (preeclampsia, chronic hypertension). Table 97-5 lists the problems of infants with IUGR.

ASSESSMENT OF GESTATIONAL AGE AT BIRTH

When compared with a premature infant of appropriate weight, an infant with IUGR has a reduced birthweight and may appear to have a disproportionately larger head relative to body size; infants in both groups lack subcutaneous fat. Neurologic maturity (nerve conduction velocity) in the absence of asphyxia correlates with gestational age despite reduced fetal weight. Physical signs may be useful in estimating gestational age at birth. Commonly used, the Ballard scoring system is accurate to ±2 wk (Figs. 97-5 to 97-7). An infant should be presumed to be at high risk for mortality or morbidity if a discrepancy exists between the estimation of gestational age by physical examination, the mother's estimated date of her last menstrual period, and fetal ultrasonographic evaluation.

Table 97-5 Problems of Infants Small for Gestational Age or with Intrauterine Growth Retardation*

PROBLEM	PATHOGENESIS
Intrauterine fetal demise	Hypoxia, acidosis, infection, lethal anomaly
Perinatal asphyxia	↓ Uteroplacental perfusion during labor ± chronic fetal hypoxia–acidosis; meconium aspiration syndrome
Hypoglycemia	↓ Tissue glycogen stores, ↓ gluconeogenesis, hyperinsulinism, ↑ glucose needs of hypoxia, hypothermia, large brain
Polycythemia–hyperviscosity	Fetal hypoxia with ↑ erythropoietin production
Reduced oxygen consumption/hypothermia	Hypoxia, hypoglycemia, starvation effect, poor subcutaneous fat stores
Dysmorphology	Syndrome anomalads, chromosomal-genetic disorders, oligohydramnios-induced deformation, TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) infection

*Other problems include pulmonary hemorrhage and those common to the gestational age-related risks of prematurity if born at less than 37 wk.
↓, Decreased; ↑, increased.

SPECTRUM OF DISEASE IN LOW-BIRTHWEIGHT INFANTS

Immaturity increases the severity but reduces the distinctiveness of the clinical manifestations of most neonatal diseases. Immature organ function, complications of therapy, and the specific disorders that caused the premature onset of labor contribute to the neonatal

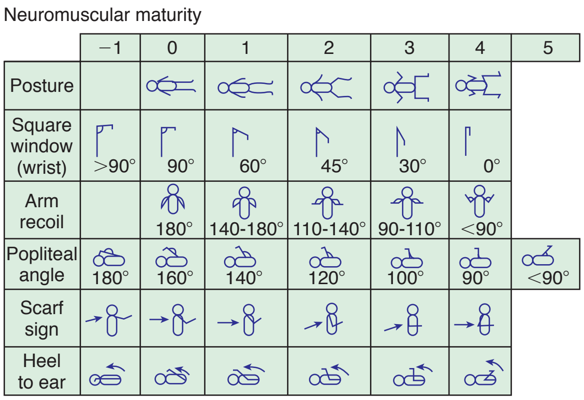

Figure 97-6 **Neuromuscular criteria for maturity.** The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. *(From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants, J Pediatr 119:417–423, 1991.)*

Physical maturity

	−1	0	1	2	3	4	5
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40-50 mm:–1 <40 mm: –2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases on ant. 2/3	Creases over entire sole	
Breast	Impercep-tible	Barely perceptible	Flat areola–no bud	Stripped areola, 1-2 mm bud	Raised areola, 3-4 mm bud	Full areola, 5-10 mm bud	
Eye/ear	Lids fused loosely (–1), tightly (–2)	Lids open, pinna flat, stays folded	Slightly curved pinna; soft; slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals, male	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals, female	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Figure 97-5 **Physical criteria for maturity.** The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. *(From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants, J Pediatr 119:417–423, 1991.)*

Maturity Rating

Score	Weeks
– 10	20
– 5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Figure 97-7 **Maturity rating.** The physical and neurologic scores are added to calculate gestational age. *(From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants,* J Pediatr *119:417–423, 1991.)*

morbidity and mortality associated with premature, LBW infants (Table 97-6). Among VLBW infants, morbidity is inversely related to birthweight. Respiratory distress syndrome is noted in approximately 80% of infants weighing 501-750 g; in 65% of those weighing 751-1,000 g; in 45% of those weighing 1,001-1,250 g; and in 25% of those weighing 1,251-1,500 g. Severe intraventricular hemorrhage (IVH) is noted in approximately 25% of infants weighing 501-750 g; in 12% of those weighing 751-1,000 g; in 8% of those weighing 1,001-1,250 g; and in 3% of those weighing 1,251-1,500 g. Overall, the risk of late sepsis (24%), bronchopulmonary dysplasia (23%), severe IVH (11%), necrotizing enterocolitis (7%), and prolonged hospitalization (45-125 days) is high in VLBW infants. Problems associated with IUGR LBW infants are noted in Table 97-5; these added problems are often superimposed on those noted in Table 97-6 if an infant with IUGR is also premature. Poor postnatal growth is an important problem for both preterm and IUGR infants.

Table 97-6	Neonatal Problems Associated with Premature Infants
RESPIRATORY	
Respiratory distress syndrome (hyaline membrane disease)*	
Bronchopulmonary dysplasia	
Pneumothorax, pneumomediastinum; interstitial emphysema	
Congenital pneumonia	
Apnea*	
CARDIOVASCULAR	
Patent ductus arteriosus*	
Hypotension	
Bradycardia (with apnea)*	
HEMATOLOGIC	
Anemia (early or late onset)	
GASTROINTESTINAL	
Poor gastrointestinal function—poor motility*	
Necrotizing enterocolitis	
Hyperbilirubinemia—direct and indirect*	
Spontaneous gastrointestinal isolated perforation	
METABOLIC-ENDOCRINE	
Hypocalcemia*	
Hypoglycemia*	
Hyperglycemia*	
Late metabolic acidosis	
Hypothermia*	
Euthyroid but low thyroxine status	
Osteopenia	
CENTRAL NERVOUS SYSTEM	
Intraventricular hemorrhage*	
Periventricular leukomalacia	
Seizures	
Retinopathy of prematurity	
Deafness	
Hypotonia*	
RENAL	
Hyponatremia*	
Hypernatremia*	
Hyperkalemia*	
Renal tubular acidosis	
Renal glycosuria	
Edema	
OTHER	
Infections* (congenital, perinatal, nosocomial: bacterial, viral, fungal, protozoal)	

*Common.

NURSERY CARE

At birth, the measures needed to clear the airway, initiate breathing, care for the umbilical cord and eyes, and administer vitamin K are the same for immature infants as for those of normal weight and maturity (see Chapter 94). Special care is required to maintain a patent airway. Additional considerations are the need for (1) thermal control and monitoring of the heart rate and respiration, (2) oxygen therapy, and (3) special attention to the details of fluid requirements and nutrition. Safeguards against infection can never be relaxed. Routine procedures that disturb these infants may result in hypoxia. The need for regular and active participation by the parents in the infant's care in the nursery, the need to instruct the mother in at-home care of her infant, and the question of prognosis for later growth and development require special consideration.

Thermal Control

The survival rate of LBW and sick infants is higher when they are cared for at or near their **neutral thermal environment.** This environment is a set of thermal conditions, including air and radiating surface temperatures, relative humidity, and airflow, at which heat production (measured experimentally as oxygen consumption) is minimal and the infant's core temperature is within the normal range. The neutral thermal environment is a function of the size and postnatal age of an infant; larger, older infants require lower environmental temperatures than smaller, younger infants do. Incubators or radiant warmers can be used to maintain body temperature. Body heat is conserved through provision of a warm environment and humidity. The optimal environmental temperature for minimal heat loss and oxygen consumption for an unclothed infant is one that maintains the infant's core temperature at 36.5-37.0°C (97.7-98.6°F). It depends on an infant's size and maturity; the smaller and more immature the infant, the higher the environmental temperature required. An additional acrylic resin (Plexiglas) heat shield or head cap and body clothing may be required to keep an extremely LBW (ELBW) preterm infant warm. Infant warmth can be maintained by heating the air to a desired temperature or by servocontrolling the infant's body temperature at a desired set point. Continuous monitoring of the infant's temperature is required so that the environmental temperature can be adjusted to maintain optimal body temperature. **Kangaroo mother care** with direct skin-to-skin contact and a hat and blanket covering the infant is a safe alternative, with careful monitoring to avoid the risk of serious hypothermia when

incubators are unavailable or when the infant is stable and the parent desire close contact with their infant.

Maintaining a relative humidity of 40-60% aids in stabilizing body temperature by reducing heat loss at lower environmental temperatures; by preventing drying and irritation of the lining of respiratory passages, especially during the administration of oxygen and after or during endotracheal intubation (usually 100% humidity); and by thinning viscid secretions and reducing insensible water loss from the lungs. An infant should be weaned and then removed from the incubator or radiant warmer only when the gradual change to the atmosphere of the nursery does not result in a significant change in the infant's temperature, color, activity, or vital signs.

Administering oxygen to reduce the risk of injury from hypoxia and circulatory insufficiency must be balanced against the risk of hyperoxia to the eyes (retinopathy of prematurity) and oxygen injury to the lungs. Oxygen should be administered via a head hood, nasal cannula, continuous positive airway pressure apparatus, or endotracheal tube to maintain stable and safe inspired oxygen concentrations. Although cyanosis must be treated immediately, oxygen is a drug, and its use must be carefully regulated to maximize benefit and minimize potential harm. The concentration of inspired oxygen must be adjusted in accordance with the oxygen tension of arterial blood (Pa_{O_2}) or a noninvasive method such as continuous pulse oximetry or transcutaneous oxygen measurements. Capillary blood gas determinations are inadequate for estimating arterial oxygen levels.

Fluid Requirements

Fluid needs vary according to gestational age, environmental conditions, and disease states. Assuming minimal water loss in the stool of infants not receiving oral fluids, their water needs are equal to their insensible water loss, excretion of renal solutes, growth, and any unusual ongoing losses. Insensible water loss is indirectly related to gestational age; very immature preterm infants (<1,000 g) may lose as much as 2-3 mL/kg/hr, partly because of immature skin, lack of subcutaneous tissue, and a large exposed surface area. Insensible water loss is increased under radiant warmers, during phototherapy, and in febrile infants. High humidity can be used to reduce insensible water losses. The loss is diminished when an infant is clothed, is covered by an acrylic resin inner heat shield, breathes humidified air, or is of advanced postnatal age. A larger premature infant (2,000-2,500 g) nursed in an incubator may have an insensible water loss of approximately 0.6-0.7 mL/kg/hr.

Adequate fluid intake is essential for excretion of the urinary solute load (urea, electrolytes, phosphate). The amount varies with dietary intake and the anabolic or catabolic state of nutrition. Formulas with a high solute load, high protein intake, and catabolism increase the end products that require urinary excretion and thus increase the requirement for water. **Renal solute loads** may vary between 7.5 and 30 mOsm/kg. Newborn infants, especially VLBW ones, are also less able to concentrate urine, so they need higher fluid intake to excrete solutes.

Fluid intake in term infants is usually begun at 60-70 mL/kg on day 1 and increased to 100-120 mL/kg by days 2-3. Smaller, more premature infants may need to start with 70-80 mL/kg on day 1 and advance gradually to 150 mL/kg/day. Fluid volumes should be titrated individually, although it is unusual to exceed 150 mL/kg/24 hr. Infants weighing <750 g in the 1st wk of life have immature skin and a large surface area, characteristics that lead to a high rate of transepidermal fluid loss, at times requiring higher rates of intravenous fluids. Daily weights, urine output, and serum urea nitrogen and sodium levels should be monitored carefully to determine water balance and fluid needs. Clinical observation and physical examination are poor indicators of the state of hydration of premature infants. Conditions that increase fluid loss, such as glycosuria, the polyuric phase of acute tubular necrosis, and diarrhea, may place additional strain on kidneys that have not yet acquired their maximal capacity to conserve water and electrolytes, the result of which may be severe dehydration. Alternatively, fluid overload may lead to edema, heart failure, patent ductus arteriosus, and bronchopulmonary dysplasia.

Parenteral Nutrition

Before complete enteral feeding has been established or when enteral feeding is impossible for prolonged periods, total intravenous alimentation may provide sufficient fluid, calories, amino acids, electrolytes, and vitamins to sustain the growth of ill infants. This technique has been lifesaving for VLBW and preterm infants and infants who have had intractable diarrheal syndromes or extensive bowel resection. Infusions may be administered through a percutaneously or, less often, surgically placed indwelling central venous catheter or through a peripheral vein. The umbilical vein may also be used for up to 2 wk.

The goal of parenteral alimentation is to deliver sufficient calories from glucose, protein, and lipids to promote optimal growth. The infusate should contain 2.5-3.5 g/dL of synthetic amino acids and usually 10-15 g/dL of glucose, in addition to appropriate quantities of electrolytes, trace minerals, and vitamins. If a peripheral vein is used, it is advisable to keep the glucose concentration below 12.5 g/dL. If a central vein is used, glucose concentrations as high as 25 g/dL may be used (rarely). Intravenous fat emulsions such as Intralipid 20% (2.2 kcal/mL) may be administered to provide calories without an appreciable osmotic load, thereby decreasing the need for infusion of the higher concentrations of glucose by central or peripheral vein while preventing the development of essential fatty acid deficiency. A 20% fat emulsion may be initiated at 0.5 g/kg/24 hr and advanced to 3 g/kg/24 hr, if triglyceride levels remain normal; 0.5 g/kg/24 hr is sufficient to prevent essential fatty acid deficiency. Electrolytes, trace minerals, and vitamin additives are included in amounts approximating established intravenous maintenance requirements. The content of each day's infusate should be determined after careful assessment of the infant's clinical and biochemical status. Slow and continuous infusion is advisable. A well-trained pharmacist should mix all solutions under a laminar flow hood.

After a caloric intake of >100 kcal/kg/24 hr is established by total parenteral intravenous nutrition, the infants can be expected to gain about 15 g/kg/24 hr, with a positive nitrogen balance of 150-200 mg/kg/24 hr, in the absence of episodes of sepsis, surgical procedures, and other severe stress. This goal can usually be achieved (and the catabolic tendency during the 1st wk of life reversed, with subsequent weight gain) by peripheral vein infusion of 2.5-3.5 g/kg/24 hr of an amino acid mixture, 10 g/dL of glucose, and 2-3 g/kg/24 hr of a 20% fat emulsion.

Complications of intravenous alimentation are related to both the catheter and the metabolism of the infusate. Sepsis, the most important problem of central vein infusions, can be minimized only by meticulous catheter care and aseptic preparation of the infusate; a vancomycin–heparin solution also reduces the risk of line sepsis. Coagulase-negative *Staphylococcus* is the most common infecting organism. Treatment includes appropriate antibiotics. If an infection persists (repeatedly positive blood culture results while the infant is receiving appropriate antibiotics), the line must be removed. Thrombosis, extravasation of fluid, and accidental dislodgment of catheters have also occurred. Although sepsis is less often attributable to peripheral vein infusion, phlebitis, cutaneous sloughing, and superficial infection may occur. Metabolic complications of parenteral nutrition include hyperglycemia from the high glucose concentration of the infusate, which may lead to osmotic diuresis and dehydration; azotemia; a possible increased risk of nephrocalcinosis; hypoglycemia from sudden accidental cessation of the infusate; hyperlipidemia and possibly hypoxemia from intravenous lipid infusions; and hyperammonemia, which may result from high levels of certain amino acids. Metabolic bone disease and/or cholestatic jaundice and liver disease may develop in infants who require long-term parenteral nutrition and receive no enteral nutrition. Biochemical and physiologic monitoring of infants receiving intravenous alimentation is indicated because of the frequency and seriousness of complications.

Feeding

The method of feeding each LBW or preterm infant should be individualized. It is important to avoid fatigue and aspiration of food

through regurgitation or the feeding process. No feeding method averts these problems unless the person feeding the infant has been well trained in the method. Oral feeding (nipple) should not be initiated or should be discontinued in infants with respiratory distress, hypoxia, circulatory insufficiency, excessive secretions, gagging, sepsis, central nervous system depression, severe immaturity, or signs of serious illness. These high-risk infants require parenteral nutrition or gavage feeding to supply calories, fluid, and electrolytes. The process of oral alimentation requires, in addition to a strong sucking effort, coordination of swallowing, epiglottal and uvular closure of the larynx and nasal passages, and normal esophageal motility, a synchronized process that is usually absent before 34 wk of gestation.

Preterm infants at 34 wk of gestation or more can often be fed by bottle or at the breast. Because the effort of sucking is usually the limiting factor, direct breastfeeding is less likely to succeed in very preterm infants until they mature. Bottle-feeding of expressed breast milk may be a temporary alternative. In bottle-feeding, the infant's effort may be reduced by use of special small, soft nipples with large holes. Smaller or less vigorous infants should be fed by gavage: A soft plastic tube with No. 5 French external and approximately 0.05 cm internal diameters and with a rounded atraumatic tip and two holes on alternate sides is preferable. The tube is passed through the nose until approximately 2.5 cm (1 inch) of the lower end is in the stomach. The free end of the tube has an adapter into which the tip of a syringe is fitted, and a measured amount of fluid is given by pump or by gravity. Such a tube may be left in place for 3-7 days before being replaced by a similar tube through the other nostril. Infants occasionally have enough local irritation from an indwelling tube that they may gag or troublesome secretions may gather around it in the nasopharynx. In such cases, a catheter may be passed through the mouth by a skilled person and removed at the end of each feeding.

The infant may be fed with intermittent bolus feedings or continuous feeding. In the occasional infant with feeding intolerance, nasojejunal feeding may be successful. Intestinal perforation is a risk with nasojejunal feeding. A change to breast- or bottle-feeding may be instituted gradually as soon as an infant displays general vigor adequate for oral feeding without fatigue.

Gastrostomy feeding is not usually indicated in premature or LBW infants except as an adjunct to surgical management of specific gastrointestinal conditions or in patients with permanent neurologic injuries who are unable to suck and swallow normally.

Initiation of Feeding

The optimal time to introduce enteral feeding to a sick premature or LBW infant is controversial. **Trophic feeding** is the practice of feeding very small amounts of enteral nourishment to VLBW preterm infants to stimulate development of the immature gastrointestinal tract. The benefits of trophic feeding include enhanced gut motility, improved growth, decreased need for parenteral nutrition, fewer episodes of sepsis, and shortened hospital stay. Once the infant is stable, small-volume feedings are given in addition to intravenous fluids/nutrition. Feeding is gradually advanced, and parenteral nutrition decreased. This approach may reduce the incidence of necrotizing enterocolitis. The main principle in feeding premature infants is to proceed cautiously and gradually. Careful early feeding of breast milk or formula tends to reduce the risk of hypoglycemia, dehydration, and hyperbilirubinemia without the additional risk of aspiration, provided that there is no indication for withholding oral feedings, such as the presence of respiratory distress or other disorders.

If an infant is well, is making sucking movements, and is in no distress, oral feeding may be attempted, although most infants weighing <1,500 g require tube feeding because they are unable to coordinate breathing, sucking, and swallowing. Intestinal tract readiness for feeding may be determined by active bowel sounds, passage of meconium, and the absence of abdominal distention, bilious gastric aspirates, and emesis. For infants <1,000 g, the initial trophic feedings can be given at 10-20 mL/kg/24 hr as a continuous nasogastric tube drip (or given by intermittent gavage every 2-3 hr) for

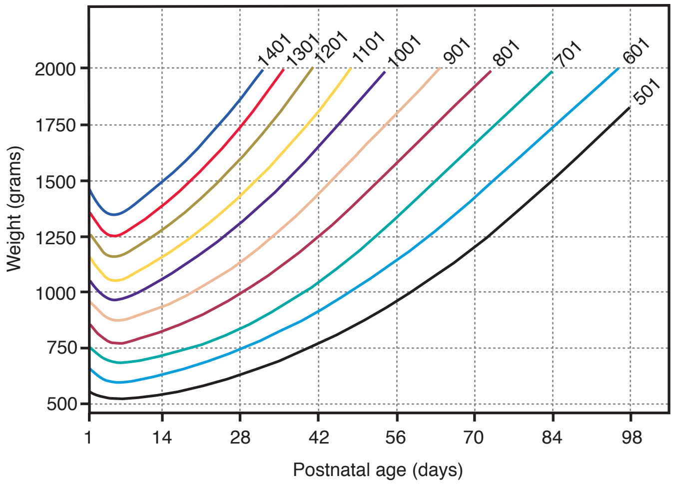

Figure 97-8 Average daily body weight versus postnatal age in days for infants stratified by 100-g birthweight intervals. *(From Ehrenkranz RA, Younes N, Lemons JA, et al: Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 104:280-289, 1999.)*

5-10 days. If the initial feedings are tolerated, the volume is increased by 20-30 mL/kg/24 hr. Once a volume of 150 mL/kg/24 hr has been achieved, the caloric content may be increased to 24 or 27 kcal/oz. With high caloric density, infants are at risk for dehydration, edema, lactose intolerance, diarrhea, flatus, and delayed gastric emptying with emesis. Intravenous fluids are needed until feedings provide approximately 120 mL/kg/24 hr. The feeding protocol for premature infants weighing >1,500 g is initiated at a volume of 20-30 mL/kg/24 hr with increments in total daily formula volume of 20-30 mL/kg/24 hr. Figure 97-8 projects the expected weight increments for premature infants of various birthweights. Infants with IUGR may not demonstrate the marked initial weight loss noted in premature infants.

Regurgitation, vomiting, abdominal distention, or gastric residuals from previous feedings should arouse suspicion of sepsis, necrotizing enterocolitis, or intestinal obstruction; these conditions are indications to stop feedings, at least temporarily, and to increase subsequent feedings slowly only as tolerated or to change to intravenous alimentation and evaluate the infant for more serious problems (see Chapter 102.2). Weight gain may not be achieved for 10-12 days. Alternatively, in infants whose feeding schedule is advanced successfully in calories or volume, weight gain may appear within a few days.

When tube feeding is used, the contents of the stomach should be aspirated before each feeding. If only air or small amounts of mucus are obtained, the feeding is given as planned. If all or a substantial part of the previous feeding is aspirated, it is advisable to withhold feedings or to reduce the amount of the feeding and proceed more gradually with subsequent increases, depending on the physical findings and other evidence of feeding intolerance.

The digestive enzyme systems of infants older than 28 wk of gestation are mature enough to permit adequate digestion and absorption of protein and carbohydrate. Fat is less-well absorbed, primarily because of inadequate amounts of bile salt; unsaturated fats and the fat of human milk are absorbed better than the fat of cow's milk. The weight gain of infants weighing <2,000 g at birth should be adequate when either human milk or "humanized" milk premature formula (40% casein and 60% whey) with a protein intake of 2.25-2.75 g/kg/24 hr is fed. These 2 alternatives should provide all amino acids essential for premature infants, including tyrosine, cystine, and histidine. Higher protein intake may be well tolerated and is generally safe, especially in older, rapidly growing infants. Protein intake >4-5 g/kg/24 hr may be hazardous. Although they may promote linear growth, high-protein formulas may cause abnormal plasma

aminogram results; elevations in blood urea nitrogen, ammonia, and sodium concentrations; metabolic acidosis (cow's milk formulas); and untoward effects on neurologic development. Furthermore, the high protein and mineral contents of balanced cow's milk formulas with a high caloric content constitute a large solute load for the kidneys, a fact important in maintaining water balance, especially in infants with diarrhea or fever.

Breast milk from their mothers is the preferred milk for all infants, including VLBW infants. In addition to nutritional advantages, the benefits of breast milk include protection against a wide range of infections (through both specific and nonspecific anti-infective factors in breast milk and beneficial effects on intestinal flora), a decreased risk of necrotizing enterocolitis in preterm infants, a lower risk of sudden infant death syndrome, and possible long-term effects, including a lower risk of childhood/adolescent obesity and improved neurodevelopmental outcome. Once a premature infant takes 120 mL/kg/24 hr, **breast milk fortifiers** are added to supplement breast milk with protein, calcium, and phosphorus. If breast milk is unavailable, special preterm formulas should be used.

Properly fed premature infants may have from 1 to 8 daily stools of semisolid consistency; a sudden increase in their number, the appearance of occult or gross blood, or change to a watery consistency is more reason for concern than any arbitrarily stated stooling frequency.

Vitamins

Although formula in amounts necessary for adequate growth probably contains adequate quantities of all vitamins, the volume of milk sufficient to satisfy these requirements may not be ingested for several weeks. Therefore, LBW and preterm infants should be given supplemental vitamins. Because requirements for these infants have not been precisely established, the recommended daily allowances for term infants should be given (see Chapter 44). Furthermore, infants may have a special need for certain vitamins. Intermediary metabolism of phenylalanine and tyrosine depends, in part, on vitamin C. Decreased fat absorption with increased fecal fat loss may be associated with decreased absorption of vitamin D, other fat-soluble vitamins, and calcium in premature infants. VLBW infants are particularly prone to the development of osteopenia, but their total intake of vitamin D should not exceed 1,500 IU/24 hr. Folic acid is essential for the formation of DNA and production of new cells; serum and erythrocyte levels decrease in preterm infants during the 1st few wk of life and remain low for 2-3 mo. Therefore, folic acid supplementation is recommended, although it does not result in improved growth or an increased hemoglobin concentration. Deficiency of vitamin E is uncommon, but is associated with increased hemolysis and, if severe, with anemia and edema in premature infants. Vitamin E functions as an antioxidant to prevent the peroxidation of excessive polyunsaturated fatty acids in red blood cell membranes; its need may increase because of the higher membrane content of these fatty acids when formulas with high polyunsaturated fatty acids are used. Vitamin A supplementation reduces bronchopulmonary dysplasia in ELBW infants. Vitamin K deficiency is discussed in Chapter 97.4.

In LBW and premature infants, **physiologic anemia** from postnatal suppression of erythropoiesis is exacerbated by smaller fetal iron stores and greater expansion of blood volume from the more rapid growth than that of term infants; therefore, the anemia develops earlier and reaches a lower ultimate level. Fetal or neonatal blood loss accentuates this problem. Iron stores, even in a VLBW neonate, are usually adequate until an infant's birthweight has doubled; iron supplementation (2 mg/kg/24 hr) should then be started. If erythropoietin is used, iron supplementation is also required.

Prevention of Infection

Premature infants have an increased susceptibility to infection, and thus meticulous attention to infection control is required. Prevention strategies include strict compliance with handwashing and universal precautions, minimizing the risk of catheter contamination and duration, meticulous skin care, encouraging early appropriate advancement of enteral feeding, education and feedback to staff, and surveillance of nosocomial infection rates in the nursery. Although no one with an active infection should be permitted in the nursery, the risks of infection must be balanced against the disadvantages of limiting the infant's contact with the family. Early and frequent participation by parents in the nursery care of their infant does not increase the risk of infection when preventive precautions are maintained.

Preventing transmission of infection from infant to infant is difficult because often neither term nor premature newborn infants have clear clinical evidence of an infection early in its course. When epidemics occur within a nursery, cohort nursing and isolation rooms should be used. Universal precautions require gloves to be worn with all patient contact. Because premature infants have immature immune function, some will develop nosocomial infection even when all precautions are followed.

Routine immunizations should be given on the regular schedule at standard doses (see Chapter 172).

IMMATURITY OF DRUG METABOLISM

Renal clearance of almost all substances excreted in the urine is diminished in newborn infants, but more so in premature ones. The glomerular filtration rate rises with increasing gestational age; therefore drug dosing recommendations vary with age. Intervals between doses may therefore need to be extended with administration of drugs excreted chiefly by the kidneys. Longer intervals are required for many drugs administered to preterm infants. Drugs that are detoxified in the liver or require chemical conjugation before renal excretion should also be given with caution and in doses smaller than usual.

When possible, blood levels should be determined for potentially toxic drugs, especially if renal or hepatic dysfunction is present. Decisions about the choice and dose of antibacterial agents and the route of administration should be made on an individual basis rather than routinely because of the dangers of (a) development of infections with organisms resistant to antibacterial agents, (b) inhibition of intestinal bacteria that manufacture significant amounts of essential vitamins (vitamin K and thiamine), and (c) harmful interference in important metabolic processes.

Many drugs apparently safe for adults on the basis of toxicity studies may be harmful to newborn infants, especially premature ones. Oxygen and a number of drugs have proved toxic to premature infants in amounts not harmful to term infants (Table 97-7). Thus, administering any drug, particularly in high doses, that has not undergone pharmacologic testing in premature infants should be undertaken carefully after risks have been weighed against benefits.

PROGNOSIS

Infants born weighing 1,501-2,500 g have a 95% or greater chance of survival, but those weighing still less have significantly higher mortality (see Fig. 97-1). Intensive care has extended the period during which a VLBW infant is at increased risk of dying of complications of prematurity, such as bronchopulmonary dysplasia, necrotizing enterocolitis, and nosocomial infection (Table 97-8). The postdischarge mortality rate of LBW infants is higher than that of term infants during the 1st 2 yr of life. Because many of the deaths are attributable to infection (e.g., respiratory syncytial virus), they are at least theoretically preventable. In addition, premature infants have an increased incidence of failure to thrive, sudden infant death syndrome, child abuse, and inadequate maternal-infant bonding. The biologic risk associated with poor cardiorespiratory regulation as a result of immaturity or complications of underlying perinatal disease and the social risk associated with poverty also contribute to the high mortality and morbidity of these infants. Congenital anomalies are present in approximately 3-7% of LBW infants.

In the absence of congenital abnormalities, central nervous system injury, VLBW, or marked IUGR, the **physical growth** of LBW infants tends to approximate that of term infants by the 2nd yr; the approximation occurs earlier in premature infants with larger birth size. VLBW infants may not catch up, especially if they have severe chronic sequelae, insufficient nutritional intake, or an inadequate caretaking

Table 97-7 Potential Adverse Reactions to Drugs Administered to Premature Infants

DRUG	REACTION(S)
Oxygen	Retinopathy of prematurity, bronchopulmonary dysplasia
Sulfisoxazole	Kernicterus
Chloramphenicol	Gray baby syndrome—shock, bone marrow suppression
Vitamin K analogs	Jaundice
Novobiocin	Jaundice
Hexachlorophene	Encephalopathy
Benzyl alcohol	Acidosis, collapse, intraventricular bleeding
Intravenous vitamin E	Ascites, shock
Phenolic detergents	Jaundice
$NaHCO_3$	Intraventricular hemorrhage
Amphotericin	Anuric renal failure, hypokalemia, hypomagnesemia
Reserpine	Nasal stuffiness
Indomethacin	Oliguria, hyponatremia, intestinal perforation
Cisapride	Prolonged QTc interval
Tetracycline	Enamel hypoplasia
Tolazoline	Hypotension, gastrointestinal bleeding
Calcium salts	Subcutaneous necrosis
Aminoglycosides	Deafness, renal toxicity
Enteric gentamicin	Resistant bacteria
Prostaglandins	Seizures, diarrhea, apnea, hyperostosis, pyloric stenosis
Phenobarbital	Altered state, drowsiness
Morphine	Hypotension, urine retention, withdrawal
Pancuronium	Edema, hypovolemia, hypotension, tachycardia, vecuronium contractions, prolonged hypotonia
Iodine antiseptics	Hypothyroidism, goiter
Fentanyl	Seizures, chest wall rigidity, withdrawal
Dexamethasone	Gastrointestinal bleeding, hypertension, infection, hyperglycemia, cardiomyopathy, reduced growth
Furosemide	Deafness, hyponatremia, hypokalemia, hypochloremia, nephrocalcinosis, biliary stones
Heparin (not low-dose prophylactic use)	Bleeding, intraventricular hemorrhage, thrombocytopenia
Erythromycin	Pyloric stenosis

environment (see Table 97-8). Infrequently, infants with IUGR (SGA) grow poorly and do not demonstrate catch-up growth. These infants may benefit from recombinant human growth hormone therapy beginning at age 4 yr.

Premature birth in itself may adversely affect later development. The greater the immaturity and the lower the birthweight, the greater the likelihood of intellectual and neurologic deficit; as many as 50% of 500-750 g infants have significant neurodevelopmental impairment (mental retardation, cerebral palsy, blindness, deafness). Small head circumference at birth may be related to a poor neurobehavioral prognosis. Many surviving LBW infants have hypotonia before 8 mo corrected age, which improves by the time they are 8 mo to 1 yr old. This transient hypotonia is not a poor prognostic sign. Thirty percent to 50% of VLBW children have poor school performance at 7 yr of age (repeating of grades, special classes, learning disorders, poor speech and language), despite a normal IQ. Factors posing a risk for poor academic performance include birthweight below 750 g, severe IVH, periventricular leukomalacia, bronchopulmonary dysplasia, cerebral atrophy, posthemorrhagic hydrocephalus, IUGR, low socioeconomic status, and, possibly, low thyroxine levels. Antenatal exposure to magnesium sulfate may have neuroprotective effects and may reduce the incidence of cerebral palsy in high-risk neonates. Adolescents who were VLBW report satisfactory health; 94% are integrated in regular classes despite neurosensory disabilities (hearing, vision, cerebral palsy, cognition) in 24%.

Table 97-8 Sequelae of Low Birthweight

IMMEDIATE	LATE
Hypoxia, ischemia	Mental retardation, spastic diplegia, microcephaly, seizures, poor school performance
Intraventricular hemorrhage	Mental retardation, spasticity, seizures, hydrocephalus
Sensorineural injury	Hearing, visual impairment, retinopathy of prematurity, strabismus, myopia
Respiratory failure	Bronchopulmonary dysplasia, cor pulmonale, bronchospasm, malnutrition, subglottic stenosis
Necrotizing enterocolitis	Short-bowel syndrome, malabsorption, malnutrition, infectious diarrhea
Cholestatic liver disease	Cirrhosis, hepatic failure, malnutrition
Nutrient deficiency	Osteopenia, fractures, anemia, growth failure
Social stress	Child abuse or neglect, failure to thrive, divorce
Other	Sudden infant death syndrome, infections, inguinal hernia, cutaneous scars (chest tube, patent ductus arteriosus ligation, intravenous infiltration), gastroesophageal reflux, hypertension, craniosynostosis, cholelithiasis, nephrocalcinosis, cutaneous hemangiomas

Both premature and IUGR infants are at risk for significant metabolic conditions (obesity, type II diabetes) and cardiovascular disorders (ischemic heart disease, hypertension) as adults. This **fetal origins** hypothesis of adult morbidities may involve insulin resistance, which may be evident in early childhood.

PREDICTING NEONATAL MORTALITY

Birthweight and gestational age have traditionally been used as strong indicators for the risk of neonatal death. Indeed, survival at 22 wk of gestation is poor, particularly in those infants requiring aggressive resuscitation in the delivery room. With increasing gestational age, survival rates rise to approximately 15% at 23 wk, 56% at 24 wk, and 79% at 25 wk. The survival of infants of <24 wk gestation, weighing <750 g, and with a 1-min Apgar score <3 is 30%. Antenatal steroids to increase lung maturation, female sex, and singleton pregnancy increase the chance for survival. However, extremely premature infants are also at risk for poor neurodevelopmental outcome.

Birthweight-specific neonatal diseases such as IVH, group B streptococcal sepsis/pneumonia, and pulmonary hypoplasia also contribute to a poor outcome. **Scoring systems** that have been developed take into consideration physiologic abnormalities (hypotension–hypertension, acidosis, hypoxia, hypercapnia, anemia, neutropenia), as in the **Score for Neonatal Acute Physiology,** or clinical parameters (gestational age, birthweight, anomalies, acidosis, FIO_2), as in the **Clinical Risk Index for Babies.** The Clinical Risk Index for Babies includes 6 parameters collected in the 1st 12 hr after birth, and the Score for Neonatal Acute Physiology has 26 variables collected in the 1st 24 hr. Prediction models can be used before birth, but additional data from throughout the hospitalization improve the identification of infants at high risk for death or neurodevelopmental impairment. Combining a physician's judgment and an objective score may produce a more accurate assessment of the risk of death.

DISCHARGE FROM THE HOSPITAL

Before discharge, a premature infant should be taking all nutrition by nipple, either bottle or breast (Table 97-9). Some medically fragile infants may be discharged home while receiving gavage feedings after the parents have received appropriate training and education. Growth should be occurring at steady increments of approximately 30 g/day. Temperature should be stabile in an open crib. Infants should have had no recent episodes of apnea or bradycardia, and parenteral drug administration should have been discontinued or converted to oral dosing. Stable infants recovering from bronchopulmonary dysplasia may be discharged on a regimen of oxygen given by nasal cannula as long as careful follow-up is arranged with frequent pulse oximetry monitoring and outpatient visits. All infants with birthweight <1,500 g and those with birthweights between 1,500 and 2,000 g with an unstable clinical course requiring oxygen should undergo an eye examination to screen for retinopathy of prematurity. All infants should have a hearing test prior to discharge. In those who had indwelling umbilical arterial catheters, blood pressure should be measured to check for renal vascular hypertension. The hemoglobin level or hematocrit should be determined to evaluate for possible anemia. If all major medical problems have resolved and the home setting is adequate, premature infants may then be discharged when their weight approaches 1,800-2,100 g; close follow-up plus easy access to healthcare providers is essential for early discharge protocols. Alternatively, if the medical or social environment is not ideal, high-risk neonates who have been transported to neonatal intensive care units and whose major illnesses have resolved may be returned to their hospital of birth for an additional period of hospitalization. Standard vaccinations with full doses should commence after discharge or, if infants are still in the hospital, with vaccines that do not contain live viruses. For respiratory syncytial virus prophylaxis, see Chapter 260.

Table 97-9	Readiness for Discharge of High-Risk Infants Criteria

Resolution of acute life-threatening illnesses
Ongoing follow-up for chronic but stable problems:
Bronchopulmonary dysplasia
Intraventricular hemorrhage
Necrotizing enterocolitis after surgery or recovery
Ventricular septal defect, other cardiac lesions
Anemia
Retinopathy of prematurity
Hearing problems
Apnea
Cholestasis
Stable temperature regulation
Gain of weight with oral feedings:
Breastfeeding
Bottle-feeding
Gastric tube
Free of significant apnea; home monitoring for apnea if needed
Appropriate immunizations and planning for respiratory syncytial virus prophylaxis if indicated
Hearing screenings
Ophthalmologic examination if <27 wk of gestation or <1,250 g at birth
Mother's knowledge, skill, confidence documented in:
  Administration of medications (diuretics, methylxanthines, aerosols, etc.)
  Use of oxygen, apnea monitors, oximeters
Nutritional support:
  Timing
  Volume
  Mixing concentrated formulas
Recognition of illness and deterioration
Basic cardiopulmonary resuscitation
Infant safety (see Table 97-1)
Scheduling of referrals:
Primary care provider
Neonatal follow-up clinic
Occupational therapy/physical therapy
Imaging (head ultrasound)
Assessment of and solution to social risks (see Table 97-1)

Adapted from American Academy of Pediatrics, American College of Obstetricians: Guidelines for perinatal care, *ed 7, Elk Grove Village, IL, 2013, American Academy of Pediatrics.*

HOME CARE

While the infant is in the hospital, the mother should receive instruction on how to care for the baby after discharge and should be allowed to provide infant care in the hospital. Ideally, a home care program should include at least 1 home visit by someone capable of evaluating domestic arrangements and advising about any needed improvements. Early developmental intervention programs focused on parent-infant relationship and/or infant development after discharge improve cognitive development in the short to medium term (up to preschool) but do not improve motor outcomes. However these benefits are not sustained at school age.

Bibliography is available at Expert Consult.

97.3 Postterm Infants

Waldemar A. Carlo

Postterm infants are those born after 42 completed weeks of gestation, as calculated from the mother's last menstrual period, regardless of weight at birth. Historically, approximately 12% of pregnancies ended after the 294th day. Obstetric interventions often occur earlier, and the rate of postterm births is decreasing. The cause of postterm birth or postmaturity is unknown.

CLINICAL MANIFESTATIONS

Postterm infants have normal length and head circumference but may have decreased weight if there is placental insufficiency. Infants born postterm in association with presumed placental insufficiency may have various physical signs. Desquamation, long nails, abundant hair, pale skin, alert faces, and loose skin, especially around the thighs and buttocks, give them the appearance of having recently lost weight; meconium-stained nails, skin, vernix, umbilical cord, and placental membranes may also be noted (see Fig. 88-1 in Chapter 88). Common complications of postmaturity include perinatal depression, meconium aspiration, persistent pulmonary hypertension, hypoglycemia, hypocalcemia, and polycythemia.

PROGNOSIS

When delivery is delayed 3 wk or more beyond term, mortality is significantly increased and, in some series, has been approximately 3 times that of a control group of infants born at term. Mortality has been lowered markedly through improved obstetric management.

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MANAGEMENT

Careful obstetric monitoring, including nonstress testing, biophysical profile, or Doppler velocimetry, usually provides a rational basis for choosing one of three courses: nonintervention, induction of labor, or cesarean section. Induction of labor or cesarean section may be indicated in older primigravidas more than 2-4 wk beyond term, particularly if evidence of fetal distress is present. Medical problems in the newborn are treated if they arise.

97.4 Large-for-Gestational-Age Infants

Waldemar A. Carlo

See also Chapter 101.1.

Infants with birthweight > the 90th percentile for gestational age are called **large for gestational age** (LGA). Neonatal mortality rates decrease with increasing birthweight until approximately 4,000 g, after which they increase. These oversized infants are usually born at term, but preterm infants with weights high for gestational age also have a significantly higher mortality than infants of the same size born at term; maternal diabetes and obesity are predisposing factors. Some infants are constitutionally large because of large parental size. LGA infants, regardless of their gestational age, have a higher incidence of birth injuries, such as cervical and brachial plexus injuries, phrenic nerve damage with paralysis of the diaphragm, fractured clavicles, cephalohematomas, subdural hematomas, and ecchymoses of the head and face. LGA infants are also at increased risk for hypoglycemia and polycythemia.

The incidence of congenital anomalies, particularly congenital heart disease, is also higher in LGA infants than in term infants of normal weight. Intellectual and developmental retardation is statistically more common in high birthweight term and preterm infants than in babies of appropriate weight for gestational age.

97.5 Infant Transport

Waldemar A. Carlo

With the advent of regionalized care of high-risk neonates, increasing numbers of high-risk mothers and sick infants are transported to hospitals with neonatal intensive care units. Neonatal transport should include consultation about the infant's problem and care before transport, ease of access to the transport team, and transport and stabilization by the team before moving the infant. Securing an airway, providing oxygen, assisting with infant ventilation, providing antimicrobial therapy, maintaining the circulation, providing a warmed environment, and placing intravenous or arterial lines or chest tubes should be initiated, if indicated, before transport. Infant and maternal records and laboratory reports should also be provided. Before departure of an infant, the mother should be briefly reassured and allowed to see her stabilized infant; the father should enter his car and follow the transport vehicle to the unit. The transport officer or nurse should also call ahead to inform the receiving unit about the nature of the patient's illness.

The transport vehicle should be equipped with appropriate medicines, fluids, oxygen tanks, catheters, chest tubes, endotracheal tubes, laryngoscopes, and an infant warming device. It should be well illuminated and have ample room for emergency procedures and monitoring equipment. With efficient transport and appropriately educated nursing and medical staff at the referring hospitals, the mortality of "outborn" neonates should be no higher than that of those born within the tertiary care center.

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Chapter 98

Clinical Manifestations of Diseases in the Newborn Period

Waldemar A. Carlo

The wide varieties of disorders that affect the newborn originate in utero, during birth, or in the immediate postnatal period. These disorders may be caused by prematurity, genetic mutations, chromosomal aberrations, or acquired diseases and injuries. Recognizing disease in newborn infants depends on knowledge of the disorder and evaluation of a limited number of relatively nonspecific clinical signs and symptoms.

Central cyanosis has respiratory, cardiac, central nervous system (CNS), hematologic, and metabolic causes (Table 98-1). Respiratory insufficiency may be a result of pulmonary conditions or may be secondary to CNS depression from drugs, intracranial hemorrhage, or anoxia. If respiratory insufficiency is caused by pulmonary conditions, respirations tend to be rapid and may be accompanied by retraction of the thoracic cage. If it is caused by the CNS depression, respirations tend to be irregular and weak and are often slow. Cyanosis unaccompanied by obvious signs of respiratory difficulty suggests cyanotic congenital heart disease or methemoglobinemia. Cyanosis resulting from congenital heart disease may, however, be difficult to distinguish clinically from cyanosis caused by respiratory disease. Episodes of cyanosis may also be the initial sign of hypoglycemia, bacteremia, meningitis, shock, or pulmonary hypertension. Peripheral acrocyanosis is common in neonates and does not usually warrant concern unless poor perfusion is suspected.

Pallor, in addition to anemia or acute hemorrhage, should suggest hypoxia, asphyxia, hypoglycemia, sepsis, shock, or adrenal failure.

Hypotension in term infants suggests shock from hypovolemia (hemorrhage, dehydration), the systemic inflammatory response syndrome (bacterial sepsis, intrauterine infection, necrotizing enterocolitis), cardiac dysfunction (left heart obstructive lesions—hypoplastic left-heart syndrome, myocarditis, asphyxia-induced myocardial stunning, anomalous coronary artery), pneumothorax, pneumopericardium, pericardial effusion, or metabolic disorders (hypoglycemia, adrenal insufficiency–salt-losing adrenogenital syndrome). Hypotension is a common problem in sick preterm infants and may also be caused by any of the problems noted in a term infant. Hypotension may develop in preterm infants with severe respiratory distress syndrome. Strategies used to support blood pressure include volume expansion (normal saline is equally as effective as 5% albumin), pressors (dopamine, dobutamine, epinephrine, norepinephrine, vasopressin), and corticosteroids. Hypotension in some infants weighing <1,000 g does not respond to fluids or inotropic agents but may respond to therapy with intravenous hydrocortisone. Sudden onset of hypotension in a very-low birthweight infant suggests pneumothorax, intraventricular hemorrhage, or subcapsular hepatic hematoma.

Seizures (see Chapter 593.7) usually point to a disorder of the CNS and suggest hypoxic–ischemic encephalopathy, intracranial hemorrhage, cerebral anomaly, subdural effusion, meningitis, hypocalcemia, hypoglycemia, cerebral infarction, benign familial seizures, or, rarely, pyridoxine dependence, hyponatremia, hypernatremia, inborn errors of metabolism, or drug withdrawal. Seizures beginning in the delivery room or shortly thereafter may be the result of the unintentional injection of maternal local anesthetic into the fetus. Seizures may also result from hyponatremia and water intoxication in the infant after the administration of large amounts of hypotonic fluid to the mother shortly before and during delivery.

Table 98-1 Differential Diagnosis of Cyanosis in the Newborn
CENTRAL OR PERIPHERAL NERVOUS SYSTEM HYPOVENTILATION
Birth asphyxia
Intracranial hypertension, hemorrhage
Oversedation (direct or through maternal route)
Diaphragm palsy
Neuromuscular diseases
Seizures
RESPIRATORY DISEASE
Airway
Choanal atresia/stenosis
Pierre Robin syndrome
Intrinsic airway obstruction (laryngeal/bronchial/tracheal stenosis)
Extrinsic airway obstruction (bronchogenic cyst, duplication cyst, vascular compression)
Lung
Respiratory distress syndrome
Transient tachypnea
Meconium aspiration
Pneumonia (sepsis)
Pneumothorax
Congenital diaphragmatic hernia
Pulmonary hypoplasia
CARDIAC RIGHT-TO-LEFT SHUNT
Abnormal connections (pulmonary blood flow normal or increased)
Transposition of great vessels
Total anomalous pulmonary venous return
Truncus arteriosus
Hypoplastic left heart syndrome
Single ventricle or tricuspid atresia with large ventricular septal defect but without pulmonic stenosis
Obstructed pulmonary blood flow (pulmonary blood flow decreased)
Pulmonic atresia with intact ventricular septum
Tetralogy of Fallot
Critical pulmonic stenosis with patent foramen ovale or atrial septal defect
Tricuspid atresia
Single ventricle with pulmonic stenosis
Ebstein malformation of the tricuspid valve
Persistent fetal circulation (persistent pulmonary hypertension of newborn)
METHEMOGLOBINEMIA
Congenital (hemoglobin M, methemoglobin reductase deficiency)
Acquired (nitrates, nitrites)
Inadequate ambient O_2 or less O_2 delivered than expected (rare)
Disconnection of O_2 supply to nasal cannula, head hood
Connection of air, rather than O_2, to a mechanical ventilator
SPURIOUS/ARTIFACTUAL
Oximeter artifact (poor contact between probe and skin, poor pulse searching)
Arterial blood gas artifact (contamination with venous blood)
OTHER
Hypoglycemia
Adrenogenital syndrome
Polycythemia
BLOOD LOSS

From Smith F: Cyanosis. In Kliegman RM: Practical strategies in pediatric diagnosis and therapy, *Philadelphia, 1996, WB Saunders.*

Seizures should be distinguished from the jitteriness that may be present in normal newborns, in infants of diabetic mothers, in those who experienced birth asphyxia or drug withdrawal, and in polycythemic neonates. An examiner may stop the jitteriness resembling simple tremors by holding the infant's extremity; this jitteriness often depends on sensory stimuli and occurs when the infant is active, and it is not associated with abnormal eye movements. Tremors are often more rapid with a smaller amplitude than those of tonic-clonic seizures. Seizures in premature infants are often subtle and associated with abnormal eye (fluttering, deviation, stare) or facial (chewing, tongue thrusting) movements; the motor component is often that of tonic extension of the limbs, neck, and trunk. Term infants may have focal or multifocal, clonic or myoclonic movements, but they may also have more subtle seizure activity. Apnea may be the first manifestation of seizure activity, particularly in a premature infant. Seizures may adversely affect the subsequent neurodevelopmental outcome and may even predispose an infant to nonneonatal seizures. Seizures should be treated aggressively.

After severe birth asphyxia, infants may have **motor automatisms** characterized by oral-buccal-lingual movements, rotary limb activities (rowing, pedaling, swimming), tonic posturing, or myoclonus. These motor activities are not usually accompanied by time-synchronized electroencephalographic discharges, may not signify cortical epileptic activity, respond poorly to anticonvulsant therapy, and are associated with a poor prognosis. Such automatisms may represent cortical depression that produces a brainstem release phenomenon or subcortical seizures.

Lethargy may be a manifestation of infection, asphyxia, hypoglycemia, hypercapnia, sedation from maternal analgesia or anesthesia, a cerebral defect, or, indeed, almost any severe disease, including an inborn error of metabolism. Lethargy appearing after the 2nd day should, in particular, suggest infection. Lethargy with emesis suggests increased intracranial pressure or an inborn error of metabolism.

Irritability may be a sign of discomfort accompanying intraabdominal conditions, meningeal irritation, drug withdrawal, infections, congenital glaucoma, or any condition producing pain. As in later infancy, the eardrums should always be examined as a possible source of pain. Hyperactivity, especially in a premature infant, may be a sign of hypoxia, pneumothorax, emphysema, hypoglycemia, hypocalcemia, CNS damage, drug withdrawal, neonatal thyrotoxicosis, bronchospasm, esophageal reflux, or discomfort from a cold environment.

Failure to feed well is seen in most sick newborn infants and should lead a careful search for infection, a central or peripheral nervous system disorder, intestinal obstruction, and other abnormal conditions.

Fever may be the result of too high an environmental temperature because of weather, overheated nurseries or incubators/radiant warmers, or too many clothes. It is also noted in "dehydration fever" of newborn infants. If these causes of fever can be eliminated, serious infection (pneumonia, bacteremia, meningitis, and viral infections, particularly herpes simplex or enteroviruses) must be considered, although such infections often occur without provoking a febrile response in newborn infants (see Chapters 176 and 177). Unexplained **hypothermia** may accompany infection or other serious disturbances of the circulation or CNS. A sudden servocontrolled increase in incubator ambient temperature to maintain body temperature is a sign of temperature instability and may be associated with sepsis or any of the conditions already mentioned.

Periods of **apnea**, particularly in premature infants, may be associated with various disturbances (see Chapter 101.2). When apnea recurs, or when the intervals are longer than 20 sec, or are associated with cyanosis or bradycardia, an immediate diagnostic evaluation is needed.

Jaundice during the 1st 24 hr of life warrants diagnostic evaluation and should be considered to be due to hemolysis until proven otherwise. Septicemia and intrauterine infections, such as syphilis, cytomegalovirus, and toxoplasmosis, should also be considered, especially in infants with an increase in direct bilirubin value.

Jaundice after the 1st 24 hr may be "physiologic" or may be caused by septicemia, hemolytic anemia, galactosemia, hepatitis, congenital atresia of the bile ducts, inspissated bile syndrome after erythroblastosis fetalis, syphilis, herpes simplex, other congenital infections, or other conditions (see Chapter 102.3).

Vomiting during the 1st day of life suggests obstruction in the upper digestive tract or increased intracranial pressure. Roentgenographic studies are indicated when obstruction is suspected. Vomiting may also be a nonspecific symptom of an illness such as septicemia. It is a common manifestation of overfeeding, inexperienced feeding technique, or normal reflux and is rarely caused by pyloric stenosis, milk allergy, duodenal ulcer, stress ulcer, an inborn error of metabolism

Table 98-2 Pain in the Neonate: General Considerations

- Pain in newborns is often unrecognized and/or undertreated.
- If a procedure is painful in adults, it should be considered painful in newborns.
- Healthcare institutions should develop and implement patient care policies to assess, prevent, and manage pain in neonates.
- Pharmacologic agents with known pharmacokinetic and pharmacodynamic properties and demonstrated efficacy in neonates should be used. Agents known to compromise cardiorespiratory function should be administered only by persons experienced in neonatal airway management and in settings with the capacity for continuous monitoring.
- Educational programs to increase the skills of healthcare professionals in the assessment and management of stress and pain in neonates should be provided.
- Further research is needed to develop and validate neonatal pain assessment tools that are useful in the clinical setting; to determine optimal behavioral and pharmacologic interventions; and to study long-term effects of pain and pain management.

Adapted from Prevention and management of pain and stress in the neonate: American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee, Pediatrics *105:454–461, 2000; and Anand KJS; International Evidence-Based Group for Neonatal Pain: Consensus statement for the prevention and management of pain in the newborn,* Arch Pediatr Adolesc Med *155:173–180, 2001.*

Table 98-3 Common Life-Threatening Congenital Anomalies

NAME	MANIFESTATIONS
Choanal atresia	Respiratory distress in delivery room, nasogastric tube cannot be passed through nares Suspect CHARGE (coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies) syndrome
Pierre Robin syndrome Stickler syndrome	Micrognathia, cleft palate, airway obstruction
Diaphragmatic hernia	Scaphoid abdomen, bowel sounds present in chest, respiratory distress
Tracheoesophageal fistula	Polyhydramnios, aspiration pneumonia, excessive salivation, nasogastric tube cannot be placed in stomach Suspect VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia) syndrome
Intestinal obstruction: volvulus, duodenal atresia, ileal atresia	Polyhydramnios, bile-stained emesis, abdominal distention Suspect trisomy 21, cystic fibrosis, cocaine
Gastroschisis, omphalocele	Polyhydramnios, intestinal obstruction
Renal agenesis, Potter syndrome	Oligohydramnios, anuria, pulmonary hypoplasia, pneumothorax
Neural tube defects: anencephalus, meningomyelocele	Polyhydramnios, elevated α-fetoprotein, decreased fetal activity
Ductus-dependent congenital heart disease	Cyanosis, hypotension, murmur

(hyperammonemia, metabolic acidosis), or adrenal insufficiency. Vomitus containing dark blood is usually a sign of a serious illness; the benign possibility of swallowed maternal blood should also be considered. Bile-stained vomitus strongly suggests obstruction below the ampulla of Vater and warrants contrast-enhanced radiography in many cases.

Diarrhea may be a symptom of overfeeding (especially high–caloric density formula), acute gastroenteritis, or malabsorption, or it may be a nonspecific symptom of infection. Diarrhea may occur in conditions accompanied by compromised circulation of part of the intestinal or genital tract, such as mesenteric thrombosis, necrotizing enterocolitis, strangulated hernia, intussusception, and torsion of the ovary or testis.

Abdominal distention, usually a sign of intestinal obstruction or an intraabdominal mass, may also be seen in infants with enteritis, necrotizing enterocolitis, isolated intestinal perforation, ileus accompanying sepsis, respiratory distress, ascites, or hypokalemia.

Failure to move an extremity **(pseudoparalysis)** suggests fracture, dislocation, or nerve injury. It is also seen in osteomyelitis and other infections that cause pain on movement of the affected part.

Pain in neonates may be unrecognized and/or undertreated. The intensive care of neonates may involve a number of painful procedures, including blood sampling (heelstick, venous or arterial puncture), endotracheal intubation and suctioning, mechanical ventilation, and insertion of chest tubes and intravascular catheters. Pain in neonates results in obvious distress and acute physiologic stress responses, which may have developmental implications for pain in later life. Moreover, the knowledge that infants may experience pain contributes to the stress of parents of sick newborns.

Pain and discomfort are potentially avoidable problems during the treatment of sick infants. Preemptive relief from painful stimuli should be provided before pain or anxiety develops. The most frequently used drugs are intermittent or continuous doses of opioids (morphine, fentanyl) and benzodiazepines (midazolam, lorazepam). Although the long-term effects of opioids and sedatives are not well established, the first concern should be the treatment and/or prevention of acute pain. Continuous opiate infusions should be used with caution. Some minor but painful procedures performed in well neonates can be managed with oral sucrose solutions (Table 98-2).

CONGENITAL ANOMALIES

Congenital anomalies are a major cause of stillbirths and neonatal deaths. In the United States and other developed countries, congenital anomalies are one of the main causes of neonatal mortality. In addition, congenital anomalies are a major cause of acute illness and long-term morbidity. Anomalies are discussed in general in Chapters 81 and 108, and specifically in the chapters on the various systems of the body. Early recognition of anomalies is important for planning care; with some, such as congenital heart disease, tracheoesophageal fistula, diaphragmatic hernia, choanal atresia, and intestinal obstruction, immediate medical and/or surgical therapy is essential for survival (Table 98-3). Parents are likely to feel anxious and guilty upon learning of the existence of a congenital anomaly and require sensitive counseling.

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Chapter 99

Nervous System Disorders

Waldemar A. Carlo and Namasivayam Ambalavanan

Central nervous system (CNS) disorders are important causes of neonatal mortality and both short- and long-term morbidity. The CNS can be damaged as a result of asphyxia, hemorrhage, trauma, hypoglycemia, or direct cytotoxicity. The etiology of CNS damage is often multifactorial and includes perinatal complications, postnatal hemodynamic instability, and developmental abnormalities that may be genetic and/or environmental. Predisposing factors for brain injury include chronic and acute maternal illness resulting in uteroplacental dysfunction, intrauterine infection, macrosomia/dystocia, malpresentation, prematurity, and intrauterine growth restriction. Acute and often unavoidable emergencies during the delivery process sometimes result in mechanical and/or hypoxic–ischemic brain injury.

99.1 The Cranium

Waldemar A. Carlo and Namasivayam Ambalavanan

Erythema, abrasions, ecchymoses, and subcutaneous fat necrosis of facial or scalp soft tissues may be noted after a normal delivery or after forceps or vacuum-assisted deliveries. Their location depends on the area of contact with the pelvic bones or of application of the forceps. Traumatic hemorrhage may involve any layer of the scalp as well as intracranial contents (Fig. 99-1).

Caput succedaneum is a diffuse, sometimes ecchymotic, edematous swelling of the soft tissues of the scalp involving the area presenting during vertex delivery (see Fig. 99-1). It may extend across the midline and across suture lines. The edema disappears within the 1st few days of life. Molding of the head and overriding of the parietal bones are frequently associated with caput succedaneum and become more evident after the caput has receded; they disappear during the 1st few wk of life. Rarely, a hemorrhagic caput may result in shock and require blood transfusion. Analogous swelling, discoloration, and distortion of the face are seen in face presentations. No specific treatment is needed, but if extensive ecchymoses are present, hyperbilirubinemia may develop.

Cephalohematoma (Fig. 99-2) is a subperiosteal hemorrhage, hence always limited to the surface of 1 cranial bone. Cephalohematomas occur in 1-2% of live births. No discoloration of the overlying scalp occurs, and swelling is not usually visible for several hours after birth because subperiosteal bleeding is a slow process. The lesion becomes a firm tense mass with a palpable rim localized over 1 area of the skull. Most cephalohematomas are resorbed within 2 wk-3 mo, depending on their size. They may begin to calcify by the end of the 2nd wk. A few remain for years as bony protuberances and are detectable on radiographs as widening of the diploic space; cystlike defects may persist for months or years. An underlying skull fracture, usually linear and not depressed, may be associated with 10-25% of cases. A sensation of central depression suggesting but not indicative of an underlying fracture or bony defect is usually encountered on palpation of the organized rim of a cephalohematoma. Cephalohematomas require no treatment, although phototherapy may be necessary to treat hyperbilirubinemia. Infection of the hematoma is a very rare complication.

A **subgaleal hemorrhage** is a collection of blood beneath the aponeurosis that covers the scalp and serves as the insertion for the occipitofrontalis muscle. Bleeding can be very extensive into this large potential space and may even dissect into the subcutaneous tissues of the neck. There is often an association with vacuum-assisted delivery. The mechanism of injury is most likely secondary to rupture of emissary veins connecting the dural sinuses within the skull with the superficial veins of the scalp, sometimes associated with skull fractures, suture diastasis, and fragmentation of the superior margin of the parietal bone. Extensive subgaleal bleeding is occasionally secondary to a hereditary coagulopathy (hemophilia). A subgaleal hemorrhage manifests as a fluctuating mass that straddles cranial sutures or fontanels that increases in size after birth. Some patients have a consumptive coagulopathy owing to massive blood loss. Patients should be monitored for hypotension, anemia, and the development of hyperbilirubinemia. These lesions typically resolve over 2-3 wk.

Fractures of the skull may occur as a result of pressure from forceps or from the maternal symphysis pubis, sacral promontory, or ischial spines. Linear fractures, the most common, cause no symptoms and require no treatment. Depressed fractures are usually indentations of the calvaria similar to the dents in a ping-pong ball; they are generally a complication of forceps delivery or fetal compression. Affected infants may be asymptomatic unless they have associated intracranial injury; it is advisable to elevate severe depressions to prevent cortical injury from sustained pressure. Although some may elevate spontaneously, some require treatment. Percutaneous microscrew elevation is one method successfully used to elevate depressed skull fractures. Fracture of the occipital bone with separation of the basal and squamous portions frequently causes fatal hemorrhage because of disruption of the underlying vascular sinuses. Such fractures may result

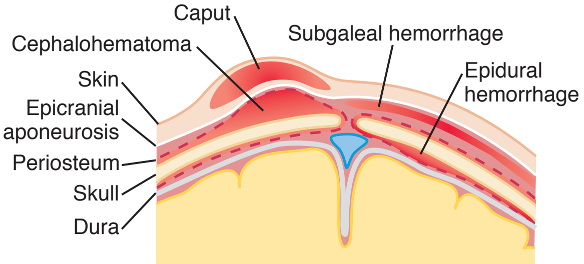

Figure 99-1 Sites of extracranial (and extradural) hemorrhages in the newborn. Schematic diagram of important tissue planes from skin to dura. *(From Volpe JJ:* Neurology of the newborn, *ed 4, Philadelphia, 2001, WB Saunders.)*

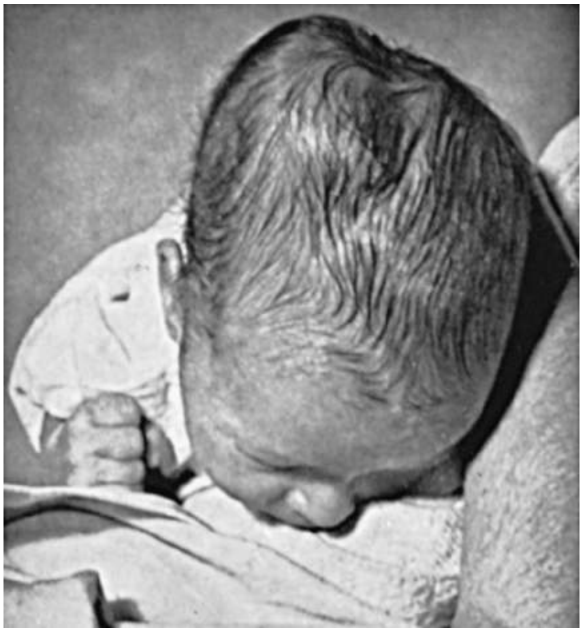

Figure 99-2 Cephalohematoma of the right parietal bone.

during breech deliveries from traction on the hyperextended spine of the infant while the head is fixed in the maternal pelvis.

Subconjunctival and **retinal hemorrhages** are frequent; petechiae of the skin of the head and neck are also common. All are probably secondary to a sudden increase in intrathoracic pressure during passage of the chest through the birth canal. Parents should be assured that these hemorrhages are temporary and the result of normal events of delivery. The lesions resolve rapidly within the 1st 2 wk of life.

99.2 Traumatic, Epidural, Subdural, and Subarachnoid Hemorrhage

Waldemar A. Carlo and Namasivayam Ambalavanan

Traumatic **epidural, subdural, or subarachnoid hemorrhage** is especially likely when the fetal head is large in proportion to the size of the mother's pelvic outlet, with prolonged labor, in breech or precipitous deliveries, or as a result of mechanical assistance with delivery. Asymptomatic subdural hemorrhage may be noted within 48 hr of birth after vaginal or cesarean delivery. Massive **subdural hemorrhage**, often associated with tears in the tentorium cerebelli or, less frequently, in the falx cerebri, is rare but is encountered more often in full-term than in premature infants. Patients with massive hemorrhage caused by tears of the tentorium or falx cerebri rapidly deteriorate and may die soon after birth. The majority of **subdural and epidural hemorrhages** resolve without intervention; consultation with a neurosurgeon is recommended. The diagnosis of subdural hemorrhage may be delayed until the chronic subdural fluid volume expands and produces megalocephaly, frontal bossing, a bulging fontanel, anemia, and, sometimes, seizures. CT scan and MRI are useful imaging techniques to confirm these diagnoses. Symptomatic subdural hemorrhage in large term infants should be treated by removal of the subdural fluid collection with a needle placed through the lateral margin of the anterior fontanel. In addition to birth trauma, **child abuse** must be suspected in all infants with subdural effusion after the immediate neonatal period; asymptomatic subdural hemorrhages following labor should resolve by 4 wk of age.

Subarachnoid hemorrhage is rare and typically is clinically silent. The anastomoses between the penetrating leptomeningeal arteries or the bridging veins are the most likely source of the bleeding. The majority of affected infants have no clinical symptoms, but the subarachnoid hemorrhage may be detected because of an elevated number of red blood cells in a lumbar puncture sample. Some infants experience benign seizures, which tend to occur on the 2nd day of life. Rarely, an infant has a life-threatening catastrophic hemorrhage and dies. There are usually no neurologic abnormalities during the acute episode or on follow-up. Significant neurologic findings should suggest an arteriovenous malformation; this lesion can easily be detected on CT or MRI; ultrasonography is a less-sensitive tool.

99.3 Intracranial–Intraventricular Hemorrhage and Periventricular Leukomalacia

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ETIOLOGY

Intracranial hemorrhage usually develops spontaneously; less commonly, it may be caused by trauma or asphyxia, and rarely, it occurs from a primary hemorrhagic disturbance or congenital vascular anomaly. Intracranial hemorrhage often involves the ventricles (**intraventricular hemorrhage** [IVH]) of premature infants delivered spontaneously without apparent trauma. Primary hemorrhagic disturbances and vascular malformations are rare and usually give rise to subarachnoid or intracerebral hemorrhage. In utero hemorrhage associated with maternal idiopathic or, more often, fetal alloimmune thrombocytopenia may occur as severe cerebral hemorrhage or a porencephalic cyst after resolution of a fetal cortical hemorrhage. Intracranial bleeding may be associated with disseminated intravascular coagulopathy, isoimmune thrombocytopenia, and neonatal vitamin K deficiency, especially in infants born to mothers receiving phenobarbital or phenytoin.

EPIDEMIOLOGY

The overall incidence of IVH has decreased over the past decades as a result of improved perinatal care and increased use of antenatal corticosteroids, surfactant to treat respiratory distress syndrome (RDS), and, possibly, prophylactic indomethacin; however, it continues to be an important cause of morbidity in preterm infants. Approximately 30% of premature infants <1,500 g have IVH. The risk is inversely related to gestational age and birthweight, with the smallest and most immature infants being at the highest risk; 7% of infants weighing 1,001-1,500 g have a severe IVH (grade III or IV), compared with 14% of infants weighing 751-1,000 g and 24% of infants weighing ≤750 g. In 3% of infants weighing <1,000 g, **periventricular leukomalacia (PVL)** develops.

PATHOGENESIS

The major neuropathologic lesions associated with very-low-birthweight (VLBW) infants are IVH and PVL. IVH in premature infants occurs in the gelatinous subependymal germinal matrix. This periventricular area is the site of origin for embryonal neurons and fetal glial cells, which migrate outwardly to the cortex. Immature blood vessels in this highly vascular region of the developing brain combined with poor tissue vascular support predispose premature infants to hemorrhage. The germinal matrix involutes as the infant approaches full-term gestation and the tissue's vascular integrity improves; therefore IVH is much less common in the term infant. **Periventricular hemorrhagic infarction** often develops after a large IVH owing to venous congestion. Predisposing factors for IVH include prematurity, RDS, hypoxic–ischemic or hypotensive injury, reperfusion injury of damaged vessels, increased or decreased cerebral blood flow, reduced vascular integrity, increased venous pressure, pneumothorax, thrombocytopenia, hypervolemia, and hypertension.

Understanding of the pathogenesis of PVL is evolving, and it appears to involve both intrauterine and postnatal events. A complex interaction exists between the development of the cerebral vasculature and the regulation of cerebral blood flow (both of which are gestational age-dependent), disturbances in the oligodendrocyte precursors required for myelination, and maternal/fetal infection and/or inflammation. Similar factors (hypoxia–ischemia), venous obstruction from an IVH, or undetected fetal stress may result in decreased perfusion to the brain, leading, in turn, to periventricular hemorrhage and necrosis. PVL is characterized by focal necrotic lesions in the periventricular white matter and/or more diffuse white matter damage. The risk for PVL increases in infants with severe IVH and/or ventriculomegaly. The corticospinal tracts descend through the periventricular white matter, hence the association between cerebral white matter injury/PVL and motor abnormalities, including cerebral palsy.

CLINICAL MANIFESTATIONS

The majority of patients with IVH, including some with moderate to severe hemorrhages, have no initial clinical signs. Some premature infants in whom severe IVH develops may have acute deterioration on the 2nd or 3rd day of life. Hypotension, apnea, pallor, or cyanosis; poor suck; abnormal eye signs; a high-pitched, shrill cry; convulsions, or decreased muscle tone; metabolic acidosis; shock; and a decreased hematocrit or failure of the hematocrit to increase after transfusion may be the first clinical indications. IVH may rarely manifest at birth; 50% of cases are diagnosed within the 1st day of life, and up to 75% within the 1st 3 days. A small percentage of infants have late hemorrhage, between days 14 and 30. IVH as a primary event is rare after the 1st mo of life.

PVL is usually clinically asymptomatic until the neurologic sequelae of white matter damage become apparent in later infancy as spastic motor deficits. PVL may be present at birth but usually occurs later as

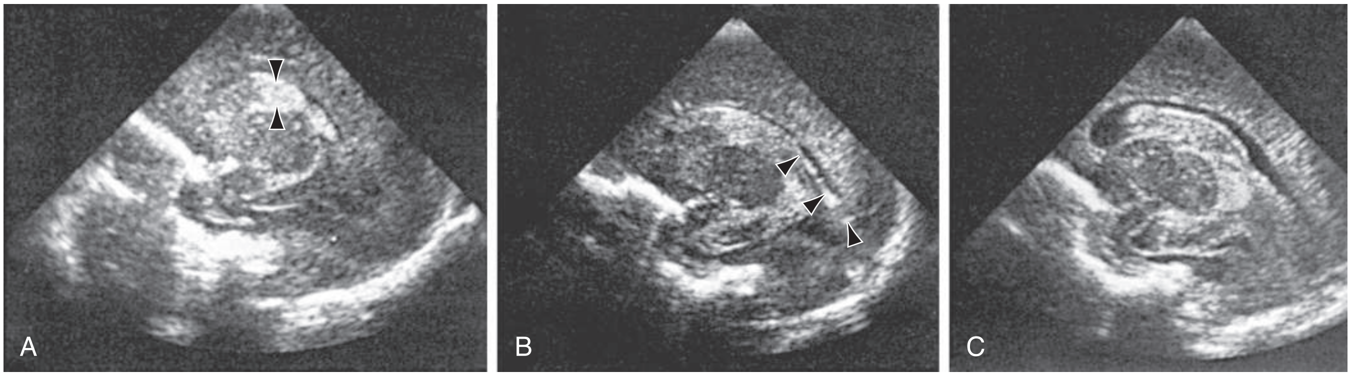

Figure 99-3 Grading the severity of germinal matrix intraventricular hemorrhage with parasagittal ultrasound scans. *A,* Grade I: Note the echogenic blood in the germinal matrix *(arrowheads)* just anterior to the anterior tip of the choroid plexus, which (normally) is also echogenic. *B,* Grade II: Note the echogenic blood *(arrowheads)* filling <50% of the ventricular area. *C,* Grade III: Note the large blood clot nearly completely filling and distending the entire lateral ventricle. *(From Intracranial hemorrhage: germinal matrix-intraventricular hemorrhage of the premature infant. In Volpe JJ:* Neurology of the newborn, *ed 4, Philadelphia, 2001, WB Saunders.)*

an early echodense phase (3-10 days of life), followed by the typical echolucent (cystic) phase (14-20 days of life).

The severity of hemorrhage may be defined on cranial imaging by the location and degree of bleeding and ventricular dilation. In a **grade I** hemorrhage, bleeding is isolated to the subependymal area. In **Grade II** hemorrhage, there is bleeding within the ventricle but without evidence of ventricular dilation. **Grade III** hemorrhage consists of IVH with ventricular dilation. In **Grade IV** hemorrhage, there is intraventricular and parenchymal hemorrhage. Another grading system describes 3 levels of increasing severity of IVH detected on ultrasound: In **grade I,** bleeding is confined to the germinal matrix–subependymal region or to <10% of the ventricle (≈35% of IVH cases); **grade II** is defined as intraventricular bleeding with 10-50% filling of the ventricle (≈40% of IVH cases) and in **grade III**, more than 50% of the ventricle is involved, with dilated ventricles (Fig. 99-3). **Ventriculomegaly** is defined as mild (0.5-1 cm dilation), moderate (1.0-1.5 cm dilation), or severe (>1.5 cm dilation).

DIAGNOSIS

Intracranial hemorrhage is suspected on the basis of the history, clinical manifestations, and knowledge of the birthweight-specific risks for IVH. The associated clinical signs of IVH are typically nonspecific or absent; therefore, it is recommended that premature infants <32 wk of gestation be evaluated with routine real-time cranial ultrasonography through the anterior fontanel to screen for IVH. Infants <1,000 g are at highest risk and should undergo cranial ultrasonography within the 1st 3-7 days of age, when approximately 75% of lesions will be detectable. Ultrasonography is the preferred imaging technique for screening because it is noninvasive, portable, reproducible, and sensitive and specific for detection of IVH. All at-risk infants should undergo follow-up ultrasonography at 36-40 wk of postmenstrual age to evaluate adequately for PVL, because cystic changes related to perinatal injury may not be visible for at least 2-4 wk. In one study, 29% of low-birthweight (LBW) infants who later experienced cerebral palsy did not have radiographic evidence of PVL until after 28 days of age. Ultrasonography also detects the precystic and cystic symmetric lesions of PVL and the asymmetric intraparenchymal echogenic lesions of cortical hemorrhagic infarction. Furthermore, the delayed development of cortical atrophy, porencephaly, and the severity, progression, or regression of posthemorrhagic hydrocephalus can be determined by serial ultrasonographic examinations.

Approximately 3-5% of VLBW infants develop **posthemorrhagic hydrocephalus (PHH)** that sometimes requires ventriculoperitoneal shunt insertion; if the initial ultrasonography findings are abnormal, additional interval ultrasonographic studies are indicated to monitor for the development of hydrocephalus.

IVH represents only 1 facet of brain injury in the term or preterm infant. MRI is a more sensitive tool for evaluation of extensive periventricular injury and may be more predictive of adverse long-term outcome. CT or, more reliably, diffusion-weighted MRI is indicated for term infants in whom brain injury or stroke is suspected, because ultrasonography may not reveal edema or intraparenchymal hemorrhage and infarction.

PROGNOSIS

The degree of IVH and the presence of PVL are strongly linked to neurodevelopmental impairment. For infants with a birthweight of <1,000 g, the incidences of severe neurologic impairment (defined as Bayley Scales of Infant Development II mental developmental index <70, psychomotor development index <70, cerebral palsy, blindness, or deafness) are approximately 50%, 55%, and 70% for infants with grade II, grade III, and grade IV IVH, respectively (Table 99-1). In contrast, the rate of neurodevelopmental impairment is approximately 40% in infants (weighing <1,000 g) without IVH and those with grade I IVH. PVL, cystic PVL, and progressive hydrocephalus requiring shunt insertion are each independently associated with a poorer prognosis.

Most infants with IVH and acute ventricular distention do not have **PHH.** Ten percent to 15% of LBW neonates with IVH demonstrate PHH, which may initially be present without clinical signs, such as an enlarging head circumference, lethargy, a bulging fontanel or widely split sutures, apnea, and bradycardia. In infants in whom symptomatic hydrocephalus develops, clinical signs may be delayed 2-4 wk despite progressive ventricular distention with compression and thinning of the cerebral cortex. Many infants with PHH have spontaneous regression; 3-5% of VLBW infants with PHH require shunt insertion. Infants with PHH requiring shunt insertion have lower cognitive and psychomotor performance at 18-22 mo.

PREVENTION

Improved perinatal care is imperative to minimize traumatic brain injury and decrease the risk of preterm delivery. The incidence of traumatic intracranial hemorrhage may be reduced by judicious management of cephalopelvic disproportion and operative (forceps, vacuum) delivery. Fetal or neonatal hemorrhage caused by maternal idiopathic thrombocytopenic purpura or alloimmune thrombocytopenia may be reduced by maternal treatment with steroids, intravenous immunoglobulin, fetal platelet transfusion, or cesarean section. Meticulous care of the LBW infant's respiratory status and fluid and electrolyte management—including avoidance of acidosis, hypocarbia, hypoxia, hypotension, wide fluctuations in neonatal blood pressure or P_{CO_2}, and pneumothorax—are important factors that may affect the risk for development of IVH and PVL.

A single course of antenatal corticosteroids is recommended in pregnancies 24-34 wk of gestation that are at risk for preterm delivery. Antenatal steroids decrease the risk of death, grades III and IV IVH,

Table 99-1 Percentage of Infants with Each Neurologic Outcome at 18 to 22 Mo Corrected Age by Head Ultrasound Findings*

HEAD ULTRASOUND VARIABLE	NDI (N = 929)	MDI > 70 (N = 174)	PDI < 70 (N = 478	CEREBRAL PALSY (N = 478)	BLINDNESS (N = 66)	DEAFNESS (N = 42)	NONINDEPENDENT WALKING (N = 260)	NONINDEPENDENT FEEDING (N = 318)
Normal (n = 1308)	39.4	31.9	18.8	10.1	1.6	1.5	7.7	12.8
Intracranial hemorrhage:								
Grade 1 (n = 244)	40.6	31.5	18.0	17.2	2.9	1.2	10.7	13.9
Grade 2 (n = 151)	51.0	36.9	22.3	17.2	4.0	3.3	9.3	13.9
Grade 3 (n = 215)	55.4	43.3	36.7	31.3	7.0	2.8	25.1	23.4
Grade 4 (n = 145)	69.7	52.6	55.5	51.4	11.2	4.9	42.4	28.5
Periventricular leukomalacia (n = 134)	72.4	60.3	52.8	50.0	10.5	3.7	44.0	29.1
Cystic periventricular leukomalacia (n = 50)	76.0	60.4	64.6	64.0	18.0	6.3	50.0	32.0

*All infants were counted only once and were assigned the highest grade of intracranial hemorrhage/leukomalacia from either head ultrasound scan. Missing values in either the row or column variable were excluded from the analysis.

MDI, Mental Developmental Index; NDI, neurodevelopment impairment; PDI, Psychomotor Developmental Index.

Data from Broitman E, Ambalavanan N, Higgins RD, et al: Clinical data predict neurodevelopmental outcome better than head ultrasound in extremely low birth weight infants, J Pediatr *151:500–505, 2007.*

and PVL in the neonate. The prophylactic administration of low-dose indomethacin (0.1 mg/kg/day for 3 days) to VLBW preterm infants reduces the incidence of severe IVH.

TREATMENT

Although no treatment is available for IVH, it may be associated with other complications that require therapy. Seizures should be treated with anticonvulsant drugs. Anemia and coagulopathy require transfusion with packed red blood cells or fresh-frozen plasma. Shock and acidosis are treated with the judicious and slow administration of sodium bicarbonate and fluid resuscitation.

Insertion of a ventriculoperitoneal shunt is the preferred method to treat progressive and symptomatic PHH; some infants require temporary cerebrospinal fluid diversion before a permanent shunt can be safety inserted. Diuretics and acetazolamide are not effective. Serial lumbar punctures, ventricular taps or reservoirs, and externalized ventricular drains are potential temporizing interventions; they have an associated risk of infection and of "puncture porencephaly" owing to injury to the surrounding parenchyma. A ventriculosubgaleal shunt inserted from the ventricle into a surgically created subgaleal pocket provides a closed system for constant ventricular decompression without these additional risk factors. Decompression is regulated by the pressure gradient between the ventricle and the subgaleal pocket.

Bibliography is available at Expert Consult.

99.4 Brain Injury from Inflammation, Infection, and Medications

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Severe IVH and PVL are the most commonly associated risk factors for adverse outcome in the VLBW infant. Other factors are also involved in the etiology of perinatal brain injury. Cytokines and

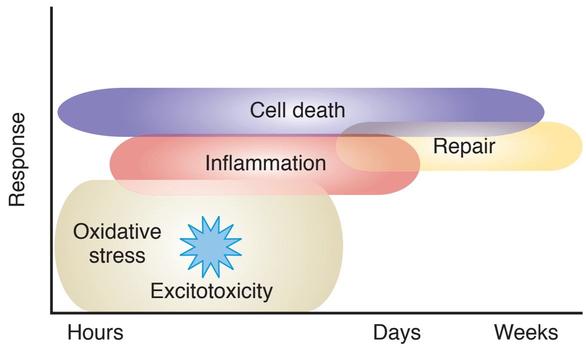

Figure 99-4 **Mechanisms of brain injury in the term neonate.** Oxidative stress and excitotoxicity, through downstream intracellular signaling, produce both inflammation and repair. Cell death begins immediately and continues during a period of days to weeks. The cell-death phenotype changes from an early necrotic morphology to a pathology resembling apoptosis. This evolution is called the necrosis-apoptosis continuum. *(From Ferriero DM: Neonatal brain injury,* N Engl J Med *351:1985–1995, 2004.Copyright © 2004 Massachusetts Medical Society. All rights reserved.)*

prenatal or postnatal infection or inflammation may contribute to brain injury. A systemic inflammatory response syndrome in the mother, fetus, or infant may induce the production of various inflammatory mediators that are directly cytotoxic or cause decreased CNS perfusion (Fig. 99-4). Preterm infants with evidence (often subclinical) of intrauterine or postnatal infection or maternal chorioamnionitis are more likely than uninfected infants to have adverse neurodevelopmental outcome including cerebral palsy.

In utero infections may involve the developing CNS and directly impair cell growth or produce cell neurosis, resulting in microcephaly, developmental delay, mental retardation, or cerebral palsy. These specific congenital or perinatal acquired infections include those caused by cytomegalovirus (see Chapter 255), toxoplasmosis (see Chapter

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290), herpes simplex (see Chapter 252), syphilis (see Chapter 218), rubella (see Chapter 247), and human immunodeficiency virus (see Chapter 276). Postnatal acquired bacterial meningitis in the 1st yr, but even more so in the 1st mo of life, is another major risk factor for CNS injury and associated adverse neurodevelopmental outcome (see Chapter 603).

Long-term adverse neurodevelopmental outcomes are also associated with high-dose postnatal corticosteroid use in VLBW infants. Early postnatal exposure to dexamethasone, within the 1st wk of life, is associated with metabolic derangements, poor growth, increased risk for sepsis, and an increased risk of spontaneous bowel perforation. Infants exposed to postnatal steroids after the 1st wk of life have an increased risk of cerebral palsy and developmental delay. The risk may be increased with prolonged steroid use (>6 wk). At 8 yr of age, dexamethasone-treated children are smaller, have smaller head circumferences, poorer motor skills and coordination, more difficulty with visual motor integration, and lower full-scale verbal IQ and performance IQ scores. It is recommended that postnatal corticosteroid use in VLBW infants be limited to exceptional clinical circumstances and that parents of infants in whom corticosteroids are used be informed of the potential adverse side effects, including increased risk for developmental delay, cerebral palsy, and impaired growth.

Necrotizing enterocolitis (NEC) affects approximately 9-14% of LBW infants and is associated with significant morbidity and mortality (see Chapter 102.2). Patients with NEC requiring surgery are more likely to have Mental Developmental Index (MDI) scores <70, Psychomotor Developmental Index (PDI) scores <70, and evidence of overall neurodevelopmental impairment. Infants with severe NEC are reported to have a higher incidence of PVL, postnatal infections, and poor growth.

Bibliography is available at Expert Consult.

99.5 Hypoxic–Ischemic Encephalopathy

Namasivayam Ambalavanan and Waldemar A. Carlo

Anoxia is a term used to indicate the consequences of complete lack of oxygen as a result of a number of primary causes. **Hypoxemia** refers to decreased arterial concentration of oxygen. **Hypoxia** refers to a decreased oxygenation to cells or organs. **Ischemia** refers to blood flow to cells or organs that is insufficient to maintain their normal function. **Hypoxic–ischemic encephalopathy (HIE)** is an important cause of permanent damage to CNS tissues that may result in neonatal death or manifest later as cerebral palsy or developmental delay. Approximately 20-30% of infants with HIE die in the neonatal period, and ≈33-50% of survivors are left with permanent neurodevelopmental abnormalities (cerebral palsy, mental retardation). The greatest risk of adverse outcome is seen in infants with severe fetal acidosis (pH <6.7) (90% death/impairment) and a base deficit >25 mmol/L (72% mortality). Multiorgan failure and insult can occur (Table 99-2).

Table 99-2 Multiorgan Systemic Effects of Asphyxia

SYSTEM	EFFECT(S)
CNS	HIE, infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia, hypertonia
Cardiovascular	Myocardial ischemia, poor contractility, cardiac stunning, tricuspid insufficiency, hypotension
Pulmonary	Pulmonary hypertension, pulmonary hemorrhage, RDS
Renal	Acute tubular or cortical necrosis
Adrenal	Adrenal hemorrhage
Gastrointestinal	Perforation, ulceration with hemorrhage, necrosis
Metabolic	Inappropriate secretion of antidiuretic hormone, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria
Integument	Subcutaneous fat necrosis
Hematology	Disseminated intravascular coagulation

ETIOLOGY

Most neonatal encephalopathic or seizure disorders, in the absence of major congenital malformations or syndromes, appear to be caused by perinatal events. Brain MRI or autopsy findings in full-term neonates with encephalopathy demonstrate that 80% have acute injuries, <1% have prenatal injuries, and 3% have non–hypoxic-ischemic diagnoses. Fetal hypoxia may be caused by various disorders in the mother, including (1) inadequate oxygenation of maternal blood from hypoventilation during anesthesia, cyanotic heart disease, respiratory failure, or carbon monoxide poisoning; (2) low maternal blood pressure from acute blood loss, spinal anesthesia, or compression of the vena cava and aorta by the gravid uterus; (3) inadequate relaxation of the uterus to permit placental filling as a result of uterine tetany caused by the administration of excessive oxytocin; (4) premature separation of the placenta; (5) impedance to the circulation of blood through the umbilical cord as a result of compression or knotting of the cord; and (6) placental insufficiency from toxemia or postmaturity.

Placental insufficiency often remains undetected on clinical assessment. Intrauterine growth restriction may develop in chronically hypoxic fetuses without the traditional signs of fetal distress. Doppler umbilical waveform velocimetry (demonstrating increased fetal vascular resistance) and cordocentesis (demonstrating fetal hypoxia and lactic acidosis) identify a chronically hypoxic infant (see Chapter 96). Uterine contractions may further reduce umbilical oxygenation, depressing the fetal cardiovascular system and CNS and resulting in low Apgar scores and respiratory depression at birth.

After birth, hypoxia may be caused by (1) failure of oxygenation as a result of severe forms of cyanotic congenital heart disease or severe pulmonary disease; (2) severe anemia (severe hemorrhage, hemolytic disease); or (3) shock severe enough to interfere with the transport of oxygen to vital organs from overwhelming sepsis, massive blood loss, and intracranial or adrenal hemorrhage.

PATHOPHYSIOLOGY AND PATHOLOGY

The topography of injury typically correlates with areas of decreased cerebral blood flow. After an episode of hypoxia and ischemia, anaerobic metabolism occurs and generates increased amounts of lactate and inorganic phosphates. Excitatory and toxic amino acids, particularly glutamate, accumulate in the damaged tissue. Increased amounts of intracellular sodium and calcium may result in tissue swelling and cerebral edema. There is also increased production of free radicals and nitric oxide in these tissues. The initial circulatory response of the fetus is increased shunting through the ductus venosus, ductus arteriosus, and foramen ovale, with transient maintenance of perfusion of the brain, heart, and adrenals in preference to the lungs, liver, kidneys, and intestine.

The pathology of hypoxia–ischemia depends on the affected organ and the severity of the injury. Early congestion, fluid leak from increased capillary permeability, and endothelial cell swelling may then lead to signs of coagulation necrosis and cell death. Congestion and petechiae are seen in the pericardium, pleura, thymus, heart, adrenals, and meninges. Prolonged intrauterine hypoxia may result in inadequate perfusion of the periventricular white matter, resulting, in turn, in PVL. Pulmonary arteriole smooth muscle hyperplasia may develop, which predisposes the infant to pulmonary hypertension (see Chapter 101.7). If fetal distress produces gasping, the amniotic fluid contents (meconium, squames, lanugo) may be aspirated into the trachea or lungs.

The combination of chronic fetal hypoxia and acute hypoxic-ischemic injury around the time of birth results in gestational age–specific neuropathology (Table 99-3). Term infants demonstrate neuronal necrosis of the cortex (later, cortical atrophy) and parasagittal

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Table 99-3 Topography of Brain Injury in Term Infants with HIE and Clinical Correlates

AREA OF INJURY	LOCATION OF INJURY	CLINICAL CORRELATE(S)	LONG-TERM SEQUELA(E)
Selective neuronal necrosis	Entire neuraxis, deep cortical area, brainstem and pontosubicular	Stupor or coma Seizures Hypotonia Oculomotor abnormalities Suck/swallow abnormalities	Cognitive delay Cerebral palsy Dystonia Seizure disorder Ataxia Bulbar and pseudobulbar palsy
Parasagittal injury	Cortex and subcortical white matter Parasagittal regions, especially posterior	Proximal limb weakness Upper extremities affected more than lower extremities	Spastic quadriparesis Cognitive delay Visual and auditory processing difficulty
Focal ischemic necrosis	Cortex and subcortical white matter Vascular injury (usually middle cerebral artery distribution)	Unilateral findings Seizures common and typically focal	Hemiparesis Seizures Cognitive delays
Periventricular injury	Injury to motor tracts, especially lower extremity	Bilateral and symmetric weakness in lower extremities More common in preterm infants	Spastic diplegia

Modified from Volpe JJ: Neurology of the newborn, *ed 4, Philadelphia, 2001, WB Saunders.*

ischemic injury. Preterm infants demonstrate PVL (later, spastic diplegia), status marmoratus of the basal ganglia, and IVH. Term more often than preterm infants have focal or multifocal cortical infarcts that manifest clinically as focal seizures and hemiplegia.

CLINICAL MANIFESTATIONS

Intrauterine growth restriction with increased vascular resistance may be the first indication of fetal hypoxia. During labor, the fetal heart rate slows and beat-to-beat variability declines. Continuous heart rate recording may reveal a variable or late deceleration pattern (see Fig. 96-4). Particularly in infants near term, these signs should lead to the administration of high concentrations of oxygen to the mother and consideration of immediate delivery to avoid fetal death and CNS damage.

At delivery, the presence of meconium-stained amniotic fluid indicates that fetal distress may have occurred. At birth, affected infants may be depressed and may fail to breathe spontaneously. During the ensuing hours, they may remain hypotonic or change from a hypotonic to a hypertonic state, or their tone may appear normal (Tables 99-4 and 99-5). Pallor, cyanosis, apnea, a slow heart rate, and unresponsiveness to stimulation are also signs of HIE. Cerebral edema may develop during the next 24 hr and result in profound brainstem depression. During this time, seizure activity may occur; it may be severe and refractory to the usual doses of anticonvulsants. Though most often a result of the HIE, seizures in asphyxiated newborns may also be a result of hypocalcemia, hypoglycemia, or infection.

In addition to CNS dysfunction, systemic organ dysfunction is noted in up to 80% of affected neonates; heart failure and cardiogenic shock, persistent pulmonary hypertension, RDS, gastrointestinal perforation, and acute kidney injury are associated with perinatal asphyxia secondary to inadequate perfusion (see Table 99-2).

The severity of neonatal encephalopathy depends on the duration and timing of injury. Symptoms develop over a series of days, making it important to perform serial neurologic examinations (see Tables 99-4 and 99-5). During the initial hours after an insult, infants have a depressed level of consciousness. Periodic breathing with apnea or bradycardia is present, but cranial nerve functions are often spared with intact pupillary responses and spontaneous eye movement. Seizures are common with extensive injury. Hypotonia is also common as an early manifestation.

DIAGNOSIS

Diffusion-weighted MRI is the preferred imaging modality in neonates with HIE because of its increased sensitivity and specificity early in the process and its ability to outline the topography of the lesion (Figs. 99-5 to 99-8, Table 99-6). CT scans are helpful in identifying focal hemorrhagic lesions, diffuse cortical injury, and damage to the basal ganglia; CT has limited ability to identify cortical injury during the 1st few days of life. Ultrasonography has limited utility in evaluation of hypoxic injury in the term infant; it is the initial preferred modality in evaluation of the preterm infant.

Table 99-4 Predictor Variables, Odds Ratios, and Scores Assigned to Each Variable for Death/Disability Scoring in Infants with HIE

VARIABLE	LEVEL OF VARIABLE	ODDS RATIO	SCORE*
Posture	Normal Distal flexion Decerebrate	0.037 0.401 1	1 11 27
Spontaneous activity	Normal/decreased None	0.147 1	1 7
Base deficit of first postnatal blood gas analysis	<15 mmol/L 15-22 mmol/L >22 mmol/L	0.073 0.304 1	1 4 14
Apgar score at 5 min	7-10 4-6 0-3	0.082 0.676 1	14 8 12
Chronic hypertension/ preeclampsia/eclampsia	Yes No	0.2 1	1 5

*The total score is obtained by adding the scores for each of the variables. Interpretation of the total score is as follows: <23: no death or moderate/severe disability even without hypothermia; 23-28: probable benefit from hypothermia; 29-52: possible benefit; >52: death/disability likely despite hypothermia. =172.

From Ambalavanan, N, Carlo WA, Shankaran S, et al; National Institute of Child Health and Human Development Neonatal Research Network: Predicting outcomes of neonates diagnosed with hypoxemic-ischemic encephalopathy, Pediatrics *118:2084–2093, 2006.*

Amplitude-integrated electroencephalography (aEEG) may help to determine which infants are at highest risk for long-term brain injury. A single-channel tracing is generated from 2 electrodes placed in the biparietal area. A filter is used to filter and attenuate the signal between 2 Hz and 15 Hz. This technique is simple to perform and correlates with standard electroencephalogram (EEG) It has good reliability, a positive predictive value of 85%, and a negative predictive value of 91-96% for infants who will have adverse neurodevelopmental outcome. The technique provides information quickly within the window during which intervention is most likely to be useful. Also, aEEG is able to detect seizure activity, which is common in patients

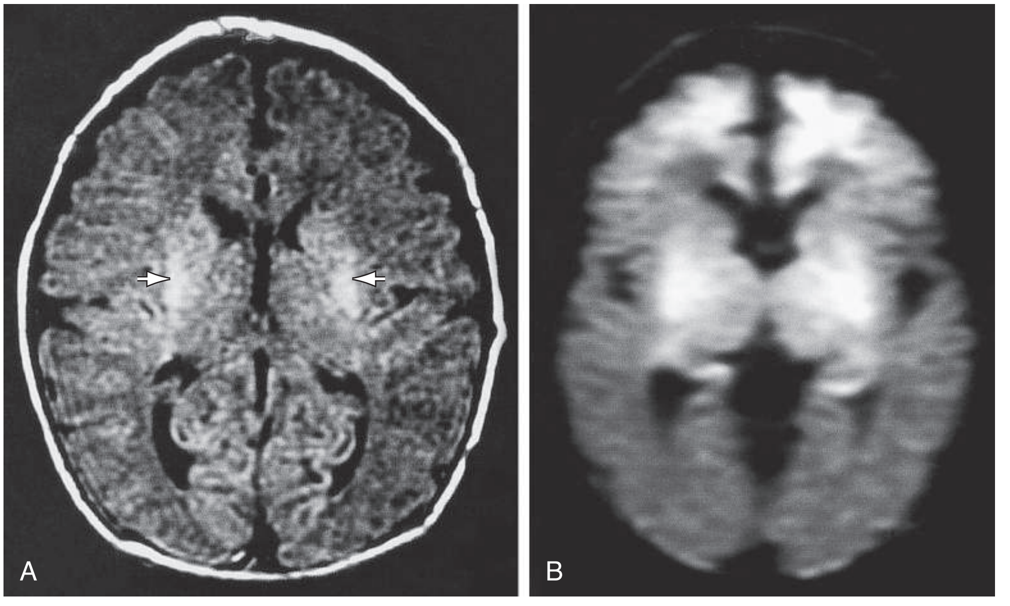

Figure 99-5 **MR images of selective neuronal injury.** The infant experienced intrapartum asphyxia and had seizures on the 1st postnatal day. MRI was performed on the 5th postnatal day. *A,* An axial, fluid-attenuated inversion recovery image shows increased signal in the putamen bilaterally *(arrows)* but no definite abnormality in the cerebral cortex. *B,* By contrast, a diffusion-weighted image shows striking increased signal intensity (i.e., decreased diffusion) in the frontal cortex (in addition to a more pronounced basal ganglia abnormality). *(From Volpe JJ, editor:* Neurology of the newborn, *ed 5, Philadelphia, 2008, Saunders/Elsevier, p. 420.)*

Table 99-5 HIE in Term Infants

SIGNS	STAGE 1	STAGE 2	STAGE 3
Level of consciousness	Hyperalert	Lethargic	Stuporous, coma
Muscle tone	Normal	Hypotonic	Flaccid
Posture	Normal	Flexion	Decerebrate
Tendon reflexes/clonus	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriasis	Miosis	Unequal, poor light reflex
Seizures	None	Common	Decerebration
Electroencephalographic findings	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	<24 hr if progresses; otherwise, may remain normal	24 hr-14 days	Days to weeks
Outcome	Good	Variable	Death, severe deficits

Modified from Sarnat HB, Sarnat MS: Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study, Arch Neurol *33:696–705, 1976. Copyright 1976, American Medical Association.*

with HIE. Continuous aEEG monitoring detects subclinical seizure activity during the subacute phase.

TREATMENT

Whole body (systemic) or selective cerebral therapeutic hypothermia reduces mortality or major neurodevelopmental impairment in term and near-term infants with HIE. Hypothermia decreases the rate of apoptosis and suppresses production of mediators known to be neurotoxic, including extracellular glutamate, free radicals, nitric oxide, and lactate.

Isolated cerebral cooling or more often systemic induced servo controlled hypothermia to a core (rectal) temperature of 33.5°C (92.3°F) within the 1st 6 hr after birth (duration 72 hr) reduces mortality and major neurodevelopmental impairment at 18 mo of age. Systemic hypothermia may result in more uniform cooling of the brain and deeper CNS structures. Infants treated with systemic hypothermia have a lower incidence of cortical neuronal injury on MRI. Complications of induced hypothermia include thrombocytopenia (usually without bleeding), reduced heart rate, and subcutaneous fat necrosis (associated with hypercalcemia in some) and the potential for overcooling and the cold injury syndrome. The latter is avoided with a servocontrolled cooling system. Therapeutic hypothermia may theoretically alter drug metabolism, prolong the QT interval, and effect the interpretation of blood gases. In practice, none of these concerns have been observed during therapeutic hypothermia.

Phenobarbital, the drug of choice for seizures, is given with an intravenous loading dose (20 mg/kg); additional doses of 5-10 mg/kg (up to 40-50 mg/kg total) may be needed. Phenytoin (20 mg/kg

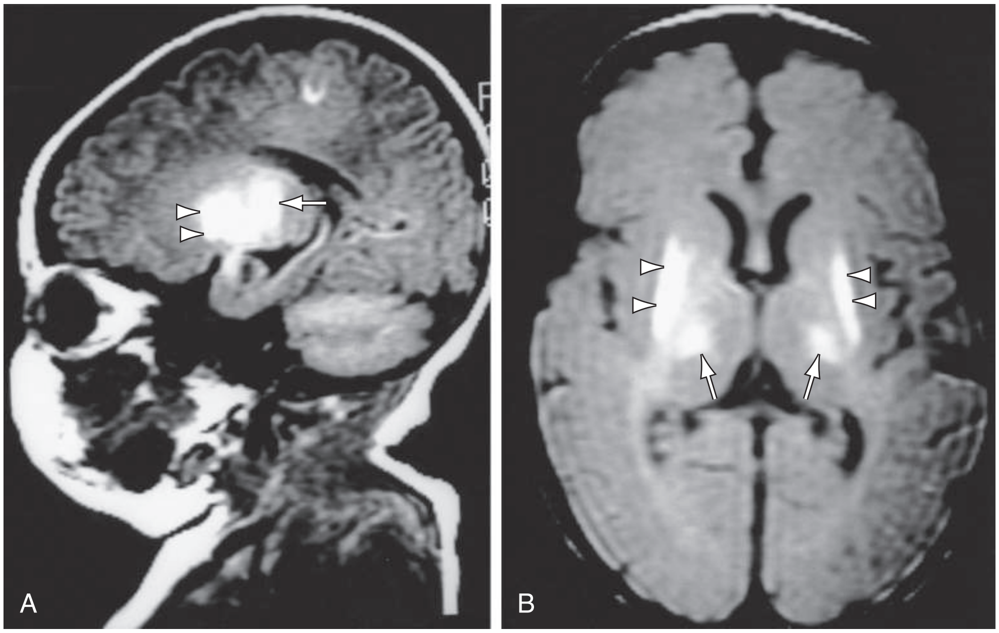

Figure 99-6 **MR images of hypoxic-ischemic injury to basal ganglia and thalamus.** MRI was performed in a 5 day old infant who experienced severe perinatal asphyxia. *A,* Note, in this parasagittal T1-weighted image, the markedly increased signal intensity in the basal ganglia, especially the putamen *(arrowheads)* and the thalamus *(arrow). B,* An axial proton density image also demonstrates the injury well in the same distribution. *(From Volpe JJ, editor:* Neurology of the newborn, *ed 5, Philadelphia, 2008, Saunders/Elsevier, p. 420.)*

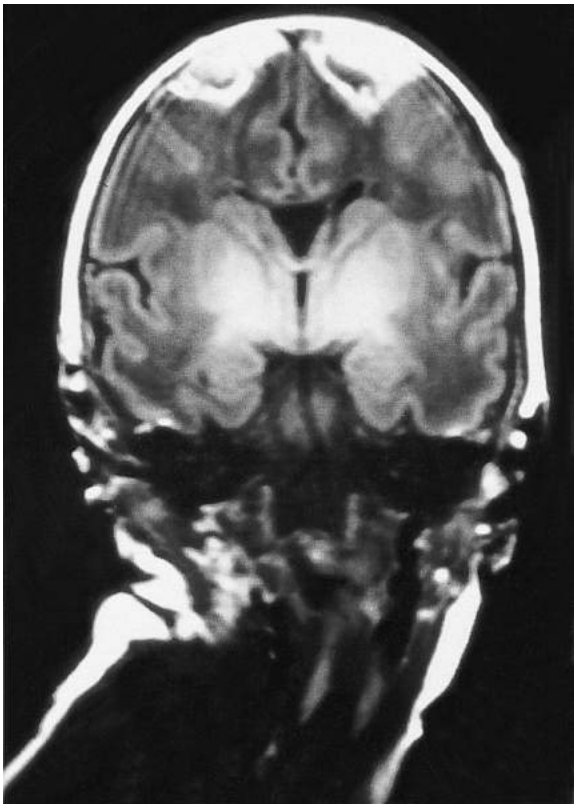

Figure 99-7 **MR image of a parasagittal cerebral injury.** A coronal T1-weighted image, obtained on the 5th postnatal day in an asphyxiated term infant, shows striking triangular lesions in the parasagittal areas bilaterally; increased signal intensity is also apparent in the basal ganglia and thalamus bilaterally. *(From Volpe JJ, editor:* Neurology of the newborn, *ed 5, Philadelphia, 2008, Saunders/Elsevier, p. 421.)*

Table 99-6	Major Aspects of MRI in the Diagnosis of HIE in the Term Infant
Major Conventional MRI Findings in the First Week	
Cerebral cortical gray-white differentiation lost (on T1W or T2W)	
Cerebral cortical high signal (T1W and FLAIR), especially in parasagittal perirolandic cortex	
Basal ganglia–thalamus, high signal (T1W and FLAIR, usually associated with the cerebral cortical changes but possibly alone with increased signal in brainstem tegmentum in cases of acute severe insults	
Parasagittal cerebral cortex, subcortical white matter, high signal (T1W and FLAIR)	
Periventricular white matter, decreased signal (T1W) or increased signal (T2W)	
Posterior limb of internal capsule, decreased signal (T1W or FLAIR)	
Cerebrum in a vascular distribution, decreased signal (T1W), but much better visualized as decreased diffusion (increased signal) on diffusion-weighted MRI	
Diffusion-weighted MRI more sensitive than conventional MRI, especially in 1st days after birth, when former shows decreased diffusion (increased signal) in injured areas	

FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; T1W and T2W, T1- and T2-weighted images.

(From Volpe JJ, editor: Neurology of the newborn, *ed 5, Philadelphia, 2008, Elsevier, Table 9-16, p. 419.)*

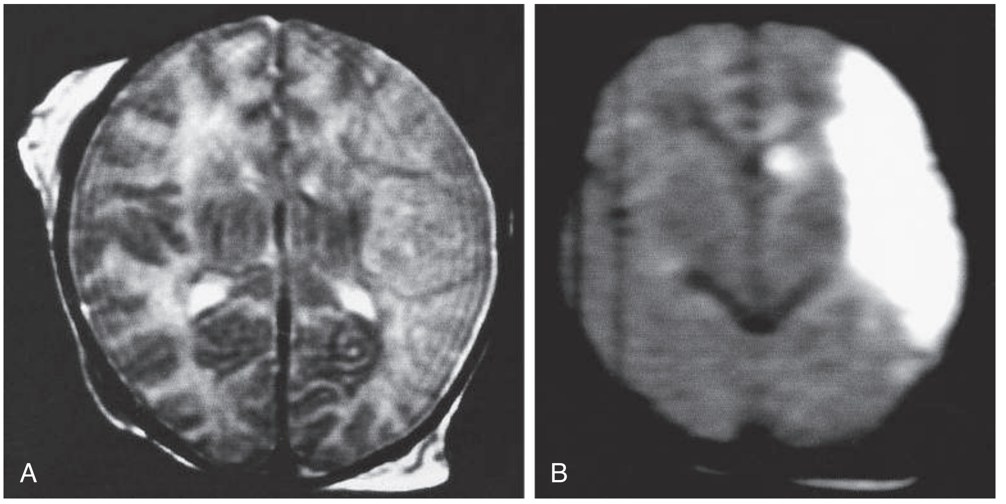

Figure 99-8 MR images of focal ischemic cerebral injury. MRI was performed on the 3rd postnatal day. *A,* An axial T2-weighted image shows a lesion in the distribution of the main branch of the left middle cerebral artery. *B,* A diffusion-weighted image demonstrates the lesion more strikingly. *(From Volpe JJ, editor:* Neurology of the newborn, *ed 5, Philadelphia, 2008, Saunders/Elsevier, p. 422.)*

loading dose) or lorazepam (0.1 mg/kg) may be needed for refractory seizures. Phenobarbital levels should be monitored 24 hr after the loading dose has been given and maintenance therapy (5 mg/kg/24hr) is begun. Therapeutic phenobarbital levels are 20-40 µg/mL. There is some clinical evidence that high-dose prophylactic phenobarbital may decrease neurodevelopmental impairment in infants with HIE. Status epilepticus, multifocal seizures and multiple anticonvulsant medications during therapeutic hypothermia, is associated with a poor prognosis. Subclinical (EEG detected) seizures have a better prognosis.

Additional therapy for infants with HIE includes supportive care directed at management of organ system dysfunction. Hyperthermia has been found to be associated with impaired neurodevelopment, so it is important to prevent hyperthermia before initiation of hypothermia. Careful attention to ventilatory status and adequate oxygenation, blood pressure, hemodynamic status, acid–base balance, and possible infection is important. Secondary hypoxia or hypotension from complications of HIE must be prevented. Aggressive treatment of seizures is critical and may necessitate continuous EEG monitoring. In addition hyperoxia, hypocarbia, and hypoglycemia are associated with poor outcomes so careful attention to resuscitation, ventilation, and blood glucose homeostasis are essential.

PROGNOSIS

The outcome of HIE, which correlates with the timing and severity of the insult, ranges from complete recovery to death. The prognosis varies depending on the severity of the insult and the treatment. Infants with initial cord or initial blood pH <6.7 have a 90% risk for death or severe neurodevelopmental impairment at 18 mo of age. In addition, infants with Apgar scores of 0-3 at 5 min, high base deficit (>20-25 mmol/L), decerebrate posture, severe basal ganglia–thalamic lesions, persistence of severe HIE at 72 hr, and lack of spontaneous activity are also at increased risk for death or impairment. These predictor variables can be combined to determine a score that helps with prognosis (see Table 99-4). Infants with the highest risk are likely to die or have severe disability despite aggressive treatment including hypothermia. Those with intermediate scores are likely to benefit from treatment. In general, severe encephalopathy, characterized by flaccid coma, apnea, absence of oculocephalic reflexes, and refractory seizures, is associated with a poor prognosis (see Table 99-5). A low Apgar score at 20 min, absence of spontaneous respirations at 20 min of age, and persistence of abnormal neurologic signs at 2 wk of age also predict death or severe cognitive and motor deficits. The combined use of early EEG and MRI is of some help in predicting outcome in term infants with HIE. Normal MRI and EEG findings are associated with a good recovery, whereas severe MRI and EEG abnormalities predict a poor outcome. Microcephaly and poor head growth during the 1st year of life also correlate with injury to the basal ganglia and white matter and adverse developmental outcome at 12 mo. All survivors of moderate to severe encephalopathy require comprehensive high-risk medical and developmental follow-up. Early identification of neurodevelopmental problems allows prompt referral for developmental, rehabilitative, neurologic care, and early intervention services so that the best possible outcome can be achieved.

Brain death after neonatal HIE is diagnosed from the clinical findings of coma unresponsive to pain, auditory, or visual stimulation; apnea with P_{CO_2} rising from 40 to >60 mm Hg without ventilatory support; and absence of brainstem reflexes (pupillary, oculocephalic, oculovestibular, corneal, gag, sucking) (see Chapter 68.1). These findings must occur in the absence of hypothermia, hypotension, and elevations of depressant drugs (phenobarbital). An absence of cerebral blood flow on radionuclide scans and of electrical activity on EEG (electrocerebral silence) is inconsistently observed in clinically brain-dead neonatal infants. Persistence of the clinical criteria for 2 days in term infants and 3 days in preterm infants predicts brain death in most asphyxiated newborns. Nonetheless, no universal agreement has been reached regarding the definition of neonatal brain death. Consideration of withdrawal of life support should include discussions with the family, the healthcare team, and, if there is disagreement, an ethics committee. The best interest of the infant involves judgments about the benefits and harm of continuing therapy or avoiding ongoing futile therapy.

Bibliography is available at Expert Consult.

99.6 Spine and Spinal Cord

Waldemar A. Carlo and Namasivayam Ambalavanan

Injury to the spine/spinal cord during birth is rare but can be devastating. Strong traction exerted when the spine is hyperextended or when the direction of pull is lateral, or forceful longitudinal traction on the trunk while the head is still firmly engaged in the pelvis, especially when combined with flexion and torsion of the vertical axis, may produce fracture and separation of the vertebrae. Such injuries are most likely to occur when difficulty is encountered in delivering the shoulders in cephalic presentations and the head in breech presentations. The injury occurs most commonly at the level of the 4th cervical vertebra with cephalic presentations and the lower cervical–upper thoracic vertebrae with breech presentations. Transection of the cord may

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occur with or without vertebral fractures; hemorrhage and edema may produce neurologic signs that are indistinguishable from those of transection except that they may not be permanent. Areflexia, loss of sensation, and complete paralysis of voluntary motion occur below the level of injury, although the persistence of a withdrawal reflex mediated through spinal centers distal to the area of injury is frequently misinterpreted as representing voluntary motion. If the injury is severe, the infant, who from birth may be in poor condition because of respiratory depression, shock, or hypothermia, may deteriorate rapidly to death within several hours before any neurologic signs are obvious. Alternatively, the course may be protracted, with symptoms and signs appearing at birth or later in the 1st wk; immobility, flaccidity, and associated brachial plexus injuries may not be recognized for several days. Constipation may also be present. Some infants survive for prolonged periods, their initial flaccidity, immobility, and areflexia being replaced after several weeks or months by rigid flexion of the extremities, increased muscle tone, and spasms. Apnea on day 1 and poor motor recovery by 3 mo are poor prognostic signs.

The **differential diagnosis** of spine/spinal cord injury includes amyotonia congenita and myelodysplasia associated with spina bifida occulta. Ultrasonography or, more often, MRI confirms the diagnosis. Treatment of the survivors is supportive, including home ventilation; patients often remain permanently disabled. When a fracture or dislocation is causing spinal compression, the prognosis is related to the time elapsed before the compression is relieved.

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99.7 Peripheral Nerve Injuries

Waldemar A. Carlo and Namasivayam Ambalavanan

BRACHIAL PALSY

Brachial plexus injury is a common problem, with an incidence of 0.6-4.6/1,000 live births. Injury to the brachial plexus may cause paralysis of the upper part of the arm with or without paralysis of the forearm or hand or, more commonly, paralysis of the entire arm. These injuries occur in macrosomic infants and when lateral traction is exerted on the head and neck during delivery of the shoulder in a vertex presentation, when the arms are extended over the head in a breech presentation, or when excessive traction is placed on the shoulders. Approximately 45% of brachial plexus injuries are associated with shoulder dystocia. In **Erb-Duchenne paralysis**, the injury is limited to the 5th and 6th cervical nerves. The infant loses the power to abduct the arm from the shoulder, rotate the arm externally, and supinate the forearm. The characteristic position consists of adduction and internal rotation of the arm with pronation of the forearm. Power to extend the forearm is retained, but the biceps reflex is absent; the Moro reflex is absent on the affected side (Fig. 99-9). The outer aspect of the arm may have some sensory impairment. Power in the forearm and hand grasps is preserved unless the lower part of the plexus is also injured; the presence of hand grasp is a favorable prognostic sign. When the injury includes the phrenic nerve, alteration in diaphragmatic excursion may be observed with ultrasonography or fluoroscopy. **Klumpke paralysis** is a rare form of brachial palsy, in which injury to the 7th and 8th cervical nerves and the 1st thoracic nerve produces a paralyzed hand and ipsilateral ptosis and miosis **(Horner syndrome)** if the sympathetic fibers of the 1st thoracic root are also injured. Mild cases may not be detected immediately after birth. Differentiation must be made from cerebral injury; from fracture, dislocation, or epiphyseal separation of the humerus; and from fracture of the clavicle. MRI demonstrates nerve root rupture or avulsion.

Full recovery occurs in most patients; prognosis depends on whether the nerve was merely injured or was lacerated. If the paralysis was a result of edema and hemorrhage about the nerve fibers, function should return within a few months; if it was because of laceration, permanent damage may result. Involvement of the deltoid is usually the most serious problem and may result in shoulder drop secondary to muscle atrophy. In general, paralysis of the upper part of the arm has a better prognosis than paralysis of the lower part.

Figure 99-9 Brachial palsy of the left arm (asymmetric Moro reflex).

Treatment consists of initial conservative management with monthly follow-up and a decision for surgical intervention by 3 mo if function has not improved. Partial immobilization and appropriate positioning are used to prevent the development of contractures. In upper arm paralysis, the arm should be abducted 90 degrees with external rotation at the shoulder, full supination of the forearm, and slight extension at the wrist with the palm turned toward the face. This position may be achieved with a brace or splint during the 1st 1-2 wk. Immobilization should be intermittent throughout the day while the infant is asleep and between feedings. In lower arm or hand paralysis, the wrist should be splinted in a neutral position, and padding placed in the fist. When the entire arm is paralyzed, the same treatment principles should be followed. Gentle massage and range-of-motion exercises may be started by 7-10 days of age. Infants should be closely monitored with active and passive corrective exercises. If the paralysis persists without improvement for 3 mo, neuroplasty, neurolysis, end-to-end anastomosis, and nerve grafting offer hope for partial recovery.

The type of treatment and the prognosis depend on the mechanism of injury and the number of nerve roots involved. The mildest injury to a peripheral nerve (neurapraxia) is due to edema and heals spontaneously within a few weeks. Axonotmesis is more severe and is a consequence of nerve fiber disruption with an intact myelin sheath; function usually returns in a few months. Total disruption of nerves (neurotmesis) or root avulsion is the most severe, especially if it involves C5-T1; microsurgical repair may be indicated. Fortunately, most (75%) injuries are at the root level C5-C6, involve neurapraxia and axonotmesis, and should heal spontaneously. Botulism toxin may be used to treat biceps-triceps co-contractions.

PHRENIC NERVE PARALYSIS

Phrenic nerve injury (3rd, 4th, 5th cervical nerves) with diaphragmatic paralysis must be considered when cyanosis and irregular and labored respirations develop. Such injuries, usually unilateral, are associated with ipsilateral upper brachial palsy. Because breathing is thoracic in type, the abdomen does not bulge with inspiration. Breath

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sounds are diminished on the affected side. The thrust of the diaphragm, which may often be felt just under the costal margin on the normal side, is absent on the affected side. The diagnosis is established by ultrasonographic or fluoroscopic examination, which reveals elevation of the diaphragm on the paralyzed side and seesaw movements of the 2 sides of the diaphragm during respiration.

No specific treatment is available; infants should be placed on the involved side and given oxygen if necessary. Initially, intravenous feedings may be needed; later, progressive gavage or oral feeding may be started, depending on the infant's condition. Pulmonary infections are a serious complication. Recovery usually occurs spontaneously by 1-3 mo; rarely, surgical plication of the diaphragm may be indicated.

FACIAL NERVE PALSY

Facial palsy is usually a peripheral paralysis that results from pressure over the facial nerve in utero, from efforts during labor, or from forceps use during delivery. Rarely, it may result from nuclear agenesis of the facial nerve. Peripheral paralysis is flaccid and, when complete, involves the entire side of the face, including the forehead. When the infant cries, movement occurs only on the nonparalyzed side of the face, and the mouth is drawn to that side. On the affected side the forehead is smooth, the eye cannot be closed, the nasolabial fold is absent, and the corner of the mouth droops. The forehead wrinkles on the affected side with central paralysis because only the lower 2/3 of the face is involved. The infant also usually has other manifestations of intracranial injury, most commonly 6th nerve palsy. The prognosis depends on whether the nerve was injured by pressure or the nerve fibers were torn. Improvement occurs within a few weeks in the former instance. Care of the exposed eye is essential. Neuroplasty may be indicated when the paralysis is persistent. Facial palsy may be confused with absence of the depressor muscles of the mouth, which is a benign problem.

Other peripheral nerves are seldom injured in utero or at birth except when they are involved in fractures or hemorrhage.

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Chapter 100

Delivery Room Emergencies

Waldemar A. Carlo

Most infants complete the transition to extrauterine life without difficulty; however, a small percentage requires resuscitation after birth. The most common delivery room emergency for neonates is secondary to failure to initiate and maintain effective respirations. Less frequent, but of major importance, are shock (see Chapter 98), severe anemia (see Chapter 103.1), plethora (see Chapter 103.3), convulsions (see Chapter 593.7), and management of life-threatening congenital malformations (see Chapter 98). Improved perinatal care and prenatal diagnosis of fetal anomalies allow for appropriate maternal transports for high-risk deliveries.

RESPIRATORY DISTRESS AND FAILURE

Disorders of respiration in newborn infants can be categorized as either central nervous system (CNS) failure, representing depression or failure of the respiratory center, or peripheral respiratory difficulty, indicating interference with the alveolar exchange of oxygen and carbon dioxide. Cyanosis occurs in both groups (see Table 98-1). Respiratory problems encountered in the delivery room are most frequently those of airway obstruction and depression of the CNS (maternal medications, asphyxia) with an absence of adequate respiratory effort. Respiratory distress in the presence of good respiratory effort should lead to an immediate consideration of the underlying cause and is an indication for radiographic examination of the chest.

If respiratory movements are made with the mouth closed but the infant fails to move air in and out of the lungs, bilateral **choanal atresia** (see Chapter 376) or other obstruction of the upper respiratory tract should be suspected. The mouth should be opened, and the mouth and pharynx cleared of secretions with gentle suction. An oropharyngeal airway should be inserted, and the source of the obstruction sought immediately. If effective respiratory flow is not produced by opening the infant's mouth and clearing the airway, laryngoscopy is indicated. With obstructive malformations of the mandible, epiglottis, larynx, or trachea, an endotracheal tube should be inserted; prolonged endotracheal intubation or tracheostomy may be required. Respiratory failure caused by CNS depression or injury may require continuous mechanical ventilation.

Hypoplasia of the mandible (Pierre Robin, Stickler, DiGeorge, and other syndromes; see Chapters 308 and 311) with posterior displacement of the tongue may result in symptoms similar to those of choanal atresia and may be temporarily relieved by pulling the tongue or mandible forward or placing the infant in the prone position. A scaphoid abdomen suggests a **diaphragmatic hernia** or **eventration,** as does asymmetry in contour or movement of the chest or a shift of the apical impulse of the heart; these latter manifestations are also compatible with **tension pneumothorax.** A pneumothorax can be the presenting symptom in infants with pulmonary hypoplasia, renal malformations, or both.

Pulmonary causes of respiratory difficulty are discussed in Chapter 101.

FAILURE TO INITIATE OR SUSTAIN RESPIRATION

Failure to initiate or sustain respiratory effort is common at birth. Infants with **primary apnea** respond to stimulation by establishing normal breathing. Infants with secondary apnea need ventilatory assistance. **Secondary apnea** usually originates in the CNS as a result of asphyxia or peripherally because of neuromuscular disorders. Prematurity alone is seldom a causative factor, except in infants weighing <1,500 g. Intrapulmonary problems, such as respiratory distress syndrome, pulmonary hypoplasia associated with oligohydramnios as in Potter syndrome or neuromuscular diseases, bilateral pleural effusions (hydrops fetalis), pneumothorax, and severe intrauterine pneumonia, may at times result in poor ventilation despite strong respiratory efforts. The lungs in affected infants may be noncompliant, and efforts to begin respirations may be inadequate to initiate sufficient ventilation.

Respiratory depression may occur from administration of morphine, meperidine, fentanyl, barbiturates, or tranquilizers to the mother shortly before delivery or from maternal anesthesia given during the 2nd stage of labor. This sequela may be minimized by the use of appropriate analgesic and anesthetic practices. Treatment includes initial physical stimulation and securing of a patent airway. If effective ventilation is not initiated, artificial breathing with a bag and mask must be instituted. At the same time, if the respiratory depression is caused by an opiate, naloxone hydrochloride (Narcan), 0.1 mg/kg, should be given intravenously or intramuscularly. Naloxone is contraindicated in infants born to mothers with opiate addiction as it may precipitate acute neonatal withdrawal with seizures. If depression is a consequence of other anesthetics or analgesics, artificial respiration should be continued until the infant is able to sustain ventilation. CNS-stimulant drugs should not be used because they are ineffective and may be harmful. External cardiac massage, correction of acidosis, and circulatory support with drugs may be important adjuncts to ventilation in the severely asphyxiated infant.

NEONATAL RESUSCITATION

Although the majority of babies undergo a smooth physiologic transition and breathe effectively after delivery, 5-10% requires active intervention to establish normal cardiorespiratory function. The goals of neonatal resuscitation are to prevent the morbidity and mortality

associated with hypoxic–ischemic tissue (brain, heart, kidney) injury and to reestablish adequate spontaneous respiration and cardiac output. High-risk situations should be anticipated from the history of the pregnancy, labor, and delivery and identification of signs of fetal distress. Infants who are born limp, cyanotic, apneic, or pulseless require immediate resuscitation before assignment of the 1-min Apgar score. Rapid and appropriate resuscitative efforts improve the likelihood of preventing brain damage and achieving a successful outcome.

Guidelines for neonatal resuscitation propose an "integrated" assessment/response approach for the initial evaluation of an infant, consisting of simultaneous assessment of infant color, general appearance, and risk factors. The fundamental principles include evaluation of the airway, establishing effective respiration and adequate circulation; the guidelines also highlight the assessment and response to the neonatal heart rate and the management of infants with meconium-stained amniotic fluid.

Immediately after birth, an infant *in need of resuscitation* should be placed under a radiant heater and dried (to avoid passive hypothermia), positioned with the head down and slightly extended; the airway should be cleared by suctioning, and gentle tactile stimulation provided (slapping the foot, rubbing the back). Simultaneously, the infant's color, heart rate, and respiratory effort should be assessed (Fig. 100-1).

The steps in neonatal resuscitation follow the ABCs: **A,** anticipate and establish a patent airway by suctioning and, if necessary, performing endotracheal intubation; **B,** initiate breathing by using tactile stimulation or positive-pressure ventilation with a bag-and-mask or through an endotracheal tube; **C,** maintain the circulation with chest compression and medications, if needed. Figure 100-1 outlines the steps to follow for immediate neonatal evaluation and resuscitation (see also Chapter 67).

If no respirations are noted, or if the heart rate is <100 beats/min, positive-pressure ventilation is given through a tightly fitted face-bag-and-mask for 15-30 sec. In infants with severe respiratory depression that does not respond to positive-pressure ventilation via bag-and-mask, endotracheal intubation should be performed. Many authorities recommend early intubation for extremely low birthweight preterm infants. Table 100-1 lists guidelines for endotracheal tube size and depth of insertion in infants with different birthweights. If the heart rate does not improve after 30 sec with bag-and-mask (or endotracheal) ventilation and remains below 100 beats/min, ventilation is continued and chest compression should be initiated over the lower third of the sternum at a rate of 90 compressions/min. The ratio of compressions to ventilation is 3:1 (90 compressions:30 breaths). If the heart rate remains <60 beats/min despite effective compressions and ventilation, administration of epinephrine should be considered. Persistent bradycardia in neonates is usually attributable to hypoxia resulting from respiratory arrest and often responds rapidly to effective ventilation alone. Persistent bradycardia despite what appears to be adequate resuscitation suggests inadequate ventilation or more severe cardiac compromise. Poor response to ventilation may be a result of a loosely fitted mask, poor positioning of the endotracheal tube, intraesophageal intubation, airway obstruction, insufficient pressure, pleural effusions, pneumothorax, excessive air in the stomach, asystole, hypovolemia, diaphragmatic hernia, or prolonged intrauterine asphyxia.

In the past, the inspired gas for neonatal resuscitation had been 100% oxygen. *Resuscitation with room air in term infants is equally effective and may reduce the risk of hyperoxia, which is associated with decreased cerebral blood flow and generation of oxygen free radicals.* Room air is the preferred initial gas for neonatal resuscitation in term infants; if the neonate does not achieve normal oxygen saturation levels within 90 sec, increasing concentrations of oxygen should be blended in (up to 100% oxygen) until normal oxygen saturation levels are achieved. If pulmonary hypertension is suspected (meconium aspiration, diaphragmatic hernia) one may consider 100% oxygen as the initial gas for resuscitation. Particular attention is required during the resuscitation of very-low birthweight neonates, to monitor oxygen saturation and adjust oxygen concentration using an oxygen blender so as to minimize the risk of hyperoxia and hypoxia.

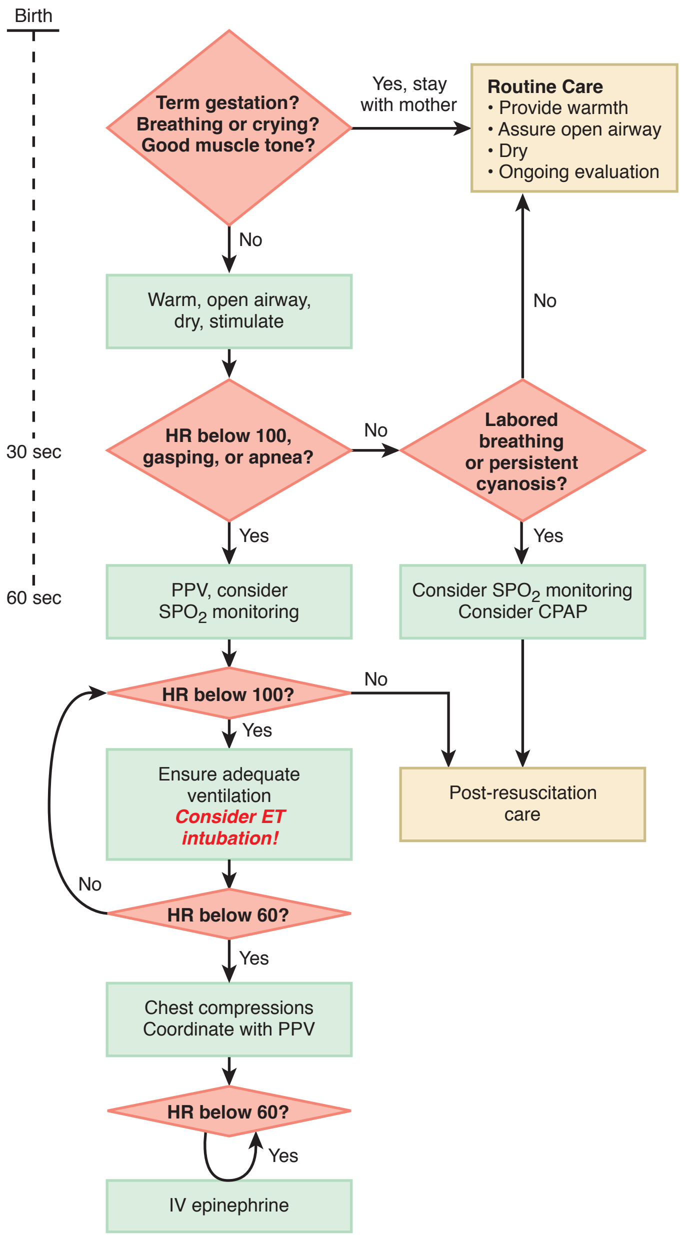

Figure 100-1 **Newborn resuscitation algorithm.** CPAP, continuous positive airway pressure; ET, endotracheal; HR, heart rate; IV, intravenous; PPV, positive pressure ventilation. *(From the American Academy of Pediatrics:* Textbook of Neonatal Resuscitation, *ed 6, Elk Grove Village, IL, 2011, AAP.)*

Although the first breath normally requires pressures as low as 15-20 cm H_2O, pressures as high as 30-40 cm H_2O may be needed. Subsequent breaths are given at a rate of 40-60/min with a pressure of 15-20 cm H_2O. Noncompliant stiff lungs secondary to respiratory distress syndrome, congenital pneumonia, pulmonary hypoplasia, or meconium aspiration may require higher pressures. Successful ventilation is signified by adequate chest rise, symmetric breath sounds, improved pink color, heart rate >100 beats/min, spontaneous respirations, presence of end-tidal CO_2, and improved tone. Various devices to detect exhaled CO_2 and to confirm accurate placement of an endotracheal tube are available commercially. A laryngeal mask airway may be an effective tool to establish an airway, especially if bag and mask ventilation is ineffective or intubation is unsuccessful.

Table 100-1 Guidelines for Tracheal Tube Size and Depth of Insertion

TUBE SIZE (MM INTERNAL DIAMETER)	DEPTH OF INSERTION FROM UPPER LIP (cm)	WEIGHT (g)	GESTATION (wk)
2.5	6.5-7	<1,000	<28
3	7-8	1,000-2,000	28-34
3/3.5	8-9	2,000-3,000	34-38
3.5/4.0	≥9	>3,000	>38

From Kattwinkel J, Niermeyer S, Nadkarni V, et al: ILCOR advisory statement: resuscitation of the newly born infant: an advisory statement from the Pediatric Working Group of the International Liaison Committee on Resuscitation, Circulation *99:1927–1938, 1999. By permission of the American Heart Association, Inc.*

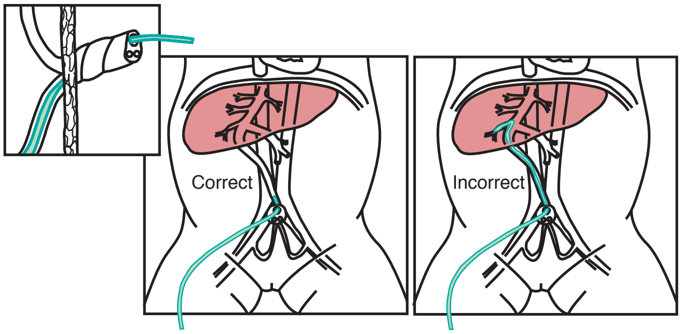

Figure 100-2 Use of the umbilical vein for administration of medications during neonatal resuscitation. *(From Kattwinkel J, Bloom RS, editors:* Neonatal resuscitation textbook, *ed 5, Elk Grove, IL, 2006, American Academy of Pediatrics, American Heart Association.)*

If the infant has respiratory depression and the mother has received an analgesic narcotic drug within 4 hr prior to delivery, naloxone hydrochloride (0.1 mg/kg) is given while adequate ventilation is maintained. Breathing in the depressed infant should be maintained until a response to naloxone is noted. Continuous observation of the infant is important because repeated doses of naloxone may be needed even after the infant has been transferred to the nursery owing to the short half-life of naloxone.

Medications are rarely required but should be administered when the heart rate is <60 beats/min after 30 sec of combined ventilation and chest compressions or during asystole. The umbilical vein can generally be readily cannulated and used for immediate administration of medications during neonatal resuscitation (Fig. 100-2). The endotracheal tube may be used for the administration of epinephrine if intravenous access is not available and/or for naloxone. Epinephrine (0.1-0.3 mL/kg of a 1 : 10,000 solution, given intravenously or intratracheally) is given for asystole or for failure to respond to 30 sec of combined resuscitation. The dose may be repeated every 3-5 min. Data in neonates are insufficient to recommend higher doses in infants who are unresponsive to the standard dose. Emergency volume expansion is accomplished with 10-20 mL/kg of an isotonic crystalloid solution or type O Rh-negative red blood cells (in acute hemorrhage). Volume infusions should be used cautiously during the resuscitation of a very-low birth-weight infant. Sodium bicarbonate (2 mEq/kg, 0.5 mEq/mL of a 4.2% solution) is sometimes given and should be administered slowly (1 mEq/kg/min) if metabolic acidosis has been documented and the resuscitation is prolonged. Sodium bicarbonate should be given only after effective ventilation has been established, because such therapy may increase the blood CO_2 concentration and produce respiratory acidosis, complicating an existing metabolic acidosis. Restoration of oxygenation and tissue perfusion is the main treatment of metabolic acidosis associated with asphyxia.

Severe asphyxia may also depress myocardial function and cause cardiogenic shock despite the recovery of heart and respiratory rates. Dopamine or dobutamine administered as a continuous infusion (5-20 μg/kg/min) and fluids should be started after the initial resuscitation effort, to improve cardiac output in an infant with poor peripheral perfusion, weak pulses, hypotension, tachycardia, and poor urine output. Epinephrine (0.1-1.0 μg/kg/min) may be indicated for infants in severe shock that does not respond to dopamine or dobutamine (see Chapter 67).

Less-severe degrees of poor cardiopulmonary transition in the delivery room can usually be managed by brief periods of bag-and-mask ventilation. Chest compression and medications are not needed for most neonates who have mild to moderate birth depression. Regardless of the severity of asphyxia or the response to resuscitation, asphyxiated infants should be monitored closely for signs of multiorgan hypoxic–ischemic tissue injury (see Table 99-1 in Chapter 99).

MECONIUM

Meconium staining of the amniotic fluid may be an indication of fetal stress; therefore, personnel skilled at endotracheal intubation and resuscitation should be present at the delivery. Previously the decision to intubate a neonate was based on the presence and thickness/consistency of the meconium-stained fluid; *current evidence no longer supports this practice*. If the infant is vigorous with good respiratory effort and a heart rate >100 beats/min, tracheal intubation to aspirate meconium **should not be attempted**; the mouth and nose may be suctioned with a bulb or suction catheter. If the infant is depressed with poor muscle tone and/or a heart rate <100 beats/min, tracheal intubation and suctioning should be performed. The endotracheal tube should be attached to a suction device, and free-flow oxygen should be provided throughout the procedure.

SHOCK

Circulatory insufficiency may be present at birth as a result of severe asphyxia or hemorrhage during gestation, labor, or delivery. Causes of blood loss include hemolysis; placental abruption or tear, placenta previa; traumatic injury to the umbilical cord or internal organs; and intracranial bleeding. Clinical manifestations include signs of respiratory distress, cyanosis, pallor, flaccidity, cold mottled skin, tachycardia or bradycardia, hepatosplenomegaly, and, rarely, convulsions. Edema and hepatosplenomegaly suggest hydrops fetalis or heart failure without shock. Shock from overwhelming infection may be present immediately after birth.

Supportive treatment with type O Rh-negative blood or normal saline is indicated for hemorrhage or hypovolemia, respectively. Oxygen should be administered and the metabolic acidosis corrected with sodium bicarbonate. A sympathomimetic agent such as dopamine or dobutamine may be needed to support cardiac output and blood pressure. The diagnosis and treatment of erythroblastosis fetalis are discussed in Chapter 103.2. If infection is present, appropriate antibiotics must be started as soon as possible.

After supportive measures have stabilized the infant's condition, a specific diagnosis should be established, and appropriate continuing treatment instituted.

PNEUMOTHORAX

Infants may experience pneumothorax in the delivery room, resulting in respiratory distress and hypoxia. Approximately 1-2% of infants have pneumothorax after birth; only 0.05-0.07% have symptoms (see Chapter 101.12). The risk is higher in infants requiring positive pressure ventilation or those with meconium-stained amniotic fluid. Rarely, an infant has a congenital malformation that results in lung hypoplasia, such as congenital diaphragmatic hernia or renal agenesis. Clinically, the infant demonstrates respiratory distress and has diminished breath sounds on the affected side. Transillumination may be helpful to confirm the diagnosis, particularly in the low birth-weight infant. Emergency evacuation of a pneumothorax without

radiographic confirmation is indicated in an infant who is unresponsive to resuscitation efforts, and has asymmetric breath sounds, bradycardia, and cyanosis. A 23-gauge butterfly needle or angiocatheter attached to a stopcock and syringe should be inserted perpendicular to the chest wall above the rib in the 4th intercostal space at the level of the nipple (Fig. 100-3). The air is evacuated. The catheter is then inserted with constant negative pressure, and the air evacuated.

AIRWAY OBSTRUCTION

Critical fetal and then neonatal airway obstruction represents an emergency in the delivery room. The **ex utero intrapartum treatment (EXIT) procedure** allows time to secure the airway in an infant known to have airway obstruction for a variety of causes, including laryngeal atresia or stenosis, teratomas, hygromas, and oral tumors, before the infant is separated from the placenta. Uteroplacental gas exchange is maintained throughout the procedure. High-risk perinatal care has led to more frequent prenatal diagnosis of many disorders known to cause the **critical high airway obstruction syndrome (CHAOS)** (Fig. 100-4).

ABDOMINAL WALL DEFECTS

Appropriate management of patients with abdominal wall defects (omphalocele, gastroschisis) in the delivery room prevents excessive fluid loss and minimizes the risk for injury to the exposed viscera.

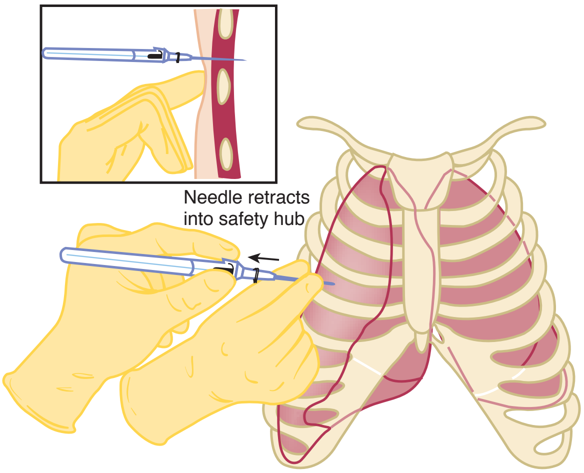

Figure 100-3 Decompression of a pneumothorax. *(From Kattwinkel J, Bloom RS, editors:* Neonatal resuscitation textbook, *ed 5, Elk Grove, IL, 2006, American Academy of Pediatrics, American Heart Association.)*

Gastroschisis is the more common defect and typically the intestines are not covered by a membrane. The exposed intestines should be gently placed in a sterile clear plastic bag after delivery. A membrane often covers an omphalocele, and care should be taken to prevent its rupture. The infant should be transferred to a tertiary referral center for surgical consultation and evaluation for other associated anomalies (see Chapter 105).

INJURY DURING DELIVERY

Central Nervous System

See Chapter 99.

Viscera

The **liver** is the only internal organ other than the brain that is injured with any frequency during the delivery process. Damage usually results from pressure on the liver during delivery of the head in breech presentations. Large infant size, intrauterine asphyxia, coagulation disorders, extreme prematurity, and hepatomegaly are contributing factors. Incorrect cardiac massage is a less-frequent cause. Hepatic rupture may result in the formation of a **subcapsular hematoma,** but the capsule may tamponade further bleeding. Affected infants may appear normal for the 1st 1-3 days. Nonspecific signs related to loss of blood into the hematoma may appear early and include poor feeding, listlessness, pallor, jaundice, tachypnea, and tachycardia. A mass may be palpable in the right upper quadrant, and the abdomen or inguinal area may appear blue. The hematoma may be large enough to cause anemia. Shock and death may occur if the hematoma ruptures into the peritoneal cavity, where the reduced pressure may allow fresh hemorrhage. Early suspicion, ultrasonographic diagnosis, and prompt supportive therapy can decrease the mortality associated with this disorder. Surgical repair of a laceration may be required. Rupture of the spleen may occur alone or in connection with rupture of the liver. The causes, complications, treatment, and prevention are similar.

Although **adrenal hemorrhage** occurs with some frequency, especially after breech delivery, in infants who are large for gestational age or have diabetic mothers, its cause is often undetermined; it may be due to trauma, anoxia, or severe stress, as in overwhelming infection. Ninety percent of adrenal hemorrhages are unilateral; 75% are right-sided. Calcified central hematomas of the adrenal, identified on radiographs or at autopsy in older infants and children, suggest that not all adrenal hemorrhages are immediately fatal. In severe cases, the diagnosis is usually made at postmortem examination. The symptoms are profound shock and cyanosis. A mass may be present in the flank along with overlying skin discoloration; jaundice may also develop. If adrenal hemorrhage is suspected, abdominal ultrasonography may be helpful, and treatment of acute adrenal failure may be indicated (see Chapter 569).

Figure 100-4 EXIT procedure. Baby with teratoma and critical high airway obstruction syndrome (CHAOS). Trachea is displaced to the lateral neck. *(Courtesy of Dr. Mark Wulkan, Pediatric Surgery, Emory University.)*

Fractures

Clavicle

The clavicle is fractured during labor and delivery more frequently than any other bone; it is particularly vulnerable with difficult delivery of the shoulder in vertex presentations and the extended arms in breech deliveries. The infant characteristically does not move the arm freely on the affected side; crepitus and bony irregularity may be palpated, and discoloration is occasionally visible over the fracture site. The Moro reflex is absent on the affected side, and spasm of the sternocleidomastoid muscle with obliteration of the supraclavicular depression at the site of the fracture can be noted. Infants with greenstick clavicle fractures may not have any limitation of movement, and the Moro reflex may be present. The prognosis for this fracture is excellent. **Treatment,** if any, consists of immobilization of the arm and shoulder on the affected side. A remarkable degree of palpable callus develops at the site within a week and may be the initial evidence of the fracture. Fracture of the humerus or brachial palsy may also be responsible for limitation of movement of an arm and absence of a Moro reflex on the affected side.

Extremities

In fractures of the long bones, spontaneous movement of the extremity is usually absent (**pseudoparalysis**). The Moro reflex is often absent from the involved extremity. Associated nerve involvement may occur. Satisfactory results of treatment of a fractured humerus are obtained with 2-4 wk of immobilization, during which the arm is strapped to the chest, a triangular splint and a Velpeau bandage are applied, or a cast is applied. For fracture of the femur, good results are achieved with traction-suspension of both lower extremities, even if the fracture is unilateral; the legs are immobilized in a spica cast. Splints are effective for treatment of fractures of the forearm or leg. Healing is usually accompanied by excess callus formation. The prognosis is excellent for fractures of the extremities. Fractures in very-low birthweight infants may be related to osteopenia of prematurity (see Chapter 106).

Dislocations and epiphyseal separations rarely result from birth trauma. The upper femoral epiphysis may be separated by forcible manipulation of the infant's leg as, for example, in breech extraction or after version. The affected leg shows swelling, slight shortening, limitation of active motion, painful passive motion, and external rotation. The diagnosis is established radiographically. The prognosis is good for milder injuries, but coxa vara frequently results from extensive displacement.

Nose

The most prevalent injury to the nose is dislocation of the cartilaginous portion of the septum from the vomerine groove and the columella. The affected infant may have difficulty nursing and some impairment of nasal respiration. On physical examination, the nares appear asymmetric and the nose is flattened. An oral airway is rarely needed, and surgical consultation should be obtained for definitive treatment.

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Chapter 101

Respiratory Tract Disorders

Waldemar A. Carlo and Namasivayam Ambalavanan

Respiratory disorders are the most frequent cause of admission for neonatal intensive care in both term and preterm infants. Signs and symptoms of respiratory distress include cyanosis, grunting, nasal flaring, retractions, tachypnea, decreased breath sounds with or without rales and/or rhonchi, and pallor. A wide variety of pathologic lesions may be responsible for respiratory disturbances, including pulmonary, airway, cardiovascular, central nervous, infection, and other disorders (Fig. 101-1).

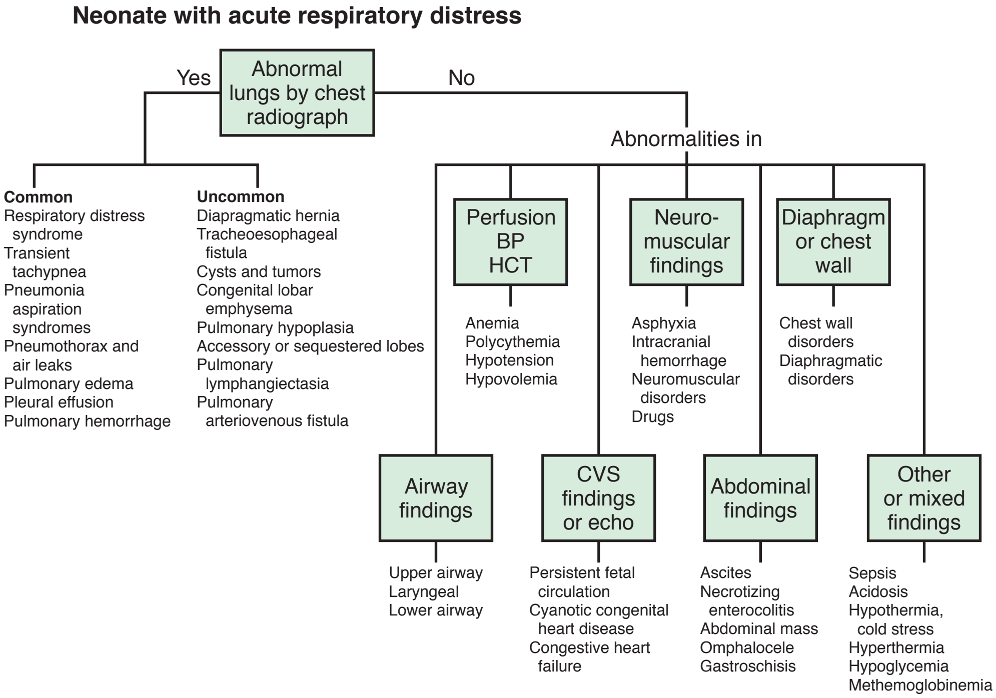

Figure 101-1 **Neonate with acute respiratory distress.** BP, blood pressure; CVS, cardiovascular system; HCT, hematocrit. *(From Battista MA, Carlo WA: Differential diagnosis of acute respiratory distress in the neonate. In Frantz ID, editor:* Tufts University of School of Medicine and Floating Hospital for Children reports on neonatal respiratory diseases, *vol 2, issue 3, Newtown, PA, 1992, Associates in Medical Marketing Co.)*

It is occasionally difficult to distinguish respiratory from nonrespiratory etiologies on the basis of clinical signs alone. Signs of respiratory distress are an indication for a physical examination and diagnostic evaluation, including a blood gas or pulse oximetry determination and chest x-ray. Timely and appropriate therapy is essential to improve outcome.

101.1 Transition to Pulmonary Respiration

Waldemar A. Carlo

Successful establishment of adequate lung function at birth depends on airway patency, functional lung development, and maturity of respiratory control. Fetal lung fluid must be removed and replaced with gas. This process begins before birth as active sodium transport across the pulmonary epithelium drives liquid from the lung lumen into the interstitium with subsequent absorption into the vasculature. Increased levels of circulating catecholamines, vasopressin, prolactin, and glucocorticoids enhance lung fluid adsorption and trigger the change in lung epithelia from a chloride-secretory to a sodium-reabsorptive mode. Functional residual capacity (FRC) must be established and maintained in order to develop a ventilation–perfusion relationship that will provide optimal exchange of oxygen and carbon dioxide between alveoli and blood (see Chapter 421).

THE FIRST BREATH

During vaginal delivery, intermittent compression of the thorax facilitates removal of lung fluid. Surfactant lining the alveoli enhances the aeration of gas-free lungs by reducing surface tension, thereby lowering the pressure required to open alveoli. Although spontaneously breathing infants do not need to generate an opening pressure to create airflow, infants requiring positive-pressure ventilation at birth need an opening pressure of 13-32 cm H_2O and are more likely to establish FRC if they generate a spontaneous, negative pressure breath. Expiratory esophageal pressures associated with the first few spontaneous breaths in term newborns range from 45-90 cm H_2O. This high pressure, due to expiration against a partially closed glottis, may aid in the establishment of FRC but would be difficult to mimic safely with use of artificial ventilation. The higher pressures needed to initiate respiration are required to overcome the opposing forces of surface tension (particularly in small airways) and the viscosity of liquid remaining in the airways, as well as to introduce about 50 mL/kg of air into the lungs, 20-30 mL/kg of which remains after the first breath to establish FRC. Air entry into the lungs displaces fluid, decreases hydrostatic pressure in the pulmonary vasculature, and increases pulmonary blood flow. The greater blood flow, in turn, increases the blood volume of the lung and the effective vascular surface area available for fluid uptake. The remaining fluid is removed via the pulmonary lymphatics, upper airway, mediastinum, and pleural space. Fluid removal may be impaired after cesarean section or as a result of surfactant deficiency, endothelial cell damage, hypoalbuminemia, high pulmonary venous pressure, or neonatal sedation.

Initiation of the first breath is caused by a decline in Pa_{O_2} and pH and a rise in Pa_{CO_2} as a result of interruption of the placental circulation, a redistribution of cardiac output, a decrease in body temperature, and various tactile and sensory inputs. The relative contributions of these stimuli to the onset of respiration are uncertain.

When compared with term infants, preterm infants have a very compliant chest wall and may be at a disadvantage in establishing FRC. The FRC is lowest in the most immature infants because of the decrease in alveolar number. Abnormalities in ventilation : perfusion ratio are greater and persist for longer periods in preterm infants and may lead to hypoxemia and hypercarbia as a result of atelectasis, intrapulmonary shunting, hypoventilation, and gas trapping. The smallest immature infants have the most profound disturbances as a consequence of respiratory distress syndrome (RDS). However, even in healthy term infants, oxygenation is impaired immediately after birth, and oxygen saturation improves to exceed 90% only around 5 min. In addition, right-to-left shunting is common soon after birth; if pulse oximetry is performed soon after birth, the recommendation is to measure oxygen saturation in the right upper extremity.

BREATHING PATTERNS IN NEWBORNS

During sleep in the 1st few mo after birth, normal full-term infants may have episodes when regular breathing is interrupted by short pauses. This **periodic breathing** pattern, which shifts from a regular rhythmicity to cyclic brief episodes of intermittent apnea, is more common in preterm infants, who may have apneic pauses of 5-10 sec followed by a burst of rapid respirations at a rate of 50-60 breaths/min for 10-15 sec. They rarely have an associated change in color or heart rate, and periodic breathing often stops without apparent reason. Periodic breathing, a normal characteristic of neonatal respiration, has no prognostic significance.

101.2 Apnea

Waldemar A. Carlo

Apnea is a common problem in preterm infants that may be the result of prematurity or an associated illness. In term infants, apnea is always worrisome and demands prompt diagnostic evaluation. Periodic breathing must be distinguished from prolonged apneic pauses, because the latter may be associated with serious illnesses. Apnea is a feature of many primary diseases that affect neonates (Table 101-1). These disorders produce apnea by direct depression of the central nervous system's control of respiration (hypoglycemia, meningitis, drugs, hemorrhage, seizures), disturbances in oxygen delivery (shock, sepsis, anemia), or ventilation defects (obstruction of the airway, pneumonia, muscle weakness).

Idiopathic apnea of prematurity occurs in the absence of identifiable predisposing diseases. Apnea is a disorder of respiratory control and may be obstructive, central, or mixed. **Obstructive apnea** (pharyngeal instability, neck flexion) is characterized by absence of airflow but persistent chest wall motion. Pharyngeal collapse may follow the negative airway pressures generated during inspiration or it may result from incoordination of the tongue and other upper airway muscles

Table 101-1 Potential Causes of Neonatal Apnea and Bradycardia

Central nervous system	Intraventricular hemorrhage, drugs, seizures, hypoxic injury, herniation, neuromuscular disorders, Leigh syndrome, brainstem infarction or anomalies (e.g., olivopontocerebellar atrophy), spinal cord injury after general anesthesia
Respiratory	Pneumonia, obstructive airway lesions, upper airway collapse, atelectasis, extreme prematurity, laryngeal reflex, phrenic nerve paralysis, pneumothorax, hypoxia
Infectious	Sepsis, meningitis (bacterial, fungal, viral), respiratory syncytial virus, pertussis
Gastrointestinal	Oral feeding, bowel movement, necrotizing enterocolitis, intestinal perforation
Metabolic	↓ Glucose, ↓ calcium, ↓/↑ sodium, ↑ ammonia, ↑ organic acids, ↑ ambient temperature, hypothermia
Cardiovascular	Hypotension, hypertension, heart failure, anemia, hypovolemia, vagal tone
Other	Immaturity of respiratory center, sleep state

involved in maintaining airway patency. In **central apnea,** which is caused by decreased central nervous system (CNS) stimuli to respiratory muscles, both airflow and chest wall motion are absent. Gestational age is the most important determinant of respiratory control, with the frequency of apnea being inversely related to gestational age. The immaturity of the brainstem respiratory centers is manifested by an attenuated response to carbon dioxide and a paradoxical response to hypoxia that results in apnea rather than the hyperventilation observed after the 1st few mo of life. The most common pattern of idiopathic apnea in preterm neonates is **mixed apnea** (50-75% of cases), with obstructive apnea preceding (usually) or following central apnea. Short episodes of apnea are usually central, whereas prolonged ones are often mixed. Apnea depends on the sleep state; its frequency increases during active (rapid eye movement) sleep.

CLINICAL MANIFESTATIONS

The incidence of idiopathic apnea of prematurity varies inversely with gestational age. The onset of idiopathic apnea can be during the 1st 1-2 wk after birth but is often delayed if there is RDS or other causes of respiratory distress. Apneic episodes have been noted to be as frequent on day 1 as throughout the 1st wk in premature infants without respiratory disease. In preterm infants, **serious apnea** is defined as cessation of breathing for longer than 20 sec or for any duration if accompanied by cyanosis and bradycardia. The incidence of associated bradycardia increases with the length of the preceding apnea and correlates with the severity of hypoxia. Short apnea episodes (10 sec) are rarely associated with bradycardia, whereas longer episodes (>20 sec) have a higher incidence of bradycardia. Bradycardia follows the apnea by 1-2 sec in more than 95% of cases and is most often sinus, but on occasion it can be nodal. Vagal responses and, rarely, heart block are causes of bradycardia without apnea. Short oxygen desaturation episodes noted with oxygen saturation monitoring are normal in neonates, and treatment is not necessary.

TREATMENT

Infants at risk for apnea should get cardiorespiratory monitoring. Gentle tactile stimulation is often adequate therapy for mild and intermittent episodes. The onset of apnea in a previously well preterm neonate after the 2nd wk of life or in a term infant at any time is a critical event that warrants prompt investigation. Recurrent apnea of prematurity may be treated with caffeine or theophylline. Methylxanthines increase central respiratory drive by lowering the threshold of response to hypercapnia as well as enhancing contractility of the diaphragm and preventing diaphragmatic fatigue. Caffeine and theophylline are as effective, *but caffeine has fewer side effects (less tachycardia and feeding intolerance)*. Loading doses of 5-7 mg/kg of theophylline (orally) or aminophylline (intravenously) should be followed by doses of 1-2 mg/kg given every 6-12 hr by the oral or intravenous route. Loading doses of 20 mg/kg of **caffeine citrate** are followed 24 hr later by maintenance doses of 5 mg/kg/24 hr qd, either orally or intravenously. These doses should be monitored through observation of vital signs and clinical response. Serum drug determinations (therapeutic levels: theophylline, 6-10 µg/mL; caffeine, 8-20 µg/mL) are optional because important side effects of these medications are rare. Higher doses of methylxanthines may be more effective, do not necessarily result in more frequent side effects, and may reduce major neurodevelopmental disabilities. Withholding respiratory stimulants in infants with RDS may result in ventilator dependency, increased bronchopulmonary dysplasia (BPD), and death. Doxapram, known to be a potent respiratory stimulant, acts predominantly on peripheral chemoreceptors and is effective in neonates with apnea of prematurity that is unresponsive to methylxanthines. Transfusion of packed red blood cells to reduce the incidence of idiopathic apnea is reserved for severely anemic infants. Gastroesophageal reflux is common in neonates, but data do not support a causal relationship between gastroesophageal reflux and apneic events or the use of antireflux medications to reduce the frequency of apnea in preterm infants.

Nasal continuous positive airway pressure (continuous positive airway pressure [CPAP], 3-5 cm H_2O) and high-flow humidification using nasal cannula (1-2.5 L/min) are therapies for mixed or obstructive apnea, but CPAP is preferred because of its proven efficacy and safety. The efficacy of CPAP is related to its ability to splint the upper airway and prevent airway obstruction.

PROGNOSIS

Apnea of prematurity does not alter an infant's prognosis unless it is severe, recurrent, and refractory to therapy. The associated problems of intraventricular hemorrhage (IVH), BPD, and retinopathy of prematurity are critical in determining the prognosis for apneic infants. Apnea of prematurity usually resolves by 37 wk of postconceptional age, although it may persist beyond term gestation, particularly in extremely preterm infants born at <28 wk of gestation, and does not predict future episodes of sudden infant death syndrome (SIDS). Some infants with persistent apnea are discharged with cardiorespiratory monitoring performed at home. In the absence of significant events, home monitoring can be safely discontinued after 44 wk postconceptional age.

APNEA AND SUDDEN INFANT DEATH SYNDROME

Although preterm infants are at higher risk for SIDS, apnea of prematurity is not a risk factor for SIDS. The epidemiologic evidence that positioning the babies to sleep on their backs reduces the rate of SIDS deaths by more than 50% suggests that position, and not prematurity, has been the primary cause of SIDS. Avoidance of cigarette smoke exposure and of overheating the infant are also important in the prevention of SIDS.

Bibliography is available at Expert Consult.

101.3 Respiratory Distress Syndrome (Hyaline Membrane Disease)

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INCIDENCE

Respiratory distress syndrome occurs primarily in premature infants; its incidence is inversely related to gestational age and birthweight. It occurs in 60-80% of infants <28 wk of gestational age, in 15-30% of those between 32 and 36 wk of gestational age, and rarely in those >37 wk of gestational age. The risk for development of RDS increases with maternal diabetes, multiple births, cesarean delivery, precipitous delivery, asphyxia, cold stress, and a maternal history of previously affected infants. The incidence is highest in preterm male or white infants. The risk of RDS is reduced in pregnancies with chronic or pregnancy-associated hypertension, maternal heroin use, prolonged rupture of membranes, and antenatal corticosteroid prophylaxis.

ETIOLOGY AND PATHOPHYSIOLOGY

Surfactant deficiency (decreased production and secretion) is the primary cause of RDS. The failure to attain an adequate FRC and the tendency of affected lungs to become atelectatic correlate with high surface tension and the absence of pulmonary surfactant. The major constituents of surfactant are dipalmitoyl phosphatidylcholine (lecithin), phosphatidylglycerol, apoproteins (surfactant proteins SP-A, SP-B, SP-C, and SP-D), and cholesterol (Fig. 101-2). With advancing gestational age, increasing amounts of phospholipids are synthesized and stored in type II alveolar cells (Fig. 101-3). These surface-active agents are released into the alveoli, where they reduce surface tension and help maintain alveolar stability by preventing the collapse of small air spaces at end-expiration. Because of immaturity, the amounts produced or released may be insufficient to meet postnatal demands. Surfactant is present in high concentrations in fetal lung homogenates by 20 wk of gestation, but it does not reach the surface of the lungs until later. It appears in amniotic fluid between 28 and 32 wk of gestation. Mature levels of pulmonary surfactant are present usually after 35 wk of gestation.

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Although rare, genetic disorders may contribute to respiratory distress. Abnormalities in surfactant protein B and C genes as well as a gene responsible for transporting surfactant across membranes (ABC transporter 3 *[ABCA3]*) are associated with severe and often lethal familial respiratory disease. Other familial causes of neonatal respiratory distress (not RDS) include alveolar capillary dysplasia, acinar dysplasia, pulmonary lymphangiectasia, and mucopolysaccharidosis.

Synthesis of surfactant depends in part on normal pH, temperature, and perfusion. Asphyxia, hypoxemia, and pulmonary ischemia, particularly in association with hypovolemia, hypotension, and cold stress, may suppress surfactant synthesis. The epithelial lining of the lungs may also be injured by high oxygen concentrations and the effects of respirator management, thereby resulting in a further reduction in surfactant.

Alveolar atelectasis, hyaline membrane formation, and interstitial edema make the lungs less compliant in RDS, so greater pressure is required to expand the alveoli and small airways. The chest wall of the preterm infant, which is highly compliant, offers less resistance than that of the mature infant to the natural tendency of the lungs to collapse. Thus, at end-expiration, the volume of the thorax and lungs tends to approach residual volume, and atelectasis may develop.

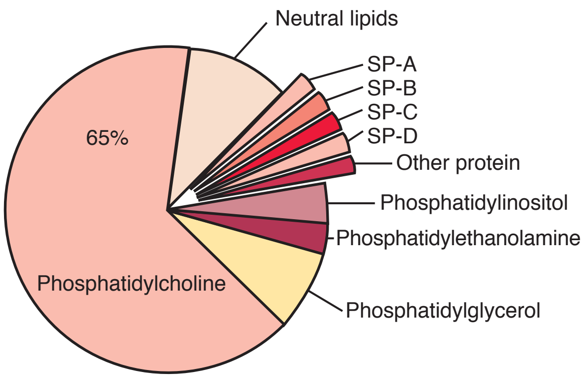

Figure 101-2 Composition of surfactant recovered by alveolar wash. The quantities of the different components are similar for surfactant from the mature lungs of mammals. SP, surfactant protein. *(From Jobe AH: Fetal lung development, tests for maturation, induction of maturation, and treatment. In Creasy RK, Resnick R, editors:* Maternal-fetal medicine: principles and practice, *ed 3, Philadelphia, 1994, WB Saunders.)*

Deficient synthesis or release of surfactant, together with small respiratory units and a compliant chest wall, produces atelectasis and results in perfused but not ventilated alveoli, causing **hypoxia.** Decreased lung compliance, small tidal volumes, increased physiologic dead space, and insufficient alveolar ventilation eventually result in **hypercapnia.** The combination of hypercapnia, hypoxia, and acidosis produces pulmonary arterial vasoconstriction with increased right-to-left shunting through the foramen ovale and ductus arteriosus and within the lung itself. Progressive injury to epithelial and endothelial cells from atelectasis (atelectrauma), volutrauma, ischemic injury, and oxygen toxicity results in effusion of proteinaceous material into the alveolar spaces (Fig. 101-4).

CLINICAL MANIFESTATIONS

Signs of RDS usually appear within minutes of birth, although they may not be recognized for several hours in larger premature infants until rapid, shallow respirations become more obvious. A later onset of tachypnea should suggest other conditions. Some patients require resuscitation at birth because of intrapartum asphyxia or initial severe respiratory distress (especially with a birthweight <1,000 g). Characteristically, tachypnea, prominent (often audible) grunting, intercostal and subcostal retractions, nasal flaring, and cyanosis are noted. Breath sounds may be normal or diminished with a harsh tubular quality, and on deep inspiration, fine crackles may be heard. The natural course of untreated RDS is characterized by progressive worsening of cyanosis and dyspnea. If the condition is inadequately treated, blood pressure may fall; cyanosis and pallor increase, and grunting decreases or disappears, as the condition worsens. Apnea and irregular respirations are ominous signs requiring immediate intervention. Untreated patients may also have a mixed respiratory-metabolic acidosis, edema, ileus, and oliguria. Respiratory failure may occur in infants with rapid progression of the disease. In most cases, the signs reach a peak within 3 days, after which improvement is gradual. Improvement is often heralded by spontaneous diuresis and improved blood gas values at lower inspired oxygen levels and/or lower ventilator support. Death can result from severe impairment of gas exchange, alveolar air leaks (interstitial emphysema, pneumothorax), pulmonary hemorrhage, or IVH. BPD is a form of chronic lung disease that often develops in infants with severe RDS.

DIAGNOSIS

The clinical course, chest x-ray findings, and blood gas and acid–base values help establish the clinical diagnosis. On x-ray, the lungs may have a characteristic but not pathognomonic appearance that includes

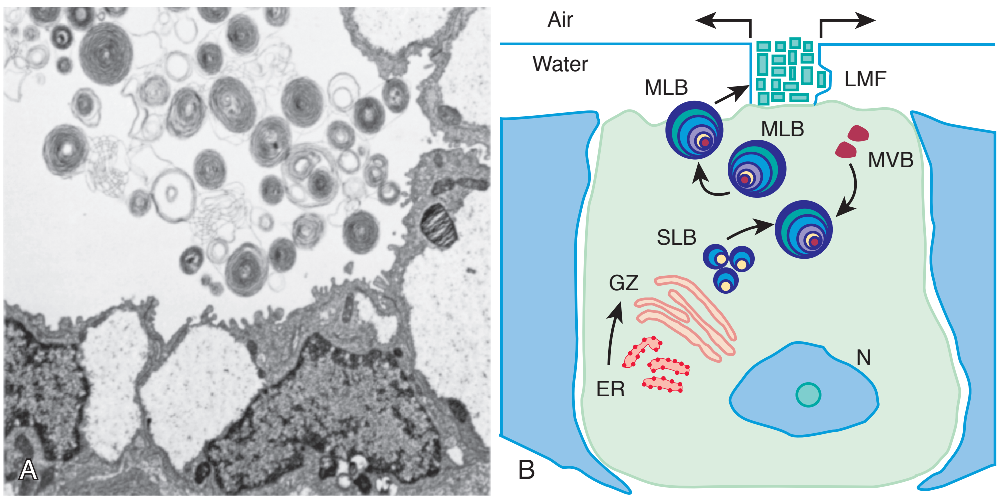

Figure 101-3 A, Fetal rat lung (low magnification), day 20 (term: day 22) showing developing type II cells, stored glycogen *(pale areas),* secreted lamellar bodies, and tubular myelin. **B,** Possible pathway for transport, secretion, and reuptake of surfactant. ER, endoplasmic reticulum; GZ, Golgi zone; LMF, lattice (tubular) myelin figure; MLB, mature lamellar body; MVB, multivesicular body; N, nucleus; SLB, small lamellar body. *(**A** courtesy of Mary Williams, MD, University of California, San Francisco; **B** from Hansen T, Corbet A: Lung development and function. In Taeusch HW, Ballard RA, Avery MA, editors:* Schaffer and Avery's diseases of the newborn, *ed 6, Philadelphia, 1991, WB Saunders.)*

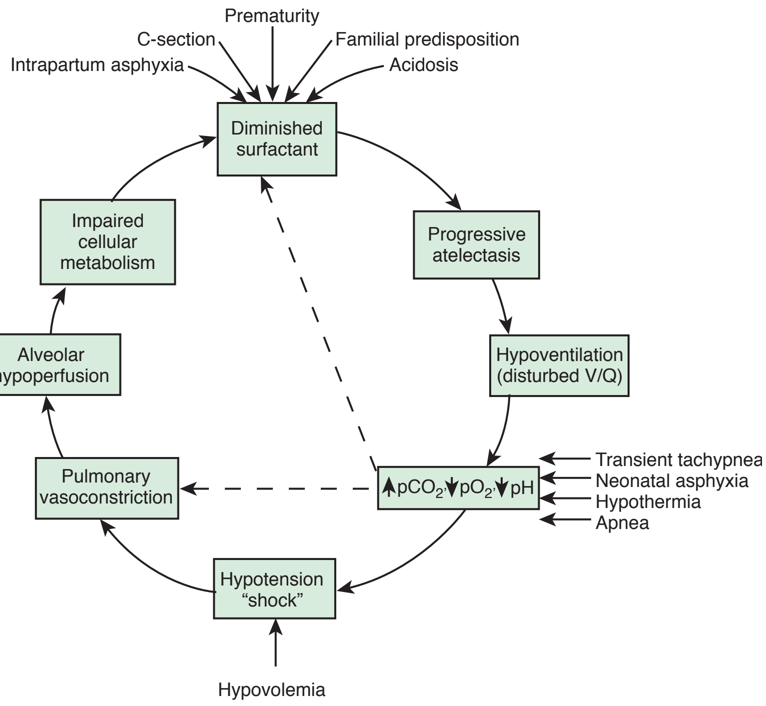

Figure 101-4 **Contributing factors in the pathogenesis of hyaline membrane disease.** The potential "vicious circle" perpetuates hypoxia and pulmonary insufficiency. *(From Farrell P, Zachman R: Pulmonary surfactant and the respiratory distress syndrome. In Quilligan EJ, Kretchmer N, editors:* Fetal and maternal medicine, *New York, 1980, Wiley. Reprinted by permission of John Wiley and Sons, Inc.)*

a fine reticular granularity of the parenchyma and air bronchograms, which are often more prominent early in the left lower lobe because of superimposition of the cardiac shadow (Fig. 101-5). The initial x-ray appearance is occasionally normal, with the typical pattern developing during the first day. Considerable variation in radiographic findings may be seen, depending on the phase of respiration (inspiratory vs. expiratory radiograph) and the use of CPAP or positive end-expiratory pressure (PEEP); this variation often results in poor correlation between radiographic findings and the clinical course. Laboratory findings are characterized initially by hypoxemia and later by progressive hypoxemia, hypercapnia, and variable metabolic acidosis.

In the differential diagnosis**, early-onset sepsis** may be indistinguishable from RDS. In neonates with **pneumonia**, the chest radiograph may be identical to that for RDS. Maternal group B streptococcal colonization, identification of organisms on Gram staining of gastric or tracheal aspirates or a buffy coat smear, and/or the presence of marked neutropenia may suggest the diagnosis of early-onset sepsis. **Cyanotic heart disease** (in particular, total anomalous pulmonary venous return) can also mimic RDS both clinically and radiographically. Echocardiography with color-flow imaging should be performed in infants who show no response to surfactant replacement to rule out cyanotic congenital heart disease as well as ascertain patency of the ductus arteriosus and assess pulmonary vascular resistance (PVR). **Persistent pulmonary hypertension, aspiration (meconium, amniotic fluid) syndromes, spontaneous pneumothorax, pleural effusions**, and **congenital anomalies,** such as cystic adenomatoid malformation, pulmonary lymphangiectasia, diaphragmatic hernia, and lobar emphysema, must be considered in patients with an atypical clinical course, but can generally be differentiated from RDS through radiographic and other evaluations. **Transient tachypnea** may be distinguished by its shorter and milder clinical course and is characterized by low or no need for oxygen supplementation. Congenital alveolar proteinosis (congenital surfactant protein B deficiency) is a rare familial disease that manifests as severe and lethal RDS in predominantly term and near-term infants (see Chapter 405). In atypical cases of RDS, a lung profile (lecithin : sphingomyelin ratio and phosphatidylglycerol determination) performed on a tracheal aspirate can be helpful in establishing a diagnosis of surfactant deficiency.

PREVENTION

Avoidance of unnecessary or poorly timed early cesarean section (<39 wk) or induction of labor, appropriate management of high-risk pregnancy and labor (including administration of antenatal corticosteroids), and prediction of pulmonary immaturity with possible in utero acceleration of maturation (see Chapter 98) are important preventive strategies. Antenatal and intrapartum fetal monitoring may decrease the risk of fetal asphyxia; asphyxia is associated with an increased incidence and severity of RDS.

Administration of antenatal corticosteroids to women before 34 wk of gestation significantly reduces the incidence and mortality of RDS as well as overall neonatal mortality. Antenatal steroids also reduce (1) overall mortality, (2) the need for and duration of ventilatory support and admission to a neonatal ICU, and (3) the incidence of severe IVH, necrotizing enterocolitis, and neurodevelopmental impairment. Postnatal growth is not adversely affected. Antenatal steroids do not increase the risk of maternal death, chorioamnionitis, or puerperal sepsis. Steroid administration is recommended for all women in preterm labor who are likely to deliver a fetus within 1 wk. Antenatal steroids act synergistically with postnatal exogenous surfactant therapy so they should be given even though surfactant therapy is effective. Betamethasone and dexamethasone have both been used antenatally. Betamethasone may reduce neonatal death to a greater extent as compared to dexamethasone.

In the past administration of surfactant into the trachea of symptomatic premature infants immediately after birth (prophylactic) or during the 1st few hr of life (early rescue) showed reduced air leak and mortality from RDS. *CPAP started at birth is as effective as prophylactic or early surfactant and is the approach of choice for the delivery room management of a preterm neonate at risk for RDS.*

TREATMENT

The basic defect requiring treatment in RDS is inadequate pulmonary exchange of oxygen and carbon dioxide; metabolic acidosis and circulatory insufficiency are secondary manifestations. Early supportive care of premature infants, especially in the treatment of acidosis, hypoxia, hypotension (see Chapter 98), and hypothermia, may lessen the severity of RDS. Therapy requires careful and frequent monitoring

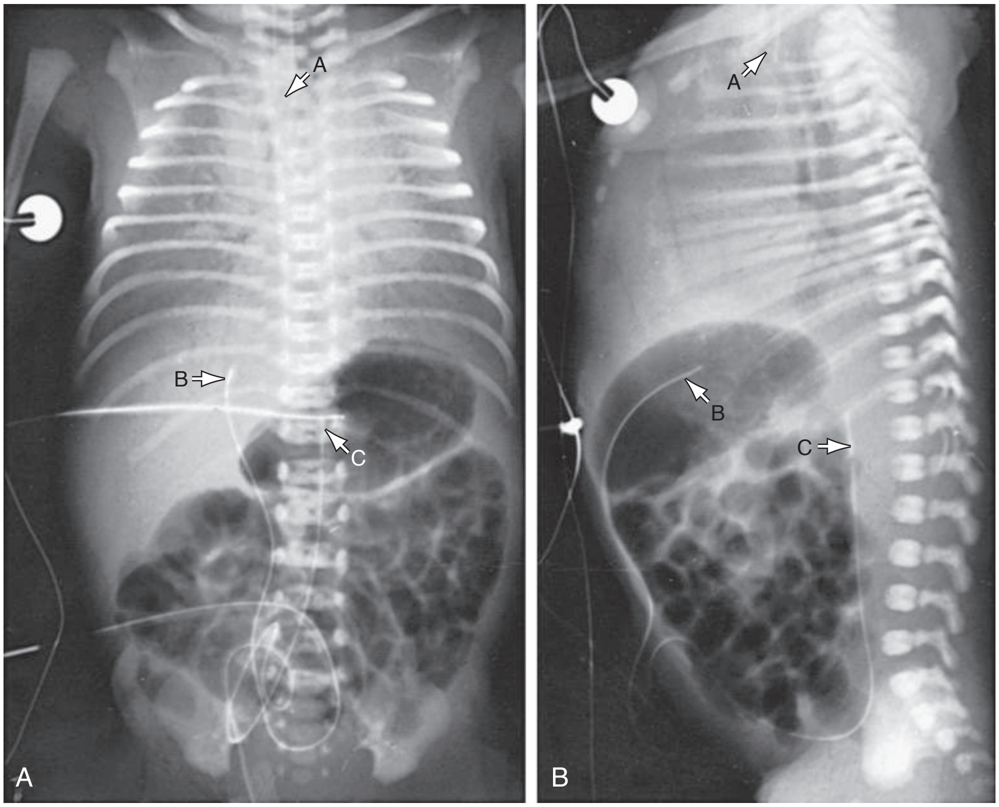

Figure 101-5 Infant with respiratory distress syndrome. Note the granular lungs, air bronchogram, and air-filled esophagus. Anteroposterior (**A**) and lateral (**B**) roentgenograms are needed to distinguish the umbilical artery from the vein catheter and to determine the appropriate level of insertion. The lateral view clearly shows that the catheter has been inserted into an umbilical vein and is lying in the portal system of the liver. *A* indicates endotracheal tube; *B* indicates the umbilical venous catheter at the junction of the umbilical vein, ductus venosus, and portal vein; *C* indicates the umbilical artery catheter passed up the aorta to T12. *(Courtesy of Walter E. Berdon, Babies Hospital, New York City.)*

of heart and respiratory rates, oxygen saturation, Pa_{O_2}, Pa_{CO_2}, pH, serum bicarbonate, electrolytes, glucose, hematocrit, blood pressure, and temperature. Arterial catheterization is frequently necessary. Because most cases of RDS are self-limited, the goal of treatment is to minimize abnormal physiologic variations and superimposed iatrogenic problems. Treatment of infants with RDS is best carried out in the neonatal ICU.

The general principles for supportive care of any premature infant should be adhered to, including developmental care and scheduled "touch times." To avoid hypothermia and minimize oxygen consumption, the infant should be placed in an incubator or radiant warmer, and core temperature maintained between 36.5 and 37°C (97.7 and 98.6°F) (see Chapters 97 and 98). Use of an incubator is preferable in very-low birthweight (VLBW) infants owing to the high insensible water losses associated with radiant heat. Calories and fluids should initially be provided intravenously. For the 1st 24 hr, 10% glucose solution with additional amino acids in extremely premature infants, should be infused through a peripheral vein at a rate of 65-75 mL/kg/24 hr. Electrolytes should be added on day 2 in the most mature infants and on days 3-7 in the more immature ones. Fluid volume is increased gradually over the 1st wk. Excessive fluids (>140 mL/kg/day) contribute to the development of patent ductus arteriosus (PDA) and BPD.

Warm humidified oxygen should be provided at a concentration initially sufficient to keep arterial oxygen pressure between 50 and 70 mm Hg (91-95% saturation) in order to maintain normal tissue oxygenation while minimizing the risk of oxygen toxicity. If oxygen saturation cannot be kept >90% at inspired oxygen concentrations of 40-70% or greater, applying CPAP at a pressure of 5-10 cm H_2O via nasal prongs is indicated and usually produces a rapid improvement in oxygenation. CPAP reduces collapse of surfactant-deficient alveoli and improves both FRC and ventilation–perfusion matching. *Early use of CPAP for stabilization of at-risk preterm infants beginning as early as in the delivery room reduces ventilatory needs.* Another approach is to intubate the preterm infant, administer intratracheal surfactant and then extubate the infant and begin CPAP. The amount of CPAP required usually decreases after approximately 72 hr of age, and most infants can be weaned from CPAP shortly thereafter. If an infant with RDS undergoing CPAP cannot keep oxygen saturation >90% while breathing 40-70% oxygen, assisted ventilation and surfactant are indicated.

Infants with respiratory failure or persistent apnea require assisted mechanical ventilation. Reasonable measures of respiratory failure are: (1) arterial blood pH <7.20, (2) arterial blood P_{CO_2} of 60 mm Hg or higher, and (3) oxygen saturation <90% at oxygen concentrations of 40-70% and CPAP of 5-10 cm H_2O. Infants with persistent apnea also need mechanical ventilation. Intermittent positive pressure ventilation delivered by time-cycled, pressure-limited, continuous flow ventilators is a common method of conventional ventilation for newborns. Other methods of conventional ventilation are synchronized intermittent mandatory ventilation (the set rate and pressure synchronized with the patient's own breaths), pressure support (the patient triggers each breath and a set pressure is delivered), and volume ventilation (a mode in which a specific tidal volume is set and the delivered pressure varies), and combinations thereof. Assisted ventilation for infants with RDS should always include appropriate PEEP (see Chapter 71.1). High ventilatory rates (≥60/min) with lower tidal volumes result in fewer air leaks. With use of high ventilatory rates, sufficient expiratory time should be allowed to avoid the inadvertent PEEP.

The **goal of mechanical ventilation** is to improve oxygenation and elimination of carbon dioxide without causing pulmonary injury or oxygen toxicity. Acceptable ranges of blood gas values, after the risks of hypoxia and acidosis are balanced against those of mechanical ventilation, vary among institutions: Pa_{O_2} 50-70 mm Hg, Pa_{CO_2} 45-65 mm

Hg (and higher after the first few days when the risk of IVH is less), and pH 7.20-7.35. During mechanical ventilation, **oxygenation** is improved by increasing either the fraction of inspired oxygen (FIO_2) or the mean airway pressure. The latter can be increased by raising the peak inspiratory pressure, PEEP gas flow, or inspiratory-expiratory ratio. Pressure changes are usually most effective. However, excessive PEEP may impede venous return, thereby reducing cardiac output and decreasing oxygen delivery despite improvement in PaO_2. PEEP levels of 4-6 cm H_2O are usually safe and effective. **Carbon dioxide elimination** is achieved by increasing the peak inspiratory pressure (tidal volume) or the rate of the ventilator.

A strategy to minimize ventilator-associated lung injury is the use of CPAP instead of endotracheal intubation. The decreased need for ventilator support with the use of CPAP may allow lung inflation to be maintained but may prevent volutrauma from overdistention and/or atelectasis. Early nasal CPAP is beneficial as compared to intubation and prophylactic surfactant, including lower mortality or BPD with CPAP treatment.

An effective strategy with conventional mechanical ventilation is the use of high rates and presumably small tidal volumes as $PaCO_2$ levels were kept in comparable ranges. Meta-analyses of the randomized controlled trials comparing high (>60 breaths/min) and low (usually 30-40 breaths/min) rates (and presumed low vs. high tidal volumes, respectively) revealed that the high ventilatory rate strategy led to fewer air leaks and a trend for increased survival.

If mechanical ventilation is needed, a ventilatory approach using small tidal volumes and permissive hypercapnia can be employed. **Permissive hypercapnia** is a strategy for the management of patients receiving ventilatory support in which priority is given to the prevention or limitation of lung injury from the ventilator by tolerating relatively high levels of $PaCO_2$ rather than maintenance of normal blood gas values. Permissive hypercapnia can be implemented during CPAP and mechanical ventilation. Volume-targeted ventilation allows the clinician to set a tidal volume that may prevent volutrauma. There are limited data on volume-targeted ventilation, but this mode of ventilation may decrease the rates of pneumothorax and BPD.

Hyperoxia may also contribute to lung injury in preterm infants. However, a lower target range of oxygenation (85-89%), as compared with a higher range (91-95%) increases mortality, and does not alter rates of BPD, BPD/death, blindness, or neurodevelopmental impairment. **Therefore, the currently recommended range of oxygen saturation targets is 91-95%.**

Many ventilated neonates receive sedation or pain relief with benzodiazepines or opiates (morphine, fentanyl), respectively. Midazolam is approved for use in neonates and has demonstrated sedative effects. Adverse hemodynamic effects and myoclonus have been associated with its use in neonates. If midazolam is used, a continuous infusion or administration of individual doses over at least 10 min is recommended to reduce these risks. Data are insufficient to assess the efficacy and safety of lorazepam. Diazepam is not recommended owing to its long half-life, its long-acting metabolites, and concern about the benzyl alcohol content of diazepam injection. Continuous infusion of morphine in VLBW neonates requiring mechanical ventilation does not reduce mortality rates, severe IVH, or periventricular leukomalacia. The need for additional doses of morphine is associated with poor outcome.

High-frequency ventilation (HFV) achieves desired alveolar ventilation by using smaller tidal volumes and higher rates (300-1,200 breaths/min or 5-20 Hz). HFV may improve elimination of carbon dioxide and improve oxygenation in patients who show no response to conventional ventilators and those who have severe RDS, interstitial emphysema, recurrent pneumothoraces, or meconium aspiration pneumonia. High-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation are the most frequently used methods of HFV. HFOV reduces BPD but may raise the risk for intracranial hemorrhage. HFOV strategies that promote lung recruitment, combined with surfactant therapy, may improve gas exchange. High-frequency jet ventilation facilitates resolution of air leaks. Elective use of either method, in comparison with conventional ventilation, generally does not offer advantages if used as the initial ventilation strategy to treat infants with RDS.

Surfactant deficiency is the primary pathophysiology of RDS. Immediate effects of surfactant replacement therapy include improved alveolar-arterial oxygen gradients, reduced ventilatory support, increased pulmonary compliance, and improved chest radiograph appearance. In neonates with RDS who fail CPAP, **treatment** with endotracheal surfactant should be initiated immediately after intubation. Repeated dosing is given every 6-12 hr for a total of 2 to 4 doses, depending on the preparation. Exogenous surfactant should be given by a physician who is qualified in neonatal resuscitation and respiratory management. Additional onsite staff support required includes nurses and respiratory therapists experienced in the ventilatory management of preterm infants. Appropriate monitoring equipment (radiology, blood gas laboratory, pulse oximetry) must also be available. Complications of surfactant therapy include transient hypoxia, hypercapnia, bradycardia and hypotension, blockage of the endotracheal tube, and pulmonary hemorrhage (see Chapter 101.13).

A number of surfactant preparations are available, including synthetic surfactants and natural surfactants derived from animal sources. The lack of reduction in BPD rates following surfactant replacement is probably, in part, a result of the survival of infants with severe RDS who would have died without surfactant administration. Infants requiring ventilator support after 1 wk of age may experience transient episodes of surfactant dysfunction associated with deficiencies of SP-B and SP-C, which are temporally associated with episodes of infection and respiratory deterioration. Surfactant treatment may be beneficial in these infants.

Strategies for weaning infants from ventilators vary widely and are influenced by lung mechanics as well as the availability of ventilatory modes (pressure support). Once extubated, many infants are transitioned to nasal CPAP to avoid postextubation atelectasis and reduce re-intubation. Synchronized nasal intermittent ventilation decreases the need for re-intubation in premature infants. High flow (1-2 L/min) or warmed, humidified high-flow (2-8 L/min) nasal cannula oxygen is commonly used to support term and near-term infants following extubation and to wean premature infants from nasal CPAP. Preloading with methylxanthines may enhance the success of extubation.

Pharmacologic Therapies

Systemic corticosteroids have been used to treat infants with RDS, to selectively treat infants who continue to require respiratory support, and to treat those in whom BPD develops. Mortality and/or BPD at 36 wk decrease with moderately early (7-14 days) administration of corticosteroids. Early (<96 hr) and delayed (>2-3 wk) administration of systemic steroids has also been assessed with meta-analyses, and the results are qualitatively similar. However, there are **short-term adverse** effects, including hyperglycemia, hypertension, gastrointestinal bleeding, gastrointestinal perforation, hypertrophic obstructive cardiomyopathy, poor weight gain, poor growth of the head, and a trend toward a higher incidence of periventricular leukomalacia. Furthermore, data showing an increased incidence of neurodevelopmental delay and cerebral palsy in infants randomly assigned to receive systemic corticosteroids raise serious concerns about adverse long-term outcomes of this therapy. Thus, routine use of systemic corticosteroids for the prevention or treatment of BPD is not recommended by the Consensus Group of the American Academy of Pediatrics and the Canadian Pediatric Society. Administration of inhaled steroids to ventilated preterm infants during the 1st 2 wk after birth reduced the need for systemic steroids and tended to decrease rates of death and/or BPD at 36 wk without an increase in adverse effects.

Inhaled nitric oxide has been evaluated in preterm infants following the observation of its effectiveness in term and near-term infants with hypoxemic respiratory failure. **Inhaled nitric oxide (iNO)** decreases the need for extracorporeal membrane oxygenation (ECMO) in term and near-term infants with hypoxic respiratory failure or persistent pulmonary hypertension of the neonate. Trials in preterm infants report heterogeneous effects on BPD, mortality, and other important outcomes. The most current data do not support the

routine administration of iNO in preterm infants with hypoxemic respiratory failure.

Prevention of extubation failure has been attempted with use of various pharmacologic approaches. Methylxanthines appear to have a large effect on reducing extubation failure. Similarly, use of systemic steroids before extubation reduces the need for reintubation (from 10% to 1%). In contrast, administration of racemic epinephrine after extubation does not improve pulmonary function or the rate of extubation failure.

Metabolic acidosis in RDS may be a result of perinatal asphyxia and hypotension and is often encountered when an infant has required prolonged resuscitation (see Chapter 100). Sodium bicarbonate, 1-2 mEq/kg, may be administered over 15-20 min through a peripheral or umbilical vein, followed by an acid–base determination within 30 min, or it may be administered over several hours. Often, sodium bicarbonate is administered on an emergency basis through an umbilical venous catheter. Alkali therapy may result in skin sloughing from infiltration, increased serum osmolarity, hypernatremia, hypocalcemia, hypokalemia, and liver injury when concentrated solutions are administered rapidly through an umbilical vein catheter wedged in the liver.

Monitoring of aortic blood pressure through an umbilical or peripheral arterial catheter or by oscillometric technique is useful in managing the shock-like state that may occur during the 1st hr or so in premature infants who have been asphyxiated or have severe RDS (see Fig. 100-2 in Chapter 100). The position of a radiopaque umbilical catheter should be checked radiographically after insertion (see Fig. 101-5). The tip of an umbilical artery catheter should lie at L3-L5 just above the bifurcation of the aorta or at T6-T10. Preferred sites for peripheral catheters are the radial or posterior tibial arteries. The placement and supervision should be carried out by skilled and experienced personnel. Catheters should be removed as soon as patients no longer have any indication for their continued use—usually when an infant is stable and the FIO_2 is <40%. Hypotension and low flow in the superior vena cava have been associated with higher rates of CNS morbidity and mortality and should be treated with cautious administration of volume (crystalloid) and early use of vasopressors. Dopamine is more effective in raising blood pressure than dobutamine. Hypotension may be refractory to pressors, but responsive to glucocorticoids, especially in neonates <1,000 g. This hypotension may result from transient adrenal insufficiency in the ill premature infant, which may be treated with intravenous hydrocortisone at 1-2 mg/kg/dose q 6-12 hr (see Chapter 98).

Periodic **monitoring of PaO_2, $PaCO_2$, and pH** is an important part of the management; if assisted ventilation is being used, such monitoring is essential. Oxygenation may be assessed continuously from transcutaneous electrodes or pulse oximetry (oxygen saturation). Capillary blood samples are of limited value for determining PO_2 but may be useful for evaluating PCO_2 and pH.

Because of the difficulty of distinguishing **group B streptococcal** or other bacterial infections from RDS, empirical antibiotic therapy is indicated until the results of blood cultures are available. Penicillin or ampicillin with an aminoglycoside is suggested, although the choice of antibiotics should be based on the recent pattern of bacterial sensitivity in the hospital where the infant is being treated (see Chapter 109).

COMPLICATIONS OF RESPIRATORY DISTRESS SYNDROME AND INTENSIVE CARE

The most serious complications of **tracheal intubation** are pneumothorax and other air leaks, asphyxia from obstruction or dislodgment of the tube, bradycardia during intubation or suctioning, and the subsequent development of subglottic stenosis. Other complications include bleeding from trauma during intubation, posterior pharyngeal pseudodiverticula, need for tracheostomy, ulceration of the nares caused by pressure from the tube, permanent narrowing of the nostril as a result of tissue damage and scarring from irritation or infection around the tube, erosion of the palate, avulsion of a vocal cord, laryngeal ulcer, papilloma of a vocal cord, and persistent hoarseness, stridor, or edema of the larynx.

Measures to reduce the incidence of these complications include skillful intubation, adequate securing of the tube, use of polyvinyl endotracheal tubes, use of the smallest tube that will provide effective ventilation in order to reduce local pressure necrosis and ischemia, avoidance of frequent changes and motion of the tube in situ, avoidance of too frequent or too vigorous suctioning, and prevention of infection through meticulous cleanliness and frequent sterilization of all apparatus attached to or passed through the tube. The personnel inserting and caring for the endotracheal tube should be experienced and skilled in such care.

Risks associated with **umbilical arterial catheterization** include vascular embolization, thrombosis, spasm, and vascular perforation; ischemic or chemical necrosis of abdominal viscera; infection; accidental hemorrhage; hypertension; and impairment of circulation to a leg with subsequent gangrene. Aortography has demonstrated that clots form in or about the tips of 95% of catheters placed in an umbilical artery. Aortic ultrasonography can also be used to investigate for the presence of thrombosis. The risk of a serious clinical complication resulting from umbilical catheterization is probably between 2% and 5%.

Transient blanching of the leg may occur during catheterization of the umbilical artery. It is usually caused by reflex arterial spasm, the incidence of which is lessened by using the smallest available catheter, particularly in very small infants. The catheter should be removed immediately; catheterization of the other artery may then be attempted. Persistent spasm after removal of the catheter may be relieved by a small amount of topical nitroglycerin paste applied to the affected area or by warming the other leg. Blood sampling from a radial artery may similarly result in spasm or thrombosis, and the same treatment is indicated. Intermittent severe spasm or unrelieved spasm may respond to the cautious use of topical nitroglycerin. Spasm or thrombosis unresponsive to treatment may result in gangrene of the organ or area supplied by the vessel.

Serious hemorrhage upon removal of the catheter is rare. Thrombi may form in the artery or in the catheter, the incidence of which can be lowered by using a smooth-tipped catheter with a hole only at its end, by rinsing the catheter with a small amount of saline solution containing heparin, or by continuously infusing a solution containing 1-2 units/mL of heparin. The risk of thrombus formation with potential vascular occlusion can also be reduced by removing the catheter when early signs of thrombosis, such as narrowing of pulse pressure and disappearance of the dicrotic notch, are noted. Some authorities prefer to use the umbilical artery for blood sampling only and to leave the catheter filled with heparinized saline between samplings. **Renovascular hypertension** may occur days to weeks after umbilical arterial catheterization in a small proportion of neonates.

Umbilical vein catheterization is associated with many of the same risks as umbilical artery catheterization. Additional risks are cardiac perforation and pericardial tamponade; portal hypertension can develop from portal vein thrombosis, especially in the presence of omphalitis.

Air leaks are a common complication of the management of infants with RDS (see Chapter 101.12).

Some neonates with RDS may have clinically significant shunting through a **PDA.** Delayed closure of the PDA is associated with hypoxia, acidosis, increased pulmonary pressure secondary to vasoconstriction, systemic hypotension, immaturity, and local release of prostaglandins, which dilate the ductus. Shunting through the PDA may initially be bidirectional or right-to-left. As RDS resolves, PVR decreases, and left-to-right shunting may occur, leading to left ventricular volume overload and pulmonary edema. Manifestations of PDA may include (1) a hyperdynamic precordium, bounding peripheral pulses, wide pulse pressure, and a continuous or systolic murmur with or without extension into diastole or an apical diastolic murmur, or multiple clicks resembling the shaking of dice; (2) radiographic evidence of cardiomegaly and increased pulmonary vascular markings; (3) hepatomegaly; (4) increasing oxygen dependence; and (5) carbon dioxide retention. The **diagnosis** is confirmed by echocardiographic visualization of a PDA with Doppler flow imaging that demonstrates left-to-right or

bidirectional shunting. Prophylactic "closure" before signs of a PDA, closure of the asymptomatic but clinically detected PDA, and closure of the symptomatic PDA are 3 strategies to manage a PDA. Interventions include fluid restriction, the use of cyclooxygenase inhibitors (indomethacin or ibuprofen) to close the ductus, and surgical closure. Short-term benefits have to be balanced against adverse effects such as transient renal dysfunction and a possible increase in the risk of intestinal perforation with indomethacin. Much uncertainty about "best practice" in the management of a PDA remains. Many cases respond to general supportive measures, including fluid restriction. Medical and/or surgical ductal closure is indicated in the premature infant with a large PDA when there is a delay in clinical improvement or deterioration after initial clinical improvement of RDS. Intravenous indomethacin (0.1-0.2 mg/kg/dose) is given in 3 doses every 12-24 hr; treatment may be repeated once. A second course may be needed in a few symptomatic patients. If closure does not occur in a symptomatic patient, surgical ligation is usually the next step. Prophylactic low-dose indomethacin given soon after birth reduces the incidence of both IVH and PDA and improves the rate of permanent ductus closure even in the most immature infants. **Contraindications** to indomethacin include thrombocytopenia (<50,000 platelets/mm^3), bleeding disorders, oliguria (urine output <1 mL/kg/hr), necrotizing enterocolitis, isolated intestinal perforation, and an elevated plasma creatinine value (>1.8 mg/dL). The infant whose symptomatic PDA fails to close with indomethacin or who has contraindications to indomethacin is a candidate for surgical closure. Surgical mortality is very low even in the extremely low-birthweight infants. Complications of surgery include Horner syndrome, injury to the recurrent laryngeal nerve, chylothorax, transient hypertension, pneumothorax, and bleeding from the surgical site. Inadvertent ligation of the left pulmonary artery or the transverse aortic arch has rarely been reported.

Intravenous ibuprofen may be an alternative to indomethacin; it can be as effective in closing a PDA without reducing cerebral, mesenteric, or renal blood flow velocity. Compared with indomethacin, therapeutic ibuprofen has a lower risk of oliguria.

BPD is a result of lung injury in infants requiring mechanical ventilation and supplemental oxygen. The clinical, radiographic, and lung histology of **classic BPD** described in 1967, in an era before the widespread use of antenatal steroids and postnatal surfactant, was that of a disease of more mature preterm infants with RDS who were treated with positive-pressure ventilation and oxygen. The **new BPD** is a disease primarily of infants with birthweight <1,000 g who were born at <28 wk of gestation, some of whom have little or no lung disease at birth but experience progressive respiratory failure over the 1st few wk of life.

The lung histology currently found in infants with the new BPD include alveolar hypoplasia, variable saccular wall fibrosis, and minimal airway disease. Some specimens also have decreased pulmonary microvasculature development. The histopathology of BPD indicates interference with normal alveolar septation and microvascular maturation, which may prevent subsequent lung growth and development. The pathogenesis of BPD is multifactorial and affects both the lungs and the heart. RDS is a disease of progressive alveolar collapse. Alveolar collapse (**atelectrauma**) as a consequence of surfactant deficiency, together with ventilator-induced phasic overdistention of the lung (**volutrauma**), promotes injury. Oxygen induces injury by producing free radicals that cannot be metabolized by the immature antioxidant systems of VLBW neonates. Mechanical ventilation and oxygen injure the lung through their effect on alveolar and vascular development. Inflammation (detected with measurement of circulating neutrophils, neutrophils and macrophages in alveolar fluid, and proinflammatory cytokines) contributes to the progression of lung injury. Several clinical factors, including immaturity, chorioamnionitis, infection, symptomatic PDA, and malnutrition, contribute to the development of BPD.

The occurrence of BPD is inversely related to gestational age. Additional associations include the presence of interstitial emphysema, male sex, low $Pa{CO_2}$ during the treatment of RDS, PDA, high peak inspiratory pressure, increased airway resistance in the 1st wk of life, increased pulmonary artery pressure, and, possibly, a family history of atopy or asthma. Genetic polymorphisms may increase the risk for development of BPD. In some VLBW infants without RDS who require mechanical ventilation for apnea or respiratory insufficiency, BPD that does not follow the classic pattern may develop. Overhydration during the 1st days of life may also contribute to the development of BPD. Vitamin A supplementation (5,000 IU intramuscularly 3 times/wk for 4 wk) in VLBW infants reduces the risk of BPD (1 case prevented for every 14-15 infants treated). Early use of nasal CPAP and rapid extubation with transition to nasal CPAP are associated with a decreased risk of BPD.

Instead of showing improvement on the 3rd or 4th day, which would be consistent with the natural course of RDS, some infants demonstrate an increased need for oxygen and ventilatory support. Respiratory distress persists or worsens and is characterized by hypoxia, hypercapnia, oxygen dependence, and, in severe cases, the development of right-sided heart failure. The chest radiograph may reveal pulmonary interstitial emphysema, wandering atelectasis with concomitant hyperinflation, and cyst formation (Fig. 101-6). Four distinct pathologic stages of classic BPD have been identified: acute lung injury, exudative bronchiolitis, proliferative bronchiolitis, and obliterative fibroproliferative bronchiolitis. Histologic study at this stage (10-20 days) shows residual hyaline membrane formation, progressive alveolar coalescence with atelectasis of the surrounding alveoli, interstitial edema, coarse focal thickening of the basement membrane, and widespread bronchial and bronchiolar mucosal metaplasia and hyperplasia. These findings correspond to a severe maldistribution of ventilation. Pathologic examination of infants who die later in the course of BPD reveals cardiac enlargement and pulmonary changes consisting of focal areas of emphysema with hypertrophy of the peribronchial smooth muscle of the tributary bronchioles, perimucosal fibrosis, widespread metaplasia of the bronchiolar mucosa, thickening of basement membranes, and separation of the capillaries from the alveolar epithelial cells.

BPD can be classified according to the need for oxygen supplementation (Table 101-2). Neonates receiving positive pressure support or ≥30% supplemental oxygen at 36 wk or at discharge (whichever occurs first) are diagnosed as having severe BPD. Those needing supplementation with 22-29% oxygen at this age are diagnosed as having moderate BPD. Those who need oxygen supplementation for >28 days but are breathing room air at 36 wk or at discharge are diagnosed as having mild BPD. Those receiving <30% oxygen should undergo a stepwise 2% reduction in supplemental oxygen to room air while under continuous observation and with oxygen saturation monitoring to determine whether they can be weaned off oxygen (physiologic definition of BPD). This test is highly reliable and correlated with discharge home on oxygen, length of hospital stay, and hospital readmissions in the 1st yr of life.

Severe BPD requires prolonged mechanical ventilation. Gradual weaning should be attempted despite elevations in $Pa{CO_2}$, because hypercapnia may be the result of gas trapping rather than inadequate minute ventilation. Acceptable blood gas concentrations include hypercapnia with pH >7.20 and a $Pa{O_2}$ of 50-70 mm Hg with an oxygen saturation of 91-95%. Lower levels of $Pa{O_2}$ may exacerbate pulmonary hypertension with resultant cor pulmonale, so the lower limit of oxygenation targets in neonates with BPD are higher than those in neonates with RDS. Airway obstruction in BPD may be due to mucus and edema production, bronchospasm, and airway collapse from acquired tracheobronchomalacia. These events may contribute to "blue spells." Alternatively, blue spells may be the result of acute pulmonary vasospasm or right ventricular dysfunction.

Treatment of BPD includes nutritional support, fluid restriction, drug therapy, maintenance of adequate oxygenation, and prompt treatment of infection. Growth must be monitored because recovery depends on the growth of lung tissue and remodeling of the pulmonary vascular bed. Nutritional supplementation to provide added calories (24-30 calories/30 mL formula), protein (3-3.5 g/kg/24 hr), and fat (3 g/kg/24 hr) is needed for growth. Diuretic therapy results in a short-term improvement in lung mechanics and may lead to decreased oxygen and ventilatory requirements. Furosemide (1 mg/kg/dose

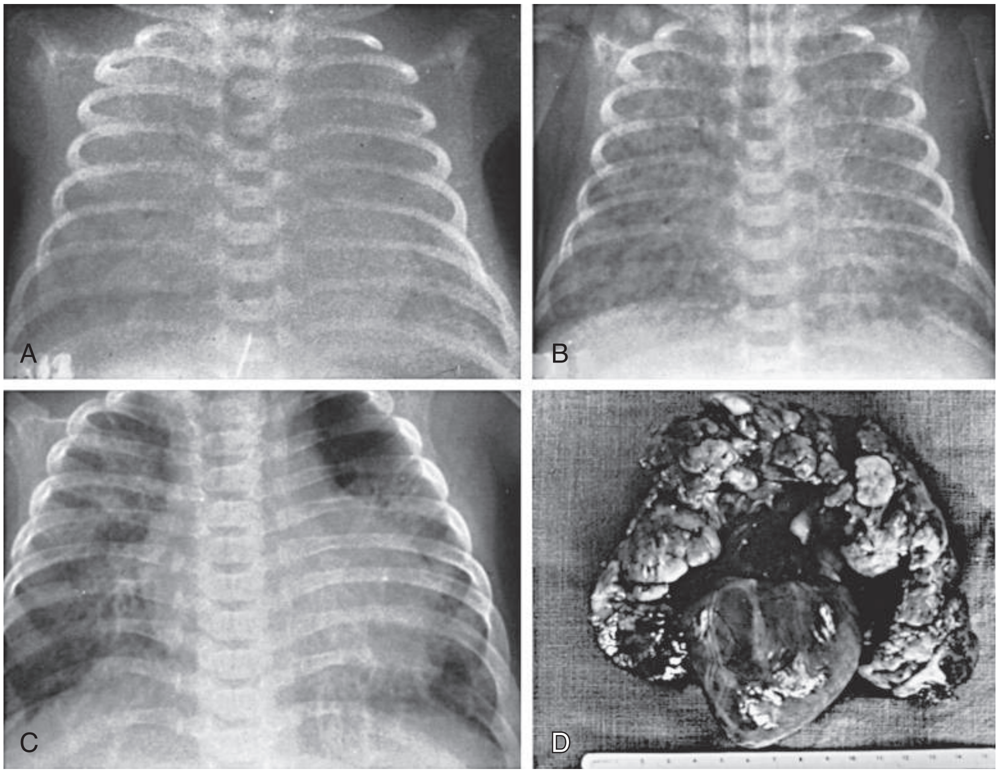

Figure 101-6 **Pulmonary changes in infants treated with prolonged, intermittent positive-pressure breathing with air containing 80-100% oxygen in the immediate postnatal period for the clinical syndrome of hyaline membrane disease. A,** A 5 day old infant with nearly complete opacification of the lungs. **B,** A 13 day old infant with "bubbly lungs" simulating the roentgenographic appearance of the Wilson-Mikity syndrome. **C,** A 7 mo old infant with irregular, dense strands in both lungs, hyperinflation, and cardiomegaly suggestive of chronic lung disease. **D,** Large right ventricle and a cobbly, irregular aerated lung of an infant who died at 11 mo of age. This infant also had a PDA. *(From Northway WH Jr, Rosan RC, Porter DY: Pulmonary disease following respirator therapy of hyaline-membrane disease,* N Engl J Med *276:357–368, 1967.)*

Table 101-2 Definition of BPD: Diagnostic Criteria*

	GESTATIONAL AGE	
	<32 Wk	**≥32 Wk**
Time point of assessment	36 wk postmenstrual age or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days **plus**	>28 days but <56 days postnatal age or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days **plus**
Mild BPD	Breathing room air at 36 wk postmenstrual age or discharge home, whichever comes first	Breathing room air by 56 days postnatal age or discharge home, whichever comes first
Moderate BPD	Need† for <30% oxygen at 36 wk postmenstrual age or discharge home, whichever comes first	Need† for <30% oxygen at 56 days postnatal age or discharge home, whichever comes first
Severe BPD	Need† for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 wk postmenstrual age or discharge home, whichever comes first	Need† for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days postnatal age or discharge home, whichever comes first

*BPD usually develops in neonates being treated with oxygen and PPV for respiratory failure, most commonly respiratory distress syndrome. Persistence of the clinical features of respiratory disease (tachypnea, retractions, crackles) is considered common to the broad description of BPD and has not been included in the diagnostic criteria describing the severity of BPD. Infants treated with >21% oxygen and/or PPV for nonrespiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless parenchymal lung disease also develops and they have clinical features of respiratory distress. A day of treatment with >21% oxygen means that the infant received >21% oxygen for more than 12 hr on that day. Treatment with >21% oxygen and/or PPV at 36 wk postmenstrual age or at 56 days postnatal age or discharge should not reflect an "acute" event, but should rather reflect the infant's usual daily therapy for several days preceding and after 36 wk postmenstrual age, 56 days postnatal age, or discharge.

†A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range.

BPD, bronchopulmonary dysplasia; NCPAP, nasal continuous positive airway pressure; PPV, positive-pressure ventilation.

From Jobe AH, Bancalari E: Bronchopulmonary dysplasia, Am J Respir Crit Care Med *163:1723–1729, 2001.*

intravenously twice daily [bid] or 2 mg/kg/dose orally bid) is the treatment of choice for acute fluid overload in infants with BPD. This loop diuretic has been demonstrated to decrease pulmonary interstitial emphysema and PVR, improve pulmonary function, and facilitate weaning from mechanical ventilation and oxygen. Adverse effects of long-term diuretic therapy are common and include hyponatremia, hypokalemia, alkalosis, azotemia, hypocalcemia, hypercalciuria, cholelithiasis, renal stones, nephrocalcinosis, and ototoxicity. Potassium chloride supplementation is often necessary. Hyponatremia should be treated with fluid restriction and a decrease in the dose or frequency of furosemide. Thiazide diuretics have been used in infants with BPD. Several trials of thiazide diuretics combined with spironolactone have

shown increased urine output with or without improvement in pulmonary mechanics in infants with BPD. Adverse effects include electrolyte imbalance.

Inhaled bronchodilators improve lung mechanics by decreasing airway resistance. Albuterol is a specific β_2-agonist used to treat bronchospasm in infants with BPD. Albuterol may improve lung compliance by decreasing airway resistance secondary to smooth muscle cell relaxation. Changes in pulmonary mechanics may last as long as 4-6 hr. Adverse effects include hypertension and tachycardia. Ipratropium bromide is a muscarinic antagonist related to atropine, but with more potent bronchodilator effects. Improvements in pulmonary mechanics have been demonstrated in BPD after ipratropium bromide inhalation. Combination therapy using albuterol and ipratropium bromide may be more effective than either agent alone. Few adverse effects have been noted. With current aerosol administration strategies, exactly how much medication is delivered to the airways and lungs of infants with BPD, especially if they are ventilator dependent, is unclear. Because significant smooth muscle relaxation does not appear to occur within the 1st few wk of life, aerosol therapy in the early stages of BPD is not indicated. Methylxanthines are used to increase respiratory drive, decrease apnea, and improve diaphragmatic contractility. Methylxanthines may also decrease PVR and increase lung compliance in infants with BPD, probably through direct smooth muscle relaxation. They also exhibit diuretic effects. These effects may accelerate weaning from mechanical ventilation. Synergy between theophylline and diuretics has been demonstrated. Theophylline has a half-life of 30-40 hr, is metabolized primarily to caffeine in the liver and may have adverse effects, such as tachycardia, gastroesophageal reflux, agitation, and seizures. Caffeine has a longer half-life than theophylline. Both are available in intravenous and enteral formulations.

Preventive therapy of BPD with postnatal dexamethasone may reduce the time to extubation and may decrease the risk of BPD but is associated with substantial short- and long-term risks, including hypertension, hyperglycemia, gastrointestinal bleeding and perforation, hypertrophic cardiomyopathy, sepsis, and poor weight gain and head growth. Survival is not improved, and infants who have been treated with dexamethasone have an increased risk of neurodevelopmental delay and cerebral palsy. The use of dexamethasone for the prevention of BPD is not recommended unless an infant has severe pulmonary disease, for example is ventilator dependent for at least 1 to 2 wk after birth. A rapid tapering course of therapy, starting at 0.25 mg/kg/day and lasting for 5-7 days, may be adequate. Inhaled beclomethasone does not prevent BPD but does decrease the need for systemic steroids. Inhaled corticosteroids facilitate earlier extubation of ventilated infants with BPD.

Physiologic abnormalities of the pulmonary circulation in BPD include elevated PVR and abnormal vasoreactivity. Acute exposure to even modest levels of hypoxemia causes large elevations in pulmonary artery pressure in infants with BPD with pulmonary hypertension. Higher oxygen saturations are effective in lowering pulmonary artery pressure. The current recommendation for treatment of patients with BPD and pulmonary hypertension is to maintain oxygen saturation values in the 91-95% range.

Low-dose iNO has no acute effects on lung function, cardiac function, or oxygenation in evolving BPD. The use of low-dose iNO may improve oxygenation in some infants with severe BPD, allowing decreased FIO_2 and ventilator support.

PROGNOSIS

Early provision of intensive observation and care of high-risk newborn infants can significantly reduce the morbidity and mortality associated with RDS and other acute neonatal illnesses. Antenatal steroids, postnatal surfactant use, and improved modes of ventilation have resulted in low mortality from RDS (≈10%). Mortality increases with decreasing gestational age. Optimal results depend on the availability of experienced and skilled personnel, care in specially designed and organized regional hospital units, proper equipment, and lack of complications such as severe asphyxia, intracranial hemorrhage, or irremediable congenital malformation. Surfactant therapy has reduced mortality from RDS by approximately 40%, but the incidence of BPD has not been measurably affected.

Although 85-90% of all infants surviving RDS after requiring ventilatory support with respirators are normal, the outlook is much better for those weighing >1,500 g. The long-term prognosis for normal pulmonary function in most infants surviving RDS is excellent. Survivors of severe neonatal respiratory failure may have significant pulmonary and neurodevelopmental impairment.

Prolonged ventilation, IVH, pulmonary hypertension, cor pulmonale, and oxygen dependence beyond 1 yr of life are poor prognostic signs. Mortality in infants with BPD ranges from 10-25% and is highest in infants who remain ventilator dependent for longer than 6 mo. Cardiorespiratory failure associated with cor pulmonale and acquired infection (respiratory syncytial virus) are common causes of death. Survivors with BPD often go home on a regimen of oxygen, diuretics, and bronchodilator therapy.

Pulmonary function slowly improves in most survivors owing to continued lung and airway growth and healing. Rehospitalization for impaired pulmonary function is most common during the 1st 2 yr of life. There is a gradual decrease in symptom frequency in children ages 6-9 yr from the frequency during the 1st 2 yr of life. Persistence of respiratory symptoms and abnormal pulmonary function test results are present in children ages 7-10 yr. Pulmonary function testing in children with a history of BPD shows persistent abnormalities in clinical moderate expiratory flow obstruction. Approximately 25-50% of very-low birthweight infants and more than 50% of children born at less than 26 wk of gestation continue to have abnormal spirometry as preadolescents. Many have asthma and respond to bronchodilators. Infants are at risk for severe respiratory syncytial virus infections and must receive prophylactic therapy (see Chapter 260). Airway obstruction and hyperactivity and hyperinflation are noted in some adolescent and adult survivors of BPD. High-resolution chest CT scanning or MRI studies in children and adults with a history of BPD reveal lung abnormalities that correlate directly with the degree of pulmonary function abnormality.

Noncardiorespiratory complications of BPD include growth failure, psychomotor retardation, and parental stress, as well as sequelae of therapy, such as nephrolithiasis, osteopenia, and electrolyte imbalance. Airway problems, such as tonsillar and adenoidal hypertrophy, vocal cord paralysis, subglottic stenosis, and tracheomalacia, are common and may aggravate or cause pulmonary hypertension. Subglottic stenosis may require tracheotomy or an anterior cricoid split procedure to relieve upper airway obstruction. Cardiac complications of BPD include pulmonary hypertension, cor pulmonale, systemic hypertension, left ventricular hypertrophy, and the development of aortopulmonary collateral vessels, which, if large, may cause heart failure.

Bibliography is available at Expert Consult.

101.4 Transient Tachypnea of the Newborn

Namasivayam Ambalavanan and Waldemar A. Carlo

Transient tachypnea is most common after term cesarean delivery. It is characterized by the early onset of tachypnea, sometimes with retractions, or expiratory grunting and, occasionally, cyanosis that is relieved by minimal oxygen supplementation (<40%). Most infants recover rapidly, usually within 3 days. The chest generally sounds clear without crackles or wheeze, and the chest radiograph shows prominent pulmonary vascular markings, fluid in the intralobar fissures, overaeration, flat diaphragms, and, rarely, small pleural effusions. Hypercapnia and acidosis are uncommon. Distinguishing the disease from RDS and other respiratory disorders (e.g., pneumonia) may be difficult, and transient tachypnea is frequently a diagnosis of exclusion; the distinctive features of transient tachypnea are rapid recovery of the infant and the absence of radiographic findings for RDS (hypoaeration, diffuse reticulogranular pattern, air bronchograms) and other lung disorders. The syndrome is believed to be secondary to slow absorption of fetal

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lung fluid, resulting in decreased pulmonary compliance and tidal volume and increased dead space. In severe cases, retained fetal lung fluid may interfere with the normal postnatal fall in PVR, resulting in persistent pulmonary hypertension; a mild surfactant deficiency may be present. Treatment is supportive. There is no evidence supporting the use of oral furosemide or racemic epinephrine in this disorder. One study demonstrated efficacy of inhaled salbutamol in enhancing resolution of transient tachypnea of the newborn.

Severe respiratory morbidity and mortality have been reported in infants born by elective cesarean section before full term (late preterm infants) who initially present with signs and symptoms of transient tachypnea. These infants often demonstrate refractory hypoxemia as a result of pulmonary hypertension and require ECMO support. The term "malignant transient tachypnea of the newborn" has been used to describe this condition. The initial approach to these infants is similar to that of RDS plus the concern for pulmonary hypertension.

Bibliography is available at Expert Consult.

101.5 Aspiration of Foreign Material (Fetal Aspiration Syndrome, Aspiration Pneumonia)

Waldemar A. Carlo

With fetal distress, infants often initiate vigorous respiratory movements in utero because of interference with the supply of oxygen through the placenta. Under such circumstances, the infant may aspirate amniotic fluid containing vernix caseosa, epithelial cells, meconium, blood, or material from the birth canal, which may block the smallest airways and interfere with alveolar exchange of oxygen and carbon dioxide. Pathogenic bacteria may accompany the aspirated material, and pneumonia may ensue, but even in noninfected cases, respiratory distress accompanied by radiographic evidence of aspiration is seen (Fig. 101-7).

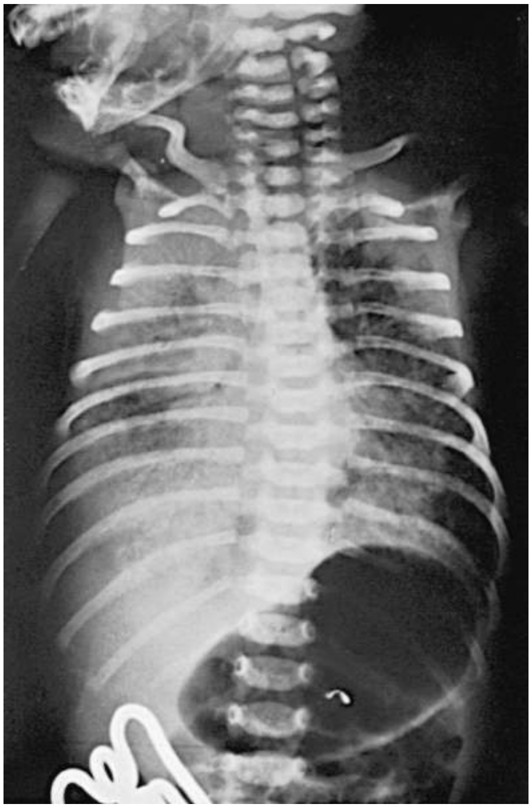

Figure 101-7 Fetal aspiration syndrome (aspiration pneumonia). Note the coarse granular pattern with irregular aeration typical of fetal distress from the aspiration of material contained in amniotic fluid, such as vernix caseosa, epithelial cells, and meconium. *(From Goodwin SR, Grave SA, Haberkern CM: Aspiration in intubated premature infants,* Pediatrics *75:85–88, 1985.)*

Postnatal pulmonary aspiration may also occur in newborn infants as a result of prematurity, tracheoesophageal fistula, esophageal and duodenal obstruction, gastroesophageal reflux, improper feeding practices, and administration of depressant medicines. To avoid aspiration of gastric contents, the stomach should be aspirated using a soft catheter just before surgery or other major procedures that require anesthesia or conscious sedation. The treatment of aspiration pneumonia is symptomatic and may include respiratory support and systemic antibiotics (see Chapters 109.8 and 397). Gradual improvement generally occurs over 3-4 days.

101.6 Meconium Aspiration

Namasivayam Ambalavanan and Waldemar A. Carlo

Meconium-stained amniotic fluid is found in 10-15% of births and usually occurs in term or postterm infants. Meconium aspiration syndrome (MAS) develops in 5% of such infants; 30% require mechanical ventilation and 3-5% die. Usually, but not invariably, fetal distress and hypoxia occur before the passage of meconium into amniotic fluid. The infants are meconium stained and may be depressed and require resuscitation at birth. Figure 101-8 shows the pathophysiology of the MAS. Infants with MAS are at increased risk of persistent pulmonary hypertension (see Chapter 101.7).

CLINICAL MANIFESTATIONS

Either in utero or with the first breath, thick, particulate meconium is aspirated into the lungs. The resulting small airway obstruction may produce respiratory distress within the first hours, with tachypnea, retractions, grunting, and cyanosis observed in severely affected infants. Partial obstruction of some airways may lead to pneumomediastinum, pneumothorax, or both. Overdistention of the chest may be prominent. The condition usually improves within 72 hr, but when its course requires assisted ventilation, it may be severe with a high risk for mortality. Tachypnea may persist for many days or even several weeks. The typical chest radiograph is characterized by patchy infiltrates, coarse streaking of both lung fields, increased anteroposterior diameter, and flattening of the diaphragm. A normal chest roentgenogram in an infant with severe hypoxemia and no cardiac malformation suggests the diagnosis of pulmonary hypertension (see Chapter 101.7).

PREVENTION

The risk of meconium aspiration may be decreased by rapid identification of fetal distress and initiation of prompt delivery in the presence of late fetal heart rate deceleration or poor beat-to-beat fetal heart rate variability. Despite initial enthusiasm for amnioinfusion, it does not reduce the risk of MAS, cesarean delivery, or other major indicators of maternal or neonatal morbidity. Intrapartum nasopharyngeal suctioning in infants with meconium-stained amniotic fluid does not reduce the risk for MAS.

TREATMENT

Routine intubation to aspirate the lungs of vigorous infants born through meconium-stained fluid is not effective in reducing the MAS or other major adverse outcomes. Depressed infants (those with hypotonia, bradycardia, or decreased respiratory effort) are at higher risk of MAS and may benefit from endotracheal intubation and suction to remove meconium from the airway before the first breath in the delivery room, but the data are inconclusive.

Treatment of the MAS includes supportive care and standard management for respiratory distress. The beneficial effect of mean airway pressure on oxygenation must be weighed against the risk of

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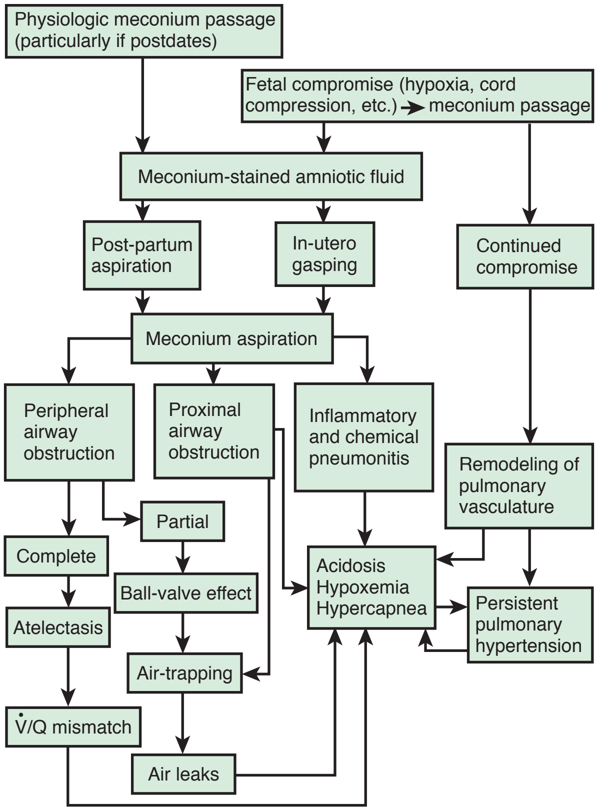

Figure 101-8 Pathophysiology of meconium passage and the meconium aspiration syndrome. $\dot{V}/\dot{Q}$, ventilation-perfusion ratio. *(From Wiswell TE, Bent RC: Meconium staining and the meconium aspiration syndrome: unresolved issues,* Pediatr Clin North Am *40:955–981, 1993.)*

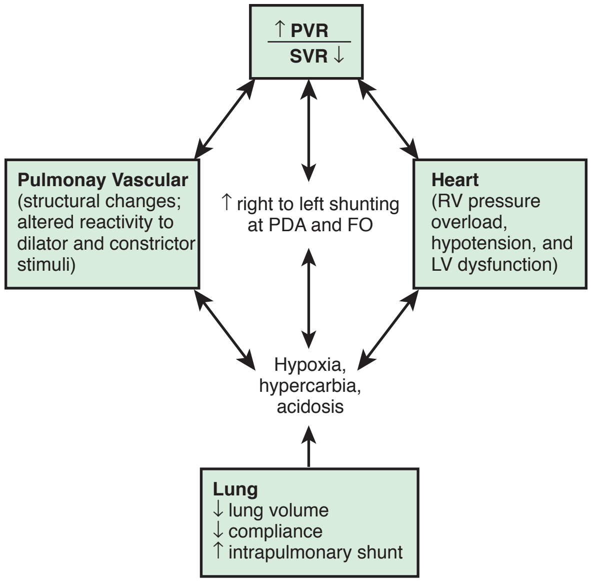

Figure 101-9 Cardiopulmonary interactions in PPHN. FO, foramen ovale; LV, left ventricular; PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; RV, right ventricular; SVR, systemic vascular resistance. *(From Kinsella JP, Abman SH: Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn,* J Pediatr *126:853–864, 1995.)*

pneumothorax. Administration of exogenous surfactant and/or iNO to infants with MAS and hypoxemic respiratory failure, or pulmonary hypertension requiring mechanical ventilation, decreases the need for ECMO, which is needed by the most severely affected infants who show no response to therapy. Severe meconium aspiration may be complicated by persistent pulmonary hypertension. Patients with MAS that is refractory to conventional mechanical ventilation may benefit from HFV or ECMO (see Chapter 101.7).

PROGNOSIS

The mortality rate of meconium-stained infants is considerably higher than that of nonstained infants. The decline in neonatal deaths caused by MAS during the last decades is related to improvements in obstetric and neonatal care. Residual lung problems are rare, but include symptomatic cough, wheezing, and persistent hyperinflation for up to 5-10 yr. The ultimate prognosis depends on the extent of CNS injury from asphyxia and the presence of associated problems such as pulmonary hypertension.

Bibliography is available at Expert Consult.

101.7 Persistent Pulmonary Hypertension of the Newborn (Persistent Fetal Circulation)

Namasivayam Ambalavanan and Waldemar A. Carlo

Persistent pulmonary hypertension of the newborn (PPHN) occurs mostly in in term and postterm infants. Predisposing factors include birth asphyxia, MAS, early-onset sepsis, RDS, hypoglycemia, polycythemia, maternal use of nonsteroidal antiinflammatory drugs with in utero constriction of the ductus arteriosus, maternal late trimester use of selective serotonin reuptake inhibitors, and pulmonary hypoplasia caused by diaphragmatic hernia, amniotic fluid leak, oligohydramnios, or pleural effusions. PPHN is often idiopathic. Some patients with PPHN have low plasma arginine and NO metabolite concentrations and polymorphisms of the carbamoyl phosphate synthase gene, findings suggestive of a possible subtle defect in NO production. The incidence is 1/500-1,500 live births with a wide variation among clinical centers.

PATHOPHYSIOLOGY

Persistence of the fetal circulatory pattern of right-to-left shunting through the PDA and foramen ovale after birth is a result of excessively high PVR. Fetal PVR is usually elevated relative to fetal systemic or postnatal pulmonary pressure. This fetal state normally permits shunting of oxygenated umbilical venous blood to the left atrium (and brain) through the foramen ovale, from which it bypasses the lungs through the ductus arteriosus and passes to the descending aorta. After birth, PVR normally declines rapidly as a consequence of vasodilation secondary to lung inflation, a rise in postnatal Pao_2, a reduction in $Paco_2$, increased pH, and release of vasoactive substances. Increased neonatal PVR may be (1) maladaptive from an acute injury (not demonstrating normal vasodilation in response to increased oxygen and other changes after birth); (2) the result of increased pulmonary artery medial muscle thickness and extension of smooth muscle layers into the usually nonmuscular, more peripheral pulmonary arterioles in response to chronic fetal hypoxia; (3) a consequence of pulmonary hypoplasia (diaphragmatic hernia, Potter syndrome); or (4) obstructive as a result of polycythemia or total anomalous pulmonary venous return, or of alveolar capillary dysplasia, which is a lethal autosomal recessive disorder characterized by thickened alveolar septa, increased muscularization of the pulmonary arterioles, a reduced number of capillaries, and misalignment of the intrapulmonary veins. Regardless of etiology, profound hypoxemia from right-to-left shunting and normal or elevated $Paco_2$ are present (Fig. 101-9).

CLINICAL MANIFESTATIONS

Infants with PPHN usually become ill in the delivery room or within the 1st 12 hr after birth. PPHN related to polycythemia, idiopathic

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causes, hypoglycemia, hypothermia, or asphyxia may result in severe cyanosis with tachypnea, although initial signs of respiratory distress may be minimal. Infants who have PPHN associated with meconium aspiration, group B streptococcal pneumonia, diaphragmatic hernia, or pulmonary hypoplasia usually exhibit cyanosis, grunting, flaring, retractions, tachycardia, and shock. Multiorgan involvement may be present (see Table 98-1 in Chapter 98). Myocardial ischemia, papillary muscle dysfunction with mitral and tricuspid regurgitation, and biventricular dysfunction produce cardiogenic shock with decreases in pulmonary blood flow, tissue perfusion, and oxygen delivery. The hypoxemia is often labile and out of proportion to the findings on chest radiographs.

DIAGNOSIS

PPHN should be suspected in all term infants who have cyanosis independent of a history of fetal distress, intrauterine growth restriction, meconium-stained amniotic fluid, hypoglycemia, polycythemia, diaphragmatic hernia, pleural effusions, or birth asphyxia. Hypoxemia is universal and is at least intermittently unresponsive to 100% oxygen given by oxygen hood, but it may respond transiently to hyperoxic hyperventilation administered after endotracheal intubation or to the application of a bag and mask. A Pao_2 or oxygen saturation gradient between a preductal (right radial artery) and a postductal (umbilical artery) site of blood sampling suggests right-to-left shunting through the ductus arteriosus. Foramen ovale shunting does not lead to a Pao_2 or oxygen saturation gradient.

Real-time echocardiography combined with Doppler flow imaging is very helpful in evaluating PPHN. Systolic flattening of the interventricular septum as the right ventricular systolic pressure approaches the left ventricular systolic pressure can be used to estimate the degree of pulmonary hypertension. The peak velocity of the tricuspid valve regurgitation jet, when present, yields a quantitative estimate of the right ventricular systolic pressure. Likewise, the direction and velocity of a shunt across the PDA provides a quantitative comparison between the aortic and pulmonary artery pressures. In advanced cases, right-to-left or bidirectional shunting across a PDA and/or a patent foramen ovale can be observed.

In asphyxia-associated and idiopathic PPHN, chest x-ray findings are normal, whereas in PPHN associated with pneumonia and diaphragmatic hernia, parenchymal opacification and bowel and/or liver in the chest, respectively, are seen. The **differential diagnosis** of PPHN includes cyanotic heart disease (especially obstructed total anomalous pulmonary venous return) congenital surfactant deficiency syndromes, alveolar-capillary dysplasia, and the associated etiologic entities that predispose to PPHN (hypoglycemia, polycythemia, sepsis, hypothermia).

TREATMENT

Therapy is directed toward correcting any predisposing condition (hypoglycemia, polycythemia, others) and improving poor tissue oxygenation. The response to therapy is often unpredictable, transient, and complicated by the adverse effects of drugs or mechanical ventilation. Initial management includes oxygen administration and correction of acidosis, hypotension, and hypercapnia. Persistent hypoxemia should be managed with intubation and mechanical ventilation.

The optimal approach to mechanical ventilation has evolved. In the pre-iNO era, treatment of severe PPHN consisted of instituting mechanical ventilation with 1 or more of the following: muscle relaxants, hyperventilation, and alkalinization with sodium bicarbonate. These therapies may lead to complications associated with hypocarbia including reduced cerebral blood flow, cerebral palsy, and deafness; volutrauma; and impaired cardiac function which have resulted in less use of these practices. Currently, infants with PPHN are usually managed without hyperventilation and/or alkalinization. In skilled hands, "gentle ventilation" with normocarbia or permissive hypercarbia and avoidance of hypoxemia result in excellent outcomes and a low incidence of chronic lung disease and ECMO use.

Because of their instability and ability to fight the ventilator, newborns with PPHN usually require sedation. The use of paralytic agents is controversial and reserved for the newborn that cannot be treated with sedatives alone. Muscle relaxants may promote atelectasis of dependent lung regions and ventilation–perfusion mismatch and may be associated with an increased risk of death.

Inotropic therapy is frequently needed to support blood pressure and perfusion. Whereas dopamine is frequently used as a first-line agent, other agents, such as dobutamine, epinephrine, and milrinone may be helpful when myocardial contractility is poor. Some of the sickest newborns with PPHN demonstrate hypotension refractory to vasopressor administration. This results from desensitization of the cardiovascular system to catecholamines by overwhelming illness and relative adrenal insufficiency. Hydrocortisone rapidly upregulates cardiovascular adrenergic receptor expression and serves as a hormone substitute in cases of adrenal insufficiency.

NO is an endothelium-derived signaling molecule that relaxes vascular smooth muscle and can be delivered to the lung by inhalation. Use of iNO reduces the need for ECMO support by approximately 40%. The optimal starting dose is 20 ppm. Higher doses have not been shown to be more effective and are associated with side effects including methemoglobinemia and increased levels of nitrogen dioxide, a pulmonary irritant. Most newborns require iNO for <5 days. Although NO has been used as long-term therapy in children and adults with primary pulmonary hypertension, prolonged dependency is rare in neonates and suggests the presence of lung hypoplasia, congenital heart disease, or alveolar capillary dysplasia. The maximal safe duration of iNO therapy is unknown. The dose can be weaned to 5 ppm after 6-24 hr of therapy. The dose can then be weaned slowly and discontinued when the Fio_2 is <0.6 and the iNO dose is 1 ppm. Abrupt discontinuation should be avoided as it may cause rebound pulmonary hypertension. iNO should be used only at institutions that offer ECMO support or have the capability of transporting an infant on iNO therapy if a referral for ECMO is necessary. Some infants with PPHN do not respond adequately to iNO. Therapy with continuous inhaled or intravenous prostacyclin (prostaglandin I_2) has improved oxygenation and outcome in infants with PPHN. The safety and efficacy of sildenafil (a type 5 phosphodiesterase inhibitor) in newborns with PPHN is under investigation; initial results are promising.

Extracorporeal Membrane Oxygenation

In 5-10% of patients with PPHN, the response to 100% oxygen, mechanical ventilation, and drugs is poor. In such patients, two parameters have been used to predict mortality, the alveolar-arterial oxygen gradient (PAO_2–Pao_2), and the oxygenation index, which is calculated as follows: Fio_2 (as %) × MAP/Pao_2.

An alveolar–arterial gradient >620 for 8-12 hr and an oxygenation index >40 that is unresponsive to iNO predict a high mortality rate (>80%) and are indications for ECMO. ECMO is used to treat carefully selected, severely ill infants with hypoxemic respiratory failure caused by RDS, meconium aspiration pneumonia, congenital diaphragmatic hernia, PPHN, or sepsis.

ECMO is a form of cardiopulmonary bypass that augments systemic perfusion and provides gas exchange. Most experience has been with venoarterial bypass, which requires carotid artery ligation and the placement of large catheters in the right internal jugular vein and carotid artery. Venovenous bypass avoids carotid artery ligation and provides gas exchange, but it does not support cardiac output. Blood is initially pumped through the ECMO circuit at a rate that approximates 80% of the estimated cardiac output, 150-200 mL/kg/min. Venous return passes through a membrane oxygenator, is rewarmed, and returns to the aortic arch in venoarterial ECMO and to the right atrium in venovenous ECMO. Venous oxygen saturation values are used to monitor tissue oxygen delivery and subsequent extraction for infants undergoing venoarterial ECMO, whereas arterial oxygen saturation values are used to monitor oxygenation for infants receiving venovenous ECMO.

Because ECMO requires complete heparinization to prevent clotting in the circuit, it cannot be used in patients with or at high risk for IVH (weight <2 kg, gestational age <34 wk). In addition, infants for whom ECMO is being considered should have reversible lung

disease, no signs of systemic bleeding, an absence of severe asphyxia or lethal malformations, and they should have been ventilated for less than 10 days. Complications of ECMO include thromboembolism, air embolization, bleeding, stroke, seizures, atelectasis, cholestatic jaundice, thrombocytopenia, neutropenia, hemolysis, infectious complications of blood transfusions, edema formation, and systemic hypertension.

PROGNOSIS

Survival in patients with PPHN varies with the underlying diagnosis. The long-term outcome for infants with PPHN is related to the associated hypoxic-ischemic encephalopathy and the ability to reduce PVR. The long-term prognosis for infants who have PPHN and who survive after treatment with hyperventilation is comparable to that for infants who have underlying illnesses of equivalent severity (birth asphyxia, hypoglycemia, polycythemia). The outcome for infants with PPHN who are treated with ECMO is also favorable; >80-90% survive, and 60-75% of survivors appear normal at 1-3.5 yr of age. Survival of infants born with congenital diaphragmatic hernia (CDH) has increased over the past 10 yr to 67%; benchmark institutions are reporting survival rates >80%. Those infants with CDH who require ECMO continue to have a lower survival than the general neonatal population undergoing ECMO (~50%).

Bibliography is available at Expert Consult.

101.8 Diaphragmatic Hernia

Akhil Maheshwari and Waldemar A. Carlo

A diaphragmatic hernia is defined as a communication between the abdominal and thoracic cavities with or without abdominal contents in the thorax (Fig. 101-10). The etiology is usually congenital but may be traumatic. The symptoms and prognosis depend on the location of the defect and associated anomalies. The defect may be at the esophageal hiatus (hiatal), paraesophageal (adjacent to the hiatus), retrosternal (Morgagni), or at the posterolateral (Bochdalek) portion of the diaphragm. The term *congenital diaphragmatic hernia* typically refers to the Bochdalek form. These lesions may cause significant respiratory distress at birth, can be associated with other congenital anomalies, and have significant mortality and long-term morbidity. The overall survival from the CDH Study Group is 67%. The Bochdalek hernia accounts for up to 90% of the hernias seen in the newborn period, with 80-90% occurring on the left side. The Morgagni hernia accounts for 2-6% of congenital diaphragmatic defects. The size of the defect is highly variable, ranging from a small hole to complete agenesis of this area of the diaphragm.

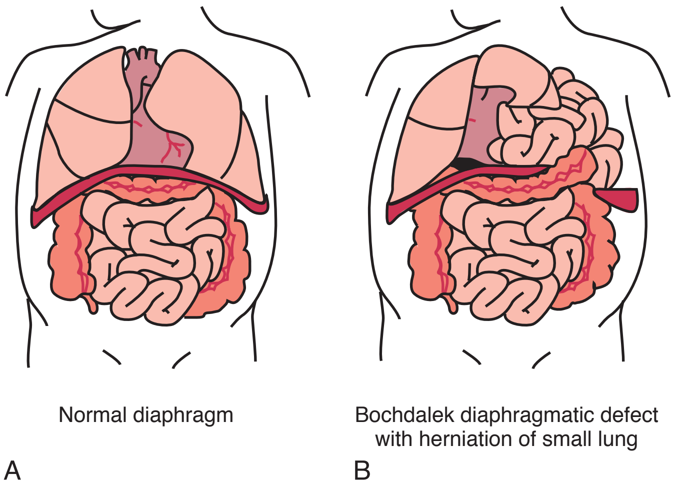

Figure 101-10 A, A normal diaphragm separating the abdominal and thoracic cavity. **B,** Diaphragmatic hernia with a small lung and abdominal contents in the thoracic cavity.

CONGENITAL DIAPHRAGMATIC HERNIA (BOCHDALEK)

Pathology and Etiology

Although CDH is characterized by a structural diaphragmatic defect, a major limiting factor for survival is the associated **pulmonary hypoplasia.** Lung hypoplasia was initially thought to be solely caused by the compression of the lung from the herniated abdominal contents, which impaired lung growth. However, emerging evidence indicates that pulmonary hypoplasia, at least in some cases, may precede the development of the diaphragmatic defect.

Pulmonary hypoplasia is characterized by a reduction in pulmonary mass and the number of bronchial divisions, respiratory bronchioles, and alveoli. The pathology of pulmonary hypoplasia and CDH includes abnormal septa in the terminal saccules, thickened alveoli, and thickened pulmonary arterioles. Biochemical abnormalities include relative surfactant deficiencies, increased glycogen in the alveoli, and decreased levels of phosphatidylcholine, total DNA, and total lung protein, all of which contribute to limited gas exchange.

Epidemiology

The incidence of CDH is between 1/2,000 and 1/5,000 live births, with females affected twice as often as males. Defects are more common on the left (85%) and are occasionally (<5%) bilateral. Pulmonary hypoplasia and malrotation of the intestine are part of the lesion, not associated anomalies. Most cases of CDH are sporadic, but familial cases have been reported. Associated anomalies have been reported in up to 30% of cases; these include CNS lesions, esophageal atresia, omphalocele, and cardiovascular lesions. CDH is recognized as part of several chromosomal syndromes: trisomy 21, trisomy 13, trisomy 18, Fryns, Brachmann-de Lange, Pallister-Killian, and Turner.

Diagnosis and Clinical Presentation

CDH can be diagnosed on prenatal ultrasonography (between 16 and 24 wk of gestation) in >50% of cases. High-speed fetal MRI can further define the lesion. Findings on ultrasonography may include polyhydramnios, chest mass, mediastinal shift, gastric bubble or a liver in the thoracic cavity, and fetal hydrops. Certain imaging features may predict outcome; these include lung : head size ratio. Nonetheless, no definitive characteristic reliably predicts outcome. After delivery, a chest radiograph is needed to confirm the diagnosis (Fig. 101-11). In some infants with an echogenic chest mass, further imaging is required. The **differential diagnosis** may include other diaphragm disorders such as eventration, a cystic lung lesion (pulmonary sequestration, cystic adenomatoid malformation), and others.

Arriving at the diagnosis early in pregnancy allows for prenatal counseling, possible fetal interventions, and planning for postnatal care. A referral to a center providing high-risk obstetrics, pediatric surgery, and tertiary care neonatology is advised. Careful evaluation for other anomalies should include echocardiography and amniocentesis. To avoid unnecessary pregnancy termination and unrealistic expectations, an experienced multidisciplinary group must carefully counsel the parents of a child diagnosed with a diaphragmatic hernia.

Respiratory distress is a cardinal sign in babies with CDH. It may occur immediately after birth or there may be a "honeymoon" period of up to 48 hr during which the baby is relatively stable. Early respiratory distress, within 6 hr after birth, is thought to be a poor prognostic sign. Respiratory distress is characterized clinically by tachypnea, grunting, use of accessory muscles, and cyanosis. *Children with CDH may also have a scaphoid abdomen and increased chest wall diameter.* Bowel sounds may also be heard in the chest with decreased breath sounds bilaterally. The point of maximal cardiac impulse may be displaced away from the side of the hernia if mediastinal shift has occurred. A chest x-ray and passage of a nasal gastric tube are all that is usually required to confirm the diagnosis.

A small group of infants with CDH present beyond the neonatal period. Patients with a delayed presentation may experience vomiting

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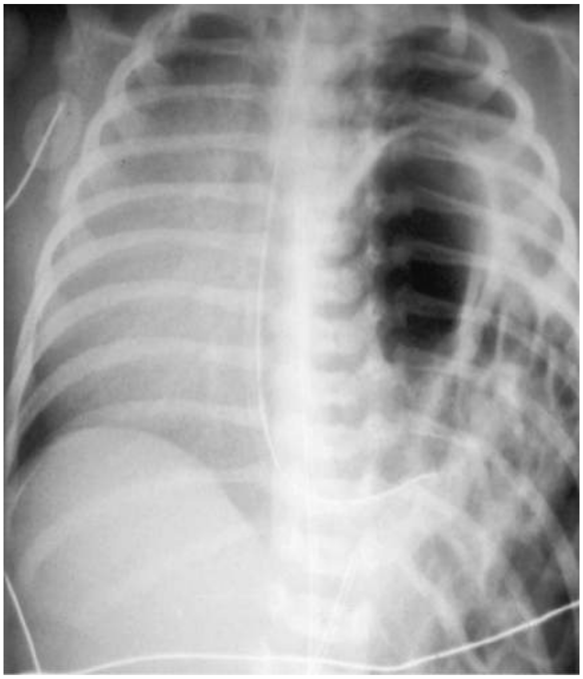

Figure 101-11 This chest radiograph shows a stomach, nasogastric tube, and small bowel contents in the thoracic cavity, consistent with a CDH.

as a result of intestinal obstruction or mild respiratory symptoms. Occasionally, incarceration of the intestine proceeds to ischemia with sepsis and shock. Unrecognized diaphragmatic hernia is a rare cause of sudden death in infants and toddlers. Group B streptococcal sepsis has been associated with delayed onset of symptoms and a CDH (often right side).

Treatment

Initial Management

Aggressive respiratory support is often needed in children with CDH. This includes rapid endotracheal intubation, sedation, and possibly paralysis. Arterial (preductal and postductal) and central venous (umbilical) lines are mandated, as are a urinary catheter and nasogastric tube. A preductal arterial oxygen saturation (Spo_2) value ≥85% should be the minimum goal. *Prolonged mask ventilation in the delivery room, which enlarges the stomach and small bowel and thus makes oxygenation more difficult, must be avoided.* Volutrauma is a significant problem. Gentle ventilation with **permissive hypercapnia** reduces lung injury, need for ECMO, and mortality. Factors that contribute to pulmonary hypertension (hypoxia, acidosis, hypothermia) should be avoided. Echocardiography is important to guide therapeutic decisions by measuring pulmonary and system vascular pressures and defining the presence of cardiac dysfunction. Routine use of inotropes is indicated in the presence of left ventricular dysfunction. Babies with CDH may be surfactant deficient. Although surfactant is commonly used, no study has proven that it is beneficial in treatment of CDH.

Ventilation Strategies

Conventional mechanical ventilation, HFOV, and ECMO are the 3 main strategies to support respiratory failure in the newborn with CDH. The goal is to maintain oxygenation and carbon dioxide elimination without inducing volutrauma. The first modality to be used is conventional ventilation. Hyperventilation to induce alkalosis and decrease ductal shunting has not proved effective and should be avoided. Permissive hypercapnia has reduced lung injury and mortality rates in several studies. HFOV can be used early to prevent lung injury by using lower airway pressures.

NO is a selective pulmonary vasodilator. Its use reduces ductal shunting and pulmonary pressures and results in improved oxygenation. Although it has been helpful in PPHN, randomized trials have not demonstrated improved survival or reduced need for ECMO when NO is used in newborns with CDH. Nonetheless, it is used in patients with CDH before ECMO is started (see Chapter 101.7).

Extracorporeal Membrane Oxygenation

The availability of ECMO and the utility of preoperative stabilization have improved survival of babies with CDH. ECMO is the therapeutic option in children in whom conventional ventilation or conventional ventilation and HFOV fail. ECMO is most commonly used before repair of the defect. Several objective criteria for ECMO have been developed (see Chapter 101.7).

Birthweight and the 5-min Apgar score may be the best predictors of outcome in patients treated with ECMO. The lower limit of weight for ECMO is 2,000 g.

The duration of ECMO for neonates with diaphragmatic hernia is longer (7-14 days) than for those with persistent fetal circulation or meconium aspiration, and may last up to 2-4 wk. Timing of repair of the diaphragm while the infant receives ECMO is controversial; some experts prefer early repair to allow a greater duration of ECMO after the repair, whereas many defer repair until the infant has demonstrated the ability to tolerate weaning from ECMO. The recurrence of pulmonary hypertension is associated with a high mortality, and weaning from ECMO support should be cautious. If the patient cannot be weaned from ECMO after repair of CDH, options include discontinuing support and, in rare cases, lung transplantation.

Novel Strategies for Infants with Congenital Diaphragmatic Hernia

The most reliable prenatal prognosticators of outcomes in children with CDH studied is fetal ultrasonography. A prospective study using this modality at 24-26 wk compared fetal lung : head size ratio. There were no survivors when the lung : head size ratio was <1, and all babies with lung : head size ratio >1.4 survived. A second important consideration was the presence of liver in the thoracic cavity, which is a poor prognostic feature. Human studies have shown no benefit for in utero repair of CDH.

Tracheal occlusion in utero is based on the observation that in utero fetal lung fluid plays a critical role in lung growth and maturity. A deficiency of lung fluid results in pulmonary hypoplasia. Initial studies in affected fetuses have not demonstrated success, but new preliminary reports are showing some efficacy. Partial liquid ventilation after birth is an experimental therapy under investigation in adults and children with severe respiratory failure. Partial liquid ventilation increases FRC by recruiting collapsed alveoli, thereby improving ventilation–perfusion mismatches and compliance. It also may reduce lung injury and increase surfactant production.

Surgical Repair

The ideal time to repair the diaphragmatic defect is under debate. Most experts wait at least 48 hr after stabilization and resolution of the pulmonary hypertension. Good relative indicators of stability are the requirement for conventional ventilation only, a low peak inspiratory pressure, and a FIO_2 <50. If the newborn is on ECMO, an ability to be weaned from this support should be a consideration before surgical repair. In some centers, the repair is done with the cannulas in place; in other centers, the cannulas are removed. A subcostal approach is the most frequently used (Fig. 101-12). This allows for good visualization of the defect and, if the abdominal cavity cannot accommodate the herniated contents, a polymeric silicone (Silastic) patch can be placed. Both laparoscopic and thoracoscopic repairs have been reported, but these should be reserved for only the most stable infants.

The defect size and amount of native diaphragm present are variable. Whenever possible, a primary repair using native tissue is performed. If the defect is too large, a porous polytetrafluoroethylene (Gore-Tex) patch is used.

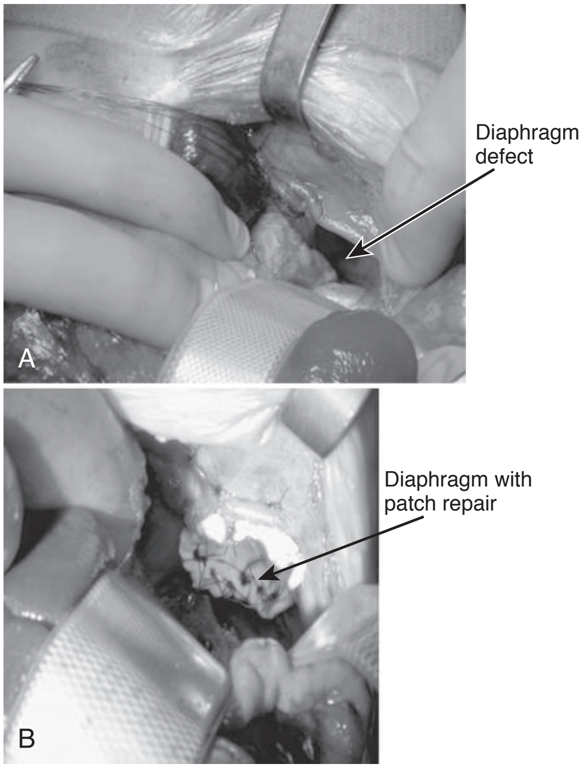

Figure 101-12 **A,** An intraoperative picture of a CDH before repair. **B,** An intraoperative picture of a patch repair of a CDH.

There is a higher recurrence rate of CDH among children with patches (the patch does not grow as the child grows) than among those with repairs with native tissue. A loosely fitted patch may reduce the recurrence rates. Pulmonary hypertension must be monitored carefully, and in some instances, a postoperative course of ECMO is needed. Other recognized complications include bleeding, chylothorax, and bowel obstruction.

Outcome and Long-Term Survival

Overall survival of liveborn infants with CDH is 67%. The incidence of spontaneous fetal demise is 7-10%. Relative predictors of a poor prognosis include an associated major anomaly, symptoms before 24 hr of age, severe pulmonary hypoplasia, herniation to the contralateral lung, and the need for ECMO.

Pulmonary problems continue to be a source of morbidity for long-term survivors of CDH. Children receiving CDH repair who were studied at 6-11 yr of age demonstrated significant decreases in forced expiratory flow at 50% of vital capacity and decreased peak expiratory flow. Both obstructive and restrictive patterns can occur. Those without severe pulmonary hypertension and barotrauma do the best. Those at highest risk include children who required ECMO and patch repair, but the data clearly show that CDH survivors who did not require ECMO also need frequent attention to pulmonary issues. At discharge, up to 20% of infants require oxygen, but only 1-2% require oxygen past 1 yr of age. **BPD** is frequently documented radiographically but will improve as more alveoli develop and the child ages.

Gastroesophageal reflux disease is reported in more than 50% of children with CDH. It is more common in those children whose diaphragmatic defect involves the esophageal hiatus. Intestinal obstruction is reported in up to 20% of children and may result from a midgut volvulus, adhesions, or a recurrent hernia that became incarcerated. Recurrent diaphragmatic hernia is reported in 5-20% in most series. Children with patch repairs are at highest risk.

Children with CDH typically have **delayed growth** in the 1st 2 yr of life. Contributing factors include poor intake, gastroesophageal reflux disease, and a caloric requirement that may be higher because of the energy required to breathe. Many children normalize and "catch up" in growth by the time they are 2 yr old.

Neurocognitive defects are common and may result from the disease or the interventions. The incidence of neurologic abnormalities is higher in infants who require ECMO (67% vs. 24% of those who do not). The abnormalities are similar to those seen in neonates treated with ECMO for other diagnoses and include transient and permanent developmental delay, abnormal hearing or vision, and seizures. Serious hearing loss may occur in up to 28% of children who underwent ECMO. The majority of neurologic abnormalities are classified as mild to moderate.

Other long-term problems occurring in this population include pectus excavatum and scoliosis. Survivors of CDH repair, particularly those requiring ECMO support, have a variety of long-term abnormalities that appear to improve with time but require close monitoring and multidisciplinary support.

Bibliography is available at Expert Consult.

Figure 101-13 A chest radiograph demonstrating a Morgagni hernia.

101.9 Foramen of Morgagni Hernia

Akhil Maheshwari and Waldemar A. Carlo

The anteromedial diaphragmatic defect through the foramen of Morgagni accounts for 2-6% of diaphragmatic hernias. Failure of the sternal and crural portions of the diaphragm to meet and fuse produces this defect. These defects are usually small, with a greater transverse than anteroposterior diameter, and are more commonly right-sided (90%) but may be bilateral (Fig. 101-13). The transverse colon or small intestine or liver is usually contained in the hernial sac. The majorities of children with these defects are asymptomatic and are diagnosed beyond the neonatal period. The diagnosis is usually made on chest radiograph when a child is evaluated for another reason. The anteroposterior radiograph shows a structure behind the heart, and a lateral film localizes the mass to the retrosternal area. Chest CT or MRI will confirm the diagnosis. When symptoms occur, they can be recurrent respiratory infections, cough, vomiting, or reflux; in rare instances, incarceration may occur. Repair is recommended for all patients, in view of the risk of bowel strangulation, and can be accomplished laparoscopically or by an open approach. Prosthetic material is rarely required.

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101.10 Paraesophageal Hernia

Akhil Maheshwari and Waldemar A. Carlo

Paraesophageal hernia is differentiated from hiatal hernia in that the gastroesophageal junction is in the normal location. The herniation of the stomach alongside or adjacent to the gastroesophageal junction is prone to incarceration with strangulation and perforation. A previous Nissen fundoplication and other diaphragmatic procedures are risk factors. This unusual diaphragmatic hernia should be repaired promptly after identification.

101.11 Eventration

Akhil Maheshwari and Waldemar A. Carlo

Eventration of the diaphragm is an abnormal elevation, consisting of a thinned diaphragmatic muscle that causes elevation of the entire hemidiaphragm or, more commonly, the anterior aspect of the hemidiaphragm. This elevation produces a paradoxical motion of the affected hemidiaphragm. Most eventrations are asymptomatic and do not require repair. A congenital form is the result of either incomplete development of the muscular portion or central tendon or abnormal development of the phrenic nerves. Congenital eventration may affect lung development, but it has not been associated with pulmonary hypoplasia. The **differential diagnosis** includes diaphragmatic paralysis, diaphragmatic hernia, traction injury, and iatrogenic injury after heart surgery. Eventration is also associated with pulmonary sequestration, congenital heart disease, and chromosomal trisomies. Most eventrations are asymptomatic and do not require repair. The indications for surgery include continued need for mechanical ventilation, recurrent infections, and failure to thrive. Large or symptomatic eventrations can be repaired by plication through an abdominal or thoracic approach that is minimally invasive.

Bibliography is available at Expert Consult.

101.12 Extrapulmonary Air Leaks (Pneumothorax, Pneumomediastinum, Pulmonary Interstitial Emphysema, Pneumopericardium)

Waldemar A. Carlo

Asymptomatic pneumothorax, usually unilateral, is estimated to occur in 1-2% of all newborn infants; symptomatic pneumothorax and pneumomediastinum are less common (see Chapter 94). The incidence of pneumothorax is increased in infants with lung diseases such as meconium aspiration and RDS; in those who receive assisted ventilation, especially if high ventilator support is necessary; and in infants with urinary tract anomalies or oligohydramnios.

ETIOLOGY AND PATHOPHYSIOLOGY

The most common cause of pneumothorax is overinflation resulting in alveolar rupture. It may be "spontaneous" or caused by underlying pulmonary disease, such as lobar emphysema or rupture of a congenital lung cyst or pneumatocele, to trauma, or to a "ball-valve" type of bronchial or bronchiolar obstruction resulting from aspiration.

Pneumothorax associated with **pulmonary hypoplasia** is common, tends to occur during the 1st few hr after birth, and is caused by reduced alveolar surface area and poorly compliant lungs. It is associated with disorders of decreased amniotic fluid volume (Potter syndrome, renal agenesis, renal dysplasia, chronic amniotic fluid leak), decreased fetal breathing movement (oligohydramnios, neuromuscular disease), pulmonary space-occupying lesions (diaphragmatic hernia, pleural effusion, chylothorax), and thoracic abnormalities (thoracic dystrophies).

Gas from a ruptured alveolus escapes into the interstitial spaces of the lung, where it may cause interstitial emphysema or dissect along the peribronchial and perivascular connective tissue sheaths to the hilum of the lung. If the volume of escaped air is great enough, it may collect in the mediastinal space (**pneumomediastinum**) or rupture into the pleural space (**pneumothorax**), subcutaneous tissue (**subcutaneous emphysema**), peritoneal cavity (**pneumoperitoneum**), and/or pericardial sac (**pneumopericardium**). Rarely, increased mediastinal pressure may compress the pulmonary veins at the hilum and thereby interfere with pulmonary venous return to the heart and cardiac output. On occasion, air may embolize into the circulation (**pulmonary air embolism**) and produce cutaneous blanching, air in intravascular catheters, an air-filled heart and vessels on chest roentgenograms, and death.

Tension pneumothorax occurs if an accumulation of air within the pleural space is sufficient to elevate intrapleural pressure above atmospheric pressure. Unilateral tension pneumothorax results in impaired ventilation not only in the ipsilateral lung but also in the contralateral lung owing to a shift in the mediastinum toward the contralateral side. Compression of the vena cava and torsion of the great vessels may interfere with venous return.

CLINICAL MANIFESTATIONS

The physical findings of a clinically asymptomatic **pneumothorax** are hyperresonance and diminished breath sounds over the involved side of the chest with or without tachypnea.

Symptomatic pneumothorax is characterized by respiratory distress, which varies from merely high respiratory rate to severe dyspnea, tachypnea, and cyanosis. Irritability and restlessness or apnea may be the earliest signs. The onset is usually sudden but may be gradual; an infant may rapidly become critically ill. The chest may appear asymmetric with an increased anteroposterior diameter and bulging of the intercostal spaces on the affected side; other signs may be hyperresonance and diminished or absence of breath sounds. The heart is displaced toward the unaffected side, resulting in displacement of the cardiac apex and point of maximal impulse of the heart. The diaphragm is displaced downward, as is the liver with right-sided pneumothorax, and may result in abdominal distention. Because pneumothorax may be bilateral in approximately 10% of patients, symmetry of findings does not rule it out. In tension pneumothorax, signs of shock may be noted.

Pneumomediastinum can occur in patients with pneumothorax and is usually asymptomatic. The degree of respiratory distress depends on the amount of trapped gas. If it is great, bulging of the midthoracic area is observed, the neck veins are distended, and blood pressure is low. The last 2 findings are a result of tamponade of the systemic and pulmonary veins. Although often asymptomatic, subcutaneous emphysema in newborn infants is almost pathognomonic of pneumomediastinum.

Pulmonary interstitial emphysema may precede the development of a pneumothorax or may occur independently and lead to increasing respiratory distress as a result of decreased compliance, hypercapnia, and hypoxemia. Hypoxemia is caused by an increased alveolar–arterial oxygen gradient and intrapulmonary shunting. Progressive enlargement of blebs of gas may result in cystic dilation and respiratory deterioration resembling pneumothorax. In severe cases, pulmonary interstitial emphysema precedes the development of BPD. Avoidance of high inspiratory or mean airway pressures may prevent the development of pulmonary interstitial emphysema. Treatment may include bronchoscopy in patients with evidence of mucous plugging, selective intubation and ventilation of the uninvolved bronchus, oxygen, general respiratory care, and HFV.

DIAGNOSIS

Pneumothorax and other air leaks should be suspected in newborn infants who show signs of respiratory distress, are restless or irritable, or have a sudden change in condition. The diagnosis of pneumothorax is established by radiography, with the edge of the collapsed

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lung standing out in relief against the pneumothorax (Fig. 101-14); pneumomediastinum is signified by hyperlucency around the heart border and between the sternum and the heart border (Fig. 101-15). Transillumination of the thorax is often helpful in the emergency diagnosis of pneumothorax; the affected side transmits excessive light. Associated renal anomalies are identified by ultrasonography. Pulmonary hypoplasia is suggested by signs of uterine compression (extremity contractures), a small thorax on chest roentgenograms, severe hypoxia with hypercapnia, and signs of the primary disease (hypotonia, diaphragmatic hernia, Potter syndrome).

Pneumopericardium may be asymptomatic, requiring only general supportive treatment, but it usually manifests as sudden shock with tachycardia, muffled heart sounds, and poor pulses suggesting tamponade. **Pneumoperitoneum** from air dissecting through the diaphragmatic apertures during mechanical ventilation may be confused with intestinal perforation. Abdominal paracentesis can be helpful in differentiating the two conditions. The presence of organisms on Gram stain of intestinal contents suggests the latter. Occasionally, pneumoperitoneum can result in an abdominal compartment syndrome requiring decompression.

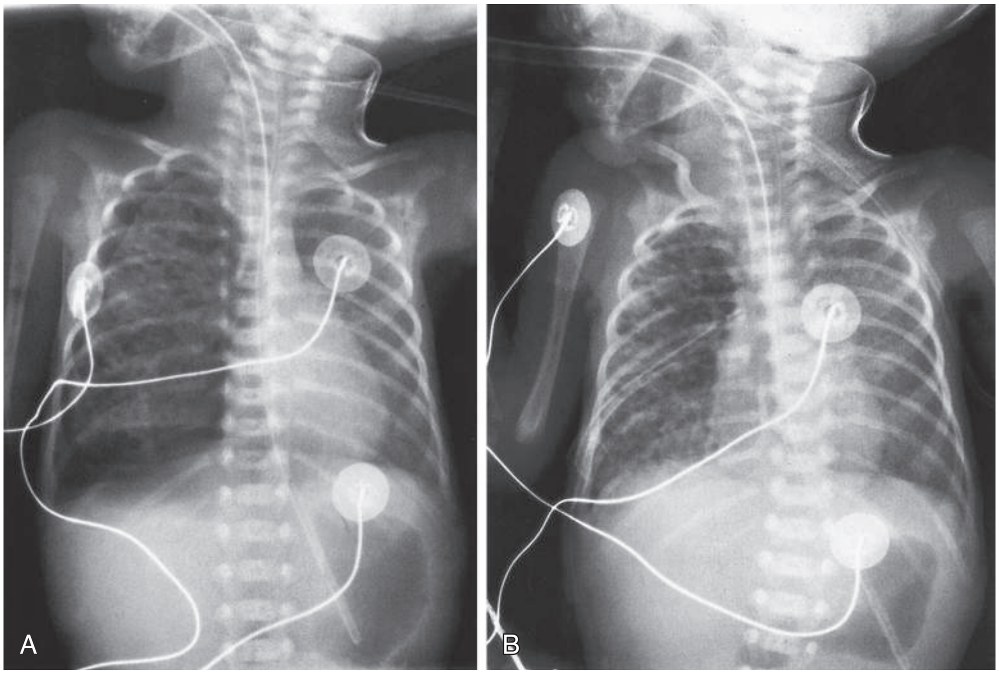

Figure 101-14 **A,** Right-sided tension pneumothorax and widespread right lung pulmonary interstitial emphysema in a preterm infant receiving intensive care. **B,** Resolution of pneumothorax with a chest tube in place. Pulmonary interstitial emphysema (PIE) persists. *(From Meerstadt PWD, Gyll C:* Manual of neonatal emergency x-ray interpretation, *Philadelphia, 1994, WB Saunders, p. 73.)*

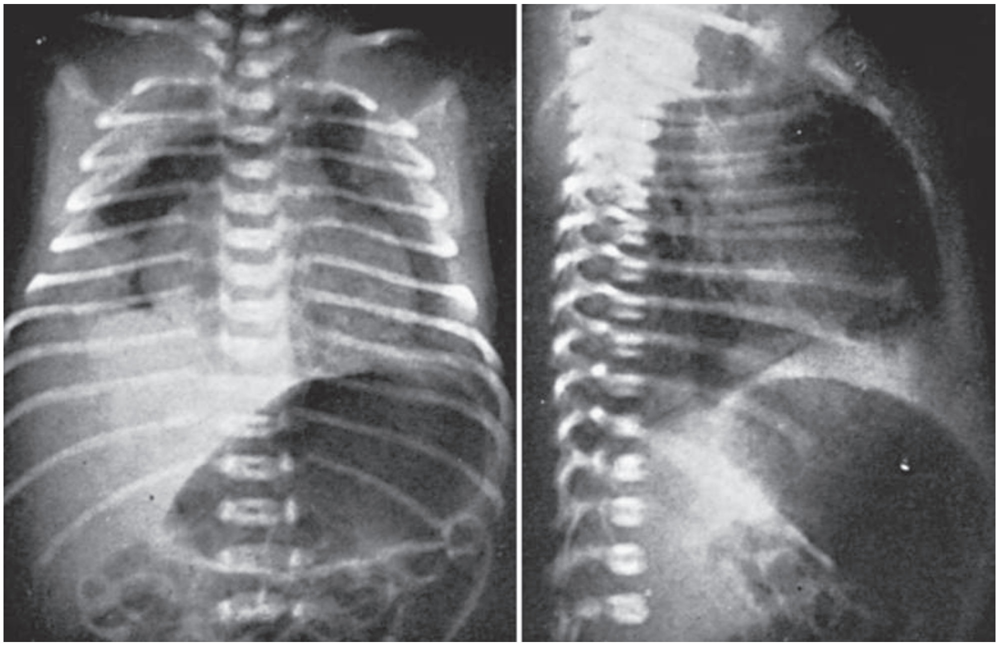

Figure 101-15 **Pneumomediastinum in a newborn infant.** The anteroposterior view (*left*) demonstrates compression of the lungs, and the lateral view (*right*) shows bulging of the sternum, each resulting from distention of the mediastinum by trapped air.

TREATMENT

Without a continued air leak, asymptomatic and mildly symptomatic small pneumothoraces require only close observation. Conservative management of a pneumothorax is effective even in selected infants requiring ventilatory support. Frequent small feedings may prevent gastric dilation and minimize crying, which can further compromise ventilation and worsen the pneumothorax. Breathing 100% oxygen in term infants may accelerate the resorption of free pleural air into blood by reducing the nitrogen tension in blood and producing a resultant nitrogen pressure gradient from the trapped gas in the blood, but the clinical effectiveness is not proven and the benefit must be weighed against the risks of oxygen toxicity. With severe respiratory or circulatory embarrassment, emergency aspiration using a soft small catheter introduced with a needle is indicated. Either immediately or after catheter aspiration, a chest tube should be inserted and attached to underwater seal drainage (see Fig. 101-14). If the air leak is ongoing, continuous suction (−5 to −20 cm H_2O) may be needed to evacuate the pneumothorax completely. A pneumopericardium requires prompt evacuation of entrapped air. Severe localized interstitial emphysema may respond to selective bronchial intubation. Judicious use of sedation in an infant fighting a ventilator may reduce the risk of pneumothorax. Surfactant therapy for RDS reduces the incidence of pneumothorax.

Bibliography is available at Expert Consult.

101.13 Pulmonary Hemorrhage

Namasivayam Ambalavanan and Waldemar A. Carlo

Massive pulmonary hemorrhage is a relatively uncommon, but catastrophic complication with a high risk of morbidity and mortality. Some degree of pulmonary hemorrhage occurs in about 10% of extremely preterm infants. However, massive pulmonary hemorrhage is less common and can be fatal. Autopsy demonstrates massive pulmonary hemorrhage in 15% of neonates who die in the 1st 2 wk of life. The reported incidence at autopsy varies from 1 to 4/1,000 live births. Approximately 75% of affected patients weigh <2,500 g at birth. Prophylactic indomethacin in extremely low birthweight infants reduces the incidence of pulmonary hemorrhage.

Most infants with pulmonary hemorrhage have had symptoms of respiratory distress that are indistinguishable from those of RDS. The onset may occur at birth or may be delayed several days. Hemorrhagic pulmonary edema is the source of blood in many cases and is associated with significant ductal shunting and high pulmonary blood flow or severe left-sided heart failure resulting from hypoxia. In severe cases, sudden cardiovascular collapse, poor lung compliance, profound cyanosis, and hypercapnia may be present. Radiographic findings are varied and nonspecific, ranging from minor streaking or patchy infiltrates to massive consolidation.

The incidence of pulmonary hemorrhage is increased in association with acute pulmonary infection, severe asphyxia, RDS, assisted ventilation, PDA, congenital heart disease, erythroblastosis fetalis, hemorrhagic disease of the newborn, thrombocytopenia, inborn errors of ammonia metabolism, and cold injury. Pulmonary hemorrhage is the only severe complication whose rate is *increased* with surfactant treatment. Pulmonary hemorrhage is seen with all surfactants; the incidence ranges from 1-5% of treated infants and is higher with natural surfactant. Bleeding is predominantly alveolar in approximately 65% of cases and interstitial in the rest. Bleeding into other organs is observed at autopsy of severely ill neonates, suggesting the possibility of an additional bleeding diathesis such as disseminated intravascular coagulation.

Treatment of pulmonary hemorrhage includes blood replacement, suctioning to clear the airway, intratracheal administration of epinephrine, and, in some cases, HFV. Although surfactant treatment has been associated with the development of pulmonary hemorrhage, administration of exogenous surfactant after the bleeding has occurred can improve lung compliance, because the presence of intra-alveolar blood and protein can inactivate surfactant.

Acute pulmonary hemorrhage may rarely occur in previously healthy full-term infants. The cause is unknown. Pulmonary hemorrhage may manifest as hemoptysis or blood in the nasopharynx or airway with no evidence of upper respiratory or gastrointestinal bleeding. Patients present with acute, severe respiratory failure requiring mechanical ventilation. Chest radiographs usually demonstrate bilateral alveolar infiltrates. The condition usually responds to intensive supportive treatment (see Chapter 407).

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Chapter 102

Digestive System Disorders

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VOMITING

Vomiting or, more often, regurgitation is a relatively frequent symptom during the neonatal period. In the 1st few hr after birth, infants may vomit mucus, occasionally blood streaked. This vomiting rarely persists after the first few feedings; it may be caused by irritation of the gastric mucosa by material swallowed during delivery. If vomiting is protracted, gastric lavage with physiologic saline solution may relieve it.

When vomiting occurs shortly after birth and is persistent, the possibilities of intestinal obstruction, metabolic disorders, and increased intracranial pressure must be considered. A history of maternal polyhydramnios suggests upper gastrointestinal (esophageal, duodenal, ileal) atresia. Bile-stained emesis suggests intestinal obstruction beyond the duodenum but may also be idiopathic. Abdominal radiographs (kidney-ureter-bladder and cross-table lateral views) should be performed in neonates with persistent emesis and in all infants with bile-stained emesis to detect air–fluid levels, distended bowel loops, characteristic patterns of obstruction (double bubble: duodenal atresia), and pneumoperitoneum (that may be a result of intestinal perforation). A contrast swallow roentgenogram with small bowel follow-through is indicated in the presence of bilious emesis.

Obstructive lesions of the digestive tract are the most frequent gastrointestinal anomalies (see Chapters 319, 329, 330, and 332). Vomiting (and drooling) from esophageal obstruction occurs before or with the first feeding. The diagnosis of esophageal atresia can be suspected if unusual drooling from the mouth is observed and if resistance is encountered during an attempt to pass a catheter into the stomach. The diagnosis should be made before the infant has trouble with oral feedings and aspiration pneumonia develops. Infantile achalasia (cardiospasm), a rare cause of vomiting in newborn infants, is demonstrable radiographically as obstruction at the cardiac end of the esophagus without organic stenosis. Regurgitation of feedings because of continuous relaxation of the esophageal–gastric sphincter, or chalasia, is a cause of vomiting. Keeping the infant in a semiupright position, thickening the feeding, or administering prokinetic drugs can control it.

Vomiting caused by obstruction of the small intestine usually begins on the 1st day of life and is frequent, persistent, usually nonprojectile, copious, and, unless the obstruction is above the ampulla of Vater, bile-stained; it is associated with abdominal distention, visible deep peristaltic waves, and reduction or absence of bowel movements. Malrotation with obstruction from **midgut volvulus** is an acute emergency that must be not only considered but also urgently evaluated by an upper gastrointestinal contrast radiographic series. Radiographs of the

abdomen show the distribution of air in the intestine, which may point to the anatomic location of an obstruction; malrotation can be identified only by contrast studies. Normally, air can be demonstrated by radiographs in the jejunum by 15-60 min, in the ileum by 2-3 hr, and in the colon by 3 hr after birth. Absence of rectal gas at 24 hr is abnormal. Persistent vomiting may occur with congenital diaphragmatic hernia. The vomiting associated with pyloric stenosis may begin any time after birth but may not assume its characteristic pattern before the 2nd-3rd wk. Vomiting with obstipation is a common early sign of **Hirschsprung disease.** Vomiting may occur with many other disturbances that do not obstruct the digestive tract, such as milk allergy, adrenal hyperplasia of the salt-losing variety, galactosemia, hyperammonemias, organic acidemias, increased intracranial pressure, septicemia, meningitis, and urinary tract infection. In many infants, it is simply regurgitation from overfeeding or from failure to permit the infant to eructate swallowed air. (See Chapter 323 for a discussion of gastric emptying and gastroesophageal reflux.)

DIARRHEA

See Chapters 340 and 341.

CONSTIPATION

More than 90% of full-term newborn infants pass meconium within the 1st 24 hr. The possibility of intestinal obstruction should be considered in any infant who does not pass meconium by 24-36 hr. Intestinal atresia, stricture, or stenosis; Hirschsprung disease; milk bolus obstruction; meconium ileus; or meconium plugs may manifest as constipation or, more often, obstipation. Approximately 20% of very-low birthweight (VLBW) infants do not pass meconium within the 1st 24 hr. Constipation not present from birth but appearing during the 1st mo of life may be a sign of short-segment congenital aganglionic megacolon, hypothyroidism, strictures after necrotizing enterocolitis (NEC), or anal stenosis. It must be kept in mind that infrequent bowel movements do not necessarily mean constipation. A breastfed infant usually has frequent bowel movements, whereas a formula-fed infant may have 1-2 movements a day or every other day.

MECONIUM PLUGS

Lower colonic or anorectal plugs (Fig. 102-1) with a lower-than-normal water content may cause intestinal obstruction. Rarely, a firm mass of meconium may form elsewhere in the intestine and cause intrauterine intestinal obstruction and meconium peritonitis unrelated to cystic fibrosis (CF). Anorectal plugs may also cause mucosal ulceration and intestinal perforation. **Meconium plugs** are associated with small left colon syndrome in infants of diabetic mothers and with CF, rectal aganglionosis, maternal opiate use, and magnesium sulfate therapy for preeclampsia. The plug may be evacuated by glycerin suppository or rectal irrigation with isotonic saline. Enemas with the iodinated contrast medium Gastrografin (meglumine diatrizoate, a hyperosmolar, water-soluble, radiopaque solution containing 0.1% polysorbate 80 [Tween 80] and 37% organically bound iodine) usually induce passage of the plug, presumably because the high osmolarity (1,900 mOsm/L) of the solution draws fluid rapidly into the intestinal lumen and loosens inspissated material. Such rapid loss of fluid into the bowel may result in acute dehydration and shock, so it is advisable to dilute the contrast material with an equal amount of water, correct any existing dehydration, and provide intravenous fluids during and for several hours after the procedure. After removal of a meconium plug, the infant should be observed closely for the possible presence of congenital aganglionic megacolon.

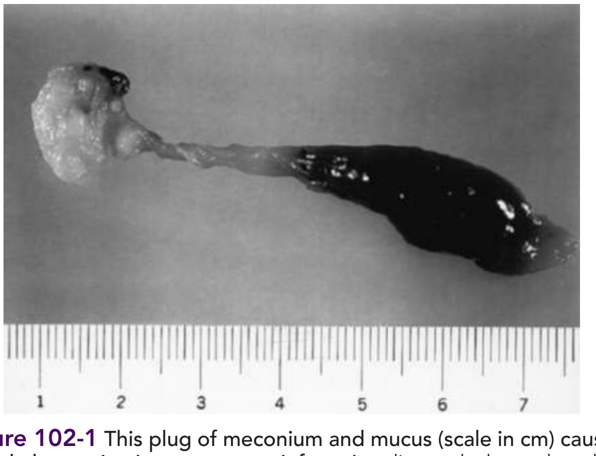

Figure 102-1 This plug of meconium and mucus (scale in cm) caused bowel obstruction in a premature infant. A radiograph showed marked gaseous distention and multiple fluid levels at 30 hr of age. Dramatic improvement occurred when the plug was passed after an enema. *(From The abnormal fetus. In Beischer NA, Mackay EV, Colditz PB, editors:* Obstetrics and the newborn, *ed 3, Philadelphia, 1997, WB Saunders.)*

102.1 Meconium Ileus in Cystic Fibrosis

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Impaction of meconium causes intestinal obstructions and may be associated with CF. The absence of fetal pancreatic enzymes in CF limits normal digestive activities in the intestine, and meconium becomes viscid and mucilaginous. It clings to the intestinal wall and moves with difficulty. The inspissated and impacted meconium fills the intestinal canal but is most concentrated in the lower part of the ileum. Clinically, the pattern is that of congenital intestinal obstruction with or without intestinal perforation. Abdominal distention is prominent, and vomiting becomes persistent. Infrequently, 1 or more inspissated meconium stools may be passed shortly after birth.

Meconium ileus is primarily associated with CF transmembrane regulator (CFTR) mutations F508del, G542X, W1282X, R553X, and G551D. Patients with 2 copies of the F508del mutation have a 25% chance of presenting with meconium ileus. F508del plus any "other" CF mutation confers 17% chance, and 2 "other" CF mutations confer a 12% chance of meconium ileus. In addition, non-CFTR genetic "modifier" genes influence meconium ileus. In families that already have at least 1 child with CF complicated by meconium ileus, there is a 39% recurrence rate for meconium ileus in subsequent children, which is more than the rates expected with autosomal recessive inheritance. In a twin study, 82% of monozygotic twins showed concordance for meconium ileus, whereas only 22% of dizygotic and 24% of 2 affected siblings showed concordance.

The **differential diagnosis** involves other causes of intestinal obstruction, including intestinal pseudoobstruction and other causes of pancreatic insufficiency (see Chapter 349). A presumptive diagnosis can be made on the basis of a history of CF in a sibling, via palpation of doughy or cordlike masses of intestines through the abdominal wall, and from the radiographic appearance. In contrast to the generally evenly distended intestinal loops above an atresia, the loops may vary in width and are not as evenly filled with gas. At points of heaviest meconium concentration, the infiltrated gas may create a bubbly granular appearance (Figs. 102-2 and 102-3). It is technically difficult to perform a sweat test in a neonate. Genetic testing confirms the diagnosis of CF.

Treatment for meconium ileus is high Gastrografin enema as described previously for meconium plugs. If the procedure is unsuccessful or perforation of the bowel wall is suspected, a laparotomy is performed and the ileum is opened at the point of largest diameter of the impaction. Approximately 50% of these infants have associated intestinal atresia, stenosis, or volvulus that requires surgery. The inspissated meconium is removed by gentle and patient irrigation with warm isotonic sodium chloride or *N*-acetylcysteine (Mucomyst) solution through a catheter passed between the impaction and the bowel wall. Most infants with meconium ileus survive the neonatal period. If meconium ileus is associated with CF, the long-term prognosis depends on the severity of the underlying disease (see Chapter 403).

Figure 102-2 **Meconium ileus.** Impacted meconium with small amounts of air interspersed can be seen in loops of intestine on the right side of the abdomen. The intestinal loops above this impaction are greatly distended.

Figure 102-3 **Meconium ileus.** The colon, outlined by contrast material, is small because meconium has not reached it.

MECONIUM PERITONITIS

Perforation of the intestine may occur in utero or shortly after birth. Frequently, the intestinal perforation seals naturally with relatively little meconium leakage into the peritoneal cavity. In some cases, with long-standing perforation, meconium peritonitis is more pronounced. Perforations occur most often as a complication of meconium ileus in infants with CF but are occasionally the result of a meconium plug or in utero intestinal obstruction of another cause. Cases at the most severe end of the spectrum may be diagnosed on prenatal ultrasonography with fetal ascites, polyhydramnios, bowel dilation, intraabdominal calcifications, and hydrops fetalis. At the other end are cases in which an intestinal perforation may seal spontaneously with only a minor meconium leak, so the event may never be detected except when meconium becomes calcified and is later discovered on radiographs of the abdomen. Alternatively, the clinical picture may be dominated by the signs of intestinal obstruction (as in meconium ileus) or chemical peritonitis. Characteristic clinical findings include abdominal distention, vomiting, and absence of stools. Treatment consists primarily of elimination of the intestinal obstruction and drainage of the peritoneal cavity.

102.2 Necrotizing Enterocolitis

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NEC is the most common life-threatening emergency of the gastrointestinal tract in the newborn period. The disease is characterized by various degrees of mucosal or transmural necrosis of the intestine. The cause of NEC remains unclear but is most likely multifactorial. The incidence of NEC is 1-5% of infants in neonatal ICUs. Both incidence and case fatality rates increase with decreasing birth weight and gestational age. Because very small, ill preterm infants are particularly susceptible to NEC, a rising incidence may reflect improved survival of this high-risk group of patients.

PATHOLOGY AND PATHOGENESIS

Many factors may contribute to the development of a the pathologic findings of NEC including necrotic segment of intestine, gas accumulation in the submucosa of the bowel wall **(pneumatosis intestinalis),** and progression of the necrosis to perforation, peritonitis, sepsis, and death. The distal part of the ileum and the proximal segment of colon are involved most frequently; in fatal cases, gangrene may extend from the stomach to the rectum. Although NEC is a multifactorial disease primarily associated with intestinal immaturity, the concept of "risk factors" for NEC is controversial. The triad of intestinal ischemia (injury), enteral nutrition (metabolic substrate), and bacterial translocation has classically been linked to NEC. The greatest risk factor for NEC is prematurity. The disorder probably results from an interaction between loss of mucosal integrity due to a variety of factors (ischemia, infection, inflammation) and the host's response to that injury (circulatory, immunologic, inflammatory), leading to necrosis of the affected area. Coagulation necrosis is the characteristic histologic finding in intestinal specimens. Clustering of cases suggests a primary role for an infectious agent. Various bacterial and viral agents, including *Escherichia coli, Klebsiella, Clostridium perfringens, Staphylococcus epidermidis,* astrovirus, norovirus, and rotavirus, have been recovered from cultures. Nonetheless, in most situations, a pathogen is not identified. NEC rarely occurs before the initiation of enteral feeding and is much less common in infants fed human milk. Aggressive enteral feeding may predispose to the development of NEC.

Although nearly 90% of all cases of NEC occur in preterm infants, the disease can occur in full-term neonates. NEC in term infants is often a "secondary" disease, seen more frequently in infants with history of birth asphyxia, Down syndrome, congenital heart disease, rotavirus infections, and Hirschsprung disease.

CLINICAL MANIFESTATIONS

Infants with NEC have a variety of signs and symptoms and may have an insidious or sudden catastrophic onset (Table 102-1). The onset of NEC is usually in the 2nd or 3rd wk of life but can be as late as 3 mo in VLBW infants. Age of onset is inversely related to gestational age. The first signs of impending disease may be nonspecific, including lethargy and temperature instability, or related to gastrointestinal pathology, such as abdominal distention and gastric retention. In some

Table 102-1	Signs and Symptoms Associated with Necrotizing Enterocolitis
GASTROINTESTINAL Abdominal distention Abdominal tenderness Feeding intolerance Delayed gastric emptying Vomiting Occult/gross blood in stool Change in stool pattern/diarrhea Abdominal mass Erythema of abdominal wall	
SYSTEMIC Lethargy Apnea/respiratory distress Temperature instability "Not right" Acidosis (metabolic and/or respiratory) Glucose instability Poor perfusion/shock Disseminated intravascular coagulopathy Positive results of blood cultures	

From Kanto WP Jr, Hunter JE, Stoll BJ: Recognition and medical management of necrotizing enterocolitis, Clin Perinatol *21:335–346, 1994.*

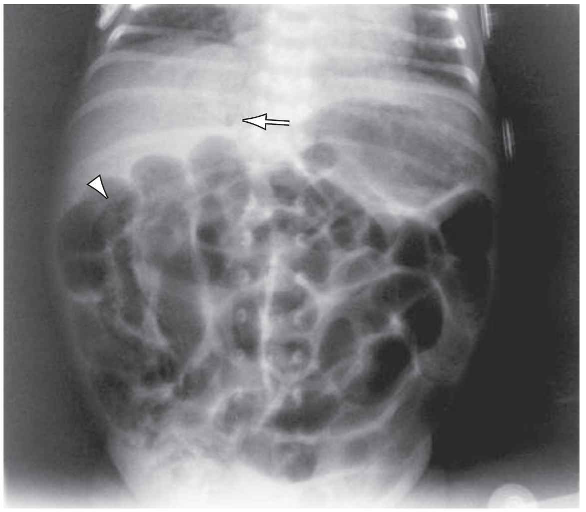

Figure 102-4 NEC. A kidney-ureter-bladder film demonstrates abdominal distention, hepatic portal venous gas *(arrow),* and a bubbly appearance of pneumatosis intestinalis (*arrowhead;* right lower quadrant). The latter 2 signs are thought to be pathognomonic for neonatal NEC.

extremely low birthweight infants, NEC may develop following a red cell transfusion. Bloody stools are seen in 25% of patients. Because of nonspecific signs, sepsis may be suspected before NEC. The spectrum of illness is broad, ranging from mild disease with only guaiac-positive stools to severe illness with bowel perforation, peritonitis, systemic inflammatory response syndrome, shock, and death. Progression may be rapid, but it is unusual for the disease to progress from mild to severe after 72 hr.

DIAGNOSIS

A very high index of suspicion in treating preterm at-risk infants is crucial. Plain abdominal radiographs are essential to make a diagnosis of NEC. The finding of pneumatosis intestinalis (air in the bowel wall) confirms the clinical suspicion of NEC and is diagnostic; 50-75% of patients have pneumatosis when treatment is started (Fig. 102-4). Portal venous gas is a sign of severe disease, and pneumoperitoneum indicates a perforation (Figs. 102-4 and 102-5). Hepatic sonography may detect portal venous gas in some infants with normal abdominal x-rays.

The **differential diagnosis** of NEC includes specific infections (systemic or intestinal), gastrointestinal obstruction, volvulus, and isolated intestinal perforation. Idiopathic focal intestinal perforation can occur spontaneously or after the early use of postnatal steroids and indomethacin. Pneumoperitoneum develops in such patients, but they are usually less ill than those with NEC.

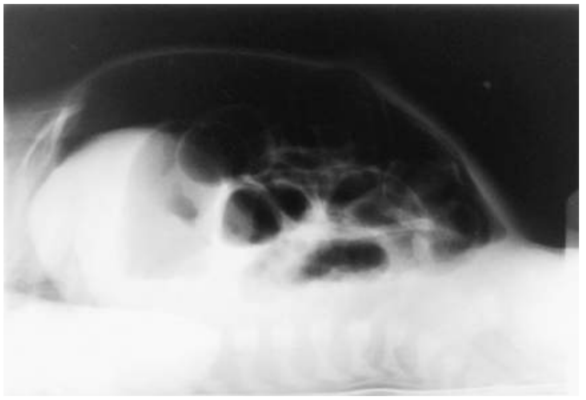

Figure 102-5 Intestinal perforation. A cross-table abdominal roentgenogram in a patient with a neonatal NEC demonstrates marked distention and massive pneumoperitoneum as evidenced by the free air below the anterior abdominal wall.

TREATMENT

Rapid initiation of therapy is required for suspected as well as proven cases of NEC. There is no definitive treatment for established NEC, so therapy is directed at giving supportive care and preventing further injury with cessation of feeding, nasogastric decompression, and administration of intravenous fluids. Careful attention to respiratory status, coagulation profile, and acid–base and electrolyte balances are important. Once blood has been drawn for culture, systemic antibiotics (with broad coverage based on the antibiotic sensitivity patterns of the gram-positive, Gram-negative, and anaerobic organisms in the particular neonatal ICU) should be started immediately. If present, umbilical catheters should be removed, but good intravenous access needs to be maintained. Ventilation should be assisted in the presence of apnea or if abdominal distention is contributing to hypoxia and hypercapnia. Intravascular volume replacement with crystalloid or blood products, cardiovascular support with fluid boluses and/or inotropes, and correction of hematologic, metabolic, and electrolyte abnormalities are essential to stabilize the infant with NEC.

The patient's course should be monitored closely by means of frequent physical assessments; sequential anteroposterior and cross-table lateral or lateral decubitus abdominal radiographs to detect intestinal perforation; and serial determinations of hematologic, electrolyte, and acid–base status. Gown and glove isolation and grouping of infants at similar increased risks into cohorts separate from other infants should be instituted to contain an epidemic.

A surgeon should be consulted early in the course of treatment. **Indications for surgery** include evidence of perforation on abdominal x-ray (pneumoperitoneum) or positive result of abdominal paracentesis (stool or organism on Gram stain preparation from peritoneal fluid). Failure of medical management, a single fixed bowel loop on radiographs, abdominal wall erythema, and a palpable mass are relative indications for exploratory laparotomy. Ideally, surgery should be performed after intestinal necrosis develops but before perforation and peritonitis occur. In unstable premature infants with perforated NEC, **peritoneal drainage** can be cautiously considered as an alternative to **exploratory laparotomy**, although the best surgical approach in these infants remains unresolved. The type of surgical operation did not

influence survival or other clinically important early outcomes in one multicenter study, but another large randomized trial showed that a majority of infants who were initially treated with peritoneal drains required a delayed secondary laparotomy. There are also some concerns about the long-term outcome (death or neurodevelopmental outcome) for infants treated with peritoneal drainage.

Patients with isolated intestinal perforation (not related to NEC) tend to have a lower birthweight, are less likely to be receiving oral feeding, and are prone to perforation at an earlier postnatal age than are patients with perforation related to NEC. In many patients with isolated intestinal perforation treated by drainage, no further surgical procedure is needed; a small subgroup may require later surgery to repair an intestinal stricture or fistula.

PROGNOSIS

Medical management fails in approximately 20-40% of patients with pneumatosis intestinalis at diagnosis; of these, 10-30% die. Early postoperative complications include wound infection, dehiscence, and stomal problems (prolapse, necrosis). Later complications include **intestinal strictures**, which develop at the site of the necrotizing lesion in approximately 10% of surgically or medically managed patients. Resection of the obstructing stricture is curative. After massive intestinal resection, complications from postoperative NEC include **short-bowel syndrome** (malabsorption, growth failure, malnutrition), complications related to central venous catheters (sepsis, thrombosis), and cholestatic jaundice. Preterm infants with NEC who require surgical intervention or who have concomitant bacteremia are at increased risk for adverse growth and neurodevelopmental outcome.

PREVENTION

Newborns exclusively breastfed have a reduced risk of NEC. There have been concerns about early and aggressive increase in feeding volumes in raising the risk of NEC in VLBW infants, although a safe feeding regimen remains unknown. Gut stimulation protocols consisting of minimal enteral feeds followed by judicious volume advancement decreased the incidence of NEC in smaller study cohorts, but significant benefits were not detected in a meta-analysis of all randomized studies. In other studies, slow advancement or delayed introduction of enteral feedings did not protect against NEC. Emerging evidence indicates that the use of inhibitors of gastric acid secretion (H_2-receptor blockers, proton pump inhibitors) or prolonged empirical antibiotics in early neonatal period is associated with increased risk of NEC. Prophylactic enteral antibiotics reduced the risk of NEC in a study but although concerns about adverse outcomes persist, particularly related to the development of resistant bacteria. Extensive data and meta-analyses show that probiotic preparations decrease the incidence of severe NEC (stage II or higher) and mortality in preterm infants but an FDA-approved preparation is not available.

Bibliography is available at Expert Consult.

102.3 Jaundice and Hyperbilirubinemia in the Newborn

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Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. Jaundice is observed during the 1st wk after birth in approximately 60% of term infants and 80% of preterm infants. The yellow color usually results from the accumulation of unconjugated, nonpolar, lipid-soluble bilirubin pigment in the skin. This unconjugated bilirubin (designated **indirect-acting** by nature of the Van den Bergh reaction) is an end product of heme-protein catabolism from a series of enzymatic reactions by heme-oxygenase and biliverdin reductase and nonenzymatic reducing agents in the reticuloendothelial cells. It may also be partly caused by deposition of pigment from conjugated bilirubin, the end product from indirect, unconjugated bilirubin that has undergone conjugation in the liver cell microsome by the enzyme uridine diphosphoglucuronic acid (UDP)–glucuronyl transferase to form the polar, water-soluble glucuronide of bilirubin **(direct-reacting).** Although bilirubin may have a physiologic role as an antioxidant, elevations of indirect, unconjugated bilirubin are potentially neurotoxic. Even though the conjugated form is not neurotoxic, direct hyperbilirubinemia indicates a potentially serious hepatic disorders or a systemic illness.

ETIOLOGY

During the neonatal period, metabolism of bilirubin is in transition from the fetal stage, during which the placenta is the principal route of elimination of the lipid-soluble, unconjugated bilirubin, to the adult stage, during which the water-soluble conjugated form is excreted from hepatic cells into the biliary system and gastrointestinal tract. Unconjugated hyperbilirubinemia may be caused or increased by any factor that (a) increases the load of bilirubin to be metabolized by the liver (hemolytic anemias, polycythemia, bruising or internal hemorrhage, shortened red blood cell life as a result of immaturity or transfusion of cells, increased enterohepatic circulation, infection); (b) damages or reduces the activity of the transferase enzyme or other related enzymes (genetic deficiency, hypoxia, infection, thyroid deficiency); (c) competes for or blocks the transferase enzyme (drugs and other substances requiring glucuronic acid conjugation); or (d) leads to an absence or decreased amounts of the enzyme or to reduction of bilirubin uptake by liver cells (genetic defect, and prematurity). Gene polymorphisms in the hepatic uridine diphosphate glucuronosyltransferase isoenzyme 1A1 (*UGT1A1*) and the solute carrier organic anion transporter 1B1 (*SLCO1B1*) alone or in combination influence the incidence of neonatal hyperbilirubinemia. The toxic effects of elevated serum concentrations of unconjugated bilirubin are increased by factors that reduce the retention of bilirubin in the circulation (hypoproteinemia, displacement of bilirubin from its binding sites on albumin by competitive binding of drugs such as sulfisoxazole and moxalactam, acidosis, and increased free fatty acid concentration secondary to hypoglycemia, starvation, or hypothermia). Neurotoxic effects are directly related not only to the permeability of the blood–brain barrier and nerve cell membranes but also to neuronal susceptibility to injury, all of which are adversely influenced by asphyxia, prematurity, hyperosmolality, and infection. Early and frequent feeding decreases, whereas breastfeeding and dehydration increase, serum levels of bilirubin. Delay in passage of meconium, which contains 1 mg bilirubin/dL, may contribute to jaundice by enterohepatic recirculation after deconjugation by intestinal glucuronidase (Fig. 102-6). Drugs such as oxytocin (in the mother) and chemicals used in the nursery such as phenolic detergents may also produce unconjugated hyperbilirubinemia. Table 102-2 lists the risk factors for unconjugated hyperbilirubinemia. Additional risk factors include polycythemia, infection, prematurity, and having a diabetic mother.

CLINICAL MANIFESTATIONS

Jaundice usually appears during the early neonatal period, depending on etiology. Jaundice usually becomes apparent in a cephalocaudal progression, starting on the face and progressing to the abdomen and then the feet, as serum levels increase. Dermal pressure may reveal the anatomic progression of jaundice (face, ≈ 5 mg/dL; mid-abdomen, ≈ 15 mg/dL; soles, ≈ 20 mg/dL), but clinical examination cannot be depended on to estimate serum levels. Jaundice to the midabdomen, signs or symptoms, high-risk factors that suggest nonphysiologic jaundice, or hemolysis must be evaluated further (see Tables 102-2 and 102-3). Noninvasive techniques for transcutaneous measurement of bilirubin that correlate with serum levels may be used to screen infants, but determination of serum bilirubin level is indicated in patients with elevated age-specific transcutaneous bilirubin measurement, progressing jaundice, or risk for either hemolysis or sepsis. Whereas jaundice from deposition of indirect bilirubin in the skin tends to appear bright yellow or orange, jaundice of the obstructive type (direct bilirubin) has a greenish or muddy yellow cast. Infants with severe hyperbilirubinemia may present with lethargy and poor feeding and, without

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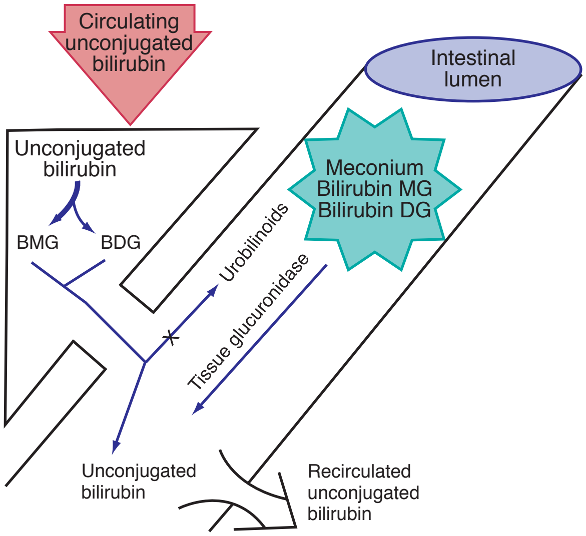

Figure 102-6 **The neonatal production rate of bilirubin is 6-8 mg/kg/24 hr (in contrast to 3-4 mg/kg/24 hr in adults).** Water-insoluble bilirubin is bound to albumin. At the plasma-hepatocyte interface, a liver membrane carrier (bilitranslocase) transports bilirubin to a cytosolic binding protein (ligandin or Y protein, now known to be glutathione S-transferase), which prevents back-absorption to plasma. Bilirubin is converted to bilirubin monoglucuronide (BMG). Neonates excrete more BMG than adults do. In the fetus, conjugated lipid-insoluble BMG and bilirubin diglucuronide (BDG) must be deconjugated by tissue β-glucuronidases to facilitate placental transfer of lipid-soluble unconjugated bilirubin across the placental lipid membranes. After birth, intestinal or milk-containing glucuronidases contribute to the enterohepatic recirculation of bilirubin and possibly to the development of hyperbilirubinemia.

Table 102-2	Risk Factors for Development of Severe Hyperbilirubinemia in Infants ≥35 Wk of Gestation (in Approximate Order of Importance)
MAJOR RISK FACTORS	
Predischarge TSB or TcB level in the high-risk zone (see Fig. 102-8)	
Jaundice observed in the 1st 24 hr	
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (glucose-6-phosphate dehydrogenase deficiency), elevated end-title CO concentration	
Gestational age 35-36 wk	
Previous sibling received phototherapy	
Cephalohematoma or significant bruising	
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive	
East Asian race*	
MINOR RISK FACTORS	
Predischarge TSB or TcB level in the high intermediate-risk zone	
Gestational age 37-38 wk	
Jaundice observed before discharge	
Previous sibling with jaundice	
Macrosomic infant of a diabetic mother	
Maternal age ≥25 yr	
Male gender	
DECREASED RISK (THESE FACTORS ARE ASSOCIATED WITH DECREASED RISK OF SIGNIFICANT JAUNDICE, LISTED IN ORDER OF DECREASING IMPORTANCE)	
TSB or TcB level in the low-risk zone (see Fig. 102-8)	
Gestational age ≥41 wk	
Exclusive bottle-feeding	
Black race	
Discharge from hospital after 72 hr	

*Race as defined by mother's description.
TcB, transcutaneous bilirubin; TSB, total serum bilirubin.
From AAP Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, Pediatrics 114:297–316, 2004.

Table 102-3 Laboratory Evaluation of the Jaundiced Infant ≥35 Wk of Gestation

INDICATIONS	ASSESSMENTS
Jaundice in 1st 24 hr	Measure TcB and/or TSB
Jaundice appears excessive for infant's age	Measure TcB and/or TSB
Infant receiving phototherapy or TSB rising rapidly (i.e., crossing percentiles [see Fig. 102-8]) and unexplained by history and physical examination	Blood type and Coombs test, if not obtained with cord blood Complete blood count and smear Measure direct or conjugated bilirubin It is an option to perform reticulocyte count, G6PD, and $ETCO_c$, if available Repeat TSB in 4-24 hr depending on infant's age and TSB level
TSB concentration approaching exchange levels or not responding to phototherapy	Perform reticulocyte count, G6PD, albumin, ETCO if available
Elevated direct (or conjugated) bilirubin level	Do urinalysis and urine culture Evaluate for sepsis if indicated by history and physical examination
Jaundice present at or beyond age 3 wk, or sick infant	Total and direct (or conjugated) bilirubin level If direct bilirubin elevated, evaluate for causes of cholestasis Check results of newborn thyroid and galactosemia screen, and evaluate infant for signs or symptoms of hypothyroidism

$ETCO_c$, end tidal carbon monoxide concentration; G6PD, glucose-6-phosphate dehydrogenase; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.
From AAP Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, Pediatrics *114:297–316, 2004.*

treatment, can progress to acute bilirubin encephalopathy (kernicterus) (see Chapter 102.4).

DIFFERENTIAL DIAGNOSIS

Jaundice, consisting of either indirect or direct bilirubin, that is present at birth or appears within the 1st 24 hr after birth requires immediate attention and may be due to erythroblastosis fetalis, concealed hemorrhage, sepsis, or congenital infections, including syphilis, cytomegalovirus, rubella, and toxoplasmosis. Hemolysis is suggested by a rapid rise in serum bilirubin concentration (>0.5 mg/dL/hr), anemia, pallor, reticulocytosis, hepatosplenomegaly, and a positive family history. An unusually high proportion of direct-reacting bilirubin may characterize jaundice in infants who have received intrauterine transfusions for erythroblastosis fetalis. Jaundice that first appears on the 2nd or 3rd day is usually **physiologic** but may represent a more severe form. Familial nonhemolytic icterus **(Crigler-Najjar syndrome)** and early-onset breastfeeding jaundice are seen initially on the 2nd or 3rd day. Jaundice appearing after the 3rd day and within the 1st wk suggests bacterial sepsis or urinary tract infection; it may also be due to other infections, notably syphilis, toxoplasmosis, cytomegalovirus, and enterovirus. Jaundice secondary to extensive ecchymosis or blood extravasation may occur during the 1st day or later, especially in premature infants. Polycythemia may also lead to early jaundice.

There is a long differential diagnosis for jaundice first recognized *after* the 1st wk of life, including breast milk jaundice, septicemia, congenital atresia or paucity of the bile ducts, hepatitis, galactosemia, hypothyroidism, CF, and congenital hemolytic anemia crises related to red blood cell morphology and enzyme deficiencies (Fig. 102-7). The differential diagnosis for persistent jaundice during the 1st mo of life includes hyperalimentation-associated cholestasis, hepatitis, cytomegalic inclusion disease, syphilis, toxoplasmosis, familial nonhemolytic icterus, congenital atresia of the bile ducts, galactosemia, and inspissated bile syndrome following hemolytic disease of the newborn. Rarely, physiologic jaundice may be prolonged for several weeks, as in infants with hypothyroidism or pyloric stenosis.

Full-term, low-risk, asymptomatic infants with jaundice may be evaluated by monitoring of total serum bilirubin levels. Regardless of gestation or time of appearance of jaundice, patients with significant hyperbilirubinemia and those with symptoms or signs require a complete diagnostic evaluation, which includes determination of direct and indirect bilirubin fractions, hemoglobin, reticulocyte count, blood type, Coombs test, and examination of a peripheral blood smear. Indirect hyperbilirubinemia, reticulocytosis, and a smear with evidence of red blood cell destruction suggest hemolysis (see Table 102-3). In the absence of blood group incompatibility, nonimmunologically induced hemolysis should be considered. If the reticulocyte count, Coombs test result, and direct bilirubin value are normal, physiologic or pathologic indirect hyperbilirubinemia may be present (see Fig. 102-7). If direct hyperbilirubinemia is present, hepatitis, congenital bile duct disorders (biliary atresia, paucity of bile ducts, Byler disease), cholestasis, inborn errors of metabolism, CF, and sepsis are diagnostic possibilities.

PHYSIOLOGIC JAUNDICE (ICTERUS NEONATORUM)

Under normal circumstances, the level of indirect bilirubin in umbilical cord serum is 1-3 mg/dL and rises at a rate of <5 mg/dL/24 hr; thus, jaundice becomes visible on the 2nd or 3rd day, usually peaking

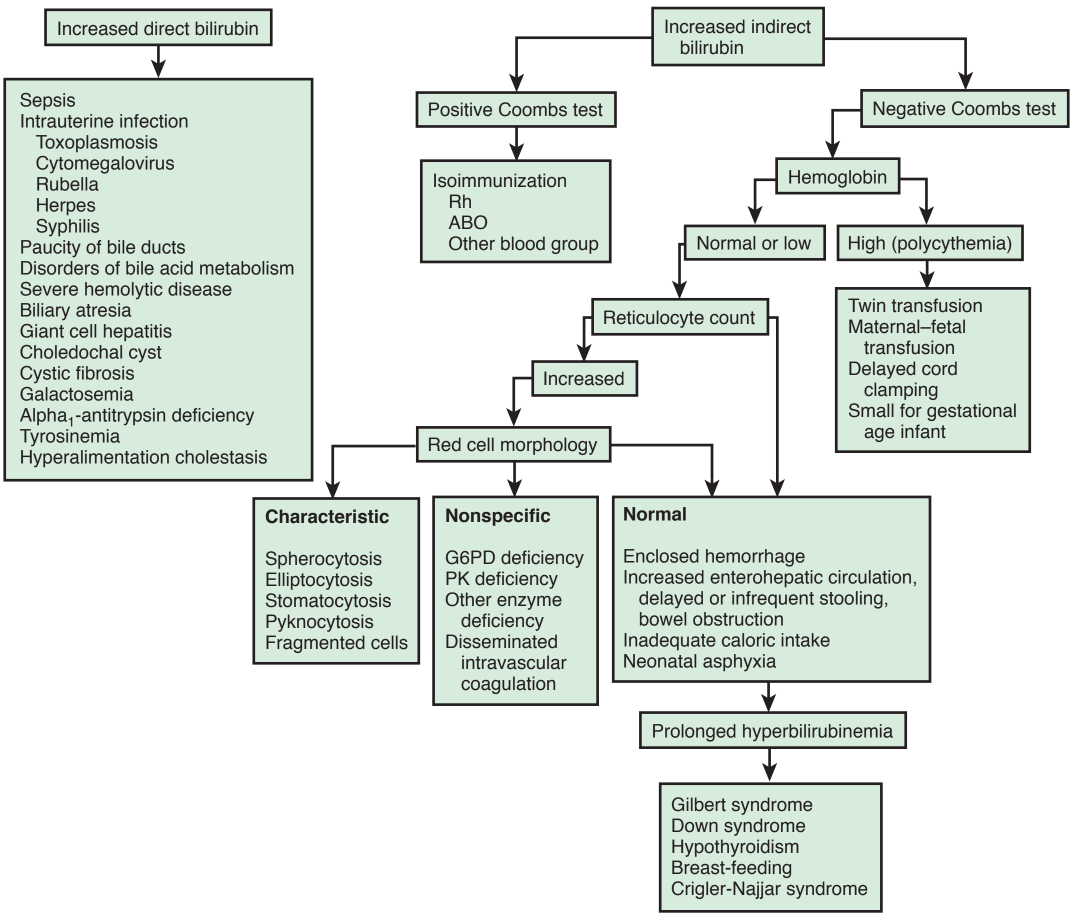

Figure 102-7 Schematic approach to the diagnosis of neonatal jaundice. G6PD, glucose-6-phosphate dehydrogenase; PK, pyruvate kinase. *(From Oski FA: Differential diagnosis of jaundice. In Taeusch HW, Ballard RA, Avery MA, editors:* Schaffer and Avery's diseases of the newborn, *ed 6, Philadelphia, 1991, WB Saunders.)*

between the 2nd and 4th days at 5-6 mg/dL and decreasing to <2 mg/dL between the 5th and 7th days after birth. Jaundice associated with these changes is designated *physiologic* and is believed to be the result of increased bilirubin production from the breakdown of fetal red blood cells combined with transient limitation in the conjugation of bilirubin by the immature neonatal liver.

Overall, 6-7% of full-term infants have indirect bilirubin levels >13 mg/dL and less than 3% have levels >15 mg/dL. Risk factors for elevated indirect bilirubin include maternal age, race (Chinese, Japanese, Korean, and Native American), maternal diabetes, prematurity, drugs (vitamin K_3, novobiocin), altitude, polycythemia, male sex, trisomy 21, cutaneous bruising, blood extravasation (cephalohematoma), oxytocin induction, breastfeeding, weight loss (dehydration or caloric deprivation), delayed bowel movement, and a family history of or a sibling who had physiologic jaundice (see Table 102-2). In infants without these variables, indirect bilirubin levels rarely rise above 12 mg/dL, whereas infants with several risk factors are more likely to have higher bilirubin levels. A combination of breastfeeding, variant-glucuronosyltransferase activity (1A1), and alterations of the organic anion transporter 2 gene increases the risk of hyperbilirubinemia. Predicting which neonates are at risk for exaggerated physiologic jaundice can be based on hour-specific bilirubin levels in the 1st 24-72 hr of life (Fig. 102-8). Transcutaneous measurements of bilirubin are linearly correlated with serum levels and can be used for screening. Indirect bilirubin levels in full-term infants decline to adult levels (1 mg/dL) by 10-14 days of life. Persistent indirect hyperbilirubinemia beyond 2 wk suggests hemolysis, hereditary glucuronyl transferase deficiency, breast milk jaundice, hypothyroidism, or intestinal obstruction. Jaundice associated with pyloric stenosis may be the result of caloric deprivation, relative deficiency of hepatic UDP-glucuronyl transferase, or an increase in the enterohepatic circulation of bilirubin from the ileus. In premature infants, the rise in serum bilirubin tends to be the same or somewhat slower but of longer duration than in term infants. Peak levels of 8-12 mg/dL are not usually reached until the 4th-7th day, and jaundice is infrequently observed after the 10th day, corresponding to the maturation of mechanisms for bilirubin metabolism and excretion.

The diagnosis of physiologic jaundice in term or preterm infants can be established only by excluding known causes of jaundice on the basis of the history, clinical findings, and laboratory data (Table 102-4). In general, a search to determine the cause of jaundice should be made if (1) it appears in the 1st 24-36 hr after birth, (2) serum bilirubin is rising at a rate faster than 5 mg/dL/24 hr, (3) serum bilirubin is >12 mg/dL in a full-term infant (especially in the absence of risk factors) or 10-14 mg/dL in a preterm infant, (4) jaundice persists after 10-14 days after birth, or (5) direct bilirubin fraction is >2 mg/dL at any time. Other factors suggesting a nonphysiologic cause of jaundice are family history of hemolytic disease, pallor, hepatomegaly, splenomegaly, failure of phototherapy to lower the bilirubin level, vomiting, lethargy, poor feeding, excessive weight loss, apnea, bradycardia, abnormal vital signs (including hypothermia), light-colored stools, dark urine positive for bilirubin, and signs of kernicterus (see Chapter 102.4).

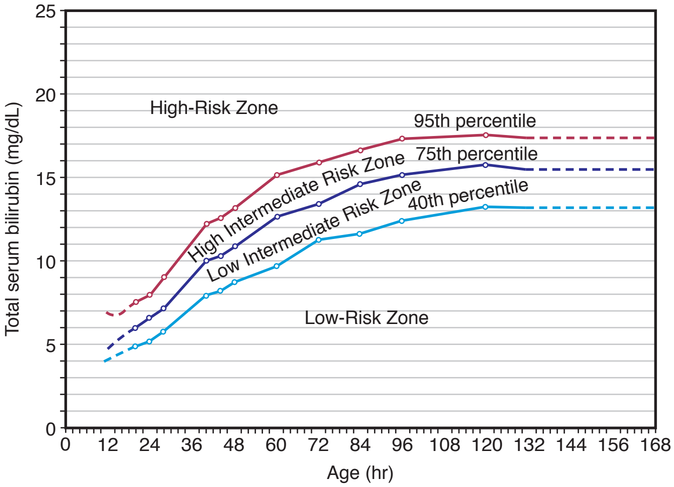

Figure 102-8 **Risk designation of term and near-term well newborns based on their hour-specific serum bilirubin values.** The high-risk zone is subdivided by the 95th percentile track. The intermediate -risk zone is subdivided into upper and lower risk zones by the 75th percentile track. The low-risk zone has been electively and statistically defined by the 40th percentile track. *(From Bhutani VK, Johnson L, Sivieri EM: Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns,* Pediatrics *103:6–14, 1999.)*

PATHOLOGIC HYPERBILIRUBINEMIA

Jaundice and its underlying hyperbilirubinemia are considered pathologic if the time of appearance, duration, or pattern varies significantly from that of physiologic jaundice or if the course is compatible with physiologic jaundice but other reasons exist to suspect that the infant is at special risk for neurotoxicity. It may not be possible to determine the precise cause of an abnormal elevation of unconjugated bilirubin, but many infants with this finding have associated risk factors such as Asian race, prematurity, breastfeeding, and weight loss. Frequently, the terms *exaggerated physiologic jaundice* and *hyperbilirubinemia of the newborn* are used in infants whose primary problem is probably a deficiency or inactivity of bilirubin glucuronyl transferase (**Gilbert syndrome**) rather than an excessive load of bilirubin for excretion (see Table 102-2). The combination of glucose-6-phosphate dehydrogenase (G6PD) deficiency and a mutation of the promoter region of UDP-glucuronyl transferase-1 produces indirect hyperbilirubinemia in the absence of signs of hemolysis. Nonphysiologic hyperbilirubinemia may also be caused by mutations in the gene for bilirubin UDP-glucuronyl transferase.

The greatest risk associated with indirect hyperbilirubinemia is the development of bilirubin-induced neurologic dysfunction, which typically occurs with high indirect bilirubin levels (see Chapter 102.4). The development of kernicterus (bilirubin encephalopathy) depends on the level of indirect bilirubin, duration of exposure to bilirubin elevation, the cause of jaundice, and the infant's well-being. Neurologic injury including kernicterus may occur at lower bilirubin levels in preterm infants and in the presence of asphyxia, intraventricular hemorrhage, hemolysis, or drugs that displace bilirubin from albumin. The exact serum indirect bilirubin level that is harmful for VLBW infants is unclear.

JAUNDICE ASSOCIATED WITH BREAST-FEEDING

Significant elevation in unconjugated bilirubin (*breast milk jaundice*) develops in an estimated 2% of breastfed term infants after the 7th day, with maximal concentrations as high as 10-30 mg/dL reached during the 2nd-3rd wk. If breastfeeding is continued, the bilirubin gradually decreases but may persist for 3-10 wk at lower levels. If nursing is discontinued, the serum bilirubin level falls rapidly, reaching normal range within a few days. With resumption of breastfeeding, bilirubin seldom returns to previously high levels. Phototherapy may be of benefit (see Chapter 102.4). Although uncommon, kernicterus can occur in patients with breast milk jaundice. The etiology of breast milk jaundice is not entirely clear but may be attributed to the presence of glucuronidase in some breast milk.

The late jaundice associated with breastfeeding should be distinguished from an early-onset, accentuated unconjugated hyperbilirubinemia known as *breastfeeding jaundice*, which occurs in the 1st wk after birth in breastfed infants, who normally have higher bilirubin levels than formula-fed infants (Fig. 102-9). Hyperbilirubinemia (>12 mg/dL) develops in 13% of breastfed infants during the 1st wk and may be a result of decreased milk intake with dehydration and/or reduced caloric intake. Prophylactic supplements of glucose water to breastfed infants are associated with higher bilirubin levels, in part because of reduced intake of the higher–caloric density breast milk. Frequent breastfeeding (>10/24 hr), rooming-in with night feeding,

Table 102-4 Diagnostic Features of the Various Types of Neonatal Jaundice

DIAGNOSIS	NATURE OF VAN DEN BERGH REACTION	JAUNDICE		PEAK BILIRUBIN CONCENTRATION		BILIRUBIN RATE OF ACCUMULATION (mg/dL/day)	REMARKS
		Appears	Disappears	mg/dL	Age in Days		
"Physiologic jaundice":							Usually relates to degree of maturity
Full-term	Indirect	2-3 days	4-5 days	10-12	2-3	<5	
Premature	Indirect	3-4 days	7-9 days	15	6-8	<5	
Hyperbilirubinemia caused by metabolic factors:							Metabolic factors: hypoxia, respiratory distress, lack of carbohydrate
Full-term	Indirect	2-3 days	Variable	>12	1st wk	<5	Hormonal influences: cretinism, hormones, Gilbert syndrome
Premature	Indirect	3-4 days	Variable	>15	1st wk	<5	Genetic factors: Crigler-Najjar syndrome, Gilbert syndrome Drugs: vitamin K, novobiocin
Hemolytic states and hematoma	Indirect	May appear in 1st 24 hr	Variable	Unlimited	Variable	Usually >5	Erythroblastosis: Rh, ABO, Kell congenital hemolytic states: spherocytic, nonspherocytic Infantile pyknocytosis Drug: vitamin K Enclosed hemorrhage—hematoma
Mixed hemolytic and hepatotoxic factors	Indirect and direct	May appear in 1st 24 hr	Variable	Unlimited	Variable	Usually >5	Infection: bacterial sepsis, pyelonephritis, hepatitis, toxoplasmosis, cytomegalic inclusion disease, rubella, syphilis Drug: vitamin K
Hepatocellular damage	Indirect and direct	Usually 2-3 days; may appear by 2nd wk	Variable	Unlimited	Variable	Variable, can be >5	Biliary atresia; paucity of bile ducts, familial cholestasis, galactosemia; hepatitis and infection

From Brown AK: Neonatal jaundice, Pediatr Clin North Am *9:575–603, 1962.*

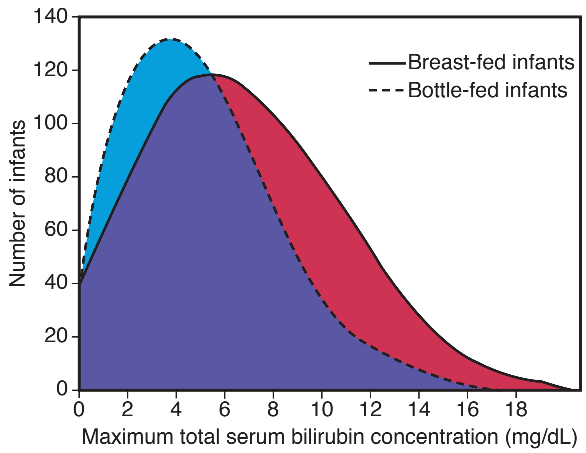

Figure 102-9 Distribution of maximal bilirubin levels during the 1st wk of life in breastfed and formula-fed white infants weighing more than 2,500 g. *(From Maisels MJ, Gifford K: Normal serum bilirubin levels in the newborn and the effect of breast-feeding,* Pediatrics *78:837–843, 1986.)*

and ongoing lactation support may reduce the incidence of early breastfeeding jaundice. Even when breastfeeding jaundice develops, breastfeeding should be continued if possible. It is an option to temporarily interrupt breast-feedings and substitute formula for a day or two. In addition, frequent feeding and supplementation with formula or expressed breast milk is appropriate if the intake seems inadequate, weight loss is excessive, or the infant appears dehydrated.

NEONATAL HEPATITIS

See Chapter 356.1.

CONGENITAL ATRESIA OF THE BILE DUCTS

See Chapter 356.1.

Jaundice persisting for more than 2 wk or associated with acholic stools and dark urine suggests biliary atresia. All infants with such findings must undergo an immediate diagnostic evaluation, including determination of direct bilirubin.

INSPISSATED BILE SYNDROME

See Late Complications in Chapter 103.2.

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102.4 Kernicterus

Namasivayam Ambalavanan and Waldemar A. Carlo

Kernicterus, or bilirubin encephalopathy, is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei. The pathogenesis of kernicterus is multifactorial and involves an interaction between unconjugated bilirubin levels, albumin binding and unbound bilirubin levels, passage across the blood-brain barrier, and neuronal susceptibility to injury. Disruption of the blood–brain barrier by disease, asphyxia, and other factors and maturational changes in blood–brain barrier permeability affect risk.

The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable, but in a large series, kernicterus occurred only in infants with a bilirubin >20 mg/dL. Ninety percent of the infants in whom kernicterus developed were in previously healthy, predominantly breastfed term and near-term infants. The duration of exposure to high bilirubin levels needed to produce toxic effects are unknown. The more immature the infant is, the greater the susceptibility to kernicterus. Chapter 102.3 discusses the factors that potentiate the movement of bilirubin across the blood–brain barrier and into brain cells.

CLINICAL MANIFESTATIONS

Signs and symptoms of kernicterus usually appear 2-5 days after birth in term infants and as late as the 7th day in preterm infants, but hyperbilirubinemia may lead to encephalopathy at any time during the neonatal period. The early signs may be subtle and indistinguishable from those of sepsis, asphyxia, hypoglycemia, intracranial hemorrhage, and other acute systemic illnesses in a neonate. Lethargy, poor feeding, and loss of the Moro reflex are common initial signs. Subsequently, the infant may appear gravely ill and prostrate, with diminished tendon reflexes and respiratory distress. Opisthotonos with a bulging fontanel, twitching of the face or limbs, and a shrill high-pitched cry may follow. In advanced cases, convulsions and spasm occur, with affected infants stiffly extending their arms in an inward rotation with the fists clenched (Table 102-5). Rigidity is rare at this late stage.

Many infants who progress to these severe neurologic signs die; the survivors are usually seriously damaged but may appear to recover and for 2-3 mo show few abnormalities. Later in the 1st yr, opisthotonos, muscle rigidity, irregular movements, and convulsions tend to recur. In the 2nd yr, the opisthotonos and seizures abate, but irregular, involuntary movements, muscle rigidity, or, in some infants, hypotonia increase steadily. By 3 yr of age, the complete neurologic syndrome is often apparent; it consists of bilateral choreoathetosis with involuntary muscle spasms, extrapyramidal signs, seizures, mental deficiency, dysarthric speech, high-frequency hearing loss, squinting, and defective upward eye movements. Pyramidal signs, hypotonia, and ataxia occur in a few infants. In mildly affected infants, the syndrome may be characterized only by mild to moderate neuromuscular incoordination, partial deafness, or "minimal brain dysfunction," occurring singly or in combination; these problems may be unapparent until the child enters school (see Table 102-5).

Table 102-5	Clinical Features of Kernicterus
ACUTE FORM	
Phase 1 (1st 1-2 days): poor suck, stupor, hypotonia, seizures	
Phase 2 (middle of 1st wk): hypertonia of extensor muscles, opisthotonos, retrocollis, fever	
Phase 3 (after the 1st wk): hypertonia	
CHRONIC FORM	
1st year: hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills	
After 1st yr: movement disorders (choreoathetosis, ballismus, tremor), upward gaze, sensorineural hearing loss	

From Dennery PA, Seidman DS, Stevenson DK: Neonatal hyperbilirubinemia, N Engl J Med *344:581–590, 2001.*

INCIDENCE AND PROGNOSIS

By pathologic criteria, kernicterus develops in 30% of infants (all gestational ages) with untreated hemolytic disease and bilirubin levels >25-30 mg/dL. The incidence at autopsy in hyperbilirubinemic preterm infants is 2-16% and is related to the risk factors discussed in Chapter 102.3. Reliable estimates of the frequency of the clinical syndrome are not available because of the wide spectrum of manifestations. Overt neurologic signs have a grave prognosis; more than 75% of infants die, and 80% of affected survivors have bilateral choreoathetosis with involuntary muscle spasms. Mental retardation, deafness, and spastic quadriplegia are common.

PREVENTION

Although kernicterus has been thought to be a disease of the past, there are reports of neurotoxic effects of bilirubin in term and near-term infants who were discharged as healthy newborns. Experts recommend universal screening for hyperbilirubinemia in the 1st 24-48 hr after birth to detect infants at high risk for severe jaundice and bilirubin-induced neurologic dysfunction.

Effective prevention requires ongoing vigilance and a practical, system-based approach in order to distinguish infants with benign newborn jaundice from those whose course may be less predictable and potentially harmful. Protocols using the hour-specific bilirubin nomogram (see Fig. 102-8), physical examination, and clinical risk factors have been successful in identifying patients at risk for hyperbilirubinemia and candidates for targeted management. The American Academy of Pediatrics has identified potentially preventable causes of kernicterus, as follows: (1) early discharge (<48 hr) with no early follow-up (within 48 hr of discharge); this problem is particularly important in near-term infants (35-37 wk of gestation); (2) failure to check the bilirubin level in an infant noted to be jaundiced in the 1st 24 hr; (3) failure to recognize the presence of risk factors for hyperbilirubinemia; (4) underestimation of the severity of jaundice by clinical (visual) assessment; (5) lack of concern regarding the presence of jaundice; (6) delay in measuring the serum bilirubin level despite marked jaundice or delay in initiating phototherapy in the presence of elevated bilirubin levels; and (7) failure to respond to parental concern regarding jaundice, poor feeding, or lethargy. Figure 102-10 is an evidence-based management algorithm for infants. In addition, it is recommended to determine before discharge each infant's risk factors from established protocols (see Table 102-2).

The following approach is further recommended: (1) any infant who is jaundiced before 24 hr requires measurement of total and direct serum bilirubin levels and, if it is elevated, evaluation for possible hemolytic disease and (2) follow-up should be provided within 2-3 days of discharge to all neonates discharged earlier than 48 hr after birth. Early follow-up is particularly important for infants younger than 38 wk of gestation. The timing of follow-up depends on the age at discharge and the presence of risk factors. In some cases, follow-up within 24 hr is necessary. Postdischarge follow-up is essential for early recognition of problems related to hyperbilirubinemia and disease progression. Parental communication with regard to concerns about infant's skin color and behavioral activities should be addressed early and frequently, including education about potential risks and neurotoxicity. Ongoing lactation promotion, education, support, and follow-up services are essential throughout the neonatal period. Mothers should be advised to nurse their infants every 2-3 hr and to avoid routine supplementation with water or glucose water in order to ensure adequate hydration and caloric intake.

TREATMENT OF HYPERBILIRUBINEMIA

Regardless of the cause, the goal of therapy is to prevent neurotoxicity related to indirect-reacting bilirubin while not causing undue harm. Phototherapy and, if it is unsuccessful, exchange transfusion remain the primary treatment modalities used to keep the maximal total serum bilirubin below pathologic levels (Figs. 102-11 and 102-12;

Table 102-6 Suggested Maximal Indirect Serum Bilirubin Concentrations (mg/dL) in Preterm Infants

BIRTHWEIGHT (g)	UNCOMPLICATED*	COMPLICATED*
<1,000	12-13	10-12
1,000-1,250	12-14	10-12
1,251-1,499	14-16	12-14
1,500-1,999	16-20	15-17
2,000-2,500	20-22	18-20

*Complications include perinatal asphyxia, acidosis, hypoxia, hypothermia, hypoalbuminemia, meningitis, intraventricular hemorrhage, hemolysis, hypoglycemia, or signs of kernicterus. Phototherapy is usually started at 50-70% of the maximal indirect level. If values greatly exceed this level, if phototherapy is unsuccessful in reducing the maximal bilirubin level, or if signs of kernicterus are evident, exchange transfusion is indicated.

Table 102-6). The risk of injury to the central nervous system from bilirubin must be balanced against the potential risk of treatment. There is lack of consensus regarding the exact bilirubin level at which to initiate phototherapy. Because phototherapy may require 6-12 hr to have a measurable effect, it must be started at bilirubin levels below those indicated for exchange transfusion. When identified, underlying medical causes of elevated bilirubin and physiologic factors that contribute to neuronal susceptibility should be treated, with antibiotics for septicemia and correction of acidosis (Table 102-7).

Phototherapy

Clinical jaundice and indirect hyperbilirubinemia are reduced by exposure to a high intensity of light in the visible spectrum. Bilirubin absorbs light maximally in the blue range (420-470 nm). Broad-spectrum white, blue, and special narrow-spectrum (super) blue lights have been effective in reducing bilirubin levels. Bilirubin in the skin absorbs light energy, causing several photochemical reactions. One major product from phototherapy is a result of a reversible photoisomerization reaction converting the toxic native unconjugated 4Z,15Z-bilirubin into an unconjugated configurational isomer, 4Z,15E-bilirubin, which can then be excreted in bile without conjugation. The other major product from phototherapy is lumirubin, which is an irreversible structural isomer converted from native bilirubin that can be excreted by the kidneys in the unconjugated state.

The therapeutic effect of phototherapy depends on the light energy emitted in the effective range of wavelengths, the distance between the lights and the infant, and the surface area of exposed skin, as well as the rate of hemolysis and in vivo metabolism and excretion of bilirubin. Available commercial phototherapy units vary considerably in spectral output and the intensity of radiance emitted; therefore, the wattage can be accurately measured only at the patient's skin surface. Dark skin does not reduce the efficacy of phototherapy. Maximal intensive phototherapy should be used when indirect bilirubin levels approach those noted in Figure 102-11 and Table 102-7. Such therapy includes using "special blue" fluorescent tubes, placing the lamps within 15-20 cm of the infant, and putting a fiberoptic phototherapy blanket under the infant's back to increase the exposed surface area. Aggressive phototherapy may improve neurodevelopmental outcome in infants <1,000 g.

The use of phototherapy has decreased the need for exchange transfusion in term and preterm infants with hemolytic and nonhemolytic jaundice. When indications for exchange transfusion are present, phototherapy should not be used as a substitute; however, phototherapy may reduce the need for repeated exchange transfusions in infants with hemolysis. Conventional phototherapy is applied continuously, and the infant is turned frequently for maximal skin surface area exposure. It should be discontinued as soon as the indirect bilirubin concentration has reduced to levels considered safe with respect to the infant's age and condition. Serum bilirubin levels and hematocrit should be monitored every 4-8 hr in infants with hemolytic disease and those with bilirubin levels near toxic range for the individual infant. Others, particularly older neonate, may be monitored less frequently. Serum bilirubin monitoring should continue for at least 24 hr after cessation of phototherapy in patients with hemolytic disease, because unexpected rises in bilirubin may occur, requiring further treatment. Skin color cannot be relied on for evaluating the effectiveness of phototherapy; the skin of babies exposed to light may appear to be almost without jaundice in the presence of marked hyperbilirubinemia. Although not necessary for all affected infants, intravenous fluid supplementation added to oral feedings may be beneficial in dehydrated patients or infants with bilirubin levels nearing those requiring exchange transfusion.

Complications associated with phototherapy include loose stools, erythematous macular rash, purpuric rash associated with transient porphyrinemia, overheating, dehydration (increased insensible water loss, diarrhea), hypothermia from exposure, and a benign condition called bronze baby syndrome (which occurs in the presence of direct hyperbilirubinemia). Phototherapy is contraindicated in the presence of porphyria. Before phototherapy is initiated, the infant's eyes should be closed and adequately covered to prevent light exposure and corneal damage. Body temperature should be monitored, and the infant should be shielded from bulb breakage. Irradiance should be measured directly. In infants with hemolytic disease, care must be taken to monitor for the development of anemia, which may require transfusion. *Anemia may develop despite lowering of bilirubin levels.* Clinical experience suggests that long-term adverse biologic effects of phototherapy are absent, minimal, or unrecognized.

The term **bronze baby syndrome** refers to a sometimes-noted dark, grayish brown skin discoloration in infants undergoing phototherapy. Almost all infants observed with this syndrome have had significant elevation of direct-reacting bilirubin and other evidence of obstructive liver disease. The discoloration may result from photo-induced modification of porphyrins, which are often present during cholestatic jaundice and may last for many months. Despite the bronze baby syndrome, phototherapy can continue if needed.

Intravenous Immunoglobulin

The administration of intravenous immunoglobulin is an adjunctive treatment for hyperbilirubinemia caused by *isoimmune hemolytic disease*. Its use is recommended when serum bilirubin is approaching exchange levels despite maximal interventions including phototherapy. Intravenous immunoglobulin (0.5-1.0 g/kg/dose; repeat in 12 hr) reduces the need for exchange transfusion in both ABO and Rh hemolytic disease, presumably by reducing hemolysis.

Metalloporphyrins

A potentially important alternative therapy is the use of metalloporphyrins for hyperbilirubinemia. The metalloporphyrin Sn-mesoporphyrin (SnMP) offers promise as a drug candidate. The proposed mechanism of action is competitive enzymatic inhibition of the rate-limiting conversion of heme-protein to biliverdin (an intermediate metabolite in the production of unconjugated bilirubin) by heme-oxygenase. A single intramuscular dose on the 1st day of life may reduce the need for subsequent phototherapy. Such therapy may be beneficial when jaundice is anticipated, particularly in patients with ABO incompatibility or G6PD deficiency, or when blood products are objected to, as with Jehovah's Witness patients. Complications from metalloporphyrins include transient erythema if the infant is receiving phototherapy. Administration of SnMP may reduce bilirubin levels and decrease both the need for phototherapy and the duration of hospital stay; however, it remains unclear whether treatment with metalloporphyrins for unconjugated hyperbilirubinemia will alter the risk of kernicterus or long-term neurodevelopment impairment. Data on efficacy, toxicity, and long-term benefit are currently being evaluated.

Exchange Transfusion

Double-volume exchange transfusion is performed if intensive phototherapy has failed to reduce bilirubin levels to a safe range and if the

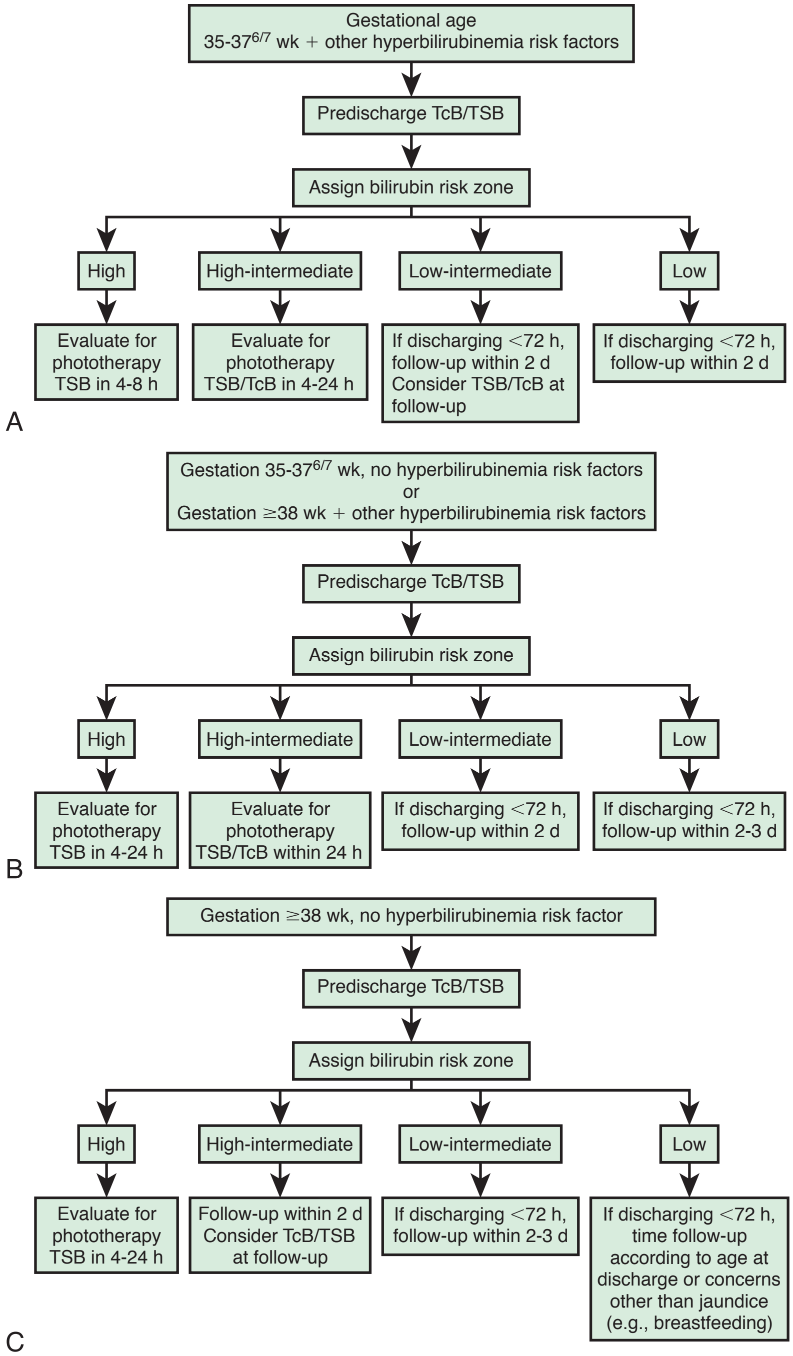

- Provide lactation evaluation and support for all breastfeeding mothers.
- Recommendation for timing of repeat TSB measurement depends on age at measurement and how far the TSB level is above the 95th percentile. Higher and earlier initial TSB levels require an earlier repeat TSB measurment.
- Perform standard clinical evaluation at all follow-up visits.
- For evaluation of jaundice see 2004 AAP guideline.
- In hospital or as outpatient. Follow-up recommendations can be modified according to level of risk for hyperbilirubinemia; depending on the circumstances in infants at low risk, later follow-up can be considered.

Figure 102-10 **Algorithm providing recommendations for management and follow-up according to predischarge bilirubin measurements, gestation, and risk factors for subsequent hyperbilirubinemia.** TcB, transcutaneous bilirubin; TSB, total serum bilirubin. *(From Maisels MJ, Bhutani VK, Bogen D, et al: Hyperbilirubinemia in the newborn infant ≥35 weeks' gestation: an update with clarifications,* Pediatrics *124:1193–1198, 2009.)*

risk of kernicterus exceeds the risk of the procedure. Potential complications from exchange transfusion are not trivial and include metabolic acidosis, electrolyte abnormalities, hypoglycemia, hypocalcemia, thrombocytopenia, volume overload, arrhythmias, NEC, infection, graft-versus-host disease, and death. This widely accepted treatment is repeated if necessary to keep indirect bilirubin levels in a safe range (see Fig. 102-12 and Table 102-7). See "Exchange Transfusion" in Chapter 103.

Various factors may influence the decision to perform a double-volume exchange transfusion in an individual patient. The appearance of clinical signs suggesting kernicterus is an indication for exchange transfusion at any level of serum bilirubin. A healthy full-term infant

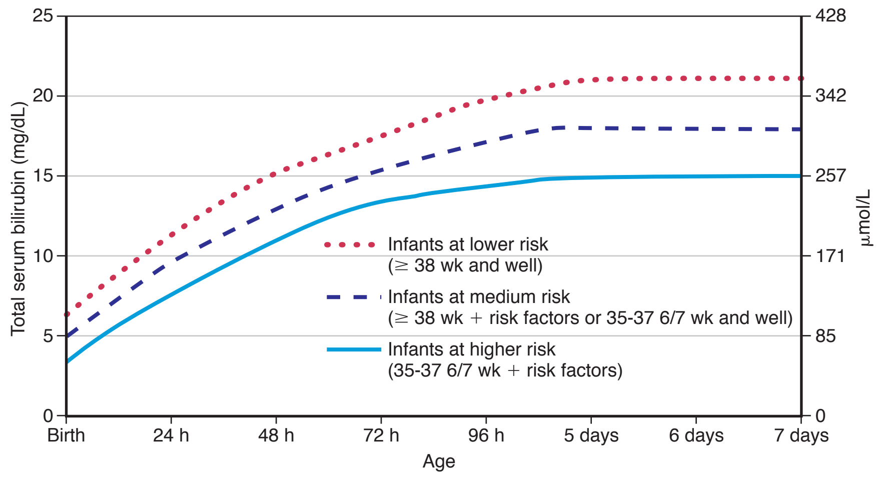

- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0 g/dL (if measured).
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50 mmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

Figure 102-11 Guidelines for phototherapy in hospitalized infants of ≥35 wk of gestation. *Note:* These guidelines are based on limited evidence, and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy, which should be used when the total serum bilirubin (TSB) exceeds the line indicated for each category. Infants are designated as "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood–brain barrier, and the susceptibility of the brain cells to damage by bilirubin. "Intensive phototherapy" implies irradiance in the blue-green spectrum (wavelengths approximately 430-490 nm) of at least 30 µW/cm^2/nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's skin surface area as possible. Note that irradiance measured below the center of the light source is much greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system. If TSB levels approach or exceed the exchange transfusion line (see Fig. 102-12), the sides of the bassinette, incubator, or warmer should be lined with aluminum foil or white material, to increase both the surface area of the infant exposed and the efficacy of phototherapy. The presence of hemolysis is strongly suggested if the TSB does not decrease or continues to rise in an infant who is receiving intensive phototherapy. Infants who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin value (cholestatic jaundice) may inconsistently have the bronze-baby syndrome. G6PD, glucose-6-phosphate dehydrogenase. *(From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation,* Pediatrics *114:297–316, 2004.)*

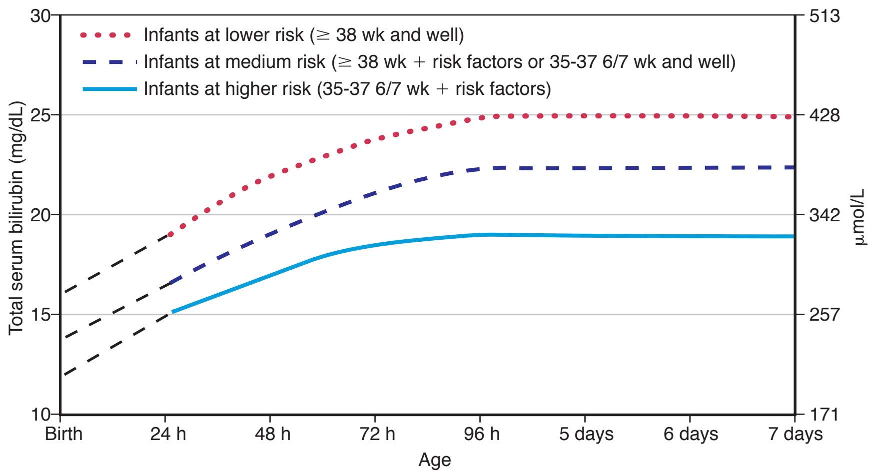

- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥ 5 mg/dL (85 µmol/L) above these lines.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (see legend).
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 wk (median risk), can individualize TSB levels for exchange based on actual gestational age.

Figure 102-12 Guidelines for exchange transfusion in hospitalized infants of ≥35 wk of gestation. *Note:* These suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the total serum bilirubin (TSB) rises to these levels despite intensive phototherapy. In a readmitted infant, if the TSB level is above the exchange level, TSB measurement should be repeated every 2-3 hr; exchange transfusion should be considered if the TSB remains above the levels indicated after intensive phototherapy for 6 hr. The following B : A (bilirubin : albumin) ratios can be used together with, but not in lieu of, the TSB level as an additional factor in determining the need for exchange transfusion. G6PD, glucose-6-phosphate dehydrogenase. *(From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation,* Pediatrics *114:297–316, 2004.)*

Table 102-7 Example of a Clinical Pathway for Management of the Newborn Infant Readmitted for Phototherapy or Exchange Transfusion

TREATMENT
Use intensive phototherapy and/or exchange transfusion as indicated in Figs. 102-11 and 102-12
LABORATORY TESTS
TSB and direct bilirubin levels
Blood type (ABO, Rh)
Direct antibody test (Coombs)
Serum albumin
Complete blood cell count with differential and smear for red cell morphology
Reticulocyte count
End-tidal CO concentration (if available)
Glucose-6-phosphate dehydrogenase if suggested by ethnic or geographic origin or if poor response to phototherapy
Urine for reducing substances
If history and/or presentation suggest sepsis, perform blood culture, urine culture, and cerebrospinal fluid for protein, glucose, cell count, and culture
INTERVENTIONS
If TSB ≥25 mg/dL (428 µmol/L) or ≥20 mg/dL (342 µmol/L) in a sick infant or infant <38 wk gestation, obtain a type and crossmatch, and request blood in case an exchange transfusion is necessary
In infants with isoimmune hemolytic disease and TSB level rising in spite of intensive phototherapy or within 2-3 mg/dL (34-51 µmol/L) of exchange level (see Fig. 102-12), administer intravenous immunoglobulin 0.5-1 g/kg over 2 hr and repeat in 12 hr if necessary
If infant's weight loss from birth is >12% or there is clinical or biochemical evidence of dehydration, recommend formula or expressed breast milk. If oral intake is in question, give intravenous fluids
FOR INFANTS RECEIVING INTENSIVE PHOTOTHERAPY:
Breastfeed or bottle-feed (formula or expressed breast milk) every 2-3 hr
If TSB ≥25 mg/dL (428 µmol/L), repeat TSB within 2-3 hr
If TSB 20-25 mg/dL (342-428 µmol/L), repeat within 3-4 hr. If TSB <20 mg/dL (342 µmol/L), repeat in 4-6 hr. If TSB continues to fall, repeat in 8-12 hr
If TSB is not decreasing or is moving closer to level for exchange transfusion or the TSB/albumin ratio exceeds levels shown in Fig. 102-12, consider exchange transfusion (see Fig. 102-12 for exchange transfusion recommendations)
When TSB is <13-14 mg/dL (239 µmol/L), discontinue phototherapy
Depending on the cause of the hyperbilirubinemia, it is an option to measure TSB 24 hr after discharge to check for rebound

TSB, total serum bilirubin.

From AAP Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, Pediatrics *114:297–316, 2004.*

with physiologic or breast milk jaundice may tolerate a concentration slightly higher than 25 mg/dL with no apparent ill effect, whereas kernicterus may develop in a sick premature infant at a significantly lower level. A level approaching that considered critical for the individual infant may be an indication for exchange transfusion during the 1st or 2nd day after birth when a further rise is anticipated, but not typically after the 4th day in a term infant or after the 7th day in a preterm infant because an imminent fall may be anticipated as the hepatic conjugating mechanism becomes more effective.

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Chapter 103

Blood Disorders

Akhil Maheshwari and Waldemar A. Carlo

103.1 Anemia in the Newborn Infant

Akhil Maheshwari and Waldemar A. Carlo

Hemoglobin increases with advancing gestational age: at term, cord blood hemoglobin is 16.8 g/dL (14-20 g/dL); hemoglobin levels in very-low birthweight (VLBW) infants are 1-2 g/dL below those in term infants (Fig. 103-1). A hemoglobin value less than the normal range of hemoglobin for birthweight and postnatal age is defined as anemia (Table 103-1). A "physiologic" decrease in hemoglobin content is noticed at 8-12 wk in term infants (hemoglobin, 11 g/dL) and at approximately 6 wk in premature infants (7-10 g/dL).

Infants born by cesarean section may have a lower hematocrit than those born vaginally. **Anemia at birth** manifests as pallor, heart failure, or shock (Fig. 103-2). It may be caused by acute or chronic fetal blood loss, hemolysis, or underproduction of erythrocytes. Specific causes include hemolytic disease of the newborn, tearing or cutting of the umbilical cord during delivery, abnormal cord insertion, communicating placental vessels, placenta previa or abruptio, nuchal cord, incision into the placenta, internal hemorrhage (liver, spleen, intracranial), α-thalassemia, congenital parvovirus infection or other hypoplastic anemias, and twin–twin transfusion in monozygotic twins with arteriovenous placental connections (see Chapter 98).

Transplacental hemorrhage with bleeding from the fetal into the maternal circulation has been reported in 5-15% of pregnancies, but, unless severe, it is not usually sufficient to cause clinically apparent anemia at birth. The cause of transplacental hemorrhage is not clear, but its occurrence has been proven by demonstration of significant amounts of fetal hemoglobin and red blood cells (RBCs) in maternal blood on the day of delivery by the **Kleihauer-Betke** test or by flow cytometry methods to detect fetal cells in maternal blood. If the infant has severe anemia with heart failure, emergency exchange transfusion to restore hematocrit and oxygen-carrying capacity may be needed.

Acute blood loss usually results in severe distress at birth, initially with a normal hemoglobin level, no hepatosplenomegaly, and early onset of shock. In contrast, chronic blood loss in utero produces

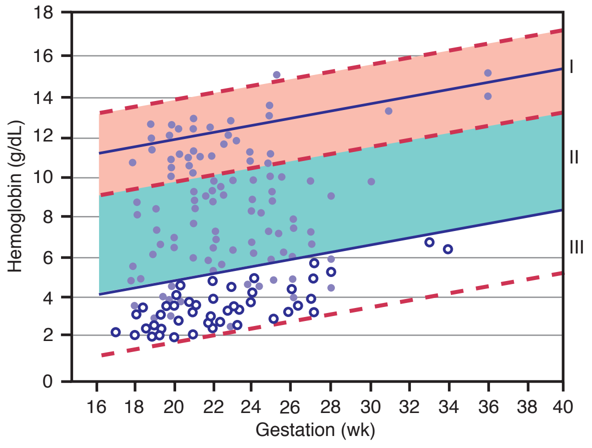

Figure 103-1 Range (mean and 95% confidence limits) of hemoglobin concentration from 10-40 wk of gestational age in normal (zone I) fetuses obtained by cordocentesis (percutaneous umbilical blood sample). *Solid circles* depict maternal red blood cell isoimmunization; *open circles* indicate hemoglobin levels in fetuses with ultrasonographic evidence of hydrops (zone III). *(From Soothill PW: Cordocentesis: role in assessment of fetal condition,* Clin Perinatol *16:755–770, 1989.)*

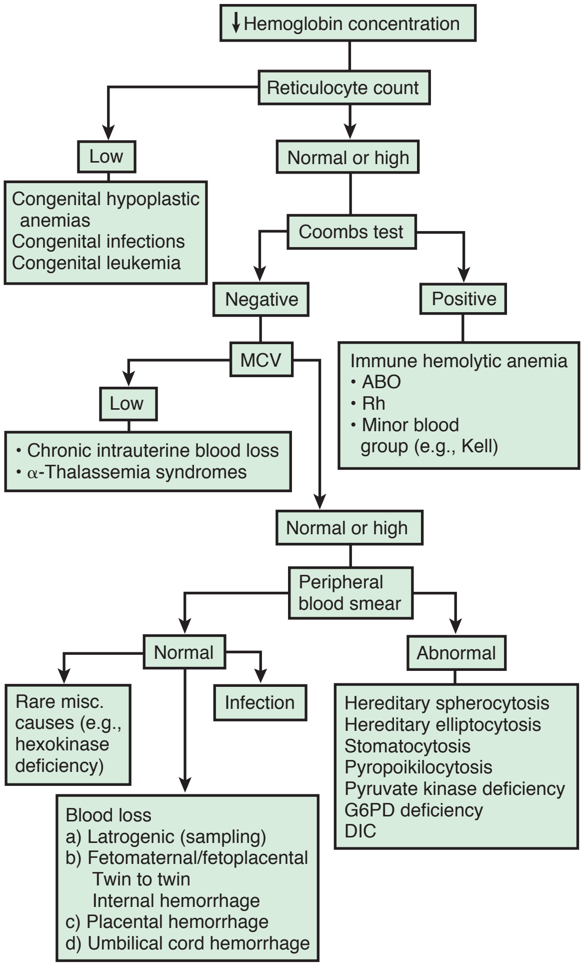

Figure 103-2 Diagnostic approach to anemia in newborn infants. DIC, disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; MCV, mean corpuscular volume. *(Modified from Blanchette VS, Zipursky A: Assessment of anemia in newborn infants,* Clin Perinatol *11:489–510, 1984.)*

marked pallor, less distress, a low hemoglobin level with microcytic indices, and, if severe, heart failure.

Anemia appearing in the first few days after birth is also most frequently a result of hemolytic disease of the newborn. Other causes are hemorrhagic disease of the newborn, bleeding from an improperly tied or clamped umbilical cord, large cephalohematoma, intracranial hemorrhage, and subcapsular bleeding from rupture of the liver, spleen, adrenals, or kidneys. Rapid decreases in hemoglobin or hematocrit values during the first few days of life may be the initial clue to these conditions.

Later in the neonatal period, delayed anemia may develop as a result of hemolytic disease of the newborn, with or without exchange transfusion or phototherapy. Congenital hemolytic anemia (spherocytosis) occasionally appears during the 1st mo of life, and hereditary nonspherocytic hemolytic anemia has been described during the neonatal period secondary to deficiency of glucose-6-phosphate dehydrogenase and pyruvate kinase. Bleeding from hemangiomas of the upper gastrointestinal tract or from ulcers caused by aberrant gastric mucosa in a Meckel diverticulum or duplication is a rare source of anemia in newborns. Repeated blood sampling of infants requiring frequent monitoring of blood gas and chemistry parameters is a common cause of anemia among hospitalized infants. Deficiency of minerals such as copper may cause anemia in infants maintained on total parenteral nutrition.

Anemia of prematurity occurs in low birthweight infants 1-3 mo after birth, is associated with hemoglobin levels <7-10 g/dL, and is clinically manifested as pallor, poor weight gain, decreased activity, tachypnea, tachycardia, and feeding problems. Repeated phlebotomy for blood tests, shortened RBC survival, rapid growth, and the physiologic effects of the transition from fetal (low Pao_2 and hemoglobin saturation) to neonatal life (high Pao_2 and hemoglobin saturation) contribute to anemia of prematurity. The oxygen available to neonatal tissue is lower than that in adults, but a neonate's erythropoietin response is attenuated for the degree of anemia, and as a result, hemoglobin and reticulocyte levels are low. In VLBW infants, delayed clamping of the umbilical cord with the infant held below the level of the placenta may enhance placental-infant transfusion and reduce postnatal transfusion needs. This maneuver should not delay any needed resuscitation and may lead to hyperviscosity.

Delayed cord clamping (30-180 sec or after cessation of cord pulsation) may be beneficial in otherwise well newborns in preventing anemia in full-term infants, with effects extending beyond the neonatal period. The benefits of delayed cord clamping persist for 2-6 mo as improved hematocrit, iron status as measured by ferritin concentration and stored iron, and a clinically important reduction in the risk of anemia in infancy. Late clamping may result in delivery of an extra 20-40 mL of blood and 30-35 mg of iron to the newborn. Polycythemia is a risk with delayed clamping but is often asymptomatic.

Treatment of neonatal anemia by blood transfusion depends on the severity of symptoms, the hemoglobin level, and the presence of comorbid diseases (bronchopulmonary dysplasia, cyanotic congenital heart disease, respiratory distress syndrome) that interfere with oxygen delivery. The need for treatment with blood should be balanced against the risks of transfusion, including hemolytic transfusion reactions, exposure to blood product preservatives and other potential toxins, volume overload, possible increased risk of retinopathy of prematurity and necrotizing enterocolitis, graft-versus-host (GVH) reaction, and transfusion-acquired infection (cytomegalovirus [CMV], HIV, parvovirus, hepatitides B and C) (see Chapter 474). The risk of CMV infection can be almost eliminated by the use of leukoreduced blood. In the infant who weighs <1,500 g, CMV antibody-negative leukoreduced blood should be used. The risk of acquiring HIV and hepatitides B and C viruses is reduced but not eliminated by antibody screening of donated blood. Blood-banking techniques that limit multiple donor exposure should be encouraged.

Although transfusion guidelines for preterm infants have been proposed (Table 103-2), they have not been subjected to rigorous clinical study. Nonetheless, these guidelines have led to a decline in the number of unnecessary transfusions. The use of restrictive vs more liberal transfusion guidelines has been examined in 2 randomized trials, one conducted at University of Iowa and a second multicentric trial known as the PINT (Premature Infants in Need of Transfusion) study. The restrictive guidelines in the 2 groups were generally similar. In the Iowa trial, the transfusion thresholds in the liberal- and restrictive-transfusion groups were <46% and <34%, respectively, in tracheally intubated infants receiving assisted ventilation; <38% and <28%, respectively, in infants receiving nasal continuous positive airway pressure or supplemental oxygen; and <30% and <22%, respectively, in infants breathing room air. The transfusion thresholds for the liberal groups were higher in the Iowa trial than in the PINT study. In both trials, the use of restrictive thresholds resulted in fewer transfusions and also increased the number of infants who received no transfusions at all. However, in the Iowa trial (but not in the PINT study), restrictive transfusion thresholds were associated with increases in major cranial ultrasonographic abnormalities and in the frequency of apneic spells. Although these findings need further evaluation in clinical studies, the issue of finding an appropriate transfusion threshold in premature infants remains unresolved.

Asymptomatic full-term infants with a hemoglobin level of 10 g/dL may be monitored, whereas symptomatic neonates born after abruptio placentae or with severe hemolytic disease of the newborn need immediate transfusion. Preterm infants who have repeated episodes of apnea and bradycardia despite theophylline therapy and a hemoglobin level ≤8 g/dL may benefit from RBC transfusion. In addition, infants with respiratory distress syndrome or severe bronchopulmonary dysplasia

Table 103-1 Normal Red Blood Cell Values from 18 Wk of Gestation to 14 Wk of Life

AGE	HEMOGLOBIN (g/dL)	HEMATOCRIT (%)	MCV (μ^3)	RETICULOCYTES (%)
GESTATIONAL (WK)				
18-20*	11.5 ± 0.8	36 ± 3	134 ± 8.8	N/A
21-22*	12.3 ± 0.9	39 ± 3	130 ± 6.2	N/A
23-25*	12.4 ± 0.8	39 ± 2	126 ± 6.2	N/A
26-27	19.0 ± 2.5	62 ± 8	132 ± 14.4	9.6 ± 3.2
28-29	19.3 ± 1.8	60 ± 7	131 ± 13.5	7.5 ± 2.5
30-31	19.1 ± 2.2	60 ± 8	127 ± 12.7	5.8 ± 2.0
32-33	18.5 ± 2.0	60 ± 8	123 ± 15.7	5.0 ± 1.9
34-35	19.6 ± 2.1	61 ± 7	122 ± 10.0	3.9 ± 1.6
36-37	19.2 ± 1.7	64 ± 7	121 ± 12.5	4.2 ± 1.8
38-40	19.3 ± 2.2	61 ± 7	119 ± 9.4	3.2 ± 1.4
POSTNATAL (DAYS)				
1	19.0 ± 2.2	61 ± 7	119 ± 9.4	3.2 ± 1.4
2	19.0 ± 1.9	60 ± 6	115 ± 7.0	3.2 ± 1.3
3	18.7 ± 3.4	62 ± 9	116 ± 5.3	2.8 ± 1.7
4	18.6 ± 2.1	57 ± 8	114 ± 7.5	1.8 ± 1.1
5	17.6 ± 1.1	57 ± 7	114 ± 8.9	1.2 ± 0.2
6	17.4 ± 2.2	54 ± 7	113 ± 10.0	0.6 ± 0.2
7	17.9 ± 2.5	56 ± 9	118 ± 11.2	0.5 ± 0.4
POSTNATAL (WK)				
1-2	17.3 ± 2.3	54 ± 8	112 ± 19.0	0.5 ± 0.3
2-3	15.6 ± 2.6	46 ± 7	111 ± 8.2	0.8 ± 0.6
3-4	14.2 ± 2.1	43 ± 6	105 ± 7.5	0.6 ± 0.3
4-5	12.7 ± 1.6	36 ± 5	101 ± 8.1	0.9 ± 0.8
5-6	11.9 ± 1.5	36 ± 6	102 ± 10.2	1.0 ± 0.7
6-7	12.0 ± 1.5	36 ± 5	105 ± 12.0	1.2 ± 0.7
7-8	11.1 ± 1.1	33 ± 4	100 ± 13.0	1.5 ± 0.7
8-9	10.7 ± 0.9	31 ± 3	93 ± 12.0	1.8 ± 1.0
9-10	11.2 ± 0.9	32 ± 3	91 ± 9.3	1.2 ± 0.6
10-11	11.4 ± 0.9	34 ± 2	91 ± 7.7	1.2 ± 0.7
11-12	11.3 ± 0.9	33 ± 3	88 ± 7.9	0.7 ± 0.3
12-14	11.9	37	86.8	0.9

*Based on samples collected in utero. Results expressed as mean value ±1 standard deviation from the mean except for postnatal weeks 12-14 in which only the mean value is given.

From Bizzarro MJ, Colson E, Ehrenkranz RA: Differential diagnosis and management of anemia in the newborn, Pediatr Clin North Am *51:1087–1107, 2004.*

Table 103-2 Transfusion Protocol

HEMATOCRIT (%)	HEMOGLOBIN (g/dL)	RESPIRATORY SUPPORT AND/OR SYMPTOMS	TRANSFUSION VOLUME
≤35	≤11	Infants requiring moderate or significant mechanical ventilation (mean arterial pressure >8 cm H_2O and FIO_2 >0.4)	15 mL/kg PRBCs* over 2-4 hr
≤30	≤10	Infants requiring minimal respiratory support (any mechanical ventilation or endotracheal/nasal continuous positive airway pressure >6 cm H_2O and FIO_2 ≤0.4)	15 mL/kg PRBCs over 2-4 hr
≤25	≤8	Infants not requiring mechanical ventilation but who are receiving supplemental O_2 or CPAP with an FIO_2 ≤0.4 and in whom 1 or more of the following is present: • ≤24 hr of tachycardia (heart rate >180 beats/min) or tachypnea (respiratory rate >80 breaths/min) • An increased oxygen requirement from the previous 48 hr, defined as a ≥4-fold increase in nasal canula flow (i.e., from 0.25 to 1 L/min) or an increase in nasal CPAP ≥20% from the previous 48 hr (i.e., 5-6 cm H_2O) • Weight gain <10 g/kg/day over the previous 4 days while infant is receiving ≥100 kcal/kg/day • An increase in episodes of apnea and bradycardia (>9 episodes in a 24-hr period or ≥2 episodes in 24 hr requiring bag and mask ventilation) while infant is receiving therapeutic doses of methylxanthines • Undergoing surgery	20 mL/kg PRBCs over 2-4 hr (divide into 2 10-mL/kg volumes if infant is fluid sensitive)
≤20	≤7	Asymptomatic and an absolute reticulocyte count <100,000 cells/µL	20 mL/kg PRBCs over 2-4 hr (2 10-mL/kg volumes)

*RBCs should be irradiated prior to transfusion.

CPAP, continuous positive airway pressure; FIO_2, fractional inspired oxygen; PRBCs, packed red blood cells.

From Ohls RK, Ehrenkranz RA, Wright LL, et al: Effects of early erythropoietin therapy on the transfusion requirements of preterm infants below 1250 grams birth weight: a multicenter, randomized, controlled trial, Pediatrics *108:934–942, 2001.*

may need hemoglobin levels of 12-14 g/dL to improve oxygen delivery. No transfusion is needed to replace blood removed for testing or for mild asymptomatic anemia. Asymptomatic neonates with reticulocytopenia and hemoglobin levels ≤7 g/dL may require transfusion; if a transfusion is not provided, close observation is essential. Packed RBC transfusion (10-20 mL/kg) is given at a rate of 2-3 mL/kg/hr to raise the hemoglobin concentration; 2 mL/kg raises the hemoglobin level 0.5-1 g/dL. Hemorrhage should be treated with whole blood if available; alternatively, fluid resuscitation is initiated, followed by packed RBC transfusion.

Recombinant human erythropoietin (rHuEPO) may be considered in the treatment of chronic or anticipated anemia in an attempt to decrease or eliminate transfusions when families, for religious reasons, request all possible measures to avoid transfusions. Therapy with rHuEPO must be supplemented with oral iron. Doses and regimens vary. In anemia of prematurity, rHuEPO does not provide a major reduction in transfusion requirements or the number of donors; therefore, *routine* use of erythropoietin in VLBW infants is not recommended. Early initiation of rHuEPO therapy may produce a small reduction in the total transfusion volume per infant. There were concerns about an increased risk of severe retinopathy of prematurity in the rHuEPO group. The effects of *late* initiation of rHuEPO (≥8 days) have also been associated with small reductions in the total blood volume transfused per infant and the number of transfusions per infant. In pilot studies, a single-dose treatment with darbepoetin alfa, a long-acting form of recombinant erythropoietin, has shown promise as a stimulant of erythropoiesis in convalescing premature infants.

Bibliography is available at Expert Consult.

103.2 Hemolytic Disease of the Newborn (Erythroblastosis Fetalis)

Akhil Maheshwari and Waldemar A. Carlo

Erythroblastosis fetalis is caused by the transplacental passage of maternal antibody active against paternal RBC antigens of the infant and is characterized by an increased rate of RBC destruction. It is an important cause of anemia and jaundice in newborn infants despite the development of a method of preventing maternal isoimmunization by Rh antigens. Although more than 60 different RBC antigens are capable of eliciting an antibody response, significant disease is associated primarily with the D antigen of the Rh group and with incompatibility of ABO factors. Rarely, hemolytic disease may be caused by C or E antigens or by other RBC antigens, such as C^W, C^X, D^U, K (Kell), M, Duffy, S, P, MNS, Xg, Lutheran, Diego, and Kidd. Anti-Lewis antibodies do not cause disease.

HEMOLYTIC DISEASE OF THE NEWBORN CAUSED BY RH INCOMPATIBILITY

The Rh antigenic determinants are genetically transmitted from each parent, determine the Rh type, and direct the production of a number of blood group factors (C, c, D, d, E, and e). Each factor can elicit a specific antibody response under suitable conditions; 90% are caused by D antigen and the remainder to C or E antigen.

Pathogenesis

Isoimmune hemolytic disease from D antigen is approximately 3 times more frequent among white persons than among black persons. When Rh-positive blood is infused into an Rh-negative woman through error, or when small quantities (usually >1 mL) of Rh-positive fetal blood containing D antigen inherited from an Rh-positive father enter the maternal circulation during pregnancy, with spontaneous or induced abortion, or at delivery, antibody formation against D antigen may be induced in the unsensitized Rh-negative recipient mother. Once sensitization has taken place, considerably smaller doses of antigen can stimulate an increase in antibody titer. Initially, a rise in immunoglobulin (Ig) M antibody occurs, which is later replaced by IgG antibody; the latter readily crosses the placenta to cause hemolytic manifestations.

Hemolytic disease rarely occurs during a first pregnancy because transfusion of Rh-positive fetal blood into an Rh-negative mother occurs near the time of delivery, too late for the mother to become sensitized and transmit antibody to her infant before delivery. The facts that 55% of Rh-positive fathers are heterozygous (D/d) and may have Rh-negative offspring and that fetal-to-maternal transfusion occurs in only 50% of pregnancies, reduce the chance of sensitization, as does small family size, in which the opportunities for its reoccurrence are reduced. The disparity between the numbers of incompatible versus alloimmunized maternal-fetal pairs can also be the result of a threshold effect of fetomaternal transfusions (a certain amount of the immunizing blood cell antigen is required to activate the maternal immune system), the type of antibody response (IgG antibodies are more efficiently transferred across the placenta to the fetus), differential immunogenicity of blood group antigens, and differences in maternal immune response, presumably related to differences in the efficiency of antigen presentation by various major histocompatibility loci. Thus, the overall incidence of isoimmunization of Rh-negative mothers at risk is low, with antibody to antigen D detected in >10% of those studied, even after five or more pregnancies; only approximately 5% ever have babies with hemolytic disease.

When the mother and fetus are also incompatible with respect to group A or B, the mother is partially protected against sensitization by the rapid removal of Rh-positive cells from her circulation by her preexisting anti-A or anti-B antibodies, which are IgM antibodies and do not cross the placenta. Once a mother has been sensitized, her infant is likely to have hemolytic disease. The severity of Rh illness worsens with successive pregnancies. The possibility that the first affected infant after sensitization may represent the end of the mother's childbearing potential for Rh-positive infants argues urgently for the prevention of sensitization. *The injection of anti-D gammaglobulin (RhoGAM) into the mother immediately after the delivery of each Rh-positive infant has been a successful strategy to reduce Rh hemolytic disease.*

Clinical Manifestations

A wide spectrum of hemolytic disease occurs in affected infants born to sensitized mothers, depending on the nature of the individual immune response. The severity of the disease may range from only laboratory evidence of mild hemolysis (15% of cases) to severe anemia with compensatory hyperplasia of erythropoietic tissue leading to massive enlargement of the liver and spleen. When the compensatory capacity of the hematopoietic system is exceeded, profound anemia occurs and results in pallor, signs of cardiac decompensation (cardiomegaly, respiratory distress), massive anasarca, and circulatory collapse. This clinical picture of excessive abnormal fluid in 2 or more fetal compartments (skin, pleura, pericardium, placenta, peritoneum, amniotic fluid), termed **hydrops fetalis,** frequently results in death in utero or shortly after birth. With the use of RhoGAM to prevent Rh sensitization, nonimmune (nonhemolytic) conditions have become frequent causes of hydrops (Table 103-3). The severity of hydrops is related to the level of anemia and the degree of reduction in serum albumin (oncotic pressure), which is partly a result of hepatic dysfunction. Alternatively, heart failure may increase right heart pressure, with the subsequent development of edema and ascites. Failure to initiate spontaneous effective ventilation because of pulmonary edema or bilateral pleural effusions results in birth asphyxia; after successful resuscitation, severe respiratory distress may develop. Petechiae, purpura, and thrombocytopenia may also be present in severe cases as a result of decreased platelet production or the presence of concurrent disseminated intravascular coagulation.

Jaundice may be absent at birth because of placental clearance of lipid-soluble unconjugated bilirubin, but in severe cases, bilirubin pigments stain the amniotic fluid, cord, and vernix caseosa yellow. Jaundice is generally evident on the 1st day of life because the infant's bilirubin-conjugating and excretory systems are unable to cope with the load resulting from massive hemolysis. Indirect-reacting bilirubin

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Table 103-3 Etiology of Hydrops Fetalis*

CATEGORY	DISORDER(S)
Anemia	Immune (Rh, Kell) hemolysis α-Thalassemia Red blood cell enzyme deficiencies (glucose-6-phosphate dehydrogenase) Fetomaternal hemorrhage Donor in twin-to-twin transfusion Diamond-Blackfan syndrome
Cardiac dysrhythmias	Supraventricular tachycardia Atrial flutter Congenital heart block
Structural heart lesions	Premature closure of foramen ovale Tricuspid insufficiency Hypoplastic left heart Endocardial cushion defect Cardiomyopathy Endocardial fibroelastosis Tuberous sclerosis with cardiac rhabdomyoma Pericardial teratoma
Vascular	Chorioangioma of placenta, chorionic vessels, or umbilical vessels Umbilical artery aneurysm Angiomyxoma of umbilical cord True knot of umbilical cord Hepatic hemangioma Cerebral arteriovenous malformation (aneurysm of vein of Galen) Angioosteohypertrophy (Klippel-Trénaunay syndrome) Thrombosis of renal or umbilical vein or inferior vena cava Recipient in twin-to-twin transfusion
Lymphatic	Lymphangiectasia Cystic hygroma Chylothorax, chylous ascites Noonan syndrome Multiple pterygium syndrome
Central nervous system	Absent corpus callosum Encephalocele Intracranial hemorrhage Holoprosencephaly
Thoracic lesions	Cystic adenomatoid malformation of lung Mediastinal teratoma Diaphragmatic hernia Sequestered lung
Teratomas	Choriocarcinoma Sacrococcygeal teratoma
Tumors and storage diseases	Neuroblastoma Hepatoblastoma Gaucher disease Niemann-Pick disease Mucolipidosis GM_1 gangliosidosis Mucopolysaccharidosis
Chromosome abnormalities	Trisomy 13, 15, 16, 18, 21 XX/XY, 45XO Partial duplication of chromosomes 11, 15, 17, 18 Partial deletion of chromosomes 13, 18 Triploidy Tetraploidy
Bone diseases	Osteogenesis imperfecta Asphyxiating thoracic dystrophy Skeletal dysplasias
Congenital infections	Cytomegalovirus Parvovirus Rubella Toxoplasmosis Syphilis Leptospirosis Chagas disease
Others	Bowel obstruction with perforation and meconium peritonitis, volvulus Hepatic fibrosis Beckwith-Wiedemann syndrome Prune-belly syndrome Congenital nephrosis Infant of a diabetic mother Myotonic dystrophy Neu-Laxova syndrome Maternal therapy with indomethacin Fetal akinesia
Idiopathic	Multiple congenital anomaly syndromes

*The incidence of nonimmune (nonhemolytic) hydrops fetalis is 1/2,000-1/3,500 live births.
Modified from Phibbs R. In Polin N, Fox W, editors: Fetal and neonatal physiology, *ed 2, Philadelphia, 1998, WB Saunders.*

therefore accumulates postnatally and may rapidly reach extremely high levels and present a significant risk of bilirubin encephalopathy. The risk of development of kernicterus from hemolytic disease is greater than from comparable nonhemolytic hyperbilirubinemia, although the risk in an individual patient may be affected by other complications (hypoxia, acidosis). Hypoglycemia occurs frequently in infants with severe isoimmune hemolytic disease and may be related to hyperinsulinism and hypertrophy of the pancreatic islet cells in these infants.

Infants born after intrauterine transfusion for prenatally diagnosed erythroblastosis may be severely affected because the indications for transfusion are evidence of already severe disease in utero (hydrops, fetal anemia). Such infants usually have very high (but extremely variable) cord levels of bilirubin, reflecting the severity of the hemolysis and its effects on hepatic function. Infants treated with intraumbilical vein transfusions in utero may also have a benign postnatal course if the anemia and hydrops resolve before birth. Anemia from continuing hemolysis may be masked by the previous intrauterine transfusion, and the clinical manifestations of erythroblastosis may be superimposed on various degrees of immaturity resulting from spontaneous or induced premature delivery.

Laboratory Data

Before treatment, the direct Coombs test result is usually positive and anemia is generally present. The cord blood hemoglobin content varies and is usually proportional to the severity of the disease; with hydrops fetalis it may be as low as 3-4 g/dL. Alternatively, despite hemolysis, it may be within the normal range because of compensatory bone marrow and extramedullary hematopoiesis. The blood smear typically shows polychromasia and a marked increase in nucleated RBCs. The reticulocyte count is increased. The white blood cell count is usually normal but may be elevated; thrombocytopenia may develop in severe cases. Cord bilirubin is generally between 3 and 5 mg/dL; the direct-reacting (conjugated) bilirubin content may also be elevated, especially if there was an intrauterine transfusion. Indirect- reacting bilirubin content rises rapidly to high levels in the 1st 6 hr of life.

After intrauterine transfusions, cord blood may show a normal hemoglobin concentration, negative direct Coombs test result, predominantly type O Rh-negative adult RBCs, and relatively normal smear findings.

Diagnosis

Definitive diagnosis of erythroblastosis fetalis requires demonstration of blood group incompatibility and corresponding antibody bound to the infant's RBCs.

Antenatal Diagnosis

In Rh-negative women, a history of previous transfusions, abortion, or pregnancy should suggest the possibility of sensitization. Expectant parents' blood types should be tested for potential incompatibility, and the maternal titer of IgG antibodies to D antigen should be assayed at 12-16, 28-32, and 36 wk of gestation. Fetal Rh status may be determined by isolating fetal cells or fetal DNA (plasma) from the maternal circulation. The presence of elevated antibody titers at the beginning of pregnancy, a rapid rise in titer, or a titer of 1 : 64 or greater suggests significant hemolytic disease, although the exact titer correlates poorly with the severity of disease. If a mother is found to have antibody against D antigen at a titer of 1 : 16 (15 IU/mL in Europe) or greater at any time during a subsequent pregnancy, the severity of fetal disease should be monitored by Doppler ultrasonography of the middle cerebral artery and then percutaneous umbilical blood sampling (PUBS) if indicated (see Chapter 96). If the mother has a history of a previously affected infant or a stillbirth, an Rh-positive infant is usually equally or more severely affected than the previous infant, and the severity of disease in the fetus should be monitored.

Assessment of the fetus may require information obtained from ultrasonography and PUBS. Real-time ultrasonography is used to detect the progression of disease, with hydrops defined as skin or scalp edema, pleural or pericardial effusions, and ascites. Early ultrasonographic signs of hydrops include organomegaly (liver, spleen, heart), the double–bowel wall sign (bowel edema), and placental thickening. Progression to polyhydramnios, ascites, pleural or pericardial effusions, and skin or scalp edema may then follow. If pleural effusions precede ascites and hydrops by a significant time, causes other than fetal anemia should be suspected (see Table 96-2 in Chapter 96). Extramedullary hematopoiesis and, less so, hepatic congestion compress the intrahepatic vessels and produce venous stasis with portal hypertension, hepatocellular dysfunction, and decreased albumin synthesis.

Hydrops is present with a fetal hemoglobin level <5 g/dL, frequent with a level <7 g/dL, and variable with levels between 7 and 9 g/dL. Real-time ultrasonography predicts fetal well-being by means of the biophysical profile (see Table 96-2 in Chapter 96), whereas Doppler ultrasonography assesses fetal distress by demonstrating increased vascular resistance in fetal arteries (middle cerebral). In pregnancies with ultrasonographic evidence of hemolysis (hepatosplenomegaly), early or late hydrops, or fetal distress, further and more direct assessment of fetal hemolysis should be performed.

Amniocentesis was classically used to assess fetal hemolysis. Hemolysis of fetal RBCs produces hyperbilirubinemia before the onset of severe anemia. Bilirubin is cleared by the placenta, but a significant proportion enters the amniotic fluid and can be measured by spectrophotometry. Ultrasonographically guided transabdominal aspiration of amniotic fluid may be performed as early as 18-20 wk of gestation. Spectrophotometric scanning of amniotic fluid wavelengths demonstrates a positive optical density deviation of absorption for bilirubin from normal at 450 nm. Amniocentesis and cordocentesis are invasive procedures with risks to both the fetus and mother, including fetal death, bleeding, or bradycardia, worsening of alloimmunization, premature rupture of membranes, preterm labor, and chorioamnionitis. *Noninvasive measurements to detect fetal anemia are desirable*. In fetuses without hydrops, moderate to severe anemia can be detected noninvasively by demonstration of an increase in the peak velocity of systolic blood flow in the middle cerebral artery by Doppler ultrasonography.

PUBS is the standard approach to assessment of the fetus if Doppler and real-time ultrasonography findings suggest that the fetus has erythroblastosis fetalis. PUBS is performed to determine fetal hemoglobin levels and to transfuse packed RBCs in those with serious fetal anemia (hematocrit 25-30%).

Postnatal Diagnosis

Immediately after the birth of any infant to an Rh-negative woman, blood from the umbilical cord or from the infant should be examined for ABO blood group, Rh type, hematocrit and hemoglobin, and reaction to the direct Coombs test. If the Coombs test result is positive, a baseline serum bilirubin level should be measured, and a commercially available RBC panel should be used to identify RBC antibodies present in the mother's serum, both tests being performed not only to establish the diagnosis but also to ensure selection of the most compatible blood for exchange transfusion should it be necessary. The direct Coombs test result is usually strongly positive in clinically affected infants and may remain so for a few days up to several months.

Treatment

The main goals of therapy are to (1) prevent intrauterine or extrauterine death from severe anemia and hypoxia, and (2) avoid neurotoxicity from hyperbilirubinemia.

Treatment of an Unborn Infant

Survival of severely affected fetuses has been improved by the use of fetal ultrasonography to identify the need for in utero transfusion. Intravascular (umbilical vein) transfusion of packed RBCs is the treatment of choice for fetal anemia, replacing intrauterine transfusion into the fetal peritoneal cavity. Hydrops or fetal anemia (hematocrit < 30%) is an indication for umbilical vein transfusion in infants with pulmonary immaturity (see Fig. 103-1). **Intravascular fetal transfusion** is facilitated by maternal and hence fetal sedation with diazepam and by fetal paralysis with pancuronium. Packed RBCs are given by slow-push infusion after being cross-matched against the mother's serum. The cells should be obtained from a CMV-negative donor and irradiated to kill lymphocytes to avoid GVH disease. *Of note, leukoreduction alone (without irradiation) does not prevent GVH disease*. Transfusions should achieve a posttransfusion hematocrit of 45-55% and can be repeated every 3-5 wk. Indications for delivery include pulmonary maturity, fetal distress, complications of PUBS, and 35-37 wk of gestation. The survival rate for intrauterine transfusions is 89%; the complication rate is 3%. Complications include rupture of the membranes and preterm delivery, infection, fetal distress requiring emergency cesarean section, and perinatal death.

Treatment of a Liveborn Infant

The birth should be attended by a physician skilled in neonatal resuscitation. Fresh, low-titer, group O, leukoreduced, and irradiated Rh-negative blood cross-matched against maternal serum should be immediately available. If clinical signs of severe hemolytic anemia (pallor, hepatosplenomegaly, edema, petechiae, ascites) are evident at birth, immediate resuscitation and supportive therapy, temperature stabilization, and monitoring before proceeding with exchange transfusion may save some severely affected infants. Such therapy should include correction of acidosis with 1-2 mEq/kg of sodium bicarbonate; a small transfusion of compatible packed RBCs to correct anemia; volume expansion for hypotension, especially in those with hydrops; and provision of assisted ventilation for respiratory failure.

Exchange Transfusion

When an infant's clinical condition at birth does not require an immediate full or partial exchange transfusion, the decision to perform one should be based on a judgment that the infant has a high risk of rapid development of a dangerous degree of anemia or hyperbilirubinemia. Cord hemoglobin value of 10 g/dL or less and bilirubin concentration of 5 mg/dL or more suggest severe hemolysis but inconsistently predict the need for exchange transfusion. Some physicians consider previous kernicterus or severe erythroblastosis in a sibling, reticulocyte counts

>15%, and prematurity to be additional factors supporting a decision for early exchange transfusion (see Chapters 102.3 and 102.4). Intrauterine, intravascular transfusions have decreased the need for exchange transfusion.

The hemoglobin concentration, hematocrit, and serum bilirubin level should be measured at 4-6 hr intervals initially, with extension to longer intervals if and as the rate of change diminishes. The decision to perform an exchange transfusion is based on the likelihood that the trend of bilirubin levels plotted against hours of age indicates that serum bilirubin will reach the levels indicated in Figure 102-12 and Table 102-7, both in Chapter 102. Term infants with bilirubin levels ≥20 mg/dL have an increased risk of kernicterus. Ordinary transfusions of compatible Rh-negative, leukoreduced, and irradiated RBCs may be necessary to correct anemia at any stage of the disease up to 6-8 wk of age, when the infant's own blood-forming mechanism may be expected to take over. Weekly determinations of hemoglobin or hematocrit values should be performed until a spontaneous rise has been demonstrated.

Careful monitoring of the serum bilirubin level is essential until a falling trend has been demonstrated in the absence of phototherapy (see Chapter 102.3). Even then, an occasional infant, particularly if premature, may experience an unpredicted significant rise in serum bilirubin as late as the 7th day of life. Attempts to predict the attainment of dangerously high levels of serum bilirubin on the basis of observed levels exceeding 6 mg/dL in the 1st 6 hr or 10 mg/dL in the 2nd 6 hr of life or on rates of rise exceeding 0.5-1.0 mg/dL/hr can be unreliable.

Blood for exchange transfusion should be as fresh as possible. Heparin or citrate-phosphate-dextrose-adenine solution may be used as an anticoagulant. If the blood is obtained before delivery, it should be taken from a type O, Rh-negative donor with a low titer of anti-A and anti-B antibodies and should be determined compatible with the mother's serum by the indirect Coombs test. After delivery, blood should be obtained from an Rh-negative donor whose cells are compatible with both the infant's and the mother's sera; when possible, type O donor cells are generally used, but cells of the infant's ABO blood type may be used when the mother has the same type. A complete cross match, including an indirect Coombs test, should be performed before the second and subsequent transfusions. Blood should be gradually warmed and maintained at a temperature between 35 and 37°C (95 and 98.6°F) throughout the exchange transfusion. It should be kept well mixed by gentle squeezing or agitation of the bag to avoid sedimentation; otherwise, the use of supernatant serum with a low RBC count at the end of the exchange will leave the infant anemic. Whole blood or packed leukoreduced and irradiated RBCs reconstituted with fresh-frozen plasma to an hematocrit of 40% should be used. The infant's stomach should be emptied before transfusion to prevent aspiration, and body temperature should be maintained and vital signs monitored. A competent assistant should be present to help monitor, tally the volume of blood exchanged, and perform emergency procedures.

With strict aseptic technique, the umbilical vein is cannulated with a polyvinyl catheter to a distance no greater than 7 cm in a full-term infant. When free flow of blood is obtained, the catheter is usually in a large hepatic vein or the inferior vena cava. Alternatively, the exchange may be performed through peripheral arterial (drawn out) and venous (infused in) lines. The exchange should be carried out over 45-60 min, with aspiration of 20 mL of infant blood alternating with infusion of 20 mL of donor blood. Smaller aliquots (5-10 mL) may be indicated for sick and premature infants. The goal should be an isovolumetric exchange of approximately two blood volumes of the infant (2 × 85 mL/kg).

Infants with acidosis and hypoxia from respiratory distress, sepsis, or shock may be further compromised by the significant acute acid load contained in citrated blood, which usually has a pH between 7 and 7.2. The subsequent metabolism of citrate may result in metabolic alkalosis later if citrated blood is used. Fresh heparinized blood avoids this problem. During the exchange, blood pH and Pao_2 should be serially monitored because infants often become acidotic and hypoxic during exchange transfusions. Symptomatic hypoglycemia may occur before or during an exchange transfusion in moderately to severely affected infants; it may also occur 1-3 hr after exchange. Acute complications, noted in 5-10% of infants, include transient bradycardia with or without calcium infusion, cyanosis, transient vasospasm, thrombosis, apnea with bradycardia requiring resuscitation, and death. Infectious risks include CMV, HIV, and hepatitis. Necrotizing enterocolitis is a rare complication of exchange transfusion.

The risk of death from an exchange transfusion performed by an experienced physician is 0.3/100 procedures. With the decreasing use of this procedure because of the use of phototherapy and prevention of sensitization, the general level of physician competence is diminishing. Thus, it is best if this procedure is performed in experienced neonatal referral centers.

After exchange transfusion, the bilirubin level must be determined at frequent intervals (every 4-8 hr) because bilirubin may rebound 40-50% within hours. Repeated exchange transfusions should be carried out to keep the indirect fraction from exceeding the levels indicated in Table 102-7 in Chapter 102 for preterm infants and 20 mg/dL for term infants. Symptoms suggestive of kernicterus are mandatory indications for exchange transfusion at any time.

Intravenous Immunoglobulin

Early administration of intravenous immunoglobulin (IVIG) may reduce hemolysis, peak serum bilirubin levels, and the need for exchange transfusions. IVIG administration reduces the need for exchange transfusion, the duration of phototherapy, and the length of hospitalization. A dose of 0.5-1 g/kg may be used.

Late Complications

Infants who have hemolytic disease or who have had an exchange or an intrauterine transfusion must be observed carefully for the development of anemia and cholestasis. **Late anemia** may be hemolytic or hyporegenerative. Treatment with supplemental iron, blood transfusion, or erythropoietin may be indicated. A mild GVH reaction may manifest as diarrhea, rash, hepatitis, or eosinophilia.

Inspissated bile syndrome refers to the rare occurrence of persistent icterus in association with significant elevations in direct and indirect bilirubin levels in infants with hemolytic disease. The cause is unclear, but the jaundice clears spontaneously within a few weeks or months.

Portal vein thrombosis and portal hypertension may occur in children who have been subjected to exchange transfusion as newborn infants. It is probably associated with prolonged, traumatic, or septic umbilical vein catheterization.

Prevention of Rh Sensitization

The risk of initial sensitization of Rh-negative mothers has been reduced to less than 1% by the intramuscular injection of 300 μg of human anti-D globulin (1 mL of RhoGAM) within 72 hr of delivery of an Rh-positive infant, ectopic pregnancy, abdominal trauma in pregnancy, amniocentesis, chorionic villus biopsy, or abortion. This quantity is sufficient to eliminate ≈ 10 mL of potentially antigenic fetal cells from the maternal circulation. Large fetal-to-maternal transfers of blood may require proportionately more human anti-D globulin. RhoGAM administration of human anti-D globulin at 28-32 wk and again at birth (40 wk) is more effective than a single dose. The use of this technique, combined with improved methods of detecting maternal sensitization and measuring the extent of fetal-to-maternal transfusion, plus the use of fewer obstetric procedures that increase the risk of such fetal-to-maternal bleeding (version, manual separation of the placenta), should further reduce the incidence of erythroblastosis fetalis.

HEMOLYTIC DISEASE OF THE NEWBORN CAUSED BY BLOOD GROUP A AND B INCOMPATIBILITY

ABO incompatibility is the most common cause of hemolytic disease of the newborn. Approximately 15% of live births are at risk, but

Table 103-4 Hemolytic Disease of the Newborn

	Rh	ABO	KELL
BLOOD GROUPS			
Mother	Rh-negative	O (occasionally B)	K1-negative
Infant	Positive (D, sometimes C)	A (sometimes B)	K1-positive
CLINICAL FEATURES OF HEMOLYTIC DISEASE IN THE NEWBORN			
Occurrence in first-born	5%	40-50%	Rare
Severity in subsequent pregnancies:	Predictable	Difficult to predict	Somewhat predictable
Stillbirth/hydrops	Frequent	Rare	10%
Severe anemia	Frequent	Rare	Frequent
Jaundice	Prominent, severe	Mild-moderate	Mild
LABORATORY TESTS:			
Direct Coombs test result (infant)	Positive	Positive or negative	Positive or negative
Reticulocyte count	High	High	May not be high
Maternal antibodies	Usually detectable	May not be detectable	Usually detectable
	Maternal antibody titers can help predict the severity of fetal disease	Titers may not correlate with fetal disease	Titers may not correlate with fetal disease; fetus affected at titers lower than for Rh-mediated hemolysis

manifestations of disease develop in only 0.3-2.2%. Major blood group incompatibility between the mother and fetus generally results in milder disease than Rh incompatibility does. Maternal antibody may be formed against B cells if the mother is type A or against A cells if the mother is type B. Usually, the mother is type O and the infant is type A or B. Although ABO incompatibility occurs in 20-25% of pregnancies, hemolytic disease develops in only 10% of the offspring in such pregnancies, and the infants are generally type A_1, which is more antigenic than A_2. Low antigenicity of the ABO factors in the fetus and newborn infant may account for the low incidence of severe ABO hemolytic disease relative to the incidence of incompatibility between the blood groups of the mother and child. Although antibodies against A and B factors occur without previous immunization ("natural" antibodies), they are usually IgM antibodies that do not cross the placenta. However, IgG antibodies to A antigen may be present and these do cross the placenta, so A-O isoimmune hemolytic disease may be found in first-born infants. Mothers who have become immunized against A or B factors from a previous incompatible pregnancy also exhibit IgG antibody. These "immune" antibodies are the primary mediators in ABO isoimmune disease.

Clinical Manifestations

Most cases are mild, with jaundice being the only clinical manifestation. The infant is not generally affected at birth; pallor is not present, and hydrops fetalis is extremely rare. The liver and spleen are not greatly enlarged, if at all. Jaundice usually appears during the 1st 24 hr. Rarely, it may become severe, and symptoms and signs of kernicterus develop rapidly.

Diagnosis

A presumptive diagnosis is based on the presence of ABO incompatibility, a weakly to moderately positive direct Coombs test result, and spherocytes in the blood smear, which may at times suggest the presence of hereditary spherocytosis. Hyperbilirubinemia is often the only other laboratory abnormality. The hemoglobin level is usually normal but may be as low as 10-12 g/dL. Reticulocytes may be increased to 10-15%, with extensive polychromasia and increased numbers of nucleated RBCs. In 10-20% of affected infants, the unconjugated serum bilirubin level may reach 20 mg/dL or more unless phototherapy is administered.

Treatment

Phototherapy may be effective in lowering serum bilirubin levels (see Chapter 102.4). In severe cases, IVIG administration can reduce the rate of hemolysis and the need for exchange transfusion. Exchange transfusions with type O blood of the same Rh type as the infant may be needed in some cases to correct dangerous degrees of anemia or hyperbilirubinemia. Indications for this procedure are similar to those previously described for hemolytic disease caused by Rh incompatibility. Some infants with ABO hemolytic disease may require transfusion of packed RBCs at several weeks of age because of slowly progressive anemia. Postdischarge monitoring of hemoglobin or hematocrit is essential in newborns with ABO hemolytic disease.

OTHER FORMS OF HEMOLYTIC DISEASE

Blood group incompatibilities other than Rh or ABO account for <5% of hemolytic disease of the newborn. The direct Coombs test result is invariably positive, and exchange transfusion may be indicated for hyperbilirubinemia and anemia. Hemolytic disease, anemia, and hydrops fetalis as a result of anti-Kell antibodies are not predictable from the previous obstetric history, amniotic fluid bilirubin determinants, or the maternal antibody titer. Erythroid suppression may contribute to the anemia; PUBS is beneficial in actually measuring the fetal hematocrit. Kell-alloimmunized infants often have inappropriately low numbers of circulating reticulocytes in comparison with other forms of hemolytic disease, which can cause difficulties in the laboratory confirmation of the hemolytic etiology of hyperbilirubinemia. The clinical characteristics of hemolytic disease caused by Rh, ABO, and Kell antigen systems are summarized in Table 103-4.

Bibliography is available at Expert Consult.

103.3 Plethora in the Newborn Infant (Polycythemia)

Akhil Maheshwari and Waldemar A. Carlo

See also Chapter 467.

Plethora, a ruddy, deep red-purple appearance associated with a high hematocrit, is often due to polycythemia, defined as a central hematocrit of 65% or higher. Peripheral (heelstick) hematocrit values are higher than central values, whereas Coulter counter results are lower than hematocrit values determined by microcentrifugation. The incidence of neonatal polycythemia is increased at high altitudes (5% in Denver vs. 1.6% in Texas); in postmature (3%) versus term (1-2%) infants; in small for gestational age (8%) versus large for gestational age (3%) versus average for gestational age (1-2%) infants; during the 1st day of life (peak, 2-3 hr); in the recipient infant of a twin–twin transfusion; after delayed clamping of the umbilical cord; in infants of diabetic mothers; in trisomy 13, 18, or 21; in adrenogenital syndrome;

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in neonatal Graves disease; in hypothyroidism; in infants of hypertensive mothers or those on propranolol; and in Beckwith-Wiedemann syndrome. Infants of diabetic or hypertensive mothers and those with growth restriction may have been exposed to chronic fetal hypoxia, which stimulates erythropoietin production and increases RBC production.

Clinical manifestations include irritability, lethargy, tachypnea, respiratory distress, cyanosis, feeding disturbances, hyperbilirubinemia, hypoglycemia, and thrombocytopenia. Severe complications include seizures, stroke, pulmonary hypertension, necrotizing enterocolitis, renal vein thrombosis, and renal failure. *Many affected infants are asymptomatic*. Hyperviscosity is present in many infants with central hematocrit values of 65% or higher and accounts for the symptoms of polycythemia. Hyperviscosity determined at constant shear rates (11.5 sec^{-1}) is present when whole blood viscosity is >18 cycles/sec. Hyperviscosity is accentuated because neonatal RBCs have decreased deformability and filterability, which predispose to stasis in the microcirculation.

The treatment of polycythemia is controversial. Asymptomatic infants whose central hematocrits are between 60% and 70% can be monitored closely and aggressively hydrated with adequate enteral intake or administration of intravenous fluids. **Treatment** of symptomatic polycythemic newborns is partial exchange transfusion (with normal saline). A partial exchange transfusion should be considered if the hematocrit is ≥70-75% or even lower if signs of hyperviscosity are present. Partial exchange transfusion lowers the Hematocrit and viscosity and improves acute symptoms, but may not affect long-term outcome in these infants. The volume to be exchanged is calculated from the following formula:

$$\text{Volume of exchange (mL)} = \text{Blood volume} \times (\text{Observed} - \text{Desired hematocrit}) / \text{Observed hematocrit}$$

Infants treated with partial exchange may be at increased risk of necrotizing enterocolitis and should be carefully monitored. The long-term prognosis of polycythemic infants is unclear. Reported adverse outcomes include speech deficits, abnormal fine motor control, reduced IQ, school problems, and other neurologic abnormalities. The underlying etiology (chronic intrauterine hypoxia) and hyperviscosity is thought to contribute to adverse outcomes. It is unclear whether partial exchange transfusion improves the long-term outcome. Most asymptomatic infants develop normally.

Bibliography is available at Expert Consult.

103.4 Hemorrhage in the Newborn Infant

Akhil Maheshwari and Waldemar A. Carlo

HEMORRHAGIC DISEASE OF THE NEWBORN

A moderate decrease in factors II, VII, IX, and X normally occurs in all newborn infants by 48-72 hr after birth, with a gradual return to birth levels by 7-10 days of age. This transient deficiency of vitamin K–dependent factors is probably caused by lack of free vitamin K from the mother and absence of the bacterial intestinal flora normally responsible for the synthesis of vitamin K. Rarely in term infants, and more frequently in premature infants, accentuation and prolongation of this deficiency between the 2nd and 7th days of life result in spontaneous and prolonged bleeding. Breast milk is a poor source of vitamin K, but hemorrhagic complications are more frequent in breastfed than in formula-fed infants. This classic form of hemorrhagic disease of the newborn, which is responsive to and prevented by vitamin K therapy, must be distinguished from disseminated intravascular coagulopathy and from the more infrequent congenital deficiencies of one or more of the other factors that are unresponsive to vitamin K (see Chapter 476). Early-onset life-threatening vitamin K deficiency–induced bleeding (onset from birth to 24 hr) also occurs if the mother has been treated with drugs (phenobarbital, phenytoin) that interfere with vitamin K function. Late onset (>2 wk) is often associated with vitamin K malabsorption, as noted in neonatal hepatitis or biliary atresia (Table 103-5).

Hemorrhagic disease of the newborn resulting from severe transient deficiencies in vitamin K–dependent factors is characterized by bleeding that tends to be gastrointestinal, nasal, subgaleal, intracranial, or post-circumcision. Prodromal or warning signs (mild bleeding) may occur before serious intracranial hemorrhage. The prothrombin time, blood coagulation time, and partial thromboplastin time are prolonged, and levels of prothrombin (II) and factors VII, IX, and X are decreased. Vitamin K facilitates posttranscriptional carboxylation of factors II, VII, IX, and X. In the absence of carboxylation, such factors form PIVKA (proteins induced in vitamin K absence), which is a sensitive marker for vitamin K status. Bleeding time, fibrinogen, factors V and VIII, platelets, capillary fragility, and clot retraction are normal for maturity.

Intramuscular administration of 1 mg of vitamin K at the time of birth **prevents** the decrease in vitamin K–dependent factors in full-term infants, but it is not uniformly effective in the prophylaxis of hemorrhagic disease of the newborn, particularly in breastfed and in

Table 103-5 Hemorrhagic Disease of the Newborn

	EARLY-ONSET DISEASE	CLASSIC DISEASE	LATE-ONSET DISEASE
Age	0-24 hr	2-7 days	1-6 mo
Site of hemorrhage	Cephalohematoma Subgaleal Intracranial Gastrointestinal Umbilicus Intraabdominal	Gastrointestinal Ear-nose-throat-mucosal Intracranial Circumcision Cutaneous Gastrointestinal Injection sites	Intracranial Gastrointestinal Cutaneous Ear-nose-throat-mucosal Injection sites Thoracic
Etiology/risks	Maternal drugs (phenobarbital, phenytoin, warfarin, rifampin, isoniazid) that interfere with vitamin K Inherited coagulopathy	Vitamin K deficiency Breastfeeding	Cholestasis—malabsorption of vitamin K (biliary atresia, cystic fibrosis, hepatitis) Abetalipoprotein deficiency Idiopathic in Asian breastfed infants Warfarin ingestion
Prevention	Possibly, administrations of vitamin K to infant at birth or to mother (20 mg) before birth Avoid high-risk medications	Prevented by parenteral vitamin K at birth Oral vitamin K regimens require repeated dosing over time	Prevented by parenteral and high-dose oral vitamin K during periods of malabsorption or cholestasis
Incidence	Very rare	≈ 2% if infant not given vitamin K	Dependent on primary disease

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premature infants. The disease may be effectively **treated** with a slow intravenous infusion of 1-5 mg of vitamin K_1, with improvement in coagulation defects and cessation of bleeding noted within a few hours. Serious bleeding, particularly in premature infants or those with liver disease, may require a transfusion of **fresh-frozen plasma** or whole blood. The mortality rate is low in treated patients.

A particularly severe form of deficiency of vitamin K–dependent coagulation factors has been reported in infants born to mothers receiving anticonvulsive medications (phenobarbital and phenytoin) during pregnancy. The infants may have severe bleeding, with onset within the 1st 24 hr of life; the bleeding is usually corrected by vitamin K_1, although in some the response is poor or delayed. A prothrombin time should be measured in cord blood, and the infant given 1-2 mg of vitamin K intravenously. If the prothrombin time is greatly prolonged and fails to improve, 10 mL/kg of fresh-frozen plasma should be administered.

The routine use of intramuscular vitamin K for prophylaxis in the United States is safe and is not associated with an increased risk of childhood cancer or leukemia. Although oral vitamin K (birth, discharge, 3-4 wk: 1-2 mg) has been suggested as an alternative, oral vitamin K is less effective in preventing the late onset of bleeding due to vitamin K deficiency and thus cannot be recommended for routine therapy. The intramuscular route remains the method of choice.

Other forms of bleeding may be clinically indistinguishable from hemorrhagic disease of the newborn responsive to vitamin K, but they are neither prevented nor successfully treated with vitamin K. A clinical pattern identical to that of hemorrhagic disease of the newborn may also result from any of the congenital defects in blood coagulation (see Chapters 476 and 477). Hematomas, melena, and postcircumcision and umbilical cord bleeding may be present; only 5-35% of cases of factor VIII and IX deficiency become clinically apparent in the newborn period. Treatment of the rare congenital deficiencies of coagulation factors requires fresh-frozen plasma or specific factor replacement.

Disseminated intravascular coagulopathy in newborn infants results in consumption of coagulation factors and bleeding. Affected infants are often premature; the clinical course is frequently characterized by asphyxia, hypoxia, acidosis, shock, hemangiomas, or infection. Treatment is directed at correcting the primary clinical problem, such as infection, interrupting consumption of clotting factors, and replacing them (see Chapter 483).

Infants with central nervous system or other bleeding posing an immediate threat to life should receive fresh-frozen plasma, vitamin K, and blood if needed as soon as possible after a blood specimen has been obtained for coagulation studies, which should include a determination of the number of platelets.

The **swallowed blood syndrome,** in which blood or bloody stools are passed, usually on the 2nd or 3rd day of life, may be confused with hemorrhage from the gastrointestinal tract. The blood may be swallowed during delivery or from a fissure in the mother's nipple. Differentiation from gastrointestinal hemorrhage is based on the fact that the infant's blood contains mostly fetal hemoglobin, which is alkali-resistant, whereas swallowed blood from a maternal source contains adult hemoglobin, which is promptly changed to alkaline hematin after the addition of alkali. Apt devised the following test for this differentiation: (1) Rinse a blood-stained diaper or some grossly bloody (red) stool with a suitable amount of water to obtain a distinctly pink supernatant hemoglobin solution; (2) centrifuge the mixture and decant the supernatant solution; (3) add 1 part of 0.25 N (1%) sodium hydroxide to 5 parts of the supernatant fluid. Within 1-2 min, a color reaction takes place: A yellow-brown color indicates that the blood is maternal in origin; a persistent pink indicates that it is from the infant. A control test with known adult or infant blood, or both, is advisable.

Widespread subcutaneous ecchymoses in premature infants at or immediately after birth are apparently a result of fragile superficial blood vessels rather than a coagulation defect. Administering vitamin K_1 to the mother during labor has no effect on the incidence of ecchymoses. Occasionally, an infant is born with petechiae or a generalized bluish suffusion limited to the face, head, and neck, probably as a result of venous obstruction by a nuchal cord or sudden increases in intrathoracic pressure during delivery. It may take 2-3 wk for such suffusions to disappear.

NEONATAL THROMBOCYTOPENIC PURPURA

See Chapter 484.

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Chapter **104**

Genitourinary System

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See also Part XXIV.

Urinary tract anomalies (hydronephrosis, dysplasia, agenesis, cystic or solitary kidney) can often be identified by prenatal ultrasonography (see Table 96-1). After birth, the presence/extent of anomalies needs to be confirmed and followed by detailed evaluation and appropriate management. Multicystic and polycystic forms of kidney disease have high risk for mortality and renal morbidity. In contrast, the majority of mild dilatations have no clinical consequences but cause unnecessary anxiety in many cases.

One or both kidneys are often easily palpable in a newborn infant. When both are palpable and similar, infants usually do not have any particular diagnostic problems, but when only one kidney can be felt, a frequent impression is that it is larger than normal or is displaced by an intrinsic or extrinsic mass. Fetal lobulation may contribute to this impression. The problem usually resolves as the kidney becomes progressively less easily palpable during the early months of life. Because palpable enlargement or displacement of a kidney in a newborn may be due to hydronephrosis, neuroblastoma, mesoblastic nephroma, adrenal hemorrhage, or a cystic malformation, ultrasound examination is indicated.

RENAL VEIN THROMBOSIS

See Chapter 519.7.

Circumcision

Male circumcision is an elective procedure currently performed in many countries and in some religious and cultural groups. In the United States, the rate of male circumcision varies between 50% and 75% among various populations but has been declining recently. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologist have endorsed a policy statement in support of circumcision because of the health benefits.

The health benefits of circumcision include reduced acquisition and/or transmission of several sexually transmitted diseases (human immunodeficiency virus, human papillomavirus, herpes simplex virus type 2, and syphilis), possible prevention of urinary tract infections, and penile cancer. There is fair evidence that there are no significant differences in sexual function between circumcised and uncircumcised males. Even though the benefits of circumcision outweigh the rare but important complications (amputation of the penis or glans, infection), the health benefits are not large enough to recommend circumcision of all male infants. With appropriate counseling, parents can make a decision on what they think is the best interest of their baby in the context of their medical, ethical, religious, and cultural beliefs (see also Chapter 544).

Male circumcision entails the surgical removal of some of the foreskin (prepuce) of the penis. The surgery is performed under penile

nerve block anesthesia and under sterile conditions. The surgery includes dilation of the preputial orifice to visualize the glans, freeing the preputial epithelium from the epithelium of the glans, placement of the circumcision device (Gomco clamp, Plastibell, or Mogen clamp) to enhance hemostasis, and removal of foreskin.

Parents should be instructed on the care of the penis. The circumcised penis should be washed gently. A gauze with petroleum jelly can be used to cover the glans until the glans heals. The uncircumcised penis should be washed with soap and water on the outside. At birth, the foreskin is attached to the glans and cannot be retracted. The foreskin will separate naturally over several months. After separation, the foreskin is pulled back and the penis and inside of the foreskin can be washed with soap and water. After cleaning, the foreskin should be pulled back over the glans.

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Chapter 105
The Umbilicus

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UMBILICAL CORD

The umbilical cord contains the 2 umbilical arteries, the umbilical vein, the rudimentary allantois, the remnant of the omphalomesenteric duct, and a gelatinous substance called Wharton jelly. The sheath of the umbilical cord is derived from the amnion. The muscular umbilical arteries contract readily, but the vein does not. The vein retains a fairly large lumen after birth. The normal cord at term is 55 cm long on average. Abnormally short cords are associated with antepartum abnormalities, including fetal hypotonia, oligohydramnios, and uterine constraint, and with increased risk for complications of labor and delivery for both mother and infant. Long cords (>70 cm) increase risk for true knots, wrapping around fetal parts (neck, arm), and/or prolapse. Straight untwisted cords are associated with fetal distress, anomalies, and intrauterine fetal demise.

When the cord sloughs after birth, portions of these structures remain in the base. The blood vessels are functionally closed but anatomically patent for 10-20 days. The arteries become the lateral umbilical ligaments; the vein, the ligamentum teres; and the ductus venosus, the ligamentum venosum. During this interval, the umbilical vessels are potential portals of entry for infection. The umbilical cord usually sloughs within 2 wk. Delayed separation of the cord, after more than 1 mo, has been associated with neutrophil chemotactic defects and overwhelming bacterial infection (see Chapter 130).

A single umbilical artery is present in approximately 5-10/1,000 births; the frequency is approximately 35-70/1,000 in twin births. Approximately 30% of infants with a single umbilical artery have congenital abnormalities, usually more than one; many such infants are stillborn or die shortly after birth. Trisomy 18 is one of the more frequent abnormalities. Because abnormalities may not be apparent on physical examination, it is important that at every delivery, the cut cord and the maternal and fetal surfaces of the placenta be inspected. The number of arteries present is an aid to the early suspicion and identification of abnormalities in the infants. For infants with a single umbilical artery but no other anomalies, the need for renal ultrasonography is controversial.

Patency of the omphalomesenteric (vitelline) duct may be responsible for intestinal obstruction, intestinal fistula with fecal or bilious draining, prolapse of the bowel, a polyp (cyst), or a Meckel diverticulum (see Chapter 331.2). **Therapy** is surgical excision of the anomaly.

A persistent urachus (urachal cyst, sinus, patent urachus, or diverticulum) is a result of failure of closure of the allantoic duct and is associated with bladder outlet obstruction. Patency should be suspected if a clear, light yellow, urine-like fluid is being discharged from the umbilicus. Symptoms include drainage, a mass or cyst, abdominal pain, local erythema, and infection. Urachal anomalies should be investigated by ultrasonography and a cystogram. **Therapy** is surgical excision of the anomaly and correction of any bladder outlet obstruction if present.

CONGENITAL OMPHALOCELE

An omphalocele is a herniation or protrusion of the abdominal contents into the base of the umbilical cord (Figs. 105-1 and 105-2). In contrast to the more common umbilical hernia, the sac is covered with peritoneum without overlying skin. The size of the sac that lies outside the abdominal cavity depends on its contents. Herniation of intestines into the cord occurs in approximately 1/5,000 births, and herniation of liver and intestines in 1/10,000 births. The abdominal cavity is

Figure 105-1 Small intact sac at the base of the umbilical cord. *(From Clark DA, Thompson JE, Barnemeyer BM:* Atlas of neonatology, *ed 7, Philadelphia, 2000, WB Saunders.)*

Figure 105-2 Intact sac with healthy organs visible. *(From Clark DA, Thompson JE, Barnemeyer BM:* Atlas of neonatology, *ed 7, Philadelphia, 2000, WB Saunders.)*

proportionately small because the impetus to grow and develop is deficient. Immediate surgical repair, before infection has taken place and before the tissues have been damaged by drying (saline-soaked sterile dressings should be applied immediately) or by rupture of the sac, is essential for survival. Mersilene mesh or similar synthetic material may be used to cover the viscera if the sac has ruptured or if excessive mobilization of the skin would be necessary to cover the mass and its intact sac. The majority (≈75%) of infants with omphalocele have associated congenital anomalies/syndromes, including Beckwith-Wiedemann syndrome (omphalocele, macrosomia, hypoglycemia), and other chromosomal (29%, including trisomies 13 and 18) and nonchromosomal (45%) multiple and isolated congenital anomalies (musculoskeletal, 24%; urogenital, 20%; cardiovascular, 15%; and central nervous system, 9%). The survival rate is approximately 80% overall, but in infants with isolated omphalocele, the survival rate is >90%.

TUMORS

Tumors of the umbilicus are rare and include angioma, enteroteratoma, dermoid cyst, myxosarcoma, and cysts of urachal or omphalomesenteric duct remnants.

HEMORRHAGE

Hemorrhage from the umbilical cord may be the result of trauma, inadequate ligation of the cord, or failure of normal thrombus formation. It may also indicate hemorrhagic disease of the newborn or other coagulopathies (especially factor XIII deficiency), septicemia, or local infection. The infant should be observed frequently during the first few days of life so that if hemorrhage does occur, it will be detected promptly.

GRANULOMA

The umbilical cord usually dries and separates within 6-8 days after birth. The raw surface becomes covered by a thin layer of skin; scar tissue forms, and the wound is usually healed within 12-15 days. The presence of saprophytic organisms delays separation of the cord and increases the possibility of invasion by pathogenic organisms. Mild infection or incomplete epithelialization may result in a moist granulating area at the base of the cord with a slight mucoid or mucopurulent discharge. Good results are usually obtained by cleansing with alcohol several times daily.

Persistence of granulation tissue at the base of the umbilicus is common. The tissue is soft, 3-10 mm in size, vascular and granular, and dull red or pink, and it may have a seropurulent secretion. **Treatment** is cauterization with silver nitrate, repeated at intervals of several days until the base is dry.

Umbilical granuloma must be differentiated from **umbilical polyp,** a rare anomaly resulting from persistence of all or part of the omphalomesenteric duct or the urachus. The tissue of the polyp is firm and resistant, is bright red, and has a mucoid secretion. If the polyp is communicating with the ileum or bladder, small amounts of fecal material or urine may be discharged intermittently. Histologically, the polyp consists of intestinal or urinary tract mucosa. **Treatment** is surgical excision of the entire omphalomesenteric or urachal remnant.

INFECTIONS

Although aseptic delivery and routine cord care (application of triple dye and other antiseptics to the umbilical stump and surrounding skin) decrease bacterial colonization and umbilical infection, the necrotic tissue of the umbilical cord is an excellent medium for bacterial growth. In a meta-analysis, triple dye was found to be more effective than alcohol in reducing omphalitis. Soap and water or dry care is not as effective in the prevention of omphalitis. Topical application of 4% chlorhexidine to the umbilical cord reduces neonatal mortality and omphalitis in community and primary care settings in developing countries. **Omphalitis** may remain localized or may spread to the abdominal wall, the peritoneum, the umbilical or portal vessels, or the liver. Infants with abdominal wall cellulitis or those with **necrotizing fasciitis** have a high incidence of associated bacteremia. Portal vein phlebitis may develop and result in the later onset of **extrahepatic portal hypertension.** The general manifestations may be minimal (periumbilical erythema), even when septicemia or hepatitis has resulted. Treatment includes prompt antibiotic therapy (with agents effective against *Staphylococcus aureus* and *Escherichia coli*) and, if abscess formation has occurred, surgical incision and drainage. Necrotizing fasciitis is often polymicrobial and has a high mortality.

UMBILICAL HERNIA

Often associated with diastasis recti, an umbilical hernia is due to imperfect closure or weakness of the umbilical ring. Predisposing factors include black race and low birthweight. The hernia appears as a soft swelling covered by skin that protrudes during crying, coughing, or straining and can be reduced easily through the fibrous ring at the umbilicus. The hernia consists of omentum or portions of the small intestine. The size of the defect varies from <1 cm in diameter to as much as 5 cm, but large defects are rare. Most umbilical hernias that appear before the age of 6 mo disappear spontaneously by 1 yr of age. Even large hernias (5-6 cm in all dimensions) have been known to disappear spontaneously by 5-6 yr of age. Strangulation is extremely rare. It is generally agreed that "strapping" is ineffective. Surgery is not advised unless the hernia persists to the age of 4-5 yr, causes symptoms, becomes strangulated, or becomes progressively larger after the age of 1-2 yr. Defects exceeding 2 cm are less likely to close spontaneously.

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Chapter 106

Metabolic Disturbances

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HYPERTHERMIA IN THE NEWBORN

Elevations in temperature (38-39°C [100-103°F]) are occasionally noted on the 2nd or 3rd day after birth in infants whose clinical course has been otherwise satisfactory. This disturbance is especially likely to occur in breastfed infants whose intake of fluid has been particularly low or in infants who are overdressed or are exposed to high environmental temperatures, either in an incubator, in a bassinette near a radiator, or in the sun.

The infant may lose weight. A consistent relationship may not be seen between the fever and the extent of weight loss or inadequacy of fluid intake. Urinary output and the frequency of voiding diminish. The fontanel may be depressed. The infant takes fluids avidly, and the apparent vigor of the infant is not consistent with the usual appearance of "being sick" from an infection. The rise in temperature may be associated with increases in serum levels of protein and sodium and in hematocrit. The possibility of local or systemic infection should be evaluated. Lowering the environmental temperature leads to prompt reduction of the fever and alleviation of symptoms. Oral hydration should be accomplished with additional breast milk or formula feeding and not with water, because of the risk of hyponatremia.

A more severe form of neonatal hyperthermia occurs in both newborn and older infants when they are warmly dressed. The diminished sweating capacity of newborn infants is a contributing factor. Warmly dressed infants left near stoves or radiators, traveling in well-heated automobiles, or left with bright sunlight shining directly on them through the windows of a closed room or automobile are likely to be victims. Body temperature may become as high as 41-44°C (106-111°F). The skin is hot and dry, and initially the infant usually appears

flushed and apathetic. The extremities are warm. Tachypnea and irritability may be noted. This stage may be followed by stupor, grayish pallor, coma, and convulsions. Hypernatremia may contribute to the convulsions. Mortality and morbidity (brain damage) rates are high. Hyperthermia has been associated with sudden infant death, and **hemorrhagic shock and encephalopathy syndrome** (see Chapter 70). The condition is prevented by dressing infants in clothing suitable for the temperature of the immediate environment. In newborn infants, exposure of the body to usual room temperature or immersion in tepid water usually suffices to bring the temperature back to normal levels. Older infants may require cooling for a longer time by repeated immersion. Attention to possible fluid and electrolyte disturbance is essential.

Hyperthermia a few days after birth can result from infection, particularly herpes sepsis. Infants with infection appear ill with cold extremities, in contrast to the warm extremities of those in whom hyperthermia is from environmental causes.

NEONATAL COLD INJURY

Neonatal cold injury usually occurs in abandoned infants, infants in inadequately heated homes during cold spells when the outside temperature is low, and in preterm infants (see Chapter 76). The initial features are apathy, refusal of food, oliguria, and coldness to touch. The body temperature is usually between 29.5 and 35°C (85 and 95°F), and immobility, edema, and redness of the extremities, especially the hands and feet, and of the face are observed. Bradycardia and apnea may also occur. The facial erythema frequently gives a false impression of health and delays recognition that the infant is ill. Local hardening over areas of edema may lead to confusion with scleredema. Hypoglycemia and acidosis are common. Hemorrhagic manifestations are frequent; massive pulmonary hemorrhage is a common finding at autopsy. Hypothermia in preterm infants can be prevented with special plastic wraps that reduce evaporation and heat loss. Because of their high ratio of surface area to body mass, preterm infants are very vulnerable to evaporation heat loss. Infants at <28-30 wk of gestation should be placed inside a clear polyethylene bag without prior drying at birth. Neonatal cold injury occurs in even late preterm infants in low-resource settings and can be prevented with skin-to-skin (kangaroo mother) care and polyethylene plastic wraps. **Treatment** consists of warming and paying scrupulous attention to recognition and correction of hypotension and metabolic imbalances, particularly hypoglycemia. Prevention consists of providing adequate environmental heat. The mortality rate is approximately 10%; approximately 10% of survivors have evidence of brain damage.

EDEMA

Generalized edema occurs in association with **hydrops fetalis** (see Chapter 103.2) and in the offspring of diabetic mothers. In preterm infants, edema is often a consequence of a decreased ability to excrete water or sodium, although some have considerable edema without identifiable cause. Infants with respiratory distress syndrome may become edematous without heart failure. Edema of the face and scalp may be caused by pressure from the umbilical cord around the neck, and transient localized swelling of the hands or feet may similarly be caused by intrauterine pressure. Edema may be associated with heart failure. A lag in renal excretion of electrolytes and water may result in edema after a sudden large increase in intake of electrolytes, particularly with feeding of concentrated cow's milk formulas. Rarely, idiopathic hypoproteinemia with edema lasting weeks or months is observed in term infants. The cause is unclear, and the disturbance is benign. Persistent edema of 1 or more extremities may represent congenital lymphedema (Milroy disease) or, in females, Turner syndrome. Generalized edema with hypoproteinemia may be seen in the neonatal period with congenital nephrosis and rarely with Hurler syndrome or after feeding hypoallergenic formulas to infants with cystic fibrosis of the pancreas. Chapter 647 describes sclerema.

HYPOCALCEMIA (TETANY)

See also Chapter 51.

Metabolic Bone Disease

Metabolic bone disease is a common complication in preterm infants. The smallest, sickest infants are at greatest risk. Progressive osteopenia with demineralized bones and, occasionally, pathologic fractures may develop. The major cause is inadequate intake of calcium and phosphorus to meet the requirements for growth. Poor intake of vitamin D is an additional risk factor. Contributing factors include prolonged parenteral nutrition, vitamin D and calcium malabsorption, intake of unsupplemented human milk, immobilization, and urinary calcium losses from long-term diuretic use. The serum alkaline phosphatase level is used to monitor metabolic bone disease and can be >1,000 units/L in severe cases. Fortified human milk and formulas designed for preterm infants provide higher amounts of calcium, phosphorus, and vitamin D; promote bone mineralization; and reduce metabolic bone disease. Treatment of fractures requires immobilization and administration of calcium, phosphorus, and, if needed, vitamin D (not more than 1,000 IU/day unless severe cholestasis or vitamin D resistance is present). See also Chapters 51 and 570.

Hypomagnesemia

Rarely, hypomagnesemia of unknown cause may occur in newborn infants, usually in association with hypocalcemia. It may also be associated with insufficient stores of skeletal magnesium secondary to deficient placental transfer, decreased intestinal absorption, neonatal hypoparathyroidism, hyperphosphatemia, renal loss (primary or secondary to drugs, e.g., amphotericin B), a defect in magnesium and calcium homeostasis, or iatrogenic deficiency caused by loss incurred during exchange transfusion or insufficient replacement during total intravenous alimentation. Infants of diabetic mothers may have lower than normal serum magnesium levels. The clinical manifestations of hypomagnesemia are indistinguishable from those of hypocalcemia and tetany and may, in fact, contribute to the accompanying hypocalcemia.

Hypomagnesemia occurs when serum magnesium levels fall below 1.5 mg/dL (0.62 mmol/L), although clinical signs do not usually develop until serum magnesium levels fall below 1.2 mg/dL. During exchange transfusion with citrated blood, which is low in magnesium because of binding by citrate, serum magnesium decreases about 0.5 mg/dL (0.2 mmol/L); approximately 10 days are required for return to normal. In noniatrogenic hypomagnesemia, the serum magnesium level may be <0.5 mg/dL. Serum calcium in either instance is usually at levels noted in hypocalcemic tetany, but the serum phosphorus value is normal or high. Because the hypocalcemia accompanying hypomagnesemia is inadequately corrected by administration of calcium alone, hypomagnesemia should also be suspected in any patient with tetany not responding to calcium therapy.

Immediate **treatment** consists of intramuscular injection of magnesium sulfate. For newborn infants, 25-50 mg/kg/dose every 8 hr for 3-4 doses usually suffices. The accompanying hypocalcemia usually corrects itself as the hypomagnesemia resolves. The same daily dose can be given for oral maintenance therapy. Four to 5 times higher doses may be required in malabsorptive states. In most cases, the metabolic defect is transient, and treatment can be discontinued after 1-2 wk. A few patients appear to have a permanent form of the disease that requires continuous oral supplementation with magnesium to prevent recurrence of hypomagnesemia. No residual damage to the central nervous system is evident after prompt treatment.

HYPERMAGNESEMIA

Hypermagnesemia may occur in newborn infants of mothers treated with magnesium sulfate during labor. At high serum levels, the central nervous system is depressed and infants have respiratory depression that may require mechanical ventilation. Lower levels may result in hypoventilation, lethargy, flaccidity, hyporeflexia, and poor sucking. Hypermagnesemia may be associated with failure to pass meconium. The upper limit of normal magnesium is 2.8 mg/dL (1.15 mmol/L), but serious symptoms rarely occur at levels <5 mg/dL (2.1 mmol/L). In most cases, no specific therapy (beyond supportive care and maintenance of respiratory support) is required. Intravenous calcium and

diuresis will reduce the magnesium levels. In rare cases, exchange transfusion has been used for rapid removal of magnesium ion from the blood.

SUBSTANCE ABUSE AND NEONATAL ABSTINENCE (WITHDRAWAL)

Substance abuse during pregnancy can be a serious problem for both the mother and her newborn. The mother may suffer adverse consequences of her addiction, including episodes of drug withdrawal during pregnancy and illnesses related to high-risk behavior. Effects on the fetus and newborn include chronic or intermittent drug exposure, poor maternal nutrition, acute withdrawal shortly after birth, and long-term effects on physical growth and neurodevelopment. Because infants with in utero drug exposure often have social and environmental risk factors and may have been exposed to multiple substances, it may be difficult to evaluate the effects of specific in utero drug exposure on long-term neurodevelopmental outcome.

Pregnancies in women who use illegal drugs or alcohol are high risk. Prenatal care is usually inadequate, and these women have a higher incidence of sexually transmitted infections, including syphilis, HIV, and hepatitis. In addition, the risk of preterm labor, intrauterine growth restriction, premature rupture of membranes, and perinatal morbidity and mortality is higher. Physiologic addiction to narcotics occurs in most infants born to actively addicted mothers because opiates cross the placenta. Withdrawal may manifest even before birth as increased activity of the fetus when the mother feels a need for the drug or withdrawal symptoms develop. The clinical syndrome associated with opioid withdrawal has been termed the neonatal abstinence syndrome. Withdrawal signs develop during the 1st wk after birth in 55-94% of newborn infants exposed to opioids in utero. Neonatal withdrawal signs have also been described in infants exposed antenatally to benzodiazepines, barbiturates, alcohol, and other drugs. **Heroin addiction** results in a 50% incidence of low birthweight infants, half of whom are small for gestational age. Chronic infections, maternal undernutrition, and a direct fetal growth–inhibiting effect are possible causes. The rate of stillbirths increases, but not the incidence of congenital anomalies. Clinical manifestations of withdrawal occur in 50-75% of infants, usually beginning within the 1st 48 hr, depending on the daily maternal dose (<6 mg/24 hr is associated with no or mild symptoms), the duration of addiction (duration >1 yr has a >70% incidence of withdrawal), and the time of the last maternal dose (the incidence is higher if the last dose was taken within 24 hr of birth). Rarely, symptoms may appear as late as 4-6 wk of age. The incidence of respiratory distress syndrome and hyperbilirubinemia may be decreased in preterm infants of heroin users; accelerated production of pulmonary surfactant may explain the former, and enzyme induction of hepatic glucuronyl transferase the latter.

Tremors and hyperirritability are the most prominent symptoms. The tremors may be fine or jittery and indistinguishable from those of hypoglycemia, but they are more often coarse, "flapping," and bilateral; the limbs are frequently rigid, hyperreflexic, and resistant to flexion and extension. Irritability and hyperactivity are generally marked and may lead to skin abrasions. Other signs include wakefulness, hyperacusis, hypertonicity, tachypnea, diarrhea, vomiting, high-pitched cry, fist sucking, poor feeding with weight loss (disorganized sucking), and fever. Sneezing, yawning, hiccups, myoclonic jerks, convulsions, abnormal sleep cycles, nasal stuffiness, apnea, flushing alternating rapidly with pallor, and lacrimation are less common. The Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) is a useful way to evaluate neonates exposed to opiates or other drugs (Table 106-1). The risk of sudden infant death syndrome is higher in such neonates. The diagnosis is generally established from the history and clinical findings. Examining the urine for opiates may reveal only low levels during withdrawal, but quinine, which is often mixed with heroin, may be present in higher concentrations. Meconium testing is more accurate than neonatal urine drug testing. Hypoglycemia and hypocalcemia should be excluded.

Methadone treatment of the mother is associated with severe withdrawal symptoms, the incidence varying from 20-90%. Mothers taking methadone usually have better prenatal care than those taking heroin; these mothers have a high incidence of polysubstance abuse, including alcohol, barbiturates, and tranquilizers, and they are often heavy smokers. The incidence of congenital anomalies is not increased. The average birthweight of infants of mothers taking methadone is higher than that of infants of heroin-addicted mothers; the clinical manifestations are similar, except that the former group has a higher incidence of seizures (10-20%) and later onset (2-6 wk of age) of withdrawal. Women who continue to abuse heroin, even if they enter a methadone program, are more likely to have preterm and/or low birthweight infants than those born to women who stop using heroin. They are also more likely to suffer withdrawal and have a higher risk of neonatal mortality.

Table 106-1 Neurobehavioral Scale

DOMAIN	ITEMS
Physiologic	Labored breathing Nasal flaring
Autonomic	Sweating Spit-up Hiccoughing Sneezing Nasal stuffiness Yawning
Central nervous system	Abnormal sucking Choreiform movements Athetoid postures and movements Tremors Cogwheel movements Startles Hypertonia Back arching Fisting Cortical thumb Myoclonic jerks Generalized seizures Abnormal posture
Skin	Pallor Mottling Lividity Overall cyanosis Circumoral cyanosis Periocular cyanosis
Visual	Gaze aversion during orientation Pull-down during orientation Fuss/cry during orientation Obligatory following during orientation End-point nystagmus during orientation Sustained spontaneous nystagmus Visual locking Hyperalertness Setting sun sign Roving eye movements Strabismus Tight blinking Other abnormal eye signs
Gastrointestinal	Gagging/choking Loose stools, watery stools Excessive gas, bowel sounds
State	High-pitched cry Monotone-pitch cry Weak cry No cry Extreme irritability Abrupt state changes Inability to achieve quiet awake state (state 4)

From Lester BM, Tronick EZ, Brazelton TB: The Neonatal Intensive Care Unit Network Neurobehavioral Scales procedures, Pediatrics 113:641–667, 2004.

Table 106-2 Pharmacologic Therapy for Neonatal Abstinence Syndrome

DRUG	INITIAL DOSING	DOSING INCREASES	RESCUE DOSING	ADD ADJUVANT THERAPY	WEANING SCHEDULE
Morphine	0.1 mg kg^{-1} $dose^{-1}$ orally every 4 hr	Increase by 20–30% every 12 hr until scores <8 × 24 hr	Repeat previous dose between scheduled dose intervals	At morphine dose of 1.25 mg kg^{-1} $dose^{-1}$, add phenobarbital or clonidine	Decrease by 10% every 24 hr, while scores <8. Discontinue when 0.15 kg^{-1} $dose^{-1}$
Methadone	0.1 mg kg^{-1} $dose^{-1}$ orally every 12 hr	Calculate entire methadone dose for previous 24 hr and divide by two for BID dosing	Additional dosing of 0.025 mg kg^{-1} $dose^{-1}$ every 4 hr while scoring >8. Max dose 0.5 mg kg^{-1} $dose^{-1}$	When max dosing has been reached	Decrease by 10% every 1-2 wk. Discontinue when 0.05 mg kg^{-1} $dose^{-1}$
Buprenorphine	15.9 µg kg^{-1} $dose^{-1}$ divided in 3 doses, orally	Increase by 25%	Max dose 60 µg kg^{-1} $dose^{-1}$		After 3 days of stabilization, decrease by 10% while scores <8. Discontinue when dose is 10% of initial dose
Phenobarbital	20 mg/kg loading	Maintenance dose 5 mg/kg		Adjuvant	
Clonidine	0.5 to 1.5 µg/kg orally	Increase by over 1 to 2 days to target dose 3 to 5 µg kg^{-1} day^{-1}, divided every 4–6 hr		Adjuvant	No taper required

From Cramton REM, Gruchala NE: Babies breaking bad: neonatal and iatrogenic withdrawal syndromes. Curr Opin Pediatr *25:532–542, 2013, Table 4, p. 538.*

Buprenorphine (a partial µ-opioid agonist) is a synthetic opioid often used for the treatment of opioid dependence, used either alone (Subutex) or in combination with naloxone (Suboxone), Although the incidence of neonatal symptoms after maternal treatment with methadone and buprenorphine may be similar, the pattern of symptoms may be different; more tremor and hyperactive Moro reflex with methadone and more nasal stuffiness, sneezing, and loose stools with buprenorphine. Infants born to mothers treated with buprenorphine develop abstinence symptoms 1-2 days later than those of mothers on methadone. Infants born to buprenorphine-treated mothers also require less postnatal morphine doses, have a shorter duration of treatment, and are discharged from the hospital approximately 5 days sooner than methadone-exposed infants.

Alcohol withdrawal is uncommon. Infants of women who have been drinking immediately before delivery may have alcohol on their breath for several hours because it rapidly crosses the placenta. Blood levels in the infant are similar to those in the mother. Hypoglycemia and metabolic acidosis may be present. Infants in whom withdrawal symptoms develop often become agitated and hyperactive, with marked tremors lasting 72 hr, followed by about 48 hr of lethargy before return to normal activity. Seizures may develop.

Phenobarbital withdrawal usually occurs in infants of mothers addicted to the drug. Symptoms begin at a median age of 7 days (range: 2-14 days). Infants may have a brief acute stage consisting of irritability, constant crying, sleeplessness, hiccups, and mouthing movements, followed by a subacute stage consisting of voracious appetite, frequent regurgitation and gagging, episodic irritability, hyperacusis, sweating, and a disturbed sleep pattern, all of which may last 2-4 mo.

Cocaine abuse in pregnant women is common, but withdrawal in their infants is unusual; the pregnancy may be complicated by premature labor, abruptio placentae, and fetal asphyxia. Infants may have intrauterine growth restriction and neurobehavioral deficits characterized by impaired state regulation, impaired auditory information processing, developmental delay, and learning disabilities. At 24 mo of age, they score lower on the mental portion of the Bayley Scales of Infant Development and are twice as likely to have developmental delay. Family disorganization, polysubstance abuse, sexually transmitted infections, and child abuse and neglect may also be present. At 4 yr of age, children exposed prenatally to cocaine demonstrate specific cognitive impairments (visual–spatial and math skills; general knowledge) and are less likely to have an IQ above the normative mean. With a more enriching home environment, IQ scores of cocaine-exposed children are similar to those of nonexposed children.

Treatment

The decision to use drug therapy for neonatal drug withdrawal should be based on the presence of signs of withdrawal. Infants with confirmed drug exposure who do not have signs of withdrawal do not require pharmacologic treatment. Drug withdrawal is a self-limiting process. However, withdrawal from sedative-hypnotic drugs or narcotics can be life-threatening. Indications for drug treatment include seizures, poor feeding, diarrhea, excessive vomiting, inability to sleep, and fever. Several methods to assess severity of the withdrawal are available.

Infants who are undergoing opiate withdrawal require care in a quiet environment with reduction of external stimuli and swaddling. Pharmacologic treatment of heroin and methadone withdrawal requires opiate replacement during the 1st wk or 2 of life (Table 106-2). Methadone is often the drug of choice, but oral or sublingual buprenorphine is an alternate approach. Adjunct treatment with phenobarbital or clonidine is rarely necessary. Methadone withdrawal may require larger amounts of medication for longer periods to control clinical manifestations than are needed for heroin withdrawal. The Modified Finnegan's Neonatal Abstinence Scoring Tool, Lipsitz Neonatal Drug-Withdrawal Scoring System, or other semiobjective scoring tools may be used by clinicians to evaluate withdrawal and help with decisions regarding initiation or adjustment of therapy. The dose and duration of therapy may be adjusted according to the clinical response. Parenteral administration of fluids may be necessary to prevent aspiration or dehydration until the symptoms are brought under control.

Mortality from withdrawal is <5% and may be negligible with early recognition and treatment. The prognosis for normal development is affected by the adverse circumstances of high-risk pregnancy and delivery and by the environment to which the infant is returned after recovery, as well as by the effects of the particular drug on fetal and subsequent neonatal development.

106.1 Maternal Selective Serotonin Reuptake Inhibitors and Neonatal Behavioral Syndromes

Waldemar A. Carlo

Women of childbearing age have a combined incidence of depression and anxiety of approximately 19%. Selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine) and, less often, serotonin norepinephrine reuptake inhibitors (venla-

faxine, duloxetine) have been used to treat pregnant women with depression or anxiety disorders. Exposure to these agents during pregnancy may inconsistently produce congenital malformations (see Chapter 96). In addition, poor neonatal adaptation has been noted with the use of many of these agents, but most often with paroxetine and fluoxetine.

It is unclear whether poor neonatal adaptation is a result of serotonin overstimulation **(serotonin syndrome)** or withdrawal **(serotonin discontinuation syndrome).** Indeed, both conditions may occur with different agents. Paroxetine has a short half-life and few if any active metabolites, and is also a potent muscarinic blocking agent. Serum paroxetine levels after birth decline rapidly. Neonatal adaptive symptoms after late pregnancy exposure to paroxetine may be withdrawal with cholinergic overdrive. Symptoms may also be delayed. In contrast, fluoxetine and its active metabolite (nor-fluoxetine) have long half-lives and may produce a serotonin syndrome of acute toxicity. Onset may be at birth or in the 1st 24 hr of life. The cord blood level of fluoxetine is equal to blood level in the mother. All agents cross the placental and blood–brain barriers.

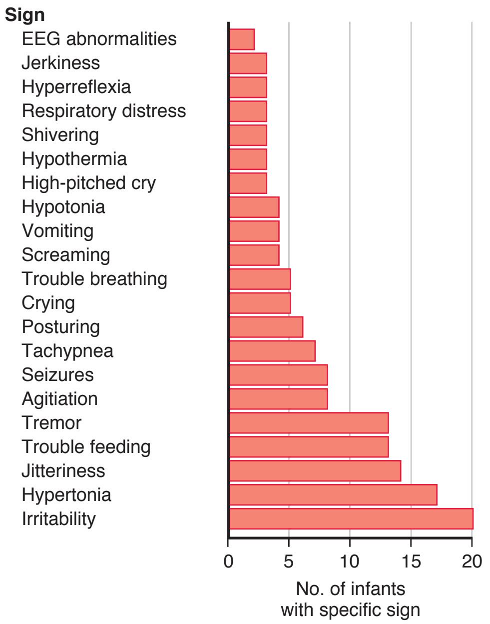

Figure 106-1 **Neonatal signs after late in utero exposure to serotonin reuptake inhibitors.** Frequencies of specific signs reported to the U.S. Food and Drug Administration (FDA) Adverse Events Reporting System. Ordered by frequency of occurrence (*n* = 57 infants). EEG, electroencephalographic. *(From Moses-Kolko EL, Bogen D, Perel J, et al: Neonatal signs after late in utero exposure to serotonin reuptake inhibitors,* JAMA *293:2372–2383, 2005.)*

A neonatal behavioral syndrome that has features of both direct serotonin toxicity and withdrawal (cholinergic overdrive) is noted in Figure 106-1 and is characterized by central nervous system (irritability, excess or restless sleep), motor (agitation, tremor, hyperreflexia, rigidity, hypotonia or hypertonia), respiratory (nasal congestion, respiratory distress, tachypnea), gastrointestinal (diarrhea, emesis, poor feeding) and systemic (hypothermia or hyperthermia, hypoglycemia) manifestations. Most infants have only mild symptoms that resolve within 2 wk; a severe syndrome characterized by seizures, dehydration, weight loss, hyperpyrexia, and respiratory failure is present in 1%. No deaths have been reported.

Treatment is directed at the individual manifestations and accompanied by supportive therapies. A method of prevention of neonatal SSRI withdrawal has been proposed that consists of weaning the mother from the SSRI in the 3rd trimester of pregnancy. The advantages of this approach for the fetus must be weighed against the risk for the mother of recurrence of psychiatric symptoms during the last trimester and postpartum period.

106.2 Fetal Alcohol Syndrome

Waldemar A. Carlo

High levels of alcohol ingestion during pregnancy can be damaging to embryonic and fetal development. A specific pattern of malformation identified as *fetal alcohol syndrome* has been documented, and major and minor components of the syndrome are expressed in 1-2 infants/1,000 live births (Table 106-3). Both moderate and high levels of alcohol intake during early pregnancy may result in alterations in

Table 106-3 Fetal Alcohol Syndrome Surveillance Network Case Definition Categories

	PHENOTYPE POSITIVE		
Case Definition Category	**Face**	**Central Nervous System**	**Growth**
Confirmed FAS phenotype with or without maternal alcohol exposure*	Abnormal facial features consistent with FAS as reported by a physician *or* Two of the following: short palpebral fissures, abnormal philtrum, thin upper lip	Frontal-occipital circumference ≤10th percentile at birth or any age *or* Standardized measure of intellectual function ≤1 SD below the mean *or* Standardized measure of developmental delay ≤1 SD below the mean *or* Developmental delay or mental retardation diagnosed by a qualified examiner (e.g., psychologist or physician) *or* Attention deficit disorder diagnosed by a qualified evaluator	Intrauterine weight or height corrected for gestational age ≤10th percentile *or* Postnatal weight or height ≤10th percentile for age *or* Postnatal weight for height ≤10th percentile
Probable FAS phenotype with or without maternal alcohol exposure*	Required; facial features same as above	Must meet either central nervous system or growth criteria as outlined above	

*Documentation in the records of some level of maternal alcohol use during the index pregnancy.
FAS, fetal alcohol syndrome; SD, standard deviation.
From Fetal alcohol syndrome—Alaska, Arizona, Colorado and New York, 1995-1997, MMWR Morb Mortal Wkly Rep *51:433–435, 2002.*

Figure 106-2 **Characteristics of fetal alcohol syndrome.** At birth *(A)* and at 4 yr of age *(B).* Note the short palpebral fissures; long, smooth philtrum with vermillion border; and hirsutism in the newborn. *(From Jones KL, Smith DW: Recognition of the fetal alcohol syndrome in early infancy,* Lancet *2:999–1001, 1973.)*

growth and morphogenesis of the fetus; the greater the intake, the more severe the signs. The risk of abnormality for infants born to heavy drinkers is twice that for infants born to moderate drinkers; in one study, 32% of infants born to heavy drinkers had congenital anomalies, compared with 9% of those born to abstinent mothers and 14% of those born to moderate drinkers. Additional maternal risk factors associated with fetal alcohol syndrome are advanced maternal age, low socioeconomic status, poor psychological indicators, and binge drinking.

Characteristics of fetal alcohol syndrome include (a) prenatal onset and persistence of growth deficiency for length, weight, and head circumference; (b) facial abnormalities, including short palpebral fissures, epicanthal folds, maxillary hypoplasia, micrognathia, smooth philtrum, and a thin, smooth upper lip (Fig. 106-2); (c) cardiac defects, primarily septal defects; (d) minor joint and limb abnormalities, including some restriction of movement and altered palmar crease patterns; and (e) delay of development and mental deficiency varying from borderline to severe (see Table 106-2). Fetal alcohol syndrome is a common identifiable cause of mental retardation. The severity of dysmorphogenesis may range from severely affected infants with full manifestations of fetal alcohol syndrome to those mildly affected with only a few manifestations.

The detrimental effects may be a consequence of the alcohol itself or to one of its breakdown products. Some evidence suggests that alcohol may impair placental transfer of essential amino acids and zinc, both of which are necessary for protein synthesis, an effect that may account for the intrauterine growth restriction.

Treatment of infants with fetal alcohol syndrome is difficult because no specific therapy exists. These infants may remain hypotonic and tremulous despite sedation, and the prognosis is poor. Counseling with regard to recurrence is important. Prevention is achieved by eliminating alcohol intake after conception.

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Chapter 107

The Endocrine System

Waldemar A. Carlo and
Namasivayam Ambalavanan

The endocrinopathies are discussed in detail in Part XXVI.

Pituitary dwarfism is not usually apparent at birth, although male infants with panhypopituitarism may have neonatal hypoglycemia, hyperbilirubinemia, and micropenis. Conversely, constitutional dwarfs usually have length and weight suggestive of prematurity when born after a normal gestational period; otherwise, their physical appearance is normal.

Congenital hypothyroidism is one of the most common preventable causes of mental retardation. Congenital screening followed by thyroid hormone replacement treatment started within 2 wk after birth can normalize cognitive development in children with congenital hypothyroidism. Congenital hypothyroidism occurs in approximately 1/4,000 births (see Chapter 565). Because most infants with congenital hypothyroidism are asymptomatic at birth, all states screen for it. Even though screening is standard in many countries, millions of infants born throughout the world are not screened for congenital hypothyroidism. Thyroid deficiency may also be apparent at birth in genetically determined cretinism or in infants of mothers treated with antithyroid medications or during a pregnancy complicated by maternal hyperthyroidism. Constipation, prolonged jaundice, goiter, lethargy, or poor peripheral circulation as shown by persistently mottled skin or cold extremities should suggest cretinism. Thyroid hormone treatment is aimed to maintain total thyroxine or free thyroxine in the upper half of the normal range during the 1st 3 yr after birth. Early diagnosis and treatment of congenital thyroid hormone deficiency improve intellectual outcome and are facilitated by screening of all newborn infants for this deficiency.

Transient hypothyroxinemia of prematurity is most common in ill and very premature infants. These infants have low thyroxine levels but normal levels of serum thyrotropin and other tests of the pituitary–hypothalamic axis indicating that they are probably chemically euthyroid. Trials of thyroid hormone replacement have reported no difference in developmental outcomes or other morbidities. Current practice is to follow thyroxine levels until they normalize. **Transient hyperthyroidism** may occur at birth in infants of mothers with hyperthyroidism or in infants whose mothers have been receiving thyroid medication.

Transient hypoparathyroidism may manifest as tetany of the newborn (see Chapter 571).

The adrenal glands are subject to numerous disturbances, which may become apparent and require lifesaving treatment during the neonatal period. Acute **adrenal hemorrhage** and failure may occur after breech or other traumatic deliveries or in association with overwhelming infection. Signs of adrenal insufficiency and shock can occur. **Congenital adrenal hyperplasia** is suggested by vomiting, diarrhea, dehydration, hyperkalemia, hyponatremia, shock, ambiguous genitals, or clitoral enlargement. Some infants have ambiguous genitals and hypertension. Because the condition is genetically determined, newborn siblings of patients with the salt-losing variety of adrenocortical hyperplasia should be closely observed for manifestations of adrenal insufficiency. Newborn screening and early diagnosis and therapy for this disorder may prevent severe salt wasting and adverse outcomes. Congenitally hypoplastic adrenal glands may also give rise to adrenal insufficiency during the 1st few wk of life.

Female infants with webbing of the neck, lymphangiectatic edema, hypoplasia of the nipples, cutis laxa, low hairline at the nape of the neck, low-set ears, high-arched palate, deformities of the nails, cubitus valgus, and other anomalies should be suspected of having gonadal dysgenesis.

Transient diabetes mellitus (see Chapter 589) is rare and is encountered only in newborns. It usually manifests as dehydration, loss of weight, or acidosis in infants who are small for gestational age.

Bibliography is available at Expert Consult.

107.1 Infants of Diabetic Mothers

Waldemar A. Carlo

Women with diabetes in pregnancy (type 1, type 2, and gestational) are at increased risk for adverse pregnancy outcomes. Adequate glycemic control before and during pregnancy is crucial to improving outcome.

Diabetic mothers have a high incidence of polyhydramnios, preeclampsia, pyelonephritis, preterm labor, and chronic hypertension; their fetal mortality rate is greater than that of nondiabetic mothers, especially after 32 wk of gestation. Fetal loss throughout pregnancy is associated with poorly controlled maternal diabetes (especially ketoacidosis) and congenital anomalies. Most infants born to diabetic mothers are large for gestational age. If the diabetes is complicated by vascular disease, infants may be growth restricted, especially those born after 37 wk of gestation. The neonatal mortality rate is >5 times that of infants of nondiabetic mothers and is higher at all gestational ages and in every birthweight for gestational age category.

PATHOPHYSIOLOGY

The probable pathogenic sequence is that maternal hyperglycemia causes fetal hyperglycemia, and the fetal pancreatic response leads to fetal hyperinsulinemia; fetal hyperinsulinemia and hyperglycemia then cause increased hepatic glucose uptake and glycogen synthesis, accelerated lipogenesis, and augmented protein synthesis (Fig. 107-1). Related pathologic findings are hypertrophy and hyperplasia of the pancreatic islet β cells, increased weight of the placenta and infant organs except for the brain, myocardial hypertrophy, increased amount of cytoplasm in liver cells, and extramedullary hematopoiesis. Hyperinsulinism and hyperglycemia produce fetal acidosis, which may result

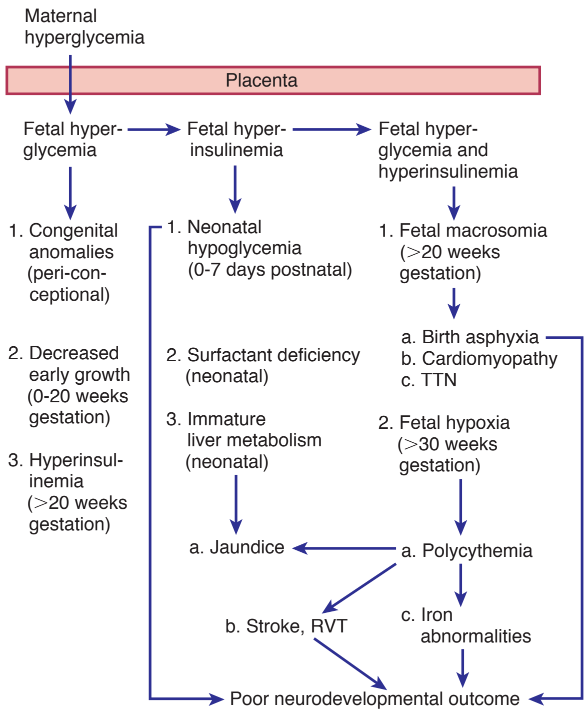

Figure 107-1 The fetal and neonatal events attributable to fetal hyperglycemia *(column 1)*, fetal hyperinsulinemia *(column 2)*, or both in synergy *(column 3)*. Time of risk is denoted in *parentheses*. RVT, renal vein thrombosis; TTN, transient tachypnea of the newborn. *(From Nold JL, Georgieff MK: Infants of diabetic mothers,* Pediatr Clin North Am *51:619-637, 2004.)*

in an increased rate of stillbirth. Separation of the placenta at birth suddenly interrupts glucose infusion into the neonate without a proportional effect on the hyperinsulinism, and hypoglycemia and attenuated lipolysis may develop during the 1st few hr after birth.

Hyperinsulinemia has been documented in infants of mothers with gestational diabetes and in those of mothers with insulin-dependent diabetes (diabetic mothers) without insulin antibodies. The former group also has significantly higher fasting plasma insulin levels than normal newborns do despite similar glucose levels; they also respond to glucose with an abnormally prompt elevation in plasma insulin and assimilate a glucose load more rapidly. After arginine administration, they also have an enhanced insulin response and increased disappearance rates of glucose in comparison with normal infants. In contrast, fasting glucose production and utilization rates are diminished in infants of mothers with gestational diabetes. The lower free fatty acid levels in infants of mothers with insulin-dependent diabetes reflect their hyperinsulinemia. With good prenatal diabetic control, the incidence of macrosomia and hypoglycemia has decreased.

Although hyperinsulinism is probably the main cause of hypoglycemia, the diminished epinephrine and glucagon responses that occur may be contributing factors. Congenital anomalies correlate with poor metabolic control during the periconception and organogenesis periods and may be the result of hyperglycemia-induced teratogenesis. Chronic fetal hypoxia, indicated by elevated amniotic fluid erythropoietin values, is associated with increased fetal and neonatal morbidity.

CLINICAL MANIFESTATIONS

Infants of mothers with diabetic and those of mothers with gestational diabetes often bear a surprising resemblance to each other (Fig. 107-2). They tend to be large and plump as a result of increased body fat and enlarged viscera, with puffy, plethoric facies resembling that of patients who have been receiving corticosteroids. These infants may also,

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Figure 107-2 Large, plump, plethoric infant of a mother with gestational diabetes. The baby was born at 38 wk of gestation but weighed 9 lb, 11 oz (4,408 g). Mild respiratory distress was the only symptom other than appearance.

however, be of normal or low birthweight, particularly if they are delivered before term or if their mothers have associated vascular disease.

Hypoglycemia develops in approximately 25-50% of infants of diabetic mothers and 15-25% of infants of mothers with gestational diabetes, but only a small percentage of these infants become symptomatic. The probability that hypoglycemia will develop in such an infant increases, and glucose levels are likely to be lower with higher cord or maternal fasting blood glucose levels. The nadir in an infant's blood glucose concentration is usually reached between 1 and 3 hr; spontaneous recovery may begin by 4-6 hr.

The infants tend to be jittery, tremulous, and hyperexcitable during the 1st 3 days after birth, although hypotonia, lethargy, and poor sucking may also occur. They may have any of the diverse manifestations of hypoglycemia. Early appearance of these signs is more likely to be related to hypoglycemia, and their later appearance to hypocalcemia; these abnormalities may also occur together. Perinatal asphyxia may produce similar signs. Hypomagnesemia may be associated with the hypocalcemia. These manifestations may also occur in the absence of hypoglycemia, hypocalcemia, and asphyxia.

Tachypnea develops in many infants of diabetic mothers during the 1st 2 days after birth and may be a manifestation of hypoglycemia, hypothermia, polycythemia, cardiac failure, transient tachypnea, or cerebral edema from birth trauma or asphyxia. Infants of diabetic mothers have a higher incidence of **respiratory distress syndrome** than do infants of nondiabetic mothers born at comparable gestational age; the greater incidence is possibly related to an antagonistic effect of insulin on stimulation of surfactant synthesis by cortisol.

Cardiomegaly is common (30%), and heart failure occurs in 5-10% of infants of diabetic mothers. Asymmetric septal hypertrophy may occur and may manifest as transient idiopathic hypertrophic subaortic stenosis. Inotropic agents worsen the obstruction and are contraindicated. Congenital heart disease is more common in infants of diabetic mothers. Birth trauma is also a common sequela of fetal macrosomia.

Neurologic development and ossification centers tend to be immature and to correlate with brain size (which is not increased) and gestational age rather than total body weight. In addition, these infants have an increased incidence of hyperbilirubinemia, polycythemia, and renal vein thrombosis; the last should be suspected in the infant with a flank mass, hematuria, and thrombocytopenia.

The incidence of **congenital anomalies** is increased 3-fold in infants of diabetic mothers; cardiac malformations (ventricular or atrial septal defect, transposition of the great vessels, truncus arteriosus, double-outlet right ventricle, tricuspid atresia, coarctation of the aorta) and lumbosacral agenesis are most common. Additional anomalies include neural tube defects, hydronephrosis, renal agenesis and dysplasia, duodenal or anorectal atresia, situs inversus, double ureter, and holoprosencephaly. These infants may also demonstrate abdominal distention caused by a transient delay in development of the left side of the colon, the small left colon syndrome.

TREATMENT

Prophylactic treatment of infants of diabetic mothers should be initiated before birth by means of preconception and frequent prenatal evaluations of all women with diabetes and pregnant women with gestational diabetes, evaluation of fetal maturity, biophysical profile, Doppler velocimetry, and planning of the delivery of these infants in hospitals where expert obstetric and pediatric care is continuously available. Periconception glucose control reduces the risk of anomalies and other adverse outcomes, and glucose control during labor reduces the incidence of neonatal hypoglycemia. Women with type 1 diabetes who have tight glucose control during pregnancy (average daily glucose levels <95 mg/dL) deliver infants with birthweights and anthropomorphic features similar to those of infants of nondiabetic mothers. Treatment of gestational diabetes also reduces complications; dietary advice, glucose monitoring, metformin, and insulin therapy as needed decrease the rate of serious perinatal outcomes (death, shoulder dystocia, bone fracture, or nerve palsy). Women with gestational diabetes may also be treated successfully with glyburide, which may not cross the placenta. In these mothers, the incidence of macrosomia and neonatal hypoglycemia is similar to that in mothers with insulin-treated gestational diabetes.

Regardless of size, infants of diabetic mothers should initially receive close observation and care (Fig. 107-3). Infants should initiate feedings within 1 hr after birth. A screen glucose test should be performed within 30 minutes of the first feed. Transient hypoglycemia is common during the 1st 2-3 hr after birth and may be part of normal adaptation to extrauterine life. The target plasma glucose concentration is ≥45 mg/dL before feeds. Clinicians need to assess the overall metabolic and physiologic status, considering these in the management of hypoglycemia. According to a statement from the American Academy of Pediatrics, treatment is indicated if the plasma glucose is <40 mg/dL and clinical symptoms of hypoglycemia are present. In asymptomatic infants, treatment is indicated if the plasma glucose is <30 mg/dL. Feeding is the initial treatment for hypoglycemia. Gavage feeding with breast milk or formula can be given. Recurrent hypoglycemia can be treated with repeat feedings or intravenous glucose as needed. Infants with persistent glucose levels <25 mg/dL during the 1st 4 hr after birth and <35 mg/dL during 4-24 hr after birth should be treated with intravenous glucose. A dose of 200 mg/kg of dextrose (2 mL/kg of 10% dextrose) should be administered to infants with plasma glucoses below these limits. If question arises about an infant's ability to tolerate oral feeding, a continuous peripheral intravenous infusion at a rate of 4-8 mg/kg/min should be given. Bolus injections of hypertonic glucose should be avoided because they may cause further hyperinsulinemia and potentially produce rebound hypoglycemia.

For treatment of hypocalcemia and hypomagnesemia, see Chapter 106; for respiratory distress syndrome treatment, see Chapter 101.3; for treatment of polycythemia, see Chapter 103.3.

PROGNOSIS

The subsequent incidence of diabetes mellitus in infants of diabetic mothers is higher than that in the general population. Physical development is normal, but oversized infants may be predisposed to childhood obesity that may extend into adult life. Disagreement persists

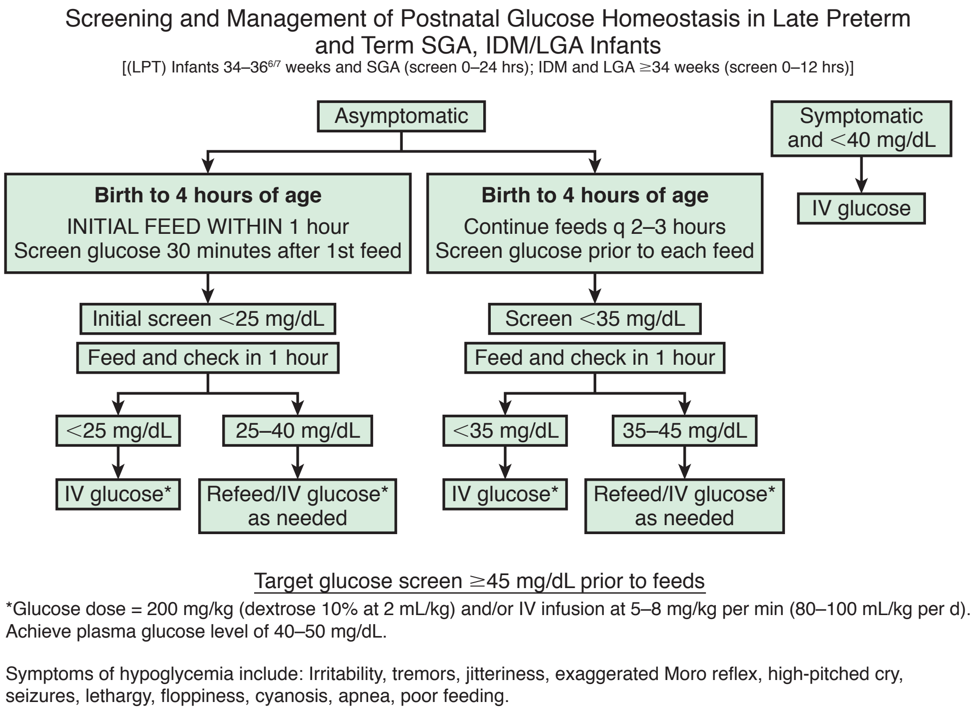

Figure 107-3 Screening for and management of postnatal glucose homeostasis in late-preterm (LPT 34-36 wk) and term small-for-gestational age (SGA) infants and infants who were born to mothers with diabetes (IDM)/large-for-gestational age (LGA) infants. LPT and SGA, screen 0-24 hr; IDM and LGA ≥34 wk, screen 0-12 hr. IV indicates intravenous. *(American Academy of Pediatrics Committee of Fetus and Newborn: Postnatal glucose homeostasis in late-preterm and term infants.* Pediatrics *127:575-579, 2011, Fig. 1, p. 576.)*

about whether these infants have a slightly increased risk of impaired intellectual development unrelated to hypoglycemia; symptomatic hypoglycemia increases the risk, as does maternal ketonuria.

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Chapter 108

Dysmorphology

Anne Slavotinek

Dysmorphology is the study of abnormalities of human form and the mechanisms that cause them. It is estimated that 1 in 40, or 2.5% of newborns, have a recognizable malformation or malformations at birth. In about half of these newborns, a single isolated malformation is found, whereas in the other half, there are multiple malformations. It is estimated that 10% of pediatric hospital admissions involve known genetic conditions, 18% involve congenital defects of unknown etiology, and 40% of surgical admissions are of patients with congenital malformations. Between 20% and 30% of infant deaths and 30-50% of deaths after the neonatal period are a result of congenital abnormalities (http://www.marchofdimes.com/peristats/). In 2001, birth defects accounted for 1 in 5 infant deaths in the United States, with a rate of 137.6 deaths per 100,000 live births, which is higher than other causes, such as preterm/low birthweight (109.5/100,000), sudden infant death syndrome (55.5/100,000), maternal complications of pregnancy (37.3/100,000), and respiratory distress syndrome (25.3/100,000).

CLASSIFICATION OF BIRTH DEFECTS

Congenital birth defects either are isolated, single defects or manifest as multiple anomalies in a single individual. Single primary defects can be classified according to the nature of the presumed cause of the defect as a malformation, dysplasia, deformation, or disruption (Table 108-1, Fig. 108-1), although most are malformations. Malformations and dysplasias both affect intrinsic structure. A **malformation** is a primary structural defect arising from a localized error in morphogenesis and resulting in the abnormal formation of a tissue or organ (Fig. 108-1*A*). **Dysplasia** refers to an abnormal organization of cells into tissues (Fig. 108-1*D*). The distinction of a malformation from a dysplasia may be helpful, but there is much overlap. Deformations and disruptions are secondary effects that result from forces generated extrinsic to the affected tissue or organ. A **deformation** is an alteration in shape or structure of a structure or organ that has differentiated normally (Fig. 108-1*B*). A **disruption** is a structural defect resulting from the destruction of a structure that had formed normally before the insult (Fig. 108-1*C*).

More than 1,000 of the ≈1,750 inherited human disorders with altered morphogenesis display multiple malformations. When several malformations occur in a single individual, they are classified as syndromes, sequences, or associations. A **syndrome** is defined as a pattern of multiple abnormalities that are related by pathophysiology and result from a single, defined etiology. **Sequences** consist of multiple malformations that are caused by a single event that can have many etiologies. An **association** refers to a nonrandom collection of malformations in which there is an unclear or unknown relationship among the malformations such that they do not fit the criteria for a syndrome or sequence.

Malformations and/or Dysplasias

Human malformations and dysplasias are caused by the interactions of genes and environmental factors (Table 108-2; see Fig. 108-1). Some malformations are caused by single-gene defects or abnormalities of multiple genes acting in concert, and the environment causes others. In 1996, it was thought that malformations were caused by monogenic

Figure 108-1 The four major types of problems in morphogenesis: malformation, deformation, disruption, and dysplasia. **A,** An infant with camptomelic dysplasia syndrome, which results in a multiple malformation syndrome caused by a mutation in SOX9. **B,** An infant with oligohydramnios deformation sequence caused by premature rupture of membranes from 17 wk of gestation until birth at 36 wk; the infant was delivered from persistent transverse lie. **C,** A fetus with early amnion rupture sequence with attachment of the placenta to the head and resultant disruption of craniofacial structures with distal limb contractures. **D,** An infant with diastrophic dysplasia caused by inherited autosomal recessive mutations in a sulfate transporter protein. *(From Graham Jr JM:* Smith's recognizable patterns of human deformation, *ed 3, Philadelphia, 2007, Saunders, Fig. 1-1, p. 4.)*

Table 108-1 Mechanisms, Terminology, and Definitions of Dysmorphology

TERMINOLOGY	DEFINITION	EXAMPLE
Malformation sequence	Single, local tissue morphogenesis abnormality that produces a chain of subsequent defects	DiGeorge sequence of primary fourth branchial arch and 3rd and 4th pharyngeal pouch defects that lead to aplasia or hypoplasia of the thymus and parathyroid glands, aortic arch anomalies, and micrognathia
Deformation sequence	Mechanical (uterine) forces that alter structure of intrinsically normal tissue	Oligohydramnios produces deformations by in utero compression of limbs (dislocated hips, equinovarus foot deformity), crumpled ears, dislocated nose, or small thorax
Disruption sequence	In utero tissue destruction after a period of normal morphogenesis	Amnionic membrane rupture sequence, leading to amputation of fingers/toes, tissue fibrosis, and destructive tissue bands
Dysplasia sequence	Poor organization of cells into tissues or organs	Neurocutaneous melanosis sequence with poor migration of melanocyte precursor cells from the neural crest to the periphery, manifesting as melanocytic hamartosis of skin, meninges, and so forth
Malformation syndrome	Appearance of multiple malformations in unrelated tissues without an understandable unifying cause; with enhanced genetic investigation, a single etiology may become identified	Trisomy 21 Teratogens

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier Saunders.*

defects in 7.5% of patients; by chromosomal anomalies in 6%; by multigenic defects in 20%; and by known environmental factors, such as maternal diseases, infections, and teratogens, in 6-7% (Table 108-3); in the remaining 60-70% of patients, malformations were classified as caused by unknown etiologies. A decade later, the percentages were somewhat higher for all categories of known causes of malformations, a change resulting from improved cytogenetic methods for detecting small chromosomal abnormalities as well as techniques for mapping and cloning disease genes. Since the previous edition of this book, it has been discovered that an additional 10-20% of birth defects result from even smaller chromosomal abnormalities detectable by whole genome arrays using comparative genomic hybridization (array CGH) methodology. In spite of these advances, we still do not know the causes for 40-50% of birth defects.

Many developmental abnormalities are caused by mutations in a single gene and display characteristic mendelian patterns of inheritance. The molecular etiology for more than 250 single-gene disorders is known. Affected genes are often part of evolutionarily conserved signal transduction pathways, transcription factors, or regulatory proteins required for key developmental events. Some examples are listed in Table 108-2; they include autosomal recessive spondylocostal dysostosis (SCD) syndrome, the autosomal recessive Smith-Lemli-Opitz syndrome (SLOS), the autosomal dominant Rubinstein-Taybi syndrome, and the X-linked lissencephaly ("smooth brain") syndrome. The SCD syndromes are etiologically heterogeneous and are often caused by mutations in the gene coding for delta-like 3 (*DLL3*), a ligand of the Notch receptors. The Notch/delta pathway is conserved throughout evolution and regulates a number of developmental events. Patients with SCD display a characteristic pattern of abnormal vertebral segmentation associated with a number of other malformations, such as neural tube defects. SLOS (Fig. 108-2) results from mutations in the sterol delta-7-dehydrocholesterol reductase (*DHCR7*) gene, an

Table 108-2 Examples of Malformations with Distinct Causes, Clinical Features, and Pathogenesis

DISORDER	CAUSE/INHERITANCE	CLINICAL FEATURES	PATHOGENESIS
Spondylocostal dysostosis syndromes	Mendelian autosomal recessive	Abnormal vertebral segmentation Neural tube defects	*DLL3* mutations; mutations can also be present in other genes
Rubinstein-Taybi syndrome	Mendelian autosomal recessive	Mental retardation Broad thumbs, toes Hypoplastic maxillae Prominent nose Congenital heart disease	*CBP* mutations or haploinsufficiency
X-linked lissencephaly	Mendelian X-linked	Male: Severe mental retardation Seizures Female: Variable	*DCX* mutation
Aniridia	Autosomal semidominant	Reduced or absent iris	*PAX6* mutations
Waardenburg syndrome	Autosomal semidominant	Deafness White forelock Wide-spaced eyes Pale eye pigment	*PAX3* mutations *MITF* mutations
Holoprosencephaly	Loss of function or heterozygosity	Microcephaly Cyclopia Single central incisor	*SHH* mutations
Velocardiofacial syndrome	Microdeletion 22q11.2	Conotruncal congenital heart disease Cleft palate T-cell defects Facial anomalies	*TBX1* haploinsufficiency/mutations; haploinsufficiency for other genes in the deleted interval
Down syndrome	Chromosomal	Mental retardation Characteristic dysmorphic features Congenital heart disease Increased risk of leukemia Alzheimer disease	50% increase of estimated 250 genes on chromosome 21 Trisomy 21
Neural tube defects	Multifactorial	Meningomyelocele	Defects in folate sensitive enzymes or folic acid uptake
Fetal alcohol syndrome	Teratogenic	Microcephaly Developmental delay Facial abnormalities Behavioral abnormalities	Ethanol toxicity to developing brain
Retinoic acid embryopathy	Teratogenic	Microtia Congenital heart disease	Isotretinoin effects on neural crest and branchial arch development

enzyme important in cholesterol biosynthesis. Patients with SLOS display syndactyly (fusion of the fingers and toes), polydactyly, an upturned (anteverted) nose, ptosis, cryptorchidism, and holoprosencephaly. These mutations link cholesterol biosynthesis pathogenetically to the sonic hedgehog (SHH) pathway, because many of the features of the former disorder are related to defects in SHH, which is post-translationally modified by cholesterol (see Chapter 86). Rubinstein-Taybi syndrome (see Fig. 108-2) results from heterozygous, loss-of-function mutations in the gene coding for a broadly acting transcriptional coactivator called CBP, or CREB-binding protein. The CBP coactivator regulates the transcription of a number of genes, a fact that helps explain why patients with mutations in *CBP* have a wide-ranging phenotype that includes mental retardation, broad thumbs and toes, and congenital heart disease. One of the transcription factors that binds to CBP is *GLI3*, a transcription factor that is part of the SHH pathway (see Fig. 108-2). X-linked lissencephaly—a severe neuronal migration defect that in males causes a smooth brain with reduction or absence of gyri and sulci and in females gives rise to a variable pattern of mental retardation and seizures—is caused by mutations in *DCX*. The DCX protein regulates the activity of dynein motors and moves the nucleus during neuronal migration.

Other malformation syndromes are caused by chromosomal imbalance, multifactorial inheritance, and teratogens (see Tables 108-2 and 108-3). Down syndrome results from an extra dose of part or all of chromosome 21, a small chromosome that contains ≈200 known or predicted genes. It is most commonly caused by trisomy 21, which means that individuals with Down syndrome have an increased dose of as many as 250 genes contained on this chromosome (see Chapter 81.1). Neural tube defects (NTDs) are an example of a disorder that displays multifactorial inheritance in the majority of cases. NTDs and a number of other congenital malformations, such as cleft lip and palate, recur in families, but several genes and environmental factors together contribute to the pathogenesis (see Table 108-2). Many of the genes involved in NTDs are unknown, so one cannot predict with certainty a mode of inheritance or a precise recurrence risk. Empiric risks can be provided on the basis of population studies and the presence of single or multiple relatives with the same malformation. However, an important gene/environment interaction has been identified for NTDs (see Chapter 591.1). Folic acid status is associated with NTDs and can result from a combination of dietary deficiencies and increased utilization during pregnancy as well as from a common variant in the gene for an enzyme in the folate recycling pathway,

Table 108-3	Causes of Congenital Malformations
MONOGENIC (7.5% of major anomalies) X-linked hydrocephalus Achondroplasia Ectodermal dysplasia Apert syndrome Treacher Collins syndrome	
CHROMOSOMAL (6% of major anomalies) Trisomy 21, 18, 13 XO, XXY Deletions 4p–, 5p–, 7q–, 13q–, 18p–, 18q–, 22q– Prader-Willi syndrome (50% of affected patients have deletion of chromosome 15)	
MATERNAL INFECTION (2% of major anomalies) Intrauterine infections (e.g., herpes simplex virus, cytomegalovirus, varicella-zoster virus, rubella virus, and toxoplasmosis)	
MATERNAL ILLNESS (3.5% of major anomalies) Diabetes mellitus Phenylketonuria Hyperthermia	
UTERINE ENVIRONMENT (% unknown) Deformation Uterine pressure, oligohydramnios: clubfoot, torticollis, congenital hip dislocation, pulmonary hypoplasia, 7th nerve palsy Disruption Amniotic bands, congenital amputations, gastroschisis, porencephaly, intestinal atresia Twinning	
ENVIRONMENTAL AGENTS (% unknown) Polychlorinated biphenyls Herbicides Mercury Alcohol	
MEDICATIONS (% unknown) Thalidomide Diethylstilbestrol Phenytoin Warfarin Cytotoxic drugs Paroxetine Angiotensin-converting enzyme inhibitors Isotretinoin (vitamin A) D-Penicillamine Valproic acid	
UNKNOWN ETIOLOGIES Polygenetic Associated with infertility (spontaneous or with treatment) Anencephaly/spina bifida Cleft lip/palate Pyloric stenosis Congenital heart disease	
SPORADIC SYNDROME COMPLEXES VATER (vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, and radial and renal anomalies) syndrome Pierre Robin syndrome Prune-belly syndrome	
NUTRITIONAL Low folic acid–neural tube defects	

From Behrman RE, Kliegman RM, editors: Nelson's essentials of pediatrics, *ed 4, Philadelphia, 2002, WB Saunders.*

5,10-methylene-tetrahydrofolate reductase, that makes this enzyme less stable. These discoveries led to the recommendation that all women supplement their diets with 400-800 µg of folic acid per day 1 mo before pregnancy and during the 1st 2 mo of pregnancy. This supplementation has resulted in a reduction in the incidence of NTDs by 75%. Several teratogenic causes of birth defects have been described (see Tables 108-2 and 108-3). Ethanol causes a recognizable malformation syndrome called fetal alcohol syndrome (see Chapter 106.2). Children with fetal alcohol syndrome display microcephaly, developmental delay, hyperactivity, and facial dysmorphic features. Ethanol, which is toxic to the developing central nervous system, causes cell death in developing neurons.

Deformations

Most deformations involve the musculoskeletal system (see Figs. 108-1*B* and 108-3). Fetal movement is required for the proper development of the normal musculoskeletal system, and anything that restricts fetal movement can cause a musculoskeletal deformation from intrauterine molding. It is important to recognize that deformations can be caused by problems either intrinsic or extrinsic to the developing fetus. Two major intrinsic causes of deformations are primary neuromuscular disorders and oligohydramnios, or decreased amniotic fluid, which is caused by renal defects. The major extrinsic causes of deformation are those that result in fetal crowding to restrict fetal movement. Examples of such extrinsic causes are oligohydramnios from chronic leakage of amniotic fluid, breech presentation (see Figs. 108-1*B* and 108-4), and abnormal shape of the amniotic cavity. When a fetus is in the breech position, the incidence of deformations is increased 10-fold. The shape of the amniotic cavity has a profound effect on the shape of the fetus and is influenced by many factors, including uterine shape; volume of amniotic fluid; size and shape of the fetus; presence of more than 1 fetus; site of placental implantation; presence of uterine tumors; shape of the abdominal cavity, which is influenced by the pelvis, sacral promontory, and neighboring abdominal organs; and tightness of the abdominal musculature.

It is important to determine whether deformations result from intrinsic or extrinsic causes. Most children with deformations from extrinsic causes are otherwise completely normal, and their prognosis is usually excellent. Correction usually occurs spontaneously. Deformations caused by intrinsic factors, such as multiple joint contractures resulting from central nervous system defects, would have a different prognosis and a far greater significance for the child.

Disruption

Disruption defects are caused by destruction of a previously normally formed part. At least 2 basic mechanisms are known to produce disruption. One involves entanglement followed by tearing apart or amputation of a normally developed structure, usually a digit, arm, or leg, by strands of amnion floating within amniotic fluid **(amniotic bands)** (see Figs. 108-1*C* and 108-5). The second involves interruption of the blood supply to a developing part, which can lead to infarction, necrosis, and/or resorption of structures distal to the insult. If interruption of the blood supply occurs early in gestation, the disruptive defect seen at term usually involves **atresia,** or absence of a particular part. If the infarction occurs later, necrosis is more likely to be present. Genetic factors usually play a minor role in the pathogenesis of disruptions; most are sporadic events in otherwise normal families. The prognosis for a disruptive defect is determined entirely by the extent and location of the tissue loss.

Multiple Anomalies: Syndrome and Sequence

The pattern of multiple anomalies that occurs when a single primary defect in early morphogenesis produces multiple abnormalities through a cascading process of secondary and tertiary errors in morphogenesis is called a **sequence** (see Figs. 108-6 and 108-7). When evaluating a child with multiple anomalies, the physician must differentiate multiple anomalies secondary to a single localized error in morphogenesis (a sequence) from a multiple malformation syndrome. In the former, recurrence risk counseling for the multiple anomalies depends entirely on the risk of recurrence for the single localized malformation. The Pierre-Robin malformation sequence is a pattern of multiple anomalies produced by mandibular hypoplasia. Because the tongue is relatively large for the oral cavity, it drops back (glossoptosis), blocks closure of the posterior palatal shelves, and causes a

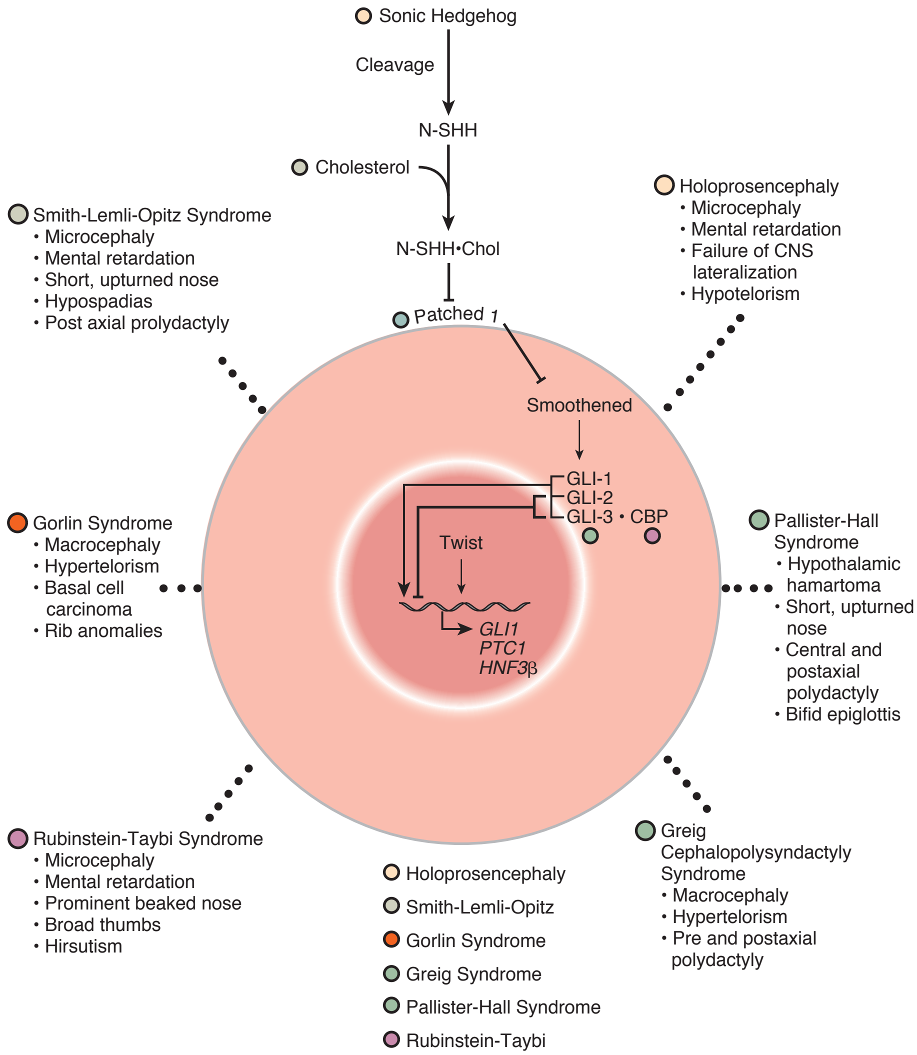

Figure 108-2 **Mutations in genes that function together in a genetic developmental pathway commonly have overlapping clinical manifestations.** Several components of the sonic hedgehog (SHH) pathway have been identified, and their relationships elucidated (see text for further details). Mutations in several members of this pathway result in phenotypes that have facial dysmorphisms, seen in holoprosencephaly, SLOS, Gorlin syndrome, Greig cephalopolysyndactyly syndrome, Pallister-Hall syndrome, and Rubinstein-Taybi syndrome.

U-shaped cleft palate. There are numerous causes of mandibular hypoplasia, all of which can result in characteristic features of Pierre-Robin sequence.

MOLECULAR MECHANISMS OF MALFORMATIONS

Inborn Errors of Development

The genes mutated in malformation syndromes (as well as genes whose expression is disrupted by environmental agents or teratogens) are part of evolutionarily conserved signal transduction pathways, transcription factors, or regulatory proteins required for key developmental events. We should consider malformations to be inborn errors of development. Consideration of malformations as alterations of important developmental pathways provides a molecular framework for understanding human birth defects.

Sonic Hedgehog Pathway as Model

The SHH pathway is developmentally important during embryogenesis to induce controlled proliferation in a tissue-specific manner; disruption of specific steps in this pathway results in a variety of related developmental disorders and malformations (see Fig. 108-2). Activation of this pathway in the adult leads to abnormal proliferation and cancer. The SHH pathway transduces an external signal in the form of a ligand into changes in gene transcription by binding of the ligand to specific cellular receptors. SHH is a ligand expressed in the embryo in a variety of areas important for development of the brain, face, limbs, and the gut. Sporadic and inherited mutations are found to cause **holoprosencephaly** (see Figs. 108-2 and 108-6), a variably severe midline defect with phenotypes ranging from a single maxillary incisor with hypotelorism to cyclopia. SHH is processed by proteolytic cleavage to an active N-terminal form, which is then further modified by the addition of cholesterol. Defects in cholesterol biosynthesis, in particular the sterol delta-7-dehydrocholesterol reductase gene, result in **SLOS** (see Fig. 108-2). SLOS is also associated with holoprosencephaly. The modified and active form of SHH binds to its transmembrane receptor Patched (PTCH); there are 2 family members: PTCH1 and PTCH2. SHH binding to PTCH inhibits the activity of the transmembrane protein Smoothened (SMOH). SMOH act to suppress downstream targets of the SHH pathway, the GLI family of transcription factors, so inhibition of SMOH by PTCH results in activation of GLI1, GLI2, and GLI3, resulting in alteration of transcription of GLI targets. Somatic inactivating mutations in *PTCH1* and *PTCH2* act as tumor suppressors, whereas activating mutations in SMOH function as oncogenes, particularly in basal cell carcinomas and medulloblastomas. Germline inactivating mutations in *PTCH1* result in **Gorlin syndrome** (see Fig. 108-2), an autosomal dominant disorder characterized by dysmorphic features (short metacarpals, rib defects, broad face, and dental abnormalities), basal cell nevi that undergo malignant transformation, and an increased risk of cancers such as rhabdomyosarcoma and medulloblastoma. *GLI1* amplification has been found in several human tumors, including glioblastoma, osteosarcoma, rhabdomyosarcoma, and B-cell lymphomas; mutations or alterations in *GLI3* have been found in Greig cephalopolysyndactyly syndrome (GCPS), **Pallister-Hall syndrome** (PHS), and postaxial polydactyly type A (and

A/B) and preaxial polydactyly type IV (see Fig. 108-2). GCPS consists of hypertelorism, syndactyly, preaxial polydactyly, and broad thumbs and great toes. PHS is an autosomal dominant disorder characterized by postaxial polydactyly, syndactyly, hypothalamic hamartomas, imperforate anus, and, occasionally, holoprosencephaly. GLI3 binds to CBP, the protein that is haploinsufficient in the **Rubinstein-Taybi syndrome**. Disorders that are caused by mutations in genes that function together in a genetic developmental pathway commonly have overlapping clinical manifestations. These overlapping manifestations result from the expression domains of SHH important for development of the brain, face, limbs, and gut in the embryo. Brain defects are found in holoprosencephaly, SLOS, and PHS. Facial abnormalities are found in holoprosencephaly, Gorlin syndrome, GCPS, and PHS. Limb defects are found in SLOS, Gorlin syndrome, GCPS, PHS, and the polydactyly syndromes. Overexpression or activating mutations of the SHH pathway results in cancer, including basal cell carcinoma, medulloblastoma, glioblastoma, and rhabdomyosarcoma.

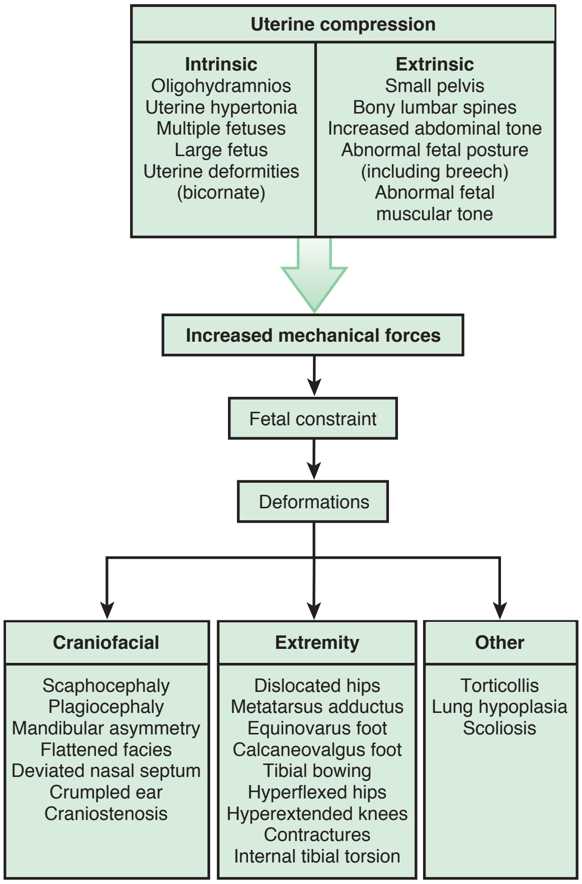

Figure 108-3 Deformation abnormalities resulting from uterine compression. *(From Kliegman RM, Jenson HB, Marcdante KJ, et al, editors:* Nelson essentials of pediatrics, *ed 5, Philadelphia, 2005, Saunders.)*

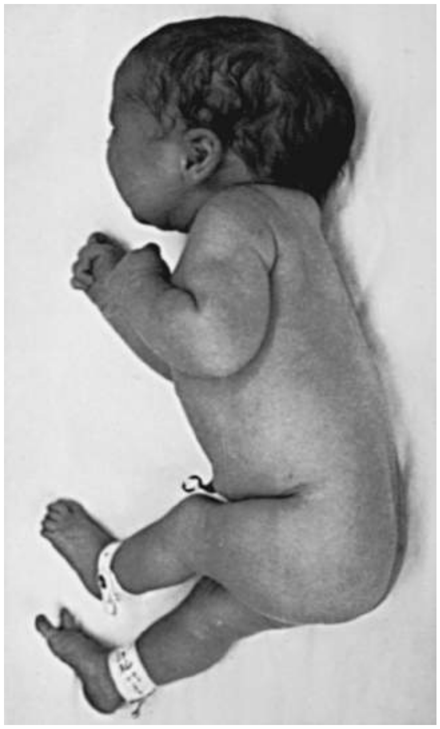

Figure 108-4 Breech deformation sequence.

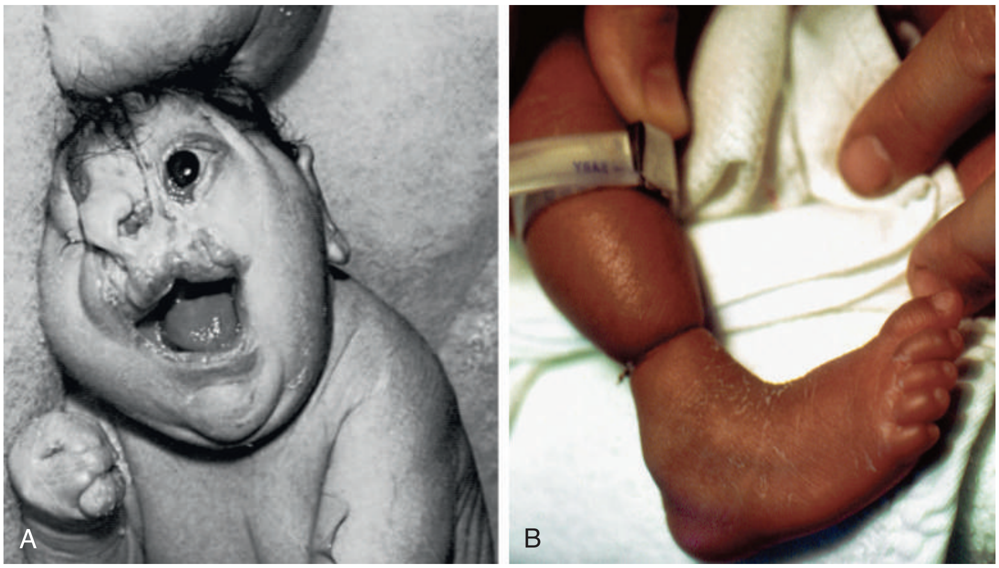

Figure 108-5 A, Amniotic band disruption sequence. **B,** Bands constricting the ankle leading to deformational defects and amputations. *(From Jones KJ:* Smith's recognizable patterns of human malformation, *ed 6, Philadelphia, 2006, Saunders.)*

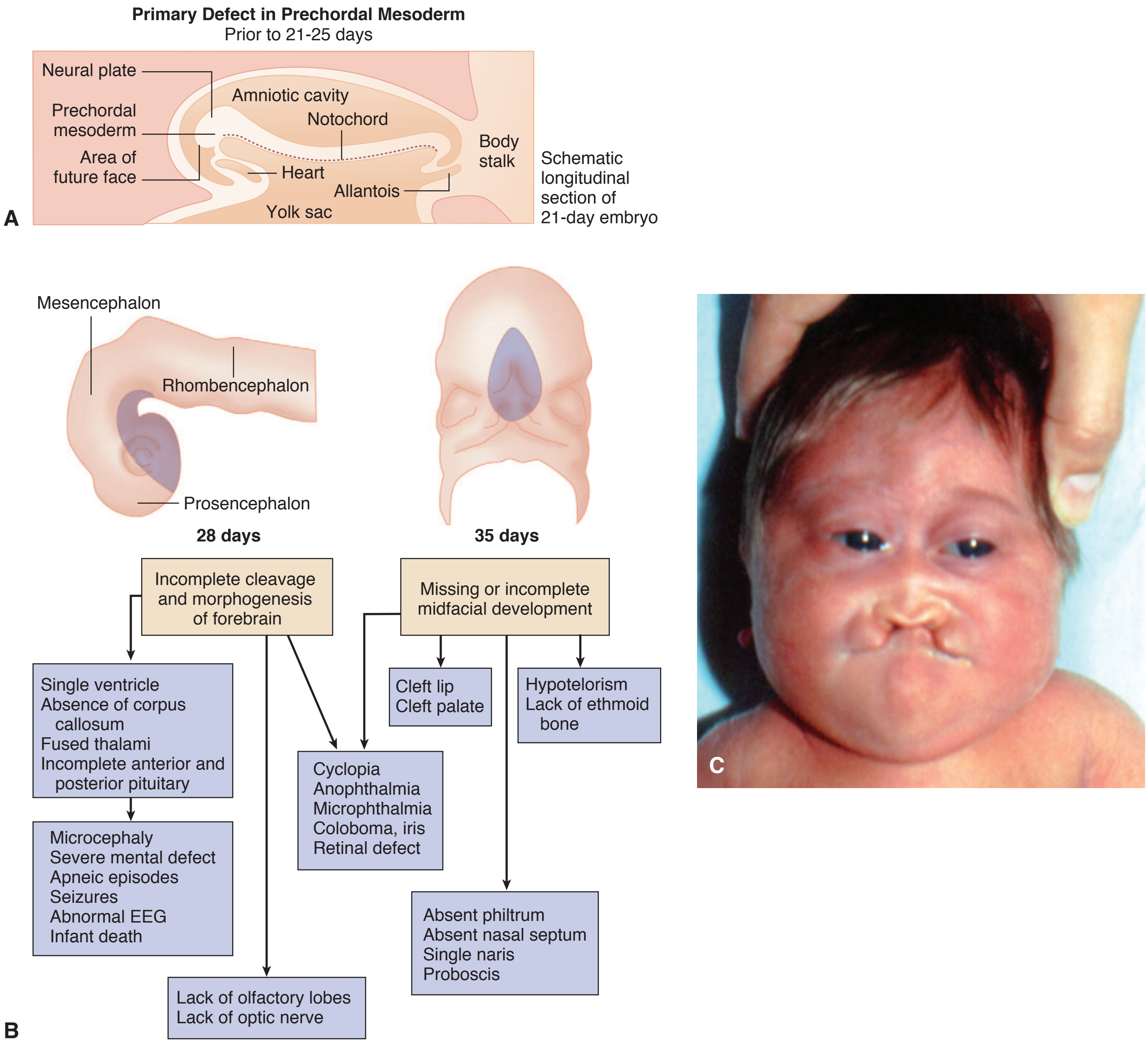

Figure 108-6 Holoprosencephaly sequence. **A,** Schematic longitudinal section of 21-day embryo. **B,** Developmental pathogenesis of the sequence. *C,* Affected individual. *(From Jones KL, Jones MC, Del Campo M, editors:* Smith's recognizable patterns of human malformation, *ed 7, Philadelphia, 2013 Elsevier, Fig. 1, pp. 802-803.)*

The SHH pathway has been shown to interact with the primary cilium, and this interaction is critical to transduce the SHH extracellular signal through to the nuclear machinery. In fact, a host of disorders, including Bardet-Biedl syndrome, oral facial digital syndrome type 1, and Joubert syndrome, are known to be caused by mutations in genes that function in the primary cilium (Table 108-4). These disorders overlap phenotypically with a number of the phenotypes described previously, again demonstrating that perturbations of conserved developmental pathways cause overlapping phenotypes.

Chromosomal Imbalances

It has been recognized for more than 50 yr that genomic imbalances that result from an additional copy of 1 whole human chromosome can result in a characteristic and recognizable syndrome. As previously discussed, an additional copy of chromosome 21 results in Down syndrome (see Chapter 81); loss of 1 of the X chromosomes results in Turner syndrome (see Chapter 81 for discussion of syndromes with whole chromosomal imbalances). With the advent of higher-resolution cytogenetics techniques and standardization of chromosome identification using chromosomal preparations, it became possible to identify subchromosomal deletions and duplications. A number of recurrent deletions and duplications were identified that resulted in characteristic and recognizable syndrome (see Chapter 81, Table 81-12), such as Williams syndrome (deletion of 7q11.23), Miller-Dieker syndrome (deletion of 17p13.3), Smith-Magenis syndrome (deletion of 17p11.2), and velocardiofacial/DiGeorge syndrome (deletion of 22q11.2). Array CGH (or single-nucleotide polymorphism–based genotyping with dosage detection) has made it possible to uncover smaller microdeletions and microduplications associated with various birth defects, mental retardation, and neuropsychiatric disorders. The sensitivity and

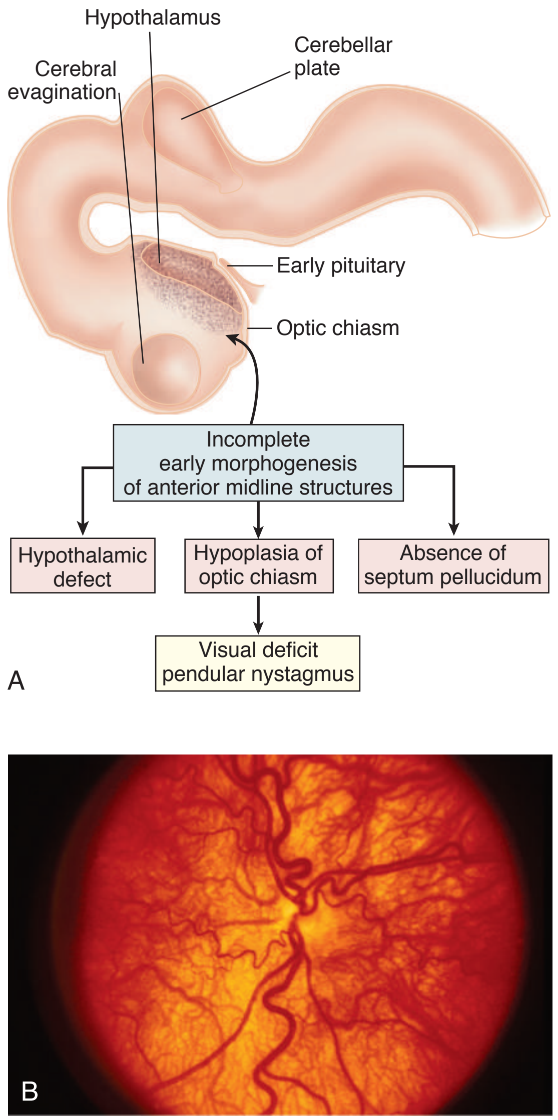

Figure 108-7 Septooptic dysplasia sequence. **A,** Presumed localization of early single defect (stippled area) as shown in sagittal view of 38 day brain. **B,** Photo of retina of 4 yr old patient with the septooptic dysplasia sequence who had reduced vision, pendular nystagmus, and growth deficiency secondary to pituitary growth hormone deficiency. Note the hypoplastic optic nerve heads and aberrant vascular arrangement. *(From Jones KL, Jones MC, Del Campo M, editors:* Smith's recognizable patterns of human malformation, *ed 7, Philadelphia, 2013, Elsevier, Fig. 1, p. 809.)*

specificity of array CGH has made it the technique of choice for the initial evaluation of a child with multiple congenital anomalies and/or mental retardation, although it is important to note that all individuals carry dozens of small microdeletions and microduplications as normal variants. Therefore, it is important to examine any of these findings in children with birth defects with parents and with databases of normal variants detected in individuals without such birth defects. Array CGH is the preferred method for detecting possible genomic abnormalities associated with multiple congenital anomalies and/or mental retardation.

APPROACH TO THE DYSMORPHIC CHILD

One approach to the dysmorphic child is the pattern-recognition approach, which compares the manifestations in the patient against an enormous and memorized (or computerized) knowledge of human pleiotropic disorders. Although this approach can be appropriate for a small number of experienced dysmorphologists, the systematic genetic-mechanism approach can be used by clinicians who are not experts in dysmorphology. By gathering and analyzing these clinical data, the general pediatrician can either diagnose the patient in the straightforward case or initiate a referral process to an appropriate expert.

History

The history for a child with birth defects includes a number of elements that are related to etiologic factors. The first is the pedigree or family history that is necessary to assess the **inheritance pattern,** or lack thereof, of the disorder. For disorders that have simple mendelian inheritance patterns, the recognition of that pattern can be critical to help narrow the differential diagnosis. A number of common birth defects have complex genetic contributions, such as isolated cleft palate and spina bifida. The recognition of a close relative (or the fetus of a close relative) affected with a birth defect that is similar to that of the proband can be quite useful. A 3-generation pedigree is sufficient for this purpose (see Chapter 80).

The perinatal history is an essential component of the history (see Chapter 94.1). It includes the pregnancy history of the mother (useful for recognition of recurrent miscarriages that may be a sign of a familial chromosomal disorder), factors that may relate to deformations or disruptions (oligohydramnios), and maternal exposures to teratogenic drugs or chemicals (methyl mercury, isotretinoin, and ethanol are potential causes of microcephaly). Although recognition of known teratogens is an important part of the history, it is important to know that many more agents are impugned as teratogenic than are confirmed as such. Physicians are encouraged to consult experts in teratology and expert information sources such as Teris (http://depts.washington.edu/~terisweb/teris) to analyze specific potential teratogens.

One final component to the history that is often useful is the natural history of the phenotype. Malformation syndromes caused by chromosomal aneuploidy or aneusomy and single-gene pleiotropic disorders are usually static. Although the patients can experience new complications over time, the phenotype is not progressive. In contrast, disorders that cause dysmorphic features by the mechanism of metabolic perturbations (e.g., Hunter syndrome, Sanfilippo syndrome) are either mild or not apparent at birth and progress relentlessly, causing deterioration of the patient over time.

Physical Examination

The physical examination is essential to the diagnosis of a dysmorphic syndrome. The essential element of the evaluation is objective assessment of the structure of the child. The clinician needs to perform an organized and systematic cataloguing of the size and structure of various body structures. Familiarity with the nomenclature of dysmorphic signs is helpful (Table 108-5). The size and shape of the head is relevant, as many children with Down syndrome have mild microcephaly and brachycephaly (shortened anteroposterior dimension of the skull). Eye position and shape are useful signs for many disorders. There are a number of reference standards with which pediatric physical measurements (e.g., interpupillary distance) can be compared. It is also useful to categorize abnormalities as "major" or "minor" birth defects. The former are those that either cause dysfunction (absence of a digit) or require surgical correction (polydactyly), and the latter those that cause neither significant dysfunction nor require surgical correction (mild cutaneous syndactyly) (Table 108-6 and Fig. 108-8). By cataloging every available physical parameter, the clinician can recognize the diagnosis or at least have enough information for intelligent discussion of the patient with a consultant.

Imaging Studies

Imaging studies can be critical in the diagnosis of a dysmorphic disorder. If short stature or disproportionate stature (long trunk and short limbs) is noted, a full skeletal survey should be performed. The skeletal survey can yield numerous abnormal features that can be used to narrow the differential diagnosis. When there are abnormal neurologic signs or symptoms, central nervous system imaging is indicated. Some

Table 108-4 Childhood Diseases and Syndromes Associated with Motile and Sensory Ciliopathies

PEDIATRIC CILIOPATHY	CLINICAL MANIFESTATIONS	GENE(S)
MOTOR		
Primary ciliary dyskinesia	Chronic bronchitis, rhinosinusitis, otitis media, laterality defects, infertility, CHD	*DNAI1, DNAH5, DNAH11, DNAI2, KTU, TXNDC3, LRRC50, RSPH9, RSPH4A, CCDC40, CCDC39*
SENSORY		
Autosomal recessive polycystic kidney disease	RFD, CHF	*PKHD1*
Nephronophthisis	RFD, interstitial nephritis, CHF, RP	*NPHP1-8, ALMS1, CEP290*
Bardet-Biedl syndrome	Obesity, polydactyly, ID, RP, renal anomalies, anosmia, CHD	*BBS1-12, MKS1, MKS3, CEP290*
Meckel-Gruber syndrome	RFD, polydactyly, ID, CNS anomalies, CHD, cleft lip, cleft palate	*MKS1-6, CC2D2A, CEP290, TMEM216*
Joubert syndrome	CNS anomalies, ID, ataxia, RP, polydactyly, cleft lip, cleft palate	*NPHP1, JBTS1, JBTS3, JBTS4, CORS2, AHI1, CEP290, TMEM216*
Alstrom syndrome	Obesity, RP, DM, hypothyroidism, hypogonadism, skeletal dysplasia, cardiomyopathy, pulmonary fibrosis	*ALMS1*
Orofaciodigital syndrome type 1	Polydactyly, syndactyly, cleft lip, cleft palate, CNS anomalies, ID, RFD	*OFD1*
Ellis van Creveld syndrome	Chondrodystrophy, polydactyly, ectodermal dysplasia, CHD	*EVC, EVC2*
Jeune asphyxiating thoracic dystrophy	Narrow thorax, RFD, RP, dwarfism, polydactyly	*IFT80*
Sensenbrenner syndrome	Dolichocephaly, ectodermal dysplasia, dental dysplasia, narrow thorax, RFD, CHD	*IFT122, IFT43, WDR35*
Short rib-polydactyly syndromes	Narrow thorax, short limb dwarfism, polydactyly, renal dysplasia	*WDR35, DYNC2H1, NEK1*

CHD, congenital heart disease; CHF, congenital hepatic fibrosis; CNS, central nervous system; DM, diabetes mellitus; ID, intellectual disabilities; RFD, renal fibrocystic disease; RP, retinitis pigmentosa.

From Ferkol TW, Leigh MW: Ciliopathies: the central role of cilia in a spectrum of pediatric disorders. J Pediatr *160:366-371, 2012.*

Table 108-5 Definitions of Common Clinical Signs of Dysmorphic Syndromes

SIGN	DEFINITION
Brachycephaly	A condition in which head shape is shortened from front to back along the sagittal plane; the back of the skull and face are flatter than normal
Brachydactyly	A condition of having short digits
Brushfield spots	Speckled white rings about ⅔ of the distance to the periphery of the iris of the eye
Camptodactyly	Permanent flexion of one or more fingers associated with missing inner phalangeal creases indicating lack of finger movement from before 8 wk of gestation
Clinodactyly	A medial or lateral curving of the fingers; usually refers to incurving of the 5th finger
Hypoplastic nail	An unusually small nail on a digit
Low-set ears	This designation is made when the helix meets the cranium at a level below a horizontal plane that is an extension of a line through both inner canthi
Melia	A suffix meaning "limb" (e.g., amelia—missing limb; brachymelia—short limb)
Ocular hypertelorism	Increased distance between the pupils of the 2 eyes, also known as increased interpupillary distance)
Plagiocephaly	A condition in which head shape is asymmetric in the sagittal or coronal plane that can result from asymmetry in suture closure or from asymmetry of brain growth
Posterior parietal hair whorl	A single whorl occurs to the right or left of midline and within 2 cm anterior to the posterior fontanel in 95% of cases. The whorl represents the focal point from which the posterior scalp skin was under growth tension during brain growth between the 10th and 16th wk of fetal development. Aberrant position of the whorl reflects an early defect in brain development
Postaxial polydactyly	Extra finger or toe present on the lateral side of the hand or foot
Preaxial polydactyly	Extra finger or toe present on the medial side of the hand or foot
Prominent lateral palatine ridges	Relative overgrowth of the lateral palatine ridges secondary to a deficit of tongue thrust into the hard palate
Scaphocephaly	A condition in which the head is elongated from front to back in the sagittal plane; most normal skulls are scaphocephalic, Also termed dolichocephaly.
Shawl scrotum	The scrotal skin joins around the superior aspect of the penis and represents a mild deficit in full migration of the labial-scrotal folds
Short palpebral fissures	Decreased horizontal distance of the eyelid folds based on measurement from the inner to the outer canthus
Syndactyly	Incomplete separation of the fingers. It most commonly occurs between the 3rd and 4th fingers and between the 2nd and 3rd toes
Synophrys	Eyebrows that meet in the midline
Telecanthus	Lateral displacement of the inner canthi. The inner canthal distance (ICD) is increased, but the interpupillary distance (IPD) is normal.
Widow's peak	V-shaped midline, downward projection of the scalp hair in the frontal region. It represents an upper forehead intersection of the bilateral fields of periocular hair growth suppression. It usually occurs because the fields are widely spaced, as in ocular hypertelorism

Table 108-6	Minor Anomalies and Phenotype Variants*
CRANIOFACIAL Large fontanel Flat or low nasal bridge Saddle nose, upturned nose Mild micrognathia Cutis aplasia of scalp	
EYE Inner epicanthal folds Telecanthus Slanting of palpebral fissures Hypertelorism Brushfield spots	
EAR Lack of helical fold Posteriorly rotated pinna Preauricular with or without auricular skin tags Small pinna Auricular (preauricular) pit or sinus Folding of helix Darwinian tubercle Crushed (crumpled) ear Asymmetric ear sizes Low-set ears	
SKIN Dimpling over bones Capillary hemangioma (face, posterior neck) Dermal melanosis (African Americans, Asians) Sacral dimple Pigmented nevi Redundant skin Cutis marmorata	
HAND Simian creases Bridged upper palmar creases Clinodactyly of 5th digit Hyperextensibility of thumbs Single flexion crease of 5th digit (hypoplasia of middle phalanx) Partial cutaneous syndactyly Polydactyly Short, broad thumb Narrow, hyperconvex nails Hypoplastic nails Camptodactyly Shortened 4th digit	
FOOT Partial syndactyly of 2nd and 3rd toes Asymmetric toe length Clinodactyly of 2nd toe Overlapping toes Nail hypoplasia Wide gap between hallux and 2nd toe (wide sandal gap) Deep plantar crease between hallux and 2nd toe	
OTHERS Mild calcaneovalgus Hydrocele Shawl scrotum Hypospadias Hypoplasia of labia majora	

*Approximately 15% of newborns have 1 minor anomaly, 0.8% have 2 minor anomalies, and 0.5% have 3 minor anomalies. If 2 minor anomalies are present, the probability of an underlying syndrome or a major anomaly (congenital heart disease, renal, central nervous system, limbic) is 5-fold that in the general population. If 3 minor anomalies are present, the probability that there is a major anomaly is 20-30%.

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, Elsevier Saunders, 2004.*

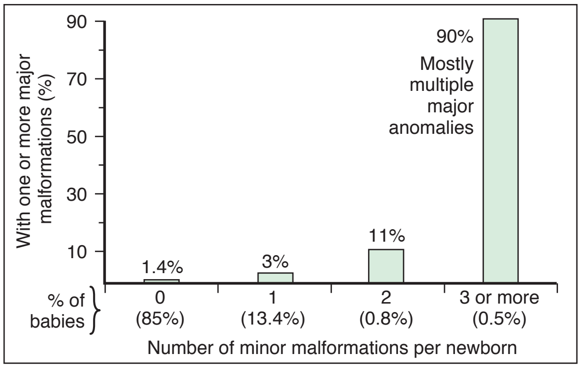

Figure 108-8 Frequency of major malformations in relation to the number of minor anomalies detected in a given newborn baby. *(From Marden PM, Smith DW, McDonald MJ: Congenital anomalies in the newborn infant, including minor variations: a study of 4,412 babies by surface examination for anomalies and buccal smear for sex chromatin.* J Pediatr *64:357, 1964.)*

Table 108-7	Clinical Indications for Chromosome Analysis, or Array CGH*
At least 1 major and 2 minor malformations At least 2 major malformations Developmental *or* growth retardation with 2 or more major or minor anomalies	

**Note:* These are guidelines, and prudence dictates the use of the chromosome analysis in cases that may not meet these general guidelines. The guidelines are for situations in which such an analysis is strongly recommended.

children with microcephaly will be recognized to have abnormal cortical migration (lissencephaly), a discovery that markedly narrows the differential diagnosis for microcephaly. Other studies, such as echocardiography and renal ultrasonography, can be useful to identify additional major or minor malformations.

Laboratory Studies

The laboratory evaluation of the dysmorphic child is helpful but complex. Cytogenetics with a Giemsa-banded (G-banded) peripheral leukocyte karyotype (or chromosome) analysis was the gold standard and was previously performed in most evaluations of the dysmorphic child (Table 108-7). Array CGH and single-nucleotide polymorphism genotyping **with copy number variation** (dosage detection) are the most sensitive methods for the detection of cytogenomic alterations associated with multiple congenital anomalies. A practical reason for ordering cytogenetic studies early in the diagnostic process is that it typically takes 7-12 days for results.

Molecular testing for mutations that cause pleiotropic developmental anomaly syndromes is available for many disorders. In most cases, however, such testing should not be performed as a screening test, but instead should be ordered thoughtfully after the differential diagnosis has been narrowed. High-throughput genomic DNA sequencing (exome sequencing or whole genome sequencing) are increasingly used as a diagnostic tool.

Historically, dysmorphic and metabolic disorders were considered distinct classes of disease. However, as in the case of the SLOS, metabolic abnormalities of the fetus can cause malformations. A general metabolic screen should be performed unless the differential diagnosis leads the clinician to strongly suspect a non-metabolic disease.

Diagnosis

The examining physician should gather data on the patient's pedigree and perinatal and pediatric (for older children) history and should

have an appreciation for the natural history of the disorder. At this point, the physician has examined the child, identified abnormal physical features, and obtained appropriate imaging studies and preliminary interpretations.

The clinician should now organize the findings by their specificity into potential developmental pathophysiologic processes. The specificity assessment is the simplest. If a child has a patent ductus arteriosus, mild growth retardation, mild microcephaly, and holoprosencephaly (MRI finding of failure to lateralize the forebrain), micropenis, and ptosis, these findings can be prioritized. The patent ductus arteriosus, ptosis, mild growth retardation, and mild microcephaly are nonspecific findings (present in many disorders or often present as isolated features not part of a syndrome), whereas holoprosencephaly and micropenis are present in fewer syndromes and are never normal variants. With this recognition, the clinician can search for disorders that include both holoprosencephaly and micropenis. The search can be performed manually using the features index of a textbook such as *Smith's Recognizable Patterns of Human Malformation* or a computerized database such as the Winter-Baraitser Dysmorphology Database (www.lmdatabases.com/about_lmd.html). Searching for disorders with both findings leads quickly to a modest list of only 21 disorders. One of these is SLOS. The identification of this possible diagnosis prompts the physician to return to the bedside, realize that many of the nonspecific features in the child are common in SLOS, and make a tentative diagnosis of this disorder. Although holoprosencephaly is an uncommon manifestation of SLOS, this manifestation makes sense because of the known pathogenetic link between sonic hedgehog and cholesterol biosynthesis. Because this disorder is caused by mutations in the sterol delta-7-dehydrocholesterol reductase gene and is associated with elevated 7-dehydrocholesterol, the pediatrician can initiate a consultation with the clinical geneticist for suspected SLOS. The consultant can then confirm the diagnosis and begin the process of identifying a laboratory to verify the diagnosis.

Management and Counseling

Management of the affected patient and genetic counseling are essential aspects of the approach to the dysmorphic patient. Children with Down syndrome have a high incidence of hypothyroidism, and children with achondroplasia have a high incidence of cervicomedullary junction constriction. Herein lies one of the many benefits of early and accurate diagnosis, because anticipatory guidance and medical monitoring of patients for syndrome-specific medical risks can prolong and improve their quality of life. When a diagnosis is made, the treating physicians can refer to published information on the natural history and management of particular syndromes through articles, genetics reference texts, online databases and, for more common disorders, general pediatric texts.

The second major benefit of an accurate diagnosis is that it provides data for appropriate recurrence risk estimates. Genetic disorders may have direct effects on only one member of the family, but the diagnosis of the condition has implications for the entire family. One or both parents may be carriers; siblings may be carriers or may wish to know their at-risk status when they reach their reproductive years. Recurrence risk provision is 1 facet of genetic counseling, which should be a component of all evaluations for families affected with birth defects or other heritable disorders (see Chapter 77).

As we understand the underlying pathophysiology of genetic disorders, particularly with respect to the developmental pathways that are disrupted by mutant genes, it will likely be possible to identify potential therapeutic targets amenable to pharmacologic intervention. Once such potential therapies are devised, the precise delineation of the syndrome responsible for the multiple congenital anomalies displayed by an individual will lead to institution of the appropriate intervention for modulating symptoms or even to ameliorate aspects of the phenotype.

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Chapter 109

Infections of the Neonatal Infant

Barbara J. Stoll and Andi L. Shane

109.1 Pathogenesis and Epidemiology

Despite advances in maternal and neonatal care, infections remain a frequent and important cause of neonatal and infant morbidity and mortality. As many as 2% of fetuses are infected in utero, and up to 10% of infants have infections in the 1st mo of life. Neonatal infections are unique in several ways:

1. Infectious agents can be transmitted from the mother to the fetus or newborn infant by diverse modes.
2. The fetus and newborn infant are less capable of responding to infection because of immunologic immaturity. Preterm infants are at particular risk.
3. Coexisting conditions often complicate the diagnosis and management of neonatal infections.
4. The clinical manifestations of newborn infections vary and include subclinical infection, mild to severe manifestations of focal or systemic infection, and, rarely, congenital syndromes resulting from in utero infection. The timing of exposure, inoculum size, immune status, and virulence of the etiologic agent influence the expression of disease.
5. Maternal infection, the source of transplacental fetal infection, is often undiagnosed during pregnancy because the mother was either asymptomatic or had nonspecific signs and symptoms at the time of acute infection.
6. A wide variety of etiologic agents infect the newborn, including bacteria, viruses, fungi, protozoa, and mycoplasmas.

Although survival has increased for immature, very-low birth-weight (VLBW) newborns, they remain in the hospital for a long time in an environment that puts them at continuous risk for acquired infections.

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109.2 Modes of Transmission and Pathogenesis

PATHOGENESIS OF INTRAUTERINE INFECTION

Intrauterine infection is a result of clinical or subclinical maternal infection with a variety of agents (cytomegalovirus [CMV], *Treponema pallidum, Toxoplasma gondii,* rubella virus, varicella virus, parvovirus B19) and hematogenous transplacental transmission to the fetus. Transplacental infection may occur at any time during gestation, and signs and symptoms may be present at birth or may be delayed for months or years (Fig. 109-1). Infection may result in early spontaneous abortion, congenital malformation, intrauterine growth restriction, premature birth, stillbirth, acute or delayed disease in the neonatal period, or asymptomatic persistent infection with sequelae later in life. In some cases, no apparent effects are seen in the newborn infant.

The timing of infection during gestation affects the outcome. First-trimester infection may alter embryogenesis, with resulting congenital malformations (congenital rubella) (see Chapter 247). Third-trimester infection often results in active infection at the time of delivery (toxoplasmosis, syphilis) (see Chapters 290 and 218). Infections that occur late in gestation may lead to a delay in clinical manifestations until after birth (syphilis).

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Maternal infection is a necessary prerequisite for transplacental infection. For some etiologic agents (rubella), maternal immunity is effective and antibody is protective for the fetus. For other agents (CMV), maternal antibody may ameliorate the outcome of infection or may have no effect (see Chapter 255). Even without maternal antibody, transplacental transmission of infection to a fetus is variable because the placenta may function as an effective barrier.

PATHOGENESIS OF ASCENDING BACTERIAL INFECTION

In most cases, the fetus or neonate is not exposed to potentially pathogenic bacteria until the membranes rupture and the infant passes through the birth canal and/or enters the extrauterine environment. The human birth canal is colonized with aerobic and anaerobic organisms that may result in ascending amniotic infection and/or colonization of the neonate at birth. Vertical transmission of bacterial agents that infect the amniotic fluid and/or vaginal canal may occur in utero or, more commonly, during labor and/or delivery (Fig. 109-2). **Chorioamnionitis** results from microbial invasion of amniotic fluid, often as a result of prolonged rupture of the chorioamniotic membrane. Amniotic infection may also occur with apparently intact membranes or with a relatively brief duration of membrane rupture. The term *chorioamnionitis* refers to the clinical syndrome of intrauterine infection, which includes maternal fever, with or without local or systemic signs of chorioamnionitis (uterine tenderness, foul-smelling vaginal discharge/amniotic fluid, maternal leukocytosis, maternal and/or fetal tachycardia). Chorioamnionitis may also be asymptomatic, diagnosed only by amniotic fluid analysis or pathologic examination of the placenta. The rate of histologic chorioamnionitis is inversely related to gestational age at birth (Fig. 109-3) and directly related to duration of membrane rupture. Rupture of membranes for longer than 24 hr was once considered prolonged because microscopic evidence of inflammation of the membranes is uniformly present when the duration of rupture exceeds 24 hr. At 18 hr of membrane rupture, however, the incidence of early-onset disease with group B streptococcus (GBS) increases significantly; 18 hr is the appropriate cutoff for increased risk of neonatal infection.

Bacterial colonization does not always result in disease. Factors influencing which colonized infant will experience disease are not well understood but include prematurity, underlying illness, invasive procedures, inoculum size, virulence of the infecting organism, genetic predisposition, the innate immune system, host response, and transplacental maternal antibodies (Fig. 109-4). Aspiration or ingestion of bacteria in amniotic fluid may lead to congenital pneumonia or systemic infection, with manifestations becoming apparent before delivery (fetal distress, tachycardia), at delivery (failure to breathe, respiratory distress, shock), or after a latent period of a few hours (respiratory distress, shock). Aspiration or ingestion of bacteria during the birth process may lead to infection after an interval of 1-2 days.

Resuscitation at birth, particularly if it involves endotracheal intubation, insertion of an umbilical vessel catheter, or both, is associated with an increased risk of bacterial infection. Explanations include the presence of infection at the time of birth or acquisition of infection during the invasive procedures associated with resuscitation.

PATHOGENESIS OF LATE-ONSET POSTNATAL INFECTIONS

After birth, neonates are exposed to infectious agents in the nursery or in the community (including family). Postnatal infections may be

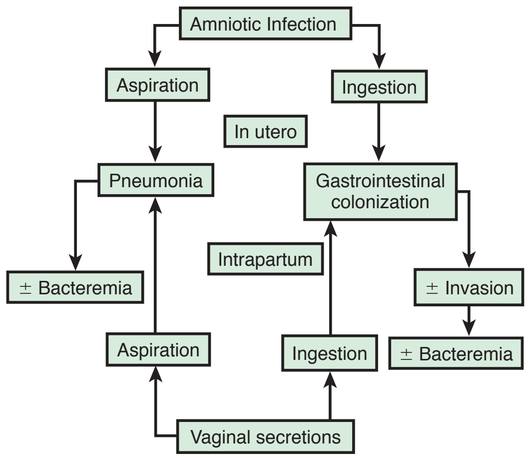

Figure 109-2 Pathways of ascending or intrapartum infection.

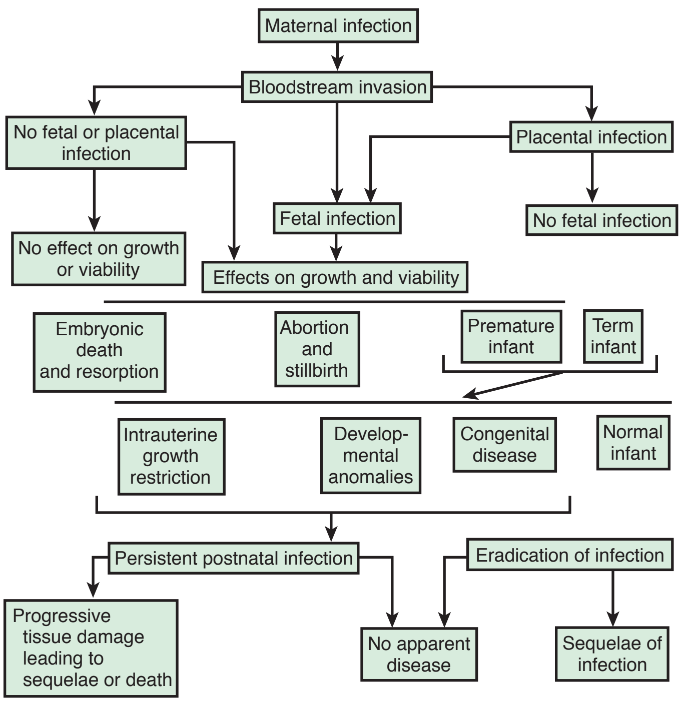

Figure 109-1 Pathogenesis of hematogenous transplacental infections. *(From Klein JO, Remington JS: Current concepts of infections of the fetus and newborn infant. In Remington JS, Klein JO, editors:* Infectious diseases of the fetus and newborn infant, *ed 5, Philadelphia, 2002, WB Saunders.)*

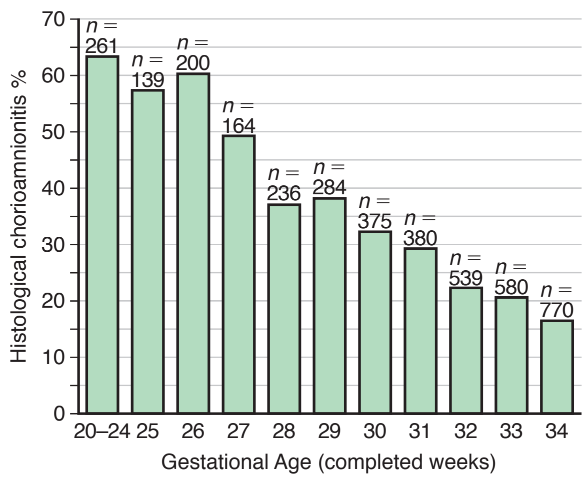

Figure 109-3 Histologic chorioamnionitis in liveborn preterm babies by gestational age (n = 3,928 babies). *(From Lahra MM, Jeffery HE: A fetal response to chorioamnionitis is associated with early survival after preterm birth,* Am J Obstet Gynecol *190:147–151, 2004.)*

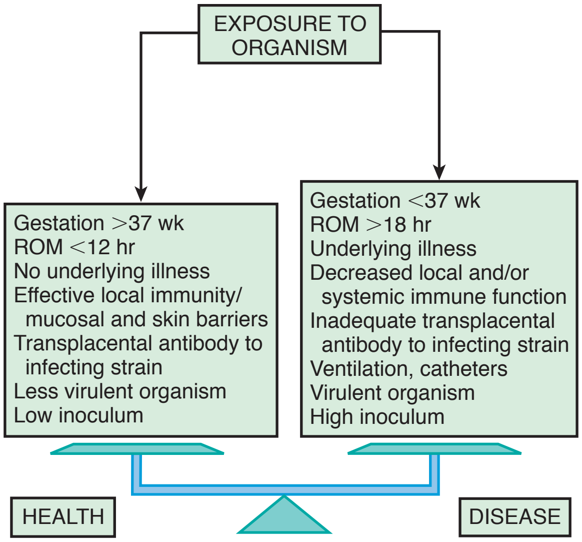

Figure 109-4 **Factors influencing the balance between health and disease in neonates exposed to a potential pathogen.** ROM, rupture of membranes. *(Adapted from Baker CJ: Group B streptococcal infections,* Clin Perinatol *24:59–70, 1997.)*

transmitted by direct contact with hospital personnel, the mother, or other family members; from breast milk (HIV, CMV); or from inanimate sources such as contaminated equipment. The most common source of postnatal infections in hospitalized newborns is hand contamination of healthcare personnel, underscoring the importance of handwashing.

Most cases of meningitis result from hematogenous dissemination. Less often, meningitis results from contiguous spread as a result of contamination of open neural tube defects, congenital sinus tracts, or penetrating wounds from fetal scalp sampling or internal fetal electrocardiographic monitors. Abscess formation, ventriculitis, septic infarcts, hydrocephalus, and subdural effusions are complications of meningitis that occur more often in newborn infants than in older children.

Bibliography is available at Expert Consult.

109.3 Immunity

During the 1st 3 mo of life, the innate immune system, including phagocytes, natural killer cells, antigen presenting cells, and complement provide defense against pathogens. With advancing age and exposures, the acquired immune system develops and assumes a more prominent role in host defense. Decreased function of neutrophils and low concentrations of immunoglobulins increases the susceptibility of preterm infants to invasive infection. Group B streptococci, *Escherichia coli*, herpes simplex virus (HSV), CMV, varicella-zoster virus (VZV), respiratory syncytial virus (RSV), enteroviruses, and *Candida* species are notable pathogens in the early neonatal period.

IMMUNOGLOBULIN

Immunoglobulin (Ig) G is actively transported across the placenta, with concentrations in a full-term infant comparable to or higher than maternal levels, because of a combination of both acquired and neonatally produced IgG in the third trimester. In premature infants, cord IgG levels are directly proportional to gestational age; at 18-20 wk, IgG levels are <100 mg/dL and reach 400 mg/dL by 30-32 wk of gestation. Levels of maternally derived IgG fall rapidly after birth in a process termed “physiologic hypogammaglobulinemia,” with notable implications for premature and small-for-gestational-age neonates, whose IgG levels are often reduced compared with term and appropriate-for-gestational-age neonates. Other classes of immunoglobulins (IgA, IgM, IgD, and IgE) are not transferred across the placenta, therefore elevated cord blood levels of IgA and IgM may be evidence of an intrauterine infection. A predisposition to Gram-negative infections in the neonate may be explained by the inefficiency of neonatally produced IgM to provide opsonins to these organisms. Maternal IgG is an efficient opsonin for Gram-positive organisms but is less so for Gram-negative pathogens.

Term and premature infants are able to mount immune responses to protein antigens including tetanus, diphtheria, hepatitis, and polio but are impaired in their ability to respond to polysaccharide antigens such as *Haemophilus influenzae* type b and group B streptococci. Conjugate vaccines join polysaccharide antigens to immunogenic proteins giving the appearance of a T-cell dependent antigen to the immature neonatal immune system.

COMPLEMENT

A fetus begins to synthesize complement components during weeks 6-14 of gestation; transplacental passage of complement from the maternal circulation does not occur. The complement system mediates bactericidal activity against certain organisms such as *E. coli* and functions as an opsonin with antibody in the phagocytosis of GBS. Full-term newborn infants have slightly diminished classical pathway complement activity and moderately diminished alternative pathway activity. Considerable variability, however, is seen in both the concentration and activity of complement components. Premature infants have lower levels of complement components and less complement activity, and have notably reduced levels of C9, important for Gram-negative bacterial lysis and assembly of the membrane attack complex. These deficiencies contribute to diminished complement-derived chemotactic activity and to a lesser ability to opsonize certain organisms in the absence of antibody.

NEUTROPHILS

Neutrophil Function

Term and late preterm neonates have impaired neutrophil function compared with that of older infants. Quantitative and qualitative deficiencies of the phagocyte system contribute to the newborn's susceptibility to infection. Neutrophil migration (chemotaxis), adhesion, aggregation, and deformability, all of which may be impaired in the neonate, may delay the response to infection. Abnormal expression of cell membrane adhesion molecules (the β_2 integrins and selectins) and abnormalities in the neonatal neutrophil cytoskeleton contribute to impaired chemotaxis. Impairment of the oxidative respiratory burst of neonatal neutrophils is a factor in the increased risk of sepsis, especially in preterm infants. Neutrophil granules contain enzymes; one noted protein is bactericidal/permeability-increasing protein (BPI) that binds to the endotoxin in the cell wall of Gram-negative bacteria. BPI facilitates opsonization and prevents the inflammatory response to endotoxin. BPI activity may be decreased in neonates.

Neutrophil Number

Neutropenia appears to be a better predictor of neonatal sepsis than leukocytosis, although neutropenic ranges differ by gestational age, mode of delivery, altitude of location of birth, and sampling methods. Neonates have a 70-80% reduction in bone marrow neutrophil stores compared to adults and therefore are impaired in their response to infectious and noninfectious stressors. Increasing neutrophil number with granulocyte colony-stimulating factors (G-CSFs) or granulocyte-macrophage colony-stimulating factors (GM-CSFs), cytokines that stimulate myeloid progenitor cells, does not appear to affect clinical outcomes. Band neutrophils constitute less than 15% in normal newborns and may increase in newborns with infection and other stress responses, such as asphyxia.

Natural Killer Cells

Natural killer (NK) cells are a subgroup of lymphocytes that are cytolytic against cells infected with viruses. NK cells also lyse cells coated with antibody in a process called antibody-dependent cell-mediated cytotoxicity. NK cells appear early in gestation and are present in cord

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blood in numbers equivalent to those in adults; neonatal NK cells have an approximately 50% decrease in cytotoxic activity and antibody-dependent cell-mediated cytotoxicity in comparison with NK cells from adults.

CYTOKINES/INFLAMMATORY MEDIATORS

Several adverse outcomes, including brain injury, necrotizing enterocolitis, and bronchopulmonary dysplasia (BPD), may be mediated by an unbalanced cytokine (proinflammatory vs. antiinflammatory) response to infection. The release of tumor necrosis factor-α, interleukin (IL)-1 (IL-1), IL-4, IL-6, IL-8, IL-10, IL-12, platelet-activating factor, and the leukotrienes offers the potential opportunity to facilitate an early laboratory diagnosis of infection.

Functional categorization of T-helper (Th) 1 and Th2 responses is based on cytokine secretion and function. The Th1 response is directed against intracellular organisms and is relatively impaired in neonates, possibly accounting for the predisposition to severe clinical outcomes with infections with intracellular pathogens.

Innate immunity involves nonspecific cellular and humoral responses to an infectious agent without previous exposure. Recognition of pathogens is initiated by soluble components in plasma (including mannose-binding lectin) and by recognition of receptors on monocytes and other cells. Toll-like receptors play an important role in pathogen recognition.

Bibliography is available at Expert Consult.

109.4 Etiology of Fetal and Neonatal Infection

A number of bacterial and nonbacterial (Table 109-1) agents may infect newborns in utero, intrapartum, or postpartum. Intrauterine transplacental infections of significance to the fetus and/or newborn include syphilis, rubella, CMV, toxoplasmosis, parvovirus B19, and varicella. Although HSV, HIV, hepatitis B virus, hepatitis C virus, and tuberculosis (TB) can each result in transplacental infection, the most common mode of transmission for these agents is intrapartum, during labor and delivery with passage through an infected birth canal (HIV, HSV, hepatitis B virus), or postpartum, from contact with an infected mother or caretaker (TB) or with infected breast milk (HIV).

Any microorganism inhabiting the genitourinary or lower gastrointestinal tract may cause intrapartum and postpartum infection. The most common bacteria are GBS and *E. coli*. The more common viruses are CMV, HSV, enteroviruses, and HIV.

Agents that commonly cause **healthcare-associated infections (HAIs)** in the newborn include coagulase-negative staphylococci, Gram-negative bacilli *(E. coli, Klebsiella pneumoniae, Enterobacter, Pseudomonas aeruginosa),* enterococci, *Staphylococcus aureus,* and *Candida.* Viruses contributing to HAIs in the neonate include enteroviruses, CMV, hepatitis A, adenoviruses, influenza, RSV, rhinovirus, parainfluenza, HSV, and rotavirus. Community-acquired pathogens such as *Streptococcus pneumoniae* may also cause infection in newborn infants after discharge from the hospital.

Congenital pneumonia may be caused by CMV, rubella virus, and *T. pallidum* and, less commonly, by the other agents producing transplacental infection (Table 109-2). Microorganisms causing pneumonia acquired during labor and delivery include GBS, Gram-negative enteric aerobes, *Listeria monocytogenes,* genital *Mycoplasma, Chlamydia trachomatis,* CMV, HSV, and *Candida* species.

Bacteria responsible for most cases of nosocomial pneumonia typically include staphylococcal species, Gram-negative enteric aerobes, and occasionally, *Pseudomonas.* Fungi are responsible for an increasing number of systemic infections, usually acquired during prolonged hospitalization of preterm neonates. Respiratory viruses cause isolated cases and outbreaks of nosocomial pneumonia. These viruses, usually endemic during the winter months and acquired from infected hospital staff or visitors to the nursery, include RSV, parainfluenza virus, influenza viruses, and adenovirus. Respiratory viruses are the single most important cause of community-acquired pneumonia and are usually contracted from infected household contacts.

The most common bacterial causes of **neonatal meningitis** are GBS, *E. coli,* and *L. monocytogenes. S. pneumoniae,* other streptococci, nontypable *H. influenzae,* both coagulase-positive and coagulase-negative staphylococci, *Klebsiella, Enterobacter, Pseudomonas, T. pallidum,* and *Mycobacterium tuberculosis* infection involving the central nervous system may also result in meningitis.

Bibliography is available at Expert Consult.

Table 109-1 Nonbacterial Causes of Systemic Neonatal Infections

VIRUSES	MYCOPLASMA / FUNGI / PROTOZOA
Adenovirus	**MYCOPLASMA**
CMV	*Mycoplasma hominis*
Enteroviruses	*Ureaplasma urealyticum*
Parechoviruses	**FUNGI**
Hepatitis B virus	*Candida* species
HSV	*Malassezia* species
HIV	**PROTOZOA**
Parvovirus	Plasmodia
Rubella virus	*Toxoplasma gondii*
VZV	*Trypanosoma cruzi*

109.5 Epidemiology of Early- and Late-Onset Neonatal Infections

The terms *early-onset infection* and *late-onset infection* refer to the different ages at onset of infection in the neonatal period. Although these disorders were originally divided arbitrarily into infections occurring before and after 1 wk of life, it is more useful to separate early- and late-onset infections according to peripartum pathogenesis. Early-onset infections are acquired before or during delivery (vertical mother-to-child transmission). Late-onset infections develop after delivery from organisms acquired in the hospital or the community. The age at onset depends on the timing of exposure and virulence of the infecting organism. Very-late-onset infections (onset after 1 mo of

Table 109-2 Etiologic Agents of Neonatal Pneumonia According to Timing of Acquisition

TRANSPLACENTAL / PERINATAL	POSTNATAL
TRANSPLACENTAL	Adenovirus
CMV	*Candida* species*
HSV	Coagulase-negative staphylococci
Mycobacterium Tuberculosis	CMV
Rubella virus	Enteric bacteria*
Treponema pallidum	Enteroviruses
VZV	Influenza viruses A, B
PERINATAL	Parainfluenza
Anaerobic bacteria	*Pseudomonas**
Chlamydia	RSV
CMV	*Staphylococcus aureus*
Enteric bacteria	*Mycobacterium tuberculosis*
Group B streptococci	
Haemophilus influenzae	
HSV	
Listeria monocytogenes	
Mycoplasma	

*More likely with mechanical ventilation or indwelling catheters, or after abdominal surgery.

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life) may also occur, particularly in VLBW preterm infants or term infants requiring prolonged neonatal intensive care.

The incidence of neonatal bacterial sepsis varies from 1-4/1,000 live births, with geographic variation and changes over time. Studies suggest that term male infants have a higher incidence of sepsis than term females. This sex difference is less clear in preterm low birthweight (LBW) infants. Attack rates of neonatal sepsis increase significantly in LBW infants in the presence of maternal chorioamnionitis, congenital immune defects, mutations of genes involved in the innate immune system, asplenia, galactosemia *(E. coli),* and malformations leading to high inocula of bacteria (obstructive uropathy).

Data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network documented rates of early-onset sepsis among almost 400,000 live births at Network centers. The overall rate of early-onset sepsis was 0.98 cases per 1,000 live births with rates inversely related to birthweight (401-1500 g birthweight, 10.96/1000; 1501-2500 g birthweight, 1.38/1000; >2500 g birthweight, 0.57/1000) (Table 109-3).

Intrapartum antibiotics are used to reduce vertical transmission of GBS as well as to lessen neonatal morbidity after preterm rupture of membranes. With introduction of selective intrapartum antibiotic prophylaxis to prevent perinatal transmission of GBS, rates of early-onset neonatal GBS infection in the United States declined from 1.7/1,000 live births to 0.25/1,000, according to U.S. Centers for Disease Control and Prevention (CDC) surveillance data. Intrapartum chemoprophylaxis does not reduce the rates of late-onset GBS disease and has no effect on the rates of infection with non-GBS pathogens. Of concern is a possible increase in gram-negative infections (especially *E. coli*) in VLBW and possibly term infants in spite of a reduction in early GBS sepsis by intrapartum antibiotics.

The incidence of meningitis is 0.2-0.4/1,000 live births in newborn infants and is higher in preterm infants. Bacterial meningitis may be associated with sepsis or may occur as a local meningeal infection. *Up to one-third of VLBW infants with late-onset meningitis have negative blood culture results.* The discordance between results of blood and cerebrospinal fluid (CSF) cultures suggests that meningitis may be underdiagnosed among VLBW infants and emphasizes the need for culture of CSF in VLBW infants when late-onset sepsis is suspected and in all infants who have positive blood culture results.

PREMATURITY

The most important neonatal factor predisposing to infection is prematurity or LBW. Preterm LBW infants have a 3- to 10-fold higher incidence of infection than full-term normal birthweight infants. Possible explanations include: (a) maternal genital tract infection is considered to be an important cause of preterm labor, with an increased risk of vertical transmission to the newborn (Fig. 109-5); (b) the frequency of intraamniotic infection is inversely related to gestational age (see Fig. 109-3); (c) premature infants have documented immune dysfunction; and (d) premature infants often require prolonged

Table 109-3 Rates of Early-Onset Sepsis Per 1,000 Live Births: NICHD Neonatal Research Network/CDC Surveillance Study of Early-Onset Sepsis

	BIRTHWEIGHT (g)			
	401-1,500	**1,501-2,500**	**>2,500**	**All**
All	10.96	1.38	0.57	0.98
GBS	2.08	0.38	0.35	0.41
Escherichia coli	5.09	0.54	0.07	0.28

Modified from Stoll BJ, Hansen NI, Sanchez PJ, et al: Early onset neonatal sepsis: the burden of group B streptococcal and E. coli *disease continues,* Pediatrics *127(5):817–826, 2011.*

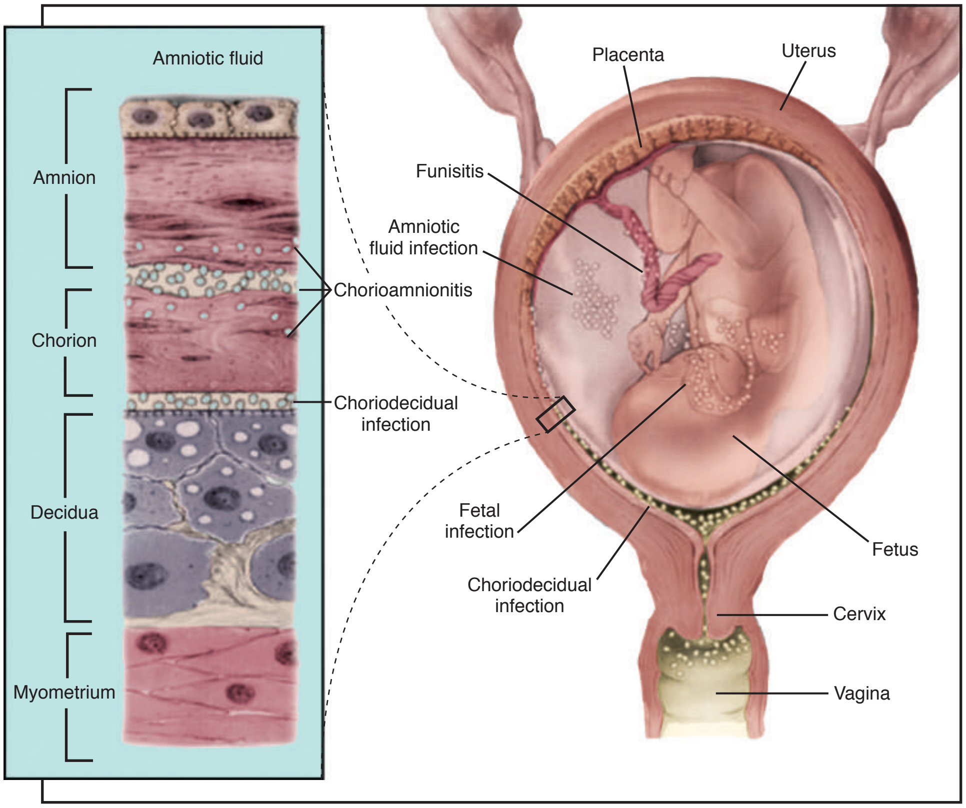

Figure 109-5 Potential sites of bacterial infection within the uterus. *(From Goldenberg RL, Hauth JA, Andrews WW: Intrauterine infection and preterm delivery,* N Engl J Med *342:1500–1507, 2000. Copyright 2000, Massachusetts Medical Society.)*

intravenous access, endotracheal intubation, or other invasive procedures that provide a portal of entry or impair barrier and clearance mechanisms, putting them at continued risk for hospital-acquired infections.

Bibliography is available at Expert Consult.

109.6 Healthcare–Associated Infections (HAI)

HAIs are responsible for significant morbidity and late mortality in hospitalized newborns, with almost 25% of VLBW infants (<1,500 g birthweight) experiencing 1 or more nosocomial infections. The majority of HAIs occur in preterm or term infants who require intensive care. Risk factors for HAIs in these infants include prematurity, low birthweight, invasive procedures, indwelling vascular catheters, parenteral nutrition with lipid emulsions, endotracheal tubes, ventricular shunts, alterations in the skin and/or mucous membrane barriers, frequent use of broad-spectrum antibiotics, and prolonged hospitalization. The most frequent HAIs are bloodstream infections associated with intravascular catheters and ventilator-associated pneumonia. HAIs may also occur in the absence of a catheter or ventilator. Infants receiving intensive care are at risk for community or HAIs during seasonal epidemics (RSV, influenza). Neonatal immunization during the birth hospitalization is the most reliable point of healthcare contact.

Rates of HAIs increase with decreasing birthweight and gestational age. The NICHD Neonatal Research Network has reported rates of 43% for infants weighing 401-750 g; 28% for those weighing 751-1,000 g; 15% for those weighing 1,001-1,250 g; and 7% for those weighing 1,251-1,500 g. It also reports rates of 36% for infants 22-28 wk gestational age (58% at 22 wk; 62% at 23 wk; 55% at 24 wk; 46% at 25 wk; 35% at 26 wk; 27% at 27 wk and 20% at 28 wk). The CDC National Healthcare Safety Network monitors device-associated nosocomial infection rates. Rates are inversely related to birthweight, and in level III neonatal intensive care units (NICUs), they range from 3.7 infections per 1,000 central line days for infants weighing <750 g to 2.0 infections per 1,000 central line days for those weighing >2,500 g. The widespread differences in practice regarding the inclusion of lumbar puncture (LP) in the diagnostic evaluation of an infant with suspected sepsis make it more difficult to determine rates of late-onset meningitis. The mean age at onset of the first episode of late-onset HAI sepsis occurs during 2-3 wk of life, independent of the infecting pathogen. HAIs increase the risk of adverse outcomes, including prolonged hospitalization and mortality.

Various bacterial and fungal agents colonize hospitalized infants, healthcare workers, and visitors. Pathogenic agents can be transmitted by direct contact or indirectly via contaminated equipment, intravenous fluids, medications, blood products, or enteral feedings. Colonization of the infant's skin, umbilicus, and respiratory or gastrointestinal tract with pathogenic agents often precedes the development of infection. Antibiotic use interferes with colonization by normal flora, thereby permitting colonization with more virulent pathogens.

Coagulase-negative staphylococci are the most frequent neonatal HAI. In a cohort of 6,215 VLBW infants in the NICHD Neonatal Research Network, Gram-positive organisms were associated with 70%, Gram-negative with 18%, and fungi with 12% of episodes of late-onset sepsis; coagulase-negative staphylococci, the single most common organism, was isolated in 48% of these infections. The emergence of bacterial pathogens resistant to multiple antibiotics is a growing concern. The emergence of methicillin-resistant *S. aureus,* vancomycin-resistant enterococci, and multidrug-resistant Gram-negative pathogens are particularly alarming. Organisms responsible for neonatal bacterial sepsis and meningitis as well as HAIs fluctuate with antimicrobial pressure.

Viral pathogens including RSV, varicella, influenza, rotavirus, and enteroviruses may be responsible for sporadic infections or for outbreaks in the NICU. Infection prevention policies, including immunization of healthcare providers, visitors, and neonates, when feasible, are essential to prevent and/or contain nursery infection outbreaks. During clusters of infections, outbreaks, or epidemics, investigation of possible reservoirs of infection, modes of transmission, and risk factors is necessary. Identification of colonized infants and nursery personnel may be helpful. Prevention of transmission includes adherence to standard precautions with all patient contact, maintaining a manageable unit census with appropriate nurse : patient ratios, strict compliance with hand hygiene, meticulous neonatal skin care, minimizing the risk of catheter contamination, decreasing the number of venipunctures and heelsticks, reducing the duration of catheter and mechanical ventilation days, encouraging appropriate advancement of enteral feedings, providing education and feedback to nursery personnel, and ongoing monitoring and surveillance of HAIs in the NICU. Evidenced-based care bundles have been developed for many procedures that may predispose a neonate to an HAI. Among those frequently practiced, intravascular central catheter insertion and care practices are frequently bundled.

Hand hygiene remains the most important and effective means of reducing HAIs. Proper hand hygiene with either soap and water or alcohol-based hand sanitizers is essential before and after each patient contact. The use of gloves does not obviate the need for hand hygiene. Skin to skin contact has proven beneficial to the neonate, however ensuring that the contact is with pathogen-free skin is essential. Ongoing education of staff regarding practices that are likely to reduce HAIs and promote active surveillance are important components of infection prevention.

Bibliography is available at Expert Consult.

109.7 Clinical Manifestations of Transplacental Intrauterine Infections

Infection with agents that cross the placenta (CMV, *T. pallidum, T. gondii,* rubella, parvovirus B19) may be asymptomatic at birth or may cause a spectrum of disease ranging from relatively mild symptoms to multisystem involvement with severe and life-threatening complications. For some agents, disease is characterized by chronicity, recurrence, or both, and the agent may cause ongoing injury. Clinical signs and symptoms do not help make a specific etiologic diagnosis but, rather, raise suspicion of an intrauterine infection and help distinguish these infections from acute bacterial infections that occur during labor and delivery. The following signs and symptoms are common to many of these agents (Table 109-4): intrauterine growth restriction, microcephaly or hydrocephalus, intracranial calcifications, chorioretinitis, cataracts, myocarditis, pneumonia, hepatosplenomegaly, direct hyperbilirubinemia, anemia, thrombocytopenia, hydrops fetalis, and skin manifestations. Many of these agents cause late sequelae, even if the infant is asymptomatic at birth. These adverse outcomes include sensorineural hearing loss, visual disturbances (including blindness), seizures, and neurodevelopmental abnormalities.

BACTERIAL SEPSIS

Neonates with bacterial sepsis may have either nonspecific signs and symptoms or focal signs of infection (Table 109-5), including temperature instability, hypotension, poor perfusion with pallor and mottled skin, metabolic acidosis, tachycardia or bradycardia, apnea, respiratory distress, grunting, cyanosis, irritability, lethargy, seizures, feeding intolerance, abdominal distention, jaundice, petechiae, purpura, and bleeding. Table 109-6 lists World Health Organization international criteria for bacterial sepsis. The initial manifestation may involve only limited symptomatology and only 1 system, such as apnea alone or tachypnea with retractions, or tachycardia, or the infant may present with an acute catastrophic manifestation with multiorgan dysfunction. Infants should be reevaluated over time to determine whether the symptoms have progressed from mild to severe. Later complications

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Table 109-4 Clinical Manifestations of Transplacental Infections

MANIFESTATION	PATHOGEN
Intrauterine growth restriction	CMV, *Plasmodium*, rubella, toxoplasmosis, *Treponema pallidum, Trypanosoma cruzi*, VZV
Congenital anatomic defects:	
Cataracts	Rubella
Cardiac defects	Rubella
Hydrocephalus	HSV, lymphocytic choriomeningitis virus, rubella, toxoplasmosis
Intracranial calcification	CMV, HIV, toxoplasmosis, *T. cruzi*
Limb hypoplasia	VZV
Microcephaly	CMV, HSV, rubella, toxoplasmosis
Microphthalmos	CMV, rubella, toxoplasmosis
Neonatal organ involvement:	
Anemia	CMV, parvovirus, *Plasmodium,* rubella, toxoplasmosis, *T. cruzi, T. pallidum*
Carditis	Coxsackieviruses, rubella, *T. cruzi*
Encephalitis	CMV, enteroviruses, HSV, rubella, toxoplasmosis, *T. cruzi, T. pallidum*
Hepatitis	CMV, enteroviruses, HSV
Hepatosplenomegaly	CMV, enteroviruses, HIV, HSV, *Plasmodium,* rubella, *T. cruzi, T. pallidum*
Hydrops	Parvovirus, *T. pallidum,* toxoplasmosis
Lymphadenopathy	CMV, HIV, rubella, toxoplasmosis, *T. pallidum*
Osteitis	Rubella, *T. pallidum*
Petechiae, purpura	CMV, enteroviruses, rubella, *T. cruzi*
Pneumonitis	CMV, enteroviruses, HSV, measles, rubella, toxoplasmosis, *T. pallidum,* VZV
Retinitis	CMV, HSV, lymphocytic choriomeningitis virus, rubella, toxoplasmosis, *T. pallidum,* West Nile virus
Rhinitis	Enteroviruses, *T. pallidum*
Skin lesions	Enteroviruses, HSV, measles, rubella, *T. pallidum,* VZV
Thrombocytopenia	CMV, enteroviruses, HIV, HSV, rubella, toxoplasmosis, *T. pallidum*
Late sequelae:	
Convulsions	CMV, enteroviruses, rubella, toxoplasmosis
Deafness	CMV, rubella, toxoplasmosis
Dental/skeletal problems	Rubella, *T. pallidum*
Endocrinopathies	Rubella, toxoplasmosis
Eye pathology	HSV, rubella, toxoplasmosis, *T. cruzi, T. pallidum,* VZV
Hepatitis	Hepatitis B
Mental retardation	CMV, HIV, HSV, rubella, toxoplasmosis, *T. cruzi,* VZV
Nephrotic syndrome	*Plasmodium, T. pallidum*

of sepsis include respiratory failure, pulmonary hypertension, cardiac failure, shock, renal failure, liver dysfunction, cerebral edema or thrombosis, adrenal hemorrhage and/or insufficiency, bone marrow dysfunction (neutropenia, thrombocytopenia, anemia), and disseminated intravascular coagulopathy (DIC).

A variety of noninfectious conditions can occur together with neonatal infection or can make the diagnosis of infection more difficult. Respiratory distress syndrome (RDS) secondary to surfactant deficiency can coexist with bacterial pneumonia. Because bacterial sepsis can be rapidly progressive, the physician must be alert to the signs and symptoms of possible infection and must initiate diagnostic evaluation and empirical therapy in a timely manner. The **differential diagnosis** of many of the signs and symptoms that suggest infection is extensive; noninfectious disorders must also be considered (Table 109-7).

Table 109-5 Initial Signs and Symptoms of Infection in Newborn Infants

GENERAL Fever, temperature instability "Not doing well" Poor feeding Edema	CARDIOVASCULAR SYSTEM Pallor; mottling; cold, clammy skin Tachycardia Hypotension Bradycardia
GASTROINTESTINAL SYSTEM Abdominal distention Vomiting Diarrhea Hepatomegaly	CENTRAL NERVOUS SYSTEM Irritability, lethargy Tremors, seizures Hyporeflexia, hypotonia Abnormal Moro reflex Irregular respirations Full fontanel High-pitched cry
RESPIRATORY SYSTEM Apnea, dyspnea Tachypnea, retractions Flaring, grunting Cyanosis	HEMATOLOGIC SYSTEM Jaundice Splenomegaly Pallor Petechiae, purpura Bleeding
RENAL SYSTEM Oliguria	

Table 109-6 Clinical Criteria for the Diagnosis of Sepsis in the International Setting

Integrated Management of Childhood Illness (IMCI) and WHO Criteria for Severe Infections in Children
NEUROLOGIC: convulsions, drowsy or unconscious, decreased activity, bulging fontanel
RESPIRATORY: respiratory rate >60 breaths/min, grunting, severe chest indrawing, central cyanosis
CARDIAC: poor perfusion, rapid and weak pulse
GASTROINTESTINAL: jaundice, poor feeding, abdominal distention
DERMATOLOGIC: skin pustules, periumbilical erythema or purulence
MUSCULOSKELETAL: edema or erythema overlying bones or joints
OTHER: Temperature >37.7°C (99.9°F; or feels hot) or <35.5°C (95.9°F; or feels cold)

Adapted from World Health Organization: Pocket book of hospital care for children: guidelines for the management of common childhood illnesses *ed 2, 2013:45–69. Available at* http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/*, accessed July 2013.*

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

The clinical manifestations of infection depend on the virulence of the infecting organism and the body's inflammatory response. The term *systemic inflammatory response syndrome (SIRS)* is most frequently used to describe this unique process of infection and the subsequent systemic response (see Chapters 70 and 177). In addition to infection, SIRS may result from trauma, hemorrhagic shock, other causes of ischemia, necrotizing enterocolitis, and pancreatitis.

Patients with SIRS have a spectrum of clinical symptoms that represent progressive stages of the pathologic process. In adults, SIRS is defined by the presence of 2 or more of the following: (1) fever or hypothermia, (2) tachycardia, (3) tachypnea, and (4) abnormal white blood cell (WBC) count or an increase in immature forms. In neonates

Table 109-7 Serious Systemic Illness in Newborns: Differential Diagnosis of Neonatal Sepsis

CARDIAC Congenital: hypoplastic left heart syndrome, other structural disease, persistent pulmonary hypertension of the newborn (PPHN) Acquired: myocarditis, hypovolemic or cardiogenic shock, PPHN
GASTROINTESTINAL Necrotizing enterocolitis Spontaneous gastrointestinal perforation Structural abnormalities Hepatic failure (inborn errors of metabolism, neonatal iron storage disease)
HEMATOLOGIC Neonatal purpura fulminans Immune-mediated thrombocytopenia Immune-mediated neutropenia Severe anemia Malignancies (congenital leukemia) Langerhans cell histiocytosis Hereditary clotting disorders Familial hemophagocytosis syndrome
METABOLIC Hypoglycemia Adrenal disorders: Adrenal hemorrhage, adrenal insufficiency, congenital adrenal hyperplasia Inborn errors of metabolism: Organic acidurias, lactic acidoses, urea cycle disorders, galactosemia
NEUROLOGIC Intracranial hemorrhage: spontaneous, caused by child abuse Hypoxic-ischemic encephalopathy Neonatal seizures Infant botulism
RESPIRATORY Respiratory distress syndrome Aspiration pneumonia: amniotic fluid, meconium, or gastric contents Lung hypoplasia Tracheoesophageal fistula Transient tachypnea of the newborn

and pediatric patients, SIRS manifests as temperature instability, respiratory dysfunction (altered gas exchange, hypoxemia, acute respiratory distress syndrome), cardiac dysfunction (tachycardia, delayed capillary refill, hypotension), and perfusion abnormalities (oliguria, metabolic acidosis) (Table 109-8). Increased vascular permeability results in capillary leak into peripheral tissues and the lungs, with resultant peripheral and pulmonary edema. DIC results in the more severely affected cases. The cascade of escalating tissue injury may lead to multisystem organ failure and death.

Table 109-8 Definitions of Systemic Inflammatory Respiratory Response Syndrome and Sepsis in Pediatric Patients

SIRS: The systemic inflammatory response to a variety of clinical insults, manifested by 2 or more of the following conditions:
- Temperature instability <35°C (95°F) or >38.5°C (101.3°F)
- Respiratory dysfunction:
  - Tachypnea >2 SD above the mean for age
  - Hypoxemia (PaO_2 <70 mm Hg on room air)

Cardiac dysfunction:
- Tachycardia >2 SD above the mean for age
- Delayed capillary refill >3 sec
- Hypotension >2 SD below the mean for age

Perfusion abnormalities:
- Oliguria (urine output <0.5 mL/kg/hr)
- Lactic acidosis (elevated plasma lactate and/or arterial pH <7.25)
- Altered mental status

Sepsis: The systemic inflammatory response to an infectious process

From Adams-Chapman I, Stoll BJ: Systemic inflammatory response syndrome, Semin Pediatr Infect Dis *12:5–16, 2001.*

Fever

Only approximately 50% of infected newborn infants have a temperature higher than 37.8°C (100°F) (axillary) (see Chapters 176, 177). Fever in newborn infants does not always signify infection; it may be caused by increased ambient temperature, isolette or radiant warmer malfunction, dehydration, central nervous system (CNS) disorders, hyperthyroidism, familial dysautonomia, or ectodermal dysplasia. A single temperature elevation is infrequently associated with infection; fever sustained over 1 hr is more likely to be caused by infection. Most febrile infected infants have additional signs compatible with infection, although a focus of infection is not always apparent. Acute febrile illnesses occurring later in the neonatal period may be caused by urinary tract infection, meningitis, pneumonia, osteomyelitis, or gastroenteritis, in addition to sepsis, thus underscoring the importance of a diagnostic evaluation that includes blood culture, urine culture, LP, and other studies as indicated. Many agents may cause these late infections, including HSV, enteroviruses, RSV, and bacterial pathogens. In premature infants, hypothermia or temperature instability requiring increasing ambient (isolette, warmer) temperatures is more likely to accompany infection.

Rash

Cutaneous manifestations of infection include omphalitis, cellulitis, mastitis, and subcutaneous abscesses. **Ecthyma gangrenosum** is indicative of infection with *Pseudomonas* species. The presence of small salmon-pink papules suggests *L. monocytogenes* infection. A vesicular rash is consistent with herpesvirus infection. The mucocutaneous lesions of *Candida albicans* are discussed elsewhere (see Chapter 234.1). Petechiae and purpura may have an infectious cause. Purple papulonodular lesions are referred to as "blueberry muffin" rash and represent dermal erythropoiesis. Causes include congenital viral infections (CMV, rubella, and parvovirus), congenital neoplastic disease, and Rh hemolytic disease.

Omphalitis

Omphalitis is a neonatal infection resulting from unhygienic care of the umbilical cord, which continues to be a problem, particularly in developing countries. The umbilical stump is colonized by bacteria from the maternal genital tract and the environment (see Chapter 105). The necrotic tissue of the umbilical cord is an excellent medium for bacterial growth. Omphalitis may remain a localized infection or may spread to the abdominal wall, the peritoneum, the umbilical or portal vessels, or the liver. Abdominal wall cellulitis or necrotizing fasciitis, with associated sepsis and a high mortality rate, may develop in infants with omphalitis. Prompt diagnosis and treatment are necessary to avoid serious complications.

Tetanus

See also Chapter 211.

Neonatal tetanus is a serious neonatal infection in developing countries. It results from unclean delivery and unhygienic management of the umbilical cord in an infant born to a mother who has not been immunized against tetanus. The surveillance **case definition** of neonatal tetanus requires the ability of a newborn to suck at birth and for the 1st few days of life, followed by an inability to suck starting between 3 and 10 days of age, difficulty swallowing, spasms, stiffness, seizures, and death. Bronchopneumonia, presumably resulting from aspiration, is a common complication and cause of death. Neonatal tetanus is a preventable disease. It can be prevented by immunizing mothers before or during pregnancy and by ensuring a clean delivery, sterile cutting of the umbilical cord and proper cord care after birth.

Pneumonia

Early signs and symptoms of pneumonia may be nonspecific, including poor feeding, lethargy, irritability, cyanosis, temperature instability, and the overall impression that the infant is not well. Respiratory symptoms of increasing severity are grunting, tachypnea, retractions, flaring of the alae nasi, cyanosis, apnea, and progressive respiratory failure. If the infant is premature, signs of progressive respiratory distress may be superimposed upon RDS or BPD. For infants on mechanical ventilation, the need to increase ventilator support may indicate infection.

Signs of pneumonia on physical examination, such as dullness to percussion, change in breath sounds, and the presence of rales or rhonchi, are very difficult to appreciate in a neonate. Radiographs of the chest may reveal new infiltrates or an effusion, but if the neonate has underlying RDS or BPD, it is very difficult to determine whether the radiographic changes represent a new process or worsening of the underlying disease.

The progression of neonatal pneumonia can be variable. Fulminant infection is most commonly associated with pyogenic organisms such as GBS (see Chapter 184). Onset may occur during the 1st hours or days of life, with the infant often manifesting rapidly progressive circulatory collapse and respiratory failure. With early-onset pneumonia, the clinical course and radiographs of the chest may be indistinguishable from those with severe RDS.

In contrast to the rapid progression of pneumonia caused by pyogenic organisms, an indolent course may be seen in nonbacterial infection. The onset can be preceded by upper respiratory tract symptoms or conjunctivitis. The infant may demonstrate a nonproductive cough, and the degree of respiratory compromise is variable. Fever is usually absent, and radiographic examination of the chest shows focal or diffuse interstitial pneumonitis. Infection is generally caused by *C. trachomatis,* CMV, *Ureaplasma urealyticum,* or 1 of the respiratory viruses. Rhinovirus has been reported to cause severe respiratory compromise in infants, particularly those who are preterm. Although *Pneumocystis (carinii) jiroveci* was implicated in the original description of this syndrome, its etiologic role is now in doubt, except in newborns infected with HIV.

Bibliography is available at Expert Consult.

109.8 Intrapartum and Peripartum Infections

The maternal history provides important information about maternal exposures to infectious diseases, bacterial colonization, immunity (natural and acquired), and obstetric risk factors (prematurity, prolonged ruptured membranes, maternal chorioamnionitis).

Sexually transmitted infections (STIs) acquired by a pregnant woman are of particular concern to the fetus and newborn because of the potential for intrauterine or perinatal transmission. All pregnant women and their partners should be queried about a history of STIs. Women should also be counseled about the need for timely diagnosis and therapy for infections during pregnancy. The CDC recommends the following screening tests and treatment when indicated:

1. All pregnant women should be offered voluntary and confidential HIV testing at the first prenatal visit, as early in pregnancy as possible. HIV screening should be part of routine prenatal testing, unless the mother declines testing (opt-out screening). For women at high risk of infection during pregnancy (multiple sexual partners or STIs during pregnancy, intravenous drug use, HIV-infected partners), repeat testing in the 3rd trimester is recommended. Rapid HIV screening is indicated for any women who presents in labor with an undocumented HIV status, unless she declines testing.
2. A serologic test for syphilis should be performed on all pregnant women at the first prenatal visit. Repeat screenings early in the 3rd trimester and again at delivery are recommended for women in whom syphilis test results in the 1st trimester were positive and for those at high risk for infection during pregnancy. Infants should not be discharged from the hospital unless the syphilis status of the mother has been determined at least once during pregnancy and preferably again at delivery.
3. Serologic testing for hepatitis B surface antigen (HBsAg) should be performed at the first prenatal visit, even if the woman has been previously vaccinated or tested. Women who were not screened prenatally, those who are at high risk for infection (multiple sexual partners, intravenous drug use, HBsAg-positive sex partner) and those with clinical hepatitis should be retested at the time of delivery.
4. A maternal genital culture for *C. trachomatis* should be performed at the first prenatal visit. Young women (<25 yr) and those at increased risk for infection (new or multiple partners during pregnancy) should be retested during the 3rd trimester.
5. A maternal culture for *Neisseria gonorrhoeae* should be performed at the first prenatal visit. Those at high risk for infection should be retested in the 3rd trimester.
6. All pregnant women at high risk for hepatitis C infection (intravenous drug use, blood transfusion or organ transplantation before 1992) should be screened for hepatitis C antibodies at the first prenatal visit.
7. Evidence does not support routine testing for bacterial vaginosis in pregnancy. For asymptomatic women at high risk for preterm delivery, testing may be considered. Symptomatic women should be tested and treated.
8. The CDC recommends universal screening for rectovaginal GBS colonization of all pregnant women at 35-37 wk gestation, and a screening-based approach to selective intrapartum antibiotic prophylaxis against GBS (Table 109-9 and Figs. 109-6 and 109-7; Chapter 184). Figure 109-8 shows the approach to the infant born after intrapartum prophylaxis.

Suspected Intrauterine Infection

The acronym *TORCH* refers to toxoplasmosis, other agents (syphilis, varicella, parvovirus B19, HIV), rubella, CMV, and HSV. Although the acronym may be helpful in remembering some of the etiologic agents of intrauterine infection, the TORCH battery of serologic tests has a poor diagnostic yield. *Instead, individual diagnostic studies should be selected for each etiologic agent under consideration*. CMV and HSV require culture or polymerase chain reaction (PCR) methods; toxoplasmosis is diagnosed by serologic tests and PCR, whereas syphilis and rubella are diagnosed by serologic methods. Furthermore, reaching a definitive diagnosis of a congenital infection and dating the infection may require assessment of maternal diagnostic testing. Neonatal antibody titers are often difficult to interpret because (1) IgG is acquired from the mother by transplacental passage and (2) determination of neonatal IgM titers to specific pathogens is technically difficult to perform and is not universally available. IgM titers to specific pathogens have high specificity but only moderate sensitivity; they should not be used to preclude infection. Paired maternal and fetal-neonatal IgG titers showing higher newborn IgG levels or rising IgG titers during infancy may be used to diagnose some congenital infections (syphilis). Total cord blood IgM or IgA (neither is actively transported across the placenta to the fetus) and the presence of IgM–rheumatoid factor in neonatal serum are nonspecific tests for intrauterine infection.

If the likelihood of maternal infection with a known teratogenic agent is high, fetal ultrasound examination is recommended. If the examination demonstrates either a physical abnormality or delayed growth for gestational age, examination of a fetal blood sample may be warranted. **Cordocentesis** can provide a sufficient sample for both total and pathogen-specific IgM assays, for PCR, or for culture. The total IgM value is important because the normal fetal IgM level is <5 mg/dL. Any elevation in total IgM may indicate an underlying fetal infection. Specific IgM antibody tests are available for CMV, *T. pallidum,* parvovirus B19, and toxoplasmosis. IgM tests are useful when the

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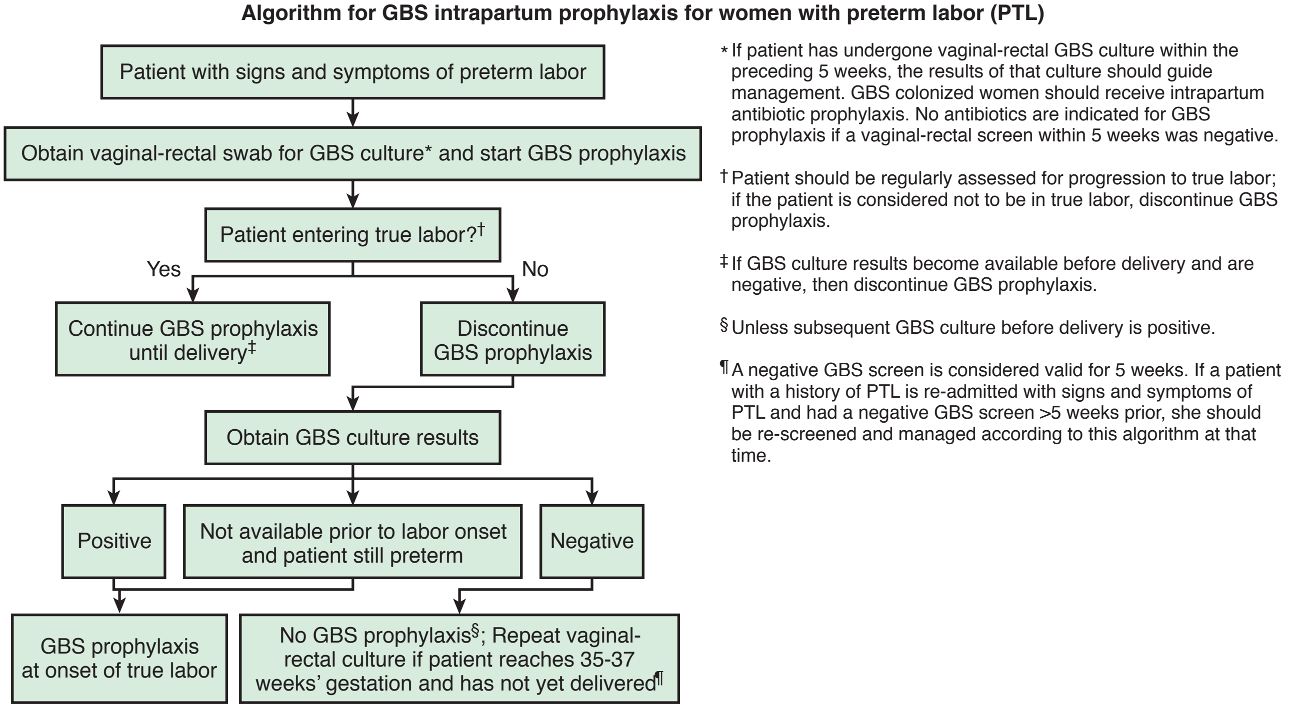

Figure 109-6 Algorithm for GBS intrapartum prophylaxis for women with preterm labor. *(From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010,* MMWR Recomm Rep *59[RR-10]:1–36, 2010.)*

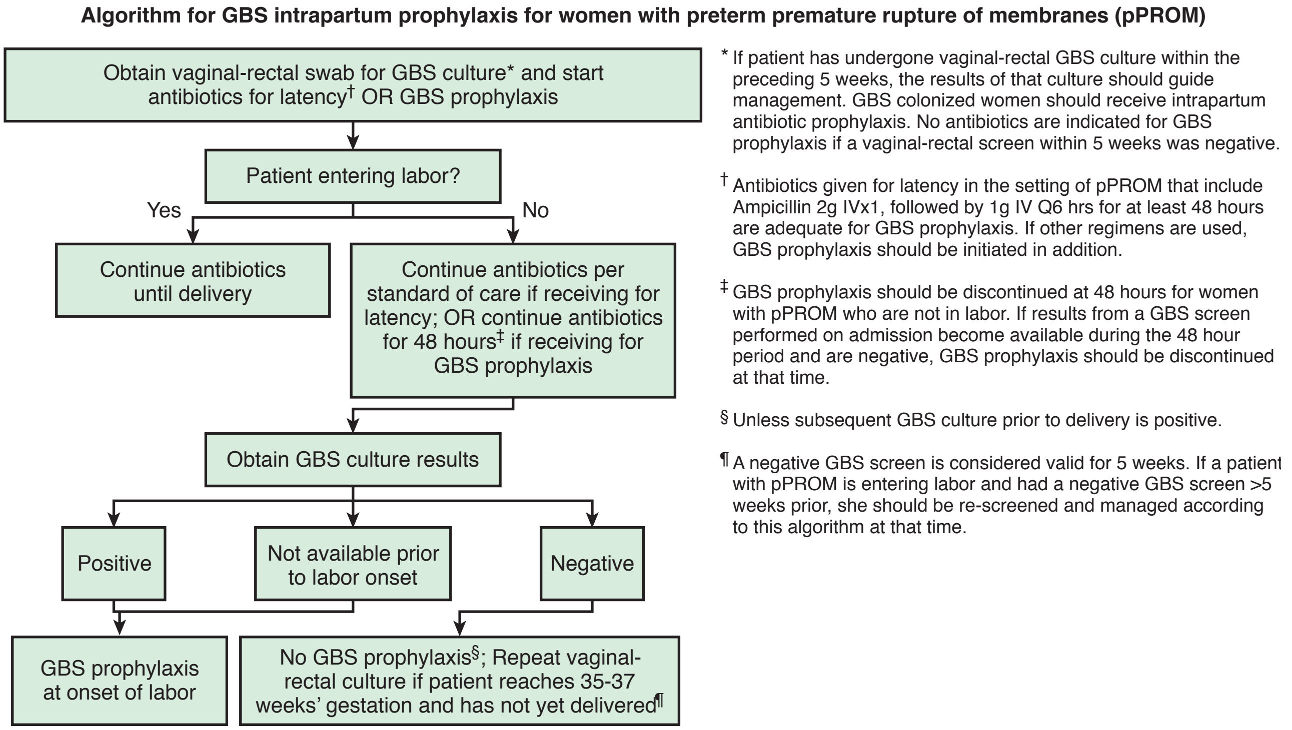

Figure 109-7 Algorithm for GBS intrapartum prophylaxis for women with preterm premature rupture of membranes. *(From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010,* MMWR Recomm Rep *59[RR-10]:1–36, 2010.)*

results are strongly positive; however a negative pathogen-specific IgM result does not rule out that pathogen as a cause of fetopathy.

If maternal serologic studies point to a specific pathogen, it is sometimes possible to detect the organism in amniotic fluid or fetal blood (culture, PCR). Amniocentesis can be performed and the fluid sent for analysis. The presence of CMV, *Toxoplasma*, or parvovirus in amniotic fluid indicates that the fetus is infected and at high risk, but it does not always mean that the fetus will have severe sequelae. In contrast, HSV and VZV are rarely isolated from amniotic fluid samples. Parvovirus does not grow in the cell cultures commonly available in the virology

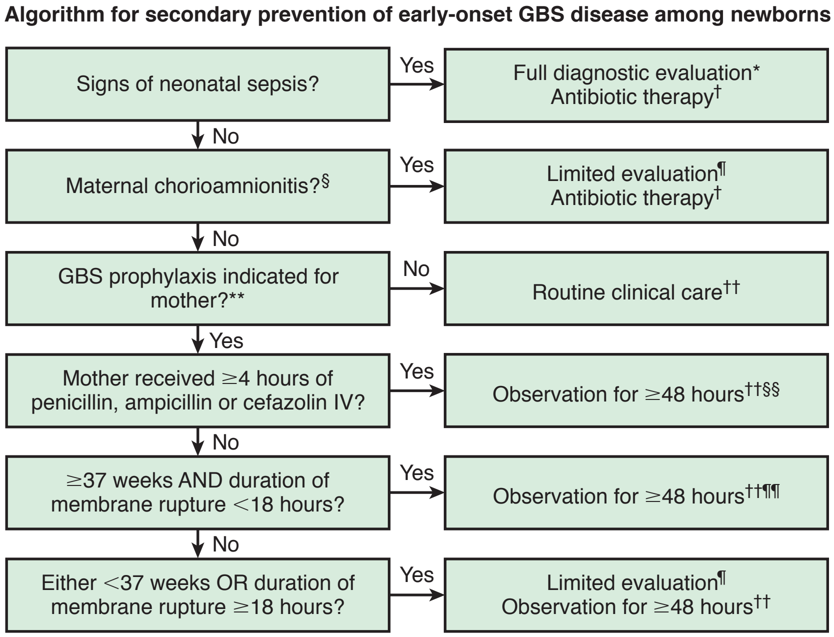

* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and LP (if patient stable anough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens), and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth), and CBC with differential and platelets (at birth and/or at 6-12 hours of life).

** GBS prophylaxis indicated in one or more of the following: (1) mother GBS positive within preceding 5 weeks, (2) GBS status unknown with one or more intrapartum risk factors including <37 weeks' gestation, ROM ≥18 hours or T ≥100.4°F (38.0°C), (3) GBS bacteriuria during current pregnancy, (4) history of a previous infant with GBS disease.

†† If signs of sepsis develop, a full diagnostic evaluation should be done and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, there is ready access to medical care, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at 6-12 hours of age.

Figure 109-8 Algorithm for secondary prevention of early-onset GBS disease among newborns. *(From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010, MMWR Recomm Rep 59[RR-10]:1–36, 2010.)*

Table 109-9 Indications for Intrapartum Antibiotic Prophylaxis to Prevent Early-Onset GBS Disease

INTRAPARTUM GBS PROPHYLAXIS INDICATED	INTRAPARTUM GBS PROPHYLAXIS NOT INDICATED
Previous infant with invasive GBS disease	Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
GBS bacteriuria during any trimester of the current pregnancy	GBS bacteriuria during previous pregnancy (unless another indication for GBS prophylaxis is present for current pregnancy)
Positive GBS screening culture during current pregnancy (unless a cesarean delivery is performed before onset of labor or amniotic membrane rupture)	Cesarean delivery before onset of labor or amniotic membrane rupture, regardless of GBS colonization status or gestational age
Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following: Delivery at <37 weeks' gestation* Amniotic membrane rupture ≥18 hr Intrapartum temperature ≥38.0°C (100.4°F)† Intrapartum NAAT‡ positive for GBS	Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

*Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Figures 109-7 and 109-8.
†If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.
‡If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 weeks' gestation, amniotic membrane rupture ≥18 hr, or temperature ≥38.0°C[100.4°F]) is present, then intrapartum antibiotic prophylaxis is indicated.
GBS, group B streptococcus; NAAT, nucleic acid amplification test.
From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010, MMWR Recomm Rep *59(RR-10):1–36, 2010.*

laboratory. An IgM response is dependent on the timing of the primary infection in relationship to specimen acquisition. When fetal parvovirus infection is suspected, testing of fetal blood or amniotic fluid by PCR is recommended in addition to testing for a specific IgM response in the fetus. PCR may also be used for the diagnosis of toxoplasmosis, CMV, HSV, rubella, and syphilis.

Neonatal infections with CMV, *Toxoplasma,* rubella, HSV, and syphilis present a diagnostic dilemma because (1) their clinical features overlap and may initially be indistinguishable; (2) disease may be unapparent; (3) maternal infection is often asymptomatic; (4) special laboratory studies may be needed; and (5) appropriate management of toxoplasmosis, syphilis, CMV, and HSV, is predicated on an accurate diagnosis. Common shared features that should suggest the diagnosis of an intrauterine infection include intrauterine growth restriction, hematologic involvement (anemia, neutropenia, thrombocytopenia, petechiae, purpura), ocular signs (chorioretinitis, cataracts, keratoconjunctivitis, glaucoma, microphthalmos), CNS involvement (microcephaly, aseptic meningitis, hydrocephaly, intracranial calcifications), other organ system involvement (pneumonia, myocarditis, nephritis, hepatitis with hepatosplenomegaly, jaundice), and nonimmune hydrops. Diagnostic studies in newborns with suspected intrauterine infections should test for each potential etiology individually with acute and convalescent titers. Hepatic dysfunction, with abnormal liver functions tests, may be seen in infants with CMV, HSV, and enteroviral infections. Neonatal HSV disease should be confirmed by PCR identification of HSV from the CSF and blood. Given that approximately 30% of infants infected with HSV present with isolated mucocutaneous manifestations, swabs of any skin lesions, the conjunctiva, and oral and rectal mucosa should also be performed in all infants with suspected HSV disease. Enzyme Linked Virus Inducible System (ELVIS), a simple, 24-hr cell culture test for detecting HSV, compares favorably to standard cell culture sensitivity. HIV PCR testing should be routinely performed on infants with suspected or confirmed congenital infections that may have been cotransmitted with another etiology (HSV, toxoplasmosis). Although exposure cannot be differentiated from infection until 4-6 mo of age, empiric treatment and monitoring may prevent the sequelae of a vertically transmitted HIV infection. Maternal HIV testing is essential to provide guidance regarding breastfeeding practices to the mother of a potentially exposed/infected neonate.

Bibliography is available at Expert Consult.

109.9 Suspected Bacterial or Fungal Infections

Bacterial and fungal infections are diagnosed by isolating the etiologic agent from a normally sterile body site (blood, CSF, urine, joint fluid). Obtaining 2 blood culture specimens by venipuncture from different sites avoids confusion caused by skin contamination and increases the likelihood of bacterial detection. Samples for blood culture should be obtained from an umbilical catheter only at the time of initial insertion. A peripheral venous sample should also be obtained when blood is drawn for culture from central venous catheters or from peripherally inserted central catheters (PICC lines). Although blood cultures are usually the basis for a diagnosis of bacterial infection, the bacteremic phase of the illness may be missed by poor timing of cultures or inadequate blood volume sampled. Low-level bacteremia (<10 colony-forming units/mL) has been observed in some infants from birth to 2 mo of age with positive culture results, however 1-2 mL of blood should increase microorganism recovery in the face of low-colony-count sepsis. Automated blood culture systems (BACTEC, Becton Dickinson; BacT/Alert, Organon Teknika), which continuously monitor blood cultures by checking each bottle every few minutes, result in earlier detection of bacterial growth. After positive signaling in the automated system, the specific pathogen is identified by biochemical tests. PCR technology is emerging for more rapid accurate identification of a number of viral and bacterial agents. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry may assist with early identification of pathogens from blood cultures, optimizing empirical antibiotic therapy in the setting of bloodstream infections. This emerging technique is superior to immunological methods of detection and more rapid than culture, especially of slow-growing organisms.

Documentation of a positive blood culture result is the first diagnostic criterion that must be met for sepsis (Table 109-10). However, some neonates with bacterial infection may have negative blood culture results ("clinical infection" or "clinical sepsis"), and other approaches to identification of etiology are needed. Commonly used diagnostic tests include the total WBC count and differential count and the ratio

Table 109-10 Evaluation of a Newborn for Infection or Sepsis
HISTORY (SPECIFIC RISK FACTORS)
Maternal infection during gestation or at parturition (type and duration of antimicrobial therapy):
Urinary tract infection
Chorioamnionitis
Maternal colonization with group B streptococci, *N. gonorrhoeae*, herpes simplex
Gestational age/birthweight
Multiple birth
Duration of membrane rupture
Complicated delivery
Fetal tachycardia (distress)
Age at onset (in utero, birth, early postnatal, late)
Location at onset (hospital, community)
Medical intervention:
Vascular access
Endotracheal intubation
Parenteral nutrition
Surgery
EVIDENCE OF OTHER DISEASES*
Congenital malformations (heart disease, neural tube defect)
Respiratory tract disease (respiratory distress syndrome, aspiration)
Necrotizing enterocolitis
Metabolic disease, e.g., galactosemia
EVIDENCE OF FOCAL OR SYSTEMIC DISEASE
General appearance, neurologic status
Abnormal vital signs
Organ system disease
Feeding, stools, urine output, extremity movement
LABORATORY STUDIES
Evidence of Infection
Culture from a normally sterile site (blood, CSF, other)
Demonstration of a microorganism in tissue or fluid
Molecular detection (blood, urine, CSF)
Maternal or neonatal serology (syphilis, toxoplasmosis)
Autopsy
Evidence of Inflammation
Leukocytosis, increased immature/total neutrophil count ratio
Acute-phase reactants: C-reactive protein, erythrocyte sedimentation rate
Cytokines: interleukin-6, interleukin-B, tumor necrosis factor
Pleocytosis in CSF or synovial or pleural fluid
Disseminated intravascular coagulation: fibrin degradation products, D-dimer
Evidence of Multiorgan System Disease
Metabolic acidosis: pH, P_{CO_2}
Pulmonary function: P_{O_2}, P_{CO_2}
Renal function: blood urea nitrogen, creatinine
Hepatic injury/function: bilirubin, alanine aminotransferase, aspartate aminotransferase , ammonia, prothrombin time, partial thromboplastin time
Bone marrow function: neutropenia, anemia, thrombocytopenia

*Diseases that increase the risk of infection or may overlap with signs of sepsis

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of immature to total neutrophils. Although both have limitations in sensitivity and specificity, an immature : total neutrophil ratio of ≥0.2 suggests bacterial infection. Neutropenia is more common than neutrophilia in severe neonatal sepsis, but neutropenia also occurs in association with maternal hypertension, preeclampsia, and intrauterine growth restriction. Thrombocytopenia is a nonspecific indicator of infection and in some situations may suggest a fungal etiology. Tests to demonstrate an inflammatory response include determinations of C-reactive protein, procalcitonin, haptoglobin, fibrinogen, proteomic markers in amniotic fluid, inflammatory cytokines (including IL-6, IL-8, and tumor necrosis factor-α), and cell surface markers. Some of these modalities are readily available in clinical laboratories, while others are limited to research settings. Some investigators have attempted to develop and validate "sepsis scores" by incorporating different combinations of inflammatory response parameters and clinical presentation, but a single score has not proven to be consistently reliable.

When the clinical findings suggest an acute infection and the site of infection is unclear, LP with culture of CSF, urine culture, and a chest radiograph should be considered in addition to blood cultures. Urine should be collected by catheterization or suprapubic aspiration to avoid contamination. Urine culture for bacteria can be omitted in suspected early-onset infections because hematogenous spread to the urinary tract is rare in the 1st few days of life. Examination of the buffy coat with Gram or methylene blue stain may demonstrate intracellular pathogens. Demonstration of bacteria and inflammatory cells in Gram-stained gastric aspirates on the 1st day of life may reflect maternal amnionitis, which is a risk factor for early-onset infection. Stains of endotracheal secretions in infants with early-onset pneumonia may demonstrate intracellular bacteria, and cultures may reveal either pathogens or upper respiratory tract flora. However, rapid colonization of the neonatal respiratory tract after intubation may make tracheal aspirates less useful as a diagnostic modality for infection. Careful pathologic and microbiologic examination of the placenta can be helpful in the diagnosis of both chronic and acute intrauterine infections.

Diagnostic evaluation (including blood culture) is indicated for asymptomatic infants born to mothers with chorioamnionitis. The probability of neonatal infection correlates with the degree of prematurity and bacterial contamination of the amniotic fluid. Some experts recommend presumptive treatment with antibiotics, usually ampicillin and gentamicin or cefotaxime. In contrast, all symptomatic infants should be treated with antibiotics, usually ampicillin and gentamicin, or cefotaxime, after blood cultures are obtained. There is controversy over whether a LP is necessary for all term infants with suspected early-onset sepsis. Signs and symptoms of sepsis may be nonspecific and may include temperature instability, decreased responsiveness, respiratory distress, poor feeding, emesis, and diarrhea. Findings commonly observed in older infants with bacterial meningitis including stiff neck, bulging fontanel, convulsions, and opisthotonus, are rare in neonates with bacterial meningitis, making identification of neonatal meningitis from a clinical examination challenging. *If a pathogen is isolated from blood culture or if an infant develops signs and symptoms consistent with sepsis, a LP is indicated.* Some organisms such as GBS may be present only in the CSF and not in the blood at the time of an early onset sepsis evaluation. If the mother has been treated with antibiotics for chorioamnionitis, the newborn's blood culture result may be negative, and the clinician must rely on clinical observation and other laboratory tests (Table 109-11).

PNEUMONIA AND PNEUMONITIS

The **differential diagnosis** of pneumonitis in neonates is broad and includes RDS, meconium aspiration syndrome, persistent pulmonary hypertension, diaphragmatic hernia, transient tachypnea of the newborn, congenital heart disease, and BPD. The diagnosis of infectious pneumonia in a neonate is usually presumptive; microbiologic proof of infection is generally lacking because lung tissue is not easily cultured. CDC definitions of ventilator-associated pneumonia were developed to assist with monitoring of this condition in premature and low birthweight infants. Bacteriologic cultures of tracheal aspirates often reflect upper respiratory tract commensal organisms and usually have no etiologic significance. Culture of fluid obtained by bronchoalveolar lavage in a neonate is unreliable because the small bronchoscopes used in neonates cannot be protected from contamination as they are introduced into the distal airways. Short of tissue obtained by lung biopsy, the only reliable bacteriologic cultures are those performed on specimens obtained from blood or pleural fluid. Unfortunately, blood culture results are usually negative in the presence of a clinical pneumonia, and sufficient pleural fluid for culture is rarely present. Culture of pleural fluid obtained from a chest tube is not considered to be from a sterile site unless the specimen was obtained at the time of thoracostomy.

Cultures of respiratory secretions for *U. urealyticum* and other genital *Mycoplasma* species are of little value because neonates are often colonized with these agents as a result of ingestion of colonized secretions from the maternal genital tract. Neonatal *C. trachomatis* may be manifest by an elevated antichlamydial IgM titer, peripheral eosinophilia and elevated serum immunoglobulin levels as well as identification of the organism from the maternal genital tract. Giemsa-stained smears of conjunctivae or nasopharyngeal mucosa may reveal inclusion bodies confirming the diagnosis. Assessments of neonates for the presence of respiratory viruses by molecular analyses of nasopharyngeal specimens and enteroviruses by molecular analysis of blood and CSF may be beneficial during endemic seasons. Other tests of potential value in evaluating neonates with possible infectious pneumonitis are discussed under diagnosis of infections (see Chapter 109.7).

MENINGITIS

The diagnosis of meningitis is confirmed by examination of CSF and identification of a bacterium, virus, or fungus by culture, antigen, or molecular analysis. The importance of the LP as part of the diagnostic evaluation of the neonate with suspected sepsis has been the subject of debate and clinical practice varies. For term infants with suspected early-onset sepsis, many clinicians routinely obtain blood cultures and a complete blood count, because the etiology of 70-85% of term neonates with bacterial meningitis may be demonstrated by blood culture. Examination and culture of CSF may subsequently be undertaken in term infants with symptoms and/or bacteremia. Many clinicians defer the LP in severely ill infants with suspected early-onset infection because of the fear of respiratory and/or cardiovascular compromise associated with positioning for the procedure. In these situations, blood cultures should be performed and treatment initiated for presumed meningitis until an LP can be safely performed. In some situations, pretreatment with antibiotics makes interpretation of the LP results difficult and some experts would empirically treat the neonate for presumptive meningitis, using higher meningitic doses of antimicrobials and for an extended duration based on the suspected pathogen(s).

Term uninfected infants in the 1st wk of life may have the following CSF findings: protein 84 ± 45 mg/dL, glucose 46 ± 10 mg/dL, and leukocyte count 11 ± 10/mm^3 with the 90th percentile for leukocyte count being 22/mm^3. The proportion of polymorphonuclear leukocytes is 2.2 ± 3.8% with the 90th percentile being 6. A cross-sectional study that included neonates ≤56 days of age (15% premature) during 2005-2007 who underwent LP as part of a sepsis evaluation without an anatomical or procedural reason for CSF pleocytosis, and with a negative enterovirus CSF PCR, noted a significantly higher median CSF WBC count in infants ≤28 days old (3/mm^3, 95th percentile: 19/mm^3) than in infants 29–56 days old (2/mm^3, 95th percentile: 9/mm^3). Elevated CSF protein values and leukocyte counts and hypoglycorrhachia may develop in preterm infants after intraventricular hemorrhage. Many nonpyogenic congenital infections (toxoplasmosis, CMV, HSV, syphilis producing an aseptic meningitis) can also produce alterations in CSF protein values and leukocyte counts.

Gram staining of CSF yields an organism in most neonates with bacterial meningitis. The leukocyte count is usually elevated, with a predominance of neutrophils (>70-90%); the number is often >1,000

Table 109-11 Culture-Based and Non–Culture-Based Diagnostics for Neonatal Sepsis

CATEGORY	PARAMETER	OPTIMAL TIMING, VOLUME OF SPECIMEN, ROUTINE/INVESTIGATIONAL	APPLICABILITY FOR NEONATAL SEPSIS
Culture-based			
Blood	Culture	>1 mL of whole blood ROUTINE*	Gold standard for bacteremia
Cerebrospinal fluid (CSF)	Culture	When clinically feasible ROUTINE	Optimize antimicrobial therapy
Urine	Culture	>72 hr of life ROUTINE	Not useful for EOS; potential benefits for LOS
Tracheal aspirate	Culture	ROUTINE	Usually reflects colonization
Non–culture-based			
Immune function	MHC II TNF-α	INVESTIGATIONAL† INVESTIGATIONAL	Both decreased in chorioamnionitis and sepsis
Neutrophil indices	Neutropenia Absolute neutrophil count Absolute immature neutrophil count	After 12 hr of life Consider GA, delivery mode, altitude, arterial versus venous sampling, time since birth ROUTINE	Neutropenia better predictor for sepsis than leukocytosis
Neutrophil markers	CD64	Elevated for 24 hr after infection Requires 50 μL blood Results within hours INVESTIGATIONAL	Cut points between 2.38–3.62 optimal sensitivity, specificity and NPV for EOS
Platelet count	Thrombocytopenia and thrombocytosis	Late findings; slow to respond ROUTINE	Thrombocytopenia associated with fungal infection
CSF cell count	CSF WBC	Uninfected neonates mean 10 cells/mm^3. Range up to 20 cells/mm^3 ROUTINE	Does not predict culture-proven meningitis
CSF chemistries	CSF protein CSF glucose	Term <100 mg/dL preterm higher; 70–80% of serum glucose ROUTINE	Elevated in fungal meningitis Low glucose specific for bacterial meningitis
Acute phase reactants	CRP Procalcitonin	8–24 hr after infection 2–12 hr after infection ROUTINE/INVESTIGATIONAL	Good NPV Better sensitivity but less specificity than CRP
Sepsis panels/scores		After 24 hr of life INVESTIGATIONAL	Most useful for NPV and discontinuation of antimicrobial therapy

*ROUTINE refers to an assay or parameter that is routinely available and widely used.
†INVESTIGATIONAL refers to an assay or parameter that is undergoing evaluation for clinical use and applicability.
CRP, C-reactive protein; CSF, cerebrospinal fluid; EOS, early-onset sepsis; GA, gestational age; LOS, late-onset sepsis; MHC II, major histocompatibility complex class II; NPV, negative predictive value; TNF, tumor necrosis factor; WBC, white blood cell count.
Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. Am J Perinatol *30(2):131–141, 2013.*

but may be <100 in infants with neutropenia or when the CSF is obtained early in the disease course. Microorganisms are recovered from most patients who have not been pretreated with antibiotics. Bacterial organisms have also been noted microscopically and grown from CSF without an abnormal number of WBCs (<25) or with a normal protein level (<200 mg/dL), thus underscoring the importance of performing a culture and Gram stain on all CSF specimens. Contamination of CSF by bacteremia after traumatic LP may occur rarely. Culture-negative meningitis may be seen with antibiotic pretreatment, a brain abscess, or infection with *Mycobacterium hominis, U. urealyticum, Bacteroides fragilis,* enterovirus, or HSV. Use of PCR has improved the ability to detect pathogens rapidly in CSF, especially enteroviruses and HSV. Head ultrasonography or, more often, CT with contrast enhancement may be helpful in diagnosing ventriculitis and brain abscess.

Bibliography is available at Expert Consult.

109.10 Management

EMPIRIC THERAPY

The optimal course of management of neonates with a suspected bacterial infection is determined by the age of the neonate, the prenatal and postnatal environment, and epidemiology (Table 109-12). Once appropriate culture specimens have been obtained intravenous or, less often, intramuscular antibiotic therapy should be instituted immediately. Although it is preferable to have specimens obtained prior to the initiation of antimicrobial therapy to optimize recovery of bacterial organisms, antimicrobial therapy administration should **not be delayed for specimen collection** in clinically ill neonates. Initial empirical treatment of early-onset bacterial infections should consist of ampicillin and an aminoglycoside (usually gentamicin), or cefotaxime. HAIs acquired in a NICU are more likely to be caused by staphylococci, various Enterobacteriaceae, *Pseudomonas* species, or *Candida* species. Thus, an antistaphylococcal drug (oxacillin or nafcillin for *S. aureus* or, more often, vancomycin for coagulase-negative staphylococci or methicillin-resistant *S. aureus*) should be substituted for ampicillin in a previously hospitalized neonate. A history of recent antimicrobial therapy or the presence of antibiotic-resistant infections in the NICU suggests the need for modification of empiric antimicrobial choices. When the history or the presence of necrotic skin lesions suggests *Pseudomonas* infection, initial therapy should consist of antipseudomonal agent, such as piperacillin, ticarcillin, meropenem, or ceftazidime, and an aminoglycoside. Fungal infections, including candidiasis or aspergillosis, should also be considered when necrotic skin lesions at former sites of adhesive tape are observed. These require immediate surgical intervention as well as antifungal therapy.

Involvement of a pharmacist with expertise in neonatal infections and/or use of a guide containing neonatal dosing by weight and

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Table 109-12 Management and Prevention of Neonatal Sepsis

CONDITION	THERAPY	ADDITIONAL CONSIDERATIONS
Empiric management		
Early-onset sepsis	Ampicillin + aminoglycoside. 10 days for bacteremia; 14 days for GBS and uncomplicated meningitis; extend to 21-28 days for complicated infections.	Consider a third-generation cephalosporin (cefotaxime preferred) or carbapenem for meningitis. Tailor therapy to pathogen. Consider discontinuation of therapy if pathogen not isolated.
Late-onset sepsis	Vancomycin + aminoglycoside. Duration dependent on pathogen and site.	Alternatives to vancomycin may be considered based on local epidemiology and clinical presentation. Aminoglycoside based regimen preferred to cephalosporin given reduced risk of resistance. Consider cephalosporin if meningitis suspected. Consider a carbapenem if third-generation cephalosporin recently received. Consider amphotericin for fungal etiologies. Tailor therapy to pathogen. Consider discontinuation of therapy if pathogen not isolated.
Nonantimicrobial treatment strategies		
Recombinant G-CSF Recombinant G-MSF	Enhance neutrophil number and function, but no reduction in infection when administered as prophylaxis or improvement in survival when administered as therapy.	Insufficient evidence to support the clinical use of G-CSF or GM-CSF either as treatment or prophylaxis to prevent systemic infections.
IVIG[§]	Augments antibody-dependent cytotoxicity and improves neutrophilic function, *but* no evidence that IVIG in suspected or proven sepsis reduces death.	Insufficient evidence from 10 RCTs or quasi-RCTs to support use in neonates with confirmed or suspected sepsis.
Prevention strategies		
IAP	Administration of penicillin or ampicillin 4 hr prior to parturition.	Successfully reduces rates of EOS caused by GBS. No effect on LOS GBS.
Fluconazole prophylaxis	Administration of weight-based dosing to neonates weighing less than 1,500 g.	Most beneficial in NICUs with high baseline rates of invasive candidiasis.
BLF supplementation with a probiotic, *Lactobacillus rhamnosus* (GG)	BLF is a human milk glycoprotein with a role in innate immune response. LGG enhances the activity of lactoferrin.	BLF supplementation with and without LGG reduced the incidence of 1st LOS in 472 VLBW neonates in large randomized, double-blind RCT. Additional confirmatory studies warranted.

BLF, bovine lactoferrin supplementation; EOS, early-onset sepsis; GBS, group B streptococcus; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IAP, intrapartum antimicrobial prophylaxis; IVIG, intravenous immunoglobulin, LGG, *Lactobacillus rhamnosus* GG; LOS, late-onset sepsis; NICUs, neonatal intensive care unit; RCTs, randomized, controlled trials; VLBW, very low birthweight.

Created with data from Carr R, Modi N, Doré C: G-CSF and GM-CSF for treating or preventing neonatal infections. Cochrane Database Syst Rev *(3):CD003066, 2003; Brocklehurst P, Farrell B, King A, et al; INIS Collaborative Group: Treatment of neonatal sepsis with intravenous immune globulin.* N Engl J Med *365:1201–1211, 2011; Manzoni P, Decembrino L, Stolfi I, et al; Italian Task Force for the Study and Prevention of Neonatal Fungal Infections; Italian Society of Neonatology. Lactoferrin and prevention of late-onset sepsis in the pre-term neonates.* Early Hum Dev *86(Suppl 1):59–61, 2010.*

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gestational age may optimize antimicrobial utilization. Peak and trough measurements of antimicrobials may be useful to ensure therapeutic levels and minimize toxicity if the agent is administered for more than 2-3 days and is indicated for certain infections such as meningitis where CSF penetration and levels must be monitored. Trough measurements may be indicated in infants with compromised kidney or liver function who are receiving potentially nephrotoxic or hepatotoxic agents.

Treatment of newborn infants whose mothers received antibiotics during labor should be individualized. If early-onset sepsis is thought to be likely, treatment of the infant should continue until the infant remains asymptomatic for 24-72 hr and clinical and laboratory evidence of recovery is apparent. Furthermore, in the context of intrapartum antibiotic use, it is important to consider that the organism causing infection may be resistant to the intrapartum therapy, thus influencing selection of empiric antibiotics for the infant. For dosing regimens, see organism-specific chapters in Part XVII of this textbook.

DIRECTED THERAPY

Once the pathogen has been identified and its susceptibility determined, the most appropriate antimicrobial should be administered. For most Gram-negative enteric bacteria, ampicillin and an aminoglycoside or a third-generation cephalosporin (cefotaxime or ceftazidime if *Pseudomonas* coverage is needed) should be used. Enterococci should be treated with both a penicillin-containing antibiotic and an aminoglycoside, if the *Enterococcus* is susceptible to gentamicin. The addition of gentamicin to a penicillin provides synergistic bactericidal and postantibiotic effects. Ampicillin alone is adequate for *L. monocytogenes,* and penicillin suffices for GBS. Clindamycin or metronidazole is appropriate for anaerobic infections; metronidazole is preferred for anaerobic infections that involve the CNS because of its better CNS penetration, compared to clindamycin.

Third-generation cephalosporins, such as cefotaxime, are valuable additions for treating documented neonatal sepsis and meningitis because (1) the minimal inhibitory concentrations of these agents needed for treatment of Gram-negative enteric bacilli are much lower than those of the aminoglycosides, (2) excellent penetration into CSF occurs, and (3) relatively higher doses may be administered with less toxicity. The end result is much higher bactericidal titers in serum and CSF than is achievable with ampicillin-aminoglycoside combinations. However, the *routine* use of third-generation cephalosporins for suspected sepsis in neonates is not optimal without a clear indication for broader spectrum empiric therapy. Routine third-generation cephalosporin use has been linked to the rapid emergence of resistant organisms, *Candida* sepsis, and antibiotic-associated diarrhea in neonates.

ANTIMICROBIAL RESISTANCE

The emergence of antibiotic resistance among pathogens that infect newborns is of great concern. Vancomycin-resistant enterococci and vancomycin-insensitive *S. aureus* are emerging pathogens resulting from the widespread use of vancomycin. Although vancomycin use cannot be avoided in neonatal units where methicillin-resistant *S. aureus* is endemic, its use can be reduced by limiting empirical therapy to patients with a high suspicion of severe infection with coagulase-negative staphylococci (severely ill neonate with an indwelling intravascular catheter) and by discontinuing therapy after 2-3 days when blood culture results are negative. When susceptibility results are available and there is no evidence of CNS or endovascular involvement, clindamycin may be a suitable alternative for therapy of uncomplicated bacteremia and skin and soft tissue infections in a neonate.

BACTEREMIA

If a neonate's condition permits, it is ideal to obtain a repeat blood culture from the site of the positive culture at the time of identification of the organism. This second culture may be helpful, especially in situations where the organism isolated would not be susceptible to the empiric or directed therapy that a neonate is receiving. Therapy for most bloodstream infections should be continued for a total of 7-10 days, or for at least 5-7 days after a clinical response has occurred. The duration of therapy is optimally calculated from the date of first negative culture. If successive blood cultures are notable for the presence of pathogens, the possibility of an infected indwelling catheter, endocarditis, an infected thrombus, an occult abscess, subtherapeutic antibiotic levels, or resistant organisms should be considered. A change in antibiotics, longer duration of therapy, or removal of the catheter may be indicated. Consultation with a pediatric infectious disease specialist may be indicated.

PNEUMONIA

A combination of ampicillin and an aminoglycoside or cefotaxime is appropriate for pneumonia that develops during the 1st 7-10 days of life. Nosocomial pneumonia, which generally manifests in the 2nd wk of life can be treated empirically with ampicillin or vancomycin and an aminoglycoside or a third-generation cephalosporin. *Pseudomonas* pneumonia should be treated with an agent to which the organism is susceptible. Some experts would consider the use of dual therapy for multidrug resistant organisms; however, the benefits of this therapy may vary based on host and pathogen. Pneumonia caused by *C. trachomatis* usually presents between the 1st and 3rd mo of life and is usually treated with oral erythromycin. The effectiveness of erythromycin in treating pneumonia caused by *C. trachomatis* is approximately 80%; in certain clinical situations, a second course of therapy might be required. Data are limited regarding the use of macrolides, such as azithromycin, for neonatal *C. trachomatis* pneumonia, although some practitioners prefer this agent to erythromycin because of the shorter course of azithromycin and the slightly increased risk of pyloric stenosis associated with oral erythromycin in neonates <6 wk of age. *U. urealyticum* infections may be treated with erythromycin.

MENINGITIS

Empiric antimicrobial therapy for bacterial meningitis should include ampicillin in doses used for meningitis, unless staphylococci are likely, in which case vancomycin may be considered. Neonates with shunts may be predisposed to developing meningitis and ventriculitis attributable to resistant Gram-positive organisms. Cefotaxime or gentamicin in meningitic doses are appropriate choices for empiric Gram-negative coverage. Susceptibility testing of Gram-negative organisms is important because resistance to cephalosporins and aminoglycosides is common. Most aminoglycosides administered by parenteral routes do not achieve sufficiently high antibiotic levels in the lumbar CSF or ventricles to inhibit the growth of Gram-negative bacilli. Therefore, some experts recommend a combination of intravenous ampicillin and a third-generation cephalosporin for the treatment of neonatal Gram-negative meningitis. Cephalosporins should not be used as *empirical monotherapy* in neonates <3 mo of age when early or late onset listeriosis is suspected because *L. monocytogenes* is resistant to cephalosporins. Although a rare cause of meningitis in the neonate, enterococci are also resistant to cephalosporins.

Meningitis caused by GBS usually responds clinically within 24-48 hr of antimicrobial therapy. Therapy should be continued for 14-21 days. Gram-negative bacilli may continue to grow from repeated CSF samples for 72-96 hr after the initiation of effective therapy, as a result of the intracellular habitat of many organisms. Treatment of Gram-negative meningitis should be continued for 21 days or for at least 14 days after sterilization of the CSF, whichever is longer. *P. aeruginosa* meningitis should be treated with ceftazidime or meropenem, assuming that the isolate is susceptible. Metronidazole is the treatment of choice for infection caused by *B. fragilis* and other anaerobic organisms. Prolonged antibiotic administration, with or without surgical drainage is indicated for neonatal cerebral abscesses. Imaging is recommended for patients with suspected ventriculitis, hydrocephalus, or cerebral abscess (initial and follow-up assessments) and for those with an unexpectedly complicated course (prolonged coma, focal neurologic deficits, persistent or recurrent fever).

Neonates with suspected neonatal herpes meningoencephalitis should receive intravenous acyclovir; empirical antibacterial therapy may be considered in symptomatic infants with a CSF mononuclear pleocytosis, but this should be discontinued and acyclovir continued if bacterial cultures are negative and a CSF HSV PCR is positive. Supportive care is the current recommended management for severe enteroviral infections such as meningoencephalitis, carditis, and hepatitis. There are currently no Food and Drug Administration-licensed therapies for neonatal enteroviral infections. The effectiveness of intravenous immunoglobulin is unknown. A phase II double-blind, placebo controlled virologic efficacy trial of pleconaril in neonatal enteroviral sepsis syndrome concluded enrollment in 2010 and data analysis is ongoing.

ADJUNCTIVE THERAPIES

Treatment of neonatal infections may be divided into antimicrobial therapy for the suspected or known pathogen and supportive care. Careful attention to respiratory and cardiovascular status is mandatory. Adequate oxygenation of tissues should be maintained; ventilatory support is frequently necessary for respiratory failure caused by sepsis, pneumonia, pulmonary hypertension, or acute respiratory distress syndrome. Refractory hypoxia and shock may require extracorporeal membrane oxygenation, which has reduced mortality rates in full-term infants with respiratory failure. Shock and metabolic acidosis should be identified and managed with fluid resuscitation and inotropic agents as needed. Corticosteroids should be administered only for adrenal insufficiency and in cases of TB meningitis. Fluids, electrolytes, and glucose levels should be monitored carefully with correction of hypovolemia, hyponatremia, hypocalcemia, and hypoglycemia/hyperglycemia. Hyperbilirubinemia should be monitored and treated aggressively with phototherapy and/or exchange transfusion, because the risk of kernicterus increases in the presence of sepsis and meningitis. Seizures should be treated with anticonvulsants. Parenteral nutrition is needed for any infant who cannot sustain enteral feeding.

DIC may complicate neonatal septicemia. Platelet counts, hemoglobin levels, and clotting times should be monitored. DIC is treated by management of the underlying infection, but if bleeding occurs, DIC management may require fresh-frozen plasma, platelet transfusions, or whole blood.

Because neutrophil storage pool depletion has been associated with a poor prognosis, therapies that increase the number or improve the quality of neutrophils have been studied, including granulocyte transfusions, GM-CSF, and G-CSF. The use of G-CSF or GM-CSF abolishes sepsis-induced neutropenia, but none of these therapies has been shown to definitively improve survival.

It is important to remember that nonbacterial infectious agents can produce the syndrome of neonatal sepsis. HSV infection requires immediate specific treatment, as does systemic *Candida* infection. Treatment and other aspects of various nonbacterial infections are discussed in detail in other sections: TB (see Chapter 215), syphilis (see

Chapter 218), genital mycoplasmas (see Chapter 224.2), *C. trachomatis* (see Chapter 226.2), *Candida* (see Chapter 234.1), rubella (see Chapter 250), enteroviruses (see Chapter 250), parvovirus B19 (see Chapter 251), HSV (see Chapter 252), VZV (see Chapter 253), and CMV (see Chapter 255).

Bibliography is available at Expert Consult.

109.11 Complications and Prognosis

Complications of bacteremic infections include endocarditis, septic emboli, abscess formation, septic joints with residual disability, and osteomyelitis and bone destruction. Recurrent bacteremia is rare (<5% of patients). Candidemia may lead to vasculitis, endocarditis, and endophthalmitis, as well as to abscesses in the kidneys, liver, lungs, and brain. Sequelae of sepsis may result from septic shock, DIC, or organ failure.

Mortality rates from the sepsis syndrome depend on the definition of sepsis. In adults, the mortality rate approaches 50%, and the rate in newborn infants is probably at least that high. Reported mortality rates in neonatal sepsis are as low as 10%, because all bacteremic infections are included in the definition. Several studies have documented that the sepsis case fatality rate is highest for Gram-negative and fungal infections.

The case fatality rate for neonatal bacterial meningitis is between 20% and 25%. Many of these patients have associated sepsis. Risk factors for death or for moderate or severe disability include seizure duration >72 hr, coma, need for inotropic agents, and leukopenia. Immediate complications of meningitis include ventriculitis, cerebritis, and brain abscess. Late complications of meningitis occur in 40-50% of survivors and include hearing loss, abnormal behavior, developmental delay, cerebral palsy, focal motor disability, seizure disorders, and hydrocephalus. Advanced imaging (CT, MRI) has demonstrated cerebritis, brain abscess, infarct, subdural effusions, cortical atrophy, and diffuse encephalomalacia in newborns surviving meningitis. A number of these sequelae may be encountered in infants with sepsis but without meningitis, as a result of cerebritis or septic shock. Extremely low birthweight infants (<1,000 g) with sepsis are at increased risk for poor neurodevelopmental and growth outcomes in early childhood.

Bibliography is available at Expert Consult.

109.12 Prevention

MATERNAL STRATEGIES

Maternal immunization protects the mother against vaccine-preventable diseases that can cause intrauterine infections (rubella, hepatitis B, VZV) and may also protect the infant via passive transfer of protective maternal antibodies (tetanus). CMV vaccines are under study. Toxoplasmosis is preventable with appropriate diet and avoidance of exposure to aged cat feces. Malaria during pregnancy can be minimized with chemoprophylaxis and use of insecticide-treated bed nets. Congenital syphilis is preventable by timely diagnosis and appropriate early treatment of infected pregnant women.

Aggressive management of suspected maternal chorioamnionitis with antibiotic therapy during labor, along with rapid delivery of the infant, reduces the risk of early-onset neonatal sepsis. Vertical transmission of GBS and early-onset GBS disease is significantly reduced by selective intrapartum chemoprophylaxis (see Chapter 184). A number of candidate GBS vaccines are currently being studied. Neonatal infection with *Chlamydia* can be prevented by identification and treatment of infected pregnant women (see Chapter 226). Mother-to-child transmission of HIV is significantly reduced by maternal antiretroviral therapy during pregnancy, labor, and delivery, cesarean section delivery prior to rupture of membranes, and antiretroviral treatment of the infant after birth (see Chapter 276).

ANTIFUNGAL PROPHYLAXIS

Prophylactic administration of fluconazole during the 1st 6 wk of life reduces fungal colonization and invasive fungal infection in extremely low birth weight infants—those with birth weights <1000 g. In addition to the individual benefit afforded by prophylaxis for VLBW neonates, fluconazole prophylaxis may have a community impact by decreasing the overall fungal burden of a NICU. Results from more than 14 trials at multiple institutions with 3,100 neonates suggests that fluconazole prophylaxis decreases colonization of the urine, gastrointestinal tract, and integument, without promoting the development of resistance and without adverse effects. Based on an annual United States preterm birth cohort of approximately 30,000 VLBW infants, it has been estimated that fluconazole prophylaxis could prevent approximately 2,000-3,000 cases of invasive candidiasis, approximately 200-300 deaths, and the adverse neurodevelopmental outcomes of invasive candidiasis in approximately 400-500 infants per year. Differing baseline rates of fungal infections, practices related to central venous catheter removal, severity of illness, and practices related to the use of broad-spectra antimicrobials make universal recommendations regarding prophylaxis challenging.

Neonatal practices that may reduce the risks of invasive candidiasis include, limited use of broad spectrum antimicrobials, use of an aminoglycoside instead of a cephalosporin for empiric therapy when meningitis or antimicrobial resistance is not suspected, limitation of postnatal steroid use in VLBW infants, early enteral feeding, and the establishment of the neonatal gut microbiome with human milk feeding

OTHER STRATEGIES FOR PREVENTION OF HEALTHCARE-ASSOCIATED INFECTIONS

Because of the burden of disease, additional strategies including lactoferrin and probiotic supplementation and the administration of antistaphylococcal monoclonal antibodies have been explored as strategies to prevent HAIs. Although antistaphylococcal monoclonal antibodies have not proven to be of benefit, preliminary data suggest that bovine lactoferrin (BLF) supplementation alone and in combination with probiotics may reduce late onset sepsis. A prospective, multicenter, double-blind, randomized placebo-controlled trial in 11 tertiary care NICUs compared BLF alone or in combination with the probiotic *Lactobacillus rhamnosus* GG (LGG). Over a 9 mo period from 2007-2008, 472 VLBW neonates received placebo, LGG and BLF, or BLF only, daily from birth through 30 days of life or 45 days. Compared with placebo, BLF supplementation with and without LGG reduced the incidence of the first late-onset sepsis episode in VLBW neonates. Further studies of lactoferrin, with and without probiotics, to reduce risk of neonatal sepsis are indicated

ANTIMICROBIAL STEWARDSHIP

Antimicrobial utilization practices in NICUs influence the types of microorganisms responsible for neonatal sepsis and their resistance patterns. The CDC has initiated a campaign to prevent antimicrobial resistance in healthcare settings. This effort is designed to increase clinician awareness and to improve diagnosis and appropriate treatment of infection. The campaign supports involving infectious disease and pharmacy consultants, treating infections with an antimicrobial with the narrowest spectrum and discontinuing therapy when adequate therapy has been administered. Prevention of infections through optimizing infection control and enhanced surveillance are additional components of the campaign.

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Adolescent Medicine

PART XIII

Chapter 110
Adolescent Development

See also Part XVI and Chapters 561 and 562.

110.1 Adolescent Physical and Social Development

Cynthia Holland-Hall and Gale R. Burstein

During the preteen, teenage, and young adult years, young people undergo not only dramatic changes in physical appearance, but also rapid changes in physiologic, psychological, and social functioning. Hormonally driven physiologic changes and ongoing neurologic development occur in the setting of social structures that foster the transition from childhood to adulthood. This period of development comprises *adolescence*, which is divided into 3 phases—early, middle, and late adolescence—each marked by a characteristic set of biologic, cognitive, and psychosocial milestones (Table 110-1). Although individual variations in the timing and pace of development undoubtedly exist, these changes follow a fairly predictable pattern of occurrence. Gender and culture profoundly affect the developmental course, as do physical, social, and environmental influences. Given the interaction of these domains, a biopsychosocial approach is best suited to approach the healthcare of the adolescent.

PHYSICAL DEVELOPMENT

Puberty is the biologic transition from childhood to adulthood. Pubertal changes include the appearance of the secondary sexual characteristics, increase in height, change in body composition, and development of reproductive capacity. Adrenal production of androgen (chiefly **dehydroepiandrosterone sulfate [DHEAS]**) may occur as early as 6 yr of age, with development of underarm odor and faint genital hair (adrenarche). Maturation of the **gonadotropin-releasing hormone** pulse generator is among the earliest neuroendocrine changes associated with the onset of puberty. Under the influence of gonadotropin-releasing hormone, the pituitary gland secretes **luteinizing hormone** and **follicle-stimulating hormone**; initially this occurs in a pulsatile fashion primarily during sleep, but this diurnal variation diminishes throughout puberty. Luteinizing hormone and follicle-stimulating hormone stimulate corresponding increases in gonadal androgens and estrogens. The triggers for these changes are incompletely understood, but may involve the hormone leptin, high concentrations of which are associated with increased body fat and earlier onset of puberty.

Sexual Development

The progression of the development of the secondary sex characteristics may be described using the **sexual maturity rating (SMR) scale (ranging from 1, preadolescence, to 5, sexual maturity)**, or **Tanner stages**. Figures 110-1 and 110-2 depict the physical findings of breast and pubic hair maturation at each SMR. Figures 110-3 and 110-4 depict the typical sequence of pubertal changes in males and females, respectively. The range of normal progress through sexual maturation is wide, and is affected by genetics, the psychosocial environment, nutrition, and overall health status. Environmental exposures may play a role as well.

In males, the first visible sign of puberty and the hallmark of SMR 2 is testicular enlargement, beginning as early as 9.5 yr, followed by the development of pubic hair. This is followed by penile growth during SMR 3. Peak growth occurs when testis volumes reach approximately 9-10 cm^3 during SMR 4. Under the influence of luteinizing hormone and testosterone, the seminiferous tubules, epididymis, seminal vesicles, and prostate enlarge. Sperm may be found in the urine by SMR 3; nocturnal emissions may be noted at this time as well. Some degree of breast tissue growth, typically bilateral, occurs in 40-65% of males during SMR 2-3 as a consequence of a relative excess of estrogenic stimulation. This generally resolves with ongoing maturation.

In females, typically the first visible sign of puberty and the hallmark of SMR 2 is the appearance of breast buds (thelarche), between 8 and 12 yr of age. A significant minority of females develops pubic hair (pubarche) prior to thelarche. Less visible changes include enlargement of the ovaries, uterus, labia, and clitoris, and thickening of the endometrium and vaginal mucosa. A clear vaginal discharge may be present prior to menarche (physiologic leukorrhea). Menses typically begins 2.5 yr after the onset of puberty, during SMR 3-4 (average age: 12.5 yr; normal range: 9-15 yr) (see Fig. 110-4). The timing of menarche is determined largely by genetics; contributing factors likely include adiposity, chronic illness, nutritional status, and the psychosocial environment. Early menstrual cycles often are anovulatory, and therefore somewhat irregular, but typically occur every 21-45 days and include 3-7 days of bleeding.

The onset of puberty and menarche appear to be occurring at earlier ages than previously reported in the United States. Several studies from 1948-1981 identified the average age for the onset of breast development as ranging from 10.6-11.2 yr of age. Multiple reports since 1997 suggest a significantly earlier average age of onset, ranging from 8.9-9.5 yr in African-American females and 10.0-10.4 yr in white females. Nearly 25% of African-American females and 10% of white females initiate breast development by 7 yr of age. There also appears to be a trend toward decreasing ages for the onset of pubic hair development and menarche. Data from the National Health and Nutrition Examination Survey, a nationally representative, longitudinal survey in the United States, show a decline in the average age of menarche of 4.9 mo between the 1960s and 2002. Changes in the timing of menarche *within* ethnic groups, however, were significantly smaller. The larger change seen in the population as a whole may be partially explained by changes in the ethnic makeup of the sample. The reasons for the larger decrease in age for breast development have been postulated to include the epidemic of childhood obesity as well as exposure to estrogen-like environmental toxins (endocrine disruptors), but further research in this area is needed.

Although fewer data are available on changes in the timing of puberty in males, they may be experiencing a similar trend. Although the method of assessing the onset of puberty (i.e., inspection vs. palpation of the testes) varies between studies, it appears that the average age for the onset of genital and pubic hair development may have decreased by 1-2 yr over the past several decades in many industrialized countries. An association of obesity with later onset of puberty in males has been theorized, but has not been consistently demonstrated.

Somatic Growth (See Also Fig. 13-1)

Linear growth acceleration begins in early adolescence for both genders, with 15-20% of adult height accrued during puberty. Females attain a peak height velocity (PHV) of 8-9 cm/yr at SMR 2-3, approximately 6 mo before menarche. Males typically begin their growth

Table 110-1 Milestones in Early, Middle, and Late Adolescent Development

VARIABLE	EARLY ADOLESCENCE	MIDDLE ADOLESCENCE	LATE ADOLESCENCE
Approximate age range	10-13 yr	14-17 yr	18-21 yr
Sexual maturity rating*	1-2	3-5	5
Physical	• Females: Secondary sex characteristics (breast, pubic, axillary hair), start of growth spurt • Males: testicular enlargement, start of genital growth	• Females: peak growth velocity, menarche (if not already attained) • Males: growth spurt, secondary sex characteristics, nocturnal emissions, facial and body hair, voice changes • Change in body composition • Acne	• Physical maturation slows • Increased lean muscle mass in males
Cognitive and moral	• Concrete operations • Egocentricity • Unable to perceive long-term outcome of current decisions • Follow rules to avoid punishment	• Emergence of abstract thought (formal operations) • May perceive future implications, but may not apply in decision making • Strong emotions may drive decision making • Sense of invulnerability • Growing ability to see others' perspectives	• Future-oriented with sense of perspective • Idealism • Able to think things through independently • Improved impulse control • Improved assessment of risk vs. reward • Able to distinguish law from morality
Self-concept/identity formation	• Preoccupied with changing body • Self-consciousness about appearance and attractiveness	• Concern with attractiveness • Increasing introspection	• More stable body image • Attractiveness may still be of concern • Consolidation of identity
Family	• Increased need for privacy • Exploration of dependence/independence boundaries	• Conflicts over control and independence • Struggle for greater autonomy • Increased separation from the parents	• Emotional and physical separation from family • Increased autonomy • Reestablishment of "adult" relationship with parents
Peers	• Same-sex peer affiliations	• Intense peer group involvement • Preoccupation with peer culture • Conformity	• Peer group and values recede in importance
Sexual	• Increased interest in sexual anatomy • Anxieties and questions about pubertal changes • Limited capacity for intimacy	• Testing ability to attract partner • Initiation of relationships and sexual activity • Questions of sexual orientation	• Consolidation of sexual identity • Focus on intimacy and formation of stable relationships • Planning for future and commitment

*See text and Figures 110-1 and 110-2.

acceleration at a later SMR stage, achieve a PHV of 9-10 cm/yr later in the course of puberty (SMR 3-4), and continue their linear growth for approximately 2-3 yr after females have stopped growing (Fig. 110-5). The growth spurt begins distally, with enlargement of the hands and feet, followed by the arms and legs, and finally, the trunk and chest. This growth pattern imparts a characteristic "awkward" appearance to some early adolescents. Body composition changes as well, following the attainment of PHV. Males undergo an increase in lean body mass (sometimes referred to as the "strength spurt"), whereas females develop a higher proportion of body fat. Scoliosis, if present, may progress with rapid axial skeleton growth (see Chapter 679.1). One-half to ⅔ of total body calcium is laid down during puberty. Bone growth precedes increases in bone mineralization and bone density, which may increase the adolescent's risk of fracture during times of rapid growth. Since skeletal growth precedes muscle growth, sprains and strains may be more common during this time as well.

Cardiovascular changes in middle adolescence include increased heart size, higher blood pressure, and increases in blood volume and hematocrit, particularly in males. Coupled with an increase in lung vital capacity, these changes lead to greater aerobic capacity. Androgenic stimulation of sebaceous and apocrine glands may result in acne and body odor. Rapid enlargement of the larynx, pharynx, and lungs leads to changes in vocal quality in males, typically preceded by vocal instability (voice cracking). Elongation of the optic globe often results in myopia (see Chapter 620). Dental changes include jaw growth, loss of the final deciduous teeth, and eruption of the permanent cuspids, premolars, and finally, molars (see Chapter 307). Orthodontic appliances may be needed, secondary to growth exacerbations of bite disturbances. Physiologic changes in sleep patterns and increased sleep requirements occur, causing many adolescents to delay sleep onset at night, with subsequent difficulty awakening for early school start times in the morning (see Chapter 19).

NEUROLOGIC, COGNITIVE, AND MORAL DEVELOPMENT

Cognitive development correlates more closely with chronologic age than pubertal maturation. As children progress through adolescence, they develop and refine their ability to use formal operational thought processes. Abstract, symbolic, and hypothetical thinking replaces the need to manipulate concrete objects. Middle and late adolescents develop the ability to consider multiple options and to assess the long-term consequences of their actions. The capacity for verbal expression is enhanced. Since adolescents' decision-making and subsequent behaviors are the largest determinants of their mortality and morbidity, understanding these cognitive processes is of critical importance.

The belief that major structural brain development is completed in childhood is outdated. It is now clear that neuromaturation continues into the third decade. This maturation is characterized by decreases in gray matter, increases in white matter, and an apparent increase in the efficiency of communication and connectivity between different brain regions. Gray matter volume peaks in the frontal lobes in preadolescence, then decreases. This decrease is a consequence of selective "pruning" of rarely used synaptic connections. Increased white matter volume is believed to reflect increasing myelination and subsequent

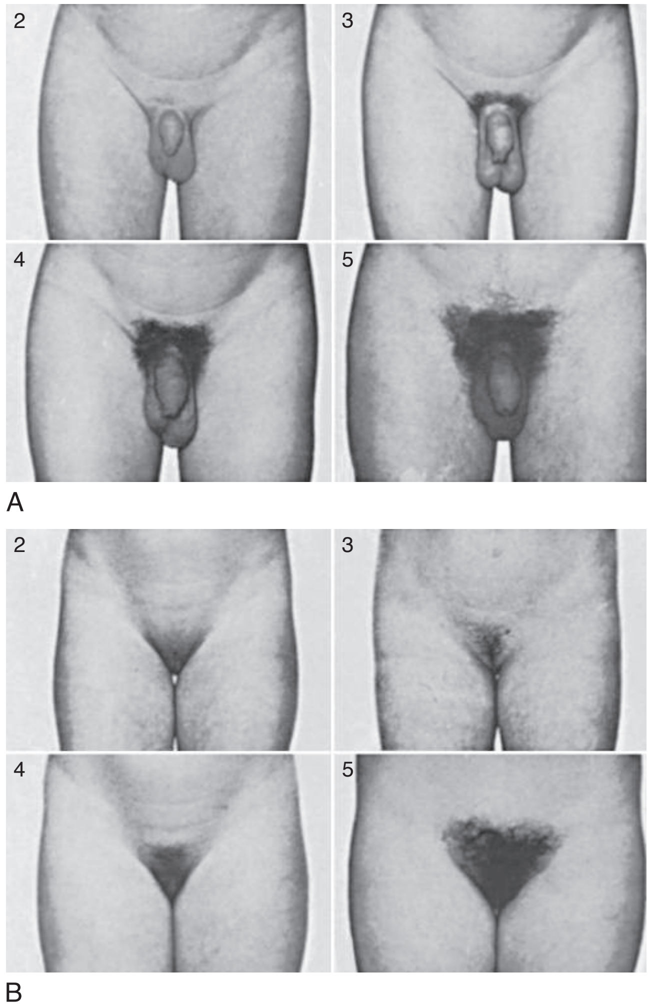

Figure 110-1 Sexual maturity ratings (2-5) of pubic hair changes in adolescent males *(A)* and females *(B)* (see Tables 110-2 and 110-3). *(Courtesy of J.M. Tanner, MD, Institute of Child Health, Department for Growth and Development, University of London, London, England.)*

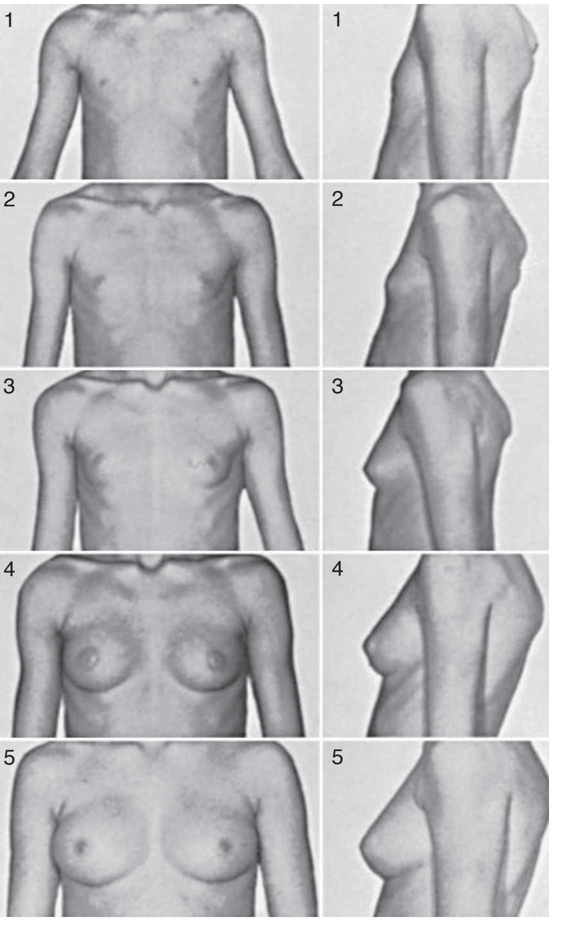

Figure 110-2 **Sexual maturity ratings (1-5) of breast changes in adolescent females.** *(Courtesy of J.M. Tanner, MD, Institute of Child Health, Department for Growth and Development, University of London, London, England.)*

facilitation of integrated brain activity and more efficient transmission of information between different regions of the brain. These changes are first seen in the posterior cortex (sensory and motor regions), and progress anteriorly (Fig. 110-6). The frontal lobes are among the last areas of the brain to mature, including the prefrontal cortex, the region of the brain associated with executive function: the coordination of complex cognitive processes including impulse control, working memory, the consideration of multiple options and their possible consequences, and the evaluation of risk and reward, among others. (see Chapter 7).

The behavioral correlates of these anatomical changes are speculative; adolescent behaviors may in part be biologically driven and reflect the relative immaturity of the prefrontal cortex and its communication with other regions of the brain. The earlier maturation of the amygdala and other limbic structures, which are involved in the experience of fear and emotion, relative to the frontal executive function systems, which facilitate the regulation and interpretation of those emotional experiences, could explain why adolescents are more likely to make poor decisions in highly emotionally charged situations, relative to mature adults. These so-called "hot cognition" processes may result in the adolescent making a different decision in the context of a strong affective experience than he or she would in a less emotional state ("cool cognition"). These 2 types of cognitive processes may not develop at the same rate; the adolescent may be able to use higher brain structures and functions more effectively when in states of lower

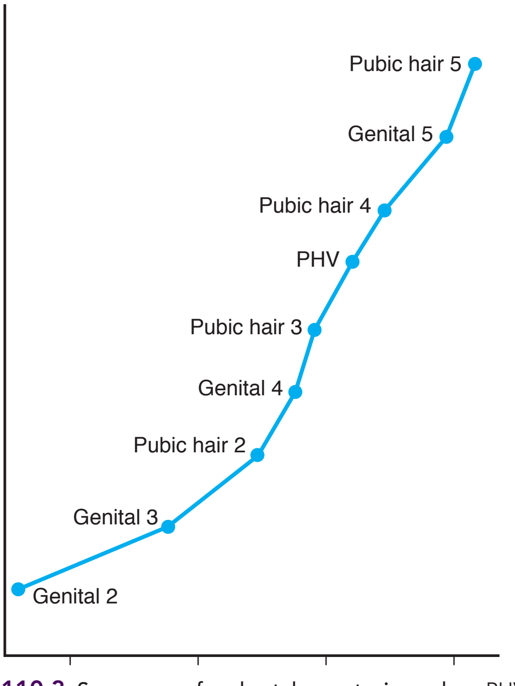

Figure 110-3 **Sequence of pubertal events in males.** PHV, peak height velocity. *(From Root AW: Endocrinology of puberty,* J Pediatr *83:1, 1973.)*

Table 110-2 Sexual Maturity Rating Stages in Females

SMR STAGE	PUBIC HAIR	BREASTS
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound; diameter of areola increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant, but less than in adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

SMR, sexual maturity rating.
From Tanner JM: Growth at adolescence, *ed 2, Oxford, England, 1962, Blackwell Scientific.*

Table 110-3 Sexual Maturity Rating Stages in Males

SMR STAGE	PUBIC HAIR	PENIS	TESTES
1	None	Preadolescent	Preadolescent
2	Scanty, long, slightly pigmented	Minimal change/enlargement	Enlarged scrotum, pink, texture altered
3	Darker, starting to curl, small amount	Lengthens	Larger
4	Resembles adult type, but less quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

SMR, sexual maturity rating.
From Tanner JM: Growth at adolescence, *ed 2, Oxford, England, 1962, Blackwell Scientific.*

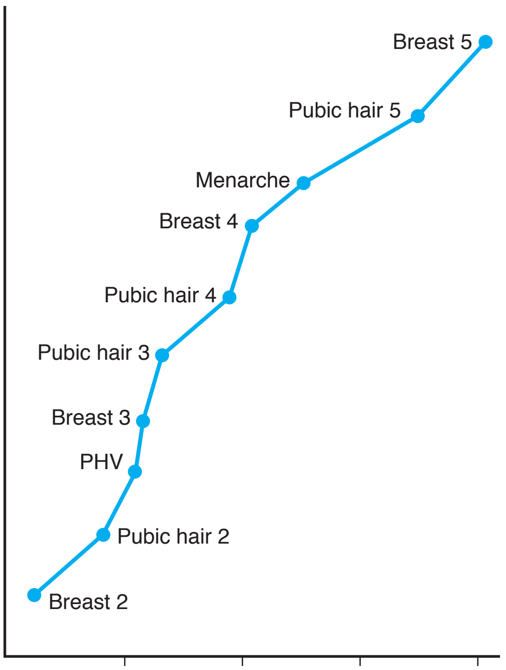

Figure 110-4 Sequence of pubertal events in females. PHV, peak height velocity. *(From Root AW: Endocrinology of puberty,* J Pediatr *83:1, 1973.)*

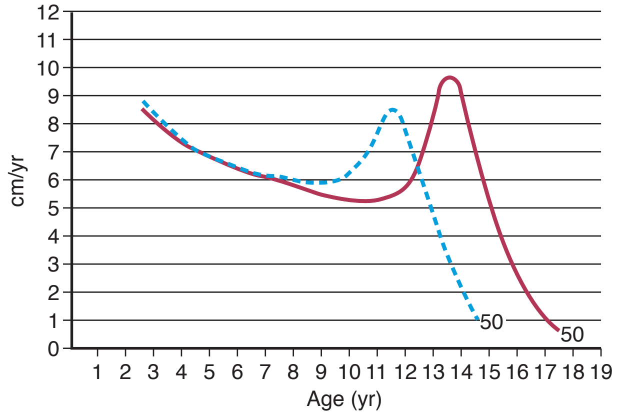

Figure 110-5 Height velocity curves for American males *(solid line)* and females *(dashed line)* who have their peak height velocity at the average age (i.e., average growth tempo). *(From Tanner JM, Davies PSW: Clinical longitudinal standards for height and height velocity for North American children,* J Pediatr *107:317, 1985.)*

emotional arousal. Adolescents' risk taking, desire for immediate gratification, and increased sensation and novelty seeking are similarly believed to result, in part, from this asynchronous brain maturation.

Early adolescents often continue to employ the concrete operational cognitive processes of childhood. Although formal operational cognition is developing, it may be applied inconsistently across different domains. A young adolescent may be able to use abstract thought when completing schoolwork, but not when working through a personal dilemma. Early adolescence also is characterized by egocentricity, the adolescent's belief that they are the center of everyone's attention. Despite being largely imagined, this perception of always being "on stage" can be stressful to the adolescent, who may feel that others are constantly judging or evaluating the adolescent. Early adolescents express a greater need for privacy than they did in childhood, and begin to appreciate the privacy of their own thoughts. With ongoing cognitive development, middle adolescents are more able to consider the needs and feelings of other people. Their creativity and intellectual abilities are enhanced. Perhaps as a result of their increased capacity for abstract thought in combination with a persistent perception of uniqueness, middle adolescents may feel a sense of immortality and immunity to the consequences of risky behaviors. Late adolescents are more future-oriented and able to delay gratification. They can think more independently, consider others' views, and compromise. They have a stronger sense of self, and more stable interests. Under times of

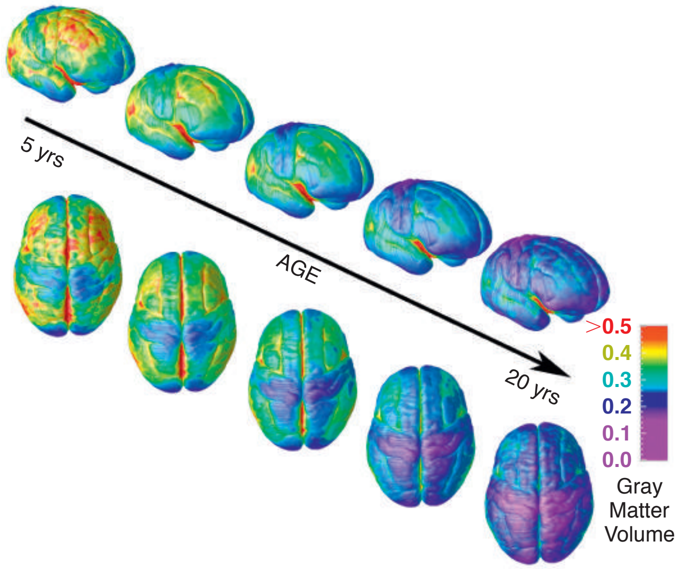

Figure 110-6 Brain Maturation ages 5-20 yr. Constructed from MRI scans of healthy children and teens, figure compresses 15 yr of brain development (ages 5-20) Red = more gray matter, blue = less gray matter. Gray matter wanes in a back-to-front wave as the brain matures and neural connections are pruned. *(Courtesy of Paul Thompson, PhD. UCLA Laboratory of Neuroimaging.)*

stress, adolescents may temporarily revert back to the cognitive processes and coping strategies used at younger ages.

Moral development generally accompanies cognitive development. Preadolescents, concrete and individualistic, follow rules in order to please authority figures and avoid punishment. As they move into early adolescence, they develop a stronger sense of right and wrong, but are likely to perceive these as absolute and unquestionable. Middle and late adolescents may establish a sense of morality driven by their desire to be seen as a good person, to behave in a manner according to their perceived place in society, or by their sense of obligation to care for others. Moral decision making still may be highly subject to emotional context, however. Late adolescents may develop a rational conscience and an independent system of values, though these often are ultimately consistent with parental values. While going through this complex developmental process, religious or political organizations that promote simple answers to complex social or moral questions may hold great appeal to the adolescent.

PSYCHOSOCIAL DEVELOPMENT

In contrast to cognitive development, psychosocial development correlates more strongly with pubertal status and physical maturation than with chronologic age. While cognitive development is more biologically determined, psychosocial development is subject to greater environmental and cultural influences. Indeed, cultural variation can be dramatic. Some late adolescents move immediately from high school into marriage, childbearing, working, and financial independence; others remain dependent on the parents while pursuing their own education for several more years, in a period sometimes referred to as *emerging adulthood*. Psychosocial development also may be nonlinear, with different domains of growth progressing along different timelines. An overriding theme of psychosocial development is the concept of identity formation and consolidation as the adolescent moves away from the nurturing protection of the family, develops an increased affiliation with the peer group(s), and ultimately defines himself or herself as an individual.

Separation from the parents is a hallmark of adolescent development. Early adolescents start to seek out more privacy at home, spending less time with the parents. They begin to reject parental advice and involvement in their decision-making as they explore the boundaries of their dependence on, and independence from, their parents. With evolving cognitive skills, an adolescent has the ability to conceive of an ideal parent, and contrast this ideal with his or her own parents. Adolescents may seek out alternative adult role models, such as teachers, coaches, or parents of friends. Parent–child conflict often peaks during middle adolescence, with disagreements over privileges, independence, and other limits set by the parents. Adolescents may appear intermittently to seek and reject parental acceptance. It is theorized that perhaps the adolescent *needs* to conceive of the parents as "wrong" in order to ameliorate the pain of separating from them. Throughout this time, however, the parents remain a critical source of nurturing and support for the adolescent, and continue to exert significant influence over the adolescent's decision making. Paradoxically, frequent arguments and conflict may coexist with strong emotional bonds and closeness. The late adolescent may reestablish a more "adult–adult" type of relationship with the parents, once again seeking out and considering parental advice and guidance as they enter adulthood.

Increasing importance of the peer group also may buffer the emotional trauma of separating from the parents. Early adolescents tend to socialize largely with same sex peers, both in their individual friendships and larger groups. Females' peer groups tend to be more relationship oriented, whereas males' peer groups are more likely to be centered around a particular activity. In both cases, group cohesion and a sense of belonging become important. Peers become increasingly important in middle adolescence, during which time the adolescent may experiment with being a part of different groups and "try on" different identities. These groups may include both genders. Peer groups may arise from organized activities, such as sports or clubs, or may simply be friendship based. Gang membership is another form of peer acceptance. Conformity with the peers in manners of dress, speech, and behavior is a normal part of this process, and should not necessarily be viewed negatively. Similarly, peer pressure may exist, but its influence over the adolescent's decision making may be positive, negative, or negligible. Acceptance and successful navigation of peer groups during adolescence may give the individual more confidence to move into and out of various social, academic, and professional groups in the future. Late adolescents are less vulnerable to peer group influence, having moved closer to establishing their own stable identity. Their cognitive skills allow them to choose selectively among different peer groups, endorsing and adopting individual values and behaviors that best reflect who they are becoming.

Early adolescents have increased **sexual awareness and interest**, which may manifest as sexual talk and gossip, and often is focused on sexual anatomy. Masturbation and other sexual exploration, sometimes with same-sex peers, are common. The prevalence of other forms of sexual behavior varies by culture; in general, these behaviors are less common in early adolescents. Romantic relationships, if they exist at all, lack emotional depth. Sexual curiosity, experimentation, and activity become more common among middle adolescents. Same-sex attraction is common; sexual orientation may become clear to some adolescents, but still may be evolving in others during this time. Dating behaviors may be seen, but this is culture dependent and may not be a popular construct for all adolescents. Individual relationships often continue to emphasize sexual attraction over emotional intimacy, the latter of which may not be seen until late adolescence. At this time, relationships increasingly involve love and commitment, and demonstrate greater stability.

Body image may affect (and be affected by) adolescents' psychosocial development as well. Early and middle adolescence are commonly the ages at which poor or distorted body image and eating disorders develop. Early adolescents undergo rapid physical changes and may experience uncertainty about whether all of these anatomic and physiologic changes are progressing normally. Reassurance from adults, including their healthcare providers, may be comforting. As puberty comes to an end and these changes slow, the middle adolescent's preoccupation may shift to whether the adolescent is attractive to others. A strong emphasis on physical appearance during this time is normal. Although this focus on physical appearance may continue into adulthood, late adolescence generally is characterized by a shifting balance

toward introspection, with somewhat less emphasis placed on external characteristics.

The **timing of pubertal changes** also can affect psychosocial development and well-being. The progression of pubertal changes in males is generally associated with a positive self-image. Females may initially perceive these changes in their physical appearance more negatively. This appears to be especially true for early-maturing females, some of whom experience greater decreases in self-esteem, engage in more disruptive behaviors, and have more conflict with their parents than do on-time or late-maturing females. Perhaps because they are more comfortable associating with older peers, they are vulnerable to making poor decisions when exposed to high-risk situations, still lacking the cognitive skills to effectively navigate these situations. Early-maturing males tend to have greater self-confidence, social, and academic success, while later-maturing males are at risk for more internalizing behaviors and diminished self-esteem. Many other factors influence how adolescents experience puberty, and supportive peers and adults can have a positive impact on psychosocial development. With successful navigation of these domains, the emerging adult moves into the world with a strong sense of personal identity and their place in society. They are able to work toward a vocation and financial independence, and to manage the responsibilities of adulthood.

IMPLICATIONS FOR PROVIDERS AND PARENTS

Providers can help parents approach their child's adolescent years by reframing some of the "challenges" of adolescence as normal developmental milestones that should be anticipated and accepted. Puberty and emerging sexuality should be approached as positive and health-affirming life changes, rather than focusing discussions only on the negative reproductive risks and outcomes. Even good-natured teasing about bodily changes can be detrimental to the adolescent's self-image. Early-maturing females and late-maturing males should be supported, recognizing their potential increased risk for psychosocial challenges. Emerging positive coping strategies should be promoted in all youth, particularly those with chronic illness or other challenges. Providers need to determine the young adolescents' cognitive development and capacity for abstract thought, and to tailor their communication and counseling style accordingly. Physical examinations should be performed in private with the parent outside the exam room (provided the adolescent is comfortable with this), which also affords the adolescent and provider an opportunity to discuss confidential issues. Reassurance of normal development should be provided.

As adolescents develop more independence and parent–child conflict peaks, providers should remind parents that this is typical, and that arguing does not mean the adolescent does not value the parents' input and perspectives. Although some may rebel initially, most adolescents ultimately adopt a value system very similar to that of their parents. Even if discussions feel ineffective to parents, they should continue to demonstrate and model these values to their child. Similarly, rather than categorically dismissing their child's "negative" interests, such as playing a violent video game, parents should be encouraged to use these opportunities to model critical thinking about the impact of such an activity. Potentially negative peer groups may be approached the same way, while fostering the development of positive peer networks. Authoritative parenting, in which clear and appropriate negotiated limits are set in the context of a caring and mutually respectful parent–child relationship, is most strongly associated with positive psychosocial development. Parental connectedness and close supervision or monitoring of the youth's activities and peer group can be protective against early onset of sexual activity and involvement in other risk-taking behaviors, and can foster positive youth development. Parents should also assume an active role in their adolescent's transition to adulthood to ensure that their child receives appropriate preventive health services.

Parents and providers may each work with adolescents to foster good decision making. In addition to providing adolescents with accurate and complete health information, the adolescent's cognitive ability to use this information in various contexts must be considered. Adolescents may find themselves needing to make important decisions in highly affectively charged situations, in which they may be unable to effectively manage their emotions and use their higher cognitive functions to think through the consequences of their decision. For example, if a romantic couple gets "carried away" in a sexual situation with high emotional arousal, they may make the decision to proceed with unprotected intercourse. By anticipating this situation ahead of time, under conditions of lower emotional arousal, and making a plan for how they will deal with this should it occur, it is possible they may make a different decision (e.g., stick with their prior decision never to have sex without protection), when the time comes. Parents and healthcare providers are in a position to encourage and foster this anticipation and planning under conditions of "cool cognition."

Providers may need to help parents distinguish normal adolescent development and risk-taking behaviors from possible signs of a more serious mental health or conduct problem. Bids for autonomy, such as avoiding family activities, demanding privacy, and increasing argumentativeness, are normal; extreme withdrawal or antagonism may be dysfunctional. Bewilderment and dysphoria at the start of middle school are normal; continued failure to adapt several months later suggests a more serious problem. Although some degree of risk-taking is normal, progressive escalation of risk-taking behaviors is problematic. In general, when the adolescent's behaviors cause significant dysfunction in the domains of home life, academics, or peer relationships, they should be addressed by the parents and healthcare provider, and referral to a mental health provider may be considered. In most cases, parents can be reassured that although adolescence can pose unique challenges, their adolescent, like most adolescents, will come through it to become a successful and happy adult.

Bibliography is available at Expert Consult.

110.2 Sexual Identity Development

Walter O. Bockting

TERMS AND DEFINITIONS

Sex and Sexual Identity

Sex is multifaceted, with at least 9 components: chromosomal sex, gonadal sex, fetal hormonal sex (prenatal hormones produced by the gonads), internal morphologic sex (internal genitalia), external morphologic sex (external genitalia), hypothalamic sex (sex of the brain), sex of assignment and rearing, pubertal hormonal sex, and gender identity and role. *Sexual identity* is a self-perceived identification distilled from any or all aspects of sexuality, and has at least 4 components: sex assigned at birth, gender identity, social sex role, and sexual orientation.

Sex Assigned at Birth

A newborn is assigned a sex before (typically through ultrasound) or at the time of birth based on the external genitalia (natal sex). In case of a *disorder of sex development*, these genitalia may appear ambiguous, and additional components of sex (e.g., chromosomal, gonadal, hormonal sex) are assessed. In consultation with specialists, parents assign the child a sex that they believe is most likely to be consistent with gender identity, which cannot be assessed until later in life (see Chapter 588).

Gender Identity, Gender Role, and Social Sex Role

Gender identity refers to a person's basic sense of being a boy/man, girl/woman, or other gender (e.g., transgender). *Gender role* refers to one's role in society, typically either the male or female role. Gender identity needs to be distinguished from *social sex role* (also referred to as gender expression), which refers to characteristics in personality, appearance, and behavior that are, in a given culture and time, considered masculine or feminine. Gender role is about one's presentation as a boy/man or girl/woman, whereas social sex role is about the masculine and/or

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feminine characteristics one exhibits in a given gender role. Both boys/men, girls/women, and transgender persons can be masculine and/or feminine to varying degrees; gender identity and social sex role are not necessarily congruent. A child or adolescent might be *gender role nonconforming*, that is, a predominantly feminine boy or a predominantly masculine girl.

Sexual Orientation and Behavior

Sexual orientation refers to attractions, behaviors, fantasies, and emotional attachments toward men, women, or both. *Sexual behavior* refers to any sensual activity to pleasure oneself or another person sexually.

Gender Variant and Transgender

Gender variant refers to any gender identity or role that varies from what is typically associated with one's sex assigned at birth. Sometimes the term *gender variant identity* is used to refer to variation in gender identity and in that case is synonymous with transgender. *Transgender* people are a diverse group of individuals who cross or transcend culturally defined categories of gender. They include *transsexuals* (who typically live in the cross-gender role and seek hormonal and/or surgical interventions to modify primary or secondary sex characteristics); *cross-dressers* or *transvestites* (who wear clothing and adopt behaviors associated with the other sex for emotional or sexual gratification and may spend part of the time in the cross-gender role); *drag queens* and *kings* (female and male impersonators); and individuals identifying as *bigender* (both man and woman) or *genderqueer* (gender variant). Transgender individuals may be attracted to men, women, or other transgender persons.

FACTORS THAT INFLUENCE SEXUAL IDENTITY DEVELOPMENT

During prenatal sexual development, a gene located on the Y chromosome (*XRY*) induces the development of testes. The hormones produced by the testes direct sexual differentiation in the male direction resulting in the development of male internal and external genitalia. In the absence of this gene in XX chromosomal females, ovaries develop and sexual differentiation proceeds in the female direction resulting in female internal and external genitalia. These hormones may also play a role in sexual differentiation of the brain. In disorders of sex development, chromosomal and prenatal hormonal sex varies from this typical developmental pattern and may result in ambiguous genitalia at birth.

Gender identity develops early in life and is typically fixed by 2-3 yr of age. Children first learn to identify their own and others' sex (*gender labeling*), then learn that gender is stable over time (*gender constancy*), and finally learn that gender is permanent (*gender consistency*). What determines gender identity remains largely unknown, but it is thought to be an interaction of biologic, environmental, and sociocultural factors.

Some evidence has been found for the impact of biologic and environmental factors on social sex role and gender role behavior, while their impact on gender identity remains less clear. Animal research shows the influence of prenatal hormones on sexual differentiation of the brain. In humans, prenatal exposure to unusually high levels of androgens in girls with congenital adrenal hyperplasia is associated with more masculine gender role behavior, gender variant identity, and same-sex sexual orientation, but cannot account for all of the variance found (see Chapter 576). Research on environmental factors has focused on the influence of sex-typed socialization. Social sex role stereotypes develop early in life. Until later in adolescence, boys and girls are typically socially segregated by gender, reinforcing sex-typed characteristics such as boys' focus on rough-and-tumble play and asserting dominance, and girls focus on verbal communication and creating relationships. Parents, other adults, teachers, peers, and the media serve as gender socializing role models and agents by treating boys and girls differently.

For information on the development of sexual orientation, see Chapter 110.3.

GENDER VARIANCE/GENDER ROLE NONCONFORMITY AMONG CHILDREN AND ADOLESCENTS

Prevalence

Gender variance and gender role nonconformity need to be distinguished from a transgender or a gender variant identity. The former operate on the level of social sex role, whereas the latter is about variation in core gender identity. Gender role nonconformity is more common among girls (7%) than boys (5%), but boys are referred more often than girls for concerns regarding gender identity and role. This is likely a result of parents, teachers, and peers being less tolerant of gender-variant behaviors in boys than in girls.

Gender variance as part of exploring one's gender identity and role is part of normal sexual development. Gender variance in childhood may or may not persist into adolescence. Marked gender variance in adolescence often persists into adulthood. Only a minority of gender-variant children develop an adult transgender identity; most develop a gay or lesbian identity, and some, a heterosexual identity.

Etiology of Gender-Variant Behavior

Prenatal hormones play a role in the development of gender role nonconformity, but cannot completely account for all of the variance. A heritable component of gender-variant behavior exists, but twin studies indicate that genetic factors do not account for all of the variance. Family of origin factors hypothesized to play a role in the development of gender variance lack empirical support. Maternal psychopathology and emotional absence of the father are the only factors shown to be associated with gender variance, yet it is unclear whether these factors are cause or effect.

Stigma, Stigma Management, and Advocacy

Children with gender variance are subject to ostracism and bullying (see Chapter 39.1) from peers, which may negatively impact their psychosocial adjustment and lead to social isolation, loneliness, low self-esteem, depression, suicide, and behavioral problems. To assist children and families, individual stigma management strategies, as well as interventions to change the environment, can be offered. Stigma management might involve consultation with a health professional to provide support and education, normalizing the gender-variant behavior and encouraging the child and family to build on the child's strengths and interests to foster self-esteem. It might also involve making choices about certain preferences (e.g., a boy who likes to wear head bands) to limit these to times and environments that are more accepting. *Most health professionals agree that too much focus on curtailing gender-variant behavior leads to increased shame and undermines the child's self-esteem.*

The health professional and family can also assist the child or adolescent to find others with similar interests (within and beyond the gender-related interests) to strengthen positive peer support. Equally important are interventions in school and society to raise awareness and promote accepting and positive attitudes, take a stand against bullying and abuse, and implement antibullying policies and initiatives. *Gay, lesbian, bisexual, transgender, and straight alliance groups are helpful in providing a haven for gender-variant youth, as well as recognizing them as part of diversity to be respected and embraced within the school system.*

GENDER-VARIANT AND TRANSGENDER IDENTITY AMONG CHILDREN AND ADOLESCENTS

Prevalence

Approximately 1% of parents of 4-11 yr old boys report that their son wished to be of the opposite sex; for girls this percentage is 3.5% for 4-11 yr olds.

Boys are referred by caregivers more often than girls for concerns regarding gender identity. Only a minority of children's gender identity concerns persist into adolescence (20% in 1 study of boys). Persistence of gender identity concerns from adolescence into adulthood is higher; the majority identify as transgender in adulthood and may pursue sex

reassignment. On the basis of adults enrolled in a national sex reassignment program in the Netherlands, the prevalence of transsexual adults is estimated at 1 : 11,900 for male-to-females and 1 : 30,400 for female-to-males. The prevalence of transgender adults in the United Sates is estimated at 1:200.

Etiology of a Gender Variant Identity

The etiology of transgender identity remains unknown. Factors hypothesized to play a role in the development of a transgender identity include environmental and biologic factors. Gender variant children seem to have more trouble than other children with basic cognitive concepts concerning their gender. They may experience emotional distance from their father. Whether these factors are cause or effect remains unclear.

There may be an influence of prenatal and perinatal hormones on sexual differentiation of the brain. Some girls with congenital adrenal hyperplasia develop a male gender identity, yet most do not. The size of the sex-dimorphic central part of the bed nucleus of the stria terminalis in the hypothalamus of male-to-female transgender individuals is smaller than in males and within the range of nontransgender women; the opposite is true for female-to-male transgender individuals. This structure is regulated by hormones in animals, but in humans no evidence yet exists of a direct relationship between prenatal and perinatal hormones and the sexually dimorphic nature of this nucleus.

Clinical Presentation

Children with a gender variant identity may experience 2 sources of stress: internal distress inherent to the incongruence between sex assigned at birth and gender identity (gender dysphoria) or distress associated with social stigma. The first source of distress is reflected in discomfort with the developing primary and secondary sex characteristics and the gender role assigned at birth. The second source of distress relates to feeling different, not fitting in, peer ostracism, and social isolation, and may result in shame, low self-esteem, anxiety, or depression.

Boys with a gender variant identity may at an early age identify as a girl, expect to grow up female, or express the wish to do so. They may experience distress about being a boy and/or having a male body, prefer to urinate in a sitting position, and express a specific dislike of their male genitals and even want to cut off their genitals. They may dress up in girls' clothes as part of playing dress up or in private. Girls may identify as a boy, expect or wish to grow up male. They may experience distress about being a girl and/or having a female body, pretend to have a penis, or expect to grow one. Girls may express a dislike of feminine clothing and hairstyles. In early childhood, children may spontaneously express these concerns, yet depending on the response of the social environment, these feelings may go underground and be kept more private. The distress may intensify by the onset of puberty; the physical changes of puberty are described by many transgender adolescents and adults as traumatic.

Gender variant children and transgender adolescents may struggle with a number of general behavior problems. Both boys and girls have a predominance of internalizing (anxious and depressed) as opposed to externalizing behavioral difficulties. Boys are more prone to anxiety, have more negative emotions and a higher stress response, and are rated lower in self-worth, social competence, and psychological well-being. Gender variant children have more peer relationship difficulties than controls. Both femininity in boys and masculinity in girls are socially stigmatized, although the former seems to carry a higher level of stigma. Boys have been shown to be teased more than girls; teasing for boys increases with age. Poor peer relations is the strongest predictor of behavior problems in both boys and girls.

Transgender adolescents may struggle with a number of adjustment problems as a result of social stigma and lack of access to transgender-specific healthcare. Transgender youth, especially those of ethnic/racial minority groups, are vulnerable to verbal and physical abuse, academic difficulties, school dropout, illicit hormone and silicone use, substance use, difficulty finding employment, homelessness, sex work, forced sex, incarceration, HIV/sexually transmitted infections (STIs), and suicide. Parental support can buffer against psychologic distress, yet many parents react negatively to their child's gender variance, although mothers tend to be more supportive than fathers.

The Diagnosis of Gender Dysphoria: Criteria and Critique

Gender dysphoria (or incongruence) is classified as a mental disorder in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and International Classification of Diseases, which, particularly for children, is controversial (Table 110-4). Critics have argued that the distress children experience is mainly the result of social stigma rather than being inherent to gender variance per se and hence should not be considered a mental disorder. Critics have also expressed concern about children with normal variation in gender role being labeled with a mental disorder perpetuating social stigma, yet there is a tendency of clinicians to underdiagnose rather than overdiagnose children whose gender variance goes beyond behavior and who report gender dysphoria. These children will benefit from the diagnosis to receive early treatment in the form of support, education, advocacy, and, in case of persistent puberty-delaying hormone therapy as a precursor to feminizing or masculinizing hormone therapy.

Transgender Identity Development

A stage model of coming out might be helpful to understand the experience and potential challenges transgender youth might face. In the *pre–coming out* stage, the individual is aware that their gender identity is different from that of most boys and girls. In addition to a gender identity that varies from sex assigned at birth, some of these children are also gender-role nonconforming while others are not. Those who are also gender-role nonconforming cannot hide their transgender identity, are noticed for who they are, and may face teasing, ridicule, abuse, and rejection. They must learn to cope with these challenges at an early age and usually proceed quickly to the next stage of *coming out*. Children who are not visibly gender role nonconforming are able to avoid stigma and rejection by hiding their transgender feelings. They often experience a split between their gender identity cherished in private and expressed in fantasy and a false self-presented outwardly to fit in and meet gendered expectations. These individuals often proceed to coming out later in life.

Coming out involves acknowledging one's transgender identity to self and others (parents, other caregivers, trusted health providers, peers). An open and accepting attitude is essential; rejection can perpetuate stigma and its negative emotional consequences. By accessing transgender community resources, including peer support (either online or offline), the transgender youth can then proceed to the *exploration* stage. This is a time of learning as much as possible about being transgender, getting to know similar others, and experimenting with various options for gender expression. Changes in gender role are carefully considered, as are medical interventions to feminize or masculinize the body to alleviate dysphoria. Successful resolution of this stage is a sense of pride in being transgender and comfort with gender role.

Once gender dysphoria has been alleviated, the individual can proceed with other human development tasks, including dating and relationships in the *intimacy* stage. As a result of social stigma and rejection, transgender individuals may struggle with feeling unlovable. Sexual development has often been compromised by gender and genital dysphoria. Now that greater comfort has been achieved with gender identity and role, dating and sexual intimacy have a greater chance of succeeding. Finally, in the *integration* stage, transgender is no longer the most important signifier of identity but one of several important parts of overall identity.

Interventions and Treatment

Health providers can assist gender variant children, adolescents, and their families by directing them to resources and by helping them to make informed decisions about changes in gender role and the available medical interventions to reduce intense and persistent gender dysphoria. To alleviate socially induced distress, interventions focus on stigma management and stigma reduction. It might be in the child's best interest to set reasonable limits on transgender expression

Table 110-4 Summary of DSM 5 Diagnostic Criteria for Gender Dysphoria

GENDER DYSPHORIA IN CHILDREN (302.6) (F64.2)

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 6 of the following (1 of which must be criterion A1):
   1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
   2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
   3. A strong preferences for cross-gender roles in make-believe play or fantasy play.
   4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
   5. A strong preference for playmates of the other gender.
   6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
   7. A strong dislike of one's sexual anatomy.
   8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

SPECIFY IF WITH A DISORDER OF SEX DEVELOPMENT (E.G., CONGENITAL ADRENAL HYPERPLASIA OR ANDROGEN INSENSITIVITY SYNDROME)

GENDER DYSPHORIA IN ADOLESCENTS OR ADULTS

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 2 of the following:
   1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
   2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
   3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
   4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
   5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

SPECIFY IF WITH A DISORDER OF SEX DEVELOPMENT (E.G., CONGENITAL ADRENAL HYPERPLASIA OR ANDROGEN INSENSITIVITY SYNDROME)

SPECIFY IF POSTTRANSITION: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen, namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

Adapted from the American Psychiatric Association, Diagnostic and statistical manual of mental disorders, *ed 5, Washington, DC, 2013, American Psychiatric Publishing.*

contributing to teasing and ridicule. The main goal of these interventions is not to change the child's gender variant behavior but to assist families, schools, and the wider community to create a supportive environment in which the child can thrive and safely explore his or her gender identity and expression. Decisions to change gender roles, particularly in school, are not to be taken lightly and are best carefully anticipated and planned in consultation with parents, child, teachers, school counselor, and other providers involved in the adolescent's care. Medical interventions are available as early as Tanner Stage 2. Such treatment is guided by the Standards of Care set forth by the World Professional Association for Transgender Health. Although some controversy still exists about the appropriateness of early medical intervention, follow up studies of adolescents treated in accordance with these guidelines show it to be effective in alleviating intense and persistent gender dysphoria. Care needs to be taken not to foreclose the child's exploration of identity.

Pediatricians who encounter transgender youth in their practice should be careful not to make assumptions about gender and sexual identity, but rather ask youth how they would describe themselves. This includes asking if they like being a boy or girl, have ever questioned this, or wished they were born the other sex; have a preferred nickname or pronoun (*he* or *she;* if not sure, avoid pronouns); and how they feel about their maturing body and sex characteristics, and what they would change about that if they could. Extra caution should be exercised during physical and genital exams because transgender youth may be particularly uncomfortable with their anatomy. When considering contraceptive options for female-to-males, alternatives to feminizing agents should be explored. For transgender-specific medical interventions, transgender youth should be referred to specialists in the treatment of gender dysphoria (see World Professional Association for Transgender Health, www.wpath.org). For other health concerns, ensure referral to transgender or lesbian, gay, bisexual, transgender (LGBT)-friendly providers, especially in the case of gender segregated treatment facilities. Gender Spectrum (www.genderspectrum.org), Advocates for Youth (www.advocatesforyouth.org), and Parents, Families and Friends of Lesbians and Gays (www.pflag.org) offer excellent support resources for transgender youth and their families.

Bibliography is available at Expert Consult.

110.3 Gay, Lesbian, and Bisexual Adolescents

Stewart L. Adelson and Mark A. Schuster

Understanding a child or adolescent's sexual and emotional development is an essential part of any comprehensive pediatric evaluation. For youth who are or might be gay, lesbian, or bisexual (GLB), such understanding is particularly important. GLB youth as a group have the same health and developmental needs as all youth, and their sexual orientation is a normal variation of human sexuality; however, they encounter distinct developmental challenges and can have additional health and mental health needs related to their orientation and others'

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reaction to it. Their sexual orientation is often different from that expected by family, peers, and society and they must cope with peer rejection, bullying, or family nonacceptance more frequently than most youth. Although the majority of GLB adolescents grow up physically and mentally healthy, they are at increased risk for certain medical and psychological problems as a result of these stresses and the epidemiology of health threats like HIV and other STIs. Pediatric healthcare providers are key in monitoring for such issues, supporting healthy development, and intervening when necessary to prevent or treat the problems for which GLB youth are at risk.

DEFINITIONS

Sexual orientation is the degree of attraction to the people of a particular sex. It encompasses emotional and erotic desires, physiologic arousal, sexual behavior, sexual identity, and social role. As sexuality develops, youth can be oriented entirely toward males, females, or both to various degrees on a continuum. Romantic attraction to the opposite sex is heterosexuality, to the same sex is homosexuality, and to both is bisexuality. **Gay** is a common term for homosexual, in both males and females; **lesbian** refers to homosexual females. Those unsure of their orientation are **curious** or **questioning**. The term **young men who have sex with men** (**MSM**) is sometimes used in the research literature to denote male youth who are engaging in sexual activity with other males, regardless of how they identify themselves.

PREVALENCE OF HOMOSEXUALITY AND BISEXUALITY IN YOUTH

Some junior high and high school students are unsure of their sexual orientation, while others say they are gay, lesbian, or bisexual. Some who do not identify as GLB report same-sex attraction, fantasies, or behavior. Certainty about sexual orientation and identity increases through adolescence with sexual experience. Those who fear nonacceptance may try to suppress or deny their orientation. Consequently, various aspects of orientation—feelings, behavior, and identity—may not be consistent in an individual, and may change during development. Only some youth with homosexual experience identify as "gay," consistent with reluctance about having or revealing a gay identity and underscoring the difference between identity and behavior. Population surveys of youth from 2001-2009 found a median of 2.5% reported that they were "unsure" of their sexual orientation, 1.3% said they were "gay/lesbian," and 3.7% said they were "bisexual." In New York City in 2005-2007, 38.9% of adolescents with only same- or both-sex partners identified as straight.

DEVELOPMENT OF SEXUAL ORIENTATION IN CHILDHOOD AND ADOLESCENCE

See also Chapter 110.2.

Sexual orientation development begins prenatally and continues through childhood and adolescence and into adulthood. Both gender role behavior in childhood and sexual orientation in puberty and adolescence are partly influenced by prenatal genetic and neuroendocrine factors. Sociocultural and psychological factors also influence sexual development. A gay or lesbian sexual orientation is sometimes preceded developmentally by childhood **gender nonconformity**, or variation from population averages in **gender role behavior**. These are activities, interests, styles, and other attributes recognized as masculine or feminine, like toy preferences and preference for opposite-sex playmates. Although childhood gender nonconformity is not experienced by all gay people—and not all gender nonconforming children grow up to be gay—nonconformity is not uncommon (particularly among males) and leads many gay or lesbian people to feel different from peers in childhood, even before sexual desire or identity emerges. When not protected from stigma, gender-nonconforming children may experience ostracism, bullying, or family nonacceptance. These reactions to gender nonconformity can lead to later difficulty integrating a healthy, positive self-image and to long-term mental health problems.

Less frequently, gay or lesbian sexual orientation in adolescence is preceded by childhood *gender incongruity/dysphoria*, a distinct phenomenon in which an individual's gender identity differs from phenotypic sex and assigned gender at birth.

STIGMA, RISK, AND RESILIENCE

Homosexuality has been documented across cultures and historical periods; its meaning and acceptance vary greatly with social context. Gay people are now generally more visible and accepted than previously in the United States; still, youth are often exposed to antihomosexual attitudes. For many GLB youth, revealing their sexual orientation ("coming out") to family, peers, healthcare providers, and others is a significant step. Specific racial/ethnic groups may experience unique developmental stressors; African-American youth report feeling less comfortable than white peers with a gay identity and less comfortable disclosing it.

Some GLB youth experience difficulty coping with stigma. Family nonacceptance, feeling unsafe because of school harassment, and peer bullying related to sexual orientation elevate risk in GLB adolescents for depression, anxiety, substance abuse, suicidal thoughts and attempts, and social problems like truancy, dropping out, running away, and homelessness. Even when not overtly threatened, GLB youth frequently encounter negative attitudes that force them to hide at a developmental period when acceptance holds great significance. Mental health problems, risk taking, or substance use may increase exposure to HIV/STIs. Stigma may also impede access to healthcare in some communities. Thus, along with factors influencing exposure and susceptibility to health threats, stigma partly mediates elevated risk for health and mental health problems in GLB youth.

It is important to reduce stigma against, support acceptance of, and promote resilient coping among GLB youth. Family connectedness and school support and safety are important protective factors against depression, suicidal thoughts and attempts, and substance abuse. GLB antiharassment policies and gay-straight alliances as well as anti-bullying programs increase school safety.

HEALTH AND MENTAL HEALTH

Depression and Suicidality

Rates of suicidality are about 2 or 3 times higher among gay and lesbian youth, and up to 5 times higher among bisexual youth, than among the general population. Family rejection, bullying, and other victimization motivated by homophobia accounts statistically for increased depression and suicidal thoughts and attempts in GLB adolescents. Suicidal thoughts or attempts are highest during the interval following a same-sex sexual experience and prior to self-acceptance as gay.

Sexually Transmitted Infections

The epidemiology of STIs (see Chapter 120), related to specific sexual practices, as well as prevalence of certain STIs in GLB communities, informs recommended counseling, screening, and treatment strategies. Anal intercourse has been shown to be the most efficient route of infection by hepatitis B (see Chapter 358), cytomegalovirus (see Chapter 255), and HIV (see Chapter 276). Oral–anal and digital–anal contact can transmit enteric pathogens, such as hepatitis A. Unprotected oral sex also can lead to oropharyngeal disease in the receptive partner and gonococcal and nongonococcal urethritis in the insertive partner. Certain STIs, particularly ulcerative diseases, such as syphilis (see Chapter 218) and herpes simplex virus infection (see Chapter 252.5), facilitate spread of HIV.

Among U.S. adolescents and young adults, young MSM continue to face the greatest toll of HIV/AIDS for various reasons, including misinformation, noncommunication with partners about risk reduction, potentially false assumptions about partners' serostatus, substance use, and impaired reasoning and judgment. Rates are especially high among black young MSM. Although possible, female-to-female sexual transmission of HIV is inefficient, and females who only engage in same-sex behavior are less likely than other youth to acquire an STI. However, boys and girls who identify as gay or lesbian may engage in sexual activity with partners of the other gender, so counseling and screening for all types of STIs are still relevant.

Substance Abuse

See also Chapter 114.

A subset of GLB youth display increased rates of alcohol and substance use, including more binge drinking and earlier onset and more rapid trajectory of substance use. Problem drinking may be greatest in youth who do not identify as GLB but have same-sex attractions or engage in same-sex sexual behavior. Marijuana and other illicit drug use is more common among bisexual females, but studies have found no increased rates among young gay and bisexual males, and males with bisexual behavior and identity are less likely to drink than young heterosexual males. Smoking is increased among bisexual adolescent females and possibly in adolescent lesbians; studies are conflicting regarding smoking in other GLB adolescent groups.

Obesity and Disordered Eating

See also Chapter 26.

Existing studies suggest certain GLB youth are at risk for disordered eating. Compared with heterosexual girls, lesbian and bisexual girls generally have a more positive body image, although they are more likely to be overweight. In contrast, young gay and bisexual males are more likely to have body image concerns and are more likely to restrict eating or engage in compensatory weight loss strategies. Binge eating may also be more common in GLB youth. Behaviorally bisexual youth may be at greatest risk for disordered eating.

Psychosocial Problems

Academic underachievement, truancy, and dropping out among GLB adolescents are frequently associated with homophobic victimization, harassment, violence, and feeling unsafe at school. Youth who eventually identify as GLB appear to experience higher rates than other youth of child abuse, running away, or being thrown out of their homes. Homosexual young people are overrepresented in homeless and runaway populations across the United States. Life on the streets or in shelters exposes them to drugs and sexual abuse and promotes illegal conduct for survival.

RECOMMENDATIONS FOR CARE

Evaluation

The goal of GLB pediatric care is physical health, social and emotional well-being, and promotion of healthy development. Physicians should provide nonjudgmental care to all adolescents, including those who are GLB or questioning. They should receive the age-appropriate history, examination, and anticipatory guidance recommended for adolescents in general. With some exceptions noted below, the physical examination and laboratory evaluation of GLB and questioning adolescents are the same as for any teenager. However, providers should screen for special potential medical and psychosocial threats to GLB teenagers' health appropriately.

A nonjudgmental healthcare environment, with open communication and a positive relationship with youth and families, is important. In the waiting room, written material about sexual orientation, support groups, and community resources will signal openness to discussing sexuality. Registration forms recognizing the possibility of same-gender parents signal a safe setting (e.g., forms can list parent/guardian #1, parent/guardian #2). Sexual history questions should avoid heterosexual assumptions (e.g., "are you dating someone" instead of "do you have a boyfriend/girlfriend?"). This is important at all ages. Discussing confidentiality and incorporating into each adolescent visit private time with no parent in the room (see Chapter 112) may facilitate discussing sexual orientation, as may use of appropriate health history forms, like the American Medical Association's Guidelines for Adolescent Prevention Services Questionnaire.

Clinicians should remember that any youth might be GLB whether or not they are identified or perceived as such, so clinicians should not presuppose a particular orientation. Competency in conveying sensitivity, acceptance, and respectfulness; effective communication skills; and appropriate attention to privacy and confidentiality (including practices related to billing and record requests; see Chapter 112.1) are fundamental to providing high-quality care. While attuned to youth's' preferences—explicit or implied—for discussing sexual orientation, providers should take the lead tactfully, if necessary, regarding any pressing areas of clinical concern.

Medical and Sexual Health

Sexually transmitted infections (see Chapter 120) pose additional issues specific to GLB youth. Use of latex condoms for anal and oral intercourse should be discussed with boys, and the use of dental dams, cut open latex condoms, or plastic wrap during oral sex should be discussed with girls; the use of latex condoms for sexual appliances are recommended as well. It is important to emphasize that people who have been using alcohol or other drugs are at increased likelihood for engaging in riskier sexual activity. It is important not to assume that a gay boy or lesbian girl who does not identify as bisexual has not had sex with the opposite gender. Lesbians can have an unplanned pregnancy. Similarly, youth who identify as heterosexual and are attracted only to the opposite sex may still have sexual activity with a partner of the same sex.

Although vaccination against hepatitides A and B is recommended for all children, it is particularly recommended that nonvaccinated adolescent males who are having sex or are likely to have sex with males get catchup vaccines. The same recommendation applies to the quadrivalent human papillomavirus vaccine for males. The Centers for Disease Control and Prevention recommends that males who are engaging in sexual activity with males have annual testing for HIV, hepatitis A, hepatitis B, syphilis, urethral gonorrhea and chlamydia (if engaging in insertive oral or anal intercourse), oral gonorrhea (if engaging in receptive oral intercourse), and rectal gonorrhea and chlamydia (if engaging in receptive anal intercourse). For treatment of STIs, see Chapter 120.

Mental Health

Awareness of mental health and social problems is important when caring for GLB youth, as for all youth (see Chapter 111). Clinicians should monitor for depression, suicidality, anxiety, and substance abuse, and know their community's mental health resources. Minor psychosocial problems might be handled by referral to a support group for patients (e.g., Gay, Lesbian & Straight Education Network [GLSEN]) or for parents and others (e.g., Parents, Families, & Friends of Lesbians and Gays [PFLAG]). In some communities, agencies and organizations serving the GLB community can help with social, educational, vocational, housing, and other needs.

Individuals or families who harbor negative attitudes may inquire about mental health treatment to avert or change a homosexual or bisexual orientation. GLB orientation is not an illness, and leading health organizations, including the American Academy of Pediatrics, the American Academy of Family Physicians, the Society for Adolescent Health and Medicine, the American Academy of Child and Adolescent Psychiatry, and the American Medical Association, have concluded that such change is neither possible nor warranted. It is important to distinguish between a GLB orientation, which is not a mental illness, and mental health problems like depression for which GLB youth are at elevated risk. While understanding different families' values, clinicians must recognize the morbidity and mortality associated with stigma and aim to foster physical and emotional health. Individual or family therapy might be indicated for some.

Clinicians should also monitor for specific stressors such as bullying and other homophobic victimization, family nonacceptance, and abuse. Failure to confront harassment constitutes tacit assent.

Anticipatory guidance, referral, and substance abuse treatment should be considered for the subset of GLB youth who use alcohol, drug, or tobacco; some of whom may be using these to manage painful feelings related to conflicts over their sexuality.

Adolescents with serious psychiatric symptoms, such as suicidality, depression, and substance abuse should be referred to mental health specialists with competency in treating GLB adolescents. It is essential to know how to recognize and manage psychiatric emergencies such as suicidal thoughts and attempts (see Chapter 27).

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Chapter 111

The Epidemiology of Adolescent Health Problems

Gale R. Burstein

Adolescence is the first period of life where the major determinants of morbidity and mortality are behavioral rather than congenital or infectious. As adolescents make the transition from childhood to adulthood, they establish behaviors that affect both their current and future health. Adolescence is a time of immense biologic, psychologic, and social change (see Chapter 110). Many of the psychological changes have a biologic substrate in the development and eventual maturation of the central nervous system, particularly the frontal lobe areas responsible for executive functioning (Fig. 111-1). In addition to cognitive development, there are both risk and protective factors for adverse adolescent health behaviors that are dependent on the social environment as well as the mental health of an adolescent (Table 111-1).

Many adolescents continually confront the task of making healthy choices while struggling with impulsivity that can lead to unintentional consequences, such as injuries, sexually transmitted infections, or drug overdoses. Adolescents are also challenged with adopting behaviors that will affect their future adult health, such as eating nutritiously, engaging in physical activity, and choosing not to use tobacco. Environmental factors, such as family, peers, school, community, and religiosity, also contribute to adolescents' health and risk behaviors. The Centers for Disease Control and Prevention (CDC) Youth Risk Behavior Surveillance Survey, a school-based survey of a nationally representative sample of U.S. high school students, demonstrates that youth begin engaging in behaviors that place their health at risk during adolescence (Fig. 111-2).

Although according to the 2012 CDC National Health Interview Survey, a probability sample survey conducted annually, an estimated 81% of 12-17 yr olds report excellent or very good health, 23% missed 3-5 school days in the past year, 9% are uninsured, 6% have no usual place of healthcare, 11% have asthma, 11% have respiratory allergies, 10% have a learning disability, 12% have attention deficit hyperactivity disorder, and 17% take prescription medications routinely. In 2010, the mortality rate among adolescents 15-19 yr of age was 49 deaths per 100,000 population. While varying by gender, the leading causes of death overall among adolescents 15-19 yr of age are (1) unintentional injuries; (2) homicide; and (3) suicide (Table 111-2).

Within the adolescent population, disparities in health occur. Adolescent health outcomes and behaviors vary among populations that can be defined by race or ethnicity, gender, education or income, disability, geographic location (e.g., rural or urban), or sexual orientation. Health disparities result from multiple factors, including poverty, environmental threats, inadequate access to healthcare, individual and behavioral factors, and educational inequalities (Table 111-3).

Table 111-1 Identified Risk and Protective Factors for Adolescent Health Behaviors

BEHAVIOR	RISK FACTORS	PROTECTIVE FACTORS
Smoking	Depression and other mental health problems, alcohol use, disconnectedness from school or family, difficulty talking with parents, minority ethnicity, low school achievement, peer smoking	Family connectedness, perceived healthiness, higher parental expectations, low prevalence of smoking in school
Alcohol and drug misuse	Depression and other mental health problems, low self-esteem, easy family access to alcohol, working outside school, difficulty talking with parents, risk factors for transition from occasional to regular substance misuse (smoking, availability of substances, peer use, other risk behaviors)	Connectedness with school and family, religious affiliation
Teenage pregnancy	Deprivation, city residence, low educational expectations, lack of access to sexual health services, drug and alcohol use	Connectedness with school and family, religious affiliation
Sexually transmitted infections	Mental health problems, substance misuse	Connectedness with school and family, religious affiliation

Adapted from McIntiosh N, Helms P, Smyth R, editors. Fofar and Arneil's textbook of pediatrics, *ed. 6, Edinburgh, 2003, Churchill Livingstone, pp. 1757-1768; and Viner R, Macfarlane A: Health promotion,* BMJ *330:527-529, 2005.*

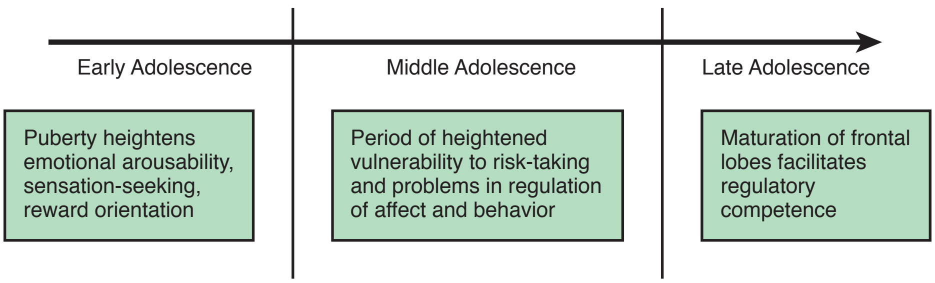

Figure 111-1 It has been speculated that the impact of puberty on arousal and motivation occurs before the maturation of the frontal lobes is complete. This gap may create a period of heightened vulnerability to problems in the regulation of affect and behavior, which might help to explain the increased potential in adolescence for risk taking, recklessness, and the onset of emotional and behavioral problems. *(From Steinberg L: Cognitive and affective development in adolescence,* Trends Cogn Sci *9:69–74, 2005.)*

Table 111-2 Leading Causes of Death Among 15-19 Yr Olds by Gender, United States, 2010*

LEADING CAUSES OF DEATH	MALE	FEMALE
#1	Accidents (unintentional injuries)	Accidents (unintentional injuries)
#2	Assault (homicide)	Intentional self-harm (suicide)
#3	Intentional self-harm (suicide)	Assault (homicide)

*Based on data from Heron M: Deaths: Leading causes for 2009. National vital statistics reports; vol 62. No. 6. Hyattsville, MD, 2013, National Center for Health Statistics.

Table 111-3 Adolescent Health Outcomes by Race/Ethnicity, United States, 2010-2012

OUTCOME	WHITE	BLACK	AI/AN	API	HISPANIC
Deaths*	47.5	70.6	61.5	22.8	41.5
Births§	20.5	43.9	34.9	9.7	46.3
Obese†	11.5	18.2	N/A	N/A	14.1
Asthma†	22.8	26.8	N/A	N/A	20.3
Depressed†	27.2	24.7	N/A	N/A	32.6
Chlamydia*	830.1	4,977.7	2,509.8	313.0***	1,191.0
Gonorrhea*	85.3	1,513.5	324.6	36.5***	139.7
HIV*	2.5	46.3	5.8	2.9***	8.1

*Rates of death in 2010, per 100,000 15-19 year old population by race/ethnicity.
**Rates of infection in 2011 per 100,000 15-19 year old population by race/ethnicity.
***Rates of Asian-only race.
†Percent high school students reporting health outcome.
§Rates of births in 2011 per 1,000 15-19 yr old females by race/ethnicity.
AI/AN, American Indian or Alaska Native; API, Asian or Pacific Islander; HIV, human immunodeficiency virus; N/A, not available.

ACCESS TO HEALTHCARE

Access to healthcare may be limited for adolescents compared to other age groups. Adolescents in the United States make fewer visits to physicians for ambulatory office visits than does any other age group; school-age children and adolescents are more likely than younger children to have unmet health needs and delayed medical care. Adolescents and young adults are less likely to be insured than all other age groups. Young adults 18-24 yr are more likely to be uninsured because until the passage in 2010 of America's Affordable Care Act, many were no longer eligible to receive benefits from their parents' health plans or public insurance programs. In addition, health insurance status differs based on income and race/ethnicity. Adolescents and young adults who are near poor (100-199% federal poverty level) and poor (below 100% federal poverty level) are less likely to have health insurance coverage than those with higher family incomes; and Hispanic and black adolescents and young adults are less likely to have health insurance coverage than their non-Hispanic white and Asian peers. Uninsured children and adolescents are less likely to receive preventive visits and have a regular source of care than the insured, and are more likely to go without treatment of symptoms.

Adolescents who actually receive preventive care may still not have access to time alone with their provider or discuss important confidential health issues, such as sexually transmitted infections, HIV, or pregnancy prevention. Less than half (40%) of adolescents have time alone with their healthcare provider during a preventive healthcare visit; sexually experienced teens report sexual health discussions more often than nonsexually experienced teens, but the frequency is still low at 64% and 33.5% for sexually experienced females and males, respectively.

Under the Patient Protection and Affordable Care Act, healthcare providers will strive to improve the health of their patient population. Healthy People provides science-based, 10-year national objectives for measuring and improving the health of all Americans by establishing benchmarks and monitoring progress over time. The Healthy People 2020 agenda includes 11 adolescent-specific objectives with a goal of improving the healthy development, health, safety, and well-being of adolescents and young adults over the next 10 yr (Table 111-4). This

Table 111-4 Healthy People 2020 Adolescent Health (AH) Objectives

- **AH-1**: Increase the proportion of adolescents who have had a wellness checkup in the past 12 months
- **AH-2**: Increase the proportion of adolescents who participate in extracurricular and out-of-school activities
- **AH-3**: Increase the proportion of adolescents who are connected to a parent or other positive adult caregiver
  - **AH-3.1**: Increase the proportion of adolescents who have an adult in their lives with whom they can talk about serious problems
  - **AH-3.2**: Increase the proportion of parents who attend events and activities in which their adolescents participate
- **AH-4**: (Developmental) Increase the proportion of adolescents and young adults who transition to self-sufficiency from foster care
- **AH-5**: Increase educational achievement of adolescents and young adults
  - **AH-5.1** ***(Leading Health Indicator)***: Increase the proportion of students who graduate with a regular diploma 4 years after starting 9th grade
  - **AH-5.2**: Increase the proportion of students who are served under the Individuals with Disabilities Education Act who graduate high school with a diploma
  - **AH-5.3**: Increase the proportion of students whose reading skills are at or above the proficient achievement level for their grade
  - **AH-5.4**: Increase the proportion of students whose mathematics skills are at or above the proficient achievement level for their grade
  - **AH-5.5**: Increase the proportion of adolescents who consider their school work to be meaningful and important
  - **AH-5.6**: Decrease school absenteeism among adolescents due to illness or injury
- **AH-6**: Increase the proportion of schools with a school breakfast program
- **AH-7**: Reduce the proportion of adolescents who have been offered, sold, or given an illegal drug on school property
- **AH-8**: Increase the proportion of adolescents whose parents consider them to be safe at school
- **AH-9**: (Developmental) Increase the proportion of middle and high schools that prohibit harassment based on a student's sexual orientation or gender identity
- **AH-10**: Decrease the proportion of public schools with a serious violent incident
- **AH-11**: Reduce adolescent and young adult perpetration of, as well as victimization by, crimes
  - **AH-11.1**: Decrease the rate of minor and young adult perpetration of violent crimes
  - **AH-11.2**: Decrease the rate of minor and young adult perpetration of serious property crimes
  - **AH-11.3**: (Developmental) Decrease the percentage of counties and cities reporting youth gang activity
  - **AH-11.4**: (Developmental) Reduce the rate of adolescent and young adult victimization from crimes of violence

From U.S. Department of Health and Human Services: Healthy People 2020, *available at: www.hhs.gov/ash/oah/resources-and-publications/healthy-people-2020.html.*

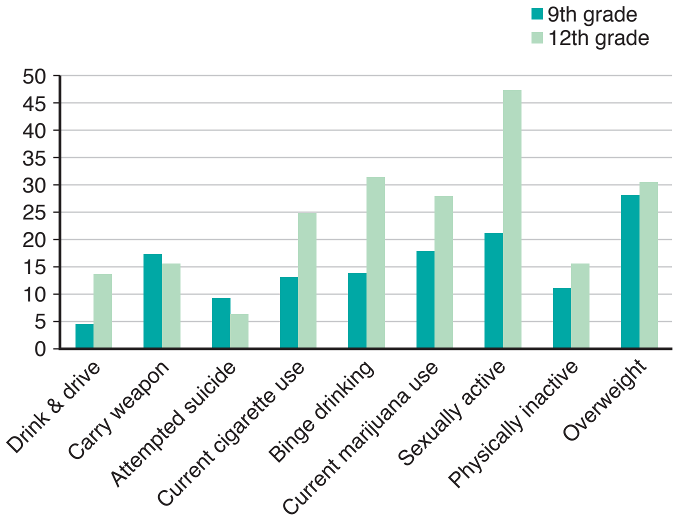

Figure 111-2 Selected health behaviors among 9th and 12th grade high school students. *(Data from Centers for Disease Control and Prevention:* 2011 Youth risk behavior surveillance system. http://www.cdc.gov/healthyyouth/yrbs/index.htm.*)*

science-based initiative is centered around a framework for public health prevention priorities and actions to improve the health status of U.S. youth.

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Chapter 112

Delivery of Healthcare to Adolescents

Gale R. Burstein

Healthcare providers play an important role in nurturing healthy behaviors among adolescents because the leading causes of death and disability among adolescents are preventable. Adolescence provides a unique opportunity to prevent or modify health conditions arising from behaviors that develop in the second decade of life and that can lead to substantial morbidity and mortality, such as trauma, cardiovascular and pulmonary disease, type 2 diabetes, reproductive health disease, and cancer.

Health systems in each community should be in place to ensure comprehensive and high-quality care to adolescents. **Health insurance coverage** that is affordable, continuous, and not subject to exclusion for preexisting conditions, should be available for all adolescents and young adults who have no access to private insurance. **Comprehensive, coordinated benefits** should meet the developmental needs of adolescents, particularly for reproductive, mental health, dental, and substance abuse services. **Safety net providers and programs that provide confidential services,** such as school-based health centers, federally qualified health centers, family planning services, and clinics that treat sexually transmitted infections (STIs) in adolescents and young adults, need to have assured funding for viability and sustainability. **Quality-of-care** data should be collected and analyzed by age so that the performance measures for age-appropriate healthcare needs of adolescents are monitored. **Affordability** is important for access to preventive services. Family involvement should be encouraged, but **confidentiality** and adolescent consent are critically important. **Healthcare providers, trained and experienced** to care for adolescents, should be available in all communities. Healthcare providers should be adequately **compensated** to support the range and intensity of services required to address the developmental and health service needs of adolescents. The creation and dissemination of provider education about adolescent preventive health guidelines have been demonstrated to improve the content of recommended care (Table 112-1). The ease of recognition or expectation that an adolescent's needs can be addressed in a setting relates to the **visibility and flexibility** of sites and services. Staff at sites should be approachable, linguistically capable, and culturally competent. Health services should be **coordinated** to respond to goals for adolescent health at the local, state, and national levels. The coordination should address service financing and delivery in a manner that reduces disparities in care.

Table 112-1 Bright Futures/American Academy of Pediatrics Recommendations for Preventive Healthcare for 11-21 Yr Olds

	PERIODICITY AND INDICATIONS
HISTORY	Annual
MEASUREMENTS	
Body mass index	Annual
Blood pressure	Annual
SENSORY SCREENING	
Vision	At 11, 15, and 18 yr visits or if risk assessment positive
Hearing	If risk assessment positive
DEVELOPMENTAL/BEHAVIORAL ASSESSMENT	
Developmental surveillance	Annual
Psychosocial/behavioral assessment	Annual
Alcohol and drug use assessment	If risk assessment positive
PHYSICAL EXAMINATION	Annual
PROCEDURES	
Immunization*	Annual
Hematocrit or hemoglobin	If risk assessment positive
Tuberculin test	If risk assessment positive
Dyslipidemia screening	If risk assessment positive
STI screening	If sexually active
HIV screening§	Discussed and offer
Cervical dysplasia screening†	Beginning at age 21 yr
ORAL HEALTH	Annual refer to dental home or administer oral health risk assessment
ANTICIPATORY GUIDANCE	Annual‡

*Schedules as per the Advisory Committee on Immunization Practices, published annually at http://www.cdc.gov/vaccines/schedules/hcp/index.html and in the January issue of *Pediatrics.*

†Screening for Cervical Cancer. April 2012. U.S. Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm.

‡Refer to specific guidance by age as listed in *Bright Futures Guidelines.*

§CDC recommends universal, voluntary HIV screening of all sexually active people, beginning at age 13 yr. The American Academy of Pediatrics recommends offering routine HIV screening to all adolescents at least once by 16-18 yr of age and to those younger if at risk. U.S. Preventive Services Task Force recommends offering routine HIV screening to all adolescents age 15 yr and older at least once and to those younger if at risk. Patients who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.

Adapted from Bright Futures and American Academy of Pediatrics Committee on Practice and Ambulatory Medicine. 2014 Recommendations for Pediatric Preventive Health Care. Pediatrics 133:568-570, 2014.

Although most adolescents in the United States have seen a healthcare provider in the past year and report a usual source of healthcare, adolescents are less likely to receive preventive care services. According to the 2011 National Health Interview Survey, an estimated 90% of 12-17 yr old U.S. adolescents had 1 or more contacts with a healthcare professional in the past year, 98% identify a usual source of care at a doctor's office or clinic, and 17% made at least 1 emergency department visit in the past year. Uninsured adolescents are the least likely to receive care. In 2011, an estimated 9% of 12-17 yr olds were without health insurance, 2% had unmet healthcare needs and 4% delayed healthcare because of cost. However, even among adolescents who are fully insured with a usual source of care, most do not receive preventive healthcare. An analysis of claims data from a large Minnesota health plan with approximately 700,000 members found that among patients ages 11-18 yr who were enrolled for at least 4 yr between 1998 and 2007, few received preventive care visits. One-third of adolescents had no preventive care visits from age 13 through 17 yr, and another 40% had only a single such visit. Nonpreventive care visits were more frequent in all age-groups, averaging about 1 per yr at age 11 yr, climbing to about 1.5 per yr at age 17 yr. Among older adolescence, females had both more preventive care and more nonpreventive care visits than did males (Table 112-2).

The Patient Protection and Affordable Care Act (ACA), enacted in March, 2010, has significantly expanded access to both commercial health plans and Medicaid for young adults age 19-26 yr (Fig. 112-1). From June 2010 through June 2012, the proportion of young adults with insurance increased from 65.7% to 73.8%. ACA provisions require that commercial health plans (a) continuing dependent coverage to 26 yr, regardless of the young adults' financial or dependent status, marriage, or educational enrollment; (b) mandate university and college student health plans to enhance consumer protections for students; (c) provide financial assistance for young adults to enroll into health insurance exchanges with incomes ranging from 133% to 399% of the federal poverty level; and offer preventive healthcare services free of any cost sharing, deductibles or copayments. For Medicaid, states must offer enrollment to all adults with incomes less than 133% of the federal poverty level.

The complexity and interaction of physical, cognitive, and psychosocial developmental processes during adolescence require sensitivity and skill on the part of the health professional (see Chapter 110). Health education and promotion, as well as disease prevention, should be the focus of every visit. In 2008, the American Academy of Pediatrics in collaboration with the U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau, published the 3rd edition of *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*, which offers providers a strategy for delivery of adolescent preventive health services with screening and counseling recommendations for early, middle, and late adolescence (Table 112-3). Bright Futures is rooted in the philosophy of preventive care and reflects the concept of caring for children in a "medical home." These guidelines emphasize effective partnerships with parents and the community to support the adolescent's health and development.

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices currently recommends routine adolescent vaccines for universal administration beginning at the 11-12 yr old visit or as soon as possible, (a) tetanus–diphtheria–acellular pertussis vaccine (Tdap), (b) the meningococcal conjugate vaccine (MCV4), and (c) the human papillomavirus vaccine (see Chapter 172). The Advisory Committee on Immunization Practices recommends annual influenza vaccination and hepatitis A vaccination (HAV) to adolescents and young adults who have not previously received the HAV vaccine series if immunity against HAV is desired or for those at increased risk for infection, such as men who have sex with men, injection drug users, and those with chronic liver disease or clotting factor disorders, or who live in areas that target older children for HAV vaccine.

The time spent on various elements of the screening will vary with the issues that surface during the assessment. For gay and lesbian youth (see Chapter 110.3), emotional and psychologic issues related to their experiences, from fear of disclosure to the trauma of homophobia, may direct the clinician to spend more time assessing emotional and psychologic supports in the young person's environment. For youth with

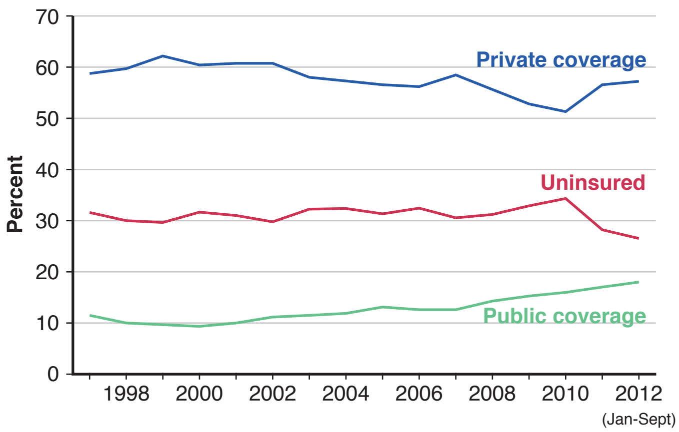

Figure 112-1 Percentage of adults age 19-25 yr with health insurance by coverage type and percentage uninsured at the time of the interview: United States, 1997–September, 2012. Note: Estimates for 2012 are based on data collected in January through September. Data are based on household interviews of a sample of the civilian noninstitutionalized population. *(Data from CDC/NCHS, National Health Interview Survey, 1997-2012, Family Core Component.)*

Table 112-2 Adjusted Mean Number of Preventive and Nonpreventive Care Visits Among Continuously Enrolled Adolescents Between the Ages of 13 and 18 Yr, Health Partners 1998-2007

CHARACTERISTIC	PREVENTIVE CARE VISITS MEAN NUMBER (SD)	*P* VALUE	NONPREVENTIVE CARE VISITS MEAN NUMBER (SD)	*P* VALUE
INSURANCE TYPE				
Commercial	1.070 (0.947)	<0.001	6.829 (6.756)	<0.005
Governmental	1.1781 (1.094)		6.412 (8.009)	
SEX				
Male	1.162 (0.985)	<0.001	7.729 (7.514)	<0.001
Female	0.991 (0.916)		5.918 (5.937)	

Note: Among adolescents with continuous enrollment (>333 days between birthdays) for 4 or more yr. Regression model adjusted mutually for insurance type and sex.
SD: standard deviation.
From Nordin JD, Solberg LI, Parker ED: Adolescent primary care visit patterns. Ann Fam Med *8:511–516, 2010.*

Table 112-3 Adolescent Screening Recommendations

		11-14 YR OLD VISIT	15-17 YR OLD VISIT	18-21 YR OLD VISIT
Universal Screening		**Action**	**Action**	**Action**
Vision (once during each of 3 adolescent age groups)		Snellen test	Snellen test	Snellen test
Dyslipidemia		Lipid screen (once between 9-11 yr)	NA	Lipid screen (once between 18-21 yr)
Selective Screening	**Risk Assessment**	**Action If RA+**	**Action If RA+**	**Action If RA+**
Vision at other ages	+ on risk screening questions	Snellen test	Snellen test	Snellen test
Hearing	+ on risk screening questions	Audiometry	Audiometry	Audiometry
Anemia	+ on risk screening questions	Hemoglobin or hematocrit	Hemoglobin or hematocrit	Hemoglobin or hematocrit
Tuberculosis	+ on risk screening questions	Tuberculin skin test	Tuberculin skin test	Tuberculin skin test
Dyslipidemia	+ on risk screening questions and not previously screened with normal results	Lipid screen	Lipid screen	Lipid screen
STIs	Sexually active	Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)	Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)	Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)
	Sexually active and + on risk screening questions	Syphilis test	Syphilis test	Syphilis test
HIV	Discuss and offer	HIV test*	HIV test*	HIV test*
Pregnancy	Sexually active, without contraception, late menses or amenorrhea	Urine hCG	Urine hCG	Urine hCG (without late or absent menses or heavy or irregular bleeding)
Cervical dysplasia†	NA	NA	NA	Pap smear at age 21 yr
Alcohol or drug use	+ on risk screening questions	Administer alcohol and drug screening tool	Administer alcohol and drug screening tool	Administer alcohol and drug screening tool

*CDC recommends universal, voluntary HIV screening of all sexually active people, beginning at age 13 yr. American Academy of Pediatrics recommends routine HIV screening offered to all adolescents at least once by 16-18 yr of age and to those younger if at risk. U.S. Preventive Services Task Force recommends routine HIV screening offered to all adolescents age 15 yr and older at least once and to those younger if at risk. Patients who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.

†Screening for Cervical Cancer. April 2012. U.S. Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm.

hCG, human chorionic gonadotropin; NA, not applicable; RA, risk assessment.

Adapted from Hagan JF, Shaw JS, Duncan PM, eds. Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents, *3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008; and American Academy of Pediatrics, Committee on Practice and Ambulatory Medicine, Bright Futures Periodicity Schedule Workgroup: 2014 recommendations for pediatric preventive health care,* Pediatrics *133(3):568–570, 2014.*

chronic illnesses or special needs, the assessment of at-risk behaviors should not be omitted or deemphasized by assuming they do not experience the "normal" adolescent vulnerabilities.

Bibliography is available at Expert Consult.

112.1 Legal Issues

Gale R. Burstein

The rights of an individual, including those of adolescents, vary widely between nations. In the United States, the right of a minor to consent to treatment without parental knowledge differs between states and is governed by state-specific minor consent laws. Some consent laws are based on a minor's status, such as minors who are emancipated, parents, married, pregnant, in the armed services, or mature. In some states, minors can be considered *emancipated* if they are or have served in the armed services or are living apart from parents and are economically independent through gainful employment. A *mature minor* is a minor who is emotionally and intellectually mature enough to give informed consent and who lives under the supervision of a parent or guardian. Courts have held that if a minor is mature, a physician is not liable for providing beneficial treatment. There is no formal process for recognition of a mature minor. The determination is made by the healthcare provider.

Some minor consent laws are based on services a minor is seeking, such as emergency care, sexual healthcare, substance abuse, or mental healthcare (Table 112-4). All 50 states and the District of Columbia explicitly allow minors to consent for their own health services for STIs. Approximately 25% of states require that minors be a certain age (generally 12-14 yr) before they are allowed to consent for their own care for STIs. No state requires parental consent for STI care or requires that providers notify parents that an adolescent minor child has received STI services, except in limited or unusual circumstances.

Minors' right to consent for contraceptive services varies from state to state. Nearly 50% of states and the District of Columbia explicitly authorize all minors to consent for their own contraceptive services; and 50% of states permit minors to consent for their own contraceptive services under specific circumstances, such as being married, a parent, currently or previously pregnant, over a certain age, or a high school graduate, or per physician's discretion.

A minor's right to consent for mental healthcare and substance abuse treatment services vary by state and age of minor, whether care is medical versus nonmedical (e.g., counseling), and whether care is delivered as an inpatient versus outpatient basis. Minor consent laws often contain provisions regarding confidentiality and disclosure, even when general state consent laws do not have such provisions.

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Table 112-4 Types of Minor Consent Statutes or Rules of Common Law That Allow for the Medical Treatment of a Minor Patient Without Parental Consent

LEGAL EXCEPTIONS TO INFORMED CONSENT REQUIREMENT	MEDICAL CARE SETTING
The "emergency" exception	• The child is suffering from an emergent condition that places his or her life or health in danger • The child's legal guardian is unavailable or unable to provide consent for treatment or transport • Treatment or transport cannot be safely delayed until consent can be obtained • The professional administers only treatment for emergent conditions that pose an immediate threat to the child
The "emancipated minor" exception	• Married • Economically self-supporting and not living at home • Active-duty status in the military • In some states, a minor who is a parent or pregnant • Some states might require a court to declare the emancipation of a minor
The "mature minor" exception	Most states recognize a mature minor, in which a minor, usually ≥14 yr, displays sufficient maturity and intelligence to understand and appreciate the benefits, risks, and alternatives of the proposed treatment and to make a voluntary and reasonable choice on the basis of that information. States vary or whether a judicial determination is required
Exceptions based on specific medical condition (state laws vary)	Minor seeks: • Mental health services • Pregnancy and contraceptive services • Testing or treatment for human immunodeficiency virus infection or acquired immunodeficiency syndrome • Sexually transmitted infection testing and treatment • Drug and alcohol addiction treatment

Data from American Academy of Pediatrics: Consent for emergency medical services for children and adolescents, Pediatrics *128:427–433, 2011.*

The confidentiality of medical information and records of a minor who has consented for his or her own *reproductive healthcare* is governed by numerous federal and state laws. Laws in some states explicitly protect the confidentiality of STI or contraceptive services for which minors have given their own consent and do not allow disclosure of the information without the minor's consent. In other states, laws grant physicians discretion to disclose information to parents.

The confidentiality of medical information and records of a minor who has consented for his or her own *healthcare* is also governed by numerous federal and state laws. Laws in some states explicitly protect the confidentiality of STI, contraceptive, or mental health services for which minors have given their own consent and do not allow disclosure of the information without the minor's consent. In other states, laws grant physicians discretion to disclose information to parents. Title X and Medicaid both provide confidentiality protection for family planning services provided to minors with funding from these programs.

Federal regulations issued under the Federal Health Insurance Portability and Accountability Act of 1996, known as the HIPAA Privacy Rule, defer to state and "other applicable laws" with respect to the question of whether parents' have access to information about care for which a minor has given consent. Thus both the state laws that either prohibit or permit disclosure of confidential information and the federal Title X and Medicaid laws that protect the confidentiality of care for adolescents are important under the HIPAA Privacy Rule in determining when confidential information about health services for minors can be disclosed to parents.

Billing for confidential services is complex. Commercial health plans send home an *explanation of benefit* to the primary insured or the primary beneficiary listing services rendered by the provider and reimbursed by the health plan. An explanation of benefit documenting that confidential health services were rendered to their adolescent dependent that is received by a parent may disclose those services. In addition, copayments automatically generated with certain billing codes for office visits and medications can be a barrier for adolescents receiving care, including treatment.

Providers may elect to establish a policy of discussing with their adolescent patients when medical records and other information will be disclosed and developing a mechanism to alert office staff as to what information in the chart is confidential. For legal and other reasons, a chaperone should be present whenever an adolescent female patient is examined by a male physician.

Bibliography is available at Expert Consult.

112.2 Screening Procedures

Gale R. Burstein

INTERVIEWING THE ADOLESCENT

The preparation for a successful interview with an adolescent patient varies based on the history of the relationship with the patient. Patients (and their parents) who are going from preadolescence to adolescence while seeing the same provider, should be guided through the transition. Although the rules for confidentiality are the same for new and continuing patients, the change in the physician-patient relationship, allowing more privacy during the visit and more autonomy in the health process, may be threatening for the parent as well as the adolescent. For new patients, the initial phases of the interview are more challenging given the need to establish rapport rapidly with the patient in order to meet the goals of the encounter. Issues of confidentiality and privacy should be explicitly stated along with the conditions under which that confidentiality may need to be altered, that is, in life- or safety-threatening situations. For new patients, the parents should be interviewed with the adolescent or before the adolescent to ensure that the adolescent does not perceive a breach of confidentiality. The clinician who takes time to listen avoids judgmental statements and the use of street jargon and shows respect for the adolescent's emerging maturity will have an easier time communicating with the adolescent. The use of open-ended questions, rather than closed-ended questions, will further facilitate history taking. (The closed-ended question "Do you get along with your father?" leads to the answer "yes" or "no," in contrast to the question, "What might you like to be different in your relationship with your mother?" which may lead to an answer such as "I would like her to stop always worrying about me.")

The goals of the interview or clinical encounter are to establish an information base, identify problems and issues from the patient's perspective, and identify problems and issues from the perspective of the

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clinician based on knowledge of the health and other issues relevant to the adolescent age group. The adolescent should be given an opportunity to express concerns and the reasons for seeking medical attention. The adolescent as well as the parent should be given an opportunity to express the strengths and successes of the adolescent, in addition to communicating problems.

The effectiveness of an interview can be compromised when the interviewer is distracted by other events or individuals in the office, when there are extreme time limitations obvious to either party, or when there is expressible discomfort with either the patient or the interviewer. The need for an interpreter when a patient is hearing impaired or if the patient and interviewer are not language compatible provides a challenge but not necessarily a barrier under most circumstances (see Chapter 4). Observations during the interview can be useful to the overall assessment of the patient's maturity, presence or absence of depression, and the parent-adolescent relationship. Given the key role of a successful interview in the screening process, adequate training and experience should be sought by clinicians wishing to give comprehensive care to adolescent patients.

PSYCHOSOCIAL ASSESSMENT

A few questions should be asked in order to identify the adolescent who is having difficulty with peer relationships ("Do you have a best friend with whom you can share even the most personal secret?"), self-image ("Is there anything you would like to change about yourself?"), depression ("What do you see yourself doing 5 yr from now?"), school ("How are your grades this year compared with last year?"), personal decisions ("Are you feeling pressured to engage in any behavior for which you do not feel you are ready?"), and an eating disorder ("Do you ever feel that food controls you rather than vice versa?"). Bright Futures materials provide questions and patient encounter forms to structure the assessments that are available at their website (*http://brightfutures.aap.org/index.html*). The **HEADS/SF/FIRST** mnemonic, basic or expanded, can be useful in guiding the interview if encounter forms are not available (Table 112-5). Based on the assessments, appropriate counseling or referrals are recommended for more thorough probing or for in-depth interviewing.

Table 112-5	HEADS/SF/FIRST
Home. Space, privacy, frequent geographic moves, neighborhood.	
Education/School. Frequent school changes, repetition of a grade/in each subject, teachers' reports, vocational goals, after-school educational clubs (language, speech, math, etc.), learning disabilities	
Abuse. Physical, sexual, emotional, verbal abuse; parental discipline	
Drugs. Tobacco, alcohol, marijuana, inhalants, "club drugs," "rave" parties, others. Drug of choice, age at initiation, frequency, mode of intake, rituals, alone or with peers, quit methods, and number of attempts	
Safety. Seat belts, helmets, sports safety measures, hazardous activities, driving while intoxicated	
Sexuality/Sexual Identity. Reproductive health (use of contraceptives, presence of sexually transmitted infections, feelings, pregnancy)	
Family and Friends. Family: Family constellation, genogram, single/married/separated/divorced/blended family, family occupations and shifts; history of addiction in 1st- and 2nd-degree relatives, parental attitude toward alcohol and drugs, parental rules; chronically ill physically or mentally challenged parent. **Friends:** peer cliques and configuration ("preppies," "jocks," "nerds," "computer geeks," cheerleaders), gang or cult affiliation	
Image. Height and weight perceptions, body musculature and physique, appearance (including dress, jewelry, tattoos, body piercing as fashion trends or other statement)	
Recreation. Sleep, exercise, organized or unstructured sports, recreational activities (television, video games, computer games, Internet and chat rooms, church or community youth group activities [e.g., Boy/Girl Scouts; Big Brother/Sister groups, campus groups]). How many hours per day, days per week involved?	
Spirituality and Connectedness. Use HOPE* or FICA† acronym; adherence, rituals, occult practices, community service or involvement	
Threats and Violence. Self-harm or harm to others, running away, cruelty to animals, guns, fights, arrests, stealing, fire setting, fights in school	

*HOPE, hope or security for the future; organized religion; personal spirituality and practices; effects on medical care and end of life issues.

†FICA, faith beliefs; importance and influence of faith; community support.

From Dias PJ: Adolescent substance abuse. Assessment in the office, Pediatr Clin North Am *49:269–300, 2002.*

PHYSICAL EXAMINATION

Vision Testing

The pubertal growth spurt may involve the optic globe, resulting in its elongation and myopia in genetically predisposed individuals (see Chapter 621). Vision testing should, therefore, be performed in order to detect this problem before it affects school performance.

Audiometry

Highly amplified music of the kind enjoyed by many adolescents may result in hearing loss (see Chapter 637). A hearing screening is recommended by the Bright Futures guidelines for adolescents who are exposed to loud noises regularly, have had recurring ear infections, or report problems.

Blood Pressure Determination

Criteria for a diagnosis of hypertension are based on age-specific norms that increase with pubertal maturation (see Chapter 445). An individual whose blood pressure exceeds the 95th percentile for his or her age is suspect for having hypertension, regardless of the absolute reading. Those adolescents with blood pressure between the 90th and 95th percentiles should receive appropriate counseling relative to weight and have a follow-up examination in 6 mo. Those with blood pressure above the 90th percentile should have their blood pressure measured on three separate occasions to determine the stability of the elevation before moving forward with an intervention strategy. The technique is important; false-positive results may be obtained if the cuff covers less than two thirds of the upper arm. The patient should be seated, and an average should be taken of the 2nd and 3rd consecutive readings, using the change rather than the disappearance as the diastolic pressure. Most adolescents with elevations of blood pressure have labile hypertension. If the blood pressure is below 2 SD for age, anorexia nervosa and Addison disease should be considered.

Scoliosis

See Chapter 679.

Approximately 5% of male and 10-14% of female adolescents have a mild curvature of the spine. This is 2-4 times the rate in younger children. Scoliosis is typically manifested during the peak of the height velocity curve, at approximately 12 yr in females and 14 yr in males. Curves measuring greater than 10 degrees should be monitored by an orthopedist until growth is complete.

Breast Examination

See Chapters 115 and 551.

Examination of the female adolescent's breasts is performed to detect masses, evaluate progression of sexual maturation, provide reassurance about development, and teach the technique of self-examination with the hope that this practice will continue into the higher risk later years. However, there is disagreement on the justification for promoting this routinely, given the rare instances of malignant breast masses in this age group.

Scrotum Examination

The peak incidence of germ cell tumors of the testes is in late adolescence and early adulthood. Palpation of the testes may have an immediate yield and should serve as a model for instruction of self-examination. Because varicoceles often appear during puberty, the examination also provides an opportunity to explain and reassure the patient about this entity (see Chapter 545).

Pelvic Examination

See Chapter 548.

Laboratory Testing

The increased incidence of iron-deficiency anemia after menarche mandates the performance of a hematocrit annually in females with moderate to heavy menses. The reference standard for this test changes with progression of puberty, as estrogen suppresses erythropoietin (see Chapter 446). Populations with nutritional risk should also have the hematocrit monitored. Androgens have the opposite effect, causing the hematocrit to rise during male puberty; Sexual Maturity Rating 1 males have an average hematocrit of 39%, whereas those who have completed puberty (sexual maturity rating 5; see Chapter 110) have an average value of 43%. Tuberculosis testing on an annual basis is important in adolescents with risk factors, such as an adolescent with HIV, living in the household with someone with HIV, the incarcerated adolescent, or those with other risk factors, because puberty has been shown to activate this disease in those not previously treated. Hepatitis C virus screening should be offered to adolescents who report risk factors, such as injection drug use, received blood products or organ donation before 1992, or long-term hemodialysis.

Sexually active adolescents should undergo screening for STIs as per Centers for Disease Control and Prevention guidelines, regardless of symptoms (see Chapter 120). There are clear indications for chlamydia and gonorrhea screening of females 24 yr old and younger, but less sufficient evidence to support routine screening in young men. Based on feasibility, efficacy, and cost-effectiveness, evidence is insufficient to recommend routine chlamydia screening in all sexually active young men. However, screening of sexually active young males should be considered in clinical settings associated with high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, and sexually transmitted disease clinics) and should be offered to young men who have sex with men. HIV screening should be discussed and offered to all adolescents aged 15 yr and older and to younger adolescents who are at increased risk. Routine screening of adolescents who are asymptomatic for certain STIs (e.g., syphilis, trichomoniasis, herpes simplex virus, and human papillomavirus) is not recommended. However, young men who have sex with men and pregnant adolescent females might require more thorough evaluation for all sexually transmitted diseases. Because cervical cancer incidence low and complications from procedures may outweigh benefits of screening adolescent females, cervical cancer screening should not begin until age 21 yr.

Bibliography is available at Expert Consult.

112.3 Transitioning to Adult Care

Cynthia Holland-Hall and Gale R. Burstein

The importance of successfully transitioning the care of adolescents with special healthcare needs (SHCN) from pediatric to adult services has been recognized for over a decade. Successful transition is associated with improved health outcomes and quality of life; poorly managed transition may lead to worsening of chronic disease control. Nonetheless, few pediatric practices incorporate explicit, comprehensive transition services into the care of their patients with SHCN. Barriers to providing transition services include lack of access to appropriate providers of adult primary and subspecialty care, time, and reimbursement by insurance companies. Internists accepting young adult patients with SHCN also perceive a need for better training in congenital and child-onset medical conditions. Families may experience anxiety about leaving trusted pediatric providers, or fear that their child is incapable of assuming care for his or her medical condition. Among the patients themselves, a higher degree of self-efficacy for disease management and independently negotiating the healthcare system, as well as a positive attitude toward transition, lead to a greater perceived readiness to transition their care to an adult model. Medical providers, family members, and adolescent patients therefore each play a critical role in implementing and executing a plan for successful transition.

Table 112-6	Key Elements of the Transition of Health Care Process

- Written Transition Policy to be shared with youth, families, providers, and staff, explaining the process and the responsibilities of all team members
- Transitioning Youth Registry to track the progress of each patient through the transition process
- Longitudinal Readiness Checklists assessing the youth's ability for independence, self-management, and communicating with the adult healthcare system, as well as the family's readiness to assist the patient in achieving these goals
- Written Transition Plan documenting the steps to be conducted to meet the needs identified in the readiness assessment, as well as identifying appropriate adult care resources
- For youth with SHCN, expanded transition services including attention to insurance, entitlements, guardianship, and vocational needs in addition to adult subspecialty care
- Appropriate communication between the pediatric and adult medical home and subspecialists, including a Portable Medical Summary and care plan delivered to the patient and caregivers
- Transfer of care, within the 18- to 21-year age range, to adult providers, to whom pediatric providers continue to serve as a resource until transition is complete

The American Academy of Pediatrics, in conjunction with other key professional societies, has published detailed, comprehensive guidelines for incorporating transition services into the medical home for all adolescents, regardless of the presence or absence of SHCN. These guidelines are based on expert opinion, since the evidence on transition outcomes is limited. Transition encompasses much more than simply the transfer of care to another provider. In fact, many of the elements of transition apply even to family physicians who do not intend to transfer the patient's care, but who still should assist the patient in adapting to an adult model of healthcare delivery. Table 112-6 includes the key elements of healthcare transition. Tools to assist providers with all of these steps are available online from the National healthcare Transition Center (www.gottransition.org).

The process begins with the development of a transition policy and its dissemination to all families of young adolescents, ensuring that families understand that transition planning will be an element of health maintenance and chronic care management visits throughout the adolescent years. By middle adolescence, a transition plan should be developed with the youth and family caregivers, and this plan should be updated at subsequent visits until the patient is ready for implementation of the adult care model in early adulthood. Critical to the transition process is skills training for the adolescent in communication, self-advocacy, and self-care. The ultimate goal is to help all young people maximize their potential as they become young adults.

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Chapter 113

Violent Behavior

Margaret M. Stager

Violence is recognized by the World Health Organization (WHO) as a leading worldwide public health problem. WHO defines violence as "The intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community that either results in or has a high likelihood of resulting in injury, death, psychologic harm, maldevelopment or deprivation" (see Chapter 39). Youths may be perpetrators, victims, or observers of violence (or any combination of the 3 roles) with varying severity of impact on the individual, family, and larger community. Multiple factors have been identified that may increase the risk of a youth engaging in violence, including poverty, war, substance abuse, mental health disorders, and poor family functioning.

EPIDEMIOLOGY

In 2010, homicide in the United States was the second leading cause of death for 10-24 yr olds totaling 4,828 deaths, which were largely males (86%) killed by a handgun (82.8%). The 2010 homicide rate for teens ages 12-17 yr was 3.0/100,000 youth down 65% from 8.4/100,000 youth in 1993. The WHO reports that other than the United States, where the youth and young adult homicide rate was 11 per 100,000, most countries with homicide rates above 10 per 100,000 are developing nations or countries with rapid socioeconomic changes. The prevalence of behaviors that contribute to violence has not decreased from 1999 to 2011; fighting and weapon carrying remain prevalent among U.S. youth. The rate of homicide by handgun is considerably higher than homicide by other weapon type, suggesting that access to firearms may play a major role in youth injuries and deaths (Fig. 113-1). Gang-related homicides among youths in 5 major U.S. cities are more likely to involve young (15-19 yr) males (80%), racial/ethnic minority (73%), and a firearm (90%) in comparison to nongang homicides. In addition, gang homicides are more likely to occur in public places, in the afternoon/evening hours, and rarely are related to drug trade/use. One quarter of the gang homicides are classified as drive-by shootings.

Violence at schools in the United States remains a significant problem with 32.8% of students reported being in a fight on school property 1 or more times in the preceding 12 mo. The 2011 Youth Risk Behavior Surveillance System reported 16.6% youths overall carried a weapon such as a gun, knife, or club in the last 30 days; 5.4% carried the weapon to school; and 7.4% reported being threatened or injured with a type of weapon on school property. Males are more likely than females to carry a gun or weapon and therefore may need increased monitoring at home and at school. Weapon carrying is highest among white males overall, which may begin as early as 9th grade. Student reports of physical fighting at schools have nearly tripled in the last 4 yr. These violence-related behaviors at school affect the students' perception of safety. More than 5% of students did not go to school on 1 or more days in the preceding 30 days because they felt it was unsafe at school.

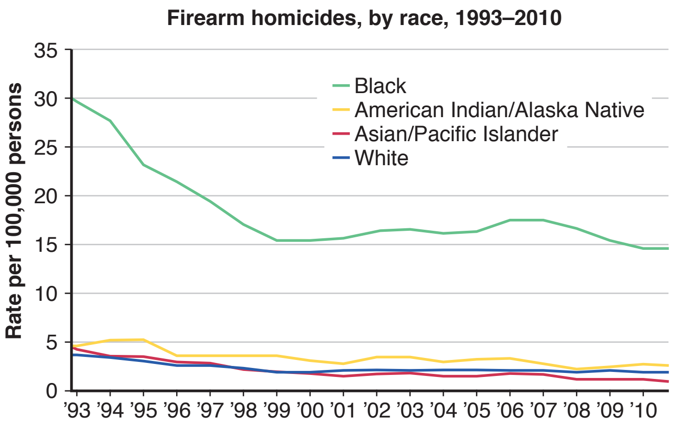

Figure 113-1 Firearm homicides, by race, 1993-2010. *(Data from Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Web-based Injury Statistics Query and Reporting System (WISQARS), 1993–2010. Retrieved March 2013 from http://www.cdc.gov/ncipc/wisqars.)*

Dating violence (or intimate partner violence) occurs between 2 people in a close relationship and can be physical (punching, kicking, hitting or shoving), emotional (shaming, bullying, controlling or stalking), or sexual (forcing one's partner to engage in a sexual act when he/she does not consent to it). Incidents of dating violence often occur during the adolescent years with 22.4% of women and 15% of men experiencing some type of partner violence between the ages of 11 and 17 yr. The highest prevalence rates are seen in African-American students and older students. It may start with teasing, name calling, or shaming. It may progress electronically, such as frequent calls, texting, or posting sexual pictures of a partner on social media. Risk factors for being a victim of dating violence includes those who use alcohol, believe dating violence is acceptable, have lack of parental supervision, or have a friend who is in a violent relationship. Most teens do not report the behaviors because they fear retaliation from the partner. Teens who are victims of dating violence are more likely to experience decreased school performance, use drugs and alcohol, have an eating disorder, or experience depression. School-based prevention programs that address attitudes and behaviors linked with dating violence, such as Safe Dates, offer training experiences to change social norms amongst teens. School-based prevention programs initiated at the elementary school level have been found to decrease violent behaviors in students. Increased surveillance of students is warranted both on and around school property to improve student safety.

ETIOLOGY

The WHO places youth violence in a model within the context of 3 larger types of violence: self-inflicted, interpersonal, and collective. **Interpersonal violence** is subdivided into violence largely between family members or partners and includes child abuse. **Community violence** occurs between individuals who are unrelated. **Collective violence** incorporates violence by people who are members of an identified group against another group of individuals with social, political, or economic motivation. The types of violence in this model have behavioral links, in that child abuse victims are more likely to experience violent and aggressive interpersonal behavior as adolescents and adults. Overlapping risk factors exist for the types of violence, such as firearm availability, alcohol use, and socioeconomic inequalities. The benefit to identifying common risk factors for the types of violence lies in the potential for intervening with prevention efforts and gaining positive outcomes for more than one type of violent behavior. The model further acknowledges 4 categories that explore the potential nature of violence as involving physical, sexual, or psychological force, or deprivation.

There may be 2 types of antisocial youth: 1 that is life-course persistent and 1 that is life-course limited. **Adolescent-limited offenders** have no childhood aberrant behaviors and are more likely to commit status offenses such as vandalism, running away, and other behaviors symbolic of their struggle for autonomy from parents. **Life course–persistent offenders** exhibit aberrant behavior in childhood, such as problems with temperament, behavioral development, and cognition; as adolescents they participate in more victim-oriented crimes. The public health model emphasizes the environment and other external influences. A third theoretical model examines violent behaviors across the spectrum occurring within and outside the family and is referred to as the **cycle of violence.** This hypothesis proposes that precursors such as child abuse and neglect, a child witnessing violence, adolescent sexual and physical abuse, and adolescent exposure to violence and

violent assaults predispose youths to outcomes of violent behavior, violent crime, delinquency, violent assaults, suicide, or premature death. An additional common paradigm for high-risk violence behavior poses a balance of risk and protective factors at the individual, family, and community levels.

CLINICAL MANIFESTATIONS

There are several identified risk factors for youth violence, including poverty, association with delinquent peers, poor school performance/low education status, disconnection from adult role models or mentors, prior history of violence or victimization, poor family functioning, childhood abuse, substance abuse, and certain mental health disorders. The most common disorders associated with aggressive behavior in adolescents are mental retardation, learning disabilities, moderately severe language disorders, and mental disorders such as attention-deficit/hyperactivity and mood disturbances. The link between severe mental illness and violent behaviors is strongest for those with cooccurring alcohol or substance abuse or dependence.

Inability to master prosocial skills such as the establishment and maintenance of positive family and peer relations and poor resolution of conflict may put adolescents with these disorders at higher risk of physical violence and other risky behaviors. **Conduct disorder** and **oppositional defiant disorder** are specific psychiatric diagnoses whose definitions are associated with violent behavior (Table 113-1). They occur comorbidly with other disorders, such as attention-deficit/hyperactivity disorder (see Chapter 30), and increase an adolescent's vulnerability for juvenile delinquency, substance use or abuse, sexual promiscuity, adult criminal behavior, incarceration, and antisocial personality disorder. Other cooccurring risk factors for youth violence include use of anabolic steroids, gang tattoos, belief in one's premature death, preteen alcohol use, and placement in a juvenile detention center.

DIAGNOSIS

The assessment of an adolescent at risk or with a history of violent behavior or victimization should be a part of the health maintenance visit of all adolescents. The answers to questions about recent history of involvement in a physical fight, carrying a weapon, or firearms in the household, as well as concerns that the adolescent may have about his or her personal safety may suggest a problem requiring a more in-depth evaluation. The **FISTS** mnemonic provides guidance for structuring the assessment (Table 113-2). The additional factors of physical or sexual abuse, serious problems at school, poor school performance and attendance, multiple incidents of trauma, substance use, and symptoms associated with mental disorders are indications for evaluation by a mental health professional. In a situation of acute trauma, assault victims are not always forthcoming about the circumstances of their injuries for fear of retaliation or police involvement. Stabilization of the injury or the gathering of forensic evidence in sexual assault is the treatment priority; however, once this is achieved, addressing a more comprehensive set of issues surrounding the assault is appropriate.

TREATMENT

In the instance of acute injury secondary to violent assault, the treatment plan should follow standards established by the American Academy of Pediatrics model protocol, which includes, but is not limited to, the stabilization of the injury, evaluation and treatment of the injury, evaluation of the assault circumstance, psychologic evaluation and support, social service evaluation of the circumstance surrounding the assault, and a treatment plan on discharge that is designed to protect the adolescent from subsequent injury episodes and minimize the development of psychologic disability. Victims as well as witnesses of violence are at risk for posttraumatic stress disorder, and future aggressive and/or violent behavior.

Multiple treatment modalities are used simultaneously in managing adolescents with persistent violent and aggressive behavior and range from cognitive-behavioral therapy involving the individual and family to specific family interventions (parent management training, multisystemic treatment) and pharmacotherapy. Treatment of existing comorbid conditions, such as attention-deficit/hyperactivity disorder, depression, and substance abuse, appears to reduce aggressive behavior.

PREVENTION

The WHO recognizes a multifactorial approach to prevention: individual approaches, relationship approaches, community approaches, and societal approaches (Table 113-3). **Individual approaches** concentrate on changing attitudes and behaviors to avoid aggressive and

Table 113-2	FISTS Mnemonic to Assess an Adolescent's Risk of Violence
F: Fighting (How many fights were you in last year? What was the last?)	
I: Injuries (Have you ever been injured? Have you ever injured someone else?)	
S: Sex (Has your partner hit you? Have you hit your partner? Have you ever been forced to have sex?)	
T: Threats (Has someone with a weapon threatened you? What happened? Has anything changed to make you feel safer?)	
S: Self-defense (What do you do if someone tries to pick a fight? Have you carried a weapon in self-defense?)	

The FISTS mnemonic is adapted with permission from the Association of American Medical Colleges. Alpert EJ, Sege RD, Bradshaw YS. Interpersonal violence and the education of physicians. Acad Med *72:S41–S50, 1997.*

Table 113-1 Oppositional Defiant Disorder, Conduct Disorder, and Juvenile Delinquency

PSYCHIATRIC DISORDER LABELS		
Oppositional Defiant Disorder	**Conduct Disorder**	**Legal Label Juvenile Delinquency**
Recurrent pattern of negativistic, defiant, disobedient, and hostile behavior toward authority figures that has a significant adverse effect on functioning (e.g., social, academic, occupational)	Repetitive and persistent pattern of behavior that violates the basic rights of others or major age-appropriate societal norms or rules	Offenses that are illegal because of age; illegal acts
Examples: losing temper; arguing with adults; defying or refusing to comply with request or rules of adults; annoying behavior; blaming others; and being irritable, spiteful, resentful	Examples: physical fighting, deceitfulness, stealing, destruction of property, threatening or causing physical harm to people or animals, driving without a license, prostitution, rape (even if not adjudicated in the legal system)	Examples: single or multiple instances of being arrested or adjudicated for any of the following: stealing, destruction of property, threatening or causing physical harm to people or animals, driving without a license, prostitution, rape
Diagnosed by a mental health clinician	Diagnosed by a mental health practitioner	Adjudicated in the legal system

From Greydanus DE, Pratt HD, Patel DR, et al: The rebellious adolescent, Pediatr Clin North Am *44:1460, 1997.*

Table 113-3 Public Health Approach to Youth Violence Prevention Model with Examples

	VICTIM (HOST)	PERPETRATOR (VECTOR)	FIREARM (AGENT)	SOCIAL ENVIRONMENT	PHYSICAL ENVIRONMENT
Primary prevention	Conflict resolution Violence anticipatory guidance	Substance abuse treatment Home visiting programs for new and single parents	Handgun and assault weapons ban Firearm registration	Job opportunities Adult-supervised activities	Better lighting Zoning-enforced limits in liquor licenses
Secondary prevention	Medical services Psychologic services	Job training Psychosocial rehabilitation	Handgun locks Public education on risks of ownership	School incident debriefing Safe havens	Increased police presence Graffiti removal
Tertiary prevention	Physical rehabilitation Psychosocial services	Incarceration Educational-psychosocial rehabilitation	Firearm surveillance	Foster care Alternative schools	Urban planning, e.g., decrease population density in public housing and mixture of income levels

From Calhoun AD, Clark-Jones F: Theoretical frameworks: developmental psychopathology, the public health approach to violence, and the cycle of violence, Pediatr Clin North Am *45:287, 1998.*

violent behavior as well as teaching coping strategies and nonviolent conflict resolution for all children as well as youths who have already displayed some violent tendencies. **Relationship approaches** focus more on victims, families, and peer relationships, especially those with the potential to trigger aggressive or violent responses. Solutions include improving skills in coping or problem solving in recent perceived crises, interpersonal conflicts, and close relationships. Family-based programs provide training for parents in areas of effective communication, child development, and solving problems in nonviolent methods. **Community-based approaches** raise public awareness in an effort to stimulate action by community members to reduce violence and protect vulnerable community members. Universal school-based violence prevention programs have been found to be effective in reducing violent and aggressive behaviors. Interventions beginning as early as preschool have been found to have positive outcomes years later. **Societal approaches** include broader advocacy and legislative actions, as well as changing the cultural norm toward violent behaviors. A specific prevention strategy can incorporate several approaches, such as the handgun/firearm prevention recommendations that include gun-lock safety, public education, and legislative advocacy. Other efforts are directed toward establishing a national database to track and define the problem of youth violence. The National Violent Death Reporting System collects and analyzes violent death data from 18 states and aims to improve surveillance of current trends, to share information state to state, to build partnerships among state and community organizations, and to develop and implement prevention and intervention programs. Ultimately, the National Violent Death Reporting System will be expanded to include all 50 states. The CDC characterizes specific successful programs and summarizes program content on its website (www.cdc.gov).

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Chapter 114

Substance Abuse

Margaret M. Stager

Although varying in percentages by nation and culture, a substantial proportion of adolescents will engage in use of a wide range of substances such as alcohol, tobacco, or marijuana. Their reactions to and the consequences of these exposures are influenced by a complex interaction between biologic and psychosocial development, environmental messages, and societal attitudes. Occasional or situational use of certain substances, such as alcohol in the United States, may be viewed as normative given the proportion of youths who report some experience with these substances. Others view the potential for adverse outcomes even with occasional use in immature adolescents, such as motor vehicle crashes and other injuries, sufficient justification to consider any drug use in younger adolescents a considerable risk.

Individuals who initiate drug use at an early age are at a greater risk for becoming addicted than those who try drugs in early adulthood. Drug use in younger, less-experienced adolescents can act as a substitute for developing age-appropriate coping strategies and enhance vulnerability to poor decision making. The first use of the most commonly used drugs occurs before age 18 yr, with 88% of people reporting age of first alcohol use at <21 yr old, the legal drinking age in the United States. Inhalants have been identified as a popular first drug for youth in grade 8. When drug use begins to negatively alter functioning in adolescents at school and at home, and risk-taking behavior is seen, intervention is warranted. Serious drug use is not an isolated phenomenon. It occurs across every segment of the population and is 1 of the most challenging public health problems facing society. The challenge to the clinician is to identify youths at risk for substance abuse and offer early intervention. The challenge to the community and society is to create norms that decrease the likelihood of adverse health outcomes for adolescents and promote and facilitate opportunities for adolescents to choose healthier and safer options. Recognizing those drugs with the greatest *harm*, and at times focusing on *harm reduction* with or without abstinence, is an important modern approach to adolescent substance abuse (Figs. 114-1 and 114-2).

ETIOLOGY

Substance abuse is biopsychosocially determined (Fig. 114-3). Biologic factors, including genetic predisposition, are established contributors. Behaviors such as rebelliousness, poor school performance, delinquency, and criminal activity and personality traits such as low self-esteem, anxiety, and lack of self-control are frequently associated with or predate the onset of drug use. Psychiatric disorders are often comorbidly associated with adolescent substance use. Conduct disorders and antisocial personality disorders are the most common diagnoses coexisting with substance abuse, particularly in males. Teens with depression (see Chapter 26), attention deficit disorder (see Chapter 33), and eating disorders (see Chapter 28) have high rates of substance use. The determinants of adolescent substance use and abuse are explained using a number of theoretical models, with factors at the individual level, the level of significant relationships with others, and the level of the setting or environment. Models include a balance of risk and protective or coping factors contributing to individual differences among adolescents with similar risk factors who escape adverse outcomes.

Risk factors for adolescent *drug use* may differ from those associated with adolescent *drug abuse*. Adolescent *use* is more commonly related to social and peer factors, whereas *abuse* is more often a function of psychological and biologic factors. The likelihood that an otherwise normal adolescent would experiment with drugs may be dependent on the availability of the drug to the adolescent, the perceived positive or otherwise functional value to the adolescent, the perceived risk associated with use, and the presence or absence of restraints as determined by the adolescent's cultural or other important value systems. An abusing adolescent may have genetic or biologic factors coexisting with dependence on a particular drug for coping with day-to-day activities.

Specific historical questions can assist in determining the severity of the drug problem through a rating system (Table 114-1). The type of drug used (marijuana vs. heroin), the circumstances of use (alone or

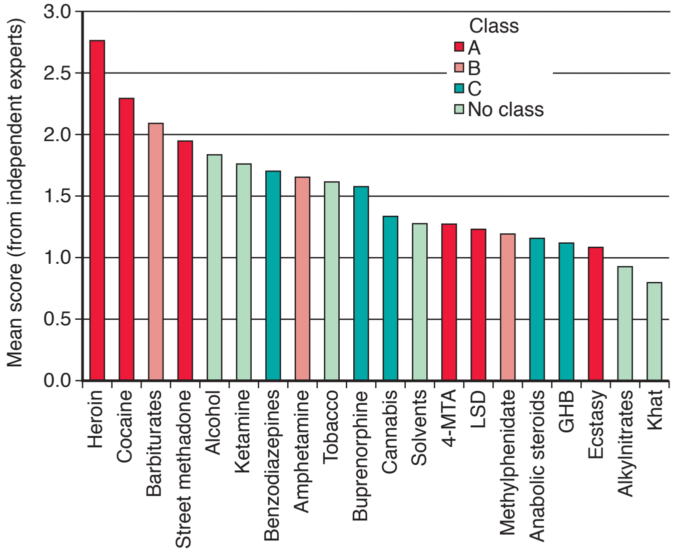

Figure 114-1 **Mean harm scores for 20 substances as determined by an expert panel based on 3 criteria: physical harm to user; potential for dependence; and effect on family, community, and society.** Classification under the Misuse of Drugs Act, when appropriate, is shown by the color of each bar. Class A drugs are deemed potentially most dangerous; class C least dangerous. *(From Nutt D, King LA, Saulsbury W, et al: Development of a rational scale to access the harm of drugs of potential misuse,* Lancet *369:1047–1053, 2007.)*

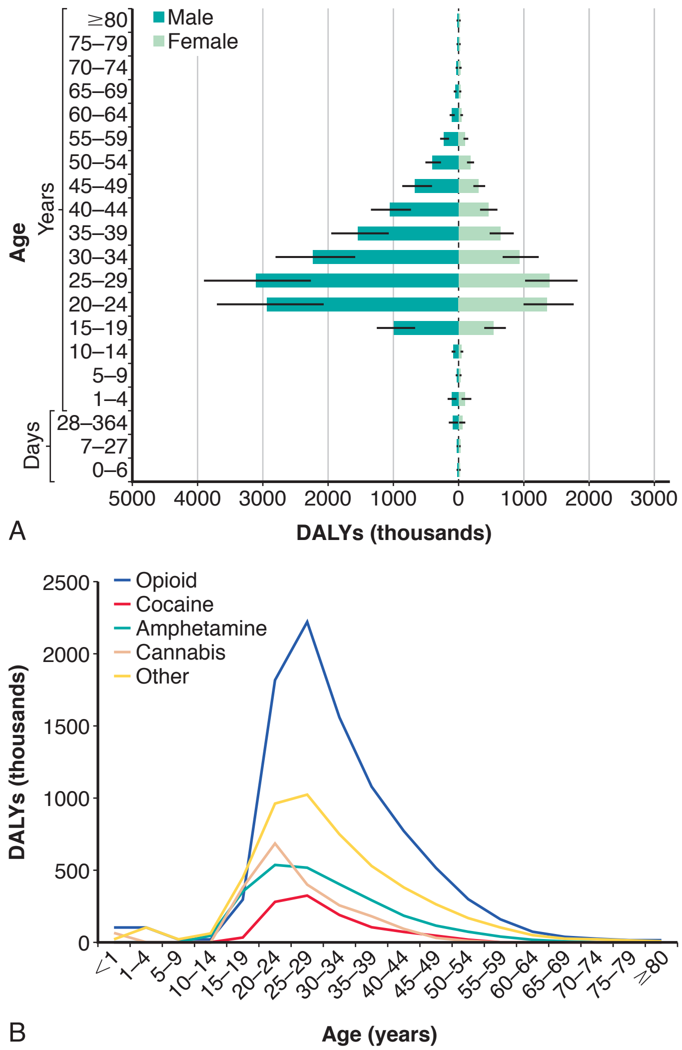

Figure 114-2 **Total burden (DALYs) of drug dependence by age and sex in 2010. A,** DALYs attributable to drug dependence, by age and sex. **B,** DALYs attributable to each type of drug dependence by age. DALYs, disability-adjusted life years. *(From: Degenhardt L, Whitford HA, Ferrari AJ, et al: Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease study 2010.* Lancet *382:1564-1574, 2013, Fig. 2, p. 1569.)*

Table 114-1 Assessing the Seriousness of Adolescent Drug Abuse

VARIABLE	0	+1	+2
Age (yr)	>15	<15	
Sex	Male	Female	
Family history of drug abuse		Yes	
Setting of drug use	In group		Alone
Affect before drug use	Happy	Always poor	Sad
School performance	Good, improving		Recently poor
Use before driving	None		Yes
History of accidents	None		Yes
Time of week	Weekend	Weekdays	
Time of day		After school	Before or during school
Type of drug	Marijuana, beer, wine	Hallucinogens, amphetamines	Whiskey, opiates, cocaine, barbiturates

Total score: 0-3, less worrisome; 3-8, serious; 8-18, very serious.

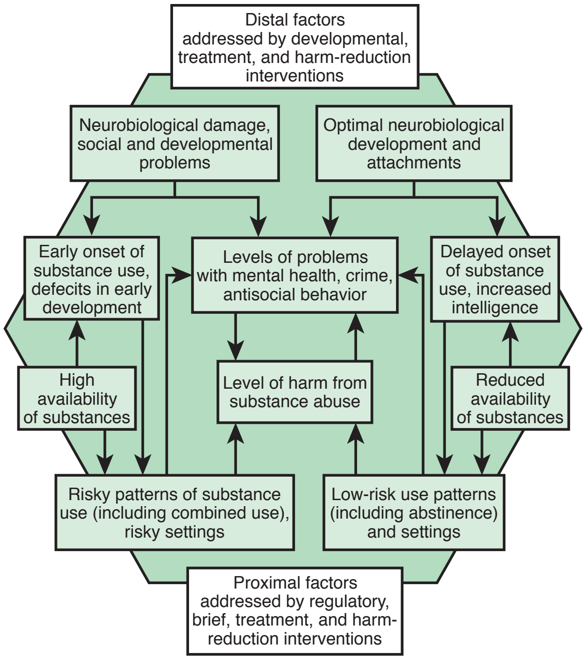

Figure 114-3 **Protection and risk model for distal and proximal determinants of risky substance use and related harms.** *(From Toumbourou JW, Stockwell T, Neighbors C, et al: Interventions to reduce harm associated with adolescent substance use,* Lancet *369:1391–1401, 2007.)*

in a group setting), the frequency and timing of use (daily before school vs. rarely on a weekend), the premorbid mental health status (depressed vs. happy), as well as the teenager's general functional status should all be considered in evaluating any youngster found to be abusing a drug. The stage of drug use/abuse should also be considered (Table 114-2). A teen may spend months or years in the experimentation phase trying a variety of illicit substances, including the most common drugs, cigarettes, alcohol, and marijuana. Often it is not until regular use of drugs resulting in negative consequences (problem use) that the teen is identified as having a problem, either by parents, teachers, or a physician. Certain protective factors play a part in buffering the risk factors as well as assisting in anticipating the long-term outcome of experimentation. Having emotionally supportive parents with open communication styles, involvement in organized school activities, having mentors or role models outside of the home, and recognition of the importance of academic achievement are examples of the important protective factors.

EPIDEMIOLOGY

Alcohol, cigarettes, and marijuana are the most commonly reported substances used among U.S. teens (Table 114-3). The prevalence of substance use and associated risky behaviors vary by age, gender, race/ethnicity, and other sociodemographic factors. Younger teenagers tend to report less use of drugs than do older teenagers, with the exception of inhalants (in 2012, 6.0% in 8th grade, 5.1% in 10th grade, 4.7% in 12th grade). Males have higher rates of both licit and illicit drug use than females, with greatest differences seen in their higher rates of frequent use of smokeless tobacco, cigars, and anabolic steroids. In school surveys, drug use rates of Hispanics are between whites and African-Americans, with the exception of 12th grade Hispanics reporting highest rates of cocaine use. African-Americans report less use of drugs across all drug categories (including levels of cigarette use) in comparison to whites and Hispanics. In examining trends in drug use, positive findings are that fewer students reported cigarette, alcohol, or stimulant use than in the previous 3 yr. Marijuana use continues to decline with daily use of marijuana in 2012 as 1.1% in 8th graders, 3.5% in 10th graders, and 6.5% in 12th graders.

Table 114-2 Stages of Adolescent Substance Abuse

STAGE	DESCRIPTION
1	Potential for abuse • Decreased impulse control • Need for immediate gratification • Available drugs, alcohol, inhalants • Need for peer acceptance
2	Experimentation: learning the euphoria • Use of inhalants, tobacco, marijuana, and alcohol with friends • Few, if any, consequences • Use may increase to weekends regularly • Little change in behavior
3	Regular use: seeking the euphoria • Use of other drugs, e.g., stimulants, LSD, sedatives • Behavioral changes and some consequences • Increased frequency of use; use alone • Buying or stealing drugs
4	Regular use: preoccupation with the "high" • Daily use of drugs • Loss of control • Multiple consequences and risk taking • Estrangement from family and "straight" friends
5	Burnout: use of drugs to feel normal • Polysubstance use/cross-addiction • Guilt, withdrawal, shame, remorse, depression • Physical and mental deterioration • Increased risk taking, self-destructive, suicidal

Table 114-3 Thirty Day Prevalence Use of Alcohol, Cigarettes, Marijuana, and Inhalants in 8th Graders, 10th Graders, and 12th Graders, 2010 and 2012

	8TH GRADERS (%)	10TH GRADERS (%)	12TH GRADERS (%)
ALCOHOL (ANY USE)			
2010	13.8	28.9	41.2
2012	11.0	27.6	41.5
CIGARETTES (ANY USE)			
2005	7.1	13.6	19.2
2008	4.9	10.8	17.1
SMOKELESS TOBACCO			
2010	4.1	7.5	8.5
2012	2.8	6.4	7.9
MARIJUANA/HASHISH			
2010	8.0	16.7	21.4
2012	6.5	17.0	22.9
INHALANTS			
2010	3.6	2.0	1.4
2012	2.7	1.4	0.9
AMPHETAMINES			
2010	0.5	0.6	0.9
2012	0.5	0.5	1.0

National Institute of Drug Abuse: *2012 Monitoring the Future Study,* www.drugabuse.gov

Prescription drug abuse, or nonmedical use of a prescription drug or an over-the counter (OTC) medicine has gained popularity among teens in the last 3 yr (Table 114-4). In 2012, 14.8% of high school seniors had used a prescription drug or an OTC medicine for nonmedical reasons in the past year. The most commonly used substances were Adderall (7.6%), Vicodin (7.5%), OTC cough medicine (5.6%),

Table 114-4 Commonly Abused Prescription Drugs

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Commonly Abused Prescription Drugs

Visit NIDA at www.drugabuse.gov

National Institutes of Health
U.S. Department of Health and Human Services

Substances: Category and Name	Examples of *Commercial* and Street Names	DEA Schedule*/How Administered	*Intoxication Effects*/Health Risks
Depressants			
Barbiturates	*Amytal, Nembutal, Seconal, Phenobarbital:* barbs, reds, red birds, phennies, tooies, yellows, yellow jackets	II, III, IV/injected, swallowed	*Sedation/drowsiness, reduced anxiety, feelings of well-being, lowered inhibitions, slurred speech, poor concentration, confusion, dizziness, impaired coordination and memory/*slowed pulse, lowered blood pressure, slowed breathing, tolerance, withdrawal, addiction; increased risk of respiratory distress and death when combined with alcohol *for barbiturates—euphoria, unusual excitement, fever, irritability/*life-threatening withdrawal in chronic users
Benzodiazepines	*Ativan, Halcion, Librium, Valium, Xanax, Klonopin:* candy, downers, sleeping pills, tranks	IV/swallowed	
Sleep Medications	*Ambien (zolpidem), Sonata (zaleplon), Lunesta (eszopiclone)*	IV/swallowed	
Opioids and Morphine Derivatives**			
Codeine	*Empirin with Codeine, Fiorinal with Codeine, Robitussin A-C, Tylenol with Codeine:* Captain Cody, Cody, schoolboy; (with glutethimide: doors & fours, loads, pancakes and syrup)	II, III, IV/injected, swallowed	*Pain relief, euphoria, drowsiness, sedation, weakness, dizziness, nausea, impaired coordination, confusion, dry mouth, itching, sweating, clammy skin, constipation/*slowed or arrested breathing, lowered pulse and blood pressure, tolerance, addiction, unconsciousness, coma, death; risk of death increased when combined with alcohol or other CNS depressants *for fentanyl*—80–100 times more potent analgesic than morphine *for oxycodone*—muscle relaxation/twice as potent analgesic as morphine; high abuse potential *for codeine*—less analgesia, sedation, and respiratory depression than morphine *for methadone*—used to treat opioid addiction and pain; significant overdose risk when used improperly
Morphine	*Roxanol, Duramorph:* M, Miss Emma, monkey, white stuff	II, III/injected, swallowed, smoked	
Methadone	*Methadose, Dolophine:* fizzies, amidone, (with MDMA: chocolate chip cookies)	II/swallowed, injected	
Fentanyl and analogs	*Actiq, Duragesic, Sublimaze:* Apache, China girl, dance fever, friend, goodfella, jackpot, murder 8, TNT, Tango and Cash	II/injected, smoked, snorted	
Other Opioid Pain Relievers: Oxycodone HCL Hydrocodone Bitartrate Hydromorphone Oxymorphone Meperidine Propoxyphene	*Tylox, Oxycontin, Percodan, Percocet:* Oxy, O.C., oxycotton, oxycet, hillbilly heroin, percs *Vicodin, Lortab, Lorcet:* vike, Watson-387 *Dilaudid:* juice, smack, D, footballs, dillies *Opana, Numorphan, Numorphone:* biscuits, blue heaven, blues, Mrs. O, octagons, stop signs, O Bomb *Demerol, meperidine hydrochloride:* demmies, pain killer *Darvon, Darvocet*	II, III, IV/chewed, swallowed, snorted, injected, suppositories	
Stimulants			
Amphetamines	*Biphetamine, Dexedrine, Adderall:* bennies, black beauties, crosses, hearts, LA turnaround, speed, truck drivers, uppers	II/injected, swallowed, smoked, snorted	*Feelings of exhilaration, increased energy, mental alertness/*increased heart rate, blood pressure, and metabolism, reduced appetite, weight loss, nervousness, insomnia, *seizures, heart attack, stroke* *for amphetamines—rapid breathing, tremor, loss of coordination, irritability, anxiousness, restlessness/*delirium, panic, paranoia, hallucinations, impulsive behavior, aggressiveness, tolerance, addiction *for methylphenidate*—increase or decrease in blood pressure, digestive problems, loss of appetite, weight loss
Methylphenidate	*Concerta, Ritalin:* JIF, MPH, R-ball, Skippy, the smart drug, vitamin R	II/injected, swallowed, snorted	
Other Compounds			
Dextromethorphan (DXM)	*Found in some cough and cold medications:* Robotripping, Robo, Triple C	not scheduled/swallowed	*Euphoria, slurred speech/*increased heart rate and blood pressure, dizziness, nausea, vomiting, confusion, paranoia, distorted visual perceptions, impaired motor function

** Schedule I and II drugs have a high potential for abuse. They require greater storage security and have a quota on manufacturing, among other restrictions. Schedule I drugs are available for research only and have no approved medical use. Schedule II drugs are available only by prescription and require a new prescription for each refill. Schedule III and IV drugs are available by prescription, may have five refills in 6 months, and may be ordered orally. Most Schedule V drugs are available over the counter.*

*** Taking drugs by injection can increase the risk of infection through needle contamination with staphylococci, HIV, hepatitis, and other organisms. Injection is a more common practice for opioids, but risks apply to any medication taken by injection.*

Courtesy of the National Institute on Drug Abuse, U.S. Department of Health and Human Services, National Institutes of Health, www.drugabuse.gov.

tranquilizers (5.3%), sedatives (4.5%), and OxyContin (4.3%). Rural adolescents were 26% more likely than urban adolescents to have used prescription drugs nonmedically; use was associated with decreased health status, major depressive episode(s), and other drug (marijuana, cocaine, hallucinogens, and inhalants) and alcohol use. In a large-scale study of 16,209 adolescent exposures to prescription drugs, 52.4% were females, and the mean age was 16.6 yr (SD ± 1.7 yr). The 5 most frequently misused or abused drugs were hydrocodone (32%), amphetamines (18%), oxycodone (15%), methylphenidate (14%), and tramadol (11%). Many of these drugs can be found in the parents' home, some are OTC, while others are purchased from drug dealers at schools and colleges. Teen users of nonmedical opioids use other substances concurrently with the opioid use. Most frequently the teens combine opioids with marijuana, alcohol, cocaine, and tranquilizers putting them at risk for serious complications and overdose.

Anonymous screening of urine sampled from public inner city rest rooms in London demonstrated the presence of various amphetamine derivatives, cocaine, ketamine and cannabis as well as cathinone/cathine metabolites.

CLINICAL MANIFESTATIONS

Although manifestations vary by the specific substance of use, adolescents who use drugs often present in an office setting with no obvious physical findings. Drug use is more frequently detected in adolescents who experience trauma such as motor vehicle crashes, bicycle injuries, or violence. Eliciting appropriate historical information regarding substance use, followed by blood alcohol and urine drug screens, is recommended in emergency settings; while waning in popularity, the illicit substances known as "club drugs" still need to be considered in the differential diagnosis of a teen with an altered sensorium (Table 114-5). An adolescent presenting to an emergency setting with an impaired sensorium should be evaluated for substance use as a part of the differential diagnosis (Table 114-6). Screening for substance use is recommended for patients with psychiatric and behavioral diagnoses. Other clinical manifestations of substance use are associated with the route of use; intravenous drug use is associated with venous "tracks" and needle marks, while nasal mucosal injuries are associated with nasal insufflation of drugs. Seizures can be a direct effect of drugs such as cocaine and amphetamines or an effect of drug withdrawal in the case of barbiturates or tranquilizers.

SCREENING FOR SUBSTANCE ABUSE DISORDERS

In a primary care setting the annual health maintenance examination provides an opportunity for identifying adolescents with substance use or abuse issues. The direct questions as well as the assessment of school performance, family relationships, and peer activities may necessitate a more in-depth interview if there are suggestions of difficulties in those areas. Additionally, there are several self-report screening questionnaires available with varying degrees of standardization, length, and reliability. The **CRAFFT mnemonic** is specifically designed to screen for adolescents' substance use in the primary setting (Table 114-7). Privacy and confidentiality need to be considered when asking the teen about specifics of their substance experimentation or use. Interviewing the parents can provide additional perspective on early warning signs that go unnoticed or disregarded by the teen. Examples of early warning signs of teen substance use are change in mood, appetite, or sleep pattern; decreased interest in school or school performance; loss of weight; secretive behavior about social plans; or valuables such as money or jewelry missing from the home. The use of urine drug screening is recommended when select circumstances are present: (1) psychiatric symptoms to rule out comorbidity or dual diagnoses, (2) significant changes in school performance or other daily behaviors, (3) frequently occurring accidents, (4) frequently occurring episodes of respiratory problems, (5) evaluation of serious motor vehicular or other injuries, and (6) as a monitoring procedure for a recovery program. Table 114-8 demonstrates the types of tests commonly used for detection by substance, along with the approximate retention time between the use and the identification of the substance in the urine. Most initial screening uses an immunoassay method such as the enzyme-multiplied immunoassay technique followed by a confirmatory test using highly sensitive, highly specific gas chromatography–mass spectrometry. The substances that can cause false-positive results should be considered, especially when there is a discrepancy between the physical findings and the urine drug screen result. In 2007 the American of Academy of Pediatrics released guidelines that strongly discourage home-based or school-based testing.

DIAGNOSIS

The *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* no longer identifies substance use disorders as those of *abuse* or of *dependence* as was done in previous editions. A substance use disorder is defined by a cluster of cognitive, behavioral, and physiologic symptoms that indicate that an adolescent is using a substance even though there is evidence that the substance is harming the adolescent. Even after detoxification, a substance abuse disorder may leave persisting changes in brain circuits with resulting behavioral changes. There are 11 criteria that describe a pathologic pattern of behaviors related to use of the substance, falling into 4 categories. The **first category** includes the criterion of *impaired control, social impairment, risky use, and pharmacologic criteria*. These criteria describe an individual taking increasing amounts of the substance and one who expresses a persistent desire to cut down substance use with unsuccessful efforts and the increased time, effort, and other resources the teen may be using to obtain the substance. The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects and expresses an intense desire for the drug that is most likely to occur in in settings in which the drug had been available, such as a specific type of social situation. The **second cluster** of criterion (5-7) reflects social impairment, including the inability to perform as expected in school, home or at a job, increasing social problems and withdrawing from the individual's family. The **third cluster** of 2 criteria addresses increased risk-involvement associated with use of the substance, and the **final cluster** includes 2 criteria addressing pharmacologic responses (tolerance and/or withdrawal). The total number of criterion present is associated with a determination of a mild, moderate, or severe disorder.

These criteria may have limitations in use with adolescents because of differing patterns of use, developmental implications, and other age-related consequences. Adolescents who meet diagnostic criteria should be referred to a program for substance use disorder treatment unless the primary care physician has additional training in addiction medicine.

COMPLICATIONS

Substance use in adolescence is associated with comorbidities and acts of juvenile delinquency. Youth may engage in other high-risk behaviors such as robbery, burglary, drug dealing, or prostitution for the purpose of acquiring the money necessary to buy drugs or alcohol. Regular use of any drug eventually diminishes judgment and is associated with unprotected sexual activity with its consequences of pregnancy and sexually transmitted infections, including HIV, as well as physical violence and trauma. Drug and alcohol use is closely associated with trauma in the adolescent population. Several studies of adolescent trauma victims have identified cannabinoids and cocaine in blood and urine samples in significant proportions (40%), in addition to the more common identification of alcohol. Any use of injected substances involves the risk of hepatitides B and C viruses as well as HIV (see Chapter 276).

TREATMENT

Adolescent drug abuse is a complex condition requiring a multidisciplinary approach that attends to the needs of the individual, not just drug use. Fundamental principles for treatment include accessibility to treatment; utilizing a multidisciplinary approach; employing individual or group counseling; offering mental health services; monitoring of drug use while in treatment; and understanding that recovery from drug abuse/addiction may involve multiple relapses. For most patients,

Table 114-5 Common Names and Salient Features of Club Drugs Used Recreationally

	MDMA	EPHEDRINE	γ-HYDROXYBUTYRATE	γ-BUTYROLACTONE	1,4-BUTANEDIOL	KETAMINE	FLUNITRAZEPAM	NITRITES	BATH SALTS
Common name	Ecstasy, XTC, E, X, Adam, hug drug, Molly	Herbal Ecstasy, herbal fuel, zest	Liquid Ecstasy, goop soap, Georgia homeboy, grievous bodily harm	Blue nitro, longevity, revivarant, GH revitalizer, gamma G, nitro, insom-X, remforce, firewater, invigorate	Thunder nectar, serenity, pine needle extract, zen, enliven, revitalize plus, lemon drops	K, special K, vitamin K, ket, kat	Roofies, circles, rophies, rib, roche, roaches, forget pill, R2, Mexican valium, roopies ruffies	Poppers, ram, rock hard, thrust, TNT	White lightning, Ivory wave, Cloud 9, Zoom, White rush
Duration of action	4-6 hr	4-6 hr	1.5-3.5 hr	1.5-3.5 hr	1.5-3.5 hr	1-3 hr	6-12 hr	Minutes	2-8 hr.
Elimination half-life	8-9 hr	5-7 hr	27 min	ND	ND	2 hr	9-25 hr	ND	Prolonged
Peak plasma concentration	1-3 hr	2-3 hr	20-60 min*	15-45 min	15-45 min	20 min	1 hr	Seconds	Varies
Physical dependence	No	No	Yes	Yes	Yes	No	Yes	No	Yes
Antidote	No	No	No	No	No	No	Yes	No	Treat with benzodiazepine
DEA schedule	I	None	III	None	None	III	IV	None	I
Detection with routine drug screen	Yes†	Yes†	No	No	No	No‡	No‡	No	In progress
Best detection method (time frame)	GC/MS (4 hr-2 days)	GC/MS (4 hr-2 days)	GC/MS (1-12 hr)	GC/MS (1-12 hr)	GC/MS (1-12 hr)	GC/MS (1 day)	GC/MS (1-12 hr)	GC/MS (1-12 hr)	GC/MS (1-12 hr)

*Depends on dose.

†Concentrations that are sufficiently high can give positive results for amphetamine because of cross-reactions.

‡Flunitrazepam can give positive results for benzodiazepines; ketamine can give positive results for phencyclidine.

DEA, U.S. Drug Enforcement Agency, currently reviewing possibility of flunitrazepam being placed into schedule of the U.S. Controlled Substance Act; GC/MS, gas chromatography–mass spectroscopy. Duration, half-life, and peak plasma are probably different after high or sequential doses because of nonlinear kinetics; ND, not determined in human beings.

Modified from Ricaurte GA, McCann UD: Recognition and management of complications of new recreational drug use. Lancet *365:2137–2145, 2005.*

Table 114-6 The Most Common Toxic Syndromes

ANTICHOLINERGIC SYNDROMES	
Common signs	Delirium with mumbling speech, tachycardia, dry, flushed skin, dilated pupils, myoclonus, slightly elevated temperature, urinary retention, and decreased bowel sounds. Seizures and dysrhythmias may occur in severe cases.
Common causes	Antihistamines, antiparkinsonian medication, atropine, scopolamine, amantadine, antipsychotic agents, antidepressant agents, antispasmodic agents, mydriatic agents, skeletal muscle relaxants, and many plants (notably jimson weed and Amanita muscaria).
SYMPATHOMIMETIC SYNDROMES	
Common signs	Delusions, paranoia, tachycardia (or bradycardia if the drug is a pure α-adrenergic agonist), hypertension, hyperpyrexia, diaphoresis, piloerection, mydriasis, and hyperreflexia. Seizures, hypotension, and dysrhythmias may occur in severe cases.
Common causes	Cocaine, amphetamine, methamphetamine (and its derivatives 3,4-methylenedioxyamphetamine, 3,4-met hylenedioxymethamphetamine, 3,4-methylenedioxyethamphetamine, and 2,5-dimethoxy-4-bromoamphetamine), and OTC decongestants (phenylpropanolamine, ephedrine, and pseudoephedrine). In caffeine and theophylline overdoses, similar findings, except for the organic psychiatric signs, result from catecholamine release.
OPIATE, SEDATIVE, OR ETHANOL INTOXICATION	
Common signs	Coma, respiratory depression, miosis, hypotension, bradycardia, hypothermia, pulmonary edema, decreased bowel sounds, hyporeflexia, and needle marks. Seizures may occur after overdoses of some narcotics, notably propoxyphene.
Common causes	Narcotics, barbiturates, benzodiazepines, ethchlorvynol, glutethimide, methyprylon, methaqualone, meprobamate, ethanol, clonidine, and guanabenz.
CHOLINERGIC SYNDROMES	
Common signs	Confusion, central nervous system depression, weakness, salivation, lacrimation, urinary and fecal incontinence, gastrointestinal cramping, emesis, diaphoresis, muscle fasciculations, pulmonary edema, miosis, bradycardia or tachycardia, and seizures.
Common causes	Organophosphate and carbamate insecticides, physostigmine, edrophonium, and some mushrooms.

From Kulig K: Initial management of ingestions of toxic substances, N Engl J Med *326:1678, 1992.*

Table 114-7 CRAFFT Mnemonic Tool

- Have you ever ridden in a **C**ar driven by someone (including yourself) who was high or had been using alcohol or drugs?
- Do you ever use alcohol or drugs to **R**elax, feel better about yourself or fit in?
- Do you ever use alcohol or drugs while you are by yourself (**A**lone)?
- Do you ever **F**orget things you did while using alcohol or drugs?
- Do your Family or **F**riends ever tell you that you should cut down on your drinking or drug use?
- Have you ever gotten into **T**rouble while you were using alcohol or drugs?

From the Center for Adolescent Substance Abuse Research (CeASAR). The CRAFFT Screening Interview. © John R. Knight, MD, Boston Children's Hospital, 2015.

Table 114-8 Urine Screening for Drugs Commonly Abused by Adolescents

DRUG	MAJOR METABOLITE	INITIAL	FIRST CONFIRMATION	SECOND CONFIRMATION	APPROXIMATE RETENTION TIME
Alcohol (blood)	Acetaldehyde	GC	IA		7-10 hr
Alcohol (urine)	Acetaldehyde	GC	IA		10-13 hr
Amphetamines		TLC	IA	GC, GC/MS	48 hr
Barbiturates		IA	TLC	GC, GC/MS	Short-acting (24 hr); long-acting (2-3 wk)
Benzodiazepines		IA	TLC	GC, GC/MS	3 days
Cannabinoids	Carboxy- and hydroxymetabolites	IA	TLC	GC/MS	3-10 days (occasional user); 1-2 mo (chronic user)
Cocaine	Benzoylecgonine	IA	TLC	GC/MS	2-4 days
Methaqualone	Hydroxylated metabolites	TLC	IA	GC/MS	2 wk
Opiates					
Heroin	Morphine Glucuronide	IA	TLC	GC, GC/MS	2 days
Morphine	Morphine Glucuronide	IA	TLC	GC, GC/MS	2 days
Codeine	Morphine Glucuronide	IA	TLC	GC, GC/MS	2 days
Phencyclidine		TLC	IA	GC, GC/MS	8 days

GC, gas chromatography; IA, immunoassay; MS, mass spectrometry; TLC, thin-layer chromatography.

Modified from Drugs of abuse—urine screening [physician information sheet]. Los Angeles, Pacific Toxicology. From MacKenzie RG, Kipke MD: Substance use and abuse. In Friedman SB, Fisher M, Schonberg SK, editors: Comprehensive adolescent health care, *St. Louis, 1998, Mosby.*

Table 114-9 Domains of Risk and Protective Factors for Substance Abuse Prevention

RISK FACTORS	DOMAIN	PROTECTIVE FACTORS
Early aggressive behavior	Individual	Self-control
Lack of parental supervision	Family	Parental monitoring
Substance abuse	Peer	Academic competence
Drug availability	School	Anti–drug use policies
Poverty	Community	Strong neighborhood attachment

From National Institute on Drug Abuse: Preventing drug use among children and adolescents. A research based guide for parents, educators, and community leaders. *NIH publication No. 04-4212(B), ed 2, Bethesda, MD, 2003, National Institute on Drug Abuse.*

Table 114-10 Risk Factors for a Teen Developing a Drinking Problem

FAMILY RISK FACTORS
- Low parental supervision
- Poor parent to teen communication
- Family conflicts
- Severe or inconsistent family discipline
- Having a parent with an alcohol or drug problem

INDIVIDUAL RISK FACTORS
- Poor impulse control
- Emotional instability
- Thrill seeking behaviors
- Behavioral problems
- Perceived risk of drinking is low
- Begins drinking before age 14 yr

remaining in treatment for a minimum period of 3 mo will result in a significant improvement.

PROGNOSIS

For adolescent substance abusers who have been referred to a drug treatment program, positive outcomes are directly related to regular attendance in posttreatment groups. For males with learning problems or conduct disorder, outcomes are poorer than for those without such disorders. Peer use patterns and parental use have a major influence on outcome for males. For females, factors such as self-esteem and anxiety are more important influences on outcomes. The chronicity of a substance use disorder makes relapse an issue that must always be kept in mind when managing patients after treatment, and appropriate assistance from a health professional qualified in substance abuse management should be obtained.

PREVENTION

Preventing drug use among children and teens requires prevention efforts aimed at the individual, family, school, and community levels. The National Institute on Drug Abuse (NIDA) has identified essential principles of successful prevention programs. Programs should enhance protective factors (parent support) and reduce risk factors (poor self-control); should address all forms of drug abuse (legal and illegal); should address the specific type(s) of drug abuse within an identified community; and should be culturally competent to improve effectiveness (Table 114-9). The highest risk periods for substance use in children and adolescents are during life transitions such as the move from elementary school to middle school, or from middle school to high school. Prevention programs need to target these emotionally and socially intense times for teens in order to adequately anticipate potential substance use or abuse. Examples of effective research-based drug abuse prevention programs featuring a variety of strategies are listed on the NIDA website (www.drugabuse.gov), and on the Center for Substance Abuse Prevention website (www.prevention.samhsa.gov).

Bibliography is available at Expert Consult.

114.1 Alcohol

Margaret M. Stager

Alcohol is the most popular drug among teens in the United States. By 12th grade, approximately 75% of adolescents in high schools report ever having an alcoholic drink, with 20.5% having their first drink before age 13 yr. Multiple factors can affect a young teen's risk of developing a drinking problem at an early age (Table 114-10). One-third of high school seniors admit to combining drinking behaviors with other risky behaviors, such as driving or taking additional substances. Binge drinking remains especially problematic among the older teens and young adults. Thirty-one percent of high school seniors report having 5 or more drinks in a row in the last 30 days. Higher use is seen in males (23.8%) than in females (19.8%), and whites (24.0%) and Hispanics (24.2%) than in blacks (12.4%). Overall, the prevalence of binge drinking decreased from 2009 (24.2%) to 2011 (21.9%). Teens with binge drinking patterns are more likely to be assaulted, engage in high risk sexual behaviors, have academic problems, and acquire injuries than those teens without binge drinking patterns.

Alcohol contributes to more deaths in young individuals in the United States than all the illicit drugs combined. Among studies of adolescent trauma victims, alcohol is reported to be present in 32-45% of hospital admissions. Motor vehicle crashes are the most frequent type of event associated with alcohol use, but the injuries spanned several types, including self-inflicted wounds.

Alcohol is often mixed with energy drinks (caffeine, taurine, sugars), which can result in a spectrum of alcohol related negative behaviors. Caffeine may counter the sedative effects of alcohol resulting in more alcohol consumption and a perception of not being intoxicated thus leading to risk taking behavior like driving while intoxicated. In addition, aggressive behavior, including sexual assaults and motor vehicle or other injuries has been reported. Both alcohol and caffeine overdoses have also been reported.

PHARMACOLOGY AND PATHOPHYSIOLOGY

Alcohol (ethyl alcohol or ethanol) is rapidly absorbed in the stomach and is transported to the liver and metabolized by 2 pathways. The primary metabolic pathway contributes to the excess synthesis of triglycerides, a phenomenon that is responsible for producing a **fatty liver,** even in those who are well nourished. Engorgement of hepatocytes with fat causes necrosis, triggering an inflammatory process **(alcoholic hepatitis),** which is later followed by fibrosis, the hallmark of **cirrhosis.** Early hepatic involvement may result in elevation in γ-glutamyl transpeptidase and serum glutamic-pyruvic transaminase. The second metabolic pathway, which is utilized at high serum alcohol levels, involves the microsomal enzyme system of the liver, in which the cofactor is reduced nicotinamide-adenine dinucleotide phosphate. The net effect of activation of this pathway is to decrease metabolism of drugs that share this system and to allow for their accumulation, enhanced effect, and possible toxicity.

CLINICAL MANIFESTATIONS

Alcohol acts primarily as a central nervous system depressant. It produces euphoria, grogginess, talkativeness, impaired short-term memory, and an increased pain threshold. Alcohol's ability to produce vasodilation and hypothermia is also centrally mediated. At very high serum levels, respiratory depression occurs. Its inhibitory effect on pituitary antidiuretic hormone release is responsible for its diuretic effect. The gastrointestinal complications of alcohol use can occur from a single large ingestion. The most common is acute erosive **gastritis,** which is manifested by epigastric pain, anorexia, vomiting, and

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Table 114-11 Alcohol Use Disorders Identification Test (AUDIT)

	SCORE (0-4)*
1. How often do you have a drink containing alcohol?	Never (0) to more than 4 per wk (4)
2. How many drinks containing alcohol do you have on a typical day?	One or 2 (0) to more than 10 (4)
3. How often do you have 6 or more drinks on 1 occasion?	Never (0) to daily or almost daily (4)
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never (0) to daily or almost daily (4)
5. How often during the last year have you failed to do what was normally expected from you because of drinking?	Never (0) to daily or almost daily (4)
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never (0) to daily or almost daily (4)
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never (0) to daily or almost daily (4)
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never (0) to daily or almost daily (4)
9. Have you or someone else been injured as a result of your drinking?	No (0) to yes, during the last year (4)
10. Has a relative, friend, doctor or other health worker been concerned about your drinking or suggested that you should cut down?	No (0) to yes, during the last year (4)

*Score ≥8 = problem drinking.
From Schuckit MA: Alcohol-use disorders, Lancet *373:492–500, 2009, Table 1.*

heme-positive stools. Less commonly, vomiting and midabdominal pain may be caused by acute alcoholic **pancreatitis;** diagnosis is confirmed by the finding of elevated serum amylase and lipase levels.

DIAGNOSIS

Primary care settings provide opportunity to screen teens for alcohol use or problem behaviors. Brief alcohol screening instruments (CRAFFT [see Table 114-7] or AUDIT [Alcohol Use Disorders Identification Test, Table 114-11]) perform well in a clinical setting as techniques to identify alcohol use disorders. A score of ≥8 on the AUDIT questionnaire identifies people who drink excessively and who would benefit from reducing or ceasing drinking (Table 114-11)**.** Teenagers in the early phases of alcohol use exhibit few physical findings. Recent use of alcohol may be reflected in elevated γ-glutamyl transferase and aspartate amino transferase.

In acute care settings, the **alcohol overdose syndrome** should be suspected in any teenager who appears disoriented, lethargic, or comatose. Although the distinctive aroma of alcohol may assist in diagnosis, confirmation by analysis of blood is recommended. At levels >200 mg/dL, the adolescent is at risk of death, and levels >500 mg/dL (median lethal dose) are usually associated with a fatal outcome. When the level of obtundation appears excessive for the reported blood alcohol level, head trauma, hypoglycemia, or ingestion of other drugs should be considered as possible confounding factors.

TREATMENT

The usual mechanism of death from the alcohol overdose syndrome is respiratory depression, and artificial ventilatory support must be provided until the liver can eliminate sufficient amounts of alcohol from the body. In a patient without alcoholism, it generally takes 20 hr to reduce the blood level of alcohol from 400 mg/dL to zero. Dialysis should be considered when the blood level is >400 mg/dL. As a follow-up to acute treatment, referral for treatment of the alcohol use disorder is indicated. Group counseling, individualized counseling, and multifamily educational intervention have been found to be quite effective interventions for teens.

Bibliography is available at Expert Consult.

114.2 Tobacco

Margaret M. Stager

CIGARETTES

The average smoker in the United States starts at age 12 yr, and most are regular smokers by age 14 yr. More than 90% of adolescent smokers become adult smokers. Factors associated with youth tobacco use include exposure to smokers (friends, parents), availability of tobacco, low socioeconomic status, poor school performance, low self-esteem, lack of perceived risk of use, and lack of skills to resist influences to tobacco use.

Current smoking rates among U.S. high school students (as is the case for students in many industrialized nations) have trended downward over the last decade for lifetime cigarette use (from 20.0% to 12.4%) and current frequent cigarette use (from 16.8% to 6.4%). Overall, more whites report current tobacco use (20.3%) than Hispanics (17.5%) or blacks (10.5%). Clove cigarettes (kreteks) and flavored cigarettes (bidis) are popular with younger students. Both types of flavored cigarettes contain tobacco with other additives and deliver more nicotine and other harmful substances because they are unfiltered. Use of cigars and mini-cigars (cigarillos) has not changed in the past 3 yr, with 13.1% of students reporting smoking at least 1 during the 30 days prior to the survey. Cigar/cigarillo use is highest among males (17.8% vs. females 8.0%), and high school seniors (23.9%) versus lower grades (9th grade 12.3%, 10th grade 15.4% and 11th grade 20.4%). Tobacco use is linked to other high-risk behaviors. Teens who smoke are more likely than nonsmokers to use alcohol and engage in unprotected sex, are 8 times more likely to use marijuana, and are 22 times more likely to use cocaine.

Tobacco is used by teens in all regions of the world, although the form of tobacco used differs. In the Americas and Europe, cigarette smoking prevalence is higher than other tobacco use, although cigars and smokeless tobacco are also used; in the Eastern Mediterranean, shisha (flavored tobacco smoked in hookah pipes) is prevalent; in Southeast Asia, smokeless tobacco products are used; in the Western Pacific, betel nut is chewed with tobacco; and pipe, snuff, and rolled tobacco leaves are used in Africa. Cigarette use rates by teens in low- and middle-income nations are increasing.

PHARMACOLOGY

Nicotine, the primary active ingredient in cigarettes, is addictive. Nicotine is absorbed by multiple sites in the body, including the lungs, skin, gastrointestinal tract, and buccal and nasal mucosa. The action of nicotine is mediated through nicotinic acetylcholine receptors located on noncholinergic presynaptic and postsynaptic sites in the brain and causes increased levels of dopamine. Nicotine also stimulates the adrenal glands to release epinephrine, causing an immediate elevation in blood pressure, respiration and heart rate. The average nicotine content of 1 cigarette is 10 mg and the average nicotine intake per cigarette ranges from 1-3 mg. Nicotine, as delivered in cigarette smoke, has a half-life of about 2 hr. **Cotinine** is the major metabolite of nicotine via C-oxidation. It has a biologic half-life of 19-24 hr and can be detected in urine, serum, and saliva.

CLINICAL MANIFESTATIONS

Adverse health effects from regular smoking include an increased prevalence of chronic cough, sputum production, and wheezing.

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Smoking during pregnancy is associated with an average decrease in fetal weight of 200 g; this decrease, added to the already smaller size of infants born to teenagers, increases perinatal morbidity and mortality. Tobacco smoke induces hepatic smooth endoplasmic reticulum enzymes and, as a result, may also influence metabolism of drugs such as phenacetin, theophylline, and imipramine. Withdrawal symptoms can occur when adolescents try to quit. Irritability, decreased concentration, increased appetite, and strong cravings for tobacco are common withdrawal symptoms.

ELECTRONIC CIGARETTES (E-CIGARETTES)

E-cigarettes are electronic nicotine delivery systems that are battery operated, which heat and then vaporize nicotine dissolved in propylene glycol, glycerin, or other solvents. They come in tobacco, mint, cherry, or chocolate flavors, and are highly marketed to adolescents. They have the potential to create nicotine dependency and have not been effective in smoking-cessation programs.

Adverse effects include dry cough, throat irritation, and lipoid pneumonia. Potentially toxic substances have been detected in the vapor (diethylene glycol) as well as carcinogens (nitrosamines). Second-hand exposure is a possibility. These products have been banned in some countries; they are not regulated by the FDA.

SMOKELESS TOBACCO

The 2 forms of smokeless tobacco (SLT) are "chew," a leafy tobacco product sold in pouches, and "snuff," a finely ground tobacco product sold in tins or packets. Users place the SLT along the gum line of the lower jaw whereby the nicotine is absorbed by the mucous membranes. Smokeless tobacco use is largely reported by males in 10th (11.2%) and 12th grades (13.5%) for the 30-day prevalence rates. Snus, is a Swedish tobacco product that is available as a loose powder, or in a small teabag-like sachet. It is placed under the lower lip and unlike American chewing tobacco there is no need to spit. Annual prevalence of Snus use in 2012 was 2.4%, 6.9%, and 7.9% among 8th, 10th, and 12th graders, respectively.

Introduced in 2009, there are several dissolvable SLT products on the market. The Orbs are pellets of ground tobacco that resemble candy and come in various flavors. The Sticks are twin, matchstick-like ground tobacco, and the Strips are flat sheets that quickly dissolve in the mouth. All of these products are small and easily concealed, and therefore can be used throughout the day without detection, especially as there is no need to spit.

Exposure to SLT increases the users risk for oral cancers of the mouth, pharynx, larynx, and esophagus, as well as gum disease and nicotine addiction. Use of SLT among high school boys exceeds 20% in Arkansas, Kentucky, Montana, North Dakota, Oklahoma, South Dakota, Tennessee, Wyoming, and West Virginia (the latter with the highest rate at 25.5%).

TREATMENT

The approach to smoking cessation in adolescents includes the **5 As (Ask, Advise, Assess, Assist, and Arrange)** and use of nicotine replacement therapy in addicted teens who are motivated to quit and are not using SLT. Consensus panels recommend the 5 As, although evidence of efficacy in adolescents is limited. Nicotine patch studies to date in adolescents suggest a positive effect on reducing withdrawal symptoms and that pharmacotherapy should be combined with behavioral therapy to reach higher cessation and lower relapse rates. In a limited number of students, cessation rates of 15% were reported at 3 and 6 mo. Nicotine replacement therapy is also available as a gum, inhaler, nasal spray, lozenge, or microtab (Table 114-12). However, the nicotine patch and nasal spray were found to have numerous side effects in adolescent subjects. Medications such as bupropion are not FDA approved for use in adolescents <18 yr old; some pilot studies in adolescents report cessation efficacy with 150 mg or 300 mg of bupropion daily. Varenicline has successfully been used in adults; however, it now includes a black box warning of neuropsychiatric side effects such as agitation, hostility, depressed mood, and suicidal ideation.

The American Lung Association's Not-On-Tobacco Program (NOT) is a nationally recognized best-practice model for teen smoking cessation. More than 100,000 teens in 48 states have participated in the NOT, which resulted in either quitting (15% on average) or decreased tobacco use. The NOT is a 10 wk, developmentally appropriate, teen-focused, small group program that addresses topics such as stress management, effects of smoking, preparing to quit, dealing with peer pressure, and establishing support networks. The program is available as a train-the-trainer model, including training manuals and student materials (see www.lung.org).

In keeping with teens' high use of cell phones, support for teen smoking cessation is now available as a text-messaging service. Smokefree TXT, a free text messaging service, is offered by the National Cancer Institute and aims to engage teens to quit smoking using daily text messaging on their cell phone. Teens can sign up online (teen.smokefree.gov) or text QUIT to iQUIT (47848). Another cell phone

Table 114-12 Smoking Cessation Pharmacotherapy Available in the United States

THERAPY BRAND	NAME	STRENGTHS	FDA-APPROVED ADULT DOSING	AVAILABILITY*	STUDIED IN ADOLESCENTS	QUIT DATE
NICOTINE REPLACEMENT THERAPY						
Gum[‡]	Nicorette	2 mg, 4mg	The 0.4-mg strength should be used by patients who smoke 25 or more cigarettes a day; otherwise the 2-mg strength should be used Wk 1-6: 1 piece every 1-2 hr Wk 7-9: 1 piece every 2-4 hr Wk 10-12: 1 piece every 4-8 hr	OTC*	Yes	
Inhaler	Nicotrol Inhaler	4 mg	6-16 cartridges a day for up to 12 wks	Rx	No	
Lozenge	CommitTM, Nicorette mini	2 mg, 4 mg	The 4-mg strength should be used by patients who smoke their first cigarette within 30 minutes of waking; otherwise, the 2-mg strength should be used Wk 1-6: 1 lozenge every 1-2 hr Wk 7-9: 1 lozenge every 2-4 hr Wk 10-12: 1 lozenge every 4-8 hr	OTC	No	Prior to beginning nicotine replacement therapy

Table 114-12 Smoking Cessation Pharmacotherapy Available in the United States—cont'd

THERAPY BRAND	NAME	STRENGTHS	FDA-APPROVED ADULT DOSING	AVAILABILITY*	STUDIED IN ADOLESCENTS	QUIT DATE
Nasal Spray	Nicotrol NS	0.5 mg/spray	1-2 sprays/hr up to a maximum of 80 sprays per day	Rx	Yes	
Transdermal Patch[‡]	NicoDerm CQ	7, 14, 21 mg/24 hr	For patients who smoke >10 cigarettes daily: Step 1: one 21-mg patch daily for wks 1-6 Step 2: one 14-mg patch daily for wks 7-8 Step 3: one 7-mg patch daily for wks 9-10 For patients who smoke <10 cigarettes daily: begin with the 14-mg patch daily for 6 wks, followed by the 7-mg patch for 2 wks	OTC	Yes	
NONNICOTINE THERAPY						
Bupropion SR[‡]	Zyban	150-mg sustained release tablets	150 mg by mouth in the morning for 3 days, then increase to 150 mg by mouth twice daily	Rx	Yes	1 wk after starting therapy
Varenicline	Chantix	0.5-, 1-mg tablets	0.5 mg by mouth in the morning for 3 days; increase to 0.5 mg by mouth twice daily for 4 days, then increase to 1 mg by mouth twice daily	Rx	No	

*OTC indicates available over the counter; Rx indicates it is a prescription product.
[†]None are FDA-approved for use in patients younger than 18 yr.
[‡]Generics available.
From JP Karpinski, et al: Smoking cessation treatment for adolescents J Pediatr Pharmacol Ther *15(4):249–260, 2010, Table 2.*

application, QuitSTART, is available for teens as an interactive cell phone-based guide that helps them track cravings, monitor moods, offer cessation tips, and follow quit attempts. Both Smokefree TXT and QuitSTART link teens to social media webpages which offer additional information on cessation tools and programs.

Bibliography is available at Expert Consult.

114.3 Marijuana

Margaret M. Stager

Marijuana (THC, "pot," "weed," "hash," "grass"), derived from the *Cannabis sativa* hemp plant, is the most commonly abused illicit drug. The main active chemical, tetrahydrocannabinol (THC), is responsible for its hallucinogenic properties. THC is absorbed rapidly by the nasal or oral routes, producing a peak of subjective effect at 10 min and 1 hr, respectively. Marijuana is generally smoked as a cigarette ("reefer" or "joint") or in a pipe. Although there is much variation in content, each cigarette contains 8-10% THC. Another popular form that is smoked, a "blunt," is a hollowed-out small cigar refilled with marijuana. Hashish is the concentrated THC resin in a sticky black liquid or oil. Although marijuana use by U.S. teens has declined in the last decade, 23.1% of high school students have used marijuana at least once during the previous 30 days, and current marijuana use is highest in black males and seniors. Eight percent of students report having tried marijuana before the age of 13 yr, with a range from 4.3-18.5% across various states, indicating the need for early prevention efforts.

CLINICAL MANIFESTATIONS

In addition to the "desired" effects of elation and euphoria, marijuana may cause impairment of short-term memory, poor performance of tasks requiring divided attention (e.g., those involved in driving), loss of critical judgment, decreased coordination, and distortion of time perception (Table 114-13). Visual hallucinations and perceived body distortions occur rarely, but there may be "flashbacks" or recall of frightening hallucinations experienced under marijuana's influence that usually occur during stress or with fever.

Smoking marijuana for a minimum of 4 days/wk for 6 mo appears to result in dose-related suppression of plasma testosterone levels and spermatogenesis, prompting concern about the potential deleterious effect of smoking marijuana before completion of pubertal growth and development. There is an antiemetic effect of oral THC or smoked marijuana, often followed by appetite stimulation, which is the basis of the drug's use in patients receiving cancer chemotherapy. Although the possibility of teratogenicity has been raised because of findings in animals, there is no evidence of such effects in humans. An **amotivational syndrome** has been described in long-term marijuana users who lose interest in age-appropriate behavior, yet proof of the causative relationship remains equivocal. Chronic use is associated with increased anxiety and depression, learning problems, poor job performance, hyperemesis, and respiratory problems such as pharyngitis, sinusitis, bronchitis, and asthma (see Table 114-13).

The increased THC content of marijuana of 5-15–fold compared to that of the 1970s, is related to the observation of a **withdrawal syndrome,** occurring 24-48 hr after discontinuing the drug. Heavy users experience malaise, irritability, agitation, insomnia, drug craving, shakiness, diaphoresis, night sweats, and gastrointestinal disturbance. The symptoms peak by the 4th day, and they resolve in 10-14 days. Certain drugs may interact with marijuana to potentiate sedation (alcohol, diazepam), potentiate stimulation (cocaine, amphetamines), or be antagonistic (propranolol, phenytoin).

Behavioral interventions, including cognitive-behavioral therapy and motivational incentives, have shown to be effective in treating marijuana dependency.

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Table 114-13	Acute and Chronic Adverse Effects of Cannabis Use
ACUTE ADVERSE EFFECTS • Anxiety and panic, especially in naïve users • Psychotic symptoms (at high doses) • Road crashes if a person drives while intoxicated	
CHRONIC ADVERSE EFFECTS • Cannabis dependence syndrome (in around 1 in 10 users) • Chronic bronchitis and impaired respiratory function in regular smokers • Psychotic symptoms and disorders in heavy users, especially those with a history of psychotic symptoms or a family history of these disorders • Impaired educational attainment in adolescents who are regular users • Subtle cognitive impairment in those who are daily users for 10 yr or more	

From Hall W, Degenhardt L: Adverse health effects of non-medical cannabis use, Lancet *374:1383–1390, 2009.*

SYNTHETIC MARIJUANA

Spice, K2, crazy clown, aroma, black mamba, blaze, dream, and funky monkey are common street names for synthetic marijuana, which is a mixture of herbs or plant materials that have been sprayed with artificial chemicals similar to THC, the psychoactive ingredient in marijuana. One active group of chemicals is the carboxamides, which are not detected by assays to detect THC. In the United States, the chemicals in Spice are designated a schedule I controlled substance by the DEA, thereby making it illegal to sell, buy, or possess them. Nonetheless, synthetic marijuana is the second most common illicit drug used by high school seniors. More than 1 in 10 high school seniors used synthetic marijuana in the last year.

Synthetic marijuana is mainly used by smoking, or mixed with marijuana, or brewed as a tea for drinking. The chemicals in synthetic marijuana affect the same receptors as THC and produce similar effects as seen in marijuana such as relaxation, elevated mood, and altered perception. In addition, sympathomimetic symptoms are quite common and are the cause of significant toxicity. Symptoms of intoxication include vomiting, tachycardia, hypertension, hyperthermia, confusion, extreme anxiety, profuse sweating, agitation, aggression, dysphoria, hallucinations, seizures, rhabdomyolysis, dystonia, unresponsiveness, confusion, and myocardial ischemia. In response to legislation to ban the chemicals in OTC synthetic marijuana products, manufacturers alter and substitute the chemicals in the product, keeping it on the legal market and leaving teens particularly vulnerable to potential health effects.

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114.4 Inhalants

Margaret M. Stager

Inhalants, found in many common household products, comprise a diverse group of volatile substances whose vapors can be inhaled to produce psychoactive effects. The practice of inhalation is popular among younger adolescents and decreases with age. Young adolescents are attracted to these substances because of their rapid action, easy availability, and low cost. Products that are abused as inhalants include volatile solvents (paint thinners, glue), aerosols (spray paint, hair spray), gases (propane tanks, lighter fluid), nitrites ("poppers" or "video head cleaner") and propellants used in whipped cream dispensers. The most popular inhalants among young adolescents are glue, shoe polish, and spray paint. The various products contain a wide range of chemicals with serious adverse health effects (Table 114-14). **Huffing,** the practice of inhaling fumes can be accomplished using a paper bag containing a chemical-soaked cloth, spraying aerosols directly into the nose/mouth, or using a balloon, plastic bag, or soda can filled with fumes. The percentage of adolescents using inhalants has remained stable, with 11.4% of high school students reporting having ever used inhalants in. Eighth and 9th graders report highest use, suggesting targeted prevention strategies are warranted for this age group.

Table 114-14	Hazards of Chemicals Found in Commonly Abused Inhalants
Amyl nitrite, butyl nitrite *("poppers," "video head cleaner")*: sudden sniffing death syndrome, suppressed immunologic function, injury to red blood cells (interfering with oxygen supply to vital tissues)	
Benzene *(found in gasoline)*: bone marrow injury, impaired immunologic function, increased risk of leukemia, reproductive system toxicity	
Butane, propane *(found in lighter fluid, hair and paint sprays)*: sudden sniffing death syndrome via cardiac effects, serious burn injuries (because of flammability)	
Freon *(used as a refrigerant and aerosol propellant)*: sudden sniffing death syndrome, respiratory obstruction and death (from sudden cooling/cold injury to airways), liver damage	
Methylene chloride *(found in paint thinners and removers, degreasers)*: reduction of oxygen-carrying of blood, changes to the heart muscle and heartbeat	
Nitrous oxide *("laughing gas")*, **hexane**: death from lack of oxygen to the brain, altered perception and motor coordination, loss of sensation, limb spasms, blackouts caused by blood pressure changes, depression of heart muscle functioning	
Toluene *(found in gasoline, paint thinners and removers, correction fluid)*: brain damage (loss of brain tissue mass, impaired cognition, gait disturbance, loss of coordination, loss of equilibrium, limb spasms, hearing and vision loss), liver and kidney damage	
Trichloroethylene *(found in spot removers, degreasers)*: sudden sniffing death syndrome, cirrhosis of the liver, reproductive complications, hearing and vision damage	

CLINICAL MANIFESTATIONS

The major effects of inhalants are psychoactive (Table 114-15). The intoxication lasts only a few minutes, so a typical user will huff repeatedly over an extended period of time (hours) in order to maintain the high. The immediate effects of inhalants are similar to alcohol: euphoria, slurred speech, decreased coordination, and dizziness. Toluene, the main ingredient in model airplane glue and some rubber cements, causes relaxation and pleasant hallucinations for up to 2 hr. Euphoria is followed by violent excitement; coma may result from prolonged or rapid inhalation. Volatile nitrites, such as amyl nitrite, butyl nitrite, and related compounds marketed as room deodorizers, are used as euphoriants, enhancers of musical appreciation, and sexual enhancements among older adolescents and young adults. They may result in headaches, syncope, and lightheadedness; profound hypotension and cutaneous flushing followed by vasoconstriction and tachycardia; transiently inverted T waves and depressed ST segments on electrocardiography; methemoglobinemia; increased bronchial irritation; and increased intraocular pressure.

COMPLICATIONS

Model airplane glue is responsible for a wide range of complications, related to chemical toxicity, to the method of administration (in plastic bags, with resultant suffocation), and to the often dangerous setting in which the inhalation occurs (inner-city roof tops). Common neuromuscular changes reported in chronic inhalant abusers include difficulty coordinating movement, gait disorders, muscle tremors, and spasticity, particularly in the legs (Table 114-16). Chronic use may cause pulmonary hypertension, restrictive lung defects or reduced

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Table 114-15	Stages in Symptom Development After Use of Inhalants
STAGE	**SYMPTOMS**
1: Excitatory	Euphoria, excitation, exhilaration, dizziness, hallucinations, sneezing, coughing, excess salivation, intolerance to light, nausea and vomiting, flushed skin and bizarre behavior
2: Early CNS depression	Confusion, disorientation, dullness, loss of self-control, ringing or buzzing in the head, blurred or double vision, cramps, headache, insensitivity to pain, and pallor or paleness
3: Medium CNS depression	Drowsiness, muscular uncoordination, slurred speech, depressed reflexes, and nystagmus or rapid involuntary oscillation of the eyeballs
4: Late CNS depression	Unconsciousness that may be accompanied by bizarre dreams, epileptiform seizures, and EEG changes

CNS, central nervous system; EEG, electroencephalogram
From Harris D: Volatile substance abuse, Arch Dis Child Educ Pract Ed *91:ep93-ep100, 2006, Table 1.*

Table 114-16	Documented Clinical Presentations of Volatile Substance Abuse
CLINICAL PRESENTATIONS OF ACUTE AND CHRONIC VOLATILE SUBSTANCE ABUSE	
Ventricular fibrillation	Muscle weakness
Asystolic cardiac arrest	Abdominal pain
Myocardial infarction	Cough
Ataxia	Aspiration pneumonia
Agitation	Chemical pneumonitis
Limb and trunk uncoordination	Coma
Tremor	Visual and auditory hallucinations
Visual loss	Acute delusions
Tinnitus	Nausea and vomiting
Dysarthria	Pulmonary edema
Vertigo	Photophobia
Hyperreflexia	Rash
Acute confusional state	Jaundice
Conjunctivitis	Anorexia
Acute paranoia	Slurred speech
Depression	Diarrhea
Oral and nasal mucosal ulceration	Weight loss
Halitosis	Epistaxis
Convulsions/fits	Rhinitis
Headache	Cerebral edema
Peripheral neuropathy	Visual loss
Methemoglobinemia	Burns
Acute trauma	Renal tubular acidosis

From Harris D: Volatile substance abuse, Arch Dis Child Educ Pract Ed *91:ep93-ep100, 2006, Table 2.*

diffusion capacity, peripheral neuropathy, hematuria, tubular acidosis, and possibly cerebral and cerebellar atrophy. Chronic inhalant abuse has long been linked to widespread brain damage and cognitive abnormalities that can range from mild impairment (poor memory, decreased learning ability) to severe dementia. High-frequency inhalant users were significantly more likely than moderate- and low-frequency users to experience adverse consequences of inhalant intoxication such as behavioral, language, and memory problems. Certain risky behaviors and consequences, such as engaging in unprotected sex or fighting while high on inhalants, were dramatically more common among high-frequency inhalant users than among low-frequency inhalant users. Death in the acute phase may result from cerebral or pulmonary edema or myocardial involvement (Table 114-16).

DIAGNOSIS

Diagnosis of inhalants is difficult because of the ubiquitous nature of the products and decreased parental awareness of their dangers. In the primary care setting, providers need to enquire of parents if they have witnessed any unusual behaviors in their teen; noticed high-risk products in their bedrooms; seen paint on the teen's hands, nose, or mouth; or found paint coated or chemical coated rags. Complete blood counts, coagulation studies, and hepatic and renal function studies may identify the complications. In extreme intoxication, a user may manifest symptoms of restlessness, general muscle weakness, dysarthria, nystagmus, disruptive behavior, and occasionally hallucinations. Toluene is excreted rapidly in the urine as hippuric acid, with the residual detectable in the serum by gas chromatography.

TREATMENT

Treatment is generally supportive and directed toward control of arrhythmia and stabilization of respirations and circulation. Withdrawal symptoms do not usually occur.

Bibliography is available at Expert Consult.

114.5 Hallucinogens

Margaret M. Stager

Several naturally occurring and synthetic substances are used by adolescents for their hallucinogenic properties. They have chemical structures similar to neurotransmitters such as serotonin, yet their exact mechanism of action remains unclear. Lysergic acid diethylamide (LSD) and methylenedioxymethamphetamine (MDMA) (Ecstasy or Molly) are the most commonly reported hallucinogens used.

LYSERGIC ACID DIETHYLAMIDE

LSD (acid, big "d," blotters) is a very potent hallucinogen that is made from lysergic acid found in ergot, a fungus that grows on rye and other grains. Its high potency allows effective doses to be applied to absorbent paper, or it can be taken as a liquid or a tablet. The onset of action can be between 30 and 60 min, and it peaks between 2 and 4 hr. By 10-12 hr, an individual returns to the predrug state. Four percent of U.S. 12th graders report trying LSD at least once.

Clinical Manifestations

The effects of LSD can be divided into 3 categories: somatic (physical effects), perceptual (altered changes in vision and hearing), and psychic effects (changes in sensorium). The common somatic symptoms are dizziness, dilated pupils, nausea, flushing, elevated temperature, and tachycardia. The sensation of synesthesia, or "seeing" smells and "hearing" colors, as well as major distortions of time and self, have been reported with high doses of LSD. Delusional ideation, body distortion, and suspiciousness to the point of toxic psychosis are the more serious of the psychic symptoms. LSD is not considered to be an addictive drug as it does not typically produce drug-seeking behavior.

Treatment

An individual is considered to have a "bad trip" when the sensory experiences causes the user to become terrified or panicked. These episodes should be treated by removing the individual from the aggravating situation and placing him in a quiet room with a calming friend. In situations of extreme agitation or seizures, use of benzodiazepines may be warranted. "Flashbacks" or LSD-induced states after the drug has worn off and tolerance to the effects of the drug are additional complications of its use.

METHYLENEDIOXYMETHAMPHETAMINE

MDMA ("X," Ecstasy, Molly), a phenylisopropylamine hallucinogen, is a synthetic compound similar to hallucinogenic mescaline and the stimulant methamphetamine. Like other hallucinogens, this drug is

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proposed to interact with serotoninergic neurons in the central nervous system (CNS). It is the preferred drug at "raves," all-night dance parties, and is also known as one of the "club drugs" along with γ-hydroxybutyrate (GHB) and ketamine (see Table 114-5). Between 2009 and 2010, past-year use of MDMA increased among both 8th and 10th graders in the US but then declined in both grades. Nationwide, the prevalence of having ever used MDMA was 8.2% of students with highest use reported among males and Hispanics (10.6%). MDMA use increased among high school students from 2009-2011 (8.2%). LSD use remained stable during this time period (2009: 8%; 2011: 8.7%).

Clinical Manifestations

Euphoria, a heightened sensual awareness, and increased psychic and emotional energy are acute effects. Compared to other hallucinogens, MDMA is less likely to produce emotional lability, depersonalization, and disturbances of thought. Nausea, jaw clenching, teeth grinding, and blurred vision are somatic symptoms, whereas anxiety, panic attacks, and psychosis are the adverse psychiatric outcomes. A few deaths have been reported after ingestion of the drug. In high doses, MDMA can interfere with the body's ability to regulate temperature. The resultant hyperthermia in association with vigorous dancing at a "rave" has resulted in severe liver, kidney, and cardiovascular system failure and death. There are no specific treatment regimens recommended for acute toxicity. Chronic MDMA use can lead to changes in brain function, affecting cognitive tasks and memory. These symptoms may occur because of MDMA's effects on neurons that use serotonin as a neurotransmitter. The serotonin system plays an important role in regulating mood, aggression, sexual activity, sleep, and sensitivity to pain. A high rate of dependence has been found among MDMA users. MDMA exposure may be associated with long-term neurotoxicity and damage to serotonin-containing neurons. In nonhuman primates, exposure to MDMA for only 4 days caused damage to serotonin nerve terminals that was evident 6-7 yr later. There are no specific pharmacologic treatments for MDMA addiction. Drug abuse recovery groups are recommended.

PHENCYCLIDINE

Phencyclidine (PCP) (sternyl, angel dust, "hog," "peace pill," "sheets") is an arylcyclohexalamine whose popularity is related, in part, to its ease of synthesis in home laboratories. One of the by-products of home synthesis causes cramps, diarrhea, and hematemesis. It is a "dissociative drug" that produces feelings of detachment from the surrounding environment and self. The drug is thought to potentiate adrenergic effects by inhibiting neuronal reuptake of catecholamines. PCP is available as a tablet, liquid, or powder, which may be used alone or sprinkled on cigarettes ("joints"). The powders and tablets generally contain 2-6 mg of PCP, whereas joints average 1 mg for every 150 mg of tobacco leaves, or approximately 30-50 mg per joint. The prevalence of PCP use (hallucinogenic drug) among U.S. high school students remained stable from 2009 (8.0%) to 2011 (8.7%).

Clinical Manifestations

The clinical manifestations are dose related and produce alterations of perception, behavior, and autonomic functions. Euphoria, nystagmus, ataxia, and emotional lability occur within 2-3 min after smoking 1-5 mg and last for 4-6 hr. At these low doses the user is likely to experience shallow breathing, flushing, generalized numbness of extremities, and loss of motor coordination. Hallucinations may involve bizarre distortions of body image that often precipitate panic reactions. With doses of 5-15 mg, a toxic psychosis may occur, with disorientation, hypersalivation, and abusive language lasting for >1 hr. Hypotension, generalized seizures, and cardiac arrhythmias commonly occur with plasma concentrations from 40-200 mg/dL. Death has been reported during psychotic delirium, from hypertension, hypotension, hypothermia, seizures, and trauma. The coma of PCP may be distinguished from that of the opiates by the absence of respiratory depression; the presence of muscle rigidity, hyperreflexia, and nystagmus; and lack of response to naloxone. PCP psychosis may be difficult to distinguish from schizophrenia. In the absence of a history of use, analysis of urine must be depended on for diagnosis.

Treatment

Management of the PCP-intoxicated patient includes placement in a darkened, quiet room on a floor pad, safe from injury. Acute alcohol intoxication may be present also. For recent oral ingestion, gastric absorption is poor and induction of emesis or gastric lavage is useful. Diazepam, in a dose of 5-10 mg orally or 2-5 mg intravenously, may be helpful if the patient is agitated and not comatose. Rapid excretion of the drug is promoted by acidification of the urine. Supportive therapy of the comatose patient is indicated with particular attention to hydration, which may be compromised by PCP-induced diuresis. Inpatient and/or behavioral treatments can be helpful for chronic PCP users.

Bibliography is available at Expert Consult.

114.6 Cocaine

Margaret M. Stager

Cocaine, an alkaloid extracted from the leaves of the South American *Erythroxylum coca,* is supplied as the hydrochloride salt in crystalline form. With "snorting" it is rapidly absorbed into the bloodstream from the nasal mucosa, detoxified by the liver, and excreted in the urine as benzoylecgonine. Smoking the cocaine alkaloid ("freebasing") involves inhaling the cocaine vapors in pipes, or cigarettes mixed with tobacco or marijuana. Accidental burns are potential complications of this practice. With crack cocaine, the crystallized rock form, the smoker feels "high" in <10 sec. The risk of addiction with this method is higher and more rapidly progressive than from snorting cocaine. Tolerance develops and the user must increase the dose or change the route of administration, or both, to achieve the same effect. To sustain the high, cocaine users repeatedly use cocaine in short periods of time known as "binges." Drug dealers often place cocaine in plastic bags or condoms and swallow these containers during transport. Rupture of a container produces a sympathomimetic crisis (see Table 114-6). Cocaine use among high school students has decreased in the last decade, with 8.5% of 12th graders having tried the drug (any route) at least once. Current cocaine use in last 30 days remains stable at 3% of students.

CLINICAL MANIFESTATIONS

Cocaine is a strong CNS stimulant that increases dopamine levels by preventing reuptake. Cocaine produces euphoria, increased motor activity, decreased fatigability, and mental alertness. Its sympathomimetic properties are responsible for pupillary dilation, tachycardia, hypertension, and hyperthermia. Snorting cocaine chronically results in loss of sense of smell, nosebleeds, and chronic rhinorrhea. Injecting cocaine increases risk for HIV infection. Chronic abusers experience anxiety, irritability, and sometimes paranoid psychosis. Lethal effects are possible, especially when cocaine is used in combination with other drugs, such as heroin, in an injectable form known as a "speedball." Cocaine, when taken with alcohol, is metabolized by the liver to produce cocaethylene, a substance that enhances the euphoria and is associated with a greater risk of sudden death than cocaine alone. Pregnant adolescents who use cocaine place their fetus at risk of premature delivery, complications of low birthweight, and possibly developmental disorders.

TREATMENT

There are no FDA-approved medications for treatment of cocaine addiction. Cognitive-behavioral therapy has been shown to be effective when provided in combination with additional services and social support.

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114.7 Amphetamines

Margaret M. Stager

Methamphetamine, commonly known as "ice," is a nervous system stimulant and schedule II drug with a high potential for abuse. Most of the methamphetamine currently abused is produced in illegal laboratories. It is a white, odorless, bitter tasting powder that is particularly popular among adolescents and young adults because of its potency and ease of absorption. It can be ingested orally, by smoking, needle injection, or absorption across mucous membranes. Amphetamines have multiple CNS effects, among them the release of neurotransmitters and an indirect catecholamine agonist effect. In recent years, there has been a general decline of methamphetamine use among high school students. In the 2012 Monitoring the Future Study, 1.1% of 12th graders report using methamphetamine at least once reflecting a steady decline in use over the last 10 yr.

CLINICAL MANIFESTATIONS

Methamphetamine rapidly increases the release and blocks the reuptake of dopamine, a powerful "feel good" neurotransmitter (Table 114-17). The effects of amphetamines can be dose related. In small amounts amphetamine effects resemble other stimulants: increased physical activity, rapid and/or irregular heart rate, increased blood pressure and decreased appetite. High doses produce slowing of cardiac conduction in the face of ventricular irritability. Hypertensive and hyperpyrexic episodes can occur as seizures (see Table 114-6). Binge effects result in the development of psychotic ideation with the potential for sudden violence. Cerebrovascular damage, psychosis, severe receding of the gums with tooth decay, and infection with HIV and hepatitis B and C can result from long-term use. There is a withdrawal syndrome associated with amphetamine use, with early, intermediate, and late phases (Table 114-17). The early phase is characterized as a "crash" phase with depression, agitation, fatigue, and desire for more of the drug. Loss of physical and mental energy, limited interest in the environment, and anhedonia mark the intermediate phase. In the final phase, drug craving returns, often triggered by particular situations or objects.

TREATMENT

Acute agitation and delusional behaviors can be treated with haloperidol or droperidol. Phenothiazines are contraindicated and may cause a rapid drop in blood pressure or seizure activity. Other supportive treatment consists of a cooling blanket for hyperthermia and treatment of the hypertension and arrhythmias, which may respond to sedation with lorazepam or diazepam. For the chronic user, comprehensive cognitive-behavioral interventions have been shown to effective treatment options.

Bibliography is available at Expert Consult.

114.8 Opiates

Margaret M. Stager

Heroin is a highly addictive synthetic opiate drug made from a naturally occurring substance (morphine) in the opium poppy plant. It is a white or brown powder that can be injected (intravenously or subcutaneously), snorted/sniffed, or smoked. Intravenous injection produces an immediate effect, whereas effects from the subcutaneous route occur in minutes, and from snorting, in 30 minutes. After injection, heroin crosses the blood–brain barrier, is converted to morphine, and binds to opiate receptors. Tolerance develops to the euphoric effect, and the chronic user must use more heroin to achieve the same intense effect. Heroin use among teens peaked in the mid-1990s but is resurgent in some suburban communities, as is the use of prescription opioids found in the home. Nationwide 2.9% of high school students report having tried heroin at least once. Highest use is seen in black males, with a growing prevalence in suburban high school students; ranges vary from 0.8% to 5.3% across large urban, suburban, and rural school districts.

CLINICAL MANIFESTATIONS

The clinical manifestations are determined by the purity of the heroin or its adulterants, combined with the route of administration. The immediate effects include euphoria, diminution in pain, flushing of the skin, and pinpoint pupils (see Table 114-17). An effect on the hypothalamus is suggested by the lowering of body temperature. The most common dermatologic lesions are the "tracks," the hypertrophic linear scars that follow the course of large veins. Smaller, discrete peripheral scars, resembling healed insect bites, may be easily overlooked. The adolescent who injects heroin subcutaneously may have fat necrosis, lipodystrophy, and atrophy over portions of the extremities. Attempts to conceal these stigmata may include amateur tattoos in unusual sites.

Table 114-17 Signs and Symptoms of Intoxication and Withdrawal

	OPIATES	AMPHETAMINES/COCAINE	BENZODIAZEPINES
INTOXICATION			
Behavior	Apathy and sedation; disinhibition; psychomotor retardation; impaired attention and judgment	Euphoria and sensation of increased energy; hypervigilance; grandiosity, aggression, argumentative; labile mood; repetitive stereotyped behaviors; hallucinations, usually with intact orientation; paranoid ideation; interference with personal functioning	Euphoria; apathy and sedation; abusiveness or aggression; labile mood; impaired attention; anterograde amnesia; impaired psychomotor performance; interference with personal functioning
Signs	Drowsiness; slurred speech; pupillary constriction (except anoxia from severe overdose—dilation); decreased level of consciousness	Dilated pupils; tachycardia (occasionally bradycardia, cardiac arrhythmias); hypertension; nausea/vomiting; sweating and chills; evidence of weight loss; dilated pupils; chest pain; convulsions	Unsteady gait; difficulty in standing; slurred speech; nystagmus; decreased level consciousness; erythematous skin lesions or blisters
Overdose	Respiratory depression; hypothermia	Sympathomimetic symptoms	Hypotension; hyperthermia; depression of gag reflex; coma
Withdrawal	Craving to use; lacrimation; yawning; rhinorrhea/sneezing; muscle aches or cramps; abdominal cramps; nausea/vomiting/diarrhoea; sweating; dilated pupils; anorexia; irritability; tremor; piloerection/chills; restlessness; disturbed sleep	Dysphoric mood (sadness/anhedonia); lethargy and fatigue; psychomotor retardation or agitation; craving; increased appetite; insomnia or hypersomnia; bizarre or unpleasant dreams	Tremor of tongue, eyelids, or outstretched hands; nausea or vomiting; tachycardia; postural hypotension; psychomotor agitation; headache; insomnia; malaise or weakness; transient visual, tactile, or auditory hallucinations or illusions; paranoid ideation; grand mal convulsions

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Skin abscesses secondary to unsterile techniques of drug administration are commonly found. There is a loss of libido; the mechanism is unknown. The chronic heroin user may resort to prostitution to support the habit, thus increasing the risk of sexually transmitted diseases (including HIV), pregnancy, and other infectious diseases. Constipation results from decreased smooth muscle propulsive contractions and increased anal sphincter tone. The absence of sterile technique in injection may lead to cerebral microabscesses or endocarditis, usually caused by *Staphylococcus aureus or Pseudomonas aeruginosa.* Abnormal serologic reactions are also common, including false-positive Venereal Disease Research Laboratory and latex fixation tests.

WITHDRAWAL

After a period of ≥8 hr without heroin, the addicted individual undergoes, during a 24-36 hr period, a series of physiologic disturbances referred to collectively as "withdrawal" or the **abstinence syndrome** (see Table 114-17). The earliest sign is yawning, followed by lacrimation, mydriasis, restlessness, insomnia, "goose flesh," cramping of the voluntary musculature, bone pain, hyperactive bowel sounds and diarrhea, tachycardia, and systolic hypertension. Although the administration of methadone is the most common method of detoxification, the addition of buprenorphine, an opiate agonist–antagonist, is available for detoxification and maintenance treatment of heroin and other opiates. Buprenorphine has the advantage of offering less risk of addiction and overdose, and withdrawal effects and can be dispensed in the privacy of a physician's office. Combined with behavioral interventions, it has a greater success rate of detoxification. A combination drug, buprenorphine + naloxone, has been formulated to minimize abuse during detoxification.

OVERDOSE SYNDROME

The overdose syndrome is an acute reaction after the administration of an opiate. It is the leading cause of death among drug users. The clinical signs include stupor or coma, seizures, miotic pupils (unless severe anoxia has occurred), respiratory depression, cyanosis, and pulmonary edema. The differential diagnosis includes CNS trauma, diabetic coma, hepatic (and other) encephalopathy, Reye syndrome, as well as overdose of alcohol, barbiturates, PCP, or methadone. Diagnosis of opiate toxicity is facilitated by intravenous administration of the opiate antagonist naloxone, 0.01 mg/kg (2 mg is a common initial dose for an adolescent), which causes dilation of pupils constricted by the opiate. Diagnosis is confirmed by the finding of morphine in the serum.

TREATMENT

Treatment of acute heroin overdose consists of maintaining adequate oxygenation and continued administration of naloxone, a pure opioid antagonist. It may be given intravenously, intramuscularly, subcutaneously, or through the endotracheal tube. Naloxone has an ultrarapid onset of action (1 min) and a duration of action of 20-60 min. If there is no response, other etiologies for the respiratory depression must be explored. Naloxone may have to be continued for 24 hr if methadone, rather than shorter-acting heroin, has been taken. Admission to the intensive care unit is indicated for patients who require continuous naloxone infusions (rebound coma, respiratory depression), and for those with life-threatening arrhythmias, shock, and seizures.

Bibliography is available at Expert Consult.

114.9 Bath Salts

Margaret M. Stager

Bath salts refers to a group of previously OTC, but now illicit, substances containing 1 or more synthetic chemicals similar to cathinone, an amphetamine-like stimulant found in the Khat plant. The bath salts, marketed under brand names such as Ivory Wave, Cloud Nine, or Vanilla Sky, are sold online or in drug paraphernalia stores as a white or brown crystalline powder and can be ingested, inhaled, or injected. The most current information about teen use of bath salts is derived from the 2012 Monitoring the Future survey of 8th, 10th, and 12th grade students, who use at 0.8%, 0.6%, and 1.3%, respectively. The synthetic cathinones found in bath salts include methylone, mephedrone, and 3,4-methylenedioxypyrovalerone (MDPV) all of which are chemically similar to amphetamines and ecstasy (MDMA). The chemicals in bath salts raise brain dopamine levels causing the user to feel a surge of euphoria, increased sociability and sex drive. In addition, the user may experience a surge in norepinephrine, causing reactions such as an elevated heart rate, chest pain, vasoconstriction, diaphoresis, hyperthermia, dilated pupils, seizures, arrhythmias, and high blood pressure. Users also experience psychiatric symptoms such as aggressive behavior, panic attacks, paranoia, psychosis, delirium, self-mutilation, and hallucinations as a consequence of elevations of serotonin. Intoxication from bath salts may cause excited delirium syndrome, which includes dehydration, rhabdomyolysis, and kidney failure. Treatment of overdose should be directed at specific complications but often includes benzodiazepines or propofol for agitation and other neuropsychiatric manifestations. The synthetic cathinones in bath salts are highly addictive, triggering intense cravings in those who consume them frequently. This may result in dependence, tolerance, and strong withdrawal symptoms as seen in other highly addictive substances. The sale of 2 of the synthetic cathinones, mephedrone and MDPV, is illegal in the United States.

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Chapter 115

The Breast

Cynthia Holland-Hall and Gale R. Burstein

Breast development is often the first visible sign of puberty in the adolescent female. Pediatric practitioners must be able to distinguish normal breast development, including normal variants, from pathologic breast disorders. Visual inspection of the breast tissue should routinely be a component of the young adolescent's general physical examination. Breast development during puberty is described using the Sexual Maturity Rating (SMR) scale, progressing from SMR 1 to SMR 5 as the breast becomes more mature (see Fig. 110-2 in Chapter 110).

FEMALE DISORDERS

See Chapter 551.

MALE DISORDERS

Pubertal gynecomastia (see Chapter 585), occurring in up to 60% of normal adolescent males, has long been attributed to a transient imbalance of estrogen and androgen concentrations. Onset typically is between 10 and 13 yr, peaking at SMR 3-4. This physiologic condition usually regresses within 18-24 mo. Careful physical examination is essential to distinguish between true gynecomastia, characterized by a discreet disc of palpable glandular tissue under the nipple–areolar complex, and pseudogynecomastia, characterized by more diffuse adiposity of the anterior chest wall. Reassurance and continued observation are recommended in most cases; surgery may be indicated in severe or persistent cases. No medical therapies for gynecomastia have been approved for use in adolescents by the U.S. Food and Drug Administration. Small, noncontrolled trials of antiestrogens, such as tamoxifen, appear promising, but more evidence is needed. Conditions associated with nonphysiologic gynecomastia include endocrine disorders, liver disease, neoplasms, chronic disease, and trauma. Although

dozens of medications are implicated as possible causes of gynecomastia, convincing evidence exists only for a few, including several antiandrogens and other exogenous hormones, antiretrovirals, and histamine$_2$-receptor blockers. Calcium channel blockers, certain antipsychotics, and proton pump inhibitors may be causative. Among drugs of abuse, alcohol and anabolic steroids may be associated with gynecomastia, but very little evidence supports an association with marijuana, opiates, or amphetamines.

Other breast pathology in males is uncommon. Benign masses such as neurofibromas, lipomas, and dermoid cysts have been reported in the male breast. Males with Klinefelter syndrome have an elevated risk of breast cancer (see Chapter 583), but this malignancy is otherwise exceedingly rare in adolescents.

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Chapter 116

Menstrual Problems

Gina S. Sucato and Gale R. Burstein

See also Chapter 550.

Menstrual disturbances—including delayed onset, irregularity, heavy flow, and pain—occur in 75% of females during adolescence. Menstrual problems vary in presentation. For adolescents with minor variations from normal (Table 116-1), an explanation of symptoms and reassurance of reproductive health may be all that is needed. Severe dysmenorrhea or prolonged menstrual bleeding can be not only frightening, but a cause of persistent morbidity requiring more aggressive management, potentially including referral to a specialist in adolescent gynecology.

NORMAL MENSTRUATION

The average age of **menarche**, or first menses, varies according to the racial/ethnic background of the population and (possibly) socioeconomic status. There is often a close concordance of the age at menarche between mother and daughter, suggesting that genetic factors are determinants, as well as individual factors such as weight, exercise level, and chronic medical conditions. In the United States, the age of menarche has been relatively stable over the last few decades. The average age at menarche is 12.6 yr for non-Hispanic whites, 12.1 yr for non-Hispanic blacks, and 12.3 yr for Hispanic Americans. Age of menarche has declined in countries and populations experiencing improved nutritional standards and other living conditions. For example, in South Africa, average menarcheal age for blacks has been decreasing at a rate of approximately 0.50 yr/decade compared to an average decline of 0.22 yr/decade for whites.

Menarche typically occurs within 2.5 yr (range: 0.5-3 yr) of the onset of breast budding (thelarche), which is the first sign of puberty in most females. Menarche usually occurs during breast sexual maturity rating (SMR; i.e., Tanner) stage 4. Periods gradually become more regular, and by 3 yr after menarche, 90% of females have an average cycle length of between 21 and 45 days. The older the age at which menarche occurs, the longer it takes for consistently ovulatory cycles to be established. However, for most adolescents, by 5-6 yr after menarche, menstrual cycles are similar to that of adults: between 21 and 35 days long with 75% of cycles being ovulatory.

Table 116-1	Characteristics of Normal Menses*
Cycle length	21-35 days from the 1st day of one period to the 1st day of the next (during 1st 3 yr after menarche can be 21-45 days)
Duration of menses	7 or fewer days
Blood flow	6 or fewer (soaked) pads or tampons per day

*Adolescents with 2 or more cycles outside this range or who skip their period for 3 consecutive mo warrant more thorough evaluation.

MENSTRUAL IRREGULARITIES

In young adolescents, many variations in menstruation are explained by anovulation that results from immaturity of the hypothalamic-pituitary-ovarian axis that governs menstrual cyclicity. However, organic pathology should be considered and excluded in a logical and cost-effective manner. An accurate menstrual history is an important, but often lacking, first step toward a diagnosis. At the time of menarche, all patients should be encouraged to track their periods, something several free smart phone and tablet applications can facilitate.

Previously, a range of terms have been used to describe abnormal menstrual bleeding. These include menorrhagia to indicate regularly occurring bleeding that was excessive in amount or duration, and metrorrhagia to indicate irregular bleeding between periods. Such terms are imprecise, confusing, and not linked to any specific underlying pathology. Abnormal uterine bleeding (AUB) is the preferred term for uterine bleeding that is abnormal in regularity, volume, frequency, or duration. AUB is further specified by adding terms that describe the bleeding as heavy menstrual bleeding, or intermenstrual bleeding. A qualifying letter is added to indicate the etiology of the abnormal bleeding. Of the nine categories of etiologies, the three most relevant to adolescents are ovulatory dysfunction (AUB-O), previously referred to as dysfunctional uterine bleeding, discussed in Chapter 116.2, coagulopathy (AUB-C), and not yet classified (AUB-N).

In addition to a standard medical history noting hospitalizations, chronic illness, and medication use, a complete history for evaluating a patient with menstrual irregularity should include: the timing of pubertal milestones, such as onset of pubic and axillary hair and breast development; a detailed patient menstrual history; age of menarche and overall menstrual pattern of mother and sisters; and a family history of gynecologic problems. The complete review of systems should elicit any changes in headache pattern or vision; the presence of galactorrhea; and any changes in skin, hair, or bowel patterns. Changes in diet, level of exercise, and sports participation are also important factors when generating a differential diagnosis. As with all adolescent visits, the patient should be interviewed alone and the confidential history should assess substance use, consensual sexual activity, forced sexual behavior, abuse, and other psychosocial stressors.

In addition to the basic growth parameters of weight, height, blood pressure, heart rate, and body mass index, a careful review of the patient's growth chart is indicated. Physical exam should document SMR; signs of androgen excess, such as hirsutism or severe acne; and signs suggestive of an eating disorder (see Chapter 28), such as lanugo or knuckle calluses. A careful external genital examination should be performed, but in the absence of sexual activity, an internal pelvic examination is rarely necessary. If being considered for the young adolescent, an internal exam should be performed by someone with expertise in this age group using proper equipment and technique. Trans-abdominal pelvic ultrasound can be a useful adjunct for evaluating anatomic abnormalities in the adolescent.

Bibliography is available at Expert Consult.

116.1 Amenorrhea

Gina S. Sucato and Gale R. Burstein

Amenorrhea, the absence of menstruation, generally requires evaluation if there has been no menstruation within 4 yr of the onset of

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puberty (**primary amenorrhea**), or for the length of 3 previous cycles in a postmenarchal patient (**secondary amenorrhea**). However the following caveats exist: Lack of any pubertal signs by age 13 yr in a girl should prompt evaluation for pubertal delay, and in sexually active patients, or those with other symptoms suggesting pathology, evaluation should be initiated without waiting for 3 missed cycles. The evaluation of a patient presenting with amenorrhea should begin by ascertaining whether she has ever had any previous menstrual bleeding. Some aspects of the evaluation of both primary and secondary amenorrhea are identical; entities that can interrupt the menstrual cycle can also prevent menarche. However, in females with primary amenorrhea consideration must also be given to the possibility of genetic and anatomic conditions.

The differential diagnosis of amenorrhea is broad (Table 116-2) and requires a careful history and physical exam to guide any necessary diagnostic studies. Key to the evaluation is understanding the timing and tempo of the patient's pubertal milestones. Age 15 yr is commonly considered the age at which an evaluation for primary amenorrhea should be undertaken. Evaluation should begin sooner if 4 yr have elapsed since the onset of puberty (breast development in most females). Conversely, expectant management with close follow-up can be considered in a patient whose history, physical (showing some signs of pubertal development), and family history suggest constitutional delay of puberty. When a patient presents with primary amenorrhea, genetic and anatomic conditions are added to the differential diagnosis (Table 116-3).

HISTORY AND PHYSICAL EXAMINATION

Important elements of the history include dietary intake, exercise level, and a thorough review of any ongoing symptoms, including fever, headache, vision changes, chronic respiratory or gastrointestinal complaints, changes in bowel history, galactorrhea, changes in hair or nails, excessive body hair, severe acne, unexplained musculoskeletal complaints, and changes in vaginal discharge (which can disappear in females who are hypoestrogenic for reasons such as poor caloric intake). Any underlying medical conditions and the adequacy of their control should be noted, as well as the presence of any known renal or skeletal anomalies, which can be associated with reproductive system anomalies. Medications, particularly those for psychiatric conditions, should be documented. Family history of menarchal age, eating disorders (see Chapter 28), and **polycystic ovary syndrome (PCOS**; see Chapter 552) should be elicited. A thorough social history is necessary, especially concerning the presence or absence of sexual activity or abuse (see Chapter 40).

Physical examination should begin with careful attention to growth chart trajectories. In addition to a search for undiagnosed systemic disease, clues to an eating disorder, thyroid disease, or hyperandrogenism should be sought. The exam should assess for **body mass index**, orthostatic pulses, blood pressure, abnormal dentition, anosmia or hyposmia (suggestive of Kallmann syndrome; see Chapter 583.2), parotid enlargement, thyroid gland palpation, hepatosplenomegaly or other abdominal mass, lymphadenopathy, presence or absence of breast tissue (by palpation not inspection) and **SMR** (see Chapter 110). Skin exam should note any lanugo, dry or doughy skin, loss of hair from scalp or eyebrows, striae, acanthosis nigricans, or acne. The genital exam should note SMR and appearance of the vagina which should be pink and moist; thin, dry and reddened mucosa suggests estrogen deficiency. The clitoral width should be <1 cm. In the patient with primary amenorrhea, vaginal patency can be assessed painlessly using a slender saline-moist swab (e.g., a urethral swab) and careful avoidance of the hymen. If physical exam assessment of the cervix and uterus is not tolerated, a pelvic ultrasound is advisable in patients with primary amenorrhea.

LABORATORY STUDIES

Diagnostic tests in the patient presenting with amenorrhea should be tailored to her history and physical exam (Table 116-4). However, a urine pregnancy test, serum levels of prolactin, thyroid-stimulating hormone, and follicle-stimulating hormone (FSH) are reasonable to measure in all patients (Fig. 116-1). Elevation of FSH (>30 mIU/mL) in an amenorrheic female suggests ovarian insufficiency, and, if confirmed with repeat testing, should be followed with a pelvic ultrasound, karyotype, and specialist referral.

In patients with signs of androgen excess (e.g., severe acne or hirsutism) or physical stigmata associated with PCOS (rapid pubertal weight gain, acanthosis nigricans) consider measuring levels of 17-hydroxyprogesterone (17-OHP) (morning, in the follicular/preovulatory phase), free and total testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione. PCOS affects approximately 5% of premenopausal females; diagnostic criteria for adolescents are controversial but include variations of menstrual irregularity (ranging from amenorrhea to dysfunctional uterine bleeding), polycystic ovarian morphology identified on ultrasound, and physical or biochemical evidence of androgen excess.

With the exceptions of pregnancy, constitutional delay and imperforate hymen, conditions that cause primary amenorrhea limit fertility and diagnosis may cause profound emotional responses in patients and

Table 116-2	Causes of Amenorrhea (Primary or Secondary)
Pregnancy (regardless of history can cause primary or secondary amenorrhea)	
Functional hypothalamic causes (stress, weight loss, undernutrition, high levels of exercise, energy deficit even at normal weight)	
Female athlete triad (low energy availability, amenorrhea, and low bone density)	
Eating disorders	
Premature ovarian insufficiency (autoimmune, idiopathic, galactosemia, or secondary to radiation or chemotherapy)	
Hypothalamic and/or pituitary damage (e.g., irradiation, tumor, traumatic brain injury, surgery, hemochromatosis, midline central nervous system defects such as septooptic dysplasia, and autoimmune pituitary hypophysitis)	
Thyroid disease (hyper- or hypo-, although the latter usually associated with increased bleeding)	
Prolactinoma	
Systemic disease (e.g., inflammatory bowel disease, cyanotic congenital heart disease, sickle cell disease, cystic fibrosis, celiac disease)	
Hyperandrogenism (polycystic ovary syndrome, nonclassic congenital adrenal hyperplasia, adrenal tumor or dysfunction)	
Drugs and medications (e.g., illicit drugs, atypical antipsychotics, hormones)	
Turner syndrome mosaicism	

Table 116-3	Additional Causes of Primary Amenorrhea
Physiologic/constitutional delay	
Anatomic abnormalities	
Müllerian agenesis	
Imperforate hymen	
Transverse vaginal septum	
Genetic disorders	
46 XY disorders of sexual development (e.g., androgen insensitivity syndrome, 5α-reductase deficiency and 17α-hydroxylase deficiency)	
Mixed gonadal dysgenesis (associated with a number of different chromosome patterns)	
Turner syndrome (resulting from 45X or a variety of mosaic or other abnormal karyotypes)	
Genetic hypogonadotropic hypogonadism (e.g., X-linked Kallmann syndrome)	

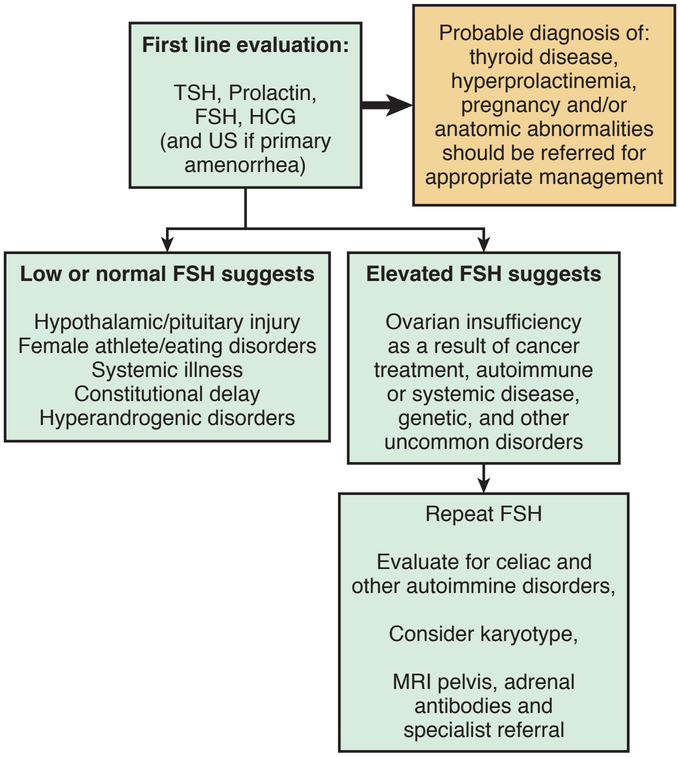

Figure 116-1 Initial diagnostic testing to evaluate amenorrhea

Table 116-4 Laboratory Tests to Evaluate Patients with Abnormal Uterine Bleeding
Complete blood count with platelets
Urine pregnancy test (regardless of history)
Sexually transmitted infections testing
Prothrombin and partial thromboplastin times
Ferritin
von Willebrand factor antigen, ristocetin cofactor, and factor VIII* activities
Liver, kidney, and thyroid function studies
Total and free testosterone†
Pelvic ultrasound (if diagnosis is elusive or anatomic abnormality suspected)

*Any abnormalities should be followed with a ristocetin-induced platelet aggregation and von Willebrand factor multimers. Testing in the 1st 3 days of menses and before any estrogen treatment is started minimizes the chances of false-negative tests. Repeat testing can be warranted in patients for whom there is a high pretest suspicion.

†In patients with signs or symptoms suggestive of PCOS, such as acne, hirsutism, obesity, acanthosis nigricans, and a history of infrequent menses.

families. Thus, before ordering studies to confirm these diagnoses (e.g., karyotype, MRI of reproductive anatomy) the clinician should carefully consider the implications and be prepared to refer to specialists with experience managing the long term treatment of such diagnoses with families.

In patients presumed to have hypothalamic amenorrhea on the basis of a low FSH and prepubertal baseline ultrasensitive assay for luteinizing hormone, and consistent history and physical, MRI of the brain is not necessary in all patients. However, MRI should be considered for patients presenting with a headache history that is a change from baseline; persistent emesis; change in thirst, urination, or vision; elevated prolactin or galactorrhea; or other neurologic symptoms.

TREATMENT

Treatment for amenorrhea varies widely depending upon the underlying cause. Many diagnoses require referral to clinicians in specialties such as endocrinology, adolescent medicine, gynecology, and other surgical subspecialists, and often collaboration with other disciplines such as psychology or nutrition is indicated. For patients with PCOS, the mainstay of treatment is lifestyle modifications and suppression of ovarian androgens (typically with combined oral contraceptive [COC] pills, i.e., estrogen and progestin). Many patients benefit from the addition of metformin and spironolactone as an androgen receptor blocker; all require ongoing monitoring of lipids and periodic screening with an oral glucose tolerance test as a result of the high prevalence of metabolic syndrome in PCOS. For patients with eating disorders or other conditions of energy imbalance that render them hypoestrogenic, normalizing weight and improving nutritional status are the keys to treatment; whether exogenous hormones will adequately protect bone health in these patients is unproven. For females with amenorrhea based on ovarian insufficiency (or absence) exogenous hormones are required for all pubertal development. Experts recommend starting at age 10-12 yr with low-dose transdermal estrogen, progressing to increased doses of estrogen and cyclic progestin, and then continuing maintenance therapy with higher dose combination products such as those found in typical combined hormone contraceptive pills, patches and rings.

For patients with secondary amenorrhea, use of hormones to bring on monthly bleeding (for example with combined hormonal contraception) in the absence of a clear indication (such as PCOS or contraception) is not recommended as doing so will mask the patient's subsequent menstrual pattern. However, in those patients with normal postpubertal estrogen levels progesterone can be useful to periodically (every 4-12 wk) induce shedding of the endometrial lining to avoid build up and subsequent heavy menses. One commonly used regimen is medroxyprogesterone 10 mg daily for the 1st 12 days of the month.

Bibliography is available at Expert Consult.

116.2 Abnormal Uterine Bleeding (AUB)

Gina S. Sucato and Gale R. Burstein

AUB is a broad term used to describe any pattern that is outside what is considered physiologic. Clinicians are encouraged to categorize the abnormal pattern based on the patient's complaint, which will usually be menses that are irregular (AUB/IMB: intermenstrual bleeding) or heavy (AUB/HMB: heavy menstrual bleeding).

IRREGULAR MENSTRUAL BLEEDING

The American Academy of Pediatricians advocates treating menstrual status as a vital sign at routine visits. Although menses are frequently irregular in the early postmenarchal years, further evaluation is necessary when menstrual patterns vary too widely from what is normal for age. Even in the first postmenarchal year, menses should not be less frequent than every 45 days. Menses become increasingly regular with age, and by 3 yr postmenarche are typically 21-35 days long, lasting 3-7 days. An adolescent's personal cycle duration is usually established by age 19 or 20 yr.

Adolescents rarely present with complaints of unusually short or light menses. However, those females, along with those with infrequent menses, should be evaluated similarly to females presenting with secondary amenorrhea. Females whose menses are excessive are much more likely to come to attention for AUB.

In the early postmenarchal years, the most common cause of AUB in adolescents is anovulation because of immaturity of the hypothalamic–pituitary–ovarian axis. In the absence of a midcycle surge of luteinizing hormone to stimulate ovulation, there is no corpus luteum production of progesterone. Without the stabilizing effects of progesterone on the endometrial lining there is increased risk of irregular bleeding. Irregular bleeding because of anovulation, in the absence

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of anatomic, systemic, or endocrinologic disease, is categorized as AUB caused by ovulatory dysfunction (**AUB-O**; previously referred to as dysfunctional uterine bleeding). Although it is the most common cause of abnormal menstrual bleeding in adolescents, AUB-O is a diagnosis of exclusion. In generating a differential diagnosis it is important to remember that most entities that lead to amenorrhea can cause anovulation first, and anovulation is a key risk for heavy irregular bleeding. Table 116-5 lists the causes of AUB.

Breakthrough bleeding while on combined hormonal contraception may occur and is not a reason to discontinue the medication. Compliance, interacting medications (prescribed or over-the-counter: St. John's wort), and smoking may increase the risk of breakthrough bleeding. Unscheduled bleeding is more common with progestin-only contraceptives.

HEAVY AND PROLONGED MENSTRUAL BLEEDING

Irregular bleeding (Table 116-5), particularly that resulting from anovulation, can be long and heavy. However, in patients who have regular, cyclic menses that are long and/or heavy, a hematologic cause should be strongly considered, particularly if menses are heavy from the onset of menarche, or if bleeding is severe enough to warrant hospitalization. In such patients, prevalence estimates for von Willebrand disease (see Chapter 477) and platelet functions disorders (see Chapter 484) range as high as 36% and 44%, respectively. These patients may also report flooding (changing a pad or tampon more than hourly), passing clots larger than an inch in diameter, menses longer than 7 days, a history of hemorrhagic ovarian cysts, excessive bleeding from wounds or postoperatively, and 1st-degree relatives with heavy menses or epistaxis requiring medical treatment.

LABORATORY FINDINGS

Table 116-4 lists laboratory tests to be considered in patients with long heavy bleeding. Females with persistent heavy bleeding despite negative testing should be referred to a hematologist for testing for platelet function disorders, factor deficiencies and other less common disorders. In the initial evaluation, the hemoglobin is the key element as it establishes the **severity of the bleeding: mild** (hemoglobin > 10 g/dL), **moderate** (hemoglobin 8-10 g/dL), or **severe** (hemoglobin < 8 g/dL).

TREATMENT

In **mild** cases, iron supplementation is recommended, and the patient should keep a menstrual calendar to follow the subsequent flow patterns. Nonsteroidal antiinflammatory drugs (e.g., naproxen) are more effective than placebo in treating heavy bleeding and also would help any concurrent dysmenorrhea. Active bleeding typically responds well to cycling with any **COC** (i.e., estrogen and progestin) starting with twice-daily dosing if needed until bleeding stops. Patients with estrogen contraindications can be treated with progestins alone, for example, medroxyprogesterone or norethindrone acetate 10 mg orally per day, either continuously or for 12 days per month. The latter regimen will be followed by monthly bleeding.

Table 116-5 Causes of Irregular Menstrual Bleeding

CAUSES OF AUB	EXAMPLES	FEATURES
Immature hypothalamic–pituitary–ovarian axis (AUB-O)	Patient within 2 yr of menarche; patient more than 2 yr postmenarche but with history of later menarche	Painless, responds to hormonal treatment
Weight changes, disordered eating, or excessive exercise	Anorexia nervosa, bulimia, weight gain or loss of more than 10 pounds from any etiology	Weight loss more commonly results in lighter, less frequent menses
Endocrinologic causes	Thyroid disease, PCOS	Bleeding typically increases with hypothyroidism and decreases with PCOS and hyperthyroidism
Complication of pregnancy	Threatened abortion, postpartum or postabortal endometritis	History of sexual activity and/or pregnancy
Infection	Cervicitis, condyloma, pelvic inflammatory disease	Bleeding usually not heavy, may occur with sexual intercourse
Trauma	Sexual assault, bicycle accidents	History will be evident in patients of menstruating age unless there is cognitive disability
Vaginal foreign body	Toilet paper, broken condoms, tampons	Associated with odor and vaginal discharge, but usually not heavy bleeding
Hematologic causes	von Willebrand disease, platelet function disorder, thrombocytopenia (idiopathic thrombocytopenic purpura, drug induced) hemophilia carriage, clotting factor deficiency, leukemia	Bleeding is heavy and/or long and frequently regular, may present at menarche, may be accompanied by a suggestive family history (hysterectomies or uterine ablation, or cautery for epistaxis) or physical exam (ecchymoses, petechiae)
Medications	Estrogens, progestins, (in pills, patches, rings, injections, implants, and intrauterine devices) androgens, drugs that cause prolactin release (estrogens, phenothiazines, tricyclic antidepressants, metoclopramide), and anticoagulants (heparin, warfarin, aspirin, and nonsteroidal antiinflammatory drugs), and selective serotonin reuptake inhibitors	Affect the hypothalamic–pituitary–ovarian axis, endometrial lining, platelets, or coagulation pathway
Anatomic	Partial obstruction of vagina or uterus causing asynchronous bleeding, cervical or endometrial polyps or myomas, hemangioma, uterine vascular malformation, genital/reproductive tract cancer	Most of these entities are extremely rare, especially reproductive tract cancers
Systemic disease	Celiac disease, rheumatoid arthritis, Ehlers-Danlos syndrome	Accompanied by other signs of the condition

With **moderate** anemia, any of the hormonal regimens above can be used. However, it may be necessary to start with 3-4 COC (or 3-4 doses of medroxyprogesterone 10 mg) per day and taper to daily dosing over the next 2 wk. Patients with ongoing rapid bleeding, syncope or lightheadedness, or hemodynamic instability should be treated in the hospital, as should patients with a hemoglobin of <7-8 g/dL.

Patients with severe anemia should be treated with 1 of the hormone tapers described above, in addition to fluid or blood products as indicated; it is advisable to draw necessary laboratory studies prior to transfusion. Patients with emesis or other significant symptoms may be treated initially with conjugated estrogens 25 mg intravenously every 4-6 hr for 1-2 days. A COC or progestin regimen should be added within the 1st day as progestin is needed to stabilize the endometrial lining and can be used as maintenance therapy after hospital discharge. In the exceptionally rare case of a patient whose bleeding cannot be controlled hormonally, options for gynecologic interventions include intrauterine Foley balloon placement or uterine packing to tamponade the uterus mechanically. Dilation and curettage, performed frequently in adult women, is almost never indicated in adolescents.

Hormonal treatment for AUB should continue for at least 3-6 mo—depending on the patient's age, prior menstrual history, and severity of presentation—before reassessing the need for ongoing therapy. Additional options for maintenance therapy include combined hormonal transdermal patches and vaginal rings, depomedroxyprogesterone acetate 150 mg IM every 3 mo, and placement of a levonorgestrel intrauterine device, depending on the patient's concurrent need for long-term contraception. For those patients who choose to avoid (or augment) hormonal therapy, tranexamic acid 1,300 mg orally 3 times daily can be used for up to the 1st 5 days of menses. This medication, new to the United States, has been available in other countries for years. Nonetheless, published data in young adolescents remain sparse, and the clinical significance of the theoretic increased risk of thrombosis when used in conjunction with hormonal treatment is yet to be determined.

For young women with bleeding disorders, formulation of a long-term treatment plan is best done in collaboration with the patient's hematologist. Females with a known bleeding disorder may be up to 5 times more likely to develop heavy menstrual bleeding. Therefore, it can be helpful while the patient is still premenarchal to proactively put a plan in place in the event of acute heavy menstrual bleeding which can occur with a patient's first menstrual period.

Bibliography is available at Expert Consult.

116.3 Dysmenorrhea

Gina S. Sucato and Gale R. Burstein

Dysmenorrhea, painful uterine cramps that precede and accompany menses, occur in up to 93% of adolescent females based on studies from around the world. Dysmenorrhea is severe enough to interfere with school and other activities in approximately 10% of adolescents in the United States. Yet many adolescents undertreat their symptoms, and fewer still seek medical care for relief.

Dysmenorrhea may be primary or secondary. **Primary dysmenorrhea**, characterized by the absence of any specific pelvic pathologic condition, is by far the more commonly occurring form, accounting for approximately 90% of cases. After ovulation, withdrawal of progesterone results in synthesis of prostaglandins by the endometrium, which stimulate local vasoconstriction, uterine ischemia and pain, and smooth muscle contraction, explaining both uterine and gastrointestinal symptoms. Because of the association with ovulation, primary dysmenorrhea typically presents at least 12 mo after menarche.

Secondary dysmenorrhea results from underlying pathology such as anatomic abnormality, or infection such as pelvic inflammatory disease. However, the most common cause of secondary dysmenorrhea in adolescents is **endometriosis**, a condition in which implants of endometrial tissue are found outside the uterus, most commonly near the fallopian tubes and ovaries. Often there are other family members with endometriosis. Although characteristically there is severe pain at the time of menses, adolescents can present with noncyclic pain as well.

Although primary dysmenorrhea is almost always the cause, a careful history and physical examination is required for adolescents who present with pelvic pain. An internal pelvic exam is not required in females who are not sexually active and whose presentation is consistent with primary dysmenorrhea. Constipation can vary cyclically in many females, especially those with irritable bowel syndrome, and often significantly contributes to the pain. **Mittelschmerz**, brief severe

Table 116-6 Differential Diagnosis of Dysmenorrhea in Adolescents (Red Flags Indicated in Bold)

	PRESENTATION	DIAGNOSIS
Primary	Crampy pelvic pain may be accompanied by: aching/heaviness in lower back and upper thighs, nausea, emesis, diarrhea, headache, mastalgia, fatigue, and dizziness; symptoms begin at or shortly prior to onset of menstrual flow and last 1-3 days	Normal physical exam; internal exam only for sexually active adolescents. Ultrasound can be reserved for those patients with atypical presentations (e.g., onset at menarche) or those whose pain does not respond to NSAIDs and hormonal therapy
Endometriosis and adenomyosis	**Increasingly severe dysmenorrhea despite adequate therapy;** pain exacerbated during menses can occur acyclically as well. (Adenomyosis is the presence of endometrial tissue within the uterine myometrium)	Increased risk in patients with obstructive anomalies and possibly bleeding disorders; however, most teenagers with endometriosis have normal anatomy and bleeding indices; diagnosis is made visually during surgery. *Found in up to 69% of adolescents who underwent laparoscopy for persistent pelvic pain*
Müllerian anomalies with partial outflow obstruction	**Pain begins at or shortly after menarche** and occurs with bleeding; presence of **known renal tract anomaly** (often coexists with müllerian anomaly)	Pelvic ultrasound will demonstrate uterine anomalies (e.g., rudimentary uterine horn); MRI may be required to identify some lesions (e.g., obstructed hemivagina). *Found in 8% of adolescents who underwent laparoscopy for persistent pelvic pain*
Pelvic inflammatory disease	Abrupt onset of dysmenorrhea more severe than baseline in sexually active adolescent; presentation can range from mild discomfort to acute abdomen	Clinical diagnosis made by findings of uterine or adnexal tenderness on bimanual pelvic examination (see Chapter 120); supporting features include dysuria, **vaginal discharge,** fever, and increased white blood cell count
Pregnancy complication	Coincident pain and bleeding may be misdiagnosed as dysmenorrhea	Urine hCG-positive

hCG, human chorionic gonadotropin; NSAIDs, nonsteroidal antiinflammatory drugs.

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Table 116-7 Treatment for Dysmenorrhea

	MEDICATION	REGIMEN	COMMENTS
NSAIDs for up to 5 days)	Ibuprofen, 200 mg	2 tablets PO q 4-6 hr	Over-the-counter
	Naproxen sodium, 275 mg	550 mg loading dose then 275 mg PO q 6 hr	Patients may prefer the equivalent 550 mg PO q 12 hr dosing regimen
	Celecoxib (cyclooxygenase [COX]-2 inhibitor)*	400 mg then 200 mg PO q 12 hr prn pain	Can be used for patients with von Willebrand disease
Hormonal contraception	Combined oral contraceptive pills or vaginal ring	Continuous hormone regimens (as opposed to the standard 21 hormone days followed by 7 placebo days) may offer better relief but increase the risk of intermenstrual bleeding	The data favoring rings and pills over the combined hormone patch for this indication are sparse; treatment can be based on patient preference
	Progestin-only methods	DMPA 150 mg IM or 104 mg SC q 3 mo, levonorgestrel intrauterine device for up to 5 yr, etonogestrel implant for up to 3 yr	DMPA has potential side effects of bone loss and weight gain as well as a higher discontinuation rate than the 2 LARC methods
Gonadotropin-releasing hormone agonist	Depot leuprolide	11.25 mg IM q 3 mo	Consider for patients with presumed endometriosis not responsive to hormonal methods; add-back hormones are recommended to prevent bone loss

*FDA-approved for patients older than 18 yr. Should be used with caution in patient with impaired renal or liver dysfunction, heart failure, a history of gastrointestinal bleeding or ulcer. Full prescribing information can be found at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020998s033,021156s003lbl.pdf.

DMPA, depomedroxyprogesterone acetate; IM, intramuscular; LARC, long-acting reversible contraceptive; NSAIDs, nonsteroidal antiinflammatory drugs.

pain with ovulation, occurs at midcycle and can explain what initially appeared to be noncyclic pelvic pain. Table 116-6 lists the red flags for secondary dysmenorrhea. Ovarian cysts, a frequent concern of families, are usually transient and painless.

Treatment for primary dysmenorrhea is aimed at decreasing levels of prostaglandins, preferably before they are produced. Thus, the mainstay of treatment is with prostaglandin synthetase inhibition by either nonsteroidal antiinflammatory drugs, hormonal contraception, or a gonadotropin-releasing hormone agonist (Table 116-7) beginning at, or preferably the day prior to, menstruation. The high doses of around the clock treatment are rarely needed for more than the 1st 2 days. More data are needed to make specific treatment recommendations regarding exercise, but females should be reassured that participation in usual sports and extracurricular activities is not only permissible but a benchmark of adequate treatment.

For those adolescents whose pain does not respond to optimally dosed nonsteroidal antiinflammatory drugs, or who also require contraception, all of the currently available forms of hormonal contraception will improve dysmenorrhea. A number of trials have investigated adjuvant treatments including heat, aromatherapy, acupressure, acupuncture, transcutaneous nerve stimulation, herbal remedies, yoga, and dietary supplements; however, the mainstay second-line treatment is hormones. The mechanisms are not fully delineated but are presumed to include elimination of progesterone production from the corpus luteum for those methods that prevent ovulation, and decreased prostaglandin production from the diminished endometrial lining. Up to 3 cycles may be required to appreciate the full benefit. Methods and regimens that eliminate a placebo interval may provide better relief. Females whose pain persists despite more than 3 mo of adequate hormonal therapy require further evaluation and treatment.

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116.4 Premenstrual Syndrome and Premenstrual Dysphoric Disorder

Gina S. Sucato and Gale R. Burstein

Premenstrual dysphoric disorder (PMDD) is a depressive disorder that is distinguished from other depressive disorders by its timing. Symptoms of anxiety and depressed mood begin in the luteal phase of the menstrual cycle (i.e., in the second half, after ovulation) and improve within a few days after the onset of menses. PMDD causes significant distress and functional impairment and may be accompanied by physical and behavioral symptoms. PMDD occurs in 2-6% of menstruating females worldwide. Based on a large body of scientific evidence, it has been included in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) V (Table 116-8) as a distinct, treatment-responsive, depressive disorder. It is distinguished from premenstrual syndrome (PMS), which has similar timing and occurs in up to 30% of adolescents, by the severity and consequences of the affective symptoms. Premenstrual symptoms are precipitated by ovulation; symptoms recur in the luteal phase and should disappear at the end of menstruation.

Validated tools to screen for severe PMS and PMDD exist; up to half of females who report PMS do not meet diagnostic criteria when symptoms are rated prospectively. Consequently, use of a menstrual calendar to prospectively document symptoms is necessary, as it is important to distinguish PMDD from anxiety, depression, or another mental health disorder the symptoms of which are exacerbated cyclically but occur throughout the cycle.

Treatment success is gauged by improvement in patient symptoms. In mild cases of PMS, adolescents may have adequate relief following education about the relationship of symptoms to the menstrual cycle and instruction on stress management techniques, including exercise. There is not strong evidence supporting the effectiveness of most COC pills for PMS, particularly in adolescents. However, some experts suggest this treatment option for those patients who also have dysmenorrhea or contraceptive needs.

The treatment option with the most supportive evidence is use of selective serotonin reuptake inhibitors, which are first-line therapy for adult women with severe PMS and PMDD. In contrast to the treatment of depression, selective serotonin reuptake inhibitors can be rapidly effective for PMDD, and thus can be prescribed either continuously or intermittently, beginning at ovulation (or whenever in the luteal phase symptoms begin) and ending when symptoms resolve. Adolescents can be prescribed the standard doses used for adults, for example, fluoxetine 10-20 mg orally daily. Among the many dietary supplements that have been studied, the best evidence is for supplementation with calcium 1,200 mg in 3 divided doses to treat both mood and pain symptoms.

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Table 116-8	Criteria for Premenstrual Dysphoric Disorder

A. In the majority of menstrual cycles, at least 5 symptoms must be present in the final week before the onset of menses, start to *improve* with a few days after the onset of menses, and become *minimal* or absent in the week postmenses.

B. One (or more) of the following symptoms must be present:
  1. Marked affective lability (e.g., mood swings; feeling suddenly sad or tearful, or increased sensitivity to rejection).
  2. Marked irritability or anger or increased interpersonal conflicts.
  3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts.
  4. Marked anxiety, tension, and/or feelings of being keyed up or on edge.

C. One (or more) of the following symptoms must additionally be present, to reach a total of 5 symptoms when combined with symptoms from criterion B above.
  1. Decreased interest in usual activities (e.g., work, school, friends, hobbies).
  2. Subjective difficulty in concentration.
  3. Lethargy, easy fatigability, or marked lack of energy.
  4. Marked change in appetite; overeating; or specific food cravings.
  5. Hypersomnia or insomnia.
  6. A sense of being overwhelmed or out of control.
  7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "bloating," or weight gain.

Note: The symptoms in criteria A-C must have been met for most menstrual cycles that occurred in the preceding year.

D. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities; decreased productivity and efficiency at work, school, or home).

E. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders).

F. Criterion A should be confirmed by prospective daily ratings during at least two symptomatic cycles. (**Note:** The diagnosis may be made provisionally prior to this confirmation).

G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition (e.g., hyperthyroidism).

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (Copyright 2013). American Psychiatric Association, pp. 171-172.

Chapter 117

Contraception

Tara Jatlaoui and Gale R. Burstein

The untoward consequences of sexual activity (sexually transmitted infections [STIs; see Chapter 120], and early, unintended pregnancy [see Chapter 118]) all too often are experienced by adolescents. Adolescents often do not seek reproductive healthcare for 6-12 mo after initiating sex; many will become pregnant and/or acquire an STI during this interval. Appropriate counseling and educational interventions with adolescents, including the healthcare provider raising the topic of prevention, can decrease sexual risk behavior; youth who plan sexual initiation (as opposed to "it just happened") are 75% more likely to use contraception at sexual debut.

EPIDEMIOLOGY

Sexual Activity

According to the Youth Risk Behavior Surveillance System 2011, almost half (47.4%) of U.S. high school students had ever had sexual intercourse and one-third reported being currently sexually active (had sexual intercourse with at least 1 person during the 3 mo before the survey).

Although U.S. teens and European teens have similar levels of sexual activity and ages of sexual debut, U.S. teens are less likely to use contraception and less likely to use the most effective methods. Teen pregnancy rates have been declining worldwide as a result of delayed initiation of sexual activity and increased contraceptive use. Despite declines, the U.S. still had the highest 2010 teen birth rate in the Western industrialized world with 34 live births per 1,000 females 15-19 yr old (Fig. 117-1). That is nearly 2 times higher than the 2010 teen birth rate in Ireland, which has the highest rate in Western Europe, and almost 10 times higher than the lowest rate in Switzerland. Of the 750,000 teen pregnancies in the United States in 2008, 31% ended in abortion. More than 80% of these pregnancies are unintended, indicating a remaining unmet need for reliable, effective contraception that teens will consistently use.

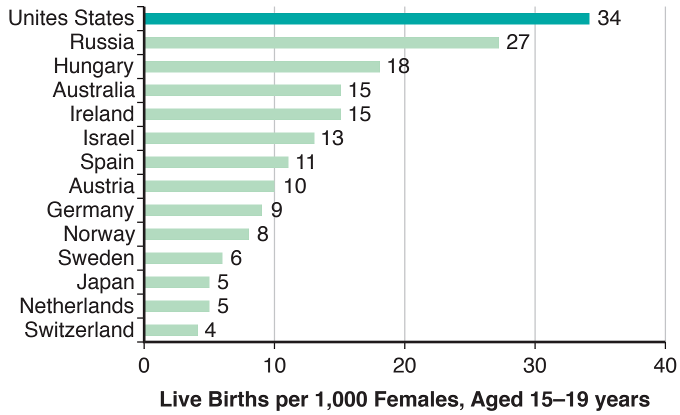

Figure 117-1 Teen birth rates in high income countries. *(From* United Nations Demographic Yearbook 2011*, available at* http://unstats.un.org/unsd/demographic/products/dyb/dyb2011.htm*, and Martin JA, Hamilton BE, Ventura SJ, et al: Births: Final data for 2010. National Vital Statistics Reports; Vol 61, No. 1, Hyattsville, MD: National Center for Vital Statistics, 2012, 1-72.)*

Contraceptive Use

According to the National Survey of Family Growth, 2006-2010, virtually all sexually experienced teens have used some method of contraception in the past. The most commonly used method is the condom, followed by withdrawal and then the pill. Use of contraception at first sex has greatly increased over the last 50 yr and the condom is currently the most common method used at first sex, as reported by more than 75% of males and females. Factors increasing contraception use at first sex include increasing age among teens up to age 17 yr; time in college; and planning their sexual debut (75% more likely to have used contraception than those who did not plan it).

To decrease rates of unintended pregnancy, more teens must use most or moderately effective contraception consistently and correctly.

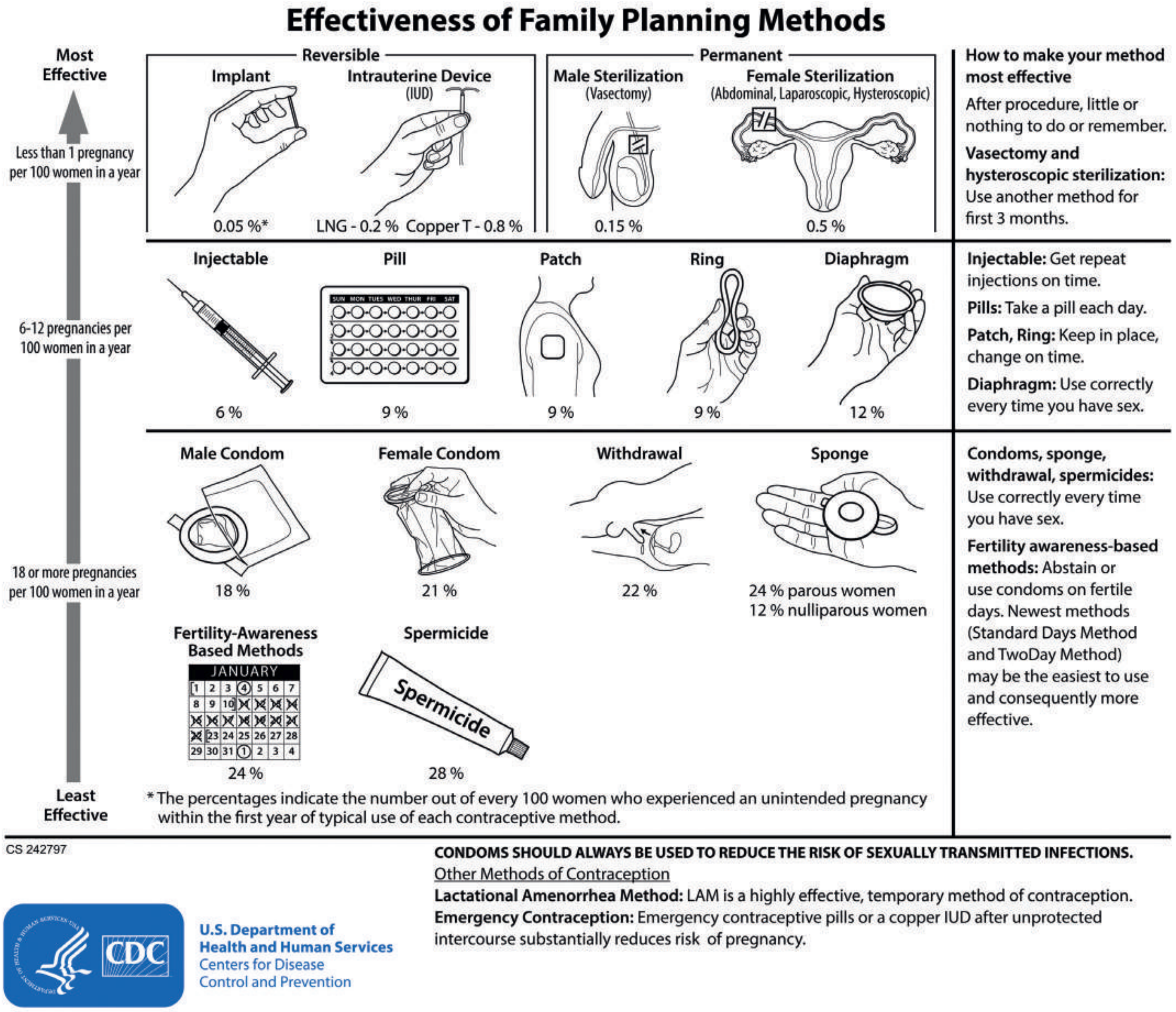

Figure 117-2 Effectiveness of contraceptive methods. *(From Centers for Disease Control and Prevention, Division of Reproductive Health, CS 242797; adapted from World Health Organization.* Comparing typical effectiveness of contraceptive methods. *Geneva, 2007, World Health Organization, and from Trussell J. Contraceptive failure in the United States.* Contraception *83:397–404, 2011.)*

The CDC Effectiveness of Contraceptive Methods Chart illustrates a tiered system of most effective (Tier 1), moderately effective (Tier 2), and least effective (Tier 3) methods (Fig. 117-2). Tier 1 methods include those with failure rates of less than 1 pregnancy per 100 women in a year of typical use. Tier 2 methods have failure rates of 6-12 pregnancies per 100 women in a year of typical use, and Tier 3 methods have failure rates of 18 or more pregnancies per 100 women per year of typical use.

More than half of sexually experienced female teens are currently using most effective or moderately effective contraceptive methods, such as an intrauterine device (IUD) or contraceptive implant, oral contraceptive pills, the contraceptive patch, the vaginal ring, an injectable contraception, or, rarely, sterilization. U.S. teens' use of hormonal methods at last intercourse is less frequent compared to teens in other developed countries: 52% of U.S. teens, 56% of Swedish 18-19 yr olds, 67% of French 15-19 yr olds, 72% of British 16-19 yr olds, and 73% of Canadian 15-19 yr olds use hormonal methods. A higher likelihood of female current contraceptive use is associated with older age at sexual initiation, aspirations for higher academic achievement, acceptance of one's own sexuality, and a positive attitude toward contraception. Condom use should also be encouraged along with effective contraception, preferably Tier 1 or 2, for dual protection against pregnancy and STIs. Only 12% of sexually active female teens who are using a most effective or moderately effective method are using condoms as well.

Contraceptive Counseling

The health screening interview during the adolescent preventive visit offers opportunities to identify and discuss unsafe sexual practices among sexually active adolescents and to identify and reinforce safe sexual behaviors including abstinence (see Chapter 112). Adolescents with medical conditions, either chronic or acute, are particularly vulnerable to having sexual and reproductive health omitted from their visits (see Chapters 42 and 717). Their comorbidities or concurrent medication use may make unintended pregnancy an increased health risk; therefore addressing sexuality and contraceptive issues at visits is imperative.

The goals of counseling with adolescents are to (1) understand adolescent perceptions and misperceptions about pregnancy and use of

contraceptives; (2) help adolescents put unprotected intercourse risk in a personal perspective; (3) educate adolescents regarding the true risks and benefits for the various methods available; and (4) help adolescents choose a safe and effective method that can either be provided on site or be easily obtained by referral. Counseling should include a review of all contraceptive methods available, starting with the most effective methods. The adolescent should be counseled using "**typical use" failure rates,** which reflect the effectiveness of a method for the average person who may not always use the method or use the method correctly (see Fig. 117-2). For example, for oral contraceptive pills, the typical use failure rate is 9% whereas perfect use failure rate is <1%. It is important to ask about use of withdrawal as more than half (58%) of teens have used it for contraception and it has a typical use failure rate of 22%. Abstinence should also be discussed as an option even if teens have engaged in sexual intercourse in the past. Situational abstinence may be the best option if they do not have another method available at a particular time.

Necessary concepts to address while discussing individual methods include how effective the method is, how long the method works, what behaviors are required for correct and consistent use, what side effects may be seen, and what signs or symptoms of complications should prompt a return visit. Reviewing common side effects allows teens to anticipate and cope with any changes with reassurance. Weighing the possibility of certain side effects with the possibility of an unintended pregnancy may also help with the conversation. It is also important to address any specific misperceptions teens may have for certain contraceptives regarding side effects or effectiveness.

Once an adolescent chooses a method, the provider and teen should discuss clear plans on correct and consistent use of the chosen method and strategies for appropriate follow-up (Table 117-1). Providers

Table 117-1 Contraceptive Methods

METHOD	FAILURE RATE (%) Typical Use	Perfect Use	DOSING	MECHANISM OF ACTION	POTENTIAL SIDE EFFECTS	ADVANTAGES
HORMONAL CONTRACEPTIVES						
Implant (Implanon or Nexplanon)	0.05	0.05	Insertion of implant into upper arm once every 3 yr	Progestin effects: thickening of cervical mucus, inhibition of ovulation, endometrial atrophy	Rare insertion complications, possible weight gain, uterine bleeding changes including amenorrhea	High efficacy, discreteness, relief of dysmenorrhea, reduced risk of ectopic pregnancy, reversibility, high acceptability and continuation rates; no estrogen
Progestin-releasing IUD (Skyla and Mirena)	0.2	0.2	3 or 5 yr Releases 14 or 20 µg/day levonorgestrel	Progestin effects (see above) and IUD effect of preventing sperm from fertilizing ovum	Breakthrough bleeding in 1st 3-6 mo, then hypo-, or amenorrhea	High efficacy, easy to use, long-acting; no estrogen Decrease in: menstrual blood loss, dysmenorrhea, endometriosis pain, PID risk
Progestin-only injection (Depo-Provera)	6	0.2	3 mo (13 wk) 150 mg depot medroxyprogesterone IM	Progestin effects (see above)	Irregular bleeding or amenorrhea, weight gain, breast tenderness, acne, depression, possible decrease in bone density	No estrogen; decrease in menstrual blood loss, dysmenorrhea, PID risk
The patch	9	0.3	Weekly for 3 wk (off on 4th wk) 20 µg ethinyl estradiol 150 µg norelgestromin released daily	Combined hormonal method: thickens cervical mucus, inhibits ovulation, inhibits sperm's ability to fertilize egg, slows tubal mobility, disrupts ovum transport, induces endometrial atrophy	Breakthrough bleeding, nausea, headaches, breast tenderness, skin site reaction, less effective if patient weighs >90 kg (198 lb)	Similar to OCPs but less-frequent dosing
Vaginal ring (NuvaRing)	9	0.3	Monthly (insert for 3 wk of each mo) Serum levels of 15 µg ethinyl estradiol Releases 150 µg norelgestromin daily	Combined hormonal method (see above)	Vaginal irritation, vaginal discharge, headache	Similar to OCs but less-frequent dosing
Combined Oral Contraceptives (OCPs)	9	0.3	Daily Varies 20-50 µg estrogen Varies 0.15-1 µg progestogen	Combined hormonal method (see above)	Breakthrough bleeding, nausea, headaches, breast tenderness	Decrease in PID risk, ectopic pregnancy risk, menstrual blood loss, dysmenorrhea, acne
Progestin-only pills (POPs)	9	0.3	Daily (within 3-hr period) 0.35 mg norethindrone or 0.075 mg norgestrel	Progestin-only hormonal method: inhibits ovulation, thickens and decreases cervical mucus, atrophies endometrium	Irregular bleeding, breast tenderness, depression	No estrogen; effective after 2 days of use

Continued

Table 117-1 Contraceptive Methods—cont'd

METHOD	FAILURE RATE (%) Typical Use	Perfect Use	DOSING	MECHANISM OF ACTION	POTENTIAL SIDE EFFECTS	ADVANTAGES
NONHORMONAL CONTRACEPTIVES						
IUD copper-containing (ParaGard)	0.8	0.6	10 yr 36 × 22 mm, copper wire wound around vertical stem of T	IUD: prevents sperm from fertilizing ova and copper ions may act as spermicide	Heavier menses	Easy to use, long-acting nonhormonal
Male condom	18	2	Every act of intercourse	Barrier method: blocks passage of semen	Latex allergy	Recommended to be used in addition to another contraceptive; only method that decreased STD, HIV risk
Female condom	21	5	Every act of intercourse	Barrier method: lines the vagina fully and perineum partially	Vaginal discomfort, partner penile irritation	Provides some protection against STD, HIV; polyurethane can be used with latex allergy
Spermicides	28	18	Every act of intercourse nonoxynol-9 (in United States). Dose varies by formulation, e.g., gel, suppository, from 52.5-150 mg	Kills sperm by destroying sperm cell membrane	Allergy or sensitivity to ingredients, recurrent urinary tract infections	Recommended to be used in addition to another barrier contraceptive

IUD, intrauterine device; OCs, oral contraceptives; PID, pelvic inflammatory disease; STD, sexually transmitted disease.
From Trussell J: Contraceptive failure in the United States, Contraception *83:397–404, 2011; Hatcher RA, Trussell J, et al, editors:* Contraceptive technology, *New York, 2011, Ardent Media; and As-Sanie S, Gantt A, Rosenthal MS: Pregnancy prevention in adolescents,* Am Fam Physician *70:1517–1524, 2004.*

should help the adolescent consider potential barriers to correct and consistent use (e.g., forgetting to take a pill daily) and develop strategies to deal with each barrier. The provider should assess whether the teen understood the information discussed and may confirm by asking the teen to repeat back key concepts. Chapter 112 discusses confidentiality and consent issues related to contraceptive management.

A pelvic examination is only required for placement of an IUD, unless otherwise indicated. STI screening is appropriate once sexual activity has begun; gonorrhea and chlamydia screening via a self-collected or provider-collected vaginal swab or urine sample is recommended unless symptoms require a pelvic exam. Guidelines from the American Congress of Obstetrics and Gynecology (ACOG) recommend that the first female teen visit to a gynecologist occur between the ages of 13 and 15 yr unless necessary at an earlier age. This visit aims to establish rapport, educate the patient and parents or guardian on healthy sexual development, and provide routine preventive services. Pap test for cervical cancer screening is not recommended until age 21 yr.

Bibliography is available at Expert Consult.

117.1 Long-Acting Reversible Contraception

Tara Jatlaoui and Gale R. Burstein

Long-acting reversible contraception (LARC) includes 2 levonorgestrel IUDs, the Copper IUD and the etonogestrel subdermal implant; LARCs are the only Tier 1 methods that are reversible (see Fig. 117-2). Considered forgettable contraception, LARCs do not require frequent office or pharmacy visits and do not depend on user compliance for effectiveness. In the CHOICE project in St. Louis, more than 9,000 women were give the contraception of their choice at no cost and were followed for 2-3 yr. The failure rates among women who use oral contraceptive pills, transdermal patch or vaginal ring was more than 20 times higher than the failure rate for women using a LARC method according to this study. Acceptance, continuation, and satisfaction in this study were also higher among teens using LARC compared to those using non-LARC methods. The ACOG recommends LARC methods as first-line contraceptives for all females. The US Medical Eligibility Criteria, 2010, supports safe use of both IUDs and implants in this population. Implants are considered category 1 for all ages, and IUDs are considered category 2 for women <20 years old and for nulliparous women (see Table 117-2 for explanation of categories of eligibility).

Table 117-2 Categories of Medical Eligibility Criteria for Contraceptive Use

1 = A condition for which there is no restriction for the use of the contraceptive method.
2 = A condition for which the advantages of using the method generally outweigh the theoretical or proven risks.
3 = A condition for which the theoretical or proven risks usually outweigh the advantages of using the method.
4 = A condition that represents an unacceptable health risk if the contraceptive method is used.

Intrauterine Devices

Intrauterine devices (IUDs) are small, flexible, plastic objects introduced into the uterine cavity through the cervix. They differ in size, shape, and the presence or absence of pharmacologically active substances. In the United States, 3 IUDs are currently available: the Copper T380A and 2 levonorgestrel IUDs. The effectiveness of the copper IUD is enhanced by the copper ions released into the uterine cavity with possible mechanisms including inhibition of sperm transport and prevention of implantation; this IUD is effective for at least 10 yr.

The levonorgestrel IUDs also have various actions, from thickening of cervical mucus and inhibiting sperm survival to suppressing the endometrium; these IUDs are effective for at least 3 and 5 yr. All 3 IUDs have typical use failure rates of less than 1% (see Fig. 117-2).

Common misconceptions of IUDs among healthcare providers are that IUDs cause infections, infertility, and generally are not safe for teens or nulliparous women to use; these misconceptions are a barrier

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to teens accessing these highly effective and acceptable methods. These IUDs does not increase risk of infertility, and the IUD may be inserted safely in teens as well as nulliparous women (see Table 117-2).

Although early studies suggested an increased risk for upper genital tract infection, theoretically as a result of the presence of a foreign body in the cervix, newer work has refuted these earlier concerns. Therefore, clinicians are encouraged to consider use of IUDs in adolescents despite relatively high prevalence rates of STIs in this population. Teens should be screened for gonorrhea and chlamydia at the time of or before IUD placement, although placement should not be delayed if results have not returned and there are no signs of infection. If STI testing returns positive with an IUD in place, the patient may be treated without removing the IUD if she wishes to continue the method.

Implants

There is currently 1 contraceptive implant available in the United States. Originally FDA-approved in 2006, the single rod that releases 60 μg/day of etonogestrel has been updated to a radiopaque rod with a new inserter. This progestin-only method keeps etonogestrel at steady serum levels for 3 yr and primarily works to inhibit ovulation. Similarly to the levonorgestrel IUD, the progestin acts on the uterus to cause an atrophic endometrium and thicken cervical mucus to block sperm penetration; its typical use failure rate is also <1% (see Fig. 117-2). Unlike the IUD, no pelvic exam is required for insertion. A trained provider can quickly place or remove the implant in the upper arm under local anesthesia. Common side effects include amenorrhea, irregular bleeding, or infrequent bleeding, and, less often, prolonged or frequent bleeding. One potential unique complication of this method relates to localized infection and other side effects after implantation, such as bleeding, hematoma, or scarring, and, if inserted too deeply into the muscle, neural damage or migration; however, these events are rare, occurring in <1% of patients. Minor side effects, such as bruising or skin irritation, are more common but tend to resolve without treatment.

Bibliography is available at Expert Consult.

117.2 Other Progestin-Only Methods

Tara Jatlaoui and Gale R. Burstein

Several progestin-only methods are available and include the levonorgestrel IUDs and implant (see Chapter 117.1), as well as an injectable and progestin-only pills. These methods do not contain estrogen and may be useful for teens with contraindications to estrogen (Table 117-3) and are considered generally safe for use in teens (see Table 117-2). Progestins thicken cervical mucus to block sperm entry into the uterine cavity as well as induce an atrophic endometrium leading to either amenorrhea or less menstrual blood loss; the implant and injectable additionally suppress ovulation. Teens should be provided anticipatory counseling regarding bleeding irregularities that may normally occur in the 1st 3-6 mo of hormonal contraception use.

DEPO-PROVERA

An *injectable progestin,* medroxyprogesterone acetate (Depo-Provera, DMPA), is a Tier 2 contraceptive method available as a deep intramuscular injection (150 mg), or as a subcutaneous injection (104 mg) with typical-use failure rates of 6% (see Fig. 117-2). Both preparations must be readministered every 3 mo (13 wk) and act to inhibit ovulation. DMPA is particularly attractive for adolescents who have difficulty with compliance, are intellectually or physically impaired, and are chronically ill or have a condition for which estrogen use is not recommended. After 1 yr of use, 50% of DMPA users develop amenorrhea, which may be an added advantage for teens with heavy menstrual bleeding, dysmenorrhea, anemias, or blood dyscrasias, or for those with impairments that make hygiene difficult. Although concern has been directed toward the potential for loss in bone mineral density in

Table 117-3	Conditions Classified as U.S. MEC Category 3 and 4 for Combined Hormonal Contraceptive Use
CATEGORY 4	
Complicated valvular heart disease	
Current breast cancer	
Severe decompensated cirrhosis	
Deep venous thrombosis/Pulmonary embolism (acute; history, not on anticoagulation or on established therapy for at least 3 mo with higher risk recurrence; major surgery with prolonged immobilization)	
Complicated diabetes with nephropathy, retinopathy, neuropathy or other vascular disease or duration of diabetes >20 yr	
Migraine with aura	
Hypertension (blood pressure above 160/100 mm Hg) or hypertension with vascular disease	
Ischemic heart disease (history of or current)	
Hepatocellular adenoma	
Malignant liver tumor	
Peripartum cardiomyopathy (diagnosed <6 mo prior or with moderately or severely impaired cardiac function)	
Postpartum <21 days	
History of cerebrovascular accident	
Systemic lupus erythematosus with positive antiphospholipid antibodies	
Thrombogenic mutations	
Viral hepatitis (acute or flare)	
CATEGORY 3	
Past breast cancer with no evidence of disease for 5 yr	
Breastfeeding and <1 mo postpartum	
Deep venous thrombosis/pulmonary embolism (history of deep venous thrombosis/pulmonary embolism with lower risk recurrence)	
Gall bladder disease (current, medically treated)	
Migraine without aura (if worsens or first starts while using combined hormonal contraceptives)	
History of malabsorptive bariatric surgery	
History of cholestasis and past combined oral contraceptive-related	
Hypertension (adequately controlled or blood pressure less than 160/100 mm Hg)	
Peripartum cardiomyopathy with mild impairment or >6 months	
Postpartum 21-42 days with other risk factors for venous thromboembolism	
Drug interactions (Ritonavir-boosted protease inhibitors; certain anticonvulsants; rifampin or rifabutin)	

From Centers for Disease Control and Prevention: U.S medical eligibility criteria for contraceptive use, 2010, MMWR Recomm Rep *59(RR-4):1–86, 2010.*

adolescents, thereby potentially increasing their risk for osteoporosis later in life, subsequent studies have found that bone density is recovered after discontinuation of the method and is considered safe for use in this population (see Table 117-2). Healthcare providers may want to consider a contraceptive containing estrogen in teens who are already at high risk for low bone density, such as those on chronic corticosteroids or those with eating disorders (see Chapter 707). Although a black box warning was issued in 2004, the American Academy of Pediatrics and ACOG do not recommend limiting DMPA use to 2 yr for all women and do not recommend routine bone mineral density screening for females using DMPA. There is also concern for weight gain in women using DMPA. A systematic review found 2 studies indicating early weight gain may be predictive of progressive gain over time; thus, those teens gaining weight in the 1st 3-6 mo should consider another method.

PROGESTIN-ONLY PILLS

Progestin-only oral contraceptives are available for the adolescent in whom the use of estrogen is potentially deleterious, such those with active liver disease, replaced cardiac valves, or hypercoagulable states (see Table 117-3). These agents ("mini-pills") are less reliable in inhibiting ovulation, are associated with a typical use failure rate of 9%, and

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Product Information

http://labeling.bayerhealthcare.com/html/products/pi/Mirena_PI.pdf.

http://labeling.bayerhealthcare.com/html/products/pi/Skyla_PI.pdf.

http://www.merck.com/product/usa/pi_circulars/n/nexplanon/nexplanon_pi.pdf.

http://hcp.paragard.com/images/ParaGard_info.pdf.

are considered Tier 2 or moderately effective contraceptives (see Fig. 117-2). Acceptance by adolescents is limited by the necessity of taking the pill daily and bleeding irregularities, including amenorrhea and breakthrough bleeding. Progestin-only pills are quickly effective after 2 days of initiation in thickening cervical mucus. Effects, however, are short-lived and pill-taking must be punctual, which may be difficult for teens. If a pill is more >3 hr late from normal time, an unintended pregnancy may occur.

Bibliography is available at Expert Consult.

117.3 Combined Hormonal Contraceptives

Tara Jatlaoui and Gale R. Burstein

Combined hormonal contraceptives (CHCs) are methods that include an estrogenic substance in combination with a progestin; methods available in the United States include several formulations of combined oral contraceptives (COCs), a transdermal patch and a vaginal ring. The major mechanism of action of the estrogen-progestin combination is to prevent the surge of luteinizing hormone and, as a result, to inhibit ovulation. Additional effects to the reproductive tract include thickening of the cervical mucus in such a way that prevents sperm penetration and thinning of the endometrial lining, which may decrease menstrual blood loss. Typical use failure rates for all CHCs are the same at 9%.

CHCs are also considered similarly in the U.S. Medical Eligibility Criteria, and recommendations mostly are concerned with estrogen exposure for a given condition or characteristic (see Table 117-3). Thrombophlebitis, hepatic adenomas, myocardial infarction, and carbohydrate intolerance are some of the more serious potential complications of exogenous estrogen use. These disorders are exceedingly rare in adolescents. Even though teenage smokers who use oral contraceptives have more than twice the risk of myocardial infarction, the likelihood of its occurrence is very small, and thus clinically insignificant, compared to the risk of dying from other pregnancy-related complications.

COMBINED ORAL CONTRACEPTIVES

Oral contraceptive pills can be either COCs or progestin-only pills and are commonly referred to as "the pill." The pill is one of the most common contraceptive methods used among women of all ages. To decrease risk of pregnancy and increase continuation, providers are encouraged to provide oral contraceptive pills at the time of patient presentation to start immediately rather than waiting for next menses, as long as the provider is reasonably sure that the patient is not pregnant. Providers are also encouraged to provide up to 13 pill packs at a time, based on evidence that more pill packs given is associated with higher continuation rates. However, most health plans will not cover costs for more than 3 pill packs dispensed at 1 time. Advanced provision of emergency contraceptive pills is also recommended should patients miss pills and have unprotected sex. The effectiveness of COCs is dependent on compliance, and unfortunately adolescents may forget to take a pill each day. Figures 117-3 and 117-4 list the rules for missed pills or following vomiting or diarrhea.

COCs contain 50, 35, 30, 25, or 20 μg of estrogenic substance, typically ethinyl estradiol, and as many as 10 progestins have been available

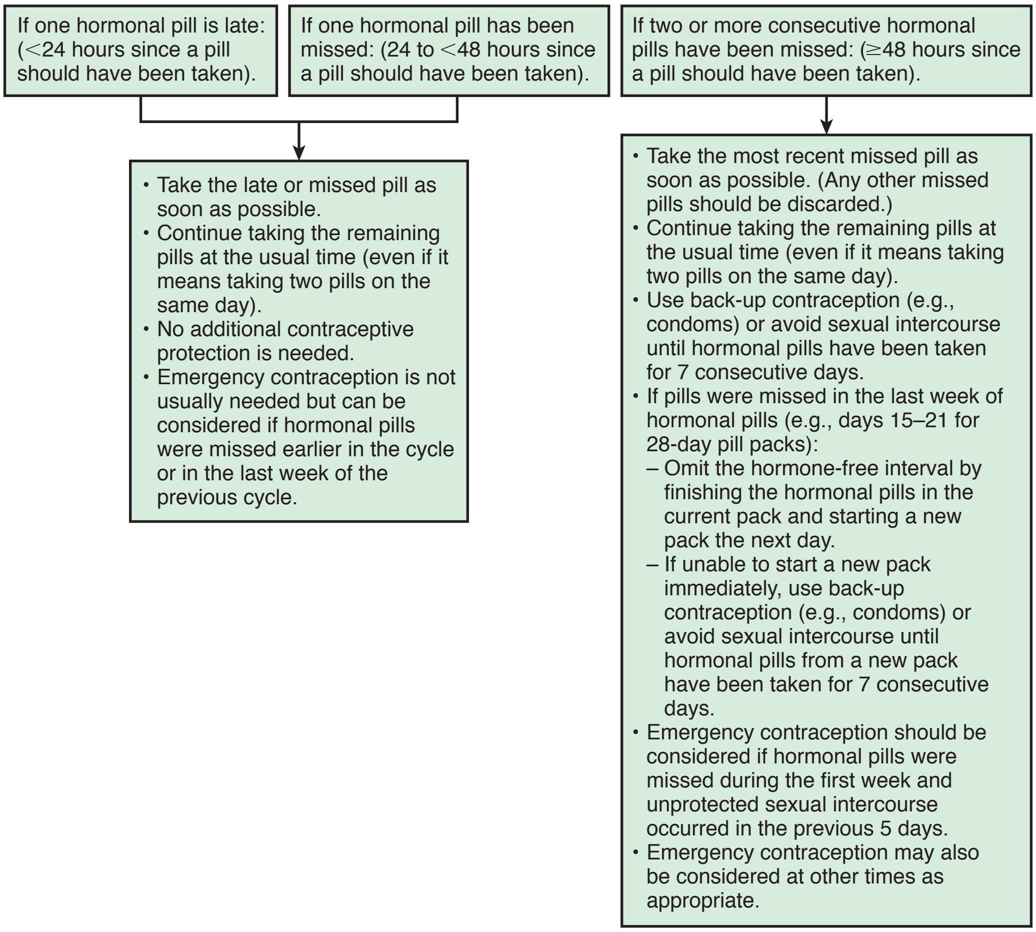

Figure 117-3 Recommended actions after late or missed combined oral contraceptives. *(From Centers for Disease Control and Prevention: US Selected Practice Recommendations for Contraceptive Use, 2013,* MMWR Recomm Rep *2013;62(RR-5):1–60, Fig. 2, p. 27).*

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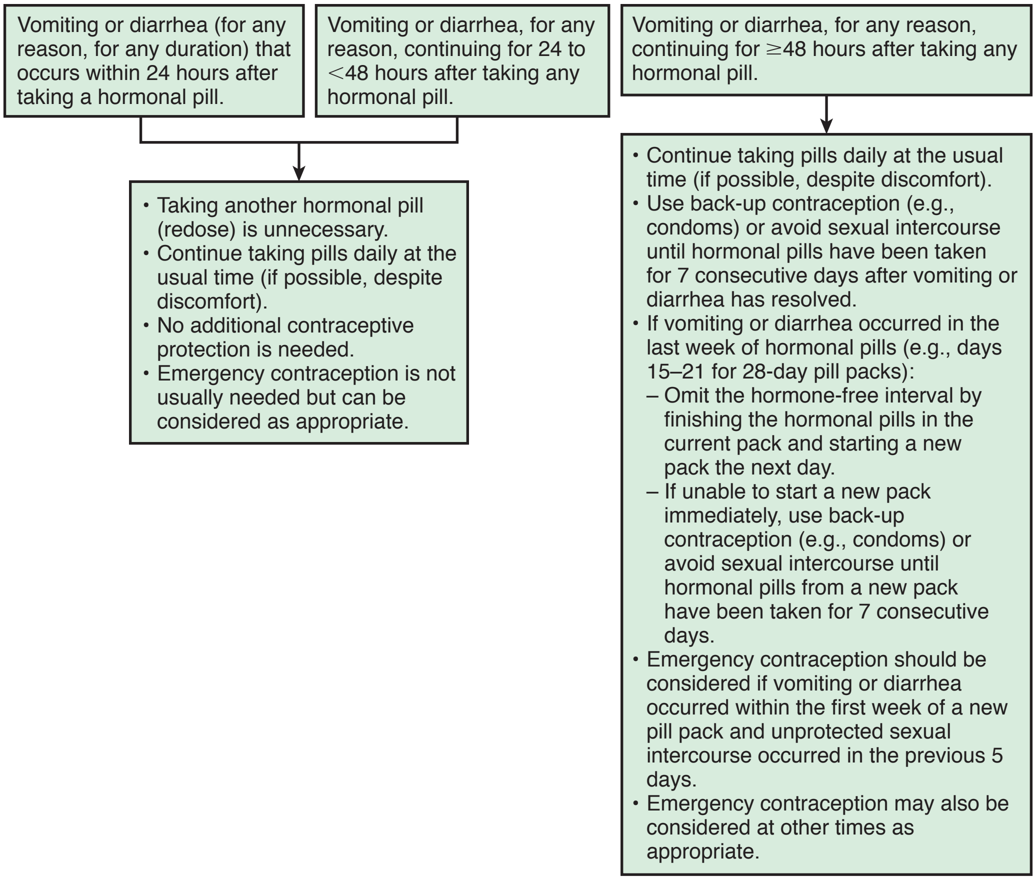

Figure 117-4 Recommended steps after vomiting or diarrhea while using combined oral contraceptives. *(From Centers for Disease Control and Prevention: US Selected Practice Recommendations for Contraceptive Use, 2013,* MMWR Recomm Rep *2013;62(RR-5):1–60, Fig. 5, p. 30).*

in the United States for combined pills. Multiple preparations are available to help select the formulation with which an individual patient will be satisfied with minimal side effects.

COCs can be packaged as 28-day monophasic pills, which contain the same dose of active pills for 21 or 24 days followed by 7 or 4 days of placebo pills, respectively. Monophasic formulations are also available for extended-cycles of 91 days or 1 yr such that withdrawal bleeding does not occur each month but at the end of each extended cycle. Extended cycling of monophasic COCs for adolescents has some anticipated benefits associated with increased ovarian activity suppression and may decrease failure rates. Other advantages include diminished frequency of hormonal withdrawal (premenstrual) effects including headaches and migraines, mood changes, and heavy monthly bleeding. The most common side effect of extended-cycle oral contraceptive pills is intermenstrual bleeding and/or spotting with the total days of bleeding over the 1st yr of treatment being similar for extended-cycle users and users following a 28-day cycle regimen. The unscheduled bleeding pattern diminishes over time. Multiphasic pill packs contain various levels of estrogen and progestin for 21 active pills and contains 7 placebo pills. Multiphasic formulations are not available for extended cycle use.

The short-term adverse effects of COCs, such as nausea and weight gain, often interfere with compliance in adolescent patients. These effects are usually transient and may be overshadowed by the beneficial effects of a shortened menses and the relief of dysmenorrhea. The inhibition of ovulation or the suppressant effect of estrogens on prostaglandin production by the endometrium makes COCs effective in preventing dysmenorrhea (see Chapter 116). Acne (see Chapter 669) may be worsened by some and improved by other oral contraceptive preparations. The pills with nonandrogenic progestins are particularly effective in reducing acne and hirsutism. Drospirenone, a progestin with antimineralocorticoid activity, has been shown to reduce premenstrual symptomatology, but the potential for hyperkalemia as a side effect eliminates patients with renal, liver, or adrenal diseases and patients on certain medications.

As of 2011, the FDA has concluded that drospirenone-containing oral contraceptives may be associated with a higher risk of blood clots compared to other progestin-containing pills. Although no studies have provided consistent estimates of the comparative risk of blood clots between birth control pills that contain drospirenone and those that do not, nor have studies accounted for patient characteristics that may affect blood clot risk, there has been a 3-fold increased risk of blood clots reported for drospirenone, as compared to products containing levonorgestrel or other progestins. As a result, the FDA is requiring that labeling be revised for the oral contraceptives marketed under the Beyaz, Safyral, Yasmin, and Yaz brands. Despite the risk of blood clots with all oral contraceptives, the risk still remains lower than the risk of developing blood clots during pregnancy or the postpartum period.

TRANSDERMAL PATCH

The *transdermal patch* (Ortho Evra) releases 20 µg ethinyl estradiol and 150 µg norelgestromin daily and is applied to the lower abdomen, buttocks, or upper body. It is worn continuously for 1 wk and changed weekly for a total of 3 wk; then no patch is worn for the fourth wk at which time bleeding occurs (see Table 117-1). It should not be applied to the breast. Limited studies in adolescents suggest higher rates of partial or full detachment compared to adults, with high patient satisfaction and 50-83% continuation rates from 3-18 mo of use (Fig. 117-5). Like other combined hormonal methods, the patch is a Tier 2 or moderately effective contraceptive.

VAGINAL RING

The *vaginal contraceptive ring* (NuvaRing) is a flexible, transparent, colorless vaginal ring that measures about 2.1 inches in diameter and

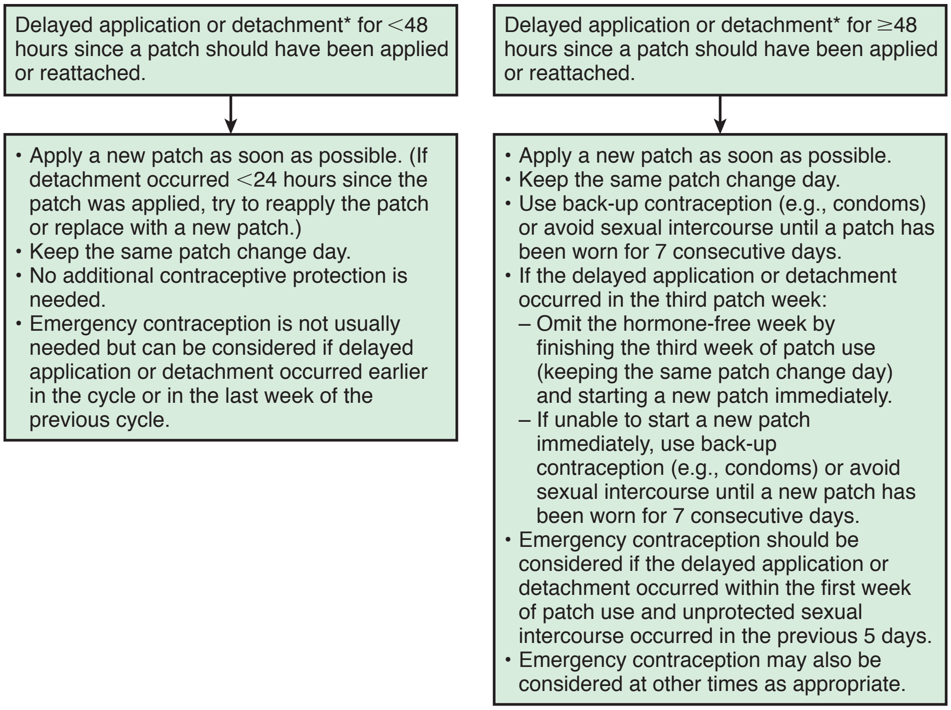

*If detachment takes place but the woman is unsure when the detachment occurred, consider the patch to have been detached for ≥48 hours since a patch should have been applied or reattached.

Figure 117-5 Recommended actions after delayed application or detachment with combined hormonal patch. *(From Centers for Disease Control and Prevention: US Selected Practice Recommendations for Contraceptive Use, 2013,* MMWR Recomm Rep *2013;62(RR-5):1–60, Fig. 3, p. 28).*

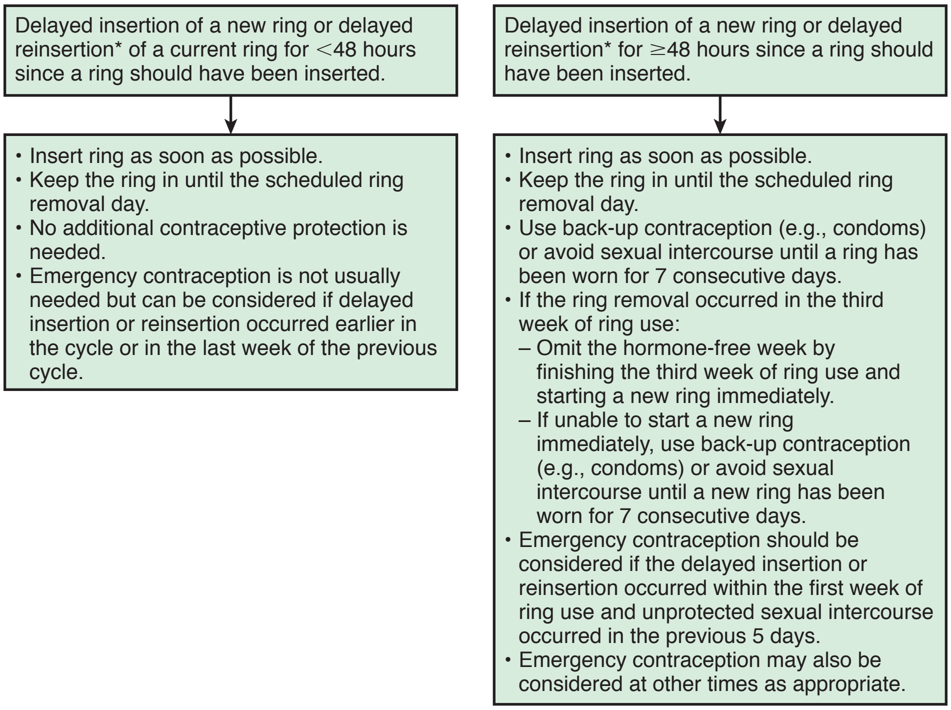

*If removal takes place but the woman is unsure of how long the ring has been removed, consider the ring to have been removed for ≥48 hours since a ring should have been inserted or reinserted.

Figure 117-6 Recommended actions after delayed insertion or reinsertion with combined vaginal ring. *(From Centers for Disease Control and Prevention: US Selected Practice Recommendations for Contraceptive Use, 2013,* MMWR Recomm Rep *2013;62(RR-5):1–60, Fig. 4, p. 29).*

is inserted into the vagina by the patient. It releases 15 μg ethinyl estradiol and 120 μg etonogestrel per day and remains in place for 3 wk, during which time these hormones are absorbed. If the ring is accidentally expelled or removed for intercourse, it should be reinserted; however, if it is out of place ≥48 hr, a backup method of contraception should be used (Fig. 117-6). Like other combined hormonal methods, the vaginal ring is a Tier 2 or moderately effective contraceptive.

Contraindications to the use of estrogen-containing methods include those conditions for which CHCs pose an unacceptable health risk (category 4) in the U.S. Medical Eligibility Criteria, 2010 (see Table 117-3): current breast cancer, severe cirrhosis, acute deep venous thrombosis/pulmonary embolism or history of deep venous thrombosis/pulmonary embolism with higher risk for recurrence, major surgery with prolonged immobilization, diabetes with nephropathy, retinopathy or neuropathy, migraines with aura, Stage II hypertension, vascular disease, ischemic heart disease, hepatocellular adenoma or malignant liver tumors, multiple risk factors for cardiovascular disease, peripartum cardiomyopathy, postpartum <21 days, complicated solid organ transplantation, history of cerebrovascular accident, systemic lupus erythematosus with positive antiphospholipid antibodies, thrombogenic mutations and complicated valvular heart disease. The initial history taken before prescribing CHCs should specifically address these risks. The U.S. Medical Eligibility Criteria provides contraceptive safety guidance with more than 1,800 recommendations for more than 120 medical conditions or characteristics (see Table 117-3).

Bibliography is available at Expert Consult.

117.4 Emergency Contraception

Tara Jatlaoui and Gale R. Burstein

Unprotected intercourse at midcycle carries a pregnancy risk of 20-30%. At other times during the cycle, the risk is 2-4%. The risk may be reduced or eliminated by interventions known collectively as emergency contraception (EC) as soon as possible after unprotected intercourse or contraceptive failure with a “window” up to 120 hr. Table 117-4 lists the indications for use of EC. Methods that can be used after unprotected intercourse for EC include the Copper IUD and various emergency contraceptive pills, which include ulipristal acetate, levonorgestrel and COCs following the Yuzpe method. Although the mechanism of action of the Copper IUD as EC is unclear, all emergency contraceptive pills work to delay ovulation and are effective only for intercourse that occurs prior to administration. Initiation of a regular contraceptive method is necessary to prevent pregnancy for any intercourse that occurs for the remainder of the cycle and for future cycles. If pregnancy has already occurred, emergency contraceptive pills will not cause an abortion or have teratogenic effects on the fetus.

Table 117-4	Potential Indications for Use of Emergency Contraception

- Lack of contraceptive use during coitus
- Mechanical failure of male condom (breakage, slippage, or leakage)
- Dislodgment, breakage, or incorrect use of diaphragm, cervical cap, or female condom
- Failure of spermicide tablet or film to melt before intercourse
- Error in practicing withdrawal (coitus interruptus)
- Missed combined oral contraceptives (any 2 consecutive pills)
- Missed progestin-only oral contraceptive (1 or more)
- Expulsion or partial expulsion of an IUD
- Exposure to potential teratogen (such as isotretinoin or thalidomide while not using effective contraception)
- Late injection of injectable contraceptive (>2 wk late of a progestin-only formulation such as depot medroxyprogesterone acetate)*
- 2 or more days late starting new vaginal ring or patch cycle
- Rape

*The usual interval for use of depot medroxyprogesterone acetate as contraception is every 12 wk; the interval for the combined monthly injectable formulation is every 28 to 30 days.

Adapted from Allen RH, Goldberg AB: Emergency contraception: a clinical review, Clin Obstet Gynecol *50:927–936, 2007.*

Teens can access EC information through a ***hotline at 1-888-NOT-2-LATE*** to obtain EC pills over the counter. The American Academy of Pediatrics recommends advance provision of EC pills for teens who are or may become sexually active. A follow-up appointment is also recommended to determine the effectiveness of treatment and to diagnose a possible early pregnancy. The visit also provides an opportunity to counsel the adolescent, explore the situation leading up to the unprotected intercourse or contraceptive failure, test for STIs, offer HIV testing, and initiate continuing contraception when appropriate. Pap smear screening is not initiated until 21 yr of age.

COPPER IUD

The Copper T380A is FDA approved for EC and has been shown to be more than 99% effective if used within 5 days (120 hr) after unprotected sex. The additional benefit of using the Copper IUD for EC is it also provides long-term reversible contraception.

ULIPRISTAL ACETATE

This is the newest formulation available for EC and was FDA approved in 2010 for use up to 120 hr after unprotected sex. It is available only by prescription regardless of age. It has been shown in a few studies to be more effective than levonorgestrel at and beyond 72 hr.

LEVONORGESTREL

In 2009, the FDA approved the emergency contraceptive drug Plan B as an over-the-counter option for women age 17 yr and older. Experience in adolescent women demonstrates more effective use of EC with advance provision and is not associated with more frequent unprotected intercourse or less condom or pill use. Nausea and vomiting are uncommon side effects, and in a recent comparison, levonorgestrel proved more effective at preventing pregnancy than the Yuzpe method.

The **Yuzpe method** has been replaced by the more effective levonorgestrel pills but may be useful for women who already have COCs at home and are in need of EC. For EC, pills consist of COCs totaling 200 μg ethinyl estradiol and 2.0 mg norgestrel or 1.0 mg levonorgestrel. This method is effective in reducing the risk of pregnancy by 75%. The most common side effects are nausea (50%) and vomiting (20%), prompting some clinicians to prescribe or recommend antiemetics along with the oral contraceptives.

Bibliography is available at Expert Consult.

117.5 Dual Protection

Tara Jatlaoui and Gale R. Burstein

Dual protection is the protection against STIs/HIV as well as effective contraception. Although condoms can provide both, providers should encourage more highly effective contraceptive methods along with condoms for each act of intercourse.

CONDOMS

This method prevents sperm from being deposited in the vagina. There are no major side effects associated with the use of a condom. The risk of HIV may have increased the use of condoms among adolescents, with 46.2% of high school students in 1991 reporting using a condom at last sexual intercourse increasing to 60.2% in 2011. The main advantages of condoms are their low price, availability without prescription, little need for advance planning, and, most important for this age

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group, their effectiveness in preventing transmission of STIs, including HIV and human papillomavirus. The typical use failure rate for male condoms is 18%. For most effective dual protection, male latex condoms are recommended as protection against STIs, and should be used with an effective contraceptive method for adolescents such as a LARC. According to the National Survey of Family Growth, only 12% of females used a highly effective method along with a condom in the mo that they were interviewed.

A female condom is available over-the-counter in single-size disposable units. It is a second choice over the male latex condom because of the complexity of properly using the device, its high typical use failure rate of 21%, and the lack of studies in humans demonstrating its effectiveness against STIs. Most adolescents would require intensive education and hands-on practice to use it effectively.

Bibliography is available at Expert Consult.

117.6 Other Barrier Methods

Tara Jatlaoui and Gale R. Burstein

DIAPHRAGM, CERVICAL CAP, AND SPONGE

These methods have few side effects but are much less likely to be used by teenagers. Typical use failure rates exceed 12%. The cervical cap and sponge have lower failure rates in nulliparous women while the diaphragm has similar rates among nulliparous or parous women. Adolescents tend to object to the messiness of the jelly or to the fact that the insertion of a diaphragm may interrupt the spontaneity of sex, or they may express discomfort about touching their genitals.

117.7 Other Methods

Tara Jatlaoui and Gale R. Burstein

SPERMICIDES

A variety of agents containing the spermicide nonoxynol-9 are available as foams, jellies, creams, films, or effervescent vaginal suppositories. They must be placed in the vaginal cavity shortly before intercourse and reinserted before each subsequent ejaculation in order to be effective. Rare side effects consist of contact vaginitis. There has been some concern regarding the vaginal and cervical mucosal damage observed with nonoxynol-9, and the overall impact on HIV transmission is unknown. The finding that nonoxynol-9 is gonococcicidal and spirocheticidal has not been substantiated in randomized clinical trials. Spermicides should be used in combination with other barrier methods as their typical use failure rate alone is 28%.

WITHDRAWAL

The pregnancy risk for use of withdrawal as a contraceptive method is probably underestimated in adolescents, and high typical use failure rate of 22% should be specifically addressed with young adolescents; especially since over half (58%) of teens have used withdrawal for contraception.

FERTILITY AWARENESS–BASED METHODS

These include the standard days method, basal body temperature method, billings method and may also include combinations as well. Since these are based on regular ovulatory cycles, which are less common in teens, these should be used with caution.

LACTATIONAL AMENORRHEA METHOD

The lactational amenorrhea method may be a highly effective temporary contraceptive method if all of the following criteria are met: (a) no return of menses, (b) the infant is <6 mo old, and (c) exclusively breastfeeding.

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Chapter 118

Adolescent Pregnancy

Dianne S. Elfenbein and
Marianne E. Felice

EPIDEMIOLOGY

In 1960, the teen birth rate in the United States was recorded as 89.1 births per 1,000 females 15-19 yr of age; by 2011, the rate had decreased to 31.3 births per 1,000 females 15-19 yr of age. Despite increases in the rates in 1990 and 2006, there has been a steady decline over the last half century (Fig. 118-1). The most dramatic decreases have been in African-American and Hispanic adolescents. Pregnancy rates, which include births, miscarriages, stillbirths, and induced abortions, have also decreased since the 1990s. In 1990, the pregnancy rate was 116.9 per 1,000 females age 15-19 yr of age; in 2008, the pregnancy rate was 67.8, indicating that the decline in birthrates was not attributable to an increase in pregnancy terminations. The improvement in U.S. female teen birth rates is attributed to 3 factors: more teens are delaying the onset of sexual intercourse, are using some form of contraception when they begin to have sexual intercourse, and are using long-lasting contraceptive agents such as injections, implants, and intrauterine devices.

In spite of the decrease in female teen births in the last 2 decades, the United States continues to have female teen birth rates markedly higher than those in most other industrialized nations. For comparison, in 2009 the United States birth rate to female teens age 15-19 yr was 37.9 per 1,000 compared to a rate of 22 among all industrialized nations. The Russian Federation reported a rate of 30.2, the UK a rate of 25.0, and Australia a rate of 16.5. Japan's rate was 5.1 births per 1,000 female teens. Among developing countries the estimated rate was 56 and among the least-developed nations, 123. Globally, the estimated rate was 52 births per 1,000 female teens. Globally, teen pregnancy rates declined from 1990 to 2000 but have leveled off since then.

ETIOLOGY

In industrialized countries with policies supporting access to protection against pregnancy and sexually transmitted infections (STIs), older adolescents are more likely to use hormonal contraceptives and condoms, resulting in a lowered risk of unplanned pregnancy. Younger teenagers are likely to be less deliberate and logical about their sexual decisions and their sexual activity is likely to be sporadic or even coercive, contributing to inconsistent contraceptive use and a greater risk of unplanned pregnancy. Better hopes for employment and higher educational goals are associated with lowered probability of childbearing in most groups. In nonindustrialized countries, laws permitting marriage of young and mid-adolescents, poverty, and limited female education are associated with increased adolescent pregnancy rates.

CLINICAL MANIFESTATIONS

Adolescents may experience the traditional symptoms of pregnancy: morning sickness (vomiting, nausea that may also occur any time of the day), swollen tender breasts, weight gain, and amenorrhea. Often the presentation is less classic. Headache, fatigue, abdominal pain, dizziness, and scanty or irregular menses are common presenting complaints.

In the pediatric office, some teens are reluctant to divulge concerns of pregnancy. Denial of sexual activity and menstrual irregularity should not preclude the diagnosis in face of other clinical or historical information. An unanticipated request for a complete checkup or a visit for contraception may uncover a suspected pregnancy. Pregnancy is still the most common diagnosis when an adolescent presents with **secondary amenorrhea.**

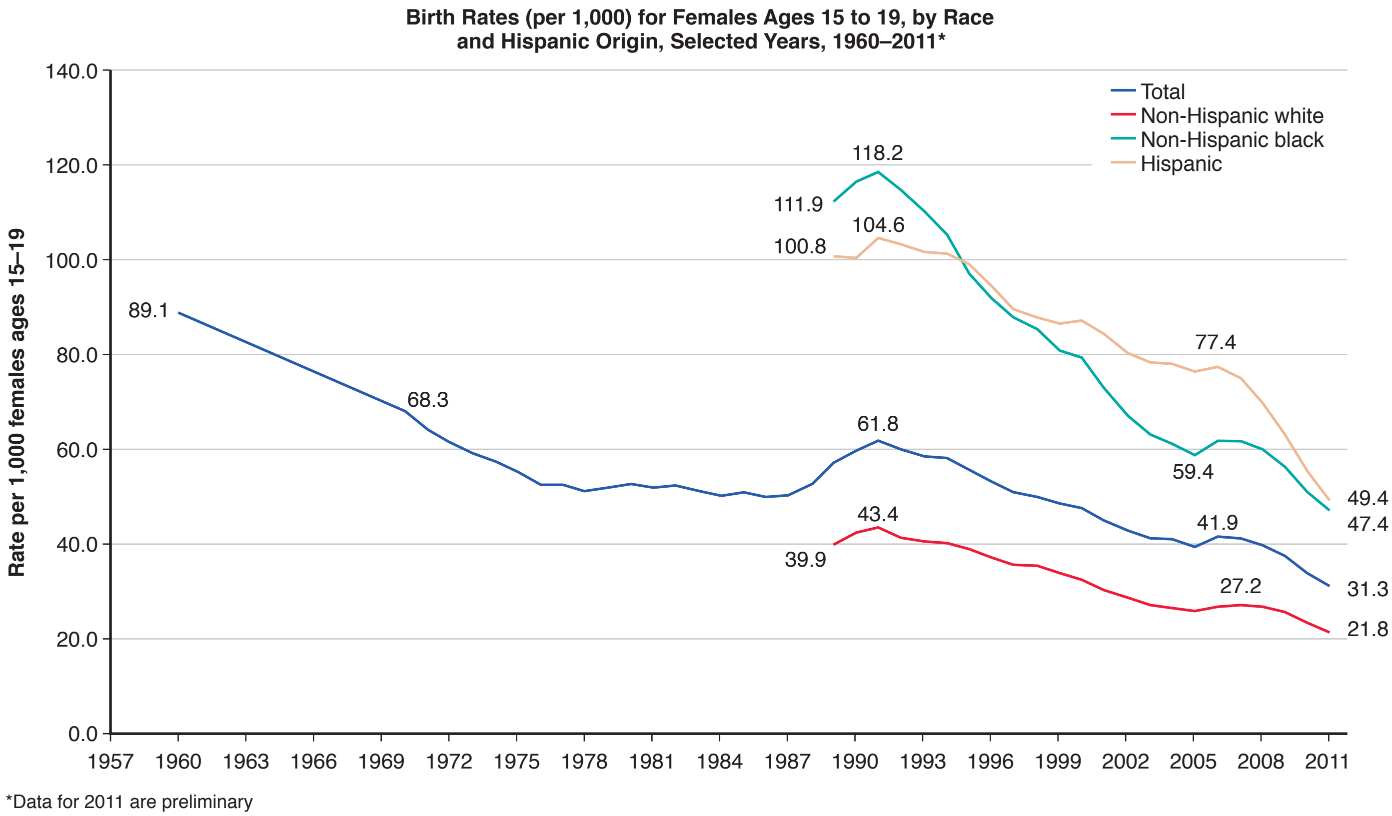

Figure 118-1 Teen birth rates (births per 1,000 females) in the United States. *(Child Trends, 2013. Teen births. Available at: http://www.childtrends.org/?indicators=teen-births. Sources: Data for 1960 from National Center for Health Statistics.* Health, United States, 2001 with urban and rural health chartbook. *Hyattsville, MD, 2001, Table 3; Data for 1970-2011 from Martin JA, Hamilton BE, Ventura JS, et al: Births: final data for 2011. Natl Vital Stat Rep 62(1). Hyattsville, MD: National Center for Health Statistics, 2013.)*

DIAGNOSIS

Table 118-1 provides information regarding the diagnosis of pregnancy.

On physical examination, the findings of an enlarged uterus, cervical cyanosis (**Chadwick sign**), a soft uterus (**Hegar sign**), or a soft cervix (**Goodell sign**) are highly suggestive of an intrauterine pregnancy. A confirmatory pregnancy test is always recommended, either *qualitative* or *quantitative*. Modern **qualitative** urinary detection methods are efficient at detecting pregnancy, whether performed at home or in the office. These tests are based on detection of the beta subunit of human chorionic gonadotropin (hCG). Although claims for nonprescription home pregnancy tests may indicate 98% detection on the day of the first missed menstrual period, sensitivity and accuracy vary considerably. Office or point-of-care tests have increased standardization and generally have increased sensitivity, with the possibility of detecting a pregnancy within 3-4 days after implantation. However, in any menstrual cycle, ovulation may be delayed, and in any pregnancy, the day of implantation may vary considerably, as may rate of production of hCG. This variability, along with variation of urinary concentration, may affect test sensitivity. **Consequently, each negative test should be repeated in 1-4 wk if there is a heightened suspicion of pregnancy.** The most sensitive pregnancy detection test is a serum **quantitative** βhCG radioimmunoassay in which results are reliable within 7 days after fertilization. This more expensive test is used primarily during evaluations for ectopic pregnancy, to detect retained placenta after pregnancy termination, or in the management of a molar pregnancy. It is generally used when serial measurements are necessary in clinical management.

Although not generally used for primary diagnosis of pregnancy, pelvic or vaginal ultrasound can be used to detect and date a pregnancy. Pelvic ultrasound will detect a gestational sac at about 5-6 wk (dated from last menstrual period) and vaginal ultrasound at 4.5-5 wk.

Table 118-1	Diagnosis of Pregnancy Dated from First Day of Last Menstrual Cycle
CLASSIC SYMPTOMS	
Missed menses, breast tenderness, nipple sensitivity, nausea, vomiting, fatigue, abdominal and back pain, weight gain, urinary frequency	
Teens may present with unrelated symptoms that enable them to visit the doctor and maintain confidentiality	
LABORATORY DIAGNOSIS	
Tests for human chorionic gonadotropin in urine or blood may be positive 7-10 days after fertilization, depending on sensitivity	
Irregular menses make ovulation/fertilization difficult to predict.	
Home pregnancy tests have a high error rate.	
PHYSICAL CHANGES	
2-3 wk after implantation: cervical softening and cyanosis	
8 wk: uterus size of orange	
12 wk: uterus size of grapefruit and palpable suprapubically	
20 wk: uterus at umbilicus	
If physical findings are not consistent with dates, ultrasound will confirm	

This tool may also be used to distinguish diagnostically between intrauterine and ectopic pregnancies.

PREGNANCY COUNSELING AND INITIAL MANAGEMENT

After the diagnosis of pregnancy is made, it is important to begin addressing the psychosocial, as well as the medical, aspects of the pregnancy. The patient's response to the pregnancy should be assessed and her emotional issues addressed. It should not be assumed that the

pregnancy was unintended. Discussion of the patient's options should be initiated. These options include (a) releasing the child to an adoptive family, (b) electively terminating the pregnancy, and (c) raising the child herself with the help of family, father of the baby, friends, and/or other social resources. Options should be presented in a supportive, informative, nonjudgmental fashion; for some young women, they may need to be discussed over several visits. Physicians who are uncomfortable in presenting options to their young patients should refer their patients to a provider who can provide this service expeditiously. Pregnancy terminations implemented early in the pregnancy are generally less risky and less expensive than those initiated later. Other issues that may need discussion are how to inform and involve the patient's parents and the father of the infant; implementing strategies for insuring continuation of the young mother's education; discontinuation of tobacco, alcohol, and illicit drug use; discontinuance and avoidance of any medications that may be considered teratogenic; starting folic acid, calcium, and iron supplements; proper nutrition; and testing for STIs. Especially in younger adolescents, the possibility of **coercive sex** (see Chapter 119) should be considered and appropriate social work/legal referrals made if abuse has occurred, although most pregnancies are not a result of coercive sex. Patients who elect to continue their pregnancies should be referred as soon as possible to an adolescent-friendly obstetric provider.

CHARACTERISTICS OF TEEN PARENTS

Young women who become parents as teenagers often come from economically disadvantaged families. Although birthrates among African-American and Hispanic teens have decreased in the past 2 decades, their rates are more than double those for non-Hispanic whites. Parenting teens frequently have poor school performance prior to becoming pregnant, and they often have a family history of low educational attainment. Learning disabilities are not uncommon. Teen mothers frequently come from single-parent families where their own mother gave birth during adolescence. A large majority (84%) of teen mothers have a baby outside of marriage. They may view pregnancy as having a positive social value and as not interfering with their long-term goals.

Teenage men who become fathers as adolescents also have poorer educational achievement than their age-matched peers. They are more likely than peers to have been involved with illegal activities and with the use of illegal substances. Adult men who father the children of teen mothers are poorer and educationally less advanced than their age-matched peers and tend to be 2-3 yr older than the mother; any combination of age differences may exist. Younger teen mothers are more likely to have a greater age difference between themselves and the father of their child, raising the issue of coercive sex or statutory rape (see Chapter 119).

Male partners have a significant influence on the young woman's decision/desire to become pregnant and to parent her child. Sensitively and appropriately including the male partner in discussions of family planning, contraception, and pregnancy options may be a useful strategy in improving outcomes for all. This can only be successful if the young female patient is willing to have her partner involved in such discussions.

MEDICAL COMPLICATIONS OF MOTHERS AND BABIES

Although pregnant teens are at higher-than-average risk for some complications of pregnancy, most teenagers have pregnancies that are without major medical complications, delivering healthy infants. The miscarriage/stillbirth risk for adolescents is estimated at 15-20%. In the United States, elective pregnancy termination rates peaked from 1985-1988 at 41-46%, decreasing since then to approximately 30% in 2008. As expected, teen mothers have low rates of age-related chronic disease (diabetes or hypertension) that might affect the outcomes of a pregnancy. They also have lower rates of twin pregnancies than older women. They tolerate childbirth well with few operative interventions. However, as compared with 20-39 yr old mothers, teens have higher incidences of low birthweight infants, preterm infants, neonatal deaths, passage of moderate to heavy fetal meconium during parturition, and infant deaths within 1 yr after birth. The highest rates of these poor outcomes occur in the youngest and most economically deprived mothers. Gastroschisis, although very rare, has a markedly higher incidence in infants of teen mothers for reasons that are unclear. Teen mothers also have higher rates of anemia, pregnancy-associated hypertension, and eclampsia, with the youngest teens having rates of pregnancy-associated hypertension higher than the rates of women in their 20s and 30s. The youngest teens also have a higher incidence of poor weight gain (<16 lb) during their pregnancy. This correlates with a decrease in the birth weights of their infants. Poor maternal weight gain also has correlated strongly with teens' late entrance into prenatal care and with inadequate utilization of prenatal care. Sexually active teens have higher rates of STIs than older sexually active women.

Globally, many young women who become pregnant have been exposed to violence or abuse in some form during their lives. There is some evidence that teenage women have the highest rates of **violence** during pregnancy of any group. Violence has been associated with injuries and death as well as preterm births, low birthweight, bleeding, substance abuse, and late entrance into prenatal care. An analysis of the Pregnancy Mortality Surveillance System indicates that in the United States from 1991 to 1999, homicide was the second leading cause of injury-related deaths in pregnant and postpartum women. Women ages 19 yr and younger had the highest pregnancy-related homicide rate (see Chapter 113).

Ectopic pregnancy occurs in 1-2% of conceptions and is more common in women with a previous history of an ectopic pregnancy, pelvic inflammatory disease, prior appendicitis, infertility, in utero exposure to diethylstilbestrol, and possibly the presence of an intrauterine contraceptive device. Most ectopic pregnancies are in the fallopian tube (tubal pregnancy). Manifestations include vaginal spotting after a missed menstrual period that may progress to more intense vaginal bleeding (which may be suggestive of a spontaneous abortion); vaginal bleeding is absent in 10-20%. Abdominal pain is associated with distention of the fallopian tube; tubal rupture results in more intense pain, hemorrhagic shock, and peritonitis. Some women have nonspecific abdominal complaints and are misdiagnosed with gastroenteritis. Cervical motion and adnexal tenderness (and adnexal mass) may be present. Transvaginal sonography (not transabdominal) is the diagnostic test of choice to detect an ectopic pregnancy and reveals an adnexal mass and no uterine pregnancy. Nonetheless, some women will have pregnancy of unknown location by transvaginal sonography; approximately 20% of these will have an ectopic pregnancy. Measurement of sensitive quantitative serum βhCG levels together with transvaginal sonography has value in diagnosing an ectopic pregnancy. If the initial βhCG is above the discriminatory zone (level at which one expects an intrauterine pregnancy) but on transvaginal sonography there is no intrauterine pregnancy, there may be an ectopic pregnancy or an abnormal uterine pregnancy. In addition, if the βhCG is below the discriminatory level (usually <3000 mIU/mL) with no definitive diagnosis by sonography, serial βhCG testing should be performed every 48 hr. In a normal uterine pregnancy, βhCG levels should increase approximately 50% every 48 hr; declining levels may suggest a miscarriage or an ectopic pregnancy. Some would perform a dilation and curettage and check for products of conception or follow serial βhCG levels. If there are no products of conception or if βhCG levels plateau or increase, an ectopic pregnancy is present. Treatment of unstable or advanced patients is usually by laparoscopic surgery or by laparotomy. Because of early detection, many patients remain stable (unruptured). Stable patients with an unruptured ectopic pregnancy may be treated with single-, or more often multiple-, dose methotrexate to induce abortion. Contraindications to methotrexate in a stable patient include size of the ectopic mass (>3.5 cm) and embryonic cardiac motion.

Prematurity and low birthweight increase the perinatal morbidity and mortality for infants of teen mothers. These infants also have higher-than-average rates of sudden infant death syndrome (see Chapter 375), possibly because of less use of the supine sleep position, and are at higher risk of both intentional and unintentional injury (see Chapter 40). One study shows the risk of homicide to be 9-10 times

Table 118-2 2012 American Academy of Pediatrics Clinical Guidelines: Care of Adolescent Parents and Their Children

Create a medical home for adolescent parents and their children	Involve both adolescent mothers and coparenting father Emphasize anticipatory guidance, parenting, and basic child care–giving skills, especially for teen dads
Provide comprehensive, multidisciplinary care	Access community resources such as special Supplemental Nutrition Program for Women, Infants, and Children Provide medical and developmental services to low-income parents and children Facilitate coordination of services
Contraceptive counseling	Emphasize condom use Encourage long-acting contraceptive methods
Encourage breastfeeding	Support breastfeeding in home, work, and school settings
Encourage high school completion	
Assess risk of domestic violence	
Encourage adolescent parenting	Work with other involved adults such as grandparents to encourage developmental growth of adolescent as parent as well as optimize infant developmental outcomes
Adapt counseling to developmental level of adolescent	Utilize school-, home-, and office-based interventions Consider use of support groups
Awareness and monitoring of developmental progression of infant and adolescent parent	Advocate for high-quality community resources for adolescents, including developmental resources, child care, and parenting classes Facilitate access to Head Start and education resources for individuals with disability

Data from Pinzon JL, Jones VF, Committee on Adolescence and Committee on Early Childhood, Care of adolescent parents and their children, Pediatrics 130(6):e1743–1755, 2012.

higher if a child born to a teen mother is not the mother's firstborn as compared with the risk to a firstborn of a woman age 25 yr or older. The perpetrator is often the father, stepfather, or boyfriend of the mother.

After childbirth, **depressive symptoms** may occur in as many as 50% of teenaged mothers. Depression seems to be greater with additional social stressors and with decreased social supports. Support from the infant's father and the teen's mother seems to be especially important in preventing depression. Pediatricians who care for parenting teens should be sensitive to the possibility of depression, as well as to inflicted injury to mother or child; appropriate diagnosis, treatment, and referral to mental health or social agencies should be offered and facilitated.

PSYCHOSOCIAL OUTCOMES/RISKS FOR MOTHER AND CHILD

Educational

Teenage mothers often do poorly in school and drop out prior to becoming pregnant. After childbirth many choose to defer completion of their education for some time. High school graduation or an equivalency degree is generally achieved eventually. Mothers who have given birth as teens generally remain 2 yr behind their age-matched peers in formal educational attainment at least through their 3rd decade. Maternal lack of education limits the income of many of these young families (see Chapter 1).

Substance Use

See also Chapter 114.

Teenagers who abuse drugs, alcohol, and tobacco have higher pregnancy rates than their peers. Most substance-abusing mothers appear to decrease or stop their substance use while pregnant. Use begins to increase again about 6 mo postpartum, complicating the parenting process and the mother's return to school.

Repeat Pregnancy

In the United States, approximately 20% of all births to adolescent mothers (age 15-19 yr) are second order or higher. Prenatal care is begun even later with a second pregnancy, and the second infant is at higher risk of poor outcome than the first birth. Mothers at risk of early repeat pregnancy include those who do not initiate long-acting contraceptives after the index birth, those who do not return to school within 6 mo of the index birth, those who are married or living with the infant's father, and those who are no longer involved with the baby's father and who meet a new boyfriend who wants to have a child. To reduce repeat pregnancy rates in these teens, programs must be tailored for this population, preferably offering comprehensive healthcare for both the young mother and her child (Table 118-2). Healthcare providers should remember to provide positive reinforcement for teen parenting successes (i.e., compliment teen parents when they are doing a good job).

Behavioral, Educational, and Social Outcomes of Children Born to Teen Mothers

Many children born to teen mothers have behavioral problems that may be seen as early as the preschool period. Many drop out of school early (33%), become adolescent parents (25%), or, if male, are incarcerated (16%). Explanations for these poor outcomes include poverty, parental learning difficulties, negative parenting styles of teen parents, maternal depression, parental immaturity, poor parental modeling, social stress, exposure to surrounding violence, and conflicts with grandparents, especially grandmothers. Continued positive paternal involvement throughout the child's life may be somewhat protective against negative outcomes. Many of these poor outcomes appear to be attributable to the socioeconomic/demographic situation in which the teen pregnancy has occurred, not solely to maternal age. Even when socioeconomic status and demographics are controlled, infants of teen mothers have lower achievement scores, lower high school graduation rates, increased risk of teen births themselves, and, at least in Illinois (where records include age of birth mother), a higher probability of abuse and neglect.

Comprehensive programs focused on supporting adolescent mothers and infants utilizing life skills training, medical care, and psychosocial support demonstrate higher employment rates, higher income, and less welfare dependency in adolescents exposed to the programs.

Prevention of Teen Pregnancies

Adolescent pregnancy is a multifaceted problem that requires multifactorial solutions. The provision of contraception and education about fertility risk from the primary care physician is important, but

Table 118-3	Common Components of Most Successful Evidence-Based Programs to Prevent Teen Pregnancy

- Information is provided about the benefits of abstinence.
- Information is provided about contraception for those who are already sexually active.
- Information is provided about the signs and symptoms of STIs and how to prevent STIs.
- Interactive sessions on peer pressure are presented.
- Teenagers are taught communication skills.
- Programs are tailored to meet the needs of specific groups of young people (young men or young women; cultural groups; younger or older teens; etc.).

Adapted from: Suellentrop K: What works 2011-2012: Curriculum-based programs that help prevent teen pregnancy. The National Campaign to Prevent Teen and Unplanned Pregnancy: Washington, DC. http://www.c-hubonline.org/sites/default/files/resources/main/What_Works_0.pdf.

insufficient to address the problem fully. Family and community involvement are essential elements for teen pregnancy prevention. Strategies for primary prevention (preventing first births) are different from the strategies needed for secondary prevention (preventing second or more births). Over the last 30 yr, many models of teen pregnancy prevention programs have been implemented and evaluated. Table 118-3 lists the common components of many successful evidence-based programs.

Abstinence-only sexual education aims to teach adolescents to wait until marriage to initiate sexual activity but, unfortunately, does not mention contraception. Abstinence education is sometimes coupled with "virginity pledges" in which teenagers pledge to remain abstinent until they marry. Other educational programs emphasize HIV and STI prevention and in the process prevent pregnancy, whereas others include both abstinence and contraception in their curricula. Sex education and teaching about contraception do not lead to an increase in sexual activity. Teenagers who participate in programs that have comprehensive sex education components generally have lower rates of pregnancy than those teenagers who have exposure solely to abstinence-only programs or no sex education at all.

In many U.S. communities, programs that engage youth in community service and/or combine sex education and youth development are also successful in deterring pregnancy. Programs vary in their sites of service from schools, to social agencies, to health clinics, to youth organizations, to churches. Programs must be tailored to the cultural background, ethnicity, age group, and gender of the group being targeted for the prevention services.

Secondary prevention programs are fewer in number. In the United States, some communities have tried to "pay" young mothers to not become pregnant again, but these efforts have not always been fruitful. Home visiting by nurses has been successful in some areas, and many communities have developed "Teen Tot" Clinics that provide a "one-stop shopping model" for healthcare for both the teen mother and the baby in the same site at the same time. Both of these latter types of programs have reported some successes.

In the practice setting, the identification of the sexually active adolescent through a confidential clinical interview is a first step in pregnancy prevention. The primary care physician should provide the teenager with factual information in a nonjudgmental manner and then guide the teenager in the decision-making process of choosing a contraceptive (see Chapter 117). The practice setting is an ideal setting to support the teenager who chooses to remain abstinent. When a teenager does become pregnant and requires prenatal care services, healthcare providers should remember that the pregnant teenager is an adolescent who has become pregnant, not a pregnant woman who happens to be an adolescent.

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Chapter 119

Adolescent Rape

Christine E. Barron and Marianne E. Felice

Rape is an act of violence, not an act of sex. Rape is coercive sexual intercourse involving physical force or psychological manipulation of a female or a male. Rape is defined as penetration of any genital, oral, or anal orifice by a part of the assailant's body or any object.

EPIDEMIOLOGY

Exact figures on the incidence of rape are unavailable because many rapes are not reported. Females exceed males as reported rape victims by 8 : 1 to 10 : 1, but male rape may be more underreported than female rape. In the United States, the annual rates of sexual victimization per 1,000 persons were reported in 2010 by the U.S. Department of Justice, National Crime Victimization Survey to be 4.1 for ages 12-17 yr, and 3.7 for ages 18-34 yr. The highest annual rate of sexual victimization has continued to be among 16-19 yr old adolescents. Rape occurs worldwide and is especially prevalent in war and armed conflicts. The World Health Organization estimates that rape and domestic violence are responsible for 5-16% of healthy years of life lost by females of reproductive age.

Female adolescents and young adults account for the highest rates of rape compared to any other age group. The normal developmental growth tasks of adolescence may contribute to this vulnerability in the following ways: (1) the emergence of independence from parents and the establishment of relationships outside the family may expose adolescents to environments with which they are unfamiliar and situations that they are unprepared to handle; (2) dating and becoming comfortable with one's sexuality may result in activities that are unwanted, but the adolescent is too inexperienced to stop the unwanted actions; and (3) young adolescents may be naïve and more trusting than they should be (see Chapter 110). Many teens are computer competent, which gives sexual perpetrators access to unsuspecting vulnerable populations who were previously beyond their reach. Chat rooms and online dating sites represent a major risk for adolescents, resulting in correspondence with individuals unknown to them or protective family members, while simultaneously providing a false sense of security because of remote electronic communications. A determined perpetrator can obtain specific information to identify the adolescent and arrange for a meeting that is primed for sexual victimization.

Some adolescents are at higher risk of being victims of rape than others (Table 119-1).

TYPES OF RAPE

Acquaintance rape (by a person known to the victim) is the most common form of rape for victims 16-24 yr of age. The acquaintance may be a neighbor, classmate, or friend of the family. The victim–assailant relationship may cause conflicting loyalties in families, and the teen's report may be received with disbelief and/or skepticism by the teen's family. Adolescent acquaintance rape differs from adult acquaintance rape because weapons are less-often used, and victims are less likely to sustain physical injuries. Victims of acquaintance rape are also more likely to delay seeking medical care, may never report the crime (males greater than females), and are less likely to proceed with criminal prosecution even after reporting the incident(s).

Date rape (by a person dating the victim) is often drug facilitated and is prevalent in adolescent populations. Date rape drugs are pharmaceuticals administered in a clandestine manner to potential victims. γ-Hydroxybutyric acid (GHB), flunitrazepam (Rohypnol), and ketamine hydrochloride are the leading agents used for these illegal purposes, but may also include alcohol, benzodiazepines, stimulants, barbiturates, opiates, and other drugs (see Chapter 114). The pharmacologic properties of these drugs make them suitable for this use as they have simple modes of administration, are easily concealed

Table 119-1	Adolescents at High Risk of Rape Victimization
MALE AND FEMALE ADOLESCENTS	
Drug and alcohol users	
Runaways	
Those with intellectual disability or developmental delay	
Street youths	
Transgender youth	
Youths with a parental history of sexual abuse	
PRIMARILY FEMALES	
Survivors of prior sexual assault	
Newcomers to a town or college	
PRIMARILY MALES	
Those in institutionalized settings (detention centers, prison)	
Young male homosexuals	

(colorless, odorless, tasteless), have rapid onsets of action with resulting induction of anterograde amnesia, and have rapid eliminations as a result of short half-lives. Detection of these drugs requires a high index of suspicion and medical evaluation within 8-12 hr, prompting specific testing because routine toxicology screening is insufficient.

Date rape victims are often new to a specific environment (college freshman, newcomer to a town) and lack strong social support. Victims may not be assertive in establishing boundaries or limits with their dates and may be intoxicated when the incident takes place. The date rape assailant may engage in more sexual activities than other men his age and often has a history of aggressive behavior toward women. He may interpret passivity as assent and deny the charge of coercion or force; he may also be intoxicated at the time of the assault.

A date rape victim often experiences long-term issues of trust, self-blame, and guilt. She may lose confidence in her judgment concerning men in the future. She is nearly always ashamed of the incident and is less likely to report the rape. She is reluctant to talk about the rape to family, friends, or a counselor and may never heal from the psychological scars that ensue.

Male rape generally refers to same-sex rape of male teens by other males. Specific subgroups of young men are at high risk of being victims of rape (see Table 119-1). Male rape is most prevalent within institutional settings. Male rape that occurs outside of institutional settings typically involves coercion of the male teen by someone considered an authority figure, either male or female. Male rape victims often experience conflicted sexual identity about whether or not they are homosexual. Issues of loss of control and powerlessness are particularly bothersome for male rape victims, and these young men commonly have symptoms of anxiety, depression, sleep disturbance, and suicidal ideation. Males are less likely than females to report rape and less likely to seek professional help.

Gang rape usually occurs when a group of young men rape a solitary female victim. This type of rape may be part of a ritualistic activity or rite of passage for some male group (gangs, college fraternity) or be displaced rage on the part of the assailants.

Female victims of gang rape may find it difficult to return to the environment in which the rape occurred for fear of confrontation with the assailants (college setting or place of employment) and may insist on moving away from the locale entirely.

Statutory rape refers to sexual activity between an adult and an adolescent under the age of legal consent, as defined by individual state law. Statutory rape laws are based on the premise that below a certain age, an individual is not legally capable of giving consent to engage in sexual intercourse. In some states in the United States, statutory rape laws apply to sexual contact or intercourse occurring between a minor and another individual with a specific age difference even when both are minors and both assert that the sexual act was voluntary (an 18 yr old male who has sexual intercourse with a 14 yr old female). The intent of such laws is to protect youths from being victimized, but they may inadvertently lead a teenager to withhold pertinent sexual information from a clinician for fear that her sexual partner will be reported to the law. A clinician must be familiar with the laws of the state or province in which the clinician is practicing medicine.

Stranger rape occurs less frequently within the adolescent population and is most similar to adult rape. Such rapes frequently occur with an abduction, use of weapons, and increased risk of physical injuries. These rapes are more likely to be reported and prosecuted.

CLINICAL MANIFESTATIONS

The adolescent's acute presentation following a rape may vary considerably, from histrionics to near-mute withdrawal. Even if they do not seem to be afraid, most victims are extremely fearful and very anxious about the incident, the rape report, examination, and the entire process including potential repercussions. Because adolescents are between the developmental lines of childhood and adulthood, their responses to rape may have elements of both child and adult behaviors. Many teens, particularly young adolescents, may experience some level of cognitive disorganization.

Adolescents may be reluctant to report rape for a variety of reasons, including self-blame, fear, embarrassment, or in the circumstances of drug-facilitated rape, uncertainty of event details. Adolescent victims, unlike child victims who elicit sympathy and support, are often faced with intense scrutiny regarding their credibility and inappropriately misplaced societal blame for the assault. This view is baseless and should not be used during an evaluation of any teenage victim, including acquaintance rape.

When adolescents do not report a rape, they may present at a future date with symptoms of posttraumatic stress disorder (see Chapters 25 and 39), such as sleep disturbances, nightmares, mood swings, and flashbacks. Other teens may present with psychosomatic complaints or difficulties with schoolwork; all adolescents should be screened for the possibility of sexual abuse at nearly all health examination visits.

INTERVIEW AND PHYSICAL EXAMINATION

Although many teens delay seeking medical care, others present to a medical facility within 72 hr (or up to 96 hr depending on the protocol used) of the rape, at which time forensic evidence collection should be completed. Experienced clinicians with training and knowledge of forensic evidence collection and medical-legal procedures should complete the rape evaluation or supervise the evaluation when possible.

The clinician's responsibilities are to provide support, to obtain the history in a nonjudgmental manner, to conduct a complete examination without retraumatizing the victim, and to collect forensic evidence. The clinician must complete laboratory testing, administer prophylaxis treatment for sexually transmitted infections (STIs) and emergency contraception, arrange for counseling services, and file a report to appropriate authorities. It is not the clinician's responsibility to decide whether a rape has occurred; the legal system will make that determination.

Ideally, a clinician trained in forensic interviewing should obtain the history. In all cases, the history should be obtained by asking *only* open-ended questions to obtain information about: (1) what happened; (2) where did it happen; (3) when did it happen; and (4) who did it. After obtaining a concise history including details of the physical contact that occurred between the victim and the assailant, the clinician should conduct a thorough and complete physical examination and document all injuries. Clinicians should provide sensitive, nonjudgmental support during the entire evaluation, as the adolescent victim has experienced a major trauma and is susceptible to retraumatization during this process. Each component of the evaluation should be explained in detail to the victim, allowing the adolescent as much control as possible, including refusal to complete any part or all of the forensic evidence collection process. It is often useful to permit a trusted supportive person, such as a family member, friend or rape crisis advocate, to be present during the evaluation if that is the adolescent's wish.

The examining clinician should be familiar with the **forensic evidence collection** kit prior to initiating the examination. In the United States, each state's forensic evidence kit is different, but most include

Table 119-2 Laboratory Data for Evaluation of Rape Victims

WITHIN 8-12 HR (IF INDICATED BY HISTORY) Urine and blood for date rape drugs (GHB, Rohypnol, and ketamine) Comprehensive toxicology screen (for other classes of drugs)
WITHIN 72 HR (OR UP TO 96 HR DEPENDING ON THE PROTOCOL USED) Forensic evidence kit Urinalysis Pregnancy test Hepatitis B screen Syphilis (rapid plasma reagin [RPR], Venereal Disease Research Laboratory [VDRL]) Herpes simplex virus titers (I and II) HIV Wet mount for the detection of spermatozoa, *Trichomonas vaginalis*, and bacterial vaginosis Cultures obtained based on history of physical contact for: Oropharynx: *Neisseria gonorrhoeae* Rectal: *N. gonorrhoeae* and *Chlamydia* Urethral (male): *N. gonorrhoeae* and *Chlamydia* Endocervical (female): *N. gonorrhoeae* and *Chlamydia*

Table 119-3 Prophylaxis Treatment for Rape Victims

*Neisseria gonorrhoeae**	Ceftriaxone 250 mg IM × 1 dose If positive for gonorrhea, treatment is: Ceftriaxone 20 mg IM × 1 dose **plus** Azithromycin 1 g PO × 1 dose *or* doxycycline 10 mg PO bid × 7 days
*Chlamydia trachomatis**	Azithromycin 1 g PO × 1 dose or Doxycycline 100 mg PO bid × 7 days
Trichomonas vaginalis and bacterial vaginosis*	Metronidazole 2 g PO × 1 dose
HIV†	Combivir 1 tab PO bid × 28 days or Truvada 1 tab PO qd x 28 days
Hepatitis B	Complete immunizations
Human papillomavirus	Complete immunizations
Emergency contraception‡	Ovral 2 tabs (0.05 mg ethinyl estradiol, 0.50 mg norgestrel) and 2nd dose in 12 hr Plan B 1 tab (0.75 mg levonorgestrel) and 2nd dose in 12 hr, or both pills together as 1 dose

*Prophylaxis is recommended for all 3 STIs.
†HIV postexposure prophylaxis is provided for patients with penetration and when the assailant is known to be HIV-positive or at high risk because of a history of incarceration, intravenous drug use, or multiple sexual partners. If provided, follow-up must be arranged.
‡Provided for patients with negative urine pregnancy screen for patients receiving emergency contraception medication other than Plan B. In addition, provide antiemetic (Compazine, Zofran) for patients receiving emergency contraception medication other than Plan B.

some or all of the following components: forensic evidence of semen deposits detected by a fluorescent lamp with a wavelength near 490 nm (many Woods lamps are inadequate); swabs of bite mark impressions to collect genetic markers (DNA, ABO group); swabs of any penetrated orifice; and documentation of acute cutaneous injuries using body diagram charts and/or photographs with visible standard measurements. Areas of restraint should be carefully inspected for injuries; these areas include extremities, neck, and the inner aspect of the oral mucosa where a dentition impression may be seen.

The genital examination of a female rape victim should be undertaken with the patient in the lithotomy position. The genital examination of a male rape victim should be undertaken with the patient in supine position. The clinician's examination should include careful inspection of the entire pelvic, genital, and perianal areas. The clinician should document any acute injuries such as edema, erythema, petechiae, hemorrhage, or tearing. Aqueous solution of toluidine blue (1%), which adheres to nucleated cells, may be used during the acute examination to improve visualization of microtrauma in the perianal area. Additionally, a colposcope may be used to provide magnification and photodocumentation of injuries.

LABORATORY DATA

The forensic evidence kit should be completed when clinically indicated and if the patient is evaluated within 72-92 hr of sexual assault. Table 119-2 lists additional laboratory studies required during initial evaluation. Follow-up evaluations should be scheduled to repeat these laboratory studies.

TREATMENT

Medical treatment includes prophylaxis treatment for STIs (see Chapter 120) and emergency contraception (see Chapter 117). The Centers for Disease Control and Prevention estimates that the risk for acquiring STIs following a sexual assault in adults is 6-12% for *Neisseria gonorrhoeae,* 4-17% for *Chlamydia trachomatis,* and 0.5-3.0% for syphilis. Antimicrobial prophylaxis is recommended for adolescent rape victims because of the risk of acquiring an STI and the risk of pelvic inflammatory disease (Table 119-3). HIV postexposure prophylaxis should be considered and consultation with an infectious disease specialist sought if higher transmission risk factors are identified (e.g., knowing that the perpetrator is HIV-positive, significant mucosal injury of the victim) to prescribe a triple antiretroviral regimen. Clinicians should review the importance for patient's compliance with medical and psychological treatment and follow-up.

At the time of presentation, the clinician should address the need for follow-up care, including psychological counseling. Adolescent victims are at increased risk of posttraumatic stress disorder, depression, self-abusive behaviors, suicidal ideation, delinquency, substance abuse, eating disorders, and sexual revictimization. It is important for the adolescent victim and parents to understand the value of timely counseling services to decrease these potential long-term sequelae. Counseling services should be arranged during the initial evaluation, with follow-up arranged with the primary care physician to improve compliance. Counseling services for family members of the victim may improve their ability to provide appropriate support to the adolescent victim. Caution parents not to use the assault as a validation of their parental guidance, as it will only serve to place blame inappropriately on the adolescent victim.

PREVENTION

Primary prevention may be accomplished through education of preadolescents and adolescents on the issues of rape, healthy relationships, Internet dangers, and drug-facilitated rape. Prevention messages should be targeted to both males and females at high schools and colleges. Particular emphasis on prevention efforts during college orientation is highly recommended. High-risk situations that may increase the likelihood of a sexual assault (use of drugs or alcohol) should be discouraged. **Secondary prevention** includes informing adolescents of the benefits of timely medical evaluations when rape has occurred. Individual clinicians should ask adolescents about past experiences of forced and unwanted sexual behaviors and offer help in dealing with those experiences. The importance of prevention cannot be overstated because adolescents are disproportionately affected by rape and they are particularly vulnerable to long-term consequences.

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Chapter 120

Sexually Transmitted Infections

Gale R. Burstein

Age-specific rates of many sexually transmitted infections (STIs) are highest among sexually experienced adolescents and young adults, after controlling for sexual activity. Although some STI pathogens present as STI syndromes with a specific constellation of symptoms, most are asymptomatic and only detected by a laboratory test. The approach to prevention and control of these infections lies in education, screening, and early diagnosis and treatment.

ETIOLOGY

Any adolescent who has had oral, vaginal, or anal sexual intercourse is at-risk for acquiring an STI. Not all adolescents are at equal risk; physical, behavioral, and social factors contribute to the adolescent's higher risk (Table 120-1). Adolescents who initiate sex at a younger age, youth residing in detention facilities, youth attending sexually transmitted diseases clinics, young men having sex with men, and youth who are injecting-drug users are at higher risk for STIs. Risky behaviors, such as sex with multiple concurrent partners or multiple sequential partners of limited duration, failure to use barrier protection consistently and correctly, and increased biologic susceptibility to infection, also contribute to risk. Although all 50 states and the District of Columbia explicitly allow minors to consent for their own sexual health services, many adolescents encounter multiple obstacles to accessing this care. Adolescents who are victims of sexual assault may not consider themselves "sexually active," given the context of the encounter, and need reassurance, protection, and appropriate intervention when these circumstances are uncovered (see Chapter 119).

EPIDEMIOLOGY

STI prevalence varies by age, gender, and race/ethnicity. In the United States, although adolescents and young adults ages 15-24 yr represent 25% of the sexually experienced population, this age group accounts for nearly 50% of all incident STIs each year. Adolescents and young adults <25 yr of age have the highest reported prevalence of gonorrheal (see Chapter 192) and chlamydial (see Chapter 226) infection; among females and males, rates are highest in the 15-24 yr old age groups (Fig. 120-1). In 2012, females 20-24 yr of age had the highest reported chlamydia rate (3,696 per 100,000 population), followed by females 15-19 yr of age (3,293 per 100,000 population). The reported 2012 chlamydia rate for 15-19 yr old females was more than 4 times higher than for 15-19 yr old males. Chlamydia is common among all races and ethnic groups; Blacks, Native American/Alaska Native, and Hispanic females are disproportionately affected. In 2011, non-Hispanic black females 20-24 yr of age had the highest chlamydia rate of any group (7,863), followed by black females 15-19 yr of age (7,719). Data from the 2007-2008 National Health and Nutrition Examination Survey estimated the prevalence of chlamydia among the U.S. population was highest among African-Americans (Fig. 120-2).

Reported rates of other bacterial STIs are also high among adolescents and young adults. In 2012, 20-24 yr old females had the highest (579 per 100,000 population) and 15-19 yr old females had the second highest gonorrhea rates (521 per 100,000 population) compared to any other age/sex group (see Chapter 192). Following a period of decreasing gonorrhea rates among 20-24 yr old, rates have increased for the past 3 yr. Primary and secondary syphilis rates among 15-19 yr old

Table 120-1	Circumstances Contributing to Adolescents' Susceptibility to Sexually Transmitted Infections
PHYSICAL Younger age at puberty Cervical ectopy Smaller introitus leading to traumatic sex Asymptomatic nature of sexually transmitted infection Uncircumcised penis	
BEHAVIOR LIMITED BY COGNITIVE STAGE OF DEVELOPMENT Early adolescence: have not developed ability to think abstractly Middle adolescence: develop belief of uniqueness and invulnerability	
SOCIAL FACTORS Poverty Limited access to "adolescent friendly" healthcare services Adolescent health-seeking behaviors (forgoing care because of confidentiality concerns or denial of health problem) Sexual abuse and violence Homelessness Young adolescent females with older male partners	

From Shafii T, Burstein G: An overview of sexually transmitted infections among adolescents, Adolesc Med Clin *15:207, 2004.*

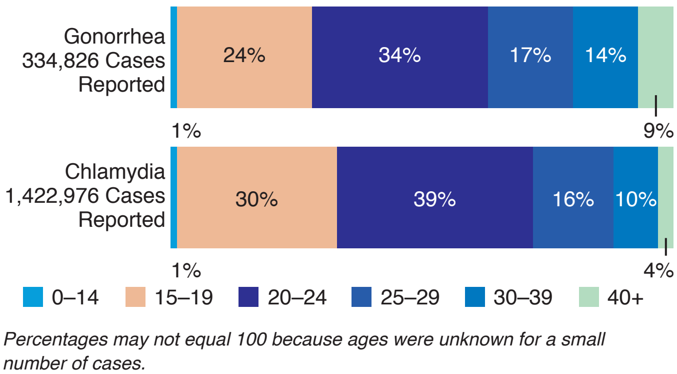

Figure 120-1 Most reported chlamydia and gonorrhea infections occur among 15-24-year-olds. *(Adapted from Centers for Disease Control and Prevention: Reported STD in the United States. http://www.cdc.gov/nchhstp/newsroom/docs/STD-Trends-508.pdf.)*

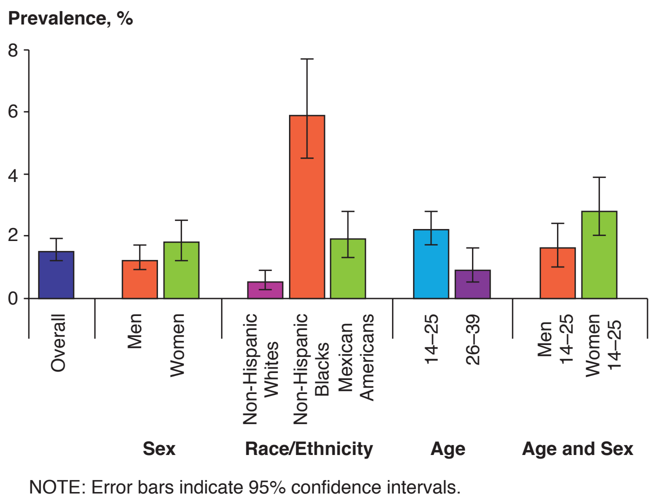

Figure 120-2 Chlamydia–prevalence among persons 14-39 yr of age by sex and survey cycle, National Health and Nutrition Examination Survey, 1999-2008. *(Adapted from Centers for Disease Control and Prevention: Sexually Transmitted Disease Surveillance 2012. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6338a3.htm.)*

females have decreased annually since 2009 from 3.3 cases per 100,000 population to 2.3 per 100,000 population in 2012 (see Chapter 218). Rates among females have been the highest each year in the 20-24 yr age group (3.9 cases per 100,000 population in 2012). Primary and secondary syphilis rates among 15-19 yr old males are much lower than those in older males, although rates among males age 20-24 yr have increased consecutively since 2002, from 5.2 cases per 100,000 males to 23.4 cases in 2011. Males age 20-24 yr also have had the highest rate of primary and secondary syphilis among males of any age group since 2008. Pelvic inflammatory disease (PID) rates are highest in females age 15-24 yr when compared to older women.

Adolescents also suffer from a large burden of viral STIs. Young people in the United States are at persistent risk for HIV infection (see Chapter 278). In 2009, youths age 13-24 yr, who represented 21% of the U.S. population, comprised 7% of persons living with HIV. In 2010, 26% of the estimated 47,500 new HIV infections were among 13-24 yr olds. Of those new infections, 57% were among blacks, 20% among Hispanic/Latinos, and 20% among whites. Nearly 75% of the 12,200 new HIV infections among youths were attributable to male-to-male sexual contact. Only a low percentage of youths have been tested for HIV, and 60% of youths with HIV are unaware of their infection.

The STI with the highest estimated incidence in the United States is human papillomavirus (HPV). The 2003-2006 National Health and Nutrition Examination Survey (NHANES) found a third of females age 14-24 yr old were actively infected with HPV. The highest HPV infection prevalence was among females age 20-24 yr (54%; 95% confidence interval [CI], 46-62%; see Chapter 266). Although HPV infection is common, studies suggest approximately 90% of infections clear within 2 yr.

Herpes simplex virus-2 (HSV-2) is the most prevalent viral STI (see Chapter 252). HSV-2 prevalence rates among adolescents in the United States and young adults appear to be decreasing. The 2005-2008 NHANES estimated that 1.4% (95% CI, 1.0-2.0) of adolescents age 14-19 yr are infected with HSV-2, which is about a 76% decrease observed from the 1988-1994 NHANES and 10.5% (95% CI, 9.0-12.3) of 20-29 yr olds are HSV-2 seropositive, which is a 39% decrease compared to the 1988-1994 NHANES.

Pathogenesis

During puberty, increasing levels of estrogen cause the vaginal epithelium to thicken and cornify and the cellular glycogen content to rise, the latter causing the vaginal pH to fall. These changes increase the resistance of the vaginal epithelium to penetration by certain organisms (including *Neisseria gonorrhoeae*) and increase the susceptibility to others (*Candida albicans* and *Trichomonas;* see Chapter 284). The transformation of the vaginal cells leaves columnar cells on the ectocervix, forming a border of the 2 cell types on the ectocervix, known as the squamocolumnar junction. The appearance is referred to as **ectopy** (Fig. 120-3). With maturation, this tissue involutes. Prior to involution, it represents a unique vulnerability to infection for adolescent females. A 15 yr old sexually active female with endocervical colonization has a 1 : 8 chance of developing PID compared to the 1 : 80 chance for a 24 yr old. As a result of these physiologic changes, gonococcal infection becomes primarily cervical and susceptibility to ascending infection is greatest during menses, when the pH is 6.8-7.0. The association of early sexual debut and younger gynecologic age with increased risk of STIs supports this explanation of the pathogenesis of infection in young adolescents.

Figure 120-3 Cervical ectopy. *(From the Seattle STD/HIV Prevention Training Center at the University of Washington, Claire E. Stevens.)*

Sexually Transmitted Infection Screening

Early detection and treatment are the primary STI control strategies. Some of the most common STIs in adolescents, including HPV, HSV, chlamydia, and gonorrhea, are usually asymptomatic and if undetected can be spread inadvertently by the infected host. Screening initiatives for chlamydial infections have demonstrated reductions in PID cases by up to 40%. Although federal and professional medical organizations recommend annual chlamydia screening for sexually active females 25 yr and younger, according to the National Center for Quality Assurance, in 2012 approximately 40% of commercially insured and 54% of Medicaid insured 16-20 yr old sexually active females were tested for chlamydia during the previous year. The lack of a dialog about STIs or the provision of STI services at annual preventive service visits to adolescents who are sexually experienced are missed opportunities for screening and education. Comprehensive, confidential, reproductive health services, including STI screening, should be offered to all sexually experienced adolescents (Table 120-2).

Definitions, Etiology, and Clinical Manifestations

STI syndromes are generally characterized by the location of the manifestation (vaginitis) or the type of lesion (genital ulcer). Certain constellations of presenting symptoms suggest the inclusion of a possible STI in the differential diagnosis.

Urethritis

Urethritis is an STI syndrome characterized by inflammation of the urethra, usually caused by an infectious etiology. Urethritis may present with urethral discharge, dysuria, urethral irritation, or meatal pruritus. Urgency, frequency of urination, erythema of the urethral meatus, and urethral pain or burning are less common clinical presentations. Approximately 30-50% of males are asymptomatic but may have signs of discharge on diagnosis. On examination, the classic finding is mucoid or purulent discharge from the urethral meatus (Fig. 120-4). If no discharge is evident on exam, providers may attempt to express discharge by applying gentle pressure to the urethra from the base distally to the meatus 3-4 times. *Chlamydia trachomatis* and *N. gonorrhoeae* are the most commonly identified pathogens. *Mycoplasma genitalium* has been associated with urethritis, but data supporting *Ureaplasma urealyticum* have been inconsistent. *Trichomonas vaginalis* can cause NGU, but the prevalence varies. HSV-1, HSV-2, and Epstein-Barr virus are also potential urethritis pathogens in some cases. Sensitive diagnostic *C. trachomatis* and *N. gonorrhoeae* tests are available for the evaluation of urethritis. However, other pathogens can be considered when NGU is not responsive to treatment, although commercial diagnostic tests are not available for males. Noninfectious causes of urethritis include urethral trauma or foreign body. Unlike in females, urinary tract infections are rare in males who have no genitourinary medical history. In the typical sexually active adolescent male, dysuria and urethral discharge suggest the presence of an STI unless proven otherwise.

Epididymitis

The inflammation of the epididymis in adolescent males is most often associated with an STI, most frequently *C. trachomatis* or *N. gonorrhoeae*. The presentation of unilateral scrotal swelling and tenderness, often accompanied by a hydrocele and palpable swelling of the epididymis, associated with the history of urethral discharge, constitute the presumptive diagnosis of epididymitis. Males who practice insertive

Table 120-2 Routine Laboratory Screening Recommendations for Sexually Transmitted Infections in Sexually Active Adolescents and Young Adults

Chlamydia trachomatis and *Neisseria gonorrhoeae* • Routinely screening for *C. trachomatis* of all sexually active females aged ≤25 yr is recommended annually • Consider screening for C. trachomatis of sexually active adolescent and young adult males annually who have a history of multiple partners in settings with high prevalence rates, such as jails or juvenile corrections facilities, national job training programs, STD clinics, high school clinics, or adolescent clinics • Routinely screening for *N. gonorrhoeae* of all sexually active females age <25 yr is recommended annually • Routinely screen sexually active adolescent and young adult MSM for rectal and urethral chlamydia and gonorrhea annually if they engage in receptive anal or insertive intercourse, respectively, and for routine gonorrhea if they engage in receptive oral sex. More frequent STD screening (i.e., at 3-6 mo intervals) is indicated for MSM who have multiple or anonymous partners or who have sex in conjunction with illicit drug use
HIV • HIV screening should be discussed and offered to all adolescents ≥15 yr in healthcare settings, unless identified at an earlier age with HIV risk factors
SYPHILIS • Syphilis screening should be offered to sexually active adolescents reporting risk factors • The majority of U.S. syphilis cases occurring among young MSM and many early syphilis cases are identified from correctional facilities • Providers should consult with their local health department regarding local syphilis prevalence and associated risk factors that are associated with syphilis acquisition
HEPATITIS C VIRUS • Screening adolescents for hepatitis C virus who report risk factors, i.e., injection drug use, MSM, received blood products or organ donation before 1992, received clotting factor concentrates before 1987, long-term hemodialysis, or high prevalence setting, i.e., correctional facilities or STD clinics

HAV, hepatitis A virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; MSM, men who have sex with men; STD, sexually transmitted diseases.

From Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2014, MMWR *http://www.cdc.gov/std/treatment/update.htm.*

Figure 120-4 Gonococcal urethral discharge. *(From the Seattle STD/HIV Prevention Training Center at the University of Washington, Connie Celum and Walter Stamm.)*

anal intercourse are also vulnerable to *Escherichia coli* infection. Testicular torsion, a surgical emergency usually presenting with sudden onset of severe testicular pain, should be considered in the differential diagnosis (see Chapter 545). The evaluation for epididymitis should include obtaining evidence of urethral inflammation by physical exam, Gram stain of urethral secretions, urine leukocyte esterase test, or urine microscopy. A *C. trachomatis* and *N. gonorrhoeae* **nucleic acid amplification test (NAAT)** should be performed.

Vaginitis

Vaginitis is a superficial infection of the vaginal mucosa frequently presenting as a vaginal discharge, with or without vulvar involvement (see Chapter 549). **Bacterial vaginosis, vulvovaginal candidiasis**, and trichomoniasis are the predominant infections associated with vaginal discharge. Bacterial vaginosis is replacement of the normal H_2O_2–producing *Lactobacillus* sp. vaginal flora by an overgrowth of anaerobic microorganisms as well as *Gardnerella vaginalis, Ureaplasma*, and *Mycoplasma*. Although bacterial vaginosis is not categorized as an STI, sexual activity is associated with increased frequency of vaginosis. Vulvovaginal candidiasis, usually caused by *C. albicans*, can trigger vulvar pruritus, pain, swelling, and redness and dysuria. Findings on vaginal exam include vulvar edema, fissures, excoriations, or thick curdy vaginal discharge. Trichomoniasis is caused by the protozoan *T. vaginalis*. Infected females may present with symptoms characterized by a diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation or may be diagnosed by screening an asymptomatic patient. Cervicitis can sometimes cause a vaginal discharge. Laboratory confirmation is recommended because clinical presentations may vary and patients may be infected with more than 1 pathogen.

Cervicitis

The inflammatory process in cervicitis involves the deeper structures in the mucous membrane of the cervix uteri. Vaginal discharge can be a manifestation of cervicitis, however, cervicitis frequently is asymptomatic, Patients also commonly present with complaints of irregular or postcoital bleeding. Two major diagnostic signs characterize cervicitis: (1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (e.g., swab sign, Fig. 120-5), commonly referred to as mucopurulent cervicitis or cervicitis, and (2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os signifying friability. Cervical changes associated with cervicitis must be distinguished from cervical ectopy in the younger adolescent to avoid the over diagnosis of inflammation (Fig. 120-6; see Fig. 120-3). The pathogens identified most commonly with cervicitis are *C. trachomatis* and *N. gonorrhoeae,* although no pathogen is identified in the majority of cases. HSV is a less-common pathogen associated with ulcerative and necrotic lesions on the cervix.

Figure 120-5 Mucopurulent cervical discharge positive swab test. *(From Seattle STD/HIV Prevention Training Center at the University of Washington, Claire E. Stevens and Ronald E. Roddy. Available at:* http://www2a.cdc.gov/stdtraining/ready-to-use/pid.htm.*)*

Figure 120-6 Inflamed cervix caused by gonococcal cervicitis. *(From Centers for Disease Control and Prevention:* STD clinical slides. http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm.*)*

Pelvic Inflammatory Disease

PID encompasses a spectrum of inflammatory disorders of the female upper genital tract, including endometritis, salpingitis, tuboovarian abscess, and pelvic peritonitis, usually in combination rather than as separate entities. *N. gonorrhoeae* and *C. trachomatis* predominate as the involved pathogenic organisms in younger adolescents, although PID should be approached as multiorganism etiology, including pathogens such as anaerobes, *G. vaginalis*, *Haemophilus influenzae*, enteric Gram-negative rods, and *Streptococcus agalactiae.* In addition, cytomegalovirus (see Chapter 255), *Mycoplasma hominis*, *U. urealyticum*, and *M. genitalium* (see Chapter 224) may be associated with PID.

PID is difficult to diagnose because of the wide variation in the symptoms and signs. Many females with PID have subtle or mild symptoms resulting in many unrecognized cases. Healthcare providers should consider the possibility of PID in young sexually active females presenting with vaginal discharge and/or abdominal pain.

The clinical diagnosis of PID is based on the presence of at least 1 of the minimal criteria, either cervical motion tenderness, uterine tenderness, or adnexal tenderness, to increase the diagnostic sensitivity and reduce the likelihood of missed or delayed diagnosis. Providers should also consider that adolescents are the population in which PID is typically diagnosed and thus should have a low threshold for initiating empiric treatment. In addition, the majority of females with PID have either mucopurulent cervical discharge or evidence of white blood cell (WBC) on a microscopic evaluation of a vaginal fluid saline preparation. If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely, and alternative causes of pain should be investigated. Specific, but not always practical, criteria for PID include evidence of endometritis on biopsy, transvaginal sonography or MRI evidence of thickened, fluid-filled tubes, or Doppler evidence of tubal hyperemia or laparoscopic evidence of PID.

Genital Ulcer Syndromes

An ulcerative lesion in a mucosal area exposed to sexual contact is the unifying characteristic of infections associated with these syndromes. These lesions are most frequently seen on the penis and vulva, but also occur on oral and rectal mucosa depending on the adolescent's sexual practices. HSV and *Treponema pallidum* (syphilis) are the most common organisms associated with genital ulcer syndromes.

Genital herpes, the most common ulcerative STI among adolescents, is a chronic, lifelong viral infection. Two sexually transmitted HSV types have been identified, HSV-1 and HSV-2. The majority of cases of recurrent genital herpes are caused by HSV-2. However, among young women and men who have sex with men, an increasing proportion of anogenital herpes has been HSV-1. Most HSV-2–infected persons are unaware of their diagnosis because they experience mild or unrecognized infections but continue to shed virus intermittently in the genital tract. Therefore, the majority of genital herpes infections are transmitted by asymptomatic persons who are unaware of their infection.

Although the initial herpetic lesion is a vesicle, by the time the patient presents clinically, the vesicle most often has ruptured spontaneously, leaving a shallow, painful ulcer (Fig. 120-7*A*) although recurrences are generally less intense and painful (Fig. 120-7*B*). Up to 50% of first genital herpes episodes are caused by HSV-1, but recurrences and subclinical shedding are much more frequent for genital HSV-2 infection.

Syphilis is a less common cause of genital ulcers in adolescents than in adults. Lymphogranuloma venereum caused by *C. trachomatis* serovars L1-L3 is uncommon, although outbreaks do occur in men who have sex with men (MSM). In these circumstances, proctitis or proctocolitis is the usual manifestation. HIV is often present in affected men. Unusual infectious causes of genital, anal, or perianal ulcers in the United States and other industrialized countries include chancroid and donovanosis.

Clinical characteristics differentiating the lesions of the most common infections associated with genital ulcers are presented in Table 120-3, along with the required laboratory diagnosis to identify the causative agent accurately. The differential diagnosis includes Behçet disease (see Chapter 161), Crohn disease (see Chapter 336), aphthous ulceration, and **acute genital ulcers** caused by cytomegalovirus (see Chapter 255) or Epstein-Barr virus (see Chapter 254). Acute genital ulcers often follow a flu or mononucleosis-like illness in an immunocompetent female and is unrelated to sexual activity. The lesions are 0.5-2.5 cm in size, bilateral, symmetric, multiple, painful, and necrotic, and are associated with inguinal lymphadenopathy. This primary infection is also associated with fever and malaise. The diagnosis may require Epstein-Barr virus titers, or polymerase chain reaction (PCR) testing. Treatment is supportive care including pain management.

Genital Lesions and Ectoparasites

Lesions that present as outgrowths on the surface of the epithelium and other limited epidermal lesions are included under this categorization of syndromes. HPV can cause genital warts and genital cervical abnormalities that can lead to cancer. Genital HPV types are classified according to their association with cervical cancer. Infections with low-risk types, such as HPV types 6 and 11, can cause benign or low-grade changes in cells of the cervix, genital warts, and recurrent

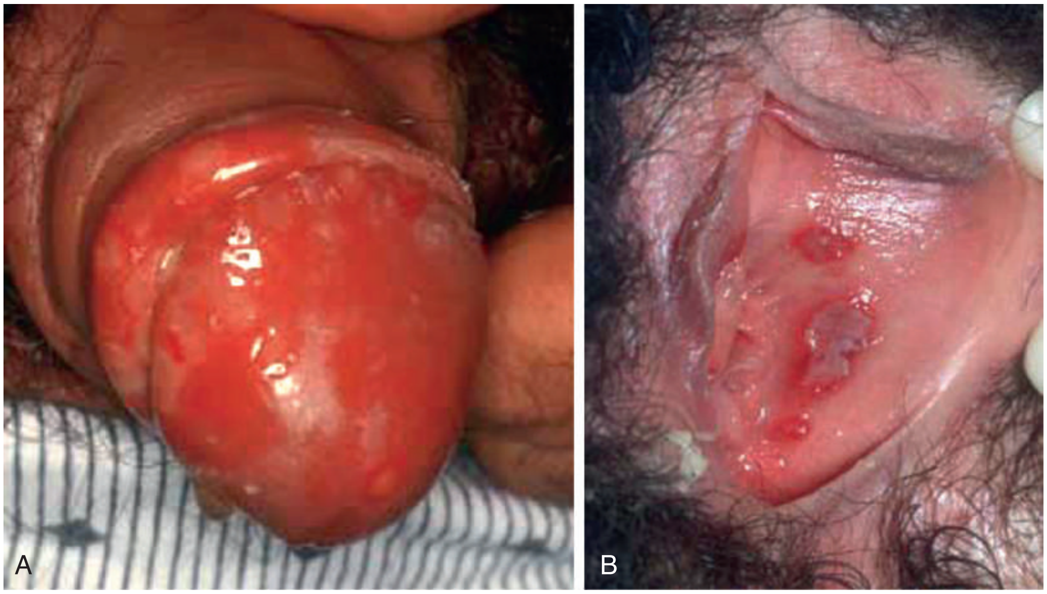

Figure 120-7 *A,* Initial herpes infection showing multiple erosions with polycyclic outlines surrounded by an erythematous halo and associated with intense pain. *B,* Erosions surrounded by an erythematous halo. Clinical signs and symptoms of recurrences are usually less intense than those of initial infection. *(From Martín JM, Villalón G, Jordá E. Update on treatment of genital herpes.* Actas Dermosifiliogr *100:22–32, 2009. Figs 1 & 2.)*

Table 120-3 Signs, Symptoms, and Presumptive and Definitive Diagnoses of Genital Ulcers

SIGNS/SYMPTOMS	HERPES SIMPLEX VIRUS	SYPHILIS (PRIMARY)	CHANCROID
Ulcers	Vesicles rupture to form shallow ulcers	Ulcer with well-demarcated indurated borders and a clean base (chancre)	Unindurated and undermined borders and a purulent base
Painful	Painful	Painless*	Painful
Number of lesions	Usually multiple	Usually single	Multiple
Inguinal lymphadenopathy	First-time infections may cause constitutional symptoms and lymphadenopathy	Usually mild and minimally tender	Unilateral or bilateral painful adenopathy in >50% Inguinal bubo formation and rupture may occur
Clinical suspicion	Typical lesions; positive HSV-2 type-specific serology test	Early syphilis: a typical chancre plus a reactive nontreponemal test (RPR, VDRL) and no history of syphilis or a 4-fold increase in a quantitative nontreponemal test in a person with a history of syphilis; positive treponemal EIA with reactive nontreponemal test (RPR, VDRL) and no prior history of syphilis treatment	Exclusion of other causes of ulcers in the presence of (a) typical ulcers and lymphadenopathy, (b) a typical Gram stain and a history of contact with a high-risk individual (prostitute) or living in an endemic area
Definitive diagnosis	Detection of HSV by culture or PCR from ulcer scraping or aspiration of vesicle fluid	Identification *Treponema pallidum,* from a chancre or lymph node aspirate, on dark-field microscopy	Detection of *Haemophilus ducreyi* by culture

*Primary syphilitic ulcers may be painful if they become coinfected with bacteria or 1 of the other organisms responsible for genital ulcers.

DFA, direct fluorescent antibody; EIA, enzyme immunoassay; HSV, herpes simplex virus; PCR, polymerase chain reaction test: RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

Data from Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2014, MMWR *http://www.cdc.gov/std/treatment/update.htm*.

respiratory papillomatosis. High-risk HPV types can cause cervical, anal, vulvar, vaginal, and head and neck cancers. High-risk HPV types 16 and 18 are detected in approximately 70% of cervical cancers. Persistent infection increases the risk of cervical cancer. Molluscum contagiosum and condyloma lata associated with secondary syphilis complete the classification of genital lesion syndromes. As a result of the close physical contact during sexual contact, common ectoparasitic infestations of the pubic area occur as pediculosis pubis or the papular lesions of scabies (see Chapter 668).

HIV Disease and Hepatitis B

HIV and hepatitis B present as an asymptomatic, unexpected occurrences in most infected adolescents. High vaccination coverage rates among infants and adolescents have resulted in substantial declines in acute hepatitis B incidence among U.S.-born adolescents. Risk factors identified in the history or routine screening during prenatal care are much more likely to result in suspicion of infection, leading to the appropriate laboratory screening, than are clinical manifestations in this age group (see Chapters 276 and 358).

Diagnosis

Most commonly, adolescents infected with viral and bacterial STI pathogens do not report symptoms suggestive of infection. With the increased use of very sensitive, noninvasive chlamydia and gonorrhea **NAAT**, providers are finding that most genital infections in females as well as many males are asymptomatic. A thorough sexual history is key to identifying adolescents who should be screened for STIs and for identifying those who require a laboratory diagnostic evaluation for a sexually transmitted disease syndrome.

When eliciting a sexual health history, discussions should be appropriate for the patient's developmental level. In addition to questions regarding vaginal or urethral discharge, genital lesions, and lower abdominal pain among females, one should ask about prior treatment of any STI symptoms, including self-treatment using nonprescription medications. **Dyspareunia** is a consistent symptom in adolescents with PID. Providers must ask about oral or anal sexual activity to determine sites for specimen collection.

Urethritis should be objectively documented by evidence of inflammation or infectious etiology. Patient complaint without objective clinical or laboratory evidence does not fulfill diagnostic criteria. Inflammation can be documented by (a) observing urethral mucopurulent discharge, (b) ≥2 WBC per high-power field on microscopic examination Gram stain urethral secretions, (c) urine microscopic findings of ≥10 WBCs per high power field of first-void urine specimen, or (d) a positive urine leucocyte esterase test of a (first-void urine) specimen. Laboratory evaluation is essential to identify the involved pathogens to determine treatment, partner notification, and disease control. *C. trachomatis* and *N. gonorrhoeae* NAATs of a urine specimen are recommended. The presence of Gram-negative intracellular diplococci on microscopy obtained from a male urethral specimen confirms the diagnosis of gonococcal urethritis.

An essential component of the diagnostic evaluation of vaginal, cervical or urethral discharge is a chlamydia and gonorrhea NAAT. NAATs are the most sensitive chlamydia and gonorrhea tests available and are licensed for use with urine, urethral, vaginal, and cervical specimens. Many of the chlamydia NAATs are approved by the Food and Drug Administration (FDA) to test patient-collected vaginal swabs in the clinical setting and liquid cytology specimens. Female vaginal swab specimens and male first-void urine are considered the optimal specimen types. Female urine remains an acceptable chlamydia and gonorrhea NAAT specimen, but may have slightly reduced performance when compared with cervical or vaginal swab specimens. Urine is the recommended specimen for male urethral infection. Gonorrhea and chlamydia NAATs perform well on rectal and oropharyngeal specimens and can be performed by clinical laboratories that have completed the appropriate verification studies to obtain Clinical Laboratory Improvement Amendments (CLIA)-approval, which include most commercial laboratories.

Evaluation of adolescent females with vaginitis includes laboratory data. Traditionally, the cause of vaginal symptoms was determined by pH and microscopic examination of the discharge. However, newer CLIA-waived point-of-care vaginitis tests are available. Using pH paper, an elevated pH (i.e., >4.5) is common with bacterial vaginosis or trichomoniasis. For microscopic exam, a slide can be made with the discharge diluted in 1-2 drops of 0.9% normal saline solution and another slide with discharge diluted in 10% potassium hydroxide (KOH) solution. Examining the saline specimen slide under a microscope may reveal motile or dead *T. vaginalis* or *clue cells* (epithelial cells with borders obscured by small bacteria), which are characteristic of bacterial vaginosis. WBCs without evidence of trichomonads or yeast are usually suggestive of cervicitis. The yeast or pseudohyphae of *Candida* species are more easily identified in the KOH specimen (Fig. 120-8). The

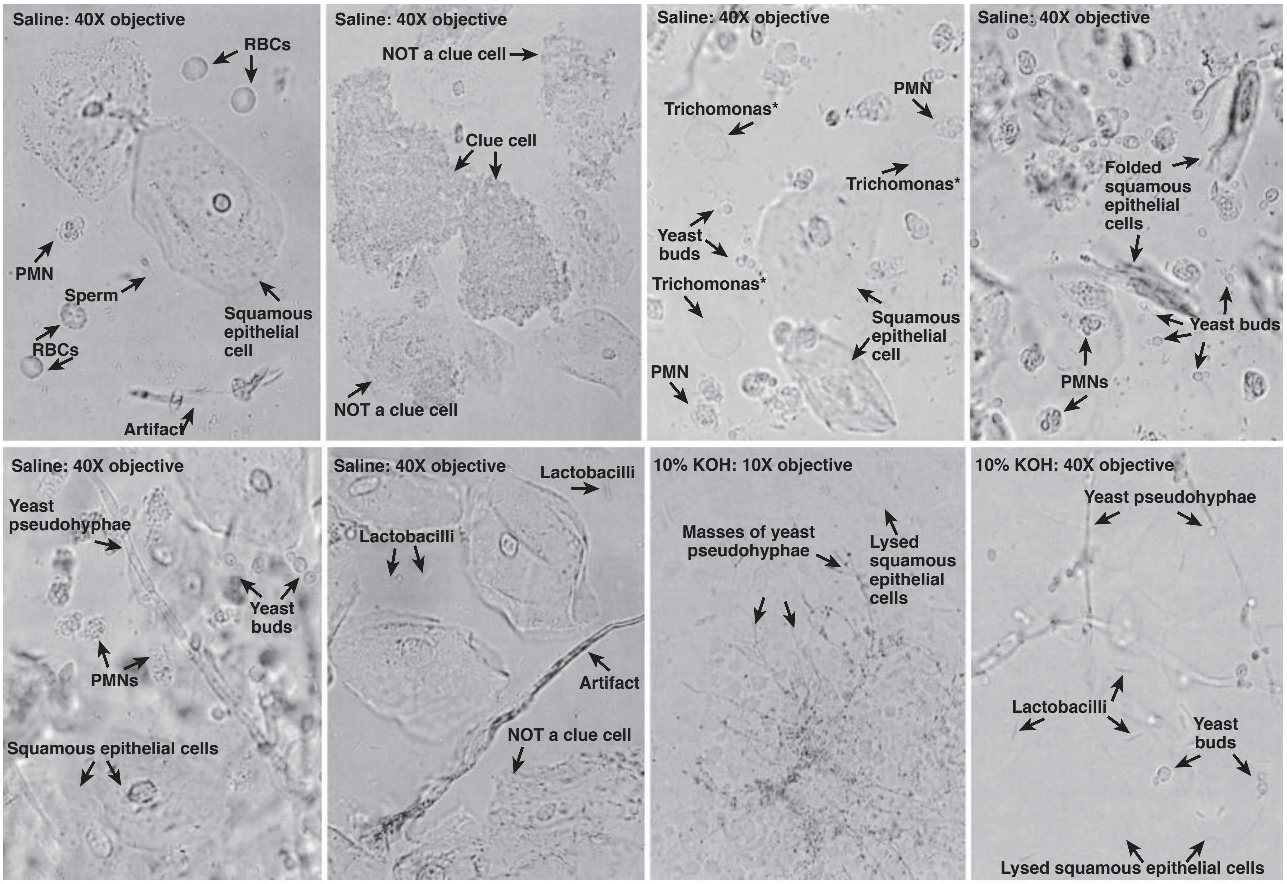

Figure 120-8 Common normal and abnormal microscopic findings during examination of vaginal fluid. KOH, potassium hydroxide solution; PMN, polymorphonuclear leukocyte; RBC, red blood cell. *(From* Adolescent medicine: state of the art reviews, *vol 14, no 2, Philadelphia, 2003, Hanley & Belfus, pp 350–351.)*

sensitivity of microscopy is approximately 50% and requires immediate evaluation of the slide for optimal results. Therefore, lack of findings does not eliminate the possibility of infection. More sensitive, point-of-care vaginitis tests include the OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Lexington, MA), an immunochromatographic capillary flow dipstick technology that reports an 83% sensitivity; and the OSOM BVBLUE Test (Sekisui Diagnostics, Lexington, MA), which detects elevated vaginal fluid sialidase activity, an enzyme produced by bacterial pathogens associated with bacterial vaginosis including *Gardnerella*, *Bacteroides*, *Prevotella*, and *Mobiluncus*, that reports a 90% sensitivity. Both of these tests are CLIA-waived with results are available within 10 minutes.

Clinical laboratory-based vaginitis tests are also available. The Affirm VPIII (Becton Dickenson, San Jose, CA), a nucleic acid probe test that evaluates for *T. vaginalis*, *G. vaginalis*, and *C. albicans*, is a moderate complexity laboratory test, has a sensitivity >83% and a specificity >97%, with results are available within 45 min. Some gonorrhea and chlamydia NAATs also offer an assay for *T. vaginalis* testing of female specimens tested for *N. gonorrhoeae* and *C. trachomatis*, which are considered the gold standard for trichomonas testing.

Objective signs of vulvar inflammation in the absence of vaginal pathogens, along with a minimal amount of discharge, suggest the possibility of mechanical, chemical, allergic, or other noninfectious irritation of the vulva (Table 120-4).

The **definitive diagnosis of PID** is difficult based on clinical findings alone. Clinical diagnosis is imprecise and no single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of acute PID. Clinical criteria have a positive predictive value of only 65-90% compared with laparoscopy. Although healthcare providers should maintain a low threshold for the diagnosis of PID, additional criteria to enhance specificity of diagnosis, such as transvaginal ultrasonography, can be considered (Table 120-5).

Cell culture and PCR are the preferred HSV tests. Viral culture sensitivity is low and false negatives do occur as a consequence of intermittent viral shedding. NAATs, including PCR assays for HSV DNA, are more sensitive and increasingly available for diagnosing genital HSV. The Tzanck test is insensitive and nonspecific and should not be relied on.

Accurate type-specific HSV serologic assays are based on the HSV-specific glycoprotein G2 (HSV-2) and glycoprotein G1 (HSV-1). Both laboratory-based and point-of-care tests are available. Because nearly all HSV-2 infections are sexually acquired, the presence of type-specific HSV-2 antibody implies anogenital infection. The presence of HSV-1 antibody alone is more difficult to interpret because of the frequency of oral HSV infection acquired during childhood. Type-specific HSV serologic assays might be useful in the following scenarios: (1) recurrent genital symptoms or atypical symptoms with negative HSV cultures; (2) a clinical diagnosis of genital herpes without laboratory confirmation; and (3) a patient with a partner with genital herpes, especially if considering suppressive antiviral therapy to prevent transmission.

For syphilis testing, nontreponemal tests, such as the rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL), and treponemal testing, such as fluorescent treponemal antibody absorbed tests, the *T. pallidum* passive particle agglutination (TP-PA) assay, various enzyme and chemiluminescence immunoassays (EIA/CIA) are recommended. However, many clinical laboratories have adopted a reverse sequence of screening in which a treponemal EIA/CIA is performed first, followed by testing of reactive sera with a nontreponemal test (e.g., RPR). A positive treponemal EIA or CIA test can identify both previously treated and untreated or incompletely treated syphilis. False-positive results can occur, particularly among populations with low syphilis prevalence. Persons with a positive treponemal screening test should have a standard nontreponemal test with titer, such as an RPR or VDRL to guide patient management decisions. If EIA/CIA and nontreponemal test (e.g., RPR or VDRL) test results are discordant, the laboratory should perform a different treponemal test to confirm the results of the initial test. Patients with discordant serologic results by EIA/CIA and RPR/VDRL testing whose sera are reactive by TP-PA testing are considered to have past or present syphilis; if sera is TP-PA nonreactive, syphilis is unlikely (Fig. 120-9).

Table 120-4 Pathologic Vaginal Discharge

INFECTIVE DISCHARGE	OTHER REASONS FOR DISCHARGE
COMMON CAUSES	COMMON CAUSES
Organisms	Retained tampon or condom
Candida albicans	Chemical irritation
Trichomonas vaginalis	Allergic responses
Chlamydia trachomatis	Ectropion
Neisseria gonorrhoeae	Endocervical polyp
Mycoplasma genitalium	Intrauterine device
Conditions	Atrophic changes
Bacterial vaginosis	LESS COMMON CAUSES
Acute pelvic inflammatory disease	Physical trauma
Postoperative pelvic infection	Vault granulation tissue
Postabortal sepsis	Vesicovaginal fistula
Puerperal sepsis	Rectovaginal fistula
LESS COMMON CAUSES	Neoplasia
Ureaplasma urealyticum	Cervicitis
Syphilis	
Escherichia coli	

From Mitchell H: Vaginal discharge—causes, diagnosis, and treatment, BMJ *328:1306–1308, 2004.*

Table 120-5 Evaluation for Pelvic Inflammatory Disease

2014 CENTERS FOR DISEASE CONTROL AND PREVENTION DIAGNOSTIC CRITERIA

Minimal Criteria
- Cervical motion tenderness
- *or*
- Uterine tenderness
- *or*
- Adnexal tenderness

Additional Criteria to Enhance Specificity of the Minimal Criteria
- Oral temperature >38.3°C (>101°F)
- Abnormal cervical or vaginal mucopurulent discharge*
- Presence of abundant numbers of white blood cells on saline microscopy of vaginal secretions*
- Elevated ESR or C-reactive protein
- Laboratory documentation of cervical *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infection

Most Specific Criteria to Enhance the Specificity of the Minimal Criteria
- Transvaginal sonography or MRI techniques showing thickened, fluid-filled tubes, with or without free pelvic fluid or tuboovarian complex, or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia)
- Endometrial biopsy with histopathologic evidence of endometritis
- Laparoscopic abnormalities consistent with PID

Differential Diagnosis (Partial List)
- GI: appendicitis, constipation, diverticulitis, gastroenteritis, inflammatory bowel disease, irritable bowel syndrome
- GYN: ovarian cyst (intact, ruptured, or torsed), endometriosis, dysmenorrhea, ectopic pregnancy, mittelschmerz, ruptured follicle, septic or threatened abortion, tuboovarian abscess
- Urinary tract: cystitis, pyelonephritis, urethritis, nephrolithiasis

*If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely and alternative causes of pain should be investigated.

ESR, erythrocyte sedimentation rate; GI, gastrointestinal; GYN, gynecologic; WBC, white blood cell.

Adapted from Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2014, MMWR *http://www.cdc.gov/std/treatment/update.htm.*

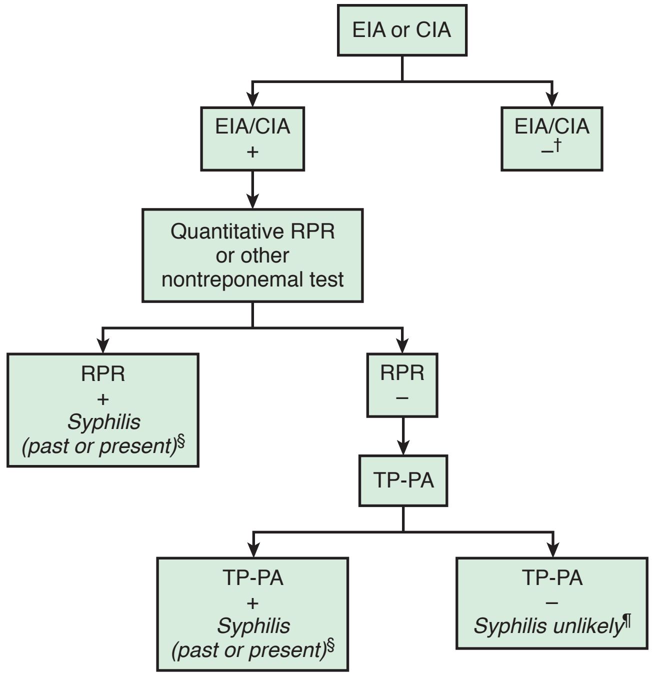

Figure 120-9 This figure shows the recommended algorithm for reverse sequence syphilis screening (treponemal test screening followed by nontreponemal test confirmation). The CDC recommends that a specimen with reactive EIA/CIA results be tested reflexively with a quantitative nontreponemal test (e.g., RPR or VDRL). If test results are discordant, the specimen should be tested reflexively using the TP-PA test as a confirmatory treponemal test. EIA/CIA, enzyme immunoassay/chemiluminescence immunoassay; RPR, rapid plasma reagin; TP-PA, *Treponema pallidum* particle agglutination. *Despite these recommendations for reverse sequence screening, CDC continues to recommend the traditional algorithm with reactive nontreponemal tests confirmed by treponemal testing. †If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units intramuscularly in a single dose. §Evaluate clinically, determine whether treated for syphilis in the past, assess risk for infection, and administer therapy according to CDC's *STD Treatment Guidelines* (available at http://www.cdc.gov/std/treatment/update.htm). ¶If at risk for syphilis, repeat RPR in several weeks. *(Adapted from CDC: Discordant results from reverse sequence syphilis screening–five laboratories, United States, 2006-2010,* MMWR Morb Mortal Wkly Rep *60:133–137, 2011.)*

HIV screening should be discussed and offered in healthcare settings to all adolescents >15 yr and to younger adolescents with HIV risk factors. Rapid HIV testing with the availability of results in 10-20 min can be useful in settings in which the likelihood of adolescents returning for their results is low. Point-of-care, CLIA-waived tests for whole blood fingerstick and oral fluid specimen testing are available. Clinical studies have demonstrated that the rapid HIV test performance is comparable to those of EIAs. Because some reactive test results may be false-positive, every reactive rapid test must be confirmed.

Treatment

See Part XVII for chapters on the treatment of specific microorganisms and Tables 120-6 to 120-8. Treatment regimens using nonprescription products for candida vaginitis and pediculosis reduce financial and access barriers to rapid treatment for adolescents, but there are potential risks for inappropriate self-treatment and complications from untreated more serious infections that must be considered before using this approach. Minimizing noncompliance with treatment, finding and treating the sexual partners, addressing prevention and contraceptive issues, offering available vaccines to prevent STIs and making every effort to preserve fertility are additional physician responsibilities.

Chlamydia and gonorrhea-infected males and females should be retested approximately 3 mo after treatment, regardless of whether they believe that their sex partners were treated or whenever persons next present for medical care in the 12 mo following initial treatment. Once an infection is diagnosed, partner evaluation, testing, and treatment are recommended for sexual contacts within 60 days of symptoms or diagnosis or the most recent partner if sexual contact was >60 days, even if the partner is asymptomatic. Abstinence is recommended for at least 7 days after both patient and partner are treated. A test for pregnancy should be performed for all females with suspected PID as the test outcome will affect management. Repeat testing 3 mo after treatment is recommended for *Trichomonas* infection.

Diagnosis and therapy are often necessarily carried out within the context of a confidential relationship between the physician and the patient. Therefore, the need to report certain STIs to health department authorities should be clarified at the outset. Health departments are HIPAA-exempt and will not violate confidentiality. The health department's role is to assure that treatment and case finding have been accomplished and that sexual partners have been notified of their STI exposure. **Expedited partner therapy (EPT),** where the patient, preferably, delivers the medication, or a prescription for the medication if medication itself is not possible to the partner for treatment without a

Table 120-6 Management Guidelines for Uncomplicated Bacterial STIs in Adolescents and Adults

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
Chlamydia trachomatis	Azithromycin 1 g orally once *or* Doxycycline 100 mg orally twice daily for 7 days	For pregnancy: Azithromycin 1 g orally once Alternative regimens: Erythromycin base 500 mg orally 4 times a day for 7 days *or* Erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days *or* Levofloxacin 500 mg orally once daily for 7 days *or* Ofloxacin 300 mg orally twice a day for 7 days
Neisseria gonorrhoeae (cervix, urethra, and rectum)	Ceftriaxone 250 mg IM in a single dose *or* Single-dose injectable cephalosporin *plus* Azithromycin 1 g orally once	Alternative if unable to offer IM: Cefixime 400 mg orally in a single dose *plus* Azithromycin 1 g orally once If azithromycin is not available or if patient is allergic to azithromycin, doxycycline 100 mg orally twice daily for 7 days may be substituted for azithromycin as the second antimicrobial Severe cephalosporin allergy: contact infectious disease specialist

Table 120-6 Management Guidelines for Uncomplicated Bacterial STIs in Adolescents and Adults—cont'd

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
Neisseria gonorrhoeae (pharynx)	Ceftriaxone 250 mg IM in a single dose *plus* Azithromycin 1 g orally once	No alternative therapy available Patients treated with an alternative regimen should return 14 days after treatment for a test of cure using either culture or NAAT. If the NAAT is positive, every effort should be made to perform a confirmatory culture
Treponema pallidum (primary and secondary syphilis or early latent syphilis, i.e., infection <12 mo)	Benzathine penicillin G 2.4 million units IM in 1 dose	Penicillin allergy: doxycycline 100 mg orally twice daily for 14 days. Limited data suggest ceftriaxone 1-2 g daily either IM or IV for 10-14 days.
Treponema pallidum (late latent syphilis or syphilis of unknown duration)	Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1 wk intervals	Penicillin allergy: doxycycline 100 mg orally twice daily for 28 days with close serologic and clinical follow-up
Haemophilus ducreyi (chancroid: genital ulcers, lymphadenopathy)	Azithromycin 1 g orally in a single dose *or* Ceftriaxone 250 mg IM in a single dose *or* Ciprofloxacin 500 mg orally twice a day for 3 days *or* Erythromycin base 500 mg orally 3 times a day for 7 days	
Chlamydia trachomatis serovars L1, L2, or L3 (lymphogranuloma venereum)	Doxycycline 100 mg orally twice daily for 21 days	Alternative: erythromycin base 500 mg orally 4 times a day for 21 days *or* Azithromycin 1 g orally once a week for 3 wk

IM, intramuscular; IV, intravenous; NAAT, nucleic acid amplification test.
Adapted for Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2014 MMWR *http://www.cdc.gov/std/treatment/update.htm*.

Table 120-7 Management Guidelines for Uncomplicated Miscellaneous Sexually Transmitted Infections in Adolescents and Adults

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
Trichomonas vaginalis	Metronidazole 2 g orally in a single dose *or* Tinidazole 2 g orally in a single dose	Metronidazole 500 mg orally twice daily for 7 days
Phthirus pubis (pubic lice)	Permethrin 1% cream rinse applied to affected areas and washed off after 10 min *or* Pyrethrins with piperonyl butoxide applied to affected areas and washed off after 10 min Launder clothing and bedding	Malathion 0.5% lotion applied for 8-12 hr and washed off *or* Ivermectin 250 μg/kg PO, repeat in 2 wk
Sarcoptes scabiei (scabies)	Permethrin 5% cream applied to all areas from the neck down, washed off after 8-14 hr or Ivermectin 200 μg/kg orally, repeated in 2 wk Launder clothing and bedding	Lindane (1%) 1 oz of lotion or 30 g of cream in thin layer to all areas of body from neck down; wash off in 8 hr

Adapted from Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2014 MMWR *http://www.cdc.gov/std/treatment/update.htm*.

clinical assessment, is a strategy to reduce further transmission of infection, particularly for male partners of women with gonorrhea and/or chlamydia who are otherwise unlikely to seek care for STI exposure. In randomized trials, EPT has reduced the rates of persistent or recurrent gonorrhea and chlamydia infection. Serious adverse reactions are rare with recommended chlamydia and gonorrhea treatment regimens, such as doxycycline, azithromycin, and cefixime. Transient gastrointestinal side effects are more common but rarely result in severe morbidity. Many states expressly permit EPT or may potentially allow its practice. Resources for information regarding EPT and state laws are available at the Centers for Disease Control and Prevention website (http://www.cdc.gov/std/ept/).

Prevention

Healthcare providers should integrate sexuality education into clinical practice with children from early childhood through adolescence. Providers should counsel adolescents regarding sexual behaviors associated with risk of STI acquisition and should educate using evidence-based prevention strategies, which include a discussion of abstinence and other risk reduction strategies, such as consistent and correct condom use. The U.S. Preventative Task Force recommends high-intensity behavioral counseling to prevent STIs for all sexually active adolescents. The HPV vaccine, either bivalent or quadrivalent, is recommended for 11 and 12 yr old female routine immunization. Catch-up vaccination is recommended for females age 13-26 yr who

Table 120-8 Management Guidelines for Uncomplicated Genital Warts and Genital Herpes in Adolescents and Adults

PATHOGEN	RECOMMENDED REGIMENS	
Human papillomaviruses external genital warts	Patient-applied: Podofilox 0.5% solution or gel self-applied to warts twice daily for 3 consecutive days each wk followed by 4 days of no therapy. May be repeated for up to 4 cycles. *or* Imiquimod 3.75% cream or 5% cream self-applied to warts at bedtime 3 times wkly for up to 16 wk; wash off after 6-10 hr *or* Sinecatechins 15% ointment self-applied 3 times daily for up to 16 wk. Do not wash off after use Provider-administered: Cryotherapy with liquid nitrogen or cryoprobe. Repeat applications every 1-2 wk *or* Trichloroacetic acid (TCA) or bichloracetic acid (BCA) 80-90%. A small amount should be applied only to the warts and allowed to dry, at which time a white "frosting" develops. Can be repeated weekly *or* Surgical removal either by tangential scissor excision, tangential shave excision, curettage, or electrosurgery	
Human papillomaviruses Cervical warts	Refer to specialist for oncologic evaluation	
Human papillomaviruses Vaginal warts	**Cryotherapy** with liquid nitrogen. Avoid cryoprobe use *or* TCA or BCA 80-90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white "frosting" develops. Can be repeated weekly *or* Surgical removal	
Human papillomaviruses Urethral meatal warts	Cryotherapy with liquid nitrogen *or* Surgical removal	
Human papillomaviruses Anal warts	Cryotherapy with liquid nitrogen *or* TCA or BCA 80-90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white "frosting" develops. Can be repeated weekly *or* Surgical removal	Warts on the rectal mucosa should be managed in consultation with a specialist. Persons with anal warts should have rectal mucosa inspected by digital examination, standard anoscopy, or high-resolution anoscopy
Herpes simplex virus (genital herpes): First clinical episode	Treat for 7-10 days with 1 of the following: Acyclovir 400 mg orally 3 times daily *or* Acyclovir 200 mg orally 5 times daily *or* Valacyclovir 1 g orally twice daily *or* Famciclovir 250 mg orally 3 times daily	Consider extending treatment if healing is incomplete after 10 days of therapy

Table 120-8 Management Guidelines for Uncomplicated Genital Warts and Genital Herpes in Adolescents and Adults—cont'd

PATHOGEN	RECOMMENDED REGIMENS	
Herpes simplex virus (genital herpes): Episodic therapy for recurrences	Acyclovir 400 mg orally 3 times daily for 5 days *or* Acyclovir 800 mg orally twice daily for 5 days *or* Acyclovir 800 mg orally 3 times daily for 2 days *or* Valacyclovir 500 mg orally twice daily for 3 days *or* Valacyclovir 1,000 mg orally once daily for 5 days *or* Famciclovir 125 mg orally twice daily for 5 days *or* Famciclovir 1,000 mg orally twice daily for 1 day *or* Famciclovir 500 mg orally once then 250 mg twice daily for 2 days	Effective episodic treatment of recurrences requires initiation of therapy within 1 day of lesion onset or during the prodrome that precedes some outbreaks. The patient should be provided with a supply or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin
Herpes simplex virus (genital herpes): Suppressive therapy to reduce frequency of recurrences	Acyclovir 400 mg orally twice daily *or* Valacyclovir 500 mg orally once daily or 1 g orally once daily *or* Famciclovir 250 mg orally twice daily	All patients should be counseled regarding suppressive therapy availability, regardless of number of outbreaks per year. Since the frequency of recurrent outbreaks diminishes over time in many patients, providers should periodically discuss the need to continue therapy Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (i.e., ≥10 episodes per year).

Adapted from Centers for Disease Control and Prevention: STD Treatment Guidelines 2014, MMWR *59 In press.*

have not yet received or completed the vaccine series. The routine use of quadrivalent HPV vaccine is recommended in males age 11 or 12 yr. The CDC's Advisory Committee on Immunization Practices also recommends vaccination with quadrivalent HPV vaccine for males age 13 through 21 yr who have not yet received or completed the vaccine series; males age 22 through 26 yr may be vaccinated.

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Chapter 121

Chronic Fatigue Syndrome

James F. Jones and Hal B. Jenson

Chronic fatigue syndrome (CFS) describes a complex, diverse, and debilitating illness characterized by chronic or intermittent fatigue accompanied by selected symptoms of >3 mo (young children) or >6 mo duration (adolescents or adults). The combination of fatigue and symptoms interferes significantly with usual daily activities and has no apparent medical explanation. The fatigue does not require exertion by the patient, nor does rest relieve it. Post-exertion malaise (i.e., worsening of fatigue and sickness symptoms after mental or physical exertion lasting more than 24 hr) is considered by some to be characteristic of CFS. A definitive causal agent or process has not been identified, although the differential diagnosis includes many infectious and inflammatory diseases. The understanding of this condition is largely from studies among adults and adolescents, with limited descriptions of chronic fatiguing illness among younger children.

This illness was formally defined in 1988 as *chronic fatigue syndrome* because persistent and unexplained fatigue was considered the principal and invariable physical symptom. A variety of names have been used to describe the syndrome (chronic mononucleosis, chronic Epstein-Barr virus infection, myalgic encephalomyelitis, post-infection syndrome, immune dysfunction syndrome), and several case definitions are in use in both clinical and research settings. Some of the more widely used definitions are the 1994 International Research Case Definition (an update of the 1988 version), the Oxford (UK) Guidelines for research, the Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical working case definition, diagnostic and treatments protocols, also commonly referred to as the Canadian Consensus Criteria for CFS/ME (2003), and the 2011 International Consensus Criteria for Myalgic Encephalomyelitis (ME). In 2006, the International Association of Chronic Fatigue Syndrome Pediatric Case Definition Working group developed a case definition specifically for children and adolescents with ME/CFS, utilizing the 3-mo duration of fatigue. In the UK, pediatric practitioners adhere to guidelines in the National Institute for Health and Clinical Excellence (NICE); Chronic fatigue syndrome/Myalgic encephalomyelitis (or encephalopathy); Diagnosis and Management (2007), which includes the 3-mo duration criterion.

The Institute of Medicine (IOM) of the National Academy of Science was commissioned by the Department of Health and Human Services (HHS) to conduct a study to evaluate existing diagnostic criteria and to develop evidence-based diagnostic criteria for use by clinicians. Their recommendations were published in February 2015. The IOM case definition is intended to apply to all ages, and the report includes a special focus on pediatrics. The IOM suggested new diagnostic criteria and a new name, *systemic exertion intolerance disease*, in part to emphasize the post-exertion malaise criterion and bring greater understanding about the illness.

EPIDEMIOLOGY

Between 0.2% and 2.3% of children or adolescents suffer from CFS based on worldwide studies. Most epidemiology studies utilize the 1994 definition. CFS is more prevalent in adolescents than in younger children. The large variation in the CFS prevalence estimates may be

due to variation in study methodology, such as the study population composition (special clinic versus general practice or general population) and data collection procedures (parent/self-reporting vs. clinical evaluation; the choice of case definition and method of applying case definition). Sex/gender distribution differs from that in adults with a more equal distribution in children less than 15 yr of age, while remaining 2- to 3-fold higher in females ages 15-18 yr. Few studies have reported the incidence of CFS among children <10 yr of age, leading to uncertainty in this age group. In adolescents in the Netherlands, the pediatrician-diagnosed incidence of CFS/ME was reported to be 0.01%, while in the UK the incidence was 0.5%.

PATHOGENESIS

Although the cause of CFS is unknown, some patients correlate the onset with a recent episode of a viruslike illness such as infectious mononucleosis (10-12%) (see Chapter 254). A potentially pathophysiologic relationship of CFS to infection is suggested because the sickness or illness behaviors elicited by the nonspecific or innate host responses in infections in general are present in CFS. CFS-like illness after infectious mononucleosis is not predicted by viremia or an altered host response to Epstein-Barr virus infection, but is associated with the severity of the primary infection. There have been a wide variety of other candidate infections associated with postinfection fatigue syndromes, particularly in adults or teenagers older than 16 yr. Efforts continue to determine if infections with these or other agents may produce the illness.

Similarities between CFS symptoms and those experienced by patients with autoimmune and other inflammatory disorders raises the issue of primary perturbations in the immune system in the pathogenesis of CFS. Immunologic alterations (hypogammaglobulinemia or hypergammaglobulinemia, immunoglobulin subclass deficiencies, elevated levels of circulating immune complexes, mild increased helper/suppressor lymphocyte ratios, natural killer cell dysfunction, and monocyte dysfunction) have been reported in adult patients with CFS. These findings have not been consistent among studies. While CFS patients as a group appear to differ from healthy controls, in most studies the laboratory values of the immune parameters are not outside the normal range.

Autonomic nervous system changes are suggested by the orthostatic intolerance experienced by some CFS patients. Orthostatic intolerance (OI) syndromes with circulatory dysfunction including neutrally mediated hypotension, instantaneous orthostatic hypotension, and postural tachycardia syndrome have been observed in some patients with CFS and could contribute to the syndrome. The pathophysiology of these manifestations among adolescents with CFS is unclear, but in postinfection states, they could be associated with failure to replenish mineral and fluid losses that accompany infections or to immune-mediated injury (auto-antibodies directed against the autonomic nervous system).

Because the widespread musculoskeletal pain in CFS is similar to that in fibromyalgia (Chapter 168.3), and fibromyalgia and CFS are often considered overlapping syndromes, they may share similarities in pathogenesis. Fibromyalgia pain is thought to be due to neurochemical imbalances in the central nervous system. Neurochemical changes represent another area for research into the origins of development and persistence of CFS.

A variety of other hypotheses for the biologic basis of this illness are being investigated. These include alterations in energy metabolism (particularly as related to exercise and post-exertion malaise), in sleep, as well as in stress response and the hypothalamic-pituitary-axis. Understanding CFS has proved so challenging because it represents more than one underlying pathophysiology. Current studies are attempting to stratify or subgroup patients to address this possibility.

CLINICAL MANIFESTATIONS

The dominant symptoms expressed by adolescents are similar to those observed in adults and include fatigue and an increased level of illness after physical or mental activity. In younger children, who frequently do not spontaneously describe symptoms, exertion induces behavioral changes manifested by a lack of their usual energy. In adolescents, the fatigue and post-exertional malaise may lead to reduced participation in school activities and time spent with friends. Cognitive problems and difficulties in concentrating are common and are indicated by a decreased ability to keep up with homework and a drop in grades. Sleep complaints include difficulty falling or staying asleep, daytime sleepiness, frequent awakening, and intense and vivid dreaming. While nonrestorative nighttime sleeping is common, diagnosed sleep disorders, such as restless legs or sleep apnea, are not. Myalgias and arthralgias may accompany fatigue and altered sleep. Sore throat and lymph node tenderness occur in some children but may be part of an inciting illness. Adolescents also have increased complaints of headaches, abdominal pain, nausea, and hypersensitivity to touch and noise.

Patients diagnosed with CFS in primary care practices are more likely to report an abrupt onset to their symptoms, often as part of an initial virus-like illness, whereas gradual onset is more common in those identified in population-based studies. School absenteeism is a major problem. In one study two thirds of adolescents missed >2 wk of school over a 6-week observation period and one third required a home tutor. Unlike school phobia, inactivity due to CFS persists on the weekends and during holidays as it does during the school week.

Although fatigue and accompanying symptoms are subjective, the magnitude of impairment of each component can be measured by questionnaires addressing pain and function or, in the case of suspected orthostatic instability, by recording routine or supine/standing heart rate and blood pressure. Fatigue should not be dismissed as a minor ailment. It is generally manifested as lassitude, profound tiredness, intolerance of exertion with easy fatigability, and general malaise.

Abnormal physical examination findings are conspicuously absent, providing reassurance and consternation to both the patient and the physician. The presence of unusual symptoms such as chest palpitations, visual blurring, paresthesias, dry eyes and mouth, diarrhea, cough, night sweats, and rash) should suggest a diagnosis other than CFS. Weight loss, as seen in chronic infections or inflammatory conditions, is uncommon in CFS.

DIAGNOSIS

There are no pathognomonic signs or diagnostic tests for CFS. The diagnosis is clinically defined based on inclusion and exclusion criteria (Fig. 121-1). The diagnostic criteria are applicable to adults and adolescents >11 yr of age because of the current requirement for a self-generated history. The 3- or 6-mo criterion in CFS case definitions does not mean that evaluation and symptom management should wait until that criterion is met before intervention can begin.

CFS is difficult to diagnose in children, who have trouble describing their symptoms and articulating their concerns. Sole reliance on parental history for diagnosis is fraught with confusion because of the inaccuracy of the historical information. A combination of child and parent reports is most effective. It is important to document the child's activity levels and worsening symptoms after physical or mental endeavors. Changes in participation in hobbies and social activities can help identify illness effects on daily activities.

The diagnosis of CFS can be established only after alternative medical and psychiatric causes of fatigue and illness, many of which are treatable, have been excluded. These include any medical condition that may explain the presence of a chronic illness, such as untreated hypothyroidism, respiratory and/or food allergies, sleep apnea, narcolepsy, drug abuse, an adverse effect of medication, or severe obesity. A previously diagnosed medical condition with uncertain resolution that may explain chronic fatigue should be clarified, such as unresolved cases of hepatitis B or C virus infection.

Certain illnesses, for example, fibromyalgia and depression, share similar symptoms with CFS, but are not exclusionary diagnoses. They should be considered in the differential diagnosis in selected cases. There is concern that CFS might be mistaken for readily identifiable psychiatric disorders, but evidence supports differences in clinical

Clinical Evaluation and Classification of Chronic Fatigue

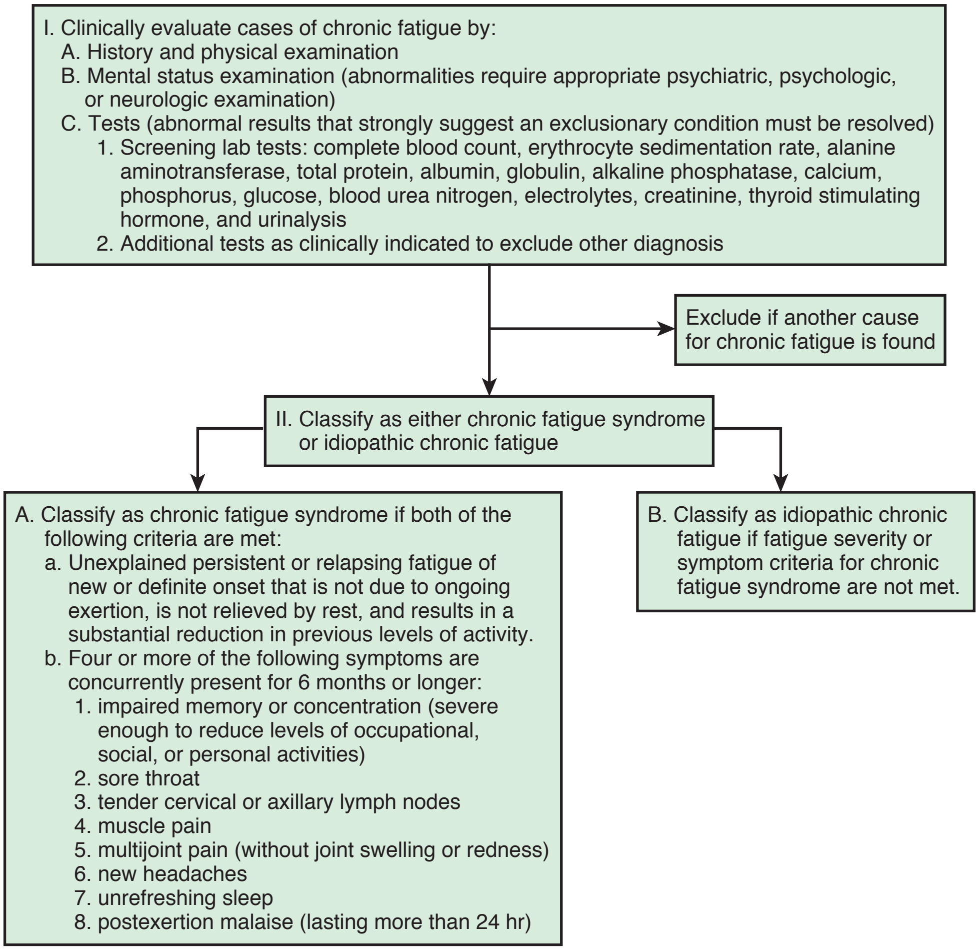

Figure 121-1 **The clinical evaluation and classification of unexplained chronic fatigue.** The case definition for chronic fatigue syndrome was proposed in 1988 (*Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition; 108:387–389*), and refined and simplified by an international working group in 1994 *(Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. 1994. Ann Intern Med; 121:953–959).*

presentation between CFS and mood/anxiety disorders. CFS should not be diagnosed in persons with prior diagnoses of a major depressive disorder with psychotic or melancholic features, bipolar affective disorders, schizophrenia of any subtype, delusional disorders of any subtype, dementias of any subtype, anorexia nervosa, bulimia nervosa, or alcohol or other substance abuse within 2 yr before the onset of the chronic fatigue or at any time afterward.

Although evaluation of each patient should be individualized, initial laboratory evaluation should be limited to screening laboratory tests to provide reassurance of the lack of significant medical illnesses (see Fig. 121-1). Further tests should be directed primarily toward excluding treatable diseases that may be suggested by the symptoms or physical findings that are present in specific patients.

MANAGEMENT

Management of CFS is based on relief of the core and most disruptive symptoms in the individual patient (Fig. 121-1). The diagnostic criterion of 3-6 mo duration of illness should not delay evaluation and symptom management, as these may be initiated as soon as the child or adolescent presents with a CFS-like picture. Problems with sleep can be addressed by encouraging patients to adopt good sleep habits using standard sleep hygiene techniques. It may be beneficial to refer the patient to a specialist for identification and treatment of sleep disorders and disturbances. Once pain is found not to be related to specific diseases or illnesses, it is best addressed through nonpharmacologic treatment (see Chapter 62).

One of the nonpharmacologic approaches to pain management, cognitive behavioral therapy (CBT), may also assist patients in coping with CFS. Through explanation and changes in perception of the origins of the illness, CBT may help patients and their families develop coping skills and provide emotional support. Improved methods of coping may allow some improved function while living with the illness. Comorbid psychiatric disorders require appropriate intervention.

While the overall goal is to help CFS patients tolerate activity, children with CFS should avoid physical or mental efforts that result in aggravated CFS symptoms. Return to school should be initiated gradually but systematically to resume normal attendance. Home tutoring may be an interim alternative. Parents can work with teachers and administrators to redefine expectations of activity and performance for children with CFS. Because of the crucial importance of learning socialization skills during childhood and adolescence, even brief periods of attendance during lunch or favorite after-school activities should be encouraged. Complete bed rest and physical inactivity perpetuates immobility and leads to deconditioning. Activities benefit children with certain chronic illnesses in ways other than overcoming deconditioning; however, rapid remobilization usually exacerbates symptoms and should be avoided.

Continued empathy and support by the treating physician are important in maintaining a physician-patient relationship conducive to managing this illness. Careful attention must be directed to the family dynamics to identify and resolve family problems or psychopathology that may be contributing to a child's perceptions of his or her

symptoms. Periodic medical reevaluation is warranted for early detection of other identifiable causes of chronic fatigue and other symptoms, especially with interval development of new symptoms. No data suggest relief of symptoms or cure of CFS by dietary or vitamin supplements.

PROGNOSIS

The clinical course of CFS is highly variable and patients should be informed that their symptoms will likely wax and wane. Children and adolescents with CFS appear to have a more optimistic outcome than adults, typically with an undulating course of gradual but substantial symptomatic improvement, or full recovery, 1-4 yr after diagnosis. Overall, a good functional outcome has been reported in up to 80% of cases. Poor prognostic factors include a gradual onset, increasing school absenteeism, lower socioeconomic status, chronic maternal health problems, and untreated comorbid individual or family psychiatric disorders. Favorable prognostic factors include patient control of their individual rehabilitation program with continued support from health professionals and family members and improvement in orthostatic factors.

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Immunology

PART XIV

Section 1

Evaluation of the Immune System

Chapter 122

Evaluation of Suspected Immunodeficiency

Rebecca H. Buckley

Recurrent infections or fevers in children are among the most frequent clinical dilemmas for primary care physicians. A major reason for the apparent high rate of recurrent infections in children is repeated exposure to common and usually benign infectious agents in childcare and other group settings.

Primary care physicians must have a high index of suspicion if defects of the immune system are to be diagnosed early enough that appropriate treatment can be instituted before irreversible damage develops. Diagnosis is difficult because, until recently, primary immunodeficiency diseases have not been screened for at any time during life anywhere in the world, and most affected do not have abnormal physical features. Screening for severe combined immunodeficiency (SCID; T-cell lymphopenia) is part of the newborn screening programs in 21 states of the United States now; the hope is that it will eventually be performed nationwide. There is also a beginning effort to do this in Europe. Extensive use of antibiotics may mask the classic presentation of many primary immunodeficiency diseases. Evaluation of immune function should be initiated in those rare infants or children who do have clinical manifestations of a specific immune disorder and in all who have a positive family history of early infant death or a known immunodeficiency disorder, unusual, chronic, or recurrent infections such as (1) 1 or more systemic bacterial infections (sepsis, meningitis); (2) 2 or more serious respiratory or documented bacterial infections (cellulitis, abscesses, draining otitis media, pneumonia, lymphadenitis) within 1 yr; (3) serious infections occurring at unusual sites (liver, brain abscess); (4) infections with unusual pathogens *(Pneumocystis jiroveci, Aspergillus, Serratia marcescens, Nocardia, Burkholderia cepacia);* and (5) infections with common childhood pathogens but of unusual severity (Table 122-1). Additional clues to immunodeficiency include failure to thrive with or without chronic diarrhea, persistent infections after receiving live vaccines, and chronic oral or cutaneous moniliasis. Tables 122-2 and 122-3 note certain clinical features that are suggestive of immunodeficiency syndromes.

Children with defects in antibody production, phagocytic cells, or complement proteins have recurrent infections with encapsulated bacteria and may grow and develop normally despite their recurring infections, unless they develop bronchiectasis from repeated lower respiratory tract bacterial infections or persistent enteroviral infections of the central nervous system. Patients with only repeated benign viral infections (with the exception of persistent enterovirus infections) are not as likely to have an immunodeficiency. By contrast, patients with deficiencies in T-cell function usually develop opportunistic infections or serious illnesses from common viral agents early in life, and they fail to thrive (Table 122-4).

The initial evaluation of immunocompetence includes a thorough history, physical examination, and family history (Table 122-5). Most immunologic defects can be excluded at minimal cost with the proper choice of screening tests, which should be broadly informative, reliable, and cost-effective (Table 122-6 and Fig. 122-1). A complete blood count (CBC), manual differential count, and erythrocyte sedimentation rate are among the most cost-effective screening tests. If the erythrocyte sedimentation rate is normal, chronic bacterial or fungal infection is unlikely. If an infant's neutrophil count is persistently elevated in the absence of any signs of infection, a leukocyte adhesion deficiency should be suspected. If the absolute neutrophil count is normal, congenital and acquired neutropenias and leukocyte adhesion defects are excluded. If the absolute lymphocyte count is normal, the patient is not likely to have a severe T-cell defect, because T cells normally constitute 70% of circulating lymphocytes and their absence results in striking lymphopenia. Normal lymphocyte counts are higher in infancy and early childhood than later in life (Fig. 122-2). Knowledge of normal values for absolute lymphocyte counts at various ages in infancy and childhood is crucial in the detection of T-cell defects. At 9 mo of age, an age when infants affected with severe T-cell immunodeficiency are likely to present, the lower limit of normal is 4,500 lymphocytes/mm^3. Absence of Howell-Jolly bodies or pitted erythrocytes by microscopic examination of erythrocytes rules against congenital asplenia. Normal platelet size or count excludes Wiskott-Aldrich syndrome. If newborn screening for T-cell lymphopenia were to be performed on all infants, SCID could be detected at birth, and lifesaving immunologic reconstitution could then be provided to all affected infants shortly after birth and before they become infected.

Patients found to have abnormalities on any screening tests should be characterized as fully as possible before any type of immunologic treatment is begun, unless there is a life-threatening illness (Table 122-7). Some "abnormalities" may prove to be laboratory artifacts and, conversely, an apparently straightforward diagnosis may prove to be a much more complex disorder. For patients with recurrent or unusual bacterial infections, evaluation of T-cell and phagocytic cell functions is indicated even if results of initial screening tests including the CBC and manual differential, immunoglobulin levels, and CH_{50} are normal.

Because of the lack of screening, the true incidence and prevalence of primary immunodeficiency diseases are unknown, although the incidence has been estimated to be 1 : 10,000 births (Table 122-8). If true, this is higher than some disorders that are part of the newborn metabolic screening program (phenylketonuria is 1 : 16,000) (see Chapter 85.1). Approximately 80% of the mutated genes causing the more than 220 known primary immunodeficiency diseases have been identified. This is information crucial for genetic counseling and that could eventually be used in neonatal screening. Newborn or early childhood screening would be extremely valuable so that timely initiation of appropriate therapy can be initiated before infections develop; it is likely that many affected patients die before a diagnosis is determined.

B CELLS

Antibody production by B cells is easily evaluated by measuring serum immunoglobulin levels and determining antibody titers to protein and polysaccharide antigens.

A simple screening test for B-cell defects is the measurement of serum immunoglobulin (Ig) A. If the IgA level is normal, selective IgA

Table 122-1 Predisposition to Specific Infections in Humans

PATHOGEN	PRESENTATION	AFFECTED GENE/ CHROMOSOMAL REGION	FUNCTIONAL DEFECT	NOTES
BACTERIA				
Streptococcus pneumoniae	Invasive disease	*IRAK-4, MyD88*	Impaired production of inflammatory cytokines following TLR stimulation	Also susceptible to other pyogenic bacteria such as *Staphylococcus aureus*
Neisseria	Invasive disease	MAC components (C5, C6, C7, C8A, C8B, C8G, C9)	MAC deficiency	
	Invasive disease, poor prognosis	*PFC*	Properdin deficiency	
Mycobacteria	MSMD	*IL12B, IL12RB1, IKBKG*	Impaired IFN-γ response to IL-12, IL-23	Also susceptible to *Salmonella typhi* infections
		IFNGR1, IFNGR2, STAT1	Impaired cellular response to IFN-γ	
Mycobacterium leprae	Leprosy	*PARK2* *LTA*	Unknown Unknown	Possible E3-ubiquitin ligase dysfunction
VIRUSES				
Herpes simplex (type 1)	Herpes simplex encephalitis	*UNC93B1, TLR3, STAT1*	Impaired production of type 1 IFNs	STAT1 and NEMO deficiency also predispose to HSV infections, amongst other infections
Epstein-Barr virus	XLP	*SH2DIA* *XIAP/BIRC4*	SAP deficiency XIAP deficiency	Fulminant infectious mononucleosis, malignant and nonmalignant lymphoproliferative disorders, dysgammaglobulinemia, autoimmunity
Human papillomaviruses	Epidermodysplasia verruciformis WHIM	*EVER1/TMC6* *EVER2/TMC8* *CXCR4*	EVER1 deficiency EVER2 deficiency Truncated CXCR4	Altered neutrophil mobilization, T-cell lymphopenia, recurrent bacterial respiratory infections chronic cutaneous/genital papillomavirus disease
PARASITES				
Plasmodium falciparum	Malaria fever episodes Severe malaria Severe malaria	10p15 *GNAS* *IFNR1*	Unknown Unknown Unknown	Linkage studies SNP association studies SNP association studies
Schistosoma mansoni	Intensity of infection Hepatic fibrosis	5q311-q33 6q22-q23, *IFNR1*	Unknown Unknown	
Leishmania donovani	Visceral leishmaniasis (kala-azar)	22q12, 2q35 *(NRAMP1)*	Unknown	
YEAST				
Candida	APECED, chronic candidiasis	*Aire, STAT1, CARD9*	Unknown	APS-1 chronic candidiasis, chronic hyperthyroidism, Addison disease
Deep dermatophytosis	Tissue invasion	*CARD9*	Unknown	Autosomal recessive

APECED, autoimmune, polyendocrinopathy, candidiasis, ectodermal dystrophy; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; MAC, membrane attack complex; MSMD, mendelian susceptibility to mycobacterial disease; NEMO, nuclear factor kappa B essential modulator; SAP, SLAM-associated protein; SNP, single-nucleotide polymorphism; TLR, Toll-like receptor; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis syndrome; XIAP, X-linked inhibitor of apoptosis; XLP, X-linked lymphoproliferative disease.

Modified from Pessach I, Walter J, Notarangelo LD: Recent advances in primary immunodeficiencies: identification of novel genetic defects and unanticipated phenotypes, Pediatr Res *65:3R–12R, 2009.*

deficiency, which is the most common B-cell defect, is excluded, as are most of the permanent types of hypogammaglobulinemia, as IgA is usually very low or absent in those conditions. If IgA is low, IgG and IgM should also be measured. Patients who are receiving corticosteroids or who have protein-losing states (nephrosis, protein-losing enteropathy) often have low serum IgG concentrations but produce antibodies normally. Thus, if immunoglobulins are low, it is crucial before starting intravenous immunoglobulin therapy that antibody titers to specific antigens are measured to determine whether the immunoglobulin levels are low because of inadequate antibody synthesis or due to protein loss. Antibody titers are not interpretable after the patient has received a blood transfusion, fresh-frozen plasma or intravenous immunoglobulin, which contains antibodies from a minimum of 10,000 normal donors.

One useful test for B-cell function is to determine the presence and titer of **isohemagglutinins,** or natural antibodies to type A and B red blood cell polysaccharide antigens. This test measures predominantly IgM antibodies. Isohemagglutinins may be absent normally in the 1st 2 yr of life and are always absent if the patient is blood type AB.

Because most infants and children are immunized with diphtheria-tetanus-pertussis, conjugated *Haemophilus influenzae* type b, and pneumococcal conjugate vaccine, it is often informative to test for specific antibodies to diphtheria, tetanus, *H. influenzae* polyribose phosphate, and pneumococcal antigens. If the titers are low, measurement of antibodies to diphtheria or tetanus toxoids before and 2 wk after a pediatric diphtheria-tetanus-pertussis or diphtheria-tetanus booster is helpful in assessing the capacity to form IgG antibodies to protein antigens. To evaluate a patient's ability to respond to

Table 122-2 Characteristic Clinical Patterns in Some Primary Immunodeficiencies

FEATURES	DIAGNOSIS
IN NEWBORNS AND YOUNG INFANTS (0-6 MO)	
Hypocalcemia, unusual facies and ears, heart disease	DiGeorge anomaly
Delayed umbilical cord detachment, leukocytosis, recurrent infections	Leukocyte adhesion defect
Persistent thrush, failure to thrive, pneumonia, diarrhea	Severe combined immunodeficiency
Bloody stools, draining ears, atopic eczema	Wiskott-Aldrich syndrome
Pneumocystis jiroveci pneumonia, neutropenia, recurrent infections	X-linked hyper-IgM syndrome
IN INFANTS AND YOUNG CHILDREN (6 MO-5 YR)	
Severe progressive infectious mononucleosis	X-linked lymphoproliferative syndrome
Recurrent staphylococcal abscesses, staphylococcal pneumonia with pneumatocele formation, coarse facial features, pruritic dermatitis	Hyper-IgE syndrome
Persistent thrush, nail dystrophy, endocrinopathies	Chronic mucocutaneous candidiasis
Short stature, fine hair, severe varicella	Cartilage hair hypoplasia with short-limbed dwarfism
Oculocutaneous albinism, recurrent infection	Chédiak-Higashi syndrome
Abscesses, suppurative lymphadenopathy, antral outlet obstruction, pneumonia, osteomyelitis	Chronic granulomatous disease
IN OLDER CHILDREN (OLDER THAN 5 YR) AND ADULTS	
Progressive dermatomyositis with chronic enterovirus encephalitis	X-linked agammaglobulinemia
Sinopulmonary infections, neurologic deterioration, telangiectasia	Ataxia-telangiectasia
Recurrent neisserial meningitis	C6, C7, or C8 deficiency
Sinopulmonary infections, splenomegaly, autoimmunity, malabsorption	Common variable immunodeficiency

Ig, immunoglobulin.
Modified from Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders.*

Table 122-3 Common Clinical Features of Immunodeficiency

Usually present	Recurrent upper respiratory infections Severe bacterial infections Persistent infections with incomplete or no response to therapy Paucity of lymph nodes and tonsils
Often present	Persistent sinusitis or mastoiditis (*Streptococcus pneumoniae, Haemophilus, Pneumocystis jiroveci, Staphylococcus aureus, Pseudomonas* spp.) Recurrent bronchitis or pneumonia Failure to thrive or growth retardation for infants or children; weight loss for adults Intermittent fever Infection with unusual organisms Skin lesions: rash, seborrhea, pyoderma, necrotic abscesses, alopecia, eczema, telangiectasia Recalcitrant thrush Diarrhea and malabsorption Hearing loss caused by chronic otitis Chronic conjunctivitis Arthralgia or arthritis Bronchiectasis Evidence of autoimmunity, especially autoimmune thrombocytopenia or hemolytic anemia Hematologic abnormalities: aplastic anemia, hemolytic anemia, neutropenia, thrombocytopenia History of prior surgery, biopsy
Occasionally present	Lymphadenopathy Hepatosplenomegaly Severe viral disease (e.g., EBV, CMV, adenovirus, varicella, herpes simplex) Chronic encephalitis Recurrent meningitis Deep infections: cellulitis, osteomyelitis, organ abscesses Chronic gastrointestinal disease, infections, lymphoid hyperplasia, sprue-like syndrome, atypical inflammatory bowel disease Autoimmune disease such as autoimmune thrombocytopenia, hemolytic anemia, rheumatologic disease, alopecia, thyroiditis, pernicious anemia Pyoderma gangrenosum Adverse reaction to vaccines Delayed umbilical cord detachment Chronic stomatitis or peritonitis

EBV, Epstein-Barr virus; CMV, cytomegalovirus.
Modified from Goldman L, Ausiello D: Cecil textbook of medicine, *ed 22, Philadelphia, 2004, WB Saunders, p 1598.*

polysaccharide antigens, anti-pneumococcal antibodies can be measured before and 3 wk after immunization with 23 valent unconjugated pneumococcal polysaccharide vaccine in patients 2-3 yr old or older. Antibodies detected in these tests are of the IgG isotype. These antibody studies can be performed in several different laboratories, but it is important to choose a reliable laboratory and to use the same laboratory for preimmunization and postimmunization titers. In children older than 2 yr of age with low anti-pneumococcal antibody titers after a pneumococcal polysaccharide vaccine immunization, it is useful to boost with conjugate pneumococcal vaccine twice, 1 mo apart, before giving a polysaccharide pneumococcal vaccine 1 mo later and then measuring antibody titers 3 wk later. Patients with significant or permanent B-cell defects do not produce either IgM or IgG antibodies normally. If results of these tests prove to be normal and the immunoglobulins remain low, studies should be performed to evaluate the possible loss of immunoglobulins through the urinary or gastrointestinal tracts (nephrotic syndrome, protein-losing enteropathies, intestinal lymphangiectasia). Very high serum concentrations of 1 or more immunoglobulin classes suggest HIV infection, chronic granulomatous disease, chronic inflammation, or autoimmune lymphoproliferative syndrome.

IgG subclass measurements are seldom helpful in assessing immune function in children with recurrent infections. It is difficult to know the biologic significance of the various mild to moderate deficiencies of IgG subclasses, particularly when completely asymptomatic individuals have been described as totally lacking IgG_1, IgG_2, IgG_4, and/or IgA_1 owing to immunoglobulin heavy-chain gene deletions. Many healthy children have been described as having low levels of IgG_2 but normal responses to polysaccharide antigens when immunized. When children with low IgG_2 subclass levels and histories of

Table 122-4 Characteristic Features of Primary Immunodeficiency

CHARACTERISTIC	PREDOMINANT T-CELL DEFECT	PREDOMINANT B-CELL DEFECT	GRANULOCYTE DEFECT	COMPLEMENT DEFECT
Age at the onset of infection	Early onset, usually 2-6 mo of age	Onset after maternal antibodies diminish, usually after 5-7 mo of age, later childhood to adulthood	Early onset	Onset at any age
Specific pathogens involved	Bacteria: common Gram-positive and Gram-negative bacteria and mycobacteria Viruses: CMV, EBV, adenovirus, parainfluenza 3, varicella, enterovirus Fungi: *Candida* and *Pneumocystis jiroveci*	Bacteria: pneumococci, streptococci, staphylococci, *Haemophilus, Campylobacter, Mycoplasma* Viruses: enterovirus* Fungi and parasites: giardia, cryptosporidia	Bacteria: staphylococci, *Pseudomonas, Serratia, Klebsiella, Salmonella* Fungi and parasites: *Candida, Nocardia, Aspergillus*	Bacteria: pneumococci, *Neisseria*
Affected organs	Extensive mucocutaneous candidiasis, lungs, failure to thrive, protracted diarrhea	Recurrent sinopulmonary infections, chronic gastrointestinal symptoms, malabsorption, arthritis, enteroviral meningoencephalitis*	Skin: abscesses, impetigo, cellulitis Lymph nodes: suppurative adenitis Oral cavity: gingivitis, mouth ulcers Internal organs: abscesses, osteomyelitis	Infections: meningitis, arthritis, septicemia, recurrent sinopulmonary infections
Special features	Graft-vs-host disease caused by maternal engraftment or nonirradiated blood transfusion Postvaccination disseminated BCG or varicella Hypocalcemic tetany in infancy[†]	Autoimmunity Lymphoreticular malignancy: lymphoma, thymoma Postvaccination paralytic polio	Prolonged attachment of umbilical cord, poor wound healing	Autoimmune disorders: SLE, vasculitis, dermatomyositis, scleroderma, glomerulonephritis, angioedema

*X-linked (Bruton) agammaglobulinemia.
[†]DiGeorge anomaly.
BCG, Bacille Calmette-Guérin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; SLE, systemic lupus erythematosus.
Modified from Woroniecka M, Ballow M: Office evaluation of children with recurrent infection, Pediatr Clin North Am *47:1211–1224, 2000.*

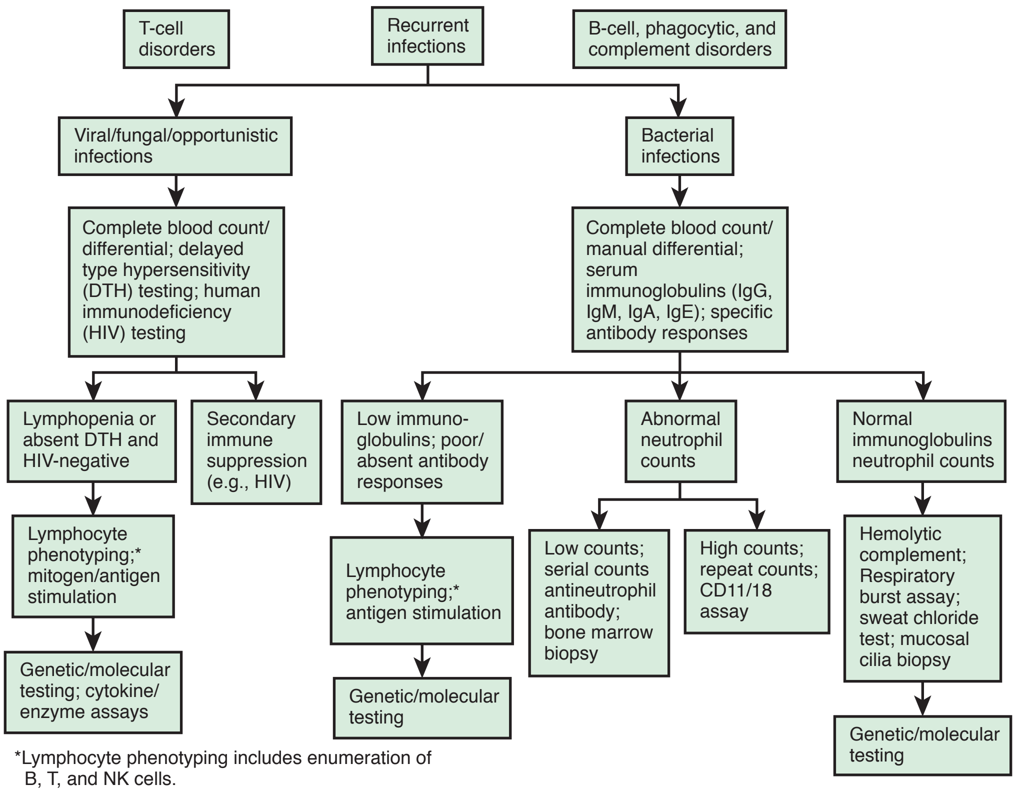

Figure 122-1 A diagnostic testing algorithm for primary immunodeficiency diseases. DTH, delayed-type hypersensitivity. *(From Lindegren ML, Kobrynski L, Rasmussen SA: Applying public health strategies to primary immunodeficiency diseases: a potential approach to genetic disorders,* MMWR Recomm Rep *53[RR-1]:1–29, 2004.)*

Table 122-5 Special Physical Features Associated with Immunodeficiency Disorders

CLINICAL FEATURES	DISORDERS
DERMATOLOGIC	
Eczema	Wiskott-Aldrich syndrome, IPEX, hyper-IgE syndromes, hypereosinophilia syndromes, IgA deficiency
Sparse and/or hypopigmented hair	Cartilage hair hypoplasia, Chédiak-Higashi syndrome, Griscelli syndrome
Ocular telangiectasia	Ataxia-telangiectasia
Oculocutaneous albinism	Chédiak-Higashi syndrome
Severe dermatitis	Omenn syndrome
Erythroderma	Omenn syndrome, SCID, graft-vs-host disease, Comel-Netherton syndrome
Recurrent abscesses with pulmonary pneumatoceles	Hyper-IgE syndromes
Recurrent organ granulomas or abscesses, lung, liver and rectum especially	Chronic granulomatous disease
Recurrent abscesses or cellulitis	Chronic granulomatous disease, hyper-IgE syndrome, leukocyte adhesion defect
Cutaneous granulomas	Ataxia telangiectasia, SCID, CVID, RAG deficiency
Oral ulcers	Chronic granulomatous disease, severe combined immunodeficiency, congenital neutropenia
Periodontitis, gingivitis, stomatitis	Neutrophil defects
Oral or nail candidiasis	T-cell immune defects, combined defects (SCIDs); mucocutaneous candidiasis; hyper-IgE syndromes; IL-12, -17, -23 deficiencies; *CARD9* deficiency; *STAT1* deficiency
Vitiligo	B-cell defects, mucocutaneous candidiasis
Alopecia	B-cell defects, mucocutaneous candidiasis
Chronic conjunctivitis	B-cell defects
EXTREMITIES	
Clubbing of the nails	Chronic lung disease due to antibody defects
Arthritis	Antibody defects, Wiskott-Aldrich syndrome, hyper-IgM syndrome
ENDOCRINOLOGIC	
Hypoparathyroidism	DiGeorge syndrome, mucocutaneous candidiasis
Endocrinopathies (autoimmune)	Mucocutaneous candidiasis
Diabetes, hypothyroid	IPEX and IPEX-like syndromes
Growth hormone deficiency	X-linked agammaglobulinemia
Gonadal dysgenesis	Mucocutaneous candidiasis
HEMATOLOGIC	
Hemolytic anemia	B- and T-cell immune defects, ALPS
Thrombocytopenia, small platelets	Wiskott-Aldrich syndrome
Neutropenia	Hyper-IgM syndrome, Wiskott-Aldrich variant, chronic granulomatous disease
Immune thrombocytopenia	B-cell immune defects, ALPS
SKELETAL	
Short-limb dwarfism	Short-limb dwarfism with T- and/or B-cell immune defects
Bony dysplasia	ADA deficiency, cartilage hair hypoplasia

ADA, Adenosine deaminase deficiency; AID, activation-induced cytidine deaminase; ALPS, autoimmune lymphoproliferative syndrome; CVID, common variable immunodeficiency; GVHD, graft-vs-host disease; Ig, immunoglobulin; IPEX, X-linked immune dysfunction enteropathy polyendocrinopathy; SCID, severe combined immunodeficiency.

From Goldman L, Ausiello D: Cecil textbook of medicine, *ed 22, Philadelphia, 2004, Saunders, p 1599.*

Table 122-6 Initial Screening Immunologic Testing of the Child with Recurrent Infections

COMPLETE BLOOD COUNT, MANUAL DIFFERENTIAL, AND ERYTHROCYTE SEDIMENTATION RATE
Absolute lymphocyte count (normal result [Chapter 727] rules against T-cell defect)
Absolute neutrophil count (normal result [Chapter 727] rules against congenital or acquired neutropenia and [usually] both forms of leukocyte adhesion deficiency, in which elevated counts are present even between infections)
Platelet count (normal result excludes Wiskott-Aldrich syndrome)
Howell-Jolly bodies (absence rules against asplenia)
Erythrocyte sedimentation rate (normal result indicates chronic bacterial or fungal infection unlikely)
SCREENING TESTS FOR B-CELL DEFECTS
Immunoglobulin (Ig) A measurement; if abnormal, IgG and IgM measurement
Isohemagglutinins
Antibody titers to blood group substances, tetanus, diphtheria, *Haemophilus influenzae*, and pneumococcus
SCREENING TESTS FOR T-CELL DEFECTS
Absolute lymphocyte count (normal result indicates T-cell defect unlikely)
Flow cytometry to examine for the presence of naïve T cells (CD3+CD45RA+ cells)
SCREENING TESTS FOR PHAGOCYTIC CELL DEFECTS
Absolute neutrophil count
Respiratory burst assay
SCREENING TEST FOR COMPLEMENT DEFICIENCY
CH_{50}

frequent infections were studied in depth, they were found to have broader immunologic dysfunction, including poor responses to protein antigens, suggesting that they may have been in the process of developing into **common variable immunodeficiency (CVID).** Only when profound antibody deficiencies are detected despite normal levels of immunoglobulins are IgG subclass measurements occasionally helpful. Children who completely lack IgG_2 are usually unable to make antibodies to polysaccharide antigens, although this may also be found among individuals with normal IgG_2. Thus, specific antibody measurements are far more cost-effective than IgG subclass determinations.

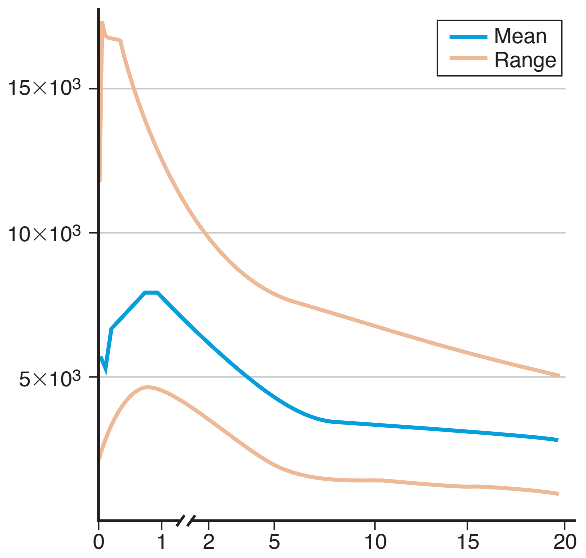

Figure 122-2 Absolute lymphocyte counts in normal individual during maturation. *(Data graphed from Altman PL:* Blood and other body fluids. *Prepared under the auspices of the Committee on Biological Handbooks. Washington, DC, 1961, Federation of American Societies for Experimental Biology.)*

Patients found to be **agammaglobulinemic** should have their blood B cells enumerated by **flow cytometry** using dye-conjugated monoclonal antibodies to B-cell–specific CD antigens (usually CD19 or CD20). Normally, approximately 8-10% of circulating lymphocytes are B cells. B cells are absent in X-linked agammaglobulinemia (XLA) and in several very rare autosomal recessive conditions, but they are present in CVID, IgA deficiency, and hyper-IgM syndromes. This distinction is important, because children with hypogammaglobulinemia from XLA and CVID can have different clinical problems, and the 2 conditions clearly have different inheritance patterns. Patients with XLA have a heightened susceptibility to persistent enteroviral infections, whereas those with CVID have more problems with autoimmune diseases and lymphoid hyperplasia. Molecular testing for XLA and other B-cell defects (see Chapter 124.1) is indicated in cases without a family history to aid genetic counseling.

T CELLS

T cells and T-cell subpopulations can be enumerated by **flow cytometry** using dye-conjugated monoclonal antibodies recognizing CD antigens present on T cells (i.e., CD2, CD3, CD4, and CD8). This is a particularly important test to perform on any infant who is lymphopenic, because $CD3^+$ T cells usually constitute 70% of peripheral lymphocytes. Regardless of molecular type, infants with SCID are unable to produce T cells so are lymphopenic at birth. The flow cytometry for infants suspected of having SCID should also include monoclonal antibodies to naïve (CD45RA) and memory (CD45RO) T cells. In normal infants, more than 95% of the T cells are CD45RA+ (naïve) T cells. If the infant is a SCID, there could be transplacentally transferred maternal T cells detected by flow cytometry, but they would be dominantly CD45RO+ T cells. SCID is a pediatric emergency that can be

Table 122-7 Laboratory Tests in Immunodeficiency

SCREENING TESTS	ADVANCED TESTS	RESEARCH/SPECIAL TESTS
B-CELL DEFICIENCY		
IgG, IgM, IgA, and IgE levels	B-cell enumeration (CD19 or CD20)	Advanced B-cell phenotyping
Isohemagglutinin titers		Biopsies (e.g., lymph nodes)
Ab response to vaccine antigens (e.g., tetanus, diphtheria, pneumococci, *Haemophilus influenzae*)	Ab responses to boosters or to new vaccines	Ab responses to special antigens (e.g., bacteriophage φX174), mutation analysis
T-CELL DEFICIENCY		
Lymphocyte count	T-cell subset enumeration (CD3, CD4, CD8)	Advanced flow cytometry
Chest x-ray examination for thymic size*	Proliferative responses to mitogens, antigens, allogeneic cells	Enzyme assays (e.g., ADA, PNP)
		Thymic imaging
Delayed skin tests (e.g., *Candida*, tetanus toxoid)	HLA typing	Mutation analysis
	Chromosome analysis	T-cell activation studies
		Apoptosis studies
		Biopsies
PHAGOCYTIC DEFICIENCY		
WBC count, morphology	Adhesion molecule assays (e.g., CD11b/CD18, selectin ligand)	Mutation analysis
Respiratory burst assay	Mutation analysis	Enzyme assays (e.g., MPO, G6PD, NADPH oxidase)
COMPLEMENT DEFICIENCY		
CH_{50} activity	AH50, activity	
C3 level	Component assays	
C4 level	Activation assays (e.g., C3a, C4a, C4d, C5a)	

*In infants only.

Ab, antibody; ADA, adenosine deaminase; C, complement; CH, hemolytic complement; G6PD, glucose-6-phosphate dehydrogenase; HLA, human leukocyte antigen; Ig, immunoglobulin; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate; PNP, purine nucleoside phosphorylase; WBC, white blood cell; φX, phage antigen.

Modified from Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, Saunders.*

Table 122-8 2003 Modified IUIS Classification of Primary and Secondary Immunodeficiencies

GROUPS AND DISEASES	INHERITANCE
A. PREDOMINANTLY ANTIBODY DEFICIENCIES	
XL agammaglobulinemia	XL
AR agammaglobulinemia	AR
Hyper-IgM syndromes	XL and AR
a. CD40L defect	XL
b. AID defect	AR
c. CD40 defect	AR
d. UNG defect	AR
e. Other hyper-IgM defects	AR
Ig heavy-chain gene deletions	AR
κ Chain deficiency mutations	AR
Selective IgA deficiency	AD
Common variable immunodeficiency	AD
B. SEVERE COMBINED IMMUNODEFICIENCIES	
$T^-B^+NK^-$ SCID	
a. X-linked (γc deficiency)	XL
b. Autosomal recessive (Jak3 deficiency)	AR
$T^-B^+NK^+$ SCID	
a. IL-7 Rα deficiency	AR
b. CD3δ, CD3ε, or CD3ζ deficiencies	AR
c. CD45 deficiency	AR
$T^-B^-NK^+$ SCID	
a. RAG-1/2 deficiency	AR
b. Artemis defect	AR
Omenn Syndrome	
a. RAG-1/2 deficiency	AR
b. IL-7Rα deficiency	AR
c. γc deficiency	XL
Combined Immunodeficiencies	
a. Purine nucleoside phosphorylase deficiency	AR
b CD8 deficiency (ZAP-70 defect)	AR
c. MHC class II deficiency	AR
d. MHC class I deficiency caused by TAP-1/2 mutations	AR
Reticular dysgenesis	AR
C. OTHER CELLULAR IMMUNODEFICIENCIES	
Wiskott-Aldrich syndrome	XL
Ataxia-telangiectasia	AR
DiGeorge anomaly	?
D. DEFECTS OF PHAGOCYTIC FUNCTION	
Chronic Granulomatous Disease	
a. XL	XL
b. AR	AR
1. p22 phox deficiency	
2. p47 phox deficiency	
3. p67 phox deficiency	
Leukocyte adhesion defect 1	AR
Leukocyte adhesion defect 2	AR
Neutrophil G6PD deficiency	XL
Myeloperoxidase deficiency	AR
Secondary granule deficiency	AR
Shwachman syndrome	AR
Severe congenital neutropenia (Kostmann)	AR
Cyclic neutropenia (elastase defect)	AR
Leukocyte mycobacterial defects	AR
IFN-γR1 or R2 deficiency	AR
IFN-γR1 deficiency	AD
IL-12Rβ1 deficiency	AR
IL-12p40 deficiency	AR
STAT1 deficiency	AD
E. IMMUNODEFICIENCIES ASSOCIATED WITH LYMPHOPROLIFERATIVE DISORDERS	
Fas deficiency	AD
Fas ligand deficiency	
FLICE or caspase 8 deficiency	
Unknown (caspase 3 deficiency)	
F. COMPLEMENT DEFICIENCIES	
C1q deficiency	AR
C1r deficiency	AR
C4 deficiency	AR
C2 deficiency	AR
C3 deficiency	AR
C5 deficiency	AR
C6 deficiency	AR
C7 deficiency	AR
C8α deficiency	AR
C8β deficiency	AR
C9 deficiency	AR
C1 inhibitor	AD
Factor I deficiency	AR
Factor H deficiency	AR
Factor D deficiency	AR
Properdin deficiency	XL
G. IMMUNODEFICIENCY ASSOCIATED WITH OR SECONDARY TO OTHER DISEASES	
Chromosomal Instability or Defective Repair	
Bloom syndrome	
Fanconi anemia	
ICF syndrome	
Nijmegen breakage syndrome	
Seckel syndrome	
Xeroderma pigmentosum	
Chromosomal Defects	
Down syndrome	
Turner syndrome	
Chromosome 18 rings and deletions	
Skeletal Abnormalities	
Short-limbed skeletal dysplasia	
Cartilage-hair hypoplasia	
Immunodeficiency with Generalized Growth Retardation	
Schimke immuno-osseous dysplasia	
Immunodeficiency with absent thumbs	
Dubowitz syndrome	
Growth retardation, facial anomalies, and immunodeficiency	
Progeria (Hutchinson-Gilford syndrome)	
Immunodeficiency with Dermatologic Defects	
Partial albinism	
Dyskeratosis congenita	
Netherton syndrome	
Acrodermatitis enteropathica	
Anhidrotic ectodermal dysplasia	
Papillon-Lefèvre syndrome	
Hereditary Metabolic Defects	
Transcobalamin 2 deficiency	
Methylmalonic acidemia	
Type 1 hereditary orotic aciduria	
Biotin-dependent carboxylase deficiency	
Mannosidosis	
Glycogen storage disease, type 1b	
Chédiak-Higashi syndrome	
Hypercatabolism of Immunoglobulin	
Familial hypercatabolism	
Intestinal lymphangiectasia	
H. OTHER IMMUNODEFICIENCIES	
Hyper-IgE syndromes	AD and AR
Chronic mucocutaneous candidiasis	
Chronic mucocutaneous candidiasis with polyendocrinopathy (APECED)	AR
Hereditary or congenital hyposplenia or asplenia	
Ivemark syndrome	
IPEX syndromes	XL
Ectodermal dysplasia (NEMO defect)	XL

AD, autosomal dominant; ADA, adenosine deaminase; AID, activation-induced cytidine deaminase; APECED, autoimmune, polyendocrinopathy, candidiasis, ectodermal dystrophy; AR, autosomal recessive; caspase, cysteinyl aspartate specific proteinase; FLICE, Fas-associating protein with death domain–like IL-1–converting enzyme; G6PD, glucose 6-phosphate dehydrogenase; ICF, immunodeficiency, centromeric instability, facial anomalies; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy; IUIS, International Union of Immunological Societies; MHC, major histocompatibility complex; NEMO, nuclear factor B essential modulator; SCID, severe combined immunodeficiency; TAP-2, transporter associated with antigen presentation; UNG, uracil-N-glycosylase; XL, X-linked.

Modified from (no authors listed) Primary immunodeficiency diseases. Report of an International Union of Immunological Studies Scientific Committee, Clin Exp Immunol *118:1–28, 1999; Chapel H, Geha R, Rosen F: IUIS PID (Primary Immunodeficiencies) Classification committee: Primary immunodeficiency diseases: an update,* Clin Exp Immunol *132:9–15, 2003; Stiehm ER, Ochs HD, Winkelstein JA:* Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders.*

successfully treated by nonablative stem cell transplantation in more than 92% of cases if diagnosed before serious, untreatable infections develop. Normally, there are roughly twice as many $CD4^+$ (helper) T cells as there are $CD8^+$ (cytotoxic) T cells. Because there are examples of severe immunodeficiency in which phenotypically normal T cells are present, tests of T-cell function are far more informative and cost-effective than enumeration of T-cell subpopulations by flow cytometry. T cells are normally stimulated through their T-cell receptors by antigen present in the groove of major histocompatibility complex molecules. The T-cell receptor can also be stimulated directly with **mitogens** such as phytohemagglutinin, concanavalin A, or pokeweed mitogen. After 3-5 days of incubation with the mitogen, the proliferation of T cells is measured by the incorporation of radiolabeled thymidine into DNA. Other stimulants that can be used to assess T-cell function in the same type of assay include antigens (*Candida,* tetanus toxoid) and allogeneic cells (see Table 122-6).

NATURAL KILLER CELLS

Natural killer (NK) cells can be enumerated by flow cytometry using monoclonal antibodies to NK-specific CD antigens, CD16 and CD56. NK function is assessed by a radiolabeled chromium-release assay, using the cell line K562, which is readily killed by NK cells.

PHAGOCYTIC CELLS

Killing defects of phagocytic cells, which should be suspected if a patient has recurrent staphylococcal abscesses or gram-negative infections, can be evaluated by screening tests measuring the neutrophil respiratory burst after phorbol ester stimulation. The most reliable and useful test of this type is a flow cytometric assessment of the respiratory burst using rhodamine dye. Leukocyte adhesion deficiencies can be easily diagnosed by flow cytometric assays of blood lymphocytes or neutrophils, using monoclonal antibodies to CD18 or CD11 (LAD1) or to CD15 (LAD2).

Phagocytic cell defects can be further defined according to their molecular cause. Mutations in the genes encoding 5 different components of the NADPH pathway have been discovered in various patients with chronic granulomatous disease. It is important to identify the specific molecular type of chronic granulomatous disease to provide appropriate genetic counseling, as 1 type is X linked and the other 4 types are autosomal recessive. Early diagnosis of leukocyte adhesion deficiency is of crucial importance because stem cell transplantation can be lifesaving.

COMPLEMENT

The most effective screening test for complement defects is a CH_{50} assay, which is a bioassay that measures the intactness of the entire complement pathway and yields abnormal results if complement has been consumed from the specimen for any reason. Genetic deficiencies in the complement system are usually characterized by extremely low CH_{50} values. The most common cause of an abnormal CH_{50} result, however, is a delay in or improper transport of the specimen to the laboratory. Specific immunoassays for C3 and C4 are commercially available, but further identification of other complement component deficiencies is usually possible only in research laboratories. Nevertheless, it is extremely important to identify which component is missing, because there are different disease susceptibilities depending on whether there are deficiencies of early or late components (see Chapter 134). Identifying the mode of inheritance is also important for genetic counseling. Properdin deficiency is X linked, but all of the other complement deficiencies are autosomal. Measurement of C4 can be helpful in assessing suspected hereditary angioedema.

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Section 2

The T-, B-, and NK-Cell Systems

Chapter 123

T Lymphocytes, B Lymphocytes, and Natural Killer Cells

Rebecca H. Buckley

Defense against infectious agents is secured through a combination of anatomic physical barriers including the skin, mucous membranes, mucous blanket, and ciliated epithelial cells, as well as the various components of the immune system. The **immune system** of vertebrates integrates 2 fundamental response mechanisms. **Innate (natural) immunity** responds to infection regardless of previous exposure to the agent and includes polymorphonuclear leukocytes, dendritic and mononuclear phagocytic cells, natural killer (NK) cells, various receptors that recognize common pathogen antigens (Toll-like receptors) and the complement system. **Acquired (adaptive) immunity** is a highly specific response that includes T and B lymphocytes. The immune system also helps protect against malignancy and autoimmunity.

LYMPHOPOIESIS IN THE FETUS

Origin of the Lymphoid System

The human immune system arises in the embryo from gut-associated tissue. Pluripotential hematopoietic stem cells first appear in the yolk sac at 2.5-3 wk of gestational age, migrate to the fetal liver at 5 wk of gestation, and later reside in the bone marrow, where they remain throughout life (Fig. 123-1). Lymphoid stem cells develop from such precursor cells and differentiate into T, B, or NK cells, depending on the organs or tissues to which the stem cells traffic. Development of the **primary lymphoid organs**—thymus and bone marrow—begins during the middle of the 1st trimester of gestation and proceeds rapidly. Development of the **secondary lymphoid organs**—spleen, lymph nodes, tonsils, Peyer patches, and lamina propria—soon follows. These organs serve as sites of differentiation of T, B, and NK lymphocytes from stem cells throughout life. Both the initial organogenesis and the continued cell differentiation occur as a consequence of the interaction of a vast array of lymphocytic and microenvironmental cell surface molecules and proteins secreted by the involved cells. The complexity and number of lymphoid cell surface molecules led to the development of an international nomenclature for **clusters of differentiation (CD)** (Table 123-1).

T and B lymphocytes are the only components of the immune system that have antigen-specific recognition capabilities and are responsible for adaptive immunity. NK cells are lymphocytes that are also derived from hematopoietic stem cells and are thought to have a role in host defense against viral infections, tumor surveillance, and immune regulation, but they do not have antigen receptors. Nonantibody proteins synthesized and secreted by T, B, and NK cells, and by the cells with which they interact, act as intercellular mediators and are referred to as **cytokines** or **interleukins (ILs)** (Table 123-2). Cytokines have the ability to act in an autocrine, paracrine, or endocrine manner

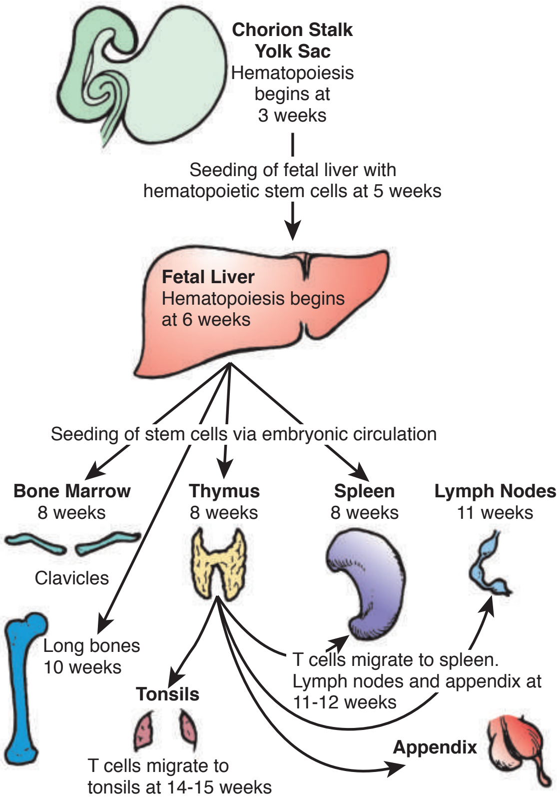

Figure 123-1 Migration patterns of hematopoietic stem cells and mature lymphocytes during human fetal development. *(From Haynes BF, Denning SM: Lymphopoiesis. In Stamatoyannopoulis G, Nienhuis A, Majerus P, editors:* Molecular basis of blood diseases, *ed 2, Philadelphia, 1994, WB Saunders.)*

to promote and facilitate differentiation and proliferation of the cells of the immune system.

T-Cell Development and Differentiation

The primitive thymic rudiment is formed from the ectoderm of the 3rd branchial cleft and endoderm of the 3rd branchial pouch at 4 wk gestation. Beginning at 7-8 wk, the right and left rudiments move caudally and fuse in the midline. Bloodborne T-cell precursors from the fetal liver then begin to colonize the perithymic mesenchyme at 8 wk gestation, and at 8-8.5 wk gestation are found intrathymically. The earliest cells to enter the thymus are found in the subcapsular region and do not express CD3, CD4, CD8, or either type of T-cell receptor. These lymphoid cell precursors are triggered to proliferate and become thymocytes through interactions with the thymic stroma. These cells express CD44 and c-kit (CD117) and slightly later the α chain of the IL-2 receptor. The cells are arrested at this stage until they productively rearrange the β chain locus of the T-cell receptor. The inframe β chain then pairs with the surrogate pre-T α chain and is expressed on the cell surface, which triggers entry into the cell cycle. The presence of small amounts of pre-T α:β on the cell surface in association with CD3 triggers rapid proliferation of these cells, the loss of CD25 and the termination of β-chain gene rearrangement. After cell proliferation ceases, CD4 and CD8 are expressed simultaneously (i.e., they are double-positive thymocytes). Fetal cortical thymocytes are among the most rapidly dividing cells in the body and increase in number by 100,000-fold within 2 wk after stem cells enter the thymus. As these cells proliferate and mature, they migrate deeper into the thymic cortex. The double-positive thymocytes begin efficient rearrangement of the α-chain locus, express low levels of an α:β **T-cell receptor (TCR)** and the associated CD3 complex and are then ready for thymic selection. TCR gene rearrangement begins shortly after colonization of the thymus with stem cells, and the establishment of the T-cell repertoire begins at 8-10 wk of gestation. The mature TCR is a heterodimer of 2 chains, either α and β or γ and δ, that is coexpressed on the cell surface with **CD3,** a complex of 5 polypeptide chains (γ, δ, ε, ζ, η). TCR gene rearrangement occurs by a process in which large, noncontiguous blocks of DNA are spliced together. These segments, known as **V (variable), D (diversity),** and **J (joining),** each have a number of variants. VDJ segments are joined to a constant region of the α gene, and VDJ segments are joined to the β gene to complete the receptor polypeptide genes. Random combinations of the segments account for much of the enormous diversity of TCRs that enables humans to recognize millions of different antigens. TCR gene rearrangement requires the presence of **recombinase activating genes,** *RAG-1* and *RAG-2,* as well as other recombinase components. This process is flawed in both mice and humans with severe combined immunodeficiency (SCID) because of mutations in genes that encode components of the VDJ recombination process. By 9.5-10 wk, more than 95% of thymocytes express CD2, CD4, CD7, CD8, and c (cytoplasmic) CD3, and ≈30% bear the CD1 inner cortical thymocyte antigen. By 10 wk, 25% of thymocytes bear αβ TCRs. Ti αβ T cells gradually increase in number during embryonic life and represent more than 95% of thymocytes postnatally.

As immature cortical thymocytes begin to express TCRs, the processes of positive and negative selection take place. **Positive selection** occurs through the interaction of immature thymocytes, which express low levels of TCR, with major histocompatibility complex (MHC) antigens present on cortical thymic epithelial cells. As a result, thymocytes with TCR capable of interacting with foreign antigens presented on self human leukocyte antigen (HLA) molecules are activated and develop to maturity. Most (>98%) of the cells die by failing to be positively selected or as a consequence of negative selection, but some are selected to mature into CD4 or CD8 single positive cells. Mature thymocytes that survive the selection process either express CD4 and are restricted to interacting with self class II HLA antigens, or express CD8 and are restricted to interacting with self class I HLA antigens when foreign antigens are presented by these MHC molecules. **Negative selection** occurs next in the medulla and is mediated by interaction of the surviving thymocytes, which have much higher levels of TCR expression, with host peptides presented by HLA class I or II antigens present on bone marrow-derived thymic macrophages, dendritic cells, and possibly B cells. This interaction mediates **apoptosis** (programmed cell death) of such autoreactive thymocytes. The thymic medulla contains only mature single-positive T cells that eventually leave the thymus and enter the bloodstream. T-cell functions are acquired concomitantly with the development of single-positive thymocytes, but they are not fully developed until the cells emigrate from the thymus. T cells begin to emigrate from the thymus to the spleen, lymph nodes, and appendix at 11-12 wk of embryonic life, and to the tonsils by 14-15 wk. They leave the thymus via the bloodstream and are distributed throughout the body, with the heaviest concentrations in the paracortical areas of lymph nodes, the periarteriolar areas of the spleen, and the thoracic duct lymph. Recent thymic emigrants coexpress the CD45RA isoforms and CD62L (L-selectin). Rearrangement of the TCR locus during intrathymic T-cell development results in the excision of DNA and the excised elements form circular episomes as a by-product. These **TCR recombination excision circles** can be detected in T cells that are recent thymic emigrants, whereas T cells that develop extrathymically do not contain these episomes. Inability to detect TCR recombination excision circles by real-time polymerase chain reaction of DNA from the dried blood spots collected from infants shortly after birth is the test used for newborn screening for SCID. The homing of lymphocytes to peripheral lymphoid organs is directed by the interaction of a lymphocyte surface adhesion molecule, L-selectin, with carbohydrate moieties on specialized regions of lymphoid organ blood vessels called **high endothelial venules.** By 12 wk gestation, T cells can proliferate in response to plant lectins, such as phytohemagglutinin and concanavalin A, and to allogeneic cells; antigen-binding T cells have been found by 20 wk gestation. **Hassall's corpuscles (bodies),** which are swirls of terminally differentiated medullary epithelial cells, are first seen in the thymic medulla at 16-18 wk of embryonic life.

Table 123-1 CD Classification of Some Lymphocyte Surface Molecules

CD NUMBER	OTHER NAMES	TISSUE/LINEAGE	FUNCTION
CD1	T6	Cortical thymocytes; Langerhans cells	Lipid antigen presentation to TCRγδ cells
CD2	SRBC receptor	T and NK cells	Binds LFA-3 (CD58); alternative pathway of T-cell activation
CD3	T3, Leu 4	T cells	TCR-associated; transduces signals from TCR
CD4	T4, Leu3a	Helper T-cell subset	Receptor for HLA class II antigens; associated with p56 *lck* tyrosine kinase
CD7	3A1, Leu 9	T and NK cells and their precursors	Comitogenic for T lymphocytes
CD8	T8, Leu2a	Cytotoxic T-cell subset; also on 30% of NK cells	Receptor for HLA class I antigens; associated with p56 *lck* tyrosine kinase
CD10	cALLA	B-cell progenitors	Peptide cleavage
CD11a	LFA-1a ∀ chain	T, B, and NK cells	With CD18, ligand for ICAMs 1, 2, and 3
CD11b, c	MAC-1, CR3; CR4	NK cells	With CD18, receptors for C3bi
CD16	FcRIII	NK cells	FcR for IgG
CD19	B4	B cells	Regulates B-cell activation
CD20	B1	B cells	Mediates B-cell activation
CD21	B2	B cells	C3d, also the receptor for EBV; CR2
CD25	IL-2Rα	T, B, and NK cells	Mediates signaling by IL-2
CD34	My10	Stem cells	Binds to L-selectin
CD38	T10	T, B, and NK cells and monocytes	Associates with hyaluronic acid
CD40	CD40	B cells and monocytes	Initiates isotype switching in B cells when ligated
CD44	CD44	Bone marrow stromal and many other cells.	Matrix adhesion molecule
CD45	Leukocyte common antigen, T200	All leukocytes	Tyrosine phosphatase that regulates lymphocyte activation; CD45R0 isoform on memory T cells, CD45RA isoform on naïve T cells
CD56	NCAM; NKH-1	NK cells	Mediates NK homotypic adhesion
CD62L	L-selectin	Marker for recent thymic emigrants. Also found on other leukocytes.	Cell adhesion molecule
CD69	CD69	T cells and NK cells	Early activation marker
CD73	Ecto-5′-nucleotidase	T and B cells	Associates with AMP
CD80	B7.1	B cells	Costimulatory with CD28 on T cells to upregulate high affinity IL-2 receptor
CD86	B7.2	B cells	Costimulatory with CD28 on T cells to upregulate high affinity IL-2 receptor
CD117	c-kit	Pro-B cells, double-negative thymocytes	Receptor for stem cell factor
CD127	IL-7Rα	T cells	Mediates IL-7 signaling
CD132	Common γ chain (γc)	T, B, and NK cells	Mediates signaling by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21
CD154	CD40 ligand, gp39	Activated $CD4^+$ T cells	Ligates CD40 on B cells and initiates isotype switching
CD278	ICOS	T cells	Interacts with B7-H2

AMP, Adenosine monophosphate; CD, cluster of differentiation; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; ICAM, intracellular adhesion molecule; ICOS, inducible costimulator; Ig, immunoglobulin; IL, interleukin; LFA, lymphocyte function-associated antigen; MAC, membrane attack complex; NCAM, neural cell adhesion molecule; NK, natural killer; SRBC, sheep red blood cell; TCR, T-cell receptor.

B-Cell Development and Differentiation

In parallel with T-cell differentiation, B-cell development begins in the fetal liver before 7 wk of gestation. Fetal liver CD34 stem cells are seeded to the bone marrow of the clavicles by 8 wk of embryonic life and to that of the long bones by 10 wk (see Fig. 123-1). **As B cells differentiate from primitive stem cells, they proceed through stages that are marked by the sequential rearrangement of immunoglobulin gene segments to generate a diverse repertoire of antigen receptors.** The early **pro-B cell** is the first descendent of the pluripotential stem cell committed to B-lineage development and in this stage, the heavy chain locus rearranges first. In the early pro-B cell, D-J rearrangements are made on both chromosomes. In the late pro-B cell, the V segment rearranges to a D-J gene segment, but it is a matter of chance whether the juxtaposed J sequence and the μ constant region sequence downstream can be read in the correct reading frame. There is a roughly 2 in 3 chance that an out-of-frame sequence will occur,

Table 123-2 Functional Classification of Cytokines*

1. Cytokines involved in natural immune responses
   - Type I interferons (IFN-α and IFN-β): inhibit viral replication, inhibit cell proliferation, activate NK cells, and upregulate class I MHC molecule expression
   - TNF-α: mediates host response to Gram-negative bacteria and other infectious agents
   - IL-1α and -1β: mediate host inflammatory response to infectious agents
   - IL-1Ra: a natural antagonist of IL-1, blocks signals delivered by IL-1
   - IL-6: mediates and regulates inflammatory responses
   - Chemokines (IL-8, monocyte chemotactic protein-1 or MCP-1, RANTES, and others): mediate leukocyte chemotaxis and activation
2. Lymphocyte regulatory cytokines
   a. Immunostimulatory or growth-promoting
      - IL-1: costimulates activation of T cells
      - IL-2: growth factor for T, B, NK cells; activates NK and T effector cells
      - IL-4: T- and B-cell growth factor; stimulates IgE production; upregulates classes I and II MHC molecules and Fc$R\epsilon$II expression on macrophages; expansion of Th2 subset
      - IL-5: B-cell growth and activation
      - IL-6: growth factor for B cells
      - IL-7: stromal cell factor; growth factor for precursor B and T cells, T-cell homeostatic factor
      - IL-10: growth and differentiation factor for B cells
      - IL-9: growth factor for T cells, B cells, mast cells, eosinophils, neutrophils, endothelial cells
      - IL-12: expansion of Th1 subset; activates effector cells
      - IL-13: growth and differentiating factor for B cells; stimulates IgE production; upregulates Classes I and II MHC molecules and Fc$R\epsilon$II expression on macrophages
      - TNF-β: stimulates effector cell function
      - IL-15: regulates NK-cell development and memory cell homeostasis
      - IL-17: promotes inflammation by acting on local tissue cells to cause them to produce chemokines, such as IL-8, that recruit neutrophils and other innate effector cells.
      - IL-18: induces IFN-γ, GM-CSF, TNF-α in immunocompetent cells
      - IL-21: together with IL-4 regulates IgG and IgE class-switching and Ig synthesis
      - IL-23: autocrine growth factor for Th17 cells
      - IL-27: produced by antigen presenting cells and regulates both T and B cell activity
      - IFN-γ: activates macrophages, NK cells; upregulates classes I and II MHC molecules expression; inhibits IL-4– or IL-13–induced IgE production

   b. Immunosuppressive
      - IL-1Rα: regulates IL-1 activities
      - TGF-β: antagonizes lymphocyte responses
      - IL-10: inhibits activities of Th1 cells
      - IFN-α/β: inhibits production of IFN-γ
3. Hematopoiesis regulating cytokines
   - GM-CSF, G-CSF, M-CSF: colony-stimulating factors
   - Erythropoietin (EPO): differentiation of erythroid precursors
   - IL-3, SCF, c-kit receptor: regulate stem cell development
   - IL-4: mast cell development
   - IL-5: eosinophil differentiation and proliferation
   - IL-6: differentiation of B cells
   - IL-7: differentiation of B and T cells
   - IL-8: promotes cell survival in response to hematopoietic cytokines
   - IL-9: mast-cell growth factor
   - IL-11: elevates platelet count in patients given chemotherapy
   - IL-12: expands and activates resting NK cells
   - IL-15: expands and activates resting NK cells
   - IL-21: limits viability of NK cells
4. Proinflammatory cytokines
   - IL-1, TNF-α, IL-6: participate in the acute-phase response and synergize to mediate inflammation, shock, and death
   - IL-12: stimulates IFN (production by T and NK cells)
   - IL-17: acts on monocytes to induce secretion of proinflammatory mediators such as IL-8, TNF, and GM-CSF
   - IL-18: induces IFN-γ, GM-CSF, TNF-α; upregulates chemokine receptors
   - IL-23: drives the development of autoreactive IL-17–producing T cells and promotes chronic inflammation
5. Antiinflammatory cytokines
   - IL-4: reduces endotoxin-induced TNF and IL-1 production
   - IL-6: inhibits TNF production
   - IL-10: suppresses lymphocyte functions and downregulates production of proinflammatory cytokines; antiatherogenic
   - IL-11: cytoprotective effect on bowel mucosa, skin and joint inflammation
   - IL-13: downregulates functions of macrophages, suppresses production of proinflammatory cytokines
   - TGF-β: has immunosuppressive effects, inhibits IL-1 and TNF gene expression
   - IL-1Rα: competes with the binding of IL-1 to its cell surface receptors and blocks IL-1R
   - TNFsR: soluble TNF receptor; by binding TNF, blocks interaction of TNF with the target cell

*This is not an exhaustive list.

G-CSF, Granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IL-1R, interleukin-1 receptor; M-CSF, macrophage colony-stimulating factor; MHC, major histocompatibility complex; MCP-1, monocyte chemotactic protein; NK, natural killer; RANTES, regulated on activation normal t cell expressed and secreted; SCF, stem cell factor; TGF, transforming growth factor; Th1, Th2, Th17, T-helper types 1, 2, and 17; TNF, tumor necrosis factor.

Modified from Whiteside TL: Cytokine measurements and interpretation of cytokine assays in human disease, J Clin Immunol *14:327–339, 1994.*

and only those cells that have productive rearrangements will survive, so a majority of cells are lost. The next stage is the **pre-B cell,** during which immunoglobulin (Ig) light chain genes are rearranged. The **pre-B cell** is distinguished by the expression of cytoplasmic μ heavy chains but no sIgM, because immunoglobulin light chains are not yet produced. The pre-B cells must rearrange the same light chain gene on both chromosomes for a productive rearrangement, so when this does not happen the cells are lost. Fewer cells are lost between the pre-B and immature B cell stages than in the pro-B to pre-B transition. Next is the **immature B-cell** stage, during which the light-chain genes have already been rearranged and sIgM but not sIgD is expressed. The last stage of antigen-independent B-cell development is the **mature or virgin B cell,** which co-expresses both sIgM and sIgD. Pre-B cells can be found in fetal liver at 7 wk gestation, sIgM+ and sIgG+ B cells at between 7 and 11 wk, and sIgD+ and sIgA+ B cells by 12-13 wk. By 14 wk of embryonic life, the percentage of circulating lymphocytes bearing sIgM and sIgD is the same as in cord blood and slightly higher than in the blood of adults.

Antigen-dependent stages of B-cell development are those that develop after the mature or virgin B cell is stimulated by antigen through its antigen receptor (sIg); the outcome is the differentiation of the cell and its progeny into sIg+ memory (CD27) B cells (for that particular antigen) and plasma cells, which synthesize and secrete antibody, which is **antigen-specific immunoglobulin.** Deficiency of activation-induced cytidine deaminase (AICDA) or of uracil DNA glycosylase (UNG), as seen in 2 forms of autosomal recessive hyper IgM, can result in a failure of isotype switching so that only IgM antibodies are formed.

There are 5 **immunoglobulin isotypes**, which are defined by unique heavy-chains: IgM, IgG, IgA, IgD, and IgE. IgG and IgM, the only complement-fixing isotypes, are the most important immunoglobulins in the blood and other internal body fluids for protection against infectious agents. IgM is confined primarily to the intravascular compartment because of its large size, whereas IgG is present in all internal body fluids. IgA is the major protective immunoglobulin of external secretions—in the gastrointestinal, respiratory, and urogenital tracts—but it is also present in the circulation. IgE, present in both internal and external body fluids, has a major role in host defense against parasites. Because of high-affinity IgE receptors on basophils and mast cells, however, IgE is the principal mediator of allergic reactions of the immediate type. The significance of IgD is still not clear. There are also **immunoglobulin subclasses** including 4 subclasses of IgG (IgG_3, IgG_2, IgG_3, and IgG_4) and 2 subclasses of IgA (IgA_1 and IgA_2). These subclasses each have different biologic roles. For example, antipolysaccharide antibody activity is found predominantly in the IgG_2 subclass. Secreted IgM and IgE have been found in abortuses as young as 10 wk, and IgG as early as 11-12 wk. Even though these B-cell developmental stages have been described in the context of B-cell ontogeny in utero, it is important to recognize that the process of B-cell development from pluripotential stem cells goes on throughout postnatal life. Despite the capacity of fetal B lymphocytes to differentiate into immunoglobulin-synthesizing and -secreting cells, plasma cells are not usually found in lymphoid tissues of a fetus until about 20 wk gestation, and then only rarely, because of the sterile environment of the uterus. Peyer patches have been found in significant numbers by the 5th intrauterine mo, and plasma cells have been seen in the lamina propria by 25 wk gestation. Before birth there may be primary follicles in lymph nodes, but secondary follicles are usually not present.

A human fetus begins to receive significant quantities of maternal IgG transplacentally at around 12 wk gestation, and the quantity steadily increases until, at birth, cord serum contains a concentration of IgG comparable to or greater than that of maternal serum. IgG is the only class to cross the placenta to any significant degree. All 4 IgG subclasses cross the placenta, but IgG_2 does so least well. A small amount of IgM (10% of adult levels) and a few nanograms of IgA, IgD, and IgE are normally found in cord serum. Because none of these proteins crosses the placenta, they are presumed to be of fetal origin. These observations raise the possibility that certain antigenic stimuli normally cross the placenta to provoke responses, even in uninfected fetuses. Some atopic infants occasionally have IgE antibodies to antigens, such as egg white, to which they have had no known exposure during postnatal life, suggesting that synthesis of these antibodies could have been induced in the fetus by antigens ingested by the mother.

Natural Killer–Cell Development

NK cell activity is found in human fetal liver cells at 8-11 wk of gestation. NK lymphocytes are also derived from bone marrow precursors. Thymic processing is not necessary for NK-cell development, although NK cells have been found in the thymus. After release from bone marrow, NK cells enter the circulation or migrate to the spleen, with very few NK cells in lymph nodes. In normal individuals, NK cells represent 8-10% of lymphocytes, but the percentages are sometimes slightly lower in cord blood.

Unlike T and B cells, NK cells do not rearrange antigen receptor genes during their development but are defined by their functional capacity to mediate non–antigen-specific cytotoxicity. NK cells have killer inhibitory receptors that recognize certain MHC antigens and inhibit the killing of normal allogeneic cells in 4 specific patterns of reactivity. The genetic loci controlling these receptors are different from MHC alloantigenic loci, and have been mapped to chromosome 19. Virtually all NK cells express CD56, and more than 90% bear CD16 (FcγRIII) on the cell surface. Other CD antigens found on NK cells include CD57 (50-60%), CD7 and CD2 (70-90%), and CD8 (30-40%) (see Table 123-1). Although NK cells share surface antigens with T and myeloid cells, the lineage relationship of NK cells to the latter is still unclear. Some humans with autosomal recessive SCID who have profound deficiencies in T and B cells, have abundant NK cells, whereas those with X-linked and Jak3-deficient SCID have no T or NK cells.

Immune Cell Interactions

Immune cell interaction is of crucial importance to all phases of the adaptive immune response. Unlike the B-cell antigen receptor (Ig), which can recognize native antigen, the TCR can recognize only processed antigenic peptides presented to it by MHC molecules such as **HLA-A, -B, and -C antigens (class I)** and **HLA-DR, -DP, and -DQ antigens (class II)**. The MHC molecules have a groove in their protein structure where peptides fit. Class I MHC molecules are found on most nucleated cells in the body. Class II MHC molecules are found on **antigen-presenting cells (APCs),** which include macrophages, dendritic cells, and B cells. The peptides found in the groove of class I HLA molecules come from proteins normally made in the cell that are degraded and inserted into the groove. The peptides include viral peptides if the cell is infected with a virus. The peptides present in the groove of class II molecules come from exogenous native antigens such as vaccine and bacterial proteins. These proteins are taken up by APCs, degraded, and expressed on the cell surface in the groove of class II HLA molecules. The TCR then interacts with the peptide-bearing HLA molecule and, through its functional and physical link to the CD3 complex of signal-transducing molecules, sends a signal to the T cell to produce cytokines that ultimately result in T-cell activation and proliferation.

Two of the main functions of T cells are to signal B cells to make antibody by producing cytokines and membrane molecules that can serve as ligands for non–antigen-receptor B-cell surface molecules and to kill virally infected cells or tumor cells. For a T cell to perform either of these functions, it first must bind to an APC or to a target cell (the immunologic synapse). For high-affinity binding of T cells to APCs or target cells, several molecules on T cells, in addition to TCRs, bind to molecules on APCs or target cells. The CD4 molecule binds directly to MHC class II molecules on APCs. CD8 on cytotoxic T cells binds the MHC class I molecule on the target cell. Both CD4 and CD8 molecules are directly involved in the regulation of T-cell activation and are physically linked intracellularly to the p56-lck protein tyrosine kinase. The cytoplasmic tail of CD45, the common leukocyte antigen, is a tyrosine phosphatase capable of regulating T-cell signal-transduction events by virtue of the fact that p56-lck is a substrate for CD45 phosphatase activity. Depending on which isoform of CD45 is present on

the T cell (CD45RO on memory T cells, CD45RA on naïve T cells), mechanisms by which CD45 could upregulate or downregulate T-cell triggering have been proposed. Indeed, one form of human SCID is caused by a deficiency of CD45. Lymphocyte function-associated antigen 1 (LFA-1) on the T cell binds a protein called ICAM-1 (intracellular adhesion molecule 1), designated CD54, on APCs. CD2 on T cells binds LFA-3 (CD58) on the APCs. With the adhesion of T cells to APCs (the immunologic synapse), T-helper (Th) cells are stimulated to make interleukins and upregulate cell surface molecules, such as the CD40 ligand (CD154), that provide help for B cells, and cytotoxic T cells are stimulated to kill their targets.

In the **primary antibody response,** native antigen is carried to a lymph node draining the site, taken up by specialized cells called **follicular dendritic cells (FDCs),** and expressed on their surfaces. Virgin B cells bearing sIg specific for that antigen then bind to the antigen on the surfaces of the FDCs. If the affinity of the B-cell sIg antibody for the antigen present on the FDCs is sufficient, and if other signals are provided by activated Th cells, the B cell develops into an antibody-producing plasma cell. If the affinity is not high enough or if T-cell signals are not received, the B cell dies through apoptosis. The signals from activated Th cells include several cytokines (IL-4, IL-5, IL-6, IL-10, IL-13, and IL-21) that they secrete (see Table 123-2) and a surface T-cell molecule, the CD40 ligand or CD154, which, on contact of the activated CD4 positive T cell with the B cell, binds to CD40 on the B-cell surface. CD40 is a type I integral membrane glycoprotein expressed on B cells, monocytes, some carcinomas, and a few other types of cells. It belongs to the tumor necrosis factor/nerve growth factor receptor family. Crosslinking of CD40 on B cells by CD154 on T cells in the presence of certain cytokines causes the B cells to undergo proliferation and to initiate immunoglobulin synthesis. In the primary immune response, only IgM antibody is usually made, and most of it is of relatively low affinity. Some B cells become memory B cells during the primary immune response. These cells switch their immunoglobulin genes so that IgG, IgA, and/or IgE antibodies of higher affinity are formed on a secondary exposure to the same antigen. The **secondary antibody response** occurs when these memory B cells again encounter that antigen. Plasma cells form, just as in the primary response; however, many more cells are rapidly generated, and IgG, IgA, and IgE antibodies are made. In addition, genetic changes in immunoglobulin genes (somatic hypermutation) lead to increased affinity of those antibodies. A lack of somatic hypermutation is seen in deficiency of activation-induced cytidine deaminase (AID) or uracil-N-glycosylase (UNG). The exact pattern of isotype response to antigen in normal individuals varies, depending on the type of antigen and the cytokines present in the microenvironment.

For NK-mediated lysis, binding to the target is of crucial importance. This is best exemplified by persons with leukocyte adhesion deficiency type I (LAD-1) who have mutations in the gene encoding CD18, or the β chain of 3 different adhesion molecules (LFA-1, CR3, and p150,95), and who lack NK function. Thus, binding of NK cells to their targets is facilitated by LFA-1-ICAM interactions. CD56 or NCAM (neural cell adhesion molecule) also mediates homotypic adhesion of NK cells. FcγRIII, or the low-affinity IgG receptor, has a higher affinity for IgG when it is present on NK cells than when it is on neutrophils. FcγRIII also permits NK cells to mediate **antibody-dependent cellular cytotoxicity,** where antibody is bound through its Fc region to the FcγRIII. The antibody-combining portion of the IgG attaches to the target cell, and the NK cell, attached to the target by the Fc portion of the antibody, kills the target cell.

POSTNATAL LYMPHOPOIESIS

T Cells and T-Cell Subsets

Although the percentage of CD3 T cells in cord blood is somewhat less than in the peripheral blood of children and adults, T cells are actually present in higher number because of a higher absolute lymphocyte count in normal infants. An additional distinction is that the ratio of CD4 to CD8 T cells is usually higher (3.5-4 : 1) in cord blood than in blood of children and adults (1.5-2 : 1). Virtually all T cells in cord blood bear the CD45RA (naïve) isoform, and a dominance of CD45RA over CD45RO T cells persists during the 1st 2-3 yr of life, after which time the numbers of cells bearing these 2 isoforms gradually equalize. Th cells can be further subdivided according to the cytokines they produce when activated. **Th1 cells** produce IL-2 and IFN-γ, which promote cytotoxic T-cell or delayed hypersensitivity types of responses, whereas **Th2 cells** produce IL-4, IL-5, IL-6, IL-13, and IL-21 (see Table 123-2), which promote B-cell responses and allergic sensitization, and **Th17** cells produce IL-17. Development of Th cells into Th17 cells occurs when IL-6 and transforming growth factor β are present but IL-4 and IL-12 are absent. Th17 cells produce IL-21, which acts in an autocrine manner to activate STAT3, a transcription factor required for their further development as Th17 cells. Th17 cells express the receptor for the cytokine IL-23, stimulation that is required for development of Th17 effector activity. Th17 promotes inflammation by acting on local tissue cells to cause them to produce chemokines, such as IL-8, that recruit neutrophils and other innate effector cells. It is thought that the absence of these cells in the autosomal dominant form of the hyper-IgE syndrome (see Chapter 126) accounts for those patients' infection susceptibility to *Candida*. There are important additional subsets of T cells that have regulatory functions. These include CD25 high + T cells (**Treg cells**), also characterized by the presence of FOXp3 (absent in IPEX syndrome [see Chapter 126]) and considered to be important in the prevention of autoimmune diseases, and T cells that have phenotypic characteristics of NK cells (NKT cells). Cord blood T cells have the capacity to respond normally to **T-cell mitogens** (phytohemagglutinin, concanavalin A, and pokeweed mitogen) and are capable of mounting a normal mixed leukocyte response. Normal newborn infants also have the capacity to develop antigen-specific T-cell responses at birth, as evidenced by vigorous tuberculin reactivity a few wk after bacillus Calmette-Guérin vaccination on day 1 of life. Because patients in the 1st few mo of life may have unrecognized severe T-cell defects, most hospitals now routinely irradiate all blood products given young infants. T-cell defects can readily be detected even at birth by calculating the absolute lymphocyte count because T cells normally constitute 70% of circulating lymphocytes and their absence results in striking lymphopenia (see Fig. 122-2). T-cell lymphopenia also serves as the basis for the currently used newborn screening test for SCID.

B Cells and Immunoglobulins

Newborn infants have increased susceptibility to infections with Gram-negative organisms because IgM antibodies, which are heat-stable opsonins, do not cross the placenta. The level of the heat-labile opsonin, C3b, is also lower in newborn serum than in adults. These factors probably account for impaired phagocytosis of some organisms by newborn polymorphonuclear cells. Maternally transmitted IgG antibodies serve quite adequately as heat-stable opsonins for most Gram-positive bacteria, and IgG antibodies to viruses afford adequate protection against those agents. Because there is a relative deficiency of the IgG_2 subclass, antibodies to capsular polysaccharide antigens may be deficient. Because premature infants have received less maternal IgG by the time of birth than full-term infants, their serum opsonic activity is low for all types of organisms.

B lymphocytes are present in cord blood in slightly higher percentages but considerably higher numbers than in the blood of children and adults, reflecting the higher absolute lymphocyte counts in all normal infants. Cord blood B cells do not synthesize the range of immunoglobulin isotypes made by B cells from children and adults when stimulated with anti-CD40 plus IL-4 or IL-10, producing primarily IgM and at a much reduced quantity.

Neonates begin to synthesize antibodies of the IgM class at an increased rate very soon after birth in response to the immense antigenic stimulation of their new environment. Premature infants appear to be as capable of doing this as do full-term infants. At about 6 days after birth, the serum concentration of IgM rises sharply. This rise continues until adult levels are achieved by ≈1 yr of age. Cord serum from noninfected normal newborns does not contain detectable IgA. Serum IgA is normally first detected at around the 13th day of postnatal life; the level gradually increases during early childhood until adult levels are achieved by 6-7 yr of age. Cord serum contains an IgG

concentration comparable to or greater than that of maternal serum. Maternal IgG gradually disappears during the 1st 6-8 mo of life, while the rate of infant IgG synthesis increases (IgG_1 and IgG_3 faster than IgG_2 and IgG_4 during the 1st yr) until adult concentrations of total IgG are reached and maintained by 7-8 yr of age. IgG_1 and IgG_4 reach adult levels first, followed by IgG_3 at 10 yr and IgG_2 at 12 yr of age. The serum IgG level in infants usually reaches a low point at ≈3-4 mo of postnatal life. The rate of development of IgE generally follows that of IgA. After adult concentrations of each of the 3 major immunoglobulins are reached, these levels remain remarkably constant for a normal individual. The capacity to produce specific antibodies to protein antigens is intact at the time of birth. Normal infants cannot usually produce antibodies to polysaccharide antigens until after 2 yr of age unless the polysaccharide is conjugated to a protein carrier, as is the case for the conjugate *Haemophilus influenzae* type b and *Streptococcus pneumoniae* vaccines.

Natural Killer Cells

The percentage of NK cells in cord blood is usually lower than in the blood of children and adults, but the absolute number of NK cells is approximately the same, owing to the higher lymphocyte count. The capacity of cord blood NK cells to mediate target lysis in either NK-cell assays or antibody-dependent cellular cytotoxicity assays is roughly two-thirds that of adults.

Lymphoid Organ Development

Lymphoid tissue is proportionally small but rather well developed at birth and matures rapidly in the postnatal period. The thymus is largest relative to body size during fetal life and at birth is ordinarily two-thirds of its mature weight, which it attains during the 1st yr of life. It reaches its peak mass, however, just before puberty, and then gradually involutes thereafter. By 1 yr of age, all lymphoid structures are mature histologically. Absolute lymphocyte counts in the peripheral blood also reach a peak during the 1st yr of life (see Fig. 122-2). Peripheral lymphoid tissue increases rapidly in mass during infancy and early childhood. It reaches adult size by approximately 6 yr of age, exceeds those dimensions during the prepubertal years, and then undergoes involution coincident with puberty. The spleen, however, gradually accrues its mass during maturation and does not reach full weight until adulthood. The mean number of Peyer patches at birth is one-half the adult number, and gradually increases until the adult mean number is exceeded during adolescent years.

INHERITANCE OF ABNORMALITIES IN T-, B-, AND NATURAL KILLER–CELL DEVELOPMENT

More than 220 immunodeficiency syndromes have been described (see Table 122-8). Specific molecular defects have been identified in approximately 80% of these diseases. Most are recessive traits, several of which are caused by mutations in genes on the X chromosome and others by mutations on autosomal chromosomes. The molecular bases of 7 X-linked immunodeficiency disorders affecting T, B, and/or NK cells are known (see Chapters 124-126): X-linked immunodeficiency with hyper-IgM, X-linked lymphoproliferative syndrome, XIAD, X-linked agammaglobulinemia, X-linked SCID, the Wiskott-Aldrich syndrome, and nuclear factor kappa B essential modulator (NEMO). A few of the autosomal defects for which the molecular basis is known include (1) combined immunodeficiencies caused by abnormalities of purine salvage pathway enzymes, either adenosine deaminase (encoded by a gene on chromosome 20q13-ter) or purine nucleoside phosphorylase (encoded by a gene on chromosome 14q13.1); (2) combined immunodeficiencies caused by mutations in the gene encoding ZAP-70 (localized to chromosome 2q12), a non-src family protein tyrosine kinase important in T-cell signaling; (3) SCID caused by mutations in the gene on chromosome 19p13.1 encoding Janus kinase 3 (Jak3), the primary signal transducer from the common cytokine receptor γ chain (γc); (4) mutations in genes on chromosome 11 that encode components of the TCR, that is, CD3 γ, δ, and ε; (5) SCID caused by mutations in recombinase activating genes (*RAG1* and *RAG2*); and (6) SCID caused by mutations in the gene on chromosome 5p13 that encodes the α chain of the IL-7 receptor. These are only a few of the conditions for which the mutated genes have been discovered and the number is steadily growing.

PRENATAL DIAGNOSIS AND CARRIER DETECTION

Intrauterine diagnosis of adenosine deaminase and purine nucleoside phosphorylase deficiencies can be established by enzyme analyses on amnion cells (fresh or cultured) obtained before 20 wk gestation. Diagnosis of X-linked or autosomal defects causing SCID, other severe T-cell deficiencies, MHC class I and/or II antigen deficiencies, chronic granulomatous disease, or Wiskott-Aldrich syndrome can be established by direct mutation analysis of cells obtained by chorionic villus sampling or by amniocentesis if the mutation is known in the family or, if not known, by appropriate tests of phenotype or function on small samples of blood obtained by fetoscopy at 18-22 wk of gestation. The same diagnostic procedures can be performed on cord blood, but the only immunodeficiency disorder being routinely screened for is SCID and only 21 states are currently doing this (see Chapter 122). Carriers of any of these conditions can be identified by direct mutation analysis if the family's mutation is known.

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Chapter 124

Primary Defects of Antibody Production

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Of all of the primary immunodeficiency diseases, those affecting antibody production are most frequent. Selective absence of serum and secretory immunoglobulin (Ig)A is the most common defect, with rates ranging from 1 in 333 to 1 in 18,000 persons among different races and ethnicities. By contrast, agammaglobulinemia is estimated to occur with a frequency of only 1 in 10,000 to 1 in 50,000 persons. Patients with antibody deficiency are usually recognized because they have recurrent infections with encapsulated bacteria, predominantly in the upper and lower respiratory tracts; some individuals with selective IgA deficiency or infants with transient hypogammaglobulinemia may have few or no infections. The defective gene products for many primary antibody deficiency disorders have been identified (Table 124-1) and localized (Fig. 124-1). Sometimes the defect is not in the B cell itself but in T cells, which are required for complete B-cell function; some disorders are caused by unknown factors or are secondary to an underlying disease or its treatment (Table 124-2).

X-LINKED AGAMMAGLOBULINEMIA

Patients with X-linked agammaglobulinemia (XLA), or **Bruton agammaglobulinemia,** have a profound defect in B-lymphocyte development resulting in severe hypogammaglobulinemia, an absence of circulating B cells, small to absent tonsils, and no palpable lymph nodes.

Genetics and Pathogenesis

The abnormal gene in XLA maps to q22 on the long arm of the X chromosome and encodes the B-cell protein tyrosine kinase **Btk (Bruton tyrosine kinase).** Btk is a member of the Tec family of cytoplasmic protein tyrosine kinases and is expressed at high levels in all B-lineage cells, including pre-B cells. It appears to be necessary for

Table 124-1 Genetic Basis of Primary Antibody Deficiency Disorders

CHROMOSOME AND REGION	GENE PRODUCT	DISORDER	FUNCTIONAL DEFICIENCIES
1q32	CD21	CVID	Low IgG, low binding of EBV-gp350
2p11	κ Chain	κ Chain deficiency	Absence of immunoglobulins bearing κ chains
2q33	ICOS	ICOS-deficient CVID	Low or absent concentrations of all immunoglobulins
5q13.1	PI3K	B-cell–negative agammaglobulinemia	Low or absent concentrations of all immunoglobulins
6p21.3	Unknown	Selective IgA deficiency; CVID	Low or absent IgA; low concentrations of all immunoglobulins and of switched memory B cells in CVID
11p15.5	CD81	CVID caused by a lack of CD19	Low IgG concentration and poor response to antigens
11q12	CD20	CVID	Low IgG concentration and poor response to polysaccharide antigens
12p13	AID*	Autosomal recessive HIGM type 2	Failure to produce IgG, IgA, and IgE antibodies
12p13	CD27	EBV Lymphoproliferation	Memory B-cell deficiency Hypogammaglobulinemia
12q23-q24.1	UNG	Autosomal recessive HIGM type 5	Failure to produce IgG, IgA, and IgE antibodies
14q32.3	Immunoglobulin heavy chains*	B-cell–negative agammaglobulinemia; in others, selective isotype deficiencies	Absence of antibody production, lack of B cells, in μ heavy-chain mutations; in others, subclasses missing but B cells present
16p11.2	CD19	CD19 deficient CVID	Low or absent concentrations of all immunoglobulins
17p11.2	TACI*	TACI-deficient CVID	Low or absent concentrations of all immunoglobulins
20	CD40*	Autosomal recessive HIGM type 3	Failure to produce IgG, IgA, and IgE antibodies
22q13.1-q13.31	BAFF-R	BAFF-R–deficient CVID	Low or absent concentrations of all immunoglobulins
Xq22	Btk*	XLA or Bruton agammaglobulinemia	Absence of antibody production, lack of B cells
Xq25	SLAM-associated protein (SH2D1A)*	XLP	Lack of anti-EBNA and long-lived T-cell immunity; low immunoglobulins
Xq26	CD154 (CD40 ligand)*	X-linked HIGM type 1	Failure to produce IgG, IgA, and IgE antibodies
Xq28	NEMO	Anhidrotic ectodermal dysplasia with immunodeficiency	Hyper-IgM or -IgG subclass and antipolysaccharide antibody deficiencies

*The gene has been cloned and sequenced.

AID, Activation-induced cytidine deaminase; BAFF-R, B-cell–activating factor of the tumor necrosis factor family receptor; Btk, Bruton tyrosine kinase; CVID, common variable immunodeficiency; EBNA, Epstein-Barr virus nuclear antigen; EBV, Epstein-Barr virus; HIGM, hyper-IgM syndrome; ICOS, inducible costimulatory; NEMO, nuclear factor κB essential modulator; PI3K, phosphatidylinositol 3 kinase; TACI, transmembrane activator, calcium modulator, and cyclophilin ligand interactor; UNG, uracil DNA glycosylase; XLA, X-linked agammaglobulinemia; XLP, X-linked lymphoproliferative disease.

pre–B-cell expansion and maturation into surface Ig-expressing B cells, but probably has a role at all stages of B-cell development; it has also been found in cells of the myeloid series. More than 500 different mutations in the human *Btk* gene are recognized; they encompass most parts of the coding portions of the gene. There is not a clear correlation between the location of the mutation and the clinical phenotype. Carriers are detected by mutation analysis, and prenatal diagnosis of affected male fetuses is possible if the mutation is known in the family.

The expression of Btk in cells of myeloid lineage is of interest because boys with XLA often have neutropenia at the height of an acute infection. It is conceivable that Btk is only one of the signaling molecules participating in myeloid maturation and that neutropenia is observed in XLA only when rapid production of such cells is needed. Some pre-B cells are found in the bone marrow; the percentage of peripheral blood B lymphocytes is <1%. The percentage of T cells is increased, ratios of T-cell subsets are normal, and T-cell function is intact. The thymus is normal.

Seven autosomal recessive defects have also been shown to result in **agammaglobulinemia with an absence of circulating B cell**s (Table 124-3), including mutations in the genes encoding: (1) the μ heavy chain gene; (2) the Igα and (3) Igβ signaling molecules; (4) B-cell linker adaptor protein (BLNK); (5) the surrogate light chain, λ5/14.1; (6) leucine-rich repeat-containing 8 (LRRC8); and (7) the p85α subunit of phosphatidylinositol-3 kinase.

Clinical Manifestations

Most boys afflicted with XLA remain well during the 1st 6-9 mo of life by virtue of maternally transmitted IgG antibodies. Thereafter, they acquire infections with extracellular pyogenic organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, unless they are given prophylactic antibiotics or immunoglobulin therapy. Infections include sinusitis, otitis media, pneumonia, or, less often, sepsis or meningitis. Infections with *Mycoplasma* are also particularly problematic. Chronic fungal infections are seen; *Pneumocystis jiroveci* pneumonia rarely occurs. Viral infections are usually handled normally with the exceptions of hepatitis viruses and enteroviruses. There were several examples of **paralysis** when live polio vaccine was administered to these patients, and chronic, eventually fatal, central nervous system infections with various echoviruses and coxsackieviruses have occurred in a significant number of them. Echovirus-associated **myositis** resembling dermatomyositis has also been observed. These observations suggest a primary role for antibody, particularly secretory IgA, in host defense against enteroviruses. Growth hormone deficiency has also been reported in association with XLA. Neutropenia, responsive to G-CSF, may be present in patients with XLA.

Diagnosis

The diagnosis of XLA should be suspected if **lymphoid hypoplasia** is found on physical examination (minimal or no tonsillar tissue and no

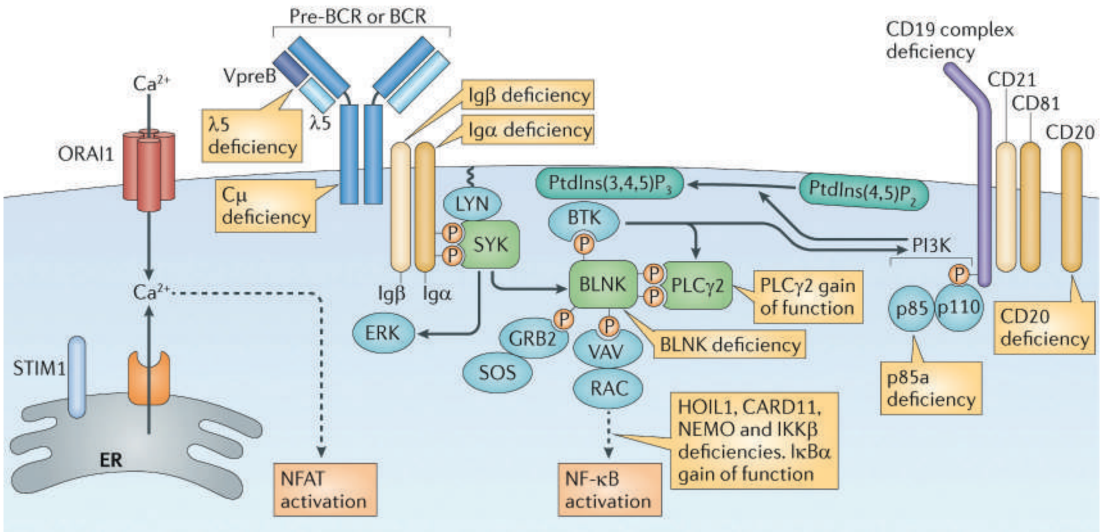

Figure 124-1 The pre-B cell receives proliferation and differentiation signals through the pre–B-cell receptor (BCR) and the coreceptors Igα and Igβ. Signaling from the pre-BCR involves the immunoreceptor tyrosine-based activation motifs (ITAMs) of the coreceptors Igα and Igβ, which scaffold and activate the tyrosine kinase SYK. SYK either activates the extracellular signal-regulated kinase (ERK) pathway or phosphorylates (P) (together with LYN) the adaptor protein B-cell linker (BLNK) and Bruton's tyrosine kinase (BTK), leading to the activation of phospholipase Cγ2 (PLCγ2) and the phosphoinositide-3 kinase (PI3K) pathway. Defects in this pathway affect the pre-BCR (in Cμ or pseudo light-chain λ5), the pre-BCR signal transduction molecules Igα and Igβ, the downstream molecules BTK, BLNK, and PI3K, components of the costimulatory CD19 complex (CD19, CD21, and CD81) and the B-cell marker CD20. The BCR triggers the canonical nuclear factor-κB (NF-κB) pathway through the scaffolding protein CARD11 and activation of the IκB kinase (IKK) complex (comprising IKKα, IKKβ, and NEMO [NF-κB essential modulator]). IKK activation leads to the phosphorylation and degradation of NF-κB inhibitor-α (IκBα) and the subsequent release of the p50-p65 NF-κB heterodimer, which then translocates to the nucleus to regulate gene transcription (not shown). Following antigen binding to antigen receptors (such as the BCR), endoplasmic reticulum Ca^{2+} stores are depleted, STIM1 is activated and ORAI1 Ca^{2+} release-activated Ca^{2+} channels open, resulting in store-operated Ca^{2+} entry. This influx results in activation of the transcription factor NFAT (nuclear factor of activated T cell). The *dashed arrows* indicate downstream signaling events. ER, endoplasmic reticulum; PAD, primary antibody deficiency; PtdIns(4,5)P_2, phosphatidylinositol-4,5-bisphosphate; PtdIns(3,4,5)P_3, phosphatidylinositol-3,4,5-trisphosphate. *(From Durandy A, Kracker S, Fischer A. Primary antibody deficiencies.* Nat Rev Immunol *13:519–533, 2013, Fig. 1, p. 521).*

palpable lymph nodes), and serum concentrations of IgG, IgA, IgM, and IgE are far below the 95% confidence limits for appropriate age- and race-matched controls usually with total immunoglobulins <100 mg/dL. Levels of natural antibodies to type A and B red blood cell polysaccharide antigens (isohemagglutinins) and antibodies to antigens given during routine immunizations are abnormally low in this disorder, whereas they are normal in transient hypogammaglobulinemia of infancy. **Flow cytometry** is an important test to demonstrate the **absence of circulating B cells**, which will distinguish this disorder from common variable immunodeficiency, the hyper-IgM syndrome and transient hypogammaglobulinemia of infancy.

COMMON VARIABLE IMMUNODEFICIENCY

Common variable immunodeficiency (CVID) is a syndrome characterized by hypogammaglobulinemia with phenotypically normal B cells. It has also been called **acquired hypogammaglobulinemia** because of a generally later age of onset of infections. CVID patients may appear similar clinically to those with XLA in the types of infections experienced and bacterial etiologic agents involved, except that echovirus meningoencephalitis is rare in patients with CVID (see Table 124-3). In contrast to XLA, the sex distribution in CVID is almost equal, the age at onset is later (although it may be present in infancy), and infections may be less severe.

Genetics and Pathogenesis

Most patients have no identified molecular diagnosis. CVID is a category of primary immunodeficiency disorders that likely consists of several different genetic defects with autosomal recessive or dominant inheritance. Genes known to produce the CVID phenotype when mutated include *ICOS* (inducible costimulator) deficiency, *SH2DIA* (responsible for X-linked lymphoproliferative disease [XLP]), *CD19, CD20, CD21, CD81, BAFF-R* (B-cell–activating factor of the tumor necrosis factor family receptors), *TACI* (transmembrane activator, calcium modulator, and cyclophilin ligand interactor), and 2 genes that encode DNA methyl transferase (DNMT3B and ZBTB24). These mutations in aggregate account for less than 10% of all cases of CVID.

Because CVID occurs in 1st-degree relatives of patients with selective IgA deficiency, and some patients with IgA deficiency later become panhypogammaglobulinemic, a large subtype of CVID may have a common genetic basis with IgA deficiency. The high incidence of abnormal immunoglobulin concentrations, autoantibodies, autoimmune disease, and malignancy in both CVID and IgA deficiency and in other members of those patients' families also suggests a shared hereditary influence. This concept is supported by the discovery of a high incidence of C4-A gene deletions and C2 rare gene alleles in the class III major histocompatibility complex (MHC) region in individuals with either IgA deficiency or CVID, suggesting that a common susceptibility gene is on chromosome 6. Only a few human leukocyte antigen (HLA) haplotypes are shared by individuals affected with IgA deficiency and CVID, with at least 1 of 2 particular haplotypes being present in 77% of those affected. In 1 large family with 13 members, 2 had IgA deficiency and 3 had CVID. All of the immunodeficient patients in the family had at least 1 copy of an MHC haplotype that is abnormally frequent in IgA deficiency and CVID: HLA-DQB1 *0201, HLA-DR3, C4B-Sf, C4A-deleted, G11-15, Bf-0.4, C2a, HSP70-7.5, TNFa-5, HLA-B8, and HLA-A1. In a study of 83 multiply affected families with IgA deficiency and CVID, increased allele sharing at chromosome 6p21 in the proximal part of the MHC was observed in a susceptibility locus now designated as *IGAD1.* More sensitive genetic analysis in 101 multiple-case and 110 single-case families further localized the defect to the *HLADQ/DR* locus. Environmental factors, particularly drugs such as phenytoin, D-penicillamine, gold, and sulfasalazine are suspected to be triggers for disease expression in individuals with the permissive genetic background.

Most cases of CVID are sporadic or follow an autosomal dominant pattern of inheritance. Patients who lack ICOS, a surface protein on

Table 124-2	Other Conditions Associated with Humoral Immunodeficiency
GENETIC DISORDERS	
Monogenic diseases	Ataxia-telangiectasia Autosomal forms of severe combined immunodeficiency (SCID) Transcobalamin II deficiency and hypogammaglobulinemia Wiskott-Aldrich syndrome X-linked lymphoproliferative disorder (Epstein-Barr virus [EBV] associated) X-linked SCID
Chromosomal anomalies	Chromosome 18q– syndrome Monosomy 22 Trisomy 8 Trisomy 21
SYSTEMIC DISORDERS	
Malignancy	Chronic lymphocytic leukemia Immunodeficiency with thymoma T-cell lymphoma
Metabolic or physical loss	Immunodeficiency caused by hypercatabolism of immunoglobulin Immunodeficiency caused by excessive loss of immunoglobulins and lymphocytes
ENVIRONMENTAL EXPOSURES	
Drug induced	Antimalarial agents Captopril Carbamazepine Glucocorticoids Fenclofenac Gold salts Imatinib Penicillamine Phenytoin Sulfasalazine
Infectious diseases	Congenital rubella Congenital infection with cytomegalovirus Congenital infection with *Toxoplasma gondii* EBV Human immunodeficiency virus

From Schroeder HW, Szymanska-Mroczek E. Primary antibody deficiencies. In Rich RR, Fleisher TA, Shearer, WT, et al, editors: Clinical immunology: principles and practice, *ed 4, St Louis, 2013, WB Saunders.*

activated T cells, have an autosomal recessive pattern of inheritance. Nine such patients from 6 families in the Black Forest of Germany have been found to have identical homozygous large genomic deletions of the *ICOS* gene, suggesting a founder effect. Those who have XLP have an X-linked pattern of inheritance and those with autosomally inherited *TACI* defects may have heterozygous or homozygous mutations.

Despite normal numbers of circulating immunoglobulin-bearing B lymphocytes and the presence of lymphoid cortical follicles, blood B lymphocytes from CVID patients do not differentiate normally into immunoglobulin-producing cells when stimulated with pokeweed mitogen in vitro, even when cocultured with normal T cells. They also have a deficiency of switched memory B cells. B cells from some CVID and some IgA-deficient patients can be stimulated both to switch isotype and to synthesize and secrete some immunoglobulin when stimulated with anti-CD40 and interleukin (IL)-4 or IL-10. T cells and T-cell subsets are usually present in normal percentages, although T-cell function is depressed in some patients.

Clinical Manifestations

The serum immunoglobulin and antibody deficiencies in CVID may be as profound as in XLA. Patients with CVID often have autoantibody formation and normal-sized or enlarged tonsils and lymph nodes; ≈25% of patients have splenomegaly. CVID has also been associated with a sprue-like enteropathy with or without nodular follicular lymphoid hyperplasia of the intestine, thymoma, alopecia areata, hemolytic anemia, gastric atrophy, achlorhydria, thrombocytopenia, and pernicious anemia. Lymphoid interstitial pneumonia, intestinal lung disease, pseudolymphoma, B-cell lymphomas, amyloidosis, and noncaseating sarcoid-like granulomas of the lungs, spleen, skin, and liver also occur. There is a 438-fold increase in lymphomas among affected women in the 5th and 6th decades of life. CVID has been reported to resolve transiently or permanently in patients who acquire HIV infection.

Recurrent or chronic infections include pneumonia, sinusitis, otitis media, and diarrhea (bacterial, giardiasis). Repeated pulmonary infections may produce bronchiectasis. Sepsis and meningitis with encapsulated bacteria occur more frequently than in the general population. There is often a delay in the diagnosis of more than 5 yr between the first infections and a definitive diagnosis.

SELECTIVE IgA DEFICIENCY

An isolated absence or near absence (<10 mg/dL) of serum and secretory IgA is the most common well-defined immunodeficiency disorder, with a disease frequency as high as 0.33% in some populations. This condition can also be and often is associated with ill health.

The basic defect resulting in IgA deficiency is unknown. Phenotypically normal blood B cells are present. IgA deficiency occasionally remits spontaneously or after discontinuation of phenytoin therapy. The occurrence of IgA deficiency in both males and females and in members of successive generations within families suggests autosomal dominant inheritance with variable expressivity. This defect also occurs commonly in pedigrees containing individuals with CVID. Indeed, IgA deficiency may evolve into CVID, and the finding of rare alleles and deletions of MHC class III genes in both conditions suggests that the susceptibility gene common to these 2 conditions may reside in the MHC region on chromosome 6. IgA deficiency is noted in patients treated with the same drugs associated with producing CVID (phenytoin, D-penicillamine, gold, and sulfasalazine), suggesting that environmental factors may trigger this disease in a genetically susceptible person.

Clinical Manifestations

Infections occur predominantly in the respiratory, gastrointestinal, and urogenital tracts. Bacterial agents responsible are the same as in other antibody deficiency syndromes. Intestinal giardiasis is common. Children with IgA deficiency vaccinated intranasally with killed poliovirus produced local IgM and IgG antibodies. Serum concentrations of other immunoglobulins are usually normal in patients with selective IgA deficiency, although IgG_2 (and other) subclass deficiency has been reported, and IgM (usually elevated) may be monomeric.

Patients with IgA deficiency often have IgG antibodies against cow's milk and ruminant serum proteins. These antiruminant antibodies may cause false-positive results in immunoassays for IgA that use goat (but not rabbit) antisera. IgA deficiency is associated with a celiac-like syndrome, which may or may not respond to a gluten-free diet. The incidence of autoantibodies, autoimmune diseases, and malignancy is increased. Serum antibodies to IgA are reported in as many as 44% of patients with selective IgA deficiency. If these antibodies are of the IgE isotype, they can cause severe or fatal anaphylactic reactions after intravenous administration of blood products containing IgA. Only 5-times washed (in 200-mL volumes) normal donor erythrocytes (frozen blood would have this done routinely), or blood products from other IgA-deficient individuals, should be administered to patients with IgA deficiency. Many intravenous immunoglobulin (IVIG) preparations contain sufficient IgA to cause anaphylactic reactions. Administration of IVIG, which is >99% IgG, is not indicated because most IgA-deficient patients make IgG antibodies normally.

IgG SUBCLASS DEFICIENCIES

Some patients have deficiencies of 1 or more of the 4 subclasses of IgG despite normal or elevated total IgG serum concentration. Some

Table 124-3 The Main Phenotypes of Primary Antibody Deficiencies

PHENOTYPE	MAIN CLINICAL FEATURES	MAIN B-CELL BIOLOGIC FEATURES	KNOWN AFFECTED PROTEINS
Pan-agammaglobulinemia (absence of IgM, IgG, and IgA)	Bacterial infections (in the respiratory tract) and enterovirus infections	Absence of CD19*B cells	λ5, BLNK, Btk, Cμ, Igα, Igβ, and PI3K
Variable pan-hypogammaglobulinemia (CVID)	Bacterial infections (in the respiratory tract and gut), autoimmunity, cancer and increased risk of granuloma	Decreased frequency of CD27* memory B cells: defective plasma cells in tissues	CD19, CD20, CD21, CD27, CD81, DNMT3B, ZBTB24, ICOS, SAP, TACI, and BAFF-R
CSR deficiencies (absence or decrease in levels of IgG and IgA)	Bacterial and opportunistic infections	Decreased frequency of CD27* memory B cells	CD40 and CD40L
	Bacterial infections, autoimmunity and lymphadenopathies	Normal frequency of CD27* memory B cells.	AID and UNG
Selective IgA deficiency	Most often asymptomatic	ND	ND
Selective IgM deficiency	Frequent infections with encapsulated bacteria	No IgM antibody production (absence of allohemagglutinins and polysaccharide-specific antibodies)	
Selective IgG_2 and/or IgG_4 deficiency	Frequent bacterial infections, diagnosis after 2 yr of age; sometimes transient in childhood	Defective polysaccharide-specific antibody production	
Selective polysaccharide antibody deficiency	Bacterial infections (after 2 yr of age)	Normal IgG (including IgG_2 and IgG_4) levels	NF-κB pathway proteins (CARD11, HIOL1 and NEMO), Btk, and CD20

AID, Activation-induced cytidine deaminase; BAFF-R, B-cell–activating factor of the tumor necrosis factor family receptor; BLNK, B-cell linker; Btk, Bruton tyrosine kinase; Cμ, constant region-μ; CD40L, CD40 ligand; CSR, class-switch recombination; CVID, common variable immunodeficiency; ICOS, inducible costimulatory; ND, not determined; NEMO, nuclear factor kappa B essential modulator; NF-κB, nuclear factor kappa B; PI3K, phosphatidylinositol 3 kinase; SAP, signaling lymphocyte activation molecule (SLAM)-associated protein; TACI, transmembrane activator, calcium modulator, and cyclophilin ligand interactor; UNG, uracil DNA glycosylase.

Modified from Durandy A, Kracker S, Fischer A. Primary antibody deficiencies. Nat Rev Immunol *13:519–533, 2013, Table, p. 524.*

patients with absent or very low concentrations of IgG_2 also have IgA deficiency. Other patients with IgG subclass deficiency have gone on to develop CVID, suggesting that the presence of IgG subclass deficiency may be a marker for more generalized immune dysfunction. The biologic significance of the numerous moderate deficiencies of IgG subclasses that have been reported is difficult to assess, particularly because commercial laboratory measurement of IgG subclasses is problematic. IgG subclass measurement is not cost-effective in evaluating immune function in the child with recurrent infection. The more relevant issue is a patient's capacity to make specific antibodies to protein and polysaccharide antigens, because profound deficiencies of antipolysaccharide antibodies have been noted even in the presence of normal concentrations of IgG_2. IVIG should not be administered to patients with IgG subclass deficiency unless they are shown to have a deficiency of antibodies to a broad array of antigens.

IMMUNOGLOBULIN HEAVY- AND LIGHT-CHAIN DELETIONS

Some completely asymptomatic individuals have been documented to have a total absence of IgG_1, IgG_2, IgG_4, and/or IgA_1 as a result of gene deletions. These abnormalities were discovered fortuitously in 16 individuals, 15 of whom had no history of undue susceptibility to infection, and all of whom produced antibodies of all other isotypes in normal quantities. These patients illustrate the importance of assessing specific antibody formation before deciding to initiate IVIG therapy in IgG subclass-deficient patients.

HYPER-IgM SYNDROME

The hyper-IgM syndrome is genetically heterogeneous and characterized by normal or elevated serum IgM levels associated with low or absent IgG, IgA, and IgE serum levels, indicating a defect in the class-switch recombination (CSR) process. Causative mutations have been identified in 2 genes on the X chromosome, the CD40 ligand (hyper-IgM syndrome type 1 [HIGM1]) and NEMO (nuclear factor κB essential modulator, XHM-ED) genes; and 3 genes on autosomal chromosomes, the activation-induced cytidine deaminase (AID) gene (hyper-IgM type 2 [HIGM2]) on chromosome 12, the uracil DNA glycosylase gene (UNG, hyper-IgM type 5 [HIGM5]), on chromosome 12, and the CD40 gene (hyper-IgM type 3 [HIGM3]) on chromosome 20. Distinctive clinical features permit presumptive recognition of the type of mutation in these patients, thereby aiding proper choice of therapy. All such patients should undergo molecular analysis to ascertain the affected gene for purposes of genetic counseling, carrier detection, and decisions regarding definitive therapy.

X-Linked Hyper-IgM Caused By Mutations in the CD40 Ligand: Hyper-IgM Type 1

HIGM1 is caused by mutations in the gene that encodes the CD40 ligand (CD154, CD40L), which is expressed on activated T-helper cells. Boys with this syndrome have very low serum concentrations of IgG and IgA, with a usually normal or sometimes elevated concentration of polyclonal IgM, may or may not have small tonsils, usually have no palpable lymph nodes, and often have profound **neutropenia.**

Genetics and Pathogenesis

B cells from boys with the CD40 ligand defect are capable of synthesizing not only IgM but also IgA and IgG when cocultured with normal activated T-helper cells, indicating that the B cells are actually normal in this condition and that the defect is in the T cells. The abnormal gene is localized to Xq26, and the gene product, CD154 (CD40L), is the ligand for CD40, which is present on B cells and monocytes. CD154 is upregulated on activated T cells. Mutations in CD154 result in an inability to signal B cells to undergo isotype switching, and thus the B cells produce only IgM. The failure of T cells to interact with B cells through this receptor–ligand pair also causes a failure of upregulation of the B cell and monocyte surface molecules CD80 and CD86 that interact with CD28/CTLA4 on T cells, resulting in failure of "crosstalk" between immune system cells. The failure of interaction of the molecules of those pathways results in a propensity for tolerogenic T-cell signaling and defective recognition of tumor cells. More than 73

distinct point mutations or deletions in the gene encoding CD154 have been identified in 87 unrelated families, giving rise to frame shifts, premature stop codons, and single amino acid substitutions, most of which are clustered in the domain with homology to tumor necrosis factor (TNF), located in the carboxyterminal region.

Clinical Manifestations

Similar to patients with XLA, boys with the CD40 ligand defect become symptomatic during the 1st or 2nd yr of life with recurrent pyogenic infections, including otitis media, sinusitis, pneumonia, and tonsillitis. They have marked susceptibility to *P. jiroveci* pneumonia, and are frequently profoundly neutropenic. Lymph node histology shows only abortive germinal center formation with severe depletion and phenotypic abnormalities of follicular dendritic cells. These patients have normal numbers of circulating B lymphocytes, but a decreased frequency of CD27+ memory B cells. Circulating T cells are also present in normal number and in vitro responses to mitogens are normal, but there is decreased antigen-specific T-cell function. In a study of patients with the CD40 ligand defect, 23.3% had died at a mean age at death of 11.7 yr. In addition to opportunistic infections such as *P. jiroveci* pneumonia, there is an increased incidence of extensive verruca vulgaris lesions, *Cryptosporidium* enteritis, subsequent liver disease, and an increased risk of malignancy. Because of the poor prognosis, the treatment of choice is an HLA-identical hematopoietic stem cell transplant at an early age. Alternative treatment for this condition is monthly infusion of IVIG. In patients with severe neutropenia, the use of granulocyte colony-stimulating factor has been beneficial.

X-Linked Hyper-IgM Caused By Mutations in the Gene Encoding Nuclear Factor κB Essential Modulator; XHM-ED

This syndrome in males is characterized most often clinically as **anhydrotic ectodermal dysplasia with associated immunodeficiency (EDA-ID).** The condition results from missense mutations in the IKBKG gene at position 28q on the X chromosome that encodes **NEMO,** a regulatory protein required for the activation of the transcription factor NF-κB. Germ line loss-of-function mutations cause the X-linked dominant condition incontinentia pigmenti in females and are lethal in male fetuses. Mutations in the coding region of IKBKG are associated with EDA-ID. The immunodeficiency is variable, with most patients showing impaired antibody responses to polysaccharide antigens. Some patients with EDA-ID have hyper-IgM. Pharmacologic inhibitors of NF-κB activation have been shown to downregulate CD154 messenger RNA and protein levels, suggesting the mechanism of hyper-IgM in this condition. The hyper-IgM patients with this defect should be easily recognizable because of the presence of ectodermal dysplasia, although there are some patients with this condition who do not have ectodermal dysplasia.

Autosomal Recessive Hyper-IgM Caused By Mutations in the Gene for Activation-Induced Cytidine Deaminase: Hyper-IgM Type 2

An autosomal recessive form of hyper-IgM syndrome is caused by mutations in the gene for AID.

Genetics and Pathogenesis

Patients with autosomal recessive hyper-IgM usually have normal numbers of circulating B lymphocytes, but, in contrast to patients with the CD40 ligand defect, B cells from these patients are not able to switch from IgM-secreting to IgG-, IgA-, or IgE-secreting cells, even when cocultured with normal T cells or with monoclonal antibodies to CD40 and a variety of cytokines. When their B cells are cultured in vitro, they spontaneously secrete large amounts of IgM, but this is not further augmented by the addition of cytokines. Thus, in these patients, there is truly an intrinsic B-cell abnormality. The defect in many such patients has been identified as due to mutations in a gene on chromosome 12p13 that encodes AID. AID is a single-stranded DNA deaminase required for somatic hypermutation (SHM) and class-switch recombination (CSR) of immunoglobulin genes. Histologic examination of the enlarged lymph nodes reveals the presence of giant germinal centers (5-10 times larger than normal) filled with highly proliferating B cells. Proliferating B cells coexpress IgM, IgD, and CD38, a phenotype previously described for a small B-cell subset corresponding to germinal center founder cells. These cells are thought to correspond to a transitional stage between follicular mantle and germinal center B cells, at the onset of somatic mutation of the Ig variable region gene and antigen-driven selection. Deficiency of AID results in impaired terminal differentiation of B cells, a failure of CSR, and lack of immunoglobulin gene SHM. They have a normal frequency of CD27+ memory B cells.

Clinical Manifestations

Concentrations of serum IgG, IgA, and IgE are very low in AID deficiency. In contrast to the CD40 ligand defect, however, the serum IgM concentration in patients with AID deficiency is usually markedly elevated and polyclonal. Patients with this form of hyper-IgM have lymphoid hyperplasia, are generally older at age at onset, do not have susceptibility to *P. jiroveci* pneumonia, often do have isohemagglutinins, and are much less likely to have neutropenia unless it occurs on an autoimmune basis. They have a tendency, however, to develop autoimmune and inflammatory disorders including diabetes mellitus, polyarthritis, autoimmune hepatitis, hemolytic anemia, immune thrombocytopenia, Crohn disease, and chronic uveitis. With early diagnosis and monthly infusions of IVIG, as well as good management of infections with antibiotics, patients with AID mutations generally have a more benign course than do boys with the CD40 ligand defect.

Autosomal Recessive Hyper-IgM Caused By Mutations in the Gene for Uracil DNA Glycosylase; Hyper-IgM Type 5

Genetics and Pathogenesis

AID deaminates cytosine into uracil in targeted DNA, which is followed by uracil removal by UNG. Severely impaired CSR was found in 3 hyper-IgM patients reported to have UNG deficiency. Their clinical characteristics were similar to those with AID deficiency, with increased susceptibility to bacterial infections and lymphoid hyperplasia. The patients had a markedly elevated serum IgM and profoundly decreased serum IgG and IgA concentrations. Their B cells had an intrinsic defect in CSR when stimulated with anti-CD40 and IL-4 and constitutively produced high quantities of IgM. They had only a partial defect in SHM, however, and they have a normal frequency of CD27+ memory B cells.

Autosomal Recessive Hyper-IgM Caused By Mutations in CD40: Hyper-IgM Type 3

Five patients with autosomal recessive hyper-IgM from 4 unrelated families failed to express CD40 on their B-cell surfaces and were found to have mutations in the CD40 gene. Clinical manifestations included recurrent sinopulmonary infections, *P. jiroveci* pneumonia and *Cryptosporidium parvum* infections. The patients had very low levels of IgG and IgA and normal or high levels of IgM. More recently, 2 patients were identified with such mutations who did express the CD40 protein on their B cells and monocytes, so mutation analysis was required to make the diagnosis.

Genetics and Pathogenesis

CD40 is a type I integral membrane glycoprotein encoded by a gene on chromosome 20 and belonging to the TNF and nerve growth factor receptor superfamily. It is expressed on B cells, macrophages, dendritic cells, and a few other types of cells. Mutations in the CD40 gene cause an autosomal recessive form of hyper-IgM syndrome that is clinically indistinguishable from HIGM1, resulting from the X-linked CD40 ligand (CD154) defect. In contrast to the CD40 ligand defect, however, the B cells in the autosomal recessive condition are intrinsically abnormal and cannot isotype switch. The T cells are normal except to the extent that they cannot cause upregulation of CD80 and CD86 on B cells and macrophages to interact with CD28/CTLA4 on T cells.

Hyper-IgM Type 4

The defective gene in a 4th autosomal recessive form of hyper-IgM syndrome has not yet been identified, but appears to be in a gene downstream of AID. These patients all have defective CSR with preserved SHM.

X-LINKED LYMPHOPROLIFERATIVE DISEASE

XLP disease, also referred to as **Duncan disease** after the original kindred in which it was described, is an X-linked recessive trait characterized by an inadequate immune response to infection with Epstein-Barr virus (EBV).

Genetics and Pathogenesis

The defective gene in XLP was localized to Xq25, cloned, and the gene product was initially named SAP (for SLAM-associated protein), but is now known officially as SH2D1A. SLAM (signaling lymphocyte activation molecule) is an adhesion molecule that is upregulated on both T and B cells with infection and other stimulation. SH2D1A is highly expressed in thymocytes and peripheral blood T and NK cells, with a prevalent expression on T-helper type 1 cells. Its presence on B lymphocytes is unclear. Thus, although antibody deficiency is frequently present, this is really a T- and natural killer (NK)-cell defect. SH2D1A competes with SHP-2 for binding to SLAM and, as such, is a regulatory molecule. In XLP patients, the absence of SH2D1A can lead to an uncontrolled cytotoxic T-cell immune response to EBV. The SH2D1A protein associates permissively with 2B4 on NK cells; thus, selective impairment of 2B4-mediated NK-cell activation also contributes to the immunopathology of XLP.

XLP type 2 is less common and is caused by a mutation in *XIAP* (X-linked inhibitor of apoptosis protein); disease manifestations are similar to XLP. X-linked immunodeficiency with magnesium defect (XMEN syndrome) is due to a loss of function mutation of the magnesium transporter protein and manifests with chronic EBV infection, EBV lymphoproliferative disorders, and CD4 lymphopenia.

Clinical Manifestations

Affected males are usually healthy until they acquire EBV infection. The mean age of presentation is <5 yr. There are 3 major clinical phenotypes: (1) fulminant, often fatal, infectious mononucleosis (50% of cases); (2) lymphomas, predominantly involving B-lineage cells (25%); and (3) acquired hypogammaglobulinemia (25%). There is a marked impairment in production of antibodies to the EBV nuclear antigen, whereas titers of antibodies to the viral capsid antigen have ranged from absent to markedly elevated. XLP has an unfavorable prognosis; 70% of affected boys die by age 10 yr. Only 2 XLP patients are known to have survived beyond 40 yr of age. Unless there is a family history of XLP, diagnosis prior to the onset of complications is difficult because affected individuals are asymptomatic initially. Using mutation analysis, it is possible to identify affected males within identified kindreds before they develop primary EBV infection. Approximately half of the few patients with XLP given HLA-identical related or unrelated stem cell transplants are surviving without signs of the disease.

Two pedigrees have been reported in which boys in one arm of each pedigree were diagnosed with CVID, whereas those in the other arms had fulminant infectious mononucleosis. The family members with CVID never gave a history of infectious mononucleosis. All affected members of each pedigree had the same distinct SH2D1A mutation, however, despite the different clinical phenotypes. Because the SH2D1A mutation was the same but the phenotype varied in these families, XLP should be considered in all males with a diagnosis of CVID, particularly if there is more than one male family member with this phenotype.

CD27 Deficiency

CD27 deficiency, an autosomal recessive condition, was found to be associated with EBV lymphoproliferation, EBV lymphoma and hypogammaglobulinemia. CD27 is commonly used as marker of memory B cells for the classification of B-cell deficiencies including common variable immune deficiency. It is a member of the TNF receptor family and interacts with CD70 to influence T-, B-, and NK-cell functions. Disturbance of this axis impairs immunity and memory generation against viruses including EBV, influenza, and others.

Bibliography is available at Expert Consult.

124.1 Treatment of B-Cell Defects

Rebecca H. Buckley

Except for the CD40 ligand defect and XLP, for which stem cell transplantation is recommended, judicious use of antibiotics to treat documented infections and regular administration of IVIG are the only effective treatments for primary B-cell disorders. The most common forms of replacement therapy are either intravenous or subcutaneous immunoglobulin (IVIG or SCIG). Broad antibody deficiency should be carefully documented before such therapy is initiated. The rationale for the use of IVIG or SCIG is to provide missing antibodies, not to raise the serum IgG or IgG subclass level. The development of safe and effective immunoglobulin preparations is a major advance in the treatment of patients with severe antibody deficiencies, although it is expensive and there have been national shortages. Almost all commercial preparations are isolated from normal plasma by the Cohn alcohol fractionation method or a modification of it. Cohn fraction II is then further treated to remove aggregated IgG. Additional stabilizing agents such as sugars, glycine, and albumin are added to prevent reaggregation and protect the IgG molecule during lyophilization. The ethanol used in preparation of immunoglobulin inactivates HIV; and an organic solvent/detergent step inactivates hepatitis B and C viruses. Some preparations are also nanofiltered to remove infectious agents. Most commercial lots are produced from plasma pooled from 10,000 to 60,000 donors and therefore contain a broad spectrum of antibodies. Each pool must contain adequate levels of antibody to antigens in various vaccines, such as tetanus and measles. However, there is no standardization based on titers of antibodies to more clinically relevant organisms, such as *S. pneumoniae* and *H. influenzae* type b.

The IVIG and SCIG preparations available in the United States have similar efficacy and safety. Rare transmission of hepatitis C virus has occurred in the past, but the potential transmission of hepatitis C virus has been resolved by additional treatment with an organic solvent/detergent mixture. There has been no documented transmission of HIV by any of these preparations. **IVIG or SCIG at a dose of 400 mg/kg per month** achieves trough IgG levels close to the normal range. Higher doses are indicated in patients with chronic or severe respiratory infections. Systemic reactions may occur, but rarely are these true anaphylactic reactions. Anaphylactic reactions caused by a patient's IgE antibodies to IgA in the IVIG or SCIG preparation may occur in patients with CVID or IgA deficiency. Newly diagnosed patients with CVID should be screened through the American Red Cross for anti-IgA antibodies. If anti-IgA antibodies are detected, IVIG therapy should consist of the one available immunoglobulin preparation containing almost no IgA (Gammagard S/D, Baxter).

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Chapter 125

Primary Defects of Cellular Immunity

Rebecca H. Buckley

In general, patients with defects in T-cell function have infections or other clinical problems that are more severe than in patients with antibody deficiency disorders (see Table 122-4). The defective gene products for some primary T-cell diseases are identified (Table 125-1). These individuals rarely survive beyond infancy or childhood. Transplantation of thymic tissue, or of major histocompatibility complex–compatible sibling or haploidentical (half-matched) parental hematopoietic stem cells, is the treatment of choice for patients with primary T-cell defects (see Chapter 135).

THYMIC HYPOPLASIA (DIGEORGE SYNDROME)

Thymic hypoplasia results from dysmorphogenesis of the 3rd and 4th pharyngeal pouches during early embryogenesis, leading to hypoplasia or aplasia of the thymus and parathyroid glands. Other structures forming at the same age are also frequently affected, resulting in anomalies of the great vessels (right-sided aortic arch), esophageal atresia, bifid uvula, congenital heart disease (conotruncal, atrial, and ventricular septal defects), a short philtrum of the upper lip, hypertelorism, an antimongoloid slant to the eyes, mandibular hypoplasia, and low-set, often notched ears (see Chapters 81 and 108). The diagnosis is often first suggested by hypocalcemic seizures during the neonatal period.

Genetics and Pathogenesis

DiGeorge syndrome occurs in both males and females. Microdeletions of specific DNA sequences from chromosome 22q11.2, the **DiGeorge chromosomal region,** are found in a majority of cases. Several candidate genes have been identified in this region. A T-box transcription family member, *TBX1,* is implicated as an etiology for most of the major signs of DiGeorge syndrome. There appears to be an excess of 22q11.2 deletions of maternal origin. Polymerase chain reaction–based genotyping using microsatellite DNA markers located within the commonly deleted region permits rapid detection of such microdeletions. Conotruncal heart defects and 22q deletions are observed in DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome. The **CATCH 22 syndrome** (*c*ardiac, *a*bnormal facies, *t*hymic hypoplasia, *c*left palate, *h*ypocalcemia) includes the broad clinical spectrum of conditions with 22q11.2 deletions. Other deletions associated with DiGeorge and velocardiofacial syndromes have been identified on chromosome 10p13 (see Chapter 81).

Variable hypoplasia of the thymus and parathyroid glands defines **partial DiGeorge syndrome,** which is more frequent than total aplasia; aplasia is present in <1% of patients with DiGeorge syndrome and defines **complete DiGeorge syndrome.** Slightly less than half of patients with complete DiGeorge syndrome are hemizygous at chromosome 22q11. Approximately 15% are born to diabetic mothers. Another 15% of infants have no identified risk factors. Approximately one-third of infants with complete DiGeorge syndrome have **CHARGE association** (*c*oloboma, *h*eart defect, choanal *a*tresia, growth or developmental *r*etardation, *g*enital hypoplasia, and *e*ar anomalies including deafness). Mutations in the chromodomain helicase DNA binding protein 7 (CHD7) gene on chromosome 8q12.2 are found in approximately 60-65% of individuals with CHARGE syndrome. Concentrations of serum immunoglobulins in DiGeorge syndrome are usually normal, but immunoglobulin (Ig) A may be diminished and IgE elevated. Other laboratory findings vary depending on the degree of thymic dysfunction.

Table 125-1 Genetic Basis of Primary Cellular Immunodeficiency Diseases

CHROMOSOME AND REGION	GENE PRODUCT	DISORDER	FUNCTIONAL DEFICIENCIES
1p35-p34.3	Lck	↓↓ CD4 CD8	Lack of T-cell responses to mitogens or to anti-CD3
2p12	CD8α	↓↓ CD8 deficiency	Lack of cytotoxic T cells
2q12	ZAP-70	CD8 deficiency	Failure of CD4 T cells to respond to usual signals
4p13	RhoH	↓ Naïve CD4+ cells	Low number of recent thymic emigrants, restricted T-cell repertoire
5q31-34	ITK	↓ Naïve CD4+ cells Absence of NKT cells	Poor T-cell responses to mitogens, antigens, and anti-CD3
10p13	Unknown	Thymic hypoplasia (DiGeorge syndrome, velocardiofacial syndrome)	Low number of T cells and impaired T-cell function
11q23	CD3γ and ε	CD3 deficiency	Poor T-cell responses to mitogens; lack of cytotoxic T cells; IgG subclass deficiency
14q11.2	TRAC	TCR αβ T-cell deficiency	Poor T-cell responses to mitogens
16p11.2	Coronin-1A	↓↓ CD4 ↓↓ CD8	Poor T-cell response to phytohemagglutinin; impaired antibody responses
20q13.12	MST1/STK4	↓ Naïve T cells Low number of recent thymic emigrants, restricted T-cell repertoire	Poor T-cell responses to mitogens, antigens, and anti-CD3 Decreased switched memory B cells
21q22.3	AIRE	APECED, chronic mucocutaneous candidiasis, parathyroid and adrenal autoimmunity	Poor response to *Candida* antigen; autoimmune responses
22q11.22	?TBX1	Thymic hypoplasia (DiGeorge syndrome, velocardiofacial syndrome)	Low number of T cells and impaired T-cell function

AIRE, Autoimmune regulator; APECED, autoimmune polyendocrinopathy-candidiasis ectodermal dysplasia; Ig, immunoglobulin; ITK, IL-2–inducible tyrosine kinase deficiency; MST1, macrophage-stimulating factor 1; NKT, natural killer T; RhoH, Ras homology family member H; STK4, serine threonine kinase 4; TCR, T-cell receptor; TRAC, T-cell receptor α chain constant region; ZAP-70, zeta-associated protein 70.

Absolute lymphocyte counts are usually only moderately low for age. The CD3 T-cell counts are variably decreased in number, corresponding to the degree of thymic hypoplasia, resulting in an increased percentage of B cells. Lymphocyte responses to mitogen stimulation are absent, reduced, or normal, depending on the degree of thymic deficiency. Thymic tissue, when found, contains Hassall corpuscles, a normal density of thymocytes, and corticomedullary distinction. Lymphoid follicles are usually present, but lymph node paracortical areas and thymus-dependent regions of the spleen show variable degrees of depletion.

Clinical Manifestations

Children with partial thymic hypoplasia may have little trouble with infections and grow normally. Patients with complete DiGeorge syndrome resemble patients with severe combined immunodeficiency in their susceptibility to infections with low-grade or opportunistic pathogens, including fungi, viruses, and *Pneumocystis jiroveci*, and to graft-versus-host disease from nonirradiated blood transfusions. Patients with complete DiGeorge syndrome can develop an atypical phenotype in which oligoclonal T-cell populations appear in the blood associated with rash and lymphadenopathy. These atypical patients appear phenotypically to be similar to patients with **Omenn syndrome** or maternal T lymphocyte engraftment.

It is critical to confirm the diagnosis of complete DiGeorge syndrome in a timely manner because this disease is fatal without treatment. A T-cell count should be obtained on all infants born with primary hypoparathyroidism, CHARGE syndrome, truncus arteriosus, and interrupted aortic arch type B. If a patient has findings consistent with DiGeorge syndrome with or without a rash and lymphadenopathy, the patient should be referred to an immunologist for evaluation.

Treatment

The immune deficiency in the complete DiGeorge syndrome is correctable by cultured unrelated thymic tissue transplants. Some have been given nonirradiated unfractionated bone marrow or peripheral blood transplants from an human leukocyte antigen–identical sibling with subsequent improved immune function because of adoptively transferred donor immunity; however, they have no way of renewing T-cell production because they have no thymus.

DEFECTIVE EXPRESSION OF THE T-CELL RECEPTOR–CD3 COMPLEX

The first type of this disorder was found in 2 brothers in a Spanish family. The proband presented with severe infections and died at 31 mo of age with autoimmune hemolytic anemia and viral pneumonia. His lymphocytes had responded poorly to mitogens and to anti-CD3 in vitro, and could not be stimulated to develop cytotoxic T cells. His antibody responses to protein antigens had been normal, indicating normal T-helper cell function. His 12 yr old brother was healthy but had almost no CD3-bearing T cells and had IgG_2 deficiency similar to his sibling. The defect in this family was caused by mutations in the gene encoding the CD3γ chain (Fig. 125-1).

The second type of this disorder was diagnosed in a 4 yr old French boy who had recurrent *Haemophilus influenzae* pneumonia and otitis media in early life but was later healthy. He had a partial defect in expression of T-cell receptor–CD3 complex, and thus the percentage of CD3 cells was about half-normal, but the level of expression was markedly decreased. The defect was caused by 2 independent CD3ε gene mutations, leading to defective CD3ε chain synthesis. There was a splice site mutation on one allele that did not totally abrogate the normal intron 7 splicing, resulting in partial expression of CD3 on the T cells. Thus, this mutation did not result in failure of T-cell development, whereas mutations in the portions of the gene that encode the extracellular component of CD3ε result in a profound deficiency of circulating mature CD3 T cells.

Two additional unrelated patients from Pakistan were discovered to lack T-cell receptor (TCR)-αβ–positive T cells and were found to have mutations in the TCR α-chain constant (*TRAC*) gene. Clinically they

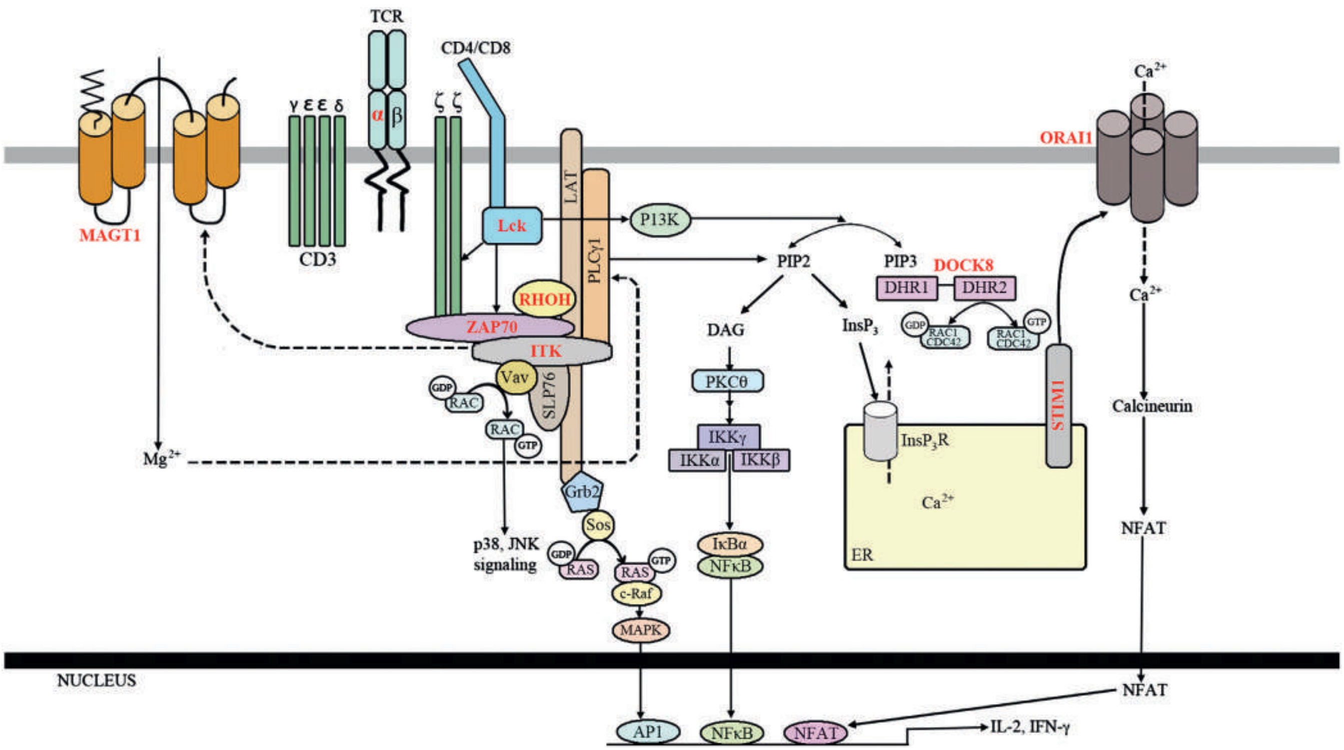

Figure 125-1 Schematic representation of signaling through the T-cell receptor–CD3 complex. Molecules the mutations of which have been associated with partial defect of T-cell development and impaired T-cell function are indicated in *red* and highlighted in *boldface*. *AP1*, Activator protein 1; *DHR*, DOCK-homology region; *Grb2*, growth factor receptor-bound protein 2; *IKK*, IκB kinase; *JNK*, c-Jun N-terminal kinase; *MAPK*, mitogen-activated protein kinase; *NFAT*, nuclear factor of activated T cells; *NFκB*, nuclear factor κB; *PI3K*, phosphoinositide-3 kinase; *PIP3*, phosphatidylinositol (3,4,5)-triphosphate. *(From Notarangelo L: Partial defects of T-cell development associated with poor T-cell function.* J Allergy Clin Immunol *131:1297–1305, 2013, Fig. 1, p. 1299.)*

had increased susceptibility to infections, autoimmunity and profound T cell dysfunction but normal antibody responses. All of their T cells contained TCR gamma delta receptors.

T-CELL ACTIVATION DEFECTS

T-cell activation defects are characterized by the presence of normal or elevated numbers of blood T cells that appear phenotypically normal but fail to proliferate or produce cytokines normally in response to stimulation with mitogens, antigens, or other signals delivered to the TCR, owing to defective signal transduction from the TCR to intracellular metabolic pathways (see Fig. 125-1). These patients have problems similar to those of other T-cell–deficient individuals, and some with severe T-cell activation defects may clinically resemble severe combined immunodeficiency patients. At least 8 new forms of T-cell activation defects have been discovered. The description of only a few of these conditions is included here (see Table 125-1) and DOCK8 deficiency is discussed in Chapter 126.

CD8 LYMPHOCYTOPENIA CAUSED BY MUTATIONS IN THE GENE ENCODING ZETA-ASSOCIATED PROTEIN 70

Patients with this T-cell activation defect present during infancy with severe, recurrent, and often fatal infections. The majority of cases are reported among Mennonites. These patients have normal or elevated numbers of blood B cells and low to elevated serum immunoglobulin concentrations. Their blood lymphocytes exhibit normal expression of the T-cell surface antigens CD3 and CD4, but CD8 cells are almost totally absent. These cells fail to respond normally to mitogens or to allogeneic cells in vitro or to generate cytotoxic T lymphocytes. Natural killer (NK) cell activity is normal. The thymus of 1 patient exhibited normal architecture with normal numbers of CD4:CD8 double-positive thymocytes, but an absence of CD8 single-positive thymocytes. This condition is caused by mutations in the gene encoding **zeta-associated protein 70 (ZAP-70),** a non-src family protein tyrosine kinase important in T-cell signaling that is localized to chromosome 2q12 (see Fig. 125-1). The normal number of CD4:CD8 double-positive T cells results because the thymocytes can use the other member of the same tyrosine kinase family, Syk, to facilitate positive selection. Syk is present at 4-fold higher levels in thymocytes than in peripheral T cells, possibly accounting for the lack of normal responses by the CD4 blood T cells.

Another condition that can result in CD8 deficiency is a mutation in the gene that encodes CD8α. There is a deficiency of cytotoxic T cells in that condition, but the functional immune defect is mild compared to that of ZAP-70 deficiency.

T-Cell Defects Characterized By Epstein-Barr Virus Lymphoproliferation/Lymphoma

In addition to the X-linked lymphoproliferative and X-linked inhibitor of apoptosis protein syndromes and CD27 deficiency characterized primarily as antibody deficiencies (see Chapter 124), there are at least 4 additional primarily T-cell defects that predispose to Epstein-Barr virus (EBV) infections or lymphomas. These include Ras homology family member H (RhoH) deficiency, macrophage-stimulating 1 (MST1)/serine threonine kinase 4 (STK4) deficiency, interleukin (IL)-2–inducible tyrosine kinase (ITK) deficiency and Coronin-1A deficiency (see Table 125-1).

RhoH Deficiency

Two siblings who had a homozygous nonsense mutation in the *RhoH* gene had persistent cutaneous human papillomavirus infections and the older sibling had Burkitt lymphoma. RhoH plays an important role in T-cell activation. Following stimulation of the TCR, RhoH becomes tyrosine phosphorylated and mediates recruitment of ZAP-70 and LCK to the TCR/linker of activation in T cells (LAT) signalosome (see Fig. 125-1). Immunologic findings in the 2 patients included a reduced number of naïve CD4+ T cells and recent thymic emigrants, restricted T-cell diversity and impaired responsiveness of the cells to anti-CD3.

MST1/STK4 Deficiency

Autosomal recessive MST1/STK4 deficiency is associated with recurrent bacterial and viral infections, candidiasis and autoimmunity. The viral infections include warts, molluscum contagiosum, and EBV lymphoproliferative disease. Congenital heart disease and moderate neutropenia have also been reported. Immunologically, there is a severe reduction in naïve T cells, a near absence of recent thymic emigrants, oligoclonal T cells and increased apoptosis of T cells. Thus, MST1/STK4 plays a major role in T-cell development, survival, and migration.

ITK Deficiency

Several patients with EBV lymphoproliferative disease have been described who had mutations in the *ITK* gene. In addition, some also had *P. jiroveci* pneumonia, candidiasis, and BK polyoma infection. The immunologic abnormalities described included marked lymphopenia, a predominance of activated T cells, an absence of NK T cells, and poor T-cell responses to mitogens, antigens and anti-CD3. ITK is a Tec nonreceptor tyrosine kinase expressed in T lymphocytes. The ITK pleckstrin homology domain binds to phosphatidylinositol monophosphates and this binding permits ITK recruitment to the T cell membrane where, upon TCR crosslinking, ITK increases phospholipase Cγ (PLCγ) 1 activation and calcium influx.

Coronin-1a Deficiency

Three siblings from a consanguineous family presented with EBV-associated B-cell lymphoproliferation at an early age (12, 7, and 14 mo) and profound naïve T-cell lymphopenia. In addition, there was impaired development of a diverse T-cell repertoire and near absent invariant NK T cells. They were discovered to have a missense mutation in the gene encoding Coronin-1A that abrogated protein expression. Coronin-1A is a member of a family of proteins that bind F-actin and the Arp2,3 complex; it has an important role in cytoskeletal organization.

LCK DEFICIENCY

A female infant presented at age 15 mo with protracted diarrhea, failure to thrive and recurrent respiratory tract infections. She developed recurring fevers, multiple nodular skin lesions and inflammation of the interphalangeal joints as well as retinal vasculitis and polyserositis. At age 29 mo, she developed a normocytic aregenerative anemia and peripheral thrombocytopenia with antiplatelet autoantibodies. She died from venoocclusive disease shortly after a chemoablated bone marrow transplant. Immunologic investigation revealed CD4 T-cell lymphopenia and low levels of CD4 and CD8 expression on the T-cell surfaces. The T cells present had an oligoclonal T-cell repertoire and exhibited a profound TCR signaling defect. She was found to have a homozygous missense mutation of the *LCK* gene.

Very closely related to this defect is a deficiency of uncoordinated 119 (UNC119), which is a chaperone involved in LCK-mediated signaling. Through LCK, UNC119 regulates T-cell proliferation, differentiation into T effector cells and immunologic synapse formation. A heterozygous dominant-negative missense mutation of the *UNC119* gene was reported in a 32 yr old female with idiopathic CD4 T lymphopenia who had a history of recurrent respiratory infections, shingles, oral herpes infections and persistent fungal infections of the skin and nails. Both LCK deficiency and UNC119 deficiency should be considered when there is idiopathic CD4 T lymphopenia.

CHRONIC MUCOCUTANEOUS CANDIDIASIS

Chronic mucocutaneous candidiasis is a syndrome characterized by impaired immune responsiveness to *Candida.* Some of the known immunodeficiencies that have this complication as a prominent feature include autoimmune polyendocrinopathy syndrome type I (APS1, or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED], described below), homozygous caspase recruitment domain-containing protein 9 *(CARD9)* mutations, both types of hyperimmunoglobulin E syndromes (see Chapter 126), an autosomal recessive deficiency in the IL-17 receptor A (IL-17RA) chain, and an

autosomal dominant deficiency of *STAT1* and of the cytokine IL-17F. IL-17RA deficiency is complete, abolishing cellular responses to IL-17A and IL-17F homo- and heterodimers. By contrast, IL-17F deficiency is partial, with mutant IL-17F–containing homo- and heterodimers displaying impaired, but not abolished, activity.

Although the underlying immune disorders are varied, the clinical presentation of chronic mucocutaneous candidiasis is usually similar. Symptoms can begin in the 1st mo of life or as late as the 2nd decade of life. The disorder is characterized by chronic and severe *Candida* skin and mucous membrane infections. Patients rarely develop systemic *Candida* disease except as noted below. Topical antifungal therapy can provide limited improvement early in the course of the disease, but systemic courses of azoles are usually necessary. The infection usually responds temporarily to treatment but is not eradicated and recurs. Patients with *CARD9* gene mutations have a more severe fungal susceptibility than typical chronic mucocutaneous candidiasis patients. Two described patients with *CARD9* gene mutations had fungal sepsis in addition to chronic mucocutaneous candidiasis; deep tissue dermatophyte infections were also present.

AUTOIMMUNE POLYENDOCRINOPATHY-CANDIDIASIS ECTODERMAL DYSPLASIA

Patients with this syndrome present with chronic mucocutaneous candidiasis and autoimmune polyendocrinopathy, usually producing hypoparathyroidism and Addison disease. Additional features include hypogonadism, chronic active hepatitis, alopecia, vitiligo, pernicious anemia, enamel hypoplasia, type 1diabetes, and Sjögren syndrome. APECED, or APS1, is caused by a mutation in the autoimmune regulator *(AIRE)* gene (see Table 125-1). The gene product, AIRE, is expressed at high levels in purified human thymic medullary stromal cells and is thought to regulate the cell surface expression of tissue-specific proteins such as insulin and thyroglobulin. Expression of these self-proteins allows for the negative selection of autoreactive T cells during their development. Failure of negative selection results in organ-specific autoimmune destruction. The overall significance of AIRE in the establishment and maintenance of T-cell self-tolerance is not well understood.

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Chapter 126

Primary Combined Antibody and Cellular Immunodeficiencies

Rebecca H. Buckley

Patients with combined antibody and cellular defects have severe, frequently opportunistic infections that lead to death in infancy or childhood unless they are provided hematopoietic stem cell transplantation early in life. These are thought to be rare defects, although the true incidences are unknown because until recently there had been no newborn screening for any of these defects. It is possible that many affected children died of infection during infancy without being diagnosed. The causative mutated genes for many combined immunodeficiencies have been identified (Table 126-1). Because life-threatening infections may occur early in infancy, the U.S. Secretary of Health and Human Services recommends that routine screening for severe combined immunodeficiency (SCID) be included in state newborn screening testing. Live, vaccine-derived rotaviral infections have already occurred during the 1st few mo of life in SCID infants, so very early knowledge of this diagnosis could prevent such vaccine-acquired infections. In addition, early identification and subsequent bone marrow transplantation before infections develop result in a very high (92%) survival rate.

126.1 Severe Combined Immunodeficiency

Rebecca H. Buckley

The syndromes of SCID are caused by diverse genetic mutations that lead to absence of all adaptive immune function and, in some, a lack of B cells and natural killer (NK) cells. Patients with this group of disorders have the most severe immunodeficiency.

PATHOGENESIS

SCID results from mutations in any 1 of at least 13 known genes that encode components of the immune system crucial for lymphoid cell development (Table 126-2). All patients with SCID have very small thymuses (<1 g) that usually fail to descend from the neck, contain no thymocytes, and lack corticomedullary distinction or Hassall corpuscles. The thymic epithelium appears histologically normal. Both the follicular and paracortical areas of the spleen are depleted of lymphocytes. Lymph nodes, tonsils, adenoids, and Peyer patches are absent or extremely underdeveloped.

CLINICAL MANIFESTATIONS

Affected infants present within the 1st few mo of life with recurrent or persistent diarrhea, pneumonia, otitis media, sepsis, and cutaneous infections. Growth may appear normal initially, but extreme wasting usually ensues after diarrhea and infections begin. Persistent infections with opportunistic organisms including *Candida albicans, Pneumocystis jiroveci*, parainfluenza 3 virus, adenovirus, respiratory syncytial virus, rotavirus vaccine virus, cytomegalovirus, Epstein-Barr virus (EBV), varicella- zoster virus, measles virus, MMR-V (measles, mumps, rubella, varicella) vaccine virus, or bacillus Calmette-Guérin (BCG) lead to death. Affected infants also lack the ability to reject foreign tissue and are therefore at risk for severe or fatal graft-versus-host disease (GVHD) from T lymphocytes in nonirradiated blood products or in allogeneic stem cell transplants or less severe GVHD from maternal immunocompetent T cells that crossed the placenta while the infant was in utero.

Because all molecular types of SCID lack T cells, the profound T-cell **lymphopenia can be detected on dried blood spots routinely collected from heel sticks shortly after** birth for the purpose of newborn screening by assaying for the presence of T-cell receptor recombination excision circles by real time polymerase chain reaction. T-cell receptor recombination excision circles are absent or extremely low in SCID infants. These infants also have an absence of lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells in vitro. Patients with adenosine deaminase (ADA) deficiency have the lowest absolute lymphocyte counts, usually <500/mm^3, but infants with all molecular types of SCID are lymphopenic because they lack T cells (normally accounting for 70% of circulating lymphocytes). Serum immunoglobulin concentrations are low or absent, and no antibodies are formed after immunizations. Analyses of lymphocyte populations and subpopulations demonstrate distinctive phenotypes for the various genetic forms of SCID (see Table 126-2). T cells are extremely low or absent in all types; when detected, in most cases they are transplacentally derived maternal T cells.

TREATMENT

SCID is a true pediatric emergency. Unless immunologic reconstitution is achieved through stem cell transplantation or gene therapy, death usually occurs during the 1st yr of life and almost invariably before 2 yr of age. If diagnosed at birth or within the 1st 3.5 mo of life, >92% of cases can be treated successfully with human leukocyte antigen (HLA)-identical or T-cell–depleted haploidentical (half-matched) parental hematopoietic stem cell transplantation without the need for pretransplant chemoablation or posttransplant GVHD prophylaxis. ADA-deficient SCID and X-linked SCID have been treated

Table 126-1 Genetic Basis of Combined Immunodeficiency Disorders

CHROMOSOME AND REGION	GENE PRODUCT	DISORDER	FUNCTIONAL DEFICIENCIES
1q	RFX5	MHC class II antigen deficiency	Low immunoglobulins, lack of T-cell responses to antigens, CD4 deficiency
1q31-q32	CD45	T–B+NK+ SCID	Absence of T- and B-cell functions
3p22.2	Myd88	Toll-receptor innate immune defect	T and B cell functions normal; Failure of activation of nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) by Toll receptor stimuli
5p13	IL-7Rα	T–B+NK+ SCID	Absence of T- and B-cell functions
6p21.3	TAP1, TAP2	MHC class I antigen deficiency	Marked deficiency of CD8 T cells; combined B- and T-cell defects
6q22-q23	IFN-γR1 IFN-γR2 IL-12Rβ_1	Disseminated mycobacterial infections	Failure of macrophages and other cells to produce TNF-α in response to IFN-γ
9p21-p13	Endoribonuclease RNase MRP*	Cartilage-hair hypoplasia	Combined B- and T-cell defects of varying severity
9p24	DOCK8	Autosomal recessive Hyper-IgE syndrome	↓↓ CD4, CD8 and Th17 T cells ↓ Naïve T cells; poor T-cell responses to mitogens; elevated serum IgE levels Decreased switched memory B cells Decreased antibody responses
10p13	Artemis	T–B–NK+ SCID	Absence of T- and B-cell functions
11p13	RAG1 or RAG2	T–B–NK+ SCID	Absence of T- and B-cell functions
11q22.3	ATM, a DNA-dependent kinase	Ataxia-telangiectasia	Selective IgA deficiency; T-cell deficiency
11q23	CD3δ or CD3ζ	T–B+NK+ SCID	Absence of T- and B-cell functions
12q12	IRAK4	Toll-receptor innate immune defect	T- and B-cell functions normal; failure of activation of NF-κB and MAPK by Toll receptor stimuli
13q	RFXAP	MHC class II antigen deficiency	Low immunoglobulins, lack of T-cell responses to antigens, CD4 deficiency
14q13.1	Purine nucleosidase	PNP deficiency	Severe T-cell deficiency; may have normal immunoglobulins
16p13	CIITA	MHC class II antigen deficiency	Low immunoglobulins, lack of T-cell responses to antigens, CD4 deficiency
17q21.3	STAT3	Autosomal dominant hyper-IgE syndrome	Elevated IgE and IgD, low CD45RO (memory) T cells, no Th17 T cells
19p13.1	Jak3	T–B+NK– SCID	Absence of T-, B-, and NK-cell functions
20q13.11	ADA	T–B–NK– SCID	Absence of T- and B-cell functions
Xp11.4-11.21	WASP	Wiskott-Aldrich syndrome	Thrombocytopenia; poor antibody production to polysaccharides; T-cell deficiency
Xp11.23	FOXP3	Immune-dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome	Early onset of diarrhea and autoimmune diseases Elevated IgE
Xq13.1	Common γ chain (γc) for several cytokine receptors (including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21)	T–B+NK– SCID	Absence of T-, B-, and NK-cell functions

ADA, Adenosine deaminase; CIITA, class II transactivator; DOCK8, dedicator of cytokinesis 8; FOXP3, forkhead-winged helix transcription factor; IFN-γR1, interferon receptor chain 1; Ig, immunoglobulin; IL, interleukin; IL-7Rα, interleukin 7 receptor α chain; IL-12Rβ_1, interleukin 12 receptor β_1 chain; IFN, interferon; IRAK4, interleukin-1 receptor-associated kinase 4; Jak3, Janus kinase 3; MHC, major histocompatibility complex; Myd88, myeloid differentiation factor 88; NK, natural killer; PNP, purine nucleoside phosphorylase; RAG1 and RAG2, recombinase activating genes 1 and 2; SCID, severe combined immunodeficiency; STAT3, signal transducer and activator of transcription 3; TAP, transporter of antigenic peptide; Th17, T-helper cell type 17; TNF, tumor necrosis factor; WASP, Wiskott-Aldrich syndrome protein.

successfully with somatic gene therapy; although serious adverse events occurred in the case of X-linked SCID. ADA-deficient SCID can also be treated with repeated injections of polyethylene glycol modified bovine ADA (PEG-ADA), although the immune reconstitution achieved is not nearly as good as with stem cell or gene therapy. PEG-ADA should not be started if nonablative stem cell transplantation is contemplated because it will enable the infant to reject the graft.

X-LINKED SEVERE COMBINED IMMUNODEFICIENCY CAUSED BY MUTATIONS IN THE GENE ENCODING THE COMMON CYTOKINE RECEPTOR γ CHAIN

X-linked SCID (X-SCID) is the most common form of SCID in the United States, accounting for 47% of cases (Fig. 126-1). Clinically, immunologically, and histopathologically, affected individuals appear

Table 126-2 Genetic Basis of SCID and SCID Variants

DISEASE	INHERITANCE	PRESUMED PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
Reticular dysgenesis	AR	Impaired mitochondrial energy metabolism and leukocyte differentiation	Severe neutropenia, deafness. Mutations in adenylate kinase 2	GCSF HSCT
Adenosine deaminase deficiency	AR	Accumulation of toxic purine nucleosides	Neurologic, hepatic, renal, lung, and skeletal and bone marrow abnormalities	HSCT, PEG-ADA, gene therapy
IL-2Rγ deficiency	X-linked	Abnormal signaling through by IL-2 receptor and other receptors containing γc (IL-4, -7, -9, -15, -21)	None	HSCT
Jak3 deficiency	AR	Abnormal signaling downstream of γc	None	HSCT
RAG1 and 2 deficiency	AR	Defective V(D)J recombination	None	HSCT
Artemis deficiency	AR	Defective V(D)J recombination, radiation sensitivity	DCLERE1C gene defects	HSCT
DNA-PK deficiency	AR	Defective V(D)J recombination	None	HSCT
DNA ligase IV deficiency	AR	Defective V(D)J recombination, radiation sensitivity	Growth delay, microcephaly, bone marrow abnormalities, lymphoid malignancies	HSCT
Cernunnos-XLF	AR	Defective V(D)J recombination, radiation sensitivity	Growth delay, microcephaly, bird-like facies, bone defects	HSCT
CD3δ deficiency	AR	Arrest of thymocytes differentiation at the CD4–CD8– stage	Thymus size may be normal	HSCT
CD3ε deficiency	AR	Arrest of thymocytes differentiation at the CD4–CD8– stage	γ/δ T cells absent	HSCT
CD3ζ deficiency	AR	Abnormal signaling	None	HSCT
IL-7Rα deficiency	AR	Abnormal IL-7R signaling	Thymus absent	HSCT
CD45 deficiency	AR		None	HSCT
Coronin-1A deficiency	AR	Abnormal T-cell egress from thymus and lymph nodes	Normal thymus size. Attention deficit disorder.	HSCT

AR, autosomal recessive; GCSF, granulocyte colony stimulating factor; HSCT, hematopoietic stem cell transplantation; IL, interleukin; Jak3, Janus kinase 3; PEG-ADA, polyethylene glycol-modified adenosine deaminase; RAG1 and RAG2, recombinase activating genes 1 and 2; V(D)J, variable, diversity, joining.

(Modified from Roifman, CM. Grunebaum E. Primary T-cell immunodeficiencies. In Rich RR, Fleisher TA, Shearer WT, et al, editors: Clinical Immunology, *ed 4. Philadelphia, 2013, WB Saunders, Tables 35-1, 35-2, 35-3, 35-4, pp. 440–441).*

similar to those with other forms of SCID except for having uniformly **low percentages of T and NK cells** and an **elevated percentage of B cells** (T–, B+, NK–), a characteristic feature shared only with Janus kinase 3 (Jak3)–deficient SCID. The abnormal gene in X-SCID was mapped to Xq13, cloned, and found to encode the common γ chain (γc) for several cytokine receptors, including interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21. The shared γc functions both to increase the affinity of the receptor for the respective cytokine and to enable the receptors to mediate intracellular signaling. Incapacitation of the receptors for all of these developmentally crucial cytokines by genetic mutations in γc provides an explanation for the severity of the immunodeficiency in X-SCID. In the 1st 136 patients studied, 95 distinct mutations spanning all 8 IL-2RG exons were identified, most of them consisting of small changes at the level of 1 to a few nucleotides. These mutations resulted in abnormal γc chains in two-thirds of the cases and absent γc protein in the remainder. Carriers can be detected by demonstrating the deleterious mutation in their lymphocytes. Unless donor B or NK cells develop, patients with X-SCID lack B- and NK-cell function after bone marrow transplantation because the abnormal γc persists in those host cells, despite excellent reconstitution of T-cell function by donor-derived T cells.

AUTOSOMAL RECESSIVE SEVERE COMBINED IMMUNODEFICIENCY

This pattern of inheritance of SCID is less common in the United States than in other countries. Mutated genes on autosomal chromosomes have been identified in 12 forms of SCID: ADA deficiency; Jak3 deficiency; IL-7 receptor α chain (IL-7Rα) deficiency; recombinase-activating gene 1 or 2 (RAG1 or RAG2) deficiency; Artemis deficiency; ligase 4 deficiency; DNA–protein kinase catalytic subunit (DNA-PKcs) deficiency; CD3δ, CD3ε, CD3ζ deficiency; and CD45 deficiency (see Fig. 126-1).

Adenosine Deaminase Deficiency

An absence of the enzyme ADA is observed in approximately 15% of patients, the second most common form of SCID, resulting from various point and deletional mutations in the ADA gene on chromosome 20q13-ter. Marked accumulations of adenosine, 2′-deoxyadenosine, and 2′-*O*-methyladenosine lead directly or indirectly to T-cell apoptosis, which causes the immunodeficiency. ADA-deficient patients usually have a much more profound **lymphopenia** than do infants with other types of SCID, with mean absolute lymphocyte counts of <500/mm^3; the absolute numbers of T, B, and NK cells are very low. NK function is normal. After T-cell function is conferred by hematopoietic stem cell transplantation without pretransplant chemotherapy, there is generally excellent B-cell function despite the fact that the B cells are of host origin. This is because ADA deficiency affects primarily T-cell function. Milder forms of ADA deficiency have led to delayed diagnosis of immunodeficiency, even to adulthood. Other **distinguishing features** of ADA-deficient SCID include the presence of rib cage abnormalities similar to a rachitic rosary and numerous skeletal abnormalities of chondroosseous dysplasia, which occur predominantly at the costochondral junctions, at the apophyses of the iliac bones, and in the vertebral bodies where a “bone-in-bone” effect is observed.

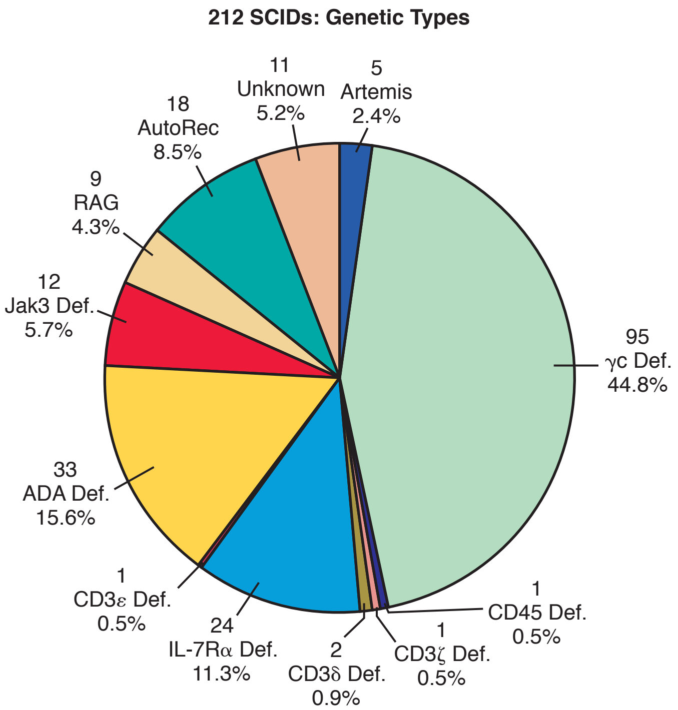

Figure 126-1 **Relative frequencies of the different genetic types among 212 patients with severe combined immunodeficiency seen consecutively over 4 decades.** *ADA*, adenosine deaminase; *IL-7Rα*, interleukin 7 receptor α chain; *Jak3*, Janus kinase 3; *RAG*, recombinase activating gene.

As with other types of SCID, ADA deficiency can be cured by HLA-identical or haploidentical T-cell–depleted stem cell transplantation without the need for pre- or posttransplant chemotherapy; this remains the treatment of choice. Enzyme replacement therapy should not be initiated if stem cell transplantation is possible because it confers graft-rejection capability. Enzyme replacement provides protective immunity but over time there is a decline of lymphocyte counts and proliferative responses. A number of infants with ADA deficiency have become successfully immune reconstituted by gene therapy in Italy, Great Britain and the United States; in all cases, PEG-ADA was withheld. Spontaneous reversion to normal of a mutation in the ADA gene has also been reported.

Jak3 Deficiency

Patients with this autosomal recessive defect resemble all other types of SCID patients clinically. They have a lymphocyte phenotype similar only to that of patients with X-SCID, with an elevated percentage of B cells and very low or no T and NK cells. Because Jak3 is the only signaling molecule known to be associated with γc, it was a candidate gene for mutations leading to autosomal recessive SCID. Jak3 deficiency accounts for 6% of SCID cases. Even after successful T-cell reconstitution by transplantation of haploidentical stem cells, patients with Jak3-deficient SCID fail to develop NK cells or normal B-cell function owing to the defective function of those host cells that bear abnormal cytokine receptors that share γc.

IL-7Rα Deficiency

Patients with IL-7Rα–deficient SCID have a distinctive lymphocyte phenotype in that, although lacking T cells, they have normal or elevated numbers of both B and NK cells (T–, B+, NK+). This is the **third most common** form of SCID, accounting for 12% of cases in the United States (see Fig. 126-1). In contrast to patients with γc- and Jak3-deficient SCID, the immunologic defect in these patients is completely correctable by T-cell reconstitution alone, because the host B and NK cells appear to be normal.

RAG1 or RAG2 Deficiencies

Infants with these causes of SCID have a different lymphocyte phenotype from those of patients with SCID caused by γc, Jak3, IL-7Rα, or ADA deficiencies in that they lack both B and T lymphocytes and have primarily NK cells in their circulation (T–, B–, NK+). This suggested a problem with their antigen receptor genes, which led to the discovery of mutations in *RAG1* or *RAG2*. Such mutations result in a functional inability to form antigen receptors through genetic recombination. **Omenn syndrome** is an autosomal recessive condition characterized by profound susceptibility to infection and by clonal T-cell infiltration of skin, intestines, liver, and spleen leading to an exfoliative erythroderma, lymphadenopathy, hepatosplenomegaly, and intractable diarrhea. Mutations in the *RAG1* and *RAG2*, as well as rarely in other SCID-causing mutated genes, have been found in patients with this condition. These infants have persistent leukocytosis with marked eosinophilia and lymphocytosis; elevated serum immunoglobulin (Ig) E; low IgG, IgA, and IgM; and low or absent B cells. There is dominance of clonal T-helper (Th)2-like cells, with severely impaired T-cell function as the result of the restricted heterogeneity of the host T-cell repertoire.

Artemis Deficiency

Another cause of SCID is a deficiency of a novel V(D)J (variable, diversity, joining) recombination/DNA repair factor, named Artemis, that belongs to the metallo-β-lactamase superfamily, which is encoded on chromosome 10p by a gene named *DCLRE1C*. Deficiency of Artemis results in an inability to repair DNA after double-stranded cuts by the *RAG1* or *RAG2* gene products in rearranging antigen receptor genes from their germline configuration. Similar to RAG1- and RAG2-deficient SCID, this defect results in failure to develop T and B cells and is, therefore, another form of T–, B–, NK+ SCID, which is called **Athabascan SCID**. There is increased radiation sensitivity of both skin fibroblasts and bone marrow cells of those affected with this type of SCID as well as with DNA-PKcs and ligase 4 deficiencies.

CD45 Deficiency

Another molecular defect causing SCID is a mutation in the gene encoding the common leukocyte surface protein CD45. This hematopoietic cell–specific transmembrane protein tyrosine phosphatase functions to regulate src kinases required for T- and B-cell antigen receptor signal transduction. Three examples of this have been reported. One was found to have a large deletion on 1 CD45 allele and a point mutation causing an alteration of the intervening sequence 13 donor splice site on the other allele. The author has evaluated and treated a third case that was caused by uniparental disomy of chromosome 1 with an inactivating mutation in the gene encoding CD45.

CD3δ, CD3ε, and CD3ζ Deficiencies

Other causes of autosomal recessive SCID are deficiencies of components of the T-cell receptor (CD3δ, CD3ε, and CD3ζ chains). Mutations in the portions of these genes that encode the extracellular components of the proteins result in a profound deficiency of circulating mature CD3 T cells. Thus, CD3δ, CD3ε, and CD3ζ appear to be essential for intrathymic development of T cells. Because only T-cell development is affected in these defects, both B and NK cells are normal. Thus, the lymphocyte phenotype resembles that of SCID infants with IL-7Rα chain deficiency (T–B+NK+).

RETICULAR DYSGENESIS

Reticular dysgenesis was first described in identical twin boys who exhibited a total lack of both lymphocytes and granulocytes in their peripheral blood and bone marrow. The thymus glands weigh <1 g, have no Hassall corpuscles, and have few or no thymocytes. Reticular dysgenesis is considered a variant of SCID. The molecular basis of this autosomal recessive disorder is caused by mutations in the gene encoding adenylate kinase 2. The condition is fatal without definitive therapy and the treatment of choice is a fully myeloablative matched sibling bone marrow transplant. However, such transplants have been successful in only 7 of 17 evaluable patients so transplanted.

126.2 Combined Immunodeficiency

Rebecca H. Buckley

Combined immunodeficiency (CID) is distinguished from SCID by the presence of low but not absent T-cell function. Similar to SCID, CID is a syndrome of diverse genetic causes (see Table 126-1). Patients with CID have recurrent or chronic pulmonary infections, failure to thrive, oral or cutaneous candidiasis, chronic diarrhea, recurrent skin infections, Gram-negative bacterial sepsis, urinary tract infections, and severe varicella in infancy. Although they usually survive longer than infants with SCID, they fail to thrive and die early in life. Neutropenia and eosinophilia are common. Serum immunoglobulins may be normal or elevated for all classes, but selective IgA deficiency, marked elevation of IgE, and elevated IgD levels occur in some cases. Although antibody-forming capacity is impaired in most patients, it is not absent.

Studies of cellular immune function show lymphopenia, profound deficiencies of T cells, and extremely low but not absent lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells in vitro. Peripheral lymphoid tissues demonstrate paracortical lymphocyte depletion. The thymus is very small, with a paucity of thymocytes and usually no Hassall corpuscles. An autosomal recessive pattern of inheritance is common.

PURINE NUCLEOSIDE PHOSPHORYLASE DEFICIENCY

More than 40 patients with CID have been found to have purine nucleoside phosphorylase deficiency. Point mutations identified in the purine nucleoside phosphorylase gene on chromosome 14q13.1 account for these deficiencies. In contrast to ADA deficiency, no characteristic physical or skeletal abnormalities have been noted, but serum and urinary uric acid are usually markedly deficient. Deaths result from generalized vaccinia, varicella, lymphosarcoma, or GVHD mediated by allogeneic T cells in nonirradiated blood or bone marrow. Two-thirds of patients have neurologic abnormalities, one-third of patients have autoimmune diseases, and some have had allergic diseases. Lymphopenia is striking, primarily because of a marked deficiency of T cells; T-cell function is decreased to various degrees. B cell function may be near normal. The proportion of circulating NK cells is increased. Prenatal diagnosis or diagnosis at birth is possible. Bone marrow transplantation is the only successful form of therapy.

CARTILAGE HAIR HYPOPLASIA

Cartilage hair hypoplasia (CHH) is an unusual form of **short-limbed dwarfism** with frequent and severe infections. It occurs predominantly among the Amish, but non-Amish patients have been described.

Genetics and Pathogenesis

CHH is an autosomal recessive condition. Numerous mutations that cosegregate with the CHH phenotype have been identified in the untranslated *RNase MRP* (*RMRP*) gene, which has been mapped to chromosome 9p21-p13 in Amish and Finnish families (see Table 126-1). The RMRP endoribonuclease consists of an RNA molecule bound to several proteins and has at least 2 functions: cleavage of RNA in mitochondrial DNA synthesis and nucleolar cleaving of pre-RNA. Mutations in RMRP cause CHH by disrupting a function of RMRP RNA that affects multiple organ systems. In vitro studies show decreased numbers of T cells and defective T-cell proliferation because of an intrinsic defect related to the G1 phase, resulting in a longer cell cycle for individual cells. NK cells are increased in number and function.

Clinical Manifestations

Clinical features include short, pudgy hands; redundant skin; hyperextensible joints of hands and feet but an inability to extend the elbows completely; and fine, sparse, light hair and eyebrows. Severe and often fatal varicella infections, progressive vaccinia, and vaccine-associated poliomyelitis have been observed. Associated conditions include deficient erythrogenesis, Hirschsprung disease, and an increased risk of malignancies. The bones radiographically show scalloping and sclerotic or cystic changes in the metaphyses and flaring of the costochondral junctions of the ribs. Three patterns of immune dysfunction have emerged: defective antibody-mediated immunity, CID (most common), and SCID. The severity of the immunodeficiency varies; in 1 series, 11 of 77 patients died before age 20 yr, but 2 were still alive at age 76 yr. Stem cell transplantation has resulted in immunologic reconstitution in some CHH patients who had the SCID phenotype.

DEFECTIVE EXPRESSION OF MAJOR HISTOCOMPATIBILITY COMPLEX ANTIGENS

The 2 main forms of immunodeficiency and abnormalities of expression of the major histocompatibility complex (MHC) are MHC class I (HLA-A, -B, and -C) antigen deficiency and MHC class II (HLA-DR, -DQ, and -DP) antigen deficiency. The associated defects of both B- and T-cell immunity and of HLA expression emphasize the important biologic role for HLA determinants in effective immune cell cooperation.

Major Histocompatibility Complex Class I Antigen Deficiency

Isolated deficiency of MHC class I (HLA-A, -B, and -C) antigens, the **bare lymphocyte syndrome**, is rare. The resulting immunodeficiency is much milder than in SCID, contributing to a later age of presentation. Sera from affected children contain normal quantities of MHC class I antigens and β_2-microglobulin, but MHC class I antigens are not detected on any cells in the body. There is a deficiency of CD8 but not CD4 T cells. Mutations have been found in 2 genes within the MHC locus on chromosome 6 that encode the peptide transporter proteins TAP1 and TAP2. TAP functions to transport antigenic peptides from the cytoplasm across the Golgi apparatus membrane to join the α chain of MHC class I antigens and β_2-microglobulin. All these are then assembled into a MHC class I complex that can then move to the cell surface. If the assembly of the complex cannot be completed because there is no antigenic peptide, the MHC class I complex is destroyed in the cytoplasm.

Major Histocompatibility Complex Class II Antigen Deficiency

Many affected with MHC class II (HLA-DR, -DQ, and -DP) deficiency are of North African descent. Patients present in early infancy with persistent diarrhea that is often associated with cryptosporidiosis and enteroviral infections (e.g., poliovirus, coxsackievirus). They also have an increased frequency of infections with herpesviruses and other viruses, oral candidiasis, bacterial pneumonia, *P. jiroveci* pneumonia, and septicemia. The immunodeficiency is not as severe as in SCID, as evidenced by their failure to develop disseminated infection after BCG vaccination or GVHD from nonirradiated blood transfusions.

Four different molecular defects resulting in impaired expression of MHC class II antigens have been identified (see Table 126-1 and Fig. 124-1). One form is a mutation in the gene on chromosome 1q that encodes a protein called RFX5, a subunit of RFX, which is a multiprotein complex that binds the X box motif of MHC-II promoters. A second form is caused by mutations in a gene on chromosome 13q that encodes a second 36-kD subunit of the RFX complex, called RFX-associated protein (RFXAP). The most common cause of MHC class II defects is a mutation in RFXANK, the gene encoding a 3rd subunit of RFX. In a 4th type, there is a mutation in the gene on chromosome 16p13 that encodes a novel MHC class II transactivator, a non–DNA-binding coactivator that controls the cell-type specificity and inducibility of MHC-II expression. All 4 of these defects cause impairment in the coordinate expression of MHC class II molecules on the surface of B cells and macrophages.

MHC class II–deficient patients have a very low number of CD4 T cells but normal or elevated numbers of CD8 T cells. Lymphopenia is only moderate. The MHC class II antigens HLA-DP, -DQ, and -DR are undetectable on blood B cells and monocytes, even though B cells are present in normal number. Patients are hypogammaglobulinemic owing to impaired antigen-specific responses caused by the absence of these antigen- presenting molecules. In addition, MHC antigen-deficient B cells fail to stimulate allogeneic cells in mixed leukocyte culture. Lymphocyte proliferation studies show normal responses to

mitogens but no response to antigens. The thymus and other lymphoid organs are severely hypoplastic, and the lack of class II molecules results in abnormal thymic selection with circulating CD4 T cells that have altered CDR3 profiles.

IMMUNODEFICIENCY WITH THROMBOCYTOPENIA AND ECZEMA (WISKOTT-ALDRICH SYNDROME)

Wiskott-Aldrich syndrome, an X-linked recessive syndrome, is characterized by atopic dermatitis, thrombocytopenic purpura with normal-appearing megakaryocytes but small defective platelets, and undue susceptibility to infection.

Genetics and Pathogenesis

The abnormal gene, on the proximal arm of the X chromosome at Xp11.22-11.23 near the centromere, encodes a 501 amino acid proline-rich cytoplasmic protein restricted in its expression to hematopoietic cell lineages. The Wiskott-Aldrich syndrome protein (WASP) binds CDC42H2 and rac, members of the Rho family of guanosine triphosphatases. Wiskott-Aldrich syndrome protein appears to control the assembly of actin filaments required for microvesicle formation downstream of protein kinase C and tyrosine kinase signaling. Carriers can be detected by demonstration of the deleterious mutation.

Clinical Manifestations

Patients often have prolonged bleeding from the circumcision site or bloody diarrhea during infancy. The thrombocytopenia is not initially due to antiplatelet antibodies. Atopic dermatitis and recurrent infections usually develop during the 1st yr of life. *Streptococcus pneumoniae* and other bacteria having polysaccharide capsules cause otitis media, pneumonia, meningitis, and sepsis. Later, infections with agents such as *P. jiroveci* and the herpesviruses become more frequent. Survival beyond the teens is rare; infections, bleeding, and EBV-associated malignancies are major causes of death.

Patients with this defect uniformly have an impaired humoral immune response to polysaccharide antigens, as evidenced by absent or markedly diminished isohemagglutinins, and poor or absent antibody responses after immunization with polysaccharide vaccines. IgG_2 subclass concentrations, surprisingly, are normal. Anamnestic responses to protein antigens are poor or absent. There is an accelerated rate of synthesis as well as hypercatabolism of albumin, IgG, IgA, and IgM, resulting in highly variable concentrations of different immunoglobulins, even within the same patient. The predominant immunoglobulin pattern is a low serum level of IgM, elevated IgA and IgE, and a normal or slightly low IgG concentration. Because of their profound antibody deficiencies, these patients should be given monthly infusions of intravenous immunoglobulin (IVIG) regardless of their serum levels of the different immunoglobulin isotypes. Percentages of T cells are moderately reduced, and lymphocyte responses to mitogens are variably depressed.

Treatment

Good supportive care includes appropriate nutrition, routine IVIG, use of killed vaccines, aggressive management of eczema and associated cutaneous infections, platelet transfusion for serious bleeding episodes, splenectomy if a transplant is not going to be done, and high-dose IVIG with systemic steroids for autoimmune complications. Bone marrow or cord blood transplantation is the treatment of choice and is usually curative.

ATAXIA-TELANGIECTASIA

Ataxia-telangiectasia is a complex syndrome with immunologic, neurologic, endocrinologic, hepatic, and cutaneous abnormalities.

Genetics and Pathogenesis

The mutated gene responsible for this defect, ataxia-telangiectasia mutation *(ATM)*, was mapped to the long arm of chromosome 11 (11q22-23) and has been cloned. The gene product is a DNA-dependent protein kinase localized predominantly to the nucleus and involved in mitogenic signal transduction, meiotic recombination, and cell-cycle control. Cells from patients, as well as from heterozygous carriers, have increased sensitivity to ionizing radiation, defective DNA repair, and frequent chromosomal abnormalities.

In vitro tests of lymphocyte function have generally shown moderately depressed proliferative responses to T- and B-cell mitogens. Percentages of CD3 and CD4 T cells are moderately reduced, with normal or increased percentages of CD8 and elevated numbers of Tiγ/δ T cells. The thymus is very hypoplastic, exhibits poor organization, and lacks Hassall corpuscles.

Clinical Manifestations

The most prominent clinical features are progressive cerebellar ataxia, oculocutaneous telangiectasias, chronic sinopulmonary disease, a high incidence of malignancy, and variable humoral and cellular immunodeficiency. Ataxia typically becomes evident soon after these children begin to walk and progresses until they are confined to a wheelchair, usually by the age of 10-12 yr. The telangiectasias begin to develop at 3-6 yr of age. The most frequent humoral immunologic abnormality is the selective absence of IgA, which occurs in 50-80% of these patients. Hypercatabolism of IgA also occurs. IgE concentrations are usually low, and the IgM may be of the low-molecular-weight variety. IgG_2 or total IgG levels may be decreased, and specific antibody titers may be decreased or normal. Recurrent sinopulmonary infections occur in approximately 80% of these patients. Although common viral infections have not usually resulted in untoward sequelae, fatal varicella has occurred. The malignancies associated with ataxia-telangiectasia are usually of the lymphoreticular type, but adenocarcinomas also occur. Unaffected relatives have an increased incidence of malignancy.

126.3 Defects of Innate Immunity

Rebecca H. Buckley

A number of defects in non–antigen-specific immunity (innate immunity) affect antigen-specific immune responses, as there is interaction between the adaptive and innate immune systems.

INTERFERON-γ RECEPTORS 1 AND 2, IL-12 RECEPTOR β_1, AND IL-12P40 MUTATIONS

Disseminated BCG and other severe nontuberculosis mycobacterial infections (sepsis, osteomyelitis) occur in patients with severe T-cell defects; however, no specific host defect is identified in approximately half of such cases. The first report was a 2.5 mo old Tunisian girl with fatal idiopathic disseminated BCG infection; 4 children from Malta had disseminated atypical mycobacterial infections in the absence of a recognized immunodeficiency. There was consanguinity in all, and all had a functional defect in the upregulation of tumor necrosis factor (TNF) α production by their blood macrophages in response to stimulation with interferon-γ (IFN-γ). All also had a mutation in the gene on chromosome 6q22-q23 that encodes the IFN-γ receptor 1 (IFN-γR1). IFN-γR1 deficiency may be inherited as a complete autosomal recessive (early onset ≈3 yr of age, more episodes, more severe disease, and higher mortality) or partial dominant (onset ≈10 yr of age) disease. Patients with mutations in the IFN-γR2 have also been identified. Related defects were found in other patients who had disseminated mycobacterial infections, who have mutations in either the gene encoding the β_1 chain of the IL-12 receptor (IL-12Rβ_1) or in the gene encoding IL-12p40. IL-12 is a powerful inducer of IFN-γ production by T and NK cells, and the mutated receptor chain gene resulted in unresponsiveness of the cells of these patients to IL-12 and inadequate IFN-γ production. The children deficient in IFN-γR1, IFN-γR2, IL-12Rβ_1, or IL-12p40 appeared not to be susceptible to infection with many agents other than mycobacteria (occasionally *Salmonella*, *Listeria*, *Histoplasma*). Th1 responses appeared to be normal in these patients, and the susceptibility to mycobacterial infections thus apparently results from an intrinsic impairment of the IFN-γ pathway response to these particular intracellular pathogens, showing that IFN-γ is obligatory for efficient macrophage antimycobacterial activity.

GERMLINE STAT-1 MUTATION

Interferons induce the formation of 2 transcriptional activators: gamma-activating factor (GAF) and interferon-stimulated gamma factor 3 (ISGF3). A natural heterozygous dominant germline *STAT-1* mutation associated with susceptibility to mycobacterial but not viral disease was found in 2 unrelated patients with unexplained mycobacterial disease. This mutation caused a loss of GAF and ISGF3 activation but was dominant for 1 cellular phenotype and recessive for the other. The mutation impaired the nuclear accumulation of GAF, but not of ISGF3, in cells stimulated by interferons, implying that the antimycobacterial but not the antiviral effects of human interferons are mediated by GAF. Two patients were identified with homozygous *STAT-1* mutations; they developed both post–BCG vaccination disseminated disease and lethal viral infections. The mutations in these patients caused a complete lack of STAT-1 and resulted in a lack of formation of both GAF and ISGF3.

IL-1R–ASSOCIATED KINASE 4 DEFICIENCY AND MYELOID DIFFERENTIATION FACTOR 88

Members of IL-1R and the Toll-like receptor superfamily share an intracytoplasmic Toll–IL-1 receptor (TIR) domain, which mediates recruitment of the IL-1R–associated kinase (IRAK) complex via TIR-containing adapter molecules. Three unrelated, otherwise healthy children with recurrent pyogenic infections caused by pneumococci and staphylococci had normal immunocompetence by standard immune studies. They had normal titers of antipneumococcal antibodies. Their blood and fibroblast cells did not activate nuclear factor κB, and mitogen-activated protein kinase and failed to induce downstream cytokines in response to any of the known ligands of TIR-bearing receptors. All were found to have an inherited deficiency of IRAK-4. The TIR-IRAK signaling pathway appears to be crucial for protective immunity against specific bacteria but is redundant against most other microorganisms. There are now more than 50 documented cases of IRAK4 deficiency, and a commonality among cases is susceptibility to pyogenic bacterial infection with pneumococcus and *Pseudomonas*. The pneumococcal infections have the potential to be invasive (even as a presenting feature) and lead to poor clinical outcomes. Severe viral and fungal infections are atypical. The myeloid differentiation factor 88 (MYD88) is an effective phenocopy of IRAK4 deficiency. While discovered later than IRAK4 deficiency, myeloid differentiation factor 88 is an upstream adaptor for IRAK4 and links it to Toll-like receptors, which results in a very similar immunologic defect and clinical syndrome.

NATURAL KILLER CELL DEFICIENCY

NK cells are the major lymphocytes of the innate immune system. NK cells recognize virally infected and malignant cells and mediate their elimination. Individuals with absence or functional deficiencies of NK cells are rare, and they typically have susceptibility to the herpesviruses (including varicella-zoster virus, herpes simplex virus, cytomegalovirus, and EBV) as well as papillomaviruses. A number of gene defects are associated with these isolated abnormalities in NK cells. Autosomal recessive CD16 gene mutations were described in 3 separate families and they altered the first immunoglobulin-like domain of this important NK cell activation receptor. Patients with these mutations have NK cells that are functionally impaired and have clinical susceptibility to herpesviruses. **Autosomal dominant** deficiency of NK cells occurs in individuals with mutations in the GATA2 transcription factor. These patients also have low numbers of monocytes. They have extreme susceptibility to human papilloma virus as well as mycobacteria—the latter presumably from the monocytic defect. **Autosomal recessive** mutations in the MCM4 gene have been identified in a cohort of consanguineous Irish who had growth failure and susceptibility to herpesviruses. These individuals possessed the immature CD56^{bright} minor subset, but lacked the major mature CD56^{dim} subset of NK cells. The reason why MCM4, which encodes a DNA helicase, would interfere with NK cell development remains unclear. Therapeutically, patients should be maintained on antiviral prophylaxis, and allogeneic stem cell transplantation has been successful in certain cases.

HYPER-IGE SYNDROMES

The hyper-IgE syndromes are relatively rare primary immunodeficiency syndromes characterized by recurrent severe staphylococcal abscesses of the skin, lungs, and other sites and markedly elevated levels of serum IgE (Table 126-3). They occur in 2 forms: autosomal dominant and autosomal recessive.

Autosomal Dominant Hyper-IgE Syndrome

This is the most common form in the United States. More than 200 patients with autosomal dominant hyper-IgE syndrome, also known as the Buckley syndrome, have been reported.

Genetics and Pathogenesis

The autosomal dominant hyper-IgE syndrome is caused by heterozygous mutations in the gene encoding STAT-3. These mutations result in a dominant negative effect on the expression of STAT-3 by the other nonmutated gene. It is not clear exactly how the STAT-3 mutation causes all parts of the syndrome, but it is thought that IL-17 deficiency may account in part for the susceptibility to *Candida* infection. IL-17 is a cytokine that acts on monocytes to induce secretion of proinflammatory mediators such as IL-8, TNF, and granulocyte-macrophage colony-stimulating factor.

Clinical Manifestations

The characteristic clinical features of the autosomal dominant form of the hyper-IgE syndrome are staphylococcal abscesses, pneumatoceles, osteopenia, and unusual facial features. There is a history from infancy of recurrent staphylococcal abscesses involving the skin, lungs, joints, viscera and other sites. Persistent pneumatoceles develop as a result of recurrent pneumonia. They often have histories of sinusitis and mastoiditis. *C. albicans* is the second most common pathogen. Allergic respiratory symptoms are usually absent. The pruritic dermatitis that occurs is not typical atopic eczema and does not always persist. The first 2 reported patients were described as having **coarse facial features**, including a prominent forehead, deep-set wide-spaced eyes, a broad nasal bridge, a wide fleshy nasal tip, mild prognathism, facial asymmetry, and hemihypertrophy. In older children, delay in shedding primary teeth, recurrent fractures, and scoliosis occur.

These patients demonstrate an exceptionally high serum IgE concentration; an elevated serum IgD concentration; usually normal concentrations of IgG, IgA, and IgM; pronounced blood and sputum eosinophilia; abnormally low anamnestic antibody responses; and poor antibody and cell-mediated responses to neoantigens. Traditionally, IgE levels >2000 IU/mL confirm the diagnosis. However, IgE levels may fluctuate and even decrease in adults. In neonates and infants with the pruritic pustular dermatosis, IgE levels will be elevated for age and are usually in the 100s. In vitro studies show normal percentages of blood T, B, and NK lymphocytes, except for a decreased percentage of T cells with the memory (CD45RO) phenotype and an absence or deficiency of Th17 T cells. Most patients have normal T-lymphocyte proliferative responses to mitogens but very low or absent responses to antigens or allogeneic cells from family members. Blood, sputum, and histologic sections of lymph nodes, spleen, and lung cysts show striking eosinophilia. Hassall corpuscles and thymic architecture are normal. Phagocytic cell ingestion, metabolism, killing, and total hemolytic complement activity are normal in all patients, and results of chemotaxis studies have been mostly normal.

Autosomal Recessive Hyper-IgE Syndrome

Genetics and Pathogenesis

With the exception of 1 patient who had a mutation in the gene encoding Tyk2, most reported patients with autosomal recessive hyper-IgE syndrome have had mutations in the gene encoding DOCK8, which is on chromosome 9. DOCK8 is a member of the 11-member DOCK protein family. DOCK8 is likely to function as a guanine exchange factor for the Rho-guanosine triphosphatases Cdc42 and Rac1. Guanosine triphosphatase activation induces dynamic filamentous actin rearrangements and lamellipodia formation, leading to cell growth, migration, and adhesion. DOCK8 may be important for the formation

Table 126-3 Hyperimmunoglobulin E Syndromes

	AUTOSOMAL DOMINANT OR SPORADIC (JOB SYNDROME)	AUTOSOMAL RECESSIVE
Gene	*STAT3*	*DOCK8:* less often *TYK2*
INFECTIONS		
Sinopulmonary		
Recurrent bacterial	*S. aureus*, pneumococcus, *H. influenzae*	*S. aureus*, pneumococcus, *H. influenzae*
Pneumatoceles/bronchiectasis	Common	No
Fungal	Aspergillus species	No
Cutaneous		
Abscesses	*S. aureus*	*S. aureus*
Viral	No	HPV, HSV, VZV, MCV
Mucocutaneous candidiasis	Common	Common
ATOPIC DISORDERS		
Newborn eosinophilic pustules	Common	No
Eczema	Common	Common
Asthma	No	Common
Allergies/Anaphylaxis	No	Common
MUSCULOSKELETAL		
Osteopenia, pathologic fractures	Common	No
Scoliosis	Common	No
Retained primary teeth	Common	No
Hyperextensible	Common	No
OTHER FEATURES		
Coarse facies*	Common in adolescent	No
Coronary artery tortuosity/aneurysm	Common	No
UBO on brain MRI	Common	No
Lymphomas	Yes	Higher incidence
Cutaneous malignancy	No	Yes
Mortality	Adulthood	Childhood

*Coarse facies includes broad nose, prominent forehead and chin, deep set eyes

HPV, human papillomavirus; HSV, herpes simplex virus; MCV, molluscum virus; UBO, unidentified bright objects of cerebral cortex on T_2 MRI; VZV, varicella-zoster virus.

of the immunologic synapse that leads to T-cell activation, proliferation, and differentiation. Of the 33 patients reported, 25 were from Turkey, 2 each were from Mexico and Iran, and 1 each was from Lebanon, Oman, Italy, and Ireland. Autosomal recessive hyper-IgE syndrome may rarely be due to mutations in phosphoglucomutase 3 (PGM3 deficiency).

Clinical Manifestations

Unlike those with the autosomal dominant form of this syndrome, a large majority of patients with autosomal recessive hyper-IgE have severe atopic dermatitis, asthma, food allergies, and anaphylaxis. They also have recurrent skin viral infections, including severe herpes simplex, herpes zoster, molluscum contagiosum, and papillomavirus skin infections (see Table 126-3). In addition, patients can have abscesses, mucocutaneous candidiasis, upper respiratory infections, and pneumonia. Neurologic problems, including strokes, meningitis, and aneurysms, are prominent. Malignancies are also more common than in the autosomal dominant form. Patients with the autosomal recessive hyper-IgE syndrome do not have pneumatoceles, a history of fractures, unusual facial features, or delayed shedding of the baby teeth, as seen with the autosomal dominant form of the hyper-IgE syndrome (see Table 126-3).

Most patients with autosomal recessive hyper-IgE have elevated serum IgE levels, low serum IgM levels, and variable IgG antibody responses. They also have eosinophilia and lymphopenia, low T-cell numbers and impaired T-cell function. Their immunologic phenotype is that of a CID.

Treatment

The most effective **therapy** for the autosomal dominant hyper-IgE syndrome is long-term administration of therapeutic doses of a penicillinase-resistant antistaphylococcal antibiotic, adding other agents as required for specific infections. IVIG should be administered to antibody-deficient patients, and appropriate thoracic surgery should be provided for superinfected pneumatoceles or those persisting beyond 6 mo. Bone marrow transplantation has been variably successful in this condition. The prognosis in the autosomal recessive form of the hyper-IgE syndrome is much poorer than in the autosomal dominant form, and most patients die early (see Table 126-3). The treatment of choice for the autosomal recessive form is allogeneic bone marrow transplantation.

126.4 Treatment of Cellular or Combined Immunodeficiency

Rebecca H. Buckley

Good supportive care, including prevention and treatment of infections, is critical while patients await more definitive therapy (Table 126-4). Having knowledge of the pathogens causing disease with specific immune defects is also useful (see Table 126-4).

Transplantation of MHC-compatible sibling or rigorously T-cell–depleted haploidentical (half-matched) parental hematopoietic stem cells is the treatment of choice for patients with fatal T-cell or combined T- and B-cell defects. The major risk to the recipient from transplants of bone marrow or peripheral blood stem cells is GVHD from donor T cells. Patients with less severe forms of cellular immunodeficiency, including some forms of CID, Wiskott-Aldrich syndrome, cytokine deficiency, and MHC antigen deficiency, reject even HLA-identical marrow grafts unless chemoablative treatment is given before transplantation. Several patients with these conditions have been treated successfully with hematopoietic stem cell transplantation after conditioning.

More than 90% of patients with primary immunodeficiency transplanted with HLA-identical related marrow will survive with immune reconstitution. T-cell–depleted haploidentical-related marrow transplants in patients with primary immunodeficiency have had their greatest success in patients with SCID, who do not require

Table 126-4 Infection in the Host Compromised by B- and T-Cell Immunodeficiency Syndromes

IMMUNODEFICIENCY SYNDROME	OPPORTUNISTIC ORGANISMS ISOLATED MOST FREQUENTLY	APPROACH TO TREATMENT OF INFECTIONS	PREVENTION OF INFECTIONS
B-cell immunodeficiencies	Encapsulated bacteria (*Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae*, and *Neisseria meningitidis*), *Pseudomonas aeruginosa, Campylobacter* sp., enteroviruses, rotaviruses, *Giardia lamblia, Cryptosporidium* sp., *Pneumocystis jiroveci, Ureaplasma urealyticum*, and *Mycoplasma pneumoniae*	1. IVIG 200-800 mg/kg 2. Vigorous attempt to obtain specimens for culture before antimicrobial therapy 3. Incision and drainage if abscess present 4. Antibiotic selection on the basis of sensitivity data	1. Maintenance IVIG for patients with quantitative and qualitative defects in IgG metabolism (400-800 mg/kg q 3-5 wk) 2. In chronic recurrent respiratory disease, vigorous attention to postural drainage 3. In selected cases (recurrent or chronic pulmonary or middle ear), prophylactic administration of ampicillin, penicillin, or trimethoprim-sulfamethoxazole
T-cell immunodeficiencies	Encapsulated bacteria (*S. pneumoniae, H. influenzae, S. aureus*), facultative intracellular bacteria (*Mycobacterium tuberculosis*, other *Mycobacterium* sp., and *Listeria monocytogenes*); *Escherichia coli; P. aeruginosa; Enterobacter* sp.; *Klebsiella* sp.; *Serratia marcescens; Salmonella* sp.; *Nocardia* sp.; viruses (cytomegalovirus, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, rotaviruses, adenoviruses, enteroviruses, respiratory syncytial virus, measles virus, vaccinia virus, and parainfluenza viruses); protozoa (*Toxoplasma gondii* and *Cryptosporidium* sp.); and fungi (*Candida* sp., *Cryptococcus neoformans, Histoplasma capsulatum*, and *P. jiroveci*)	1. Vigorous attempt to obtain specimens for culture before antimicrobial therapy 2. Incision and drainage if abscess present 3. Antibiotic selection on the basis of sensitivity data 4. Early antiviral treatment for herpes simplex, cytomegalovirus, and varicella-zoster viral infections 5. Topical and nonadsorbable antimicrobial agents frequently are useful	1. Prophylactic administration of trimethoprim-sulfamethoxazole for prevention of *P. jiroveci* pneumonia 2. Oral nonadsorbable antimicrobial agents to lower concentration of gut flora 3. No live virus vaccines or bacillus Calmette-Guérin vaccine 4. Careful tuberculosis screening

IVIG, intravenous immunoglobulin.
From Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders.*

pretransplant conditioning or GVHD prophylaxis. Of patients with SCID, 92% have survived after T-cell–depleted parental marrow is given soon after birth when the infant is healthy without pretransplant chemotherapy or posttransplant GVHD prophylaxis. Currently, bone marrow transplantation remains the most important and effective therapy for SCID. Early in 2000, there was remarkable success with gene therapy in X-SCID. Unfortunately, leukemic-like clonal T cells or lymphomas developed in 5 of 20 children so treated as a result of insertional mutagenesis, which led to a cessation of those trials. By contrast, in ADA-deficient SCID, there has been outstanding success without insertional oncogenesis. More recently, gene therapy has been successful in the Wiskott-Aldrich syndrome but unfortunately with the problem of insertional mutagenesis.

126.5 Immune Dysregulation with Autoimmunity or Lymphoproliferation

Rebecca H. Buckley

AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME

Autoimmune lymphoproliferative syndrome (ALPS), also known as Canale-Smith syndrome, is a disorder of abnormal lymphocyte apoptosis leading to polyclonal populations of T cells (double-negative T cells), which express CD3 and α/β antigen receptors but do not have CD4 or CD8 coreceptors (CD3 + T cell receptor α/β^+ $CD4^-$ $CD8^-$). These T cells respond poorly to antigens or mitogens and do not produce growth or survival factors (IL-2). The genetic deficit in most patients is a germline or somatic mutation in the Fas gene, which produces a cell-surface receptor of the TNF receptor superfamily (TNFRSF6), which, when stimulated by its ligand, will produce programmed cell death (Table 126-5). Persistent survival of these lymphocytes leads to immune dysregulation and autoimmunity. ALPS is also caused by other genes in the Fas pathway (*FASLG* and *CASP10*). In addition, ALPS-like disorders are associated with other mutations; RAS-associated autoimmune lymphoproliferative disorder (RALD), CASPASE-8 deficiency syndrome (CEDS), Fas-associated protein with death domain deficiency (FADD), and protein kinase C delta deficiency (PRKCD). These disorders have varying degrees of immune deficiency, autoimmunity and lymphoproliferation.

Clinical Manifestations

ALPS is characterized by autoimmunity, chronic persistent or recurrent lymphadenopathy, splenomegaly, hepatomegaly (in 50%), and hypergammaglobulinemia (IgG, IgA). Many patients present in the 1st yr of life, and most are symptomatic by yr 5. Lymphadenopathy can be striking (Fig. 126-2). Splenomegaly may produce hypersplenism with cytopenias. Autoimmunity also produces anemia (Coombs-positive hemolytic anemia) or thrombocytopenia or a mild neutropenia. The lymphoproliferative process (lymphadenopathy, splenomegaly) may regress over time, but autoimmunity does not and is characterized by frequent exacerbations and recurrences. Other autoimmune features include urticaria, uveitis, glomerulonephritis, hepatitis, vasculitis, glomerulonephritis, vasculitis, panniculitis, arthritis, and central nervous system involvement (seizures, headaches, encephalopathy).

Malignancies are also more common in patients with ALPS and include Hodgkin and non-Hodgkin lymphomas and solid-tissue tumors of thyroid, skin, heart, or lung. ALPS is one cause of Evan syndrome (immune thrombocytopenia and immune hemolytic anemia).

Diagnosis

Laboratory abnormalities depend on the lymphoproliferative organ response (hypersplenism) or the degree of autoimmunity (anemia, thrombocytopenia). There may be lymphocytosis or lymphopenia. Table 126-5 lists the criteria for the diagnosis. Flow cytometry helps identify the lymphocyte type (see Fig. 126-2). Functional genetic analysis for the *TNFRSF6* gene often reveals a heterozygous mutation.

Table 126-5	Diagnostic Criteria for Autoimmune Lymphoproliferative Syndrome

REQUIRED
1. Chronic nonmalignant lymphoproliferation (>6 mo lymphadenopathy and/or splenomegaly)
2. Elevated peripheral blood double-negative T cells

ACCESSORY
Primary
Defective in vitro Fas-mediated apoptosis (in 2 separate assays)
Somatic or germline mutation in ALPS causative gene (FAS, FASL, CASP10)
Secondary
1. Elevated biomarkers (Any of following)
   a. Plasma soluble FASL >200 pg/mL
   b. Plasma IL-10 >20 pg/mL
   c. Plasma or serum vitamin B_{12} >1500 ng/L
   d. Plasma IL-18 >500 pg/mL
2. Immunohistochemical findings consistent with ALPS as determined by experienced histopathologist
3. Autoimmune cytopenias and polyclonal hypergammaglobulinemia
4. Family history of ALPS or nonmalignant lymphoproliferation

DIAGNOSIS
Definitive: Required plus 1 primary accessory criterion
Probable: Required plus 1 secondary accessory criterion
Of note, probable and definitive ALPS should be treated the same in the clinic

Modified from Teachey DT: New advances in the diagnosis and treatment of autoimmune lymphoproliferative syndrome. Curr Opin Pediatr *24:1–8, 2013, Table 2, p. 4.*

Treatment

Lymphoproliferative manifestations have been managed with corticosteroids and immunosuppressive agents (Cytoxan [cyclophosphamide], methotrexate, azathioprine); once weaned, the manifestation recurs. Hypersplenism may require splenectomy. Malignancies can be treated with the usual protocols used in patients unaffected by ALPS. Stem cell transplantation is another possible option in treating the autoimmune manifestations of ALPS.

IMMUNE-DYSREGULATION, POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED SYNDROME

This immune dysregulation syndrome is characterized by onset within the 1st few wk or mo of life with watery diarrhea (autoimmune enteropathy), an eczematous rash (erythroderma in neonates), insulin-dependent diabetes mellitus, hyperthyroidism or more often hypothyroidism, severe allergies, and other autoimmune disorders (Coombs-positive hemolytic anemia, thrombocytopenia, neutropenia). Psoriasiform or ichthyosiform rashes and alopecia have also been reported,

Immune-dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is caused by a mutation in the *FOXP3* gene, which encodes a forkhead-winged helix transcription factor *(scurfin)* involved in the function and development of CD4+CD25+ regulatory T cells. The absence of regulatory cells may predispose to abnormal activation of effector T cells. Dominant gain of function mutations in *STAT1* and other gene mutations (Table 126-6) produces an IPEX-like syndrome.

Clinical Manifestations

Watery diarrhea with intestinal villous atrophy leads to failure to thrive in most patients. Cutaneous lesions (usually eczema) and

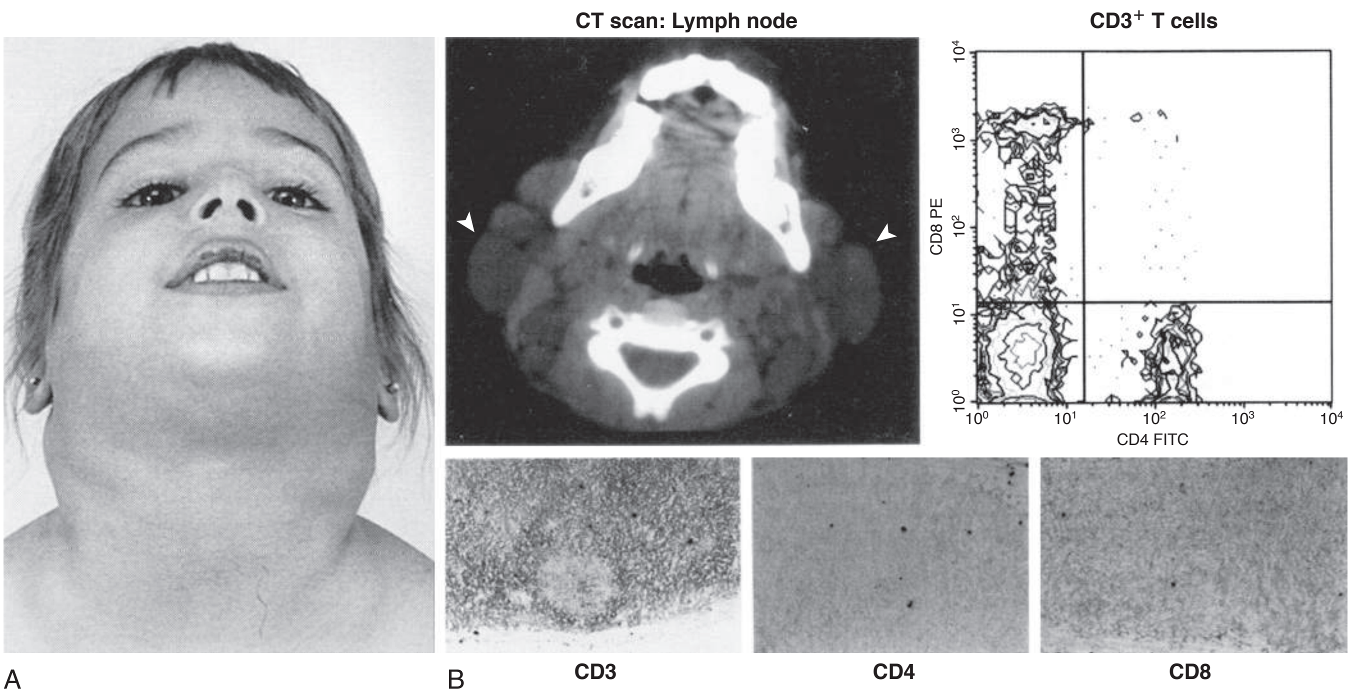

Figure 126-2 Clinical, radiographic, immunologic, and histologic characteristics of the autoimmune lymphoproliferative syndrome. **A,** Front view of the National Institutes of Health patient. **B,** *Top middle*, a CT scan of the neck is shown demonstrating enlarged preauricular, cervical, and occipital lymph nodes. *Arrowheads* denote the most prominent lymph nodes. The *top right* panels show the flow-cytometric analysis of peripheral blood T cells from a patient with autoimmune lymphoproliferative syndrome (ALPS), with CD8 expression on the vertical axis and CD4 on the horizontal axis. The *lower left quadrant* contains CD4-CD8 (double-negative) T cells, which are usually present at <1% of T cells expressing the αβ T-cell receptor. The *bottom panels* show CD3, CD4, and CD8 staining on serial sections of a lymph node biopsy specimen from a patient with ALPS and also shows that large numbers of DNCD3+ CD4-CD8 (double-negative) T cells are present in the interfollicular areas of the lymph node. *(Adapted from Siegel RM, Fleisher TA: The role of Fas and related death receptors in autoimmune and other disease states,* J Allergy Clin Immunol *103:729–738, 1999.)*

Table 126-6	Clinical and Laboratory Features of IPEX and IPEX-Like Disorders				
	IPEX	**CD25**	**STAT5B**	**STAT1**	**ITCH**
AUTOIMMUNITY					
Eczema	+++	+++	++	++	++
Enteropathy	+++	+++	++	++	++
Endocrinopathy	+++	++	+	++	++
Allergic disease	+++	+	+	++	++
Cytopenias	++	++	++	–	
Lung disease	+	++	+++	+	+++
INFECTIONS					
Yeast	–	++	–	+++	–
Herpes virus	–	+++ (EBV/CMV)	++ (VZV)	++	–
Bacterial	+/–	++	++	++	+
Associated features	None	None	Growth failure	Vascular anomalies	Dysmorphic growth failure
Serum immunoglobulins	Elevated	Elevated or normal	Elevated or normal	Low, normal, or high	Elevated
Serum IgE	Elevated	Normal or elevated	Normal or elevated	Normal or mildly elevated	Elevated
CD25 expression	Normal	Absent	Normal or low	Normal	Not tested
CD4+CD45RO	Elevated	Elevated	Elevated	Normal or high	Not tested
FOXP3 expression	Absent or normal	Normal or low	Normal or low	Normal	Not tested
IGF-1, IGFBP-3	Normal	Normal	Low	Normal	Not tested
Prolactin	Normal	Normal	Elevated	Normal	Not tested

CMV, cytomegalovirus; EBV, Epstein Barr Virus; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor–binding protein 3; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; VZV, varicella zoster virus; ITCH, ubiquitin ligase deficiency.

From: Verbsky JW, Chatila TA: Immune dysregulation, polyendocrinopathy, enteropathy, X–linked (IPEX) and IPEX–related disorders: an evolving web of heritable autoimmune diseases. Curr Opin Pediatr *25:708–715, 2013, Table 1, p. 709.*

insulin-dependent diabetes begin in infancy. Lymphadenopathy and splenomegaly are also present. Serious bacterial infections (meningitis, sepsis, pneumonia, osteomyelitis) may be related to neutropenia, malnutrition, or immune dysregulation. Laboratory features reflect the associated autoimmune diseases, dehydration, and malnutrition. In addition, serum IgE levels are elevated with normal levels of IgM, IgG, and IgA. The diagnosis is made clinically and by mutational analysis of the *FOXP3* gene.

Treatment

Inhibition of T-cell activation by cyclosporine, tacrolimus, or sirolimus with steroids is the treatment of choice, along with the specific care of the endocrinopathy and other manifestations of autoimmunity. Stem cell transplantation is the only possibility for curing IPEX. Overall, the combination of the risks for serious bacterial infection in the untreated condition and the risks of immunosuppression and bone marrow transplantation gives IPEX a poor prognosis. Untreated, most die by 2 yr of age.

Bibliography is available at Expert Consult.

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Section 3

The Phagocytic System

Chapter 127

Neutrophils

Thomas D. Coates

THE PHAGOCYTIC INFLAMMATORY RESPONSE

The phagocyte system includes both granulocytes (neutrophils, eosinophils, and basophils) and mononuclear phagocytes (monocytes and tissue macrophages). Neutrophils and mononuclear phagocytes share primary functions, including the defining properties of large particle ingestion and microbial killing. Phagocytes participate primarily in the innate immune response but also help initiate acquired immunity. Mononuclear phagocytes, including tissue macrophages and circulating monocytes, are discussed in Chapter 128.

Neutrophils provide the rapid effector arm of the innate immune system. They circulate in the bloodstream for only about 6 hr (Table 127-1), but upon encountering specific chemotactic signals, they adhere to the vascular endothelium and transmigrate into tissues, where they ingest and kill microbes and release chemotactic signals to recruit more neutrophils and to attract dendritic cells and other initiators of the acquired immune response.

HEMATOPOIESIS

The hematopoietic progenitor system can be envisioned as a continuum of functional compartments with the most primitive compartment composed of very rare **pluripotential stem cells**, which have high self-renewal capacity and give rise to more mature stem cells, including cells that are committed to either lymphoid or myeloid development (Fig. 127-1). Common lymphoid progenitor cells give rise to

Table 127-1 Neutrophil and Monocyte Kinetics

NEUTROPHILS	
Average time in mitosis (myeloblast to myelocyte)	7-9 days
Average time in postmitosis and storage (metamyelocyte to neutrophil)	3-7 days
Average half-life in the circulation	6 hr
Average total body pool	6.5×10^8 cells/kg
Average circulating pool	3.2×10^8 cells/kg
Average marginating pool	3.3×10^8 cells/kg
Average daily turnover rate	1.8×10^8 cells/kg
MONONUCLEAR PHAGOCYTES	
Average time in mitosis	30-48 hr
Average half-life in the circulation	36-104 hr
Average circulating pool (monocytes)	1.8×10^7 cells/kg
Average daily turnover rate	1.8×10^9 cells/kg
Average survival in tissues (macrophages)	Months

From Boxer LA: Function of neutrophils and mononuclear phagocytes. In Bennett JC, Plum F, editors: Cecil textbook of internal medicine, *ed 20, Philadelphia, 1996, WB Saunders.*

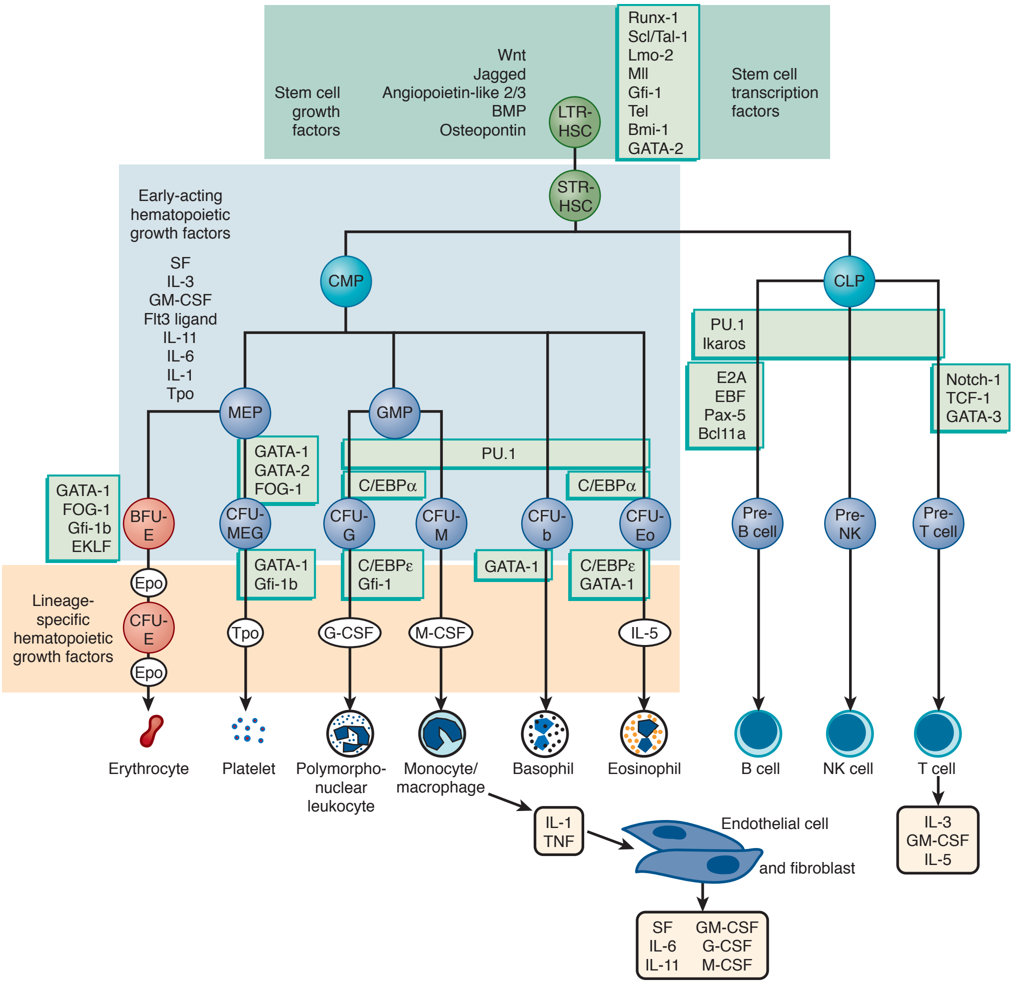

Figure 127-1 **Major cytokine sources and actions and transcription factor requirements.** Cells of the bone marrow microenvironment such as macrophages, endothelial cells, and reticular fibroblastoid cells, produce macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), interleukin (IL)-6, and probably stem cell factor (SCF) after induction with endotoxin (macrophage) or IL-1/tumor necrosis factor (TNF) (endothelial cells and fibroblasts). T-cells produce IL-3, GM-CSF, and IL-5 in response to antigenic and IL-1 stimulation. These cytokines have overlapping actions during hematopoietic differentiation, as indicated, and for all lineages optimal development requires a combination of early- and late-acting factors. Transcription factors important for survival or self-renewal of stem cells are shown at the top *(light green panel)* and stages of hematopoiesis blocked after the depletion of indicated transcription factors for multipotent and committed progenitors are shown in light green boxes throughout. *CFU-E,* erythroid colony-forming unit; *CFU-E/b/M,* erythrocyte, basophil, and megakaryocyte colony-forming unit; *CFU-Eo,* eosinophil colony-forming unit; *CFU-G,* granulocyte colony-forming unit; *CFU-M,* macrophage colony-forming unit; *MSC,* myeloid stem cells; *NK,* natural killer; *PSC,* pluripotent stem cells. *(From Nathan DG, Orkin SH, Ginsburg D, et al, editors:* Nathan and Oski's hematology of infancy and childhood, *ed 7, Philadelphia, 2009, WB Saunders.)*

T- and B-cell precursors and their mature progeny (see Chapter 123). Common myeloid progenitor cells eventually give rise to committed single-lineage progenitors of the recognizable precursors through a random process of lineage restriction in a stepwise process (see Chapter 446). The capacity of lineage-specific committed progenitors to proliferate and differentiate in response to demand provides the hematopoietic system with a remarkable range of response to changing requirements for mature blood cell production.

The proliferation, differentiation, and survival of immature hematopoietic progenitor cells are governed by hematopoietic growth factors, a family of glycoproteins (see Chapter 446). Besides regulating proliferation and differentiation of progenitors, these factors influence the survival and function of mature blood cells. During granulopoiesis and monopoiesis, multiple cytokines regulate the cells at each stage of differentiation from pluripotent stem cells to non-dividing terminally differentiated cells (monocytes, neutrophils, eosinophils, and basophils). As cells mature, they lose receptors for most cytokines, especially those that influence early cell development; however, they retain receptors for cytokines that affect their mobilization and function, such as granulocyte colony-stimulating factor and macrophage colony–stimulating factor. Mature phagocytes also express receptors for chemokines, which help direct the cells to sites of inflammation. Chemokine receptors such as CXCR4 and its ligand SDF-1 play a key role in retention of developing myeloid cells within bone marrow.

NEUTROPHIL MATURATION AND KINETICS

The process of intramedullary granulocyte maturation involves changes in nuclear configuration and accumulation of specific intracytoplasmic granules. The bone marrow microenvironment supports the normal steady-state renewal of peripheral blood neutrophils through the generation of growth and differentiation factors by stromal cells. Growth factors such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor not only stimulate cell division, but also induce the expression of transcription factors that regulate the biosynthesis of functional components of the neutrophil, such as granule proteins. The transcription factor PU.1 is essential for myelopoiesis, both as a positive regulatory element and as a suppressor of GATA-1, a transcription factor that directs nonmyeloid differentiation. Other transcription factors, such as Runx1 (AML1), c-myb, CDP, C/EBPα, C/EBPγ, and MEF, are expressed in the myeloblast and promyelocyte, and some of these are required for azurophil granule protein expression. As cells enter the myelocyte stage, RUNX1 and

myb are downregulated, whereas PU.1 and C/EBPε expression rises to initiate terminal differentiation.

Granulocytes survive for only 6-12 hr in the circulation, and therefore daily production of 2×10^4 granulocytes/µL of blood is required to maintain a level of circulating granulocytes of 5×10^3/µL (see Table 127-1). The relatively small peripheral blood pool includes the rapidly interchanging circulating and marginating pools; the latter provides entrance into the tissue phase, where neutrophils may survive for hours or days. The circulating pool is fed and buffered by a much larger marrow population of mature neutrophils and myeloid precursors, representing the marrow reserve and proliferating pools, respectively. Proliferation of myeloid cells, encompassing approximately 5 mitotic divisions, takes place only during the 1st 3 stages of neutrophil development, in myeloblasts, promyelocytes, and myelocytes. After the myelocyte stage, the cells terminally differentiate into nondividing, maturing metamyelocytes, bands, and neutrophils.

Neutrophil maturation is associated with nuclear condensation and lobulation and with the sequential production of characteristic granule populations. A myeloblast is a relatively undifferentiated cell with a large oval nucleus, a sizeable nucleolus, and a deficiency of granules. Promyelocytes acquire peroxidase-positive azurophilic (primary) granules, and then myelocytes and metamyelocytes acquire specific (secondary) granules; tertiary granules and secretory vesicles develop in the final stage of neutrophil maturation.

NEUTROPHIL FUNCTION

Neutrophil responses are initiated as circulating neutrophils flowing through the postcapillary venules detect low levels of chemokines and other chemotactic substances released from a site of infection. The sequence of events as the neutrophil moves from circulating in the blood to the encounter and destruction of bacteria is carefully orchestrated by a series of biochemical events, defects of which are associated with genetic disorders of neutrophil function (Fig. 127-2). In fact, these disorders of neutrophil function lead to our understanding of the cell biology of phagocyte function. A subset of circulating neutrophils loosely adheres to the endothelium through low-affinity receptors called selectins and rolls along the endothelium forming the marginated pool. Soluble effectors of inflammation trigger subtle changes in surface adhesion molecules on endothelial cells at the site of infection. The rolling of neutrophils allows more intense exposure of neutrophils to activating factors such as tumor necrosis factor or interleukin-1 (Fig. 127-2). Exposure of neutrophils ti these same activating factors induces

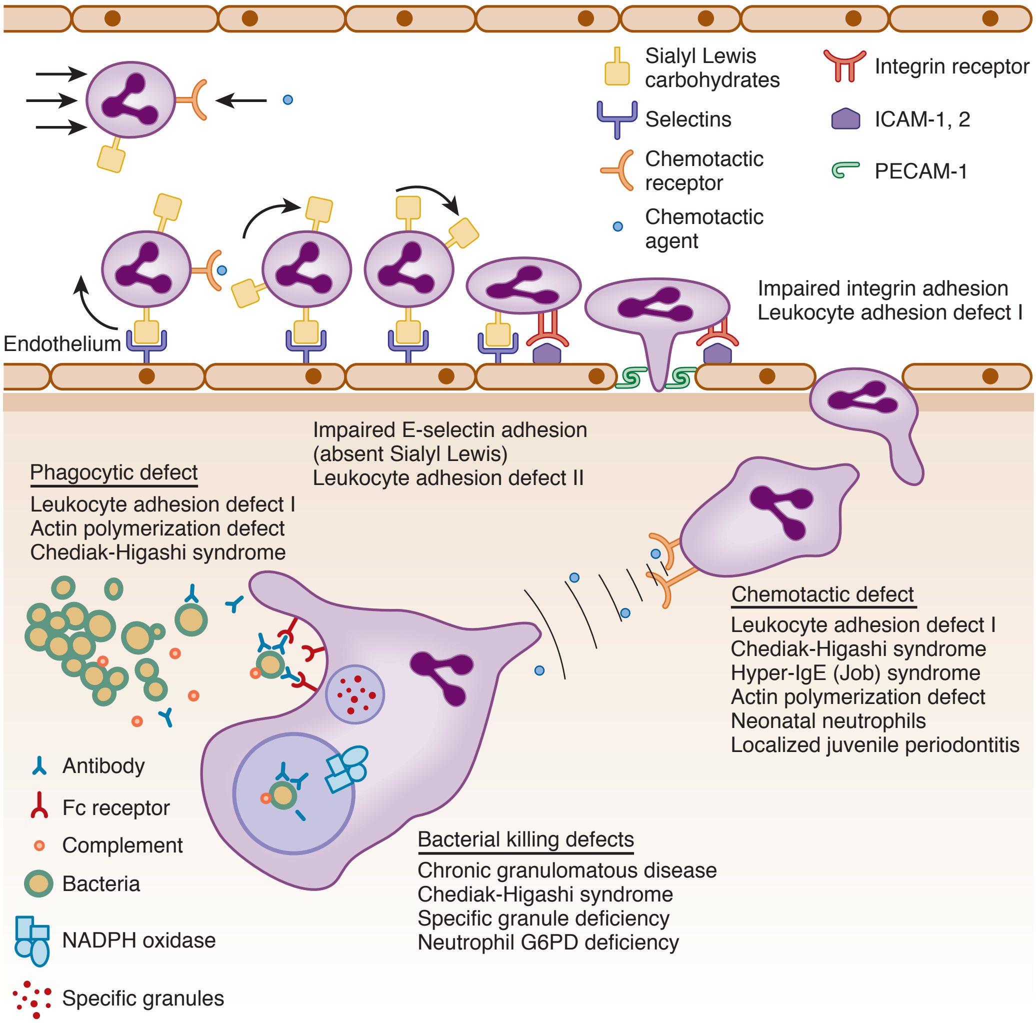

Figure 127-2 **The neutrophil-mediated inflammatory response and associated neutrophil dysfunction syndromes.** Circulating neutrophils loosely attach to endothelium via selectins and roll along the vessel wall until they arrive at the site of infection. Inflammatory monokines, interleukin 1 (IL-1), and tumor necrosis factor (TNF), activate endothelial cells to express E- and P-selectins. E- and P-selectins serve as counter receptors for neutrophils sialyl Lewis X and Lewis X to cause low-avidity neutrophil rolling. Activated endothelial cells express ICAM-1, which serves as a counter-receptor for neutrophil β_2 integrin molecules, leading to high-avidity leukocyte spreading and the start of transendothelial migration at the infection site. Neutrophils invade through the vascular basement membrane with the release of proteases and reactive oxidative intermediates, causing local destruction of surrounding tissue at sites of high concentrations of chemotactic factors and migrate to the site of infection where they ingest and kill the bacteria. *(Modified from Kyono W, Coates TD: A practical approach to neutrophil disorders.* Pediatr Clin North Am *49:929, 2002.)*

qualitative and quantitative changes in the family of β_2-integrin adhesion receptors (the CD11/CD18 group of surface molecules), leading to tight adhesion between neutrophils and endothelial cells at the site of inflammation and ultimately to transmigration of the neutrophil into the tissue.

Once through the endothelium, the neutrophil senses the gradient of chemokines or other chemoattractants and migrates to sites of infection. Neutrophil migration is a complex process involving rounds of receptor engagement, signal transduction, and remodeling of the actin-microfilaments composing in part the cytoskeleton. Actin polymerization–depolymerization occurs in approximately 8 sec cycles and drives cyclic extension and retraction of the actin-rich lamella at the front of the neutrophil. Receptors at the leading edge of the lamella detect the gradient of attractant and follow microorganisms, ingest and destroy them. When the neutrophil reaches the site of infection, it recognizes pathogens by means of Fc immunoglobulin and complement receptors, Toll-like receptors, fibronectin receptors, and other adhesion molecules.

The neutrophil ingests microbes that are coated by **opsonins**, serum proteins such as immunoglobulin and complement component C3. The pathogens are engulfed into a closed vacuole, the **phagosome** (Fig. 127-3) where 2 cellular responses essential for optimal microbicidal activity occur concomitantly: degranulation and activation of nicotinamide-adenine dinucleotide phosphate (NADPH)–dependent oxidase. Fusion of neutrophil granule membranes with the phagosome membrane delivers potent antimicrobial proteins and small peptides into the phagosome.

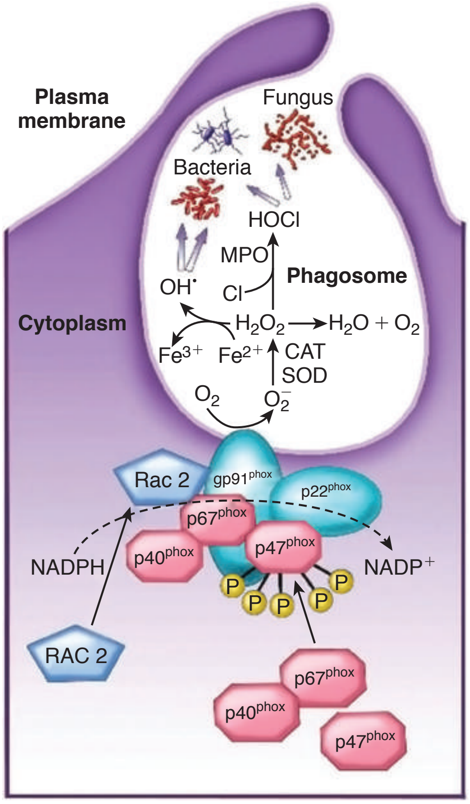

Figure 127-3 Nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase components and activation. On activation of phagocytic cells, the 3 cytosolic components *(red)* of the NADPH oxidase ($p67^{phox}$, $p47^{phox}$, and $p40^{phox}$), plus the small guanosine triphosphatase (GTPase) protein Rac2, are translocated to the membrane of the phagocytic vacuole. The $p47^{phox}$ subunit binds to the flavocytochrome$_{b558}$ membrane component *(blue-green)* of the NADPH oxidase ($gp91^{phox}$ plus $p22^{phox}$). The NADPH oxidase catalyses the formation of superoxide by transferring an electron from NADPH to molecular oxygen (O_2), thereby forming the superoxide free radical. The unstable superoxide anion is converted to hydrogen peroxide, either spontaneously or by superoxide dismutase (SOD). Hydrogen peroxide can follow different metabolic pathways into more potent reactive oxidants (such as $OH^{\bullet}$ or HOCl) or degradation to $H_2O + O_2$. *(Modified from Stiehm ER, Ochs HD, Winkelstein JA:* Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders, p 622.)*

Assembly and activation of NADPH oxidase at the phagosome membrane as well (see Fig. 127-3) generating large amounts of superoxide (O_2^-) from molecular oxygen that, in turn, decomposes to produce hydrogen peroxide (H_2O_2) and singlet oxygen. **Myeloperoxidase,** a major azurophil granule component, catalyzes the reaction of H_2O_2 with ubiquitously present chloride ions to create hypochlorous acid (HOCl) in the phagosome. Hypochlorous acid is essentially Clorox bleach. H_2O_2 and HOCl are potent microbicidal agents that break down and clear pathogens from sites of infection.

In addition, neutrophils secrete a wide variety of cytokines and chemokines that recruit more neutrophils to fight the infection, attract monocytes and macrophages that possess both microbicidal and scavenger functions, and promote antigen presentation to help initiate the adaptive immune response. Also, the reactive oxidants can inactivate chemotactic factors and may serve to terminate the process of neutrophil influx, thereby attenuating the inflammatory process. Finally, the release of reactive oxygen species, granule proteins, and cytokines can also damage local tissues, leading to the classic signs of inflammation or to more permanent impairment of tissue integrity and function.

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Chapter 128

Monocytes, Macrophages, and Dendritic Cells

Richard B. Johnston Jr.

Mononuclear phagocytes (monocytes, macrophages) are distributed across all body tissues and play a central role in maintaining homeostasis. They are essential for innate host defense against infection, tissue repair and remodeling, and the antigen-specific adaptive immune response. No human has been identified as having congenital absence of this cell line, probably because macrophages are required to remove primitive tissues during fetal development as new tissues develop to replace them. Monocytes and tissue macrophages in their several forms (Table 128-1) have variable morphology and surface markers and different transcriptional profiles but common functions, particularly phagocytosis. **Dendritic cells** (DCs) are specialized derivatives of this system that develop from myeloid–lymphoid cell precursors.

DEVELOPMENT

Monocytes develop more rapidly during bone marrow hematopoiesis and remain longer in the circulation than do neutrophils (see Table 127-1). The first recognizable monocyte precursor is the monoblast, followed by the promonocyte with cytoplasmic granules and an indented nucleus, and, finally, the fully developed monocyte with cytoplasm filled with granules containing hydrolytic enzymes. The transition from monoblast to mature circulating monocyte requires about 6 days.

Two major subsets of human blood monocytes can be identified on the basis of surface antigens: CD14++ CD16–, originally termed

Table 128-1	Principal Sites of Macrophages in Tissues
Liver (Kupffer cells)	
Lung (interstitial and alveolar macrophages)	
Connective tissue, adipose tissue, and interstitium of major organs and skin	
Serosal cavities (pleural and peritoneal macrophages)	
Synovial membrane (type A synoviocytes)	
Bone (osteoclasts)	
Brain and retina (microglial cells)	
Spleen, lymph nodes, bone marrow	
Intestinal wall	
Breast milk	
Placenta	
Granulomas (multinucleated giant cells)	

"classical monocytes" because they constitute 90-95% of total monocytes, and the more mature CD14+ CD16+ "proinflammatory" monocytes, which produce more proinflammatory tumor necrosis factor-α (TNF-α) and less immunosuppressive interleukin (IL)-10 in response to microbial stimuli. Monocytes of either subset migrate into tissues in response to localized inflammation or, apparently, randomly in the absence of inflammation.

Most organ macrophages probably arise from macrophage progenitors that develop in the embryo before hematopoiesis occurs. Exceptions are macrophage populations in the skin and intestines and at sites of active inflammation, which appear to derive commonly from blood monocytes.

Whether tissue macrophages originate from blood monocytes or in the embryo, organ-specific factors must influence differentiation of the precursor cells and endow each tissue macrophage type with its characteristic features. Monocytes or embryonic progenitors in the liver become **Kupffer cells** that bridge the sinusoids separating adjacent plates of hepatocytes. Those at the lung airway surface become large ellipsoid **alveolar macrophages,** and those in the bone become **osteoclasts.** All macrophages have at least 3 major functions in common: phagocytosis, presentation of antigens to lymphocytes, and enhancement or suppression of the immune response through release of a variety of potent hormone-like factors termed cytokines. At sites of inflammation, monocytes and macrophages can fuse to form multinucleated giant cells; these cells maintain the antimicrobial functions of macrophages.

ACTIVATION

The most important step in the maturation of tissue macrophages is the conversion from a resting to a more functionally active cell, a process driven primarily by certain cytokines and microbial products. **Macrophage activation** is a generic term, with the functional characteristics of an activated macrophage population varying with the cytokine or other stimulus (microbial, chemical) to which the population has been exposed.

Classical activation refers to a response to infection that is driven by specifically activated T-helper (Th) type 1 (Th1)–type lymphocytes and natural killer cells through their release of interferon-γ (IFN-γ). TNF-α secreted by activated macrophages amplifies their activation, as does bacterial cell wall protein or endotoxin through Toll-like receptors. **Alternative activation** is driven by Th2–type lymphocytes through release of IL-4 and IL-13, cytokines that regulate antibody responses, allergy, and resistance to parasites. Alternatively activated macrophages may have particular functional advantages, such as in wound healing and immunoregulation. In the traditional context of host defense, the term *activated macrophage* indicates that the "classically activated" cell has an enhanced capacity to kill microorganisms or tumor cells. These macrophages are larger, with more pseudopods and pronounced ruffling of the plasma membrane, and they exhibit accelerated activity of many functions (Table 128-2). Considering the variety of macrophage activities essential to the maintenance of homeostasis, it seems likely that so-called classically and alternatively activated macrophages are examples of a continuum of physiologic functions expressed by these long-lived cells in response to the specific task at hand.

Table 128-2	Upregulated Functions in Macrophages Activated in Response to Infection
Microbicidal and tumoricidal activity	
Phagocytosis (of most particles) and pinocytosis	
Phagocytosis-associated respiratory burst (O_2^-, H_2O_2)	
Generation of nitric oxide	
Chemotaxis	
Glucose transport and metabolism	
Membrane expression of MHC, CD40, TNF receptor	
Antigen presentation	
Secretion	
Complement components	
Lysozyme, acid hydrolases, and cytolytic proteinases	
Collagenase	
Plasminogen activator	
Interleukins, including IL-1, IL-12, and IL-15	
TNF-α	
Interferons, including IFN-α and IFN-β	
Antimicrobial peptides (cathelicidin, defensins)	
Angiogenic factors	

H_2O_2, hydrogen peroxide; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; O_2^-, superoxide anion; TNF, tumor necrosis factor.

Classical macrophage activation is accomplished during infection with intracellular pathogens (e.g., mycobacteria, *Listeria*) through crosstalk between Th1 lymphocytes and antigen-presenting macrophages mediated by the engagement of a series of ligands and receptors on the 2 cell types, including CD40 on macrophages and CD40 ligand on Th cells, and through secretion of cytokines. Macrophages encountering microorganisms release IL-12, which stimulates T cells to release IFN-γ. These interactions constitute the basis of cell-mediated immunity. IFN-γ is an especially important macrophage-activating cytokine; it is currently used as a therapeutic agent.

FUNCTIONAL ACTIVITIES

Numerous functions are upregulated when the macrophage is activated in response to infection (see Table 128-2). Obviously important are the ingestion and killing of intracellular pathogens such as mycobacteria, *Listeria, Leishmania, Toxoplasma,* and some fungi; however, splenic and hepatic macrophages also clear extracellular pathogens such as pneumococci from the bloodstream. Killing of the ingested organisms depends heavily on products of the respiratory burst (e.g., hydrogen peroxide) and on nitric oxide, and release of these metabolites is enhanced in activated macrophages.

The activity of mononuclear phagocytes against cancers in humans is less-well understood. This activity may involve more than the phagocytic process. Macrophages may kill tumor cells by means of secreted products, including lysosomal enzymes, nitric oxide, oxygen metabolites, cytolytic proteinases, and TNF-α. Proteolytic enzymes and cytocidal factors present on the surface membrane of monocytes may have a role in tumor rejection. In contrast, tumor-associated macrophages also appear to stimulate growth of certain tumors through secretion of growth and angiogenic factors.

The capacity to undergo diapedesis across the endothelial wall of blood vessels and to migrate to sites of microbial invasion is essential to monocyte function. Chemotactic factors for monocytes include complement products and chemokines derived from neutrophils, lymphocytes, and other cell types. Phagocytosis of the invading organisms can then occur, influenced by the presence of opsonins for the invader (antibody, complement, mannose-binding and surfactant proteins), the inherent surface properties of the microorganism, and the state of activation of the macrophage.

Monocytes migrating to intestinal mucosa are modified by stromal factors so that they lose innate receptors for microbial products such

as endotoxin, and they do not effectively produce proinflammatory cytokines. They retain, however, the capacity to ingest and kill microbes. They have been modified during evolution to allow the absence of inflammation typical of normal intestinal mucosa in spite of its constant exposure to huge numbers of microbes and their inflammatory by-products.

Macrophages play an essential role in the disposal of damaged and dying cells, helping resolve the inflammatory response and heal wounds. Brain microglia demonstrate these functions particularly well. In conditions such as stroke, neurodegenerative disease, and tumor invasion, these cells can become activated, surround damaged and dead cells, and clear cellular debris. Macrophages lining the sinusoids of the spleen are especially important in ingesting aged or autoantibody-coated erythrocytes or platelets; splenectomy is used to manage autoimmune cytopenias. Macrophages in inflammatory sites can recognize changes in phosphatidylserine on the membrane of neutrophils undergoing apoptosis, and these can be removed before they become necrotic and spill their toxic contents into the tissue. Macrophages also remove the extracellular traps exuded by inflammatory neutrophils, thus reducing the risk of autoimmunity. Macrophages can be identified early in fetal development, where they function to remove debris as one maturing embryonic tissue replaces another. They are also important in removing immune complexes, protein fragments, and inorganic particles such as elements of cigarette smoke that enter the alveoli.

Macrophages are integrally involved in the induction and expression of adaptive immune responses, including antibody formation and cell-mediated immunity. This involvement depends on their capacity to break down foreign material in phagocytic and pinocytic vesicles and then present individual antigens on their surface as peptides or polysaccharides bound to class II major histocompatibility complex (MHC) molecules. B lymphocytes and, most effectively, DCs can also present antigens to T cells for the specific immune response. Expression of MHC class II molecules is increased in activated macrophages, and antigen presentation is more effective.

The heightened capacity of activated macrophages to synthesize and release various hydrolytic enzymes and microbicidal materials (see Table 128-2) probably plays a part in their increased killing capacity, although not every macrophage product is secreted in increased amounts when the cell is activated. The macrophage is an extraordinarily active secretory cell. It has been shown to secrete more than 100 distinct substances, including cytokines, growth factors, and sterol hormones, placing it in a class with the hepatocyte. Because of the profound effect of some of these secretory products on other cells and the large number and widespread distribution of macrophages, this network of cells can be viewed as an important endocrine organ. IL-1 illustrates this point well. Microbes and microbial products, burns, ischemia–reperfusion, and other causes of inflammation or tissue damage stimulate the release of IL-1, mainly by monocytes, macrophages, and epithelial cells. In turn, IL-1 elicits fever, sleep, and release of IL-6, which induces production of acute-phase proteins.

As traumatic damage and infection subside, the macrophage population shifts toward playing an essential role in tissue repair and healing through removal of apoptotic cells and secretion of IL-10, transforming growth factor-β, lipoxins, and omega-3 fatty acid–derived resolvins, protectins, and maresins (macrophage mediators in resolving inflammation).

DENDRITIC CELLS

DCs are derived from both myeloid and lymphoid bone marrow progenitors. They are specialized to capture, process, and present antigens to T cells to generate adaptive immunity or tolerance to self-antigens. Human monocytes can be induced to differentiate into DCs in some circumstances, particularly inflammation. DCs express retractable dendritic (branched) extensions and potent endocytic capacity but are a heterogeneous population from the standpoint of location, surface markers, level of antigen-presenting activity, and function. There are 2 major functional types of DCs, *conventional DCs,* which include Langerhans cells in the epithelial surfaces of skin and mucosa, and dermal or interstitial DCs in subepithelial skin and interstitia of solid organs; and *plasmacytoid DCs*, sentinels for viral infection and principal source of antiviral IFN-α and IFN-β.

DCs migrating from the bloodstream enter skin, epithelial surfaces, and lymphoid organs where, as immature cells, they internalize self- and foreign-antigens. Microbial products, cytokines, or molecules exposed in damaged tissue ("danger signals" or "alarmins") induce DC maturation, with upregulation of cytokine receptors and MHC class II and costimulatory molecules. Stimulated DCs in the periphery migrate to lymphoid organs where they continue to mature. They function there as the most potent cells that present antigens to T lymphocytes and induce their proliferation, activities that are central to the antigen-specific adaptive immune response. Macrophage IL-10 acts to suppress DC maturation during resolution of inflammation.

DCs from cancer patients have been used in an attempt to control their cancer. The patient's DCs are amplified and matured from blood monocytes or marrow progenitor cells by cytokines, exposed to antigens from the patient's tumor, then injected into the patient as a "vaccine" against the cancer.

ABNORMALITIES OF MONOCYTE-MACROPHAGE OR DENDRITIC CELL FUNCTION

Mononuclear phagocytes, as well as neutrophils, from patients with **chronic granulomatous disease** exhibit a profound defect of phagocytic killing (see Chapter 130). The inability of affected macrophages to kill ingested organisms leads to abscess formation and characteristic granulomas at sites of macrophage accumulation beneath the skin and in the liver, lungs, spleen, and lymph nodes. IFN-γ is currently used for preventing infection in patients with chronic granulomatous disease and for treating the decreased bone resorption of **congenital osteopetrosis**, which is caused by decreased function of osteoclasts. Genetic deficiency of the CD11/CD18 complex of membrane adherence glycoproteins **(leukocyte adhesion defect-1),** which includes a receptor for opsonic complement component 3, results in impaired phagocytosis by monocytes (see Chapter 130).

The monocyte–macrophage system is prominently involved in **lipid storage diseases** called sphingolipidoses (see Chapter 86.3). In these conditions, the expression in macrophages of a systemic enzymatic defect permits the accumulation of cell debris that is normally cleared. Resistance to infection can be impaired, at least partly because of impairment in macrophage function. **Gaucher disease** is the prototype for these disorders. In this condition, the enzyme glucocerebrosidase functions abnormally, thus allowing accumulation of glucocerebroside from cell membranes in Gaucher cells throughout the body. In all locations, the Gaucher cell is an altered macrophage. These patients can be treated with infusions of the normal enzyme modified to expose mannose residues, which bind to mannose receptors on macrophages.

The cytokine IL-12 is a powerful inducer of IFN-γ production by T cells and natural killer cells. Individuals with inherited deficiency in macrophage receptors for IFN-γ or lymphocyte receptors for IL-12, or in IL-12 itself, suffer a severe, profound, and selective susceptibility to infection by nontuberculous mycobacteria such as *Mycobacterium avium* complex or bacillus Calmette-Guérin (see Chapter 126). About half of these patients have had disseminated *Salmonella* infection. These abnormalities are now grouped as **defects in the IFN-γ–IL-12 axis**.

Monocyte–macrophage function has been shown to be partially abnormal in various clinical conditions. Cultured mononuclear phagocytes of newborns are more readily infected than adult cells by HIV-1 and measles virus. Macrophages from newborns release less granulocyte colony-stimulating factor and IL-6 in culture, and this deficiency is accentuated in cells from preterm infants. This finding supports the observations that levels of granulocyte colony-stimulating factor are significantly decreased in blood from newborns, and that the marrow granulocyte storage pool is diminished in infants, particularly preterm infants. Mononuclear cells from newborns produce less IFN-γ and IL-12 than do adult cells, and macrophages cultured from cord blood are not activated normally by IFN-γ. This combination of deficiencies

would be expected to blunt the newborn's response to infection by viruses, fungi, and certain bacteria such as *Listeria*.

There are 2 disorders in which macrophage activation is pathologically excessive. **Familial and acquired hemophagocytic lymphohistiocytosis** is characterized by uncontrolled activation of T cells and macrophages, with resultant fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, marked elevation of serum proinflammatory cytokines, and macrophage hemophagocytosis (see Chapter 507). Up to 5% of children with systemic onset juvenile rheumatoid arthritis develop an acute severe complication termed **macrophage activation syndrome,** with persistent fever (rather than typical febrile spikes), hepatosplenomegaly, pancytopenia, macrophage hemophagocytosis, and coagulopathy, which can progress to disseminated intravascular coagulation and death if not recognized (see Chapter 155).

Two genetic autoinflammatory diseases result from dysregulation of the mononuclear phagocyte–produced proinflammatory cytokine IL-1. In **neonatal onset multisystem inflammatory disorder** monocytes overproduce IL-1**.** In **deficiency of the IL-1-receptor antagonist**, normal activity levels of IL-1 go unopposed. In both conditions patients present in the 1st few days or weeks of life with pustular or urticarial rash, bony overgrowth, sterile osteomyelitis, elevated sedimentation rate, and other evidence of systemic inflammation. The recombinant IL-1-receptor antagonist anakinra is effective treatment for both these disorders.

The term *histiocyte* was originally used to describe cells thought to be macrophages in fixed tissue preparations. Histiocytosis X represents a malignancy-like overgrowth of Langerhans-type DCs (see Chapter 507). Thus, the term **Langerhans cell histiocytosis** better describes this disorder, because histiocyte is a histologic term and not cell specific.

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Chapter 129

Eosinophils

Brian P. Vickery

Eosinophils are distinguished from other leukocytes by their morphology, constituent products, and association with specific diseases. Eosinophils are nondividing fully differentiated cells with a diameter of ≈8 μm and a bilobed nucleus. They differentiate from stem cell precursors in the bone marrow under the control of T-cell–derived interleukin (IL)-3, granulocyte-macrophage colony-stimulating factor, and, especially, IL-5. Their characteristic membrane-bound specific granules stain reddish brown with eosin and consist of a crystalline core made up of major basic protein (MBP) surrounded by a matrix containing the eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin. These basic proteins are cytotoxic for the larval stages of helminthic parasites and are also thought to contribute to much of the inflammation associated with chronic allergic diseases such as asthma (see Chapter 144).

Both eosinophil MBP and eosinophil cationic protein are also present in large quantities in the airways of patients who have died of asthma and are thought to inflict epithelial cell damage leading to airway hyperresponsiveness. Eosinophil granule contents also contribute to Loeffler endocarditis associated with hypereosinophilic syndrome. MBP has the potential to activate other proinflammatory cells, including mast cells, basophils, neutrophils, and platelets. Eosinophils have the capacity to generate large amounts of the lipid mediators platelet-activating factor and leukotriene C_4, both of which can cause vasoconstriction, smooth muscle contraction, and mucus hypersecretion. Eosinophils are a source of a number of proinflammatory cytokines, including IL-1, IL-3, IL-4, IL-5, IL-9, IL-13, and granulocyte-macrophage colony-stimulating factor; they can also function as antigen-presenting cells. Thus, eosinophils have considerable potential to initiate and sustain inflammatory response of the innate and acquired immune systems.

Eosinophil migration from the vasculature into the extracellular tissue is mediated by the binding of leukocyte adhesion receptors to their ligands or counterstructures on the postcapillary endothelium. Similar to neutrophils (see Fig. 127-2), transmigration begins as the eosinophil selectin receptor binds to the endothelial carbohydrate ligand in loose association, which promotes eosinophils rolling along the endothelial surface until they encounter a priming stimulus such as a chemotactic mediator. Eosinophils then establish a high-affinity bond between integrin receptors and their corresponding immunoglobulin-like ligand. Unlike neutrophils, which become flattened before transmigrating between the tight junctions of the endothelial cells, eosinophils can use unique integrins, known as VLA-4, to bind to vascular cell adhesion molecule-1, which enhances eosinophil adhesion and transmigration through endothelium. Eosinophils are recruited to tissues in inflammatory states by the chemokine **eotaxin.** These unique pathways account for selective accumulation of eosinophils in allergic and inflammatory disorders. Eosinophils normally dwell primarily in tissues, especially tissues with an epithelial interface with the environment, including the respiratory, gastrointestinal, and lower genitourinary tracts. The life span of eosinophils may extend for weeks within tissues.

IL-5 selectively enhances eosinophil production, adhesion to endothelial cells, and function. Considerable evidence shows that IL-5 has a pivotal role in promoting eosinophil accumulation. It is the predominant cytokine in allergen-induced pulmonary late-phase reaction, and antibodies against IL-5 block eosinophil infiltration into the lungs in animal models associated with airway hyperresponsiveness following allergen challenge. Eosinophils also bear unique receptors for several chemokines, including RANTES (regulated upon activation, normal T-cell expressed and secreted), eotaxin, and monocyte chemotactic proteins 3 and 4. These chemokines appear to be key mediators in the induction of tissue eosinophilia.

DISEASES ASSOCIATED WITH EOSINOPHILIA

The **absolute eosinophil count** (AEC) is used to quantify eosinophilia. Calculated as the white blood cell count/μL × percent of eosinophils, it is usually <450 cells/μL and varies diurnally, with eosinophil numbers higher in the early morning and diminishing as endogenous glucocorticoid levels rise.

Many diseases with allergic, infectious, hematologic, autoimmune, or idiopathic origins are associated with moderate (AEC 1,500-5,000 cells/μL) or severe (AEC >5,000 cells/μL) eosinophilia in peripheral blood (Table 129-1). These disorders may range from mild and transient to chronic and life-threatening, and, importantly, blood eosinophil numbers do not always reflect the extent of eosinophil involvement in disease-affected tissues. Because prolonged eosinophilia is associated with end-organ damage, especially involving the heart, patients with persistently elevated AECs should undergo a thorough evaluation to search for an underlying cause.

Allergic Diseases

Allergy is the most common cause of eosinophilia in children in the United States. Patients with allergic asthma commonly have eosinophils in the blood, sputum, and/or lung tissue. Hypersensitivity drug reactions can elicit eosinophilia, and when associated with organ dysfunction (e.g., DRESS [drug rash with eosinophilia and systemic symptoms]), these reactions can be serious (see Chapter 152). If a drug is suspected of triggering eosinophilia, biochemical evidence of organ dysfunction should be sought and if found, the drug should be discontinued. Various skin diseases have also been associated with eosinophilia, including atopic dermatitis/eczema, pemphigus, urticaria, and toxic epidermal necrolysis.

Table 129-1 Causes of Eosinophilia
ALLERGIC DISORDERS
Allergic rhinitis
Asthma
Acute and chronic urticaria
Pemphigoid
Hypersensitivity drug reactions (drug rash with eosinophilia and systemic symptoms [DRESS])
Eosinophilic gastrointestinal disorders
Interstitial nephritis
INFECTIOUS DISEASES
Tissue-Invasive Helminth Infections
Trichinosis
Toxocariasis
Strongyloidosis
Ascariasis
Filariasis
Schistosomiasis
Echinococcosis
Pneumocystis carinii
Toxoplasmosis
Scarlet fever
Amebiasis
Malaria
Bronchopulmonary aspergillosis
Coccidioidomycosis
Scabies
MALIGNANT DISORDERS
Brain tumors
Hodgkin disease and T-cell lymphoma
Acute myelogenous leukemia
Myeloproliferative disorders
Eosinophilic leukemia
GASTROINTESTINAL DISORDERS
Inflammatory bowel disease
Peritoneal dialysis
Chronic active hepatitis
Eosinophilic gastrointestinal disorders:
• Eosinophilic esophagitis
• Eosinophilic gastroenteritis
• Eosinophilic colitis
RHEUMATOLOGIC DISEASE
Rheumatoid arthritis
Eosinophilic fasciitis
Scleroderma
IMMUNODEFICIENCY DISEASE
Hyperimmunoglobulin E syndromes
Wiskott-Aldrich syndrome
Graft-versus-host disease
Omenn syndrome
Severe congenital neutropenia
Hypersensitivity pneumonia
MISCELLANEOUS
Thrombocytopenia with absent radii
Churg-Strauss syndrome (eosinophilic granulomatosis with vasculitis)
Vasculitis
Adrenal insufficiency
Postirradiation of abdomen
Histiocytosis with cutaneous involvement
Hypereosinophilic syndromes
Autoimmune lymphoproliferative syndromes (ALPS)
Immune dysregulation, polyendocrinopathy, X-linked (IPEX)

Eosinophilic gastrointestinal diseases are important emerging allergic causes of eosinophilia in tissue and, in some cases, peripheral blood (see Chapter 337). In these conditions, eosinophils are inappropriately recruited to esophagus, stomach, and/or intestine, where they induce tissue inflammation and clinical symptoms such as dysphagia, food aversion, abdominal pain, vomiting, and diarrhea. Treatment options include allergen elimination diets and swallowed topical corticosteroids.

Infectious Diseases

Eosinophilia is often associated with invasive infection with multicellular helminthic parasites, which are the most common cause in developing countries. Table 129-1 includes examples of specific organisms. The level of eosinophilia tends to parallel the magnitude and extent of tissue invasion, especially by larvae such as visceral larva migrans (see Chapter 298). Eosinophilia often *does not* occur in established parasitic infections that are well contained within tissues or are solely intraluminal in the gastrointestinal tract, such as *Giardia lamblia* and *Enterobius vermicularis* infection.

In evaluating patients with unexplained eosinophilia, the dietary history and geographic or travel history may indicate potential exposures to helminthic parasites. It is frequently necessary to examine the stool for ova and larvae at least 3 times. Additionally, the diagnostic parasite stages of many of the helminthic parasites that cause eosinophilia never appear in feces. Thus, normal results of stool examinations do not absolutely preclude a helminthic cause of eosinophilia; diagnostic blood tests or tissue biopsy may be needed. *Toxocara* causes **visceral larva migrans** usually in toddlers with pica (see Chapter 298). Most young children are asymptomatic, but some develop fever, pneumonitis, hepatomegaly, and hypergammaglobulinemia accompanied by severe eosinophilia. Isohemagglutinins are frequently elevated. Serology can establish the diagnosis.

Two fungal diseases may be associated with eosinophilia: aspergillosis in the form of **allergic bronchopulmonary aspergillosis** (see Chapter 237.1) and coccidioidomycosis (see Chapter 240) following primary infection, especially in conjunction with erythema nodosum. HIV can also be associated with peripheral eosinophilia.

Hypereosinophilic Syndrome

The idiopathic hypereosinophilic syndrome is a heterogeneous group of disorders characterized by sustained overproduction of eosinophils. The 3 diagnostic criteria for this disorder are (1) AEC >1,500 cells/µL persisting for 6 mo or longer or at least on 2 occasions or with evidence of tissue eosinophilia; (2) absence of another diagnosis to explain the eosinophilia; and (3) signs and symptoms of organ involvement. The clinical signs and symptoms of hypereosinophilic syndrome can be heterogeneous because of the diversity of potential organ (pulmonary, cutaneous, neurologic, serosal, gastrointestinal) involvement. Loeffler endocarditis, one of the most serious and life-threatening complications, can cause heart failure from endomyocardial thrombosis and fibrosis. Eosinophilic leukemia, a clonal myeloproliferative variant, may be distinguished from idiopathic hypereosinophilic syndrome by demonstrating a clonal interstitial deletion on chromosome 4q12 that fuses the platelet-derived growth factor receptor-α (PDGFRA) and FIP1-like-1 (FIP1L1) genes; this disorder is treated with imatinib mesylate, which helps target the fusion oncoprotein (Fig. 129-1).

Therapy is aimed at suppressing eosinophilia and is initiated with corticosteroids. Imatinib mesylate, a tyrosine kinase inhibitor, may be effective in FIP1L1-PDGFRA–negative patients. Hydroxyurea may be beneficial in patients unresponsive to corticosteroids. Specific anti–IL-5 monoclonal antibodies (mepolizumab) target this cytokine, which has a central role in eosinophil differentiation, mobilization and activity. With therapy, the eosinophil count declines and corticosteroid doses may be reduced. For patients with prominent organ involvement who fail to respond to therapy, the mortality is ≈75% after 3 yr.

Miscellaneous Diseases

Eosinophilia is observed in many patients with primary immunodeficiency syndromes, especially hyperimmunoglobulin E syndrome (see Chapters 122 and 126), Wiskott-Aldrich syndrome, and Omenn syndrome. Eosinophilia is also frequently present in the syndrome of thrombocytopenia with absent radii and in familial

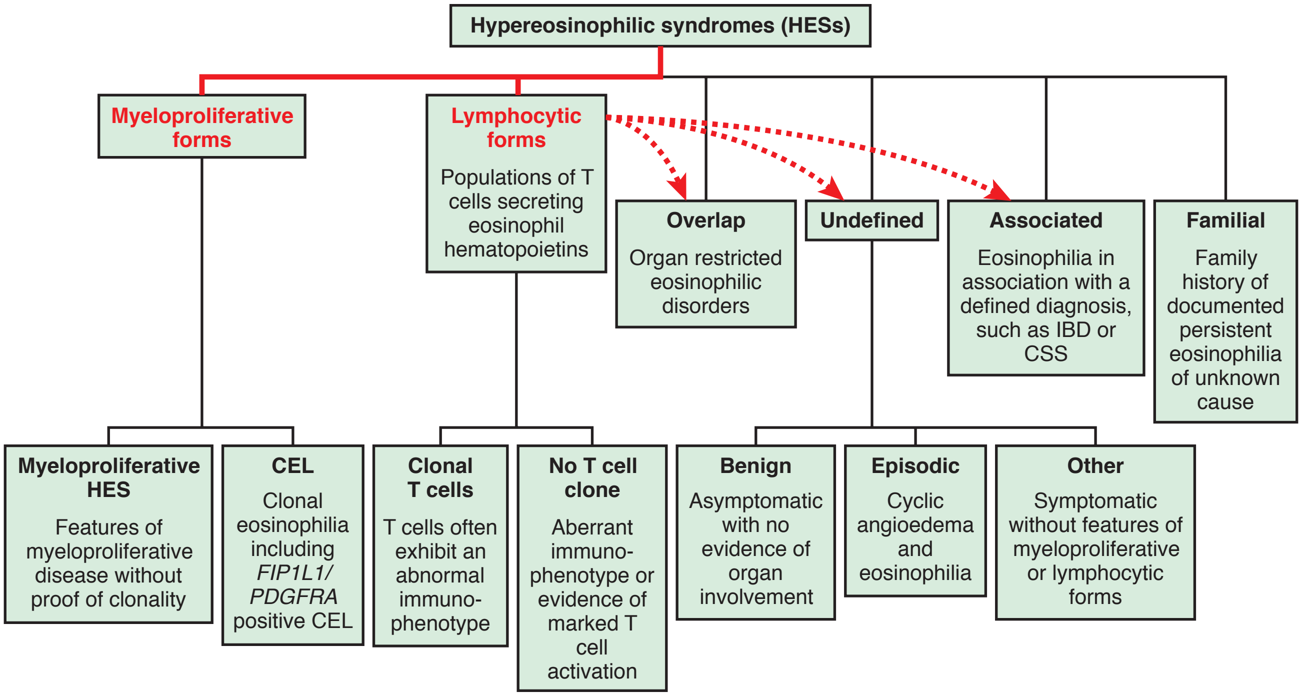

Figure 129-1 **Revised classification of hypereosinophilic syndromes.** Changes from the previous classification are indicated in *red. Dashed arrows* identify hypereosinophilic syndrome (HES) forms for which at least some patients have T-cell–driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin–producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES. *IBD*, Inflammatory bowel disease. *(From Simon HU, Rothenberg ME, Bocher BS, et al: Refining the definition of hypereosinophilic syndrome.* J Allergy Clin Immunol *126:45–49, 2010, Fig. 1, p. 47.)*

reticuloendotheliosis with eosinophilia. Eosinophilia can be found in patients with Hodgkin disease, as well as in acute lymphoid and myeloid leukemia. Other considerations include gastrointestinal disorders such as ulcerative colitis, Crohn disease during symptomatic phases, chronic hepatitis, Churg-Strauss vasculitis, and adrenal insufficiency.

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Chapter 130

Disorders of Phagocyte Function

Thomas D. Coates

Neutrophils are the first-line of defense against microbial invasion. They arrive at the site of inflammation during the critical 2-4 hr after microbial invasion to contain the infection and prevent hematogenous dissemination. This well-orchestrated process is one of the most interesting stories in modern cell biology. In fact, much of our knowledge about neutrophil function derives from studies done in patients with genetic errors in neutrophil function. These critical functions and their associated disorders are depicted in Figure 127-2. Children with phagocytic dysfunction present at a young age with recurrent infections that are often involve unusual organisms and are poorly responsive to treatment.

Primary defects of phagocytic function comprise fewer than 20% of immunodeficiencies and there is significant overlap in the presenting signs and symptoms between phagocytic disorders and lymphocyte and humeral disorders. Children with phagocytic defects present with deep tissue infection, pneumonia, adenitis, or osteomyelitis rather than blood stream infections (Tables 130-1 and 130-2, and Fig. 130-1). A few clinical features point to phagocyte defects rather than other immunodeficiencies, but correct diagnosis relies on highly specialized laboratory tests.

Chemotaxis, the direct migration of cells into sites of infection, involves a complex series of events (see Chapter 127). Disorders of adhesion or granule abnormalities can have intermediate or profound motility defects and the propensity to infections is related to a combination of these functional deficits. However, studies of a Tongan family with recessively inherited neutrophil actin dysfunction tell us that a pure severe chemotactic defect can result in fatal recurrent infection. Defective in vitro chemotaxis of neutrophils can be detected in children having various clinical conditions. However, unless chemotaxis is essentially absent, it is difficult to establish whether frequent infections arise from a primary chemotactic abnormality or occur as secondary medical complications of the underlying disorder. For example, dental infection with *Capnocytophaga* is associated with a clear neutrophil motility defect that resolves when the infection is eliminated.

Motility defects present with significant skin and mucosal infections. They can also have tender cutaneous nodular lesions that characteristically do not contain any neutrophils. In fact, presence of a true abscess makes the diagnosis of a significant chemotactic defect less likely.

Laboratory tests of chemotaxis are biologic assays and have high variability except in the most experienced of hands. The assays must be done on freshly obtained blood and are affected by many factors related to blood sampling itself. It is best to assay other features of the suspected disorder, such as surface marker expression, to establish a specific diagnosis.

LEUKOCYTE ADHESION DEFICIENCY

Leukocyte adhesion deficiency 1 (LAD-1), 2 (LAD-2), and 3 (LAD-3) are rare autosomal recessive disorders of leukocyte function. LAD-1 affects about 1 per 10 million individuals and is characterized by

Table 130-1 Infections and WBC Defects: Features That Can Be Seen in Phagocyte Disorders

SEVERE INFECTIONS		RECURRENT INFECTIONS		SPECIFIC INFECTIONS		UNUSUALLY LOCATED INFECTIONS	
TYPE OF INFECTION	DIAGNOSIS TO CONSIDER	SITE OF INFECTION	DIAGNOSIS TO CONSIDER	MICROORGANISM	DIAGNOSIS TO CONSIDER	SITE OF INFECTION	DIAGNOSIS TO CONSIDER
Cellulitis	Neutropenia, LAD CGD, HIES	Cutaneous	Neutropenia, CGD, LAD, HIES	*Staphylococcus epidermidis*	Neutropenia, LAD	Umbilical cord	LAD
Colitis	Neutropenia, CGD	Gums	LAD, neutrophil motility disorders	*Serratia marcescens, Nocardia, Burkholderia cepacia*	CGD	Liver abscess	CGD
Osteomyelitis	CGD, MSMD pathway defects	Upper and lower respiratory tract	Neutropenia, HIES, functional neutrophil disorders	*Aspergillus*	Neutropenia, CGD, HIES	Gums	LAD, neutrophil motility disorders
		Gastrointestinal tract	CGD, MSMD pathway defects (salmonella)	Nontuberculous mycobacteria, BCG	MSMD pathway defects, SCID, CGD		
		Lymph nodes	CGD, MSMD pathway defects (mycobacteria)	*Candida*	Neutropenia, CGD, MPO		
		Osteomyelitis	CGD, MSMD				

BCG, bacille Calmette-Guérin; CGD, chronic granulomatous disease; HIES, hyperimmunoglobulin E syndrome; LAD, leukocyte adhesion deficiency; MSMD, Mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency.

From Leung DYM: Pediatric allergy principles and practice, *ed 2, Philadelphia, 2010, WB Saunders, Table 12-1, p. 134.*

Table 130-2 Clinical Disorders of Neutrophil Function

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
DEGRANULATION ABNORMALITIES			
Chédiak-Higashi syndrome	Autosomal recessive; disordered coalescence of lysosomal granules; responsible gene is *CHSI/LYST*, which encodes a protein hypothesized to regulate granule fusion	Decreased neutrophil chemotaxis, degranulation, and bactericidal activity; platelet storage pool defect; impaired NK function, failure to disperse melanosomes	Neutropenia; recurrent pyogenic infections, propensity to develop marked hepatosplenomegaly as a manifestation of the hemophagocytic syndrome
Specific granule deficiency	Autosomal recessive; functional loss of myeloid transcription factor arising from a mutation or arising from reduced expression of *Gfi-1* or *C/EBPε*, which regulates specific granule formation	Impaired chemotaxis and bactericidal activity; bilobed nuclei in neutrophils; defensins, gelatinase, collagenase, vitamin B_{12}–binding protein, and lactoferrin	Recurrent deep-seated abscesses
ADHESION ABNORMALITIES			
Leukocyte adhesion deficiency 1	Autosomal recessive; absence of CD11/CD18 surface adhesive glycoproteins (β_2 integrins) on leukocyte membranes most commonly arising from failure to express CD18 messenger RNA	Decreased binding of C3bi to neutrophils and impaired adhesion to ICAM1 and ICAM2	Neutrophilia; recurrent bacterial infection associated with a lack of pus formation
Leukocyte adhesion deficiency 2	Autosomal recessive; loss of fucosylation of ligands for selectins and other glycol-conjugates arising from mutations of the GDP-fucose transporter	Decreased adhesion to activated endothelium expressing ELAM	Neutrophilia; recurrent bacterial infection without pus
Leukocyte adhesion deficiency 3 (LAD-1 variant syndrome)	Autosomal recessive; impaired integrin function arising from mutations of *FERMT3* which encodes kindlin-3 in hematopoietic cells; kindlin-3 binds to β-integrin and thereby transmits integrin activation	Impaired neutrophil adhesion and platelet activation	Neutrophilia; recurrent infections, bleeding tendency

Continued

Table 130-2 Clinical Disorders of Neutrophil Function—cont'd

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
DISORDERS OF CELL MOTILITY			
Enhanced motile responses; FMF	Autosomal recessive gene responsible for FMF on chromosome 16 which encodes for a protein called pyrin; pyrin regulates caspase-1 and thereby IL-1β secretion; mutated pyrin may lead to heightened sensitivity to endotoxin, excessive IL-1β production, and impaired monocyte apoptosis	Excessive accumulation of neutrophils at inflamed sites, which may be the result of excessive IL-1β production	Recurrent fever, peritonitis, pleuritis, arthritis, and amyloidosis
DEPRESSED MOTILE RESPONSES			
Defects in the generation of chemotactic signals	IgG deficiencies; C3 and properdin deficiency can arise from genetic or acquired abnormalities; mannose-binding protein deficiency predominantly in neonates	Deficiency of serum chemotaxis and opsonic activities	Recurrent pyogenic infections
Intrinsic defects of the neutrophil, e.g., LAD, Chédiak-Higashi syndrome, specific granule deficiency, neutrophil actin dysfunction, neonatal neutrophils	In the neonatal neutrophil there is diminished ability to express β_2 integrins, and there is a qualitative impairment in β_2-integrin function	Diminished chemotaxis	Propensity to develop pyogenic infections
Direct inhibition of neutrophil mobility, e.g., drugs	Ethanol, glucocorticoids, cyclic AMP	Impaired locomotion and ingestion; impaired adherence	Possible cause for frequent infections; neutrophilia seen with epinephrine arises from cyclic AMP release from endothelium
Immune complexes	Bind to Fc receptors on neutrophils in patients with rheumatoid arthritis, systemic lupus erythematosus, and other inflammatory states	Impaired chemotaxis	Recurrent pyogenic infections
Hyper-IgE syndrome	Autosomal dominant; responsible gene is *Stat3*	Impaired chemotaxis at times; impaired regulation of cytokine production	Recurrent skin and sinopulmonary infections, eczema, mucocutaneous candidiasis, eosinophilia, retained primary teeth, minimal trauma fractures, scoliosis, and characteristic facies
Hyper-IgE syndrome–AR	Autosomal recessive; more than 1 gene likely contributes to its etiology	High IgE levels, impaired lymphocyte activation to staphylococcal antigens	Recurrent pneumonia without pneumatoceles sepsis, enzyme, boils, mucocutaneous candidiasis, neurologic symptoms, eosinophilia
MICROBICIDAL ACTIVITY			
Chronic granulomatous disease	X-linked and autosomal recessive; failure to express functional gp91^{phox} in the phagocyte membrane in p22^{phox} (AR). Other AR forms of CGD arise from failure to express protein p47^{phox} or p67^{phox}	Failure to activate neutrophil respiratory burst leading to failure to kill catalase-positive microbes	Recurrent pyogenic infections with catalase-positive microorganisms
G6PD deficiency	Less than 5% of normal activity of G6PD	Failure to activate NADPH-dependent oxidase, and hemolytic anemia	Infections with catalase-positive microorganisms
Myeloperoxidase deficiency	Autosomal recessive; failure to process modified precursor protein arising from missense mutation	H_2O_2-dependent antimicrobial activity not potentiated by myeloperoxidase	None
Rac2 deficiency	Autosomal dominant; dominant negative inhibition by mutant protein of Rac2-mediated functions	Failure of membrane receptor–mediated O_2^- generation and chemotaxis	Neutrophilia, recurrent bacterial infections
Deficiencies of glutathione reductase and glutathione synthetase	AR; failure to detoxify H_2O_2	Excessive formation of H_2O_2	Minimal problems with recurrent pyogenic infections

AMP, adenosine monophosphate; AR, autosomal recessive; C, complement; CD, cluster of differentiation; CGD, chronic granulomatous disease; ELAM, endothelial-leukocyte adhesion molecule; FMF, familial Mediterranean fever; G6PD, glucose-6-phosphate dehydrogenase; GDP, guanosine diphosphate; ICAM, intracellular adhesion molecule; Ig, immunoglobulin; IL-1, interleukin-1; LAD, leukocyte adhesion deficiency; NADPH, nicotinamide adenine dinucleotide phosphate; NK, natural killer.

Modified from Curnutte JT, Boxer LA: Clinically significant phagocytic cell defects. In Remington JS, Swartz MN, editors: Current clinical topics in infectious disease, *ed 6, New York, 1985, McGraw-Hill, p 144.*

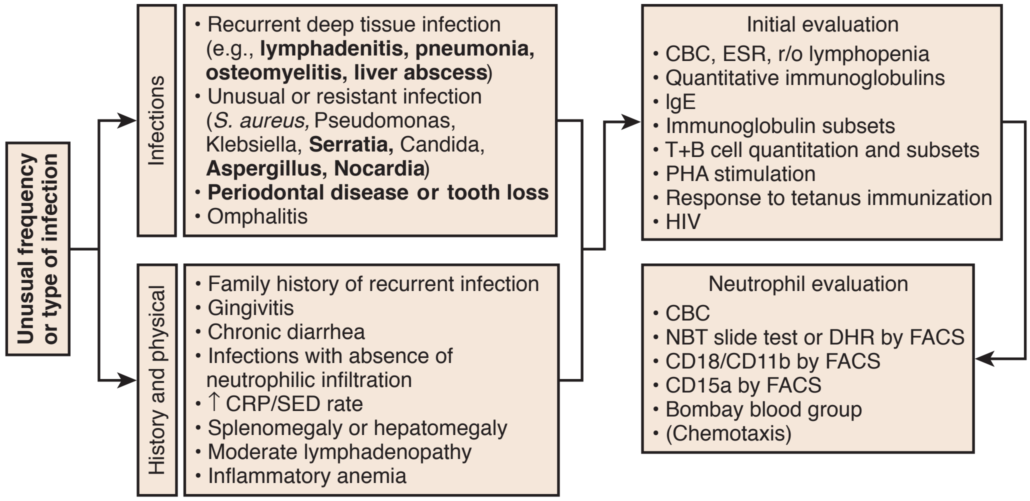

Figure 130-1 **Algorithm for clinical evaluation of patients with recurrent infections.** Shown are the evaluations that can be done in a routine clinical laboratory. The CBC can detect marked leukocytosis in LAD and giant granules of Chédiak-Higashi may be seen on the smear. Chemotaxis and all other neutrophil functions assays require highly specialized research laboratories. *CBC*, complete blood count; *CD*, cluster of differentiation; *CRP*, C-reactive protein; *DHR*, dihydrorhodamine; *ESR*, erythrocyte sedimentation rate; *HIV*, human immunodeficiency virus; *Ig*, immunoglobulin; *NBT*, nitro blue tetrazolium. *(Modified from Dinauer, MC, Coates TD, Disorders of neutrophil function. In Hoffman R, Benz EJ, Silberstein LE, Helsop H, Weitz J, Anastasi J, editors:* Hematology: basic principles and practice, *ed 6, Philadelphia, 2012, WB Saunders, pp. 655–674.)*

Table 130-3 Leukocyte Adhesion Deficiency Syndromes

LEUKOCYTE ADHESION DEFICIENCY (LAD)	TYPE 1 (LAD1)	TYPE 2 (LAD2 OR CDG-IIC)	TYPE 3 (LAD3)	E-SELECTIN DEFICIENCY	RAC2 DEFICIENCY
OMIM	116920	266265	612840	131210	602049
Inheritance pattern	Autosomal recessive	Autosomal recessive	Autosomal recessive	Unknown	Autosomal dominant
Affected protein(s)	Integrin β_2 common chain (CD18)	Fucosylated proteins (e.g., sialyl-Lewis^x, CD15s)	Kindlin 3	Endothelial E-selectin expression	Rac2
Neutrophil function affected	Chemotaxis, tight adherence	Rolling, tethering	Chemotaxis, adhesion, superoxide production	Rolling, tethering	Chemotaxis, superoxide production
Delayed umbilical cord separation	Yes (severe phenotype only)	Yes	Yes	Yes	Yes
Leukocytosis/ neutrophilia	Yes	Yes	Yes	No (mild neutropenia)	Yes

OMIM, Online Mendelian Inheritance in Man.
From Leung DYM: Pediatric allergy principles and practice, *ed 2, Philadelphia, 2010, WB Saunders, Table 12-4, p. 139.*

recurrent bacterial and fungal infections and depressed inflammatory responses despite striking blood neutrophilia (Table 130-3). The neutrophils have significant defects in adhesion, motility, and ability to phagocytose bacteria.

Genetics and Pathogenesis

LAD-1 results from mutations of the gene on chromosome 21q22.3 encoding CD18, the 95-kDa β_2-leukocyte transmembrane integrin subunit. Normal neutrophils express 4 heterodimeric adhesion molecules: LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18, also known as CR3 or iC3b receptor), p150,95 (CD11c/CD18), and α_1 β_2 (CD11d/CD18). These 4 transmembrane adhesion molecules are composed of unique extracellular α_1 encoded on chromosome 16, and share a common β_2 subunit (CD18) that links them to the membrane and connects them to intracellular signal transduction machinery. This group of leukocyte integrins is responsible for the tight adhesion of neutrophils to the endothelial cell surface, egress from the circulation, and adhesion to iC3b-coated microorganisms, which promotes phagocytosis and particulate activation of the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Some mutations of CD11/CD18 allow a low level of assembly and activity of integrin molecules, resulting in retention of some neutrophil integrin adhesion function and a moderate phenotype.

Because of their inability to adhere firmly to intercellular adhesion molecules 1 (ICAM-1) and 2 (ICAM-2) expressed on inflamed endothelial cells (see Chapter 127), neutrophils cannot transmigrate through the vessel wall and move to the site infection. Furthermore, neutrophils that do arrive at inflammatory sites fail to recognize microorganisms opsonized with complement fragment iC3b, an important stable opsonin formed by the cleavage of C3b. Hence, other neutrophil functions such as degranulation and oxidative metabolism normally triggered by iC3b binding are also markedly compromised in LAD-1 neutrophils, resulting in impaired phagocytic function and high risk for serious and recurrent bacterial infections.

Monocyte function is also impaired, with poor fibrinogen-binding function, an activity that is promoted by the CD11/CD18 complex. Consequently, such cells are unable to participate effectively in wound healing.

Children with **LAD-2** share the clinical features of LAD-1 but have normal CD11/CD18 integrins. Features unique to LAD-2 include neurologic defects, cranial facial dysmorphism, and absence of the erythrocyte ABO blood group antigen (Bombay phenotype). LAD-2 (also known as congenital disorder of glycosylation IIc) derives from mutations in the gene encoding a specific GDP-L-fucose transporter of the Golgi apparatus. This abnormality prevents the incorporation of fucose into various cell surface glycoproteins, including the carbohydrate structure sialyl Lewis X that is critical for low-affinity rolling adhesion of neutrophils to vascular endothelium. This is an important initial step necessary for subsequent integrin-mediated activation, spreading, and transendothelial migration. Infections in LAD-2 are milder than that in LAD-1.

LAD-3 is characterized by a Glanzmann thrombasthenia-like bleeding disorder, delayed separation of the umbilical cord, and serious skin and soft-tissue infections similar to that seen in LAD-1, and failure of leukocytes to undergo β_2- and β_1-integrin–mediated adhesion and migration. Mutations in *KINDLIN3* affect integrin activation.

Clinical Manifestations

Patients with the severe clinical form of LAD-1 express <0.3% of the normal amount of the β_2-integrin molecules, whereas patients with the moderate phenotype may express 2-7% of the normal amount. Children with severe forms of LAD present in infancy with recurrent, indolent bacterial infections of the skin, mouth, respiratory tract, lower intestinal tract, and genital mucosa. Significant neutrophilic leukocytosis, often >25,0000/mm^3, is a prominent feature. They may have a history of delayed separation of the umbilical cord, usually with associated infection of the cord stump. The presence of significant omphalitis is an important feature that distinguishes these rare patients from the 10% of healthy infants can have cord separation at age 3 wk or later. Skin infection may progress to large chronic ulcers with polymicrobial infection, including anaerobic organisms (Fig. 130-2). The ulcers heal slowly, need months of antibiotic treatment, and often require plastic surgery grafting. Severe gingivitis can lead to early loss of primary and secondary teeth (Fig. 130-3). Infected areas characteristically have very little neutrophilic infiltration.

The pathogens infecting patients with LAD-1 are similar to those affecting patients with severe neutropenia (see Chapter 131) and include *Staphylococcus aureus* and enteric Gram-negative organisms such as *Escherichia coli.* These patients are also susceptible to opportunistic infection by fungi such as *Candida* and *Aspergillus.* Typical signs of inflammation, such as swelling, erythema, and warmth, may be absent. Pus does not form, and few neutrophils are identified microscopically in biopsy specimens of infected tissues. Despite the paucity of neutrophils within the affected tissue, the circulating neutrophil count during infection typically exceeds 30,000/µL and can surpass 100,000/µL. During intervals between infections, the peripheral blood neutrophil count may chronically exceed 12,000/µL. LAD-1 genotypes with only moderate, rather than absent, amounts of functional integrins at the surface of the neutrophil, significantly have reduced severity and frequency of infections compared to children with the severe form, although gingival disease is still a prominent feature.

Laboratory Findings

The diagnosis of LAD-1 is established most readily by **flow cytometric** measurements of surface CD11b/CD18 in stimulated and unstimulated neutrophils. Neutrophil and monocyte adherence, aggregation, chemotaxis, and iC3b-mediated phagocytosis demonstrate striking abnormalities. However, these assays are not clinically available. Delayed-type hypersensitivity reactions are normal, and most individuals have normal specific antibody synthesis. However, some patients have impaired T-lymphocyte–dependent antibody responses. The diagnosis of LAD-2 is established by flow cytometric measurement of sialyl Lewis X (CD15) on neutrophils. It is important to note that the flow cytometric assays are not done the same as the more common lymphocyte subset analysis and require specialized approaches to detect levels of surface expression, especially to detect milder phenotypes.

Treatment

Treatment of LAD-1 depends on the phenotype as determined by the level of expression of functional CD11/CD18 integrins. Early **allogeneic hematopoietic stem cell transplantation (HSCT)** is the treatment of choice for severe LAD-1 (and LAD-3). Other treatment is largely supportive. Patients can be maintained on prophylactic trimethoprim-sulfamethoxazole and should have close surveillance for early identification of infections and initiation of empirical treatment with broad-spectrum antibiotics. Specific determination of the etiologic agent by culture or biopsy is important because of the prolonged antibiotic treatment required in the absence of neutrophil function.

Some LAD-2 patients have responded to fucose supplementation, which induced a rapid reduction in the circulating leukocyte count and appearance of the sialyl Lewis X molecules accompanied by marked improvement in leukocyte adhesion.

Prognosis

The severity of infectious complications correlates with the degree of β_2-integrin deficiency. Patients with severe deficiency may die in infancy, and those surviving infancy have a susceptibility to severe life-threatening systemic infections. Patients with moderate deficiency have infrequent life-threatening infections and relatively long survival.

Figure 130-2 Skin infection of a patient with leukocyte adhesion deficiency type 1. Failure to form pus, inability to demarcate the fibrotic skin debris, and limited inflammation. Enterococcus gallinarium was cultured from the wound. *(From Rich RR:* Clinical immunology principles and practices, *ed 4, Philadelphia, 2013, WB Saunders, Fig. 21-3, p. 273).*

Figure 130-3 Oral pathology in a patient with leukocyte adhesion deficiency type 1. Gingivitis and severe periodontitis are hallmarks of LAD 1. *(From Rich RR:* Clinical immunology principles and practices, *ed 4, Philadelphia, 2013, WB Saunders, Fig. 21-2, p. 273.)*

CHÉDIAK-HIGASHI SYNDROME

Chédiak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by increased susceptibility to infection caused by defective degranulation of neutrophils, a mild bleeding diathesis, partial oculocutaneous albinism, progressive peripheral neuropathy, and a tendency to develop a life-threatening form of hemophagocytic lymphohistiocytosis (see Chapter 507). CHS is caused by a fundamental defect in granule morphogenesis that results in abnormally large granules in multiple tissues. Pigmentary dilution involving the hair, skin, and ocular fundi results from pathologic aggregation of melanosomes. Neurologic deficits are associated with a failure of decussation of the optic and auditory nerves. Patients exhibit an increased susceptibility to infection that can be explained only in part by defects in neutrophil function. The patients have progressive neutropenia as well abnormalities in natural killer (NK) function, again related to granule dysfunction.

Genetics and Pathogenesis

LYST (for lysosomal traffic regulator), the gene mutated in CHS, is located at chromosome 1q2-q44. The LYST/CHS protein is thought to regulate vesicle transport by mediating protein–protein interaction and protein–membrane associations. Loss of function may lead to indiscriminate interactions with lysosomal surface proteins, yielding giant granules through uncontrolled fusion of lysosomes with each other.

Almost all cells of patients with CHS show some oversized and dysmorphic lysosomes, storage granules, or related vesicular structures. Melanosomes are oversized, and delivery to the keratinocytes and hair follicles is compromised, resulting in hair shafts devoid of pigment granules. This abnormality in melanosomes leads to the macroscopic impression of hair and skin that is lighter than expected from parental coloration. The same abnormality in melanocytes leads to the partial ocular albinism associated with light sensitivity.

Beginning early in neutrophil development, spontaneous fusion of giant primary granules with each other or with cytoplasmic membrane components results in huge secondary lysosomes with reduced contents of hydrolytic enzymes, including proteinases, elastase, and cathepsin G. This deficiency of proteolytic enzymes may be responsible for the impaired killing of microorganisms by CHS neutrophils.

Clinical Manifestations

Patients with CHS have light skin and silvery hair and frequently complain of solar sensitivity and photophobia that is associated with rotary nystagmus. Other signs and symptoms vary considerably, but frequent infections and neuropathy are common. The infections involve mucous membranes, skin, and respiratory tract. Affected children are susceptible to Gram-positive bacteria, Gram-negative bacteria, and fungi, with *S. aureus* being the most common offending organism. The **neuropathy** may be sensory or motor in type, and ataxia may be a prominent feature. Neuropathy often begins in the teenage years and becomes the most prominent problem.

Patients with CHS have prolonged bleeding times with normal platelet counts, resulting from impaired platelet aggregation associated with a deficiency of the dense granules containing adenosine diphosphate and serotonin.

The most life-threatening complication of CHS is the development of an accelerated phase characterized by pancytopenia, high fever, and lymphohistiocytic infiltration of liver, spleen, and lymph nodes. The onset of the accelerated phase, which can occur at any age, is now recognized to be a genetic form of **hemophagocytic lymphohistiocytosis.** This occurs in 85% of patients and usually results in death.

Laboratory Findings

The diagnosis of CHS is established by finding large inclusions in all nucleated blood cells. These can be seen on Wright-stained blood films and are accentuated by a peroxidase stain. Because of impaired egress from the bone marrow, cells containing the large inclusions may be missed on peripheral blood smear but readily identified on bone marrow examination. The patients have progressive neutropenia and abnormal platelet, neutrophil, and NK function.

Treatment

High-dose ascorbic acid (200 mg/day for infants, 2,000 mg/day for adults) may improve the clinical status of some children in the stable phase. Although controversy surrounds the efficacy of ascorbic acid, given the safety of the vitamin, it is reasonable to administer ascorbic acid to all patients.

The only curative therapy to prevent the accelerated phase is **HSCT.** Normal stem cells reconstitute hematopoietic and immunologic function, correct the NK cell deficiency, and prevent conversion to the accelerated phase, but cannot correct or prevent the neuropathy. If the patient is in the accelerated phase with active hemophagocytic lymphohistiocytosis, HSCT often fails to prevent death.

MYELOPEROXIDASE DEFICIENCY

Myeloperoxidase (MPO) deficiency is an autosomal recessive disorder of oxidative metabolism and is one of the most common inherited disorders of phagocytes, occurring at a frequency approaching 1 per 2,000 individuals. MPO is a green heme protein located in the azurophilic lysosomes of neutrophils and monocytes and is the basis for the greenish tinge to pus accumulated at a site of infection.

Clinical Manifestations

MPO deficiency is usually clinically silent. Rarely, patients may have disseminated candidiasis, usually in conjunction with diabetes mellitus. Acquired partial MPO deficiency can develop in acute myelogenous leukemia and in myelodysplastic syndromes.

Laboratory Findings

Deficiency of neutrophil and monocyte MPO can be identified by histochemical analysis. Severe MPO deficiency can cause the dihydrorhodamine (DHR) flow cytometric assay for chronic granulomatous disease to be falsely positive. Unlike chronic granulomatous disease (CGD), eosinophils in severe MPO deficiency will still reduce DHR and yield a normal reaction.

Treatment

There is no specific therapy. Aggressive treatment with antifungal agents should be provided for candidal infections. The prognosis is usually excellent.

CHRONIC GRANULOMATOUS DISEASE

CGD is characterized by neutrophils and monocytes capable of normal chemotaxis, ingestion, and degranulation, but unable to kill **catalase-positive microorganisms** because of a defect in the generation of microbicidal oxygen metabolites. CGD is a rare disease with an incidence of 4-5 per 1 million individuals; it is caused by 4 genes, 1 X-linked and 3 autosomal recessive in inheritance.

Genetics and Pathogenesis

Activation of the phagocyte NADPH oxidase requires stimulation of the neutrophils and involves assembly from cytoplasmic and integral membrane subunits (see Fig. 127-3). Oxidase activation initiates with phosphorylation of a cationic cytoplasmic protein, p47^{phox} (47-kDa phagocyte oxidase protein). Phosphorylated p47^{phox}, together with 2 other cytoplasmic components of the oxidase, p67^{phox} and the low-molecular-weight guanosine triphosphatase Rac2, translocates to the membrane where they combine with the cytoplasmic domains of the transmembrane flavocytochrome b_{558} to form the active oxidase complex (see Fig. 127-3). The flavocytochrome is a heterodimer composed of p22^{phox} and highly glycosylated gp91^{phox}. The gp91^{phox} glycoprotein catalyzes electron transport through its NADPH-binding, flavin-binding, and heme-binding domains.. Defects in any of these NADPH oxidase components can lead to CGD.

Approximately 65% of patients with CGD are males who inherit their disorder as a result of mutations in *CYBB*, an X-chromosome gene encoding gp91^{phox}. Approximately 35% of patients inherit CGD in an autosomal recessive fashion resulting from mutations in the *NCF1* gene on chromosome 7, encoding p47^{phox}. Defects in the genes

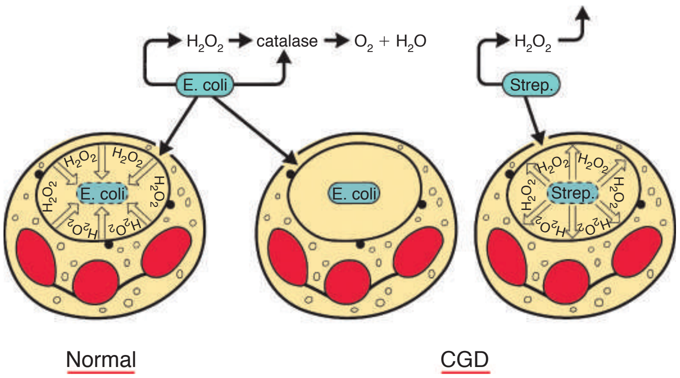

Figure 130-4 The pathogenesis of chronic granulomatous disease (CGD). The manner in which the metabolic deficiency of the CGD neutrophil predisposes the host to infection is shown schematically. Normal neutrophils stimulate hydrogen peroxide in the phagosome containing ingested *Escherichia coli*. Myeloperoxidase is delivered to the phagosome by degranulation, as indicated by the *closed circles*. In this setting, hydrogen peroxide acts as a substrate for myeloperoxidase to oxidize halide to hypochlorous acid and chloramines that kill the microbes. The quantity of hydrogen peroxide produced by the normal neutrophil is sufficient to exceed the capacity of catalase, a hydrogen peroxide-catabolizing enzyme of many aerobic microorganisms, including *Staphylococcus aureus*, most Gram-negative enteric bacteria, *Candida albicans*, and *Aspergillus*. When organisms such as *E. coli* gain entry into CGD neutrophils, they are not exposed to hydrogen peroxide because the neutrophils do not produce it, and the hydrogen peroxide generated by microorganisms themselves is destroyed by their own catalase. When CGD neutrophils ingest streptococci, which lack catalase, the organisms generate enough hydrogen peroxide to result in a microbicidal effect. As indicated *(middle)*, catalase-positive microbes such as *E. coli* can survive within the phagosome of the CGD neutrophil. *(Modified from Boxer LA: Quantitative abnormalities of granulocytes. In Beutler E, Lichtman MA, Coller BS, et al, editors:* Williams hematology, *ed 6, New York, 2001, McGraw-Hill, p. 845.)*

encoding p67*phox* (*NCF2* on chromosome 1) and p22*phox* (*CYBA* on chromosome 16) are inherited in an autosomal recessive manner and account for approximately 5% of cases of CGD.

The CGD phagocytic vacuoles lack microbicidal reactive oxygen species and remain acidic, so bacteria are not killed or digested properly (Fig. 130-4). Hematoxylin-and-eosin–stained sections from patients' tissues show multiple granulomas that give CGD its descriptive name.

Clinical Manifestations

Although the clinical presentation is variable, several features suggest the diagnosis of CGD. Any patient with recurrent pneumonia, lymphadenitis, hepatic or subcutaneous or other abscesses, osteomyelitis at multiple sites, a family history of recurrent infections, or any infection with an unusual catalase-positive organism requires evaluation. Other clinical features include chronic colitis or enteritis, gastric outlet or ureteral obstruction from granulomas, or blood stream infection caused by *Salmonella*, *Burkholderia cepacia*, or *Candida*.

The onset of clinical signs and symptoms usually occurs in early infancy, though a few patients with very rare subtypes have presented later in life. The attack rate and severity of infections are exceedingly variable thought the infection incidence does decrease in the second decade coincident with maturation of the lymphocyte and humoral immunity. The most common pathogen is *S. aureus*, although any catalase-positive microorganism may be involved. Other organisms frequently causing infections include *Serratia marcescens, B. cepacia, Aspergillus, Candida albicans, Nocardia,* and *Salmonella.* There may also be increased susceptibility to mycobacterium, including the bacillus Calmette-Guérin vaccine. Pneumonia, lymphadenitis, osteomyelitis, and skin infections are the most common illnesses encountered. Bacteremia or fungemia occurs but is much less common than focal infections and usually only occurs when local infections have been inappropriately treated for long periods of time. Patients may suffer from the sequelae of chronic infection, including anemia of chronic disease, poor growth, lymphadenopathy, hepatosplenomegaly, chronic purulent dermatitis, restrictive lung disease, gingivitis, hydronephrosis, esophageal dysmotility, and pyloric outlet narrowing. Perirectal abscesses and recurrent skin infections, including folliculitis, cutaneous granulomas, and discoid lupus erythematosus also suggest the possibility of CGD. **Granuloma formation** and inflammatory processes are a hallmark of CGD and may be the presenting symptoms that prompt testing for CGD if they cause pyloric outlet obstruction, bladder outlet or ureter obstruction, or rectal fistulas and granulomatous colitis simulating Crohn disease. More than 80% of CGD patients have positive serology for Crohn disease. Persistent fever especially with splenomegaly and cytopenia warrants an evaluation for secondary macrophage activation syndrome. This has been seen in CGD and may require treatment with steroids and discontinuation of interferon-γ treatment.

Laboratory Findings

The diagnosis is most often made by performing **flow cytometry** using dihydrorhodamine 123 (DHR) to measure oxidant production through its increased fluorescence when oxidized by H_2O_2. The nitroblue tetrazolium dye test is frequently cited in the literature but is now only rarely used clinically. The X-linked carrier state is usually easily diagnosed in the mother by DHR fluorescence by presence of a bimodal response to stimulation. It is important to test the mother as some extremely Lyonized carriers with $<5\%$ positive cells may have chronic clinical problems as well. Ideally, at least the first patient in a kindred should have DNA analysis to facilitate prenatal diagnosis and for genetic counseling purposes.

A few individuals have been described with apparent CGD caused by severe glucose-6-phosphate dehydrogenase deficiency, leading to insufficient NADPH substrate for the phagocyte oxidase. The erythrocytes of these patients also lack the enzyme, leading to chronic hemolysis.

Treatment

HSCT is the only known **cure** for CGD, although gene therapy has been transiently successful in a few patients and is the topic of active research. We strongly recommend HSCT transplant for all patients with CGD if a suitable sibling or unrelated donor can be identified. The long-term outcome for survival late into adulthood is not good even in the hands of experienced CGD clinicians.

Patients with CGD should be given daily oral trimethoprim-sulfamethoxazole as it reduces the number of bacterial infection. A placebo-controlled study found that **interferon-γ** 50 μg/m^2 3 times/wk significantly reduces the number of hospitalizations and serious infections, although the mechanism of action is unclear. **Itraconazole** (200 mg/day for patients weighing >50 kg and 100 mg/day for patients weighing <50 kg and 5 yr of age or younger) administered prophylactically reduces the frequency of fungal infections.

Management of infection is dramatically different than in normal children. CGD patients are always at risk for deep-seated, indolent bacterial infections that can become widespread if not treated properly. They also develop the same kinds of infections that occur in normal children so determination of the appropriate treatment can be difficult. The erythrocyte sedimentation rate (ESR) can be quite helpful. If the child does not have a deep-seated infection, the ESR will be normal or will normalize within several days with standard management. However, if it does not, a search for deep tissues is warranted, as is consideration of empiric antibiotics. Cultures should be obtained, but are usually negative. Because all neutrophil functions in CGD except killing are normal, there is often an exuberant inflammatory reaction to a very small number of organisms. Thus, blood cultures and direct cultures of biopsy samples are usually negative unless there are a lot of organisms. Most abscesses require surgical drainage for therapeutic

and diagnostic purposes. Prolonged use of antibiotics is required even for common bacterial infections. A simple pneumonia may require 6-8 wk of parenteral antibiotics. Infections should be treated for at least 1 wk past normalization of the sedimentation rate to prevent recurrence. Severe pneumonias can be cleared completely but may require many months of parenteral antibiotics. Especially because cultures are often not helpful, we support an "antibiotic sensitivity by sedimentation rate response" approach to treatment. The ESR rates are often in the 40-80 mm/hr or more range with severe infection and will drop monotonically over a week or so after starting antibacterial drugs. It is important to check the ESR daily or every other day as there is moderate variability in this test and changes in treatment need to be based on trends rather than individual values. If there is a clear downward trend over 3-6 days, we continue with antibacterials alone. If this is not the case, parenteral voriconazole should be added to cover *Aspergillus*. Failure of the ESR to come down suggests another antimicrobial approach needs to be tried. Because of the rarity of this disorder, it is critical to seek counsel from someone with significant direct experience with management of several CGD patients. Granulocyte transfusions have been used but it is not clear that they are very helpful. The ESR should be regularly monitored in well patients and whenever they appear ill. A high ESR itself is usually not enough to trigger treatment. However, in the presence of symptoms, one should search for sources at least by contrast CT of the sinus, chest, and abdomen. If the patient is unstable or has very high fevers, *B. cepacia* should be considered and empirically covered. This organism can cause septic shock quickly, unlike the usual smoldering infections seen in CGD. We treat with antibiotics until the ESR is normal and radiographic evidence of infection has been cleared, if possible. The overall incidence of infection decreases in the second decade of life as nonneutrophil immunity matures, but increased risk of infection is lifelong.

Corticosteroids may be useful for the treatment of children with antral and urethral obstruction or severe granulomatous colitis. They can also be helpful in pneumonia to shrink granulomas in the lung and promote drainage. We favor short (4-6 days) pulses of 1-2 mg/kg prednisone with rapid taper to avoid long-term side effects and risk of fungus. Pulses can be repeated if clinical effect has not been achieved.

Genetic Counseling

Identifying a patient's specific genetic subgroup by DNA analysis is useful primarily for genetic counseling and prenatal diagnosis. In X-linked CGD, all possibly affected females should be tested by DHR to exclude carrier state. Counseling is best done by a physician who has direct knowledge of the clinical manifestations of CGD.

Prognosis

The overall mortality rate for CGD is about 2 patient deaths/yr per 100 cases, with the highest mortality among young children. The development of effective infection prophylactic regimens, close surveillance for signs of infections, and aggressive surgical and medical interventions has improved the prognosis.

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Chapter 131
Leukopenia

Kelly J. Walkovich and Peter E. Newburger

Leukopenia refers to an abnormally low number of white blood cells (WBCs) in the circulating blood secondary to a paucity of lymphocytes, granulocytes or both. Because there are marked developmental changes in normal values for WBC counts during childhood (see Chapter 727), normal ranges must be considered in the context of age. For newborns, the mean WBC count at birth is high, followed by a rapid fall beginning at 12 hr through the 1st wk of life. Thereafter, values are stable until 1 yr of age, after which a slow steady decline in the WBC count continues throughout childhood until adult values are reached during adolescence. Evaluation of patients with leukopenia begins with a thorough history, physical examination, and at least 1 confirmatory complete blood count with differential. Further evaluation then depends upon whether the leukopenia represents a decreased number of neutrophils, lymphocytes, or both cell populations (Table 131-1). Treatment depends upon the etiology and clinical manifestations of the leukopenia.

NEUTROPENIA

Neutropenia is defined as a decrease in the absolute number of circulating segmented neutrophils and bands in the peripheral blood. The **absolute neutrophil count (ANC)** is determined by multiplying the total WBC count by the percentage of segmented neutrophils plus bands. Normal neutrophil counts must be stratified for age and race. Neutrophils predominate at birth but rapidly decrease in the 1st few days of life. During infancy, neutrophils constitute 20-30% of circulating leukocyte populations. Near equal numbers of neutrophils and lymphocytes are found in the peripheral circulation at 5 yr of age, and the characteristic 70% predominance of neutrophils that occurs in adulthood is usually attained during puberty. For white children older than 12 mo of age, the lower limit of normal for the ANC is 1,500/µL; for black children older than 12 mo of age the lower limit of normal is 1,200/µL. The relatively lower limit of normal in blacks likely reflects the prevalence of the Duffy negative (Fy–/–) blood group, which is selectively enriched in populations in the malarial belt of Africa and is associated with ANCs 200-600/µL less than those who are Duffy positive.

Neutropenia may be characterized as **mild neutropenia,** with an ANC of 1,000-1,500/µL; **moderate neutropenia,** with an ANC of 500-1,000/µL; or **severe neutropenia,** with an ANC <500/µL. ANC <200 is also termed *agranulocytosis*. This stratification aids in predicting the risk of pyogenic infection in patients who have neutropenia as a resulting from disorders of bone marrow production as only patients with severe neutropenia have a significantly increased susceptibility to life-threatening infections. Neutropenia associated with monocytopenia, lymphocytopenia, or hypogammaglobulinemia increases the risk for infection compared to isolated neutropenia. *Patients with neutropenia caused by increased destruction (e.g., autoimmune) may tolerate very low ANCs without increased frequency of infection.*

Acute neutropenia evolves over a few days and is often a result of rapid neutrophil use and/or compromised neutrophil production. **Chronic neutropenia** by definition lasts longer than 3 mo and arises from reduced production, increased destruction or excessive splenic sequestration of neutrophils. The etiology of neutropenia can be classified as either an acquired disorder or extrinsic insult (Table 131-2), or, more rarely, an inherited, intrinsic defect (Table 131-3).

Clinical Manifestations of Neutropenia

Individuals with neutrophil counts <500/µL are at substantial risk for developing infections, primarily from their endogenous flora as well as from nosocomial organisms. However, some patients with isolated chronic neutropenia may not experience many serious infections, probably because the remainder of the immune system remains intact or because neutrophil delivery to tissues is preserved, as in autoimmune neutropenias. In contrast, children whose neutropenia is secondary to acquired disorders of production such as with cytotoxic therapy, immunosuppressive drugs, or radiation therapy are likely to develop serious bacterial infections because many arms of the immune system are markedly compromised. Neutropenia associated with additional monocytopenia or lymphocytopenia, is more highly associated with serious infection than neutropenia alone. The integrity of skin and mucous membranes, the vascular supply to tissues, and nutritional status also influence the risk of infection.

The most common **clinical presentation of profound neutropenia** includes fever, aphthous stomatitis, and gingivitis. Infections

Table 131-1 Diagnostic Approach for Patients with Leukopenia

EVALUATION	ASSOCIATED CLINICAL DIAGNOSES
INITIAL EVALUATION	
• History of acute or chronic leukopenia	
• General medical history	Congenital syndromes (Shwachman-Diamond, Wiskott-Aldrich, Fanconi anemia, dyskeratosis congenita, glycogen storage disease type Ib, disorders of vesicular transport)
• Physical examination: stomatitis, gingivitis, dental defects, congenital anomalies	
• Spleen size	Hypersplenism
• History of drug exposure	Drug-associated neutropenia
• Complete blood count with differential and reticulocyte counts	Neutropenia, aplastic anemia, autoimmune cytopenias
IF ANC <1,000/µL	
Evaluation of Acute Onset Neutropenia	
• Repeat blood counts in 3-4 weeks	Transient myelosuppression (e.g., viral)
• Serology and cultures for infectious agents	Active or chronic infection with viruses (e.g., EBV, CMV), bacteria, mycobacteria, rickettsia
• Discontinue drug(s) associated with neutropenia	Drug-associated neutropenia
• Test for antineutrophil antibodies	Autoimmune neutropenia
• Measure quantitative immunoglobulins (G, A, and M), lymphocyte subsets	Neutropenia associated with disorders of immune function
IF ANC <500/µL ON 3 SEPARATE TESTS	
• Bone marrow aspiration and biopsy, with cytogenetics	Severe congenital neutropenia, Shwachman-Diamond syndrome, myelokathexis; chronic benign or idiopathic neutropenia
• Glucocorticoid stimulation test	Chronic benign or idiopathic neutropenia, some autoimmune neutropenias
• Serial CBCs (3/wk for 6 wk)	Cyclic neutropenia
• Exocrine pancreatic function	Shwachman-Diamond syndrome
• Skeletal radiographs	Shwachman-Diamond syndrome, cartilage-hair hypoplasia, Fanconi anemia
IF ALC <1000/µL	
• Repeat blood counts in 3-4 weeks	Transient leukopenia (e.g., viral)
IF ALC <1000/µL ON 3 SEPARATE TESTS	
• HIV-1 antibody or RNA test	HIV-1 infection, AIDS
• Quantitative immunoglobulins (G, A, and M), lymphocyte subsets	Congenital or acquired disorders of immune function
IF THERE IS PANCYTOPENIA	
• Bone marrow aspiration and biopsy	Bone marrow replacement by malignancy, fibrosis, granulomata, storage cells; aplastic anemia
• Bone marrow cytogenetics	Myelodysplasia, leukemia
• Vitamin B_{12} and folate levels	Vitamin deficiencies

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CBC, complete blood count; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

commonly associated with neutropenia include cellulitis, furunculosis, perirectal inflammation, colitis, sinusitis, and otitis media, as well as more serious infections such as pneumonia, deep tissue abscess, and sepsis. The most common pathogens causing infections in neutropenic patients are *Staphylococcus aureus* and Gram-negative bacteria. Isolated neutropenia does not heighten a patient's susceptibility to parasitic or viral infections or to bacterial meningitis. The usual signs and symptoms of local infection and inflammation such as exudate, fluctuance, and regional lymphadenopathy may be diminished in the absence of neutrophils because of the inability to form pus, but patients with agranulocytosis still experience fever and feel pain at sites of inflammation.

Laboratory Findings

Isolated absolute neutropenia has a limited number of causes (Tables 131-2 through 131-5). The duration and severity of the neutropenia greatly influence the extent of laboratory evaluation. Patients with chronic neutropenia since infancy and a history of recurrent fevers and chronic gingivitis should have WBC counts and differential counts determined 3 times/wk for 6-8 wk to evaluate the periodicity suggestive of **cyclic neutropenia**. Bone marrow aspiration and biopsy should be performed on select patients to assess cellularity and myeloid maturation. Additional marrow studies such as cytogenetic analysis and special stains for detecting leukemia and other malignant disorders should be obtained for patients with suspected intrinsic defects in the myeloid progenitors and for patients with suspected malignancy. If malignancy is not a concern, assessing the ANC before and 4-6 hr after a single dose of glucocorticosteroid (usually prednisone 1-2 mg/kg) measures mobilization of the bone marrow reserve pool of mature neutrophils; an increase in the ANC to a normal or only moderately low level indicates "chronic benign" or idiopathic neutropenia, and may render bone marrow examination unnecessary. Selection of further laboratory tests is determined by the duration and severity of the neutropenia and the associated findings on physical examination (see Table 131-1).

Acquired Neutropenia

Infection-Related Neutropenia. Transient neutropenia often accompanies or follows viral infections (see Table 131-4) and is the most frequent cause of neutropenia in childhood. Viruses commonly causing acute neutropenia include influenzas A and B, adenovirus, respiratory syncytial virus, enteroviruses, human herpes virus 6, measles, rubella, and varicella. Parvovirus B19 and hepatitides A and B may also cause neutropenia, but are more commonly associated with pure red cell aplasia or multiple cytopenias, respectively. Viral-associated acute neutropenia often occurs during the 1st 24-48 hr of illness and usually persists for 3-8 days, which generally corresponds to the period of viremia. The neutropenia is related to virus-induced redistribution of neutrophils from the circulating to the marginating pool. In addition, neutrophil sequestration may occur after virus-induced tissue damage or splenomegaly. Significant neutropenia also may be associated with severe bacterial, protozoal, rickettsial, and fungal infections (see Table 131-4). Bacterial sepsis is a particularly serious cause of neutropenia, especially among younger infants and

Table 131-2 Causes of Neutropenia Extrinsic to Marrow Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Infection	Viruses, bacteria, protozoa, rickettsia, fungi	Clinical features and laboratory findings of the infectious agent
Drug-induced	Phenothiazines, sulfonamides, anticonvulsants, penicillins, aminopyrine	Usually none; occasional hypersensitivity reaction (fever, lymphadenopathy, rash, hepatitis, nephritis, pneumonitis, aplastic anemia) or antineutrophil antibody
Immune neutropenia	Alloimmune, autoimmune	Myeloid hyperplasia with left shift in bone marrow (may appear to be "arrest" at metamyelocyte or band stage)
Reticuloendothelial sequestration	Hypersplenism	Anemia, thrombocytopenia
Bone marrow replacement	Malignancy (leukemia, lymphoma, metastatic solid tumor, etc.)	Anemia, thrombocytopenia, malignant cells in bone marrow
Cancer chemotherapy or radiation therapy	Suppression of myeloid cell production	Anemia, thrombocytopenia, bone marrow hypoplasia

Table 131-3 Acquired Disorders of Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Aplastic anemia	Stem cell destruction and depletion	Pancytopenia
Vitamin B_{12} or folate deficiency	Malnutrition; congenital deficiency of B_{12} absorption, transport, and storage; vitamin avoidance	Megaloblastic anemia, hypersegmented neutrophils
Acute leukemia, chronic myelogenous leukemia	Bone marrow replacement with malignant cells	Pancytopenia, leukocytosis
Myelodysplasia	Dysplastic maturation of stem cells	Bone marrow hypoplasia with megaloblastoid red cell precursors, thrombocytopenia
Prematurity with birth weight <2 kg	Impaired regulation of myeloid proliferation and reduced size of postmitotic pool	Maternal preeclampsia
Chronic idiopathic neutropenia	Impaired myeloid proliferation and/or maturation	None
Paroxysmal nocturnal hemoglobinuria	Acquired stem cell defect secondary to mutation of *PIG-A* gene	Pancytopenia, thrombosis

Table 131-4 Infections Associated with Neutropenia

Viral	Cytomegalovirus, dengue, Epstein-Barr virus, hepatitis viruses, HIV, influenza, measles, parvovirus B19, rubella, varicella
Bacterial	*Anaplasma* (formerly *Ehrlichia*) *phagocytophilum,* brucella, paratyphoid, pertussis, tuberculosis (disseminated), tularemia, typhoid; any form of sepsis
Fungal	Histoplasmosis (disseminated)
Protozoan	Malaria, leishmaniasis (kala-azar)
Rickettsial	Psittacosis, Rocky Mountain spotted fever, typhus, rickettsialpox

Table 131-5 Forms of Drug-Induced Neutropenia

	IMMUNOLOGIC	TOXIC	HYPERSENSITIVITY
Paradigm drugs	Aminopyrine, propylthiouracil, penicillins	Phenothiazines, clozapine	Phenytoin, phenobarbital
Time to onset	Days to weeks	Weeks to months	Weeks to months
Clinical appearance	Acute, often explosive symptoms	Often asymptomatic or insidious onset	May be associated with fever, rash, nephritis, pneumonitis, or aplastic anemia
Rechallenge	Prompt recurrence with small test dose	Latent period; high doses required	Latent period; high doses required
Laboratory findings	Antineutrophil antibody may be positive; bone marrow myeloid hyperplasia	Bone marrow myeloid hypoplasia	Bone marrow myeloid hypoplasia

children. Premature neonates are especially prone to exhausting their marrow reserve and rapidly succumbing to bacterial sepsis.

Chronic neutropenia often accompanies infection with Epstein-Barr virus, cytomegalovirus, or HIV. The neutropenia associated with AIDS probably arises from a combination of viral bone marrow suppression, antibody-mediated destruction of neutrophils, and effects of antiretroviral or other drugs.

Drug-Induced Neutropenia. Drugs constitute a common cause of neutropenia (see Table 131-5). The incidence of drug-induced neutropenia increases dramatically with age; only 10% of cases occur among children and young adults. The majority of cases occur among adults older than age 65 yr, likely reflecting the more frequent use of multiple medications in that age group. Almost any drug can cause neutropenia. The most common offending drug classes are antimicrobial agents, antithyroid drugs, antipsychotics, antipyretics, and antirheumatics. Drug-induced neutropenia has several underlying mechanisms—immune-mediated, toxic, idiosyncratic, hypersensitivity, idiopathic—that are distinct from the severe neutropenia that predictably occurs after administration of antineoplastic drugs or radiotherapy.

Drug-induced neutropenia from immune mechanisms usually develops abruptly, is accompanied by fever, and lasts for about 1 wk after the discontinuation of the drug. The process likely arises from effects of drugs, such as propylthiouracil or penicillin, that act as haptens to stimulate antibody formation, or drugs, such as quinine, that induce immune complex formation. Other drugs, including the antipsychotic drugs such as the phenothiazines, can cause neutropenia when given in toxic amounts, but some individuals, such as those with preexisting neutropenia, may be susceptible to levels at the high end of the usual therapeutic range. Late-onset neutropenia can occur after rituximab therapy. Idiosyncratic reactions, for example to chloramphenicol, are unpredictable with regard to dose or duration of use. Hypersensitivity reactions are rare and may involve arene oxide metabolites of aromatic anticonvulsants. Fever, rash, lymphadenopathy, hepatitis, nephritis, pneumonitis, and aplastic anemia are often associated with hypersensitivity-induced neutropenia. Acute hypersensitivity reactions such as those caused by phenytoin or phenobarbital may last for only a few days if the offending drug is discontinued. Chronic hypersensitivity may last for months to years.

Once neutropenia occurs, the most effective therapeutic measure is withdrawal of nonessential drugs, particularly drugs most commonly associated with neutropenia. Usually the neutropenia will resolve soon after withdrawal of the offending drug. If the neutropenia fails to improve with drug withdrawal and the patient is symptomatic with infection or stomatitis, subcutaneous administration of recombinant human granulocyte colony-stimulating factor (filgrastim) 5 µg/kg/day should be considered. Drug-induced neutropenia may be asymptomatic and noted only as an incidental finding or because of regular monitoring of WBC counts during drug therapy. For patients who are asymptomatic, continuation of the suspected offending drug depends on the relative risks of neutropenia vs discontinuation of a possibly essential drug. If the drug is continued, blood counts should be monitored for possible progression to agranulocytosis.

Neutropenia commonly and predictably follows the use of anticancer drugs or radiation therapy, especially radiation therapy directed at the pelvis or vertebrae, secondary to cytotoxic effects on rapidly replicating myeloid precursors. A decline in the WBC count typically occurs 7-10 days after administration of the anticancer drug and may persist for 1-2 wk. The neutropenia accompanying malignancy or following cancer chemotherapy is frequently associated with compromised cellular immunity and barrier compromise secondary to central venous lines and mucositis, thereby predisposing patients to a much greater risk of infection (see Chapter 178) than found in disorders associated with isolated neutropenia. Patients with chemotherapy/radiation-related neutropenia and fever must be treated aggressively with broad-spectrum antibiotics.

Nutrition-Related Neutropenia. Poor nutrition can contribute to neutropenia. Ineffective myelopoiesis may result in neutropenia caused by acquired dietary vitamin B_{12} or folic acid deficiency. In addition, megaloblastic pancytopenia also can result from extended use of antibiotics such as trimethoprim-sulfamethoxazole, which inhibit folic acid metabolism, and from the use of phenytoin, which may impair folate absorption in the small intestine, or from surgical resection of the small intestine. Neutropenia also occurs with starvation and marasmus in infants, with anorexia nervosa, and occasionally among patients receiving prolonged parenteral nutrition without vitamin supplementation.

Immune-Mediated Neutropenia. Immune-mediated neutropenia is usually associated with the presence of circulating antineutrophil antibodies, which may mediate neutrophil destruction by complement-mediated lysis or splenic phagocytosis of opsonized neutrophils, or by accelerated apoptosis of mature neutrophils or myeloid precursors.

Alloimmune neonatal neutropenia occurs after transplacental transfer of maternal alloantibodies directed against antigens on the infant's neutrophils, analogous to Rh hemolytic disease. Prenatal sensitization induces maternal IgG antibodies to neutrophil antigens on fetal cells. The neutropenia is often severe and infants may present within the 1st 2 wk of life with skin or umbilical infections, fever, and pneumonia caused by the usual microbes that cause neonatal disease. By 7 wk of age, the neutrophil count usually returns to normal, reflecting the decay of maternal antibodies in the infant's circulation. **Treatment** consists of supportive care and appropriate antibiotics for clinical infections, plus filgrastim for severe infections without neutrophil recovery.

Mothers with autoimmune disease may give birth to infants who develop transient neutropenia, known as **neonatal passive autoimmune neutropenia**. The duration of the neutropenia depends on the time required for the infant to clear the maternally transferred circulating immunoglobulin G antibody. It persists in most cases for a few weeks to a few months. Neonates almost always remain asymptomatic.

Autoimmune neutropenia (AIN) of infancy is a benign condition with an annual incidence of approximately 1 per 100,000 among children between infancy and 10 yr of age. Patients usually have severe neutropenia on presentation, with ANC <500/µL, but the total WBC count is generally within normal limits. Monocytosis or eosinophilia may occur but does not impact the low rate of infection. The median age of presentation is 8-11 mo with a range of 2-54 mo. There is a slight female predominance. The diagnosis is often evident when a blood count incidentally reveals neutropenia in a child with a minor infection. Occasionally, children may present with more severe infections, including abscesses, pneumonia, or sepsis. The diagnosis may be established by the presence of antineutrophil antibodies in serum; however, the test has frequent false-negative and false-positive results, so the absence of detectable antibody does not exclude the diagnosis and a positive result does not exclude other conditions. The diagnosis may also be based clinically on a benign course and normal or hyperplastic myeloid maturation in the bone marrow. There is considerable overlap between AIN of infancy and "chronic benign neutropenia."

Treatment is not generally necessary because the disease is only rarely associated with severe infection and usually remits spontaneously. Low-dose filgrastim may be useful for severe infections, to promote wound healing following surgery, or to avert emergency room visits or hospitalizations for febrile illnesses. Longitudinal studies of infants with AIN demonstrate median durations of disease ranging from 7-30 mo. Affected children generally have no evidence or risk of other autoimmune diseases.

AIN in older children can occur as an isolated process, as a manifestation of other autoimmune diseases, or as a secondary complication of infection, drugs or malignancy. In primary AIN, low circulating neutrophil counts are the only hematologic finding, and associated diseases or other factors that cause neutropenia are absent. Secondary AIN associated with immune dysregulation or other factors is more commonly identified in older children and is less likely to spontaneously remit. AIN is distinguished from other forms of neutropenia by the demonstration of antineutrophil antibodies (with caveats discussed above) and myeloid hyperplasia on bone marrow examination. The

most common antineutrophil antibody targets are human neutrophil antigens 1a, 1b, and 2.

Treatment of AIN relies on management of any underlying disorders. In addition, judicious use of appropriate antibiotics for bacterial infections, and regular dental hygiene is generally beneficial. Infections tend to be less frequent in AIN than with the corresponding degree of neutropenia from other causes, probably because tissue delivery of neutrophils is greater than that in conditions resulting from impaired production. Prophylactic antibiotics may be helpful for the management of recurrent minor infections. For patients with serious or recurrent infections, filgrastim is generally effective at raising the ANC and preventing infection. Very low doses (<1-2 μg/kg/day) are usually effective, and administration of standard doses can lead to severe bone pain as a consequence of marrow expansion.

Neutropenia Secondary to Bone Marrow Replacement. Various acquired bone marrow disorders lead to neutropenia, usually accompanied by anemia and thrombocytopenia. Hematologic malignancies, including leukemia, lymphoma, and metastatic solid tumors suppress myelopoiesis by infiltrating the bone marrow with tumor cells. Neutropenia may also accompany aplastic anemia, myelodysplastic disorders or preleukemic syndromes, which are characterized by multiple cytopenias and often macrocytosis. Treatment requires management of the underlying disease.

Neutropenia Secondary to Reticuloendothelial Sequestration. Splenic enlargement resulting from intrinsic splenic disease (storage disease), portal hypertension, or systemic causes of splenic hyperplasia (inflammation or neoplasia) can lead to neutropenia. Most often the neutropenia is mild to moderate and is accompanied by corresponding degrees of thrombocytopenia and anemia. The reduced neutrophil survival corresponds to the size of the spleen, and the extent of the neutropenia is inversely proportional to bone marrow compensatory mechanisms. Usually the neutropenia may be corrected by successfully treating the underlying disease. In selected cases, splenectomy may be necessary to restore the neutrophil count to normal, but results in increased risk of infections by encapsulated bacterial organisms. Patients undergoing splenectomy should receive appropriate presplenectomy immunizations and may benefit from antibiotic prophylaxis postsplenectomy to help mitigate the risk of sepsis. Splenectomy should be avoided in patients with common variable immunodeficiency, autoimmune lymphoproliferative disease and other immunodeficiency syndromes because of the higher risk of sepsis.

Inherited Neutropenia

Intrinsic disorders of proliferation or maturation of myeloid precursor cells are rare. Table 131-6 presents a classification based on genetics and molecular mechanisms; selected disorders are discussed below.

Primary Disorders of Granulocytopoiesis. **Cyclic neutropenia** is a rare autosomal dominant congenital granulopoietic disorder occurring with an estimated incidence of 0.5-1 cases per 1 million population. The disorder is characterized by regular, periodic oscillations, with the ANC ranging from normal to <200/μL, mirrored by reciprocal cycling of monocytes. Cyclic neutropenia is sometimes termed *cyclic hematopoiesis* because of the secondary cycling of other blood cells, such as platelets and reticulocytes. The mean oscillatory period of the cycle is 21 days (± 4 days). During the neutropenic nadir, many patients suffer from malaise, fever, oral and genital ulcers, gingivitis, periodontitis, or pharyngitis, and occasionally lymph node enlargement. More serious infections may occasionally occur, including pneumonia, mastoiditis, and intestinal perforation with peritonitis leading to life-threatening clostridial sepsis. Prior to the availability of filgrastim, approximately 10% of patients developed fatal clostridial or Gram-negative infections. Cyclic neutropenia arises from a regulatory abnormality involving early hematopoietic precursor cells and is almost invariably associated with mutations in the neutrophil elastase gene, *ELANE*, that lead to accelerated apoptosis as a result of abnormal protein folding. Many patients experience abatement of symptoms with age. The cycles tend to become less noticeable in older patients, and the hematologic picture often begins to resemble that of chronic idiopathic neutropenia.

Cyclic neutropenia is diagnosed by obtaining blood counts 3 times/wk for 6-8 wk. The requirement for repeated blood counts is necessary because some of the elastase mutations overlap with those in patients who have **severe congenital neutropenia**. Demonstrating oscillation or a lack thereof in the blood counts helps to identify the patients risk for progression to myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), a risk that is only associated with severe congenital neutropenia. The diagnosis can be confirmed with genetic studies demonstrating a mutation in the *ELANE* gene. Affected patients with neutrophil nadirs <200/μL are treated with filgrastim and their cycle of profound neutropenia changes from a 21-day period with at least 3-5 days of profound neutropenia to a 9-11 day interval with 1 day of less-profound neutropenia. The dose needed to maintain nadirs >500/μL is usually 2-4 μg/kg/day administered daily or every other day.

Severe congenital neutropenia (SCN) is a rare, genetically heterogeneous, congenital granulopoietic disorder with an estimated incidence of 1-2 cases per 1 million population. The disorder is characterized by an arrest in myeloid maturation at the promyelocyte stage in the bone marrow, resulting in ANCs consistently <200/μL and may occur sporadically, with autosomal dominant or recessive inheritance. The **dominant** form is caused most often by mutations in the *ELANE* gene, which accounts for 60-80% of SCN cases, while **recessive** forms arise from mutations in *HAX1* (the form also known as **Kostmann disease**) or *G6PC3* (encoding a myeloid-specific isoform of glucose-6-phosphatase). *HAX1* mutations may be associated with neurologic deficits, and *G6PC3* with heart defects, urogenital abnormalities, and venous angiectasia. In addition to severe neutropenia, peripheral blood counts generally show monocytosis and many also exhibit eosinophilia; chronic inflammation may lead to secondary anemia and thrombocytosis. Patients who have SCN experience frequent episodes of fever, skin infections (including omphalitis), oral ulcers, gingivitis, pneumonia and perirectal abscesses, typically appearing in the 1st few mo of life. Infections often disseminate to the blood, meninges and peritoneum, and are usually caused by *S. aureus*, *Escherichia coli,* and *Pseudomonas* species. Prior to the current era of filgrastim therapy, most patients died of infectious complications within the 1st 1-2 yr of life despite prophylactic antibiotics.

More than 95% of SCN patients respond to filgrastim treatment with an increase in the ANC and a decrease in infections. Doses required to achieve an ANC >1000/uL vary greatly. A starting dose of filgrastim 5 μg/kg/day is recommended; the dose should be gradually increased, if necessary, as high as 100 μg/kg/day to attain an ANC of 1,000-2,000/μL. The 5% of patients who do not respond to filgrastim or who require high doses (>8 μg/kg/day) should be considered for hematopoietic stem cell transplantation. Besides infections, patients with SCN are at risk for developing MDS associated with monosomy 7 and AML. For this reason, regular monitoring with blood counts and yearly bone marrow surveillance, including karyotyping and fluorescence in situ hybridization, should be performed on all SCN patients. Although clonal cytogenetic abnormalities may spontaneously remit, their appearance should be considered a strong indication for hematopoietic stem cell transplantation, which is much more likely to be successful prior to progression to MDS/AML.

Disorders of Molecular Processing. Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder classically characterized by neutropenia, pancreatic insufficiency, and short stature with skeletal abnormalities. SDS is caused by proapoptotic mutations of the *SBDS* gene, which encodes a protein that plays a role in ribosome biogenesis and RNA processing. The initial symptoms are usually steatorrhea and failure to thrive because of malabsorption, which usually develops by 4 mo of age, although the gastrointestinal symptoms may be subtle in some patients and go unrecognized. Patients have also been reported to have respiratory problems with frequent otitis media, pneumonia and eczema. Virtually all patients with SDS have neutropenia, with the ANC periodically <1000/μL. Some children have defects in chemotaxis or in the number or function of B, T, and natural killer (NK) cells that may contribute to the increased susceptibility to pyogenic infection. The diagnosis of SDS is based on clinical

Table 131-6 Intrinsic Disorders of Myeloid Precursor Cells

SYNDROME	INHERITANCE *(GENE)*	CLINICAL FEATURES (INCLUDING STATIC NEUTROPENIA UNLESS OTHERWISE NOTED)
PRIMARY DISORDERS OF MYELOPOIESIS		
Cyclic neutropenia	AD *(ELANE)*	Periodic oscillation (21-day cycles) in ANC
Severe congenital neutropenia	AD (primarily *ELANE*, also *GFI* and others)	Risk of MDS/AML
	AR *(G6PC3, HAX1)* (*HAX1* = Kostmann syndrome)	*G6PC3:* cardiac and urogenital anomalies, venous angiectasias; *HAX1:* neurologic abnormalities, risk of MDS/AML
	XL *(WAS)*	Neutropenic variant of Wiskott-Aldrich syndrome
DISORDERS OF MOLECULAR PROCESSING		
Shwachman-Diamond syndrome	Ribosomal defect: AR *(SBDS)*	Pancreatic insufficiency, metaphysical dysostosis, bone marrow failure, MDS/AML
Dyskeratosis congenita	Telomerase defects: XL *(DKC1)*, AD *(TERC)*, AR *(TERT)*	Nail dystrophy, leukoplakia, abnormal and carious teeth, lacey reticulated hyperpigmentation of the skin, bone marrow failure
DISORDERS OF VESICULAR TRAFFICKING		
Chédiak-Higashi syndrome	AR *(LYST)*	Partial albinism, giant granules in myeloid cells, platelet storage pool defect, impaired natural killer cell function, HLH
Griscelli syndrome, type II	AR *(RAB27a)*	Partial albinism, impaired natural killer cell function, neurological impairment, HLH
Cohen syndrome	AR *(COH1)*	Partial albinism, pigmentary retinopathy, developmental delay, facial dysmorphism
Hermansky-Pudlak syndrome, type II	AR *(AP3P1)*	Cyclic neutropenia, partial albinism, HLH
p14 deficiency	Probable AR *(MAPBPIP)*	Partial albinism, decreased B and T cells
VPS45 defects	AR *(VPS45)*	neutrophil dysfunction, bone marrow fibrosis, nephromegaly
DISORDERS OF METABOLISM		
Glycogen storage disease, type 1b	AR *(G6PT1)*	Hepatic enlargement, growth retardation, impaired neutrophil motility
Barth syndrome	XL *(TAZ1)*	Episodic neutropenia, dilated cardiomyopathy, methylglutaconic aciduria
Pearson syndrome	Mitochondrial (DNA deletions)	Episodic neutropenia, pancytopenia; defects in exocrine pancreas, liver, and kidneys
NEUTROPENIA IN DISORDERS OF IMMUNE FUNCTION		
Common variable immunodeficiency	Familial, sporadic *(TNFRSF13B)*	Hypogammaglobulinemia, other immune system defects
IgA deficiency	Unknown (Unknown or *TNFRSF13B*)	Decreased IgA
Severe combined immunodeficiency	AR, XL (multiple loci)	Absent humoral and cellular immune function
Hyper-IgM syndrome	XL *(HIGM1)*	Absent IgG, elevated IgM, autoimmune cytopenias
WHIM syndrome	AD *(CXCR4)*	Warts, hypogammaglobulinemia, infections, myelokathexis
Cartilage-hair hypoplasia	AR *(RMKP)*	Lymphopenia, short-limbed dwarfism, metaphyseal chondrodysplasia, fine sparse hair
Schimke immunoosseous dysplasia	Probable AR *(SMARCAL1)*	Lymphopenia, pancytopenia, spondyloepiphyseal dysplasia, growth retardation, renal failure
X-linked agammaglobulinemia	BTK	Agammaglobulinemia, neutropenia in ~25%

AD, autosomal dominant; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; AR, autosomal recessive; HLH, hemophagocytic lymphohistiocytosis; Ig, immunoglobulin; MDS, myelodysplasia; XL, X-linked, BTK, Briton tyrosine kinase.

phenotype; approximately 90% of patients have mutations identified in the *SBDS* gene. SDS may progress to bone marrow hypoplasia or to MDS/AML; cytogenetic abnormalities, particularly isochromosome i(7q) and del(20q), often precede conversion to MDS, so bone marrow monitoring is warranted. Treatment includes pancreatic enzyme replacement, plus filgrastim in patients with severe neutropenia.

Dyskeratosis congenita, a disorder of telomerase activity, most often presents as bone marrow failure rather than isolated neutropenia. The classical phenotype also includes nail dystrophy, leukoplakia, malformed teeth, and reticulated hyperpigmentation of the skin, although many patients, particularly young ones, do not exhibit these clinical features.

Vesicular Trafficking Disorders. This group of very rare **primary immunodeficiency syndromes** (see Table 131-6) derives from autosomal recessive defects in the biogenesis or trafficking of lysosomes and related endosomal organelles. As a result, the syndromes share phenotypic characteristics including defects in melanosomes contributing to partial albinism, abnormal platelet function, and immunologic defects involving not only neutrophil number, but also the function of neutrophils, B lymphocytes, NK cells, and cytotoxic T lymphocytes. The syndromes share a high risk of hemophagocytic lymphohistiocytosis (HLH) as a result of defects in T and NK cells.

Chédiak-Higashi syndrome, best known for the characteristic giant cytoplasmic granules in neutrophils, monocytes, and lymphocytes, is a disorder of subcellular vesicular dysfunction caused by mutations in the *LYST* gene, with resultant giant granules in all granule-bearing cells. Patients have increased susceptibility to infections, mild bleeding diathesis, progressive peripheral neuropathy, and predisposition to life-threatening HLH. The only curative treatment is hematopoietic stem cell transplantation.

Griscelli syndrome type II also features neutropenia, partial albinism, and a high risk of HLH, but peripheral blood granulocytes do not show giant granules. Patients often have hypogammaglobulinemia. The disorder is caused by mutations in *RAB27a*, which encodes a small guanosine triphosphatase that regulates granule secretory pathways. The only curative treatment is hematopoietic stem cell transplantation.

Disorders of Metabolism. Recurrent infections with neutropenia are a distinctive feature of **glycogen storage disease (GSD)**

type Ib. As in classic von Gierke disease (GSDIa), glycogen storage in GSDIb causes massive hepatomegaly and severe growth retardation (see Chapter 87.1). Mutations in glucose-6-phosphate transporter 1, *G6PT1*, inhibit glucose transport in GSDIb, resulting in both defective neutrophil motility and increased apoptosis associated with neutropenia and recurrent bacterial infections. **Treatment** with filgrastim can correct the neutropenia but does not correct the underlying functional neutrophil defects.

Neutropenia in Disorders of Immune Dysfunction. Congenital immunologic disorders that have severe neutropenia as a clinical feature include X-linked agammaglobulinemia, common variable immunodeficiency, the severe combined immunodeficiencies, autoimmune lymphoproliferative syndrome, hyperimmunoglobulin M syndrome, WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome, and a number of even rarer immunodeficiency disorders (see Table 131-6).

Unclassified Neutropenic Disorders. Chronic benign neutropenia of childhood represents a common group of disorders characterized by mild to moderate neutropenia that does not lead to an increased risk of pyogenic infections. Spontaneous remissions are often reported, although these may represent misdiagnosis of AIN of infancy, in which remissions occur commonly during childhood. Chronic benign neutropenia may be sporadic or inherited in either a dominant or recessive form. Because of the relatively low risk of serious infection, patients usually do not require any form of therapy.

Idiopathic chronic neutropenia is characterized by the onset of neutropenia after 2 yr of age, with no identifiable etiology. Patients with an ANC persistently <500/µL may be afflicted with recurrent pyogenic infections involving the skin, mucous membranes, lungs, and lymph nodes. Bone marrow examination reveals variable patterns of myeloid formation with arrest generally occurring between the myelocyte and band forms. The diagnosis overlaps with chronic benign and AINs.

Treatment

The management of acquired transient neutropenia associated with malignancies, myelosuppressive chemotherapy, or immunosuppressive chemotherapy differs from that of congenital or chronic forms of neutropenia. In the former situation, infections sometimes are heralded only by fever, and sepsis is a major cause of death. Early recognition and treatment of infections may be lifesaving (see Chapter 178). Therapy of severe chronic neutropenia is dictated by the clinical manifestations. Patients with benign neutropenia and no evidence of repeated bacterial infections or chronic gingivitis require no specific therapy. Superficial infections in children with mild to moderate neutropenia may be treated with appropriate oral antibiotics. In patients who have invasive or life-threatening infections, broad-spectrum intravenous antibiotics should be started promptly.

Subcutaneously administered filgrastim can provide effective treatment of severe chronic neutropenia including SCN, chronic symptomatic idiopathic neutropenia, and cyclic neutropenia. Treatment leads to dramatic increases in neutrophil counts, resulting in marked attenuation of infection and inflammation. Doses range from 2-5 µg/kg/day for cyclic, idiopathic, and autoimmune neutropenias, to 10-100 µg/kg/day for SCN. The long-term effects of filgrastim therapy include a propensity for the development of moderate splenomegaly, thrombocytopenia, and, rarely, vasculitis; only patients with SCN are at risk for MDS/AML.

Patients with SCN or SDS who develop MDS or AML respond only to hematopoietic stem cell transplantation; chemotherapy is ineffective. Hematopoietic stem cell transplantation is also the treatment of choice for aplastic anemia or HLH.

LYMPHOPENIA

The definition of **lymphopenia,** like neutropenia, is age-dependent and can be from acquired or inherited causes. **The absolute lymphocyte count (ALC)** is determined by multiplying the total WBC count by the percentage of total lymphocytes. For children younger than 12 mo old, lymphopenia is defined as an ALC <3,000 cells/µL. For older children and adults, an ALC <1,000 cells/µL is considered lymphopenia. In isolation, mild to moderate lymphopenia is generally a benign condition often detected only in the evaluation of other illnesses. However, severe lymphopenia can result in serious, life-threatening illness. Lymphocyte subpopulations can be measured by flow cytometry, which uses the pattern of lymphocyte antigen expression to quantitate and classify T, B, and NK cells.

Table 131-7	Causes of Lymphocytopenia
ACQUIRED	
Infectious diseases	AIDS, hepatitis, influenza, sepsis, tuberculosis, typhoid
Iatrogenic	Corticosteroids, cytotoxic chemotherapy, high-dose PUVA, immunosuppressive therapy, radiation, thoracic duct drainage
Systemic diseases	Hodgkin disease, lupus erythematosus, myasthenia gravis, protein-losing enteropathy, renal failure sarcoidosis
Other	Aplastic anemia, dietary deficiencies, thermal injury
INHERITED	
Aplasia of lymphopoietic stem cells	Cartilage-hair hypoplasia, ataxia-telangiectasia, SCID, thymoma, Wiskott-Aldrich syndrome

PUVA, psoralen and ultraviolet A irradiation; SCID, severe combined immunodeficiency.

Acquired Lymphopenia

Acute lymphopenia is most often a consequence of infection and/or is iatrogenic from lymphocyte-toxic medications and treatments (Table 131-7). Microbial causes include viruses (e.g., respiratory syncytial virus, cytomegalovirus, influenza, measles, and hepatitis) bacterial infections (e.g., tuberculosis, typhoid fever, histoplasmosis, and brucellosis) and malaria. The mechanisms behind infection-associated lymphopenia are not fully elucidated but probably include lymphocyte redistribution and accelerated apoptosis. Corticosteroids are a common cause of medication-induced lymphopenia, as are lymphocyte-specific immunosuppressive agents (e.g., antilymphocyte globulin, alemtuzumab, and rituximab) chemotherapy drugs, and radiation. In most cases, infectious and iatrogenic causes of acute lymphopenia are reversible, although full lymphocyte recovery from chemotherapy and lymphocyte-specific immunosuppressive agents may take several months to years. Prolonged lymphopenia (Table 131-7) may be caused by recurrent infection; persistent infections, mostly notably HIV; malnutrition; mechanical loss of lymphocytes through protein-losing enteropathy or thoracic duct leaks; or systemic diseases such as lupus erythematosus, rheumatoid arthritis, sarcoidosis, renal failure, lymphoma, and aplastic anemia.

Inherited Lymphopenia

Primary immunodeficiencies and bone marrow failure syndromes are the main cause of inherited lymphopenia in children (see Table 131-7). Primary immunodeficiency may result in a severe quantitative defect, as in X-linked agammaglobulinemia and severe combined immunodeficiency (SCID), or a qualitative or progressive defect as in Wiskott-Aldrich syndrome and common variable immunodeficiency. X-linked agammaglobulinemia is characterized by a near absence of mature B cells because of a mutation in *BTK* that results in a dysfunctional tyrosine kinase. SCIDs are a genetically heterogenous group of disorders characterized by abnormalities of thymopoiesis and T-cell maturation. Newborn screening for severe T-cell deficiency, via analysis of T-cell receptor excision circles from dried blood spot Guthrie cards, is available in many states to aid in the rapid identification and treatment of infants with SCID and other T-cell disorders. Quantitative defects in lymphocytes can also be appreciated in select forms of inherited bone marrow failure such as reticular dysgenesis, SCN secondary to *GFI1* mutation, and dyskeratosis congenita.

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Chapter 132

Leukocytosis

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Leukocytosis is an elevation in the total leukocyte or white blood cell (WBC) count that is 2 SD above the mean count for a particular age (see Chapter 727). To evaluate the patient with leukocytosis, it is critical to determine which class of WBC is elevated in conjunction with the duration and extent of the leukocytosis. For discussion of WBC elevation caused by immature leukocytes in acute and chronic leukemias, see Chapter 495.

A WBC count exceeding 50,000/µL is termed a **leukemoid reaction** because of the similarity to some features of leukemia. Leukemoid reactions are usually neutrophilic, and unlike true leukemia, show only small proportions of immature myeloid cells, consisting primarily of band forms, occasional metamyelocytes, and progressively rarer myelocytes, promyelocytes, and blasts. The process is most frequently associated with septicemia and severe bacterial infections, including shigellosis, salmonellosis, and meningococcemia.

A proportion of immature neutrophil cells >5%, termed a **left shift**, indicates rapid release of cells from the bone marrow, consisting primarily of band forms, which usually constitute 1-5% of circulating neutrophilic cells, or metamyelocytes and myelocytes, which are not usually found in the peripheral circulation. Higher degrees of left shift with more immature neutrophil precursors are indicative of serious bacterial infections and may be a dire sign of depletion of the bone marrow reserve pool of neutrophils. Marked left shift may occasionally be encountered with trauma, burns, surgery, acute hemolysis, or hemorrhage.

NEUTROPHILIA

Neutrophilia is an increase in the total number of blood neutrophils that is 2 SD above the mean count for age (see Chapter 727). Elevated absolute neutrophil counts represent disturbances of the normal equilibrium involving bone marrow neutrophil production, movement out of the marrow compartments into the circulation, and neutrophil destruction. Neutrophilia may arise either alone or in combination with enhanced mobilization into the **circulating pool** from either the bone marrow storage compartment or the peripheral blood **marginating pool,** by impaired neutrophil egress into tissues, or by expansion of the circulating neutrophil pool secondary to increased granulocytopoiesis. Myelocytes are not released to the blood except under extreme circumstances.

Acute Acquired Neutrophilia

Neutrophilia is usually an acquired, secondary finding associated with inflammation, infection, injury, or stress (Table 132-1). Acute or chronic bacterial infections, trauma, and surgery are among the most common causes encountered in clinical practice. Neutrophilia may also be associated with heatstroke, burns, diabetic ketoacidosis, or any other acute stress. Drugs commonly associated with neutrophilia include epinephrine, corticosteroids, and recombinant growth factors such as recombinant human granulocyte colony-stimulating factor (G-CSF; filgrastim) and recombinant human granulocyte-macrophage colony-stimulating factor.

Epinephrine causes release into the circulation of a sequestered pool of neutrophils that normally marginate along the vascular endothelium. Corticosteroids accelerate the release of neutrophils and bands from a large storage pool within the bone marrow and impair the migration of neutrophils from the circulation into tissues. Acute neutrophilia in response to inflammation and infections occurs because of release of neutrophils from the marrow storage pool. The postmitotic marrow neutrophil pools are approximately 10 times the size of the blood neutrophil pool, and about half of these cells are bands and segmented neutrophils. In neutrophil production disorders, such as those associated with malignancies and cancer chemotherapy, the size of this pool may be reduced and the capacity to develop neutrophilia remains impaired. Exposure of blood to foreign substances such as hemodialysis membrane activates the complement system and causes transient neutropenia followed by neutrophilia because of release of bone marrow neutrophils. G-CSF and granulocyte-macrophage colony-stimulating factor cause acute and chronic neutrophilia by mobilizing cells from the marrow reserves and by stimulating neutrophil production.

Table 132-1 Causes of Neutrophilia

TYPE	CAUSE	EXAMPLE
Acute acquired	Bacterial infections	
	Surgery	
	Acute stress	Burns, diabetic ketoacidosis, heat stroke, postneutropenia rebound, exercise
	Drugs	Corticosteroids, epinephrine, hematopoietic growth factors, lithium
Chronic acquired	Chronic inflammation	Inflammatory bowel disease, rheumatoid arthritis, vasculitis
	Persistent infection	Tuberculosis
	Persistent stress	Chronic blood loss, hypoxia, sickle cell and other chronic hemolytic anemias
	Drugs	Corticosteroids, lithium; rarely ranitidine, quinidine
	Other	Postsplenectomy, tumors, Hodgkin disease
Lifelong	Congenital asplenia	
	Hereditary disorders	Familial cold urticaria, hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes

Chronic Acquired Neutrophilia

Chronic acquired neutrophilia is usually associated with continued stimulation of neutrophil production resulting from persistent inflammatory reactions or chronic infections (e.g., tuberculosis), vasculitis, postsplenectomy states, Hodgkin disease, chronic myelogenous leukemia, chronic blood loss, sickle cell disease, some chronic hemolytic anemias, and prolonged administration of corticosteroids (see Table 132-1). Chronic neutrophilia can arise after expansion of cell production secondary to stimulation of cell divisions within the mitotic precursor pool, which consists of promyelocytes and myelocytes. Subsequently, the size of the postmitotic pool increases. These changes lead to an increase in the marrow reserve pool, which can be readily mobilized for release of neutrophils into the circulation. The neutrophil production rate can increase greatly in response to exogenously administered hemopoietic growth factors, such as G-CSF, with a maximum response taking at least 1 wk to develop.

Lifelong Neutrophilia

Congenital or acquired asplenia is associated with lifelong neutrophilia. Uncommon genetic disorders that present with neutrophilia include leukocyte function disorders such as leukocyte adhesion deficiency and Rac2 mutation (see Chapter 124), and systemic disorders such as familial cold urticarial, periodic fever syndromes, and familial myeloproliferative disease (see Table 132-1). Two kindreds have been reported with autosomal dominant hereditary neutrophilia, with 1 caused by an activating mutation in the G-CSF receptor gene that leads to an increased proliferation of neutrophil precursors and a heightened risk of myelodysplastic syndrome.

Table 132-2 Causes of Monocytosis

CAUSE	EXAMPLE
Infections	
Bacterial infections	Brucellosis, subacute bacterial endocarditis, syphilis, tuberculosis typhoid
Nonbacterial infections	Fungal infections, kala-azar, malaria, Rocky Mountain spotted fever, typhus
Hematologic disorders	Congenital and acquired neutropenias, hemolytic anemias
Malignant disorders	Acute myelogenous leukemia, chronic myelogenous leukemia, juvenile myelomonocytic leukemia, Hodgkin disease, non-Hodgkin lymphomas, preleukemia
Chronic inflammatory diseases	Inflammatory bowel disease, polyarteritis nodosa, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus
Miscellaneous	Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression

Evaluation of persistent neutrophilia requires a careful history, physical examination, and laboratory studies to search for infectious, inflammatory, and neoplastic conditions. The leukocyte alkaline phosphatase score of circulating neutrophils can differentiate chronic myelogenous leukemia, in which the level is uniformly near zero, from reactive or secondary neutrophilia, which feature normal to elevated levels.

MONOCYTOSIS

The average absolute blood monocyte count varies with age, which must be considered in the assessment of monocytosis. Given the role of monocytes in antigen presentation and cytokine secretion and as effectors of ingestion of invading organisms, it is not surprising that many clinical disorders give rise to monocytosis (Table 132-2). Most commonly, monocytosis occurs in patients recovering from myelosuppressive chemotherapy and is a harbinger of the return of the neutrophil count to normal. Monocytosis is occasionally a sign of an acute bacterial, viral, protozoal, or rickettsial infection, and may also occur in some forms of chronic neutropenia and postsplenectomy states. Chronic inflammatory conditions can stimulate sustained monocytosis, as can preleukemia, chronic myelogenous leukemia, lymphomas, and occasionally Hodgkin disease.

Lymphocytosis

The most common cause of lymphocytosis is an acute viral illness, as part of the normal T-cell response to the infection. In infectious mononucleosis, the B cells are infected with the Epstein-Barr virus and the T cells react to the viral antigens present in the B cells, resulting in **atypical lymphocytes** with characteristic large, vacuolated morphology. Other viral infections classically associated with lymphocytosis are cytomegalovirus and viral hepatitis. Chronic bacterial infections such as tuberculosis and brucellosis may lead to a sustained lymphocytosis. Pertussis is accompanied by marked lymphocytosis in approximately 25% of infants infected before 6 mo of age. Thyrotoxicosis and Addison disease are endocrine disorders associated with lymphocytosis. Persistent or pronounced lymphocytosis suggests acute lymphocytic leukemia.

Basophilia

Basophilia is defined as an absolute basophil count >120 cells/µL. Basophilia is a nonspecific sign of a wide variety of disorders and is usually of limited diagnostic importance. Basophilia is most often present in hypersensitivity reactions and frequently accompanies the leukocytosis of chronic myeloid leukemia.

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Section 4

The Complement System

Chapter 133

The Complement System

Richard B. Johnston Jr.

Complement (C) was originally defined as the nonspecific, heat-labile complementary principal required with specific antibody to lyse bacteria. The 1st 4 components were numbered in the order of their discovery and are termed the classical pathway. Unfortunately, the components fix to the immune complex in a different order, C1423. Beyond this confusing start, complement is a logical, exquisitely balanced, and highly influential system that is fundamental to the clinical expression of host defense and inflammation. In addition, it is evolutionarily ancient, and as it coevolved with other physiologic systems, it developed the capacity to perform functions beyond just host defense. Among these, it promotes phagocytic removal of dying body cells, molecular debris, and synapses during brain formation. But it can also cause harm and has been implicated in more than 30 illnesses.

The complement system, an essential component of innate immunity, is broadly conceptualized as the **classical, lectin,** and **alternative pathways,** which interact and depend on each other for their full activity; the **membrane attack complex (C5b6789),** formed from activity of any pathway; cell membrane **receptors** that bind complement components or fragments to mediate complement activity; and a large array of serum and membrane regulatory proteins (Table 133-1,

Table 133-1 Constituents of the Complement System
SERUM COMPONENTS THAT ARE THE CORE OF THE COMPLEMENT SYSTEM
Classical pathway: C1q, C1r, C1s, C4, C2, C3
Alternative pathway: Factor B, Factor D
Lectin pathway: Mannose-binding lectin (MBL), ficolins 1/2/3, MBL-associated serine proteases (MASPs) 1/2/3
Membrane attack complex: C5, C6, C7, C8, C9
Regulatory protein, enhancing: properdin
Regulatory proteins, downregulating: C1 inhibitor (C1 INH), C4-binding protein (C4-bp), factor H, factor I, vitronectin, clusterin, carboxypeptidase N (anaphylatoxin inactivator)
MEMBRANE REGULATORY PROTEINS
CR1 (CD35), membrane cofactor protein (MCP; CD46), decay-accelerating factor (DAF, CD55), CD59 (membrane inhibitor of reactive lysis; protectin)
MEMBRANE RECEPTORS
CR1 (CD35), CR2 (CD21), CR3 (CD11b/CD18), CR4 (CD11c/CD18), C3a receptor, C5a receptor, C1q receptors, complement receptor of the immunoglobulin superfamily (CRIg)

Fig. 133-1). The circulating components and regulators together comprise approximately 15% of the globulin fraction and 4% of the total proteins in serum. The normal concentrations of serum complement components vary by age (see Chapter 727); newborn infants have mild to moderate deficiencies of all components.

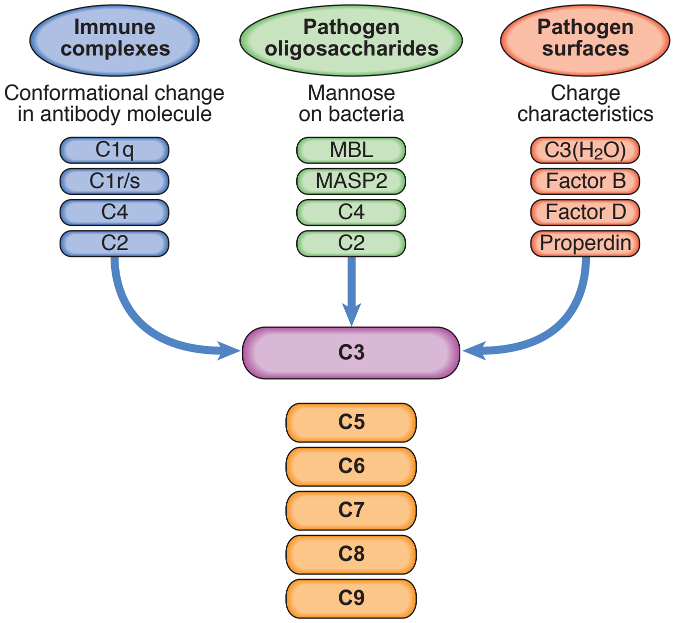

Figure 133-1 The complement cascade. The classical pathway is activated primarily by antibody while the mannose-binding lectin and alternative pathways are activated directly by pathogens. In each case, the activation arm leads to cleavage of C3. *(From Leung DYM, editor:* Pediatric allergy principles and practice, *ed 2, Philadelphia, 2010, WB Saunders, Fig. 11-1, p. 121.)*

After C1423, complement nomenclature is logical and consists of only a few rules. Fragments of components resulting from cleavage by other components acting as enzymes are assigned lowercase letters (a, b, c, d, e); with the exception of C2 fragments, the smaller piece that is released into surrounding fluids is assigned the lowercase letter *a,* and the major part of the molecule, bound to other components or to some part of the immune complex, is assigned letter *b*—for example, C3a and C3b. Components of the alternative pathway, B and D, have been assigned uppercase letters, as have the control proteins I and H, which downregulate both pathways. C3, and especially its major fragment C3b, is a component of both the classical and alternative pathways.

Complement is a system of interacting proteins. The biologic functions of the system depend on the interactions of individual components, which occur in sequential, cascade fashion. Activation of each component, except the 1st, depends on activation of the prior component or components in the sequence. Interaction occurs along 3 pathways (Fig. 133-2): the **classical pathway,** in the order antigen–antibody–C142356789; the **lectin** (carbohydrate-binding) **pathway**, in the order microbial carbohydrate–lectin (mannose-binding lectin [MBL] or ficolin)–MBL-associated serine protease–C42356789; and the **alternative pathway,** in the order activator–C3bBD–C356789. Antibody accelerates the rate of activation of the alternative pathway, but activation can occur on appropriate surfaces in the absence of antibody. The classical and the alternative pathways interact with each other through the ability of both to activate C3.

Activation of the early-acting components of complement (C1423) results in the generation of a series of active enzymes, C1, C42, and C423, on the surface of the immune complex or underlying cell. These enzymes cleave and activate the next component in the sequence. In contrast, the interaction among C5b, C6, C7, C8, and C9 is nonenzymatic and depends on changes in molecular configuration.

CLASSICAL AND LECTIN PATHWAYS

The classical pathway sequence begins with fixation of C1, by way of C1q, to the Fc, non–antigen-binding part of the antibody molecule after antigen–antibody interaction. The C1 tricomplex changes

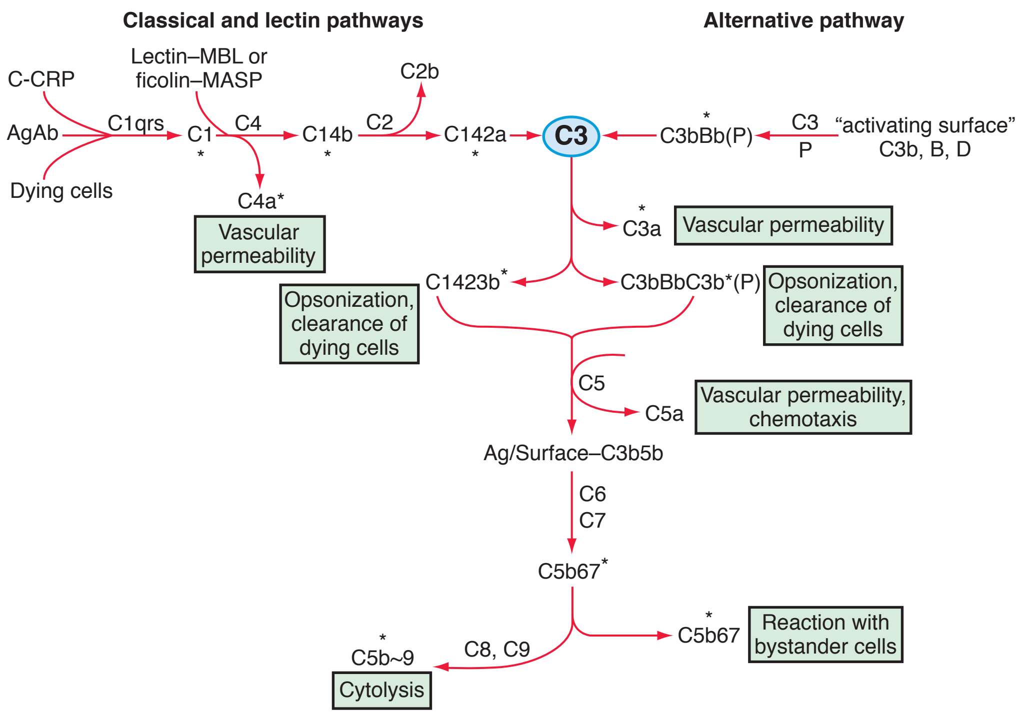

Figure 133-2 Sequence of activation of the components of the classical and lectin pathways of complement and interaction with the alternative pathway. Activation of C3 is the essential target. Functional activities generated during activation are enclosed in boxes. The multiple sites at which inhibitory regulator proteins (not shown) act are indicated by *asterisks*, emphasizing the delicate balance between action and control in this system that is essential for host defense yet capable of profound damage to host tissues. *Ab,* antibody (immunoglobulin G or M class); *Ag,* antigen (bacterium, virus, tumor or tissue cell); *B, D, I, P,* factors B, D, I, and properdin; *C-CRP*, carbohydrate–carbohydrate-reactive protein; *C4-bp*, C4-binding protein; *MASP*, MBL-associated serine protease; *MBL,* mannose-binding lectin.

configuration and the C1s subcomponent becomes an active enzyme, "C1 esterase." Certain bacteria, *Mycoplasma,* RNA viruses, and the lipid A component of bacterial endotoxin can activate C1q directly and trigger the full complement cascade.

As part of the innate immune response, broadly reactive "natural" antibodies and C-reactive protein, which reacts with carbohydrate from microorganisms and with dying cells, can substitute for specific antibody in the fixation of C1q and initiate reaction of the entire sequence. Endogenous agents, including uric acid crystals, amyloid deposits, DNA, and components of damaged cells such as apoptotic blebs and mitochondrial membranes, can activate C1q directly. But in this case, the ligand–C1q complex interacts strongly with the inhibitors C4-binding protein and factor H, allowing some C3-mediated opsonization and phagocytosis, but limiting the full inflammatory response typically triggered by microbes. C1q synthesized in the brain and retina enables the complement-dependent pruning of synapses that is essential for normal nervous system development.

There are 4 recognition molecules in the lectin pathway: MBL and ficolins 1, 2, and 3. MBL is the prototype of the collectin family of carbohydrate-binding proteins (lectins) that are believed to play an important part in innate, nonspecific immunity; its structure is homologous to that of C1q. These lectins, in association with MBL-associated serine proteases 1, 2, and 3 (MASPs 1/2/3), can bind to mannose, lipoteichoic acid, and other carbohydrates on the surface of bacteria, fungi, parasites, and viruses. MASPs then function there like C1s to cleave C4 and C2 and activate the complement cascade. The peptide C4a has weak "anaphylatoxin" activity and reacts with mast cells to release the chemical mediators of immediate hypersensitivity, including histamine. C3a and C5a, released later in the sequence, are potent anaphylatoxins, and C5a is also an important chemotactic factor. Fixation of C4b to the complex permits it to adhere to neutrophils, macrophages, B cells, dendritic cells, and erythrocytes. MASP-2 can activate clotting by generating thrombin from prothrombin, which could prevent microbial spread.

Cleavage of C3 and generation of C3b is the next step in the sequence. The serum concentration of C3 is the highest of any component, and its activation is the most crucial step in terms of biologic activity. Cleavage of C3 can be achieved through the **C3 convertase** of the classical pathway, C142, or of the alternative pathway, C3bBb. Once C3b is fixed to a complex or dead or dying host cell, it can bind to cells with receptors for C3b (complement receptor 1 [CR1]), including B lymphocytes, erythrocytes, and phagocytic cells (neutrophils, monocytes, and macrophages). Efficient **phagocytosis** of most microorganisms in vitro, especially by neutrophils, requires binding of C3 to the microbe. The severe pyogenic infections that commonly occur in C3-deficient patients indicate that phagocytosis in vivo is also inefficient without C3. The biologic activity of C3b is controlled by cleavage by **factor I** to iC3b, which promotes phagocytosis on binding to the **iC3b receptor (CR3)** on phagocytes. Further degradation of iC3b by factor I and proteases yields C3dg, then C3d; C3d binds to CR2 on B lymphocytes and thereby serves as a costimulator of antigen-induced B-cell activation.

ALTERNATIVE PATHWAY

The alternative pathway can be activated by C3b generated through classical pathway activity or proteases from neutrophils or the clotting system. It can also be activated by a form of C3 created by low-grade, spontaneous reaction of native C3 with a molecule of water, a "tick-over" that occurs constantly in plasma. Once formed, C3b or the hydrolyzed C3 can bind to any nearby cell or to factor B. Factor B attached to C3b in the plasma or on a surface can be cleaved to Bb by the protease factor D. The complex C3bBb becomes an efficient C3 convertase, which generates more C3b through an amplification loop. Properdin can bind to C3bBb, increasing stability of the enzyme and protecting it from inactivation by factors I and H, which modulate the loop and the pathway.

Certain "activating surfaces" promote alternative pathway activation if C3b is fixed to them, including bacterial teichoic acid or endotoxin, virally infected cells, antigen–immunoglobulin A complexes, and cardiopulmonary bypass and renal dialysis membranes. These surfaces act by protecting the C3bBb enzyme from the control otherwise exercised by factors I and H. Rabbit red blood cell membrane is such a surface, which serves as the basis for an assay of serum alternative pathway activity. Sialic acid on the surface of microorganisms or cells prevents formation of an effective alternative pathway C3 convertase by promoting activity of factors I and H. Nevertheless, significant activation of C3 can occur through the alternative pathway, and the resultant biologic activities are qualitatively the same as those achieved through activation by C142 (see Fig. 133-2).

MEMBRANE ATTACK COMPLEX

The sequence leading to cytolysis begins with the attachment of C5b to the C5-activating enzyme from the classical pathway, C4b2a3b, or from the alternative pathway, C3bBb3b. C6 is bound to C5b without being cleaved, stabilizing the activated C5b fragment. The C5b6 complex then dissociates from C423 and reacts with C7. C5b67 complexes must attach promptly to the membrane of the parent or a bystander cell, or they lose their activity. Next, C8 binds, and the C5b678 complex then promotes the addition of multiple C9 molecules. The C9 polymer of at least 3-6 molecules forms a transmembrane channel, and lysis ensues.

CONTROL MECHANISMS

Without control mechanisms acting at multiple points, there would be no effective complement system, and unbridled consumption of components would generate severe, potentially lethal damage to the host. At the 1st step, C1 inhibitor (C1 INH) inhibits C1r and C1s enzymatic activity and, thus, the cleavage of C4 and C2. C1 INH also inhibits MASP-2, factors XIa and XIIa of the clotting system, and kallikrein of the contact system. Activated C2 has a short half-life, and this relative instability limits the effective life of C42 and C423. The alternative pathway enzyme that activates C3, C3bBb, also has a short half-life, though it can be prolonged by the binding of properdin (P) to the enzyme complex. P can also bind directly to microbes and promote assembly of the alternative pathway C3 convertase.

Serum contains the enzyme carboxypeptidase N, which cleaves the N-terminus arginine from C4a, C3a, and C5a, thereby limiting their biologic activity. Factor I inactivates C4b and C3b; factor H accelerates inactivation of C3b by factor I; and an analogous factor, C4-binding protein (C4-bp), accelerates C4b cleavage by factor I, thus limiting assembly of the C3 convertase. Three protein constituents of cell membranes, CR1, membrane cofactor protein (MCP), and decay-accelerating factor (DAF), promote the disruption of C3 and C5 convertases assembled on those membranes. Another cell membrane-associated protein, CD59, can bind C8 or both C8 and C9 and thereby interfere with insertion of the membrane attack complex (C5b6789). The serum proteins vitronectin and clusterin can inhibit attachment of the C5b67 complex to cell membranes, bind C8 or C9 in a full membrane attack complex, or otherwise interfere with the formation or insertion of this complex. Vitronectin also promotes macrophage uptake of dying neutrophils. The genes for the regulatory proteins factor H, C4-bp, MCP, DAF, CR1, and CR2 are clustered on chromosome 1.

PARTICIPATION IN HOST DEFENSE

Neutralization of virus by antibody can be enhanced with C1 and C4 and further enhanced by the additional fixation of C3b through the classical or alternative pathway. Complement may, therefore, be particularly important in the early phases of a viral infection when antibody is limited. Antibody and the full complement sequence can also eliminate infectivity of at least some viruses by the production of typical complement "holes," as seen by electron microscopy. Fixation of C1q can opsonize (promote phagocytosis) through binding to the C1q receptor.

C4a, C3a, and C5a can bind to mast cells and thereby trigger release of histamine and other mediators, leading to vasodilation and the swelling and redness of inflammation. C5a can enhance macrophage phagocytosis of C3b-opsonized particles and induce macrophages to release the cytokines tumor necrosis factor and interleukin 1. C5a is a major chemotactic factor for neutrophils, monocytes, and eosinophils, which can efficiently phagocytize microorganisms opsonized with C3b

or cleaved C3b (iC3b). Further inactivation of cell-bound C3b by cleavage to C3d and C3dg removes its opsonizing activity, but it can still bind to B cells. Fixation of C3b to a target cell can enhance its lysis by natural killer cells or macrophages.

Insoluble immune complexes can be solubilized if they bind C3b, apparently because C3b disrupts the orderly antigen-antibody lattice. Binding C3b to a complex also allows it to adhere to C3 receptors (CR1) on red blood cells, which then transport the complexes to hepatic and splenic macrophages for removal. This phenomenon may at least partially explain the immune complex disease found in patients who lack C1, C4, C2, or C3.

The complement system serves to link the innate and adaptive immune systems. C4b or C3b coupled to immune complexes promotes their binding to antigen-presenting macrophages, dendritic cells, and B cells. Coupling of antigen to C3d allows binding to CR2 on B cells, which markedly reduces the amount of antigen needed to trigger an antibody response.

Neutralization of endotoxin in vitro and protection from its lethal effects in experimental animals require C1 INH and later-acting components of complement, at least through C6. Finally, activation of the entire complement sequence can result in lysis of virus-infected cells, tumor cells, and most types of microorganisms. Bactericidal activity of complement has not appeared to be important to host defense, except for the occurrence of *Neisseria* infections in patients lacking later-acting components of complement (see Chapter 134).

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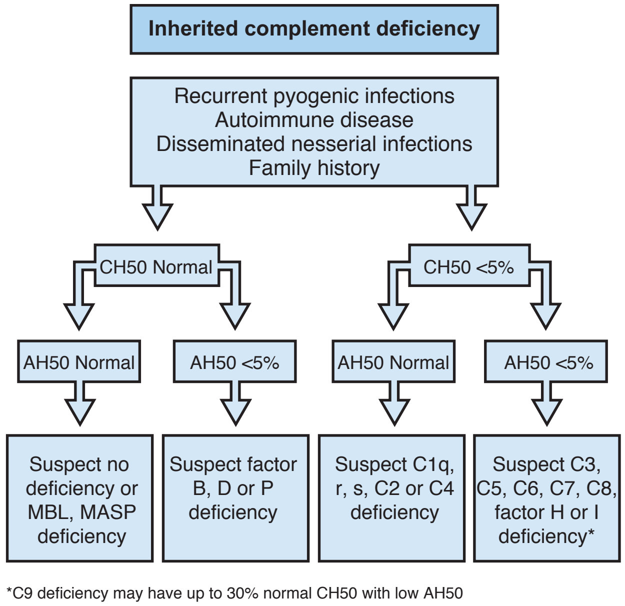

Figure 134-1 Flow chart for the evaluation of inherited complement deficiencies using hemolytic screening assays for the classical (CH_{50}) and alternative pathways (AH_{50}). For each assay, the entire activation pathway including the membrane attack complex (MAC) is required for lysis. *(Modified from Rich RR, Fleisher TA, Shearer WT, et al, editors,* Clinical immunology: principles and practice, *ed 4, Philadelphia, 2012, WB Saunders, Fig. 20-8, p. 262.)*

Chapter 134

Disorders of the Complement System

134.1 Evaluation of the Complement System

Richard B. Johnston Jr.

Testing for **total hemolytic complement activity (CH_{50})** effectively screens for most of the common diseases of the complement system. A normal result in this assay depends on the ability of all 11 components of the classical pathway and membrane attack complex to interact and lyse antibody-coated sheep erythrocytes. The dilution of serum that lyses 50% of the cells determines the end point. In **congenital deficiencies** of C1 through C8, the CH_{50} value is 0 or close to 0; in C9 deficiency, the value is approximately half-normal. Values in the acquired deficiencies vary with the type and severity of the underlying disorder. This assay does not detect deficiency of mannose-binding lectin (MBL), factors D or B of the alternative pathway, or properdin (Fig. 134-1). Deficiency of factors I or H permits consumption of C3, with partial reduction in the CH_{50} value. When clotted blood or serum sits at room temperature or warms, CH_{50} activity begins to decline, which leads to values that are falsely low but not zero. It is important to separate the serum and freeze it at −70°C (−94°F) by no more than 1 hr after blood draw.

In **hereditary angioedema,** depression of C4 and C2 during an attack significantly reduces the CH_{50}. Typically, C4 is low and C3 normal or slightly decreased. Concentrations of C1 inhibitor protein will be normal in 15% of cases; but C1 acts as an esterase, and the diagnosis can be established by showing increased capacity of patients' sera to hydrolyze synthetic esters.

A decrease in serum concentration of both C4 and C3 suggests activation of the **classical pathway** by immune complexes. Decreased C3 and normal C4 levels suggest activation of the **alternative pathway.** This difference is particularly useful in distinguishing nephritis secondary to immune complex deposition from that caused by NeF (nephritic factor). In the latter condition and in deficiency of factor I or H, factor B is consumed and C3 serum concentration is low. Alternative pathway activity can be measured with a relatively simple and reproducible hemolytic assay that depends on the capacity of rabbit erythrocytes to serve as both an activating (permissive) surface and a target of alternative pathway activity. This assay (**AP_{50}**) detects deficiency of properdin, factor D, and factor B. Immunochemical methods can be used to quantify individual components of all 3 pathways, guided by results of the screening hemolytic assays. It is possible to analyze the genes encoding most of the components.

A defect of complement function should be considered in any patient with recurrent angioedema, autoimmune disease (especially systemic lupus erythematosus [SLE]), chronic nephritis, hemolytic-uremic syndrome, or partial lipodystrophy, or with recurrent pyogenic infections, disseminated meningococcal or gonococcal infection, or a second episode of bacteremia at any age. A previously well adolescent or young adult with meningococcal meningitis caused by an uncommon serotype (not A, B, or C) should undergo screening for a late-component or alternative pathway deficiency with CH_{50} and AP_{50} assays.

Bibliography is available at Expert Consult.

134.2 Genetic Deficiencies of Complement Components

Richard B. Johnston Jr.

Congenital deficiencies of all 11 components of the classical-membrane attack pathway and of factor D and properdin of the alternative pathway are described in Table 134-1. All of the components of the

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Table 134-1 Genetic Deficiencies of Plasma Complement Components and Associated Clinical Findings

DEFICIENT COMPONENT	INFECTION*			AUTOIMMUNE/IMMUNE COMPLEX DISEASE*		
	VERY COMMON	COMMON	OCCASIONAL	VERY COMMON	COMMON	OCCASIONAL
CLASSICAL PATHWAY						
C1q			Pneumococcal B/M, other pyogenic	SLE	GN	DV/DLE
C1r, C1s, C1rs		Other pyogenic	Pneumococcal B/M, DGI	SLE	Other AD	GN
C4		Other pyogenic		SLE	GN, other AD	
C2		Other pyogenic, pneumococcal B/M, meningococcal M			SLE, GN, DV/DLE, other AD	
C3	Other pyogenic	Pneumococcal B/M, meningococcal M			GN, DV/DLE	SLE, other AD
C5	Meningococcal M	DGI	Other pyogenic			SLE, GN
C6	Meningococcal M	DGI	Other pyogenic			SLE, GN, other AD
C7	Meningococcal M		DGI, other pyogenic		SLE, other AD	
C8	Meningococcal M	DGI	Other pyogenic			SLE, GN
C9		Meningococcal M				
LECTIN PATHWAY						
MBL			Other pyogenic, fungal, HIV			SLE
MASP-2			Pneumococcal pneumonia			SLE
Ficolin-3			Other pyogenic			
ALTERNATIVE PATHWAY						
Factor D	DGI, meningococcal M, other pyogenic					
CONTROL PROTEINS						
C1 INH	Hereditary angioedema†					SLE
Factor I	Other pyogenic, meningococcal M	Pneumococcal B/M				
Factor H		Meningococcal B/M	Other pyogenic		GN, aHUS	SLE
Properdin		Meningococcal M	Pneumococcal B/M, other pyogenic		DV/DLE	
C4-binding protein						Other AD

*A finding was reported as "very common" if it occurred in 50% or more of reported cases, "common" if reported in approximately 5-50% of cases, and "occasional" if present in 1 or 2 cases or <5% of the more frequent deficiencies.

†Hereditary angioedema is not typically associated with infection or autoimmunity.

aHUS, atypical hemolytic-uremic syndrome; B/M, bacteremia and/or meningitis; DGI, disseminated gonococcal infection; DV/DLE, dermal vasculitis or typical discoid lupus erythematosus; GN, glomerulonephritis in various forms, often membranoproliferative; HIV, human immunodeficiency virus; M, meningitis; MASP, MBL-associated serine protease; MBL, mannose-binding lectin; other AD, autoimmune disease (almost all possible diagnoses have been reported); other pyogenic, serious deep or systemic infection caused by, or typically caused by, a pyogenic bacterium (abscess, osteomyelitis, pneumonia, bacteremia other than pneumococcal, meningitis other than meningococcal or pneumococcal, cellulitis, myopericarditis, and peritonitis); SLE, typical systemic lupus erythematosus or an SLE-like syndrome without characteristic serologic findings.

Data from Figueroa JE, Densen P: Infectious diseases associated with complement deficiencies, Clin Microbiol Rev *4:359–395, 1991; Ross SC, Densen P: Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency,* Medicine (Baltimore) *63:243–273, 1984; and other cases and series reported to date.*

classical and alternative pathways except properdin are inherited as autosomal recessive codominant traits. Each parent transmits a gene that codes for synthesis of half the serum level of the component. Deficiency results from inheritance of 1 null gene from each parent; the hemizygous parents typically have low normal CH_{50} levels and no consequences of the partial deficiency. Properdin deficiency is transmitted as an X-linked trait.

Most patients with primary **C1q deficiency** have SLE; some have an SLE-like syndrome without typical SLE serology, a chronic rash with underlying vasculitis, or membranoproliferative glomerulonephritis (MPGN). Some C1q-deficient children have serious infections, including septicemia and meningitis. Individuals with **C1r, C1s, combined C1r/C1s, C4, C2,** or **C3 deficiency** also have a high incidence of autoimmune syndromes (see Table 134-1), especially SLE or an SLE-like syndrome without an elevated antinuclear antibody level.

C4 is encoded by 2 genes, *C4A* and *C4B*. **C4 deficiency** represents absence of both gene products. Complete deficiency of only C4A, present in approximately 1% of the population, also predisposes to SLE, although C4 levels are only partially reduced. Patients with only C4B deficiency may be predisposed to infection. A few patients with **C5, C6, C7,** or **C8 deficiency** have SLE, but recurrent meningococcal infections are much more likely to be the major problem.

There are at least 2 possible reasons for the concurrence of complement component deficiencies, especially C1, C4, C2, or C3 deficiency, and autoimmune–immune complex diseases. First, deposition of C3 on autoimmune complexes facilitates their removal from the circulation through binding to complement receptor 1 (CR1) on erythrocytes and transport to the spleen and liver. Second, the early components, particularly C1q and C3, expedite the clearance of necrotic and apoptotic cells, which are sources of autoantigens.

Individuals with **C2 deficiency** carry the risk of life-threatening septicemic illnesses, most commonly caused by pneumococci. However, most have not had problems with increased susceptibility to infection, presumably because of the protective function of the alternative pathway. The genes for C2, factor B, and C4 are situated close to each other on chromosome 6, and a partial depression of factor B levels can occur in conjunction with C2 deficiency. Persons with a deficiency of both proteins may be at particular risk.

Because C3 can be activated by C142 or by the alternative pathway, a defect in the function of either pathway can be compensated for, at least to some extent. Without C3, however, opsonization of bacteria is inefficient, and the chemotactic fragment from C5 (C5a) is not generated. Some organisms must be well opsonized in order to be cleared, and genetic **C3 deficiency** has been associated with recurrent, severe pyogenic infections caused by pneumococci, *Haemophilus influenzae*, and meningococci.

More than half of the individuals reported to have congenital **C5, C6, C7,** or **C8 deficiency** have had meningococcal meningitis or extragenital gonococcal infection. Patients with **C9 deficiency**, which is most often reported in individuals of Japanese descent, retain about one-third normal CH_{50} titers; some of these patients have also had *Neisseria* disease. In studies of patients 10 yr of age and older with systemic meningococcal disease, 3-15% have had a genetic deficiency of C5, C6, C7, C8, C9, or properdin. Among patients with infections caused by the uncommon *Neisseria meningitidis* serogroups (X, Y, Z, W135, 29E, or nongroupable; not A, B, or C), 33-45% have an underlying complement deficiency. It is not clear why patients with a deficiency of 1 of the late-acting components suffer a particular predisposition to *Neisseria* infections. It may be that serum bacteriolysis is uniquely important in defense against this organism. Many persons with such a deficiency have no significant illness.

A few individuals have been identified with **deficiency of factor D** of the alternative pathway, all with recurrent infections, most often neisserial. Hemolytic complement activity and C3 levels in their serum were normal, but alternative pathway activity was markedly deficient or absent.

Mutations in the structural gene encoding MBL or polymorphisms in the promoter region of the gene result in pronounced interindividual variation in the level of circulating MBL. More than 90% of individuals with **MBL deficiency** do not express a predisposition to infection. Those with a very low level of MBL have a predisposition to recurrent respiratory infections in infancy and to serious pyogenic and fungal infections if there is another underlying defect of host defense. MBL-associated serine protease (**MASP)-2 deficiency** has been reported with SLE-like symptoms and recurrent pneumococcal pneumonia. Homozygous **ficolin-3 deficiency** is associated with repeated pneumonia since early childhood, cerebral abscesses, and bronchiectasis.

Bibliography is available at Expert Consult.

134.3 Deficiencies of Plasma, Membrane, or Serosal Complement Control Proteins

Richard B. Johnston Jr.

Congenital deficiencies of 5 plasma complement control proteins have been described (see Table 134-1). **Factor I deficiency** was reported originally as a deficiency of C3 resulting from hypercatabolism. The first patient described had suffered a series of severe pyogenic infections similar to those associated with agammaglobulinemia or congenital deficiency of C3. Factor I is an essential regulator of both pathways. Its deficiency permits prolonged existence of C3b as a part of the C3 convertase of the alternative pathway, C3bBb. This results in constant activation of the alternative pathway and cleavage of more C3 to C3b, in circular fashion. Intravenous infusion of plasma or purified factor I induced a prompt rise in serum C3 concentration in the patient and a return to normal of in vitro C3-dependent functions such as opsonization.

The effects of **factor H deficiency** are like those of factor I deficiency because factor H also assists in dismantling the alternative pathway C3 convertase. A trigger event such as infection initiates uninhibited continuous activation of the alternative pathway, which consumes C3, factor B, total hemolytic activity, and alternative pathway activity. Patients have sustained systemic infections due to pyogenic bacteria, particularly *N. meningitidis*. Many have had glomerulonephritis or atypical hemolytic uremic syndrome (aHUS) (see Chapter 518). Mutations in genes encoding membrane cofactor protein (MCP; CD46), factors I or B, C3, or the endothelial antiinflammatory protein thrombomodulin, or autoantibodies to factors H or B, also are associated with aHUS. The majority of patients with factor H deficiency and aHUS, typically younger than 2 yr of age, develop end-stage renal disease or die. The few patients thus far reported as having **C4-binding protein deficiency** have approximately 25% of the normal levels of the protein and no typical disease presentation, although 1 had angioedema and Behçet disease.

Persons with **properdin deficiency** have a striking predisposition to *N. meningitidis* meningitis. All reported patients have been male. The predisposition to infection in these patients demonstrates clearly the need for the alternative pathway in defense against bacterial infection. Serum hemolytic complement activity is normal in these patients, and if the patient has specific antibacterial antibody from immunization or prior exposure, the need for the alternative pathway and properdin is greatly reduced. Several patients have had dermal vasculitis or discoid lupus.

Hereditary angioedema occurs in persons unable to synthesize normal levels of active C1 inhibitor (C1 INH). In 85% of affected families, the patient has markedly reduced concentrations of inhibitor, averaging 30% of normal; the other 15% have normal or elevated concentrations of an immunologically cross-reacting but nonfunctional protein. Both forms of the disease are transmitted as autosomal dominant traits. C1 INH suppresses the complement proteases C1rs and MASP-2 and the activated proteases of the contact and fibrinolysis systems. In doing so, C1 INH is consumed as a "suicide inhibitor." In the absence of full C1 INH function, activation of any of these proteases tips the balance toward the protease. This activation leads to uncontrolled C1 and kallikrein activity with breakdown of C4 and C2 and release of bradykinin, which interacts with vascular endothelial cells to cause vasodilation, which produces localized, nonpitting edema. The biochemical triggers that induce attacks of angioedema in these patients are not well understood.

Swelling of the affected part progresses rapidly, without urticaria, itching, discoloration, or redness and often without severe pain. Swelling of the intestinal wall, however, can lead to intense abdominal cramping, sometimes with vomiting or diarrhea. Concomitant subcutaneous edema is often absent, and patients have undergone abdominal surgery or psychiatric examination before the true diagnosis was established. Laryngeal edema can be fatal. Attacks last 2-3 days and then gradually abate. They may occur at sites of trauma, especially dental, after vigorous exercise, or with menses, fever, or emotional stress. Attacks begin in the 1st 5 yr of life in almost half of patients, but are usually not severe until late childhood or adolescence. **Acquired C1 INH deficiency** can occur in association with B-cell cancer or autoantibody to C1 INH. SLE and glomerulonephritis have been reported in patients with the congenital disease.

Three of the membrane complement control proteins—CR1, MCP (CD46), and decay-accelerating factor (DAF)—prevent the formation of the full C3-cleaving enzyme, C3bBb, which is triggered by C3b deposition. CD59 (membrane inhibitor of reactive lysis) prevents the full development of the membrane attack complex that creates the "hole." **Paroxysmal nocturnal hemoglobinuria** (PNH) is a hemolytic anemia that occurs when DAF and CD59 are not expressed on the erythrocyte surface. The condition is acquired as a somatic mutation in a hematopoietic stem cell of the *PIG-A* gene on the X chromosome. The product of this gene is required for normal synthesis of a

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glycosyl-phosphatidylinositol molecule that anchors about 20 proteins to cell membranes, including DAF and CD59. One patient with **genetic isolated CD59 deficiency** had a mild PNH-like disease in spite of normal expression of membrane DAF. In contrast, **genetic isolated DAF deficiency** has not resulted in hemolytic anemia.

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134.4 Secondary Disorders of Complement

Richard B. Johnston Jr.

Partial deficiency of C1q has occurred in patients with severe combined immunodeficiency disease or hypogammaglobulinemia, apparently secondary to the deficiency of immunoglobulin (Ig) G, which normally binds reversibly to C1q and prevents its rapid catabolism.

Chronic MPGN can be caused by NeF, an IgG autoantibody to the C3-cleaving enzyme of the alternative pathway, C3bBb, which protects the enzyme from inactivation and promotes over activation of the alternative pathway. The result is increased consumption of C3 and decreased concentration of serum C3. Pyogenic infections, including meningitis, may occur if the serum C3 level drops to <10% of normal. This disorder has been found in children and adults with **partial lipodystrophy**. Adipocytes are the main source of factor D and synthesize C3 and factor B; exposure to NeF induces their lysis. An IgG NeF that binds to and inhibits the breakup of C42, the classical pathway C3 convertase, has been described in acute postinfectious nephritis and in SLE. The consumption of C3 that characterizes poststreptococcal nephritis and SLE could be caused by this factor, by complement activation by immune complexes, or by both.

Newborn infants have mild to moderate reductions in all plasma components of the complement system. Opsonization and generation of chemotactic activity in serum from full-term newborns can be markedly deficient through either the classical or alternative pathway. Complement activity is even lower in preterm infants. Patients with severe chronic cirrhosis of the liver, hepatic failure, malnutrition, or anorexia nervosa can have significant deficiency of complement components and functional activity. Synthesis of components is depressed in these conditions, and serum from some patients with malnutrition also contains immune complexes that could accelerate depletion.

Patients with **sickle cell disease** have normal activity of the classical pathway, but some have defective function of the alternative pathway in opsonization of pneumococci, in bacteriolysis and opsonization of *Salmonella,* and in lysis of rabbit erythrocytes. Deoxygenation of erythrocytes from patients with sickle cell disease alters their membranes to increase exposure of phospholipids that can activate the alternative pathway and consume its components. This activation is accentuated during painful crisis. Children with nephrotic syndrome may have decreased serum levels of factors B and D and subnormal serum opsonizing activity.

Immune complexes initiated by microorganisms or their by-products can induce complement consumption. Activation occurs primarily through fixation of C1 and initiation of the classical pathway. Formation of immune complexes and consumption of complement have been demonstrated in lepromatous leprosy, bacterial endocarditis, infected ventriculojugular shunts, malaria, infectious mononucleosis, dengue hemorrhagic fever, and acute hepatitis B. Nephritis or arthritis can develop as a result of deposition of immune complexes and activation of complement in these infections. In SLE, immune complexes activate C142, and C3 is deposited at sites of tissue damage, including kidneys and skin; depressed synthesis of C3 is also noted. The syndrome of recurrent urticaria, angioedema, eosinophilia, and hypocomplementemia secondary to activation of the classical pathway may be due to autoantibody to C1q and circulating immune complexes. Circulating immune complexes and decreased C3 have been reported in some patients with dermatitis herpetiformis, celiac disease, primary biliary cirrhosis, and Reye syndrome.

Circulating bacterial products in sepsis or tissue factors released after severe trauma can initiate activation of the classical and alternative pathways, leading to increased serum levels of C3a, C5a, and C5b-9 and systemic inflammatory response syndrome and multiple organ failure. C5a and its receptors, particularly on neutrophils, appear to be central to the pathogenesis of systemic inflammatory response syndrome. Intravenous injection of iodinated roentgenographic contrast medium can trigger a rapid and significant activation of the alternative pathway, which may explain the occasional reactions that occur in patients undergoing this procedure.

Burns can induce massive activation of the complement system, especially the alternative pathway, within a few hours after injury. Resulting generation of C3a and C5a stimulates neutrophils and induces their sequestration in the lungs, leading to shock lung. Cardiopulmonary bypass, extracorporeal membrane oxygenation, plasma exchange, or hemodialysis using cellophane membranes may be associated with a similar syndrome as a result of activation of plasma complement, with release of C3a and C5a. In patients with erythropoietic protoporphyria or porphyria cutanea tarda, exposure of the skin to light of certain wavelengths activates complement, generating chemotactic activity. This chemotactic activity leads to lysis of capillary endothelial cells, mast cell degranulation, and the appearance of neutrophils in the dermis.

Some tumor cells can avoid complement-mediated lysis by overexpressing DAF, MCP, CD59, CR1, or factor H, or by secreting proteases that cleave tumor-bound C3b. Microorganisms have evolved similar evasive mechanisms; for example, HIV-1 particles budding from infected cells acquire the membrane proteins DAF and CD59, and staphylococci can produce multiple complement inhibitors.

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134.5 Treatment of Complement Disorders

Richard B. Johnston Jr.

No specific therapy is available at present for genetic deficiencies of the components of the classical, alternative, and lectin complement pathways. Much can be done, however, to protect patients with any of these disorders from serious complications; and specific treatment is available for 3 disorders caused by control-protein deficiencies, hereditary angioedema, aHUS, and PNH.

Management of hereditary angioedema starts with avoidance of precipitating factors, usually trauma. Infusion of C1 INH concentrate (nanofiltered C1-esterase inhibitor), an inhibitor of kallikrein (ecallantide) that blocks bradykinin production, and an antagonist of the bradykinin receptor (icatibant) are approved in the United States for use in adolescents and adults for long-term prophylaxis, preparation for surgery or dental procedures, or treatment of acute attacks. The synthetic androgen oxandrolone increases the level of functional C1 INH severalfold and is approved for cautious use in children. Antihistamines, adrenalin, and corticosteroids have no effect. Eculizumab, a humanized monoclonal antibody to C5, is an effective treatment for PNH and aHUS.

Effective supportive management is available for other primary diseases of the complement system, and identification of a specific defect in the complement system can have an important impact on management. Concern for the associated complications such as autoimmune disease and infection should encourage vigorous diagnostic efforts and earlier institution of therapy. Individuals with SLE and a complement defect generally respond as well to therapy as do those without complement deficiency. With the onset of unexplained fever, cultures should be obtained and antibiotic therapy instituted more quickly and with less stringent indications than in a normal child. The parent or patient should be given letters describing any predisposition to systemic bacterial infection or autoimmune disease associated with the patient's deficiency, along with the recommended approach to management, for possible use by school, camp, or emergency room physicians. The

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patient and close household contacts should be immunized against *H. influenzae, Streptococcus pneumoniae,* and *N. meningitidis.* High titers of specific antibody might opsonize effectively without the full complement system, and immunization of household members could reduce the risk of exposing patients to these particularly threatening pathogens. Repeat immunization of patients is advisable since complement deficiency can be associated with a blunted or shorter-lived antibody response than normal.

Considering the many conditions in which complement is a central mediator of disease, there is an intensive effort to develop therapeutic complement inhibitors. These include soluble CR1 and inhibitors of C5 convertase and C3a and C5a binding. Heparin, which inhibits both classical and alternative pathways, has been used to prevent "post-pump syndrome."

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Section 5

Hematopoietic Stem Cell Transplantation

Chapter 135

Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation

Andrea Velardi and Franco Locatelli

Thousands of children have received an infusion of either **allogeneic** (from a donor) or **autologous** (from the same individual) hematopoietic stem cells to cure both malignant and nonmalignant disorders. **Autologous** transplantation is employed as a rescue strategy after delivering otherwise lethal doses of radiotherapy and chemotherapy in children with hematologic malignancies such as relapsed lymphoma or selected solid tumors (e.g., neuroblastoma, brain tumors). **Allogeneic** transplantation is used to treat children with genetic diseases of blood cells, such as thalassemia and primary immunodeficiency diseases, as well as hematologic malignancies, such as leukemia and myelodysplastic syndromes. Since 1968 and for many years, bone marrow has represented the only source of hematopoietic progenitors employed. Growth factor (granulocyte colony-stimulating factor)–mobilized peripheral blood hematopoietic stem cells and umbilical cord blood hematopoietic progenitors have been more recently introduced in the clinical practice to perform hematopoietic stem cell transplantation (HSCT).

An human leukocyte antigen (HLA)–matched sibling was once the only type of donor employed. Today, matched unrelated volunteers, full-haplotype mismatched family members, and unrelated cord blood donors have been largely employed to transplant patients lacking an HLA-identical relative.

Protocols for allogeneic HSCT consist of 2 parts: the preparative regimen and transplantation itself. During the **preparative conditioning regimen,** chemotherapy, often associated with irradiation, is administered to destroy the patient's hematopoietic system and to suppress the immune system, especially T cells, so that graft rejection is prevented. In patients with malignancies, the preparative regimen also serves to significantly reduce the tumor burden. The patient then receives an intravenous infusion of hematopoietic cells from the donor. Less-aggressive conditioning regimens, known as reduced intensity conditioning regimens, are also used in pediatric patients. These regimens are mainly immune-suppressive and aim at inducing a state of reduced immune competence of the recipient permitting to avoid the rejection of donor cells.

The immunology of HSCT is distinct from that of other types of transplant because, in addition to stem cells, the graft contains mature blood cells of donor origin, including T cells, B cells, natural killer cells, and dendritic cells. These cells repopulate the recipient's lymphohematopoietic system and give rise to a new immune system, which helps eliminate residual leukemia cells that survive the conditioning regimen. This effect is known as the **graft-versus-leukemia (GVL) effect.**

The donor immune system exerts its T-cell–mediated GVL effect through alloreactions directed against not shared recipient histocompatibility antigens displayed on recipient leukemia cells. Because some of these histocompatibility antigens are also displayed on tissues, however, T-cell–mediated alloreactions may ensue. Specifically, donor alloreactive cytotoxic CD8+ effector T cells may attack recipient tissues—in particular, the skin, gastrointestinal tract, and liver—causing acute graft-versus-host disease (GVHD), a condition of varying severity, that, in some cases, can be life-threatening or even fatal (see Chapter 137). Although the main benefit for allogeneic HSCT recipients with leukemia derives from the GVL effect displayed by immune-competent cells, disease recurrence remains the main cause of treatment failure. The risk of failing to eradicate leukemia is influenced by many variables, including disease phase, molecular lesions of tumor cells, and disparity for major or minor histocompatibility antigens in the donor/recipient pairs. Strategies for rescuing patients experiencing disease recurrence are mainly based on either second transplantation or infusion of donor leukocytes. To overcome the hurdle of tumor elusion caused by HLA-loss on malignant cells, the use of non-HLA–restricted chimeric antigen receptors (CARs) has been envisaged. This therapeutic strategy is based on genetic reprogramming of T cells through artificial immune receptors that reproducibly and efficiently redirect the antigen specificity of polyclonal T lymphocytes toward target antigens expressed by leukemic cells. When expressed by T cells, CARs mediate antigen recognition and tumor cytolysis in an major histocompatibility complex (MHC)–unrestricted fashion, and can target any molecule (protein, carbohydrate, or glycolipid) expressed on the surface of tumor cells, thus bypassing one of the major tumor escape mechanisms based on the down regulation of MHC molecules. CARs are composed of an extracellular specific antigen-binding moiety, obtained from the variable regions of a monoclonal antibody, linked together to form a single-chain antibody (scFv), and of an intracellular signaling component derived from the ζ chain of the T-cell–receptor–CD3 complex. The addition to the CAR gene construct of costimulation signals and cytokines promoting T-cell expansion and/or survival improves the antitumor efficiency of the engineered T cells and their survival in the tumor milieu. Gamma retrovirus and lentiviruses are usually used to transduce CARs into T lymphocytes to be employed in the clinical setting. These vectors have been shown to efficiently infect T lymphocytes, integrate into the host genome and produce robust expression of the gene in human T cells and their progeny.

The success of allogeneic HSCT is undermined by diversity between donors and recipients in major and minor histocompatibility antigens. MHC molecules, the HLA-A, HLA-B, and HLA-C MHC class I molecules, present peptides to CD8+ T cells, while the HLA-DR, HLA-DQ, and HLA-DP MHC class II molecules present peptides to CD4+ T cells. There are hundreds of variant forms of each class I and class II molecule, and even small differences can elicit alloreactive T-cell

responses that mediate graft rejection and/or GVHD. Disparities for HLA-A, -B, -C, or -DRB1 alleles in the donor–recipient pair are independent risk factors for both acute and chronic GVHD.

Minor histocompatibility antigens derive from differences between the HLA-matched recipient and donor in peptides that are presented by the same HLA allotype. They are a result of polymorphisms of non-HLA proteins, of differences in the level of expression of proteins, or of genetic differences between males and females. An example of the latter is represented by the H-Y antigens encoded by the Y chromosome, which can stimulate GVHD when a female donor is employed to transplant an HLA-identical male recipient. Thus, from this evidence, it is clear that GVHD may occur even when the donor and recipient are HLA identical.

The optimal donor for any patient undergoing HSCT is an HLA-identical sibling. Because polymorphic HLA genes are closely linked and usually constitute a single genetic locus, any pair of siblings has a 25% chance of being HLA identical. Thus, also in view of the limited family size in the developed countries, less than 25-30% of patients in need of an allograft can receive their transplant from an HLA-identical sibling. This percentage is even lower in patients with inherited disorders.

HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM AN HLA-IDENTICAL SIBLING DONOR

Allogeneic HSCT from an HLA-compatible sibling is the treatment of choice for children with hematological malignancies and congenital diseases (Table 135-1). Best results are achieved in patients with congenital or acquired non-malignant disorders because the risk of disease recurrence is low and the cumulative transplantation-related mortality is lower than in children receiving transplants for hematologic malignancies.

ACUTE LYMPHOBLASTIC LEUKEMIA

Allogeneic HSCT is used for pediatric patients with acute lymphoblastic leukemia (ALL), either in the first complete remission when a child is considered to be at high risk of leukemia recurrence (such as, e.g., those carrying poor-risk cytogenetic characteristics or with high levels of minimal residual disease), or in second or further complete remission after previous marrow relapse. ALL is the most common indication for HSCT in childhood. Several patient-, donor-, disease-, and transplant-related variables may influence the outcome of patients with ALL given an allogeneic HSCT. The long-term probabilities of event-free survival for patients with ALL transplanted in the 1st or 2nd complete remission is 60–70% and 40-60%, respectively. Inferior results are obtained in patients receiving transplants in more advanced disease phases. The use of radiotherapy, total body irradiation, during the preparative regimen offers an advantage in terms of better event-free survival compared to a regimen consisting of cytotoxic drugs alone (Fig. 135-1), but it can induce more long-term side effects. Less-intensive GVHD prophylaxis is also associated with a better outcome. Bone marrow is still the preferred source of stem cells to be employed for transplantation.

ACUTE MYELOID LEUKEMIA

Allogeneic HSCT from an HLA-identical sibling is largely employed as postremission treatment of pediatric patients with acute myeloid leukemia (AML). In fact, many studies show that children with AML in 1st complete remission who are given allogeneic HSCT as consolidation therapy have a better probability of event-free survival than those treated with either chemotherapy alone or with autologous transplantation. Results obtained in patients given HSCT from an HLA-identical sibling after either a total body irradiation–containing or a chemotherapy-based preparative regimen are similar, the probability of event-free survival being in the order of 70%. Children with acute promyelocytic leukemia in molecular remission at the end of treatment with chemotherapy and all-*trans*-retinoic acid, or with AML and either translocation t(8;21) or inversion of chromosome 16 (inv16) are no longer considered eligible for allogeneic HSCT in 1st complete remission in view of their excellent prognosis with alternative treatments. Studies suggest restricting the use of HSCT to those patients with poor molecular lesions, such as FLT3-internal tandem duplication, or mixed lineage leukemia abnormalities, or with high levels of minimal residual disease at time the end of induction therapy. Approximately 40% of pediatric patients with AML in the second complete remission can be rescued by an allograft from an HLA-identical sibling.

Table 135-1 Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Acute lymphoblastic leukemia

First complete remission for patients at very high risk of relapse
- Translocation t(9;22) or t(4;11)
- Early thymocyte precursor phenotype
- Nonresponder after 1 wk of corticosteroid therapy and
  - T-immunophenotype or
  - >100,000 cells/μL at diagnosis
- Not in remission at the end of the induction phase
- Marked hypodiploidy (<43 chromosomes)
- High levels of minimal residual disease at the end of induction therapy

Second complete remission

Third or later complete remission
- Acute myeloid leukemia in 1st complete remission or in advanced disease phase
- Philadelphia chromosome–positive chronic myeloid leukemia
- Myelodysplastic syndromes
- Hodgkin and non-Hodgkin lymphomas
- Selected solid tumors
  - Metastatic neuroblastoma
  - Rhabdomyosarcoma refractory to conventional treatment
  - Very-high-risk Ewing sarcoma
- Severe acquired aplastic anemia
- Fanconi anemia
- Congenital dyskeratosis
- Diamond-Blackfan anemia
- Thalassemia major
- Sickle cell disease
- Variants of severe combined immunodeficiency
- Hyperimmunoglobulin M syndrome
- Leukocyte adhesion deficiency
- Omenn syndrome
- Wiskott-Aldrich syndrome
- Chédiak-Higashi syndrome
- Kostmann syndrome (infantile malignant agranulocytosis), chronic granulomatous disease and other severe neutrophil defects
- X-linked lymphoproliferative disease (Duncan syndrome)
- Hemophagocytic lymphohistiocytosis
- Selected severe variants of platelet function disorders (e.g., Glanzmann thromboasthenia, or congenital amegakaryocytic thrombocytopenia)
- Selected types of mucopolysaccharidosis (Hurler disease) or other liposomal/peroxisomal disorders (Krabbe disease, adrenoleukodystrophy)
- Infantile malignant osteopetrosis
- Life-threatening cytopenia unresponsive to conventional treatments

CHRONIC MYELOGENOUS LEUKEMIA

For many yr, allogeneic HSCT has been considered to be the only proven curative treatment for children with Philadelphia-positive (Ph+) chronic myelogenous leukemia. Leukemia-free survival of chronic myelogenous leukemia patients after an allograft is 45-80%, the phase of disease (chronic phase, accelerated phase, blast crisis), recipient age, type of donor employed (either related or unrelated), and time interval between diagnosis and HSCT being the main factors influencing the outcome. The best results are obtained in children transplanted during the chronic phase from an HLA-identical sibling within 1 year from diagnosis. Treatment with the specific BCR-ABL tyrosine protein kinase inhibitors (imatinib mesylate, dasatinib,

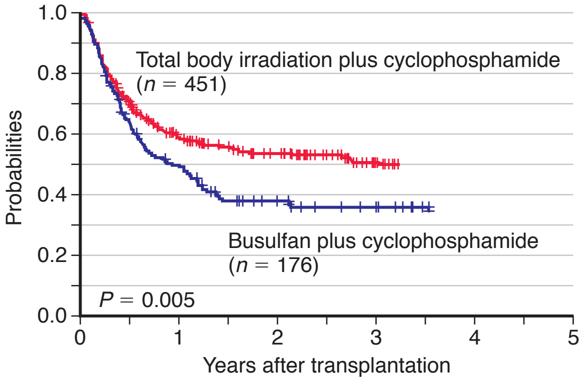

Figure 135-1 Cumulative probability of leukemia-free survival after HLA-identical sibling bone marrow transplantation for childhood acute lymphoblastic leukemia, by pretransplantation conditioning regimen of total body irradiation (TBI) plus cyclophosphamide (CY) *(upper line)* or busulfan (Bu) plus cyclophosphamide *(lower line).* There was superior survival with the TBI plus cyclophosphamide regimen. *(From Davies S, Ramsay NK, Klein JP, et al: Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia.* J Clin Oncol *18:340–347, 2000.)*

nilotinib), targeting the enzymatic activity of the BCR-ABL fusion protein, could modify the natural history of the disease and, thus, the indications for transplantation. Infusion of donor leukocytes can re-induce a state of complete remission in a large proportion of patients experiencing leukemia relapse.

JUVENILE MYELOMONOCYTIC LEUKEMIA

This is a rare hematopoietic malignancy of early childhood, representing 2–3% of all pediatric leukemias. Juvenile myelomonocytic leukemia (JMML) is characterized by hepatosplenomegaly and organ infiltration, with excessive proliferation of cells of monocytic and granulocytic lineages. Hypersensitivity to granulocyte-macrophage colony-stimulating factor and pathologic activation of the RAS-RAF-MAP (mitogen-activated protein) kinase signaling pathway play an important role in the pathophysiology. JMML usually runs an aggressive clinical course, with a median duration of survival for untreated children of <12 mo from diagnosis. Rare patients with *CBL-1* or *N-RAS* mutations can survive for years without an allograft. HSCT is able to cure approximately 50-60% of patients with JMML. Patients who receive a transplant from an unrelated donor have comparable outcome to those given HSCT from an HLA-compatible related donor. Cord blood transplantation represents a suitable alternative option for those patients with either a related or an unrelated donor. Leukemia recurrence is the main cause of treatment failure in children with JMML after HSCT, the relapse rate being as high as 40-50%. Because children with JMML frequently have massive spleen enlargement, splenectomy has been performed before transplantation. Spleen size at the time of HSCT and splenectomy before HSCT do not appear to affect the post-transplantation outcome. Although donor leukocyte infusion is not useful to rescue patients experiencing disease recurrence, a second allograft can induce sustained remission in approximately one-third of children with JMML relapsing after a 1st HSCT.

MYELODYSPLASTIC SYNDROMES OTHER THAN JUVENILE MYELOMONOCYTIC LEUKEMIA

Myelodysplastic syndromes are a heterogeneous group of clonal disorders characterized by ineffective hematopoiesis leading to peripheral blood cytopenia and a propensity to evolve toward AML. HSCT is the treatment of choice for children with refractory anemia with excess of blasts (RAEB) and for those with RAEB in transformation (RAEB-t). The probability of survival without evidence of disease for these children is 60% if the donor is an HLA-identical sibling, whereas that of patients transplanted from an alternative donor is slightly lower. It is still unclear whether patients with myelodysplastic syndromes and a blast percentage >20% benefit from pretransplantation chemotherapy. HSCT from an HLA-identical sibling is also the preferred treatment for all children with refractory cytopenia. Transplantation from an alternative donor is also employed in children with refractory cytopenia associated with monosomy 7, complex karyotype, life-threatening infections, profound neutropenia, or transfusion-dependency. For children with refractory cytopenia, the probability of event-free survival after HSCT may be as high as 80%, disease recurrence being rarely observed. This observation has provided the rationale for testing reduced-intensity regimens in these patients.

NON-HODGKIN LYMPHOMA AND HODGKIN DISEASE

Childhood non-Hodgkin lymphoma (NHL) and Hodgkin disease (HD) are quite responsive to conventional chemoradiotherapy, but some of these patients are at high risk for relapse. HSCT can cure a proportion of patients with relapsed NHL and HD and should be offered early after relapse, while the disease is still sensitive to therapy. If an HLA-identical sibling is available, allogeneic transplantation should be offered to patients with NHL to take advantage of the GVL effect. Patients with sensitive disease and limited tumor burden have favorable outcomes, with event-free survival rates of 50-60%. Studies also suggest that patients with HD can benefit from a GVL effect when given an allograft.

ACQUIRED APLASTIC ANEMIA

HSCT from an HLA-identical sibling is the treatment of choice for children with the severe form of acquired aplastic anemia, defined as 2 of the following: platelet count <20,000/mm^3, absolute neutrophil count <500/mm^3, or reticulocyte count <1% when anemia is present, together with hypoplastic bone marrow (<20% total cellularity). The probability of survival with sustained donor engraftment for these patients is <85-90%, younger patients having even better outcomes. Every child diagnosed with severe acquired aplastic anemia should undergo HLA-typing as early as possible in order to identify a suitable HLA-compatible family donor. Graft rejection represents the most important cause of treatment failure. Blood transfusion should be avoided whenever possible because sensitization to blood products increases the likelihood of graft rejection. GVHD prophylaxis combining cyclosporine and short-term methotrexate is associated with a better outcome as compared to cyclosporine alone (Fig. 135-2). Some studies suggest that the addition of antithymocyte globulin to the classical conditioning regimen consisting of cyclophosphamide (200 mg/kg) can reduce the risk of graft rejection, particularly in patients with previous heavy sensitization to blood products. The use of granulocyte colony-stimulating factor mobilized peripheral blood progenitors has provided inferior results with respect to the infusion of bone marrow cells, since it is associated with an increased risk of chronic GVHD.

CONSTITUTIONAL APLASTIC ANEMIA

Fanconi anemia and **dyskeratosis congenita** are genetic disorders associated with a high risk of developing pancytopenia. Fanconi anemia is an autosomal recessive disease characterized by spontaneous chromosomal fragility, which is increased after exposure of peripheral blood lymphocytes to DNA crosslinking agents, including clastogenic compounds, such as diepoxybutane, mitomycin C, and melphalan. Patients with Fanconi anemia, besides being at risk of pancytopenia, show a high propensity to develop clonal disorders of hematopoiesis, such as myelodysplastic syndromes and AML. HSCT can rescue aplastic anemia and prevent the occurrence of clonal hematopoietic disorders. In view of their defects in DNA repair mechanisms, which are responsible for the chromosomal fragility, Fanconi anemia patients have an exquisite sensitivity to alkylating agents. Thus, they must be prepared for the allograft with reduced doses of cyclophosphamide. Many patients were once successfully transplanted after receiving low-dose cyclophosphamide and thoracoabdominal irradiation. However, the use of this regimen is associated with an increased incidence of

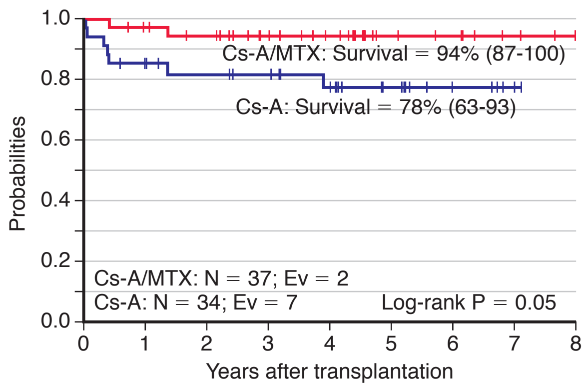

Figure 135-2 Cumulative probability of survival after HLA-identical sibling bone marrow transplantation (BMT) for aplastic anemia, by graft-versus-hostvs disease (GVHD) prophylaxis with cyclosporin alone *(dotted line)* or cyclosporine plus methotrexate *(continuous line)*. GVHD prophylaxis combining cyclosporin and short-term methotrexate is associated with superior outcome compared to cyclosporin alone. *EV*, number of events occurring in each arm of randomization; *N*, number of patients in each arm of randomization. *(From Locatelli F, Bruno B, Zecca M, et al: Cyclosporin A and short-term methotrexate versus cyclosporin A as graft versus host disease prophylaxis I patients with severe aplastic anemia given allogeneic bone marrow transplantation from an HLA-identical sibling: results of a GITMO/EMBT randomized trial.* Blood *96:1690–1697, 2000.)*

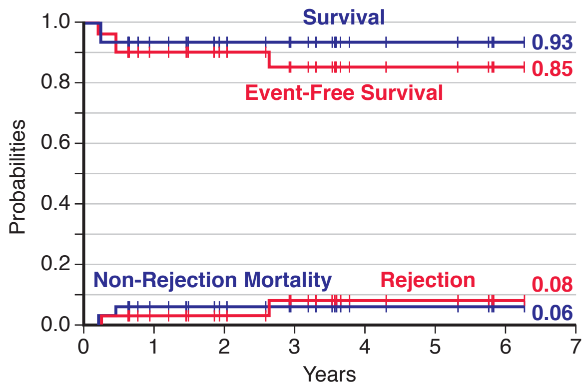

Figure 135-3 Kaplan-Meier estimates of survival and thalassemia-free survival and cumulative incidences of rejection and nonrejection mortality for 33 thalassemic patients younger than 17 yr of age. Survival was 93%, with incidence of recurrent thalassemia after transplantation of 8%. *(From Sodani P, Gaziev D, Polchi P, et al: New approach for bone marrow transplantation in patients with class 3 thalassemia aged younger than 17 years.* Blood *104:1201–1203, 2004.)*

posttransplantation head and neck cancers. Either reduced doses of cyclophosphamide alone or low-dose cyclophosphamide with fludarabine are currently employed for preparing Fanconi anemia patients to the allograft. Using these regimens, the success rate of HSCT from an HLA-identical sibling is on the order of 70-80%. Results of unrelated donor allograft have markedly improved over time and rival with those obtained using an HLA-identical sibling donor.

Allogeneic HSCT remains the only potentially curative approach for severe bone marrow failure associated with dyskeratosis congenita, a rare congenital syndrome characterized also by atrophy and reticular pigmentation of the skin, nail dystrophy, and leukoplakia of mucous membranes. Results of allograft in these patients have been relatively poor, due to occurrence of both early and late complications, reflecting increased sensitivity of endothelial cells to radiotherapy and alkylating agents.

THALASSEMIA

Conventional treatment (i.e., regular blood transfusion and iron-chelation therapy) has dramatically improved both the survival and quality of life of patients with thalassemia, changing a previously fatal disease with early death to a chronic, slowly progressive disease compatible with prolonged survival. However, HSCT remains the only curative treatment for patients with thalassemia. In patients with thalassemia, the risk of dying from transplant-related complications is primarily dependent on patient age, iron overload, and concomitant hepatic viral infections. Adults, especially when affected by chronic active hepatitis, have a poorer outcome than children. Among children, 3 classes of risk have been identified on the basis of 3 parameters, namely regularity of previous iron chelation, liver enlargement, and presence of portal fibrosis. In pediatric patients without liver disease who have received regular iron chelation (class 1 patients), the probability of survival with transfusion independence is >90%, whereas for patients with low compliance with iron chelation and signs of severe liver damage (class 3 patients), the probability of survival is 60% (Fig. 135-3). As in other nonmalignant disorders the most effective pharmacologic combinations (such as that including cyclosporine and methotrexate) should be employed to prevent GVHD. The outcome of patients transplanted from an unrelated donor has been reported to be similar to that of HLA-identical sibling recipients.

SICKLE CELL DISEASE

Disease severity varies greatly among patients with sickle cell disease, with 5-20% of the overall population suffering significant morbidity from vasoocclusive crises and pulmonary, renal, or neurologic damage. Despite the fact that hydroxyurea, an agent favoring the synthesis of fetal hemoglobin, reduces the frequency and severity of vasoocclusive crises and improves the quality of life for patients with sickle cell disease, allogeneic HSCT is the only curative treatment for this disease. Although HSCT can cure homozygous hemoglobin S disease, selecting appropriate candidates for transplantation is difficult. Patients with sickle cell disease may survive for decades, but some patients have a poor quality of life, with repeated hospitalizations for painful vasoocclusive crises and central nervous system infarcts. The main **indications for** performing HSCT in patients with sickle cell disease are history of strokes, magnetic resonance imaging of central nervous system lesions associated with impaired neuropsychologic function, failure to respond to hydroxyurea as shown by recurrent acute chest syndrome, and/or recurrent vasoocclusive crises and/or severe anemia and/or osteonecrosis. The results of HSCT are best when performed in children with an HLA-identical sibling, with a probability of cure of 80-90%. The use of antithymocyte globulin during the preparative regimen improves patient outcome, dramatically reducing the risk of graft failure.

IMMUNODEFICIENCY DISORDERS

HSCT is the **treatment of choice** for children affected by severe combined immunodeficiency, as well as for other inherited immunodeficiencies, including Wiskott-Aldrich Syndrome, leukocyte adhesion deficiency, and chronic granulomatous disease (see also Table 135-1 for details), among others. With an HLA-identical sibling, the probability of survival approaches 100%, with less-favorable results for patients transplanted from an HLA–partially matched relative. Some children with severe combined immunodeficiency, mainly those without residual natural killer activity or maternal T-cell engraftment, may be transplanted without receiving any preparative regimen, the donor lymphoid cells usually being the only elements that engraft. Sustained donor engraftment is more difficult to achieve in children with Omenn syndrome, hemophagocytic lymphohistiocytosis, or leukocyte adhesion deficiency. Life-threatening opportunistic fungal and viral infections occurring before the allograft adversely affect the patient's outcome after HSCT. Patients with the most severe immunodeficiencies must be transplanted as early as possible.

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Chapter 136

Hematopoietic Stem Cell Transplantation from Alternative Sources and Donors

Andrea Velardi and Franco Locatelli

Two-thirds of patients who need allogeneic hematopoietic stem cell transplantation (HSCT) do not have an available human leukocyte antigen (HLA)-identical sibling. Alternative donor/sources of hematopoietic stem cells are being increasingly used and include: matched unrelated donors, unrelated umbilical cord blood (UCB), and HLA-haploidentical relatives. Each of these 3 options has advantages and limitations, but rather than being considered competing alternatives, they should be regarded as complementary strategies to be chosen after a careful evaluation of the relative risks and benefits in the patient's best interest. The choice of the donor will depend on various factors related to urgency of transplantation, patient-, disease-, transplant-related factors and center experience. Physician preference is expected to influence this choice as well.

UNRELATED DONOR TRANSPLANTS

One of the most widely used strategies for children who need an allograft and do not have an available HLA-identical sibling is to identify an unrelated HLA-matched donor in a registry. Today, worldwide international registries include more than 20 million HLA-typed volunteer donors. HLA-A, -B, -C class I loci, and the DRB1 class II locus are the HLA loci most influencing outcome after HSCT from an unrelated volunteer. The roles played by other class II loci (namely, DQB1 and DP1 loci) on patient outcome remain controversial.

Data on serologic typing of HLA classes IA and IB loci are available for all donors, and there is information on DRB1 typing for approximately one-third of donors. Although in the past serologic (low-resolution) typing was used for HLA-A and -B loci, currently, the unrelated donors are selected using high-resolution (allelic) molecular typing of loci HLA-A, -B, -C, and -DRB1. The chance of finding an HLA-matched donor depends on the frequency of the HLA phenotype, which is closely linked to the ethnic origin of the registry donors and ranges from 60-70% for white patients to <10% for persons of other ethnic groups (Hispanic, black, etc).

Identifying a suitable unrelated donor is a complicated and lengthy process, the median time elapsing from the start of search to transplantation being 3-4 mo. During this period, a patient with acute leukemia may relapse and require further therapy, accumulating organ toxicity that unfavorably affects outcome. Moreover, for various different reasons, a relevant proportion of donors (sometimes reaching 10-20%) are either no longer available or refuse donation. Despite these limitations, many thousands of matched unrelated donor transplantations have been performed.

Initially, HLA polymorphism and the intrinsic limitations of conventional (i.e., serologic) HLA-typing techniques unfavorably affected the accuracy of matching, thus increasing rejection rates and the incidence of acute and chronic graft-versus-host disease (GVHD). Consequently, because the event-free survival of recipients of an unrelated donor allograft was worse than that observed when the donor was a compatible sibling transplant, there is no consensus on the use of unrelated donor transplants for nonmalignant diseases, such as thalassemia or primary immune deficiency syndromes other than severe combined immunodeficiency (SCID). DNA-based (i.e., high-resolution molecular) techniques for HLA typing have revealed an impressive number of new alleles within antigens that were previously defined by serology only. Matching by high-resolution DNA typing reduces the risk of immune complications, namely graft rejection and GVHD, but also the chance of finding a suitable donor. Nevertheless, the advent of both high-resolution molecular HLA classes I and II loci-typing coupled with progress in the prophylaxis and treatment of GVHD has resulted in a reduction of transplantation-related mortality and improvement of outcome. Indeed, outcomes from a fully matched unrelated volunteer donor are now similar to those of HSCT from an HLA-identical sibling, as indicated by results of unrelated donor transplantation in children with acute lymphoblastic leukemia in second complete remission, juvenile myelomonocytic leukemia, or thalassemia (Fig. 136-1).

Although a single locus disparity in patients with leukemia does not markedly affect the probability of event-free survival as the increased risk of toxic death may be compensated for by a reduction in the relapse rate, in patients with nonmalignant disorders optimal results are obtained only when a donor matched at the allelic level with the recipient is selected. In general, a single HLA disparity in the donor–recipient pair, irrespective of whether antigenic or allelic in nature, predicts a greater risk of nonleukemia mortality; multiple allelic disparities at different HLA loci have an additive detrimental effect and are associated with an even worse outcome. To reduce the risk of acute GVHD, **ex vivo T-cell depletion of the graft** has been employed, but has not significantly affected patient outcome, which is similar to that of patients given an unmanipulated graft and pharmacologic prophylaxis for GVHD.

The analyses on the outcome of unrelated donor HSCT include only patients who are transplanted; these numbers do not take into account patients for whom a donor is not found. For patients who urgently need a transplant, the time required to identify a suitable donor from a potential panel, establish eligibility, and harvest the cells may lead to relapse and failure to transplant. For patients who do not have a matched donor or who urgently need a transplant, attention has focused on unrelated cord blood and HLA-haploidentical, mismatched family donors.

UMBILICAL CORD BLOOD TRANSPLANTS

UCB transplantation (UCBT) is a viable option for children who need allogeneic HSCT. To date, several hundred children have been cured

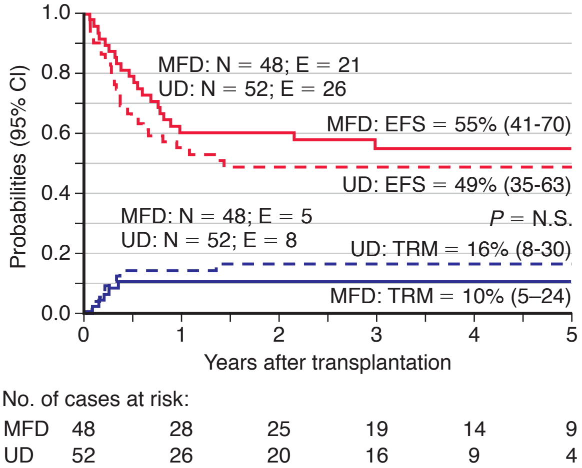

Figure 136-1 Kaplan-Meier estimates of event-free survival *(EFS) (upper lines)* and transplantation-related mortality *(TRM) (lower lines)* according to the type of donor used, matched family donor *(MFD)* or unrelated donor *(UD)*. Matched family donor was superior (55% EFS and 10% TRM) compared to unrelated donor (49% EFS and 16% TRM). *(From Locatelli F, Nöllke P, Zecca M, et al: Hematopoietic stem cell transplantation [HSCT] in children with juvenile myelomonocytic leukemia [JMML]: results of the EWOG-MDS/EBMT trial.* Blood 105:410–419, 2005.)

through transplantation of either related or unrelated UCB units. UCBT offers the advantages of absence of risks to donors, reduced risk of transmitting infections, and, for transplants from unrelated donors, immediate availability of cryopreserved cells, the median time elapsing from start of search to transplantation being only 3-4 wk. In comparison to bone marrow transplantation (BMT), the advantages of UCBT are also represented by lower incidence and severity of GVHD, easier procurement and prompter availability of cord blood cells, and the possibility of using donors showing HLA disparities with the recipient. Despite these advantages, the large experience gained over the last 2 decades has clearly demonstrated that UCBT patients may be exposed to an increased risk of early fatal complications, mainly because of a lower engraftment rate of donor hematopoiesis, delayed kinetics of neutrophil recovery, and lack of adoptive transfer of pathogen-specific memory T-cells. In fact, transfer of donor-derived, memory T cells significantly contributes to early immunologic reconstitution of children after unmanipulated allogeneic bone marrow or peripheral blood stem cell transplantation.

Concerning the issues of engraftment and hematopoietic recovery, it has been unquestionably shown that an inverse correlation between the number of nucleated cord blood cells infused per kilogram recipient body weight and the risk of dying for transplantation-related causes exists. In particular, engraftment is a major concern when the nucleated cells are $<2.5 \times 10^7$/kg of recipient body weight. As a cord blood unit usually contains between 1×10^9 and 1.8×10^9 cells, it is not surprising that UCB transplantation has been less frequently employed for adolescents or adults with body weight >40 kg. Indeed, it can be estimated that only 30% of the UCB units available in the bank inventory could suffice for a 75 kg patient according to the recommended threshold cell dose (namely more than 2.5×10^7 total nucleated cells/kg recipient body weight before thawing the unit). In view of these findings, it is not surprising that efforts have been focused on approaches capable of increasing the number of UCB cells to be transplanted. Selection of the richest cord blood units, infusion of 2 units in the same recipient (i.e., double UCBT), and transplantation of ex vivo expanded progenitors have contributed to improve the results of UCBT, opening new scenarios for a wider application of the procedure. In particular, double UCBT is largely employed as it was demonstrated to be effective in adults, significantly increasing the engraftment rate, as compared to single-unit UCBT. In the majority of double UCBT, the 2 UCB units are partially HLA-matched with the recipient, as well as with each other, and sustained hematopoiesis after double UCBT is usually derived from a single donor. This technique is of interest to pediatricians for extending the applicability of UCBT also to adolescents or to patients with a body weight exceeding 40-50 kg.

Direct intrabone transplantation of UCB cells is also a feasible and safe approach, able to overcome the problem of graft failure, even when low numbers of HLA-mismatched cord-blood cells are transplanted, and to guarantee prompt platelet recovery.

Despite the low incidence of acute and chronic GVHD observed after UCB transplantation, the risk of recurrence of leukemia is not increased. The long-term results of UCB transplants are similar to those after transplantation from other sources of hematopoietic stem cells. In particular, several published reports have compared the outcome of UCBT and BMT from unrelated donors in children with hematologic malignancies. Recipients of UCBT were transplanted from donors with greater HLA-disparities, received 1-log fewer nucleated cells, had delayed neutrophil and platelet recovery, and showed reduced incidence of GVHD as compared to children given BMT. Nevertheless, both the relapse rate and the overall survival probability did not differ in unrelated UCBT or BMT pediatric recipients. The outcome of patients receiving a fully matched UCB unit is reported to be even better than that of patients who receive a transplant from an HLA-identical, unrelated volunteer. Thus, today, there is no doubt that, in the absence of an HLA-identical family donor, unrelated UCBT can be considered a suitable option for children with malignant and nonmalignant disorders. Results of UCBT have been of particular interest in children with Hurler syndrome or Krabbe disease transplanted with cord blood cells from an unrelated donor, as well as in children with hemoglobinopathies given a related UCB transplantation. It has to be emphasized that the lower risk of GVHD associated with UCBT is of particular importance in patients affected by nonmalignant disorders.

Approximately 5% of patients receiving UCB transplantation develop an autoimmune disorder. These disorders include autoimmune hemolytic anemia, autoimmune thrombocytopenia, Evans syndrome, and immune neutropenia. Less frequently, patients have developed Graves disease, glomerulonephritis, rheumatoid arthritis, or thyroiditis. Treatment for these post-UCB transplant-related autoimmune diseases has included steroids, rituximab, and cyclosporine, with only varying degrees of success.

HAPLOIDENTICAL TRANSPLANTS

HSCT from an HLA-haploidentical (haplo-HSCT) donor offers an immediate source of hematopoietic stem cells to almost all leukemia patients who fail to find a matched donor, whether related or unrelated, or a suitable cord blood unit. Indeed, almost all children have at least 1 haploidentical–3 loci mismatched family member who is promptly available as donor. Moreover, the few patients who reject the haploidentical transplant have the advantage of another immediately available donor within the family.

Efficient T-cell depletion of the graft has been demonstrated to prevent acute and chronic GVHD even when using haploidentical parental bone marrow differing at the 3 major HLA loci. The benefits of T-cell depletion were first demonstrated in transplantation of children with SCID. More than 300 transplants in SCID patients using haploidentical donors have been performed worldwide, with a high rate of long-term partial or complete immune reconstitution.

As patients with acute leukemia have a high chance of rejecting a haploidentical bone marrow graft, a "megadose" of granulocyte colony-stimulating factor–mobilized peripheral blood stem cells has been demonstrated to be crucial for overcoming the barrier of HLA incompatibility in the donor–recipient pair and for eluding residual antidonor cytotoxic T-lymphocyte precursor activity in the recipient. Indeed, in leukemia patients, the combination of high-intensity immune-suppressive/myeloablative conditioning regimens with the infusion of great numbers of highly purified, peripheral blood CD34+ cells has been demonstrated capable to (1) guarantee the successful and sustained engraftment of donor haematopoiesis across the HLA barrier, and (2) guarantee a very low incidence of grades II-IV acute GVHD without the need for any posttransplantation immune suppression as prophylaxis. The physical elimination of mature T cells from the graft, necessary for preventing GVHD occurrence in a context of great immune genetic disparity, leads to the consequence that recipients cannot benefit from the adoptive transfer of donor memory T lymphocytes that, through their peripheral expansion, are the main factor responsible for protection from infections in the 1st few mo after transplantation. A state of profound immune deficiency lasts for at least 4-6 mo after transplantation in haplo-HSCT recipients. Sophisticated strategies of adoptive infusions of T-cell lines or clones specific for the most common and life-threatening pathogens (namely Epstein-Barr virus, human cytomegalovirus, *Aspergillus*, and adenovirus) have been envisaged and successfully tested in a few pilot trials to protect the recipients in the early posttransplantation period. Selective approaches of graft manipulation have also been developed. In particular, promising results have been obtained through a negative depletion of T lymphocytes carrying the α/β chains of the T-cell receptor. B-lymphocytes are also depleted to prevent the occurrence of Epstein-Barr virus–related lymphoproliferative disease. Through this approach the patient can benefit from the adoptive transfer of committed hematopoietic progenitors, mature natural killer (NK) cells and γ/δ+ T cells, which can confer a protection against life-threatening infections.

The outcomes of haplo-HSCT have been more extensively reported in adults than in children. The reported probability of survival at 3-4 yr after a haplo-HSCT in children with acute leukemia ranged from 18-48%. Survival was influenced by many factors, the most important being the state of remission at time of transplantation, with poorer outcomes in children with myeloid leukemias than in those with lymphoid leukemia. It has been reported that in haplotype mismatched

parent-to-child HSCT, patients with acute leukemia grafted from the mother had reduced relapse rates as compared with recipients of paternal grafts, translating into better event-free survival.

For many years the absence of the T-cell mediated graft-versus-leukemia (GVL) effect has been considered rendering the recipients of a T-cell depleted allograft more susceptible to leukemia relapse. However, it has been demonstrated that a GVL effect displayed by donor NK cells can compensate for this lack of T-specific alloreactivity when an HLA-disparate NK alloreactive relative is employed as a donor.

DONOR VERSUS RECIPIENT NATURAL KILLER–CELL ALLOREACTIVITY

Donor vs recipient NK-cell alloreactivity is a biologic phenomenon that is unique to the mismatched transplant. It derives from a mismatch between donor NK clones, carrying specific inhibitory receptors for self–major histocompatibility complex (MHC) class I molecules, and MHC class I ligands on recipient cells. NK cells are primed to kill by several activating receptors, which play an important role in the NK cell-mediated GVL effect. Human NK cells discriminate allelic forms of MHC molecules via **killer cell immunoglobulin-like receptors (KIRs),** which are clonally distributed with each cell in the repertoire bearing at least 1 receptor that is specific for self-MHC class I molecules. Because NK cells coexpress inhibitory receptors for self-MHC class I molecules, autologous cells are not killed. When faced with mismatched allogeneic targets, NK cells sense the missing expression of self–class I alleles and mediate alloreactions. In mismatched transplants, there are many donor recipient pairs in which the donor NK inhibitory cells do not recognize the recipient's class I alleles as self. Consequently, the donor NK cells are not blocked and are activated to lyse the recipient's lymphohematopoietic cells.

Haplo-HSCT trials demonstrate that MHC class I mismatches, which generate an alloreactive NK cell response in the graft-versus-host direction, eradicate leukemia cells, improve engraftment, and protect from T-cell–mediated GVHD. Lack of an NK-alloreactive donor is the strongest independent risk factor for leukemia relapse after adjustment for disease status at transplantation. The potential for donor vs recipient NK cell alloreactivity, which can be predicted by standard HLA typing, is recommended when selecting the donor of choice from among the mismatched family members.

The chance of finding a "perfect mismatch" NK-alloreactive donors in the family is on the order of 50%. From a practical point of view, first, the transplantation candidate is HLA typed. Candidates expressing class I alleles belonging to the 3 class I groups recognized by KIRs (HLA-C group 1, HLA-C group 2, and HLA-Bw4 alleles) will block all NK cells from every donor and belong to the one-third of the population that is resistant to alloreactive NK killing. Patients who express only 1 or 2 of these allele groups may find NK-alloreactive donors.

Donor HLA typing identifies family members who do not express the class I group(s) expressed by the patient and, therefore, have the potential for NK alloreactivity. Not all inhibitory KIRs are present in 100% of the population. KIR2DL2/3, the receptor for HLA-C group 1, is present in all persons; KIR2DL1, the receptor for HLA-C group 2, is present in 97% of persons; and KIR3DL1, the receptor for HLA-Bw4 alleles, is present in ≈90%. Donor KIR genotyping ensures that the donor expresses the relevant NK cells.

In HLA-Bw4 mismatches, even when the KIR3DL1 gene is present, NK repertoire studies show alloreactive NK cells in approximately two-thirds of individuals. This may be because they occur in highly variable frequencies or because allelic KIR3DL1 variants may not allow receptor expression at the cell membrane. Therefore, for HLA-Bw4 mismatches, direct assessment of the donor NK repertoire is necessary.

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Autologous transplantation, using the patient's own stored marrow, is associated with a low risk of life-threatening transplant-related complications, although the main cause of failure is disease recurrence resulting from a lack of the immune-mediated GVL effect. Bone marrow was once the only source of stem cells employed in patients given an autograft; in the past few years, the vast majority of patients treated with autologous HSCT receive hematopoietic progenitors mobilized in peripheral blood by either cytokines alone (mainly granulocyte colony-stimulating factor) or by cytokines plus cytotoxic agents. A CXCR4 antagonist (plerixafor) can be extremely effective in mobilizing hematopoietic progenitors in the periphery. When compared to bone marrow, the use of peripheral blood progenitors is associated with a faster hematopoietic recovery and a comparable outcome. A major concern in patients with malignancies given autologous HSCT is represented by the risk of reinfusing malignant cells with the graft; tumor progenitors contained in the graft can contribute to recurrence of the original malignant disease. This observation has provided the rational for **tumor purging** using elaborated strategies aimed at reducing or eliminating tumor contamination of the graft.

Table 136-1	Indications to Autologous Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Acute lymphoblastic leukemia after an isolated extramedullary relapse
- Relapsed Hodgkin or non-Hodgkin lymphoma
- Stage IV or relapsed neuroblastoma
- High-risk, relapsed, or resistant brain tumors
- Stage IV Ewing sarcoma
- Life-threatening autoimmune diseases resistant to conventional treatments

Autologous HSCT is employed primarily to prevent relapse in patients with acute myelogenous leukemia (AML) who achieve complete remission after induction therapy, and also for selected children with relapsed lymphomas and selected solid tumors (Table 136-1).

Randomized studies have not shown an advantage in terms of event-free survival for patients with AML in the 1st complete remission given an autologous HSCT as compared to those treated with chemotherapy alone. The probability of event-free survival for children with AML in the 1st complete remission given autologous HSCT is reported to range from 40-60%. Ex vivo purging of bone marrow cells with mafosfamide has been shown to reduce the risk of disease recurrence in children with AML in the 1st complete remission given an autologous transplantation.

Patients with sensitive lymphomas and little tumor burden have favorable outcomes after autologous HSCT, with disease-free survival rates of 50-60%, whereas high-risk patients with bulky tumor or poorly responsive disease have a dismal outcome, with survival rates of 10-20%.

Some studies suggest that, as compared to conventional chemotherapy and radiotherapy, autologous HSCT may offer an advantage in terms of event-free survival to children with acute lymphoblastic leukemia in the second complete remission after an isolated extramedullary relapse (i.e., central nervous system, testicular relapse).

Autologous HSCT in patients with high-risk neuroblastoma is associated with a better outcome compared to conventional chemotherapy. In these patients, posttransplantation infusion of a monoclonal antibody directed against a molecule (GD2) expressed on the surface of neuroblastoma cells confers a protection against the risk of tumor recurrence.

For children with brain tumors at high risk of relapse, or resistant to conventional chemotherapy and irradiation, the dose-limiting toxicity for intensifying therapy is myelosuppression, thus providing a role for stem cell rescue. Several studies provide encouraging results for patients with different histologic types of brain tumors treated with autologous HSCT.

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Chapter 137
Graft-Versus-Host Disease, Rejection, and Venoocclusive Disease

Andrea Velardi and Franco Locatelli

The major cause of mortality and morbidity after allogeneic hematopoietic stem cell transplantation (HSCT) is graft-versus-host disease (GVHD), which is caused by engraftment of immunocompetent donor T lymphocytes in an immunologically compromised host which show histocompatibility differences with the donor. These differences between the donor and the host may result in donor T-cell activation against either recipient major histocompatibility complex antigens or minor histocompatibility antigens. GVHD is usually subdivided in 2 forms: acute GVHD, which occurs within 3 mo after transplantation, and chronic GVHD, which, although related, is a different disease, occurring later and displaying some clinical and pathologic features that resemble those observed in selected autoimmune disorders (systemic sclerosis, Sjögren syndrome, etc.).

ACUTE GRAFT-VERSUS-HOST DISEASE

Acute GVHD is caused by the alloreactive, donor-derived T cells contained in the graft, which attack nonshared recipient's antigens on target tissues. A three-step process generates the clinical syndrome. First, conditioning-induced tissue damage activates recipient antigen-presenting cells, which present recipient alloantigens to the donor T cells transferred with the graft and secrete cytokines, such as interleukin 12, favoring the polarization of T-cell response in the type 1 direction. Second, in response to recipient antigens, donor T cells become activated, proliferate, expand, and generate cytokines such as tumor necrosis factor-α, interleukin (IL)-2, and interferon-γ. In the third step of the process, these cytokines cause tissue damage and promote differentiation of cytotoxic CD8+ T cells, which, together with macrophages, in turn, kill recipient cells and further disrupt tissues.

Acute GVHD usually develops from 2-8 wk posttransplantation. The primary **manifestations** are an erythematous maculopapular rash, persistent anorexia, vomiting and/or diarrhea, and liver disease with increased serum levels of bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase (Table 137-1). Diagnosis may benefit from skin, liver, or gastrointestinal biopsy for confirmation. Endothelial damage and lymphocytic infiltrates are seen in all affected organs. The epidermis and hair follicles of the skin are damaged, the hepatic small bile ducts show segmental disruption, and there is destruction of the crypts and mucosal ulceration of the gastrointestinal tract. Grade I acute GVHD (skin rash alone) has a favorable prognosis and often does not require treatment (Fig. 137-1). Grade II GVHD is a moderately severe multiorgan disease requiring immunesuppressive therapy. Grade III GVHD is a severe multiorgan disease, and grade IV GVHD is a life-threatening, often fatal condition. The standard **pharmacologic prophylaxis** of GVHD after an unmanipulated allograft relies mainly on posttransplant administration of immunosuppressive drugs, such as cyclosporine or tacrolimus or combinations of either with methotrexate or prednisone, anti–T-cell antibodies, mycophenolate mofetil, and other immunosuppressive agents. Infusion of cyclophosphamide on days +3 and +5 after transplantation has been proposed as a strategy to delete alloreactive donor T lymphocytes that become activated, and thus cycling, after exposure to recipient antigens. Pretransplantation infusion of either antithymocyte globulin or monoclonal antibodies such as alemtuzumab is largely used to modulate alloreactivity of donor T cells, in particular in patients given the allograft from either an unrelated donor or a partially matched relative. An alternative approach, which has been widely used in clinical practice, is the removal of T lymphocytes from the graft (T-cell depletion). Any form of GVHD prophylaxis in itself may impair posttransplantation immunologic reconstitution, increasing the risk of infection-related deaths. T-cell depletion of the graft is also associated with an increased risk of leukemia recurrence in patients transplanted from an human leukocyte antigen (HLA)-identical sibling or an unrelated volunteer.

Despite prophylaxis, significant acute GVHD develops in ≈30% of recipients of HSCT from matched siblings and in as many as 60% of HSCT recipients from unrelated donors. The risk of acute GVHD is increased by factors such as diagnosis of malignant disease, older donor and recipient ages, and, in patients given an unmanipulated allograft, GVHD prophylaxis including only 1 drug. However, the most important risk factor for acute GVHD is the present of disparities for HLA-molecules in the donor–recipient pair. Acute GVHD is usually initially treated with glucocorticoids; approximately 40-50% of patients show a complete response to steroids. The risk of transplantation-related mortality is much higher in patients who do not respond to

Table 137-1 Clinical Staging and Grading of Graft-Versus-Host Disease

STAGE	SKIN	LIVER	INTESTINAL TRACT
+	Maculopapular rash <25% of body surface	Bilirubin 2-3 mg/dL	>500 mL diarrhea/day
++	Maculopapular rash 25%–50% of body surface	Bilirubin 3-6 mg/dL	>1,000 mL diarrhea/day
+++	Generalized erythroderma	Bilirubin 6-15 mg/dL	>1,500 mL diarrhea/day
++++	Generalized erythroderma with bullous formation and desquamation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus

GVHD GRADE	SKIN STAGE	LIVER STAGE	INTESTINAL TRACT STAGE	DECREASE IN CLINICAL PERFORMANCE
I	+ to ++	0	0	None
II	+ to +++	+	+	Mild
III	++ to +++	++ to ++++	++ to +++	Marked
IV	++ to ++++	++ to ++++	++ to ++++	Extreme

Adapted from Thomas ED, Storb R, Clift RA, et al: Bone marrow transplantation [in 2 parts]. N Engl J Med *292:832–843, 895–902, 1975.*

Figure 137-1 Acute graft-versus-host disease of the skin with ear, arm, shoulder, and trunk involvement. See also color plates. *(Courtesy of Evan Farmer, MD.)*

steroids than in those showing a complete response. Mofetil mycophenolate, extracorporeal photopheresis, pentostatin, or monoclonal antibodies targeting either molecules expressed on T cells or cytokines released during the inflammatory cascade, which underlies the physiopathology of GVHD, have been used in patients with steroid-resistant acute GVHD. There are no clear data showing the superiority of one of these approaches over the others. Promising results in children with steroid-resistant acute GVHD have been obtained using mesenchymal stromal cells, which are able to blunt the inflammatory response associated with acute GVHD.

CHRONIC GRAFT-VERSUS-HOST DISEASE

Chronic GVHD develops or persists >3 mo posttransplantation and is the most frequent late complication of allogeneic HSCT with an incidence of ≈25% in pediatric patients. Chronic GVHD is the major cause of nonrelapse mortality and morbidity in long-term HSCT survivors. Acute GVHD is recognized as the most important factor predicting the development of the chronic form of the disease. The use of matched unrelated volunteers as donors, and of peripheral blood as the stem cell source, has increased the incidence and severity of chronic GVHD. Other factors that predict occurrence of chronic GVHD include older donor and recipient ages, female donor for male recipient, diagnosis of malignancy, and use of total-body irradiation as part of the preparative regimen.

Chronic GVHD is a disorder of immune regulation characterized by autoantibody production, increased collagen deposition and fibrosis, and clinical symptoms similar to those seen in patients with autoimmune diseases. The predominant cytokines involved in the pathophysiology of chronic GVHD are usually type II cytokines such as IL-4, IL-5, and IL-13. IL-4 and IL-5 contribute to eosinophilia, B-cell hyperactivity with elevated immunoglobulin (Ig) M, IgG, and IgE titers. Associated monoclonal gammopathies indicate clonal dysregulation. Chronic GVHD is dependent on the development and persistence of donor T cells that are not tolerant to the recipient. Maturation of transplanted stem cells within a damaged thymus could lead to errors in negative selection and production of cells that have not been tolerized to recipient antigens and are, therefore, autoreactive or, more accurately, **recipient reactive.** This ongoing immune reactivity results in clinical features resembling a systemic autoimmune disease with lichenoid and sclerodermatous skin lesions, malar rash, sicca syndrome, arthritis, joint contractures, obliterative bronchiolitis, and bile duct degeneration with cholestasis.

Patients with chronic GVHD involving only the skin and liver have a favorable course (Fig. 137-2). Extensive multiorgan disease may be associated with a very poor quality of life, recurrent infections associated with prolonged immunosuppressive regimens to control GVHD, and a high mortality rate. Morbidity and mortality are highest in patients with a **progressive onset** of chronic GVHD that directly

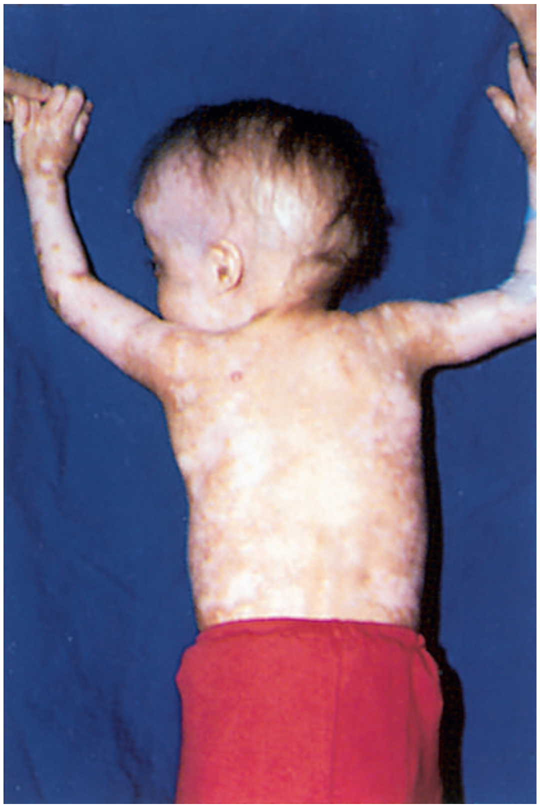

Figure 137-2 Chronic graft-versus-host disease of the skin with sclerodermoid changes. *(Courtesy of Evan Farmer, MD.)*

follows acute GVHD, intermediate in those with a **quiescent onset** after resolution of acute GVHD, and lowest in patients with **de novo onset** in the absence of acute GVHD. Single-agent prednisone is standard treatment at present, although other agents, including extracorporeal photopheresis, mofetil mycophenolate, anti-CD20 monoclonal antibody, and pentostatin, have been employed with variable success. Treatment with imatinib mesylate, which inhibits the synthesis of collagen, has been shown to be effective in patients with chronic GVHD and sclerotic features. As a consequence of prolonged immunosuppression, patients with chronic GVHD are particularly susceptible to infections and should receive appropriate antibiotic prophylaxis, including trimethoprim-sulfamethoxazole. Chronic GVHD resolves in most pediatric patients but may require 1-3 yr of immunosuppressive therapy before the drugs can be withdrawn without the disease recurring. Chronic GVHD promotes also the development of secondary neoplasms, in particular in patients with Fanconi anemia.

Graft failure is a serious complication exposing patients to a high risk of fatal infection. **Primary graft failure** is defined as failure to achieve a neutrophil count of 0.2×10^9/L by 21 days posttransplantation. **Secondary graft failure** is loss of peripheral blood counts following initial transient engraftment of donor cells. Causes of graft failure after autologous and allogeneic transplantation include transplantation of an inadequate stem cell dose (more frequently observed in children given cord blood transplantation), and viral infections such as with cytomegalovirus or human herpesvirus type 6, which are often associated with activation of recipient macrophages. Graft failure after allogeneic transplantation, however, is mainly caused by immunologically mediated rejection of the graft by residual recipient-type T cells that survive the conditioning regimen. **Diagnosis** of graft failure resulting from immunologic mechanisms is based on examination of peripheral blood and marrow aspirate and biopsy, along with molecular analysis of chimerism status. Persistence of lymphocytes of host origin in allogeneic transplant recipients with graft failure indicates immunologic

rejection. The risk of immune-mediated graft rejection is higher in patients given HLA-disparate, T-cell–depleted grafts, reduced-intensity conditioning regimens, and transplantation of low numbers of stem cells, and in recipients who are sensitized toward HLA antigens or, less frequently, minor histocompatibility antigens. Allosensitization develops as a consequence of preceding blood product transfusions and is observed particularly in recipients with aplastic anemia, sickle cell disease, and thalassemia. In HSCT for nonmalignant diseases, such as mucopolysaccharidoses, graft failure is also facilitated by the absence of previous treatment with cytotoxic and immunosuppressive drugs. In thalassemia, graft failure is promoted by expansion of recipient hematopoietic cells. GVHD prophylaxis with methotrexate, an antimetabolite, and antiinfective prophylaxis with trimethoprim-sulfamethoxazole or ganciclovir may also delay engraftment.

Treatment of graft failure usually requires removing all potentially myelotoxic agents from the treatment regimen and attempting a short trial of hematopoietic growth factors, such as granulocyte colony-stimulating factor. A second transplant, usually preceded by a highly immune-suppressive regimen, is frequently employed to rescue patients experiencing graft failure. High-intensity regimens are generally tolerated poorly if administered within 100 days from a 1st transplant because of cumulative toxicities.

VENOOCCLUSIVE DISEASE

Hepatic venoocclusive disease, also known as sinusoidal obstruction syndrome, presents with hepatomegaly, right upper quadrant tenderness, jaundice, and weight gain from fluid retention and ascites. Onset is usually within 30 days of transplantation, with an incidence of approximately 15%, depending on the intensity of the conditioning protocol. Risk factors include young age, prior hepatic disease (fibrosis, cirrhosis), abdominal radiation, repeated transplantations, neuroblastoma, osteopetrosis and familial hemophagocytic lymphohistiocytosis. The severe form of venoocclusive disease has a high mortality rate; treatment results for severe disease are poor.

Prophylaxis has traditionally used heparin and ursodeoxycholic acid; however, only defibrotide has demonstrated some efficacy in preventing venoocclusive disease. Defibrotide is a combination of porcine oligodeoxyribonucleotides that reduces procoagulant activity and enhances fibrinolytic properties of endothelial cells.

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Chapter 138

Infectious Complications of Hematopoietic Stem Cell Transplantation

Andrea Velardi and Franco Locatelli

Hematopoietic stem cell transplantation (HSCT) recipients experience a transient but profound state of immune deficiency. Immediately after transplantation, because neutrophils are absent or markedly reduced, patients are particularly susceptible to bacterial and fungal infections. Consequently, most centers start prophylactic antibiotic or antifungal treatment during the conditioning regimen. Despite these prophylactic measures, most patients will develop fever and signs of infection in the early posttransplantation period. The common pathogens include enteric bacteria and fungi such as *Candida* and *Aspergillus*. An indwelling central venous line, routinely employed in all children given HSCT, is a significant risk factor for bacterial and fungal infections, staphylococcal species and *Candida* being the most frequent pathogens in catheter-related infections (see Chapter 178). Emergence of multidrug resistant strains of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* has become a serious problem, being associated with a high case : fatality ratio.

HSCT recipients remain at increased risk of developing severe infections even after the neutrophil count has normalized, because T-cell number and function remain below normal for months after transplantation. Unrelated donor transplant recipients are at increased risk of developing graft-versus-host disease (GVHD), which is itself an additional risk factor for fungal and viral opportunistic infections, as are the associated immunosuppressive treatments. After cord blood transplantation, infections are the consequence of both the slow neutrophil engraftment and donor T-cell naïveté. In haploidentical transplantation, the increased risk of infection observed in the 1st 4-6 mo after the allograft is the consequence of T-cell depletion of the graft. Indeed, patients given this type of transplantation, as well as those receiving cord blood transplantation, cannot benefit from the adoptive transfer of donor-derived, antigen-experienced T cells.

Among HSCT recipients, invasive aspergillosis, cytomegalovirus (CMV) infection, disseminated adenovirus infections, and Epstein-Barr virus (EBV)–related lymphoproliferative disorders represent peculiar, life-threatening complications that significantly affect patient's outcome.

Invasive **aspergillosis** remains a significant cause of infectious morbidity and mortality in HSCT recipients. Despite prompt and aggressive administration of potent antifungal agents, proven cases of aspergillosis remain difficult to treat, with case-fatality rates of 80-90%. The annual incidence of invasive aspergillosis has risen with use of stem cells from alternative sources. The incidence is 7.3% in recipients of an human leukocyte antigen (HLA)-matched related donor transplant and 10.5% in patients given the allograft from either an HLA-mismatched family donor or an unrelated donor volunteer. Most cases of aspergillosis are diagnosed from 40-180 days after HSCT, with 30% diagnosed <40 days before and 17% more than 6 mo after transplantation. The risk of developing aspergillosis is mainly influenced by the duration of neutropenia, GVHD occurrence, use of corticosteroid therapy, posttransplant CMV infection, viral respiratory tract infections, advanced disease status, older age, and T-cell depletion of the graft. Patients with a previous history of invasive aspergillosis are at particular risk.

Aspergillus infection often originates from the upper airway mucosa. Early lesions in the nose should be sought in patients with neutropenia who have fever and minimal epistaxis. Rapid extension into the adjacent paranasal sinuses, orbit, or face is usual, with or without the appearance of lung lesions. In the lung, invasive aspergillosis generally presents as an acute, rapidly progressive, densely consolidated pulmonary infiltrate. Infection progresses by direct extension across tissue and by hematogenous dissemination to brain and other organs. The earliest CT finding is one or more small pulmonary nodules. As a nodule enlarges, the dense central core of infarcted tissue becomes surrounded by edema or hemorrhage, forming a hazy rim, the **halo sign.** This rim disappears in a few days as the dense core enlarges. In neutropenic patients, when bone marrow function recovers, the infarcted central core cavitates, creating the **crescent sign.** Repeated positivity for serum galactomannan represents a useful biomarker for confirming/suspecting a diagnosis of invasive aspergillosis. Antifungal prophylaxis includes isolation of the patient in a laminar air flow or positive pressure room. Liposomal amphotericin B, azole compounds (itraconazole, voriconazole, posaconazole) and echinocandins (caspofungin, micafungin, anidulafungin) are useful for both preventing and treating the fungal infection. Voriconazole represents the treatment of choice for patients with invasive pulmonary and brain aspergillosis. However, often, aspergillosis does not respond satisfactorily to antifungal agents alone, and patients remain at risk until T-cell counts and function recover. This observation provides the rationale

for developing strategies to accelerate the recovery of pathogen-specific immune responses.

CMV infection remains the most common and potentially severe viral complication in patients given allogeneic HSCT. Seropositivity for CMV is an independent risk factor for mortality, even in recipients of matched sibling or unrelated donor transplants. CMV is itself immunosuppressive, as it impairs dendritic cell and T-lymphocyte function. Moreover, ganciclovir, the most frequently used anti-CMV agent, may cause leukopenia and T-cell immune suppression.

The period of maximal risk for CMV infection is 1-4 mo after transplantation. Until CMV-specific T-cell responses develop months after transplant, CMV infection may result in a variety of syndromes including fever, leukopenia, thrombocytopenia, hepatitis, pneumonitis, retinitis, esophagitis, gastritis, and colitis. CMV pneumonia, the most life-threatening complication related to viral infection, has been reported to occur in up to 15-20% of bone marrow transplant recipients, with a case fatality rate of 85%. The risk is greatest between 5 and 13 wk after transplantation. Risk factors include T-cell depletion of the graft, donor seronegative status together with recipient seropositive status, acute GVHD, and patient older age.

Tachypnea, hypoxia, and unproductive cough signals respiratory involvement. Chest x-ray often reveals bilateral interstitial or reticulonodular infiltrates, which begin in the periphery of the lower lobes and spread centrally and superiorly. The differential diagnosis includes infection with *Pneumocystis jiroveci* or other viral, bacterial, or fungal pathogens, pulmonary hemorrhage, and injury secondary to irradiation or to treatment with cytotoxic drugs. Gastrointestinal CMV involvement may lead to ulcers of the esophagus, stomach, small intestine, and colon that may result in bleeding or perforation.

Fatal CMV infections are often associated with persistent viremia and multiorgan involvement. In the 1980s, antiviral treatment was deferred until overt clinical symptoms of CMV infection developed, which led to a high incidence of fatal events. CMV disease has largely been **prevented** through prophylaxis and a preemptive approach. Prophylaxis is based on administration of antiviral drugs to all transplanted patients for a median duration of 3 mo after transplantation. The major drawbacks of this approach refer to drug toxicity, occurrence of late CMV disease, mainly pneumonia, after withdrawal of prophylaxis, treatment of patients who do not need antiviral therapy as they would not have reactivated CMV infection, and low cost-effectiveness. Preemptive, or presymptomatic, therapy aims at treating only patients who experience CMV reactivation and, thus, are at risk of developing overt disease; it starts only upon detection of CMV in blood by any assay. The most widely used assay is CMV detection of CMV DNA in blood, which have been used to decide inception of treatment when it either becomes positive or reaches a predetermined threshold. Although in the past treatment usually started after this assay became positive, nowadays therapy is usually initiated when a certain viral load is reached. Moreover, quantification of CMV DNA in blood provides a reliable approach for deciding interruption of treatment. The major drawback of this strategy is the need of serial monitoring that is required for the period in which patients are at risk of developing CMV disease. In this regard, approaches to reliably prove the restoration of virus-specific immunity have been developed. Generally, ganciclovir, or less frequently foscarnet, is usually used for prophylaxis and preemptive treatment of CMV infection. Treatment is usually discontinued when repeated negative controls have been obtained.

Disseminated adenovirus infection is a life-threatening complication of HSCT recipients. Clinical manifestations include fever, hepatitis, enteritis, meningoencephalitis, and pneumonia. Young children are at particular risk of developing this complication. Diagnosis is based on the demonstration of high levels of adenovirus DNA in blood or on recovery of virus in tissue biopsies. Pharmacologic treatment of adenovirus infections is based on the use of cidofovir, which has significant renal toxicity and sometimes is unable to control viral replication. Recovery of immune system function is associated with a greater chance to survive adenovirus disseminated infection.

EBV-related **lymphoproliferative** disease (EBV-LPD) is a major complication in HSCT and solid-organ transplantation. In patients given HSCT, selective procedures of T-cell-depletion–sparing B lymphocytes, as well as the use of HLA partially matched family and unrelated donors, are risk factors for the development of EBV-LPD. These disorders usually present in the 1st 4-6 mo after transplantation as high-grade diffuse large-cell B-cell lymphomas, which are oligoclonal or monoclonal, express the full array of EBV antigens, and are of donor origin. High levels of EBV-DNA in blood and in vitro spontaneous growth of EBV-lymphoblastoid cell lines predict development of EBV-LPD.

In immunocompromised hosts, EBV-LPD originates from a deficiency of virus-specific cytotoxic T lymphocytes (CTLs), which control outgrowth of EBV-infected B cells. This finding provided the rationale for developing strategies of adoptive cell therapy to restore EBV-specific immune competence. Unselected donor leukocyte infusion, the first attempt at EBV-directed adoptive immunotherapy in humans, can induce EBV-LPD remission but exposes patients to a high risk of developing clinically relevant GVHD and is not suitable for patients transplanted from an HLA-mismatched donor. A safer approach is infusion of in vitro generated EBV-specific CTL lines of donor origin containing both CD8+ and CD4+ T lymphocytes. These CTL lines prevent lymphoproliferative disorders in patients considered at high risk, such as patients given T-cell depleted HSCT from HLA-disparate donors, and cure clinically overt LPD. Infusion of EBV-specific CTLs from third-party donors sharing HLA-class I molecules with the recipient can be also useful. In recent years, use of monoclonal antibodies directed against CD20, a molecule expressed on B cells, has significantly contributed to reduce the incidence and severity of EBV-related LPD, although it can be associated with the emergence of neoplasms in which cells are CD19+ but CD20 negative, thus rendering patients no longer susceptible to the treatment with the monoclonal antibody.

Chapter 139

Late Effects of Hematopoietic Stem Cell Transplantation

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Many children given hematopoietic stem cell transplantation (HSCT) become long-term survivors. Besides chronic graft-versus-host disease (GVHD), long-term complications that may develop in pediatric transplant recipients include impaired growth, neuroendocrine dysfunction, delayed puberty, infertility, second malignancies, cataracts and other ocular complications, leukoencephalopathy, and cardiac and pulmonary dysfunction.

Children given HSCT before puberty may develop **growth impairment,** precluding achievement of the genetic target for adult height. The decrease in growth velocity is similar for boys and girls and is more frequently observed in patients given total-body irradiation (TBI) as part of the preparative regimen. Fractionation of irradiation has a less-adverse impact on height than does single-dose TBI, whereas the use of craniospinal radiotherapy before transplantation plays a synergistic detrimental role with TBI in favoring growth impairment. A study of 175 children younger than 6 yr of age, 6-12 yr of age, or 12-15 yr of age receiving TBI-based regimens and not treated with growth hormone reported a mean final adult height of 3.49, 1.92, and 0.37 SD below average, respectively. Chronic GVHD and its treatment with corticosteroids may also contribute to growth impairment. Serial studies of children given a busulfan-based preparative regimen indicate busulfan

has much less impact on growth but produces the same gonadal failure as TBI-based regimens. Preparative regimens using only cyclophosphamide for children transplanted for aplastic anemia have little, if any, detrimental effect on growth and development.

Growth impairment of patients given TBI is mainly a result of direct damage of cartilage plates and to the effect of TBI on the hypothalamic–pituitary axis, which leads to an inappropriately low production of growth hormone (GH). GH deficiency is susceptible to at least partial correction through administration of hormonal replacement therapy. Annual growth evaluation should be performed in all children after HSCT. Children showing a decreased growth velocity should be further investigated through evaluation of bone age and secretion of GH in response to pharmacologic stimulus. Current studies are aimed at identifying children with GH deficiencies at an earlier age and administering hormonal replacement therapy. Initial concerns about potential risks of favoring disease recurrence or promoting development of second malignancies in GH substitute therapy have not been confirmed and GH replacement therapy is widely employed.

The use of TBI during the preparative regimen involves the thyroid gland in the irradiation field and may result in **hypothyroidism.** Some children who have received single-dose TBI develop either compensated (28-56%) or overt (9-13%) hypothyroidism. The use of fractionated TBI reduces the incidence of both compensated (10-14%) and overt (<5%) hypothyroidism. Children younger than 7 yr old at the time of allograft are at greater risk of developing hypothyroidism. Chemotherapy-only preparative regimens have far fewer adverse effects on normal thyroid function. The site of injury by irradiation is at the level of the thyroid gland rather than at the pituitary or hypothalamus. Therapy with thyroxine is very effective for overt hypothyroidism, but treatment of compensated hypothyroidism is more controversial, although there is evidence that hormonal replacement therapy may reduce the risk of thyroid carcinoma through a suppression of thyroid-stimulating hormone. Despite treatment of hypothyroidism, the incidence of thyroid carcinoma is not negligible. An annual echo of the thyroid gland is indicated for timely identification of nodules in the thyroid gland suspected to be of neoplastic origin. When a nodule with echo characteristics suggestive for a carcinoma is identified, a needle biopsy is indicated to clarify the histologic nature of the nodule. The cumulative incidence of hypothyroidism increases over time, underscoring the importance of annual thyroid function studies.

Gonadal hormones are essential for normal pubertal growth, as well as for development of secondary sexual characteristics. A significant proportion of patients receiving TBI-containing preparative regimens show **delayed development of secondary sexual characteristics,** resulting from primary ovarian or testicular failure. Laboratory evaluation of these patients reveals elevated follicle-stimulating hormone and luteinizing hormone levels with depressed estradiol and testosterone serum levels. These patients benefit from careful follow-up with evaluation of annual Tanner scores and endocrine function. Supplementation of gonadal hormones is useful for primary gonadal failure and is administered with GH to promote pubertal growth. The incidence of sex hormone deficiency is lower in patients given a busulfan-based regimen, while infertility during adulthood is a common problem of these children, as well as of those prepared to the allograft with TBI. The use of reduced-intensity regimens can have the advantage of sparing fertility in a large proportion of patients.

The overall risk of developing a **secondary form of cancer** is significantly higher after HSCT than in the general population. Although few studies have specifically analyzed pediatric patients, available evidence indicates that the cumulative incidence of second malignancies shows a slight, but continuous, tendency to increase over time. Several types of secondary tumors have been identified in patients given HSCT. The most frequently diagnosed neoplasms are thyroid carcinoma, brain tumors, and epithelial cancers. Young age, male gender, use of TBI during the preparative regimen, chronic GVHD, and an intrinsic genetic predisposition to develop cancer (Fanconi anemia) have been reported to be risk factors for development of secondary malignancies after HSCT.

Cataracts mainly occur in children given a radiotherapy-based preparative regimen. The incidence of cataracts is particularly high if TBI is delivered as a single-fraction (800-1,000 cGy). The introduction of fractionated TBI has led to a marked reduction of this complication to ≈10-20% of patients, one-third of whom require surgical intervention. Corticosteroids, frequently employed for treating GVHD, also promote development of cataracts. A dry eye syndrome, or keratoconjunctivitis sicca, may also affect HSCT recipients. It is often related to chronic GVHD and postradiotherapy fibrosis of the lacrimal gland and is treated with artificial tears and lubricants.

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Allergic Disorders

PART XV

Chapter 140

Allergy and the Immunologic Basis of Atopic Disease

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Allergic or atopic patients have an altered state of reactivity to common environmental and food antigens that do not cause clinical reactions in unaffected people. Patients with clinical allergy usually produce immunoglobulin (Ig) E antibodies to the antigens that trigger their illness. The term *allergy* represents the clinical expression of IgE-mediated allergic diseases that have a familial predisposition and that manifest as hyperresponsiveness in target organs such as the lung, skin, gastrointestinal tract, and nose. There has been a significant increase in the prevalence of allergic diseases during the last few decades. This increase is attributed to changes in environmental factors (exposure to tobacco smoke, air pollution, indoor and outdoor allergens, respiratory viruses, obesity and perhaps a decline in certain infectious diseases [hygiene hypothesis]).

KEY ELEMENTS OF ALLERGIC DISEASES

Allergens

Allergens are almost always proteins, but not all proteins are allergens. For a protein antigen to display allergenic activity, it must induce IgE production, which must lead to a type 1 hypersensitivity response upon subsequent exposure to the same protein. Biochemical properties of the allergen, stimulating factors of the innate immune response around the allergen substances at the time of exposure, stability of the allergen in the tissues, digestive system, skin, or mucosa, and the dose and time of stay in lymphatic organs during the interaction with the immune system are all factors that may cause an antigen to become an allergen. This is distinguished from general antigen responses, which induce a state of immune responsiveness without associated IgE production.

Most allergens are proteins of 10-70 kDa molecular weight; molecules <10 kDa do not bridge adjacent IgE antibody molecules on the surfaces of mast cells or basophils; most molecules >70 kDa do not pass through mucosal surfaces, a feature needed to reach antigen-presenting cells (APCs) for stimulation of the immune system. Allergens frequently contain proteases, which promote barrier dysfunction and increase allergen penetration into host tissues. Low-molecular-weight moieties, such as drugs, can become allergens by reacting with serum proteins or cell membrane proteins to be recognized by the immune system. Carbohydrate structures can also be allergens and are most relevant with the increasing use of biologics in clinical practice; patients with cetuximab-induced anaphylaxis have IgE antibodies specific for galactose-α-1,3-galactose (see Chapter 151).

T Cells

Everyone is exposed to potential allergens. Atopic individuals respond to allergen exposure with rapid expansion of **T-helper type 2 (Th2)** cells that secrete cytokines, such as interleukin (IL)-4, IL-5, and IL-13, favoring IgE synthesis and eosinophilia. Allergen-specific IgE antibodies associated with atopic response are detectable by serum testing or positive immediate reactions to allergen extracts on prick skin testing (see Chapter 141). The Th2 cytokines IL-4 and IL-13 play a key role in immunoglobulin isotype switching to IgE (Fig. 140-1). IL-5 and IL-9 are important in differentiation and development of eosinophils. The combination of IL-3, IL-4, and IL-9 contributes to mast cell activation. Th2 cytokines are important effector molecules in the pathogenesis of asthma and allergic diseases; acute allergic reactions are characterized by infiltration of Th2 cells into affected tissues. In addition, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) contribute to Th2 response and eosinophilia.

A fraction of the immune response to allergen results in proliferation of **T helper type 1 (Th1)** cells. Th1 cells are typically involved in the eradication of intracellular organisms, such as mycobacteria, because of the ability of Th1 cytokines to activate phagocytes and promote the production of opsonizing and complement-fixing antibodies. The Th1 component of allergen-specific immune response contributes to chronicity and the effector phase in allergic disease. Activation and apoptosis of epithelial cells induced by Th1 cell–secreted interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and Fas ligand constitute an essential pathogenetic event for the formation of eczematous lesions in atopic dermatitis and bronchial epithelial cell shedding in asthma.

Chronic lesions of allergic reactions are characterized by infiltration of Th1 and **Th17 cells**. This is important because Th1 cytokines such as IFN-γ can potentiate the function of allergic inflammatory effector cells such as eosinophils and thereby contribute to disease severity. Th17 and Th22 cells link the immune response to tissue inflammation; IL-17A and IL-17F and IL-22 are their respective prototype cytokines. Although both T-helper cell subsets play roles in immune defense to extracellular bacteria, IL-17 augments inflammation, whereas IL-22 plays a tissue-protective role. Cytokines in the IL-17 family act on multiple cell types, including epithelial cells and APCs, to cause the release of chemokines, antimicrobial peptides, and proinflammatory cytokines to enhance inflammation and antimicrobial responses. In addition, recently identified Th9 cells produce IL-9, but not other typical Th1, Th2, and Th17 cytokines, and constitute a distinct population of effector T cells that promotes tissue inflammation. Figure 140-2 depicts the complex cytokine cascades involving Th1, Th2, Th9, Th17 and Th22 cells.

T-regulatory (Treg) cells are a subset of T cells thought to play a critical role in expression of allergic and autoimmune diseases. These cells have the ability to suppress effector T cells of either the Th1 or Th2 phenotypes (Fig. 140-3). Treg cells express $CD4^+CD25^+$ surface molecules and immunosuppressive cytokines such as IL-10 and transforming growth factor-β (TGF-β_1). The forkhead box/winged-helix transcription factor gene *FOXP3* is expressed specifically by $CD4^+CD25^+$ Treg cells and programs their development and function. Adoptive transfer of Treg cells inhibits the development of airway eosinophilia and protects against airway hyperreactivity in animal models of asthma. T-cell response to allergens in healthy individuals shows a wide range, from no detectable response to involvement of active peripheral tolerance mechanisms mediated by different subsets of Treg cells. Individuals who are not allergic even though they are exposed to high doses of allergens, such as beekeepers and cat owners, show a detectable allergen-specific IgG4 response accompanied by IL-10–producing Treg cells. It is thought that $CD4^+CD25^+$ Treg cells play an important role in mitigating the allergic immune response and that the lack of such cells may predispose to the development of allergic diseases. Patients with mutations in the human *FOXP3* gene lack $CD4^+CD25^+$ Treg cells and develop severe immune dysregulation, with polyendocrinopathy, food allergy, and high serum IgE levels (XLAAD/

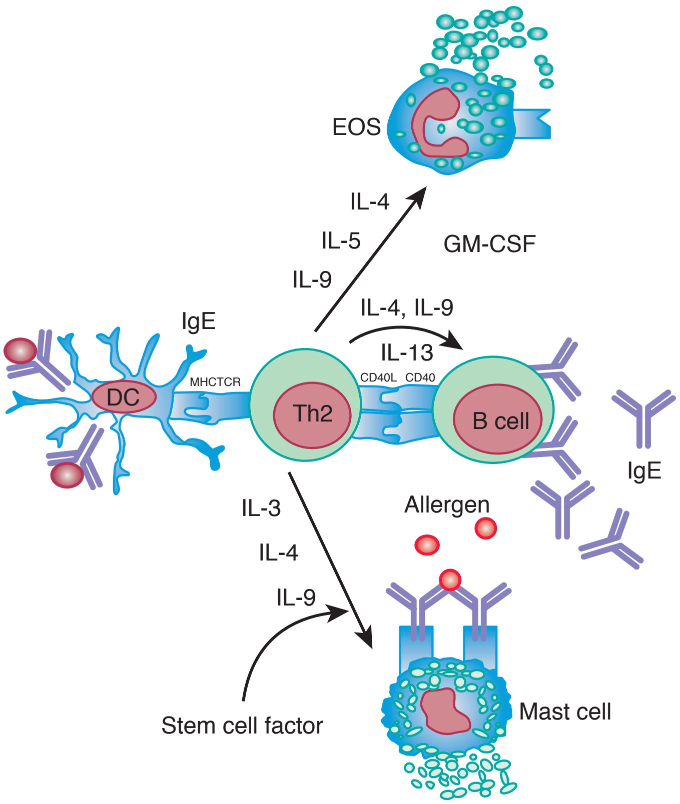

Figure 140-1 **Role of Th2 cytokines in allergic cascade.** DC, dendritic cell; EOS, eosinophil; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; Th2, T-helper type 2 cell.

IPEX disease) (see Chapter 126). In addition to Treg cells, IL-10 secreting and allergen-specific Breg cells that increase during allergen-specific immunotherapy, and may play a role in allergen tolerance were recently demonstrated.

Antigen-Presenting Cells

Dendritic cells, Langerhans cells, monocytes, and macrophages have the ability to present allergens to T cells and thereby modulate allergic inflammation by controlling the type of T-cell development. APCs are a heterogeneous group of cells that share the property of antigen presentation in the context of the major histocompatibility complex (MHC) and are found primarily in lymphoid organs and the skin. Dendritic cells (DCs) and Langerhans cells are unique in their ability to prime naïve T cells and are responsible for the primary immune response, or the **sensitization phase** of allergy. Monocytes and macrophages are thought to contribute to activating memory T-cell responses upon reexposure to allergen, which characterizes the **elicitation phase** of allergy.

Peripheral DCs residing in sites such as the skin, intestinal lamina propria, and lung are relatively immature. These immature DCs take up antigens in tissues and then migrate to the T-cell areas in locally draining lymph nodes. The DCs undergo phenotypic and functional changes during migration, characterized by increased expression of MHC class I, MHC class II, and costimulatory molecules that react with CD28 expressed on T cells. In the lymph nodes, they directly present processed antigens to resting T cells to induce their proliferation and differentiation.

Mature DCs have been designated as myeloid DC or plasmacytoid DC on the basis of their ability to favor Th1 or Th2 differentiation, respectively. The critical factor for polarization to Th1 cells is the level of IL-12 produced by myeloid DC. By contrast, plasmacytoid DC have low levels of IL-12. Plasmacytoid DC particularly play a role in antiviral immunity by rapid production of high amounts of interferon

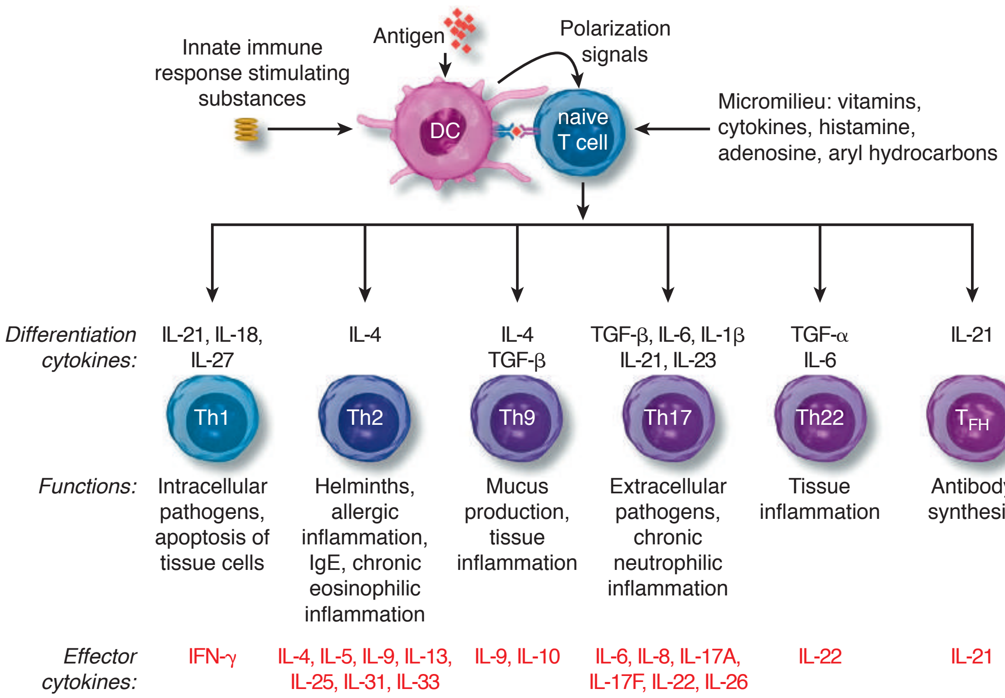

Figure 140-2 **Effector T-cell subsets.** Following antigen presentation by dendritic cells (DCs), naïve T cells differentiate into Th1, Th2, Th9, Th17, Th22, and follicular helper TFH effector subsets. Their differentiation requires cytokines and other cofactors that are released from dendritic cells and also expressed in the micromilieu. T-cell activation in the presence of interleukin-4 (IL-4) enhances differentiation and clonal expansion of Th2 cells, perpetuating the allergic response. IFN-γ, interferon-γ; TGF-β, transforming growth factor-β. *(From Akdis M, Palomares O, van de Veen W, van Splunter M, Akdis CA. TH17 and TH22 cells: a confusion of antimicrobial response with tissue inflammation versus protection,* J Allergy Clin Immunol *129:1438–1449, 2012.)*

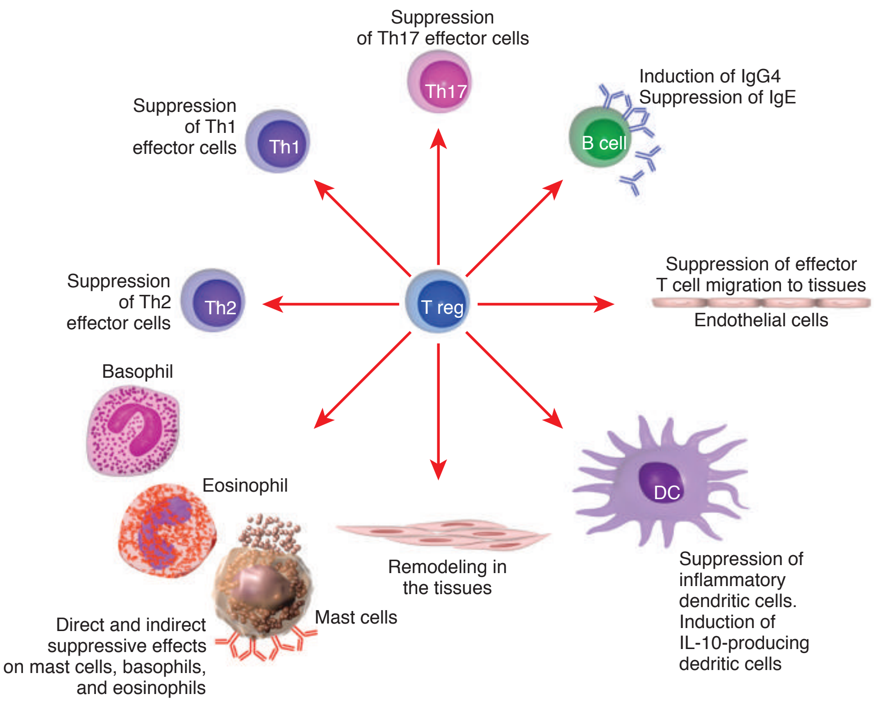

Figure 140-3 FoxP3⁺, CD4⁺, CD25⁺, and Tr1 cells contribute to the control of allergen-specific immune responses in several major ways: Suppression of dendritic cells that support the generation of effector T-cells; suppression of Th1, Th2, and Th17 cells; suppression of allergen-specific IgE, and induction of IgG_4 and/or IgA; suppression of mast cells, basophils, and eosinophils; interaction with resident tissue cells and remodeling, and suppression of effector T-cell migration to tissues. IL-10, interleukin 10. *(From Akdis CA, Akdis M: Mechanisms and treatment of allergic disease in the big picture of regulatory T cells,* J Allergy Clin Immunol *123:735–746, 2009.)*

(IFN)-α and also help B cells for antibody production. There is considerable interest in the role of TSLP, which is overexpressed in the mucosal surfaces and skin of atopic individuals. TSLP enhances Th2 cell differentiation by inducing expression of OX40L on immature myeloid DCs in the absence of IL-12 production.

Presence of allergen-specific IgE on the cell surfaces of APCs is a unique feature of atopy. Importantly, the formation of high-affinity IgE receptor I (FcεRI)/IgE/allergen complexes on APC cell surfaces markedly facilitates allergen uptake and presentation. The clinical importance of this phenomenon is supported by the observation that FcεRI-positive Langerhans cells bearing IgE molecules are a prerequisite for skin-applied, aeroallergen provocation of eczematous lesions in patients with atopic dermatitis. The role of the low-affinity IgE receptor II (FcεRII, CD23) on monocytes-macrophages is less clear, although it appears that under certain conditions it can also facilitate antigen capture. Cross-linking of FcεRII, as well as FcεRI, on monocytes-macrophages leads to the release of inflammatory mediators. There is a critical role for DCs in induction of oral tolerance; tolerogenic DCs are compartmentalized within the mucosa and present antigen through a mechanism designed to produce a Th1/Treg–suppressive response that ablates allergen-specific T cells.

Immunoglobulin E and its Receptors

The acute allergic response depends on IgE and its ability to bind selectively to the α chain of the high-affinity FcεRI or the low-affinity FcεRII (CD23). Cross-linking of receptor-bound IgE molecules by allergen initiates a complex intracellular signaling cascade followed by the release of various mediators of allergic inflammation from mast cells and basophils. The FcεRI molecule is also found on the surface of antigen-presenting DCs (e.g., Langerhans cells), but differs from the structure found on mast cells/basophils in that the FcεRI molecule found on DCs lacks the β chain. CD23 is found on B cells, eosinophils, platelets, and DCs. Cross-linking and FcεRI aggregation on mast cells and basophils can also lead to anaphylaxis (see Chapter 149). Differential expression of tyrosine kinases responsible for positive and negative regulation of mast cell/basophil degranulation are thought to be responsible for this aberrant allergic response.

The induction of IgE synthesis requires 2 major signals. The first signal (signal 1) initiates IL-4 or IL-13 activation of germline transcription at the ε Ig locus, which dictates isotype specificity. The second signal (signal 2) involves the engagement of CD40 on B cells by CD40 ligand expressed on T cells. This engagement results in activation of the recombination machinery, resulting in DNA switch recombination. Interactions between several costimulatory molecule pairs (CD28 and B7; lymphocyte function–associated antigen-1 and intercellular adhesion molecule-1; CD2 and CD58) can further amplify signal 1 and signal 2 to enhance IgE synthesis. Factors that inhibit IgE synthesis include Th1-type cytokines (IL-12, IFN-α, IFN-γ) and microbial DNA containing CpG (cytosine-phosphate-guanine) repeats.

Eosinophils

Allergic diseases are characterized by peripheral blood and tissue eosinophilia. Eosinophils participate in both innate and adaptive immune responses and, like mast cells, contain dense intracellular granules that are sources of inflammatory proteins. These granule proteins include major basic protein, eosinophil-derived neurotoxin, peroxidase, and cationic protein. Eosinophil granule proteins damage epithelial cells, induce airway hyperresponsiveness, and cause degranulation of basophils and mast cells. Major basic protein released from eosinophils can bind to an acidic moiety on the M2 muscarinic receptor and block its function, thereby leading to increased acetylcholine levels and the development of increased airway hyperreactivity. Eosinophils are also a rich source of prostaglandins and leukotrienes; in particular, cysteinyl leukotriene C4 contracts airway smooth muscle and increases vascular permeability. Other secretory products of eosinophils include cytokines (IL-4, IL-5, TNF-α), proteolytic enzymes, and reactive oxygen intermediates, all of which significantly enhance allergic tissue inflammation.

Several cytokines regulate the function of eosinophils in allergic disease. Eosinophils develop and mature in the bone marrow from myeloid precursor cells activated by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Allergen exposure of allergic patients causes resident hematopoietic CD34 cells to express the IL-5 receptor. The IL-5 receptor activation induces eosinophil maturation, causing eosinophils to synthesize granule proteins, prolonging their survival, potentiating degranulation of eosinophils, and stimulating release of eosinophils from the bone marrow. GM-CSF also enhances proliferation, cell survival, cytokine production, and degranulation of eosinophils. Certain chemokines, such as RANTES (regulated upon activation, normal T-cell expressed and secreted),

macrophage inflammatory protein-1α (MIP-1α), and eotaxins, are important for recruiting eosinophils into local allergic tissue inflammatory reactions. Eotaxins mobilize IL-5–dependent eosinophil colony–forming progenitor cells from the bone marrow. These progenitors are rapidly cleared from the blood and either return to the bone marrow or are recruited to inflamed tissue sites.

Mast Cells

Mast cells are derived from CD34 hematopoietic progenitor cells that arise in bone marrow. Upon entering the circulation, they travel to peripheral tissue, where they undergo tissue-specific maturation. Mast cell development and survival relies on interactions between the tyrosine kinase receptor c-kit expressed on the surface of mast cells and the fibroblast-derived c-kit ligand stem cell factor. Unlike mature basophils, mature mast cells do not typically circulate in the blood. They are, instead, widely distributed throughout connective tissues, where they often lie adjacent to blood vessels and beneath epithelial surfaces that are exposed to the external environment, such as the respiratory tract, gastrointestinal tract, and skin. So placed, mast cells are positioned anatomically to participate in allergic reactions. At least 2 subpopulations of human mast cells are recognized: mast cells with tryptase and mast cells with both tryptase and chymase. Mast cells with tryptase are the predominant type found in the lung and small intestinal mucosa, whereas mast cells with both tryptase and chymase are the predominant type found in skin, the gastrointestinal submucosa, and blood vessels.

Mast cells contain, or produce on appropriate stimulation, a diverse array of mediators that have different effects on allergic inflammation and organ function. They include preformed granule-associated mediators (histamine, serine proteases, proteoglycans) and membrane-derived lipid, cytokine, and chemokine mediators arising from de novo synthesis and release. The most important mast cell-derived lipid mediators are the cyclooxygenase and lipoxygenase metabolites of arachidonic acid, which have potent inflammatory activities. The major cyclooxygenase product of mast cells is prostaglandin D_2, and the major lipoxygenase products are the sulfidopeptide leukotrienes (LTs): LTC_4 and its peptidolytic derivatives LTD_4 and LTE_4. Mast cells also can produce cytokines that promote Th2-type responses (IL-4, IL-13, GM-CSF) and inflammation (TNF-α, IL-6), and regulate tissue remodeling (TGF, vascular endothelial cell growth factor). Immunologic activation of mast cells and basophils typically begins with cross-linkage of IgE bound to the FcεRI with multivalent allergen. Mast cell surface FcεRI is increased by IL-4 and IgE. Surface levels of FcεRI decrease in subjects receiving treatment with anti-IgE antibody that lowers serum IgE, which is of potential therapeutic interest.

MECHANISMS OF ALLERGIC TISSUE INFLAMMATION

IgE-mediated immune responses can be classified chronologically according to 3 reaction patterns. The **early-phase response** is the immediate response after allergen is introduced into target organs. This response is characterized by mast cell degranulation and release of preformed mediators, occurring within an immediate time frame of between 1 and 30 min after allergen exposure and resolving within 1-3 hr. Acute reactions are associated with increased local vascular permeability, which leads to leakage of plasma proteins, tissue swelling, and increased blood flow, as well as itching, sneezing, wheezing, and acute abdominal cramps in the skin, nose, lung, and gastrointestinal tract, respectively, depending on the targeted organ.

A second, **late-phase response** can occur within hours of allergen exposure, reaching a maximum at 6-12 hr and resolving by 24 hr. Late-phase responses are characterized in the skin by edema, redness, and induration; in the nose by sustained nasal blockage; and in the lung by airway obstruction and persistent wheezing. In general, late-phase responses are associated with early infiltration of neutrophils and eosinophils followed by basophils, monocytes, macrophages, and Th2-type cells. Recruitment of inflammatory cells from the circulation requires increased expression of adhesion molecules on their cell surfaces and expression of their ligand on endothelial cells, which are under the control of cytokines. Several hours after allergen exposure, TNF-α released by activated mast cells induces the vascular endothelial expression of cell adhesion molecules, and this change leads to transendothelial migration of various inflammatory cells. Preferential accumulation of eosinophils occurs through interactions between selective adhesion molecules on the eosinophil cell surface (e.g., $\alpha_4\beta_1$ integrin or very late antigen-4); vascular cell adhesion molecule-1 surface expression can be enhanced by IL-4 and IL-13 on endothelial cells.

Chemokines are chemotactic cytokines that play a central role in tissue-directed migration of inflammatory cells. RANTES, MIP-1α, monocyte chemotactic protein (MCP)-3, and MCP-4 are chemoattractants for eosinophils and mononuclear cells, whereas eotaxins are relatively selective for eosinophils. These chemoattractants have been detected in epithelium, macrophages, lymphocytes, and eosinophils at sites of late-phase responses and allergic tissue inflammation. Blockade of these chemokines leads to significant reduction in tissue-directed migration of allergic effector cells.

In the third reaction pattern, **chronic allergic disease,** tissue inflammation can persist for days to years. Several factors contribute to persistent tissue inflammation, including recurrent exposure to allergens and microbial agents. The repeated stimulation of allergic effector cells such as mast cells, basophils, eosinophils, and Th2 cells contributes to unresolved inflammatory conditions. Additionally, Th2-type cytokines (IL-3, IL-5, GM-CSF) secreted during allergic reactions can prolong survival of allergic effector cells by delaying apoptosis. Local differentiation of tissue-infiltrating eosinophil precursors induced by IL-5 results in self-generation of eosinophils, further sustaining damage of local tissue. Tissue remodeling leading to irreversible changes in target organs is also a feature of chronic allergic disease. In asthma, **remodeling** involves thickening of the airway walls and submucosal tissue, as well as smooth muscle hypertrophy and hyperplasia, which are associated with a decline in lung function. This is an unexpected role for eosinophils in airway remodeling as well as chronic inflammation. In atopic dermatitis, lichenification is an obvious manifestation of skin remodeling.

Th2 cytokines can not only maintain allergic inflammation but also influence tissue remodeling by activating resident cells in target organs; IL-4, IL-9, and IL-13 induce mucus hypersecretion and metaplasia of mucus cells; IL-4 and IL-13 stimulate fibroblast growth and synthesis of extracellular matrix proteins; and IL-5 and IL-9 increase subepithelial fibrosis. TGF-β produced by eosinophils and fibroblasts can enhance subepithelial fibrosis. IL-11 expressed by eosinophils and epithelial cells also contributes to subepithelial fibrosis, in addition to enhancing deposition of collagen and the accumulation of fibroblasts. Additional interleukins released from epithelial cells and DCs, such as IL-25, IL-31, and IL-33, also contribute to the Th2 and eosinophilic inflammation in the affected tissues. The resulting tissue injury amplifies further epithelial injury through proinflammatory cytokine release, extracellular matrix deposition in target organs, and angiogenesis. Genetic predisposition to aberrant injury-repair responses may contribute to chronicity of illness. Once the allergic immune response is established, it can be self-perpetuating and can lead to chronic disease in genetically predisposed individuals. The subsequent infiltration of Th1 cells and Th17 cells enhances the inflammatory potential of allergic effector cells and contributes to chronic tissue inflammatory responses through the release of proinflammatory cytokines and chemokines. In addition, an autoimmune response might be playing a causative role in allergic inflammation resulting from possible mechanisms through IgE autoantibodies, IgG autoantibodies, and Th1 cell and Th17 cell autoreactivity.

GENETIC BASIS OF ATOPY

Allergic diseases are complex genetic conditions susceptible to environmental triggers. Several major groups of genes are associated with allergic diseases: genes that regulate systemic expression of atopy (increased IgE synthesis, eosinophilia, mast cell responses) that are commonly expressed among various allergic diseases, genes that control barrier function in specific target organs (e.g., the skin in atopic

dermatitis, the lung in asthma, the gastrointestinal tract in food allergy), and genes encoding pattern-recognition receptors of the innate immune system that engage microbial pathogens and influence adaptive immune responses. Once allergic responses have been initiated, a genetic predisposition to chronic allergic inflammation and aberrant injury-repair responses contribute to tissue remodeling and persistent disease.

Atopic diseases have a strong familial predisposition, with approximately 60% heritability found in twin studies of asthma and atopic dermatitis. The 5q23-35 region comprises several genes implicated in allergic disease pathogenesis, including genes coding for Th2 cytokines (IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF). Among these, *IL4* is a well-studied potential candidate gene. A nucleotide change at position 589 of the *IL4* promoter region is associated with the formation of a unique binding site for NF-AT (**n**uclear **f**actor for **a**ctivated **T** cells) transcription factor, increased IL-4 gene transcription, higher NF-AT binding affinity, and increased IgE production. Similarly, *IL13* coding region variants have been associated with asthma and atopic dermatitis. An association between atopy and a gain-of-function polymorphism on chromosome 16, which codes for the α subunit of the IL-4R, has been found. This finding is consistent with the important role of IL-4, IL-13, and their receptors in the immunopathogenesis of allergic diseases.

Genome-wide searches have also linked atopy to chromosome region 11q13. The gene encoding the β subunit of FcεRI-β has been proposed to be the candidate gene in this region. The β subunit gene modifies the FcεRI activity on mast cells, and several genetic variants of FcεRI-β are associated with asthma and atopic dermatitis. Chromosome 6 contains genes coding for human leukocyte antigen class I and class II molecules, which regulate the specificity and intensity of the immune responses to specific allergens. IgE responses to specific allergens, such as ragweed antigen Amb a V and mite allergen *Der p* I, have been linked to specific MHC class II loci. TNF-α, a key cytokine that contributes to the influx of inflammatory cells, is also located on chromosome 6. TNF-α polymorphisms are associated with asthma.

Barrier dysfunction has a key role in the pathogenesis of allergic diseases. Genetic linkage studies of atopic dermatitis have demonstrated the importance of chromosome 1q21, which contains a cluster of genes involved in epidermal differentiation. Filaggrin is a protein that is essential in the formation of the stratum corneum. Null mutations of the filaggrin gene are strongly associated with early onset and severe atopic dermatitis. Mutations in the gene encoding the serine protease inhibitor SPINK5 has been shown to cause **Netherton disease**, a single-gene disorder associated with erythroderma, food allergy, and high serum IgE levels. A common polymorphism in SPINK5 (in particular, Glu420Lys) increases the risk of developing atopic dermatitis and asthma. SPINK5 is expressed in the outer epidermis and is thought to be critical to neutralizing the proteolytic activity of *Staphylococcus aureus* and common allergens such as *Der p* I, which use these proteases to penetrate the skin to induce allergic responses. Barrier dysfunction is involved in other allergic diseases, such as asthma and rhinosinusitis, but likely involves other barrier genes, such as those encoding gap junctions.

Candidate genes associated with asthma susceptibility have been identified by positional cloning: *GPRA* (G-protein coupled receptor for asthma susceptibility on chromosome 7p14), *ADAM-33* (a disintegrin and metalloproteinase 33 on chromosome 20p), and *DPP10* (dipeptidyl peptidase 10 on chromosome 2q14). The functions of these genes do not fit into classical pathways of atopy and therefore provide new insights into asthma pathogenesis. *GPRA* encodes a G-protein coupled receptor, with isoforms expressed in bronchial epithelial cells and smooth muscle in asthmatic persons, suggesting an important role for these tissues in asthma. *ADAM-33* is expressed in bronchial smooth muscle and has been linked to bronchial hyperresponsiveness. *DPP10* encodes a dipeptidyl dipeptidase that can remove the terminal 2 peptides from certain proinflammatory chemokines, a change that may modulate allergic inflammation.

Pattern-recognition receptors of the innate immune system, which are expressed by epithelial cells and DCs, are associated with disease susceptibility. These receptors recognize specific microbial components. Polymorphisms in CD14 (engages endotoxin), Toll-like receptor 2 (which engages *S. aureus*), and T-cell immunoglobulin domain and mucin domain (which engage hepatitis A virus) correlate with asthma and/or atopic dermatitis susceptibility. Dysregulation of these frontline immune defense systems would permit abnormal response to common environmental allergens.

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Chapter 141

Diagnosis of Allergic Disease

Jennifer S. Kim, Supinda Bunyavanich, and Scott H. Sicherer

ALLERGY HISTORY

Obtaining a complete history from the allergic patient involves eliciting a description of all symptoms along with their timing and duration, exposure to common allergens, and responses to previous therapies. Because patients often suffer from more than 1 allergic disease, the presence or absence of other allergic diseases, including allergic rhinoconjunctivitis, asthma, food allergy, eosinophilic esophagitis, atopic dermatitis, and drug allergy should be determined. A family history of allergic disease is common and is one of the most important factors predisposing a child to the development of allergies. The risk of allergic disease in a child approaches 50% when 1 parent is allergic and 66% when both parents are allergic, with maternal history of atopy having a greater effect than paternal history.

Several characteristic behaviors are often seen in allergic children. Because of nasal pruritus and rhinorrhea, children with allergic rhinitis often perform the **allergic salute** by rubbing their nose upward with the palm of their hand. This repeated maneuver may give rise to the **nasal crease,** a horizontal wrinkle over the bridge of the nose. Characteristic vigorous **grinding** of the eyes with the thumb and side of the fist is frequently observed in children with allergic conjunctivitis. The **allergic cluck** is produced when the tongue is placed against the roof of the mouth to form a seal and withdrawn rapidly in an effort to scratch the palate. The presence of other symptoms, such as fever, unilateral nasal obstruction, and purulent nasal discharge, suggests other diagnoses.

The timing of onset and the progression of symptoms are relevant. The onset of recurrent or persistent nasal symptoms coinciding with placement in a daycare center might suggest recurrent infection rather than allergy. When patients present with a history of episodic acute symptoms, it is important to review the setting in which symptoms occur as well as the activities and exposures that immediately precede their onset. Symptoms associated with lawn mowing suggest allergy to grass pollen or fungi, whereas if symptoms occur in homes with pets, animal dander sensitivity is an obvious consideration. Reproducible reactions after ingestion of a specific food raise the possibility of food allergy. When symptoms wax and wane but evolve gradually and are more chronic in duration, a closer look at whether the timing and progression of symptoms correlate with exposure to a seasonal aeroallergen is warranted.

Aeroallergens, such as pollens and fungal spores, the concentrations of which in outdoor air fluctuate seasonally, are prominent causes of allergic disease. Correlating symptoms with seasonal pollination patterns of geographically relevant plants and trees along with information provided by local pollen counts can aid in identifying the allergen. Throughout most of the United States, trees pollinate in the early spring, grasses pollinate in the late spring and early summer, and

weeds pollinate in late summer through the fall. The presence of fungal spores in the atmosphere follows a seasonal pattern in the northern United States with spore counts rising with the onset of warmer weather and peaking in late summer months, only to recede again with the first frost through the winter. In warmer regions of the southern United States, fungal spores and grass pollens may cause symptoms on a perennial basis.

Rather than experiencing seasonal symptoms, some patients suffer allergic symptoms year-round. In these patients, sensitization to perennial allergens usually found indoors, such as dust mites, animal dander, cockroaches, and fungi, warrants consideration. Species of certain fungi, such as *Aspergillus* and *Penicillium,* are found indoors whereas *Alternaria* is found in both indoor and outdoor environments. Cockroach allergens are often problematic in inner city environments. Patients sensitive to perennial allergens often also become sensitized to seasonal allergens and experience baseline symptoms year-round with worsening during the pollen seasons.

The age of the patient is an important consideration in identifying potential allergens. Infants and young children are first sensitized to allergens that are in their environment on a continuous basis, such as dust mites, animal dander, and fungi. Sensitization to seasonal allergens usually takes several seasons of exposure to develop and is thus unlikely to be a significant trigger of symptoms in infants and toddlers.

Food allergies are more common in infants and young children, resulting primarily in cutaneous, gastrointestinal, and, less frequently, respiratory symptoms. Symptoms of immediate or immunoglobulin (Ig) E-mediated hypersensitivity food reactions develop within minutes to 2 hr after ingestion of the offending food. Symptoms of non–IgE-mediated food allergies are often delayed or chronic (see Chapter 151).

Complete information from previous evaluations and prior treatments for allergic disease should be reviewed, including impact of changes in local environment (e.g., home vs. school), response to medications, elimination diets, and duration and impact of allergen immunotherapy (if applicable). Improvement in symptoms with medications or avoidance strategies used to treat allergic disease provides additional evidence for an allergic process.

A thorough environmental survey should be performed, focusing on potential sources of allergen and/or irritant exposure, particularly when respiratory symptoms (upper and/or lower) are reported. The age and type of the dwelling, how it is heated and cooled, the use of humidifiers or air filtration units, and any history of water damage should be noted. Forced air heating may stir up dust mite, fungi, and animal allergens. The irritant effects of wood-burning stoves, fireplaces, and kerosene heaters may provoke respiratory symptoms. Increased humidity or water damage in the home is often associated with greater exposure to dust mites and fungi. Carpeting serves as a reservoir for dust mites, fungi, and animal dander. The number of domestic pets and their movements about the house should be ascertained. Special attention should be focused on the bedroom, where a child spends a significant proportion of time. The age and type of bedding, the number of stuffed animals, type of window treatments, and the accessibility of pets to the room should be reviewed. The number of smokers in the home and where they smoke is useful information. Activities that might result in exposure to allergens or respiratory irritants such as paint fumes, cleansers, sawdust, or glues should be identified. Similar information should be obtained in regard to other environments where the child spends large portions of time, such as a relative's home or school setting.

PHYSICAL EXAMINATION

In patients with **asthma,** spirometry should be performed. If respiratory distress is observed, pulse oximetry should be performed.

The child presenting with a chief complaint of rhinitis or rhinoconjunctivitis should be observed for mouth breathing, paroxysms of sneezing, sniffing/snorting, throat clearing, and rubbing of the nose and eyes (representing pruritus). Infants should be observed during feeding for nasal obstruction severe enough to interfere with feeding or for more obvious signs of aspiration or gastroesophageal reflux. The frequency and nature of coughing that occurs during the interview and any positional increase in coughing or wheezing should be noted. Children with asthma should be observed for congested or wet cough, tachypnea at rest, retractions, and audible wheezes, which may worsen with crying. Patients with atopic dermatitis should be monitored for repetitive scratching and the extent of skin involvement.

Because children with severe asthma as well as those receiving chronic or frequent oral corticosteroids may suffer growth suppression, an accurate height should be plotted at regular intervals. However, long-term follow-up studies suggest that use of inhaled glucocorticoids in prepubertal children is associated with a small initial decrease in attained height (~1 cm) that may persist as a reduction in adult height that is not progressive or cumulative. Poor weight gain in a child with chronic chest symptoms should prompt consideration of cystic fibrosis. Anthropometric measures are also important to monitor in those on restricted diets because of multiple food allergies or eosinophilic esophagitis. Blood pressure should be measured to evaluate for steroid-induced hypertension. The patient with acute asthma may present with **pulsus paradoxus,** defined as a drop in systolic blood pressure during inspiration >10 mm Hg. Moderate to severe airways obstruction is indicated by a decrease of >20 mm Hg. An increased heart rate may be the result of an asthma flare or the use of a β-agonist or decongestant. Fever is not caused by allergy alone and should prompt consideration of an infectious process, which may exacerbate asthma.

Parents are often concerned about blue-gray to purple discolorations beneath their child's lower eyelids, which can be attributed to venous stasis and are referred to as **allergic shiners.** They are found in up to 60% of allergic patients and almost 40% of patients *without* allergic disease. Thus, "shiners" may suggest, but are not diagnostic of, allergic disease. In contrast, the **Dennie-Morgan folds** (Dennie lines) are a feature of atopic dermatitis. These are prominent infraorbital skin folds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin.

In patients with **allergic conjunctivitis,** involvement of the eyes is bilateral. Examination of the conjunctiva reveals varying degrees of lacrimation, conjunctival injection, and edema. In severe cases, periorbital edema involving primarily the lower eyelids or **chemosis** (conjunctival edema that is gelatinous in appearance) may be observed. The classic discharge associated with allergic conjunctivitis is usually described as "stringy" or "ropy." In children with vernal conjunctivitis, a more severe, chronic phenotype, examination of the tarsal conjunctiva may reveal cobblestoning. **Keratoconus,** or protrusion of the cornea, may occur in patients with vernal conjunctivitis or periorbital atopic dermatitis as a result of repeated trauma produced by persistent rubbing of the eyes. Children treated with high-dose or chronic corticosteroids are at risk for development of posterior subcapsular cataracts.

The external ear should be examined for eczematous changes in patients with atopic dermatitis, including the postauricular area and base of the earlobe. Because otitis media with effusion is common in children with allergic rhinitis, pneumatic otoscopy should be performed to evaluate for the presence of fluid in the middle ear and to exclude infection.

Examination of the nose in allergic patients may reveal the presence of a nasal crease. Nasal patency should be assessed, and the nose examined for structural abnormalities affecting nasal airflow, such as septal deviation, turbinate hypertrophy, and nasal polyps. Decrease or absence of the sense of smell should raise concern about chronic sinusitis or nasal polyps. Nasal polyps in children should raise concerns of cystic fibrosis. The nasal mucosa in allergic rhinitis is classically described as pale to purple in comparison with the beefy red mucosa of patients with nonallergic rhinitis. Allergic nasal secretions are typically thin and clear. Purulent secretions suggest another cause of rhinitis. The frontal and maxillary sinuses should be palpated to identify tenderness to pressure that might be associated with acute sinusitis.

Examination of the lips may reveal cheilitis caused by drying of the lips from continuous mouth breathing or repeated licking of the lips in an attempt to replenish moisture and relieve discomfort (**lip licker's dermatitis**). Tonsillar and adenoidal hypertrophy along with a history of impressive snoring raises the possibility of obstructive

sleep apnea. The posterior pharynx should be examined for the presence of postnasal drip and posterior pharyngeal lymphoid hyperplasia ("cobblestoning").

Chest findings in asthmatic children vary significantly and may depend on disease duration, severity, and activity. In a child with well-controlled asthma, the chest should appear entirely normal on examination between asthma exacerbations. Examination of the same child during an acute episode of asthma may reveal hyperinflation, tachypnea, use of accessory muscles, wheezing, and decreased air exchange with a prolonged expiratory time. Tachycardia may be caused by the asthma exacerbation or accompanied by jitteriness after treatment with β-agonists. Decreased airflow or rhonchi and wheezes over the right chest may be noted in children with mucus plugging and right middle lobe atelectasis. The presence of cyanosis indicates severe respiratory compromise. Unilateral wheezing after an episode of coughing and choking in a small child without a history of previous respiratory illness suggests **aspiration of a foreign body.** Wheezing limited to the larynx in association with inspiratory stridor may be seen in older children and adolescents with **vocal cord dysfunction.** Digital clubbing is rarely seen in patients with uncomplicated asthma and should prompt further evaluation to rule out other potential chronic diagnoses, such as cystic fibrosis.

The skin of the allergic patient should be examined for evidence of urticaria/angioedema or atopic dermatitis. **Xerosis,** or dry skin, is the most common skin abnormality of allergic children. **Keratosis pilaris**, often found on facial cheeks and extensor surfaces of the upper arms and thighs, is a benign condition characterized by skin-colored or slightly pink papules caused by keratin plugs lodged in the openings of hair follicles. Examination of the skin of the palms and soles may reveal thickened skin and exaggerated palmar and plantar creases (hyperlinearity) in children with moderate-to-severe atopic dermatitis.

DIAGNOSTIC TESTING

In Vitro Tests

Allergic diseases are often associated with increased numbers of eosinophils circulating in the peripheral blood and invading the tissues and secretions of target organs. Eosinophilia, defined as the presence of >500 eosinophils/μL in peripheral blood, is the most common hematologic abnormality of allergic patients. Seasonal increases in the number of circulating eosinophils may be observed in sensitized patients after exposure to allergens such as tree, grass, and weed pollens. The number of circulating eosinophils can be suppressed by certain infections and systemic corticosteroids. In certain pathologic conditions, such as drug reactions, eosinophilic pneumonias, and eosinophilic esophagitis, significantly increased numbers of eosinophils may be present in the target organ in the absence of peripheral blood eosinophilia. Increased numbers of eosinophils are observed in a wide variety of disorders in addition to allergy (Table 141-1; see Chapter 129). Eosinophil counts >1500 without an identifiable etiology should suggest 1 of the 2 hypereosinophilic syndromes (Table 141-1; see Chapter 129).

Nasal and bronchial secretions may be examined for the presence of eosinophils. The presence of eosinophils in the sputum of asthmatic patients is classic. An increased number of eosinophils in a smear of nasal mucus with Hansel stain is a more sensitive indicator of nasal allergies than peripheral blood eosinophilia and can aid in distinguishing allergic rhinitis from other causes of rhinitis. An elevated IgE value is often found in the serum of allergic patients, because IgE is the primary antibody associated with immediate hypersensitivity reactions. IgE values are measured in international units (IU), with 1 IU equal to 2.4 ng of IgE. Maternal IgE (unlike IgG) does not cross the placenta. Serum IgE levels gradually rise over the first years of life to peak in the teen years and decrease steadily thereafter. Additional factors, such as genetic influences, race, gender, certain diseases, and exposure to cigarette smoke and allergens, also affect serum IgE levels. Total serum IgE levels may increase 2- to 4-fold during and immediately after the pollen season and then gradually decline until the next pollen season. Comparison of total IgE levels among patients with allergic diseases reveals that those with atopic dermatitis tend to have the highest levels while patients with allergic asthma generally have higher levels than those with allergic rhinitis. Although average total IgE levels are higher in populations of allergic patients than in comparable populations without allergic disease, the overlap in levels is such

Table 141-1 Differential Diagnosis of Childhood Eosinophilia
PHYSIOLOGIC
Prematurity
Infants receiving hyperalimentation
Hereditary
INFECTIOUS
Parasitic (with tissue-invasive helminths, e.g., trichinosis, strongyloidiasis, pneumocystosis, filariasis, cysticercosis, cutaneous and visceral larva migrans, echinococcosis)
Bacterial (brucellosis, tularemia, cat-scratch disease, *Chlamydia*)
Fungal (histoplasmosis, blastomycosis, coccidioidomycosis, allergic bronchopulmonary aspergillosis)
Mycobacterial (tuberculosis, leprosy)
Viral (HIV-1, HTLV-1, hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus)
PULMONARY
Allergic (rhinitis, asthma)
Churg-Strauss syndrome
Loeffler syndrome
Hypersensitivity pneumonitis
Eosinophilic pneumonia (chronic, acute)
Pulmonary interstitial eosinophilia
DERMATOLOGIC
Atopic dermatitis
Pemphigus
Dermatitis herpetiformis
Infantile eosinophilic pustular folliculitis
Eosinophilic fasciitis (Schulman syndrome)
Eosinophilic cellulitis (Wells syndrome)
Kimura disease (angiolymphoid hyperplasia with eosinophilia)
HEMATOLOGIC/ONCOLOGIC
Neoplasm (lung, gastrointestinal, uterine)
Leukemia/lymphoma
Myelofibrosis
Myeloproliferative (FIP1L1-PDGFRA–positive) hypereosinophilic syndrome
Lymphatic hypereosinophilic syndrome
Systemic mastocytosis
IMMUNOLOGIC
T-cell immunodeficiencies
Hyperimmunoglobulin E (Job) syndrome
Wiskott-Aldrich syndrome
Graft-versus-host disease
Drug hypersensitivity
Postirradiation
Postsplenectomy
ENDOCRINE
Addison disease
Hypopituitarism
CARDIOVASCULAR
Loeffler disease (fibroplastic endocarditis)
Congenital heart disease
Hypersensitivity vasculitis
Eosinophilic myocarditis
GASTROINTESTINAL
Benign proctocolitis
Inflammatory bowel disease
Eosinophilic gastrointestinal diseases (EGID)

FIP1L1-PDGFRA, FIP1-like 1–platelet-derived growth factor receptor α.

that the diagnostic value of a total IgE level is poor. Approximately one-half of patients with allergic disease have total IgE levels in the normal range. However, measurement of total IgE is indicated when the diagnosis of **allergic bronchopulmonary aspergillosis** is suspected because total serum IgE concentration >1,000 ng/mL is a criterion for diagnosis of this disorder (see Chapter 237.1). Total serum IgE may also be elevated in several nonallergic diseases (Table 141-2; see Chapter 126).

The presence of IgE specific for a particular allergen can be documented in vivo by skin testing or in vitro by the measurement of **allergen-specific IgE (sIgE)** levels in the serum (Table 141-3). The first test for documenting the presence of sIgE was called the radioallergosorbent test because it used a radiolabeled anti-IgE antibody. The radioallergosorbent test has been replaced by an improved generation of automated enzymatic sIgE immunoassays. These assays use solid-phase supports to which allergens of an individual allergen extract are bound. A small amount of the patient's serum is incubated with the allergen-coated support. The allergen-coated support bound to the patient's sIgE is then incubated with enzyme-conjugated antihuman IgE. Incubation of this sIgE–antihuman IgE complex with a fluorescent substrate of the conjugated enzyme results in the generation of fluorescence that is proportional to the amount of sIgE in the serum sample. The amount of sIgE in the serum sample is calculated by interpolation from a standard calibration curve and reported in arbitrary mass units (kilo-IU of allergen-specific antibody per unit volume of sample [kU_A/L]). Laboratory reports may specify classes, counts, or units, but quantification of results in kU_A/L is most useful. There are 3 commercial detection systems approved by the U.S. Food and Drug Administration that have excellent performance characteristics, but the individual systems do not measure sIgE antibodies with comparable efficiencies and thus are not interchangeable. **Component testing** refers to emerging diagnostic tests where sIgE is measured to specific proteins that comprise allergens (e.g., Ara h 2 from peanut or Bet v 1 from birch pollen), rather than to a mixture of the allergens extracted from the source. Testing sIgE to component allergens may add additional diagnostic value by differentiating immune responses that are directed toward clinically relevant allergenic proteins.

Table 141-2 Nonallergic Diseases Associated with Increased Serum IgE Concentrations

PARASITIC INFESTATIONS
Ascariasis
Capillariasis
Echinococcosis
Fascioliasis
Filariasis
Hookworm
Onchocerciasis
Malaria
Paragonimiasis
Schistosomiasis
Strongyloidiasis
Trichinosis
Visceral larva migrans

INFECTIONS
Allergic bronchopulmonary aspergillosis
Candidiasis, systemic
Coccidioidomycosis
Cytomegalovirus mononucleosis
Human immunodeficiency virus type 1 infections
Infectious mononucleosis (Epstein-Barr virus)
Leprosy
Pertussis
Viral respiratory infections

IMMUNODEFICIENCY
Autosomal dominant hyperimmunoglobulin E syndrome (*STAT3* mutations)
Autosomal recessive hyperimmunoglobulin E syndrome (*DOCK8, TYK2* mutations)
IgA deficiency, selective
Nezelof syndrome (cellular immunodeficiency with immunoglobulins)
Thymic hypoplasia (DiGeorge anomaly)
Wiskott-Aldrich syndrome

NEOPLASTIC DISEASES
Hodgkin disease
IgE myeloma
Bronchial carcinoma

OTHER DISEASES AND DISORDERS
Alopecia areata
Bone marrow transplantation
Burns
Cystic fibrosis
Dermatitis, chronic acral
Erythema nodosum, streptococcal infection
Guillain-Barré syndrome
Kawasaki disease
Liver disease
Medications
Nephritis, drug-induced interstitial
Nephrotic syndrome
Pemphigus, bullous
Polyarteritis nodosa, infantile
Primary pulmonary hemosiderosis
Rheumatoid arthritis

In Vivo Tests

Allergen skin testing is the primary in vivo procedure for the diagnosis of allergic disease. Mast cells with sIgE antibodies attached to high-affinity receptors on their surfaces reside in the skin of allergic patients. The introduction of minute amounts of an allergen into the skin of the sensitized patient results in cross-linking of IgE antibodies on the mast cell surface, thereby triggering local mast cell activation. Once activated, these mast cells release a variety of preformed and newly generated mediators that act on surrounding tissues. Histamine is the mediator most responsible for the immediate wheal and flare reactions observed in skin testing. Examination of the site of a positive skin test result reveals a pruritic wheal surrounded by erythema. The time course of these reactions is rapid in onset, reaching a peak within 10-20 min and usually resolving over the next 30 min.

Skin testing is performed using the **prick/puncture technique.** With this technique, a small drop of allergen is applied to the skin surface, and a tiny amount is introduced into the epidermis by lightly pricking or puncturing the outer layer of skin through the drop of extract with a small needle or other device. When the **skin prick test**

Table 141-3 Determination of Specific IgE by Skin Testing Versus In Vitro Testing

VARIABLE	SKIN TEST*	sIgE ASSAY
Risk of allergic reaction	Yes (especially ID)	No
Relative sensitivity	High	High
Affected by antihistamines	Yes	No
Affected by corticosteroids	Usually not	No
Affected by extensive dermatitis or dermographism	Yes	No
Broad selection of antigens	Fewer	Yes
Immediate results	Yes	No
Expensive	No	Yes
Lability of allergens	Yes	No
Results evident to patient	Yes	No

*Skin testing may be the prick test or intradermal (ID) injection.

(SPT) result is negative but the history suggestive, selective skin testing (for vaccines, venom, drugs, and aeroallergens) using the **intradermal technique** may be performed. This technique involves using a 26-gauge needle to inject 0.01-0.02 mL of an allergen extract diluted 1,000- to 100-fold into the dermis of the arm. Intradermal skin tests are *not recommended for use with food allergens* because of the risk of triggering anaphylaxis. Irritant rather than allergic reactions can occur with intradermal skin testing if higher concentrations of extracts are used. Although skin prick testing is less sensitive than intradermal skin testing, positive SPT results tend to correlate better with clinical symptoms.

The number of skin tests performed should be individualized, with the allergens suggested by the history taken into account. A positive and negative control SPT, using histamine and saline, respectively, is performed with each set of skin tests. A negative control is necessary to assess for dermatographism, in which reactions are caused merely by applying pressure to overly sensitive skin. A positive control is necessary to establish the presence of a cutaneous response to histamine. Medications with antihistaminic properties in addition to adrenergic agents such as ephedrine and epinephrine suppress skin test responses and should be avoided for appropriate intervals (≈5 half-lives) prior to skin testing. Prolonged courses of systemic corticosteroids may suppress cutaneous reactivity by decreasing the number of tissue mast cells as well as their ability to release mediators.

Whether identified via serologic or skin testing, detection of sIgE denotes a sensitized state (i.e., atopy or a tendency toward development of allergic disease) but is not equivalent to a clinically relevant allergic diagnosis. *Many children with positive tests have no clinical symptoms upon exposure to the allergen*. Increasingly strong tests (higher serum sIgE results or larger SPT wheal sizes) generally correlate with increasing likelihood of clinical reactivity (but not severity). The limitations of these test modalities underscore the need for the clinician to obtain a detailed medical history that can guide the selection and interpretation of test results. Large panels of indiscriminately performed screening tests may, therefore, provide misleading information.

Both serum sIgE tests and SPT are sensitive and have similar diagnostic properties. The benefits of the serologic immunoassays are that performance is not limited by presence of skin disease (i.e., active atopic dermatitis) or medication use (i.e., antihistamines). Advantages of skin testing are that they provide rapid results to the patient/family during the clinic visit, do not require venipuncture, and are less costly.

Under certain circumstances, **provocation testing** is performed to examine the association between allergen exposure and the development of symptoms. The bronchial provocation test most frequently performed clinically is the methacholine challenge, which causes potent bronchoconstriction of asthmatic but not of normal airways. **Methacholine challenge testing** is performed to document the presence and degree of bronchial hyperreactivity in a patient in whom asthma is suspected. After baseline spirometry values are obtained, increasing concentrations of nebulized methacholine are inhaled until a drop occurs in lung function, specifically a 20% decrease in FEV_1 (forced expiratory volume in the first second of expiration), or the patient is able to tolerate the inhalation of a set concentration of methacholine, typically 25 mg/mL.

Oral **food challenges** are performed to determine whether a specific food causes symptoms or whether a suspected food can be added to the diet. Food challenges are performed for those foods incriminated by the history and results of skin tests and/or immunoassays for sIgE. These challenges may be performed in an open, single-blind, double-blind, or double-blind placebo-controlled fashion and involve the ingestion of gradually increasing amounts of the suspected food at set time intervals until the patient either experiences a reaction or tolerates a normal portion (i.e., 1 serving size) of the food openly. Because of the potential for significant allergic reactions, these challenges should be performed only in an appropriately equipped facility with personnel experienced in the performance of food challenges and the treatment of anaphylaxis, including cardiopulmonary resuscitation.

Upper gastrointestinal **endoscopy** is required to confirm the diagnosis of eosinophilic esophagitis. One or more biopsy specimens from the proximal and distal esophagus must show eosinophil-predominant inflammation. With few exceptions, 15 eosinophils/hpf (high power field) (peak value) is considered a minimum threshold for the diagnosis.

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Chapter 142

Principles of Treatment of Allergic Disease

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The basic principles of the treatment of allergic disease include the avoidance of exposure to allergens and irritants that trigger symptoms and the pharmacologic management of symptoms caused by unavoidable acute and chronic allergen exposures. In selected patients, allergen immunotherapy may be considered.

ENVIRONMENTAL CONTROL MEASURES

Children spend the majority of their time in indoor environments, including the home. In an effort to save energy, houses and buildings have been built more tightly and with more insulation with limited air exchange. These factors have led to an increase in indoor humidity and higher concentrations of allergens and irritants. Examination of indoor environments suggests that house dust mite, cat, and cockroach allergens are the most common significant triggers of allergic disease in these settings; exposures to allergens from other pets, pests, mold, and respiratory irritants such as cigarette smoke are also a problem.

More than 30,000 species of mites have been identified, but the term *dust mites* usually refers to the pyroglyphid mites *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* and *Euroglyphus maynei,* which are the major sources of allergen in house dust. Respiration and water vapor exchange occur through the skin of dust mites, rendering them sensitive to humidity and temperature extremes. The regular use of humidifiers promotes dust mite survival. Mites do not survive with relative humidity <50%. They feed on animal and human skin scales and other debris, which is why they exist in large numbers in mattresses and bedding, carpet, and upholstered furniture. They may also be found in flour and mixes for baked goods. Anaphylaxis has been reported following the ingestion of baked goods, such as waffles and pancakes, prepared with flour infested with dust mites ("pancake syndrome"). Dust mite fecal pellets are a major source of allergens. They consist of partially digested food combined with digestive enzymes encased in a permeable membrane, which keeps the fecal pellets intact. These fecal pellets have been likened to pollen grains, given their similarities in size (10-40 μm), the amount of allergen they contain, and their ability to release allergens rapidly on contact with moist mucous membranes. Mites can persist in imported furnishings for at least 2 yr; mite allergens have been shown to remain stable under domestic conditions for periods of at least 4 yr. Dust mite allergens become airborne during normal household activities; a vigorous disturbance, such as vacuuming without a vacuum bag, shaking a bed sheet, or a pillow fight, can launch significant amounts of dust mite allergens into the air. Once airborne, dust mite allergen particles settle out of the air relatively rapidly because of their size and weight. Nonetheless, dust mite allergen exposure likely occurs during sleep on mite-infested pillows and mattresses and during normal household activities when dust mite concentrations in the home are high. Levels of dust mite allergens as

Table 142-1 Environmental Control of Allergen Exposure

ALLERGEN	CONTROL MEASURES
Dust mites	Encase bedding in airtight, allergen-impermeable covers Wash bedding weekly in water at temperatures >54.4°C (130°F) Remove wall-to-wall carpeting Replace curtains with blinds Remove upholstered furniture Reduce indoor humidity Minimize bedroom and living room clutter
Animal dander	Avoid furred pets Keep animals out of patient's bedroom
Cockroaches	Control available food and water sources Keep kitchen/bathroom surfaces dry and free of standing water Seal cracks in walls Use professional extermination services; safe pesticide should be used in baits
Mold	Repair moisture-prone areas Avoid high humidity in patient's bedroom Use high-efficiency particulate air (HEPA) filters in living areas Repair water leaks Replace carpets with hardwood floors Regularly check basements, attics, and crawl spaces for standing water and mold
Pollen	Keep automobile and house windows closed Control timing of outdoor exposure Restrict camping, hiking, and leaf raking Drive in an air-conditioned automobile Air-condition the home Install portable HEPA filters

Modified from Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *St. Louis, 2010, Mosby, p. 297.*

low as 2 μg/g of house dust can lead to sensitization, whereas levels of 10 μg/g of house dust are associated with symptoms.

Appropriate environmental control measures can significantly reduce exposure to dust mite allergens (Table 142-1). Major emphasis should be placed on reducing exposure to dust mite allergens in the bedroom and living areas in which the child spends a large amount of time. Encasements impermeable to dust mite allergens should be placed on all pillows, the mattress, and the box spring. Dust should be removed from the surfaces of these covers and the bed frame by vacuuming weekly. The sheets and mattress pad should be washed weekly in hot water at a temperature of >54.4°C (130°F). Minimizing the number of items in the room that collect dust, such as books, drapes, toys, stuffed animals, and any clutter, is recommended. Major reservoirs of dust mite allergen that are often more difficult to deal with include the carpet and upholstered furniture, which should be vacuumed weekly with an efficient double-thickness-bagged vacuum cleaner. The actual benefit of applying acaricides or denaturing agents to carpets and upholstered furniture remains unclear, and the amount of effort required may be more than most families are willing to invest. If possible, carpet removal, at least in the bedroom, may prove a better choice for eliminating a large reservoir of dust mite allergen. Other measures for dust mite allergen control include maintaining the indoor relative humidity at <50% and keeping the air conditioning set at the lowest level during the warmer months.

In many countries, more than half of the households have pets, the most common of which are cats and dogs. The major sources of allergens from cats, dogs, and horses are hair, dander, and saliva, whereas the major source of allergens from rodents is urine. Studies of airborne cat allergen have shown that a significant portion is found on small particles. As much as 30% of airborne cat allergen may reside on particles <5 μm. Particles this small may not be adequately filtered by the nose and could potentially be deposited in the airways. Their small size enables these particles to remain airborne for longer periods and to be suspended repeatedly by air currents from heating and ventilation systems or just by walking across the carpet or sitting in an upholstered chair. **Fel d 1,** the major cat allergen, is a highly charged protein that readily sticks to a variety of surfaces, including walls, carpeting, and upholstered furniture. Owing to this adhesiveness, cat allergens bind to the cat owner's clothing and are routinely transported to public buildings, including schools, where they have been measured in moderately high amounts. From these sites, significant amounts of cat allergen can subsequently be carried into homes without cats. Analysis of house dust from homes with cats reveals levels of Fel d 1 ranging from 8 μg to 1.5 mg/g of house dust. Levels of Fel d 1 in homes without cats vary from 0.2 to 80 μg/g of house dust. Sensitization to cat allergen is associated with levels ranging from 1 to 8 μg/g of house dust. Carpets, upholstered furniture, and bedding serve as reservoirs of cat allergens, resulting in the persistence of significant amounts in the home for months after a cat has been removed. Complete avoidance of cat allergen is virtually impossible, although significant reduction in exposure to cat allergens is achievable.

Removing the pet from the home is obviously the most effective means of reducing exposure to animal allergens, although it has been demonstrated that without other interventions, such as removing carpeting and upholstered furniture and wiping down walls, it takes 6 mo or more for the levels of cat allergen to drop to a level found in houses without a cat. As a result, cat owners who remove their pets from their homes should be informed not to expect immediate results. Unfortunately, advice to remove a pet from the home or keep it outdoors is often ignored. In contrast to dust mite allergens, cat allergen is light and remains suspended in the air for long periods. As a result, **air cleaners with high-efficiency particulate air (HEPA) filters** are helpful in reducing the amount of airborne cat allergen. Other suggested methods include washing the cat regularly and maintaining a cat allergen–free bedroom from which the cat is excluded and where mattress covers and air-filtering devices are used. The cat should also be restricted from other living areas where the sensitized child spends large amounts of time, such as the family room and other play areas (see Table 142-1). Regular vacuuming with a HEPA-filtered and double-thickness bag vacuum cleaner is also encouraged. Similar measures are suggested for the control of exposure to other animal allergens, although whether these measures reduce exposure to levels resulting in clinical improvement as demonstrated by decreased symptoms, improved peak flows, or decreases in bronchial hyperreactivity remains to be documented by appropriately controlled studies.

Infestation of the home by insects and other pests, such as mice and rats, is another potential source of significant indoor allergen exposure. Studies have identified exposure to cockroach allergens as a major risk factor for the development of asthma in inner-city children. Once sensitized, inner-city cockroach-sensitive asthmatic children with continued exposure to high levels of cockroach allergens in their bedrooms are at higher risk for urgent care visits and hospitalization than are inner-city asthmatic children who are not allergic to cockroaches. Recommended methods to decrease cockroach allergen exposure include reducing cockroaches' access to the home by sealing cracks in the flooring and walls and removing sources of food and water by repairing leaky pipes, putting away food in sealed containers, and frequent cleaning (see Table 142-1). Regular extermination using baits or chemical treatment of infested areas is also advised.

Efforts to improve indoor air quality should also encompass reducing exposure to respiratory irritants. Passive exposure to environmental tobacco smoke worsens asthma and increases nasal symptoms in patients with allergic nasal disease. Smoking cessation should be repeatedly encouraged, and smoking indoors should never be permitted. The use of wood-burning stoves, fireplaces, and kerosene heaters should also be discouraged.

Although exposure to pollens and molds occurs primarily outdoors, these allergens are detectable indoors during the warmer months,

when their indoor levels often reflect their prevalence in the outdoor environment. During the winter, when the outdoor levels of other molds are lowest, the indoor molds *Aspergillus* and *Penicillium* are the most prevalent. Molds are often found in damp basements and thrive in conditions associated with increased moisture in the home, such as water leaks, flooding, and increased humidity promoted by the excessive use of humidifiers or swamp coolers. Exposure to indoor mold allergens can be reduced by maintaining the indoor relative humidity at <50%, removing contaminated carpets, and wiping down washable surfaces prone to fungal growth, such as shower stalls, shower curtains, sinks, drip trays, and garbage pails, with the use of solutions of detergent and 5% bleach (see Table 142-1). Dehumidifiers should be placed in damp basements. Standing water at any site in the home should be eliminated, and the cause addressed. Removing all items from the home that are prone to mold contamination is also encouraged. Keeping the windows and doors closed and using air conditioning to filter outdoor air can keep both indoor pollen and mold levels to a minimum during the warmer months, when outdoor levels of these allergens are at their peak. The use of window or attic fans is to be avoided. Laundry should be dried in a dryer rather than on a clothesline. Measures to avoid pollens and mold spores when out of the house include closing the windows and using the air conditioner when traveling in the car, avoiding moldy vegetation, and wearing a mask when these materials cannot be avoided. Outdoor activities during periods of high pollen counts should be kept to a minimum. Pollen travels best on warm, dry, breezy days but counts are lowest during chilly, wet periods. Someone other than the sensitized patient should mow the lawn and rake leaves. Hand washing after outdoor play is suggested to avoid transferring pollens from the hands to the eyes and nose. At the end of the day, showering and shampooing are suggested to avoid contamination of the bed with allergens.

PHARMACOLOGIC THERAPY

Adrenergic Agents

Adrenergic agents exert their effects through the stimulation of cell surface α- and β-adrenergic receptors in a variety of target tissues. In general, α-adrenergic receptor stimulation results in excitatory responses such as vasoconstriction, whereas β-adrenergic stimulation leads to inhibitory responses such as bronchodilation. The α-adrenergic receptors have been classified into α_1- and α_2-adrenergic receptors. There are 3 subtypes of α_1-adrenergic receptors and 3 subtypes of α_2-adrenergic receptors. The β-adrenergic receptors are further divided into 3 subtypes: β_1, β_2, and β_3. Each of these adrenergic receptors exhibits a distinctive tissue distribution. The physiologic response in a given tissue to the administration of an adrenergic agent depends on the specific receptor-binding characteristics of the drug as well as the numbers and distribution of the various types of adrenergic receptors in the tissue. Epinephrine remains the drug of choice for the treatment of anaphylaxis because of its combined α- and β-adrenergic effects. Epinephrine autoinjectors are prescribed for ease of administration and are available in 2 dosages: 0.15 mg for children who weigh <30 kg, and 0.30 mg for children who weigh ≥30 kg, according to manufacturer recommendations. Consider prescribing the 0.15 mg dose for children who weigh ≥25 kg to avoid under-dosing.

The α-adrenergic agents are effective in the treatment of allergic nasal disease because of their decongestant effects (see Tables 143-4 and 143-5). In the nose, stimulation of α_1-adrenergic receptors on postcapillary venules and of α_2-adrenergic receptors on precapillary arterioles leads to vasoconstriction, resulting in a reduction in nasal congestion. The oral decongestants currently in clinical use include pseudoephedrine and phenylephrine. These medications are available individually or in combination with antihistamines in liquid and tablet forms, including sustained-release preparations. Pseudoephedrine is rapidly and thoroughly absorbed, whereas phenylephrine, the less effective of the 2 drugs, is incompletely absorbed, resulting in a significantly lower bioavailability of ≈38%. Peak plasma concentrations of these drugs are reached between 30 min and 2 hr of administration, but the decongestant effect has not been directly correlated to the plasma concentration. Pseudoephedrine is excreted essentially unchanged by the kidney. The use of oral decongestants should be avoided in patients <6 yr of age and in patients with hypertension, coronary artery disease, glaucoma, or metabolic disorders, such as diabetes and hyperthyroidism. Reported **adverse effects** of oral decongestants include excitability, headache, nervousness, palpitations, tachycardia, arrhythmias, hypertension, nausea, vomiting, and urinary retention. Decongestants available as topical nasal sprays include phenylephrine, oxymetazoline, naphthazoline, tetrahydrozoline, and xylometazoline. Given their efficacy and rapid onset of action, the potential for excessive use of topical nasal decongestants resulting in rebound nasal congestion (rhinitis medicamentosa) is high and patients should be carefully counseled to prevent dependency on the product. Thus, limiting the use of these sprays to 2-3 days is generally recommended.

Drugs that stimulate β-adrenergic receptors have been used for years in the treatment of asthma because of their potent bronchodilator effects (see Table 144-16). The subclassification of β-adrenergic receptors into β_1 and β_2 subtypes led to the development of drugs selective for the β_2-adrenergic receptor, such as albuterol, levalbuterol, and pirbuterol, that have the advantage of producing significant bronchodilation with less cardiac stimulation. *The long-acting inhaled β_2-adrenergic agonists (LABAs) salmeterol and formoterol,* with a 12-hr duration of action, are approved for use in children ≥4 yr of age. LABAs are not recommended for the treatment of acute asthma exacerbations because of their relatively slow onset of action. Concern about an increased risk of asthma-related adverse events is why LABAs are not recommended as monotherapy for the long-term control of persistent asthma, but are promoted as best used in conjunction with an inhaled steroid. Dry powder inhaled and metered-dose inhaler preparations combining a *LABA with an inhaled corticosteroid have had significant impact on treatment of moderate persistent asthma.* In addition to their bronchodilating effects, β_2-adrenergic agonists have been reported to improve mucociliary clearance, decrease microvascular permeability, inhibit cholinergic nerve transmission, and reduce mediator release in mast cells, basophils, and eosinophils. Although β-adrenergic agonists can be delivered orally, by inhalation, or by injection, the inhaled route is preferred because of the rapid onset of action and fewer adverse effects. Reported **adverse effects** of β-adrenergic agents include tremor, palpitations, tachycardia, arrhythmias, central nervous system stimulation, hyperglycemia, hypokalemia, hypomagnesemia, and a transient increase in hypoxia, which is attributed to an increase in perfusion to inadequately ventilated areas of the asthmatic lung.

Anticholinergic Agents

Anticholinergic drugs inhibit vagally mediated reflexes by antagonizing the action of acetylcholine at muscarinic receptors. Of the available anticholinergic agents, **ipratropium bromide** is the most commonly used. It is a quaternary amine that is poorly absorbed across mucosal surfaces and does not readily cross the blood–brain barrier. As a bronchodilator, it has a slower onset of action than short-acting inhaled β_2-agonists and takes longer to reach maximal effect, making it less effective as a rescue medication. There is increasing support, particularly in children, for combination therapy using ipratropium bromide and β-agonist therapy in more severe asthma exacerbations. Multiple doses of combined therapy can decrease risk of hospitalization in children by 25%. Ipratropium is available by prescription as a metered-dose inhaler delivering 17 µg/spray and as a 0.02% nebulized solution (500 µg/2.5 mL).

Ipratropium given as a nasal spray (0.03-0.06%) is effective in the reduction of rhinorrhea resulting from perennial nonallergic rhinitis, the common cold, and vasomotor rhinitis. The use of ipratropium is suboptimal in the treatment of moderate to severe allergic rhinitis because it does not alter other common allergic nasal symptoms, such as sneezing, nasal congestion, and pruritus. Nasal dryness and epistaxis are occasionally encountered with use of the nasal spray.

Antihistamines

The release of histamine and its effects on surrounding tissues is central to the development of symptoms classically associated with the allergic response. Histamine exerts its effects through binding with 1 of its 4

receptors, as H_1-, H_2-, H_3-, or H_4-receptor. Histamine effects triggered through H_1-receptor binding are those most relevant to allergic inflammation, and include pain, pruritus, vasodilation, increased vascular permeability, smooth muscle contraction, mucus production, and the stimulation of parasympathetic nerve endings and reflexes. The antimuscarinic effect of some of the early H_1-type antihistamines may be explained by the reported 45% homology of the H_1-receptor with the human muscarinic receptor. The H_1-type antihistamines prevent the effects of H_1-receptor activation through reversible, competitive inhibition of histamine by binding to the H_1-receptor. Antihistamines work best in preventing rather than reversing the actions of histamine and are most effective when given at doses and dosing intervals resulting in the persistent saturation of target organ tissue histamine receptors.

The H_1-type antihistamines are traditionally divided into 6 classes on the basis of differences in their chemical structures (Tables 142-2 and 143-3). These antihistamines are further divided into first-generation antihistamines, which, because of their lipophilicity, cross the blood–brain barrier to exert effects on the central nervous system, and second-generation antihistamines, which exert minimal, if any, central nervous system effects because of their inability to cross the blood-brain barrier owing to their size, charge, and lipophilicity. The sedative effects and cognitive impairment associated with the use of first-generation antihistamines are well documented. Thus, a primary advantage of second-generation antihistamines is that they are nonsedating or much less sedating than first-generation antihistamines. Although fexofenadine is considered the least sedating of the available nonprescription antihistamines (0% occupation of central nervous system H_1-receptors), cetirizine has the most potential for sedation (26-30%). Both first- and second-generation antihistamines are available in oral preparations. Many first-generation and second-generation antihistamines are available in nonprescription form, including diphenhydramine, loratadine, fexofenadine, and cetirizine. Other antihistamines require a prescription, such as hydroxyzine and cyproheptadine. Antihistamines available as an intranasal spray are azelastine and olopatadine, the latter also functioning as a mast cell stabilizer. The benefit of this form of administration is the potential for a rapid onset of action, within 15 min. Azelastine, which is systemically absorbed and can cross the blood–brain barrier, has the potential for central nervous system effects in some patients and is not currently approved for use in children <12 yr of age. Patients often experience a bitter metallic taste in their mouths when using azelastine, which is a common reason for nonadherence.

Orally administered antihistamines are well absorbed and reach peak serum concentrations within ~2 hr. High tissue concentrations of antihistamines are usually achieved, likely accounting for the sustained suppression of wheal and flare reactions even after serum levels have significantly declined. Most antihistamines are metabolized by the hepatic cytochrome P450 enzyme system. Elimination of antihistamines may be reduced in patients with hepatic impairment or by the simultaneous ingestion of inhibitors of this pathway, such as erythromycin and other macrolide antibiotics, ciprofloxacin, ketoconazole, itraconazole, and certain antidepressants, such as nefazodone and fluvoxamine. Some antihistamines, such as hydroxyzine and loratadine, are converted to clinically active metabolites. Clearance of fexofenadine and cetirizine is reduced in patients with impaired renal function. Cetirizine clearance is also reduced in patients with hepatic dysfunction. Fruit juices (apple, orange, grapefruit) are organic anion transporter inhibitors and interfere with the absorption of fexofenadine: juices should be avoided 4 hr before or 1-2 hr after taking fexofenadine.

The efficacy of antihistamines in the treatment of seasonal and perennial allergic rhinoconjunctivitis is well documented (see Chapter 143). Compared with other medications in regard to the relief of allergic nasal symptoms, antihistamines are more effective than cromolyn sodium, but significantly less effective than intranasal corticosteroids. Improvement in symptom relief in patients with allergic rhinitis has been reported when an antihistamine is given in combination with a decongestant or with an intranasal steroid. Numerous formulations combining antihistamines and decongestants are available. Antihistamines have also been shown to be beneficial in the treatment of acute and chronic urticaria/angioedema. With regard to asthma, a significant clinical effect of antihistamines at conventional doses is difficult to document, other than the possible improvement offered by better control of allergic nasal symptoms.

Second-generation antihistamines are preferable over first-generation antihistamines for the treatment of allergic disease in children because of negligible sedative and anticholinergic effects without a sacrifice in efficacy. Most second-generation antihistamines are effective with convenient once-daily dosing, which may improve therapy adherence. The widespread availability of first-generation antihistamines and their lower cost account for their continued use. The **adverse effects** most often encountered with second-generation agents include the performance impairment and anticholinergic effects noted with first-generation antihistamines although generally to a lesser degree. The anticholinergic adverse effects encountered may include drying of the mouth and eyes, urinary retention, constipation, excitation, nervousness, palpitations, and tachycardia. Prolongation of the QT interval and ventricular tachycardia (torsades de pointes) has been noted in older no longer available second-generation antihistamines; current antihistamines are not associated with concerning cardiac effects.

Table 142-2 Classification of Antihistamines (H_1-Antagonists)

CLASS	EXAMPLES
ETHYLENEDIAMINES	
First-generation	Antazoline, pyrilamine, tripelennamine
TYPE II ETHANOLAMINES	
First-generation	Carbinoxamine, clemastine, diphenhydramine
TYPE III ALKYLAMINES	
First-generation	Brompheniramine, chlorpheniramine, triprolidine
Second-generation	Acrivastine
TYPE IV PIPERAZINES	
First-generation	Cyclizine, hydroxyzine, meclizine
Second-generation	Cetirizine, levocetirizine
TYPE V PIPERIDINES	
First-generation	Azatadine, cyproheptadine, ketotifen
Second-generation	Fexofenadine, loratadine, desloratadine
TYPE VI PHENOTHIAZINES	
First-generation	Methdilazine, promethazine

Chromones

Cromolyn sodium and nedocromil sodium are the 2 chromones used to treat allergic disorders. Neither cromolyn nor nedocromil is absorbed well orally, with only 1% of the swallowed dose absorbed. These drugs must be applied topically to the mucosal surface of the target organ to be effective. Both drugs inhibit mast cell degranulation and mediator release. They suppress the activation of a variety of cells, such as eosinophils, neutrophils, macrophages, and epithelial cells. They also suppress the activity of afferent C-type sensory nerve fibers of the nonadrenergic, noncholinergic nervous system. Both drugs inhibit the intracellular increase in free calcium after mast cell activation and phosphorylate a mast cell protein resembling moesin, which is thought to be involved in terminating mediator release.

Cromolyn and nedocromil prevent early- and late-phase allergic responses when administered before allergen exposure. They block allergen-induced increases in bronchial hyperresponsiveness, as well as seasonal increases in nonspecific bronchial hyperresponsiveness. With prolonged use, both drugs are capable of reducing bronchial hyperresponsiveness. These drugs have no bronchodilator properties but can inhibit the bronchoconstrictive effects of a variety of stimuli, such as allergen challenge, exercise, hyperventilation with cold air,

ultrasonically nebulized distilled water, and exposure to atmospheric and industrial pollutants.

Cromolyn and nedocromil are used as alternative, but not preferred, therapy for the treatment of mild persistent asthma. Because of their lack of bronchodilator properties, neither drug is useful for the treatment of acute asthma, although both may be used as preventive treatment before vigorous exercise or unavoidable known allergen exposure. Nedocromil is the more potent of the two, but no formulation of nedocromil is currently available for asthma in the United States. Cromolyn is available for the treatment of asthma by prescription as a 1% solution (20 mg/2 mL) for nebulization. The suggested dose for the treatment of asthma is 20 mg of cromolyn 2-4 times/24 hr by nebulization. In numerous studies, cromolyn has been found useful in the treatment of allergic rhinitis and allergic conjunctivitis. Preparations for the nasal and ocular administration of cromolyn are available without a prescription. The suggested dose for the treatment of allergic rhinitis is one spray in each nostril 3 to 4 times daily of a nasal spray containing 5.2 mg of cromolyn per spray (see Table 143-5). For the treatment of allergic conjunctivitis, the suggested dose is 1 drop in each eye 4-6 times a day of a 4% ophthalmic solution. A 2% solution of nedocromil is available by prescription for the treatment of allergic conjunctivitis at a suggested dose of 1-2 drops in each eye twice daily.

The safety of these drugs, even with prolonged administration, is well documented. Because of their favorable safety profile, the chromones are often chosen for use during pregnancy.

Glucocorticoids

Glucocorticoids are widely used in the treatment of allergic disorders because of their potent antiinflammatory properties. The diverse antiinflammatory actions of glucocorticoids are mediated via the glucocorticoid receptor, which is present in all inflammatory effector cells, as well as by direct inhibition of cytokines and mediators. Glucocorticoids are administered topically in ophthalmic preparations, nasal sprays, creams and ointments, metered-dose inhalers, and as a solution for nebulization. Systemic administration is accomplished orally or parenterally. The proper use and efficacy of glucocorticoids in the treatment of allergic disease along with the adverse effects associated with their use are presented in discussions of individual allergic diseases (see Chapters 142-152).

Leukotriene-Modifying Agents

Drugs that alter the leukotriene pathway exert their clinical effects either by inhibiting leukotriene production or by blocking receptor binding. These agents possess mild antiinflammatory properties and exhibit bronchodilator effects. In addition to inhibiting the early- and late-phase allergic responses to inhaled allergen, they diminish bronchoconstriction induced by exercise and exposure to allergen, aspirin, and cold air. Leukotriene-modifying agents have some use in the treatment of asthma (see Chapter 144) and are modestly effective in the treatment of allergic rhinitis (see Chapter 143).

Theophylline

Because of its bronchodilating effects, theophylline (1,3-dimethylxanthine) had been used for yr for the treatment of acute and chronic asthma. The bronchodilator effect of theophylline is likely caused by its action as a phosphodiesterase inhibitor, whereas its ability to antagonize adenosine receptors may play a role in other effects, such as the attenuation of diaphragmatic muscle fatigue and diminishing adenosine-enhanced mast cell mediator release. Theophylline inhibits the immediate- and late-phase pulmonary responses to allergen challenge and exhibits modest protective effects. The therapeutic and toxic effects of theophylline are related to the serum concentration, with the incidence of toxic effects significantly increasing as the serum levels approach and exceed 20 μg/mL. A variety of conditions and medications are capable of increasing or decreasing theophylline metabolism. The **toxic effects** of theophylline, ranging from mild nausea, insomnia, irritability, tremors, and headache to cardiac arrhythmias, seizures, and death, necessitate the routine monitoring of theophylline serum levels. Because of the introduction of other effective therapies for the treatment of acute and chronic asthma, the need to monitor drug serum levels routinely, and the potential for significant toxicity, the role of theophylline in the treatment of asthma has contracted significantly (see Chapter 144).

Lodoxamide Tromethamine

A mast cell stabilizer, lodoxamide tromethamine is more effective than topical cromolyn sodium in alleviating signs and symptoms of allergic ocular disease (see Chapter 147). It is used in children >2 yr of age for vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis. Occasional adverse effects have included transient burning or stinging after instillation.

Combination Mast Cell Stabilizer and Antihistamine

Olopatadine, epinastine, and ketotifen are examples of combination mast cell stabilizers and H_1-receptor antagonists effective in relieving signs and symptoms of allergic conjunctivitis after topical instillation, although all H_1-antihistamines likely have some mast cell stabilizing activity. Dosing is typically twice per day, except of olopatadine, which is dosed once daily.

Antiimmunoglobulin E

Monoclonal antiimmunoglobulin E antibodies (anti-IgE) bind to circulating IgE at a site that prevents its subsequent attachment to the high-affinity receptors for IgE on the mast cell surface. The parenteral administration of anti-IgE reduces free serum IgE concentrations, inhibits skin test responses in allergic patients, suppresses early- and late-phase responses to allergens, and decreases sputum eosinophilia in asthmatic persons. Anti-IgE has a beneficial effect in the treatment of patients with asthma, allergic rhinitis, and urticaria. An anti-IgE preparation **(omalizumab)** is available for the treatment of children ≥12 yr of age with documented allergen-induced asthma that is inadequately controlled by inhaled corticosteroids. Although this agent is usually well tolerated, local reactions at the injection site and rare episodes of anaphylaxis have been reported. Anti-IgE may also be beneficial in the treatment of other allergic disorders, such as anaphylaxis and food allergy, but more studies are needed. One monoclonal antibody preparation of anti-IgE used in the treatment of adults with peanut allergy resulted in a significant increase in the symptom threshold dose of peanuts. The cost of anti-IgE therapy and need for regular injections requires careful patient selection, special consideration being given to those patients with persistent symptoms despite aggressive pharmacotherapy, significant adverse effects of current therapy, and more than 1 allergic disorder.

Nasal Saline Irrigation

Irrigation with nasal saline can improve symptoms for those with mild allergic rhinitis. Nasal saline irrigation can be used alone or before topical medication. Squeeze bottle kits for this purpose are available over the counter, and typically about 200 mL are irrigated through the nares. Patients may make their own irrigation solutions or buy commercially-prepared solutions. Patients should use boiled or distilled water, as cases of sinus infection with amoebas found in tap water have been reported.

New Therapies

Recombinant soluble interleukin (IL)-4 receptor antagonists exert their effects by binding to and inactivating IL-4 before it can attach to its cell surface receptor. Although initial studies of an inhaled soluble IL-4 receptor in patients with moderate asthma requiring inhaled corticosteroids suggested a beneficial clinical effect, subsequent clinical studies of the effects of anti–IL-4 drugs in the treatment of asthma revealed these therapies to be safe, but clinical efficacy was lacking. Clinical trials of humanized monoclonal anti–IL-5 antibodies administered by injection to asthmatic patients revealed a decrease in circulating eosinophils and sputum eosinophilia, but a lesser reduction of eosinophils from the bronchial submucosa, and this effect was

unaccompanied by a reduction in methacholine reactivity or a suppression of the early- or late-phase response to allergen.

The use of cytokines with antiinflammatory effects in the treatment of allergic disorders is under investigation. Unfortunately, initial studies have not demonstrated a beneficial effect of IL-10 or interferons in the treatment of asthma. Although studies have documented that IL-12 administration is associated with a decrease in eosinophil accumulation in response to allergen challenge, inhibition of early- and late-phase responses to allergen and decreases in bronchial hyperreactivity have not been observed. In addition, the high incidence of significant adverse effects encountered with IL-12 administration limits its potential as a viable therapeutic option.

ALLERGEN IMMUNOTHERAPY

Allergen immunotherapy involves administering gradually increasing doses of allergens to a person with allergic disease for the purpose of reducing or eliminating the patient's adverse clinical response to subsequent natural exposure to those allergens. When properly administered to an appropriate candidate, allergen immunotherapy is a safe, effective form of therapy capable not only of reducing or preventing symptoms but also of potentially altering the natural history of the disease by minimizing disease duration and preventing disease progression. Conventional allergen immunotherapy is given subcutaneously under the direction of an experienced allergist. Sublingual immunotherapy (SLIT) is widely used in Europe for aeroallergens but is not yet FDA-approved in the United States. Sublingual and oral immunotherapy (OIT) for foods are being investigated and are also not FDA-approved.

Indications and Contraindications

Allergen immunotherapy is reserved for patients with an allergic disease demonstrated to respond to this form of therapy, such as seasonal or perennial allergic rhinoconjunctivitis, asthma triggered by allergen exposures, and insect venom sensitivity. Proof of the efficacy of conventional allergen immunotherapy for the treatment of food allergy, atopic dermatitis, latex allergy, and acute or chronic urticaria is lacking; consequently, conventional allergen immunotherapy is not recommended for the treatment of these disorders. Before allergen immunotherapy is considered, sensitivity of the patient to the allergens to be administered should be documented by a positive skin test result or an in vitro test revealing an increased serum level of allergen-specific IgE. The clinical relevance of these allergens should be supported by a history of symptoms upon known exposure or a timing of symptoms that correlates well with suspected allergen exposure, such as the presence of allergic nasal and ocular symptoms throughout the late summer and fall in a child with a positive ragweed skin test response. The duration and severity of the patient's symptoms, as well as the patient's preferences, should warrant the expense, effort, and risk associated with the administration of allergen immunotherapy. The presence of disabling symptoms in spite of a trial of allergen avoidance and appropriate medications at a suitable dose should be documented. Venom immunotherapy (VIT) is indicated in children <16 yr of age who have experienced respiratory or cardiovascular symptoms following a sting. For those ≥16 yr, VIT is indicated for any systemic reaction, including those limited to skin but not contiguous from the site of the sting (see Chapter 146).

Other factors that may affect the decision to institute allergen immunotherapy include quality-of-life issues, such as the amount of school missed or medical resource utilization, the age of the patient, and other logistical factors. With the exception of VIT, few data for the efficacy of allergen immunotherapy in children <5 yr of age are available. Allergen immunotherapy is not recommended for children <5 yr of age because of their increased risk of systemic reactions, the special expertise required to treat anaphylaxis in this age group, their potential inability to communicate clearly with the physician in the event of an allergic reaction, and their age-related potential for emotional distress with frequent injections. Other important logistic factors include the willingness of the patient to comply with a schedule of frequent injections over the course of several yr, cost considerations, and the availability of an appropriate medically supervised setting for administering allergen immunotherapy.

Allergen immunotherapy is **contraindicated** in children undergoing β-blocker therapy as well as those with certain immunologic or autoimmune disorders, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, severe psychiatric disturbance, or a medical condition that would impair the ability to survive an allergic reaction. Pregnancy is a contraindication to the initiation of allergen immunotherapy or dosing increases, although a pregnant adolescent can continue to receive her usual maintenance dose. Patients with unstable asthma should not be started on allergen immunotherapy because of their increased risk for anaphylaxis. Allergen immunotherapy is not used for the treatment of allergic bronchopulmonary aspergillosis or hypersensitivity pneumonitis because it has no benefit. Children receiving β-blockers and angiotensin-converting enzyme-inhibitors are not ideal candidates for allergen immunotherapy because of an increased intensity of allergic reactions and a poor response of conventional therapy to these reactions with β-blocker therapy. Allergen immunotherapy is usually avoided in patients with autoimmune disorders because of the theoretical concern for stimulation of the immune system (formation of antigen–antibody complexes), which might result in disease activation.

Allergen Extracts

The potency of the aqueous extracts used in allergen immunotherapy is affected by numerous factors. Allergens from weed and grass pollens are more easily extracted in aqueous solutions and, as a result, are more potent than extracts obtained from other sources, such as molds, tree pollens, and dust mites. Owing to their complexity, allergen extracts from mold allergens are more variable than extracts from pollen allergens. Refrigeration and appropriate handling of allergen extracts used in allergen immunotherapy are important because degradation of many allergen extracts, such as those from tree, grass, weed pollens, and dust mites, may occur at higher temperatures. Dilute extracts are more susceptible to loss of potency resulting from adherence of allergen to the glass vial than are more concentrated extracts. To combat this effect, preservatives such as 0.03% human serum albumin or 10-50% glycerin may be added to dilute allergen extracts. Some allergen extracts, such as those from cockroaches, dust mites, and molds, contain proteases capable of degrading other allergens in the extract. It is often recommended that these allergens not be mixed with those from tree, grass, and weed pollens. Insect venoms are never mixed with other allergens. When available, the use of standardized allergen extracts is preferred to ensure consistency in dosing and to avoid the variability in allergen content encountered with nonstandardized allergen extracts.

Allergen Extract Administration

The goal of allergen immunotherapy is to increase gradually the dose of allergen extract administered until the injection of an "optimal" maintenance dose containing 4-12 μg of each major allergen in the extract is reached. The mixture of allergen extracts administered during the course of allergen immunotherapy is individually formulated for each patient on the basis of the patient's documented sensitivities. Although various dosing schedules are used, initial injections are most often given at 5-10–day intervals year-round. Schedules of allergen administration are selected according to the sensitivity of the patient to the allergens in the extract. The most sensitive patients are advanced to a maintenance dose more gradually. Doses of allergen immunotherapy are increased according to a set schedule, although the reaction to the previous injection is also taken into account. A systemic reaction to the previous dose would result in a significant reduction in the next dose, whereas reducing the dose solely on the basis of a large local reaction does not reduce the rate of systemic reactions. Usually 5-6 mo of weekly injections is required to reach the maintenance dose, although it may take longer in highly sensitive patients. Unique schedules for the administration of insect venoms, which differ from those for the administration of other allergens (see Chapter 146), are used. Once the maintenance dose is reached and well tolerated, the interval between injections is increased to a few weeks

or a month. Because allergen extracts gradually lose potency, the first dose from a fresh replacement vial of maintenance allergen extract is reduced by 25-75% and is then increased in increments weekly until the usual maintenance dose is reached. The recommended length for a course of allergen immunotherapy is 3-5 yr. Insect VIT may be continued indefinitely in patients with a history of life-threatening anaphylaxis. Patients who have not shown improvement after 1 year of receiving maintenance doses of an appropriate allergen extract are unlikely to benefit, and allergen immunotherapy should be discontinued. Most patients enjoy a sustained improvement after allergen immunotherapy whereas others experience a gradual return of symptoms. Those who experience a relapse would be expected to respond upon resuming immunotherapy.

Rush immunotherapy is the administration of multiple injections either in a single day or over several days in an attempt to reach maintenance dose more rapidly. The risk of adverse reactions, including systemic reactions, is higher than with traditional allergen immunotherapy schedules. Patients to undergo rush immunotherapy are often pretreated with antihistamines and corticosteroids. Children are at even greater risk for adverse reactions with rush immunotherapy; thus the benefits and risks should be fully considered. Preadministration of omalizumab (anti-IgE therapy) reduces the incidence of systemic reactions associated with the use of this form of immunotherapy.

Although allergen immunotherapy is regarded as safe, the potential for anaphylaxis always exists when patients are injected with extracts containing allergens to which they are sensitized. Allergen immunotherapy should be offered in only medical settings where a physician with access to emergency equipment and medications required for the treatment of anaphylaxis is available (see Chapter 149). Allergen injections should never be given at home or by untrained personnel. The patient should remain in the office for 30 min after the injection because most reactions to allergen immunotherapy begin within this time frame. Fatal anaphylaxis triggered by allergen immunotherapy, although rare, is estimated to occur at an incidence of 1 per 2 million injections. The risk of an adverse reaction is increased by dosage errors and the use of rush immunotherapy schedules. Particular caution is warranted when injections from a new vial are given. Patients with exquisite sensitivity or unstable asthma and those experiencing exacerbations of allergic rhinitis or asthma are also at increased risk for adverse reactions to allergen immunotherapy. Precautions to reduce significant adverse reactions include using standardized extracts, having extract vials personalized for each patient, allowing only trained personnel to administer injections, paying careful attention to detail when giving injections, ensuring beforehand that the patient is medically stable, having appropriate medications and equipment available, and requiring the patient to remain in the office for 30 min after each injection. Checking peak flow or spirometry before an injection is advisable for some asthmatic patients. It is also prudent to advise patients to carry self-injectable epinephrine for 24 hr following each injection. While uncommon, delayed systemic reactions have been reported following immunotherapy injections.

Other approaches to immunotherapy are under investigation; they include chemical or genetic manipulation of the allergen and linking of the principle allergenic moiety of a relevant allergen to a highly active adjuvant, such as an immunostimulatory sequence mimicking patterns of bacterial DNA.

Local nasal immunotherapy is administered by having the patient spray allergen solutions into the nose at scheduled intervals. Although symptom amelioration has been noted, a lack of a significant systemic immunologic response has decreased interest in pursuing this form of therapy. SLIT involves the sublingual administration of high-dose allergen, which is then swallowed. SLIT is now FDA-approved for a limited number of pollens, and its use is expected to increase given its favorable safety profile and convenience of administration.

Efficacy

The positive impact of allergen immunotherapy on seasonal or perennial allergic rhinitis or rhinoconjunctivitis is well documented. In regard to the treatment of allergic rhinitis, birch, mountain cedar, grass, ragweed, and *Cladosporium* are allergens for which allergen immunotherapy has been effective. Effectiveness of allergen immunotherapy with other allergens commonly used for the treatment of allergic rhinitis is inconclusive. Most of the controlled trials examining the effects of allergen immunotherapy on seasonal or perennial allergic asthma also report favorable results. A meta-analysis of 20 trials examining the effects of allergen immunotherapy on allergic asthma revealed a significant increase in the odds for improvement after treatment along with fewer symptoms, improved pulmonary functions, less need for medication, and a reduction in bronchial hyperreactivity. The most convincing data for the benefit of allergen immunotherapy in the treatment of allergic asthma are available for birch, mountain cedar, grass, ragweed, and dust mite with less conclusive but suggestive data available for *Cladosporium, Alternaria,* and cat allergens. Studies examining the effects of allergen immunotherapy in the treatment of patients with allergic rhinitis and allergic asthma have documented increases in circulating allergen-specific IgG and decreases in allergen-specific IgE after treatment. Reductions in sensitivity to administered allergens have been demonstrated in nasal and bronchial challenges. These studies have often shown that the late-phase response after allergen challenge is ablated or significantly reduced. The protective benefit as well as the safety of VIT in patients with sensitivity to *Hymenoptera* venoms has also been well documented in several large studies. The efficacy of allergen immunotherapy for the treatment of urticaria and latex allergy has not been documented. Dust mite allergen immunotherapy may be helpful in patients with atopic dermatitis. Studies using OIT, involving the oral administration of gradually increasing doses of a food allergen under close medical observation followed by a prolonged maintenance phase of daily fixed-dose food allergen administration at home, has been shown to desensitize patients but has not yet proven to induce tolerance. Although still under investigation, OIT and perhaps SLIT are promising therapeutic approaches to the treatment of food allergy in the future.

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Chapter 143

Allergic Rhinitis

Henry Milgrom and Scott H. Sicherer

Allergic rhinitis (AR) is an inflammatory disorder of the nasal mucosa marked by nasal congestion, rhinorrhea, and itching, often accompanied by sneezing and conjunctival inflammation. Its recognition as a major chronic respiratory disease of children rests largely on its high prevalence, detrimental effects on quality of life and school performance, and comorbidities. Children with AR often have related conjunctivitis, sinusitis, otitis media, serous otitis, hypertrophic tonsils and adenoids, and eczema. Childhood AR is associated with a 3-fold increase in risk for asthma at an older age. Over the past 50 yr an upsurge in AR has been observed throughout the world, particularly in areas where its prevalence previously had been low. In prosperous societies, 20-40% of children suffer from AR. The symptoms may appear in infancy; with the diagnosis generally established by the time the child reaches age 6 yr. The prevalence peaks late in childhood.

Risk factors include family history of atopy and serum immunoglobulin (Ig) E higher than 100 IU/mL before age 6 yr. Early life exposures and/or their absence have a profound influence on the development of the allergic phenotype. The risk increases in children whose mothers smoke heavily, even before delivery and especially before the infants are 1 yr old, and those with heavy exposure to indoor allergens. A critical period exists early in infancy when the genetically susceptible individual is at greatest risk of sensitization. Delivery by

cesarean section is associated with AR and atopy in children with a parental history of asthma or allergies. This association may be explained by the lack of exposure to maternal vaginal/fecal flora during delivery. Children between 2 and 3 yr old who have elevated anticockroach and antimouse IgE are at increased risk of wheezing, AR, and atopic dermatitis. The occurrence of 3 or more episodes of rhinorrhea in the first year of life is associated with AR at age 7 yr. Intriguingly, the exposure to dogs, cats, and endotoxin early in childhood protects against the development of atopy. Prolonged breastfeeding is beneficial, but it does not need to be exclusive There is also a decreased risk of asthma, AR, and atopic sensitization with early introduction to wheat, rye, oats, barley, fish and eggs.

ETIOLOGY AND CLASSIFICATION

Two factors necessary for expression of AR are sensitivity to an allergen and the presence of the allergen in the environment. AR classification as **seasonal** or **perennial** is giving way to the designations **intermittent** and **persistent.** The 2 sets of terms are based on different suppositions, but inhalant allergens are the main cause of all forms of AR irrespective of terminology. AR may also be categorized as **mild-intermittent, moderate-severe intermittent, mild-persistent,** and **moderate-severe persistent** (Fig. 143-1). The symptoms of intermittent AR occur on <4 days per week or for <4 consecutive weeks. In persistent AR symptoms occur on >4 days per week and/or for >4 consecutive weeks. The symptoms are considered mild when they are not troublesome, the sleep is normal, there is no impairment in daily activities, and no incapacity at work or school. Severe symptoms result in sleep disturbance, and impairment in daily activities and school (Fig. 143-1).

In temperate climates, airborne pollen responsible for exacerbation of intermittent AR appear in distinct phases: trees pollinate in the spring, grasses in the early summer, and weeds in the late summer. In temperate climates, mold spores persist outdoors only in the summer, but in warm climates throughout the year. Symptoms of intermittent AR typically cease with the appearance of frost. Knowledge of the time of occurrence of symptoms, of the regional patterns of pollination and mold sporulation, and of the patient's specific IgE is necessary for the recognition of the cause of intermittent AR. Persistent AR is most often associated with the indoor allergens: house dust mites, animal danders, mice, and cockroaches. Cat and dog allergies are of major importance in the United States. The allergens from saliva and sebaceous secretions may remain airborne for a prolonged time. The ubiquitous major cat allergen, Fel d 1, may be carried on cat owners' clothing into such "cat-free" settings as schools and hospitals.

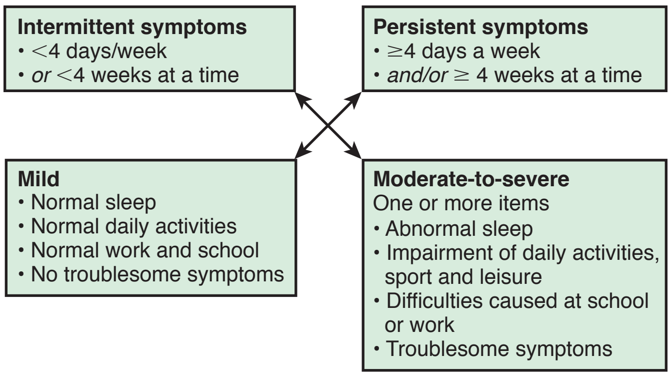

Figure 143-1 ARIA classification of allergic rhinitis. Every box can be subclassified further into seasonal or perennial on the basis of timing of symptoms or when causative and allergen therapeutic factors are considered. For example, a UK patient with grass pollen allergy might have moderate-to-severe persistent seasonal rhinitis in June and July and be suitable for specific allergen immunotherapy. *(From Scadding GK, Durham SR, Mirakian R, et al: BASCI guidelines for the management of allergic and non-allergic rhinitis.* Clin Exp Allergy *38:19-42, 2008 [Fig 2, p. 22].)*

PATHOGENESIS

The exposure of an atopic host to an allergen leads to specific IgE production. The clinical reactions on reexposure to the allergen have been designated as early-phase and late-phase allergic responses. Bridging of the IgE molecules on the surface of mast cells by allergen initiates early-phase allergic response, characterized by degranulation of mast cells and release of preformed and newly generated inflammatory mediators including histamine, prostaglandin 2, and the cysteinyl leukotrienes. Late-phase allergic response appears 4-8 hr following allergen exposure. Inflammatory cells, including basophils, eosinophils, neutrophils, mast cells, and mononuclear cells, infiltrate the nasal mucosa. Eosinophils release proinflammatory mediators, including cysteinyl leukotrienes, cationic proteins, eosinophil peroxidase, and major basic protein, and serve as a source of interleukin (IL)-3, IL-5, granulocyte-macrophage colony-stimulating factor, and IL-13. Repeated intranasal introduction of allergens causes "priming"—a more brisk response even with a lesser provocation. Over the course of an allergy season a multifold increase in submucosal mast cells takes place. These cells, once thought to have a role exclusively in the early-phase allergic response, have an important function in sustaining chronic allergic disease. Allergens, autoantigens, and components of superimposed infectious agents activate the immune system.

CLINICAL MANIFESTATIONS

Symptoms of AR may be ignored or mistakenly attributed to a respiratory infection. Older children blow their noses, but younger children tend to sniff and snort. Nasal itching brings on grimacing, twitching, and picking of the nose that may result in epistaxis. Children with AR often perform the allergic salute, an upward rubbing of the nose with an open palm or extended index finger. This maneuver relieves itching and briefly unblocks the nasal airway. It also gives rise to the nasal crease, a horizontal skin fold over the bridge of the nose. The diagnosis of AR is based on symptoms in the absence of an upper respiratory tract infection and structural abnormalities. Typical complaints include intermittent nasal congestion, itching, sneezing, clear rhinorrhea, and conjunctival irritation. Symptoms increase with greater exposure to the responsible allergen. The patients may lose their sense of smell and taste. Some experience headaches, wheezing, and coughing. Nasal congestion is often more severe at night, causing mouth breathing and snoring, interfering with sleep, and arousing irritability.

Signs on physical exam include abnormalities of facial development, dental malocclusion, and the "allergic gape" or continuous open-mouth breathing, chapped lips, "allergic shiners" (dark circles under the eyes), and the transverse nasal crease. Conjunctival edema, itching, tearing, and hyperemia are frequent findings. A nasal exam performed with a source of light and a speculum may reveal clear nasal secretions; edematous, boggy, and bluish mucus membranes with little or no erythema; and swollen turbinates that may block the nasal airway. It may be necessary to use a topical decongestant to perform an adequate examination. Thick, purulent nasal secretions indicate the presence of infection.

DIFFERENTIAL DIAGNOSIS

Evaluation of AR calls for a thorough history, including details of the patient's environment and diet and family history of allergic conditions such as eczema, asthma, and AR, physical examination, and laboratory evaluation. The history and laboratory findings provide clues to the provoking factors. Symptoms that include sneezing, rhinorrhea, nasal itching, and congestion and the laboratory findings of elevated IgE, specific IgE antibodies, and positive allergy skin test results typify AR. Intermittent AR differs from persistent AR by history and skin test results. Nonallergic rhinitides cause sporadic symptoms. Their causes are often unknown. Nonallergic inflammatory rhinitis with eosinophils imitates AR in presentation and response to treatment, but without elevated IgE antibodies. Vasomotor rhinitis is characterized by excessive responsiveness of the nasal mucosa to physical stimuli. Other nonallergic conditions, such as infectious rhinitis; structural problems, including nasal polyps and septal deviation; rhinitis medicamentosa (caused by the overuse of topical vasoconstrictors); hormonal rhinitis

Table 143-1 Causes of Nonallergic Rhinitis

Structural/mechanical factors:
• Deviated septum/septal wall anomalies
• Hypertrophic turbinates
• Adenoidal hypertrophy
• Foreign bodies
Nasal tumors:
• Benign
• Malignant
• Choanal atresia
Infectious:
• Acute
• Chronic
Inflammatory/immunologic:
• Granulomatosis with polyangiitis
• Sarcoidosis
• Midline granuloma
• Systemic lupus erythematosus
• Sjögren syndrome
• Nasal polyposis
Physiologic:
• Ciliary dyskinesia syndrome
• Atrophic rhinitis
Hormonally induced:
• Hypothyroidism
• Pregnancy
• Oral contraceptives
• Menstrual cycle
• Exercise
• Atrophic
Drug induced:
• Rhinitis medicamentosa
• Oral contraceptives
• Antihypertensive therapy
• Aspirin
• Nonsteroidal antiinflammatory drugs
Reflex induced:
• Gustatory rhinitis
• Chemical or irritant induced
• Posture reflexes
• Nasal cycle
• Environmental factors:
• Odors
• Temperature
• Weather/barometric pressure
• Occupational
• Nonallergic rhinitis with eosinophilia syndrome
• Perennial nonallergic rhinitis (vasomotor rhinitis)
• Emotional factors

From Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *St. Louis, 2003, Mosby, p. 290.*

associated with pregnancy or hypothyroidism; neoplasms; vasculitides; and granulomatous disorders may mimic AR (Table 143-1, Fig. 143-2). Occupational risks for rhinitis include exposure to allergens (grain dust, insects, latex, enzymes) and irritants (wood dust, paint, solvents, smoke, cold air).

COMPLICATIONS

AR is frequently associated with complications and comorbid conditions. Children with AR experience frustration over their appearance. Allergic conjunctivitis, characterized by itching, redness and swelling of the conjunctivae, has been reported in at least 20% of the population and in more the 70% of patients with AR, most frequently in older children and young adults. The 2 conditions share pathophysiologic mechanisms and epidemiologic characteristics (see Chapter 147). Chronic sinusitis is a common complication of AR, sometimes associated with purulent infection, but most patients have negative bacterial cultures despite marked mucosal thickening, and sinus opacification. The inflammatory process is characterized by marked eosinophilia. Allergens, possibly fungal, are the inciting agents. The sinusitis of triad asthma (asthma, sinusitis with nasal polyposis, and aspirin sensitivity) often responds poorly to therapy. Patients who undergo repeated endoscopic surgery derive diminishing benefit with each successive procedure.

Rhinitis that coexists with asthma may be taken too lightly or completely overlooked. Up to 78% of patients with asthma have AR, and 38% of patients with AR have asthma. Aggravation of AR coincides with exacerbation of asthma, and treatment of nasal inflammation reduces bronchospasm, asthma-related emergency department visits, and hospitalizations. Postnasal drip associated with AR commonly causes persistent or recurrent cough. Eustachian tube obstruction and middle ear effusion are frequent complications. Chronic allergic inflammation causes hypertrophy of adenoids and tonsils that may be associated with eustachian tube obstruction, serous effusion, otitis media, and obstructive sleep apnea. AR is linked to snoring in children. The association between rhinitis and sleep abnormalities and subsequent daytime fatigue is well documented.

The Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) is suitable for children 6-12 yr old, and the Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (ARQLQ) is appropriate for patients 12-17 yr of age. Children with rhinitis have anxiety and physical, social, and emotional issues that affect learning and the ability to integrate with peers. The disorder contributes to headaches and fatigue, limits daily activities, and interferes with sleep. There is evidence of impaired cognitive functioning and learning that may be exacerbated by the adverse effects of sedating medications. Rhinitis is an important cause of lost school attendance, resulting in more than 2 million days of absence in the United States annually.

LABORATORY FINDINGS

Epicutaneous skin tests provide the best method for detection of allergen-specific IgE (positive predictive value of 48.7% for the epidemiologic diagnosis of AR). They are inexpensive and sensitive, and the risks and discomfort are minimal. Responses to seasonal respiratory allergens are rare before 2 seasons of exposure, and children <1 yr seldom display positive skin test responses to these allergens. To avoid false-negative results, montelukast should be withheld for 1 day, most sedating antihistamine preparations for 3-4 days, and nonsedating antihistamines for 5-7 days. Serum immunoassays for specific IgE to allergens provide a suitable alternative (positive predictive value 43.5%) for patients with dermatographism or extensive dermatitis, those taking medications that interfere with mast cell degranulation, others at high risk for anaphylaxis, and some who cannot cooperate with the procedure. Presence of eosinophils in nasal smear supports the diagnosis of AR, and of neutrophils infectious rhinitis. Eosinophilia and measurements of total serum IgE concentrations have relatively low sensitivity.

TREATMENT

Safe and effective prevention and/or relief of symptoms are the current goals of treatment. Specific measures to limit indoor allergen exposure may reduce the risk of sensitization and symptoms of allergic respiratory disease. Sealing the patient's mattress, pillow, and covers in allergen-proof encasings reduces the exposure to mite allergen. Bed linen and blankets should be washed every week in hot water (>54.4°C [130°F]). The only effective measure for avoiding animal allergens in the home is the removal of the pet. Avoidance of pollen and outdoor molds can be accomplished by staying in a controlled environment. Air conditioning allows for keeping windows and doors closed, reducing the pollen exposure. High-efficiency particulate air filters lower the counts of airborne mold spores.

Oral antihistamines help reduce sneezing, rhinorrhea and ocular symptoms. Administered as needed they provide acceptable treatment for mild-intermittent disease. Antihistamines have been classified as first generation (relatively sedating) or second generation (relatively nonsedating). Antihistamines usually are administered by mouth, but they are also available for topical ophthalmic and intranasal use. Both first- and second-generation antihistamines are available as nonprescription drugs. Second-generation antihistamines are preferred

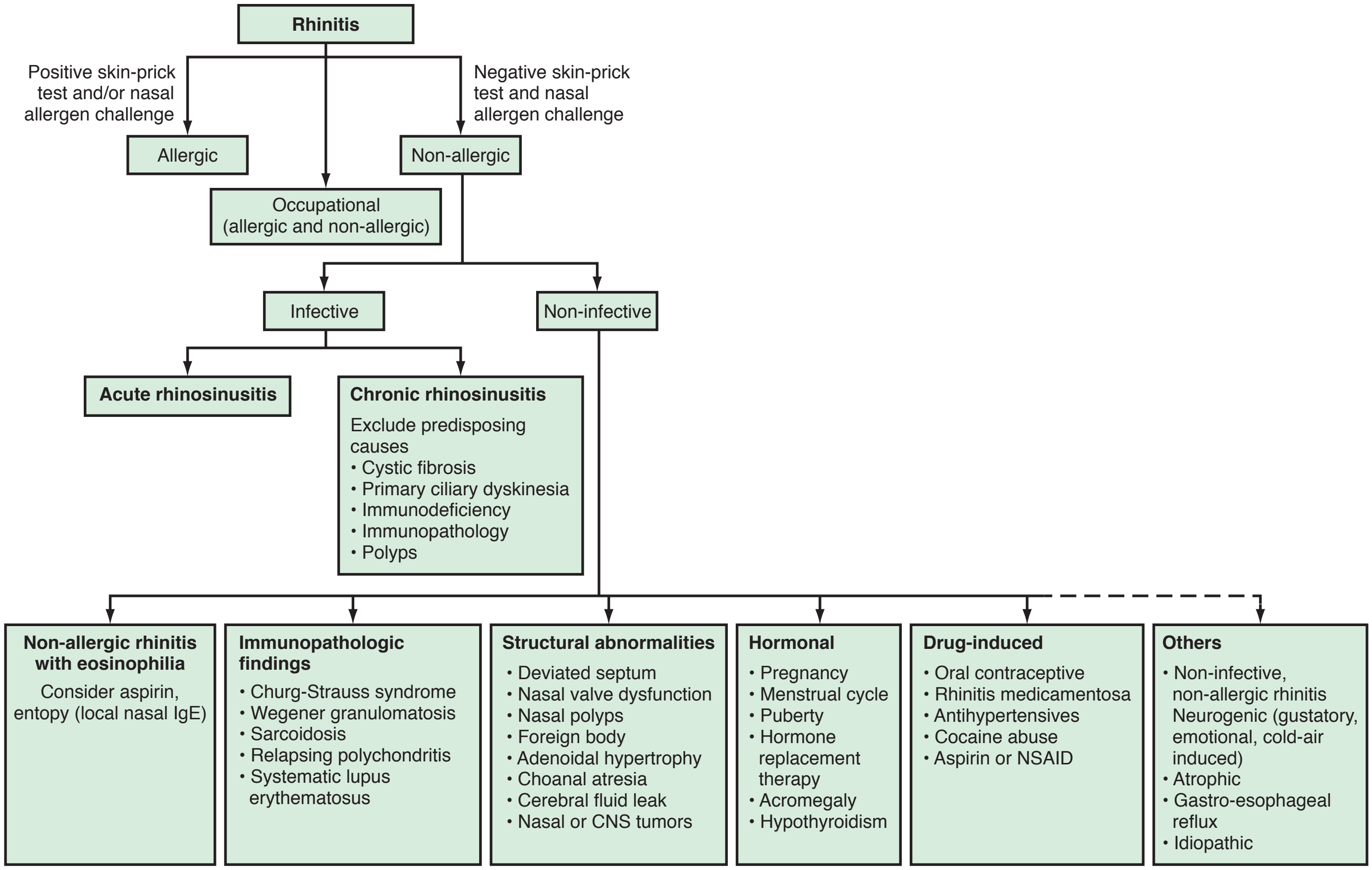

Figure 143-2 **Diagnostic algorithm for rhinitis.** Nasal allergen challenge is a research procedure and is not undertaken routinely. Causes likely to be seen in children are highlighted in italics. NSAID, nonsteroidal antiinflammatory drug. *(From Greiner AN, Hellings PW, Rotiroti G, Scadding GK: Allergic rhinitis. Lancet 378:2112-2120, 2011 [Fig. 3, p. 2116].)*

because they cause less sedation. Preparations containing pseudoephedrine, typically in combination with other agents, are used for relief of nasal and sinus congestion and pressure and other symptoms such as rhinorrhea, sneezing, lacrimation, itching eyes, oronasopharyngeal itching, and cough. Pseudoephedrine is available without prescription (generally in fixed combination with other agents such as first-generation antihistamines: brompheniramine, chlorpheniramine, triprolidine; second-generation antihistamines: desloratadine, fexofenadine, loratadine; antipyretics: acetaminophen, ibuprofen; antitussives: guaifenesin, dextromethorphan; anticholinergic: methscopolamine). Pseudoephedrine is an oral vasoconstrictor disfavored for causing irritability and insomnia and for its association with infant mortality. Because younger children (2-3 yr of age) are at increased risk of overdosage and toxicity, some manufacturers of oral nonprescription cough and cold preparations have voluntarily revised their product labeling to warn against the use of preparations containing pseudoephedrine for children younger than 4 yr. Pseudoephedrine is misused as a starting material for the synthesis of methamphetamine and methcathinone. Oral agents for treatment of AR are shown in Tables 143-2, 143-3, and 143-4.

The anticholinergic nasal spray ipratropium bromide is effective for the treatment of serous rhinorrhea (Table 143-5). Intranasal decongestants (oxymetazoline and phenylephrine) should be used for less than 5 days, not to be repeated more than once a month in order to avoid rebound nasal congestion. Sodium cromoglycate (available as nonprescription drug) is effective but requires frequent administration, q4h. Leukotriene-modifying agents have a modest effect on rhinorrhea and nasal blockage (see Chapter 144 for additional indications and side effects). Nasal saline irrigation is a good adjunctive option with all other treatments of AR. Patients with more persistent, severe symptoms require intranasal corticosteroids, the most effective therapy for AR, a treatment that may be beneficial also for concomitant allergic conjunctivitis (Table 143-6). These agents reduce the symptoms of AR with eosinophilic inflammation, but not those of rhinitis associated with neutrophils or free of inflammation. Beclomethasone, triamcinolone, and flunisolide are absorbed from the gastrointestinal tract, as well as from the respiratory tract; budesonide, fluticasone, mometasone, and ciclesonide offer greater topical activity with lower systemic exposure. More severely affected patients may benefit from simultaneous treatment with oral antihistamines and intranasal corticosteroids.

Allergy immunotherapy is an effective treatment for AR and allergic conjunctivitis. In addition to reducing symptoms, it may change the course of allergic disease and induce allergen-specific immune tolerance. Immunotherapy administered by subcutaneous injection should be considered for children in whom IgE-mediated allergic symptoms cannot be adequately controlled by avoidance and medication, especially in the presence of comorbid conditions. Sublingual immunotherapy has been used successfully in Europe and South America. Sublingual immunotherapy is considered investigational in the United States, and there are no extracts for sublingual administration licensed by the FDA. Omalizumab (anti-IgE antibody) given subcutaneously has a dose-dependent effect on seasonal AR; its role compared with standard therapy has yet to be determined.

Typically, treatment of AR with oral antihistamines and inhaled corticosteroids provides sufficient relief for most cases of coexisting allergic conjunctivitis. If it fails, additional therapies directed primarily to allergic conjunctivitis may be added (see Chapter 147). Intranasal corticosteroids are of some value for the treatment of ocular symptoms, but ophthalmic corticosteroids remain the most potent pharmacologic agents for ocular allergy. They carry the risk of adverse effects, such as delayed wound healing, secondary infection, elevated intraocular

Table 143-2 Oral Allergic Rhinitis Treatments (Prescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
SECOND-GENERATION ANTIHISTAMINES			
Desloratadine			
Clarinex Reditabs*	2.5 mg, 5 mg	Orally disintegrating tablet	Children 6-11 mo of age: 1 mg once daily
Clarinex Tablets	5 mg	Tabs	Children 12 mo-5 yr of age: 1.25 mg once daily
Clarinex Syrup	0.5 mg/mL	Syrup	Children 6-11 yr of age: 2.5 mg once daily
			Adults and adolescents ≥12 yr of age: 5 mg once daily
Levocetirizine dihydrochloride			
Xyzal Oral Solution	0.5 mg/mL	Solution	6 mo-5 yr: max 1.25 mg once daily in the P.M. 6-11 yr: max 2.5 mg once daily in the P.M.
LEUKOTRIENE ANTAGONIST			
Montelukast			
Singulair	10 mg	Tablets	6 mo-5 yr: 4 mg daily
Singulair Chewables*	4 mg, 5 mg	Chewable tablets	6-14 yr: 5 mg daily
Singulair Oral Granules	4 mg/packet	Oral granules	>14 yr: 10 mg daily

*Contains phenylalanine.

Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, *ed 19. Philadelphia, 2012 Mosby.*

Table 143-3 Oral Allergic Rhinitis Treatments (Nonprescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
FIRST-GENERATION H_1 ANTAGONISTS			
Chlorpheniramine maleate			
Chlor-Trimeton	4 mg	Tablets	2-5 yr: 1 mg every 4-6 hr (maximum 6 mg/day)
Chlor-Trimeton Syrup	2 mg/5 mL	Syrup	6-11 yr: 2 mg every 4-6 hr (maximum 12 mg/day)
			>12 yr 4 mg every 4-6 hr (maximum 24 mg/day)
SECOND-GENERATION H_1 ANTAGONISTS			
Cetirizine			
Children's Zyrtec Allergy Syrup	1 mg/mL	Syrup	6-12 mo: 2.5 mg once daily
Children's Zyrtec Chewable	5 mg, 10 mg	Chewable tablets	12-23 mo: initial: 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily
Zyrtec tablets	5 mg, 10 mg	Tablets	2-5 yr: 2.5 mg/day; may be increased to a maximum of 5 mg/day given either as a single dose or divided into 2 doses
Zyrtec Liquid Gels	10 mg	Liquid-filled gels	≥6 yr: 5-10 mg/day as a single dose or divided into 2 doses
Fexofenadine HCl			
Children's Allegra	30 mg	Tablet	
Children's Allegra ODT*	30 mg	Orally disintegrating tablets	6 mo-<2 yr: 15 mg (2.5 mL) every 12 hr
Children's Allegra Oral Suspension	30 mg/5 mL	Suspension	>2-11 yr: 30 mg every 12 hr
Allegra	Tabs 30, 60, 180 mg	Tablet	>12 yr-adult: 60 mg every 12 hr; 180 mg once daily
Loratadine			
Alavert ODT*	10 mg	Orally disintegrating tablets	2-5 yr: 5 mg once daily.
	10 mg	Tablets	>6 yr: 10 mg once daily or 5 mg twice daily
	10 mg	Liquid-filled caps	
	5 mg	Chewable tablets	
	1 mg/mL	Syrup	

*Contains phenylalanine.

Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, *ed 19, Philadelphia, 2012, Mosby.*

Table 143-4 Combined Antihistamine + Sympathomimetic (Examples)

GENERIC	STRENGTH	FORMULATIONS	DOSING
Chlorpheniramine maleate Phenylephrine HCl Sudafed Sinus & Allergy	4 mg 10 mg	Tablets	>12 yr: 1 tablet every 4 hr not to exceed 6 tablets per day
Cetirizine + pseudoephedrine Zyrtec-D 12 hour	5 mg cetirizine + 120 mg pseudoephedrine	Extended release tablet	>12 yr: 1 tablet every 12 hr

Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, *ed 19, Philadelphia, 2012, Mosby.*

Table 143-5 Miscellaneous Intranasal Sprays

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Ipratropium bromide: Atrovent nasal spray (0.06%)	*I:* Symptomatic relief of rhinorrhea *M:* Anticholinergic Colds (symptomatic relief of rhinorrhea): 5-12 yr: 2 sprays in each nostril 3 times/day ≥12 yr and adults: 2 sprays in each nostril 3-4 times/day	Atrovent inhalation aerosol is contraindicated in patients with hypersensitivity to soy lecithin Safety and efficacy of use beyond 4 days in patients with the common cold have not been established *Adverse effects:* Epistaxis, nasal dryness, nausea
Azelastine: Astelin	*I:* Treatment of rhinorrhea, sneezing, and nasal pruritus *M:* Antagonism of histamine H_1-receptor 6-12 yr: 1 spray bid >12 yr: 1-2 sprays bid	May cause drowsiness *Adverse effects:* Headache, somnolence, bitter taste
Cromolyn sodium: NasalCrom	*I:* AR. *M:* Inhibition of mast cell degranulation >2 yr: 1 spray tid-qid; max ×6 /day	Not effective immediately; requires frequent administration
Oxymetazoline: Afrin, Nostrilla	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic agonist, vasoconstricting agent 0.05% solution: instill 2-3 sprays into each nostril twice daily; therapy should not exceed 3 days	Excessive dosage may cause profound central nervous system (CNS) depression Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month Use with caution in patients with hyperthyroidism, heart disease, hypertension, and diabetes *Adverse effects:* Hypertension, palpitations, reflex bradycardia, nervousness, dizziness, insomnia, headache, CNS depression, convulsions, hallucinations, nausea, vomiting, mydriasis, elevated intraocular pressure, blurred vision
Phenylephrine: Neo-Synephrine	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic, vasoconstricting agent 2-6 yr: 1 drop every 2-4 hr of 0.125% solution as needed. *Note:* Therapy should not exceed 3 continuous days 6-12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% solution as needed. *Note:* Therapy should not exceed 3 continuous days >12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% to 0.5% solution as needed; 1% solution may be used in adults with extreme nasal congestion. *Note:* Therapy should not exceed 3 continuous days	Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month 0.16% and 0.125% solutions are not commercially available *Adverse effects:* Reflex bradycardia, excitability, headache, anxiety, and dizziness

Table 143-6 Intranasal Inhaled Corticosteroids

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Beclomethasone: Beconase AQ (42 µg/spray) Qnasl (80 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 6-12 yr: 1 spray in each nostril bid; may increase if needed to 2 sprays in each nostril bid >12 yr: 1 or 2 sprays in each nostril bid	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Flunisolide	6-14 yr: 1 spray each nostril 3 times daily *or* 2 sprays in each nostril twice daily; not to exceed 4 sprays/day in each nostril ≥15 yr: 2 sprays each nostril twice daily (morning and evening); may increase to 2 sprays 3 times daily; maximum dose: 8 sprays/day in each nostril (400 µg/day)	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth

Continued

Table 143-6 Intranasal Inhaled Corticosteroids—cont'd

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Triamcinolone Nasacort AQ (55 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 2-6 yr; 1 spray in each nostril qd 6-12 yr: 1-2 sprays in each nostril qd ≥12 yr: 2 sprays in each nostril qd	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Fluticasone propionate (available as a generic preparation): Flonase (50 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator ≥4 yr: 1-2 sprays in each nostril qd	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril Ritonavir significantly increases fluticasone serum concentrations and may result in systemic corticosteroid effects Use fluticasone with caution in patients receiving ketoconazole or other potent cytochrome P450 3A4 isoenzyme inhibitor *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Fluticasone furoate: Veramyst (27.5 µg/spray)	2-12 yr: Initial dose: 1 spray (27.5 µg/spray) per nostril once daily (55 µg/day) Patients who do not show adequate response may use 2 sprays per nostril once daily (110 µg/day) Once symptoms are controlled, dosage may be reduced to 55 µg once daily Total daily dosage should not exceed 2 sprays in each nostril (110 µg)/day ≥12 yr and adolescents: Initial dose: 2 sprays (27.5 µg/spray) per nostril once daily (110 µg/day) Once symptoms are controlled, dosage may be reduced to 1 spray per nostril once daily (55 µg/day) Total daily dosage should not exceed 2 sprays in each nostril (110 µg)/day	
Mometasone: Nasonex (50 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 2-12 yr: 1 spray in each nostril qd >12 yr: 2 sprays in each nostril qd	Mometasone and its major metabolites are undetectable in plasma after nasal administration of recommended doses Preventive treatment of seasonal AR should begin 2-4 wk prior to pollen season Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Budesonide: Rhinocort Aqua (32 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 6-12 yr: 2 sprays in each nostril qd >12 yr: up to 4 sprays in each nostril qd (maximum dose)	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Ciclesonide: Omnaris Zetonna (50 µg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 2-12 yr: 1-2 sprays in each nostril qd >12 yr: 2 sprays in each nostril qd	Prior to initial use, gently shake, then prime the pump by actuating 8 times If the product is not used for 4 consecutive days, gently shake and reprime with 1 spray or until a fine mist appears
Azelastine/fluticasone (137 µg azelastine/50 µg fluticasone) Dymista	>12 yr: 1 spray in each nostril bid	Shake bottle gently before using. Blow nose to clear nostrils. Keep head tilted downward when spraying. Insert applicator tip ¼ to ½ inch into nostril, keeping bottle upright, and close off the other nostril. Breathe in through nose. While inhaling, press pump to release spray

pressure, and formation of cataracts. These agents are only suited for the treatment of allergic conjunctivitis that does not respond to the medications discussed above. Sound practice calls for the assistance of an ophthalmologist.

PROGNOSIS

Therapy with nonsedating antihistamines and topical corticosteroids, when taken faithfully, significantly improves health-related quality-of-life measures in patients. The reported rates of remission among children are between 10% and 23%. Pharmacotherapy that will target cells and cytokines involved in inflammation and treat allergy as a systemic process is on the horizon, and more selective targeting of drugs based on the development of specific biomarkers and genetic profiling may soon be realized.

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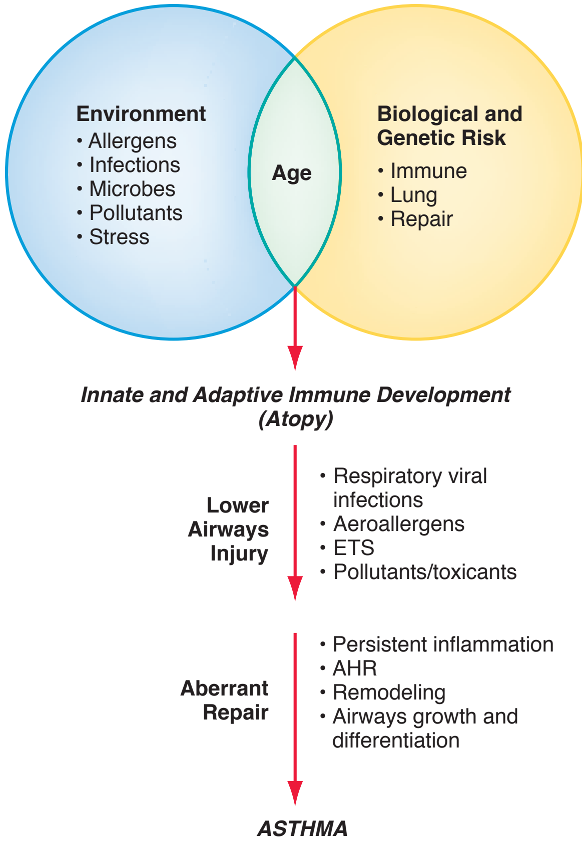

Figure 144-1 Etiology and pathogenesis of asthma. A combination of environmental and genetic factors in early life shape how the immune system develops and responds to ubiquitous environmental exposures. Respiratory microbes, inhaled allergens, and toxins that can injure the lower airways target the disease process to the lungs. Aberrant immune and repair responses to airways injury underlie persistent disease. AHR, airways hyperresponsiveness; ETS, environmental tobacco smoke.

Chapter **144**

Childhood Asthma

Andrew H. Liu, Ronina A. Covar, Joseph D. Spahn, and Scott H. Sicherer

Asthma is a chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction. This chronic inflammation heightens the twitchiness of the airways—airways hyperresponsiveness (AHR)—to provocative exposures. Asthma management is aimed at reducing airways inflammation by minimizing proinflammatory environmental exposures, using daily controller antiinflammatory medications, and controlling comorbid conditions that can worsen asthma. Less inflammation typically leads to better asthma control, with fewer exacerbations and decreased need for quick-reliever asthma medications. Nevertheless, exacerbations can still occur. Early intervention with systemic corticosteroids greatly reduces the severity of such episodes. Advances in asthma management and, especially, pharmacotherapy enable all but the uncommon child with difficult asthma to live normally.

ETIOLOGY

Although the cause of childhood asthma has not been determined, a combination of environmental exposures and inherent biologic and genetic susceptibilities has been implicated (Fig. 144-1). In the susceptible host, immune responses to common airways exposures (e.g., respiratory viruses, allergens, tobacco smoke, air pollutants) can stimulate prolonged, pathogenic inflammation and aberrant repair of injured airways tissues. Lung dysfunction (AHR, reduced airflow) and airway remodeling develop. These pathogenic processes in the growing lung during early life adversely affect airways growth and differentiation, leading to altered airways at mature ages. Once asthma has developed, ongoing inflammatory exposures appear to worsen it, driving disease persistence and increasing the risk of severe exacerbations.

Genetics

To date, more than 100 genetic loci have been linked to asthma, although relatively few have consistently been linked to asthma in different study cohorts. Replicating variants include genetic loci containing proallergic, proinflammatory genes. Because epigenetic marks are heritable, are responsive to environmental exposures, and can result in rapid and persistent changes in gene expression it is conceivable that epigenetic modification of genes play a role in the transmission of asthma.

Environment

Recurrent wheezing episodes in early childhood are associated with common respiratory viruses, especially common cold rhinoviruses, and also respiratory syncytial virus, influenza virus, adenovirus, parainfluenza virus, and human metapneumovirus. This association implies that host features affecting immunologic host defense, inflammation, and the extent of airways injury from ubiquitous viral pathogens underlie susceptibility to recurrent wheezing in *early* childhood. Other airways exposures can also exacerbate ongoing airways inflammation, increase disease severity, and drive asthma persistence. Home allergen exposures in sensitized individuals can initiate airways inflammation and hypersensitivity to other irritant exposures, and are strongly linked to disease severity and persistence. Consequently, eliminating the offending allergen(s) can lead to resolution of asthma symptoms and can sometimes cure asthma. Environmental tobacco smoke and common air pollutants can aggravate airways inflammation and increase asthma severity. Cold, dry air, hyperventilation from physical play or exercise, and strong odors can trigger bronchoconstriction. Although many exposures that trigger and aggravate asthma are well recognized, the causal environmental features underlying the development of host susceptibilities to the various common airway exposures are not well defined.

EPIDEMIOLOGY

Asthma is a common chronic disease, causing considerable morbidity. In 2011, more than 10 million children (14% of U.S. children) had ever been diagnosed with asthma, with 70% of this group reporting current asthma. Male gender and living in poverty are demographic risk factors for having childhood asthma in the U.S. Fifteen percent of boys

compared to 13% of girls have had asthma; and 18% of all children living in poor families (incomes less than $25,000 per year), compared to 12% of children in families not classified as poor, have had asthma.

Childhood asthma is among the most common causes of childhood emergency department visits, hospitalizations, and missed school days. In the United States in 2006, childhood asthma accounted for 593,000 emergency department visits, 155,000 hospitalizations, and 167 deaths. A disparity in asthma outcomes links high rates of asthma hospitalization and death with poverty, ethnic minorities, and urban living. In the past 2 decades, black children have had 2-7 times more emergency department visits, hospitalizations, and deaths as a result of asthma than nonblack children. Although current asthma prevalence is higher in black than in nonblack U.S. children (in 2011, 16.5% vs 8.1% for white and 9.8% for Latino children), prevalence differences cannot fully account for this disparity in asthma outcomes.

Worldwide, childhood asthma appears to be increasing in prevalence, despite considerable improvements in our management and pharmacopeia to treat asthma. Numerous studies conducted in different countries have reported an increase in asthma prevalence of approximately 50% per decade. Globally, childhood asthma prevalence varies widely in different locales. A study of childhood asthma prevalence in 233 centers in 97 countries (International Study of Asthma and Allergies in Childhood, Phase 3) found a wide range in the prevalence of current wheeze in 6-7 yr (2.4-37.6%) and 13-14 yr old children (0.8-32.6%). Asthma prevalence correlated well with reported allergic rhinoconjunctivitis and atopic eczema prevalence. Childhood asthma seems more prevalent in modern metropolitan locales and more affluent nations, and is strongly linked with other allergic conditions. In contrast, children living in rural areas of developing countries and farming communities with domestic animals are less likely to experience asthma and allergy.

Approximately 80% of all asthmatic patients report disease onset prior to 6 yr of age. However, of all young children who experience recurrent wheezing, only a minority go on to have persistent asthma in later childhood. Early childhood risk factors for persistent asthma have been identified (Table 144-1) and have been described as major (parent asthma, eczema, inhalant allergen sensitization) and minor (allergic rhinitis, wheezing apart from colds, ≥4% peripheral blood eosinophils, food allergen sensitization) risk factors. Allergy in young children with recurrent cough and/or wheeze is the strongest identifiable factor for the persistence of childhood asthma.

Types of Childhood Asthma

There are 2 common types of childhood asthma based on different natural courses: (1) **recurrent wheezing** in *early* childhood, primarily triggered by common respiratory viral infections, usually resolves during the preschool/lower school years; and (2) **chronic asthma** associated with allergy that persists into later childhood and often adulthood (Table 144-2). School-age children with mild-moderate persistent asthma generally improve as teenagers, with some (~40%) developing intermittent disease. Milder disease is more likely to remit. Inhaled corticosteroid controller therapy for children with persistent asthma does not alter the likelihood of outgrowing asthma in later childhood; however, because children with asthma generally improve with age, their need for controller therapy subsequently lessens and often resolves. Progressive decline in lung function can be a feature of severe, persistent disease.

Asthma is also classified by disease severity (e.g., intermittent or persistent [mild, moderate, or severe]) or control (e.g., well, not well, or very poorly controlled), especially for asthma management purposes. Because most children with asthma can be well controlled with conventional management guidelines, children with asthma can also be characterized according to treatment response and medication requirements as being: (1) easy-to-treat: well controlled with low

Table 144-1	Early Childhood Risk Factors for Persistent Asthma

Parental asthma
Allergy:
- Atopic dermatitis (eczema)
- Allergic rhinitis
- Food allergy
- Inhalant allergen sensitization
- Food allergen sensitization

Severe lower respiratory tract infection:
- Pneumonia
- Bronchiolitis requiring hospitalization

Wheezing apart from colds
Male gender
Low birthweight
Environmental tobacco smoke exposure
Reduced lung function at birth

Table 144-2	Asthma Patterns in Childhood, Based on Natural History and Asthma Management

TRANSIENT NONATOPIC WHEEZING
Common in early preschool years
Recurrent cough/wheeze, primarily triggered by common respiratory viral infections
Usually resolves during the preschool and lower school years, without increased risk for asthma in later life
Reduced airflow at birth, suggestive of relatively narrow airways. AHR near birth. Improves by school age

PERSISTENT ATOPY-ASSOCIATED ASTHMA
Begins in early preschool years
Associated with atopy in early preschool years:
- Clinical (e.g., atopic dermatitis in infancy, allergic rhinitis, food allergy)
- Biologic (e.g., early inhalant allergen sensitization, increased serum immunoglobulin E, increased blood eosinophils)
- Highest risk for persistence into later childhood and adulthood

Lung function abnormalities:
- Those with onset before 3 yr of age acquire reduced airflow by school age
- Those with later onset of symptoms, or with later onset of allergen sensitization, are less likely to experience airflow limitation in childhood

ASTHMA WITH DECLINING LUNG FUNCTION
Children with asthma with progressive increase in airflow limitation
Associated with hyperinflation in childhood, male gender

ASTHMA MANAGEMENT TYPES
(From national and international asthma management guidelines)
SEVERITY CLASSIFICATION*
- Intrinsic disease severity while not on asthma medications

Intermittent
Persistent:
- Mild
- Moderate
- Severe

CONTROL CLASSIFICATION*
- Clinical assessment while asthma being managed and treated

Well controlled
Not well controlled
Very poorly controlled
MANAGEMENT PATTERNS
- **Easy-to-treat:** well controlled with low levels of daily controller therapy
- **Difficult-to-treat:** well controlled with multiple and/or high levels of controller therapies
- **Exacerbators:** despite being well controlled, continue to have severe exacerbations
- **Refractory:** continue to have poorly controlled asthma despite multiple and high levels of controller therapies

*From National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3): *Guideline for the diagnosis and management of asthma.* NIH Publication No. 07-4051. Bethesda, MD, 2007, U.S. Department of Health and Human Services; National Institutes of Health, National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.
AHR, airways hyperresponsiveness.

levels of controller therapy; (2) difficult-to-treat: well controlled with multiple and/or high levels of controller therapies; (3) exacerbators: despite being well controlled, continue to have severe exacerbations; and (4) refractory asthma: continue to have poorly controlled asthma despite multiple and high levels of controller therapies (Table 144-2). Different airways pathologic processes, causing airways inflammation, AHR, and airways congestion and blockage, are believed to underlie these different types of asthma.

PATHOGENESIS

Airflow obstruction in asthma is the result of numerous pathologic processes. In the small airways, airflow is regulated by smooth muscle encircling the airway lumen; bronchoconstriction of these bronchiolar muscular bands restricts or blocks airflow. A cellular inflammatory infiltrate and exudates distinguished by eosinophils, but also including other inflammatory cell types (neutrophils, monocytes, lymphocytes, mast cells, basophils), can fill and obstruct the airways and induce epithelial damage and desquamation into the airways lumen. Helper T lymphocytes and other immune cells that produce proallergic, proinflammatory cytokines (interleukin [IL]-4, IL-5, IL-13), and chemokines (eotaxins) mediate this inflammatory process. Pathogenic immune responses and inflammation may also result from a breach in normal immune regulatory processes (such as regulatory T lymphocytes that produce IL-10 and transforming growth factor-β) that dampen effector immunity and inflammation when they are no longer needed. Hypersensitivity or susceptibility to a variety of provocative exposures or triggers (Table 144-3) can lead to airways inflammation, AHR, edema, basement membrane thickening, subepithelial collagen deposition, smooth muscle and mucous gland hypertrophy, and mucus hypersecretion—all processes that contribute to airflow obstruction.

Table 144-3	Asthma Triggers
Common viral infections of the respiratory tract Aeroallergens in sensitized asthmatic patients	
INDOOR ALLERGENS • Animal dander • Dust mites • Cockroaches • Molds	
SEASONAL AEROALLERGENS • Pollens (trees, grasses, weeds) • Seasonal molds	
AIR POLLUTANTS • Environmental tobacco smoke • Ozone • Nitrogen dioxide • Sulfur dioxide • Particulate matter • Wood- or coal-burning smoke • Mycotoxins • Endotoxin • Dust	
STRONG OR NOXIOUS ODORS OR FUMES • Perfumes, hairsprays • Cleaning agents	
OCCUPATIONAL EXPOSURES • Farm and barn exposures • Formaldehydes, cedar, paint fumes Cold dry air Exercise Crying, laughter, hyperventilation	
COMORBID CONDITIONS • Rhinitis • Sinusitis • Gastroesophageal reflux	
DRUGS • Aspirin and other nonsteroidal antiinflammatory drugs • β-Blocking agents • Sulfiting agents • Tartrazine	

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Intermittent dry coughing and expiratory wheezing are the most common chronic symptoms of asthma. Older children and adults report associated shortness of breath and chest congestion and tightness; younger children are more likely to report intermittent, nonfocal chest pain. Respiratory symptoms can be worse at night, associated with sleep, especially during prolonged exacerbations triggered by respiratory infections or inhalant allergens. Daytime symptoms, often linked with physical activities (exercise-induced) or play, are reported with greatest frequency in children. Other asthma symptoms in children can be subtle and nonspecific, including self-imposed limitation of physical activities, general fatigue (possibly resulting from sleep disturbance), and difficulty keeping up with peers in physical activities. Asking about previous experience with asthma medications (bronchodilators) may provide a history of symptomatic improvement with treatment that supports the diagnosis of asthma. Lack of improvement with bronchodilator and corticosteroid therapy is inconsistent with underlying asthma and should prompt more vigorous consideration of asthma-masquerading conditions.

Asthma symptoms can be triggered by numerous common events or exposures: physical exertion and hyperventilation (laughing), cold or dry air, and airways irritants (see Table 144-3). Exposures that induce airways inflammation, such as infections with common respiratory pathogens (rhinovirus, respiratory syncytial virus, metapneumovirus, parainfluenza virus, influenza virus, adenovirus, *Mycoplasma pneumoniae, Chlamydia pneumoniae*), and inhaled allergens in sensitized children, also increase AHR to dry cold air and irritant exposures. An environmental history is essential for optimal asthma management (see Chapter 141).

The presence of risk factors, such as a history of other allergic conditions (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergies), parental asthma, and/or symptoms apart from colds, supports the diagnosis of asthma. During routine clinic visits, children with asthma commonly present without abnormal signs, emphasizing the importance of the medical history in diagnosing asthma. Some may exhibit a dry, persistent cough. The chest findings are often normal. Deeper breaths can sometimes elicit otherwise undetectable wheezing. In clinic, quick resolution (within 10 min) or convincing improvement in symptoms and signs of asthma with administration of a short-acting inhaled β-agonist (SABA; e.g., albuterol) is supportive of the diagnosis of asthma.

During asthma exacerbations, expiratory wheezing and a prolonged exhalation phase can usually be appreciated by auscultation. Decreased breath sounds in some of the lung fields, commonly the right lower posterior lobe, are consistent with regional hypoventilation caused by airways obstruction. Rhonchi and crackles (or rales) can sometimes be heard, resulting from excess mucus production and inflammatory exudate in the airways. The combination of segmental crackles and poor breath sounds can indicate lung segmental atelectasis that is difficult to distinguish from bronchial pneumonia and can complicate acute asthma management. In severe exacerbations, the greater extent of airways obstruction causes labored breathing and respiratory distress, which manifests as inspiratory and expiratory wheezing, increased prolongation of exhalation, poor air entry, suprasternal and intercostal retractions, nasal flaring, and accessory respiratory muscle use. In extremis, airflow may be so limited that wheezing cannot be heard (Table 144-4).

DIFFERENTIAL DIAGNOSIS

Many childhood respiratory conditions can present with symptoms and signs similar to those of asthma (Table 144-5). Besides asthma, other common causes of chronic, intermittent coughing include gastroesophageal reflux (GER) and rhinosinusitis. Both GER and chronic sinusitis can be challenging to diagnose in children. Often, GER is clinically silent in children, and children with chronic sinusitis do not report sinusitis-specific symptoms, such as localized sinus pressure and

Table 144-4 Formal Evaluation of Asthma Exacerbation Severity in the Urgent or Emergency Care Setting*

	MILD	MODERATE	SEVERE	SUBSET: RESPIRATORY ARREST IMMINENT
SYMPTOMS				
Breathlessness	While walking	While at rest (infant—softer, shorter cry, difficulty feeding)	While at rest (infant—stops feeding)	
	Can lie down	Prefers sitting	Sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
SIGNS				
Respiratory rate†	Increased	Increased	Often >30 breaths/min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate; often only end-expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse rate (beats/min)‡	<100	100-120	>120	Bradycardia
Pulsus paradoxus	Absent <10 mm Hg	May be present 10-25 mm Hg	Often present >25 mm Hg (adult) 20-40 mm Hg (child)	Absence suggests respiratory muscle fatigue
FUNCTIONAL ASSESSMENT				
Peak expiratory flow (value predicted or personal best)	≥70%	Approx. 40-69% or response lasts <2 hr	<40%	<25%§
Pa_{O_2} (breathing air)	Normal (test not usually necessary)	≥60 mm Hg (test not usually necessary)	<60 mm Hg; possible cyanosis	
and/or				
P_{CO_2}	<42 mm Hg (test not usually necessary)	<42 mm Hg (test not usually necessary)	≥42 mm Hg; possible respiratory failure	
Sa_{O_2} (breathing air) at sea level	>95% (test not usually necessary)	90-95% (test not usually necessary)	<90%	
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents			

*Notes:
- The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
- Many of these parameters have not been systematically studied, especially as they correlate with each other. Thus, they serve only as general guides.
- The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and follow-up.

†Normal breathing rates in awake children by age: <2 mo, <60 breaths/min; 2-12 mo, <50 breaths/min; 1-5 yr, <40 breaths/min; 6-8 yr, <30 breaths/min.
‡Normal pulse rates in children by age: 2-12 mo, <160 beats/min; 1-2 yr, <120 beats/min; 2-8 yr, <110 beats/min.
§Peak expiratory flow testing may not be needed in very severe attacks.
Modified from EPR–3. Expert panel report 3: guidelines for the diagnosis and management of asthma, *NIH Publication No. 07-4051, Bethesda, MD, 2007, U.S. Department of Health and Human Services; National Institutes of Health, National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.*

tenderness. In addition, both GER and rhinosinusitis are often comorbid with childhood asthma and, if not specifically treated, may make asthma difficult to manage.

In early life, chronic coughing and wheezing can indicate recurrent aspiration, tracheobronchomalacia, a congenital anatomic abnormality of the airways, foreign-body aspiration, cystic fibrosis, or bronchopulmonary dysplasia.

In older children and adolescents, vocal cord dysfunction (VCD) can manifest as intermittent daytime wheezing (Table 144-6). In this condition, the vocal cords involuntarily close inappropriately during inspiration and sometimes exhalation, producing shortness of breath, coughing, throat tightness, and often audible laryngeal wheezing and/or stridor. In most cases of VCD, spirometric lung function testing reveals "truncated" and inconsistent inspiratory and expiratory flow-volume loops, a pattern that differs from the reproducible pattern of airflow limitation in asthma that improves with bronchodilators. VCD can coexist with asthma. Flexible rhinolaryngoscopy in the patient with symptomatic VCD can reveal paradoxical vocal cord movements with anatomically normal vocal cords. This condition can be well managed with specialized speech therapy training in the relaxation and control of vocal cord movement. Furthermore, treatment of underlying causes of vocal cord irritability (e.g., high GER/aspiration, allergic rhinitis, rhinosinusitis, asthma) can improve VCD. During acute VCD exacerbations, in addition to relaxation breathing techniques in conjunction with inhalation of heliox (a mixture of 70% helium and 30% oxygen) can relieve vocal cord spasm and VCD symptoms.

Exercise-induced laryngeal obstruction must be considered in children with a presumptive diagnosis of exercise-induced asthma. The diagnosis is confirmed by continuous video laryngoscopy during exercise.

In some locales, hypersensitivity pneumonitis (farming communities, homes of bird owners), pulmonary parasitic infestations (rural areas of developing countries), or tuberculosis may be common causes of chronic coughing and/or wheezing. Rare asthma-masquerading conditions in childhood include bronchiolitis obliterans, interstitial lung diseases, primary ciliary dyskinesias, humoral immune deficiencies, allergic bronchopulmonary mycoses, congestive heart failure, mass lesions in or compressing the larynx, trachea, or bronchi, and coughing and/or wheezing that is an adverse effect of medication. *Chronic pulmonary diseases often produce clubbing, but clubbing is a very unusual finding in childhood asthma.*

LABORATORY FINDINGS

Lung function tests can help to confirm the diagnosis of asthma and to determine disease severity.

Pulmonary Function Testing

Forced expiratory airflow measures are helpful in diagnosing and monitoring asthma and in assessing efficacy of therapy. Lung function testing is particularly helpful in children with asthma who are poor perceivers of airflow obstruction or when physical signs of asthma do not occur until airflow obstruction is severe.

Table 144-5 Differential Diagnosis of Childhood Asthma

UPPER RESPIRATORY TRACT CONDITIONS
Allergic rhinitis*
Chronic rhinitis*
Sinusitis*
Adenoidal or tonsillar hypertrophy
Nasal foreign body

MIDDLE RESPIRATORY TRACT CONDITIONS
Laryngotracheobronchomalacia*
Laryngotracheobronchitis (e.g., pertussis)*
Laryngeal web, cyst, or stenosis
Exercise-induced laryngeal obstruction
Vocal cord dysfunction*
Vocal cord paralysis
Tracheoesophageal fistula
Vascular ring, sling, or external mass compressing on the airway (e.g., tumor)
Foreign body aspiration*
Chronic bronchitis from environmental tobacco smoke exposure*
Toxic inhalations

LOWER RESPIRATORY TRACT CONDITIONS
Bronchopulmonary dysplasia (chronic lung disease of preterm infants)
Viral bronchiolitis*
Gastroesophageal reflux*
Causes of bronchiectasis:
  Cystic fibrosis
  Immune deficiency
  Allergic bronchopulmonary mycoses (e.g., aspergillosis)
  Chronic aspiration
Immotile cilia syndrome, primary ciliary dyskinesia
Bronchiolitis obliterans
Interstitial lung diseases
Hypersensitivity pneumonitis
Pulmonary eosinophilia, Churg-Strauss vasculitis
Pulmonary hemosiderosis
Tuberculosis
Pneumonia
Pulmonary edema (e.g., congestive heart failure)
Medications associated with chronic cough:
  Acetylcholinesterase inhibitors
  β-Adrenergic antagonists
Angiotensin-converting enzyme inhibitors

*More common asthma masqueraders.

Table 144-6 Similarities and Differences Between Vocal Cord Dysfunction and Asthma

VOCAL CORD DYSFUNCTION	ASTHMA
Extrathoracic	Intrathoracic
Rare (?never) hypoxemia	+ Hypoxemia
No hypercapnia/acidosis	+ Hypercapnia/acidosis
Normal expiratory spirometry	Reduced expiratory flow
Abnormal inspiratory loop (in some)	Normal inspiratory loop
Start/stop abruptly; few symptoms between episodes	Persistent symptoms
Frequent emergency department/office visits	Frequent emergency department/office visits
Multiple medications	Multiple medications

From Noyes BE, Kemp JS: Vocal cord dysfunction in children. Paediat Respir Rev *8:155–163, 2007 (Table 2, p. 159).*

Table 144-7 Lung Function Abnormalities in Asthma

Spirometry (in clinic):
- Airflow limitation:
- Low FEV_1 (relative to percentage of predicted norms)
- FEV_1:FVC ratio <0.80

Bronchodilator response (to inhaled β-agonist):
- Improvement in FEV_1 ≥12% and ≥200 mL*

Exercise challenge:
- Worsening in FEV_1 ≥15%*

Daily peak flow or FEV_1 monitoring: day to day and/or A.M.-to-P.M. variation ≥20%*

*Main criteria consistent with asthma.
FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

Many asthma guidelines promote spirometric measures of airflow and lung volumes during forced expiratory maneuvers as standard for asthma assessment. **Spirometry** is a helpful objective measure of airflow limitation (Fig. 144-2). Spirometry is an essential assessment tool in children who are at risk for severe asthma exacerbations and those who have poor perception of asthma symptoms. Knowledgeable personnel are needed to perform and interpret findings of spirometry tests. Valid spirometric measures depend on a patient's ability to properly perform a full, forceful, and prolonged expiratory maneuver, usually feasible in children >6 yr of age (with some younger exceptions). Reproducible spirometric efforts are an indicator of test validity; i.e., the **FEV_1** (forced expiratory volume in 1 sec) should be reproducible within 5% on 3 measurements, and the *highest* value taken as the reported measure effort of the 3 is used. This standard utilization of the highest of 3 reproducible efforts is indicative of the effort dependence of reliable spirometric testing.

In asthma, airways blockage results in reduced airflow with forced exhalation (see Fig. 144-2). Because asthmatic patients typically have hyperinflated lungs, FEV_1 can be simply adjusted for full expiratory lung volume—the forced vital capacity (FVC)—with an FEV_1:FVC ratio. Generally, an FEV_1:FVC ratio <0.80 indicates significant airflow obstruction (Table 144-7). Normative values for FEV_1 have been determined for children on the basis of height, gender, and ethnicity. Abnormally low FEV_1 as a percentage of predicted norms is 1 of 6 criteria used to determine asthma severity and control in asthma management guidelines sponsored by the U.S. National Institutes of Health (NIH) and the Global Initiative for Asthma (GINA).

Such measures of airflow alone are not diagnostic of asthma, because numerous other conditions can cause airflow reduction. Bronchodilator response to an inhaled β-agonist (e.g., albuterol) is greater in asthmatic patients than nonasthmatic persons; an improvement in FEV_1 ≥12% or >200 mL is consistent with asthma. Bronchoprovocation challenges can be helpful in diagnosing asthma and optimizing asthma management. Asthmatic airways are hyperresponsive and therefore more sensitive to inhaled methacholine, mannitol, and cold or dry air. The degree of AHR to these exposures correlates to some extent with asthma severity and airways inflammation. Although bronchoprovocation challenges are carefully dosed and monitored in an investigational setting, their use is rarely practical in general practice. Exercise challenges (aerobic exertion or "running" for 6-8 min) can help to identify children with exercise-induced bronchospasm. Although the airflow response of nonasthmatic persons to exercise is to increase functional lung volumes and improve FEV_1 slightly (5-10%), exercise often provokes airflow obstruction in persons with inadequately treated asthma. Accordingly, in asthmatic patients, FEV_1 typically decreases during or after exercise by >15% (see Table 144-7). The onset of exercise-induced bronchospasm is usually within 15 min after a vigorous exercise challenge and can spontaneously resolve within 30-60 min. Studies of exercise challenges in school-age children typically identify an additional 5-10% with exercise-induced bronchospasm and previously unrecognized asthma. There are 2 caveats regarding exercise challenges: first,

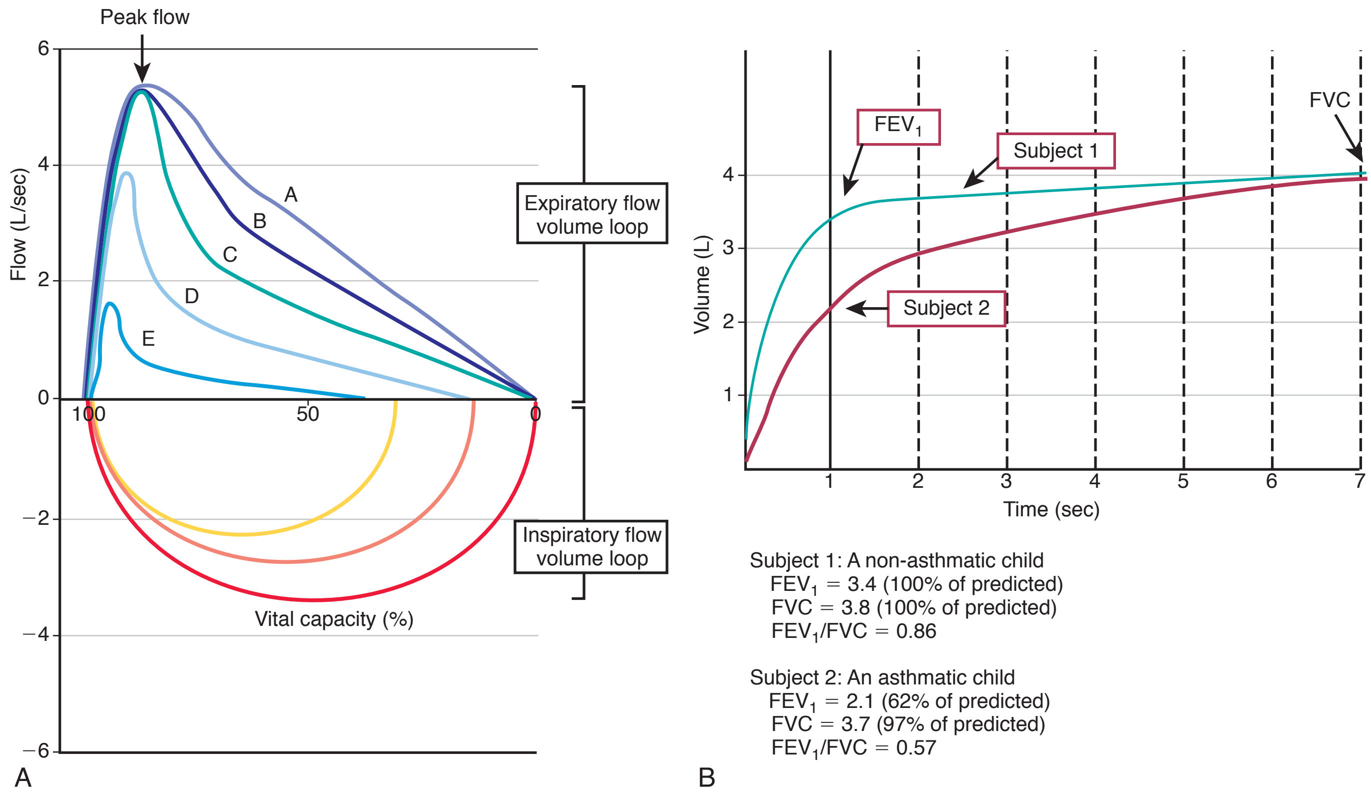

Figure 144-2 Spirometry. *A,* Spirometric flow-volume loops. A is an expiratory flow-volume loop of a nonasthmatic person without airflow limitation. B through E are expiratory flow-volume loops in asthmatic patients with increasing degrees of airflow limitation (B is mild; E is severe). Note the "scooped" or concave appearance of the asthmatic expiratory flow-volume loops; with increasing obstruction, there is greater "scooping." *B,* Spirometric volume-time curves. Subject 1 is a nonasthmatic person; subject 2 is an asthmatic patient. Note how the FEV_1 and FVC lung volumes are obtained. The FEV_1 is the volume of air exhaled in the 1st sec of a forced expiratory effort. The FVC is the total volume of air exhaled during a forced expiratory effort, or forced vital capacity. Note that subject 2's FEV_1 and FEV_1:FVC ratio are smaller than subject 1's, demonstrating airflow limitation. Also, subject 2's FVC is very close to what is expected.

treadmill challenges in the clinic are not completely reliable and can miss exertional asthma that can be demonstrated on the playing field; and second, exercise challenges can induce severe exacerbations in at-risk patients. Careful patient selection for exercise challenges and preparedness for severe asthma exacerbations are required.

Measuring **exhaled nitric oxide** (FE_{NO}), a marker of airway inflammation in allergy-associated asthma, may possibly help adjust antiinflammatory management and confirm the diagnosis of asthma.

Peak expiratory flow (PEF) monitoring devices provide simple and inexpensive home-use tools to measure airflow and can be helpful in a number of circumstances (Fig. 144-3). Similarly to spirometry in clinics, poor perceivers of asthma can benefit by monitoring PEFs at home to assess their airflow as an indicator of asthma control or problems. PEF devices vary in the ability to detect airflow obstruction: they are generally less sensitive and reliable than spirometry to detect airflow obstruction such that, in some patients, PEF values decline only when airflow obstruction is severe. Therefore, PEF monitoring should be started by measuring morning and evening PEFs (best of 3 attempts) for several weeks for patients to practice the technique, to determine diurnal variation and a "personal best," and to correlate PEF values with symptoms (and ideally spirometry). Diurnal variation in PEF >20% is consistent with asthma (see Fig. 144-3 and Table 144-7).

Radiology

The findings of chest radiographs (posteroanterior and lateral views) in children with asthma often appear to be normal, aside from subtle and nonspecific findings of hyperinflation (e.g., flattening of the diaphragms) and peribronchial thickening (Fig. 144-4). Chest radiographs can help identify abnormalities that are hallmarks of asthma masqueraders (aspiration pneumonitis, hyperlucent lung fields in bronchiolitis obliterans) and complications during asthma exacerbations (atelectasis, pneumomediastinum, pneumothorax). Some lung abnormalities can be better appreciated with high-resolution, thin-section chest CT scans. Bronchiectasis, which is sometimes difficult to appreciate on chest radiograph but is clearly seen on CT scan, implicates an asthma masquerader such as cystic fibrosis, allergic bronchopulmonary mycoses (aspergillosis), ciliary dyskinesias, or immune deficiencies.

Other tests, such as allergy testing to assess sensitization to inhalant allergens, help with the management and prognosis of asthma. In a comprehensive U.S. study of 5-12 yr old asthmatic children (Childhood Asthma Management Program [CAMP]), 88% of the subjects had inhalant allergen sensitization according to results of allergy prick skin testing.

TREATMENT

The NIH-sponsored *National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma 2007* is available online (www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm). Similar guidelines *From the Global Strategy for Asthma Management and Prevention,* GINA 2012, are also available online (www.ginaasthma.org). The key components to optimal asthma management are specified (Fig. 144-5). **Management** of asthma should have the following components: (1) assessment and monitoring of disease activity; (2) education to enhance patient and family knowledge and skills for self-management; (3) identification and management of precipitating factors and comorbid conditions that worsen asthma; and (4) appropriate selection of medications to address the patient's needs. The long-term goal of asthma management is attainment of optimal asthma control.

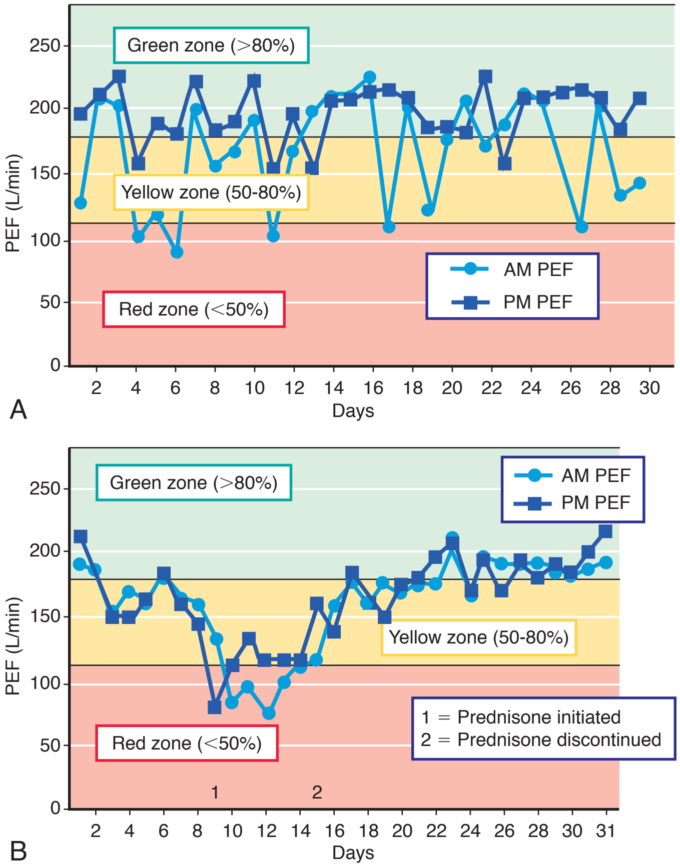

Figure 144-3 An example of the role of peak flow monitoring in childhood asthma. *A,* PEFs performed and recorded twice daily, in the morning (A.M.) and evening (P.M.), over 1 mo in an asthmatic child. This child's "personal best" PEF value is 220 L/min; therefore, the green zone (>80-100% of best) is 175-220 L/min; the yellow zone (50-80%) is 110-175 L/min; and the red zone (<50%) is <110 L/min. Note that this child's P.M. PEF values are almost always in the green zone, whereas his A.M. PEFs are often in the yellow or red zone. This pattern illustrates the typical diurnal A.M.-to-P.M. variation of inadequately controlled asthma. *B,* PEFs performed twice daily, in the morning (A.M.) and evening (P.M.), over 1 mo in an asthmatic child in whom an asthma exacerbation developed from a viral respiratory tract infection. Note that the child's PEF values were initially in the green zone. A viral respiratory tract infection led to asthma worsening, with a decline in PEF to the yellow zone that continued to worsen until PEF values were in the red zone. At that point, a 4-day prednisone course was administered, followed by improvement in PEF back to the green zone.

Component 1: Regular Assessment and Monitoring

Regular assessment and monitoring are based on the concepts of asthma severity, asthma control, and responsiveness to therapy. **Asthma severity** is the intrinsic intensity of disease, and assessment is generally most accurate in patients not receiving controller therapy. Hence, assessing asthma severity directs the initial level of therapy. The 2 general categories are **intermittent** asthma and **persistent** asthma, the latter being further subdivided into **mild, moderate,** and **severe.** In contrast, **asthma control** refers to the degree to which symptoms, ongoing functional impairments, and risk of adverse events are minimized, and goals of therapy are met. In children receiving controller therapy, assessment of asthma control is important in adjusting therapy and is categorized in 3 levels: well-controlled, not well-controlled, and very poorly controlled. **Responsiveness to therapy** is the ease or difficulty with which asthma control is attained by treatment.

Classification of asthma severity and control is based on the domains of **impairment** and **risk.** These domains may not correlate with each other and may respond differently to treatment. In some children with asthma, day-to-day impairment is well controlled, but the risk of severe exacerbations remains. The NIH guidelines have distinct criteria for 3 childhood age groups—0-4 yr, 5-11 yr, and ≥12 yr—for the evaluation of both severity (Table 144-8) and control (Table 144-9). The level of asthma severity or control is based on the most severe impairment or risk category. In assessing asthma severity, **impairment** consists of an assessment of the patient's recent symptom frequency (daytime and nighttime, with subtle differences in numeric cutoffs between the 3 age groups), SABA usage for quick relief, ability to engage in normal or desired activities, and airflow compromise evaluated by spirometry in children 5 yr and older. **Risk** refers to the likelihood of developing severe asthma exacerbations. Of note, in the absence of frequent symptoms, persistent asthma should be considered, and therefore long-term controller therapy should be initiated for infants or children who have risk factors for asthma (see earlier) and 4 or more episodes of wheezing over the past year that lasted longer than 1 day and affected sleep, or 2 or more exacerbations in 6 mo requiring systemic corticosteroids.

Asthma management can be optimized through regular clinic visits every 2-6 wk until good asthma control is achieved. For children already on controller medication therapy, management is tailored to the child's level of control. The NIH guidelines provide tables for evaluating asthma control for the 3 age groups (see Table 144-9). In evaluation of asthma control, as in severity assessment, impairment includes an assessment of the patient's symptom frequency (daytime and nighttime), SABA usage for quick relief, ability to engage in normal or desired activities, and, for older children, airflow measurements. Furthermore, with respect to risk assessment, besides considering severity and frequency of exacerbations requiring systemic corticosteroids, tracking of lung growth in older children and monitoring adverse effects of medications is also warranted. The degree of impairment and presence of risk are used to determine the patient's level of asthma control as well-controlled, not well-controlled, or very poorly controlled. Children with *well-controlled asthma* have daytime symptoms ≤2 days/wk and need a rescue bronchodilator ≤2 days/wk; an FEV_1 of >80% of predicted (and an FEV_1:FVC ratio >80% for children 5-11 yr of age); no interference with normal activity; and <2 exacerbations in the past year. The impairment criteria vary slightly depending on age group: there are different thresholds in the frequency of nighttime awakenings; addition of FEV_1:FVC ratio criteria for children 5-11 yr old and addition of validated impairment questionnaires (e.g., Asthma Control Test [ACT] for ages ≥12 yr, Childhood ACT for ages 4-11 yr). Children whose status does not meet all of the criteria defining well-controlled asthma are determined to have either not-well-controlled or very poorly controlled asthma, which is determined by the single criterion with the poorest rating.

Two to 4 asthma checkups per year are recommended for reassessing and maintaining good asthma control. Lung function testing (spirometry) is recommended at least annually and more often if asthma is poorly perceived, inadequately controlled and/or lung function is abnormally low. PEF monitoring at home can be helpful in the assessment of asthmatic children with poor symptom perception, other causes of chronic coughing in addition to asthma, moderate to severe asthma, or a history of severe asthma exacerbations. PEF monitoring is feasible in children as young as 4 yr who are able to master this skill. Use of a **stoplight zone system** tailored to each child's "personal best" PEF values can optimize effectiveness and interest (see Fig 144-3): The green zone (80-100% of personal best) indicates good control; the yellow zone (50-80%) indicates less-than-optimal control and necessitates increased awareness and treatment; the red zone (<50%) indicates poor control and greater likelihood of an exacerbation, requiring immediate intervention. In actuality, these ranges are approximate and may need to be adjusted for many asthmatic children by raising the ranges that indicate inadequate control (in the yellow zone, 70-90%). Once-daily PEF monitoring is preferable in the morning when peak flows are typically lower.

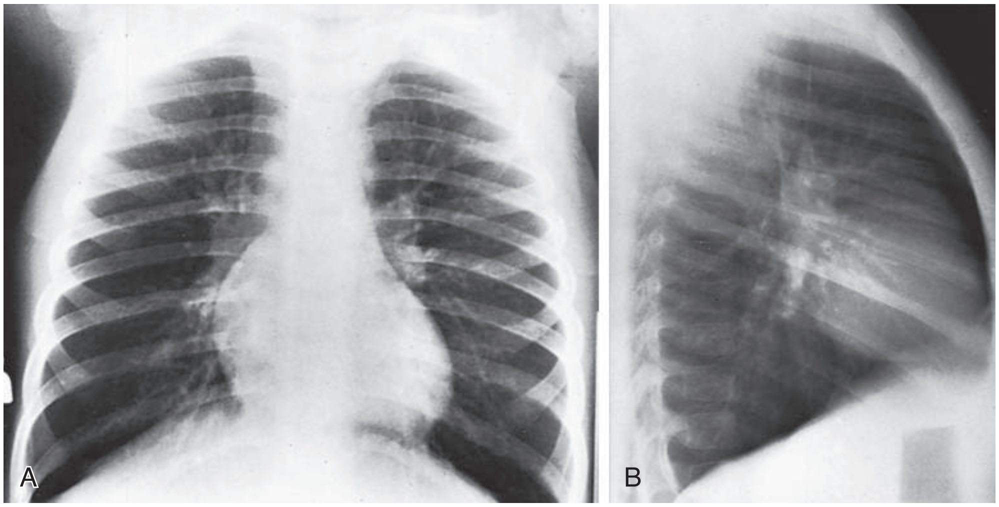

Figure 144-4 **A 4-year-old boy with asthma.** Frontal *(A)* and lateral *(B)* radiographs show pulmonary hyperinflation and minimal peribronchial thickening. No asthmatic complication is apparent.

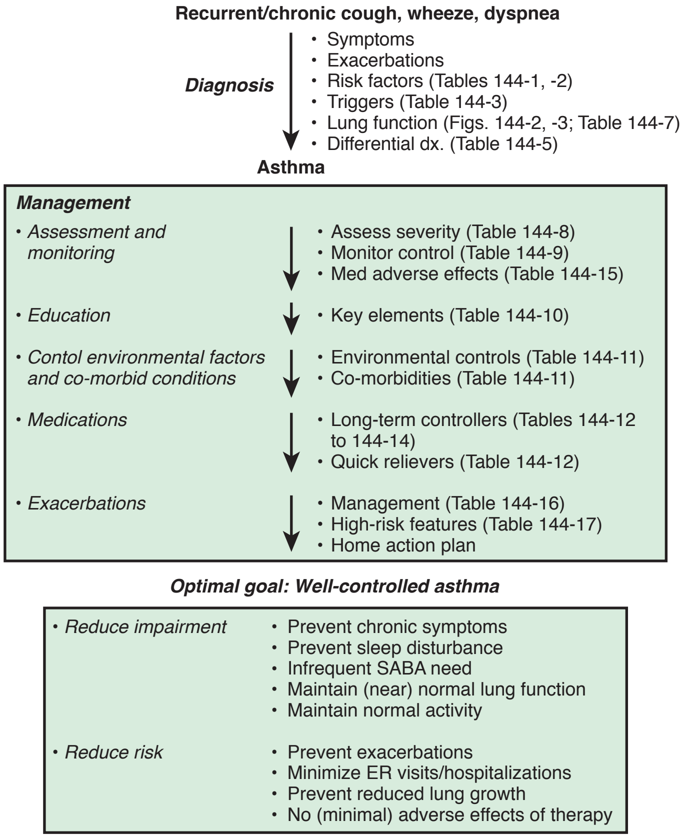

Figure 144-5 The key elements to optimal asthma management. SABA, short-acting β-agonist.

Component 2: Patient Education

Specific educational elements in the clinical care of children with asthma are believed to make an important difference in home management and in adherence of families to an optimal plan of care and eventually impacting patient outcomes (Table 144-10). Every visit presents an important opportunity to educate the child and family, allowing them to become knowledgeable partners in asthma management, because optimal management depends on their daily assessments and implementation of any management plan. Effective communications take into account sociocultural and ethnic factors of children and their families, provide an open forum for concerns about asthma and its treatment to be raised and addressed, and include patients and families as active participants in the development of treatment goals and selection of medications. Self-management skills should be reevaluated regularly (e.g., inhaler medication technique).

During initial patient visits, a basic understanding of the pathogenesis of asthma (chronic inflammation and AHR underlying a clinically intermittent presentation) can help children with asthma and their parents understand the importance of recommendations aimed at reducing airways inflammation to achieve and maintain good asthma control. It is helpful to specify the expectations of good asthma control resulting from optimal asthma management (see Fig. 144-5). Addressing concerns about potential adverse effects of asthma pharmacotherapeutic agents, especially their risks relative to their benefits, is essential in achieving long-term adherence with asthma pharmacotherapy and environmental control measures.

Children with asthma and their families, particularly patients with moderate or severe persistent or poorly controlled asthma and patients who have had severe exacerbations, benefit from a written asthma management plan. This plan has 2 main components: (1) a daily "routine" management plan describing regular asthma medication use and other measures to keep asthma under good control; and (2) an action plan to manage worsening asthma, describing indicators of impending exacerbations, identifying what medications to take, and specifying when and how to contact the regular physician and/or obtain urgent/emergency medical care.

Regular follow-up visits are recommended to help to maintain optimal asthma control. In addition to determining disease control level and revising daily and exacerbation management plans accordingly, follow-up visits are important teaching opportunities to encourage open communication of concerns with asthma management recommendations (e.g., daily administration of controller medications). Reassessing patients' and parents' understanding of the role of different medications in asthma management and control, and their technique in using inhaled medications, can be insightful and can help guide teaching to improve adherence to a management plan that might not have been adequately or properly implemented.

ADHERENCE

Asthma is a chronic condition that is usually best managed with daily controller medication. However, symptoms wax and wane, severe exacerbations are infrequent, and when asthma is asymptomatic, a natural tendency is to reduce or discontinue daily controller therapies. As such, adherence to a daily controller regimen is commonly suboptimal;

Table 144-8 Assessing Asthma Severity and Initiating Treatment for Patients Who Are Not Currently Taking Long-Term Control Medications*

	CLASSIFICATION OF ASTHMA SEVERITY			
		PERSISTENT		
	Intermittent	Mild	Moderate	Severe
COMPONENTS OF SEVERITY				
Impairment				
Daytime symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
Nighttime awakenings:				
Age 0-4 yr	0	1-2×/mo	3-4×/mo	>1×/wk
Age ≥5 yr	≤2×/mo	3-4×/mo	>1×/wk but not nightly	Often 7×/wk
Short-acting β_2-agonist use for symptoms (not for prevention of exercise-induced bronchospasm)	≤2 days/wk	>2 days/wk but not daily, and not more than 1× on any day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
Lung function:				
FEV_1 % predicted, age ≥5 yr	Normal FEV_1 between exacerbations >80% predicted	≥80% predicted	60-80% predicted	<60% predicted
FEV_1:FVC ratio†:				
Age 5-11 yr	>85%	>80%	75-80%	<75%
Age ≥12 yr	Normal	Normal	Reduced 5%	Reduced >5%
Risk				
Exacerbations requiring systemic corticosteroids:				
Age 0-4 yr	0-1/yr (see notes)	≥2 exacerbations in 6 mo requiring systemic corticosteroids **or** ≥4 wheezing episodes/yr lasting >1 day *and* risk factors for persistent asthma		
Age ≥ 5 yr	0-1/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)
Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.				
RECOMMENDED STEP FOR INITIATING THERAPY				
All ages	Step 1	Step 2		
Age 0-4 yr			Step 3	Step 3
Age 5-11 yr			Step 3, medium-dose ICS option	Step 3, medium-dose ICS option **or** Step 4
Age ≥12 yr			Consider a short course of systemic corticosteroids	Consider a short course of systemic corticosteroids
	In 2-6 wk, evaluate level of asthma control that is achieved and adjust therapy accordingly. If no clear benefit is observed within 4-6 wk, consider adjusting therapy or alternative diagnoses.			

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether a patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 mo, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

†Normal FEV_1:FVC: 8-19 yr, 85%; 20-39 yr, 80%.

FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; ICS, inhaled corticosteroids.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007.*

inhaled corticosteroids (ICSs) are underused 60% of the time. In one study, children with asthma who required an oral corticosteroid course for an asthma exacerbation had used their daily controller ICS 15% of the time. Misconceptions about controller medication time to onset, efficacy, and safety often underlie poor adherence and can be addressed by asking about such concerns at each visit.

Component 3: Control of Factors Contributing to Asthma Severity

Controllable factors that can worsen asthma can be generally grouped as (1) environmental exposures and (2) comorbid conditions (Table 144-11).

Eliminating and Reducing Problematic Environmental Exposures

The majority of children with asthma have an allergic component to their disease; steps should be taken to investigate and minimize allergen exposures in sensitized asthmatic patients. The medical history should address potential allergen triggers (see below), but often patients have chronic symptoms and cannot identify potential triggers. Therefore, allergy testing should be considered for at least those with persistent asthma. For asthmatic patients who are allergic to allergens in their homes, reducing or eliminating these home allergen exposures can decrease asthma symptoms, medication requirements, AHR, severe exacerbations, and disease persistence. Common home allergen

Table 144-9 Assessing Asthma Control and Adjusting Therapy in Children*

	CLASSIFICATION OF ASTHMA CONTROL		
	Well-Controlled	**Not Well-Controlled**	**Very Poorly Controlled**
COMPONENTS OF CONTROL			
Impairment			
Symptoms	≤2 days/wk but not more than once on each day	>2 days/wk or multiple times on ≤2 days/wk	Throughout the day
Nighttime awakenings:			
Age 0-4 yr	≤1×/mo	>1×/mo	>1×/wk
Age 5-11 yr	≤1×/mo	≥2×/mo	≥2×/wk
Age ≥12 yr	≤2×/mo	1-3×/wk	≥4×/wk
Short-acting β_2-agonist use for symptoms (not for exercise-induced bronchospasm pretreatment)	≤2 days/wk	>2 days/wk	Several times per day
Interference with normal activity	None	Some limitation	Extremely limited
Lung function:			
Age 5-11 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
FEV_1/FVC:	>80%	75-80%	<75%
Age ≥ 12 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
Validated questionnaires[†]:			
Age ≥ 12 yr:			
ATAQ	0	1-2	3-4
ACQ	≤0.75	≤1.5	N/A
ACT	≥20	16-19	≤15
Risk			
Exacerbations requiring systemic corticosteroids:			
Age 0-4 yr	0-1/yr	2-3/yr	>3/yr
Age ≥5 yr	0-1/yr	≥2/yr (see notes)	
Consider severity and interval since last exacerbation.			
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Reduction in lung growth *or* progressive loss of lung function	Evaluation requires long-term follow-up care.		
RECOMMENDED ACTION FOR TREATMENT	Maintain current step. Regular follow-up every 1-6 mo to maintain control. Consider step down if well-controlled for at least 3 mo.	Step up[‡] (1 step) and reevaluate in 2-6 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative options.	Consider short course of oral corticosteroids. Step up[§] (1-2 steps) and reevaluate in 2 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative options.

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

[†]Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain) and definition of minimal important difference (MID) for each:
- ATAQ, Asthma Therapy Assessment Questionnaire; MID = 1.0
- ACQ, Asthma Control Questionnaire; MID = 0.5
- ACT, Asthma Control Test; MID not determined

[‡]ACQ values of 0.76-1.40 are indeterminate regarding well-controlled asthma.

[§]Before step-up therapy: (a) review adherence to medications, inhaler technique, and environmental control; (b) if alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007.*

Table 144-10	Key Elements of Productive Clinic Visits for Asthma

Specify goals of asthma management
Explain basic facts about asthma:
- Contrast normal vs asthmatic airways
- Link airways inflammation, "twitchiness," and bronchoconstriction
- Long-term-control and quick-relief medications
- Address concerns about potential adverse effects of asthma pharmacotherapy

Teach, demonstrate, and have patient show proper technique for:
- Inhaled medication use (spacer use with metered-dose inhaler)
- Peak flow measures

Investigate and manage factors that contribute to asthma severity:
- Environmental exposures
- Comorbid conditions

Create written 2-part asthma management plan:
- Daily management
- Action plan for asthma exacerbations

Regular follow-up visits:
- Twice yearly (more often if asthma not well-controlled)
- Monitor lung function annually

Table 144-11	Control of Factors Contributing to Asthma Severity

ELIMINATE OR REDUCE PROBLEMATIC ENVIRONMENTAL EXPOSURES:
Environmental tobacco smoke elimination or reduction in home and automobiles
Allergen exposure elimination or reduction in sensitized asthmatic patients:
- Animal danders: pets (cats, dogs, rodents, birds)
- Pests (mice, rats)
- Dust mites
- Cockroaches
- Molds

Other airway irritants:
- Wood- or coal-burning smoke
- Strong chemical odors and perfumes (e.g., household cleaners)
- Dusts

TREAT COMORBID CONDITIONS:
- Rhinitis
- Sinusitis
- Gastroesophageal reflux

exposures include furred or feathered animals as pets (cats, dogs, rodents, birds) or as pests (mice, rats), and occult indoor allergens, such as dust mites, cockroaches, and molds. Although some sensitized children may report an increase in asthma symptoms on exposure to the allergen source, improvement from allergen avoidance may not become apparent without a sustained period of days to weeks away from the offending exposure. Tobacco, wood and coal smoke, dusts, strong odors, and noxious air pollutants can all aggravate asthma. These airways irritants should be eliminated from or reduced in the homes and automobiles used by children with asthma. School classrooms and daycare settings can also be sites of environmental exposures that worsen asthma. Eliminating or minimizing these exposures (e.g., furred or feathered pets in classrooms of sensitized children with asthma) can reduce asthma symptoms, disease severity, and the amount of medication needed to achieve good asthma control. Annual influenza vaccination continues to be recommended for all children with asthma, although influenza is not responsible for the large majority of virus-induced asthma exacerbations experienced by children.

Aspirin-exacerbated respiratory disease, formerly called aspirin-induced asthma, is also associated with chronic eosinophilic rhinitis and nasal polyposis. Inhibition of cyclooxygenase by aspirin and other nonsteroidal antiinflammatory drugs (including cyclooxygenase [COX]-2 inhibiting agents) is thought to be the primary mechanism, which leads to exacerbations of disease, predominantly in patients with moderate to severe persistent asthma. Acetaminophen, a weak COX-1 inhibitor, is safe in low doses, but may produce symptoms if high doses are taken. The incidence is between 5% and 10% of predominantly adolescents with asthma; it is rare in children <10 yr of age. Following ingestion of the drug, symptoms may appear between 30 and 120 min and include profuse rhinorrhea, nasal congestion, and tearing, accompanied by bronchospasm. Vocal cord spasm and an anaphylactic-like reaction are rare complications. Aspirin and related drugs should be avoided in these patients; an alternative approach is aspirin desensitization by an allergist.

Treating Comorbid Conditions

Rhinitis, sinusitis, and GER often accompany asthma and worsen disease severity. They can also mimic asthma symptoms and lead to misclassification of asthma severity and control. Indeed, these conditions with asthma are the most common causes of chronic coughing. Effective management of these comorbid conditions may improve asthma symptoms and disease severity, such that less asthma medication is needed to achieve good asthma control.

GER is observed in 43% of children with persistent asthma. GER may worsen asthma through 2 postulated mechanisms: (1) aspiration of refluxed gastric contents (micro- or macro-aspiration); and (2) vagally mediated reflex bronchospasm. Occult GER should be suspected in individuals with difficult-to-control asthma, especially patients who have prominent asthma symptoms while eating or sleeping (in a horizontal position) or who prop themselves up in bed to reduce nocturnal symptoms. GER can be demonstrated by reflux of barium into the esophagus during a barium swallow procedure or by esophageal probe monitoring. Because radiographic studies lack sufficient sensitivity and specificity, extended esophageal monitoring is the method of choice for diagnosing GER. If significant GER is noted, reflux precautions should be instituted (no food 2 hr before bedtime, head of the bed elevated 6 in, avoidance of caffeinated foods and beverages) and medications such as proton pump inhibitors (omeprazole, lansoprazole) or H_2-receptor antagonists (cimetidine, ranitidine) administered for 8-12 wk. Proton pump inhibition did not improve asthma control in a study of children with persistent, poorly controlled asthma and GER.

Rhinitis is usually comorbid with asthma, detected in ≈90% of children with asthma. Rhinitis can be seasonal and/or perennial, with allergic and nonallergic components. Rhinitis complicates and worsens asthma via numerous direct and indirect mechanisms. Nasal breathing may improve asthma and reduce exercise-induced bronchospasm by humidifying and warming inspired air and filtering out allergens and irritants that can trigger asthma and worsen airway inflammation. Reduction of nasal congestion and obstruction can help the nose to perform these humidifying, warming, and filtering functions. In asthmatic patients, improvement in rhinitis is also associated with improvement in AHR, lower airways inflammation, asthma symptoms, and asthma medication use. Optimal rhinitis management in children is similar to asthma management in regard to the importance of interventions to reduce nasal inflammation (see Chapter 143).

Radiographic evidence for **sinus disease** is common in patients with asthma. There is usually significant improvement in asthma control in patients diagnosed and treated for sinus disease. A coronal, "screening" or "limited" CT scan of the sinuses is the gold standard test for sinus disease and can be helpful if recurrent sinusitis has been suspected and repeatedly treated without such evidence. In comparison, sinus X-rays are inaccurate. If the patient with asthma has clinical and radiographic evidence for sinusitis, topical therapy to include nasal saline irrigations, intranasal corticosteroids, and a 2-3–wk course of antibiotics should be considered.

Component 4: Principles of Asthma Pharmacotherapy

The current version of NIH asthma guidelines (2007) provides treatment recommendations that vary by age groups and are based on current evidence (Table 144-12). The goals of therapy are to achieve a well-controlled state by reducing the components of both impairment (e.g., preventing chronic and troublesome symptoms, allowing infrequent need of quick-reliever medications, maintaining "normal" lung function, maintaining normal activity levels including physical activity and school attendance, meeting families' expectations and satisfaction

Table 144-12 Stepwise Approach for Managing Asthma in Children*

AGE	THERAPY†	INTERMITTENT ASTHMA	PERSISTENT ASTHMA: DAILY MEDICATION				
			← STEP DOWN if possible (and asthma is well controlled at least 3 months)		ASSESS CONTROL	STEP UP if needed (first check inhaler technique, adherence, environmental control, and comorbid condition) →	
		Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**
0-4 yr	Preferred	SABA prn	Low-dose ICS	Medium-dose ICS	Medium-dose ICS + *either* LABA *or* LTRA	High-dose ICS + *either* LABA *or* LTRA	High-dose ICS + *either* LABA *or* LTRA *and* Oral corticosteroid
	Alternative		Cromolyn or montelukast				
5-11 yr	Preferred	SABA prn	Low-dose ICS	*Either* low-dose ICS ± LABA, LTRA, or theophylline *or* Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA	High-dose ICS + LABA *and* Oral corticosteroid
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline		Medium-dose ICS + *either* LTRA *or* Theophylline	High-dose ICS + *either* LTRA *or* Theophylline	High-dose ICS + *either* LTRA *or* Theophylline *and* Oral corticosteroid
≥12 yr	Preferred	SABA prn	Low-dose ICS	Low-dose ICS + LABA *or* Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA *and* Consider omalizumab for patients with allergies	High-dose ICS + LABA + oral corticosteroid *and* Consider omalizumab for patients with allergies
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline	Low-dose ICS + LTRA, theophylline, or zileuton	Medium-dose ICS + LTRA, theophylline, or zileuton		

Each step: Patient education, environmental control, and management of comorbidities.

Age ≥5 yr: Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.

QUICK-RELIEF MEDICATION FOR ALL PATIENTS

SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-min intervals as needed. Short course of oral systemic corticosteroids may be needed.

Caution: Use of SABA >2 days/wk for symptom relief (not prevention of exercise-induced bronchospasm) generally indicates inadequate control and the need to step up treatment.

For ages 0-4 yr: With viral respiratory infection: SABA q4-6h up to 24 hr (longer with physician consult). Consider short course of systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4-6 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children age 0-4 yr are limited. The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.
- Theophylline is a less desirable alternative because of the need to monitor serum concentration levels.
- Zileuton is less desirable alternative because of limited studies as adjunctive therapy and the need to monitor liver function.

†Alphabetical order is used when more than 1 treatment option is listed within *either* preferred or alternative therapy.

ICS, inhaled corticosteroid; LABA, inhaled long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; prn, as needed; SABA, inhaled short-acting β_2-agonist.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007.*

with asthma care) and risk (e.g., preventing recurrent exacerbations, reduced lung growth, and medications' adverse effects). The recommendations for initial therapy are based on assessment of asthma severity. For patients who are already using controller therapy, modification of treatment is based on assessment of asthma control and responsiveness to therapy. A major objective of this approach is to identify and treat all "persistent" and inadequately controlled asthma with antiinflammatory controller medication. Daily controller therapy is not recommended for children with "intermittent asthma." *Management of intermittent asthma is simply the use of a SABA as needed for symptoms and for pretreatment in those with exercise-induced bronchospasm (Step 1 therapy; see Table 144-12).*

The preferred treatment for all patients with persistent asthma is daily ICS therapy, as monotherapy or in combination with adjunctive therapy. The type(s) and amount(s) of daily controller medications to be used are determined by the asthma severity and control rating. Alternative medications for Step 2 therapy include a leukotriene receptor antagonist (montelukast), nonsteroidal antiinflammatory agents (cromolyn and nedocromil), and theophylline (for youths). For young children (≤4 yr) with moderate or severe persistent asthma, medium-dose ICS monotherapy is recommended (Step 3); combination therapy is recommended only as a Step 4 treatment for uncontrolled asthma.

Along with medium-dose ICSs, combination therapy with an ICS plus any of the following adjunctive therapies (depending on age group) is recommended as Steps 3 and 4 treatment for moderate persistent asthma, or as step-up therapy for uncontrolled persistent asthma: long-acting inhaled β_2-agonists (LABAs), leukotriene-modifying agents, chromones, and theophylline. In a study of children with uncontrolled asthma while on low-dose ICS, the addition of LABA provided more improvement than either adding a leukotriene receptor antagonist (LTRA) or increasing ICS dosage. However, some children had a good response to ICS or LTRA, justifying them as step-up controller therapy options.

Children with severe persistent asthma (treatment Steps 5 and 6) should receive high-dose ICS and LABA. Long-term administration of oral corticosteroids as controller therapy can be effective, but is rarely needed with the availability of potent ICS and LABA combination formulations in single devices. In addition, omalizumab can be used in children ≥12 yr old with severe allergic asthma. A rescue course of systemic corticosteroids may be necessary at any step. For children age ≥5 yr with allergic asthma requiring Steps 2-4 care, allergen immunotherapy can be considered.

"Step-Up, Step-Down" Approach

The NIH guidelines emphasize initiating higher-level controller therapy at the outset to establish prompt control, with measures to "step down" therapy once good asthma control is achieved. Initially, airflow limitation and the pathology of asthma may limit the delivery and efficacy of ICS such that stepping up to higher doses and/or combination therapy may be needed to gain asthma control. Furthermore, ICS requires weeks to months of daily administration for optimal efficacy to occur. Combination pharmacotherapy can achieve relatively immediate improvement while also providing daily ICS to improve long-term control and reduce exacerbation risk.

Asthma therapy can be stepped down after good asthma control has been achieved and ICS has had time to achieve optimal efficacy. By determining the lowest number or dose of daily controller medications that can maintain good control, the potential for medication adverse effects is reduced. If a child has had well-controlled asthma for at least 3 mo, the guidelines suggest decreasing the dose or number of the child's controller medication(s) to establish the minimum required medications to maintain well-controlled asthma. Regular follow-up is still emphasized because the variability of asthma's course is well recognized. In contrast, if a child has not-well-controlled asthma, the therapy level should be increased by 1 step and close monitoring is recommended. For a child with very poorly controlled asthma, the recommendations are that treatment go up 2 steps and/or a short course of oral corticosteroid therapy be given, with evaluation within 2 wk. As step-up therapy is being considered at any point, it is important to check inhaler technique and adherence, implement environmental control measures, and identify and treat comorbid conditions.

Referral to Asthma Specialist

Referral to an asthma specialist for consultation or co-management is recommended if there are difficulties in achieving or maintaining control. For children younger than 4 yr, referral is recommended for moderate persistent asthma or if the patient requires at least Step 3 care, and should be considered if the patient requires Step 2 care. For children 5 yr of age and older, consultation with a specialist is recommended if the patient requires Step 4 care or higher, and should be considered if Step 3 is required. Referral is also recommended if allergen immunotherapy or anti–immunoglobulin (Ig) E therapy is being considered.

Long-Term Controller Medications

All levels of persistent asthma should be treated with daily medications to improve long-term control (see Table 144-12). Such medications include ICSs, LABAs, leukotriene modifiers, nonsteroidal antiinflammatory agents, and sustained-release theophylline. An anti-IgE preparation, omalizumab (Xolair), is approved by the FDA for use as an add-on therapy in children ≥12 yr who have moderate to severe allergic asthma that is difficult to control. Corticosteroids are the most potent and most effective medications used to treat both the acute (administered systemically) and chronic (administered by inhalation) manifestations of asthma. They are available in inhaled, oral, and parenteral forms (Tables 144-13 and 144-14).

Inhaled Corticosteroids

The NIH guidelines recommend daily ICS therapy as the treatment of choice for all patients with persistent asthma (see Table 144-12). ICS therapy improves lung function as well as reduces asthma symptoms, AHR, and use of "rescue" medications; most importantly, it reduces urgent care visits, hospitalizations, and prednisone use for asthma exacerbations by approximately 50%. ICS therapy may lower the risk of death attributable to asthma. It can achieve all of the goals of asthma management and, as a result, is viewed as first-line treatment for persistent asthma.

Six ICSs are approved for use in children by the FDA, and the NIH guidelines provide an equivalence classification (see Table 144-14), although direct comparisons of efficacy and safety outcomes in children are lacking. ICSs are available in metered-dose inhalers (MDIs), in dry powder inhalers (DPIs), or in suspension for nebulization. Fluticasone propionate, mometasone furoate, ciclesonide, and, to a lesser extent, budesonide are considered "second-generation" ICSs, in that they have greater antiinflammatory potency and diminished systemic bioavailability for potential adverse effects, owing to extensive first-pass hepatic metabolism. The selection of the initial ICS dose is based on the determination of disease severity. A fraction of the initial ICS dose is often sufficient to maintain good control after this goal has been achieved.

Although ICS therapy has been widely used in adults with persistent asthma, its application in children has lagged because of concerns about the potential for adverse effects with long-term use. Generally, clinically significant adverse effects that occur with long-term systemic corticosteroid therapy have not been seen or have only very rarely been reported in children receiving ICSs in recommended doses. The risk of adverse effects from ICS therapy is related to the dose and frequency with which ICSs are given (Table 144-15). High doses (≥1,000 µg/day in children) and frequent administration (4 times/day) are more likely to have local and systemic adverse effects. Children who receive maintenance therapy with higher ICS doses are also likely to require systemic corticosteroid courses for asthma exacerbations, further increasing the risk of corticosteroid adverse effects.

The most commonly encountered **adverse effects** of ICSs are local: oral candidiasis (thrush) and dysphonia (hoarse voice). Thrush results from propellant-induced mucosal irritation and local immunosuppression. Dysphonia occurs from vocal cord myopathy. These effects are

Table 144-13 Usual Dosages for Long-Term Control Medications

Medication	AGE 0-4 yr	5-11 yr	≥12 yr
INHALED CORTICOSTEROIDS (see Table 144-13) Methylprednisolone: 2, 4, 8, 16, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL, 15 mg/5 mL Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/mL, 5 mg/5 mL	• 0.25-2 mg/kg daily in single dose in A.M. or qod as needed for control • Short-course "burst": 1-2 mg/kg/day; maximum 30 mg/day for 3-10 days	• 0.25-2 mg/kg daily in single dose in A.M. or qod as needed for control • Short-course "burst": 1-2 mg/kg/day; maximum 60 mg/day for 3-10 days	• 7.5-60 mg daily in a single dose in A.M. or qod as needed for control • Short-course "burst" to achieve control: 40-60 mg/day as single or 2 divided doses for 3-10 days
Fluticasone/salmeterol: DPI: 100, 250, or 500 mg/50 mg HFA: 45 µg/21 µg, 115 µg/21 µg, 230 µg/21 µg	NA	1 inhalation bid; dose depends on level of severity or control	1 inhalation bid; dose depends on level of severity or control 2 inhalations bid; dose depends on level of severity or control
Budesonide/formoterol: HFA: 80 µg/4.5 µg, 160 µg/4.5 µg	NA		2 inhalations bid; dose depends on level of severity or control
Mometasone/formoterol HFA: 100 µg/5 µg, 200 µg/5 µg			2 inhalations bid; dose depends on level of severity or control
Cromolyn: Nebulizer 20 mg/ampule	1 ampule qid; NA <2 yr of age	1 ampule qid	1 ampule qid
Leukotriene receptor antagonists: Montelukast: 4 or 5 mg chewable tablet 4 mg granule packets 10 mg tablet	4 mg qhs (1-5 yr of age)	5 mg qhs (6-14 yr)	10 mg qhs
Zafirlukast: 10- or 20-mg tablet	NA	10 mg bid (7-11 yr)	40 mg daily (20 mg tablet bid)
5-Lipoxygenase inhibitor: Zileuton CR: 600-mg tablet	NA	NA	1,200 mg twice daily (give 2 tablets bid)
Theophylline: Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day; usual max: • <1 yr of age: 0.2 (age in wk) + 5 = mg/kg/day • >1 yr of age: 16 mg/kg/day	Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day	Starting dose 10 mg/kg/day up to 300 mg maximum; usual maximum 800 mg/day
Immunomodulators: Omalizumab (anti-IgE): Subcutaneous injection, 150 mg/1.2 mL after reconstitution with 1.4 mL sterile water for injection	NA	NA	150-375 mg SC q 2-4 wk, depending on body weight and pretreatment serum IgE level

bid, Twice a day; DPI, dry powder inhaler; HFA, hydrofluoroalkane Ig, immunoglobulin; MDI, metered-dose inhaler; q, every; qhs, every night; qid, 4 times a day; qod, every other day; SC, subcutaneous.

dose-dependent and are most common in individuals receiving high-dose ICS and/or oral corticosteroid therapy. The incidence of these local effects can be greatly minimized by using a spacer with an MDI ICS, because spacers reduce oropharyngeal deposition of the drug and propellant. Mouth rinsing using a "swish and spit" technique after ICS use is also recommended.

The potential for growth suppression and osteoporosis with long-term ICS use has been a concern. In the long-term, prospective NIH-sponsored CAMP study of children with mild to moderate asthma, after ≈4.3 yr of ICS therapy and 5 yr after the trial, there was a significant 1.7 cm decrease in height in girls, but not in boys. There was also a slight dose-dependent effect of ICS therapy on bone mineral accretion in boys, but not girls. A greater effect on bone mineral accretion was observed with increasing numbers of courses of oral corticosteroid burst therapy for asthma, as well as an increase in risk for osteopenia, again limited to boys. Although this study cannot predict a significant effect of ICS therapy in childhood on osteoporosis in later adulthood, improved asthma control with ICS therapy may result in a need for fewer courses of oral corticosteroid burst therapy over time. These findings were with use of budesonide at doses of about 400 µg/day; higher ICS doses, especially of agents with increased potency, have a greater potential for adverse effects. Hence, corticosteroid adverse effects screening and osteoporosis prevention measures are recommended for patients receiving higher ICS doses, as these patients are also likely to require systemic courses for exacerbations (see Table 144-15).

Systemic Corticosteroids

ICS therapy has allowed the large majority of children with asthma to maintain good disease control without maintenance oral corticosteroid therapy. Oral corticosteroids are used primarily to treat asthma exacerbations and, rarely, in patients with severe disease who remain symptomatic despite optimal use of other asthma medications. In these severely asthmatic patients, every attempt should be made to exclude any comorbid conditions and to keep the oral corticosteroid dose at ≤20 mg qod. Doses exceeding this amount are associated with numerous adverse effects (see Chapter 577). To determine the need for continued oral corticosteroid therapy, tapering of the oral corticosteroid

Table 144-14 Estimated Comparative Inhaled Corticosteroid Doses

	LOW DAILY DOSE BY AGE			MEDIUM DAILY DOSE BY AGE			HIGH DAILY DOSE BY AGE		
Drug	**0-4 yr**	**5-11 yr**	**≥12 yr**	**0-4 yr**	**5-11 yr**	**≥12 yr**	**0-4 yr**	**5-11 yr**	**≥12 yr**
Beclomethasone HFA, 40 or 80 µg/puff	NA	80-160 µg	80-240 µg	NA	>160-320 µg	>240-480 µg	NA	>320 µg	>480 µg
Budesonide DPI 90, 180, or 200 µg/inhalation	NA	180-400 µg	180-600 µg	NA	>400-800 µg	>600-1200 µg	NA	>800 µg	>1200 µg
Budesonide inhaled suspension for nebulization, 0.25, 0.5, and 1.0 mg dose	0.25-0.5 mg	0.5 mg	NA	>0.5-1.0 mg	1.0 mg	NA	>1.0 mg	2.0 mg	NA
Flunisolide, 250 µg/puff	NA	500-750 µg	500-1000 µg	NA	1000-1250 µg	>1000-2000 µg	NA	>1250 µg	>2000 µg
Flunisolide HFA, 80 µg/puff	NA	160 µg	320 µg	NA	320 µg	>320-640 µg	NA	≥640 µg	>640 µg
Fluticasone HFA/MDI: 44, 110, or 220 µg/puff	176 µg	88-176 µg	88-264 µg	>176-352 µg	>176-352 µg	>264-440 µg	>352 µg	>352 µg	>440 µg
Fluticasone DPI, 50, 100, or 250 µg/inhalation	NA	100-200 µg	100-300 µg	NA	>200-400 µg	>300-500 µg	NA	>400 µg	>500 µg
Mometasone DPI, 110 µg and 220 µg/inhalation	NA	NA	220 µg	NA	NA	440 µg	NA	NA	>440 µg
Triamcinolone acetonide, 75 µg/puff	NA	300-600 µg	300-750 µg	NA	>600-900 µg	>750-1500 µg	NA	>900 µg	>1500 µg

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; NA, not approved and no data available for this age group.

Adapted, from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007.*

Table 144-15 Risk Assessment for Corticosteroid Adverse Effects

	CONDITIONS	RECOMMENDATIONS
Low risk	(≤1 risk factor*) Low- to medium-dose ICS (see Table 144-11)	• Monitor blood pressure and weight with each physician visit • Measure height annually (stadiometry); monitor periodically for declining growth rate and pubertal developmental delay • Encourage regular physical exercise • Ensure adequate dietary calcium and vitamin D with additional supplements for daily calcium if needed • Avoid smoking and alcohol • Ensure TSH status if patient has history of thyroid abnormality
Medium risk	(If >1 risk factor,* consider evaluating as high risk) High-dose ICS (see Table 144-11) At least 4 courses oral corticosteroid/yr	As above, plus: • Yearly ophthalmologic evaluations to monitor for cataracts or glaucoma • Baseline bone densitometry (DEXA scan) • Consider patient at increased risk for adrenal insufficiency, especially with physiologic stressors (e.g., surgery, accident, significant illness)
High risk	Chronic systemic corticosteroids (>7.5 mg daily or equivalent for >1 mo) ≥ 7 oral corticosteroid burst treatments/year Very-high-dose ICS (e.g., fluticasone propionate ≥800 µg/day)	As above, plus: • DEXA scan: if DEXA Z score ≤1.0, recommend close monitoring (every 12 mo) • Consider referral to a bone or endocrine specialist • Bone age assessment • Complete blood count • Serum calcium, phosphorus, alkaline phosphatase determinations • Urine calcium and creatinine measurements • Measurements of testosterone in males, estradiol in amenorrheic premenopausal women, vitamin D (25-OH and 1,25-OH vitamin D), parathyroid hormone, and osteocalcin • Urine telopeptides for those receiving long-term systemic or frequent oral corticosteroid treatment • Assume adrenal insufficiency for physiologic stressors (e.g., surgery, accident, significant illness)

*Risk factors for osteoporosis: Presence of other chronic illness(es), medications (corticosteroids, anticonvulsants, heparin, diuretics), low body weight, family history of osteoporosis, significant fracture history disproportionate to trauma, recurrent falls, impaired vision, low dietary calcium and vitamin D intake, and lifestyle factors (decreased physical activity, smoking, and alcohol intake).

DEXA, dual-energy x-ray absorptiometry; ICS, inhaled corticosteroid; TSH, thyroid-stimulating hormone.

dose (over several weeks to months) should be considered, with close monitoring of the patient's symptoms and lung function.

When administered orally, prednisone, prednisolone, and methylprednisolone are rapidly and completely absorbed, with peak plasma concentrations occurring within 1-2 hr. Prednisone is an inactive prodrug that requires biotransformation via first-pass hepatic metabolism to prednisolone, its active form. Corticosteroids are metabolized in the liver into inactive compounds, with the rate of metabolism influenced by drug interactions and disease states. Anticonvulsants (phenytoin, phenobarbital, carbamazepine) increase the metabolism of prednisolone, methylprednisolone, and dexamethasone, with methylprednisolone most significantly affected. Rifampin also enhances the clearance of corticosteroids and can result in diminished therapeutic effect. Other medications (ketoconazole, oral contraceptives) can significantly delay corticosteroid metabolism. Macrolide antibiotics (erythromycin, clarithromycin, troleandomycin) delay the clearance of only methylprednisolone.

Children who require long-term oral corticosteroid therapy are at risk for development of associated adverse effects over time. Essentially all major organ systems can be adversely affected by long-term oral corticosteroid therapy (see Chapter 577). Some of these effects occur immediately (metabolic effects). Others can develop insidiously over several months to years (growth suppression, osteoporosis, cataracts). Most adverse effects occur in a cumulative dose- and duration-dependent manner. Children who require routine or frequent short courses of oral corticosteroids, especially with concurrent high-dose ICSs, should receive corticosteroid adverse effects screening (see Table 144-15) and osteoporosis preventive measures (see Chapter 707).

Long-Acting Inhaled β-Agonists

LABAs (salmeterol, formoterol) are considered to be daily controller medications, *not intended* for use as rescue medication for acute asthma symptoms or exacerbations, nor as monotherapy for persistent asthma. Controller formulations that combine an ICS with a LABA (fluticasone/salmeterol, budesonide/formoterol, mometasone/formoterol) are available and recommended, in lieu of separate inhaler delivery devices. Salmeterol has a prolonged onset of action, with maximal bronchodilation approximately 1 hr after administration, whereas formoterol has an onset of action within 5-10 min. Both medications have a prolonged duration of effect, at least 12 hr. Given their long duration of action, they are well suited for patients with nocturnal asthma and for individuals who require frequent SABA use during the day to prevent exercise-induced bronchospasm. Their major role is as an add-on agent in patients whose asthma is suboptimally controlled with ICS therapy alone. For those patients, the addition of a LABA to ICS therapy is superior to doubling the dose of ICS, especially on day and nocturnal symptoms. Of note, the FDA requires all LABA-containing medications to be labeled with a warning of an increase in severe asthma episodes associated with these agents. Some studies have reported a higher number of asthma-related deaths among patients receiving LABA therapy in addition to their usual asthma care than in patients not receiving LABAs. This notice reinforces the appropriate use of LABAs in the management of asthma. Specifically, *LABA products should not be initiated as first-line or sole asthma therapy without the concomitant use of an ICS,* used with worsening wheezing, or used for acute control of bronchospasm. LABAs should be stopped once asthma control is achieved, and the asthma should be maintained with the use of an asthma controller agent (ICS). Fixed-dose preparations (with an ICS) are recommended to ensure compliance with these guidelines.

Leukotriene-Modifying Agents

Leukotrienes are potent proinflammatory mediators that can induce bronchospasm, mucus secretion, and airways edema. Two classes of leukotriene modifiers have been developed: inhibitors of leukotriene synthesis and LTRAs. Zileuton, the only leukotriene synthesis inhibitor, is not approved for use in children <12 yr of age. Because zileuton can result in elevated liver function enzyme values in 2-4% of patients, and interacts with medications metabolized via the cytochrome P450 system, it is rarely prescribed for children with asthma.

LTRAs have bronchodilator and targeted antiinflammatory properties and reduce exercise-, aspirin-, and allergen-induced bronchoconstriction. *LTRAs are recommended as alternative treatment for mild persistent asthma and as add-on medication with ICS for moderate persistent asthma.* Two LTRAs are FDA-approved for use in children: montelukast and zafirlukast. Both medications improve asthma symptoms, decrease the need for rescue β-agonist use, and improve lung function. Montelukast is FDA-approved for use in children ≥1 yr of age and is administered once daily. Zafirlukast is FDA-approved for use in children ≥5 yr of age and is administered twice daily. Although incompletely studied in children with asthma, LTRAs appear to be less effective than ICSs in patients with mild persistent asthma. In general, ICSs improve lung function by 5-15%, whereas LTRAs improve lung function by 2-7.5%. LTRAs are not thought to have significant adverse effects, although case reports described a Churg-Strauss–like vasculitis (pulmonary infiltrates, eosinophilia, cardiomyopathy) in adults with corticosteroid-dependent asthma treated with LTRAs. It remains to be determined whether these patients have a primary eosinophilic vasculitis masquerading as asthma, which was "unmasked" as the oral corticosteroid dose was tapered, or whether the disease is a very rare adverse effect of LTRA. Montelukast has rarely been associated with mood changes and suicidality.

Nonsteroidal Antiinflammatory Agents

Cromolyn and nedocromil are nonsteroidal antiinflammatory agents that can inhibit allergen-induced asthmatic responses and reduce exercise-induced bronchospasm. Both drugs are considered alternative antiinflammatory drugs for children with mild persistent asthma. Although largely devoid of adverse effects, these medications must be administered frequently (2-4 times/day) and are not nearly as effective daily controller medications as ICSs and leukotriene-modifying agents. Because they inhibit exercise-induced bronchospasm, they can be used in place of SABAs, especially in children who develop unwanted adverse effects with β-agonist therapy (tremor and elevated heart rate). Cromolyn and nedocromil can also be used in addition to a SABA in a combination pretreatment for exercise-induced bronchospasm in patients who continue to experience symptoms with use of SABA pretreatment alone. Nedocromil has been taken off the market and cromolyn is only available in a solution for nebulization.

Theophylline

In addition to its bronchodilator effects, theophylline has antiinflammatory properties as a phosphodiesterase inhibitor, although the extent of its clinical relevance has not been clearly established. When used long-term, theophylline can reduce asthma symptoms and the need for rescue SABA use. Although it is considered an alternative monotherapy controller agent for older children and adults with mild persistent asthma, it is no longer considered a first-line agent for young children, in whom there is significant variability in the absorption and metabolism of different theophylline preparations, necessitating frequent dose monitoring (drug blood levels) and adjustments. Because theophylline may have some corticosteroid-sparing effects in individuals with oral corticosteroid–dependent asthma, it is still sometimes used in this group of asthmatic children. Theophylline has a narrow therapeutic window; therefore, when it is used, serum theophylline levels need to be routinely monitored, especially if the patient has a viral illness associated with a fever or is started on a medication known to delay theophylline clearance, such as a macrolide antibiotic, cimetidine, an oral antifungal agent, an oral contraceptive, a leukotriene synthesis inhibitor, or ciprofloxacin. Theophylline overdosage and elevated theophylline levels have been associated with headaches, vomiting, cardiac arrhythmias, seizures, and death.

Anti–Immunoglobulin E (Omalizumab)

Omalizumab is a humanized monoclonal antibody that binds IgE, thereby preventing its binding to the high-affinity IgE receptor and blocking IgE-mediated allergic responses and inflammation. Because it is unable to bind IgE that is already bound to high-affinity IgE

receptors, the risk of anaphylaxis via direct IgE cross linking by the drug is circumvented. It is FDA-approved for patients >12 yr old with moderate to severe asthma, documented hypersensitivity to a perennial aeroallergen, and inadequate disease control with inhaled and/or oral corticosteroids. Omalizumab is given every 2-4 wk subcutaneously, the dosage based on body weight and serum IgE levels. Asthmatic patients receiving omalizumab have fewer asthma exacerbations and symptoms while able to reduce their ICS and/or oral corticosteroid doses. This agent is generally well tolerated, although local injection site reactions can occur. Hypersensitivity reactions (including anaphylaxis) and malignancies have been very rarely associated with omalizumab use. The FDA requires packaging of omalizumab to contain a black box warning of potentially serious and life-threatening anaphylactic reactions with omalizumab treatment. On the basis of reports from approximately 39,500 patients, anaphylaxis following omalizumab treatment occurred in at least 0.1% of treated people. Although most of these reactions occurred within 2 hr of omalizumab injection, there are reports of serious delayed reactions 2-24 hr or even longer after injections. Anaphylaxis occurred after any omalizumab dose (including the first dose). Omalizumab-treated patients should be observed in the facility for an extended period after the drug is given, and medical providers who administer the injection should be prepared to manage life-threatening anaphylactic reactions. Patients who receive omalizumab should be fully informed about the signs and symptoms of anaphylaxis, their chance of development of delayed anaphylaxis following each injection, and how to treat it, including the use of autoinjectable epinephrine.

Mepolizumab, an anti–IL-5 antibody, has been shown to improve asthma control, reduce prednisone dose and lower sputum and blood eosinophil events in adults with prednisone-dependent asthma who also had sputum eosinophils. Dupilumab, an anti–IL-4 receptor antibody and another monoclonal antibody against IL-13, have also shown promise in adult studies.

Quick-Reliever Medications

Quick-reliever or "rescue" medications (SABAs, inhaled anticholinergics, and short-course systemic corticosteroids) are used in the management of acute asthma symptoms (Table 144-16).

Table 144-16 Management of Asthma Exacerbation (Status Asthmaticus)

RISK ASSESSMENT ON ADMISSION	
Focused history	• Onset of current exacerbation • Frequency and severity of daytime and nighttime symptoms and activity limitation • Frequency of rescue bronchodilator use • Current medications and allergies • Potential triggers • History of systemic steroid courses, emergency department visits, hospitalization, intubation, or life-threatening episodes
Clinical assessment	• Physical examination findings: vital signs, breathlessness, air movement, use of accessory muscles, retractions, anxiety level, alteration in mental status • Pulse oximetry • Lung function (defer in patients with moderate to severe distress or history of labile disease)
Risk factors for asthma morbidity and death	See Table 144-17

TREATMENT

Drug and Trade Name	Mechanisms of Action and Dosing	Cautions and Adverse Effects
Oxygen (mask or nasal cannula)	Treats hypoxia	• Monitor pulse oximetry to maintain O_2 saturation >92% • Cardiorespiratory monitoring
Inhaled short-acting β-agonists:	Bronchodilator	• During exacerbations, frequent or continuous doses can cause pulmonary vasodilation, $\dot{V}/\dot{Q}$ mismatch, and hypoxemia • Adverse effects: palpitations, tachycardia, arrhythmias, tremor, hypoxemia
Albuterol nebulizer solution (5 mg/mL concentrate; 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	Nebulizer: 0.15 mg/kg (minimum: 2.5 mg) as often as every 20 min for 3 doses as needed, then 0.15-0.3 mg/kg up to 10 mg every 1-4 hr as needed, or up to 0.5 mg/kg/hr by continuous nebulization	• Nebulizer: when giving concentrated forms, dilute with saline to 3 mL total nebulized volume
Albuterol MDI (90 μg/puff)	2-8 puffs up to every 20 min for 3 doses as needed, then every 1-4 hr as needed	• For MDI: use spacer/holding chamber
Levalbuterol (Xopenex) nebulizer solution (1.25 mg/0.5 mL concentrate; 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL)	0.075 mg/kg (minimum: 1.25 mg) every 20 min for 3 doses, then 0.075-0.15 mg/kg up to 5 mg every 1-4 hr as needed, or 0.25 mg/kg/hr by continuous nebulization	• Levalbuterol 0.63 mg is equivalent to 1.25 mg of standard albuterol for both efficacy and side effects
Systemic corticosteroids:	Antiinflammatory	• If patient has been exposed to chickenpox or measles, consider passive immunoglobulin prophylaxis; also, risk of complications with herpes simplex and tuberculosis • For daily dosing, 8 A.M. administration minimizes adrenal suppression • Children may benefit from dosage tapering if course exceeds 7 days • Adverse effects monitoring: Frequent therapy bursts risk numerous corticosteroid adverse effects (see Chapter 578); see Table 144-15 for adverse effects screening recommendations

Continued

Table 144-16 Management of Asthma Exacerbation (Status Asthmaticus)—cont'd

Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets Methylprednisolone (Medrol): 2, 4, 8, 16, 24, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL and 15 mg/5 mL solution	0.5-1 mg/kg every 6-12 hr for 48 hr, then 1-2 mg/kg/day bid (maximum: 60 mg/day)	
Depo-Medrol (IM); Solu-Medrol (IV)	Short-course "burst" for exacerbation: 1-2 mg/kg/day qd or bid for 3-7 days	
Anticholinergics:	Mucolytic/bronchodilator	• Should not be used as first-line therapy; added to β_2-agonist therapy
Ipratropium:		
Atrovent (nebulizer solution 0.5 mg/2.5 mL; MDI 18 µg/inhalation)	Nebulizer: 0.5 mg q6-8h (tid-qid) as needed MDI: 2 puffs qid	
Ipratropium with albuterol:		
DuoNeb nebulizer solution (0.5 mg ipratropium + 2.5 mg albuterol/3 mL vial)	1 vial by nebulizer qid	• Nebulizer: may mix ipratropium with albuterol
Injectable sympathomimetic epinephrine:	Bronchodilator	• For extreme circumstances (e.g., impending respiratory failure despite high-dose inhaled SABA, respiratory failure)
Adrenalin 1 mg/mL (1 : 1000) EpiPen autoinjection device (0.3 mg; EpiPen Jr 0.15 mg)	SC or IM: 0.01 mg/kg (max dose 0.5 mg); may repeat after 15-30 min	
Terbutaline:		• Terbutaline is β-agonist–selective relative to epinephrine • Monitoring with continuous infusion: cardiorespiratory monitor, pulse oximetry, blood pressure, serum potassium • Adverse effects: tremor, tachycardia, palpitations, arrhythmia, hypertension, headaches, nervousness, nausea, vomiting, hypoxemia
Brethine 1 mg/mL	Continuous IV infusion (terbutaline only): 2-10 µg/kg loading dose, followed by 0.1-0.4 µg/kg/min Titrate in 0.1-0.2 µg/kg/min increments every 30 min, depending on clinical response	
RISK ASSESSMENT FOR DISCHARGE		
Medical stability	Discharge to home if there has been sustained improvement in symptoms and bronchodilator treatments are at least 3 hr apart, physical findings are normal, PEF >70% of predicted or personal best, and oxygen saturation >92% when breathing room air	
Home supervision	Capability to administer intervention and to observe and respond appropriately to clinical deterioration	
Asthma education	See Table 144-9	

IM, intramuscular; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting β-agonist; SC, subcutaneous; $\dot{V}/\dot{Q}$, ventilation–perfusion.

Short-Acting Inhaled β-Agonists

Given their rapid onset of action, effectiveness, and 4-6 hr duration of action, SABAs (albuterol, levalbuterol, terbutaline, pirbuterol) are the drugs of choice for acute asthma symptoms ("rescue" medication) and for preventing exercise-induced bronchospasm. β-Agonists cause bronchodilation by inducing airway smooth muscle relaxation, reducing vascular permeability and airways edema, and improving mucociliary clearance. Levalbuterol, or the r-isomer of albuterol, is associated with less tachycardia and tremor, which can be bothersome to some asthmatic patients. Overuse of β-agonists is associated with an increased risk of death or near-death episodes from asthma. This is a major concern for some patients with asthma who rely on the frequent use of SABAs as a "quick fix" for their asthma, rather than using controller medications in a preventive manner. It is helpful to monitor the frequency of SABA use, in that use of at least 1 MDI/mo or at least 3 MDIs/year (200 inhalations/MDI) indicates inadequate asthma control and necessitates improving other aspects of asthma therapy and management.

Anticholinergic Agents

As bronchodilators, the anticholinergic agents (ipratropium bromide) are less potent than the β-agonists. Inhaled ipratropium is used primarily in the treatment of acute severe asthma. When used in combination with albuterol, ipratropium can improve lung function and reduce the rate of hospitalization in children who present to the emergency department with acute asthma. Ipratropium is the anticholinergic formulation of choice for children because it has few central nervous system adverse effects and it is available in both MDI and nebulizer formulations. Although widely used in children with asthma exacerbations of all ages, it is approved by the FDA for use in children >12 yr of age. A long-acting inhaled anticholinergic agent, tiotropium, is gaining interest as a potential add-on controller therapy (i.e., in addition to ICS with or without LABA) for adults with asthma.

Delivery Devices and Inhalation Technique

Inhaled medications are delivered in aerosolized form in a MDI, as a DPI formulation, or in a suspension or solution form delivered via a

nebulizer. In the past, MDIs, which require coordination and use of a spacer device, have dominated the market. MDIs are now using hydrofluoroalkane propellant for its ozone-friendly properties, rather than chlorofluorocarbon. Spacer devices, recommended for the administration of all MDI medications, are simple and inexpensive tools that: (1) decrease the coordination required to use MDIs, especially in young children; (2) improve the delivery of inhaled drug to the lower airways; and (3) minimize the risk of propellant-mediated adverse effects (thrush). Optimal inhalation technique for each puff of MDI-delivered medication is a slow (5 sec) inhalation, then a 5-10 sec breathhold. No waiting time between puffs of medication is needed. Young, preschool-age children cannot perform this inhalation technique. MDI medications can also be delivered with a spacer and mask, using a different technique: Each puff is administered with regular breathing for about 30 sec or 5-10 breaths, a tight seal must be maintained, and talking, coughing, or crying will blow the medication out of the spacer. This technique will not deliver as much medication per puff as the optimal MDI technique used by older children and adults.

DPI devices (e.g., Diskus, Flexhaler Autohaler, Twisthaler, Aerolizer) are popular because of their simplicity of use, albeit adequate inspiratory flow is needed. They are breath-actuated (the drug comes out only as it is breathed in) and spacers are not needed. Mouth rinsing is recommended after ICS use to rinse out ICS deposited on the oral mucosa and reduce the swallowed ICS and the risk of thrush.

Nebulizers have been the mainstay of aerosol treatment for infants and young children. An advantage of using nebulizers is the simple technique required of relaxed breathing. The preferential nasal breathing, small airways, low tidal volume, and high respiratory rate of infants markedly increase the difficulty of inhaled drug therapy targeting the lung airways. Disadvantages of nebulizers include need for a power source, inconvenience in that treatments take about 5 min, expense, and potential for bacterial contamination.

Asthma Exacerbations and Their Management

Asthma exacerbations are acute or subacute episodes of progressively worsening symptoms and airflow obstruction. Airflow obstruction during exacerbations can become extensive, resulting in life-threatening respiratory insufficiency. Often, asthma exacerbations worsen during sleep (between midnight and 8 A.M.), when airways inflammation and hyperresponsiveness are at their peak. Importantly, SABAs, which are first-line therapy for asthma symptoms and exacerbations, increase pulmonary blood flow through obstructed, unoxygenated areas of the lungs with increasing dosage and frequency. When airways obstruction is not resolved with SABA use, ventilation–perfusion mismatching can cause significant hypoxemia, which can perpetuate bronchoconstriction and further worsen the condition. Severe, progressive asthma exacerbations need to be managed in a medical setting, with administration of supplemental oxygen as first-line therapy and close monitoring for potential worsening. Complications that can occur during severe exacerbations include atelectasis and air leaks in the chest (pneumomediastinum, pneumothorax).

A severe exacerbation of asthma that does not improve with standard therapy is termed **status asthmaticus.** Immediate management of an asthma exacerbation involves a rapid evaluation of the severity of obstruction and assessment of risk for further clinical deterioration (see Tables 144-15 and 144-16). For most patients, exacerbations improve with frequent bronchodilator treatments and a course of systemic (oral or intravenous) corticosteroid. However, the optimal management of a child with an asthma exacerbation should include a more comprehensive assessment of the events leading up to the exacerbation and the underlying disease severity. Indeed, the frequency and severity of asthma exacerbations help define the severity of a patient's asthma. Whereas most children who experience life-threatening asthma episodes have moderate to severe asthma by other criteria, some children with asthma appear to have mild disease except when they suffer severe, even near-fatal exacerbations. The biologic, environmental, economic, and psychosocial risk factors associated with asthma morbidity and death can further guide this assessment (Table 144-17).

Table 144-17	Risk Factors for Asthma Morbidity and Mortality
BIOLOGIC	
Previous severe asthma exacerbation (intensive care unit admission, intubation for asthma)	
Sudden asphyxia episodes (respiratory failure, arrest)	
Two or more hospitalizations for asthma in past year	
Three or more emergency department visits for asthma in past year	
Increasing and large diurnal variation in peak flows	
Use of >2 canisters of short-acting β-agonists per month	
Poor response to systemic corticosteroid therapy	
Male gender	
Low birthweight	
Nonwhite (especially black) ethnicity	
Sensitivity to *Alternaria*	
ENVIRONMENTAL	
Allergen exposure	
Environmental tobacco smoke exposure	
Air pollution exposure	
Urban environment	
ECONOMIC AND PSYCHOSOCIAL	
Poverty	
Crowding	
Mother <20 yr old	
Mother with less than high school education	
Inadequate medical care:	
Inaccessible	
Unaffordable	
No regular medical care (only emergency)	
Lack of written asthma action plan	
No care sought for chronic asthma symptoms	
Delay in care of asthma exacerbations	
Inadequate hospital care for asthma exacerbation	
Psychopathology in the parent or child	
Poor perception of asthma symptoms or severity	
Alcohol or substance abuse	

Asthma exacerbations characteristically vary among individuals but tend to be similar in the same patient. Severe asthma exacerbations, resulting in respiratory distress, hypoxia, hospitalization, and/or respiratory failure, are the best predictors of future life-threatening exacerbations or a fatal asthma episode. In addition to distinguishing such high-risk children, some experience exacerbations that come on over days, with airflow obstruction resulting from progressive inflammation, epithelial sloughing, and cast impaction of small airways. When such a process is extreme, respiratory failure as a result of fatigue can ensue, necessitating mechanical ventilation for numerous days. In contrast, some children experience abrupt-onset exacerbations that may result from extreme AHR and physiologic susceptibility to airways closure. Such exacerbations, when extreme, are asphyxial in nature, often occur outside medical settings, are initially associated with very high arterial partial pressure of carbon dioxide (P_{CO_2}) levels, and tend to require only brief periods of supportive ventilation. Recognizing the characteristic differences in asthma exacerbations is important for optimizing their early management.

Home Management of Asthma Exacerbations

Families of all children with asthma should have a **written action plan** to guide their recognition and management of exacerbations, along with the necessary medications and tools to manage them. Early recognition of asthma exacerbations in order to intensify treatment early can often prevent further worsening and keep exacerbations from becoming severe. A written home action plan can reduce the risk of asthma death by 70%. The NIH guidelines recommend immediate treatment with "rescue" medication (inhaled SABA, up to 3 treatments in 1 hr). A good response is characterized by resolution of symptoms within 1 hr, no further symptoms over the next 4 hr, and improvement in PEF value to at least 80% of personal best. The child's physician

should be contacted for follow-up, especially if bronchodilators are required repeatedly over the next 24-48 hr. If the child has an incomplete response to initial treatment with rescue medication (persistent symptoms and/or a PEF value <80% of personal best), a short course of oral corticosteroid therapy (prednisone 1-2 mg/kg/day [not to exceed 60 mg/day] for 4 days), in addition to inhaled β-agonist therapy, should be instituted. The physician should also be contacted for further instructions. Immediate medical attention should be sought for severe exacerbations, persistent signs of respiratory distress, lack of expected response or sustained improvement after initial treatment, further deterioration, or high-risk factors for asthma morbidity or mortality (previous history of severe exacerbations). For patients with severe asthma and/or a history of life-threatening episodes, especially if abrupt-onset in nature, providing an epinephrine autoinjector and, possibly, portable oxygen at home should be considered. Use of either of these extreme measures for home management of asthma exacerbations would be an indication to call 911 for emergency support services.

Emergency Department Management of Asthma Exacerbations

In the emergency department, the primary goals of asthma management include correction of hypoxemia, rapid improvement of airflow obstruction, and prevention of progression or recurrence of symptoms. Interventions are based on clinical severity on arrival, response to initial therapy, and presence of risk factors that are associated with asthma morbidity and mortality (see Table 144-17). Indications of a severe exacerbation include breathlessness, dyspnea, retractions, accessory muscle use, tachypnea or labored breathing, cyanosis, mental status changes, a silent chest with poor air exchange, and severe airflow limitation (PEF or FEV_1 value <50% of personal best or predicted values). Initial treatment includes supplemental oxygen, inhaled β-agonist therapy every 20 min for 1 hr, and, if necessary, systemic corticosteroids given either orally or intravenously (see Table 144-16). Inhaled ipratropium may be added to the β-agonist treatment if no significant response is seen with the first inhaled β-agonist treatment. An intramuscular injection of epinephrine or other β-agonist may be administered in severe cases. Oxygen should be administered and continued for at least 20 min after SABA administration to compensate for possible ventilation-perfusion abnormalities caused by SABAs.

Close monitoring of clinical status, hydration, and oxygenation are essential elements of immediate management. A poor response to intensified treatment in the 1st hr suggests that the exacerbation will not remit quickly. The patient may be discharged to home if there is sustained improvement in symptoms, normal physical findings, PEF >70% of predicted or personal best, an oxygen saturation >92% while the patient is breathing room air for 4 hr. Discharge medications include administration of an inhaled β-agonist up to every 3-4 hr plus a 3-7 day course of an oral corticosteroid. Optimizing controller therapy before discharge is also recommended. The addition of ICS to a course of oral corticosteroid in the emergency department setting reduces the risk of exacerbation recurrence over the subsequent month.

Hospital Management of Asthma Exacerbations

For patients with moderate to severe exacerbations that do not adequately improve within 1-2 hr of intensive treatment, observation and/or admission to the hospital, at least overnight, is likely to be needed. Other indications for hospital admission include high-risk features for asthma morbidity or death (see Table 144-17). Admission to an intensive care unit is indicated for patients with severe respiratory distress, poor response to therapy, and concern for potential respiratory failure and arrest.

Supplemental oxygen, frequent or continuous administration of an inhaled bronchodilator, and systemic corticosteroid therapy are the conventional interventions for children admitted to the hospital for status asthmaticus (see Table 144-16). Supplemental oxygen is administered because many children hospitalized with acute asthma have or eventually have hypoxemia, especially at night and with increasing SABA administration. SABAs can be delivered frequently (every 20 min to 1 hr) or continuously (at 5-15 mg/hr). When administered continuously, significant systemic absorption of β-agonist occurs and, as a result, continuous nebulization can obviate the need for intravenous β-agonist therapy. Adverse effects of frequently administered β-agonist therapy include tremor, irritability, tachycardia, and hypokalemia. Patients requiring frequent or continuous nebulized β-agonist therapy should have ongoing cardiac monitoring. Because frequent β-agonist therapy can cause ventilation–perfusion mismatch and hypoxemia, oximetry is also indicated. Inhaled ipratropium bromide is often added to albuterol every 6 hr if patients do not show a remarkable improvement, although there is little evidence to support its use in hospitalized children receiving aggressive inhaled β-agonist therapy and systemic corticosteroids. In addition to its potential to provide a synergistic effect with a β-agonist agent in relieving severe bronchospasm, ipratropium bromide may be beneficial in patients who have mucous hypersecretion or are receiving β-blockers.

Short-course systemic corticosteroid therapy is recommended for use in moderate to severe asthma exacerbations to hasten recovery and prevent recurrence of symptoms. Corticosteroids are effective as single doses administered in the emergency department, short courses in the clinic setting, and both oral and intravenous formulations in hospitalized children. Studies in children hospitalized with acute asthma have found corticosteroids administered orally to be as effective as intravenous corticosteroids. Accordingly, oral corticosteroid therapy can often be used, although children with sustained respiratory distress who are unable to tolerate oral preparations or liquids are obvious candidates for intravenous corticosteroid therapy.

Patients with persistent severe dyspnea and high-flow oxygen requirements require additional evaluations, such as complete blood cell counts, measurements of arterial blood gases and serum electrolytes, and chest radiograph, to monitor for respiratory insufficiency, comorbidities, infection, and/or dehydration. Hydration status monitoring is especially important in infants and young children, whose increased respiratory rate (insensible losses) and decreased oral intake put them at higher risk for dehydration. Further complicating this situation is the association of increased antidiuretic hormone secretion with status asthmaticus. Administration of fluids at or slightly below maintenance fluid requirements is recommended. Chest physical therapy, incentive spirometry, and mucolytics are **not** recommended during the early acute period of asthma exacerbations as they can trigger severe bronchoconstriction.

Despite intensive therapy, some asthmatic children remain critically ill and at risk for respiratory failure, intubation, and mechanical ventilation. Complications (air leaks) related to asthma exacerbations increase with intubation and assisted ventilation; every effort should be made to relieve bronchospasm and prevent respiratory failure. Several therapies, including parenterally administered epinephrine, β-agonists, methylxanthines, magnesium sulfate (25-75 mg/kg, maximum dose 2.5 g, given intravenously over 20 min), and inhaled heliox (helium and oxygen mixture) have demonstrated some benefit as adjunctive therapies in patients with severe status asthmaticus. Administration of either methylxanthine or magnesium sulfate requires monitoring of serum levels and cardiovascular status. Parenteral (subcutaneous, intramuscular, or intravenous) epinephrine or terbutaline sulfate may be effective in patients with life-threatening obstruction that is not responding to high doses of inhaled β-agonists, because in such patients, inhaled medication may not reach the lower airway.

Rarely, a severe asthma exacerbation in a child results in respiratory failure, and intubation and mechanical ventilation become necessary. Mechanical ventilation in severe asthma exacerbations requires the careful balance of enough pressure to overcome airways obstruction while reducing hyperinflation, air trapping, and the likelihood of barotrauma (pneumothorax, pneumomediastinum) (see Chapter 411). To minimize the likelihood of such complications, mechanical ventilation should be anticipated, and asthmatic children at risk for the development of respiratory failure should be managed in a pediatric ICU. Elective tracheal intubation with rapid-induction sedatives and paralytic agents is safer than emergency intubation. Mechanical ventilation aims to achieve adequate oxygenation while tolerating mild to

moderate hypercapnia (P_{CO_2} 50-70 mm Hg) to minimize barotrauma. Volume-cycled ventilators, using short inspiratory and long expiratory times, 10-15 mL/kg tidal volume, 8-15 breaths/min, peak pressures <60 cm H_2O, and without positive end-expiratory pressure are starting mechanical ventilation parameters that can achieve these goals. As measures to relieve mucous plugs, chest percussion and airways lavage are not recommended because they can induce further bronchospasm. One must consider the nature of asthma exacerbations leading to respiratory failure; those of rapid or abrupt onset tend to resolve quickly (hours to 2 days), whereas those that progress gradually to respiratory failure can require days to weeks of mechanical ventilation. Such prolonged cases are further complicated by muscle atrophy and, when combined with corticosteroid-induced myopathy, can lead to severe muscle weakness requiring prolonged rehabilitation. This myopathy should not be confused with the rare occurrence of an asthma-associated flaccid paralysis (Hopkins syndrome), which is of unknown etiology but prolongs the intensive care stay.

In children, management of severe exacerbations in medical centers is usually successful, even when extreme measures are required. Consequently, asthma deaths in children rarely occur in medical centers; most occur at home or in community settings before lifesaving medical care can be administered. This point highlights the importance of home and community management of asthma exacerbations, early intervention measures to keep exacerbations from becoming severe, and steps to reduce asthma severity. A follow-up appointment within 1-2 wk of a child's discharge from the hospital after resolution of an asthma exacerbation should be used to monitor clinical improvement and to reinforce key educational elements, including action plans and controller medications.

Special Management Circumstances

Management of Infants and Young Children. Recurrent wheezing episodes in preschool-age children are very common, occurring in as much as one-third of this population. Of them, most improve and even become asymptomatic during the prepubescent school-age years, whereas others have lifelong persistent asthma. All require management of their recurrent wheezing problems (see Tables 144-5, 144-7, and 144-12). The updated NIH guidelines recommend risk assessment to identify preschool-age children who are likely to have persistent asthma. One implication of this recommendation is that these at-risk children may be candidates for conventional asthma management, including daily controller therapy and early intervention with exacerbations (see Tables 144-8, 144-9, and 144-12). Nebulized budesonide and montelukast appear to be more effective than cromolyn. For young children with a history of moderate to severe exacerbations, nebulized budesonide is FDA approved, and its use as a controller medication could prevent subsequent exacerbations.

Using aerosol therapy in infants and young children with asthma presents unique challenges. There are 2 delivery systems for inhaled medications for this age group, the nebulizer and the MDI with spacer/holding chamber and face mask. Multiple studies demonstrate the effectiveness of both nebulized albuterol in acute episodes and nebulized budesonide in the treatment of recurrent wheezing in infants and young children. In such young children, inhaled medications administered via MDI with spacer and face mask may be acceptable, although perhaps not preferred owing to limited published information and lack of FDA approval for children <4 yr of age.

Asthma Management in Pregnancy. The goals of asthma management during pregnancy should include prevention of exacerbations and control of chronic symptoms through the use of medications that pose minimal risk to the mother and fetus because most drugs cross the placenta. It is considered safer for pregnant asthmatic women to be treated with controller medications than it is to have uncontrolled symptoms and severe exacerbations. Albuterol is the preferred SABA for use during pregnancy. There is reassuring efficacy and safety data from prospective cohort studies supporting ICS use in pregnant women with asthma. Budesonide is currently the preferred ICS for pregnant women, attaining an FDA Pregnancy Category B rating because of substantial reassuring safety data. Nonmedication approaches to improve asthma control are encouraged. A multidisciplinary approach with monthly evaluations (including pulmonary function tests when not contraindicated) and ongoing consultation with the obstetrician and asthma specialist is recommended. Frequent fetal and maternal surveillance is especially important for adolescents with suboptimal asthma control, those with moderate to severe asthma, and those with a recent exacerbation.

Asthma Management During Surgery. Patients with asthma are at risk from disease-related complications from surgery, such as bronchoconstriction and asthma exacerbation, atelectasis, impaired coughing, respiratory infection, and latex exposure, that may induce asthma complications in patients with latex allergy. All patients with asthma should be evaluated before surgery, and those who are inadequately controlled should allow time for intensified treatment in order to improve asthma stability before surgery if possible. A systemic corticosteroid course may be indicated for the patient who is having symptoms and/or FEV_1 or PEF values <80% of the patient's personal best. In addition, patients who have received >2 wk of systemic corticosteroid and/or moderate- to high-dose ICS therapy may be at risk for intraoperative adrenal insufficiency. For these patients, anesthesia services should be alerted to provide "stress" replacement doses of systemic corticosteroid for the surgical procedure and possibly the postoperative period if needed.

PROGNOSIS

Recurrent coughing and wheezing occurs in 35% of preschool-age children. Of these, approximately one-third continue to have persistent asthma into later childhood, and approximately two-thirds improve on their own through their teen years. Asthma severity by the ages of 7-10 yr is predictive of asthma persistence in adulthood. Children with moderate to severe asthma and with lower lung function measures are likely to have persistent asthma as adults. Children with milder asthma and normal lung function are likely to improve over time, with some becoming periodically asthmatic (disease-free for months to years); however, complete remission for 5 yr in childhood is uncommon.

PREVENTION

Although chronic airways inflammation may result in pathologic remodeling of lung airways, conventional anti-inflammatory interventions—the cornerstone of asthma control—do not help children outgrow their asthma. Although controller medications reduce asthma morbidities, most children with moderate to severe asthma continue to have symptoms into young adulthood. Investigations into the environmental and lifestyle factors responsible for the lower prevalence of childhood asthma in rural areas and farming communities suggest that early immunomodulatory intervention might prevent asthma development. A *hygiene hypothesis* purports that naturally occurring microbial exposures in early life might drive early immune development away from allergic sensitization, persistent airways inflammation, and remodeling. If these natural microbial exposures truly have an asthma-protective effect, without significant adverse health consequences, then these findings may foster new strategies for asthma prevention.

Several nonpharmacotherapeutic measures with numerous positive health attributes—avoidance of environmental tobacco smoke (beginning prenatally), prolonged breastfeeding (>4 mo), an active lifestyle, and a healthy diet—might reduce the likelihood of asthma development. Immunizations are currently not considered to increase the likelihood of development of asthma; therefore, all standard childhood immunizations are recommended for children with asthma, including varicella and annual influenza vaccines.

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Chapter 145

Atopic Dermatitis (Atopic Eczema)

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Atopic dermatitis (AD), or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects 10-30% of children worldwide and frequently occurs in families with other atopic diseases, such as asthma, allergic rhinitis, and food allergy. Infants with AD are predisposed to development of allergic rhinitis and/or asthma later in childhood, a process called “the atopic march.”

ETIOLOGY

AD is a complex genetic disorder that results in a defective skin barrier, reduced skin innate immune responses, and exaggerated T-cell responses to environmental allergens and microbes that lead to chronic skin inflammation.

PATHOLOGY

Acute AD skin lesions are characterized by **spongiosis,** or marked intercellular edema, of the epidermis. In AD, dendritic antigen-presenting cells in the epidermis, such as Langerhans cells, exhibit surface-bound immunoglobulin (Ig) E molecules. These antigen-presenting cells play an important role in cutaneous allergen presentation to T-helper type 2 (Th2) cells (see Chapter 140). There is a marked perivenular T-cell infiltrate with occasional monocyte-macrophages in acute AD lesions. Mast cells are found in normal numbers but in different stages of degranulation. Chronic, lichenified AD is characterized by a hyperplastic epidermis with hyperkeratosis, and minimal spongiosis. There are predominantly IgE-bearing Langerhans cells in the epidermis, and macrophages in the dermal mononuclear cell infiltrate. Mast cell and eosinophil numbers are increased, contributing to skin inflammation.

PATHOGENESIS

Two forms of AD have been identified. **Atopic eczema** is associated with IgE-mediated sensitization (at onset or during the course of eczema) and occurs in 70-80% of patients with AD. **Nonatopic eczema** is not associated with IgE-mediated sensitization and is seen in 20-30% of patients with AD. Both forms of AD are associated with eosinophilia. In atopic eczema, circulating T cells expressing the skin homing receptor **cutaneous lymphocyte-associated antigen** produce increased levels of Th2 cytokines, including interleukin (IL)-4 and IL-13, which induce isotype switching to IgE synthesis. Another cytokine, IL-5, plays an important role in eosinophil development and survival. Nonatopic eczema is associated with lower IL-4 and IL-13 production than is atopic eczema.

Compared with the skin of healthy subjects, both unaffected skin and acute skin lesions of patients with AD have an increased number of cells expressing IL-4 and IL-13. Chronic AD skin lesions, by contrast, have significantly fewer cells that express IL-4 and IL-13, but increased numbers of cells that express IL-5, granulocyte-macrophage colony-stimulating factor, IL-12, and interferon (IFN)-γ than acute AD lesions. Chronic AD is characterized by a shift from a Th2-dominant to a Th1-dominant profile. The infiltration of IL-22–expressing T cells correlates with severity of AD, blocks keratinocyte differentiation, and induces epidermal hyperplasia.

The development of AD skin lesions is orchestrated by local tissue expression of proinflammatory cytokines and chemokines, which play a central role in defining the nature of the inflammatory infiltrate in AD. The chemotactic protein, CCL27, is highly upregulated in AD and preferentially attracts cutaneous lymphocyte-associated antigen-positive T cells to the skin. Other C-C chemokines, RANTES (regulated on activation, normal T-cell expressed and secreted), monocyte chemotactic protein-4, and eotaxin are increased in AD skin lesions, resulting in chemotaxis of eosinophils, macrophages, and Th2 lymphocytes expressing their receptor (CCR3).

In healthy people, the skin acts as a protective barrier against external irritants, moisture loss, and infection. Proper function of the skin depends on adequate moisture and lipid content, functional immune responses, and structural integrity. **Severely dry skin is a hallmark of AD.** This results from compromise of the epidermal barrier, which leads to excess transepidermal water loss, allergen penetration, and microbial colonization. **Filaggrin**, a structural protein in the epidermis, and its breakdown products are critical to skin barrier function. Genetic mutations in the filaggrin gene family have been identified in up to 50% of patients with severe AD. Cytokines found in allergic inflammation, such as IL-4, IL-13, IL-22, IL-25, and tumor necrosis factor, can also reduce filaggrin expression. AD patients thereby have increased risk of bacterial, viral, and fungal infection related to impairment of innate immunity, including a loss of barrier function and impaired generation of antimicrobial peptides.

CLINICAL MANIFESTATIONS

AD typically begins in infancy. Approximately 50% of patients experience symptoms in the 1st yr of life, and an additional 30% are diagnosed between 1 and 5 yr of age. Intense **pruritus**, especially at night, and **cutaneous reactivity** are the cardinal features of AD. Scratching and excoriation cause increased skin inflammation that contributes to the development of more pronounced eczematous skin lesions. Foods (cow milk, egg, peanut, tree nuts, soy, wheat, fish, shellfish), aeroallergens (pollen, grass, animal dander, dust mites), infection (staphylococcus, herpes simplex, molluscum), reduced humidity, excessive sweating, and irritants (wool, acrylic, soaps, toiletries, fragrances, detergents) can exacerbate (trigger) pruritus and scratching.

Acute AD skin lesions are intensely pruritic with erythematous papules (Figs. 145-1 and 145-2). Subacute dermatitis manifests as erythematous, excoriated, scaling papules. In contrast, chronic AD is characterized by **lichenification** (Fig. 145-3), or thickening of the skin with accentuated surface markings, and **fibrotic papules.** In chronic AD, all

Figure 145-1 Atopic dermatitis, typical cheek involvement. *(From Eichenfield LF, Friedan IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 242.)*

Figure 145-2 Crusted lesions of atopic dermatitis on the face. *(From Eichenfield LF, Friedan IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 242.)*

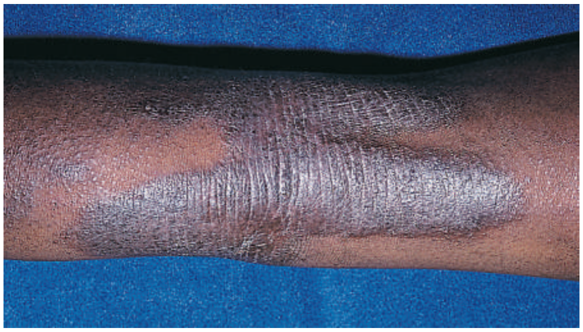

Figure 145-3 Lichenification of the popliteal fossa from chronic rubbing of the skin in atopic dermatitis. *(From Weston WL, Lane AT, Morelli JG:* Color textbook of pediatric dermatology, *ed 2, St. Louis, 1996, Mosby, p. 33.)*

3 types of skin reactions may coexist in the same individual. Most patients with AD have dry, lackluster skin irrespective of their stage of illness. Skin reaction pattern and distribution vary with the patient's age and disease activity. AD is generally more acute in infancy and involves the face, scalp, and extensor surfaces of the extremities. The diaper area is usually spared. Older children and children with chronic AD have lichenification and localization of the rash to the flexural folds of the extremities. AD often goes into remission as the patient grows older, leaving an adolescent or adult with skin prone to itching and inflammation when exposed to exogenous irritants.

LABORATORY FINDINGS

There are no specific laboratory tests to diagnose AD. Many patients have peripheral blood eosinophilia and increased serum IgE levels. Serum IgE measurement or prick skin testing can identify the allergens to which patients are sensitized. The diagnosis of clinical allergy to these allergens requires confirmation by history and environmental challenges.

Table 145-1	Clinical Features of Atopic Dermatitis
MAJOR FEATURES	
Pruritus	
Facial and extensor eczema in infants and children	
Flexural eczema in adolescents	
Chronic or relapsing dermatitis	
Personal or family history of atopic disease	
ASSOCIATED FEATURES	
Xerosis	
Cutaneous infections (*Staphylococcus aureus,* group A streptococcus, herpes simplex, coxsackievirus, vaccinia, molluscum, warts)	
Nonspecific dermatitis of the hands or feet	
Ichthyosis, palmar hyperlinearity, keratosis pilaris	
Nipple eczema	
White dermatographism and delayed blanch response	
Anterior subcapsular cataracts, keratoconus	
Elevated serum immunoglobulin E levels	
Positive results of immediate-type allergy skin tests	
Early age at onset	
Dennie lines (Dennie-Morgan infraorbital folds)	
Facial erythema or pallor	
Course influenced by environmental and/or emotional factors	

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

AD is diagnosed on the basis of 3 major features: pruritus, an eczematous dermatitis that fits into a typical presentation, and a chronic or chronically relapsing course (Table 145-1). Associated features, such as a family history of asthma, hay fever, elevated IgE, and immediate skin test reactivity, are variably present.

Many inflammatory skin diseases, immunodeficiencies, skin malignancies, genetic disorders, infectious diseases, and infestations share symptoms with AD and should be considered and excluded before a diagnosis of AD is established (Table 145-2). Severe combined immunodeficiency syndrome (see Chapter 126.1) should be considered for infants presenting in the 1st yr of life with diarrhea, failure to thrive, generalized scaling rash, and recurrent cutaneous and/or systemic infection. Histiocytosis (see Chapter 507) should be excluded in any infant with AD and failure to thrive. Wiskott-Aldrich syndrome (see Chapter 126.2), an X-linked recessive disorder associated with thrombocytopenia, immune defects, and recurrent severe bacterial infections, is characterized by a rash almost indistinguishable from that in AD. One of the hyper-IgE syndromes (see Chapter 126.2) is characterized by markedly elevated serum IgE values, recurrent deep-seated bacterial infections, chronic dermatitis, and refractory dermatophytosis. Many of these patients have disease as a result of autosomal dominant STAT3 mutations. In contrast, some patients with hyper-IgE syndrome present with increased susceptibility to viral infections and an autosomal recessive pattern of disease inheritance. These patients may have a Dock 8 (Dedicator of cytokinesis 8) mutation. This diagnosis should be considered in young children with severe eczema, food allergy, and disseminated skin viral infections.

Adolescents who present with an eczematous dermatitis but no history of childhood eczema, respiratory allergy, or atopic family history may have allergic **contact dermatitis** (see Chapter 655.1). A contact allergen may be the problem in any patient whose AD does not respond to appropriate therapy. Sensitizing chemicals, such as parabens and lanolin, can be irritants for patients with AD and are commonly found as vehicles in therapeutic topical agents. Topical glucocorticoid contact allergy has been reported in patients with chronic dermatitis on topical corticosteroid therapy. Eczematous dermatitis has also been reported with HIV infection as well as with a variety of infestations such as scabies. Other conditions that can be confused with AD include psoriasis, ichthyoses, and seborrheic dermatitis.

Table 145-2	Differential Diagnosis of Atopic Dermatitis
CONGENITAL DISORDERS Netherton syndrome Familial keratosis pilaris	
CHRONIC DERMATOSES Seborrheic dermatitis Contact dermatitis (allergic or irritant) Nummular eczema Psoriasis Ichthyoses	
INFECTIONS AND INFESTATIONS Scabies HIV-associated dermatitis Dermatophytosis Insect bites Onchocerciasis	
MALIGNANCIES Cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome) Letterer-Siwe disease (Langerhans cell histiocytosis)	
AUTOIMMUNE DISORDERS Dermatitis herpetiformis Pemphigus foliaceus Graft-versus-host disease Dermatomyositis	
IMMUNODEFICIENCIES Wiskott-Aldrich syndrome Severe combined immunodeficiency syndrome Hyperimmunoglobulin E syndromes (autosomal dominant and recessive types) Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome	
METABOLIC DISORDERS Zinc deficiency Pyridoxine (vitamin B_6) and niacin Multiple carboxylase deficiency Phenylketonuria	

Modified from Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *St. Louis, 2003, Mosby, p. 562.*

TREATMENT

The treatment of AD requires a systematic, multifaceted approach that incorporates skin hydration, topical anti-inflammatory therapy, identification and elimination of flare factors (Table 145-3), and, if necessary, systemic therapy. Assessment of the severity also helps direct therapy (Table 145-4).

Cutaneous Hydration

Because patients with AD have impaired skin barrier function from reduced lipid levels, they present with diffuse, abnormally dry skin, or **xerosis.** *Moisturizers are first-line therapy.* Lukewarm soaking baths for 15-20 min followed by the application of an occlusive emollient to retain moisture provide symptomatic relief. Hydrophilic ointments of varying degrees of viscosity can be used according to the patient's preference. Occlusive ointments are sometimes not well tolerated because of interference with the function of the eccrine sweat ducts and may induce the development of folliculitis. In these cases, less occlusive agents should be used. Several prescription (classified as a medical device) "therapeutic moisturizers/barrier creams" are available, containing components such as ceramides and filaggrin acid metabolites intended to improve skin barrier function. There are little data demonstrating their efficacy over standard emollients.

Hydration by baths or wet dressings promotes transepidermal penetration of topical glucocorticoids. Dressings may also serve as effective barriers against persistent scratching, in turn promoting healing of excoriated lesions. Wet dressings are recommended for use on severely affected or chronically involved areas of dermatitis refractory to skin care. It is critical that wet dressing therapy be followed by topical emollient application to avoid potential drying and fissuring from the therapy. Wet dressing therapy can be complicated by maceration and secondary infection and should be closely monitored by a physician.

Topical Corticosteroids

Topical corticosteroids are the cornerstone of antiinflammatory treatment for acute exacerbations of AD. Patients should be carefully instructed on their use of topical glucocorticoids in order to avoid potential adverse effects. There are 7 classes of topical glucocorticoids, ranked according to their potency as determined by vasoconstrictor assays (Table 145-5). Because of their potential adverse effects, the

Table 145-3	List of Aggravating Factors and Counselling for AD Patients
Clothing: avoid skin contact with irritating fibers (wool, large-fiber textiles); do not use tight and too warm clothing to avoid excessive sweating. New nonirritating clothing designed for AD children is being evaluated	
Tobacco: avoid exposure	
Cool temperature in bedroom and avoid too many bed covers	
Increase emollient use with cold weather	
Avoid exposure to herpes sores; urgent visit if flare of unusual aspect	
Vaccines: normal schedule in noninvolved skin, including egg-allergic patients (see text)	
Sun exposure: no specific restriction. Usually helpful because of improvement of epidermal barrier. Encourage summer holidays in altitude or at beach resorts	
Physical exercise, sports: no restriction. If sweating induces flares of AD, progressive adaptation to exercise. Shower and emollients after swimming pool	
Food allergens	
Maintain breast feeding until 4 mo if possible	
Otherwise normal diet, unless an allergy work-up has proven the need to exclude a specific food	
Indoor aeroallergens	
House dust mites	
Use adequate ventilation of housing; keep the rooms well aerated even in winter	
Avoid wall-to-wall carpeting	
Remove dust with a wet sponge	
Vacuum floors and upholstery with an adequately filtered cleaner once a week	
Avoid soft toys in bed (cradle), except washable ones	
Wash bed sheets at a temperature higher than 55° every 10 days	
Use bed and pillow encasings made of Gore-Tex or similar material	
Furred pets: advise to avoid. If allergy is demonstrated, be firm on avoidance measures, such as pet removal	
Pollen: close windows during peak pollen season on warm and dry weather and restrict, if possible, stays outdoors. Windows may be open at night and early in the morning or during rainy weather. Avoid exposure to risk situations (lawn mowing). Use pollen filters in car. Clothes and pets can vectorize aeroallergens, including pollen	

From Darsow U, Wollenberg A, Simon D, et al: ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol *24:317–328, 2010 (Table 2, p. 321).*

Table 145-4	Categorization of Physical Severity of Atopic Eczema

Clear—Normal skin, with no evidence of atopic eczema
Mild—Areas of dry skin, infrequent itching (with or without small areas of redness)
Moderate—Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening)
Severe—Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation)

From Lewis-Jones S, Mugglestone MA; Guideline Development Group: Management of atopic eczema in children aged up to 12 years: summary of NICE guidance, BMJ *335:1263–1264, 2007.*

Table 145-5	Selected Topical Corticosteroid Preparations*
GROUP 1	
Clobetasol propionate (Temovate) 0.05% ointment/cream	
Betamethasone dipropionate (Diprolene) 0.05% ointment/lotion/gel	
Fluocinonide (Vanos) 0.1% cream	
GROUP 2	
Mometasone furoate (Elocon) 0.1% ointment	
Halcinonide (Halog) 0.1% cream	
Fluocinonide (Lidex) 0.05% ointment/cream	
Desoximetasone (Topicort) 0.25% ointment/cream	
Betamethasone dipropionate (Diprolene) 0.05% cream	
GROUP 3	
Fluticasone propionate (Cutivate) 0.005% ointment	
Halcinonide (Halog) 0.1% ointment	
Betamethasone valerate (Valisone) 0.1% ointment	
GROUP 4	
Mometasone furoate (Elocon) 0.1% cream	
Triamcinolone acetonide (Kenalog) 0.1% ointment/cream	
Fluocinolone acetonide (Synalar) 0.025% ointment	
GROUP 5	
Fluocinolone acetonide (Synalar) 0.025% cream	
Hydrocortisone valerate (Westcort) 0.2% ointment	
GROUP 6	
Desonide (DesOwen) 05% ointment/cream/lotion	
Alclometasone dipropionate (Aclovate) 0.05% ointment/cream	
GROUP 7	
Hydrocortisone (Hytone) 2.5% , 1%, 0.5% ointment/cream/lotion	

*Representative corticosteroids are listed by group from 1 (superpotent) through 7 (least potent).

Adapted from Stoughton RB: Vasoconstrictor assay-specific applications. In Malbach HI, Surber C, editors: Topical corticosteroids, *Basel, Switzerland, 1992, Karger, pp. 42–53.*

ultrahigh-potency glucocorticoids should not be used on the face or intertriginous areas and should be used only for very short periods on the trunk and extremities. Mid-potency glucocorticoids can be used for longer periods to treat chronic AD involving the trunk and extremities. Long-term control can be maintained with twice-weekly applications of topical fluticasone or mometasone to areas that have healed but are prone to relapse, once control of AD is achieved after a daily regimen of topical corticosteroids. Compared with creams, ointments have a greater potential to occlude the epidermis, resulting in enhanced systemic absorption. Adverse effects of topical glucocorticoids can be divided into local adverse effects and systemic adverse effects, the latter of which result from suppression of the hypothalamic–pituitary–adrenal axis. Local adverse effects include the development of striae and skin atrophy. Systemic adverse effects are related to the potency of the topical corticosteroid, site of application, occlusiveness of the preparation, percentage of the body surface area covered, and length of use. The potential for adrenal suppression from potent topical corticosteroids is greatest in infants and young children with severe AD requiring intensive therapy.

Topical Calcineurin Inhibitors

The nonsteroidal topical calcineurin inhibitors are effective in reducing AD skin inflammation. Pimecrolimus cream 1% (Elidel) is indicated for mild to moderate AD. Tacrolimus ointment 0.1% and 0.03% (Protopic) is indicated for moderate to severe AD. Both are approved for short-term or intermittent long-term treatment of AD in patients ≥2 yr whose disease is unresponsive to or who are intolerant of other conventional therapies or for whom these therapies are inadvisable owing to potential risks. Topical calcineurin inhibitors may be better than topical corticosteroids in the treatment of patients whose AD is poorly responsive to topical steroids, of patients with steroid phobia, and of patients with face and neck dermatitis, in which ineffective, low-potency topical corticosteroids are usually used because of fears of steroid-induced skin atrophy.

Tar Preparations

Coal tar preparations have antipruritic and antiinflammatory effects on the skin; however, the antiinflammatory effects are usually not as pronounced as those of topical glucocorticoids or calcineurin inhibitors. Tar preparations are useful in reducing the potency of topical glucocorticoids required in long-term maintenance therapy of AD. Tar shampoos can be particularly beneficial for scalp dermatitis. Adverse effects associated with tar preparations include skin irritation, folliculitis, and photosensitivity.

Antihistamines

Systemic antihistamines act primarily by blocking the histamine H_1 receptors in the dermis, thereby reducing histamine-induced pruritus. Histamine is only one of many mediators that induce pruritus of the skin, so patients may derive minimal benefit from antihistaminic therapy. Because pruritus is usually worse at night, sedating antihistamines (hydroxyzine, diphenhydramine) may offer an advantage with their soporific side effects when used at bedtime. Doxepin hydrochloride has both tricyclic antidepressant and H_1- and H_2-receptor blocking effects. Short-term use of a sedative to allow adequate rest may be appropriate in cases of severe nocturnal pruritus. Studies of newer nonsedating antihistamines have shown variable effectiveness in controlling pruritus in AD, although they may be useful in the small subset of patients with AD and concomitant urticaria.

Systemic Corticosteroids

Systemic corticosteroids are rarely indicated in the treatment of chronic AD. The dramatic clinical improvement that may occur with systemic corticosteroids is frequently associated with a severe rebound flare of AD after therapy discontinuation. Short courses of oral corticosteroids may be appropriate for an acute exacerbation of AD while other treatment measures are being instituted in parallel. If a short course of oral corticosteroids is given, it is important to taper the dosage and begin intensified skin care, particularly with topical corticosteroids and frequent bathing followed by application of emollients, to prevent rebound flaring of AD.

Cyclosporine

Cyclosporine is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine gene transcription. Cyclosporine forms a complex with an intracellular protein, cyclophilin, and this complex, in turn, inhibits calcineurin, a phosphatase required for

activation of NFAT (nuclear factor of activated T cells), a transcription factor necessary for cytokine gene transcription. Cyclosporine (5 mg/kg/day) for short-term and long-term (1 yr) use has been beneficial for children with severe, refractory AD. Possible adverse effects include renal impairment and hypertension.

Antimetabolites

Mycophenolate mofetil is a purine biosynthesis inhibitor used as an immunosuppressant in organ transplantation that has been used for treatment of refractory AD. Aside from immunosuppression, herpes simplex retinitis and dose-related bone marrow suppression have been reported with its use. Of note, not all patients benefit from treatment. Therefore, the medication should be discontinued if the disease does not respond within 4-8 wk. Methotrexate is an antimetabolite with potent inhibitory effects on inflammatory cytokine synthesis and cell chemotaxis. Methotrexate has been used for patients with recalcitrant AD. In AD, dosing is more frequent than the weekly dosing used for psoriasis. Azathioprine is a purine analog with antiinflammatory and antiproliferative effects that has been used for severe AD. Myelosuppression is a significant adverse effect, and thiopurine methyl transferase levels may identify individuals at risk for it. Before any of these drugs is used, patients should be referred to an AD specialist who is familiar with treatment of severe AD to weigh relative benefits of alternative therapies.

Phototherapy

Natural sunlight is often beneficial to patients with AD as long as sunburn and excessive sweating are avoided. Many phototherapy modalities are effective for AD, including ultraviolet A-1, ultraviolet B, narrow-band ultraviolet B, and psoralen plus ultraviolet A. Phototherapy is generally reserved for patients in whom standard treatments fail. Maintenance treatments are usually required for phototherapy to be effective. Short-term adverse effects with phototherapy include erythema, skin pain, pruritus, and pigmentation. Long-term adverse effects include predisposition to cutaneous malignancies.

Unproven Therapies

Other therapies that may be considered in patients with refractory AD are as follows.

Interferon-γ

IFN-γ is known to suppress Th2-cell function. Several studies, including a multicenter, double-blind, placebo-controlled trial and several open trials, have demonstrated that treatment with recombinant human IFN-γ results in clinical improvement of AD. Reduction in clinical severity of AD correlated with the ability of IFN-γ to decrease total circulating eosinophil counts. Influenza-like symptoms are commonly observed side effects during the treatment course.

Omalizumab

Treatment of patients who have severe AD and elevated serum IgE values with monoclonal anti-IgE may be considered in those with allergen-induced flares of AD. However, there have been no published double-blind, placebo-controlled trials of its use. Most reports have been case studies and show inconsistent responses to anti-IgE.

Allergen Immunotherapy

In contrast to its acceptance for treatment of allergic rhinitis and extrinsic asthma, immunotherapy with aeroallergens in the treatment of AD is controversial. There are reports of both disease exacerbation and improvement. Studies suggest specific immunotherapy in patients with AD sensitized to dust mite allergen showed improvement in severity of skin disease, as well as reduction in topical steroid use.

Probiotics

Perinatal administration of the probiotic *Lactobacillus rhamnosus* strain GG has been shown to reduce the incidence of AD in at-risk children during the first 2 yr of life. The treatment response has been found to be more pronounced in patients with positive skin prick test results and elevated IgE values. Other studies have not demonstrated a benefit.

Chinese Herbal Medications

Several placebo-controlled clinical trials have suggested that patients with severe AD may benefit from treatment with traditional Chinese herbal therapy. The subjects had significantly reduced skin disease and decreased pruritus. The beneficial response of Chinese herbal therapy is often temporary, and effectiveness may wear off despite continued treatment. The possibility of hepatic toxicity, cardiac side effects, or idiosyncratic reactions remains a concern. The specific ingredients of the herbs also remain to be elucidated, and some preparations have been found to be contaminated with corticosteroids. At present, Chinese herbal therapy for AD is considered investigational.

Vitamin D

Vitamin D deficiency often accompanies severe AD. Vitamin D enhances skin barrier function, reduces corticosteroid requirements to control inflammation and augments skin antimicrobial function. Several small clinical studies suggest vitamin D can enhance antimicrobial peptide expression in the skin and reduce severity of skin disease especially in patients with low baseline vitamin D, for example, during the wintertime when exacerbation of AD often occurs. Patients with AD might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake.

AVOIDING TRIGGERS

It is essential to identify and eliminate triggering factors, both during the period of acute symptoms and on a long-term basis to prevent recurrences (see Table 145-3).

Irritants

Patients with AD have a low threshold response to irritants that trigger their itch-scratch cycle. Soaps or detergents, chemicals, smoke, abrasive clothing, and exposure to extremes of temperature and humidity are common triggers. Patients with AD should use soaps with minimal defatting properties and a neutral pH. New clothing should be laundered before wearing to decrease levels of formaldehyde and other chemicals. Residual laundry detergent in clothing may trigger the itch-scratch cycle; using a liquid rather than powder detergent and adding a second rinse cycle facilitates removal of the detergent.

Every attempt should be made to allow children with AD to be as normally active as possible. A sport such as swimming may be better tolerated than others that involve intense perspiration, physical contact, or heavy clothing and equipment. Rinsing off chlorine immediately and lubricating the skin after swimming are important. Although ultraviolet light may be beneficial to some patients with AD, high sun protection factor sunscreens should be used to avoid sunburn.

Foods

Food allergy is comorbid in approximately 40% of infants and young children with moderate to severe AD (see Chapter 151). Undiagnosed food allergies in patients with AD may induce eczematous dermatitis in some patients and urticarial reactions, wheezing, or nasal congestion in others. Increased severity of AD symptoms and younger age correlate directly with the presence of food allergy. Removal of food allergens from the diet leads to significant clinical improvement but requires a great deal of education, because most common allergens (egg, milk, peanut, wheat, soy) contaminate many foods and are difficult to avoid.

Potential allergens can be identified by a careful history and performing selective skin prick tests or in vitro blood testing for allergen-specific IgE. Negative skin and blood test results for allergen-specific IgE have a high predictive value for excluding suspected allergens. Positive results of skin or blood tests using foods often do not correlate with clinical symptoms and should be confirmed with controlled food challenges and elimination diets. Extensive elimination diets, which can be nutritionally deficient, are rarely required. Even with multiple

positive skin test results, the majority of patients react to fewer than 3 foods under controlled challenge conditions.

Aeroallergens

In older children, AD flares can occur after intranasal or epicutaneous exposure to aeroallergens such as fungi, animal dander, grass, and ragweed pollen. Avoiding aeroallergens, particularly dust mites, can result in clinical improvement of AD. Avoidance measures for dust mite–allergic patients include using dust mite–proof encasings on pillows, mattresses, and box springs; washing bedding in hot water weekly; removing bedroom carpeting; and decreasing indoor humidity levels with air conditioning.

Infections

Patients with AD have increased susceptibility to bacterial, viral, and fungal skin infections. Antistaphylococcal antibiotics are very helpful for treating patients who are heavily colonized or infected with *Staphylococcus aureus.* Erythromycin and azithromycin are usually beneficial for patients who are not colonized with a resistant *S. aureus* strain; a first-generation cephalosporin (cephalexin) is recommended for macrolide-resistant *S. aureus*. Topical mupirocin is useful in the treatment of localized impetiginous lesions, with systemic antibiotics for widespread infections. Cytokine-mediated skin inflammation contributes to skin colonization with *S. aureus;* this fact indicates the importance of combining effective anti-inflammatory therapy with antibiotics for treating moderate to severe AD to avoid the need for repeated courses of antibiotics, which can lead to the emergence of antibiotic-resistant strains of *S. aureus.* Dilute bleach baths (½ cup of bleach in 40 gallons of water) twice weekly may be also considered to reduce *S. aureus* colonization. In one randomized trial the group who received the bleach baths plus intranasal mupirocin (5 days/mo) had significantly decreased severity of AD at 1 and 3 mo compared with placebo. Patients rinse off after the soaking. Further studies are needed to validate this technique.

Herpes simplex virus (HSV) can provoke recurrent dermatitis and may be misdiagnosed as *S. aureus* infection. The presence of punched-out erosions, vesicles, and infected skin lesions that fail to respond to oral antibiotics suggests HSV infection, which can be diagnosed by a Giemsa-stained Tzanck smear of cells scraped from the vesicle base or by viral polymerase chain reaction or culture. Topical corticosteroids should be temporarily discontinued if HSV infection is suspected. Reports of life-threatening dissemination of HSV infections in patients with AD who have widespread disease mandate antiviral treatment. Persons with AD are also susceptible to **eczema vaccinatum,** which is similar in appearance to eczema herpeticum and historically follows smallpox (vaccinia virus) vaccination. Cutaneous warts and molluscum contagiosum are additional viral infections affecting children with AD.

Dermatophyte infections also can contribute to exacerbation of AD. Patients with AD have been found to have a greater susceptibility to *Trichophyton rubrum* fungal infections than nonatopic control subjects. There has been particular interest in the role of *Malassezia furfur* (formerly known as *Pityrosporum ovale*) in AD because it is a lipophilic yeast commonly present in the seborrheic areas of the skin. IgE antibodies against *M. furfur* have been found in patients with head and neck dermatitis. A reduction of AD severity has been observed in those patients after treatment with antifungal agents.

COMPLICATIONS

Exfoliative dermatitis may develop in patients with extensive skin involvement. It is associated with generalized redness, scaling, weeping, crusting, systemic toxicity, lymphadenopathy, and fever, and is usually caused by superinfection (e.g., with toxin-producing *S. aureus* or HSV infection) or inappropriate therapy. In some cases, the withdrawal of systemic glucocorticoids used to control severe AD precipitates exfoliative erythroderma.

Eyelid dermatitis and chronic blepharitis may result in visual impairment from corneal scarring. **Atopic keratoconjunctivitis** is usually bilateral and can have disabling symptoms that include itching, burning, tearing, and copious mucoid discharge. Vernal conjunctivitis is associated with papillary hypertrophy or cobblestoning of the upper eyelid conjunctiva. It typically occurs in younger patients and has a marked seasonal incidence with spring exacerbations. **Keratoconus** is a conical deformity of the cornea believed to result from chronic rubbing of the eyes in patients with AD. Cataracts may be a primary manifestation of AD or from extensive use of systemic and topical glucocorticoids, particularly around the eyes.

PROGNOSIS

AD generally tends to be more severe and persistent in young children, particularly if they have null mutations in their filaggrin genes. Periods of remission occur more frequently as patients grow older. Spontaneous resolution of AD has been reported to occur after age 5 yr in 40-60% of patients affected during infancy, particularly for mild disease. Earlier studies suggested that approximately 84% of children outgrow their AD by adolescence; however, later studies reported that AD resolves in approximately 20% of children monitored from infancy until adolescence and becomes less severe in 65%. Of those adolescents treated for mild dermatitis, >50% may experience a relapse of disease as adults, which frequently manifests as hand dermatitis, especially if daily activities require repeated hand wetting. Predictive factors of a poor prognosis for AD include widespread AD in childhood, filaggrin gene null mutations, concomitant allergic rhinitis and asthma, family history of AD in parents or siblings, early age at onset of AD, being an only child, and very high serum IgE levels.

PREVENTION

Breastfeeding or a feeding with a hypoallergenic hydrolyzed formula may be beneficial. Probiotics and prebiotics may also reduce the incidence or severity of AD, but this approach is unproven. If an infant with AD is diagnosed with food allergy, the breast feeding mother may need to eliminate the implicated food allergen from her diet. Identification and elimination of triggering factors is the mainstay for prevention of flares as well as for the long-term treatment of AD.

Emollient therapy applied to the whole body for the first few months of life may enhance the cutaneous barrier and reduce the risk of eczema.

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Chapter 146

Insect Allergy

Julie Wang and Scott H. Sicherer

Allergic responses to stinging or, more rarely, biting insects vary from localized cutaneous reactions to systemic anaphylaxis. Allergic reactions that are caused by inhalation of airborne particles of insect origin result in acute and chronic respiratory symptoms of seasonal or perennial rhinitis, conjunctivitis, and/or asthma.

ETIOLOGY

Most reactions to stinging and biting insects, such as those induced by wasps, mosquitoes, flies, and fleas, are limited to a primary lesion isolated to the area of the sting or bite and do not represent an allergic response. Occasionally, insect stings or bites induce pronounced localized reactions or systemic reactions that may be based on immediate or delayed hypersensitivity reactions. Systemic allergic responses to insects are attributed most typically to immunoglobulin (Ig) E antibody–mediated responses, which are caused primarily by stings from venomous insects of the order Hymenoptera and more rarely from ticks, spiders, scorpions, and *Triatoma* (kissing bug). Members of the order Hymenoptera include apids (honeybee, bumblebee), vespids

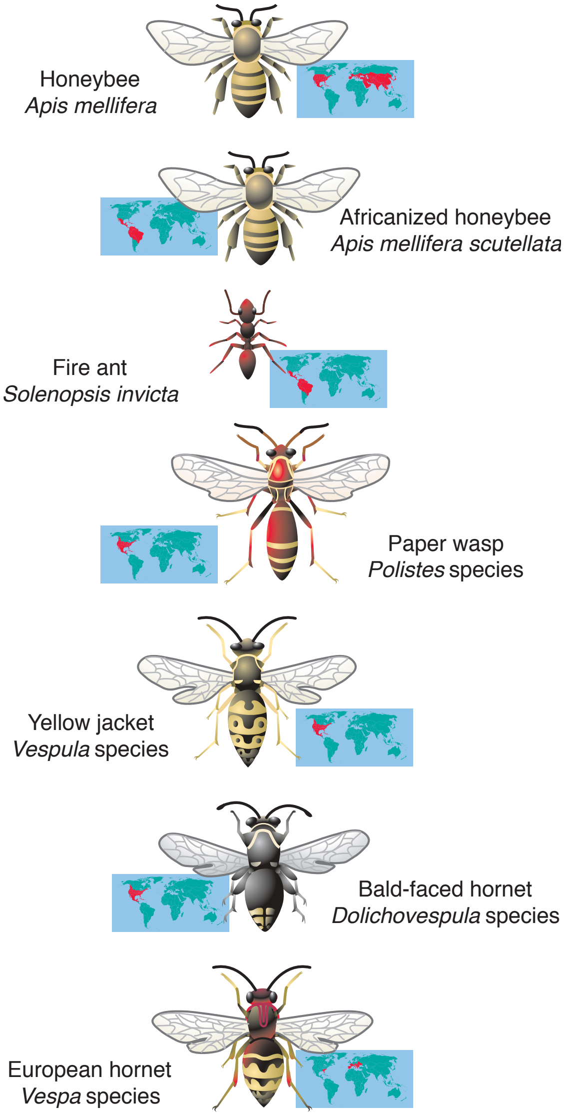

Figure 146-1 Species of Hymenoptera and their geographical distribution. *(From Freeman TM: Hypersensitivity to Hymenoptera stings,* N Engl J Med *351:1978–1984, 2004.)*

(yellow jacket, wasp, hornet), and formicids (fire and harvester ants) (Fig. 146-1). Among winged stinging insects, yellow jackets are the most notorious for stinging because they are aggressive and ground dwelling, and they linger near activities involving food. Hornets nest in trees, whereas wasps build honeycomb nests in dark areas such as under porches; both are aggressive if disturbed. Honeybees are less aggressive, nest in tree hollows, and, unlike the stings of other flying Hymenoptera, honeybee stings almost always leave a barbed stinger with venom sac.

In the United States, fire ants are found increasingly in the Southeast, living in large mounds of soil. When disturbed, the ants attack in large numbers, anchor themselves to the skin by their mandibles, and sting multiple times in a circular pattern. Sterile pseudopustules form at the sting sites. Systemic reactions to stinging insects occur in 0.4-0.8% of children and 3% of adults and account for approximately 40 deaths each year in the United States.

Although reactions to insect bites are common, IgE-mediated reactions are infrequently reported and anaphylaxis is rare. The *Triatoma* (kissing bug) bite causes an erythematous plaque that is painless. Mosquito bites generally result in local reactions that are pruritic. Large local reactions to mosquito bites can occur in some young children; this is known as Skeeter syndrome, and is often misdiagnosed as cellulitis. The tabanid species (horsefly, deerfly), commonly found in rural and suburban areas, are large flies that induce painful bites.

IgE antibody–mediated allergic responses to airborne particulate matter carrying insect emanations contribute to seasonal and perennial symptoms affecting the upper and lower airways. Seasonal allergy is attributed to exposures to a variety of insects, particularly aquatic insects such as the caddis fly and midge, or lake fly, at a time when larvae pupate and adult flies are airborne. Perennial allergy is attributed to sensitization to insects such as cockroaches and ladybugs, as well as house dust mite, which is phylogenetically related to spiders rather than insects and has 8 rather than 6 legs.

PATHOGENESIS

Hymenoptera venoms contain numerous components with toxic and pharmacologic activity and with allergenic potential. These constituents include vasoactive substances such as histamine, acetylcholine, and kinins; enzymes such as phospholipase and hyaluronidase; apamin; melittin; and formic acid. The majority of patients who experience systemic reactions after Hymenoptera stings have IgE-mediated sensitivity to antigenic substances in the venom. Some venom allergens are homologous among members of the Hymenoptera order; others are family specific. There is substantial cross-reactivity among vespid venoms, but these venom allergies are distinct from honeybee venom allergies.

Localized skin responses to biting insects are caused primarily by vasoactive or irritant materials derived from insect saliva, and rarely occur from IgE-associated responses. Systemic IgE-mediated allergic reactions to salivary proteins of biting insects such as mosquitoes are reported but uncommon.

A variety of proteins derived from insects can become airborne and induce IgE-mediated respiratory responses, causing inhalant allergies. The primary allergen from the caddis fly is a hemocyanin-like protein, and that from the midge fly is derived from hemoglobin. Allergens from the cockroach are the best studied and are derived from cockroach saliva, secretions, fecal material, and debris from skin casts.

CLINICAL MANIFESTATIONS

Clinical reactions to stinging venomous insects are categorized as local, large local, generalized cutaneous, systemic, toxic, and delayed/late. Simple **local reactions** involve limited swelling and pain, and generally last <24 hr. **Large local reactions** develop over hours and days, involve swelling of extensive areas (>10 cm) that are contiguous with the sting site, and may last for days. **Generalized cutaneous reactions** typically progress within minutes and include cutaneous symptoms of urticaria, angioedema, and pruritus beyond the site of the sting. **Systemic reactions** are identical to anaphylaxis from other triggers and may include symptoms of generalized urticaria, laryngeal edema, bronchospasm, and hypotension. Stings from a large number of insects at once may result in **toxic reactions** of fever, malaise, emesis, and nausea owing to the chemical properties of the venom in large doses. Serum sickness, nephrotic syndrome, vasculitis, neuritis, or encephalopathy may occur as **delayed/late reactions** to stinging insects.

Insect bites are usually urticarial but may be papular or vesicular. Papular urticaria affecting the lower extremities in children is usually caused by multiple bites. Occasionally, individuals have large local reactions. IgE antibody–associated immediate- and late-phase allergic responses to mosquito bites sometimes mimic cellulitis.

Inhalant allergy caused by insects results in clinical disease similar to that induced by other inhalant allergens such as pollens. Depending on individual sensitivity and exposure, reactions may result in seasonal or perennial rhinitis, conjunctivitis, and/or asthma.

DIAGNOSIS

The diagnosis of allergy from stinging and biting insects is generally evident from the history of exposure, typical symptoms, and physical findings. The diagnosis of Hymenoptera allergy rests in part on the identification of venom-specific IgE by prick skin testing or in vitro testing. The primary reasons to pursue testing are to confirm reactivity when venom immunotherapy (VIT) is being considered or when it is clinically necessary to confirm venom hypersensitivity as a cause of a reaction. Venoms of 5 Hymenoptera (honeybee, yellow jacket, yellow

hornet, white-faced hornet, and wasp), as well as the jack jumper ant in Australia and whole-body extract of fire ant, are available for skin testing. Although skin tests are considered to be the most sensitive modality for detection of venom-specific IgE, additional evaluation with an in vitro serum assay for venom-specific IgE is recommended if skin test results are negative in the presence of a convincing history of a severe systemic reaction. With in vitro tests, there is a 20% incidence of both false-positive and false-negative results, so it is not appropriate to exclude venom hypersensitivity based on this test alone. If initial skin prick and in vitro test results are negative in the context of a convincing history of a severe reaction, repeat testing is recommended before concluding that allergy is unlikely. Skin tests are usually accurate within 1 wk of a sting reaction, but occasionally a refractory period is observed that warrants retesting after 4-6 wk if the initial results are negative. If repeat skin prick and in vitro results are still negative despite a convincing history, occult mast cell disorders should be considered and a baseline serum tryptase should be measured. As many as 40% of skin test–positive subjects may not experience anaphylaxis on sting challenge, so testing without an appropriate clinical history is potentially misleading.

The diagnosis of inhalant insect allergy may be evident from a history of typical symptoms. A chronic respiratory symptom during long-term exposure, as may occur with cockroach allergy, is less amenable to identification by history alone. Skin prick or in vitro immunoassay tests for specific IgE to the insect are used to confirm inhalant insect allergy. Allergy tests may be particularly warranted for potential cockroach allergy in patients with persistent asthma and known cockroach exposure.

TREATMENT

For local cutaneous reactions caused by insect stings and bites, treatment with cold compresses, topical medications to relieve itching, and, occasionally, the use of a systemic antihistamine and oral analgesic are appropriate. Stingers should be removed promptly by scraping, with caution not to squeeze the venom sac because doing so could inject more venom. Sting sites rarely become infected, possibly owing to the antibacterial actions of venom constituents. Vesicles left by fire ant stings that are scratched open should be cleansed to prevent secondary infection.

Anaphylactic reactions after a Hymenoptera sting are treated exactly like anaphylaxis from any cause; epinephrine is the drug of choice. Adjunctive treatment includes antihistamines, corticosteroids, intravenous fluids, oxygen, and transport to the emergency room. (see Chapter 149). Referral to an allergist-immunologist should be considered for patients who have experienced a generalized cutaneous or systemic reaction to an insect sting, need education about avoidance and emergency treatment, may be candidates for VIT, or have a condition that may complicate management of anaphylaxis (e.g., use of β-blockers).

Venom Immunotherapy

Hymenoptera VIT is highly effective (95-97%) in decreasing the risk for severe anaphylaxis. The selection of patients for VIT depends on several factors (Table 146-1). Individuals with local reactions regardless of age are not at increased risk for severe systemic reactions on a subsequent sting and are not candidates for VIT. The risk of a systemic reaction for those who experienced a large local reaction is no more than 5-10%; testing or VIT is usually not recommended, and prescription of self- injectable epinephrine is considered optional but usually not necessary. There is growing evidence that VIT can reduce the size and duration of large, local reactions, and therefore VIT may be considered for those with frequent or unavoidable large, local reactions. *Those who experience severe systemic reactions, such as airway involvement or hypotension, and have specific IgE to venom allergens should receive immunotherapy.* Immunotherapy against winged Hymenoptera is not usually indicated for children ≤16 yr of age in whom stings have caused only generalized urticaria or angioedema, because their risk for a systemic reaction after a subsequent sting is approximately 10%. If a systemic reaction does occur, it is likely to be isolated skin reactions, with <5% risk of a more severe reaction and <1% risk of life-threatening anaphylaxis. The risk could be reduced to 1% after treatment with VIT, so it is an option to consider if multiple future stings are anticipated. *Immunotherapy against Hymenoptera is indicated in those ≥17 yr of age who have specific IgE to venom allergens and a history of generalized urticaria or a systemic reaction,* because their risk for future systemic reactions is 30-60%. VIT is usually not indicated if there is no evidence of IgE to venom.

The incidence of adverse effects in the course of treatment is not trivial in adults, as 50% experience large local reactions and about 10% experience systemic reactions. The incidence of both local and systemic reactions is much lower in children. Patients treated with honeybee venom are at higher risk for systemic reactions to VIT than those receiving treatment with vespid venom. Individuals with mast cell disorders are at increased risk for severe anaphylaxis and more frequent systemic reactions with VIT.

It is uncertain how long immunotherapy with Hymenoptera venom should continue. In general, a 3-5 year treatment duration is recommended because >80% of adults who have received 5 yr of therapy tolerate challenge stings without systemic reactions for 5-10 yr after completion of treatment. Long-term responses to treatment are even better for children. Follow-up over a mean of 18 yr of children with moderate to severe insect sting reactions who received VIT for a mean treatment period of 3-5 yr and were stung again showed a reaction rate of only 5%; untreated children experienced a reaction rate of 32%. Whereas duration of therapy with VIT may be individualized, it is clear that a significant number of untreated children retain their allergy. Lifelong treatment may be considered for those who have had severe life-threatening anaphylaxis with insect stings, those with honeybee allergy, and those with occupational exposures to Hymenoptera. Lifelong VIT should also be considered for those with mast cell disorders as these individuals have a higher rate of failure of VIT and relapse when VIT is discontinued.

Less is known about the natural history of fire ant hypersensitivity and efficacy of immunotherapy for this allergy. The criteria for starting immunotherapy are similar to those for hypersensitivities to other Hymenoptera, but there is stronger consideration to treat children ≤16 yr of age with VIT if they have experienced only generalized

Table 146-1 Indications for Venom Immunotherapy Against Winged Hymenoptera

SYMPTOMS	AGE	SKIN TEST/IN VITRO TEST	RISK OF SYSTEMIC REACTION IF UNTREATED*	VIT RECOMMENDED
Large local reaction	Any	Usually not indicated	5-10%	Usually not indicated
Generalized cutaneous reaction	≤16 yr	Usually not indicated	10%	Usually not indicated
	≥17 yr	Positive result	20%	Yes
		Negative result	—	No
Systemic reaction	Any	Positive result	Child: 40% Adult: 30-60%	Yes
		Negative result	—	Usually no

*Risks generally decrease after 10 yr.

urticaria. Only whole-body fire ant extract is commercially available for diagnostic skin testing and immunotherapy.

Inhalant Allergy

The symptoms of inhalant allergy caused by insects are managed as for other causes of seasonal or perennial rhinitis (see Chapter 143), conjunctivitis (see Chapter 147), and asthma (see Chapter 144).

PREVENTION

Avoidance of stings and bites is essential. To reduce the risk of stings, sensitized individuals should avoid attractants such as perfumes and bright-colored clothing outdoors, wear gloves when gardening, and wear long pants and shoes with socks when walking in the grass or through fields. Typical insect repellents do not guard against Hymenoptera. Nests of these insects should be removed if they are close to the home.

Individuals who have had generalized cutaneous or systemic reactions to Hymenoptera stings should have immediate access to **self-injectable epinephrine.** Adults responsible for allergic children, and older patients who can self-treat, must be carefully taught the indications for and technique of administration of this medication. Particular attention is necessary for children in out-of-home daycare centers, at school, or attending camps, to ensure that an emergency action plan is in place. The individual at risk for anaphylaxis from an insect sting should also wear an identification bracelet indicating the allergy.

Avoidance of the insect is the preferred management of inhalant allergy. This can prove difficult, particularly, for instance, for those living in multiple-dwelling apartments, where eradication of cockroaches is problematic. Immunotherapy for dust mites is effective and should be considered in conjunction with avoidance measures. In contrast, there is limited data regarding the efficacy of cockroach immunotherapy.

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Chapter 147
Ocular Allergies

Mark Boguniewicz, Christine B. Cho, and Scott H. Sicherer

The eye is a common target of allergic disorders because of its marked vascularity and direct contact with allergens in the environment. The conjunctiva is the most immunologically active tissue of the external eye. Ocular allergies can occur as isolated target organ disease or more commonly in conjunction with nasal allergies. Ocular symptoms can significantly affect quality of life.

CLINICAL MANIFESTATIONS

There are a few distinct entities that constitute allergic eye disease, all of which have bilateral involvement. Sensitization is necessary for all of these except for giant papillary conjunctivitis. Vernal keratoconjunctivitis and atopic keratoconjunctivitis are potentially sight-threatening.

Allergic Conjunctivitis

Allergic conjunctivitis is the most common hypersensitivity response of the eye, affecting approximately 25% of the general population and 30% of children with atopy. It is caused by direct exposure of the mucosal surfaces of the eye to environmental allergens. Patients complain of variable ocular itching, rather than pain, with increased tearing. Clinical signs include bilateral injected conjunctivae with vascular congestion that may progress to chemosis, or conjunctival swelling, and a watery discharge (Fig. 147-1). Allergic conjunctivitis occurs in a seasonal or, less commonly, perennial form. **Seasonal allergic conjunctivitis** is typically associated with allergic rhinitis (see Chapter 143) and is most commonly triggered by pollens. Major pollen groups in the temperate zones include trees (late winter to early spring), grasses (late spring to early summer), and weeds (late summer to early fall), but seasons can vary significantly in different parts of the country. Mold spores can also cause seasonal allergy symptoms, principally in the summer and fall. Seasonal allergy symptoms may be aggravated by coincident exposure to perennial allergens. **Perennial allergic conjunctivitis** is triggered by allergens such as animal danders or dust mites that are present throughout the year. Symptoms are usually less severe than with seasonal allergic conjunctivitis. Because pollens and soil molds may be present intermittently by season, and exposure to allergens such as furred animals may be perennial, classification as intermittent (symptoms present <4 days/wk or for <4 wk) and persistent (symptoms present >4 days/wk and for >4 wk) has been proposed.

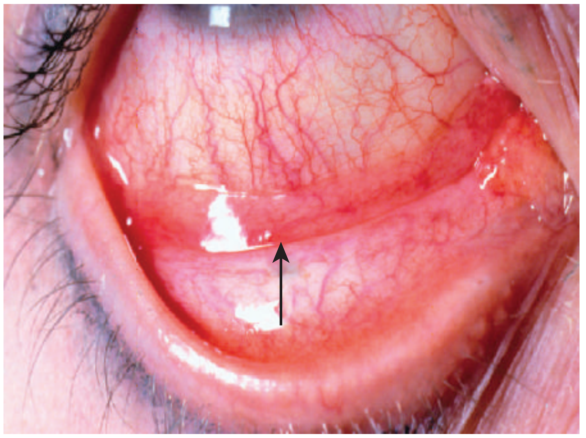

Figure 147-1 Allergic conjunctivitis. Arrow indicates area of chemosis in the conjunctivitis. *(From Adkinson NF Jr, Bochner BS, Busse WW, et al, editors:* Middleton's allergy principles and practice, *ed 7, vol 2, Philadelphia, Elsevier, 2009, p. 1121.)*

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis is a severe bilateral chronic inflammatory process of the upper tarsal conjunctival surface that occurs in a limbal or palpebral form. It may threaten eyesight if there is corneal involvement. Although vernal keratoconjunctivitis is not immunoglobulin E mediated, it occurs most frequently in children with seasonal allergies, asthma, or atopic dermatitis. Vernal keratoconjunctivitis affects boys twice as often as girls and is more common in persons of Asian and African descent. It affects primarily children in temperate areas, with exacerbations in the spring and summer. Symptoms include severe ocular itching exacerbated by exposure to irritants, light, or perspiration. In addition, patients may complain of severe photophobia, foreign-body sensation, and lacrimation. Giant papillae occur predominantly on the upper tarsal plate and are typically described as **cobblestoning** (Fig. 147-2). Other signs include a stringy or thick, ropey discharge, cobblestone papillae, transient yellow-white points in the limbus (Trantas dots) and conjunctiva (Horner points), corneal "shield" ulcers, and Dennie lines (Dennie-Morgan folds), which are prominent symmetric skinfolds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin. Children with vernal keratoconjunctivitis have measurably longer eyelashes, which may represent a reaction to ocular inflammation.

Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis is a **chronic** inflammatory ocular disorder most commonly involving the lower tarsal conjunctiva. It may threaten eyesight if there is corneal involvement. Almost all patients have **atopic dermatitis,** and a significant number have asthma. Atopic

keratoconjunctivitis rarely presents before late adolescence. Symptoms include severe bilateral ocular itching, burning, photophobia, and tearing with a mucoid discharge that are much more severe than in allergic conjunctivitis and persist throughout the year. The bulbar conjunctiva is injected and chemotic; cataracts may occur. Trantas dots or giant papillae may also be present. Eyelid eczema can extend to the periorbital skin and cheeks with erythema and thick, dry scaling. Secondary staphylococcal blepharitis is common because of eyelid induration and maceration.

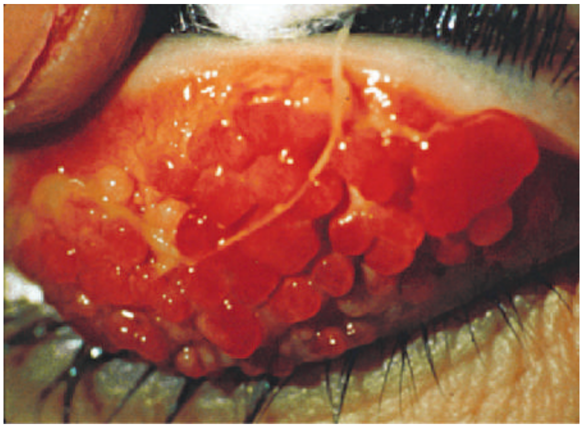

Figure 147-2 Vernal keratoconjunctivitis. Cobblestone papillae and ropey discharge are seen on the underside (tarsal conjunctiva) of the upper eyelid. *(From Adkinson NF Jr, Bochner BS, Busse WW, et al, editors:* Middleton's allergy principles and practice, *ed 7, vol 2, Philadelphia, Mosby/Elsevier, 2009, p. 1124.)*

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis has been linked to chronic exposure to foreign bodies, such as contact lenses, both hard and soft, ocular prostheses, and sutures. Symptoms and signs include mild bilateral ocular itching, tearing, a foreign-body sensation, and excessive ocular discomfort with mild mucoid discharge with white or clear exudate on awakening, which may become thick and stringy. Trantas dots, limbal infiltration, bulbar conjunctival hyperemia, and edema may develop.

Contact Allergy

Contact allergy typically involves the eyelids but can also involve the conjunctivae. It is being recognized more frequently in association with increased exposure to topical medications, contact lens solutions, and preservatives.

DIAGNOSIS

Nonallergic conjunctivitis can be viral, bacterial, or chlamydial in origin. It is typically unilateral but can be bilateral with symptoms initially developing in 1 eye (see Chapter 626). Symptoms include stinging or burning rather than itching and often a foreign-body sensation. Ocular discharge can be watery, mucoid, or purulent. Masqueraders of ocular allergy also include nasolacrimal duct obstruction, foreign body, blepharoconjunctivitis, dry eye, uveitis, and trauma.

TREATMENT

Primary treatment of ocular allergies includes avoidance of allergens, cold compresses, and lubrication. Secondary treatment regimens include the use of oral or topical antihistamines and, if necessary, topical decongestants, mast cell stabilizers, and antiinflammatory agents (Table 147-1). Drugs with dual antihistamine and mast cell blocking activities provide the most advantageous approach in treating allergic conjunctivitis, with both fast-acting symptomatic relief and

Table 147-1 Topical Ophthalmic Medications for Allergic Conjunctivitis

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	CAUTIONS AND ADVERSE EVENTS
Azelastine hydrochloride 0.05% Optivar	Antihistamine Children ≥3 yr: 1 gtt bid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Emedastine difumarate 0.05% Emadine	Antihistamine Children ≥3 yr: 1 gtt qid	Soft contact lenses should not be worn if the eye is red. Wait at least 10 min after administration before inserting soft contact lenses.
Levocabastine hydrochloride 0.05% Livostin	Antihistamine Children ≥12 yr: 1 gtt bid-qid up to 2 wk	Not for use in patients wearing soft contact lenses during treatment.
Pheniramine maleate	Antihistamine/vasoconstrictor	Avoid prolonged use (>3-4 days) to avoid rebound symptoms. Not for use with contact lenses.
0.3%/Naphazoline hydrochloride 0.025% Naphcon-A, Opcon-A	Children >6 yr: 1-2 gtt qid	
Cromolyn sodium 4% Crolom, Opticrom	Mast cell stabilizer Children >4 yr 1-2 gtt q4-6h	Can be used to treat giant papillary conjunctivitis and vernal keratitis. Not for use with contact lenses.
Lodoxamide tromethamine 0.1% Alomide	Mast cell stabilizer Children ≥2 yr: 1-2 gtt qid up to 3 mo	Can be used to treat vernal keratoconjunctivitis. Not for use in patients wearing soft contact lenses during treatment.
Nedocromil sodium 2% Alocril	Mast cell stabilizer Children ≥3 yr 1-2 gtt bid	Avoid wearing contact lenses while exhibiting the signs and symptoms of allergic conjunctivitis.
Pemirolast potassium 0.1% Alamast	Mast cell stabilizer Children >3 yr: 1-2 gtt qid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Epinastine hydrochloride 0.05% Elestat	Antihistamine/mast cell stabilizer Children ≥3 yr 1 gtt bid	Contact lenses should be removed prior to use. Wait at least 15 min after administration before inserting soft contact lenses. Not for the treatment of contact lens irritation.

Continued

Table 147-1 Topical Ophthalmic Medications for Allergic Conjunctivitis—cont'd		
DRUG AND TRADE NAMES	**MECHANISM OF ACTION AND DOSING**	**CAUTIONS AND ADVERSE EVENTS**
Ketotifen fumarate 0.025% Zaditor	Antihistamine/mast cell stabilizer Children ≥3 yr 1 gtt bid q8-12h	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Olopatadine hydrochloride 0.1%, 0.2% Patanol Pataday	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid (8 hr apart) 1 gtt q day	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Alcaftadine, 0.25% Lastacaft	Antihistamine/mast cell stabilizer Children > 2 yr: 1 gtt bid q8-12 hr	Contact lenses should be removed prior to application, may be inserted after 10 minutes. Not for the treatment of contact lens irritation.
Bepotastine besilate 1.5% Bepreve	Antihistamine/mast cell stabilizer Children >2 yr: 1 gtt bid q8-12 hr	Contact lenses should be removed prior to application, may be inserted after 10 minutes. Not for the treatment of contact lens irritation.
Ketorolac tromethamine 0.5% Acular	NSAID Children ≥3 yr: 1 gtt qid	Avoid with aspirin or NSAID sensitivity. Use ocular product with caution in patients with complicated ocular surgeries, corneal denervation or epithelial defects, ocular surface diseases (e.g., dry eye syndrome), repeated ocular surgeries within a short period of time, diabetes mellitus, or rheumatoid arthritis; these patients may be at risk for corneal adverse events that may be sight-threatening. Do not use while wearing contact lenses.
Fluorometholone 0.1%, 0.25% suspension (0.1%, 0.25%) and ointment (0.1%) FML, FML Forte, Flarex	Fluorinated corticosteroid Children ≥2 yr, 1 gtt into conjunctival sac of affected eye(s) bid-qid. During initial 24–48 hr, dosage may be increased to 1 gtt q 4 hr. Ointment (approximately 1.3 cm in length) into the conjunctival sac of affected eye(s) 1–3 times daily. May be applied q 4 hr during initial 24–48 hr of therapy	If improvement does not occur after 2 days, patient should be reevaluated. Patient should remove soft contact lenses prior to administering (contains benzalkonium chloride) and delay reinsertion of lenses for ≥15 minutes after administration. Close monitoring for development of glaucoma and cataracts.

NSAID, nonsteroidal antiinflammatory drug.

disease-modifying action. Children often complain of stinging or burning with use of topical ophthalmic preparations and usually prefer oral antihistamines for allergic conjunctivitis. It is important not to contaminate topical ocular medications by allowing the applicator tip to contact the eye or eyelid. Using refrigerated medications may decrease some of the discomfort associated with their use. Topical decongestants act as vasoconstrictors, reducing erythema, vascular congestion, and eyelid edema, but do not diminish the allergic response. Adverse effects of topical vasoconstrictors include burning or stinging and rebound hyperemia or conjunctivitis medicamentosa with chronic use. Combined use of an antihistamine and a vasoconstrictive agent is more effective than use of either agent alone. Use of topical nasal corticosteroids for allergic rhinoconjunctivitis decreases ocular symptoms, presumably through a naso-ocular reflex.

Tertiary treatment of ocular allergy includes topical or, rarely, oral corticosteroids and should be conducted in conjunction with an ophthalmologist. Local administration of topical corticosteroids may be associated with increased intraocular pressure, viral infections, and cataract formation. Other immunomodulatory medications, such as topical tacrolimus or topical cyclosporine are used as steroid-sparing agents by ophthalmologists. Allergen immunotherapy can be very effective in seasonal and perennial allergic conjunctivitis, especially when associated with rhinitis, and can decrease the need for oral or topical medications to control allergy symptoms.

Because vernal conjunctivitis and atopic keratoconjunctivitis can be associated with visual morbidity, if these diagnoses are suspected, the patient should be referred to an ophthalmologist.

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Chapter 148

Urticaria (Hives) and Angioedema

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Urticaria and angioedema affect 20% of individuals at some point in their lives. Episodes of hives that last for <6 wk are considered acute, whereas those that occur on most days of the week for >6 wks are designated chronic. The distinction is important, because the causes and mechanisms of urticaria formation and the therapeutic approaches are different in each instance.

ETIOLOGY AND PATHOGENESIS

Acute urticaria and angioedema are often caused by an allergic immunoglobulin (Ig) E–mediated reaction (Table 148-1). This form of urticaria is a self-limited process that occurs when an allergen activates mast cells in the skin. Common causes of acute generalized urticaria include foods, drugs (particularly antibiotics), and stinging insect venoms. If an allergen (latex, animal dander) penetrates the skin locally, hives often can develop at the site of exposure. Acute urticaria can also result from non–IgE-mediated stimulation of mast cells,

Table 148-1	Etiology of Acute Urticaria
Foods	Egg, milk, wheat, peanuts, tree nuts, soy, shellfish, fish, strawberries (direct mast cell degranulation)
Medications	Suspect all medications, even nonprescription or homeopathic
Insect stings	Hymenoptera (honeybee, yellow jacket, hornets, wasp, fire ants), biting insects (papular urticaria)
Infections	Bacterial (streptococcal pharyngitis, *Mycoplasma*, sinusitis); viral (hepatitis, mononucleosis [Epstein-Barr virus], coxsackieviruses A and B); parasitic *(Ascaris, Ancylostoma, Echinococcus, Fasciola, Filaria, Schistosoma, Strongyloides, Toxocara, Trichinella);* fungal (dermatophytes, *Candida*)
Contact allergy	Latex, pollen, animal saliva, nettle plants, caterpillars
Transfusion reactions	Blood, blood products, or IV immunoglobulin administration

From Lasley MV, Kennedy MS, Altman LC: Urticaria and angioedema. In Altman LC, Becker JW, Williams PV, editors: Allergy in primary care, *Philadelphia, 2000, WB Saunders, p. 232.*

caused by radiocontrast agents, viral agents (including hepatitis B and Epstein-Barr virus), opiates, and nonsteroidal antiinflammatory agents. The diagnosis of chronic urticaria is established when lesions occur on most days of the week for >6 wk and are not physical urticaria or recurrent acute urticaria with repeated exposures to a specific agent (Table 148-2). In about half the cases, chronic urticaria is accompanied by angioedema. Rarely, angioedema occurs without urticaria. Angioedema without urticaria is often a result of allergy, but recurrent angioedema raises a question about other diagnoses.

A typical hive is an erythematous, pruritic raised wheal that blanches with pressure, is transient, and resolves without residual lesions, unless the area was intensely scratched. In contrast, urticaria associated with serum sickness reactions, systemic lupus erythematosus or other vasculitides, in which a skin biopsy reveals a small-vessel vasculitis, often have distinguishing clinical features. Lesions that burn more than itch, last >24 hr, do not blanch, blister, heal with scarring, or are associated with bleeding into the skin (purpura) suggest urticarial vasculitis. Atypical aspects of the gross appearance of the hives or associated symptoms should heighten concern that the urticaria or angioedema may be the manifestation of a systemic disease process.

PHYSICAL URTICARIA

Physically induced urticaria and angioedema share the common property of being induced by an environmental stimulus, such as a change in temperature or direct stimulation of the skin with pressure, stroking, vibration, or light (Table 148-3).

Cold-Dependent Disorders

Cold urticaria is characterized by the development of localized pruritus, erythema, and urticaria/angioedema after exposure to a cold stimulus. Total-body exposure as seen with swimming in cold water can cause massive release of vasoactive mediators, resulting in hypotension, loss of consciousness and even death if not promptly treated. The diagnosis is confirmed by challenge testing for an isomorphic cold reaction by holding an ice cube in place on the patient's skin for 4 min. In patients with cold urticaria, an urticarial lesion develops about 10 minutes after removal of the ice cube and upon rewarming of the chilled skin. Cold urticaria can be associated with the presence of **cryoproteins,** such as cold agglutinins, cryoglobulins, cryofibrinogen, and the Donath-Landsteiner antibody seen in secondary syphilis

Table 148-2	Etiology of Chronic Urticaria
Idiopathic/autoimmune	Approximately 30% of chronic urticaria cases are physical urticaria and 60-70% are idiopathic. Of the idiopathic cases approximately 35-40% have anti-IgE or anti-FcεRI (high-affinity IgE receptor α chain) autoantibodies (autoimmune chronic urticaria)
Physical	Dermatographism Cholinergic urticaria Cold urticaria Delayed pressure urticaria Solar urticaria Vibratory urticaria Aquagenic urticaria
Autoimmune diseases	Systemic lupus erythematosus Juvenile idiopathic arthritis Thyroid (Graves, Hashimoto) Celiac disease Inflammatory bowel disease Leukocytoclastic vasculitis
Autoinflammatory/ periodic fever syndromes	NOMID (neonatal onset multisystem inflammatory disease) Muckle-Wells syndrome Familial cold autoinflammatory syndrome Cold urticarial, immunodeficiency, autoimmunity as a result of *PLCG2* deficiency
Neoplastic	Lymphoma Mastocytosis Leukemia
Angioedema	Hereditary angioedema (autosomal dominant inherited deficiency of C1-esterase inhibitor) Acquired angioedema Angiotensin-converting enzyme inhibitors

From Lasley MV, Kennedy MS, Altman LC: Urticaria and angioedema. In Altman LC, Becker JW, Williams PV, editors: Allergy in primary care, *Philadelphia, 2000, WB Saunders, p. 234.*

(paroxysmal cold hemoglobinuria). In patients with cryoglobulins, the isolated proteins appear to transfer cold sensitivity and activate the complement cascade upon in vitro incubation with normal plasma. The term **idiopathic cold urticaria** generally applies to patients without abnormal circulating plasma proteins such as cryoglobulins. Cold urticaria has also been reported after viral infections. Cold urticaria must be distinguished from the **familial cold autoinflammatory syndrome** (see "Diagnosis," later).

Cholinergic Urticaria

Cholinergic urticaria is characterized by the onset of small punctate pruritic wheals surrounded by a prominent erythematous flare associated with exercise, hot showers, and sweating. Once the patient cools down, the rash usually subsides in 30-60 min. Occasionally, symptoms of more generalized cholinergic stimulation, such as lacrimation, wheezing, salivation, and syncope, are observed. These symptoms are mediated by cholinergic nerve fibers that innervate the musculature via parasympathetic neurons and innervate the sweat glands by cholinergic fibers that travel with the sympathetic nerves. Elevated plasma histamine values parallel the onset of urticaria triggered by changes in body temperature.

Dermatographism

The ability to write on skin, termed dermatographism (also called dermographism or urticaria factitia), may occur as an isolated

Table 148-3 Diagnostic Testing for Urticaria and Angioedema

DIAGNOSIS	DIAGNOSTIC TESTING
Food and drug reactions	Elimination of offending agent, skin testing, and challenge with suspected foods
Autoimmune urticaria	Autologous serum skin test; antithyroid antibodies; antibodies against the high-affinity IgE receptor
Thyroiditis	Thyroid-stimulating hormone; antithyroid antibodies
Infections	Appropriate cultures or serology
Collagen vascular diseases and cutaneous vasculitis	Skin biopsy, CH_{50}, C1q, C4, C3, factor B, immunofluorescence of tissues, antinuclear antibodies, cryoglobulins
Malignancy with angioedema	CH_{50}, C1q, C4, C1-INH determinations
Cold urticaria	Ice cube test
Solar urticaria	Exposure to defined wavelengths of light, red blood cell protoporphyrin, fecal protoporphyrin, and coproporphyrin
Dermatographism	Stroking with narrow object (e.g., tongue blade, fingernail)
Pressure urticaria	Application of pressure for defined time and intensity
Vibratory urticaria	Vibration for 4 min
Aquagenic urticaria	Challenge with tap water at various temperatures
Urticaria pigmentosa	Skin biopsy, test for dermographism
Hereditary angioedema	C4, C2, CH_{50}, C1-INH testing by protein and function
Familial cold urticaria	Challenge by cold exposure, measurement of temperature, white blood cell count, erythrocyte sedimentation rate, and skin biopsy
C3b inactivator deficiency	C3, factor B, C3b inactivator determinations
Chronic idiopathic urticaria	Skin biopsy, immunofluorescence (negative result), autologous skin test

disorder or may accompany chronic urticaria or other physical urticaria, such as cholinergic and cold urticaria. It can be diagnosed by observing the skin after stroking it with a tongue depressor. In patients with dermatographism, a linear response occurs secondary to reflex vasoconstriction, followed by pruritus, erythema, and a linear flare caused by secondary dilation of the vessel and the extravasation of plasma.

Pressure-Induced Urticaria and Angioedema

Pressure-induced urticaria differs from most types of urticaria or angioedema in that symptoms typically occur 4-6 hr after pressure has been applied. The disorder is clinically heterogeneous. Some patients may complain of swelling secondary to pressure with normal-appearing skin (no urticaria), so the term *angioedema* is more appropriate. Other lesions are predominantly urticarial and may or may not be associated with significant swelling. When urticaria is present, an infiltrative skin lesion is seen, characterized by a perivascular mononuclear cell infiltrate and dermal edema similar to that seen in chronic idiopathic urticaria. Symptoms occur at sites of tight clothing; foot swelling is common after walking; and buttock swelling may be prominent after sitting for a few hours. This condition can coexist with chronic idiopathic urticaria or can occur separately. The diagnosis is confirmed by challenge testing in which pressure is applied perpendicular to the skin. This is often done with a sling attached to a 10 lb weight that is placed over the patient's arm for 20 min.

Solar Urticaria

Solar urticaria is a rare disorder in which urticaria develops within minutes of direct sun exposure. Typically, pruritus occurs first, in approximately 30 sec, followed by edema confined to the light-exposed area and surrounded by a prominent erythematous zone. The lesions usually disappear within 1-3 hr after cessation of sun exposure. When large areas of the body are exposed, systemic symptoms may occur, including hypotension and wheezing. Solar urticaria has been classified into 6 types, depending on (1) the wavelength of light that induces skin lesions and (2) the ability or inability to transfer the disorder passively with serum IgE. The rare inborn error of metabolism, **erythropoietic protoporphyria,** can be confused with solar urticaria because of the development of itching and burning of exposed skin immediately after sun exposure. In erythropoietic protoporphyria, fluorescence of ultraviolet-irradiated red blood cells can be demonstrated and protoporphyrins are found in the urine.

Aquagenic Urticaria

Patients with aquagenic urticaria demonstrate small wheals after contact with water, regardless of its temperature, and are thereby distinguishable from patients with cold urticaria or cholinergic urticaria. Direct application of a compress of water to the skin is used to test for the presence of aquagenic urticaria. In some of these patients, chlorine or other trace contaminants are responsible for the reaction.

CHRONIC IDIOPATHIC URTICARIA AND ANGIOEDEMA

A common disorder of unknown origin, chronic idiopathic urticaria and angioedema is often associated with normal routine laboratory values and no evidence of systemic disease. Chronic urticaria does not appear to result from an allergic reaction. It differs from allergen-induced skin reactions and from physically induced urticaria in that histologic studies reveal a cellular infiltrate predominantly around small venules. Skin examination reveals infiltrative hives with palpably elevated borders, sometimes varying greatly in size and/or shape but generally being rounded.

Biopsy of the typical lesion reveals non-necrotizing, perivascular, mononuclear cellular infiltration. Many types of histopathologic processes can occur in the skin and manifest as urticaria. Patients with **hypocomplementemia** and **cutaneous vasculitis** can have urticaria and/or angioedema. Biopsy of these lesions in patients with urticaria, arthralgias, myalgias, and an elevated erythrocyte sedimentation rate (ESR) as manifestations of necrotizing venulitis can reveal fibrinoid necrosis with a predominantly neutrophilic infiltrate. Yet the urticarial lesions may be clinically indistinguishable from those seen in the more typical, nonvasculitic cases.

There is an increased association of chronic urticaria with the presence of antithyroid antibodies. Affected patients generally have antibodies to thyroglobulin or a microsomally derived antigen (peroxidase) even if they are euthyroid. The incidence of elevated thyroid antibodies in patients with chronic urticaria is ≈12%, compared with 3-6% in the general population. Although some patients show clinical reduction of the urticaria with thyroid replacement therapy, others do not. The role of thyroid autoantibodies in chronic urticaria is uncertain. It has been proposed that their presence may reflect a tendency of the patient to develop autoantibodies, but that they may not play a direct role in chronic urticaria. Of patients with chronic urticaria, 35-40% have a positive **autologous serum skin test** result: If serum from these patients is intradermally injected into their skin, a significant wheal and flare reaction develops. Such patients frequently have a complement-activating IgG antibody directed against the α subunit of the IgE receptor that can crosslink the IgE receptor (α subunit) and degranulate mast cells and basophils. An additional 5-10% of patients

with chronic urticaria have anti-IgE antibodies rather than an anti–IgE receptor antibody. These patients, classified as having autoimmune urticaria, tend to have a more severe clinical course than patients without evidence of autoantibodies, but the difference is not dramatic.

DIAGNOSIS

The diagnosis of both acute and chronic urticaria is primarily clinical and requires that the physician be aware of the various forms of urticaria.

Urticaria is transient, pruritic, erythematous, raised wheals, with flat tops and edema that may become tense and painful. The lesions may coalesce and form polycyclic, serpiginous, or annular lesions (Figs. 148-1 and 148-2). Individual lesions usually last 20 min to 3 hr, and rarely more than 24 hr. The lesions often disappear only to reappear at another site. **Angioedema** involves the deeper subcutaneous tissues in locations such as the eyelids, lips, tongue, genitals, dorsum of the hands or feet, or wall of the gastrointestinal (GI) tract.

Drugs and foods are the most common causes of acute urticaria. Allergy skin testing for foods can be helpful in sorting out causes of acute urticaria, especially when supported by historical evidence. The role of an offending food can then be proven by elimination and careful challenge in a controlled setting. In the absence of information implicating an ingestant cause, skin testing for foods and implementation of elimination diets are generally not useful for either acute or chronic urticaria. Patients with delayed urticaria 3-6 hr after a meal consisting of mammalian meat should be evaluated for IgE to galactose-alpha-1,3-galactose ("alpha-gal"), a carbohydrate moiety. Alpha-gal has been

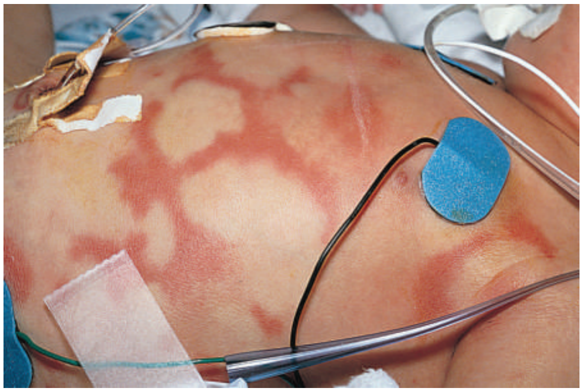

Figure 148-1 Polycyclic lesions of urticaria associated with prostaglandin E_2 infusion. *(From Eichenfield LF, Friedan IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 300.)*

Figure 148-2 Annular urticaria of unknown etiology. *(From Eichenfield LF, Friedan IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 301.)*

identified as a trigger in this circumstance, with sensitization apparently linked to tick bites in specific geographic regions, such as the mid-Atlantic area of the United States. Skin testing for aeroallergens is not indicated unless there is a concern about contact urticaria (animal dander or grass pollen). Dermatographism is frequent in patients with urticaria and can complicate allergy skin testing by causing false-positive reactions, but this distinction is usually discernable.

An exogenous cause of chronic urticaria is rarely identified, reflecting the wide variety of allergens with which we come in contact. Autoimmune diseases are rare causes of chronic urticarial or angioedema. An autologous serum skin test may be useful in establishing the diagnosis of autoimmune urticaria. In vitro testing for serum-derived activity that activates basophils involves detection of the expression of the surface marker CD63 or CD203c by donor basophils after incubation with patient serum. The clinical applicability and significance of these tests remains debated. The **differential diagnosis** of chronic urticaria includes cutaneous or systemic mastocytosis, complement-mediated mast cell degranulation as may occur with the presence of circulating immune complexes, malignancies, mixed connective tissue diseases, and cutaneous blistering disorders (e.g., bullous pemphigoid; see Table 148-2). In general, laboratory testing should be limited to a complete blood cell count with differential, ESR determination, urinalysis, thyroid autoantibody testing, and liver function tests. Further studies are warranted if the patient has fever, arthralgias, or elevated ESR (see Table 148-3). Testing for antibodies directed at the high affinity IgE receptor may be warranted in patients with intractable urticaria. Hereditary angioedema, a potentially life-threatening form of angioedema usually associated with deficient C1 inhibitor activity, is the most important familial form of angioedema (see Chapter 134.3), but is not associated with typical urticaria. In patients with eosinophilia, stools should be obtained for ova and parasite testing, because infection with helminthic parasites has been associated with urticaria. A syndrome of episodic angioedema/urticaria and fever with associated eosinophilia has been described in both adults and children. In contrast to other hypereosinophilic syndromes, this entity has a benign course.

Skin biopsy for diagnosis of possible **urticarial vasculitis** is recommended for urticarial lesions that persist at the same location for >24 hr, those with pigmented or purpuric components, and those that burn more than itch. Collagen vascular diseases such as systemic lupus may manifest urticarial vasculitis as a presenting feature. The skin biopsy in urticarial vasculitis typically shows endothelial cell swelling of postcapillary venules with necrosis of the vessel wall, perivenular neutrophil infiltrate, diapedesis of red blood cells, and fibrin deposition associated with deposition of immune complexes.

Mastocytosis is characterized by mast cell hyperplasia in the bone marrow, liver, spleen, lymph nodes, and skin. Clinical effects of mast cell activation are common, including pruritus, flushing, urtication, abdominal pain, nausea, and vomiting. The diagnosis is confirmed by a bone marrow biopsy showing increased numbers of spindle-shaped mast cells that express CD2 and CD25. **Urticaria pigmentosa** is the most common skin manifestation of mastocytosis and may occur as an isolated skin finding. It appears as small, yellow-tan to reddish brown macules or raised papules that urticate on scratching **(Darier sign).** This sign can be masked by antihistamines. The diagnosis is confirmed by a skin biopsy that shows increased numbers of dermal mast cells.

Physical urticaria should be considered in any patient with chronic urticaria and a suggestive history (see Table 148-3). Papular urticaria commonly occurs in small children, generally on the extremities. It manifests as grouped or linear, highly pruritic wheals or papules mainly on exposed skin at the sites of insect bites.

Exercise-induced anaphylaxis manifests as varying combinations of pruritus, urticaria, angioedema, wheezing, laryngeal obstruction, or hypotension after exercise (see Chapter 149). Cholinergic urticaria is differentiated by positive results of heat challenge tests and the rare occurrence of anaphylactic shock. The combination of ingestion of various food allergens (shrimp, celery, or wheat) and postprandial exercise has been associated with urticaria/angioedema and

anaphylaxis. In patients with this combination disorder, food or exercise alone does not produce the reaction.

Muckle-Wells syndrome and **familial cold autoinflammatory syndrome** are rare, dominantly inherited conditions associated with recurrent urticaria-like lesions. Muckle-Wells syndrome is characterized by arthritis and joint pain that usually appears in adolescence. It is associated with progressive nerve deafness, recurrent fever, elevated ESR, hypergammaglobulinemia, renal amyloidosis, and a poor prognosis. Familial cold autoinflammatory syndrome is characterized by a cold-induced rash that has urticarial features but is rarely pruritic. Cold exposure leads to additional symptoms such as conjunctivitis, sweating, headache, and nausea. Patient longevity is usually normal.

TREATMENT

Acute urticaria is a self-limited illness requiring little treatment other than antihistamines and avoidance of any identified trigger. Hydroxyzine and diphenhydramine are sedating but are effective and commonly used for treatment of urticaria. Loratadine, fexofenadine, and cetirizine are also effective and are preferable because of reduced frequency of drowsiness and longer duration of action (Table 148-4). Epinephrine 1 : 1,000, 0.01 mL/kg (maximum: 0.3 mL) intramuscularly usually provides rapid relief of acute, severe urticaria/angioedema but is seldom required. A short course of oral corticosteroids should be given only for very severe episodes of urticaria and angioedema that are unresponsive to antihistamines.

The best treatment of physical urticaria is avoidance of the stimulus. Antihistamines are also helpful. Cyproheptadine in divided doses is the drug of choice for cold-induced urticaria. Treatment of dermatographism consists of local skin care and antihistamines; for severe symptoms, high doses may be needed. The initial objective of therapy is to decrease pruritus so that the stimulation for scratching is diminished. A combination of antihistamines, sunscreens, and avoidance of sunlight is helpful for most patients.

Chronic urticaria only rarely responds favorably to dietary manipulation. Removal of recognized urticarial aggravators such as salicylates and β-blockers should be considered. The mainstay of therapy is the use of nonsedating or low-sedating H_1 antihistamines. In those patients not showing response to standard doses, pushing the H_1 blockade with higher than the usual recommended doses of these agents is a common next approach. The 3-drug combination of H_1 and H_2 antihistamine combined with a leukotriene receptor antagonist (montelukast) is helpful for many patients. If hives persist after maximal H_1- and/or H_2-receptor blockade has been achieved, a brief course of oral corticosteroids may be considered, but long-term steroid use is best avoided. Treatment with cyclosporine 4-6 mg/kg/day has been effective in some adults with chronic urticaria but its use is limited by hypertension and/or nephrotoxicity. Immunomodulatory agents such as omalizumab (anti-IgE antibody) that have been used with success in cases of chronic urticarial that are refractory to other therapies, but are not approved for the treatment of this condition by the FDA. These include omalizumab (anti-IgE), cyclosporine, hydroxychloroquine, sulfasalazine, colchicine, dapsone, mycophenolate, intravenous immunoglobulin, and plasmapheresis.

Table 148-4 Treatment of Urticaria and Angioedema

CLASS/DRUG	DOSE	FREQUENCY
ANTIHISTAMINES, TYPE H_1 (SECOND GENERATION)		
Fexofenadine	6-11 yr: 30 mg >12 yr: 60 mg Adult: 180 mg	bid Once daily
Loratadine	2-5 yr: 5 mg >6 yr: 10 mg	Once daily
Desloratadine	6-11 mo: 1 mg 12 mo-5 yr: 1.25 mg 6-11 yr: 2.5 mg >12 yr: 5 mg	Once daily
Cetirizine	6-23 mo: 2.5 mg 2-6 yr: 2.5-5mg >6 yr: 5-10 mg	Once daily
Levocetirizine	6 mo-5 yr: 1.25 mg 6-11 yr: 2.5 mg >12 yr: 5 mg	Once daily Once daily Once daily
ANTIHISTAMINES, TYPE H_2		
Cimetidine	Infants: 10-20 mg/kg/day Children: 20-40 mg/kg/day	Divided q6-12h
Ranitidine	1 mo-16 yr: 5-10 mg/kg/day	Divided q12h
Famotidine	3-12 mo: 1 mg/kg/day 1-16 yr: 1-2 mg/kg/day	Divided q12h
LEUKOTRIENE PATHWAY MODIFIERS		
Montelukast	12 mo-5 yr: 4 mg 6-14 yr: 5 mg >14 yr: 10 mg	Once daily
Zafirlukast	5-11 yr: 10 mg	bid
IMMUNOMODULATORY DRUGS		
Cyclosporine	4-6 mg/kg/day	Once daily*
Sulfasalazine	>6 yr: 30 mg/kg/day	Divided q6h†
Intravenous immunoglobulin (IVIG)	400 mg/kg/day	5 consecutive days

*Monitor blood pressure and serum creatinine, potassium, and magnesium levels monthly.

†Monitor complete blood count and liver function tests at baseline, every 2 wk for 3 mo, and then every 1-3 mo.

HEREDITARY ANGIOEDEMA

Hereditary angioedema (HAE) (types 1 and 2) is an inherited autosomal dominant disease caused by low functional levels of the plasma protein C1 inhibitor (C1-INH) (see Chapter 134). Patients typically report episodic attacks of angioedema or deep localized swelling, most commonly on a hand or foot, that begin during childhood and become much more severe during adolescence. Cutaneous nonpitting and nonpruritic edema not associated with urticaria is the most common symptom. The swelling usually becomes more severe over about 1.5 days and then resolves over about the same period. In some patients attacks are preceded by the development of a rash, that is erythema marginatum, that is erythematous, not raised, and not pruritic. The second major symptom complex noted by patients is attacks of severe abdominal pain caused by edema of the mucosa of any portion of the GI tract. The intensity of the pain can approximate that of an acute abdomen, often resulting in unnecessary surgery. Either constipation or diarrhea during these attacks can be noted. The GI edema generally follows the same time course to resolution as the cutaneous attacks, and often does not occur at the same time as the peripheral edema. Patients usually have a prodrome, a tightness or tingling in the area that will swell, lasting most frequently for several hours, followed by the development of angioedema.

Laryngeal edema, the most feared complication of HAE, can cause complete respiratory obstruction. Although life-threatening attacks are infrequent, more than half of patients with HAE experience laryngeal involvement at some time during their lives. Dental work with the injection of procaine HCL (Novocain) into the gums is a common precipitant, but laryngeal edema can be spontaneous. The clinical condition may deteriorate rapidly, progressing through mild discomfort to complete airway obstruction over a period of hours. Soft-tissue edema can be readily seen when the disease involves the throat and uvula. If this edema progresses to difficulty swallowing secretions or a change in the tone of the voice, the patient may require emergency intubation or even tracheostomy to ensure an adequate airway. Other presentations are less common. These patients typically do not respond well to treatment with epinephrine, antihistamines, or glucocorticoids.

In most cases the cause of the attack is unknown, but in some patients trauma or emotional stress clearly precipitates attacks. Drugs like angiotensin-converting enzyme inhibitors that inhibit the degradation of bradykinin make the disease strikingly worse, and estrogens also make attacks more severe. In some females menstruation also regularly induces attacks. The frequency of attacks varies greatly among

affected individuals and at different times in the same individual. Some individuals experience weekly episodes, whereas others may go years between attacks. Episodes can start at any age.

C1-INH is a member of the serpin family of proteases, similar to α-antitrypsin, antithrombin III, and angiotensinogen. These proteins stoichiometrically inactivate their target proteases by forming stable, 1 : 1 complexes with the protein to be inhibited. Synthesized primarily by hepatocytes, C1-INH is also synthesized by monocytes. The regulation of the protein production is not completely understood, but it is believed that androgens may stimulate C1-INH synthesis, because patients with the disorder respond clinically to androgen therapy with raised serum levels of C1-INH. C1-INH deficiency is an autosomal dominant disease, with as many as 25% of patients giving no family history. Because all C1-INH–deficient patients are heterozygous for this gene defect, it is believed that half the normal level of C1-INH is not sufficient to prevent attacks.

Although named for its action on the first component of complement (C1 esterase), C1-INH also inhibits components of the fibrinolytic, clotting, and kinin pathways. Specifically, C1-INH inactivates plasmin-activated Hageman factor (factor XII), activated factor XI, plasma thromboplastin antecedent, and kallikrein. Within the complement system, C1-INH blocks the activation of C1 and the rest of the classic complement pathway by binding to C1r and C1s. Without adequate C1-INH, unchecked activation of C1 causes cleavage of C4 and C2, the following proteins in the complement cascade. Levels of C3 are normal. The major factor responsible for the edema formation is now known to be bradykinin, an important nonapeptide mediator that can induce leakage of postcapillary venules. Bradykinin is derived from cleavage of the circulating protein high molecular weight kininogen by the plasma enzyme kallikrein.

Two genetic types of C1-INH deficiency are described that result in essentially the same phenotypic expression. The C1-INH gene is located on chromosome 11 in the p11-q13 region. The inheritance is autosomal dominant with incomplete penetrance. Persons inheriting the abnormal gene can have a clinical spectrum ranging from asymptomatic to severely affected. Type 1 HAE is the most common form, accounting for approximately 85% of cases. Synthesis of C1-INH is blocked at the site of the faulty allele or the protein is not secreted normally because of faulty protein processing, but secretion occurs at the normal allele. The result is secretion of the normal protein, yielding quantitative serum concentrations of C1-INH that are approximately 20-40% of normal. Type 2 HAE accounts for approximately 15% of cases. Mutations of one of the amino acids near the active site of the inhibitor lead to synthesis of nonfunctional C1-INH protein and again less than half of the normal functioning protein. Patients with type 2 HAE have either normal or increased concentrations of the protein and low values in assays of C1-INH function.

A clinical syndrome resembling HAE and termed type 3 HAE has been described that affects mostly women and has a tendency to cause fewer abdominal attacks and more upper airway attacks. In this condition, no abnormalities of complement or of C1-INH have been described. Approximately 20% of affected patients have been found to have a gain-of-function abnormality of clotting factor XII, but the fundamental cause is still unknown.

The FDA has approved purified C1-INH for prophylaxis to prevent attacks. Androgens like the gonadotropin inhibitor danazol were previously used to prevent attacks. Weak androgens have many side affects that preclude their use in some patients. Their use in children is problematic because of the possibility of premature closure of the epiphyses, and these agents are not used in pregnant women. The fibrinolysis inhibitor ε-aminocaproic acid is also effective in preventing attacks and has been used in children, but its use was attended by the development of severe fatigue and muscle weakness over time.

In 2008, the FDA approved, for adolescents and older, the use of purified C1-INH (Cinryze), prepared from human plasma given intravenously for prophylaxis of this disease following clinical trials. The half-life of this plasma protein is relatively short, on the order of 40 hr, and the approved regimen is 1,000 units given twice a week. In 2009, a similar purified C1-inhibitor product, Berinert, used as 20 units/kg intravenously, was approved for the treatment of acute attacks. A recombinant C1-INH product has been approved for treatment of acute attacks in Europe, but is not currently approved for treatment in the United States. In 2009, a kallikrein inhibitor, ecallantide, given subcutaneously, was approved by the FDA for acute treatment in patients age 16 yr and older. This 60 amino acid peptide causes anaphylaxis in the rare patient, and is approved to be given only by medical personnel. In 2010, a bradykinin type 2 receptor antagonist, icatibant was approved for acute treatment in patients age 18 yr and older. All treatments are most effective when given early in an attack, and begin to have noticeable effect after about 1-4 hr after treatment.

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Chapter 149

Anaphylaxis

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Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death. Anaphylaxis in children, particularly infants, is underdiagnosed. Anaphylaxis occurs when there is a sudden release of potent biologically active mediators from mast cells and basophils, leading to cutaneous (urticaria, angioedema, flushing), respiratory (bronchospasm, laryngeal edema), cardiovascular (hypotension, dysrhythmias, myocardial ischemia), and gastrointestinal (nausea, colicky abdominal pain, vomiting, diarrhea) symptoms (Table 149-1).

ETIOLOGY

The most common causes of anaphylaxis in children are different for hospital and community settings. Anaphylaxis occurring in the hospital results primarily from allergic reactions to medications and latex. Food allergy is the most common cause of anaphylaxis occurring outside the hospital, accounting for about half of the anaphylactic reactions reported in pediatric surveys from the United States, Italy, and South Australia (Table 149-2). Peanut allergy is an important cause of food-induced anaphylaxis, accounting for the majority of fatal and near-fatal reactions. In the hospital, latex is a particular problem for children undergoing multiple operations, such as patients with spina bifida and urologic disorders, and has prompted many hospitals to switch to latex-free products. Patients with latex allergy may also experience food-allergic reactions from homologous proteins in foods such as bananas, kiwi, avocado, chestnut, and passion fruit. Anaphylaxis to galactose-α-1,3-galactose has been reported 3-6 hr after eating meat.

EPIDEMIOLOGY

The overall annual incidence of anaphylaxis in the United States is estimated at 50 cases/100,000 persons/yr, totaling >150,000 cases/yr, with the highest rate for the pediatric age group (0-19 yr) at 70/100,000 persons/yr. An Australian parental survey found that 0.59% of children 3-17 yr of age had experienced at least 1 anaphylactic event. Having asthma and the severity of asthma are important anaphylaxis risk factors (Table 149-3).

PATHOGENESIS

Principal pathologic features in fatal anaphylaxis include acute bronchial obstruction with pulmonary hyperinflation, pulmonary edema, intraalveolar hemorrhaging, visceral congestion, laryngeal edema, and urticaria and angioedema. Acute hypotension is attributed to vasomotor dilation and/or cardiac dysrhythmias.

Most cases of anaphylaxis are believed to be the result of activation of mast cells and basophils via cell-bound allergen-specific

Table 149-1 Symptoms and Signs of Anaphylaxis in Infants

ANAPHYLAXIS SYMPTOMS THAT INFANTS CANNOT DESCRIBE	ANAPHYLAXIS SIGNS THAT MAY BE DIFFICULT TO INTERPRET/UNHELPFUL IN INFANTS, AND WHY	ANAPHYLAXIS SIGNS IN INFANTS
GENERAL		
Feeling of warmth, weakness, anxiety, apprehension, impending doom	Nonspecific behavioral changes such as persistent crying, fussing, irritability, fright, suddenly becoming quiet	
SKIN/MUCUS MEMBRANES		
Itching of lips, tongue, palate, uvula, ears, throat, nose, eyes, etc.; mouth-tingling or metallic taste	Flushing (may also occur with fever, hyperthermia, or crying spells)	Rapid onset of hives (potentially difficult to discern in infants with acute atopic dermatitis; scratching and excoriations will be absent in young infants); angioedema (face, tongue, oropharynx)
RESPIRATORY		
Nasal congestion, throat tightness; chest tightness; shortness of breath	Hoarseness, dysphonia (common after a crying spell); drooling or increased secretions (common in infants)	Rapid onset of coughing, choking, stridor, wheezing, dyspnea, apnea, cyanosis
GASTROINTESTINAL		
Dysphagia, nausea, abdominal pain/cramping	Spitting up/regurgitation (common after feeds), loose stools (normal in infants, especially if breastfed); colicky abdominal pain	Sudden, profuse vomiting
CARDIOVASCULAR		
Feeling faint, presyncope, dizziness, confusion, blurred vision, difficulty in hearing	Hypotension (need appropriate-size blood pressure cuff; low systolic blood pressure for children is defined as <70 mm Hg from 1 mo to 1 yr, and less than (70 mm Hg + [2 × age in yr]) from 1-10 yr; tachycardia, defined as >140 beats/min from 3 mo to 2 yr, inclusive; loss of bowel and bladder control (ubiquitous in infants)	Weak pulse, arrhythmia, diaphoresis/sweating, collapse/unconsciousness
CENTRAL NERVOUS SYSTEM		
Headache	Drowsiness, somnolence (common in infants after feeds)	Rapid onset of unresponsiveness, lethargy, or hypotonia; seizures

Adapted from Simons FER. Anaphylaxis in infants: can recognition and management be improved? J Allergy Clin Immunol *120:537–540, 2007.*

Table 149-2 Anaphylaxis Triggers in the Community*

ALLERGEN TRIGGERS (IgE-DEPENDENT IMMUNOLOGIC MECHANISM)*
Foods (e.g., peanut, tree nuts, shellfish, fish, milk, egg, wheat, soy, sesame, meat [galactose-α-1,3-galactose])
Food additives (e.g., spices, colorants, vegetable gums, and contaminants)
Stinging insects: Hymenoptera species (e.g., bees, yellow jackets, wasps, hornets, and fire ants)
Medications (e.g., β-lactam antibiotics, ibuprofen)
Biologic agents (e.g., monoclonal antibodies [infliximab, omalizumab] and allergens [challenge tests, specific immunotherapy])
Natural rubber latex
Vaccines
Inhalants (rare) (e.g., horse or hamster dander, grass pollen)
Previously unrecognized allergens (foods, venoms, biting insect saliva, medications, biologic agents)
OTHER IMMUNE MECHANISMS (IGE INDEPENDENT)
IgG mediated (infliximab, high-molecular-weight dextrans)
Immune aggregates (IVIG)
Drugs (aspirin, NSAID, opiates, contrast material, ethylene oxide/dialysis tubing)
Complement activation
Physical factors (e.g., exercise†, cold, heat, sunlight/ultraviolet radiation)
Ethanol
Idiopathic*

*In the pediatric population, some anaphylaxis triggers, such as hormones (progesterone), seminal fluid, and occupational allergens, are uncommon, as is idiopathic anaphylaxis.

†Exercise with or without a cotrigger, such as a food or medication, cold air, or cold water.

IVIG, intravenous immunoglobulin; NSAID, nonsteroidal antiinflammatory drug.

Adapted from Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *New York, 2010, Elsevier, p. 652.*

Table 149-3 Patient Risk Factors for Anaphylaxis

AGE-RELATED FACTORS Infants: anaphylaxis can be hard to recognize, especially if the first episode; patients cannot describe symptoms Adolescents and young adults: increased risk taking behaviors such as failure to avoid known triggers and to carry an epinephrine autoinjector consistently Pregnancy: risk of iatrogenic anaphylaxis—for example, from β lactam antibiotics to prevent neonatal group B streptococcal infection, agents used perioperatively during caesarean sections, and natural rubber latex Older people: increased risk of death because of concomitant disease and drugs
CONCOMITANT DISEASES Asthma and other chronic respiratory diseases Cardiovascular diseases Mastocytosis Allergic rhinitis and eczema* Depression, cognitive dysfunction, substance misuse
DRUGS β-Adrenergic blockers† Angiotensin-converting enzyme (ACE) inhibitors† Sedatives, antidepressants, narcotics, recreational drugs, and alcohol may decrease the patient's ability to recognize triggers and symptoms
COFACTORS THAT AMPLIFY ANAPHYLAXIS Exercise: anaphylaxis associated with exercise may be food dependent or food independent; nonsteroidal antiinflammatory drugs and other listed cofactors may also be relevant Acute infection such as an upper respiratory tract infection Fever Emotional stress Disruption of routine—for example, travel and jet lag Premenstrual status in women and girls

*Atopic diseases are a risk factor for anaphylaxis triggered by food, latex, and exercise, but not for anaphylaxis triggered by most drugs or by insect stings

†Patients taking β-adrenergic blockers or ACE inhibitors seem to be at increased risk for severe anaphylaxis. In addition, those taking β-adrenergic blockers may not respond optimally to epinephrine treatment and may need glucagon, a polypeptide with non–catecholamine-dependent inotropic and chronotropic cardiac effects, atropine for persistent bradycardia, or ipratropium for persistent bronchospasm.

Modified from Simons FER, Sheikh A: Anaphylaxis: the acute episode and beyond. BMJ 2013;346:f602 (Box 2, p. 32).

immunoglobulin (Ig) E molecules. Patients initially must be exposed to the responsible allergen to generate allergen-specific antibodies. In many cases, the child and the parent are unaware of the initial exposure, which may be from passage of food proteins in maternal breast milk or skin exposures. When the child is reexposed to the sensitizing allergen, mast cells and basophils, and possibly other cells, such as macrophages, release a variety of mediators (histamine, tryptase) and cytokines that can produce allergic symptoms in any or all target organs. Clinical anaphylaxis may also be caused by mechanisms other than IgE-mediated reactions, including direct release of mediators from mast cells by medications and physical factors (morphine, exercise, cold), disturbances of leukotriene metabolism (aspirin and nonsteroidal antiinflammatory drugs), immune aggregates and complement activation (blood products), probable complement activation (radiocontrast dyes, dialysis membranes), and IgG-mediated reactions (high-molecular-weight dextran, chimeric or humanized monoclonal antibodies) (see Table 149-2).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The onset of symptoms may vary depending on the cause of the reaction. Reactions from ingested allergens (foods, medications) are delayed in onset (minutes to 2 hr) compared with those from injected allergens (insect sting, medications) and tend to have more gastrointestinal symptoms. Initial symptoms may include any of the following

Table 149-4 Diagnosis of Anaphylaxis

Anaphylaxis is highly likely when any *1* of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (e.g., *generalized* hives, pruritus or flushing, swollen lips/tongue/uvula)
   AND AT LEAST 1 OF THE FOLLOWING:
   a. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a **likely** allergen for that patient* (minutes to several hours):
   a. Involvement of the skin/mucosal tissue (e.g., *generalized* hives, itch/flush, swollen lips/tongue/uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. *Persistent* gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP following exposure to ***known** allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age-specific) or >30% drop in systolic BP
   b. Adults: systolic BP <90 mm Hg or >30% drop from patient's baseline

BP, blood pressure; PEF, peak expiratory flow.

Modified from Sampson HA, Muñoz-Furlong A, Campbell RL, et al: Second symposium on the definition and management of anaphylaxis: summary report. Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, J Allergy Clin Immunol *117:391–397, 2006.*

constellation of symptoms: pruritus about the mouth and face; a sensation of warmth, weakness, and apprehension (sense of doom); flushing, urticaria and angioedema, oral or cutaneous pruritus, tightness in the throat, dry staccato cough and hoarseness, periocular pruritus, nasal congestion, sneezing, dyspnea, deep cough and wheezing; nausea, abdominal cramping, and vomiting, especially with ingested allergens; uterine contractions (manifesting as lower back pain); and faintness and loss of consciousness in severe cases. Some degree of obstructive laryngeal edema is typically encountered with severe reactions. Cutaneous symptoms may be absent in up to 20% of cases, and the acute onset of severe bronchospasm in a previously well asthmatic person should suggest the diagnosis of anaphylaxis. Sudden collapse in the absence of cutaneous symptoms should also raise suspicion of vasovagal collapse, myocardial infarction, aspiration, pulmonary embolism, or seizure disorder. Laryngeal edema, especially with abdominal pain, may also be a result of hereditary angioedema (see Chapter 148). Symptoms in infants may not be easy to identify (see Table 149-1).

LABORATORY FINDINGS

Laboratory studies may indicate the presence of IgE antibodies to a suspected causative agent, but this result is not definitive. Plasma histamine is elevated for a brief period but is unstable and difficult to measure in a clinical setting. **Plasma tryptase** is more stable and remains elevated for several hours but often is not elevated, especially in food-induced anaphylactic reactions.

DIAGNOSIS

A National Institutes of Health–sponsored expert panel has recommended an approach to the diagnosis of anaphylaxis (Table 149-4). The differential diagnosis includes other forms of shock (hemorrhagic, cardiogenic, septic), vasopressor reactions including flush syndromes such as carcinoid syndrome, excess histamine syndromes (systemic mastocytosis), ingestion of monosodium glutamate, scombroidosis, and hereditary angioedema. In addition, panic attack, vocal cord dysfunction, pheochromocytoma, and red man syndrome (caused by vancomycin) should be considered.

TREATMENT

Anaphylaxis is a medical emergency requiring aggressive management with **intramuscular (first line)** *or intravenous* ***epinephrine***, intramuscular or intravenous H_1 and H_2 antihistamine antagonists, oxygen, intravenous fluids, inhaled β-agonists, and corticosteroids (Table 149-5, Fig. 149-1). The initial assessment should ensure an adequate airway with effective respiration, circulation, and perfusion. Epinephrine is the most important medication, and there should be no delay in its administration. Epinephrine should be given by the intramuscular route to the lateral thigh (1 : 1000 dilution, 0.01 mg/kg; max 0.5 mg). For children ≥12 yr, many recommend the 0.5 mg intramuscular dose. The intramuscular dose can be repeated 2 or 3 times at intervals of 5-15 min if an intravenous continuous epinephrine infusion has not yet been started and symptoms persist. The 1 : 10,000 dilution of epinephrine should be used for intravenous administration. If IV access is not readily available, then epinephrine can be administered via the endotracheal or intraosseous routes. Anaphylaxis refractory to repeated doses of epinephrine has anecdotally been treated with glucagon or methylene blue. The patient should be placed in a supine position and lower extremities elevated when there is concern for hemodynamic compromise. Fluids are also important in patients with shock. Other drugs (antihistamines, glucocorticosteroids) have a secondary role in the management of anaphylaxis. Patients may experience **biphasic anaphylaxis,** which occurs when anaphylactic symptoms recur after apparent resolution. The mechanism of this phenomenon is unknown, but it appears to be more common when therapy is initiated late and symptoms at presentation are more severe. It does not appear to be affected by the administration of corticosteroids during the initial therapy. More than 90% of biphasic responses occur within 4 hr, so patients should be observed for at least 4 hr before being discharged from the emergency department. Referrals should be made to appropriate specialists for further evaluation and follow-up.

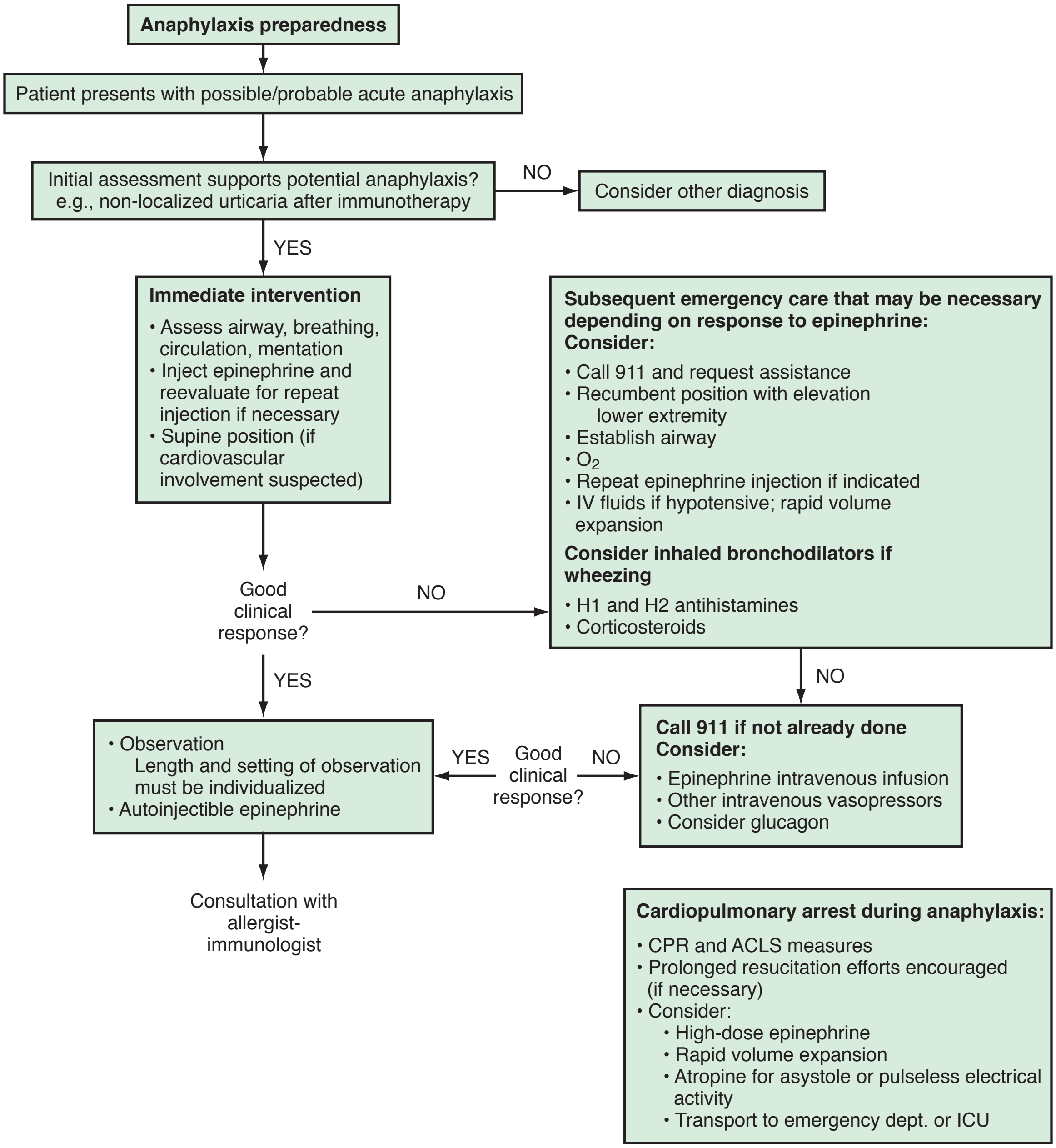

Figure 149-1 Algorithm for the treatment of anaphylactic event in the outpatient setting. IV, Intravenous. *(From Lieberman P, Nicklas RA, Oppenheimer J, et al: The diagnosis and management of anaphylaxis practice parameter: 2010 update,* J Allergy Clin Immunol *126:477–480 e471–442, 2010 [Fig. E2].)*

Table 149-5 Management of a Patient with Anaphylaxis

TREATMENT	MECHANISM(S) OF EFFECT	DOSAGE(S)	COMMENTS; ADVERSE REACTIONS
PATIENT EMERGENCY MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1, β_1, β_2 adrenergic effects	0.01 mg/kg up to 0.5 mg IM in lateral thigh Weight 8-25 kg: Adrenaclick, Auvi-Q, EpiPen Jr (0.15 mg) IM Weight >25 kg: Adrenaclick, Auvi-Q, EpiPen (0.3 mg) IM	Tachycardia, hypertension, nervousness, headache, nausea, irritability, and tremor
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid–5 mg/5 mL 0.25 mg/kg up to 10 mg PO	Hypotension, tachycardia, and somnolence
Alt: diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg up to 50 mg PO or IM	Hypotension, tachycardia, somnolence, and paradoxical excitement
Transport **to an Emergency Facility**			
EMERGENCY PERSONNEL MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1, β_1, β_2 adrenergic effects	0.01 mg/kg up to 0.5 mg IM in lateral thigh Epinephrine autoinjector: 0.15 mg for 8-25kg, 0.3 mg for >25 kg 0.01 mL/kg/dose of 1 : 1,000 solution up to 0.5 mL IM May repeat every 10-15 min For severe hypotension: 0.01 mL/kg/ dose of 1 : 10,000 slow IV push	Tachycardia, hypertension, nervousness, headache, nausea, irritability, and tremor
Supplemental oxygen and airway management			
Volume expanders			
Crystalloids (normal saline or Ringer lactate)		30 mL/kg in 1st hr	Rate titrated against blood pressure response If tolerated, place patient supine with legs raised
Colloids (hydroxyethyl starch)		10 mL/kg rapidly followed by slow infusion	Rate titrated against blood pressure response If tolerated, place patient supine with legs raised
Antihistamines			
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid–5 mg/5 mL 0.25 mg/kg up to 10 mg PO	Hypotension, tachycardia, and somnolence
Alt: diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg up to 50 mg PO, IM, or IV	Hypotension, tachycardia, somnolence, and paradoxical excitement
Ranitidine	Antihistamine (competitive of H_2 receptor)	1 mg/kg up to 50 mg IV Should be administered slowly	Headache, mental confusion
Alt: cimetidine	Antihistamine (competitive of H_2 receptor	4 mg/kg up to 200 mg IV Should be administered slowly	Headache, mental confusion
Corticosteroids			
Methylprednisolone	Antiinflammatory	Solu-Medrol (IV) 1-2 mg/kg up to 125 mg IV Depo-Medrol (IM) 1 mg/kg up to 80 mg IM	Hypertension, edema, nervousness, and agitation
Prednisone	Antiinflammatory	1 mg/kg up to 75 mg PO	Hypertension, edema, nervousness, and agitation
Nebulized albuterol	β-Agonist	(0.83 mg/mL [3 mL]) via mask with O_2	Palpitations, nervousness, central nervous system stimulation, tachycardia; use to supplement epinephrine when bronchospasm appears unresponsive; may repeat
POSTEMERGENCY MANAGEMENT			
Antihistamine		Cetirizine (5-10 mg qd) or loratadine (5-10 mg qd) for 3 days	
Corticosteroids		*Optional:* Oral prednisone (1 mg/kg up to 75 mg) daily for 3 days	
Preventive treatment			
Prescription for epinephrine autoinjector and antihistamine			
Provide written plan outlining patient emergency management (may download form from http://www.foodallergy.org)			
Follow-up evaluation to determine/confirm etiology			
Immunotherapy for insect sting allergy			
Patient education			
Instruction on avoidance of causative agent			
Information on recognizing early signs of anaphylaxis			
Stress early treatment of allergic symptoms to avoid systemic anaphylaxis			
Encourage wearing medical identification jewelry			

IM, intramuscularly; IV, intravenously; PO, by mouth.

PREVENTION

For patients experiencing anaphylactic reactions, the triggering agent should be avoided and education regarding early recognition of anaphylactic symptoms and administration of emergency medications should be provided. Patients with food allergies must be educated in allergen avoidance, including active reading of food ingredient labels and knowledge of potential contamination and high-risk situations. Any child with food allergy and a history of asthma, peanut, tree nut, fish or shellfish allergy, or a previous anaphylactic reaction should be given an epinephrine autoinjector (Adrenaclick, Auvi-Q, EpiPen), liquid cetirizine (or alternatively, diphenhydramine), and a written emergency plan in case of accidental ingestion. A form can be downloaded from Food Allergy Research & Education at http://www.foodallergy.org.

In cases of food-associated exercise-induced anaphylaxis, children must not exercise within 2-3 hr of ingesting the triggering food and, like children with exercise-induced anaphylaxis, should exercise with a friend, learn to recognize the early signs of anaphylaxis (sensation of warmth and facial pruritus), stop exercising, and seek help immediately if symptoms develop. Children experiencing a systemic anaphylactic reaction including respiratory symptoms to an insect sting should be evaluated and treated with immunotherapy, which is more than 90% protective. Reactions to medications can be reduced and minimized by using oral medications in preference to injected forms and avoidance of cross-reacting medications. Low osmolarity radiocontrast dyes and pretreatment can be used in patients in whom previous reactions are suspected. The use of nonlatex gloves and materials should be used in children undergoing multiple operations. Any child who is at risk for anaphylaxis should receive emergency medications (including epinephrine autoinjector), education on identification of signs and symptoms of anaphylaxis and proper administration of medications, and a written emergency plan in case of accidental exposure, and encouraged to wear medical identification jewelry.

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Chapter 150

Serum Sickness

Anna Nowak-Węgrzyn and
Scott H. Sicherer

Serum sickness is a systemic, immune complex–mediated hypersensitivity vasculitis classically attributed to the therapeutic administration of foreign serum proteins or other medications (Table 150-1).

ETIOLOGY

Immune complexes involving heterologous (animal) serum proteins and complement activation are important pathogenic mechanisms in serum sickness. Antibody therapies derived from the horse or sheep are available for treatment of envenomation by the black widow spider and a variety of snakes, for treatment of botulism, and for immunosuppression (antithymocyte globulin). The availability of alternative medical therapies, modified or bioengineered antibodies, and biologics of human origin have supplanted the use of nonhuman antisera, reducing the risk of serum sickness. A *serum sickness–like reaction* may be attributed to drug allergy, triggered by antibiotics (particularly cefaclor). In contrast to a true serum sickness, serum sickness–like reactions do not exhibit the immune complexes, hypocomplementemia, vasculitis, and renal lesions that are seen in serum sickness reactions.

PATHOGENESIS

Serum sickness is a classic example of a type III hypersensitivity reaction caused by antigen–antibody complexes. In the rabbit model using bovine serum albumin as the antigen, symptoms develop with the appearance of antibody against the injected antigen. As free antigen concentration falls and antibody production increases over days, antigen–antibody complexes of various sizes develop in a manner analogous to a precipitin curve. Whereas small complexes usually circulate harmlessly and large complexes are cleared by the reticuloendothelial system, intermediate-sized complexes that develop at the point of slight antigen excess may deposit in blood vessel walls and tissues. There the immune microprecipitates induce vascular (leukocytoclastic vasculitis with immune complex deposition) and tissue damage through activation of complement and granulocytes.

Complement activation (C3a, C5a) promotes chemotaxis and adherence of neutrophils to the site of immune complex deposition. The processes of immune complex deposition and of neutrophil accumulation may be facilitated by increased vascular permeability, owing to the release of vasoactive amines from tissue mast cells. Mast cells may be activated by binding of antigen to immunoglobulin (Ig) E or through contact with anaphylatoxins (C3a). Tissue injury results from the liberation of proteolytic enzymes and oxygen radicals from the neutrophils.

CLINICAL MANIFESTATIONS

The symptoms of serum sickness generally begin 7-12 days after injection of the foreign material, but may appear as late as 3 wk afterward. The onset of symptoms may be accelerated if there has been earlier exposure or previous allergic reaction to the same antigen. A few days before the onset of generalized symptoms, the site of injection may become edematous and erythematous. Symptoms usually include fever, malaise, and rashes. Urticaria and morbilliform rashes are the predominant types of skin eruptions. In a prospective study of serum sickness induced by administration of equine antithymocyte globulin, an initial rash was noted in most patients. It began as a thin serpiginous band of erythema along the sides of the hands, fingers, feet, and toes at the junction of the palmar or plantar skin with the skin of the dorsolateral surface. In most patients, the band of erythema was replaced

Table 150-1	Proteins and Medications that Cause Serum Sickness*
PROTEINS FROM OTHER SPECIES	
Antithymocyte globulin	
Antitetanus toxoid	
Antivenin (Crotalidae) polyvalent (horse serum based)	
Crotalidae polyvalent immune Fab (ovine serum based)	
Antirabies globulin	
Infliximab	
Rituximab	
Etanercept	
Anti-HIV antibodies ([PE]HRG214)	
Hymenoptera stings	
Streptokinase	
DRUGS	
Antibiotics	
Cefaclor	
Penicillins	
Trimethoprim sulfate	
Minocycline	
Meropenem	
Neurologic	
Bupropion	
Carbamazepine	
Phenytoin	
Sulfonamides	
Barbiturates	

*Based on review of most current literature. Other medications that are not listed are also cited to cause serum sickness.

HIV, human immunodeficiency virus.

From Aceves SS, Serum Sickness IN Burg FD, Ingelfinger JR, Polin RA, Gershon AA, editors, Current Pediatric Therapy, *ed 18, Philadelphia, Elsevier, 2006, Chapter 20, Table 1, p. 1138.*

by petechiae or purpura, presumably because of low platelet counts or local damage to small blood vessels. Additional symptoms include edema, myalgia, lymphadenopathy, symmetric arthralgia or arthritis involving multiple joints, and gastrointestinal complaints, including pain, nausea, diarrhea, and melena. Symptoms typically resolve within 2 wk of removal of the offending agent, although in unusual cases, symptoms can persist for as long as 2-3 mo.

Carditis, glomerulonephritis, Guillain-Barré syndrome, and peripheral neuritis are rare complications. Serum sickness–like reactions from drugs are characterized by fever, pruritus, urticaria, and arthralgias that usually begin 1-3 wk after drug exposure. The urticarial skin eruption becomes increasingly erythematous as the reaction progresses and can evolve into dusky centers with round plaques.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of serum sickness and serum sickness-like reactions includes viral illnesses with exanthems, hypersensitivity vasculitis, Kawasaki disease, acute rheumatic fever, acute meningococcal or gonococcal infection, endocarditis, systemic onset juvenile idiopathic arthritis (Still disease), Lyme disease, hepatitis and other types of drug reactions (see Chapter 152).

DIAGNOSIS

In most cases, the diagnosis of serum sickness is made clinically based upon the characteristic pattern of acute or subacute onset of a rash, fever, and severe arthralgia and myalgia disproportionate to the degree of swelling, occurring after exposure to a potential culprit.

The patients who appear moderately or severely ill, or who are not taking a medication that can be readily identified as the culprit, should be evaluated with the following laboratory tests:

- Complete blood count and differential; thrombocytopenia is often present.
- Erythrocyte sedimentation rate and C-reactive protein; erythrocyte sedimentation rate is usually elevated.
- Urinalysis; mild proteinuria, hemoglobinuria, and microscopic hematuria may be seen.
- Serum chemistries, including blood urea nitrogen, creatinine, and liver function tests.
- Complement studies, including CH50, C3, and C4; serum complement levels (C3 and C4) are generally decreased and reach a nadir at about day 10. C3a anaphylatoxin may be increased.
- Testing for specific infectious diseases, if indicated by the history or physical examination.
- Appropriate viral or bacterial cultures if an infection is suspected.

Skin biopsies are not usually necessary for confirming the diagnosis, because the findings are variable and not specific for serum sickness. Direct immunofluorescence studies of skin lesions often reveal immune deposits of IgM, IgA, IgE, or C3.

TREATMENT

There are no evidence-based guidelines or controlled trials upon which to base therapy recommendations. Treatment is primarily supportive, consisting of discontinuation of the offending agent, antihistamines for pruritus, and nonsteroidal antiinflammatory agents and analgesics for low-grade fever and mild arthralgia. When the symptoms are especially severe, for example, fever >38.5°C (101.3°F), severe arthralgia or myalgia, or renal dysfunction, systemic corticosteroids can be used. Prednisone (1-2 mg/kg/day, max 60 mg/day) for 1-2 wk is usually sufficient. Once the offending agent is discontinued and depending on its half-life, symptoms resolve spontaneously in 1-4 wk. Symptoms lasting longer suggest another diagnosis.

PREVENTION

The primary mode of prevention of serum sickness is to seek alternative therapies. In some cases, non–animal-derived formulations may be available (human-derived botulinum immune globulin). Other alternatives are partially digested antibodies of animal origin and engineered (humanized) antibodies. The potential of these therapies to elicit serum sickness–like disease appears low. When only animal-derived antitoxin/antivenom is available, skin tests should be performed before administration of serum, but this procedure indicates the risk only of anaphylaxis, not of serum sickness. For patients who have evidence of anaphylactic sensitivity to horse serum, a risk-to-benefit assessment must be made to determine the need to proceed with treatment. If needed, the serum can usually be successfully administered by a process of rapid desensitization using protocols of gradual administration outlined by the manufacturers. Serum sickness is not prevented by desensitization or by pretreatment with corticosteroids.

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Chapter 151

Food Allergy and Adverse Reactions to Foods

Anna Nowak-Węgrzyn, Hugh A. Sampson, and Scott H. Sicherer

Adverse reactions to foods consist of any untoward reaction following the ingestion of a food or food additive and are classically divided into **food intolerances** (e.g., **lactose intolerance**), which are adverse physiologic responses, and **food allergies,** which are adverse immunologic responses and can be immunoglobulin (Ig) E-mediated or non–IgE-mediated (Tables 151-1 to 151-3). Like other atopic disorders, food allergies appear to have increased over the past 3 decades, primarily in countries with a Western lifestyle. Worldwide, estimates of food allergy prevalence range from 1-10%; in the United States, food allergies affect an estimated 3.5% of the U.S. population. Up to 6% of children experience food allergic reactions in the 1st 3 yr of life, including approximately 2.5% with cow's milk allergy, 1.5% with egg allergy, and 1% with peanut allergy. Peanut allergy prevalence tripled over the past decade. Most children "outgrow" milk and egg allergies, with approximately 50% doing so by school-age. In contrast, approximately 80-90% of children with peanut, nut, or seafood allergy retains their allergy for life.

PATHOGENESIS

Food intolerances are the result of a variety of mechanisms, whereas food allergy is predominantly caused by IgE-mediated and/or cell-mediated mechanisms. In susceptible individuals exposed to certain allergens, food-specific IgE antibodies are formed that bind to Fcε receptors on mast cells, basophils, macrophages, and dendritic cells. When food allergens penetrate mucosal barriers and reach cell-bound IgE antibodies, mediators are released that induce vasodilation, smooth muscle contraction, and mucus secretion, which result in symptoms of immediate hypersensitivity (allergy). Activated mast cells and macrophages may release several cytokines that attract and activate other cells, such as eosinophils and lymphocytes, leading to prolonged inflammation. Symptoms elicited during acute IgE-mediated reactions can affect the **skin** (urticaria, angioedema, flushing), **gastrointestinal tract** (oral pruritus, angioedema, nausea, abdominal pain, vomiting, diarrhea), **respiratory tract** (nasal congestion, rhinorrhea, nasal pruritus, sneezing, laryngeal edema, dyspnea, wheezing), and **cardiovascular system** (dysrhythmias, hypotension, loss of consciousness). In the other major form of food allergies, lymphocytes, primarily food allergen–specific T cells, secrete excessive amounts of various

Table 151-1	Adverse Food Reactions

FOOD INTOLERANCE (NON–IMMUNE SYSTEM-MEDIATED, NONTOXIC, NONINFECTIOUS)
Host factors
Enzyme deficiencies—lactase (primary or secondary), sucrase/isomaltase, hereditary fructose intolerance, galactosemia
Gastrointestinal disorders—inflammatory bowel disease, irritable bowel syndrome, pseudoobstruction, colic
Idiosyncratic reactions—caffeine in soft drinks ("hyperactivity")
Psychologic—food phobias, obsessive/compulsive disorder
Migraines (rare)
Food factors (toxic or infectious or pharmacologic)
Infectious organisms—*Escherichia coli, Staphylococcus aureus, Clostridium perfringens, Shigella*, botulism, *Salmonella, Yersinia, Campylobacter*
Toxins—histamine (scombroid poisoning), saxitoxin (shellfish)
Pharmacologic agents—caffeine, theobromine (chocolate, tea), tryptamine (tomatoes), tyramine (cheese), benzoic acid in citrus fruits (perioral flare)
Contaminants—heavy metals, pesticides, antibiotics

FOOD ALLERGY
IgE-mediated
Cutaneous—urticaria, angioedema, morbilliform rashes, flushing, contact urticarial
Gastrointestinal—oral allergy syndrome, gastrointestinal anaphylaxis
Respiratory—acute rhinoconjunctivitis, bronchospasm
Generalized—anaphylactic shock, exercise induced anaphylaxis
Mixed IgE- and non–IgE-mediated
Cutaneous—atopic dermatitis, contact dermatitis
Gastrointestinal—allergic eosinophilic esophagitis and gastroenteritis
Respiratory—asthma
Non–IgE-mediated
Cutaneous—contact dermatitis, dermatitis herpetiformis (celiac disease)
Gastrointestinal—food protein–induced enterocolitis, proctocolitis, and enteropathy syndromes, celiac disease, food protein induced enteropathy
Respiratory—food-induced pulmonary hemosiderosis (Heiner syndrome)
Unclassified

IgE, immunoglobulin E.

Table 151-2	Differential Diagnosis of Adverse Food Reactions

GASTROINTESTINAL DISORDERS (WITH VOMITING AND/OR DIARRHEA)
Structural abnormalities (pyloric stenosis, Hirschsprung disease, reflux)
Enzyme deficiencies (primary or secondary):
Disaccharidase deficiency—lactase, fructase, sucrase-isomaltase
Galactosemia
Malignancy with obstruction
Other: pancreatic insufficiency (cystic fibrosis), peptic disease

CONTAMINANTS AND ADDITIVES
Flavorings and preservatives—rarely cause symptoms:
Sodium metabisulfite, monosodium glutamate, nitrites
Dyes and colorings—very rarely cause symptoms (urticaria, eczema):
Tartrazine
Toxins:
Bacterial, fungal (aflatoxin), fish-related (scombroid, ciguatera)
Infectious organisms:
Bacteria (*Salmonella, Escherichia coli, Shigella*)
Virus (rotavirus, enterovirus)
Parasites (*Giardia, Akis simplex* [in fish])
Accidental contaminants:
Heavy metals, pesticides
Pharmacologic agents:
Caffeine, glycosidal alkaloid solanine (potato spuds), histamine (fish), serotonin (banana, tomato), tryptamine (tomato), tyramine (cheese)

PSYCHOLOGIC REACTIONS
Food phobias

Table 151-3 Natural History of Food Allergy and Cross-Reactivity Between Common Food Allergies

FOOD	USUAL AGE AT ONSET OF ALLERGY	CROSS REACTIVITY	USUAL AGE AT RESOLUTION
Hen's egg white	0-1 yr	Other avian eggs	7 yr (75% of cases resolve)*
Cow's milk	0-1 yr	Goat's milk, sheep's milk, buffalo milk	5 yr (76% of cases resolve)*
Peanuts	1-2 yr	Other legumes, peas, lentils; coreactivity with tree nuts	Persistent (20% of cases resolve)
Tree nuts	1-2 yr; in adults, onset occurs after cross reactivity to birch pollen	Other tree nuts; coreactivity with peanuts	Persistent (9% of cases resolve)
Fish	Late childhood and adulthood	Other fish (low cross-reactivity with tuna and swordfish)	Persistent†
Shellfish	Adulthood (in 60% of patients with this allergy)	Other shellfish	Persistent
Wheat*	6-24 mo	Other grains containing gluten (rye, barley)	5 yr (80% of cases resolve)
Soybeans*	6-24 mo	Other legumes	2 yr (67% of cases resolve)
Kiwi	Any age	Banana, avocado, latex	Unknown
Apples, carrots, and peaches§	Late childhood and adulthood	Birch pollen, other fruits, nuts	Unknown

*Recent studies suggest that resolution may occur at a later age, especially in children with multiple food allergies and lifetime peak food-specific IgE >50 kU_A/L.
†Fish allergy that is acquired in childhood can resolve.
§Allergy to fresh apples, carrots, and peaches (**oral allergy syndrome**) is commonly caused by heat-labile proteins. Fresh fruit causes oral pruritus, but cooked fruit is tolerated. There is generally no risk of anaphylaxis, although in rare cases, allergies to cross-reactive lipid transfer protein can cause anaphylaxis after ingestion of fruits (e.g., peach) and vegetables.
Modified from Lack G: Food allergy, N Engl J Med *359:1252–1260, 2008, Table 1.*

cytokines that lead to a "delayed," more chronic inflammatory process affecting the **skin** (pruritus, erythematous rash), **gastrointestinal tract** (failure to thrive, early satiety, abdominal pain, vomiting, diarrhea), or **respiratory tract** (food-induced pulmonary hemosiderosis). Mixed IgE and cellular responses to food allergens can also lead to chronic disorders such as atopic dermatitis, asthma, and allergic eosinophilic esophagitis and gastroenteritis.

Children in whom IgE-mediated food allergies develop may be sensitized by food allergens penetrating the gastrointestinal barrier, referred to as **class 1 food allergens,** or by food allergens that are partially homologous to plant pollens penetrating the respiratory tract, referred to as **class 2 food allergens.** Any food may serve as a class 1 food allergen, but **egg, milk, peanuts, tree nuts, fish, soy, and wheat** account for 90% of food allergies during childhood. Many of the major allergenic proteins of these foods have been characterized. There is variable but significant cross-reactivity with other proteins within an individual food group. Exposure and sensitization to these proteins often occur very early in life. Virtually all milk allergies develop by 12 mo of age and all egg allergies by 18 mo of age, and the median age of first peanut allergic reactions is 14 mo, Because allergic reactions to these high-risk allergens occur in infancy, it was once thought that avoidance of these foods and delayed introduction to the diet would prevent allergy. Indeed, the opposite is probably true and delayed introduction of these foods actually increases the risk of allergy. Current recommendations are to introduce egg, peanut products, fish, wheat, and other allergenic foods after 4-6 mo of exclusive breast feeding (Table 151-4).

Class 2 food allergens are typically vegetable, fruit or nut proteins that are partially homologous with pollen proteins (see Table 151-3). With the development of seasonal allergic rhinitis from birch, grass, or ragweed pollens, subsequent ingestion of certain uncooked fruits or vegetables provokes the **oral allergy syndrome.** Intermittent ingestion of allergenic foods may lead to acute symptoms such as urticaria or anaphylaxis, whereas prolonged exposure may lead to chronic disorders such as atopic dermatitis and asthma. Cell-mediated sensitivity typically develops to class 1allergens.

CLINICAL MANIFESTATIONS

From a clinical and diagnostic standpoint, it is most useful to subdivide food hypersensitivity disorders according to the predominant target organ (Table 151-5) and immune mechanism (see Table 151-1).

Gastrointestinal Manifestations

Gastrointestinal food allergies are often the first form of allergy to affect infants and young children and typically manifest as irritability, vomiting or "spitting-up," diarrhea, and poor weight gain. Cell-mediated hypersensitivities without IgE involvement predominate, making standard allergy tests such as prick skin tests and in vitro tests for food-specific IgE antibodies of little diagnostic value.

Food protein–induced enterocolitis syndrome (FPIES) typically manifests in the first several months of life as irritability, intermittent vomiting and protracted diarrhea, and may result in dehydration (Table 151-6). Vomiting generally occurs 1-3 hr after feeding, and continued exposure may result in abdominal distention, bloody diarrhea, anemia, and failure to thrive. Symptoms are most commonly provoked by cow's milk or soy protein–based formulas. A similar enterocolitis syndrome occurs in older infants and children from rice, oat, wheat, egg, peanut, nut, chicken, turkey, or fish. Hypotension occurs in approximately 15% of cases after allergen ingestion and may initially be thought to be caused by sepsis. FPIES usually resolves by age 3 yr.

Food protein-induced proctocolitis presents in the first few mo of life as blood-streaked stools in otherwise healthy infants (see Table 151-6). Approximately 60% of cases occur among breastfed infants, with the remainder largely among infants fed cow's milk or soy

Table 151-4 Prevention of Food Allergy

Exclusive breast feeding for 4-6 mo
Introduce solid (complementary) foods after 4-6 mo of exclusive breast feeding
Introduce low-risk complementary foods 1 at a time
Introduce potentially highly allergenic foods (fish, eggs, peanut products, milk, wheat) soon after the lower-risk foods (no need to avoid or delay)
Don't avoid allergenic foods during pregnancy or nursing
Soy-based formulas do not prevent allergic disease

Table 151-5 Symptoms of Food-Induced Allergic Reactions

TARGET ORGAN	IMMEDIATE SYMPTOMS	DELAYED SYMPTOMS
Cutaneous	Erythema Pruritus Urticaria Morbilliform eruption Angioedema	Erythema Flushing Pruritus Morbilliform eruption Angioedema Eczematous rash
Ocular	Pruritus Conjunctival erythema Tearing Periorbital edema	Pruritus Conjunctival erythema Tearing Periorbital edema
Upper respiratory	Nasal congestion Pruritus Rhinorrhea Sneezing Laryngeal edema Hoarseness Dry staccato cough	
Lower respiratory	Cough Chest tightness Dyspnea Wheezing Intercostal retractions Accessory muscle use	Cough, dyspnea, and wheezing
GI (oral)	Angioedema of the lips, tongue, or palate Oral pruritus Tongue swelling	
GI (lower)	Nausea Colicky abdominal pain Reflux Vomiting Diarrhea	Nausea Abdominal pain Reflux Vomiting Diarrhea Hematochezia Irritability and food refusal with weight loss (young children)
Cardiovascular	Tachycardia (occasionally bradycardia in anaphylaxis) Hypotension Dizziness Fainting Loss of consciousness	
Miscellaneous	Uterine contractions Sense of "impending doom"	

Note: This table is presented as Table IV in the Guidelines.
GI, gastrointestinal.
From Boyce JA, Assa'ad A, Burks AW, et al: Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel, J Allergy Clin Immunol *126(6):S1–S58, 2010 (Table IV, p. S19).*

Table 151-6 Food Protein-Induced Gastrointestinal Syndromes

	FPIES	PROCTOCOLITIS	ENTEROPATHY	EOSINOPHILIC GASTROENTEROPATHIES*
Age at onset	1 day–1 year	1 day–6 months	Dependent of age of exposure to antigen, cow's milk and soy up to 2 yr	Infant to adolescent
Food proteins implicated				
Most common	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy, egg white, wheat, peanut
Less common	Rice, chicken, turkey, fish, pea	Egg, corn, chocolate	Wheat, egg	Meats, corn, rice, fruits, vegetables, fish
Multiple food hypersensitivities	>50% both cow's milk and soy	40% both cow's milk and soy	Rare	Common
Feeding at the time of onset	Formula	>50% exclusive breast feeding	Formula	Formula
Atopic background				
Family history of atopy	40-70%	25%	Unknown	~50% (often history of eosinophilic esophagitis)
Personal history of atopy	30%	22%	22%	~50%
Symptoms				
Emesis	Prominent	No	Intermittent	Intermittent
Diarrhea	Severe	No	Moderate	Moderate
Bloody stools	Severe	Moderate	Rare	Moderate
Edema	Acute, severe	No	Moderate	Moderate
Shock	15%	No	No	No
Failure to thrive	Moderate	No	Moderate	Moderate
Laboratory findings				
Anemia	Moderate	Mild	Moderate	Mild-moderate
Hypoalbuminemia	Acute	Rare	Moderate	Mild-severe
Methemoglobinemia	May be present	No	No	No
Allergy evaluation				
Food prick skin test	Negative[†]	Negative	Negative	Positive in ~50%
Serum food allergen IgE	Negative[†]	Negative	Negative	Positive in ~50%
Total IgE	Normal	Negative	Normal	Normal to elevated
Peripheral blood eosinophilia	No	Occasional	No	Present in <50%
Biopsy findings				
Colitis	Prominent	Focal	No	May be present
Lymph nodular hyperplasia	No	Common	No	Yes
Eosinophils	Prominent	Prominent	Few	Prominent; also neutrophilic infiltrates, papillary elongation and basal zone hyperplasia
Food challenge	Vomiting in 2-4 hr; diarrhea in 5-8 hr	Rectal bleeding in 6-72 hr	Vomiting, diarrhea, or both in 40-72 hr	Vomiting and diarrhea in hours to days
Treatment	Protein elimination, 80% respond to casein hydrolysate and symptoms clear in 3-10 days; rechallenge in 1.5-2 yr	Protein elimination, symptoms clear in 3 days with casein hydrolysate, resume/continue breastfeeding on maternal antigen-restricted diet	Protein elimination, symptoms clear in 1-3 wk, rechallenge and biopsy in 1-2 yr	Protein elimination, good response to casein hydrolysate, excellent response to elemental diet, symptoms clear within 2-3 wk, excellent acute response to steroids; rechallenge and biopsy in 1-2 yr
Natural history	Cow's milk: 60% resolved by 2 yr Soy: 25% resolved by 2 yr	Resolved by 9-12 months	Most cases resolve in 2-3 yr	Typically a prolonged, relapsing course
Reintroduction of the food	Inpatient food challenge	At home, gradually advancing from 1 oz to full feedings over 2 weeks	Home, gradually advancing	Home, gradually advancing

*Eosinophilic gastroenteropathies encompass esophagitis, gastritis, gastroenterocolitis.
[†]If positive, may be a risk factor for persistent disease.
FPIES, food protein-induced enterocolitis syndrome.
From Nowak-Wegrzyn A, Muraro A: Food protein-induced enterocolitis syndrome. Curr Opin Allergy Immunol *9:371-377, 2009 (Table 1, p. 372).*

protein–based formula. Blood loss is typically modest, but can occasionally produce anemia.

Food protein–induced enteropathy often manifests in the first several months of life as diarrhea, often with steatorrhea and poor weight gain (see Table 151-6). Symptoms include protracted diarrhea, vomiting in up to 65% of cases, failure to thrive, abdominal distention, early satiety, and malabsorption. Anemia, edema, and hypoproteinemia occur occasionally. **Cow's milk sensitivity** is the most common cause of this food protein–induced enteropathy in young infants, but it has also been associated with sensitivity to soy, egg, wheat, rice, chicken, and fish in older children. **Celiac disease,** the most severe form of protein-induced enteropathy, occurs in about 1 : 100 of the U.S. population, although it may be "silent" in many patients (see Chapter 338.2). The full-blown form is characterized by extensive loss of absorptive villi and hyperplasia of the crypts, leading to malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence, and weight loss or failure to thrive. Oral ulcers and other extraintestinal symptoms secondary to malabsorption may occur. Genetically susceptible individuals (HLA-DQ2 or HLA-DQ8) demonstrate a cell-mediated response to tissue transglutaminase deamidated gliadin (a fraction of gluten), which is found in wheat, rye, and barley.

Eosinophilic esophagitis (EoE) may appear from infancy through adolescence, more frequently in boys (see Chapter 324). In young children, it is primarily cell mediated and manifests as chronic gastroesophageal reflux, intermittent emesis, food refusal, abdominal pain, dysphagia, irritability, sleep disturbance, and failure to respond to conventional reflux medications. EoE is a clinicopathologic diagnosis. The diagnosis is confirmed when 15 eosinophils per high-power field are seen on esophageal biopsy during treatment with proton pump inhibitors. **Eosinophilic gastroenteritis** occurs at any age and causes symptoms similar to those of EoE as well as prominent weight loss or failure to thrive, both of which are the hallmarks of this disorder. More than 50% of patients with this disorder are atopic, however food-induced IgE-mediated reactions have been implicated only in a minority of patients. Generalized edema secondary to hypoalbuminemia may occur in some infants with marked protein-losing enteropathy.

Oral allergy syndrome (pollen-associated food allergy syndrome) is an IgE-mediated hypersensitivity that occurs in many older children with birch and ragweed pollen-induced allergic rhinitis. Symptoms are usually confined to the oropharynx and consist of the rapid onset of oral pruritus, tingling and angioedema of the lips, tongue, palate, and throat, and occasionally a sensation of pruritus in the ears and tightness in the throat. Symptoms are generally short lived and are caused by local mast cell activation following contact with fresh fruit and vegetable proteins that cross-react with birch pollen (apple, carrot, potato, celery, hazel nuts, kiwi, cherry, pear), grass pollen (potato, tomato, watermelon, kiwi), and ragweed pollen (banana, melons such as watermelon and cantaloupe).

Acute gastrointestinal allergy generally manifests as acute abdominal pain and vomiting that accompany IgE-mediated allergic symptoms in other target organs.

Skin Manifestations

Cutaneous food allergies are also common in infants and young children.

Atopic dermatitis is a form of eczema that generally begins in early infancy and is characterized by pruritus, a chronically relapsing course, and association with asthma and allergic rhinitis (see Chapter 145. Although not often apparent from history, at least 30% of children with moderate to severe atopic dermatitis have food allergies. The younger the child and the more severe the eczema, the more likely food allergy is playing a pathogenic role in the disorder.

Acute urticaria and angioedema are among the most common symptoms of food allergic reactions (see Chapter 148). The onset of symptoms may be very rapid, within minutes after ingestion of the responsible allergen. Symptoms result from activation of IgE-bearing mast cells by food allergens that are absorbed and circulated rapidly throughout the body. Foods most commonly incriminated in children include egg, milk, peanuts, and nuts, although reactions to various seeds (sesame, poppy) and fruits (kiwi) are becoming more common. Chronic urticaria and angioedema are rarely caused by food allergies.

Perioral dermatitis is often a contact dermatitis caused by substances in toothpaste, gums, lipstick, to medications. **Perioral flushing** is often noted in infants fed citrus fruits and may be caused by benzoic acid in the food. It may also occur during nursing. In both situations, it is benign. Flushing may also be caused by auriculotemporal nerve (Frey) syndrome (familial, forceps delivery), which resolves spontaneously.

Respiratory Manifestations

Respiratory food allergies are uncommon as isolated symptoms. Although many parents believe that nasal congestion in infants is often caused by milk allergy, studies show this not to be the case. **Food-induced rhinoconjunctivitis** symptoms typically accompany allergic symptoms in other target organs, such as skin, and consist of typical allergic rhinitis symptoms (periocular pruritus and tearing, nasal congestion and pruritus, sneezing, rhinorrhea). Wheezing occurs in approximately 25% of IgE-mediated food allergic reactions, but only approximately 10% of asthmatic patients have food-induced respiratory symptoms.

Anaphylaxis

Anaphylaxis is defined as a serious, multisystem allergic reaction that is rapid in onset and potentially fatal. Food allergic reactions are the single most common cause of anaphylaxis seen in hospital emergency departments in the United States. In addition to the rapid onset of cutaneous, respiratory, and gastrointestinal symptoms, patients may demonstrate cardiovascular symptoms, including hypotension, vascular collapse, and cardiac dysrhythmias, which are presumably caused by massive mast cell–mediator release. **Food-associated exercise-induced anaphylaxis** occurs more frequently among teenage athletes, especially females (see Chapter 149).

DIAGNOSIS

A thorough medical history is necessary to determine whether a patient's symptomatology represents an adverse reaction (see Table 151-2), whether the adverse food reaction is an intolerance or food allergic reaction, and if the latter, whether it is likely to be an IgE-mediated or a cell-mediated response (Fig. 151-1). The following facts should be established: (1) the food suspected of provoking the reaction and the quantity ingested, (2) the interval between ingestion and the development of symptoms, (3) the types of symptoms elicited by the ingestion, (4) whether ingesting the suspected food produced similar symptoms on other occasions, (5) whether other inciting factors, such as exercise, are necessary, and (6) the interval from the last reaction to the food.

Prick skin tests and in vitro laboratory tests are useful for demonstrating IgE sensitization, defined as presence of food-specific IgE antibodies. Many fruits and vegetables require prick-prick skin testing with fresh produce because labile proteins are destroyed during commercial preparation. A negative skin test result virtually excludes an IgE-mediated form of food allergy. Conversely, the majority of children with positive skin test responses to a food do not react when the food is ingested, so more definitive tests, such as quantitative IgE tests or food elimination and challenge, are often necessary to establish a diagnosis of food allergy. Serum food-specific IgE levels ≥15 kU_A/L for milk (≥5 kU_A/L for children ≤1 yr), ≥7 kU_A/L for egg (≥2 kU_A/L for children <2 yr), and ≥14 kU_A/L for peanut are associated with a >95% likelihood of clinical reactivity to these foods in children with suspected reactivity. In the absence of a clear history of reactivity to a food and evidence of food-specific IgE antibodies, definitive studies must be performed before recommendations are made for avoidance or the use of highly restrictive diets that may be nutritionally deficient, logistically impractical, disruptive to the family, expensive, and a potential source of future feeding disorders. IgE-mediated food allergic reactions are generally very food specific, so the use of broad exclusionary diets, such as avoidance of all legumes, cereal grains, or animal products, is not warranted (Tables 151-3 and 151-7).

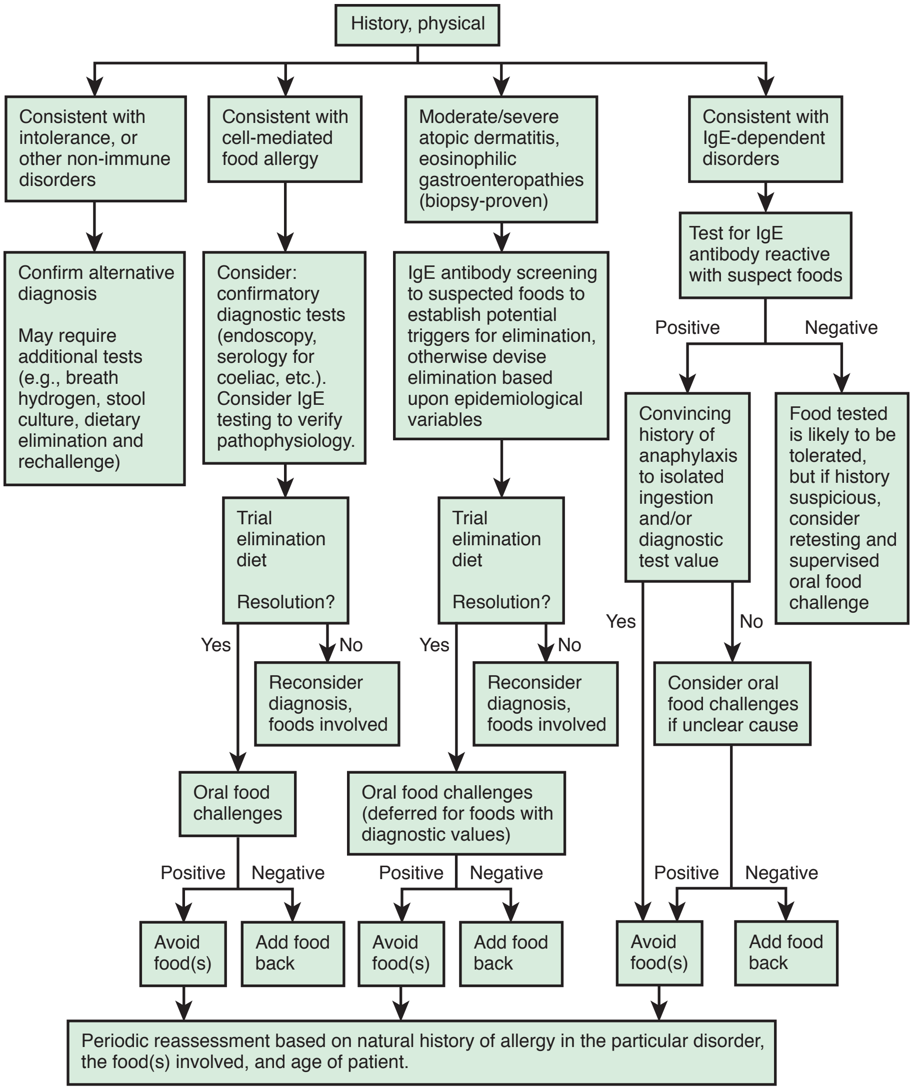

Figure 151-1 General scheme for diagnosis of food allergy. *(From Sicherer SH: Food allergy,* Lancet *360:701–710, 2002.)*

Table 151-7 Clinical Implications of Cross-Reactive Proteins in IgE-Mediated Allergy

FOOD FAMILY	RISK OF ALLERGY TO ≥1 MEMBER (%; APPROXIMATE)	FEATURE(S)
Legumes	5	Main causes of reactions are peanut, soybean, lentil, lupine, and garbanzo (chickpea)
Tree nuts (e.g., almond, cashew, hazelnut, walnut, brazil)	35	Reactions are often severe
Fish	50	Reactions can be severe
Shellfish	75	Reactions can be severe
Grains	20	
Mammalian milks	90	Cow's milk is highly cross reactive with goat's or sheep's milk (92%) but not with mare's milk (4%)
Rosaceae (pitted fruits)	55	Risk of reactions to more than three related foods is very low (<10%), symptoms are usually mild (oral allergy syndrome)
Latex-food	35	For individuals allergic to latex, banana, kiwi, fig, chestnut, and avocado are the main causes of reactions
Food-latex	11	Individuals allergic to banana, kiwi, fig, chestnut, and avocado may be at an increased risk of reactions to latex

Modified from Sicherer SH: Food allergy, Lancet *360:701–710, 2002.*

Table 151-8 ACIP and AAP Red Book Recommendations for Administering Vaccines to Patients with Egg Allergy

VACCINE	ACIP	AAP RED BOOK
MMR/MMRV	May be used	May be used
Influenza	Receive with some precautions*	Receive with some precautions*
Rabies	Use caution	No specific recommendation
Yellow fever	Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI)	Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI)

AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices.

From Boyce JA, Assa'ad A, Burks AW, et al: Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel, J Allergy Clin Immunol *126(6):S1–S58, 2010 (Table V, p S31).*

*In 2012, recommendations changed to suggest those with mild egg allergy receive the inactivated influenza vaccine in the primary care setting with a 30 minute observation and preparedness to treat anaphylaxis. Those with severe egg allergy are referred to an allergist.

There are no laboratory studies to help identify foods responsible for cell-mediated reactions. Consequently, **elimination diets followed by food challenges** are the only way to establish the diagnosis. Allergists experienced in dealing with food allergic reactions and able to treat anaphylaxis should perform food challenges. Before a food challenge is initiated, the suspected food should be eliminated from the diet for 10-14 days for IgE-mediated food allergy and up to 8 wk for some cell-mediated disorders, such as EoE. Some children with cell-mediated reactions to cow's milk do not tolerate hydrolysate formulas and must receive amino acid–derived formulas. If symptoms remain unchanged despite appropriate elimination diets, it is unlikely that food allergy is responsible for the child's disorder.

TREATMENT

Appropriate identification and elimination of foods responsible for food hypersensitivity reactions are the only validated treatments for food allergies. Complete elimination of common foods (milk, egg, soy, wheat, rice, chicken, fish, peanut, nuts) is very difficult because of their widespread use in a variety of processed foods. The lay organization Food Allergy Research and Education (FARE, www.foodallergy.org) provides excellent information to help parents deal with both the practical and emotional issues surrounding these diets. Validated educational materials are also available through the Consortium of Food Allergy Research (www.cofargroup.org). Children with asthma and IgE-mediated food allergy, peanut or nut allergy, or a history of a previous severe reaction should be given self-injectable epinephrine and a written emergency plan in case of accidental ingestion (see Chapter 149). Because many food allergies are outgrown, children should be reevaluated periodically by an allergist to determine whether they have lost their clinical reactivity. A number of clinical trials are beginning to evaluate the efficacy of oral, sublingual, and epicutaneous (patch) immunotherapy for the treatment of IgE-mediated food allergies (milk, egg, peanut). Combining oral immunotherapy with anti-IgE treatment (omalizumab) may be even more effective than oral immunotherapy alone. Furthermore, extensively heated milk or egg in baked products are tolerated by the majority of milk and egg allergic children. Regular ingestion of baked products with milk and egg appears to accelerate resolution of milk and egg allergy. Management of egg-allergic children who require immunizations is noted in Table 151-8.

PREVENTION

There is no consensus as to whether food allergies can be prevented. At present there is insufficient evidence to support the practice of restricting the maternal diet during pregnancy or breastfeeding or of delaying introduction of various allergenic foods to infants from atopic families (see Table 151-4). Exclusive breastfeeding for the first 4-6 mo of life may reduce allergic disorders in the first few years of life in infants at high risk for development of allergic disease. Potentially allergenic foods (eggs, milk, wheat, soy, peanut and tree nut products, fish) should be introduced after this period of exclusive breastfeeding and may prevent the development of allergies later in life. Use of partially hydrolyzed whey formulas may be beneficial if breast feeding cannot be continued for 4-6 mo or after weaning, especially to prevent eczema in high risk families, but his approach remains controversial. Probiotic supplements may also reduce the incidence and severity of eczema. Because some *skin preparations* contain peanut oil, which may sensitize young infants, especially those with cutaneous inflammation, such preparations should be avoided.

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Chapter 152

Adverse Reactions to Drugs

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Adverse drug reactions can be divided into predictable (type A) and unpredictable reactions (type B). **Predictable drug reactions,** including drug toxicity, drug interactions, and adverse effects, are dose dependent, can be related to known pharmacologic actions of the drug, and occur in patients without any unique susceptibility. **Unpredictable drug reactions** are dose independent, often are not related to the pharmacologic actions of the drug, and occur in patients who are genetically predisposed. These include idiosyncratic reactions, allergic (hypersensitivity) reactions, and pseudoallergic reactions. Allergic reactions require prior sensitization, manifest as signs or symptoms characteristic of an underlying allergic mechanism such as anaphylaxis or urticaria, and occur in genetically susceptible individuals. They can occur at doses significantly below the therapeutic range. **Pseudoallergic reactions** resemble allergic reactions but are caused by non–immunoglobulin (Ig) E-mediated release of mediators from mast cells and basophils. Drug-independent cross-reactive antigens can induce sensitization manifesting as drug allergy. Patients with cetuximab-induced anaphylaxis have IgE antibodies in pretreatment samples specific for galactose-α-1,3-galactose. Galactose-α-1,3-galactose is present on the antigen-binding portion of the cetuximab heavy chain and is similar to structures in the ABO blood group.

Table 152-1 Heterogeneity of Drug-Induced Allergic Reactions

ORGAN-SPECIFIC REACTIONS	CLINICAL FEATURES	EXAMPLES OF CAUSATIVE AGENTS
CUTANEOUS		
Exanthems	Diffuse fine macules and papules evolve over days after drug initiation Delayed-type hypersensitivity	Allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, and antibacterial sulfonamides
Urticaria, angioedema	Onset within minutes of drug initiation Potential for anaphylaxis Often IgE mediated	IgE mediated: β-lactam antibiotics Bradykinin mediated: ACEI
Fixed drug eruption	Hyperpigmented plaques Recur at same skin or mucosal site	Tetracycline, NSAIDs, and carbamazepine
Pustules	Acneiform Acute generalized eczematous pustulosis (AGEP)	Acneiform: corticosteroids, sirolimus AGEP: antibiotics, calcium-channel blockers
Bullous	Tense blisters Flaccid blisters	Furosemide, vancomycin Captopril, penicillamine
SJS	Fever, erosive stomatitis, ocular involvement, purpuric macules on face and trunk with <10% epidermal detachment	Antibacterial sulfonamides, anticonvulsants, oxicam NSAIDs, and allopurinol
TEN	Similar features as SJS but >30% epidermal detachment Mortality as high as 50%	Same as SJS
Cutaneous lupus	Erythematous/scaly plaques in photodistribution	Hydrochlorothiazide, calcium-channel blockers, ACEIs
Hematologic	Hemolytic anemia, thrombocytopenia, granulocytopenia	Penicillin, quinine, sulfonamides
Hepatic	Hepatitis, cholestatic jaundice	Para-aminosalicylic acid, sulfonamides, phenothiazines
Pulmonary	Pneumonitis, fibrosis	Nitrofurantoin, bleomycin, methotrexate
Renal	Interstitial nephritis, membranous glomerulonephritis	Penicillin, sulfonamides, gold, penicillamine, allopurinol
MULTIORGAN REACTIONS		
Anaphylaxis	Urticaria/angioedema, bronchospasm, gastrointestinal symptoms, hypotension IgE- and non–IgE-dependent reactions	β-Lactam antibiotics, monoclonal antibodies
DRESS	Cutaneous eruption, fever, eosinophilia, hepatic dysfunction, lymphadenopathy	Anticonvulsants, sulfonamides, minocycline, allopurinol
Serum sickness	Urticaria, arthralgias, fever	Heterologous antibodies, infliximab
Systemic lupus erythematosus	Arthralgias, myalgias, fever, malaise	Hydralazine, procainamide, isoniazid
Vasculitis	Cutaneous or visceral vasculitis	Hydralazine, penicillamine, propylthiouracil

ACEI, angiotensin-converting enzyme inhibitor; DRESS, drug rash with eosinophilia and systemic symptoms; NSAID, nonsteroidal antiinflammatory drug (NSAID); SJS, Stevens-Johnson syndrome.

From Khan DA, Solensky R: Drug allergy, J Allergy Clin Immunol *125:S126–S137, 2010 (Table 1, p. S127).*

EPIDEMIOLOGY

The incidence of adverse drug reactions in the general as well as pediatric populations remains unknown, although data from hospitalized patients show it to be 6.7%, with a 0.32% incidence of fatal adverse drug reactions. Databases such as the FDA MedWatch program (http://www.fda.gov/medwatch/index.html) likely suffer from underreporting. Cutaneous reactions are the most common form of adverse drug reactions, with ampicillin, amoxicillin, penicillin, and trimethoprim-sulfamethoxazole being the most commonly implicated drugs (Tables 152-1 and 152-2). Although the majority of adverse drug reactions do not appear to be allergic in nature, 6-10% can be attributed to an allergic or immunologic mechanism. Importantly, given the high probability of recurrence of allergic reactions, these reactions should be preventable, and information technology–based interventions may be especially useful to reduce risk of reexposure.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Immunologically mediated adverse drug reactions have been classified according to the **Gell and Coombs classification:** immediate hypersensitivity reactions (type I), cytotoxic antibody reactions (type II), immune complex reactions (type III), and delayed-type hypersensitivity reactions (type IV). Immediate hypersensitivity reactions occur when a drug or drug metabolite interacts with preformed drug-specific IgE antibodies that are bound to the surfaces of tissue mast cells and/or circulating basophils. The cross-linking of adjacent receptor-bound IgE by antigen causes the release of preformed and newly synthesized mediators, such as histamine and leukotrienes, that contribute to the clinical development of urticaria, bronchospasm, or anaphylaxis. Cytotoxic reactions involve IgG or IgM antibodies that recognize drug antigen on the cell membrane. In the presence of serum complement, the antibody-coated cell is either cleared by the monocyte–macrophage system or is destroyed. Examples are drug-induced hemolytic anemia and thrombocytopenia. Immune complex reactions are caused by soluble complexes of drug or metabolite in slight antigen excess with IgG or IgM antibodies. The immune complex is deposited in blood vessel walls and causes injury by activating the complement cascade, as seen in serum sickness. Clinical manifestations include fever, urticaria, rash, lymphadenopathy, and arthralgias. Symptoms typically appear 1-3 wk after the last dose of an offending drug and subside when the drug and/or its metabolite is cleared from the body. Delayed-type hypersensitivity reactions are mediated by drug-specific T lymphocytes. Sensitization usually occurs via the topical route of administration, resulting in allergic contact dermatitis. Commonly implicated drugs include neomycin and local anesthetics in topical formulations.

Certain adverse drug reactions, including drug fever and the morbilliform rash seen with use of ampicillin or amoxicillin in the setting of Epstein-Barr virus infection, are not easily classified. Studies point to the role of T cells and eosinophils in delayed maculopapular reactions to a number of antibiotics. The mechanisms of T-cell–mediated drug hypersensitivity are not well understood. A novel hypothesis, the p-i concept, suggests pharmacologic interactions of drugs with immune receptors as another class of drug hypersensitivity. In T-cell–mediated

Table 152-2 Serious Non–IgE-Mediated Drug Eruptions

DIAGNOSIS	MUCOSAL LESIONS	TYPICAL SKIN LESIONS	PRODROMAL SIGNS AND SYMPTOMS	DRUG ASSOCIATED (%)	DRUGS MOST OFTEN IMPLICATED	TYPICAL TIME TO ONSET (wk)	ALTERNATIVE CAUSES NOT RELATED TO DRUGS
Drug hypersensitivity syndrome (DHS) or drug rash with eosinophilia and systemic symptoms (DRESS) syndrome	Infrequent	Severe exanthematous rash (could become edematous, pustular, purpuric), exfoliative dermatitis	30-50% involve fever, lymphadenopathy, hepatitis, nephritis, carditis, eosinophilia, atypical lymphocytes	≥90	Phenytoin, carbamazepine, phenobarbital, sulfonamides, allopurinol, minocycline, nitrofurantoin, terbinafine, vancomycin, dapsone, abacavir, nevirapine, nonsteroidal antiinflammatory drugs (NSAIDs)	1-6	Cutaneous lymphoma
Stevens-Johnson syndrome (SJS)	Erosions at ≥2 sites	Crops of lesions on skin, conjunctivae, mouth, and genitalia; detachment of ≤10% of body surface area	High fever, sore throat, rhinorrhea, cough	48-64	Sulfonamides, phenytoin, carbamazepine, barbiturates, allopurinol, aminopenicillins, NSAIDs	1-3	
Toxic epidermal necrolysis (TEN)	Erosions at ≥2 sites	Lesions similar to those with SJS; confluent epidermis separates readily with lateral pressure; detachment of ≥30% of body surface area	Fever, headache, sore throat; nearly all cases involve fever, "acute skin failure," leukopenia, lesions of the respiratory and/or gastrointestinal tracts	43-65	Sulfonamides, phenytoin, carbamazepine, barbiturates, allopurinol, aminopenicillins, NSAIDs	1-3	Exanthematous stage of Kawasaki disease; staphylococcal scalded-skin syndrome

Revised from Segal AR, Doherty KM, Leggott J, et al: Cutaneous reactions to drugs in children, Pediatrics *120:e1082–e1096, 2007.*

allergic drug reactions, the specificity of the T-cell receptor that is stimulated by the drug may be directed to a cross-reactive major histocompatibility complex–peptide compound. This information suggests that even poorly reactive native drugs are capable of transmitting a stimulatory signal via the T-cell receptor, which activates T cells and results in proliferation, cytokine production, and cytotoxicity. Previous contact with the causative drug is not obligatory, and an immune mechanism should be considered as the cause of hypersensitivity, even in reactions that occur with first exposure. Such reactions have been described for radiocontrast media and neuromuscular blocking agents.

Drug Metabolism and Adverse Reactions

Most drugs and their metabolites are not immunologically detectable until they have become covalently attached to a macromolecule. This multivalent hapten–protein complex forms a new immunogenic epitope that can elicit T- and B-lymphocyte responses. The penicillins and related β-lactam antibiotics are highly reactive with proteins and can directly haptenate protein carriers, possibly accounting for the frequency of immune-mediated hypersensitivity reactions with this class of antibiotics.

Incomplete or delayed metabolism of some drugs can give rise to toxic metabolites. Hydroxylamine, a reactive metabolite produced by cytochrome P450 oxidative metabolism, may mediate adverse reactions to sulfonamides. Patients who are slow acetylators appear to be at increased risk (see Chapter 59). In addition, cutaneous reactions in patients with AIDS treated with trimethoprim-sulfamethoxazole, rifampin, or other drugs may be a result of glutathione deficiency resulting in toxic metabolites. Serum sickness–like reactions in which immune complexes have not been documented, which occur most commonly with cefaclor, may result from an inherited propensity for hepatic biotransformation of drugs into toxic or immunogenic metabolites.

Risk Factors for Hypersensitivity Reactions

Risk factors for adverse drug reactions include prior exposure, previous reactions, age (20-49 yr), route of administration (parenteral or topical), dose (high), and dosing schedule (intermittent), as well as genetic predisposition (slow acetylators). Atopy does not appear to predispose patients to allergic reactions to low-molecular-weight compounds, but atopic patients in whom an allergic reaction develops have a significantly increased risk of serious reaction. Atopic patients also appear to be at greater risk for pseudoallergic reactions induced by radiocontrast media. Pharmacogenomics has an important role in identifying individuals at risk for certain drug reactions (see Chapter 59).

DIAGNOSIS

An accurate medical history is an important first step in evaluating a patient with a possible adverse drug reaction. Suspected drugs need to be identified along with dosages, route of administration, previous exposures, and dates of administration. In addition, underlying hepatic or renal disease may influence drug metabolism. A detailed description of past reactions may yield clues to the nature of the adverse drug reaction. The propensity for a particular drug to cause the suspected reaction can be checked with information in *Physicians' Desk Reference, Drug Eruption Reference Manual,* or directly from the drug manufacturer. It is important to remember, however, that the history may be unreliable, and many patients are inappropriately labeled as being drug allergic. This label can result in inappropriate withholding of a needed drug or class of drugs. In addition, relying solely on the history can lead to overuse of drugs reserved for special indications, such as vancomycin in patients in whom penicillin allergy is suspected. Approximately 90% of patients with a clinical history of penicillin allergy do not have evidence of penicillin-specific IgE antibodies on testing.

Skin testing is the most rapid and sensitive method of demonstrating the presence of *IgE antibodies* to a specific allergen. It can be performed with high-molecular-weight compounds, such as foreign antisera, hormones, enzymes, and toxoids. Reliable skin testing can also be performed with penicillin, but not with most other antibiotics. Most immunologically mediated adverse drug reactions are caused by metabolites rather than by parent compounds, and the metabolites for most drugs other than penicillin have not been defined. In addition, many metabolites are unstable or must combine with larger proteins to be useful for diagnosis. Testing with nonstandardized reagents requires caution in interpretation of both positive and negative results, because some drugs can induce nonspecific irritant reactions. Whereas a wheal-and-flare reaction is suggestive of drug-specific IgE antibodies, a negative skin test result does not exclude the presence of such antibodies because the relevant immunogen may not have been used as the testing reagent.

A positive skin test response to the major or minor determinants of penicillin has a 60% positive predictive value for an immediate hypersensitivity reaction to penicillin. In patients in whom skin test responses to the major and minor determinants of penicillin are negative, 97-99% (depending on the reagents used) tolerate the drug without an immediate reaction. At present, the major determinant of penicillin testing reagent PrePen (benzylpenicilloyl-polylysine) in the United States is available, but the minor determinant mixture has not been approved by the FDA as a testing reagent. Limited studies utilizing serum tests for IgE to β-lactams suggest high specificity (97-100%) but low sensitivity (29-68%). The positive and negative predictive values of skin testing for antibiotics other than penicillin are not well established. Nevertheless, positive immediate hypersensitivity skin test responses to nonirritant concentrations of nonpenicillin antibiotics may be interpreted as a presumptive risk of an immediate reaction to such agents.

Results of direct and indirect Coombs tests are often positive in drug-induced hemolytic anemia. Assays for specific IgG and IgM have been shown to correlate with a drug reaction in immune cytopenia, but, in most other reactions, such assays are not diagnostic. In general, many more patients express humoral or T-cell immune responses to drug determinants than express clinical disease. Serum tryptase is elevated with systemic mast cell degranulation and can be seen with drug-associated mast cell activation, although it is not pathognomonic for drug hypersensitivity, and nonelevated tryptase values can be seen in well-defined anaphylaxis.

TREATMENT

Specific **desensitization,** *which involves the progressive administration of an allergen to render effector cells less reactive, is reserved for patients with IgE antibodies to a particular drug for whom an alternative drug is not available or appropriate.* Specific protocols for many different drugs have been developed. Desensitization should be performed in a hospital setting, usually in consultation with an allergist and with resuscitation equipment available at all times. Although mild complications, such as pruritus and rash, are fairly common and often respond to adjustments in the drug dose or dosing intervals and medications to relieve symptoms, more severe systemic reactions can occur. Oral desensitization may be less likely to induce anaphylaxis than parenteral administration. Pretreatment with antihistamines or corticosteroids is not usually recommended. It is important to recognize that desensitization to a drug is effective only while the drug continues to be administered and that after a period of interruption or discontinuation, hypersensitivity can recur.

Graded challenges based on the administration of a drug in an incremental fashion until a therapeutic dose is achieved can be attempted with drugs causing non–IgE-mediated reactions, including trimethoprim-sulfamethoxazole. Graded challenges in aspirin- or nonsteroidal antiinflammatory drug (NSAID)–intolerant patients, particularly those with respiratory reactions, can also be performed. Patients with severe non–IgE-mediated hypersensitivity reactions should not receive the predisposing agents even in the small amounts used for skin testing (see Table 152-2).

β-Lactam Hypersensitivity

Penicillin is a frequent cause of anaphylaxis and is responsible for the majority of all drug-mediated anaphylactic deaths in the United States.

Although IgE-mediated reactions may occur after administration of penicillin by any route, parenteral administration is more likely to cause anaphylaxis. If a patient requires penicillin and has a previous history suggestive of penicillin allergy, it is necessary to perform skin tests on the patient for the presence of penicillin-specific IgE, ideally with both the major and minor determinants of penicillin. Skin tests for minor determinants of penicillin are important because approximately 20% of patients with documented anaphylaxis do not demonstrate skin reactivity to the major determinant. The major determinant is commercially available (Pre-Pen). The minor determinant mixture is currently not licensed and is synthesized as a nonstandardized testing reagent at select academic centers. Penicillin G is often used as a substitute for the minor determinant mixture, and may have negative predictive value similar to testing with major and minor determinants. Patients should be referred to an allergist capable of performing appropriate testing. If the skin test response is positive to either major or minor determinants of penicillin, the patient should receive an alternative non–cross-reacting antibiotic. If administration of penicillin is deemed necessary, desensitization can be performed by an allergist in an appropriate medical setting. Skin testing for penicillin-specific IgE is not predictive for delayed-onset cutaneous, bullous, or immune complex reactions. In addition, penicillin skin testing does not appear to resensitize the patient.

Other β-lactam antibiotics, including semisynthetic penicillins, cephalosporins, carbacephems, and carbapenems, share the β-lactam ring structure. Patients with late-onset morbilliform rashes with amoxicillin are not considered to be at risk for IgE-mediated reactions to penicillin and do not require skin testing before penicillin administration. Many patients with Epstein-Barr virus infections treated with ampicillin or amoxicillin can experience a nonpruritic rash. Similar reactions occur in patients who receive allopurinol as treatment for elevated uric acid or have chronic lymphocytic leukemia. If the rash to ampicillin or amoxicillin is urticarial or systemic or the history is unclear, the patient should undergo penicillin skin testing if a penicillin is needed. There have been reports of antibodies specific for semisynthetic penicillin side chains in the absence of β-lactam ring–specific antibodies, although the clinical significance of such side chain–specific antibodies is unclear.

Varying degrees of in vitro cross-reactivity have been documented between cephalosporins and penicillins. Although the risk of allergic reactions to cephalosporins in patients with positive skin test responses to penicillin appears to be low (<2%), anaphylactic reactions have occurred after administration of cephalosporins in patients with a history of penicillin anaphylaxis. If a patient has a history of penicillin allergy and requires a cephalosporin, skin testing for major and minor determinants of penicillin should preferably be performed to determine whether the patient has penicillin-specific IgE antibodies. If skin test results are negative, the patient can receive a cephalosporin with no greater risk than found in the general population. If skin test results are positive for penicillin, recommendations may include: administration of an alternative antibiotic; cautious graded challenge with appropriate monitoring, with the recognition that there is a 2% chance of inducing an anaphylactic reaction; and desensitization to the required cephalosporin. Cross-reactivity is most likely when the cephalosporin shares the same side chain as the penicillin (Table 152-3).

Conversely, patients who require penicillin and have a history of an IgE-mediated reaction to a cephalosporin should also undergo penicillin skin testing. Patients with a negative result can receive penicillin. Patients with a positive result should either receive an alternative medication or undergo desensitization to penicillin. In patients with a history of allergic reaction to one cephalosporin who require another cephalosporin, skin testing with the required cephalosporin can be performed, with the recognition that the negative predictive value of such testing is unknown. If the skin test response to the cephalosporin is positive, the significance of the test should be checked further in control subjects to determine whether the positive response is IgE mediated or an irritant response. The drug can then be administered by graded challenge or desensitization.

Carbapenems (imipenem, meropenem) represent another class of β-lactam antibiotics with a bicyclic nucleus that demonstrate a high degree of cross-reactivity with penicillins, although prospective studies suggest incidence of cross-reactivity on skin testing of approximately 1%. In contrast to β-lactam antibiotics, monobactams (aztreonam) have a monocyclic ring structure. Aztreonam-specific antibodies have been shown to be predominantly side chain–specific; data suggest that aztreonam can be safely administered to most penicillin-allergic subjects. On the other hand, administration of aztreonam to a patient with ceftazidime allergy may be associated with increased risk of allergic reaction owing to similarity of side chains.

Sulfonamides

The most common type of reaction to sulfonamides is a maculopapular eruption often associated with fever that occurs after 7-12 days of therapy. Immediate reactions, including anaphylaxis, as well as other immunologic reactions, have also been suggested. Hypersensitivity reactions to sulfonamides occur with much greater frequency in HIV-infected individuals. For patients in whom maculopapular rashes develop after sulfonamide administration, both graded challenge and desensitization protocols have been shown to be effective. These regimens should not be used in individuals with a history of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Hypersensitivity reactions to sulfasalazine used for treatment of inflammatory bowel disease appear to result from the sulfapyridine moiety. Slow desensitization over ≈1 mo permits tolerance of the drug in many patients. In addition, oral and enema forms of 5-aminosalicylic acid, thought to be the pharmacologically active agent in sulfasalazine, are effective alternative therapies.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Blistering mucocutaneous disorders induced by drugs encompass a spectrum of reactions, including SJS and TEN (see Chapters 654.2 and 654.3). Epidermal detachment of <10% is suggestive of SJS, 30% detachment suggests TEN, and 10-30% detachment suggests overlap of the 2 syndromes. The features of SJS include confluent purpuric macules on face and trunk and severe, explosive mucosal erosions, usually at more than 1 mucosal surface, accompanied by fever and constitutional symptoms. Ocular involvement may be particularly severe, and the liver, kidneys, and lungs may also be involved. TEN, which appears to be related to keratinocyte apoptosis, manifests as

Table 152-3 Groups of β-Lactam Antibiotics That Share Identical R1-Group Side Chains*

Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephradine Cephaloglycin Loracarbef	Cefditoren Ceftizoxime Cefmenoxime			

*Each column represents a group with identical R1 side chains.

From Solensky R, Khan DA: Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol *105:273e1–273e78, 2010 (Table 16, p. 273e49).*

widespread areas of confluent erythema followed by epidermal necrosis and detachment with severe mucosal involvement. The risk of infection and mortality are high. Skin biopsy differentiates subepidermal cleavage characteristic of TEN from intraepidermal cleavage characteristic of the scalded-skin syndrome induced by staphylococcal toxins. TEN must be treated in a burn unit. Corticosteroids are contraindicated because they can significantly increase the risk of infection. High intravenous doses of immunoglobulin have been shown to be beneficial in patients with TEN, likely because of inhibition of Fas-mediated keratinocyte cell death by naturally occurring Fas-blocking antibodies in the intravenous immunoglobulin preparation.

Hypersensitivity to Antiretroviral Agents

A growing number of adverse drug reactions have been observed with antiretroviral agents, including reverse transcriptase inhibitors, protease inhibitors, and fusion inhibitors. Hypersensitivity to abacavir is a well-recognized, multiorgan, potentially life-threatening reaction that occurs in HIV-infected children. The reaction is independent of dose, with onset generally within 9-11 days of initiation of drug therapy. Rechallenge can be accompanied by significant hypotension and potential mortality (rate of 0.03%), and thus hypersensitivity to abacavir is an absolute contraindication for any subsequent use. Prophylaxis with prednisolone does not appear to prevent hypersensitivity reactions to abacavir. Importantly, genetic susceptibility appears to be conferred by the HLA-B*5701 allele, with a positive predictive value of >70% and a negative predictive value of 95-98%. Genetic screening would be cost-effective in white populations but not in populations of African or Asian descent, in which HLA-B*5701 allele frequency is <1%.

Chemotherapeutic Agents

Hypersensitivity reactions to chemotherapeutic drugs have been described, including to monoclonal antibodies. Rapid desensitization to a variety of unrelated agents, including carboplatin, paclitaxel, and rituximab, can be safely achieved in a 12-step protocol. Of note, this approach appears to be successful in both IgE-mediated and non–IgE-mediated reactions.

Biologics

An increasing number of biologic agents have become available for the treatment of autoimmune, allergic, cardiovascular, infectious, and neoplastic diseases. Their use may be associated with a variety of adverse reactions, including hypersensitivity reactions. Given the occurrence of anaphylaxis, including cases with delayed onset and protracted progression in spontaneous postmarketing adverse event reports, the FDA issued a boxed warning regarding risk of anaphylaxis and need for patient monitoring with use of omalizumab (see Chapter 144).

Vaccines

Measles-mumps-rubella vaccine has been shown to be safe in egg-allergic patients (although rare reactions to gelatin or neomycin can occur). The ovalbumin content in influenza vaccine is generally low and the majority of egg-allergic patients tolerate the vaccine. Skin testing with the influenza vaccine is not recommended for egg-allergic patients, but may be helpful if allergy to the vaccine itself is suspected. Egg-allergic patients should be given the injectable, not the live intranasal vaccine and be observed for 30 min after vaccination, in a setting prepared to treat anaphylaxis. For those with egg-allergic reactions resulting in more than urticaria, administration by an allergist is recommended.

Perioperative Agents

Anaphylactoid (non–IgE-mediated anaphylaxis) reactions occurring during general anesthesia may be caused by induction agents (thiopental) or muscle-relaxing agents (succinylcholine, pancuronium). Quaternary ammonium muscle relaxants (succinylcholine) can act as bivalent antigens in IgE-mediated reactions. Negative skin test results do not necessarily predict that a drug will be tolerated. Latex allergy should always be considered in the differential diagnosis of a perioperative reaction.

Local Anesthetics

Adverse drug reactions associated with local anesthetic agents are primarily toxic reactions resulting from rapid drug absorption, inadvertent intravenous injection, or overdose. Local anesthetics are classified as esters of benzoic acid (group I) or amides (group II). Group I includes benzocaine and procaine; group II includes lidocaine, bupivacaine, and mepivacaine. In suspected local anesthetic allergy, skin testing followed by a graded challenge can be performed or an anesthetic agent from a different group can be used.

Insulin

Insulin use has been associated with a spectrum of adverse drug reactions, including local and systemic IgE-mediated reactions, hemolytic anemia, serum sickness reactions, and delayed-type hypersensitivity. In general, human insulin is less allergenic than porcine insulin, which is less allergenic than bovine insulin, but for individual patients, porcine or bovine insulin may be the least allergenic. Patients treated with nonhuman insulin have had systemic reactions to recombinant human insulin even on the first exposure. More than 50% of patients who receive insulin develop antibodies against the insulin preparation, although there may not be any clinical manifestations. Local cutaneous reactions usually do not require treatment and resolve with continued insulin administration, possibly owing to IgG-blocking antibodies. More severe local reactions can be treated with antihistamines or by splitting the insulin dose between separate administration sites. Local reactions to the protamine component of neutral protamine Hagedorn insulin may be avoided by switching to Lente insulin. Immediate-type reactions to insulin, including urticaria and anaphylactic shock, are unusual and almost always occur after reinstitution of insulin therapy in sensitized patients. Insulin therapy should not be interrupted if a systemic reaction to insulin occurs and continued insulin therapy is essential. Skin testing may identify a less-antigenic insulin preparation. The dose following a systemic reaction is usually reduced to one-third, and successive doses are increased in 2-5 unit increments until the dose resulting in glucose control is attained. Insulin skin testing and desensitization are required if insulin treatment is subsequently interrupted for more than 24-48 hr. Immunologic resistance usually occurs when high titers of predominantly IgG antibodies to insulin develop. A rare form of insulin resistance caused by circulating antibodies to tissue insulin receptors is associated with acanthosis nigricans and lipodystrophy. Coexisting insulin allergy may be present in up to a third of patients with insulin resistance. Approximately half of affected patients benefit from substitution with a less-reactive insulin preparation, based on skin testing.

Drug-Induced Hypersensitivity Syndrome

Drug-induced hypersensitivity syndrome, also referred to as DRESS (drug rash with eosinophilia and systemic symptoms) syndrome, is a potentially life-threatening syndrome that has been described primarily with anticonvulsants, although many other medications have been implicated (see Tables 152-1 and 152-2). It is characterized by fever, maculopapular rash, facial edema, eosinophilia, generalized lymphadenopathy, and potentially life-threatening damage of 1 or more organs, usually renal or hepatic. Onset is delayed, usually weeks after initiation of the medication. It has been associated with reactivation of human herpesvirus 6. *Treatment is withdrawal of the medication, systemic steroids, and supportive care, but symptoms can worsen or persist for weeks to months after the drug has been discontinued.*

Red Man Syndrome

Red man syndrome is caused by nonspecific histamine release and is most commonly described with administration of intravenous vancomycin. It can be prevented by slowing the vancomycin infusion rate or by preadministration of H_1-blockers.

Radiocontrast Media

Anaphylactoid reactions to radiocontrast media or dye can occur after intravascular administration and during myelograms or retrograde pyelograms. No single pathogenic mechanism has been defined, but it

is likely that mast cell activation accounts for the majority of these reactions. Complement activation has also been described. There is no evidence that sensitivity to seafood or iodine predisposes to radiocontrast media reactions. Predictive tests are not available. Patients who have atopic profiles, who are using β-blockers, and who have had prior anaphylactoid reactions are at increased risk. Other diagnostic alternatives should be considered, or patients can be given low-osmolality radiocontrast media with a pretreatment regimen including oral prednisone, diphenhydramine, and albuterol, with or without cimetidine or ranitidine.

Narcotic Analgesics

Opiates such as morphine and related narcotics can induce direct mast cell degranulation. Patients may experience generalized pruritus, urticaria, and occasionally, wheezing. If there is a suggestive history and analgesia is required, a nonnarcotic medication should be considered. If this intervention does not control pain, graded challenge with an alternative opiate is an option.

Aspirin and Nonsteroidal Antiinflammatory Drugs

Aspirin and NSAIDs can cause anaphylactoid reactions or urticaria and/or angioedema in children, and, rarely, asthma with or without rhinoconjunctivitis in adolescents. There is no skin or in vitro test to identify patients who may react to aspirin or other NSAIDs. Once aspirin or NSAID intolerance has been established, options include avoidance and pharmacologic desensitization and subsequent continued treatment with aspirin or NSAIDs, if indicated. A number of studies suggest that cyclooxygenase-2 inhibitors are tolerated by the majority of patients with NSAID-induced adverse reactions.

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Rheumatic Diseases of Childhood

PART XVI

Chapter 153

Evaluation of Suspected Rheumatic Disease

C. Egla Rabinovich

Rheumatic diseases are defined by the constellation of results of the physical examination, autoimmune marker and other serologic tests, tissue pathology, and imaging. Defined diagnostic criteria exist for most rheumatic diseases. Recognition of clinical patterns remains essential for diagnosis because there is no single diagnostic test and results may be positive in the absence of disease. Further complicating the diagnosis, children sometimes present with partial criteria that evolve over time or with features of more than one rheumatic disease (**overlap syndromes**). The primary mimics of rheumatic diseases are infection and malignancy but also include metabolic, orthopedic, and chronic pain conditions. Exclusion of possible mimicking disorders is essential before initiation of treatment for a presumptive diagnosis, especially corticosteroids. After careful evaluation has excluded nonrheumatic causes, referral to a pediatric rheumatologist for confirmation of the diagnosis and treatment should be considered.

SYMPTOMS SUGGESTIVE OF RHEUMATIC DISEASE

There are no classic symptoms of a rheumatic disease, but common symptoms include joint pain, fever, fatigue, and rash. Presenting signs and symptoms help direct the evaluation and limit unnecessary testing. Once a differential diagnosis is developed on the basis of history and physical findings, a directed assessment assists in determining the diagnosis.

Arthralgias are common in childhood and are a frequent reason for referral to pediatric rheumatologists. Arthralgias without physical findings for arthritis suggest infection, malignancy, orthopedic conditions, benign syndromes, or pain syndromes such as fibromyalgia (Table 153-1). Although rheumatic diseases may manifest as arthralgias, arthritis is a stronger predictor of the presence of rheumatic disease and a reason for referral to a pediatric rheumatologist. The timing of joint pain along with associated symptoms including poor sleep and interference with normal activities provides important clues. Poor sleep, debilitating generalized joint pain that worsens with activity, school absences, and normal physical and laboratory findings in an adolescent suggest a **pain syndrome** (e.g., fibromyalgia). If arthralgia is accompanied by a history of dry skin, hair loss, fatigue, growth disturbance, and/or cold intolerance, testing for **thyroid disease** is merited. Nighttime awakenings because of severe pain along with decreased platelet count or white blood cell count or, alternatively, a very high white blood cell count, may lead to the diagnosis of malignancy, especially marrow-occupying lesions such as **acute lymphocytic leukemia** and **neuroblastoma**. Pain with physical activity suggests a mechanical problem such as an overuse syndrome or orthopedic condition. An adolescent girl presenting with knee pain aggravated by walking up stairs and on patellar distraction likely has **patellofemoral syndrome**. Children ages 3 to 10 yr who have a history of episodic pain that occurs at night after increased daytime physical activity that is relieved by rubbing, but who have no limp or complaints in the morning, likely have **growing pains**. There is often a positive family history for growing pains, which may aid in this diagnosis. Intermittent pain in a child, especially a girl age 3 to 10 yr, that is increased with activity and is associated with hyperextensible joints on exam is likely **benign hypermobility syndrome**. Many febrile illnesses cause arthralgias that improve when the temperature normalizes, and arthralgias are part of the diagnostic criteria for **acute rheumatic fever** (ARF; see Chapter 183.1).

Arthralgia may also be a presenting symptom of pediatric **systemic lupus erythematosus** (**SLE**) and chronic childhood arthritis such as **juvenile idiopathic arthritis (JIA).** Interestingly, many children with JIA do not complain of joint symptoms at presentation. Other symptoms more suggestive of arthritis include morning stiffness, joint swelling, limited range of motion, pain with joint motion, gait disturbance, fever, and fatigue and/or stiffness after physical inactivity (gelling phenomenon). A diagnosis of chronic juvenile arthritis cannot be made without the finding of arthritis on physical examination (see Chapters 155 and 156), and there are no laboratory tests diagnostic of juvenile rheumatoid arthritis or any other chronic inflammatory arthritis in childhood.

Fatigue is a nonspecific symptom that may point to the presence of a rheumatic disease but is also common in nonrheumatic causes such as viral infections, pain syndromes, depression, and malignancy. Fatigue, rather than the specific complaints of muscle weakness, is a common presenting complaint in **juvenile dermatomyositis (JDM)**. It is also commonly present in SLE, vasculitis, and the chronic childhood arthritides. Overwhelming fatigue with inability to attend school is more suggestive of chronic fatigue syndrome, pediatric fibromyalgia, or other amplified pain syndrome.

SIGNS SUGGESTIVE OF RHEUMATIC DISEASE

A complete physical examination is mandated in any child in whom a rheumatic disease is suspected, because many rheumatic diseases have associated subtle physical findings that will further refine the differential diagnosis. In addition, many rheumatic diseases have multisystem effects, and a stepped assessment should focus on delineating the extent of organ system involvement (e.g., skin, joints, muscle, hepatic, renal, cardiopulmonary).

Presence of a photosensitive malar rash that spares the nasolabial folds is suggestive of SLE (Table 153-2; see Fig. 158-1*A*), especially in an adolescent girl. Diffuse facial rash is more indicative of JDM. A hyperkeratotic rash on the face or around the ears of an adolescent African-American girl may represent discoid lupus (see Fig. 158-1*D*). A palpable purpuric rash on the extensor surfaces of the lower extremities points to **Henoch-Schönlein purpura** (see Fig. 167-1*A*). Less localized purpuric rashes and petechiae are present in systemic vasculitis or blood dyscrasias including coagulopathies. Nonblanching erythematous papules on the palms are seen in vasculitis and SLE. Gottron papules (see Fig. 159-2) and heliotrope rashes (see Fig. 159-1) along with erythematous rashes on the elbows and knees are pathognomonic of JDM. Dilated capillary loops in the nail beds (periungual telangiectasias; see Fig. 159-3) are common in JDM, scleroderma, and secondary Raynaud phenomenon. An evanescent macular rash associated with fever is part of the diagnostic criteria for systemic onset arthritis (see Fig. 155-12). Sun sensitivity or photosensitive rashes are indicative of SLE or JDM but can also be caused by antibiotics.

Mouth ulcers are part of the diagnostic criteria for SLE and Behçet disease (see Fig. 158-1*D*); painless nasal ulcers and erythematous macules on the hard palate are also common in SLE. Cartilage loss in the nose, causing a saddle nose deformity, is classically present in granulomatosis with polyangiitis (formally Wegener granulomatosis; see Fig. 167-4) but is also seen in relapsing polychondritis and syphilis.

Table 153-1 Symptoms Suggestive of Rheumatic Disease

SYMPTOM	RHEUMATIC DISEASE(S)	POSSIBLE NONRHEUMATIC DISEASES CAUSING SIMILAR SYMPTOMS
Fevers	Systemic JIA, SLE, vasculitis, acute rheumatic fever, sarcoidosis, MCTD	Malignancies, infections and post-infectious syndromes, inflammatory bowel disease, periodic fever (autoinflammatory) syndromes, Kawasaki disease, HSP
Arthralgias	JIA, SLE, rheumatic fever, JDM, vasculitis, scleroderma, sarcoidosis	Hypothyroidism, trauma, endocarditis, other infections, pain syndromes, growing pains, malignancies, overuse syndromes
Weakness	JDM, myositis secondary to SLE, MCTD, and deep localized scleroderma	Muscular dystrophies, metabolic and other myopathies, hypothyroidism
Chest pain	Juvenile rheumatoid arthritis, SLE (with associated pericarditis or costochondritis)	Costochondritis (isolated), rib fracture, viral pericarditis, panic attack, hyperventilation
Back pain	Enthesitis related arthritis, juvenile ankylosing spondylitis	Vertebral compression fracture, diskitis, intraspinal tumor, spondylolysis, spondylolisthesis, bone marrow–occupying malignancy, pain syndromes, osteomyelitis, muscle spasm, injury
Fatigue	SLE, JDM, MCTD, vasculitis, JIA	Pain syndromes, chronic infections, chronic fatigue syndrome, depression

HSP, Henoch-Schönlein purpura; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus.

Table 153-2 Signs Suggestive of Rheumatic Disease

SIGN	RHEUMATIC DISEASES	COMMENTS	NONRHEUMATIC CAUSES
Malar rash	SLE, JDM	SLE classically spares nasolabial folds	Sunburn, parvovirus B19 (fifth disease), Kawasaki disease
Oral ulcers	SLE, Behçet disease	Behçet disease also associated with genital ulcers	HSV infection, PFAPA syndrome
Purpuric rash	Vasculitis, e.g., ANCA-associated vasculitis, HSP	HSP typically starts as small lesions on lower extremities and buttocks that coalesce	Meningococcemia, thrombocytopenia, clotting disorders
Gottron papules	JDM	Look for associated heliotrope rash, periungual telangiectasias	Psoriasis, eczema
Arthritis	Juvenile idiopathic arthritis, SLE, vasculitis, HSP, MCTD, scleroderma, acute rheumatic fever, reactive arthritis	Chronic joint swelling (>6 wk) required for diagnosis of chronic arthritis of childhood; MCTD associated with diffuse puffiness of hands	Postviral arthritis, reactive arthritis, trauma, infection, Lyme disease, Kawasaki disease, malignancy, overuse syndromes

ANCA, antineutrophilic cytoplasmic antibody; HSP, Henoch-Schönlein purpura; HSV, herpes simplex virus; JDM, juvenile dermatomyositis; MCTD, mixed connective tissue disease; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis; SLE, systemic lupus erythematosus.

Alopecia can be associated with SLE but is also found in localized scleroderma (see Fig. 160-4) and JDM. **Raynaud phenomenon** may be a primary benign idiopathic disorder or can be a presenting complaint in the child with scleroderma, lupus, mixed connective tissue disease (MCTD), or an overlap syndrome. Diffuse lymphadenopathy is present in many rheumatic diseases, including SLE, polyarticular JIA, and systemic JIA. Irregular pupils may represent the insidious and unrecognized onset of uveitis associated with juvenile arthritis. Erythematous conjunctiva may be a result of uveitis or episcleritis associated with juvenile rheumatoid arthritis, SLE, sarcoidosis, spondyloarthropathies, or vasculitis.

A pericardial rub and orthopnea are suggestive of pericarditis, often seen in systemic JIA, SLE, and sarcoid. Coronary artery dilation is strongly suggestive of Kawasaki disease but may also be a finding in systemic arthritis and other forms of systemic vasculitis. Interstitial lung disease, suggested by dyspnea on exertion or the finding of basilar rales with decreased carbon monoxide diffusion capacity, occurs in SLE, MCTD, and systemic sclerosis. Signs consistent with pulmonary hemorrhage points to Wegener granulomatosis, microscopic angiitis, or SLE. Pulmonary vascular aneurysms are indicative of Behçet disease.

Arthritis is defined by the presence of intraarticular swelling or 2 or more of the following findings on joint examination: pain on motion, loss of motion, erythema, and heat. Arthritis is present in all of the chronic childhood arthritis syndromes, along with SLE, JDM, vasculitis, Behçet disease, sarcoidosis, Kawasaki disease, and Henoch-Schönlein purpura. Nonrheumatic causes of arthritis include malignancy, infections such as septic arthritis, Lyme disease, osteomyelitis, viral infections (such as rubella, hepatitis B, parvovirus B19), and postinfectious etiologies such as Epstein-Barr virus, ARF, and reactive arthritis. ARF typically involves a migratory (lasting hours to days), painful arthritis. Pain on palpation of long bones is suggestive of malignancy. Specific muscle testing for weakness should be performed in a child presenting with fatigue or difficulty with daily tasks, as both of these symptoms may be manifestations of muscle inflammation.

LABORATORY TESTING

There are no specific screening tests for rheumatologic disease. Once a differential diagnosis is determined, appropriate testing can be performed (Tables 153-3 and 153-4). Initial studies are generally performed in standard local laboratories. Screening for specific autoantibodies can be performed in commercial laboratories, but confirmation of results in a tertiary care center immunology laboratory is often necessary.

One essential laboratory test for rheumatic disease assessment is the complete blood count, as it yields many diagnostic clues. Elevated white blood cell count is compatible with malignancy, infection, systemic JIA, and vasculitis. Leukopenia can be caused by postinfectious, especially viral, etiologies, SLE, or malignancy. Lymphopenia is more specific for SLE than is leukopenia. Platelets are acute-phase reactants and are therefore elevated with inflammatory markers. Exceptions are a bone marrow–occupying malignancy, such as leukemia or neuroblastoma, SLE, and early Kawasaki disease. Anemia is nonspecific and may

Table 153-3 Autoantibody Specificity and Disease Associations

ANTIBODY	DISEASE	PREVALENCE (%)	SPECIFICITY
Antinuclear antibody (ANA)	SLE, juvenile rheumatoid arthritis, dermatomyositis, scleroderma, psoriatic arthritis, MCTD	—	Associated with increased risk of uveitis in JIA and psoriatic arthritis Up to 30% of children testing positive for ANAs have no underlying rheumatic disease
Double-stranded DNA (dsDNA)	SLE	60-70	High specificity for SLE; associated with lupus nephritis
Smith (Sm)	SLE	20-30	Highly specific for SLE; associated with lupus nephritis
Smooth muscle (Sm)	Autoimmune hepatitis	—	—
Pm-Scl (polymyositis-scleroderma)	Sclerodermatomyositis	—	—
SSA (Ro)	SLE, Sjögren syndrome	25-30	Associated with neonatal lupus syndrome, subacute cutaneous lupus, thrombocytopenia
SSB (La)	SLE, Sjögren syndrome	25-30	Usually coexists with anti-SSA antibody
Ribonuclease protein (RNP)	MCTD, SLE	30-40	Suggestive of MCTD unless meets criteria for SLE
Histone	Drug-induced lupus, SLE	—	—
Centromere	Limited cutaneous systemic sclerosis	70	Nonspecific for systemic sclerosis
Topoisomerase I (Scl-70)	Systemic sclerosis	—	Rare in childhood
Antineutrophil cytoplasmic antibodies (ANCAs)	Vasculitis	—	—
Cytoplasmic (cANCAs)/ PR3-ANCA		—	cANCAs associated with granulomatosis with polyangiitis (Wegener), cystic fibrosis
Perinuclear (pANCAs)/ MPO-ANCA		—	pANCAs associated with microscopic polyangiitis, polyarteritis nodosa, SLE, inflammatory bowel disease, cystic fibrosis, primary sclerosing cholangitis, Henoch-Schönlein purpura, Kawasaki disease, Churg-Strauss syndrome
Anticitrullinated protein (ACPA) also called anti-cyclic citrullinated protein (anti-CCP)	RF positive JIA	50-90	Specific for JIA (RF+), may be positive before RF

MCTD, mixed connective tissue disease; MPO-ANCA, antimyeloperoxidase; PR3-ANCA, antiproteinase 3; RF, rheumatoid factor; SLE, systemic lupus erythematosus.
Modified from Aggerwal A: Clinical application of tests used in rheumatology, Indian J Pediatr *69:889–892, 2002.*

be caused by any chronic illness, but hemolytic anemia (positive Coombs test result) may point to SLE or MCTD. Rheumatoid factor is present in less than 10% of children with JIA and thus has poor sensitivity as a diagnostic tool; it may be elevated by infections such as endocarditis, tuberculosis, syphilis, viral infections (parvovirus B19, hepatitides B and C, mycoplasma) as well as primary biliary cirrhosis and malignancies. In a child with chronic arthritis, rheumatoid factor serves as a prognostic indicator.

Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein level) are nonspecific and are elevated in infections and malignancies as well as rheumatic diseases. Their levels may also be normal in rheumatic diseases such as arthritis, scleroderma, and dermatomyositis. Inflammatory marker measurements are more useful in rheumatic diseases for following response to treatment than as diagnostic tests. Muscle enzymes include aspartate aminotransferase, alanine aminotransferase, creatinine phosphokinase, aldolase, and lactate dehydrogenase, any of which may be elevated in JDM as well as in other diseases causing muscle breakdown. Muscle-building supplements, medications, and extreme physical activity may also cause muscle breakdown and enzyme elevations. Aspartate aminotransferase, alanine aminotransferase, and aldolase are also elevated secondary to liver disease, and a γ-glutamyltransferase measurement may help differentiate whether the source is muscle or liver.

The use of an antinuclear antibody (ANA) measurement as a screening test is not recommended, as it has low specificity. A positive ANA test result may be induced by infection, especially Epstein-Barr virus infection, endocarditis, and parvovirus B19 infection. The ANA test result is also positive in up to 30% of normal children and the level of ANA is increased in those with a 1st-degree relative with a known rheumatic disease. In the majority of children with a positive ANA test result without signs of a rheumatic disease on initial evaluation, autoimmune disease does not develop disease over time, so this finding does not necessitate referral to a pediatric rheumatologist. A positive ANA test result is found in many rheumatic diseases, including JIA, in which it serves as a predictor of the risk for inflammatory eye disease. Once a positive ANA test result is discovered in a child, the need for specific autoantibody testing is directed by the presence of clinical signs and symptoms (see Table 153-3).

IMAGING STUDIES

Plain radiographs are useful in evaluation of arthralgias and arthritis, as they offer reassurance in benign pain syndromes and their findings are often abnormal in malignancies, osteomyelitis, and long-standing chronic juvenile arthritis. Radionucleotide bone scans help localize areas of abnormality in the patient with diffuse pains caused by osteomyelitis, neuroblastoma, chronic multifocal osteomyelitis, and systemic arthritis. MRI findings are abnormal in inflammatory myositis and suggest the optimal site for biopsy. MRI is more sensitive than plain radiographs in detecting the presence of early erosive arthritis and demonstrates increased joint fluid, synovial enhancement, and sequela of trauma with internal joint derangement. Cardiopulmonary evaluation is suggested for diseases commonly affecting the heart and

Table 153-4	Evaluation Based on Suspected Diagnosis		
SUSPECTED RHEUMATIC DISEASE(S)	**INITIAL EVALUATION**	**FURTHER EVALUATION**	**SUBSPECIALTY EVALUATION**
SLE, MCTD	CBC, ESR, ANA, ALT, AST, CPK, creatinine, albumin, total protein, urinalysis, BP, thyroid profile	If ANA test result is positive: anti–SSA (Ro), anti–SSB (La), anti-Smith, and anti-RNP Abs; anti-dsDNA Ab, C3, C4, Coombs, spot urine protein/creatinine ratio, CXR	Antiphospholipid Abs, lupus anticoagulant, anti–β_2-glycoprotein, echocardiogram; consider renal biopsy, PFTs, bronchoscopy with lavage, HRCT of chest; consider lung biopsy
JDM	CBC, CPK, ALT, AST, LDH, aldolase, ANA; check gag reflex	Consider MRI of muscle	Consider electromyography and possible muscle biopsy, PFTs, swallowing study, serum neopterin
JIA	CBC, ESR, creatinine, ALT, AST, consider anti–streptolysin O/anti–DNAase B for streptococcus-induced arthritis, Epstein-Barr virus titers, Lyme titer, parvovirus B19 titer, plain radiograph of joints	Consider Ab titers to unusual infectious agents, purified protein derivative, RF, ANA, HLA-B27, anti-CCP	MRI
Granulomatosis with polyangiitis (Wegener granulomatosis)	CBC, ANCA, AST, ALT, albumin, creatinine, ESR, urinalysis, CXR, BP	Spot urine protein/creatinine ratio, anti–myeloperoxidase and anti–proteinase-3 Abs, PFTs	Bronchoscopy with lavage, HRCT chest; consider lung and kidney biopsies
Sarcoidosis	CBC, electrolytes, AST, ALT, albumin, creatinine, calcium, phosphorous, ACE, BP	CXR, PFTs	Consider testing for Blau syndrome in infants (see Chapter 159); HRCT of chest; consider renal and lung biopsy
Localized scleroderma	Skin biopsy, CBC, ESR		Serum immunoglobulin G, ANA, RF, single-stranded DNA Ab, antihistone Ab, CPK
Systemic scleroderma	ANA, CBC, ESR, BP, AST, ALT, CPK, creatinine, CXR	Anti-Scl70, PFTs	HRCT of chest, echocardiogram, upper gastrointestinal radiography series

Ab, antibody; ACE, angiotensin-converting enzyme (normally elevated in childhood; interpret with caution); ALT, alanine aminotransferase; ANA, antinuclear antibody; anti-dsDNA Ab, anti–double stranded DNA antibody; AST, aspartate aminotransferase; BP, blood pressure; CBCD, complete blood count with differential; CCP, cyclic citrullinated protein; CPK, creatine phosphokinase; CXR, chest radiograph; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HRCT, high-resolution CT; LDH, lactate dehydrogenase; PFTs, pulmonary function tests; RF, rheumatoid factor.

lung, including SLE, systemic scleroderma, MCTD, JDM, and sarcoid, as clinical manifestations may be subtle. This evaluation, which may include echocardiogram, pulmonary function tests, and high-resolution CT of the lungs along with consideration of bronchoalveolar lavage, is generally performed by a pediatric rheumatologist to whom the patient is referred (see Table 153-4).

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Chapter 154

Treatment of Rheumatic Diseases

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Nonpharmacologic as well as pharmacologic interventions are often necessary to meet the desired goals of disease management. Optimal disease management requires family-centered care delivered by a multidisciplinary team of healthcare professionals providing medical, psychological, social, and school support. Rheumatologic conditions most often follow a course marked by flares and periods of remission, although some children have unremitting disease. The goals of treatment are to control disease, relieve discomfort, avoid or limit drug toxicity, prevent or reduce organ damage, and maximize the physical function and quality of life of affected children. Nonpharmacologic therapy is an important adjunct to medical management of rheumatic diseases. A key predictor of long-term outcome consists of early recognition and referral to a rheumatology team experienced in the specialized care of children with rheumatic diseases. Significant differences in outcome are seen 10 yr after disease onset in patients with juvenile idiopathic arthritis (JIA) depending on whether referral to a pediatric rheumatology center was accomplished within 6 mo of onset.

PEDIATRIC RHEUMATOLOGY TEAMS AND PRIMARY CARE PHYSICIANS

The **multidisciplinary pediatric rheumatology team** (Table 154-1) offers coordinated services for children and their families. General principles of treatment include: early recognition of signs and symptoms of rheumatic disease with timely referral to rheumatology for prompt initiation of treatment; monitoring for disease complications and adverse effects of treatment; coordination of subspecialty care and rehabilitation services with communication of clinical information; and child- and family-centered chronic illness care, including self-management support, alliance with community resources, partnership with schools, resources for dealing with the financial burdens of disease, and connection with advocacy groups. Planning for transition to adult care providers needs to start in adolescence. Central to effective care is partnership with the primary care provider, who helps coordinate care, monitor compliance with treatment plans, ensure appropriate immunization, monitor for medication toxicities, and

Table 154-1	Multidisciplinary Treatment of Rheumatic Diseases in Childhood
Accurate diagnosis and education of family	Pediatric rheumatologist Pediatrician Nurse: • Disease-related education • Medication administration (injection teaching) • Safety monitoring Social worker: • Facilitation of school services • Resource identification (community, government, financial, advocacy groups, vocational rehabilitation)
Physical medicine and rehabilitation	Physical therapy: • Addressing deficits in joint or muscle mobility, limb length discrepancies, gait abnormalities, weakness Occupational therapy: • Splinting to reduce joint contractures/ deformities and lessen stress on joints; adaptive devices for activities of daily living
Consultant team	Ophthalmology: • Eye screening for uveitis (see Table 155-4) • Screening for medication-related ocular toxicity (hydroxychloroquine, glucocorticoids) Nephrology Orthopedics Dermatology Gastroenterology
Physical and psychosocial growth and development	Nutrition: • Addressing undernourishment from systemic illness, obesity/ overnourishment from glucocorticoids School integration: • Individualized Educational Plan (IEP) or 504 plan Peer group relationships Individual and/or family counseling
Coordination of care	Involvement of patient and family as active team members Communication among healthcare providers Involvement of school (school nurse) and community (social worker) resources

identify disease exacerbations and concomitant infections. Communication between the primary care provider and subspecialty team permits timely intervention when needed.

THERAPEUTICS

A key principle of pharmacologic management of rheumatic diseases is that early disease control, striving for induction of remission, leads to less tissue and organ damage with improved short- and long-term outcomes. Medications are chosen from broad therapeutic classes on the basis of diagnosis, disease severity, anthropometrics, and adverse effect profile. Many drug therapies used do not have U.S. Food and Drug Administration (FDA) indications for pediatric rheumatic diseases given the relative rarity of these conditions. The evidence base may be limited to case series, uncontrolled studies, or extrapolation from use in adults. The exception is JIA, for which there is a growing body of randomized control trial evidence, particularly for newer therapeutics. Therapeutic agents used for treatment of childhood rheumatic diseases (Table 154-2) have various mechanisms of action, but all suppress inflammation. **Both biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs) directly affect the immune system**. DMARDs should be prescribed by specialists. Live vaccines are contraindicated in patients taking immunosuppressive glucocorticoids or DMARDs. A negative test result for tuberculosis (purified protein derivative and/or QuantiFERON-TB Gold) should be verified and the patient's immunization status updated, if possible, before such treatment is initiated. Killed vaccines are not contraindicated, and annual injectable influenza vaccine is recommended.

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) are prescribed to decrease both the pain and acute and chronic inflammation associated with arthritis, pleuritis, pericarditis, uveitis, and cutaneous vasculitis, but they are not disease modifying. NSAID antiinflammatory effects require regular administration at adequate doses based on weight (mg/kg) or body surface area (mg/m^2), for longer periods than needed for analgesia alone. The mean time to achieve antiinflammatory effect in JIA is 4-6 wk of consistent administration. NSAIDs work primarily by inhibiting the enzyme **cyclooxygenase (COX),** which is critical in the production of **prostaglandins,** a family of substances that promote inflammation. Two types of COX receptors have been demonstrated; **selective COX-2 inhibitors** (such as celecoxib and meloxicam) inhibit receptors responsible for promoting inflammation with potential for fewer gastrointestinal (GI) adverse effects. Clinical trials in children with JIA found celecoxib and meloxicam to be similar, in effectiveness and tolerability, to the nonselective NSAID naproxen.

The most frequent adverse effects of NSAIDs in children are nausea, decreased appetite, and abdominal pain. Gastritis or ulceration occurs less frequently in children. Less-common adverse effects, occurring in ≤5% of children undergoing long-term NSAID therapy, include mood change, concentration difficulty that can simulate attention deficit disorder, sleepiness, irritability, headache, tinnitus, alopecia, anemia, elevated liver enzyme values, proteinuria, and hematuria. Certain agents (indomethacin) have a higher risk of toxicity than others (ibuprofen); naproxen has an intermediate risk. These NSAID-associated adverse effects reverse quickly once the medication is stopped. Additional rare NSAID-specific adverse reactions may also occur. Aseptic meningitis has been associated with ibuprofen, primarily in patients with lupus. Naproxen is more likely than other NSAIDs to cause a unique skin reaction called **pseudoporphyria,** which is characterized by small hypopigmented depressed scars occurring in areas of minor skin trauma, such as fingernail scratches. Pseudoporphyria is more likely to occur in fair-skinned individuals and on sun-exposed areas. If pseudoporphyria develops, the inciting NSAID should be discontinued because scars can persist for years or be permanent. NSAIDs should be used cautiously in patients with dermatomyositis or systemic vasculitis because of an increased frequency of GI ulceration with these disorders. *Salicylates have been supplanted by other NSAIDs owing to the relative frequency of salicylate hepatotoxicity and the association with Reye syndrome.*

The response to NSAIDs varies greatly among individual patients, but overall, 40-60% of children with JIA experience improvement in their arthritis with NSAID therapy. Patients may try several different NSAIDs for 6-wk trials before finding one that demonstrates clinical benefit. NSAIDs with longer half-lives or sustained-release formulations allow for once- or twice-daily dosing and improve compliance. Laboratory monitoring for toxicity includes a complete blood count (CBC), serum creatinine, liver function tests (LFTs), and urinalysis every 6-12 mo, though guidelines for frequency of testing are not established.

Nonbiologic Disease-Modifying Antirheumatic Drugs

Methotrexate

Methotrexate (MTX), an antimetabolite, is a cornerstone of therapy in pediatric rheumatology because of its sustained effectiveness and relative low toxicity over prolonged periods of treatment. The mechanism of action low-dose MTX in arthritis is complex but is believed

Table 154-2 Therapeutics for Childhood Rheumatic Diseases*

CLASSIFICATION	THERAPEUTIC[†]	DOSE	INDICATION[†]	ADVERSE REACTIONS	MONITORING
Nonsteroidal antiinflammatory drugs (NSAIDs)[‡]	Etodolac[a]	PO once-daily dose: 20-30 kg: 400 mg 31-45 kg: 600 mg 46-60 kg: 800 mg >60 kg: 1,000 mg	JIA Spondyloarthropathy Pain Serositis Cutaneous vasculitis Uveitis	GI intolerance (abdominal pain, nausea), gastritis, hepatitis, tinnitus, anemia, pseudoporphyria, aseptic meningitis, headache, renal disease	CBC, LFTs, BUN/creatinine, urinalysis at baseline, then every 6-12 mo
	Ibuprofen[a]	40 mg/kg/day PO divided 3 times daily Max 2400 mg per day			
	Naproxen[a]	15 mg/kg/day PO in 2 divided doses Maximum 1,000 mg per day			
	Celecoxib[a]	10-25 kg: 50 mg PO twice daily >25 kg: 100 mg PO twice daily			
	Meloxicam[a]	0.125 mg/kg, maximum 7.5 mg, PO once daily			
Disease modifying antirheumatic drugs (DMARDs)	Methotrexate[a]	10-20 mg/m^2/wk (0.35-0.65 mg/kg/wk) PO 20-30 mg/m^2/wk (0.65-1 mg/kg/wk) SC; higher doses better absorbed by SC injection	JIA Uveitis	GI intolerance (nausea, vomiting), hepatitis, myelosuppression, mucositis, teratogenesis, lymphoma, interstitial pneumonitis	CBC, LFTs at baseline, monthly × 3, then every 8-12 wk
	Leflunomide	PO once daily: 10 to <20 kg: 10 mg 20-40 kg: 15 mg >40 kg: 20 mg	JIA	hepatitis, hepatic necrosis, cytopenias, mucositis, teratogenesis, peripheral neuropathy	CBC, LFTs, at baseline, monthly × 6, then every 8-12 wk
	Hydroxychloroquine	5-6 mg/kg PO once daily; do not exceed 6.5 mg/kg/daily Maximum dose 400 mg daily	SLE JDMS Antiphospholipid antibody syndrome	Retinal toxicity, GI intolerance, rash, skin discoloration, anemia, cytopenias, myopathy, CNS stimulation, death (overdose)	Ophthalmologic screening every 6-12 mo
	Sulfasalazine[a]	30-50 mg/kg/day divided in twice-daily doses Adult maximum 3 g/day	Spondyloarthropathy, JIA	GI intolerance, rash, hypersensitivity reactions, Stevens-Johnson syndrome, cytopenias, hepatitis, headache	CBC, LFTs, BUN/creatinine, urinalysis at baseline, every other wk × 3 mo, monthly × 3, then every 3 mo
Tumor necrosis factor α (TNF-α) antagonists	Adalimumab[a]	SC once every other wk: 15 to <30 kg: 20 mg ≥30 kg: 40 mg	JIA, spondyloarthropathy, psoriatic arthritis, uveitis	Injection site reaction, infection, rash, cytopenias, lupus-like syndrome, potential increased malignancy risk	TB test; anti-dsDNA, CBC
	Etanercept[a]	0.8 mg/kg SC once weekly (maximum 50 mg/dose) or 0.4 mg/kg SC twice weekly (maximum 25 mg/dose)	JIA	Injection site reactions, infections, rash, demyelinating disorders, cytopenias, potential increased malignancy risk	TB test; CBC
	Infliximab	5-10 mg/kg IV q4-8wk	JIA Spondyloarthropathy Uveitis Sarcoidosis	Infusion reactions, hepatitis, potential increased malignancy risk	TB test; anti-dsDNA, LFTs

*Consult a clinical pharmacology reference for current dosing and monitoring guidelines, and complete list of known adverse effects.

Continued

Table 154-2 Therapeutics for Childhood Rheumatic Diseases—cont'd

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
Modulate T-cell activation	Abatacept[a]	IV every 2 wk × 3 doses, then monthly for ≥6 yr of age: <75 kg: 10 mg/kg 75-100 kg: 750 mg >100 kg: 1,000 mg	JIA	Infection, headache, potential increased malignancy risk	
Anti-CD20 (B cell) antibody	Rituximab	575 mg/m^2, maximum 1,000 mg, IV on days 1 and 15	SLE	Infusion reactions, lymphopenia, reactivation hepatitis B, rash, serum sickness, arthritis, PML	CBC, BMP; consider monitoring quantitative IgG
Anti-BLyS antibody	Belimumab[e]	10 mg/kg IV every 2 wk × 3 doses, then every 4 wk	SLE	Infusion reactions, infection, depression	
Interleukin 1 antagonist	Anakinra	1-2 mg/kg/daily Adult maximum 100 mg	Systemic JIA CAPS	Injection site reactions, infection	CBC
	Canakinumab[b]	Given SC every 8 wk (CAPS) every 4 wk (Systemic JIA): 15-40 kg: 2 mg/kg (up to 3 mg/kg if needed) >40 kg: 150 mg	CAPS Systemic JIA	Injection site reaction, infection, diarrhea, nausea, vertigo, headache	
Interleukin-6 antagonist	Tocilizumab[a]	≥2 yr and ≥30 kg, 8 mg/kg/dose every 2 wk; ≥2 yr and ≤30 kg, 12 mg/kg/dose every 2 wk	Systemic JIA	Infusion reactions, elevated LFTs, elevated lipids, thrombocytopenia, infections	CBC, LFTs, platelet count, serum lipid profile
Intravenous immunoglobulin	IVIG[c]	1,000-2,000 mg/kg IV infusion For JDMS, give monthly	Kawasaki disease JDMS SLE	Infusion reaction, aseptic meningitis, renal failure	Serum creatinine, BUN, IgG level
Cytotoxic	Cyclophosphamide	0.5-1 g/m^2 IV (maximum 1.5 g) monthly for 6-mo induction, then every 2-3 mo Oral regimen: 1-2 mg/kg/daily; maximum 150 mg/daily	SLE Vasculitis JDMS Pulmonary hemorrhage	Nausea, vomiting, myelosuppression, mucositis, hyponatremia, alopecia, hemorrhagic cystitis, gonadal failure, teratogenesis, secondary malignancy	CBC
Immunosuppressive	Mycophenolate mofetil	Oral suspension: maximum 1,200 mg/m^2/day PO (up to 2 g/day) divided twice daily Capsules: maximum 1,500 mg/day PO for BSA 1.25-1.5 m^2, 2 g/day PO for BSA >1.5 m^2 divided twice daily	SLE Uveitis	GI intolerance (diarrhea, nausea, vomiting), renal impairment, neutropenia, teratogenesis, secondary malignancy, PML	CBC, BMP

Table 154-2 Therapeutics for Childhood Rheumatic Diseases—cont'd

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
Glucocorticoids	Prednisone[a,d-f]	0.05-2 mg/kg/day PO given in 1-4 divided doses; maximum varies by individual (80 mg/daily) Adverse effects are dose dependent; lowest effective dose should be used	SLE JDMS Vasculitis JIA Uveitis Sarcoidosis	Cushing syndrome, osteoporosis, increased appetite, weight gain, striae, hypertension, adrenal suppression, hyperglycemia, infection, avascular necrosis	Blood glucose, potassium Blood pressure
	Methylprednisolone[a,d-g]	0.5-1.7 mg/kg/day or 5-25 mg/m²/day IM/IV in divided doses q6-12h For severe manifestations: 30 mg/kg/dose (maximum 1 g) daily for 1-5 days	SLE JDMS Vasculitis Sarcoidosis Localized scleroderma		
	Intraarticular	Dose varies by joint and formulation	JIA	Subcutaneous atrophy, skin hypopigmentation, calcification, infection	
	Prednisolone ophthalmic suspension	1-2 drops into eye up to every hr while awake Needs monitoring by ophthalmologist	Uveitis	Ocular hypertension, glaucoma, nerve damage, cataract, infection	Ophthalmologic exam

Blys, B-lymphocyte stimulator; BMP, basic metabolic panel; BSA, body surface area; BUN, blood urea nitrogen; CAPS, cryopyrin-associated periodic syndrome; CBC, complete blood count; CNS, central nervous system; dsDNA, double-stranded DNA; GI, gastrointestinal; Ig, immunoglobulin; IM, intramuscular(ly); IV, intravenous(ly); IVIG, intravenous immunoglobulin; JDMS, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; LFTs, liver function tests; PML, progressive multifocal leukoencephalopathy; PO, by mouth; SC, subcutaneous(ly); SLE, systemic lupus erythematosus; TB, tuberculosis.

†Therapeutics used in practice may not have a FDA-approved indication. Individual therapeutics annotated with FDA-approved indication as follows: a, JIA; b, CAPS; c, Kawasaki disease; d, sarcoidosis; e, SLE; f, uveitis; g, dermatomyositis.

‡Many more products available in this class.

to result from the inhibition of folate-dependent processes by MTX polyglutamates, primarily their effect on the enzyme 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase leading to an increase of extracellular adenosine and consequently, cyclic adenosine monophosphate, which inhibits the production of proinflammatory cytokines including tumor necrosis factor (TNF)-α and interleukin (IL)-1β and their downstream effects on lymphocyte activation and proliferation.

MTX has a central role in the treatment of arthritis, especially in children with polyarticular JIA. The response to oral MTX (10 mg/m² once a week) is better than the response to placebo (63% vs. 36%). Children who show no response to standard doses of MTX often do show response to higher doses (15 or 30 mg/m²/wk). Subcutaneous administration of MTX is similar in absorption and pharmacokinetic properties to intramuscular injection, with less pain. MTX is commonly used in treatment of juvenile dermatomyositis as a steroid-sparing agent, with efficacy in 70% of patients. It has also been used successfully at a dosage of 10-20 mg/m²/wk in patients with systemic lupus erythematosus (SLE) to treat arthritis, serositis, and rash.

Because of the lower dose used in treating rheumatic diseases, MTX is well tolerated by children with toxicity being milder and qualitatively different from that observed with treatment of neoplasms. In 8 published studies including 288 patients with JIA taking MTX, adverse effects included elevated liver enzyme values (15%), GI toxicity (13%), stomatitis (3%), headache (1-2%), and leukopenia, interstitial pneumonitis, rash, and alopecia (<1%). Hepatotoxicity observed among adults with rheumatoid arthritis treated with MTX has raised concern about similar problems in children. Analysis of liver biopsy specimens in children with JIA undergoing long-term MTX treatment has revealed occasional mild fibrosis and no evidence of even moderate liver damage. Children receiving MTX should be counseled to avoid alcohol, smoking, and pregnancy. *Folic acid* 1 mg daily is given as an adjunct to minimize adverse effects. Lymphoproliferative disorders have been reported in adults treated with MTX, primarily in association with Epstein-Barr virus infection. Regression of lymphoma may follow withdrawal of MTX.

Monitoring laboratory tests for MTX toxicity include CBC and LFTs at regular intervals, initially every 4 wk for the 1st 3 mo of treatment, then every 8-12 wk, with more frequent intervals after dosing adjustments or in response to abnormal values.

Hydroxychloroquine

Hydroxychloroquine sulfate is an antimalarial drug important in the treatment of SLE and dermatomyositis, particularly cutaneous manifestations of disease and to reduce lupus flares. It is not indicated to treat JIA because of lack of efficacy. The most significant potential adverse effect is retinal toxicity, which occurs rarely but results in irreversible color blindness or loss of central vision. Complete ophthalmologic examinations, including assessment of peripheral vision and color fields, are conducted at baseline and every 6-12 mo to screen for retinal toxicity. Retinal toxicity is rare (1/5,000 patients) and is associated with weight-based dosing exceeding 6.5 mg/kg/day; therefore, recommended dosing is <6.5 mg/kg/day not to exceed 400 mg/day. Other potential adverse effects include rash, skin discoloration, gastric irritation, bone marrow suppression, central nervous system stimulation, and myositis.

Leflunomide

Leflunomide is a DMARD approved for treatment of rheumatoid arthritis that offers an alternative to MTX for treatment of JIA. MTX outperformed leflunomide for treatment of JIA in a randomized trial (at 16 wk, 89% of patients receiving MTX achieved a 30% response rate vs. 68% of those receiving leflunomide), although both drugs were effective. Dosing is oral, once daily, and weight based: 10 mg for children 10 to <20 kg, 15 mg for children 20-40 kg, and 20 mg for children >40 kg. Adverse reactions include paresthesias and peripheral neuropathy, GI intolerance, elevated liver transaminases and hepatic failure, cytopenias, alopecia, and teratogenesis. Leflunomide has a long half-life, and in cases in which discontinuation of the agent is required, a drug elimination protocol with *cholestyramine* may be indicated. Avoidance of pregnancy is essential. Monitoring laboratory tests include CBC, LFTs, every 4 wk for the 1st 6 mo of treatment, then every 8-12 wk.

Sulfasalazine

Sulfasalazine is used to treat children with polyarticular JIA oligoarticular JIA, and the peripheral arthritis and enthesitis associated with juvenile ankylosing spondylitis. In JIA, sulfasalazine 50 mg/kg/day (adult maximum: 3,000 mg/day) achieves greater improvement in joint inflammation, global assessment parameters, and laboratory parameters than placebo. More than 30% of sulfasalazine-treated patients withdraw from the treatment because of adverse effects, primarily GI irritation and skin rashes. Sulfasalazine is associated with severe systemic hypersensitivity reactions, including Stevens-Johnson syndrome. Sulfasalazine is generally considered contraindicated in children with active systemic JIA because of increased hypersensitivity reactions. Sulfasalazine should not be used in patients with sulfa or salicylate hypersensitivity or porphyria.

Monitoring laboratory tests for sulfasalazine toxicity include CBC, LFTs, serum creatinine/blood urea nitrogen (BUN), and urinalysis, every other week for the 1st 3 mo of treatment, monthly for 3 mo, every 3 mo for 1 yr, then every 6 mo.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive drug approved by the FDA for organ transplant rejection. In rheumatology, MMF is used primarily for treatment of lupus, uveitis, and autoimmune skin manifestations. In adult clinical trials, MMF was noninferior to cyclophosphamide for induction therapy of lupus nephritis, with a potential for less-adverse effects (infection, gonadal toxicity). Dosing is based on body surface area: 600 mg/m^2 orally twice daily, with maximum dosage limits varying by formulation and body surface area. The most common adverse reaction is GI intolerance. Infections, cytopenias, and secondary malignancies are among other adverse reactions reported.

Glucocorticoids

Glucocorticoids are given through oral, intravenous, ocular, topical, and intraarticular administration as part of treatment of rheumatic disease. Oral steroids are foundational treatment for moderate to severe lupus, dermatomyositis, and most forms of vasculitis; their long-term use is associated with a long list of well-described, dose-dependent complications, including linear growth suppression, Cushingoid features, osteoporosis, avascular necrosis, hypertension, impaired glucose tolerance, mood disturbance, and increased infection risk. Glucocorticoids should be tapered to the lowest effective dose over time, and DMARDs introduced as **steroid-sparing agents.**

Intravenous steroids have been used to treat severe, acute manifestations of systemic rheumatic diseases such as SLE, dermatomyositis, and vasculitis. The intravenous route allows for higher doses to obtain an immediate, profound antiinflammatory effect. **Methylprednisolone,** 10-30 mg/kg/dose up to a maximum of 1 g, given over 1 hr daily for 1-5 days, is the intravenous preparation of choice. Although generally associated with fewer adverse effects than oral steroids, intravenously administered steroids are associated with significant and occasionally life-threatening toxicities, such as cardiac arrhythmia, acute hypertension, hypotension, hyperglycemia, shock, pancreatitis, and avascular necrosis.

Ocular steroids are prescribed by ophthalmologists as ophthalmologic drops or injections into the soft tissue surrounding the globe (sub–Tenon capsule injection) for active uveitis. Long-term ocular steroid use leads to cataract formation and glaucoma. Current ophthalmologic management has significantly decreased the frequency of blindness as a complication of JIA-associated uveitis.

Intraarticular steroids are being used with increasing frequency as initial therapy for children with oligoarticular JIA or as bridge therapy while awaiting efficacy of a DMARD in polyarticular disease. Most patients have significant clinical improvement within 3 days. Duration of response depends on steroid preparation used, joint affected, and arthritis subtype, with the anticipated response rate to knee injection being between 60% and 80% at 6 mo. Intraarticular administration may result in subcutaneous atrophy and hypopigmentation of the skin at the injection site, as well as subcutaneous calcifications along the needle track.

Biologic Agents

Biologic agents are proteins that have been engineered to target and modulate specific components of the immune system with the goal of decreasing the inflammatory response. Antibodies have been developed to target specific cytokines such as IL-1 and IL-6 or to interfere with specific immune cell function through depletion of B cells or suppression of T-cell activation (Table 154-3). The availability of these agents has dramatically increased the therapeutic options for treating rheumatic disease recalcitrant to nonbiologic therapies and they are, in some instances, becoming first-line interventions. A primary concern regarding biologic therapy is that when use is combined with other immunosuppressants, risk of malignancy may be increased.

Tumor Necrosis Factor-α Antagonists

Currently, 2 TNF antagonists have an FDA indication for treatment of children with moderate to severe polyarticular JIA (etanercept and adalimumab). *Etanercept* is a genetically engineered fusion protein consisting of 2 identical chains of the recombinant extracellular TNF receptor monomer fused with the Fc domain of human immunoglobulin G_1. Etanercept binds both TNF-α and lymphotoxin-α (formerly

Table 154-3 Summary of Biologic Therapies Studied in Juvenile Idiopathic Arthritis and Their Method of Action

DRUG	METHOD OF ACTION
Etanercept	Soluble TNF p75 receptor fusion protein that binds to and inactivates TNF-α
Infliximab	Chimeric human/mouse monoclonal antibody that binds to soluble TNF-α and its membrane-bound precursor, neutralizing its action
Adalimumab	A humanized IgG_1 monoclonal antibody that binds to TNF-α
Abatacept	Soluble, fully human fusion protein of the extracellular domain of (CTLA-4, linked to a modified Fc portion of the human IgG_1. It acts as a costimulatory signal inhibitor by binding competitively to CD80 or CD86, where it selectively inhibits T-cell activation
Tocilizumab	A humanized anti–human IL-6 receptor monoclonal antibody
Anakinra	An IL-1 receptor antagonist (IL-1RA)

CTLA, cytotoxic T lymphocyte–associated antigen; Ig, immunoglobulin; IL, interleukin; TNF, tumor necrosis factor.

From Beresford MW, Baildam EM: New advances in the management of juvenile idiopathic arthritis—2: the era of biologicals, Arch Dis Child Educ Pract Ed *94:151–156, 2009.*

called TNF-β) and inhibits their activity. Three fourths of children with active polyarticular JIA that fails to respond to MTX demonstrate response to etanercept after 3 mo of therapy. Dosing is 0.8 mg/kg subcutaneous weekly (maximum 50 mg/dose) or 0.4 mg/kg subcutaneously twice a week (maximum 25 mg/dose). Adalimumab is a fully human anti-TNF monoclonal antibody used alone or in combination with MTX. In a placebo-controlled withdrawal-design study, children continuing to receive adalimumab were less likely to experience disease flares (43% vs. 71%) even if they were also taking MTX (37% vs. 65%). Adalimumab is administered subcutaneously every other week at a dose of 20 mg for children weighing 15-30 kg and 40 mg for those weighing >30 kg.

Infliximab, a chimeric mouse-human monoclonal antibody, was tested in a randomized controlled clinical trial for use in JIA but did not achieve study end points. However, it is FDA approved for pediatric inflammatory bowel disease and has been used "off label" for treatment of polyarticular JIA, uveitis, Behçet syndrome, and sarcoidosis. Two additional anti-TNF agents—*golimumab*, a human monoclonal antibody against TNF, and *certolizumab pegol*, a pegylated humanized antibody against TNF—have been approved by the FDA for rheumatoid arthritis in adults and are currently in pediatric trials.

The most common adverse reactions are injection-site reactions that diminish over time. TNF blockade is associated with an increased frequency of serious systemic infections, including sepsis, dissemination of latent tuberculosis, and invasive fungal infections in endemic areas. TNF blockade should not be initiated in subjects with history of chronic or frequent recurrent infections. Tuberculosis should be tested for prior to initiation of therapy with TNF antagonists. If test results are positive, antitubercular treatment must be administered before anti-TNF treatment can be started. There is a theoretically increased risk of malignancy with TNF-α antagonists, and there have been reports of development of lupus-like syndromes, leukocytoclastic vasculitis, interstitial lung disease, demyelinating syndromes, antibody formation to the drug, rashes, cytopenias, anaphylaxis, serum sickness, and other reactions. The benefit : risk profile appears favorable after a decade of experience with this therapeutic class; the safety of longer-term suppression of TNF function is unknown.

Modulator of T-Cell Activation

Abatacept is a selective inhibitor of T-cell costimulation resulting in T-cell anergy. It is FDA approved for treatment of moderate to severe polyarticular JIA. In a double-blind, randomized controlled withdrawal trial in children whose disease had not responded to DMARDs, 53% of placebo-treated patients, compared with 20% of abatacept-treated patients, experienced disease flares during the double-blind withdrawal period. The frequency of adverse events did not differ between the groups. Abatacept is administered IV every other week for 3 doses (<75 kg: 10 mg/kg/dose; 75-100 kg: 750 mg/dose; >100 kg: 1,000 mg/dose; maximum 1,000 mg/dose at 0, 2, and 4 wk) and then monthly thereafter.

B-Cell Depletion

Rituximab is a chimeric monoclonal antibody to the antigen CD20, a transmembrane protein on the surface of B-cell precursors and mature B lymphocytes. This antibody induces B-cell apoptosis and causes depletion of circulating and tissue-based B cells. Antibody production is not completely abrogated as plasma cells are not removed. Rituximab is licensed for treatment of B-cell non-Hodgkin lymphoma and is FDA approved for use in adult rheumatoid arthritis and idiopathic thrombocytopenic purpura but does not have a pediatric indication. Rituximab may also have a role in treatment of SLE, particularly its hematologic manifestations. Adverse events include serious infusion reactions, cytopenias, hepatitis B virus reactivation, hypogammaglobulinemia, infections, serum sickness, vasculitis, and a rare but fatal side effect, progressive multifocal leukoencephalopathy. Resistance to rituximab may develop over time in patients being treated for lymphoma.

Belimumab is a human monoclonal antibody to B-lymphocyte stimulator that negatively affects B-cell proliferation, differentiation, and long-term survival. It was FDA-approved in March 2011 for treatment of SLE in adults and studies of long-term safety and efficacy are ongoing. Currently, belimumab is not FDA approved for use in pediatric SLE.

Interleukin-1 Antagonists

Anakinra, a recombinant form of the human IL-1 receptor antagonist, competitively inhibits binding of IL-1α and IL-1β to the natural receptor, interrupting the cytokine proinflammatory cascade. Anakinra has been approved for rheumatoid arthritis in adults. In meta-analyses of treatments for rheumatoid arthritis, anakinra was outperformed by TNF-α antagonists but has a special niche in pediatric rheumatology for treatment of systemic JIA (SoJIA) and other autoinflammatory syndromes, such as cryopyrin-associated periodic syndromes. The medication is dosed subcutaneously, 1-2 mg/kg, once daily. An IL-1β monoclonal antibody, *canakinumab* is FDA approved for use in cryopyrin-associated periodic syndromes dosed subcutaneously every 8 wk and SoJIA dosed subcutaneously every 4 wk. Adverse reactions include significant injection site reactions and increased bacterial infections.

Interleukin-6 Receptor Antagonist

Tocilizumab, is an anti-IL-6 receptor antibody binding to both soluble as well as membrane-associated receptors. Tocilizumab has FDA approval for treatment of SoJIA and polyarticular JIA. Adverse reactions include transaminase and lipid elevations. Tocilizumab is given as an IV infusion every 2 (SoJIA) to 4 (polyarticular JIA) wk.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is thought to be beneficial in various clinical conditions. IVIG significantly improves the short- and long-term natural history of Kawasaki disease. Open studies have supported benefit for juvenile dermatomyositis, lupus-associated thrombocytopenia, and polyarticular JIA. IVIG is given as 1-2 g/kg/dose, administered once monthly. It has been occasionally associated with severe systemic allergic–like reactions and post-infusion aseptic meningitis (headache, stiff neck).

Cytotoxics

Cyclophosphamide

Cyclophosphamide requires metabolic conversion in the liver to its active metabolites, which alkylate the guanine in DNA, leading to immunosuppression by the inhibition of the S2 phase of mitosis. The subsequent decrease in numbers of T and B lymphocytes results in diminished humoral and cellular immune responses. Cyclophosphamide infusions (500-1,000 mg/m^2) given monthly for 6 mo, and then every 3 mo for 12-18 mo, have been shown to reduce the frequency of renal failure in patients with lupus and diffuse proliferative glomerulonephritis. Open trials suggest efficacy in severe central nervous system lupus. Oral cyclophosphamide (1-2 mg/kg/day) is effective as induction treatment of severe antineutrophilic cytoplasmic antibody-associated vasculitis and other forms of systemic vasculitis as well as interstitial lung disease or pulmonary hemorrhage associated with rheumatic disease. Cyclophosphamide is a potent cytotoxic drug associated with significant toxicities. Potential short-term adverse effects include nausea, vomiting, anorexia, alopecia, mucositis, hemorrhagic cystitis, and bone marrow suppression. Long-term complications include an increased risk for sterility and cancer, especially leukemia, lymphoma, and bladder cancer. Thirty percent to 40% of adult women with lupus treated with intravenous cyclophosphamide become infertile; the risk of ovarian failure appears to be significantly lower in adolescent and premenarchal girls. Ovarian suppression with an inhibitor of gonadotropin-releasing hormone to preserve fertility is currently being studied.

Other Drugs

Azathioprine is sometimes used to treat antineutrophilic cytoplasmic antibody-associated vasculitis following induction therapy or to treat SLE. *Cyclosporine* has been used occasionally in the treatment of dermatomyositis on the basis of uncontrolled studies and is helpful in the

treatment of macrophage activation syndrome complicating SoJIA (see Chapter 155). There are case reports describing the successful use of *thalidomide*, or its analog *lenalidomide*, as treatment for SoJIA, inflammatory skin disorders, and Behçet disease. Several drugs commonly used in the past to treat arthritis are no longer part of standard treatment, including salicylates, gold compounds, and D-penicillamine.

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Chapter 155

Juvenile Idiopathic Arthritis

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Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and one of the more common chronic illnesses of childhood. JIA represents a heterogeneous group of disorders all sharing the clinical manifestation of arthritis. The etiology and pathogenesis of JIA are largely unknown, and the genetic component is complex, making clear distinction among various subtypes difficult. As a result, several classification schemas exist, each with its own limitations. The former classification scheme of the American College of Rheumatology uses the term *juvenile rheumatoid arthritis* and categorizes the disease into 3 onset types (Table 155-1). Attempting to standardize nomenclature, The International League of Associations for Rheumatology (ILAR) proposed a different classification using the term **JIA** (Table 155-2), inclusive of all subtypes of chronic juvenile arthritis. We refer to the ILAR classification criteria; see Chapter 156 for enthesitis-related arthritis (ERA) and psoriatic JIA (Tables 155-3 and 155-4).

EPIDEMIOLOGY

The worldwide incidence of JIA ranges from 0.8-22.6/100,000 children per year, with prevalence ranges from 7-401/100,000. These wide-ranging numbers reflect population differences, particularly environmental exposure and immunogenetic susceptibility, along with variations in diagnostic criteria, difficulty in case ascertainment, and lack of population-based data. It is estimated that 300,000 children in the United States have arthritis, including 100,000 with a form of JIA. Oligoarthritis is the most common subtype (40-50%), followed by polyarthritis (25-30%) and systemic JIA (5-15%) (see Table 155-4). There is no sex predominance in systemic JIA (sJIA), but more girls than boys are affected in both oligoarticular (3 : 1) and polyarticular (5 : 1) JIA. The peak age at onset is between 2 and 4 yr for oligoarticular disease. Age of onset has a bimodal distribution in polyarthritis, with peaks at 2-4 yr and 10-14 yr. sJIA occurs throughout childhood with a peak between 1 and 5 yr.

Table 155-1	Criteria for the Classification of Juvenile Rheumatoid Arthritis
Age at onset: <16 yr Arthritis (swelling or effusion, or the presence of 2 or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in ≥1 joint Duration of disease: ≥6 wk Onset type defined by type of articular involvement in the 1st 6 mo after onset: Polyarthritis: ≥5 inflamed joints Oligoarthritis: ≤4 inflamed joints Systemic-onset disease: arthritis with rash and a characteristic quotidian fever Exclusion of other forms of juvenile arthritis	

Modified from Cassidy JT, Levison JE, Bass JC, et al: A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis, Arthritis Rheum *29:174–181, 1986.*

ETIOLOGY

The etiology and pathogenesis of JIA are not completely understood, though both immunogenetic susceptibility and an external trigger are considered necessary. JIA is a complex genetic trait in which multiple genes may affect disease susceptibility. Variants in major histocompatibility complex (MHC) class I and class II regions have indisputably been associated with different JIA subtypes. Non-HLA candidate loci are also associated with JIA, including polymorphisms in the genes encoding protein tyrosine phosphatase nonreceptor 22 (PTPN22), tumor necrosis factor (TNF)-α, macrophage inhibitory factor, interleukin (IL)-6, and IL-1α. There is evidence that the IL-6 gene confers susceptibility to sJIA, with increased transmission of the −174G allele in patients older than 5 yr. Possible nongenetic triggers include bacterial and viral infections, enhanced immune responses to bacterial or mycobacterial heat shock proteins, abnormal reproductive hormone levels, and joint trauma.

PATHOGENESIS

JIA is an autoimmune disease associated with alterations in both humoral and cell-mediated immunity. T lymphocytes have a central role, releasing proinflammatory cytokines favoring a type 1 helper T-lymphocyte response. Studies of T-cell receptor expression confirm recruitment of T lymphocytes specific for synovial non–self antigens. B-cell activation, immune complex formation, and complement activation also promote inflammation. Inheritance of specific cytokine alleles may predispose to upregulation of inflammatory networks, resulting in systemic disease or more severe articular disease.

sJIA is characterized by dysregulation of the innate immune system with a lack of autoreactive T cells and autoantibodies. It therefore may be more accurately classified as an **autoinflammatory disorder**, more like familial Mediterranean fever, than the other subtypes of JIA. This theory is also supported by work demonstrating similar expression patterns of a phagocytic protein (S100A12) in sJIA and familial Mediterranean fever, as well as the same marked responsiveness to IL-1 inhibitors.

All these immunologic abnormalities cause inflammatory synovitis, characterized pathologically by villous hypertrophy and hyperplasia with hyperemia and edema of the synovial tissue. Vascular endothelial hyperplasia is prominent and is characterized by infiltration of mononuclear and plasma cells with a predominance of T lymphocytes (Fig. 155-1). Advanced and uncontrolled disease leads to pannus formation and progressive erosion of articular cartilage and contiguous bone (Figs. 155-2 and 155-3).

CLINICAL MANIFESTATIONS

Arthritis must be present to make a diagnosis of any JIA subtype. Arthritis is defined by intraarticular swelling or the presence of 2 or more of the following signs: limitation in range of motion, tenderness or pain on motion, and warmth. Initial symptoms may be subtle or acute and often include morning stiffness with a limp or gelling after inactivity. Easy fatigability and poor sleep quality may be associated. Involved joints are often swollen, warm to touch, and painful on movement or palpation with reduced range of motion, but usually are not erythematous. Arthritis in large joints, especially knees, initially accelerates linear growth and causes the affected limb to be longer, resulting in a discrepancy in limb lengths. Continued inflammation stimulates rapid and premature closure of the growth plate, resulting in shortened bones.

Table 155-2 International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis (JIA)

CATEGORY	DEFINITION	EXCLUSIONS
Systemic	Arthritis in ≥1 joint with, or preceded by, fever of at least 2 wk in duration that is documented to be daily ("quotidian"*) for at least 3 days and accompanied by ≥1 of the following: 1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly or splenomegaly or both 4. Serositis†	a. Psoriasis or a history of psoriasis in the patient or a 1st-degree relative b. Arthritis in an HLA-B27–positive boy beginning after the 6th birthday c. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis, or a history of one of these disorders in a 1st-degree relative d. Presence of immunoglobulin M RF on at least 2 occasions at least 3 mo apart
Oligoarthritis	Arthritis affecting 1-4 joints during the 1st 6 mo of disease. Two subcategories are recognized: 1. Persistent oligoarthritis—affecting ≤4 joints throughout the disease course 2. Extended oligoarthritis—affecting >4 joints after the 1st 6 mo of disease	a, b, c, d (above) plus e. Presence of systemic JIA in the patient
Polyarthritis (RF-negative)	Arthritis affecting ≥5 joints during the 1st 6 mo of disease; a test for RF is negative	a, b, c, d, e
Polyarthritis (RF-positive)	Arthritis affecting ≥5 joints during the 1st 6 mo of disease; ≥2 tests for RF at least 3 mo apart during the 1st 6 mo of disease are positive	a, b, c, e
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis‡ 2. Nail pitting§ and onycholysis 3. Psoriasis in a 1st-degree relative	b, c, d, e
Enthesitis-related arthritis	Arthritis and enthesitis,‖ or arthritis or enthesitis with at least 2 of the following: 1. Presence of or a history of sacroiliac joint tenderness or inflammatory lumbosacral pain or both¶ 2. Presence of HLA-B27 antigen 3. Onset of arthritis in a male >6 yr old 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis in a 1st-degree relative	a, d, e
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in ≥2 of the above categories.	

RF, rheumatoid factor.
Quotidian fever is defined as a fever that rises to 39°C (102.2°F) once a day and returns to 37°C (98.6°F) between fever peaks.
†*Serositis* refers to pericarditis, pleuritis, or peritonitis, or some combination of the 3.
‡*Dactylitis* is swelling of ≥1 digits, usually in an asymmetric distribution, that extends beyond the joint margin.
§A minimum of 2 pits on any 1 or more nails at any time.
‖*Enthesitis* is defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.
¶*Inflammatory lumbosacral pain* refers to lumbosacral pain at rest with morning stiffness that improves on movement.
From Firestein GS, Budd RC, Harris ED Jr, et al, editors: Kelley's textbook of rheumatology, *ed 8, Philadelphia, 2009, Saunders.*

Table 155-3 Characteristics of the American College of Rheumatology (ACR) and International League of Associations for Rheumatology (ILAR) Classifications of Childhood Chronic Arthritis

PARAMETER	ACR (1977)	ILAR (1997)
Term	Juvenile rheumatoid arthritis (JRA)	Juvenile idiopathic arthritis (JIA)
Minimum duration	≥6 wk	≥6 wk
Age at onset	<16 yr	<16 yr
≤4 joints in 1st 6 mo after presentation	• Pauciarticular	• Oligoarthritis: a. Persistent: <4 joints for course of disease b. Extended: >4 joints after 6 mo
>4 joints in 1st 6 mo after presentation	• Polyarticular	• Polyarthritis rheumatoid factor–negative • Polyarthritis rheumatoid factor–positive
Fever, rash, arthritis	• Systemic-onset	• Systemic
Other categories included	Exclusion of other forms	• Psoriatic arthritis • Enthesitis-related arthritis • Undifferentiated: a. Fits no other category b. Fits more than 1 category
Inclusion of psoriatic arthritis, inflammatory bowel disease, ankylosing spondylitis	No (see Chapter 156)	Yes

Table 155-4 Overview of the Main Features of the Subtypes of Juvenile Idiopathic Arthritis

INTERNATIONAL LEAGUE OF ASSOCIATIONS FOR RHEUMATOLOGY SUBTYPE	PEAK AGE OF ONSET (Yr)	FEMALE:MALE RATIO	PERCENTAGE OF ALL JIA CASES	ARTHRITIS PATTERN	EXTRAARTICULAR FEATURES	LABORATORY INVESTIGATIONS	NOTES ON THERAPY
Systemic arthritis	1-5	1:1	5-15	Polyarticular, often affecting knees, wrists, and ankles; also fingers, neck, and hips	Daily fever; evanescent rash; pericarditis; pleuritis	Anemia; WBC ↑↑; ESR ↑↑; CRP ↑↑; ferritin ↑; platelets ↑↑ (normal or ↓ in MAS)	Less responsive to standard treatment with MTX and anti-TNF agents; consider IL-1 or IL-6 inhibitors in resistant cases or as first-line therapy
Oligoarthritis	2-4	3:1	40-50 (but ethnic variation)	Knees ++; ankles, fingers +	Uveitis in ≈30% of cases	ANA positive in ≈60%; other test results usually normal; may have mildly ↑ ESR/CRP	NSAIDs and intraarticular steroids; MTX occasionally required
Polyarthritis: RF-negative	2-4 and 10-14	3:1 and 10:1	20-35	Symmetric or asymmetric; small and large joints; cervical spine; temporomandibular joint	Uveitis in ≈10%	ANA positive in 40%; RF negative; ESR ↑ or ↑↑; CRP ↑/normal; mild anemia	Standard therapy with MTX and NSAIDs; then, if nonresponsive, anti-TNF agents or other biologics, including abatacept, indicated as first-line therapy
RF-positive	9-12	9:1	<10	Aggressive symmetric polyarthritis	Rheumatoid nodules in 10%; low-grade fever	RF positive; ESR ↑↑; CRP ↑/normal; mild anemia	Long-term remission unlikely; early aggressive therapy is warranted
Psoriatic arthritis	2-4 and 9-11	2:1	5-10	Asymmetric arthritis of small or medium-sized joints	Uveitis in 10%; psoriasis in 50%	ANA positive in 50%; ESR ↑; CRP ↑/normal; mild anemia	NSAIDs and intraarticular steroids; MTX, anti-TNF agents
Enthesitis-related arthritis	9-12	1:7	5-10	Predominantly lower limb joints affected; sometimes axial skeleton (but less than in adult, ankylosing spondylitis)	Acute anterior uveitis; association with reactive arthritis and inflammatory bowel disease	80% of patients positive for HLA-B27	NSAIDs and intra-articular steroids; consider sulfasalazine as alternative to MTX; anti-TNF agents

ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; MAS, macrophage activation syndrome; MTX, methotrexate; NSAID, nonsteroidal antiinflammatory drug; RF, rheumatoid factor; TNF, tumor necrosis factor; WBC, white blood cell count.

From Firestein GS, Budd RC, Harris ED Jr, et al, editors: Kelley's textbook of rheumatology, *ed 8, Philadelphia, 2009, Saunders.*

Figure 155-1 Synovial biopsy specimen from a 10 yr old child with **oligoarticular juvenile idiopathic arthritis.** There is a dense infiltration of lymphocytes and plasma cells in the synovium.

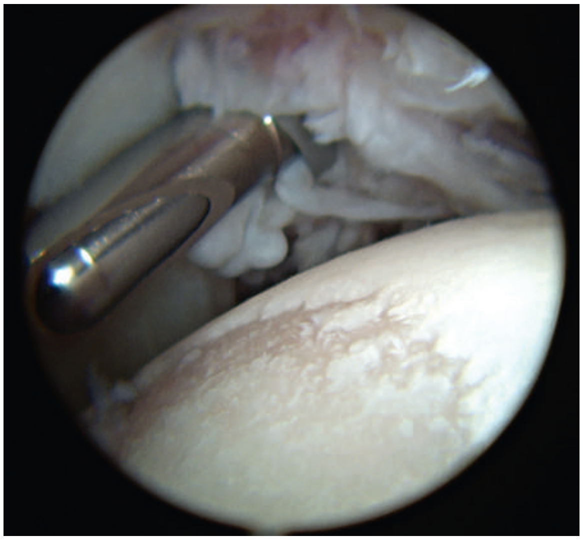

Figure 155-2 Arthroscopy in the shoulder of a child with juvenile idiopathic arthritis showing pannus formation and cartilage erosions. *(Courtesy of Dr. Alison Toth.)*

Oligoarthritis is defined as involving ≤4 joints within the 1st 6 mo of disease onset, and often only a single joint is involved (see Table 155-4). It predominantly affects the large joints of the lower extremities, such as the knees and ankles (Fig. 155-4). Isolated involvement of upper extremity large joints is less common. Those in whom disease never develops in more than 4 joints are regarded as having **persistent oligoarticular JIA**, whereas evolution of disease in more than 4 joints after 6 mo changes the classification to **extended oligoarticular JIA** and is associated with a worse prognosis. Isolated involvement of the hip is *almost never* a presenting sign and suggests ERA (see Chapter 156) or a nonrheumatic cause. The presence of a positive antinuclear antibody (ANA) confers increased risk for asymptomatic anterior uveitis, requiring periodic slit-lamp examination (Table 155-5). ANA positivity may also be correlated with younger age at disease onset, female sex, asymmetric arthritis, and lower number of involved joints over time.

Polyarthritis is characterized by inflammation of ≥5 joints in both upper and lower extremities (Figs. 155-5 and 155-6). Rheumatoid factor (RF)–positive polyarthritis resembles the characteristic symmetric presentation of adult rheumatoid arthritis. **Rheumatoid nodules** on the extensor surfaces of the elbows, spine, and over the Achilles tendons, although unusual, are associated with a more severe course and almost exclusively occur in RF-positive individuals (Fig. 155-7). **Micrognathia** reflects chronic temporomandibular joint disease

Figure 155-3 MRI with gadolinium of a 10 yr old child with juvenile idiopathic arthritis (same patient as in Fig. 155-1). The dense white signal in the synovium near the distal femur, proximal tibia, and patella reflects inflammation. MRI of the knee is useful to exclude ligamentous injury, chondromalacia of the patella, and tumor.

Figure 155-4 Oligoarticular juvenile idiopathic arthritis with swelling and flexion contracture of the right knee.

Table 155-5 Frequency of Ophthalmologic Examination in Patients with Juvenile Idiopathic Arthritis

TYPE	ANTINUCLEAR ANTIBODY TEST RESULT	AGE AT ONSET (Yr)	DURATION OF DISEASE (Yr)	RISK CATEGORY	EYE EXAMINATION FREQUENCY (Mo)
Oligoarthritis or polyarthritis	+	≤6	≤4	High	3
	+	≤6	>4	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	–	≤6	≤4	Moderate	6
	–	≤6	>4	Low	12
	–	>6	NA	Low	12
Systemic disease	NA	NA	NA	Low	12

From Cassidy J, Kivlin J, Lindsley C, et al: Section on Rheumatology; Section on Ophthalmology: Ophthalmologic examinations in children with juvenile rheumatoid arthritis, Pediatrics *117:1843–1845, 2006.*

Figure 155-5 Hands and wrists of a girl with polyarticular juvenile idiopathic arthritis, rheumatoid factor–negative. Notice the symmetric involvement of the wrists, metacarpophalangeal joints, and proximal and distal interphalangeal joints. In this photograph, there is cream with occlusive dressing on the patient's right hand in preparation for placement of an intravenous line for administration of a biologic agent.

(Fig. 155-8). Cervical spine involvement (Fig. 155-9), manifesting as decreased neck extension, occurs with a risk of atlantoaxial subluxation and neurologic sequelae. Hip disease may be subtle, with findings of decreased or painful range of motion on exam (Fig. 155-10).

sJIA is characterized by arthritis, fever, rash, and prominent visceral involvement, including hepatosplenomegaly, lymphadenopathy, and serositis (pericarditis). The characteristic fever, defined as spiking temperatures to ≥39°C (102.2°F), occurs on a daily or twice-daily basis for at least 2 wk, with a rapid return to normal or subnormal temperatures (Fig. 155-11). The fever is often present in the evening and is frequently accompanied by a characteristic faint, erythematous, macular rash. The evanescent **salmon-colored lesions,** classic for sJIA, are linear or circular and are most commonly distributed over the trunk and proximal extremities (Fig. 155-12). The classic rash is nonpruritic and migratory with lesions lasting <1 hr. **Koebner phenomenon,** a cutaneous hypersensitivity in which classic lesions are brought on by superficial trauma, is often present. Heat can also evoke rash. Fever, rash, hepatosplenomegaly, and lymphadenopathy are present in >70% of affected children. Without arthritis, the differential diagnosis includes the episodic fever syndromes, infection, and malignancy. Some children initially present with only systemic features, and evolve over time, but definitive diagnosis requires presence of arthritis. Arthritis may affect any number of joints, but the course is classically polyarticular, may be very destructive, and can include hip, cervical spine, and temporomandibular joint involvement.

Macrophage activation syndrome (MAS) is a rare but potentially fatal complication of sJIA that can occur at any time (onset, medication change, active or remission) during the disease course. It is also referred to as secondary hemophagocytic syndrome or hemophagocytic lymphohistiocytosis (HLH) (see Chapter 507). There is increasing evidence that sJIA/MAS and HLH share similar functional defects in granule-dependent cytotoxic lymphocyte activity. MAS classically manifests as acute onset of high spiking fevers, lymphadenopathy, hepatosplenomegaly, and encephalopathy. Laboratory evaluation shows thrombocytopenia and leukopenia with elevated liver enzymes, lactate dehydrogenase, ferritin, and triglycerides. Patients may have purpura and mucosal bleeding, as well as elevated fibrin split product values and prolonged prothrombin and partial prothromboplastin times. The erythrocyte sedimentation rate (ESR) falls because of hypofibrinogenemia and hepatic dysfunction, a feature useful in distinguishing MAS from a flare of systemic disease (Table 155-6). Although finalized diagnostic criteria for MAS do not currently exist, the features that were decided by an international consensus panel as the most important indicators of MAS include a falling platelet count, extreme hyperferritinemia, evidence of macrophage hemophagocytosis in the bone marrow, increased liver enzymes, falling leukocyte count, persistent, continuous fever ≥38°C (100.4°F), falling ESR, hypofibrinogenemia, and hypertriglyceridemia. *A relative change in laboratory values is likely more relevant in making an early diagnosis than are absolute normal values.* The diagnosis is suggested by clinical criteria and is confirmed by bone marrow biopsy demonstrating hemophagocytosis (Table 155-6). Emergency treatment with high-dose intravenous methylprednisolone, cyclosporine, or anakinra may be effective. Severe cases may require therapy similar to that for primary HLH (see Chapter 507).

Bone mineral metabolism and skeletal maturation are adversely affected in children with JIA, regardless of subtype. Children with JIA have decreased bone mass (osteopenia), which appears to be associated with increased disease activity. Increased levels of cytokines such as TNF-α and IL-6, both key regulators in bone metabolism, have deleterious effects on bone within the joint as well as systemically in the axial and appendicular bones. Abnormalities of skeletal maturation become most prominent during the pubertal growth spurt.

DIAGNOSIS

JIA is a clinical diagnosis without any diagnostic laboratory tests. The meticulous clinical exclusion of other diseases and many mimics is therefore essential. Laboratory studies, including tests for ANA and RF, are only supportive or prognostic, and their results may be normal in patients with JIA (see Tables 155-1 to 155-4).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for arthritis is broad and a careful, thorough investigation for other underlying etiology is imperative (Table 155-7). History, physical exam, laboratory tests, and radiography may help exclude other possible causes. Arthritis can be a presenting manifestation for any of the multisystem rheumatic diseases of childhood, including systemic lupus erythematosus (see Chapter 158), juvenile dermatomyositis (see Chapter 159), sarcoidosis (see Chapter 165), and

Figure 155-6 Progression of joint destruction in a girl with polyarticular juvenile idiopathic arthritis, rheumatoid factor–positive, despite doses of corticosteroids sufficient to suppress symptoms in the interval between the radiographs shown in **A** and **B. A,** Radiograph of the hand at onset. **B,** Radiograph taken 4 yr later, showing a loss of articular cartilage and destructive changes in the distal and proximal interphalangeal and metacarpophalangeal joints as well as destruction and fusion of wrist bones.

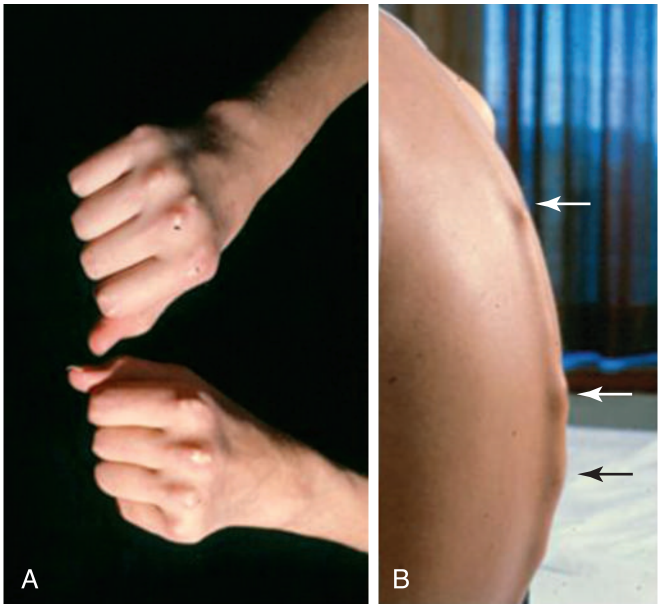

Figure 155-7 Rheumatoid nodules overlying bony prominences in an adolescent with rheumatoid factor–positive polyarthritis. *(From Rosenberg AM, Oen KG: Polyarthritis. In Cassiday JT, Petty RE, Laxer RM, et al, editors:* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders Elsevier,* Fig. 15-5, *p. 257.)*

Figure 155-8 CT scan of the temporomandibular joint of a patient with juvenile idiopathic arthritis exhibiting destruction on the right.

the vasculitic syndromes (see Chapter 167). In scleroderma (see Chapter 160), limited range of motion as a consequence of sclerotic skin overlying a joint may be confused with sequelae from chronic inflammatory arthritis. **Acute rheumatic fever** is characterized by exquisite joint pain and tenderness, a remittent fever, and a migratory polyarthritis. **Autoimmune hepatitis** can also be associated with an acute arthritis.

Many infections are associated with arthritis, and a recent history of infectious symptoms may help make a distinction. Viruses, including parvovirus B19, rubella, Epstein-Barr virus, hepatitis B virus, and HIV,

Figure 155-9 Radiograph of the cervical spine of a patient with active juvenile idiopathic arthritis, showing fusion of the neural arch between joints C2 and C3, narrowing and erosion of the remaining neural arch joints, obliteration of the apophyseal space, and loss of the normal lordosis.

Figure 155-10 Severe hip disease in a 13 yr old boy with active systemic juvenile idiopathic arthritis. Radiograph shows destruction of the femoral head and acetabula, joint space narrowing, and subluxation of left hip. The patient had received corticosteroids systemically for 9 yr.

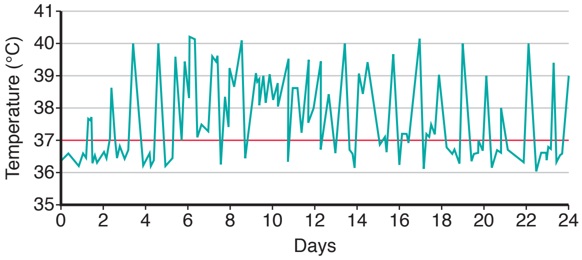

Figure 155-11 High-spiking intermittent fever in a 3 yr old patient with systemic juvenile idiopathic arthritis. *(From Ravelli A, Martini A: Juvenile idiopathic arthritis,* Lancet *369:767–778, 2007.)*

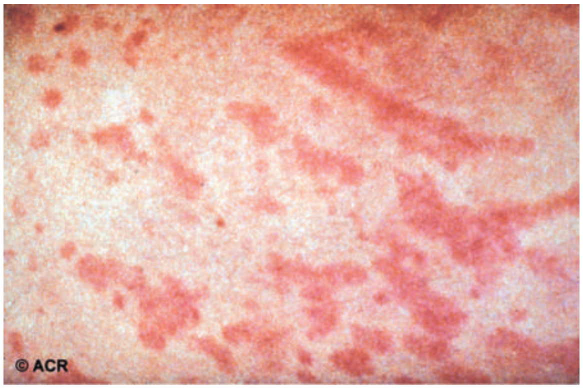

Figure 155-12 The rash of systemic juvenile idiopathic arthritis. The rash is salmon-colored, macular, and nonpruritic. Individual lesions are transient and occur in crops over the trunk and extremities. *(Reprinted from the American College of Rheumatology:* Clinical slide collection on the rheumatic diseases, *Atlanta, copyright 1991, 1995, 1997, ACR. Used with permission of the American College of Rheumatology.)*

Table 155-6	Main Clinical, Laboratory, and Pathologic Features of Macrophage Activation Syndrome
LABORATORY CRITERIA	
1. Cytopenias	
2. Abnormal liver function tests	
3. Coagulopathy (hypofibrinogenemia)	
4. Decreased erythrocyte sedimentation rate	
5. Hypertriglyceridemia	
6. Hyponatremia	
7. Hypoalbuminemia	
8. Hyperferritinemia	
9. Elevated sCD25 and sCD163	
CLINICAL CRITERIA	
1. Nonremitting fever	
2. Hepatomegaly	
3. Splenomegaly	
4. Lymphadenopathy	
5. Hemorrhages	
6. Central nervous system dysfunction (headache, seizures, lethargy, coma, disorientation)	
HISTOPATHOLOGIC CRITERIA	
1. Macrophage hemophagocytosis in the bone marrow aspirate	
2. Increased CD163 staining of the bone marrow	

From Ravelli A, Grom A, Behrens E, Cron R: Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment, Genes Immun *13:289–298, 2012.*

can induce a transient arthritis. Arthritis may follow enteric infections (see Chapter 157). **Lyme disease** (see Chapter 222) should be considered in children with oligoarthritis living in or visiting endemic areas. Although a history of tick exposure, preceding flu-like illness, and subsequent rash should be sought, they are not always present. Monoarticular arthritis unresponsive to antiinflammatory treatment may be the result of chronic mycobacterial or other infection such as *Kingella kingae*, and the diagnosis is established by synovial fluid analysis or biopsy. Acute onset of fever and a painful, erythematous, hot joint suggests septic arthritis. Isolated hip pain with limited motion raises the possibility of suppurative arthritis (see Chapter 685), osteomyelitis (see Chapter 684), toxic synovitis, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, and chondrolysis of the hip (see Chapter 678).

Lower-extremity arthritis and tenderness over insertion of ligaments and tendons, especially in a boy, raises the possibility of ERA (see Chapter 156). **Psoriatic arthritis** can manifest as limited joint involvement in an unusual distribution (e.g., small joints of the hand and

Table 155-7 Conditions Causing Arthritis or Extremity Pain

Conditions Causing Arthritis or Extremity Pain	
RHEUMATIC AND INFLAMMATORY DISEASES Juvenile idiopathic arthritis Systemic lupus erythematosus Juvenile dermatomyositis Polyarteritis nodosa Scleroderma Sjögren syndrome Behçet disease Overlap syndromes Antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis Sarcoidosis Kawasaki syndrome Henoch-Schönlein purpura Chronic recurrent multifocal osteomyelitis	**BONE AND CARTILAGE DISORDERS** Trauma Patellofemoral syndrome Hypermobility syndrome Osteochondritis dissecans Avascular necrosis (including Legg-Calvé-Perthes disease) Hypertrophic osteoarthropathy Slipped capital femoral epiphysis Osteolysis Benign bone tumors (including osteoid osteoma) Histiocytosis Rickets
SERONEGATIVE SPONDYLOARTHROPATHIES Juvenile ankylosing spondylitis Inflammatory bowel disease Psoriatic arthritis Reactive arthritis associated with urethritis, iridocyclitis, and mucocutaneous lesions	**NEUROPATHIC DISORDERS** Peripheral neuropathies Carpal tunnel syndrome Charcot joints
INFECTIOUS ILLNESSES Bacterial arthritis (septic arthritis, *Staphylococcus aureus, Kingella kingae*, pneumococcus, gonococcus, *Haemophilus influenzae*) Lyme disease Viral illness (parvovirus, rubella, mumps, Epstein-Barr virus, hepatitis B, Chikungunya virus) Fungal arthritis Mycobacterial infection Spirochetal infection Endocarditis	**NEOPLASTIC DISORDERS** Leukemia Neuroblastoma Lymphoma Bone tumors (osteosarcoma, Ewing sarcoma) Histiocytic syndromes Synovial tumors
REACTIVE ARTHRITIS Acute rheumatic fever Reactive arthritis (postinfectious caused by *Shigella, Salmonella, Yersinia, Chlamydia*, or meningococcus) Serum sickness Toxic synovitis of the hip Postimmunization	**HEMATOLOGIC DISORDERS** Hemophilia Hemoglobinopathies (including sickle cell disease)
IMMUNODEFICIENCIES Hypogammaglobulinemia Immunoglobulin A deficiency Human immunodeficiency virus	**MISCELLANEOUS DISORDERS** Autoinflammatory diseases Recurrent multifocal osteomyelitis Pigmented villonodular synovitis Plant-thorn synovitis (foreign-body arthritis) Myositis ossificans Eosinophilic fasciitis Tendinitis (overuse injury) Raynaud phenomenon
CONGENITAL AND METABOLIC DISORDERS Gout Pseudogout Mucopolysaccharidoses Thyroid disease (hypothyroidism, hyperthyroidism) Hyperparathyroidism Vitamin C deficiency (scurvy) Hereditary connective tissue disease (Marfan syndrome, Ehlers-Danlos syndrome) Fabry disease Farber disease Amyloidosis (familial Mediterranean fever)	**PAIN SYNDROMES** Fibromyalgia Growing pains Depression (with somatization) Reflex sympathetic dystrophy Regional myofascial pain syndromes

ankle) years prior to onset of cutaneous disease. **Inflammatory bowel disease** may manifest as oligoarthritis, usually affecting joints in the lower extremities, as well as gastrointestinal symptoms, elevations in ESR, and microcytic anemia.

Many conditions present solely with arthralgias (i.e., joint pain). Hypermobility may cause joint pain, especially in the lower extremities. Growing pains should be suspected in a child between the ages of 4-12 yr complaining of leg pain in the evenings with normal investigative studies and no morning symptoms. Nocturnal pain also alerts to the possibility of a malignancy. An adolescent with missed school days may suggest a diagnosis of fibromyalgia (see Chapter 168).

Children with **leukemia** or **neuroblastoma** may have joint or bone pain resulting from malignant infiltration of the bone, synovium, or, more often, the bone marrow, sometimes mo before demonstrating lymphoblasts on peripheral blood smear. Physical examination may reveal no tenderness, a deeper pain with palpation of the bone, or pain out of proportion to exam findings. Malignant pain often awakens the child from sleep and may cause cytopenias. Because platelets are an acute-phase reactant, a high ESR with leukopenia and a low normal platelet count may also be a clue to underlying leukemia. In addition, the characteristic quotidian fever of sJIA is absent in malignancy. Bone marrow examination is necessary for diagnosis. Some diseases, such as cystic fibrosis, diabetes mellitus, and the glycogen storage diseases, have associated arthropathies (see Chapter 169). Swelling that extends beyond the joint can be a sign of lymphedema or Henoch-Schönlein purpura (see Chapter 515). A peripheral arthritis indistinguishable from JIA occurs in the humoral immunodeficiencies (see Chapter 124), such as common variable immunodeficiency and

X-linked agammaglobulinemia. Skeletal dysplasias associated with a degenerative arthropathy are diagnosed from their characteristic radiologic abnormalities.

Systemic onset of JIA often presents as an fever of unknown origin (see Chapter 177). Important considerations in the differential diagnosis include infections (endocarditis, brucellosis, cat scratch disease, Q fever, mononucleosis), autoinflammatory disease (see Chapter 163) malignancy (leukemia, lymphoma, neuroblastoma) and HLH (see Chapter 507.2).

LABORATORY FINDINGS

Hematologic abnormalities often reflect the degree of systemic or articular inflammation, with elevated white blood cell and platelet counts and a microcytic anemia. Inflammation may also cause elevations in ESR and C-reactive protein, although it is not unusual for both to be normal in children with JIA.

Elevated ANA titers are present in 40-85% of children with oligoarticular or polyarticular JIA, but are rare with sJIA. ANA seropositivity is associated with increased risk of **chronic uveitis** in JIA. Approximately 5-15% of patients with polyarticular JIA are seropositive for RF. Anti–cyclic citrullinated peptide antibody, like RF, is a marker of more aggressive disease. Both ANA and RF seropositivity can occur in association with transient events, such as viral infection.

Children with sJIA usually have striking elevations in inflammatory markers and white blood cell and platelet counts. Hemoglobin levels are low, typically in the range of 7-10 g/dL, with indices consistent with anemia of chronic disease. The ESR is usually high, except in MAS. Although immunoglobulin levels tend to be high, ANA and RF are uncommon. **Ferritin values** are typically elevated and can be markedly increased in MAS (>10,000 ng/mL). In the setting of MAS, all cell lines have the potential to decline precipitously owing to the consumptive process. A low or normal white blood cell count and/or platelet count in a child with active sJIA should raise concerns for MAS.

Early radiographic changes of arthritis include soft tissue swelling, periarticular osteopenia, and periosteal new-bone apposition around affected joints (Fig. 155-13). Continued active disease may lead to subchondral erosions, loss of cartilage, with varying degrees of bony destruction, and fusion. Characteristic radiographic changes in cervical spine, most frequently in the neural arch joints at C2-C3 (see Fig. 155-9) may progress to atlantoaxial subluxation. MRI is more sensitive than radiography to detect early changes (Fig. 155-14).

TREATMENT

The goals of treatment are to achieve disease remission, prevent or halt joint damage, and foster normal growth and development. All children with JIA need individualized treatment plans, and management is tailored according to disease subtype and severity, presence of poor

Figure 155-13 **Early (6 mo duration) radiographic changes of juvenile idiopathic arthritis.** Soft-tissue swelling and periosteal new bone formation appear adjacent to the 2nd and 4th proximal interphalangeal joints.

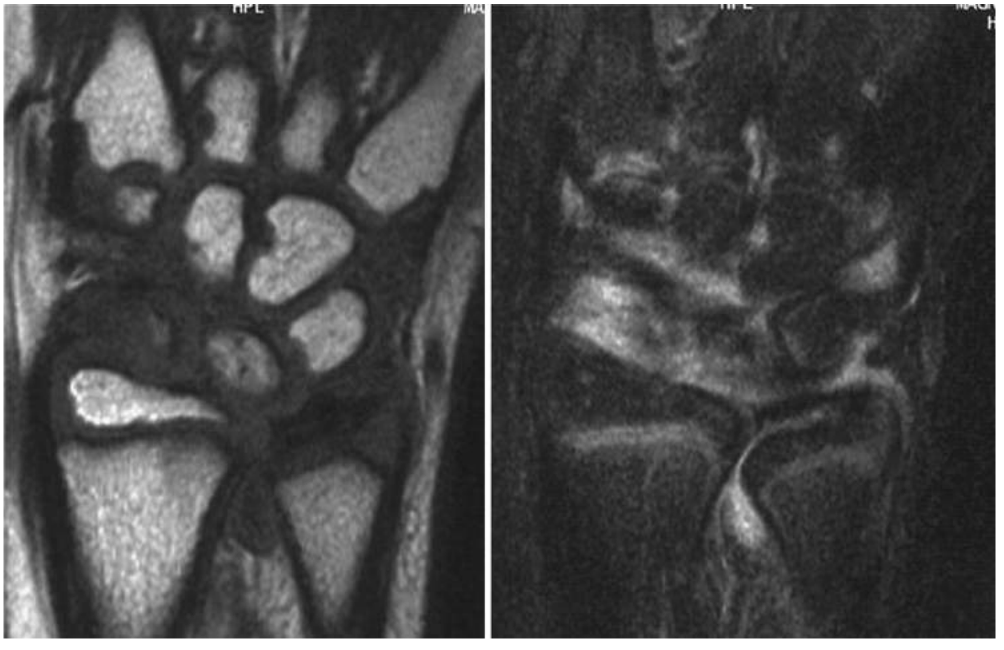

Figure 155-14 **MRI of the wrist in a child with wrist arthritis.** Image on the *left* shows multiple erosions of carpal bones. Image on the *right*, obtained after administration of gadolinium contrast agent, reveals uptake consistent with active synovitis.

Table 155-8 Pharmacologic Treatment of Juvenile Idiopathic Arthritis (JIA)

TYPICAL MEDICATIONS	TYPICAL DOSES	JIA SUBTYPE	SIDE EFFECT(S)
NONSTEROIDAL ANTIINFLAMMATORY DRUGS			
Naproxen	15 mg/kg/day PO divided bid (maximum dose 500 mg bid)	Polyarthritis Systemic Oligoarthritis	Gastritis, renal and hepatic toxicity, pseudoporphyria
Ibuprofen	40 mg/kg/day PO divided tid (maximum dose 800 mg tid)	Same as above	Same as above
Meloxicam	0.125 mg/kg PO once daily (maximum dose 15 mg daily)	Same as above	Same as above
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS			
Methotrexate	0.5-1 mg/kg PO or SC weekly (maximum dose 25 mg/wk)	Polyarthritis Systemic Persistent or extended oligoarthritis	Nausea, vomiting, oral ulcerations, hepatic toxicity, blood count dyscrasias, immunosuppression, teratogenicity
Sulfasalazine	Initial 12.5 mg/kg PO daily; increase by 10 mg/kg/day Maintenance: 40-50 mg/kg divided bid (maximum dose 2 g/day)	Polyarthritis	GI upset, allergic reaction, pancytopenia, renal and hepatic toxicity, Stevens-Johnson syndrome
Leflunomide*	10-20 mg PO daily	Polyarthritis	GI upset, hepatic toxicity, allergic rash, alopecia (reversible), teratogenicity (needs washout with cholestyramine)
BIOLOGIC AGENTS			
Anti–Tumor Necrosis Factor-α			
Etanercept	0.8 mg/kg SC weekly or 0.4 mg/kg SC twice weekly (maximum dose 50 mg/wk)	Polyarthritis Systemic Persistent or extended oligoarthritis	Immunosuppressant, concern for malignancy, demyelinating disease, lupus-like reaction, injection site reaction
Infliximab*	3-10 mg/kg IV q4-8wk	Same as above	Same as above, infusion reaction
Adalimumab	<30 kg: 20 mg SC every other week >30 kg: 40 mg SC every other week	Same as above	Same as above
Anticytotoxic T-Lymphocyte–Associated Antigen-4 Immunoglobulin			
Abatacept	<75 kg: 10 mg/kg/dose IV q4wk 75-100 kg: 750 mg/dose IV q4wk >100 kg: 1,000 mg/dose IV q4wk	Polyarthritis	Immunosuppressant, concern for malignancy, infusion reaction
Anti-CD20			
Rituximab*	750 mg/m2 IV 2 wk × 2 (maximum dose 1,000 mg)	Polyarthritis	Immunosuppressant, infusion reaction, progressive multifocal encephalopathy
Interleukin-1 Inhibitors			
Anakinra*	1-2 mg/kg SC daily (maximum dose 100 mg/day)	Systemic	Immunosuppressant, GI upset, injection site reaction
Canakinumab	15-40 kg: 2 mg/kg/dose SC q8wk >40 kg: 150 mg SC q8wk	Systemic	Immunosuppressant, headache, GI upset, injection site reaction
Rilonacept*	2.2 mg/kg/dose SC weekly (maximum dose 160 mg)	Systemic	Immunosuppressant, allergic reaction, dyslipidemia, injection site reaction
Interleukin-6 Receptor Antagonist			
Tocilizumab	<30 kg: 12 mg/kg/dose q2wk >30 kg: 8 mg/kg/dose q2wk (maximum dose 800 mg)	Systemic Polyarthritis	Immunosuppressant, hepatic toxicity, dyslipidemia, cytopenias, GI upset, infusion reaction

bid, Twice daily; GI, gastrointestinal; IV, intravenous; PO, oral; SC, subcutaneous; tid, 3 times daily.
*Not indicated by the U.S. Food and Drug Administration for use in JIA.

prognostic indicators, and response to medications. Disease management also requires monitoring for potential medication toxicities (see Chapter 154).

Children with oligoarthritis often show partial response to nonsteroidal antiinflammatory drugs (NSAIDs), with improvement in inflammation and pain (Table 155-8). Those who have no or partial response after 4-6 wk of treatment with NSAIDs or who have functional limitations, such as joint contracture or leg-length discrepancy, benefit from injection of intraarticular corticosteroids. Triamcinolone hexacetonide is a long-lasting preparation that provides a prolonged response. A minority of patients with oligoarthritis show no response to NSAIDs and injections, and therefore require treatment with disease-modifying antirheumatic drugs (DMARDs), methotrexate, and, if no response, TNF inhibitors.

NSAIDs alone rarely induce remission in children with polyarthritis or sJIA. Methotrexate is the oldest and least toxic of the DMARDs available for adjunctive therapy. It may take 6-12 wk to see the effects of methotrexate. Failure of methotrexate monotherapy warrants the addition of a biologic DMARD. Biologic medications that inhibit proinflammatory cytokines, such as TNF-α, IL-1, and IL-6, demonstrated excellent disease control. TNF-α antagonists (e.g., etanercept, adalimumab) are used to treat children with an inadequate response to methotrexate, with poor prognostic factors, or with severe disease onset. Early aggressive therapy with a combination of methotrexate and a TNF-α antagonist may result in earlier achievement of clinically inactive disease.

TNF inhibition is not as effective for the systemic symptoms found in sJIA. When systemic symptoms dominate systemic steroids are started followed by the initiation of IL-1 or IL-6 antagonist therapy, which often induces a dramatic and rapid response. Patients with severe disease activity may go directly to anakinra. Canakinumab, an IL-1β inhibitor, and tocilizumab, an IL-6 receptor antagonist, are

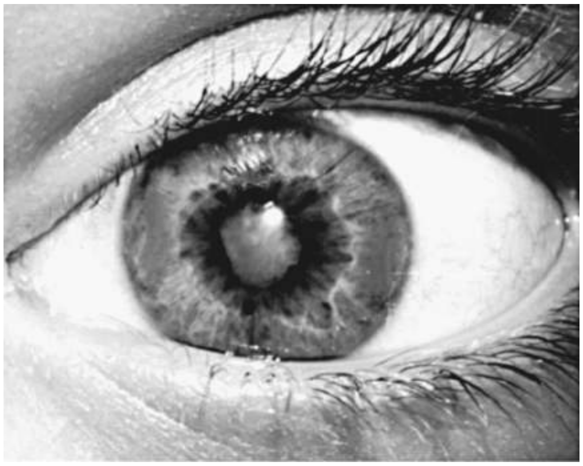

Figure 155-15 **Chronic anterior uveitis, or iridocyclitis, of juvenile idiopathic arthritis.** Extensive posterior synechiae have resulted in a small, irregular pupil. A well-developed cataract and early band keratopathy can be seen at the medial and lateral margins of the cornea.

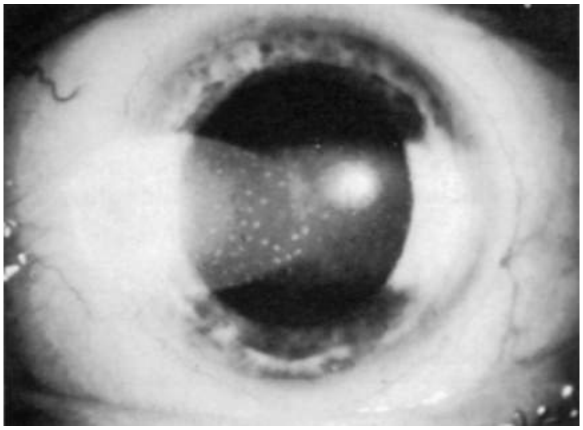

Figure 155-16 A slit-lamp examination shows "flare" in the fluid of the anterior chamber (caused by increased protein content) and keratic precipitates on the posterior surface of the cornea, representing small collections of inflammatory cells. *(Courtesy of Dr. H.J. Kaplan. From Petty RE, Rosenbaum JT: Uveitis in juvenile idiopathic arthritis. In Cassidy JT, Petty RE, Laxer RM, et al, editors,* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders, Fig. 20-3, p. 309.)*

FDA-approved treatments for sJIA in children older than 2 yr. Standardized consensus treatment plans have been published to guide therapy for sJIA. These outline 4 treatment plans based on glucocorticoids, methotrexate, anakinra, or tocilizumab with optional glucocorticoid use in the latter 3 plans as clinically indicated.

With the advent of newer DMARDs, the use of systemic corticosteroids can often be avoided or minimized. Systemic steroids are recommended only for management of severe systemic illness, for **bridge therapy** during the wait for therapeutic response to a DMARD, and for control of uveitis. Steroids impose risks of severe toxicities, including Cushing syndrome, growth retardation, and osteopenia, and they do not prevent joint destruction.

Oral Janus kinase (JAK) inhibitors (tofacitinib, ruxolitinib) inhibit JAK signaling pathways involved in immune activation and inflammation. Tofacitinib is FDA approved for adults with rheumatoid arthritis.

Management of JIA must include periodic slit-lamp ophthalmologic examinations to monitor for asymptomatic uveitis (see Table 155-5; Figs. 155-15 and 155-16). Optimal treatment of uveitis requires collaboration between the ophthalmologist and rheumatologist. Initial management of uveitis may include mydriatics and corticosteroids used topically, systemically, or through periocular injection. DMARDs allow for a decrease in exposure to steroids, and methotrexate and antibodies to TNF-α (adalimumab and infliximab) are effective in treating severe uveitis.

Dietary evaluation and counseling to ensure appropriate calcium, vitamin D, protein, and caloric intake are important for children with JIA. Physical therapy and occupational therapy are invaluable adjuncts to any treatment program. A social worker and nurse clinician can be important resources for families, to recognize stresses imposed by a chronic illness, to identify appropriate community resources, and to aid compliance with the treatment protocol.

PROGNOSIS

Although the course of JIA in an individual child is unpredictable, some prognostic generalizations can be made on the basis of disease type and course. Studies analyzing management of JIA in the pre-TNF-α era indicate that up to 50% of patients with JIA have active disease persisting into early adulthood, often with severe limitations of physical function.

Children with persistent oligoarticular disease fare well, with a majority achieving disease remission. Those with extended oligoarticular disease have a poorer prognosis. Children with oligoarthritis, particularly girls who are ANA-positive and with onset of arthritis earlier than 6 yr of age, are at greatest risk for development of chronic uveitis. There is no association between the activity or severity of arthritis and uveitis. Persistent, uncontrolled anterior uveitis (see Fig. 155-15) can cause posterior synechiae, cataracts, glaucoma, and band keratopathy, with resultant blindness. Morbidity can be averted with early diagnosis and implementation of systemic therapy.

The child with polyarticular JIA often has a more prolonged course of active joint inflammation and requires early and aggressive therapy. Predictors of severe and persistent disease include young age at onset, RF seropositivity or rheumatoid nodules, the presence of anti–cyclic citrullinated peptide antibodies, and large numbers of affected joints. Disease involving the hip and hand and wrist is also associated with a poorer prognosis and may lead to significant functional impairment.

sJIA is often the most difficult to control in terms of both articular inflammation and systemic manifestations. Poorer prognosis is related to polyarticular distribution of arthritis, fever lasting >3 mo, and increased inflammatory markers, such as platelet count and ESR, for >6 mo. IL-1 and IL-6 inhibitors, have changed the management and improved the outcomes for children with severe and prolonged systemic disease.

Orthopedic complications include leg length discrepancy and flexion contractures, particularly of the knees, hips, and wrists. Discrepancies in leg length can be managed with a shoe lift on the shorter side to prevent secondary scoliosis. Joint contractures require aggressive medical control of arthritis, often in conjunction with intraarticular corticosteroid injections, appropriate splinting, and stretching of the affected tendons. Popliteal cysts may require no treatment if they are small or respond to intraarticular corticosteroid injection in the anterior knee.

Psychosocial adaptation may be affected by JIA. Studies indicate that, compared with control subjects, a significant number of children with JIA have problems with lifetime adjustment and employment. Disability not directly associated with arthritis may continue into young adulthood in as many as 20% of patients, together with continuing chronic pain syndromes at a similar frequency. Psychological complications, including problems with school attendance and socialization, may respond to counseling by mental health professionals.

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Chapter 156

Ankylosing Spondylitis and Other Spondyloarthritides

Pamela F. Weiss and Robert A. Colbert

The diseases collectively referred to as **spondyloarthritides** include ankylosing spondylitis (AS), arthritis associated with inflammatory bowel disease (IBD) and psoriasis, and reactive arthritis following gastrointestinal or genitourinary infections (Tables 156-1 and 156-2). Many children with spondyloarthritis are classified in the juvenile idiopathic arthritis (JIA) category of **enthesitis-related arthritis (ERA). Children and adolescents with spondyloarthritis, who may not meet ERA criteria, include arthritis associated with psoriasis or IBD, juvenile AS (JAS), and reactive arthritis.**

EPIDEMIOLOGY

JIA is diagnosed in 90 per 100,000 children in the United States every year (see Chapter 155). ERA accounts for 10-20% of JIA, and has a mean age of onset of 12 yr. Unlike other JIA categories, males are affected more often than females, accounting for 60% of ERA cases. AS occurs in 0.2-0.5% of adults, with approximately 15% of cases beginning in childhood. These disorders can be familial, largely as a result of the influence of HLA-B27, which is found in 90% of JAS and 50% of ERA compared to 7% of healthy individuals. Approximately 20% of children with ERA have a family history of HLA-B27–associated disease, such as reactive arthritis, AS, or IBD with sacroiliitis.

ETIOLOGY AND PATHOGENESIS

Spondyloarthritides are complex diseases in which susceptibility is largely genetically determined. HLA-B27 is responsible for 23.3% of AS heritability, with genes encoding the interleukin (IL)-23 receptor (*IL23R*), ERAP1 (endoplasmic reticulum aminopeptidase-1), IL-12p40 (*IL12B*), and others having important roles, but together accounting for only approximately 2% of heritability. Infection with certain gastrointestinal or genital pathogens can trigger reactive arthritis (see Chapter 157 and Table 156-2); environmental triggers for other forms of spondyloarthritis have not been identified. Unusual properties of HLA-B27, such as its tendency to misfold and form unusual cell surface structures, may have a role. Inflamed joints and entheses in spondyloarthritides contain T cells, B cells, macrophages, osteoclasts, proliferating fibroblasts and osteoblasts. Bone loss and osteoproliferation in and around vertebral bodies and facet joints in long-standing AS contribute to significant morbidity.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical manifestations that help distinguish spondyloarthritis from other forms of juvenile arthritis include arthritis of the axial skeleton (sacroiliac joints) and hips, enthesitis (inflammation at the site of tendon, ligament, or joint capsule attachment to bone), symptomatic eye inflammation (acute anterior uveitis), and gastrointestinal inflammation (even in the absence of IBD) (see Table 156-1).

Enthesitis-Related Arthritis

Children have ERA if they have *either* arthritis and enthesitis *or* arthritis or enthesitis, with at least 2 of the following characteristics: (1) sacroiliac joint tenderness or inflammatory lumbosacral pain, (2) the presence of HLA-B27, (3) onset of arthritis in a male older than 6 yr,

Table 156-2 Etiologic Microorganisms of Reactive Arthritis

PROBABLE	POSSIBLE
Chlamydia trachomatis	*Neisseria gonorrhoeae*
Shigella flexneri	*Mycoplasma fermentans*
Salmonella enteritidis	*Mycoplasma genitalium*
Salmonella typhimurium	*Ureaplasma urealyticum*
Yersinia enterocolitica	*Escherichia coli*
Yersinia pseudotuberculosis	*Cryptosporidium*
Campylobacter jejuni	*Entamoeba histolytica*
	Giardia lamblia
	Brucella abortus
	Clostridium difficile
	Streptococcus pyogenes
	Chlamydia pneumoniae
	Chlamydia psittaci

From Kim PS, Klausmeier TL, Orr DP: Reactive arthritis: a review. J Adolesc Health 44:309–315, 2009, Table 2, p. 311.

Table 156-1 Overlapping Characteristics of the Spondyloarthritides

CHARACTERISTIC	JUVENILE ANKYLOSING SPONDYLITIS	JUVENILE PSORIATIC ARTHRITIS	INFLAMMATORY BOWEL DISEASE	REACTIVE ARTHRITIS
Enthesitis	+++	+	+	++
Axial arthritis	+++	++	++	+
Peripheral arthritis	+++	+++	+++	+++
HLA-B27 positive	+++	+	+++	+++
Antinuclear antibody positive	–	++	–	–
Rheumatoid factor positive	–	–	–	–
Systemic disease:				
Eyes	+	+	+	+
Skin	–	+++	+	+
Mucous membranes	–	–	+	+
Gastrointestinal tract	–	–	++++	+++

Frequency of characteristics: –, absent; +, <25%; ++, 25-50%; +++, 50-75%, ++++, 75% or more.
From Cassidy JT, Petty RE: Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Elsevier/Saunders.*

(4) acute anterior uveitis, and (5) a family history of an HLA-B27–associated disease (ERA, sacroiliitis with IBD, reactive arthritis, or acute anterior uveitis) in a 1st-degree relative. Patients with psoriasis (or a family history of psoriasis in a 1st-degree relative), a positive rheumatoid factor test result, or systemic arthritis are excluded from this group. During the 1st 6 mo of disease the arthritis is typically asymmetric and involves 4 or fewer joints. The most frequently affected joints are the knees, ankles, and hips. Inflammation of the small joints of the foot, or tarsitis, is highly suggestive of ERA. Enthesitis is typically symmetric and most commonly affects the lower limbs. Up to 40% of children develop clinical or radiographic evidence of sacroiliac joint arthritis as part of their disease. When the sacroiliac or other axial joints are involved, children may experience inflammatory back pain (Table 156-3) and alternating buttock pain. Patients may also experience pain with palpation of the lower back or with pelvic compression. Untreated sacroiliitis may evolve into AS, but risk factors for progression are unclear.

Psoriatic Arthritis

Psoriatic arthritis accounts for approximately 10% of JIA. Common clinical features of psoriatic arthritis are nail pitting (Fig. 156-1), onycholysis, and dactylitis (sausage-like swelling of the fingers or toes).

Children have psoriatic arthritis if they have arthritis and psoriasis *or* arthritis and at least 2 of the following: (1) dactylitis, (2) nail pitting or onycholysis, or (3) psoriasis in a 1st-degree relative. The presence of psoriasis aids in diagnosis but is not required. Disease onset peaks during the preschool and early adolescent years. Children with onset during the preschool years are more often female, antinuclear antibody–positive, and at risk for asymptomatic ocular inflammation.

Table 156-3	Symptoms Characteristic of Inflammatory Back Pain
Pain at night with morning stiffness (and improvement upon arising)	
No improvement with rest	
Improvement with exercise	
Insidious onset	
Good response to nonsteroidal antiinflammatory drugs	

Disease onset during adolescence is equally common among males and females. In the majority of children, the arthritis is asymmetric and affects 4 or fewer joints at presentation. Large (knees and ankles) and small (fingers and toes) joints may be involved. Although distal interphalangeal joint involvement is uncommon, it is highly suggestive of the diagnosis. Enthesitis is detectable in 20-60% of patients and seems to be more frequent in those who present at an older age. Axial (sacroiliac) and root (hip) joints may be affected in up to 30% of children; the risk of axial arthritis is highest in those who are HLA-B27–positive.

Juvenile Ankylosing Spondylitis

JAS frequently begins with oligoarthritis and enthesitis. The arthritis occurs predominantly in the lower extremities and often involves the hips. In comparison to adult-onset AS, axial disease and inflammatory back pain are less frequent at disease onset, while enthesitis and peripheral arthritis are more common. AS is diagnosed according to the modified NY criteria if there is sufficient radiographic evidence of sacroiliitis (sacroiliitis of grade 2 or greater bilaterally or at least grade 3 unilaterally) and if the patient meets at least one clinical criterion involving inflammatory back pain, limitation of motion in the lumbar spine (Fig. 156-2), or limitation of chest expansion. JAS is present if the patient is <16 yr old. Juvenile *onset* AS is frequently used to describe adult AS when the symptoms began before 16 yr of age, but full criteria were not met until later.

To fulfill the modified New York criteria for AS, patients must have radiographic changes in the sacroiliac joints as well as clinical sequelae of axial disease. Because radiographic sacroiliitis can take many years to develop in adults and even longer in children, and clinical sequelae may lag further behind, criteria to identify pre-radiographic axial spondyloarthritis have been developed by the Assessment of SpondyloArthritis International Society. To meet criteria for axial spondyloarthritis patients must have at least 3 mo of back pain and sacroiliitis on imaging (acute inflammation on MRI or definite radiographic sacroiliitis by the New York criteria) plus 1 feature of spondyloarthritis (i.e., inflammatory back pain, arthritis, enthesitis [heel], uveitis, dactylitis, psoriasis, Crohn disease/ulcerative colitis, good response to nonsteroidal antiinflammatory drugs [NSAIDs], family history for spondyloarthritis, HLA-B27, or elevated C-reactive protein). Alternatively, patients can fulfill axial spondyloarthritis criteria if

Figure 156-1 Nail pitting *(arrowhead)* and "sausage digit" (dactylitis) of the left index finger of a girl with juvenile psoriatic arthritis. *(From Petty RE, Malleson P: Spondyloarthropathies of childhood,* Pediatr Clin North Am *33:1079–1096, 1986.)*

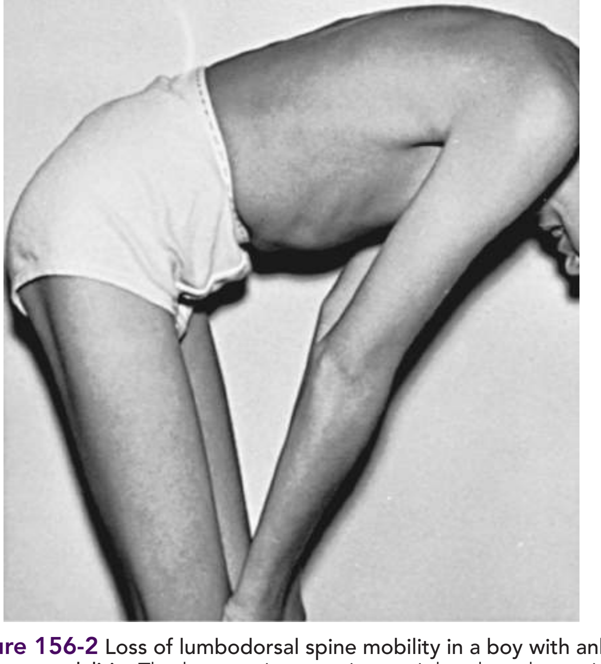

Figure 156-2 Loss of lumbodorsal spine mobility in a boy with ankylosing spondylitis. The lower spine remains straight when the patient bends forward.

they are HLA-B27–positive and have at least 2 features of spondyloarthritis. These criteria have not been validated in the pediatric population but may be useful as a guide to evaluating preradiographic spondyloarthritis.

Arthritis with Inflammatory Bowel Disease

The presence of erythema nodosum, pyoderma gangrenosum, fever, weight loss, or anorexia in a child with chronic arthritis should raise suspicion of IBD. Two patterns of arthritis complicate IBD. Polyarthritis affecting large and small joints is most common and often reflects the activity of the intestinal inflammation. Less frequently, arthritis of the axial skeleton, including the sacroiliac joints, occurs, resulting in AS. As with psoriatic arthritis, the presence of HLA-B27 is a risk factor for the development of axial disease. The severity of axial involvement is independent of the activity of the gastrointestinal inflammation.

LABORATORY FINDINGS

Laboratory evidence of systemic inflammation with elevation of the erythrocyte sedimentation rate and/or C-reactive protein value is variable in most spondyloarthritides and may or may not be present at the onset of disease. Rheumatoid factor and antinuclear antibodies are absent, except in patients with psoriatic arthritis, of which as many as 50% are antinuclear antibody–positive. HLA-B27 is present in ≈90% of children with JAS, compared with ≈7% of healthy individuals but is less frequent in ERA and other types of spondyloarthritis.

Imaging

Conventional radiographs detect chronic bony changes and damage but not active inflammation. Early radiographic changes in the sacroiliac joints include indistinct margins and erosions that can result in joint space widening. Sclerosis typically starts on the iliac side of the joint (Fig. 156-3). Peripheral joints may exhibit periarticular osteoporosis, with loss of sharp cortical margins in areas of enthesitis, which may eventually show erosions or bony spurs (enthesophytes). Squaring of the corners of the vertebral bodies and syndesmophyte formation resulting in the classic "bamboo spine" characteristic of advanced AS is rare in early disease, particularly in childhood. CT, like radiographs, can detect chronic bony changes but not active inflammation and has the disadvantage of more radiation exposure. The **gold standard** for early visualization of sacroiliitis is evidence of bone marrow edema adjacent to the joint on **MRI** with short T1 inversion recovery (STIR) sequences. Gadolinium does not add value to the study if STIR is used. MRI will reveal abnormalities before the plain radiograph. Whole body MRI is also used to evaluate the axial skeleton in adults with early disease as it can detect vertebral lesions in addition to sacroiliac changes.

Figure 156-3 Well-developed sacroiliitis in a boy with ankylosing spondylitis. Both sacroiliac joints show extensive sclerosis, erosion of joint margins, and apparent widening of the joint space.

DIFFERENTIAL DIAGNOSIS

The onset of arthritis following a recent history of diarrhea or symptoms of urethritis or conjunctivitis may suggest reactive arthritis (see Chapter 157). Lower back pain can be caused by suppurative arthritis of the sacroiliac joint, osteomyelitis of the pelvis or spine, osteoid osteoma of the posterior elements of the spine, pelvic muscle pyomyositis, or malignancies. In addition, mechanical conditions such as spondylolysis, spondylolisthesis, and Scheuermann disease should be considered. Back pain secondary to fibromyalgia usually affects the soft tissues of the upper back in a symmetric pattern and is associated with well-localized tender points and sleep disturbance (see Chapter 168.1). Legg-Calvé-Perthes disease (avascular necrosis of the femoral head), slipped capital femoral epiphysis, and chondrolysis may also manifest as pain over the inguinal ligament and loss of internal rotation of the hip joint, but without other features of spondyloarthritis, such as involvement of other entheses and/or joints. Radiography or MRI is critical for distinguishing these conditions.

TREATMENT

The goals of therapy are to control inflammation, minimize pain, preserve function, and prevent **ankylosis** (fusion of adjacent bones) using a combination of antiinflammatory medications, physical therapy, and education. Treatment regimens for spondyloarthritis include monotherapy or combination therapy with NSAIDs, disease-modifying antirheumatic drugs, or biologic agents. NSAIDs, such as naproxen (15-20 mg/kg/day), are frequently used initially and may reduce structural damage (syndesmophyte formation and growth) if used continually. With relatively mild disease, intraarticular corticosteroids (e.g., triamcinolone hexacetonide) may also help to control peripheral joint inflammation. However, for moderate disease and JAS, it is typically necessary to add a second-line agent. Disease-modifying antirheumatic drugs such as sulfasalazine (up to 50 mg/kg/day; maximum 3 g/day) or methotrexate (10 mg/m^2) may be beneficial for peripheral arthritis, but these medications have not been shown to improve axial disease in adults. Tumor necrosis factor-α inhibitors (e.g., etanercept, infliximab, adalimumab) have been efficacious in reducing symptoms and improving function in adults with AS, and there is evidence that similar responses are seen in children. It remains unclear whether tumor necrosis factor inhibitors have an impact on structural damage in established AS, underscoring the need for earlier recognition and better therapies.

Physical therapy and low-impact exercise should be included in the treatment program for all children with spondyloarthritis. Exercise to maintain range of motion in the back, thorax, and affected joints should be instituted early in the disease course. Custom-fitted insoles are particularly useful in management of painful entheses around the feet, and the use of pillows to position the lower extremities while the child is in bed can be helpful.

PROGNOSIS

Observational studies suggest that ongoing disease activity for greater than 5 yr in juvenile spondyloarthritis predicts disability. Disease remission occurs in less than 20% of children with spondyloarthritis 5 yr after diagnosis. Factors associated with disease progression include tarsitis, HLA-B27 positivity, hip arthritis within the 1st 6 mo, and disease onset after age 8. Important questions, such as which patients with ERA will go on to have JAS/AS, have yet to be addressed. Outcomes for JAS compared with adult-onset AS suggest that hip disease requiring replacement is more common in children but axial disease is more severe in adults.

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Chapter 157

Reactive and Postinfectious Arthritis

Pamela F. Weiss and Robert A. Colbert

In addition to causing arthritis by means of direct microbial infection (i.e., septic arthritis; see Chapter 685), infection can lead to the generation and deposition of immune complexes as well as antibody or T cell–mediated cross-reactivity with self. Microbes may influence the immune response in ways that indirectly affect susceptibility to immune-mediated inflammatory diseases such as systemic lupus erythematosus, inflammatory bowel disease, juvenile idiopathic arthritis, and spondyloarthritis. **Reactive and postinfectious arthritis** are defined as joint inflammation caused by a sterile inflammatory reaction following a recent infection. We use *reactive arthritis* to refer to arthritis that occurs following enteropathic or urogenital infections and *postinfectious arthritis* to describe arthritis that occurs after infectious illnesses not classically considered in the reactive arthritis group, such as infection with group A streptococcus or viruses. In some cases, nonviable components of the initiating organism have been demonstrated in affected joints, and the presence of viable, yet nonculturable, bacteria within the joint remains an area of investigation.

The course of **reactive arthritis** is variable and may remit or progress to a chronic spondyloarthritis including ankylosing spondylitis (see Chapter 156). In **postinfectious arthritis**, the pain or joint swelling is usually transient, lasting less than 6 wk, and does not necessarily share the typical spondyloarthritis pattern of joint involvement. The distinction between postinfectious arthritis and reactive arthritis is not always clear, either clinically or in terms of pathophysiology.

PATHOGENESIS

Reactive arthritis typically follows enteric infection with *Salmonella* sp., *Shigella flexneri, Yersinia enterocolitica, Campylobacter jejuni*, or genitourinary tract infection with *Chlamydia trachomatis*. *Escherichia coli* and *Clostridium difficile* are also causative enteric agents, although less common (see Table 156-2 in Chapter 156). Although similar in some respects to reactive arthritis, acute rheumatic fever caused by group A streptococcus (see Chapters 183.1 and 438), arthritis associated with infective endocarditis (see Chapter 437), and the tenosynovitis associated with *Neisseria gonorrhoeae* are considered in later chapters.

Approximately 75% of patients with reactive arthritis are HLA-B27–positive. Incomplete elimination of bacteria and bacterial products, such as DNA, has been proposed as a factor in reactive arthritis. A relationship with clinical characteristics of specific infectious disorders is not present. In postinfectious arthritis, several viruses (rubella, varicella-zoster, herpes simplex, cytomegalovirus) have been isolated from the joints of patients. Antigens from other viruses (e.g., hepatitis B, adenovirus) have been identified in immune complexes from joint tissue.

Patients with reactive arthritis who are HLA-B27–positive have an increased frequency of acute and symptomatic uveitis and other extraarticular features. In addition, HLA-B27 is a risk factor for persistent gastrointestinal inflammation following enteric infections, even after resolution of the initial infection, and significantly increases the risk that the individual will develop chronic spondyloarthritis. Nevertheless, reactive arthritis also occurs in HLA-B27–negative patients, emphasizing the importance of other genes in disease susceptibility.

CLINICAL MANIFESTATIONS AND DIFFERENTIAL DIAGNOSIS

Symptoms of reactive arthritis begin approximately 2-4 wk following infection. The classic triad of arthritis, urethritis, and conjunctivitis is relatively uncommon in children. The arthritis is typically oligoarticular, with a predilection for lower extremities. Dactylitis may occur, and enthesitis (Fig. 157-1) is common (affects as many as 90% of patients; see Chapter 156). Cutaneous manifestations can occur and may include circinate balanitis, ulcerative vulvitis, oral lesions, erythema nodosum, and keratoderma blennorrhagica, which is similar in appearance to pustular psoriasis (Fig. 157-2). Systemic symptoms may include fever, malaise, and fatigue. Early in the disease course, markers of inflammation—erythrocyte sedimentation rate, C-reactive protein, and platelets—may be markedly elevated. The clinical manifestations may last for weeks to months.

Familiarity with other causes of postinfectious arthritis is vital when a diagnosis of reactive arthritis is being considered. Numerous viruses are associated with postinfectious arthritis (Table 157-1) and may result in particular patterns of joint involvement. Rubella and hepatitis B virus typically affect the small joints, whereas mumps and varicella often involve large joints, especially the knees. The **hepatitis B arthritis–dermatitis syndrome** is characterized by urticarial rash and a symmetric migratory polyarthritis resembling that of serum sickness. Rubella-associated arthropathy may follow natural rubella infection and, infrequently, rubella immunization. It typically occurs in young women, with an increased frequency with advancing age, and is uncommon in preadolescent children and in males. Arthralgia of the knees and hands usually begins within 7 days of onset of the rash or 10-28 days after immunization. Parvovirus B19, which is responsible

Figure 157-1 Enthesitis—swelling of the posterior aspect of the left heel and lateral aspect of the ankle. *(Courtesy of Nora Singer, Case Western Reserve University and Rainbow Babies' Hospital.)*

Figure 157-2 Keratoderma blennorrhagica. *(Courtesy of Dr. M.F. Rein and The Centers for Disease Control and Prevention Public Health Image Library, 1976. Image #6950.)*

Table 157-1 Viruses Associated with Arthritis

TOGAVIRUSES	ADENOVIRUSES Adenovirus 7
RUBIVIRUS Rubella	HERPESVIRUSES Epstein-Barr Cytomegalovirus Varicella-zoster Herpes simplex
ALPHAVIRUSES Ross River Chikungunya O'nyong-nyong Mayaro Sindbis Ockelbo Pogosta	PARAMYXOVIRUSES Mumps
	HEPADNAVIRUS Hepatitis B
ORTHOPOXVIRUSES Variola virus (smallpox) Vaccinia virus Parvoviruses	ENTEROVIRUSES Echovirus Coxsackievirus B

Adapted from Cassidy JT, Petty RE: Infectious arthritis and osteomyelitis. In Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Saunders.*

for erythema infectiosum (fifth disease), can cause arthralgia, symmetric joint swelling, and morning stiffness, particularly in adult women and less frequently in children. Arthritis occurs occasionally during cytomegalovirus infection and may occur during varicella infections but is rare after Epstein-Barr virus infection. Varicella may also be complicated by suppurative arthritis, usually secondary to group A streptococcus infection. HIV is associated with an arthritis that resembles psoriatic arthritis more than juvenile idiopathic arthritis (see Chapter 155).

Poststreptococcal arthritis is a postinfectious arthritis that may follow infection with either group A or group G streptococcus. It is typically oligoarticular, affecting lower extremity joints, and mild symptoms can persist for months. Poststreptococcal arthritis differs from rheumatic fever, which typically manifests with painful migratory polyarthritis of brief duration. Because valvular lesions have occasionally been documented by echocardiography after the acute illness, some clinicians consider poststreptococcal arthritis to be an incomplete form of acute rheumatic fever (see Chapter 183.1). Certain HLA-DRB1 types may predispose children to development of either poststreptococcal arthritis (HLA-DRB1*01) or acute rheumatic fever (HLA-DRB1*16).

Transient synovitis (toxic synovitis), another form of postinfectious arthritis, typically affects the hip, often after an upper respiratory tract infection (see Chapter 678.2). Boys from 3-10 yr of age are most commonly affected and have acute onset of severe pain in the hip (groin), with referred pain to the thigh or knee, lasting approximately 1 wk. The erythrocyte sedimentation rate and white blood cell count are usually normal. Radiologic or ultrasound examination may confirm widening of the joint space secondary to an effusion. Aspiration of joint fluid is often necessary to exclude septic arthritis and typically results in dramatic clinical improvement. The trigger is presumed to be viral, although responsible microbes have not been identified.

Nonsuppurative arthritis has been reported in children, usually adolescent boys, in association with **severe truncal acne**. Patients often have fever and persistent infection of the pustular lesions. **Pyogenic (sterile) arthritis, pyoderma gangrenosum and acne (cystic)** syndrome, an autosomal dominant disorder caused by a mutation in the *PSTPIP1* gene, is a difficult-to-treat but rare autoinflammatory disorder that has responded to anakinra or anti–tumor necrosis factor antibody therapy in a few patients. Recurrent episodes of erosive arthritis begin in childhood, while cystic acne and the painful ulcerating lesions of pyoderma gangrenosum begin during adolescence. Recurrent episodes may also be associated with a sterile myopathy and may last for several months.

Infective endocarditis can be associated with arthralgia, arthritis, or signs suggestive of vasculitis, such as Osler nodes, Janeway lesions, and Roth spots. Postinfectious arthritis, perhaps because of immune complexes, also occurs in children with *N. gonorrhoeae, Neisseria meningitidis, Haemophilus influenzae* type b, and *Mycoplasma pneumoniae* infections.

DIAGNOSIS

A recent genitourinary or gastrointestinal infection may suggest the diagnosis of reactive arthritis, but there is no diagnostic test. A complete blood count, acute phase reactants, complete metabolic panel, and urinalysis may be helpful to exclude other etiologies. Although stool or urogenital tract cultures can be performed in an attempt to isolate the triggering organism, the offending agent is not typically found at the time arthritis presents. Imaging findings are nonspecific or normal. Documenting previous streptococcal infection with antibody testing (anti-streptolysin O and anti-DNAse B) may help to diagnose postinfectious arthritis. Serum sickness associated with the antibiotic treatment of preceding infection must be excluded.

Because the preceding infection can be remote or mild and often not recalled by the patient, it is also important to rule out other causes of arthritis. Acute and painful arthritis affecting a single joint suggests septic arthritis, mandating joint aspiration; osteomyelitis may cause pain and an effusion in an adjacent joint but is more often associated with focal bone pain and tenderness at the site of infection. Arthritis affecting a single joint, particularly the knee, may also be secondary to Lyme in endemic areas. The diagnosis of postinfectious arthritis is often established by exclusion, and after the arthritis has resolved. Arthritis associated with gastrointestinal symptoms or abnormal liver function test results may be triggered by infectious or autoimmune hepatitis. Arthritis or spondyloarthritis may occur in children with inflammatory bowel disease, such as Crohn disease or ulcerative colitis (see Chapter 336). When 2 or more blood cell lines are low or progressively decrease in a child with arthritis, parvovirus infection, macrophage activation (hemophagocytic) syndrome, and leukemia should be strongly considered. Persistent arthritis (>6 wk) suggests the possibility of a chronic rheumatic disease, including juvenile idiopathic arthritis (see Chapters 155 and 156) and systemic lupus erythematosus (see Chapter 158).

TREATMENT

Specific treatment is unnecessary for most cases of reactive or postinfectious arthritis. Nonsteroidal antiinflammatory agents are often needed for management of pain and functional limitation. Unless ongoing *Chlamydia* infection is suspected, attempts to treat the offending organism are not warranted. If swelling or arthralgia recurs, further evaluation may be necessary to exclude active infection or evolving rheumatic disease. Intraarticular steroid injections may be utilized for refractory or severely involved joints once acute infection has been ruled out. Systemic steroids or disease-modifying anti-rheumatic drugs are rarely indicated but may be considered for chronic disease. Participation in physical activity should be encouraged, and physical therapy may be needed to maintain normal function and prevent muscle atrophy. For postinfectious arthritis due to streptococcal disease, current recommendations include penicillin prophylaxis for at least 1 yr. Long-term prophylaxis is often recommended, but the duration is controversial and may need to be individualized.

COMPLICATIONS AND PROGNOSIS

Postinfectious arthritis following viral infections usually resolves without complications unless it is associated with involvement of other organs, such as encephalomyelitis. Children with reactive arthritis after enteric infections occasionally experience inflammatory bowel disease months to years after onset. Both uveitis and carditis have been reported in children diagnosed with reactive arthritis. Reactive arthritis, especially after bacterial enteric infection or genitourinary tract infection with *C. trachomatis,* has the potential for evolving to chronic arthritis, particularly spondyloarthritis (see Chapter 156). The presence of HLA-B27 or significant systemic features increases the risk of chronic disease.

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Chapter 158

Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem inflammation and the presence of circulating autoantibodies directed against self-antigens. SLE occurs in both children and adults, disproportionately affecting females of reproductive age. Although nearly every organ may be affected, most commonly involved are the skin, joints, kidneys, blood-forming cells, blood vessels, and the central nervous system. Compared with adults, children and adolescents with SLE have more severe disease and more widespread organ involvement.

ETIOLOGY

The pathogenesis of SLE remains largely unelucidated, but several factors likely influence risk and severity of disease, including genetics, hormonal milieu, and environmental exposures.

A genetic predisposition to SLE is suggested by the association with **specific genetic abnormalities,** including congenital deficiencies of C1q, C2, and C4, as well as several polymorphisms (e.g., interferon regulatory factor 5 and protein tyrosine phosphatase N22), and familial clustering of SLE or other autoimmune disease. In addition, certain human leukocyte antigen (HLA) types (including HLA-B8, HLA-DR2, and HLA-DR3) occur with increased frequency in patients with SLE. Although SLE clearly has a genetic component, its occurrence is sporadic in families and its concordance is incomplete (estimated at 2-5% among dizygotic twins and 25-60% among monozygotic twins), suggesting that multiple genes are involved and that epigenetic and nongenetic factors are also important in disease expression.

Because SLE preferentially affects females, especially during their reproductive years, it is suspected that hormonal factors are important in pathogenesis. Of individuals with SLE, 90% are female, making gender the strongest risk factor for SLE. Estrogens are likely to play a role in SLE, and both in vitro and animal model studies suggest that estrogen exposure promotes B-cell autoreactivity. Estrogen-containing oral contraceptives do not appear to induce flares in quiescent SLE, though the risk of flares may be increased in postmenopausal women receiving hormone replacement.

Environmental exposures that may trigger the development of SLE remain largely unknown; certain viral infections (including Epstein-Barr virus) may play a role in susceptible individuals, and ultraviolet light exposure is known to aggravate SLE disease activity. Environmental influences also may induce epigenetic modifications to DNA, which increase the risk of SLE and drug-induced lupus; in mouse models, drugs such as procainamide and hydralazine can promote lymphocyte hypomethylation causing a lupus-like syndrome.

EPIDEMIOLOGY

The reported prevalence of SLE in children and adolescents (1-6/100,000) is lower than that in adults (20-70/100,000). Prevalence of SLE is highest among African-Americans, Asians, Hispanics, Native Americans, and Pacific Islanders for both adult and pediatric populations. SLE predominantly affects females, with reported 2-5 : 1 ratio prior to puberty, 9 : 1 ratio during reproductive years, and return to near prepubertal ratios in the postmenopausal period. Childhood SLE is rare before 5 yr of age and is usually diagnosed in adolescence, with a median age at diagnosis of 11-12 yr. Up to 20% of all individuals with SLE are diagnosed prior to age 16 yr.

PATHOLOGY

Histologic features most suggestive of SLE include findings in the kidney and skin, especially the discoid rash. Renal manifestations of SLE are classified histologically according to the criteria of the International Society of Nephrology (see Chapter 514). The finding of diffuse proliferative glomerulonephritis (class IV) significantly increases risk for renal morbidity. Renal biopsies are helpful to establish the diagnosis of SLE and to stage disease. Immune complexes are commonly found with "full house" deposition of immunoglobulin and complement. The characteristic **discoid rash** depicted in Figure 158-1*D* is characterized on biopsy by hyperkeratosis, follicular plugging, and infiltration of mononuclear cells into the dermal-epidermal junction. The histopathology of photosensitive rashes can be nonspecific, but immunofluorescence examination of both affected and nonaffected skin may reveal deposition of immune complexes within the dermal–epidermal junction. This finding is called the **lupus band test**, which is specific for SLE.

PATHOGENESIS

A hallmark of SLE is the generation of **autoantibodies** directed against self-antigens, particularly nucleic acids. These intracellular antigens are ubiquitously expressed but are usually inaccessible and cloistered within the cell. During cell necrosis or **apoptosis**, the antigens are released. SLE skin cells are highly susceptible to damage from ultraviolet light, and the resulting cell death leads to release of cell contents, including nucleic antigens. Individuals with SLE may have markedly increased levels of apoptosis or significantly impaired ability to clear cell debris, causing prolonged exposure to nucleic antigens in the bloodstream and increased opportunity for recognition by immune cells, leading to B cell autoantibody production. Circulating autoantibodies form immune complexes and deposit in tissues, leading to local complement activation, initiation of a proinflammatory cascade, and,

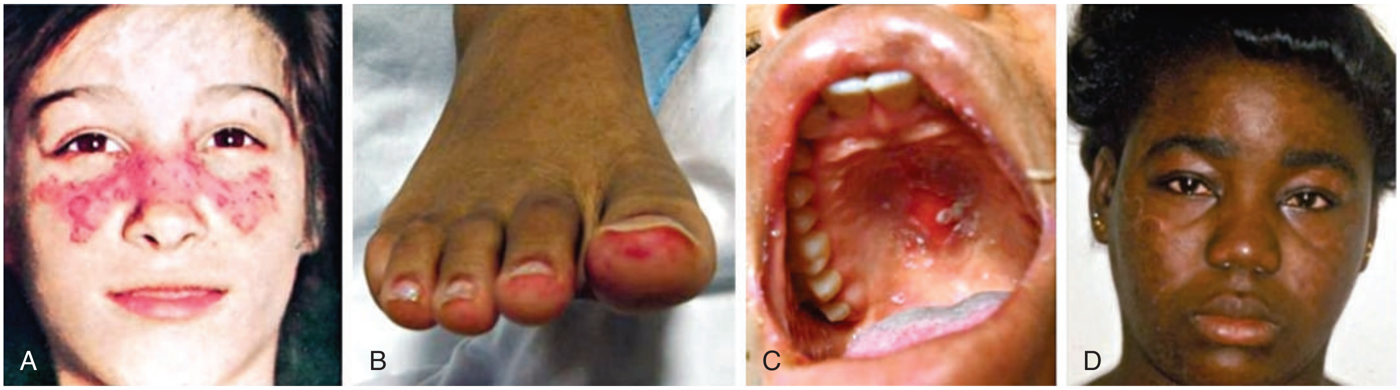

Figure 158-1 Mucocutaneous manifestations of SLE. **A,** Malar rash; **B,** vasculitic rash on toes; **C,** oral mucosal ulcers; **D,** discoid rash in malar distribution.

ultimately, tissue damage. Antibodies to double-stranded DNA can form immune complexes, deposit in glomeruli, and initiate inflammation leading to glomerulonephritis. However, many individuals with SLE have circulating antibodies to double-stranded DNA yet do not have nephritis, suggesting that autoantibodies are not the only pathway leading to end organ damage in SLE.

Both the innate and adaptive arms of the immune system have been implicated in the dysregulation of the immune system seen in SLE. High levels of interferon-α production by plasmacytoid dendritic cells promote expression of other proinflammatory cytokines and chemokines, maturation of monocytes into myeloid dendritic cells, promotion of autoreactive B and T cells, and loss of self-tolerance. Many, but not all, patients with SLE exhibit this cytokine profile, known as the **type I interferon signature.** Other cytokines with increased expression in SLE include interleukin (IL)-1, IL-2, IL-6, IL-10, IL-12, IL-17, IL-21, interferon-γ, B-lymphocyte stimulator (BLyS), and anti–tumor necrosis factor-α.

Both B and T cells demonstrate functional impairments in SLE. In active SLE, B-cell populations have impaired tolerance and increased autoreactivity, enhancing B cells' ability to produce autoantibodies following exposure to self-antigen. In addition, cytokines such as BLyS may promote abnormal B-cell number and function. T-cell abnormalities in SLE include increased numbers of memory T cells and decreased number and function of T-regulatory cells. SLE T cells display aberrant signaling and increased autoreactivity. As a result, they are resistant to attrition by normal apoptosis pathways.

CLINICAL MANIFESTATIONS

Any organ system can be involved in SLE, so the potential clinical manifestations are myriad (Table 158-1). The presentation of SLE in childhood or adolescence differs from that in adults. The most common presenting complaints of children with SLE include fever, fatigue, hematologic abnormalities, arthralgia, and arthritis. Arthritis is usually present in the 1st yr of diagnosis, may be asymptomatic (morning stiffness, painless swelling) but is often a symmetric polyarthritis affecting large and small joints. Tenosynovitis is often present, but radiologic joint changes are very rare. Pediatric lupus may develop in patients previously diagnosed with polyarticular or systemic juvenile idiopathic arthritis (see Chapter 155).

Renal disease in SLE is often asymptomatic, underscoring the need for careful monitoring of blood pressure and urinalyses; in adolescents, SLE often presents with nephrotic syndrome and/or renal failure with the predominant symptoms being edema, fatigue, changes in urine color, and nausea/vomiting. Because SLE symptoms and findings may develop serially over several years and not be present at one time, the diagnosis may require longitudinal follow up. SLE is often characterized by periods of flare and disease quiescence or may follow a more smoldering disease course. The neuropsychiatric complications of SLE may occur with or without apparently active SLE, posing a particularly difficult diagnostic challenge in adolescents, who are already at high risk for mood disorders (Fig. 158-2). Long-term complications of SLE and its therapy, including accelerated atherosclerosis and osteoporosis, become clinically evident in young to middle adulthood. SLE is a disease that evolves over time in each affected individual, and new manifestations may arise even many years after diagnosis.

DIAGNOSIS

The diagnosis of SLE requires a comprehensive clinical and laboratory assessment revealing characteristic multisystem disease and excluding other etiologies, including infection and malignancy. Presence of 4 of the 11 **American College of Rheumatology (ACR) 1997 Revised Classification Criteria for SLE** (Table 158-2) simultaneously or cumulatively over time establishes the diagnosis of SLE. Of note, although a positive antinuclear antibody (ANA) test result is not required for the diagnosis of SLE, ANA-negative lupus is extremely rare. Although ANA is very sensitive for SLE (95-99%), it is not very specific (~50%). Antibodies against double-stranded DNA and anti-Smith are specific for SLE (~98%) but not as sensitive (40-65%). Hypocomplementemia, although common in SLE, is not represented among the ACR classification criteria; hypocomplementemia has been added to **updated criteria validated by the Systemic Lupus International Collaborating Clinics (SLICC) in 2012** (Table 158-3). Other differences in the SLICC criteria include addition of nonscarring alopecia, additional cutaneous and neurologic manifestations of lupus, and a positive direct Coombs test in the absence of hemolytic anemia.

Table 158-1 Potential Clinical Manifestations of Systemic Lupus Erythematosus

TARGET ORGAN	POTENTIAL CLINICAL MANIFESTATIONS
Constitutional	Fatigue, anorexia, weight loss, fever, lymphadenopathy
Musculoskeletal	Arthritis, myositis, tendonitis, arthralgias, myalgias, avascular necrosis, osteoporosis
Skin	Malar rash, discoid (annular) rash, photosensitive rash, cutaneous vasculitis (petechiae, palpable purpura, digit ulcers, gangrene, urticaria), livedo reticularis, periungual capillary abnormalities, Raynaud phenomenon, alopecia, oral and nasal ulcers, panniculitis, chilblains, alopecia
Renal	Hypertension, proteinuria, hematuria, edema, nephrotic syndrome, renal failure
Cardiovascular	Pericarditis, myocarditis, conduction system abnormalities, Libman-Sacks endocarditis
Neurologic	Seizures, psychosis, cerebritis, stroke, transverse myelitis, depression, cognitive impairment, headaches, migraines, pseudotumor, peripheral neuropathy (mononeuritis multiplex) , chorea, optic neuritis, cranial nerve palsies, acute confusional states, dural sinus thrombosis
Pulmonary	Pleuritis, interstitial lung disease, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism
Hematologic	Immune-mediated cytopenias (hemolytic anemia, thrombocytopenia or leukopenia), anemia of chronic inflammation, hypercoagulability, thrombocytopenic thrombotic microangiopathy
Gastroenterology	Hepatosplenomegaly, pancreatitis, vasculitis affecting bowel, protein-losing enteropathy, peritonitis
Ocular	Retinal vasculitis, scleritis, episcleritis, papilledema, dry eyes, optic neuritis

DIFFERENTIAL DIAGNOSIS

Multiorgan disease is the hallmark of SLE, and given its wide array of potential clinical manifestations, SLE is in the differential diagnosis of many clinical scenarios, including unexplained fevers, joint pain, arthritis, rash, cytopenias, neurologic or cardiopulmonary abnormalities, nephritis, and nephrotic syndrome. For patients ultimately diagnosed with pediatric SLE, the initial differential diagnosis often includes infections (sepsis, Epstein-Barr virus, parvovirus B19, endocarditis), malignancies (leukemia and lymphoma), poststreptococcal glomerulonephritis, other rheumatologic conditions (systemic onset juvenile idiopathic arthritis, vasculitides), and drug-induced lupus.

Drug-induced lupus refers to the presence of SLE manifestations triggered by exposure to specific medications, including minocycline, many anticonvulsants, sulfonamides, antiarrhythmic agents, and other drugs (Table 158-4). In individuals prone to SLE, these agents may act as a trigger for true SLE. In others, these agents provoke a reversible lupus-like syndrome. Unlike SLE, drug-induced lupus affects males and females equally. A genetic predisposition toward slow drug acetylation may increase the risk of drug-induced lupus. Circulating antihistone

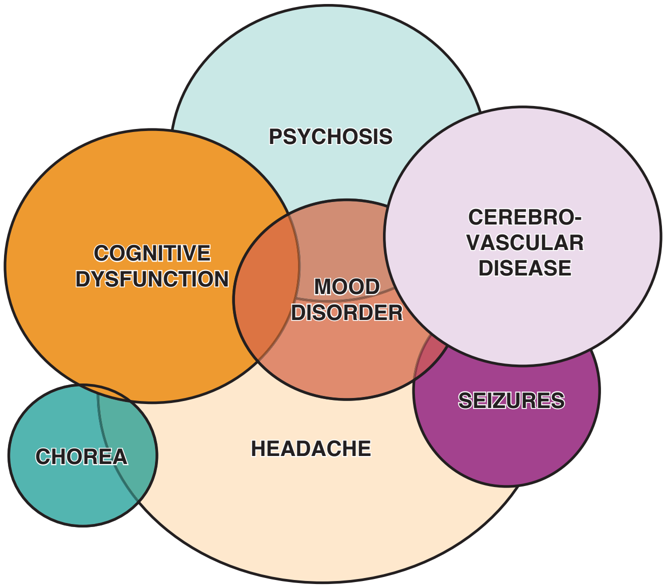

Figure 158-2 **Overlapping neuropsychiatric symptoms in pediatric SLE.** Patients with pediatric SLE most commonly have more than 1 neuropsychiatric symptom—in particular for seizures. *(From Silverman E, Eddy A: Systemic lupus erythematosus. In Cassidy JT, Petty RE, Laxer RM, et al, editors,* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders/Elsevier,* Fig. 21-17, *p. 329.)*

Table 158-2 American College of Rheumatology 1997 Revised Classification Criteria for Systemic Lupus Erythematosus*

Criteria
Malar rash
Discoid rash
Photosensitivity
Oral or nasal ulcers
Arthritis
Nonerosive, ≥2 joints
Serositis
Pleuritis, pericarditis or peritonitis
Renal manifestations†
Consistent renal biopsy
Persistent proteinuria or renal casts
Seizure or psychosis
Hematologic manifestations†
Hemolytic anemia
Leukopenia (<4,000 leukocytes/mm^3)
Lymphopenia (<1,500 leukocytes/mm^3)
Thrombocytopenia (<100,000 thrombocytes/mm^3)
Immunologic abnormalities†
Positive anti–double-stranded or anti-Smith antibody
False-positive rapid plasma regain test result, positive lupus anticoagulant test result, or elevated anticardiolipin immunoglobulin (Ig) G or IgM antibody
Positive antinuclear antibody test result

*The presence of 4 of 11 criteria establishes the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.

†Each of these criteria counts as a single criterion whether 1 or more definitions are satisfied.

Adapted from Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, Arthritis Rheum *40:1725, 1997.*

Table 158-3 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus*

CLINICAL CRITERIA	IMMUNOLOGIC CRITERIA
Acute cutaneous lupus Malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus **Chronic cutaneous lupus** Classic discoid rash, lupus panniculitis, mucosal lupus, lupus erythematous tumidus, chilblains lupus, discoid lupus/lichen planus overlap **Oral or nasal ulcers** **Nonscarring alopecia** **Synovitis** (≥2 joints) **Serositis** Pleurisy or pericardial pain ≥1 day, pleural effusion or rub, pericardial effusion or rub, ECG evidence of pericarditis **Renal** Presence of red blood cell casts or urine protein/creatinine ratio representing >500 mg protein/24 hours **Neurologic** Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state **Hemolytic anemia** **Leukopenia** (<4,000/mm^3) or lymphopenia (<1,000/mm^3) **Thrombocytopenia** (<100,000/mm^3)	**Positive antinuclear antibody** **Positive double-stranded DNA antibody** **Positive anti-Smith antibody** **Antiphospholipid antibody positivity** Positive lupus anticoagulant, false-positive test for rapid plasma regain, medium to high titer anticardiolipin antibody level (IgA, IgG, IgM), or positive anti–B_2-glycoprotein I antibody (IgA, IgG, IgM) **Low complement** Low C3, C4, or Ch50 level **Positive direct Coombs test** (in the absence of hemolytic anemia)

*The presence of 4 criteria (including at least 1 clinical and 1 immunologic criterion) establishes the diagnosis of SLE. Biopsy-proven lupus nephritis with positive ANA or anti–double-stranded DNA also satisfies the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.

Adapted from Petri M: Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus, Arthritis Rheum *64(8):2677–2686, 2012.*

Table 158-4	Medications Associated with Drug-Induced Lupus
DEFINITE ASSOCIATION Minocycline, procainamide, hydralazine, isoniazid, penicillamine, diltiazem, interferon-α, methyldopa, chlorpromazine, etanercept, infliximab, adalimumab	
PROBABLE ASSOCIATION Phenytoin, ethosuximide, carbamazepine, sulfasalazine, amiodarone, quinidine, rifampin, nitrofurantoin, beta blockers, lithium, captopril, interferon-γ, hydrochlorothiazide, glyburide, docetaxel, penicillin, tetracycline, statins, gold, valproate, griseofulvin, gemfibrozil, propylthiouracil	

antibodies are often present in drug-induced SLE; these antibodies are only detected in up to 20% of individuals with SLE. Hepatitis, which is rare in SLE, is more common in drug-induced lupus. Individuals with drug-induced lupus are less likely to demonstrate antibodies to double-stranded DNA, hypocomplementemia, and significant renal or neurologic disease. In contrast to SLE, manifestations of drug-induced lupus typically resolve after withdrawal of the offending medication; however, complete recovery may take several months to years.

LABORATORY FINDINGS

A positive ANA test result is present in 95-99% of individuals with SLE. This test has poor specificity for SLE, as up to 20% of healthy individuals also have a positive ANA test result, making the ANA a poor screening test for SLE. ANA titers are not reflective of disease activity; therefore, repeating ANA titers is not helpful in disease management. Antibodies to double-stranded DNA are more specific for SLE, and in some individuals, anti–double-stranded DNA levels correlate with disease activity, particularly those with significant nephritis. Anti-Smith antibody, although found specifically in patients with SLE, does not correlate with disease activity. Serum levels of total hemolytic complement (CH_{50}), C3, and C4 are typically decreased in active disease and often improve with treatment; although hypocomplementemia is not included in the ACR classification criteria, it has been added to 2012 SLICC criteria, along with direct Coombs positivity. Table 158-5 lists autoantibodies found in SLE along with their clinical associations. Hypergammaglobulinemia is a common but nonspecific finding. Inflammatory markers, particularly erythrocyte sedimentation rate, are often elevated in active disease. C-reactive protein (CRP) correlates less well with disease activity and acutely elevated CRP values may reflect infection, while chronic mild elevation of CRP may indicate increased cardiovascular risk.

Antiphospholipid antibodies, which increase clotting risk, can be found in up to 66% of children and adolescents with SLE. Antiphospholipid antibodies can be detected by several means, and laboratory features that point to the presence of these antibodies include the presence of anticardiolipin antibodies, prolonged phospholipid-dependent coagulation test results (partial thromboplastin time, dilute Russell viper-venom time), and a circulating **lupus anticoagulant** (which confirms that a prolonged partial thromboplastin time is not corrected with mixing studies). When an arterial or venous clotting event occurs in the presence of an antiphospholipid antibody, **antiphospholipid antibody syndrome** is diagnosed. Antiphospholipid antibody syndrome can occur in the context of SLE or independent of SLE (see Chapter 479).

TREATMENT

Treatment of SLE is tailored to the individual and is based on specific disease manifestations and medication tolerability. For all patients, sunscreen and avoidance of prolonged direct sun exposure and other ultraviolet light may help control disease and should be reinforced at every visit with the patient. Hydroxychloroquine (5-7 mg/kg/day up to 400 mg/day) is recommended for all individuals with SLE if tolerated. In addition to treating mild SLE manifestations such as rash and mild arthritis, hydroxychloroquine prevents SLE flares, improves lipid profiles, and may have a beneficial impact on mortality and renal outcomes. Potential toxicities include retinal pigmentation and color vision impairment; therefore, ophthalmology exams every 6-12 mo are recommended for patients taking hydroxychloroquine. Nonsteroidal antiinflammatory agents can be useful for management of arthralgias and arthritis; it is important to keep in mind their potential hepatic, renal, and cardiovascular toxicities.

Table 158-5	Autoantibodies Commonly Associated with Systemic Lupus Erythematosus (SLE)
ANTIBODY	**CLINICAL ASSOCIATION**
Anti–double-stranded DNA	Correlates with disease activity, especially nephritis, in some with SLE
Anti-Smith antibody	Specific for the diagnosis of SLE
Antiribonucleoprotein antibody	Increased risk for Raynaud phenomenon and pulmonary hypertension High titer may suggest diagnosis of mixed connective tissue disorder
Anti-Ro antibody (anti-SSA antibody) Anti-La antibody (anti-SSB antibody)	Associated with sicca syndrome May suggest diagnosis of Sjögren syndrome Increased risk of neonatal lupus in offspring (congenital heart block) May be associated with cutaneous and pulmonary manifestations of SLE May be associated with isolated discoid lupus
Antiphospholipid antibodies (including anticardiolipin antibodies)	Increased risk for venous and arterial thrombotic events
Antihistone antibodies	Present in a majority of patients with drug-induced lupus May be present in SLE

Corticosteroids are a mainstay for treatment of significant manifestations of SLE and work quickly to improve acute deterioration; side effects often limit patient compliance, especially in adolescence, and potential toxicities are worrisome. It is important to limit dose and length of exposure to corticosteroids whenever possible. Potential consequences of corticosteroid therapy include growth disturbance, weight gain, striae, acne, hyperglycemia, hypertension, cataracts, avascular necrosis, and osteoporosis. The optimal dosing of corticosteroids in children and adolescents with SLE remains unknown; severe disease is often treated with high doses of intravenous methylprednisolone (e.g., 30 mg/kg/day for 3 days, followed by weekly pulses) or high doses of oral prednisone (1-2 mg/kg/day). As disease manifestations improve, corticosteroid dosages are gradually tapered over months. It often becomes necessary to introduce steroid-sparing immunosuppressive medications in order to limit cumulative steroid exposure.

Steroid-sparing immunosuppressive agents often used in the treatment of pediatric SLE include methotrexate, leflunomide, azathioprine, mycophenolate mofetil, cyclophosphamide, and belimumab. Methotrexate, leflunomide, and azathioprine are often used to treat persistent moderate disease, including arthritis, significant cutaneous or hematologic involvement, and pleural disease. Intravenous or oral cyclophosphamide is reserved for the most severe, potentially life-threatening SLE manifestations, such as renal, neurologic, and cardiopulmonary disease. Although cyclophosphamide is highly effective in controlling disease, the potential toxicities are significant, including cytopenias, infection, hemorrhagic cystitis, premature gonadal failure, and increased risk of future malignancy. Attention to adequate hydration can attenuate the risk of hemorrhagic cystitis. Fortunately, young girls are at much lower risk of gonadal failure than older women, and the use of gonadotropin-releasing hormone agonists, such as leuprolide acetate, may help prevent gonadal failure. Clinical trial data on the

use of rituximab in SLE with treatment-resistant glomerulonephritis has been largely disappointing, but results from the LUNAR study suggest there may be benefit for subpopulations of SLE patients. The FDA has approved the use of belimumab (a monoclonal antibody against BLyS, also called B-cell activating factor); when added to standard SLE therapy, belimumab improves multiple markers of disease severity. BLyS levels are elevated in SLE and relate to disease activity. Treatment reduces the number of SLE flares and decreases the dose of prednisone. Side effects include fever, nausea, and diarrhea.

The Childhood Arthritis Rheumatology Research Alliance has developed a consensus treatment plan induction therapy of newly-diagnosed proliferative lupus nephritis that is specific to the pediatric SLE population; these guidelines advise 6 mo of therapy with either cyclophosphamide or mycophenolate mofetil, used in combination with a standardized glucocorticoid regimen. For patients who fail to achieve a partial response in 6 mo it is appropriate to switch agents. Consensus statements for maintenance therapy of lupus nephritis recommend use of mycophenolate mofetil, every 3 mo IV cyclophosphamide or azathioprine for 12 mo after completing induction therapy.

Given the lifelong nature of SLE, optimal care of children and adolescents with this disease also involves preventive practices. Owing to the enhanced risk of atherosclerosis in SLE, attention to cholesterol levels, smoking status, body mass index, blood pressure, and other traditional cardiovascular risk factors is warranted. Even though the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) study failed to support placing all children with SLE on a statin, ad hoc analyses suggest that statins may be considered for primary prevention of atherosclerotic disease in certain clinical circumstances, particularly pubertal patients with an elevated CRP. For all SLE patients, adequate intake of calcium and vitamin D is necessary to prevent future osteoporosis. Infections commonly complicate SLE, so routine immunization is recommended, as well as annual influenza vaccination and administration of the 23-valent pneumococcal vaccine. Prompt attention to febrile episodes should include an evaluation for serious infections. It should be remembered that pregnancy can worsen SLE, and obstetric complications are more common in SLE. In addition, many of the medications used to treat SLE are teratogenic. As a consequence, it is important to counsel adolescent girls about these risks and appropriate contraceptive options. SLE patients with antiphospholipid antibody syndrome are treated with long-term anticoagulation to prevent thrombotic events.

COMPLICATIONS

Within the 1st several yr of diagnosis, the most common causes of death in individuals with SLE include infection and complications of glomerulonephritis and neuropsychiatric disease (Table 158-6). Over the long-term, the most common causes of mortality also include complications of atherosclerosis and malignancy. The increased risk of premature atherosclerosis in SLE is not explained by traditional risk factors and is partly a result of the chronic immune dysregulation and inflammation associated with SLE. Increased malignancy rates may be caused by immune dysregulation as well as exposure to medications with carcinogenic potential.

Table 158-6	Morbidity in Childhood Lupus
Renal	Hypertension, dialysis, transplantation
Central nervous system	Organic brain syndrome, seizures, psychosis, neurocognitive dysfunction
Cardiovascular	Atherosclerosis, myocardial infarction, cardiomyopathy, valvular disease
Immune	Recurrent infection, functional asplenia, malignancy
Musculoskeletal	Osteopenia, compression fractures, avascular necrosis
Ocular	Cataracts, glaucoma, retinal detachment, blindness
Endocrine	Diabetes, obesity, growth failure, infertility, fetal wastage

From Cassidy JT, Petty RE: Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Elsevier/Saunders.*

PROGNOSIS

The severity of disease in pediatric SLE is notably worse than the typical course for most adult-onset SLE. However, owing to advances in the diagnosis and treatment of SLE, survival has improved dramatically over the past 50 yr. Currently, the 5 yr survival rate for pediatric SLE is ~95%, though the 10 yr survival rate remains ~80-90%. Given their long burden of disease, children and adolescents with SLE face a high risk of future morbidity and mortality from the disease and its complications, especially atherosclerosis and malignancy (see Table 158-6). Given the complex and chronic nature of SLE, it is optimal for children and adolescents with SLE to be treated by pediatric rheumatologists in a multidisciplinary clinic.

Bibliography is available at Expert Consult.

158.1 Neonatal Lupus

Deborah Friedman, Rebecca E. Sadun, Stacy P. Ardoin, and Laura E. Schanberg

Neonatal lupus, an entity distinct from SLE, is one of the few rheumatic disorders manifesting in the neonate. Clinical manifestations of neonatal lupus include a characteristic annular or macular rash typically affecting the face (especially the periorbital area), trunk, and scalp (Fig. 158-3). The rash typically appears within the 1st 6 wk of life after exposure to ultraviolet light and lasts 3-4 mo; however, it can be present at birth. Infants may also have cytopenias and hepatitis, but the most feared complication is congenital heart block. Conduction system abnormalities range from prolongation of the PR interval to complete heart block, with development of progressive

Figure 158-3 **Neonatal lupus syndrome.** Typical rash, often photosensitive with a malar distribution, appearing as annular plaques with erythema and scaling. *(Reproduced, with written parental permission, from Pain C, Beresford MW: Neonatal lupus syndrome,* Paediatr Child Health *17:223–227, 2007.)*

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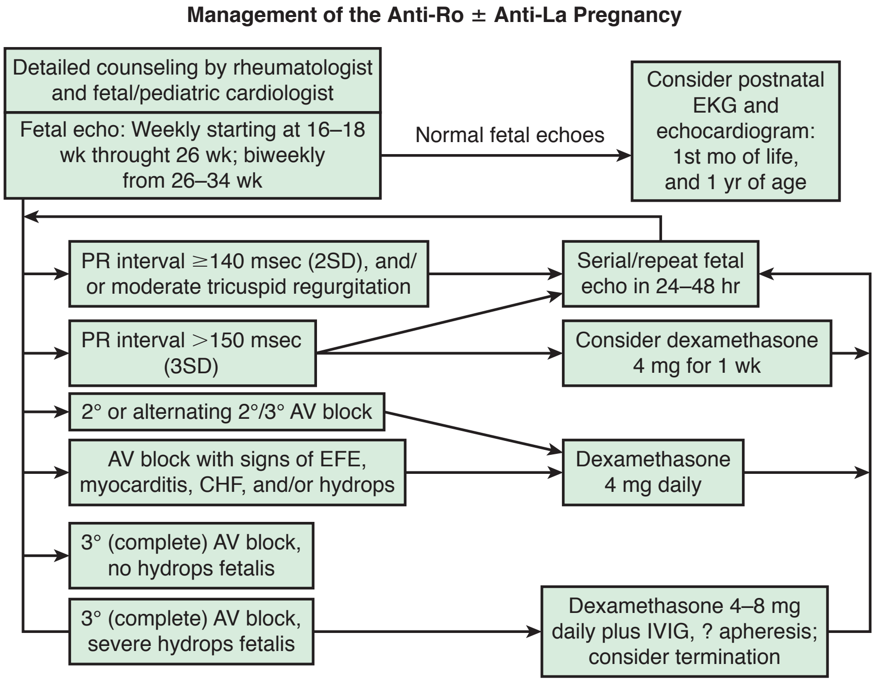

Figure 158-4 **Algorithm for the management of the anti-Ro ± anti-La pregnancy.** All such pregnancies should include counseling and serial fetal echocardiograms.

cardiomyopathy in the most severe cases. The noncardiac manifestations of neonatal lupus are usually reversible, whereas congenital heart block is permanent. Conduction system abnormalities can be detected in utero by fetal echocardiogram beginning at 16 wk of gestational age.

Neonatal lupus results from the passive transfer of maternal immunoglobulin G autoantibodies to the fetus. The vast majority of neonatal lupus cases are associated with maternal anti-Ro (also known as SSA) and anti-La antibodies (also known as SSB). Despite the clear association with maternal autoantibodies, their presence alone is not sufficient to cause disease, as ~2% of offspring born to mothers with anti-Ro and anti-La antibodies experience congenital heart block.

In vitro studies suggest that during cardiac development, Ro and La antigens may be exposed on the surface of cardiac cells in the proximity of the atrioventricular node, making the antigens accessible to maternal autoantibodies. Binding incites a local immune response, resulting in fibrosis within the conduction system as well as more extensive disease in fatal cases. In the skin, exposure to ultraviolet light results in cell damage and the subsequent exposure of Ro and La antigens, inducing a similar local inflammatory response that produces the characteristic rash.

Although the scant clinical trial data have been mixed, fluorinated corticosteroids (dexamethasone or betamethasone), intravenous immunoglobulin, plasmapheresis, hydroxychloroquine, and terbutaline (combined with steroids) have been used in pregnant women with anti-Ro or anti-La antibodies to prevent occurrence or progression of fetal cardiac abnormalities, including congenital heart block, endocardial fibroelastosis, and hydrops fetalis. Most encouraging are retrospective cohort studies suggesting maternal treatment with hydroxychloroquine may provide effective prophylaxis against congenital heart block. The mechanisms of action probably involve changes in acidification of endosomes and their interaction with Toll-like receptors. All clinical data on the use of hydroxychloroquine in pregnancy points to safety, and there are ongoing prospective clinical studies examining efficacy in the prevention of neonatal lupus syndrome in pregnant women known to be anti-Ro and/or anti-La positive.

Fluorinated corticosteroids seem to improve cases of hydrops. Significant conduction system abnormalities after birth are treated with cardiac pacing and occasionally intravenous immunoglobulin and steroids, while severe cardiomyopathy may require cardiac transplantation. Transient, noncardiac manifestations are conservatively managed, with topical steroids used occasionally to treat the rash.

Because maternal autoantibodies gain access to the fetus via the placenta at the 16th wk of gestation, all pregnant women with circulating anti-Ro or anti-La antibody (or those with a history of offspring with neonatal lupus or congenital heart block) are monitored by a pediatric cardiologist with regular fetal electrocardiography from 16 wk of gestation until delivery. If fetal bradycardia is found unexpectedly during in utero monitoring, screening for maternal anti-Ro and anti-La antibodies is warranted.

In contrast to SLE, neonatal lupus is not characterized by ongoing immune dysregulation, although infants with neonatal lupus may be at some increased risk for development of future autoimmune disease. A mother who has borne a child with congenital heart block caused by neonatal lupus has an approximately 17% risk of recurrence with future pregnancies. With cardiac pacing, children with conduction system disease in the absence of cardiomyopathy have an excellent prognosis. If the conduction defect is not addressed, affected children are at risk for exercise intolerance, arrhythmias, and death. A proposed management algorithm is presented in Figure 158-4.

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Chapter 159

Juvenile Dermatomyositis

Angela Byun Robinson and Ann M. Reed

Juvenile dermatomyositis (JDM) is the most common inflammatory myositis in children, distinguished by proximal muscle weakness and a characteristic rash. Inflammatory cell infiltrates result in vascular inflammation, the underlying pathology in this disorder.

ETIOLOGY

Evidence suggests that the etiology of JDM is multifactorial, based on genetic predisposition and an unknown environmental trigger. Human

leukocyte antigen (HLA) alleles such as B8, DRB1*0301, DQA1*0501, and DQA1*0301 are associated with increased susceptibility to JDM in selected populations. Maternal microchimerism may play a part in the etiology of JDM by causing graft-versus-host disease or autoimmune phenomena. Persistent maternal cells have been found in blood and tissue samples of children with JDM. An increased number of these maternal cells are positive for HLA-DQA1*0501, which may assist with transfer or persistence of chimeric cells. Specific cytokine polymorphisms in tumor necrosis factor-α promoter and variable number tandem repeats of the interleukin-1 receptor antagonist may increase genetic susceptibility. These polymorphisms are common in the general population. A history of infection in the 3 mo prior to disease onset is commonly reported; multiple studies have failed to produce a causative organism. Constitutional signs and upper respiratory symptoms predominate, but one-third of patients report preceding gastrointestinal (GI) symptoms. Group A streptococcus, upper respiratory infections, GI infections, coxsackievirus B, toxoplasma, enteroviruses, parvovirus B19, and multiple other organisms have been postulated as possible pathogens in the etiology of JDM. Despite these concerns, results of serum antibody testing and polymerase chain reaction amplification of the blood and muscle tissue for multiple infectious diseases have not been revealing. Environmental factors may also play a contributing role, with geographic and seasonal clustering reported; however, no clear theory of etiology has emerged.

EPIDEMIOLOGY

The incidence of JDM is approximately 3 cases/1 million children/yr without racial predilection. Peak age of onset is between 4 and 10 yr. There is a second peak of dermatomyositis onset in late adulthood (45-64 yr), but adult-onset dermatomyositis appears to be a distinctly separate entity in prognosis and etiology. In the United States, the ratio of girls to boys with JDM is 2 : 1. Multiple cases of myositis in a single family are rare, but familial autoimmune disease may be increased in families with children who have JDM than in families of healthy children. Reports of seasonal association have not been confirmed, although clusters of cases may occur.

PATHOGENESIS

Interferon upregulates genes critical in immunoregulation and major histocompatibility complex (MHC) class I expression, activates natural killer cells, and supports dendritic cell maturation. Upregulation of gene products controlled by type I interferons occurs in patients with dermatomyositis, potentially correlating with disease activity and holding promise as clinical biomarkers.

It appears that children with genetic susceptibility to JDM (HLA-DQA1*0501, HLA-DRB*0301) may have prolonged exposure to maternal chimeric cells and/or an unknown environmental trigger. Once triggered, an inflammatory cascade with type I interferon response leads to upregulation of MHC class I expression and maturation of dendritic cells. Overexpression of MHC class I upregulates adhesion molecules, which influence migration of lymphocytes, leading to inflammatory infiltration of muscle. In an autoregulatory feedback loop, muscle inflammation increases the type I interferon response, regenerating the cycle of inflammation. Cells involved in the inflammatory cascade include natural killer cells (CD56), T-cell subsets (CD4, CD8, Th17), monocytes/macrophages (CD14), and plasmacytoid dendritic cells. Neopterin, interferon-inducible protein 10, monocyte chemoattractant protein, myxovirus resistance protein, and von Willebrand factor products, as well as other markers of vascular inflammation may be elevated in patients with JDM who have active inflammation.

Table 159-1 Diagnostic Criteria for Juvenile Dermatomyositis

Classic rash	Heliotrope rash of the eyelids Gottron papules
Plus 3 of the following:	
Weakness	Symmetric Proximal
Muscle enzyme elevation (≥1)	Creatine kinase Aspartate aminotransferase Lactate dehydrogenase Aldolase
Electromyographic changes	Short, small polyphasic motor unit potentials Fibrillations Positive sharp waves Insertional irritability Bizarre, high-frequency repetitive discharges
Muscle biopsy	Necrosis Inflammation

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Table 159-2 Clinical Features of Juvenile Dermatomyositis During the Course of the Disease

FEATURE	%
Muscle weakness	90-100
Dysphagia or dysphonia	13-40
Muscle atrophy	10
Muscle pain and tenderness	30-83
Skin lesions	85-100
Heliotrope rash of eyelids	66-83
Gottron papules	57-91
Erythematous rash of malar/facial area	42-100
Periungual capillary changes	80
Photosensitive rash	5-42
Ulcerations	22-30
Calcinosis	12-30
Lipodystrophy	11-14
Raynaud phenomenon	2-15
Arthritis and arthralgia	22-58
Joint contractures	26-27
Fever	16-46
Gastrointestinal signs and symptoms	8-22
Restrictive pulmonary disease	4-32
Interstitial lung disease	1-7
Cardiac involvement	0-3

From Rider LG, Lindsley CB, Cassidy JT: Juvenile dermatomyositis. In Cassidy JT, Petty RE, Laxer RM, et al, editors, Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders, Table 24-20, p. 410.*

CLINICAL MANIFESTATIONS

Children with JDM present with either rash, insidious onset of weakness, or both. Fevers, dysphagia or dysphonia, arthritis, muscle tenderness, and fatigue are also commonly reported at diagnosis (Tables 159-1 and 159-2).

Rash develops as the first symptom in 50% of cases and appears concomitant with weakness only 25% of the time. Children often exhibit extreme photosensitivity to ultraviolet light exposure with generalized erythema in sun-exposed areas. If seen over the chest and neck, this erythema is known as the **"shawl sign."** Erythema is also commonly seen over the knees and elbows. The characteristic **heliotrope rash** (Fig. 159-1) is a blue-violet discoloration of the eyelids that may be associated with periorbital edema. Facial erythema crossing the

nasolabial folds is also common, in contrast to the malar rash without nasolabial involvement typical of systemic lupus erythematosus. Classic **Gottron papules** (Fig. 159-2) are bright pink or pale, shiny, thickened or atrophic plaques over the proximal interphalangeal joints and distal interphalangeal joints and occasionally on the knees, elbows, small joints of the toes, and ankle malleoli. The rash of JDM is sometimes mistaken for eczema or psoriasis. Rarely, a thickened erythematous and scaly rash develops in children over the palms (known as **mechanic's hands)** and soles along the flexor tendons, which is associated with anti–Jo-1 antibodies.

Evidence of small vessel inflammation is often visible in the nailfolds and gums as individual capillary loops that are thickened, tortuous, or absent (Fig. 159-3). Telangiectasias may be visible to the naked eye but are more easily visualized under capillaroscopy or with use of a magnifier such as an ophthalmoscope. Severe vascular inflammation causes cutaneous ulcers on toes, fingers, axillae, or epicanthal folds.

Weakness associated with JDM is often insidious and difficult to differentiate from fatigue at onset. It is typically symmetric, affecting proximal muscles such as the neck flexors, shoulder girdle, and hip flexors. Parents may report difficulty climbing stairs, combing hair, and getting out of bed. Examination reveals inability to perform a sit-up, head lag in a child after infancy, and **Gower sign** (use of hands on thighs to stand from a sitting position). Patients with JDM may roll to the side rather than sit straight up from lying to compensate for truncal weakness. Approximately half of children exhibit muscle tenderness as a result of muscle inflammation.

Esophageal and respiratory muscles are also affected, resulting in aspiration or respiratory failure. It is essential to assess for dysphonia or nasal speech, palatal elevation with gag, dysphagia, and gastroesophageal reflux by means of history, physical exam, and swallow study, if symptoms are present. Respiratory muscle weakness can be a medical emergency and lead to respiratory failure. Children with respiratory muscle weakness do not manifest typical symptoms of impending respiratory failure with increased work of breathing, instead demonstrating hypercarbia rather than hypoxemia.

Lipodystrophy and **calcinosis** (Fig. 159-4) are thought to be associated with long-standing or undertreated disease. Dystrophic deposition of calcium phosphate, hydroxyapatite, or fluoroapatite crystals occurs in subcutaneous plaques or nodules, resulting in painful ulceration of the skin with extrusion of crystals or calcific liquid. Calcinosis is reported in up to 40% of children with JDM, but the prevalence is thought to be lower in children who are treated early and aggressively. In rare instances, an "exoskeleton" of calcium deposition forms, greatly limiting mobility. Lipodystrophy results in progressive loss of subcutaneous and visceral fat, typically over the face and upper body, and may be associated with a metabolic syndrome similar to polycystic ovarian syndrome with insulin resistance, hirsutism, acanthosis,

Figure 159-1 **The facial rash of juvenile dermatomyositis.** There is erythema over the bridge of the nose and malar areas with violaceous (heliotropic) discolorations of the upper eyelids.

Figure 159-2 **The rash of juvenile dermatomyositis.** The skin over the metacarpal and proximal interphalangeal joints may be hypertrophic and pale red (Gottron papules).

Figure 159-3 **Nailfold capillary pattern in rheumatic disease. A,** Normal nailfold capillary pattern in a healthy child with a homogeneous distribution and uniform appearance of capillary loops. **B,** The nailfold capillary pattern in a child with juvenile dermatomyositis shows dropout of capillary end loops, resulting in a wide band of avascularity. Dilated, tortuous capillaries can also be seen. **C,** Severe periungual telangiectasias may be seen without microscopy.

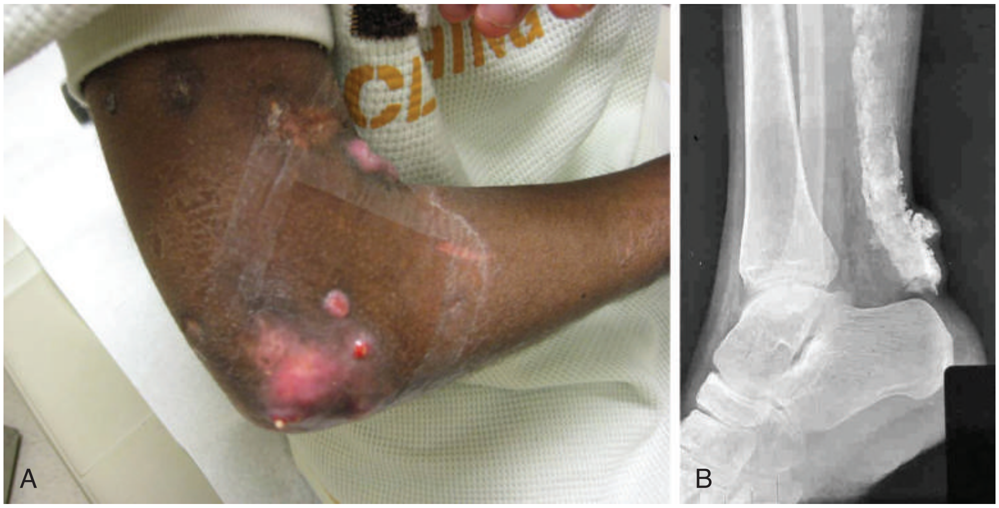

Figure 159-4 Rash and calcifications in dermatomyositis. **A,** Skin effects of calcification. **B,** Radiographic evidence of calcification.

hypertriglyceridemia, and abnormal glucose tolerance. Lipodystrophy may be generalized or localized.

Rarely, vasculitis of the GI tract develops in children with severe JDM, with crampy abdominal pain, pancreatitis, GI bleeding, and potential for intestinal perforation or infarction. Involvement of the cardiac muscle with pericarditis, myocarditis, and conduction defects has been reported. An association with malignancy at disease onset is observed in adults with dermatomyositis but very rarely in children.

DIAGNOSIS

Diagnosis of dermatomyositis requires the presence of characteristic rash as well as at least three signs of muscle inflammation and weakness (see Table 159-1). Diagnostic criteria developed in 1975 predate the use of MRI and have not been validated in children. Diagnosis is often delayed because of the insidious nature of disease onset.

Electromyography shows signs of myopathy (increased insertional activity, fibrillations, and sharp waves) as well as muscle fiber necrosis (decreased action potential amplitude and duration). Nerve conduction studies are typically normal unless severe muscle necrosis and atrophy are present. It is important that electromyography (EMG) be performed in a center with experience in pediatric EMG and its interpretation. Muscle biopsy is typically indicated when diagnosis is in doubt or for grading disease severity. Biopsy of involved muscle reveals focal necrosis and phagocytosis of muscle fibers, fiber regeneration, endomysial proliferation, inflammatory cell infiltrates and vasculitis, and tubuloreticular inclusion bodies within endothelial cells. Findings of lymphoid structures and vasculopathy may portend more severe disease.

Some children present with classic rash but no apparent muscle weakness or inflammation; this variation is called **amyopathic JDM or dermatomyositis sine myositis**. It is unclear whether these children have isolated skin disease or mild undetected muscle inflammation, risking progression to more severe muscle involvement with long-term sequelae such as calcinosis and lipodystrophy if untreated.

Differential diagnosis depends on the presenting symptoms. If the presenting complaint is solely weakness without rash or atypical disease, other causes of myopathy should be considered, including polymyositis, infection-related myositis (influenza A and B, coxsackievirus B, and other viral illnesses), muscular dystrophies (Duchenne and Becker as well as others), myasthenia gravis, Guillain-Barré syndrome, endocrinopathies (hyperthyroidism, hypothyroidism, Cushing syndrome, Addison disease, parathyroid disorders), mitochondrial myopathies, and metabolic disorders (glycogen and lipid storage diseases). Infections associated with prominent muscular symptoms include trichinosis, *Bartonella* infection, toxoplasmosis, and staphylococcal pyomyositis. Blunt trauma and crush injuries may lead to transient rhabdomyolysis with myoglobinuria. Myositis in children may also be associated with vaccinations, drugs, growth hormone, and graft-versus-host disease. The rash of JDM may be confused with eczema, dyshidrosis, psoriasis, malar rash from systemic lupus erythematosus, capillary telangiectasias from Raynaud phenomenon, and other rheumatic diseases. Muscle inflammation is also seen in children with systemic lupus erythematosus, juvenile idiopathic arthritis, mixed connective tissue disease, inflammatory bowel disease, and antineutrophil cytoplasmic antibody–positive vasculitides. Table 159-3 compares other juvenile inflammatory myositis disorders.

LABORATORY FINDINGS

Elevated serum levels of **muscle-derived enzymes** (creatine kinase, aldolase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase) reflect muscle inflammation. Not all enzyme levels rise with inflammation in a specific individual; alanine aminotransferase is most commonly elevated on initial presentation, whereas the creatine kinase level may be normal. The erythrocyte sedimentation rate is often normal, and the rheumatoid factor test result is typically negative. There may be anemia consistent with chronic disease. Antinuclear antibody is present in >80% of children with JDM. Results of tests for antibodies to SSA, SSB, Sm, ribonucleoprotein, and double-stranded DNA are generally negative. Antibodies to Pm/Scl identify a small, distinct subgroup of myopathies with a protracted disease course, often complicated by pulmonary interstitial fibrosis and/or cardiac involvement. Similar to what is seen in adults, the presence of myositis-specific autoantibodies in JDM such as anti–Jo-1, anti–Mi-2, anti-p155/140, anti-NXP2, and other myositis-specific autoantibodies help define distinct clinical subsets and may predict the development of complications, although differences remain in certain aspects such as malignancy between adults and children.

Radiographic studies aid both diagnosis and medical management. MRI using T2-weighted images and fat suppression (Fig. 159-5) identifies active sites of disease, reducing sampling error and increasing the sensitivity of muscle biopsy and EMG, results of which are nondiagnostic in 20% of instances if the procedures are not directed by MRI. Extensive rash and abnormal MRI findings may be found despite normal serum levels of muscle-derived enzymes. Muscle biopsy often demonstrates evidence of disease activity and chronicity that is not suspected from the levels of the serum enzymes alone.

A contrast swallow study may document palatal dysfunction and risk of aspiration. Pulmonary function testing detects a restrictive defect consistent with respiratory weakness and reduced diffusion capacity of carbon monoxide from alveolar fibrosis associated with other connective tissue diseases. Serial measurement of vital capacity or negative inspiratory force can document changes in respiratory weakness, especially in an inpatient setting. Calcinosis is seen easily on radiographs, along the fascial planes and within muscles.

Table 159-3 Phenotypic Characteristics of the Clinical Subgroups of Juvenile Myositis*

CHARACTERISTIC	JDM	JPM	JCTM
Demographics			
Median age at diagnosis (yr)	Youngest (7.4 yr)	Oldest (12.1 yr)	Intermediate (10.2 yr)
Race	Predominantly white (71.2%)	Black (39.4%)	Black or other (49.0%)
Severity at onset	Mild or moderate severity	**Severe or very severe onset**	Mild or moderate severity
Median delay to diagnosis (mo)	4 mo	3.5 mo	Longer delay (7 mo)
Clinical features	Gottron papules Heliotrope rash **Periungual capillary abnormalities** **Malar rash** *Photosensitivity* *Linear extensor erythema*† Cuticular overgrowth Mucous membrane involvement "V-sign" and "shawl-sign" rashes Skin ulcerations Dyspnea on exertion	*Weight loss* Falling episodes Raynaud phenomenon Abnormal PFT Dyspnea on exertion Cardiac abnormalities on EKG or ECHO	Gottron papules Heliotrope rash **Malar rash** **Raynaud phenomenon** **Interstitial lung disease** **Arthralgia** *Linear extensor erythema*† *Mucous membrane involvement* *Arthritis* *Photosensitivity* *Sclerodactyly* *Periungual capillary abnormalities*† Cuticular overgrowth Abdominal pain, GI bleeding Dyspnea on exertion Weight loss
Autoantibodies	Intermediate ANA titer (median, 1:320) *Anti-p155/140*† Anti-MJ Anti-Mi-2	Intermediate ANA titer (median, 1:320) Anti-SRP Anti-aminoacyl-tRNA synthetase (anti–Jo-1)	Highest ANA titer (median, 1:1280) **Anti-U1-RNP** Anti-PM-Sc1 Anti-Ro Anti-SM Anti-La All other U-RNP autoantibodies
Laboratory features	*Lowest CK level (median, 829 U/L)*	**Highest CK level (median, 5027 U/L)** Highest levels of aldolase and ALT	Intermediate CK level (median 1208 U/L)
Outcome	Low mortality (2.4%) Calcinosis (34.0%)	Medium mortality (6.3%) **Frequently hospitalized (71.9%)** Wheelchair use	Highest mortality (14.6%)

ALT, alanine aminotransferase; ANA, antinuclear antibody; CK, creatine kinase; ECHO, echocardiogram; EKG, electrocardiogram; GI, gastrointestinal; JCTM, juvenile myositis overlapping with another autoimmune or connective tissue disease; JDM, juvenile dermatomyositis; JPM, juvenile polymyositis; PFT, pulmonary function test; tRNA, transfer RNA.

*__Bold__ indicates significant in logistic regression; *italics* indicates top variables entered in pruned-down random forest models. Other variables included in this table were significant in univariable analysis to p ≤0.01.

†Removed from logistic regression analyses because variable was either 100% or 0% in 1 of the compared subgroups. Gottron papules and heliotrope rash, which were part of the definition of cases of dermatomyositis, were not entered into multivariable analyses.

Modified from Shah M, Mamyrova G, Targoff IN, et al: The clinical phenotypes of the juvenile idiopathic inflammatory myopathies. Medicine (Baltimore) *92:25–41, 2013, Table 9, p. 36.*

TREATMENT

The aid of an experienced pediatric rheumatologist is invaluable in outlining an appropriate course of treatment for a child with JDM. Prior to the advent of corticosteroids, one-third of patients spontaneously improved, one-third had a chronic, lingering course, and one-third died from the disease. Corticosteroids have altered the course of disease, lowering morbidity and mortality. Methotrexate decreases the length of treatment with corticosteroids, thereby reducing morbidity from steroid toxicity. Intravenous gammaglobulin is frequently used as an adjunct for treatment of severe disease.

Corticosteroids are still the mainstay of treatment. In a clinically stable child without debilitating weakness, oral prednisone at 2 mg/kg/day (maximum 60 mg daily) is usually started. Children with GI involvement have decreased absorption of oral steroids and require intravenous administration. In more-severe cases with respiratory or oropharyngeal weakness, high-dose pulse methylprednisolone is used (30 mg/kg/day for 3 days, maximum dose 1 g/day) with ongoing weekly or monthly IV dosing along with daily oral corticosteroids as needed. Corticosteroid dosage is slowly tapered over a period of 12 mo, after indicators of inflammation (muscle enzymes) normalize and strength improves.

Weekly oral, intravenous, or subcutaneous methotrexate (the lesser of 1 mg/kg or 15 mg/m^2, maximum 40 mg) is commonly used as a steroid-sparing agent in JDM. The concomitant use of methotrexate halves the cumulative dosage of steroids needed for disease control. Risks of methotrexate include immunosuppression, blood count dyscrasias, chemical hepatitis, pulmonary toxicity, nausea/vomiting, and teratogenicity. Folic acid is typically given with methotrexate starting at a dose of 1 mg daily to reduce toxicity and side effects of folate inhibition (oral ulcers, nausea, and anemia). Children who are taking immunosuppressive medications such as methotrexate should avoid live-virus vaccination, although inactivated influenza vaccination is recommended yearly.

Hydroxychloroquine has little toxicity risk and is used as a secondary disease-modifying agent to reduce rash and maintain remission. Typically, it is administered at doses between 4 and 6 mg/kg/day orally

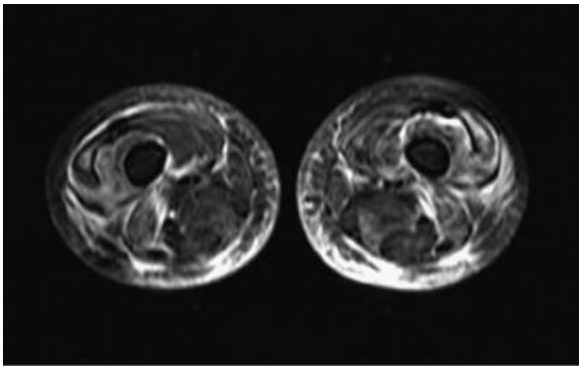

Figure 159-5 **MRI using T2-weighting and fat suppression of the proximal muscle of the lower extremities of a child with juvenile dermatomyositis with normal muscle enzyme levels.** There is focal inflammatory myopathy. The bright areas reflect the inflammatory response in involved muscle. The darker areas are more normal. Identification of involved areas by MRI directs the location of the muscle biopsy or electromyography.

in either tablet or liquid form. Ophthalmologic follow-up 1-2 times per year to monitor for rare retinal toxicity is recommended. Other side effects include hemolysis in patients with glucose-6-phosphate deficiency, GI intolerance, and skin/hair discoloration.

The use of rituximab in a trial of steroid-dependent patients with resistant inflammatory myopathies, including JDM, did not meet the primary study end point showing a difference in time to improvement between subjects given rituximab at baseline or at 8 wk, but overall, 83% of all subjects met the definition of improvement in the trial. Reports of the use of other biologic agents are based on case reports with mixed results.

Other medications for severe unresponsive disease include intravenous immunoglobulin, mycophenolate mofetil, cyclosporine, and cyclophosphamide. Children with pharyngeal weakness may need nasogastric or gastrostomy feedings to avoid aspiration, whereas those with GI vasculitis require full bowel rest. Rarely, children with severe respiratory weakness require ventilator therapy and even tracheostomy until the respiratory weakness improves.

Physical therapy and occupational therapy are integral parts of the treatment program, initially for passive stretching early in the disease course and then for direct reconditioning of muscles to regain strength and range of motion. Therapy may improve strength muscle measures and cardiovascular fitness. Bed rest is not indicated, because weight bearing improves bone density and prevents contractures. Social work and psychology services may facilitate adjustment to the frustration of physical impairment in a previously active child and aid with sleep disturbances associated with rheumatic disease.

All children with JDM should avoid sun exposure and apply high sun protection factor sunscreen daily, even in winter and on cloudy days. Vitamin D and calcium supplements are indicated for all children undergoing long-term corticosteroid therapy, in an attempt to reduce osteopenia and osteoporosis from medication.

COMPLICATIONS

Most complications from JDM are related to prolonged and severe weakness, including muscle atrophy, to cutaneous calcifications and scarring or atrophy, and to lipodystrophy. Secondary complications from medical treatments are also common. Children with acute and severe weakness are at risk for aspiration pneumonia and respiratory failure and occasionally require nasogastric feeding and mechanical ventilation until weakness improves. Crampy abdominal pain and occult GI bleeding may indicate bowel wall vasculitis and lead to ischemia, GI bleeding, and perforation if not treated with complete bowel rest and aggressive treatment for the underlying inflammation. Surgery should be avoided if possible, because the GI vasculitis is diffuse and not easily amenable to surgical intervention. Contrast-enhanced CT may show dilation or thickening of the bowel wall, intraluminal air, or evidence of bowel necrosis. Cardiac involvement by JDM is rare but includes arrhythmias.

Pathologic calcifications may be related to severity of disease and prolonged delay to treatment and potentially to genetic polymorphisms of tumor necrosis factor -α-308. Calcium deposits tend to form in subcutaneous tissue and along muscle. Some ulcerate through the skin and drain a soft calcific liquid, and others manifest as hard nodules along extensor surfaces or embedded along muscle. Draining lesions serve as a nidus for cellulitis or osteomyelitis. Nodules cause skin inflammation that may mimic cellulitis. Spontaneous regression of calcium deposits may occur, but there is no evidence-based recommendation for treatment of calcinosis.

Lipodystrophy manifests in 10-40% of patients with JDM and can be difficult to recognize. Fat atrophy may be generalized, partial, or local. Lipodystrophy has been associated with insulin resistance, acanthosis nigricans, dyslipidemia, hypertension, and menstrual irregularity, similar to features seen in polycystic ovarian disease or metabolic syndrome.

Children receiving prolonged corticosteroid therapy are prone to complications such as cessation of linear growth, weight gain, hirsutism, adrenal suppression, immunosuppression, striae, cushingoid fat deposition, mood changes, osteoporosis, cataracts, avascular necrosis, and steroid myopathy. Families should be counseled on the effects of corticosteroids and advised to use medical alert identification and to consult a nutritionist regarding a low-salt, low-fat diet with adequate vitamin D and calcium supplementation.

PROGNOSIS

The mortality rate in JDM has decreased since the advent of corticosteroids, from 33% to currently approximately 1%; little is known about the long-term consequences of persistent vascular inflammation. The period of active symptoms has decreased from about 3.5 yr to <1.5 yr with more aggressive immunosuppressive therapy; the vascular, skin, and muscle symptoms of children with JDM generally respond well to therapy. At 7 yr of follow-up, 75% of patients have little to no residual disability, but 25% continue to have chronic weakness and 40% have chronic rash. Up to one-third may need long-term medications to control their disease. Children with JDM appear able to repair inflammatory damage to vasculature and muscle.

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Chapter 160

Scleroderma and Raynaud Phenomenon

Heather A. Van Mater and C. Egla Rabinovich

Juvenile scleroderma encompasses a range of conditions unified by the presence of fibrosis of the skin. Juvenile scleroderma is divided into 2 major categories, **juvenile localized scleroderma** (**JLS**, also known as **morphea**), which is largely limited to the skin, and juvenile **systemic sclerosis** (**JSSc**), with multisystem organ involvement. Localized disease is the predominant type seen in pediatric populations (>95%), but systemic sclerosis is associated with mortality and severe morbidity.

ETIOLOGY AND PATHOGENESIS

The etiology of scleroderma is unknown, but the mechanism of disease appears to be a combination of a vasculopathy, autoimmunity, immune activation, and fibrosis. Triggers, including trauma, infection, and, possibly, subclinical graft-versus-host reaction from persistent maternal cells (microchimerism), injure vascular endothelial cells, resulting in increased expression of adhesion molecules. These molecules entrap platelets and inflammatory cells, resulting in vascular changes with manifestations such as Raynaud phenomenon and pulmonary hypertension. Inflammatory cells infiltrate the area of initial vascular damage, causing further vascular damage and resulting in thickened artery walls and reduction in capillary numbers. Macrophages and other inflammatory cells then migrate into affected tissues and secrete cytokines that induce fibroblasts to reproduce and synthesize excessive amounts of collagen, resulting in fibrosis and subsequent lipoatrophy, dermal fibrosis, with loss of sweat glands and hair follicles. In late stages, the entire dermis may be replaced by compact collagen fibers.

Autoimmunity is believed to be a key process in the pathogenesis of both localized and systemic scleroderma, given the high percentage of affected children with autoantibodies. Children with localized disease often have a positive antinuclear antibody (ANA) test result (42%), and 47% of this subgroup have antihistone antibodies. Children with JSSc have higher rates of ANA positivity (80.7%) and may have anti-Scl 70 antibody (34%, antitopoisomerase I). The relationship between specific autoantibodies and the various forms of scleroderma is not well understood, and all antibody test results may be negative, especially in JLS.

CLASSIFICATION

Localized scleroderma is distinct from systemic scleroderma and rarely progresses to systemic disease. Within the category of JLS there are several subtypes that are differentiated by both the distribution of the lesions and the depth of involvement (Table 160-1). Up to 15% of children have a combination of 2 or more subtypes.

Table 160-1 Classification of Pediatric Scleroderma (Morphea)

LOCALIZED SCLERODERMA
Plaque Morphea
Confined to dermis, occasionally superficial panniculus
Well-circumscribed circular area of induration, often a central waxy, ivory-colored area surrounded by a violaceous halo; unilateral
Generalized Morphea
Involves dermis primarily, occasionally panniculus
Defined as confluence of individual morphea plaques or lesions in 3 or more anatomic sites; more likely to be bilateral
Bullous Morphea
Bullous lesions that can occur with any of the subtypes of morphea
Linear Scleroderma
Linear lesions can extend through the dermis, subcutaneous tissue, and muscle to underlying bone; more likely unilateral
Limbs/trunk:
One or more linear streaks of the extremities or trunk
Flexion contracture occurs when lesion extends over a joint; limb length discrepancies
En coup de sabre:
Involves the scalp and/or face; lesions can extend into the central nervous system, resulting in neurologic sequelae, most commonly seizures and headaches
Parry Romberg syndrome:
Hemifacial atrophy without a clearly definable en coup de sabre lesion; can also have neurologic involvement
Deep Morphea
Involves deeper layers, including panniculus, fascia, and muscle; more likely to be bilateral
Subcutaneous morphea:
Primarily involves the panniculus or subcutaneous tissue
Plaques are hyperpigmented and symmetric
Eosinophilic fasciitis:
Fasciitis with marked blood eosinophilia
Fascia is the primary site of involvement; typically involves extremities
Classic description is "peau d'orange" or orange peel texture, but early disease manifests as edema (see Fig. 160-2)
Morphea profunda:
Deep lesion extending to fascia and sometimes muscle, but may be limited to a single plaque, often on trunk
Disabling pansclerotic morphea of childhood:
Generalized full-thickness involvement of skin on the trunk, face and extremities, sparing finger tips and toes
SYSTEMIC SCLEROSIS
Diffuse
Most common type in childhood
Symmetric thickening and hardening of the skin (sclerosis) with fibrous and degenerative changes of viscera
Limited
Rare in childhood
Previously known as CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome

EPIDEMIOLOGY

Juvenile scleroderma is rare, with an estimated prevalence of 1/100,000. Localized scleroderma is far more common than SSc in children, by a 10 : 1 ratio, with **linear scleroderma** being the most common subtype. LS is predominantly a pediatric condition, with 65% of patients diagnosed before age 18 yr. After age 8 yr the female : male ratio for both LS and SSc is approximately 3 : 1, whereas in patients younger than 8 yr there is no sex predilection.

CLINICAL MANIFESTATIONS

Localized Scleroderma

The onset of scleroderma is generally insidious, and manifestations vary according to disease subtype. The initial skin manifestations of localized disease usually include erythema or a bluish hue seen around an area of waxy induration; subtle erythema may be the only presenting sign (Fig. 160-1). Edema and erythema are followed by indurated, hypopigmented or hyperpigmented, atrophic lesions (Fig. 160-2). **LS** varies in size from a few centimeters to the entire length of the extremity, with varying depth. Patients sometimes present with arthralgias, synovitis, or flexion contractures (Fig. 160-3). Children also experience limb length discrepancies as a result of growth impairment caused by involvement of muscle and bone. Children with **en coup de sabre** (Fig. 160-4) may have symptoms unique to central nervous system involvement, such as seizures, hemifacial atrophy, ipsilateral uveitis, and learning/behavioral changes.

Up to 25% of children with LS have extracutaneous manifestations, most commonly arthritis (47%) and neurologic symptoms (17%) associated with en coup de sabre.

Systemic Scleroderma

SSc also has an insidious onset with a prolonged course characterized by periods of remission and exacerbation, ending in either remission or, more commonly, chronic disability and death.

The skin manifestations of SSc include an early phase of edema that spreads proximally from the dorsum of the hands and fingers and includes the face. An eventual decrease in edema is followed by induration and fibrosis of skin, ultimately resulting in loss of subcutaneous fat, sweat glands, and hair follicles. Later, atrophic skin becomes shiny and waxy in appearance. As lesions spread proximally, flexion contractures develop at the elbows, hips, and knees associated with secondary muscle weakness and atrophy. In the face, this process results in a small oral stoma with decreased mouth aperture. Skin ulceration over pressure points, such as the elbows, may be associated with subcutaneous calcifications. Severe Raynaud phenomenon causes ulceration of the fingertips with subsequent loss of tissue pulp and tapered fingers (**sclerodactyly**) (Fig. 160-5). Resorption of the distal tufts of the distal phalanges may occur (**acroosteolysis**). Hyperpigmented postinflammatory changes surrounded by atrophic depigmentation gives a

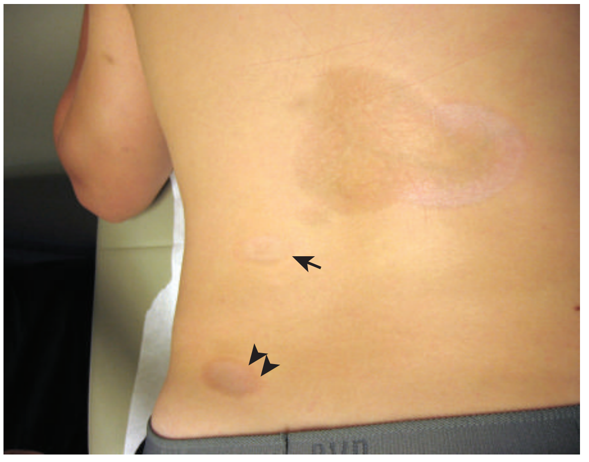

Figure 160-1 Boy with generalized morphea. Note the active circular lesion *(arrowheads)* with a surrounding rim of erythema. The largest lesion has areas of postinflammatory hyperpigmentation and depression with an area of erythema on the right. The small lesion *(arrow)* demonstrates depression caused by lipoatrophy.

Figure 160-2 Inactive linear scleroderma demonstrating hyperpigmented lesion with areas of normal skin (skip lesions).

Figure 160-3 Child with untreated linear scleroderma resulting in knee contracture, immobility of ankle, chronic skin breakdown of scar on the lateral knee, and areas of hypopigmentation and hyperpigmentation. The affected leg is 1 cm shorter.

Figure 160-4 Child with en coup de sabre lesion on scalp extending down to forehead. Prior to treatment the skin on the scalp was bound down with chronic skin breakdown. Note the area of hypopigmentation extending down the forehead *(arrows)*.

Figure 160-5 Sclerodactyly and finger ulcerations in a patient with systemic sclerosis who is poorly compliant with treatment.

salt-and-pepper appearance to skin. Over a period of years, remodeling of lesions sometimes results in focal improvement in skin thickening.

Pulmonary disease is the most common visceral manifestation of SSc and includes both arterial and interstitial involvement (alveolitis). Symptoms range from asymptomatic disease to exercise intolerance, dyspnea at rest, and right-sided heart failure. **Pulmonary arterial hypertension** is a poor prognostic sign, developing either as a consequence of lung disease or independently as part of the vasculopathy. Clinical manifestations of pulmonary arterial hypertension in children appear late in the course, are subtle, and include cough and dyspnea on exertion. Pulmonary evaluation should include pulmonary function testing, bronchioalveolar lavage, and high-resolution chest CT. Pulmonary function tests reveal decreased vital capacity and decreased diffusion of carbon monoxide capacity, while neutrophilia and/or eosinophilia on bronchioalveolar lavage suggest active alveolitis. Chest CT is much more sensitive than chest radiographs, which are often normal, showing typical basilar ground-glass abnormalities, reticular linear opacities, nodules, honeycombing, and mediastinal adenopathy.

Other organ systems include gastrointestinal tract disease, which is seen in 25% of children with the disease. Common manifestations include esophageal and intestinal dysmotility resulting in dysphagia, reflux, dyspepsia, gastroparesis, bacterial overgrowth, dilated bowel loops and pseudoobstruction, and dental caries, as well as malabsorption and failure to thrive. Renal arterial disease can cause chronic or severe episodic hypertension; unlike adult disease, renal crisis is rare. Cardiac fibrosis is associated with arrhythmias, ventricular hypertrophy, and decreased cardiac function. Mortality from JSSc is most commonly a result of cardiopulmonary disease.

Raynaud Phenomenon

Raynaud phenomenon (RP) is the most frequent initial symptom in pediatric systemic sclerosis, present in 70% of affected children months to years before other manifestations. RP refers to the classic triphasic sequence of blanching, cyanosis, and erythema of the digits induced

Table 160-2 Classification of Raynaud Phenomenon

Isolated Raynaud phenomenon
Occupational Raynaud phenomenon:
Cold injury
Vibrating tools
Polyvinyl chloride exposure
Secondary Raynaud phenomenon:
Systemic sclerosis
Mixed connective tissue disease
Sjögren syndrome
Systemic lupus erythematosus
Polymyositis/dermatomyositis
Rheumatoid arthritis
Arteritis
Antiphospholipid antibody syndrome
Primary biliary cirrhosis
Carpal tunnel syndrome
Cryoglobulinemia
Leukemia
Vasospastic disorders (migraine, Prinzmetal angina)
Infection:
Hepatitis B and C (cryoglobulinemia)
Cytomegalovirus (?)
Obstructive vascular disease:
Thromboangiitis obliterans
Thoracic outlet syndrome (cervical rib)
Metabolic syndrome:
Hypothyroid
Carcinoid syndrome
Drug-induced:
Antimigraine medications
β-Blocker
Bleomycin
Interferons
Ergotamine derivatives

From Firestein GS, Budd RC, Harris ED Jr, et al, editors: Kelley's textbook of rheumatology, *ed 8, vol II, Philadelphia, 2009, Saunders/Elsevier.*

by cold exposure and/or emotional stress. RP is most commonly independent of an underlying rheumatic disease (**Raynaud disease**), but it can be a consequence of rheumatic diseases such as scleroderma, systemic lupus erythematosus, and mixed connective tissue disease (Table 160-2). The color changes are brought about by (1) initial arterial vasoconstriction, resulting in hypoperfusion and pallor (blanching), (2) venous stasis (cyanosis), and (3) reflex vasodilation caused by the factors released from the ischemic phase (erythema). The color change is classically reproduced by immersing the hands in iced water and reversed by warming. During the blanching phase, there is inadequate tissue perfusion in the affected area, associated with pain and paresthesias and resulting in ischemic damage only when associated with a rheumatic disease. The blanching usually affects the distal fingers, but may also involve thumbs, toes, ears, and tip of the nose. The affected area is usually well demarcated and uniformly white. Digital ulcers associated with RP are indicative of underlying rheumatic disease.

Raynaud disease often begins in adolescence and is characterized by symmetric occurrence, the absence of tissue necrosis and gangrene, and the lack of manifestations of an underlying rheumatic disease. Children have normal nail-fold capillaries (absence of periungual telangiectasias). RP should be distinguished from **acrocyanosis** and **chilblains.** Acrocyanosis is a vasospastic disorder resulting in cool, painless, bluish discoloration in the hands and sometimes feet despite normal tissue perfusion. It may be exacerbated by stimulant medications used to treat attention deficit disorder. Chilblains is a condition with episodic color changes and the development of nodules related to severe cold exposure and spasm-induced vessel and tissue damage; this condition has been associated with systemic lupus erythematosus.

Table 160-3 Provisional Criteria for the Classification of Juvenile Systemic Sclerosis (SSc)

MAJOR CRITERION (REQUIRED)*
Proximal skin sclerosis/induration of the skin proximal to metacarpophalangeal or metatarsophalangeal joints
MINOR CRITERIA (AT LEAST 2 REQUIRED)
Cutaneous: sclerodactyly
Peripheral vascular: Raynaud phenomenon, nailfold capillary abnormalities (telangiectasias), digital tip ulcers
Gastrointestinal: dysphagia, gastroesophageal reflux
Cardiac: Arrhythmias, heart failure
Renal: Renal crisis, new-onset arterial hypertension
Respiratory: pulmonary fibrosis (high-resolution computed tomography/radiography), decreased diffusing capacity for carbon monoxide, pulmonary arterial hypertension
Neurologic: neuropathy, carpal tunnel syndrome
Musculoskeletal: tendon friction rubs, arthritis, myositis
Serologic: antinuclear antibodies—SSc-selective autoantibodies (anticentromere, antitopoisomerase I [Scl-70], antifibrillarin, anti-PM/Scl, antifibrillin or anti-RNA polymerase I or III

*Diagnosis requires at least 1 major and at least 2 minor criteria.

From Zulian F, Woo P, Athreya BH, et al: The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. Arthritis Rheum *57:203–212, 2007.*

DIAGNOSIS

The diagnosis of localized scleroderma is based on the distribution and depth of characteristic lesions. Biopsy is helpful to confirm the diagnosis. The diagnosis of JSSc requires proximal sclerosis/induration of the skin as well as the presence of 2 of 20 minor criteria (Table 160-3).

DIFFERENTIAL DIAGNOSIS

The most important condition to differentiate from JLS is JSSc. Contractures and synovitis from juvenile arthritis can be differentiated from those due to linear scleroderma by the absence of skin changes. Other conditions to consider include chemically induced scleroderma-like disease, **diabetic cheiroarthropathy**, **pseudoscleroderma**, and **scleredema**. Pseudoscleroderma is composed of a group of unrelated diseases characterized by patchy or diffuse cutaneous fibrosis without the other manifestations of scleroderma. These include phenylketonuria, syndromes of premature aging, and localized idiopathic fibrosis. **Scleredema** is a transient, self-limited disease of both children and adults that has sudden onset after a febrile illness (especially streptococcal infections) and is characterized by patchy sclerodermatous lesions on the neck and shoulders and extending to the face, trunk, and arms.

LABORATORY FINDINGS

There are no laboratory studies diagnostic of either localized or systemic scleroderma. Although the results of complete blood counts, serum chemistry analyses, and urinalysis are normal, children may have elevated erythrocyte sedimentation rate, eosinophilia, or hypergammaglobulinemia, all of which normalize with treatment. Elevations of muscle enzymes, particularly aldolase, can be seen with muscle involvement. Patients with JSSc may have anemia, leukocytosis, and eosinophilia and autoantibodies (ANA, anti-Scl 70). Imaging studies delineate the affected area and can be used to follow disease progression. MRI is useful in en coup de sabre and Parry Romberg syndrome for determination of central nervous system or orbital involvement. Infrared thermography utilizes the temperature variation between areas of active and inactive cutaneous disease to help differentiate active disease from damage. The role of ultrasound to look at lesion activity is evolving. High-resolution CT, pulmonary function tests, echocardiography, and manometry are useful tools for diagnosing and monitoring visceral involvement in JSSc.

TREATMENT

Treatment for scleroderma varies according to the subtype and severity. Superficial morphea may benefit from topical corticosteroids or ultraviolet therapy. For lesions involving deeper structures, systemic therapy is recommended. A combination of methotrexate and corticosteroids is effective in treating JLS by preventing lesion extension and resulting in significant skin softening and improved range of motion of affected joints. The treatment plan for JLS and includes: (1) weekly subcutaneous methotrexate given at 1/mg/kg weekly (maximum dose: 25 mg); (2) weekly methotrexate as in (1) plus either 3 mo of high-dose intravenous corticosteroids (30 mg/kg, maximum dose: 1,000 mg) for 3 consecutive days a month *or* weekly corticosteroids at the same dose for 3 mo; (3) high daily oral corticosteroids (2 mg/kg/day, maximum: 60 mg) with a slow taper over 48 wk. Mycophenolate mofetil is a second-line agent for recalcitrant disease. Physical and occupational therapy are important adjuncts to pharmacologic treatment. Eosinophilic fasciitis often responds well to corticosteroids and methotrexate.

Treatments for JSSc target specific disease manifestations. RP is treated with cold avoidance with pharmacologic interventions are reserved for severe disease. Calcium channel blockers (nifedipine 30-60 mg of sustained-release form daily, amlodipine 2.5-10 mg daily) are the most common pharmacologic interventions. Additional potential therapies for RP include losartan, prazosin, bosentan, and sildenafil. Angiotensin-converting enzyme inhibitors (captopril, enalapril) are recommended for hypertension associated with renal disease. Methotrexate or mycophenolate mofetil may be beneficial for skin manifestations. Cyclophosphamide and mycophenolate mofetil are used to treat pulmonary alveolitis and prevent fibrosis. Corticosteroids should be used cautiously in systemic sclerosis because of an association with renal crisis. Adults with systemic sclerosis have been successfully treated with high-dose cyclophosphamide, antithymocyte globulin and autologous stem cell transplantation.

The treatment of RP begins with avoiding cold stimuli, use of hand and foot warmers, and avoiding carrying bags by their handles (impairs circulation). Nifedipine (10-20 mg tid adult dose) reduces but does not eliminate the number and severity of episodes. Side effects include headache, flushing, and hypotension. Topical nitrates may result in digital vasodilation and may reduce the severity of an episode.

PROGNOSIS

Localized scleroderma is generally self-limited, with initial inflammatory stage followed by a period of stabilization and then softening for an average disease duration of 3-5 yr; however there are reports of active disease lasting up to 20 yr. Prolonged disease activity is associated primarily with linear and deep disease subtypes. Localized scleroderma, especially linear and deep subtypes, can result in significant morbidity, disfigurement, and disability as a result of joint contractures, muscle atrophy, limb shortening, facial asymmetry, and hyper- and hypopigmentation. Death from a **en coup de sabre** lesion with progressive neurologic decline has been reported.

JSSc has a more variable prognosis. Although many children have a slow, insidious course, others demonstrate a rapidly progressive form with early organ failure and death. Skin manifestations reportedly soften years after disease onset. Overall, the prognosis of JSSc is better than that of the adult form, with 5-, 10-, and 15-year survival rates, respectively, in children of 89%, 80-87%, and 74-87%. The most common cause of death is heart failure caused by myocardial and pulmonary fibrosis.

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Chapter 161

Behçet Disease

Seza Özen

Behçet disease (BD) is classified as a primary *variable vessel vasculitis*, emphasizing the involvement of any size and type (arterial, venous) of vessel. BD is also recognized as an autoinflammatory disease. Originally described with recurrent oral ulcerations, uveitis and skin abnormalities, the spectrum is much broader.

EPIDEMIOLOGY

BD has a high prevalence in countries along the *Silk Road,* extending from Japan to the eastern Mediterranean. It is increasingly recognized among people of European ancestry. BD has a prevalence of 5-7 per 100,000 adults, which makes it more frequent than the other vasculitides such as granulomatosis polyangiitis (Wegener disease). The increased disease recognition might have had a role in the rising prevalences as well as the immigrations of the 20th century. Prevalence in children is probably not more than 10% of the adult counterparts in eastern Mediterranean countries. In children, boys and girls are equally affected. Family history of BD is present in approximately 20% of the cases. Onset in children is 8-12 yr of age; newborns of affected mothers have demonstrated symptoms of BD.

ETIOLOGY AND PATHOGENESIS

BD is a polygenic autoinflammatory disorder. Genetic contribution to BD is evident through the well-known association with HLA-B5101, the familial cases, the sibling and twin recurrence rate, the specific frequency of the disease among people along the *Silk Road*, evidence for genetic anticipation and the genome wide analysis studies that support the genetic contribution in the pathogenesis. Genome wide analysis studies among Turkish and Japanese BD patients confirm the marked association with HLA-B5101. Other significant associations include interleukin (IL)-10 and IL-23R/IL-12RB2 genes. Other possible susceptibility loci in a Turkish cohort demonstrate associations in STAT4 (a transcription factor in a signaling pathway related to cytokines such as IL-12, type I interferons, and IL-23), and ERAP1 (an endoplasmic reticulum–expressed aminopeptidase that functions in processing of peptides onto major histocompatibility complex class I).

The autoinflammatory nature of the disease is suggested by the episodic nature of the disease, the prominent innate immune system activation, the absence of identifiable autoantibodies and the co-association with the *MEFV* (Mediterranean fever) gene. An infectious agent may be responsible for inducing the aberrant innate immune system attacks in the genetically predisposed host. A number of infectious agents have been implicated and include streptococci, herpes simplex virus type 1, and parvovirus B19.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The course of BD is characterized by exacerbations and remissions. There is also marked heterogeneity in disease manifestation (Table 161-1).

The mean age of the first symptom is between 8 and 12 yr. The most frequent initial symptom is a painful **oral ulcer** (Fig. 161-1). The oral ulcers are often recurrent, may be single or multiple, range from 2-10 mm, and may be in any location in the oral cavity. They are often very painful. The oral ulcers last 3-10 days and heal without scarring. In contrast, the genital ulcers heal with scars. Genital scars are noted in 60% of the patients, usually occur after puberty, and are seen on the labia, scrotum, penis, or the anal area.

Another key feature of BD that has significant morbidity is bilateral eye involvement seen in 30-60% of pediatric patients. The main symptoms of **anterior uveitis** are blurred vision, redness, periorbital or

global pain, and photophobia. Although it is often in the form of panuveitis, anterior uveitis may be seen in females. Uveitis in general is more common in males. Vitreitis and retinal vasculitis are the most prominent features of posterior involvement. Complications of uveitis include blindness (unusual with treatment), glaucoma, and cataracts. Retinal vasculitis, retinal detachment, and retrobulbar neuritis (optic neuritis) are less-common eye manifestations of BD.

The **skin lesions** of BD range from erythema nodosum, papulopustular acneiform lesions, folliculitis, purpura, and ulcers. **Pathergy** is also a skin feature that is a pustular reaction occurring 24-48 hr after a sterile needle puncture or saline injection; it is not pathognomonic of BD.

Table 161-1 Criteria of the International Study Group for the Diagnosis of Behçet disease

CRITERION	DESCRIPTION
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration recurring at least 3 times in one 12 mo period, observed by physician or patient
Plus 2 of the following:	
Recurrent genital ulcers	Aphthous ulceration or scarring observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, cells in vitreous on slit-lamp examination, or retinal vasculitis observed by an ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions, or acneiform nodules observed by physician in postadolescent patient not on corticosteroid treatment
Pathergy	Skin reaction to a needle prick observed by physician at 24-48 hr

From International Study Group for Behçet's Disease: Criteria for diagnosis of Behçet's disease, Lancet *335:1070–1080,1990.*

Figure 161-1 Oral aphthous lesion in a girl with Behçet disease. *(From Ozen S, Petty RE: Behçet disease. In Cassidy JT, Petty RE, Laxer RM, et al, editors,* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders, Fig. 36-1, p. 554.)*

The **vasculitis** of BD involves both arterial or venous thrombosis and aneurysm formation or occlusions or stenosis in arteries of any size. In children deep venous thrombosis of the lower limbs is the most frequent vasculitic feature. If the hepatic vein is thrombosed Budd-Chiari syndrome may occur. Pulmonary aneurysms are the most severe feature of pediatric BD, associated with the highest mortality. Coronary artery aneurysms may confuse BD with Kawasaki disease. Microvascular involvement may be noted in the nail bed capillaries.

Central nervous system (CNS) manifestations in children include meningoencephalitis (headache, meningismus, cerebrospinal fluid pleocytosis), encephalomyelitis, pseudotumor cerebri, dural sinus thrombosis, and organic psychiatric disorders (psychosis, depression, dementia). Dural sinus thrombosis is the most common CNS manifestation in children.

Gastrointestinal involvement manifests with abdominal pain, diarrhea, and intestinal ulcerations, most often in the ileocecal region. Gastrointestinal BD may be difficult to distinguish from inflammatory bowel disease. Oligoarticular **arthritis/arthralgia** is present in more than 50% of the patients and can be recurrent, but is nondeforming. Other rare manifestations include orchitis, renal vasculitis, glomerulonephritis, or amyloidosis and cardiac involvement.

DIAGNOSIS

The International Study Group criteria are most widely used and require the presence of oral ulcers (at least 3 times per year) along with 2 other major features, including genital ulcers, a positive pathergy test, uveitis, and the characteristic skin lesions (see Table 161-1). If only 1 of the criteria is present along with oral ulcerations, the term *incomplete* or *partial Behçet disease* is applied. There are no specific laboratory tests. Acute-phase reactants are often mildly elevated. The diagnosis relies on the constellation of symptoms and excluding other causes.

TREATMENT AND PROGNOSIS

Azathioprine is highly recommended to treat inflammatory eye disease. For oral and genital ulcers topical treatment is recommended (sucralfate, steroids). Colchicine is recommended for erythema nodosum or arthritis in males and females and for genital ulcers in females. There is no evidence-based treatment for gastrointestinal disease, but thalidomide, sulfasalazine, steroids, azathioprine and anti–tumor necrosis factor (TNF) agents have been recommended. For CNS disease and vasculitis, steroids, azathioprine, cyclophosphamide, interferon alpha, and in unresponsive CNS disease anti-TNF agents are suggested. There is no consensus about the benefit of anticoagulation in the management of vein thrombosis in BD.

In patients without major organ involvement, colchicine significantly improves oral and genital ulcers, skin features, and disease activity. In pediatric patients with vascular involvement with venous thrombosis, steroids and azathioprine have been used, whereas those with pulmonary arterial or cardiac involvement are initially treated with cyclophosphamide; follow-up of at least 18 mo demonstrated that those treated are free of vascular relapses. Patients treated with anti-TNF drugs have had persistent responses in 90%, 89%, 100%, and 91% of patients with resistant mucocutaneous, ocular, gastrointestinal, and central nervous system involvement, respectively.

Mortality in children with BD is low except for the pulmonary aneurysms. However, BD is a chronic disease associated with significant morbidity. Early diagnosis and effective treatment improves the outcome of BD.

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Chapter 162

Sjögren Syndrome

C. Egla Rabinovich

Sjögren syndrome is a chronic, inflammatory, autoimmune disease characterized by progressive lymphocytic and plasma cell infiltration of the exocrine glands, especially salivary and lacrimal, with potential for systemic manifestations. It is rare in children and predominantly affects middle-age women with classic symptoms of dry eyes (**keratoconjunctivitis sicca**) and dry mouth (**xerostomia**).

EPIDEMIOLOGY

Sjögren syndrome typically manifests at 35-45 yr of age, with 90% of cases among women, but it is underrecognized in children as symptoms often start in childhood. The mean age at diagnosis in children is 9-10 yr; 75% are girls. The disease can occur as an isolated disorder, referred to as *primary Sjögren syndrome (sicca complex)*, or as a *secondary Sjögren syndrome* in association with other rheumatic disorders such as systemic lupus erythematosus, scleroderma, or mixed connective tissue disease, and usually precedes the associated autoimmune disease by years.

ETIOLOGY AND PATHOGENESIS

The etiology of Sjögren syndrome is complex and includes genetic predisposition and possibly an infectious trigger. Lymphocytes and plasma cells infiltrate salivary glands, forming distinct periductal and periacinar foci that become confluent and may replace epithelial structure. Several genes regulating apoptosis influence the chronicity of lymphocytic infiltration.

CLINICAL MANIFESTATIONS

International classification criteria have been developed for the diagnosis of Sjögren syndrome in adult patients, but these criteria apply poorly to children. Although diagnostic criteria in children have been proposed, they have not been validated (Table 162-1). Recurrent parotid gland enlargement and parotitis are the most common manifestations in children (>70%), whereas sicca syndrome (dry mouth, painful mucosa, sensitivity to spicy foods, halitosis, widespread dental caries) predominate in adults. In a cross sectional study of children with Sjögren syndrome, manifestations included recurrent parotitis (72%), sicca symptoms (38%), polyarthritis (18%), vulvovaginitis (12%), hepatitis (10%), Raynaud phenomenon (10%), fever (8%), renal tubular acidosis (9%), lymphadenopathy (8%), and central nervous system involvement (5%).

Subjective symptoms of xerostomia complaints are relatively rare in juvenile cases, perhaps indicating that Sjögren syndrome is a slowly progressive disease; however increased dental caries is seen clinically in children. Serologic markers (antinuclear antibodies, and antibodies to Ro [SSA] and SSB [La]) and articular manifestations are significantly more frequent in adults. Frequencies of the finding of antinuclear antibodies and SSA and SSB antibodies in children are reported to be 78%, 75%, and 65%, respectively, with rheumatoid factor present in 67%. Additional clinical manifestations from a variety of organ involvement patterns include a decreased sense of smell, hoarseness, chronic otitis media, leukocytoclastic vasculitis (purpura), and internal organ exocrine disease involving the lungs (diffuse interstitial lymphocytosis), pancreas, hepatobiliary system, gastrointestinal tract, kidneys (renal tubular acidosis), musculoskeletal (arthritis and arthralgia), hematologic (cytopenias), peripheral nervous system (sensory and autonomic neuropathy), and central nervous system (optic neuritis, transverse myelitis, meningoencephalitis).

Table 162-1 Proposed Criteria for Pediatric Sjögren Syndrome

I. CLINICAL SYMPTOMS
  1. Oral: recurrent parotitis or enlargement of parotid gland, dry mouth (xerostomia)
  2. Ocular: dry eyes (xerophthalmia) recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca
  3. Other mucosal: recurrent vaginitis
  4. Systemic: fever, non-inflammatory arthralgias, hypokalemic paralysis, abdominal pain

II. IMMUNOLOGIC ABNORMALITIES: presence of at least 1 of the following antibodies: anti-SSA, anti-SSB, high titer antinuclear antibody, rheumatoid factor

III. OTHER ABNORMALITIES OR INVESTIGATIONS
  1. Biochemical: elevated serum amylase
  2. Hematologic: leukopenia, high sedimentation rate
  3. Immunologic: polyclonal hyperimmunoglobulinemia
  4. Renal: renal tubular acidosis
  5. Histologic proof of lymphocytic infiltration of salivary glands or other organs (i.e., liver)
  6. Objective documentation of ocular dryness (Bengal red staining or Schirmer test)
  7. Positive findings of parotid gland scintigraphy

IV. Exclusion of all other autoimmune diseases

Diagnosis requires ≥4 criteria.
From Bartunkova J. Primary Sjögren syndrome in children and adolescents: proposal for diagnostic criteria, Clin Exp Rheumatol *17:381–386, 1999.*

Non–exocrine disease manifestations of Sjögren syndrome may be related to inflammatory vascular disease (in skin, muscle and joints, serosal surfaces, and peripheral and central nervous systems), noninflammatory vascular disease (Raynaud phenomenon), mediator-induced disease (hematologic cytopenias, fatigue, and fever), and autoimmune endocrinopathy (thyroiditis).

DIAGNOSIS

Clinical presentation of recurrent parotitis and or recurrent parotid gland swelling in a child or adolescent is characteristic and should raise the suspicion for this disorder. The diagnosis is based on clinical features supported by biopsy of salivary or parotid glands demonstrating foci of lymphocytic infiltration, the current gold standard for diagnosis. Children are more likely to have normal minor salivary gland but abnormal parotid gland biopsies. Supporting laboratory abnormalities include cryoglobulinemia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, positive rheumatoid factor, and detection of SSA and SSB antibodies. Anti–β-fodrin autoantibodies, directed against an apoptotic cleavage product of α-fodrin, are a useful diagnostic marker for juvenile Sjögren syndrome. The **Schirmer test** detects abnormal tear production (≤5 mm of wetting of filter paper strip in 5 min) and **Rose-Bengal staining** detects damaged ocular epithelial conjunctival and corneal cells. Imaging studies, including MRI, technetium ^{99m}Tc scintigraphy, and sialography, are useful in the diagnostic evaluation for Sjögren syndrome (Fig. 162-1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Sjögren syndrome in children includes **juvenile recurrent parotitis**, characterized by intermittent unilateral parotid swelling typically lasting only a few days. It is frequently associated with fever and may undergo remission with puberty. Unlike in Sjögren syndrome, there is a male predominance, it is seen in the younger children (3-6 yr of age), and there is a lack of focal lymphocytic infiltrates on biopsy. Other conditions in the differential diagnosis include eating disorders, infectious parotitis (mumps, streptococcal and staphylococcal infections, Epstein-Barr virus, cytomegalovirus, HIV, parainfluenza, influenza enterovirus) and local trauma to the buccal mucosa. Rarely, polycystic parotid disease, tumors, and sarcoidosis may present with recurrent parotid swelling. In these conditions,

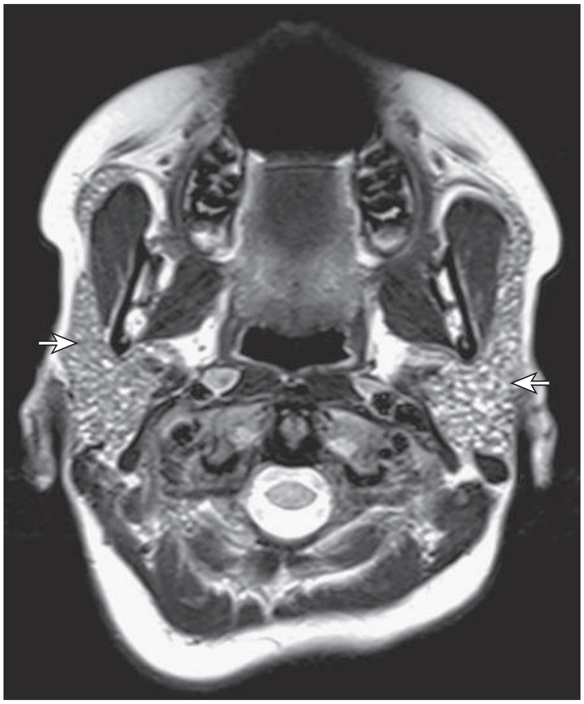

Figure 162-1 T2-weighted MRI of child with Sjögren syndrome showing parotitis *(arrows).*

sicca complex, rash, arthralgia, and antinuclear antibodies are usually absent.

TREATMENT

Symptomatic treatment of Sjögren syndrome includes the use of artificial tears, massage of the parotids, oral lozenges, and fluids to limit the damaging effects of decreased secretions. Corticosteroids, nonsteroidal antiinflammatory drugs, and hydroxychloroquine are among the more commonly used agents for treatment, with reports of methotrexate and etanercept used for treatment of arthritis. Stronger immunosuppressive agents, such as cyclosporine and cyclophosphamide, are reserved for severe functional disorders and life-threatening complications.

COMPLICATIONS AND PROGNOSIS

The symptoms of Sjögren syndrome develop and progress slowly. Diminished salivary flow typically remains constant for years. Because monoclonal B-lymphocyte disease originates chiefly from lymphocytic foci within salivary glands or from parenchymal internal organs, there is increased risk for mucosa-associated lymphoid tissue lymphoma. Maternal Sjögren syndrome can be an antecedent to the neonatal lupus syndrome (see Chapter 158.1).

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Chapter 163

Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases

Amanda K. Ombrello and Daniel L. Kastner

The hereditary periodic fever syndromes are a group of monogenic diseases that present with recurrent bouts of fever and associated pleural and/or peritoneal inflammation, arthritis, and various types of skin rash. They are subsumed among a larger group of disorders, the systemic autoinflammatory diseases, that were first recognized for their seemingly unprovoked episodes of inflammation, without the high-titer autoantibodies or antigen-specific T cells commonly seen in autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis. Whereas the autoimmune diseases are disorders of the adaptive immune system, with its lymphocyte effector cells and receptors that somatically rearrange and mutate, the autoinflammatory diseases largely represent disorders of the phylogenetically more primitive innate immune system, mediated by myeloid effector cells and germline-encoded receptors. The autoinflammatory diseases can cause an intense acute phase response with elevation of the erythrocyte sedimentation rate, C-reactive protein, and serum amyloid A, in some cases leading to amyloid A (AA) amyloidosis (see Chapter 164).

The hereditary periodic fever syndromes include 2 illnesses with an autosomal recessive mode of inheritance, familial Mediterranean fever (FMF; MIM249100) and the hyperimmunoglobulinemia D with periodic fever syndrome (HIDS; MIM260920). Hereditary periodic fever syndromes with an autosomal dominant mode of inheritance include the tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS; MIM191190) and a spectrum of disorders known as the cryopyrin-associated periodic syndromes (CAPSs), or cryopyrinopathies. From mildest to most severe, CAPS includes the familial cold autoinflammatory syndrome (FCAS1; MIM120100), Muckle-Wells syndrome (MWS; MIM191100), and neonatal-onset multisystem inflammatory disease (NOMID; MIM607115) (also known as chronic infantile neurologic cutaneous and articular syndrome, or CINCA) (Table 163-1).

There are a number of other mendelian autoinflammatory diseases that present in childhood and are not considered hereditary periodic fever syndromes. These include the syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA; MIM604416), deficiency of the interleukin 1 (IL-1) receptor antagonist (DIRA; MIM612852), Blau syndrome (also known as early-onset sarcoidosis; MIM186580), chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE; MIM256040), autoinflammation with phospholipase Cγ_2-associated antibody deficiency and immune dysregulation (APLAID; MIM614878), and deficiency of adenosine deaminase-2 (DADA2) (Table 163-2). Other disorders include congenital sideroblastic anemia with B-cell immunodeficiency, periodic fevers and developmental delay (SIFD) due to biallelic mutations of the *TRNT1* gene as well as disease produced by mutations in the phospholipase *C*γ_2 gene (cold-induced urticaria, granulomatous rash, bronchiolitis, enterocolitis, eye inflammation) or by mutations in the cat-eye syndrome chromosome region, candidate 1 (*CECR1*) causing fever, stroke, rash, and vasculitis. An interferonopathy due to upregulation of *TMEM173* that encodes STING (stimulation of

Table 163-1 Differential Diagnosis of Familial Autoinflammatory Syndromes

		Mevalonate Kinase Deficiency (MKD)			Cryopyrin-Associated Periodic Syndrome (CAPS)			
	FAMILIAL MEDITERRANEAN FEVER (FMF)	HYPERIMMUNOGLOBULIN D SYNDROME (HIDS)	MEVALONIC ACIDURIA	TUMOR NECROSIS FACTOR RECEPTOR–ASSOCIATED PERIODIC SYNDROME (TRAPS)	FAMILIAL COLD AUTOINFLAMMATORY SYNDROME (FCAS)	MUCKLE-WELLS SYNDROME (MWS)	CHRONIC INFANTILE NEUROLOGIC CUTANEOUS AND ARTICULAR SYNDROME (CINCA)	DEFICIENCY OF IL-1 RECEPTOR ANTAGONIST (DIRA)
Mode of Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive
Age at Onset (yr)	<20	<1	<1	<20	<1	<20	<1	Birth, <4 wk
Duration of attack (days)*	<2	4-6	4-5	>14	<2	1-2	?	Continuous
Cutaneous Involvement	Erysipelas-like erythema	Maculopapular rash	Morbilliform rash	Migratory rash, overlying area of myalgia	Cold-induced urticaria-like lesions	Urticaria-like rash	Urticaria-like lesions	Generalized pustulosis
Musculoskeletal Involvement	Monoarthritis common	Arthralgia, occasional oligoarthritis	Arthralgia common	Severe myalgia common; occasional frank monoarthritis	Arthralgia common; occasional mild myalgia	Lancing limb pain, arthralgia common; arthritis can occur	Epiphyseal bone formation	Sterile pustulous osteomyelitis
Abdominal Involvement	Sterile peritonitis common	Splenomegaly, severe pain common	Splenomegaly, pain may occur	Severe pain common	None	May occur	Hepatosplenomegaly	
Eye Involvement	Uncommon	Uncommon	Uncommon	Conjunctivitis and periorbital edema common	Conjunctivitis	Conjunctivitis; sometimes optic nerve elevation	Papilledema with possible loss of vision, uveitis	
Distinguishing Clinical Symptoms	Erysipelas-like erythema	Prominent cervical lymphadenopathy	Dysmorphic features, neurologic symptoms	Migratory nature of myalgia and rash, periorbital edema	Cold-induced urticaria-like lesions	Sensorineural hearing loss	Chronic aseptic meningitis, sensorineural hearing loss, arthropathy	
Gene Involved	*MEFV*	*MVK*	*MVK*	*TNFRSF1A*	*CIAS1 = NLRP3*	*CIAS1 = NLRP3*	*CIAS1 = NRLP3*	*IL-1RN*
Protein Involved	Pyrin (marenostrin)	Mevalonate kinase	Mevalonate kinase	Type 1 tumor necrosis factor receptor	Cryopyrin	Cryopyrin	Cryopyrin	IL-1RA

Note: For details on Blau syndrome, DIRA, and pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, see text.
*Duration may vary; this is a typical duration.
Modified from Hull KM, Shoham N, Chae JJ, et al: The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations, Curr Opin Rheumatol *15:61–69, 2003.*

Table 163-2 Clinical Grouping of Autoinflammatory Diseases by Fever and Skin Manifestations

1. Nonspecific maculopapular rashes with recurrent episodic fever and abdominal pain (the classic "periodic fever syndromes")
   Recurrent fever attacks of short duration (typically <7 days)
   - FMF: familial Mediterranean fever
   - HIDS: mevalonate kinase deficiency/hyperimmunoglobulinemia D with periodic fever syndrome

   Recurrent fever attacks of longer duration (typically >7 days)
   - TRAPS: TNF receptor-associated periodic fever syndrome
2. Neutrophilic urticaria (the cryopyrinopathies)
   Recurrent fever attacks of short duration (typically <24 hr)
   - CAPS/FCAS: familial cold autoinflammatory syndrome
   - CAPS/MWS: Muckle-Wells syndrome

   Continuous low-grade fever
   - CAPS/NOMID: neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular syndrome (CINCA)
3. Granulomatous skin lesions and minimal or low-grade fever attacks
   - Blau syndrome/early-onset sarcoidosis (pediatric granulomatous arthritis)
4. Pustular skin rashes and episodic fever
   With inflammatory bone disease
   - DIRA: deficiency of interleukin-1 receptor agonist
   - Majeed syndrome

   With pyogenic arthritis
   - PAPA: pyogenic arthritis, pyoderma gangrenosum, and acne syndrome

   With inflammatory bowel disease
   - Early-onset inflammatory bowel disease

   Without other organ involvement
   - DITRA: deficiency of interleukin-36-receptor antagonist
   - CAMPS: CARD14-mediated psoriasis
5. Atypical neutrophilic dermatosis with histiocytic-like infiltrate
   - PRAAS: proteasome associated autoinflammatory syndromes
6. Syndromes with autoinflammation and immunodeficiency
   - PLAID: PLCγ_2-associated antibody deficiency and immune dysregulation
   - APLAID: autoinflammation and PLCγ_2-associated antibody deficiency and immune dysregulation
   - HOIL-1 deficiency

From Almeida de Jesus A, Goldbach-Mansky R: Monogenic autoinflammatory diseases: concept and clinical manifestations. Clin Immunol *147:155-174, 2013, Table 1.*

interferon genes) produces infantile onset of neutrophilic rash, increased acute-phase reactants, fever, interstitial lung disease, paratracheal adenopathy, and facial nodules.

There are also a number of autoinflammatory disorders with a complex mode of inheritance. These include the syndrome of periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) and chronic recurrent multifocal osteomyelitis (CRMO; MIM259680) (Table 163-3). Other genetically complex disorders that are sometimes considered autoinflammatory are covered elsewhere in this volume: systemic-onset juvenile idiopathic arthritis (see Chapter 155), Behçet disease (see Chapter 161), and Crohn disease (see Chapter 336). Distinguishing one disorder from the others may be difficult; Tables 163-4 and 163-5 and Figures 163-1 and 163-2 can be helpful to this end.

FAMILIAL MEDITERRANEAN FEVER

FMF is a recessively inherited autoinflammatory disease usually characterized by recurrent 1-3 day self-limited episodes of fever, serositis, mono- or pauciarticular arthritis, or an erysipeloid rash, sometimes complicated by AA amyloidosis.

Etiology

FMF is caused by mutations in *MEFV*, a 10 exon gene located on the short arm of chromosome 16 encoding a 781 amino acid protein denoted pyrin (from the Greek for fever). Pyrin is expressed in granulocytes, monocytes, and dendritic cells, and in peritoneal, synovial, and dermal fibroblasts. The N-terminal ~90 amino acids of pyrin are the prototype for a motif (the PYRIN domain) that mediates protein-protein interactions and is found in more than 20 different human proteins that regulate inflammation and apoptosis. Through PYRIN-domain interactions, pyrin can activate caspase-1, the enzyme that converts the 31 kDa pro–IL-1β molecule into the biologically active 17 kDa IL-1β, which is a major mediator of fever and inflammation.

Many of the FMF-associated mutations in pyrin are found at the C-terminal B30.2 domain of pyrin, encoded by exon 10 of *MEFV*. More than 50 such FMF mutations are listed in an online database (http://fmf.igh.cnrs.fr/ISSAID/infevers/), nearly all of which are missense substitutions. Homozygosity for the M694V mutation may be associated with an earlier age of onset, arthritis, and an increased risk of amyloidosis. The substitution of glutamine for glutamic acid at residue 148 (E148Q), is considered to be either a mild mutation or a functional polymorphism in the pyrin protein. The combined frequencies of FMF mutations among several Mediterranean populations are extraordinarily high (up to 1 : 3), suggesting the possibility of a heterozygote advantage. It is also noteworthy that there is a small percentage of patients of typical ethnicity and the clinical findings of FMF who have no demonstrable *MEFV* mutations, suggesting the possibility of a second FMF locus.

Epidemiology

FMF occurs primarily among ethnic groups of Mediterranean ancestry, most commonly Jews, Turks, Armenians, Arabs, and Italians. Owing to a higher frequency of the M694V mutation, FMF is more severe and more readily recognized in the Sephardic (North African) than the Ashkenazi (East European) Jewish population. Nevertheless, due to demographics, most Jewish FMF patients in the US are of Ashkenazi ancestry. With the advent of genetic testing, mutation-positive FMF has been documented worldwide, although at lower frequency than in the Mediterranean basin and Middle East. Most patients present with symptoms in childhood, with 90% of patients presenting prior to the age of 20 yr.

Pathogenesis

It appears that FMF mutations lead to a gain-of-function and IL-1β–dependent inflammation, with a gene-dosage effect. These results may explain why many heterozygous carriers of FMF mutations have biochemical evidence of inflammation, why as many as 30% of symptomatic FMF patients have only 1 demonstrable *MEFV* mutation, and why IL-1 inhibitors have a therapeutic effect in FMF.

Table 163-3 Autoinflammatory Bone Disorders

	CRMO	Majeed Syndrome	DIRA	Cherubism	cmo and lupo Mice
Ethnicity	Worldwide, but mostly European	Arabic	European, Puerto Rican, Arabic	Worldwide	Occurs in various backgrounds
Fever	Uncommon	Common	Uncommon	No	Not assessed
Sites of osseous involvement	Metaphyses of long bones > vertebrae, clavicle, sternum, pelvis, others	Similar to CRMO	Anterior rib ends, metaphyses of long bones, vertebrae, others	Mandible > maxilla Rarely ribs	Vertebrae hind > forefeet
Extraosseous manifestations	PPP, psoriasis, IBD, others	Dyserythropoietic anemia, Sweet syndrome, HSM, growth failure	Generalized pustulosis, nail changes, lung disease, vasculitis	Cervical lymphadenopathy	Dermatitis, extramedullary hematopoiesis, splenomegaly
Family history of inflammatory disorders	Psoriasis, PPP, arthritis, IBD, others	Psoriasis in some obligate carriers	No known associations	No known associations	Heterozygotes normal
Inheritance	Not clear	Autosomal recessive	Autosomal recessive	Autosomal dominant; incomplete penetrance	Autosomal recessive
Gene defect	Unknown	*LPIN2*	*IL1RN*	*SH3BP2* ≫ *PTPN11*	*Pstpip2*
Protein name	?	Lipin2	IL-1Ra	SH3BP2	PSTPIP2 (a.k.a. MAYP)
Protein function	?	Fat metabolism: (PAP enzyme activity), ↑ message to oxidative stress, ? role in mitosis	Antagonist of IL-1 receptor	↑ Myeloid cell response to M-CSF and RANKL, ↑ TNF-α expression in macrophages	Macrophage proliferation, macrophage recruitment to sites of inflammation, cytoskeletal function
Cytokine abnormalities	↑ serum TNF-α	Not tested	↑ IL-1α, IL-1β, MIP-1α, TNF-α, IL-8, IL-6 ex vivo monocyte assay; skin reveals ↑ IL-17 staining	↑ serum TNF-α in mouse model	cmo: ↑serum IL-6, MIP-1α, TNF-α, CSF-1, IP-10 Lupo: ↑ serum MIP-1α, IL-4, RANTES, TGF-β

CRMO, chronic recurrent multifocal osteomyelitis; CSF, colony-stimulating factor; DIRA, deficiency of interleukin-1 receptor antagonist; HSM, hepatosplenomegaly; IBD, inflammatory bowel disease; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; IP-10, interferon-inducible protein-10; M-CSF, macrophage–colony-stimulating factor; MIP-1α, macrophage inflammatory protein-1α; PAP, phosphatidate phosphatase; PPP, palmer-plantar pustulosis; PSTPIP2, proline-serine-threonine phosphatase interacting protein; RANKL, receptor activator of nuclear factor-κB ligand; RANTES, regulated upon activation, normal T-cell expressed and secreted; SH3BP2, SH3 binding protein 2; TGF, transforming growth factor; TNF-α, tumor necrosis factor α.

From Ferguson PJ, Laxer RM: Autoinflammatory bone disorders. In Cassidy JT, Petty RE, Laxer RM, et al, editors: Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2010, Saunders, Table 44-2.*

Clinical Manifestations

Clinical features of FMF may include fever, serositis presenting as pleuritic chest pain or severe abdominal pain, arthritis, and rash. The pleural pain is typically unilateral, whereas the abdominal pain can be generalized or localized to 1 quadrant, similar to other forms of peritonitis. FMF-associated arthritis occurs primarily in the large joints, may be accompanied by large, neutrophil-rich effusions, and is usually nonerosive and nondestructive. The hallmark cutaneous finding is an erysipeloid erythematous rash that overlies the ankle or dorsum of the foot (Fig. 163-3). Other clinical findings include scrotal pain caused by inflammation of the tunica vaginalis testis, febrile myalgia, exercise-induced myalgia (particularly common in children), and an association with various forms of vasculitis, including Henoch-Schönlein purpura in as many as 5% of pediatric patients. FMF episodes may be triggered by stress, menses, or infections. Between flares, patients are generally symptom-free but may have persistent elevation of their inflammatory markers. The attack frequency can vary from weekly to 1-2 flares/year.

Diagnosis

The diagnosis of FMF can often be made clinically, paying special attention to the duration and recurrence of episodes, documentation of fever, the characteristic serositis, synovitis, or erysipeloid rash, responsiveness to daily colchicine prophylaxis, and the absence of other causative factors. The differential diagnosis includes other hereditary periodic fever syndromes, and, depending on the specific circumstances, may include PFAPA, systemic-onset juvenile idiopathic arthritis (Still disease), cyclic hematopoiesis, gynecologic disorders (when abdominal pain predominates), porphyria, hereditary angioedema, septic arthritis, and the crystalline arthritides.

Genetic testing can be used as adjunctive evidence in ambiguous cases, and in circumstances in which the clinician has little experience with FMF or related conditions. Although FMF is often regarded as a recessively inherited disorder, with the attendant expectation that patients will have 2 mutations in *trans,* it should be noted that in some series as many as 30–50% of patients with typical FMF, responsive to colchicine, have only a single demonstrable mutation, and a small percentage have no identifiable *MEFV* mutation. The interpretation of genetic testing may be further complicated by the presence of complex alleles in which 2 mutations may be found in *cis* (usually an exon 10 mutation with E148Q in exon 2).

Treatment

Prophylactic daily oral colchicine decreases the frequency, duration, and intensity of FMF flares. This regimen also prevents the development of systemic AA amyloidosis. Colchicine is generally well-tolerated and safe in children, with the most common side effects being diarrhea and other gastrointestinal complaints. Some patients develop lactose intolerance while taking colchicine. Gastrointestinal side effects can be minimized by initiating therapy at a low dose (for young children, 0.3 mg/day) and slowly titrating upward. A dose-related transaminitis may also be observed; bone marrow suppression is rarely seen at the dosages prescribed for FMF. Pediatric patients may require doses of colchicine similar to those needed in adults (1-2 mg/day), reflecting the fact that children metabolize the drug more rapidly than adults. It is not always possible to find a tolerated dose of colchicine at which all

Table 163-4 Clues That May Assist in the Diagnosis of Autoinflammatory Syndromes

AGE OF ONSET	
At birth	NOMID, DIRA, FCAS
Infancy and 1st yr of life	HIDS, FCAS, NLRP12
Toddler	PFAPA
Late childhood	PAPA
Most common of autoinflammatory syndromes to have onset in adulthood	TRAPS, DITRA
Variable (mostly in childhood)	All others
ETHNICITY AND GEOGRAPHY	
Armenians, Turks, Italian, Sephardic Jews	FMF
Arabs	FMF, DITRA (Arab Tunisian)
Dutch, French, German, Western Europe	HIDS, MWS, NLRP12
United States	FCAS
Can occur in blacks (West Africa origin)	TRAPS
Eastern Canada, Puerto Rico	DIRA
Worldwide	All others
TRIGGERS	
Vaccines	HIDS
Cold exposure	FCAS, NLRP12
Stress, menses	FMF, TRAPS, MWS, PAPA, DITRA
Minor trauma	PAPA, MWS, TRAPS, HIDS
Exercise	FMF, TRAPS
Pregnancy	DITRA
Infections	All, especially DITRA
ATTACK DURATION	
<24 h	FCAS, FMF
1–3 d	FMF, MWS, DITRA (fever)
3–7 d	HIDS, PFAPA
>7 d	TRAPS, PAPA
Almost always "in attack"	NOMID, DIRA
INTERVAL BETWEEN ATTACKS	
3–6 wk	PFAPA, HIDS
>6 wk	TRAPS
Mostly unpredictable	All others
Truly periodic	PFAPA, cyclic neutropenia
USEFUL LABORATORY TESTS	
Acute-phase reactants must be normal between attacks	PFAPA
Urine mevalonic acid in attack	HIDS
IgD > 100 mg/dL	HIDS
Proteinuria (amyloidosis)	FMF, TRAPS, MWS, NOMID
RESPONSE TO THERAPY	
Corticosteroid dramatic	PFAPA
Corticosteroid partial	TRAPS, FCAS, MWS, NOMID, PAPA*
Colchicine	FMF, PFAPA (30% effective)
Cimetidine	PFAPA (30% effective)
Etanercept	TRAPS, FMF arthritis
Anti–IL-1 dramatic	DIRA (anakinra), FCAS, MWS, NOMID, PFAPA
Anti–IL-1 mostly	TRAPS, FMF
Anti–IL-1 partial	HIDS, PAPA

DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist (generalized pustular psoriasis); FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NLRP, nucleotide oligomerization domain–like receptor family, pyrin domain; NOMID, neonatal-onset multisystem inflammatory disorder; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; TRAPS, tumor necrosis factor receptor–associated periodic syndrome.

*For intraarticular steroids.

From Hashkes PJ, Toker O: Autoinflammatory syndromes. Pediatr Clin North Am *59:447–470, 2012, Table 2.*

Table 163-5 Differential Diagnosis of Periodic Fever

1 Hereditary (see Table 163-1)
2 Nonhereditary
 a Infectious
  i Hidden infectious focus (e.g., aortoenteric fistula, Caroli disease)
  ii Recurrent reinfection (e.g., chronic meningococcemia, host defense defect)
  iii Specific infection (e.g., Whipple disease, malaria)
 b Noninfectious inflammatory disorder, e.g.:
  i Adult-onset Still disease
  ii Juvenile chronic rheumatoid arthritis
  iii Periodic fever, aphthous stomatitis, pharyngitis, and adenitis
  iv Schnitzler syndrome
  v Behçet syndrome
  vi Crohn disease
  vii Sarcoidosis
  viii Extrinsic alveolitis
  ix Humidifier lung, polymer fume fever
 c Neoplastic
  i Lymphoma (e.g., Hodgkin disease, angioimmunoblastic lymphoma)
  ii Solid tumor (e.g., pheochromocytoma, myxoma, colon carcinoma)
 d Vascular (e.g., recurrent pulmonary embolism)
 e Hypothalamic
 f Psychogenic periodic fever
 g Factitious or fraudulent

From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors: Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Table 97-2.*

symptoms are suppressed, but approximately 90% of patients have a marked improvement in disease-related symptoms. Colchicine is generally continued during pregnancy and lactation.

A small percentage of FMF patients are either unresponsive to or intolerant of therapeutic doses of colchicine. Based on the role of pyrin in IL-1β activation, a randomized placebo-controlled trial demonstrated the safety and effectiveness of rilonacept, an IL-1 inhibitor, in FMF, and there are case reports of the effectiveness of anakinra, a recombinant IL-1 receptor antagonist.

Complications and Prognosis

Amyloidosis is the most serious complication of FMF, and in its absence FMF patients may live a normal life span. Amyloidosis may develop when serum AA, an acute-phase reactant found at extremely high levels in the blood during FMF attacks, is cleaved to produce a 76 amino acid fragment that misfolds and deposits ectopically, most commonly in the kidneys, gastrointestinal tract, spleen, lungs, testes, thyroid, and adrenals. Rarely, cardiac amyloidosis may develop; macroglossia and amyloid neuropathy are generally not seen with the amyloidosis of FMF. The most common presenting sign of AA amyloidosis is proteinuria. The diagnosis is then usually confirmed by rectal or renal biopsy. There are a small number of case reports, mostly from the Middle East, in which amyloidosis may actually precede overt FMF attacks, presumably because of subclinical inflammation.

Risk factors for the development of amyloidosis in FMF include homozygosity for the M694V *MEFV* mutation, polymorphisms of the *serum AA* gene (encoding AA), noncompliance with colchicine treatment, male gender, and a positive family history of AA amyloid. For reasons that are unclear, country of origin is also a major risk factor for amyloidosis in FMF, with patients raised in the Middle East having a much higher risk than genotypically identical patients raised in the West. Aggressive lifelong suppression of the acute phase reactants should be the goal in patients with FMF amyloidosis, and there are documented cases in which this may result in resorption of amyloid deposits. The natural history of untreated amyloidosis in FMF is the inexorable progression to renal failure, often within 3–5 yr.

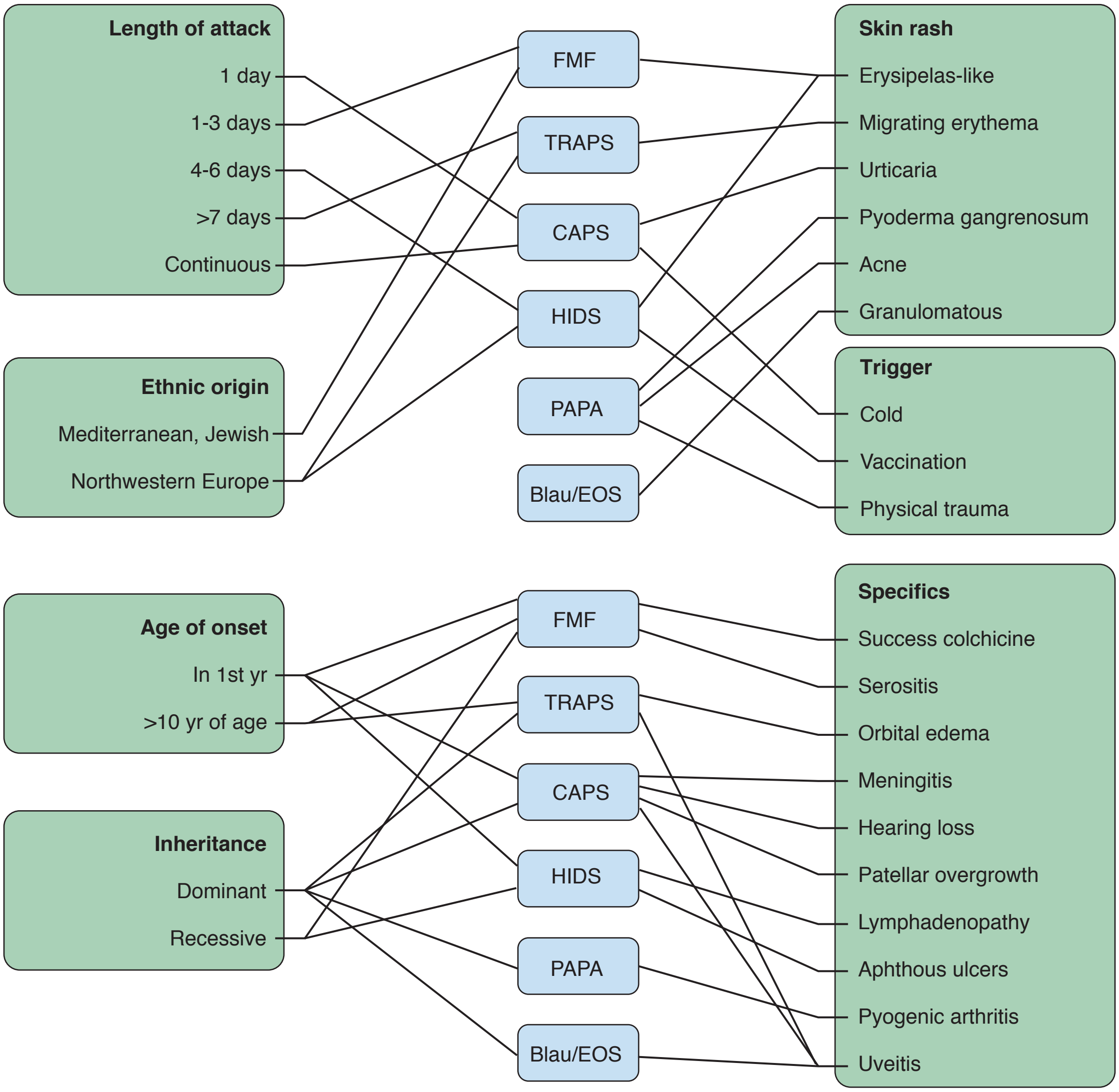

Figure 163-1 Differential diagnosis of the familial autoinflammatory syndromes. First exclude other, more common causes of fever and inflammation in the patient. When a familial autoinflammatory syndrome seems likely, check the clinical characteristics found in the patient on the *right* and *left* of the diagram, and assign 1 point to each syndrome that is linked to these characteristics by a line (1 characteristic could lead to or point to more than 1 syndrome). The final combined score assigns a rank for the likelihood of the disorders in this patient and offers help in deciding on the correct subsequent diagnostic tests. This algorithm is not evidence based but is solely derived from expert opinion. CAPS, cryopyrin-associated periodic syndrome; EOS, early-onset sarcoidosis; FMF, familial Mediterranean fever; HIDS, hyper-IgD syndrome; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, and acne; TRAPS, tumor necrosis factor receptor–associated periodic syndrome. *(From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-2.)*

HYPERIMMUNOGLOBULINEMIA D WITH PERIODIC FEVER SYNDROME

HIDS, also known as **mevalonate kinase deficiency**, was initially described in a cohort of Dutch patients and occurs primarily in patients of Northern European descent. HIDS is recessively inherited and caused by mutations of *MVK*, a gene located on the long arm of chromosome 12 that encodes mevalonate kinase (MK). HIDS-associated mutations are distributed throughout the MK protein, but the 2 most common mutations are the substitution of isoleucine for valine at residue 377 (V377I), a variant that is quite common in the Dutch population, and the substitution of threonine for isoleucine at residue 268 (I268T).

MK is expressed in multiple tissues, and catalyzes the conversion of mevalonic acid to 5-phosphomevalonic acid in the biosynthesis of cholesterol and nonsterol isoprenoids. Patients with HIDS-associated mutations have markedly reduced, but not absent, MK enzymatic activity. HIDS patients usually have low-normal serum cholesterol levels, but the deficiency of isoprenoids may cause increased IL-1β production by aberrant activation of the small guanosine triphosphatase Rac1. Temperature elevation may further exacerbate this process by more complete inhibition of MK activity, leading to a possible positive feedback loop. Complete genetic deficiency of MK results in a more severe phenotype known as mevalonic aciduria (see Chapter 85).

The clinical features of HIDS generally appear within the 1st 6 mo of life. Febrile attacks last between 3 and 7 days with abdominal pain that is often accompanied by diarrhea, nausea, and vomiting. Other clinical manifestations include cervical lymphadenopathy, diffuse macular rash, aphthous ulcers, headaches, and occasional splenomegaly (Figs. 163-4 to 163-6). Arthritis/arthralgia can be present in an oligoarticular or polyarticular pattern. Inflammatory disease–like illness and Kawasaki disease–like presentation have also been reported. Attacks are often precipitated by intercurrent illness, immunizations, and surgery. Families frequently recount flares around the time of birthdays, holidays, and family vacations. Patients with mevalonic

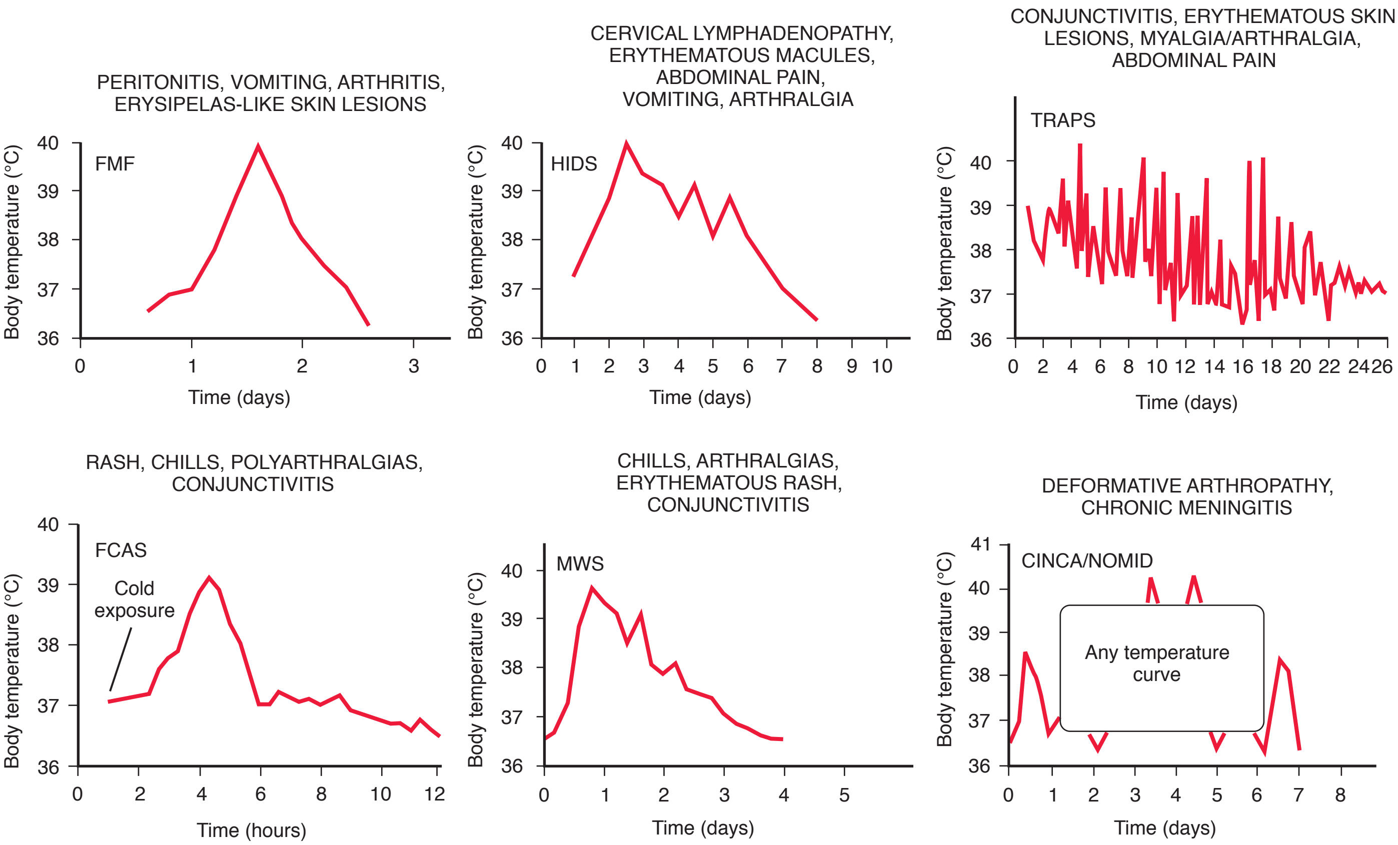

Figure 163-2 **Characteristic patterns of body temperature during inflammatory attacks in the familial autoinflammatory syndromes.** Interindividual variability for each syndrome is considerable, and even for the individual patient, the fever pattern may vary greatly from episode to episode. Note the different time scales on the x-axes. CINCA/NOMID, chronic infantile neurologic cutaneous and articular syndrome/neonatal-onset multisystemic inflammatory disease; FCAS, familial cold autoinflammatory syndrome; HIDS, hyper-IgD syndrome; MWS, Muckle-Wells syndrome; TRAPS, tumor necrosis factor receptor–associated periodic syndrome. *(From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-1.)*

Figure 163-3 **Characteristic erysipeloid erythema associated with familial Mediterranean fever.** This rash appears during a flare and overlies the ankle or dorsum of the foot.

Figure 163-4 **Polymorphic rash on the hands, arms, and legs of a patient with hyperimmunoglobulinemia D syndrome (HIDS).** *(From Takada K, Aksentijevich I, Mahadevan V, et al. Favorable preliminary experience with etanercept in two patients with the hyperimmunoglobulinemia D and periodic fever syndrome.* Arthritis Rheum *48:2646, 2003.)*

aciduria present with severe mental retardation, ataxia, myopathy, cataracts, and failure to thrive (see Chapter 85).

The diagnosis of HIDS may be confirmed either by the presence of 2 mutations in *MVK* (approximately 10% of patients with seemingly typical disease have only a single identifiable mutation) and/or elevated levels of mevalonate in the urine during acute attacks. The eponymous elevation in serum IgD levels is not universally present, especially in young children, and is thought to be an epiphenomenon. Conversely, serum IgD levels may be increased in other autoinflammatory diseases as well as some chronic infections. During attacks, leukocytosis and increased serum levels of acute-phase reactants and proinflammatory cytokines are commonly present.

The symptoms of HIDS may persist for years but tend to become less prominent in adulthood. Patients with HIDS usually have a normal life span. Unlike FMF and TRAPS, the incidence of AA amyloidosis is quite low. Standards for the treatment of HIDS are evolving. Very few

Figure 163-5 Petechiae on the leg of a hyper-IgD syndrome patient during a febrile attack. *(From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-7.)*

Figure 163-6 Aphthous ulceration detected on the tongue of a patient with hyper-IgD syndrome. *(Courtesy Dr. K. Antila, North Carelian Central Hospital, Joensuu, Finland; from Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-8.)*

patients respond to colchicine; milder disease may respond to nonsteroidal antiinflammatory drugs. Corticosteroids are of limited utility. Small trials of both etanercept and either intermittent or daily anakinra in HIDS are promising.

THE TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED PERIODIC SYNDROME

Like FMF and HIDS, TRAPS is characterized by recurrent fevers and localized inflammation, but it is inherited in an autosomal dominant fashion and has a number of distinguishing clinical and immunologic features. TRAPS was first recognized in patients of Irish descent and denoted *familial Hibernian fever* to draw a contrast with FMF, but the current nomenclature was proposed when mutations in *TNFRSF1A* were discovered not only in the original Irish family, but in families from a number of other ethnic backgrounds. *TNFRSF1A* is located on the short arm of chromosome 12, and encodes the 55 kDa receptor (denoted p55, TNFR1, or CD120a) for TNF that is widely expressed on a number of cell types. A second 75 kDa receptor largely restricted to leukocytes is encoded on chromosome 1.

TRAPS was originally defined as an autoinflammatory disorder resulting from *TNFRSF1A* mutations, and thus genetic testing is required to make the diagnosis. To date, more than 90 disease-associated *TNFRSF1A* mutations are listed on the online *Infevers* database, as well as a smaller number of variants of unknown significance. Nearly all of the TRAPS-associated mutations in are in the extracellular domain of the TNFR1 protein, with about one-third involving the substitution of another amino acid for a highly conserved cysteine residue, thus disrupting disulfide bonds and leading to protein misfolding. A number of other missense mutations not involving cysteine residues have been shown to have a similar effect on TNFR1 protein folding. Misfolded TNFR1 aggregates intracellularly and leads to constitutive signaling through mitogen-activated protein kinases, resulting in the release of proinflammatory cytokines such as IL-1β and TNF-α. The substitution of glutamine for arginine at residue 92 (R92Q) and the substitution of leucine for proline at residue 46 (P46L) are seen in greater than 1% of the white and African-American populations, respectively. These variants do not lead to the same biochemical or signaling abnormalities seen with more-severe TRAPS mutations, and, like E148Q in FMF, there is debate as to whether they are mild mutations or functional polymorphisms.

Patients with TRAPS typically present within the 1st decade of life. Flares can occur with variable frequency but the duration is often substantially longer when compared to FMF or HIDS flares. The febrile episodes of TRAPS last at least 3 days and can persist for weeks at a time. As in FMF, there may be pleural and/or peritoneal involvement. At times patients present with signs of an acute abdomen; on exploration such patients have sterile peritonitis, sometimes with adhesions from previous episodes. Patients may also have nausea and frequently report constipation at the onset of flares that progresses to diarrhea by the conclusion. Ocular signs include periorbital edema and conjunctivitis. TRAPS patients may also experience severe myalgia and on imaging the muscle groups may have focal areas of edema. There are a number of rashes that can be seen in TRAPS patients, but the most common is an erythematous macular rash that on biopsy contains superficial and deep perivascular infiltrates of mononuclear cells. Patients often report that the rash migrates distally on a limb during its course with an underlying myalgia and can resemble cellulitis. Other rashes include erythematous annular patches as well as a serpiginous rash (Fig. 163-7). Approximately 10-15% of patients with TRAPS may develop AA amyloidosis; the presence of cysteine mutations and a positive family history are risk factors for this complication. If amyloidosis does not develop, TRAPS patients have a normal life expectancy.

Colchicine is generally not effective in TRAPS. For relatively mild disease, nonsteroidal anti-inflammatory agents may suffice. For more severe disease with infrequent attacks, corticosteroids at the time of an attack may be effective, but it is not unusual for steroid requirements to increase over time. Because some patients with TRAPS exhibit a defect in activation-induced TNF receptor shedding, and have diminished levels of immune modulatory soluble TNFR in the blood, etanercept, the soluble p75 TNFR : Fc fusion protein has been studied in this disorder. Etanercept is often effective in reducing the severity and frequency of flares, but longitudinal follow-up of TRAPS patients treated with etanercept indicates waning efficacy with time. Of note, treatment of TRAPS with anti-TNF monoclonal antibodies has sometimes led to a paradoxical worsening of disease. Experience with both anakinra, a recombinant IL-1 receptor antagonist, and canakinumab, a monoclonal anti–IL-1β antibody, has been favorable in TRAPS patients.

Figure 163-7 **Cutaneous manifestations of tumor necrosis factor receptor-associated periodic syndrome. A,** Right flank of a patient with the T50M mutation. **B,** Serpiginous rash involving the face, neck, torso, and upper extremities of a child with the C30S mutation. **C,** Erythematous, macular patches with crusting on the flexor surface of the right arm of a patient with the T50M mutation. *(From Hull KM, Drewe, Aksentijevich I, et al: The TNF receptor-associated periodic syndrome [TRAPS]: emerging concepts of an autoinflammatory syndrome,* Medicine (Baltimore) *81:349–368, 2002.)*

CRYOPYRIN-ASSOCIATED PERIODIC FEVER SYNDROMES

CAPS represents a spectrum of clinical disorders, including FCAS, MWS, and NOMID/CINCA. Although 3 separate clinical diagnoses have been defined, it should be emphasized that the cryopyrinopathies are really a continuum, and that patients may present with overlap syndromes that do not fit neatly into a single diagnosis. This spectrum of illness is caused by mutations in *NLRP3* (formerly known as *CIAS1*), located on the long arm of chromosome 1, which encodes a protein variously denoted cryopyrin or NLRP3. More than 100 disease-associated *NLRP3* mutations have been enumerated on the *Infevers* online database. Advances in next-generation sequencing have also permitted the identification of symptomatic individuals with somatic *NLRP3* mosaicism.

NLRP3 is a PYRIN domain-containing protein that is strongly expressed in myeloid cells, and to a lesser degree in other tissues. It is a part of a macromolecular complex termed the NLRP3 inflammasome that activates pro–IL-1β to its mature form in response to a variety of endogenous danger-associated molecular patterns and pathogen-associated molecular patterns. Patients with cryopyrinopathies have gain-of-function mutations in *NLRP3* that result in constitutive or easily-triggered activation of the NLRP3 inflammasome.

The cryopyrinopathies are characterized by recurrent fevers and an urticaria-like rash that develops early in infancy (Fig. 163-8). Histopathologic examination reveals a perivascular neutrophilic infiltrate without the mast cells or mast cell degranulation seen with true urticaria. In patients with FCAS, febrile attacks generally begin 1-3 hr after generalized cold exposure. FCAS patients also experience polyarthralgia of the hands, knees, and ankles, and conjunctivitis may also develop during attacks. FCAS episodes are self-limited and generally resolve within 24 hr. AA amyloidosis rarely occurs in FCAS.

In contrast to FCAS, the febrile episodes of MWS are not cold-induced, but are characterized by the same urticarial rash seen in FCAS (Fig. 163-9). Many MWS patients also develop progressive sensorineural hearing loss, and, untreated, approximately 30% of MWS patients develop AA amyloidosis. NOMID patients present in the neonatal

Figure 163-8 **Urticarial rash.** Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

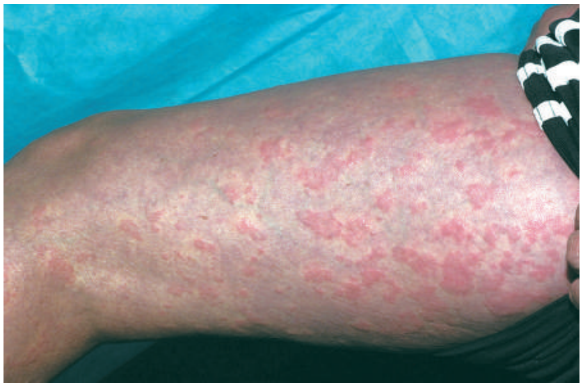

Figure 163-9 **Urticarial skin rash in a patient with Muckle-Wells syndrome.** *(Courtesy Dr. D. L. Kastner, National Institutes of Health, Bethesda, Maryland; from Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-14.)*

Figure 163-10 **A 3 yr old girl with neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular (CINCA) disease.** Note the markedly deformed hands, rash, frontal bossing, and large head. *(From Padeh S: Periodic fever syndromes,* Pediatr Clin North Am *52:577–560, 2005.)*

period with a diffuse, urticarial rash, daily fevers, and dysmorphic features. Significant joint deformities, particularly of the knees, may develop because of bony overgrowth of the epiphyses of the long bones (Figs. 163-10 and 163-11). NOMID patients also develop chronic aseptic meningitis, leading to increased intracranial pressure, optic disc edema, visual impairment, progressive sensorineural hearing loss, and intellectual disability (Fig. 163-12). Because of the severe disabilities associated with untreated NOMID, this disorder appeared to be sporadic before *NLRP3* mutations were identified in these patients.

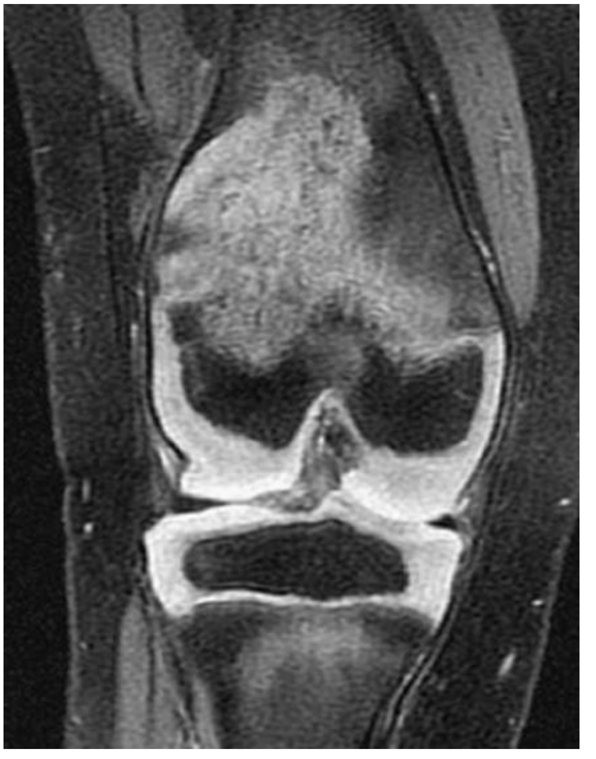

Figure 163-11 **Metaphyseal bone overgrowth.** Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

Targeted therapy with anakinra, a recombinant IL-1 receptor antagonist, has been life-changing for NOMID patients, not only controlling fever and rash, but also preventing end-organ damage. Anakinra was FDA-approved for NOMID. Rilonacept, a soluble IL-1 receptor decoy, and canakinumab, a long-acting, fully humanized IgG_1 anti–IL-1β monoclonal antibody, are effective in both FCAS and MWS, and are FDA-approved for both conditions. Aggressive IL-1 blockade has resulted in attenuation of amyloidosis in the cryopyrinopathies.

OTHER MENDELIAN AUTOINFLAMMATORY DISEASES

The Syndrome of Pyogenic Arthritis with Pyoderma Gangrenosum and Acne

PAPA syndrome is a rare autosomal dominant disorder caused by mutations in *PSTPIP1,* a gene located on chromosome 15 that encodes the cytoskeletal proline serine threonine phosphatase-interacting (PSTPIP) protein. The PSTPIP1 protein interacts with a number of immunologically important molecules, including CD2, the Wiskott-Aldrich syndrome protein (WASP), and pyrin. PAPA-associated PSTPIP1 mutations markedly increase its affinity to pyrin and cause increased IL-1β production.

Clinical manifestations of PAPA syndrome include recurrent episodes of sterile, pyogenic arthritis that leads to erosions and joint destruction, and appears to develop spontaneously or after minor trauma. The onset of arthritis is often in early childhood. Cutaneous manifestations tend to develop in adolescence, at which time patients are prone to developing severe cystic acne. Additionally, PAPA patients commonly develop ulcerating pyoderma gangrenosum lesions (Fig. 163-13), and some develop pathergy reactions.

The treatment of PAPA syndrome may involve the use of corticosteroids, IL-1 antagonists, and TNF inhibitors, sometimes in combination. The joint manifestations of PAPA appear to respond to IL-1

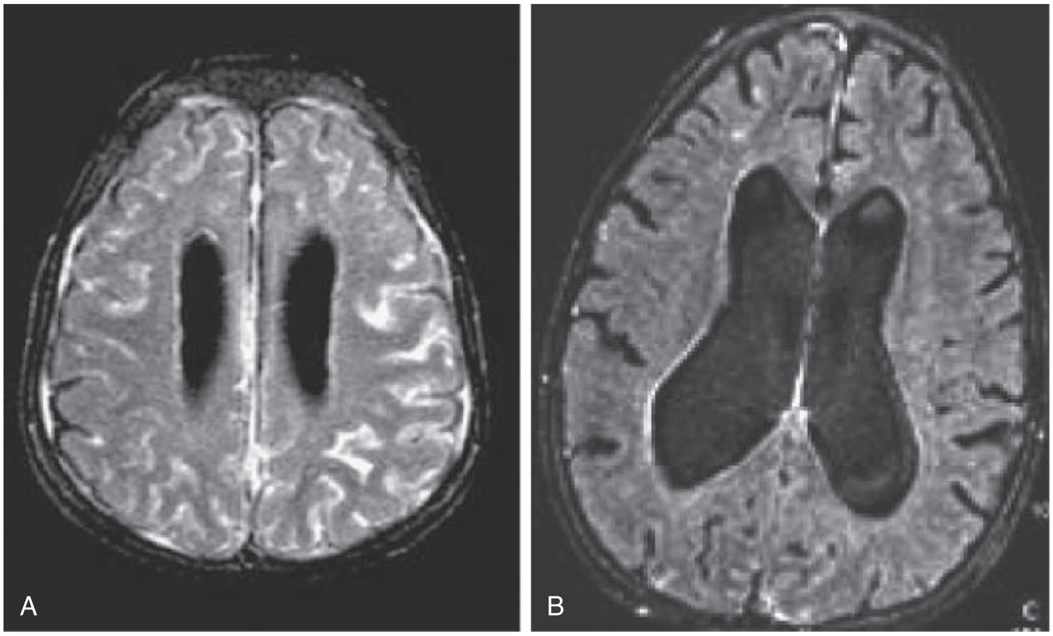

Figure 163-12 **A,** Leptomeningeal enhancement; **B,** hydrocephalus and cerebral atrophy. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

Figure 163-13 Pyoderma gangrenosum lesions in a patient with PAPA syndrome and the A230T mutation in *PSTPIP1.* Note the diffuse scarring indicative of prior lesions on his upper back.

blockade, whereas the cutaneous manifestations seem to respond more favorably to TNF blockade. Local measures, such as joint aspiration and drainage and intensive wound care, are also important in the care of PAPA patients, as is pain management for cutaneous disease. Caution should be taken when prescribing sulfonamides because some PAPA patients develop pancytopenia.

Deficiency of the Interleukin-1 Receptor Antagonist

DIRA is an autosomal recessive autoinflammatory disease that is distinct from the cryopyrinopathies. DIRA is characterized by systemic inflammation and a neutrophilic pustulosis, sterile multifocal osteomyelitis, widening of the anterior ends of the ribs, periostitis, osteopenia, and usually a neonatal onset (Figs. 163-14 and 163-15). Although fever is not a prominent clinical feature, patients do have markedly elevated acute-phase reactants. DIRA is caused by loss-of-function mutations in *IL1RN*, encoding the IL-1 receptor antagonist. The treatment of choice is anakinra, a recombinant form of the protein these patients lack.

Figure 163-14 **Pustular rash.** Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

Blau Syndrome

Blau syndrome is a rare autosomal dominant disorder that manifests as early-onset granulomatous arthritis, uveitis, and rash. The arthritis may affect the ankles and wrists, and may lead to flexion contractures of the fingers and toes (camptodactyly). **Early-onset sarcoidosis** presents with a similar clinical picture, sometimes with visceral involvement, and both conditions are caused by mutations in *CARD15/*

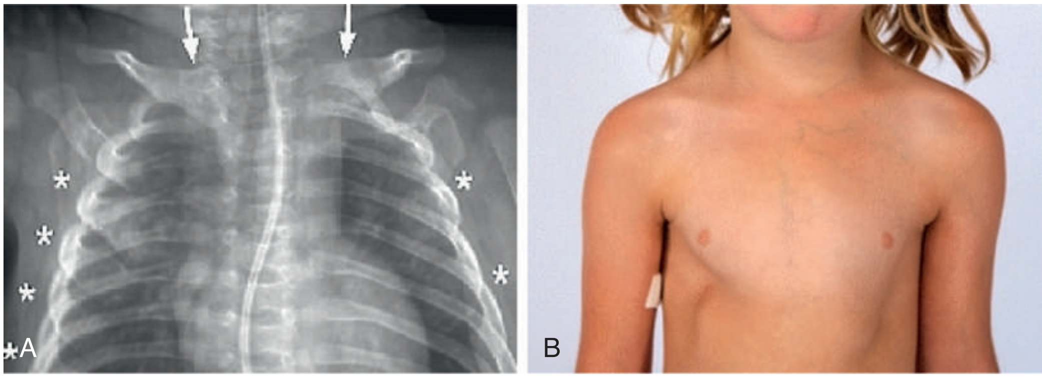

Figure 163-15 **A,** Widening of multiple ribs (*) and clavicles *(arrows)* in DIRA osteomyelitis; **B,** chest deformity. Inflammatory clinical manifestations and organ damage in the IL-1-mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

NOD2 on chromosome 16. The protein encoded by this gene, variously denoted caspase recruitment domain protein 15 or nucleotide-binding oligomerization domain 2 protein, is an intracellular sensor of bacterial products in dendritic cells, myelomonocytic cells, and Paneth cells. Mutations in the NACHT oligomerization domain of this protein cause Blau syndrome/early-onset sarcoidosis, while variants primarily in the leucine-rich repeat domain of this protein are associated with susceptibility to Crohn disease. Corticosteroids have been the mainstay of therapy for Blau syndrome. There are a number of case reports of the beneficial effects of TNF inhibitors, in Blau syndrome.

Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature

CANDLE is an autosomal recessive disease resulting from mutations in *PSMB8.* This gene encodes the β5i subunit of the immunoproteasome, a macromolecular complex that degrades proteins in immune cells for presentation on major histocompatibility complex class I molecules. Disease-associated mutations result in a loss of function. Patients present in the 1st yr of life with recurrent fevers, violaceous swollen eyelids, purpuric skin lesions with a mixed mononuclear and neutrophilic infiltrate, arthralgia, delayed physical development, and anemia. Acute-phase reactants are also elevated in these patients and, over time, they develop progressive lipodystrophy. On gene expression profiling, CANDLE patients have a robust interferon signature. There is no established treatment for CANDLE, although the interferon pathway may represent a therapeutic target. Two other disorders, **Nakajo-Nishimura syndrome** and the **syndrome of joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy**, are clinically similar to CANDLE and are also caused by mutations in *PSMB8.*

Autoinflammation with Phospholipase $C\gamma_2$-Associated Antibody Deficiency and Immune Dysregulation

APLAID is a dominantly-inherited disorder characterized by recurrent blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, enterocolitis, absence of autoantibodies, and mild immunodeficiency. It is caused by gain-of-function mutations in *PLCG2,* leading to increased signaling through the phospholipase $C\gamma_2$ pathway in immune cells. To date there is no established therapy for APLAID.

Deficiency of Adenosine Deaminase 2

DADA2 is an autoinflammatory disorder caused by loss-of-function mutations in *CECR1*, encoding adenosine deaminase 2, characterized by recurrent fevers and a spectrum of vascular manifestations that includes livedo racemosa, early-onset ischemic lacunar strokes, and polyarteritis nodosa. Patients may also present with hepatosplenomegaly and a mild immunodeficiency. ADA2 is a protein produced primarily by monocytes and macrophages, which appear to act as a growth factor both for endothelial cells and for the antiinflammatory M2 subset of macrophages. Patients experience a vicious circle of vasculopathy and inflammation. Although there is no established therapy, there is anecdotal evidence supporting the use of etanercept.

GENETICALLY COMPLEX AUTOINFLAMMATORY DISEASES

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis

PFAPA is the most common recurrent fever syndrome in children. It usually presents between the ages of 2 and 5 yr with recurring episodes of fever, malaise, exudative-appearing tonsillitis with negative throat cultures, cervical lymphadenopathy, oral aphthae, and, less commonly, headache, abdominal pain, and arthralgia. The episodes last 4-6 days, regardless of antipyretic or antibiotic treatment, and often occur with clock-like regularity on 3-6 wk cycles. Findings during the episodes may include mild hepatosplenomegaly, mild leukocytosis, and elevated acute-phase reactants. Both the frequency and the intensity of the episodes diminish with increasing age.

The etiology and pathogenesis of PFAPA remain unknown. The majority of patients show dramatic response to a single oral dose of prednisone (0.6-2.0 mg/kg), although this approach does not prevent recurrence and may actually shorten the interval between flares. Cimetidine given at doses of 20-40 mg/kg/day is effective at preventing recurrences in approximately one-third of cases. Complete resolution has also been reported after tonsillectomy in some but not all patients. A pilot study of anakinra (1 mg/kg subcutaneously) given for 1-2 days at the onset of symptoms showed promising results.

Chronic Recurrent Multifocal Osteomyelitis

CRMO is a form of inflammatory bone disease most commonly seen in children (see Table 163-3). Histologically and radiologically, CRMO is virtually indistinguishable from infectious osteomyelitis. Patients typically present with bone pain and may also have fever, soft-tissue swelling, and elevated acute-phase reactants. Cultures are sterile. The etiology of sporadic CRMO is unknown. Rarely CRMO can occur with congenital dyserythropoietic anemia (Majeed syndrome), caused by mutations in *LPIN2.* CRMO has also been seen in association with inflammatory bowel disease and inflammatory skin disease such as palmoplantar pustulosis. There is evidence for reduced production of the antiinflammatory cytokine IL-10 in CRMO. Initial therapy includes nonsteroidal antiinflammatory medications. Second-line treatments include corticosteroids, TNF inhibitors, and bisphosphonates.

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Chapter 164

Amyloidosis

Karyl S. Barron and Amanda Ombrello

Amyloidosis comprises a group of diseases characterized by extracellular deposition of insoluble, fibrous amyloid proteins in various body tissues.

ETIOLOGY

Amyloidosis is a disease caused by protein misfolding. These misfolded proteins infiltrate, aggregate, and form insoluble fibrils that can affect the normal function of a number of vital organs.

In the amyloidosis nomenclature, there is a distinction made between amyloidosis that develops from mutations in the *amyloid fibril protein itself* versus amyloidosis associated with genetic mutation in nonamyloid proteins. The former are referred to as hereditary amyloidoses; examples include mutations in the genes for transthyretin and apolipoprotein A, both of which are uncommon in children. This is in contrast to amyloid A (AA) amyloidosis, which develops in patients with chronic inflammatory states. It is estimated that, worldwide, approximately 45% of all amyloid cases are AA amyloidosis. In the past, chronic infectious diseases such as tuberculosis, malaria, leprosy, and chronic osteomyelitis accounted for most cases of AA amyloidosis. With effective treatment for these infections, other causes of AA have become more common. A number of chronic inflammatory rheumatic diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis, as well as hereditary autoinflammatory diseases, have an increased risk for the development of AA amyloidosis. AA amyloidosis has also been associated with granulomatous diseases such as sarcoidosis, cystic fibrosis, Crohn disease, malignancies such as mesothelioma and Hodgkin diseases, intravenous drug abuse, and other infections, such as bronchiectasis and HIV. Approximately 6% of AA amyloidosis cases have no identified disease association. AL amyloidosis (formally known as idiopathic amyloidosis or myeloma-associated amyloidosis) is extremely rare in children, occurring in middle-aged or older individuals.

EPIDEMIOLOGY

Only AA amyloidosis affects children in appreciable numbers. The factors that determine the risk for amyloidosis as a complication of inflammation are not clear, because many individuals with long-standing inflammatory disease do not demonstrate tissue amyloid deposition, while some children with relatively recent onset of disease may develop amyloid. In developed countries, prior to the initiation of therapy with disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents, RA was the most common inflammatory disease associated with AA amyloidosis. Patients who had a long history of poorly controlled severe disease with extraarticular manifestations were the most at risk for developing amyloidosis and the median time from first symptoms of their rheumatic condition to the diagnosis of amyloidosis was 212 mo. The full effect of DMARD and biologic therapy in RA-associated amyloidosis has yet to be fully appreciated, but studies are showing a sustained decline in the number of new cases.

JIA is another rheumatic disease that is associated with the development of AA amyloidosis with the highest prevalence in patients with systemic JIA followed by those with polyarticular disease (see Chapter 155). In the pre-DMARD and biologic era, the prevalence of AA amyloidosis in JIA patients ranged from 1-10%. Higher prevalence was seen in Northern European patients, especially Polish patients who had a prevalence of 10.6%; lower prevalence was observed in North America. The reasons for this discrepancy are not completely understood although it is speculated that selection bias, genetic background, and tendency toward more early aggressive therapy in North Americans may have played a role.

The **hereditary autoinflammatory diseases** define a group of illnesses that are characterized by attacks of seemingly unprovoked recurrent inflammation without significant levels of either autoantibodies or antigen-specific T cells, which are typically found in patients with autoimmune diseases (see Chapter 163). Whereas autoimmune diseases such as systemic lupus erythematosus and RA result from a derangement in the adaptive immune system, the autoinflammatory syndromes are a result of malfunctions in the innate immune system. The inflammatory attacks are mediated by cells of the innate immune system (neutrophils and macrophages). Although seemingly unprovoked, these attacks are often initiated by stress, immunization, or trauma, suggesting that gene–environment interactions play an important role in pathogenesis. Although there is some variability among the autoinflammatory diseases, common findings include fevers, cutaneous rashes, arthritis, serositis, and ocular involvement. The inflammatory attacks are accompanied by intense acute phase responses (erythrocyte sedimentation rate and C-reactive protein) and high levels of serum amyloid A (SAA). Amyloidosis AA is associated with some but not all the hereditary autoinflammatory diseases.

Familial Mediterranean fever (FMF) is the most common of the mendelian autoinflammatory diseases and is seen most frequently in the Armenian, Arab, Turkish, and Sephardi Jewish populations. FMF is an autosomal recessive disease that results from mutations in the *MEFV* gene, which encodes the pyrin/marenostrin protein. *MEFV* mutations affecting the M680 and M694 amino acid residues are associated with early onset of FMF, severe disease, and an increased risk of AA amyloidosis. Patients residing in Armenia, Turkey, and Arabian countries have an increased risk of developing AA amyloidosis compared to patients with the same mutations of *MEFV* living in North America.

Tumor necrosis factor receptor associated periodic syndrome (TRAPS) is associated with mutations in the *TNFRSF1A* gene, which encode the 55 kDa tumor necrosis factor (TNF) receptor protein (TNFR1). It is estimated that 14-25% of patients with TRAPS develop AA amyloidosis. Patients with mutations in *TNFRSF1A* that affect cysteine residues have the highest risk of developing AA amyloidosis. It is thought that these cysteine residues participate in assembly of disulfide bonds important for TNFR1 folding and disruption of these bonds affects protein folding.

Mutations in the *NLRP3* gene (also known as *CIAS1*, **cold-induced autoinflammatory syndrome 1)** cause 3 clinically distinct diseases: familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease (NOMID) that is also known as chronic infantile neurologic cutaneous and articular (CINCA) syndrome. Mutations in *NLRP3* are inherited in an autosomal dominant fashion or as *de novo* mutations in patients with the most severe disease. Familial cold autoinflammatory syndrome is generally the least severe of the cryopyrinopathies and is rarely associated with AA amyloidosis. MWS presents with fevers, myalgias, arthralgias, urticarial-like rash, and progressive sensorineural hearing loss. AA amyloidosis is quite common in MWS, affecting up to one-third of the patients. NOMID/CINCA is the most severe cryopyrinopathy. Historically 20% of patients died before reaching adulthood but with current therapies, many are living longer lives. There have been NOMID patients who develop AA amyloidosis as they get older, although cases are not as frequent as those with MWS, possibly due to a shortened life span in these patients.

Hyper IgD syndrome (HIDS) is another autoinflammatory disease that presents in early childhood with chills, high fevers, abdominal pain, lymphadenopathy, and occasional rash. HIDS is an autosomal recessive disease that involves loss of function mutations in the *MVK* gene that encodes the mevalonate kinase enzyme. Inflammatory markers, including SAA, are high during attacks and may remain elevated in the intercurrent period. AA amyloidosis is rare in HIDS but has been reported.

Although seen less frequently than in the hereditary periodic fever syndromes, the risk of AA amyloidosis has been well established in patients with Crohn disease. It is estimated that AA amyloidosis occurs in approximately 1% of patients in the United States and up to 3% in Northern European patients. Conversely, AA amyloidosis presenting

in patients with ulcerative colitis is extremely rare, with estimated prevalence of 0.07%. The patients have a long-standing history of aggressive, poorly controlled disease; however there are reports of amyloidosis in patients with well-controlled inflammatory markers.

PATHOGENESIS

The deposition of AA amyloid fibrils is a result of a prolonged inflammatory state that leads to misfolding of the AA amyloid protein and deposition into tissues. The precursor protein of the fibrils in AA amyloidosis is an apolipoprotein called SAA. SAA is produced in the liver in response to proinflammatory cytokines such as interleukin (IL)-1, IL-6, and TNF-α and can increase more than 1,000-fold during inflammation. It has been speculated that SAA has a role as a chemoattractant and in lipid metabolism. Supporting this theory is the finding that amyloid deposition occurs initially in organs that are major sites of lipid and cholesterol metabolism such as the kidney, liver, and spleen.

Under normal circumstances SAA is secreted by the liver and completely degraded by macrophages. The secreted SAA protein is 104 amino acids in length and is primarily secreted in an α-helix structure. For reasons not completely understood, patients with AA amyloidosis have a flaw resulting in incomplete degradation and accumulation of intermediate SAA products. In these patients, SAA is transferred to the lysosome where the c-terminal portion of the SAA protein is cleaved, allowing the remaining protein to fold into a β-pleated sheet configuration. Deposited amyloid contains only 66-76 amino acids compared to the 104 in secreted SAA. These cleaved fragments polymerize and form fibrils that are deposited in the extracellular space and bind proteoglycans and other proteins such as serum amyloid P. These fibrils then become resistant to proteolysis and deposit in organ tissues.

CLINICAL MANIFESTATIONS

Although organ involvement may vary, AA amyloidosis most commonly affects the kidneys; 90% of patients have some degree of renal involvement. Unexplained proteinuria may be the presenting feature in some patients. Nephrotic syndrome and renal failure may develop if the underlying inflammatory condition is not controlled or if diagnosis is delayed. Median survival after diagnosis has been reported to be 133 mo; patients with higher SAA levels had significantly higher risk of death than those with lower SAA levels. Gastrointestinal involvement is seen in approximately 20% of patients and usually manifests as chronic diarrhea, gastrointestinal bleeding, abdominal pain, and malabsorption, whereas testes are frequently involved (87%). Relatively uncommon findings associated with AA amyloidosis include anemia, amyloid goiter, hepatomegaly, splenomegaly, adrenal involvement, and pulmonary involvement. Tissues, such as the heart, tongue, and skin, are rarely involved.

DIAGNOSIS

The diagnosis of amyloidosis is established by biopsy demonstrating amyloid fibril proteins in affected tissues. The tissues most commonly tested include kidney, rectum, abdominal fat pad, and gingiva. Amyloid deposits are composed of seemingly homogeneous eosinophilic material that stains with Congo red dye and demonstrates the pathognomonic "apple-green birefringence" in polarized light. Amyloid can also be recognized with routine hematoxylin and eosin staining and electron microscopy.

LABORATORY FINDINGS

Patients with AA amyloidosis usually show elevated acute-phase reactants and high levels of immunoglobulins. Specific laboratory testing is possible only for AL amyloidosis, and most patients with this form of amyloidosis show increased plasma cells in the bone marrow and serum or urine monoclonal immunoglobulin (Ig) or free light chain. A biopsy showing amyloid deposition along with a monoclonal serum protein distinguishes AL amyloidosis from monoclonal gammopathy of uncertain significance, which is common in older adults.

TREATMENT

There is no established therapy to AA amyloidosis and, thus, the primary means of treatment of AA amyloidosis is aggressive management of the underlying inflammatory or infectious disease, which decreases levels of SAA protein. As newer therapies have been developed to treat the underlying condition, there is emerging evidence that the incidence of AA amyloidosis is decreasing. Colchicine is effective not only in controlling the attacks of FMF but also in preventing the development of amyloidosis associated with FMF. Children with FMF who are homozygous for the M694V mutation in the *MEFV* gene are at greater risk for development of amyloidosis and should be monitored closely.

Unlike AA amyloidosis associated with FMF, AA amyloidosis associated with other autoinflammatory diseases (including TRAPS, cryopyrin-associated periodic syndrome, and HIDS) and chronic rheumatic diseases (JIA, RA, and ankylosing spondylitis) do not respond to colchicine. Although AA amyloidosis associated with JIA may respond to chlorambucil, this drug is associated with chromosome breakage and a risk of subsequent malignancy.

Increasing use of biologic medicines against proinflammatory cytokines to treat RA, JIA, spondyloarthropathies, and the hereditary autoinflammatory diseases seems to impact risk factors for the development of AA amyloidosis. The class of medications referred to as the anti–TNF-α drugs have been paramount in the management of RA and other autoimmune disease. In both autoimmune and autoinflammatory conditions with accompanying AA amyloidosis, there are reports documenting the effectiveness of anti-TNF agents in blunting the progression of amyloidosis. Adverse effects of anti-TNF medications include reactivation of tuberculosis and hepatitis B, thus careful screening should be performed before instituting therapy. Additionally, the development of various antibodies, autoantibodies, and autoimmune disease has been noted in patients taking anti-TNF agents. Extreme caution should be used in prescribing anti-TNF agents to patients with a history of heart failure or demyelinating disease, as use can cause exacerbations in their underlying cardiac and neurologic diseases.

The IL-1 pathway is the target of multiple biologic medications used in autoimmune and autoinflammatory diseases. The 3 available IL-1 antagonists are anakinra (IL-1 receptor antagonist), rilonacept (soluble IL-1 receptor decoy), and canakinumab (long-acting fully humanized IgG_1 anti–IL-1β monoclonal antibody). The various IL-1 inhibitors have been successful at slowing the progression of AA amyloidosis, and in some cases treatment results in regression of amyloid associated proteinuria.

Tocilizumab, an anti–IL-6 receptor antibody, has been shown to attenuate experimental AA amyloid and to reverse AA amyloidosis complicating JIA and RA. Eprodisate disodium is currently in international trial in patients with AA amyloidosis–associated nephropathy. By binding the amyloidogenic precursor proteins, eprodisate disodium attempts to prevent the deposition of amyloid in organ, hence preserving renal function.

COMPLICATIONS AND PROGNOSIS

End-stage renal failure is the underlying cause of death in 40-60% of patients with amyloidosis, with a median survival time from diagnosis of 2-10 yr. According to a large-scale study of 374 patients with AA amyloidosis, the factors associated with a poor prognosis include older age, a lower albumin serum level, end-stage renal disease at baseline, and prolonged serum elevation of SAA. An elevated SAA value was the most powerful risk factor for end-stage renal disease and death from AA amyloidosis.

PREVENTION

The primary means of preventing AA amyloidosis is treatment of the underlying inflammatory or infectious disease, resulting in decreases in the level of SAA protein and the risk of amyloid deposition. Although the period of latency between the onset of inflammation (of the underlying disease) and the initial clinical signs of AA amyloidosis may vary and is often prolonged, progression of the amyloid depositions can be rapid.

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Chapter 165

Sarcoidosis

Eveline Y. Wu and Esi Morgan-DeWitt

Sarcoidosis is a rare multisystem granulomatous disease of unknown etiology. The name is derived from a Greek word meaning "flesh-like condition," in reference to the characteristic skin lesions. There appear to be 2 age-dependent distinct patterns of disease among children with sarcoidosis. The clinical features in older children are similar to those in adults (pediatric onset adult sarcoidosis), with frequent systemic features (fever, weight loss, malaise), pulmonary involvement and lymphadenopathy. In contrast, early-onset sarcoidosis manifesting in children <4 yr of age is characterized by the triad of rash, uveitis, and polyarthritis.

ETIOLOGY

The etiology of sarcoidosis remains obscure but likely results from exposure of a genetically susceptible individual to 1 or more unidentified antigens. This exposure initiates an exaggerated immunologic response that ultimately leads to the formation of granulomas. The human major histocompatibility complex is located on chromosome 6, and specific human leukocyte antigen class I and class II alleles are associated with disease phenotype. Genetic polymorphisms involving various cytokines and chemokines may also have a role in development of sarcoidosis. Familial clustering supports the contribution of genetic factors to sarcoidosis susceptibility. Environmental and occupational exposures are also associated with disease risk. There are positive associations between sarcoidosis and agricultural employment, occupational exposure to insecticides, and moldy environments typically associated with microbial bioaerosols.

Blau syndrome is an autosomal dominant, familial form of sarcoidosis and is typified by the early onset of granulomatous inflammation involving the skin, eyes, and joints. Missense mutations in the *CARD15/NOD2* gene on chromosome 16 have been found in affected family members and appear to be associated with development of sarcoidosis. The 2 most common amino acid substitutions are R334W (arginine to glutamine) and R334Q (arginine to tryptophan). Similar genetic mutations also have been found in individuals with a sporadic **early-onset sarcoidosis (EOS)** (rash, uveitis, arthritis), suggesting that this nonfamilial form and Blau syndrome are genetically and phenotypically identical (see Chapter 163).

EPIDEMIOLOGY

A nationwide patient registry of childhood sarcoidosis in Denmark estimated the annual incidence to be 0.22-0.27 per 100,000 children. The incidence increases with age, and peak onset occurs at 20-39 yr. The most common age of reported childhood cases is 13-15 yr. Annual incidence is about 11 per 100,000 in adult white Americans and is 3 times higher in African-Americans. There is no clear sex predominance in childhood sarcoidosis. Within the United States, the majority of childhood sarcoidosis cases are reported in the Southeastern and South Central states.

An international registry and Spanish cohort of Blau syndrome and EOS reported the mean age of disease onset as 30 mo and 36 mo, respectively. All but 3 of these young patients presented before 5 yr of age. There does not appear to be a sex preference in either condition.

PATHOLOGY AND PATHOGENESIS

Noncaseating, epithelioid granulomatous lesions are a cardinal feature of sarcoidosis. Activated macrophages, epithelioid cells, and multinucleated giant cells as well as CD4+ T lymphocytes accumulate and become tightly packed in the center of the granuloma. The causative agent that initiates this inflammatory process is not known. The periphery of the granuloma contains a loose collection of monocytes, CD4+ and CD8+ T lymphocytes, and fibroblasts. The interaction between the macrophages and CD4+ T lymphocytes is important in the formation and maintenance of the granuloma. The activated macrophages secrete high levels of tumor necrosis factor-α (TNF-α) and other proinflammatory mediators. The CD4+ T lymphocytes differentiate into type 1 helper T cells and release interleukin (IL)-2 and interferon-γ, promoting proliferation of lymphocytes. Granulomas may heal or resolve with complete preservation of the parenchyma. In approximately 20% of the lesions, the fibroblasts in the periphery proliferate and produce fibrotic scar tissue, leading to significant and irreversible organ dysfunction.

The sarcoid macrophage is able to produce and secrete 1,25-$(OH)_2$-vitamin D or calcitriol, an active form of vitamin D typically produced in the kidneys. The hormone's natural functions are to increase intestinal absorption of calcium and bone resorption and to decrease renal excretion of calcium and phosphate. An excess of calcitriol may result in hypercalcemia and hypercalciuria in patients with sarcoidosis.

CLINICAL MANIFESTATIONS

Sarcoidosis is a multisystem disease, and granulomatous lesions may occur in any organ of the body. The clinical manifestations depend on the extent and degree of granulomatous inflammation and are extremely variable. Children may present with nonspecific symptoms, such as fever, weight loss, and general malaise. In adults and older children, pulmonary involvement is most frequent, with infiltration of the thoracic lymph nodes and lung parenchyma. Isolated bilateral hilar adenopathy (Fig. 165-1) on chest radiograph is the most common finding, but parenchymal infiltrates and miliary nodules may also be seen (Fig. 165-2). Patients with lung involvement are commonly found to have restrictive changes on pulmonary function testing. Symptoms of pulmonary disease are seldom severe and generally consist of a dry, persistent cough.

Extrathoracic lymphadenopathy and infiltration of the liver, spleen, and bone marrow also occur often. Infiltration of the liver and spleen typically leads to isolated hepatomegaly and splenomegaly, respectively, but actual organ dysfunction is rare. Cutaneous disease, such as plaques, nodules, erythema nodosum in acute disease, or lupus pernio in chronic sarcoidosis, appears in one quarter of cases and is usually present at onset. Red-brown to purple maculopapular lesions < 1 cm

Figure 165-1 Chest radiograph demonstrating a stage I disease with enlarged mediastinal and hilar lymph nodes. *(From Iannuzzi M: Sarcoidosis. In Goldman L, Schafer AI, editors,* Goldman's Cecil medicine, *ed 24, Philadelphia, 2012, Saunders, Fig. 95-1, p. 582.)*

Figure 165-2 Chest radiograph of a 10 yr old girl with sarcoidosis showing widely disseminated peribronchial infiltrates, multiple small nodular densities, hyperaeration of the lungs, and hilar lymphadenopathy.

Figure 165-3 Sarcoidosis nodules on the face. *(From Shah BR, Laude TA:* Atlas of pediatric clinical diagnosis, *Philadelphia, 2000, Saunders.)*

on the face, neck, upper back, and extremities are the most common skin finding (Fig. 165-3). Ocular involvement is frequent and has variable manifestations, including anterior or posterior uveitis, conjunctival granulomas, eyelid inflammation, and orbital or lacrimal gland infiltration. The arthritis in sarcoidosis can be confused with juvenile idiopathic arthritis. Central nervous system (CNS) involvement is rare in early childhood but may manifest as seizures, cranial nerve involvement, intracranial mass lesions, and hypothalamic dysfunction. Kidney disease also occurs infrequently in children but typically manifests as renal insufficiency, proteinuria, transient pyuria, or microscopic hematuria as a result of either early monocellular infiltration or granuloma formation in kidney tissue. Only a small fraction of children have hypercalcemia or hypercalciuria, which is therefore an infrequent cause of kidney disease. Sarcoid granulomas can also infiltrate the heart and lead to cardiac arrhythmias and, rarely, sudden death. Other rare sites of disease involvement include blood vessels of any size, the gastrointestinal tract, parotid gland, muscles, bones, and testes.

In contrast to the variable clinical presentation of sarcoidosis in older children, Blau syndrome and EOS (NOD2-associated sarcoidosis) classically manifest as the triad of uveitis, arthritis, and rash. Pulmonary disease and lymphadenopathy are less common. The arthritis is polyarticular and symmetric, with large boggy effusions. Large and small joints are involved; tenosynovitis is an associated finding. Joints are stiff and moderately tender. The rash may wax and wane and is diffuse (mostly truncal), erythematous or tan, macular–papular, and often desquamates at times being confused with eczema or ichthyosis vulgaris. Tender subcutaneous nodules resembling erythema nodosum may be seen on the legs. Noncaseating granulomas are demonstrated with biopsy of the skin or joint synovium.

Granulomatous iridocyclitis and posterior uveitis may progress to panuveitis, which has a high risk for vision loss. Iris nodules, photophobia, erythema, cataracts, or glaucoma may be present or develop over time.

Patients with NOD2 mutations in particular display this more restricted phenotype but may also have visceral disease, whereas those without a NOD2 mutation often show extended manifestations, including fever, hepatosplenomegaly, lymphadenopathy, and lung, kidney, and CNS involvement.

Infantile onset panniculitis with uveitis and systemic granulomatosis is an uncommon manifestation of sarcoidosis. Sarcoidosis has also been reported in adults treated with type 1 interferons for hepatitis or multiple sclerosis.

LABORATORY FINDINGS

There is no single standard laboratory test diagnostic of sarcoidosis. Anemia, leukopenia, and eosinophilia may be seen. Other nonspecific findings include hypergammaglobulinemia and elevations in acute-phase reactants, including erythrocyte sedimentation rate and C-reactive protein value. Hypercalcemia and/or hypercalciuria occur in only a small proportion of children with sarcoidosis. Angiotensin-converting enzyme (ACE) is produced by the epithelioid cells of the granuloma, and its serum value may be elevated, but this finding lacks diagnostic sensitivity and specificity. ACE levels are estimated to be elevated in more than 50% of children with sarcoidosis. In addition, ACE values may be difficult to interpret because reference values for serum ACE are age dependent. Fluorodeoxyglucose F18 positron emission tomography can help identify nonpulmonary sites for a diagnostic biopsy.

DIAGNOSIS

Definitive diagnosis ultimately requires demonstration of the characteristic noncaseating granulomatous lesions in a biopsy specimen (usually taken from the most readily available affected organ) and exclusion of other known causes of granulomatous inflammation. Skin and transbronchial lung biopsies have higher yield, greater specificity, and fewer associated adverse events than biopsy of mediastinal lymph nodes or liver. Additional diagnostic testing should include chest radiography, pulmonary function testing with measurement of diffusion capacity, hepatic enzyme measurements, and renal function assessment. Ophthalmologic slit-lamp examination is essential, as ocular findings are frequent in sarcoidosis and vision loss is a sequela of untreated disease.

Bronchoalveolar lavage may be used to assess for disease activity, and the fluid typically reveals an excess of lymphocytes with an increased CD4+:CD8+ ratio of 2-13:1. In addition to flexible bronchoscopy with transbronchial biopsy, endosonographic guided intrathoracic node aspiration has been valuable in obtaining tissue to assess for noncaseating granulomas.

DIFFERENTIAL DIAGNOSIS

Because of its protean manifestations, the differential diagnosis of sarcoidosis is extremely broad and depends largely on the initial clinical manifestations. **Granulomatous infections**, including tuberculosis, cryptococcosis, pulmonary mycoses (histoplasmosis, blastomycosis, coccidioidomycosis), brucellosis, tularemia, and toxoplasmosis, must be excluded. Other causes of granulomatous inflammation are

granulomatosis with polyangiitis (formerly Wegener granulomatosis), hypersensitivity pneumonia, chronic berylliosis, and other occupational exposures to metals. Immunodeficiencies that may manifest with granulomatous lesions include common variable immunodeficiency, selective immunoglobulin A deficiency, chronic granulomatous disease, ataxia telangiectasia, and severe combined immunodeficiency. Granulomas of the lung, skin or lymph nodes have been reported in patients treated with anti-TNF agents. Lymphoma should be ruled out in cases of hilar or other lymphadenopathy. Sarcoid arthritis may mimic juvenile idiopathic arthritis. Evaluation for endocrine disorders is needed in the setting of hypercalcemia or hypercalciuria.

TREATMENT

Treatment should be based on disease severity as well as the number and type of organs involved. Corticosteroids are the mainstay of treatment for most acute and chronic disease manifestations. The optimal dose and duration of corticosteroid therapy in children have not been established. Induction treatment typically begins with oral prednisone or prednisolone (1-2 mg/kg/day up to 40 mg daily) for 8-12 wk until manifestations improve. Corticosteroid dosage is then gradually decreased over 6-12 mo to the minimal effective maintenance dose (e.g., 5-10 mg/day) that controls symptoms, or discontinued if symptoms resolve. Methotrexate or leflunomide may be effective as a corticosteroid-sparing agent. On the basis of the role of TNF-α in the formation of granulomas, there is rationale for use of TNF-α antagonists. Results of small clinical trials showed modest effects with infliximab and adalimumab treatment of selected disease manifestations (CNS, lupus pernio, pulmonary, ocular), whereas etanercept does not appear to be particularly effective. Other therapeutics used for sarcoidosis manifestations include topical corticosteroids (eye), inhaled corticosteroids (lung), azathioprine (CNS), cyclophosphamide (cardiac, CNS), hydroxychloroquine (skin), mycophenolate mofetil (CNS, skin), thalidomide or its analogs (skin), and nonsteroidal antiinflammatory drugs (joints).

With regard to treatment of EOS, there are also few case reports on the successful use of thalidomide and infliximab. Findings of elevated IL-1 levels and response to human IL-1 receptor antagonist (anakinra) in EOS, however, have been inconsistent.

PROGNOSIS

The prognosis of childhood sarcoidosis is not well defined. The disease may be self-limited with complete recovery or may persist with a progressive or relapsing course. Outcome is worse in the setting of multiorgan or CNS involvement. Most children requiring treatment experience considerable improvement with corticosteroids, though a significant number have morbid sequelae, mainly involving the lungs and eyes. Children with EOS have a poorer prognosis and generally experience a more chronic, progressive disease course. The greatest morbidity is associated with ocular involvement, including cataract formation, development of synechiae, and loss of visual acuity or blindness; long-term systemic treatment may be required for the eye disease. Progressive polyarthritis may result in joint destruction. The overall mortality rate in childhood sarcoidosis is low.

Serial pulmonary function tests and chest radiographs are useful in following the course of lung involvement. Monitoring for other organ involvement should also include electrocardiogram with consideration of an echocardiogram, urinalysis, renal function tests, and measurements of hepatic enzymes and serum calcium. Other potential indicators of disease activity include inflammatory markers and serum ACE, although changes in ACE level do not always correlate with other indicators of disease status. Given the frequency of asymptomatic eye disease and the ocular morbidity associated with pediatric sarcoidosis, all patients should have an ophthalmologic examination at presentation with monitoring at regular intervals, perhaps every 3-6 mo as recommended in children with juvenile idiopathic arthritis.

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Chapter 166

Kawasaki Disease

Mary Beth F. Son and Jane W. Newburger

Kawasaki disease (KD), formerly known as **mucocutaneous lymph node syndrome** and **infantile polyarteritis nodosa,** is an acute febrile illness of childhood seen worldwide with the highest incidence occurring in Asian children. KD is a vasculitis with a predilection for the coronary arteries. Approximately 20-25% of untreated children develop coronary artery abnormalities (CAA) including aneurysms, whereas <5% of children treated with intravenous gammaglobulin (IVIG) develop CAA. Nonetheless, KD is the leading cause of acquired heart disease in children in most developed countries, including the United States and Japan.

ETIOLOGY

The cause of KD remains unknown, but certain epidemiologic and clinical features support an infectious origin. These features include the young age group affected, epidemics with wave-like geographic spread of illness, the self-limited nature of the acute febrile illness, and the clinical features of fever, rash, enanthem, conjunctival injection, and cervical lymphadenopathy. Further evidence of an infectious trigger includes the infrequent occurrence of the illness in infants younger than 3 mo, likely the result of maternal antibodies, and the rarity of cases in adults, likely the result of prior exposures with subsequent immunity. However, there are features that are not consistent with an infectious origin. For example, it is unusual to have multiple cases present at the same time within a family or daycare center. Furthermore, no single infectious etiologic agent has been successfully identified, despite a comprehensive search.

A genetic role in the pathogenesis of KD seems likely, as evidenced by the higher risk of KD in Asian children regardless of country of residence, and in siblings and children of individuals with a history of KD. Furthermore, linkage studies and genome-wide association studies have identified significant associations between polymorphisms in the *ITPKC* gene, a T-cell regulator, with increased susceptibility to KD and to more-severe disease. Polymorphisms in a high-affinity receptor for immunoglobulin G (*FCGR2A)* have also been identified as significant variants in KD patients.

EPIDEMIOLOGY

For the majority of patients, KD is a disease of early childhood and nearly all epidemiologic studies show a higher susceptibility to KD in boys. Utilizing the Kids Inpatient Database to study trends in KD hospitalizations in 2006, Holman et al reported that more than 75% of all KD-associated hospitalizations in patients <18 yr were recorded in children <5 yr, with a mean age of 3 yr. Children of Asian and Pacific Islander descent had the highest hospitalization rate of 30.3/100,000 children, compared with 17.5/100,000 black, non-Hispanic children, 15.7/100,000 Hispanic children, and 12/100,000 white, non-Hispanic children. The hospitalization rate for KD in 2006 was 20.8/100,000 in children <5 yr of age, which was consistent with the prior 10 yr of hospitalization rates in the United States. In other countries, such as the United Kingdom, Korea, and Japan, the rate of KD seems to be increasing.

In Japan, nationwide surveys have been administered every 2 yr to monitor trends in KD incidence. In 2010, the highest recorded rate thus far of 239.6 per 100,000 children ages 0-4 yr was described, with the highest rate in very young children ages 6-11 mo. Infants <6 mo and children >5 yr were at the highest risk for CAA in the latest Japanese survey.

Several risk stratification models have been constructed to determine which patients with KD are at highest risk for CAA. Predictors of poor outcome across several studies include young age, male gender,

persistent fever, poor response to IVIG, and laboratory abnormalities including neutrophilia, thrombocytopenia, transaminitis, hyponatremia, hypoalbuminemia, elevated levels of N-terminal-probrain natriuretic protein and elevated C-reactive protein levels. Asian and Pacific Islander race and Hispanic ethnicity are also risk factors for CAA. Three specific risk scores have been constructed by Japanese researchers; of these, the Kobayashi score is the most widely used and has high sensitivity and specificity. Unfortunately, application of these risk scores in non-Japanese populations does not appear to accurately identify all children at risk for IVIG resistance and CAA.

PATHOLOGY

KD is a vasculitis that predominantly affects the medium-size arteries. The coronary arteries are the most commonly involved, although other arteries, such as the popliteal and brachial arteries, can also develop dilation. A 3-phase process to the arteriopathy of KD has been described. The 1st phase is a neutrophilic necrotizing arteritis occurring in the 1st 2 wk of illness that begins in the endothelium and moves through the coronary wall. Saccular aneurysms may form from this arteritis. The second phase is a subacute/chronic vasculitis driven by lymphocytes, plasma cells, and eosinophils, which may last weeks to years and results in fusiform aneurysms. The vessels affected by the subacute/chronic vasculitis then develop smooth muscle cell myofibroblasts, which cause progressive stenosis. Thrombi may form in the lumen and obstruct blood flow.

CLINICAL MANIFESTATIONS

Fever is characteristically high (≥38.3°C [101°F]), unremitting, and unresponsive to antibiotics. The duration of fever without treatment is generally 1-2 wk, but may persist for 3-4 wk. In addition to fever, the **5 principal clinical criteria** of KD are: bilateral **nonexudative** conjunctival injection with limbal sparing; erythema of the oral and pharyngeal mucosa with strawberry tongue and red, cracked lips; edema and erythema of the hands and feet; rash of various forms (maculopapular, erythema multiforme, or scarlatiniform); and nonsuppurative cervical lymphadenopathy, usually unilateral, with node size >1.5 cm (Table 166-1; Figs. 166-1 to 166-4). Perineal desquamation is common in the acute phase. Periungual desquamation of the fingers and toes begins 2-3 wk after the onset of illness and may progress to involve the entire hand and foot (Fig. 166-5).

Symptoms other than the clinical criteria are common in the 10 days prior to diagnosis of KD, which may be explained in part by the finding that up to a third of patients with KD have confirmed, concurrent infections. Gastrointestinal symptoms (vomiting, diarrhea, or abdominal pain) occur in more than 60% of patients, and at least 1 respiratory symptom (rhinorrhea or cough) occurs in 35%. Other clinical findings include significant irritability that is especially prominent in infants and likely a consequence of aseptic meningitis, mild hepatitis, hydrops of the gallbladder, urethritis and meatitis with sterile pyuria, and arthritis. Arthritis may occur early in the illness or may develop in the 2nd or 3rd wk. Small or large joints may be affected, and the arthralgias

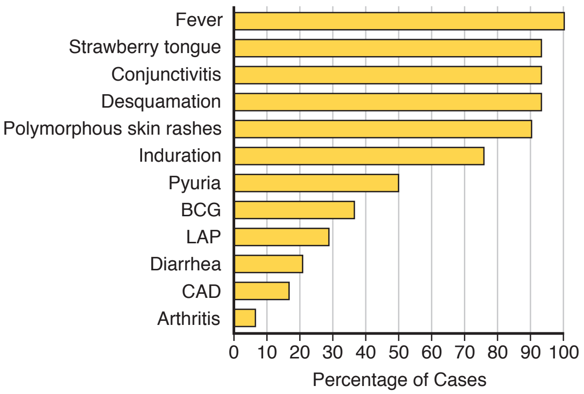

Figure 166-1 Clinical symptoms and signs of Kawasaki disease. A summary of the clinical features from 110 cases of Kawasaki disease seen in Kaohsiung, Taiwan. LAP, lymphadenopathy in head and neck area; BCG, reactivation of bacille Calmette-Guérin inoculation site; CAD, coronary artery dilation, defined by an internal diameter >3 mm. *(From Wang CL, Wu YT, Liu CA, et al: Kawasaki disease: infection, immunity and genetics,* Pediatr Infect Dis J *24:998–1004, 2005.)*

Table 166-1 Clinical and Laboratory Features of Kawasaki Disease
EPIDEMIOLOGIC CASE DEFINITION (CLASSIC CLINICAL CRITERIA)*
Fever persisting at least 5 days[†]
Presence of at least 4 principal features:
Changes in extremities:
Acute: Erythema of palms, soles; edema of hands, feet
Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
Polymorphous exanthem
Bilateral bulbar conjunctival injection without exudate
Changes in lips and oral cavity: erythema, lip cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
Exclusion of other diseases with similar findings[‡]
OTHER CLINICAL AND LABORATORY FINDINGS
Cardiovascular findings:
Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
Coronary artery abnormalities
Aneurysms of medium-size noncoronary arteries
Raynaud phenomenon
Peripheral gangrene
Musculoskeletal system:
Arthritis, arthralgias
Gastrointestinal tract:
Diarrhea, vomiting, abdominal pain
Hepatic dysfunction
Hydrops of gallbladder
Central nervous system:
Extreme irritability
Aseptic meningitis
Sensorineural hearing loss
Genitourinary system:
Urethritis/meatitis
Other findings:
Erythema, induration at bacille Calmette-Guérin inoculation site
Anterior uveitis (mild)
Desquamating rash in groin
LABORATORY FINDINGS IN ACUTE KAWASAKI DISEASE
Leukocytosis with neutrophilia and immature forms
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Anemia
Abnormal plasma lipids
Hypoalbuminemia
Hyponatremia
Thrombocytosis after week 1[§]
Sterile pyuria
Elevated serum transaminases
Elevated serum gamma glutamyl transpeptidase
Pleocytosis of cerebrospinal fluid
Leukocytosis in synovial fluid

*Patients with fever at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by 2-dimensional echocardiography or angiography.

[†]In the presence of ≥4 principal criteria, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many patients with Kawasaki disease may establish diagnosis before day 4.

[‡]See differential diagnosis (Table 166-2).

[§]Some infants present with thrombocytopenia and disseminated intravascular coagulation.

From Newburger JW, Takahashi M, Gerber MA, et al: Diagnosis, treatment, and long-term management of Kawasaki disease, Pediatrics *114:1708–1733, 2004.*

Figure 166-2 Strawberry tongue in mucocutaneous lymph node syndrome (Kawasaki disease). *(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S:* Clinical pediatric dermatology, *ed 2, Philadelphia, 1993, Saunders.)*

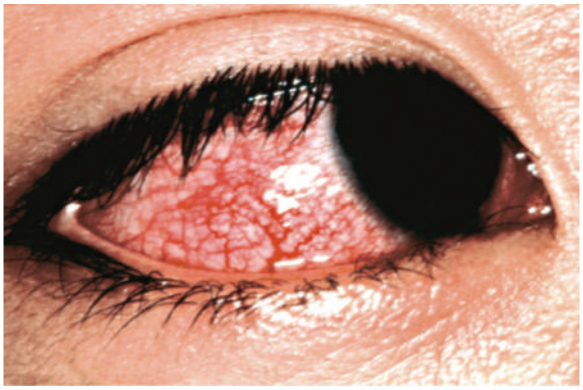

Figure 166-3 Congestion of bulbar conjunctiva in a patient with mucocutaneous lymph node syndrome (Kawasaki disease). *(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S:* Clinical pediatric dermatology, *ed 2, Philadelphia, 1993, Saunders.)*

Figure 166-4 Indurative edema of the hands in mucocutaneous lymph node syndrome (Kawasaki disease). *(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S:* Clinical pediatric dermatology, *ed 2, Philadelphia, 1993, Saunders.)*

Figure 166-5 Desquamation of the fingers in a patient with mucocutaneous lymph node syndrome (Kawasaki disease). *(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S:* Clinical pediatric dermatology, *ed 2, Philadelphia, 1993, Saunders.)*

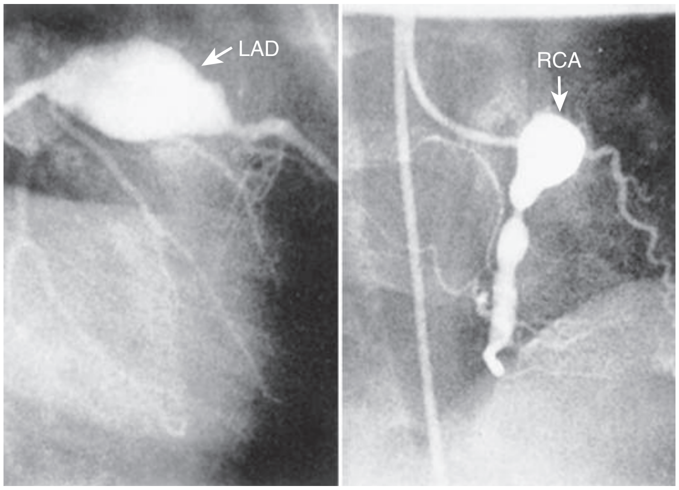

Figure 166-6 Coronary angiogram demonstrating giant aneurysm of the left anterior descending coronary artery (LAD) with obstruction and giant aneurysm of the right coronary artery (RCA) with an area of severe narrowing in 6 yr old boy. *(From Newburger JW, Takahashi M, Gerber MA, et al: Diagnosis, treatment, and long-term management of Kawasaki disease,* Pediatrics *114:1708–1733, 2004.)*

may persist for several weeks. Clinical features that are less consistent with KD include exudative conjunctivitis, exudative pharyngitis, generalized lymphadenopathy, discrete oral lesions, and bullous, pustular, or vesicular rashes.

Cardiac involvement is the most important manifestation of KD. Myocarditis occurs in most patients with acute KD and manifests as tachycardia disproportionate to fever, along with diminished left ventricular systolic function. Occasionally, patients with KD present in cardiogenic shock (KD shock syndrome), with markedly diminished left ventricular function. Pericarditis with a small pericardial effusion can also occur during the acute illness. Mitral regurgitation of at least mild severity is evident on echocardiography in 10-25% of patients at presentation but diminishes over time, except among rare patients with coronary aneurysms and ischemic heart disease. CAA develop in up to 25% of untreated patients in the 2nd to 3rd wk of illness. Giant coronary artery aneurysms (classic definition of >8 mm internal diameter) pose the greatest risk for rupture, thrombosis or stenosis, and myocardial infarction (Fig. 166-6). Axillary, popliteal, iliac, or other arteries may also become dilated, which manifest as a localized pulsating mass.

Occasionally KD initially presents with only fever and lymphadenopathy (node-first KD). This presentation may be confused with

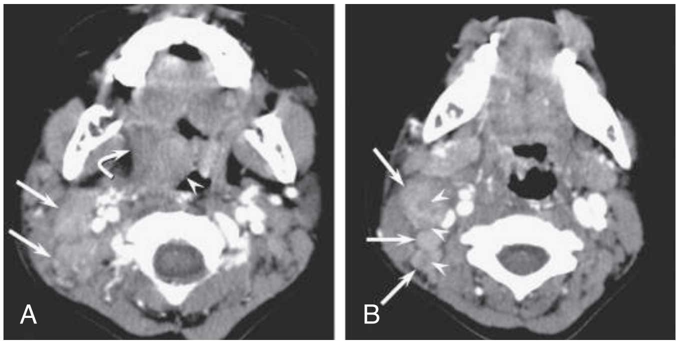

Figure 166-7 Kawasaki disease in a 3 yr old boy. **A,** Contrast-enhanced CT shows right-sided cervical lymphadenopathy *(arrows)*, peritonsillar hypodense area *(curved arrow)*, and swelling of right palatine tonsil *(arrowhead)*. **B,** Contrast-enhanced CT shows right-sided cervical lymphadenopathy with perinodal infiltration *(arrows)* and intranodal focal low attenuation *(arrowheads)*. *(From Kato H, Kanematsu M, Kato Z, et al: Computed tomographic findings of Kawasaki disease with cervical lymphadenopathy.* J Comput Assist Tomogr *36(1):138–142, 2012, Fig. 1, p. 139.)*

Table 166-2	Differential Diagnosis of Kawasaki Disease
VIRAL INFECTIONS • Adenovirus • Enterovirus • Measles • Epstein-Barr virus • Cytomegalovirus	
BACTERIAL INFECTIONS • Scarlet fever • Rocky Mountain spotted fever • Leptospirosis • Bacterial cervical lymphadenitis • Meningococcemia	
RHEUMATOLOGIC DISEASE • Systemic-onset juvenile idiopathic arthritis • Behçet disease	
OTHER • Toxic shock syndromes • Staphylococcal scalded skin syndrome • Drug hypersensitivity reactions • Stevens-Johnson syndrome	

bacterial or viral cervical lymphadenopathy/lymphadenitis and may delay the diagnosis of KD. Persistence of high fever, unresponsive to antibiotics and the eventual development of other signs of KD result in the diagnosis. Children with node-first KD tend to be older (4 vs. 2 yr) and have more days of fever and higher C-reactive protein levels. In addition to cervical adenopathy, many had retropharyngeal and peritonsillar inflammation on CT scans (Fig. 166-7).

KD can be divided into 3 clinical phases. The **acute febrile phase** is characterized by fever and the other acute signs of illness and usually lasts 1-2 wk. The **subacute phase** is associated with desquamation, thrombocytosis, the development of CAA, the highest risk of sudden death in patients in whom aneurysms have developed, and generally lasts about 3 wk. The **convalescent phase** begins when all clinical signs of illness have disappeared and continues until the erythrocyte sedimentation rate (ESR) returns to normal, typically about 6-8 wk after the onset of illness.

LABORATORY AND RADIOLOGY FINDINGS

There is no diagnostic test for KD, but patients usually have characteristic laboratory findings. The leukocyte count is often elevated, with a predominance of neutrophils and immature forms. Normocytic, normochromic anemia is common. The platelet count is generally normal in the 1st wk of illness and rapidly increases by the 2nd to 3rd wk of illness, sometimes exceeding 1,000,000/mm^3. An elevated ESR and/or C-reactive protein value is universally present in the acute phase of illness. The ESR may remain elevated for weeks, in part from the effect of IVIG. Sterile pyuria, mild elevations of the hepatic transaminases, hyperbilirubinemia, and cerebrospinal fluid pleocytosis may also be present.

Two-dimensional echocardiography is the most useful test to monitor for development of CAA and should be performed by a pediatric cardiologist. Although frank aneurysms are rarely detected early in the illness, lack of normal tapering of the vessels is typical. Moreover, coronary artery dimensions, adjusted for body surface area, may be increased in the 1st 5 wk after presentation. Body surface area–adjusted coronary artery dimensions on baseline echocardiography in the 1st 10 days of illness appear to be good predictors of involvement during early follow-up. However, children with non-KD febrile illnesses also have mildly increased z scores as compared to nonfebrile controls, but not to the same degree as patients with KD. Aneurysms have been defined with use of absolute dimensions by the Japanese Ministry of Health and are classified as small (<5 mm internal diameter), medium (5-8 mm internal diameter), or giant (>8 mm internal diameter). Some experts believe that a z-score–based system for classification of aneurysm size may be more discriminating given the range in sizes of patients with KD. Under such a system, a z score ≥10 is considered giant and hence defines the threshold at which anticoagulation should be initiated.

Echocardiography should be performed at diagnosis and again after 2-3 wk of illness. If the results are normal, a repeat study should be performed 6-8 wk after onset of illness. If results of either of the initial studies are abnormal or the patient has recurrent fever or symptoms, more frequent echocardiography or other studies may be necessary. In patients without coronary abnormalities at any time during the illness, performance of echocardiography and a lipid profile is recommended 1 year later. After this time, periodic evaluation for preventive cardiology counseling is warranted, and some experts recommend cardiologic follow-up every 5 yr. For patients with coronary abnormalities, the type of testing and the frequency of cardiology follow-up visits are tailored to the patients' coronary status.

DIAGNOSIS

The diagnosis of KD is based on the presence of characteristic clinical signs. For **classic KD,** the diagnostic criteria require the presence of fever for at least 4 days and at least 4 of 5 of the other principal characteristics of the illness (see Table 166-1). In **atypical or incomplete KD,** patients have persistent fever but fewer than 4 of the 5 characteristics. In these patients, laboratory and echocardiographic data can assist in the diagnosis (Fig. 166-8). Incomplete cases are most frequent in infants, who, unfortunately, also have the highest likelihood of development of CAA. Ambiguous cases should be referred to a center with experience in the diagnosis of KD. Establishing the diagnosis with prompt institution of treatment is essential to prevent potentially devastating coronary artery disease.

DIFFERENTIAL DIAGNOSIS

Adenovirus, measles, and scarlet fever lead the list of common childhood infections that mimic KD (Table 166-2). Children with adenovirus typically have exudative pharyngitis and exudative conjunctivitis, allowing differentiation from KD. A common clinical problem is the differentiation of scarlet fever from KD in a child who is a group A streptococcal carrier. Patients with scarlet fever typically have a rapid clinical response to appropriate antibiotic therapy. Such treatment for 24-48 hr with clinical reassessment generally clarifies the diagnosis. Furthermore, ocular findings are quite rare in group A streptococcal pharyngitis and may assist in the diagnosis of KD.

Features of measles that distinguish it from KD include exudative conjunctivitis, Koplik spots, rash that begins on the face and hairline and behind the ears, as well as leukopenia. Cervical lymphadenitis can

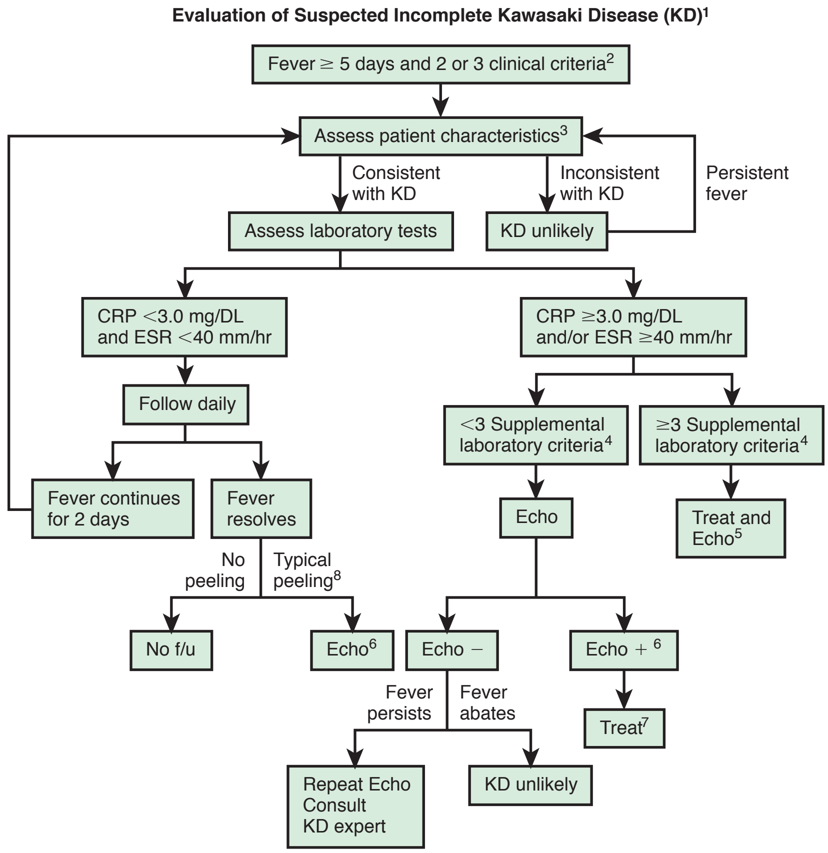

Figure 166-8 Algorithm for evaluation of suspected incomplete Kawasaki disease (KD). (1) In the absence of a gold standard for diagnosis, this algorithm cannot be evidence based, but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought anytime assistance is needed. (2) Infants ≤6 mo old on day ≥7 of fever or later without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, given an echocardiogram (Echo), even if they have no clinical criteria. (3) Patient characteristics suggesting KD are listed in Table 166-1. Characteristics suggesting disease other than KD include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, and generalized adenopathy. Consider alternative diagnoses (see Table 166-2). (4) Supplemental laboratory criteria include albumin ≤3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelet count after 7 days ≥450,000/mm^3, white blood cell count ≥15,000/mm^3, and urine white blood cell count ≥10/high-power field. (5) Can treat before performing echocardiogram. (6) Echocardiogram findings are considered positive (Echo+) for purposes of this algorithm if any of 3 conditions are met: *z* score of left anterior descending coronary artery (LAD) or right coronary artery (RCA) ≥2.5; coronary arteries meet Japanese Ministry of Health criteria for aneurysms; ≥3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased left ventricle (LV) function, mitral regurgitation, pericardial effusion, or *z* scores in LAD or RCA of 2-2.5. (7) If echocardiogram findings are positive, treatment should be given to children within 10 days of fever onset and to those beyond day 10 with clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. (8) Typical peeling begins under nail beds of fingers and then toes. Echo–, negative echocardiogram findings; f/u, follow-up. *(From Newburger JW, Takahashi M, Gerber MA, et al: Diagnosis, treatment, and long-term management of Kawasaki disease,* Pediatrics *114:1708–1733, 2004.)*

be the initial diagnosis in children who are ultimately recognized to have KD. Less common infections such as Rocky Mountain spotted fever and leptospirosis are occasionally confused with KD. Rocky Mountain spotted fever is a potentially lethal bacterial infection and appropriate antibiotics should not be withheld if the diagnosis is under consideration. Its distinguishing features include pronounced myalgias and headache at onset, centripedal rash, and petechiae on the palms and soles. Leptospirosis can also be an illness of considerable severity. Risk factors include exposure to water contaminated with urine from infected animals. The classic description of leptospirosis is of a biphasic illness with a few asymptomatic days between an initial period of fever and headache and a late phase with renal and hepatic failure. In contrast, patients with KD have consecutive days of fever at diagnosis and rarely have renal or hepatic failure.

Children with KD and pronounced myocarditis may demonstrate hypotension with a clinical picture similar to that of toxic shock syndrome. Features of toxic shock syndrome that are not commonly seen in KD include renal insufficiency, coagulopathy, pancytopenia, and myositis. Drug hypersensitivity reactions, including Stevens-Johnson syndrome, share some characteristics with KD. Drug reaction features such as the presence of periorbital edema, oral ulcerations, and a normal or minimally elevated ESR are not seen in KD. Systemic-onset juvenile idiopathic arthritis is also characterized by fever and rash, but physical findings include diffuse lymphadenopathy and hepatosplenomegaly. Arthritis is required to develop at some point in the disease course to make the diagnosis, but may not be present in the 1st few wk of illness. Laboratory findings may include coagulopathy, elevated fibrin degradation product values, and hyperferritinemia. Interestingly, there are reports of children with systemic-onset juvenile idiopathic arthritis who have echocardiographic evidence of abnormal coronary arteries. Coronary aneurysms have also been reported in Behçet disease, primary cytomegalovirus infection, and meningococcemia.

TREATMENT

Patients with acute KD should be treated with 2 g/kg of IVIG and high-dose aspirin (80-100 mg/kg/day divided q6h) within 10 days of disease onset and ideally as soon as possible after diagnosis (Table 166-3). The

Table 166-3 Treatment of Kawasaki Disease

ACUTE STAGE • Intravenous immunoglobulin 2 g/kg over 10-12 hr *and* • Aspirin 80-100 mg/kg/day divided every 6 hr orally until patient is afebrile for at least 48 hr
CONVALESCENT STAGE • Aspirin 3-5 mg/kg once daily orally until 6-8 wk after illness onset if normal coronary findings throughout course
LONG-TERM THERAPY FOR PATIENTS WITH CORONARY ABNORMALITIES • Aspirin 3-5 mg/kg once daily orally • Clopidogrel 1 mg/kg/day (maximum: 75 mg/day) • Most experts add warfarin or low-molecular-weight heparin for those patients at particularly high risk of thrombosis
ACUTE CORONARY THROMBOSIS • Prompt fibrinolytic therapy with tissue plasminogen activator or other thrombolytic agent under supervision of a pediatric cardiologist

mechanism of action of IVIG in KD is unknown, but treatment results in defervescence and resolution of clinical signs of illness in approximately 85% of patients. The prevalence of coronary disease, 20-25% in children treated with aspirin alone, is <5% in those treated with IVIG and aspirin within the 1st 10 days of illness. Strong consideration should be given to treating patients with persistent fever and/or signs of systemic inflammation who are diagnosed after the 10th day of fever. The dose of aspirin is usually decreased from antiinflammatory to antithrombotic doses (3-5 mg/kg/day as a single dose) after the patient has been afebrile for 48 hr, although some experts prescribe high-dose aspirin until the 14th day of illness. Aspirin is continued for its antithrombotic effect until 6-8 wk after illness onset and is then discontinued in patients who have had normal echocardiography findings throughout the course of their illness. Patients with CAA continue with aspirin therapy and may require anticoagulation, depending on the degree of coronary dilation (see later).

Corticosteroids have been trialed as primary therapy with the first dose of IVIG in hopes of improving coronary outcomes. A North American trial using a single pulse dose of intravenous methylprednisolone (30 mg/kg) with IVIG as primary therapy did not improve coronary outcomes. However, a trial in Japan utilizing the Kobayashi score to identify high-risk children demonstrated improved coronary outcomes with a regimen of prednisolone (2 mg/kg) plus IVIG as primary therapy. Despite these promising results, administration of corticosteroids, as primary therapy to all children with KD awaits the development of a risk score that identifies high-risk children in a multiracial population.

IVIG-resistant KD occurs in approximately 15% of patients and is defined by persistent or recrudescent fever 36 hr after completion of the initial IVIG infusion. Patients with IVIG resistance are at increased risk for CAA. Typically, another dose of IVIG at 2 g/kg is administered to patients with IVIG resistance. Corticosteroids in varying doses and via different routes have also been used as secondary or "rescue" therapy when fever persists after the first IVIG. However, the lack of clear data regarding the most effective way to administer corticosteroids as rescue therapy has led to significant practice variation across centers. Tumor necrosis factor inhibitors, including infliximab and etanercept, have also been given for the treatment of IVIG-resistant disease. To date, there is no evidence of improved coronary outcomes with the use of these medications.

COMPLICATIONS

The patient with KD who has had a small solitary aneurysm should continue aspirin indefinitely. Patients with larger or numerous aneurysms may require the addition of other antiplatelet agents or anticoagulation; such decisions should be made in consultation with a pediatric cardiologist. Acute thrombosis may occasionally occur in an aneurysmal or stenotic coronary artery; thrombolytic therapy may be lifesaving in this circumstance.

Long-term follow-up of patients with coronary artery aneurysms should include periodic echocardiography with stress testing and possibly angiography if large aneurysms are present. Catheter intervention with percutaneous transluminal coronary rotational ablation, directional coronary atherectomy, and stent implantation have been used for the management of coronary stenosis due to KD, with some patients requiring coronary artery bypass grafting.

Patients undergoing long-term aspirin therapy should receive annual influenza vaccination to reduce the risk of Reye syndrome. A different antiplatelet agent can be substituted for aspirin during the 6 wk after varicella vaccination. As IVIG may interfere with the immune response to live virus vaccines as a result of specific antiviral antibody, the measles-mumps-rubella and varicella vaccinations should generally be deferred until 11 mo after IVIG administration. Non-live vaccinations do not need to be delayed.

PROGNOSIS

The vast majority of patients with KD return to normal health, as timely treatment reduces the risk of coronary aneurysms to less than 5%. Acute KD recurs in 1-3% of cases. The prognosis for patients with coronary abnormalities depends on the severity of coronary disease; therefore, recommendations for follow-up and management are stratified according to coronary artery status. Published fatality rates are very low, generally <1.0%. Overall, 50% of coronary artery aneurysms regress to normal lumen diameter by 1-2 yr after the illness, with smaller aneurysms being more likely to regress. Intravascular ultrasonography has demonstrated that regressed aneurysms are associated with marked myointimal thickening and abnormal functional behavior of the vessel wall. Giant aneurysms are less likely to regress to normal lumen diameter and are most likely to lead to thrombosis or stenosis. Coronary artery bypass grafting may be required if myocardial perfusion is significantly impaired; it is best accomplished with the use of arterial grafts, which grow with the child and are more likely than venous grafts to remain patent over the long-term. Heart transplantation has been required in rare cases in which revascularization is not feasible because of distal coronary stenoses, distal aneurysms, or severe ischemic cardiomyopathy. A study from Japan reported outcomes in adult patients with a history of KD and giant aneurysms. These patients required multiple cardiac and surgical procedures, but the 30-year survival rate approached 90%.

Whether children who have had KD and normal echocardiography findings throughout their course are at higher risk for the development of atherosclerotic heart disease in adulthood remains unclear, as studies of endothelial dysfunction in children with a history of KD and normal coronary dimensions have produced conflicting results. Reassuring data suggest that the standardized mortality ratio among adults in Japan who had KD in childhood without aneurysms is indistinguishable from that of the general population. All children with a history of KD should be counseled regarding a heart-healthy diet, adequate amounts of exercise, tobacco avoidance, and intermittent lipid monitoring. Among children with coronary aneurysms, the American Heart Association recommends treatment thresholds for risk factors for atherosclerotic heart disease that are lower than those for the normal population.

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Chapter 167

Vasculitis Syndromes

Stacy P. Ardoin and Edward Fels

Childhood vasculitis encompasses a broad spectrum of diseases that share in common inflammation of the blood vessels as the central pathophysiology. The pathogenesis of the vasculitides is generally idiopathic; some forms of vasculitis are associated with infectious agents and medications; others may occur in the setting of preexisting autoimmune disease. The pattern of vessel injury provides insight into the form of vasculitis and serves as a framework to delineate the different vasculitic syndromes. The distribution of vascular injury includes small vessels (capillaries, arterioles, and postcapillary venules), medium vessels (renal arteries, mesenteric vasculature, and coronary arteries), and large vessels (the aorta and its proximal branches). Additionally, some forms of small vessel vasculitis are characterized by the presence of antineutrophil cytoplasmic antibodies (ANCAs) (Table 167-1), whereas others are associated with immune complex deposition in affected tissues. A combination of clinical features, histologic appearance of involved vessels, and laboratory data is utilized to classify vasculitis (Tables 167-2 to 167-4).

Childhood vasculitis varies from a relatively benign and self-limited disease such as Henoch-Schönlein purpura to catastrophic disease with end-organ damage as can be seen in granulomatosis with polyangiitis (formerly Wegener granulomatosis). Vasculitis generally manifests as a heterogeneous multisystem disease. Although some features, such as purpura, are easily identifiable, others, such as hypertension secondary to renal artery occlusion or glomerulonephritis, can be more subtle. Ultimately, the key to recognizing vasculitis relies heavily on pattern recognition. Demonstration of vessel injury and inflammation on biopsy or vascular imaging is required to confirm a diagnosis of vasculitis.

Bibliography is available at Expert Consult.

Table 167-1 Common Disease Associations with Antibodies to Neutrophil Cytoplasmic Antigens

ANTIGEN	ANCA PATTERN	DISEASE ASSOCIATION	FREQUENCY (%)
PR3	cANCA	Wegener granulomatosis Churg-Strauss	30 to 90 25 to 50
MPO	pANCA	Microscopic polyarteritis Ulcerative colitis Sclerosing cholangitis Crohn disease	25 to 75 40 to 80 65 to 85 10 to 40
BPI	ANCA	Cystic fibrosis	80 to 90
Actin	pANCA	Autoimmune hepatitis type 1	70 to 75

ANCA, Antibodies directed at neutrophil cytoplasmic antigen; BPI, Bactericidal permeability increasing protein. cANCA, cytoplasmic ANCA; pANCA, perinuclear ANCA.

From Cabral D, Benseler S: Granulomatous vasculitis, microscopic polyangiitis and primary angiitis of the central nervous system. In Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors, Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Elsevier/Saunders, Table 34-3, p. 526.*

Table 167-2 Classification of Childhood Vasculitis

I. Predominantly Large Vessel Vasculitis
- Takayasu arteritis

II. Predominantly Medium Vessel Vasculitis
- Childhood polyarteritis nodosa
- Cutaneous polyarteritis nodosa
- Kawasaki disease

III. Predominantly Small Vessel Vasculitis

A. Granulomatous:
- Granulomatosis with polyangiitis (Wegener granulomatosis)*
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)*

B. Nongranulomatous:
- Microscopic polyangiitis*
- Henoch-Schönlein purpura
- Isolated cutaneous leukocytoclastic vasculitis
- Hypocomplementemic urticarial vasculitis

IV. Other Vasculitides
- Behçet disease
- Vasculitis secondary to infection (including hepatitis B–associated polyarteritis nodosa), malignancies, and drugs, including hypersensitivity vasculitis
- Vasculitis associated with connective tissue disease
- Isolated vasculitis of the central nervous system
- Cogan syndrome
- Unclassified

*Associated with antineutrophil cytoplasmic antibody.

Adapted from Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis *69:798-806; 2010.*

Table 167-3 Features That Suggest a Vasculitic Syndrome

CLINICAL FEATURES
- Fever, weight loss, fatigue of unknown origin
- Skin lesions (palpable purpura, vasculitic urticaria, livedo reticularis, nodules, ulcers)
- Neurologic lesions (headache, mononeuritis multiplex, focal central nervous system lesions)
- Arthralgia or arthritis, myalgia, or myositis
- Serositis
- Hypertension
- Pulmonary infiltrates or hemorrhage

LABORATORY FEATURES
- Increased erythrocytes sedimentation rate or C-reactive protein level
- Leukocytosis, anemia
- Eosinophilia
- Antineutrophil cytoplasmic antibodies
- Elevated factor VIII–related antigen (von Willebrand factor)
- Cryoglobulins
- Circulating immune complexes
- Hematuria, proteinuria, elevated serum creatinine

From Cassidy JT, Petty RE: Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.*

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Table 167-4 Clinical and Pathologic Characteristics of Some Vasculitides in Childhood

SYNDROME	FREQUENCY	VESSELS AFFECTED	CHARACTERISTIC PATHOLOGY
POLYARTERITIS			
Polyarteritis nodosa	Rare	Medium-size and small muscular arteries and sometimes arterioles	Focal segmental (often near bifurcations); fibrinoid necrosis; gastrointestinal, renal microaneurysms; lesions at various stages of evolution
Kawasaki disease	Common	Coronary and other muscular arteries	Thrombosis, fibrosis, aneurysms, especially of coronary vessels
LEUKOCYTOCLASTIC VASCULITIS			
Henoch-Schönlein purpura	Common	Arterioles and venules, often small arteries and veins	Leukocytoclasis; mixed cells, eosinophils, immunoglobulin A deposits in affected vessels
Hypersensitivity angitis	Rare	Arterioles and venules	Leukocytoclastic or lymphocytic, varying eosinophils, occasionally granulomatous; widespread lesions at same stage of evolution
GRANULOMATOUS VASCULITIS			
Granulomatosis with polyangiitis	Rare	Small arteries and veins, occasionally larger vessels	Upper and lower respiratory tract, necrotizing granulomata glomerulonephritis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Rare	Small arteries and veins, often arterioles and venules	Necrotizing extravascular granulomata; lung involvement; eosinophilia
GIANT CELL ARTERITIS			
Takayasu arteries	Uncommon	Large arteries	Granulomatous inflammation, giant cells; aneurysms, dissection
Temporal arteritis	Rare	Medium-size and large arteries	Granulomatous inflammation, giant cell arteries

Adapted from Cassidy JT, Petty RE: Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.*

167.1 Henoch-Schönlein Purpura

Stacy P. Ardoin and Edward Fels

Henoch-Schönlein purpura (HSP) is the most common vasculitis of childhood and is characterized by leukocytoclastic vasculitis and immunoglobulin (Ig) A deposition in the small vessels in the skin, joints, gastrointestinal tract, and kidney.

EPIDEMIOLOGY

HSP occurs worldwide and affects all ethnic groups but is more common in white and Asian populations. The incidence of HSP is estimated at 14-20/100,000 children per year and affects males more than females, with a 1.2-1.8 : 1 male : female ratio. Approximately 90% of HSP cases occur in children, usually between the ages of 3 and 10 yr. HSP is distinctly less common in adults, in whom severe and chronic complications are often encountered. HSP is more common in the winter and spring, and is unusual in summer months. Many cases of HSP follow a documented upper respiratory infection.

PATHOLOGY

Skin biopsies demonstrate vasculitis of the dermal capillaries and postcapillary venules. The inflammatory infiltrate includes neutrophils and monocytes. Renal histopathology typically shows endocapillary proliferative glomerulonephritis, ranging from a focal segmental process to extensive crescentic involvement. In all tissues, immunofluorescence identifies IgA deposition in walls of small vessels (Fig. 167-1), accompanied to a lesser extent by deposition of C3, fibrin, and IgM.

PATHOGENESIS

The exact pathogenesis of HSP remains unknown. Given the seasonality of HSP and the frequency of preceding upper respiratory infections, infectious triggers such as group A β-hemolytic streptococcus, *Staphylococcus aureus,* mycoplasma, and adenovirus have been suspected. The common finding of deposition of IgA, specifically IgA_1, suggests that HSP is a disease mediated by IgA and IgA immune complexes. HSP occasionally clusters in families, suggesting a genetic component. HLA-B34 and HLA-DRB1*01 alleles have been linked to HSP nephritis. Patients with familial Mediterranean fever, hereditary periodic fever syndromes, and complement deficiencies are at increased risk for developing HSP, suggesting that genetically determined immune dysregulation may contribute.

CLINICAL MANIFESTATIONS

The hallmark of HSP is its rash: palpable purpura starting as pink macules or wheals and developing into petechiae, raised purpura, or larger ecchymoses. Occasionally, bullae and ulcerations develop. The skin lesions are usually symmetric and occur in gravity-dependent areas (lower extremities) or on pressure points (buttocks) (see Figs. 167-1 and 167-2). The skin lesions often evolve in groups, typically lasting 3-10 days, and may recur up to 4 mo after initial presentation. Subcutaneous edema localized to the dorsa of hands and feet, periorbital area, lips, scrotum, or scalp is also common.

Musculoskeletal involvement, including arthritis and arthralgias, is common, occurring in up to 75% of children with HSP. The arthritis tends to be self-limited and oligoarticular, with a predilection for the lower extremities, and does not lead to deformities. The arthritis usually resolves within 2 wk but can recur.

Gastrointestinal manifestations of HSP occur in up to 80% of children with HSP and include abdominal pain, vomiting, diarrhea, paralytic ileus and melena; intussusception, mesenteric ischemia, intestinal perforation are uncommon. Endoscopic evaluation is usually not needed but may identify purpura of the intestinal tract.

Renal involvement occurs in up to 50% of children with HSP, manifesting as microscopic hematuria, proteinuria, hypertension, frank nephritis, nephrotic syndrome, and acute or chronic renal failure. Progression to end-stage renal disease is uncommon in children (1-2%) (see Chapter 515).

Neurologic manifestations of HSP, caused by hypertension or central nervous system (CNS) vasculitis, may also occur. They include intracerebral hemorrhage, seizures, headaches, and behavior changes. Other less-common potential manifestations of HSP are orchitis, carditis, inflammatory eye disease, testicular torsion, and pulmonary hemorrhage.

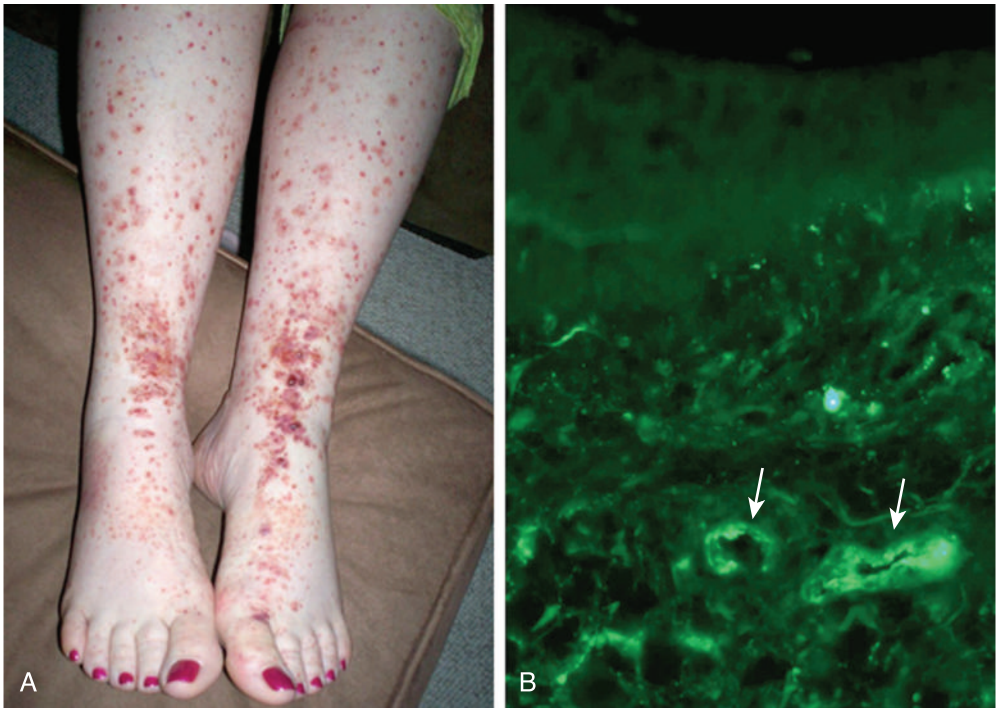

Figure 167-1 **A,** Typical palpable purpura in the lower extremities of a girl with Henoch-Schönlein purpura. **B,** Skin biopsy of lesion from the same patient, showing direct immunofluorescence of immunoglobulin A within the walls of dermal capillaries.

Figure 167-2 Henoch-Schönlein purpura. *(From Korting GW:* Hautkrankheiten bei Kindern und Jungendlichen, *ed 3, Stuttgart, 1982, FK Schattaur Verlag.)*

DIAGNOSIS

The diagnosis of HSP is a clinical one and is often straightforward when the typical rash is present. However, in at least 25% of cases, the rash appears after other manifestations, making early diagnosis challenging. Table 167-5 summarizes the classification criteria for HSP. The differential diagnosis for HSP depends on specific organ involvement but usually includes other small vessel vasculitides, infections, acute post streptococcal glomerulonephritis, hemolytic-uremic syndrome, coagulopathies, and other acute intraabdominal processes.

Acute hemorrhagic edema (AHE), an isolated cutaneous leukocytoclastic vasculitis that affects infants <2 yr of age, resembles HSP clinically. AHE manifests as fever; tender edema of the face, scrotum, hands, and feet; and ecchymosis (usually larger than the purpura of HSP) on the face and extremities (Fig. 167-3). The trunk is spared, but petechiae may be seen in mucous membranes. The patient usually appears well except for the rash. The platelet count is normal or elevated, and the urinalysis results are normal. The younger age, the nature of the lesions, absence of other organ involvement, and a biopsy may help distinguish AHE from HSP.

Papular-purpuric gloves-and-socks syndrome is most commonly caused by parvovirus B19 and initially manifests with symmetric edema and erythema over the hands and feet. These well-demarcated lesions end at the ankle and wrist and evolve into purpuric papules. Fever, oral lesions, and leukopenia are inconsistent findings. Complications include mononeuritis multiplex. Adolescents are more often affected than young children. In contrast to erythremia infectiosum, patients with papular-purpuric gloves-and-socks syndrome are usually infectious at the time of appearance of the rash.

LABORATORY FINDINGS

No laboratory finding is diagnostic of HSP. Common but nonspecific findings include leukocytosis, thrombocytosis, mild anemia, and elevations of erythrocyte sedimentation rate (ESR) and C-reactive protein

Figure 167-3 Typical lesions of acute hemorrhagic edema on the arm of an infant. *(From Eichenfield LF, Frieden IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders.)*

Table 167-5	Classification Criteria for Henoch-Schönlein Purpura*
AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA† Two of the following criteria must be present: • Palpable purpura • Age at onset ≤20 yr • Bowel angina (postprandial abdominal pain, bloody diarrhea) • Biopsy demonstrating intramural granulocytes in small arterioles and/or venules	
EUROPEAN LEAGUE AGAINST RHEUMATISM/PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY CRITERIA‡ Palpable purpura (in absence of coagulopathy or thrombocytopenia) and 1 or more of the following criteria must be present: • Abdominal pain (acute, diffuse, colicky pain) • Arthritis or arthralgia • Biopsy of affected tissue demonstrating predominant immunoglobulin A deposition • Renal involvement (proteinuria >3 grams/24 hr), hematuria or red cell casts	

*Classification criteria are developed for use in research and not validated for clinical diagnosis.

†Developed for use in adult and pediatric populations. Adapted from Mills JA, Michel BA, Bloch DA, et al: The American College of Rheumatology 1990 criteria for classification of Henoch-Schönlein purpura, *Arthritis Rheum* 33:1114–1121, 1990.

‡Developed for use in pediatric populations only.

Adapted from Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis *69:798–806; 2010.*

(CRP). The platelet count is normal in HSP. Occult blood is frequently found in stool specimens. Serum albumin levels may be low due to renal or intestinal protein loss. Autoantibody testing is not useful diagnostically except to exclude other diseases. Serum IgA values are often elevated but are not routinely measured. Assessment of renal involvement with blood pressure, urinalysis, and serum creatinine is necessary.

Ultrasound is often used in the setting of gastrointestinal complaints to look for bowel wall edema or the rare occurrence of an associated intussusception. Barium enema can also be used to both diagnose and treat intussusception. Although often unnecessary in typical HSP, biopsies of skin and kidney can provide important diagnostic information, particularly in atypical or severe cases, and characteristically show IgA deposition in affected tissues.

TREATMENT

Treatment for mild and self-limited HSP is supportive, with an emphasis on assuring adequate hydration, nutrition, and analgesia. Steroids are most often used to treat significant gastrointestinal involvement or other life-threatening manifestations. Prednisone (1 mg/kg/day for 1-2 wk, followed by taper) reduces abdominal and joint pain but does not alter overall prognosis nor prevent renal disease. Rapid tapering of corticosteroids may lead to a flare of HSP symptoms. Although few data are available to demonstrate efficacy, intravenous immune globulin and plasma exchange are sometimes used in the setting of severe disease. In some cases, chronic HSP renal disease is managed with a variety of immunosuppressants, including azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil. End-stage renal disease develops in up to 8% of children with HSP nephritis.

COMPLICATIONS

Acutely, serious gastrointestinal involvement such as intestinal perforation imparts significant morbidity and mortality. Renal disease is the major long-term complication, occurring in 1-2% of children with HSP. Renal disease can develop up to 6 mo after diagnosis but rarely does so if the initial urinalyses findings are normal. It is recommended that children with HSP undergo serial monitoring of blood pressure and urinalyses for several months after diagnosis to monitor for the development of nephritis.

PROGNOSIS

Overall, the prognosis for childhood HSP is excellent, and most children experience an acute, self-limited course lasting on average 4 wk. From 15-60% of children with HSP experience 1 or more recurrences, typically within 4-6 mo of diagnosis. With each relapse, symptoms are usually milder than at presentation. Children with a more-severe initial course are at higher risk for relapse. The long-term prognosis usually depends upon the severity and duration of gastrointestinal or renal involvement. Chronic renal disease develops in 1-2% of children with HSP, and approximately 8% of those with HSP nephritis go on to have end-stage renal disease. The risk of HSP recurrence and graft loss following renal transplantation is estimated at 7.5% after 10 yr.

Bibliography is available at Expert Consult.

167.2 Takayasu Arteritis

Stacy P. Ardoin and Edward Fels

Takayasu arteritis (TA), also known as "**pulseless disease**," is a chronic large vessel vasculitis of unknown etiology that predominantly involves the aorta and its major branches.

EPIDEMIOLOGY

Although TA occurs worldwide and can affect all ethnic groups, the disease is most common in Asians. Age of onset is typically between 10 and 40 yr. Most children are diagnosed as adolescents, on average at 13 yr of age. Up to 20% of individuals with TA are diagnosed prior to age 19 yr. Younger children may be affected but diagnosis in infancy is rare. TA preferentially affects females with a reported 2-4 : 1 female : male ratio in children and adolescents and a 9 : 1 ratio among

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adults. Occlusive complications are more common in the United States, Western Europe, and Japan, whereas aneurysms predominate in Southeast Asia and Africa.

PATHOLOGY

TA is characterized by inflammation of the vessel wall, starting in the vas vasorum. Involved vessels are infiltrated by T cells, natural killer cells, plasma cells, and macrophages. Giant cells and granulomatous inflammation develop in the media. Persistent inflammation damages the elastic lamina and muscular media, leading to blood vessel dilation and the formation of aneurysms. Progressive scarring and intimal proliferation can result in stenotic or occluded vessels. The subclavian, renal, and carotid arteries are the most commonly involved aortic branches; pulmonary, coronary, and vertebral arteries may also be affected.

PATHOGENESIS

The etiology of TA remains unknown. The presence of abundant T cells with a restricted repertoire of T-cell receptors in TA vascular lesions points to the importance of cellular immunity and suggests the existence of a specific but unknown aortic tissue antigen. Expression of interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α) is reported to be higher in patients with active TA than in patients with inactive TA and in healthy controls. In some patient populations, IL-1 genetic polymorphisms are linked to TA. Some individuals with TA have elevated serum values of antiendothelial antibodies. The increased prevalence of TA in certain ethnic populations and its occasional occurrence in monozygotic twins and families suggest a genetic predisposition to the disease.

CLINICAL MANIFESTATIONS

The diagnosis of TA is challenging, because early disease manifestations are often nonspecific. As a result, diagnosis can be delayed for several months, and the time to diagnosis is usually longer in children than in adults. Fever, malaise, weight loss, headache, hypertension, myalgias, arthralgias, dizziness, and abdominal pain are common early complaints in the "pre-pulseless" phase of the disease. Among children, hypertension and headache are particularly common presenting manifestations and should prompt consideration of TA when present without alternative explanation. Some individuals with TA report no systemic symptoms and instead present with vascular complications. It is only after substantial vascular injury that evidence of hypoperfusion becomes clinically evident. Later manifestations of disease include diminished pulses, asymmetric blood pressures, claudication, Raynaud phenomenon, renal failure, and symptoms of pulmonary or cardiac ischemia. Inflammation can extend to the aortic valve, resulting in valvular insufficiency. Other findings may include pericardial effusion, pericarditis, pleuritis, splenomegaly, and arthritis.

Supradiaphragmatic (aortic arch) disease often manifests with CNS (stroke, transient ischemic attack), and cardiac (heart failure, palpitations) symptoms, while infradiaphragmatic (mid-aortic syndrome) disease may produce hypertension, abdominal bruits, and pain. Most patients have involvement in both areas.

DIAGNOSIS

Specific pediatric criteria for TA have been proposed (Table 167-6). Radiographic demonstration of large vessel vasculitis is necessary. A thorough physical examination is required to detect an aortic murmur, diminished or asymmetric pulses, and vascular bruits. Four extremity blood pressures should be measured >10 mm Hg; asymmetry in systolic pressure is indicative of disease.

DIFFERENTIAL DIAGNOSIS

In the early phase of TA, when nonspecific symptoms predominate, the differential diagnosis includes a wide array of systemic infections, autoimmune conditions, and malignancies. Although giant cell arteritis, also known as "temporal arteritis," is a common large vessel vasculitis in older adults, this entity is exceedingly rare in childhood. Noninflammatory conditions that can cause large vessel compromise include fibromuscular dysplasia, Marfan syndrome, and Ehlers-Danlos syndrome.

Table 167-6 Proposed Classification Criteria for Pediatric-Onset Takayasu Arteritis

Angiographic abnormalities (conventional, CT, or magnetic resonance angiography) of the aorta or its main branches and at least one of the following criteria:

- Decreased peripheral artery pulse(s) and/or claudication of extremities
- Blood pressure difference between arms or legs of >10 mm Hg
- Bruits over the aorta and/or its major branches
- Hypertension (defined by childhood normative data)
- Elevated acute phase reactant (erythrocyte sedimentation rate or C-reactive protein)

Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. *Ann Rheum Dis* 69:798–806; 2010.

LABORATORY FINDINGS

The laboratory findings in TA are nonspecific, and there is no specific diagnostic laboratory test. ESR and CRP value are typically elevated, and other nonspecific markers of chronic inflammation may include leukocytosis, thrombocytosis, anemia of chronic inflammation, and hypergammaglobulinemia. Autoantibodies are not useful in diagnosing TA except to help exclude other autoimmune diseases.

Radiographic assessment is essential to establish large vessel arterial involvement. Conventional arteriography of the aorta and major branches, including carotid, subclavian, pulmonary, renal, and mesenteric branches can identify luminal defects, including dilation, aneurysms, and stenoses, even in smaller vessels such as the mesenteric arteries. Figure 167-4 shows a conventional arteriogram in a child with TA. Although not yet thoroughly validated in TA, magnetic resonance angiography and CT angiography also provide important information about vessel wall thickness and enhancement, although they may not image smaller vessels as well as conventional angiography. Positron emission tomography may detect vessel wall inflammation but has not been studied extensively. Ultrasound with duplex color-flow Doppler imaging also identifies vessel wall thickening and assesses arterial flow. Echocardiography is recommended to assess for aortic valvular involvement. Serial vascular imaging is usually necessary to assess response to treatment and to detect progressive vascular damage.

TREATMENT

Glucocorticoids are the mainstay of therapy, typically starting with high doses (1-2 mg/kg/day of prednisone) followed by gradual dosage tapering. When TA progresses or recurs, steroid-sparing therapy is often required, usually involving methotrexate or azathioprine. Cyclophosphamide is reserved for severe or refractory disease. Results of small case series also suggest that mycophenolate mofetil, tocilizumab or anti–TNF-α therapy may be beneficial in select patients. Antihypertensive medications are often necessary to control blood pressure caused by renovascular disease.

COMPLICATIONS

Progressive vascular damage can result in arterial stenoses, aneurysms, and occlusions, which produce ischemic symptoms and can be organ- or life-threatening. Potential ischemic complications include stroke, renal impairment or failure, myocardial infarction, mesenteric ischemia, and limb-threatening arterial disease. When these complications occur or are imminent, intervention with surgical vascular grafting or catheter-based angioplasty and stent placement may be necessary to restore adequate blood flow. A high rate of recurrent stenosis has been reported following angioplasty and stent placement. Aortic valve replacement may be required if significant aortic insufficiency develops.

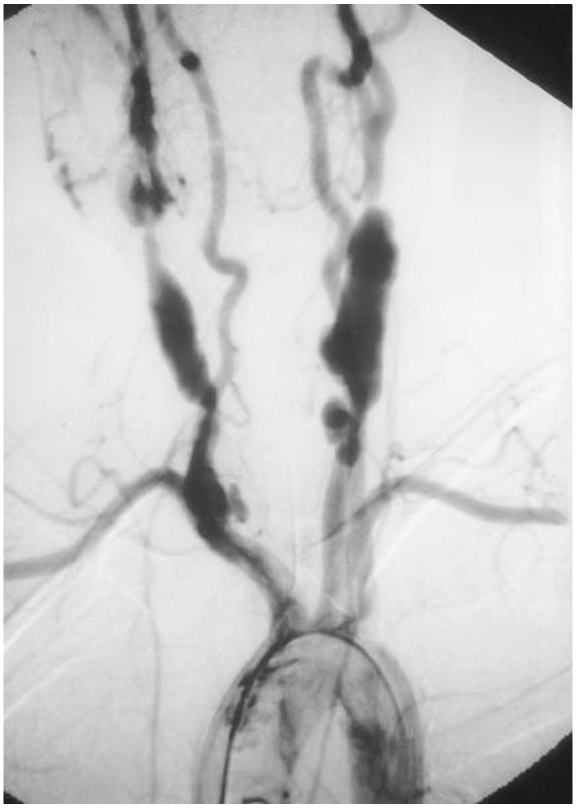

Figure 167-4 Conventional angiogram in a child with Takayasu arteritis showing massive bilateral carotid dilation, stenosis, and poststenotic dilation.

PROGNOSIS

Although up to 20% of individuals with TA have a monophasic course and achieve sustained remission, most suffer relapses. Survival for individuals with TA has improved considerably over the decades, although higher mortality rates are reported in children and adolescents. The overall estimated survival for individuals with TA is 93% at 5 yr and 87% at 10 yr. However, morbidity from vascular complications remains high, particularly when there is evidence of ongoing active inflammation as detected by elevated CRP or ESR. Given the chronic endothelial insult and inflammation, children and adolescents with TA are probably at high risk for accelerated atherosclerosis. Early detection and treatment are critical to optimizing outcome in TA.

Bibliography is available at Expert Consult.

167.3 Polyarteritis Nodosa and Cutaneous Polyarteritis Nodosa

Stacy P. Ardoin and Edward Fels

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis affecting small and medium-size arteries. Aneurysms and stenoses form at irregular intervals throughout affected arteries. Cutaneous PAN is limited to the skin.

EPIDEMIOLOGY

PAN is rare in childhood. Boys and girls are equally affected, and the mean age at presentation is 9 yr. The cause is unknown, but the development of PAN following infections, including group A streptococcus and chronic hepatitis B, suggests that PAN may represent a postinfectious autoimmune response. Infections with other organisms, including Epstein-Barr virus, *Mycobacterium tuberculosis*, cytomegalovirus, parvovirus B19, and hepatitis C virus, have also been associated with PAN. As in Henoch-Schönlein purpura, there is a possible association between PAN and familial Mediterranean fever.

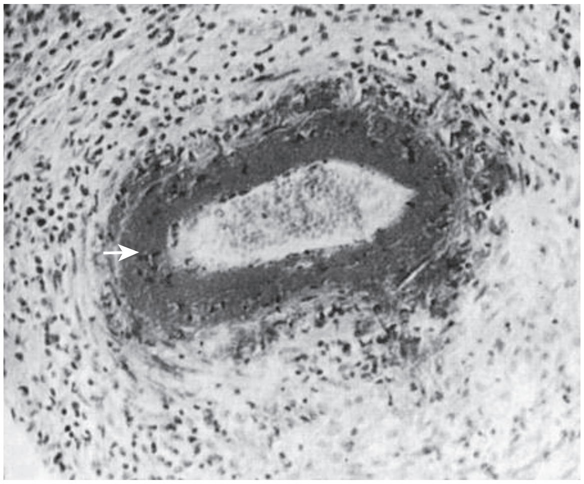

Figure 167-5 Biopsy specimen from a medium-size muscular artery that exhibits marked fibrinoid necrosis of the vessel wall *(arrow). (From Cassidy JT, Petty RE: Polyarteritis and related vasculitides. In* Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.)*

PATHOLOGY

Biopsies show necrotizing vasculitis with granulocytes and monocytes infiltrating the walls of small and medium-size arteries (Fig. 167-5). Involvement is usually segmental and tends to occur at vessel bifurcations. Granulomatous inflammation is not present, and deposition of complement and immune complexes is rarely observed. Different stages of inflammation are found, ranging from mild inflammatory changes to panmural fibrinoid necrosis associated with aneurysm formation, thrombosis, and vascular occlusion.

PATHOGENESIS

Immune complexes are believed to be pathogenic, but the mechanism is poorly understood. There is no clear genetic association with PAN, and it is not known why PAN has a predilection for small- and medium-size blood vessels. The inflamed vessel wall becomes thickened and narrowed, impeding blood flow and contributing to end-organ damage characteristic of this disease. Familial disease in Georgian Jewish patients has been reported to be due to mutations in the *CECR1* gene, which encodes adenosine deaminase 2.

CLINICAL MANIFESTATIONS

The clinical presentation of PAN is variable but generally reflects the distribution of inflamed vessels. Constitutional symptoms are present in most children at disease onset. Weight loss and severe abdominal pain suggest mesenteric arterial inflammation and ischemia. Renovascular arteritis can cause hypertension, hematuria, or proteinuria, although glomerulonephritis is not typical. Cutaneous manifestations include purpura, livedo reticularis, ulcerations, digital ischemia and painful nodules. Arteritis affecting the nervous system can result in cerebrovascular accidents, transient ischemic attacks, psychosis, and ischemic motor or sensory peripheral neuropathy (mononeuritis multiplex). Myocarditis or coronary arteritis can lead to heart failure and myocardial ischemia; pericarditis and arrhythmias have also been reported. Arthralgias, arthritis, or myalgias are frequently present. Less common symptoms include testicular pain that mimics testicular torsion, bone pain, and vision loss as a result of retinal arteritis. The pulmonary vasculature is usually spared in PAN.

DIAGNOSIS

The diagnosis of PAN requires demonstration of vessel involvement on biopsy or angiography (Table 167-7). Biopsy of cutaneous lesions

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Table 167-7	Proposed Classification Criteria for Pediatric-Onset Polyarteritis Nodosa*
Histopathology	Necrotizing vasculitis in medium or small arteries
Angiographic abnormalities	Angiography showing aneurysm, stenosis, or occlusion of a medium or small size artery not from a noninflammatory cause
Cutaneous findings	Livedo reticularis, tender subcutaneous nodules, superficial skin ulcers, deep skin ulcers, digital necrosis, nail bed infarctions or splinter hemorrhages
Muscle involvement	Myalgia or muscle tenderness
Hypertension	Systolic or diastolic blood pressure >95th percentile for height
Peripheral neuropathy	Sensory peripheral neuropathy, motor mononeuritis multiplex
Renal involvement	Proteinuria (>300 mg/24 hr equivalent), hematuria or red blood cell casts, impaired renal function (glomerular filtration rate <50% normal)

*The presence of all 5 criteria provides 89.6% sensitivity and 99.6% specificity for the diagnosis of childhood onset polyarteritis nodosa.

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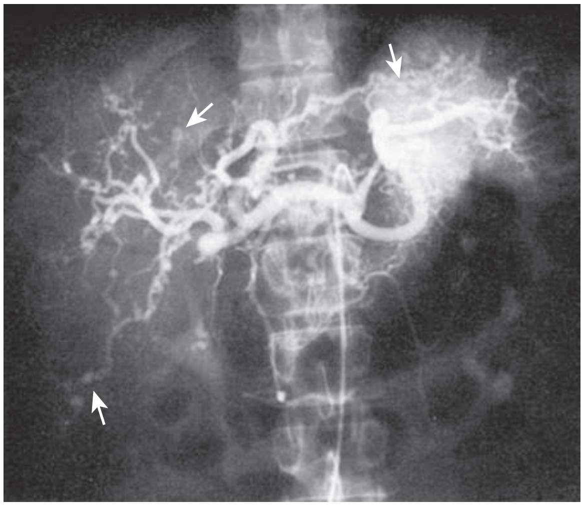

Figure 167-6 Celiac angiography in an 18 yr old boy showing aneurysms in multiple vessels. *(From Cassidy JT, Petty RE: Polyarteritis and related vasculitides. In* Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.)*

shows small or medium vessel vasculitis (see Fig. 167-5). Kidney biopsy in patients with renal manifestations may show necrotizing arteritis. Electromyography in children with peripheral neuropathy identifies affected nerves, and sural nerve biopsy may reveal vasculitis. Conventional arteriography is the gold standard diagnostic imaging study for PAN and reveals areas of aneurysmal dilation and segmental stenosis, the classic "beads on a string" appearance (Fig. 167-6). Magnetic resonance angiography and CT angiography, less-invasive imaging alternatives, are gaining acceptance, but may not be as effective in identifying small vessel disease or in younger children.

DIFFERENTIAL DIAGNOSIS

Early skin lesions may resemble those of HSP, although the finding of nodular lesions and presence of systemic features help distinguish PAN. Because pulmonary vascular involvement is very rare in PAN, pulmonary lesions suggest ANCA-associated vasculitis or Goodpasture disease. Other rheumatic diseases, including systemic lupus erythematosus, have characteristic target organ involvement and associated autoantibodies distinguishing them from PAN. Prolonged fever and weight loss should also prompt consideration of inflammatory bowel disease or malignancy.

LABORATORY FINDINGS

Nonspecific laboratory findings include elevations of ESR and CRP, anemia, leukocytosis, and hypergammaglobulinemia. Abnormal urine sediment, proteinuria, and hematuria indicate renal disease. Laboratory findings may be normal in cutaneous PAN or similar to those of systemic PAN. Elevated hepatic enzyme values may suggest hepatitis B or C infection. Serologic tests for hepatitis (hepatitis B surface antigen and hepatitis C antibody) should be performed in all patients.

TREATMENT

Oral (1-2 mg/kg/day) and intravenous pulse (30 mg/kg/day) prednisone is the mainstay of therapy. Oral or intravenous cyclophosphamide are often used as adjunctive therapy, and plasma exchange may be warranted for life-threatening disease. If hepatitis B is identified, appropriate antiviral therapy should be initiated (see Chapter 358). Most cases of cutaneous PAN can be treated with less-intense therapy such as corticosteroids alone, nonsteroidal antiinflammatory agents, and methotrexate. Azathioprine, mycophenolate mofetil, intravenous immunoglobulin, thalidomide, cyclosporine, and anti-TNF have all been reported as successful in treatment of refractory cutaneous or systemic PAN, although clinical trials are lacking. If an infectious trigger for PAN is identified, antibiotic prophylaxis can be considered.

COMPLICATIONS

Cutaneous nodules may ulcerate and become infected. Hypertension and chronic renal disease may develop from renovascular involvement in PAN. Cardiac involvement may lead to decreased cardiac function or coronary artery disease. Mesenteric vasculitis can predispose to bowel infarction, rupture, and malabsorption. Stroke and rupture of hepatic arterial aneurysm are uncommon complications of this disorder.

PROGNOSIS

The course of PAN varies from mild disease with few complications to a severe, multiorgan disease with high morbidity and mortality. Poor prognostic factors in PAN include elevated serum creatinine, proteinuria, severe gastrointestinal involvement, cardiomyopathy, and CNS involvement. Early and aggressive immunosuppressive therapy increases the likelihood of clinical remission. Compared with disease in adults, childhood PAN is associated with less mortality. Cutaneous PAN is unlikely to transition to systemic disease. Early recognition and treatment of the disease are important to minimizing potential long-term vascular complications.

Bibliography is available at Expert Consult.

167.4 Antineutrophilic Cytoplasmic Antibody–Associated Vasculitis

Stacy P. Ardoin and Edward Fels

The ANCA-associated vasculitides are characterized by small vessel involvement, circulating ANCAs, and pauci-immune complex deposition in affected tissues. ANCA-associated vasculitis is categorized into 3 distinct forms: **granulomatosis with polyangiitis (GPA; formerly**

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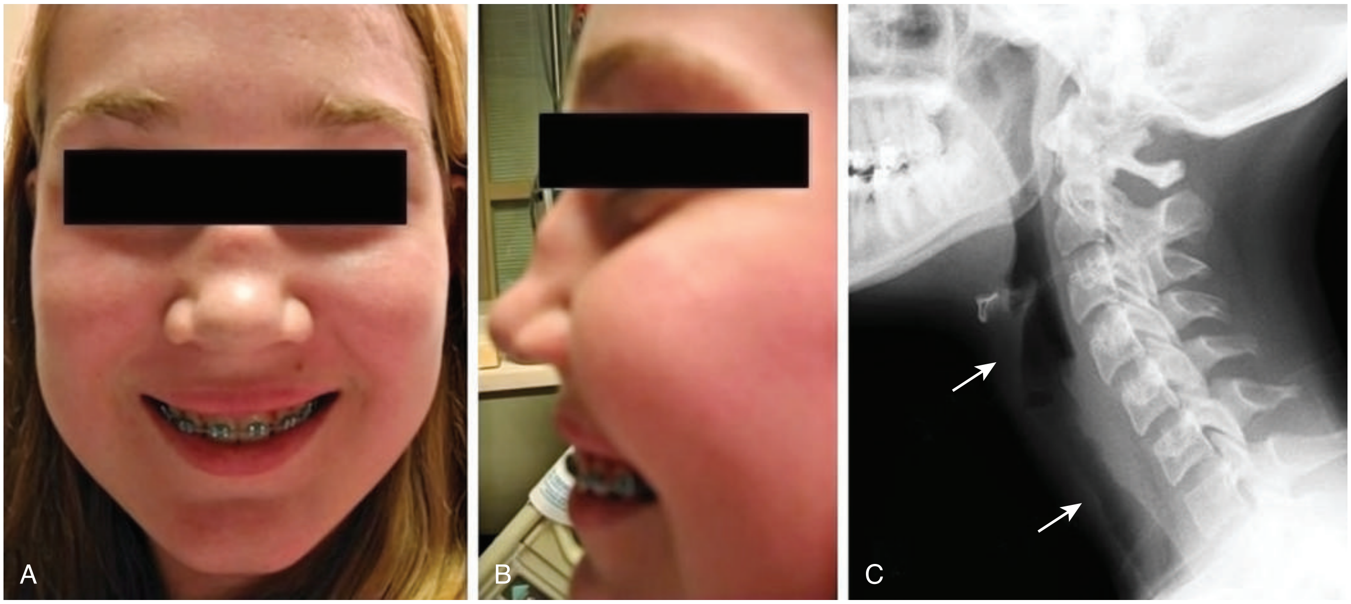

Figure 167-7 **A** and **B,** Anterior and lateral views of saddle nose deformity in an adolescent girl with Wegener granulomatosis. **C,** Segment of subglottic posterior tracheal irregularity (between *arrows*) on lateral neck radiograph in the same patient.

Wegener granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis, formerly called **Churg-Strauss syndrome (CSS)** (see Table 167-1).

EPIDEMIOLOGY

GPA is a necrotizing granulomatous small and medium vessel vasculitis that occurs at all ages and targets the upper and lower respiratory tracts and the kidneys. Although most cases of GPA occur in adults, the disease also occurs in children with a mean age at diagnosis of 14 yr. There is a female predominance of 3-4 : 1, and pediatric GPA is most prevalent in whites.

MPA is a small vessel necrotizing vasculitis with clinical features similar to those of GPA. **CSS** is a small vessel necrotizing granulomatous (allergic granulomatosis) vasculitis associated with a history of refractory asthma and peripheral eosinophilia. MPA and CSS are rare in children, and there does not appear to be a gender predilection in either disease.

PATHOLOGY

Necrotizing vasculitis is the cardinal histologic feature in both GPA and MPA. Kidney biopsies typically demonstrate crescentic glomerulonephritis with little or no immune complex deposition ("pauci-immune"), in contrast to biopsies from patients with systemic lupus erythematosus. Although granulomatous inflammation is common in GPA and CSS, it is typically not present in MPA. Biopsies showing perivascular eosinophilic infiltrates distinguish CSS syndrome from both MPA and GPA (see Table 167-7).

PATHOGENESIS

The etiology of ANCA-associated vasculitis remains unknown, although neutrophils, monocytes, and endothelial cells are involved in disease pathogenesis. Neutrophils and monocytes are activated by ANCAs, specifically by the ANCA-associated antigens proteinase-3 (PR3) and myeloperoxidase (MPO), and release proinflammatory cytokines such as TNF-α and IL-8. Localization of these inflammatory cells to the endothelium results in vascular damage characteristic of the ANCA vasculitides. Why the respiratory tract and kidneys are preferential targets in GPA and MPA is unknown.

CLINICAL MANIFESTATIONS

Early disease course is characterized by nonspecific constitutional symptoms, including fever, malaise, weight loss, myalgias, and arthralgias. In **GPA**, upper airway involvement can manifest as sinusitis, nasal ulceration, epistaxis, otitis media, and hearing loss. Lower respiratory tract symptoms in GPA include cough, wheezing, dyspnea, and hemoptysis. Pulmonary hemorrhage can cause rapid respiratory failure. Compared with adults, childhood GPA is more frequently complicated by subglottic stenosis (see Fig. 167-5). Inflammation-induced damage to the nasal cartilage can produce a saddle nose deformity (Fig. 167-7). Ophthalmic involvement includes conjunctivitis, scleritis, uveitis, optic neuritis, and invasive orbital pseudotumor (causing proptosis). Perineural vasculitis or direct compression on nerves by granulomatous lesions can cause cranial and peripheral neuropathies. Hematuria, proteinuria, and hypertension in GPA signal renal disease. Cutaneous lesions include palpable purpura and ulcers. Venous thromboembolism is a rare but potentially fatal complication of GPA. The frequencies of organ system involvement throughout the disease course in GPA are: respiratory tract, 84%; kidneys, 88%; joints, 44%; eyes, 60%; skin, 48%; sinuses, 56%; and nervous system, 12%. Table 167-8 outlines the classification criteria for pediatric-onset GPA.

The clinical presentation of **MPA** closely resembles that of GPA, although sinus disease is less common; systemic features of fever, malaise, weight loss, myalgias, arthralgias may be dominant. MPA predominantly affects the kidney and lungs; other organ systems include skin, CNS, muscle, heart, and eyes. **CSS** frequently causes inflammation of the upper and lower respiratory tracts, but cartilage destruction is rare. CSS may initially demonstrate chronic or recurrent rhinitis/sinusitis, nasal polyposis, and difficult to treat asthma. Eosinophilia with pulmonary infiltrates may precede a vasculitic phase. Other organ involvement includes skin, cardiac, peripheral nerves, gastrointestinal tract, and muscle. Renal involvement in CSS is uncommon.

DIAGNOSIS

GPA should be considered in children who have recalcitrant sinusitis, pulmonary infiltrates, and evidence of nephritis. Chest radiography often fails to detect pulmonary lesions, and chest CT may show nodules, ground-glass opacities, mediastinal lymphadenopathy, and cavitary lesions (Fig. 167-8). The diagnosis is confirmed by the presence of anti-PR3–specific ANCAs (PR3-ANCAs) and the finding of necrotizing granulomatous vasculitis on pulmonary, sinus, or renal biopsy. The ANCA test result is positive in approximately 90% of children with GPA, and the presence of anti-PR3 increases the specificity of the test.

In **MPA**, ANCAs are also frequently present but have reactivity to MPO (MPO-ANCAs). MPA can be distinguished from PAN by the

presence of ANCAs and the tendency for small vessel involvement. The ANCA test result is positive in approximately 70% of cases of **CSS**, and MPO-ANCAs are more common than PR3-ANCAs. The presence of chronic asthma and peripheral eosinophilia suggests the diagnosis of CSS.

Table 167-8 EULAR/PReS Classification Criteria for Pediatric-Onset Granulomatosis with Polyangiitis*

Criteria
Histopathology showing granulomatous inflammation
Upper airway involvement
Laryngeal, tracheal or bronchial involvement
ANCA positivity
Renal involvement
Proteinuria, hematuria, red blood cell casts, necrotizing pauci-immune glomerulonephritis

*Diagnosis requires 3 of 6 criteria.
Adapted from: Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis *69:798–806; 2010.*

DIFFERENTIAL DIAGNOSIS

ANCAs are absent in other granulomatous diseases, such as sarcoidosis and tuberculosis. Goodpasture disease is characterized by antibodies to glomerular basement membrane. Medications such as propylthiouracil, hydralazine, and minocycline are associated with drug-induced ANCA (usually perinuclear ANCA) vasculitis. Systemic lupus erythematous and HSP can manifest as pulmonary hemorrhage and nephritis.

LABORATORY FINDINGS

Elevated ESR and CRP values, leukocytosis, and thrombocytosis are present in most patients with an ANCA-associated vasculitis but are nonspecific. Anemia may be caused by chronic inflammation or pulmonary hemorrhage. ANCA antibodies show 2 distinct immunofluorescence patterns: perinuclear and cytoplasmic. In addition, ANCAs can also be defined by their specificity for PR3 or MPO antigen. GPA is strongly associated with cytoplasmic ANCAs/anti-PR3 antibodies (see Tables 167-1 and 167-9).

TREATMENT

When the lower respiratory tract or kidneys are significantly involved, initial induction therapy usually consists of corticosteroids (2 mg/kg/day oral or 30 mg/kg/day × 3 days given intravenously) in conjunction with daily oral cyclophosphamide (2 mg/kg/day). Rituximab is an option for induction therapy in ANCA positive vasculitides although

Table 167-9 Differential Diagnostic Features of Small Vessel Vasculitis

FEATURE	HENOCH-SCHÖNLEIN PURPURA	GRANULOMATOSIS WITH POLYANGIITIS	CHURG-STRAUSS SYNDROME	MICROSCOPIC POLYANGIITIS
Signs and symptoms of small vessel vasculitis*	+	+	+	+
Immunoglobulin A–dominant immune deposits	+	–	–	–
Circulating antineutrophil cytoplasmic antibodies	–	+ (PR3)	+ (MPO > PR3)	+ (MPO)
Necrotizing vasculitis	–	+	+	+
Granulomatous inflammation	–	+	+	–
Asthma and eosinophilia	–	–	+	–

MPO, myeloperoxidase-reactive antibodies; PR3, proteinase 3–reactive antibodies; +, presence; –, absent.
*Signs and symptoms of small vessel vasculitis include purpura, other rash, arthralgias, arthritis, and constitutional symptoms.
Adapted from Jeannett JC, Falk RJ: Small-vessel vasculitis, N Engl J Med *337:1512–1523, 1997.*

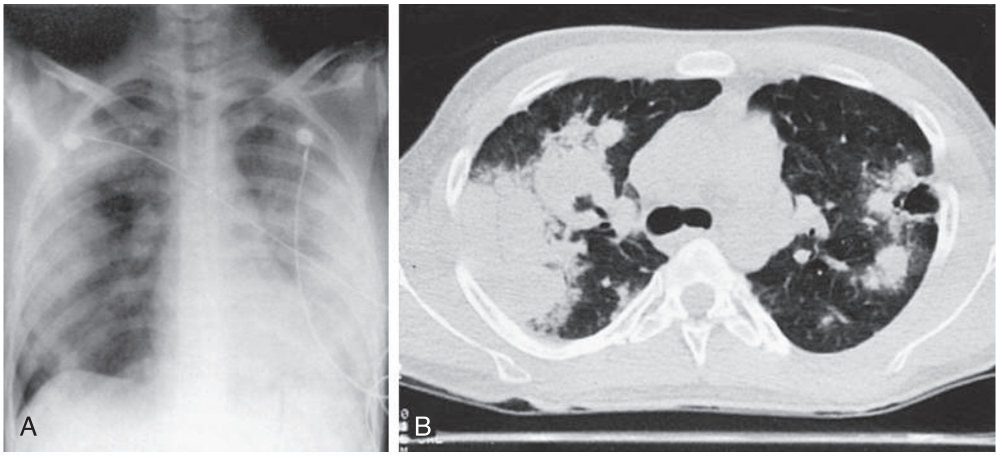

Figure 167-8 **Radiographs of lower respiratory tract disease in granulomatosis with polyangiitis. A,** A chest radiograph of a 14 yr old girl with Wegener granulomatosis and pulmonary hemorrhage. Extensive bilateral, fluffy infiltrates are visualized. **B,** CT scan of the chest in a 17 yr old boy with Wegener granulomatosis. Air space consolidation, septal thickening, and a single cavitary lesion are present. *(**A,** From Cassidy JT, Petty RE: Granulomatous vasculitis, giant cell arteritis and sarcoidosis. In* Textbook of pediatric rheumatology, *ed 3, Philadelphia, 1995, WB Saunders; **B,** From Kuhn JP, Slovis TL, Haller JO:* Caffey's pediatric diagnostic imaging, *ed 10, vol 1, Philadelphia, 2004, Mosby.)*

has been studied primarily in adults. Patients are transitioned to a less toxic maintenance medication (usually methotrexate, azathioprine, or mycophenolate mofetil) within 3-6 mo once remission is achieved. Trimethoprim-sulfamethoxazole (one 180 mg/800 mg tablet 3 days/wk) is often prescribed both for prophylaxis against *Pneumocystis jiroveci* infection and to reduce upper respiratory bacterial colonization with *S. aureus,* which may trigger disease activity. If disease is limited to the upper respiratory tract, corticosteroids (1-2 mg/kg/day) and methotrexate (0.5-1.0 mg/kg/wk) may be first-line treatment.

COMPLICATIONS

Upper respiratory tract lesions can invade the orbit and threaten the optic nerve, and lesions in the ear can cause permanent hearing loss. Respiratory complications include potentially life-threatening pulmonary hemorrhage and upper airway obstruction due to subglottic stenosis. Chronic lung disease secondary to granulomatous inflammation, cavitary lesions, and scarring can predispose to infectious complications. Chronic glomerulonephritis may progress to end-stage renal disease in a subset of patients with advanced or undertreated disease.

PROGNOSIS

The course is variable but disease relapse occurs in up to 60% of patients. Mortality has been reduced with the introduction of cyclophosphamide and other immunosuppressive agents. Compared with adults, children are more likely to develop multiple organ involvement, renal involvement, and subglottic stenosis.

Bibliography is available at Expert Consult.

167.5 Other Vasculitis Syndromes

Stacy P. Ardoin and Edward Fels

In addition to the more common vasculitides discussed earlier in this chapter, other vasculitic conditions can occur in childhood, the most common of which is Kawasaki disease (see Chapter 166). **Hypersensitivity vasculitis** is a cutaneous vasculitis triggered by medication or toxin exposure. The rash consists of palpable purpura or other nonspecific rash. Skin biopsies reveal characteristic changes of **leukocytoclastic vasculitis** (small vessels with neutrophilic perivascular or extravascular neutrophilic infiltration). **Hypocomplementemic urticarial vasculitis** involves small vessels and manifests as recurrent urticaria that resolves over several days but leaves residual hyperpigmentation. This condition is associated with low levels of complement component C1q and systemic findings that include fever, gastrointestinal symptoms, arthritis, and glomerulonephritis. **Cryoglobulinemic vasculitis** can complicate mixed essential cryoglobulinemia and is a small vessel vasculitis affecting skin, joints, kidneys, and lungs.

Primary angiitis of the CNS represents vasculitis confined to the CNS and requires exclusion of other systemic vasculitides. Large vessel disease (angiography positive) may manifest with focal deficits similar to an occlusive stroke with hemiparesis, focal gross or fine motor deficits, language disorders, or cranial nerve deficits. Diffuse cognitive, memory, and concentration deficits plus behavioral disorders are seen in 30-40%. Small vessel (angiography negative, biopsy positive) involvement more often demonstrates language problems and diffuse deficits such as cognitive, memory, behavior, and concentration problems as well as focal seizures.

Benign angiitis of the CNS, also known as transient CNS angiopathy, represents a self-limited variant. **Cogan syndrome** is rare in children; its potential clinical manifestations include constitutional symptoms, inflammatory eye disease, vestibuloauditory dysfunction, arthritis, and aortitis.

Identification of these vasculitis syndromes requires a comprehensive history and physical exam. Table 167-10 outlines other diagnostic considerations. Although treatment is tailored to disease severity, treatment generally includes prednisone (up to 2 mg/kg/day) plus steroid-sparing immunosuppressive medications if necessary. For hypersensitivity vasculitis, withdrawal of the triggering medication or toxin is indicated if possible.

Bibliography is available at Expert Consult.

Table 167-10 Diagnostic Considerations for Other Vasculitis Syndromes

VASCULITIS SYNDROME	APPROACH TO DIAGNOSIS
Hypersensitivity vasculitis	Skin biopsy demonstrating leukocytoclastic vasculitis
Hypocomplementemic urticarial vasculitis	Biopsy of affected tissue demonstrating small vessel vasculitis Low levels of circulating C1q
Cryoglobulinemic vasculitis	Biopsy of affected tissue demonstrating small vessel vasculitis Measurement of serum cryoglobulins Exclusion of hepatitides B and C infections
Primary angiitis of the CNS	Conventional, CT, or MR angiographic evidence of CNS vasculitis Consideration of dura or brain biopsy
Benign angiitis of the CNS	Conventional, CT, or MR angiographic evidence of CNS vasculitis
Cogan syndrome	Ophthalmology and audiology evaluations Conventional, CT, or MR angiographic evidence of CNS or aortic vasculitis

CNS, central nervous system; CT, computed tomography; MR, magnetic resonance.

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Chapter 168

Musculoskeletal Pain Syndromes

Kelly K. Anthony and Laura E. Schanberg

Musculoskeletal pain is a frequent complaint of children presenting to general pediatricians and is the most common presenting problem of children referred to pediatric rheumatology clinics. Prevalence estimates of persistent musculoskeletal pain in community samples range from roughly 10-30%. Although diseases such as juvenile idiopathic arthritis and systemic lupus erythematosus may manifest as persistent musculoskeletal pain, the majority of musculoskeletal pain complaints in children turn out to be benign in nature and attributable to trauma, overuse, and normal skeletal growth variations. There is a subset of children in whom chronic pain complaints develop in the absence of physical and laboratory abnormalities. Children with idiopathic musculoskeletal pain syndromes, also typically develop marked subjective distress and functional impairment. Therefore, the treatment of children with musculoskeletal pain syndromes optimally includes both pharmacologic and nonpharmacologic interventions.

CLINICAL MANIFESTATIONS

Chronic musculoskeletal pain syndromes involve pain complaints of at least 3 mo in duration in the absence of objective abnormalities on physical examination and laboratory screening. Additionally, children and adolescents with musculoskeletal pain syndromes often complain

of persistent pain despite previous treatment with nonsteroidal antiinflammatory drugs and analgesic agents. The location varies, with pain complaints either localized to a single extremity or more diffuse and involving multiple extremities. It is not uncommon for the pain to start in a single area of the body before intensifying and radiating to other areas over time. The prevalence of musculoskeletal pain syndromes increases with age and is higher in females, thus rendering adolescent girls at highest risk.

The somatic complaints of children and adolescents with musculoskeletal pain syndromes are commonly accompanied by psychological distress, sleep difficulties, and functional impairment across home, school, and peer domains. Psychological distress may include symptoms of anxiety and depression, such as frequent crying spells, fatigue, sleep disturbance, feelings of worthlessness, poor concentration, and frequent worry. Indeed, a substantial number of children with musculoskeletal pain syndromes display the full range of psychological symptoms warranting an additional diagnosis of a comorbid mood or anxiety disorder (e.g., major depressive episode, generalized anxiety disorder). **Sleep disturbance** in children with musculoskeletal pain syndromes may include difficulty falling asleep, multiple night awakenings, disrupted sleep-wake cycles with increased daytime sleeping, nonrestorative sleep, and fatigue.

For children and adolescents with musculoskeletal pain syndromes, the constellation of pain, psychological distress, and sleep disturbance often leads to a high degree of functional impairment. Poor school attendance is common, and children may struggle to complete other daily activities relating to self-care and participation in household chores. Decreased physical fitness can also occur, as well as changes in gait and posture, as children avoid contact with or use of the body area affected by pain. Peer relationships may also be disrupted due to decreased opportunities for social interaction due to pain. As such, children and adolescents with musculoskeletal pain syndromes often report loneliness and social isolation characterized by having few friends and lack of participation in extracurricular activities.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of a musculoskeletal pain syndrome is typically one of exclusion when careful, repeated physical examinations and laboratory testing do not reveal an etiology. At initial presentation, children with pain complaints require a thorough clinical history and a complete physical examination to look for an obvious etiology (e.g., sprains, strains, or fractures), characteristics of the pain (localized or diffuse), and evidence of systemic involvement. A comprehensive history can be particularly useful in providing clues to the possibility of underlying illness or systemic disease. The presence of current or recent fever can be indicative of an inflammatory or neoplastic process if the pain is also accompanied by worsening symptoms over time or weight loss.

Subsequent, repeated physical examinations of children with musculoskeletal pain complaints may reveal eventual development and manifestations of rheumatic or other diseases. The need for additional testing should be individualized, depending on the specific symptoms and physical findings. Laboratory screening and/or radiographs should be pursued if there is suspicion of certain underlying disease processes. Possible indicators of a serious, as opposed to a benign, cause of musculoskeletal pain include pain present at rest and relieved by activity, objective joint swelling on physical examination, stiffness or limited range of motion in joints, bony tenderness, muscle weakness, poor growth and/or weight loss, and constitutional symptoms (e.g., fever, malaise) (Table 168-1). In the case of laboratory screenings, a complete blood count and erythrocyte sedimentation rate are likely to be abnormal in children whose pain is secondary to a bone or joint infection, systemic lupus erythematosus, or a malignancy. Bone tumors, fractures, and other focal pathology resulting from infection, malignancy, or trauma can often be indentified through imaging studies, including plain film x-rays, MRI, and technetium-99m bone scans.

The presence of persistent pain, accompanied by psychological distress, sleep disturbance, and/or functional impairment, in the absence of objective laboratory or physical examination abnormalities, suggest the diagnosis of a musculoskeletal pain syndrome. All pediatric musculoskeletal pain syndromes share this general constellation of symptoms at presentation. Several more specific pain syndromes routinely seen by pediatric practitioners can be differentiated by anatomic region and associated symptoms. Pediatric musculoskeletal pain syndromes are listed in Table 168-2 and includes growing pains (see Chapter 168.1), fibromyalgia (see Chapter 168.3), complex regional pain syndrome (see Chapter 168.4), localized pain syndromes, low back pain, and chronic sports-related pain syndromes (e.g., Osgood-Schlatter disease).

TREATMENT

The primary goal of treatment for pediatric musculoskeletal pain syndromes is to improve function rather than relieve pain, and these two desirable outcomes may not occur simultaneously. Indeed, it is common for children with musculoskeletal pain syndromes to continue complaining of pain even as they resume normal function (e.g., increased school attendance and participation in extracurricular activities). For all children and adolescents with pediatric musculoskeletal pain syndromes, regular school attendance is crucial, as this is a hallmark of normal functioning in this age group. The dual nature of treatment, targeting both function and pain, needs to be clearly

Table 168-1 Potential Indicators of Benign Versus Serious Causes of Musculoskeletal Pain

CLINICAL FINDING	BENIGN CAUSE OF MUSCULOSKELETAL PAIN	SERIOUS CAUSE OF MUSCULOSKELETAL PAIN
Effects of rest versus activity on pain	Relieved by rest and worsened by activity	Relieved by activity and present at rest
Time of day pain occurs	End of the day and nights	Morning*
Objective joint swelling	No	Yes
Joint characteristics	Hypermobile/normal	Stiffness, limited range of motion
Bony tenderness	No	Yes
Muscle strength	Normal	Muscle weakness
Growth	Normal growth pattern or weight gain	Poor growth and/or weight loss
Constitutional symptoms (e.g., fever, malaise)	Fatigue without other constitutional symptoms	Yes
Lab findings	Normal CBC, ESR, CRP	Abnormal CBC, raised ESR and CRP
Radiographic findings	Normal	Effusion, osteopenia, radiolucent metaphyseal lines, joint space loss, bony destruction

CBC, complete blood count; CRP, C-reactive protein level; ESR, erythrocyte sedimentation rate.
*Cancer pain is often severe and worst at night.
Adapted from Malleson PN, Beauchamp RD: Diagnosing musculoskeletal pain in children. CMAJ *165:183–188, 2001.*

Table 168-2 Common Musculoskeletal Pain Syndromes in Children by Anatomic Region

ANATOMICAL REGION	PAIN SYNDROMES	
Shoulder	Impingement syndrome	
Elbow	Little League elbow Avulsion fractures Osteochondritis dissecans	Tennis elbow Panner disease
Arm	Localized hypermobility syndrome Complex regional pain syndrome	
Pelvis and hip	Avulsion injuries Legg-Calvé-Perthes syndrome	Slipped capital femoral epiphysis Congenital hip dysplasia
Knee	Osteochondritis dissecans Osgood-Schlatter disease Sinding-Larsen syndrome	Patellofemoral syndrome Malalignment syndromes
Leg	Growing pains Complex regional pain syndrome Localized hypermobility syndrome	Shin splints Stress fractures Compartment syndromes
Foot	Plantar fasciitis Tarsal coalition Stress fractures	Achilles tendonitis Juvenile bunion
Spine	Musculoskeletal strain Spondylolisthesis Spondylolysis	Scoliosis Scheuermann disease (kyphosis) Low back pain
Generalized	Hypermobility syndrome Juvenile fibromyalgia Generalized pain syndrome	

Adapted from Anthony KK, Schanberg LE. Box 1 in assessment and management of pain syndromes and arthritis pain in children and adolescents. Rheum Dis Clin North Am *33:625–660, 2007.*

explained to children and their families to better outline the goals by which treatment success will be measured. Indeed, children and families need to be supported in disengaging from the sole pursuit of pain relief and embracing broader treatment goals of improved functioning.

Recommended treatment modalities typically include physical and/or occupational therapy, pharmacologic interventions, and cognitive-behavioral and/or other psychotherapeutic interventions. The overarching goal of physical therapy is to improve children's physical function and should emphasize participation in aggressive, but graduated aerobic exercise. Pharmacologic interventions should be used judiciously. Low-dose tricyclic antidepressants (amitriptyline 10-50 mg orally 30 min before bedtime) are indicated for treatment of sleep disturbance; selective serotonin reuptake inhibitors (sertraline 10-20 mg daily) may prove useful in treating symptoms of depression and anxiety if present. Referral for psychological evaluation is warranted if these symptoms do not resolve with initial treatment efforts or if suicidal ideation is present. Cognitive-behavioral and/or other psychotherapeutic interventions are typically designed to teach children and adolescents coping skills for controlling the behavioral, cognitive, and physiologic responses to pain. Specific components often include cognitive restructuring, relaxation, distraction, and problem-solving skills; additional targets of therapy include sleep hygiene and activity scheduling, all with the goal of restoring normal sleep patterns and activities of daily living. Parent education and involvement in the psychological intervention is important to ensure maintenance of progress. More intensive family-based approaches are warranted if barriers to treatment success are identified at the family level. These could include parenting strategies or family dynamics that serve to maintain children's pain complaints, such as overly solicitous responses to child pain, and maladaptive models for pain coping in the family.

COMPLICATIONS AND PROGNOSIS

Musculoskeletal pain syndromes can negatively affect child development and future role functioning. Worsening pain and the associated symptoms of depression and anxiety can lead to substantial school absences, peer isolation, and developmental delays later in adolescence and early adulthood. Specifically, adolescents with musculoskeletal pain syndromes may fail to achieve the level of autonomy and independence necessary for age-appropriate activities such as attending college, living away from home, and maintaining a job. Fortunately, not all children and adolescents with musculoskeletal pain syndromes experience this degree of impairment and the likelihood of positive health outcomes is increased with multidisciplinary treatment.

168.1 Growing Pains

Kelly K. Anthony and Laura E. Schanberg

More appropriately termed **benign nocturnal pains of childhood** growing pains affect 10-20% of children, with a peak age incidence between 4 and 12 yr. Pain does not occur during periods of rapid growth or at growth sites. The most common cause of recurrent musculoskeletal pain in children, growing pains are intermittent and bilateral, predominantly affecting the anterior thigh, shin, and calf but not joints. Occasionally there may be bilateral upper extremity pain associated with leg pain; isolated upper extremity pain does not occur. Children most commonly describe cramping or aching that occurs in the late afternoon or evening. Pain may wake the child from sleep and may last a few minutes to hours, but resolves quickly with massage or analgesics; pain is never present the following morning (Table 168-3). Pain often follows a day with exercise or other physical activities. Physical findings are normal, and gait is not impaired. Growing pains are generally considered a benign, time-limited condition; there is evidence suggesting that growing pains represent a pain amplification syndrome. Indeed, growing pains persist in a significant percentage of children, with some children developing other pain syndromes such as abdominal pain and headaches. Growing pains are more likely to persist in children with a parent who has a history of a pain syndrome and in children who have lower pain thresholds. Treatment should also focus on reassurance, education, and healthy sleep hygiene. Massage

Table 168-3 Definition of "Growing Pains"

	INCLUSIONS	EXCLUSIONS
Nature of pain	Intermittent; some pain-free days and nights, deep aching, cramping	Persistent; increasing intensity, pain during the day
Unilateral or bilateral	Bilateral	Unilateral
Location of pain	Anterior thigh, calf, posterior knee—in muscles	Articular, back, or groin pain
Onset of pain	Late afternoon or evening	Pain still present next morning
Physical findings	Normal	Swelling, erythema, tenderness; local trauma or infection; reduced joint range of motion; limping, fever, weight loss, mass
Laboratory findings	Normal	Objective evidence of abnormalities; increased erythrocyte sedimentation rate, C-reactive protein, abnormal complete blood count, radiography, bone scan or MRI

From Evans AM, Scutter SD: Prevalence of "growing pains" in young children, J Pediatr 145:255–258, 2004.

during the episode is very effective, and nonsteroidal antiinflammatory drugs agents may be useful for frequent episodes.

Restless leg syndrome, seen more commonly among adults, is a sensorimotor disturbance that may be confused with growing pains (see Chapter 19). Restless leg syndrome is a difficult to control urge to move the leg that is exacerbated during rest and at night and is relieved by movement.

168.2 Small Fiber Polyneuropathy

Kelly K. Anthony and Laura E. Schanberg

Many patients with juvenile onset widespread pain syndromes, as well as patients with pediatric fibromyalgia (see Chapter 168.3), complex regional pain syndrome type I (see Chapter 168.4), and erythromelalgia have evidence of a small fiber polyneuropathy causing dysfunctional or degeneration of small diameter unmyelinated C-fibers and thinly myelinated A-delta fibers that mediate nociception and the autonomic nervous system. Fibromyalgia (see Chapter 168.3) includes chronic widespread pain defined as ≥3 mo duration of axial pain that is often bilateral and also affects the upper and lower extremities. In addition, many patients have associated chronic cardiovascular (dizziness, postural orthostasis syndrome) symptoms, as well as chronic abdominal pain and ileus, headaches, fatigue and erythromelalgia, suggestive of dysautonomia.

There are no typical findings on physical exam or standard laboratory tests. The diagnosis of small fiber polyneuropathy requires distal leg skin immunolabeled biopsy to identify epidermal nociceptive fibers and autonomic function testing to examine cardiovagal, adrenergic, and sudomotor small fiber function.

Treatment of patients with small fiber polyneuropathy and isolated juvenile-onset widespread pain syndrome, or those subsets of patients with small fiber polyneuropathy and fibromyalgia, complex regional pain syndrome, or erythromelalgia is evolving and has included prednisone or intravenous immunoglobulin.

Bibliography is available at Expert Consult.

168.3 Fibromyalgia

Kelly K. Anthony and Laura E. Schanberg

Juvenile primary fibromyalgia syndrome (JPFS) is a common pediatric musculoskeletal pain syndrome. Approximately 25-40% of children with chronic pain syndromes can be diagnosed with JPFS. Although specific diagnostic criteria for JPFS have not been determined, children and adolescents with JPFS have diffuse, multifocal, waxing and waning, and at times migratory musculoskeletal pain in at least 3 areas of the body that persists for at least 3 mo in the absence of an underlying condition. Results of laboratory tests are normal, and physical examination reveals at least 5 well-defined tender points (Fig. 168-1). Children and adolescents with JPFS also present with many associated symptoms, including nonrestorative sleep, fatigue, paresthesias, chronic anxiety or tension, chronic headaches, subjective soft-tissue swelling, and pain modulated by physical activity, weather, and anxiety or stress. There is considerable overlap among symptoms associated with JPFS and complaints associated with other **functional disorders** (e.g., irritable bowel disease, migraines, temporomandibular joint disorder, premenstrual syndrome, mood and anxiety disorders, and chronic fatigue syndrome), raising speculation that these disorders may be part of a larger spectrum of related syndromes.

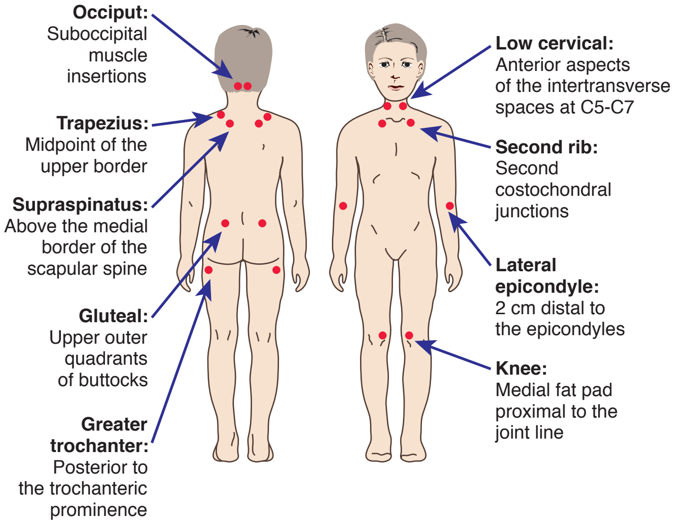

Figure 168-1 Fibromyalgia tender points.

Although the precise cause of JPFS is unknown, there is an emerging understanding that the development and maintenance of JPFS are related both to biologic and psychological factors. JPFS is an abnormality of central pain processing characterized by disordered sleep physiology, enhanced pain perception with abnormal levels of substance P in cerebrospinal fluid, disordered mood, and dysregulation of hypothalamic–pituitary–adrenal and other neuroendocrine axes resulting in lower tender-point pain thresholds and increased pain sensitivity. Children and adolescents with fibromyalgia often find themselves in a vicious cycle of pain, whereby symptoms build upon one another and contribute to the onset and maintenance of new symptoms (Fig. 168-2).

JPFS has a chronic course that can detrimentally affect child health and development. Adolescents with JPFS who do not receive

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Figure 168-2 Vicious cycle promoting juvenile primary fibromyalgia syndrome symptom maintenance. *(Adapted from Anthony KK, Schanberg LE. Juvenile primary fibromyalgia syndrome.* Curr Rheumatol Rep *3:167–171, 2001, Fig. 1.)*

treatment or are inadequately treated may withdraw from school and the social milieu, complicating their transition to adulthood. Treatment of JPFS generally follows consensus statements of the American Pain Society. The major goals are to restore function and alleviate pain, as well as improve comorbid mood and sleep disorders. Treatment strategies include parent/child education, pharmacologic interventions, exercise-based interventions, and psychological interventions. Graduated aerobic exercise is the recommended exercise-based intervention, whereas psychological interventions should include training in pain coping skills, stress management skills, emotional support, and sleep hygiene. Cognitive-behavioral interventions are particularly effective in reducing symptoms of depression in children and adolescents with JPFS and also help to reduce functional disability. Drug therapies, although largely unsuccessful in isolation, may include tricyclic antidepressants (amitriptyline 10-50 mg orally 30 min before bedtime), selective serotonin reuptake inhibitors (sertraline 10-20 mg daily), and anticonvulsants. Pregabalin and duloxetine hydrochloride are approved by the FDA for treatment of fibromyalgia in adults (18 yr of age and older), but neither has been studied in children. Muscle relaxants are generally not used in children because they affect school performance.

Evolving evidence suggests that up to 50% of patients with fibromyalgia may have a small fiber polyneuropathy (see Chapter 168.2).

Bibliography is available at Expert Consult.

168.4 Complex Regional Pain Syndrome

Kelly K. Anthony and Laura E. Schanberg

Complex regional pain syndrome (CRPS) is characterized by ongoing burning limb pain that is subsequent to an injury, immobilization, or another noxious event affecting the extremity. CRPS1, formerly called reflex sympathetic dystrophy, has no evidence of nerve injury, whereas CRPS2, formerly called causalgia, follows a prior nerve injury. Key associated features are pain disproportionate to the inciting event, persisting **allodynia** (a heightened pain response to normally non-noxious stimuli), **hyperalgesia** (exaggerated pain reactivity to noxious stimuli), swelling of distal extremities, and indicators of **autonomic dysfunction** (i.e., cyanosis, mottling, and hyperhidrosis) (Table 168-4).

The diagnosis requires the following: an initiating noxious event or immobilization; continued pain, allodynia, and hyperalgesia out of proportion to the inciting event; evidence of edema, skin blood flow abnormalities, or sudomotor activity; and exclusion of other disorders. Associated features include atrophy of hair or nails; altered hair growth; loss of joint mobility; weakness, tremor, dystonia; and sympathetically maintained pain.

Table 168-4 Diagnostic Criteria for Complex Regional Pain Syndrome*

NEUROPATHIC DESCRIPTORS	AUTONOMIC DYSFUNCTION
Burning	Cyanosis
Dysesthesia	Mottling
Paresthesia	Hyperhidrosis
Allodynia	Coolness (≥3°)
Cold hyperalgesia	Edema

*A diagnosis of CRPS requires regional pain, sensory symptoms, plus 2 neuropathic pain descriptors and 2 physical signs of autonomic dysfunction.

Data from Wilder RT, Berde CB, Wolohan, M, et al. Reflex sympathetic dystrophy in children: clinical characteristics and follow-up of seventy patients. J Bone Joint Surg Am *74: 910–919, 1992.*

Although the majority of pediatric patients with CRPS present with a history of minor trauma or repeated stress injury (e.g., caused by competitive sports), a sizeable proportion are unable to identify a precipitating event. Usual age of onset is between 8 and 16 yr, and girls outnumber boys with the disease by as much as 6:1. Childhood CRPS differs from the adult form in that lower extremities, rather than upper extremities, are most commonly affected. The incidence of CRPS in children is unknown, largely because it is often undiagnosed or diagnosed late, with the diagnosis frequently delayed by nearly a year. Left untreated, CRPS can have severe consequences for children including bone demineralization, muscle wasting, and joint contractures.

An evidence-based approach to the treatment of CRPS continues to suggest a multistage treatment approach. Aggressive physical therapy should be initiated as soon as the diagnosis is made and cognitive-behavioral interventions (CBT) added as needed. Physical therapy (PT) is recommended 3-4 times per week, and children may need analgesic premedication at the onset, particularly prior to PT sessions. PT is initially limited to desensitization and then moves to weight-bearing, range-of-motion, and other functional activities. CBT used as an adjunctive therapy targets psychosocial obstacles to fully participating in PT and provides pain coping skills training. Sympathetic and epidural nerve blocks should be attempted only under the auspices of a pediatric pain specialist. The intent of both pharmacologic and adjunctive treatments for CRPS is to provide sufficient pain relief to allow the child to participate in aggressive physical rehabilitation. If CRPS is identified and treated early, the majority of children and adolescents with the disease can be treated successfully with low-dose amitriptyline (10-50 mg orally 30 min prior to bedtime), aggressive PT, and CBT interventions. Opioids and anticonvulsants such as gabapentin can also be helpful. Notably, multiple studies have shown noninvasive treatments, particularly PT and CBT, are at least as efficacious as nerve blocks in helping children with CRPS achieve resolution of their symptoms.

There is growing evidence that some patients with CRPS I have a small fiber polyneuropathy (see Chapter 168.2).

Bibliography is available at Expert Consult.

168.5 Erythromelalgia

Laura E. Schanberg

Children with **erythromelalgia** experience episodes of intense pain, erythema, and heat in their hands and feet (Fig. 168-3). Less commonly involved are the face, ears, or knees. Symptoms may be triggered by exercise and exposure to heat, lasting for hours and occasionally for days. It is more common in girls and in the teenage years and diagnosis is often delayed for years. Although most cases are sporadic, an

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Figure 168-3 Typical redness and edema of the foot in erythromelalgia. *(From Pfund Z, Stankovics J, Decsi T, Illes Z. Childhood steroid-responsive acute erythromelalgia with axonal neuropathy of large myelinated fibers: A dysimmune neuropathy?* Neuromuscul Disord *19:49-52, 2009, Fig. 1A, p. 50.)*

autosomal dominant hereditary form results from mutations of the SCN9A gene on chromosome 2q31-32, causing a painful channelopathy. Secondary erythromelalgia is associated with an array of disorders, including myeloproliferative diseases, peripheral neuropathy, frostbite, hypertension, and rheumatic disease. Treatment includes avoidance of heat exposure as well as other precipitating situations and the utilization of cooling techniques that do not cause tissue damage during attacks. Nonsteroidal antiinflammatories, narcotics, anesthetic agents (lidocaine patch), anticonvulsants (oxcarbazepine, carbamazepine, gabapentin), and antidepressants, as well as biofeedback and hypnosis may be useful in helping manage pain. Drugs acting on the vascular system (aspirin, sodium nitroprusside, magnesium, misoprostol) may also be somewhat effective. However, a reliably efficacious treatment is not available, resulting in substantial negative impact on physical and mental health.

There is growing evidence that some patients with erythromelalgia have a small fiber polyneuropathy (see Chapter 168.2).

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Chapter 169

Miscellaneous Conditions Associated with Arthritis

Reut Gurion, Angela Byun Robinson, and C. Egla Rabinovich

RELAPSING POLYCHONDRITIS

Relapsing polychondritis (RP) is a rare condition characterized by episodic chondritis causing cartilage destruction and deformation of the ears (sparing the earlobes), nose, larynx and tracheobronchial tree. Antibodies to matrillin-1 and collagen (types II, IX and XI) are present in approximately 60% of patients with RP, suggesting an autoimmune pathogenesis. Patients may experience arthritis, uveitis, and hearing loss due to inflammation near the auditory and vestibular nerves. Children may initially relate episodes of intense erythema over the outer ears. Other dermatologic manifestations such as erythema nodosum, maculopapular rash and purpura may be seen. Cardiac involvement, including conduction defects and coronary vasculitis, has been reported. Severe, progressive, and potentially fatal disease resulting from destruction of the tracheobronchial tree and airway obstruction is unusual in childhood. Diagnostic criteria established for adults are useful guidelines for evaluating children with suggestive symptoms (Table 169-1). The clinical course of RP is variable; flares of disease are often associated with elevations of acute-phase reactants and may remit spontaneously. Although seen more commonly in the adult population, RP may coexist with other inflammatory diseases, such as systemic lupus erythematosus, Sjögren syndrome, and Henoch-Schönlein purpura. The differential diagnosis includes antineutrophilic cytoplasmic antibody–associated vasculitis (granulomatosis with polyangiitis) (see Chapter 167.4) and Cogan syndrome, which is characterized by auditory nerve inflammation and keratitis but not chondritis. Many children respond to nonsteroidal antiinflammatory drugs, but some require corticosteroids or other immunosuppressive agents (azathioprine, methotrexate, hydroxychloroquine, colchicine, cyclophosphamide, cyclosporine, and anti–tumor necrosis factor agents), as reported in small series and case reports.

Table 169-1	Empiric Diagnostic Criteria for Relapsing Polychondritis*
MAJOR CRITERIA	
Proven inflammatory episodes involving auricular cartilage	
Proven inflammatory episodes involving nasal cartilage	
Proven inflammatory episodes involving laryngotracheal cartilage	
MINOR CRITERIA	
Ocular inflammation (conjunctivitis, keratitis, episcleritis, uveitis)	
Hearing loss	
Vestibular dysfunction	
Seronegative inflammatory arthritis	

*The diagnosis is established by the presence of 2 major criteria or of 1 major and 2 minor criteria. Histologic examination of affected cartilage is not required.

From Michet CJ Jr, McKenna CH, Luthra HS, et al: Relapsing polychondritis: survival and predictive role of early disease manifestations, Ann Intern Med *104:74–78, 1986.*

MUCHA-HABERMANN DISEASE/PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA

Pityriasis lichenoides et varioliformis acuta (PLEVA) is a benign, self-limited cutaneous vasculitis characterized by episodes of macules, papules, and papulovesicular lesions that can develop central ulceration, necrosis, and crusting. Different stages of development are usually seen at once. **PLEVA fulminans** or **febrile ulceronecrotic Mucha-Habermann disease** is the severe, life-threatening form of PLEVA. Large coalescing ulceronecrotic lesions are seen, and are accompanied by high fever and an elevated erythrocyte sedimentation rate. Systemic manifestations can include interstitial pneumonitis, abdominal pain, malabsorption, arthritis, and neurologic manifestations. There is a male predominance and it occurs more frequently in childhood. The diagnosis is confirmed by biopsy of skin lesions that reveal perivascular and intramural lymphocytic inflammation affecting capillaries and venules in the upper dermis that may lead to keratinocyte necrosis. When disease is severe, corticosteroids have been used with questionable effect, and methotrexate has been reported to induce rapid remission in resistant cases. Cyclosporine and anti–tumor necrosis factor agents have been efficacious in case reports.

SWEET SYNDROME

Sweet syndrome, or **acute febrile neutrophilic dermatosis,** is a rare entity in children. It is characterized by fever, elevated neutrophil count, and raised, tender erythematous plaques and nodules over the

Table 169-2 Diagnostic Criteria for Classic Sweet Syndrome*

MAJOR CRITERIA
Abrupt onset of painful erythematous plaques or nodules
Histopathologic evidence of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis
MINOR CRITERIA
Pyrexia >38°C (100.4°F)
Association with underlying hematologic or visceral malignancy, inflammatory disease or pregnancy, *or* preceded by an upper respiratory or gastrointestinal infection or vaccination
Excellent response to systemic corticosteroids or potassium iodide
Abnormal laboratory values at presentation (3 of 4): erythrocyte sedimentation rate >20 mm/hr, positive C-reactive protein test result, >8,000 leukocytes/mm^3, >70% neutrophils/mm^3

*The diagnosis is established by the presence of 2 major criteria plus 2 of the 4 minor criteria.

From Cohen PR: Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis, Orphanet J Rare Dis *2:34, 2007.*

face, extremities, and trunk. Skin biopsy reveals neutrophilic perivascular infiltration in the upper dermis. Female predominance is seen in the adult population, whereas in children, gender distribution is equal. Established criteria are useful for diagnosis (Table 169-2). Children can also have arthritis, sterile osteomyelitis, myositis, and other extracutaneous manifestations. The syndrome may be idiopathic or secondary to malignancy (particularly acute myelogenous leukemia), drugs (granulocyte colony-stimulating factor), or rheumatic diseases (Behçet disease, antiphospholipid antibody syndrome, systemic lupus erythematosus). The condition usually responds to treatment with corticosteroids.

HYPERTROPHIC OSTEOARTHROPATHY

Children with chronic disease, especially pulmonary or cardiac disease, can demonstrate clubbing of the terminal phalanges, and have associated periosteal reaction and arthritis. These findings characterize the classic presentation of **hypertrophic osteoarthropathy (HOA)**. HOA can be primary (idiopathic), or secondary. Although rare, secondary HOA is more common in children, and is seen in children with chronic pulmonary disease (cystic fibrosis), congenital heart disease, gastrointestinal disease (malabsorption syndromes, biliary atresia, inflammatory bowel disease), and malignancies (nasopharyngeal sarcoma, osteosarcoma, Hodgkin disease). HOA may precede diagnosis of cardiopulmonary disease or malignancy. The pathogenesis of HOA is unknown; symptoms often improve if the underlying condition is treated successfully. HOA-related pain can be disabling, and in adults management with bisphosphonates has been reported. Evaluation of children presenting with HOA should include a chest radiograph to evaluate for pulmonary disease or intrathoracic mass.

PLANT THORN SYNOVITIS

A diagnosis of plant thorn synovitis should be considered in children with monoarticular arthritis nonresponsive to antiinflammatory therapy. Acute or chronic arthritis can occur after a plant thorn or other foreign object penetrates a joint. Unlike septic arthritis, children with plant thorn synovitis are commonly afebrile. The most common organism seen with plant thorn synovitis is *Pantoea agglomerans*, although cultures are often negative. The initial injury may be unknown or forgotten, making diagnosis difficult. Ultrasound or magnetic resonance imaging can be useful in identifying the foreign body. Removal of the foreign body via arthroscopy followed by an antibiotic course is the accepted therapy.

PIGMENTED VILLONODULAR SYNOVITIS

Proliferation of synovial tissue is seen in **pigmented villonodular synovitis** (PVNS). This proliferation is either localized or diffuse, and can affect the joint, tendon sheath or bursa. Macrophages and multinucleated giant cells with brownish hemosiderin are present histologically. It is unclear if the etiology of PVNS is inflammatory or neoplastic in nature. Although findings are not pathognomonic, MRI with contrast is a useful diagnostic tool where PVNS can be seen as a mass or bone erosion. Brown or bloody synovial fluid is seen with arthrocentesis, but the diagnosis is made by tissue biopsy. Surgical removal of the affected tissue is the therapeutic modality, and with diffuse disease, a total synovectomy is recommended.

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Infectious Diseases

PART XVII

Section 1

General Considerations

Chapter 170

Diagnostic Microbiology

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Laboratory evidence to support the diagnosis of an infectious disease may be based on 1 or more of the following: direct examination of specimens using microscopic or antigen detection techniques, isolation of microorganisms in culture, serologic testing, host gene expression patterns, and molecular detection of an organism, resistance determinant, or virulence factor. Additional important roles of the diagnostic microbiology lab are antimicrobial susceptibility testing to guide in the selection of the most appropriate antimicrobial therapy and supporting hospital infection prevention in the detection and characterization of pathogens associated with nosocomial infections.

SPECIMEN COLLECTION

The success of microbiology cultures, that is, isolation of a pathogen if present, is directly linked to specimen collection techniques. In general, this means collecting the correct specimen type for the disease or condition in question and promptly transporting the specimen to the laboratory for analysis. Although for some conditions swab specimens may be necessary, in general, a swab is a suboptimal specimen. A swab is only able to hold a very small amount of specimen (approximately 100 μL), and using a traditional swab, only a small fraction of organisms that are absorbed onto a swab will be released back into the culture. Flocked swabs, coupled with transport medium, improve organism recovery. However, when possible, fluid or tissue should be submitted to the laboratory for analysis. If anaerobic infection is suspected, the sample should be transported in appropriate medium to preserve viability of anaerobic bacteria. For the recovery of some organism types, such as viruses and *Neisseria gonorrhoeae*, specific transport media may be required. Considerations specific to the collection of blood cultures will be addressed in the blood culture section.

LABORATORY DIAGNOSIS OF BACTERIAL AND FUNGAL INFECTIONS

Although the scope and availability of molecular methods for detection of bacterial and fungal pathogens is increasing at a rapid pace, the state-of-the art for the diagnosis of many of these infections is dependent upon microscopic detection of organisms or cultivation of organisms on culture media.

Microscopy

The Gram stain is an extremely valuable diagnostic technique to provide rapid and inexpensive information regarding the absence or presence of inflammatory cells and organisms in clinical specimens. For some specimen types, the presence of inflammatory and epithelial cells is used to judge the suitability of a specimen for culture. For example, the presence of more than 10 epithelial cells per low-power field in a sputum specimen is highly suggestive of a specimen contaminated with oral secretions. In addition, a preliminary assessment of the etiologic agent can be made based upon the morphology (e.g., cocci vs rods) and stain reaction (e.g., Gram-positive isolates are purple; Gram-negative are red) of the microorganisms. However, a negative Gram stain does not rule out infection as 10^4 to 10^5 microorganisms per mL in the specimen are required for detection by this method.

In addition to the Gram stain, many other stains are used in microbiology, both to detect organisms and to help infer their identity. Table 170-1 provides an overview of the most commonly used stains.

Isolation and Identification

The approach to isolation of microorganisms in a clinical specimen will vary depending on the body site and pathogen suspected. For body sites that are usually sterile, such as cerebrospinal fluid, nutrient-rich media such as sheep blood agar and chocolate agar are used to aid in the recovery of fastidious pathogens. In contrast, stool specimens contain abundant amounts of commensal bacteria and thus to isolate pathogens, selective and differential media must be used. Selective media will inhibit the growth of some organisms to aid in isolation of suspect pathogens; differential media rely on growth characteristics or carbohydrate assimilation characteristics to impart a growth pattern that differentiates organisms. MacConkey agar supports growth of Gram-negative rods while suppressing Gram-positive organisms, and a color change in the media from clear to pink distinguishes lactose-fermenting organisms from other Gram-negative rods. Special media, such as Sabouraud dextrose agar and inhibitory mold agar, are used to recover fungi in clinical specimens. Many pathogens, including *Bartonella*, *Bordetella pertussis*, *Legionella*, *Mycoplasma*, and certain fungal pathogens such as *Malassezia furfur*, require specialized growth media or incubation conditions. Consultation with the laboratory is advised when these pathogens are suspected.

Once an organism is recovered in culture, additional testing will be performed to identify the isolate. Confirmation of microbial identity has classically been performed using phenotypic tests that rely on the phenotypic properties of an isolate. Some examples include carbohydrate assimilation patterns, indole production, and motility. However, these methods are not able to resolve all organisms to species level and require incubation time. In some instances, sequence based identification, for bacteria usually based on sequence analysis of the **bacterial 16S rRNA gene**, is used for organism identification (particularly organisms that are difficult to culture).

Matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a rapid and accurate technique that is based on generating a protein fingerprint of an organism and comparing that fingerprint to a library of known organisms to produce an identification. This method can identify bacteria or yeast growing in culture in a matter of minutes, and the consumable costs for these analyses are minimal.

Blood Culture

The performance of blood cultures is one of the most important functions of the clinical microbiology laboratory. Most blood cultures are performed by collecting blood into bottles of nutrient-rich broth to facilitate the growth of bacteria and yeast. Some blood culture media contain resins or other agents to help neutralize antibiotics that may be present in the patients' blood. Blood culture bottles are then incubated on an automated blood culture incubator that will monitor the blood culture bottle at regular intervals for evidence of growth. Once the instrument detects evidence of microbial growth, it will alarm to

Table 170-1 Stains Used for Microscopic Examination

TYPE OF STAIN	CLINICAL USE
Gram stain	Stains bacteria (with differentiation of Gram-positive and Gram-negative organisms), fungi, leukocytes, and epithelial cells
Potassium hydroxide (KOH)	A 10% solution dissolves cellular and organic debris and facilitates detection of fungal elements in clinical specimens
Calcofluor white stain	Nonspecific fluorochrome that binds to cellulose and chitin in fungal cell walls, can be combined with 10% KOH to dissolve cellular material
Ziehl-Neelsen and Kinyoun stains	Acid-fast stains, using basic carbolfuchsin, followed by acid–alcohol decolorization and methylene blue counterstaining Acid-fast organisms (e.g., *Mycobacterium*) resist decolorization and stain pink A weaker decolorizing agent is used for partially acid-fast organisms (e.g., *Nocardia, Cryptosporidium, Cyclospora, Isospora*)
Auramine-rhodamine stain	Acid-fast stain using fluorochromes that bind to mycolic acid in mycobacterial cell walls and resist acid–alcohol decolorization; usually performed directly on clinical specimens Acid-fast organisms stain orange-yellow against a black background
Acridine orange stain	Fluorescent dye that intercalates into DNA, used to aid in differentiation of organisms from debris during direct specimen examination, and also for detection of organisms that are not visible with Gram stain Bacteria and fungi stain orange, and background cellular material stains green
Lugol iodine stain	Added to wet preparations of fecal specimens for ova and parasites to enhance contrast of the internal structures (nuclei, glycogen vacuoles)
Wright and Giemsa stains	Primarily for detecting blood parasites (*Plasmodium, Babesia,* and *Leishmania*), detection of amoeba in preparations of cerebral spinal fluid, and fungi in tissues (yeasts, *Histoplasma*)
Trichrome stain	Stains stool specimens for identification of protozoa
Direct fluorescent-antibody stain	Used for direct detection of a variety of organisms in clinical specimens by using specific fluorescein-labeled antibodies (e.g., *Pneumocystis jiroveci,* many viruses)

alert the laboratory. Approximately 80% of blood cultures that will ultimately be positive are identified within the 1st 24 hr of incubation. A portion of broth from a blood culture bottle that has signaled positive is then Gram-stained and cultured onto appropriate growth media so that the organism can be isolated and identified. There are numerous pre-analytical variables that can influence the accuracy of blood culture results. In order to facilitate accurate interpretation of a positive blood culture, a minimum of 2 blood cultures drawn from different sites should be collected whenever possible. Growth of an organism that is part of the normal skin flora from a single blood culture raises concern that the isolate resulted from contamination of the culture.

To maximize detection of bloodstream infection, up to 4 blood cultures should be collected during a 24 hr period. Proper skin antisepsis is essential prior to blood collection. Chlorhexidine is frequently used for this purpose, but alcohol is also used. If blood is collected through an indwelling line, proper antisepsis prior to collection is also very important. The practice of obtaining blood for culture from intravascular catheters without accompanying peripheral venous blood cultures should be discouraged because it is difficult to determine the significance of coagulase-negative staphylococci and other skin flora or environmental organisms isolated from blood obtained from line cultures. Differential time to positivity of 2 hr or more between paired blood cultures drawn simultaneously from a catheter and peripheral vein is a useful indicator of catheter-related bloodstream infection.

The volume of blood collected is also an important factor in the recovery of bloodstream pathogens, especially as the number of organisms per milliliter of blood in sepsis may be low. The optimal amount of blood to collect from a pediatric patient varies depending on the weight of the child. The Clinical and Laboratory Standards Institute and Cumitech documents provide guidance on the amount of blood that is safe to collect from children of different sizes. Paired collection of aerobic and anaerobic blood culture bottles will result in maximal recovery of pathogens if present.

There are a number of rapid diagnostic assays that can be used directly on positive blood culture broth to identify pathogens commonly associated with bacteremia and some antimicrobial resistance determinants. Most of these rapid diagnostic assays are based on nucleic acid detection techniques. An example of this is the **Verigene system**, which can identify a number of streptococcal and enterococcal species, as well as *mecA* and *vanA* genes, in positive blood culture broth, in approximately 2 hr. MALDI-TOF MS can also be performed on blood culture broth that is positive for growth of microorganisms. These assays can help shorten the interval between a positive blood culture and definitive organism identification, with the goal of early optimization of antimicrobial therapy.

Detection of mycobacteria and some filamentous fungi (such as *Histoplasma capsulatum* and *Fusarium*) from the bloodstream is maximized using lysis-centrifugation techniques, such as the Isolator system (Wampole, Cranbury, NJ).

Cerebrospinal Fluid Culture

Cerebrospinal fluid (CSF) should be transported quickly to the laboratory and then cytocentrifuged to concentrate organisms for microscopic examination. CSF is routinely cultured on blood agar and chocolate agar, which support the growth of common pathogens causing meningitis. If tuberculosis is suspected, cultures for mycobacteria should be specifically requested. Culture of larger volumes of CSF (>5 mL) significantly improves yield of mycobacteria.

Historically, rapid antigen detection tests for bacterial pathogens such as *Haemophilus influenzae* type b and *Streptococcus pneumoniae* were used to attempt to detect organisms in CSF without the need for culture. These techniques have now been proven to lack sensitivity and, in some cases, specificity. It has been demonstrated that a cytospin Gram stain is as sensitive as bacterial antigen tests for detection of microorganisms in CSF. In contrast, the cryptococcal antigen test can be useful when cryptococcal meningitis is suspected. Historically, India Ink preparations were used to detect *Cryptococcus* in CSF,

but this method is insensitive compared to the antigen detection assay.

In the postvaccine era, the epidemiology of infectious meningitis is rapidly changing, and acute bacterial meningitis is now a relatively infrequent event in North America. Many CSF infections are associated with shunts or other hardware, and *Propionibacterium* and coagulase-negative staphylococci are the organisms most frequently isolated from shunt infections. The laboratory should include media to facilitate the growth of *Propionibacterium* in CSF specimens received from neurosurgery patients.

Urine Culture

Urine for culture (including colony count) can be obtained by collecting clean-voided midstream specimens, by catheterization, or by suprapubic aspiration. Urine samples collected by placing bags on the perineum are unacceptable for culture because samples are often contaminated. Rapid transport of urine to the laboratory (<2 hr) is imperative, and delay in transport or plating of specimens renders colony counts unreliable. Refrigeration or urine transport devices with boric acid preservative may be used when delay is unavoidable.

The specific colony counts used to define growth in a urine culture as "significant" are somewhat controversial and vary somewhat by laboratory. Urine obtained by suprapubic aspirate is normally sterile, and thus any organism growth is typically considered significant. Urine collected by catheterization is likely to reflect infection if there are $\geq 10^3$ to 10^4 organisms/mL. Clean-voided urine is considered abnormal if $\geq 10^4$ to 10^5 organisms/mL are present.

Genital Culture

N. gonorrhoeae is a fragile organism, and collection and transport in special medium is essential for efficient recovery. Selective agar, such as modified Thayer-Martin medium, should be used to enhance recovery of *N. gonorrhoeae* in clinical specimens, such as genital, anorectal, and pharyngeal swabs. Antimicrobial resistance is increasing in *N. gonorrhoeae,* although few clinical laboratories have the ability to perform antimicrobial susceptibility testing for this organism. In pediatric patients, the identification of an organism as *N. gonorrhoeae* should be confirmed using 2 independent methods.

Specimens for *Chlamydia trachomatis* culture are obtained by cotton-tipped, aluminum-shafted urethral swabs. Endocervical specimens, using swabs with aluminum or plastic shafts, should be collected by rubbing the swab vigorously against the endocervical wall to obtain as much cellular material as possible. *C. trachomatis* is an obligate intracellular organism and is cultured by inoculation into cell culture systems, followed by immunofluorescent staining with monoclonal antibody against the organism. Nonculture methods such as enzyme immunoassay (EIA) tests, direct immunofluorescent staining by monoclonal antibodies, and DNA amplification methods are widely used and are more cost-effective than culture.

Although **nucleic acid amplification assays (NAAT assays)** for *N. gonorrhoeae* and *C. trachomatis* are not FDA cleared for use in children, these assays are frequently used in this population to detect these organisms in urine specimens, endocervical and vaginal swabs, and penile swabs. The NAAT assays exhibit superior sensitivity compared to culture-based techniques. Some laboratories take the approach of confirming all NAAT-positive specimens with an alternative NAAT test that detects an alternative genetic target.

Throat and Respiratory Culture

Streptococcal pharyngitis and tonsillitis is a common diagnosis in pediatric patients; vigorous swabbing of the tonsillar area and posterior pharynx can be done to obtain a specimen for detection of group A streptococcus *(Streptococcus pyogenes).* Rapid antigen detection assays are frequently used when group A streptococcus pharyngitis is suspected. Negative rapid antigen assays should be confirmed using culture based techniques. NAAT assays for detection of group A streptococcus are also being used with increasing frequency. Most laboratories screen throat cultures exclusively for the presence of group A streptococci. However, large colony variants of group C and group G streptococci also cause pharyngitis, but are not associated with the same postinfectious sequelae attributed to group A streptococcus; laboratory practices for detecting and reporting group C and group G streptococci are variable and an area of controversy.

In addition to the detection of pathogenic streptococci, the clinical laboratory may query for diphtheria, gonococcal pharyngitis, or infection with *Arcanobacterium haemolyticum* in throat specimens. The laboratory should be notified if any of these pathogens are suspected to ensure that appropriate methods are used to recover these organisms if present.

Cultures for *Bordetella pertussis* can be obtained by aspiration or swabbing of the nasopharynx using a Dacron or calcium alginate swab. The aspirate or swab is inoculated onto special charcoal-blood (Regan-Lowe) or Bordet-Gengou media, although molecular assays are now frequently used for detection of *B. pertussis* in these specimens.

The cause of lower-respiratory-tract disease in children is frequently difficult to confirm microbiologically because of the challenge of obtaining adequate sputum specimens. Gram-stained smears of specimens should be performed to assess the adequacy of sputum samples; specimens with large numbers of epithelial cells (>10 per high-powered field) or with few neutrophils are unsuitable for culture, as there is a lack of correlation between upper respiratory tract flora and organisms causing lower-respiratory tract disease. For patients with cystic fibrosis, special media should be used to detect pathogens important in cystic fibrosis, such as *Burkholderia cepacia.*

Endotracheal aspirates from intubated patients may be useful if the Gram stain shows abundant neutrophils and bacteria, although pathogens recovered from such specimens might still reflect only contamination from the endotracheal tube or upper airway. Quantitative cultures of bronchoalveolar lavage fluid may be valuable for distinguishing upper respiratory tract contamination from lower tract disease.

If infection with *Legionella* is suspected, the laboratory should be alerted so that the specimen can be inoculated to special media (such as buffered charcoal yeast extract agar) to facilitate the recovery of this pathogen. The *Legionella* urinary antigen test is a sensitive and specific, noninvasive method for rapid detection of *Legionella pneumophila* serogroup 1.

The diagnosis of pulmonary tuberculosis in young children is best made by culture of early-morning gastric aspirates, obtained on 3 consecutive days. Sputum induction for obtaining specimens for mycobacterial culture has also proved useful in young children but requires skilled personnel and containment facilities to prevent exposure of healthcare workers. Cultures for *Mycobacterium tuberculosis* should be processed only in laboratories equipped with appropriate biologic safety cabinets and containment facilities. NAAT tests for detection of *M. tuberculosis* in smear-positive respiratory specimens are becoming more widely available.

Detection of Enteric Pathogens

In pediatric patients with diarrheal illnesses, culture of stool for enteric pathogens may be requested. A fresh stool specimen is preferred, but is not always possible to obtain. If there is an unavoidable delay in specimen transport, the specimens should be placed into an appropriate transport medium, such as Cary-Blair. Rectal swabs for enteric culture are also acceptable specimens if the swab is visibly soiled. In general, enteric cultures should be performed on specimens from outpatients or patients who have been hospitalized for fewer than 3 days, as nosocomial acquisition of an enteric pathogen is very unusual.

Stool specimens are typically plated on a series of selective and differential media to decrease the overgrowth of normal flora and recover pathogenic organisms if present. The specific pathogens queried vary by laboratory. Most laboratories in North America will routinely culture for *Salmonella*, *Shigella*, *Campylobacter,* and Shiga toxin–producing strains of *Escherichia coli*. The CDC recommends that all laboratories use an agar-based medium for recovery of *E. coli* O157 in addition to an assay for detection of Shiga toxin production for all specimens submitted for enteric culture. Practices surrounding the routine culture for *Yersinia enterocolitica*, *Vibrio cholerae*, *Edwardsiella*, *Aeromonas,* and *Plesiomonas* will vary with local epidemiology, and the

laboratory should always be notified if one of these pathogens is specifically suspected.

Clostridium difficile is an important cause of antibiotic-associated diarrhea. *C. difficile* was long characterized as a nosocomial pathogen of older adults, but community-associated disease is emerging and the incidence and severity of *C. difficile* infection in children is increasing. Although for many years laboratories relied on EIAs for detection of *C. difficile* toxins, these assays lack adequate sensitivity. Laboratories use nucleic acid detection methods to aid in the diagnosis of *C. difficile*. Testing for *C. difficile* in children <1 yr of age should be discouraged as a result of the high incidence of colonization in this patient population.

Viruses are an important cause of gastroenteritis in pediatric patients. Methods for viral detection will vary but may include antigen detection (e.g., for rotavirus or adenovirus 40/41) or nucleic acid detection methods (such as for norovirus).

In North America, the burden of parasitic gastroenteritis is low. Complete microscopic exams for ova and parasite detection in stool samples is usually of low yield, and antigen detection assays for *Cryptosporidium* and *Giardia*, the most commonly encountered agents, are a sensitive and cost-effective method for detection of these pathogens.

Multiplex nucleic acid detection tests for simultaneous detection of a dozen or more enteric pathogens, including bacteria, viruses, and parasites are emerging. It is not completely clear how these assays will be deployed by clinical laboratories.

Culture of Other Fluids and Tissues

Abscesses, wounds, pleural fluid, peritoneal fluid, joint fluid, and other purulent fluids are cultured onto solid agar and, in some cases, broth media. Whenever possible, fluid rather than swabs from infected sites should be sent to the laboratory, because culture of a larger volume of fluid can detect organisms present in low concentration. Anaerobic organisms are involved in many abdominal and wound abscesses. These specimens should be collected and transported to the laboratory rapidly in anaerobic transport tubes.

Although *Staphylococcus aureus* is the most common cause of bone and joint infections, *Kingella kingae* is an important cause of septic arthritis in children, especially in children <4 yr of age. The detection of *K. kingae* is maximized by inoculation of synovial fluid into blood culture broth in addition to plating on solid medium, as well as by molecular detection of *K. kingae* in specimens from young patients with suspected septic arthritis.

Screening Cultures

Clinical laboratories may perform surveillance cultures for specific pathogens either to assist infection control in identifying patients requiring contact isolation or for outbreak investigation. Screening cultures for detection of methicillin-resistant *S. aureus* or vancomycin-resistant enterococci may be routinely performed in certain patient populations. In addition, hospitals with carbapenem-resistant *Enterobacteriaceae* may screen patients for rectal carriage of these organisms. Chromogenic media are frequently used for this purpose. These media contain proprietary compounds to select for the agent of interest and result in growth of colored colonies to identify pathogens of interest.

ANTIMICROBIAL SUSCEPTIBILITY TESTING

Antimicrobial susceptibility tests are generally performed on organisms of clinical significance for which standards and interpretive criteria for susceptibility testing exist. In North America, most laboratories use commercial, automated systems for susceptibility testing. The output from these systems is a minimum inhibitory concentration (MIC) value and interpretation of that value as susceptible, intermediate, or resistant. The next most common technique is Kirby-Bauer disk diffusion, in which a standardized inoculum of the organism is seeded onto an agar plate. Antibiotic-impregnated filter paper disks are then placed on the agar surface. After overnight incubation, the zone of inhibition of bacterial growth around each disk is measured and compared with nationally determined standards for susceptibility or resistance.

A less-commonly used technique is broth or microbroth dilution testing. A standard concentration of a microorganism is inoculated into serially diluted concentrations of antibiotic, and the MIC in µg/mL, the lowest concentration of antibiotic required to inhibit growth of the microorganism, is determined. The E-test is a hybrid of disk diffusion and broth dilution and can be used to determine the MIC of individual antibiotics on an agar plate. It uses a paper strip impregnated with a known continuous concentration gradient of antibiotic that diffuses across the agar surface, inhibiting microbial growth in an elliptic zone. The MIC is read off the printed strip at the point at which the zone intersects the strip. Major advantages of the E-test are reliable interpretation, reproducibility, and applicability to organisms that require special media or growth conditions.

In addition to providing data to guide the treatment of individual patients, laboratories use aggregate susceptibility testing data to generate institution specific antibiogram reports. These reports summarize susceptibility trends for common organisms and can be used to guide empirical therapy prior to the availability of specific susceptibility testing results.

Antimicrobial susceptibility patterns are rapidly changing as microbes evolve new resistance mechanisms. Recommendations for performance standards for antimicrobial susceptibility tests and their interpretation are regularly updated by the Clinical and Laboratory Standards Institute.

FUNGAL CULTURES

Special growth media is used to recover fungi, both yeasts and molds, in clinical specimens. As most fungi prefer reduced growth temperatures, and some species grow slowly, fungal cultures are incubated at 30°C (86°F) for 4 wk.

Most yeasts are identified using methods similar to those used for bacteria. In contrast, the identification of filamentous fungi has not changed in nearly a century. The laboratory takes into consideration the growth rate, color, and colony characteristics of an isolate and then prepares the specimen in lactophenol alanine blue for microscopic evaluation. These features in aggregate are used to identify the isolate. In some cases, DNA sequencing is used for fungal identification and MALDI-TOF MS is also emerging for identification of filamentous fungi. All manipulations of filamentous fungi should take place in the biologic safety cabinet to avoid infecting laboratory personnel and prevent laboratory contamination.

Antigen detection assays are also available for some fungal pathogens such as *Cryptococcus neoformans* and *H. capsulatum*. Assays to detect galactomannan, a molecule found in the cell wall of *Aspergillus*, are commercially available and increasingly used to assist in making the diagnosis of invasive aspergillosis in immunocompromised populations.

POINT-OF-CARE DIAGNOSTICS

Some assays to detect infections may be performed in the office setting, provided the site is certified as meeting appropriate quality-assurance standards specified by the Clinical Laboratory Improvement Amendments (CLIA) of 1988. These include procedures listed under the category of "provider-performed microscopy" such as wet mounts, potassium hydroxide preparations, pinworm examinations, and urinalysis.

Many pediatric offices perform rapid antigen testing for detection of group A streptococcal pharyngitis. The sensitivity of point of case testing is dependent upon specimen collection technique, the type of kit used and on the concentration of streptococci present in the sample. However, in light of the fact that up to 30% of group A streptococcal rapid antigen tests are falsely negative, it is recommended that all negative results should be confirmed by culture.

Office laboratories licensed to perform waived tests are limited to performing these tests and avoid having to undergo inspections and proficiency testing, although they are still subject to CLIA certification requirements specific to these tests. Gram staining, culture inoculation, and isolation of bacteria are considered moderately to highly complex tests under CLIA specifications. Any office laboratory performing

Gram stains or cultures must comply with the same requirements and inspections for quality assurance, proficiency testing, and personnel requirements as fully licensed microbiology laboratories.

LABORATORY DETECTION OF PARASITIC INFECTIONS

Most parasites are detected by microscopic examination of clinical specimens. *Plasmodium* and *Babesia* can be detected in stained blood smears, *Leishmania* can be detected in stained bone marrow smears, and helminth eggs, *Entamoeba histolytica,* and *Giardia lamblia* can be detected in stained fecal smears (see Table 170-1). Serologic tests are important in documenting exposure to certain parasites that are not typically found in stool or blood, and thus are difficult to demonstrate in clinical specimens, such as *Trichinella*.

Pinworm is a relatively common parasitic infection in pediatric patients. A diagnosis of pinworm can be made by evaluating a "pinworm prep." The best time to obtain this specimen is first thing in the morning, before the patient has bathed or had a bowel movement. A piece of clear scotch tape is pressed onto the perianal region of the patient and then the tape is applied to a clear microscope slide. The slide is then examined for recovery of pinworm eggs or worms.

Fecal specimens should not be contaminated with water or urine, because water can contain free-living organisms that can be confused with human parasites, and urine can destroy motile organisms. Mineral oil, barium, and bismuth interfere with the detection of parasites, and specimen collection should be delayed for 7-10 days after ingestion of these substances. Because *Giardia* and many worm eggs are shed intermittently into feces, a minimum of 3 specimens on nonconsecutive days are required to adequately exclude the diagnosis of an enteric parasite. Because many protozoan parasites are easily destroyed, collection kits with appropriate stool preservatives (commonly a 2-vial system with formalin and polyvinyl alcohol fixatives) should be used if delay between time of specimen collection and transport to the laboratory is anticipated.

Ova and parasite examination of fecal specimens includes a wet mount (to detect motile organisms if fresh stool is received), concentration (to improve yield), and permanent staining, such as trichrome, for microscopic examination. *Cryptosporidium*, *Cyclospora,* and *Isospora* are detected by modified acid-fast stain, and microsporidia by a modification of the trichrome stain. In addition, *Cyclospora* and *Isospora* autofluoresce under UV microscopy. The laboratory should be alerted if these parasites are suspected. Detection of certain intestinal parasites, especially *Giardia* and *Cryptosporidium*, can be simplified by using antigen detection tests.

Amebic encephalitis, caused by *Acanthamoeba*, *Balamuthia*, or *Naegleria*, is a rare but devastating and rapidly progressive disease. Special laboratory stains and procedures are required to detect these organisms. The laboratory should be notified if this infection is suspected.

Rapid antigen detection tests for *Plasmodium* species are available. The sensitivity and specificity of these tests vary depending on the burden of parasite in the sample, and the specific *Plasmodium* species. In general, these tests are most sensitive for detecting *Plasmodium falciparum* and least sensitive for detecting *Plasmodium malariae*. These tests are particularly useful for laboratories lacking personnel trained in evaluation of thick and thin smears for malaria, or to provide a rapid preliminary result while awaiting microscopy. All positive and negative rapid malaria assays should be confirmed with blood smear analysis.

Trichomonas vaginalis is a sexually transmitted protozoan parasite that can also be transmitted on household fomites. Infected individuals may be asymptomatic or may have mild inflammation or severe inflammation and discomfort. *Trichomonas* may be detected using a wet mount, but this method is insensitive. Rapid antigen assays are available. Culture-based detection or nucleic acid amplification techniques are the most sensitive way to make the diagnosis.

SEROLOGIC DIAGNOSIS

Serologic tests are primarily used in the diagnosis of infectious agents that are difficult to culture in vitro or detect by direct examination, such as *Bartonella, Francisella, Legionella, Borrelia* (Lyme disease), *Treponema pallidum, Mycoplasma, Rickettsia,* some viruses (HIV, Epstein-Barr virus [EBV], hepatitis A virus), and parasites *(Toxoplasma, Trichinella).*

Antibody tests may be specific for immunoglobulin (Ig) G or IgM or can measure antibody response regardless of immunoglobulin class. In very general terms, the IgM response occurs earlier in the illness, generally peaking at 7-10 days after infection, and usually disappears within a few weeks, but for some infections (e.g., hepatitis A, West Nile Virus) it can persist for months. The IgG response peaks at 4-6 wk and often persists for life. Because the IgM response is transient, the presence of IgM antibody in most cases correlates with recent infection. Methods for IgM antibody detection are difficult to standardize, however, and false-positive results commonly occur with some tests. The presence of IgG antibody can indicate new seroconversion or past exposure to the pathogen. To confirm a new infection using IgG testing, it is essential to demonstrate either seroconversion or a rising IgG titer. A 4-fold increase in a convalescent titer obtained 3-4 wk following the acute titer is considered diagnostic in most situations. In neonates, interpretation of serologic tests is very difficult because of passive transfer of maternal IgG that can persist for 6-18 mo after birth.

Context is extremely important in the interpretation of serologic findings. Important considerations are the ability of the host to mount an immune response, the background rate of seropositivity (especially for IgG detection assays), and, for some diseases, the antibody titer. In addition, interpretation of some serologic assays, such as those used to diagnose Lyme disease, are problematic because of lack of specificity of the immunoassays. A confirmatory immunoblot (Western blot) is required for all positive and equivocal EIA results for Lyme disease.

LABORATORY DIAGNOSIS OF VIRAL INFECTIONS

Viral diseases are extremely important in pediatrics, and diagnostic virology has long been important to pediatric practice, especially in the inpatient setting.

Specimens

Specimens for viral diagnosis are selected on the basis of knowledge of the site that is most likely to yield the suspected pathogen. When evaluating patients with acute viral infections, specimens should be collected early in the course of infection when viral shedding tends to be maximal. Swabs should be rubbed vigorously against mucosal or skin surfaces to obtain as much cellular material as possible and sent in viral transport media that contain antibiotics to inhibit bacterial growth. Rectal swabs should contain visible fecal material. "Flocked" swabs have been shown to provide more material for the laboratory with consequent improvement in the performance of diagnostic tests. Fluids and respiratory secretions should be collected in sterile containers and promptly delivered to the laboratory. All specimens should be transported on ice if delay is anticipated. Freezing specimens, especially at −20°C (−4°F), can result in a significant decrease in culture sensitivity. Consultation with the laboratory is recommended, because some commercial diagnostic test kits used by laboratories may require specific collection devices.

Laboratory diagnosis of viral infections may be by electron microscopy, antigen detection, virus isolation in culture, serologic testing, or molecular techniques to detect viral nucleic acids. In the past few years, molecular tests have emerged as the primary means for detecting viral infections, with some virology laboratories abandoning the use of viral culture altogether. Serologic testing still has a role, especially for arboviral infections such as West Nile, acute EBV infections, HIV, hepatitides A to C, and diseases of childhood such as measles, rubella, and mumps. Serology is also uniquely useful for defining immunity to specific viral infections.

Antigen Detection Tests

Immunofluorescent-antibody (IFA) techniques or other methods, such as EIA, that use antibodies to detect viral antigens directly in clinical specimens to permit rapid identification of viruses, were the mainstay

of the diagnosis of respiratory viral infections but are now being replaced by molecular tests. Smears of cellular material from respiratory secretions stained by immunologic reagents can identify the antigens of respiratory syncytial virus (RSV), adenovirus, influenza A and B viruses, parainfluenza virus types 1-3, and human metapneumovirus within 2-3 hr after the specimen is received. The sensitivity of IFA staining for RSV exceeds that of culture in many laboratories. For influenzas A and B, IFA sensitivity approaches that of culture, whereas for parainfluenza viruses and adenoviruses, sensitivity of IFA is lower. Novel influenza strains, such as the one responsible for H1N1 pandemic influenza, may be poorly detected by IFA and other antigen detection techniques and require molecular tests for optimal sensitivity.

Sensitive IFA staining techniques are also commercially available for identifying varicella-zoster virus and herpes simplex virus (HSV). These specific methods have supplanted the Tzanck smear for multinucleated giant cells characteristic of varicella-zoster virus or HSV infections. A method for detecting cytomegalovirus (CMV) pp65 antigen in blood of immunocompromised patients is also available but is being replaced by molecular testing. IFA is not useful for detecting viruses in specimens that do not contain an adequate number of infected cells.

Rapid antigen tests usually based on lateral flow immunochromatography have been approved by the FDA for detection of influenzas A and B and RSV. Some of these tests have "waived" status under CLIA, meaning that they can be performed by personnel who are not trained laboratory technologists, with relatively little formal quality control other than controls that are incorporated into the test devices. Some require as little as 10 min to perform. Consequently, these tests can be performed in a doctor's office or an emergency unit. Sensitivity in children is higher than in adults and is in the range of 50-80%. Rapid antigen tests can be useful in managing patients with acute respiratory infections, provided the caregiver keeps in mind that a negative test does not rule out the diagnosis of influenza or RSV. Positive tests that are properly read tend to be reliable, but it is also important to keep in mind that the presence of a virus such as influenza or RSV does not rule out the presence of concomitant bacterial infection.

In addition to their role in respiratory virus infections, antigen-detection EIA tests are commonly used for the diagnosis of viruses that are difficult to culture, such as rotavirus, enteric adenovirus, and hepatitis B virus. The detection of the p24 antigen of HIV along with HIV antibodies is included in "fourth-generation" EIA tests used for the diagnosis of HIV.

Viral Culture

Viruses require living cells for propagation; the cells used most often are human- or animal-derived tissue culture monolayers, such as human embryonic lung fibroblasts or monkey kidney cells. Historically, in vivo methods such as inoculation of suckling mice were also used, but are rarely used today. Viral growth in susceptible cell culture is usually accomplished by detecting characteristic cytopathic effect that is visible by light microscopy under low magnification in the cultured cells. For some viruses (e.g., influenza, parainfluenza, and mumps viruses), this method is supplemented by hemadsorption, based on the production of virally encoded hemagglutinins on infected cell membranes that cause adherence of erythrocytes to infected cells. The most reliable confirmatory method for viral detection in cell culture involves fluorescein- or enzyme-labeled monoclonal antibody staining of infected cell monolayers. An important technical improvement in respiratory viral cultures is the development of cell culture systems that include more than 1 type of cell (R-Mix, Diagnostic Hybrids/Quidel, San Diego, CA) and employ IFA staining for virus detection. This system provides results in 16-40 hr from the time the specimen is received in the laboratory, compared to 2-10 days for conventional cultures. Cell culture methods are now being steadily replaced by molecular tests, which are faster, may be more sensitive, and have the potential to detect viruses that do not grow readily in cell cultures.

Molecular Diagnostics

Most molecular tests to detect viruses use the polymerase chain reaction (PCR) and other nucleic acid amplification tests. The first application of PCR to become widely accepted was a test to detect HSV DNA in CSF in patients with possible HSV encephalitis. The first FDA-cleared test for this purpose was approved in 2014. Many laboratories still use laboratory-developed tests, whose performance characteristics must be validated as specified by CLIA. The consequence of this situation is that testing is not standardized and the performance characteristics of this testing (sensitivity and specificity) may vary from laboratory to laboratory. At its best, PCR has sensitivity and specificity greater than 95% for HSV encephalitis. PCR is also increasingly used to diagnose mucocutaneous HSV and varicella-zoster virus infections. This testing is more sensitive than virus culture and provides a more rapid turnaround time.

An FDA-cleared test for enterovirus in CSF (GeneXpert, Cepheid, Sunnyvale, CA) provides sensitive detection of enteroviruses with a performance time of approximately 3 hr. Because this testing is simple to perform, some hospital laboratories are able to offer testing at all times, thus maximizing the clinical utility of the test. The parechoviruses, which may cause illnesses similar to those caused by enteroviruses, especially in infants <6 mo of age, must be detected by separate molecular assays. No parechovirus assays are currently approved by the FDA.

FDA-cleared molecular tests for respiratory viruses are increasingly replacing antigen detection and culture. Several FDA-cleared multiplex molecular tests are available for detection of influenza A and B and RSV. As of 2014, 4 multiplex tests that detect larger numbers of respiratory viruses are also available (Table 170-2). Viruses detected by these tests include influenza A and B, RSV, parainfluenza 1-4, human metapneumovirus, adenovirus, rhinovirus/enterovirus, and coronaviruses OC43, 229E, NL63, and OC43. The performance of each test for each of the viral targets must be approved or cleared by the FDA, so the tests vary among one another in the specific virus targets for which they have achieved FDA approval/clearance (Table 170-2). In addition, 1 of the tests (FilmArray) is also cleared for the detection of the bacterial agents *B. pertussis, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae*. This test is also notable because the performance time is only

Table 170-2 Multiplex Assays for the Detection of Respiratory Viruses

TEST	MANUFACTURER	VIRUSES DETECTED*
xTag	Luminex, Austin, TX	Flu A, AH1, AH3, Flu B, RSV, PIV 1-3, Ad B/C/E, HMPV, rhinovirus/enterovirus†
FAST	Luminex, Austin, TX	Flu A, AH1, AH3, Flu B, RSV, Ad B/C/E, HMPV, rhinovirus/enterovirus†
FilmArray	Biofire, Salt Lake City, UT	Flu A, AH1, AH1(2009), AH3, Flu B, RSV, PIV 1-4, rhinovirus/enterovirus†, HMPV, adenovirus, coronaviruses OC43, 229E, NL63, HKU1
eSensor	GenMark	Flu A, AH1, AH1(2009), AH3, Flu B, RSV, PIV 1-3, HMPV, adenovirus B/C/E, rhinovirus

*Cleared by the FDA as of July, 2013. Other versions that detect additional viruses are available outside of the United States.
†Detects rhinoviruses and enteroviruses but does not distinguish between them.
Ad, adenovirus; AH1, influenza A, hemagglutinin type 1; AH3, influenza A, hemagglutinin type 3; flu A, influenza A; flu B, influenza B; HMPV, human metapneumovirus; PIV, parainfluenza virus; RSV, respiratory syncytial virus.

approximately 1 hr, permitting very rapid turnaround time. A multiplex assay for the detection of viruses (norovirus and rotavirus), as well as important bacterial and parasitic pathogens (xTAG Gastrointestinal Panel, Luminex, Austin, TX), has been cleared by the FDA and similar tests are being developed by numerous other companies.

Another important area of application of molecular testing is the detection of viruses in the blood. FDA-approved assays to detect HIV and hepatitis C RNAs are essential for the management of these infections, including the prevention of transmission from mother to infant. Hepatitis B molecular testing is also increasingly used. In addition, molecular testing is now widely used for viruses that cause systemic disease in immunocompromised patients, especially CMV, EBV, HSV, the BK polyomavirus, and adenovirus. For these viruses, as well as for HIV and the hepatitisviruses, quantitative testing is required. An FDA-approved PCR assay for the quantitative measurement of CMV DNA in plasma is now available. In addition, international standards for CMV have been developed. This is important because it makes possible better comparability among different quantitative CMV assays if they are each referenced to the international standard. Testing for the other viruses must be carried out using laboratory-developed tests, sometimes with the use of analyte-specific reagents, a class of reagents that are regulated by the FDA although not incorporated into complete diagnostic test kits.

Laboratory-developed PCR and other molecular assays are used by some laboratories for numerous other viruses, including parvovirus B19; human herpesvirus 6; mumps, measles, and rubella viruses; and the JC polyomavirus.

Host gene expression patterns in whole blood have been used to differentiate viral from bacterial infections. This microarray-based assay may rapidly identify a viral or bacterial profile of host gene expression reprise, thus greatly shortening the time to diagnosis and potentially avoiding inappropriate treatment while suggesting indicated therapies.

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Chapter 171
The Microbiome and Pediatric Health

Patrick C. Seed

From the time of birth, the human infant is exposed to a myriad of microbes found on the mother and in the surrounding environment. Microbes rapidly form assemblages across exposed areas of the body, including the skin and enteral tract. The microbial communities are called the **microbiota** and make a substantial impact on short- and long-term physiology, including immunologic and metabolic development and function. Together the number of body-associated bacterial cells is estimated to be 10 times greater than the number of human cells in the body. In aggregate, the totality of the microbes, including their microbial genes and environmental interactions, constitute the microbiome, and the microbial genes in the human microbiome are estimated to exceed the number of human genes by at least 100-fold, together making a macroorganism with an inseparable collective physiology. Current evidence indicates that the microbiome evolves over the life span to influence health and disease.

MEASURING THE MICROBIOME

Prior knowledge of microbes on and around the human body was based on specific methods to cultivate organisms. Molecular technologies have revolutionized the identification of poorly cultivatable microbes, rare microbes, and microbes in complex communities like those associated with the human body (Fig. 171-1). The development of the polymerase chain reaction and the availability of modern nucleic acid sequencing have improved the sensitivity of detection of many organisms and have also resulted in the discovery of new organisms. Modern sequencing technologies, so-called next-generation sequencing platforms, allow sequencing in high volume and depth, with millions of sequences obtained from a single biologic sample. Three major approaches have utilized next-generation sequencing to understand the composition, diversity, and activity of the microbiome: (1) sequencing species-specific regions of genomes such as ribosomal RNA-encoding tracks and intergenic regions, (2) total DNA sequencing and assembly of sequence fragments into large genome pieces termed *metagenomics*, and (3) RNA transcript sequencing to decipher the composition and, as a surrogate for functional activity, the transcriptional activity of a microbiome. New bioinformatics tools have allowed the analysis and comparison of the large datasets arising from these methods.

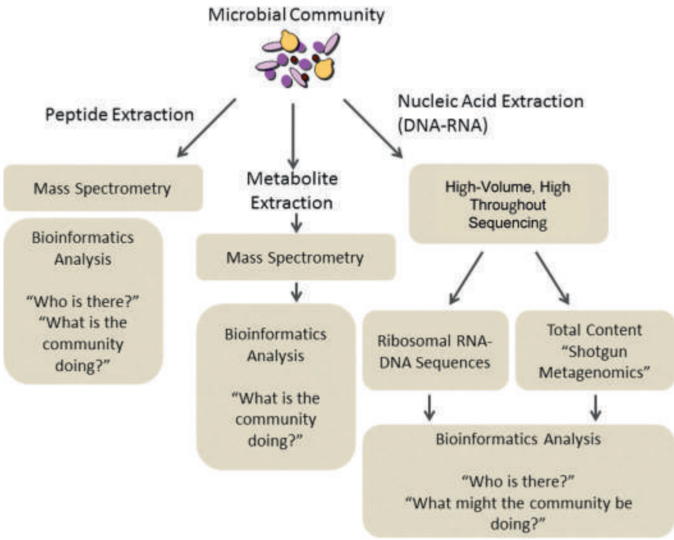

Figure 171-1 Common molecular methodologies for identifying the components and the functions of complex microbial communities.

Two additional approaches to measure the microbiome have been rapidly developing as well. First, large-scale measurements of the peptide composition of the microbiota, called **proteomics**, have been increasingly used to describe the activity of a microbiome sample, as peptides provide information about the composition and function of a microbiome. Second, in a complementary approach called **metabolomics**, microbiome-derived metabolites are measured using advanced mass spectrometry techniques. Together, proteomics and metabolomics better describe the activity of a microbiome than the nucleotide-sequencing approaches; however, at this point in time, they provide less depth of resolution and specificity of the composition of a microbiome.

Despite the power of these new methodologies to interrogate the microbiome, they do not yet replace cultivation of microbes in many clinical circumstances. Cultivation of organisms still represents the most practical means to differentiate potential pathogenic species from more benign species and to provide key information such as susceptibility to antimicrobials.

EARLY-CHILDHOOD DEVELOPMENT OF THE MICROBIOME

In healthy, uncomplicated term deliveries, infants are believed to be sterile until birth. The rupture of the fetal membranes and subsequent delivery is likely the first major exposure to colonizing microbes. Exceptions may be prematurity as a complication of infection of the

fetal membranes and either subclinical or clinical chorioamnionitis, where molecular analyses suggest that in utero exposure to microbes is common. Mode of delivery has a major influence on the early-life microbiome, with vaginally delivered infants becoming acutely colonized with intestinal organisms that reflect the mother's vaginal tract and infants delivered by cesarian section becoming colonized with intestinal organisms reflective of the maternal skin.

In the term infant delivered by vaginal delivery, the first intestinal microbes, so-called pioneering organisms, include aerobic organisms such as Enterobacteriaceae (e.g., *E. coli*), Streptococcaceae, and Staphylococcaceae. Some infants have anaerobes in their early colonizing microbiota, including Clostridiaceae and Bacteroidaceae. However, anaerobes are uncommon, likely because of the aerobic environment of the neonatal intestinal tract, the underdeveloped mucus layer, and relatively high intestinal motility. Exclusive breastfeeding has been reported to result in high levels of bifidobacteria and *Lactobacillus* in the week following the start of feeding. These probiotic organisms have unique capacities to exclude would-be pathogens from colonization by sequestering nutrients and producing antimicrobial factors while stimulating the intestinal epithelium to tighten cellular junctions and express antimicrobial peptides. However, these genera have been notably deficient from some breastfed infant cohorts, particularly within the United States.

The premature infant is more likely to be delivered by cesarian section and will often be colonized with skin-related organisms such as coagulase-negative staphylococci, similar to the term infant delivered through a similar mode of delivery. However, the premature infant may fail to progress through the same stages of expansion and diversification of the microbiome over the 1st wk to mo of life as the term infant. The factors related to the delayed maturation are not fully clear but are predictably related to delayed or limited enteral feeding, normal environmental exposure to the household environment, and exposure to medical interventions such as antimicrobials.

The most significant shift in the intestinal microbiota appears to occur after weaning and the introduction of solid foods. As the infant transitions from breast milk to a solid food diet containing complex plant-derived polysaccharides, the microbiota begins to reshape progressively into a more mature composition beginning to resemble the adult microbiota. A partial transition occurs from aerobic and facultative anaerobes such as streptococci and coliform enterics like *E. coli* to more strict anaerobes such as *Bacteroides* spp.; however, more studies are required in large numbers of children to fully understand the developmental stages of maturation and the likeness to the mature, healthy adult state.

Currently, development of the oral and skin microbiomes in childhood is not well understood. Past studies revealed remarkable diversity of the composition of the microbiota within the oral cavity in the presence of full adult dentition, with an estimated 1,000 bacterial species. Even with oral health, there is substantial diversity in the gingiva of different types of teeth, so-called geodiversity, and the diversity changes dramatically with the development of oral disease such as periodontitis. However, the oral microbiome predentition, during tooth eruption and during the transition from primary to secondary dentition is currently poorly understood. Furthermore, the placement and removal of oral hardware for orthodontics is common in childhood and may produce important alterations in the microbiome of the oral cavity.

The adult skin microbiome displays a high degree of geodiversity—differences in composition depending on site and local physiology with major differences in dry and wet skin sites. However, the linkage between skin development in childhood and maturation of the skin microbiome remains a key subject of future study.

Social structure and family interactions likely play a large role in the development of the early life microbiome. Breast milk feeding provides a microbiologic link between mothers and infants, including transmission of probiotic-like organisms such as lactobacilli and bifidobacteria, each of which may have some protective effects including protection against diarrheal diseases and atopy. Pediatricians have long been aware of the infectious disease risks and benefits of daycare attendance, with examples of shared pneumococcal strains producing otitis media and outbreaks of respiratory syncytial virus infection and associations with reduced atopy, allergy, and possibly asthma. Family contacts are risks for acquisition of methicillin-resistant *S. aureus* and subsequent disease. Recent studies demonstrate that at least parts of the human microbiome are transmitted between household individuals and domesticated pets such as dogs and cats. For instance, family members share the same strains of *E. coli* known to produce urinary tract infections in 1 of the household members. There may be differences in the oral microbiota among infants for whom the parents did and did not use the practice of pacifier sucking for cleaning. Thus, development of the microbiome during childhood is a complex process that is just beginning to be understood.

THE MICROBIOME AND PHYSIOLOGIC DEVELOPMENT

The microbiome has increasingly complex roles in the development of mammalian physiology (Fig. 171-2). These include the development of the enteral tract, the immunologic system, the hematologic system, the metabolic-endocrine system, and the neurologic system. The details of how the microbiome contributes to these developmental processes in humans are still under intense investigation; however, modeling in other mammalian systems predicts that the microbiome will have a critical role.

Microbiome and Metabolism

Soon after entry into the physical world, the mammalian enteral tract is colonized and the interaction of early pioneering microbes in the enteral tract stimulates the development of the intestinal mucosa. In neonatal and juvenile animal models, delayed or absent intestinal colonization results in incomplete development of the epithelium, flattening of the intestinal crypts, loss of vasculature, and severely reduced enzymatic function, including alkaline phosphatase and glucosidases.

The enteric microbiota has a large number of roles in the physiology of the intestinal tract. In addition to its function in mucosal and systemic immune development as well as development and regeneration of the epithelium, the microbiota plays a role in key aspects of metabolism: (1) the digestion of otherwise indigestible plant polysaccharides; (2) production of vitamins and cofactors; (3) metabolism of xenobiotics, including clinically relevant drugs; and (4) stimulation of local and systemic metabolism, including lipid storage. Germ-free animals lacking the enteric microbiota have limited nutrient extraction and have a failure to thrive phenotype.

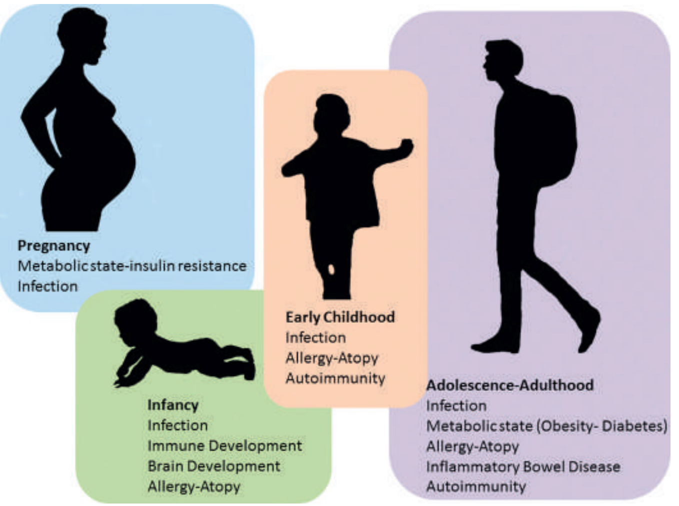

Figure 171-2 Physiologic and pathologic roles of the microbiome relevant to pediatrics. The human microbiome has an impact on health and development from pregnancy through to adulthood, including infection and non–infection-related processes.

Mice born into a sterile environment have been colonized with human fecal microbial communities. Feeding of "humanized" mice diets with and without polysaccharides, akin to the weaning to solid food transition, results in dramatic alterations in central metabolites. "Humanized mice" transitioned from a polysaccharide-rich, low-fat diet to a more "Westernized" diet high in fat and monosaccharides undergo a blossoming of the phyla Actinobacteria and Firmicutes in the enteric microbiota with a commensurate reduction in Bacteroidetes, similar to observations of increased Firmicutes and reduced Bacteroidetes in obesity.

Common patterns of mature enteric microbiota community composition and predicted function may exist among humans. Sequencing of the fecal microbes from adults across multiple nations revealed 3 common patterns of microbial community compositions, called enterotypes. Significant increases in the proportions of *Bacteroides, Prevotella,* and *Ruminococcus* were found as sentinels of the different enterotypes, and these enterotypes could be identified in individuals from multiple continents, including North America, Europe, and Asia. The different enterotypes among infants and children are not well defined, with the possibility that mature, stable enterotypes form in the early postweaning period or after infancy. Breast milk and formula feeding enterotypes have been described, with notable enrichment of enteric Gram-negative bacteria such as *E. coli* and anaerobic *Clostridia* spp. among the formula-fed infants.

Microbiome, Inflammation, and Immunity

The organisms that compose the microbiome are critical for early immune programming, the development of immune tolerance, and overall maintenance of immune set points. Cells produce a variety of receptors to recognize microbial ligands, in a process called *pattern recognition*. In turn, microbes produce intentional and unintentional stimulation of those cellular receptors to activate and repress inflammatory pathways. Classic examples of such regulatory interactions include peptidoglycan on bacteria binding to Toll-like receptor 2 (in complex with Toll-like receptor 3 and Toll-like receptor 6), lipopolysaccharide of Gram-negative bacteria binding to Toll-like receptor 4, and glucans of fungi binding to the dectin receptor. The results of these receptor interactions include the production of chemokines and cytokines, cell differentiation and development, alteration in metabolism, and stimulation of cell death and survival programs, all contingent on the type of cell, the state of the cell, and the magnitude of stimulation.

Microbial stimulation of these microbial recognition systems is so critical in development that animals raised in the absence of microbes have diminished innate immune responses such as antimicrobial peptides at mucosal surfaces, dysregulated proinflammatory and immunologic tolerance responses, and reduced T- and B-cell populations. Following restoration of normal colonization weeks after being sterile, animals have long-term aberrant cytokine responses with hyperactive proinflammatory responses to stimuli, demonstrating the long-lasting consequences of altering early microbial acquisition. Different early life colonization patterns also correlate with long-term immune development. In a Scandinavian study, children with persistent early life *E. coli* colonization had higher sustained memory B-cell (CD3+CD20+CD27+) levels by 1.5 yr of life compared to children with lower levels of *E. coli* colonization, even despite abundant colonization with prototypical probiotic bacteria *Lactobacillus* spp.

Microbiome-Neurobiologic Connections

Emerging studies are demonstrating a gut–brain axis that may be altered by the composition and activity of the enteric microbiome. Investigations in animal models have shown that the microbiome alters the hypothalamic-pituitary-adrenal system. Germ-free mice have exaggerated stress–anxiety behavior accompanied by elevated corticosterone and adrenocorticotropin levels compared with conventionally colonized, pathogen-free mice. Functional MRI has shown that the ingestion of 5 strains of probiotic-like bacteria alters brain activity in humans, resulting in decreased brain responses to emotional attention tasks in sensory and emotional input regions of the brain. Although the mechanism underlying these changes can only be inferred, the tractus solitarius and thus the vagus nerve appear to mediate the enteral tract-brain connection.

Another mechanism through which the enteric microbiome may alter brain activity is by the metabolites it produces. Administration of fermented milk with probiotic like organisms, most notably *Bifidobacterium animalis* subsp. *lactis*, to monozygotic human twins and to mice did not dramatically change the intestinal microbiome composition but did alter its transcriptional profiles, with a shift to increased carbohydrate fermentation to fatty acids, thought to attenuate sad emotional behavior in humans.

CONTRIBUTIONS OF MICROBIOME TO DISEASE

Studies demonstrate that some microbial communities may act in concert to exert negative health effects, whereas other communities may be restorative or resistant to disease. A number of examples of this concept of altered microbial communities, also termed **dysbiosis**, are provided in the sections to follow.

Microbiome of Premature Birth

While the etiology of premature birth is multifactorial, inflammatory conditions including subclinical and clinically overt infections of the mother and/or fetus have been proposed to be instigators of premature birth. Inflammatory biomarker profiling highlights this point, as women who proceed to preterm birth have increased angiotensin, interleukin 8, and tumor necrosis factor receptor 1, along with a number of race-specific alterations in additional cytokines and chemokines. Prior work reported that women experiencing preterm birth have increased vaginal colonization with *Gardnerella* spp. and *Lactobacillus crispatus.* There may be a lower diversity in microbiota of the posterior vaginal fornix of women experiencing preterm birth. A meta-analysis of early treatment of vaginosis with clindamycin prior to 22 wk of pregnancy demonstrated a reduction in spontaneous preterm birth at <37 wk, consistent with an association between dysbiosis of the pregnancy-associated microbiota and preterm birth.

Traditionally, the amniotic cavity and the fetus have been presumed to be sterile prior to the rupture of the fetal membranes and birth. However, several reports identify evidence for bacterial DNA in meconium with 2 predominant meconium types regardless of mode of delivery: (1) dominated by Enterobacteriaceae, and (2) dominated by Leuconostocaceae, Enterococcaceae, and Streptococcaceae. Furthermore, data indicate that the amniotic fluid in subclinical and clinically apparent chorioamnionitis has evidence of vaginal-derived microbes present, including poorly or noncultivatable organisms such as *Mycoplasma* spp., *Ureaplasma* spp., *Bacteroides* spp., *Fusobacterium, Sneathia sanguinegens,* and *Leptotrichia amnionii*. A correlation exists between the burden of intraamniotic organisms and the degree of prematurity. Microbial invasion of the amniotic space may lead to induction of inflammatory pathways through innate immune microbial pattern recognition receptors such as the Toll-like receptors. The result may be the induction of labor and physiologic stress on the fetus and mother. Exposure to microbial factors may have consequences on lung and intestinal development, setting the stage for postnatal pathology including necrotizing enterocolitis. Beyond the acute threat to the maternal-fetal dyad, chorioamnionitis may not produce the long-term neurodevelopmental consequences it once was thought to cause, with formerly premature infants born to women with chorioamnionitis having similar cognitive and neuropsychiatric outcomes even to age 18 yr as infants not exposed to chorioamnionitis.

Changes in the Microbiome with Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a devastating disease of the neonatal intestine that disproportionately affects severely premature infants who weigh less than 1,500 g at birth. The pathologic steps in NEC include intestinal inflammation with loss-of-barrier function, microbial invasion of the bowel, and eventual death of the affected bowel. Years of research implicated specific organisms as the cause of NEC in case

series; however, none of the proposed specific etiologies proved to be common to all cases of NEC and, instead, appeared to be the emergent organisms after serious intestinal pathology had ensued.

Contemporarily, a model of dysbiosis of the early life intestinal microbiome has been favored in the pathogenesis of NEC. Epidemiologic studies in very-low-birthweight infants have demonstrated an association of cephalosporins and duration of antibiotic exposure with the development of NEC, consistent with the idea that shifts in the microbiota predispose to or incite NEC. Studies demonstrate decreased diversity of the microbiota preceding and during NEC. The NEC microbiota at the time of clinical symptoms resembles the microbiota 72 hr prior to onset but not the microbiota 1 wk prior to onset of symptoms, suggesting that a shift in the intestinal microbiota begins well in advance of the appearance of NEC. Some differences in early colonization following birth may portend an increased risk for NEC.

Microbiome and Allergic Disorders

Given the role of the microbiome in the development and modulation of innate and adaptive immune responses, considerable interest has been given to its role in the development and exacerbation of allergic conditions such as atopic dermatitis.

The microbiome of the skin has been studied prior to, during, and following treatment of flares of atopic dermatitis. Flares result in the loss of diversity of bacteria on the affected area, and treatment introduces new diversity. *S. aureus* and *Staphylococcus epidermidis* increase prior to and during atopic flares, whereas *Streptococcus* spp. and *Corynebacterium* spp. increase immediately preceding and during clinical improvement. In mice, oral treatment of infant animals with nonabsorbable antibiotics increases serum immunoglobulin (Ig) E, increases clinical symptoms such as itching, and produces atopic-like features. These data suggest that atopic dermatitis is influenced by the local skin microbiome and more distant microbiomes such as in the intestinal tract, also suggesting why the administration of oral probiotics such as *Lactobacillus* spp. may decrease atopic dermatitis with an accompanying shift in the T-cell Th1/Th2 balance and increased interferon-γ, which are part of immune tolerance.

The respiratory tract is a common site of allergic disease, and infections have long been associated with allergic exacerbations of the respiratory tract. Traditional teaching is that the lower respiratory tree is sterile; however, studies of the airway microbiome in healthy and asthmatic children and adults indicate that this teaching is incorrect. Measured through careful bronchoscopic sampling and cytology brushings, the airways have a diverse microbiota during good health.

Measurement of the microbiota in the lower respiratory tract of healthy and asthmatic children indicates significant differences. Past culture-based studies indicate that early life colonization of the neonatal respiratory tree by *H. influenzae, Moraxella catarrhalis,* and *S. pneumoniae* is associated with an increased risk for childhood asthma. These same organisms also are closely associated with exacerbations of asthma. *M. pneumoniae* has been proposed as a major bacterial inducer of childhood asthma exacerbations when infection is identified. The employment of culture-independent measurements of lower airway microbiota composition (see Fig. 171-1) indicates that children with asthma are more likely to have higher levels of Proteobacteria, including *H. influenzae,* as well as Firmicutes such as *Staphylococcus* spp. and *Streptococcus* spp. Remarkably, healthy children are more likely than age-matched asthmatic children to have lower airway Bacteroidetes, particularly *Prevotella* spp., a group of anaerobic bacteria. The association of healthy airways with a lower respiratory tree anaerobic bacterial population is surprising because the high oxygen tension environment has been assumed to be toxic to anaerobes. This study indicates that the airway environment is significantly different than previously understood, and the potentially protective attributes of a native health-associated microbiota needs to be studied to determine if these associations are also causal.

Airway Microbiome of Cystic Fibrosis

Cystic fibrosis is characterized by progressive airway disease and inflammation with acute exacerbations accompanied by loss of pulmonary function. Cystic fibrosis has long been known to have an age-dependent change in lower airway colonization, which starts in early childhood with *S. aureus* and *H. influenzae* and progressively shifts toward more intrinsically multidrug-resistant organisms, including the notoriously persistent and treatment-refractory bacteria *Pseudomonas aeruginosa* and *B. cepacia* complex. Culture-independent molecular analysis of the lung-associated microbiota in cystic fibrosis has revealed far more complex microbial communities than previously expected and has demonstrated an association with patient age and disease severity. In addition to the presence of a variety of previously unexpected airway organisms such as anaerobes and mycobacteria, disease severity is inversely related to the lower airway microbial community diversity with less advanced disease associated with greater species richness and evenness. In contrast, the loss of diversity, including the shift from less complex microbial communities to those dominated by *P. aeruginosa,* is strongly correlated with disease severity, and levels of *H. influenzae,* the early childhood colonizer, have a negative correlation with disease severity. Although antibiotics decrease the rate of progressive lung function, they also decrease the community diversity, thus suggesting a balance between a diverse microbiota and reducing the dominance of certain organisms such as *P. aeruginosa*.

Microbiome During Antibiotic-Associated Diarrhea and *Clostridium difficile* Colitis

Treatment with oral and parenteral antibiotics results in a rapid and significant alteration of the intestinal microbiota. Studies of normal individuals taking ciprofloxacin demonstrated dramatic but individualized responses to the antibiotic, with significant reductions in bacteria outside the expected spectrum of the antibiotic, emphasizing the intradependence of microbial community members on one another for their stability in the community as a whole. Furthermore, the response to ciprofloxacin among subjects varied by individual, suggesting different degrees of stability of the microbiota and resilience under stress such as antibiotics. In general, with the exception of some rare members of the community, the community was largely restored within 4 wk after the completion of the antibiotic course.

Some antibiotics, such as amoxicillin-clavulanate, for which antibiotic-associated diarrhea is a well-known adverse event, produce a loss of *Clostridium* and *Bacteroides*, known to be important in the production of short-chain fatty acids (SCFA) and the metabolism of otherwise undigestible carbohydrates. Together, their loss may decrease the metabolic integrity of the intestinal epithelium that uses SCFA for energy while resulting in a high osmotic environment in which fluid is drawn into the intestinal lumen. Antibiotic-associated diarrhea may result from these combined effects.

One of the most serious complications from antibiotic exposure is the development of *C. difficile*–associated diarrhea (CDAD), which has high associated morbidity and even mortality. Microbiologic surveys suggest that *C. difficile* is a common constituent of the developing microbiota early in life with less prevalence over the life span. Over 30% of infants are colonized with *C. difficile* in the 1st mo of life, continuing until approximately 6 mo of age. By 1 yr of age, colonization ranges between approximately 15% and 70% and then declines through to adulthood, when carriage is estimated to be <3%. Although *C. difficile* has been found within the vaginal microbiota of pregnant women, vaginal delivery has not been associated with increased rates of neonatal *C. difficile* colonization, with vaginal and cesarian delivery having rates of colonization at 30% and 37%, respectively. CDAD has been reported to result in 35-45 hospitalizations per 10,000 pediatric admissions among children 1-9 yr of age.

Although the studies have not yet determined how the intestinal microbiome is altered preceding, during, and with resolution of CDAD in children, molecular studies of the intestinal microbiota in adults provide some details of the consequences of CDAD on the intestinal microbiota. Studies employing deep sequencing of stool from individuals with CDAD and *C. difficile* colonization without disease have revealed depletion of certain bacterial genera accompanying the presence of *C. difficile* colonization. These genera include *Blautia,*

Pseudobutyrivibrio, Roseburia, Faecalibacterium, Anaerostipes, Subdoligranulum, Ruminococcus, Streptococcus, Dorea, and *Coprococcus*. The relationship of cause and effect and the events triggering the transition from colonization to symptomatic disease remain unknown. Similar to the studies of antibiotic-associated diarrhea, these studies also demonstrate a reduction in butyrate-producing *Clostridium* spp., which are proposed to be important for producing butyrate as an energy sources for the intestinal epithelium and its robust integrity.

Although antibiotics such as metronidazole and vancomycin have been employed to treat CDAD, traditional treatment does not eliminate recurrent CDAD to the extent that might be expected. To address this problem, **fecal transplantation** or administration of feces from healthy donors to CDAD recipients is effective in treating CDAD and, more importantly, superior to these antibiotics in reducing the likelihood of recurrent disease. Accompanying clinical resolution is repletion of Bacteroidetes and *Clostridium* clusters IV and XIVa with a matched decrease in Proteobacteria. Most of the experience with fecal transplantation has been gained from adults with only a single published pediatrics report, although research studies are underway.

Microbiome and Association with Inflammatory Bowel Disease

Crohn disease and ulcerative colitis are chronic inflammatory diseases of the enteric tract and are believed to be the result of the intersection of host susceptibility and a dysbiosis, an alteration in the intestinal microbiota. Twin-twin studies indicate concordance rates in monozygotic twins of 10-15% in ulcerative colitis and 30-35% in Crohn disease, thus demonstrating a genetic component for each disease while highlighting environmental factors that likely induce and drive disease progression. More than 150 single-nucleotide polymorphisms are associated with the diseases, revealing potential defects in handling microbes, including those involved in barrier function, innate immunity, autophagy, adaptive immunity, and metabolism and cellular homeostasis.

In inflammatory bowel disease (IBD), the microbiota undergoes a shift in association with the disease throughout the intestinal tract. Although considerable heterogeneity has been described, IBD is often demonstrated to be accompanied by a decrease in bacteroides, clostridia, bifidobacteria, and Firmicutes. Reciprocally, outgrowths of *E. coli* and other Enterobacteriaceae are described. Increased sulfur-metabolizers have been described with IBD as well. Antibiotics along with biologic therapies such as antibodies directed at neutralizing tumor necrosis factor have been employed to manage the IBD dysbiosis and inflammatory reaction. Trials of fecal transplantation are underway to determine if a noninflammatory microbiota from a healthy donor may mitigate IBD symptoms and progression.

Microbiome of Obesity

Obesity and the metabolic syndrome are associated with notable changes in the intestinal microbiome in terms of composition and metabolic function, ultimately resulting in greater energy extraction from the diet. "Typical" changes in the microbiome include an increase in the ratio of the phyla Firmicutes : Bacteroidetes. Additional work has indicated that Prevotellaceae, a family within the Bacteroidetes phylum, may be specifically increased with obesity. However, there remains considerable debate about obesity-specific changes in the microbiome, as studies other than those mentioned previously have demonstrated decreased Firmicutes : Bacteroidetes ratios in the fecal microbiota from obese individuals compared to lean controls. Further studies show that proportions of phyla-level groups may be less important than changes in Firmicutes subgroups that produce butyrate, a known fatty acid substrate easily acquired and utilized by the intestinal epithelium, and thus ready calories for the host.

The intestinal microbiome benefits the host in important ways, including enhancing caloric extraction from indigestible substrates such as polysaccharides in the diet. The microbiome produces degradative enzymes to break down these substrates where enzymes with comparable functions, such as some glycosyl hydrolases, are not encoded in the human genome. Molecular studies indicate that the intestinal microbiome may also interact with the intestinal epithelium in such a way as to alter general energy homeostasis and fat storage. For instance, the intestinal microbiome may produce SCFA that, in turn, alter endocrine peptide expression such as glucagon-like peptide 1 and peptide YY, which alter glucose homeostasis and satiety, respectively. Furthermore through the production of SCFA and ketones, the microbiota may alter sympathetic tone. Certain microbiomes are known to suppress others to induce fastening-induced adipose factor (also called angiopoietin-like protein 4), a lipoprotein lipase inhibitor of intestinal, hepatic, and adipose origins. Colonization with a diverse microbiota suppresses fastening-induced adipose factor expression, and dietary supplementation of a Western diet with *Lactobacillus paracasei* further suppressed otherwise high fastening-induced adipose factor expression. Mice fed a Western diet developed adiposity, which was transferrable to recipient lean mice following transplantation with the obese mice microbiota. Reciprocally, obese mice treated with antibiotics experienced less insulin resistance, lower fasting glycemic indices, and improved glucose tolerance compared to untreated counterparts, further implicating the microbiome in these physiologic changes.

Microbiome During Malnutrition

Malnutrition is a leading cause of morbidity and mortality across the world. In its most severe form, malnutrition may result in kwashiorkor, which is characterized by generalized edema, anorexia, fatty enlarged liver, skin ulcerations, and irritability. Ready-to-use foods are employed to try to restore nutrition in areas with severe food restrictions. Monozygotic and dizygotic twins in Malawi were studied for the alterations in the microbiome in association with moderate to severe malnutrition, including kwashiorkor. Among the twins with discordant degrees of malnutrition on food supplements, the twins with mild preexisting malnutrition had intestinal microbiota that changed significantly over the course of supplementation. In contrast, the twins with preexisting kwashiorkor had microbiota with poor to no change in response to nutritional supplementation. These findings were recapitulated to some extent following transplantation of the twins' microbiota into previous sterile mice. Those mice receiving the microbiota of Malawian twins with kwashiorkor experienced more dramatic weight loss on a Malawian-type diet and more rapid loss of their weight gain once off ready to use food supplements than did mice transplanted with the feces of more healthy twins. The mice with the transplanted kwashiorkor microbiota had sustained problems with carbohydrate, lipid, and amino acid metabolism despite nutritional supplementation of the Malawian diet. Together these data indicate that severe malnutrition results from the combination of nutritional deficits and a microbiome with altered metabolic capabilities that are not readily restored with contemporary nutritional supplementation treatments.

THERAPEUTIC MANIPULATION OF THE MICROBIOME

Therapeutic manipulation of the microbiome falls into 5 general categories: (1) antimicrobials, (2) prebiotics, (3) probiotics, (4) postbiotics, and (5) fecal transplantation. Brief mention of fecal transplantation was discussed in the sections on *C. difficile* diarrhea and IBD. Postbiotics are nonviable microbial components or metabolites that may alter the microbiota or produce physiologic changes in the host. Insufficient data exist to warrant a discussion of postbiotic therapeutics here.

Prebiotics

"Prebiotic" is defined as "nondigestible food components that beneficially affect the host by selectively stimulating the growth and/or activity of 1 or a limited number of bacteria in the colon and thereby improving host health." While antimicrobials deplete portions of the microbiota, prebiotics aim to promote the growth of beneficial organisms such as bifidobacteria and lactobacteria. Typically, prebiotics are carbohydrates such as oligosaccharides that may be selectively metabolized by constituents of the microbiota. They may not only stimulate outgrowth of desirable organisms but also may be catabolized to beneficial end products such as SCFA, which may, in turn, be utilized as

energy substrates by the intestinal epithelium. Prebiotic oligosaccharides are naturally found in breast milk and have been used as supplements to human breast milk and formula.

Administration of prebiotics to term infants has demonstrated the expected outgrowth of bacteria; however, clinically significant benefits from prebiotic supplementation have not been clearly established. Treatment of term infants with fructooligosaccharides increases fecal bifidobacteria but without a change in infant growth, despite some infants having increased SCFA in the fecal mass. A systematic review of the topic provided a similar conclusion.

Preterm infants have low to absent levels of bifidobacteria and lactobacilli in their intestinal tracts, despite full breast milk nutrition. Prebiotic supplementation has been proposed as a means to increase these bacterial populations in the preterm infant intestinal tract. Among the proposed benefits may be a decrease in NEC. However, appropriately powered, randomized trials have not been performed to demonstrate the validity of this hypothesis.

Probiotics

Probiotics are viable organisms that have health benefits following administration. Nearly all probiotics are isolates from the human microbiota, although they may not necessarily reside in the individual taking them for therapeutic purposes. Alternatively, probiotics may be administrated to increase the levels of an organism already present within the microbiota. Generally, probiotics have been administered orally or as vaginal suppositories.

Multiple bacterial and fungal genera and species have been studied for probiotic effects. Common bacterial genera include bifidobacteria, lactobacilli, streptococci, enterococci, and *E. coli*. Fewer nonbacterial organisms, have been studied for probiotic effects. *Saccharomyces boulardii* is related to baker's yeast (*Saccharomyces cerevisiae*) but was isolated for specific beneficial effects.

These probiotic organisms should not be confused with more pathogenic strains within their genera and species. Most probiotics have been isolated on the basis of being associated with healthy states. For instance, bifidobacteria and lactobacilli are common to breast milk and stool among infants with low rates of diarrheal diseases and allergy. With the exception of individuals with significant immunodeficiencies, severely compromised mucosal barriers, and central line catheters, where many of these organisms may adhere to the catheter plastic with otherwise benign transient translocation from the intestinal tract, these bacterial probiotics have proven to be relatively safe even with the administration of billions of colony forming units. The most common adverse events associated with probiotics include abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance.

Although bacterial probiotics have been administered widely to humans, evidence for their efficacy is limited to a small number of conditions. Probiotics have consistently shown efficacy for specific conditions, including antibiotic-associated diarrhea, prevention and reduction of atopy in high risk children, and reductions in duration and recurrence of *C. difficile* infection. Trials indicate a reduction in NEC among preterm infants. Probiotics may reduce the risk for respiratory infections and recurrent UTI while reducing the symptoms and frequency of flares in IBD.

Antibiotic-associated diarrhea is reduced in frequency and duration. Metaanalysis indicated a relative risk of antibiotic-associated diarrhea with probiotic administration of 0.58 (95% confidence interval [CI], 0.05-0.68) among combined studies using *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and/or *Bacillus*. Administration of combinations of organisms has not generally resulted in greater efficacy.

Metaanalysis specifically for the efficacy of probiotics in decreasing the incidence of CDAD demonstrated moderate evidence for the practice. In an analysis of more than 1,800 trials, including many in the pediatric population, probiotics reduced CDAD by 64% with a relative risk of 0.36 (95% CI, 0.26-0.51). A pediatric subgroup was analyzed across relevant studies, revealing benefit in pediatric patients and a well child subgroup (relative risk 0.37; 95% CI 0.23-0.60). A number of probiotics were used, including different *Lactobacillus* strains and *S. boulardii*.

More than 15 trials have been performed to study the effect of probiotic administration during pregnancy and to infants to prevent atopic dermatitis. Metaanalysis suggests a modest benefit from probiotic administration to prevent the development of atopic dermatitis. Trials have primarily involved the administration of *Lactobacillus rhamnosus*. Studies included administration to the pregnant mother, or the infant, or both. The overall relative risk of 0.79 (95% CI, 0.71-0.88) was generally consistent regardless of the treatment of the mother or child, or both. The duration was generally >6 mo; however, duration did not appear to significantly alter the effect. The RR was similar for the prevention of IgE- and non-IgE–associated atopic dermatitis.

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Section 2

Preventive Measures

Chapter 172

Immunization Practices

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Immunization is one of the most beneficial and cost-effective disease-prevention measures available. As a result of effective and safe vaccines, smallpox has been eradicated, polio is close to worldwide eradication, and measles and rubella are no longer endemic in the United States, although cases of vaccine-preventable diseases, including measles, rubella, and pertussis, continue to occur in the United States. For most diseases of childhood preventable by vaccination, incidence of most vaccine-preventable diseases of childhood has been reduced by ≥99% from the annual morbidity prior to development of the corresponding vaccine (Table 172-1a), with newer vaccines not achieving quite the same percentage decrease (Table 172-1b). An analysis of effective prevention measures recommended for widespread use by the U.S. Preventive Services Task Force reported that childhood immunization received a perfect score, based on clinically preventable disease burden and cost-effectiveness.

Immunization is the process of inducing immunity against a specific disease. Immunity can be induced either **passively** through administration of antibody-containing preparations or **actively** by administering a vaccine or toxoid to stimulate the immune system to produce a prolonged humoral and/or cellular immune response. As of 2015, infants, children, and adolescents in the United States routinely are immunized against 16 diseases: diphtheria, tetanus, pertussis, poliomyelitis, *H. influenzae* type b (Hib) disease, hepatitis A, hepatitis B, measles, mumps, rubella, rotavirus, varicella, pneumococcal disease, meningococcal disease, influenza, and human papillomavirus (HPV) infection.

PASSIVE IMMUNITY

Passive immunity is achieved by administration of preformed antibodies to induce transient protection against an infectious agent. Products used include:

- Immunoglobulin (Ig) administered intramuscularly (IM)
- Specific or hyperimmune immunoglobulin preparations administered IM
- Intravenous immunoglobulin (IVIG)

Table 172-1a Comparison of 20th Century Annual Morbidity and Current Morbidity: Vaccine-Preventable Diseases

DISEASE	20TH CENTURY ANNUAL MORBIDITY*	2013 REPORTED CASES†	PERCENT DECREASE
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Measles	530,217	187	>99%
Mumps	162,344	584	>99%
Pertussis	200,752	28,639	86%
Polio (paralytic)	16,316	1	>99%
Rubella	47,745	9	>99%
Congenital Rubella Syndrome	152	1	99%
Tetanus	580	26	96%
Haemophilus influenzae	20,000	31‡	>99%

*Roush SW, Murphy TV, Vaccine-Preventable Disease Table Working Group: Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA* 298(18):2155–2163, 2007.
†Centers for Disease Control and Prevention (CDC). Notice to readers: Final 2013 reports of nationally notifiable infectious diseases. *MMWR Morb Mortal Wkly Rep*:63(32):702, 2014.
‡*Haemophilus influenzae* type b (Hib) <5 yr of age. An additional 10 cases of Hib are estimated to have occurred among the 185 reports of *H. influenzae* (<5 yr of age) with unknown serotype.

Table 172-1b Comparison of Pre–Vaccine Era Estimated Annual Morbidity with Current Estimate: Vaccine-Preventable Diseases

DISEASE	PRE–VACCINE ERA ANNUAL ESTIMATE*	2013 ESTIMATE (UNLESS OTHERWISE SPECIFIED)	PERCENT DECREASE
Hepatitis A	117,333*	2,890†	98%
Hepatitis B (acute)	66,232*	18,800†	72%
Pneumococcus (invasive)			
All ages	63,067*	33,500§	47%
<5 yr of age	16,069*	1,900‖	88%
Rotavirus (hospitalizations, <3 yr of age)	62,500‡	1,2500¶	80%
Varicella	4,085,120*	167,490**	96%

*Roush SW, Murphy TV and Vaccine-Preventable Disease Table Working Group: Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA* 298(18):2155–2163, 2007.
†Centers for Disease Control and Prevention (CDC): Viral Hepatitis Surveillance–United States, 2011.
‡Centers for Disease Control and Prevention (CDC): Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 58(RR-2): 1–25, 2009.
§Centers for Disease Control and Prevention (CDC): Active bacterial core surveillance provisional report; *S. pneumoniae* 2013.
‖Centers for Disease Control and Prevention (CDC). Active bacterial core surveillance [unpublished].
¶New Vaccine Surveillance Network 2013 data [unpublished]. U.S. rotavirus disease now has biennial pattern.
**Centers for Disease Control and Prevention (CDC). Varicella Program 2013 data [unpublished].

- Specific or hyperimmunoglobulin preparations administered IV
- Subcutaneous (SC) human immunoglobulin, which has been licensed to treat patients with primary immunodeficiencies
- Antibodies of animal origin
- Monoclonal antibodies

Passive immunity also can be induced naturally through transplacental transfer of maternal antibodies (IgG) during gestation. Maternally derived transplacental antibodies can provide protection during an infant's 1st mo of life and longer during breastfeeding. Protection for some diseases can persist for as long as 1 year after birth, depending on the quantity of antibody transferred and the time until levels fall below those considered protective.

The major indications for passive immunity are to provide protection to immunodeficient children with B-lymphocyte defects who have difficulties making antibodies, for people exposed to infectious diseases or who are at imminent risk of exposure where there is not adequate time for them to develop an active immune response to a vaccine, and for people with an infectious disease as part of specific therapy for that disease (Table 172-2).

Intramuscular Immunoglobulin

Immunoglobulin is a sterile antibody-containing solution, usually derived through cold ethanol fractionation of large pools of human plasma from adults. Antibody concentrations reflect the infectious disease exposure and immunization experience of plasma donors. Immunoglobulin contains 15-18% protein, is predominantly IgG, and is administered IM. IV use of human intramuscular immunoglobulin is contraindicated. Immunoglobulin is not known to transmit infectious agents, including viral hepatitis and HIV.

The major indications for immunoglobulin are:

- Replacement therapy for children with antibody deficiency disorders
- Measles prophylaxis
- Hepatitis A prophylaxis

For replacement therapy, the usual dose of intramuscular immunoglobulin is 100 mg/kg (equivalent to 0.66 mL/kg) monthly. The usual interval between doses is 2-4 wk depending on trough IgG serum concentrations and clinical response. In practice, **IVIG** has replaced intramuscular immunoglobulin for replacement therapy. Intramuscular immunoglobulin can be used to prevent or modify measles if administered to susceptible children within 6 days of exposure (usual dose: 0.5 mL/kg of body weight; maximum dose: 15 mL). The recommended dose of IVIG is 400 mL/kg. Data suggest that measles vaccine, if given within 72 hr of measles exposure, will provide protection in some cases. Measles vaccine and immunoglobulin should not be administered at the same time.

Two methods are available for postexposure prophylaxis against hepatitis A. In people 12 mo through 40 yr of age, hepatitis A immunization is preferred over immunoglobulin for postexposure prophylaxis and for protection of people traveling to areas where hepatitis A is endemic. Immunoglobulin may be administered to children <12 mo of age and people >40 yr of age for prophylaxis of hepatitis A and for postexposure prophylaxis for people traveling internationally to hepatitis A–endemic areas (0.06 mL/kg). In children <12 mo of age, adults >40 yr of age, and susceptible children and adults with underlying immunodeficiencies or chronic liver disease, immunoglobulin is preferred over hepatitis A immunization.

The most common adverse reaction to immunoglobulin is pain and discomfort at the injection site and, less commonly, flushing, headache, chills, and nausea. Serious adverse events are rare and include chest pain, dyspnea, anaphylaxis, and systemic collapse. Immunoglobulin should not be administered to people with selective IgA deficiency. Patients with selective IgA deficiency can produce antibodies against the trace amounts of IgA in immunoglobulin preparations and develop reactions after repeat doses. These reactions can include fever, chills,

Table 172-2 Immunoglobulin and Animal Antisera Preparations

PRODUCT	MAJOR INDICATIONS
Immunoglobulin for intramuscular injection	Replacement therapy in primary immunodeficiency disorders Hepatitis A prophylaxis Measles prophylaxis
Intravenous immunoglobulin (IVIG)	Replacement therapy in primary immune-deficiency disorders Kawasaki disease Pediatric HIV infection Hypogammaglobulinemia in chronic B-lymphocyte lymphocytic leukemia Immune-mediated thrombocytopenia Hematopoietic cell transplantation in adults to prevent graft-versus-host disease and infection May be useful in a variety of other conditions
Hepatitis B immunoglobulin (IM)	Postexposure prophylaxis Prevention of perinatal infection in infants born to hepatitis B surface antigen–positive mothers
Rabies immunoglobulin (IM)	Postexposure prophylaxis
Tetanus immunoglobulin (IM)	Wound prophylaxis Treatment of tetanus
Varicella-zoster immunoglobulin (IM) or IVIG	Postexposure prophylaxis of susceptible people at high risk for complications from varicella
Cytomegalovirus IVIG	Prophylaxis of disease in seronegative transplant recipients
Subcutaneous immunoglobulin	Treatment of patients with primary immunodeficiencies
Vaccinia immunoglobulin (IV)	Prevent or modify serious adverse events following smallpox vaccination caused by vaccinia replication
Botulism IVIG human	Treatment of infant botulism
Diphtheria antitoxin, equine	Treatment of diphtheria
Heptavalent botulinum antitoxin against all 7 (A-G) botulinum toxin types	Treatment of food and wound botulism
Palivizumab (monoclonal antibody) (IM)	Prophylaxis for infants against respiratory syncytial virus (see Chapter 260)

American Academy of Pediatrics, Passive immunization. In Pickering LK, Baker CJ, Kimberlin DW, Long SL, editors: Red book 2012: report of the Committee on Infectious Diseases, *Elk Grove Village, IL, 2012, American Academy of Pediatrics, pp. 56–63.*

and a shock-like syndrome. Because these reactions are rare, testing for selective IgA deficiencies is not recommended.

Intravenous Immunoglobulin

IVIG is a highly purified preparation of immunoglobulin antibodies prepared from adult plasma donors using alcohol fractionation and is modified to allow IV use. IVIG is more than 95% IgG, and is tested to ensure minimum antibody titers to *Corynebacterium diphtheriae*, hepatitis B virus, measles virus, and poliovirus. Antibody concentrations against other pathogens vary widely among products and even among lots from the same manufacturer. Liquid and lyophilized powder preparations are available. IVIG does not contain thimerosal.

Not all IVIG products are approved by the FDA for all indications. The major **recommended indications** for IVIG for which there is approval by the FDA are:

- Replacement therapy for primary immunodeficiency disorders
- Kawasaki disease to prevent coronary artery abnormalities and shorten the clinical course
- Replacement therapy for prevention of serious bacterial infections in children infected with HIV
- Prevention of serious bacterial infections in people with hypogammaglobulinemia in chronic B-lymphocyte leukemia
- Immune-mediated thrombocytopenia to increase platelet count
- Prophylaxis of infection following bone marrow transplantation

IVIG may be helpful for patients with severe toxic shock syndrome, Guillain-Barré syndrome, and anemia caused by parvovirus B19. IVIG is used for many other conditions based on clinical experience. IVIG may be used for varicella postexposure if varicella-zoster immune globulin is not available.

Reactions to IVIG range from 1-15%. Some of these reactions appear to be related to the rate of infusion and can be mitigated by decreasing the rate. Such reactions include fever, headache, myalgia, chills, nausea, and vomiting. More serious reactions rarely have been reported, including anaphylactoid events, thromboembolic disorders, aseptic meningitis, and renal insufficiency. Renal failure occurs mainly in patients with preexisting renal dysfunction.

Specific immunoglobulin preparations are derived from donors with high titers of antibodies to specific agents and designed to provide protection against those agents (see Table 172-2).

Subcutaneous Immunoglobulin

Subcutaneous administration of immunoglobulin is safe and effective in children and adults with primary immune deficiency disorders. Smaller doses administered less frequently (weekly) result in less fluctuation of serum IgG concentrations over time. Systemic reactions are less frequent than with IVIG and the most common adverse effects of subcutaneous immunoglobulin are injection-site reactions. There are no data on administration of intramuscular immunoglobulin by the subcutaneous route.

Hyperimmune Animal Antisera Preparations

Animal antisera preparations are derived from horses. The immunoglobulin fraction is concentrated using ammonium sulfate, and some products are further treated with enzymes to decrease reactions to foreign proteins. As of 2014, 2 equine antisera preparations are available for humans:

- Diphtheria antitoxin, which can be obtained from the CDC (http://www.cdc.gov/diphtheria/dat.html) and is used to treat diphtheria.
- Heptavalent botulinum antitoxin, which is available from the CDC (770-488-7100) for use in adults with botulism. This product contains antitoxin against all 7 (A-G) botulinum toxin types.

Great care must be exercised before administering animal-derived antisera because of the potential for severe allergic reactions. Due caution includes testing for sensitivity before administration; desensitization, if necessary; and treating potential reactions, including febrile events, serum sickness, and anaphylaxis. *For infant botulism, IVIG (BabyBIG), a human-derived antitoxin, is licensed and should be used.*

Monoclonal Antibodies

Monoclonal antibodies are antibody preparations produced against a single antigen. They are mass-produced from a hybridoma, created by fusing an antibody-producing B lymphocyte with a fast-growing immortal cell such as a cancer cell. **Palivizumab** is a monoclonal antibody that is used for prevention of severe disease from respiratory syncytial virus among children 24 mo of age and younger with chronic lung disease (also called bronchopulmonary dysplasia), with a history of premature birth or with congenital heart lesions or neuromuscular diseases. The American Academy of Pediatrics (AAP) has

developed specific recommendations for use of palivizumab (see Chapter 260). Respiratory syncytial virus–IVIG, a hyperimmunoglobulin formulated for intravenous administration, is no longer produced in the United States. Monoclonal antibodies also are used to prevent transplant rejection and to treat some types of cancer and autoimmune diseases. Monoclonal antibodies against interleukin 2 and tumor necrosis factor α are being used as part of the therapeutic approach to patients with a variety of malignant and autoimmune diseases.

Serious adverse events associated with palivizumab primarily are rare cases of anaphylaxis and hypersensitivity reactions. Adverse reactions to monoclonal antibodies directed at modifying the immune response, such as antibodies against interleukin 2 or tumor necrosis factor, can be more serious, and include cytokine release syndrome, fever, chills, tremors, chest pain, immunosuppression, and infection with various organisms, including mycobacteria.

ACTIVE IMMUNIZATION

Vaccines are defined as whole or parts of microorganisms administered to prevent an infectious disease. Vaccines can consist of whole inactivated microorganisms (e.g., polio and hepatitis A), parts of the organism (e.g., acellular pertussis, HPV, and hepatitis B), polysaccharide capsules (e.g., pneumococcal and meningococcal polysaccharide vaccines), polysaccharide capsules conjugated to protein carriers (e.g., Hib, pneumococcal, and meningococcal conjugate vaccines), live-attenuated microorganisms (measles, mumps, rubella, varicella, rotavirus, and live-attenuated influenza vaccines), and toxoids (tetanus and diphtheria) (Table 172-3). A **toxoid** is a modified bacterial toxin that is made nontoxic but is still able to induce an active immune response against the toxin.

Immunizing agents can contain a variety of other constituents besides the immunizing antigen. **Suspending fluids** may be sterile water or saline but could be a complex fluid containing small amounts of proteins or other constituents derived from the biologic system used to grow the immunobiologic. **Preservatives, stabilizers, and antimicrobial agents** are used to inhibit bacterial growth and to prevent degradation of the antigen. Such components can include gelatin, 2-phenoxyethanol, and specific antimicrobial agents. Preservatives are added to multidose vials of vaccines, primarily to prevent bacterial contamination on repeated entry of the vial. In the past, many vaccines for children contained thimerosal, a preservative containing ethyl mercury. Beginning in 1999, removal of thimerosal as a preservative from vaccines for children was begun as a precautionary measure in the absence of any data on harm from the preservative. This objective was accomplished by switching to single-dose packaging. Vaccines in the recommended schedule for young children that contain thimerosal as a preservative are some preparations of influenza vaccine. The thimerosal content in U.S.-licensed vaccines currently being manufactured can be found at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm096228.htm#pres. **Adjuvants** are used in some vaccines to enhance the immune response. In the United States, the only adjuvants currently licensed by the **FDA to be part of vaccines are aluminum salts and arsenate (AsO_4), an adjuvant that** contains aluminum hydroxide and monophosphoryl lipid A. Vaccines with adjuvants should be injected deeply into muscle masses to avoid local irritation, granuloma formation, and necrosis associated with SC or intracutaneous administration.

Vaccines can induce immunity by stimulating antibody formation, cellular immunity, or both. Protection induced by most vaccines is thought to be mediated primarily by B lymphocytes, which produce antibodies. Such antibodies can inactivate toxins, neutralize viruses and prevent their attachment to cellular receptors, facilitate phagocytosis and killing of bacteria, interact with complement to lyse bacteria, and prevent adhesion to mucosal surfaces by interacting with the bacterial cell surface.

Most B-lymphocyte responses require the assistance of CD4 helper T lymphocytes. These T-lymphocyte–dependent responses tend to induce high levels of functional antibody with high avidity, mature over time from primarily an IgM response to a long-term persistent IgG response, and induce immunologic memory that leads to enhanced responses upon boosting. **T-lymphocyte–dependent vaccines,** which include protein moieties, induce good immune responses even in young infants. In contrast, polysaccharide antigens induce B-lymphocyte responses in the absence of T-lymphocyte help. These **T-lymphocyte–independent vaccines** are associated with poor immune responses in children <2 yr of age, short-term immunity, and absence of an enhanced or booster response on repeat exposure to the antigen. With some polysaccharide vaccines, repeat doses actually are associated with reduced responses, as measured by antibody concentrations, compared to 1st doses (i.e., hyporesponsive). To overcome problems of plain polysaccharide vaccines, polysaccharides have been **conjugated,** or covalently linked, to protein carriers, converting the vaccine to a T-lymphocyte–dependent vaccine. In contrast to plain polysaccharide vaccines, conjugate vaccines induce higher-avidity antibody, immunologic memory leading to booster responses on repeat exposure to the antigen, long-term immunity, and herd protection by decreasing carriage of the organism (Table 172-4). As of 2014 in the United States, there were licensed conjugate vaccines to prevent Hib, pneumococcal, and meningococcal diseases.

Serum antibodies may be detected as soon as 7-10 days after injection of antigen. Early antibodies are usually of the IgM class that can fix complement. IgM antibodies tend to decline as IgG antibodies increase. The IgG antibodies tend to peak approximately 1 mo after vaccination and with most vaccines persist for some time after a primary vaccine course. Secondary or booster responses occur more rapidly and result from rapid proliferation of memory B and T lymphocytes.

Assessment of the immune response to most vaccines is performed by measuring serum antibodies. Although detection of serum antibody at levels considered protective after vaccination can indicate immunity, loss of detectable antibody over time does not necessarily mean susceptibility to disease. Some vaccines induce immunologic memory, leading to a booster or anamnestic response on exposure to the microorganism, with resultant protection from disease. In some instances, cellular immune response is used to evaluate immune status. For some vaccines (e.g., acellular pertussis), there is no accepted serologic correlate of protection.

Live-attenuated vaccines routinely recommended for children and adolescents include measles, mumps, and rubella (MMR); MMR and varicella (MMRV); rotavirus; and varicella. In addition, a cold-adapted, live-attenuated quadrivalent influenza vaccine (LAIV) is available for people 2 through 49 yr of age who do not have conditions that place them at high risk for complications from influenza. Live-attenuated vaccines tend to induce long-term immune responses. They replicate, often similarly to natural infections, until an immune response inhibits reproduction. Most live vaccines are administered in 1 or 2 dose schedules. The purpose of repeat doses, such as a 2nd dose of the MMR or MMRV vaccine, is to induce an initial immune response in people who failed to respond to the 1st dose. Influenza vaccines, including LAIV, are recommended to be administered yearly to provide protection against changes in circulating influenza strains.

The remaining vaccines in the recommended schedule for children and adolescents are inactivated vaccines. Inactivated vaccines tend to require multiple doses to induce an adequate immune response and are more likely to need booster doses to maintain that immunity than live-attenuated vaccines. However, some inactivated vaccines appear to induce long-term immunity, perhaps lifelong immunity, after a primary series, including hepatitis B vaccine and inactivated polio vaccine (IPV).

VACCINATION SYSTEM IN THE UNITED STATES

Vaccine Development

Basic scientific knowledge about an organism, its pathogenesis, and the immune responses thought to be associated with protection are financed primarily through government sponsorship of academic research and research conducted by private industry (Fig. 172-1). Private industry usually assumes the lead role for guiding potential

Table 172-3 Currently* Available Vaccines in the United States by Type

PRODUCT	TYPE
Anthrax vaccine adsorbed	Cell-free filtrate of components including protective antigen
Bacille Calmette-Guérin (BCG) vaccine	Live-attenuated mycobacterial strain used to prevent tuberculosis in very limited circumstances
Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine	Toxoids of diphtheria and tetanus and purified and detoxified components from *Bordetella pertussis*
DTaP–hepatitis B–inactivated polio vaccine (DTaP-HepB-IPV)	DTaP with hepatitis B surface antigen (HBsAg) produced through recombinant techniques in yeast with inactivated whole polioviruses
DTaP with IPV and Hib (DTaP-IPV/Hib)	DTaP with inactivated whole polioviruses and Hib polysaccharide conjugated to tetanus toxoid
DTaP and inactivated polio vaccine (DTaP-IPV)	DTaP with inactivated whole polioviruses
Hib conjugate vaccine (Hib)	Polysaccharide conjugated to either tetanus toxoid or meningococcal group B outer membrane protein
Hepatitis A vaccine (HAV)	Inactivated whole virus
Hepatitis A–hepatitis B vaccine (HAV-HBV)	Combined hepatitis A and B vaccine
Hepatitis B vaccine (HBV)	HBsAg produced through recombinant techniques in yeast
Hepatitis B–Hib vaccine (Hib-HBV)	Combined hepatitis B–Hib vaccine; the Hib component is polysaccharide conjugated to meningococcal group B outer membrane protein
Human papillomavirus vaccine (bivalent) (HPV2), (quadrivalent) (HPV4), and 9-valent (HPV9)	The L1 capsid proteins of HPV types 6, 11, 16, and 18 to prevent cervical cancer and genital warts (HPV4) and types 16 and 18 to prevent cervical cancer (HPV2); HPV9 also contains types 31, 33, 45, 52, and 58.
Influenzavirus vaccine inactivated (IIV)	Available either as trivalent (A/H_3N_2, A/H_1N_1, and B) split and purified inactivated vaccines containing the hemagglutinin (H) and neuraminidase (N) of each type or as quadrivalent preparations (which include representative strains from 2 B-lymphocyte clades in addition to the 2 influenza A strains in trivalent inactivated influenza vaccine)
Influenzavirus vaccine live, intranasal (LAIV)	Live-attenuated, temperature-sensitive, cold-adapted trivalent vaccine containing the H and N genes from the wild strains reassorted to have the 6 other genes from the cold-adapted parent, only available as quadrivalent preparation
Japanese encephalitis vaccine	Inactivated whole virus that is purified
Measles, mumps, rubella (MMR) vaccine	Live-attenuated viruses
Measles, mumps, rubella, varicella (MMRV) vaccine	Live-attenuated viruses
Meningococcal conjugate vaccine against serogroups A, C, W135, and Y (MCV4)	Polysaccharide from each serogroup conjugated to diphtheria toxoid or CRM 197
Meningococcal conjugate vaccine against serogroups C and Y and Hib conjugate vaccine	Polysaccharide from each serogroup conjugated to diphtheria toxoid and Hib polysaccharide conjugated to tetanus toxoid
Meningococcal polysaccharide vaccine against serogroups A, C, W135, and Y (MPSV4)	Polysaccharides from each of the serogroups
Pneumococcal conjugate vaccine (13 valent) (PCV13)	Pneumococcal polysaccharides conjugated to a nontoxic form of diphtheria toxin CRM197 Contains 13 serotypes that accounted for >80% of invasive disease in young children prior to vaccine licensure
Pneumococcal polysaccharide vaccine (23 valent) (PPSV23)	Pneumococcal polysaccharides of 23 serotypes responsible for 85-90% of bacteremic disease in the United States
Poliomyelitis (inactivated, enhanced potency) (IPV)	Inactivated whole virus
Rabies vaccines (human diploid and purified chick embryo cell)	Inactivated whole virus
Rotavirus vaccines (RV5 and RV1)	Bovine rotavirus pentavalent vaccine (RV5) live reassortment attenuated virus, and human live-attenuated virus (RV1)
Smallpox vaccine	Vaccinia virus, an attenuated poxvirus that provides cross-protection against smallpox
Tetanus and diphtheria toxoids, adsorbed (Td, adult use)	Tetanus toxoid plus a reduced quantity of diphtheria toxoid compared to diphtheria toxoid used for children <7 yr of age
Tetanus and diphtheria toxoids adsorbed plus acellular pertussis (Tdap) vaccine	Tetanus toxoid plus a reduced quantity of diphtheria toxoid plus acellular pertussis vaccine to be used in adolescents and adults and in children 7 through 9 yr of age who have not been appropriately immunized with DTaP
Typhoid vaccine (polysaccharide)	Vi capsular polysaccharide of *Salmonella typhi*
Typhoid vaccine (oral)	Live-attenuated Ty21a strain of *S. typhi*
Varicella vaccine	Live-attenuated Oka strain
Yellow fever vaccine	Live-attenuated 17D strain

*As of January 2015.

Data from Centers for Disease Control and Prevention: U.S. vaccine names. http://www.cdc.gov/vaccines/about/terms/USvaccines.html

vaccine candidates through preclinical testing in humans into human clinical trials. There are 3 phases of prelicensure clinical trials: **phase I,** generally involving <100 participants to gauge safety and dosing; **phase II,** involving several hundred or more participants to refine safety and dosing; and **phase III** or pivotal trials that can involve thousands or tens of thousands of participants. Data from phase III trials form the major basis for licensure. Following successful clinical development, the vaccine sponsor applies to the FDA for vaccine licensure. Estimates for the cost of development for each vaccine range to $800 million or more. Following licensure by the FDA, recommendations for use are made by the Advisory Committee on Immunization Practices (ACIP) and postlicensure monitoring is performed on hundreds of thousands to millions of people to monitor vaccine safety and effectiveness.

Vaccine Production

Vaccine production is primarily a responsibility of private industry. Many of the vaccines recommended routinely for children are produced by only 1 of the vaccine manufacturers. Only Hib, hepatitis B, HPV, rotavirus, MCV4 (meningococcal conjugate vaccine against serogroups A, C, W135, and Y), diphtheria and tetanus toxoids and acellular pertussis (DTaP), and tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccines for adolescents and adults have multiple manufacturers. IPV as an IPV-only vaccine has only 1 manufacturer, but IPV also is available in combination products DTaP–hepatitis B–IPV, DTaP-IPV/Hib, and DTaP-IPV from different manufacturers. Influenza vaccine for children 2 yr of age or younger is produced by fewer manufacturers (see http://www.cdc.gov/flu/protect/vaccine/vaccines.htm for available influenza vaccines). MMR, MMRV, varicella, pneumococcal conjugate vaccine (13 valent) (PCV13), and tetanus and diphtheria (Td) vaccines also are produced by single manufacturers.

Table 172-4 Characteristics of Polysaccharide and Conjugate Vaccines

CHARACTERISTIC	CONJUGATE	POLYSACCHARIDE
T-lymphocyte dependent immune response	Yes	No
Immune memory	Yes	No
Persistence of protection	Yes	No
Booster effect	Yes	No
Reduction of carriage	Yes	No
Herd protection	Yes	No
Lack of hyporesponsiveness	Yes	No

Vaccine Policy

There are 2 major committees that make vaccine policy recommendations for children: the Committee on Infectious Diseases (COID) of the AAP (the Red Book Committee) and the ACIP of the CDC. Annually, the AAP, the ACIP, and the American Academy of Family Physicians issue a **harmonized** childhood and adolescent immunization schedule (http://www.cdc.gov/vaccines/schedules/index.html). The COID consists primarily of academic pediatric infectious disease specialists with liaisons from practicing pediatricians, professional organizations, and government agencies including the FDA, CDC, National Institutes of Health, and National Vaccine Program Office. Recommendations of the COID must be approved by the AAP Board of Directors. The ACIP consists of 15 voting members who are academic infectious disease experts (for both children and adults), family physicians, state and local public health officials, nurses, and 1 consumer representative. The ACIP also has representatives from 29 liaison organizations, including major medical societies, professional organizations, managed care, and others, as well as 8 ex officio government entities that deal with vaccines. Only ACIP members vote on vaccine recommendations. Since October 2011, the ACIP has used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process to develop evidence-based vaccine recommendations. The ACIP recommendations, available at http://www.cdc.gov/vaccines/acip/recs/index.html, are official only after adoption by the CDC director, which leads to publication in the *Morbidity and Mortality Weekly Report (MMWR Morb Mortal Wkly Rep)*. The AAP recommendations are published in the *Red Book* and in issues of *Pediatrics*.

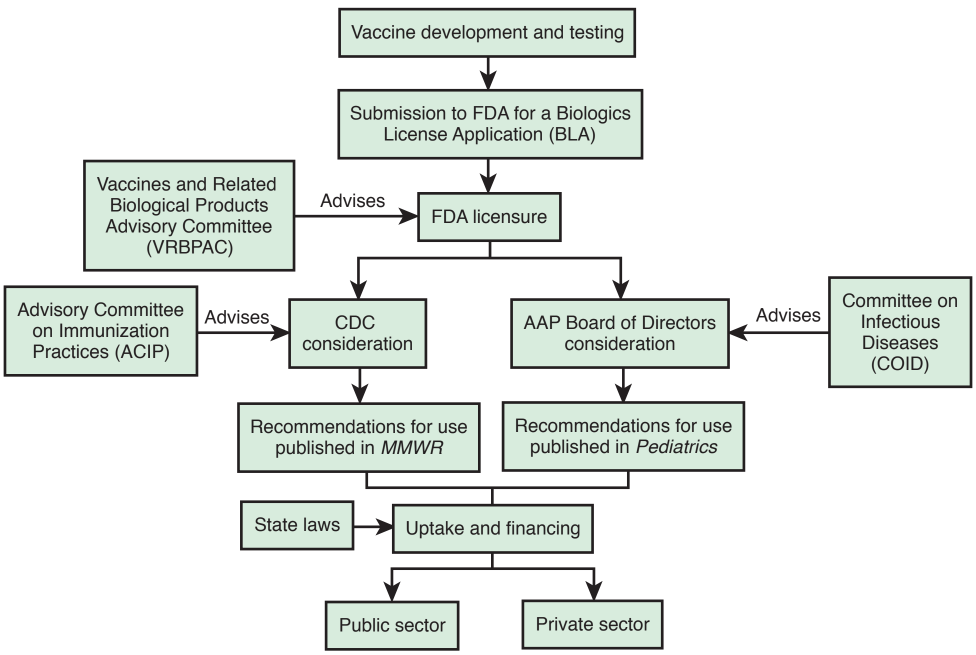

Figure 172-1 Vaccine development and testing. *(Modified from Pickering LK, Orenstein WE: Development of pediatric vaccine recommendations and policies,* Semin Pediatr Infect Dis *13[3]:148–154, 2002.)*

Vaccine Financing

Approximately 50% of vaccines routinely administered to children and adolescents <19 yr of age are purchased thorough a contract negotiated by the federal government with licensed vaccine manufacturers. There are 3 major sources of funds that can purchase vaccines through this contract.

The greatest portion comes from the Vaccines for Children (VFC) program (http://www.cdc.gov/vaccines/programs/vfc/index.html), a federal entitlement program established in 1993. The VFC program covers children on Medicaid, children without any insurance (uninsured), and Native Americans and Alaska Natives. In addition, children who have insurance but whose insurance does not cover immunization (underinsured) can be covered through VFC but only if they go to a federally qualified health center (http://www.cms.gov/center/fqhc.asp). In contrast to other public funding sources that require approval of discretionary funding by legislative bodies, VFC funds are immediately available for new recommendations provided the ACIP votes the vaccine and the recommendation for its use into the VFC program, the federal government negotiates a contract, and the Office of Management and Budget apportions funds. The VFC program can provide free vaccines to participating private providers for administration to children eligible for coverage under the program.

The second major federal funding source is the Section 317 Discretionary Federal Grant Program to states and selected localities. These funds must be appropriated annually by Congress, but in contrast to VFC, they have not had eligibility requirements for use. The third major public source of funds is state appropriations. The VFC program itself does not cover vaccine administration costs. Medicaid covers the administration fees for children enrolled in that program. Parents of other children eligible for VFC must pay administration fees out of pocket, although there is a stipulation in the law that no one eligible for the program can be denied vaccines because of inability to pay the administration fee. The Affordable Care Act states that all vaccines recommended by ACIP and included in the immunization schedules must be provided by qualified insurance programs with no copay and no deductible.

Vaccine Safety Monitoring

Monitoring vaccine safety is the responsibility of the FDA, CDC, and vaccine manufacturers. A critical part of that monitoring depends on reports provided to the Vaccine Adverse Event Reporting System. Adverse events following immunization can be reported by completing a Vaccine Adverse Event Reporting System form that can be obtained from http://www.vaers.hhs.gov, or by calling 1-800-822-7967. Individual Vaccine Adverse Event Reporting System case reports may be helpful in generating hypotheses about whether vaccines are causing certain clinical syndromes, but in general they are not helpful in evaluating the causal role of vaccines in the adverse event. This is because most clinical syndromes that follow vaccination are similar to syndromes that occur in the absence of vaccination, which constitute background rates. For causality assessment, epidemiologic studies are often necessary, comparing the incidence rate of the adverse event after vaccination with the rate in the unvaccinated. A statistically significant higher rate in the vaccinated would be consistent with causation.

The Vaccine Safety Datalink consists of inpatient and outpatient records of some of the largest managed-care organizations in the United States and facilitates causality evaluation. In addition, the clinical immunization safety assessment network has been established to advise primary care physicians on evaluation and management of adverse events (http://www.cdc.gov/vaccinesafety/Activities/CISA.html).

The Institute of Medicine (IOM) has reviewed independently a variety of vaccine safety concerns and published reports (available at http://www.iom.edu/Reports.aspx?Search=vaccine%20safety) summarizing its findings. From 2001 through 2004, the IOM released 8 reports concluding that the body of epidemiologic evidence did not show an association with vaccines and autism.

In 2011, the IOM released a report entitled "Adverse Effects of Vaccines: Evidence and Causality" (http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx), in which the IOM Committee reviewed a list of reported adverse effects associated with 8 vaccines to evaluate the scientific evidence, if any, of an event–vaccine relationship. For the purposes of the report, the committee developed 158 causality conclusions and assigned each relationship between a vaccine and an adverse health problem to 1 of 4 causation categories. The committee concluded that available evidence convincingly supported a causal relationship between MMR, varicella-zoster, influenza, hepatitis B, meningococcal, and tetanus-containing vaccines and anaphylaxis. Additionally, evidence favored rejection of 5 vaccine–adverse event relationships, including MMR vaccine and autism, inactivated influenza vaccines and asthma episodes, as well as Bell palsy, and MMR and DTaP and type 1 diabetes mellitus. For the majority of cases (135 vaccine–adverse event pairs), the evidence was inadequate to accept or reject a causal relationship because of rarity of the events. Overall, the committee concluded that few health problems are caused by or clearly associated with vaccines.

In 2013, the IOM released a report entitled "Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies" (http://www.iom.edu/Reports/2013/The-Childhood-Immunization-Schedule-and-Safety.aspx). The IOM committee uncovered no evidence of major safety concerns associated with adherence to the recommended childhood immunization schedule. For more information on IOM reports, see http://www.iom.edu/.

The National Vaccine Injury Compensation Program, established in 1988, is designed to compensate people injured by vaccines in the childhood and adolescent immunization schedule. The program is funded through an excise tax of $0.75 per disease prevented per dose. As of 2013, all of the routinely recommended vaccines that protect children against 16 diseases are covered by this program. The National Vaccine Injury Compensation Program was established to provide a no-fault system. There is a table of related injuries and time frames. All people alleging injury from covered vaccines must first file with the program. If the injury meets the requirements of the table, compensation is automatic. If not, the claimant has the responsibility to prove causality. If compensation is accepted, the claimant cannot sue the manufacturer or physician administering the vaccine. If the claimant rejects the judgment of the compensation system, the claimant can enter the tort system, which is uncommon. Information on the National Vaccine Injury Compensation Program is available at http://www.hrsa.gov/vaccinecompensation, or by calling 1-800-338-2382. All physicians administering a vaccine covered by the program are required by law to give the approved Vaccine Information Statement to the child's parent or guardian at each visit before administering vaccines. Information on the Vaccine Information Statement can be obtained from http://www.cdc.gov/vaccines/hcp/vis/index.html.

Vaccine Delivery

To ensure potency, vaccines should be stored at recommended temperatures before and after reconstitution. A comprehensive resource for providers on vaccine storage and handling recommendations and best practice strategies is available at http://www.cdc.gov/vaccines/recs/storage/default.htm. Expiration dates should be noted, and expired vaccines should be discarded. Lyophilized vaccines often have long shelf lives. However, the shelf life of reconstituted vaccines generally is short, ranging from 30 min for varicella vaccine to 8 hr for MMR vaccine.

All vaccines have a preferred route of administration, which is specified in package inserts and in AAP and ACIP recommendations. Most inactivated vaccines, including DTaP, hepatitis A, hepatitis B, Hib, inactivated influenza vaccine (IIV), HPV, PCV13, MCV4, and Tdap, are administered IM. In contrast, MPVS4 and the commonly used live-attenuated vaccines, MMR, MMRV, and varicella, should be dispensed by the SC route and rotavirus vaccine is administered orally. IPV and PPS23 (pneumococcal polysaccharide vaccine) can be given IM or SC. One influenza vaccine, LAIV, is administrated intranasally, and another influenza vaccine by the intradermal route. For IM injections, the anterolateral thigh muscle is the preferred site for infants and young children. The recommended needle length varies depending on

age and size: ⅝ inch for newborn infants, 1 inch for infants 2 through 12 mo of age, and 1-1.25 inches for older children. For adolescents and adults, the deltoid muscle of the arm is the preferred site for IM administration with needle lengths of 1-1.25 inches depending on the size of the patient. Most IM injections can be made with 23-25 gauge needles. For SC injections, needle lengths generally range from ⅝ to ¾ inches with 23-25 gauge needles.

Other areas dealing with various aspects of immunization are important for pediatricians and other healthcare providers. Table 172-5 lists websites providing information in these areas.

RECOMMENDED IMMUNIZATION SCHEDULE

All children in the United States should be vaccinated against 16 diseases (Figs. 172-2 and 172-3) (annually updated schedule available at http://www.cdc.gov/vaccines/schedules/index.html).

Hepatitis B vaccine is recommended in a 3 dose schedule starting at birth. The birth dose, as well as hepatitis B immunoglobulin, is critical for infants born to mothers who are hepatitis B surface antigen (HBsAg)–positive or whose hepatitis B immune status is unknown, but the recommendation is to administer hepatitis B vaccine to all newborns before hospital discharge.

The DTaP series consists of 5 doses administered at 2, 4, 6, and 15 through 18 mo of age, and 4 through 6 yr of age. The 4th dose of DTaP may be administered as early as 12 mo of age, provided 6 mo has elapsed since the 3rd dose. The 5th (booster) dose of DTaP vaccine is not necessary if the 4th dose was administered at 4 yr of age or older. One dose of an adult preparation of Tdap is recommended for all adolescents at 11 through 12 yr of age. Adolescents 13 through 18 yr of age who missed the 11 through 12 yr of age Tdap booster dose should receive a single dose of Tdap if they have completed the diphtheria, tetanus, and pertussis (DTP)/DTaP series. Tdap may be given at any interval following the last Td. Table 172-6 lists preparations in which DTaP is combined with other vaccines.

There are 3 licensed preparations of single-antigen Hib vaccines. The vaccine conjugated to tetanus toxoid (PRP-T) is given in a 4 dose series at 2, 4, 6, and 12 through 15 mo of age, and the Hib vaccine conjugated to meningococcal outer membrane protein (PRP-OMP) is recommended in a 3 dose series at 2, 4, and 12 through 15 mo of age. The 3rd Hib vaccine is licensed as a booster for children 15 mo through 4 yr of age. There are several vaccines in which Hib is a component, in addition to single-antigen Hib conjugate vaccines (Table 172-7).

Influenza vaccine is recommended for all children beginning at 6 mo of age, with a minimum age of 6 mo for IIVs and 24 mo of age for LAIVs. Various influenza vaccine preparations are FDA licensed for different age groups (see http://www.cdc.gov/flu/protect/vaccine/vaccines.htm and http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml#flu). Children 6 mo of age through 8 yr of age being vaccinated for the first time should receive 2 doses at least 4 wk apart. If such children only received a single dose of IIV the prior season, they need 2 doses the following season. For additional guidelines, follow dosing instructions in the influenza statement, which is updated annually by the CDC. Influenza vaccine usually is given in October or November, although there are benefits even when administered as late as February or March because influenza seasons most commonly peak in February. People 9 yr of age and older should receive 1 dose of influenza vaccine annually.

IPV should be administered at 2, 4, and 6 through 18 mo of age with a booster dose at 4 through 6 yr of age. The final dose in the series should be administered on or after 4 yr of age and at least 6 mo after the previous dose. The final dose in the IPV series should be administered at 4 yr of age or older regardless of the number of previous doses, and the minimal interval from dose 3 to dose 4 is 6 mo. For catch-up vaccine recommendations, see the recommended childhood immunization schedule at http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html.

MMR should be administered at 12 through 15 mo of age followed by a 2nd dose at 4 through 6 yr of age. Two doses of varicella vaccine should be given, the 1st at 12 through 18 mo of age and the 2nd at 4 through 6 yr of age. MMR and MMRV preparations are available. The quadrivalent MMRV vaccine is preferred in place of separate MMR and varicella vaccines at the 4 through 6 yr old visit. Because of a slight increase in febrile seizures associated with combined MMRV vaccine compared to the separate products, use of MMRV is not preferred over use of separate MMR and varicella vaccines for the initial dose at 12 through 15 mo of age.

Protection against pneumococcal and meningococcal disease can be provided by either conjugated or polysaccharide vaccines. Conjugated vaccines offer several benefits over polysaccharide vaccines (see Table 172-4). PCV13 is recommended as a 4 dose series at 2, 4, 6, and 12 through 15 mo of age. For children 14 through 59 mo of age who have received an age-appropriate series of PCV7, administer a single supplemental dose of PCV13. PPSV23 is recommended for select children with conditions that place them at risk for pneumococcal disease.

A 2 dose series of MCV4 includes a recommended dose for all adolescents at 11 through 12 yr of age and a booster dose at 16 yr of age. If the 1st dose is administered at 13 through 15 yr of age, a booster dose should be administered at 16 through 18 yr of age. No booster dose is needed if the 1st dose is administered at 16 yr of age. In addition, MCV4 should be administered to people 2 mo through 55 yr of age with underlying conditions that place them at high risk of meningococcal disease. People with high-risk conditions should receive 2 doses of MCV4 at 0 and 2 mo followed by booster doses.

Hepatitis A vaccine, licensed for administration to children 12 mo of age and older, is recommended for universal administration to all children at 12 through 23 mo of age and for certain high-risk groups. The 2 doses in the series should be separated by at least 6 mo. Children who have received 1 dose of hepatitis A vaccine before 24 mo of age should receive a 2nd dose 6-18 mo after the 1st dose. For anyone 2 yr of age or older who has not yet received the 2 dose hepatitis A vaccine series, 2 doses of vaccine separated by 6-18 mo may be administered if immunity against hepatitis A infection is desired.

Administer a 3 dose series of HPV vaccine to all adolescents 11 through 12 yr of age. Either HPV4 or HPV2 is recommended in a 3 dose series to females, and only HPV4 in the same schedule is recommended for males. The vaccine series can be started at 9 yr of age. Administer the 2nd dose at 1-2 mo after the 1st dose, and the 3rd dose 6 mo after the 1st dose (at least 24 wk after the 1st dose).

Two rotavirus vaccines are available, RotaTeq (RV5) and Rotarix (RV1). With both vaccines, the 1st dose can be administered as early as 6 wk of age and must be administered by 14 wk 6 days. The final dose in the series must be administered no later than 8 mo of age. The RV5 vaccine is administered in 3 doses at least 4 wk apart. The RV1 vaccine is administered in 2 doses at least 4 wk apart. Immunization should not be initiated for infants 15 wk of age and older as stated in the immunization schedule.

The present schedule, excluding influenza vaccine, can require as many as 34 doses, including 31 that must be administered by injection. Of the doses, 25 are recommended prior to 2 yr of age, including 22 injections. Influenza vaccination, starting at 6 mo of age, can add an additional 20 injections through 18 yr of age. To reduce the injection burdens, several combination vaccines are available (see Table 172-7).

The recommended childhood and adolescent immunization schedule establishes a routine adolescent visit at 11 through 12 yr of age. MCV4, a Tdap booster, and HPV vaccine should be administered during this visit. Influenza vaccine should be administered annually. In addition, the 11 through 12 yr old visit is an opportune time to review all of the immunizations the adolescent has received previously, to provide any doses that were missed, and to review other age-appropriate preventive services. The 11 through 12 year old visit establishes an important platform for incorporating other vaccines. Information on the current status of new vaccine licensure and recommendations for use can be obtained at http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml and http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833.

For children who are at least 1 mo behind in their immunizations, catch-up immunization schedules are available for children 4 mo

Text continued on p. 1254

Table 172-5 Vaccine Websites and Resources

ORGANIZATION	WEBSITE
HEALTH PROFESSIONAL ASSOCIATIONS	
American Academy of Family Physicians (AAFP)	http://www.familydoctor.org/online/famdocen/home.html
American Academy of Pediatrics (AAP)	http://www.aap.org/
AAP Childhood Immunization Support Program	http://www.aap.org/immunization/
American Association of Occupational Health Nurses (AAOHN)	http://www.aaohn.org/
American College Health Association (ACHA)	http://www.acha.org/
American College of Obstetricians and Gynecologists (ACOG)–Immunization for Women	http://www.immunizationforwomen.org/
American Medical Association (AMA)	http://www.ama-assn.org/
American Nurses Association (ANA)	http://www.nursingworld.org/
American Pharmacists Association (APhA)	http://www.pharmacist.com/
American School Health Association (ASHA)	http://www.ashaweb.org/i4a/pages/index.cfm?pageid=1
American Travel Health Nurses Association (ATHNA)	http://www.ashaweb.org/i4a/pages/index.cfm?pageid=1
Association for Professionals in Infection Control and Epidemiology (APIC)	http://www.apic.org/
Association of State and Territorial Health Officials (ASTHO)	http://www.astho.org/
Association of Teachers of Preventive Medicine (ATPM)	http://www.atpm.org/
National Medical Association (NMA)	http://www.nmanet.org/
Society of Teachers of Family Medicine—Group on Immunization Education	http://www.immunizationed.org/
NONPROFIT GROUPS AND UNIVERSITIES	
Albert B. Sabin Vaccine Institute	http://www.sabin.org/
Allied Vaccine Group (AVG)	http://www.vaccine.org/
Brighton Collaboration	https://brightoncollaboration.org/public
Center for Vaccine Awareness and Research—Texas Children's Center	http://www.texaschildrens.org/Locate/Departments-and-Services/Vaccine/
Children's Vaccine Program	http://www.path.org/vaccineresources/
Every Child by Two (ECBT)	http://www.ecbt.org/
Families Fighting Flu	http://www.familiesfightingflu.org/
Global Alliance for Vaccines and Immunization (GAVI)	http://www.gavialliance.org/
Health on the Net Foundation (HON)	http://www.hon.ch/
Immunization Action Coalition (IAC)	http://www.immunize.org/
Infectious Diseases Society of America (IDSA)	http://www.idsociety.org/Index.aspx
Institute for Vaccine Safety (IVS), Johns Hopkins Bloomberg School of Public Health	http://www.vaccinesafety.edu/
Institute of Medicine (IOM)	http://www.iom.edu/Activities/PublicHealth/ImmunizationSafety.aspx
National Alliance for Hispanic Health	http://www.hispanichealth.org/
National Foundation for Infectious Diseases (NFID)	http://www.idsociety.org/Index.aspx
National Foundation for Infectious Diseases (NFID)—Childhood Influenza Immunization Coalition (CIIC)	http://www.preventchildhoodinfluenza.com/
National Healthy Mothers, Healthy Babies Coalition (HMHB)	http://www.hmhb.org/
National Network for Immunization Information (NNii)	http://www.immunizationinfo.org/
Parents of Kids with Infectious Diseases (PKIDS)	http://www.pkids.org/
PATH Vaccine Resource Library	http://www.cdc.gov/vaccines/acip/index.html
The Vaccine Education Center at the Children's Hospital of Philadelphia	http://www.chop.edu/service/vaccine-education-center/home.html
The Vaccine Place	http://www.vaccineplace.com/?fa=home
Vaccinate Your Baby	http://www.vaccinateyourbaby.org/
GOVERNMENT ORGANIZATIONS	
Centers for Disease Control and Prevention (CDC)	
Advisory Committee on Immunization Practices (ACIP)	http://www.cdc.gov/vaccines/acip/index.html
ACIP Vaccine Recommendations	http://www.cdc.gov/vaccines/hcp/acip-recs/index.html
Current Vaccine Delays and Shortages	http://www.cdc.gov/vaccines/vac-gen/shortages/
Public Health Image Library	http://www.phil.cdc.gov/phil/home.asp
Travelers' Health	http://www.cdc.gov/travel/
Vaccine Adverse Events Reporting System (VAERS)	http://www.cdc.gov/vaccinesafety/Activities/vaers.html
Vaccine Administration: Recommendations and Guidelines	http://www.cdc.gov/vaccines/recs/vac-admin/default.htm
Vaccines and Immunizations	http://www.cdc.gov/vaccines/
Vaccines for Children Program	http://www.cdc.gov/vaccines/programs/vfc/index.html
Vaccines for Children—Vaccine Price List	http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html
Vaccine Safety	http://www.cdc.gov/vaccinesafety/index.html
Vaccine Storage and Handling	http://www.cdc.gov/vaccines/recs/storage/default.htm
Department of Health and Human Services (HHS)	
National Vaccine Program Office (NVPO)	http://www.hhs.gov/nvpo/
Health Resources and Services Administration	
National Vaccine Injury Compensation Program	http://www.hrsa.gov/vaccinecompensation/
National Institute of Allergy and Infectious Diseases (NIAID)	
Vaccines	http://www.niaid.nih.gov/topics/vaccines/Pages/Default.aspx
World Health Organization (WHO)	
Immunization, Vaccines, and Biologicals	http://www.who.int/immunization/en/

Figure 172-2 Recommended immunization schedule for persons aged 0 through 18 years – United States, 2015.

(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 172-3]).

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 172-2. To determine minimum intervals between doses, see the catch-up schedule (Figure 172-3). School entry and adolescent vaccine age groups are shaded.

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13–15 yrs	16–18 yrs
Hepatitis B[1] (HepB)	1st dose	←2nd dose→			←3rd dose→											
Rotavirus[2] (RV) RV1 (2-dose series); RV5 (3-dose series)			1st dose	2nd dose	See footnote 2											
Diphtheria, tetanus, & acellular pertussis[3] (DTaP: <7 yrs)			1st dose	2nd dose	3rd dose			←4th dose→				5th dose				
Tetanus, diphtheria, & acellular pertussis[4] (Tdap: ≥7 yrs)														(Tdap)		
Haemophilus influenzae type b[5] (Hib)			1st dose	2nd dose	See footnote 5		←3rd or 4th dose, See footnote 5→									
Pneumococcal conjugate[6] (PCV13)			1st dose	2nd dose	3rd dose		←4th dose→									
Pneumococcal polysaccharide[6] (PPSV23)																
Inactivated poliovirus[7] (IPV: <18 yrs)			1st dose	2nd dose	←3rd dose→							4th dose				
Influenza[8] (IIV; LAIV) 2 doses for some: See footnote 8					Annual vaccination (IIV only) 1 or 2 doses						Annual vaccination (LAIV or IIV) 1 or 2 doses		Annual vaccination (LAIV or IIV) 1 dose only			
Measles, mumps, rubella[9] (MMR)					See footnote 9		←1st dose→					2nd dose				
Varicella[10] (VAR)							←1st dose→					2nd dose				
Hepatitis A[11] (HepA)							←2-dose series, See footnote 11→									
Human papillomavirus[12] (HPV2: females only; HPV4: males and females)														(3-dose series)		
Meningococcal[13] (Hib-MenCY ≥ 6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥ 2 mos)			See footnote 13											1st dose		Booster

Range of recommended ages for all children | Range of recommended ages for catch-up immunization | Range of recommended ages for certain high-risk groups | Range of recommended ages during which catch-up is encouraged and for certain high-risk groups | Not routinely recommended

This schedule includes recommendations in effect as of January 1, 2015. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm) or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (http//www.cdc.gov/vaccines/acip), the American Academy of Pediatrics (http://www.aap.org), the American Academy of Family Physicians (http://www.aafp.org), and the American College of Obstetricians and Gynecologists (http://www.acog.org).

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Footnotes — Recommended immunization schedule for persons aged 0 through 18 years—United States, 2015

For further guidance on the use of the vaccines mentioned below, see: http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
For vaccine recommendations for persons 19 years of age and older, see the Adult Immunization Schedule.

Additional information

- For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the relevant ACIP statement available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
- Vaccine doses administered 4 days or less before the minimum interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum interval or minimum age should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see *MMWR, General Recommendations on Immunization and Reports* / Vol. 60 / No. 2; Table 1. *Recommended and minimum ages and intervals between vaccine doses* available online at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.
- Information on travel vaccine requirements and recommendations is available at http://wwwnc.cdc.gov/travel/destinations/list.
- For vaccination of persons with primary and secondary immunodeficiencies, see Table 13, *"Vaccination of persons with primary and secondary immunodeficiencies,"* in *General Recommendations on Immunization* (ACIP), available at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.; and American Academy of Pediatrics. "Immunization in Special Clinical Circumstances," in Pickering LK, Baker CJ, Kimberlin DW, Long SS eds. *Red Book: 2012 report of the Committee on Infectious Diseases. 29th ed.* Elk Grove Village, IL: American Academy of Pediatrics.

1. **Hepatitis B (HepB) vaccine. (Minimum age: birth)**

Routine vaccination:

At birth:
- Administer monovalent HepB vaccine to all newborns before hospital discharge.
- For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series at age 9 through 18 months (preferably at the next well-child visit).
- If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG for infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days.

Doses following the birth dose:
- The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
- Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible. See Figure 2.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the **first** dose. The final (third or fourth) dose in the HepB vaccine series should be administered **no earlier than age 24 weeks**.
- Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose.

Catch-up vaccination:
- Unvaccinated persons should complete a 3-dose series.
- A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
- For other catch-up guidance, see Figure 172-3.

2. **Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV1 [Rotarix] and RV5 [RotaTeq])**

Routine vaccination:

Administer a series of RV vaccine to all infants as follows:
1. If Rotarix is used, administer a 2-dose series at 2 and 4 months of age.
2. If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months.
3. If any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

Catch-up vaccination:
- The maximum age for the first dose in the series is 14 weeks, 6 days; vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
- The maximum age for the final dose in the series is 8 months, 0 days.
- For other catch-up guidance, see Figure 172-3.

3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks. Exception: DTaP-IPV [Kinrix]: 4 years)**

Routine vaccination:
- Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose. However, the fourth dose of DTaP need not be repeated if it was administered at least 4 months after the third dose of DTaP.

Figure 172-2 Recommended immunization schedule for persons aged 0 through 18 yr—United States, 2015. *(From Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html)*

Continued

3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine (cont'd)**

Catch-up vaccination:
- The fifth dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
- For other catch-up guidance, see Figure 172-3.

4. **Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for both Boostrix and Adacel)**

Routine vaccination:
- Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
- Tdap may be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.
- Administer 1 dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferred during 27 through 36 weeks' gestation) regardless of time since prior Td or Tdap vaccination.

Catch-up vaccination:
- Persons aged 7 years and older who are not fully immunized with DTaP vaccine should receive Tdap vaccine as 1 dose (preferably the first) in the catch-up series; if additional doses are needed, use Td vaccine. For children 7 through 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose at age 11 through 12 years should NOT be administered. Td should be administered instead 10 years after the Tdap dose.
- Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoid (Td) booster doses every 10 years thereafter.
- Inadvertent doses of DTaP vaccine:
  - If administered inadvertently to a child aged 7 through 10 years may count as part of the catch-up series. This dose may count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11 through 12 years.
  - If administered inadvertently to an adolescent aged 11 through 18 years, the dose should be counted as the adolescent Tdap booster.
- For other catch-up guidance, see Figure 172-3.

5. ***Haemophilus influenzae* type b (Hib) conjugate vaccine. (Minimum age: 6 weeks for PRP-T [ACTHIB, DTaP-IPV/Hib (Pentacel) and Hib-MenCY (MenHibrix)], PRP-OMP [PedvaxHIB or COMVAX], 12 months for PRP-T [Hiberix])**

Routine vaccination:
- Administer a 2- or 3-dose Hib vaccine primary series and a booster dose (dose 3 or 4 depending on vaccine used in primary series) at age 12 through 15 months to complete a full Hib vaccine series.
- The primary series with ActHIB, MenHibrix, or Pentacel consists of 3 doses and should be administered at 2, 4, and 6 months of age. The primary series with PedvaxHib or COMVAX consists of 2 doses and should be administered at 2 and 4 months of age; a dose at age 6 months is not indicated.
- One booster dose (dose 3 or 4 depending on vaccine used in primary series) of any Hib vaccine should be administered at age 12 through 15 months. An exception is Hiberix vaccine. Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years who have received at least 1 prior dose of Hib-containing vaccine.
- For recommendations on the use of MenHibrix in patients at increased risk for meningococcal disease, please refer to the meningococcal vaccine footnotes and also to *MMWR* February 28, 2014 / 63(RR01);1-13, available at http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.

Catch-up vaccination:
- If dose 1 was administered at ages 12 through 14 months, administer a second (final) dose at least 8 weeks after dose 1, regardless of Hib vaccine used in the primary series.
- If both doses were PRP-OMP (PedvaxHIB or COMVAX), and were administered before the first birthday, the third (and final) dose should be administered at age 12 through 59 months and at least 8 weeks after the second dose.
- If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a third (and final) dose at age 12 through 15 months or 8 weeks after second dose, whichever is later.
- If first dose is administered before the first birthday and second dose administered at younger than 15 months, a third (and final) dose should be given 8 weeks later.
- For unvaccinated children aged 15 months or older, administer only 1 dose.
- For other catch-up guidance, see Figure 172-3. For catch-up guidance related to MenHibrix, please see the meningococcal vaccine footnotes and also *MMWR* February 28, 2014 / 63(RR01);1-13, available at http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.

Vaccination of persons with high-risk conditions:
- Children aged 12 through 59 months who are at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, immunoglobulin deficiency, or early component complement deficiency, who have received either no doses or only 1 dose of Hib vaccine before 12 months of age, should receive 2 additional doses of Hib vaccine 8 weeks apart; children who received 2 or more doses of Hib vaccine before 12 months of age should receive 1 additional dose.
- For patients younger than 5 years of age undergoing chemotherapy or radiation treatment who received a Hib vaccine dose(s) within 14 days of starting therapy or during therapy, repeat the dose(s) at least 3 months following therapy completion.
- Recipients of hematopoietic stem cell transplant (HSCT) should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 to 12 months after successful transplant, regardless of vaccination history; doses should be administered at least 4 weeks apart.
- A single dose of any Hib-containing vaccine should be administered to unimmunized* children and adolescents 15 months of age and older undergoing an elective splenectomy; if possible, vaccine should be administered at least 14 days before procedure.
- Hib vaccine is not routinely recommended for patients 5 years or older. However, 1 dose of Hib vaccine should be administered to unimmunized* persons aged 5 years or older who have anatomic or functional asplenia (including sickle cell disease) and unvaccinated persons 5 through 18 years of age with human immunodeficiency virus (HIV) infection.

** Patients who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered unimmunized.*

6. **Pneumococcal vaccines. (Minimum age: 6 weeks for PCV13, 2 years for PPSV23)**

Routine vaccination with PCV13:
- Administer a 4-dose series of PCV13 vaccine at ages 2, 4, and 6 months and at age 12 through 15 months.
- For children aged 14 through 59 months who have received an age-appropriate series of 7-valent PCV (PCV7), administer a single supplemental dose of 13-valent PCV (PCV13).

Catch-up vaccination with PCV13:
- Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- For other catch-up guidance, see Figure 172-3.

Vaccination of persons with high-risk conditions with PCV13 and PPSV23:
- All recommended PCV13 doses should be administered prior to PPSV23 vaccination if possible.
- For children 2 through 5 years of age with any of the following conditions: chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; solid organ transplantation; or congenital immunodeficiency:
  1. Administer 1 dose of PCV13 if any incomplete schedule of 3 doses of PCV (PCV7 and/or PCV13) were received previously.
  2. Administer 2 doses of PCV13 at least 8 weeks apart if unvaccinated or any incomplete schedule of fewer than 3 doses of PCV (PCV7 and/or PCV13) were received previously.
  3. Administer 1 supplemental dose of PCV13 if 4 doses of PCV7 or other age-appropriate complete PCV7 series was received previously.
  4. The minimum interval between doses of PCV (PCV7 or PCV13) is 8 weeks.
  5. For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.
- For children aged 6 through 18 years who have cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; generalized malignancy; solid organ transplantation; or multiple myeloma:
  1. If neither PCV13 nor PPSV23 has been received previously, administer 1 dose of PCV13 now and 1 dose of PPSV23 at least 8 weeks later.
  2. If PCV13 has been received previously but PPSV23 has not, administer 1 dose of PPSV23 at least 8 weeks after the most recent dose of PCV13.
  3. If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23.
- For children aged 6 through 18 years with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus, alcoholism, or chronic liver disease, who have not received PPSV23, administer 1 dose of PPSV23. If PCV13 has been received previously, then PPSV23 should be administered at least 8 weeks after any prior PCV13 dose.
- A single revaccination with PPSV23 should be administered 5 years after the first dose to children with sickle cell disease or other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; generalized malignancy; solid organ transplantation; or multiple myeloma.

7. **Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)**

Routine vaccination:
- Administer a 4-dose series of IPV at ages 2, 4, 6 through 18 months, and 4 through 6 years. The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

Catch-up vaccination:
- In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk of imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
- If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years and at least 6 months after the previous dose.
- A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age. IPV is not routinely recommended for U.S. residents aged 18 years or older.
- For other catch-up guidance, see Figure 172-3.

8. **Influenza vaccines. (Minimum age: 6 months for inactivated influenza vaccine [IIV], 2 years for live, attenuated influenza vaccine [LAIV])**

Routine vaccination:
- Administer influenza vaccine annually to all children beginning at age 6 months. For most healthy, nonpregnant persons aged 2 through 49 years, either LAIV or IIV may be used. However, LAIV should NOT be administered to some persons, including 1) persons who have experienced severe allergic reactions to LAIV, any of its components, or to a previous dose of any other influenza vaccine; 2) children 2 through 17 years receiving aspirin or aspirin-containing products; 3) persons who are allergic to eggs; 4) pregnant women; 5) immunosuppressed persons; 6) children 2 through 4 years of age with asthma or who had wheezing in the past 12 months; or 7) persons who have taken influenza antiviral medications in the previous 48 hours. For all other contraindications and precautions to use of LAIV, see *MMWR* August 15, 2014 / 63(32);691-697 [40 pages] available at http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf.

Figure 172-2, cont'd

8. **Influenza vaccines (cont'd)**

For children aged 6 months through 8 years:
- For the 2014-15 season, administer 2 doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time. Some children in this age group who have been vaccinated previously will also need 2 doses. For additional guidance, follow dosing guidelines in the 2014-15 ACIP influenza vaccine recommendations, *MMWR* August 15, 2014 / 63(32);691-697 [40 pages] available at http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf.
- For the 2015–16 season, follow dosing guidelines in the 2015 ACIP influenza vaccine recommendations.

For persons aged 9 years and older:
- Administer 1 dose.

9. **Measles, mumps, and rubella (MMR) vaccine. (Minimum age: 12 months for routine vaccination)**

Routine vaccination:
- Administer a 2-dose series of MMR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
- Administer 1 dose of MMR vaccine to infants aged 6 through 11 months before departure from the United States for international travel. These children should be revaccinated with 2 doses of MMR vaccine, the first at age 12 through 15 months (12 months if the child remains in an area where disease risk is high), and the second dose at least 4 weeks later.
- Administer 2 doses of MMR vaccine to children aged 12 months and older before departure from the United States for international travel. The first dose should be administered on or after age 12 months and the second dose at least 4 weeks later.

Catch-up vaccination:
- Ensure that all school-aged children and adolescents have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks.

10. **Varicella (VAR) vaccine. (Minimum age: 12 months)**

Routine vaccination:
- Administer a 2-dose series of VAR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

Catch-up vaccination:
- Ensure that all persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007 / 56 [No. RR-4], available at http://www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2 doses of varicella vaccine. For children aged 7 through 12 years, the recommended minimum interval between doses is 3 months (if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid); for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

11. **Hepatitis A (HepA) vaccine. (Minimum age: 12 months)**

Routine vaccination:
- Initiate the 2-dose HepA vaccine series at 12 through 23 months; separate the 2 doses by 6 to 18 months.
- Children who have received 1 dose of HepA vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.
- For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of HepA vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired.

Catch-up vaccination:
- The minimum interval between the two doses is 6 months.

Special populations:
- Administer 2 doses of HepA vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection. This includes persons traveling to or working in countries that have high or intermediate endemicity of infection; men having sex with men; users of injection and non-injection illicit drugs; persons who work with HAV-infected primates or with HAV in a research laboratory; persons with clotting-factor disorders; persons with chronic liver disease; and persons who anticipate close personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. The first dose should be administered as soon as the adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.

12. **Human papillomavirus (HPV) vaccines. (Minimum age: 9 years for HPV2 [Cervarix] and HPV4 [Gardasil])**

Routine vaccination:
- Administer a 3-dose series of HPV vaccine on a schedule of 0, 1-2, and 6 months to all adolescents aged 11 through 12 years. Either HPV4 or HPV2 may be used for females, and only HPV4 may be used for males.
- The vaccine series may be started at age 9 years.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks); administer the third dose 24 weeks after the first dose and 16 weeks after the second dose (minimum interval of 12 weeks).

Catch-up vaccination:
- Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals (see Routine vaccination above) for vaccine series catch-up.

13. **Meningococcal conjugate vaccines. (Minimum age: 6 weeks for Hib-MenCY [MenHibrix], 9 months for MenACWY-D [Menactra], 2 months for MenACWY-CRM [Menveo])**

Routine vaccination:
- Administer a single dose of Menactra or Menveo vaccine at age 11 through 12 years, with a booster dose at age 16 years.
- Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV) infection should receive a 2-dose primary series of Menactra or Menveo with at least 8 weeks between doses.
- For children aged 2 months through 18 years with high-risk conditions, see below.

Catch-up vaccination:
- Administer Menactra or Menveo vaccine at age 13 through 18 years if not previously vaccinated.
- If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks between doses.
- If the first dose is administered at age 16 years or older, a booster dose is not needed.
- For other catch-up guidance, see Figure 172-3.

Vaccination of persons with high-risk conditions and other persons at increased risk of disease:
- Children with anatomic or functional asplenia (including sickle cell disease):
  1. Menveo
     - o *Children who initiate vaccination at 8 weeks through 6 months:* Administer doses at 2, 4, 6, and 12 months of age.
     - o *Unvaccinated children 7 through 23 months:* Administer 2 doses, with the second dose at least 12 weeks after the first dose AND after the first birthday.
     - o *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
  2. MenHibrix
     - o *Children 6 weeks through 18 months:* Administer doses at 2, 4, 6, and 12 through 15 months of age.
     - o If the first dose of MenHibrix is given at or after 12 months of age, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
  3. Menactra
     - o *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart. If Menactra is administered to a child with asplenia (including sickle cell disease), do not administer Menactra until 2 years of age and at least 4 weeks after the completion of all PCV13 doses.
- Children with persistent complement component deficiency:
  1. Menveo
     - o *Children who initiate vaccination at 8 weeks through 6 months:* Administer doses at 2, 4, 6, and 12 months of age.
     - o *Unvaccinated children 7 through 23 months:* Administer 2 doses, with the second dose at least 12 weeks after the first dose AND after the first birthday.
     - o *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
  2. MenHibrix
     - o *Children 6 weeks through 18 months:* Administer doses at 2, 4, 6, and 12 through 15 months of age.
     - o If the first dose of MenHibrix is given at or after 12 months of age, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
  3. Menactra
     - o *Children 9 through 23 months:* Administer 2 primary doses at least 12 weeks apart.
     - o *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
- For children who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or the Hajj, administer an age-appropriate formulation and series of Menactra or Menveo for protection against serogroups A and W meningococcal disease. Prior receipt of MenHibrix is not sufficient for children traveling to the meningitis belt or the Hajj because it does not contain serogroups A or W.
- For children at risk during a community outbreak attributable to a vaccine serogroup, administer or complete an age- and formulation-appropriate series of MenHibrix, Menactra, or Menveo.
- For booster doses among persons with high-risk conditions, refer to *MMWR* 2013 / 62(RR02);1-22, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm.

For other catch-up recommendations for these persons, and complete information on use of meningococcal vaccines, including guidance related to vaccination of persons at increased risk of infection, see MMWR March 22, 2013 / 62(RR02);1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf.

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Figure 172-2, cont'd

FIGURE 172-3. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind —United States, 2015.

The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with Figure 1 and the footnotes that follow.

Children age 4 months through 6 years					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Hepatitis B[1]	Birth	4 weeks	8 weeks *and* at least 16 weeks after first dose. Minimum age for the final dose is 24 weeks.		
Rotavirus[2]	6 weeks	4 weeks	4 weeks[2]		
Diphtheria, tetanus, and acellular pertussis[3]	6 weeks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[5]	6 weeks	4 weeks if first dose was administered before the 1st birthday. 8 weeks (as final dose) if first dose was administered at age 12 through 14 months. No further doses needed if first dose was administered at age 15 months or older.	4 weeks[5] if current age is younger than 12 months **and** first dose was administered at younger than age 7 months, **and** at least 1 previous dose was PRP-T (ActHib, Pentacel) or unknown. 8 weeks *and* age 12 through 59 months (as final dose)[5] • if current age is younger than 12 months **and** first dose was administered at age 7 through 11 months; OR • if current age is 12 through 59 months **and** first dose was administered before the 1st birthday, **and** second dose administered at younger than 15 months; OR • if both doses were PRP-OMP (PedvaxHIB; Comvax) **and** were administered before the 1st birthday. No further doses needed if previous dose was administered at age 15 months or older.	8 weeks (as final dose) This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal[6]	6 weeks	4 weeks if first dose administered before the 1st birthday. 8 weeks (as final dose for healthy children) if first dose was administered at the 1st birthday or after. No further doses needed for healthy children if first dose administered at age 24 months or older.	4 weeks if current age is younger than 12 months and previous dose given at <7months old. 8 weeks (as final dose for healthy children) if previous dose given between 7-11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months. No further doses needed for healthy children if previous dose administered at age 24 months or older.	8 weeks (as final dose) This dose only necessary for children aged 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus[7]	6 weeks	4 weeks[7]	4 weeks[7]	6 months[7] (minimum age 4 years for final dose).	
Meningococcal[13]	6 weeks	8 weeks[13]	See footnote 13	See footnote 13	
Measles, mumps, rubella[9]	12 months	4 weeks			
Varicella[10]	12 months	3 months			
Hepatitis A[11]	12 months	6 months			
Children and adolescents age 7 through 18 years					
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis[4]	7 years[4]	4 weeks	4 weeks if first dose of DTaP/DT was administered before the 1st birthday. 6 months (as final dose) if first dose of DTaP/DT was administered at or after the 1st birthday.	6 months if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus[12]	9 years	Routine dosing intervals are recommended.[12]			
Hepatitis A[11]	Not applicable (N/A)	6 months			
Hepatitis B[1]	N/A	4 weeks	8 weeks **and** at least 16 weeks after first dose.		
Inactivated poliovirus[7]	N/A	4 weeks	4 weeks[7]	6 months[7]	
Meningococcal[13]	N/A	8 weeks[13]			
Measles, mumps, rubella[9]	N/A	4 weeks			
Varicella[10]	N/A	3 months if younger than age 13 years. 4 weeks if age 13 years or older.			

NOTE: The above recommendations must be read along with the footnotes of this schedule in Fig. 172-2.

Figure 172-3 Catch-up immunization schedule for persons aged 4 mo through 18 yr who start late or who are more than 1 mo old–United States, 2015. *(From Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/vaccines/schedules/downloads/child/catchup-schedule-pr.pdf)*

through 18 yr of age (http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html). Also available are interactive immunization schedulers for children <6 yr of age at https://www.vacscheduler.org and for adolescents at http://www.cdc.gov/recs/scheduler/AdolscentScheduler.htm.

VACCINES RECOMMENDED IN SPECIAL CIRCUMSTANCES

There are 4 vaccines (PCV13, PPSV23, MCV4, and Hib) recommended for children and adolescents at increased risk for complications from vaccine-preventable diseases or children who have an increased risk for exposure to these diseases, who are outside the age groups for which these vaccines are normally recommended (PPSV23 is not routinely recommended for any age group of children and is only used for children with high-risk conditions; see Table 172-7). Specific recommendations for use of these vaccines in children with various underlying conditions can be found in the recommended immunization schedule.

PCV13 is recommended for all children <5 yr of age who have conditions that place them at high risk for pneumococcal disease. This recommendation includes children with sickle cell disease and other hemoglobinopathies, including hemoglobin SS, hemoglobin S-C, or hemoglobin S–β-thalassemia, or children who are functionally or anatomically asplenic; children with HIV infection; and children who have chronic disease (see Table 172-7). Children at high risk for pneumococcal disease also should receive PPSV23 to provide immunity to serotypes not contained in the 13-valent conjugate vaccine. PPSV23 should be administered on or after the 2nd birthday and should follow completion of the PCV13 series by at least 6-8 wk. Two doses of PPSV23 are recommended, with an interval of 5 yr between doses. Immunization of previously unvaccinated children with high-risk conditions who are >5 yr of age can be performed with either a dose of PCV13 or a dose of PPSV23.

MCV4 is recommended for people with HIV, children with functional or anatomic asplenia, persistent complement component or properdin deficiencies, and as part of outbreak-control programs. Hib

Table 172-6 Combination Vaccines Licensed and Available in the United States

VACCINE PRODUCT (MANUFACTURER)*	TRADE NAME (YEAR LICENSED)	COMPONENTS	Recommended Ages: PRIMARY SERIES	Recommended Ages: BOOSTER DOSE
Hib-HepB[†‡] (Merck & Co, Inc.)	Comvax (1996)	PRP-OMP + HepB vaccine	2, 4 mo of age	12 through 15 mo of age
MenCY/Hib (GlaxoSmithKline)	MenHibRix (2013)	MenCY + PRP-T	2, 4, 6 mo of age	12 through 15 mo of age
DTaP-IPV/Hib (Sanofi Pasteur)	Pentacel (2008)	DTaP-IPV + PRP-T	2, 4, 6 mo of age	15 through 18 mo of age
DTaP-HepB-IPV (GlaxoSmithKline)	Pediarix (2002)	DTaP + HepB + IPV	2, 4, 6 mo of age	
DTaP-IPV (GlaxoSmithKline)	Kinrix (2008)	DTaP + IPV		4 through 6 yr of age: • booster for 5th dose of DTaP • booster for 4th dose of IPV
HepA-HepB (GlaxoSmithKline)	Twinrix (2001)	HepA + HepB	>18 yr of age; 0, 1, and 6 mo schedule	
MMRV (Merck & Co, Inc.)	ProQuad (2005)	MMR + varicella	12 through 15 mo of age	4 through 6 yr of age

*Dash (-) indicates that products are supplied in their final form by the manufacturer and do not require mixing or reconstitution by user; slash (/) indicates that products are mixed or reconstituted by user.
[†]If a PRP-OMP vaccine is not administered as both doses in the primary series or if there is uncertainty about which products were administered previously, a 3rd dose of Hib conjugate vaccine is needed to complete the primary series.
[‡]Preferred for American Indian/Alaska Native children.
DTap, diphtheria and tetanus toxoids and acellular pertussis vaccine; HepA, hepatitis A vaccine; HepB, hepatitis B vaccine; IPV/Hib, trivalent inactivated polio vaccine and *Haemophilus influenzae* type b vaccine; MMRV, measles-mumps-rubella and varicella vaccine.
Modified from MMWR 62(2):1-28, 2013.

Table 172-7 Vaccines Recommended for Children and Adolescents with Underlying Conditions or at High Risk

VACCINES	CONDITIONS

PCV13 (and PPSV23 in certain conditions)	• Immunocompetent children with:
	  • Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure)
	  • Chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy)
	  • Diabetes mellitus
	  • Cerebrospinal fluid leaks
	  • Cochlear implant
	• Anatomic or functional asplenia (including sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia or splenic dysfunction)
	• Immunocompromising conditions: HIV infection; chronic renal failure and nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease or solid organ transplantation; congenital immunodeficiency

MCV4	• Anatomic or functional asplenia (including sickle cell disease) • Persistent complement component deficiency • Residents of or travelers to countries in African meningitis belt or pilgrims on the Haj • During outbreaks caused by a vaccine serogroup
Hib	• Anatomic or functional asplenia (including sickle cell disease) • Immunocompromising conditions: HIV disease; immunosuppressive therapy for malignant neoplasms; immunoglobulin deficiency including immunoglobulin G_2 subclass deficiency or early complement deficiency; recipients of a hematopoietic stem cell transplant (HSCT)

vaccine is recommended for children with certain high-risk conditions (see Table 172-7).

A variety of vaccines are available for children who will be **traveling** to areas of the world where certain infectious diseases are common in addition to vaccines in the recommended childhood and adolescent schedule (Table 172-8). Vaccines for travelers include typhoid fever, hepatitis A, hepatitis B, Japanese encephalitis, MCV4 or MPS4, rabies, and yellow fever, depending on the location and circumstances of travel. Measles is endemic in many parts of the world. Children 6 through 11 mo of age should receive a dose of MMR before international travel. However, doses of measles vaccine received before 12 mo of age should not be counted in determining compliance with the recommended 2 dose MMR schedule. Additional information on vaccines for international travel can be found at http://wwwnc.cdc.gov/travel/.

Vaccine recommendations for children with **immunocompromising conditions**, either primary (inherited) or secondary (acquired), vary according to the underlying condition, the degree of immune deficit, the risk for exposure to disease, and the vaccine (Table 172-9). Immunization of children with immunocompromise poses the following potential concerns: the incidence or severity of some vaccine-preventable diseases is higher, and therefore certain vaccines are recommended specifically for certain conditions; vaccines may be less effective during the period of altered immunocompetence and may need to be repeated when immune competence is restored; and because of altered immunocompetence, some children and adolescents may be

Table 172-8 Recommended Immunizations for Travelers to Developing Countries*

IMMUNIZATIONS	Length of Travel		
	BRIEF, <2 WK	INTERMEDIATE, 2 WK-3 MO	LONG-TERM RESIDENTIAL, >3 MO
Review and complete age-appropriate childhood and adolescent schedule (see text for details)	+	+	+
• DTaP, poliovirus, pneumococcal, and *Haemophilus influenzae* type b vaccines may be given at 4-wk intervals if necessary to complete the recommended schedule before departure • Measles: 2 additional doses given if <12 mo of age at 1st dose • Rotavirus • Varicella • HPV • Hepatitis B† • Tdap • MCV4			
Yellow fever‡	+	+	+
Hepatitis A§	+	+	+
Typhoid fever‖	±	+	+
Meningococcal disease¶	±	±	±
Rabies**	±	+	+
Japanese encephalitis††	±	±	+

*See disease-specific chapters in the Red Book for details. For further sources of information, see text.
†If there is insufficient time to complete 6 mo primary series, accelerated series can be given.
‡For regions with endemic infection, see Health Information for International Travel (http://www.cdc.gov/travel).
§Indicated for travelers to areas with intermediate or high endemic rates of hepatitis A virus infection.
‖Indicated for travelers who will consume food and liquids in areas of poor sanitation.
¶Recommended for regions of Africa with endemic infection and during local epidemics, and required for travel to Saudi Arabia for the Hajj.
**Indicated for people with high risk for animal exposure (especially to dogs) and for travelers to countries with endemic infection.
††For regions with endemic infection (see Health Information for International Travel). For high-risk activities in areas experiencing outbreaks, vaccine is recommended, even for brief travel.
+, Recommended; ±, consider; DTaP, diphtheria and tetanus toxoids and acellular pertussis.
Modified Pickering LK, Baker CJ, Kimberlin DW, Long SL, editors: Red Book 2012: report of the Committee on Infectious Diseases, *Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 104.*

at increased risk for an adverse event following receipt of a live viral vaccine. Live-attenuated vaccines generally are contraindicated in immunocompromised people. The exceptions include MMR, which may be given to a child with HIV infection provided the child is asymptomatic or symptomatic without evidence of severe immunosuppression, and varicella vaccine, which may be given to HIV-infected children if the $CD4^+$ lymphocyte count is at least 15%. MMRV is not recommended in these situations.

Altered immunocompetence is considered a precaution for rotavirus; however, the vaccine is contraindicated in children with severe combined immunodeficiency disease. Inactivated vaccines may be administered to immunocompromised children, although, depending on the immune deficit, their effectiveness might not be optimal. Children with complement deficiency disorders may receive all vaccines, including live-attenuated vaccines. In contrast, children with phagocytic disorders may receive both inactivated and live-attenuated viral vaccines but not live-attenuated bacterial vaccines.

Corticosteroids can suppress the immune system. Children receiving corticosteroids (≥2 mg/kg/day or ≥20 mg/day of prednisone or equivalent) for 14 or more days should not receive live vaccines until therapy has been discontinued for at least 1 mo. Children on the same dose levels but for <2 wk may receive live viral vaccines as soon as therapy is discontinued, although some experts would wait 2 wk after therapy has been discontinued. Children receiving lower doses of corticosteroids may be vaccinated while receiving therapy.

Children and adolescents with malignancy, and those who have undergone solid organ or hematopoietic stem cell transplantation and immunosuppressive or radiation therapy, should not receive live virus and live bacterial vaccines depending on their immune status. Children who have undergone chemotherapy for leukemia may need to be reimmunized with age-appropriate single doses of previously administered vaccines.

Preterm infants generally can be vaccinated at the same chronologic age as full-term infants according to the recommended childhood immunization schedule. An exception is the birth dose of hepatitis B vaccine. Infants weighing ≥2 kg and who are stable may receive a birth dose. However, hepatitis B vaccination should be deferred in infants weighing <2 kg at birth until 30 days of age, if born to an HBsAg-negative mother. All preterm, low birthweight infants born to HBsAg-positive mothers should receive hepatitis B immunoglobulin and hepatitis B vaccine within 12 hr of birth. However, such infants should receive an additional 3 doses of vaccine starting at 30 days of age (see Fig. 172-2).

Some children have situations that are not addressed directly in current immunization schedules. There are general rules that physicians can use to guide immunization decisions in some of these instances. In general, vaccines may be given simultaneously on the same day, whether inactivated or live. Different inactivated vaccines can be administered at any interval between doses. However, because of theoretical concerns about viral interference, different live-attenuated vaccines (MMR, varicella, LAIV) if not administered on the same day, should be given at least 1 mo apart. An inactivated and a live vaccine may be spaced at any interval from each other.

Immunoglobulin does not interfere with killed vaccines. However, immunoglobulin can interfere with the immune response to measles vaccine and by inference to varicella vaccine. In general, immunoglobulin, if needed, should be administered at least 2 wk after measles vaccine. Depending on the dose of immunoglobulin received, MMR

Table 172-9 Vaccination of Persons with Primary and Secondary Immune Deficiencies

PRIMARY

CATEGORY	SPECIFIC IMMUNODEFICIENCY	CONTRAINDICATED VACCINES*	RISK-SPECIFIC RECOMMENDED VACCINES*	EFFECTIVENESS AND COMMENTS
B lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV[†] Smallpox LAIV BCG Ty21a (live typhoid) YF	Pneumococcal Consider measles and varicella vaccination	The effectiveness of any vaccine will be uncertain if it depends only on the humoral response (e.g., PPSV, MPSV) IVIG interferes with the immune response to measles vaccine and possibly varicella vaccine
	Less-severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV[†] BCG YF Other live vaccines appear to be safe	Pneumococcal	All vaccines probably effective Immune response may be attenuated
T lymphocyte (cell-mediated and humoral)	Complete defects (e.g., SCID, complete DiGeorge syndrome)	All live vaccines[‡§‖]	Pneumococcal	Vaccines may be ineffective
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines[‡§‖]	Pneumococcal Meningococcal Hib (if not administered in infancy)	Effectiveness of any vaccine depends on degree of immune suppression
Complement	Persistent complement, properdin, or factor B deficiency	None	Pneumococcal Meningococcal	All routine vaccines probably effective
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defect, and myeloperoxidase deficiency	Live bacterial vaccines[‡]	Pneumococcal[¶]	All inactivated vaccines safe and probably effective Live viral vaccines probably safe and effective

SECONDARY

SPECIFIC IMMUNODEFICIENCY	CONTRAINDICATED VACCINES*	RISK-SPECIFIC RECOMMENDED VACCINES*	EFFECTIVENESS AND COMMENTS
HIV/AIDS	OPV[†] Smallpox BCG LAIV Withhold MMR and varicella in severely immunocompromised persons	Pneumococcal Consider Hib (if not administered in infancy) and meningococcal vaccination	MMR, varicella, rotavirus, and all inactivated vaccines, including inactivated influenza, may be effective[#]
Malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial, depending on immune status[‡§]	Pneumococcal	Effectiveness of any vaccine depends on degree of immune suppression
Asplenia	None	Pneumococcal Meningococcal Hib (if not administered in infancy)	All routine vaccines probably effective
Chronic renal disease	LAIV	Pneumococcal Hepatitis B**	All routine vaccines probably effective

*Other vaccines that are universally or routinely recommended should be given if not contraindicated.
[†]OPV is no longer recommended for routine use in the United States.
[‡]Live bacterial vaccines: BCG and oral Ty21a *Salmonella typhi* vaccine.
[§]Live viral vaccines: MMR, MMRV, OPV, LAIV, YF, zoster, rotavirus, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.
[‖]Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for SCID.
[¶]Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease.
[#]HIV-infected children should receive immunoglobulin after exposure to measles and may receive varicella, measles, and YF vaccine if CD4+ lymphocyte count is greater than 15%. (For YF vaccine, CD4+ T-lymphocyte count between 15% and 24% is a precaution.)
**Indicated based on the risk from dialysis-based bloodborne transmission.
BCG, bacille Calmette-Guérin vaccine; Hib, *Haemophilus influenzae* type b vaccine; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IVIG, intravenous immunoglobulin; LAIV, live-attenuated influenza vaccine; MMR, measles, mumps, rubella vaccine; MPSV, quadrivalent meningococcal polysaccharide vaccine; OPV, oral poliovirus vaccine (live); PPSV, pneumococcal polysaccharide vaccine; SCID, severe combined immunodeficiency disease; YF, yellow fever.
Adapted from American Academy of Pediatrics: Passive immunization. In Pickering LK, Baker CJ, Kimberlin DW, Long SS, editors: Red book 2012 report of the Committee on Infectious Diseases, *Elk Grove Village, IL, 2012, American Academy of Pediatrics, pp. 75–77.*

should be deferred for as long as 3 through 11 mo. Immunoglobulin is not expected to interfere with the immune response to LAIV or rotavirus vaccines.

PRECAUTIONS AND CONTRAINDICATIONS

Observation of valid precautions and contraindications is critical to ensure that vaccines are used in the safest manner possible and to obtain optimal immunogenicity. When a child presents for immunization with a clinical condition considered a precaution, the physician must weigh benefits and risks to that individual child. If benefits are judged to outweigh risks, then the vaccine or vaccines in question may be administered. A contraindication means the vaccine should not be administered under any circumstances.

A general contraindication for all vaccines is anaphylactic reaction to a prior dose. Anaphylactic hypersensitivity to vaccine constituents is also a contraindication. However, if a vaccine is essential, there are desensitizing protocols for some vaccines. The major constituents of concern are egg proteins for vaccines grown in eggs; gelatin, a stabilizer in many vaccines; and antimicrobial agents. The measles and mumps components of MMR are grown in chick embryo fibroblast tissue culture. However, the amount of egg protein in MMR is so small as not to require any special procedures before administering vaccine to someone with a history of anaphylaxis following egg ingestion.

Vaccines usually should be deferred in children with moderate to severe acute illnesses, regardless of the presence of fever, until the child recovers. However, children with mild illnesses may be vaccinated. Studies of undervaccinated children have documented opportunities that were missed because mild illness was used as an invalid contraindication. Complete tables of contraindications and contraindication misperceptions can be found at http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm.

IMPROVING IMMUNIZATION COVERAGE

Standards for child and adolescent immunization practices have been developed to support achievement of high levels of immunization coverage while providing vaccines in a safe and effective manner and educating parents about risks and benefits of vaccines (Table 172-10).

Despite benefits that vaccines have to offer, many children are underimmunized as a result of not receiving recommended vaccines or not receiving them at the recommended ages. Much of the underimmunization problem can be solved through physician actions. Most children have a regular source of healthcare. However, missed opportunities to provide immunizations at healthcare visits include failure to provide all recommended vaccines that could be administered at a single visit during that visit, failure to provide immunizations to children outside of well-child care when the conditions children may have are not contraindications to immunizations, and referral of children to public health clinics because of inability to pay for vaccines. Simultaneous administration of multiple vaccines generally is safe and effective. When the benefits of simultaneous vaccination are explained, many parents prefer such immunization rather than making an extra visit. Providing all needed vaccines simultaneously should be the standard of practice.

Only valid contraindications and precautions to vaccine administration should be observed. Ideally, immunizations should be provided during well-child visits, but using other visits to administer vaccines if there are no contraindications, particularly if a child is behind in the schedule, is important. There is no good evidence that providing immunizations outside of well-child care ultimately decreases well-child visits.

Financial barriers to immunization should be minimized. Participation in the Vaccines for Children program allows physicians to receive vaccines at no cost for their eligible patients, which helps such patients be immunized in their medical home.

Several interventions have been shown to help physicians increase immunization coverage in their practices. Reminder systems for children before an appointment or recall systems for children who fail to keep appointments have repeatedly been demonstrated to improve coverage. Assessment and feedback is also an important intervention. Many physicians overestimate the immunization coverage among patients they serve and thus are not motivated to make any changes in their practices to improve performance. Assessing the immunization coverage of patients served by an individual physician and feedback of results can be a major motivator for improvement. Often public health departments can be contacted to provide the assessments and feedback. Alternatively, physicians can perform some self-assessments. Review of approximately 60 consecutive charts of 2 yr old children may provide a reasonable estimate of practice coverage. Another approach is to have a staff member review the chart of every patient coming in for a visit and placing immunization needs reminders on the chart for the physician. Electronic medical records can be designed to accomplish this goal.

Some parents refuse, delay, or space out immunizations for their children. Pediatricians should try to open a dialog with such parents to understand reasons for refusal and try to work with them to overcome their concerns over time during the course of visits. Discussion should be based on the reason for refusal and the knowledge of the parent. Pediatricians should refer patients to reputable sources

Table 172-10	Standards for Child and Adolescent Immunization Practices
AVAILABILITY OF VACCINES	
Vaccination services are readily available.	
Vaccinations are coordinated with other healthcare services and provided in a medical home when possible.	
Barriers to vaccination are identified and minimized.	
Patient costs are minimized.	
ASSESSMENT OF VACCINATION STATUS	
Healthcare professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated.	
Healthcare professionals assess for and follow only medically accepted contraindications.	
EFFECTIVE COMMUNICATION ABOUT VACCINE BENEFITS AND RISKS	
Parents or guardians and patients are educated about the benefits and risks of vaccination in a culturally appropriate manner and in easy-to-understand language.	
PROPER STORAGE AND ADMINISTRATION OF VACCINES AND DOCUMENTATION OF VACCINATIONS	
Healthcare professionals follow appropriate procedures for vaccine storage and handling.	
Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered.	
Persons who administer vaccines and staff who manage or support vaccine administration are knowledgeable and receive ongoing education.	
Healthcare professionals simultaneously administer as many indicated vaccine doses as possible.	
Vaccination records for patients are accurate, complete, and easily accessible.	
Healthcare professionals report adverse events following vaccination promptly and accurately to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a separate program, the National Vaccine Injury Compensation Program (VICP).	
All personnel who have contact with patients are appropriately vaccinated.	
IMPLEMENTATION OF STRATEGIES TO IMPROVE VACCINATION COVERAGE	
Systems are used to remind parents or guardians, patients, and healthcare professionals when vaccinations are due and to recall those who are overdue.	
Office- or clinic-based patient record reviews and vaccination coverage assessments are performed annually.	
Healthcare professionals practice community-based approaches.	

From the National Vaccine Advisory Committee: Standards for child and adolescent immunization practices, Pediatrics *112:958–963, 2003.*

for vaccine information (see Table 172-6) and discuss risks and benefits of vaccines. Provider resources for vaccine conversations with parents are available at http://www.cdc.gov/vaccines/hcp/patient-ed/conversations/index.html. Physician concerns about liability should be addressed by appropriate documentation of discussions in the chart. The Committee on Bioethics of the AAP has published guidelines for dealing with parents' refusal of immunization. Physicians also might wish to consider having parents sign a refusal waiver. A sample of a refusal to vaccinate waiver can be found at http://www2.aap.org/immunization/pediatricians/pdf/refusaltovaccinate.pdf.

Bibliography is available at Expert Consult.

172.1 International Immunization Practices

Jean-Marie Okwo-Bele and John David Clemens

Vaccines are used to prevent infectious diseases around the world. However, the types of vaccines in use, the indications and contraindications, and the immunization schedules vary substantially. Most developing countries follow the immunization schedules promulgated by the World Health Organization's Immunization Programme; the latest update is available at http://www.who.int/immunization/policy/Immunization_routine_table2.pdf.

According to this schedule, all children should be vaccinated at birth against tuberculosis with bacille Calmette-Guérin vaccine. Many children also receive a dose of the live-attenuated oral polio vaccine (OPV) at this time. Immunization visits are scheduled for 6, 10, and 14 wk of age when DTP vaccine and OPV are administered. Two doses of measles vaccines are recommended, with the first dose given between 9-12 mo and the second dose between 15-18 mo. Nearly all developing countries have implemented hepatitis B vaccination. Two schedule options may be used, depending on epidemiologic and programmatic considerations. Hepatitis B vaccine can be given at the same time as DTP vaccine doses at 6, 9, and 14 wk of age, often in combination vaccines. To prevent perinatal transmission, the 1st dose should be administered as soon as possible after birth (<24 hr) and at 6 and 14 wk of age. Yellow fever and Japanese encephalitis vaccines are recommended for infants 9 mo of age living in endemic areas. Substantial efforts have been made to incorporate Hib vaccines into all but 3 developing countries that are eligible for support by the GAVI Alliance, often within a DPT-based combination vaccine.

In the past few years, the support from the GAVI Alliance has facilitated the adoption of rotavirus and pneumococcal conjugate vaccines into developing country immunization programs. The increased coverage with these additional vaccines will considerably reduce the global childhood morbidity and mortality caused by pneumonia, meningitis, and diarrheal diseases.

In 1988, the World Health Assembly endorsed the goal of eradicating polio from the world by the end of 2000. Although that goal has not been reached, endemic polio transmission was contained to 3 countries worldwide (Afghanistan, Nigeria, and Pakistan) by the end of 2014. The principal strategy is use of OPV both for routine immunization and in mass campaigns, at least twice per year, during which all children <5 yr of age are targeted for immunization, regardless of prior immunization status. Once termination of wild polio virus transmission is achieved, the goal is to stop use of OPV, which rarely can cause vaccine-associated polio and which is capable of mutating and taking on the phenotypic characteristics of the wild viruses.

Latin American countries have maintained the elimination of indigenous circulation of measles since 2002. The strategy called for attainment of high routine immunization coverage of infants with a dose at 9 mo of age, a 1 time mass campaign targeting all persons 9 mo-14 yr of age regardless of prior immunization status, and follow-up campaigns of children born since the prior campaign, generally every 3-5 yr. While global measles deaths have decreased by 78% worldwide in recent years—from 562,000 deaths in 2000 to 122,000 in 2012—measles is still common in many developing countries, particularly in parts of Africa and Asia. Latin American countries have achieved the elimination of indigenous rubella with strategies consisting of both routine immunization and mass campaigns.

Immunization schedules in the industrialized world are substantially more variable than in the developing world. Immunization recommendations for Canada are developed by the Canadian National Advisory Committee on Immunization but are implemented somewhat differently by each province. The Canadian schedule is similar to the U.S. immunization schedule (http://www.phac-aspc.gc.ca/im/is-cv/index-eng.php), with a few exceptions. A birth dose of hepatitis B vaccine is not specifically recommended as it is in the United States. Conjugate meningococcal vaccine is recommended in a 3 dose series at 2, 4, and 6 mo of age. A single dose is recommended after 12 mo of age if the child has never been immunized or has received <3 doses in infancy. In contrast to the situation in the United States, hepatitis A vaccine is not recommended as a routine pediatric immunization.

There is tremendous variation in vaccines used and the immunization schedules recommended in Europe. European immunization schedules can be reviewed at http://apps.who.int/immunization_monitoring/globalsummary. As an example, the United Kingdom developed an immunization schedule during the late 1980s that includes visits at 2, 3, and 4 mo of age where a combination DTaP-Hib-IPV vaccine is administered. Following evidence that a 3 dose series of Hib vaccine at these ages was insufficient to ensure long-term, high-grade protection, a booster dose was added at 12-13 mo of age. MMR is recommended in a 2 dose schedule at 13 mo and 40 mo of age. During the 2nd MMR visit, a booster of DTaP and IPV is provided. A Td/IPV booster is recommended between 13 and 18 yr of age. PCV13 is recommended at 2, 4, and 12-13 mo of age. The United Kingdom was the first country to use conjugate meningococcal C vaccine (MCV-C) during a massive catch-up campaign for children, adolescents, and young adults. The effectiveness of the vaccine in the 1st yr was 88% or greater, and herd immunity was induced with an approximate two-thirds reduction in the incidence among unvaccinated children. MCV-C is administered at 3, 4, and 12-13 mo of age. In September 2008, HPV vaccine was recommended for girls 12-13 yr old. As of April, 2013, the UK schedule did not include hepatitis B vaccine, varicella vaccine, or influenza vaccine for universal childhood immunization (see http://www.nhs.uk/conditions/vaccinations/pages/vaccination-schedule-age-checklist.aspx).

The Japanese immunization schedule in 2013 is substantially different from that in the United States. The Japanese do not use MMR and rely on individual vaccines for measles and rubella or combined MR. Japanese children also are vaccinated routinely against polio with OPV; against diphtheria, tetanus, and pertussis with DTaP; against Japanese encephalitis; and against tuberculosis with bacille Calmette-Guérin. Adults 65 yr of age and older receive annual influenza vaccinations. A law passed in March 2013 made vaccination of children against Hib, pneumococci, and HPV mandatory.

Some children come to the United States having started or completed international immunization schedules with vaccines produced outside of the United States. In general, doses administered in other countries should be considered valid if administered at the same ages as recommended in the United States. For missing doses, age-inappropriate doses, lost immunization records, or other concerns, pediatricians have 2 options: administer or repeat missing or inappropriate doses or perform serologic tests, and if they are negative, administer vaccines.

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Chapter 173

Infection Prevention and Control

Michael J. Chusid and Mary M. Rotar

Infection prevention and control are playing an ever more important role in pediatric medicine. To be fully effective, such programs require a functional infrastructure that addresses collaboration with the public health system, widespread immunizations, and use of appropriate techniques to prevent transmission of infection within the general population and within healthcare institutions. The national focus upon preventing nosocomial infection is emphasized by the fact that 5 of the 15 elements of the Joint Commission's 2013 National Patient Safety Goals related to reduction and prevention of healthcare-associated infections (HAIs). Governmental agencies and insurance providers have reduced or eliminated payment to institutions for expenses associated with certain HAIs and a host of national organizations have been established to monitor and report rates of HAI at healthcare facilities. Ratings of healthcare facilities by periodicals such as *Parents Magazine* and *US News and World Report* incorporate institutional HAI rates in their reviews and rankings of facilities.

HAIs or nosocomial infections refer to infections acquired during hospitalization or acquired in other healthcare settings, such as nursing homes or ambulatory surgical care centers. An estimated 3-5% of children admitted to hospitals acquire an HAI. HAI rates are highest in patients undergoing invasive procedures. Infections can also be acquired in emergency departments, physicians' offices, daycare, and long-term care settings. Medical device-associated infections occur in both the home and hospital. Adequate education of home health providers as well as of families is essential to prevent or minimize device-associated infections as ever-greater numbers of children are sent home from the hospital with intravenous catheters and other medical devices in place.

Factors that increase susceptibility to HAIs include host factors, recent invasive procedures, presence of catheters or other devices, prolonged use of antibiotics, contaminated physical environment, and exposure to other patients, visitors, or healthcare providers with active contagious infections or colonized with invasive microorganisms. Host factors increasing the risk for HAIs include anatomic abnormalities (dermal sinuses, cleft palate, obstructive uropathy), abnormal skin, organ dysfunction, malnutrition, and underlying diseases or comorbidities. Invasive procedures can introduce potential pathogens by breaching normal anatomic host barriers. Intravenous and other catheters provide direct access to sterile anatomic sites for usually minimally pathogenic organisms, as well as adherent surfaces for microbial binding, and can disrupt patterns of normally protective flow of mucus (e.g., nasotracheal tubes and sinus ostia). Antibiotic use can alter the composition of bowel flora and encourage the multiplication and emergence of toxigenic or invasive organisms already present in small numbers in the gut, such as *C. difficile* and *Salmonella*.

Transmission of infectious agents occurs by various routes, but by far the most common and important route is via the hands. Medical equipment, toys, and hospital and office furnishings can become microbially contaminated and thus have a role in transmission of potential pathogens. Pagers, phones, computer keyboards, and even neckties become easily contaminated. These inanimate objects serve as fomites for bacteria. There is increasing recognition of the importance of the healthcare environment in the acquisition of organisms such as methicillin-resistant *S. aureus*, vancomycin-resistant enterococci, carbapenem-resistant Enterobacteriaceae, *C. difficile,* and respiratory syncytial virus. Thermometers and other equipment that come in contact with mucous membranes pose special risks. Some agents are easily disseminated via airborne transmission, such as varicella virus, measles virus, and *M. tuberculosis.* Food can be contaminated and has been involved in hospital outbreaks of nosocomial infection. The hospital physical environment can also serve as a risk factor for infection, particularly for immunocompromised patients. In particular, rainwater or plumbing leaks are associated with bacterial and fungal infections, new construction or renovation with airborne fungal infection, and contamination of an institution's potable water supply with bacterial, fungal, and atypical mycobacterial nosocomial infections.

Common causes of HAI in children are seasonal viruses such as rotavirus and respiratory viral agents, staphylococci, and Gram-negative bacilli. Fungi and multidrug-resistant organisms are common causes of infection in immunocompromised children, as well as those requiring intensive care and prolonged hospitalization. Common sites of infection are the respiratory tract, gastrointestinal tract, bloodstream, skin, and urinary tract.

Liberalization of visitation policies and spread of in-hospital animal visitation have increased the likelihood of HAI acquisition. The widespread use of contaminated pharmaceutical products like injectable depot corticosteroids has led to recent large outbreaks of fatal fungal HAIs.

HAIs cause considerable morbidity and occasional mortality of hospitalized children. Infections prolong hospital stays and increase healthcare costs. Surveillance, the initial step in identifying such infections and suggesting methods for prevention, is the responsibility of **infection preventionists.** Within hospitals, oversight of such surveillance is usually the responsibility of the **infection prevention and control committee**, a multidisciplinary group that collects and reviews surveillance data, establishes institutional policies, and investigates intrainstitutional infection outbreaks. The chair of the committee is often an infectious disease specialist. Surveillance in outpatient settings and during home care is often less-well defined. Local, state, and federal health departments play important roles in identifying and controlling outbreaks and in establishing public health policy.

HAND HYGIENE

The most important tool in any infection control program is good hand hygiene. Although much attention is directed at the type of cleansing agent employed, the most important aspect of hand washing is placing the hands under water and using friction with or without soap. Studies show that a 15 sec scrub removes the majority of transient flora but does not alter hand permanent flora. A variety of hand gels and rubs can be used in place of hand washing. **Waterless hand hygiene** products increase hand hygiene compliance and save time; these agents are the preferred agents for routine hand hygiene when hands are not visibly soiled. These products are effective in killing most microbes but do not remove dirt or debris. However, they are ineffective against *C. difficile* spores, requiring the use of other cleansing products during hospital *C. difficile* outbreaks. Hands should be cleaned before and after every patient encounter. In hospital hand washing compliance studies, physicians are usually the least-compliant group studied, and compliance programs must pay special attention to this group of caregivers.

STANDARD PRECAUTIONS

Standard precautions, formerly known as universal precautions, are intended to protect healthcare workers from pathogens and should be used whenever there is direct contact with patients. Infected patients are often contagious before symptoms of disease develop. Asymptomatic, infected patients are quite capable of transmitting infectious agents. Standard precautions involve the use of barriers—gloves, gowns, masks, goggles, and face shields—as needed, to prevent transmission of microbes associated with contact with blood and body fluids (Table 173-1).

ISOLATION

Isolation of patients infected with transmissible pathogens decreases the risk of nosocomial transmission of organisms to staff and other patients. The specific type of isolation depends upon the infecting agent and potential route of transmission. Transmission by contact is the most common mode of pathogen transmission and involves direct contact with the patient or contact with a contaminated intermediate object. **Contact isolation** requires the use of gown and gloves when in contact with the patient or immediate surroundings. Transmission by droplets involves the propulsion of infectious large particles over a short distance (<3 ft), with deposition on another's mucous membranes or skin. **Droplet isolation** requires the use of gloves and gowns, as well as masks and eye guards, when closer than 3-6 ft to the patient. Airborne transmission occurs by dissemination of evaporated droplet nuclei (≤5 μm) or dust particles carrying an infectious agent. **Airborne isolation** requires the use of masks and negative-pressure air-handling systems to prevent spread of the infectious agent. In the case of active pulmonary tuberculosis in older children and adults, severe acute respiratory syndrome, or avian influenza, the use of special high-density masks (N-95) or self-contained breathing systems (PAPR) is recommended. Positive-pressure HEPA-filtered air handling systems are used in some institutions for housing seriously immunocompromised patients.

Standard precautions are indicated for all patients and are appropriate for use in the clinic as well as the hospital. Additionally, for hospitalized patients, further transmission-based precautions are indicated for certain infections (Table 173-2). For contact and droplet isolation, single rooms are preferred but not required. Cohorting children infected with the same pathogen is acceptable, but the etiologic diagnosis should be confirmed by laboratory methods before exposing infected children to one another. Transmission-based isolation precautions should be continued for as long as a patient is considered contagious.

The use of isolation techniques in outpatient settings has not been well studied. Professional offices should establish procedures to ensure that proper cleaning, disinfection, and sterilization methods are employed. Many practices and clinics provide separate waiting areas

Table 173-1 Recommendations for Application of Standard Precautions for Care of All Patients in All Healthcare Settings

COMPONENT	RECOMMENDATIONS
Hand hygiene	Before and after each patient contact, regardless of whether gloves are used. After contact with blood, body fluids, secretions, excretions, or contaminated items; immediately after removing gloves; before and after entering patient rooms. Alcohol-containing antiseptic hand rubs preferred except when hands are visibly soiled with blood or other proteinaceous materials or if exposure to spores (e.g., *Clostridium difficile, Bacillus anthracis*) is likely to have occurred; in those cases, soap and water necessary.
PERSONAL PROTECTIVE EQUIPMENT	
Gloves	For touching blood, body fluids, secretions, excretions, or contaminated items; for touching mucous membranes and nonintact skin. Employ hand hygiene before and after glove use.
Gown	During procedures and patient-care activities when contact of clothing or exposed skin with blood/body fluids, secretions, or excretions is anticipated.
Mask, eye protection (goggles), face shield	During procedures and patient-care activities likely to generate splashes or sprays of blood, body fluids, or secretions, such as suctioning and endotracheal intubation, to protect healthcare personnel. For patient protection, use of a mask by the person inserting an epidural anesthesia needle or performing myelograms when prolonged exposure of the puncture site is likely to occur.
Soiled patient-care equipment	Handle in a manner that prevents transfer of microorganisms to others and to the environment. Wear gloves if equipment is visibly contaminated. Perform hand hygiene.
ENVIRONMENT	
Environmental control	Develop procedures for routine care, cleaning, and disinfection of environmental surfaces, especially frequently touched surfaces in patient care areas.
Textiles (linens) and laundry	Handle in a manner that prevents transfer of microorganisms to others and the environment.
PATIENT CARE	
Injection practices (use of needles and other sharps)	Do not recap, bend, break, or handle used needles; if recapping is required, use a 1-handed scoop technique only. Use needle-free safety devices when available, placing used sharps in puncture-resistant container. Use a sterile, single-use, disposable needle and syringe for each injection. Single-dose medication vials preferred when medications may be administered to more than 1 patient.
Patient resuscitation	Use mouthpiece, resuscitation bag, or other ventilation devices to prevent contact with mouth and oral secretions.
Patient placement	Prioritize for single-patient room if patient is at increased risk for transmission, is likely to contaminate the environment, is unable to maintain appropriate hygiene, or is at increased risk for acquiring infection or developing adverse outcome following infection.
Respiratory hygiene/cough etiquette (source containment of infectious respiratory secretions in symptomatic patients) beginning at the initial point of encounter in such triage or reception areas in an emergency department or physician offices	Instruct symptomatic persons to cover nose/mouth when sneezing or coughing; use tissues with disposal in no-touch receptacles. Employ hand hygiene after soiling of hands with respiratory secretions. Wear surgical mask if tolerated or maintain spatial separation (>3 ft if possible).

From Pickering LK, editor: Red book 2012: report of the Committee on Infectious Diseases, *ed. 29, Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 162.*

Table 173-2 Clinical Syndromes or Conditions Warranting Empiric Transmission-Based Precautions in Addition to Standard Precautions Pending Confirmation of Diagnosis*

CLINICAL SYNDROME OR CONDITION†	POTENTIAL PATHOGENS‡	EMPIRIC PRECAUTIONS (ALWAYS INCLUDES STANDARD PRECAUTIONS)
DIARRHEA		
Acute diarrhea with a likely infectious cause in an incontinent or diapered patient	Enteric pathogens§	Contact precautions (pediatrics and adult)
Meningitis	*Neisseria meningitidis*	Droplet precautions for 1st 24 hr of antimicrobial therapy; mask and face protection for intubation
	Enteroviruses	Contact precautions for infants and children
	Mycobacterium tuberculosis	Airborne precautions if pulmonary infiltrate Airborne precautions plus contact precautions if potentially infectious draining body fluid present
RASH OR EXANTHEMS, GENERALIZED, ETIOLOGY UNKNOWN		
Petechial/ecchymotic with fever (general)	*Neisseria meningitides*	Droplet precautions for 1st 24 hr of antimicrobial therapy
If positive history of travel to an area with an ongoing outbreak of VHF in the 10 days before onset of fever	Ebola, Lassa, Marburg viruses	Droplet precautions plus contact precautions, with face/eye protection, emphasizing safety sharps and barrier precautions when blood exposure likely. Use N-95 or higher respiratory protection when aerosol-generating procedure performed
Vesicular	Varicella-zoster, herpes simplex, variola (smallpox), vaccinia viruses	Airborne plus contact precautions
	Vaccinia virus	Contact precautions only if herpes simplex, localized zoster in an immunocompetent host or vaccinia viruses likely
Maculopapular with cough, coryza, and fever	Rubeola (measles) virus	Airborne precautions
RESPIRATORY INFECTIONS		
Cough/fever/upper lobe pulmonary infiltrate in an HIV-negative patient or a patient at low risk for human immunodeficiency virus (HIV) infection	*M. tuberculosis*, respiratory viruses, *Streptococcus pneumoniae*, *Staphylococcus aureus* (MSSA or MRSA)	Airborne precautions plus contact precautions
Cough/fever/pulmonary infiltrate in any lung location in an HIV-infected patient or a patient at high risk for HIV infection	*M. tuberculosis*, respiratory viruses, *S. pneumoniae*, *S. aureus* (MSSA or MRSA)	Airborne precautions plus contact precautions Use eye/face protection if aerosol-generating procedure performed or contact with respiratory secretions anticipated If tuberculosis is unlikely and there are no AIIRs and/or respirators available, use droplet precautions instead of airborne precautions Tuberculosis more likely in HIV-infected individual than in HIV-negative individual
Cough/fever/pulmonary infiltrate in any lung location in a patient with a history of recent travel (10-21 days) to countries with active outbreaks of SARS, avian influenza	*M. tuberculosis*, severe acute respiratory syndrome virus (SARS-CoV), avian influenza	Airborne plus contact precautions plus eye protection. If SARS and tuberculosis unlikely, use droplet precautions instead of airborne precautions
Respiratory infections, particularly bronchiolitis and pneumonia, in infants and young children	Respiratory syncytial virus, parainfluenza virus, adenovirus, influenzavirus, human metapneumovirus	Contact plus droplet precautions; droplet precautions may be discontinued when adenovirus and influenza have been ruled out
SKIN OR WOUND INFECTION		
Abscess or draining wound that cannot be covered	*S. aureus* (MSSA or MRSA), group A streptococcus	Contact precautions Add droplet precautions for the 1st 24 hr of appropriate antimicrobial therapy if invasive Group A streptococcal disease is suspected

*Infection control professionals should modify or adapt this table according to local conditions. To ensure that appropriate empiric precautions are implemented always, hospitals must have systems in place to evaluate patients routinely according to these criteria as part of their preadmission and admission care.

†Patients with the syndromes or conditions listed in the table may present with atypical signs or symptoms (e.g., neonates and adults with pertussis may not have paroxysmal or severe cough). The clinician's index of suspicion should be guided by the prevalence of specific conditions in the community, as well as clinical judgment.

‡The organisms listed under the column "Potential Pathogens" are not intended to represent the complete, or even most likely, diagnoses, but rather possible etiologic agents that require additional precautions beyond Standard Precautions until they can be ruled out.

§These pathogens include enterohemorrhagic *Escherichia coli* O157:H7, *Shigella* spp., hepatitis A virus, noroviruses, rotavirus, *Clostridium difficile*.

AIIR, airborne infection isolation rooms; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus;* SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome-associated coronavirus; VHF, viral hemorrhagic fever.

Adapted from Siegel JD, Rhinehart E, Jackson M, Chiarello L, and the Healthcare Infection Control Practices Advisory Committee. 2007 Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings. Centers for Disease Control and Prevention. Table 2. Available at: http://www.cdc.gov/hicpac/2007ip/2007ip_table2.html

for sick and well children. Triage of patients is essential to ensure that contagious children or adults are not present in waiting areas. Outbreaks of measles and varicella in patients within the waiting area have been reported where the air exhaust from examination rooms is allowed to enter the waiting area. Cleaning the clinic environment is important, especially in "high touch" areas. Toys and items that are shared among patients should be cleaned between uses; if feasible, disposable toys should be used. Toys contaminated with blood or body fluids should be autoclaved or discarded.

ADDITIONAL MEASURES

Other preventive measures include aseptic technique, catheter care, prudent use of antibiotics, isolation of contagious patients, periodic cleaning of the environment, disinfection and sterilization of medical equipment, reporting of infections, safe handling of needles and other sharp instruments, and establishment of employee health services. Aseptic technique must be used for all invasive procedures, including catheter placement and manipulation. The use of barrier techniques at the time of intravenous catheter placement has reduced the rate of catheter-related bloodstream infections by half. Appropriate catheter use also includes limiting the duration and number of catheters employed, scrubbing catheter hubs periodically, and removing catheters as soon as they become unnecessary.

SURGICAL PROPHYLAXIS

Surgical antibiotic prophylaxis should be employed when there is a high risk of postoperative infection or when the consequences of such infection would be catastrophic. The choice of prophylactic antibiotic depends on the surgical site and type of surgery (Table 173-3). A useful classification of surgical procedures based upon infectious risk recognizes 4 preoperative wound categories: clean wounds, clean-contaminated wounds, contaminated wounds, and dirty and infected wounds. Clinical recommendations regarding antibiotic prophylaxis have been made by the American College of Surgeons, the Surgical Infection Society, and the American Academy of Pediatrics.

Clean wounds are uninfected operative wounds where no inflammation is noted at the operative site and respiratory, alimentary, and genitourinary tracts and the oropharynx are not entered. Such wounds are often the result of nonemergent procedures with primary closure or drained via a closed system. Operative incisional wounds after nonpenetrating trauma are included in this category. For clean wounds, prophylactic antimicrobial therapy is *not* recommended except in patients at high risk for infection and in circumstances in which the consequences of infection would be potentially life threatening, as with implantation of a foreign body such as a prosthetic heart valve or cerebrospinal fluid shunt, open heart surgery for repair of structural defects, and surgery in immunocompromised patients or small infants.

Clean-contaminated wounds are operative wounds in which the respiratory, alimentary, or genitourinary tract is entered under controlled conditions and that do not have unusual bacterial contamination preoperatively. These wounds occur in operations that involve the biliary tract, appendix, vagina, and oropharynx where no evidence of infection or major break in technique is encountered, as well as in urgent or emergency surgery in an otherwise clean procedure. In procedures involving clean-contaminated wounds, the risk for bacterial contamination and infection is variable. Recommendations for pediatric patients derived from data on adults suggest that antibiotic prophylaxis be provided for procedures in children with obstructive jaundice, certain alimentary tract procedures, and urinary tract surgery or instrumentation in the presence of bacteriuria or obstructive uropathy.

Contaminated wounds include open, fresh, and accidental wounds; major breaks in otherwise sterile operative technique; gross spillage from the gastrointestinal tract; penetrating trauma occurring <4 hr earlier; and incisions in which acute nonpurulent inflammation is encountered.

Dirty and infected wounds include penetrating traumatic wounds >4 hr prior to surgery, those with retained devitalized tissue, and those in which clinical infection is apparent or in which the viscera have been perforated. In contaminated and dirty or infected wound procedures, antimicrobial therapy is indicated and may need to be continued for several days. In these cases, antibiotic therapy is considered therapeutic rather than truly prophylactic.

Table 173-3 Common Surgical Procedures for Which Perioperative Prophylactic Antibiotics Are Recommended

SURGICAL PROCEDURE	LIKELY PATHOGENS	RECOMMENDED DRUGS	NON–β-LACTAM ALTERNATIVE
CLEAN WOUNDS			
Cardiac surgery (e.g., open heart surgery) Vascular surgery Neurosurgery Orthopedic surgery (e.g., joint replacement)	Skin flora, enteric Gram-negative bacilli	Cefazolin or cefuroxime	Clindamycin or vancomycin
CLEAN CONTAMINATED WOUNDS			
Head and neck surgery involving the oral cavity or pharynx	Skin flora, oral anaerobes, oral streptococci	Cefazolin + metronidazole, ampicillin-sulbactam	Clindamycin
Gastrointestinal and genitourinary surgery	Enteric Gram-negative bacilli, anaerobes, Gram-positive cocci	Cefazolin + metronidazole, cefotetan or piperacillin-tazobactam If colon is involved, consider bacterial reduction with PO neomycin and erythromycin	Clindamycin
CONTAMINATED WOUNDS			
Traumatic wounds (e.g., compound fracture)	Skin flora	Cefazolin	Clindamycin, vancomycin
DIRTY WOUNDS			
Appendectomy, penetrating abdominal wounds, colorectal surgery	Enteric Gram-negative bacilli, anaerobes, Gram-positive cocci	Cefazolin + metronidazole, cefoxitin, cefotetan or ampicillin-sulbactam	Clindamycin + aminoglycoside

Adapted from Bratzler DW, Dellinger PD, Olsen KM et al. Clinical practice guidelines from antimicrobial prophylaxis in surgery. Am J Health Syst Pharm *70:195–283, 2013.*

Prophylactic antibiotics should be administered, preferably intravenously, within an hour prior to skin incision, with the intent of having peak serum concentrations of the drug present in blood and tissues around the time of incision. Adequate plasma and tissue concentration of the antibiotic should be maintained until the incision is closed. Intraoperative antibiotic dosing may be necessary if surgery is prolonged and/or the antibiotic being employed has a short intravascular half-life. Continuation of prophylactic therapy after the procedure is not recommended. In cases of contaminated surgical sites, antibiotics are continued as therapy for infection at the site. For patients undergoing colonic procedures, additional oral antibiotics may be employed and should also be given on the day before surgery.

The selection of antibiotic regimen for prophylaxis is based on the procedure, the likely contaminating organisms, and antibiotic. Because of the variety of antibiotics available, many regimens are acceptable (see Table 173-2).

EMPLOYEE HEALTH

Employee health is important in hospital-based infection control because employees are at risk for acquiring infection from patients and infected employees pose a potential risk to patients. This risk is minimized by use of standard precautions and hand hygiene before and after all patient contacts. Within hospitals, employee health services or departments of occupational safety and health manage employee health issues. New employees should be screened for the presence of infectious diseases. Their immunization history should be noted, and necessary immunizations should be offered.

All healthcare workers (medical and nonmedical, paid or volunteer, full time or part time, student or nonstudent, with or without patient care responsibilities) who work within facilities providing healthcare, inpatient or outpatient, should be immune to measles, rubella, and varicella. All workers who are at risk of exposure to blood or body fluids should be immunized against hepatitis B. In pediatric institutions, employees with patient contact should be urged to receive the pertussis booster vaccine. Annual influenza immunization is strongly recommended for all healthcare workers, and institutions are being ranked publically regarding employee immunization rates as a measure of quality of care. Many healthcare facilities have now made annual influenza vaccination mandatory for employees unless there are legitimate medical reasons for nonimmunization. Such a program reduces staff illness and absenteeism and decreases HAI. Immunizations should be encouraged and should be provided free of charge whenever possible to enhance compliance.

All healthcare workers with duties involving face-to-face contact with patients with suspected or confirmed tuberculosis (including transport staff) should be included in a tuberculosis screening program at the time of hiring and may require periodic retesting if the workplace is determined to be a high-prevalence environment for tuberculosis. Each medical office and hospital must comply with the rules developed by the Occupational Safety and Health Administration. Each office and hospital should have written policies about exclusion of infected and ill staff from direct patient care. Staff should be encouraged to not report for work if they are ill. Regular educational sessions should be performed to ensure that staff are aware of prevention and control methods and that they adhere to such policies.

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Chapter 174

Childcare and Communicable Diseases

Linda A. Waggoner-Fountain

More than 25 million children <5 yr of age attend a childcare facility. These facilities can include some type of out-of-home care on a routine basis, such as nursery school, preschool, or a full-day program based either in a childcare center or in another person's home. Regardless of the age at entry, children entering daycare are more prone to infections. Exposure to larger groups of children increases a child's probability of getting sick. Childcare facilities can be classified on the basis of size of enrollment, ages of attendees, health status of the children enrolled, and type of setting. As defined in the United States, **childcare facilities** consist of childcare centers, small and large family childcare homes, and facilities for ill children or for children with special needs. Centers are licensed and regulated by state governments and care for a larger number of children than are cared for in family homes. In contrast, **family childcare homes** are designated as small (1-6 children) or large (7-12 children), may be full day or part day, and may be designed for either daily or sporadic attendance. Family childcare homes generally are not licensed or registered, depending on state requirements.

Although the majority of children who attend childcare facilities are cared for in childcare home settings, most studies of infectious diseases among children in out-of-home childcare have been conducted among infants (birth to 12 mo of age) and toddlers (13-36 mo of age) who are enrolled in a childcare center. Almost any organism has the potential to be spread and to cause disease in a childcare setting. Epidemiologic studies have established that children in childcare facilities are 2-18 times more likely to acquire a variety of infectious diseases than are children not enrolled in childcare (Table 174-1). Children in childcare facilities are more likely both to receive more courses of antimicrobial agents for longer periods and to acquire antibiotic-resistant organisms. Transmission of infectious agents in group care depends on the age and immune status of the children, season, hygiene practices, crowding, environmental characteristics of the facilities, and characteristics of the pathogen, including its infectivity, survivability in the environment, and virulence. Rates of infection, duration of illness, and risk for hospitalization tend to decrease among children in childcare facilities after the 1st 6 mo of attendance and decline to levels observed among home-bound children after 3 yr of age. Adult caregivers are also at increased risk for acquiring and transmitting infectious diseases, particularly in the 1st yr of contact with children in these settings.

EPIDEMIOLOGY

Infectious illnesses among children in childcare and their contacts occur in several different patterns. With many viral infections, children often are infectious 2-3 days before they exhibit symptoms of illness. Respiratory tract infections and diarrhea are the most common diseases associated with childcare. These infections occur in children, childcare staff, and household contacts, and can spread to the community. Respiratory tract pathogens and enteric pathogens can infect both children and adults in these settings but may have varying degrees of impact, depending on the person's underlying health, previous exposures, and age. Infections caused by hepatitis A virus might not be clinically apparent in young children who attend childcare, but can cause major clinical disease among older children and adult contacts, including childcare staff and household contacts. Other diseases, such as otitis media and varicella, usually affect children rather than adults. Some common infections, such as cytomegalovirus (CMV) and parvovirus B19 infections, can have serious consequences for the fetuses

Table 174-1 Infectious Diseases in the Childcare Setting

DISEASE	INCREASED INCIDENCE WITH CHILDCARE
RESPIRATORY TRACT INFECTIONS	
Otitis media	Yes
Sinusitis	Probably
Pharyngitis	Probably
Pneumonia	Yes
GASTROINTESTINAL TRACT INFECTIONS	
Diarrhea (rotavirus, calicivirus, astrovirus, enteric adenovirus, *Giardia lamblia, Cryptosporidium, Shigella, Escherichia coli* O157:H7, and *Clostridium difficile*)	Yes
Hepatitis A	Yes
SKIN DISEASES	
Impetigo	Probably
Scabies	Probably
Pediculosis	Probably
Tinea (ringworm)	Probably
INVASIVE BACTERIA INFECTIONS	
Haemophilus influenzae type b	No*
Neisseria meningitidis	Probably
Streptococcus pneumoniae	Yes
ASEPTIC MENINGITIS	
Enteroviruses	Probably
HERPESVIRUS INFECTIONS	
Cytomegalovirus	Yes
Varicella-zoster virus	Yes
Herpes simplex virus	Probably
BLOOD-BORNE INFECTIONS	
Hepatitis B	Few case reports
HIV	No cases reported
Hepatitis C	No cases reported
VACCINE-PREVENTABLE DISEASES	
Measles, mumps, rubella, diphtheria, pertussis, tetanus	Not established
Polio	No
H. influenzae type b	No*
Varicella	Yes
Rotavirus	Yes

*Not in the postvaccine era; yes in the prevaccine era.

of pregnant women or for immunocompromised persons. Hepatitis B virus (HBV) transmission has been reported rarely in a childcare setting. Transmission of hepatitis C virus (HCV), hepatitis D virus (HDV), and HIV has never been reported in a childcare setting. Both infections and infestations of the skin and hair may be acquired through contact with contaminated linens or through close personal contact.

RESPIRATORY TRACT INFECTIONS

Respiratory tract infections account for the majority of childcare-related illnesses. Children <2 yr of age who attend childcare centers have more upper and lower respiratory tract infections than do age-matched children not in childcare. The organisms responsible for these illnesses are similar to those that circulate in the community and include respiratory syncytial virus, parainfluenza viruses, influenza viruses, adenoviruses, rhinoviruses, coronaviruses, parvovirus B19, and *S. pneumoniae.* The risk for developing otitis media is 2-3 times greater among children who attend childcare centers than among children cared for at home. Most prescriptions for antibiotics for children <3 yr of age in childcare are to treat otitis media. These children also are at increased risk for recurrent otitis media, which further increases use of antimicrobial agents in this population. Pharyngeal carriage of group A streptococcus occurs earlier among children in childcare, although outbreaks of clinical infections with this organism are uncommon. Airborne droplets from the respiratory tract can spread via direct contact with another person's mucous membranes or by touching surfaces contaminated with secretions. This intimate contact is a routine part of the play and care of young children, regardless of setting. The most common surfaces from which airborne droplets can be spread are the hands; consequently, the most efficient form of infection control in the childcare setting is good hand washing.

GASTROINTESTINAL TRACT INFECTIONS

Acute infectious diarrhea is 2-3 times more common among children in childcare than among children cared for in their homes. Outbreaks of diarrhea, which occur frequently in childcare centers, usually are caused by enteric viruses such as rotaviruses, caliciviruses including norovirus, enteric adenoviruses, and astroviruses, or by enteric parasites such as *G. lamblia* or *Cryptosporidium.* The most common enteropathogens, such as rotavirus and *G. lamblia,* are characterized by low infective doses and high rates of asymptomatic excretion among children in childcare. Bacterial enteropathogens such as *Shigella* and *E. coli* O157:H7 and, less commonly, *Campylobacter, C. difficile,* and *Bacillus cereus* also have caused outbreaks of diarrhea in childcare settings. *Salmonella* rarely is associated with outbreaks of diarrhea in childcare settings, because person-to-person spread of this organism is uncommon. Outbreaks of hepatitis A in children enrolled in childcare facilities have resulted in community-wide outbreaks. Hepatitis A usually is mild or asymptomatic in young children and often is identified only after symptomatic illness becomes apparent among either older children or adult contacts of children in childcare. Enteropathogens and hepatitis A virus are transmitted in childcare facilities by the fecal-oral route and only rarely by contaminated food or water. Children in diapers constitute a high risk for the spread of gastrointestinal infections through the fecal-oral route. Enteric illness and hepatitis A are more common in centers that care for children who are not toilet trained and where proper hygienic practices are not followed.

SKIN DISEASES

The most commonly recognized skin infections or infestations in children in childcare are impetigo caused by *S. aureus* or group A streptococcus, pediculosis, scabies, tinea capitis, and tinea corporis. Many of these diseases are spread by contact with infected linens, clothing, hairbrushes, and hats and through direct personal contact; they more often affect children >2 yr of age. The magnitude of these infections and infestations in children in childcare is not known. Parvovirus B19, which causes fifth disease (erythema infectiosum), is spread through the respiratory route, and outbreaks have occurred in childcare centers. The rash of fifth disease is a systemic manifestation of parvovirus B19 infection; the child is no longer contagious once the rash is present (see Chapter 251). The greatest health hazard is for pregnant women and immunocompromised hosts, owing to their respective risks for fetal loss and aplastic crisis.

INVASIVE ORGANISMS

Prior to universal immunization, primary *H. influenzae* type b invasive disease was more common among children in childcare, although evidence for increased risk for secondary cases from *H. influenzae* type b in a childcare setting remains less convincing. There is an indication that the risk for primary disease caused by *Neisseria meningitidis* is higher among children in childcare than among children cared for at home. Childcare attendance is associated with nasopharyngeal carriage of penicillin-resistant *S. pneumoniae* and invasive pneumococcal disease, especially among children with a history of recurrent otitis media and use of antibiotics. Secondary spread of *S. pneumoniae* and *N. meningitidis* has been reported, indicating the potential for outbreaks to occur in this setting. Routine use of pneumococcal conjugate vaccine has decreased the incidence of invasive disease and reduced carriage of serotypes of *S. pneumoniae* contained in the vaccine both

in the child and in younger siblings. The use of conjugate meningococcal vaccine in children <2 yr of age is anticipated in the near future and will alter the epidemiology of meningococcal disease in this age group. Outbreaks of aseptic meningitis from echovirus 30 have been reported among children in childcare centers, as well as among their parents and their teachers.

HERPESVIRUSES

Studies of CMV infection in childcare centers show that as many as 70% of diapered children continuously shed CMV in urine and saliva after they become infected. CMV-infected children often transmit the virus to other children with whom they have contact, as well as to their care providers and their mothers, at a rate of 8-20% per yr. Transmission occurs as a result of contact with either saliva or urine. The overwhelming majority of primary infection with and reactivation of CMV in otherwise healthy children results in asymptomatic shedding of CMV; nonetheless, this shedding can pose a health risk for previously uninfected pregnant childcare providers or immunocompromised persons (see Chapter 255). Varicella often is transmitted in childcare centers, but routine use of varicella vaccine has reduced this risk. Vaccinated children who become infected with varicella often have mild, atypical symptoms and signs of disease that can result in delayed recognition and spread of infection to susceptible contacts. The role of childcare facilities in the spread of herpes simplex virus, especially during episodes of gingivostomatitis, requires further clarification.

BLOOD-BORNE PATHOGENS

Because it is impossible to identify every child who might have a blood-borne infection such as hepatitis B, C, or D, or HIV, it is critical that standard universal precautions be observed routinely to reduce the risk for transmitting these viruses. Transmission of hepatitis B among children in childcare has been documented in a few rare instances, but the risk for transmission, which already was low, declined with implementation of universal immunization of infants with hepatitis B vaccine. Transmission of hepatitis C or D in childcare settings has not been reported.

Issues about HIV in childcare include the potential risk for HIV transmission within the childcare setting and concerns of opportunistic infections of HIV-infected children. No cases of HIV transmission in out-of-home childcare have been reported. Children with HIV infection enrolled in childcare facilities should be monitored for exposure to infectious diseases, and their health and immune status should be evaluated frequently.

Some infections are spread through contact of contaminated blood with either a mucous membrane or an open wound. Although it is theoretically possible, infection is unlikely to spread via toddler biting in a group setting. Most of these bites do not break the skin, and if a bite does break the skin, the mouth of the biter does not stay on the victim long enough for blood to transfer from the victim to the biter. If there are concerns about transmission of hepatitis B, hepatitis C, or HIV infection, it is recommended to check the status of the biter rather than the bite victim as part of the initial evaluation process.

ANTIBIOTIC USE AND BACTERIAL RESISTANCE

Antibiotic resistance has become a significant problem in childcare facilities, because the incidence of infection by organisms resistant to frequently used antimicrobial agents has increased dramatically. The estimated annual rate of antibiotic use among children in childcare is 2-4 times higher than among age-matched children cared for at home and the mean duration of antibiotic treatment is 4 times longer among children in childcare. This frequency of antibiotic use combined with the propensity for person-to-person transmission of pathogens in a crowded environment has resulted in an increased prevalence of antibiotic-resistant bacteria in the respiratory and intestinal tracts, including *S. pneumoniae, H. influenzae, M. catarrhalis, E. coli* O157:H7, and *Shigella* species. Preliminary data do not demonstrate a difference between methicillin-resistant *S. aureus* and methicillin-susceptible *S. aureus* strains in children in childcare.

PREVENTION

Written policies designed to prevent or to control the spread of infectious agents in a childcare center should be available and should be reviewed regularly. It is suggested that all programs use a health consultant to help with development and implementation of infection-control policies. Standards for environmental and personal hygiene should include maintenance of current immunization records for both children and staff; appropriate policies for exclusion of ill children and caretakers; targeting of potentially contaminated areas for frequent cleaning; adherence to appropriate procedures for changing diapers; appropriate handling of food; management of pets; and surveillance for and reporting of communicable diseases. Staff whose primary function is preparing food should not change diapers. Strategies for improving adherence to these standards should be implemented. Appropriate and thorough hand hygiene is the most important factor for reducing infectious diseases in the childcare setting. Children at risk for introducing an infectious disease should not attend childcare until they are no longer contagious (Tables 174-2 and 174-3).

In the United States, there are 15 diseases and organisms for which all children should be immunized unless there are contraindications: diphtheria, pertussis, tetanus, measles, mumps, rubella, polio, hepatitides A and B, varicella, *H. influenzae* type b, *S. pneumoniae,* rotavirus, *N. meningitidis,* and influenza. Rates of immunization among children in licensed childcare facilities are high, in part because of laws in almost all states that require age-appropriate immunizations of children who attend licensed childcare programs. Routine vaccination has had a significant beneficial effect on the health of children in childcare settings. Vaccines against influenza, *H. influenzae* type b, hepatitis B, rotavirus, varicella, *S. pneumoniae,* and hepatitis A are of particular benefit to children in childcare centers. Influenza vaccination of younger infants reduces influenza infection and secondary sequelae in both children and the adults who care for them in both their home and in childcare settings. Childcare providers should receive all immunizations that are recommended routinely for adults and have a preemployment health evaluation, including a tuberculin skin test. Local public

Table 174-2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
HAV infection	Serologic testing to confirm HAV infection in suspected cases Exclusion until 1 wk after onset of jaundice	If ≥1 case is confirmed in child or staff attendees or ≥2 cases in households of staff or attendees, HAV vaccine or Ig should be administered within 14 days of exposure to unimmunized staff and attendees In centers without diapered children, HAV vaccine or Ig should be given to unimmunized classroom contacts of index case Asymptomatic Ig recipients may return after receipt of Ig
Impetigo	Exclusion until 24 hr after treatment has been initiated Lesions on exposed skin covered with watertight dressing	No intervention needed unless additional lesions develop

Table 174-2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare—cont'd

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
Measles	Exclusion until 4 days after beginning of rash and when the child is able to participate	Immunize exposed children without evidence of immunity within 72 hr of exposure Children who do not receive vaccine within 72 hr or who remain unimmunized after exposure should be excluded until at least 2 wk after onset of rash in the last case of measles
Mumps	Exclusion until 5 days after onset of parotid gland swelling	In outbreak setting, people without documentation of immunity should be immunized or excluded Immediate readmission may occur following immunization Unimmunized people should be excluded for ≥26 days following onset of parotitis in last case
Pediculosis capitis (head lice)	Treatment at end of program day and readmission on completion of 1st treatment	Household and close contacts should be examined and treated if infested No exclusion is necessary
Pertussis	Exclusion until 5 days of appropriate antimicrobial therapy course have been completed	Immunization and chemoprophylaxis should be administered as recommended for household contacts Symptomatic children and staff should be excluded until completion of 5 days of antimicrobial therapy course Untreated adults should be excluded until 21 days after onset of cough
Rubella	Exclusion until 6 days after onset of rash for postnatal infection	Pregnant contacts should be evaluated
Salmonella serotype Typhi infection	Exclusion until diarrhea resolves 3 Negative stool culture results required before readmission	Stool cultures should be performed for attendees and staff; infected people should be excluded on the basis of age
Non–serotype Typhi *Salmonella* infection	Exclusion until diarrhea resolves. Negative stool culture results not required for non–serotype Typhi *Salmonella* species	Symptomatic contacts should be excluded until symptoms resolve Stool cultures are not required for asymptomatic contacts Antimicrobial therapy is not recommended for asymptomatic infection or uncomplicated diarrhea or for contacts
Scabies	Exclusion until after treatment given	Close contacts with prolonged skin-to-skin contact should have prophylactic therapy Bedding and clothing in contact with skin of infected people should be laundered
Shiga toxin–producing *Escherichia coli*, including *E. coli* O157:H7, or *Shigella* infection	Exclusion until diarrhea resolves and results of 2 stool cultures are negative for these organisms, depending on state regulations	Meticulous hand hygiene; stool cultures should be performed for contacts Center(s) with cases should be closed to new admissions during *E. coli* O157:H7 outbreak
Staphylococcus aureus skin infections	Exclusion only if skin lesions are draining and cannot be covered with a watertight dressing	Meticulous hand hygiene Cultures of contacts are not recommended
Streptococcal pharyngitis	Exclusion until 24 hr after treatment has been initiated and the child is able to participate in activities	Symptomatic contacts of documented cases of group A streptococcal infection should be tested and treated if test results are positive
Tuberculosis	For active disease, exclusion until determined to be noninfectious by physician or health department authority May return to activities after therapy is instituted, symptoms have diminished, and adherence to therapy is documented No exclusion for latent tuberculosis infection	Local health department personnel should be informed for contact investigation
Varicella	Exclusion until all lesions have dried and crusted, usually 6 days after onset of rash in immunocompetent people; may be longer in immunocompromised people	Varicella vaccine should be administered by 3-5 days after exposure, and varicella-zoster Ig should be administered up to 96 hr after exposure when indicated

HAV, hepatitis A virus; Ig, immunoglobulin.

From Pickering LK, Baker CJ, Kimberlin DW, et al, editors: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29, Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

Table 174-3 General Recommendations for Exclusion of Children in Out-of-Home Childcare

SYMPTOM(S)	MANAGEMENT
Illness preventing participation in activities, as determined by childcare staff	Exclusion until illness resolves and able to participate in activities
Illness that requires care greater than staff can provide without compromising health and safety of others	Exclusion or placement in care environment where appropriate care can be provided without compromising care of others
Severe illness suggested by fever with behavior changes, lethargy, irritability, persistent crying, difficulty breathing, progressive rash	Medical evaluation and exclusion until symptoms have resolved
Rash with fever or behavioral change	Medical evaluation and exclusion until illness is determined not to be communicable
Persistent abdominal pain (≥2 hr) or intermittent abdominal pain associated with fever, dehydration, or other systemic signs and symptoms	Medical evaluation and exclusion until symptoms have resolved
Vomiting ≥2 times in preceding 24 hr	Exclusion until symptoms have resolved, unless vomiting is determined to be caused by a noncommunicable condition and child is able to remain hydrated and participate in activities
Diarrhea or stools containing blood or mucus	Medical evaluation and exclusion until symptoms have resolved
Oral lesions	Exclusion until child or staff member is considered to be noninfectious (lesions crusted and dry)

From Pickering LK, Baker CJ, Kimberlin DW, et al, editors: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29, Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

health authorities should be notified of cases of reportable communicable disease that occur in children or providers in childcare settings.

STANDARDS

Every state has specific standards for licensing and reviewing childcare centers and family childcare homes. The American Academy of Pediatrics, the American Public Health Association, and the National Resource Center jointly publish comprehensive health and safety performance standards that can be used by pediatricians and other healthcare professionals to guide decisions about management of infectious diseases and other health-related matters in childcare facilities (available at http://cfoc.nrckids.org/). Specific standards set by all states also are available on this website.

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Chapter 175

Health Advice for Children Traveling Internationally

Stephen J. Swanson and Chandy C. John

Children are traveling internationally with increasing frequency and to more "exotic" destinations that pose unique injury and disease risks. Compared to adults, children are *less* likely to receive pretravel advice and *more* likely to be seen by a medical provider or be hospitalized upon return for a travel-related illness. Primary care providers are confronted with the challenge of trying to ensure safe, healthy travel for their patient, whether travel is occurring for purposes of tourism, study abroad, visiting friends and relatives, or volunteerism. Whenever possible, health professionals are encouraged to consult with Travel Medicine specialists, especially when uncertain about pretravel advice, unique travel medicine vaccines (e.g., yellow fever, Japanese encephalitis, typhoid, rabies), and recommendations for malaria medications.

Travel medicine is a unique specialty, and experienced travel medicine practitioners provide specialized guidance on the infectious and noninfectious risks based on age, itinerary, duration, season, purpose of travel, and underlying traveler characteristics (health and vaccination status). A pretravel consultation includes the essential elements of (1) safety and preventive counseling against injuries and diseases; (2) routine, recommended, and required vaccinations, based on individual risk assessment; (3) counseling and medications for self-treatment of traveler's diarrhea; and (4) when indicated by itinerary, malaria chemoprophylaxis.

In the United States, recommendations and vaccine requirements for travel to different countries are provided by the Centers for Disease Control and Prevention (CDC) and are available online at http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/travel-vaccines-and-malaria-information-by-country. *Some travel vaccines and medications may not be recommended based on specifics of travel itinerary, trip duration, or patient characteristics. Alternatively, some vaccinations are not approved for younger children because of lack of data or limited immunologic response, but may still confer potential benefit to the young traveler with off-label vaccine administration. In both scenarios, consultation or referral to a knowledgeable travel medicine practitioner is encouraged, especially if uncertainty exists regarding pretravel recommendations.*

THE PEDIATRIC TRAVEL MEDICINE CONSULTATION

Parents of traveling children should seek medical consultation at least 4-6 wk before departure to review the travel itinerary, obtain safety and preventive counseling, ensure adequate vaccinations (routine, recommended, and required), receive necessary medications for chronic health conditions, and obtain important medications for self-treatment of traveler's diarrhea and, when indicated, malaria chemoprophylaxis with counseling. Preparing a child to travel internationally should begin with an emphasis on the positive aspects of the upcoming trip rather than solely focusing on travel risks and diseases. Subsequent advice, vaccinations, and medications should be emphasized as important measures with the provider goal of *keeping the child healthy during travel rather than to discourage traveling*.

Pediatric Travelers Visiting Friends and Relatives

Compared to most children traveling internationally, the pediatric visiting-friends-and-relatives (VFR) traveler is a vulnerable population uniquely at risk for travel-related illnesses. VFR travelers may include immigrants, refugees, migrants, students, or displaced persons who are traveling back to their country of origin for purposes of visiting friends and relatives. Pediatric VFR travelers are typically children accompanying their parents or family members back to their ancestral country, where relational, social, and cultural connections remain. Compared to tourist travelers, VFR travelers are more likely to travel for longer durations, visit more remote destinations, travel by higher-risk local transportation modes, experience closer contact with the local population, and utilize fewer insect, food, and water precautions. Adult and pediatric VFR travelers are also less likely to perceive a risk of travel-related illnesses, seek pretravel advice, receive travel immunizations, or use effective malaria prophylaxis upon arrival in the destination country. VFR travel comprises 50-84% of imported malaria in children in the United States (i.e., malaria acquired outside the United States), and pediatric VFR travelers are reported to be 4 times more likely to acquire malaria than tourist travelers. Among all travelers, pediatric VFR travelers remain at higher risk for contracting hepatitis A and having symptomatic illness. Several studies suggest that VFR travelers are at disproportionate risk of acquiring typhoid fever and possibly tuberculosis. Providers should inquire if their foreign-born patients will be traveling internationally and seek opportunities to encourage pretravel consultation for VFR travelers.

SAFETY AND PREVENTIVE COUNSELING TOPICS

Health and Evacuation Insurance, Underlying Health Conditions, and Medications

Parents should be made aware that their medical insurance policy might not provide coverage for hospitalizations or medical emergencies in foreign countries and is unlikely to cover the high cost of an emergency medical evacuation. Supplemental travel medical insurance and evacuation insurance may be purchased and are especially recommended for prolonged travel itineraries, for remote destinations, and for children with higher-risk preexistent health conditions going to countries where inpatient care at a level comparable to the traveler's home country may not be available. A list of medical and evacuation insurance providers can be found at the U.S. Department of State's International Travel advisory website (http://travel.state.gov/travel/cis_pa_tw/cis/cis_1470.html).

Parents of children with medical conditions should take with them a brief medical summary and a sufficient supply of prescription medications for their children, with bottles that are clearly identified by prescription labels. For children requiring care by specialists, an international directory for that specialty can be consulted. A directory of physicians worldwide who speak English and who have met certain qualifications is available from the International Association for Medical Assistance to Travelers (http://www.iamat.org/index.cfm). If medical care is needed urgently when abroad, sources of information include the American embassy or consulate, hotel managers, travel agents catering to foreign tourists, and missionary hospitals.

A travel health kit consisting of prescription medications and nonprescription items, such as acetaminophen, an antihistamine, oral rehydration solution packets, antibiotic ointment, bandages, insect repellent, and sunscreen, is highly recommended for all children. Children with persistent asthma should have bronchodilators and oral steroids prescribed for treatment of any acute asthma exacerbations encountered during overseas travel. Children with a history of angioedema, anaphylaxis, or severe allergies to food or insects should have an epinephrine autoinjector (EpiPen) and antihistamines available for use during travel.

Parents and family members should be aware of the prevalence of counterfeit medication and lack of quality control of medications in many areas of the world, particularly in low- and middle-income countries. Critical medications, including insulin and newly prescribed antimalarials, should be purchased prior to international travel and packed in original prescription containers.

Safety and Injury Prevention

Motor vehicle accidents are a leading cause of traumatic injuries to, hospitalizations of, and deaths of pediatric and adult travelers. Differences in traffic patterns should be emphasized to children, and the use of safety belts should be reinforced. When possible, child safety seats should be taken on the trip. Parents should also be aware of additional risks for small children that may exist overseas, such as open balconies, windows without screens or bars, exposed wires and electrical outlets, paint chips, pest and rodent poison, and stray animals. Water-related activities also are associated with significant injuries in pediatric travelers, and pools and oceanfronts are often unsupervised and without lifeguards at overseas destinations.

Animal Contact

Among travelers, attacks from domestic or stray animals are far more likely to occur than attacks from wild animals. Wounds from animal bites present a risk for bacterial infections, tetanus, and rabies. Dogs are responsible for more than 95% of all rabies transmission in Asia, Africa, and Latin America. Globally, the World Health Organization (WHO) estimates that there are approximately 55,000 human deaths from rabies each year, with the vast majority of cases occurring in South Asia, Southeast Asia, and Africa. Reports of rabies transmission have less commonly occurred following bites from cats and other carnivores, monkeys, and bats. Macaque monkeys, native to Asia and North Africa, can be found in urban centers and tourist sites and pose a risk for rabies and herpes B virus infections following bites and scratches.

Young children are more likely to be bitten and experience more severe facial wounds related to their short stature. As such, they are at higher risk for rabies exposure from dogs and other animals during travel and require greater supervision. Parents should always encourage their children to report bite injuries and to avoid petting, feeding, or handling dogs, monkeys, and stray animals. Before travel, tetanus vaccinations need to be current for all travelers. Children, long-term travelers, expatriates, and all individuals likely to come into contact with animals in a rabies-endemic region (primarily Africa and South and Southeast Asia) should consider preexposure vaccination for rabies before international travel (see "Rabies" below). Bite or scratch wounds should be washed thoroughly and for a prolonged time (15 min) with copious water and soap. Local wound care will substantially reduce the risk of canine and other mammalian rabies transmission. Rabies postexposure vaccination and rabies immunoglobulin should be considered. Antibiotics (amoxicillin–clavulanate) may need to be administered to a child to prevent secondary infections, especially for animal bites involving the hands and head/neck areas.

ROUTINE CHILDHOOD VACCINATIONS REQUIRED FOR PEDIATRIC TRAVEL

Parents should allow 4 or more weeks before departure for optimal administration of vaccines to their children. All children who travel should be immunized according to the routine childhood immunization schedule with all vaccines appropriate for their age. The immunization schedule can be accelerated to maximize protection for traveling children, especially for unvaccinated or incompletely vaccinated children (see Fig. 172-4 in Chapter 172). Routine and catch-up childhood vaccine schedules for healthcare professionals can be found at the CDC website (http://www.cdc.gov/vaccines/schedules/index.html).

Live-attenuated viral vaccines should be administered concurrently or 4 or more weeks apart to minimize immunologic interference. Intramuscular immunoglobulin interferes with the immune response to measles immunization and possibly to varicella immunization. If a child requires measles or varicella immunization, the vaccines should be given either 2 wk before or 3 mo after immunoglobulin administration (longer with higher doses of intravenous immunoglobulin).

Immunoglobulin does not interfere with the immune response to oral typhoid, poliovirus, or yellow fever vaccines.

Vaccine products produced in eggs (yellow fever, influenza) may be associated with hypersensitivity responses, including anaphylaxis in persons with known severe egg sensitivity. Screening by inquiring about adverse effects when eating eggs is a reasonable way to identify those at risk for anaphylaxis from receiving influenza or yellow fever vaccines. Although measles and mumps vaccines are produced in chick embryo cell cultures, children with egg allergy are at very low risk for anaphylaxis with these vaccines.

Diphtheria-Tetanus-Pertussis

Children traveling internationally should be fully vaccinated with diphtheria and tetanus toxoids and acellular pertussis (DTaP), having completed the 4th or 5th booster dose by 4-6 yr of age. A single dose of an adolescent/adult preparation of tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine is recommended at 11-12 yr of age for those who have completed the recommended primary DTaP (or DTP) series.

Adolescents and adults should receive a single Tdap booster if more than 5 yr have elapsed since the last dose, as a tetanus-containing booster (Td or Tdap) may not be readily available for tetanus-prone wounds during international travel or in remote settings (adventure travel, wilderness).

Haemophilus influenzae Type B

Haemophilus influenzae type b remains a leading cause of meningitis in children 6 mo to 3 yr of age in many low- and middle-income countries. Before they travel, all unimmunized children <5 yr of age should be vaccinated (see Chapter 172). A single dose of *H. influenzae* type b vaccine should also be administered to unvaccinated or partially vaccinated children who are 5 yr of age or older if they have anatomic or functional asplenia, sickle cell disease, HIV infection, leukemia, malignancy, or other immunocompromising condition. Unvaccinated children who are >5 yr of age do not need vaccination unless they have a high-risk condition.

Hepatitis A

Hepatitis A is a routine childhood vaccine in the United States but requires special considerations in the traveling pediatric patient, and protection from hepatitis A in specific children may also involve the provision of immunoglobulin. For this reason, hepatitis A vaccination is covered below in "Specialized Pediatric Travel Vaccinations."

Hepatitis B

Hepatitis B is a travel-associated infection. Hepatitis B is highly prevalent throughout much of the world, including areas of South America, sub-Saharan Africa, eastern and southeastern Asia, and most of the Pacific basin. In certain parts of the world, 8-15% of the population may be chronically infected. Disease can be transmitted via blood transfusions not screened for hepatitis B surface antigen, exposure to unsterilized needles, close contact with local children who have open skin lesions, and sexual exposure. Exposure to hepatitis B is more likely for travelers residing for prolonged periods in endemic areas. Partial protection may be provided by 1 or 2 doses, but ideally 3 doses should be given before travel. For unvaccinated adolescents, the 1st 2 doses are 4 wk apart and are followed by a 3rd dose 8 wk later (at least 16 wk after 1st dose).

All unvaccinated children and adolescents should receive the accelerated hepatitis B vaccine series prior to travel. Because 1 or 2 doses provide some protection, hepatitis B vaccination should be initiated even if the full series cannot be completed before travel.

Influenza and Avian Influenza

Influenza remains the most common vaccine-preventable disease occurring among pediatric and adult travelers. The risk for exposure to influenza during international travel varies depending on the time of yr, destination, and intermingling of persons from different parts of the world where influenza may be circulating. In tropical areas, influenza can occur throughout the year, whereas in the temperate regions of the Southern hemisphere, most activity occurs from April through September. In the Northern hemisphere, influenza generally occurs from November through March. Seasonal influenza vaccination is strongly recommended for all pediatric and adolescent travelers who do not have a contraindication or severe egg allergy.

Currently, there is no available vaccine effective against avian influenza, the H5N1 virus, which has become an increasing concern worldwide. However, there are precautions for those traveling to endemic areas, which include parts of Asia, Africa, Eastern Europe, and the Middle East (see the CDC's website for a detailed list of countries). Because H5N1 influenza is spread through contact with infected birds, these precautions include avoiding direct contact with birds or surfaces with bird droppings, avoiding poultry farms or bird markets, eating only well-cooked bird meat or products, and washing hands frequently. Human-to-human transmission has been reported but is very rare and has not involved spread past 1 person. Oseltamivir is the antiviral of choice to treat avian influenza, because the virus is resistant to amantadine and rimantadine. Oseltamivir is FDA-approved for children 1 yr of age and older but can be also be administered for treatment of influenza during infancy with weight-based dosing (http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm).

Measles-Mumps-Rubella

Measles is still endemic in many low- and middle-income countries and in some industrialized nations. It remains a leading cause of vaccine-preventable death in much of the world. Vaccine status for measles is important for all traveling children, particularly if they are traveling to low- and middle-income countries or areas with measles outbreaks. Measles vaccine, preferably in combination with mumps and rubella vaccines (MMR), should be given to all children at 12-15 mo of age and at 4-6 yr of age, unless there is a contraindication (see Chapter 172.2). In children traveling internationally, the 2nd vaccination can be given as soon as 4 wk after the 1st, to induce immunity among those children who did not respond to the 1st MMR vaccine.

Children between the ages of 6 and 12 mo who are traveling to the low- and middle-income world should be vaccinated with monovalent measles vaccine. If the monovalent vaccine is unavailable, MMR should be used. Early vaccination (i.e., between 6-12 mo of age) will provide some immunity to measles, but antibody response is not durable or lasting. Any MMR vaccine before 12 mo of age does not count toward the routine vaccination schedule; children vaccinated early for purposes of international travel must be revaccinated on or after their 1st birthday with 2 doses, separated by at least 4 wk. Infants <6 mo of age are generally protected by maternal antibodies and should not receive early MMR vaccination prior to travel.

Pneumococcal Vaccines

Streptococcus pneumoniae is the leading cause of childhood bacterial pneumonia and is among the leading causes of bacteremia and bacterial meningitis in children in low- and middle-income and industrialized nations. Preparing a child to travel internationally includes routine or catch-up vaccination with 13-valent pneumococcal conjugate vaccine (PCV13) and, for children with certain high-risk conditions, use of 23-valent pneumococcal polysaccharide vaccine (PPSV23). A single dose of PCV13 should be administered to previously unvaccinated children 6-18 yr old with underlying high-risk medical conditions: anatomic or functional asplenia (including sickle cell disease), HIV infection, a congenital immunodeficiency or immunocompromising condition, chronic heart or lung disease, chronic renal failure or nephrotic syndrome, diabetes mellitus, cerebrospinal fluid leak, or cochlear implant. The Advisory Committee on Immunization Practices also recommends that high-risk children age 2 yr and older receive the PPSV23 vaccine 8 or more weeks after their last PCV13 dose. Recommendations of the Advisory Committee on Immunization Practices on prevention of pneumococcal disease among infants and children using PCV13 and PPSV23 can be found at http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html.

Polio Vaccine

Poliomyelitis was eradicated from the Western hemisphere in 1991. Polio remains endemic in 3 countries—Afghanistan, Nigeria, and Pakistan—with additional surrounding countries at risk for importation of polio. A number of countries continue to experience periodic outbreaks of importation polio, particularly countries extending from west Africa to the Horn of Africa. The poliovirus vaccination schedule in the United States is now a 4-dose, all-inactivated poliovirus (IPV) regimen (see Chapter 172). Traveling infants should begin IPV series as early as 6 wk of age. For an accelerated dosing schedule for children, see Figure 172-4 in Chapter 172. Length of immunity conferred by IPV immunization is not known; a single booster dose of IPV is therefore recommended for previously vaccinated adolescents and adults traveling to polio-endemic areas if approximately 10 yr has elapsed since they completed their primary series. Oral poliovirus vaccine is no longer available in the United States.

Varicella

All children 12 mo of age and older who have no history of varicella vaccination or chickenpox should be vaccinated unless there is a contraindication to vaccination (see Chapter 172). Infants <6 mo of age are generally protected by maternal antibodies. All children now require 2 doses, the 1st at 12 mo of age and the 2nd at 4-6 yr of age. The 2nd dose can be given as soon as 3 mo after the 1st dose. For unvaccinated children 13 yr of age and older, the 1st and 2nd doses can be separated by 4 wk.

SPECIALIZED PEDIATRIC TRAVEL VACCINATIONS

Table 175-1 summarizes the dosages and age restrictions of vaccines specifically given to children traveling internationally.

Cholera

Cholera is present in many low- and middle-income countries, but the risk for infection among travelers to these countries is extremely low. At present, there is no cholera vaccine available for travelers in the United States, although an effective vaccine is available in other countries. Travelers entering countries reporting cholera outbreaks are at minimal risk of acquiring cholera if they take adequate safe food and water precautions and utilize frequent handwashing. No country or territory currently requires cholera vaccination as a condition for entry.

Table 175-1 Travel Vaccinations for Children

VACCINE	PRIMARY SERIES	AGE AT VACCINATION	BOOSTER/COMMENTS
HEPATITIS A			
Havrix, Vaqta	0.5 mL IM × 2 doses ≥6 mo apart	>1 yr	No booster; see text about off-label administration (age 6-11 mo)
Immunoglobulin (Ig)	Travel <2 mo: 0.02 mL/kg IM once Travel >2 mo: 0.06 mL/kg IM once	Birth	See text about restrictions with live virus vaccinations (i.e., MMR) following Ig administration
INFLUENZA			
Inactivated	6-35 mo: 0.25 mL IM, 1 or 2 doses 3-8 yr: 0.5 mL IM, 1 or 2 doses >9 yr: 0.5 mL IM once	>6 mo	New vaccine yearly In children 6 mo-9 yr, 2 doses should be given ≥1 mo apart if no prior vaccination
Live-attenuated	0.25 mL in each nostril, 1 or 2 doses	>2 yr	New vaccine yearly
JAPANESE B ENCEPHALITIS			
Ixiaro (inactivated)	2 mo-2 yr: 0.25 mL IM on days 0 and 28	2 mo to <3 yr	Booster 1-2 yr after primary series
	>3 yr: 0.5 mL IM on days 0 and 28	>3 yr	Booster 1-2 yr after primary series
MEASLES			
MMR	Recommended schedule: 12-15 mo and 4-6 yr If >12 mo and traveling internationally, 2nd MMR dose can be administered 4 wk later	>6-11 mo: 1 dose recommended if traveling to measles-endemic area	See text. MMR at 6-11 mo does not count toward primary series; MMR should be administered simultaneously with other recommended/required live-virus travel vaccines (yellow fever)
MENINGOCOCCAL DISEASE			
Conjugate A/C/Y/W-135	0.5 mL IM 9-23 mo: 2 doses, 3 mo apart	9-23 mo	Booster 3 yr after primary series
	0.5 mL IM once	>2–6 yr >7 yr	Booster after 3 yr (age 2-6 yr) Booster after 5 yr (age >7 yr) Children with functional/anatomic asplenia receive 2 dose primary series, 2 mo apart; conjugate vaccine recommended over polysaccharide A/C/Y/W-135
Polysaccharide A/C/Y/W-135	0.5 mL SC once	>2 yr	<4 yr of age: every 2 yr >4 yr of age: every 3-5 yr
RABIES			
	Preexposure: 1.0 mL IM × 3 doses, days 0, 7, and 21 or 28 days	Any age	See text for follow-up vaccination if bitten
TYPHOID			
Intramuscular Vi	0.5 mL IM once	≥2 yr	Every 2-3 yr
Oral Ty21	4 doses: 1 capsule PO every other day	≥6 yr	Every 5 yr; see text for administration
YELLOW FEVER			
	0.5 mL SC once	>9 mo	Every 10 yr (see text)

A/C/Y/W-135, serogroup A, C, Y, and W135 meningococcal vaccine.

Hepatitis A Vaccination and Preexposure Immunoglobulin

Hepatitis A virus is endemic in most of the world, and travelers are at risk, even if their travel is restricted to the usual tourist routes. Hepatitis A infection can occur as a result of eating shellfish harvested from sewage-contaminated waters, eating unwashed vegetables or fruits, or eating food prepared by an asymptomatic carrier of hepatitis A virus. Young children infected with hepatitis A are often asymptomatic but can transmit infection to older children and adults, who are more likely to develop clinical hepatitis. Few areas carry no risk of this infection, and therefore immunization is recommended for all travelers. Hepatitis A vaccine is recommended in the United States for universal immunization of all children 12 mo of age or older, administered as 2 doses 6 mo apart. A single dose of hepatitis A vaccine given to travelers will provide adequate protection in most instances. Protective immunity develops within 2 wk after the initial vaccine dose. A combined 3 dose hepatitis A and hepatitis B vaccine (Twinrix, GlaxoSmithKline) is available in the United States but is licensed for use only in adolescents >18 yr of age. Pediatric combination hepatitis A–hepatitis B vaccine (Twinrix-Junior, GlaxoSmithKline) is licensed for use in children 1-18 yr in Canada and Europe.

Children <1 yr of age are at lower risk of clinical hepatitis A infection, especially if they are breastfed or residing in areas with safe water for formula reconstitution. Some experts recommend use of preexposure intramuscular immunoglobulin for children <12 mo who are traveling internationally to higher-risk destinations, particularly low-income destinations or regions where hygienic or sanitary conditions are limited. However, administration of immunoglobulin diminishes the immunogenicity of live-virus vaccines, in particular measles vaccine, that may be needed for infant travelers. Vaccination against measles should occur 2 or more weeks prior to any immunoglobulin administration, and a 3 mo interval is suggested between immunoglobulin administration and subsequent measles immunization.

Providers should be aware that infant travelers 6 mo of age or older who are being considered for preexposure immunoglobulin may also need measles (MMR) vaccination, as measles-endemic countries frequently overlap with higher-risk travel destinations for hepatitis A virus infection. For this reason, and on the basis of vaccine safety data, many travel medicine experts recommend immunization with hepatitis A vaccine rather than administration of intramuscular immunoglobulin to infants 6-11 mo of age who will be traveling to a hepatitis A virus–endemic area. Several studies demonstrate that infants as young as 6 mo old will develop antibodies following hepatitis A vaccine, especially if there are no interfering maternal antibodies from prior maternal vaccination or disease. There is potential for a more durable immune response to the hepatitis A vaccination especially in later infancy, when potential interfering maternal antibody concentrations are lower. If early hepatitis A vaccination is given rather than immunoglobulin to infant travelers (age 6-11 mo), it should not count toward the routine 2 dose vaccine series. Similar to MMR vaccination, an informed decision should be made, with the parents balancing the risk of travel-associated disease and vaccine adverse events with the potential protective benefit to the traveling infant.

Japanese Encephalitis

Japanese encephalitis is a disease transmitted by mosquitoes in many areas of Asia, especially in rural farming areas. Although it is a leading cause of vaccine-preventable encephalitis in children in many Asian countries and parts of western Pacific countries, the risk of disease to nonimmune travelers is low. A map showing where Japanese encephalitis transmission occurs can be found at http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/japanese-encephalitis#2473.

Most human infections with Japanese encephalitis virus are asymptomatic, and <1% of individuals develop clinical disease. With symptomatic disease, the fatality rate is 20-30% and the incidence of neurologic or psychiatric sequelae in survivors is 30-50%. The risk of Japanese encephalitis disease for pediatric travelers is unknown, but among all travelers, it is estimated to be less than 1 case per 1 million travelers to Asia. Risk of Japanese encephalitis neurologic disease following mosquito-bite transmission is thought to be higher in children than adults. The disease occurs primarily from June to September in temperate zones and throughout the entire year in tropical zones. Vaccination is recommended for travelers planning visits of longer than 1 mo to rural areas of Asia, where the disease is endemic, especially areas of rice or pig farming. Vaccination is recommended for shorter visits to such areas if the traveler will often be outdoors (e.g., camping or hiking). Risk for infection can be greatly reduced by following the standard precautions to avoid mosquito bites.

The inactivated Vero-cell culture-derived Japanese encephalitis vaccine (Ixiaro) has replaced the older inactivated mouse-brain-derived vaccine (JE-VAX), which is no longer manufactured. Japanese encephalitis (Ixiaro) vaccine efficacy is >95% in adults who receive 2 doses administered 28 days apart. The licensed range for Japanese encephalitis vaccine (Ixiaro) has been extended to include children as young as age 2 mo, with a dose administered on days 0 and 28.

Meningococcal Vaccines

There are currently 2 forms of meningococcal vaccine available in the United States: a quadrivalent polysaccharide A/C/Y/W-135 vaccine (Menomune) and 2 quadrivalent conjugate A/C/Y/W-135 vaccines (Menactra, Menveo). A single-dose conjugate quadrivalent A/C/Y/W-135 vaccine, Nimenrix (manufactured by GlaxoSmithKline), is licensed in Europe and Canada for individuals from 12 mo-55 yr of age.

Children traveling to those equatorial countries in sub-Saharan Africa where the incidence of meningococcal disease is highest should receive a *Neisseria meningitidis* vaccine, especially if travel is prolonged or occurs during the dry season of December to June. Risk is greatest in the "meningitis belt" of sub-Saharan Africa (see the map at http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/meningococcal-disease), with rates of meningococcal disease in endemic regions reaching up to 1,000 cases per 100,000 population per year. Children 9-23 mo of age who are traveling to these equatorial African countries where meningococcal disease is hyperendemic or epidemic should receive a 2 dose series of Menactra brand MCV4, 8-12 wk apart. Conjugate vaccine is preferred in children over the less-effective polysaccharide vaccine (Menomune). Booster doses of conjugate A/C/Y/W-135 should occur every 3-5 yr for travelers returning to endemic areas, depending on age of pediatric traveler. Providers may also wish to consider meningococcal vaccination for other pediatric travelers, especially if there is remote or rural travel to low-income countries with limited healthcare access, as meningococcal outbreaks can occur anywhere in the world. Proof of receipt of quadrivalent meningococcal vaccination is also necessary for individuals traveling to Mecca, Saudi Arabia, for the annual Hajj or Umrah pilgrimages.

Serogroups A and C are most commonly associated with epidemics of meningitis in sub-Saharan Africa, especially in the "meningitis belt" of equatorial Africa during the dry season mo (December to June). Serogroups Y and W-135 have also been found in meningococcal outbreaks. Serogroup B, currently not included in any licensed meningococcal vaccine in the United States, is associated with more sporadic cases of invasive meningococcal disease in industrialized countries, including the United States. Additional vaccine information on meningococcal vaccination regimens and booster intervals can be found at the CDC website (http://www.cdc.gov/vaccines/vpd-vac/mening/#recs).

Rabies

Rabies is endemic in many countries in Africa, Asia, and Central and South America. Children are at particular risk because they are less likely to report bites and because facial bites are more common in children. Rabies has the potential for an extended latency period (months) and is uniformly fatal once the clinical symptoms emerge. Preexposure prophylaxis is recommended for ambulatory children with extended travel to high-risk regions, especially expatriate children and younger children traveling to or living in rural areas where enzootic dog rabies is endemic. Rabies preexposure vaccination should also

be considered for adventure travelers (hikers, bikers), individuals likely to come into contact with rabies vectors (i.e., students working with animal or bat conservation), or travelers with itineraries to rabies-endemic regions where timely, effective postexposure prophylaxis might not be available following an animal bite. Most animal bites in a rabies-endemic area should be considered a medical emergency, especially bites from stray dogs, other carnivores, and bats. Immediate wound care washing should be followed by prompt administration of appropriate postexposure rabies prophylaxis at a medical facility. Postexposure prophylaxis is required even for persons who received preexposure vaccination. Algorithms for pre- and postexposure vaccination are the same regardless of patient age.

Numerous rabies vaccine formulations exist around the world. In the United States, 2 rabies vaccines are available: human diploid cell vaccine (HDCV; Imovax, Sanofi Pasteur, SA) and purified chick embryo cell (PCEC; RabAvert, Novartis) vaccine. Preexposure prophylaxis is given either intramuscularly (HDCV or PCEC) as 3 doses (1 mL) on days 0, 7, and 21 or 28. Postexposure prophylaxis is given as 4 doses (1 mL) of HDCV or PCEC vaccine intramuscularly on days 0, 3, 7, and 14 if previously unvaccinated and 2 doses (1 mL) intramuscularly on days 0 and 3 if previously vaccinated. Previously unvaccinated persons should also receive rabies immunoglobulin (RIG, 20 IU/kg), with as much of the dose as possible infiltrated around the wound site at the time of initial postexposure prophylaxis. Previously vaccinated persons should not receive RIG. Unpurified or purified equine RIG preparations are still used in some low- and middle-income countries and are associated with a higher risk for severe reactions, including serum sickness and anaphylaxis. Purified cell culture–derived vaccines are also not always available abroad; travelers should be aware that any rabies vaccines derived from neural tissue carry an increased risk for adverse reactions, often with neurologic sequelae. If rabies prophylaxis is initiated abroad, neutralizing titers should be checked on return and immunization completed with a cell culture–derived vaccine. If rabies prophylaxis cannot be provided abroad, children with high-risk bites (e.g., stray dog) should be emergently transported to a site where they can receive prophylaxis, as the vaccinations should be started as soon as possible after the bite and ideally within 24 hr. Infants and young children respond well to rabies vaccine, and both pre- and postexposure vaccinations can be given at any age, using the same dose and schedule as adults. Individual travelers simultaneously receiving mefloquine or chloroquine may have limited immune reactions to intradermal rabies vaccine and should be vaccinated intramuscularly.

Tuberculosis

The risk for tuberculosis in the typical traveler is low. Pre- and post-travel testing for tuberculosis is controversial, and should be done on an individualized basis depending on the itinerary, duration, and activities (i.e., working in a hospital setting). Immunization with bacillus Calmette-Guérin is even more controversial. It has variable efficacy in reducing severe tuberculosis disease in infants and young children, is not available in the United States, and is generally not recommended for pediatric travelers. Infection with *Mycobacterium bovis* can be prevented through avoiding consumption of unpasteurized dairy products.

Typhoid

Salmonella typhi infection, or typhoid fever, is common in many low- and middle-income countries in Asia, Africa, and Latin America (see Chapter 198). Typhoid vaccination is recommended for most children 2 yr of age or older who are traveling to the Indian subcontinent, as the incidence of typhoid is 10-100 times higher for travelers to the Indian subcontinent than all other travel destinations. Vaccination should be strongly considered for other travelers to low- and middle-income countries, particularly if they are visiting friends and relatives, lack access to reliable clean water and food, are traveling for a prolonged duration, or are adventurous eaters.

Two typhoid vaccines, the intramuscular Vi-polysaccharide vaccine and oral Ty21a strain live-attenuated vaccine, are recommended for use in children in the United States. Both produce a protective response in 50-80% of recipients. Neither vaccination offers meaningful protection against *Salmonella paratyphi*, another cause of enteric fever. Travelers who have had prior diagnoses of “typhoid fever” should still receive vaccination, as past infection does not confer long-term immunity.

The intramuscular Vi-polysaccharide vaccine is licensed for use in children 2 yr of age and older. It can be given any time before departure, but it should ideally be administered 2 wk before travel, with a booster needed 2-3 yr later. The oral Ty21a vaccine can only be used in children 6 yr of age or older and is given in 4 doses over a 1 wk period. Enteric-coated capsules are to be swallowed with a cool or room-temperature drink, at least 1 hr before a meal, every other day until the 4 doses are completed. Oral typhoid capsules must remain refrigerated (not frozen). Capsules should never be broken open, as vaccine efficacy is dependent on capsules being swallowed whole in order to get past the acidic stomach contents. The oral vaccine is associated with an immune response lasting 5-7 yr (depending on national labeling). Antibiotics inhibit the immune response to the oral Ty21a vaccine; the vaccine should not be given within 72 hr of antibiotic treatment, and antibiotics should be avoided until 7 days after completing the vaccine series. Studies demonstrate that mefloquine, chloroquine, and atovaquone-proguanil can be given concurrently with the oral Ty21a vaccine without affecting the immunogenicity of the vaccine. Oral Ty21a vaccine should not be given to immunocompromised children; these children should receive the intramuscular Vi-polysaccharide vaccine.

Yellow Fever

Yellow fever (see Chapter 270) is a mosquito-borne viral illness resembling other viral hemorrhagic fevers (see Chapter 271) but with more prominent hepatic involvement. Yellow fever is present in tropical areas of South America and Africa.

Yellow fever vaccination is indicated in children >9 mo of age traveling to an endemic area. Many countries require yellow fever vaccination by law for travelers arriving from endemic areas, and some African countries require evidence of vaccination from all entering travelers. Current recommendations can be obtained by contacting state or local health departments or the Division of Vector-Borne Infectious Diseases of the CDC (telephone: 404-332-4555; or website: http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/yellow-fever). Most countries accept a medical waiver for children who are too young to be vaccinated (<6 mo of age) and for persons with a contraindication to vaccination. Children with asymptomatic HIV infection may be vaccinated if exposure to yellow fever virus cannot be avoided.

Yellow fever vaccine (0.5 mL SC), a live-attenuated vaccine (17D strain) developed in chick embryos, is safe and highly effective in children >9 mo of age, but in young infants it is associated with a markedly increased risk for vaccine-associated encephalitis (0.5-4/1,000) and other severe reactions. Yellow fever vaccine should **never be given** to infants <6 mo of age; infants 6-8 mo of age should be vaccinated only in consultation with the CDC or a travel medicine expert to assess the current epidemiology, travel itinerary and duration, and whether the yellow fever virus exposure is greater than vaccine risks. In children >9 mo, adverse effects are rare, although vaccine-associated neurotropic and viscerotropic disease associated with the vaccine have been reported. The risk of these reactions is higher in those with thymus disease, altered immune status, age >60 yr, or multiple sclerosis and in infants <9 mo of age (neurotropic disease). Yellow fever vaccination is generally contraindicated in pregnancy and for nursing mothers, unless extended travel to a yellow fever–endemic area is unavoidable.

Children with immunodeficiency or an immunosuppressed state, a thymic disorder or dysfunction (i.e., DiGeorge syndrome), or a history of anaphylactic reactions to eggs should not receive yellow fever vaccine. Long-lived immunity develops with this vaccine, perhaps even lasting for a lifetime; however, international travel certificates require proof of immunization within 10 yr.

Traveler's Diarrhea

Ingestion of contaminated food or water makes travel-associated diarrhea the most common health complaint among international travelers. Traveler's diarrhea, characterized by a 2-fold or greater increase in the frequency of unformed bowel movements, occurs in as many as 40% of all travelers overseas (see Chapter 340.1). Children, especially those <3 yr of age, have a higher incidence of diarrhea, more-severe symptoms, and more-prolonged symptoms than adults, with a reported attack rate of 60% for those <3 yr of age in 1 study.

An important risk factor for traveler's diarrhea is the country of destination. High-risk areas (attack rates of 25-50%) include low- and middle-income countries of Latin America, Africa, the Middle East, and Asia. Intermediate risk occurs in the Mediterranean, China, and Israel. Low-risk areas include North America, Northern Europe, Australia, and New Zealand. Fecal-oral diarrheal pathogens that children acquire during travel are similar to those acquired by adults and include enterotoxigenic and enteroaggregative *Escherichia coli*, *Campylobacter, Salmonella* (nontyphoidal serotypes predominate), and *Shigella* species. Enteric protozoa are a much less common cause of traveler's diarrhea than bacterial pathogens—*G. lamblia* is the most likely protozoal cause of persistent diarrhea. Less-common travel-associated protozoa include *Cryptosporidium* species, *E. histolytica,* and *Cyclospora*. Viral infections, particularly rotavirus infections, may also cause travel-associated diarrhea in children. Clinicians should be aware that not all diarrheal illness in children is food borne or waterborne—febrile children with malaria may also present with vomiting and/or nonbloody diarrhea and may be misdiagnosed as having traveler's diarrhea.

Guidance on Prevention of Traveler's Diarrhea

Food and water hygiene remain important measures to reduce the incidence of traveler's diarrhea in children. However, creating long lists of foods to avoid or offering the popular, simple advice of "Boil it, peel it, cook it, or forget it!" is generally an ineffective method of reducing traveler's diarrhea. Most studies show that these kinds of dietary directives are difficult to keep and may have little impact on the incidence of traveler's diarrhea. In adult studies, the risk of developing traveler's diarrhea appears to be more associated with *where you eat rather than what you eat*. Eating in a relative's or friend's home is generally safer than eating in a restaurant, where restaurant kitchen hygiene and proper refrigeration may be lacking and employee handwashing may be sporadic.

In general, travel medicine providers can provide some common sense food and water advice to family travelers. Boiled or bottled water, hot beverages, and canned or bottled beverages are generally safe to consume. Ice should be avoided. In low- and middle-income countries, tap water is generally unsafe for drinking or brushing teeth. Boiling water for 1 min or longer (or 3 min at altitudes >2000 m) remains a reliable method of disinfecting water. Food that is thoroughly cooked and served hot is almost always safe to eat. Dry foods, such as pastry items, breads, and cookies, are generally safe to eat. Unpasteurized milk or other dairy products (cheese) should always be avoided. Breastfeeding should be encouraged for young children, especially infants <6 mo of age, to reduce exposure to contaminated water/formula. All children should be reminded to wash their hands before eating and after playing around soil or animals. Chemoprophylactic agents for traveler's diarrhea are not recommended for children.

Management of Traveler's Diarrhea

Dehydration is the greatest threat presented by a diarrheal illness in a small child. Parents should be made aware of the symptoms and signs of dehydration and should be given instructions on how to administer rehydration solutions. Prepackaged WHO oral rehydration solution packets, which are available at stores or pharmacies in almost all low- and middle-income countries, should be part of a child's travel kit. Oral rehydration solution should be mixed as directed with bottled or boiled water and given slowly, as tolerated, to the child while symptoms persist.

Antimotility agents such as diphenoxylate (Lomotil) and loperamide (Imodium) should be avoided in infants and young children, and the American Academy of Pediatrics does not recommend their routine use in acute gastroenteritis. Use of antimotility agents may be beneficial in older children and adolescents with afebrile, nonbloody traveler's diarrhea. In general, antimotility agents should not distract parents from giving frequent oral rehydration solution, as ongoing intestinal fluid losses likely continue despite a decrease in stooling. Bismuth subsalicylate for acute gastroenteritis should be avoided because of concern for toxicity and Reye syndrome.

Presumptive Antibiotic Treatment

Oral rehydration is the mainstay of treatment for pediatric traveler's diarrhea. However, antibiotics should be prescribed for the pediatric traveler, with parental instructions to start presumptive treatment early in the diarrheal illness. Systemic antibiotics can shorten the duration and severity of diarrheal illness, especially if presumptive antibiotics are initiated immediately after onset of traveler's diarrhea. For children, the drug of choice is azithromycin (10 mg/kg once daily for up to 3 days, with maximum daily dose of 500 mg). Ciprofloxacin (10 mg/kg per dose twice a day for up to 3 days, maximum dose of 500 mg twice a day) is an alternative for children >1 yr of age, but should not be prescribed for traveler's traveling to the Indian subcontinent or Southeast Asia, where fluoroquinolone resistance is common. Shiga-toxin producing *E. coli* such as *E. coli* O157:H7 is an extremely uncommon cause of pediatric traveler's diarrhea in nonindustrialized countries, and the benefit of presumptive antibiotic therapy in traveling children, even with bloody diarrhea, typically outweighs the low risk of developing hemolytic-uremic syndrome.

Azithromycin is highly effective against most bacterial pathogens that cause traveler's diarrhea, and is the preferred antibiotic among many travel experts. Azithromycin can be prescribed in powder form that can be reconstituted with safe water into a liquid suspension when needed. In addition, azithromycin 250 mg tablets can be cut to the nearest $\frac{1}{4}$ tablet size to achieve a dosage of approximately 10 mg/kg, and then crushed and mixed with food or water for younger children. Amoxicillin, trimethoprim-sulfamethoxazole (cotrimoxazole), and erythromycin should not be prescribed for self-treatment of traveler's diarrhea, because of widespread resistance among diarrheal pathogens. Traveler's diarrhea that results in bloody stools, persistently high fevers, systemic chills and rigors, severe or localizing abdominal pain, or continued fluid losses should prompt additional medical evaluation.

INSECT-BORNE INFECTIONS

Insect-borne infections for which traveling children are most at risk include malaria, dengue, chikungunya, yellow fever, and Japanese encephalitis, depending on the area of travel. Malaria is transmitted by night-biting *Anopheles* mosquitoes, whereas dengue occurs from mosquito species *(Culex*, *Aedes)* that are predominantly active during the day. Families should be encouraged to protect children against daytime and nighttime biting mosquitoes, as many regions of the world in which malaria is found also have diseases transmitted by daytime biting mosquitoes (dengue, chikungunya).

Exposure to insect bites can be reduced by wearing appropriate attire and using insect repellents containing *N,N*-diethyl-*m*-toluamide (DEET) or picaridin. The American Academy of Pediatrics recommends avoiding DEET-containing repellants in children <2 mo of age. Rare instances of neurologic events have been reported in very young children with exposure to inappropriate, frequent applications of DEET-containing repellants (>10 times a day) or who licked off DEET. Concentrations of 25-30% DEET need be applied every 4-6 hr as needed, whereas 5-7% DEET provides only 1-2 hr of protection time. DEET concentrations >40-50% do not confer a substantially longer protection time for children and generally should be avoided.

Picaridin is a newer insect repellant in the United States but has been used widely in Europe and Australia for yr. Picaridin is fragrance-free, effective, and generally well tolerated on exposed skin and faces. It has similar efficacy to DEET but with less inhalational or dermal irritation.

Picaridin at concentrations of 20% or higher provides adequate protection against *Anopheles* mosquitoes that have potential to transmit malaria. When applying sunscreen and insect repellant, sunscreen should be applied 1st followed by DEET or picaridin.

Spraying or treating clothing with permethrin, a synthetic pyrethroid, is a safe and effective method of further reducing insect bites in children. Permethrin can be applied to directly to clothing, bed nets, shoes, and hats, and should be allowed to fully dry before use. As an insecticide, permethrin should never be applied to skin. Permethrin-treated garments retain both repellency and insecticidal activity, even with repeated laundering. Clothing will eventually need to be retreated to maintain repellency, according to the product label. Bed nets, particularly permethrin-impregnated bed nets, also decrease the risk of insect bites, and their use is highly recommended in malarial areas.

Malaria Chemoprophylaxis

Malaria, a mosquito-borne infection, is the leading parasitic cause of death in children worldwide (see Chapter 288). Of the 4 *Plasmodium* species that infect humans, *Plasmodium falciparum* causes the greatest morbidity and mortality. Each yr, more than 8 million U.S. citizens visit parts of the world where malaria is endemic (sub-Saharan Africa, Central and South America, India, Southeast Asia, Oceania). Children accounted for 15-20% of imported malaria cases in a WHO study in Europe. Given the major resurgence of malaria and increased travel among families with young children, physicians in industrialized countries are increasingly required to give advice on prevention, diagnosis, and treatment of malaria. Risk factors for severe malaria and death include inadequate adherence to chemoprophylaxis, delay in seeking medical care, delay in diagnosis, and nonimmune status, but the case fatality rate of imported malaria remains <1% in children from nonendemic countries. The CDC maintains updated information at http://www.cdc.gov/malaria/travelers/index.html, as well as a malaria hotline for physicians (770-488-7788). It is important to check this updated information, because recommendations for prophylaxis and treatment are often modified owing to changes in the risk for developing malaria in different areas of the world, changing *Plasmodium* resistance patterns, and the availability of new antimalarial medications.

Avoidance of mosquitoes and barrier protection from mosquitoes are an important part of malaria prevention for travelers to endemic areas. The *Anopheles* mosquito feeds from dusk to dawn. Travelers should remain in well-screened areas, wear clothing that covers most of the body, sleep under a bed net (ideally one impregnated with permethrin), and use insect repellents with DEET during these hours. Parents should be discouraged from taking a young child on a trip that will entail evening or nighttime exposure in areas endemic for *P. falciparum.*

Chemoprophylaxis is the cornerstone of malaria prevention for nonimmune children and adults who travel to malaria-endemic areas but it is not a replacement for other protective measures. Travelers often do not take malaria prophylaxis as prescribed or at all. They are more likely to use prophylactic antimalarial drugs if their physicians provide appropriate recommendations and education before departure. However, in 1 survey, only 14% of persons who sought medical advice obtained correct information about malaria prevention and prophylaxis. Families with children visiting friends and relatives are particularly less likely to take malaria prophylaxis or seek pretravel medical advice.

Resistance of *P. falciparum* to the traditional chemoprophylactic agent, chloroquine, is widespread, and in most areas of the world other agents must be used (Table 175-2). Factors that must be considered in choosing appropriate chemoprophylaxis medications and dosing schedules include age of the child, travel itinerary (including whether the child will be traveling to areas of risk within a particular country and whether chloroquine-resistant *P. falciparum* is present in the country), vaccinations being given, allergies or other known adverse reactions to antimalarial agents, and the availability of medical care during travel.

Children traveling to areas with chloroquine-resistant *P. falciparum* can be given mefloquine, atovaquone-proguanil, or doxycycline (if >8 yr of age) as malaria prophylaxis. For trips shorter than 4 wk, atovaquone-proguanil is the preferred medication, because it is given for only a short period before and after travel. Atovaquone-proguanil or doxycycline is also indicated for travel of any duration to western Cambodia and the Thailand–Cambodia and Thailand–Myanmar borders because of mefloquine resistance in these areas. For periods of travel longer than 4 wk to all other areas with chloroquine-resistant *P. falciparum,* mefloquine is the preferred medication because it can be taken weekly.

Mefloquine is FDA-approved only for children weighing more than 15 kg, but the CDC recommends mefloquine prophylaxis for all children regardless of weight because the risk for acquiring severe malaria outweighs the risk for potential mefloquine toxicity. Adults taking mefloquine prophylaxis have a 10-25% incidence of sleep disturbance and dysphoria and, less frequently, more serious neuropsychiatric symptoms. These side effects appear to be less common in children. Other potential side effects of mefloquine therapy include nausea and vomiting. The lack of a liquid or suspension formulation can make chloroquine and mefloquine administration difficult. For children who cannot take tablets, parents should take a chloroquine or mefloquine prescription to a compounding pharmacy, which can pulverize the tablets and place exact dosages into gel capsules. Parents can then open the gel capsules and sprinkle the powder into food. “Disguising” these medications, which have a bitter taste, is important; chocolate syrup has been used successfully as a vehicle for the medication. Persons with depression, neuropsychiatric disorders, seizure disorders, and cardiac conduction defects should not take mefloquine.

Atovaquone-proguanil fixed combination (Malarone) is an effective and safe chemoprophylaxis for travelers to chloroquine-resistant malaria-endemic areas, but it is fairly expensive. Adverse effects are infrequent and mild (abdominal pain, vomiting, and headache) and infrequently result in discontinuation of the medication. Atovaquone-proguanil prophylaxis must be taken every day with food, so it is better suited for prophylaxis during short periods of exposure. Recent data allow dosing down to 5 kg of body weight, although the use of atovaquone-proguanil at a weight between 5 and 10 kg is considered off-label.

Daily doxycycline is an alternative chemoprophylaxis regimen for chloroquine-resistant *P. falciparum* malaria that is considerably less expensive than atovaquone-proguanil. Doxycycline has been used extensively and is highly effective, but it cannot be used in children <8 yr of age owing to the risk of permanent tooth staining, and adverse effects (nausea, vomiting, photosensitivity, vaginal candidiasis) are not uncommon. Persons given doxycycline prophylaxis should be warned to decrease exposure to direct sunlight to minimize the possibility of photosensitivity. Primaquine has also been used successfully as chemoprophylaxis, especially in areas of high prevalence of *Plasmodium vivax* and *Plasmodium ovale,* but there are limited data about its use in nonimmune children. Primaquine prophylaxis for children should only be given in consultation with the CDC or a travel medicine specialist. Chloroquine, chloroquine-proguanil, and azithromycin do not provide adequate protection for children traveling to a chloroquine-resistant malaria-endemic area.

In areas of the world where *P. falciparum* remains fully chloroquine-sensitive (Haiti, the Dominican Republic, Central America north of the Panama Canal, and some countries in the Middle East), weekly chloroquine is the drug of choice for malaria chemoprophylaxis. Updated information on chloroquine susceptibility and recommended malaria prophylaxis is available at http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/malaria.

On leaving an area endemic for *P. vivax* or *P. ovale* after a prolonged visit (usually >3 mo), travelers should consider terminal prophylaxis with primaquine (0.5 mg/kg base) daily, up to a maximum dose of 30 mg base or 52.6 mg salt, for 14 days, to eliminate extraerythrocytic forms of *P. vivax* and *P. ovale* and prevent relapses. Screening for

Table 175-2 Chemoprophylaxis of Malaria for Children

AREA	DRUG	DOSAGE (ORAL)	ADVANTAGES	DISADVANTAGES	BEST USE
Chloroquine-resistant area	Mefloquine*†	weight <10 kg: 4.6 mg base (5 mg salt)/kg/wk weight 10-19 kg: ¼ tab/wk weight 20-30 kg: ½ tab/wk weight 31-45 kg: ¾ tab/wk weight >45 kg: 1 tab/wk (228 mg base)	Once-weekly dosing	Bitter taste No pediatric formulation Side effects of sleep disturbance, vivid dreams	Children going to malaria-endemic area for 4 wk or more Children unlikely to take daily medication
	Doxycycline‡	2 mg/kg daily (max: 100 mg)	Inexpensive	Cannot give to children <8 yr old Daily dosing Must take with food or causes stomach upset Photosensitivity	Children going to area for <4 wk who cannot take or cannot obtain atovaquone-proguanil
	Atovaquone/proguanil§ (Malarone)	Pediatric tabs: 62.5 mg atovaquone/25 mg proguanil Adult tabs: 250 mg proguanil/100 mg proguanil weight 5-8 kg: ½ pediatric tab once daily (off-label) weight 9-10 kg: ¾ pediatric tab once daily (off-label) weight 11-20 kg: 1 pediatric tab once daily weight 21-30 kg: 2 pediatric tabs once daily weight 31-40 kg: 3 pediatric tabs once daily weight >40 kg: 1 adult tab once daily	Pediatric formulation Generally well tolerated	Daily dosing Expensive Can cause stomach upset	Children going to malaria-endemic area for <4 wk
Chloroquine-susceptible area	Chloroquine phosphate	5 mg base/kg/wk (max: 300 mg base)	Once-weekly dosing Inexpensive Generally well tolerated	Bitter taste No pediatric formulation	Best medication for children traveling to areas with *Plasmodium falciparum* or *Plasmodium vivax* that is chloroquine susceptible
	Drugs used for chloroquine-resistant areas can also be used in chloroquine-susceptible areas				

*Chloroquine and mefloquine should be started 1-2 wk prior to departure and continued for 4 wk after last exposure.
†Mefloquine resistance exists in western Cambodia and along the Thailand–Cambodia and Thailand–Myanmar borders. Travelers to these areas should take doxycycline or atovaquone-proguanil. See text for precautions about mefloquine use.
‡Doxycycline should be started 1-2 days prior to departure and continued for 4 wk after last exposure. Do not use in children <8 yr of age or in pregnant women.
§Atovaquone-proguanil (Malarone) should be started 1-2 days prior to departure and continued for 7 days after last exposure. Should be taken with food or a milky drink. Not recommended in pregnant women, children who weigh <5 kg, and women breastfeeding infants who weigh <5 kg. Contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min).

glucose-6-phosphate dehydrogenase deficiency is mandatory before primaquine treatment, because primaquine is contraindicated in glucose-6-phosphate dehydrogenase–deficient persons because it can cause severe hemolysis in these persons.

Small amounts of antimalarial drugs are secreted into breast milk. The amounts of transferred drug are not considered to be either harmful or sufficient to provide adequate prophylaxis against malaria. Prolonged infant exposure to doxycycline via breast milk is not advisable.

Self-treatment of presumptive malaria during travel remains controversial. It should never be substituted for seeking appropriate medical care, but it can be considered in special circumstances such as travel to remote areas, intolerance of prophylaxis, or refusal of chemoprophylaxis by the traveler. Self-treatment medication should be different than the prescribed chemoprophylaxis. The CDC or a travel medicine specialist should be consulted if self-treatment medication is being considered for a traveler.

THE RETURNING TRAVELER

Posttravel evaluations are part of travel medicine and continuing care. Physicians unfamiliar with diseases that occur in low- and middle-income countries often misdiagnose the cause of illness in a child returning from travel abroad. Among returning patients identified from GeoSentinal sites who were ill, the common disorders included, in descending order of frequency, malaria, giardiasis, dengue fever, campylobacteriosis, cutaneous larva migrans, enteric fever, spotted

Table 175-3	Patterns of Illness Among Returning International Travelers
SYSTEMIC FEBRILE ILLNESS	
Malaria	
Dengue	
Enteric fever (typhoid/paratyphoid)	
Chikungunya virus	
Spotted fever rickettsia	
Hepatitis A	
Acute HIV	
Leptospirosis	
Measles	
Infectious mononucleosis	
Respiratory causes (pneumonia, influenza)	
Undetermined fever source	
ACUTE DIARRHEA	
Campylobacter	
Shigella spp.	
Salmonella spp.	
Diarrheagenic *Escherichia coli* (enterotoxigenic *E. coli*, enteroadherent *E. coli*–not tested for by routine stool culture methods)	
Giardiasis (acute, persistent, or recurrent)	
Entamoeba histolytica	
Cryptosporidium spp.	
Cyclospora cayetanensis	
Presumed viral enteritis	
DERMATOLOGIC MANIFESTATIONS	
Rash with fever (dengue)	
Arthropod-related dermatitis (insect bites)	
Cutaneous larva migrans *(Ancylostoma brasiliense)*	
Bacterial skin infections—pyoderma, impetigo, ecthyma, erysipelas	
Myiasis (tumbu and botfly)	
Scabies	
Tungiasis	
Superficial mycosis	
Animal bite	
Leishmaniasis	
Rickettsial diseases	
Marine envenomation/dermatitis	
Photoallergic and phytophotodermatitis	

fever (rickettsiosis), chikungunya fever, hepatitis A, and influenza. Returning pediatric travelers who are severely ill or with continued fevers should be seen in consultation with a pediatric travel medicine or infectious diseases physician.

There is very little literature that specifically addresses the causes of illness in children returning from travel. Among all persons returning from travel (children and adults), 3 major patterns of illness have been noted (Table 175-3). The etiology of each of these disease presentations in part depends on the country or geographic region visited.

Fever is a particularly worrisome symptom. Children with a febrile/systemic illness following recent travel to a malarial destination should be promptly evaluated for malaria, especially if having traveled to sub-Saharan Africa and Papua New Guinea. *P. falciparum* malaria will generally present within 1-2 mo after return from travel to a malaria-endemic area, but can occur within the 1st year after return. In contrast, symptoms of *P. vivax/P. ovale* malaria are typically later in onset following travel (i.e., several months), are milder in disease severity, and may occur in a relapsing pattern if undiagnosed or improperly untreated. Other symptoms of malaria can be nonspecific and include chills, malaise, headache, myalgias, vomiting, diarrhea, cough, and possible seizures. Children are more likely than adults to have higher fevers and also gastrointestinal symptoms, hepatomegaly, splenomegaly, and severe anemia. Thrombocytopenia (without increased bleeding) and fever in a child returning from an endemic area are highly suggestive of malaria.

Thick and thin blood smears need to be performed for diagnosis *if* malaria is clinically suspected. If results are negative initially, 2 or more additional smears should be done 12-24 hr after the initial smear. Rapid malaria antigen tests (Binax Now) are FDA-approved and sensitive for diagnosing falciparum malaria. Treatment should be initiated immediately once the diagnosis is confirmed or empirically if presentation is severe with suspected malaria. Treatment should be determined in consultation with a pediatric infectious disease specialist and the CDC, which has updated information on the drugs of choice, which are similar to those for adults (see Chapter 288 for more details on malaria infection). Great caution should be used with young children, nonimmune patients, and pregnant patients with falciparum malaria, and hospitalization of these patients should be strongly considered until reliable improvement is observed.

Enteric (typhoid) fever should be considered in children with persistent or recurrent fevers following return from the Indian subcontinent. Multiple blood cultures and a stool culture may both be necessary to diagnosis enteric fever. Dengue is another cause of fever and systemic illness in ill travelers, particularly when returning from Southeast Asia, the Caribbean, Central and South America, or the Indian subcontinent. Many bacterial and protozoal causes of acute traveler's diarrhea may also result in fever and systemic symptoms in children. Additional travel-associated febrile, diarrheal, and dermatologic illnesses exist, of which the most common etiologies can be found in Table 175-3.

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Chapter 176

Fever

Linda S. Nield and Deepak Kamat

DEFINITION

Fever is defined as a rectal temperature ≥38°C (100.4°F), and a value >40°C (104°F) is called hyperpyrexia. Body temperature fluctuates in a defined normal range (36.6-37.9°C [97.9-100.2°F] rectally), so that the highest point is reached in early evening and the lowest point is reached in the morning. Any abnormal rise in body temperature should be considered a symptom of an underlying condition.

PATHOGENESIS

Body temperature is regulated by thermosensitive neurons located in the preoptic or anterior hypothalamus that respond to changes in blood temperature as well as by cold and warm receptors located in skin and muscles. Thermoregulatory responses include redirecting blood to or from cutaneous vascular beds, increased or decreased sweating, regulation of extracellular fluid volume via arginine vasopressin, and behavioral responses, such as seeking a warmer or cooler environmental temperature.

Three different mechanisms can produce fever: pyrogens, heat production exceeding loss, and defective heat loss.

The first mechanism involves endogenous and exogenous pyrogens that raise the hypothalamic temperature set point. Endogenous pyrogens include the cytokines interleukins 1 and 6, tumor necrosis factor α, and interferons β and γ. Stimulated leukocytes and other cells produce lipids that also serve as endogenous pyrogens. The best-studied lipid mediator is prostaglandin E_2, which attaches to the prostaglandin receptors in the hypothalamus to produce the new temperature set point. Along with infectious diseases and drugs, malignancy and inflammatory diseases can cause fever through the production of endogenous pyrogens. Some substances produced within the

body are not pyrogens but are capable of stimulating endogenous pyrogens. Such substances include antigen–antibody complexes in the presence of complement, complement components, lymphocyte products, bile acids, and androgenic steroid metabolites.

Exogenous pyrogens or substances that come from outside the body include mainly infectious pathogens and drugs. Microbes, microbial toxins, or other products of microbes are the most common exogenous pyrogens and stimulate macrophages and other cells to produce endogenous pyrogens. Endotoxin is one of the few substances that can directly affect thermoregulation in the hypothalamus as well as stimulate endogenous pyrogen release.

Many drugs cause fever, and the mechanism for increasing body temperature varies with the class of drug. Drugs that are known to cause fever include vancomycin, amphotericin B, and allopurinol.

Heat production exceeding heat loss is the second mechanism that leads to fever, with examples including salicylate poisoning and malignant hyperthermia. Defective heat loss is the third mechanism of fever genesis; for example, in children with ectodermal dysplasia or victims of severe heat exposure.

ETIOLOGY

The causes of fever can be organized into 4 main categories: infectious, inflammatory, neoplastic, and miscellaneous. Self-limited viral infections (common cold, gastroenteritis) and uncomplicated bacterial infections (otitis media, pharyngitis, sinusitis) are the most common causes of acute fever. The body temperature rarely rises above potentially lethal levels (42°C [107.6°F]) in the neurologically intact child unless extreme hyperthermic environmental conditions are present or other extenuating circumstances exist, such as underlying malignant hyperthermia or thyrotoxicosis.

The pattern of the fever can provide clues to the underlying etiology. Viral infections typically are associated with a slow decline of fever over a wk, whereas bacterial infections are often associated with a prompt resolution of fever after effective antimicrobial treatment is employed. Although administration of antimicrobial agents can result in a very rapid elimination of bacteria, if tissue injury has been extensive, the inflammatory response and fever can continue for days after all microbes have been eradicated.

Intermittent fever is an exaggerated circadian rhythm that includes a period of normal temperatures on most days; extremely wide fluctuations may be termed septic or hectic fever. Sustained fever is persistent and does not vary by more than 0.5°C (0.9°F)/day. Remittent fever is persistent and varies by more than 0.5°C (0.9°F)/day. Relapsing fever is characterized by febrile periods that are separated by intervals of normal temperature; tertian fever occurs on the 1st and 3rd days (malaria caused by *Plasmodium vivax*), and quartan fever occurs on the 1st and 4th days (malaria caused by *Plasmodium malariae*). Diseases characterized by relapsing fevers (Table 176-1) should be distinguished from infectious diseases that have a tendency to relapse. Biphasic fever indicates a single illness with 2 distinct periods (camelback fever pattern); poliomyelitis is the classic example. A biphasic course is also characteristic of other enteroviral infections, leptospirosis, dengue fever, yellow fever, Colorado tick fever, spirillary rat bite fever *(Spirillum minus)*, and the African hemorrhagic fevers (Marburg, Ebola, and Lassa fevers). The term *periodic fever* is used narrowly to describe fever syndromes with a regular periodicity (cyclic neutropenia and periodic fever, aphthous stomatitis, pharyngitis, and adenopathy) or more broadly to include disorders characterized by recurrent episodes of fever that do not follow a strictly periodic pattern (familial Mediterranean fever, tumor necrosis factor receptor–associated periodic syndrome [Hibernian fever], hyperimmunoglobulin D syndrome, the Muckle-Wells syndrome) (see Chapter 163). Factitious fever, or self-induced fever, may be caused by intentional manipulation of the thermometer or injection of pyrogenic material.

The double quotidian fever (or fever that peaks twice in 24 hr) is classically associated with inflammatory arthritis. In general, a single isolated fever spike is not associated with an infectious disease. Such a spike can be attributed to the infusion of blood products and some drugs, as well as to some procedures, or to manipulation of a catheter on a colonized or infected body surface. Similarly, temperatures in excess of 41°C (105.8°F) are most often associated with a noninfectious cause. Causes for very high temperatures (>41°C [105.8°F]) include central fever (resulting from central nervous system dysfunction involving the hypothalamus), malignant hyperthermia, malignant neuroleptic syndrome, drug fever, or heatstroke. Temperatures that are lower than normal (<36°C [96.8°F]) can be associated with overwhelming sepsis but are more commonly related to cold exposure, hypothyroidism, or overuse of antipyretics.

Table 176-1 Fevers Prone to Relapse
INFECTIOUS CAUSES
Relapsing fever *(Borrelia recurrentis)*
Trench fever *(Bartonella quintana)*
Q fever *(Coxiella burnetii)*
Typhoid fever *(Salmonella typhi)*
Syphilis *(Treponema pallidum)*
Tuberculosis
Histoplasmosis
Coccidioidomycosis
Blastomycosis
Melioidosis *(Pseudomonas pseudomallei)*
Lymphocytic choriomeningitis (LCM) infection
Dengue fever
Yellow fever
Chronic meningococcemia
Colorado tick fever
Leptospirosis
Brucellosis
Oroya fever *(Bartonella bacilliformis)*
Acute rheumatic fever
Rat bite fever *(Spirillum minus)*
Visceral leishmaniasis
Lyme disease *(Borrelia burgdorferi)*
Malaria
Babesiosis
Noninfluenza respiratory viral infection
Epstein-Barr virus infection
NONINFECTIOUS CAUSES
Behçet disease
Crohn disease
Weber-Christian disease (panniculitis)
Leukoclastic angiitis syndromes
Sweet syndrome
Systemic lupus erythematosus and other autoimmune disorders
PERIODIC FEVER SYNDROMES (see Chapter 163)
Familial Mediterranean fever
Cyclic neutropenia
Periodic fever, aphthous stomatitis, pharyngitis, adenopathy (PFAPA)
Hyperimmunoglobulin D syndrome
Hibernian fever (tumor necrosis factor superfamily immunoglobulin A–associated syndrome [TRAPS])
Muckle-Wells syndrome
Others

CLINICAL FEATURES

The clinical features of fever can range from no symptoms at all to extreme malaise. Children might complain of feeling hot or cold, display facial flushing, and experience shivering. Fatigue and irritability may be evident. Parents often report that the child looks ill or pale and has a decreased appetite. The underlying etiology also produces accompanying symptoms. Although the underlying etiologies can manifest in varied ways clinically, there are some predictable features. For instance, fever with petechiae in an ill-appearing patient indicates the high possibility of life-threatening conditions such as meningococcemia, Rocky Mountain spotted fever, or acute bacterial endocarditis.

Table 176-2	Evaluation of Acute Fever

Thorough history: onset, other symptoms, exposures (daycare, school, family, pets, playmates), travel, medications, other underlying disorders, immunizations
Physical examination: complete, with focus on localizing symptoms
Laboratory studies on a case-by-case basis:
- Rapid antigen testing
- Nasopharyngeal: respiratory viruses by polymerase chain reaction
- Throat: group A *Streptococcus*
- Stool: rotavirus
- Blood: complete blood count, blood culture, C-reactive protein, sedimentation rate, procalcitonin
- Urine: urinalysis, culture
- Stool: Hemoccult, culture
- Cerebrospinal fluid: cell count, glucose, protein, Gram stain, culture
- Chest radiograph or other imaging studies on a case-by-case basis

Changes in heart rate, most commonly tachycardia, accompany fever. Normally heart rate rises by 10 beats/min per 1°C (1.8°F) rise in temperature for children >2 mo of age. Relative tachycardia, when the pulse rate is elevated disproportionately to the temperature, is usually caused by noninfectious diseases or infectious diseases in which a toxin is responsible for the clinical manifestations. Relative bradycardia (temperature–pulse dissociation), when the pulse rate remains low in the presence of fever, can accompany typhoid fever, brucellosis, leptospirosis, or drug fever. Bradycardia in the presence of fever also may be a result of a conduction defect resulting from cardiac involvement with acute rheumatic fever, Lyme disease, viral myocarditis, or infective endocarditis.

EVALUATION

Most acute febrile episodes in a normal host can be diagnosed by a careful history and physical examination and require few, if any, laboratory tests. Because infection is the most likely etiology of the acute fever, the evaluation should initially be geared to discovering an underlying infectious cause (Table 176-2). The details of the history should include the onset and pattern of fever and any accompanying signs and symptoms. The patient often displays signs or symptoms that provide clues to the cause of the fever. Exposures to other ill persons at home, daycare, and school should be noted, along with any recent travel or medications. The past medical history should include information about underlying immune deficiencies or other major illnesses and receipt of childhood vaccines.

Physical examination should begin with a complete evaluation of vital signs, which should include pulse oximetry because hypoxia may indicate lower respiratory infection. In the acutely febrile child, the physical examination should focus on any localized complaints, but a complete head-to-toe screen is recommended, because clues to the underlying diagnosis may be found. For example, palm and sole lesions may be discovered during a thorough skin examination and provide a clue for infection with coxsackievirus.

If a fever has an obvious cause, then laboratory evaluation may not be required, and management is tailored to the underlying cause with as-needed reevaluation. If the cause of the fever is not apparent, then further diagnostic evaluation should be considered on a case-by-case basis. The history of presentation and abnormal physical examination findings guide the evaluation. The child with respiratory symptoms and hypoxia may require a chest radiograph or rapid antigen testing for respiratory syncytial virus or influenza. The child with pharyngitis can benefit from rapid antigen detection testing for group A *Streptococcus* and a throat culture. Dysuria, back pain, or a history of vesicoureteral reflux should prompt a urinalysis and urine culture, and bloody diarrhea should prompt a stool culture. A complete blood count and blood culture should be considered in the ill-appearing child, along with cerebrospinal fluid studies if the child has neck stiffness or if the possibility of meningitis is considered. Well-defined high-risk groups require a more-extensive evaluation on the basis of age, associated disease, or immunodeficiency status, and might warrant prompt antimicrobial therapy before a pathogen is identified. The evaluations of infants <3 mo of age and children with recurrent fevers are discussed in Chapter 177.

MANAGEMENT

Although fear of fever is a common parental worry, evidence is lacking to support the belief that high fever can result in brain damage or other bodily harm, except in rare instances of febrile status epilepticus and heatstroke. *Treating fever in self-limiting illnesses for the sole reason of bringing the body temperature back to normal is not necessary in the otherwise healthy child.* Most evidence suggests that fever is an adaptive response and should be treated only in selected circumstances. In humans, increased temperatures are associated with decreased microbial replication and an increased inflammatory response. Although fever can have beneficial effects, it also increases oxygen consumption, carbon dioxide production, and cardiac output, and can exacerbate cardiac insufficiency in patients with heart disease or chronic anemia (e.g., sickle cell disease), pulmonary insufficiency in patients with chronic lung disease, and metabolic instability in patients with diabetes mellitus or inborn errors of metabolism. Children between the ages of 6 mo and 5 yr are at increased risk for simple febrile seizures. *The focus of the evaluation and treatment of febrile seizures is aimed at determining the underlying cause of the fever.* Children with idiopathic epilepsy also often have an increased frequency of seizures associated with a fever. High fever during pregnancy may be teratogenic.

Fever with temperatures <39°C (102.2°F) in healthy children generally does not require treatment. However, as temperatures become higher, patients tend to become more uncomfortable, and treatment of fever is then reasonable. If a child is included in 1 of the high-risk groups or if the child's caregiver is concerned that the fever is adversely affecting the child's behavior and causing discomfort, treatment may be given to hasten the resolution of the fever. Other than providing symptomatic relief, antipyretic therapy does not change the course of infectious diseases. Encouraging good hydration is the first step to replace fluids that are lost related to the increased metabolic demands of fever. Antipyretic therapy is beneficial in high-risk patients who have chronic cardiopulmonary diseases, metabolic disorders, or neurologic diseases and in those who are at risk for febrile seizures. Hyperpyrexia (>41°C [105.8°F]) indicates high probability of hypothalamic disorders or central nervous system hemorrhage and should be treated with antipyretics. Some studies show that hyperpyrexia may be associated with a significantly increased risk of serious bacterial infection, but other studies have not substantiated this relationship. Acetaminophen at a dose of 10-15 mg/kg/dose every 4 hr and ibuprofen in children >6 mo at a dose of 5-10 mg/kg/dose every 8 hr are the most commonly employed antipyretics. Antipyretics reduce fever by reducing production of prostaglandins. If used appropriately, antipyretics are safe; potential adverse effects include liver damage (acetaminophen) and gastrointestinal or kidney disturbances (ibuprofen). To reduce fever most safely, the caregiver should choose 1 type of medication and clearly record the dose and time of administration, so overdosage does not occur, especially if multiple caregivers are involved in the management. Physical measures such as tepid baths and cooling blankets are not considered effective to reduce fever. Evidence is also scarce for the use of complementary and alternative medicine interventions.

Fever caused by specific underlying etiologies resolves when the condition is properly treated. Examples include administration of intravenous immunoglobulin to treat Kawasaki disease or the administration of antibiotics to treat bacterial infections.

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Chapter 177
Fever Without a Focus

Linda S. Nield and Deepak Kamat

Fever without a focus refers to a rectal temperature of 38°C (100.4°F) or higher as the sole presenting feature. The terms "fever without localizing signs" and "fever of unknown origin" (FUO) are subcategories of fever without a focus.

FEVER WITHOUT LOCALIZING SIGNS

Fever of acute onset, with duration of <1 wk and without localizing signs, is a common diagnostic dilemma in children <36 mo of age. The etiology and evaluation of fever without localizing signs depends on the age of the child. Traditionally, 3 age groups are considered: neonates or infants to 1 mo of age, infants >1 mo to 3 mo of age, and children >3 mo to 3 yr of age. In 1993, practice guidelines were published to aid the clinician in evaluating the otherwise healthy 0-36 mo old child with fever without a source. However, with the advent and extensive use of the conjugate *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* vaccines, the rates of infections with these 2 pathogens have decreased substantially. As a consequence, modifications to the 1993 guidelines have been advocated as described in the section "3-36 Months of Age." Children in high-risk groups (Table 177-1) require a more aggressive diagnostic approach and consideration of a broader differential diagnosis.

Table 177-1 Febrile Patients at Increased Risk for Serious Bacterial and Viral Infections

RISK GROUP	DIAGNOSTIC CONSIDERATIONS
IMMUNOCOMPETENT PATIENTS	
Neonates (<28 days)	Sepsis and meningitis caused by group B *Streptococcus, Escherichia coli, Listeria monocytogenes;* neonatal herpes simplex virus infection, enteroviruses, parechovirus
Infants 1-3 mo	Serious bacterial disease in 5-15%, including bacteremia in 5%; urinary tract infection most common serious bacterial infection; *E. coli* most common pathogen; enterovirus, parechovirus, influenza
Infants and children 3-36 mo	Occult bacteremia in <0.5% of children immunized with both *Haemophilus influenzae* type b and pneumococcal conjugate vaccines; urinary tract infections
Hyperpyrexia (>40°C [104°F])	Meningitis, bacteremia, pneumonia, heatstroke, hemorrhagic shock-encephalopathy syndrome
Fever with petechiae	Bacteremia and meningitis caused by *Neisseria meningitidis, H. influenzae* type b, and *Streptococcus pneumoniae* Rickettsial disease Viral exanthem
IMMUNOCOMPROMISED PATIENTS	
Sickle cell disease	Sepsis, pneumonia, and meningitis caused by *S. pneumoniae*, osteomyelitis caused by *Salmonella* and *Staphylococcus aureus*
Asplenia	Bacteremia and meningitis caused by *N. meningitidis, H. influenzae* type b, *S. pneumoniae*, and *Capnocytophaga* sp.
Complement or properdin deficiency	Sepsis caused by *N. meningitidis*
Agammaglobulinemia	Bacteremia, sinopulmonary infections
AIDS	*S. pneumoniae, H. influenzae* type b, and *Salmonella* infections
Congenital heart disease	Infective endocarditis; brain abscess with right-to-left shunting
Central venous line	*S. aureus*, coagulase-negative staphylococci, *Candida*
Malignancy	Bacteremia with gram-negative enteric bacteria, *S. aureus*, and coagulase-negative staphylococci; fungemia with *Candida* and *Aspergillus*

Neonates

Neonates who experience fever without focus are a challenge to evaluate because they display limited signs of infection, making it difficult to clinically distinguish between a serious bacterial or viral (herpes simplex virus [HSV]) infection and self-limited viral illness. Immature immune responses in the 1st few mo of life also increase the significance of fever in the young infant. In general, neonates who have a fever and do not appear ill have a 7% risk of having a serious bacterial infection. Serious bacterial infections include bacteremia, meningitis, pneumonia, osteomyelitis, septic arthritis, enteritis, and urinary tract infections. Although neonates with serious infection can acquire community pathogens, they are mainly at risk for late-onset neonatal bacterial diseases (group B streptococci, *E. coli,* and *Listeria monocytogenes*) and perinatally acquired herpes simplex virus (HSV) infection.

Practice guidelines recommend that if a neonate has had a fever recorded at home by a reliable parent, the patient should be treated as a febrile neonate. If excessive clothing and blankets encasing the infant are suspected of falsely elevating the body temperature, then the excessive coverings should be removed and the temperature retaken in 15-30 min. If body temperature is normal after the covers are removed, then the infant is considered afebrile.

Owing to the unreliability of physical findings and the presence of an immature immune system, all febrile neonates should be hospitalized; blood, urine, and cerebrospinal fluid (CSF) should be cultured, and the child should receive empirical intravenous antibiotics. CSF studies should include cell counts, glucose and protein levels, Gram stain, and culture; HSV and enterovirus polymerase chain reaction should be considered. Stool culture and chest radiograph may also be part of the evaluation. Combination antibiotics, such as ampicillin and cefotaxime or ampicillin and gentamicin, are recommended. Acyclovir should be included if HSV infection is suspected because of seizures, hypotension, transaminase elevation, CSF pleocytosis, or known maternal history of genital HSV, especially at the time of delivery.

1 to 3 Months of Age

The large majority of children with fever without localizing signs in the 1-3 mo age group likely have a viral syndrome. In contrast to bacterial infections, most viral diseases have a distinct seasonal pattern: respiratory syncytial virus and influenza A virus infections are more common during the winter, whereas enterovirus and parechovirus infections usually occur in the summer and fall. Although a viral infection is the most likely etiology, fever in this age group should always suggest the possibility of serious bacterial disease. Organisms to consider include *E. coli*, group B *Streptococcus*, *L. monocytogenes*, *Salmonella enteritidis*, *N. meningitidis, S. pneumoniae, H. influenzae* type b, and *S. aureus*. Pyelonephritis is the most common serious bacterial infection in this age group and is also more common in uncircumcised infant boys and infants with urinary tract anomalies. *E. coli* is the most common pathogen identified in bacteremic infants, the majority having pyelonephritis. Group B *Streptococcus* followed by *S. aureus* are the next most frequently identified pathogens causing bacteremia; pneumococcus tends to be seen in older infants. Most significant blood cultures turn positive within 24 hr (91%), with 99% positive by 48 hr. Other potential bacterial diseases in this age group include otitis media, pneumonia, omphalitis, mastitis, and other skin and soft tissue infections.

Ill-appearing (toxic) febrile infants 3 mo of age or younger require prompt hospitalization and immediate parenteral antimicrobial therapy after cultures of blood, urine, and CSF are obtained. Ampicillin (to cover *L. monocytogenes* and *Enterococcus*) plus either ceftriaxone

or cefotaxime is an effective initial antimicrobial regimen for ill-appearing infants without focal findings. This regimen is effective against the usual bacterial pathogens causing sepsis, urinary tract infection, and enteritis in young infants. However, if meningitis is suspected because of CSF abnormalities, vancomycin should be included to treat possible penicillin-resistant *S. pneumoniae* until the results of culture and susceptibility tests are known.

Many academic institutions have investigated the optimal management of low-risk patients in this age group with fever without a focus (Table 177-2). The use of viral diagnostic studies (enteroviruses, parechovirus, respiratory viruses, rotavirus, and herpesvirus) in combination with the Rochester Criteria or similar criteria can enhance the ability to determine which infants are at high risk for serious bacterial infections (Table 177-2). Febrile infants in whom a virus has been detected are at low or no risk of a serious bacterial infection. Well-appearing infants 1-3 mo of age can be managed safely using low-risk laboratory and clinical criteria as indicated in Table 177-2 if reliable parents are involved and close follow-up is assured.

Table 177-2 Low-Risk Criteria in a Child 1-3 Months Old with Fever

BOSTON CRITERIA

Infants are at low risk if they appear well, have a normal physical examination, and have a caretaker reachable by telephone and if laboratory tests are as follows:

- CBC: <20,000 WBC/μL
- Urine: negative leukocyte esterase
- CSF: leukocyte count less than 10×10^6/L

PHILADELPHIA PROTOCOL

Infants are at low risk if they appear well and have a normal physical examination and if laboratory tests are as follows:

- CBC: <15,000 WBC/μL; band: total neutrophil ratio <0.2
- Urine: <10 WBC/HPF; no bacteria on Gram stain
- CSF: <8 WBC/μL; no bacteria on Gram stain
- Chest radiograph: no infiltrate
- Stool: no RBC; few to no WBC

PITTSBURGH GUIDELINES

Infants are at low risk if they appear well and have a normal physical examination and if laboratory tests are as follows:

- CBC: 5,000-15,000 WBC/μL; peripheral absolute band count <1,500/μL
- Urine (enhanced urinalysis): 9 WBC/μL and no bacteria on Gram stain
- CSF: 5 WBC/μL and negative Gram stain; if bloody tap, then WBC:RBC ≤1 : 500
- Chest radiograph: no infiltrate
- Stool: 5 WBC/HPF with diarrhea

ROCHESTER CRITERIA

Infants are at low risk if they appear well and have a normal physical examination and if laboratory findings are as follows:

- CBC: 5,000-15,000 WBC/μL; absolute band count ≤1,500/μL
- Urine: <10 WBC/HPF at 40×
- Stool: <5 WBC/HPF if diarrhea

CBC, complete blood count; CSF, cerebrospinal fluid; HPF, high-powered field; RBC, red blood cell; WBC, white blood cell.

Infants 1-3 mo of age with fever who appear generally well; who have been previously healthy; who have no evidence of skin, soft tissue, bone, joint, or ear infection; and who have a peripheral white blood cell (WBC) count of 5,000-15,000 cells/μL, an absolute band count of <1,500 cells/μL, and normal urinalysis and negative culture (blood and urine) results are unlikely to have a serious bacterial infection. The negative predictive value with 95% confidence of these criteria for any serious bacterial infection is >98% and for bacteremia is >99%. Among serious bacterial infections, pyelonephritis is the most common and may be seen in well-appearing infants who have fever without a focus or in those who appear ill. Urinalysis may be negative in infants <2 mo of age with pyelonephritis. Bacteremia is present in <30% of infants with pyelonephritis. Procalcitonin, erythrocyte sedimentation rate (ESR), and C-reactive protein are biologic markers that may be considered in the evaluation of a child with fever. Host-based microarray gene expression profiles determined on the patient's leukocytes may be able to detect RNA transcriptional patterns (biosignatures) that distinguish viral from bacterial infection (Fig. 177-1).

The decision to obtain CSF studies in the well-appearing 1-3 mo old infant depends on the decision to administer empirical antibiotics. If close observation without antibiotics is planned, a lumbar puncture may be deferred. If the child deteriorates clinically, a full sepsis evaluation should be performed, and intravenous antibiotics should be administered. If empirical antibiotics are initiated, CSF studies should be obtained, preferably before administering antibiotics.

3 to 36 Months of Age

Approximately 30% of febrile children in the 3-36 mo age group have no localizing signs of infection. Viral infections are the cause of the vast majority of fevers in this population, but serious bacterial infections do occur and are caused by the same pathogens listed for patients 1-3 mo of age, except for the perinatally acquired infections. *S. pneumoniae*, *N. meningitidis*, and *Salmonella* account for most cases of occult bacteremia. *H. influenzae* type b was an important cause of occult bacteremia in young children before universal immunization with conjugate Hib vaccines and remains common in underdeveloped countries that have not implemented these vaccines in their immunization schedule.

Risk factors indicating increased probability of occult bacteremia include temperature ≥39°C (102.2°F), WBC count ≥15,000/μL, and

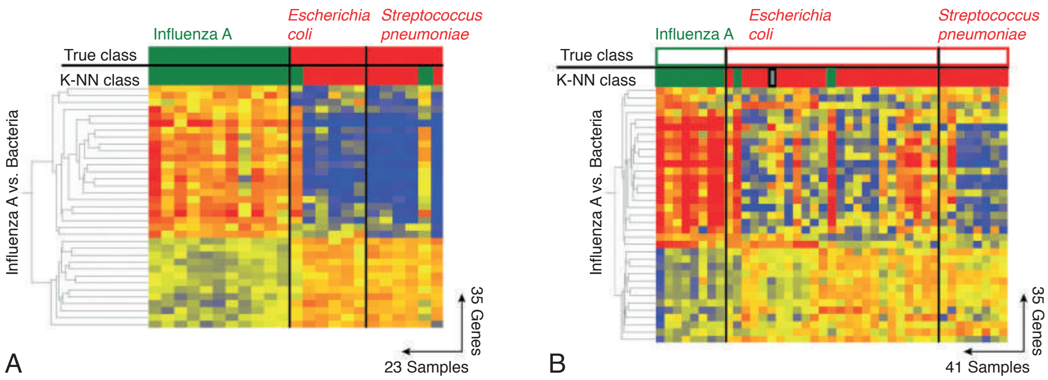

Figure 177-1 Gene expression patterns may discriminate viral vs bacterial infections. **A,** Set of 35 genes that discriminates patients with viral infections (influenza A; *green*) and bacterial infections (*Escherichia coli* and *Streptococcus pneumoniae*; *red*). The discriminative pattern is shown by the gene expression patterns in the heat map (*red* indicates overexpressed genes; *blue* indicates underexpressed genes). **B,** The diagnostic signature was tested in an independent set of patients that confirmed its accuracy. *K-NN* indicates nearest neighbor algorithm. *(Modified from Ramilo O, Allman W, Chung W, et al: Gene expression patterns in blood leukocytes discriminate patients with acute infections,* Blood *109:2066-2077, 2007. Fig 1.)*

elevated absolute neutrophil count, band count, erythrocyte sedimentation rate (ESR), or C-reactive protein. The probability of bacteremia and/or pneumonia or pyelonephritis among infants 3-36 mo of age increases as the temperature (especially >40°C [104°F]) and WBC count (especially >25,000/µL) increase. However, no combination of laboratory tests or clinical assessment is sensitive enough to predict the presence of occult bacteremia. Socioeconomic status, race, gender, and age (within the range of 3-36 mo) do not appear to affect the risk for occult bacteremia.

The pattern of sequelae of occult bacteremia may be related to host factors and the offending organism. In some children, the occult bacteremic illness can represent the early signs of serious localized infection rather than a transient disease state. Without therapy, occult bacteremia caused by pneumococcus can resolve spontaneously without sequelae, can persist, or can lead to localized infections such as meningitis, pneumonia, cellulitis, pericarditis, osteomyelitis, or suppurative arthritis. Among patients with pneumococcal bacteremia (occult or focal), spontaneous resolution occurs in 30-40%, with a higher rate of spontaneous resolution among well-appearing children.

Hib bacteremia is characteristically associated with a higher risk for localized serious infection than is bacteremia caused by *S. pneumoniae*. Hospitalized children with Hib bacteremia often develop focal infections, such as meningitis, epiglottitis, cellulitis, pericarditis, or osteoarticular infection, and spontaneous resolution of bacteremia is rare. Important bacterial infections among children 3-36 mo of age with localizing signs include otitis media, sinusitis, pneumonia (not always evident without a chest radiograph), enteritis, urinary tract infection, osteomyelitis, and meningitis.

Management of toxic-appearing febrile children 3-36 mo of age who do not have focal signs of infection includes hospitalization and prompt institution of antimicrobial therapy after specimens of blood, urine, and CSF are obtained for culture. Consensus practice guidelines published in 1993 recommended that children 3-36 mo of age who have a temperature of <39°C (102.2°F) and do not appear toxic be observed as outpatients without performing diagnostic tests or administering antimicrobial agents. For nontoxic-appearing infants with a rectal temperature of ≥39°C (102.2°F), options include obtaining a blood culture and administering empirical antibiotic therapy (ceftriaxone, a single dose of 50 mg/kg, not to exceed 1 g); if the WBC count is >15,000/µL, obtaining a blood culture and beginning empirical ceftriaxone; or obtaining a blood culture and observing as outpatients without empirical antibiotic therapy, with return for reevaluation within 24 hr. Guidelines for managing febrile children 3-36 mo of age who have received both Hib and *S. pneumoniae* conjugate vaccines have not been established, but careful observation without empirical administration of antibiotic therapy is generally prudent. Because fully vaccinated young children are at a much lower risk of occult bacteremia and meningitis as the cause of acute fever without localizing signs, some advocate that the only laboratory tests needed in this age group when temperature is >39°C (102.2°F) are a urinalysis and urine culture for circumcised boys <6 mo of age and uncircumcised boys and all girls <24 mo of age. Regardless of the management option (Table 177-3), the family should be instructed to return immediately if the child's condition deteriorates or new symptoms develop.

Empirical antibiotic therapy for well-appearing children <36 mo of age who have not received Hib and *S. pneumoniae* conjugate vaccines and who have a rectal temperature of >39°C (102.2°F) and a WBC count of >15,000/µL is strongly recommended. If blood cultures are obtained and *S. pneumoniae* is isolated from the blood, the child should return to the physician as soon as possible after the culture results are known. If the child appears well, is afebrile, and has a normal physical exam, a second blood culture should be obtained and the child should be treated with 7-10 days of oral antimicrobial therapy. If the child appears ill and continues to have fever with no identifiable focus of infection at the time of follow-up, or if *H. influenzae* or *N. meningitidis* is present in the initial blood culture, the child

Table 177-3 Management of Fever Without Localizing Signs

GROUP	MANAGEMENT
Any toxic-appearing child 0-36 mo and temperature ≥38°C (100.4°F)	Hospitalize, broad cultures plus other tests,* parenteral antibiotics
Child <1 mo and temperature ≥38°C (100.4°F)	Hospitalize, broad cultures plus other tests,* parenteral antibiotics
Child 1-3 mo and temperature ≥38°C (100.4°F)	Two-step process 1. Determine risk based on history, physical examination, and laboratory studies. Low risk: • Uncomplicated medical history • Normal physical examination • Normal laboratory studies • Urine: negative leukocyte esterase, nitrite and <10 WBC/HPF • Peripheral blood: 5,000-15,000 WBC/mm^3; <1,500 bands or band: total neutrophil ratio <0.2 • Stool studies if diarrhea (no RBC and <5 WBC/HPF) • CSF cell count (<8 WBC/µL) and negative Gram stain • Chest radiograph without infiltrate 2. If child fulfills all low-risk criteria, administer no antibiotics, ensure follow-up in 24 hr and access to emergency care if child deteriorates. Daily follow-up should occur until blood, urine, and CSF cultures are final. If any cultures are positive, child returns for further evaluation and treatment. If child does not fulfill all low-risk criteria, hospitalize and administer parenteral antibiotics until all cultures are final and definitive diagnosis determined and treated
Child 3-36 mo and temperature 38-39°C (100.4-102.2°F)	Reassurance that diagnosis is likely self-limiting viral infection, but advise return with persistence of fever, temperatures >39°C (102.2°F), and new signs and symptoms
Child 3-36 mo and temperature >39°C (102.2°F)	Two-step process: 1. Determine immunization status 2. If received conjugate pneumococcal and *Haemophilus influenzae* type b vaccines, obtain urine studies (urine WBC, leukocyte esterase, nitrite, and culture) for all girls, all boys <6 mo old, all uncircumcised boys <2 yr, all children with recurrent urinary tract infections If did not receive conjugate pneumococcal and *H. influenzae* type b vaccines, manage according to the 1993 Guidelines (see Baraff et al. *Ann Emerg Med* 22:1198-1210, 1993.)

*Other tests may include chest radiograph, stool studies, herpes simplex polymerase chain reaction.
CSF, cerebrospinal fluid; HPF, high-powered field; RBC, red blood cell; WBC, white blood cell.

should have a repeat blood culture, be evaluated for meningitis (including lumbar puncture), and receive treatment in the hospital with appropriate intravenous antimicrobial agents. If the child develops a localized infection, therapy should be directed toward the likely pathogens.

FEVER OF UNKNOWN ORIGIN

The classification of fever of unknown origin (FUO) is best reserved for children with fever documented by a healthcare provider and for which the cause could not be identified after 3 wk of evaluation as an outpatient or after 1 wk of evaluation in the hospital (Table 177-4).

Etiology

The many causes of FUO in children are infections, rheumatologic (connective tissue or autoimmune) diseases, or autoinflammatory diseases (see Chapter 163) (Table 177-5). Neoplastic disorders should also be seriously considered, although most children with malignancies do not have fever alone. The possibility of drug fever should be considered if the patient is receiving any drug. Drug fever is usually sustained and not associated with other symptoms. Discontinuation of the drug is associated with resolution of the fever, generally within 72 hr, although certain drugs, such as iodides, are excreted for a prolonged period with fever that can persist for as long as 1 mo after drug withdrawal.

Most fevers of unknown or unrecognized origin result from atypical presentations of common diseases. In some cases, the presentation as an FUO is characteristic of the disease, such as juvenile idiopathic arthritis, but the definitive diagnosis can be established only after prolonged observation because initially there are no associated or specific findings on physical examination and all laboratory results are negative or normal.

In the United States, the systemic infectious diseases most commonly implicated in children with FUO are salmonellosis, tuberculosis, rickettsial diseases, syphilis, Lyme disease, cat-scratch disease, atypical prolonged presentations of common viral diseases, Epstein-Barr virus infection, cytomegalovirus (CMV) infection, viral hepatitis, coccidioidomycosis, histoplasmosis, malaria, and toxoplasmosis. Less-common infectious causes of FUO include tularemia, brucellosis, leptospirosis, and rat bite fever. AIDS alone is not usually responsible for FUO, although febrile illnesses often occur in patients with AIDS as a result of opportunistic infections (see Table 177-4).

Juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus are the connective tissue diseases associated most commonly with FUO. Inflammatory bowel disease and Kawasaki disease are also commonly reported as causes of FUO. If factitious fever (inoculation of pyogenic material or manipulation of the thermometer by the patient or parent) is suspected, the presence and pattern of fever should be documented in the hospital. Prolonged and continuous observation, which can include electronic or video surveillance, of patients is imperative. FUO lasting longer than 6 mo is uncommon in children and suggests granulomatous, autoinflammatory, or autoimmune disease.

Table 177-4 Summary of Definitions and Major Features of the 4 Subtypes of Fever of Unknown Origin

FEATURE	CLASSIC FUO	HEALTHCARE-ASSOCIATED FUO	IMMUNE-DEFICIENT FUO	HIV-RELATED FUO
Definition	>38°C (100.4°F), >3 wk, >2 visits or 1 wk in hospital	≥38°C (100.4°F), >1 wk, not present or incubating on admission	≥38°C (100.4°F), >1 wk, negative cultures after 48 hr	≥38°C (100.4°F), >3 wk for outpatients, >1 wk for inpatients, HIV infection confirmed
Patient location	Community, clinic, or hospital	Acute care hospital	Hospital or clinic	Community, clinic, or hospital
Leading causes	Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia	Healthcare-associated infections, postoperative complications, drug fever	Majority caused by infections, but cause documented in only 40-60%	HIV (primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS)
History emphasis	Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel, contacts, stage of HIV infection
Examination emphasis	Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower-limb deep veins	Wounds, drains, devices, sinuses, urine	Skin folds, IV sites, lungs, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area
Investigation emphasis	Imaging, biopsies, sedimentation rate, skin tests	Imaging, bacterial cultures	CXR, bacterial cultures	Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging
Management	Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Time course of disease	Months	Weeks	Days	Weeks to months
Tempo of investigation	Weeks	Days	Hours	Days to weeks

CMV, cytomegalovirus; CXR, chest radiograph; FUO, fever of unknown origin.

Adapted from Mandell GL, Bennett, JE, Dolin R, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, *ed 7, Philadelphia, 2010, Churchill Livingstone/Elsevier, p. 780, Table 51-1.*

Table 177-5 Diagnostic Considerations of Fever of Unknown Origin in Children

ABSCESSES Abdominal Brain Dental Hepatic Pelvic Perinephric Rectal Subphrenic Psoas	**RHEUMATOLOGIC DISEASES** Behçet disease Juvenile dermatomyositis Juvenile idiopathic arthritis Rheumatic fever Systemic lupus erythematosus
BACTERIAL DISEASES Actinomycosis *Bartonella henselae* (cat-scratch disease) Brucellosis *Campylobacter* *Francisella tularensis* (tularemia) *Listeria monocytogenes* (listeriosis) Meningococcemia (chronic) *Mycoplasma pneumoniae* Rat bite fever (*Streptobacillus moniliformis;* streptobacillary form of rat bite fever) *Salmonella* Tuberculosis Whipple disease Yersiniosis	**HYPERSENSITIVITY DISEASES** Drug fever Hypersensitivity pneumonitis Serum sickness Weber-Christian disease
LOCALIZED INFECTIONS Cholangitis Infective endocarditis Mastoiditis Osteomyelitis Pneumonia Pyelonephritis Sinusitis	**NEOPLASMS** Atrial myxoma Cholesterol granuloma Hodgkin disease Inflammatory pseudotumor Leukemia Lymphoma Pheochromocytoma Neuroblastoma Wilms tumor
SPIROCHETES *Borrelia burgdorferi* (Lyme disease) Relapsing fever *(Borrelia recurrentis)* Leptospirosis Rat bite fever (*Spirillum minus;* spirillary form of rat bite fever) Syphilis	**GRANULOMATOUS DISEASES** Crohn disease Granulomatous hepatitis Sarcoidosis Angiitis
FUNGAL DISEASES Blastomycosis (extrapulmonary) Coccidioidomycosis (disseminated) Histoplasmosis (disseminated) *Chlamydia* Lymphogranuloma venereum Psittacosis	**FAMILIAL AND HEREDITARY DISEASES** Anhidrotic ectodermal dysplasia Autonomic neuropathies Fabry disease Familial dysautonomia Familial Hibernian fever Familial Mediterranean fever and the many other autoinflammatory diseases (see Chapter 163) Hypertriglyceridemia Ichthyosis Sickle cell crisis Spinal cord/brain injury
RICKETTSIA *Ehrlichia canis* Q fever Rocky Mountain spotted fever Tick-borne typhus	**MISCELLANEOUS** Addison disease Castleman disease Chronic active hepatitis Cyclic neutropenia Diabetes insipidus (nonnephrogenic and nephrogenic) Factitious fever Hemophagocytic syndromes Hypothalamic-central fever Infantile cortical hyperostosis Inflammatory bowel disease Kawasaki disease Kikuchi-Fujimoto disease Metal fume fever Pancreatitis Periodic fever syndromes Poisoning Pulmonary embolism Thrombophlebitis Thyrotoxicosis, thyroiditis
VIRUSES Cytomegalovirus Hepatitis viruses HIV Epstein-Barr virus	
PARASITIC DISEASES Amebiasis Babesiosis Giardiasis Malaria Toxoplasmosis Trichinosis Trypanosomiasis Visceral larva migrans *(Toxocara)*	

Repeat interval evaluation, including history, physical examination, laboratory evaluation, and imaging studies, is required.

Diagnosis

The evaluation of FUO requires a thorough history and physical examination supplemented by a few screening laboratory tests and additional laboratory and imaging evaluation as indicated by the history or abnormalities on examination or initial screening tests (see Table 177-5).

History

A detailed fever history including onset, frequency, duration of fever, response or nonresponse to therapy, recurrence, and associated symptoms should be obtained. Repetitive chills and temperature spikes are common in children with septicemia (regardless of cause), particularly when associated with kidney disease, liver or biliary disease, infective endocarditis, malaria, brucellosis, rat bite fever, or a loculated collection of pus.

The age of the patient is helpful in evaluating FUO. Children >6 yr of age often have a respiratory or genitourinary tract infection, localized infection (abscess, osteomyelitis), JIA, or, rarely, leukemia. Adolescent patients are more likely to have inflammatory bowel disease, autoimmune processes, lymphoma, or tuberculosis, in addition to the causes of FUO found in younger children.

A history of exposure to wild or domestic animals should be solicited. The incidence of zoonotic infections in the United States is increasing, and these infections are often acquired from pets that are not overtly ill. Immunization of dogs against specific disorders such as leptospirosis can prevent canine disease but does not always prevent the animal from carrying and shedding leptospires, which may be transmitted to household contacts. A history of ingestion of rabbit or squirrel meat might provide a clue to the diagnosis of oropharyngeal, glandular, or typhoidal tularemia. A history of tick bite or travel to tick- or parasite-infested areas should be obtained.

Any history of pica should be elicited. Ingestion of dirt is a particularly important clue to infection with *Toxocara canis* (visceral larva migrans) or *Toxoplasma gondii* (toxoplasmosis).

A history of unusual dietary habits or travel as early as the birth of the child should be sought. Malaria, histoplasmosis, and coccidioidomycosis can reemerge years after visiting or living in an endemic area. It is important to identify prophylactic immunizations and precautions taken by the patient against ingestion of contaminated water or food during foreign travel. Rocks, dirt, and artifacts from geographically distant regions that have been collected and brought into the home as souvenirs can serve as vectors of disease.

A medication history should be pursued rigorously. This history should elicit information about nonprescription preparations and topical agents, including eyedrops, that may be associated with atropine-induced fever.

The genetic background of a patient also is important. Descendants of the Ulster Scots may have FUO because they are afflicted with nephrogenic diabetes insipidus. Familial dysautonomia (Riley-Day syndrome), a disorder in which hyperthermia is recurrent, is more common among Jews than among other population groups. Ancestry from the Mediterranean region should suggest the possibility of familial Mediterranean fever. Both familial Mediterranean fever and hyperimmunoglobulin D syndrome are inherited as autosomal recessive disorders. Tumor necrosis factor receptor–associated periodic syndrome and Muckle-Wells syndrome are inherited as autosomal dominant traits.

Physical Examination

A complete physical examination is essential to search for any clues to the underlying diagnosis (Table 177-6). The child's general appearance, including sweating during fever, should be noted. The continuing absence of sweat in the presence of an elevated or changing body temperature suggests dehydration due to vomiting, diarrhea, or central or nephrogenic diabetes insipidus. It also should suggest anhidrotic ectodermal dysplasia, familial dysautonomia, or exposure to atropine. The general activity of the patient and the presence or absence of rashes should also be noted.

A careful ophthalmic examination is important. Red, weeping eyes may be a sign of connective tissue disease, particularly polyarteritis nodosa. Palpebral conjunctivitis in a febrile patient may be a clue to measles, coxsackievirus infection, tuberculosis, infectious mononucleosis, lymphogranuloma venereum, or cat-scratch disease. In contrast, bulbar conjunctivitis in a child with FUO suggests Kawasaki disease or leptospirosis. Petechial conjunctival hemorrhages suggest infective

Table 177-6 Examples of Subtle Physical Findings Having Special Significance in Patients with Fever of Unknown Origin

BODY SITE	PHYSICAL FINDING	DIAGNOSIS
Head	Sinus tenderness	Sinusitis
Temporal artery	Nodules, reduced pulsations	Temporal arteritis
Oropharynx	Ulceration Tender tooth	Disseminated histoplasmosis, SLE, IBD, Behcet syndrome, periodic fever syndromes Periapical abscess
Fundi or conjunctivae	Choroid tubercle Petechiae, Roth spot	Disseminated granulomatosis* Endocarditis
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective or marantic endocarditis
Abdomen	Enlarged iliac crest lymph nodes, splenomegaly	Lymphoma, endocarditis, disseminated granulomatosis*
Rectum	Perirectal fluctuance, tenderness Prostatic tenderness, fluctuance	Abscess Abscess
Genitalia	Testicular nodule Epididymal nodule	Periarteritis nodosa, cancer Disseminated granulomatosis
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis

*Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, granulomatosis with polyangiitis, and syphilis.

From Mandell GL, Bennett, JE, Dolin R, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, *ed 7, Philadelphia, 2010, Churchill Livingstone/Elsevier, p. 785, Table 51-8.*

endocarditis. Uveitis suggests sarcoidosis, JIA, systemic lupus erythematosus, Kawasaki disease, Behçet disease, and vasculitis. Chorioretinitis suggests CMV, toxoplasmosis, and syphilis. Proptosis suggests an orbital tumor, thyrotoxicosis, metastasis (neuroblastoma), orbital infection, Wegener granulomatosis, or pseudotumor.

The ophthalmoscope should also be used to examine nailfold capillary abnormalities that are associated with connective tissue diseases such as juvenile dermatomyositis and systemic scleroderma. Immersion oil or lubricating jelly is placed on the skin adjacent to the nail bed, and the capillary pattern is observed with the ophthalmoscope set on +40.

FUO is sometimes caused by hypothalamic dysfunction. A clue to this disorder is failure of pupillary constriction because of absence of the sphincter constrictor muscle of the eye. This muscle develops embryologically when hypothalamic structure and function also are undergoing differentiation.

Fever resulting from familial dysautonomia may be suggested by lack of tears, an absent corneal reflex, or a smooth tongue with absence of fungiform papillae. Tenderness to tapping over the sinuses or the upper teeth suggests sinusitis. Recurrent oral candidiasis may be a clue to various disorders of the immune system especially involving the T lymphocytes. Hyperactive deep tendon reflexes can suggest thyrotoxicosis as the cause of FUO.

Fever blisters are common findings in patients with pneumococcal, streptococcal, malarial, and rickettsial infection as well as periodic fever syndromes. These lesions also are common in children with meningococcal meningitis (which usually does not manifest as FUO) but rarely are seen in children with meningococcemia. Fever blisters also are occasionally seen with *Salmonella* or staphylococcal infections.

Hyperemia of the pharynx, with or without exudate, suggests streptococcal infection, Epstein-Barr virus infection, CMV infection, toxoplasmosis, salmonellosis, tularemia, Kawasaki disease, or leptospirosis.

The muscles and bones should be palpated carefully. Point tenderness over a bone can suggest occult osteomyelitis or bone marrow invasion from neoplastic disease. Tenderness over the trapezius muscle may be a clue to subdiaphragmatic abscess. Generalized muscle tenderness suggests dermatomyositis, trichinosis, polyarteritis, Kawasaki disease, or mycoplasmal or arboviral infection.

Rectal examination can reveal perirectal lymphadenopathy or tenderness, which suggests a deep pelvic abscess, iliac adenitis, or pelvic osteomyelitis. A guaiac test should be obtained; occult blood loss can suggest granulomatous colitis or ulcerative colitis as the cause of FUO.

Laboratory Evaluation

The laboratory evaluation of the child with FUO and whether the evaluation will occur in the inpatient or outpatient realm are determined on a case-by-case basis. Hospitalization may be required for laboratory or imaging studies that are unavailable or impractical in an ambulatory setting, for more-careful observation, or for temporary relief of parents' anxiety. The tempo of diagnostic evaluation should be adjusted to the tempo of the illness; haste may be imperative in a critically ill patient, but if the illness is more chronic, the evaluation can proceed in systematic fashion and can be carried out in an outpatient setting. If there are no clues in the patient's history or on physical examination that suggest a specific infection or area of suspicion, it is unlikely that diagnostic studies will be helpful. In that common scenario, continued surveillance and repeated reevaluations of the child should be employed to detect any new clinical findings.

Although ordering a large number of diagnostic tests in every child with FUO according to a predetermined list is discouraged, certain studies should be considered in the evaluation. A complete blood cell count with a differential WBC count and a urinalysis should be part of the initial laboratory evaluation. An absolute neutrophil count of <5,000/µL is evidence against indolent bacterial infection other than typhoid fever. Conversely, in patients with a polymorphonuclear leukocyte count of >10,000/µL or a nonsegmented polymorphonuclear leukocyte count of >500/µL a severe bacterial infection is highly likely. Direct examination of the blood smear with Giemsa or Wright stain can reveal organisms of malaria, trypanosomiasis, babesiosis, or relapsing fever.

An ESR of >30 mm/hr indicates inflammation and the need for further evaluation for infectious, autoimmune, autoinflammatory, or malignant diseases, tuberculosis, Kawasaki disease, or autoimmune disease. A low ESR does not eliminate the possibility of infection or JIA. C-reactive protein is another acute-phase reactant that becomes elevated and returns to normal more rapidly than the ESR. Experts recommend checking 1 of the 2 because there is no evidence that measuring both the ESR and C-reactive protein in the same patient with FUO is clinically useful.

Blood cultures should be obtained aerobically. Anaerobic blood cultures have an extremely low yield and should be obtained only if there are specific reasons to suspect anaerobic infection. Multiple or repeated blood cultures may be required to detect bacteremia associated with infective endocarditis, osteomyelitis, or deep-seated abscesses. Polymicrobial bacteremia suggests factitious self-induced infection or gastrointestinal (GI) pathology. The isolation of leptospires, *Francisella,* or *Yersinia* requires selective media or specific conditions not routinely used. Therefore, it is important to inform the laboratory what organisms you are suspecting in a particular case. Urine culture should be obtained in all cases.

Tuberculin skin testing should be performed with intradermal placement of 5 units of purified protein derivative that has been kept appropriately refrigerated.

Imaging studies of the chest, sinuses, mastoids, or GI tract may be indicated by specific historical or physical findings. Radiographic evaluation of the GI tract for inflammatory bowel disease may be helpful in evaluating selected children with FUO and no other localizing signs or symptoms.

Examination of the bone marrow can reveal leukemia; metastatic neoplasm; mycobacterial, fungal, or parasitic infections; histiocytosis; hemophagocytosis; or storage diseases. If a bone marrow aspirate is performed, cultures for bacteria, mycobacteria, and fungi should be obtained.

Serologic tests can aid in the diagnosis of Epstein-Barr virus infection, CMV infection, toxoplasmosis, salmonellosis, tularemia, brucellosis, leptospirosis, cat-scratch disease, Lyme disease, rickettsial disease, and, on some occasions, JIA. The clinician should be aware that the reliability and sensitivity and specificity of these tests vary; for instance, serologic tests for Lyme disease outside of reference laboratories have been generally unreliable.

Radionuclide scans may be helpful in detecting abdominal abscesses as well as osteomyelitis, especially if the focus cannot be localized to a specific limb or multifocal disease is suspected. Gallium citrate localizes inflammatory tissues (leukocytes) associated with tumors or abscesses. Technetium-99m phosphate is useful for detecting osteomyelitis before plain roentgenograms demonstrate bone lesions. Granulocytes tagged with indium or iodinated immunoglobulin G may be useful in detecting localized pyogenic processes. ^{18}F-fluorodeoxyglucose positron emission tomography is a helpful imaging modality in adults with an FUO and can contribute to an ultimate diagnosis in 30-60% of patients. Echocardiograms can demonstrate the presence of a vegetation on the leaflets of heart valves, suggesting infective endocarditis. Ultrasonography can identify intraabdominal abscesses of the liver, subphrenic space, pelvis, or spleen.

Total-body CT or MRI (both with contrast) is usually the first imaging study of choice; both permit detection of neoplasms and collections of purulent material without the use of surgical exploration or radioisotopes. CT and MRI are helpful in identifying lesions of the head, neck, chest, retroperitoneal spaces, liver, spleen, intraabdominal and intrathoracic lymph nodes, kidneys, pelvis, and mediastinum. CT or ultrasound-guided aspiration or biopsy of suspicious lesions has reduced the need for exploratory laparotomy or thoracotomy. MRI is particularly useful for detecting osteomyelitis or myositis if there is concern about a specific limb. Diagnostic imaging can be very helpful in confirming or evaluating a suspected diagnosis; in the case of CT scans, the child is exposed to large amounts of radiation.

Biopsy is occasionally helpful in establishing a diagnosis of FUO. Bronchoscopy, laparoscopy, mediastinoscopy, and GI endoscopy can provide direct visualization and biopsy material when organ-specific manifestations are present. When employing any of the more-invasive testing procedures, the risk:benefit ratio for the patient must always be taken into consideration before proceeding further.

Management

The ultimate treatment of FUO is tailored to the underlying diagnosis. Fever and infection in children are not synonymous; antimicrobial agents should not be used as antipyretics, and empirical trials of medication should generally be avoided. An exception may be the use of antituberculous treatment in critically ill children with suspected disseminated tuberculosis. Empirical trials of other antimicrobial agents may be dangerous and can obscure the diagnosis of infective endocarditis, meningitis, parameningeal infection, or osteomyelitis. After a complete evaluation, antipyretics may be indicated to control fever associated with adverse symptoms.

Prognosis

Children with FUO have a better prognosis than do adults. The outcome in a child depends on the primary disease process, which is usually an atypical presentation of a common childhood illness. In many cases, no diagnosis can be established and fever abates spontaneously. In as many as 25% of children in whom fever persists, the cause of the fever remains unclear, even after thorough evaluation.

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Chapter **178**

Infections in Immunocompromised Persons

Marian G. Michaels and Michael Green

Infection and disease develop when the host immune system fails to adequately protect against potential pathogens. In individuals with an intact immune system, infection occurs in the setting of naiveté to the microbe and absence or inadequate preexisting microbe-specific immunity or when protective barriers of the body such as the skin have been breached. Healthy children are able to meet the challenge of most infectious agents with an immunologic armamentarium capable of preventing significant disease. Once an infection begins to develop, an array of immune responses is set into action to control the disease and prevent it from reappearing. In contrast, immunocompromised children might not have this same capability. Depending on the level and type of immune defect, the affected child might not be able to contain the pathogen or to develop an appropriate immune response to prevent recurrence (see Chapter 122).

General practitioners are likely to see children with abnormal immune systems in their practices because increasing numbers of children survive with primary immunodeficiencies or receive immunosuppressive therapy for treatment of malignancy, autoimmune disorders, or transplantation.

Primary immunodeficiencies are compromised states that result from genetic defects affecting 1 or more arms of the immune system (Table 178-1). **Acquired, or secondary, immunodeficiencies** may result from infection (e.g., infection with HIV), from malignancy, or as an adverse effect of immunomodulating or immunosuppressing medications. Such immunosuppressing medications include medications that affect T cells (steroids, calcineurin inhibitors, tumor necrosis factor inhibitors, and chemotherapy), neutrophils (myelosuppressive agents, idiosyncratic or immune-mediated neutropenia), specific immune regulatory cells (tumor necrosis factor blockers, interleukin-2 inhibitors), or all immune cells (chemotherapy). Perturbations of the mucosal and skin barriers or normal microbial flora can also be characterized as secondary immunodeficiencies, predisposing the host open to infections, if only for a temporary period.

The major pathogens causing infections among immunocompetent hosts are also the main pathogens responsible for infections among children with immunodeficiencies. In addition, less-virulent organisms, including normal skin flora, commensal bacteria of the oral pharynx or gastrointestinal tract, environmental fungi, and common community viruses of low-level pathogenicity, can cause severe, life-threatening illnesses in immunocompromised patients (Table 178-2). For this reason, close communication with the diagnostic laboratory is critical so that the laboratory does not disregard normal flora and organisms normally considered to be contaminants as being unimportant.

Table 178-1	Major Causes of Increased Risk for Infection in Immunocompromised Hosts
PRIMARY IMMUNODEFICIENCIES	
Antibody deficiency (B-cell defects; see Chapter 124)	
• X-linked agammaglobulinemia	
• Common variable immunodeficiency	
• Selective immunoglobulin IgA deficiency	
• IgG subclass deficiencies	
• Hyper-IgM syndrome	
• Transient hypogammaglobulinemia of infancy	
Cell-mediated deficiency (T-cell defects)	
• Thymic dysplasia (DiGeorge syndrome)	
• Defective T-cell receptor	
• Defective cytokine production	
• T-cell activation defects	
• CD8 lymphocytopenia	
• Chronic mucocutaneous candidiasis	
Combined B- and T-cell defects (see Chapter 126)	
• Severe combined immunodeficiency	
• Combined immunodeficiency	
• Omenn syndrome	
• Thrombocytopenia and eczema (Wiskott-Aldrich syndrome)	
• Ataxia-telangiectasia	
• Hyper-IgE syndrome	
Phagocyte defects (see Chapter 130)	
• Leukocyte adhesion deficiency	
• Chédiak-Higashi syndrome	
• Myeloperoxidase deficiency	
• Chronic granulomatous disease	
Leukopenia (see Chapter 131)	
• Congenital neutropenia (Kostmann syndrome)	
• Shwachman-Diamond syndrome	
Disorders of the complement system (see Chapter 133)	
SECONDARY IMMUNODEFICIENCIES	
HIV (see Chapter 276)	
Malignancies (and cancer chemotherapy)	
Transplantation (see Chapters 135, 339, 368, 443, 444, and 536)	
• Bone marrow and hematopoietic stem cell	
• Solid organ	
Burns	
Sickle cell disease	
Cystic fibrosis (see Chapter 403)	
Diabetes mellitus	
Immunosuppressive drugs	
Asplenia including heterotaxy syndrome	
Implanted foreign body	
Malnutrition	

Table 178-2	Most Common Causes of Infections in Immunocompromised Children
BACTERIA, AEROBIC*	
Acinetobacter	
Bacillus	
Burkholderia cepacia	
Citrobacter	
Corynebacterium	
Enterobacter spp.	
Enterococcus faecalis	
Enterococcus faecium	
Escherichia coli	
Klebsiella spp.	
Listeria monocytogenes	
Mycobacterium spp.	
Neisseria meningitidis	
Nocardia	
Pseudomonas aeruginosa	
Staphylococcus aureus	
Staphylococcus, coagulase-negative	
Streptococcus pneumoniae	
Streptococcus, viridans group	
BACTERIA, ANAEROBIC*	
Bacillus	
Clostridium	
Fusobacterium	
Peptococcus	
Peptostreptococcus	
Propionibacterium	
Veillonella	
FUNGI*	
Aspergillus	
Candida albicans	
Other *Candida* spp.	
Cryptococcus neoformans	
Fusarium spp.	
Pneumocystis jiroveci	
Zygomycoses *(Mucor, Rhizopus, Rhizomucor)*	
VIRUSES*	
Adenoviruses	
Cytomegalovirus	
Epstein-Barr virus	
Herpes simplex virus	
Human herpesvirus 6	
Polyomavirus (BK)	
Respiratory and enteric community-acquired viruses	
Varicella-zoster virus	
PROTOZOA*	
Cryptosporidium parvum	
Giardia lamblia	
Toxoplasma gondii	

*Listed alphabetically.

178.1 Infections Occurring with Primary Immunodeficiencies

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More than 120 genes have been identified, accounting for >150 different primary immunodeficiencies.

ABNORMALITIES OF THE PHAGOCYTIC SYSTEM

Children with abnormalities of the phagocytic and neutrophil system have problems with bacteria as well as environmental fungi. Disease manifests as recurrent infections of the skin, mucous membranes, lungs, liver, and bones. Dysfunction of this arm of the immune system can be a result of inadequate numbers, abnormal movement properties, or aberrant function of neutrophils (see Chapter 130).

Neutropenia is defined as an absolute neutrophil count of <1,000 cells/mm^3 and can be associated with significant risk for developing severe bacterial and fungal disease, particularly when the absolute count is <500 cells/mm^3 (see Chapter 127). Although acquired neutropenia secondary to bone marrow suppression from a virus or medication is common, genetic causes of neutropenia also exist. Primary congenital neutropenia most often manifests during the 1st yr of life with cellulitis, perirectal abscesses, or stomatitis from *Staphylococcus aureus* or *Pseudomonas aeruginosa.* Episodes of severe disease, including bacteremia or meningitis, are also possible. Bone marrow evaluation shows a failure of maturation of myeloid precursors. Most forms of congenital neutropenia are autosomal dominant, but some, such as Kostmann syndrome (see Chapter 127) and Shwachman-Diamond syndrome (see Chapter 469), are caused by autosomal recessive mutations. Cyclic neutropenia can be associated with autosomal dominant inheritance or de novo sporadic mutations and manifests as fixed cycles of severe neutropenia between periods of normal granulocyte numbers. Often the neutrophil count has normalized by the time the patient presents with symptoms, thus hampering the diagnosis. The cycles classically occur every 21 days (range: 14-36 days), with neutropenia lasting 3-6 days. Most often the disease is characterized by recurrent aphthous ulcers and stomatitis during the periods of neutropenia. However, life-threatening necrotizing myositis or cellulitis and systemic disease can occur, especially with *Clostridium septicum* or *Clostridium perfringens.* Many of the neutropenic syndromes respond to colony-stimulating factor.

Leukocyte adhesion defects are caused by defects in the β chain of integrin (CD18), which is required for the normal process of neutrophil aggregation and attachment to endothelial surfaces (see Chapter 130). In the most-severe form there is a total absence of CD18. Children with this defect can have a history of delayed cord separation and recurrent infections of the skin, oral mucosa, and genital tract beginning early in life. Ecthyma gangrenosum also occurs. Because the defect involves leukocyte migration and adherence, the neutrophil count in the peripheral blood is usually extremely elevated but pus is not found at the site of infection. Survival is usually <10 yr in the absence of hematopoietic stem cell transplantation (HSCT).

Chronic granulomatous disease is an inherited neutrophil dysfunction syndrome, which can be either X-linked or autosomal recessive (see Chapter 130). In addition, chronic granulomatous disease can develop in response to spontaneous mutations in the genes associated with heritable chronic granulomatous disease. Neutrophils and other myeloid cells have defects in their nicotinamide-adenine dinucleotide phosphate oxidase function, rendering them incapable of generating superoxide and thereby impairing intracellular killing. Accordingly, microbes that destroy their own hydrogen peroxide (*S. aureus, Serratia marcescens, B. cepacia, Nocardia* spp., *Aspergillus*) cause recurrent infections in these children. Infections have a predilection to involve the lungs, liver, and bone. In addition, these children can present with recurrent abscesses affecting the skin or perirectal region or lymph nodes. Prophylaxis with trimethoprim-sulfamethoxazole, recombinant human interferon-γ, and oral antifungal agents that have activity against *Aspergillus* spp., such as itraconazole or newer azoles, substantially reduce the incidence of severe infections. Patients with life-threatening infections are also reported to benefit from aggressive treatment with white cell transfusions in addition to antimicrobial agents directed against the specific pathogen. In addition, HSCT can be curative but because of associated risks is not routinely performed.

DEFECTIVE SPLENIC FUNCTION, OPSONIZATION, OR COMPLEMENT ACTIVITY

Children who have congenital asplenia or splenic dysfunction associated with polysplenia or hemoglobinopathies, such as sickle cell disease, as well as those who have undergone splenectomy, are at risk for serious infections from encapsulated bacteria and blood-borne protozoa such as *Plasmodium* and *Babesia.* Prophylaxis against bacterial

infection with penicillin should be considered for these patients, particularly children <5 yr of age. The most common causative organisms include *S. pneumoniae, H. influenzae* type b, and *Salmonella*, which can cause sepsis, pneumonia, meningitis, and osteomyelitis. Defects in the early complement components, particularly C2 and C3, can also be associated with severe infection from these bacteria. **Terminal complement defects** (C5, C6, C7, C8, and C9) are associated with recurrent infections with *Neisseria*. Patients with complement deficiency also have an increased incidence of autoimmune disorders. Vaccines for *S. pneumoniae, H. influenzae* type b, and *N. meningitidis* should be administered to all children with abnormalities in opsonization or complement pathways (see Chapter 134).

B-CELL DEFECTS (HUMORAL IMMUNODEFICIENCIES)

Antibody deficiencies account for the majority of primary immunodeficiencies among humans (see Chapter 124). Patients with defects in the B-cell arm of the immune system fail to develop appropriate antibody responses, with abnormalities that range from complete agammaglobulinemia to isolated failure to produce antibody against a specific antigen or organism. Antibody deficiencies found in children with diseases such as X-linked agammaglobulinemia or common variable immunodeficiency predispose to infections with encapsulated organisms such as *S. pneumoniae* and *H. influenzae* type b. Other bacteria can also be problematic in these children (see Table 178-2). Even though most other classes of microbes do not cause problems for these patients, some notable exceptions exist. Rotavirus can lead to chronic diarrhea, and enteroviruses can disseminate and cause a chronic meningoencephalitis syndrome in these patients. Paralytic polio has developed after immunization with live polio vaccine. Protozoan infections such as giardiasis can be severe and persistent. Children with B-cell defects can develop bronchiectasis over time following chronic or recurrent pulmonary infections.

Children with antibody deficiencies are usually asymptomatic until 5-6 mo of age, when maternally derived antibody levels begin to wane. These children begin to develop recurrent episodes of otitis media, bronchitis, pneumonia, bacteremia, and meningitis. Many of these infections respond quickly to antibiotics, which can delay the recognition of antibody deficiency. Children who require myringotomy tube placement before 2 yr of age because of recurrent episodes of otitis media (≥3 episodes within 6 mo, or ≥4 episodes within 12 mo) should be considered for screening measurement of immunoglobulin levels.

The significance and impact of specific **immunoglobulin (Ig) G subclass deficiencies** is less-well understood and remains controversial. Deficiencies of specific IgG subclasses were first noted in healthy adult blood donors in whom no increased susceptibility to infections was documented. However, others have identified specific IgG deficiencies to be associated with a predisposition to recurrent bacterial sinopulmonary infection, bacteremia, meningitis, osteomyelitis, and pyoderma. Deficiency of subclass IgG_2 is associated with poor antibody production after exposure to polysaccharide antigens, either after vaccination or after infection with a polysaccharide-encapsulated organism such as *S. pneumoniae* or *H. influenzae* type b.

Selective IgA deficiency leads to a lack of production of secretory antibody at the mucosal membranes (see Chapter 124). Even though most patients have no increased risk for infections, some have mild to moderate disease at sites of mucosal barriers. Accordingly, recurrent sinopulmonary infection and gastrointestinal disease are the major clinical manifestations. These patients also have an increased incidence of allergies and autoimmune disorders compared with the normal population.

Hyper-IgM syndrome is caused by a defect in the CD40 ligand on the T cell and is associated with a deficiency in the production of IgG and IgA antibody (see Chapter 124). In addition, recurrent neutropenia, hemolytic anemia, or aplastic anemia can be present. Similar to patients with agammaglobulinemia, these patients are at risk for bacterial sinopulmonary infections, *Pneumocystis jiroveci* pneumonia (PCP), and *Cryptosporidium* intestinal infection.

Replacement of antibody with **immunoglobulin, administered intravenously every 3-4 wk** or weekly, using a subcutaneous formulation, has been the mainstay of treatment for most of the primary IgG antibody deficiencies. Immunoglobulin replacement is not advocated for IgA deficiency, because it does not correct the defect. Prophylaxis with specific antibiotic regimens is controversial and should be individualized for patients who do not respond to immunoglobulin replacement.

T-CELL DEFECTS (CELL-MEDIATED IMMUNODEFICIENCIES)

Children with primary cell-mediated immunodeficiencies, either isolated or more commonly in combination with B-cell defects, present early in life and are susceptible to viral, fungal, and protozoan infections. Clinical manifestations include chronic diarrhea, mucocutaneous candidiasis, and recurrent pneumonia, rhinitis, and otitis media. In thymic hypoplasia (DiGeorge syndrome), hypoplasia or aplasia of the thymus and parathyroid glands occurs during fetal development in association with the presence of other congenital abnormalities. Hypocalcemia and cardiac anomalies are usually the presenting features of DiGeorge syndrome, which should prompt evaluation of the T-cell system. **Chronic mucocutaneous candidiasis** is a rare immunodeficiency associated primarily with T-cell dysfunction (see Chapter 125). These patients might not demonstrate delayed hypersensitivity to skin tests for *Candida* antigen despite having chronic superficial infection with yeast, but they do not appear to be at increased risk for systemic yeast infections. Endocrinopathies are commonly associated with chronic mucocutaneous candidiasis.

COMBINED B-CELL AND T-CELL DEFECTS

Patients with defects in both the T-cell and B-cell components of the immune system have variable manifestations depending on the extent of the defect (see Chapter 126). Complete or almost complete immunodeficiency is found with **severe combined immunodeficiency disorder**, whereas partial defects can be present in such states as ataxia-telangiectasia, Wiskott-Aldrich syndrome, hyper-IgE syndrome, and X-linked lymphoproliferative disorder. Rather than 1 disorder, it is now recognized that severe combined immunodeficiency disorder represents a heterogeneous group of genetic defects that leave the infant globally immune deficient and present in the 1st 6 mo of life with recurrent and typically severe infections caused by a variety of bacteria, fungi, and viruses. Failure to thrive, chronic diarrhea, mucocutaneous or systemic candidiasis, PCP, or cytomegalovirus (CMV) infections are common early in life. Passive maternal antibody is relatively protective against the bacterial pathogens during the 1st few mo of life, but thereafter patients are susceptible to both Gram-positive and Gram-negative organisms. Exposure to live virus vaccines can also lead to disseminated disease; accordingly, the use of live vaccines (including rotavirus vaccine) is contraindicated in patients with suspected or proven severe combined immunodeficiency disorder. Without stem cell transplantation or gene therapy, most affected children succumb to opportunistic infections within the 1st yr of life.

Children with **ataxia-telangiectasia** develop late onset of recurrent sinopulmonary infections from both bacteria and respiratory viruses. In addition, these children experience an increased incidence of malignancies. Wiskott-Aldrich syndrome is an X-linked recessive disease associated with eczema, thrombocytopenia, a reduced number of CD3 lymphocytes, moderately suppressed mitogen responses, and impaired antibody response to polysaccharide antigens. Accordingly, infections with *S. pneumoniae* or *H. influenzae* type b and PCP are common. Children with hyper-IgE syndrome have markedly elevated levels of IgE and present with recurrent episodes of *S. aureus* abscesses of the skin, lungs, and musculoskeletal system. Although the antibody abnormality is notable, these patients also have marked eosinophilia and poor cell-mediated responses to neoantigens and are also at increased risk for fungal infections.

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178.2 Infections Occurring with Acquired Immunodeficiencies

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Immunodeficiencies can be secondarily acquired as a result of infections or as a consequence of other underlying disorders such as malignancy, cystic fibrosis, diabetes mellitus, sickle cell disease, or malnutrition. Immunosuppressive medications used to prevent rejection after organ transplantation, to prevent graft-versus-host disease after stem cell transplantation (see Chapter 137), or to treat malignancies can also leave the host vulnerable to infections. Similarly, medications used to control rheumatologic or other autoimmune diseases may be associated with an increased risk for developing infection. Any process that disrupts the normal mucosal and skin barriers (e.g., burns, surgery, indwelling catheters) can lead to an increased risk for infection.

ACQUIRED IMMUNODEFICIENCY FROM INFECTIOUS AGENTS

Infection with HIV, the causative agent of AIDS, is the most important infectious cause of acquired immunodeficiency (see Chapter 276). Left untreated, HIV infection has profound effects on many parts of the immune system but in particular T-cell–mediated immunity that leads to susceptibility to the same types of infections as with primary T-cell immunodeficiencies.

Other organisms can also lead to temporary alterations of the immune system. Very rarely transient neutropenia associated with community-acquired viruses can lead to significant disease with bacterial infections. Secondary infections can occur because of impaired immunity or disruption of normal mucosal immunity, as exemplified by the increased risk for pneumonia from *S. pneumoniae* or *S. aureus* following influenza infection and group A streptococcus cellulitis and fasciitis following varicella.

MALIGNANCIES

The immune systems of children with malignancies are compromised by the therapies used to treat the cancer and, at times, by direct effects of the cancer itself. The type, duration, and intensity of anticancer therapy remain the major risk factors for infections in these children and often affect multiple arms of the immune system. The presence of mucous membrane abnormalities, indwelling catheters, malnutrition, prolonged exposure to antibiotics, and frequent hospitalizations adds to the risk for infection in these children.

Even though several arms of the immune system can be affected, the major abnormality predisposing to infection in children with cancer is **neutropenia**. The depth and duration of neutropenia are the primary predictors of the risk of infection in children being treated for cancer. Patients are at particular risk for bacterial and fungal infections if the absolute neutrophil count decreases to <500 cells/mm^3, and the risk is highest in those anticipated to have counts <100 cells/mm^3. Counts of >500 cells/mm^3 but <1,000 cells/mm^3 incur some increased risk for infection but not nearly as great. The lack of neutrophils can lead to a loss of inflammatory response, limiting the ability to localize sites of infection and potentially leaving fever as the only manifestation of infection. Accordingly, the absence of physical signs and symptoms does not reliably exclude the presence of infection, resulting in the need for empirical antibiotics (Fig. 178-1). Because patients with **fever** and **neutropenia** might only have subtle signs and symptoms of infection, the presence of fever warrants a thorough physical examination with careful attention to the oropharynx, lungs, perineum and anus, skin, nail beds, and intravascular catheter insertion sites (Table 178-3). A comprehensive laboratory evaluation, including a complete blood cell count, serum creatinine, blood urea nitrogen, and serum transaminases, should be obtained. Blood cultures should be taken from each port of any central venous catheter. Consideration should also be given to obtaining a peripheral venous sample for blood culture, especially in children with 1 or more positive cultures from a central venous catheter, facilitating localization of the source of the infection. Other microbiologic studies should be done if there are associated clinical symptoms, including nasal aspirate for viruses in patients with upper respiratory findings; stool for rotavirus in the winter months and for *C. difficile* toxin in patients with diarrhea; urinalysis and culture in young children or in older patients with symptoms of urgency, frequency, dysuria, or hematuria; and biopsy and culture of cutaneous lesions. Chest radiographs should be obtained in any patient with lower respiratory tract symptoms, although pulmonary infiltrates may be absent in children with severe neutropenia. Sinus films should be obtained for children >2 yr of age if rhinorrhea is prolonged. Abdominal CT scans should also be considered in children with profound neutropenia and abdominal pain to evaluate for the presence of typhlitis. Chest CT scan and galactomannan testing should be considered for children not responding to broad-spectrum antibiotics who have continued fever and neutropenia for longer than 96 hr. Biopsies for cytology, Gram stain, and culture should be considered if abnormalities are found during endoscopic procedures or if lung nodules are identified radiographically.

Before the routine institution of empirical antimicrobial therapy for fever and neutropenia, 75% of children with fever and neutropenia were ultimately found to have a documented site of infection, suggesting that most children with fever and neutropenia will have an underlying infection (see Table 178-3). Currently, Gram-positive cocci are the most common pathogens identified in these patients; however, Gram-negative organisms such as *P. aeruginosa, E. coli*, and *Klebsiella* can cause life-threatening infection and must be considered in the empirical treatment regimen. Other multidrug-resistant Enterobacteriaceae are increasingly recovered in these children. Although coagulase-negative staphylococci often cause infections in these

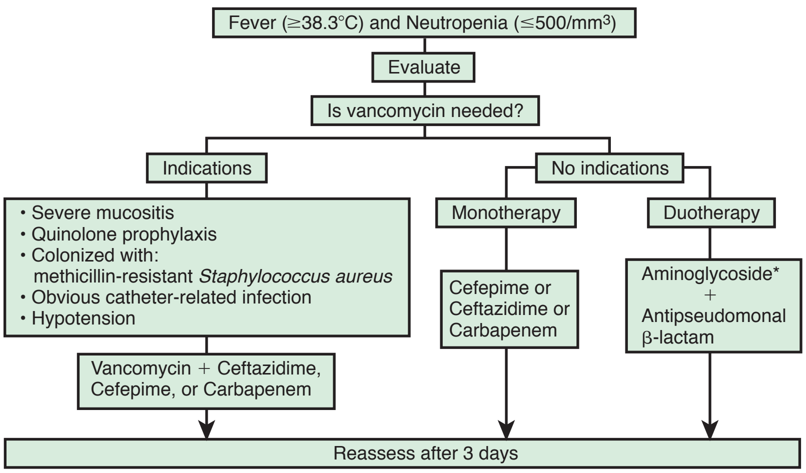

Figure 178-1 Guide to the initial management of the febrile neutropenic patient. Monotherapy can be considered with cefepime, imipenem/cilastatin, meropenem, piperacillin-tazobactam, or ticarcillin-clavulanic acid. *Aminoglycoside antibiotics should be avoided if the patient is also receiving nephrotoxic, ototoxic, or neuromuscular blocking agents; has renal or severe electrolyte dysfunction; or is suspected of having meningitis (because of poor blood–brain perfusion). *(Adapted from Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America.* Clin Infect Dis *52:e56–e93, 2011.)*

Table 178-3 Possible Causes of Fever in Neutropenic Patients Not Responding to Broad-Spectrum Antibiotics

CAUSES	APPROXIMATE FREQUENCY IN HIGH-RISK PATIENTS (%)
Fungal infections susceptible to empirical therapy	40
Fungal infections resistant to empirical antifungal therapy	5
Bacterial infections (with cryptic foci, biofilms, and resistant organisms)	10
Toxoplasma gondii, mycobacteria, or fastidious pathogens *(Legionella, Mycoplasma, Chlamydophila pneumoniae, Bartonella)*	5
Viral infections (herpesviruses, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, varicella-zoster virus, herpes simplex virus, parainfluenza virus, respiratory syncytial virus, influenzaviruses)	5
Graft-versus-host disease after hematopoietic stem cell transplantation	10
Undefined (e.g., drug fever, toxic effects of chemotherapy, antitumor responses, undefined pathogens)	25

From Mandell GL, Bennett JE, Dolin R, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, *ed 7. Philadelphia, 2010, Churchill Livingstone.*

children in association with central venous catheters, these infections are typically indolent, and a short delay in treatment usually does not lead to a detrimental outcome. Other Gram-positive bacteria, such as *S. aureus* and *S. pneumoniae*, can cause more-fulminant disease and require prompt institution of therapy. Viridans streptococci are important potential pathogens in patients with the oral mucositis that is often associated with use of cytarabine and in patients who experience selective pressure from treatment with certain antibiotics such as quinolones. Infection caused by this organism can present as acute septic shock syndrome. Patients with prolonged neutropenia are at increased risk for opportunistic fungal infections, with *Candida* spp. and *Aspergillus* spp. being the most commonly identified fungi. Other fungi that can cause serious disease in these children include *Mucor* spp., *Fusarium* spp., and dematiaceous molds.

FEVER AND NEUTROPENIA

The use of empiric antimicrobial treatment as part of the management of fever and neutropenia decreases the risk of progression to sepsis, septic shock, acute respiratory distress syndrome, organ dysfunction, and death. In 2010, the Infectious Diseases Society of America updated a comprehensive guideline for the use of antimicrobial agents in neutropenic children and adults with cancer (see Fig. 178-1).

First-line antimicrobial therapy should take into consideration the types of microbes anticipated and the local resistance patterns encountered at each institution as well as the level of risk for severe infection associated with a given patient. In addition, antibiotic choices may be limited by specific circumstances, such as the presence of drug allergy and renal or hepatic dysfunction. The empirical use of oral antibiotics has been shown to be safe in some low-risk adults who have no evidence of bacterial focus or signs of significant illness (rigors, hypotension, mental status changes) and for whom a quick recovery of the bone marrow is anticipated. Guidelines for the management of fever and neutropenia in children with cancer and/or undergoing HSCT, which were published on 2012, conclude that the use of oral antimicrobial therapy as either initial or stepdown therapy can be considered in low-risk children who can tolerate oral antibiotics and in whom careful monitoring can be ensured. However, the authors of this guideline point out that oral medication use may present major challenges in children, including availability of liquid formulations of appropriate antibiotics, cooperation of young children, and presence of mucositis potentially interfering with absorption. Accordingly, decisions to implement this approach should be reserved for a very select subset of these children presenting with fever and neutropenia.

The decision to initially use intravenous monotherapy vs an expanded regimen of antibiotics depends on the severity of illness of the patient, history of previous colonization with resistant organisms, and obvious presence of catheter-related infection. Vancomycin should be added to the empiric initial regimen if the patient has hypotension or other evidence of septic shock, an obvious catheter-related infection, or a history of colonization with methicillin-resistant *S. aureus*, or if the patient is at high risk for viridans streptococci (severe mucositis, acute myelogenous leukemia, or prior use of quinolone prophylaxis). Monotherapy can be considered with cefepime, imipenem/cilastatin, meropenem, piperacillin-tazobactam, or ticarcillin-clavulanic acid. Ceftazidime should not be used as monotherapy if concern exists for Gram-positive organisms or resistant Gram-negative bacteria. The addition of a 2nd Gram-negative bacterial agent for empiric therapy can be considered in patients who are clinically unstable when resistant organisms are suspected.

Regardless of the regimen chosen initially, it is critical to carefully and continually evaluate the patient for response to therapy, development of secondary infections, and adverse effects. Management recommendations for these children are evolving. Based upon the 2012 published guidelines, patients who have negative blood cultures at 48 hr, who have been afebrile for at least 24 hr, and who have evidence of bone marrow recovery (absolute neutrophil counts of >100 cells/mm^3) can have antibiotics discontinued. However, if symptoms persist or evolve, intravenous antibiotics should be continued. Continuation of antibiotics in children whose fever has abated and who are clinically well but continue to have depression of neutrophils is more controversial. The 2012 pediatric guidelines advocate pediatric guidelines advocate discontinuing antibiotics in low-risk patients at 72 hr for patients who have negative blood cultures and who have been afebrile for at least 24 hr regardless of bone marrow recovery, as long as careful follow-up is ensured. In contrast, others continue to advocate for continuing antibiotics in this circumstance to prevent recurrence of fever.

Patients without an identified etiology but with **persistent fever** should be reassessed after 3-5 days. Those remaining clinically well may continue on the same regimen, although consideration should be given to discontinuing vancomycin or double Gram-negative bacterial coverage if they were included initially. Patients who remain febrile with clinical progression warrant the addition of vancomycin if it was not included initially and certain risk factors exist; clinicians should also consider changing the empirical antibacterial regimen to cover for the potential presence of antimicrobial resistance in these children. If fever persists for longer than 96 hr, the addition of an **antifungal agent** with antimold activity should be considered, particularly for those at high risk for invasive fungal infection (those with acute myelogenous leukemia or relapsed acute lymphocytic leukemia or who are receiving highly myelosuppressive chemotherapies for other cancers or with allogeneic HSCT). Medications, including liposomal amphotericin products or caspofungin, have been studied in children; voriconazole itraconazole, posaconazole, and micafungin have all been successfully used in adults. Studies comparing caspofungin to liposomal amphotericin for children with malignancies and fever and neutropenia showed caspofungin to be noninferior. The use of **antiviral agents** in fever and neutropenia is not warranted without specific evidence of viral disease. Active herpes simplex or varicella-zoster lesions merit treatment to decrease the time of healing; even if these lesions are not the source of fever, they are potential portals of entry

Table 178-4 Host Defense Defects and Common Pathogens by Time After Bone Marrow Transplantation/Hematopoietic Stem Cell Transplantation

TIME PERIOD	HOST DEFENSE DEFECTS	CAUSES	COMMON PATHOGENS
Pretransplant	Neutropenia Abnormal anatomic barriers	Underlying disease Prior chemotherapy	Aerobic Gram-negative bacilli
Preengraftment	Neutropenia Abnormal anatomic barriers	Chemotherapy Radiation Indwelling catheters	Aerobic Gram-positive cocci Aerobic Gram-negative bacilli *Candida* *Aspergillus* Herpes simplex virus (in previously infected patients) Community-acquired viral pathogens
Postengraftment	Abnormal cell-mediated immunity Abnormal anatomic barriers	Chemotherapy Immunosuppressive medications Radiation Indwelling catheters Unrelated cord blood donor	Gram-positive cocci Aerobic Gram-negative bacilli Cytomegalovirus Adenoviruses Community-acquired viral pathogens *Pneumocystis jiroveci*
Late posttransplant	Delayed recovery of immune function (cell-mediated, humoral, and abnormal anatomic barriers)	Time required to develop donor-related immune function Graft-versus-host disease	Varicella-zoster virus *Streptococcus pneumoniae*

for bacteria and fungi. CMV is a rare cause of fever in children with cancer and neutropenia. If CMV infection is suspected, assays to evaluate viral load in the blood and organ-specific infection should be obtained. Ganciclovir, foscarnet, or cidofovir may be considered while evaluation is pending, although ganciclovir can cause bone marrow suppression and foscarnet and cidofovir can be nephrotoxic (see Chapter 255). If influenza is identified, specific treatment with antiviral agents should be administered. Choice of treatment (oseltamivir, zanamivir) should be based on the anticipated susceptibility of the circulating influenza (see Chapter 258).

The use of **hematopoietic growth factors** shortens the duration of neutropenia but has not been proved to reduce morbidity or mortality. Accordingly, the 2010 recommendations from the Infectious Diseases Society of America do not endorse the routine use of hematopoietic growth factors in patients with established fever and neutropenia, although the recommendations do note that hematopoietic growth factors can be considered as prophylaxis in those with neutropenia who have a high risk for fever. Infections occur in children with cancer even without neutropenia. Most often these infections are viral in etiology. However, *P. jiroveci* can cause pneumonia regardless of the neutrophil count. Prophylaxis with trimethoprim-sulfamethoxazole against PCP is an effective preventive strategy and should be provided to all children undergoing active treatment for malignancy (see Chapter 244). Environmental fungi such as *Cryptococcus, Histoplasma*, and *Coccidioides* can also cause disease. *Toxoplasma gondii* is an uncommon but occasional pathogen in children with cancer. Infections encountered in healthy children (*S. pneumoniae,* group A *Streptococcus*) can cause disease in children with cancer regardless of the granulocyte count.

TRANSPLANTATION

Transplantation of hematopoietic stem cells and solid organs (including heart, liver, kidney, lungs, pancreas, and intestines) is increasingly used as therapy for a variety of disorders. Children undergoing transplantation are at risk for infections caused by many of the same microbial agents that cause disease in children with primary immunodeficiencies. Although the types of infections after transplantation are similar in general among all recipients of these procedures, some differences exist between patients depending on the type of transplantation performed, the type and amount of immunosuppression given, and the child's preexisting immunity to specific pathogens.

Stem Cell Transplantation

Infections following HSCT can be classified as occurring during the **pretransplantation period, preengraftment period** (0-30 days after transplantation), **postengraftment period** (30-100 days), or **late posttransplantation period** (>100 days). Specific defects in host defenses predisposing to infection vary within each of these periods (Table 178-4). Neutropenia and abnormalities in cell-mediated and humoral immune function occur predictably during specific periods of time following transplantation. In contrast, breaches of anatomic barriers caused by indwelling catheters and mucositis secondary to radiation or chemotherapy create defects in host defenses that may be present any time following transplantation.

Pretransplantation Period

Children come to HSCT with a heterogeneous history of underlying diseases, chemotherapy exposure, degree of immunosuppression, and previous infections. Approximately 12% of all infections among adult HSCT recipients occur during the pretransplantation period. These infections are often caused by aerobic Gram-negative bacilli and manifest as localized infections of the skin, soft tissue, and urinary tract. Importantly, the development of infection during this period does not delay or adversely affect the success of engraftment.

Preengraftment Period

Bacterial infections predominate in the preengraftment period (0-30 days). Bacteremia is the most common documented infection and occurs in as many as 50% of all HSCT recipients during the 1st 30 days following transplantation. Bacteremia is typically associated with the presence of either mucositis or an indwelling catheter, but may also be seen with pneumonia. Similarly, more than 40% of children undergoing HSCT experienced 1 or more infections in the preengraftment period. Gram-positive cocci, Gram-negative bacilli, yeast, and, less commonly, other fungi cause infection during this period. *Aspergillus* has been identified in 4-20% of HSCT recipients, most often after 3 wk of neutropenia. Infections caused by the emerging fungal pathogens *Fusarium* and *Pseudallescheria boydii* are associated with the prolonged neutropenia during the preengraftment period.

Viral infections also occur during the preengraftment period. Among adults, reactivation of herpes simplex virus is the most common viral disease observed, but this is less common among children, which is likely related to absence of the virus in the recipient before HSCT. A history of herpes simplex infection or seropositivity indicates the need for prophylaxis. Nosocomial exposure to community-acquired viral pathogens, including respiratory syncytial virus (RSV), influenza virus, adenovirus, and rotavirus, represents another important source of infection during this period. There is growing evidence that community-acquired viruses cause increased morbidity and mortality for HSCT

recipients during this period. Adenovirus is a particularly important viral pathogen that can occur early, although it typically presents after engraftment.

Postengraftment Period

The predominant defect in host defenses in the postengraftment period is altered cell-mediated immunity. Accordingly, organisms historically categorized as opportunistic pathogens predominate during this period. The risk is especially accentuated 50-100 days after transplantation when host immunity is lost and donor immunity is not yet established. *P. jiroveci* presents during this period if patients are not maintained on appropriate prophylaxis. Reactivation of *T. gondii,* a rare cause of disease among HSCT recipients, can also occur after engraftment. Hepatosplenic candidiasis often presents during the postengraftment period, although seeding likely occurred during the neutropenic phase.

CMV is an important cause of morbidity and mortality among HSCT recipients. Unlike patients undergoing solid-organ transplantation where primary infection from the donor causes the greatest harm, CMV reactivation in an HSCT recipient whose donor is naïve to the virus can cause severe disease. Disease risk from CMV after HSCT is also increased in recipients of matched unrelated T cell–depleted transplants and those who suffer from graft-versus-host disease. **Adenovirus** is another important viral pathogen; it has been recovered from up to 5% of adult and pediatric HSCT recipients and causes invasive disease in approximately 20% of cases. Children receiving matched unrelated donor organs or unrelated cord blood cell transplants have an incidence of adenovirus infection as high as 14% during this early postengraftment period. **Polyomaviruses** such as BK virus have been increasingly recognized as a cause of renal dysfunction and hemorrhagic cystitis after bone marrow transplantation. Infections with other herpesviruses (Epstein-Barr virus [EBV] and human herpesvirus 6), as well as community-acquired pathogens, are associated with excess morbidity and mortality during this period, similar to the preengraftment period.

Late Posttransplantation Period

Infection is unusual after 100 days in the absence of chronic graft-versus-host disease. However, the presence of chronic graft-versus-host disease significantly affects anatomic barriers and is associated with defects in humoral, splenic, and cell-mediated immune function (see Chapter 137). Viral infections, including primary infection with or reactivation of varicella-zoster virus, are responsible for more than 40% of infections during this period. Bacterial infections, particularly of the upper and lower respiratory tract, account for approximately 30% of infections. These may be associated with deficiencies in immunoglobulin production, especially IgG_2. Fungal infections account for <20% of confirmed infections during the late posttransplantation period.

Solid-Organ Transplantation

Factors predisposing to infection after organ transplantation include those that either existed before transplantation or are secondary to intraoperative events or posttransplantation therapies (Table 178-5). Some of these additional risks cannot be prevented, and some risks acquired during or after the operation depend on decisions or actions of members of the transplant team. Similar to other children who have undergone surgical procedures, surgical site infections are a frequent cause of infection early after transplantation. Beyond this, the need for immunosuppressive agents to prevent rejection is the major factor predisposing to infection following transplantation. Despite efforts to optimize immunosuppressive regimens to prevent or treat rejection with minimal impairment of immunity, all current regimens interfere with the ability of the immune system to prevent infection. The primary target of the majority of these immunosuppressive agents is the cell-mediated immune system, but regimens can and do impair many other aspects of the transplant recipient's immune system as well.

Timing

The timing of specific types of infections is generally predictable, regardless of which organ is transplanted (Table 178-6). Infectious complications typically develop in 1 of 3 time intervals: early (0-30 days after transplantation), intermediate (30-180 days), and late (>180 days); most infections present in the 1st 180 days after transplantation. Table 178-6 should be used as a general guideline to the types of infections encountered but may be modified with the introduction of newer immunosuppressive therapies and by the use of prophylaxis.

Table 178-5 Risk Factors for Infections Following Solid-Organ Transplantation in Children
PRETRANSPLANTATION FACTORS
Age of patient
Underlying disease, malnutrition
Specific organ transplanted
Previous exposures to infectious agents
Previous immunizations
Presence of infection in the donor
INTRAOPERATIVE FACTORS
Duration of transplant surgery
Exposure to blood products
Technical problems
Organisms transmitted with donor organ
POSTTRANSPLANTATION FACTORS
Immunosuppression
Induction immunosuppression
Maintenance immunosuppression
Augmented treatment for rejection
Indwelling catheters
Nosocomial exposures
Community exposures

Early infections are usually the result of a complication of the transplant surgery itself, the unexpected acquisition of a bacterial or fungal pathogen from the donor, or the presence of an indwelling catheter. In contrast, infections during the intermediate period typically result from a complication of the immunosuppression, which tends to be at its greatest intensity during the 1st 6 mo following transplantation. This is the period of greatest risk for infections caused by opportunistic pathogens such as CMV, EBV, and *P. jiroveci.* Anatomic abnormalities, such as bronchial stenosis and biliary stenosis, that develop as a consequence of the transplant surgery can also predispose to recurrent infection in this period.

Infections developing late after transplantation typically result as a consequence of uncorrected anatomic abnormalities, chronic rejection, or exposure to community-acquired pathogens. Acquisition of infection from community-acquired pathogens such as RSV can result in severe infection secondary to the immunocompromised state of the transplant recipient during the early and intermediate periods. Compared with the earlier periods, community-acquired infections in the late period are usually benign, because immunosuppression is typically maintained at significantly lower levels. However, certain pathogens such as varicella-zoster virus and EBV may be associated with severe disease even at this late period.

Bacterial and Fungal Infections

Although there are important graft-specific considerations for bacterial and fungal infections following transplantation, some principles are generally applicable to all transplant recipients. Bacterial and fungal infections following organ transplantation are usually a direct consequence of the surgery, a breach in an anatomic barrier, the presence of a foreign body, or an abnormal anatomic narrowing or obstruction. With the exception of infections related to the use of indwelling catheters, sites of bacterial infection tend to occur at or near the transplanted organ. Infections following abdominal transplantation (liver, intestine, or renal) usually occur in the abdomen or at the surgical wound. The pathogens are typically enteric Gram-negative bacteria, *Enterococcus,* and occasionally *Candida.* Infections following thoracic transplantation (heart, lung) usually occur in the lower respiratory tract or at the surgical wound. Pathogens associated with these infections include *S. aureus* and Gram-negative bacteria.

Table 178-6 Timing of Infectious Complications Following Solid-Organ Transplantation

EARLY PERIOD (0-30 DAYS)
Bacterial Infections
Gram-negative enteric bacilli
• Small bowel, liver, neonatal heart
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
Gram-positive organisms
• All transplant types
Fungal Infections
All transplant types
Viral Infections
Herpes simplex virus
• All transplant types
Nosocomial respiratory viruses
• All transplant types
MIDDLE PERIOD (1-6 MO)
Viral Infections
Cytomegalovirus
• All transplant types
• Seronegative recipient of seropositive donor
Epstein-Barr virus
• All transplant types (small bowel highest risk group)
• Seronegative recipient
Varicella-zoster virus
• All transplant types
• Opportunistic infections
Pneumocystis jiroveci
• All transplant types
Toxoplasma gondii
• Seronegative recipient of cardiac transplant from a seropositive donor
Bacterial Infections
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
Gram-negative enteric bacilli
• Small bowel
LATE PERIOD (>6 MO)
Viral Infections
Epstein-Barr virus
• All transplant types, but less risk than middle period
Varicella-zoster virus
• All transplant types
Community-acquired viral infections
• All transplant types
Bacterial Infections
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
• Lung transplants with chronic rejection
Gram-negative bacillary bacteremia
• Small bowel
Fungal Infections
Aspergillus
• Lung transplants with chronic rejection

Adapted from Green M, Michaels MG: Infections in solid organ transplant recipients. In Long SS, Pickering L, Prober C, editors: Principles and practice of pediatric infectious disease, *ed 4. New York, 2012, WB Saunders.*

Patients undergoing lung transplantation for cystic fibrosis experience a particularly high rate of infectious complications, because they are often colonized with *P. aeruginosa* or *Aspergillus* before transplantation. Even though the infected lungs are removed, the sinuses and upper airways remain colonized with these pathogens, and subsequent reinfection of the transplanted lungs can occur. Children receiving organ transplants are often hospitalized for long periods and receive many antibiotics; thus, recovery of bacteria with multiple antibiotic resistance patterns is common after all types of organ transplantation. Infections caused by *Aspergillus* are less common but occur after all types of organ transplantation and are associated with high rates of morbidity and mortality.

Viral Infections

Viral pathogens, especially herpesviruses, are a major source of morbidity and mortality following solid organ transplantation. In addition, BK virus is a major cause of renal disease following kidney transplantation. The patterns of disease associated with individual viral pathogens are generally similar among all organ transplant recipients. However, the incidence, mode of presentation, and severity differ according to type of organ transplanted and, for many viral pathogens, pretransplant serologic status of the recipient.

Viral pathogens can be generally categorized as latent pathogens, which cause infection through reactivation in the host or via acquisition from the donor (e.g., CMV and EBV), or as community-acquired viruses (e.g., RSV). For CMV and EBV, primary infection occurring after transplantation is associated with the greatest degree of morbidity and mortality. The highest risk is seen in a naïve host who receives an organ from a donor who previously was infected with 1 of these viruses. This “mismatched” state is frequently associated with severe disease. However, even if the donor is negative for CMV and EBV, primary infection can be acquired from a close contact or via blood products. Secondary infections (reactivation of a latent strain within the host or superinfection with a new strain) tend to result in milder illness unless the patient is highly immunosuppressed, which can occur in the setting of treatment of significant rejection.

CMV is one of the most commonly recognized transplant viral pathogens. Disease from CMV has decreased significantly with the use of preventive strategies including antiviral prophylaxis as well as viral load monitoring to inform preemptive antiviral therapy. Clinical manifestations of CMV disease can range from a syndrome of fatigue and fever to disseminated disease that most often affects the liver, lungs, and gastrointestinal tract.

Infection caused by EBV is another important complication of solid-organ transplantation. Clinical symptoms range from a mild mononucleosis syndrome to disseminated **posttransplant lymphoproliferative disorder**. Posttransplant lymphoproliferative disorder is more common among children than adults because primary EBV infection in the immunosuppressed host is more likely to lead to uncontrolled proliferative disorders, including posttransplant lymphoma.

Other viruses, such as adenovirus, have the capacity to be donor associated, but appear to be less common. The unexpected development of donor-associated viral pathogens, including hepatitis B virus, hepatitis C virus, and HIV, is rare today owing to intensive donor screening.

Community-acquired viruses, including those associated with respiratory tract infection (RSV, influenza virus, adenovirus, and parainfluenza) and gastrointestinal infection (enteroviruses, rotavirus), can cause important disease in children following organ transplantation. In general, risk factors for more-severe infection include young age, acquisition of infection early after transplantation, and augmented immune suppression. Infection in the absence of these risk factors typically results in a clinical illness that is comparable with that seen in immunocompetent children. However, some community-acquired viruses, such as adenovirus, can be associated with graft dysfunction even when acquired late after transplantation.

Opportunistic Pathogens

Children undergoing solid-organ transplantation are also at risk for symptomatic infections from pathogens that do not usually cause clinical disease in immunocompetent hosts. Although these most commonly present in the intermediate period, these infections can also occur late in patients requiring prolonged and high levels of immunosuppression. *P. jiroveci* is a well-recognized cause of pneumonia following solid-organ transplantation, although routine prophylaxis has essentially eliminated this problem. *T. gondii* can complicate cardiac transplantations because of tropism of the organism for cardiac muscle and risk for donor transmission; less commonly it complicates other types of organ transplantation.

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178.3 Prevention of Infection in Immunocompromised Persons

Marian G. Michaels and Michael Green

Infections cannot be completely prevented in children who have defects in one or more arms of their immune system, although some measures can decrease the risks for infection. Replacement immunoglobulin is a benefit to children with primary B-cell deficiencies. Interferon-γ, trimethoprim-sulfamethoxazole, and oral antifungal agents reduce the number of infections occurring in children with chronic granulomatous disease. Children who have depressed cellular immunity resulting from primary diseases, advanced HIV infection, or immunosuppressive medications benefit from prophylaxis against *P. jiroveci*. Immunizations prevent many infections and are particularly important for children with compromised immune systems. When possible, immunizations should be administered before any treatment that would compromise the child's immune system.

Although immunodeficient children are a heterogeneous group, some principles of prevention are generally applicable. The use of inactivated vaccines does not lead to an increased risk for adverse effects, although their efficacy may be reduced due to an impaired immune response. In most cases, children with immunodeficiencies should receive all of the recommended inactivated vaccines. Live-attenuated virus vaccinations can cause disease in some children with immunologic defects, and therefore alternative immunizations should be used whenever possible, such as inactivated influenza vaccine rather than live virus attenuated influenza vaccine. In general, live virus vaccines should not be used in children with primary T-cell abnormalities; efforts should be made to ensure that close contacts are all immunized to decrease the risk of exposure. In some instances in which wild-type viral infection can be severe, immunizations, even with live virus vaccine, are warranted in the immunosuppressed child. For example, children with HIV infection and a CD4 percentage of >15% should receive vaccinations against measles and varicella. Some vaccines should be given to children with immunodeficiencies in addition to routine vaccinations. As an example, children with asplenia or splenic dysfunction should receive meningococcal vaccine and both the polysaccharide pneumococcal vaccine and the conjugate pneumococcal vaccine. Influenza vaccination is recommended for immunocompromised children as well as all household contacts to minimize risk for transmission to the immunocompromised child.

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Chapter 179

Infection Associated with Medical Devices

Joshua Wolf and Patricia M. Flynn

Use of implanted synthetic and prosthetic devices has revolutionized pediatric practice by providing long-term venous access, limb-salvage surgery, and successful treatment of hydrocephalus, urinary retention, and renal failure. However, infectious complications of these devices remain a major concern. These infections are related to the development of biofilms, organized communities of microorganisms protected from the immune system and antimicrobial therapy, on the device surface. A number of factors are important to the development of infection, including the host susceptibility, device composition, duration of implantation, and exposure to colonizing organisms.

INTRAVASCULAR ACCESS DEVICES

Intravascular access devices range from short, stainless steel needles or plastic cannulae inserted for brief periods to multilumen implantable synthetic plastic catheters that are expected to remain in use for years. Infectious complications include local skin and soft tissue infections such as exit site, tunnel, and device-pocket infections, and **catheter-related bloodstream infections (CRBSIs).** The use of central venous devices has improved the quality of life of high-risk patients but has also increased the risk of infection.

Catheter Types

Short-term peripheral cannulae are most commonly used in pediatric patients, and infectious complications occur infrequently. The rate of peripheral CRBSIs in children is <0.15%. Patient age <1 yr, duration of use for longer than 144 hr, and some infusates are associated with increased risk for catheter-related infection. Catheter-associated phlebitis is more common (1-6%) but is rarely infective and can be treated conservatively.

Central venous catheters (CVCs), which terminate in a central vein such as the superior vena cava or inferior vena cava, are widely used in both adults and pediatric patients and are responsible for the majority of catheter-related infections. These catheters are commonly used in critically ill patients, including neonates, who have many other risk factors for nosocomial infection. Patients in an intensive care unit with a CVC in place have a 5-fold greater risk for developing a nosocomial bloodstream infection than those without.

The use of **peripherally inserted central catheters,** which are inserted into a peripheral vein and terminate in a central vein, has increased in pediatric patients. Infection rates seem to be similar to long-term tunneled CVCs (~2/1,000 days), but other complications such as fracture, dislodgement, and occlusion are more common.

When prolonged intravenous access is required, a cuffed silicone rubber (Silastic) or polyurethane catheter may be inserted into the superior vena cava through the subclavian, cephalic, or jugular vein. The extravascular segment of the catheter passes through a subcutaneous tunnel before exiting the skin, usually on the superior aspect of the chest (Broviac or Hickman catheter). A cuff around the catheter near the exit site induces a fibrotic reaction to seal the tunnel. Totally implanted devices also include a subcutaneous reservoir or port with a self-sealing silicone septum immediately under the skin that permits repeated percutaneous needle access.

The incidence of local (exit site, tunnel, and pocket) infection with long-term catheters is 0.2-2.8/1,000 catheter-days. The incidence of Broviac or Hickman CRBSI is 0.5-11.0/1,000 catheter days, whereas that for implantable devices is 0.3-1.8/1,000 catheter-days. The risk for CRBSI is increased among premature infants, young children, and patients receiving total parenteral nutrition.

Catheter-Associated Skin and Soft Tissue Infection

A number of local infections can occur in the presence of a CVC. The **clinical manifestations** of local infection include erythema, tenderness, and purulent discharge at the exit site or along the subcutaneous tunnel tract of the catheter. **Exit-site infection** denotes infection localized to the exit site, without significant tracking along the tunnel, often with purulent discharge. **Tunnel-tract infection** indicates infection in the subcutaneous tissues tracking along a tunneled catheter, which may also include serous or serosanguineous discharge from a draining sinus along the path. **Pocket infection** indicates suppurative infection of a subcutaneous pocket containing a totally implanted device. Bloodstream infection may coexist with local infection.

The diagnosis of local infection is established clinically, but a gram-stained smear and culture of any exit-site drainage should be performed to identify the microbiologic cause. The source is usually contamination by skin or gastrointestinal flora, and the most common organisms are *S. aureus*, coagulase-negative staphylococci,

P. aeruginosa, Candida spp., and mycobacteria. Green discharge is strongly suggestive of mycobacterial infection and appropriate stains and culture should be performed.

Treatment of local infection related to a short-term peripheral cannula or CVC should include device removal. Exit-site infection may resolve with device removal alone, but systemic symptoms should be managed with antimicrobial therapy as recommended below for treatment of CRBSI. In the case of long-term CVCs, exit-site infections usually respond to local care with topical or systemic antibiotics alone. However, tunnel or pocket infections require removal of the catheter and systemic antibiotic therapy in most cases. When a CVC is removed as a result of tunnel infection, the cuff should also be removed and sent for culture if possible. In cases of mycobacterial infection, wide surgical debridement of the tissues is usually required for cure.

Catheter-Related Bloodstream Infection

CRBSI occurs when microorganisms attached to the CVC are shed into the bloodstream leading to bacteremia. On the device, the organisms are embedded in biofilms as organized communities. Colonization may be present even in the absence of symptoms or positive cultures.

Organisms may contaminate the external surface of the CVC during insertion, or the intraluminal surface through handling of the catheter hub or contaminated infusate. Most cases of CRBSI appear to be caused by intraluminal colonization, but external colonization may play a greater role in infections related to recently inserted (<30 days) catheters. Gram-positive cocci predominate, with around half of infections caused by coagulase-negative staphylococci. Gram-negative enteric bacteria are isolated in approximately 20-30% of episodes, and fungi account for 5-10% of episodes.

Fever without an identifiable focus is the most common clinical presentation of CRBSI; local soft tissue symptoms and signs are usually absent. Onset of fever or rigors during or soon after flushing of a catheter is highly suggestive of CRBSI. Symptoms and signs of complicated infection, such as septic thrombophlebitis, endocarditis, or ecthyma gangrenosum, may also be present.

Blood cultures collected prior to the beginning of antibiotic therapy are generally positive from both the CVC and peripheral blood. It is important not to collect cultures unless infection is suspected, as blood-culture contamination may occur and can lead to inappropriate therapy. Blood culture should be collected from at least 2 sites, preferably including all lumens of a CVC *and* the peripheral blood, before initiation of antibiotic therapy to help interpret positive cultures with common skin contaminants.

Tests to differentiate CRBSI from other sources of bacteremia in the presence of a CVC include culture of the catheter tip, quantitative blood cultures, or **differential time to positivity** of blood cultures drawn from different sites. Definitive diagnosis of CRBSI can be important to identify those patients who might benefit from catheter removal or adjunctive therapy. Although CVC tip culture can identify CRBSI, it precludes salvage of the catheter. The most readily available technique to confirm CRBSI without catheter removal is calculation of differential time to positivity between blood cultures drawn through a catheter and from a peripheral vein or separate lumen. During CRBSI, blood obtained through the responsible lumen will usually indicate growth at least 2-3 hr before peripheral blood or uncolonized lumens because of a higher intraluminal microorganism burden. Identical volumes of blood must be collected simultaneously from each site and a continuously monitored blood culture system is required. Specificity of this test is good (94-100%), and sensitivity is good when a peripheral blood culture is available (~90%) but poorer when comparing 2 lumens of a CVC (64%). Where available, quantitative blood culture showing at least a 3-fold higher number of organisms from central compared with peripheral blood is similarly diagnostic.

Treatment of CRBSI related to **long-term vascular access devices** (Hickman, Broviac, totally implantable devices) with systemic antibiotics is successful for many bacterial infections without removal of the device. Antibiotic therapy should be directed to the isolated pathogen and given for a total of 10-14 days from the date of blood culture clearance. Until identification and susceptibility testing are available, empiric therapy, based on local antimicrobial susceptibility data and usually including vancomycin plus an antipseudomonal aminoglycoside (e.g., gentamicin), penicillin (e.g., piperacillin-tazobactam), or cephalosporin (e.g., ceftazidime or cefepime) is indicated. An echinocandin should be initiated if fungemia is suspected. **Antibiotic lock or dwell therapy,** with administration of solutions of high concentrations of antibiotics or ethanol that remain in the catheter for up to 24 hr, might improve outcome when used as an adjuvant to systemic therapy and appear safe, but insufficient data are available to strongly recommend their use. If blood cultures remain positive after 72 hr of appropriate therapy, or if a patient deteriorates clinically, the device should be removed. Failure of CRBSI salvage therapy is very common in infections caused by *S. aureus* (~50%), *Candida* spp. (>70%), and *Mycobacterium* spp. (>70%), although some case reports of cure with antimicrobial lock therapy are promising. Other indications for removing a long-term catheter include severe sepsis, suppurative thrombophlebitis, and endocarditis. Prolonged therapy (4-6 wk) is indicated for persistent bacteremia or fungemia despite catheter removal. The decision to attempt catheter salvage should weigh the risk and clinical impact of persistent or relapsed infection against the risk of surgical intervention.

CRBSI may be complicated by other intravascular infections such as septic thrombophlebitis or endocarditis. Presence of these conditions may be suggested by preexisting risk factors (such as congenital heart disease), signs and symptoms, or persistent bacteremia or fungemia 72 hr after device removal and appropriate therapy. Screening for these complications in otherwise low-risk children, even those with *S. aureus* infection, is not recommended, as the overall frequency is low and the tests can be difficult to interpret and may lead to inappropriate therapy.

Prevention of Infection

Catheters should routinely be removed as soon as they are no longer needed. Although prevalence of infection increases with prolonged duration of catheter use, routine replacement of a required CVC, either at a new site or over a guidewire, results in significant morbidity and is not recommended. Optimal prevention of infections related to long-term vascular access devices includes "bundles" of interventions, including meticulous aseptic surgical insertion technique in an operating room–like environment, avoidance of bathing or swimming (except with totally implantable devices), and careful catheter care. Use of antibiotic or ethanol lock solutions, heparin with preservatives, and alcohol-impregnated caps and use of antimicrobial-impregnated or coated catheters may also be appropriate to reduce the risk for catheter-associated bloodstream infections in high-risk populations. Although the Centers for Disease Control and Prevention recommends that short-term peripheral catheters be replaced every 72-96 hr to prevent phlebitis, pediatric data do not support this practice.

CEREBROSPINAL FLUID SHUNTS

Cerebrospinal fluid (CSF) shunting is required for the treatment of many children with hydrocephalus. The usual procedure uses a silicone rubber device with a proximal portion inserted into the ventricle, a unidirectional valve, and a distant segment that diverts the CSF from the ventricles to either the peritoneal cavity (ventriculoperitoneal [VP] shunt) or right atrium (ventriculoatrial [VA] shunt). The incidence of shunt infection ranges from 1-20%, with an average of 10%. The highest rates are reported in young infants, prior shunt infections, and certain etiologies of hydrocephalus. Most infections are a result of intraoperative contamination of the surgical wound by skin flora. Accordingly, coagulase-negative staphylococci are isolated in more than half of the cases. *S. aureus* is isolated in approximately 20% and Gram-negative bacilli in 15% of cases.

Four distinct clinical syndromes have been described: colonization of the shunt, infection associated with wound infection, distal infection with peritonitis, and infection associated with meningitis.

The most common type of infection is colonization of the shunt with symptoms that reflect shunt malfunction as opposed to frank infection. Symptoms associated with colonized VP shunts include lethargy, headache, vomiting, a full fontanel, and abdominal pain. Fever is common but may be <39°C (102.2°F). Symptoms usually occur within months of the surgical procedure. Colonization of a VA shunt results

in more severe systemic symptoms and specific symptoms of shunt malfunction are often absent. Septic pulmonary emboli, pulmonary hypertension, and infective endocarditis are frequently reported complications of VA shunt colonization. Chronic VA shunt colonization may cause hypocomplementemic glomerulonephritis as a consequence of antigen–antibody complex deposition in the glomeruli, commonly called shunt nephritis; clinical findings include hypertension, microscopic hematuria, elevated blood urea nitrogen and serum creatinine levels, and anemia.

Diagnosis is by Gram stain, microscopy, biochemistry, and culture of CSF. CSF should be obtained by direct aspiration of the shunt, as CSF obtained from either lumbar or ventricular puncture is often sterile. It is unusual to observe signs of ventriculitis, and CSF findings can be only minimally abnormal. Blood culture results are usually positive in VA shunt colonization but negative in cases of VP colonization.

Wound infection presents with obvious erythema, swelling, discharge, or dehiscence along the shunt tract and most often occurs within days to weeks of the surgical procedure. *S. aureus* is the most common isolate. In addition to the physical findings, fever is common, and signs of shunt malfunction eventually ensue in most cases.

Distal infection of VP shunts with peritonitis presents with abdominal symptoms, usually without evidence of shunt malfunction. The pathogenesis is likely related to perforation of bowel at the time of VP shunt placement or translocation of bacteria across the bowel wall. Thus, Gram-negative isolates predominate and mixed infection is common. The infecting organisms are often isolated from only the distal portion of the shunt.

Common pathogens responsible for community-acquired meningitis, including *S. pneumoniae, N. meningitidis*, and *H. influenzae* type b, can also cause bacterial meningitis in patients with shunts. The clinical presentation is similar to that for acute bacterial meningitis in other children (see Chapter 602.1).

Treatment of shunt colonization includes removal of the shunt and systemic antibiotic therapy directed against the isolated organisms. After collection of appropriate samples for culture, empiric therapy is usually with vancomycin plus an antipseudomonal agent with relatively good CSF penetration such as ceftazidime or meropenem. Definitive therapy should be directed toward the isolate and account for poor penetration of most antibiotics into the CSF across noninflamed meninges. Accordingly, intraventricular antibiotics may be indicated but are usually reserved unless there is evidence of treatment failure. If the isolate is susceptible, a parenteral antistaphylococcal penicillin with or without intraventricular vancomycin is the treatment of choice. If the organism is resistant to penicillins, systemic vancomycin and possibly intraventricular vancomycin are recommended. In cases of Gram-negative infections, a combination of a third-generation cephalosporin with or without intraventricular aminoglycoside is optimal. When using intraventricular antibiotics, monitoring of CSF levels is necessary to avoid toxicity.

Removal of the colonized device is required for cure, and final replacement should be delayed until clearance of CSF cultures is documented. Many neurosurgeons immediately remove the shunt and place an external ventricular drain to relieve intracranial pressure, with a 2nd-stage shunt replacement once CSF sterilization has been confirmed. Others opt to initially exteriorize the distal end of the shunt, and replace the shunt in a single-stage procedure once CSF cultures remain sterile for 48-72 hr. Daily CSF cultures should be collected until clearance has been documented on 2-3 consecutive specimens, and antibiotics should be continued for at least 10 days after documented sterilization of the CSF. Gram-negative organisms may require a longer duration of therapy (up to 21 days). The CSF white cell count generally increases for the 1st 3-5 days of appropriate therapy and should not prompt concern for treatment failure. Distal shunt infection with peritonitis and wound infection are managed in a similar fashion.

Treatment of bacterial meningitis with typical community-acquired pathogens such as meningococcus or pneumococcus usually requires only systemic antibiotic therapy. Shunt replacement is not required in the absence of device malfunction, poor clinical response, persistent CSF culture positivity, or relapse of infection after antibiotic therapy.

Prevention of Infection

Prevention of shunt infection includes meticulous cutaneous preparation and surgical technique. Systemic and intraventricular antibiotics, antibiotic-impregnated shunts, and soaking the shunt tubing in antibiotics are used to reduce the incidence of infection, with varying success. Systemic prophylactic antibiotics given prior to shunt insertion reduce the risk for infection and should be used routinely. Antibiotic-impregnated catheters also appear to reduce the risk of infection, although limited evidence is available, and may be used in high-risk patients where the devices are available.

URETHRAL CATHETERS

Urinary catheters are a frequent cause of nosocomial infection, with about 14 infections per 1,000 admissions. Like other devices, microorganisms adhere to the catheter surface and establish a biofilm that allows proliferation. The physical presence of the catheter reduces the normal host defenses by preventing complete emptying of the bladder, thus providing a medium for growth, distending the urethra, and blocking periurethral glands. Almost all patients catheterized for longer than 30 days develop bacteriuria. The organism burden in catheter-associated urinary tract infection is typically ≥10,000 colony-forming units/mL. Lower thresholds may be used where there is a high index of suspicion, but these episodes may represent colonization rather than infection. Urine culture should only be performed in catheterized patients when infection is suspected, as asymptomatic colonization is ubiquitous and may lead to overtreatment and subsequent development of bacterial resistance. Gram-negative bacilli and *Enterococcus* spp. are the predominant organisms isolated in catheter-related urinary tract infection; coagulase-negative staphylococci are implicated in approximately 15% of cases. Symptomatic urinary tract infections should be treated with antibiotics and catheter removal. Catheter colonization with *Candida* spp. is common but rarely leads to invasive infection, and treatment does not have a long-term impact on colonization. Treatment for asymptomatic candiduria is therefore not recommended except in neonates, immunocompromised patients, and those with urinary tract obstruction.

Prevention of Infection

All urinary catheters introduce a risk for infection, and their casual use should be avoided. When they are in place, their duration of use should be minimized. Technologic advances have led to development of silver- or antibiotic-impregnated urinary catheters that are associated with lower rates of infection. Prophylactic antibiotics do not significantly reduce the infection rates for long-term catheters but clearly increase the risk for infection with antibiotic resistant organisms.

PERITONEAL DIALYSIS CATHETERS

During the 1st yr of peritoneal dialysis for end-stage renal disease, 65% of children will have 1 or more episodes of peritonitis. Bacterial entry comes from luminal or periluminal contamination of the catheter or by translocation across the intestinal wall. Hematogenous infection is rare. Infections can be localized at the exit site or associated with peritonitis, or both. Organisms responsible for peritonitis include coagulase-negative staphylococci (30-40%), *S. aureus* (10-20%), streptococci (10-15%), *E. coli* (5-10%), *Pseudomonas* spp. (5-10%), other Gram-negative bacteria (5-15%), *Enterococcus* spp. (3-6%), and fungi (2-10%). *S. aureus* is more common in localized exit-site or tunnel-tract infections (42%). Most infectious episodes are caused by a patient's own flora, and carriers of *S. aureus* have increased rates of infection as compared with noncarriers.

The **clinical manifestations** of peritonitis may be subtle and include low-grade fever with mild abdominal pain or tenderness. Cloudy peritoneal dialysis fluid may be the first and predominant sign. With peritonitis, the peritoneal fluid cell count is usually >100 white blood cells/μL. When peritonitis is suspected, the effluent dialysate should be submitted for a cell count, Gram stain, and culture. The Gram stain is positive in up to 40% of cases of peritonitis.

Patients with cloudy fluid and clinical symptoms should receive empiric therapy, preferably guided by results of a Gram stain. If no organisms are visualized, vancomycin and either an aminoglycoside or

third or fourth generation cephalosporin with antipseudomonal activity should be given via the intraperitoneal route. Blood levels should be measured for glycopeptides and aminoglycosides. Patients without cloudy fluid and with minimal symptoms may have therapy withheld pending culture results. Once the cause is identified by culture, changes in the therapeutic regimen may be needed. Oral rifampin may be added for *S. aureus* infections. Fungal peritonitis should be treated with a combination of oral flucytosine and intraperitoneal or oral fluconazole. The duration of therapy is a minimum of 14 days, with longer treatment of 21-28 days for episodes of *S. aureus*, *Pseudomonas* spp., and resistant Gram-negative bacteria and of 28-42 days for fungi. Repeat episodes of peritonitis within 4 wk of previous therapy represent "apparently relapsing" peritonitis. If the patient responds to reinstitution of antimicrobial therapy, a course of up to 6 wk should be continued. In all cases, if the infection fails to clear following appropriate therapy or if a patient's condition is deteriorating, the catheter should be removed. Exit-site and tunnel infections may occur independently of peritonitis or may precede it. Appropriate antibiotics should be administered on the basis of Gram stain and culture findings and are typically given systemically only unless peritonitis is also present. Some experts recommend that the peritoneal catheter be removed if *Pseudomonas* or fungal organisms are isolated.

Prevention of Infection

In addition to usual hygienic practices, regular application of mupirocin or gentamicin cream to the catheter exit site reduces exit-site infections and peritonitis. Some practitioners recommend against the use of gentamicin cream because of the risk of infection with gentamicin-resistant bacteria. Systemic antibiotic prophylaxis should be considered at the time of catheter insertion, if there is accidental contamination, and at the time of dental procedures. Antifungal prophylaxis can be considered during antibiotic therapy to prevent fungal infection.

ORTHOPEDIC PROSTHESES

Orthopedic prostheses are used infrequently in children. Infection most often follows introduction of microorganisms at surgery through airborne contamination or direct inoculation; via hematogenous spread; or via contiguous spread from an adjacent infection. Early postoperative infection occurs within 2-4 wk of surgery with typical manifestations that include fever, pain, and local symptoms of wound infection. Rapid assessment, including isolation of the infecting organism by joint aspiration or intraoperative culture, operative debridement, and antimicrobial treatment may allow salvage of the implant if the duration of symptoms is less than 1 mo, the prosthesis is stable, and the pathogen is susceptible to antibiotics. Chronic infection presents >1 mo after surgery and is often caused by organisms of low virulence that contaminated the implant at the time of surgery. Typical manifestations include pain and deterioration in function. Local symptoms such as erythema, swelling, or drainage may also occur. These infections respond poorly to antibiotic treatment and usually require removal of the implant using either a 1- or 2-stage procedure. Surgical debridement of the site with long-term suppressive antibiotic therapy may be considered, but eradication of infection is uncommon. Acute hematogenous infections are most often observed 2 yr or more after surgery. Retention of the prosthesis is sometimes attempted, but there are inadequate long-term data to determine the success rate. If salvage therapy is attempted, prompt debridement and appropriate antibiotic therapy are recommended. As with other long-term implanted devices, the most common organisms are about equally divided between coagulase-negative staphylococci and *S. aureus*. With prior antibiotic therapy, the prosthesis culture may be negative; in these situations, determining 16S ribosomal RNA typing may help identify the organism.

The use of systemic antibiotic prophylaxis, antibiotic-containing bone cement, and operating rooms fitted with laminar airflow all have been proposed as beneficial in reducing infection. To date, results from clinical studies are conflicting.

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Section 3

Antibiotic Therapy

Chapter 180

Principles of Antibacterial Therapy

Mark R. Schleiss

Antibacterial therapy in infants and children presents many challenges. A daunting problem is the paucity of pediatric data regarding pharmacokinetics and optimal dosages; as a consequence, pediatric recommendations are commonly extrapolated from studies in adults. A second challenge is the need for the clinician to consider important differences among various age groups with respect to the pathogenic species responsible for pediatric bacterial infections. Age-appropriate antibiotic dosing and toxicities must be considered, taking into account the developmental status and physiology of infants and children. Finally, the style of usage of antibiotics has some important differences compared with usage in adult patients. Specific antibiotic therapy is optimally driven by a **microbiologic diagnosis,** predicated on isolation of the pathogenic organism from a sterile body site, and supported by antimicrobial susceptibility testing. Given the inherent difficulties that can arise in collecting specimens from pediatric patients, and given the high risk of mortality and disability associated with serious bacterial infections in very young infants, much of pediatric infectious diseases practice is based on a **clinical diagnosis** with **empirical** use of antibacterial agents, administered before or even without eventual identification of the specific pathogen.

Several key considerations influence decisions about the appropriate empirical use of antibacterial agents in infants and children. It is important to know the age-appropriate differential diagnosis with respect to likely pathogens. This information affects the choice of antimicrobial agent and also the dose, dosing interval, and route of administration (oral vs parenteral). A complete history and physical examination, combined with appropriate laboratory and radiographic studies, are necessary to identify specific diagnoses, in turn affecting the choice, dosing, and degree of urgency of administration of antimicrobial agents. The vaccination history may reflect reduced risk for some invasive infections, but not necessarily elimination of risk. The risk of serious bacterial infection in pediatric practice is also affected by the child's immunologic status, which may be compromised by immaturity (neonates), underlying disease, and associated treatments (see Chapter 178). Infections in immunocompromised children may result from bacteria that are not considered pathogenic in immunocompetent children. The presence of foreign bodies also increases the risk of bacterial infections (see Chapter 179). The likelihood of central nervous system (CNS) involvement must be considered in all pediatric patients with serious bacterial infections, because many of the more common bacteremic infections in childhood, including disease caused by *Haemophilus influenzae* type b, pneumococcus, *Salmonella*, and meningococcus, carry a significant risk for hematogenous spread to the CNS.

The patterns of **antimicrobial resistance** in the community and for the potential causative pathogen being empirically treated must also be considered. Resistance to penicillin and cephalosporins is commonplace among strains of *Streptococcus pneumoniae,* often necessitating the use of other classes of antibiotics. Similarly, the striking emergence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections has complicated antibiotic choices for

this pathogen. Furthermore, carbapenem-resistant *Enterobacteriaceae* are an increasing problem among hospitalized patients.

Antimicrobial resistance occurs through many modifications of the bacterial genome (Tables 180-1 and 180-2). Mechanisms include enzyme inactivation of the antibiotic, decreased cell membrane permeability to intracellularly active antibiotics, efflux of antibiotics out of the bacteria, protection or alteration of the antibiotic target site, excessive production of the target site, and bypassing the antimicrobial site of action.

Antimicrobial resistance has reached **crisis proportions,** driven by the emergence of new resistance mechanisms (such as carbapenemases) and by overuse of antibiotics, both in healthcare and in other venues, such as agriculture. This increase in antibiotic resistance has rendered some bacterial infections encountered in clinical practice virtually untreatable. Accordingly, there is an urgent need to develop new antimicrobials. In addition, it is important for practitioners to use antibiotics only as necessary, with the narrowest feasible antimicrobial spectrum, to help thwart emergence of resistance. Advocacy for vaccines, particularly conjugate pneumococcal vaccine, can also decrease the selective pressure that excessive antimicrobial use exerts on resistance.

Effective antibiotic action requires achieving therapeutic levels of the drug at the site of infection. Although measuring the level of antibiotic at the site of infection is not always possible, one may measure the serum level and use this level as a surrogate marker for achievement of the desired effect at the tissue level. Various target serum levels are appropriate for different antibiotic agents and are assessed by the peak and trough serum levels, and the area under the therapeutic drug level curve (Fig. 180-1). These levels are, in turn, a reflection of the route of administration, drug absorption (IM, PO), volume of distribution, and drug elimination half-life, as well as of drug-drug interactions that might enhance or impede enzymatic inactivation of an antibiotic or result in antimicrobial synergism or antagonism (Fig. 180-2).

Table 180-1 Mechanisms of Resistance to β-Lactam Antibiotics

I. Alter target site (PBP)
  A. Decrease affinity of PBP for β-lactam antibiotic
    1. Modify existing PBP
      a. Create mosaic PBP
        Insert nucleotides obtained from neighboring bacteria (e.g., penicillin-resistant *Streptococcus pneumoniae*)
        Mutate structural gene of PBP(s) (e.g., ampicillin-resistant β-lactamase–negative *Haemophilus influenzae*)
    2. Import new PBP (e.g., mecA in methicillin-resistant *Staphylococcus aureus*)
II. Destroy β-lactam antibiotic
  A. Increase production of β-lactamases, carbapenemases
    1. Acquire more efficient promoter
      a. Mutate existing promoter
      b. Import new promoter
    2. Deregulate control of β-lactamase production
      a. Mutate regulator genes (e.g., ampD in "stably derepressed" *Enterobacter cloacae*)
  B. Modify structure of resident β-lactamase
    1. Mutate structural gene (e.g., extended-spectrum β-lactamases in *Klebsiella pneumoniae*)
  C. Import new β-lactamase(s) with different spectrum of activity
III. Decrease concentration of β-lactam antibiotic inside cell
  A. Restrict its entry (loss of porins)
  B. Pump it out (efflux mechanisms)

PBP, penicillin-binding protein.

Table 180-2 Aminoglycoside-Modifying Enzymes

ENZYMES	USUAL ANTIBIOTICS MODIFIED	COMMON GENERA
PHOSPHORYLATION		
APH(2″)	K, T, G	SA, SR
APH(3′)-I	K	E, PS, SA, SR
APH(3′)-III	K ± A	E, PS, SA, SR
ACETYLATION		
AAC(2′)	G	PR
AAC(3)-I	±T, G	E, PS
AAC(3)-III, -IV, OR-V	K, T, G	E, PS
AAC(6′)	K, T, A	E, PS, SA
ADENYLATION		
ANT(2″)	K, T, G	
ANT(4′)	K, T, A	SA

A, amikacin; AAC, aminoglycoside acetyltransferase; ANT, aminoglycoside nucleotidyltransferase; APH, aminoglycoside phosphotransferase; E, *Enterobacteriaceae*; G, gentamicin; K, kanamycin; PR, *Providencia-Proteus;* PS, pseudomonads; SA, staphylococci; SR, streptococci; T, tobramycin.

AGE- AND RISK-SPECIFIC USE OF ANTIBIOTICS IN CHILDREN

Neonates

The causative pathogens of neonatal infections are typically acquired around the time of delivery. Thus, empirical antibiotic selection must take into account the importance of these pathogens in neonates (see Chapter 109). Among the causes of neonatal sepsis in infants, group B streptococcus is the most common, although intrapartum antibiotic prophylaxis administered to women at increased risk for transmission of this pathogen to the infant has greatly decreased the incidence of this infection in neonates (see Chapter 184). Gram-negative enteric organisms acquired from the maternal birth canal, in particular *Escherichia coli,* are other common causes of neonatal sepsis. Although rare, *Listeria monocytogenes* is also an important pathogen, insofar as it is intrinsically resistant to cephalosporin antibiotics, which are often used as empirical therapy for serious bacterial infections in young children. *Salmonella* species are also being increasingly recognized as important pathogens in infancy. All of these organisms can be associated with meningitis in the neonate; therefore, lumbar puncture should always be considered in the setting of bacteremic infections in this age group, and, if meningitis cannot be excluded, antibiotic management should include agents capable of crossing the blood–brain barrier.

Older Children

Antibiotic choices in toddlers and young children were once driven by the high risk of this age group to invasive disease caused by *H. influenzae* type b (see Chapter 194). With the advent of conjugate vaccines against *H. influenzae* type b, invasive disease has declined dramatically. However, outbreaks of invasive disease still occur, particularly in the setting of parental refusal of vaccines. It is, therefore, still important to utilize antimicrobials that are active against this pathogen in many clinical settings, particularly if meningitis is a consideration. Other particularly important pathogens to be considered in this age group include *E. coli*, *S. pneumoniae, Neisseria meningitidis,* and *S. aureus*. Antimicrobial resistance is commonly exhibited by *S. pneumoniae* and *S. aureus*. Strains of *S. pneumoniae* that are resistant to penicillin and cephalosporin antibiotics are frequently encountered in clinical practice. Similarly, MRSA is highly prevalent in many regions. Resistance of *S. pneumoniae*, as well as MRSA, is a result of mutations that confer alterations in penicillin-binding proteins, the molecular targets of penicillin and cephalosporin activity (see Table 180-1).

Depending on the specific clinical diagnosis, other pathogens that are commonly encountered among older children include *Moraxella catarrhalis,* nontypable strains of *H. influenzae,* and *Mycoplasma pneumoniae,* which cause upper respiratory tract infections and pneumonia; group A streptococcus, which causes pharyngitis, skin and soft-tissue infections, osteomyelitis, septic arthritis, and, rarely, bacteremia with toxic shock syndrome; *Kingella kingae,* which causes bone and joint infections; viridans streptococci and *Enterococcus,* which cause endocarditis; and *Salmonella,* which causes enteritis, bacteremia, osteomyelitis, and septic arthritis. This complexity underscores the

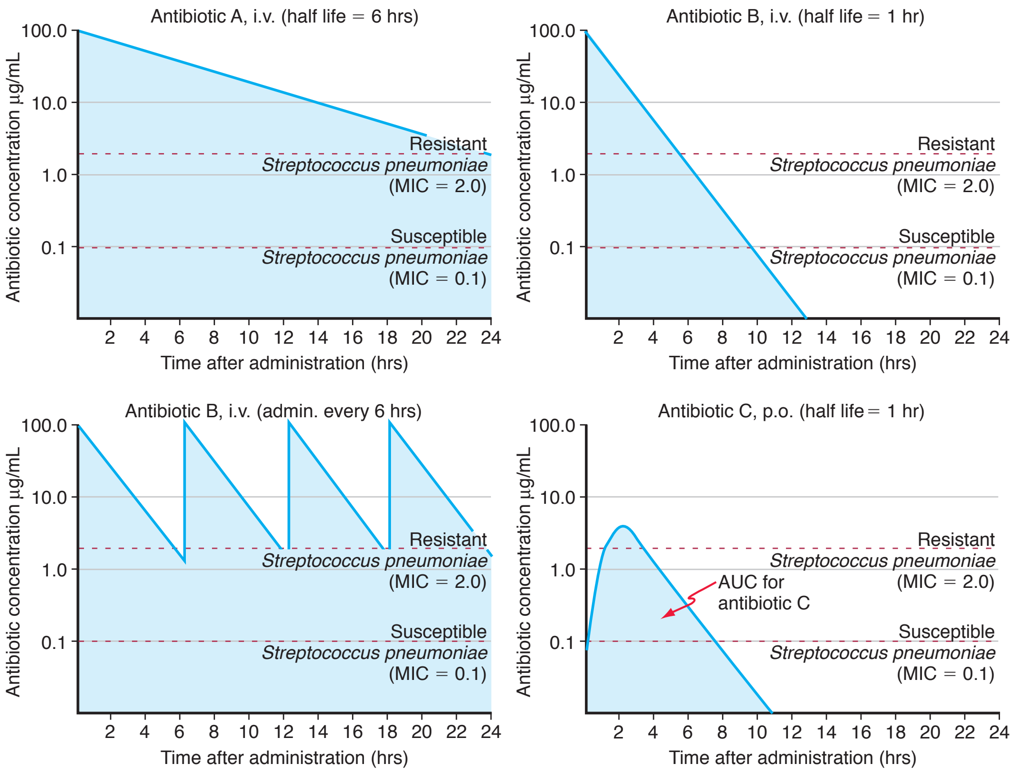

Figure 180-1 **The area under the curve *(shaded area)* for different antibiotics.** The area under the curve provides a measure of antibiotic exposure to bacterial pathogens. The greatest exposure comes with antibiotics that have a long serum half-life and are administered parenterally (*upper left panel*, antibiotic A). The lowest exposure occurs with oral administration (*lower right panel*, antibiotic C). Dosing of antibiotic B once a day *(upper right panel)* provides far less exposure than dosing the same antibiotic every 6 hr *(lower left panel)*. MIC, minimal inhibitory concentration. *(From Pong AL, Bradley JS: Guidelines for the selection of antibacterial therapy in children,* Pediatr Clin North Am *52:869–894, 2005.)*

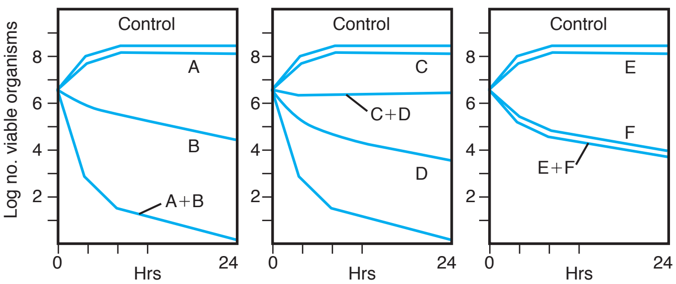

Figure 180-2 **Antibacterial effects of antibiotic combinations.** *Left:* Curve of A + B illustrates synergism (increased killing). *Center:* Curve of C + D illustrates antagonism (D is less effective when C is added). *Right:* Curve of E + F illustrates indifference, or additive effect (addition of E to F has no effect on F). *(From Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases, *ed 6. Philadelphia, 2005, Elsevier, p. 247.)*

importance of formulation of a clear clinical diagnosis, including an assessment of the severity of the infection, in concert with knowledge of local susceptibility patterns in the community.

Immunocompromised and Hospitalized Patients

It is important to consider the risks associated with immunocompromising conditions (malignancy, solid-organ, or hematopoietic stem cell transplantation) and the risks conferred by conditions leading to prolonged hospitalization (intensive care, trauma, burns). Serious viral infections, particularly with influenza, can also predispose to invasive bacterial infections, especially with *S. aureus*. Immunocompromised children are predisposed to develop a wide range of bacterial, viral, fungal, or parasitic infections. Prolonged hospitalization can lead to nosocomial infections, often associated with indwelling lines and catheters and commonly caused by Gram-negative enteric organisms. In addition to the usual bacterial pathogens, *Pseudomonas aeruginosa* and enteric organisms, including *E. coli, Klebsiella pneumoniae, Enterobacter*, and *Serratia*, are important considerations as opportunistic pathogens in these settings. Selection of appropriate antimicrobials is challenging because of the diverse causes and scope of antimicrobial resistance exhibited by these organisms. Many strains of enteric organisms have resistance because of extended spectrum β-lactamases (see Table 180-1). Class B metallo-β-lactamases that hydrolyze all β–lactam antibiotics except aztreonam are increasingly being described. A worrisome development is the increasing reports of carbapenemases in *Enterobacteriaceae*. Carbapenemase-producing *Enterobacteriaceae* are different from other multidrug-resistant microorganisms in that they are susceptible to few (if any) antibacterial agents. *P. aeruginosa* encodes proteins that function as efflux pumps to eliminate multiple classes of antimicrobials from the cytoplasm or periplasmic space. In addition to these Gram-negative pathogens, infections caused by *Enterococcus faecalis* and *Enterococcus faecium* are inherently difficult to treat. These organisms may cause urinary tract infection or infective endocarditis in immunocompetent children and may be responsible for a variety of syndromes in immunocompromised patients, especially in the setting of prolonged intensive care. The emergence of infections caused by **vancomycin-resistant *Enterococcus* (VRE)** has further complicated antimicrobial selection in high-risk patients and has necessitated the development of newer antimicrobials that target these highly resistant Gram-positive bacteria. Although experience with many of these newer agents in the management of complex hospitalized pediatric patients is limited, they are important agents to be aware of (described below).

Infections Associated with Medical Devices

A special situation affecting antibiotic use is the presence of an indwelling medical device, such as a venous catheter, ventriculoperitoneal shunt, stent, or other catheter (see Chapter 179). In addition to *S. aureus,* coagulase-negative staphylococci are also a major

consideration. Coagulase-negative staphylococci seldom cause serious disease without a risk factor such as an indwelling catheter. Empirical antibiotic regimens must take this risk into consideration. In addition to appropriate antibiotic therapy, removal or replacement of the colonized prosthetic material is commonly required for cure.

ANTIBIOTICS COMMONLY USED IN PEDIATRIC PRACTICE

Table 180-3 lists commonly used antibiotics.

Penicillins

Although there has been ever-increasing emergence of resistance to penicillins, these agents remain valuable and are commonly used for management of many pediatric infectious diseases.

Penicillins remain the drugs of choice for pediatric infections caused by group A and group B *Streptococcus*, *Treponema pallidum* (syphilis), *L. monocytogenes*, and *N. meningitidis*. The **semisynthetic penicillins** (nafcillin, cloxacillin, dicloxacillin) are useful for management of susceptible staphylococcal infections, although the increasing incidence of MRSA has limited the usefulness of these drugs. The **aminopenicillins** (ampicillin, amoxicillin) were developed to provide broad-spectrum activity against Gram-negative organisms, including *E. coli* and *H. influenzae*, but the emergence of resistance has limited their utility in many clinical settings. The **carboxypenicillins** (carbenicillin, ticarcillin) and **ureidopenicillins** (piperacillin, mezlocillin, azlocillin) also have bactericidal activity against most strains of *P. aeruginosa*.

Text continued on p. 1311

Table 180-3 Antibacterial Medications (Antibiotics)*

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Amikacin sulfate Amikin Injection: 50 mg/mL, 250 mg/mL	**Aminoglycoside antibiotic active against Gram-negative bacilli, especially *Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days: weight 1,200-2,000 g: 7.5 mg/kg q 12-18 hr IV or IM; weight >2,000 g: 10 mg/kg q 12 hr IV or IM; postnatal age >7 days: weight 1,200-2,000 g IV or IM: 7.5 mg/kg q 8-12 hr IV or IM; weight >2,000 g: 10 mg/kg q 8 hr IV or IM Children: 15-25 mg/kg/24 hr divided q 8-12 hr IV or IM Adults: 15 mg/kg/24 hr divided q 8-12 hr IV or IM	*Cautions:* Anaerobes, *Streptococcus* (including *S. pneumoniae*) are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs *Target serum concentrations:* Peak 25-40 mg/L; trough <10 mg/L
Amoxicillin Amoxil, Polymox Capsule: 250, 500 mg Tablet: chewable: 125, 250 mg Suspension: 125 mg/5 mL, 250 mg/5 mL Drops: 50 mg/mL	**Penicillinase-susceptible β-lactam: Gram-positive pathogens except *Staphylococcus; Salmonella, Shigella, Neisseria, E. coli,* and *Proteus mirabilis*** Children: 20-50 mg/kg/24 hr divided q 8-12 hr PO. Higher dose of 80-90 mg/kg 24 hr PO for otitis media Adults: 250-500 mg q 8-12 hr PO Uncomplicated gonorrhea: 3 g with 1 g probenecid PO	*Cautions:* Rash, diarrhea, abdominal cramping. Drug eliminated renally *Drug interaction:* Probenecid
Amoxicillin-clavulanate Augmentin Tablet: 250, 500, 875 mg Tablet, chewable: 125, 200, 250, 400 mg Suspension: 125 mg/5 mL, 200 mg/5 mL, 250 mg/5 mL, 400 mg/5 mL	**β-Lactam (amoxicillin) combined with β-lactamase inhibitor (clavulanate) enhances amoxicillin activity against penicillinase-producing bacteria. *S. aureus* (not methicillin-resistant organism), *Streptococcus, Haemophilus influenzae, Moraxella catarrhalis, E. coli, Klebsiella, Bacteroides fragilis*** Neonates: 30 mg/kg/24 hr divided q 12 hr PO Children: 20-45 mg/kg 24 hr divided q 8-12 hr PO. Higher dose 80-90 mg/kg/24 hr PO for otitis media	*Cautions:* Drug dosed on amoxicillin component. May cause diarrhea, rash. Drug eliminated renally *Drug interaction:* Probenecid *Comment:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae*
Ampicillin Polycillin, Omnipen Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL Injection	**β-Lactam with same spectrum of antibacterial activity as amoxicillin** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 50 mg/kg/24 hr IV or IM q 12 hr (meningitis: 100 mg/kg/24 hr divided q 12 hr IV or IM); weight >2,000 g: 75 mg/kg/24 hr divided q 8 hr IV or IM (meningitis: 150 mg/kg/24 hr divided q 8 hr IV or IM). Postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV or IM q 12 hr (meningitis: 100 mg/kg/24 hr divided q 12 hr IV or IM); weight 1,200-2,000 g: 75 mg/kg/24 hr divided q 8 hr IV or IM (meningitis: 150 mg/kg/24 hr divided q 8 hr IV or IM); weight >2,000 g: 100 mg/kg/24 hr divided q 6 hr IV or IM (meningitis: 200 mg/kg/24 hr divided q 6 hr IV or IM) Children: 100-200 mg/kg/24 hr divided q 6 hr IV or IM (meningitis: 200-400 mg/kg/24 hr divided q 4-6 hr IV or IM) Adults: 250-500 mg q 4-8 hr IV or IM	*Cautions:* Less bioavailable than amoxicillin, causing greater diarrhea *Drug interaction:* Probenecid
Ampicillin-sulbactam Unasyn Injection	**β-Lactam (ampicillin) and β-lactamase inhibitor (sulbactam) enhances ampicillin activity against penicillinase-producing bacteria: *S. aureus, H. influenzae, M. catarrhalis, E. coli, Klebsiella, B. fragilis*** Children: 100-200 mg/kg/24 hr divided q 4-8 hr IV or IM Adults: 1-2 g q 6-8 hr IV or IM (max daily dose: 8 g)	*Cautions:* Drug dosed on ampicillin component. May cause diarrhea, rash. Drug eliminated renally *Note:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae* *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Azithromycin Zithromax Tablet: 250 mg Suspension: 100 mg/5 mL, 200 mg/5 mL	**Azalide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Mycoplasma, Legionella, Chlamydia trachomatis*** Children: 10 mg/kg PO on day 1 (max dose: 500 mg) followed by 5 mg/kg PO q 24 hr for 4 days Group A streptococcus pharyngitis: 12 mg/kg/24 hr PO (max dose: 500 mg) for 5 days. Adults: 500 mg PO day 1 followed by 250 mg for 4 days Uncomplicated *C. trachomatis* infection: single 1 g dose PO	*Note:* Very long half-life permitting once-daily dosing. No metabolic-based drug interactions (unlike erythromycin and clarithromycin), limited gastrointestinal distress. Shorter-course regimens (e.g., 1-3 days) under investigation. 3 day, therapy (10 mg/kg/24 hr × 3 days) and single-dose therapy (30 mg/kg): use with increasing frequency (not for streptococcus pharyngitis)
Aztreonam Azactam Injection	**β-Lactam (monobactam) antibiotic with activity against Gram-negative aerobic bacteria, *Enterobacteriaceae*, and *Pseudomonas aeruginosa*** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 60 mg/kg/24 hr divided q 12 hr IV or IM; weight >2,000 g: 90 mg/kg/24 hr divided q 8 hr IV or IM; postnatal age >7 days weight <1,200 g: 60 mg/kg/24 hr divided q 12 hr IV or IM; weight 1,200-2,000 g: 90 mg/kg/24 hr divided q 8 hr IV or IM; weight >2,000 g: 120 mg/kg/24 hr divided q 6-8 hr IV or IM Children: 90-120 mg/kg/24 hr divided q 6-8 hr IV or IM. For cystic fibrosis up to 200 mg/kg/24 hr IV Adults: 1-2 g IV or IM q 8-12 hr (max dose: 8 g/24 hr)	*Cautions:* Rash, thrombophlebitis, eosinophilia. Renally eliminated *Drug interaction:* Probenecid
Carbenicillin Geopen Injection Geocillin oral tablet	**Extended-spectrum penicillin (remains susceptible to penicillinase destruction) active against *Enterobacter*, indole-positive *Proteus*, and *Pseudomonas*** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 225 mg/kg/24 hr divided q 8 hr IV or IM; weight >2,000 g: 300 mg/kg/24 hr divided q 6 hr IV or IM; >7 days: 300-400 mg/kg/24 hr divided q 6 hr IV or IM Children: 400-600 mg/kg/24 hr divided q 4-6 hr IV or IM	*Cautions:* Painful given intramuscularly; rash; each gram contains 5.3 mEq sodium. Interferes with platelet aggregation at high doses, increases in liver transaminase levels. Renally eliminated. Oral tablet for treatment of urinary tract infection only *Drug interaction:* Probenecid
Cefaclor Ceclor Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 187 mg/5 mL, 250 mg/5 mL, 375 mg/5 mL	**Second-generation cephalosporin active against *S. aureus, Streptococcus* including *S. pneumoniae, H. influenzae, E. coli, Klebsiella*, and *Proteus*** Children: 20-40 mg/kg/24 hr divided q 8-12 hr PO (max dose: 2 g) Adults: 250-500 mg q 6-8 hr PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia) with high incidence of serum sickness reaction. Renally eliminated *Drug interaction:* Probenecid
Cefadroxil Duricef, Ultracef Capsule: 500 mg Tablet: 1,000 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus*** Children: 30 mg/kg/24 hr divided q 12 hr PO (max dose: 2 g) Adults: 250-500 mg q 8-12 hr PO	*Cautions:* β-lactam safety profile (rash, eosinophilia). Renally eliminated. Long half-life permits q 12-24 hr dosing *Drug interaction:* Probenecid
Cefazolin Ancef, Kefzol Injection	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus*** Neonates: Postnatal age ≤7 days 40 mg/kg/24 hr divided q 12 hr IV or IM; >7 days 40-60 mg/kg/24 hr divided q 8 hr IV or IM Children: 50-100 mg/kg/24 hr divided q 8 hr IV or IM Adults: 0.5-2g q 8 hr IV or IM (max dose: 12 g/24 hr)	*Caution:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS *Drug interaction:* Probenecid
Cefdinir Omnicef Capsule: 300 mg Oral suspension: 125 mg/5 mL	**Extended-spectrum, semisynthetic cephalosporin** Children 6 mo-12 yr: 14 mg/kg/24 hr in 1 or 2 doses PO (max dose: 600 mg/24 hr) Adults: 600 mg q 24 hr PO	*Cautions:* Reduce dosage in renal insufficiency (creatinine clearance <60 mL/min). Avoid taking concurrently with iron-containing products and antacids because absorption is markedly decreased; take at least 2 hr apart *Drug interaction:* Probenecid
Cefepime Maxipime Injection	**Expanded-spectrum, fourth-generation cephalosporin active against many Gram-positive and Gram-negative pathogens, including *P. aeruginosa* many multidrug-resistant pathogens** Children: 100-150 mg/kg/24 hr q 8-12 hr IV or IM Adults: 2-4 g/24 hr q 12 hr IV or IM	*Adverse events:* Diarrhea, nausea, vaginal candidiasis Cautions: β-lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd		
DRUG (TRADE NAMES, FORMULATIONS)	**INDICATIONS (MECHANISM OF ACTION) AND DOSING**	**COMMENTS**
Cefixime Suprax Tablet: 200, 400 mg Suspension: 100 mg/5 mL	**Third-generation cephalosporin active against streptococci, *H. influenzae, M. catarrhalis, Neisseria gonorrhoeae, Serratia marcescens*, and *Proteus vulgaris*. No antistaphylococcal or antipseudomonal activity** Children: 8 mg/kg/24 hr divided q 12-24 hr PO Adults: 400 mg/24 hr divided q 12-24 hr PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS *Drug interaction:* Probenecid
Cefoperazone sodium Cefobid Injection	**Third-generation cephalosporin active against many Gram-positive and Gram-negative pathogens** Neonates: 100 mg/kg/24 hr divided q 12 hr IV or IM Children: 100-150 mg/kg/24 hr divided q 8-12 hr IV or IM Adults: 2-4 g/24 hr divided q 8-12 hr IV or IM (max dose: 12 g/24 hr)	*Cautions:* Highly protein-bound cephalosporin with limited potency reflected by weak antipseudomonal activity. Variable Gram-positive activity. Primarily hepatically eliminated in bile *Drug interaction:* Disulfiram-like reaction with alcohol
Cefotaxime sodium Claforan Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens. No antipseudomonal activity** Neonates: ≤7 days: 100 mg/kg/24 hr divided q 12 hr IV or IM; >7 days: weight <1,200 g 100 mg/kg/24 hr divided q 12 hr IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q 8 hr IV or IM Children: 150 mg/kg/24 hr divided q 6-8 hr IV or IM (meningitis: 200 mg/kg/24 hr divided q 6-8 hr IV) Adults: 1-2 g q 8-12 hr IV or IM (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Each gram of drug contains 2.2 mEq sodium. Active metabolite *Drug interaction:* Probenecid
Cefotetan disodium Cefotan Injection	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus*, and *Bacteroides*. Inactive against *Enterobacter*** Children: 40-80 mg/kg/24 hr divided IV or IM q 12 hr Adults: 2-4 g/24 hr divided q 12 hr IV or IM (max dose: 6 g/24 hr)	*Cautions:* Highly protein-bound cephalosporin, poor CNS penetration; β-lactam safety profile (rash, eosinophilia), disulfiram-like reaction with alcohol. Renally eliminated (~20% in bile)
Cefoxitin sodium Mefoxin Injection	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus*, and *Bacteroides*. Inactive against *Enterobacter*** Neonates: 70-100 mg/kg/24 hr divided q 8-12 hr IV or IM Children: 80-160 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 1-2 g q 6-8 hr IV or IM (max dose: 12 g/24 hr)	*Cautions:* Poor CNS penetration; β-lactam safety profile (rash, eosinophilia). Renally eliminated. Painful given intramuscularly *Drug interaction:* Probenecid
Cefpodoxime proxetil Vantin Tablet: 100 mg, 200 mg Suspension: 50 mg/5 mL, 100 mg/5 mL	**Third-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, N. gonorrhoeae, E. coli, Klebsiella*, and *Proteus*. No antipseudomonal activity** Children: 10 mg/kg/24 hr divided q 12 hr PO Adults: 200-800 mg/24 hr divided q 12 hr PO (max dose: 800 mg/24 hr) Uncomplicated gonorrhea: 200 mg PO as single-dose therapy	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. Increased bioavailability when taken with food *Drug interaction:* Probenecid; antacids and H-2 receptor antagonists may decrease absorption
Ceftaroline fosamil Teflaro Injection	**Fifth-generation cephalosporin active against *S. aureus* (including MRSA when used for skin and soft-tissue infection), *Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumoniae, H. influenzae*, and *Klebsiella oxytoca*** *Children: 24 mg/kg/24 hr divided q 8 hr IV (<6 mo of age); 36 mg/kg/24 hr divided q 8 hr IV (weight ≤33 kg); 400 mg q 8 hr IV (weight >33 kg) Adults: 600 mg q 12 hr IV *Suggested dose; safety and effectiveness in pediatric patients have not yet been established	*Caution:* β-Lactam safety profile (rash, eosinophilia) *Drug interaction:* Probenecid
Cefprozil Cefzil Tablet: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, M. catarrhalis, Klebsiella*, and *Proteus*** Children: 30 mg/kg/24 hr divided q 8-12 hr PO Adults: 500-1,000 mg/24 hr divided q 12 hr PO (max dose: 1.5 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Good bioavailability; food does not affect bioavailability *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Ceftazidime Fortaz, Ceptaz, Tazicef, Tazidime Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens, including *P. aeruginosa*** Neonates: Postnatal age ≤7 days: 100 mg/kg/24 hr divided q 12 hr IV or IM; >7 days weight ≤1,200 g: 100 mg/kg/24 hr divided q 12 hr IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q 8 hr IV or IM Children: 150 mg/kg/24 hr divided q 8 hr IV or IM (meningitis: 150 mg/kg/24 hr IV divided q 8 hr) Adults: 1-2 g q 8-12 hr IV or IM (max dose: 8-12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Increasing pathogen resistance developing with long-term, widespread use *Drug interaction:* Probenecid
Ceftizoxime Cefizox Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens. No antipseudomonal activity** Children: 150 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 1-2 g q 6-8 hr IV or IM (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Ceftriaxone sodium Rocephin Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens. No antipseudomonal activity** Neonates: 50-75 mg/kg q 24 hr IV or IM Children: 50-75 mg/kg q 24 hr IV or IM (meningitis: 75 mg/kg dose 1 then 80-100 mg/kg/24 hr divided q 12-24 hr IV or IM) Adults: 1-2 g q 24 hr IV or IM (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Eliminated via kidney (33-65%) and bile; can cause sludging. Long half-life and dose-dependent protein binding favors q 24 hr rather than q 12 hr dosing. Can add 1% lidocaine for IM injection *Drug interaction:* Probenecid. In neonates, coadministration with calcium-containing products can result in severe precipitation and attendant embolic complications
Cefuroxime (cefuroxime axetil for oral administration) Ceftin, Kefurox, Zinacef Injection Suspension: 125 mg/5 mL Tablet: 125, 250, 500 mg	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, M. catarrhalis, Klebsiella*, and *Proteus*** Neonates: 40-100 mg/kg/24 hr divided q 12 hr IV or IM Children: 200-240 mg/kg/24 hr divided q 8 hr IV or IM; PO administration: 20-30 mg/kg/24 hr divided q 8 hr PO Adults: 750-1,500 mg q 8 hr IV or IM (max dose: 6 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Food increases PO bioavailability *Drug interaction:* Probenecid
Cephalexin Keflex, Keftab Capsule: 250, 500 mg Tablet: 500 mg, 1 g Suspension: 125 mg/5 mL, 250 mg/5 mL, 100 mg/mL drops	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus*** Children: 25-100 mg/kg/24 hr divided q 6-8 hr PO Adults: 250-500 mg q 6 hr PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Cephradine Velosef Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus*** Children: 50-100 mg/kg/24 hr divided q 6-12 hr PO Adults: 250-500 mg q 6-12 hr PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Chloramphenicol Chloromycetin Injection Capsule: 250 mg Ophthalmic, otic solutions Ointment	**Broad-spectrum protein synthesis inhibitor active against many Gram-positive and Gram-negative bacteria, *Salmonella*, vancomycin-resistant *Enterococcus faecium, Bacteroides*, other anaerobes, *Mycoplasma, Chlamydia*, and *Rickettsia*; usually inactive against *Pseudomonas*** Neonates: Initial loading dose 20 mg/kg followed 12 hr later by: postnatal age ≤7 days: 25 mg/kg/24 hr q 24 hr IV; >7 days: weight ≤2,000 g: 25 mg/kg/24 hr q 24 hr IV; weight >2,000 g: 50 mg/kg/24 hr divided q 12 hr IV Children: 50-75 mg/kg/24 hr divided q 6-8 hr IV or PO (meningitis: 75-100 mg/kg/24 hr IV divided q 6 hr) Adults: 50 mg/kg/24 hr divided q 6 hr IV or PO (max dose: 4 g/24 hr)	*Cautions:* Gray-baby syndrome (from too-high dose in neonate), bone marrow suppression aplastic anemia (monitor hematocrit, free serum iron) *Drug interactions:* Phenytoin, phenobarbital, rifampin may decrease levels *Target serum concentrations:* Peak 20-30 mg/L; trough 5-10 mg/L

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Ciprofloxacin Cipro Tablet: 100, 250, 500, 750 mg Injection Ophthalmic solution and ointment Otic suspension Oral suspension: 250 and 500 mg/5 mL	**Quinolone antibiotic active against *P. aeruginosa, Serratia, Enterobacter, Shigella, Salmonella, Campylobacter, N. gonorrhoeae, H. influenzae, M. catarrhalis,* some *S. aureus*, and some *Streptococcus*** Neonates: 10 mg/kg q 12 hr PO or IV Children: 15-30 mg/kg/24 hr divided q 12 hr PO or IV; cystic fibrosis: 20-40 mg/kg/24 hr divided q 8-12 hr PO or IV Adults: 250-750 mg q 12 hr; 200-400 mg IV q 12 hr PO (max dose: 1.5 g/24 hr)	*Cautions:* Concerns of joint destruction in juvenile animals not seen in humans; tendonitis, superinfection, dizziness, confusion, crystalluria, some photosensitivity *Drug interactions:* Theophylline; magnesium-, aluminum-, or calcium-containing antacids; sucralfate; probenecid; warfarin; cyclosporine
Clarithromycin Biaxin Tablet: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Macrolide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Legionella, Mycoplasma,* and *C. trachomatis*** Children: 15 mg/kg/24 hr divided q 12 hr PO Adults: 250-500 mg q 12 hr PO (max dose: 1 g/24 hr)	*Cautions:* Adverse events less than erythromycin; gastrointestinal upset, dyspepsia, nausea, cramping *Drug interactions:* Same as erythromycin: astemizole carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus
Clindamycin Cleocin Capsule: 75, 150, 300 mg Suspension: 75 mg/5 mL Injection Topical solution, lotion, and gel Vaginal cream	**Protein synthesis inhibitor active against most Gram-positive aerobic and anaerobic cocci except *Enterococcus*** Neonates: Postnatal age ≤7 days weight <2,000 g; 10 mg/kg/24 hr divided q 12 hr IV or IM; weight >2,000 g: 15 mg/kg/24 hr divided q 8 hr IV or IM; >7 days weight <1,200 g: 10 mg/kg/24 hr IV or IM divided q 12 hr; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 8 hr IV or IM; weight >2,000 g: 20 mg/kg/24 hr divided q 8 hr IV or IM Children: 10-40 mg/kg/24 hr divided q 6-8 hr IV, IM, or PO Adults: 150-600 mg q 6-8 hr IV, IM, or PO (max dose: 5 g/24 hr IV or IM or 2 g/24 hr PO)	*Cautions:* Diarrhea, nausea, *Clostridium difficile*–associated colitis, rash Administer slow IV over 30-60 min Topically active as an acne treatment
Cloxacillin sodium Tegopen Capsule: 250, 500 mg Suspension: 125 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci** Children: 50-100 mg/kg/24 hr divided q 6 hr PO Adults: 250-500 mg q 6 hr PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily hepatically eliminated; requires dose reduction in renal disease. Food decreases bioavailability *Drug interaction:* Probenecid
Colistin (Colistimethate sodium; polymyxin E) Injection Inhalation	**Treatment of multidrug resistant Gram-negative organisms (*Enterobacteriaceae* including extended-spectrum betalactamase and carbapenemase-producing strains)** Children: 2.5-5 mg/kg/day divided in 2-4 divided doses IV Adults: 300 mg/day in 2-4 divided doses IV	*Cautions:* Nephrotoxicity (~3% in young children; higher rates in adolescents and adults); adjust dose for renal insufficiency; neurotoxicity (headaches, paresthesia, ataxia) *Drug interactions:* Should not be administered concomitantly with polymyxins or aminoglycosides
Co-trimoxazole (trimethoprim-sulfamethoxazole; TMP-SMZ) Bactrim, Cotrim, Septra, Sulfatrim Tablet: SMZ 400 mg and TMP 80 mg Tablet DS: SMZ 800 mg and TMP 160 mg Suspension: SMZ 200 mg and TMP 40 mg/5 mL Injection	**Antibiotic combination with sequential antagonism of bacterial folate synthesis with broad antibacterial activity: *Shigella, Legionella, Nocardia, Chlamydia, Pneumocystis jiroveci.* Dosage based on TMP component** Children: 6-20 mg TMP/kg/24 hr or IV divided q 12 hr PO *Pneumocystis carinii* pneumonia: 15-20 mg TMP/kg/24 hr divided q 12 hr PO or IV *P. carinii* prophylaxis: 5 mg TMP/kg/24 hr or 3 times/wk PO Adults: 160 mg TMP q 12 hr PO	*Cautions:* Drug dosed on TMP (trimethoprim) component. Sulfonamide skin reactions: rash, erythema multiforme, Stevens-Johnson syndrome, nausea, leukopenia. Renal and hepatic elimination; reduce dose in renal failure *Drug interactions:* Protein displacement with warfarin, possibly phenytoin, cyclosporine

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Daptomycin Cubicin	**Disrupts bacterial cell membrane function, causing depolarization leading to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death. Active against enterococci (including glycopeptide-resistant strains), staphylococci (including MRSA), streptococci, and corynebacteria. Approved for skin and soft-tissue infections. Acceptable for bacteremia and right-sided endocarditis with susceptible strains** Adults: In skin and soft-tissue infections, 4 mg/kg daptomycin is given intravenously once daily. For *S. aureus* bacteremia or right-sided endocarditis, the approved dose is 6 mg/kg given intravenously once daily Children: Unknown. Doses of 5-9 mg/kg/day in once-daily dosing have been reported in pediatric clinical trials	*Cautions:* Should not be used for pneumonia as drug inactivated by surfactants. Associated with rash, renal failure, anemia, headache. Is reported to cause myopathy, rhabdomyolysis, and eosinophilic pneumonia *Drug interactions:* Should not be administered with statins
Demeclocycline Declomycin Tablet: 150, 300 mg Capsule: 150 mg	**Tetracycline active against most Gram-positive cocci except *Enterococcus*, many Gram-negative bacilli, anaerobes, *Borrelia burgdorferi* (Lyme disease), *Mycoplasma*, and *Chlamydia*** Children: 8-12 mg/kg/24 hr divided q 6-12 hr PO Adults: 150 mg PO q 6-8 hr Syndrome of inappropriate antidiuretic hormone secretion: 900-1,200 mg/24 hr or 13-15 mg/kg/24 hr divided q 6-8 hr PO with dose reduction based on response to 600-900 mg/24 hr	*Cautions:* Teeth staining, possibly permanent (if administered <8 yr of age) with prolonged use; photosensitivity, diabetes insipidus, nausea, vomiting, diarrhea, superinfections *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc- and iron-containing food, milk, dairy products may decrease absorption
Dicloxacillin Dynapen, Pathocil Capsule: 125, 250, 500 mg Suspension: 62.5 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci** Children: 12.5-100 mg/kg/24 hr divided q 6 hr PO Adults: 125-500 mg q 6 hr PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily renally (65%) and bile (30%) elimination. Food may decrease bioavailability *Drug interaction:* Probenecid
Doripenem Doribax Injection	**Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *P. aeruginosa* and anaerobes** Children: dose unknown. Adults: 500 mg q 8 hr IV	*Cautions:* β-Lactam safety profile; does not undergo hepatic metabolism. Renal elimination (70-75%); dose adjustment for renal failure *Drug interactions:* Valproic acid, probenecid
Doxycycline Vibramycin, Doxy Injection Capsule: 50, 100 mg Tablet: 50, 100 mg Suspension: 25 mg/5 mL Syrup: 50 mg/5 mL	**Tetracycline antibiotic active against most Gram-positive cocci except *Enterococcus*, many Gram-negative bacilli, anaerobes, *B. burgdorferi* (Lyme disease), *Mycoplasma*, and *Chlamydia*** Children: 2-5 mg/kg/24 hr divided q 12-24 hr PO or IV (max dose: 200 mg/24 hr) Adults: 100-200 mg/24 hr divided q 12-24 hr PO or IV	*Cautions:* Teeth staining, possibly permanent (<8 yr of age) with prolonged use; photosensitivity, nausea, vomiting, diarrhea, superinfections *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc-, iron-, kaolin-, and pectin-containing products, food, milk, dairy products may decrease absorption. Carbamazepine, rifampin, barbiturates may decrease half-life
Erythromycin E-Mycin, Ery-Tab, Eryc, Ilosone Estolate 125, 500 mg Tablet EES: 200 mg Tablet base: 250, 333, 500 mg Suspension: estolate 125 mg/5 mL, 250 mg/5 mL, EES 200 mg/5 mL, 400 mg/5 mL Estolate drops: 100 mg/mL. EES drops: 100 mg/2.5 mL. Available in combination with sulfisoxazole (Pediazole), dosed on erythromycin content	**Bacteriostatic macrolide antibiotic most active against Gram-positive organisms, *Corynebacterium diphtheriae*, and *Mycoplasma pneumoniae*** Neonates: Postnatal age ≤7 days: 20 mg/kg/24 hr divided q 12 hr PO; >7 days weight <1,200 g: 20 mg/kg/24 hr divided q 12 hr PO; weight >1,200 g: 30 mg/kg/24 hr divided q 8 hr PO (give as 5 mg/kg/dose q 6 hr to improve feeding intolerance) Children: Usual max dose 2 g/24 hr Base: 30-50 mg/kg/24 hr divided q 6-8 hr PO Estolate: 30-50 mg/kg/24 hr divided q 8-12 hr PO Stearate: 20-40 mg/kg/24 hr divided q 6 hr PO Lactobionate: 20-40 mg/kg/24 hr divided q 6-8 hr IV Gluceptate: 20-50 mg/kg/24 hr divided q 6 hr IV; usual max dose 4 g/24 hr IV Adults: Base: 333 mg PO q 8 hr; estolate/stearate/base: 250-500 mg q 6 hr PO	*Cautions:* Motilin agonist leading to marked abdominal cramping, nausea, vomiting, diarrhea. Associated with hypertrophic pyloric stenosis in young infants. Many different salts with questionable tempering of gastrointestinal adverse events. Rare cardiac toxicity with IV use. Dose of salts differ. Topical formulation for treatment of acne *Drug interactions:* Antagonizes hepatic CYP 3A4 activity: astemizole, carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus, carbamazepine

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Gentamicin Garamycin Injection Ophthalmic solution, ointment, topical cream	**Aminoglycoside antibiotic active against Gram-negative bacilli, especially *E. coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 2.5 mg/kg q 12-18 hr IV or IM; weight <2,000 g: 2.5 mg/kg q 12 hr IV or IM; postnatal age >7 days weight 1,200-2,000 g: 2.5 mg/kg q 8-12 hr IV or IM; weight >2,000 g: 2.5 mg/kg q 8 hr IV or IM Children: 2.5 mg/kg/24 hr divided q 8-12 hr IV or IM. Alternatively may administer 5-7.5 mg/kg/24 hr IV once daily Intrathecal: Preservative-free preparation for intraventricular or intrathecal use: neonate: 1 mg/24 hr; children: 1-2 mg/24 hr intrathecal; adults: 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q 8 hr IV or IM	Cautions: Anaerobes, *S. pneumoniae,* and other *Streptococcus* are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs *Target serum concentrations:* Peak 6-12 mg/L; trough >2 mg/L with intermittent daily dose regimens only
Imipenem-cilastatin Primaxin Injection	**Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *P. aeruginosa* and anaerobes. No activity against *Stenotrophomonas maltophilia*** Neonates: Postnatal age ≤7 days weight <1,200 g: 20 mg/kg q 18-24 hr IV or IM; weight >1,200 g: 40 mg/kg divided q 12 hr IV or IM; postnatal age >7 days weight 1,200-2,000 g: 40 mg/kg q 12 hr IV or IM; weight >2,000 g: 60 mg/kg q 8 hr IV or IM Children: 60-100 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 2-4 g/24 hr divided q 6-8 hr IV or IM (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), nausea, seizures. Cilastatin possesses no antibacterial activity; reduces renal imipenem metabolism. Primarily renally eliminated *Drug interaction:* Possibly ganciclovir
Linezolid Zyvox Tablet: 400, 600 mg Oral suspension: 100 mg/5 mL Injection: 100 mg/5 mL	**Oxazolidinone antibiotic active against Gram-positive cocci (especially drug-resistant organisms), including *Staphylococcus, Streptococcus, E. faecium,* and *Enterococcus faecalis.* Interferes with protein synthesis by binding to 50S ribosome subunit** Children: 10 mg/kg q 12 hr IV or PO Adults: Pneumonia: 600 mg q 12 hr IV or PO; skin infections: 400 mg q 12 hr IV or PO	*Adverse events:* Myelosuppression, pseudomembranous colitis, nausea, diarrhea, headache *Drug interaction:* Probenecid
Loracarbef Lorabid Capsule: 200 mg Suspension: 100 mg/5 mL, 200 mg/5 mL	**Carbacephem very closely related to cefaclor (second-generation cephalosporin) active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, E. coli, Klebsiella,* and *Proteus*** Children: 30 mg/kg/24 hr divided q 12 hr PO (max dose: 2 g) Adults: 200-400 mg q 12 hr PO (max dose: 800 mg/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Meropenem Merrem Injection	**Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *P. aeruginosa* and anaerobes. No activity against *S. maltophilia*** Children: 60 mg/kg/24 hr divided q 8 hr IV meningitis: 120 mg/kg/24 hr (max dose: 6 g/24 hr) q 8 hr IV Adults: 1.5-3 g q 8 hr IV	*Cautions:* β-Lactam safety profile; appears to possess less CNS excitation than imipenem. 80% renal elimination *Drug interaction:* Probenecid
Metronidazole Flagyl, Metro I.V., Topical gel, vaginal gel Injection Tablet: 250, 500 mg	**Highly effective in the treatment of infections caused by anaerobes. Oral therapy of *C. difficile* colitis** Neonates: weight <1,200 g: 7.5 mg/kg 48 hr PO or IV; postnatal age ≤7 days weight 1,200-2,000 g: 7.5 mg/kg/24 hr q 24 hr PO or IV; weight 2,000 g: 15 mg/kg/24 hr divided q 12 hr PO or IV; postnatal age <7 days weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 12 hr PO or IV; weight >2,000 g: 30 mg/kg/24 hr divided q 12 hr PO or IV Children: 30 mg/kg/24 hr divided q 6-8 hr PO or IV Adults: 30 mg/kg/24 hr divided q 6 hr PO or IV (max dose: 4 g/24 hr)	*Cautions:* Dizziness, seizures, metallic taste, nausea, disulfiram-like reaction with alcohol. Administer IV slow over 30-60 min. Adjust dose with hepatic impairment *Drug interactions:* Carbamazepine, rifampin, phenobarbital may enhance metabolism; may increase levels of warfarin, phenytoin, lithium

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Mezlocillin sodium Mezlin Infection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia*, and *Bacteroides;* limited antipseudomonal activity** Neonates: Postnatal age ≤7 days: 150 mg/kg/24 hr divided q 12 hr IV; >7 days: 225 mg/kg divided q 8 hr IV Children: 200-300 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis 300-450 mg/kg/24 hr IV Adults: 2-4 g/dose q 4-6 hr IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.8 mEq sodium. Interferes with platelet aggregation with high doses; increases noted in liver function test results. Renally eliminated. Inactivated by β-lactamase enzyme *Drug interaction:* Probenecid
Mupirocin Bactroban Ointment	**Topical antibiotic active against *Staphylococcus* and *Streptococcus*** Topical application: Nasal (eliminate nasal carriage) and to the skin 2-4 times per day	*Caution:* Minimal systemic absorption as drug metabolized within the skin.
Nafcillin sodium Nafcil, Unipen Injection Capsule: 250 mg Tablet: 500 mg	**Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q 12 hr IV or IM; weight >2,000 g: 75 mg/kg/24 hr divided q 8 hr IV or IM; postnatal age >7 days weight 1,200-2,000 g: 75 mg/kg/q 8 hr; weight >2,000 g: 100 mg/kg divided q 6-8 hr IV (meningitis: 200 mg/kg/24 hr divided q 6 hr IV) Children: 100-200 mg/kg/24 hr divided q 4-6 hr IV Adults: 4-12 g/24 hr divided q 4-6 hr IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), phlebitis; painful given intramuscularly; oral absorption highly variable and erratic (not recommended) *Adverse effect:* Neutropenia
Nalidixic acid NegGram Tablet: 250, 500, 1,000 mg Suspension: 250 mg/5 mL	**First-generation quinolone effective for short-term treatment of lower urinary tract infections caused by *E. coli, Enterobacter, Klebsiella*, and *Proteus*** Children: 50-55 mg/kg/24 hr divided q 6 hr PO; suppressive therapy 25-33 mg/kg/24 hr divided q 6-8 hr PO Adults: 1 g q 6 hr PO; suppressive therapy: 500 mg q 6 hr PO	*Cautions:* Vertigo, dizziness, rash. Not for use in systemic infections *Drug interactions:* Liquid antacids
Neomycin sulfate Mycifradin Tablet: 500 mg Topical cream, ointment Solution: 125 mg/5 mL	**Aminoglycoside antibiotic used for topical application or orally before surgery to decrease gastrointestinal flora (nonabsorbable) and hyperammonemia** Infants: 50 mg/kg/24 hr divided q 6 hr PO Children: 50-100 mg/kg/24 hr divided q 6-8 hr PO Adults: 500-2,000 mg/dose q 6-8 hr PO	*Cautions:* In patients with renal dysfunction because small amount absorbed may accumulate *Adverse events:* Primarily related to topical application, abdominal cramps, diarrhea, rash Aminoglycoside ototoxicity and nephrotoxicity if absorbed
Nitrofurantoin Furadantin, Furan, Macrodantin Capsule: 50, 100 mg Extended-release capsule: 100 mg Macrocrystal: 50, 100 mg Suspension: 25 mg/5 mL	**Effective in the treatment of lower urinary tract infections caused by Gram-positive and Gram-negative pathogens** Children: 5-7 mg/kg/24 hr divided q 6 hr PO (max dose: 400 mg/24 hr); suppressive therapy 1-2.5 mg/kg/24 hr divided q 12-24 hr PO (max dose: 100 mg/24 hr) Adults: 50-100 mg/24 hr divided q 6 hr PO	*Cautions:* Vertigo, dizziness, rash, jaundice, interstitial pneumonitis. Do not use with moderate to severe renal dysfunction *Drug interactions:* Liquid antacids
Ofloxacin Ocuflox 0.3% ophthalmic solution: 1, 5, 10 mL Floxin 0.3% otic solution: 5, 10 mL	**Quinolone antibiotic for treatment of conjunctivitis or corneal ulcers (ophthalmic solution) and otitis externa or chronic suppurative otitis media (otic solution) caused by susceptible Gram-positive, Gram-negative, anaerobic bacteria, or *C. trachomatis*** *Child >1-12 yr:* Conjunctivitis: 1-2 drops in affected eye(s) q 2-4 hr for 2 days, then 1-2 drops qid for 5 days Corneal ulcers: 1-2 drops q 30 min while awake and at 4 hr intervals at night for 2 days, then 1-2 drops hourly for 5 days while awake, then 1-2 drops q 6 hr for 2 days Otitis externa (otic solution): 5 drops into affected ear bid for 10 days Chronic suppurative otitis media: treat for 14 days *Child >12 yr and adults:* Ophthalmic solution doses same as for younger children. Otitis externa (otic solution): Use 10 drops bid for 10 or 14 days as for younger children	*Adverse events:* Burning, stinging, eye redness (ophthalmic solution), dizziness with otic solution if not warmed

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Oxacillin sodium Prostaphlin Injection Capsule: 250, 500 mg Suspension: 250 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q 12 hr IV; weight >2,000 g: 75 mg/kg/24 hr IV divided q 8 hr IV; postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV divided q 12 hr IV; weight 1,200-2,000 g: 75 mg/kg/24 hr divided q 8 hr IV; weight >2,000 g: 100 mg/kg/24 hr IV divided q 6 hr IV Infants: 100-200 mg/kg/24 hr divided q 4-6 hr IV Children: PO 50-100 mg/kg/24 hr divided q 4-6 hr IV Adults: 2-12 g/24 hr divided q 4-6 hr IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia) Moderate oral bioavailability (35-65%) Primarily renally eliminated *Drug interaction:* Probenecid *Adverse effect:* Neutropenia
Penicillin G Injection Tablets	**Penicillin active against most Gram-positive cocci; *S. pneumoniae* (resistance is increasing), group A *Streptococcus*, and some Gram-negative bacteria (e.g., *N. gonorrhoeae, N. meningitidis*)** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50,000 units/kg/24 hr divided q 12 hr IV or IM (meningitis: 100,000 units/kg/24 hr divided q 12 hr IV or IM); weight >2,000 g: 75,000 units/kg/24 hr divided q 8 hr IV or IM (meningitis: 150,000 units/kg/24 hr divided q 8 hr IV or IM); postnatal age >7 days weight ≤1,200 g: 50,000 units/kg/24 hr divided q 12 hr IV (meningitis: 100,000 units/kg/24 hr divided q 12 hr IV); weight 1,200-2,000 g: 75,000 units/kg/24 hr q 8 hr IV (meningitis: 225,000 units/kg/24 hr divided q 8 hr IV); weight >2,000 g: 100,000 units/kg/24 hr divided q 6 hr IV (meningitis: 200,000 units/kg/24 hr divided q 6 hr IV) Children: 100,000-250,000 units/kg/24 hr divided q 4-6 hr IV or IM (max dose: 400,000 units/kg/24 hr) Adults: 2-24 million units/24 hr divided q 4-6 hr IV or IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with marked renal disease. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin G, benzathine Bicillin Injection	**Long-acting repository form of penicillin effective in the treatment of infections responsive to persistent, low penicillin concentrations (1-4 wk), e.g., group A *Streptococcus* pharyngitis, rheumatic fever prophylaxis** Neonates weight >1,200 g: 50,000 units/kg IM once Children: 300,000-1.2 million units/kg q 3-4 wk IM (max dose: 1.2-2.4 million units/dose) Adults: 1.2 million units IM q 3-4 wk	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin G, procaine Crysticillin Injection	**Repository form of penicillin providing low penicillin concentrations for 12 hr** Neonates weight >1,200 g: 50,000 units/kg/24 hr IM Children: 25,000-50,000 units/kg/24 hr IM for 10 days (max dose: 4.8 million units/dose) Gonorrhea: 100,000 units/kg (max dose: 4.8 million units/24 hr) IM once with probenecid 25 mg/kg (max dose: 1 g) Adults: 0.6-4.8 million units q 12-24 hr IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia) allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin V Pen VK, V-Cillin K Tablet: 125, 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Preferred oral dosing form of penicillin, active against most Gram-positive cocci; *S. pneumoniae* (resistance is increasing), other streptococci, and some Gram-negative bacteria (e.g., N. *gonorrhoeae, N. meningitidis*)** Children: 25-50 mg/kg/24 hr divided q 4-8 hr PO Adults: 125-500 mg q 6-8 hr PO (max dose: 3 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with renal disease. Substantial pathogen resistance. Primarily renally eliminated. Inactivated by penicillinase *Drug interaction:* Probenecid
Piperacillin Pipracil Injection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia, P. aeruginosa,* and *Bacteroides*** Neonates: Postnatal age ≤7 days 150 mg/kg/24 hr divided q 8-12 hr IV; >7 days; 200 mg/kg divided q 6-8 hr IV Children: 200-300 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis: 350-500 mg/kg/24 hr IV Adults: 2-4 g/dose q 4-6 hr (max dose: 24 g/24 hr) IV	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium. Interferes with platelet aggregation/serum sickness-like reaction with high doses; increases in liver function tests. Renally eliminated. Inactivated by penicillinase *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Piperacillin-tazobactam Zosyn Injection	**Extended-spectrum penicillin (piperacillin) combined with a β-lactamase inhibitor (tazobactam) active against *S. aureus, H. influenzae, E. coli, Enterobacter, Serratia, Acinetobacter, P. aeruginosa,* and *Bacteroides*** Children: 300-400 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 3.375 g q 6-8 hr IV or IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium Interferes with platelet aggregation, serum sickness–like reaction with high doses, increases in liver function test results. Renally eliminated *Drug interaction:* Probenecid
Quinupristin/dalfopristin Synercid IV injection: powder for reconstitution, 10 mL contains 150 mg quinupristin, 350 mg dalfopristin	**Streptogramin antibiotic (quinupristin) active against vancomycin-resistant *E. faecium* (VRE) and methicillin-resistant *S. aureus* (MRSA). Not active against *E. faecalis*** Children and adults: VRE: 7.5 mg/kg q 8 hr IV for VRE; skin infections: 7.5 mg/kg q 12 hr IV	*Adverse events:* Pain, edema, or phlebitis at injection site, nausea, diarrhea *Drug interactions*: Synercid is a potent inhibitor of CYP 3A4
Sulfadiazine Tablet: 500 mg	**Sulfonamide antibiotic primarily indicated for the treatment of lower urinary tract infections caused by *E. coli, P. mirabilis,* and *Klebsiella*** Toxoplasmosis: Neonates: 100 mg/kg/24 hr divided q 12 hr PO with pyrimethamine 1 mg/kg/24 hr PO (with folinic acid) Children: 120-200 mg/kg/24 hr divided q 6 hr PO with pyrimethamine 2 mg/kg/24 hr divided q 12 hr PO ≥3 days then 1 mg/kg/24 hr (max dose: 25 mg/24 hr) with folinic acid Rheumatic fever prophylaxis: weight ≤30 kg: 500 mg/24 hr q 24 hr PO; weight >30 kg: 1 g/24 hr q 24 hr PO	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life ~10 hr *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate
Sulfamethoxazole Gantanol Tablet: 500 mg Suspension: 500 mg/5 mL	**Sulfonamide antibiotic used for the treatment of otitis media, chronic bronchitis, and lower urinary tract infections due to susceptible bacteria** Children: 50-60 mg/kg/24 hr divided q 12 hr PO Adults: 1 g/dose q 12 hr PO (max dose: 3 g/24 hr)	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life 12 hr. Initial dose often a loading dose (doubled) *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate
Sulfisoxazole Gantrisin Tablet: 500 mg Suspension: 500 mg/5 mL Ophthalmic solution, ointment	**Sulfonamide antibiotic used for the treatment of otitis media, chronic bronchitis, and lower urinary tract infections caused by susceptible bacteria** Children: 120-150 mg/kg/24 hr divided q 4-6 hr PO (max dose: 6 g/24 hr) Adults: 4-8 g/24 hr divided q 4-6 hr PO	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life ~7-12 hr. Initial dose often a loading dose (doubled) *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate
Ticarcillin Ticar Injection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia, P. aeruginosa,* and *Bacteroides*** Neonates: Postnatal age ≤7 days weight <2,000 g: 150 mg/kg/24 hr divided q 8-12 hr IV; >7 days weight <2,000 g: 225 mg/kg/24 hr divided q 8 hr IV; >7 days weight <1,200 g: 150 mg/kg/24 hr divided q 12 hr IV; weight 1,200-2,000 g: 225 mg/kg/24 hr divided q 8 hr IV; weight >2,000 g: 300 mg/kg/24 hr divided q 6-8 hr IV Children: 200-400 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis: 400-600 mg/kg/24 hr IV Adults: 2-4 g/dose q 4-6 hr IV (max dose: 24 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 5-6 mEq sodium. Interferes with platelet aggregation; increases in liver function tests. Renally eliminated. Inactivated by penicillinase *Drug interaction:* Probenecid
Ticarcillin-clavulanate Timentin Injection	**Extended-spectrum penicillin (ticarcillin) combined with a β-lactamase inhibitor (clavulanate) active against *S. aureus, H. influenzae, Enterobacter, E. coli, Serratia, P. aeruginosa, Acinetobacter,* and *Bacteroides*** Children: 280-400 mg/kg/24 hr q 4-8 hr IV or IM Adults: 3.1 g q 4-8 hr IV or IM (max dose: 18-24 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 5-6 mEq sodium. Interferes with platelet aggregation; increases in liver function tests. Renally eliminated *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Tigecycline Tygacil Injection	**Tetracycline-class antibiotic (glycylcycline) active against Enterobacteriaceae, including extended spectrum β-lactamase producers; streptococci (including VRE); staphylococci (including MRSA); and anaerobes** Children: unknown Adults: 100 mg loading dose followed by 50 mg q 12 hr IV	*Cautions:* Pregnancy; children <8 yr of age; photosensitivity; hypersensitivity to tetracyclines; hepatic impairment (~60% hepatic clearance) *Drug interaction:* Warfarin; mycophenolate mofetil
Tobramycin Nebcin, Tobrex Injection Ophthalmic solution, ointment	**Aminoglycoside antibiotic active against Gram-negative bacilli, especially *E. coli, Klebsiella, Enterobacter, Serratia, Proteus,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days, weight 1,200-2,000 g: 2.5 mg/kg q 12-18 hr IV or IM; weight >2,000 g: 2.5 mg/kg q 12 hr IV or IM; postnatal age >7 days, weight 1,200-2,000 g: 2.5 mg/kg q 8-12 hr IV or IM; weight >2,000 g: 2.5 mg/kg q 8 hr IV or IM Children: 2.5 mg/kg/24 hr divided q 8-12 hr IV or IM. Alternatively may administer 5-7.5 mg/kg/24 hr IV. Preservative-free preparation for intraventricular or intrathecal use: neonate: 1 mg/24 hr; children: 1-2 mg/24 hr; adults: 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q 8 hr IV or IM	*Cautions: S. pneumoniae*, other *Streptococcus,* and anaerobes are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs *Target serum concentrations:* Peak 6-12 mg/L; trough <2 mg/L
Trimethoprim Proloprim, Trimpex Tablet: 100, 200 mg	**Folic acid antagonist effective in the prophylaxis and treatment of *E. coli, Klebsiella, P. mirabilis,* and *Enterobacter* urinary tract infections; *P. carinii* pneumonia** Children: For urinary tract infection: 4-6 mg/kg/24 hr divided q 12 hr PO Children >12 yr and adults: 100-200 mg q 12 hr PO. *P. carinii* pneumonia (with dapsone): 15-20 mg/kg/24 hr divided q 6 hr for 21 days PO	*Cautions:* Megaloblastic anemia, bone marrow suppression, nausea, epigastric distress, rash *Drug interactions:* Possible interactions with phenytoin, cyclosporine, rifampin, warfarin
Vancomycin Vancocin, Lyphocin Injection Capsule: 125 mg, 250 mg Suspension	**Glycopeptide antibiotic active against most Gram-positive pathogens including staphylococci (including MRSA and coagulase-negative staphylococci), *S. pneumoniae* including penicillin-resistant strains, *Enterococcus* (resistance is increasing), and *C. difficile*–associated colitis** Neonates: Postnatal age ≤7 days, weight <1,200 g: 15 mg/kg/24 hr divided q 24 hr IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 12-18 hr IV; weight >2,000 g: 30 mg/kg/24 hr divided q 12 hr IV; postnatal age >7 days, weight <1,200 g: 15 mg/kg/24 hr divided q 24 hr IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 8-12 hr IV; weight >2,000 g: 45 mg/kg/24 hr divided q 8 hr IV Children: 45-60 mg/kg/24 hr divided q 8-12 hr IV; *C. difficile*–associated colitis; 40-50 mg/kg/24 hr divided q 6-8 hr PO.40-50 mg/kg/24 hr divided q 6-8 hr PO	*Cautions:* Ototoxicity and nephrotoxicity particularly when co-administered with other ototoxic and nephrotoxic drugs Infuse IV over 45-60 min. Flushing (red man syndrome) associated with rapid IV infusions, fever, chills, phlebitis (central line is preferred). Renally eliminated *Target serum concentrations:* Peak (1 hr after 1 hr infusion) 30-40 mg/L; trough 5-10 mg/L

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Resistance to penicillin is mediated by a variety of mechanisms (see Table 180-1). The production of β-lactamase is a common mechanism exhibited by many organisms that may be overcome, with variable success, by including a β-lactamase inhibitor with the penicillin. Such combination products (ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam) are potentially very useful for management of resistant isolates, but only if the resistance is β-lactamase mediated. Notably, *S. aureus* and *S. pneumoniae* mediate β-lactam resistance through mechanisms other than β-lactamase production, rendering these combination agents of little value for the management of β-lactam–resistant *S. aureus* and *S. pneumoniae* infections.

Table 180-4 lists adverse reactions to penicillins.

Cephalosporins

Cephalosporins differ structurally from penicillins insofar as the β-lactam ring exists as a 6-member ring, compared to the 5-member ring structure of the penicillins. These agents are widely used in pediatric practice, both in oral and parenteral formulations (Table 180-5). The **first-generation cephalosporins** (e.g., cefazolin, a parenteral formulation, and cephalexin, an oral equivalent) are commonly used for management of skin and soft-tissue infections caused by susceptible strains of *S. aureus* and group A *Streptococcus*. The **second-generation cephalosporins** (e.g., cefuroxime, cefoxitin) have better activity against Gram-negative bacterial infections than do first-generation cephalosporins and are used to treat respiratory tract infections, urinary tract infections, and skin and soft-tissue infections. A variety of orally administered second-generation agents (cefaclor, cefprozil, loracarbef, cefpodoxime) are commonly used in the outpatient management of sinopulmonary infections and otitis media. The **third-generation cephalosporins** (cefotaxime, ceftriaxone, and ceftazidime) are typically used for serious pediatric infections, including meningitis and sepsis. Ceftazidime is highly active against most strains of

Table 180-4 Adverse Reactions to Penicillins*

TYPE OF REACTION	FREQUENCY (%)	OCCURS MOST FREQUENTLY WITH*
ALLERGIC		
Immunoglobulin E antibody	0.004-0.4	Penicillin G
• Anaphylaxis		
• Early urticaria (<72 hr)		
Cytotoxic antibody	Rare	Penicillin G
• Hemolytic anemia		
Antigen–antibody complex disease	Rare	Penicillin G
• Serum sickness		
Delayed hypersensitivity	4-8	Ampicillin
• Contact dermatitis		
IDIOPATHIC	4-8	Ampicillin
Skin rash		
Fever		
Late-onset urticaria		
GASTROINTESTINAL	2-5	
Diarrhea	2-5	Ampicillin
Enterocolitis	<1	Ampicillin
HEMATOLOGIC		
Hemolytic anemia	Rare	Penicillin G
Neutropenia	1-4	Penicillin G, nafcillin, oxacillin, piperacillin
Platelet dysfunction	3	Ticarcillin
HEPATIC		
Elevated serum aspartate transaminase level	1-4	Flucloxacillin, nafcillin, oxacillin
ELECTROLYTE DISTURBANCE		
Sodium overload	Variable	Ticarcillin
Hypokalemia	Variable	Ticarcillin
Hyperkalemia—acute	Rare	Penicillin G
NEUROLOGIC		
Seizures	Rare	Penicillin G
Bizarre sensations		Procaine penicillin
RENAL		
Interstitial nephritis	<1%	Any penicillin

*All the reactions can occur with any of the penicillins.

Adapted from Mandell GL, Bennett JE, Dolin R, editors: Principles and practice of infectious diseases, *ed 7. Philadelphia, 2010, Elsevier, Table 21-7.*

P. aeruginosa, making this a useful agent for febrile, neutropenic oncology patients. Ceftriaxone should not be mixed or reconstituted with a calcium-containing product, such as Ringer or Hartmann solution or parenteral nutrition containing calcium, because particulate formation can result. Cases of fatal reactions with ceftriaxone–calcium precipitates in lungs and kidneys in neonates have been reported. **A fourth-generation cephalosporin,** called cefepime, has activity against *P. aeruginosa* and retains good activity against methicillin-susceptible staphylococcal infections. A **fifth-generation cephalosporin**, ceftaroline has been licensed. It is the active metabolite of the prodrug ceftaroline fosamil and is a broad-spectrum cephalosporin with bactericidal activity against resistant Gram-positive organisms, including MRSA, and common Gram-negative pathogens. It has been licensed in adult patients for use in skin and soft-tissue infection and community-acquired bacterial pneumonia. It is indicated for MRSA only in the treatment of skin and soft-tissue infection and not MRSA pneumonia. Its activity is attributed to its ability to bind to penicillin-binding protein 2a with higher affinity than other β-lactams. Its role in pediatric practice remains to be defined. Another fifth-generation cephalosporin, ceftobiprole, has been approved for use in Canada and the European Union. Another novel cephalosporin with activity against *P. aeruginosa*, ceftolozane, is approaching licensure and will be combined with the β-lactamase inhibitor, tazobactam, in its final licensed formulation.

Table 180-6 lists adverse reactions to cephalosporins.

Carbapenems

The carbapenems include imipenem formulated in combination with cilastatin, meropenem, ertapenem, and doripenem. The basic structure of these agents is similar to that of β-lactam antibiotics, and these drugs have a similar mechanism of action. The carbapenems provide the broadest spectrum of antibacterial activity of any licensed class of antibiotics and are active against Gram-positive, Gram-negative, and anaerobic organisms. Among the carbapenems, meropenem is the only agent licensed for treatment of pediatric meningitis. At this time, ertapenem and doripenem are not approved for pediatric use. Importantly, MRSA and *E. faecium* are not susceptible to carbapenems. Carbapenems also tend to be poorly active against *Stenotrophomonas maltophilia,* rendering their use for cystic fibrosis patients who are infected with this organism problematic. Ertapenem is poorly active against *P. aeruginosa* and *Acinetobacter* species and should be avoided when these pathogens are encountered. Although imipenem-cilastatin is the first carbapenem approved for clinical use and the carbapenem with which there is the greatest clinical experience, this antibiotic unfortunately has a propensity to cause seizures in children, particularly in the setting of intercurrent meningitis. Accordingly, meropenem is typically more suitable for pediatric use, where meningitis is commonly a consideration.

Other carbapenems in various stages of clinical trials include panipenem, biapenem, razupenem, tomopenem, and tebipenem/pivoxil (the first oral carbapenem). Panipenem and biapenem are licensed in Japan, but there is minimal experience with pediatric dosing.

Glycopeptides

Glycopeptide antibiotics include vancomycin and teicoplanin, the less commonly available analog. These agents are bactericidal and act via inhibition of cell wall biosynthesis. The antimicrobial activity of the glycopeptides is limited to Gram-positive organisms, including *S. aureus,* coagulase-negative staphylococci, pneumococcus, enterococci, *Bacillus,* and *Corynebacterium.* Vancomycin is frequently employed in pediatric practice and is of particular value for serious infections, including meningitis, caused by MRSA and penicillin- and cephalosporin-resistant *S. pneumoniae.* Vancomycin is also commonly used for infections in the setting of fever and neutropenia in oncology patients, in combination with other antibiotics (see Chapter 178), and for infections associated with indwelling medical devices (see Chapter 179). Oral formulations of vancomycin are occasionally used to treat pseudomembranous colitis caused by *Clostridium difficile* infections; intrathecal therapy may also be used for selected CNS infections. Vancomycin must be administered with care because of its propensity to produce red man syndrome, which is a reversible adverse effect that is rare in young children and can typically be readily managed by slowing the rate of infusion of the drug. Newer glycopeptides antibiotics include oritavancin, dalbavancin, and the glycolipodepsipeptide agent, ramoplanin. Telavancin has been approved by FDA for the treatment of skin and soft-tissue infections suspected or known to be caused by MRSA for situations where other alternatives are not suitable.

Aminoglycosides

Aminoglycoside antibiotics include streptomycin, kanamycin, gentamicin, tobramycin, netilmicin, and amikacin. The most commonly used aminoglycosides in pediatric practice are gentamicin and tobramycin. They exert their mechanism of action via inhibition of bacterial protein synthesis. Although they are most commonly used to treat Gram-negative infections, the aminoglycosides are broad-spectrum agents: they have activity against *S. aureus* and provide synergistic activity against group B streptococcus, *L. monocytogenes,* viridans

Table 180-5 Classification of Parenteral and Oral Cephalosporins

CEPHALOSPORINS	FIRST GENERATION	SECOND GENERATION	CEPHAMYCINS	THIRD GENERATION	FOURTH GENERATION	FIFTH GENERATION
Parenteral	Cefazolin (Ancef, Kefzol) Cephalothin (Keflin, Seffin) Cephapirin (Cefadyl) Cephradine (Velosef)	Cefamandole (Mandol) Cefonicid (Monocid) Cefuroxime (Kefurox, Zinacef)	Cefmetazole (Zefazone) Cefotetan (Cefotan) Cefoxitin (Mefoxin)	Cefoperazone (Cefobid) Cefotaxime (Claforan) Ceftazidime (Fortaz) Ceftizoxime (Cefizox) Ceftriaxone (Rocephin)	Cefepime (Maxipime) Cefpirome (Cefrom) Ceftolozane (combined with tazobactam; CXA-101)	Ceftaroline (Teflaro) Ceftobiprole (Zeftera)
Oral	Cefadroxil (Duricef, Ultracef) Cephalexin (Keflex, Biocef, Keftab) Cephradine (Velosef)	Cefaclor (Ceclor) Cefprozil (Cefzil) Cefuroxime-axetil (Ceftin) Loracarbef (Lorabid)		Cefdinir (Omnicef) Cefditoren (Spectracef) Cefixime (Suprax) Cefpodoxime (Vantin) Ceftibuten (Cedax)		

Adapted from Mandell GL, Bennett JE, Dolin R, editors: Principles and practice of infectious diseases, *ed 7. Philadelphia, 2010, Elsevier, Table 22-1.*

streptococci, corynebacteria JK, *Pseudomonas, Staphylococcus epidermidis,* and *Enterococcus* when coadministered with a β-lactam agent. Aminoglycoside use has decreased with the development of newer alternatives, but they still play a key role in pediatric practice in the management of neonatal sepsis, urinary tract infections, Gram-negative sepsis, and complicated intraabdominal infections; infections in cystic fibrosis patients (including both parenteral and aerosolized forms of therapy); and in oncology patients with fever and neutropenia. Aminoglycosides, in particular streptomycin, are also important in the management of *Francisella tularensis, Mycobacterium tuberculosis,* and atypical mycobacterial infections. Toxicities of aminoglycoside therapy include nephrotoxicity and ototoxicity (cochlear and/or vestibular), and serum levels as well as renal function and hearing should be monitored for patients on long-term therapy. Toxicities of aminoglycosides may be reduced by the use of once-daily dosing regimens with appropriate monitoring of serum levels. Hypokalemia, volume depletion, hypomagnesemia, and other nephrotoxic drugs may increase the renal toxicity of aminoglycosides. A rare complication of aminoglycosides is neuromuscular blockade, which may occur in the presence of other neuromuscular blocking agents and in the setting of infant botulism.

Tetracyclines

The tetracyclines (tetracycline hydrochloride, doxycycline, demeclocycline, and minocycline) are bacteriostatic antibiotics that exhibit their antimicrobial effect by binding to the bacterial 30S ribosomal subunit, inhibiting protein translation. These agents have a broad spectrum of antimicrobial activity against Gram-positive and Gram-negative bacteria, rickettsia, and some parasites. The oral bioavailability of these agents facilitates oral dosing for many infections, including Rocky Mountain spotted fever, ehrlichiosis, Lyme disease, and malaria. Tetracyclines must be prescribed judiciously to children younger than 9 yr of age, because they can cause staining of teeth, hypoplasia of dental enamel, and abnormal bone growth in this age group. Tigecycline, a semisynthetic derivative of minocycline, is licensed in the United States. It is a parenteral agent of a new class of antibiotics (glycylcyclines). It has a broader spectrum of activity (bacteriostatic) than traditional tetracyclines, but retains the side–effect profile of tetracyclines. Tigecycline is active against tetracycline-resistant Gram-positive and Gram-negative pathogens, including MRSA, and possibly VRE, but not *Pseudomonas.*

Complications of tetracyclines include eosinophilia, leukopenia and thrombocytopenia (tetracycline), pseudotumor cerebri, anorexia, emesis and nausea, candidal superinfection, hepatitis, photosensitivity, and a hypersensitivity reaction (urticaria, asthma exacerbation, facial edema, dermatitis) as well as a systemic lupus erythematosus–like syndrome (minocycline). The FDA issued a black box warning regarding tigecycline in 2013 based on a meta-analysis of 10 studies that showed increased mortality among patients receiving this drug. A salutary side effect of demeclocycline has been identified: it is occasionally used as an off-label treatment of hyponatremia resulting from the syndrome of inappropriate antidiuretic hormone.

Sulfonamides

Trimethoprim and the sulfonamides are bacteriostatic agents that inhibit the bacterial folate synthesis pathway, in the process impairing both nucleic acid and protein synthesis. Sulfonamides interfere with the synthesis of dihydropteroic acid from paraaminobenzoic acid, whereas trimethoprim acts at a site further downstream, interfering with synthesis of tetrahydrofolic acid from dihydrofolic acid. The sulfonamides are available in both parenteral and oral formulations. Although there have historically been a large number of sulfonamide antibiotics developed for clinical use, relatively few remain available for pediatric practice. The most important agent is the combination of trimethoprim-sulfamethoxazole (TMP-SMZ), which is commonly used for treatment of urinary tract infections. TMP-SMZ has also emerged as a commonly prescribed agent for staphylococcal skin and soft-tissue infections, since this antibiotic retains activity against MRSA. TMP-SMZ also plays a unique role in immunocompromised patients, as a prophylactic and therapeutic agent for *Pneumocystis jiroveci* infection. Other commonly used sulfonamides include sulfisoxazole, which is useful in the management of urinary tract infections, and sulfadiazine, which is a drug of choice in the treatment of toxoplasmosis.

Table 180-6	Potential Adverse Effects of Cephalosporins	
TYPE	**SPECIFIC**	**FREQUENCY**
Hypersensitivity	Rash Urticaria Serum sickness Anaphylaxis	1-3% <1% <1% 0.01%
Gastrointestinal	Diarrhea Nausea, vomiting Transient transaminase elevation Biliary sludge	1-19% 1-6% 1-7% 20-46%*
Hematologic	Eosinophilia Neutropenia Thrombocytopenia Hypoprothrombinemia Impaired platelet aggregation Hemolytic anemia	1-10% <1% <1-3% <1% <1% <1%
Renal	Interstitial nephritis	<1%
Central nervous system	Seizures Encephalopathy	<1% <1%
False-positive laboratory	Coombs positive Glucosuria Serum creatinine	3% Rare Rare
Other	Drug fever Disulfiram-like reaction* Superinfection Phlebitis Calcium-antibiotic precipitation (ceftriaxone)	Rare Rare Rare Rare Unknown; is associated with embolic events

*Cephalosporins with thiomethyl tetrazole ring (MTT) side chain.
Adapted from: Mandell GL, Bennett JE, Dolin R, editors: Principles and practice of infectious diseases, *ed 7. Philadelphia, 2010, Elsevier, Table 22-6.*

Macrolides

The macrolide antibiotics most commonly used in pediatric practice include erythromycin and the newer agents, clarithromycin and azithromycin. This class of antimicrobials exerts its antibiotic effect through binding to the 50S subunit of the bacterial ribosome, producing a block in elongation of bacterial polypeptides. Clarithromycin is metabolized to 14-hydroxy clarithromycin, and interestingly this active metabolite also has potent antimicrobial activity. The spectrum of antibiotic activity includes many Gram-positive bacteria. Unfortunately, resistance to these agents among *S. aureus* and group A *Streptococcus* is fairly widespread, limiting the usefulness of macrolides for many skin and soft-tissue infections and for streptococcal pharyngitis. Azithromycin and clarithromycin have demonstrated efficacy for otitis media. All of the members of this class have an important role in the management of pediatric respiratory infections, including atypical pneumonia caused by *M. pneumoniae, Chlamydia pneumoniae,* and *Legionella pneumophila,* as well as infections caused by *Bordetella pertussis.*

Telithromycin is a ketolide antibiotic derived from erythromycin. It was initially approved by the FDA for the treatment in adults of mild to moderate community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute sinusitis, having good activity against the agents causing these infections (*S. pneumoniae*, *M. pneumoniae, C. pneumoniae,* and *L. pneumophila* for community-acquired pneumonia; *M. catarrhalis* and *H. influenzae* for sinusitis). Reports of liver failure and myasthenia gravis from telithromycin in particular prompted the withdrawal of the indication for sinusitis and bronchitis by the FDA.

Drug interactions are common with erythromycin and telithromycin and to a lesser extent with clarithromycin. These agents can inhibit the CYP 3A4 enzyme system, resulting in increased levels of certain drugs such as astemizole, cisapride, statins, pimozide, and theophylline. Itraconazole may increase macrolide levels, while rifampin, carbamazepine, and phenytoin may decrease macrolide levels. There are few reported adverse drug interactions with azithromycin. *Cross-resistance may develop between a macrolide and the subsequent use of clindamycin.*

Lincosamides

The prototype of the lincosamide class of antibiotics is clindamycin, which acts at the ribosomal level to exert its antimicrobial effect. The 50S subunit of the bacterial ribosome is the molecular target of this agent. Its spectrum of activity includes Gram-positive aerobes and anaerobes. Clindamycin has no significant activity against Gram-negative organisms. An important role for clindamycin has emerged in the management of MRSA infections. Because of its outstanding penetration into body fluids (excluding the CNS) and tissues and bone, clindamycin can be utilized for therapy of serious infections caused by MRSA. Clindamycin is also useful in the management of invasive group A *Streptococcus* infections and in the management of many anaerobic infections, often in combination with a β-lactam. There is a form of **inducible clindamycin resistance** exhibited by some strains of MRSA; therefore, consultation with the clinical microbiology laboratory is necessary before treating a serious MRSA infection with clindamycin. Pseudomembranous colitis, a complication of clindamycin therapy commonly encountered in adults, is seldom observed in pediatric patients. Clindamycin also plays an important role in the treatment of malaria and babesiosis (when coadministered with quinine), *P. jiroveci* pneumonia (when coadministered with primaquine), and toxoplasmosis.

Quinolones

The fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, besifloxacin) are antimicrobials that inhibit bacterial DNA replication by binding to the topoisomerases of the target pathogen, inhibiting the bacterial enzyme DNA gyrase. This class has very broad-spectrum activity against both Gram-positive and Gram-negative organisms. Some of the fluoroquinolones exhibit activity against penicillin-resistant *S. pneumoniae* as well as MRSA. These agents uniformly exhibit excellent activity against Gram-negative pathogens, including the *Enterobacteriaceae* and respiratory tract pathogens such as *M. catarrhalis* and *H. influenzae.* Quinolones are also very active against pathogens associated with atypical pneumonia, particularly *M. pneumoniae* and *L. pneumophila.*

Although these agents are not approved for use in children, there is a reasonable body of evidence that the fluoroquinolones are generally safe, well tolerated, and effective against a variety of bacterial infections commonly encountered in pediatric practice. Parenteral quinolones are appropriate for critically ill patients with Gram-negative infections. The use of oral quinolones in stable outpatients may also be reasonable for treatment of infections that would otherwise require parenteral antibiotics (*P. aeruginosa* soft-tissue infections such as osteochondritis) or selected genitourinary tract infections. However, they should be reserved for situations where no other oral antibiotic alternative is feasible. In 2013, the FDA announced that it was changing the warning labels for fluoroquinolones to more adequately describe the risk of permanent peripheral neuropathy associated with this class of antimicrobials. Additional risks include arrhythmias and retinal detachment. Moreover, in situations of overuse (such as typhoid fever and gonococcal infection), organisms have been demonstrated to rapidly develop resistance. Thus, the use of fluoroquinolones in pediatric practice should still be approached with continued caution, and consultation with an expert is recommended.

Streptogramins and Oxazolidinones

The emergence of highly resistant Gram-positive organisms, in particular VRE, has necessitated development of new classes of antibiotics.

One such class that is especially useful for resistant Gram-positive infections is the streptogramins. The currently licensed agent in this category is **dalfopristin-quinupristin,** which is available in a parenteral formulation. It is appropriate for treatment of MRSA, coagulase-negative staphylococci, penicillin-susceptible and penicillin-resistant *S. pneumoniae,* and vancomycin-resistant *E. faecium* but not *E. faecalis.*

Another licensed class of antibiotics for highly resistant Gram-positive infections is the oxazolidinone class. The prototype in this group is **linezolid,** which is available in both oral and parenteral formulations and is approved for use in pediatric patients. Its mechanism of action involves inhibition of ribosomal protein synthesis. It is indicated for MRSA, VRE, coagulase-negative staphylococci, and penicillin-resistant *S. pneumoniae*. There is little information on dalfopristin-quinupristin and linezolid in treatment of CNS infections, and neither agent is approved for pediatric meningitis. Linezolid can cause anemia and thrombocytopenia and is a monoamine oxidase inhibitor.

Daptomycin

Daptomycin is a novel member of the cyclic lipopeptide class of antibiotics. Its spectrum of activity includes virtually all Gram-positive organisms, including *E. faecalis* and *E. faecium* (including VRE) and *S. aureus* (including MRSA). The structure of daptomycin is a 13-member amino acid peptide linked to a 10-carbon lipophilic tail, which results in a novel mechanism of action of disruption of the bacterial membrane through the formation of transmembrane channels. These channels cause leakage of intracellular ions, leading to depolarization of the cellular membrane and inhibition of macromolecular synthesis. A theoretical advantage of daptomycin for serious infections is its bactericidal activity against MRSA and enterococci. It is administered IV. Experience in children is limited. Myopathy and elevations in creatine phosphokinase have been described. An FDA warning has been issued linking some cases of eosinophilic pneumonitis to the use of daptomycin. Daptomycin is inactivated by surfactant and should not be used to treat pneumonia.

Miscellaneous Agents

Although rarely used today because of safety concerns and limited availability, **chloramphenicol** occasionally plays a role in the management of pediatric infections, particularly those involving the CNS. This agent binds peptidyl transferase, a component of the 50S ribosome, inhibiting bacterial protein synthesis. **Metronidazole**, which functions by disruption of DNA synthesis, has a unique role as an antianaerobic agent and also possesses antiparasitic and anthelmintic activity. **Rifampin** is a rifamycin antibiotic that inhibits bacterial RNA polymerase and has a major role in the management of tuberculosis. It is also of value in the management of other bacterial infections in pediatric patients, usually used as a second (synergistic) agent in the treatment of *S. aureus* infections or to eliminate nasopharyngeal colonization of *H. influenzae* type b or *N. meningitidis.* **Rifaximin** is a nonabsorbed rifamycin that has been used as an adjunct agent to treat patients with multiple recurrences of *C. difficile* infection. The emerging crisis in antimicrobial resistance has also necessitated the "rediscovery" of antimicrobial agents seldom used in clinical practice in recent decades, such as **colistin (colistimethate sodium).** This agent is a member of the polymyxin family of antibiotics (polymyxin E). Polymyxins have a general structure consisting of a cyclic peptide with hydrophobic tails. After binding to lipopolysaccharide in the outer membrane of Gram-negative bacteria, polymyxins disrupt both the outer and inner membranes, leading to cell death. Colistin is broadly active against the *Enterobacteriaceae* family, including *P. aeruginosa.* It is also active against extended-spectrum β-lactamase– and carbapenemase-producing strains. Toxicities are chiefly renal and neurologic.

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Section 4

Gram-Positive Bacterial Infections

Chapter 181

Staphylococcus

James T. Gaensbauer and James K. Todd

Staphylococci are hardy, aerobic, Gram-positive bacteria that grow in pairs and clusters and are ubiquitous as normal flora of humans and present on fomites and in dust. They are resistant to heat and drying and may be recovered from nonbiologic environments weeks to months after contamination. Strains are classified as *Staphylococcus aureus* if they are coagulase positive or as 1 of the many species of **coagulase-negative staphylococci** (e.g., *Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus haemolyticus,* etc.). Often, *S. aureus* produces a yellow or orange pigment and β-hemolysis on blood agar and *S. epidermidis* produces a white pigment with variable hemolysis results, although definitive species confirmation requires further testing. *S. aureus* has many virulence factors that mediate various serious diseases, whereas coagulase-negative staphylococci tend to be less pathogenic unless an indwelling foreign body (e.g., intravascular catheter) is present. Since 2000, *S. aureus* strains resistant to β-lactam antibiotics, commonly referred to as methicillin-resistant *S. aureus* (MRSA) have become a significant problem in both community and hospital settings. Vancomycin resistance is rare, but MRSA have been reported with an elevated vancomycin minimal inhibitory concentration (≥ 1.5 mg/L).

181.1 *Staphylococcus aureus*

James T. Gaensbauer and James K. Todd

S. aureus is the most common cause of pyogenic infection of the skin and soft tissues. Bacteremia (primary and secondary) is common and can be associated with or result in osteomyelitis, suppurative arthritis, pyomyositis, deep abscesses, pneumonia, empyema, endocarditis, pericarditis, and rarely meningitis. Toxin-mediated diseases, including food poisoning, staphylococcal scarlet fever, scalded skin syndrome, and toxic shock syndrome (TSS), are caused by certain *S. aureus* strains.

ETIOLOGY

Strains of *S. aureus* can be identified and characterized by the virulence factors they produce. These factors tend to play 1 or more of 4 pathogenic roles in human disease: *S. aureus* protecting the organism from host defenses, localizing infection, causing local tissue damage, and affecting noninfected sites through toxin elaboration.

Most strains of *S. aureus* possess factors that protect the organism from host defenses. Many staphylococci produce a loose polysaccharide capsule, or **slime layer,** which may interfere with opsonophagocytosis. Production of clumping factor and/or **coagulase** differentiates *S. aureus* from coagulase-negative staphylococci. Clumping factor interacts with fibrinogen to cause large clumps of organisms, interfering with effective phagocytosis. Coagulase causes plasma to clot by interacting with fibrinogen and this may have an important role in localization of infection (abscess formation). **Protein A** is present in most strains of *S. aureus* but not coagulase-negative staphylococci and reacts specifically with immunoglobulin G (IgG_1, IgG_2, and IgG_4). It is

located on the outermost coat of the cell wall and can absorb serum immunoglobulins, preventing antibacterial antibodies from acting as opsonins and thus inhibiting phagocytosis. Other enzymes elaborated by staphylococci include **catalase** (inactivates hydrogen peroxide, promoting intracellular survival), **penicillinase** or **β-lactamase** (inactivates penicillin at the molecular level), and lipase (associated with skin infection).

Many strains of *S. aureus* produce substances that cause local tissue destruction. A number of immunologically distinct hemolysins that act on cell membranes and cause tissue necrosis have been identified (α-toxin, β-hemolysin, δ-hemolysin). Much attention has been given to the **Panton-Valentine leukocidin,** a protein that *S. aureus* combines with phospholipid in the leukocytic cell membrane, producing increased permeability and eventual death of the cell. Strains of *S. aureus* that produce Panton-Valentine leukocidin are associated with more-severe and invasive skin disease, pneumonia, and osteomyelitis. Many strains of *S. aureus* release 1 or more exotoxins. **Exfoliatins A and B** are serologically distinct proteins that produce localized (bullous impetigo) or generalized (scalded skin syndrome, staphylococcal scarlet fever) dermatologic manifestations (see Chapter 659). Exfoliatins produce skin separation by splitting the desmosome and altering the intracellular matrix in the stratum granulosum.

S. aureus can produce more than 20 distinct enterotoxins (types A-V). Ingestion of preformed enterotoxin, particularly types A or B, can result in **food poisoning,** resulting in vomiting and diarrhea and, in some cases, profound hypotension. By 10 yr of age, almost all individuals have antibodies to at least 1 enterotoxin.

Toxic shock syndrome toxin-1 (TSST-1) is associated with TSS related to menstruation and focal staphylococcal infection. TSST-1 is a superantigen that induces production of interleukin-1 and tumor necrosis factor, resulting in hypotension, fever, and multisystem involvement. Enterotoxins A and B also may be associated with nonmenstrual TSS.

S. aureus also possesses intrinsic factors that can contribute to pathogenesis, including **teichoic acid** in the cell wall, which mediates adhesion to mucosal cells proteins that promote adhesion to fibrinogen, fibronectin, collagen, and other human proteins. Expression of proteins that mediate antibiotic resistance is also of critical importance. Though historically sensitive to penicillin, *S. aureus* isolates now almost universally produce penicillinase, an enzyme that disrupts the β-lactam structure of penicillin. Production of altered penicillin-binding proteins (PBPs) in the bacterial cell wall mediates resistance to penicillinase resistant antibiotics; an **altered PBP-2A** is responsible for the methicillin resistance of MRSA isolates. MRSA strains appear to be at least as virulent as their methicillin-sensitive counterparts.

EPIDEMIOLOGY

Approximately 20-40% of normal individuals carry at least 1 strain of *S. aureus* in the anterior nares at any given time, with intermittent carriage occurring in up to 70% of individuals. The organisms may be transmitted from the nose to the skin, where colonization is more transient. Persistent umbilical, vaginal, and perianal carriage may also occur. Many neonates are colonized within the 1st wk of life. Rates of colonization with MRSA in the general population are typically less than 2% but have increased since 2000. MRSA colonization rates greater than 20-30% have been reported in higher risk populations with significant healthcare exposure.

Exposure to *S. aureus* generally occurs by autoinoculation or direct contact with the hands of other colonized individuals. Heavily colonized nasal carriers (often aggravated by a viral upper respiratory tract infection) are particularly effective disseminators. Spread via fomites is rare, though an outbreak occurring in a high school football team was attributed to sharing towels. Infection control policies in healthcare facilities, particularly those emphasizing good hand hygiene, have been shown to decrease rates of nosocomial staphylococcal infection.

Outside of the hospital setting, outbreaks of staphylococcal disease, in particular disease due to methicillin-resistant strains, have been reported among athletes, military personnel, young children, veterinarians, injection drug users, and inmates in correctional facilities. Increased disease frequency is noted among household contacts of a MRSA colonized or infected individual. Skin infections caused by *S. aureus* are considerably more prevalent among persons living in low socioeconomic circumstances and particularly among those in tropical climates.

The burden of staphylococcal disease is significant. Most important is the role of *S. aureus,* including MRSA, in hospital acquired infections, including infections of the bloodstream, infection of surgical sites, and ventilator-associated pneumonia. *S. aureus* is a significant cause of morbidity and mortality in neonatal intensive care units. Two population-based studies suggested a decline in rates of MRSA-related hospital-acquired infection, possibly reflecting the benefits of aggressive infection control procedures.

Community-acquired staphylococcal infections are estimated to result in 14 million outpatient healthcare visits. In 2005 an estimated 478,000 hospitalizations were associated with *S. aureus* infection in the United States, over half of which were caused by MRSA.

PATHOGENESIS

Except in the case of food poisoning resulting from ingestion of preformed enterotoxins, disease associated with *S. aureus* typically begins with colonization as described above. Subsequent disease manifestations in susceptible individuals results either directly from tissue invasion or injury caused by various toxins and enzymes produced by the organism (Fig. 181-1).

The most significant risk factor for the development of infection is disruption of intact skin, including breaches from wounds, skin disease such as eczema, epidermolysis bullosa or burns, ventriculoperitoneal shunts, and indwelling intravascular or intrathecal catheters. Additional risk factors include corticosteroid treatment, malnutrition, and azotemia. Antibiotic therapy with a drug to which *S. aureus* is resistant favors colonization and the development of infection. Viral infections of the respiratory tract, especially influenza virus, may predispose to secondary bacterial infection with staphylococci in certain individuals.

Congenital defects in chemotaxis (Job syndrome, Chédiak-Higashi syndrome, Wiskott-Aldrich syndrome) and defective phagocytosis and killing (neutropenia, chronic granulomatous disease) increase the risk for staphylococcal infections. Patients with HIV infection have neutrophils that are defective in their ability to kill *S. aureus* in vitro. Patients with recurrent staphylococcal infection should be evaluated for immune defects, especially those involving neutrophil dysfunction.

Infants may acquire type-specific humoral immunity to staphylococci transplacentally. Older children and adults develop antibodies to staphylococci as a result of colonization or minor infections. Antibody to the various *S. aureus* toxins appears to protect against those specific toxin-mediated diseases, but humoral immunity does not necessarily protect against focal or disseminated *S. aureus* infection with the same organisms.

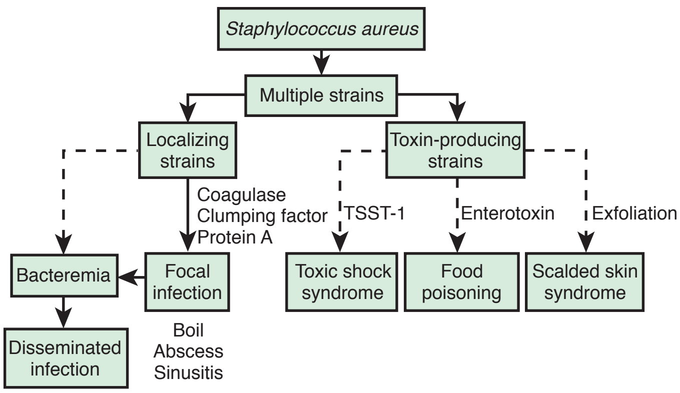

Figure 181-1 Relationship of virulence factors and diseases associated with *Staphylococcus aureus.* TSST-1, toxic shock syndrome toxin-1.

CLINICAL MANIFESTATIONS

Signs and symptoms vary with the location of the infection, which is most commonly the skin but may be any tissue. Disease states of various degrees of severity are generally a result of local suppuration, systemic dissemination with metastatic infection, or systemic effects of toxin production.

Newborn

S. aureus is an important cause of neonatal infections (see Chapter 109.5).

Skin

S. aureus is an important cause of pyogenic skin infections, including impetigo contagiosa, ecthyma, bullous impetigo, folliculitis, hydradenitis, furuncles (boils), carbuncles (multiple coalesced boils), paronychia, staphylococcal scalded skin syndrome, and staphylococcal scarlet fever. Infection may also cause superinfection of other noninfectious skin disease, for example, eczema, or bug bites. Recurrent furunculosis is associated with repeated episodes of pyoderma over months to years. Recurrent skin and soft-tissue infections are commonly noted with community-associated MRSA and often affect the lower extremities and buttocks. *S. aureus* is also an important cause of traumatic and surgical wound infections and can cause deep soft-tissue involvement, including cellulitis and rarely necrotizing fasciitis.

Respiratory Tract

Infections of the upper respiratory tract (otitis media, sinusitis) caused by *S. aureus* are rare, in particular considering the frequency with which the anterior nares are colonized. *S. aureus* sinusitis is relatively common in children with cystic fibrosis or defects in leukocyte function and may be the only focus of infection in some children with TSS. Suppurative parotitis is a rare infection, but *S. aureus* is a common cause of this infection. A membranous **tracheitis** that complicates viral croup may be a result of infection with *S. aureus,* but other organisms are also possible. Patients typically have high fever, leukocytosis, and evidence of severe upper airway obstruction. Direct laryngoscopy or bronchoscopy shows a normal epiglottis with subglottic narrowing and thick, purulent secretions within the trachea. Treatment requires careful airway management and appropriate antibiotic therapy.

Pneumonia (see Chapter 400) caused by *S. aureus* may be primary or secondary after a viral infection such as influenza. Hematogenous pneumonia may be secondary to septic emboli from right-sided endocarditis or septic thrombophlebitis, with or without the presence of intravascular devices. Inhalation pneumonia is caused by alteration of mucociliary clearance, leukocyte dysfunction, or bacterial adherence initiated by a viral infection. Common symptoms and signs include high fever, abdominal pain, tachypnea, dyspnea, and localized or diffuse bronchopneumonia or lobar disease. *S. aureus* often causes a **necrotizing pneumonitis** that may be associated with early development of empyema, pneumatoceles, pyopneumothorax, and bronchopleural fistulas.

Sepsis

S. aureus bacteremia and sepsis may be primary or associated with any localized infection. The onset may be acute and marked by nausea, vomiting, myalgia, fever, and chills. Organisms may localize subsequently at any site (usually a single deep focus) but are found especially in the heart valves, lungs, joints, bones, muscles, and deep tissue abscesses.

In some instances, especially in young adolescent males, disseminated *S. aureus* disease occurs, characterized by fever, persistent bacteremia despite antibiotics, and focal involvement of 2 or more separate tissue sites (skin, bone, joint, kidney, lung, liver, heart). In these cases, endocarditis and septic thrombophlebitis must be ruled out. All patients with primary *S. aureus* bacteremia, especially those with persistently positive blood cultures should be evaluated for endocarditis with transthoracic, and if that is negative, transesophageal, echocardiography.

Muscle

Localized staphylococcal abscesses in muscle sometimes without septicemia have been called **pyomyositis.** This disorder is reported most frequently from tropical areas and is termed tropical pyomyositis, but also occurs frequently in the United States in otherwise healthy children. Multiple abscesses occur in 30-40% of cases. History may include prior trauma at the site of the abscess. Surgical drainage and appropriate antibiotic therapy are essential.

Bones and Joints

S. aureus is the most common cause of osteomyelitis and suppurative arthritis in children (see Chapters 684 and 685).

Central Nervous System

Meningitis (see Chapter 603.1) caused by *S. aureus* is not common; it is associated with penetrating cranial trauma and neurosurgical procedures (craniotomy, cerebrospinal fluid [CSF] shunt placement), and less frequently with endocarditis, parameningeal foci (epidural or brain abscess), diabetes mellitus, or malignancy. The CSF profile of *S. aureus* meningitis is indistinguishable from that in other forms of bacterial meningitis.

Heart

S. aureus is a common cause of acute endocarditis (see Chapter 437) on native valves, and results in high rates of morbidity and mortality. Perforation of heart valves, myocardial abscesses, heart failure, conduction disturbances, acute hemopericardium, purulent pericarditis, and sudden death may ensue.

Kidney

S. aureus is a common cause of renal and perinephric abscess (see Chapter 538), usually of hematogenous origin. Pyelonephritis and cystitis caused by *S. aureus* are unusual.

Toxic Shock Syndrome

S. aureus is the principal cause of TSS (see Chapter 181.2), which should be suspected in anyone with fever, shock, and/or a scarlet fever-like rash.

Intestinal Tract

Staphylococcal enterocolitis rarely follows overgrowth of normal bowel flora by *S. aureus*, which can occur as a result of broad-spectrum oral antibiotic therapy. Diarrhea is associated with blood and mucus. Peritonitis associated with *S. aureus* in patients receiving long-term ambulatory peritoneal dialysis usually involves the catheter tunnel. Removal of the catheter is required to achieve a bacteriologic cure.

Food poisoning (see Chapter 340) may be caused by ingestion of **preformed** enterotoxins produced by staphylococci in contaminated foods. The source of contamination is often colonized or infected food workers. Approximately 2-7 hr after ingestion of the toxin, sudden, severe vomiting begins. Watery diarrhea may develop, but fever is absent or low. Symptoms rarely persist longer than 12-24 hr. Rarely, shock and death may occur.

DIAGNOSIS

The diagnosis of *S. aureus* infection depends on isolation of the organism from nonpermissive sites such as cellulitis aspirates, abscess cavities, blood, bone or joint aspirates, or other sites of infection. Swab cultures of surfaces are not as useful, as they may reflect surface contamination rather than the true cause of infection. Tissue samples or fluid aspirates in a syringe provide the best culture material. Cellulitic lesions are ideally cultured using a needle aspirate from the most inflamed area, inoculated directly into a blood culture bottle; use of injected saline and targeting the leading edge are less effective. Isolation from the nose or skin does not necessarily imply causation because these sites may be normally colonized sites. Because of the high prevalence of MRSA, the increasing severity of *S. aureus* infections, and the fact that bacteremia is not universally present even in severe *S. aureus* infections, it is important to obtain a nonpermissive culture of any

potential focus of infection as well as a blood culture prior to starting antibiotic treatment. The organism can be grown readily in liquid and on solid media. After isolation, identification is made on the basis of Gram stain and coagulase, clumping factor, and protein A reactivity. Patterns of susceptibility to antibiotics should be assessed in serious cases, as antimicrobial resistance is increasingly common. Identification of MRSA infection or colonization has become increasingly important, from both a therapeutic and infection control standpoint. Inoculation of samples onto selective (e.g., cefoxitin-containing) media or use of latex agglutination to identify altered PBP-2a in positive cultures are 2 commonly used methods. Molecular (polymerase chain reaction) techniques are being used increasingly for the rapid identification of colonized patients on admission to the hospital or intensive care unit. Polymerase chain reaction for ribosomal RNA is emerging as an technique for identifying bacterial pathogens and may eventually complement or replace traditional culture methods.

Diagnosis of *S. aureus* food poisoning is usually made on the basis of epidemiologic and clinical findings. Food suspected of contamination may be cultured and can be tested for enterotoxin.

Differential Diagnosis

Many of the clinical entities discussed above can also be caused by other bacterial pathogens, and consideration of the differential is particularly important when making empiric antibiotic choices prior to definitive identification of the offending pathogen. Skin lesions caused by *S. aureus* may be indistinguishable from those caused by group A streptococci, although the former usually expand slowly, while the latter are prone to spread more rapidly and can be very aggressive. Fluctuant skin and soft-tissue lesions also can be caused by other organisms, including *Mycobacterium tuberculosis,* atypical mycobacteria, *Bartonella henselae* (cat-scratch disease), *Francisella tularensis,* and various fungi, among others. Noncavitary *S. aureus* pneumonia can be difficult to differentiate from more common etiologies, although children with *S. aureus* are generally more ill. *S. aureus* pneumonia is often suspected after failure to improve on standard treatment which does not cover *Staphylococcus*, or on the basis of chest roentgenograms that reveal pneumatoceles, pyopneumothorax, or lung abscess (Fig. 181-2). Other etiologies of cavitary pneumonias include *Klebsiella pneumoniae* and *M. tuberculosis*. In bone and joint infections, culture is the only reliable way to differentiate *S. aureus* from other less-common etiologies including group A streptococci and in young children, *Kingella kingae*.

TREATMENT

Antibiotic therapy alone is rarely effective in individuals with undrained abscesses or with infected foreign bodies. Loculated collections of purulent material should be relieved by incision and drainage. Foreign bodies should be removed, if possible. Therapy always should be initiated with an antibiotic consistent with the local staphylococcal susceptibility patterns as well as the severity of infection. For most patients with serious *S. aureus* infection, intravenous treatment is recommended until the patient has become afebrile and other signs of infection have improved. Oral therapy is often continued for a period of time, especially in patients with chronic infection or underlying host defense problems. Serious *S. aureus* infections, with or without abscesses, tend to persist and recur, necessitating prolonged therapy.

The antibiotic used as well as the dose, route, and duration of treatment depend on the site and severity of infection, the response of the patient to treatment, and the susceptibility of the organisms recovered. Treatment of *S. aureus* osteomyelitis (see Chapter 684), meningitis (see Chapter 603.1), and endocarditis (see Chapter 437) is discussed in the respective chapters on these diagnoses.

Initial treatment for serious infections thought to be caused by methicillin-susceptible *S. aureus* (MSSA) should include semisynthetic penicillin (e.g., nafcillin) or a first-generation cephalosporin (e.g., cefazolin). Penicillin and ampicillin are not appropriate, because more than 90% of all staphylococci isolated, regardless of source, are resistant to these agents. Addition of a β-lactamase inhibitor (clavulanic acid, sulbactam, tazobactam) to a penicillin-based drug also confers antistaphylococcal activity but has no effect on MRSA. The spectrum of these agents (which includes Gram-negative bacteria) can be an advantage when broad empiric coverage is needed, but more narrow coverage should be selected once *S. aureus* is identified. Antistaphylococcal penicillins and cephalosporins do not provide activity against MRSA. For initial treatment for penicillin-allergic individuals and those with suspected serious infections caused by MRSA, vancomycin can be used. Serum levels of vancomycin should be monitored, with serum trough concentrations of 10-20 μg/mL, depending on the case. Many, but not all MSSA and community-acquired MRSA strains are susceptible to clindamycin, and initial treatment with IV clindamycin, followed by a transition to oral clindamycin has been effective in bone, joint, and soft-tissue infection. Inducible clindamycin resistance in isolates initially reported as susceptible must be ruled out by D-test or molecular methods. Clindamycin is bacteriostatic and should not be used to treat endocarditis, brain abscess, or meningitis caused by *S. aureus*. Given that the mechanism of action of clindamycin involves inhibition or protein synthesis, many experts use clindamycin to treat *S. aureus* toxin–mediated illnesses (TSS) to inhibit toxin production.

MRSA is also resistant to carbapenems and is unreliably susceptible to the quinolones. Rare vancomycin intermediate and vancomycin-resistant strains of *S. aureus* have also been reported, mostly in patients being treated with vancomycin. Linezolid, daptomycin, and

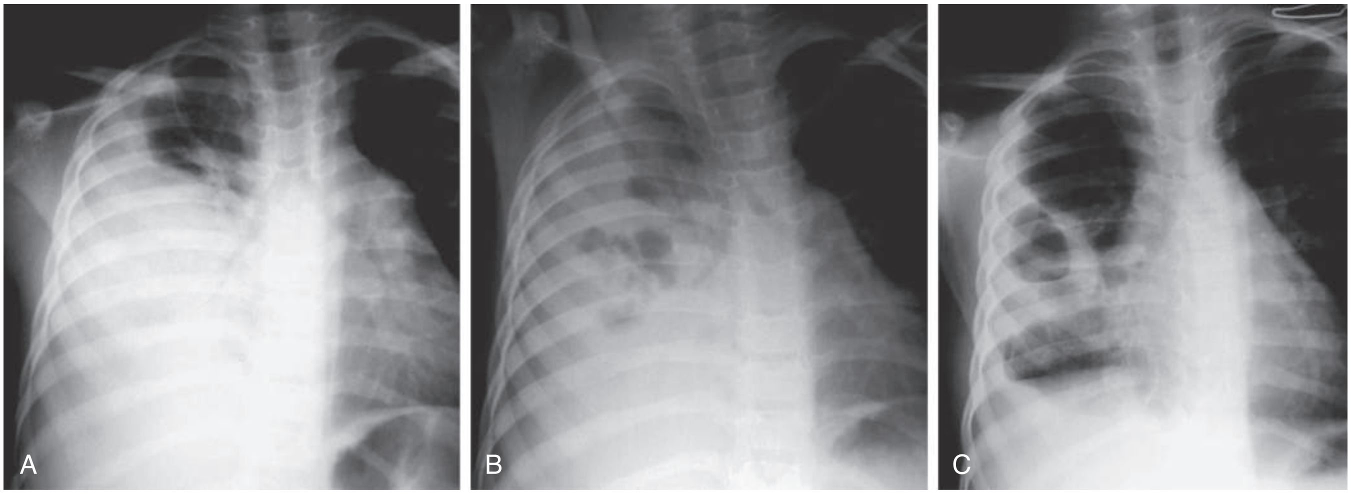

Figure 181-2 Pneumatocele formation. **A,** A 5 yr old child with *Staphylococcus aureus* pneumonia initially demonstrated consolidation of the right middle and lower zones. **B,** Seven days later, multiple lucent areas are noted as pneumatoceles develop. **C,** Two weeks later, significant resolution is evident, with a rather thick-walled pneumatocele persisting in the right midzone associated with significant residual pleural thickening. *(From Kuhn JP, Slovis TL, Haller JO:* Caffey's pediatric diagnostic imaging, *ed 10. Philadelphia, 2004, Mosby, pp. 1003–1004.)*

quinupristin-dalfopristin are useful for serious *S. aureus* infections highly resistant to other antibiotics (Table 181-1). Nonetheless, most *S. aureus* isolates with higher minimal inhibitory concentrations against vancomycin (≥1.5 mg/L) have been successfully treated with appropriate dosing of vancomycin. Ceftaroline (IV), a broad-spectrum antistaphylococcal cephalosporin, is approved for MRSA skin infections in adults, but pediatric experience is limited. Three new FDA approved antibiotics for adults with skin and soft tissue MRSA infections are oritavancin, dalbavancin, and tedizolid. Rifampin or gentamicin may be added to a β-lactam or vancomycin for synergy in serious infections such as endocarditis, particularly when prosthetic valve material is involved.

In many infections, oral antimicrobials may be substituted to complete the course of treatment after an initial period of parenteral therapy and determination of antimicrobial susceptibilities, or can be utilized as initial treatment in less-severe infections. Dicloxacillin (50-100 mg/kg/24 hr divided 4 times per day PO) and cephalexin (25-100 mg/kg/24 hr divided 3-4 times per day PO) are absorbed well orally and are effective against MSSA. Amoxicillin-clavulanate (40-80 mg amoxicillin/kg/24 hr divided 3 times per day PO) is also effective, as is clindamycin (30-40 mg/kg/24 hr divided 3-4 times per day PO). Trimethoprim-sulfamethoxazole may be an effective oral antibiotic for many strains of both MSSA and MRSA. Despite in vitro susceptibility of *S. aureus* to ciprofloxacin and other quinolone antibiotics, these agents should not be used in serious staphylococcal infections, because their use is associated with rapid development of resistance.

The duration of oral therapy depends on the response as determined by the clinical response and in some cases, roentgenographic and laboratory findings.

Table 181-1 Parenteral Antimicrobial Agent(s) for Treatment of Bacteremia and Other Serious *Staphylococcus aureus* Infections

SUSCEPTIBILITY	ANTIMICROBIAL AGENTS	COMMENTS
I. INITIAL EMPIRIC THERAPY (ORGANISM OF UNKNOWN SUSCEPTIBILITY)		
Drugs of choice:	Vancomycin (15 mg/kg Q6-H + nafcillin or oxacillin)	For life-threatening infections (i.e., septicemia, endocarditis, CNS infection); linezolid could be substituted if the patient has received several recent courses of vancomycin
	Vancomycin (15 mg/kg Q8H)	For non–life-threatening infection without signs of severe sepsis (e.g., skin infection, cellulitis, osteomyelitis, pyarthrosis) when rates of MRSA colonization and infection in the community are substantial
	Clindamycin	For non–life-threatening infection without signs of severe sepsis when rates of MRSA colonization and infection in the community are substantial and prevalence of clindamycin resistance is low
II. METHICILLIN-SUSCEPTIBLE, PENICILLIN-RESISTANT *S. AUREUS*		
Drugs of choice:	Nafcillin or oxacillin†	
Alternatives (depending on susceptibility results):	Cefazolin	
	Clindamycin	Only for patients with a serious penicillin allergy and clindamycin-susceptible strain
	Vancomycin	Only for penicillin- and cephalosporin-allergic patients
	Ampicillin + sulbactam	
III. MRSA (OXACILLIN MIC, 4 µG/ML OR GREATER)		
A. Healthcare-Associated (Multidrug-Resistant)		
Drugs of choice:	Vancomycin + gentamicin†	
Alternatives: susceptibility testing results available before alternative drugs are used	Trimethoprim-sulfamethoxazole	
	Linezolid‡	
	Quinupristin-dalfopristin‡	
	Fluoroquinolones	Not recommended for people younger than 18 yr of age or as monotherapy
B. Community (Not Multidrug-Resistant)		
Drugs of choice:	Vancomycin + gentamicin†	For life-threatening infections
	Clindamycin (if strain susceptible)	For pneumonia, septic arthritis, osteomyelitis, skin or soft tissue infections
	Trimethoprim-sulfamethoxazole	For skin or soft tissue infections
Alternatives:	Vancomycin	
IV. VANCOMYCIN INTERMEDIATELY SUSCEPTIBLE OR *S. AUREUS*† (MIC, 4 TO 16 µG/ML)‡		
Drugs of choice:	Optimal therapy is not known	Dependent on in vitro susceptibility test results
	Linezolid‡	
	Daptomycin§	
	Quinupristin-dalfopristin‡	
	Tigecycline‡	
Alternatives:	Vancomycin + linezolid ± gentamicin	
	Vancomycin + trimethoprim-sulfamethoxazole†	

†One of the adjunctive agents, gentamicin or rifampin, should be added to the therapeutic regimen for life-threatening infections such as endocarditis or CNS infection or infections with a vancomycin-intermediate *S. aureus* strain. Consultation with an infectious diseases specialist should be considered to determine which agent to use and duration of use.

‡Linezolid, quinupristin-dalfopristin, and tigecycline are agents with activity in vitro and efficacy in adults with multidrug-resistant, Gram-positive organisms, including *S. aureus*. Because experience with these agents in children is limited, consultation with an infectious diseases specialist should be considered before use.

§Daptomycin is active in vitro against multidrug-resistant, Gram-positive organisms, including *S. aureus*, but has not been evaluated in children. Daptomycin is approved by the US FDA only for the treatment of complicated skin and skin structure infections and for *S. aureus* bloodstream infections. Daptomycin is ineffective for treatment of pneumonia and is not indicated for patients 18 yr of age and older.

CNS, central nervous system; MRSA, methicillin-resistant *S. aureus*; MIC, minimum inhibitory concentration.

From Pickering LK, editor: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

PROGNOSIS

Untreated *S. aureus* septicemia is associated with a high fatality rate, which has been reduced significantly by appropriate antibiotic treatment. *S. aureus* pneumonia can be fatal at any age but is more likely to be associated with high morbidity and mortality in young infants or in patients whose therapy has been delayed. Prognosis also may be influenced by numerous host factors, including nutrition, immunologic competence, and the presence or absence of other debilitating diseases. In most cases with abscess formation, surgical drainage is necessary.

PREVENTION

S. aureus infection is transmitted primarily by direct contact. Strict attention to handwashing techniques is the most effective measure for preventing the spread of staphylococci from 1 individual to another (see Chapter 173). Use of a hand wash containing chlorhexidine or alcohol is recommended. In hospitals or other institutional settings, all persons with acute *S. aureus* infections should be isolated until they have been treated adequately. There should be constant surveillance for nosocomial *S. aureus* infections within hospitals. When MRSA is recovered, strict isolation of affected patients has been shown to be the most effective method for preventing nosocomial spread of infection. Thereafter, control measures should be directed toward identification of new isolates and strict isolation of newly colonized or infected patients. Clusters of cases may be defined by molecular typing. If associated with a singular molecular strain, it may also be necessary to identify colonized hospital personnel and attempt to eradicate carriage in affected individuals.

A number of protocols exist aimed at decolonization in patients with recurrent *S. aureus* skin infection, particularly in individuals colonized with MRSA. These often involve various combinations of decontaminating baths (hypochlorite, 1 teaspoon common bleach solution per gallon of water, or chlorhexidine 4% soap), an appropriate oral antibiotic, and nasal mupirocin. Although success is not universal, recurrent infections may be reduced, particularly when eradication is done in both patient and frequent or household contacts. Most cases of mild, recurrent disease will resolve in time without these measures.

Food poisoning (see Chapter 340) may be prevented by excluding individuals with *S. aureus* infections of the skin from the preparation and handling of food. Prepared foods should be eaten immediately or refrigerated appropriately to prevent multiplication of *S. aureus* with which the food may have been contaminated.

Bibliography is available at Expert Consult.

181.2 Toxic Shock Syndrome

James T. Gaensbauer and James K. Todd

Toxic shock syndrome (TSS) is an acute and potentially severe illness characterized by fever, hypotension, erythematous rash with subsequent desquamation on the hands and feet, and multisystem involvement, including vomiting, diarrhea, myalgias, nonfocal neurologic abnormalities, conjunctival hyperemia, and strawberry tongue.

ETIOLOGY

TSS is caused by TSST-1–producing and some enterotoxin-producing strains of *S. aureus,* which may colonize the vagina or cause focal sites of staphylococcal infection.

EPIDEMIOLOGY

TSS continues to occur in the United States in men, women, and children, with highest rates in menstruating women 15-25 yr of age. **Nonmenstrual TSS** is associated with *S. aureus* infected nasal packing and wounds, sinusitis, tracheitis, pneumonia, empyema, abscesses, burns, osteomyelitis, and primary bacteremia. Most strains of *S. aureus* associated with TSS are methicillin susceptible. While USA300, the predominant isolate of community-acquired MRSA in the United States, does not contain genes expressing the most common TSS superantigens, MRSA-associated TSS does occasionally occur.

PATHOGENESIS

The primary toxin associated with TSS is TSST-1, though a significant proportion of nonmenstrual TSS is caused by 1 or more staphylococcal enterotoxins. These toxins act as a superantigens, which trigger cytokine release causing massive loss of fluid from the intravascular space and end-organ cellular injury. Epidemiologic and in vitro studies suggest that these toxins are selectively produced in a clinical environment consisting of a neutral pH, a high P_{CO_2}, and an "aerobic" P_{O_2}, which are the conditions found in abscesses and the vagina with tampon use during menstruation. The risk factors for symptomatic disease include a nonimmune host colonized with a toxin-producing organism, which is exposed to focal growth conditions (menstruation plus tampon use or abscess) that induce toxin production. It appears that some hosts may have a varied cytokine response to exposure to TSST-1, helping to explain a spectrum of severity of TSS that may include staphylococcal scarlet fever. The overall mortality rate of treated patients is 3-5% with early treatment.

Approximately 90% of adults have antibody to TSST-1 without a history of clinical TSS, suggesting that most individuals are colonized at some point with a toxin-producing organism at a site (anterior nares) where low-grade or inactive toxin exposure results in an immune response without disease.

CLINICAL MANIFESTATIONS

The diagnosis of TSS is based on clinical manifestations (Table 181-2). The onset is abrupt, with high fever, vomiting, and diarrhea, and is accompanied by sore throat, headache, and myalgias. A diffuse erythematous macular rash (sunburn-like or scarlatiniform) appears within 24 hr and may be associated with hyperemia of pharyngeal, conjunctival, and vaginal mucous membranes. A strawberry tongue is common. Symptoms often include alterations in the level of consciousness, oliguria, and hypotension, which in severe cases may progress to shock and disseminated intravascular coagulation. Complications, including acute respiratory distress syndrome, myocardial dysfunction, and renal failure, are commensurate with the degree of shock. Recovery occurs within 7-10 days and is associated with

Table 181-2	Diagnostic Criteria of Staphylococcal Toxic Shock Syndrome
MAJOR CRITERIA (ALL REQUIRED)	
Acute fever; temperature >38.8°C (101.8°F)	
Hypotension (orthostatic, shock; blood pressure below age-appropriate norms)	
Rash (erythroderma with convalescent desquamation)	
MINOR CRITERIA (ANY 3 OR MORE)	
Mucous membrane inflammation (vaginal, oropharyngeal or conjunctival hyperemia, strawberry tongue)	
Vomiting, diarrhea	
Liver abnormalities (bilirubin or transaminase greater than twice upper limit of normal)	
Renal abnormalities (urea nitrogen or creatinine greater than twice upper limit of normal, or greater than 5 white blood cells per high-power field)	
Muscle abnormalities (myalgia or creatinine phosphokinase greater than twice upper limit of normal)	
Central nervous system abnormalities (alteration in consciousness without focal neurologic signs)	
Thrombocytopenia (100,000/mm^3 or less)	
EXCLUSIONARY CRITERIA	
Absence of another explanation	
Negative blood cultures (except occasionally for *Staphylococcus aureus*)	

Data from Pickering LK, editor: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

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desquamation, particularly of palms and soles; hair and nail loss have also been observed after 1-2 mo. Immunity to the toxins is slow to develop, so recurrences can occur, especially if there is inadequate antibiotic treatment and/or recurrent tampon use. Many cases of apparent scarlet fever without shock may be caused by TSST-1-producing *S. aureus* strains.

DIAGNOSIS

There is no specific laboratory test, and diagnosis is dependent on meeting certain clinical and laboratory criteria in the absence of an alternate diagnosis (see Fig. 181-2). Appropriate tests reveal involvement of multiple organ systems, including the hepatic, renal, muscular, gastrointestinal, cardiopulmonary, and central nervous systems. Bacterial cultures of the associated focus (vagina, abscess) before administration of antibiotics usually yield *S. aureus,* although this is not a required element of the definition.

Differential Diagnosis

Group A *Streptococcus* can cause a similar TSS-like illness, termed **streptococcal TSS** (see Chapter 183), which is often associated with severe streptococcal sepsis or a focal streptococcal infection such as cellulitis, necrotizing fasciitis, or pneumonia.

Kawasaki disease closely resembles TSS clinically but is usually not as severe or rapidly progressive. Both conditions are associated with fever unresponsive to antibiotics, hyperemia of mucous membranes, and an erythematous rash with subsequent desquamation. However, many of the clinical features of TSS are usually absent or rare in Kawasaki disease, including diffuse myalgia, vomiting, abdominal pain, diarrhea, azotemia, hypotension, acute respiratory distress syndrome, and shock (see Chapter 166). Kawasaki disease typically occurs in children younger than 5 yr. Scarlet fever, Rocky Mountain spotted fever, leptospirosis, toxic epidermal necrolysis, sepsis, and measles must also be considered in the differential diagnosis.

TREATMENT

Recommended antibiotic therapy for TSS should include the combination of a β-lactamase–resistant antistaphylococcal antibiotic (nafcillin, oxacillin, or a first-generation cephalosporin) plus clindamycin to reduce toxin production. Though TSS is most commonly caused by MSSA, clinicians should consider use of vancomycin in place of the β-lactam in areas where MRSA rates are very high, when hospital acquired MRSA is suspected, and when the clinical picture overlaps with staphylococcal sepsis. Drainage of the vagina by removal of any retained tampons in menstrual TSS and of focally infected sites in nonmenstrual TSS is important for successful treatment. Antistaphylococcal therapy and avoidance of tampon use may also reduce the risk for recurrence in menstrual TSS.

TSS often requires intensive supportive care, including aggressive fluid replacement to prevent or treat hypotension, renal failure, and cardiovascular collapse. Inotropic agents may be needed to treat shock; corticosteroids and intravenous immunoglobulin may be helpful in severe cases.

PREVENTION

The risk for acquiring menstrual TSS (1-2 cases/100,000 menstruating women) is low. Changing tampons at least every 8 hr is recommended. If a fever, rash, or dizziness develops during menstruation, any tampon should be removed immediately and medical attention should be sought.

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181.3 Coagulase-Negative Staphylococci

James K. Todd

At present, there are approximately 30 species of coagulase negative staphylococci (CoNS) affecting or colonizing humans. *Staphylococcus epidermidis*, and less commonly *Staphylococcus hominis, S. haemolyticus,* and others, are widely distributed on the skin and are significant causes of nosocomial infection, particularly in the bloodstream of neonatal and immunocompromised hosts, in surgical patients and those with indwelling catheters and other medical devices. *S. saprophyticus* is a common cause of urinary tract infection. *Staphylococcus lugdunensis* has been increasingly recognized as cause of potentially severe infection.

EPIDEMIOLOGY

In the United States, CoNS are the most common cause of hospital acquired infection, particularly in neonatal units. In many instances, growth of CoNS from clinical specimens represents contamination from skin, rather than a cause of true disease, posing significant challenges for clinicians and infection control specialists. CoNS are normal inhabitants of the human skin, throat, mouth, vagina, and urethra. *S. epidermidis* is the most common and persistent species, representing 65-90% of staphylococci present on the skin and mucous membranes. Colonization, sometimes with strains acquired from hospital staff, precedes infection; alternatively, direct inoculation during surgery may initiate infection of CSF shunts, prosthetic valves, or indwelling vascular lines. For epidemiologic purposes, CoNS can be identified on the basis of molecular DNA methods.

PATHOGENESIS

CoNS produce an **exopolysaccharide** protective biofilm, or **slime layer,** that surrounds the organism and may enhance adhesion to foreign surfaces, resist phagocytosis, and impair penetration of antibiotics. However, the low virulence of CoNS usually requires the presence of another factor for development of clinical disease. Of these, the most significant is the presence of an indwelling catheter or other medical device, including hemodialysis shunts and grafts, CSF shunts (meningitis), peritoneal dialysis catheters (peritonitis), pacemaker wires and electrodes (local infection), prosthetic cardiac valves (endocarditis), and prosthetic joints (arthritis). Other risk factors for the development of infection include immature or compromised immunity and significant exposure to antibiotics.

CLINICAL MANIFESTATIONS

Bacteremia

CoNS, specifically *S. epidermidis,* are the most common cause of nosocomial bacteremia, usually in association with central vascular catheters. In neonates, CoNS bacteremia, with or without a central venous catheter, may be manifested as apnea, bradycardia, temperature instability, abdominal distention, hematochezia, meningitis in the absence of CSF pleocytosis, and cutaneous abscesses. Persistence of positive blood cultures despite adequate antimicrobial therapy is common, particularly when catheters are not removed. In older children, CoNS bacteremia is indolent and is not usually associated with overwhelming septic shock.

Endocarditis

Infection of native heart valves or the right atrial wall secondary to an infected thrombosis at the end of a central line may produce endocarditis. *S. epidermidis* and other CoNS may rarely produce native valve subacute endocarditis in previously normal patients without a central venous catheter. CoNS is a common cause of prosthetic valve endocarditis, presumably a result of inoculation at the time of surgery. Infection of the valve sewing ring, with abscess formation and dissection, produces valve dysfunction, dehiscence, arrhythmias, or valve obstruction (see Chapter 437). *S. lugdunensis* has been increasingly associated with severe endocardial infection in adults, but its role as a significant pediatric pathogen is unclear.

Central Venous Catheter Infection

Central venous catheters become infected through the exit site and subcutaneous tunnel, which provide a direct path to the bloodstream. *S. epidermidis* is the most frequent pathogen, owing in part to its high rate of cutaneous colonization. **Line sepsis** is usually manifested as

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fever and leukocytosis; tenderness and erythema may be present at the exit site or along the subcutaneous tunnel. Catheter thrombosis may complicate line sepsis. Disease severity with CoNS is often less severe than other etiologies of line infection.

Cerebrospinal Fluid Shunts

CoNS, introduced at the time of surgery, is the most common pathogen associated with CSF shunt meningitis. Most (70-80%) infections occur within 2 mo of the operation and are manifested by signs of meningeal irritation, fever, increased intracranial pressure (headache), or peritonitis from the intraabdominal position of the distal end of the shunt tubing.

Urinary Tract Infection

S. saprophyticus is a common cause of primary urinary tract infections in sexually active females. Manifestations are similar to those characteristics of urinary tract infection caused by *Escherichia coli* (see Chapter 538). CoNS also cause asymptomatic urinary tract infection in hospitalized patients with urinary catheters and after urinary tract surgery or transplantation.

DIAGNOSIS

Because *S. epidermidis* is a common skin inhabitant and may contaminate poorly collected blood cultures, differentiating bacteremia from contamination is often difficult. True bacteremia should be suspected if blood cultures grow rapidly (within 24 hr), ≥2 blood cultures are positive with the same CoNS strain, cultures from both line and peripheral sites are positive, and clinical and laboratory signs and symptoms compatible with CoNS sepsis are present and subsequently resolve with appropriate therapy. No blood culture that is positive for CoNS in a neonate or patient with intravascular catheter should be considered contaminated without careful assessment of the foregoing criteria and examination of the patient. Before initiating presumptive antimicrobial therapy in such patients, it is always prudent to draw 2 separate blood cultures to facilitate subsequent interpretation if CoNS is grown.

TREATMENT

Most CoNS strains are resistant to methicillin. *Vancomycin is the drug of choice for methicillin-resistant strains*. The addition of rifampin to vancomycin may increase antimicrobial efficacy. Other antibiotics with good in vitro activity against CoNS may be considered in certain circumstances. These include linezolid, quinupristin-dalfopristin, and daptomycin. Antibiotics with potential activity include teicoplanin, clindamycin, and trimethoprim-sulfamethoxazole. Removal of an infected catheter is ideal. However, this is not always possible owing to the therapeutic requirements of the underlying disease (nutrition for short bowel syndrome, chemotherapy for malignancy). A trial of intravenous vancomycin is indicated to attempt to preserve the use of the central line as long as systemic manifestations of infection are not severe. Antibiotic therapy given through an infected central venous catheter (alternating lumens if multiple), and the use of antibiotic locks in conjunction with systemic therapy may increase the likelihood of curing CoNS line sepsis without line removal. In many cases of CoNS infection associated with foreign bodies, the catheter, valve, or shunt must be removed to ensure a cure. Prosthetic heart valves and CSF shunts usually have to be removed to treat the infection adequately.

Peritonitis caused by *S. epidermidis* in patients on continuous ambulatory peritoneal dialysis is an infection that may be treated with intravenous or intraperitoneal antibiotics without removing the dialysis catheter. If the organism is resistant to methicillin, vancomycin adjusted for renal function is appropriate therapy. Unlike most CoNS, *S. saprophyticus* is usually methicillin susceptible, and urinary tract infection can typically be treated with a first-generation cephalosporin (cephalexin), amoxicillin-clavulanic acid, or trimethoprim-sulfamethoxazole.

PROGNOSIS

Most episodes of CoNS bacteremia respond successfully to antibiotics and removal of any foreign body that is present. Poor prognosis is associated with malignancy, neutropenia, and infected prosthetic or native heart valves. CoNS increases morbidity, the duration of hospitalization, and mortality rates among patients with underlying complicated illnesses.

PREVENTION

Iatrogenic morbidity and resource utilization caused by contaminated blood cultures, can be reduced by the use of gloves, good skin preparatory techniques, and through the use of trained, dedicated personnel to draw blood cultures. Prevention of CoNS infection of indwelling lines include basic techniques such as good hand hygiene, adequate decontamination of hubs and ports prior to access, minimizing frequency of access, and frequent replacement of external connections/infusion materials. Antibiotic impregnated catheters, antiseptic impregnated dressings, and the use of antibiotic or ethanol locks are being evaluated for reducing line-associated bloodstream infections.

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Chapter 182

Streptococcus pneumoniae (Pneumococcus)

James B. Wood and Timothy R. Peters

Streptococcus pneumoniae (pneumococcus) is a very important pathogen that kills more than 1 million children each year. Childhood pneumococcal disease is prevalent and commonly severe, causes numerous clinical syndromes, and is a major cause of life-threatening pneumonia, bacteremia, and meningitis. Antimicrobial resistance in pneumococcus is a major public health problem, with 15-30% of isolates worldwide classified as multidrug-resistant (MDR; resistant to ≥3 classes of antibiotics). Pneumococcal polysaccharide-protein conjugate vaccines (PCVs) developed for infants have been highly successful in the control of disease caused by virulent vaccine-specific serotypes. Epidemiologic surveillance reveals a dynamic pneumococcal ecology with emergence of highly virulent, MDR serotypes. Ongoing vaccine development and distribution efforts remain our best approach to control of this threat to childhood health.

ETIOLOGY

S. pneumoniae is a Gram-positive, lancet-shaped, polysaccharide encapsulated diplococcus, occurring occasionally as individual cocci or in chains. More than 90 serotypes have been identified by type-specific capsular polysaccharides. Antisera to some pneumococcal polysaccharides crossreact with other pneumococcal types, defining serogroups (e.g., 6A and 6B). Encapsulated strains cause most serious disease in humans. Capsular polysaccharides impede phagocytosis. Virulence is related in part to capsular size, but pneumococcal types with capsules of the same size can vary widely in virulence.

On solid media, *S. pneumoniae* forms unpigmented, umbilicated colonies surrounded by a zone of incomplete (α) hemolysis. *S. pneumoniae* is bile soluble (i.e., 10% deoxycholate) and Optochin-sensitive. *S. pneumoniae* is closely related to the viridans groups of *Streptococcus mitis*, which typically overlap phenotypically with pneumococci. The conventional laboratory definition of pneumococci continues to rely on bile and Optochin sensitivity, although considerable confusion occurs in distinguishing pneumococci and other α-hemolytic streptococci. Pneumococcal capsules can be microscopically visualized and typed by exposing organisms to type-specific antisera that combine with their unique capsular polysaccharide, rendering the capsule

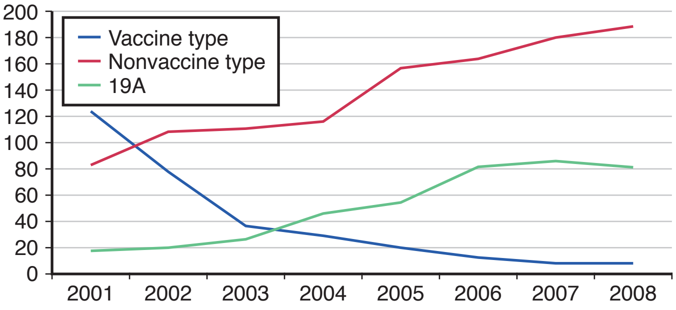

Figure 182-1 Number of invasive pneumococcal isolates (*y*-axis) that were vaccine serotype, nonvaccine serotype, or 19A in children from 8 children's hospitals according to study year from 2001-2008. The total annual admissions among the 8 children's hospitals were 91,950 in 2001, 94,055 in 2002, 95,809 in 2003, 96,472 in 2004, 99,008 in 2005, 101,116 in 2006, 103,524 in 2007, and 105,367 in 2008. *(From Kaplan SL, Barson WJ, Lin PL, et al: Serotype 19A is the most common serotype causing invasive pneumococcal infections in children,* Pediatrics *125:429–436, 2010.)*

refractile (Quellung reaction). Specific antibodies to capsular polysaccharides confer protection on the host, promoting opsonization and phagocytosis. Additionally, $CD4^+$ T cells have a direct role in antibody-independent immunity to pneumococcal nasopharyngeal colonization. Conjugated PCVs promote T-cell immunity and protect against pneumococcal colonization, in contrast to the pneumococcal polysaccharide vaccine (PPSV23) that is used in adults and certain high-risk pediatric populations and that does not affect nasopharyngeal colonization.

Table 182-1 Children at Increased Risk of Invasive Pneumococcal Infection

RISK GROUP	CONDITION
Immunocompetent children	Chronic heart disease* Chronic lung disease† Diabetes mellitus Cerebrospinal fluid leaks Cochlear implant
Children with functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies Congenital or acquired asplenia, or splenic dysfunction
Children with immunocompromising conditions	HIV infection Chronic renal failure and nephrotic syndrome Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas and Hodgkin disease; or solid-organ transplantation Congenital immunodeficiency‡

*Particularly cyanotic congenital heart disease and cardiac failure.
†Including asthma if treated with high-dose oral corticosteroid therapy.
‡Includes B-(humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1,C2,C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).
Adapted from Centers for Disease Control and Prevention (CDC): Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010, MMWR Morb Mortal Wkly Rep *59:258–261, 2010, Table 1.*

EPIDEMIOLOGY

Most healthy individuals carry various *S. pneumoniae* serotypes in their upper respiratory tract; more than 90% of children between 6 mo and 5 yr of age harbor *S. pneumoniae* in the nasopharynx at some time. A single serotype usually is carried by a given individual for an extended period (45 days to 6 mo). Carriage does not consistently induce local or systemic immunity sufficient to prevent later reacquisition of the same serotype. Rates of pneumococcal carriage peak during the 1st and 2nd yr of life and decline gradually thereafter. Carriage rates are highest in institutional setting and during the winter, and rates are lowest in summer. Nasopharyngeal carriage of pneumococci is common among young children attending out-of-home care, with rates of 21-59% in point prevalence studies.

Prior to the introduction of heptavalent pneumococcal conjugate vaccine (PCV7) in 2000, serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F caused most invasive childhood pneumococcal infections in the United States. The introduction of PCVs resulted in a marked decrease in invasive pneumococcal infections (IPIs) in children. However, by 2005 IPIs began to increase slightly as a result of an increase in non-PCV7 serotypes, particularly serotype 19A (Fig. 182-1). The occurrence of "serotype replacement" can result from expansion of existing nonvaccine serotypes, as well as from vaccine type pneumococci acquiring the polysaccharide capsule of a nonvaccine serotype (serotype switching). Since the introduction of PCV13 in 2010 in the United States, there has been a decline in IPIs caused by new vaccine serotypes, including 19A. Indirect protection of unvaccinated persons has occurred since PCV introduction, and this herd protection is likely a result of decreases in nasopharyngeal carriage of virulent pneumococcal vaccine serotypes.

S. pneumoniae is the most frequent cause of bacteremia, bacterial pneumonia, otitis media, and bacterial meningitis in children. The decreased ability in children younger than 2 yr of age to produce antibody against the T-cell–independent polysaccharide antigens and the high prevalence of colonization may explain an increased susceptibility to pneumococcal infection and the decreased effectiveness of polysaccharide vaccines. Children at increased risk of pneumococcal infections include those with sickle cell disease, asplenia, deficiencies in humoral (B cell) and complement-mediated immunity, HIV infection, certain malignancies (e.g., leukemia, lymphoma), chronic heart, lung, or renal disease (particularly nephrotic syndrome), cerebrospinal fluid leak, and cochlear implants. Table 182-1 lists other high-risk groups. Some American Indian, Alaska Native, and African-American children may also be at increased risk. Children younger than 5 yr of age in out-of-home daycare are at increased risk (approximately 2-fold higher) of experiencing IPIs than other children. Males are more commonly affected than females.

Pneumococcal disease usually occurs sporadically but can be spread from person to person by respiratory droplet transmission. *S. pneumoniae* is an important cause of secondary bacterial pneumonia in patients with influenza. During influenza epidemics and pandemics, most deaths result from bacterial pneumonia, and *Pneumococcus* is the predominant bacterial pathogen isolated in this setting. Pneumococcal copathogenicity may be important in disease caused by other respiratory viruses as well.

PATHOGENESIS

Invasion of the host is affected by a number of factors. Nonspecific defense mechanisms, including the presence of other bacteria in the nasopharynx, may limit multiplication of pneumococci. Aspiration of secretions containing pneumococci is hindered by the epiglottic reflex and by respiratory epithelial cell cilia, which move infected mucus toward the pharynx. Similarly, normal ciliary flow of fluid from the middle ear through the eustachian tube and sinuses to the nasopharynx usually prevents infection with nasopharyngeal flora, including pneumococci. Interference with these normal clearance mechanisms by allergy, viral infection, or irritants (e.g., smoke) may allow colonization and subsequent infection with these organisms in otherwise normally sterile sites.

Virulent pneumococci are intrinsically resistant to phagocytosis by alveolar macrophages. Pneumococcal disease frequently is facilitated by viral respiratory tract infection, which may produce mucosal injury, diminish epithelial cell ciliary activity, and depress the function of alveolar macrophages and neutrophils. Phagocytosis may be impeded by respiratory secretions and alveolar exudate. In the lungs and other tissues, the spread of infection is facilitated by the antiphagocytic

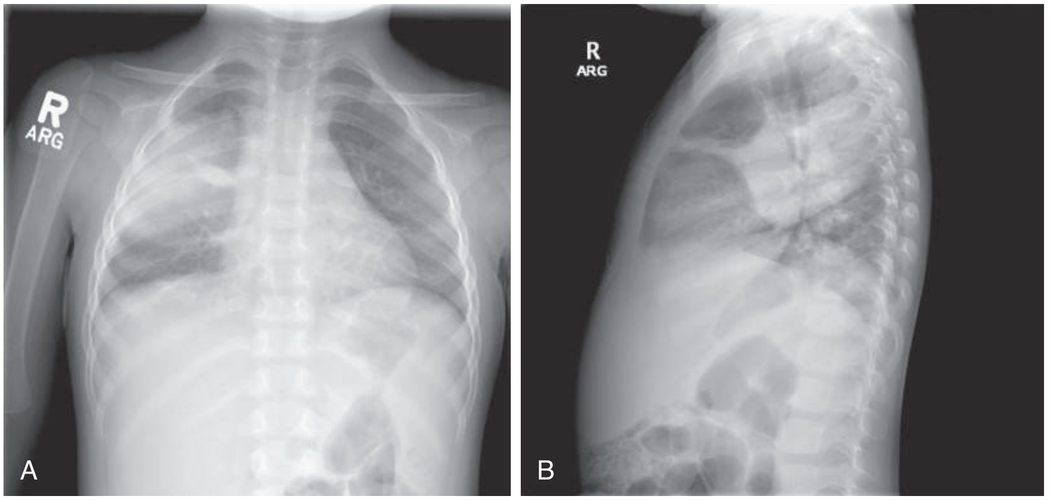

Figure 182-2 Bacterial pneumonia. "Round" pneumonia caused by *Streptococcus pneumoniae* in a 2 yr old girl with a 2-day history of cough, high fever, leukocytosis, and back pain.

properties of the pneumococcal capsule. Surface fluids of the respiratory tract contain only small amounts of immunoglobulin G and are deficient in complement. During inflammation, there is limited influx of immunoglobulin G, complement, and neutrophils. Phagocytosis of bacteria by neutrophils may occur, but normal human serum may not opsonize pneumococci and facilitate phagocytosis by alveolar macrophages. In tissues, pneumococci multiply and spread through the lymphatics or bloodstream or, less commonly, by direct extension from a local site of infection (e.g., sinuses). In bacteremia, the severity of disease is related to the number of organisms in the bloodstream and to the integrity of specific host defenses. A poor prognosis correlates with very large numbers of pneumococci and high concentrations of capsular polysaccharide in the blood and cerebrospinal fluid.

Invasive pneumococcal disease is 30- to 100-fold more prevalent in children with sickle cell disease and other hemoglobinopathies and in children with congenital or surgical asplenia than in the general population. This risk is greatest in infants younger than 2 yr of age, as at that age antibody production to most serotypes is poor. The increased frequency of pneumococcal disease in asplenic persons is related to both deficient opsonization of pneumococci as well as absence of clearance by the spleen of circulating bacteria. Children with sickle cell disease also have deficits in the antibody-independent properdin (alternative) pathway of complement activation, in addition to functional asplenia. Both complement pathways contribute to antibody-independent and antibody-dependent opsonophagocytosis of pneumococci. With advancing age (e.g., >5 yr), children with sickle cell disease produce anticapsular antibody, augmenting antibody-dependent opsonophagocytosis and greatly reducing, but not eliminating, the risk of severe pneumococcal disease. Deficiency of many of the complement components (e.g., C2 and C3) is associated with recurrent pyogenic infection, including *S. pneumoniae* infection. The efficacy of phagocytosis also is diminished in patients with B- and T-cell immunodeficiency syndromes (e.g., agammaglobulinemia, severe combined immune deficiency) or loss of immune globulin (e.g., nephrotic syndrome) and is largely caused by a deficiency of opsonic anticapsular antibody. These observations suggest that opsonization of pneumococci depends on the alternative complement pathway in antibody-deficient persons and that recovery from pneumococcal disease depends on the development of anticapsular antibodies that act as opsonins, enhancing phagocytosis and killing of pneumococci. Children with HIV infection also have high rates of IPI similar to or greater than rates in children with sickle cell disease, although rates of invasive pneumococcal disease decreased after the introduction of highly active antiretroviral therapy.

CLINICAL MANIFESTATIONS

The signs and symptoms of pneumococcal infection are related to the anatomic site of disease. Common clinical syndromes include otitis media (see Chapter 640), sinusitis (see Chapter 380), pneumonia (Fig. 182-2) (see Chapter 400), and sepsis (see Chapter 70). Before routine use of PCVs, pneumococci caused >80% of bacteremia episodes in infants 3-36 mo of age with fever without an identifiable source (i.e., occult bacteremia). Bacteremia may be followed by meningitis (see Chapter 603), osteomyelitis (see Chapter 684), suppurative arthritis (see Chapter 685), endocarditis (see Chapter 437), and, rarely, brain abscess (see Chapter 604). Primary peritonitis (see Chapter 371) may occur in children with peritoneal effusions due to nephrotic syndrome and other conditions. Local complications of infection may occur, causing empyema, pericarditis, mastoiditis, epidural abscess, periorbital cellulitis, or meningitis. Hemolytic-uremic syndrome (see Chapter 484.4) and disseminated intravascular coagulation also occur as rare complications of pneumococcal infections. Epidemic conjunctivitis caused by nonencapsulated or encapsulated pneumococci occurs as well.

DIAGNOSIS

The diagnosis of pneumococcal infection is established by recovery of *S. pneumoniae* from the site of infection or the blood/sterile body fluid. Although pneumococci may be found in the nose or throat of patients with otitis media, pneumonia, septicemia, or meningitis, cultures of these locations are generally not helpful for diagnosis, as they are not indicative of causation. Blood cultures should be obtained in children with pneumonia, meningitis, arthritis, osteomyelitis, peritonitis, pericarditis, or gangrenous skin lesions. Because of the implementation of universal vaccination with PCVs, there has been a substantial decrease in the incidence of occult bacteremia, but blood cultures should still be considered in febrile patients with clinical toxicity or significant leukocytosis. Leukocytosis often is pronounced, with total white blood cell counts frequently >15,000/μL. In severe cases of pneumococcal disease, white blood cell count may be low.

Pneumococci can be identified in body fluids as Gram-positive, lancet-shaped diplococci. Early in the course of pneumococcal meningitis, many bacteria may be seen in relatively acellular cerebrospinal fluid. With current methods of continuously monitored blood culture systems, the average time to isolation of pneumococcal organisms is 14-15 hr. Pneumococcal latex agglutination tests for urine or other body fluids suffer from poor sensitivity and add little to Gram-stained fluids and standard cultures.

TREATMENT

Antimicrobial resistance among *S. pneumoniae* continues to be a serious healthcare concern, especially for the widely used β-lactams, macrolides and fluoroquinolones. Serotypes 6A, 6B, 9V, 14, 19A, 19F, and 23F are the most common serotypes associated with resistance to penicillin. Consequently, the introduction of the 7- and 13-valent

pneumococcal conjugate vaccines (PCV7 and PCV13) has altered antimicrobial resistance patterns.

Resistance in pneumococcal organisms to penicillin and the extended-spectrum cephalosporins cefotaxime and ceftriaxone is defined by the minimum inhibitory concentration (MIC), as well as clinical syndrome. Pneumococci are considered susceptible, intermediate, or resistant to various antibacterial agents based on specific MIC breakpoints. For patients with pneumococcal meningitis, penicillin-susceptible strains have an MIC ≤0.06 μg/mL and penicillin-resistant strains have an MIC ≥0.12 μg/mL. For patients with nonmeningeal pneumococcal infections, breakpoints are higher; in particular, penicillin susceptible strains have an MIC ≤2 μg/mL, and penicillin resistant strains have an MIC ≥8 μg/mL. For patients with meningitis, cefotaxime and ceftriaxone susceptible strains have an MIC ≤0.5 μg/mL and resistant strains have an MIC ≥2.0 μg/mL. For patients with nonmeningeal pneumococcal disease, breakpoints are higher, and cefotaxime- and ceftriaxone-susceptible strains have an MIC ≤1 μg/mL and resistant strains have an MIC ≥4 μg/mL. In cases where the pneumococcus is resistant to erythromycin but sensitive to clindamycin, **a D-test should be performed** to determine whether clindamycin resistance can be induced; if the D-test is positive, clindamycin should not be used to complete treatment of the patient. More than 30% of pneumococcal isolates are resistant to trimethoprim-sulfamethoxazole; levofloxacin resistance is low, but has also been reported. All isolates from children with severe infections should be tested for antibiotic susceptibility given widespread pneumococcal MDR strains. Resistance to vancomycin has not been seen to as of the writing of this chapter, but vancomycin-tolerant pneumococci that are killed at a slower rate have been reported, and these tolerant pneumococci may be associated with a worse clinical outcome. Linezolid is an oxazolidinone antibacterial with activity against MDR Gram-positive organisms, including *Pneumococcus*, and has been used in the treatment of MDR pneumococcal pneumonia, meningitis, and severe otitis. Despite early favorable studies, use of this drug is limited by myelosuppression and high cost, and linezolid resistance in *Pneumococcus* is reported.

Children 1 mo of age or older with suspected pneumococcal meningitis should be treated with combination therapy using vancomycin (60 mg/kg/24 hr divided q 6 hr IV), and high-dose cefotaxime (300 mg/kg/24 hr divided q 8 hr IV) or ceftriaxone (100 mg/kg/24 hr divided q 12 hr IV). Proven pneumococcal meningitis can be treated with penicillin alone, or cefotaxime or ceftriaxone alone, if the isolate is penicillin-susceptible. If the organism is nonsusceptible (i.e., intermediate or full resistance) to penicillin but susceptible to cefotaxime and ceftriaxone, pneumococcal meningitis can be treated with cefotaxime or ceftriaxone alone. However, if the organism is nonsusceptible to penicillin and to cefotaxime or ceftriaxone, pneumococcal meningitis should be treated with combination vancomycin plus cefotaxime or ceftriaxone, not with vancomycin alone, and consideration should be given to the addition of rifampin. Some experts recommend use of corticosteroids in pneumococcal meningitis early in the course of disease, but data demonstrating clear benefit in children is lacking.

In 2011 the Infectious Diseases Society of America published guidelines for the management of community-acquired pneumonia in infants and children. Per these guidelines, amoxicillin may be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate uncomplicated community-acquired pneumonia. Ampicillin or penicillin G may be administered to the fully immunized infant or school-age child admitted to a hospital ward with uncomplicated community-acquired pneumonia, when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *S. pneumoniae*. Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents widespread penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia, given the degree of drug resistance currently seen in the United States.

For individuals who are allergic to penicillin, clindamycin, erythromycin (or related macrolides, e.g., azithromycin or clarithromycin), cephalosporins (standard dosing), and trimethoprim-sulfamethoxazole may provide effective alternative therapy for susceptible strains, depending on the site of infection (e.g., clindamycin may be effective for pneumococcal infections other than meningitis). Higher doses of amoxicillin (80-100 mg/kg/24 hr) have been successful in the treatment of otitis media caused by penicillin-nonsusceptible strains. Empirical treatment of pneumococcal disease should be based on knowledge of susceptibility patterns in specific communities.

PROGNOSIS

Prognosis depends on the integrity of host defenses, virulence and numbers of the infecting organism, the age of the host, the site and extent of the infection, and the adequacy of treatment. The mortality rate for pneumococcal meningitis is approximately 10% in most studies. Pneumococcal meningitis results in sensorineural hearing loss in 20-30% of patients and can cause other serious neurologic sequelae, including paralysis, epilepsy, blindness, and intellectual deficits.

PREVENTION

The highly successful PCVs have resulted in a marked decrease in IPIs in children. PCVs (Table 182-2) provoke protective antibody responses in 90% of infants given these vaccines at 2, 4, and 6 mo of age, and greatly enhanced responses (e.g., immunologic memory) are apparent after vaccine doses given at 12-15 mo of age. In a large clinical trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by up to 97% and to reduce invasive disease caused by all serotypes, including serotypes not in the vaccine, by 89%. Children who received PCV7 had 7% fewer episodes of acute otitis media and underwent 20% fewer tympanostomy tube placements than did unvaccinated children. In preliminary studies following PCV 13, a 42% reduction in IPIs caused by vaccine serotypes has been seen. The greatest reduction in the number of cases occurred in children younger than 24 mo of age. Mastoiditis cases, which have been especially associated with serotype 19A isolates, had the greatest percentage decrease. In addition, pneumococcal conjugate vaccines significantly reduce nasopharyngeal carriage of vaccine serotypes. PCVs have significantly decreased rates of invasive pneumococcal disease in children with sickle cell disease, and studies suggest substantial protection for HIV-infected children and splenectomized adults. Adverse events after the administration of PCV have included local swelling and redness and slightly

Table 182-2 Comparison of Pneumococcal Vaccines Licensed in United States*

CARRIER PROTEIN	PNEUMOCOCCAL CAPSULAR POLYSACCHARIDES	MANUFACTURER
Diphtheria CRM_{197} protein	**4, 6B, 9V, 14, 18C, 19F, 23F**	Wyeth Lederle (PCV7, Prevnar)
Diphtheria CRM_{197} protein	1, 3, **4,** 5, 6A, **6B,** 7F, **9V, 14, 18C,** 19A, **19F, 23F**	Wyeth Lederle (PCV13, Prevnar 13)
None	1, 2, 3, **4,** 5, **6B,** 7F, 8, 9N, **9V,** 10A, 11A, 12F, **14,** 15B, 17F, **18C,** 19A, **19F,** 20, 22F, **23F,** 33F	Sanofi Pasteur MSD (PPSV23, Pneumovax II)

*PCV7 serotypes in bold.

increased rates of fever, when used in conjunction with other childhood vaccines.

Immunologic responsiveness and efficacy following administration of pneumococcal polysaccharide vaccines (PPSV23) is unpredictable in children younger than 2 yr of age. PPSV23 contains purified polysaccharide of 23 pneumococcal serotypes responsible for more than 95% of cases of invasive disease. The clinical efficacy of PPSV23 is controversial and studies have yielded conflicting results.

Immunization with PCV13 is recommended for all infants on a schedule for primary immunization, in previously unvaccinated infants, and for transition for those partially vaccinated with PCV7 (Tables 182-3 and 182-4). High-risk children 2 yr of age and older, such as those with asplenia, sickle cell disease, some types of immune deficiency (e.g., antibody deficiencies), HIV infection, cochlear implant, cerebrospinal fluid leak, diabetes mellitus, and chronic lung, heart, or kidney disease (including nephrotic syndrome), may benefit also from PPSV23 administered after 2 yr of age following priming with the scheduled doses of PCV13. Thus, it is recommended that children 2 yr of age and older with these underlying conditions receive supplemental vaccination with PPSV23. A 2nd dose of PPSV23 is recommended 5 yr after the 1st dose of PPSV23 for persons age 2 yr or older who are immunocompromised, have sickle cell disease, or functional or anatomic asplenia. Additional recommendations have been made for at-risk children between 6-18 yr (Table 182-5).

Immunization with pneumococcal vaccines also may prevent pneumococcal disease caused by nonvaccine serotypes that are serotypically related to a vaccine strain. However, because current vaccines do not eliminate all pneumococcal invasive infections, penicillin prophylaxis is recommended for children at high risk of invasive pneumococcal disease, including children with asplenia or sickle cell disease. Oral penicillin V potassium (125 mg bid for children <3 yr; 250 mg bid for children ≥3 yr) decreases the incidence of pneumococcal sepsis in children with sickle cell disease. Once-monthly intramuscular benzathine penicillin G (600,000 units q 3-4 wk for children weighing <60 lb; 1,200,000 units q 3-4 wk for children weighing ≥60 lb) may also provide prophylaxis. Erythromycin may be used in children with penicillin allergy, but its efficacy is unproved. Prophylaxis in sickle cell disease has been safely discontinued after the 5th birthday in children who have received all recommended pneumococcal vaccine doses and who had not experienced invasive pneumococcal disease. Prophylaxis is often administered for at least 2 yr after splenectomy or up to 5 yr of age. Efficacy in children older than 5 yr of age and adolescents is unproved. If oral antibiotic prophylaxis is used, strict compliance must

Table 182-3 Recommended Routine Vaccination Schedule for 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Among Infants and Children Who Have Not Received Previous Doses of 7-Valent Vaccine (PCV7) or PCV13, by Age at First Dose—Advisory Committee on Immunization Practices (ACIP), United States, 2010

AGE AT 1ST DOSE (MO)	PRIMARY PCV13 SERIES*	PCV13 BOOSTER DOSE†
2-6	3 doses	1 dose at age 12-15 mo
7-11	2 doses	1 dose at age 12-15 mo
12-23	2 doses	—
24-59 (healthy children)	1 dose	—
24-71 (children with certain chronic diseases or immunocompromising conditions)	2 doses	—

*Minimum interval between doses is 8 wk except for children vaccinated at age <12 mo for whom minimum interval between doses is 4 wk. Minimum age for administration of 1st dose is 6 wk.

†Given at least 8 wk after the previous dose.

From Centers for Disease Control and Prevention (CDC): Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010, MMWR Morb Mortal Wkly Rep *59:258–261, 2010, Table 2.*

Table 182-4 Recommended Transition Schedule from 7-Valent Pneumococcal Conjugate Vaccine (PCV7) to 13-Valent Vaccine (PCV13) Vaccination Among Infants and Children, According to Number of Previous PCV7 Doses Received—Advisory Committee on Immunization Practices (ACIP), United States, 2010

INFANT SERIES			BOOSTER DOSE	SUPPLEMENTAL PCV13 DOSE
2 mo	4 mo	6 mo	≥12 mo*	14-59 mo†
PCV7	PCV13	PCV13	PCV13	—
PCV7	PCV7	PCV13	PCV13	—
PCV7	PCV7	PCV7	PCV13	—
PCV7	PCV7	PCV7	PCV7	PCV13

*No additional PCV13 doses are indicated for children age 12-23 mo who have received 2 or 3 doses of PCV before age 12 mo and at least 1 dose of PCV13 at age ≥12 mo.

†For children with underlying medical conditions (see Table 182-1), a single supplemental PCV13 dose is recommended through age 71 mo.

From Centers for Disease Control and Prevention (CDC): Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010, MMWR Morb Mortal Wkly Rep *59:258–261, 2010, Table 3.*

Table 182-5 Medical Conditions or Other Indications for Administration of PCV13,* and Indications for PPSV23† Administration, and Revaccination for Children Age 6–18 Years‡

RISK GROUP	UNDERLYING MEDICAL CONDITION	PCV13 RECOMMENDED	PPSV23 RECOMMENDED	REVACCINATION 5 YR AFTER 1ST DOSE
Immunocompetent persons	Chronic heart disease§		✓	
	Chronic lung disease‖		✓	
	Diabetes mellitus		✓	
	Cerebrospinal fluid leaks	✓	✓	
	Cochlear implants	✓	✓	
	Alcoholism		✓	
	Chronic liver disease		✓	
	Cigarette smoking		✓	
Persons with functional or anatomic asplenia	Sickle cell disease/other hemoglobinopathies	✓	✓	✓
	Congenital or acquired asplenia	✓	✓	✓

Table 182-5	Medical Conditions or Other Indications for Administration of PCV13,* and Indications for PPSV23† Administration, and Revaccination for Children Age 6–18 Years‡—cont'd			
RISK GROUP	**UNDERLYING MEDICAL CONDITION**	**PCV13 RECOMMENDED**	**PPSV23 RECOMMENDED**	**REVACCINATION 5 YR AFTER 1ST DOSE**
Immunocompromised persons	Congenital or acquired immunodeficiencies¶	✓	✓	✓
	Human immunodeficiency virus infection	✓	✓	✓
	Chronic renal failure	✓	✓	✓
	Nephrotic syndrome	✓	✓	✓
	Leukemia	✓	✓	✓
	Lymphoma	✓	✓	✓
	Hodgkin disease	✓	✓	✓
	Generalized malignancy	✓	✓	✓
	Iatrogenic immunosuppression**	✓	✓	✓
	Solid organ transplant	✓	✓	✓
	Multiple myeloma	✓	✓	✓

*13-valent pneumococcal conjugate vaccine.
†23-valent pneumococcal polysaccharide vaccine.
‡Children age 2-5 yr with chronic conditions (e.g., heart disease or diabetes), immunocompromising conditions (e.g., HIV), functional or anatomic asplenia (including sickle cell disease), cerebrospinal fluid leaks, or cochlear implants, and who have not previously received PCV13, have been recommended to receive PCV13 since 2010.
§Including congestive heart failure and cardiomyopathies.
||Including chronic obstructive pulmonary disease, emphysema, and asthma.
¶Includes B-(humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).
**Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy.
From Centers for Disease Control and Prevention CDC): Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: recommendations of the advisory committee on immunization practices (ACIP). MMWR Morb Mortal Wkly Rep *62:521–524, 2013.*

be encouraged. Given the rapid emergence of penicillin-resistant pneumococci, especially in children receiving long-term, low-dose therapy, prophylaxis cannot be relied on to prevent disease. High-risk children with fever should be promptly evaluated and treated regardless of vaccination or penicillin prophylaxis history.

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Chapter 183

Group A Streptococcus

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Group A streptococcus (GAS), also known as *Streptococcus pyogenes,* is a very common cause of infections of the upper respiratory tract (pharyngitis) and the skin (impetigo, pyoderma) in children and less frequently causes perianal cellulitis, vaginitis, septicemia, pneumonia, endocarditis, pericarditis, osteomyelitis, suppurative arthritis, myositis, cellulitis, and omphalitis. This organism also causes distinct clinical entities (scarlet fever and erysipelas), as well as streptococcal toxic shock syndrome and necrotizing fasciitis. GAS is also the cause of 2 potentially serious nonsuppurative complications: rheumatic fever (see Chapters 183.1 and 438) and acute glomerulonephritis (see Chapter 511.1).

ETIOLOGY

Group A streptococci are Gram-positive coccoid-shaped bacteria that tend to grow in chains. They are broadly classified by their hemolytic activity on mammalian (typically sheep) red blood cells. The zone of complete hemolysis that surrounds colonies grown on blood agar distinguishes β-hemolytic (complete hemolysis) from α-hemolytic (green or partial hemolysis) and γ (nonhemolytic) species. The β-hemolytic streptococci can be divided into groups by a group-specific polysaccharide **(Lancefield C carbohydrate)** located in the bacterial cell wall. More than 20 serologic groups are identified, designated by the letters A through V. Serologic grouping by the Lancefield method is precise, but group A organisms can be identified more readily by any one of a number of latex agglutination, coagglutination, or enzyme immunoassay procedures. Group A strains can also be distinguished from other groups by differences in sensitivity to bacitracin. A disk containing 0.04 units of bacitracin inhibits the growth of most group A strains, whereas other groups are generally resistant to this antibiotic. This method is approximately 95% accurate. GAS can be subdivided into more than 220 serotypes on the basis of the **M protein** antigen, which is located on the cell surface and in fimbriae that project from the outer surface of the cell. Currently, a molecular approach to M typing GAS isolates using the polymerase chain reaction is based on sequencing the terminal portion of the *emm* gene of GAS that encodes the M protein. More than 220 distinct M types have been identified using *emm* typing, and there is excellent correlation between known serotypes and *emm* types. Immunity is largely based upon type-specific opsonic anti-M antibody.

M serotyping is valuable for epidemiologic studies; specific GAS diseases tend to be associated with certain M types. Types 1, 12, 28, 4, 3, and 2 (in that order) are the most common causes of uncomplicated streptococcal pharyngitis in the United States. M types commonly associated with pharyngitis rarely cause skin infections, and the M types commonly associated with skin infections rarely cause pharyngitis. A few **pharyngeal** strains (e.g., M type 12) are associated with glomerulonephritis, but many more **skin** strains (e.g., M types 49, 55, 57, and 60) are considered nephritogenic. Several pharyngeal serotypes (e.g., M types 1, 3, 5, 6, 18, 29), but no skin strains, are associated with acute rheumatic fever in North America. Rheumatogenic potential is not solely dependent on serotype but is likely a characteristic of specific strains within several serotypes.

EPIDEMIOLOGY

Humans are the natural reservoir for GAS. These bacteria are highly communicable and can cause disease in normal individuals of all ages who do not have type-specific immunity against the particular serotype involved. Disease in neonates is uncommon in developed countries, probably because of maternally acquired antibody. The incidence of pharyngeal infections is highest in children 5-15 yr of age, especially in young school-age children. These infections are most common in the northern regions of the United States, especially during winter and early spring. Children with untreated acute pharyngitis spread GAS by

airborne salivary droplets and nasal discharge. Transmission is favored by close proximity; therefore, schools, military barracks, and homes are important environments for spread. The incubation period for pharyngitis is usually 2-5 days. GAS has the potential to be an important upper respiratory tract pathogen and to produce outbreaks of disease in the daycare setting. Foods containing GAS occasionally cause explosive outbreaks of pharyngotonsillitis. Children are usually no longer infectious 24 hr after appropriate antibiotic therapy has been started. Chronic pharyngeal carriers of GAS rarely transmit this organism to others.

Streptococcal pyoderma (impetigo, pyoderma) occurs most frequently during the summer in temperate climates, or year round in warmer climates, when the skin is exposed and abrasions and insect bites are more likely to occur (see Chapter 665). Colonization of healthy skin by GAS usually precedes the development of impetigo. Because GAS cannot penetrate intact skin, impetigo usually occurs at the site of open lesions (insect bites, traumatic wounds, burns). Although impetigo serotypes may colonize the throat, spread is usually from skin to skin, not via the respiratory tract. Fingernails and the perianal region can harbor GAS and play a role in disseminating impetigo. Multiple cases of impetigo in the same family are common. Both impetigo and pharyngitis are more likely to occur among children living in crowded homes and in poor hygienic circumstances.

The incidence of **severe invasive** GAS infections, including bacteremia, streptococcal toxic shock syndrome, and necrotizing fasciitis, has increased in recent decades. The incidence appears to be highest in the very young and in the elderly. Prior to the routine use of varicella vaccine, varicella was the most commonly identified risk factor for invasive GAS infection in children. Other risk factors include diabetes mellitus, HIV infection, intravenous drug use, and chronic pulmonary or chronic cardiac disease. The portal of entry is unknown in almost 50% of cases of severe invasive GAS infection; in most cases, it is believed to be skin or mucous membrane. Severe invasive disease rarely follows clinically apparent GAS pharyngitis.

PATHOGENESIS

Virulence of GAS depends primarily on the M protein, and strains rich in M protein resist phagocytosis in fresh human blood, whereas M-negative strains do not. M protein stimulates the production of protective opsonophagocytic antibodies that are type-specific, protecting against infection with a homologous M type but much less so against other M types. Therefore, multiple GAS infections attributable to various M types are common during childhood and adolescence. By adult life, individuals are probably immune to several or many of the common M types in the environment.

GAS produces a large variety of extracellular enzymes and toxins, including erythrogenic toxins (known as *streptococcal pyrogenic exotoxins*). Streptococcal **pyrogenic exotoxins** A, B, and C are responsible for the **rash of scarlet fever** and are elaborated by streptococci that contain a particular bacteriophage. These exotoxins stimulate the formation of specific antitoxin antibodies that provide immunity against the scarlatiniform rash but not against other streptococcal infections. GAS can produce up to 12 different pyrogenic exotoxins, and repeat attacks of scarlet fever are possible. Streptococcal pyrogenic exotoxins A, B, and C, as well as several newly discovered exotoxins, appear to be involved in the pathogenesis of invasive GAS disease, including the **streptococcal toxic shock syndrome.**

The importance of other streptococcal toxins and enzymes in human disease is not yet established. Many of these extracellular substances are antigenic and stimulate antibody production after an infection. However, these antibodies do not confer immunity. Their measurement is useful for establishing evidence of a recent streptococcal infection to aid in the diagnosis of postinfectious illnesses. Tests for antibodies against streptolysin O (antistreptolysin O) and DNAse B (anti–DNAse B) are the most commonly used antibody determinations. Because the immune response to extracellular antigens varies among individuals as well as with the site of infection, it is sometimes necessary to measure other streptococcal antibodies.

CLINICAL MANIFESTATIONS

The most common infections caused by GAS involve the respiratory tract and the skin and soft tissues.

Respiratory Tract Infections

GAS is an important cause of acute pharyngitis (see Chapter 381) and pneumonia (see Chapter 400).

Scarlet Fever

Scarlet fever is an upper respiratory tract infection associated with a characteristic rash, which is caused by an infection with **pyrogenic exotoxin (erythrogenic toxin)**–producing GAS in individuals who do not have antitoxin antibodies. It is now encountered less commonly and is less virulent than in the past, but the incidence is cyclic, depending on the prevalence of toxin-producing strains and the immune status of the population. The modes of transmission, age distribution, and other epidemiologic features are otherwise similar to those for GAS pharyngitis.

The rash appears within 24-48 hr after onset of symptoms, although it may appear with the first signs of illness (Fig. 183-1*A*). It often begins around the neck and spreads over the trunk and extremities. The rash is a diffuse, finely papular, erythematous eruption producing bright red discoloration of the skin, which blanches on pressure. It is often accentuated in the creases of the elbows, axillae, and groin. The skin has a goose-pimple appearance and feels rough. The cheeks are often erythematous with pallor around the mouth. After 3-4 days, the rash begins to fade and is followed by desquamation, initially on the face, progressing downward, and often resembling a mild sunburn. Occasionally, sheet-like desquamation may occur around the free margins of the fingernails, the palms, and the soles. Examination of the pharynx of a patient with scarlet fever reveals essentially the same findings as with GAS pharyngitis. In addition, the tongue is usually coated and the papillae are swollen (Fig. 183-1*B*). After desquamation, the reddened papillae are prominent, giving the tongue a strawberry appearance (Fig. 183-1*C*).

Typical scarlet fever is not difficult to diagnose; the milder form with equivocal pharyngeal findings can be confused with viral exanthems, Kawasaki disease, and drug eruptions. Staphylococcal infections are occasionally associated with a scarlatiniform rash. A history of recent exposure to a GAS infection is helpful. Identification of GAS in the pharynx confirms the diagnosis.

Impetigo

Impetigo (or pyoderma) has traditionally been classified into 2 clinical forms: bullous and nonbullous (see Chapter 665). Nonbullous impetigo is the more common form and is a superficial infection of the skin that appears first as a discrete papulovesicular lesion surrounded by a localized area of redness. The vesicles rapidly become purulent and covered with a thick, confluent, amber-colored crust that gives the appearance of having been stuck onto the skin. The lesions may occur anywhere but are most common on the face and extremities. If untreated, nonbullous impetigo is a mild but chronic illness, often spreading to other parts of the body, but occasionally self-limited. Regional **lymphadenitis** is common. Nonbullous impetigo is generally not accompanied by fever or other systemic signs or symptoms. Impetiginized excoriations around the nares are seen with active GAS infections of the nasopharynx particularly in young children. However, impetigo is not usually associated with an overt streptococcal infection of the upper respiratory tract.

Bullous impetigo is less common and occurs most often in neonates and young infants. It is characterized by flaccid, transparent bullae usually <3 cm in diameter on previously untraumatized skin. The usual distribution involves the face, buttocks, trunk, and perineum. Although *Staphylococcus aureus* has traditionally been accepted as the sole pathogen responsible for bullous impetigo, there has been confusion about the organisms responsible for nonbullous impetigo. In most episodes of nonbullous impetigo, either GAS or *S. aureus,* or both, is isolated. Earlier investigations suggested that GAS was the causative agent in most cases of nonbullous impetigo and that *S. aureus* was only

Figure 183-1 Scarlet fever. **A,** Punctate, erythematous rash (2nd day). **B,** White strawberry tongue (1st day). **C,** Red strawberry tongue (3rd day). *(Courtesy Dr. Franklin H. Top, Professor and Head of the Department of Hygiene and Preventive Medicine, State University of Iowa, College of Medicine, Iowa City, IA; and Parke, Davis & Company's Therapeutic Notes. From Gershon AA, Hotez PJ, Katz SL:* Krugman's infectious diseases of children, *ed 11, Philadelphia, 2004, Mosby, plate 53.)*

a secondary invader. However, *S. aureus* has emerged recently as the causative agent in most cases of nonbullous impetigo. Culture of the lesions is the only way to distinguish nonbullous impetigo caused by *S. aureus* from that caused by GAS.

Erysipelas

Erysipelas is a now relatively rare acute GAS infection involving the deeper layers of the skin and the underlying connective tissue. The skin in the affected area is swollen, red, and very tender. Superficial blebs may be present. The most characteristic finding is a sharply defined, slightly elevated border. At times, reddish streaks of lymphangitis project out from the margins of the lesion. The onset is abrupt, and signs and symptoms of a systemic infection, such as high fever, are often present. Cultures obtained by needle aspirate of the advancing margin of the inflamed area often reveal the causative agent.

Perianal Dermatitis

Perianal dermatitis, also called perianal cellulitis or **perianal streptococcal disease,** is a distinct clinical entity characterized by well-demarcated, perianal erythema associated with anal pruritus, painful defecation, and occasionally blood-streaked stools. Physical examination reveals flat, pink to beefy-red perianal erythema with sharp margins extending as far as 2 cm from the anus. Erythema may involve the vulva and vagina. Lesions may be very tender and, particularly when chronic, may fissure and bleed. Systemic symptoms and fever are unusual. Culture or a rapid strep test of a perianal swab will yield group A streptococci or detect antigen.

Vaginitis

GAS is a common cause of vaginitis in prepubertal girls (see Chapter 549). Patients usually have a serous discharge with marked erythema and irritation of the vulvar area, accompanied by discomfort in walking and in urination.

Severe Invasive Disease

Invasive GAS infection is defined by isolation of GAS from a normally sterile body site and includes 3 overlapping clinical syndromes. The 1st is **GAS toxic shock syndrome**, which is differentiated from other types of invasive GAS infections by the presence of shock and multiorgan system failure early in the course of the infection (Table 183-1). The 2nd is **GAS necrotizing fasciitis** characterized by extensive local necrosis of subcutaneous soft tissues and skin. The 3rd is the group of focal and systemic infections that do not meet the criteria for toxic shock syndrome or necrotizing fasciitis and includes bacteremia with no identified focus, meningitis, pneumonia, peritonitis, puerperal sepsis, osteomyelitis, suppurative arthritis, myositis, and surgical wound infections. GAS toxic shock syndrome, necrotizing fasciitis, and focal and systemic infections can be present in any combination.

Table 183-1	Definition of Streptococcal Toxic Shock Syndrome
CLINICAL CRITERIA	
Hypotension plus 2 or more of the following:	
Renal impairment	
Coagulopathy	
Hepatic involvement	
Adult respiratory distress syndrome	
Generalized erythematous macular rash	
Soft-tissue necrosis	
DEFINITE CASE	
Clinical criteria plus group A streptococcus from a normally sterile site	
PROBABLE CASE	
Clinical criteria plus group A streptococcus from a nonsterile site	

The pathogenic mechanisms responsible for severe, invasive GAS infections, including streptococcal toxic shock syndrome and necrotizing fasciitis, have yet to be defined completely, but an association with streptococcal pyrogenic exotoxins is strongly suspected. The 3 original streptococcal pyrogenic exotoxins (A, B, C), the newly discovered streptococcal pyrogenic exotoxins, and potentially other as yet unidentified toxins produced by GAS act as superantigens, which stimulate intense activation and proliferation of T lymphocytes and macrophages, resulting in the production of large quantities of proinflammatory cytokines. These cytokines are capable of inducing shock and tissue injury and appear to mediate many of the clinical manifestations of severe, invasive GAS infections.

DIAGNOSIS

When deciding whether to perform a diagnostic test on a patient presenting with acute pharyngitis, the clinical and epidemiologic findings should be considered. A history of close contact with a well-documented case of GAS pharyngitis is helpful, as is an awareness of a high prevalence of GAS infections in the community. The signs and symptoms of streptococcal and nonstreptococcal pharyngitis overlap too broadly to allow the requisite diagnostic precision on clinical grounds alone. The

clinical diagnosis of GAS pharyngitis cannot be made with reasonable accuracy even by the most experienced physicians, and bacteriologic confirmation is required. The only exception to this statement are those patients with overt viral signs and symptoms such as rhinorrhea, cough, mouth ulcers, and hoarseness, who generally do not need a diagnostic test performed.

Culture of a throat swab on a sheep blood agar plate is effective for documenting the presence of GAS in the upper respiratory tract and for confirming the clinical diagnosis of acute GAS pharyngitis. When performed correctly, a single throat swab cultured on a sheep blood-agar plate has a sensitivity of 90-95% for detecting the presence of GAS in the pharynx.

A significant disadvantage of culturing a throat swab on a blood-agar plate is the delay (overnight or longer) in obtaining the culture result. **Rapid antigen detection** tests are available for the identification of GAS directly from throat swabs. Although these rapid tests are more expensive than the blood-agar culture, the advantage they offer over the traditional procedure is the speed with which they can provide results, often less than 10-15 minutes. Rapid identification and treatment of patients with streptococcal pharyngitis can reduce the risk for spread of GAS, allowing the patient to return to school or work sooner, and can reduce the acute morbidity of this illness.

Almost all currently available rapid antigen detection tests have excellent specificity of >95% when compared with blood-agar plate cultures. False-positive test results are quite unusual, and, therefore, therapeutic decisions can be made with confidence on the basis of a positive test result. Unfortunately, the sensitivity of most of these tests is 80-90%, sometimes lower, when compared with blood-agar plate culture. Therefore, a negative rapid test does not completely exclude the presence of GAS, and a confirmatory throat culture should be performed in children and adolescents but not necessarily in adults, who are at exceptionally low risk for developing acute rheumatic fever. Definitive studies to determine whether some rapid antigen detection tests are significantly more sensitive than others, and, whether any of these tests are sensitive enough to be used routinely in children and adolescents without throat culture confirmation of negative test results, are not available. Some experts believe that physicians who use a rapid antigen detection test without culture backup should compare the results with that specific test to those of throat cultures to confirm adequate sensitivity in their practice.

Nucleic acid amplification tests including isothermal loop amplification are also available to detect GAS pharyngitis with a high degree of specificity and sensitivity as well as a rapid turn-around time.

GAS infection can also be diagnosed retrospectively on the basis of an elevated or increasing streptococcal antibody titer. The antistreptolysin O assay is the streptococcal antibody test most commonly used. Because streptolysin O also is produced by groups C and G streptococcus, the test is not specific for group A infection. The antistreptolysin O response can be feeble following streptococcal skin infection. In contrast, the anti–DNase B responses are generally present after either skin or throat infections. A significant antibody increase is usually defined as an increase in titer of 2 or more dilution increments (≥4-fold rise) between the acute phase and convalescent phase specimens, regardless of the actual height of the antibody titer. Physicians frequently misinterpret streptococcal antibody titers because of a failure to appreciate that the normal levels of these antibodies are substantially higher among school-age children compared to adults. Both the traditional antistreptolysin O and anti–DNase B tests are neutralization assays. Newer tests use latex agglutination or nephelometric assays. Unfortunately, these newer tests often have not been well-standardized against the traditional neutralization assays. Physicians should be aware of these potential problems when interpreting the results of streptococcal serologic testing.

A commercially available slide agglutination test for the detection of antibodies to several streptococcal antigens is the Streptozyme test (Wampole Laboratories, Stamford, CT). This test is much-less-well standardized and less reproducible than other antibody tests, and it should not be used as a test for evidence of a preceding GAS infection.

Differential Diagnosis

Viruses are the most common cause of acute pharyngitis in children. Respiratory viruses such as influenza virus, parainfluenza virus, rhinovirus, coronavirus, adenovirus, and respiratory syncytial virus are frequent causes of acute pharyngitis. Other viral causes of acute pharyngitis include enteroviruses and herpes simplex virus. Epstein-Barr virus is a frequent cause of acute pharyngitis that is often accompanied by other clinical findings of infectious mononucleosis (e.g., splenomegaly, generalized lymphadenopathy). Systemic infections with other viral agents including cytomegalovirus, rubella virus, measles virus, and HIV may be associated with acute pharyngitis.

GAS is by far the most common cause of bacterial pharyngitis, accounting for 15-30% of cases of acute pharyngitis in children and a lower proportion in adults. Groups C and G β-hemolytic streptococcus (see Chapter 185) also cause acute pharyngitis, typically in teens and young adults. *Arcanobacterium haemolyticum* and *Fusobacterium necrophorum* are additional less common causes. *Neisseria gonorrhoeae* can occasionally cause acute pharyngitis in sexually active adolescents. Other bacteria, such as *Francisella tularensis* and *Yersinia enterocolitica,* as well as mixed infections with anaerobic bacteria (Vincent angina), are rare causes of acute pharyngitis. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* have been implicated as causes of acute pharyngitis, particularly in adults. *Corynebacterium diphtheriae* (see Chapter 187) is a serious cause of pharyngitis but is rare because of universal immunization. Although other bacteria, such as *S. aureus, Haemophilus influenzae,* and *Streptococcus pneumoniae,* are frequently cultured from the throats of children with acute pharyngitis, their etiologic role in pharyngitis has not been established.

GAS pharyngitis is the only common cause of acute pharyngitis for which antibiotic therapy is definitely indicated. Therefore, when confronted with a patient with acute pharyngitis, the clinical decision that usually needs to be made is whether or not the pharyngitis is attributable to GAS.

TREATMENT

Antibiotic therapy for patients with GAS pharyngitis can prevent acute rheumatic fever, shorten the clinical course of the illness, reduce transmission of the infection to others, and prevent suppurative complications. For the patient with classic scarlet fever, antibiotic therapy should be started immediately, but for the vast majority of patients who present with much less distinctive findings, treatment should be withheld until there is some form of bacteriologic confirmation, either by throat culture or rapid antigen detection test. Rapid antigen detection tests, because of their high degree of specificity, have made it possible to initiate antibiotic therapy immediately for one with a positive test result.

GAS is exquisitely sensitive to penicillin and cephalosporins, and resistant strains have never been encountered. Penicillin or amoxicillin is therefore the drug of choice (except in patients who are allergic to penicillins) for pharyngeal infections as well as for suppurative complications. Oral penicillin V (250 mg/dose bid-tid for children weighing ≤60 lb and 500 mg/dose bid-tid for children weighing >60 lb PO) is recommended but must be taken for a full 10 days even though there is symptomatic improvement within 3-4 days. Penicillin V (phenoxyethylpenicillin) is preferred over penicillin G because it may be given without regard to mealtime. The major concern with all forms of oral therapy is the risk that the drug will be discontinued before the 10-day course has been completed. Therefore, when oral treatment is prescribed, the necessity of completing a full course of therapy must be emphasized. If the parents seem unlikely to comply with oral therapy because of family disorganization, difficulties in comprehension, or other reasons, parenteral therapy with a single intramuscular injection of benzathine penicillin G (600,000 IU for children weighing ≤60 lb and 1.2 million IU for children weighing >60 lb, IM) is the most efficacious and often the most practical method of treatment. Disadvantages include soreness around the site of injection, which may last for several days, and potential for injection into nerves or blood vessels if not administered correctly. The local reaction is diminished when benzathine penicillin G is combined in a single injection with procaine

penicillin G, although it is necessary to ensure that an adequate dose of benzathine penicillin G is administered.

In several comparative clinical trials, once-daily amoxicillin (50 mg/kg, maximum: 1,000 mg) for 10 days has been demonstrated to be effective in treating GAS pharyngitis. This somewhat broader-spectrum agent has the advantage of once-daily dosing, which may enhance adherence. In addition, amoxicillin is relatively inexpensive and is considerably more palatable than penicillin V suspension.

A 10-day course of a narrow spectrum oral cephalosporin is recommended for most penicillin-allergic individuals. It has been suggested that a 10-day course with an oral cephalosporin is superior to 10 days of oral penicillin in eradicating GAS from the pharynx. Analysis of these data suggests that the difference in eradication is mainly the result of a higher rate of eradication of carriers included unintentionally in these clinical trials. Some penicillin-allergic persons (up to 10%) are also allergic to cephalosporins, and these agents should be avoided in patients with immediate (anaphylactic-type) hypersensitivity to penicillin. Most oral broad-spectrum cephalosporins are considerably more expensive than penicillin or amoxicillin, and the former agents are more likely to select for antibiotic-resistant flora.

Oral clindamycin is an appropriate agent for treating penicillin-allergic patients, and resistance to clindamycin among GAS isolates in the United States is currently only approximately 1%. An oral macrolide (erythromycin or clarithromycin) or azalide (azithromycin) is also an appropriate agent for patients allergic to penicillins. Ten days of therapy is indicated except for azithromycin, which is given at 12 mg/kg once daily for 5 days. Erythromycin is associated with substantially higher rates of gastrointestinal side effects than the other agents. In recent years, macrolide resistance rates among pharyngeal isolates of GAS in most areas of the United States have been approximately 5-8%. Sulfonamides and the tetracyclines are not indicated for treatment of GAS infections.

Most oral antibiotics must be administered for the conventional 10 days to achieve maximal pharyngeal eradication rates of GAS and prevention of rheumatic fever, but certain newer agents are reported to achieve comparable bacteriologic and clinical cure rates when given for 5 days or less. However, definitive results from comprehensive studies are not available to allow full evaluation of these proposed shorter courses of oral antibiotic therapy. Therefore, they cannot be recommended at this time. In addition, these antibiotics have a much broader spectrum than penicillin and are generally more expensive, even when administered for short courses.

The majority of patients with GAS pharyngitis respond clinically to antimicrobial therapy, and GAS is eradicated from the pharynx. Posttreatment throat cultures are indicated only in the relatively few patients who remain symptomatic, whose symptoms recur, or who have had rheumatic fever or rheumatic heart disease and are, therefore, at unusually high risk for recurrence.

Antibiotic therapy for a patient with nonbullous impetigo can prevent local extension of the lesions, spread to distant infectious foci, and transmission of the infection to others. However, the ability of antibiotic therapy to prevent poststreptococcal glomerulonephritis has not been demonstrated. Patients with a few superficial, isolated lesions and no systemic signs can be treated with topical antibiotics. Mupirocin is a safe and effective agent that has become the topical treatment of choice. If there are widespread lesions or systemic signs, oral therapy with coverage for both GAS and *S. aureus* is needed. With the rapid emergence of methicillin-resistant *S. aureus* in many communities, consideration should be given to using clindamycin alone or a combination of trimethoprim-sulfamethoxazole and amoxicillin as first-line therapy. Oral cefuroxime is an effective treatment of perianal streptococcal disease.

Theoretical considerations and experimental data suggest that intravenous clindamycin is a more effective agent for the treatment of severe, invasive GAS infections than intravenous penicillin. However, because a small proportion (approximately 1%) of GAS isolates in the United States are resistant to clindamycin, clindamycin initially should be used in combination with penicillin for these infections until susceptibility to clindamycin has been established. If **necrotizing fasciitis** is suspected, immediate surgical exploration or biopsy is required to identify a deep soft-tissue infection that should be debrided immediately. Patients with **streptococcal toxic shock syndrome** require rapid and aggressive fluid replacement, management of respiratory or cardiac failure, if present, and anticipatory management of multiorgan system failure. Limited data suggest that intravenous immunoglobulin is effective as adjunctive therapy in the management of streptococcal toxic shock syndrome.

COMPLICATIONS

Suppurative complications from the spread of GAS to adjacent structures were extremely common in the preantibiotic era. Cervical lymphadenitis, peritonsillar abscess, retropharyngeal abscess, otitis media, mastoiditis, and sinusitis still occur in children in whom the primary illness has gone unnoticed or in whom treatment of the pharyngitis has been inadequate. GAS pneumonia can also occur.

Acute rheumatic fever (see Chapter 183.1) and acute poststreptococcal glomerulonephritis (see Chapter 511.1) are both nonsuppurative sequelae of infections with GAS that occur after an asymptomatic latent period. They are both characterized by disease remote from the site of the primary GAS infection. Acute rheumatic fever and acute glomerulonephritis differ in their clinical manifestations, epidemiology, and potential morbidity. In addition, acute glomerulonephritis follows a GAS infection of either the upper respiratory tract or the skin, but acute rheumatic fever only follows an infection of the upper respiratory tract.

Poststreptococcal Reactive Arthritis

Poststreptococcal reactive arthritis (PSRA) has been used to describe a syndrome characterized by the onset of acute arthritis following an episode of GAS pharyngitis in a patient whose illness does not fulfill the Jones criteria for the diagnosis of acute rheumatic fever. It is still unclear whether this entity represents a distinct syndrome or is a variant of acute rheumatic fever. Although PSRA usually involves the large joints like the arthritis of acute rheumatic fever, it may involve small peripheral joints, as well as the axial skeleton, and is typically nonmigratory, characteristics distinct from the arthritis of acute rheumatic fever. The latent period between the antecedent episode of GAS pharyngitis and PSRA may be considerably shorter (usually <10 days) than that typically seen with acute rheumatic fever (usually 14-21 days). In contrast to the arthritis of acute rheumatic fever, PSRA does not respond dramatically to therapy with aspirin or other nonsteroidal antiinflammatory agents. In addition, PSRA is usually not migratory, and fewer patients have a fever >38°C (100.4°F). Even though no more than half of patients with PSRA who have a throat culture performed have GAS isolated, all have serologic evidence of a recent GAS infection. Because a very small proportion of patients with PSRA have been reported to develop valvular heart disease subsequently, these patients should be carefully observed for several months for clinical evidence of carditis. Some recommend that these patients receive secondary prophylaxis for up to 1 yr. If clinical evidence of carditis is not observed, the prophylaxis can then be discontinued. If valvular disease is detected, the patient should be classified as having had acute rheumatic fever and should continue to receive secondary prophylaxis.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with *Streptococcus pyogenes*

Pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus pyogenes* (PANDAS) is a term proposed for a group of neuropsychiatric disorders (particularly obsessive-compulsive disorder, tic disorder, and Tourette syndrome) for which a possible relationship with GAS infections has been hypothesized (see Chapter 24). This relationship has not been proven. It has been proposed that this subset of patients with obsessive-compulsive and tic disorders may produce autoimmune antibodies in response to a GAS infection that crossreact with brain tissue similar to the autoimmune response believed to be responsible for the manifestations of Sydenham chorea. It has also been

suggested that secondary prophylaxis that prevents recurrences of rheumatic fever, including Sydenham chorea, might also be effective in preventing exacerbations of obsessive-compulsive and tic disorders in these patients, but clinical trials have not confirmed this. It has also been proposed that these patients may benefit from immunoregulatory therapy such as plasma exchange or intravenous immunoglobulin therapy, but these unproven modalities should only be utilized in a clinical research trial. That PANDAS may represent an extension of the spectrum of acute rheumatic fever is intriguing, but it should be considered only as a yet-unproven hypothesis. Until carefully designed and well-controlled studies have established a causal relationship between neurobehavioral abnormalities and GAS infections, routine diagnostic laboratory testing for GAS and antistreptococcal antibodies, long-term antistreptococcal prophylaxis, or immunoregulatory therapy (e.g., intravenous immunoglobulin, plasma exchange) to treat exacerbations of this disorder clearly are not recommended (see Chapter 24). It has also been suggested that a broad spectrum of infectious agents may have the ability to trigger exacerbations in children with these neurobehavioral disorders.

PROGNOSIS

The prognosis for appropriately treated GAS pharyngitis is excellent, and complete recovery is the rule. When therapy is instituted within 9 days of the onset of symptoms and continued for the full course, acute rheumatic fever is almost always prevented. There is no comparable evidence that acute poststreptococcal glomerulonephritis can be prevented once pharyngitis or pyoderma with a nephritogenic strain of GAS has occurred. In rare instances, particularly in neonates or in children whose response to infection is compromised, fulminant pneumonia, septicemia, and death may occur despite usually adequate therapy.

PREVENTION

The only specific indication for long-term use of an antibiotic to prevent GAS infections is for patients with a history of acute rheumatic fever and/or rheumatic heart disease. Mass prophylaxis is generally not feasible except to reduce the number of infections during epidemics of impetigo and to control epidemics of pharyngitis in military populations and in schools. Because the ability of antimicrobial agents to prevent GAS infections is limited, a group A streptococcal vaccine offers the possibility of a more effective approach.

Several candidate vaccines are in development, including a 30-valent M protein-based recombinant vaccine, another recombinant vaccine that includes several conserved non-M protein epitopes that induce protective antibody, and a M-protein vaccine that includes an epitope in a very conserved region of M protein to provide broad immunity. All of these vaccines are in relatively early stages of development.

Bibliography is available at Expert Consult.

183.1 Rheumatic Fever

Stanford T. Shulman

ETIOLOGY

Considerable evidence supports the link between antecedent GAS upper pharyngitis tract infections and acute rheumatic fever and rheumatic heart disease. As many as two-thirds of patients with an acute episode of rheumatic fever have history of an upper respiratory tract infection several weeks before, and the peak age and seasonal incidence of acute rheumatic fever closely parallel that of GAS pharyngitis. Patients with acute rheumatic fever almost always have serologic evidence of a recent GAS infection. Their antibody titers are usually considerably higher than those seen in patients with uncomplicated GAS infections. Outbreaks of GAS pharyngitis in closed communities, such as boarding schools or military bases, may be followed by outbreaks of acute rheumatic fever. Antimicrobial therapy that eliminates GAS from the pharynx also prevents initial episodes of acute rheumatic fever, and long-term, continuous antibiotic prophylaxis that prevents GAS pharyngitis also prevents recurrences of acute rheumatic fever.

Not all serotypes of GAS can cause rheumatic fever. When some GAS strains (e.g., M type 4) caused acute pharyngitis in a very susceptible rheumatic population, no recurrences of rheumatic fever occurred. In contrast, episodes of pharyngitis caused by other serotypes in the same population led to frequent recurrences of acute rheumatic fever, suggesting that the latter organisms were rheumatogenic. The concept of rheumatogenicity is further supported by the observation that although serotypes of GAS frequently associated with skin infection can often be isolated also from the upper respiratory tract, they rarely cause recurrences of rheumatic fever in individuals with a previous history of rheumatic fever or first episodes of rheumatic fever. In addition, certain serotypes of GAS (M types 1, 3, 5, 6, 18, 29) are more frequently isolated from patients with acute rheumatic fever than are other serotypes.

EPIDEMIOLOGY

The annual incidence of acute rheumatic fever in some developing countries exceeds 50 per 100,000 children, and very high rates are also seen in ethnic minority populations within Australia and New Zealand. Worldwide, rheumatic heart disease remains the most common form of acquired heart disease in all age groups, accounting for as much as 50% of all cardiovascular disease and as much as 50% of all cardiac admissions in many developing countries. Striking differences in the incidence of acute rheumatic fever and rheumatic heart disease among different ethnic groups are often evident within the same country; these differences are partially related to differences in socioeconomic status, and there is a genetic basis for increased susceptibility.

In the United States at the beginning of the 20th century, acute rheumatic fever was a leading cause of death among children and adolescents, with annual incidence rates of 100-200 per 100,000 population. In addition, rheumatic heart disease was a leading cause of heart disease among adults younger than 40 yr of age. At that time, as many as 25% of hospital beds in the United States were occupied by patients with acute rheumatic fever or its complications. By the 1940s, the annual incidence of acute rheumatic fever had decreased to 50 per 100,000 population, and over the next 4 decades, the decline in incidence accelerated rapidly. By the early 1980s, the annual incidence in some areas of the United States was as low as 0.5 per 100,000 population. This sharp decline in the incidence of acute rheumatic fever has been observed in other industrialized countries as well.

The explanation for this dramatic decline in the incidence of acute rheumatic fever and rheumatic heart disease in the United States and other industrialized countries is not clear but is likely related in large part to decline in circulating rheumatogenic strains causing acute pharyngitis. Historically, acute rheumatic fever was associated with poverty and overcrowding, particularly in urban areas. Much of the decline in the incidence of acute rheumatic fever in industrialized countries during the preantibiotic era is probably the result of improved living conditions. Of the various manifestations of poverty, crowding, which facilitates spread of GAS infections, is most closely associated with the incidence of acute rheumatic fever. The decline in incidence of acute rheumatic fever in industrialized countries over the past 4 decades is also attributable to the greater availability of medical care and to the widespread use of antibiotics. Antibiotic therapy of GAS pharyngitis is important in preventing initial attacks and, particularly, recurrences of the disease. In addition, the decline in the United States is attributed to a shift in the prevalent strains of GAS from rheumatogenic to nonrheumatogenic strains.

A dramatic outbreak of acute rheumatic fever in the Salt Lake City area began in early 1985, and 198 cases were reported by the end of 1989. Other outbreaks were reported between 1984 and 1988 in Columbus and Akron, OH; Pittsburgh, PA; Nashville and Memphis, TN; New York, NY; Kansas City, MO; Dallas, TX; and among Navy

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recruits in California and Army recruits in Missouri. In virtually all areas of the United States rates now have declined very substantially.

Certain rheumatogenic serotypes (types 1, 3, 5, 6, and 18) that were isolated infrequently during the 1970s and early 1980s dramatically reappeared during rheumatic fever outbreaks, and their appearance in selected communities was probably a major factor. GAS that are associated with rheumatogenicity often form highly mucoid colonies on throat culture plates.

In addition to the specific characteristics of the infecting strain of GAS, the risk of developing acute rheumatic fever is also dependent on various host factors. The incidence of both initial attacks and recurrences of acute rheumatic fever peaks in children 5-15 yr of age, the age of greatest risk for GAS pharyngitis. Patients who have had an attack of acute rheumatic fever tend to have recurrences, and the clinical features of the recurrences tend to mimic those of the initial attack. In addition, there appears to be a genetic predisposition to acute rheumatic fever. Studies in twins show a higher concordance rate of acute rheumatic fever in monozygotic than in dizygotic twin pairs. Some investigators have also demonstrated an association between susceptibility to rheumatic fever and specific human leukocyte antigen markers.

PATHOGENESIS

The details of the pathogenic link between a GAS infection of the upper respiratory tract and an attack of acute rheumatic fever, characterized by organ and tissue involvement at sites far removed from the pharynx, is still not clear. A major obstacle to understanding the pathogenesis of acute rheumatic fever and rheumatic heart disease has been the inability to establish an animal model. Several theories of pathogenesis have been proposed, notably the cytotoxicity theory and immunologic theories.

The cytotoxicity theory suggests that a GAS toxin is involved in the pathogenesis of acute rheumatic fever and rheumatic heart disease. GAS produces a number of enzymes that are cytotoxic for mammalian cardiac cells, such as streptolysin O, which has a direct cytotoxic effect on mammalian cells in tissue culture. Most proponents of the cytotoxicity theory have focused on this enzyme. However, a major problem with the cytotoxicity hypothesis is its inability to explain the substantial latent period (approximately 2-4 wk) between GAS pharyngitis and the onset of acute rheumatic fever.

An immune-mediated pathogenesis for acute rheumatic fever and rheumatic heart disease has been suggested by its clinical similarity to other illnesses with an immunopathogenesis and by the latent period between the GAS infection and acute rheumatic fever. The antigenicity of several GAS cellular and extracellular epitopes and their immunologic crossreactivity with cardiac antigenic epitopes also lends support to the hypothesis of molecular mimicry. Common epitopes are shared between certain GAS components (e.g., M protein, cell membrane, group A cell wall carbohydrate, capsular hyaluronate) and specific mammalian tissues (e.g., heart valve, sarcomere, brain, joint). For example, certain rheumatogenic M proteins (M1, M5, M6, and M19) share epitopes with human myocardial proteins such as tropomyosin and myosin. Additionally, the involvement of GAS superantigens such as pyrogenic exotoxins in the pathogenesis of acute rheumatic fever has been proposed.

A more recently proposed pathogenetic hypothesis is that the binding of an M protein N-terminus domain to a region of collagen type IV leads to an antibody response to the collagen, resulting in ground substance inflammation especially in subendothelial areas like cardiac valves and myocardium.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Because no clinical or laboratory finding is pathognomonic for acute rheumatic fever, T. Duckett Jones, in 1944, proposed guidelines to aid in diagnosis and to limit overdiagnosis. The **Jones Criteria,** as revised in 2015 by the American Heart Association (AHA) (Table 183-2), is now intended for diagnosis of the initial attack of acute rheumatic fever and recurrent attacks. There are **5 major** and **4 minor criteria** and a requirement of evidence of recent GAS infection. The 2015 revision now includes separate criteria for Low-Risk populations (defined as those with incidence ≤2 per 100,000 school-age children per year or all-age rheumatic heart disease prevalence of ≤1 per thousand population) and Moderate/High-Risk populations (defined as those with higher incidence or prevalence rates). Virtually all of the United States, Canada, and Western Europe are Low Risk, whereas Moderate/High-Risk populations include Maoris in New Zealand, aborigines in Australia, Pacific Islanders, and most developing countries. Diagnosis of a first attack or recurrent attack of acute rheumatic fever can be established when a patient fulfills 2 major or 1 major and 2 minor criteria and has evidence of preceding GAS infection. Diagnosis of recurrent acute rheumatic fever can also be made only in the Moderate/High Risk population by presence of 3 minor criteria with evidence of preceding GAS infection. In the 2015 Jones Criteria revision, a major change from previous versions expands the definition of the major criterion–carditis–to include subclinical evidence (i.e., in the absence of a murmur, echocardiographic evidence of mitral regurgitation [MR] meeting specific criteria to distinguish physiologic from pathologic MR) (Table 183-3). Areas in which the Jones Criteria differ in Low-Risk populations from Moderate/High-Risk populations relate to the major criterion of arthritis and in the minor criteria of arthralgia, definition of fever, and of elevated inflammatory markers (see Table 183-2

Table 183-2 Guidelines for the Diagnosis of Initial or Recurrent Attack of Rheumatic Fever (Jones Criteria, Updated 2015)[1-5]

MAJOR MANIFESTATIONS	MINOR MANIFESTATIONS	SUPPORTING EVIDENCE OF ANTECEDENT GROUP A STREPTOCOCCAL INFECTION
Carditis Polyarthritis Erythema marginatum Subcutaneous nodules Chorea	**Clinical features:** Arthralgia Fever **Laboratory features:** Elevated acute phase reactants: Erythrocyte sedimentation rate C-reactive protein	Positive throat culture or rapid streptococcal antigen test Elevated or increasing streptococcal antibody titer
	Prolonged P-R interval	

From Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 2015 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association (in press).

1. *Initial attack:* 2 major manifestations, or 1 major and 2 minor manifestations, plus evidence of recent GAS infection. *Recurrent attack:* 2 major, or 1 major and 2 minor, or 3 minor manifestations (the latter only in the Moderate/High-Risk population), plus evidence of recent GAS infection (see text).
2. Low-Risk population is defined as ARF incidence <2 per 100,000 school-age children per year, or all-age RHD prevalence of <1 per 1000 population. Moderate/High-Risk population is defined as ARF incidence >2 per 100,000 school-age children per year, or all-age RHD prevalence of >1 per 1000 population.
3. Carditis is now defined as clinical and/or subclinical (echocardiographic valvulitis). See Table 183-3.
4. Arthritis (major) refers only to polyarthritis in Low-Risk populations, but also to monoarthritis or polyarthralgia in Moderate/High-Risk populations.
5. Minor criteria for Moderate/High-Risk populations only include monoarthralgia (polyarthralgia for Low-Risk populations), fever of >38° C (>38.5° C in Low-Risk populations), ESR >30 mm/hr (>60 mm/hr in Low-Risk populations).

Table 183-3 Echocardiographic Findings in Rheumatic Valvulitis

PATHOLOGIC MITRAL REGURGITATION (ALL 4 MET)	PATHOLOGIC AORTIC REGURGITATION (ALL 4 MET)
1. Seen in at least 2 views	1. Seen in at least 2 views
2. Jet length ≥2 cm in at least 1 view	2. Jet length ≥1 cm in at least 1 view
3. Peak velocity >3 meters/second	3. Peak velocity >3 meters/second
4. Pan-systolic jet in at least 1 envelope	4. Pan-diastolic jet in at least 1 envelope

and text below). These changes are designed to make it easier to fulfill the Jones Criteria in patients from Moderate/High-Risk populations. Even with strict application of the Jones criteria, overdiagnosis as well as underdiagnosis of acute rheumatic fever may occur. There are 3 circumstances in which the diagnosis of acute rheumatic fever can be made without strict adherence to the Jones criteria: (1) when chorea occurs as the only major manifestation of acute rheumatic fever, (2) when indolent carditis is the only manifestation in patients who first come to medical attention only months after the apparent onset of acute rheumatic fever, and (3) in a limited number of patients with recurrences of acute rheumatic fever in particularly high-risk populations.

The 5 Major Criteria

Migratory Polyarthritis

Arthritis occurs in approximately 75% of patients with acute rheumatic fever and typically involves larger joints, particularly the knees, ankles, wrists, and elbows. Involvement of the spine, small joints of the hands and feet, or hips is uncommon. Rheumatic joints are classically hot, red, swollen, and exquisitely tender, with even the friction of bedclothes being uncomfortable. The pain can precede and can appear to be disproportionate to the objective findings. The joint involvement is characteristically migratory in nature; that is, a severely inflamed joint can become normal within 1-3 days without treatment, even as 1 or more other large joints become involved. Severe arthritis can persist for several weeks in untreated patients. Monoarticular arthritis is unusual unless antiinflammatory therapy is initiated prematurely, aborting the progression of the migratory polyarthritis. If a child with fever and arthritis is suspected to have acute rheumatic fever, it is frequently useful to withhold salicylates and observe for migratory progression. A dramatic response to even low doses of salicylates is another characteristic feature of the arthritis, and the absence of such a response should suggest an alternative diagnosis. Rheumatic arthritis is almost never deforming. Synovial fluid in acute rheumatic fever usually has 10,000-100,000 white blood cells/µL with a predominance of neutrophils, a protein level of approximately 4 g/dL, a normal glucose level, and forms a good mucin clot. Frequently, arthritis is the earliest manifestation of acute rheumatic fever and may correlate temporally with peak antistreptococcal antibody titers. There is often an inverse relationship between the severity of arthritis and the severity of cardiac involvement. In Moderate/High-Risk populations only, monoarthritis in the absence of prior inflammatory therapies or even polyarthralgia without frank objective signs of arthritis can fulfill this major criterion. Before polyarthralgia should be considered a major criterion in the Moderate/High-Risk population, other potential causes should be excluded.

Carditis

A major change in the 2015 revision of the Jones Criteria is the acceptance of subclinical carditis (defined as without a murmur of valvulitis but with echocardiographic evidence of valvulitis) or clinical carditis (with a valvulitis murmur) as fulfilling the major criterion of carditis in all populations. The echocardiographic features of subclinical carditis must meet those included in Table 183-3 in order to distinguish pathologic from physiologic degrees of valve regurgitation. Subclinical (echocardiographic) evidence of pathologic mitral regurgitation requires that a jet is seen in at least 2 views, the jet length is ≥2 cm in at least one view, peak jet velocity is >3 meters/second, and the peak systolic jet is in at least one envelope. Subclinical pathologic evidence of aortic regurgitation is similar except that the jet length is ≥1 cm in at least one view. Carditis and resultant chronic rheumatic heart disease are the most serious manifestations of acute rheumatic fever and account for essentially all of the associated morbidity and mortality. Rheumatic carditis is characterized by pancarditis, with active inflammation of myocardium, pericardium, and endocardium (see Chapter 438). Cardiac involvement during acute rheumatic fever varies in severity from fulminant, potentially fatal exudative pancarditis to mild, transient cardiac involvement. Endocarditis (valvulitis) is a universal finding in rheumatic carditis, whereas the presence of pericarditis or myocarditis is variable. Myocarditis and/or pericarditis without clinical evidence of endocarditis almost never is rheumatic carditis; alternate etiologies (especially viral) need to be sought. Most rheumatic heart disease is isolated mitral valvular disease or combined aortic and mitral valvular disease. Isolated aortic or right-sided valvular involvement is quite uncommon. Serious and long-term illness is related entirely to the severity of valvular heart disease as a consequence of a single attack or recurrent attacks of acute rheumatic fever. Valvular insufficiency is characteristic of both acute and convalescent stages of acute rheumatic fever, whereas mitral and/or aortic valvular stenosis usually appears years or even decades after the acute illness. However, in developing countries where acute rheumatic fever often occurs at a younger age, mitral stenosis and aortic stenosis may develop sooner after acute rheumatic fever than in developed countries and can occur in young children.

Acute rheumatic carditis usually presents as tachycardia and cardiac murmurs, with or without evidence of myocardial or pericardial involvement. Moderate to severe rheumatic carditis can result in cardiomegaly and heart failure with hepatomegaly and peripheral and pulmonary edema. Echocardiographic findings are not diagnostic but include pericardial effusion, decreased ventricular contractility, and aortic and/or mitral regurgitation. Mitral regurgitation is characterized typically by a high-pitched apical holosystolic murmur radiating to the axilla. In patients with significant mitral regurgitation, this may be associated with an apical mid-diastolic murmur of relative mitral stenosis. Aortic insufficiency is characterized by a high-pitched decrescendo diastolic murmur at the left sternal border.

Carditis occurs in approximately 50-60% of all cases of acute rheumatic fever. Recurrent attacks of acute rheumatic fever in patients who had carditis with their initial attack are associated with high rates of carditis with increasing severity of cardiac disease. The major consequence of acute rheumatic carditis is chronic, progressive valvular disease, particularly valvular stenosis, which can require valve replacement.

Chorea

Sydenham chorea occurs in approximately 10-15% of patients with acute rheumatic fever and usually presents as an isolated, frequently subtle, movement disorder. Emotional lability, incoordination, poor school performance, uncontrollable movements, and facial grimacing, all exacerbated by stress and disappearing with sleep, are characteristic. Chorea occasionally is unilateral (hemichorea). The latent period from acute GAS infection to chorea is usually substantially longer than for arthritis or carditis and can be months. Onset can be insidious, with symptoms being present for several months before recognition. Clinical maneuvers to elicit features of chorea include (1) demonstration of **milkmaid's grip** (irregular contractions and relaxations of the muscles of the fingers while squeezing the examiner's fingers), (2) spooning and pronation of the hands when the patient's arms are extended, (3) wormian darting movements of the tongue upon protrusion, and (4) examination of handwriting to evaluate fine motor movements. Diagnosis is based on clinical findings with supportive evidence of GAS antibodies. However, in the usual patient with a long latent period from the inciting streptococcal infection to onset of chorea, antibody levels have often declined to normal. Although the acute illness is distressing, chorea rarely, if ever, leads to permanent neurologic sequelae.

Figure 183-2 Polycyclic red borders of erythema marginatum in a febrile child with acute rheumatic fever. *(From Schachner LA, Hansen RC, editors:* Pediatric dermatology, *ed 3, Philadelphia, 2003, Mosby, p. 808.)*

Erythema Marginatum

Erythema marginatum is a rare (approximately 1% of patients with acute rheumatic fever) but characteristic rash of acute rheumatic fever. It consists of erythematous, serpiginous, macular lesions with pale centers that are not pruritic (Fig. 183-2). It occurs primarily on the trunk and extremities, but not on the face, and it can be accentuated by warming the skin.

Subcutaneous Nodules

Subcutaneous nodules are a rare (≤1% of patients with acute rheumatic fever) finding and consist of firm nodules approximately 1 cm in diameter along the extensor surfaces of tendons near bony prominences. There is a correlation between the presence of these nodules and significant rheumatic heart disease.

Minor Criteria

These are more nonspecific than major criteria, and the 2015 revised Jones Criteria have included some changes from previous criteria. The first of the 2 clinical minor criteria involve joint manifestations (only if arthritis is not used as a major criterion) and is defined as *polyarthralgia* in Low-Risk populations and *monoarthralgia* in Moderate/High-Risk populations. The second clinical minor manifestation is fever, defined as *at least 38.5° C* in Low-Risk populations and *at least 38.0° C* in Moderate/High-Risk populations. The 2 laboratory minor criteria are (1) elevated acute phase reactants (defined as ESR at least 60 mm/hr and/or CRP at least 3.0 mg/dl [30 mg/L] in Low-Risk populations, and ESR at least 30 mm/hr and/or CRP at least 3.0 mg/dl [30 mg/L] in Moderate/High-Risk populations) and (2) prolonged P-R interval on ECG (unless carditis is a major criterion). However, a prolonged P-R interval alone does not constitute evidence of carditis or predict long-term cardiac sequelae.

Recent Group A Streptococcus Infection

An absolute requirement for the diagnosis of acute rheumatic fever is supporting evidence of a recent GAS infection. Acute rheumatic fever typically develops 2-4 wk after an acute episode of GAS pharyngitis at a time when clinical findings of pharyngitis are no longer present and when only 10-20% of patients still harbor GAS in the throat. One-third of patients with acute rheumatic fever have no history of an antecedent pharyngitis. Therefore, evidence of an antecedent GAS infection is usually based on elevated or rising serum antistreptococcal antibody titers. A slide agglutination test (Streptozyme) purports to detect antibodies against 5 different GAS antigens. Although this test is rapid, relatively simple to perform, and widely available, it is less standardized and less reproducible than other tests and is not recommended as a diagnostic test for evidence of an antecedent GAS infection. If only a single antibody is measured (usually antistreptolysin O), only 80-85% of patients with acute rheumatic fever have an elevated titer; however, 95-100% have an elevation if 3 different antibodies (antistreptolysin O, anti–DNase B, antihyaluronidase) are measured. Therefore, when acute rheumatic fever is suspected clinically, multiple antibody tests should be performed. Except for chorea, the clinical findings of acute rheumatic fever generally coincide with peak antistreptococcal antibody responses. Most patients with chorea have elevation of antibodies to at least 1 GAS antigen. However, in patients with a long latent period from the inciting GAS infection, antibody levels may have declined to within the normal range. The diagnosis of acute rheumatic fever should *not* be made in those patients with elevated or increasing streptococcal antibody titers who do not fulfill the Jones criteria.

Table 183-4 Differential Diagnosis of Acute Rheumatic Fever

ARTHRITIS	CARDITIS	CHOREA
Juvenile idiopathic arthritis	Viral myocarditis	Huntington chorea
Reactive arthritis (e.g., *Shigella, Salmonella, Yersinia*)	Viral pericarditis	Wilson disease
Serum sickness	Infective endocarditis	Systemic lupus erythematosus
Sickle cell disease	Kawasaki disease	Cerebral palsy
Malignancy	Congenital heart disease	Tic disorder
Systemic lupus erythematosus	Mitral valve prolapse	Hyperactivity
Lyme disease *(Borrelia burgdorferi)*	Innocent murmurs	
Pyogenic arthritis		
Poststreptococcal reactive arthritis		

Differential Diagnosis

The differential diagnosis of rheumatic fever includes many infectious as well as noninfectious illnesses (Table 183-4). When children present with arthritis, a collagen vascular disease must be considered. Juvenile idiopathic arthritis in particular must be distinguished from acute rheumatic fever. Children with rheumatoid arthritis tend to be younger and usually have less joint pain relative to their other clinical findings than those with acute rheumatic fever. Spiking fevers, nonmigratory arthritis, lymphadenopathy, and splenomegaly are more suggestive of rheumatoid arthritis than acute rheumatic fever. The response to salicylate therapy is also much less dramatic with rheumatoid arthritis than with acute rheumatic fever. Systemic lupus erythematosus can usually be distinguished from acute rheumatic fever by antinuclear antibodies in systemic lupus erythematosus. Other causes of arthritis such as pyogenic arthritis, malignancies, serum sickness, Lyme disease, sickle cell disease, and reactive arthritis related to gastrointestinal infections (e.g., *Shigella, Salmonella, Yersinia*) should also be considered. Poststreptococcal reactive arthritis has been discussed earlier (see “Poststreptococcal Reactive Arthritis” above).

When carditis is the sole major manifestation of suspected acute rheumatic fever, viral myocarditis, viral pericarditis, Kawasaki disease, and infective endocarditis should also be considered. Patients with infective endocarditis may present with both joint and cardiac manifestations. These patients can usually be distinguished from patients with acute rheumatic fever by blood cultures and the presence of extracardiac findings (e.g., hematuria, splenomegaly, splinter hemorrhages). When chorea is the sole major manifestation of suspected acute rheumatic fever, Huntington chorea, Wilson disease, systemic lupus erythematosus, and various encephalitides should also be considered.

TREATMENT

All patients with acute rheumatic fever should be placed on bed rest and monitored closely for evidence of carditis. They can be allowed to ambulate when the signs of acute inflammation have subsided. However, patients with carditis require longer periods of bed rest.

Antibiotic Therapy

Once the diagnosis of acute rheumatic fever has been established and regardless of the throat culture results, the patient should receive 10 days of orally administered penicillin or amoxicillin or a single intramuscular injection of benzathine penicillin to ensure eradication of GAS from the upper respiratory tract. If penicillin-allergic, 10 days of erythromycin, azithromycin (5 days) or clindamycin is indicated. After this initial course of antibiotic therapy, long-term antibiotic prophylaxis should be instituted.

Antiinflammatory Therapy

Antiinflammatory agents (e.g., salicylates, corticosteroids) should be withheld if arthralgia or atypical arthritis is the only clinical manifestation of presumed acute rheumatic fever. Premature treatment with 1 of these agents may interfere with the development of the characteristic migratory polyarthritis and thus obscure the diagnosis of acute rheumatic fever. Acetaminophen can be used to control pain and fever while the patient is being observed for more definite signs of acute rheumatic fever or for evidence of another disease.

Patients with typical migratory polyarthritis and those with carditis without cardiomegaly or congestive heart failure should be treated with oral salicylates. The usual dose of aspirin is 50-70 mg/kg/day in 4 divided doses PO for 3-5 days, followed by 50 mg/kg/day in 4 divided doses PO for 3 wk and half that dose for another 2-4 wk. Determination of the serum salicylate level is not necessary unless the arthritis does not respond or signs of salicylate toxicity (tinnitus, hyperventilation) develop. There is no evidence that nonsteroidal antiinflammatory agents are any more effective than salicylates.

Patients with carditis and more than minimal cardiomegaly and/or congestive heart failure should receive corticosteroids. The usual dose of prednisone is 2 mg/kg/day in 4 divided doses for 2-3 wk followed by half the dose for 2-3 wk and then tapering of the dose by 5 mg/24 hr every 2-3 days. When prednisone is being tapered, aspirin should be started at 50 mg/kg/day in 4 divided doses for 6 wk to prevent rebound of inflammation. Supportive therapies for patients with moderate to severe carditis include digoxin, fluid and salt restriction, diuretics, and oxygen. The cardiac toxicity of digoxin is enhanced with myocarditis.

Termination of the antiinflammatory therapy may be followed by the reappearance of clinical manifestations or of elevated erythrocyte sedimentation rate and C-reactive protein (rebound). It may be prudent to increase salicylates or steroids until near-normalization is achieved.

Sydenham Chorea

Because chorea often occurs as an isolated manifestation after the resolution of the acute phase of the disease, antiinflammatory agents are usually not indicated. Sedatives may be helpful early in the course of chorea; phenobarbital (16-32 mg every 6-8 hr PO) is the drug of choice. If phenobarbital is ineffective, then haloperidol (0.01-0.03 mg/kg/24 hr divided bid PO) or chlorpromazine (0.5 mg/kg every 4-6 hr PO) should be initiated. Some patients may benefit from a few-week course of corticosteroids.

COMPLICATIONS

The arthritis and chorea of acute rheumatic fever resolve completely without sequelae. Therefore, the long-term sequelae of rheumatic fever are essentially limited to the heart (see Chapter 438).

The AHA has published updated recommendations regarding the use of prophylactic antibiotics to prevent infective endocarditis (see Chapter 437). The AHA recommendations no longer suggest routine prophylaxis for patients with rheumatic heart disease. However, the maintenance of optimal oral healthcare remains an important component of an overall healthcare program. For the relatively few patients with rheumatic heart disease in whom infective endocarditis prophylaxis remains recommended, such as those with a prosthetic valve or prosthetic material used in valve repair, the current AHA recommendations should be followed (see Chapter 437). These recommendations advise using an agent other than a penicillin to prevent infective endocarditis in those receiving penicillin prophylaxis for rheumatic fever because oral α-hemolytic streptococci are likely to have developed resistance to penicillin.

PROGNOSIS

The prognosis for patients with acute rheumatic fever depends on the clinical manifestations present at the time of the initial episode, the severity of the initial episode, and the presence of recurrences. Approximately 50-70% of patients with carditis during the initial episode of acute rheumatic fever recover with no residual heart disease; the more severe the initial cardiac involvement, the greater the risk is for residual heart disease. Patients without carditis during the initial episode are less likely to have carditis with recurrent attacks, but there is a stepwise increase in cardiac involvement as the number of episodes increases. In contrast, patients with carditis during the initial episode are very likely to have carditis with recurrences, and the risk for permanent heart damage increases with each recurrence. Patients who have had acute rheumatic fever are susceptible to recurrent attacks following reinfection of the upper respiratory tract with GAS, with approximately 50% risk with each GAS pharyngitis. Therefore, these patients require long-term continuous chemoprophylaxis.

Before antibiotic prophylaxis was available, 75% of patients who had an initial episode of acute rheumatic fever had one or more recurrences during their lifetimes. These recurrences were a major source of morbidity and mortality. The risk of recurrence is highest in the 1st 5 yr after the initial episode and decreases with time.

Approximately 20% of patients who present with "pure" chorea who are not given secondary prophylaxis develop rheumatic heart disease within 20 yr. Therefore, patients with chorea, even in the absence of other manifestations of rheumatic fever, require long-term antibiotic prophylaxis (see Table 183-5).

PREVENTION

Prevention of both initial and recurrent episodes of acute rheumatic fever depends on controlling GAS infections of the upper respiratory tract. Prevention of initial attacks (primary prevention) depends on identification and eradication of GAS causing acute pharyngitis. Individuals who have already suffered an attack of acute rheumatic fever are particularly susceptible to recurrences of rheumatic fever with any subsequent GAS upper respiratory tract infection, whether or not they are symptomatic. Therefore, these patients should receive continuous antibiotic prophylaxis to prevent recurrences (secondary prevention).

Primary Prevention

Appropriate antibiotic therapy instituted before the 9th day of symptoms of acute GAS pharyngitis is highly effective in preventing first attacks of acute rheumatic fever. However, approximately 30% of patients with acute rheumatic fever do not recall a preceding episode of pharyngitis and did not seek therapy.

Secondary Prevention

Secondary prevention is directed at preventing acute GAS pharyngitis in patients at substantial risk of recurrent acute rheumatic fever. Secondary prevention requires continuous antibiotic prophylaxis, which should begin as soon as the diagnosis of acute rheumatic fever has been made and immediately after a full course of antibiotic therapy has been completed. Because patients who have had carditis with their initial episode of acute rheumatic fever are at higher risk for having carditis with recurrences and for sustaining additional cardiac damage, they should receive long-term antibiotic prophylaxis well into adulthood and perhaps for life.

Patients who did not have carditis with their initial episode of acute rheumatic fever have a relatively low risk for carditis with recurrences.

Table 183-5	Chemoprophylaxis for Recurrences of Acute Rheumatic Fever (Secondary Prophylaxis)	
DRUG	**DOSE**	**ROUTE**
Penicillin G benzathine	600,000 IU for children weighing ≤60 lb 1.2 million IU for children weighing >60 lb, every 4 wk*	Intramuscular
or		
Penicillin V	250 mg, twice a day	Oral
or		
Sulfadiazine or sulfisoxazole	0.5 g, once a day for patients weighing ≤60 lb 1.0 g, once a day for patients weighing >60 lb	Oral
FOR PEOPLE WHO ARE ALLERGIC TO PENICILLIN AND SULFONAMIDE DRUGS		
Macrolide or azalide	Variable	Oral

*In high-risk situations, administration every 3 wk is recommended.

From Gerber MA, Baltimore RS, Eaton CB, et al: Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Circulation *119:1541–1551, 2009.*

Table 183-6	Duration of Prophylaxis for People Who Have Had Acute Rheumatic Fever: Recommendations of the American Heart Association
CATEGORY	**DURATION**
Rheumatic fever without carditis	5 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis but without residual heart disease (no valvular disease*)	10 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis and residual heart disease (persistent valvular disease*)	10 yr or until 40 yr of age, whichever is longer; sometimes lifelong prophylaxis

*Clinical or echocardiographic evidence.

From Gerber MA, Baltimore RS, Eaton CB, et al: Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Circulation *119:1541–1551, 2009.*

Antibiotic prophylaxis should continue in these patients until the patient reaches 21 yr of age or until 5 yr have elapsed since the last rheumatic fever attack, whichever is longer. The decision to discontinue prophylactic antibiotics should be made only after careful consideration of potential risks and benefits and of epidemiologic factors such as the risk for exposure to GAS infections.

The regimen of choice for secondary prevention is a single intramuscular injection of benzathine penicillin G (600,000 IU for children weighing ≤60 lb and 1.2 million IU for those weighing >60 lb) every 4 wk (Table 183-5). In certain high-risk patients, and in certain areas of the world where the incidence of rheumatic fever is particularly high, use of benzathine penicillin G every 3 wk may be necessary because serum concentrations of penicillin may decrease to marginally effective levels after 3 wk. In the United States, the administration of benzathine penicillin G every 3 wk is recommended only for those who have recurrent acute rheumatic fever despite adherence to a 4 wk regimen. In compliant patients, continuous oral antimicrobial prophylaxis can be used. Penicillin V 250 mg twice daily and sulfadiazine or sulfasoxazole 500 mg for those weighing ≤60 pounds or 1,000 mg for those weighing >60 pounds given once daily are equally effective when used in such patients. For the exceptional patient who is allergic to both penicillin and sulfonamides, a macrolide (erythromycin or clarithromycin) or azalide (azithromycin) may be used. Table 183-6 notes the duration of secondary prophylaxis.

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Chapter 184

Group B Streptococcus

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Group B streptococcus (GBS), or *Streptococcus agalactiae,* is a major cause of neonatal bacterial sepsis in the United States. Although advances in prevention strategies have led to a decline in the incidence of neonatal disease, GBS remains a major pathogen for neonates, pregnant women, and nonpregnant adults.

ETIOLOGY

Group B streptococci are facultative anaerobic Gram-positive cocci that form chains or diplococci in broth and small gray-white colonies on solid medium. GBS is definitively identified by demonstration of the Lancefield group B carbohydrate antigen, such as with latex agglutination techniques widely used in clinical laboratories. Presumptive identification can be established on the basis of a narrow zone of β-hemolysis on blood agar, resistance to bacitracin and trimethoprim-sulfamethoxazole, lack of hydrolysis of bile esculin, and elaboration of CAMP factor (named for the discoverers, **C**hristie, **A**tkins, and **M**unch-**P**etersen), an extracellular protein that, in the presence of the β toxin of *Staphylococcus aureus,* produces a zone of enhanced hemolysis on sheep's blood agar. Individual GBS strains are serologically classified according to the presence of 1 of the structurally distinct capsular polysaccharides, which are important virulence factors and stimulators of antibody-associated immunity. Ten GBS capsular types have been identified: types Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX.

EPIDEMIOLOGY

GBS emerged as a prominent neonatal pathogen in the late 1960s. For the next 2 decades, the incidence of neonatal GBS disease remained fairly constant, affecting 1.0-5.4/1,000 liveborn infants in the United States. Two patterns of disease were seen: **early-onset disease,** which presents at <7 days of age, and **late-onset disease,** which presents at 7 days of age or later. Since the early 1990s, widespread implementation of maternal intrapartum chemoprophylaxis has led to a striking decrease in the incidence of early-onset neonatal GBS disease in the United States, decreasing from 1.7 per 1,000 live births to 0.25 per 1,000 live births in recent years. This strategy has not had a significant effect on the incidence of late-onset disease, which has remained stable at approximately 0.3-0.4 per 1,000 live births (Fig. 184-1). The incidence of neonatal GBS disease is higher in premature and low-birthweight infants, although most cases occur in full-term infants. Rates of both early- and late-onset disease are higher in black infants.

Colonization by GBS in healthy adults is common. Vaginal or rectal colonization occurs in up to approximately 30% of pregnant women and is the usual source for GBS transmission to newborn infants. In the absence of maternal chemoprophylaxis, approximately 50% of infants born to colonized women acquire GBS colonization, and 1-2% of infants born to colonized mothers develop early-onset disease.

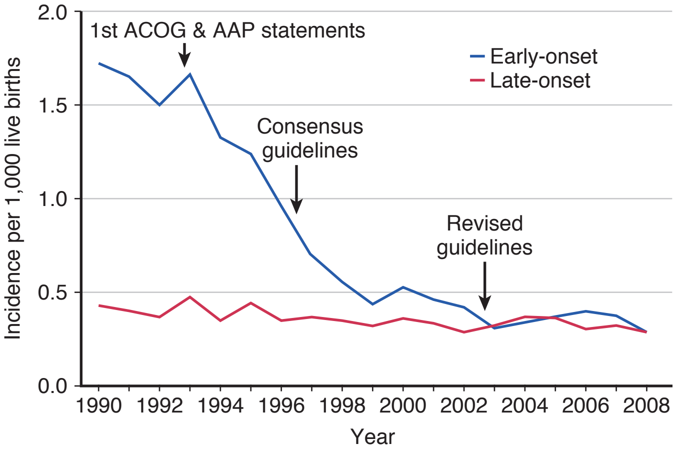

Figure 184-1 Incidence of early- and late-onset invasive group B streptococcal (GBS) disease–active bacterial core surveillance areas, 1990-2008, and activities for prevention of GBS disease. AAP, American Academy of Pediatrics; ACOG, American College of Obstetricians and Gynecologists. Incidence rates for 2008 are preliminary because the live birth denominator has not been finalized. *(Adapted from Jordan HT, Farley MM, Craig A, et al: Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease.* Pediatr Infect Dis J *27:1057–1064, 2008.)*

Heavy maternal colonization increases the risk for infant colonization and development of early-onset disease. Additional risk factors for early-onset disease include prolonged rupture of membranes, intrapartum fever, prematurity, maternal bacteriuria during pregnancy, or previous delivery of an infant who developed GBS disease. Risk factors for late-onset disease are less-well defined. Whereas late-onset disease may follow vertical transmission, horizontal acquisition from nursery or other community sources has also been described.

GBS is also an important cause of invasive disease in adults. GBS may cause urinary tract infections, bacteremia, endometritis, chorioamnionitis, and wound infection in pregnant and parturient women. In nonpregnant adults, especially those with underlying medical conditions such as diabetes mellitus, cirrhosis, or malignancy, GBS may cause serious infections such as bacteremia, skin and soft-tissue infections, bone and joint infections, endocarditis, pneumonia, and meningitis. In the era of maternal chemoprophylaxis, most invasive GBS infections occur in nonpregnant adults. Unlike neonatal disease, the incidence of invasive GBS disease in adults has increased substantially, doubling between 1990 and 2007.

The serotypes most commonly associated with neonatal GBS disease are types Ia, III, and V; Ib and IL are less frequent. Strains of serotype III are isolated in more than 50% of cases of late-onset disease and of meningitis associated with early- or late-onset disease. The serotype distribution of colonizing and invasive isolates from pregnant women is similar to that from infected newborns. In Japan, serotypes VI and VIII have been reported as common maternal colonizing serotypes, and case reports indicate that type VIII strains may cause neonatal disease indistinguishable from that caused by other serotypes.

PATHOGENESIS

A major risk factor for the development of early-onset neonatal GBS infection is maternal vaginal or rectal colonization by GBS. Infants acquire GBS via ascending infection or during passage through the birth canal. Fetal aspiration of infected amniotic fluid may occur. The incidence of early-onset GBS infection increases with the duration of rupture of membranes. Infection may also occur through seemingly intact membranes. In cases of late-onset infection, GBS may be vertically transmitted or acquired later from maternal or nonmaternal sources.

Several bacterial factors are implicated in the pathophysiology of invasive GBS disease. Foremost among these is the type-specific capsular polysaccharide. Strains that are associated with invasive disease in humans elaborate more capsular polysaccharide than do colonizing isolates. All GBS capsular polysaccharides are high-molecular-weight polymers and contain a short side chain terminating in *N*-acetylneuraminic acid (sialic acid). Studies in type III GBS show that the sialic acid component of the capsular polysaccharide prevents activation of the alternative complement pathway in the absence of type-specific antibody. Sialylated capsular polysaccharide on the GBS surface also interacts with sialic acid-binding lectins or siglecs on human leukocytes to dampen inflammatory gene activation. Thus, the capsular polysaccharide appears to exert a virulence effect by protecting the organism from opsonophagocytosis in the nonimmune host and by downregulating leukocyte activation. In addition, type-specific virulence attributes are suggested by the fact that type III strains are implicated in most cases of late-onset neonatal GBS disease and meningitis. Type III strains are taken up by brain endothelial cells more efficiently in vitro than are strains of other serotypes, although studies using acapsular mutant strains demonstrate that it is not the capsule itself that facilitates cellular invasion. A single clone of type III GBS is highly associated with late-onset disease and meningitis. This clonal group, ST-17, produces a surface-anchored protein called hypervirulent GBS adhesin (HvgA) that is not present in other GBS isolates. HvgA contributes to GBS adherence to intestinal and endothelial cells and mediates invasion into the central nervous system in an experimental infection model in mice. Other putative GBS virulence factors include GBS surface proteins, which may play a role in adhesion to host cells; C5a peptidase, which is postulated to inhibit the recruitment of polymorphonuclear cells into sites of infection; β-hemolysin, which has been associated with cell injury in vitro; and hyaluronidase, which has been postulated to act as a spreading factor in host tissues.

In a classic study among pregnant women colonized with type III GBS, those who gave birth to healthy infants had higher levels of capsular polysaccharide-specific antibody than those who gave birth to infants who developed invasive disease. In addition, there is a high correlation of antibody titer to GBS type III in mother–infant paired sera. These observations indicate that transplacental transfer of maternal antibody is critically involved in neonatal immunity to GBS. Optimal immunity to GBS also requires an intact complement system. The classical complement pathway is an important component of GBS immunity in the absence of specific antibody; in addition, antibody-mediated opsonophagocytosis may proceed via the alternative complement pathway. These and other results indicate that anticapsular antibody can overcome the prevention of C3 deposition on the bacterial surface by the sialic acid component of the type III capsule.

The precise steps between GBS colonization and invasive disease remain unclear. In vitro studies showing GBS entry into alveolar epithelial cells and pulmonary vasculature endothelial cells suggest that GBS may gain access to the bloodstream via invasion from the alveolar space, perhaps following intrapartum aspiration of infected fluid. β-Hemolysin/cytolysin may facilitate GBS entry into the bloodstream following inoculation into the lungs. However, highly encapsulated GBS strains enter eukaryotic cells poorly in vitro compared with capsule-deficient organisms are associated with virulence clinically and in experimental infection models.

GBS induces the release of proinflammatory cytokines. The group B antigen and the peptidoglycan component of the GBS cell wall are potent inducers of tumor necrosis factor-α release in vitro, whereas purified type III capsular polysaccharide is not. Even though the capsule plays a central role in virulence through avoidance of immune clearance, the capsule does not directly contribute to cytokine release and the resultant inflammatory response.

The complete genome sequences of types Ia, III, and V GBS strains have been reported, emphasizing a genomic approach to better understanding GBS. Analysis of these sequences shows that GBS is closely related to *Streptococcus pyogenes* and *Streptococcus pneumoniae.* Many known and putative GBS virulence genes are clustered in **pathogenicity islands** that also contain mobile genetic elements, suggesting that interspecies acquisition of genetic material plays an important role in genetic diversity.

Table 184-1 Characteristics of Early- and Late-Onset Group B Streptococcus Disease

	EARLY-ONSET DISEASE	LATE-ONSET DISEASE
Age at onset	0-6 days	7-90 days
Increased risk after obstetric complications	Yes	No
Common clinical manifestations	Sepsis, pneumonia, meningitis	Bacteremia, meningitis, other focal infections
Common serotypes	Ia, Ib, II, III, V	III predominates
Case fatality rate	4.7%	2.8%

Adapted from Schrag SJ, Zywicki S, Farley MM, et al: Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis, N Engl J Med *342:15–20, 2000.*

CLINICAL MANIFESTATIONS

Two syndromes of neonatal GBS disease are distinguishable on the basis of age at presentation, epidemiologic characteristics, and clinical features (Table 184-1). **Early-onset neonatal GBS disease** presents within the 1st 6 days of life and is often associated with maternal obstetric complications, including chorioamnionitis, prolonged rupture of membranes, and premature labor. Infants may appear ill at the time of delivery, and most infants become ill within the 1st 24 hr of birth. In utero infection may result in septic abortion. More than 80% of early-onset GBS disease presents as sepsis; pneumonia and meningitis are other common manifestations. Asymptomatic bacteremia is uncommon but can occur. In symptomatic patients, nonspecific signs such as hypothermia or fever, irritability, lethargy, apnea, and bradycardia may be present. Respiratory signs are prominent regardless of the presence of pneumonia and include cyanosis, apnea, tachypnea, grunting, flaring, and retractions. A fulminant course with hemodynamic abnormalities, including tachycardia, acidosis, and shock, may ensue. Persistent fetal circulation may develop. Clinically and radiographically, pneumonia associated with early-onset GBS disease is difficult to distinguish from respiratory distress syndrome. Patients with meningitis often present with nonspecific findings, as described for sepsis or pneumonia, with more specific signs of central nervous system involvement initially being absent.

Late-onset neonatal GBS disease occurs on or after 7 days of life and most commonly manifests as bacteremia (45-65%) and meningitis (25-35%). Focal infections involving bone and joints, skin and soft tissue, the urinary tract, or lungs may also be seen. Cellulitis and adenitis are often localized to the submandibular or parotid regions. In contrast to early-onset disease, maternal obstetric complications are not risk factors for the development of late-onset GBS disease. Infants with late-onset disease are often less-severely ill on presentation than infants with early-onset disease, and the disease is often less fulminant.

Invasive GBS disease in children beyond early infancy is uncommon. Bacteremia without a focus is the most common syndrome associated with childhood GBS disease beyond early infancy. Focal infections may include meningitis, pneumonia, endocarditis, and bone and joint infections.

DIAGNOSIS

A major challenge is distinguishing between respiratory distress syndrome and invasive neonatal GBS infection in preterm infants because the 2 illnesses share clinical and radiographic features. Severe apnea, early onset of shock, abnormalities in the peripheral leukocyte count, and greater lung compliance may be more likely in infants with GBS disease. Other neonatal pathogens, including *Escherichia coli* and *Listeria monocytogenes,* may cause illness that is clinically indistinguishable from that caused by GBS.

The diagnosis of invasive GBS disease is established by isolation and identification of the organism from a normally sterile site, such as blood, urine, or cerebrospinal fluid (CSF). Isolation of GBS from gastric or tracheal aspirates or from skin or mucous membranes indicates colonization and is not diagnostic of invasive disease. CSF should be examined in all neonates suspected of having sepsis, because specific central nervous system signs are often absent in the presence of meningitis, especially in early-onset disease. Antigen detection methods that use group B polysaccharide-specific antiserum, such as latex particle agglutination, are available for testing of urine, blood, and CSF, but these tests are less sensitive than culture. Moreover, antigen is often detected in urine samples collected by bag from otherwise healthy neonates who are colonized with GBS on the perineum or rectum.

Table 184-2 Recommended Duration of Therapy for Manifestations of Group B Streptococcus Disease

TREATMENT	DURATION
Bacteremia without a focus	10 days
Meningitis	2-3 wk
Ventriculitis	At least 4 wk
Septic arthritis or osteomyelitis	3-4 wk

Data from the American Academy of Pediatrics: Group B streptococcal infections. In Pickering LK, editor: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, pp. 680–685.*

LABORATORY FINDINGS

Frequently present are abnormalities in the peripheral white blood cell count, including an increased or decreased absolute neutrophil count, an elevated band count, an elevated ratio of bands to total neutrophils, or leukopenia. Elevation in the C-reactive protein level has been investigated as a potential early marker of GBS sepsis but is unreliable. Findings on chest radiograph are often indistinguishable from those of respiratory distress syndrome and may include reticulogranular patterns, patchy infiltrates, generalized opacification, pleural effusions, or increased interstitial markings.

TREATMENT

Penicillin G is the treatment of choice of confirmed GBS infection. Empirical therapy of neonatal sepsis that could be caused by GBS generally includes ampicillin and an aminoglycoside, both for the need for broad coverage pending organism identification and for synergistic bactericidal activity. Once GBS has been definitively identified and a good clinical response has occurred, therapy may be completed with penicillin alone. Especially in cases of meningitis, high doses of penicillin (450,000-500,000 units/kg/day) or ampicillin (300 mg/kg/day) are recommended because of the relatively high mean inhibitory concentration of penicillin for GBS as well as the potential for a high initial CSF inoculum. The duration of therapy varies according to the site of infection (Table 184-2) and should be guided by clinical circumstances. Extremely ill near-term patients with respiratory failure have been successfully treated with extracorporeal membrane oxygenation.

In cases of GBS meningitis, some experts recommend that additional CSF be sampled at 24-48 hr to determine whether sterility has been achieved. Persistent GBS growth may indicate an unsuspected intracranial focus or an insufficient antibiotic dose.

For **recurrent neonatal GBS** disease, standard intravenous antibiotic therapy followed by attempted eradication of GBS mucosal colonization has been suggested. This suggestion is based on the findings in several studies that invasive isolates from recurrent episodes are usually identical to each other and to colonizing isolates from the affected infant. Rifampin has most frequently been used for this purpose, but 1 report demonstrates that eradication of GBS colonization in infants is not reliably achieved by rifampin therapy. Optimal management of this uncommon situation remains unclear.

PROGNOSIS

Studies from the 1970s and 1980s showed that up to 30% of infants surviving GBS meningitis had major long-term neurologic sequelae, including developmental delay, spastic quadriplegia, microcephaly, seizure disorder, cortical blindness, or deafness; less severe neurologic complications may be present in other survivors. A study of infants who survived GBS meningitis diagnosed from 1998 through 2006 found that 19% had severe neurologic impairment and 25% had mild to moderate impairment at long-term follow-up. Periventricular leukomalacia and severe developmental delay may result from GBS disease and accompanying shock in premature infants, even in the absence of meningitis. The outcome of focal GBS infections outside of the central nervous system, such as bone or soft-tissue infections, is generally favorable.

In the 1990s, the case fatality rates associated with early- and late-onset neonatal GBS disease were 4.7% and 2.8%, respectively. Mortality is higher in premature infants; 1 study reported a case fatality rate of 30% in infants whose gestational age was <33 wk and 2% in infants whose gestational age was ≥37 wk. The case fatality rate in children aged 3 mo to 14 yr was 9%, and in nonpregnant adults was 11.5%.

PREVENTION

Persistent morbidity and mortality from perinatal GBS disease despite advances in neonatal care has spurred intense investigation into modes of prevention. Two basic approaches to GBS prevention have been investigated: (1) elimination of colonization from the mother or infant (chemoprophylaxis), and (2) induction of protective immunity (immunoprophylaxis).

Chemoprophylaxis

Administration of antibiotics to pregnant women **before** the onset of labor does not reliably eradicate maternal GBS colonization and is not an effective means of preventing neonatal GBS disease. Interruption of neonatal colonization is achievable through administration of antibiotics to the mother during labor (see Chapter 109). Infants born to GBS-colonized women with premature labor or prolonged rupture of membranes who were given intrapartum chemoprophylaxis had a substantially lower rate of GBS colonization (9% vs 51%) and early-onset disease (0% vs 6%) than did the infants born to women who were not treated. Maternal postpartum febrile illness was also decreased in the treatment group.

In the mid-1990s, guidelines for chemoprophylaxis were issued that specified administration of intrapartum antibiotics to women identified as high-risk by either culture-based or risk factor–based criteria. These guidelines were revised in 2002 after epidemiologic data indicated the superior protective effect of the culture-based approach in the prevention of neonatal GBS disease, and further revised guidelines were issued in 2010. According to current recommendations, vaginorectal GBS screening cultures should be performed for all pregnant women at 35-37 wk gestation, except for those with GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease. Any woman with a positive prenatal screening culture, GBS bacteriuria during pregnancy, or a previous infant with invasive GBS disease should receive intrapartum antibiotics. Women whose culture status is unknown (culture not done, incomplete, or results unknown) and who deliver prematurely (<37 wk gestation), experience prolonged rupture of membranes (≥18 hr), experience intrapartum fever (≥38°C [100.4°F]) or have a positive nucleic acid amplification test for GBS should also receive intrapartum chemoprophylaxis. Routine intrapartum prophylaxis is not recommended for women with GBS colonization undergoing planned cesarean delivery who have not begun labor or had rupture of membranes.

Penicillin remains the preferred agent for maternal chemoprophylaxis because of its narrow spectrum and the universal penicillin susceptibility of GBS isolates associated with human infection. Ampicillin is an acceptable alternative. If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent active against GBS should replace GBS prophylaxis. Occasional GBS isolates have demonstrated reduced in vitro susceptibility to penicillin and other β-lactam antibiotics in association with mutations in penicillin-binding proteins. However, such strains have not been reported in invasive infection. Because of recent reports indicating frequent resistance of GBS to clindamycin (up to 20%), cefazolin should be used in most cases of intrapartum chemoprophylaxis for penicillin-intolerant women. For penicillin-allergic women at high risk for anaphylaxis, clindamycin should be used, if isolates are demonstrated to be susceptible. Vancomycin should be used if isolates are resistant to, or demonstrate inducible resistance to, clindamycin or if clindamycin susceptibility is unknown.

The Centers for Disease Control and Prevention (CDC) guidelines also provide recommendations for secondary prevention of early onset GBS disease among newborns (Fig. 184-2). Extent of newborn evaluation and decision to institute empiric antibiotics is guided by clinical evaluation of the infant as well as gestational age, maternal risk factors, and receipt of intrapartum prophylaxis. In the era of maternal chemoprophylaxis, most cases of early onset disease are seen in infants born to women with negative prenatal screening cultures. Data from a large epidemiologic study indicate that the administration of maternal intrapartum antibiotics does not change the clinical spectrum or delay the onset of clinical signs in infants who developed GBS disease despite maternal prophylaxis.

A significant concern with maternal intrapartum prophylaxis has been that large-scale antibiotic use among parturient women might lead to increased rates of antimicrobial resistance or infection in infants with organisms other than GBS. To date, an increase in the incidence of non-GBS early-onset neonatal infections has been seen only in premature, low-birthweight, and very-low-birthweight infants in whom risk factors other than maternal chemoprophylaxis may play a role. At present, the substantial decline in early-onset neonatal GBS disease favors continued broad-scale intrapartum chemoprophylaxis, but continued surveillance is required.

A limitation of the maternal chemoprophylaxis strategy is that intrapartum antibiotic use is unlikely to have an impact on late-onset neonatal disease, miscarriages or stillbirths attributed to GBS, or adult GBS disease. In addition, with wider implementation of maternal chemoprophylaxis, an increasing percentage of early-onset neonatal disease has been in patients born to women with negative cultures, that is, false-negative screens.

Maternal Immunization

Human studies demonstrate that transplacental transfer of naturally acquired maternal antibody to the GBS capsular polysaccharide protects newborns from invasive GBS infection and that efficient transplacental passage of vaccine-induced GBS antibodies occurs. Conjugate vaccines composed of the GBS capsular polysaccharides coupled to carrier proteins have been produced for human use. In early clinical trials, conjugate GBS vaccines were well tolerated and induced levels of functional antibodies well above the range believed to be protective in greater than 90% of recipients. A vaccine containing type III polysaccharide coupled to tetanus toxoid was safely administered to pregnant women and elicited functionally active type-specific antibody that was efficiently transported to the fetus. Administration of a multivalent polysaccharide-protein vaccine before or during pregnancy should lead to transplacental passage of vaccine-induced antibody that protects the fetus and newborn against infection by several GBS serotypes. Such a vaccine would eliminate the need for cumbersome cultures during pregnancy, would circumvent the various risks associated with large-scale antibiotic prophylaxis, and would likely have an impact on

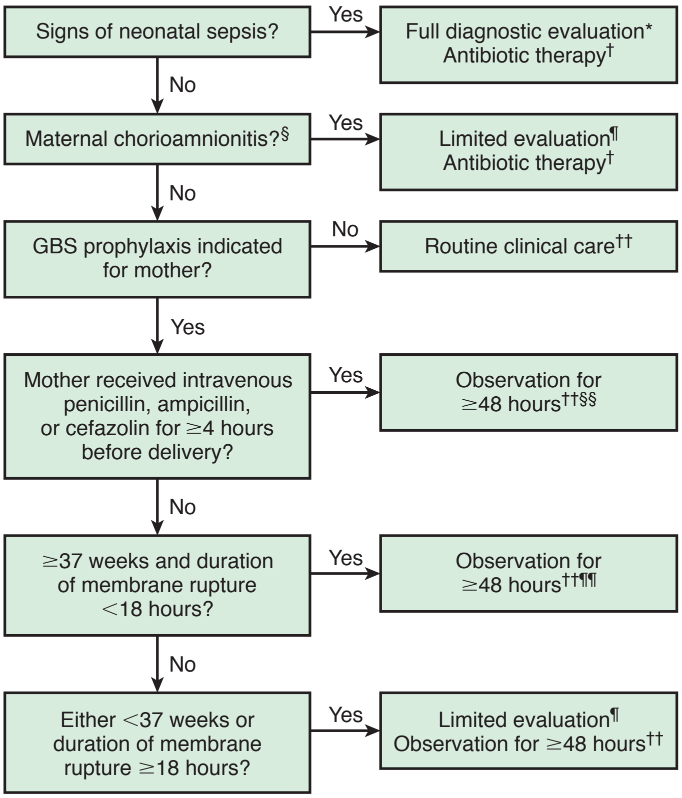

* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at age 6–12 hours.

Figure 184-2 Algorithm for secondary prevention of early-onset group B streptococcal disease among newborns. *(From Verani JR, McGee L, Schrag SJ, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC 2010.* MMWR Recomm Rep *59[RR-10]:22, 2010.)*

both early- and late-onset disease. Intrapartum chemoprophylaxis will likely remain an important aspect of prevention, particularly for women in whom opportunities for GBS immunization are missed and for infants born so early that levels of transplacentally acquired antibodies may not be high enough to be protective.

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Chapter 185

Non–Group A or B Streptococci

David B. Haslam

The genus *Streptococcus* is exceptionally diverse and includes the major human pathogens *Streptococcus pyogenes* (group A streptococcus), *Streptococcus agalactiae* (group B streptococcus) and *Streptococcus pneumoniae* (Table 185-1). Other important pathogens include large-colony species bearing groups C and G Lancefield antigens and numerous small-colony variants that may or may not express Lancefield carbohydrate antigen included among the viridians streptococci (Table 185-1). This chapter focuses on *Streptococcus dysgalactiae* subspecies *equisimilis,* commonly known as "group C and G streptococci," while Chapter 182 discusses *S. pneumoniae,* and Chapter 186 discusses enterococci, formerly classified among the streptococci but now comprising their own genus.

All members of the genus *Streptococcus* are Gram-positive, catalase-negative organisms. Lancefield carbohydrate antigen, hemolytic activity, and colony morphology have classically been used to further distinguish and classify streptococci. These features provide a useful framework for the clinician and are still the most commonly used classification schema. However, grouping based on these phenotypic features does not precisely correlate with genetic relatedness, and it is becoming clear that disease propensity is better correlated with sequence homology than Lancefield grouping or hemolytic activity. As a consequence, the streptococci are undergoing taxonomic reclassification as genome sequence information becomes available.

In this chapter, groups C and G streptococci refer exclusively to the large colony-forming organisms, often called *S. pyogenes–like,* as their microbiologic and clinical features tend to mimic those of group A streptococcus. Despite their different Lancefield antigens, the group C and G streptococci are nearly identical genetically and are placed within the *S. dysgalactiae*, *equisimilis* subspecies. Their genome sequences are approximately equidistant between *S. pyogenes* and animal pathogens that bear the group C antigen, which are classified as *S. dysgalactiae* subspecies *dysgalactiae.* It is likely that *S. dysgalactiae* will be split into distinct species in the future, when their sequence-based grouping will reflect their propensity to cause human (represented by subspecies *equisimilis*) and animal (represented by subspecies *dysgalactiae*) infections.

The groups C and G streptococci share a number of virulence factors with *S. pyogenes*, including the production of streptolysin O, M protein, streptococcal pyrogenic exotoxin B, and hyaluronidase. The M protein is similar to that of *S. pyogenes* and may account for postinfectious glomerulonephritis that is occasionally seen after infection with these organisms. A toxic-shock–like syndrome associated with groups C and G streptococcal infection has been related to production of a pyrogenic exotoxin by *S. dysgalactiae* subsp. *equisimilis.*

Groups C and G streptococci are common habitants of the pharynx, being detected in up to 5% of asymptomatic children. Other potential sites of colonization include the skin and gastrointestinal tract. Colonization of the vagina is reported and may be the source of occasional *S. dysgalactiae* subsp. *equisimilis* isolated from the umbilicus of healthy neonates.

Clinical manifestations of disease caused by groups C and G streptococci overlap those of *S. pyogenes*. In children, these organisms are implicated most commonly in pharyngitis. The true role of these organisms as a cause of pharyngitis is difficult to determine because asymptomatic colonization is common. Nevertheless, several epidemics of group C and group G streptococcal pharyngitis have been reported, including foodborne outbreaks. It is possible that primary infection with groups C and G streptococci has the same potential to

Table 185-1	Relationship of Streptococci Identified by Hemolysis and Lancefield Grouping to Sites of Colonization and Disease			
	GROUP A STREPTOCOCCUS *(S. PYOGENES)*	**GROUP B STREPTOCOCCUS *(S. AGALACTIAE)***	**OTHER β-HEMOLYTIC STREPTOCOCCI**	**VIRIDANS STREPTOCOCCI**
Hemolysis	β	β	β	α
Lancefield group	A	B	C-H, K-V Especially C and G	
Species or strains	M types (>180)	Serotypes (Ia, Ib, II, III, IV, V, VI, VII, and VIII)		*Streptococcus bovis* *Streptococcus mitis* *Streptococcus mutans* *Streptococcus sanguis* Many others
Normal flora	Pharynx, skin, anus	Gastrointestinal and genitourinary tract	Pharynx, skin, gastrointestinal and genitourinary tracts	Pharynx, nose, skin, genitourinary tract
Common human diseases	Pharyngitis, tonsillitis, erysipelas, impetigo, septicemia, wound infections, necrotizing fasciitis, cellulitis, meningitis, pneumonia, scarlet fever, toxic shock–like syndrome, rheumatic fever, acute glomerulonephritis	Puerperal sepsis chorioamnionitis, endocarditis, neonatal sepsis, meningitis, osteomyelitis, pneumonia	Wound infections, puerperal sepsis, cellulitis, sinusitis, endocarditis, brain abscess, sepsis, nosocomial infections, opportunistic infections	Endocarditis, human bite infections

α, Partial hemolysis; β, complete hemolysis; γ, no hemolysis (nonhemolytic).

result in disease as infection with *S. pyogenes,* whereas an immunologic response protects against subsequent disease, explaining why children in tropical environments are commonly colonized but less likely to have symptoms. Indeed, *S. dysgalactiae* subsp. *equisimilis* exposure may provide some cross-protection against *S. pyogenes* infection. When pharyngitis is a feature of group C or G infection, the clinical presentation is indistinguishable from *S. pyogenes*–associated pharyngitis. Isolated case reports have described group C streptococcal pneumonia in children, where abscess formation, empyema, and bacteremia are common. Additional respiratory infections include rare reports of groups C and G streptococcal epiglottitis and sinusitis.

Groups C and G streptococci are a significant cause of skin and soft-tissue infections. As with *S. pyogenes,* lymphangitis can complicate superficial infections caused by groups C and G organisms. Musculoskeletal infections, particularly pyogenic arthritis, occasionally are caused by groups C and G streptococci. Pediatric cases are uncommon but may be increasing in incidence.

These organisms can cause neonatal septicemia similar to early-onset group B streptococcal disease. Risk factors include prematurity and prolonged rupture of membranes. Respiratory distress, hypotension, apnea, bradycardia, and disseminated intravascular coagulation may be seen, and associated maternal infection is common. Neonatal toxic shock syndrome associated with *S. dysgalactiae* subsp. *equisimilis* has also been described.

Endocarditis, bacteremia, brain abscess, and toxic shock caused by groups C and G streptococcal infection have all been described but are uncommon in children. These infections generally occur in children with immune deficits or in adolescents after delayed recognition of sinusitis.

Reactive arthritis has been described after group C streptococcal infection; however, unlike *S. pyogenes*, there has been no convincing evidence of acute rheumatic fever after infection with group C streptococcus, and therefore antibiotic prophylaxis is not recommended following reactive arthritis with this this organism.

Treatment of groups C and G infections is similar to that of *S. pyogenes*. These organisms retain susceptibility to penicillin and other β-lactams. Other agents with reliable activity against groups C and G streptococci include linezolid, quinupristin-dalfopristin, and vancomycin, though occasional isolates demonstrate tolerance to vancomycin. Clindamycin and macrolides have poor bactericidal activity against these organisms, particularly against group G streptococci. Resistance to quinolones is reported, and up to 70% of group C streptococci are resistant to tetracycline.

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Chapter 186

Enterococcus

David B. Haslam

Enterococcus, long recognized as a pathogen in select populations, has become a common and particularly troublesome cause of hospital-acquired infection over the past 2 decades. Enterococci were formerly classified with *Streptococcus bovis* and *Streptococcus equinus* as Lancefield group D streptococci but are now placed in a separate genus and are notorious for their frequent resistance to antibiotics.

ETIOLOGY

Enterococci are Gram-positive, catalase-negative facultative anaerobes that grow in pairs or short chains. Most are nonhemolytic (also called γ-hemolytic) on sheep blood agar, although some isolates have α- or β-hemolytic activity. Enterococci are distinguished from most Lancefield groupable streptococci by their ability to grow in bile and hydrolyze esculin. Enterococci are able to grow in 6.5% NaCl and hydrolyze L-pyrrolidonyl-β-naphthylamide, features used by clinical laboratories to distinguish enterococci from group D streptococcus. Identification at the species level is enabled by differing patterns of carbohydrate fermentation.

EPIDEMIOLOGY

Enterococci are normal inhabitants of the gastrointestinal tract of humans, and organisms throughout the animal kingdom, suggesting

they are highly evolved to occupy this niche. Oral secretions and dental plaque, the upper respiratory tract, skin, and vagina may also be colonized by *Enterococcus. Enterococcus faecalis* is the predominant organism, with colonization commonly occurring in the 1st wk of life. By the time of adulthood, *E. faecalis* colonization is nearly ubiquitous. *Enterococcus faecium* colonization is less consistent, although approximately 25% of adults harbor this organism. Disruption of the normal intestinal microbiota by antibiotic exposure or hematopoietic stem cell transplantation markedly enriches for fecal enterococcal abundance and dramatically increases the risk of subsequent bloodstream infection.

E. faecalis accounts for approximately 80% of enterococcal infections, with almost all of the remaining infections caused by *E. faecium.* Only rarely are other species, such as *Enterococcus gallinarum* and *Enterococcus casseliflavus,* associated with invasive infection, but these organisms are notable for their intrinsic low-level vancomycin resistance. Whole-genome sequencing suggests that the patient's indigenous flora is the source of enterococcal infection in most cases. However, direct spread from person to person or from contaminated medical devices may occur, particularly within newborn nurseries and intensive care units where nosocomial spread has resulted in hospital outbreaks.

PATHOGENESIS

Enterococci are not aggressively invasive organisms, usually causing disease only in children with damaged mucosal surfaces or impaired immune response. Their dramatic emergence as a cause of nosocomial infection is predominantly a result of their resistance to antibiotics commonly used in the hospital setting. Hospital-associated enterococci generally lack CRISPR (clustered regularly interspaced short palindromic repeats) elements. Their diverse antimicrobial resistance repertoire is likely related to deficient CRISPR-mediated defense against phage-mediated horizontal gene transfer. Secreted and cell-surface molecules are implicated in pathogenesis. Adhesion-promoting factors such as the surface protein Eps likely account for the propensity of these organisms to cause endocarditis and urinary tract infections (UTIs). The ability to form biofilms likely facilitates the colonization of urinary and vascular catheters. Other proposed virulence factors include cytolysin, aggregation substance, gelatinase, and extracellular superoxide.

Antimicrobial Resistance

Enterococci are highly resistant to cephalosporins and semisynthetic penicillins such as nafcillin, oxacillin, and methicillin. They are moderately resistant to extended-spectrum penicillins such as ticarcillin and carbenicillin. Ampicillin, imipenem, and penicillin are the most active β-lactams against these organisms. Some strains of *E. faecalis* and *E. faecium* demonstrate decreased resistance to β-lactam antibiotics due to mutations in penicillin binding protein 5. In addition, occasional strains of *E. faecalis* produce a plasmid-encoded β-lactamase similar to that found in *Staphylococcus.* These isolates are completely resistant to penicillins, necessitating the combination of a penicillin plus a β-lactamase inhibitor or the use of imipenem or vancomycin. Any active drug may be insufficient if used alone for serious infections wherein high bactericidal activity is desired (Tables 186-1 and 186-2).

All enterococci have intrinsic low-level resistance to aminoglycosides because these antibiotics are poorly transported across the *Enterococcus* cell wall. Concomitant use of a cell wall active agent, such as a β-lactam or glycopeptide antibiotic, improves the permeability of the cell wall for the aminoglycosides, resulting in synergistic killing. However, some isolates demonstrate high-level resistance, defined as mean inhibitory concentration (MIC) >2,000 µg/mL a result of modification or inactivation of aminoglycoside agents. Strains demonstrating high-level resistance, and even some moderately resistant isolates, are not affected synergistically by aminoglycosides and cell wall–active antibiotics.

Resistance to almost all other antibiotic classes, including tetracyclines, macrolides, and chloramphenicol, has been described among the enterococci, necessitating individual susceptibility testing for these antibiotics when their use is considered. Despite apparent susceptibility in vitro, trimethoprim-sulfamethoxazole has poor activity in vivo and should not be used as the primary agent against *Enterococcus* infections.

Table 186-1 Intrinsic Resistance Mechanisms Among Enterococci

ANTIMICROBIAL	MECHANISM
Ampicillin, penicillin	Altered binding protein
Aminoglycoside (low level)	Decreased permeability, altered ribosomal binding
Clindamycin	Altered ribosomal binding
Erythromycin	Altered ribosomal binding
Tetracyclines	Efflux pump
Trimethoprim-sulfamethoxazole	Utilize exogenous folate

Table 186-2 Acquired Resistance Mechanisms Among Enterococci

ANTIMICROBIAL	MECHANISM
Ampicillin, penicillin (high level)	Mutation of PBP5
Aminoglycoside (high level)	Enzyme modification
Quinolones	DNA gyrase mutation
Chloramphenicol	Efflux pump
Glycopeptide	Altered cell wall binding
Quinupristin/dalfopristin	Ribosomal modification, efflux pump
Linezolid	Point mutation
Daptomycin	Unknown

Vancomycin has traditionally been effective against *Enterococcus* isolates, but resistance to vancomycin, defined as MIC >32 µg/mL, and other glycopeptides, including teicoplanin, is increasingly common. The emergence of vancomycin-resistant *Enterococcus* (VRE) has become a major challenge in the care of hospitalized patients. In particular, mortality in patients with VRE bloodstream infections is considerable, and treatment is complicated by frequent resistance of VRE to most other antibiotic classes. Both high- and moderate-level resistance are described in *E. faecalis* and *E. faecium.* High-level resistance (MIC ≥64 µg/mL) can be transferred by way of conjugation and usually results from plasmid-mediated transfer of the *vanA* gene. High-level resistance is most common among *E. faecium,* but is increasingly seen among *E. faecalis* isolates. Moderate-level resistance (MIC 8-256 µg/mL) results from a chromosomal homolog of *vanA,* known as *vanB.* Isolates that harbor the *vanB* gene are only moderately resistant to vancomycin and initially demonstrate susceptibility to teicoplanin, although resistance can emerge during therapy. Resistance to newer agents, including linezolid and daptomycin, is rare thus far. Linezolid resistance is a result of mutations in the 26S ribosomal subunit, whereas daptomycin resistance is associated with mutations in genes required for membrane synthesis and repair.

CLINICAL MANIFESTATIONS

Enterococcus infections traditionally occurred predominantly in newborn infants; infection in older children is increasingly common. Most *Enterococcus* infections occur in patients with breakdown of normal physical barriers such as the gastrointestinal tract, skin, or urinary tract. Other risk factors for *Enterococcus* infection include

prolonged hospitalization, indwelling vascular catheters, prior use of antibiotics, and compromised immunity.

Neonatal Infections

Enterococcus accounts for up to 15% of all neonatal bacteremia and septicemia. Like group B streptococcus infections, *Enterococcus* infections are seen in 2 distinct settings in neonatal patients. Early-onset infection (<7 days of age) may mimic early-onset group B streptococcus septicemia, but tends to be milder. Early-onset *Enterococcus* sepsis most often occurs in full-term infants who are otherwise healthy. Late-onset infection (≥7 days of age) is associated with risk factors such as extreme prematurity, presence of an intravascular catheter, or necrotizing enterocolitis, or it follows an intraabdominal surgical procedure. Symptoms in late-onset disease are more severe than those in early-onset disease and include apnea, bradycardia, and deteriorating respiratory function. Focal infections such as scalp abscess and catheter infection are commonly associated. Mortality rates range from 6% in early-onset septicemia to 15% in late-onset infections associated with necrotizing enterocolitis.

Enterococci are an occasional cause of meningitis. In neonates in particular, meningitis usually occurs as a complication of septicemia. Alternatively, the organism may gain access to the central nervous system by way of contiguous spread, such as through a neural tube defect or in association with an intraventricular shunt. *Enterococcus* meningitis can be associated with minimal abnormality of cerebrospinal fluid.

Infections in Older Children

Enterococcus rarely causes UTIs in healthy children but accounts for approximately 15% of cases of nosocomially acquired UTIs in both children and adults. Presence of an indwelling urinary catheter is the major risk factor for nosocomial UTIs. *Enterococcus* is frequently isolated in intraabdominal infections following intestinal perforation or surgery. The significance of enterococci in polymicrobial infections has been questioned, although reported mortality rates are higher when intraabdominal infections include enterococci. *Enterococcus* is increasingly common as a cause of nosocomial bacteremia; these organisms accounted for approximately 10% of nosocomial bloodstream infection in children, ranking second only to coagulase-negative staphylococci. Predisposing factors for enterococcal bacteremia and endocarditis include an indwelling central venous catheter, gastrointestinal surgery, immunodeficiency, and cardiovascular abnormalities. Risk factors for vancomycin-resistant enterococcal bacteremia include prolonged mechanical ventilation, immunosuppression, and recent vancomycin exposure.

TREATMENT

Treatment of invasive *Enterococcus* infections must recognize that these organisms are resistant to antimicrobial agents frequently used as empirical therapy. In particular, cephalosporins should not be relied upon in situations where *Enterococcus* is known or suspected to be involved. In general, in the immunocompetent host, minor localized infections caused by susceptible *Enterococcus* can be treated with ampicillin alone. Antibiotics containing β-lactamase inhibitors (clavulanate or sulbactam) provide advantage only for the few organisms whose resistance is owing to production of β-lactamase. In uncomplicated UTIs, nitrofurantoin is efficacious when the organism is known to be sensitive to this antibiotic.

Invasive infections, such as sepsis, meningitis, and endocarditis, are usually treated with a combination of penicillin or ampicillin and an aminoglycoside when the isolate is susceptible. Vancomycin can be substituted for the penicillins in allergic patients, but should be used with an aminoglycoside, because vancomycin alone is not bactericidal. Endocarditis from strains possessing high-level aminoglycoside resistance may relapse even after prolonged therapy. High-dose or continuous infusion penicillin has been proposed for treatment of these infections in adults, yet ultimately valve replacement may be necessary. In patients with catheter-associated enterococcal bacteremia, the catheter should be removed promptly in most cases, although salvage of infected lines has occurred with the combined use of ampicillin or vancomycin with an aminoglycoside.

Treatment of Vancomycin-Resistant Enterococci

The treatment of serious infections caused by multiresistant, vancomycin-resistant strains is particularly challenging. Linezolid, an oxazolidinone antibiotic that inhibits protein synthesis, is bacteriostatic against most *E. faecium* and *E. faecalis,* including vancomycin-resistant isolates. Response rates are generally over 90%, including cases of bacteremia and sepsis, and this antibiotic has become the preferred agent in treatment of VRE infections in many institutions. Anecdotal reports reveal the success of linezolid in treating meningitis caused by vancomycin-resistant enterococci. Unfortunately, as seen with other antibiotics, linezolid resistance is documented and nosocomial spread of these organisms can occur. Linezolid frequently causes reversible bone marrow suppression after prolonged use and is associated with rare occurrences of lactic acidosis and irreversible peripheral neuropathy. Serotonin syndrome may be seen in patients taking concomitant selective serotonin uptake inhibitor antidepressants. Oxazolidinones in development include tedizolid, which has better in vitro activity against enterococci and appears to have favorable pharmacokinetic and toxicity profiles when compared to linezolid.

Quinupristin/dalfopristin is a combined streptogramin antibiotic that inhibits bacterial protein synthesis at 2 different stages. It has activity against most *E. faecium* strains, including those with high-level vancomycin resistance. Approximately 90% of *E. faecium* strains are susceptible to quinupristin/dalfopristin in vitro. Notably, it is inactive against *E. faecalis* and therefore should not be used as the sole agent against Gram-positive organisms until culture results exclude the presence of *E. faecalis*. Studies in children suggest that this antibiotic is effective and generally well tolerated, though episodes of arthralgia and myalgia during therapy are reported. Emergence of resistance to quinupristin/dalfopristin is rare but has been demonstrated.

Newer antibiotics with reliable activity against VRE include daptomycin and tigecycline. Daptomycin is a cyclic lipopeptide that is rapidly bactericidal against a broad range of Gram-positive organisms. The antibiotic inserts into the bacterial cell wall, causing membrane depolarization and cell death. It has been approved for the treatment of adults with serious skin and soft tissue infections, right-sided endocarditis, and bacteremia due to susceptible organisms. Most strains of VRE (both *E. faecium* and *E. faecalis*) are susceptible to daptomycin in vitro, and its efficacy in adult patients with VRE appears to be similar to that of linezolid. Experience with daptomycin in children is limited, particularly in the setting of *Enterococcus* infections. However, based on the experience with adult patients, daptomycin may be an alternative to linezolid when resistance or side-effects limit utility of that antibiotic. Daptomycin dosages may need to be higher in children when compared to adults because of more rapid renal clearance. The antibiotic has unreliable activity in the lung and therefore should not be used as a sole agent to treat pneumonia. Resistance of both *Staphylococcus aureus* and *Enterococcus* to daptomycin has rarely been described, sometimes arising during therapy. Ceftaroline, a fifth-generation cephalosporin with activity against methicillin-resistant *S. aureus*, has activity against many *E. faecalis* strains and may be highly synergistic with daptomycin against daptomycin-nonsusceptible strains.

Tigecycline is the first clinically available glycylcycline antibiotic, an expended-spectrum derivative of the tetracycline family. The agent inhibits protein synthesis by binding to the 30S ribosome and is bacteriostatic against susceptible organisms. Tigecycline has broad activity against Gram-positive, Gram-negative, and anaerobic organisms, including methicillin-resistant *S. aureus* and VRE, and is approved for the treatment of adults with skin and soft-tissue infections and intraabdominal infections caused by susceptible organisms. Its efficacy in VRE infections has not yet been demonstrated in clinical trials and there is little published experience with the use of tigecycline in children thus

far. Like other tetracycline antibiotics, tigecycline use may cause discoloration of the teeth, and its use in children younger than 8 yr of age should generally be avoided. Gastrointestinal side effects are common and may be intolerable.

Prevention

Strategies for preventing enterococcal infections include timely removal of urinary and intravenous catheters and debridement of necrotic tissue. Infection control strategies, including surveillance cultures, patient and staff cohorting, and strict gown and glove isolation are effective at decreasing colonization rates with vancomycin-resistant enterococci. Unfortunately, these organisms may persist on inanimate objects such as stethoscopes, complicating efforts to limit their nosocomial spread. In order to prevent the emergence and spread of vancomycin resistant organisms, the Centers for Disease Control and Prevention has developed a series of guidelines for prudent vancomycin use. Antibiotics with broad activity against anaerobic organisms are also thought to contribute to colonization with VRE, suggesting that prudent use of such antibiotics may also help limit spread of VRE. Decolonization strategies have been attempted but are generally ineffective in eradicating skin or gastrointestinal carriage of VRE. In particular, antimicrobial therapy is not indicated for this purpose. The role of probiotic agents in eliminating VRE colonization is currently unclear, but may be a useful adjunct to prudent antimicrobial usage and other infection control interventions in limiting nosocomial spread of VRE.

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Chapter 187

Diphtheria (*Corynebacterium diphtheriae*)

E. Stephen Buescher

Diphtheria is an acute toxic infection caused by *Corynebacterium* species, typically *Corynebacterium diphtheriae* and, rarely, toxigenic strains of *Corynebacterium ulcerans.* Although diphtheria was reduced from a major cause of childhood death to a medical rarity in the Western hemisphere in the early 20th century, recurring reminders of the fragility of this success emphasize the necessity to continue vigorous promotion of those same control principles across the global community.

ETIOLOGY

Corynebacteria are aerobic, nonencapsulated, non–spore-forming, mostly nonmotile, pleomorphic, Gram-positive bacilli. *C. diphtheriae* is by far the most commonly isolated agent of diphtheria. *C. ulcerans* is more commonly isolated from animal sources and can cause similar human disease. As Corynebacteria are not fastidious in growth requirements, their isolation is enhanced by use of a selective medium (e.g., cystine-tellurite blood agar or Tinsdale agar) that inhibits growth of competing organisms and, when reduced by *C. diphtheriae,* renders colonies gray-black. Differentiation of *C. diphtheriae* from *C. ulcerans* is based on urease activity, because *C. ulcerans* is urease-positive. Four *C. diphtheriae* biotypes (mitis, intermedius, belfanti, gravis) are capable of causing diphtheria and are differentiated by colonial morphology, hemolysis, and fermentation reactions. The ability to produce diphtheritic toxin results from acquisition of a lysogenic *Corynebacteriophage* by either *C. diphtheriae* or *C. ulcerans,* which encodes the diphtheritic toxin gene and confers diphtheria-producing potential on these strains. Thus, indigenous nontoxigenic *C. diphtheriae* can be rendered toxigenic and disease-producing after importation of a toxigenic *C. diphtheriae*. Demonstration of diphtheritic toxin production or potential for toxin production by an isolate is necessary to confirm disease. The former is done in vitro using the agar immunoprecipitin technique (Elek test) or in vivo with the toxin neutralization test in guinea pigs, and the latter by polymerase chain reaction testing for carriage of the toxin gene. Toxigenic and nontoxigenic strains are indistinguishable by colony type, microscopic features, or biochemical test results.

EPIDEMIOLOGY

Unlike other **diphtheroids (coryneform bacteria),** which are ubiquitous in nature, *C. diphtheriae* is an exclusive inhabitant of human mucous membranes and skin. Spread is primarily by airborne respiratory droplets, direct contact with respiratory secretions of symptomatic individuals, or exudate from infected skin lesions. Asymptomatic respiratory tract carriage is important in transmission. Where diphtheria is endemic, 3-5% of healthy individuals can carry toxigenic organisms, but carriage is exceedingly rare if diphtheria is rare. Skin infection and skin carriage are silent reservoirs of *C. diphtheriae,* and organisms can remain viable in dust or on fomites for up to 6 mo. Transmission through contaminated milk and through an infected food handler has been proven or suspected.

In the 1920s, more than 125,000 diphtheria cases, with 10,000 deaths, were reported annually in the United States, with the highest fatality rates among the very young and the elderly. The incidence then began to decrease and, with widespread use of diphtheria toxoid in the United States after World War II, declined steadily through the late 1970s. Since then, ≤5 cases have occurred annually in the United States, with no epidemics of respiratory tract diphtheria. Similar decreases occurred in Europe. Despite the worldwide decrease in disease incidence, diphtheria remains endemic in many developing countries with poor immunization rates against diphtheria.

When diphtheria was endemic, it primarily affected children younger than 15 yr of age. Since the introduction of toxoid immunization, the disease has shifted to adults who lack natural exposure to toxigenic *C. diphtheriae* in the vaccine era and have low rates of booster immunization. In the 27 sporadic cases of respiratory tract diphtheria reported in the United States in the 1980s, 70% occurred among persons older than 25 yr of age. The largest outbreak of diphtheria in the developed world since the 1960s occurred from 1990-1996 in the newly independent countries of the former Soviet Union, involving more than 150,000 cases in 14 countries. Of these, more than 60% of cases occurred in individuals older than 14 yr of age. Case fatality rates ranged from 3-23% by country. Factors contributing to the epidemic included a large population of underimmunized adults, decreased childhood immunization rates, population migration, crowding, and failure to respond aggressively during early phases of the epidemic. Cases of diphtheria among travelers from these endemic areas were transported to many countries in Europe.

Most proven cases of respiratory tract diphtheria in the United States in the 1990s were associated with **importation** of toxigenic *C. diphtheriae,* although clonally related toxigenic *C. diphtheriae* has persisted in this country and Canada for at least 25 yr.

Cutaneous diphtheria, a curiosity when diphtheria was common, accounted for more than 50% of reported *C. diphtheriae* isolates in the United States by 1975. This indolent local infection, compared with mucosal infection, is associated with more prolonged bacterial shedding, greater contamination of the environment, and increased transmission to the pharynx and skin of close contacts. Outbreaks are associated with homelessness, crowding, poverty, alcoholism, poor hygiene, contaminated fomites, underlying dermatosis, and introduction of new strains from exogenous sources. It is no longer a tropical or subtropical disease; 1,100 *C. diphtheriae* infections were documented in a neighborhood in Seattle (site of the last major U.S.

outbreak), from 1971-1982; 86% were cutaneous, and 40% involved toxigenic strains. Cutaneous diphtheria is an important source for toxigenic *C. diphtheriae* in the United States, and its importation is frequently the source for subsequent sporadic cases of respiratory tract diphtheria.

PATHOGENESIS

Both toxigenic and nontoxigenic *C. diphtheriae* cause skin and mucosal infection and can rarely cause focal infection after bacteremia. The organism usually remains in the superficial layers of skin lesions or respiratory tract mucosa, inducing local inflammatory reaction. The major virulence of the organism lies in its ability to produce the potent 62-kDa polypeptide exotoxin, which inhibits protein synthesis and causes local tissue necrosis. Within the 1st few days of respiratory tract infection (usually in the pharynx), a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes forms, advances, and becomes a gray-brown, leather-like adherent **pseudomembrane** (*Diphthera* is Greek for leather). Removal is difficult and reveals a bleeding edematous submucosa. Paralysis of the palate and hypopharynx is an early local effect of diphtheritic toxin. Toxin absorption can lead to systemic manifestations: kidney tubule necrosis, thrombocytopenia, cardiomyopathy, and/or demyelination of nerves. Because the latter 2 complications can occur 2-10 wk after mucocutaneous infection, the pathophysiology in some cases is suspected to be immunologically mediated.

CLINICAL MANIFESTATIONS

The manifestations of *C. diphtheriae* infection are influenced by the anatomic site of infection, the immune status of the host, and the production and systemic distribution of toxin.

Respiratory Tract Diphtheria

In a classic description of 1,400 cases of diphtheria in California (1954), the primary focus of infection was the tonsils or pharynx (94%), with the nose and larynx the next 2 most common sites. After an average incubation period of 2-4 days, local signs and symptoms of inflammation develop. Infection of the anterior nares is more common among infants and causes serosanguineous, purulent, erosive rhinitis with membrane formation. Shallow ulceration of the external nares and upper lip is characteristic. In tonsillar and pharyngeal diphtheria, sore throat is the universal early symptom. Only half of patients have fever, and fewer have dysphagia, hoarseness, malaise, or headache. Mild pharyngeal injection is followed by unilateral or bilateral tonsillar membrane formation, which can extend to involve the uvula (which may cause toxin-mediated paralysis), soft palate, posterior oropharynx, hypopharynx, or glottic areas (Fig. 187-1). Underlying soft-tissue edema and enlarged lymph nodes can cause a bull-neck appearance. The degree of local extension correlates directly with profound prostration, bull-neck appearance, and fatality due to airway compromise or toxin-mediated complications (Fig. 187-2).

The characteristic adherent membrane, extension beyond the faucial area, dysphagia, and relative lack of fever help differentiate diphtheria from exudative pharyngitis caused by *Streptococcus pyogenes* or Epstein-Barr virus. Vincent angina, infective phlebitis with thrombosis of the jugular veins (Lemierre disease), and mucositis in patients undergoing cancer chemotherapy are usually differentiated by the clinical setting. Infection of the larynx, trachea, and bronchi can be primary or a secondary extension from the pharyngeal infection. Hoarseness, stridor, dyspnea, and croupy cough are clues. Differentiation from bacterial epiglottitis, severe viral laryngotracheobronchitis, and staphylococcal or streptococcal tracheitis hinges partially on the relative paucity of other signs and symptoms in patients with diphtheria and primarily on visualization of the adherent pseudomembrane at the time of laryngoscopy and intubation.

Patients with laryngeal diphtheria are at significant risk for suffocation because of local soft-tissue edema and airway obstruction by the diphtheritic membrane, a dense cast of respiratory epithelium, and necrotic coagulum. Establishment of an artificial airway and resection of the pseudomembrane can be lifesaving, but further obstructive complications are common, and systemic toxic complications are inevitable.

Figure 187-1 Tonsillar diphtheria. *(Courtesy Franklin H. Top, MD, Professor and Head of the Department of Hygiene and Preventive Medicine, State University of Iowa, College of Medicine, Iowa City, IA; and Parke, Davis & Company's Therapeutic Notes.)*

Figure 187-2 Diphtheria. Bull-neck appearance of diphtheritic cervical lymphadenopathy. *(Courtesy of the Centers for Disease Control and Prevention.)*

Cutaneous Diphtheria

Classic cutaneous diphtheria is an indolent, nonprogressive infection characterized by a superficial, ecthyma-like, nonhealing ulcer with a gray-brown membrane. Diphtheritic skin infections cannot always be differentiated from streptococcal or staphylococcal impetigo, and these conditions frequently coexist. In most cases, a primary process, such as dermatosis, laceration, burns, bite, or impetigo, becomes secondarily infected with *C. diphtheriae*. Extremities are more often affected than the trunk or head. Pain, tenderness, erythema, and exudate are typical. Local hyperesthesia or hypesthesia is unusual. Respiratory tract colonization or symptomatic infection with toxic complications occurs in the minority of patients with cutaneous diphtheria. Among infected adults in the Seattle outbreak, 3% with cutaneous infections and 21%

with symptomatic nasopharyngeal infection, with or without skin involvement, demonstrated toxic myocarditis, neuropathy, or obstructive respiratory tract complications. All had received at least 20,000 units of equine antitoxin at the time of hospitalization.

Infection at Other Sites

C. diphtheriae occasionally causes mucocutaneous infections at other sites, such as the ear (otitis externa), the eye (purulent and ulcerative conjunctivitis), and the genital tract (purulent and ulcerative vulvovaginitis). The clinical setting, ulceration, membrane formation, and submucosal bleeding help differentiate diphtheria from other bacterial and viral causes. Rare cases of septicemia are described and are universally fatal. Sporadic cases of endocarditis occur, and clusters among intravenous drug users have been reported in several countries; skin was the probable portal of entry, and almost all strains were nontoxigenic. Sporadic cases of pyogenic arthritis, mainly from nontoxigenic strains, have been reported in adults and children. Diphtheroids isolated from sterile body sites should not be routinely dismissed as contaminants without careful consideration of the clinical setting.

DIAGNOSIS

Specimens for culture should be obtained from the nose and throat and any other mucocutaneous lesion. A portion of membrane should be removed and submitted for culture along with underlying exudate. The laboratory must be notified to use selective medium. *C. diphtheriae* survives drying. If obtained in a remote area, a swab specimen can be placed in a silica gel pack and sent to the laboratory. Evaluation of a direct smear using Gram stain or specific fluorescent antibody is unreliable. Culture isolates of coryneform organisms should be identified to the species level, and toxigenicity and antimicrobial susceptibility tests should be performed for *C. diphtheriae* isolates.

COMPLICATIONS

Respiratory tract obstruction by pseudomembranes may require bronchoscopy or intubation and mechanical ventilation. Two other tissues usually remote from sites of *C. diphtheriae* infection can be significantly affected by **diphtheritic toxin:** the heart and the nervous system.

Toxic Cardiomyopathy

Toxic cardiomyopathy occurs in 10-25% of patients with respiratory diphtheria and is responsible for 50-60% of deaths. Subtle signs of myocarditis can be detected in most patients, especially the elderly, but the risk for significant complications correlates directly with the extent and severity of exudative local oropharyngeal disease as well as delay in administration of antitoxin. The first evidence of cardiac toxicity characteristically occurs during the 2nd and 3rd wk of illness as the pharyngeal disease improves but can appear acutely as early as the 1st wk of illness, a poor prognostic sign, or insidiously as late as the 6th wk. **Tachycardia** disproportionate to fever is common and may be evidence of cardiac toxicity or autonomic nervous system dysfunction. A prolonged P-R interval and changes in the ST-T wave on an electrocardiographic tracing are relatively frequent findings; dilated and hypertrophic cardiomyopathy detected by echocardiogram has been described. Single or progressive cardiac **dysrhythmias** can occur, including 1st-, 2nd-, and 3rd-degree heart block. Temporary transvenous pacing may improve outcomes. Atrioventricular dissociation and ventricular tachycardia are also described, the latter having a high associated mortality. Heart failure may appear insidiously or acutely. Elevation of the serum aspartate aminotransferase concentration closely parallels the severity of myonecrosis. Severe dysrhythmia portends death. Histologic postmortem findings are variable: little or diffuse myonecrosis with acute inflammatory response. Recovery from toxic myocardiopathy is usually complete, although survivors of more severe dysrhythmias can have permanent conduction defects.

Toxic Neuropathy

Neurologic complications parallel the severity of primary infection and are multiphasic in onset. Acutely or 2-3 wk after onset of oropharyngeal inflammation, it is common for hypesthesia and local **paralysis** of the soft palate to occur. Weakness of the posterior pharyngeal, laryngeal, and facial nerves may follow, causing a **nasal quality** in the voice, difficulty in swallowing, and risk for aspiration. **Cranial neuropathies** characteristically occur in the 5th wk, leading to oculomotor and ciliary paralysis, which can cause strabismus, blurred vision, or difficulty with accommodation. Symmetric **polyneuropathy** has its onset 10 days to 3 mo after oropharyngeal infection and causes principally motor deficits with diminished deep tendon reflexes. Distal muscle weakness in the extremities with proximal progression is more commonly described than proximal muscle weakness with distal progression. Clinical and cerebrospinal fluid findings in the former are indistinguishable from those of Guillain-Barré syndrome. Paralysis of the diaphragm may ensue. Complete neurologic recovery is likely, but rarely vasomotor center dysfunction 2-3 wk after onset of illness can cause hypotension or cardiac failure.

Recovery from the myocarditis and neuritis is often slow but usually complete. Corticosteroids do not diminish these complications and are not recommended.

TREATMENT

Specific antitoxin is the mainstay of therapy and should be administered on the basis of clinical diagnosis. Because it neutralizes only free toxin, antitoxin efficacy diminishes with elapsed time after the onset of mucocutaneous symptoms. Equine diphtheria antitoxin is available in the United States only from the Centers for Disease Control and Prevention (CDC). Physicians treating a case of suspected diphtheria should contact the CDC diphtheria duty officer (770-488-7100 at all times). Antitoxin is administered as a single empirical dose of 20,000-100,000 units based on the degree of toxicity, site and size of the membrane, and duration of illness. Antitoxin is probably of no value for local manifestations of cutaneous diphtheria, but its use is prudent because toxic sequelae can occur. Commercially available intravenous immunoglobulin preparations contain low titers of antibodies to diphtheria toxin; their use for therapy of diphtheria is not proven or approved. Antitoxin is not recommended for asymptomatic carriers.

The role of antimicrobial therapy is to halt toxin production, treat localized infection, and prevent transmission of the organism to contacts. *C. diphtheriae* is usually susceptible to various agents in vitro, including penicillins, erythromycin, clindamycin, rifampin, and tetracycline. Resistance to erythromycin is common in populations if the drug has been used broadly. Only erythromycin or penicillin is recommended; erythromycin is marginally superior to penicillin for eradication of nasopharyngeal carriage. Appropriate therapy is erythromycin (40-50 mg/kg/day divided every 6 hr by mouth [PO] or intravenously [IV]; maximum 2 g/day), aqueous crystalline penicillin G (100,000-150,000 units/kg/day divided every 6 hr IV or intramuscularly [IM]), or daily procaine penicillin (300,000 units/day IM for those <10 kg in weight; 600,000 units/day IM for those >10 kg in weight) for 14 days. Antibiotic therapy is not a substitute for antitoxin therapy. Some patients with cutaneous diphtheria have been treated for 7-10 days. Elimination of the organism should be documented by negative results of at least 2 successive cultures of specimens from the nose and throat (or skin) obtained 24 hr apart after completion of therapy. Treatment with erythromycin is repeated if either culture yields *C. diphtheriae.*

SUPPORTIVE CARE

Droplet precautions are instituted for patients with pharyngeal diphtheria; for patients with cutaneous diphtheria, contact precautions are observed until the results of cultures of specimens taken after cessation of therapy are negative. Cutaneous wounds are cleaned thoroughly with soap and water. Bed rest is essential during the acute phase of disease, usually for ≥2 wk until the risk for symptomatic cardiac damage has passed, with a return to physical activity guided by the degree of toxicity and cardiac involvement.

PROGNOSIS

The prognosis for patients with diphtheria depends on the virulence of the organism (subspecies *gravis* has the highest fatality rate), patient age, immunization status, site of infection, and speed of administration

of the antitoxin. Mechanical obstruction from laryngeal diphtheria or bull-neck diphtheria and the complications of myocarditis account for most diphtheria-related deaths. The case fatality rate of almost 10% for respiratory tract diphtheria has not changed in 50 yr; the rate was 8% in a Vietnamese series described in 2004. At recovery, administration of diphtheria toxoid is indicated to complete the primary series or booster doses of immunization, because not all patients develop antibodies to diphtheritic toxin after infection.

PREVENTION

Protection against serious disease caused by imported or indigenously acquired *C. diphtheriae* depends on immunization. In the absence of a precisely determined minimum protective level for diphtheria antitoxin, the presumed minimum is 0.01-0.10 IU/mL. In outbreaks, 90% of individuals with clinical disease have had antibody values <0.01 IU/mL, and 92% of asymptomatic carriers have had values >0.1 IU/mL. In serosurveys in the United States and Western Europe, where almost universal immunization during childhood has been achieved, 25% to >60% of adults lack protective antitoxin levels, with very low levels common in the elderly.

All suspected diphtheria cases should be reported to local and state health departments. Investigation is aimed at preventing secondary cases in exposed individuals and at determining the source and carriers to halt spread to unexposed individuals. Reported rates of carriage in household contacts of case patients are 0-25%. The risk for development of diphtheria after household exposure to a case is approximately 2%, and the risk is 0.3% after similar exposure to a carrier.

Asymptomatic Case Contacts

All household contacts and people who have had intimate respiratory or habitual physical contact with a patient are closely monitored for illness through the 7-day incubation period. Cultures of the nose, throat, and any cutaneous lesions are performed. Antimicrobial prophylaxis is presumed effective and is administered regardless of immunization status, using a single injection of benzathine penicillin G (600,000 units IM for patients younger than 6 yr of age, or 1,200,000 units IM for patients older than 6 yr of age) or erythromycin (40-50 mg/kg/day divided qid PO for 10 days; maximum: 2 g/day). Diphtheria toxoid vaccine, in age-appropriate form, is given to immunized individuals who have not received a booster dose within 5 yr. Children who have not received their 4th dose should be vaccinated. Those who have received fewer than 3 doses of diphtheria toxoid or who have uncertain immunization status are immunized with an age-appropriate preparation on a primary schedule.

Asymptomatic Carriers

When an asymptomatic carrier is identified, antimicrobial prophylaxis is given for 10-14 days and an age-appropriate preparation of diphtheria toxoid is administered immediately if a booster has not been given within 1 yr. Droplet precautions (respiratory tract colonization) or contact precautions (cutaneous colonization only) are observed until at least 2 subsequent cultures obtained 24 hr apart after cessation of therapy have negative results.

Repeat cultures are performed about 2 wk after completion of therapy for cases and carriers; if results are positive, an additional 10-day course of oral erythromycin should be given and follow-up cultures performed. Susceptibility testing of isolates should be performed, as erythromycin resistance is reported. Neither antimicrobial agent eradicates carriage in 100% of individuals. In one report, a single course of therapy failed in 21% of carriers. Transmission of diphtheria in modern hospitals is rare. Only those who have an unusual contact with respiratory or oral secretions should be managed as contacts. Investigation of the casual contacts of patients and carriers or persons in the community without known exposure has yielded extremely low carriage rates and is not routinely recommended.

Vaccine

Universal immunization with diphtheria toxoid throughout life, to provide constant protective antitoxin levels and to reduce severity of *C. diphtheriae* disease, is the only effective control measure. Although immunization does not preclude subsequent respiratory or cutaneous carriage of toxigenic *C. diphtheriae,* it decreases local tissue spread, prevents toxic complications, diminishes transmission of the organism, and provides herd immunity when at least 70-80% of a population is immunized.

Diphtheria toxoid is prepared by formaldehyde treatment of toxin, standardized for potency, and adsorbed to aluminum salts, enhancing immunogenicity. Two preparations of diphtheria toxoids are formulated according to the limit of flocculation (Lf) content, a measure of the quantity of toxoid. The pediatric (6 mo-6yr) preparations (i.e., DTaP [diphtheria and tetanus toxoids with acellular pertussis vaccine], DT [diphtheria and tetanus toxoids vaccine]) contain 6.7-25.0 Lf units of diphtheria toxoid per 0.5 mL dose; the adult preparation (dT; 10% of pediatric diphtheria toxoid dose, Tdap [diphtheria and tetanus toxoids with acellular pertussis vaccine]) contain no more than 2 Lf units of toxoid per 0.5 mL dose. The higher-potency (D) formulation of toxoid is used for primary series and booster doses for children through 6 yr of age because of superior immunogenicity and minimal reactogenicity. For individuals 7 yr of age or older, dT is recommended for the primary series and booster doses because the lower concentration of diphtheria toxoid is adequately immunogenic and increasing the content of diphtheria toxoid heightens reactogenicity with increasing age.

For children 6 wk to 6 yr of age, five 0.5 mL doses of diphtheria-containing (D) vaccine (DTaP preferred) are given in the primary series, including 3 doses at 2, 4, and 6 mo of age, and a 4th dose, an integral part of the primary series, 15-18 mo after the 3rd dose. A booster dose is given at 4-6 yr of age (unless the 4th primary dose was administered at age 4 yr or older). For persons 7 yr of age and older, three 0.5 mL doses of lower-level diphtheria-containing (d) vaccine are given in a primary series of 2 doses 4-8 wk apart and a 3rd dose 6-12 mo after the 2nd dose. The 1st dose should be Tdap, and subsequent doses should be Td. The only contraindication to tetanus and diphtheria toxoid is a history of neurologic or severe hypersensitivity reaction after a prior dose. For children younger than 7 yr of age in whom pertussis immunization is contraindicated, DT is used. Those whose immunization is begun with DTaP or DT before 1 yr of age should have a total of five 0.5 mL doses of diphtheria-containing (D) vaccines by 6 yr of age. For those whose immunization is begun at around 1 yr of age, the primary series is three 0.5 mL doses of diphtheria-containing (D) vaccine, with a booster given at 4-6 yr, unless the 3rd dose was given after the 4th birthday.

A booster dose, consisting of the adult preparation of Tdap, is recommended at 11-12 yr of age. Adolescents 13-18 yr of age who missed the Td or Tdap booster dose at 11-12 yr or in whom it has been 5 or more years since the Td booster dose also should receive a single dose of Tdap if they have completed the DTP/DTaP series.

There is no association of DT or dT with convulsions. Local adverse effects alone do not preclude continued use. The patient who experiences an Arthus-type hypersensitivity reaction or a temperature >39.4°C (103°F) after a dose of dT, which is rare, usually has high serum tetanus antitoxin levels and should not be given dT more frequently than every 10 yr, even if the patient sustains a significant tetanus-prone injury. The DT or dT preparation can be given concurrently with other vaccines. *Haemophilus influenzae* conjugate vaccines containing diphtheria toxoid (PRP-D) or the variant of diphtheria toxin, CRM197 protein (HbOC), are not substitutes for diphtheria toxoid immunization and do not affect reactogenicity.

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Chapter **188**

Listeria monocytogenes

Robert S. Baltimore and Thomas S. Murray

Listeriosis in humans is caused principally by *Listeria monocytogenes,* 1 of 6 species of the genus *Listeria* that are widely distributed in the environment and throughout the food chain. Human infections can usually be traced to an animal reservoir. Infection occurs most commonly at the extremes of age. In the pediatric population, perinatal infections predominate and usually occur secondary to maternal infection or colonization. Outside the newborn period, disease is most commonly encountered in immunosuppressed (T-cell deficiencies) children and adults and in the elderly. For most people the major risk for infection with *Listeria* is foodborne transmission. In the United States, foodborne outbreaks are caused by improperly processed dairy products and contaminated vegetables and principally affect the same individuals at risk for sporadic disease.

ETIOLOGY

Members of the genus *Listeria* are facultatively anaerobic, non–spore-forming, motile, Gram-positive bacilli that are catalase positive. In the laboratory *Listeria* can be distinguished from other Gram-positive bacilli by their characteristic tumbling motility and growth at cold temperature (4-10°C [39.2-50°F]). The 6 *Listeria* species are divided into 2 genomically distinct groups on the basis of DNA-DNA hybridization studies. One group contains the species *Listeria grayi,* considered nonpathogenic. The second group contains 5 species: the nonhemolytic species *Listeria innocua* and *Listeria welshimeri* and the hemolytic species *L. monocytogenes, Listeria seeligeri,* and *Listeria ivanovii. L. ivanovii* is pathogenic primarily in animals, and the vast majority of both human and animal disease is caused by *L. monocytogenes.*

Subtyping of *L. monocytogenes* isolates for epidemiologic purposes has been attempted with the use of heat-stable somatic O and heat-labile flagellar H antigens, phage typing, pulsed-field gel electrophoresis, ribotyping, and multilocus enzyme electrophoresis. Electrophoretic typing demonstrates the clonal structure of populations of *L. monocytogenes* as well as the sharing of populations between human and animal sources. Subtyping is an important component of determining whether cases are connected or sporadic but usually requires collaboration with a specialized laboratory.

Selected biochemical tests together with the demonstration of tumbling motility, umbrella-type formation below the surface in semisolid medium, hemolysis, and a typical cyclic adenosine monophosphate test are usually sufficient to establish a presumptive identification of *L. monocytogenes.*

EPIDEMIOLOGY

L. monocytogenes is widespread in nature, has been isolated throughout the environment, and is associated with epizootic disease and asymptomatic carriage in more than 42 species of wild and domestic animals and 22 avian species. Epizootic disease in large animals such as sheep and cattle is associated with abortion and “circling disease,” a form of basilar meningitis. *L. monocytogenes* is isolated from sewage, silage, and soil, where it survives for longer than 295 days. Human-to-human transmission rarely occurs except in maternal-fetal transmission. The annual incidence of listeriosis decreased by 36% between 1996 and 2004 and has remained level since then. However, outbreaks continue to occur. In 2002, an outbreak that resulted in 54 illnesses, 8 deaths, and 3 fetal deaths in 9 states was traced to consumption of contaminated turkey meat. In 2011, an outbreak with 84 cases and 15 deaths in 19 states was traced to cantaloupes from a single source. The cases were connected by use of pulsed-field gel electrophoresis, which showed that 4 different strains traced to the same source. The rate of listeria infections varies among states. Epidemic human listeriosis has been associated with foodborne transmission in several large outbreaks, especially in association with aged soft cheeses; improperly pasteurized milk and milk products; contaminated raw and ready-to-eat beef, pork, and poultry, and packaged meats; and vegetables grown on farms where the ground is contaminated with the feces of colonized animals. The incidence of *Listeria* infections in the United States in 2008 was 0.29 cases per 100,000 population, being highest in children younger than 4 yr of age and next highest in adults older than 60 yr of age. The ability of *L. monocytogenes* to grow at temperatures as low as 4°C (39.2°F) increases the risk for transmission from aged soft cheeses and stored contaminated food. Small clusters of nosocomial person-to-person transmission have occurred in hospital nurseries and obstetric suites. Sporadic endemic listeriosis is less well characterized. Likely routes include foodborne infection and zoonotic spread. Zoonotic transmission with cutaneous infections occurs in veterinarians and farmers who handle sick animals.

Table 188-1 Types of *Listeria monocytogenes* Infections
Listeriosis in pregnancy
Neonatal listeriosis:
Early onset
Late onset
Foodborne outbreaks/febrile gastroenteritis
Listeriosis in normal children and adults (rare)
Focal listeria infections (e.g., meningitis, endocarditis, pneumonia, liver abscess, osteomyelitis, septic arthritis)
Listeriosis in immunocompromised persons:
Lymphohematogenous malignancies
Collagen vascular diseases
Diabetes mellitus
HIV infection
Transplantation
Renal failure with peritoneal dialysis
Listeriosis in the elderly

Reported cases of listeriosis are clustered at the extremes of age. Some studies show higher rates in males and a seasonal predominance in the late summer and fall in the Northern hemisphere. Outside the newborn period and during pregnancy, disease is usually reported in patients with underlying immunosuppression, with a 100-300 times increased risk in HIV-infected persons and in the elderly (Table 188-1). In a recent surveillance study from England, malignancies accounted for one-third of cases, with special risk associated with cancer in the elderly.

The incubation period, which is defined only for common-source foodborne disease, is 21-30 days but in some cases may be longer. Asymptomatic carriage and fecal excretion are reported in 1-5% of healthy persons and 5% of abattoir workers, but duration of excretion, when studied, is short (<1 mo).

PATHOLOGY

One of the major concepts of *Listeria* pathology and pathogenesis is its ability to survive as an intracellular pathogen. *Listeria* incites a mononuclear response and elaboration of cytokines, producing multisystem disease, particularly pyogenic meningitis. Granulomatous reactions and microabscess formation develop in many organs, including liver, lungs, adrenals, kidneys, central nervous system (CNS), and, notably, the placenta. Animal models demonstrate translocation, the transfer

of intraluminal organisms across intact intestinal mucosa. Histologic examination of tissues including the placenta shows granulomatous inflammation and microabscess formation. Intracellular organisms can often be demonstrated with special stains.

PATHOGENESIS

Listeria organisms usually enter the host through the gastrointestinal tract. Gastric acidity provides some protection, and drugs that raise gastric pH may promote infection. Studies of intracellular and intercellular spread of *L. monocytogenes* have revealed a complex pathogenesis. Four pathogenic steps are described: internalization by phagocytosis, escape from the phagocytic vacuole, nucleation of actin filaments, and cell-to-cell spread. Listeriolysin, a hemolysin and the best-characterized virulence factor, probably mediates lysis of vacuoles and is responsible for the zone of hemolysis around colonies on blood-containing solid media. In cell-to-cell spread, locomotion proceeds via cytochalasin-sensitive polymerization of actin filaments, which extrude the bacteria in pseudopods, which, in turn, are phagocytosed by adjacent cells, necessitating escape from a double-membrane vacuole. This mechanism protects intracellular bacteria from the humoral arm of immunity and is responsible for the well-known requirement of T-cell–mediated activation of monocytes by lymphokines for clearance of infection and establishment of immunity. It appears that secretion of cyclic-di-adenosine monophosphate by the bacteria induces the host to produce interferon, which activates the immune system to fight the organism. The significant risk for listeriosis in patients with depressed T-cell immunity speaks for the role of this arm of the immune system. The role of opsonizing antibody in protecting against infection is unclear. In addition, siderophores scavenge iron from the host, enhancing growth of the organism and likely explaining the relatively high risk of listeriosis in iron overload syndromes.

CLINICAL MANIFESTATIONS

The clinical presentation of listeriosis is highly dependent on the age of the patient and the circumstances of the infection.

Listeriosis in Pregnancy

Pregnant women have increased susceptibility to *Listeria* infectious (approximately 20 times higher than nonpregnant women), probably owing to a relative impairment in cell-mediated immunity. *L. monocytogenes* has been grown from placental and fetal cultures of pregnancies ending in spontaneous abortion. The usual presentation in the 2nd and 3rd trimesters is a flu-like illness that may result in seeding of the uterine contents by bacteremia. Rarely is maternal listeriosis severe, but meningitis in pregnancy has been reported. Recognition and treatment at this stage are associated with normal pregnancy outcomes, but the fetus may not be infected even if listeriosis in the mother is not treated. In other instances, placental listeriosis develops with infection of the fetus that may be associated with stillbirth or premature delivery. Delivery of an infected premature fetus is associated with very high infant mortality. Disseminated disease is apparent at birth, often with a diffuse pustular rash. Infection in the mother usually resolves without specific therapy after delivery, but postpartum fever and infected lochia may occur.

Neonatal Listeriosis

Two clinical presentations are recognized for neonatal listeriosis: early-onset neonatal disease (<5 days, usually within 1-2 days of birth), which is a predominantly septicemic form, and late-onset neonatal disease (>5 days, mean 14 days of life), which is a predominantly meningitic form (Table 188-2). The principal characteristics of the 2 presentations resemble the clinical syndromes described for group B streptococcus (see Chapter 184).

Early-onset disease occurs via milder transplacental or ascending infections from the female genital tract. There is a strong association with recovery of *L. monocytogenes* from the maternal genital tract, obstetric complications, prematurity, and neonatal sepsis with multiorgan involvement without CNS localization. The mortality rate is approximately 20-30%.

Table 188-2 Characteristic Features of Early- and Late-Onset Neonatal Listeriosis

EARLY ONSET (<5 DAYS)	LATE ONSET (≥5 DAYS)
Positive result of maternal *Listeria* culture	Negative results of maternal *Listeria* culture
Obstetric complications	Uncomplicated pregnancy
Premature delivery	Term delivery
Low birthweight	Normal birthweight
Neonatal sepsis	Neonatal meningitis
Mean age at onset 1.5 days	Mean age at onset 14.2 days
Mortality rate >30%	Mortality rate <10% Nosocomial outbreaks

The epidemiology of late-onset disease is poorly understood. Onset is usually after 5 days but before 30 days of age. Affected infants frequently are full-term, and the mothers are culture negative and asymptomatic. The presenting syndrome is usually purulent meningitis, which, if adequately treated, has a mortality rate of <20%.

Postneonatal Infections

Listeriosis beyond the newborn period may rarely occur in otherwise healthy children but is most often encountered in association with underlying malignancies or immunosuppression. When associated with foodborne outbreaks, disease may cause gastrointestinal symptoms or any of the *Listeria* syndromes. The clinical presentation is usually meningitis, less commonly sepsis, and rarely other CNS involvement, such as cerebritis, meningoencephalitis, brain abscess, spinal cord abscess, or a focus outside the CNS, such as suppurative arthritis, osteomyelitis, endocarditis, peritonitis (associated with peritoneal dialysis), or liver abscess. It is not known whether the frequent gastrointestinal signs and symptoms result from enteric infection, because the mode of acquisition is often unknown.

DIAGNOSIS

Listeriosis should be included in the differential diagnosis of infections in pregnancy, of neonatal sepsis and meningitis, and of sepsis or meningitis in older children who have underlying malignancies, are receiving immunosuppressive therapy, or have undergone transplantation. The diagnosis is established by culture of *L. monocytogenes* from blood or cerebrospinal fluid (CSF). Cultures from the maternal cervix, vagina, lochia, and placenta, if possible, should be obtained when intrauterine infections lead to premature delivery or early-onset neonatal sepsis. Cultures from closed-space infections may also be useful. It is helpful to alert the laboratory to suspected cases so that *Listeria* isolates are not discarded as contaminating diphtheroids.

Histologic examination of the placenta is also useful. Polymerase chain reaction assays detect *L. monocytogenes*, but commercial assays are available only as research use only, not for diagnostic purposes. Serodiagnostic tests have not proved useful.

Differential Diagnosis

Listeriosis is indistinguishable clinically from neonatal sepsis and meningitis due to other organisms. The presence of increased peripheral blood monocytes suggests the possibility of listeriosis. Monocytosis or lymphocytosis may be modest or striking. Beyond the neonatal period, *L. monocytogenes* CNS infection is associated with fever, headache, seizures, and signs of meningeal irritation. The brainstem may be characteristically affected. The white blood cell concentration may vary from normal to slightly elevated, and the CSF laboratory findings are variable and less striking than in the more common causes of bacterial meningitis. Polymorphonuclear leukocytes or mononuclear cells may predominate, with shifts from polymorphonuclear to mononuclear

cells in sequential lumbar puncture specimens. The CSF glucose concentration may be normal but a low level mirrors the severity of disease. The CSF protein concentration is moderately elevated. *L. monocytogenes* is isolated from the blood in 40-75% of cases of meningitis due to the organism. Deep focal infections caused by *L. monocytogenes,* such as endocarditis, osteomyelitis, and liver abscess, are also indistinguishable clinically from such infections caused by more common organisms. Cutaneous infections should be suspected in patients with a history of contact with animals, especially products of conception.

TREATMENT

The emergence of multiple-antibiotic resistance mandates routine susceptibility testing of all isolates. The recommended therapy is ampicillin (100-200 mg/kg/day divided every 6 hr IV; 200-400 mg/kg/day divided every 6 hr IV if meningitis is present) alone or in combination with an aminoglycoside (5.0-7.5 mg/kg/day divided every 8 hr IV). The aminoglycoside enhances the bactericidal activity and is generally recommended in cases of endocarditis and meningitis. The adult dose is ampicillin 4-6 g/day divided every 6 hr plus an aminoglycoside. The ampicillin dose is doubled if meningitis is present. Special attention to dosing is required for neonates, who require longer dosing intervals because of the longer half-lives of the antibiotics in their bodies. *L. monocytogenes* is not susceptible to the cephalosporins, including third-generation cephalosporins. If these agents are used for empirical therapy for neonatal sepsis or meningitis in a newborn, ampicillin must be added for the possibility of *L. monocytogenes* infection. Vancomycin, vancomycin plus an aminoglycoside, trimethoprim-sulfamethoxazole, and erythromycin are alternatives. The duration of therapy is usually 2-3 wk, with 3 wk recommended for immunocompromised persons and patients with meningitis. A longer course is needed for endocarditis, brain abscess, and osteomyelitis. Antibiotic treatment is unnecessary for gastroenteritis without invasive disease.

PROGNOSIS

Early gestational listeriosis may be associated with abortion or stillbirth, although maternal infection with sparing of the fetus has been reported. There is no convincing evidence that *L. monocytogenes* is associated with repeated spontaneous abortions in humans. The mortality rate is >50% for premature infants infected in utero, 30% for early-onset neonatal sepsis, 15% for late-onset neonatal meningitis, and <10% in older children with prompt institution of appropriate antimicrobial therapy. Mental retardation, hydrocephalus, and other CNS sequelae are reported in survivors of *Listeria* meningitis.

PREVENTION

Listeriosis can be prevented by pasteurization and thorough cooking of foods. Irradiation of meat products may also be beneficial. Consumption of unpasteurized or improperly processed dairy products, especially aged soft cheeses, uncooked and precooked meat products that have been stored at 4°C (39.2°F) for extended periods, and unwashed vegetables should be avoided (Table 188-3). This avoidance is particularly important during pregnancy and for immunocompromised persons. Infected domestic animals should be avoided when possible. Education regarding risk reduction is aimed particularly at pregnant women and people being treated for cancers.

Careful handwashing is essential to prevent nosocomial spread within obstetric and neonatal units. Immunocompromised patients given prophylaxis with trimethoprim-sulfamethoxazole are protected from *Listeria* infections. Cases and especially outbreaks should be reported immediately to public health authorities so that timely investigation can be initiated in order to interrupt transmission from the contaminated source.

Bibliography is available at Expert Consult.

Table 188-3	Prevention of Food-Borne Listeriosis

General recommendations to prevent an infection with *Listeria:*	FDA recommendations for washing and handling food.
	• Rinse raw produce, such as fruits and vegetables, thoroughly under running tap water before eating, cutting, or cooking. Even if the produce will be peeled, it should still be washed first.
	• Scrub firm produce, such as melons and cucumbers, with a clean produce brush.
	• Dry the produce with a clean cloth or paper towel.
	• Separate uncooked meats and poultry from vegetables, cooked foods, and ready-to-eat foods.
	Keep your kitchen and environment cleaner and safer.
	• Wash hands, knives, countertops, and cutting boards after handling and preparing uncooked foods.
	• Be aware that *Listeria monocytogenes* can grow in foods in the refrigerator. Use an appliance thermometer, such as a refrigerator thermometer, to check the temperature inside your refrigerator. The refrigerator should be 4.5°C (40°F) or lower and the freezer –17.8°C (0°F) or lower.
	• Clean up all spills in your refrigerator right away–especially juices from hot dog and lunch meat packages, raw meat, and raw poultry.
	• Clean the inside walls and shelves of your refrigerator with hot water and liquid soap, then rinse.
	Cook meat and poultry thoroughly.
	• Thoroughly cook raw food from animal sources, such as beef, pork, or poultry to a safe internal temperature. For a list of recommended temperatures for meat and poultry, visit the safe minimum cooking temperatures chart at http://www.FoodSafety.gov.
	Store foods safely.
	• Use precooked or ready-to-eat food as soon as you can. Do not store the product in the refrigerator beyond the use-by date; follow USDA refrigerator storage time guidelines:
	  • Hot dogs–store opened package no longer than 1 wk and unopened package no longer than 2 wk in the refrigerator.
	  • Luncheon and deli meat–store factory-sealed, unopened package no longer than 2 wk. Store-opened packages and meat sliced at a local deli no longer than 3-5 days in the refrigerator.
	• Divide leftovers into shallow containers to promote rapid, even cooling. Cover with airtight lids or enclose in plastic wrap or aluminum foil. Use leftovers within 3-4 days.
	Choose safer foods.
	• Do not drink raw (unpasteurized) milk, and do not eat foods that have unpasteurized milk in them.

Continued

Table 188-3	Prevention of Food-Borne Listeriosis—cont'd
Recommendations for persons at higher risk, such as pregnant women, persons with weakened immune systems, and older adults in addition to the recommendations listed above, include:	Meats • Do not eat hot dogs, luncheon meats, cold cuts, other deli meats (e.g., bologna), or fermented or dry sausages unless they are heated to an internal temperature of 73.9°C (165°F) or until steaming hot just before serving. • Avoid getting fluid from hot dog and lunch meat packages on other foods, utensils, and food preparation surfaces, and wash hands after handling hot dogs, luncheon meats, and deli meats. • Pay attention to labels. Do not eat refrigerated pâté or meat spreads from a deli or meat counter or from the refrigerated section of a store. Foods that do not need refrigeration, like canned or shelf-stable pâté and meat spreads, are safe to eat. Refrigerate after opening. Cheeses • Do not eat soft cheese such as feta, queso blanco, queso fresco, brie, Camembert, blue-veined, or panela (queso panela) unless it is labeled as made with pasteurized milk. Make sure the label says, "MADE WITH PASTEURIZED MILK." Seafood • Do not eat refrigerated smoked seafood, unless it is contained in a cooked dish, such as a casserole, or unless it is a canned or shelf-stable product. • Refrigerated smoked seafood, such as salmon, trout, whitefish, cod, tuna, and mackerel, is most often labeled as "nova-style," "lox," "kippered," "smoked," or "jerky." • These fish are typically found in the refrigerator section or sold at seafood and deli counters of grocery stores and delicatessens. • Canned and shelf stable tuna, salmon, and other fish products are safe to eat. Follow this general FDA advice for melon safety: • Consumers and food preparers should wash their hands with warm water and soap for at least 20 sec before and after handling any whole melon, such as cantaloupe, watermelon, or honeydew. • Scrub the surface of melons, such as cantaloupes, with a clean produce brush under running water and dry them with a clean cloth or paper towel before cutting. Be sure that your scrub brush is sanitized after each use, to avoid transferring bacteria between melons. • Promptly consume cut melon or refrigerate promptly. Keep your cut melon refrigerated at, or less than 4.5°C (40°F) (0-1.1°C [32-34°F] is best), for no more than 7 days. • Discard cut melons left at room temperature for more than 4 hr.

Adapted from the Centers for Disease Control and Prevention: Listeria *(Listeriosis): prevention. Available at: http://www.cdc.gov/listeria/prevention.html*

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Chapter 189

Actinomyces

Richard F. Jacobs and Gordon E. Schutze

Actinomyces organisms are anaerobic, nonsporulating, Gram-positive bacteria that are part of the endogenous oral flora in humans and have a filamentous and branching structure. Infection caused by these bacteria is termed **actinomycosis,** which is a chronic, granulomatous, suppurative disease characterized by direct extension to contiguous tissue across natural anatomic barriers with the formation of numerous draining fistulas and sinus tracts. These infections usually involve the cervicofacial, thoracic, abdominal, or pelvic regions.

ETIOLOGY

At least 21 species of *Actinomyces* causing human infection have been identified using 16S rRNA sequencing. *Actinomyces israelii* is the predominant species causing human actinomycosis. Other implicated species include: *Propionibacterium propionicum*, *Actinomyces odontolyticus, Actinomyces meyeri, Actinomyces naeslundii, Actinomyces gerencseriae,* and *Actinomyces viscosus.*

Actinomyces organisms are part of the endogenous flora of mucous membranes and are often found in clinical specimens such as sputum, bronchial washes, purulent exudates, and tissues obtained surgically or at necropsy. Staining of crushed tissue specimens rinsed with sterile saline or purulent exudate stained with Gram or acid-fast procedures may reveal organisms within the classic sulfur granules, which are characteristically associated with pulmonary disease caused by *A. israelii* or *A. meyeri.* Cultures on brain-heart infusion agar incubated at 37°C (98.6°F) anaerobically (95% nitrogen and 5% carbon dioxide) and a separate set incubated aerobically reveal organisms within the lines of streak at 24-48 hr. *A. israelii* colonies appear as loose masses of delicate, branching filaments with a characteristic spider-like growth. Colonies of *A. naeslundii, A. viscosus,* and *P. propionicum* may have similar growth characteristics. Biochemical testing is frequently used for speciation but is limited by the complexity within this group. Newer speciation methods are based on 16S recombinant RNA sequence analysis.

EPIDEMIOLOGY

Actinomycosis occurs worldwide among people of all ages, with higher incidence among males, possibly related to increased trauma or poorer dental hygiene. There is no relationship to race, season, or occupation. In a review of 85 cases of actinomycosis, 27% were in persons younger than 20 yr of age, with 7% among children younger than 10 yr of age. The youngest patient in this series was 28 days old. The source of human infection is almost always endogenous flora. The incidence has declined as a result of improved oral hygiene and early antibiotic treatment of oral infections. Risk factors in children include trauma, dental caries, debilitation, and poorly controlled diabetes mellitus. Although actinomycosis is not a common opportunistic infection, disease has been associated with corticosteroid use, leukemia, renal failure, congenital immunodeficiency diseases, and HIV infection. In one study, antecedent disease and surgery predisposed 81 of 181 subjects to infection.

PATHOGENESIS

The 3 significant sites of *Actinomyces* infection are, in order of frequency, cervicofacial, abdominal and pelvic, and pulmonary, although infection may involve any organ in the body. Infection typically follows introduction of the organism into tissues after trauma or surgery. The hallmark of actinomycosis is spread that fails to respect tissue or fascial

planes. The use of intrauterine devices may predispose to development of pelvic actinomycosis. Pulmonary actinomycosis occurs after inhalation or aspiration of organisms, introduction of a colonized foreign body, or spread from an existing cervicofacial or abdominal actinomycotic infection.

Infection spreads contiguously and, rarely, hematogenously. Actinomycosis is a chronic, suppurative, scarring inflammatory process. Sites of infection show dense cellular infiltrates and suppuration that form many interconnecting abscesses and sinus tracts. These abscesses and sinus tracts may be followed by cicatricial healing from which the organism spreads by burrowing along fascial planes, causing deep, communicating scarred sinus tracts. **Sulfur granules** are characteristic of actinomycosis. On hematoxylin-and-eosin staining, they appear as an adherent mass of polymorphonuclear neutrophils attached to the radially arranged eosinophilic clubs of the granule, which is the host immune response. They may be microscopic or macroscopic and are typically yellow, accounting for their name, but may be white, gray, or brown.

Actinomycosis, even in closed infections, is usually, if not always, polymicrobial in nature, involving mixed bacteria. In a large study of more than 650 cases, infection with *Actinomyces* was identified in pure culture in only 1 case and in others was usually identified with other oral flora, most notably members of the **HACEK group,** which includes *Haemophilus aphrophilus, Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae. A. actinomycetemcomitans* is a fastidious, Gram-negative bacillus that is part of the oral flora and has been implicated as a pathogen in periodontal disease. Other bacterial species frequently isolated concomitantly in human actinomycosis include *Fusobacterium, Bacteroides, Capnocytophaga, Staphylococcus*, aerobic and anaerobic streptococci, and Enterobacteriaceae.

CLINICAL MANIFESTATIONS

The 3 major forms of actinomycosis—cervicofacial, abdominal and pelvic, and pulmonary—arise by different routes but may progress to other forms of the disease. Actinomycosis in children suggests an underlying immunodeficiency, especially chronic granulomatous disease (see Chapter 130).

Cervicofacial Actinomycosis

In the patient with cervicofacial actinomycosis, there is often a history of oral trauma, oral surgery, dental procedures, or caries, facilitating entry of organisms into cervicofacial tissues. Cervicofacial actinomycosis usually manifests as a painless, slow-growing, hard mass and can produce cutaneous fistulas, a condition commonly known as **lumpy jaw** (Fig. 189-1). Less frequently, cervicofacial actinomycosis manifests clinically as an acute pyogenic infection with a tender, fluctuant mass with trismus, firm swelling, and fistulas with drainage containing the characteristic sulfur granules. Bone is not involved early in the disease, but periostitis, mandibular osteomyelitis, or perimandibular abscess may develop. Infection may spread by way of sinus tracts to the cranial bones, possibly giving rise to meningitis. The ability of *Actinomyces* to burrow through tissue planes and even bone is a key difference between actinomycosis and nocardiosis. The cervicofacial form of actinomycosis has the best prognosis and is usually cured with surgical debridement and excision combined with antibiotic therapy.

Figure 189-1 A 2 yr old boy with HIV infection who has cervicofacial actinomycosis and a chronic draining fistula.

Abdominal and Pelvic Actinomycosis

In abdominal and pelvic actinomycosis, characteristically there is some disruption of the mucosa of the gastrointestinal tract, usually as a result of an acute gastrointestinal perforation or abdominal trauma. Patients often present with a history of gastrointestinal surgery, diverticulitis, or appendicitis. Of all the forms of actinomycosis, delayed diagnosis is most typical for abdominal and pelvic infection. Gastrointestinal disease clinically develops as appendicitis in 25% of cases but can be manifested as various ulcerative diseases. Infection classically appears after appendectomy as a firm, irregular mass in the ileocecal area that softens and then drains externally through a fistula. Hepatic involvement occurs in approximately 15% of cases of abdominal actinomycosis, with solitary or multiple liver abscesses or in a miliary pattern. The clinical course is indolent, with chills, fever, night sweats, and weight loss, and the presentation is similar to that of tuberculous peritonitis. Infection usually spreads by direct extension or, rarely, hematogenously, possibly involving any tissue or organ, including muscle, spleen, kidneys, fallopian tubes, ovaries, uterus, testes, bladder, and rectum.

Women using intrauterine devices are at risk for development of pelvic actinomycosis, which classically manifests as vaginal discharge, pelvic pain, abdominal pain, menorrhagia, fever, pelvic mass, and a history of pelvic inflammatory disease. The risk is higher if the intrauterine device has been in place for longer than 2-3 yr.

Pulmonary Actinomycosis

Undetected aspiration in a predisposed host is the typical mechanism for thoracic actinomycosis. Neither the clinical nor the radiographic presentation of pulmonary actinomycosis is specific. Pulmonary actinomycosis may manifest as an endobronchial infection, a tumor-like lesion, diffuse pneumonia, or a pleural effusion. Principal symptoms include fever, productive cough, chest pain, and weight loss. Infection frequently dissects along tissue planes and may extend through the chest wall or diaphragm, characteristically producing numerous sinus tracts that contain small abscesses and purulent drainage. Other complications include bony destruction of adjacent ribs, sternum, and vertebral bodies. Multiple lobe involvement of the lungs is occasionally found. Predisposing conditions include dental caries, aspiration, thermal or chemical inhalation injury, introduction of a colonized foreign body, and preexisting cervicofacial or abdominal disease. The classic radiographic triad of thoracic actinomycosis is chronic lower lobe pulmonary consolidation, empyema, and wavy periostitis of the ribs. Accurate diagnosis is difficult because of the propensity of *Actinomyces* to infect preexisting pulmonary cavities. Diagnosis can be confirmed by examination of purulent sinus tract drainage for sulfur granules, and with appropriate cultures. The significance of the presence of *Actinomyces* in sputum or bronchoscopy specimens is limited because these organisms are normal oral flora.

Other Forms

Laryngeal actinomycosis rarely has been reported in older teenagers. Oropharyngeal colonization with *Actinomyces* may be involved in the development of obstructive tonsillar hypertrophy. *Actinomyces pyogenes* has only rarely been implicated as a cause of human infection, although there are reported cases of septicemia, endocarditis, meningitis, arthritis, empyema, pneumonia, otitis media, cystitis, mastoiditis, appendicitis, and cutaneous infection.

Severe forms of periodontitis, particularly localized juvenile periodontitis, are associated with *Actinomyces,* especially in children 10-19 yr of age. *Actinomyces* has a propensity for infecting heart valves, a process that results in an insidious presentation of endocarditis, with fever present in less than half of cases.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Microscopic examination with appropriate stains and culture of purulent drainage from fistulas, abscesses, draining sinus tracts, bronchoalveolar lavage, and sputum can reveal *Actinomyces.* Except for *A. meyeri,* which is nonbranching, *Actinomyces* organisms appear as branching, filamentous rods. Inoculation of anaerobic and aerobic cultures enhances the yield of cultures. Gram, Gomori methenamine silver, or Giemsa stains of purulent material or tissue reveal diagnostic filamentous, branching bacteria at the periphery of sulfur granules. *Nocardia* is indistinguishable from *Actinomyces* on Gram stain, but unlike *Actinomyces, Nocardia* stains with the modified acid-fast stain.

Cranial CT or MRI is important to evaluate the possibility of cerebral actinomycosis in patients with cervicofacial disease or neurologic findings. Infection that invades across tissue planes and ignores anatomic boundaries is highly suggestive of actinomycosis. Abdominal CT may be helpful in identifying the presence of a contrast-enhancing, multicystic lesion, which could be approached by CT-guided needle biopsy for culture.

The mass-like lesion of actinomycosis may manifest as a tumor, necessitating invasive approaches for diagnosis. Actinomycosis must be differentiated from other chronic inflammatory infections, including tuberculosis, nocardiosis, polymicrobial bacterial infections, and fungal infections. Actinomycosis may mimic appendicitis, pseudoappendicitis caused by *Yersinia enterocolitica,* amebiasis, hepatic abscess, lung abscess, and osteomyelitis.

TREATMENT

The mainstay of treatment for actinomycosis is an appropriate surgical approach to sinus tracts and abscesses, prolonged antibiotic therapy, and management of complications such as hemoptysis. Large abscesses usually require complete surgical excision. Bone disease may require multiple debridements. Prompt initiation of antibiotics results in a high cure rate. Actinomycosis is treated with penicillin G (250,000 units/kg/day IV divided every 4-6 hr; maximum: 18-24 million units/day). Other appropriate antibiotics may include tetracycline, clindamycin, and carbapenems. Although controversy still exists about the optimal dosage and duration of therapy, appropriate therapy usually includes parenteral antibiotics for 2-6 wk followed by oral antibiotics for 3-12 mo. The oral antibiotic of choice is penicillin V (100 mg/kg/day divided every 6 hr PO). Hepatic abscesses or other deep tissue infections should be treated for 6-12 mo. Although most *A. israelii* strains are sensitive to penicillin with minimum inhibitory concentrations of 0.03-0.5 μg/mL, some resistant strains have been identified. Antibiotic susceptibility testing should be performed on all isolates from patients who have significant disease or are immunocompromised.

A. actinomycetemcomitans is a **copathogen** in at least 30% of actinomycotic infections. It is important to consider also treating this organism empirically, especially in the critically ill patient. Failure to recognize this organism and treat it adequately has resulted in clinical relapse and deterioration in patients with actinomycosis. *A. actinomycetemcomitans* is susceptible to cephalosporins, amoxicillin-clavulanate, rifampin, trimethoprim-sulfamethoxazole, aminoglycosides, ciprofloxacin, tetracycline, and azithromycin. It is susceptible to penicillin and ampicillin in vitro, but test results do not correlate necessarily with clinical outcome. In some patients with periodontitis associated with *A. actinomycetemcomitans,* mechanical periodontal treatment combined with metronidazole plus amoxicillin is effective for subgingival suppression.

PROGNOSIS

The prognosis is excellent with early diagnosis, adequate surgical debridement, and antimicrobial therapy. Removal of chronically infected tonsils and treatment of periodontitis or caries may eliminate sources of possible reinfection.

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Chapter 190

Nocardia

Richard F. Jacobs and Gordon E. Schutze

Nocardia organisms cause localized and disseminated disease in children and adults. These organisms are primarily opportunistic pathogens infecting immunocompromised persons. Infection caused by these bacteria is termed **nocardiosis,** which consists of acute, subacute, or chronic suppurative infections with a tendency for remissions and exacerbations.

ETIOLOGY

There are more than 80 species to date in the *Nocardia* genus. *Nocardia* are Gram-positive filamentous bacteria. These organisms are environmental saprophytes that are ubiquitous in soil and decaying vegetable matter. They are obligate aerobes and grow on ordinary culture media. Growth is achieved best at 37°C (98.6°F) with 10% carbon dioxide, although many isolates of *Nocardia* are thermophilic and grow at temperatures up to 50°C (122°F). Colonies appear within 1-2 wk on brain–heart infusion agar, Lowenstein-Jensen media, and simple blood agar, usually as waxy, folded, or heaped colonies at the edges. With modified Kinyoun acid-fast staining of biopsy specimens or body fluids, *Nocardia* demonstrates fragmented bacilli with stain concentrated in a **beaded pattern** along portions of the branching filaments.

Ongoing identification of new species continues to challenge microbiology laboratories. Speciation and antimicrobial susceptibility testing is critical for optimal clinical outcomes, especially in severe disease in immunocompromised patients. The most common clinical isolates of *Nocardia asteroides* have now been classified into complex groups I-VI. Valid taxonomic clusters by gene sequencing and antimicrobial susceptibility testing have led to new information to guide clinicians. The term *N. asteroides* complex I-VI now refers to a cluster of similar strains. Non–*N. asteroides* complex organisms are usually *Nocardia brasiliensis* or *Nocardia otitidiscaviarum.*

N. asteroides complex includes the most common agents of systemic nocardiosis in the United States. *N. brasiliensis* is the principal cause of localized nocardial cellulitis and lymphadenitis in immunocompetent children and can also cause pulmonary and systemic disease, especially in immunocompromised persons. *N. brasiliensis* is found more commonly in the southern United States, Central America, South America, and Asia.

EPIDEMIOLOGY

Once thought to be a rare human disease, nocardiosis is being recognized more frequently and has been diagnosed in persons from 4 wk to 82 yr of age. Almost all patients have compromised cellular immunity from an underlying disease such as organ transplantation, malignancy, corticosteroids, diabetes, HIV infection, or primary immunodeficiency, especially chronic granulomatous disease (see Chapter 130). *Nocardia* infections among stem cell transplant recipients are associated with a high rate of concomitant invasive fungal infection and a notable lack of protection with trimethoprim-sulfamethoxazole prophylaxis. An evaluation of opportunistic infections in 547 organ transplant recipients receiving alemtuzumab (humanized monoclonal CD52 antibody) revealed that 62 opportunistic infections developed in 56 patients (10%), including *Nocardia* in 4 patients.

PATHOGENESIS

Soil is the natural habitat of *Nocardia,* which has been isolated worldwide. The organism is inhaled in aerosolized dust and causes pulmonary infection, with widespread dissemination in susceptible hosts. It can be transmitted by direct cutaneous inoculation, including after

arthropod and cat bites. Although human-to-human transmission is rare, a description of *Nocardia farcinica* sternal wound infections among patients undergoing open heart surgery raises concern about *Nocardia* as a nosocomial pathogen.

CLINICAL MANIFESTATIONS

Pulmonary nocardiosis accounts for 75% of cases of infection, almost all of which occur among immunocompromised patients or patients with underlying pulmonary disease. Demonstration of tissue invasion is important for identifying active pulmonary infection because the organism occasionally exists as a respiratory saprophyte. Clinical manifestations include pneumonia and necrotizing pneumonia with single or multiple abscesses.

Single or multiple metastatic lesions may occur anywhere in the body. The brain is the most common secondary site and is involved in 15-40% of cases of pulmonary nocardiosis. Brain abscess is the most common presentation, and meningitis is the second most common presentation, manifested by pleocytosis (with a lymphocytic or neutrophilic predominance), elevated cerebrospinal fluid protein, and hypoglycorrhachia. Persistent neutrophilic meningitis with sterile culture results is classic for central nervous system (CNS) infection. The onset may be gradual or sudden and includes manifestations varying from headache to coma.

The skin is the third most commonly involved organ, manifested by **sporotrichoid nocardiosis** or superficial ulcers (Fig. 190-1). **Mycetoma** is a chronic, progressive infection developing days to months after inoculation, usually on a distal location on the limbs. Renal nocardiosis, the fourth most common type of disease, typically manifests as dysuria, hematuria, or pyuria. Lesions may extend from the cortex into the medulla. Gastrointestinal involvement may also be associated with nausea, vomiting, diarrhea, abdominal distention, and melena. Infection may spread to skin, pericardium, myocardium, spleen, liver, or adrenal glands. Bone involvement is rare. Almost all of the involved organs have several abscesses. In contrast to actinomycosis, granules are rarely found in nocardiosis.

Figure 190-1 A 2 yr old girl with multiple pustules on the dorsum of the right foot caused by *Nocardia brasiliensis*. *(Courtesy of Jaime E. Fergie, MD.)*

DIAGNOSIS

Laboratory diagnosis of nocardiosis requires direct examination of clinical material for characteristic Gram-positive, acid-fast organisms and isolation by culture methods. Smears of clinical material are stained with Gram stain or the modified Kinyoun acid-fast stain. *N. asteroides* complex and *N. brasiliensis* appear as delicately branched, Gram-positive, coccoid to bacillary bacteria that tend to fragment. In properly stained and decolorized acid-fast smears, the organisms may appear as fragmented bacilli with the stain concentrated in a beaded pattern along the portions of the filaments. Gene sequence analysis (16S rRNA; multilocus sequence analysis) is required for definitive identification. Clinical laboratory susceptibility testing is now standardized with breakpoints.

Diagnosis of pulmonary nocardiosis is established in 30% of cases in adults by sputum analysis and culture. Bronchoalveolar lavage or lung biopsy may be required to establish the diagnosis in the remaining 60% of adults and in children.

Cranial CT or MRI is recommended for all immunocompromised patients with pulmonary nocardiosis, even if asymptomatic, because of the high frequency of CNS involvement, and should also be considered for immunocompetent patients.

TREATMENT

Surgical drainage of abscesses is important. The choice, dose, and duration of antimicrobial treatment depend on the site and extent of infection, host immune status, initial clinical response, and species and susceptibility testing of the *Nocardia* isolate. The initial selection of antimicrobial therapy must be empiric. Sulfonamides have been the cornerstone of therapy for the treatment of nocardiosis since the 1940s, but increasing reports of resistance have led to the use of other regimens. Trimethoprim-sulfamethoxazole (TMP-SMX) is the formulation that is recommended, although sulfadiazine and sulfisoxazole have been used. TMP-SMX resistance ranges from 20% for *N. brasiliensis* to 80% for *N. farcinica*. A susceptibility study of 78 clinical isolates of the *N. asteroides* complex from the United States found that 95% of strains exhibited 1 of 6 antibiotic resistance patterns. The most common pattern, occurring in 35% of isolates, showed resistance to ampicillin and erythromycin, but susceptibility to cefotaxime, ceftriaxone, and carbapenems. Approximately 20% of isolates, which were subsequently identified as *N. farcinica,* were resistant to cefotaxime and ceftriaxone. Based on analysis of all strains tested to date, resistance was lowest for amikacin (5%), imipenem (30%), and ceftriaxone (52%). *N. farcinica* is typically always resistant to ertapenem. Imipenem resistant *Nocardia cyriacigeorgica* infection in a child with chronic granulomatous disease has been reported. The most active oral agents were sulfonamides (100%) and minocycline (100%). Additional antimicrobial agents with oral bioavailability are desirable because of the increasing reports of sulfonamide resistance and the adverse effects reported among patients with HIV infection. In vitro studies show susceptibility of all strains to linezolid, which appears to be an effective alternative treatment, but potential toxicity with long-term oral therapy with this agent must be kept in mind.

Combination therapy involving a carbapenem or a third-generation cephalosporin with or without amikacin is usually recommended for severely ill patients and patients with CNS involvement. The mortality rate approaches 50% when a sulfonamide is used alone for treatment. On the basis of in vitro susceptibility testing for specific *N. asteroides* complex isolates, alternative drug combinations may include erythromycin and newer macrolides (azithromycin and clarithromycin), carbapenems, streptomycin, minocycline, quinolones, third-generation cephalosporins, and linezolid. The issues to be considered for use of linezolid include the limited data of use in children and the adverse effects of long-term use. Clinical trials show that ampicillin and amoxicillin-clavulanate are effective in *N. brasiliensis* infections.

Susceptibility testing of *Nocardia* should be performed by a reference laboratory for isolates from deep-seated or disseminated

infections of strains such as *N. farcinica* and *Nocardia otitidiscaviarum* that are commonly resistant to cephalosporins, if nonsulfonamide treatment regimens are being considered, for poor response to initial therapy, and for relapse.

Superficial cutaneous infection is treated for at least 6-12 wk. Mycetoma or pulmonary or systemic nocardiosis in immunocompetent persons is treated for 6-12 mo. CNS infection is treated for at least 12 mo, using at least 2-3 antibiotics with proven susceptibility for at least the 1st 4-12 wk, until some evidence of clinical and radiographic improvement. Relapses of systemic *Nocardia* infection that had been treated for <3 mo have occurred.

PROGNOSIS

Despite appropriate therapy, the overall mortality rate for nocardiosis is >50%. This high rate may be secondary to delay in diagnosis or to the debilitated state of patients with severely compromised host defenses.

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Section 5

Gram-Negative Bacterial Infections

Chapter 191

Neisseria meningitidis (Meningococcus)

Andrew J. Pollard and Manish Sadarangani

Neisseria meningitidis (the *meningococcus*) is a commensal of the human nasopharynx in approximately 10% of the population and rarely enters the bloodstream to cause devastating invasive disease such as meningitis and meningococcal septicemia (meningococcemia). Although a rare endemic disease in most countries, the epidemiology varies widely over time and in different geographic regions with both hyperendemic and epidemic disease patterns occurring. Onset of disease in susceptible individuals may be very rapid, within hours, and the case fatality rate is high, especially among those presenting with septic shock, despite access to modern critical care. Individual susceptibility is now known to involve a complex relationship between environmental, host, and bacterial factors, and prevention of disease through behavior modification (such as avoiding tobacco smoke) and vaccination offers the best prospect for control.

ETIOLOGY

N. meningitidis was first described by Weichselbaum who observed the organism, which he called *Diplococcus intracellularis meningitidis,* in specimens from 6 patients who died of meningitis in 1887. *N. meningitidis* is a Gram-negative, fastidious, encapsulated, oxidase-positive, aerobic diplococcus. Differences in the chemistry of the polysaccharide capsule allow definition of 13 serologically distinct meningococcal capsular groups, of which 6, designated A, B, C, W (previously designated W135), X, and Y, are responsible for almost all cases of disease. Meningococcal strains may be subclassified on the basis of antigenic variation in 2 porin proteins found in the outer membrane, PorB (serotype) and PorA (serosubtype), and lipopolysaccharide (immunotype), using serology. Serologic typing is being replaced by molecular typing methods, which target genes under immune selection to provide antigen sequence typing (based on amino acid variation in various surface proteins, including PorA and FetA). Sequencing of antigen genes (such as *PorA, fHbp, NadA,* and *NHBA*) is set to be an important means of monitoring pressure on meningococcal populations by protein-based vaccines. Because meningococci readily exchange genetic material, typing based on a few antigens cannot provide an accurate picture of relatedness of strains, an important goal in monitoring epidemiology. Multilocus sequence typing, which types meningococci using variation in 7 housekeeping genes, is now widely used to map the distribution of genetic lineages of meningococci (http://pubmlst.org/neisseria/) and provides a clearer picture of the genetic and epidemiologic relatedness of strains. To provide still better definition of genetic variation, in some countries, including the United Kingdom, whole-genome sequencing is now being used to type meningococci and appears set to replace both antigen sequencing and multilocus sequence typing as costs continue to fall. The application of molecular approaches to epidemiology has established that (1) endemic meningococcal disease is caused by genetically heterogeneous strains, although only a small number of genetic lineages are associated with the majority of cases of invasive disease; and (2) outbreaks are usually clonal, caused by single strains.

EPIDEMIOLOGY

Meningococci are transmitted during close contact via aerosol droplets or exposure to respiratory secretions, such as through kissing. The organism does not survive for long periods in the environment. Enhanced rates of mucosal colonization and increased disease risk are associated with activities that increase the likelihood of exposure to a new strain or increase proximity to a carrier, thus facilitating transmission including kissing, bar patronage, binge drinking, attendance at nightclubs, and living in freshman college dormitories. Factors that damage the nasopharyngeal mucosa such as smoking and respiratory viral infection (notably influenza) are also associated with increased rates of carriage and disease, perhaps by driving upregulation of host adhesion molecules that are receptors for meningococci. Carriage is unusual in early childhood and peaks during adolescence and young adulthood.

Meningococcal disease is a global problem, but disease rates vary by a factor of 10-100–fold in different geographic locations at one point in time and in the same location at different times. Most cases of meningococcal disease are sporadic, but small outbreaks (usually in schools or colleges, representing <3% of U.S. cases), hyperendemic disease (increased rates of disease persisting for a decade or more as a result of a single clone), and epidemic disease are all recognized patterns. However, over the last decade, rates of meningococcal disease have declined in most industrialized countries partly through introduction of immunization programs, possibly aided by widespread legislation against smoking in public places. In the United States, the disease rate was 1.1 cases per 100,000 population in 1999 but had fallen to 0.2 cases per 100,000 population by 2011 (Fig. 191-1). By contrast, the rate of disease in Ireland in 1999 was >12 per 100,000 population and rates of 1,000 per 100,000 population have been described during epidemic disease in sub-Saharan Africa. Disease caused by dominant hyperendemic clones has been recognized in the last decade in Oregon, United States, across New Zealand, and in Normandy, France. Laboratory data underreport meningococcal disease incidence rates as up to 50% of cases are not culture confirmed. In the United Kingdom, polymerase chain reaction (PCR) methods are used routinely for diagnosis of suspected cases, doubling the number of confirmed cases.

The highest rate of meningococcal disease occurs in infants younger than 1 yr old, probably as a result of immunologic inexperience (antibody that recognizes meningococcal antigens is naturally acquired during later childhood), immaturity of the alternative and lectin complement pathways, and perhaps the poor responses made by infants to bacterial polysaccharides. In the absence of immunization, incidence

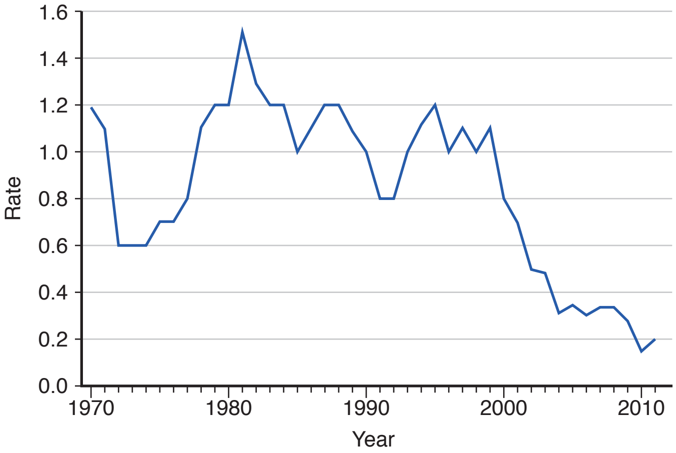

Source: CDC, Unpublished data, National Notifiable Diseases Surveillance System (NNDSS) for 1970–1996 and Active Bacterial Core surveillance (ABCs) system for 1997–2011.

* Per 100,000 population.

† ABCs cases from 1997–2011 estimated to the U.S. population. In 2010, estimated case counts from ABCs were lower than cases reported to NNDSS and might not be representative.

Figure 191-1 Rate of meningococcal disease, by year—United States, 1970-2011. *(From Cohn AC, MacNeil JR, Clark TA, et al; Centers for Disease Control and Prevention (CDC): Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep *62(RR-2):1–28, 2013.)*

rates decline through childhood, apart from a peak of disease among adolescence and young adults, which may be related to increased opportunity for exposure from social activities.

In the United States, the majority of cases of disease in the 1st yr of life are caused by serogroup B strains. After age 1 yr, disease is roughly equally distributed among serogroups B, C, and Y strains. In most other industrialized countries, serogroup B strains predominate at all ages, in part because of introduction of routine serogroup C meningococcal conjugate vaccination among infants and/or toddlers. For reasons not understood, disease in children caused by group Y strains was uncommon in the United States before the 1990s and remains relatively uncommon outside the country.

Large outbreaks of serogroup A meningococcal disease occurred during and immediately after the 1st and 2nd World Wars in both Europe and the United States, but since the 1990s almost all cases caused by serogroup A strains have occurred in Eastern Europe, Russia, and developing countries. The highest incidence of serogroup A disease has occurred in a band across sub-Saharan Africa, the "meningitis belt," with annual endemic rates of 10-25 per 100,000 population. For more than a century, this region has experienced large serogroup A epidemics every 7-10 yr, with annual rates as high as 1,000 per 100,000 population. The onset of cases in the sub-Saharan region typically begins during the dry season, possibly related to drying and damage to the nasopharyngeal mucosa, and subsides with the rainy season, and may reemerge the following dry season. Rates of serogroup A meningococcal disease are currently falling across this region as a result of a mass vaccine implementation. However, both endemic and epidemic meningococcal disease in this region is also caused by serogroup W and X strains. These strains are infrequent causes of disease in other areas of the world, although both A and W strains have been associated with outbreaks among pilgrims returning from the Hajj.

PATHOGENESIS AND PATHOPHYSIOLOGY

Colonization of the nasopharynx by *N. meningitidis* is the first step in either carriage or invasive disease. Disease usually occurs 1-14 days after acquisition of the pathogen. Initial contact of meningococci with host epithelial cells is mediated by pili, which may interact with the host CD46 molecule or an integrin. Close adhesion is then mediated by Opa and Opc binding to carcinoembryonic antigen cell adhesion molecule receptors and integrins, respectively. Subsequent internalization of meningococci by epithelial cells is followed by transcytosis through to the basolateral tissues and dissemination into the bloodstream. Immunoglobulin A_1 protease secreted by invasive bacteria degrades secretory immunoglobulin A on the mucosal surface, circumventing this first-line host defense mechanism.

Once in the bloodstream, meningococci multiply rapidly to high levels to cause septicemia. Patients with a higher bacterial load have a more rapid clinical deterioration and longer period of hospitalization, as well as a higher risk of death and permanent sequelae. Resistance to complement-mediated lysis and phagocytosis is largely mediated by the polysaccharide capsule and lipopolysaccharide (LPS). Outer membrane vesicle blebs released from the surface of the organism contain LPS, outer membrane proteins, periplasmic proteins, and phospholipid, and play a major role in the inflammatory cascade that leads to severe disease.

Much of the tissue damage is caused by host immune mechanisms activated by meningococcal components, in particular LPS. During invasive disease LPS is bound to a circulating plasma protein, known as LPS binding protein. The host receptor complex for LPS consists of toll-like receptor 4, CD14, and myeloid differentiation protein 2. Binding of LPS to toll-like receptor 4, which is upregulated on circulating leukocytes during septicemia, results in activation of a number of different cell types. An intense inflammatory reaction ensues due to the secretion of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-8, and granulocyte macrophage colony-stimulating factor, levels of which are closely associated with plasma levels of LPS. The major antiinflammatory cytokines IL-1Ra, IL-2, IL-4, and IL-12. and transforming growth factor-β are present at very low levels. Both high and low levels have been observed for IL-10 and interferon-γ.

The pathophysiologic events that occur during meningococcal septicemia are largely related to microvascular injury. This leads to increased vascular permeability and the capillary leak syndrome, pathologic vasoconstriction and vasodilation, disseminated intravascular coagulation, and profound myocardial dysfunction. Increased vascular permeability can lead to dramatic fluid loss and severe hypovolemia. Capillary leak syndrome with or without aggressive fluid resuscitation (which is essential in severe cases) leads to pulmonary edema and respiratory failure. Initial vasoconstriction is a compensatory mechanism in response to hypovolemia and results in the clinical features of pallor and cold extremities. Following resuscitation, some patients experience "warm shock," that is, intense vasodilation with bounding pulses and warm extremities, despite persistent hypotension and metabolic acidosis. Virtually all antithrombotic mechanisms appear to be dysfunctional during meningococcal sepsis, leading to a procoagulant state and disseminated intravascular coagulation. All of these factors contribute to depressed myocardial function, but there is also a direct negative cytokine effect on myocardial contractility, thought to be largely mediated via IL-6. Hypoxia, acidosis, hypoglycemia, hypokalemia, hypocalcemia, and hypophosphatemia are all common in severe septicemia and further depress cardiac function. Some patients become unresponsive to the positive inotropic effects of catecholamines and require high levels of inotropic support during intensive care management. These processes result in impairment of microvascular blood flow throughout the body and ultimately lead to multiorgan failure, which is responsible for much of the mortality.

Following invasion of the circulation, meningococci may also penetrate the blood–brain barrier and enter the cerebrospinal fluid (CSF), facilitated by pili and possibly Opc. Once there, bacteria continue to proliferate and LPS and other outer membrane products can stimulate a proinflammatory cascade similar to that observed in the blood. This leads to upregulation of specific adhesion molecules and recruitment of leukocytes into the CSF. Central nervous system damage occurs directly by meningeal inflammation and indirectly by circulatory collapse and causes a high rate of neurologic sequelae in affected patients. Death can occur from cerebral edema, which leads to raised intracranial pressure and cerebral or cerebellar herniation.

Immunity

There is an inverse correlation between the incidence of disease and the prevalence of complement-dependent serum bactericidal antibody (SBA). The level of SBA is highest at birth and among adults and lowest in children between 6 mo and 2 yr of age when the highest incidence of disease occurs. Such antibodies are naturally elicited by asymptomatic carriage of pathogenic and nonpathogenic meningococci as well as by carriage of antigenically related species such as *Neisseria lactamica*. A similar relationship was described for serogroups A, B, and C. Vaccine trials support these earlier findings. For the meningococcal serogroup C conjugate vaccine, an SBA titer of ≥1 : 8 correlated strongly with postlicensure vaccine effectiveness. For serogroup B disease the data are less certain, but the proportions of serogroup B vaccine recipients with ≥4-fold rises in SBA following vaccination or SBA titers ≥1 : 4 have been correlated with clinical efficacy in trials of outer membrane vesicle vaccines. These cutoffs are, therefore, currently used for regulatory approval of new meningococcal vaccines.

There has been increasing evidence that mechanisms other than complement-dependent bactericidal antibodies are important in determining protection against meningococcal disease. The relationship between incidence of disease and prevalence of SBA was not observed in more recent studies in the United Kingdom and Canada, where a decline in disease incidence throughout childhood was not associated with a change in the seroprevalence of SBA. In the UK study, the second peak of disease in teenagers coincided with a paradoxical increase in the proportion with an SBA titer ≥1 : 4 and adults had a low risk of disease despite a much lower prevalence of SBA activity. In addition, disease in individuals with complement deficiency has a different age distribution has less-severe clinical features and often involves unusual serogroups. In particular, complement deficiency does not appear strongly related to an increased risk of serogroup B disease. Alternative surrogate markers of protection include the opsonophagocytic assay and antibody avidity, but there are no studies that have attempted to link these laboratory tests with vaccine efficacy or even population protection, as has been found with SBA.

Host Factors

Host susceptibility is strongly related to age as described above, indicating that immunologic responsiveness and/or naivety in infancy and early childhood are key determinants of risk. Complement is a key factor in protection against meningococcal disease. Individuals with inherited deficiencies of properdin, factor D, or terminal complement components have up to a 1,000-fold higher risk for development of meningococcal disease than complement-sufficient people. The risk of meningococcal disease is also increased in patients with acquired complement deficiencies associated with diseases such as nephrotic syndrome, systemic lupus erythematosus, and hepatic failure.

Among those with complement deficiencies, meningococcal disease is more prevalent during late childhood and adolescence, when carriage rates are higher than in children younger than age 10 yr; meningococcal infections may be recurrent. Although meningococcal disease can occasionally be overwhelming in patients with late complement component deficiency, cases are more typically described as being less severe than in complement-sufficient persons (properdin deficiency being the exception), perhaps reflecting the fact that these cases are often caused by unusual capsular serogroups. In 1 study, one-third of individuals with meningococcal disease caused by serogroups X, Y, and W had a complement deficiency. Although protective against early infection, extensive complement activation and bacteriolysis may contribute to the pathogenesis of severe disease once bacterial invasion has occurred.

The sibling risk ratio for meningococcal disease is similar to that for other diseases where susceptibility shows polygenic inheritance, and there are a number of host genetic factors that have now been identified to affect either susceptibility to meningococcal disease or severity of disease. The difficulties of these studies are the requirement for large numbers of cases and controls, and the need to confirm any potential associations in more than 1 population. The molecules implicated involved polymorphisms in genes expressed at epithelial surfaces, the complement cascade, pattern recognition receptors, clotting factors, or inflammatory mediators. Deficiencies in the complement pathways are consistently associated with an increased risk of meningococcal disease, with specific polymorphisms in mannose-binding lectin, and factor H found to be associated with disease susceptibility. A genome-wide association study of 7,522 individuals in Europe identified single-nucleotide polymorphisms within genes encoding complement factor H *(CFH)* and CFH-related protein 3 (*CFHR3*), which were associated with host susceptibility to meningococcal disease. Complement-mediated bacteriolysis is known to be extremely important in protection against meningococcal disease, giving these associations biologic plausibility. In particular, factor H attaches to various binding proteins expressed on the bacterial surface, downregulating complement activation and allowing the organism to evade host responses.

In terms of disease severity, a meta-analysis performed to collate data from smaller studies found that single-nucleotide polymorphisms in genes encoding plasminogen activator inhibitor 1 *(SERPINE1),* IL-1 receptor antagonist *(IL1RN)* and IL-1β *(IL1B)* are associated with increased mortality from meningococcal disease, which, again, is predictable from the known pathophysiologic changes that occur during invasive disease. Given that any single specific single-nucleotide polymorphism is likely to have only a small impact on disease susceptibility or severity, further large genome-wide association study in genetically different populations are required.

CLINICAL MANIFESTATIONS

The most common clinical manifestation of meningococcal infection is asymptomatic carriage of the organism in the nasopharynx. In the rare cases where invasive disease occurs, the clinical spectrum of meningococcal disease varies widely, but the highest proportion of cases present with meningococcal meningitis (30-50% of cases). Other recognized presentations include bacteremia without sepsis, meningococcal septicemia with or without meningitis, pneumonia, chronic bacteremia, and occult bacteremia. Focal infections in various sites (e.g., myocardium, joints, pericardium, bone, eye, peritoneum, sinuses, and middle ear) are well recognized, and all may progress to disseminated disease. Urethritis, cervicitis, vulvovaginitis, orchitis, and proctitis may also occur.

Acute meningococcal septicemia cannot be distinguished from other viral or bacterial infections early after onset of symptoms (Table 191-1). Typical nonspecific early symptoms include fever, irritability, lethargy, respiratory symptoms, refusal to drink, and vomiting. Less commonly, diarrhea, sore throat, and chills/shivering are reported. A fine maculopapular rash, which is indistinguishable from rashes seen after viral infections, is evident in approximately 7% of cases early in the course of infection. Limb pain, myalgia, or refusal to walk may occur as the primary complaint in 7% of otherwise clinically unsuspected cases. As disease progresses, cold hands or feet and abnormal skin color may be important signs, capillary refill time becomes prolonged, and a nonblanching or petechial rash will develop in more than 80% of cases. In fulminant meningococcal septicemia, the disease progresses rapidly over several hours from fever with nonspecific signs to septic shock characterized by prominent petechiae and purpura **(purpura fulminans)** with poor peripheral perfusion, tachycardia (to compensate for reduced blood volume resulting from capillary leak), increased respiratory rate (to compensate for pulmonary edema), hypotension (a late sign of shock in young children), confusion, and coma (resulting from decreased cerebral perfusion). Coagulopathy, electrolyte disturbance (especially hypokalemia), acidosis, adrenal hemorrhage, renal failure, and myocardial failure, may all develop (Fig. 191-2). Meningitis may be present.

Meningococcal meningitis is indistinguishable from meningitis caused by other bacteria. Nonspecific symptoms and signs (see Table 191-1), including fever and headache, predominate, especially in the young and early in the illness. Children younger than 5 yr of age rarely report headache. More specific symptoms of photophobia, nuchal rigidity, bulging of the fontanel, and clinical signs of meningeal irritation may develop but are unusual in infants. Seizures and focal neurologic signs occur less frequently than in patients with meningitis

Table 191-1 Prevalence of Symptoms and Signs in Children and Young People with Meningococcal Septicemia, Meningococcal Disease and Bacterial Meningitis

	Prevalence Range (Number of Studies)		
SYMPTOM OR SIGN	BACTERIAL MENINGITIS	MENINGOCOCCAL DISEASE	MENINGOCOCCAL SEPTICEMIA
Fever	66-97% (10)	58-97% (7)	98% (1)
Vomiting or nausea	18-70% (10)	44-76% (6)	64% (1)
Rash	9-62% (6)	59-100% (9)	70% (1)
Headache	3-59% (7)	16-49% (5)	40% (1)
Lethargy	13-87% (6)	36-65% (3)	59% (1)
Coughing	N/A (0)	15-27% (2)	33% (1)
Irritable or unsettled	21-79% (8)	36-67% (3)	32% (1)
Runny nose	N/A (0)	24% (1)	31% (1)
Muscle ache or joint pain	23% (1)	7-65% (3)	30% (1)
Refusing food or drink	26-76% (4)	13-60% (3)	27% (1)
Altered mental state*	26-93% (6)	45-81% (3)	N/A (0)
Stiff neck	13-74% (13)	5-71% (6)	N/A (0)
Impaired consciousness	60-87% (4)	10-72% (2)	N/A (0)
Unconsciousness	4-18% (4)	N/A (0)	N/A (0)
Chills or shivering	N/A (0)	39% (1)	N/A (0)
Photophobia	5-16% (2)	2-31% (5)	N/A (0)
Respiratory symptoms	25-49% (4)	16-23% (2)	N/A (0)
Breathing difficulty	13-34% (4)	11% (1)	N/A (0)
Cold hands or feet	N/A (0)	43% (1)	N/A (0)
Shock	8-16% (2)	27-29% (2)	N/A (0)
Seizures	14-38% (12)	7-17% (3)	N/A (0)
Diarrhea	21-29% (2)	7-9% (2)	N/A (0)
Abdominal pain or distention	17% (1)	4% (1)	N/A (0)
Leg pain	N/A (0)	11-37% (2)	N/A (0)
Thirst	N/A (0)	8% (1)	N/A (0)
Sore throat, coryza or throat infection	18% (1)	24% (1)	N/A (0)
Ill appearance	N/A (0)	79% (1)	N/A (0)
Capillary refill time >2 sec	N/A (0)	83% (1)	N/A (0)
Hypotension	N/A (0)	28% (1)	N/A (0)
Abnormal skin color	N/A (0)	19% (1)	N/A (0)
Bulging fontanelle†	13-45% (4)	N/A (0)	N/A (0)
Ear infection or ear, nose and throat infections‡	18-49% (5)	N/A (0)	N/A (0)
Chest infection	14% (1)	N/A (0)	N/A (0)
Brudzinski sign	11-66% (2)	N/A (0)	N/A (0)
Kernig sign	10-53% (3)	N/A (0)	N/A (0)
Abnormal pupils	10% (1)	N/A (0)	N/A (0)
Cranial nerve pair involvement	4% (1)	N/A (0)	N/A (0)
Toxic or moribund state	3-49% (2)	N/A (0)	N/A (0)
Back rigidity	46% (1)	N/A (0)	N/A (0)
Paresis	6% (1)	N/A (0)	N/A (0)
Focal neurological deficit	6-47% (3)	N/A (0)	N/A (0)

Classification of conditions presented in the table reflects the terminology used in the evidence.

*This includes confusion, delirium, and drowsiness.

†The age ranges in the 4 studies are 0-14 yr, 0-2 yr, 0-12 mo, and 0-13 wk.

‡One study reported the number of children and young people with ear, nose, and throat infections; the 4 other studies reported the number of ear infections only.

N/A, not applicable.

Modified from National Collaborating Center for Women's and Children's Health (UK): Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. NICE clinical guidelines, No. 102. *London, 2010, RCOG Press.*

Figure 191-2 **A,** Purpuric rash in a 3 yr old with meningococcemia. **B,** Purpura fulminans in an 11 mo old with meningococcemia. *(From Thompson ED, Herzog KD: Fever and rash. In Zaoutis L, Chiang V, editors:* Comprehensive pediatric hospital medicine, *Philadelphia, 2007, Mosby, p. 332,* Figs. 62-6 *and* 62-7*.)*

caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* type b. A meningoencephalitis-like picture can occur that is associated with rapidly progressive cerebral edema and death from raised intracranial pressure, which may be more common with serogroup A infection.

Occult meningococcal bacteremia manifests as fever with or without associated symptoms that suggest a minor viral infection. Resolution of bacteremia may occur without antibiotics, but sustained bacteremia leads to meningitis in approximately 60% of cases and to distant infection of other tissues.

Chronic meningococcemia, which occurs rarely, is characterized by fever, nontoxic appearance, arthralgia, headache, splenomegaly, and a maculopapular or petechial rash. Symptoms are intermittent, with a mean duration of illness of 6-8 wk. Blood culture results are usually positive, but cultures may initially be sterile. Chronic meningococcemia may spontaneously resolve, but meningitis may develop in untreated cases. Some cases have been associated with complement deficiency and others with sulfonamide therapy. One report indicates that up to 47% of isolates from patients with chronic meningococcemia (compared with less than 10% in acute cases) have a mutation in the *lpxl* 1 gene*,* leading to a reduced inflammatory response and the milder course of infection.

DIAGNOSIS

The initial diagnosis of meningococcal disease should be made on clinical assessment to avoid delay in implementation of appropriate therapy. Laboratory findings are variable but may include leukocytopenia or leukocytosis, often with increased percentages of neutrophils and band forms, an anemia, thrombocytopenia, proteinuria, and hematuria. Elevations of erythrocyte sedimentation rate and C-reactive protein may occur, but in patients with rapid onset of disease, these values may be within normal limits at presentation. Conversely, a raised C-reactive protein in the presence of fever and petechiae makes the diagnosis likely. Hypoalbuminemia, hypocalcemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypoglycemia, and metabolic acidosis, often with increased lactate levels, are common in patients with meningococcal septicemia. Patients with coagulopathy have decreased serum concentrations of prothrombin and fibrinogen and prolonged coagulation times.

A confirmed diagnosis of meningococcal disease is established by isolation of *N. meningitidis* from a normally sterile body fluid such as blood, CSF, or synovial fluid. Meningococci may be identified in a Gram stain preparation and/or culture of petechial or purpuric skin lesions, although this procedure is rarely undertaken, and occasionally are seen on Gram stain of the buffy coat layer of a centrifuged blood sample. Although blood culture may be positive in more than two-thirds of cases prior to antibiotic use, culture results often are negative if the patient has been treated with antibiotics prior to collection of the culture specimen; data suggest that less than 50% are culture-positive. Isolation of the organism from the nasopharynx is not diagnostic of invasive disease because the organism is a common commensal.

PCR using primers specific for meningococcal genes (e.g., *ctrA*), has high sensitivity and specificity for detection of meningococci using whole blood samples and has increased confirmation of suspected cases by more than 40% in the United Kingdom.

Lumbar puncture should be undertaken to establish a diagnosis of meningococcal meningitis in those patients without contraindications (including presence of septic shock, coagulopathy, thrombocytopenia, respiratory distress, seizures, raised intracranial pressure, or local infection). In patients with meningococcal meningitis, the cellular and chemical characteristics of the CSF are those of acute bacterial meningitis, showing Gram-negative diplococci on Gram stain in up to 75% of cases. CSF culture results may be positive in patients with meningococcemia in the absence of CSF pleocytosis or clinical evidence of meningitis; conversely, positive CSF specimens that are positive for Gram stain are sometimes culture negative. Over-decolorized pneumococci in Gram stain preparations can be mistaken for meningococci, and, therefore, empirical therapy should not be narrowed to *N. meningitidis* infection on the basis of Gram stain findings alone.

Detection of capsular polysaccharide antigens using rapid latex agglutination tests on CSF can support the diagnosis in cases clinically consistent with meningococcal disease, but the tests have not performed adequately in clinical practice (poor sensitivity and cross reactivity of the serogroup B test with *Escherichia coli* K1 antigen) and have been replaced by molecular diagnostic methods. Urine antigen testing is insensitive and should not be used. PCR-based assays for detection of meningococci in blood and CSF have been developed, and multiplex PCR assays that detect several bacterial species associated with meningitis, including the meningococcus, are used in some laboratories.

DIFFERENTIAL DIAGNOSIS

Meningococcal disease can appear similar to sepsis or meningitis caused by many other Gram-negative bacteria, *S. pneumoniae, Staphylococcus aureus,* or group A streptococcus; to Rocky Mountain spotted fever, ehrlichiosis, or epidemic typhus; and to bacterial endocarditis. Viral and other infectious etiologies of meningoencephalitis should be considered in some cases.

Petechial rashes are common in viral infections (enteroviruses, influenza and other respiratory viruses, measles, Epstein Barr virus, cytomegalovirus, parvovirus) and may be confused with meningococcal disease. Petechial or purpuric rashes are also associated with protein C or S deficiency, platelet disorders (including idiopathic thrombocytopenic purpura), Henoch-Schönlein purpura, connective tissue disorders, drug eruptions, and trauma, including nonaccidental injury. The nonpetechial, blanching maculopapular rash observed in some cases of meningococcal disease, especially early in the course, may initially be confused with a viral exanthem.

TREATMENT

Antibiotics

Empirical antimicrobial therapy should be initiated immediately after the diagnosis of invasive meningococcal infection is suspected and cultures are obtained, using a third-generation cephalosporin to cover the most likely bacterial pathogens until the diagnosis is confirmed. In regions with a high rate of β-lactam resistant *S. pneumoniae*, empiric addition of intravenous (IV) vancomycin is recommended (see Chapter 603.1) while awaiting the outcome of bacterial identification and sensitivity, but this is unnecessary in other settings where cephalosporin

Table 191-2 Treatment of *Neisseria meningitidis* Invasive Infections

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSING INTERVAL (hr)	MAXIMUM DAILY DOSE	NOTES
Penicillin G	IM or IV	300,000 units/kg/day	4-6	12-24 million units	Does not clear carriage and "prophylaxis" is required at the end of treatment
Ampicillin	IM or IV	200-400 mg/kg/day	6	6-12 g	Does not clear carriage and "prophylaxis" is required at the end of treatment
Cefotaxime	IM or IV	200-300 mg/kg/day	6-8	8-12 g	Recommended in the neonate
Ceftriaxone	IM or IV	100 mg/kg/day	12-24	2-4 g	Preferred treatment as only once or twice daily and may reduce skin complications
ALTERNATIVE THERAPY IN THE FACE OF LIFE-THREATENING β-LACTAM ALLERGY					
Chloramphenicol*	IV	50-100 mg/kg/day	6	2-4 g	
Ciprofloxacin†	IV	30-40 mg/kg/day	12	1-1.5 g	
Meropenem‡	IV	60-120 mg/kg/day	8	1.5-6 g	

*Monitor blood levels to avoid toxicity.
†Licensed for individuals older than age 18 yr.
‡Rate of crossreactivity in penicillin-allergic adults is 2-3%.
IM, intramuscular; IV, intravenous.

resistance of pneumococci is very rare (in these settings a risk assessment of each case should be made). Once the diagnosis of β-lactam sensitive meningococcal disease is confirmed in the laboratory, some authorities recommend a switch to penicillin; however, even though there is no evidence that survival outcomes are different, there is limited evidence from 1 study that, in meningococcal purpura, necrotic skin lesions are less common among children treated with ceftriaxone than with penicillin. Furthermore, there may be cost-saving by using a once-daily dose of ceftriaxone for therapy in younger children, and this is now recommended practice in the United Kingdom (Table 191-2). No adequate studies have investigated the optimal duration of therapy for children, but the course is generally continued for 5-7 days.

Early treatment of meningococcal infections may prevent serious sequelae, but timely early diagnosis is often difficult in the absence of petechial or purpuric skin findings. Among children presenting with petechial rashes, 1-10% may have underlying meningococcal disease and protocols have been established to ensure that these patients are identified without exposing the more than 90% of cases without meningococcal disease to unnecessary parenteral antibiotic therapy (Fig. 191-3).

Isolates of *N. meningitidis* with decreased susceptibility to penicillin (minimal inhibitory concentration of penicillin of 0.1-1.0 mg/mL) have been reported from Europe, Africa, Canada, and the United States (4% of isolates in 2006). Decreased susceptibility is caused, at least in part, by altered penicillin-binding protein 2 and does not appear to adversely affect the response to therapy, and is irrelevant if third-generation cephalosporins are being used for therapy.

Supportive Care

Most children with meningococcal disease can be managed with antibiotics and simple supportive care and will improve rapidly. However, with an overall 10% case-fatality rate, the priority in initiating management of children presenting with meningococcal disease is identification of the life-threatening features of the disease: shock and raised intracranial pressure. Delayed initiation of supportive therapy is associated with poor outcome, and protocols have therefore been established to aid clinicians in a step-by-step approach (http://www.meningitis.org). In all children presenting with meningococcal disease, assessment of the airway should be made, as the airway could be compromised as a result of a depressed level of consciousness (raised intracranial pressure in meningitis or poor cerebral perfusion in shock). In patients with meningococcal septicemia supplementary oxygen should be used to treat hypoxia, which is caused by pulmonary edema (from capillary leak), and some patients will require endotracheal intubation. Hypovolemia requires both volume replacement and inotropic support to maintain cardiac output. Because ongoing fluid resuscitation may lead to pulmonary edema, endotracheal intubation and ventilation should be initiated in a patient who remains in compensated shock after 40 mL/kg of fluid resuscitation to improve oxygenation and reduce work of breathing. Biochemical and hematologic abnormalities are common in meningococcal septicemia, and protocols recommend anticipation, assessment, and correction of glucose, potassium, calcium, magnesium, phosphate, clotting factors, and blood.

Children with meningococcal meningitis should be cautiously managed with maintenance fluids (fluid restriction is not recommended and may be harmful), and those with raised intracranial pressure should be managed with close attention to maneuvers to maintain normal cerebral perfusion. If there is shock in the presence of raised intracranial pressure, the shock should be carefully corrected to ensure that cerebral perfusion pressure is maintained.

Many adjunctive therapies have been attempted in patients with severe meningococcal septicemia, but few have been subjected to randomized controlled trials. There are insufficient data to recommend use of anticoagulant or fibrinolytic agents, extracorporeal membrane oxygenation, plasmapheresis, or hyperbaric oxygen. In well-designed clinical trials, an antibody directed against endotoxin (HA1A) did not confer any benefit in children with meningococcal disease, and, although initially promising in adult sepsis, activated protein C was not useful in pediatric sepsis and was associated with an increased risk of bleeding. Recombinant bactericidal permeability increasing protein was studied in an underpowered (survival end point) trial and showed some potentially beneficial effects against secondary end points (amputations, transfusions, functional outcome) and requires further investigation.

Although the benefits of steroids for adjunctive therapy in pediatric bacterial meningitis caused by *H. influenzae* type b (Hib) are accepted, there are no pediatric data specifically demonstrating benefit in meningococcal meningitis. However, some authorities extrapolate from animal data, from experience with Hib, and from compelling data from adult meningitis and recommend use of steroids as adjunctive therapy in meningococcal meningitis given with or soon after the 1st dose of antibiotics. Therapeutic doses of steroids should not be used routinely in meningococcal septicemia. Some intensivists recommend use of replacement doses of steroids in patients with severe septic shock, since severe sepsis caused by meningococcus is associated with adrenal insufficiency caused by adrenal necrosis/hemorrhage (Waterhouse-Friderichsen syndrome).

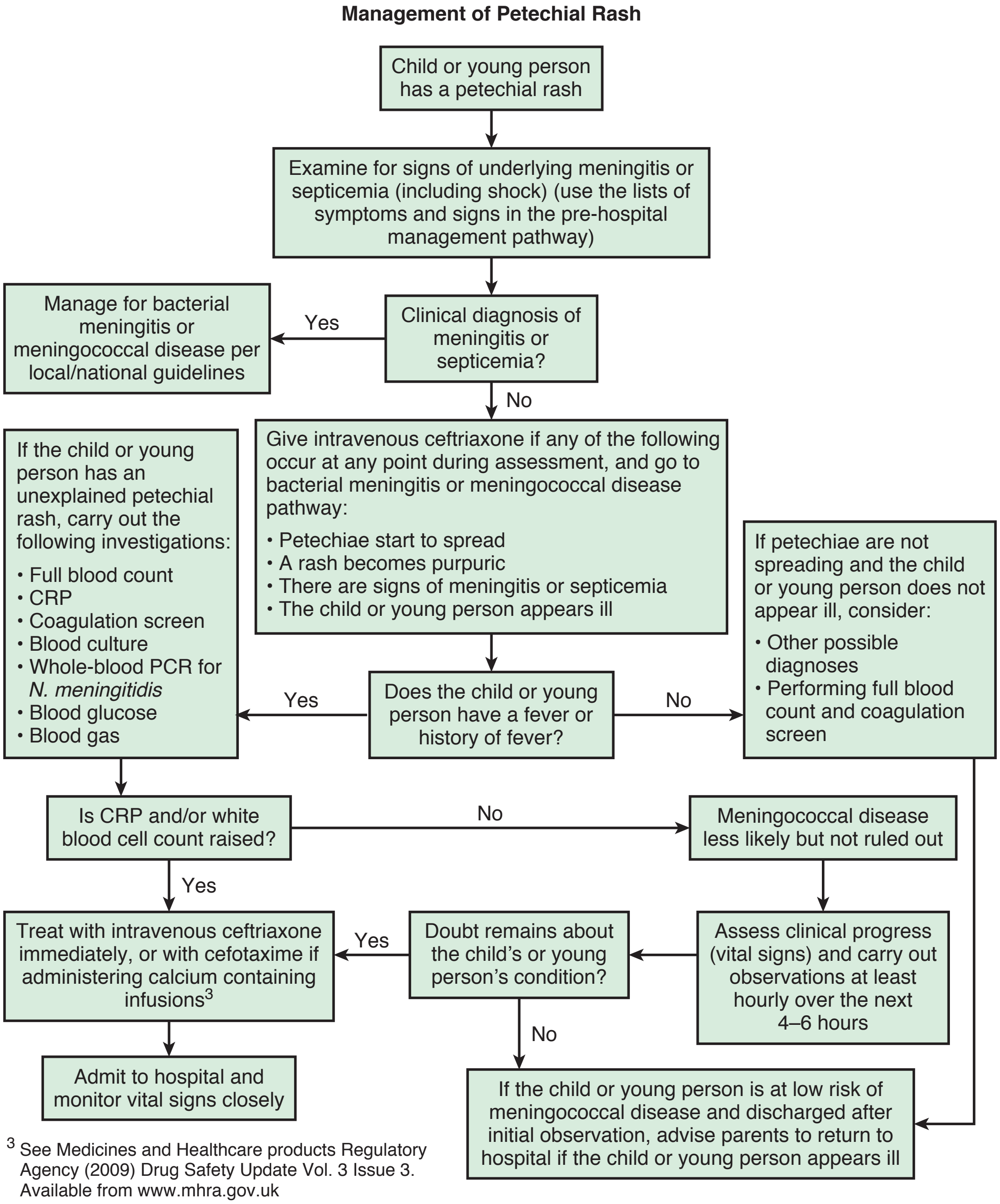

Figure 191-3 An approach to management of petechial rash. *(From National Collaborating Center for Women's and Children's Health (UK):* Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. NICE clinical guidelines, No. 102. *London, 2010, RCOG Press.)*

COMPLICATIONS

Adrenal hemorrhage, endophthalmitis, arthritis, endocarditis, pericarditis, myocarditis, pneumonia, lung abscess, peritonitis, and renal infarcts can occur during acute infection. Renal insufficiency requiring dialysis may result from prerenal failure. Reactivation of latent herpes simplex virus infections is common during meningococcal infection.

A self-limiting immune complex vasculitis may occur, usually in the 1st 10 days after onset of the disease, resulting in various manifestations, including fever, rash, arthritis, and, rarely, iritis, pericarditis, or carditis. The **arthritis** is monoarticular or oligoarticular, involves large joints, and is associated with sterile effusions that respond to nonsteroidal antiinflammatory agents. Because most patients with meningococcal meningitis become afebrile by the 7th hospital day, persistence or recrudescence of fever after 5 days of antibiotics warrants evaluation for immune complex–mediated complications.

The most common complication of acute severe meningococcal septicemia is focal skin infarction, which most commonly affects the lower limbs and can lead to substantial scarring and require skin grafting. Distal tissue necrosis in purpura fulminans may require amputation (which should be delayed to allow demarcation) in approximately 2% of survivors. Avascular necrosis of epiphyses and epiphyseal–metaphyseal defects can result from the generalized disseminated intravascular coagulation and may lead to growth disturbance and late skeletal deformities.

Deafness is the most frequent neurologic sequela of meningitis, occurring in 5-10% of children. Cerebral arterial or venous thrombosis with resultant cerebral infarction can occur in severe cases. Meningococcal meningitis is rarely complicated by subdural effusion or empyema or by brain abscess. Other rare neurologic sequelae include ataxia, seizures, blindness, cranial nerve palsies, hemiparesis or quadriparesis, and obstructive hydrocephalus (manifests 3-4 wk after onset

of illness). Finally, behavioral and psychosocial complications of the disease are frequently reported.

PROGNOSIS

The case-fatality rate for invasive meningococcal disease is 5-10%, with clear differences related to age of the patient and meningococcal genotype. Most deaths occur within 48 hr of hospitalization in children with meningococcemia. Poor prognostic factors on presentation include hypothermia or extreme hyperpyrexia, hypotension or shock, purpura fulminans, seizures, leukopenia, thrombocytopenia (including disseminated intravascular coagulation), acidosis, and high circulating levels of endotoxin and tumor necrosis factor-α. The presence of petechiae for <12 hr before admission, absence of meningitis, and low or normal erythrocyte sedimentation rate indicate rapid, fulminant progression and poorer prognosis.

Because complement deficiency is rare following capsular group B infection, s**creening** is unlikely to be useful in detecting cases caused by this group. However, with one-third or more of cases of disease caused by groups X, Y, and W apparently associated with complement deficiency, it is appropriate to screen after infection with non-B serogroups.

PREVENTION

Secondary Prevention

Close contacts of patients with meningococcal disease are at increased risk of infection because such individuals are likely to be colonized with the index's (hyperinvasive) strain. Antibiotic prophylaxis should be offered as soon as possible to individuals who have been exposed directly to a patient's oral secretions, for whom risk may be 1,000 times the background rate in the population. This includes household, kissing, and close family contacts of cases, as well as childcare and recent preschool contacts in the United States. Up to 30% of cases occur in the 1st wk, but risk persists for up to a year after presentation of the index case. Although prophylaxis is effective in preventing secondary cases, coprimary cases may occur in the days after presentation of the index case and contacts should be carefully evaluated if they develop symptoms. Advice on management of non–close contacts, such as those in daycare, nursery settings, or school and other institutions, varies in different countries because the risk of a secondary case in this situation is low and opinion on risk assessment varies. Ceftriaxone and ciprofloxacin are the most effective agents for prophylaxis, the latter being the drug of choice in some countries. Rifampin is most widely used but fails to eradicate colonization in 15% of cases (Table 191-3). Prophylaxis is not routinely recommended for medical personnel except those with exposure to aerosols of respiratory secretions, such as through mouth-to-mouth resuscitation, intubation, or suctioning before or in the 24 hr after antibiotic therapy is initiated in the index case.

Neither penicillin nor ampicillin treatment eradicates nasopharyngeal carriage and should not be routinely used for prophylaxis. Patients with meningococcal infection treated solely with penicillin or ampicillin are therefore at risk of relapse or transmission to a close contact and should receive antimicrobial prophylaxis with one of the agents listed in Table 191-3 prior to hospital discharge. As discussed above, our preference is to use ceftriaxone for treatment of the index case, in which case further prophylaxis is not required. Droplet precautions should be observed for hospitalized patients for 24 hr after initiation of effective therapy. All confirmed or probable cases of meningococcal infection must be reported to the local public health department according to national or regional regulations.

Close contacts of cases could also be immunized to further reduce the risk of secondary infection as is described below.

Table 191-3 Antibiotic Prophylaxis to Prevent *Neisseria meningitidis* Infection*

DRUG	DOSE	DURATION
RIFAMPIN†		
Infants <1 mo	5 mg/kg PO every 12 hr	2 days (4 doses)
Children ≥1 mo	10 mg/kg PO every 12 hr (maximum: 600 mg)	2 days (4 doses)
Adults	600 mg PO every 12 hr	2 days (4 doses)
CEFTRIAXONE		
Children <15 yr	125 mg IM	1 dose
Children ≥15 yr	250 mg IM	1 dose
CIPROFLOXACIN		
Children ≥1 mo†‡	20 mg/kg (maximum: 500 mg) PO	1 dose

*Recommended for household and kissing contacts. In the United States, chemoprophylaxis is recommended for:

- Household contact, especially children younger than 2 yr of age
- Childcare or preschool contact at any time during 7 days before onset of illness
- Direct exposure to index patient's secretions through kissing, sharing toothbrushes or eating utensils at any time during 7 days before onset of illness
- Mouth-to-mouth resuscitation, unprotected contact during endotracheal intubation during 7 days before onset of illness
- Frequently slept in same dwelling as index patient during 7 days before onset of illness
- Passengers seated directly next to the index case during airline flights lasting more than 8 hr

†Not recommended for pregnant women.

‡Not recommended routinely for people younger than 18 yr of age; use only if fluoroquinolone-resistant strains of *N. meningitidis* have not been identified in the community.

IM, intramuscular; PO, by mouth.

Vaccination

Meningococcal plain *polysaccharide* vaccines containing capsular polysaccharides from serogroups A + C or serogroups A, C, W, Y have been available since the 1960s and have been used in the control of outbreaks and epidemics and for high-risk groups. However, these vaccines are poorly immunogenic in infants, do not induce immunologic memory, and are associated with immunologic hyporesponsiveness (reduced response to future doses of polysaccharide). Plain polysaccharide vaccines have been superseded by meningococcal protein-polysaccharide conjugate vaccines, which are generally more immunogenic than plain polysaccharides, are immunogenic from early infancy, induce immunologic memory, and are not associated with hyporesponsiveness. The conjugate vaccines contain meningococcal polysaccharides that are chemically conjugated to a carrier protein. Three carrier proteins are used in various meningococcal conjugate vaccines: tetanus, diphtheria, and the mutant diphtheria toxin, CRM197. However, although plain polysaccharides vaccines should now be considered redundant in most industrialized countries where the new-generation conjugates are available, they may still have a role in some regions where conjugates are not yet available.

The first meningococcal conjugate vaccine to be used was a monovalent serogroup C meningococcal conjugate vaccine (MenC), which was introduced in the United Kingdom in 1999 and was administered to all children and young people under the age of 19 yr in a mass catch-up campaign before establishment in the routine infant immunization schedule. The MenC vaccine has proved highly (>95%) effective in controlling disease through both direct protection of the vaccinated population and induction of herd immunity, protecting the wider population. Herd immunity is induced through the impact of conjugate vaccines on colonization, reducing carriage and blocking transmission of meningococci among adolescents and young adults. Monovalent MenC vaccines are now used widely in the industrialized countries of Western Europe, Canada, and Australia, where disease caused by serogroup C meningococci has virtually disappeared. However, serologic surveys show that antibody levels wane, especially after infant immunization, and booster doses are now recommended during adolescence to sustain individual and population immunity.

Quadrivalent meningococcal A, C, Y, W conjugate vaccines (MenACWY) have been available since 2005 and are now routinely used for adolescents in the United States and as a single adolescent "booster" dose in some countries that had established MenC infant

programs more than a decade ago. MenACWY was initially introduced as a single dose at 11 yr of age in the United States, but concerns about waning immunity led to the adoption of a 2nd dose. The initial reports on effectiveness (>80%) of MenACWY in the U.S. program indicates that these vaccines are likely to provide control of disease caused by serogroups C, W, and Y (serogroup A being unimportant currently), although the program has taken some time to become fully established. As the population of immunized adolescents and young adults in the U.S. grows, it is likely that the effects of these vaccines on carriage of meningococci will reduce disease among other segments of the population through herd immunity, assuming that the transmission dynamics of Y and W meningococci are the same as for serogroup C. While MenACWY vaccines are not currently recommended in the United States for routine use in younger age groups in view of the low rate of disease caused by these serogroups in infancy, they may provide broader protection in countries that are already using MenC vaccines in infant programs. Other combination vaccines containing various conjugates, including Hib-MenC (used in the United Kingdom as a 12 mo booster) and Hib-MenCY, may have a role in broadening protection beyond MenC, in early life. Table 191-4 outlines the current U.S. programmatic recommendations.

Individuals at high risk of meningococcal disease, such as those with complement deficiency and travelers to regions where there is a risk of epidemic meningococcal disease caused by A or W, should receive MenACWY (Table 191-4 lists recommendations for use in the United States). The risk of disease among close contacts of cases of disease caused by vaccine serogroups may be further reduced if they are offered MenACWY in addition to antimicrobial prophylaxis. A possible association between MenACWY-diphtheria and Guillain-Barré syndrome, which caused concern early after the vaccine was first used in the United States, has not been substantiated.

A serogroup A meningococcal conjugate vaccine, MenA, has been developed for use in the sub-Saharan African meningitis belt, and implementation in 2010 through mass vaccination appears already to have interrupted disease caused by this serogroup. More than 100 million people had been vaccinated by the end of 2012.

As discussed above, the majority of disease in infants and in most industrialized countries is caused by serogroup B polysaccharide-bearing meningococci. This polysaccharide capsule has chemical identity with glycosylated protein antigens in the human fetus and, as a self-antigen, is therefore not immunogenic in humans and leads to the theoretical risk of induction of autoimmunity. Vaccine development has therefore focused on subcapsular protein antigens. Several countries (including Cuba, Norway, and New Zealand) successfully controlled serogroup B epidemics by immunizing with tailor-made outer membrane vesicle vaccines prepared from blebs of outer membrane harvested from the respective epidemic strains. The principal limitation of outer membrane vesicle vaccines is that the bactericidal antibody responses induced by immunization are limited to the vaccine strain, because the response is largely directed against the homologous PorA (serosubtype) protein, and they are therefore not considered for use in endemic settings, including the United States or most other industrialized countries.

Promising approaches for prevention of serogroup B disease have been developed over the past decade. One vaccine that was developed for adolescent immunization was licensed in the United States in 2014 and contains two variants of factor H-binding protein; it appears highly immunogenic in the target population. Recommendations for its use are awaited. Factor H-binding protein appears to be an important virulence determinant, aiding survival of meningococci in blood, and is expressed by virtually all strains.

Another 4-component meningococcal vaccine, 4CMenB, which has been licensed by the European Medicines Agency (2013) for use from infancy, is also available in various other regions and is expected to be licensed in the United States in 2015. This vaccine contains an outer membrane vesicle (derived from the New Zealand outbreak strain) and

Table 191-4 Recommendations for Meningococcal Vaccination

GENERAL POPULATION <2 YR	2-10 YR	11-21 YR	22-55 YR
Not recommended	Not recommended	A single dose of MenACWY-D or MenACWY-CRM at age 11-12 yr or at 13-18 yr if not previously vaccinated. Age 19-21 yr: not routinely recommended but may be given as catch-up for those who have not received a dose after their 16th birthday. A booster dose 5 yr later (see text)*	Not recommended

SPECIAL POPULATIONS AT INCREASED RISK OF MENINGOCOCCAL DISEASE‡

RISK FACTOR	2-18 MONTHS	9-23 MONTHS	2-55 YR†
Persistent complement deficiencies, functional or anatomic asplenia	4 doses of Hib-MenCY-TT at 2, 4, 6, and 12-15 months	2 doses of MenACWY-D 12 wk apart§	2 doses of MenACWY 8-12 wk apart‖
At risk during a community outbreak with a vaccine serogroup	4 doses of Hib-MenCY-TT at 2, 4, 6, and 12-15 months	2 doses of MenACWY-D 12 wk apart	1 dose of MenACWY
Travel to or resident of countries where meningococcal disease is hyperendemic or epidemic¶	Should receive a quadrivalent meningococcal vaccination licensed for children aged ≥9 mo prior to travel	2 doses of MenACWY-D 12 wk apart**	1 dose of MenACWY
Have HIV, if another indication for vaccination exists	—	2 doses of MenACWY-D 12 wk apart	2 doses of MenACWY 8-12 wk apart‖
Other risk factors	—	—	1 dose MenACWY

*Otherwise healthy adolescents who received a 1st dose at age 11-12 yr should receive a booster dose of a meningococcal conjugate vaccine at 16 yr of age. For those given a 1st dose at age 13-15 yr, and who have not yet reached their 21st birthday, the booster dose should be given 5 yr after the 1st dose.

†Assuming not previously vaccinated.

‡Persons previously vaccinated at 7 yr of age or older who are at prolonged increased risk should be revaccinated 5 yr after their previous meningococcal vaccine and every 5 yr thereafter. Persons previously vaccinated at ages 2 mo-6 yr who are at prolonged increased risk should be revaccinated 3 yr after their previous meningococcal vaccination and every 5 yr thereafter.

§Because of high risk for invasive pneumococcal disease, children with functional or anatomic asplenia should not be immunized with MenACWY-D before age 2 yr to avoid interference with the immune response to the pneumococcal conjugate vaccine (PCV).

‖If MenACWY-D is used, it should be administered at least 4 wk after completion of all PCV doses.

¶For example, visitors to the "meningitis belt" of sub-Saharan Africa. Vaccination also is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj.

**If receiving the vaccine prior to travel, 2 doses may be administered as early as 8 wk apart.

Adapted from American Academy of Pediatrics Committee on Infectious Diseases: Updated recommendations on the use of meningococcal vaccines. Pediatrics *134:400–403, 2014.*

3 recombinant proteins: a single variant of factor H-binding protein, neisserial adhesin A, and neisserial heparin binding antigen. 4CMenB vaccine induced bactericidal antibodies against strains containing the vaccine antigens in infants, toddlers, and adolescents in clinical trials. The vaccine appears to have a generally favorable safety profile, although induction of fever in infants and pain at the injection site in other age groups are common. This vaccine has been used to control outbreaks of capsular group B meningococcal disease at two universities in the United States and hyperendemic disease in Canada. It was recommended for routine use in the infant immunization program in the United Kingdom in 2014 if a cost-effective price could be negotiated with the manufacturer.

Bibliography is available at Expert Consult.

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Chapter 192

Neisseria gonorrhoeae (Gonococcus)

Toni Darville

Neisseria gonorrhoeae produces several forms of **gonorrhea,** an infection of the genitourinary tract mucous membranes and rarely of the mucosa of the rectum, oropharynx, and conjunctiva. Gonorrhea transmitted by sexual contact or perinatally is second only to chlamydial infections in the number of cases reported to the Centers for Disease Control and Prevention (CDC) in the United States. This high prevalence and the development of antibiotic-resistant strains have produced significant morbidity in adolescents.

ETIOLOGY

N. gonorrhoeae is a nonmotile, aerobic, non–spore-forming, Gram-negative intracellular diplococcus with flattened adjacent surfaces. Optimal growth occurs at 35-37°C (95-98.6°F) and at pH 7.2-7.6 in an atmosphere of 3-5% carbon dioxide. The specimen should be inoculated immediately onto fresh, moist, modified Thayer-Martin or specialized transport media, because gonococci do not tolerate drying. Thayer-Martin medium contains antimicrobial agents that inhibit hardier normal flora present in clinical specimens that may otherwise overgrow gonococci. Presumptive identification may be based on colony appearance, Gram stain appearance, and production of cytochrome oxidase. Gonococci are differentiated from other *Neisseria* species by the fermentation of glucose but not maltose, sucrose, or lactose. Gram-negative diplococci are seen in infected material, often within polymorphonuclear leukocytes.

Like all Gram-negative bacteria, *N. gonorrhoeae* possesses a cell envelope composed of an inner cytoplasmic membrane, a middle layer of peptidoglycan, and an outer membrane. The outer membrane contains lipooligosaccharides (endotoxin), phospholipid, and a variety of proteins that contribute to cell adherence, tissue invasion, and resistance to host defenses. The 2 systems primarily used to characterize gonococcal strains are auxotyping and serotyping. Auxotyping is based on genetically stable requirements of strains for specific nutrients or cofactors as defined by an isolate's ability to grow on chemically defined media. The most widely used serotyping system is based on a porin called PorI, a trimeric outer membrane protein that makes up a substantial part of the gonococcal envelope structure. Antibodies generated to *PorI* have been used to serotype gonococci (e.g., PorIA-4 and PorIB-12), and changes in PorI proteins present in a community are believed to occur, at least in part, as a result of selective immune pressure.

EPIDEMIOLOGY

N. gonorrhoeae infection occurs only in humans. The organism is shed in the exudate and secretions of infected mucosal surfaces and is transmitted through intimate contact, such as sexual contact or parturition, and, rarely, by contact with fomites. Gonococcal infections in the newborn period are generally acquired during delivery. Gonorrhea is the most common sexually transmitted infection found in sexually abused children. Rarely, *N. gonorrhoeae* may be spread by sexual play among children, but the index patient is likely to be a victim of sexual abuse. Gonococcal infections in children are acquired rarely through household exposure to infected caretakers. In such cases, the possibility of sexual abuse should be seriously considered.

The number of reported cases of gonorrhea increased steadily in the United States from 1964 to 1977, fluctuated through the early 1980s, and increased until 1987, when reported rates were 323 per 100,000 population. After implementation of the national gonorrhea control program, rates decreased or were stable annually from 1987 to 2004. In 2005, the national rate (116 per 100,000 population) increased for the first time since 1999. In 2009, rates were 98.1 per 100,000 population, which is the lowest since recording of gonorrhea rates began. The rate increased slightly in 2010 to 100.2 per 100,000 population and increased again in 2011 to 104.2 per 100,000 population. The report of increasing minimum inhibitory concentrations for cephalosporin antibiotics in 2011 raises alarms for a threat of untreatable gonorrhea and need for intensive surveillance. The incidence of gonorrhea is highest in high-density urban areas among persons younger than 24 yr of age who have multiple sex partners and engage in unprotected sexual intercourse. Increases in gonorrhea prevalence have been noted among men who have sex with men. Risk factors include nonwhite race, homosexuality, increased number of sexual partners, prostitution, presence of other sexually transmitted infections, unmarried status, poverty, and failure to use condoms. Auxotyping and serotyping techniques and molecular typing methods are used to analyze the spread of individual strains of *N. gonorrhoeae* within a community.

Maintenance and subsequent spread of gonococcal infections in a community require a hyperendemic, high-risk core group such as prostitutes or adolescents with multiple sexual partners. This observation reflects the fact that most persons who have gonorrhea cease sexual activity and seek care, unless economic need or other factors (e.g., drug addiction) drive persistent sexual activity. Thus, many core transmitters belong to a subset of infected persons who lack or ignore symptoms and continue to be sexually active, underscoring the importance of seeking out and treating the sexual contacts of infected persons who present for treatment.

Gonococcal infection of **neonates** usually results from peripartum exposure to infected exudate from the cervix of the mother. An acute infection begins 2-5 days after birth. The incidence of neonatal infection depends on the prevalence of gonococcal infection among pregnant women, prenatal screening for gonorrhea, and neonatal ophthalmic prophylaxis.

PATHOGENESIS AND PATHOLOGY

N. gonorrhoeae infects primarily columnar epithelium, because stratified squamous epithelium is relatively resistant to invasion. Mucosal invasion by gonococci results in a local inflammatory response that produces a purulent exudate consisting of polymorphonuclear leukocytes, serum, and desquamated epithelium. The gonococcal lipooligosaccharide (endotoxin) exhibits direct cytotoxicity, causing ciliostasis and sloughing of ciliated epithelial cells. Once the gonococcus traverses the mucosal barrier, the lipooligosaccharide binds bactericidal immunoglobulin (Ig) M antibody and serum complement, causing an acute inflammatory response in the subepithelial space. Tumor necrosis factor and other cytokines are thought to mediate the cytotoxicity of gonococcal infections.

Gonococci may ascend the urogenital tract, causing urethritis or epididymitis in postpubertal males and acute endometritis, salpingitis, and peritonitis (collectively termed **acute pelvic inflammatory disease** or **PID)** in postpubertal females**.** Dissemination from the fallopian tubes through the peritoneum to the liver capsule results in

perihepatitis (Fitz-Hugh–Curtis syndrome). Gonococci that invade the lymphatics and blood vessels may cause inguinal lymphadenopathy; perineal, perianal, ischiorectal, and periprostatic abscesses; and disseminated gonococcal infection (DGI).

A number of gonococcal virulence and host immune factors are involved in the penetration of the mucosal barrier and subsequent manifestations of local and systemic infection. Selective pressure from different mucosal environments probably leads to changes in the outer membrane of the organism, including expression of variants of pili, opacity or Opa proteins (formerly protein II), and lipooligosaccharides. These changes may enhance gonococcal attachment, invasion, replication, and evasion of the host's immune response.

For infection to occur, the gonococcus must first attach to host cells. A gonococcal IgA protease inactivates IgA_1 by cleaving the molecule in the hinge region and may be an important factor in colonization or invasion of host mucosal surfaces. Gonococci adhere to the microvilli of nonciliated epithelial cells by hair-like protein structures (pili) that extend from the cell wall. Pili are thought to protect the gonococcus from phagocytosis and complement-mediated killing. Pili undergo high-frequency antigenic variation that may aid in the organism's escape from the host immune response and may provide specific ligands for different cell receptors. Opacity proteins, most of which confer an opaque appearance to colonies, are also thought to function as ligands to facilitate binding to human cells. Gonococci that express certain Opa proteins adhere to and are phagocytosed by human neutrophils in the absence of serum.

Other phenotypic changes that occur in response to environmental stresses allow gonococci to establish infection. Examples include iron-repressible proteins for binding transferrin or lactoferrin, anaerobically expressed proteins, and proteins that are synthesized in response to contact with epithelial cells. Gonococci may grow in vivo under anaerobic conditions or in an environment with a relative lack of iron.

Approximately 24 hr after attachment, the epithelial cell surface invaginates and surrounds the gonococcus in a phagocytic vacuole. This phenomenon is thought to be mediated by the insertion of gonococcal outer membrane protein I into the host cell, causing alterations in membrane permeability. Subsequently, phagocytic vacuoles begin releasing gonococci into the subepithelial space by means of exocytosis. Viable organisms may then cause local disease (i.e., salpingitis) or disseminate through the bloodstream or lymphatics.

Serum IgG and IgM directed against gonococcal proteins and lipooligosaccharides lead to complement-mediated bacterial lysis. Stable serum resistance to this bactericidal antibody probably results from a particular type of porin protein expressed in gonococci (most contain PorIA), predisposing to disseminated disease. *N. gonorrhoeae* differentially subverts the effectiveness of complement and alters the inflammatory responses elicited in human infection. Isolates from cases of DGI typically resist killing by normal serum (i.e., are serum resistant), inactivate more C3b, generate less C5a, and result in less inflammation at local sites. PID isolates are serum sensitive, inactivate less C3b, generate more C5a, and result in more inflammation at local sites. IgG antibody directed against gonococcal reduction-modifiable protein (Rmp) blocks complement-mediated killing of *N. gonorrhoeae.* Anti-Rmp blocking antibodies may harbor specificity for outer membrane protein sequences shared with other neisserial species or *Enterobacteriaceae*, may be directed against unique Rmp upstream of cysteine loop–specific sequences, or both. Preexisting antibodies directed against Rmp facilitate transmission of gonococcal infection to exposed women; Rmp is highly conserved in *N. gonorrhoeae,* and the blocking of mucosal defenses may be one of its functions. Gonococcal adaptation also appears to be important in the evasion of killing by neutrophils. Examples include sialylation of lipooligosaccharides, increases in catalase production, and changes in the expression of surface proteins.

Host factors may influence the incidence and manifestations of gonococcal infection. Prepubertal girls are susceptible to vulvovaginitis and, rarely, experience salpingitis. *N. gonorrhoeae* infects noncornified epithelium, and the thin noncornified vaginal epithelium and alkaline pH of the vaginal mucin predispose this age group to infection of the lower genital tract. Estrogen-induced cornification of the vaginal epithelium in neonates and mature females resists infection. Postpubertal females are more susceptible to salpingitis, especially during menses, when diminished bactericidal activity of the cervical mucus and reflux of blood from the uterine cavity into the fallopian tubes facilitate passage of gonococci into the upper reproductive tract.

Populations at risk for DGI include asymptomatic carriers; neonates; menstruating, pregnant, and postpartum women; homosexuals; and immunocompromised hosts. The asymptomatic carrier state implies failure of the host immune system to recognize the gonococcus as a pathogen, the capacity of the gonococcus to avoid being killed, or both. Pharyngeal colonization has been proposed as a risk factor for DGI. The high rate of asymptomatic infection in pharyngeal gonorrhea may account for this phenomenon. Women are at greater risk for development of DGI during menstruation, pregnancy, and the postpartum period, presumably because of the maximal endocervical shedding and decreased peroxidase bactericidal activity of the cervical mucus during these periods. A lack of neonatal bactericidal IgM antibody is thought to account for the increased susceptibility of neonates to DGI. Persons with terminal complement component deficiencies (C5-C9) are at considerable risk for development of recurrent episodes of DGI.

CLINICAL MANIFESTATIONS

Gonorrhea is manifested by a spectrum of clinical presentations from asymptomatic carriage, to the characteristic localized urogenital infections, to disseminated systemic infection (see Chapter 120).

Asymptomatic Gonorrhea

The incidence of asymptomatic gonorrhea in children has not been ascertained. Gonococci have been isolated from the oropharynx of young children who have been abused sexually by male contacts; oropharyngeal symptoms are usually absent. Most genital tract infections produce symptoms in children. However, as many as 80% of sexually mature females with urogenital gonorrhea infections are asymptomatic in settings in which most infections are detected through screening or other case-finding efforts. This situation is in contrast to that in men, who are asymptomatic only 10% of the time. Asymptomatic rectal carriage of *N. gonorrhoeae* has been documented in 40-60% of females with urogenital infection. Most persons with positive rectal culture results are asymptomatic. Most pharyngeal gonococcal infections are asymptomatic. The importance of documenting pharyngeal infection is debated. Most cases resolve spontaneously, transmission from the pharynx to other patients is uncommon, and the pharynx is rarely the only site of infection. Nevertheless, asymptomatic pharyngeal infection may lead to systemic infection and is occasionally the source of transmission to sexual partners.

Uncomplicated Gonorrhea

Genital gonorrhea has an incubation period of 2-5 days in men and 5-10 days in women. Primary infection develops in the urethra of males, the vulva and vagina of prepubertal females, and the cervix of postpubertal females. Neonatal ophthalmitis (ophthalmia neonatorum) occurs in both sexes.

Urethritis is usually characterized by a purulent discharge and by dysuria without urgency or frequency. Untreated urethritis in males resolves spontaneously in several weeks or may be complicated by epididymitis, penile edema, lymphangitis, prostatitis, or seminal vesiculitis. Gram-negative intracellular diplococci are found in the discharge.

In prepubertal females, **vulvovaginitis** is usually characterized by a purulent vaginal discharge with a swollen, erythematous, tender, and excoriated vulva. Dysuria may occur. In postpubertal females, symptomatic gonococcal cervicitis and urethritis are characterized by purulent discharge, suprapubic pain, dysuria, intermenstrual bleeding, and dyspareunia. The cervix may be inflamed and tender. In urogenital gonorrhea limited to the lower genital tract, pain is not enhanced by moving the cervix, and the adnexa are not tender to palpation. Purulent material may be expressed from the urethra or ducts of the Bartholin gland. Rectal gonorrhea is often asymptomatic but may cause

proctitis with symptoms of anal discharge, pruritus, bleeding, pain, tenesmus, and constipation. Asymptomatic rectal gonorrhea may not be from anal intercourse but may represent colonization from vaginal infection.

Gonococcal **ophthalmitis** may be unilateral or bilateral and may occur in any age group after inoculation of the eye with infected secretions. **Ophthalmia neonatorum** caused by *N. gonorrhoeae* usually appears from 1-4 days after birth (see Chapter 626). Ocular infection in older patients results from inoculation or autoinoculation from a genital site. The infection begins with mild inflammation and a serosanguineous discharge. Within 24 hr, the discharge becomes thick and purulent, and tense edema of the eyelids with marked chemosis occurs. If the disease is not treated promptly, corneal ulceration, rupture, and blindness may follow.

Disseminated Gonococcal Infection

Hematogenous dissemination occurs in 1-3% of all gonococcal infections, more frequently after asymptomatic primary infections than symptomatic infections. Women account for the majority of cases, with symptoms beginning 7-30 days after infection and within 7 days of menstruation. The most common manifestations are asymmetric arthralgia, petechial or pustular acral skin lesions, tenosynovitis, suppurative arthritis, and, rarely, carditis, meningitis, and osteomyelitis. The most common initial symptom is acute onset of polyarthralgia with fever. Only 25% of patients complain of skin lesions. Most deny genitourinary symptoms; however, primary mucosal infection is documented by genitourinary cultures. Results of approximately 80-90% of cervical cultures are positive in women with DGI. In males, urethral culture results are positive in 50-60%, pharyngeal culture results are positive in 10-20%, and rectal culture results are positive in 15% of cases.

DGI is classified into 2 clinical syndromes that have some overlapping features. The 1st and more common is the **tenosynovitis-dermatitis syndrome,** which is characterized by fever, chills, skin lesions, and polyarthralgia predominantly involving the wrists, hands, and fingers. Blood culture results are positive in approximately 30-40% of cases, and results of synovial fluid cultures are almost uniformly negative. The 2nd syndrome is the **suppurative arthritis syndrome,** in which systemic symptoms and signs are less prominent and monoarticular arthritis, often involving the knee, is more common. A polyarthralgia phase may precede the monoarticular infection. In cases of monoarticular involvement, synovial fluid culture results are positive in approximately 45-55%, and synovial fluid findings are consistent with septic arthritis. Blood culture results are usually negative. DGI in neonates usually occurs as a polyarticular suppurative arthritis.

Dermatologic lesions usually begin as painful, discrete, 1-20 mm pink or red macules that progress to maculopapular, vesicular, bullous, pustular, or petechial lesions. The typical necrotic pustule on an erythematous base is distributed unevenly over the extremities, including the palmar and plantar surfaces, usually sparing the face and scalp. The lesions number between 5 and 40, and 20-30% may contain gonococci. Although immune complexes may be present in DGI, complement levels are normal, and the role of the immune complexes in pathogenesis is uncertain.

Acute endocarditis is an uncommon (1-2%) but often fatal manifestation of DGI that usually leads to rapid destruction of the aortic valve. Acute pericarditis is a rarely described entity in patients with disseminated gonorrhea. Meningitis with *N. gonorrhoeae* has been documented, and signs and symptoms are similar to those of any acute bacterial meningitis.

DIAGNOSIS

It is not possible to distinguish gonococcal from nongonococcal urethritis on the basis of symptoms and signs alone. Gonococcal urethritis and vulvovaginitis must be distinguished from other infections that produce a purulent discharge, including β-hemolytic streptococci, *Chlamydia trachomatis, Mycoplasma hominis, Trichomonas vaginalis,* and *Candida albicans.* Rarely, infection with human herpes simplex virus type 2 may produce symptoms similar to those of gonorrhea.

In males with symptomatic urethritis, a presumptive diagnosis of gonorrhea can be made by identification of Gram-negative intracellular diplococci (within leukocytes) in the urethral discharge. A similar finding in females is not sufficient because *Mima polymorpha* and *Moraxella,* which are normal vaginal flora, have a similar appearance. The sensitivity of the Gram stain for diagnosing gonococcal cervicitis and asymptomatic infections is also low. The presence of commensal *Neisseria* species in the oropharynx prevents the use of the Gram stain for diagnosis of pharyngeal gonorrhea. Nonpathogenic *Neisseria* organisms are not found intracellularly.

Specific testing for *N. gonorrhoeae* is recommended because a specific diagnosis might enhance partner notification. Highly sensitive and specific testing methods are available. Culture, nucleic acid hybridization tests, and nucleic acid amplification tests (NAATs) are available for the detection of genitourinary infection. Disadvantages of culture include its lower sensitivity than DNA amplification techniques and a 48-hr delay in availability of results. Culture can be performed of any site, including nongenital sites. Nucleic acid hybridization tests require female endocervical or male urethral swab specimens and are inferior to NAAT testing in terms of sensitivity. The FDA has approved NAATs for use with endocervical swabs, vaginal swabs, male urethral swabs, and female and male urine. Although urine specimens are acceptable for women, the sensitivity appears to be lower when compared with vaginal swab samples. In contrast, the sensitivity and specificity of urine and urethral swab specimens from men are similar. Product inserts for each NAAT vendor must be carefully examined to assess current indications. Nonculture tests are not FDA cleared for use with specimens from the rectum, pharynx, or conjunctiva. However, some laboratories have established performance specifications for NAAT testing on non-genital samples, facilitating their use for clinical management. Nonculture gonococcal tests (e.g., Gram-stained smear, nucleic acid hybridization tests, and NAATs) should not be used without standard culture in children because of the legal implications of a diagnosis of *N. gonorrhoeae* infection in a child. Nonculture tests cannot provide antimicrobial susceptibility results, so in cases of persistent gonococcal infection after treatment, clinicians should perform both culture and antimicrobial susceptibility testing.

Material for cervical cultures is obtained as follows: After the exocervix is wiped, a swab is placed in the cervical os and rotated gently for several seconds. Male urethral specimens are obtained by placement of a small swab 2-3 cm into the urethra. Rectal swabs are best obtained by passing of a swab 2-4 cm into the anal canal; specimens that are heavily contaminated by feces should be discarded. For optimal culture results, specimens should be obtained with noncotton swabs (e.g., a urethrogenital calcium alginate–tipped swab [Calgiswab, Puritan Medical Products, Guilford, ME]), inoculated directly onto culture plates, and incubated immediately. The choice of anatomic sites to culture depends on the sites exposed and the clinical manifestations. Samples from the urethra should be cultured for heterosexual men, and samples from the endocervix and rectum should be cultured for all females, regardless of a history of anal intercourse. A pharyngeal culture specimen should be obtained from both men and women if symptoms of pharyngitis are present or in the case of oral exposure to a person known to have genital gonorrhea. In a suspected case of child sexual abuse, rectal, pharyngeal, and urethral (males) or vaginal (females) swabs should be cultured. Culture of the endocervix should not be attempted until after puberty.

Specimens from sites that are normally colonized by other organisms (e.g., cervix, rectum, pharynx) should be inoculated on a selective culture medium, such as modified Thayer-Martin medium (fortified with vancomycin, colistin, nystatin, and trimethoprim to inhibit growth of indigenous flora). Specimens from sites that are normally sterile or minimally contaminated (i.e., synovial fluid, blood, cerebrospinal fluid) should be inoculated on a nonselective chocolate agar medium. If DGI is suspected, blood, pharynx, rectum, urethra, cervix, and synovial fluid (if involved) should be cultured. Cultured specimens should be incubated promptly at 35-37°C (95-98.6°F) in 3-5% carbon dioxide. When specimens must be transported to a central laboratory for culture plating, a reduced, nonnutrient holding medium (i.e.,

Amies-modified Stuart medium) preserves specimens with minimal loss of viability for up to 6 hr. When transport may delay culture plating by more than 6 hr, it is preferable to inoculate the sample directly onto a culture medium and transport it at an ambient temperature in a candle jar. The Transgrow and JEMBEC (John E. Martin Biological Environmental Chamber) systems of modified Thayer-Martin medium are alternative transport systems.

Gonococcal arthritis must be distinguished from other forms of septic arthritis as well as from rheumatic fever, rheumatoid arthritis, inflammatory bowel disease, and arthritis secondary to rubella or rubella immunization. Gonococcal conjunctivitis in the newborn period must be differentiated from chemical conjunctivitis caused by silver nitrate drops as well as from conjunctivitis caused by *C. trachomatis, Staphylococcus aureus,* group A or B streptococcus, *Pseudomonas aeruginosa, Streptococcus pneumoniae,* or human herpes simplex virus type 2.

TREATMENT

All patients who are presumed or proven to have gonorrhea should be evaluated for concurrent syphilis, hepatitis B, HIV, and *C. trachomatis* infection. The incidence of *Chlamydia* coinfection is 15-25% among males and 35-50% among females. Patients beyond the neonatal period should be treated presumptively for *C. trachomatis* infection unless a negative chlamydial NAAT result is documented at the time treatment is initiated for gonorrhea. However, if chlamydial test results are not available or if a non-NAAT result is negative for *Chlamydia*, patients should be treated for both gonorrhea and *Chlamydia* infection (see Chapter 226.2). Sexual partners exposed in the preceding 60 days should be examined, culture specimens should be collected, and presumptive treatment should be started.

N. gonorrhoeae has progressively developed resistance to the antibiotics used to treat it over the years. Antimicrobial resistance in *N. gonorrhoeae* occurs as plasmid-mediated resistance to penicillin and tetracycline and chromosomally mediated resistance to penicillins, tetracyclines, spectinomycin, fluoroquinolones, and cephalosporins. In 2007, as a consequence of widespread fluoroquinolone-resistant gonorrhea in the United States, this class of antibiotics ceased being recommended for treatment. Surveillance data (2006-2011) from the CDC's Gonococcal Isolate Surveillance Project reveal increasing minimum inhibitory concentrations for the oral cephalosporin, cefixime, and the injectable third-generation cephalosporin, ceftriaxone, leading the CDC to revise its gonorrhea treatment guidelines in 2012 to dual therapy in an attempt to preserve the last commercially available effective treatment.

Adolescent and Adult Infections

Oral cefixime is no longer recommended as a treatment option. Combination therapy with ceftriaxone (250 mg IM) and either azithromycin (1 g PO as a single dose) or doxycycline (100 mg PO twice daily for 7 days) is recommended as the most reliably effective treatment for uncomplicated urogenital, anorectal, and pharyngeal gonorrhea. Other possible single-dose cephalosporin alternatives include ceftizoxime (500 mg IM); cefotaxime (500 mg IM); or cefoxitin (2 g IM), administered with probenecid (1 g PO). These agents do not provide any advantage over injectable ceftriaxone and should also be combined with azithromycin or doxycycline. A theoretical basis exists for using 2 antimicrobials with different molecular targets to improve treatment efficacy and potentially delay emergence and spread of resistance to cephalosporins. However, there are no data to support this hypothesis, and clinical trials are urgently needed to determine the most appropriate therapy for *N. gonorrhoeae* in the face of rising antimicrobial resistance. The use of azithromycin as the second antimicrobial is preferred to doxycycline because of the convenience and compliance advantages of single-dose therapy and the higher prevalence of gonococcal resistance to tetracycline compared to azithromycin among gonococcal surveillance isolates, particularly in strains with elevated minimum inhibitory concentrations to cefixime. If persistent infection is diagnosed in a patient after treatment with the above combination regimen, cultures should be obtained from all relevant clinical sites and *N. gonorrhoeae* isolates should be tested for antimicrobial susceptibility using disc diffusion, E-test, or agar dilution techniques.

If ceftriaxone is not available, cefixime (400 mg PO) plus either azithromycin (1 g PO) or doxycycline (100 mg PO twice daily for 7 days) can be used. The use of azithromycin (2 g PO in a single dose) as a single agent should be limited to patients with severe penicillin allergy who cannot undergo β-lactam desensitization. If a patient with gonorrhea is treated with an alternative oral regimen, the patient should return 1 wk after treatment for a test-of-cure of the infected anatomic site. The test-of-cure should be performed with culture or with a NAAT for *N. gonorrhoeae* if culture is not readily available. If the NAAT is positive, every effort should be made to perform a culture. All test-of-cure specimens that reveal positive growth should undergo phenotypic antimicrobial susceptibility testing. Patients who experience treatment failure after treatment with alternative regimens should be treated with ceftriaxone (250 mg IM) as a single dose and azithromycin (2 g PO as a single dose) and should receive infectious disease consultation. The case should be reported to CDC through the local or state health department.

Spectinomycin (2 g IM as a single dose) is a safe and effective parenteral alternative for urogenital gonorrhea but is not effective for pharyngeal infection. It is not currently available in the United States.

Pregnant women should not be treated with quinolones or tetracyclines. Those infected with *N. gonorrhoeae* should be treated with ceftriaxone (250 mg IM) and azithromycin (1 g PO as a single dose). If the patient is allergic to β-lactam antibiotics, desensitization procedures should be employed prior to administration.

The initial management of DGI includes hospitalization and parenteral administration of ceftriaxone (1 g/day). Alternative cephalosporins include cefotaxime (1 g IV q8h) and ceftizoxime (1g IV q8h). Patients should also receive azithromycin (1 g PO in a single dose), for dual therapy of gonococcal infections and to cover potential *C. trachomatis* coinfection. Doxycycline (100 mg PO twice daily for 7 days) is an alternative second agent. Patients should be examined for clinical evidence of endocarditis and meningitis. Ceftriaxone treatment should be continued for at least 7 days, and those with purulent arthritis require antibiotic therapy for 7-14 days, although the dose can be changed following clinical improvement to ceftriaxone (250 mg IM daily). Because of the decreasing susceptibility of *N. gonorrhoeae* to oral agents, "stepdown" therapy to oral agents to complete therapy, such as cefixime (400 mg PO bid) and cefpodoxime (400 mg PO bid), should only be considered if culture and susceptibility testing of the isolate are available and full susceptibility to the oral agent is documented. Fluoroquinolones may be an alternative treatment option if antimicrobial susceptibility to these agents can be documented by culture. Patients with purulent arthritis should also undergo joint drainage with needle aspiration, arthroscopically, or with an open surgical procedure. Open surgical drainage should be performed in patients who exhibit continued symptoms (leukocytosis, fever, severe joint pain, and effusion) despite aspiration and appropriate antibiotic therapy.

Gonococcal conjunctivitis should be treated with ceftriaxone (1g IM in a single dose) with lavage of the infected eye with saline. Meningitis is treated with ceftriaxone (1-2 g IV q12h) for 10-14 days. Endocarditis is treated for longer than 4 wk with ceftriaxone (1-2 g IV q12h). Concurrent therapy for treatment of genital *Chlamydia* infection is important.

Infant and Pediatric Infections

Uncomplicated gonococcal infections in children should be treated with ceftriaxone in a single dose (50 mg/kg IM, not to exceed 125 mg). Children who have bacteremia or arthritis should be treated with ceftriaxone (50 mg/kg/day; maximum: 1 g/day if weighs <45 kg) for a minimum of 7 days. Meningitis should be treated for 10-14 days, and endocarditis for a minimum of 28 days, with ceftriaxone (50 mg/kg/dose q12h with maximum of 1-2 g IV q12h). Neonatal gonococcal ophthalmia is treated effectively with a single dose of ceftriaxone (50 mg/kg IM, not to exceed 125 mg); a single dose of cefotaxime (100 mg/kg IM) is an acceptable alternative. The conjunctivae should be irrigated frequently with physiologic saline solution. Infants born

to mothers who have gonococcal infection should also receive a single dose of ceftriaxone (50 mg/kg IM, not to exceed 125 mg). Neonatal sepsis should be treated parenterally for a minimum of 7 days, and meningitis for a minimum of 10 days. Cefotaxime is recommended for infants with hyperbilirubinemia, because ceftriaxone competes for bilirubin binding sites on albumin. Neonates with gonococcal ophthalmitis must be hospitalized and evaluated for DGI.

Pelvic Inflammatory Disease

PID encompasses a spectrum of infectious diseases of the upper genital tract caused by *N. gonorrhoeae, C. trachomatis,* and endogenous flora (streptococci, anaerobes, Gram-negative bacilli). For women with more-severe symptoms, parenteral therapy should be initiated in the hospital. A commonly recommended therapeutic regimen is cefoxitin (2g IV q6h) or cefotetan (2g IV q12h) plus doxycycline (100 mg PO or IV q12h). Alternative regimens include clindamycin (900 mg IV q8h) plus a loading dose of gentamicin (2 mg/kg IV) followed by maintenance gentamicin (1.5 mg/kg q8h), and ampicillin/sulbactam (3 g IV q6h) plus doxycycline (100 mg PO or IV q12h). Clinical experience should guide transition to oral therapy, which usually can be initiated within 24 hr of improvement. Thereafter, oral doxycycline is given to complete 14 days of total therapy.

Parenteral therapy and oral therapy appear to be similar in clinical efficacy for women with PID of mild to moderate severity. Clinical response to outpatient treatment is similar among younger and older women. The decision to hospitalize adolescents with acute PID should be based on clinical criteria used for older women. Those who do not show response to oral therapy within 72 hr should be reevaluated to confirm the diagnosis and then should receive parenteral therapy. Recommended oral regimens are as follows: a single dose of ceftriaxone (250 mg IM) plus doxycycline (100 mg PO bid) with or without metronidazole (500 mg PO bid) for 14 days; and single doses of cefoxitin (2 g IM) and probenecid (1 g PO) plus doxycycline (100 mg PO bid) with or without metronidazole (500 mg PO bid) for 14 days. Sexual partners should be examined and treated for uncomplicated gonorrhea. Follow-up culture (test of cure) after cephalosporin-doxycycline therapy of gonococcal infection is not recommended owing to the low treatment failure rate. Patients receiving outpatient therapy should be carefully evaluated for clinical improvement within 72 hr. A follow-up examination and culture are recommended in 1-2 mo to evaluate the possibility of reinfection or, rarely, treatment failure.

COMPLICATIONS

Complications of gonorrhea result from the spread of gonococci from a local site of invasion. The interval between primary infection and development of a complication is usually days to weeks. In postpubertal females, endometritis may occur, especially during menses, and may progress to salpingitis and peritonitis (PID). Manifestations of PID include signs of lower genital tract infection (e.g., vaginal discharge, suprapubic pain, cervical tenderness) and upper genital tract infection (e.g., fever, leukocytosis, elevated erythrocyte sedimentation rate, and adnexal tenderness or mass). The differential diagnosis includes gynecologic diseases (ovarian cyst, ovarian tumor, ectopic pregnancy) and intraabdominal disorders (appendicitis, urinary tract infection, inflammatory bowel disease).

Once inside the peritoneum, gonococci may seed the liver capsule, causing a perihepatitis with right upper quadrant pain (Fitz-Hugh–Curtis syndrome), with or without signs of salpingitis. Perihepatitis may also be caused by *C. trachomatis.* Progression to PID occurs in approximately 20% of cases of gonococcal cervicitis, and *N. gonorrhoeae* is isolated in approximately 40% of cases of PID in the United States. Untreated cases may lead to hydrosalpinx, pyosalpinx, tuboovarian abscess, and eventual sterility. Even with adequate treatment of PID, the risk for sterility from bilateral tubal occlusion approaches 20% after 1 episode of salpingitis and exceeds 60% after 3 or more episodes. The risk for ectopic pregnancy is increased approximately 7-fold after 1 or more episodes of salpingitis. Additional sequelae of PID include chronic pain, dyspareunia, and increased risk for recurrent PID.

Urogenital gonococcal infection acquired during the 1st trimester of pregnancy carries a high risk for septic abortion. After 16 wk, infection leads to chorioamnionitis, a major cause of premature rupture of the membranes and premature delivery.

PROGNOSIS

Prompt diagnosis and correct therapy ensure complete recovery from uncomplicated gonococcal disease. Complications and permanent sequelae may be associated with delayed treatment, recurrent infection, metastatic sites of infection (meninges, aortic valve), and delayed or topical therapy of gonococcal ophthalmia.

PREVENTION

Efforts to develop a gonococcal pilus vaccine have been unsuccessful thus far. The high degree of interstrain and intrastrain antigenic variability of pili poses a formidable deterrent to the development of a single effective pilus vaccine. Other gonococcal surface structures, such as the porin protein, stress proteins, and lipooligosaccharides, may prove more promising as vaccine candidates. In the absence of a vaccine, prevention of gonorrhea can be achieved through education, use of barrier contraceptives (especially condoms and spermicides), intensive epidemiologic and bacteriologic surveillance (screening sexual contacts), and early identification and treatment of infected contacts. Gonococcal ophthalmia neonatorum can be prevented by instilling erythromycin (0.5%) ophthalmic ointment into the conjunctival sac (see Chapter 626).

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Chapter 193

Kingella kingae

Pablo Yagupsky

Kingella kingae is being increasingly recognized as the most common etiology of joint and bone infections in young children.

ETIOLOGY

K. kingae is a fastidious, facultative anaerobic, β-hemolytic member of the Neisseriaceae family that appears as pairs or short chains of Gram-negative coccobacilli with tapered ends (Fig. 193-1).

EPIDEMIOLOGY

K. kingae is asymptomatically carried in the posterior pharynx. Colonization usually starts after the age of 6 mo, reaches a prevalence of 10% between 12 and 24 mo of age, and decreases in older children. Pharyngeal colonization plays a crucial role in the transmission of the organism through intimate contact between siblings and playmates. Colonizing *K. kingae* strains differ in their invasive potential. Whereas certain clones are commonly found as respiratory colonizers but are seldom cultured from sites of disease, other clones are rarely detected in healthy children and, once acquired, readily penetrate into the bloodstream and disseminate to remote sites. Daycare attendance increases the risk for colonization and transmission, and clusters of invasive infection have been reported in childcare facilities.

Invasive *K. kingae* disease is most commonly diagnosed in otherwise healthy children between the ages of 6 mo and 3 yr, coinciding with the peak prevalence of pharyngeal carriage (Fig. 193-2). In contrast, older children and adults with *K. kingae* infections often suffer from underlying chronic diseases, immunosuppressing conditions, malignancy, or cardiac valve pathology. An annual incidence of 9.4 per 100,000 culture-proven invasive infections among Israeli children younger than 5 yr of age has been estimated.

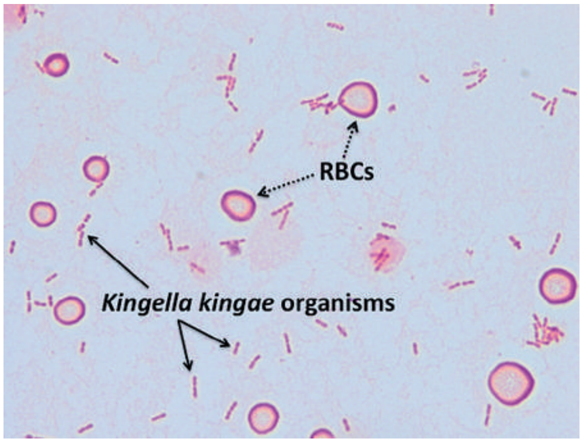

Figure 193-1 Typical Gram stain of a positive blood culture vial from a child with *K. kingae* bacteremia showing pairs and short chains of plump Gram-negative coccobacilli. *RBCs*, red blood cells.

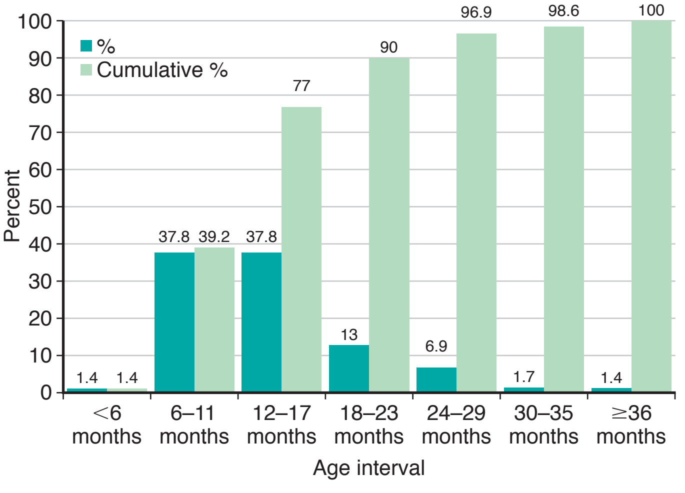

Figure 193-2 Age distribution of 291 previously healthy children with invasive *K. kingae* infections. *(Data from Dubnov-Raz G, Ephros M, Garty BZ, et al: Invasive pediatric* Kingella kingae *infections: a nationwide collaborative study. Pediatr Infect Dis J 2010; 29: 639-643.)*

PATHOGENESIS

The pathogenesis of *K. kingae* disease begins with adherence of the organism to the pharyngeal epithelium that is mediated by pili and nonpilus factors. *K. kingae* secretes a potent Repeat-in-Toxin (RTX) toxin that exhibits cytotoxic activity to respiratory epithelial cells, macrophages, and synoviocytes, suggesting that it may play a role in disrupting the respiratory epithelium, promoting survival of the bacterium in the bloodstream, and facilitating invasion of skeletal system tissues. Children with *K. kingae* disease frequently present with symptoms of an upper respiratory infection, herpetic stomatitis, or buccal aphthous ulcers, raising the possibility that viral-induced damage to the colonized mucosa facilitates invasion of the bloodstream.

CLINICAL DISEASE

Septic arthritis is the most common invasive *K. kingae* infection in children, followed by bacteremia, osteomyelitis, and endocarditis, whereas other clinical manifestations are infrequent (Table 193-1). The organism is the most frequent etiology of skeletal system infections in children 6 mo to 3 yr of age. With the exception of patients with endocarditis, the presentation of invasive *K. kingae* infections is frequently mild, and a body temperature <38°C (100.4°F), a normal C-reactive protein concentration, and a normal white blood cell count are common, requiring a high index of clinical suspicion.

Table 193-1 Clinical Spectrum and Relative Frequency of *Kingella kingae* Infections

CLINICAL DISEASE	FREQUENCY
Skeletal system	+++
Septic arthritis	+++
Osteomyelitis	++
Spondylodiscitis	+
Tenosynovitis	±
Dactylitis	±
Bursitis	±
Bacteremia with no focus	+++
Cardiac	+
Endocarditis	+
Pericarditis	±
Meningitis	±
Peritonitis	±
Cellulitis	±
Soft-tissue abscesses	±
Lower respiratory tract	±
Laryngotracheobronchitis	±
Pneumonia	±
Pleural empyema	±
Ocular	±
Keratitis	±
Corneal abscess	±
Endophthalmitis	±
Eyelid abscess	±

+++, Very common; ++, common; +, infrequent; ±, exceptional.

Septic Arthritis

Although *K. kingae*-driven arthritis especially affects the large weight-bearing joints, involvement of the small metacarpophalangeal, sternoclavicular, and tarsal joints is not unusual (see Chapter 685). The disease has an acute presentation, and children are brought to medical attention after a median of 3 days. The leukocyte count in the synovial fluid shows less than 50,000 white blood cells/µL in almost 25% of the patients, and the Gram stain of synovial fluid is positive in only a small percentage of cases.

Osteomyelitis

K. kingae osteomyelitis usually involves the long bones of the extremities (see Chapter 685). The calcaneus, talus, sternum, and clavicle are also frequently affected (and are rarely infected by other bacterial pathogens). Onset of *K. kingae* osteomyelitis is insidious, and the disease is diagnosed after 1 wk or more in 70% of patients. The MRI shows mild bone and soft tissue changes. Involvement of the epiphyseal cartilage appears to be specifically associated with the organism. Despite the frequent diagnostic delay, chronic osteomyelitis and functional orthopedic disabilities are unusual.

Spondylodiscitis

K. kingae is currently the second most common bacterium isolated in children younger than 4 yr of age with spondylodiscitis after *Staphylococcus aureus* (see Chapter 679.7). It is presumed that the organism penetrates into the rich network of blood vessels that traverse the cartilaginous vertebral endplates and enter the annulus in young children during a bacteremic episode. *K. kingae* spondylodiscitis usually involves the lumbar intervertebral spaces and, with decreasing frequency, the thoracolumbar, thoracic, lumbosacral, and cervical discs. Involvement of multiple discs is uncommon. Patients present with limping, lumbar pain, back stiffness, refusal to sit or walk, neurologic symptoms, or abdominal complaints. Radiography or MRI studies demonstrate narrowing of the intervertebral space. Patients respond

well to appropriate antibiotic treatment and recover without complications, although residual narrowing of the intervertebral space may occur.

Occult Bacteremia

Patients with *K. kingae* bacteremia and no focal infection (occult bacteremia) commonly present with mild to moderate fever, symptoms suggestive of a viral upper respiratory infection, a mean C-reactive protein level of 2.2 mg/dL, and a mean white blood cell count of 12,700/μL. Children with *K. kingae* bacteremia respond favorably to a short course of antibiotics.

Endocarditis

In contrast to other *K. kingae* infections, endocarditis is also diagnosed in school-age children, adolescents, and adult patients. The disease may affect native as well as prosthetic valves. Predisposing factors include congenital cardiac malformations or rheumatic valvular disease, but some patients have previously normal hearts. Typically, the left side of the heart is involved, usually the mitral valve. Fever and acute-phase reactants are more elevated in patients with endocarditis compared with those with uncomplicated bacteremia; no particular cutoff value accurately distinguishes between the 2 conditions. Despite the exquisite susceptibility of *K. kingae* to antibiotics, cardiac failure, septic shock, cerebrovascular accidents, and other life-threatening complications are common, and the mortality rate is high (~16%). Because of the potential severity of *K. kingae* endocarditis, routine echocardiographic evaluation of children with isolated bacteremia is indicated.

DIAGNOSIS

The diagnosis of *K. kingae* disease is established by isolation of the bacterium or by a positive nucleic acid amplification assay from a normally sterile site such as blood, synovial fluid, or bone tissue. Although *K. kingae* grows on routine bacteriologic media, its recovery from exudates is frequently unsuccessful. Detection is enhanced by inoculating synovial fluid specimens onto blood-culture vials, suggesting that diluting purulent samples in a large volume of nutrient broth reduces the concentration of detrimental factors, improving the isolation of this fastidious bacterium.

Testing bone and joint specimens by nucleic acid amplification assays that target specific *K. kingae* genes such as *cpn* or those encoding the bacterium RTX toxin, have further improved detection of the organism and reduced the fraction of "culture-negative septic arthritis" in young children.

TREATMENT

K. kingae is usually highly susceptible to penicillin and cephalosporins but exhibits decreased susceptibility to oxacillin. Although β-lactamase production is frequently detected in colonizing *K. kingae* strains, its prevalence among invasive organisms is low and shows wide geographic variation. Testing for β-lactamase production should be routinely performed in all isolates derived from normally sterile body sites.

Because of the lack of specific guidelines for treating *K. kingae* disease, patients have been administered a variety of antibiotic regimens according to protocols developed for infections caused by traditional pathogens. The first-line therapy for skeletal infections in young children usually consists of intravenous administration of a second- or third-generation cephalosporin, pending culture results. *K. kingae* is always resistant to glycopeptide antibiotics and 40% of isolates are also resistant to clindamycin, a serious concern in areas where skeletal infections caused by community-associated methicillin-resistant *S. aureus* are common, and vancomycin or clindamycin are initially administered to children with presumptive septic arthritis or osteomyelitis. The initial antibiotic regimen is frequently changed to ampicillin or cephalosporin (cefotaxime, ceftriaxone) once *K. kingae* is identified and β-lactamase production is excluded. A favorable clinical response and decreasing C-reactive protein levels to ≤20 μg/mL are used to guide switching to oral antibiotics and defining duration of therapy. Antibiotic treatment has ranged from 2-3 wk for *K. kingae* arthritis, from 3-6 wk for *K. kingae* osteomyelitis, and from 3-12 wk for *K. kingae* spondylodiscitis. Although some children with septic arthritis have been managed with repeat joint aspirations and lavage, most patients promptly respond to conservative treatment with appropriate antibiotics and do not require invasive surgical procedures.

Children with *K. kingae* bacteremia are initially treated with an intravenous β-lactam antibiotic and are subsequently switched to an oral drug once the clinical condition has improved. In most cases, the total duration of therapy ranges from 1-2 wk.

Patients with *K. kingae* endocarditis are usually treated with an intravenous β-lactam antibiotic alone or in combination with an aminoglycoside for 4-7 wk. Early surgical intervention is necessary for life-threatening complications unresponsive to medical therapy.

PREVENTION

Because the risk of asymptomatic pharyngeal carriers for developing an invasive *K. kingae* infection is low (<1% per year), in the absence of clinical disease, there is no indication to eradicate the organism from the colonized mucosal surfaces. Nonetheless, in the reported outbreaks of *K. kingae* infections in children daycare centers, 14 of 75 (18.7%) classmates developed a proven or presumptive infection, including fatal endocarditis, within a 1 mo period, indicating that the causative strains combined unusual transmissibility and virulence. Under these circumstances, administration of prophylactic antibiotics aimed to eradicate colonization in contacts and prevent further cases of disease has been attempted, employing either rifampin 10 mg/kg or 20 mg/kg twice daily for 2 days alone or in combination with amoxicillin (80 mg/kg per day) for 2 days or 4 days. The effectiveness of these regimens has ranged between 47% and 80%, indicating that eradication of *K. kingae* from colonized mucosae is difficult to achieve and precluding, at this stage, recommending routine use of prophylactic antibiotics in this setting.

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Chapter **194**

Haemophilus influenzae

Robert S. Daum

An effective vaccine to prevent *Haemophilus influenzae* type b disease, introduced in the United States and most other countries, has resulted in a dramatic decrease in the incidence of infections caused by this organism. However, mortality and morbidity from *H. influenzae* type b infection remain a problem worldwide, primarily in developing countries. Occasional cases of invasive disease caused by non–type b organisms continue to occur but are infrequent. Nontypable members of the species are an important cause of otitis media, sinusitis, and chronic bronchitis.

ETIOLOGY

H. influenzae is a fastidious, Gram-negative, pleomorphic coccobacillus that requires factor X (hematin) and factor V (phosphopyridine nucleotide) for growth. Some *H. influenzae* isolates are surrounded by a polysaccharide capsule and can be serotyped into 6 antigenically and biochemically distinct types designated a, b, c, d, e, and f.

EPIDEMIOLOGY

Before the advent of an effective type b conjugate vaccine in 1988, *H. influenzae* type b was a major cause of serious disease among children. There was a striking age distribution of cases, with more than

90% in children younger than 5 yr of age and the majority in children younger than 2 yr of age. The annual attack rate of invasive disease was 64-129 cases per 100,000 children younger than 5 yr of age. Invasive disease caused by other capsular serotypes has been much less frequent but continues to occur. The incidence of invasive disease caused by type b and non–type b serotypes has been estimated at approximately 0.08 and 1.02 cases per 100,000 children younger than 5 yr of age per year, respectively, in the United States. Nonencapsulated (nontypable) *H. influenzae* strains also occasionally cause invasive disease, especially in neonates, immunocompromised children, and children in developing countries. The estimated rate of invasive disease caused by nontypable *H. influenzae* in the United States is 1.88 per 100,000 children younger than 5 yr of age per year. Nontypable isolates are common etiologic agents in otitis media, sinusitis, and chronic bronchitis.

Humans are the only natural hosts for *H. influenzae,* which is part of the normal respiratory flora in 60-90% of healthy children. Most isolates are nontypable. Before the advent of conjugate vaccine immunization, *H. influenzae* type b could be isolated from the pharynx of 2-5% of healthy preschool and school-age children, with lower rates among infants and adults. Asymptomatic colonization with *H. influenzae* type b occurs at a much lower rate in immunized populations.

The continued circulation of the type b organism despite current vaccine coverage levels suggests that elimination of type b disease may be a formidable task. The few cases of type b invasive disease in the United States now occur in both unvaccinated and fully vaccinated children. Approximately 50% of cases occur in young infants who are too young to have received a complete primary vaccine series. Among the cases in patients who are old enough to have received a complete vaccine series, the majority are underimmunized. To highlight this point, during a recent shortage of *H. influenzae* type b vaccine, invasive disease developed in 5 children in Minnesota, all of whom were incompletely immunized. Continued efforts are necessary to provide currently available conjugate vaccines to children in developing countries, where affordability remains an important issue.

In the prevaccine era, certain groups and individuals had an increased incidence of invasive type b disease, including Alaskan Eskimos, Apaches, Navajos, and African-Americans. Persons with certain chronic medical conditions were also known to be at increased risk for invasive disease, including those with sickle cell disease, asplenia, congenital and acquired immunodeficiencies, and malignancies. Unvaccinated infants with invasive *H. influenzae* type b infection are also at increased risk for recurrence, reflecting the fact that they typically do not develop a protective immune response to *H. influenzae.*

Socioeconomic risk factors for invasive *H. influenzae* type b disease include childcare outside the home, the presence of siblings of elementary school age or younger, short duration of breastfeeding, and parental smoking. A history of otitis media is associated with an increased risk for invasive disease. Much less is known about the epidemiology of invasive disease caused by non–type b strains, and it is not clear whether the epidemiologic features of type b disease apply to disease caused by non–type b isolates.

Among age-susceptible household contacts who have been exposed to a case of invasive *H. influenzae* type b disease, there is increased risk for secondary cases of invasive disease in the 1st 30 days, especially in susceptible children younger than 24 mo of age. Whether a similar increased risk occurs for contacts of individuals with non–type b disease is unknown.

The mode of transmission is most commonly direct contact or inhalation of respiratory tract droplets containing *H. influenzae.* The incubation period for invasive disease is variable, and the exact period of communicability is unknown. Most children with invasive *H. influenzae* type b disease are colonized in the nasopharynx before initiation of antimicrobial therapy; 25-40% may remain colonized during the 1st 24 hr of therapy.

With the decline of disease caused by type b organisms, disease caused by other serotypes (a, c-f) and nontypable organisms has been recognized more clearly. There is no evidence that these non–type b infections have increased in frequency. However, clusters of type a and, less often, type f and type e infections have occurred. Data from Israel suggest that nontypable *H. influenzae* is now the most common case of invasive *H. influenzae* disease in that country.

PATHOGENESIS

The pathogenesis of disease begins with adherence to respiratory epithelium and colonization of the nasopharynx, which is mediated by pilus and nonpilus adherence factors. The mechanism of entry into the intravascular compartment is unclear but appears to be influenced by cytotoxic factors. Once in the bloodstream, *H. influenzae* type b, and perhaps other encapsulated strains, resist intravascular clearance mechanisms at least in part via the presence of a polysaccharide capsule. In the case of *H. influenzae* type b, the magnitude and duration of bacteremia influence the likelihood of dissemination of bacteria to sites such as the meninges and joints.

Noninvasive *H. influenzae* infections such as otitis media, sinusitis, and bronchitis are usually caused by nontypable strains. These organisms gain access to sites such as the middle ear and sinus cavities by direct extension from the nasopharynx. Factors facilitating spread from the pharynx include eustachian tube dysfunction and antecedent viral infections of the upper respiratory tract.

Antibiotic Resistance

Most *H. influenzae* isolates are susceptible to ampicillin or amoxicillin, but about a third produce a β-lactamase and are therefore resistant to these antibiotics. β-Lactamase–negative ampicillin-resistant isolates have been identified and manifest resistance by production of a β-lactam–insensitive cell wall synthesis enzyme called PBP3.

Amoxicillin-clavulanate is uniformly active against *H. influenzae* clinical isolates except for the rare β-lactamase–negative ampicillin-resistant isolates. Among macrolides, azithromycin has in vitro activity against a high percentage of *H. influenzae* isolates; in contrast, the activity of erythromycin and clarithromycin against *H. influenzae* clinical isolates is poor. *H. influenzae* resistance to third-generation cephalosporins has not been documented. Resistance to trimethoprim-sulfamethoxazole is infrequent (≈10%), and resistance to quinolones is believed to be rare.

Immunity

In the prevaccine era, the most important known element of host defense was antibody directed against the type b capsular polysaccharide polyribosylribitol phosphate (PRP). Anti-PRP antibody is acquired in an age-related fashion and facilitates clearance of *H. influenzae* type b from blood, in part related to opsonic activity. Antibodies directed against antigens such as outer membrane proteins or lipopolysaccharide may also have a role in opsonization. Both the classic and alternative complement pathways are important in defense against *H. influenzae* type b.

Before the introduction of vaccination, protection from *H. influenzae* type b infection was presumed to correlate with the concentration of circulating anti-PRP antibody at the time of exposure. A serum antibody concentration of 0.15-1.0 μg/mL was considered protective against invasive infection. Unimmunized infants older than 6 mo of age and young children usually lacked an anti-PRP antibody concentration of this magnitude and were susceptible to disease after encountering *H. influenzae* type b. This lack of antibody in infants and young children may have reflected a maturational delay in the immunologic response to thymus-independent type 2 antigens such as unconjugated PRP, presumably explaining the high incidence of type b infections in infants and young children in the pre-vaccine era.

The conjugate vaccines (Table 194-1) act as thymus-dependent antigens and elicit serum antibody responses in infants and young children. These vaccines are believed to prime memory antibody responses on subsequent encounters with PRP. The concentration of circulating anti-PRP antibody in a child primed by a conjugate vaccine may not correlate precisely with protection, presumably because a memory response may occur rapidly on exposure to PRP and provide protection.

Much less is known about immunity to other *H. influenzae* serotypes or to nontypable isolates. For nontypable isolates, evidence suggests that antibodies directed against 1 or more outer membrane proteins

Table 194-1 *Haemophilus influenzae* Type B Conjugate Vaccines Available in the United States

VACCINE	TRADE NAME	COMPONENTS	MANUFACTURER
PRP-T*	Hiberix*	PRP conjugated to tetanus toxoid	GlaxoSmithKline Biologicals
PRP-OMP	PedvaxHIB	PRP conjugated to OMP	Merck & Co, Inc.
PRP-OMP-HepB	Comvax	PRP-OMP + hepatitis B vaccine	Merck & Co, Inc.
PRP-T/DTaP-IPV	Pentacel	PRP-T + DTaP-IPV vaccines	Sanofi Pasteur
PRP-T	MenHibRix	PRP-T + MenCY	GlaxoSmithKline Biolgicals

*PRP-T (Hiberix) is licensed only for the final (booster) dose of the Hib vaccine series and should not be used for primary immunization in infants at 2, 4, or 6 mo of age.

DTaP, diphtheria and tetanus toxoids and acellular pertussis vaccine; HepB, hepatitis B vaccine; Hib, *H. influenzae* type b; IPV, trivalent inactivated polio vaccine; OMP, outer membrane protein complex from Neisseria meningitidis; PRP, polyribosylribitol phosphate.

are bactericidal and protect against experimental challenge. A variety of antigens have been evaluated in an attempt to identify vaccine candidates for nontypable *H. influenzae,* including outer membrane proteins (P1, P2, P4, P5, P6, D15, and Tbp A/B), lipopolysaccharide, various adhesins, and lipoprotein D.

DIAGNOSIS

Presumptive identification of *H. influenzae* is established by direct examination of the collected specimen after staining with Gram reagents. Because of its small size, pleomorphism, and occasional poor uptake of stain, as well as the tendency for proteinaceous fluids to have a red background, *H. influenzae* is sometimes difficult to visualize. Furthermore, given that identification of microorganisms on smear by either technique requires at least 10^5 bacteria/mL, failure to visualize them does not preclude their presence.

Culture of *H. influenzae* requires prompt transport and processing of specimens because the organism is fastidious. Specimens should not be exposed to drying or temperature extremes. Primary isolation of *H. influenzae* can be accomplished on chocolate agar or on blood agar plates using the staphylococcus streak technique.

Serotyping of *H. influenzae* is accomplished by slide agglutination with type-specific antisera. Accurate serotyping is essential to monitor progress toward elimination of type b invasive disease. Timely reporting of cases to public health authorities should be ensured.

CLINICAL MANIFESTATIONS AND TREATMENT

The initial antibiotic therapy of invasive infections possibly caused by *H. influenzae* should be a parenterally administered antimicrobial agent effective in sterilizing all foci of infection and effective against ampicillin-resistant strains, usually an extended-spectrum cephalosporin such as cefotaxime or ceftriaxone. These antibiotics have achieved popularity because of their relative lack of serious adverse effects and ease of administration. After the antimicrobial susceptibility of the isolate has been determined, an appropriate agent can be selected to complete the therapy. Ampicillin remains the drug of choice for the therapy of infections caused by susceptible isolates. If the isolate is resistant to ampicillin, ceftriaxone can be administered once daily in selected circumstances for outpatient therapy.

Oral antimicrobial agents are sometimes used to complete a course of therapy initiated by the parenteral route and are typically initial therapy for noninvasive infections such as otitis media and sinusitis. If the organism is susceptible, amoxicillin is the drug of choice. An oral second- or third-generation cephalosporin or amoxicillin-clavulanate may be used when the isolate is resistant to ampicillin.

Meningitis

In the prevaccine era, meningitis accounted for more than half of all cases of invasive *H. influenzae* disease. Clinically, meningitis caused by *H. influenzae* type b cannot be differentiated from meningitis caused by *Neisseria meningitidis* or *Streptococcus pneumoniae* (see Chapter 603.1). It may be complicated by other foci of infection such as the lungs, joints, bones, and pericardium.

Antimicrobial therapy should be administered intravenously for 7-14 days for uncomplicated cases. Cefotaxime, ceftriaxone, and ampicillin cross the blood–brain barrier during acute inflammation in concentrations adequate to treat *H. influenzae* meningitis. Intramuscular therapy with ceftriaxone is an alternative in patients with normal organ perfusion.

The prognosis of *H. influenzae* type b meningitis depends on the age at presentation, duration of illness before appropriate antimicrobial therapy, cerebrospinal fluid capsular polysaccharide concentration, and rapidity with which organisms are cleared from cerebrospinal fluid, blood, and urine. Clinically manifested inappropriate secretion of antidiuretic hormone and evidence of focal neurologic deficits at presentation are poor prognostic features. Approximately 6% of patients with *H. influenzae* type b meningitis are left with some hearing impairment, probably because of inflammation of the cochlea and the labyrinth. Dexamethasone (0.6 mg/kg/day divided every 6 hr for 2 days), particularly when given shortly before or concurrent with the initiation of antimicrobial therapy, decreases the incidence of hearing loss. Major neurologic sequelae of *H. influenzae* type b meningitis include behavior problems, language disorders, impaired vision, mental retardation, motor abnormalities, ataxia, seizures, and hydrocephalus.

Cellulitis

Children with *H. influenzae* type b cellulitis often have an antecedent upper respiratory tract infection. They usually have no prior history of trauma, and the infection is thought to represent seeding of the organism to the involved soft tissues during bacteremia. The head and neck, particularly the cheek and preseptal region of the eye, are the most common sites of involvement. The involved region generally has indistinct margins and is tender and indurated. Buccal cellulitis is classically erythematous with a violaceous hue, although this sign may be absent. *H. influenzae* may often be recovered directly from an aspirate of the leading edge, although this procedure is seldom performed. The blood culture may also reveal the causative organism. Other foci of infection may be present concomitantly, particularly in children younger than 18 mo of age. A diagnostic lumbar puncture should be considered at the time of diagnosis in these children.

Parenteral antimicrobial therapy is indicated until patients become afebrile, after which an appropriate orally administered antimicrobial agent may be substituted. A 7-10 day course is customary.

Preseptal Cellulitis

Infection involving the superficial tissue layers anterior to the orbital septum is termed preseptal cellulitis, which may be caused by *H. influenzae.* Uncomplicated preseptal cellulitis does not imply a risk for visual impairment or direct central nervous system extension. However, concurrent bacteremia may be associated with the development of meningitis. *H. influenzae* preseptal cellulitis is characterized by fever, edema, tenderness, warmth of the lid, and, occasionally, purple discoloration. Evidence of interruption of the integument is usually absent. Conjunctival drainage may be associated. *S. pneumoniae, Staphylococcus aureus,* and group A streptococcus cause

clinically indistinguishable preseptal cellulitis. The latter 2 pathogens are more likely when fever is absent and the integument is interrupted (e.g., an insect bite or trauma).

Children with preseptal cellulitis in whom *H. influenzae* and *S. pneumoniae* are etiologic considerations (young age, high fever, intact integument) should undergo blood culture, and a diagnostic lumbar puncture should be considered.

Parenteral antibiotics are indicated for preseptal cellulitis. Because methicillin-susceptible and methicillin-resistant *S. aureus, S. pneumoniae,* and group A β-hemolytic streptococci are other causes, empirical therapy should include agents active against these pathogens. Patients with preseptal cellulitis without concurrent meningitis should receive parenteral therapy for about 5 days, until fever and erythema have abated. In uncomplicated cases, antimicrobial therapy should be given for 10 days.

Orbital Cellulitis

Infections of the orbit are infrequent and usually develop as complications of acute ethmoid or sphenoid sinusitis. Orbital cellulitis may manifest as lid edema but is distinguished by the presence of proptosis, chemosis, impaired vision, limitation of the extraocular movements, decreased mobility of the globe, or pain on movement of the globe. The distinction between preseptal and orbital cellulitis may be difficult and is best delineated by CT.

Orbital infections are treated with parenteral therapy for at least 14 days. Underlying sinusitis or orbital abscess may require surgical drainage and more prolonged antimicrobial therapy.

Supraglottitis or Acute Epiglottitis

Supraglottitis is a cellulitis of the tissues comprising the laryngeal inlet (see Chapter 385). It has become exceedingly rare since the introduction of conjugate type b vaccines. Direct bacterial invasion of the involved tissues is probably the initiating pathophysiologic event. This dramatic, potentially lethal condition can occur at any age. Because of the risk of sudden, unpredictable airway obstruction, supraglottitis is a medical emergency. Other foci of infection, such as meningitis, are rare. Antimicrobial therapy directed against *H. influenzae* and other etiologic agents should be administered parenterally but only after the airway is secured, and therapy should be continued until patients are able to take fluids by mouth. The duration of antimicrobial therapy is typically 7 days.

Pneumonia

The true incidence of *H. influenzae* pneumonia in children is unknown because invasive procedures required to obtain culture specimens are seldom performed (see Chapter 400). In the prevaccine era, type b bacteria were believed to be the usual cause. The signs and symptoms of pneumonia caused by *H. influenzae* cannot be differentiated from those of pneumonia caused by many other microorganisms. Other foci of infection may be present concomitantly.

Children younger than 12 mo of age in whom *H. influenzae* pneumonia is suspected should receive parenteral antimicrobial therapy initially because of their increased risk for bacteremia and its complications. Older children who do not appear severely ill may be managed with an orally administered antimicrobial. Therapy is continued for 7-10 days. Uncomplicated pleural effusion associated with *H. influenzae* pneumonia requires no special intervention. However, if empyema develops, surgical drainage is indicated.

Suppurative Arthritis

Large joints, such as the knee, hip, ankle, and elbow, are affected most commonly (see Chapter 685). Other foci of infection may be present concomitantly. Although single joint involvement is the rule, multiple joint involvement occurs in approximately 6% of cases. The signs and symptoms of septic arthritis caused by *H. influenzae* are indistinguishable from those of arthritis caused by other bacteria.

Uncomplicated septic arthritis should be treated with an appropriate antimicrobial administered parenterally for at least 5-7 days. If the clinical response is satisfactory, the remainder of the course of antimicrobial treatment may be given orally. Therapy is typically given for 3 wk for uncomplicated septic arthritis, but it may be continued beyond 3 wk, until the C-reactive protein concentration is normal.

Pericarditis

H. influenzae is a rare cause of pericarditis (see Chapter 440). Affected children often have had an antecedent upper respiratory tract infection. Fever, respiratory distress, and tachycardia are consistent findings. Other foci of infection may be present concomitantly.

The diagnosis may be established by recovery of the organism from blood or pericardial fluid. Gram stain or detection of PRP in pericardial fluid, blood, or urine (when type b organisms are the cause) may aid the diagnosis. Antimicrobials should be provided parenterally in a regimen similar to that used for meningitis (see Chapter 603.1). Pericardiectomy is useful for draining the purulent material effectively and preventing tamponade and constrictive pericarditis.

Bacteremia Without an Associated Focus

Bacteremia caused by *H. influenzae* may be associated with fever without any apparent focus of infection (see Chapter 177). In this situation, risk factors for "occult" bacteremia include the magnitude of fever (≥39°C [102.2°F]) and the presence of leukocytosis (≥15,000 cells/μL). In the prevaccine era, meningitis developed in approximately 25% of children with occult *H. influenzae* type b bacteremia if left untreated. In the vaccine era, this *H. influenzae* infection has become exceedingly rare. When it does occur, the child should be reevaluated for a focus of infection and a second blood culture performed. The child should be hospitalized and given parenteral antimicrobial therapy after a diagnostic lumbar puncture and chest radiograph are obtained.

Miscellaneous Infections

Urinary tract infection, epididymoorchitis, cervical adenitis, acute glossitis, infected thyroglossal duct cysts, uvulitis, endocarditis, endophthalmitis, primary peritonitis, osteomyelitis, and periappendiceal abscess are rarely caused by *H. influenzae.*

Invasive Disease in Neonates

Neonates rarely have invasive *H. influenzae* infection. In the infant with illness within the 1st 24 hr of life, especially in association with maternal chorioamnionitis or prolonged rupture of membranes, transmission of the organism to the infant is likely to have occurred through the maternal genital tract, which may be (<1%) colonized with nontypable *H. influenzae.* Manifestations of neonatal invasive infection include bacteremia with sepsis, pneumonia, respiratory distress syndrome with shock, conjunctivitis, scalp abscess or cellulitis, and meningitis. Less commonly, mastoiditis, septic arthritis, and congenital vesicular eruption may occur.

Otitis Media

Acute otitis media is one of the most common infectious diseases of childhood (see Chapter 640). It results from the spread of bacteria from the nasopharynx through the eustachian tube into the middle ear cavity. Usually because of a preceding viral upper respiratory tract infection, the mucosa in the area becomes hyperemic and swollen, resulting in obstruction and an opportunity for bacterial multiplication in the middle ear.

The most common bacterial pathogens are *H. influenzae, S. pneumoniae,* and *Moraxella catarrhalis.* Most *H. influenzae* isolates causing otitis media are nontypable. Ipsilateral conjunctivitis may also be present. Amoxicillin (80-90 mg/kg/day) is a suitable first-line oral antimicrobial agent, because the probability that the causative isolate is resistant to amoxicillin and the risk for invasive potential are sufficiently low to justify this approach. Alternatively, in certain cases, a single dose of ceftriaxone constitutes adequate therapy.

In the case of treatment failure or if a β-lactamase–producing isolate is obtained by tympanocentesis or from drainage fluid, amoxicillin-clavulanate (Augmentin) is a suitable alternative.

Conjunctivitis

Acute infection of the conjunctivae is common in childhood (see Chapter 626). In neonates, *H. influenzae* is an infrequent cause. However, it is an important pathogen in older children. Most *H. influenzae* isolates associated with conjunctivitis are nontypable, although type b isolates and other serotypes are occasionally found. Empirical treatment of conjunctivitis beyond the neonatal period usually consists of topical antimicrobial therapy with sulfacetamide. Topical fluoroquinolone therapy is to be avoided because of its broad spectrum, high cost, and high rate of emerging resistance among many bacterial species. Ipsilateral **otitis media** caused by the same organism may be present and requires oral antibiotic therapy.

Sinusitis

H. influenzae is an important cause of acute sinusitis in children, second in frequency only to *S. pneumoniae* (see Chapter 380). Chronic sinusitis lasting longer than 1 yr or severe sinusitis requiring hospitalization is often caused by *S. aureus* or anaerobes such as *Peptococcus, Peptostreptococcus,* and *Bacteroides.* Nontypable *H. influenzae* and viridans group streptococci are also frequently recovered.

For uncomplicated sinusitis, amoxicillin is acceptable initial therapy. However, if clinical improvement does not occur, a broader-spectrum agent, such as amoxicillin-clavulanate, may be appropriate. A 10-day course is sufficient for uncomplicated sinusitis. Hospitalization for parenteral therapy is rarely required; the usual reason is suspicion of progression to orbital cellulitis.

PREVENTION

Immunization with *H. influenzae* type b conjugate vaccine is recommended for all infants. Prophylaxis is indicated if close contacts of an index patient with type b disease are unvaccinated. The contagiousness of non–type b *H. influenzae* infections is not known, and prophylaxis is not recommended.

Vaccine

Several *H. influenzae* type b conjugate vaccines are currently marketed in the United States, containing either PRP–outer membrane protein (PRP-OMP) or PRP–tetanus toxoid (PRP-T), which differ in the carrier protein used and the method of conjugating the polysaccharide to the protein (see Table 194-1 and Chapter 172). One of the combination vaccines consists of PRP-OMP combined with hepatitis B vaccine (Comvax, Merck & Co., Inc., Whitehouse Station, NJ) and can be used for doses recommended at 2, 4, and 12-15 mo of age. Another consists of PRP-T combined with DTaP vaccine (diphtheria and tetanus toxoids and acellular pertussis) and IPV vaccine (trivalent, inactivated polio vaccine) (Pentacel, Sanofi Pasteur Inc., Swiftwater, PA) and can be used for doses recommended at 2, 4, 6, and 12-15 mo of age. A third consists of PRP-T combined with *N. meningitidis* serogroups C and Y (GlaxoSmithKline Biologicals) and can be used for doses recommended at 2, 4, 6, and 12-15 mo of age for children at increased risk for *N. meningitidis* disease. PRP-T by itself is licensed for doses scheduled for children 15 mo of age or older.

The *H. influenzae* type b conjugate vaccines stimulate circulating anticapsular antibody and provide long-term immunity via B-cell memory.

Prophylaxis

Unvaccinated children younger than 48 mo of age who are in close contact with an index case of invasive *H. influenzae* type b infection are at increased risk for invasive infection. The risk for secondary disease for children older than 3 mo of age is inversely related to age. About half of the secondary cases among susceptible household contacts occur in the 1st wk after hospitalization of the index case. Because many children are now protected against *H. influenzae* type b by prior immunization, the need for prophylaxis has greatly decreased. When prophylaxis is used, rifampin is indicated for all members of the household or close contact group, including the index patient, if the group includes 1 or more children younger than 48 mo of age who are not fully immunized.

Parents of children hospitalized for invasive *H. influenzae* type b disease should be informed of the increased risk for secondary infection in other young children in the same household if they are not fully immunized. Parents of children exposed to a single case of invasive *H. influenzae* type b disease in a childcare center or nursery school should be similarly informed, although there is disagreement about the need for rifampin prophylaxis for these children.

For prophylaxis, children should be given rifampin orally (0-1 mo of age, 10 mg/kg/dose; >1 mo of age, 20 mg/kg/dose, not to exceed 600 mg/dose) once a day for 4 consecutive days. The adult dose is 600 mg once daily. Rifampin prophylaxis is not recommended for pregnant women.

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Chapter 195

Chancroid *(Haemophilus ducreyi)*

H. Dele Davies

Chancroid is a sexually transmitted disease characterized by painful genital ulceration and inguinal lymphadenopathy.

ETIOLOGY AND EPIDEMIOLOGY

Chancroid is caused by *Haemophilus ducreyi,* a fastidious Gram-negative bacillus. It is prevalent in many developing countries but occurs sporadically in the developed world. Most Western cases occur in returning travelers (90% are male) from endemic areas or occasionally in localized urban outbreaks associated with commercial sex workers. It is a risk factor for transmission of HIV. Diagnosis of chancroid in infants and children is strong evidence of sexual abuse. Male circumcision lowers the risk for chancroid. The incidence of chancroid has declined significantly and remains low in the United States since 1981.

CLINICAL MANIFESTATIONS.

The incubation period is 4-7 days with a small inflammatory papule on the preputial orifice or frenulum in men and on the labia, fourchette, or perineal region in women. The lesion becomes pustular, eroded, and ulcerative within 2-3 days. The ulcer edge is classically ragged and undermined. Without treatment, the ulcers may persist for wk to mo. Painful, tender inguinal lymphadenitis occurs in more than 50% of cases, more often among men. The lymphadenopathy can become fluctuant to form **buboes,** which can spontaneously rupture.

DIAGNOSIS

Diagnosis is usually established by the clinical presentation and the exclusion of both syphilis *(Treponema pallidum)* and herpes simplex virus infections. Gram stain of ulcer secretions may show Gram-negative coccobacilli in parallel clusters (school of fish). Culture requires expensive, special media and has a sensitivity of only 80%. Polymerase chain reaction or indirect immunofluorescence using monoclonal antibodies remain either as research tools or are performed by some clinical laboratories using their own in-house CLIA (Clinical Laboratory Improvement Amendments) verified kits. There are currently no FDA-approved polymerase chain reaction tests for *H. ducreyi*. The ulcer of chancroid is accompanied by concurrent **lymphadenopathy** that is usually unilateral, unlike lymphogranuloma venereum (see Chapter 226.4). Genital herpes is characterized by vesicular lesions with a history of recurrence (see Chapter 252).

TREATMENT

Most *H. ducreyi* organisms are resistant to penicillin and ampicillin because of plasmid-mediated β-lactamase production. Spread of plasmid-mediated resistance among *H. ducreyi* has resulted in lack of efficacy of previously useful drugs such as sulfonamides and tetracyclines. Chancroid is easy to treat if recognized early. The current treatment recommendation is for azithromycin (1g as a single dose PO) or ceftriaxone (250 mg as a single dose IM). Alternative regimens include erythromycin (500 mg tid PO for 7 days), which is most often used in developing countries, and ciprofloxacin (500 mg bid PO for 3 days, for persons ≥18 yr of age). Fluctuant nodes may require drainage. Symptoms usually resolve within 3-7 days. Relapses can usually be treated successfully with the original treatment regimen. Patients with HIV infection may require longer duration of treatment. Persistence of the ulcer and the organism following therapy should raise suspicion of resistance to the prescribed antibiotic.

Patients with chancroid should be evaluated for other sexually transmitted infections, including syphilis, hepatitis B virus, HIV, chlamydia, and gonorrhea; an estimated 10% have concomitant syphilis or genital herpes. If initial HIV or syphilis testing is negative, they should be tested for again in 3 mo because of the high rates of coinfections. In developing countries, patients with a compatible genital ulcer are treated for both chancroid and syphilis. All sexual contacts of patients with chancroid should be evaluated and treated.

COMPLICATIONS

Complications include phimosis in men and secondary bacterial infection. Bubo formation may occur in untreated cases. Genital ulceration as a syndrome increases the risk for transmission of HIV.

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Chapter 196

Moraxella catarrhalis

Timothy F. Murphy

Moraxella catarrhalis is an unencapsulated Gram-negative diplococcus and is a human-specific pathogen that colonizes the respiratory tract beginning in infancy. Colonization and infection with *M. catarrhalis* are increasing in countries in which pneumococcal conjugate vaccines are used widely. The most important clinical manifestation of *M. catarrhalis* infection in children is otitis media.

ETIOLOGY

M. catarrhalis has long been considered to be an upper respiratory tract commensal. Substantial genetic heterogeneity exists among strains of *M. catarrhalis*. Several outer membrane proteins demonstrate sequence differences among strains, particularly in regions of the proteins that are exposed on the bacterial surface. *M. catarrhalis* endotoxin lacks repeating polysaccharide side chains and is thus a lipooligosaccharide. In contrast to other Gram-negative respiratory pathogens, such as *Haemophilus influenzae* and *Neisseria meningitidis,* the lipooligosaccharide of *M. catarrhalis* is relatively conserved among strains; only 3 serotypes (A, B, and C) that are based on oligosaccharide structure have been identified. Genetic and antigenic differences among strains account for the observation that resolving an infection by 1 strain does not induce protective immunity to other strains. *M. catarrhalis* causes recurrent infections, which generally represent reinfection by new strains.

EPIDEMIOLOGY

The ecologic niche of *M. catarrhalis* is the human respiratory tract. The bacterium has not been recovered from animals or environmental sources. Age is the most important determinant of the prevalence of upper respiratory tract colonization. Common throughout infancy, nasopharyngeal colonization is a dynamic process with active turnover as a result of acquisition and clearance of strains of *M. catarrhalis*. Some geographic variation in rates of colonization is observed. On the basis of monthly or bimonthly cultures, colonization during the 1st yr of life may range from 33-100%. Several factors likely account for this variability among studies, including living conditions, daycare attendance, hygiene, environmental factors (e.g., household smoking), and genetics of the population. The prevalence of colonization steadily decreases with age. Understanding nasopharyngeal colonization patterns is important, because the pathogenesis of otitis media involves migration of the bacterium from the nasopharynx to the middle ear via the eustachian tube.

The widespread use of pneumococcal polysaccharide vaccines in some countries has resulted in alteration of patterns of nasopharyngeal colonization in the population. A relative increase in colonization by nonvaccine pneumococcal serotypes, nontypable *H. influenzae,* and *M. catarrhalis* has occurred. These changes in colonization patterns may account for the increased rates of otitis media caused by nontypable *H. influenzae* and *M. catarrhalis*. Similar shifts in etiology are being observed in children with sinusitis as well.

PATHOGENESIS OF INFECTION

Strains of *M. catarrhalis* differ in their virulence properties. The species is composed of complement-resistant and complement-sensitive genetic lineages, the complement-resistant strains being more strongly associated with virulence. Strains that cause infection in children differ in several phenotypic characteristics from strains that cause infection in adults, in whom the most common clinical manifestation is lower respiratory tract infection in the setting of chronic obstructive pulmonary disease.

The presence of several adhesin molecules with differing specificities for various host cell receptors reflects the importance of adherence to the human respiratory epithelial surface in the pathogenesis of infection. *M. catarrhalis* has long been viewed as an exclusively extracellular pathogen. However, the bacterium is now known to invade multiple cell types, including bronchial epithelial cells, small airway cells, and type 2 alveolar cells. In addition, *M. catarrhalis* resides intracellularly in lymphoid tissue, providing a potential reservoir for persistence in the human respiratory tract. Like many Gram-negative bacteria *M. catarrhalis* sheds vesicles from its surface during growth. These vesicles are internalized by respiratory epithelial cells and mediate several virulence mechanisms including B-cell activation, induction of inflammation, and delivery of β-lactamases. Analysis of genomes reveals modest genetic heterogeneity among strains.

M. catarrhalis forms biofilms in vitro and in the middle ears of children with chronic and recurrent otitis media. Biofilms are communities of bacteria encased in a matrix attached to a surface. Bacteria in biofilms are more resistant to antibiotics and to host immune responses than bacteria growing individually in planktonic form.

CLINICAL MANIFESTATIONS

M. catarrhalis causes predominantly mucosal infections in children. The mechanism of infection is migration of the infecting strains from the nasopharynx to the middle ear in the case of otitis media or to the sinuses in the case of sinusitis. The inciting event for both otitis media and sinusitis is often a preceding viral infection.

Acute Otitis Media

Approximately 80% of children have 1 or more episodes of otitis media by age 3 yr. Otitis media is the most common reason for which children receive antibiotics. On the basis of culture of middle ear fluid obtained by tympanocentesis, the predominant causes of acute otitis media are *Streptococcus pneumoniae, H. influenzae,* and *M. catarrhalis* (Fig. 196-1). Overall, *M. catarrhalis* causes 15-20% of cases of otitis media. The distribution of the causative agents of otitis media is changing as a result of widespread administration of pneumococcal conjugate vaccines, with a relative increase in *H. influenzae* and *M. catarrhalis*.

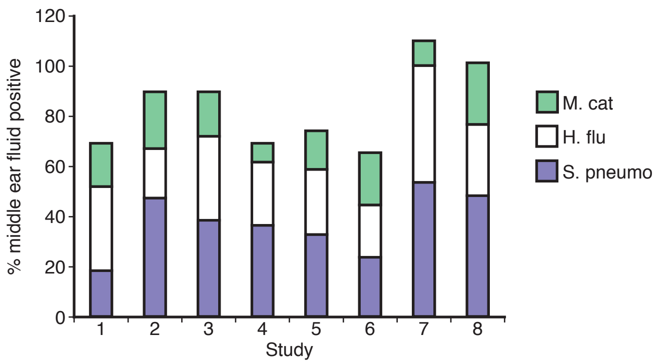

Figure 196-1 Bacterial causes of otitis media based on results of culture of middle ear fluid obtained by tympanocentesis from 8 studies published from 1992-2006. Bars represent percent-positive results of cultures of middle ear fluids. Some cultures had more than 1 species, accounting for totals greater than 100%. H. flu, nontypeable *Haemophilus influenzae;* M. cat, *Moraxella catarrhalis;* S. pneumo, *Streptococcus pneumoniae. (From Murphy TF, Paramswaran GI:* Moraxella catarrhalis, *a human respiratory tract pathogen,* Clin Infect Dis *49:124–131, 2009.)*

Acute otitis media caused by *M. catarrhalis* is clinically milder than otitis media caused by *H. influenzae* or *S. pneumoniae,* with less fever and lower prevalence of a red, bulging tympanic membrane. However, substantial overlap in symptoms is seen, making it impossible to predict etiology in an individual child on the basis of clinical features. Tympanocentesis is required to make an etiologic diagnosis but is not performed routinely, and thus, treatment of otitis media is generally empirical.

Recurrent Otitis Media and Otitis Media with Effusion

Otitis media with effusion refers to the presence of fluid in the middle ear in the absence of signs and symptoms of acute infection. Children who experience 4 or more episodes of acute otitis media in a year or who have at least 8 mo of middle ear effusion in a year are defined as *otitis prone*. These children suffer conductive hearing loss, which may lead to delays in speech and language development. Analysis of middle ear fluid from children with otitis media with effusion using sensitive molecular techniques such as polymerase chain reaction indicates that bacterial DNA is present in up to 80% of samples from such children. Indeed, *M. catarrhalis* DNA is present in a larger proportion of cases of otitis media with effusion than of acute otitis media. Biofilms may account for these observations, although definitive evidence for this conclusion is lacking.

Sinusitis

A small proportion of viral upper respiratory tract infections are complicated by bacterial sinusitis. According to findings of studies that use sinus puncture, *M. catarrhalis* accounts for approximately 20% of cases of acute bacterial sinusitis in children and a smaller proportion in adults. Sinusitis caused by *M. catarrhalis* is clinically indistinguishable from that caused by *S. pneumoniae* or *H. influenzae*.

Bacteremia

M. catarrhalis rarely causes bacteremia or invasive infections in children. When bacteremia occurs, the usual source is the respiratory tract. Some children have underlying immunocompromising conditions, but no particular immunodeficiency is associated with invasive *M. catarrhalis* infections.

DIAGNOSIS

The clinical diagnosis of otitis media is made by demonstration of fluid in the middle ear by pneumatic otoscopy. A tympanocentesis is required to establish an etiologic diagnosis, but this procedure is not performed routinely. Thus, the choice of antibiotic for otitis media is empirical and generally based on guidelines. Management of bacterial sinusitis is also empirical, because determining the etiology of sinusitis requires a sinus puncture, also a procedure that is not performed routinely.

The key to making a microbiologic diagnosis is distinguishing *M. catarrhalis* from commensal *Neisseria* that are part of the normal upper respiratory tract flora. Indeed, the difficulty in distinguishing colonies of *M. catarrhalis* from *Neisseria* species explains in part why *M. catarrhalis* has been overlooked in the past as a respiratory tract pathogen. *M. catarrhalis* produces round, opaque colonies that can be slid across the agar surface without disruption, the "hockey puck sign." In addition, after 48 hr, *M. catarrhalis* colonies tend to be larger than *Neisseria* and take on a pink color. A variety of biochemical tests distinguish *M. catarrhalis* from *Neisseria* species, and commercially available kits based on these tests are available.

Sensitive tests that employ polymerase chain reaction to detect respiratory tract bacterial pathogens in human respiratory tract secretions are in development. The application of such assays when they become available is likely to contribute new information about the epidemiology and disease patterns of *M. catarrhalis*.

TREATMENT

A proportion of cases of *M. catarrhalis* otitis media resolve spontaneously. Treatment of otitis media is empirical, and clinicians are advised to follow guidelines of the American Academy of Pediatrics (see Chapter 640).

Strains of *M. catarrhalis* rapidly acquired β-lactamase worldwide in the 1970s and 1980s, rendering essentially all strains resistant to amoxicillin. Antimicrobial susceptibility patterns have remained relatively stable since then. Most strains of *M. catarrhalis* are susceptible to amoxicillin/clavulanic acid, extended-spectrum cephalosporins, macrolides (azithromycin, clarithromycin), trimethoprim/sulfamethoxazole, and fluoroquinolones.

PREVENTION

Vaccines to prevent otitis media and other infections caused by *M. catarrhalis* are under development, but none is available yet.

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Chapter 197

Pertussis (*Bordetella pertussis* and *Bordetella parapertussis*)

Sarah S. Long

Pertussis is an acute respiratory tract infection that was well described initially in the 1500s. Sydenham first used the term *pertussis,* meaning intense cough, in 1670; it is preferable to *whooping cough* because most infected individuals do not "whoop."

ETIOLOGY

Bordetella pertussis is the cause of epidemic pertussis and the usual cause of sporadic pertussis. *Bordetella parapertussis* is an occasional cause of sporadic pertussis that contributes significantly to total cases of pertussis in Eastern and Western Europe but accounts for <5% of *Bordetella* isolates in the United States. *B. pertussis* and *B. parapertussis*

are exclusive pathogens of humans and some primates. *Bordetella holmesii*, first identified as a cause of bacteremia in immunocompromised hosts, is also reported to cause pertussis-like cough illness in healthy persons in Japan, France, and the United States. *Bordetella bronchiseptica* is a common animal pathogen. Occasional reports in humans describe a variety of body sites involved, and cases typically occur in immunocompromised persons or young children with intense exposure to animals. Protracted coughing (which in some cases is paroxysmal) can be caused by *Mycoplasma,* parainfluenza viruses, influenza viruses, enteroviruses, respiratory syncytial viruses, or adenoviruses.

EPIDEMIOLOGY

Estimates from the World Health Organization suggest that in 2008, approximately 16 million cases of pertussis and 195,000 childhood deaths occurred worldwide, 95% of which were in developing countries. The World Health Organization also estimated that in 2008, 82% of infants worldwide received 3 doses of pertussis vaccine, and that global vaccination against pertussis averted 687,000 deaths. Before vaccination was available, pertussis was the leading cause of death from communicable disease among children younger than 14 yr of age in the United States, with 10,000 deaths annually. Widespread use of whole-cell pertussis vaccine (DTP) led to a >99% decline in cases. After the low number of 1,010 cases in the United States reported in 1976, there was an increase in annual pertussis incidence to 1.2 cases per 100,000 population from 1980 through 1989, with epidemic pertussis in many states in 1989-1990, 1993, and 1996. Since then, pertussis has become increasingly endemic, with shifting burden of disease to young infants, adolescents, and adults. By 2004, the incidence of reported pertussis in the United States was 8.9 cases per 100,000 in the general population and approximately 150 per 100,000 in infants younger than 2 mo of age, resulting in a total of 25,827 cases, the highest number since 1959. Prospective and serologic studies suggested that pertussis is underrecognized, especially among adolescents and adults, in whom the actual number of cases is estimated to be 600,000 annually. A number of studies documented pertussis in 13-32% of adolescents and adults with cough illness for longer than 7 days. A total of 40 pertussis-related deaths were reported in 2005, and 16 were reported in 2006; more than 90% of these cases occurred among young infants.

Universal recommendation of tetanus toxoid, reduced content diphtheria toxoid, and acellular pertussis antigens (Tdap) in 2006 for 11-12 year olds was aimed to enhance control. With >70% uptake of Tdap in adolescents, the burden of disease in young adolescents has fallen commensurately, but without evidence of herd protection of young infants or older adolescents or adults. In fact, a new epidemiology of pertussis has emerged in this decade, with substantial evidence of rapidly waning protection following acellular pertussis vaccines (both DTaP and Tdap) and especially in those who never received, that is, were not “primed” with, DTP (whole cell), which was replaced with DTaP down to dose 1 in 1997 in the United States. The more than 42,000 cases of pertussis reported in 2012 was the highest number in more than 50 yr; increased numbers of cases were reported in all except 1 state; 10 yr old children had the highest age-related incidence after young infants.

Neither natural disease nor vaccination provides complete or lifelong immunity against pertussis reinfection or disease. Subclinical reinfection undoubtedly contributed significantly to immunity against disease ascribed previously to both vaccine and prior infection. The resurgence of pertussis has been attributed to a variety of factors, including partial control of pertussis leading to less continuous exposure, increased awareness, improved diagnostics, suboptimal vaccines, waning vaccine-induced immunity, and pathogen adaptation. Pertussis is the only vaccine-preventable disease for which universal immunization in the United States is recommended that continues to be endemic.

PATHOGENESIS

Bordetella organisms are small, fastidious, Gram-negative coccobacilli that colonize only ciliated epithelium. The exact mechanism of disease symptomatology remains unknown. *Bordetella* species share a high degree of DNA homology among virulence genes. Only *B. pertussis* expresses **pertussis toxin** (PT), the major virulence protein. PT has numerous proven biologic activities (e.g., histamine sensitivity, insulin secretion, leukocyte dysfunction). Injection of PT in experimental animals causes lymphocytosis immediately by rerouting lymphocytes to remain in the circulating blood pool but does not cause cough. PT appears to have a central, but not a singular, role in pathogenesis. *B. pertussis* produces an array of other biologically active substances, many of which are postulated to have a role in disease and immunity. After aerosol acquisition, **filamentous hemagglutinin**, some **agglutinogens** (especially fimbriae [Fim] types 2 and 3), and a 69-kDa nonfimbrial surface protein called **pertactin** (Prn) are important for attachment to ciliated respiratory epithelial cells. **Tracheal cytotoxin,** adenylate cyclase, and PT appear to inhibit clearance of organisms. Tracheal cytotoxin, dermonecrotic factor, and adenylate cyclase are postulated to be predominantly responsible for the local epithelial damage that produces respiratory symptoms and facilitates absorption of PT. Both antibody and cellular immune responses follow infection and immunization. Antibody to PT neutralizes toxin, and antibody to Prn enhances opsonophagocytosis.

Pertussis is extremely contagious, with attack rates as high as 100% in susceptible individuals exposed to aerosol droplets at close range. High airborne transmission rates were shown in a baboon model of pertussis despite vaccinated with the acellular vaccine. *B. pertussis* does not survive for prolonged periods in the environment. Chronic carriage by humans is not documented. After intense exposure as in households, the rate of subclinical infection is as high as 80% in fully immunized or previously infected individuals. When carefully sought, a symptomatic source case can be found for most patients.

CLINICAL MANIFESTATIONS

Classically, pertussis is a prolonged disease, divided into catarrhal, paroxysmal, and convalescent stages. The **catarrhal stage** (1-2 wk) begins insidiously after an incubation period ranging from 3-12 days with nondistinctive symptoms of congestion and rhinorrhea variably accompanied by low-grade fever, sneezing, lacrimation, and conjunctival suffusion. As initial symptoms wane, coughing marks the onset of the **paroxysmal stage** (2-6 wk). The cough begins as a dry, intermittent, irritative hack and evolves into the inexorable paroxysms that are the hallmark of pertussis. A well-appearing, playful toddler with insignificant provocation suddenly expresses an anxious aura and may clutch a parent or comforting adult before beginning a machine-gun burst of uninterrupted cough on a single exhalation, chin and chest held forward, tongue protruding maximally, eyes bulging and watering, face purple, until coughing ceases and a loud whoop follows as inspired air traverses the still partially closed airway. *Posttussive emesis* is common, and exhaustion is universal. The number and severity of paroxysms escalate over days to a week and remain at that plateau for days to weeks. At the peak of the paroxysmal stage, patients may have more than 1 episode hourly. As the paroxysmal stage fades into the **convalescent stage** (≥2 wk), the number, severity, and duration of episodes diminish.

Infants younger than 3 mo of age do not display the classic stages. The catarrhal phase lasts only a few days or is unnoticed, and then, after the most insignificant startle from a draft, light, sound, sucking, or stretching, a well-appearing young infant begins to choke, gasp, gag, and flail the extremities, with face reddened. Cough may not be prominent, especially in the early phase. Whoop infrequently occurs in infants younger than 3 mo of age who at the end of a paroxysm lack stature or muscular strength to create sudden negative intrathoracic pressure. Apnea and cyanosis can follow a coughing paroxysm, or apnea can occur without a cough. Apnea may be the only symptom. Apnea and cyanosis both are more common with pertussis than with neonatal infections from viruses, including respiratory syncytial virus. The paroxysmal and convalescent stages in young infants are lengthy. Paradoxically, in infants, cough and whooping may become louder and more classic in convalescence. Convalescence includes intermittent paroxysmal coughing throughout the 1st yr of life, including “exacerbations” with subsequent respiratory illnesses; these are not a result of recurrent infection or reactivation of *B. pertussis.*

Adolescents and previously immunized children have foreshortening of all stages of pertussis. Adults have no distinct stages. Classically, adolescents and adults describe a sudden feeling of strangulation followed by uninterrupted coughs, feeling of suffocation, bursting headache, diminished awareness, and then a gasping breath, usually without a whoop. Posttussive emesis and intermittency of paroxysms separated by hours of well-being are specific clues to the diagnosis in adolescents and adults. At least 30% of older individuals with pertussis have nonspecific cough illness, distinguished only by duration, which usually is longer than 21 days.

Findings on physical examination generally are uninformative. Signs of lower respiratory tract disease are not expected unless complicating secondary bacterial pneumonia is present. Conjunctival hemorrhages and petechiae on the upper body are common.

DIAGNOSIS

Pertussis should be suspected in any individual who has a pure or predominant complaint of cough, especially if the following features are absent: fever, malaise or myalgia, exanthem or enanthem, sore throat, hoarseness, tachypnea, wheezes, and rales. For sporadic cases, a clinical case definition of cough of 14 days or longer duration with at least 1 associated symptom of paroxysms, whoop, or posttussive vomiting has a sensitivity of 81% and a specificity of 58% for confirmation of pertussis. Pertussis should be suspected in older children whose cough illness is escalating at 7-10 days and whose coughing episodes are not continuous. Pertussis should be suspected in infants younger than 3 mo of age with gagging, gasping, apnea, cyanosis, or an apparent life-threatening event. Sudden infant death occasionally is caused by *B. pertussis*.

Adenoviral infections usually are distinguishable by associated features, such as fever, sore throat, and conjunctivitis. *Mycoplasma* causes protracted episodic coughing, but patients usually have a history of fever, headache, and systemic symptoms at the onset of disease as well as more continuous cough and frequent finding of rales on auscultation of the chest. Epidemics of *Mycoplasma* and *B. pertussis* in young adults can be difficult to distinguish on clinical grounds. Although pertussis often is included in the laboratory evaluation of young infants with afebrile pneumonia, *B. pertussis* is not associated with staccato cough (breath with every cough), purulent conjunctivitis, tachypnea, rales or wheezes that typify infection by *Chlamydia trachomatis,* or predominant lower respiratory tract signs that typify infection by respiratory syncytial virus. Unless an infant with pertussis has secondary pneumonia (and then appears ill), the findings on examination between paroxysms including respiratory rate are entirely normal.

Leukocytosis (15,000-100,000 cells/µL) caused by absolute lymphocytosis is characteristic in the catarrhal stage. Lymphocytes are of T- and B-lymphocyte origin and are normal small cells, rather than the large atypical lymphocytes seen with viral infections. Adults, partially immune children, and, occasionally, young infants may have less-impressive lymphocytosis. Absolute increase in neutrophils suggests a different diagnosis or secondary bacterial infection. Eosinophilia is not a manifestation of pertussis. A severe course and death are correlated with rapid-rise and extreme leukocytosis (median peak white blood cell count in fatal vs nonfatal cases, 94,000 vs 18,000/µL, respectively) and thrombocytosis (median peak platelet count in fatal vs nonfatal cases, 782,000 vs 556,000/µL, respectively). Chest radiographic findings are only mildly abnormal in the majority of hospitalized infants, showing perihilar infiltrate or edema (sometimes with a butterfly appearance) and variable atelectasis. Parenchymal consolidation suggests secondary bacterial infection. Pneumothorax, pneumomediastinum, and subcutaneous emphysema can be seen occasionally.

Current methods for confirmation of infection by *B. pertussis* (i.e., culture, polymerase chain reaction [PCR], and serology) have limitations in sensitivity, specificity, or practicality, and relative value depends on the setting, phase of disease, and purpose of use (e.g., as clinical diagnostic vs epidemiologic tool). For culture, careful attention must be directed to specimen collection, transport, and isolation technique. The specimen is obtained with deep nasopharyngeal aspiration or with the use of a flexible swab, preferably a Dacron or calcium alginate–tipped swab, held in the posterior nasopharynx for 15-30 sec (or until cough occurs). A 1% casamino acid liquid is acceptable for holding a specimen up to 2 hr; Stainer-Scholte broth or Regan-Lowe semisolid transport medium is used for longer transport periods, up to 4 days. The preferred isolation media are Regan-Lowe charcoal agar with 10% horse blood and 5-40 µg/mL cephalexin, and Stainer-Scholte media with cyclodextrin resins. Cultures are incubated at 35-37°C in a humid environment and examined daily for 7 days for slow-growing, tiny, glistening colonies. Direct fluorescent antibody testing of potential isolates using specific antibody for *B. pertussis* and *B. parapertussis* maximizes recovery rates. PCR testing on nasopharyngeal wash specimens has a sensitivity similar to that of culture and averts difficulties of isolation, but only standardized validated primers should be used. Results of culture and PCR are expected to be positive in unimmunized, untreated children during the catarrhal and early paroxysmal stages of disease. However, fewer than 20% of culture or PCR tests have positive results in partially or remotely immunized individuals tested in the paroxysmal stage. Serologic tests for detection of change in antibodies to *B. pertussis* antigens in acute and convalescent samples are the most sensitive tests in immunized individuals and are useful epidemiologically. A single serum sample showing immunoglobulin (Ig) G antibody to PT elevated >2 SD above the mean of the immunized population (>90 IU/mL) indicates recent symptomatic infection and usually is positive in the mid paroxysmal phase. Tests for IgA and IgM pertussis antibody, or antibody to antigens other than PT, are not reliable methods for serologic diagnosis of pertussis.

TREATMENT

Infants younger than 3 mo of age with suspected pertussis usually are admitted to hospital, as are many between 3 and 6 mo of age unless witnessed paroxysms are not severe, as well as are patients of any age if significant complications occur. Prematurely born young infants have a high risk for severe, potentially fatal disease, and children with underlying cardiac, pulmonary, muscular, or neurologic disorders have increased risk of poor outcome beyond infancy. Table 197-1 lists caveats in assessment and care of infants with pertussis. The specific, limited goals of hospitalization are to: (1) assess progression of disease and likelihood of life-threatening events at peak of disease; (2) maximize nutrition; (3) prevent or treat complications; and (4) educate parents in the natural history of the disease and in care that will be given at home. Heart rate, respiratory rate, and pulse oximetry are monitored continuously with alarm settings so that paroxysms can be witnessed and recorded by healthcare personnel. Detailed cough records and documentation of feeding, vomiting, and weight change provide data to assess severity. Typical paroxysms that are not life-threatening have the following features: duration <45 sec; red but not blue color change; tachycardia, bradycardia (not <60 beats/min in

Table 197-1 Caveats in Assessment and Care of Infants with Pertussis

- Infants with potentially fatal pertussis may appear well between episodes.
- A paroxysm must be witnessed before a decision is made between hospital and home care.
- Only analysis of carefully compiled cough record permits assessment of severity and progression of illness.
- Suctioning of nose, oropharynx, or trachea should not be performed on a "preventive" schedule.
- Feeding in the period following a paroxysm may be more successful than after napping.
- Family support begins at the time of hospitalization with empathy for the child's and family's experience to date, transfer of the burden of responsibility for the child's safety to the healthcare team, and delineation of assessments and treatments to be performed.
- Family education, recruitment as part of the team, and continued support after discharge are essential.

infants), or oxygen desaturation that spontaneously resolves at the end of the paroxysm; whooping or strength for brisk self-rescue at the end of the paroxysm; self-expectorated mucus plug; and posttussive exhaustion but not unresponsiveness. Assessing the need to provide oxygen, stimulation, or suctioning requires skilled personnel who can watchfully observe an infant's ability for self-rescue but who will intervene rapidly and expertly when necessary. The benefit of a quiet, dimly lighted, undisturbed, comforting environment cannot be overestimated or forfeited in a desire to monitor and intervene. Feeding children with pertussis is challenging. The risk of precipitating cough by nipple feeding does not warrant nasogastric, nasojejunal, or parenteral alimentation in most infants. The composition or thickness of formula does not affect the quality of secretions, cough, or retention. Large-volume feedings are avoided.

Within 48-72 hr, the direction and severity of disease are obvious from analysis of recorded information. Many infants have marked improvement upon hospitalization and antibiotic therapy, especially if they are hospitalized early in the course of disease or have been removed from aggravating environmental smoke, excessive stimulation, or a dry or polluting heat source. Hospital discharge is appropriate if over a 48-hr period disease severity is unchanged or diminished, intervention is not required during paroxysms, nutrition is adequate, no complication has occurred, and parents are adequately prepared for care at home. Apnea and seizures occur in the incremental phase of illness and in patients with complicated disease. Portable oxygen, monitoring, or suction apparatus should not be needed at home.

Infants who have apnea, paroxysms that repeatedly lead to life-threatening events despite passive delivery of oxygen, or respiratory failure require intubation, pharmaceutically induced paralysis, and ventilation.

Antibiotics

An antimicrobial agent always is given when pertussis is suspected or confirmed, primarily to limit the spread of infection and secondarily for possible clinical benefit. Macrolides are preferred agents and are similar to one another in terms of in vitro activity (Table 197-2). Resistance has been reported rarely. A 7-10–fold relative risk for infantile hypertrophic pyloric stenosis has been reported in neonates treated with orally administered erythromycin. Azithromycin is the preferred agent in all age groups; rare cases of infantile hypertrophic pyloric stenosis have followed its use in neonates. All young infants treated with any macrolide should be monitored for symptoms of pyloric stenosis. Benefits of postexposure prophylaxis for infants far outweigh risk of infantile hypertrophic pyloric stenosis. The FDA also warns of risk of fatal heart rhythms with use of azithromycin in patients already at risk for cardiovascular events, especially those with prolongation of the QT interval.

Adjunct Therapies

No rigorous clinical trial has demonstrated a beneficial effect of β_2-adrenergic stimulants such as salbutamol and albuterol. Fussing associated with aerosol treatment triggers paroxysms. No randomized, blinded clinical trial of sufficient size has been performed to evaluate the usefulness of corticosteroids in the management of pertussis; their clinical use is not warranted. A randomized, double blind, placebo-controlled trial of pertussis intravenous immunoglobulin was halted prematurely because of expiration/lack of additional supply of study product; there was no indication of clinical benefit. Standard intravenous immunoglobulin has not been studied and should not be used for treatment or prophylaxis.

Isolation

Patients with suspected pertussis are placed in isolation with droplet precautions to reduce close respiratory or mucous membrane contact with respiratory secretions. All healthcare personnel should wear a mask upon entering the room. Screening for cough should be performed upon entrance of patients to emergency departments, offices, and clinics to begin isolation immediately and until 5 days after initiation of macrolide therapy. Children and staff with pertussis in childcare facilities or schools should be excluded until macrolide has been taken for 5 days.

Care of Household and Other Close Contacts

A macrolide agent should be given promptly to all household contacts and other close contacts, such as those in daycare, regardless of age, history of immunization, and symptoms (see Table 197-2). The same drugs and age-related doses used for treatment are used for prophylaxis. Visitation and movement of coughing family members in the

Table 197-2 Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis, By Age Group

	Primary Agents		Alternate Agent*	
AGE GROUP	AZITHROMYCIN	ERYTHROMYCIN	CLARITHROMYCIN	TMP-SMZ
<1 mo	Recommended agent 10 mg/kg/day in a single dose for 5 days (only limited safety data available)	Not preferred Erythromycin is substantially associated with infantile hypertrophic pyloric stenosis Use if azithromycin is unavailable; 40-50 mg/kg/day in 4 divided doses for 14 days	Not recommended (safety data unavailable)	Contraindicated for infants <2 mo of age (risk for kernicterus)
1-5 mo	10 mg/kg/day in a single dose for 5 days	40-50 mg/kg/day in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses for 7 days	Contraindicated at age <2 mo For infants age ≥2 mo: TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in 2 divided doses for 14 days
Infants age ≥6 mo and children	10 mg/kg in a single dose on day 1 (maximum: 500 mg), then 5 mg/kg/day (maximum: 250 mg) on days 2-5	40-50 mg/kg/day (maximum: 2 g/day) in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses (maximum: 1 g/day) for 7 days	TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in 2 divided doses (maximum TMP: 320 mg/day) for 14 days
Adults	500 mg in a single dose on day 1 then 250 mg/day on days 2-5	2 g/day in 4 divided doses for 14 days	1 g/day in 2 divided doses for 7 days	TMP 320 mg/day, SMZ 1,600 mg/day in 2 divided doses for 14 days

*Trimethoprim-sulfamethoxazole (TMP-SMZ) can be used as an alternative agent to macrolides in patients age ≥2 mo who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis*.

From Centers for Disease Control and Prevention (CDC): Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines, MMWR Morb Mortal Wkly Rep *54:1–16, 2005.*

hospital must be assiduously controlled until a macrolide has been taken for 5 days. In close contacts younger than 7 yr of age who have received fewer than 4 doses of pertussis-containing vaccines, DTaP should be initiated or continued to complete the recommended series. Children younger than 7 yr of age who received a 3rd dose more than 6 mo before exposure or a 4th dose 3 yr or more before exposure should receive a DTaP booster dose. Individuals 9 yr of age or older should be given Tdap if they have not received Tdap previously. Unmasked healthcare personnel exposed to untreated cases should be evaluated for postexposure prophylaxis and follow-up. Coughing healthcare personnel with or without known exposure to pertussis should be promptly evaluated for pertussis.

COMPLICATIONS

Infants younger than 6 mo of age have excessive mortality and morbidity; infants younger than 2 mo of age have the highest reported rates of pertussis-associated hospitalization (82%), pneumonia (25%), seizures (4%), encephalopathy (1%), and death (1%). Infants younger than 4 mo of age account for 90% of cases of fatal pertussis. Preterm birth and young maternal age are significantly associated with fatal pertussis. Neonates with pertussis have substantially longer hospitalizations, greater need for oxygen, and greater need for mechanical ventilation than neonates with viral respiratory tract infection.

The principal complications of pertussis are apnea, secondary infections (such as otitis media and pneumonia), and physical sequelae of forceful coughing. Fever, tachypnea or respiratory distress between paroxysms, and absolute neutrophilia are clues to pneumonia. Expected pathogens include *Staphylococcus aureus, Streptococcus pneumoniae,* and bacteria of oropharyngeal flora. Increased intrathoracic and intraabdominal pressure during coughing can result in conjunctival and scleral hemorrhages, petechiae on the upper body, epistaxis, hemorrhage in the central nervous system and retina, pneumothorax and subcutaneous emphysema, and umbilical and inguinal hernias. Laceration of the lingual frenulum occurs occasionally.

The need for intensive care and mechanical ventilation usually is limited to infants younger than 3 mo of age and infants with underlying conditions. Respiratory failure from apnea may precipitate need for intubation and ventilation through the days when disease peaks; prognosis is good. Progressive pulmonary hypertension in very young infants and secondary bacterial pneumonia are severe complications of pertussis and are the usual causes of death. Pulmonary hypertension and cardiogenic shock with fatal outcome are associated with extreme elevations of lymphocyte and platelet counts. Autopsies in fatal cases show luminal aggregates of leukocytes in the pulmonary vasculature. Extracorporeal membrane oxygenation of infants with pertussis in whom mechanical ventilation failed has been associated with >80% fatality (questioning the advisability of this procedure). Exchange transfusion or leukapheresis, however, is associated with drops in lymphocyte and platelet counts, with recovery in several reported cases. Echocardiography should be performed in critically ill infants with pertussis to detect presence of pulmonary hypertension and to intervene expeditiously.

Central nervous system abnormalities occur at a relatively high frequency in pertussis and are almost always a result of hypoxemia or hemorrhage associated with coughing or apnea in young infants. Apnea or bradycardia or both may result from apparent laryngospasm or vagal stimulation just before a coughing episode, from obstruction during an episode, or from hypoxemia following an episode. Seizures usually are a result of hypoxemia, but hyponatremia from excessive secretion of antidiuretic hormone during pneumonia can occur. The only neuropathology documented in pertussis is parenchymal hemorrhage and ischemic necrosis.

Bronchiectasis has been reported rarely after pertussis. Children who have pertussis before the age of 2 yr may have abnormal pulmonary function into adulthood.

PREVENTION

Universal immunization of children with pertussis vaccine, beginning in infancy with reinforcing dose(s) through adolescence and adulthood, is central to the *control* of pertussis. *Prevention* of pertussis in young infants depends on universal maternal immunization during every pregnancy and focused full immunization of contacts, both children and adults of all ages (see Chapter 172).

DTaP Vaccines

Several diphtheria and tetanus toxoids combined with acellular pertussis vaccines (DTaP) or combination products currently are licensed in the United States for children younger than 7 yr of age. DTaP vaccines have fewer adverse effects than the vaccines containing whole-cell pertussis (DTP), which are not available in the United States but are given to infants and children in many other countries. Acellular pertussis vaccines all contain inactivated PT and 2 or more other bacterial components (filamentous hemagglutinin, Prn, and Fim 2 and 3). Clinical efficacy against severe pertussis, defined as paroxysmal cough for longer than 21 days, is approximately 85%. Mild local and systemic adverse events as well as more serious events (including high fever, persistent crying for 3 hr or longer, hypotonic hyporesponsive episodes, and seizures) occur significantly less frequently among infants who receive DTaP than in those who receive DTP vaccine. DTaP-containing vaccines can be administered simultaneously with any other vaccines used in standard schedules for children.

Four doses of DTaP should be administered during the 1st 2 yr of life, generally at ages 2, 4, 6, and 15-18 mo of age. The 4th dose may be administered as early as 12 mo of age, provided that 6 mo have elapsed since the 3rd dose. The 5th dose of DTaP is recommended for children at 4-6 yr of age; a 5th dose is not necessary if the 4th dose in the series is administered on or after the 4th birthday. DTaP should not be given to a neonate because of interference with subsequent infant immunizations, but commencement of vaccination at 6 wk of age, with monthly doses through the 3rd dose, can be considered in high-risk settings.

When feasible, the same DTaP product is recommended for all doses of the primary vaccination series. Local reactions increase in rate and severity with successive doses of DTaP, although never reaching the magnitude of reactions following similar doses of DTP. Swelling of the entire thigh or upper arm, sometimes accompanied by pain, erythema, and fever, has been reported in 2-3% of vaccinees after the 4th or 5th dose of a variety of DTaP products. Limitation of activity is less than might be expected. Swelling subsides spontaneously without sequelae. The pathogenesis is unknown. Extensive limb swelling after the 4th dose of DTaP usually is not associated with a similar reaction to the 5th dose and is not a contraindication to subsequent dose(s) of pertussis vaccines.

Exempting children from pertussis immunization should be considered only within the narrow limits as recommended. Exemptors have significantly increased risk for pertussis and play a role in outbreaks of pertussis among immunized populations. Although well-documented pertussis confers short-term protection, the duration of protection is unknown; immunization should be completed on schedule in children diagnosed with pertussis. Improper vaccine storage reduces immunity.

Tdap Vaccines

Two tetanus toxoid, reduced-diphtheria toxoid, and acellular pertussis antigen vaccine (Tdap) products were licensed in 2005 and were recommended universally in 2006 for use in individuals 11-18 yr of age and in older individuals as a single-dose booster vaccine to provide protection against tetanus, diphtheria, and pertussis. The preferred age for Tdap vaccination is 11-12 yr. Recommendations for Tdap have expanded through 2012. All adolescents and adults of any age (including 65 yr of age and older) who have not received Tdap should receive a single dose of Tdap regardless of interval since Td. Pregnant women should be given Tdap during every pregnancy to provide passive antibody protection to the infant until administration of DTaP. Optimal timing of maternal Tdap is 26 through 37 wk of gestation but Tdap can be given at any time during pregnancy. Special effort should be made to ensure that contacts of infants have received DTaP or Tdap as is universally recommended. There is no recommendation for Tdap

revaccination of persons other than pregnant women. Relatively lower burden of pertussis in older adolescents and adults, modest Tdap effectiveness, and rapidly waning protection do not support cost-effectiveness of routine revaccination. There is no contraindication to concurrent administration of any other indicated vaccine. A single dose of Tdap is recommended for children 7-10 yr old who had incomplete pertussis vaccination prior to age 7 yr.

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Chapter 198
Salmonella

Zulfiqar Ahmed Bhutta

Salmonellosis is a common and widely distributed foodborne disease that is a global major public health problem affecting millions of individuals and resulting in significant mortality.

Salmonellae live in the intestinal tracts of warm- and cold-blooded animals. Some species are ubiquitous, whereas others are specifically adapted to a particular host.

The sequencing of the *Salmonella enterica* serovar Typhi (previously called *Salmonella typhi*) and *Salmonella typhimurium* genomes indicates an almost 95% genetic homology between the organisms. However, the clinical diseases caused by the 2 organisms differ considerably. Orally ingested salmonellae survive at the low pH of the stomach and evade the multiple defenses of the small intestine so as to gain access to the epithelium. Salmonellae preferentially enter M cells, which transport them to the lymphoid cells (T and B) in the underlying Peyer patches. Once across the epithelium, *Salmonella* serotypes that are associated with systemic illness enter intestinal macrophages and disseminate throughout the reticuloendothelial system. By contrast, nontyphoidal *Salmonella* (NTS) serovars induce an early local inflammatory response, which results in the infiltration of polymorphonuclear leukocytes into the intestinal lumen and diarrhea. The NTS serovars cause a gastroenteritis of rapid onset and brief duration, in contrast to typhoid fever, which has a considerably longer incubation period and duration of illness and in which systemic illness predominates and only a small proportion of children get diarrhea. These differences in the manifestations of infection by the 2 groups of pathogens, 1 predominantly causing intestinal inflammation and the other leading to systemic disease, may be related to specific genetic pathogenicity islands in the organisms. NTS serovars are unable to overcome defense mechanisms that limit bacterial dissemination from the intestine to systemic circulation in immunocompetent individuals and produce a self-limiting gastroenteritis. In contrast, *S. typhi* may possess unique virulence traits that allow it to overcome mucosal barrier functions in immunocompetent hosts, resulting in a severe systemic illness. Interestingly, the frequencies of typhoid fever in immunocompetent and immunocompromised individuals do not differ. Nonetheless, invasive nontyphoidal salmonellae strains have been noted in Africa among HIV-positive adults and among children with either HIV, malaria, or malnutrition. The presentation may be more like typhoid fever than gastroenteritis.

The nomenclature of *Salmonella* reflects the species name *Salmonella enterica* with a number of serovars. *Salmonella* nomenclature has undergone considerable alterations. The original taxonomy was based on clinical syndromes *(S. typhi, Salmonella choleraesuis, Salmonella paratyphi)*. With adoption of serologic analysis, a *Salmonella* species was defined subsequently as "a group of related fermentation phage-type," with the result that each *Salmonella* serovar was regarded as a species in itself. Although this classification is simplistic, its use until 2004 resulted in identification of 2,501 serovars of *Salmonella,* which led to the need for further categorization to aid communication among scientists, public health officials, and the public.

All *Salmonella* serovars form a single DNA hybridization group, a single species called *S. enterica* composed of several subspecies (Table 198-1). Each subspecies contains various serotypes defined by the O and H antigens. To further simplify the nomenclature for physicians and epidemiologists, the names for the common serovars are kept for subspecies I strains, which represent >99.5% of the *Salmonella* strains isolated from humans and other warm-blooded animals.

198.1 Nontyphoidal Salmonellosis

Zulfiqar Ahmed Bhutta

ETIOLOGY

Salmonellae are motile, nonsporulating, nonencapsulated, Gram-negative rods that grow aerobically and are capable of facultative anaerobic growth. They are resistant to many physical agents but can be killed by heating to 54.4°C (130°F) for 1 hr or 60°C (140°F) for 15 min. They remain viable at ambient or reduced temperatures for days and may survive for weeks in sewage, dried foodstuffs, pharmaceutical agents, and fecal material. Like other members of the family Enterobacteriaceae, *Salmonella* possesses somatic O antigens and flagellar H antigens.

With the exception of a few serotypes that affect only 1 or a few animal species, such as *Salmonella dublin* in cattle and *S. choleraesuis* in pigs, most serotypes have a broad host spectrum. Typically, such strains cause gastroenteritis that is often uncomplicated and does not need treatment but can be severe in the young, the elderly, and patients with weakened immunity. The causes are typically *Salmonella* Enteritidis (*Salmonella enterica* serotype Enteritidis) and *Salmonella* Typhimurium (*S. enterica* serotype Typhimurium), the 2 most important serotypes for salmonellosis transmitted from animals to humans.

Table 198-1 *Salmonella* Species, Subspecies, and Serotypes and Their Usual Habitats

SALMONELLA SPECIES AND SUBSPECIES	NO. OF SEROTYPES WITHIN SUBSPECIES	USUAL HABITAT
S. enterica subsp. *enterica* (I)	1504	Warm-blooded animals
S. enterica subsp. *salmae* (II)	502	Cold-blooded animals and the environment*
S. enterica subsp. *arizonae* (IIIa)	95	Cold-blooded animals and the environment*
S. enterica subsp. *diarizonae* (IIIb)	333	Cold-blooded animals and the environment*
S. enterica subsp. *houtenae* (IV)	72	Cold-blooded animals and the environment*
S. enterica subsp. *indica* (VI)	13	Cold-blooded animals and the environment*
S. bongori (V)	22	Cold-blooded animals and the environment*
Total	2541	

*Isolates of all species and subspecies have occurred in humans.

Data from Popoff MY, Bockemühl J, Gheesling LL. Supplement 2002 (No. 46) to the Kauffmann-White scheme. Res Microbiol 155:568-570, 2004.

Nontyphoidal salmonellae have emerged as a major cause of bacteremia in Africa, especially among populations with a high incidence of HIV infection.

EPIDEMIOLOGY

Salmonellosis constitutes a major public health burden and represents a significant cost to society in many countries. Typhoid fever caused by this organism is a global problem, with more than 27 million cases worldwide each year, culminating in an estimated 217,000 deaths. Although there is little information on the epidemiology and the burden of *Salmonella* gastroenteritis in developing countries, *Salmonella* infections are recognized as major causes of childhood diarrheal illness. With the growing burden of HIV infections and malnutrition in Africa, NTS bacteremic infections have emerged as a major cause of morbidity and mortality among children and adults.

NTS infections have a worldwide distribution, with an incidence proportional to the standards of hygiene, sanitation, availability of safe water, and food preparation practices. In the developed world, the incidence of *Salmonella* infections and outbreaks has increased several-fold over the past few decades, which may be related to modern practices of mass food production that increase the potential for epidemics. The incidence of infections with NTS serovars, such as *S. enterica* serovar Typhimurium and *S.* Enteritidis cause a significant disease burden, with an estimated 93.8 million cases worldwide and 155,000 deaths each year. *Salmonella* gastroenteritis accounts for more than half of all episodes of bacterial diarrhea in the United States, with incidence peaks at the extremes of ages, among young infants and the elderly. Most human infections have been caused by *S.* Enteritidis; the prevalence of this organism has decreased over the past decade, with *S.* Typhimurium overtaking it in some countries.

The rise in *Salmonella* infections in many parts of the world over the past 3 decades may also be related to intensive animal husbandry practices, which selectively promote the rise of certain strains, especially drug-resistant varieties that emerge in response to the use of antimicrobials in food animals. Poultry products were traditionally regarded as a common source of salmonellosis, but consumption of a range of foods is now associated with outbreaks, including fruits and vegetables. Although this change in epidemiology may be related to selective pressure from the use of antimicrobials, there may be other factors, such as the rise of strains with a selective propensity to develop resistance and virulence. It appears that multidrug-resistant strains of *Salmonella* are more virulent than susceptible strains and that poorer outcome does not simply relate to the delay in treatment response because of empirical choice of an ineffective antibiotic. Strains of multidrug-resistant *Salmonella,* such as *S.* Typhimurium phage type DT104, harbor a genomic island that contains many of the drug-resistance genes. It is possible that these integrons also contain genes that encode virulence factors. The global spread of multidrug-resistant *S.* Typhimurium phage type DT104 in animals and humans may be related to the growing use of antimicrobials and may be facilitated by international and national trade of infected animals.

Several risk factors are associated with outbreaks of *Salmonella* infections. Animals constitute the principal source of human NTS disease, and cases have occurred in which individuals have had contact with infected animals, including domestic animals such as cats, dogs, reptiles, pet rodents, and amphibians. Specific serotypes may be associated with particular animal hosts; children with *S. enterica* serovar Marina typically have exposure to pet lizards. NTS serovars usually cause self-limiting diarrhea with secondary bacteremia occurring in less than 10% of patients. The NTS serovars have a broad host range, including poultry and cattle, and NTS infection is commonly from food poisoning in developed countries.

Domestic animals probably acquire the infection in the same way that humans do, through consumption of contaminated raw meat, poultry, or poultry-derived products. Animal feeds containing fishmeal or bone meal contaminated with *Salmonella* are an important source of infection for animals. Moreover, subtherapeutic concentrations of antibiotics are often added to animal feed to promote growth. Such practices promote the emergence of antibiotic-resistant bacteria, including *Salmonella,* in the gut flora of the animals, with subsequent contamination of their meat. There is strong evidence to link resistance of *S.* Typhimurium to fluoroquinolones with the use of this group of antimicrobials in animal feeds. Animal-to-animal transmission can occur, but most infected animals are asymptomatic.

An increasing number of produce-associated foodborne outbreaks in the United States that are associated with bacterial contamination are primarily from *Salmonella.* Although almost 80% of *Salmonella* infections are discrete, outbreaks can pose an inordinate burden on public health systems. During 1998-2008, a total of 1,491 outbreaks of *Salmonella* infections were reported to the Foodborne Disease Outbreak Surveillance System, and 80% of these were caused by a single serotype. Of the single-serotype outbreaks, 50% had an implicated food and 34% could be assigned to a single food commodity. Of the 47 serotypes reported, the 4 most common, causing more than two-thirds of the outbreaks, included Enteritidis, Typhimurium, Newport, and Heidelberg. Overall, eggs were the most commonly implicated food, followed by chicken, pork, beef, fruit, and turkey. *Salmonella* infections in chickens increase the risk for contamination of eggs, and both poultry and eggs are regarded as a dominant cause of common-source outbreaks. However, a growing proportion of *Salmonella* outbreaks are also associated with other food sources. The food sources include many fruits and vegetables, such as tomatoes, sprouts, watermelon, cantaloupe, lettuce, and mangoes.

In addition to the effect of antibiotic use in animal feeds, the relationship of *Salmonella* infections to prior antibiotic use among children in the previous month is well recognized. This increased risk for infection in people who have received antibiotics for an unrelated reason may be related to alterations in gut microbial ecology, which predispose them to colonization and infection with antibiotic-resistant *Salmonella* isolates. These resistant strains of *Salmonella* are also more virulent. The Centers for Disease Control and Prevention (CDC) reports resistance to ceftriaxone in approximately 3% of NTS tested and some level of resistance to ciprofloxacin in approximately 3% of isolates. Approximately 5% of NTS tested by the CDC are resistant to 5 or more types of drugs. Consequently, costs are also expected to be higher for resistant than for susceptible infections because of the severity of the former. Those patients are more likely to be hospitalized, and treatment is rendered less effective. The CDC is seeing some level of resistance to ciprofloxacin in two-thirds of *Salmonella* Typhi tested. The CDC has not yet detected resistance to ceftriaxone or azithromycin in the United States, but resistance to these antibiotics has been seen in other parts of the world.

Given the ubiquitous nature of the organism, nosocomial infections with NTS strains can also occur through contaminated equipment and diagnostic or pharmacologic preparations, particularly those of animal origin (pancreatic extracts, pituitary extracts, bile salts). Hospitalized children are at increased risk for severe and complicated *Salmonella* infections, especially with drug-resistant organisms.

PATHOGENESIS

The estimated number of bacteria that must be ingested to cause symptomatic disease in healthy adults is 10^6-10^8 *Salmonella* organisms. The gastric acidity inhibits multiplication of salmonellae, and most organisms are rapidly killed at gastric pH ≤ 2.0. Achlorhydria, buffering medications, rapid gastric emptying after gastrectomy or gastroenterostomy, and a large inoculum enable viable organisms to reach the small intestine. Neonates and young infants have hypochlorhydria and rapid gastric emptying, which contribute to their increased vulnerability to symptomatic salmonellosis. In infants who typically take fluids, the inoculum size required to produce disease is also comparatively smaller because of faster transit through the stomach.

Once they reach the small and large intestines, the ability of *Salmonella* organisms to multiply and cause infection depends on both the infecting dose and competition with normal flora. Prior antibiotic therapy may alter this relationship, as might factors such as coadministration of antimotility agents. The typical intestinal mucosal response to NTS infection is an enterocolitis with diffuse mucosal inflammation and edema, sometimes with erosions and microabscesses. *Salmonella*

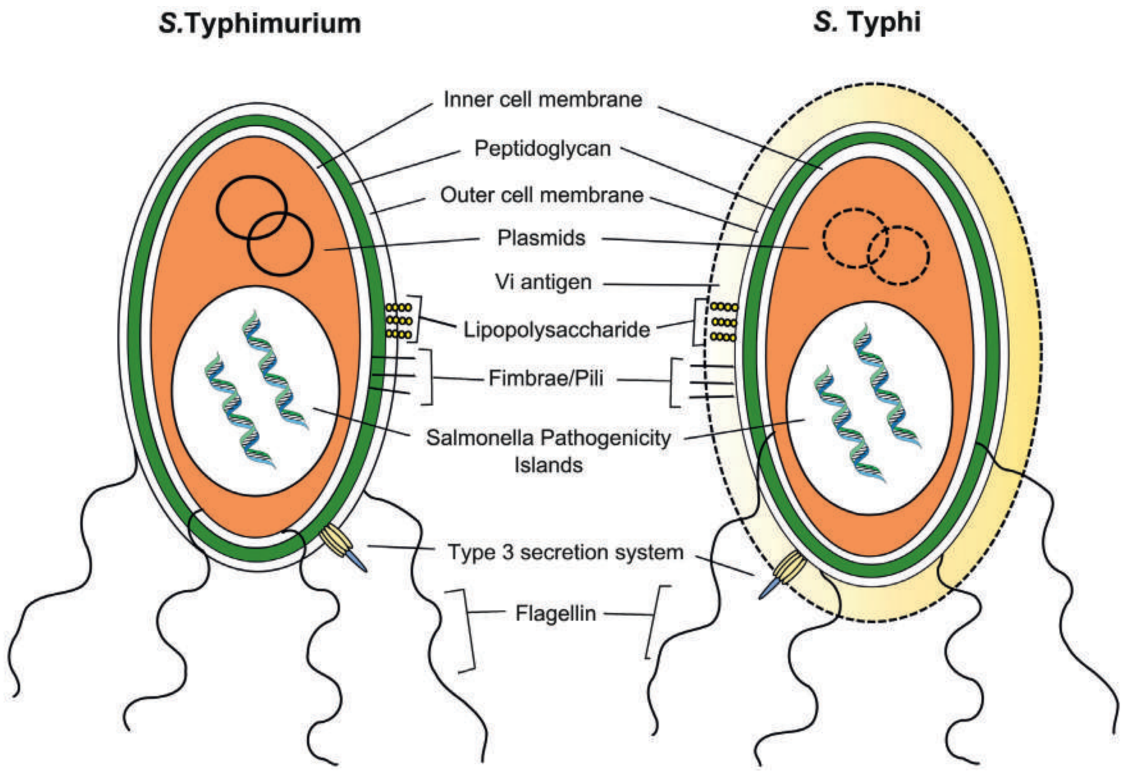

Figure 198-1 Overlapping and distinct virulence systems in *Salmonella typhi* and nontyphoidal *Salmonella. (From de Jong HK, Parry CM, van der Poll T, Wiersinga WJ. Host-pathogen interaction in invasive Salmonellosis.* PLoS Pathog *2012;8(10):e1002933.)*

organisms are capable of penetrating the intestinal mucosa, although destruction of epithelial cells and ulcers are usually not found. Intestinal inflammation with polymorphonuclear leukocytes and macrophages usually involves the lamina propria. Underlying intestinal lymphoid tissue and mesenteric lymph nodes enlarge and may demonstrate small areas of necrosis. Such lymphoid hypertrophy may cause interference with the blood supply to the gut mucosa. Hyperplasia of the reticuloendothelial system is also found within the liver and spleen. If bacteremia develops, it may lead to localized infection and suppuration in almost any organ.

Both *S.* Typhi and NTS possess overlapping and distinct virulence systems (Fig. 198-1). Although *S.* Typhimurium can cause systemic disease in humans, intestinal infection usually results in a localized enteritis that is associated with a secretory response in the intestinal epithelium. Intestinal infection also induces secretion of interleukin (IL)-8 from the basolateral surface and other chemoattractants from the apical surface, directing recruitment and transmigration of neutrophils into the gut lumen and thus preventing the systemic spread of the bacteria (Fig. 198-2).

Central to *S.* Typhimurium pathogenesis are 2 type III secretion systems encoded within the pathogenicity islands SPI-1 and SPI-2 that are responsible for the secretion and translocation of a set of bacterial proteins termed effectors into host cells with the intention of altering host cell physiology for bacterial entry and survival. Thus, once delivered by the type III secretion systems, the secreted effectors play critical roles in manipulating the host cell to allow for bacterial invasion, induction of inflammatory responses, and the assembly of an intracellular protective niche created for bacterial survival and replication. The type III secretion system encoded on SPI-1 mediates invasion of the intestinal epithelium, whereas the type III secretion system encoded on SPI-2 is required for survival within macrophages. In addition, the expression of strong agonists of innate pattern recognition receptors (lipopolysaccharide and flagellin) is important for triggering a Toll-like receptor (TLR)–mediated inflammatory response. These observations suggest that *S.* Typhimurium must have acquired additional factors that further modulate the host response during infection.

Salmonella species invade epithelial cells in vitro by a process of bacteria-mediated endocytosis involving cytoskeletal rearrangement, disruption of the epithelial cell brush-border, and the subsequent formation of membrane ruffles (Fig. 198-3). An adherent and invasive phenotype of *S.* Enterica is activated under conditions similar to those found in the human small intestine (high osmolarity, low oxygen). The invasive phenotype is mediated in part by SPI-1, a 40-kb region that encodes regulator proteins such as HilA, the type III secretion systems involved in invasion of epithelial cells, and a variety of other products. In humans the Toll-like receptor–dependent IL-12/interferon (IFN)-λ is a major immunoregulatory system that bridges innate and adaptive immunity and is responsible for restricting the systemic spread of nontyphoidal *Salmonella*.

Shortly following invasion of the gut epithelium, invasive *Salmonella* organisms encounter macrophages within the gut-associated lymphoid tissue. The interaction between *Salmonella* and macrophages results in alteration in the expression of a number of host genes, including those encoding proinflammatory mediators (inducible nitric oxide synthase, chemokines, IL-1β), receptors or adhesion molecules (tumor necrosis factor [TNF]-α receptor, CD40, intercellular adhesion molecule 1), and antiinflammatory mediators (transforming growth factor-β1 and transforming growth factor-β2). Other upregulated genes include those involved in cell death or apoptosis (intestinal epithelial cell protease, TNF-R1, Fas) and transcription factors (early growth response 1, IFN regulatory factor 1). *S.* Typhimurium can induce rapid macrophage death in vitro, which depends on the host cell protein caspase-1 and is mediated by the effector protein SipB (*Salmonella* invasion protein B). Intracellular *S.* Typhimurium is found within specialized vacuoles that have diverged from the normal endocytic pathway. This ability to survive within monocytes/macrophages is essential for *S.* Typhimurium to establish a systemic infection in the mouse. The mucosal proinflammatory response to *S.* Typhimurium infection and the subsequent recruitment of phagocytic cells to the site may also facilitate systemic spread of the bacteria.

Some virulence traits are shared by all salmonellae, but others are serotype restricted. These virulence traits have been defined in tissue

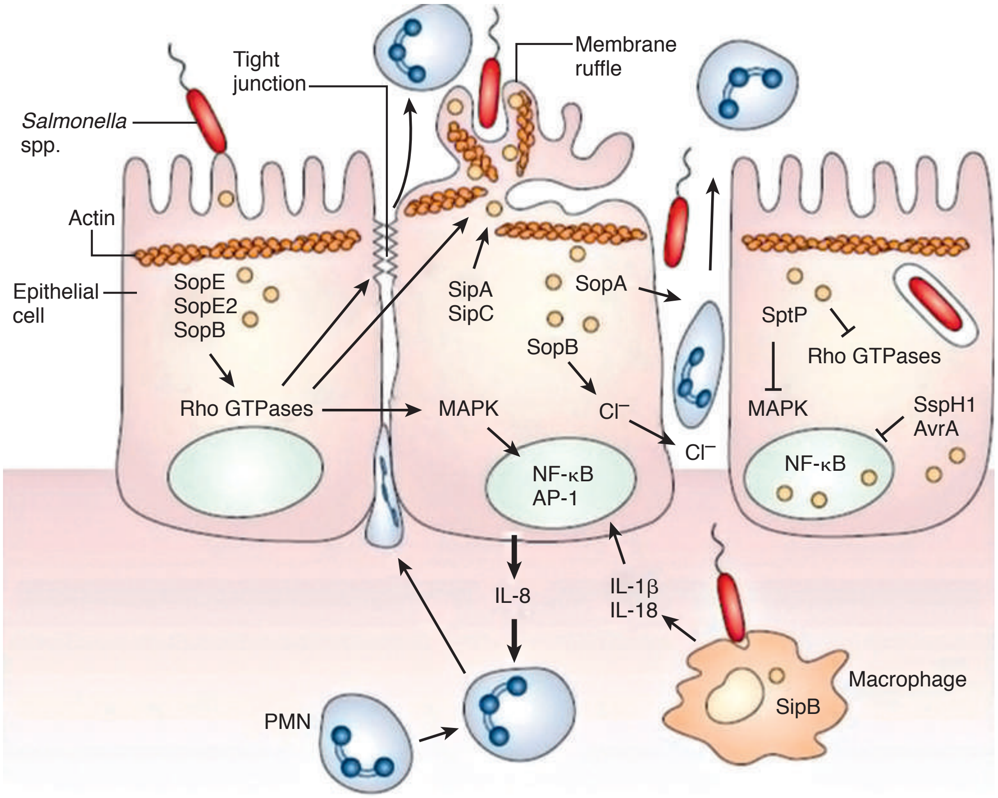

Figure 198-2 On contact with the epithelial cell, salmonellae assemble the *Salmonella* pathogenicity island 1-encoded type III secretion system (TTSS-1) and translocate effectors (*yellow spheres*) into the eukaryotic cytoplasm. Effectors such as SopE, SopE2, and SopB then activate host Rho guanosine triphosphatase (GTPase), resulting in the rearrangement of the actin cytoskeleton into membrane ruffles, induction of mitogen-activated protein kinase (MAPK) pathways, and destabilization of tight junctions. Changes in the actin cytoskeleton, which are further modulated by the actin-binding proteins SipA and SipC, lead to bacterial uptake. MAPK signaling activates the transcription factors activator protein-1 (AP-1) and nuclear factor-κB (NF-κB), which turn on production of the proinflammatory polymorphonuclear leukocyte (PMN) chemokine interleukin (IL)-8. SipB induces caspase-1 activation in macrophages, with the release of IL-1β and IL-18, augmenting the inflammatory response. In addition, SopB stimulates Cl^- secretion by its inositol phosphatase activity. The destabilization of tight junctions allows the transmigration of polymorphonuclear leukocytes (PMNs) from the basolateral to the apical surface, paracellular fluid leakage, and access of bacteria to the basolateral surface. However, the transmigration of PMNs also occurs in the absence of tight-junction disruption and is further promoted by SopA. The actin cytoskeleton is restored, and MAPK signaling is turned off by the enzymatic activities of SptP. This also results in the down-modulation of inflammatory responses, to which SspH1 and AvrA also contribute by inhibiting activation of NF-κB. *(From Haraga A, Ohlson MB, Miller SI: Salmonellae interplay with host cells,* Nat Rev Microbiol *6:53–66, 2008.)*

culture and murine models, and it is likely that clinical features of human *Salmonella* infection will eventually be related to specific DNA sequences. With most diarrhea-associated nontyphoidal salmonelloses, the infection does not extend beyond the lamina propria and the local lymphatics. Specific virulence genes are related to the ability to cause bacteremia. These genes are found significantly more often in strains of *S.* Typhimurium isolated from the blood than in strains recovered from stool. Although both *S. dublin* and *S. choleraesuis* have a greater propensity to rapidly invade the bloodstream with little or no intestinal involvement, the development of disease after infection with *Salmonella* depends on the number of infecting organisms, their virulence traits, and several host defense factors. Various host factors may also affect the development of specific complications or clinical syndromes (Table 198-2) and of these, HIV infections are assuming greater importance in Africa in all age groups.

Bacteremia is possible with any *Salmonella* serotype, especially in individuals with reduced host defenses and especially in those with altered reticuloendothelial or cellular immune function. Thus, children with HIV infection, chronic granulomatous disease, and leukemia are more likely to develop bacteremia after *Salmonella* infection, although the majority of children with *Salmonella* bacteremia in Africa are HIV-negative. Children with *Schistosoma mansoni* infection and hepatosplenic involvement, as well as chronic malarial anemia, are also at a

Table 198-2 Host Factors and Conditions Predisposing to the Development of Systemic Disease with Nontyphoidal *Salmonella* Strains
Neonates and young infants (≤3 mo of age)
HIV/AIDS
Other immunodeficiencies and chronic granulomatous disease
Immunosuppressive and corticosteroid therapies
Malignancies, especially leukemia and lymphoma
Hemolytic anemia, including sickle cell disease, malaria, and bartonellosis
Collagen vascular disease
Inflammatory bowel disease
Achlorhydria or use of antacid medications
Impaired intestinal motility
Schistosomiasis, malaria
Malnutrition

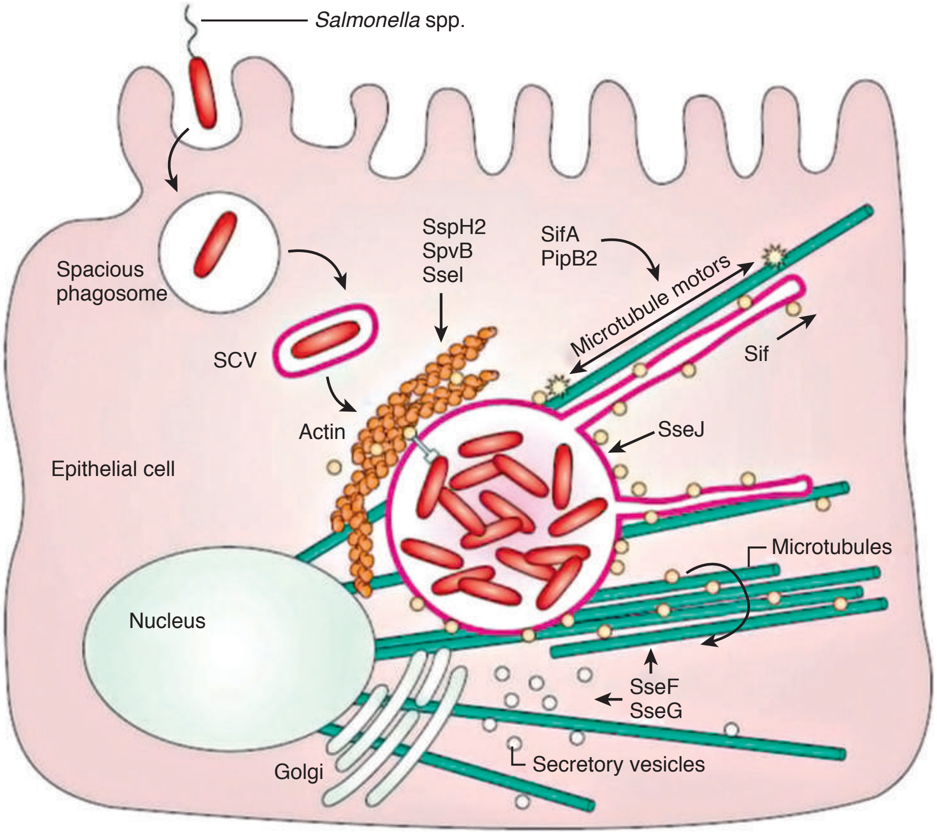

Figure 198-3 Formation of the *Salmonella*-containing vacuole (SCV) and induction of the *Salmonella* pathogenicity island 2 (SPI-2) type III secretion system (TTSS) within the host cell. Shortly after internalization by macropinocytosis, salmonellae are enclosed in a spacious phagosome that is formed by membrane ruffles. Later, the phagosome fuses with lysosomes, acidifies, and shrinks to become adherent around the bacterium, and is called the SCV. It contains the endocytic marker lysosomal-associated membrane protein 1 (LAMP-1; *purple*). The *Salmonella* SPI-2 is induced within the SCV and translocates effector proteins *(yellow spheres)* across the phagosomal membrane several hours after phagocytosis. The SPI-2 effectors SifA and PipB2 contribute to formation of *Salmonella*-induced filament along microtubules *(green)* and regulate microtubule motor *(yellow star shape)* accumulation on the Sif and the SCV. SseJ is a deacylase that is active on the phagosome membrane. SseF and SseG cause microtubule bundling adjacent to the SCV and direct Golgi-derived vesicle traffic toward the SCV. Actin accumulates around the SCV in a SPI-2 dependent manner, in which SspH2, SpvB, and SseI are thought to have a role. *(From Haraga A, Ohlson MB, Miller SI: Salmonellae interplay with host cells,* Nat Rev Microbiol *6:53–66, 2008.)*

greater risk for development of chronic salmonellosis. Children with sickle cell disease are at increased risk for *Salmonella* septicemia and osteomyelitis. This risk may be related to the presence of numerous infarcted areas in the gastrointestinal tract, bones, and reticuloendothelial system, as well as reduced phagocytic and opsonizing capacity of patients, which allow the organism to flourish.

Some inherited defects, such as IL-12 deficiency (IL-12β1 chain deficiency, IL-12p40 subunit deletion) are associated with increased risk for *Salmonella* infections, suggesting a key role for IL-12 in the clearance of *Salmonella.* IL-12 is produced by activated macrophages and is a potent inducer of IFN-γ by natural killer cells and T lymphocytes. Given the putative protective role of IL-12 against malarial infection, *Salmonella* infection of phagocytes may secondarily affect IL-12 production and thus produce a vicious circle of chronic malaria and *Salmonella* coinfection.

CLINICAL MANIFESTATIONS

Acute Enteritis

The most common clinical presentation of salmonellosis is acute enteritis. After an incubation period of 6-72 hr (mean: 24 hr), there is an abrupt onset of nausea, vomiting, and crampy abdominal pain, located primarily in the periumbilical area and right lower quadrant, followed by mild to severe watery diarrhea and sometimes by diarrhea containing blood and mucus. A large proportion of children with acute enteritis are febrile, although younger infants may exhibit a normal or subnormal temperature. Symptoms usually subside within 2-7 days in healthy children, and fatalities are rare. However, some children experience severe disease with a septicemia-like picture (high fever, headache, drowsiness, confusion, meningismus, seizures, abdominal distention). The stool typically contains a moderate number of polymorphonuclear leukocytes and occult blood. Mild leukocytosis may be detected.

Bacteremia

Although the precise incidence of bacteremia following *Salmonella* gastroenteritis is unclear, transient bacteremia can occur in 1-5% of children with *Salmonella* diarrhea. Bacteremia can occur with minimal associated symptoms in newborns and very young infants, but in older infants it typically follows gastroenteritis and can be associated with fever, chills, and septic shock. In patients with AIDS, recurrent septicemia appears despite antibiotic therapy, often with a negative stool culture result for *Salmonella* and sometimes with no identifiable focus of infection. NTS gastrointestinal infections commonly cause bacteremia in developing countries. High rates of invasive disease with *S.* Typhimurium and *S.* Enteritidis reported from Africa (38-70% of isolates) suggest an association with HIV infections and malaria.

Extraintestinal Focal Infections

Following bacteremia, salmonellae have the propensity to seed and cause focal suppurative infection of many organs. The most common focal infections involve the skeletal system, meninges, intravascular sites, and sites of preexisting abnormalities. The peak incidence of *Salmonella* meningitis is in infancy, and the infection may be

associated with a florid clinical course, high mortality, and neurologic sequelae in survivors.

COMPLICATIONS

Salmonella gastroenteritis can be associated with acute dehydration and complications that result from delayed presentation and inadequate treatment. Bacteremia in younger infants and immunocompromised individuals can have serious consequences and potentially fatal outcomes. *Salmonella* organisms can seed many organ systems, leading to osteomyelitis in children with sickle cell disease, among other infections. Reactive arthritis may follow *Salmonella* gastroenteritis, usually in adolescents with the HLA-B27 antigen.

In certain high-risk groups, especially those with impaired immunity, the course of *Salmonella* gastroenteritis may be more complicated. Neonates, infants younger than 6 mo, and children with primary or secondary immunodeficiency may have symptoms that persist for several weeks. The course of illness and complications may also be affected by coexisting pathologies. In children with AIDS, *Salmonella* infection frequently becomes widespread and overwhelming, causing multisystem involvement, septic shock, and death. In patients with inflammatory bowel disease, especially active ulcerative colitis, *Salmonella* gastroenteritis may lead to rapid development of toxic megacolon, bacterial translocation, and sepsis. In children with schistosomiasis, the *Salmonella* may persist and multiply within schistosomes, leading to chronic infection unless the schistosomiasis is effectively treated. Prolonged or intermittent bacteremia is associated with low-grade fever, anorexia, weight loss, diaphoresis, and myalgias and may occur in children with underlying problems and a reticuloendothelial system dysfunction such as hemolytic anemia or malaria.

DIAGNOSIS

Clinical features that are specific to *Salmonella* gastroenteritis and thus would allow differentiation from other bacterial causes of diarrhea are few. Definitive diagnosis of *Salmonella* infection is based on clinical correlation of the presentation and culture of and subsequent identification of *Salmonella* organisms from feces or other body fluids. In children with gastroenteritis, cultures of stools have higher yields than rectal swabs. In children with NTS gastroenteritis, prolonged fever lasting 5 or more days and young age should be recognized as risk factors closely associated with development of bacteremia. In patients with sites of local suppuration, aspirated specimens should be Gram-stained and cultured. *Salmonella* organisms grow well on nonselective or enriched media, such as blood agar, chocolate agar, and nutrient broth, but stool specimens containing mixed bacterial flora require a selective medium, such as MacConkey, xylose-lysine-deoxycholate, bismuth sulfite, or *Salmonella-Shigella* (SS) agar for isolation.

Although other rapid diagnostic methods, such as latex agglutination and immunofluorescence, have been developed for rapid diagnosis of *Salmonella* in cultures, there are few comparable tests for rapid serologic detection. Polymerase chain reaction techniques may offer a rapid alternative to classic cultures but are as yet not in widespread use in clinical settings.

TREATMENT

Appropriate therapy relates to the specific clinical presentation of *Salmonella* infection. In children with gastroenteritis, rapid clinical assessment, correction of dehydration and electrolyte disturbances, and supportive care are key (see Chapter 340). Antibiotics are not generally recommended for the treatment of isolated uncomplicated *Salmonella* gastroenteritis because they may suppress normal intestinal flora and prolong both the excretion of *Salmonella* and the remote risk for creating the chronic carrier state (usually in adults). However, given the risk for bacteremia in infants (<3 mo of age) and the risk of disseminated infection in high-risk groups with immune compromise (HIV, malignancies, immunosuppressive therapy, sickle cell anemia, immunodeficiency states), these children must receive an appropriate empirically chosen antibiotic until culture results are available (Table 198-3). The *S.* Typhimurium phage type DT104 strain is usually resistant to the following 5 drugs: ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. An increasing proportion of *S.* Typhimurium phage type DT104 isolates also have reduced susceptibility to fluoroquinolones. Given the higher mortality associated with multidrug-resistant *Salmonella* infections, it is necessary to perform susceptibility tests on all human isolates. Infections with suspected drug-resistant *Salmonella* should be closely monitored and treated with appropriate antimicrobial therapy.

Table 198-3 Treatment of *Salmonella* Gastroenteritis

ORGANISM AND INDICATION	DOSE AND DURATION OF TREATMENT
Salmonella infections in infants <3 mo of age or immunocompromised persons (in addition to appropriate treatment for underlying disorder)	Cefotaxime 100-200 mg/kg/day every 6-8 hr for 5-14 days *or* Ceftriaxone 75 mg/kg/day once daily for 7 days *or* Ampicillin 100 mg/kg/day every 6-8 hr for 7 days *or* Cefixime 15 mg/kg/day for 7-10 days

PROGNOSIS

Most healthy children with *Salmonella* gastroenteritis recover fully. However, malnourished children and children who do not receive optimal supportive treatment (see Chapters 58 and 340) are at risk for development of prolonged diarrhea and complications. Young infants and immunocompromised patients often have systemic involvement, a prolonged course, and extraintestinal foci. In particular, children with HIV infection and *Salmonella* infections can have a florid course.

After infection, NTS are excreted in feces for a median of 5 wk. A prolonged carrier state after nontyphoidal salmonellosis is rare (<1%) but may be seen in children with biliary tract disease and cholelithiasis after chronic hemolysis. Prolonged carriage of *Salmonella* organisms is rare in healthy children but has been reported in those with underlying immune deficiency. During the period of *Salmonella* excretion, the individual may infect others, directly by the fecal–oral route or indirectly by contaminating foods.

PREVENTION

Control of the transmission of *Salmonella* infections to humans requires control of the infection in the animal reservoir, judicious use of antibiotics in dairy and livestock farming, prevention of contamination of foodstuffs prepared from animals, and use of appropriate standards in food processing in commercial and private kitchens (Table 198-4). Because large outbreaks are often related to mass food production, it should be recognized that contamination of just 1 piece of machinery used in food processing may cause an outbreak; meticulous cleaning of equipment is essential. Clean water supply and education in handwashing and food preparation and storage are critical to reducing person-to-person transmission. *Salmonella* may remain viable when cooking practices prevent food from reaching a temperature greater than 65.5°C (150°F) for longer than 12 min. Parents should be advised of the risk of reptiles as pets in households with young infants.

In contrast to developed countries, relatively little is known about the transmission of NTS infections in developing countries, and it is likely that person-to-person transmission may be relatively more important in some settings. Although some vaccines have been used in animals, no human vaccine against NTS infections is currently available. Infections should be reported to public health authorities so that outbreaks can be recognized and investigated. Given the rapid rise of antimicrobial resistance among *Salmonella* isolates, it is imperative that there is rigorous regulation of the use of antimicrobials in animal feeds.

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Table 198-4	Recommendations for Preventing Transmission of *Salmonella* from Reptiles and Amphibians to Humans
Pet store owners, healthcare providers, and veterinarians should provide information to owners and potential purchasers of reptiles and amphibians about the risks for and prevention of salmonellosis from these pets.	
Persons at increased risk for infection or serious complications from salmonellosis (e.g., children <5 yr of age and immunocompromised persons) should avoid contact with reptiles and amphibians and any items that have been in contact with reptiles and amphibians.	
Reptiles and amphibians should be kept out of households that include children <5 yr of age or immunocompromised persons. A family expecting a child should remove any pet reptile or amphibian from the home before the infant arrives.	
Reptiles and amphibians should not be allowed in childcare centers.	
Persons should always wash their hands thoroughly with soap and water after handling reptiles and amphibians or their cages.	
Reptiles and amphibians should not be allowed to roam freely throughout a home or living area.	
Pet reptiles and amphibians should be kept out of kitchens and other food preparation areas. Kitchen sinks should not be used to bathe reptiles and amphibians or to wash their dishes, cages, or aquariums. If bathtubs are used for these purposes, they should be cleaned thoroughly and disinfected with bleach.	
Reptiles and amphibians in public settings (e.g., zoos and exhibits) should be kept from direct or indirect contact with patrons except in designated animal contact areas equipped with adequate handwashing facilities. Food and drink should not be allowed in animal contact areas.	

From the Centers for Disease Control and Prevention (CDC): Reptile-associated salmonellosis—selected states, 1998-2002, MMWR Morb Mortal Wkly Rep *52:1206–1210, 2003.*

198.2 Enteric Fever (Typhoid Fever)

Zulfiqar Ahmed Bhutta

Enteric fever (more commonly termed *typhoid fever*) remains endemic in many developing countries. Given the ease of modern travel, cases are regularly reported from most developed countries, usually from returning travelers.

ETIOLOGY

Typhoid fever is caused by *S. enterica* serovar Typhi (*S.* Typhi), a Gram-negative bacterium. A very similar but often less-severe disease is caused by *Salmonella* Paratyphi A and rarely by *S.* Paratyphi B (Schotmulleri) and *S.* Paratyphi C (Hirschfeldii). The ratio of disease caused by *S.* Typhi to that caused by *S.* Paratyphi is approximately 10 : 1, although the proportion of *S.* Paratyphi A infections is increasing in some parts of the world for reasons that are unclear. Although *S.* Typhi shares many genes with *Escherichia coli* and at least 95% of genes with *S.* Typhimurium, several unique gene clusters known as *pathogenicity islands* and other genes have been acquired during evolution. The inactivation of single genes, as well as the acquisition or loss of single genes or large islands of DNA, may have contributed to host adaptation and restriction of *S.* Typhi.

One of the most specific gene products is the polysaccharide capsule Vi (virulence), which is present in approximately 90% of all freshly isolated *S.* Typhi and has a protective effect against the bactericidal action of the serum of infected patients.

EPIDEMIOLOGY

It is estimated that more than 26.9 million typhoid fever cases occur annually, of which 1% result in death. The vast majority of this disease burden is witnessed in Asia. Additionally, an estimated 5.4 million cases caused by paratyphoid occur each year. In 2010, 13.5 million cases of typhoid fever were recorded, and both typhoid and paratyphoid fevers together accounted for more than 12 million disability-adjusted life years. The mortality caused by typhoid fever in the same year was found to be 7.2 per 100,000 population for the sub-Saharan region of Africa. Given the paucity of microbiologic facilities in developing countries, these figures may be more representative of the clinical syndrome rather than of culture-proven disease. In most developed countries, the incidence of typhoid fever is <15 cases per 100,000 population, with most cases occurring in travelers. In contrast, the incidence may vary considerably in the developing world, with estimated rates ranging from 100-1,000 cases per 100,000 population. There are significant differences in the age distribution and population at risk. Population-based studies from South Asia also indicate that the age-specific incidence of typhoid fever may be highest in children younger than 5 yr of age, in association with comparatively higher rates of complications and hospitalization.

Typhoid fever is notable for the emergence of drug resistance. Following sporadic outbreaks of chloramphenicol-resistant *S.* Typhi infections, many strains of *S.* Typhi have developed plasmid-mediated multidrug resistance to all 3 of the primary antimicrobials: ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. There is also a considerable increase in nalidixic acid–resistant isolates of *S.* Typhi, as well as the emergence of fluoroquinolone-resistant isolates. Nalidixic acid–resistant isolates first emerged in Southeast Asia and India, and now account for the majority of travel-associated cases of typhoid fever in the United States.

S. Typhi is highly adapted to infection of humans to the point that it has lost the ability to cause transmissible disease in other animals. The discovery of the large number of pseudogenes in *S.* Typhi suggests that the genome of this pathogen has undergone degeneration to facilitate a specialized association with the human host. Thus, direct or indirect contact with an infected person (sick or chronic carrier) is a prerequisite for infection. Ingestion of foods or water contaminated with *S.* Typhi from human feces is the most common mode of transmission, although waterborne outbreaks as a consequence of poor sanitation or contamination have been described in developing countries. In other parts of the world, oysters and other shellfish cultivated in water contaminated by sewage and the use of night soil as fertilizer may also cause infection.

PATHOGENESIS

Enteric fever occurs through the ingestion of the organism, and a variety of sources of fecal contamination have been reported, including street foods and contamination of water reservoirs.

Human volunteer experiments established an infecting dose of about 10^5-10^9 organisms, with an incubation period ranging from 4-14 days, depending on the inoculating dose of viable bacteria. After ingestion, *S.* Typhi organisms are thought to invade the body through the gut mucosa in the terminal ileum, possibly through specialized antigen-sampling cells known as *M cells* that overlie gut-associated lymphoid tissues, through enterocytes, or via a paracellular route. *S.* Typhi crosses the intestinal mucosal barrier after attachment to the microvilli by an intricate mechanism involving membrane ruffling, actin rearrangement, and internalization in an intracellular vacuole. In contrast to NTS, *S.* Typhi expresses virulence factors that allow it to downregulate the pathogen recognition receptor–mediated host inflammatory response. Within the Peyer patches in the terminal ileum, *S.* Typhi can traverse the intestinal barrier through several mechanisms, including the M cells in the follicle-associated epithelium, epithelial cells, and dendritic cells. At the villi, *Salmonella* can enter through the M cells or by passage through or between compromised epithelial cells.

On contact with the epithelial cell, S. typhi assembles type III secretion system encoded on SPI-1 and translocates effectors into the cytoplasm. These effectors activate host Rho guanosine triphosphatases, resulting in the rearrangement of the actin cytoskeleton into membrane ruffles, induction of mitogen-activated protein kinase pathways,

and destabilization of tight junctions. Changes in the actin cytoskeleton are further modulated by the actin-binding proteins SipA and SipC and lead to bacterial uptake. Mitogen-activated protein kinase signaling activates the transcription factors activator protein-1 and nuclear factor-κB, which turn on production of IL-8. The destabilization of tight junctions allows the transmigration of polymorphonuclear leukocytes from the basolateral surface to the apical surface, paracellular fluid leakage, and access of bacteria to the basolateral surface. Shortly after internalization of *S.* Typhi by macropinocytosis, salmonellae are enclosed in a spacious phagosome that is formed by membrane ruffles. Later, the phagosome fuses with lysosomes, acidifies, and shrinks to become adherent around the bacterium, forming the *Salmonella*-containing vacuole. type III secretion system encoded on SPI-2 is induced within the *Salmonella*-containing vacuole and translocates effector proteins SifA and PipB2, which contribute to *Salmonella*-induced filament formation along microtubules. The *S.* Typhi toxin has been isolated and characterized composed of 2 A subunits, PltA and CdtB, which are homologs of the A subunits of the pertussis and cytolethal distending toxins, respectively. Its single B subunit, PltB, is a homolog of 1 of the components of the heteropentameric B subunit of pertussis toxin. Although the cellular targets of the adenosine diphosphate–ribosyl transferase activity of PltA have not yet been identified, CdtB is a DNase that inflicts DNA damage and induces cell-cycle arrest. *S.* Typhi produces typhoid toxin only within mammalian cells, and the toxin is then ferried to the extracellular environment by a unique transport mechanism that involves vesicle carrier intermediates (Fig. 198-4). These findings open the door to future opportunities for developing diagnostic and preventive strategies.

After passing through the intestinal mucosa, *S.* Typhi organisms enter the mesenteric lymphoid system and then pass into the bloodstream via the lymphatics. This primary bacteremia is usually asymptomatic, and blood culture results are frequently negative at this stage of the disease. The bloodborne bacteria are disseminated throughout the body and are thought to colonize the organs of the reticuloendothelial system, where they may replicate within macrophages. After a period of bacterial replication, *S.* Typhi organisms are shed back into the blood, causing a secondary bacteremia that coincides with the onset of clinical symptoms and marks the end of the incubation period.

In vitro studies with human cell lines have shown qualitative and quantitative differences in the epithelial cell response to *S.* Typhi and *S.* Typhimurium with regard to cytokine and chemokine secretion. Thus, by avoiding the triggering of an early inflammatory response in the gut, *S.* Typhi could instead colonize deeper tissues and organ systems. Infection with *S.* Typhi produces an inflammatory response in the deeper mucosal layers and underlying lymphoid tissue, with hyperplasia of Peyer patches and subsequent necrosis and sloughing of overlying epithelium. The resulting ulcers can bleed but usually heal without scarring or stricture formation. The inflammatory lesion may occasionally penetrate the muscularis and serosa of the intestine and produce perforation. The mesenteric lymph nodes, liver, and spleen are hyperemic and generally have areas of focal necrosis as well. A mononuclear response may be seen in the bone marrow in association with areas of focal necrosis. The morphologic changes of *S.* Typhi infection are less prominent in infants than in older children and adults.

It is thought that several virulence factors, including type III secretion system encoded on SPI-2, may be necessary for the virulence properties and ability to cause systemic infection. The surface Vi polysaccharide capsular antigen found in *S.* Typhi interferes with phagocytosis by preventing the binding of C3 to the surface of the bacterium. The ability of organisms to survive within macrophages after phagocytosis is an important virulence trait encoded by the PhoP regulon and may be related to metabolic effects on host cells. The occasional occurrence of diarrhea may be explained by the presence of a toxin related to cholera toxin and *E. coli* heat-labile enterotoxin. The clinical syndrome of fever and systemic symptoms is produced by a release of proinflammatory cytokines (IL-6, IL-1β, and TNF-α) from the infected cells.

In addition to the virulence of the infecting organisms, host factors and immunity may also play an important role in predisposition to infection. There is an association between susceptibility to typhoid fever and human genes within the major histocompatibility complex class II and class III loci. Patients who are infected with HIV are at significantly higher risk for clinical infection with *S.* Typhi and *S.* Paratyphi. Similarly, patients with *Helicobacter pylori* infection have an increased risk of acquiring typhoid fever.

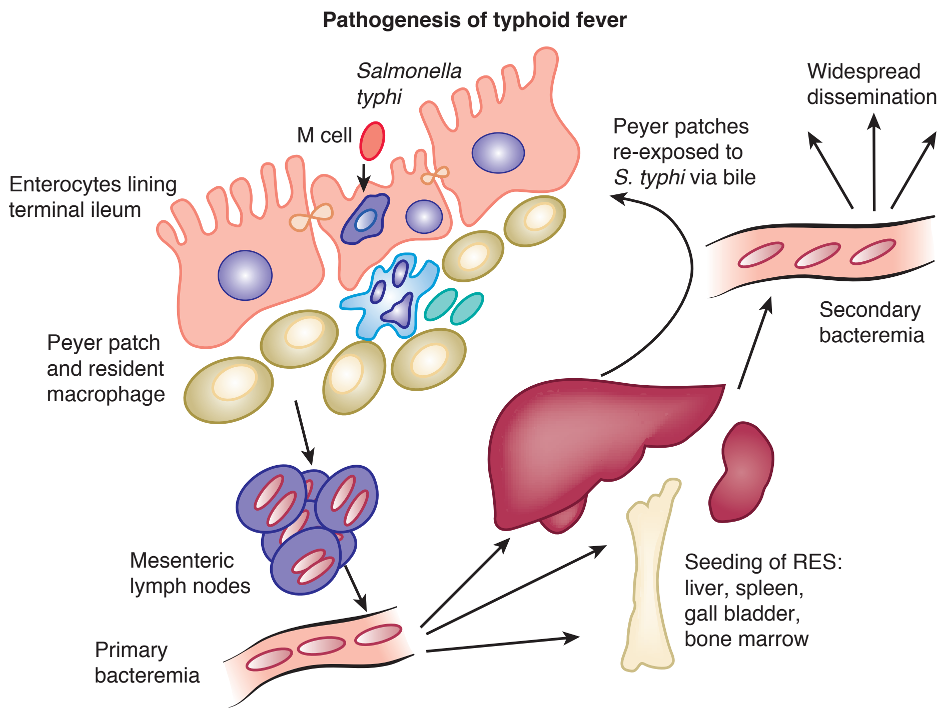

Figure 198-4 Pathogenesis of typhoid fever. *RES*, reticuloendothelial system. *(Adapted from Richens J: Typhoid fever. In Cohen J, Powderly WG, Opal SM, editors:* Infectious diseases, *ed 2, London, 2004, Mosby, pp. 1561–1566.)*

Table 198-5 Common Clinical Features of Typhoid Fever in Children*

FEATURE	RATE (%)
High-grade fever	95
Coated tongue	76
Anorexia	70
Vomiting	39
Hepatomegaly	37
Diarrhea	36
Toxicity	29
Abdominal pain	21
Pallor	20
Splenomegaly	17
Constipation	7
Headache	4
Jaundice	2
Obtundation	2
Ileus	1
Intestinal perforation	0.5

*Data collected in Karachi, Pakistan, from 2,000 children.

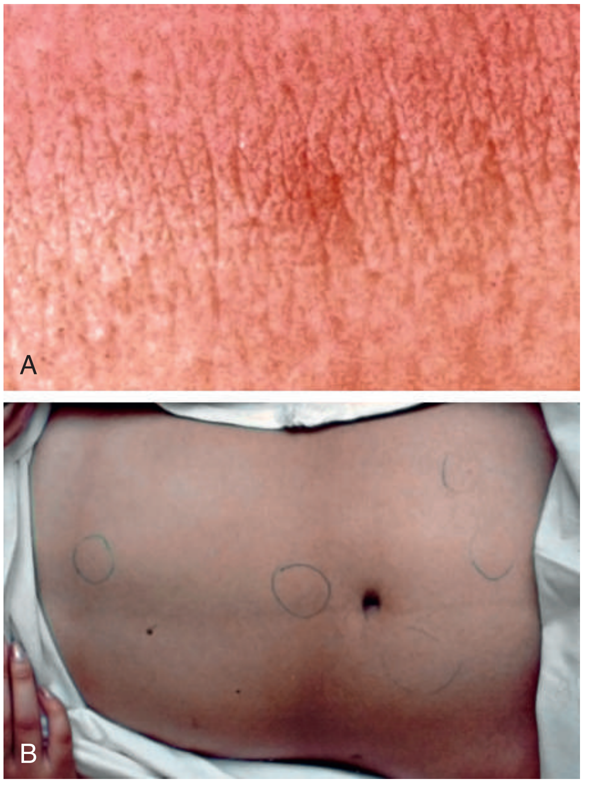

Figure 198-5 **A,** A rose spot in a volunteer with experimental typhoid fever. **B,** A small cluster of rose spots is usually located on the abdomen. These lesions may be difficult to identify, especially in dark-skinned people. *(From Huang DB, DuPont HL: Problem pathogens: extra-intestinal complications of* Salmonella enterica *serotype Typhi infection,* Lancet Infect Dis *5:341–348, 2005.)*

CLINICAL FEATURES

The incubation period of typhoid fever is usually 7-14 days but depends on the infecting dose and ranges between 3 and 30 days. The clinical presentation varies from a mild illness with low-grade fever, malaise, and slight, dry cough to a severe clinical picture with abdominal discomfort and multiple complications.

Many factors influence the severity and overall clinical outcome of the infection. They include the duration of illness before the initiation of appropriate therapy, choice of antimicrobial treatment, age, previous exposure or vaccination history, virulence of the bacterial strain, quantity of inoculum ingested, and several host factors affecting immune status.

The presentation of typhoid fever may also differ according to age. Although data from South America and parts of Africa suggest that typhoid may manifest as a mild illness in young children, presentation may vary in different parts of the world. There is emerging evidence from south Asia that the presentation of typhoid may be more dramatic in children younger than 5 yr of age, with comparatively higher rates of complications and hospitalization. Diarrhea, toxicity, and complications such as disseminated intravascular coagulopathy are also more common in infancy, resulting in higher case fatality rates. However, some of the other features and complications of typhoid fever seen in adults, such as relative bradycardia, neurologic manifestations, and gastrointestinal bleeding, are rare in children.

Typhoid fever usually manifests as high-grade fever with a wide variety of associated features, such as generalized myalgia, abdominal pain, hepatosplenomegaly, abdominal pain, and anorexia (Table 198-5). In children, diarrhea may occur in the earlier stages of the illness and may be followed by constipation. In the absence of localizing signs, the early stage of the disease may be difficult to differentiate from other endemic diseases such as malaria and dengue fever. The fever may rise gradually, but the classic stepladder rise of fever is relatively rare. In approximately 25% of cases, a macular or maculopapular rash (rose spots) may be visible around the 7th-10th day of the illness, and lesions may appear in crops of 10-15 on the lower chest and abdomen and last 2-3 days (Fig. 198-5). These lesions may be difficult to see in dark-skinned children. Patients managed as outpatients present with fever (99%) but have less emesis, diarrhea, hepatomegaly, splenomegaly, and myalgias than patients who require admission to the hospital.

The presentation of typhoid fever may be tempered by coexisting morbidities and early diagnosis and administration of antibiotics. In malaria-endemic areas and in parts of the world where schistosomiasis is common, the presentation of typhoid may also be atypical. It is also recognized that multidrug-resistant *S.* Typhi infection is a more severe clinical illness with higher rates of toxicity, complications, and case fatality rates, which may be related to the greater virulence as well as higher numbers of circulating bacteria. The emergence of typhoid infections resistant to nalidixic acid and fluoroquinolones is associated with higher rates of morbidity and treatment failure. These findings may have implications for treatment algorithms, especially in endemic areas with high rates of multidrug-resistant and nalidixic acid– or fluoroquinolone-resistant typhoid.

If no complications occur, the symptoms and physical findings gradually resolve within 2-4 wk; however, the illness may be associated with malnutrition in a number of affected children. Although enteric fever caused by *S.* Paratyphi organisms has been classically regarded as a milder illness, there have been several outbreaks of infection with drug-resistant *S.* Paratyphi A, suggesting that paratyphoid fever may also be severe, with significant morbidity and complications.

COMPLICATIONS

Although altered liver function is found in many patients with enteric fever, clinically significant hepatitis, jaundice, and cholecystitis are relatively rare and may be associated with higher rates of adverse outcome. Intestinal hemorrhage (<1%) and perforation (0.5-1%) are infrequent among children. Intestinal perforation may be preceded by a marked increase in abdominal pain (usually in the right lower quadrant), tenderness, vomiting, and features of peritonitis. Intestinal

Table 198-6 Extraintestinal Infectious Complications of Typhoid Fever Caused By *Salmonella enterica* Serotype Typhi

ORGAN SYSTEM INVOLVED	PREVALENCE (%)	RISK FACTORS	COMPLICATIONS
Central nervous system	3-35	Residence in endemic region, malignancy, endocarditis, congenital heart disease, paranasal sinus infections, pulmonary infections, meningitis, trauma, surgery, and osteomyelitis of the skull	Encephalopathy, cerebral edema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient parkinsonism, motor neuron disorders, ataxia, seizures, Guillain-Barré syndrome, psychosis
Cardiovascular system	1-5	Cardiac abnormalities—e.g., existing valvular abnormalities, rheumatic heart disease, or congenital heart defects	Endocarditis, myocarditis, pericarditis, arteritis, congestive heart failure
Pulmonary system	1-6	Residence in endemic region, past pulmonary infection, sickle cell anemia, alcohol abuse, diabetes, HIV infection	Pneumonia, empyema, bronchopleural fistula
Bone and joint	<1	Sickle cell anemia, diabetes, systemic lupus erythematosus, lymphoma, liver disease, previous surgery or trauma, extremes of age, and steroid use	Osteomyelitis, septic arthritis
Hepatobiliary system	1-26	Residence in endemic region, pyogenic infections, intravenous drug use, splenic trauma, HIV, hemoglobinopathy	Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus
Genitourinary system	<1	Urinary tract, pelvic pathology, and systemic abnormalities	Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis
Soft-tissue infections	At least 17 cases reported in the English language literature	Diabetes	Psoas abscess, gluteal abscess, cutaneous vasculitis
Hematologic	At least 5 cases reported in the English language literature		Hemophagocytosis syndrome

From Huang DB, DuPont HL: Problem pathogens: extra-intestinal complications of Salmonella enterica *serotype Typhi infection,* Lancet Infect Dis *5:341–348, 2005.*

perforation and peritonitis may be accompanied by a sudden rise in pulse rate, hypotension, marked abdominal tenderness and guarding, and subsequent abdominal rigidity. A rising white blood cell count with a left shift and free air on abdominal radiographs may be seen in such cases.

Rare complications include toxic myocarditis, which may manifest as arrhythmias, sinoatrial block, or cardiogenic shock (Table 198-6). Neurologic complications are also relatively uncommon among children; they include delirium, psychosis, increased intracranial pressure, acute cerebellar ataxia, chorea, deafness, and Guillain-Barré syndrome. Although case fatality rates may be higher with neurologic manifestations, recovery usually occurs with no sequelae. Other reported complications include fatal bone marrow necrosis, disseminated intravascular coagulopathy, hemolytic–uremic syndrome, pyelonephritis, nephrotic syndrome, meningitis, endocarditis, parotitis, orchitis, and suppurative lymphadenitis.

The propensity to become a carrier follows the epidemiology of gallbladder disease, increasing with patient age and the antibiotic resistance of the prevalent strains. Although limited data are available, rates of chronic carriage are generally lower in children than adults.

DIAGNOSIS

The mainstay of the diagnosis of typhoid fever is a positive result of culture from the blood or another anatomic site. Results of blood cultures are positive in 40-60% of the patients seen early in the course of the disease, and stool and urine culture results become positive after the 1st wk. The stool culture result is also occasionally positive during the incubation period. However, the sensitivity of blood cultures in diagnosing typhoid fever in many parts of the developing world is limited because widespread liberal antibiotic use may render bacteriologic confirmation difficult. Although bone marrow cultures may increase the likelihood of bacteriologic confirmation of typhoid, collection of the specimens is difficult and relatively invasive.

Results of other laboratory investigations are nonspecific. Although blood leukocyte counts are frequently low in relation to the fever and toxicity, there is a wide range in counts; in younger children leukocytosis is common and may reach 20,000-25,000 cells/µL. Thrombocytopenia may be a marker of severe illness and may accompany disseminated intravascular coagulopathy. Liver function test results may be deranged, but significant hepatic dysfunction is rare.

The classic Widal test measures antibodies against O and H antigens of *S.* Typhi but lacks sensitivity and specificity in endemic areas. Because many false-positive and false-negative results occur, diagnosis of typhoid fever by Widal test alone is prone to error. Other relatively newer diagnostic tests using monoclonal antibodies have been developed that directly detect *S.* Typhi–specific antigens in the serum or *S.* Typhi Vi antigen in the urine. However, few have proved sufficiently robust in large-scale evaluations. A nested polymerase chain reaction analysis using *H1-d* primers has been used to amplify specific genes of *S.* Typhi in the blood of patients; it is a promising means of making a rapid diagnosis, especially given the low level of bacteremia in enteric fever. Despite these innovations, the mainstay of diagnosis of typhoid remains clinical in much of the developing world, and several diagnostic algorithms have been evaluated in endemic areas.

DIFFERENTIAL DIAGNOSIS

In endemic areas, typhoid fever may mimic many common febrile illnesses without localizing signs. In children with multisystem features and no localizing signs, the early stages of enteric fever may be confused with alternative conditions, such as acute gastroenteritis,

bronchitis, and bronchopneumonia. Subsequently, the differential diagnosis includes malaria; sepsis with other bacterial pathogens; infections caused by intracellular microorganisms, such as tuberculosis, brucellosis, tularemia, leptospirosis, and rickettsial diseases; and viral infections such as Dengue fever, acute hepatitis, and infectious mononucleosis.

TREATMENT

An early diagnosis of typhoid fever and institution of appropriate treatment are essential. The vast majority of children with typhoid fever can be managed at home with oral antibiotics and close medical follow-up for complications or failure of response to therapy. Patients with persistent vomiting, severe diarrhea, and abdominal distention may require hospitalization and parenteral antibiotic therapy.

There are general principles of typhoid fever management. Adequate rest, hydration, and attention are important to correct fluid and electrolyte imbalance. Antipyretic therapy (acetaminophen 10-15 mg/kg every 4-6 hr PO) should be provided as required. A soft, easily digestible diet should be continued unless the patient has abdominal distention or ileus. Antibiotic therapy is critical to minimize complications (Table 198-7). It has been suggested that traditional therapy with either chloramphenicol or amoxicillin is associated with relapse rates of 5-15% and 4-8%, respectively, whereas use of the quinolones and third-generation cephalosporins is associated with higher cure rates. The antibiotic treatment of typhoid fever in children is also influenced by the prevalence of antimicrobial resistance. Over the past 2 decades, emergence of multidrug-resistant strains of *S.* Typhi (i.e., isolates fully resistant to amoxicillin, trimethoprim-sulfamethoxazole, and chloramphenicol) has necessitated treatment with fluoroquinolones, which are the antimicrobial drug of choice for treatment of salmonellosis in adults, with cephalosporins as an alternative. The emergence of resistance to quinolones places tremendous pressure on public health systems because alternative therapeutic options are limited.

Although some investigators suggest that children with typhoid fever should be treated with fluoroquinolones like adults, others question this approach on the basis of the potential development of further resistance to fluoroquinolones and the fact that quinolones are still not approved for widespread use in children. A Cochrane systematic review of the treatment of typhoid fever also indicates that there is little evidence to support the carte blanche administration of fluoroquinolones in all cases of typhoid fever. Azithromycin may be an alternative antibiotic for children with uncomplicated typhoid fever.

In addition to antibiotics, the importance of supportive treatment and maintenance of appropriate fluid and electrolyte balance must be underscored. Although additional treatment with dexamethasone (3 mg/kg for the initial dose, followed by 1 mg/kg every 6 hr for 48 hr) is recommended for severely ill patients with shock, obtundation, stupor, or coma; corticosteroids should be administered only under strict controlled conditions and supervision, because their use may mask signs of abdominal complications.

PROGNOSIS

The prognosis for a patient with enteric fever depends on the rapidity of diagnosis and institution of appropriate antibiotic therapy. Other factors are the patient's, age, general state of health, and nutrition, the causative *Salmonella* serotype, and the appearance of complications. Infants and children with underlying malnutrition and patients infected with multidrug-resistant isolates are at higher risk for adverse outcomes.

Despite appropriate therapy, 2-4% of infected children may experience relapse after initial clinical response to treatment. Individuals who excrete *S.* Typhi for 3 mo or longer after infection are regarded as chronic carriers. The risk for becoming a carrier is low in children (<2% for all infected children) and increases with age. A chronic urinary carrier state can develop in children with schistosomiasis.

PREVENTION

Of the major risk factors for outbreaks of typhoid fever, contamination of water supplies with sewage is the most important. Other risk factors for development of typhoid fever are congestion, contact with another patient or a febrile individual, and lack of water and sanitation services. During outbreaks, central chlorination as well as domestic water purification is important. In endemic situations, consumption of street foods, especially ice cream and cut fruit, is recognized as an important risk factor. The human-to-human spread by chronic carriers is also important, and attempts should be made to target food handlers and

Table 198-7 Treatment of Typhoid Fever in Children

	Optimal Therapy			Alternative Effective Drugs		
SUSCEPTIBILITY	ANTIBIOTIC	DAILY DOSE (mg/kg/day)	DAYS	ANTIBIOTIC	DAILY DOSE (mg/kg/day)	DAYS
UNCOMPLICATED TYPHOID FEVER						
Fully sensitive	Chloramphenicol	50-75	14-21	Fluoroquinolone, e.g., ofloxacin or ciprofloxacin	15	5-7*
	Amoxicillin	75-100	14			
Multidrug-resistant	Fluoroquinolone *or*	15	5-7	Azithromycin	8-10	7
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone-resistant†	Azithromycin *or*	8-10	7	Cefixime	20	7-14
	Ceftriaxone	75	10-14			
SEVERE TYPHOID FEVER						
Fully sensitive	Fluoroquinolone, e.g., ofloxacin	15	10-14	Chloramphenicol	100	14-21
				Amoxicillin	100	
Multidrug-resistant	Fluoroquinolone	15	10-14	Ceftriaxone *or*	60	10-14
				Cefotaxime	80	10-14
Quinolone-resistant	Ceftriaxone	60	10-14	Azithromycin	10-20	7
	Cefotaxime	80	10-14	Fluoroquinolone	20	7-14

*A 3-day course is also effective, particularly for epidemic containment.

†The optimum treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, third-generation cephalosporins, or high-dose fluoroquinolones for 10-14 days is effective.

Modified from World Health Organization: Treatment of typhoid fever. In: World Health Organization: Background document: the diagnosis, prevention and treatment of typhoid fever. Communicable disease surveillance and response: vaccines and biologicals, *Geneva, 2003, World Health Organization, pp. 19–23. Available at:* http://whqlibdoc.who.int/hq/2003/WHO_V&B_03.07.pdf

high-risk groups for *S.* Typhi carriage screening. Once identified, chronic carriers must be counseled as to the risk for disease transmission and the importance of handwashing.

The classic heat-inactivated whole-cell vaccine for typhoid is associated with an unacceptably high rate of side effects and has been largely withdrawn from public health use. Globally, 2 vaccines are currently available for potential use in children. An oral, live-attenuated preparation of the Ty21a strain of *S.* Typhi has good efficacy (67-82%) for up to 5 yr. Significant adverse effects are rare. The Vi capsular polysaccharide can be used in people 2 yr of age and older. It is given as a single intramuscular dose, with a booster every 2 yr, and has a protective efficacy of 70-80%. The vaccines are currently recommended for anyone traveling into endemic areas, but a few countries have introduced large-scale vaccination strategies. Previous studies in South America have demonstrated protection against typhoid fever among schoolchildren with the use of an oral attenuated Ty21 strain vaccine.

Several large-scale demonstration projects using the Vi polysaccharide vaccine in Asia have demonstrated protective efficacy against typhoid fever across all age groups, but the data on protection among young children (<5 yr) showed important differences between studies. The recent Vi-conjugate vaccine has a protective efficacy exceeding 90% in younger children and may offer protection in parts of the world where a large proportion of preschool children are at risk for the disease enteric or typhoid fever.

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Chapter 199

Shigella

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Shigella causes an acute invasive enteric infection clinically manifested by diarrhea that is often bloody. The term *dysentery* is used to describe the syndrome of bloody diarrhea with fever, abdominal cramps, rectal pain, and mucoid stools. Bacillary dysentery is a term often used to distinguish dysentery caused by *Shigella* from amoebic dysentery caused by *Entamoeba histolytica*.

ETIOLOGY

Four species of *Shigella* are responsible for bacillary dysentery: *Shigella dysenteriae* (serogroup A), *Shigella flexneri* (serogroup B), *Shigella boydii* (serogroup C), and *Shigella sonnei* (serogroup D). There are 15 serotypes in group A, 19 serotypes in group B, 19 serotypes in group C, and one serotype in group D. Species classification has important therapeutic implications because the species differ in both geographic distribution and antimicrobial susceptibility.

EPIDEMIOLOGY

It is estimated that there are approximately 80-165 million cases of shigellosis each year worldwide, resulting in more than 1 million deaths; most of these cases and deaths occur in developing countries. Studies estimate similar illness rates but fewer deaths because of a decrease in the case-fatality rates. In the United States, approximately 14,000 cases per year are documented, although it is thought that the actual frequency of infection is 450,000 cases annually. *Shigella* is the third most important pathogen identified in the Foodborne Disease Active Surveillance Network in the United States. Although infection can occur at any age, it is most common in the 2nd and 3rd yr of life. Approximately 70% of all episodes and 60% of all *Shigella*-related deaths involve children younger than 5 yr of age. Infection in the 1st 6 mo of life is rare for reasons that are not clear. Breast milk from women living in endemic areas contains antibodies to both virulence plasmid-coded antigens and lipopolysaccharides, and breastfeeding might partially explain the age-related incidence.

Asymptomatic infection of children and adults occurs commonly in endemic areas. Infection with *Shigella* occurs most often during the warm months in temperate climates and during the rainy season in tropical climates. Both sexes are affected equally. In industrialized societies, *S. sonnei* is the most common cause of bacillary dysentery, with *S. flexneri* second in frequency; in preindustrial societies, *S. flexneri* is most common, with *S. sonnei* second in frequency. *S. boydii* is found primarily in India. *S. dysenteriae* serotype 1 tends to occur in massive epidemics, although it is also endemic in Asia and Africa, where it is associated with high mortality rates (5-15%). However, *Shigella* has shown temporal procession in serogroup dominance. Recently, epidemiologic transition has favored the emergence of *S. sonnei* as the dominant serogroup in some countries, although the reason for this is not clear.

Contaminated food (often a salad or other item requiring extensive handling of the ingredients) and water are important vectors. Exposure to both fresh and saltwater is a risk factor for infection. Rapid spread within families, custodial institutions, and childcare centers demonstrates the ability of shigellae to be transmitted from 1 individual to the next and the requirement for ingestion of very few organisms to cause illness. As few as 10 *S. dysenteriae* serotype 1 organisms can cause dysentery. In contrast, ingestion of 10^8-10^{10} *Vibrio cholerae* is necessary to cause cholera.

PATHOGENESIS

Shigella has specialized mechanisms to survive the low gastric pH. *Shigella* survives the acid environment in the stomach and moves through the gut to the colon, its target organ. The basic virulence trait shared by all shigellae is the ability to invade colonic epithelial cells by turning on a series of temperature-regulated proteins. This invasion mechanism is encoded on a large (220 kb) plasmid that at body temperature synthesizes of a group of polypeptides involved in cell invasion and killing. Shigellae that lose the virulence plasmid are no longer pathogenic. Enteroinvasive *Escherichia coli* that harbor a closely related plasmid containing these invasion genes behave clinically like shigellae. The virulence plasmid encodes a type III secretion system required to trigger entry into epithelial cells and apoptosis in macrophages. This secretion system translocates effector molecules from the bacterial cytoplasm to the membrane and cytoplasm of target host cells. The type III secretion system is composed of approximately 50 proteins, including the Mxi and Spa proteins involved in assembly and regulation of the type III secretion system, chaperones (IpgA, IpgC, IpgE, and Spa15), transcription activators (VirF, VirB, and MxiE), translocators (IpaB, IpaC, and IpaD), and approximately 30 effector proteins. In addition to the major plasmid-encoded virulence traits, chromosomally encoded factors are also required for full virulence.

Shigella passes the epithelial cell barrier by transcytosis through M cells and encounters resident macrophages. The bacteria evade degradation in macrophages by inducing apoptosis, which is accompanied by proinflammatory signaling. Free bacteria invade the epithelial cells from the basolateral side, move into the cytoplasm by actin polymerization, and spread to adjacent cells. Proinflammatory signaling by macrophages and epithelial cells further activates the innate immune response involving natural killer cells and attracts polymorphonuclear leukocytes (PMNs). The influx of PMNs disintegrates the epithelial cell lining, which initially exacerbates the infection and tissue destruction by facilitating the invasion of more bacteria. Ultimately, PMNs phagocytose and kill *Shigella*, thus contributing to the resolution of the infection.

Some shigellae make toxins, including *Shiga* toxin and enterotoxins. *Shiga* toxin is a potent exotoxin that inhibits protein synthesis and is produced in significant amounts by *S. dysenteriae* serotype 1, by a subset of *E. coli*, which are known as enterohemorrhagic or *Shiga* toxin–producing *E. coli*, and occasionally by other organisms. *Shiga* toxin inhibits protein synthesis to injure vascular endothelial cells to trigger the severe complication of hemolytic-uremic syndrome.

Targeted deletion of the genes for other enterotoxins *(ShET1* and *ShET2)* has decreased the incidence of fever and dysentery in volunteers during vaccine-development studies. Lipopolysaccharides are virulence factors for all shigellae; other traits are important for only a few serotypes (e.g., *Shiga* toxin synthesis by *S. dysenteriae* serotype 1 and *ShET1* by *S. flexneri* 2a).

The pathologic changes of shigellosis take place primarily in the colon. The changes are most intense in the distal colon, although pancolitis can occur. Shigellae cross the colonic epithelium through M cells in the follicle-associated epithelium overlying the Peyer patches. Grossly, localized or diffuse mucosal edema, ulcerations, friable mucosa, bleeding, and exudate may be seen. Microscopically, ulcerations, pseudomembranes, epithelial cell death, infiltration extending from the mucosa to the muscularis mucosae by PMNs and mononuclear cells, and submucosal edema occur.

IMMUNITY

Innate immunity to *Shigella* infection is characterized by the induction of acute inflammation with massive recruitment of PMNs and subsequently massive tissue destruction. In humans, analysis of cytokine expression in rectal biopsies of infected patients at the acute phase of the disease has revealed upregulation of proinflammatory genes, such as those encoding interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-α, and tumor necrosis factor-β, although antiinflammatory genes encoding IL-10 and transforming growth factor-β are also upregulated. Control of *Shigella* invasion in intestinal epithelial cells depends on interferon-γ. *Shigella*-specific immunity elicited upon natural infection is characterized by the induction of a humoral response. Local secretory immunoglobulin A and serum immunoglobulin G are produced against lipopolysaccharide and some protein effectors (Ipas). Protection is thought to be serotype specific. Natural protective immunity arises only after several episodes of infection, is of short duration, and seems to be effective in limiting reinfection, particularly in young children.

CLINICAL MANIFESTATIONS AND COMPLICATIONS

Bacillary dysentery is clinically similar regardless of infecting serotype. There are some clinical differences, particularly relating to the greater severity and risk of complications with *S. dysenteriae* serotype 1 infection. Ingestion of shigellae is followed by an incubation period of 12 hr to several days before symptoms ensue. Severe abdominal pain, high fever, emesis, anorexia, generalized toxicity, urgency, and painful defecation characteristically occur. The diarrhea may be watery and of large volume initially, evolving into frequent, small-volume, bloody mucoid stools. Most children never progress to the stage of bloody diarrhea, but some have bloody stools from the outset. Significant dehydration is related to the fluid and electrolyte losses in feces and emesis. Untreated diarrhea can last 7-10 days; only approximately 10% of patients have diarrhea persisting for longer than 10 days. Persistent diarrhea occurs in malnourished infants, children with AIDS, and occasionally previously normal children. Even nondysenteric disease can be complicated by persistent illness.

Physical examination initially shows abdominal distention and tenderness, hyperactive bowel sounds, and a tender rectum on digital examination. Rectal prolapse may be present, particularly in malnourished children. Neurologic findings are among the most common extraintestinal manifestations of bacillary dysentery, occurring in as many as 40% of hospitalized children. Enteroinvasive *E. coli* can cause similar neurologic toxicity. Convulsions, headache, lethargy, confusion, nuchal rigidity, or hallucinations may be present before or after the onset of diarrhea. The cause of these neurologic findings is not understood. In the past, these symptoms were attributed to the neurotoxicity of *Shiga* toxin, but it is now clear that this explanation is wrong because the organisms isolated from children with *Shigella*-related seizures are usually not *Shiga* toxin producers. Seizures sometimes occur when little fever is present, suggesting that simple febrile convulsions do not explain their appearance. Hypocalcemia or hyponatremia may be associated with seizures in a small number of patients. Although symptoms often suggest central nervous system infection and cerebrospinal fluid pleocytosis with minimally elevated protein levels can occur, meningitis caused by shigellae is rare. Based on animal studies, it has been suggested that proinflammatory mediators, including tumor necrosis factor-α and IL-1β, nitric oxide, and corticotropin-releasing hormone, all play a role in the enhanced susceptibility to seizures caused by *S. dysenteriae.*

The most common complication of shigellosis is dehydration. Inappropriate secretion of antidiuretic hormone with profound hyponatremia can complicate dysentery, particularly when *S. dysenteriae* is the etiologic agent. Hypoglycemia and protein-losing enteropathy are common and are decreased by early appropriate antibiotic therapy. Severe protein-losing enteropathy is associated with prolonged illness and linear growth shortfalls. Bacteremia is uncommon except in girls or women infected with HIV, malnourished children, young infants, and children with *S. dysenteriae* serotype 1 infection. When bacteremia occurs with dysentery (<5%), it is as likely to be caused by other enteric bacteria as well as by the *Shigella* itself. The presence of *E. coli, Klebsiella*, and other enteric bacteria in blood cultures of children with shigellosis may reflect loss of the barrier function during severe colitis. The mortality rate is high (~20%) when sepsis occurs and is far more common in those with HIV than in non–HIV-infected persons. Other major complications include disseminated intravascular coagulation, particularly in very young, malnourished children. Given that shigellae penetrate the intestinal mucosal barrier, these events are surprisingly uncommon.

Neonatal shigellosis is rare. Neonates may have only low-grade fever with mild, nonbloody diarrhea. However, complications occur more commonly than in older children and include septicemia, meningitis, dehydration, colonic perforation, and toxic megacolon.

S. dysenteriae serotype 1 infection is commonly complicated by hemolysis, anemia, and hemolytic-uremic syndrome. This syndrome is caused by *Shiga* toxin–mediated vascular endothelial injury. *E. coli* that produce *Shiga* toxins (e.g., *E. coli* O157:H7, *E. coli* O111:NM, *E. coli* O26:H11, and less commonly in many other serotypes) also cause hemolytic-uremic syndrome (see Chapter 518).

Rectal prolapse, toxic megacolon or pseudomembranous colitis (usually associated with *S. dysenteriae*), cholestatic hepatitis, conjunctivitis, iritis, corneal ulcers, pneumonia, arthritis (usually 2-5 wk after enteritis), reactive arthritis, cystitis, myocarditis, and vaginitis (typically with a blood-tinged discharge associated with *S. flexneri*) are uncommon events. Although rare, surgical complications of shigellosis can be severe; the most common are intestinal obstruction and appendicitis with and without perforation.

On average, severity of illness and risk of death are least with disease caused by *S. sonnei* and greatest with infection by *S. dysenteriae* type 1. Risk groups for severe illness and poor outcomes include infants; adults older than age 50 yr; children who are not breastfed; children with HIV or who are recovering from measles; malnourished children and adults; and patients who develop dehydration, unconsciousness, or hypo- or hyperthermia, hyponatremia, lesser stool frequency, or have a history of convulsion when first seen. Death is a rare outcome in well-nourished older children. Multiple factors contribute to death in malnourished children with shigellosis, including illness in the 1st yr of life, altered consciousness, dehydration, hypothermia, thrombocytopenia, anemia, hyponatremia, renal failure, hyperkalemia hypoglycemia, bronchopneumonia, and bacteremia.

The rare syndrome of severe toxicity, convulsions, extreme hyperpyrexia, and headache followed by brain edema and a rapidly fatal outcome without sepsis or significant dehydration (Ekiri syndrome or "lethal toxic encephalopathy") is not well understood.

DIFFERENTIAL DIAGNOSIS

Although clinical features suggest shigellosis, they are insufficiently specific to allow confident diagnosis. Infection by *Campylobacter jejuni*, *Salmonella* spp., enteroinvasive *E. coli*, *Shiga* toxin–producing *E. coli* (e.g., *E. coli* O157:H7), *Yersinia enterocolitica*, *Clostridium difficile*,

and *E. histolytica,* as well as inflammatory bowel disease, can cause confusion.

DIAGNOSIS

Presumptive data supporting a diagnosis of bacillary dysentery include the finding of fecal leukocytes (usually >50 or 100 PMNs per high-power field, confirming the presence of colitis), fecal blood, and demonstration in peripheral blood of leukocytosis with a dramatic left shift (often with more bands than segmented neutrophils). The total peripheral white blood cell count is usually 5,000-15,000 cells/µL, although leukopenia and leukemoid reactions occur.

Culture of both stool and rectal swab specimens optimizes the chance of diagnosing *Shigella* infection. Culture media should include MacConkey agar as well as selective media such as xylose-lysine-deoxycholate and *Salmonella-Shigella* agar. Transport media should be used if specimens cannot be cultured promptly. Appropriate media should be used to exclude *Campylobacter* spp. and other agents. Studies of outbreaks and illness in volunteers show that the laboratory is often not able to confirm the clinical suspicion of shigellosis even when the pathogen is present. Studies using molecular methods such as polymerase chain reaction suggest that culture significantly underestimates the true frequency of infection. Quantitative polymerase chain reaction improves ascertainment of *Shigella* burden in children with moderate-to-severe diarrhea in low-income countries. However, these methods are usually available only in research laboratories. Multiple fecal cultures improve the yield of *Shigella*. The diagnostic inadequacy of cultures makes it incumbent on the clinician to use judgment in the management of clinical syndromes consistent with shigellosis. In children who appear to be toxic, blood cultures should be obtained, especially in very young or malnourished infants because of their increased risk of bacteremia.

TREATMENT

As with gastroenteritis from other causes, the first concern in a child with suspected shigellosis should be for fluid and electrolyte correction and maintenance (see Chapter 340). Drugs that retard intestinal motility (e.g., diphenoxylate hydrochloride with atropine [Lomotil] or loperamide [Imodium]) should not be used because of the risk of prolonging the illness.

Nutrition is a key concern in areas where malnutrition is common. A high-protein and high-caloric diet during convalescence enhances growth in the following 6 mo. Controlled studies show that cooked green bananas, a food rich in amylase-resistant starches, significantly improves outcome in severe disease. A single large dose of vitamin A (200,000 IU) lessens severity of shigellosis in settings where vitamin A deficiency is common. Zinc supplementation (20 mg elemental zinc for 14 days) significantly decreases the duration of diarrhea, improves weight gain during recovery and immune response to the *Shigella*, and decreases diarrheal disease in the subsequent 6 mo in malnourished children.

The next concern is a decision about the use of antibiotics. Although some authorities recommend withholding antibacterial therapy because of the self-limited nature of the infection, the cost of drugs, and the risk of emergence of resistant organisms, there is a persuasive logic in favor of empirical treatment of all children in whom shigellosis is strongly suspected. Even if not fatal, the untreated illness can cause a child to be quite ill for weeks; chronic or recurrent diarrhea can ensue. Malnutrition can develop or worsen during prolonged illness, particularly in children in developing countries. The risk of continued excretion and subsequent infection of family contacts further argues against the strategy of withholding antibiotics.

Shigella species have variable antimicrobial susceptibility. In general, *S. flexneri* tends to be more resistant than *S. boydii*. There are major geographic variations in antibiotic susceptibility of shigellae. In the United States, strains are commonly resistant to ampicillin (74%) and trimethoprim-sulfamethoxazole (TMP-SMX) (36%), but infrequently resistant to nalidixic acid (2%) or ciprofloxacin (0.5%); however, antimicrobial resistance in the United States differs by race, ethnicity, age, travel history, and species. In general, the proportion of antibiotic resistant isolates is lower in North America and Europe than in Asia or Africa. For example, in China, *S. sonnei* is commonly resistant to TMP-SMX (94.5%), ampicillin (40.3%), piperacillin (36.5%), and ceftriaxone (12.8%). In general, *Shigella* are susceptible in vitro to azithromycin, ceftriaxone, cefotaxime, cefixime, nalidixic acid, and quinolones. However, resistance to these antibiotics is being reported in several regions. For example, nalidixic acid–resistant *Shigella* has rapidly developed in Asia and Africa; resistance to ciprofloxacin is increasingly common in India; resistance to azithromycin and ceftriaxone is reported in some countries.

Currently, in most developed and developing countries, *Shigella* strains are often resistant to ampicillin and TMP-SMX; therefore, these drugs should not be used for empirical treatment of suspected shigellosis; they may be used only if the strain is known to be susceptible (e.g., in an outbreak from a defined strain). Given the frequent occurrence of resistant organisms, optimal empirical therapy in children with dysentery should include azithromycin, a third-generation cephalosporin, nalidixic acid or ciprofloxacin. Ceftriaxone (50 mg/kg/24 hr as a single daily dose IV or IM) can be used for empirical therapy, especially for small infants. The oral third-generation cephalosporin cefixime (8 mg/kg/24 hr divided every 12-24 hr) can also be used; however, oral first- and second-generation cephalosporins are inadequate as alternative drugs despite in vitro susceptibility. Nalidixic acid (55 mg/kg/24 hr orally divided 4 times/day) is also an acceptable alternative drug when available. Azithromycin (12 mg/kg/24 hr orally for the 1st day, followed by 6 mg/kg/24 hr for the next 4 days) has proven to be an effective alternative drug for shigellosis. Ciprofloxacin (20-30 mg/kg/24 hr divided into 2 doses) used to be a back-up drug to treat shigellosis but is now the drug of choice recommended by the World Health Organization for all patients with bloody diarrhea, irrespective of their ages.

Although quinolones are reported to cause arthropathy in immature animals, the risk of joint damage in children appears to be minimal and is outweighed by the value of these drugs for treatment of this potentially life-threatening disease. However, some experts recommend that these agents be reserved for seriously ill children with bacillary dysentery caused by an organism that is suspected or known to be resistant to other agents, because overuse of quinolones promotes development of resistance to these drugs.

Treatment of patients in whom *Shigella* infection is suspected on clinical grounds of should be initiated when they are first evaluated. Stool culture is obtained to exclude other pathogens and to assist in antibiotic changes should a child fail to respond to empirical therapy. A child who has typical dysentery and who responds to initial empirical antibiotic treatment should be continued on that drug for a full 5-day course even if the stool culture is negative. The logic of this recommendation is based on the proven difficulty of culturing *Shigella* from stools of ill patients during adult volunteer infection studies. In a child who fails to respond to therapy of a dysenteric syndrome in the presence of initially negative stool culture results, additional cultures should be obtained and the child should be reevaluated for other possible diagnoses.

PREVENTION

Numerous measures have been recommended to decrease the risk of *Shigella* transmission to children. Mothers should be encouraged to prolong breastfeeding of infants. Families and daycare personnel should be educated in proper handwashing techniques and encouraged to wash hands after using the toilet, changing diapers, or engaging in preparation of foods. They should be taught how to manage potentially contaminated materials such as raw vegetables, soiled diapers, and diaper-changing areas. Children with diarrhea should be excluded from childcare facilities. Children should be supervised when handwashing after they use the toilet. Caretakers should be informed of the risk of transmission if they prepare food when they are ill with diarrhea. Families should be educated regarding the risk of swallowing contaminated water from ponds, lakes, or untreated pools. In

developing countries, a safe water supply and appropriate sanitation systems are important measures for reducing the risk for shigellosis. There is not yet a vaccine that is effective for preventing infection by *Shigella*. Measles immunization can substantially reduce the incidence and severity of diarrheal diseases, including shigellosis. Every infant should be immunized against measles at the recommended age.

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Chapter 200

Escherichia coli

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Escherichia coli are important causes of enteric infections as well as urinary tract infections (see Chapter 538), sepsis and meningitis in the newborn (see Chapter 109), and bacteremia and sepsis in immunocompromised patients (see Chapter 178) and in patients with intravascular devices (see Chapter 179). In patients with non–diarrhea-associated *E. coli* infections, a significant number of these pathogens have acquired transferrable plasmids resulting in extended-spectrum β-lactamase production. This results in resistance to penicillins, cephalosporins and aztreonam; carbapenems remain effective.

E. coli species are members of the Enterobacteriaceae family. They are facultative anaerobic, Gram-negative bacilli that usually ferment lactose. Most fecal *E. coli* do not cause diarrhea. Six major groups of diarrheagenic *E. coli* have been characterized on the basis of clinical, biochemical, and molecular-genetic criteria: enterotoxigenic *E. coli* (ETEC); enteroinvasive *E. coli* (EIEC); enteropathogenic *E. coli* (EPEC); *Shiga* toxin–producing *E. coli* (STEC), also known as enterohemorrhagic *E. coli* (EHEC) or verotoxin producing *E. coli* (VTEC); enteroaggregative *E. coli* (EAEC or EggEC); and diffusely adherent *E. coli* (DAEC).

E. coli strains can also be categorized by their serogroup where O refers to the lipopolysaccharide (LPS) O-antigen or serotype where H refers to the flagellar antigen, for example, *E. coli* O157:H7. However, as each pathotype contains many serotypes (117 ETEC serotypes have been identified) and some serotypes can belong to more than 1 pathotype (e.g., O26:H11 can be either EPEC or EHEC depending on which specific virulence genes are present), serotyping frequently does not provide definitive identification of pathotypes.

Because *E. coli* are normal fecal flora, pathogenicity is defined by demonstration of virulence characteristics and association of those traits with illness (Table 200-1). The mechanism by which *E. coli* produces diarrhea typically involves adherence of organisms to a glycoprotein or glycolipid receptor, followed by production of some noxious substance that injures or disturbs the function of intestinal cells. The genes for virulence properties and for antibiotic resistance are often carried on transferable plasmids, pathogenicity islands, or bacteriophages. In the developing world, the various diarrheagenic *E. coli* cause frequent infections in the 1st few yr of life; diarrheagenic *E. coli* as a group are responsible for 30-40% of all diarrhea cases in children worldwide. They occur with increased frequency during the warm months in temperate climates and during rainy season months in tropical climates. Most diarrheagenic *E. coli* strains (except STEC) require a large inoculum of organisms to induce disease. Infection is most likely when food-handling or sewage-disposal practices are suboptimal. The diarrheagenic *E. coli* are also important in North America and Europe, although their epidemiology is less-well defined in these areas than in the developing world. In North America, the various diarrheagenic *E. coli* may be the etiology of as much as 30% of infectious diarrhea in children younger than 5 yr of age.

Many studies have found diarrheagenic *E. coli* pathotypes in a significant proportion of asymptomatic healthy children living in developing countries. Fecal contamination (human and animal), which is common in the underprivileged environments in which many young children live, facilitates the transmission of pathogens. In addition, with current modern, highly sensitive microbiologic methods, small numbers of bacteria can be detected in stool samples. Therefore, it is important to assess the prevalence of various enteropathogens in children with and without diarrhea, to interpret results. Excretion of enteropathogens by subjects without diarrhea may be explained by characteristics of the pathogens (virulence heterogeneity), the host (host susceptibility, age, nutritional status, breastfeeding, immunity), and environmental factors (inoculum size).

ENTEROTOXIGENIC *ESCHERICHIA COLI*

ETEC account for a sizeable fraction of dehydrating infantile diarrhea in the developing world (10-30%) and of traveler's diarrhea (20-60% of cases); ETEC is the most common cause of traveler's diarrhea. In a recent large multicenter diarrhea study (GEMS [global enteric multicenter study]) heat-stable enterotoxin (ST)-ETEC (with or without coexpression of heat-labile enterotoxin [LT]), was among the most important causes of diarrhea in young children in developing countries and was associated with increased risk of death. The typical signs and symptoms include explosive watery, nonmucoid, nonbloody diarrhea, abdominal pain, nausea, vomiting, and little or no fever. The illness is usually self-limited and resolves in 3-5 days but occasionally lasts longer than 1 wk.

ETEC cause few or no structural alterations in the gut mucosa. Diarrhea is caused by colonization of the small intestine and subsequent elaboration of enterotoxins. ETEC strains secrete an LT and/or an ST. LT, a large molecule consisting of 5 receptor-binding subunits and 1 enzymatically active subunit, is structurally, functionally, and immunologically related to cholera toxin produced by *Vibrio cholerae*. LT stimulates adenylate cyclase, resulting in increased cyclic adenosine monophosphate. ST is a small molecule not related to cholera toxin. ST stimulates guanylate cyclase, resulting in increased cyclic guanosine monophosphate. The genes for these toxins are encoded on plasmids.

Colonization of the intestine requires fimbrial colonization factor antigens (CFAs), which promote adhesion to the intestinal epithelium. CFAs are antigenic fimbriae that are currently targets for vaccine development. There are at least 25 CFA types; these antigens are composed of coli surface (CS) antigens and can be expressed alone or in combination. Prevalent colonization factors include CFA/I, CS1-CS7, CS14, and CS17. However, CFAs have not been detected on all ETEC strains. Although 30-50% of ETEC isolates have no characterized CFA by phenotypic screening, novel CFAs continue to be identified. The multiple CFAs and their allelic variants have made definition of immunity and development of useful vaccines difficult. A large proportion of strains produce a type IV pilus called *longus*, which functions as a colonization factor and is found among several other Gram-negative bacterial pathogens. ETEC strains also have the common pilus, produced by commensal and pathogenic *E. coli* strains. Among the nonfimbrial adhesions, TibA is a potent bacterial adhesin that mediates bacterial attachment and invasion of cells. For many years, the O serogroup was used to distinguish pathogenic from commensal *E. coli*. Because the pathogenic *E. coli* are now defined and classified by using probes or primers for specific virulence genes, determining the O serogroup has become less important. Of the more than 180 *E. coli* serogroups, only a relatively small number typically are ETEC. The most common O groups are O6, O8, O128, and O153, and based on some large retrospective studies, these serogroups only account for half of the ETEC strains.

ENTEROINVASIVE *ESCHERICHIA COLI*

Clinically, EIEC infections present either with watery diarrhea or a dysentery syndrome with blood, mucus, and leukocytes in the stools, as well as fever, systemic toxicity, crampy abdominal pain, tenesmus, and urgency. The illness resembles bacillary dysentery, because EIEC share virulence genes with *Shigella* spp. Sequencing of multiple housekeeping genes indicates that EIEC is more related to *Shigella* than to

Table 200-1 Clinical Characteristics, Pathogenesis, and Diagnosis of Diarrheagenic *E. coli*

PATHOGEN	POPULATIONS AT RISK	Characteristics of Diarrhea: WATERY	BLOODY	DURATION	Main Virulence Factors: ADHERENCE FACTORS	TOXINS	DIAGNOSIS
ETEC	>1 yr old and travelers	+++	—	Acute	Colonization factor antigens (CFs or CFAs); ECP	Heat-labile enterotoxin (LT) Heat-stable enterotoxin (ST)	Detection of enterotoxins (LT and ST) by enzyme immunoassays or PCR (*lt, st*)
EIEC	>1 yr old	+	++	Acute	Invasion plasmid antigen (IpaABCD)		Detection of invasion plasmid antigen of *Shigella* (*ipaH*) by PCR
EPEC	<2 yr old	+ + +	+	Acute, prolonged or persistent	A/E lesion, intimin/Tir, EspABD, Bfp	EspF, Map, EAST1, SPATEs (*EspC*)	Detection of intimin gene (*eae*) ± bundle-forming pili (*bfpA*) by PCR, and absence of *Shiga* toxins; HEp-2 cells adherence assay (LA, LLA)
STEC (EHEC/ VTEC)	6 mo-10 yr and the elderly	+	+++	Acute	A/E lesion, intimin/Tir, EspABD	*Shiga* toxins (Stx1, Stx2, and variants of Stx2)	Detection of *Shiga* toxins by enzyme immunoassays or PCR (*Stx*1, *Stx2*); stool culture on MacConkey-sorbitol media to detect *E. coli* O157. Simultaneous culture for O157 and nonculture assays to detect *Shiga* toxins
EAEC	<2 yr old, HIV-infected patients, and travelers	+++	+	Acute, prolonged, or persistent	Aggregative adherence fimbriae (AAF)	SPATEs (Pic, Pet), ShET1, EAST1	Detection of *AggR*, AA plasmid, and other virulence genes: *aap*, *aatA*, *astA*, *set1A* by PCR; HEp-2 cells adherence assay (AA)
DAEC	>1 yr old and travelers	++	—	Acute	Afa/Dr, AIDA-I	SPATEs (Sat)	Detection of Dr adhesins (daaC or daaD) and Dr-associated genes by PCR; HEp-2 cells adherence assay (DA)

—, Not present; +, present; ++, common; +++, very common; A/E lesion, attaching and effacing lesion; AA, aggregative adherence; Bfp, bundle-forming pili; DA, diffuse adherence; DAEC, diffusely adherent *E. coli;* EAEC, enteroaggregative *E. coli;* EAST1, enteroaggregative heat stable toxin; ECP, *E. coli* common pilus; EHEC, enterohemorrhagic *E. coli;* EIEC, enteroinvasive *E. coli;* EPEC, enteropathogenic *E. coli;* EspABD, *E. coli* secreted proteins A, B, and D; ETEC, enterotoxigenic *E. coli;* LA, localized adherence; LLA, localized-like adherence; PCR, polymerase chain reaction; ShET1, *Shigella* enterotoxin 1; SPATEs, serine protease autotransporter of Enterobacteriaceae; STEC, *Shiga* toxin–producing *E. coli;* Tir, translocated intimin receptor; VTEC, verotoxin-producing *E. coli.*

noninvasive *E. coli*. EIEC are mostly described in outbreaks; however, endemic disease occurs in developing countries where these bacteria can be isolated. In some areas of the developing world as many as 5% of sporadic diarrhea episodes and 20% of bloody diarrhea cases are caused by EIEC strains.

EIEC cause colonic lesions with ulcerations, hemorrhage, mucosal and submucosal edema, and infiltration by polymorphonuclear leukocytes. EIEC strains behave like *Shigella* in their capacity to invade gut epithelium and produce a dysentery-like illness. The invasive process involves initial entry into cells, intracellular multiplication, intracellular and intercellular spread, and host-cell death. All bacterial genes necessary for entry into the host cell are clustered within a 30-kb region of a large virulence plasmid; these genes are closely related to those found on the invasion plasmid of *Shigella* spp. This region carries genes encoding the entry-mediating proteins, which code for proteins forming a type III secretion apparatus required for secreting the invasins (IpaA-D and IpgD). IpaB and IpaC have been identified as the primary effector proteins of epithelial cell invasion. The type III secretion apparatus is a system triggered by contact with host cells; bacteria use it to transport proteins into the host cell plasma membrane and inject toxins into the cytoplasm.

EIEC encompass a small number of serogroups (O28ac, O29, O112ac, O124, O136, O143, O144, O152, O159, O164, O167, and some untypable strains). These serogroups have LPS antigens related to *Shigella* LPS, and, like shigellae, are nonmotile (they lack H or flagellar antigens) and are usually not lactose fermenting.

ENTEROPATHOGENIC *ESCHERICHIA COLI*

EPEC are a major cause of acute, prolonged, and persistent diarrhea in children younger than 2 yr of age in developing countries (20% of infant diarrhea). In developed countries, EPEC are responsible for occasional outbreaks in daycare centers and pediatric wards. Profuse watery, nonbloody diarrhea with mucus, vomiting, and low-grade fever are common symptoms. Prolonged diarrhea (>7 days) and persistent diarrhea (>14 days) can lead to malnutrition, a potentially serious outcome of EPEC infection in infants in the developing world. Studies show that breastfeeding is protective against diarrhea caused by EPEC.

EPEC colonization causes blunting of villi, inflammatory changes, and sloughing of superficial mucosal cells; these lesions can be found from the duodenum through the colon. EPEC induce a characteristic attaching and effacing histopathologic lesion, which is defined by the intimate attachment of bacteria to the epithelial surface and effacement of host cell microvilli. Factors responsible for the attaching and effacing lesion formation are encoded by the locus of enterocyte effacement, which is a pathogenicity island that contains the genes for a type III secretion system, the translocated intimin receptor (Tir) and intimin, and multiple effector proteins such as the *E. coli*–secreted proteins

(EspA-B-D). Some strains adhere to the host's intestinal epithelium in a pattern known as *localized adherence*; this trait is mediated in part by the type IV bundle-forming pilus (Bfp) encoded on a plasmid (the EAF plasmid). After initial contact, proteins are translocated through filamentous appendages forming a physical bridge between the bacteria and the host cell; bacterial effectors (EspB, EspD, Tir) are translocated through these conduits. Tir moves to the surface of host cells, where it is bound by a bacterial outer membrane protein intimin (encoded by the *eae* gene). Intimin-Tir binding triggers polymerization of actin and other cytoskeletal components at the site of attachment. The result of these cytoskeletal changes is intimate bacterial attachment to the host cell, enterocyte effacement, and pedestal formation.

Other locus of enterocyte effacement–encoded effectors include Map, EspF, EspG, EspH, and SepZ. Various other effector proteins are encoded outside the locus of enterocyte effacement and secreted by the type III secretion system (the non–locus of enterocyte effacement–encoded proteins or Nle). The contribution of these putative effectors (NleA/EspI, NleB, NleC, NleD, etc.) to virulence is still under investigation. There is variability in presence and expression of virulence genes among EPEC strains.

The *eae* (intimin) and *bfp*A genes are useful for identifying EPEC and for subdividing this group of bacteria into typical and atypical strains. *E. coli* strains that are $eae^{+}/bfpA^{+}$ are classified as "typical" EPEC; most of these strains belong to classic O:H serotypes. *E. coli* strains that are $eae^{+}/bfpA^{-}$ are classified as "atypical" EPEC. Typical EPEC have been considered for many years to be a leading cause of infantile diarrhea in developing countries and were considered rare in industrialized countries. However, current data suggest that atypical EPEC are more prevalent than typical EPEC in both developed and developing countries, even in persistent diarrhea cases. Determining which of these heterogeneous strains are true pathogens remains a work in progress. In the GEMS, typical EPEC was the main pathogen associated with increased risk of mortality, particularly in infants in Africa.

The classic EPEC serogroups include strains of 12 O serogroups: O26, O55, O86, O111, O114, O119, O125, O126, O127, O128, O142, and O158. However, various *E. coli* strains defined as EPEC based on presence of the intimin gene, belong to nonclassic EPEC serogroups, especially the atypical strains.

SHIGA TOXIN–PRODUCING *ESCHERICHIA COLI*

STEC cause a wide spectrum of diseases. STEC infections may be asymptomatic. Patients who develop intestinal symptoms can have mild diarrhea or severe hemorrhagic colitis. The gastrointestinal illness is characterized by abdominal pain with diarrhea that is initially watery but within a few days can become blood-streaked or grossly bloody. Although this pattern resembles that of shigellosis or EIEC disease, it differs in that fever is an uncommon manifestation. Most persons infected with STEC recover from the infection without further complication. However, 5-10% of children with STEC hemorrhagic colitis go on within a few days to develop systemic complications such as hemolytic–uremic syndrome (HUS), characterized by acute kidney failure, thrombocytopenia, and microangiopathic hemolytic anemia (see Chapter 518). Severe illness occurs most often among children from 6 mo-10 yr of age. STEC-positive young children with bloody diarrhea and neutrophilic leukocytosis in the early course of their diarrhea are at risk for HUS progression. The elderly can also develop HUS or thrombotic thrombocytopenic purpura.

STEC are transmitted person to person (e.g., in families and daycare centers) as well as by food and water; ingestion of a small number of organisms is sufficient to cause disease with some strains. Poorly cooked hamburger is a common cause of foodborne outbreaks, although many other foods (apple cider, lettuce, spinach, mayonnaise, salami, dry fermented sausage, and unpasteurized dairy products) have also been incriminated.

STEC affect the colon most severely. These organisms adhere to intestinal cells, and most strains that affect humans produce attaching-effacing lesions like those seen with EPEC. The attachment mechanism has genes (*intimin, Tir, EspA-D,* etc.) very closely related to those of EPEC. However, in addition to enterocyte attachment, these bacteria produce toxins that kill cells. These toxins (*Shiga* toxins [Stx]) are the key virulence factors of STEC. In the past, these toxins were also called verotoxins or *Shiga*-like toxins. There are 2 major *Shiga* toxin families, Stx1 and Stx2, with multiple subtypes identified by letters (e.g., Stx2a, Stx2c, etc.). Some STEC produce only Stx1 and others produce only one of the variants of Stx2, but many STEC have genes for several toxins. Stx1 is essentially identical to *Shiga* toxin, the protein synthesis–inhibiting exotoxin of *Shigella dysenteriae* serotype 1. Stx2 and variants of Stx2 are more distantly related to *Shiga* toxin, although they share key sequences with it.

These toxins are composed of a single A subunit noncovalently associated with a pentamer composed of identical B subunits. The B subunits bind to globotriaosylceramide (Gb_3), a glycosphingolipid receptor on host cells. The A subunit is taken up by endocytosis. The toxin target is the 28S rRNA, which is depurated by the toxin at a specific adenine residue, causing protein synthesis to cease and affected cells to die. These toxins are carried on lambdoid bacteriophages that are normally inactive when inserted into the bacterial chromosome; when the phages are induced to replicate (e.g., by the stress induced by many antibiotics), they cause lysis of the bacteria and release of large amounts of toxin. It is generally thought that the toxins enter the systemic circulation after translocation across the intestinal epithelium and damage vascular endothelial cells, resulting in activation of the coagulation cascade, formation of microthrombi, intravascular hemolysis, and ischemia.

Clinical outcome of STEC infection depends on both epithelial attachment and the toxin(s) produced by the infecting strain. The Stx2 family of toxins is associated with a higher risk of causing HUS. Strains that make only Stx1 often cause only watery diarrhea and are uncommonly associated with HUS.

The most common STEC serotypes are *E. coli* O157:H7, *E. coli* O111:NM, and *E. coli* O26:H11, although several hundred other STEC serotypes have also been described. *E. coli* O157:H7 is the most virulent serotype and the most frequently associated with HUS; however, other non-O157 serotypes also cause this illness.

ENTEROAGGREGATIVE *ESCHERICHIA COLI*

EAEC are associated with (1) acute, prolonged and persistent pediatric diarrhea in developing countries, most prominently in children younger than 2 yr of age and in malnourished children; (2) acute and persistent diarrhea in HIV-infected adults and children; and (3) acute traveler's diarrhea; EAEC is the second most common cause of travelers' diarrhea after ETEC. Typical EAEC illness is manifested by watery, mucoid, secretory diarrhea with low-grade fever and little or no vomiting. The watery diarrhea can persist for 14 days or longer. In some studies, many patients have grossly bloody stools. EAEC are associated with growth retardation and malnutrition in infants in the developing world.

EAEC form a characteristic biofilm on the intestinal mucosa and induce shortening of the villi, hemorrhagic necrosis, and inflammatory responses. The proposed model of pathogenesis of EAEC involves 3 phases: adherence to the intestinal mucosa by way of the aggregative adherence fimbriae or related adhesins; enhanced production of mucus; and production of toxins and inflammation that results in damage of the mucosa and intestinal secretion. Diarrhea caused by EAEC is predominantly secretory. The intestinal inflammatory response (elevated fecal lactoferrin, interleukin [IL]-8 and IL-1β) may be related to growth impairment and malnutrition.

EAEC are recognized by adherence to HEp-2 cells in an aggregative, stacked-brick–like pattern, called *aggregative adherence* (AA). EAEC virulence factors include the AA fimbriae (AAFI, -II, and -III) that confers the AA phenotype. Some strains produce toxins, including the plasmid-encoded enterotoxin EAST1 (encoded by *ast*A), homolog of the ETEC ST; an autotransporter toxin called Pet; other STATE toxins; and the chromosomally encoded enterotoxin ShET1 (encoded by *setA* and *setB*). Other virulence factors include outer membrane and

secreted proteins such as dispersin (*aap*), and the dispersin transport complex (aatPABCD). EAEC is a heterogeneous group of *E. coli*. The original diagnostic criteria (HEp-2 cell adherence pattern) identified many strains that are probably not true pathogens; genetic criteria appear to more reliably identify true pathogens. A transcriptional activator called AggR controls expression of plasmid-borne and chromosomal virulence factors. Identification of AggR appears to reliably identify illness-associated pathogenic EAEC strains ("typical" EAEC). It has been documented that EAEC *agg*R-positive strains carrying 1, 2, or 3 of the genes *aap*, *ast*A, and *set1A* are significantly associated with diarrhea compared with EAEC isolates lacking these genes. Other than AAF and AggR, there is a great deal of genomic diversity among EAEC strains with corresponding heterogeneity in virulence.

Strains of *E. coli* categorized as EAEC belong to multiple serogroups, including O3, O7, O15, O44, O77, O86, O126, and O127.

DIFFUSELY ADHERENT *ESCHERICHIA COLI*

Although the status of DAEC as true pathogens has been in doubt, multiple studies in both developed and developing countries have associated these organisms with diarrhea, particularly in children after the 1st yr or 2 of life. DAEC strains isolated from children and adults seem to represent 2 different bacterial populations. Discrepancies among epidemiologic studies may be explained by age-dependent susceptibility to diarrhea or by the use of inappropriate detection methods. Data suggest that these organisms also cause traveler's diarrhea in adults. DAEC produces acute watery diarrhea that is usually not dysenteric but is often prolonged.

DAEC strains have been identified on the basis of their diffuse adherence pattern on cultured epithelial cells. Two putative adherence factors have been described for DAEC strains. One of the adherence factors is the surface fimbriae (designated F1845) that are responsible for the diffuse adherence phenotype in a prototype strain. These fimbriae are homologous with members of the Afa/Dr family of adhesins, which are identified by hybridization with a specific probe, *daaC*, common to operons encoding Afa/Dr adhesions. A second putative adhesin associated with the diffuse adherence pattern phenotype is an outer membrane protein, designated AIDA-I. The contribution of other putative effectors (*icuA, fimH, afa, agg-3A, pap, astA, shET1)* to virulence is still under investigation. The only documented secreted factor associated with DAEC infection is the SPATE Sat. Bacteria expressing Afa/Dr adhesins interact with membrane-bound receptors, including decay-accelerating factor. The structural and functional lesions induced by DAEC include loss of microvilli and decrease in the expression and enzyme activities of functional brush-border–associated proteins. Afa/Dr DAEC isolates produce a secreted autotransporter toxin that induces marked fluid accumulation in the intestine. DAEC strains typically induce IL-8 production in vitro. Serogroups of DAEC strains are less-well defined than are those of other diarrheagenic *E. coli*.

ENTEROAGGREGATIVE HEMORRHAGIC *ESCHERICHIA COLI*

In 2011, a massive outbreak of an unusual O104:H4 strain of diarrheagenic *E. coli* began in Germany. Eventually more than 4,000 individuals were sickened with hemorrhagic colitis; illness involved primarily adults (<100 ill children were identified). More than 800 individuals developed HUS and more than 50 died. DNA sequencing showed that this strain was an EAEC that had acquired a lambdoid bacteriophage with genes for producing Stx2a. It was thus a hybrid pathogen with colonization mechanisms like a typical EAEC strain and toxin production typical of an STEC strain. This outbreak strain carries Pic on the chromosome and a pAA-like plasmid encoding AAF, AggR, Pet, ShET1, and dispersin. A second virulence plasmid encodes multiple antibiotic resistances. The high morbidity and mortality associated with this strain may reflect the stronger adherence of EAEC compared with STEC, allowing more Stx to be transferred and more resultant pathology. Some have called this strain an enteroaggregative hemorrhagic *E. coli* or *Shiga* toxin producing EAEC. Whether *Shiga* toxin production in an EAEC background merits separate classification is unclear. Organisms with *Shiga* toxin genes in an atypical EPEC background were designated as a separate group (referred to as STEC, EHEC or verotoxin-producing *E. coli*) before the relative importance of the various genes was clear. As noted above, EPEC are a heterogeneous group themselves. The important issue is not the nomenclature but rather the concept that virulence genes can move between *E. coli* and new variants can arise.

DIAGNOSIS

The clinical features of illness are seldom distinctive enough to allow confident diagnosis, and routine laboratory studies are of very limited value. Diagnosis currently depends heavily on laboratory studies that are not readily available to practitioners. Practical, non–DNA-dependent, methods for routine diagnosis of diarrheagenic *E. coli* have been developed primarily for the STEC. Serotype O157:H7 is suggested by isolation of an *E. coli* that fails to ferment sorbitol on MacConkey sorbitol medium; latex agglutination confirms that the organism contains O157 LPS. Other STEC can be detected in routine hospital laboratories using commercially available enzyme immunoassay or latex agglutination to detect *Shiga* toxins, although variable sensitivity of commercial immunoassays has limited their value.

Although some STEC (O157:H7 strains) can be detected in routine microbiology laboratories using selective media and appropriate antisera, the diagnosis of other diarrheagenic *E. coli* infection is typically made based on tissue culture assays (e.g., HEp-2-cells assay for EPEC, EAEC, DAEC) or identification of specific virulence factors of the bacteria by phenotype (e.g., toxins) or genotype. DNA probes for genes encoding the various virulence traits are the best diagnostic tests but are currently available only as a research tool. Multiplex, real-time, or conventional polymerase chain reaction can be used for presumptive diagnosis of isolated *E. coli* colonies. The genes commonly used for diagnostic polymerase chain reaction are *lt* and *st* for ETEC, *IpaH* or *iaL* for EIEC, *eae* and *bfp*A for EPEC, *eae, Stx1,* and *Stx2* for STEC, *AggR* or the AA plasmid for EAEC, and *daaC* or *daaD* for DAEC. Suspected organisms can be forwarded to reference or research laboratories for definitive evaluation, although such effort is seldom necessary.

Serotyping does not provide definitive identification of pathotypes (except for selected cases such as O157:H7) because each pathotype contains many serotypes and some serotypes can belong to more than 1 pathotype. Consequently, serotyping should not be used routinely for diarrheagenic *E. coli* identification in clinical laboratories (e.g., to diagnose EPEC in infantile diarrhea), except during an outbreak investigation.

Other laboratory data are at best nonspecific indicators of etiology. Fecal leukocyte examination of the stool is often positive with EIEC or occasionally positive with other diarrheagenic *E. coli*. With EIEC and STEC there may be an elevated peripheral blood polymorphonuclear leukocyte count with a left shift. Determination of *Stx2* blood levels in the early postbloody diarrhea period may be useful to identify children at risk of HUS; however, this method requires further evaluation. Fecal lactoferrin, IL-8, and IL-1β can be used as inflammatory markers. Electrolyte changes are nonspecific, reflecting only fluid loss.

TREATMENT

The cornerstone of management is appropriate fluid and electrolyte therapy. In general, this therapy should include oral replacement and maintenance with rehydration solutions such as those specified by the World Health Organization. Pedialyte and other readily available oral rehydration solutions are acceptable alternatives. After refeeding, continued supplementation with oral rehydration fluids is appropriate to prevent recurrence of dehydration. Early refeeding (within 6-8 hr of initiating rehydration) with breast milk or infant formula or solid foods should be encouraged. Prolonged withholding of feeding can lead to chronic diarrhea and malnutrition. If the child is malnourished, oral zinc should be given to speed recovery and decrease the risk of future diarrheal episodes.

Specific antimicrobial therapy of diarrheagenic *E. coli* is problematic because of the difficulty of making an accurate rapid diagnosis of these

pathogens and the unpredictability of antibiotic susceptibilities. Treatment is complicated by the fact that these organisms are often multiply resistant to antibiotics as a consequence of their previous exposure to inappropriate antibiotic therapy. Multiple studies in developing countries have found diarrheagenic *E. coli* strains to be commonly resistant to antibiotics such as trimethoprim-sulfamethoxazole (TMP-SMX) and ampicillin (60-70%). Most data come from case series or clinical trials in adults with traveler's diarrhea. ETEC respond to antimicrobial agents such as TMP-SMX when the *E. coli* strains are susceptible. ETEC cases from traveler's diarrhea trials respond to ciprofloxacin, azithromycin, and rifaximin. However, other than for a child recently returning from travel in the developing world, empirical treatment of severe *watery diarrhea* with antibiotics is seldom appropriate.

EIEC infections may be treated before the availability of culture results because the clinician suspects shigellosis and has begun empirical therapy. If the organisms prove to be susceptible, TMP-SMX is an appropriate choice. Although treatment of EPEC infection with TMP-SMX intravenously or orally for 5 days may be effective in speeding resolution, the lack of a rapid diagnostic test makes treatment decisions difficult. Ciprofloxacin or rifaximin are useful for EAEC traveler's diarrhea, but pediatric data are sparse. Specific therapy for DAEC has not been defined.

The STEC represent a particularly difficult therapeutic dilemma; many antibiotics can induce toxin production and phage-mediated bacterial lysis with toxin release. Antibiotics should not be given for STEC infection because they can increase the risk of HUS (see Chapter 518).

PREVENTION OF ILLNESS

In the developing world, prevention of disease caused by diarrheagenic *E. coli* is probably best done by maintaining prolonged breastfeeding, paying careful attention to personal hygiene, and following proper food- and water-handling procedures. People traveling to these places can be best protected by handwashing, consuming only processed water, bottled beverages, breads, fruit juices, fruits that can be peeled, or foods that are served steaming hot.

Prophylactic antibiotic therapy is effective in adult travelers but has not been studied in children and is not recommended. Public health measures, including sewage disposal and food-handling practices, have made pathogens that require large inocula to produce illness relatively uncommon in industrialized countries. Foodborne outbreaks of STEC are a problem for which no adequate solution has been found. During the occasional hospital outbreak of EPEC disease, attention to enteric isolation precautions and cohorting may be critical.

The nature of protective immunity against diarrheagenic *E. coli* is not fully understood, and no vaccines are available for clinical use in children. There are multiple vaccine candidates based on bacterial toxins and colonization factors that have shown promise for prevention of ETEC in adult travelers, but long-term protection with these vaccines has not been optimal, particularly in children.

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Chapter 201

Cholera

Anna Lena Lopez

Cholera is a dehydrating diarrheal disease that can rapidly lead to death, if appropriate treatment is not immediately initiated. One of the most outbreak-prone diseases, cholera is substantially underreported, with 590,000 cases recorded in 2011 but an estimated 2 million cases and at least 94,000 deaths occurring annually. The past decade has seen an increase in the number of cholera cases, which have been reported in 58 countries affecting all regions of the world over this period. The ongoing outbreak in Haiti that began in 2010 emphasizes how infectious diseases, including cholera, can easily reemerge in areas that have long been considered free of the disease.

ETIOLOGY

The disease is caused by *Vibrio cholerae*, a Gram-negative, comma-shaped bacillus, subdivided into serogroups by its somatic O antigen. Of the more than 200 serogroups, only serogroups O1 and O139 have been associated with epidemics, although some non-O1, non-O139 *V. cholerae* strains (e.g., O75 and O141) are pathogenic and can cause small outbreaks. A flagellar H antigen is present but is not used for species identification. The O1 serogroup is further divided into classical and the El Tor biotypes based on its biochemical characteristics. Since the turn of the 21st century, only O1 El Tor has been reported; hybrids and variants of *V. cholerae* O1 El Tor possessing classical genes have been reported worldwide. These hybrid and variant strains have been associated with more-severe disease.

Each biotype may be further subdivided into Inaba, Ogawa, and Hikojima serotypes based on the antigenic determinants on the O antigen. Inaba strains have A and C antigenic determinants, whereas Ogawa strains have A and B antigenic determinants. Hikojima strains produce all 3 antigenic determinants but are unstable and rare.

EPIDEMIOLOGY

The 1st 6 cholera pandemics originated in the Indian subcontinent and were caused by classical O1 *V. cholerae*. The 7th pandemic is the most extensive of all and is caused by *V. cholerae* O1 El Tor. It began in 1961 in Sulawesi, Indonesia, and has spread to the Indian subcontinent, Southeast Asia, Africa, Oceania, Southern Europe, and the Americas. In 1991, *V. cholerae* O1 El Tor first appeared in Peru before rapidly spreading in the Americas. Cholera becomes endemic in areas following outbreaks when a large segment of the population develops immunity to the disease after recurrent exposure. The disease is now endemic in parts of Africa and Asia and will likely be endemic in Haiti.

In 1992, the first non-O1 *V. cholerae* that resulted in epidemics was identified in India and Bangladesh and was designated *V. cholerae* O139. From 1992-1994, this organism replaced O1 as the predominant cause of cholera in South Asia but has since been an uncommon etiologic agent.

The hybrid El Tor strains were first identified sporadically in Bangladesh. In 2004, during routine surveillance in Mozambique, isolates of *V. cholerae* O1 El Tor carrying classical genes were identified. Since then, hybrid and variant El Tor strains have been reported in other parts of Asia and Africa and have caused outbreaks in India and Vietnam. Although the classical biotype has virtually disappeared, its genes remain within the El Tor biotype. The current circulating strain in Haiti is closely related to the South Asian strain.

Humans are the only known hosts for *V. cholerae* but free-living and plankton-associated *V. cholerae* exist in the marine environment. The organism thrives best in moderately salty water but can survive in rivers and freshwater if nutrient levels are high, as occurs when there is organic pollution such as human feces. The formation of a biofilm on abiotic surfaces and the ability to enter a viable but nonculturable state have been hypothesized as factors that allow *V. cholerae* to persist in the environment. Surface sea temperature, pH, chlorophyll content, the presence of iron compounds and chitin, and climatic conditions such as amount of rainfall and sea level rise are all important environmental factors that influence the survival of *V. cholerae* in the environment and the expression of cholera toxin, an important virulence determinant.

Consumption of contaminated water and ingestion of undercooked shellfish are the main modes of transmission, with the latter more often seen in developed countries. In cholera-endemic areas, the incidence is highest among children <2 yr of age; however, in epidemics, all age groups are commonly affected. Persons with blood group O, decreased gastric acidity, malnutrition, immunocompromised state, and absence of local intestinal immunity (prior exposure by infection or vaccination) are at increased risk for developing severe disease. Household

contacts of cholera-infected patients are at high risk for the disease, because the stools of infected patients contain high concentrations of *V. cholerae*. Moreover, as *V. cholerae* organisms are shed, they enter into a hyperinfective state, requiring a 10-100 times lower infectious dose compared to organisms that were not shed by humans.

PATHOGENESIS

Following ingestion of *V. cholerae* from the environment, several changes occur in the vibrios as they traverse the human intestine: increased expression of genes required for nutrient acquisition, down-regulation of chemotactic response, and expression of motility factors. Together these changes allow the vibrios to reach a hyperinfectious state, leading to lower infectious doses required in secondarily infected persons. This hyperinfectivity may remain for 5-24 hr after excretion.

Large inocula of bacteria (>10^8) are required for severe cholera to occur; however, for persons whose gastric barrier is disrupted, a much lower dose (10^5) is required. If the vibrios survive gastric acidity, they then colonize the small intestine through various factors such as toxin coregulated pili and motility, leading to efficient delivery of cholera toxin. The cholera toxin consists of 5 binding B subunits and 1 active A subunit. The B subunits are responsible for binding to the GM_1 ganglioside receptors located in the small intestinal epithelial cells. After binding, the A subunit is then released into the cell, where it stimulates adenylate cyclase and initiates a cascade of events. An increase in cyclic adenosine monophosphate leads to an increase in chloride secretion by the crypt cells, which, in turn, leads to inhibition of absorption of sodium and chloride by the microvilli. These events eventually lead to massive purging of electrolyte rich isotonic fluid in the small intestine that exceeds the absorptive capacity of the colon, resulting in rapid dehydration and depletion of electrolytes, including sodium, chloride, bicarbonate, and potassium. Metabolic acidosis and hypokalemia then ensue.

CLINICAL MANIFESTATIONS

Most cases of cholera are mild or inapparent. Among symptomatic cases, approximately 20% develop severe dehydration that can rapidly lead to death. Following an incubation period of 1-3 days (range: several hours to 5 days), acute watery diarrhea and vomiting ensues. The onset may be sudden, with profuse watery diarrhea, but some patients have a prodrome of anorexia and abdominal discomfort and the stool may initially be brown. Diarrhea can progress to painless purging of profuse rice-water stools (suspended flecks of mucus) with a fishy smell, which is the hallmark of the disease (Fig. 201-1). Vomiting with clear watery fluid is usually present at the onset of the disease.

Cholera gravis, the most severe form of the disease, results when purging rates of 500-1,000 mL/hr occur. This purging leads to dehydration manifested by decreased urine output, a sunken fontanel (in infants), sunken eyes, absence of tears, dry oral mucosa, shriveled hands and feet (washerwoman's hands), poor skin turgor, thready pulse, tachycardia, hypotension, and vascular collapse (Fig. 201-2). Patients with metabolic acidosis can present with typical Kussmaul breathing. Although patients may be initially thirsty and awake, they rapidly progress to obtundation and coma. If fluid losses are not rapidly corrected, death can occur within hours.

LABORATORY FINDINGS

Findings associated with dehydration such as elevated urine specific gravity and hemoconcentration are evident. Hypoglycemia is a common finding that is caused by decreased food intake during the acute illness. Serum potassium may be initially normal or even high in the presence of metabolic acidosis; however, as the acidosis is corrected, hypokalemia can become evident. Metabolic acidosis due to bicarbonate loss is a prominent finding in severe cholera. Serum sodium and chloride levels may be normal or decreased, depending on the severity of the disease.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In children who have acute watery diarrhea with severe dehydration residing in a cholera endemic area or who have recently traveled to an area known to have cholera, the disease may be suspected pending laboratory confirmation. Cholera differs from other diarrheal disease in that it often occurs in large outbreaks affecting both adults and children.

Figure 201-1 Rice water stool in a patient with cholera. *(Modified from Harris JB, LaRocque RC, Qadri F: Cholera.* Lancet *379:2466–2474, 2012.)*

Figure 201-2 A child, lying on a cholera cot, showing typical signs of severe dehydration from cholera. The patient has sunken eyes, lethargic appearance, and poor skin turgor, but within 2 hr was sitting up, alert, and eating normally. *(From Sack DA, Sack RB, Nair GB, et al: Cholera.* Lancet *363:223–233, 2004.)*

Treatment of dehydration should begin as soon as possible. Diarrhea caused by other etiologic causes (e.g., enterotoxigenic *Escherichia coli* or rotavirus) may be difficult to distinguish from cholera clinically. Microbiologic isolation of *V. cholerae* remains the gold standard for diagnosis. Although definitive diagnosis is not required for treatment to be initiated, laboratory confirmation is necessary for epidemiologic surveillance. *V. cholerae* may be isolated from stools, vomitus, or rectal swabs. Specimens may be transported on Cary-Blair media, if they

cannot be processed immediately. Selective media such as thiosulfate–citrate–bile salts sucrose agar that inhibit normal flora should be used. Because most laboratories in industrialized countries do not routinely culture for *V. cholerae*, clinicians should request appropriate cultures for clinically suspected cases.

Stool examination reveals few fecal leukocytes and erythrocytes because cholera does not cause inflammation. Dark-field microscopy may be used for rapid identification of typical "darting motility" in wet mounts of rice water stools, which disappears once specific antibodies against *V. cholerae* O1 or O139 are added. Rapid diagnostic tests are currently available and in the future may be used in areas with limited laboratory capacity, allowing early identification of cases at the onset of an outbreak and facilitating a timely response. Molecular identification with the use of polymerase chain reaction and DNA probes is available but often not used in areas where cholera exists.

COMPLICATIONS

Delayed initiation of rehydration therapy or inadequate rehydration often leads to complications. Renal failure from prolonged hypotension can occur. Unless potassium supplementation is provided, hypokalemia can lead to nephropathy and focal myocardial necrosis. Hypoglycemia is common among children and can lead to seizures unless it is appropriately corrected.

TREATMENT

Rehydration is the mainstay of therapy (see Chapter 57). Effective and timely case management considerably decreases mortality. Children with mild or moderate dehydration may be treated with oral rehydration solution (ORS) unless the patient is in shock, is obtunded, or has intestinal ileus. Vomiting is not a contraindication to ORS. Severely dehydrated patients require intravenous fluid, ideally with lactated Ringer solution. When available, rice-based ORS should be used during rehydration, because this fluid has been shown to be superior to standard ORS in children and adults with cholera. Close monitoring is necessary, especially during the 1st 24 hr of illness, when large amounts of stool may be passed. After rehydration, patients have to be reassessed every 1-2 hr, or more frequently if profuse diarrhea is ongoing. Feeding should not be withheld during diarrhea. Frequent, small feedings are better tolerated than less-frequent, large feedings.

Antibiotics should only be given in cases with moderately severe to severe dehydration (Table 201-1). As soon as vomiting stops (usually within 4-6 hr after initiation of rehydration therapy), an antibiotic to which local *V. cholerae* strains are sensitive must be administered. Antibiotics shorten the duration of illness, decrease fecal excretion of vibrios, decrease the volume of diarrhea, and reduce the fluid requirement during rehydration. Single-dose antibiotics increase compliance; doxycycline, ciprofloxacin, and azithromycin are effective against cholera. There are increasing reports of resistance to tetracyclines, trimethoprim-sulfamethoxazole, and other drugs. Because of these multidrug resistant strains, antibiotic treatment must be tailored based on available susceptibility results from the area. Cephalosporins and aminoglycosides are not clinically effective against cholera and therefore should not be used, even if in vitro tests show strains to be sensitive.

Zinc should be given as soon as vomiting stops. Zinc deficiency is common among children in many developing countries. Zinc supplementation among children younger than 5 yr of age shortens the duration of diarrhea and reduces subsequent diarrhea episodes when given daily for 14 days at the time of the illness. Children younger than 6 mo of age should receive 10 mg of oral zinc for 2 wk, and for children older than 6 mo, 20 mg of oral zinc may be given daily.

PREVENTION

Improved personal hygiene, access to clean water, and sanitation are the mainstays of cholera control. Appropriate case management substantially decreases case fatalities to <1%. Travelers from developed countries often have no prior exposure to cholera and are therefore at risk of developing the disease. Children traveling to cholera-affected areas should avoid drinking potentially contaminated water and eating high-risk foods such as raw or undercooked fish and shellfish. No country or territory requires vaccination against cholera as a condition for entry. There is no cholera vaccine licensed in the United States.

Alarmed by the increasing prevalence of cholera, in 2011, the World Health Assembly recommended the use of oral cholera vaccines to complement existing water, sanitation, and hygiene initiatives for cholera control. Older-generation parenteral cholera vaccines have not been recommended by World Health Organization because of the limited protection they confer and their high reactogenicity. Oral cholera vaccines are safe, protective for approximately 2-5 yr duration, and confer moderate herd protection. Two oral cholera vaccines are currently available internationally and recognized by World Health Organization (Table 201-2). An internationally licensed killed whole-cell oral cholera vaccine with recombinant B subunit (Dukoral, Crucell) has been available in more than 60 countries, including the European Union, and provides protection against cholera in endemic areas as well as cross-protection against certain strains of enterotoxigenic *E.*

Table 201-1 Recommended Antimicrobials for Cholera*

RECOMMENDING BODY	ANTIBIOTIC OF CHOICE	ALTERNATIVE
WHO† (antibiotics recommended for cases with severe dehydration)	**Adults** Doxycycline 300 mg given as a single dose PO *or* Tetracycline 500 mg 4 times a day × 3 days PO **Children** Tetracycline 12.5 mg/kg/dose 4 times a day × 3 days (up to 500 mg per dose × 3 days) PO	**Adults** Erythromycin 250 mg 4 times a day × 3 days PO **Children** Erythromycin 12.5 mg/kg/dose 4 times a day × 3 days (up to 250 mg 4 times a day × 3 days) PO
PAHO‡ (antibiotics recommended for cases with moderate to severe dehydration)	**Adults** Doxycycline 300 mg PO given as a single dose **Children** Erythromycin 12.5 mg/kg/dose 4 times a day × 3 days (up to 500 mg per dose × 3 days) *or* Azithromycin, 20 mg/kg as a single dose (up to 1 g)	**Adults** Ciprofloxacin 1g PO single dose *or* Azithromycin 1g PO single dose **Children** Ciprofloxacin 20 mg/kg PO as a single dose *or* Doxycycline 2-4 mg/kg PO as a single dose

*Antibiotic selection must be based on sensitivity patterns of strains of *Vibrio cholerae* O1 or O139 in the area.

†Adapted from World Health Organization: *The treatment of diarrhea: a manual for physicians and other senior health workers*, 4th revision, Geneva, 2005, World Health Organization.

‡Adapted from Pan American Health Organization: *Recommendations for clinical management of cholera.* Washington, DC, 4 November 2010. Available at: http://new.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=10813&Itemid=

Table 201-2 Available Oral Cholera Vaccines*

VACCINE TRADE NAME	CONTENTS	DOSING SCHEDULE
Dukoral (Crucell)	1 mg of recombinant B subunit of cholera toxin plus 2.5 × 10^{10} of the following strains of *V. cholerae*: - Formalin-killed El Tor Inaba (Phil 6973) - Heat-killed classical Inaba (Cairo 48) - Heat-killed classical Ogawa (Cairo 50) - Formalin-killed classical Ogawa (Cairo 50)	Children 2-6 yr: 3 doses, 1-6 wk apart Adults and children >6 yr: 2 doses, 1-6 wk apart
Shanchol (Shantha Biotech)	*V. cholerae* O1 - 600 EU Formalin-killed El Tor Inaba (Phil 6973) - 300 EU Heat-killed classical Inaba (Cairo 48) - 300 EU Heat-killed classical Ogawa (Cairo 50) - 300 EU Formalin-killed classical Ogawa (Cairo 50) *V. cholerae* O139-600 EU of Formalin-killed strain 4260B	Adults and children ≥1 year of age: 2 doses, 2 wk apart

*WHO prequalified vaccines.

coli. The 2nd vaccine (Shanchol, Shantha Biotech) is a variant of the 1st vaccine and contains both *V. cholerae* O1 and O139 antigens but does not contain the B-subunit. Because it does not contain the B-subunit, the vaccine does not require buffer for administration, thereby reducing administration costs and resources, making it easier to deploy.

Oral cholera vaccines have been available for more than 2 decades and are mostly used by travelers from industrialized countries going to cholera-affected regions. With the World Health Organization declaration, countries are now using oral cholera vaccines in mass vaccination campaigns where cholera remains a substantial problem. A cholera vaccine stockpile, established by WHO, is now available and can be accessed by countries at risk for cholera, supplementing efforts to lessen the impact of this ongoing cholera scourge.

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Chapter 202

Campylobacter

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Campylobacter, most commonly *Campylobacter jejuni* and *Campylobacter coli*, are found globally and are among the most common causes of human intestinal infections. Clinical presentation varies by age and underlying conditions.

ETIOLOGY

Eighteen species and 6 subspecies of *Campylobacter* are recognized at this time. Most of these have been isolated from humans, and many are considered pathogenic. The most significant of these are *C. jejuni* and *C. coli,* which may cause the majority of human enteritis. More than 100 serotypes of *C. jejuni* have been identified. *C. jejuni* has been subspeciated into *C. jejuni* subspecies *jejuni* and *C. jejuni* subspecies *doylei.* Although *C. jejuni* subspecies *doylei* has been isolated from humans, it is much less common, less hearty, and more difficult to isolate. Other species, including *Campylobacter fetus, Campylobacter lari,* and *Campylobacter upsaliensis,* among others, have been isolated from patients with diarrhea, although much less frequently (Table 202-1). Additional *Campylobacter* species have been isolated from clinical specimens, but their roles as pathogens have not been established.

Campylobacter organisms are Gram-negative, curved, thin (0.2-0.4 μm wide), non–spore-forming rods (1.5-3.5 μm long) that usually have tapered ends. They are smaller than most other enteric bacterial pathogens and have variable morphology, including short comma-shaped or S-shaped organisms and long, multispiraled, filamentous, seagull-shaped organisms. Individual organisms are usually motile with a flagellum at 1 or both poles. Such morphology enables these bacteria to colonize the mucosal surfaces of both the gastrointestinal and respiratory tracts and move through them in a spiraling motion. Most *Campylobacter* organisms are microaerophilic, occasionally partially anaerobic, and oxidase positive. Most can transform into coccoid forms under adverse conditions, especially oxidation.

C. jejuni has a circular chromosome of 1.64 million base pairs that is predicted to encode 1,654 proteins and 54 stable RNA species. The genome is unusual in that there are almost no insertion sequences or phage-associated sequences and very few repeat sequences.

EPIDEMIOLOGY

Worldwide, *Campylobacter* enteritis is a leading cause of acute diarrhea. Efforts to reduce *Campylobacter* contamination and safe handling practices have caused decreased incidence. *Campylobacter* infections can be both foodborne and waterborne, and most commonly result from ingestion of contaminated poultry (chicken, turkey) or raw milk. Less commonly, they come from drinking water, household pets (cats, dogs, hamsters), and farm animals. Infections are more common in resource-limited settings, are prevalent year-round in tropical areas, and can exhibit seasonal peaks in temperate regions (late spring with a peak midsummer in most of the United States, with a smaller secondary peak in late fall). In industrialized countries, *Campylobacter* infections peak in early childhood and again in young adulthood (15-44 yr of age). The second peak is not seen with *Salmonella* and *Shigella* infections. In developing countries, repeated infections are common in childhood, leading to increased immunity and rare disease in adulthood. Each year in the United States, there are an estimated 2.5 million cases of *Campylobacter* infection. Of these, death is rare, with 50-150 reports annually. In the Netherlands, medical record review shows that on average each resident acquires asymptomatic *Campylobacter* infection every 2 yr, progressing to symptomatic infection in approximately 1% of colonized people.

Foodborne illness is most common and can be seen with the consumption of raw or undercooked meat, as well as by cross-contamination of other foods. Although chickens are the classic source of *Campylobacter,* many animal sources of human food can also harbor *Campylobacter,* including seafood. *C. coli* has been linked to swine. Poultry is more likely to be heavily contaminated while red meats often have fewer organisms. Unpasteurized milk products are also a documented source. Additionally, many pets can carry *Campylobacter,* and insects inhabiting contaminated environments can acquire the organism. Shedding from animals can contaminate water sources. Humans can acquire infection from water, although much less frequently than from contaminated food. Airborne transmission of *Campylobacter* has occurred in farm workers. Use of antimicrobials in animal foods may

Table 202-1 *Campylobacter* Species Associated with Human Disease

SPECIES	DISEASES IN HUMANS	COMMON SOURCES
C. jejuni	Gastroenteritis, bacteremia, Guillain-Barré syndrome	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, water
C. coli	Gastroenteritis, bacteremia	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, oysters, water
C. fetus	Bacteremia, meningitis, endocarditis, mycotic aneurysm, diarrhea	Sheep, cattle, birds, dogs
C. hyointestinalis	Diarrhea, bacteremia, proctitis	Swine, cattle, deer, hamsters, raw milk, oysters
C. lari	Diarrhea, colitis, appendicitis, bacteremia, urinary tract infection	Seagulls, water, poultry, cattle, dogs, cats, monkeys, oysters, mussels
C. upsaliensis	Diarrhea, bacteremia, abscesses, enteritis, colitis, hemolytic uremic syndrome	Cats, dogs, other domestic pets
C. concisus	Diarrhea, gastritis, enteritis, periodontitis	Human oral cavity, dogs
C. sputorum	Diarrhea, bedsores, abscesses, periodontitis	Human oral cavity, cattle, swine, dogs
C. rectus	Periodontitis	
C. mucosalis	Enteritis	Swine, dogs
C. jejuni subspecies *doylei*	Diarrhea, colitis, appendicitis, bacteremia, urinary tract infection	Swine
C. curvus	Gingivitis, alveolar abscess	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, water, human oral cavity
C. gracilis	Head and neck abscesses, abdominal abscesses, empyema	Dogs
C. cryaerophila	Diarrhea	Swine

increase the prevalence of antibiotic-resistant *Campylobacter* isolated from humans.

Human infection can result from exposure to as few as 500 bacteria, although a higher dose (>9,000 bacteria) is often needed to cause illness. At times, *C. jejuni* and *C. coli* spread person to person, perinatally, and at childcare centers where diapered toddlers are present. People infected with *C. jejuni* usually shed the organism for weeks but can shed for months. Hand washing is key to preventing spread in these environments.

PATHOGENESIS

Most *Campylobacter* isolates are acid sensitive, and should, in theory, be eradicated in the stomach. Therefore, models for the pathogenesis of *C. jejuni* enteritis include mechanisms to transit the stomach, adhere to intestinal mucosal cells, and initiate intestinal lumen fluid accumulation. Host conditions associated with reduced gastric acidity, such as proton pump inhibitor use, and foods capable of shielding organisms in transit through the stomach may help allow *Campylobacter* to reach the intestine. Once there, *Campylobacter* are able to adhere to and invade intestinal mucosal cells through motility, including use of flagellae, as well as by the use of surface proteins (e.g., PEB1 and CadF), large plasmids (e.g., pVir), surface adhesins (e.g., JIpA), and chemotactic factors. Lumen fluid accumulation is associated with direct damage to mucosal cells resulting from bacterial invasion and potentially from a cholera-like toxin and other cytotoxins. Additionally, *C. jejuni* has mechanisms that enable transit away from the mucosal surface. The factors that are used are dependent on the species involved.

Campylobacter differ from other enteric bacterial pathogens in that they have both *N*- and *O*-linked glycosylation capacities. *N*-linked glycosylation is associated with molecules expressed on the bacterial surface, and *O*-linked glycosylation appears limited to flagellae. Slipped-strand mispairing in glycosylation loci results in modified, antigenically distinct surface structures. It is hypothesized that antigenic variation provides a mechanism for immune evasion.

C. fetus possesses a high-molecular-weight S-layer protein that mediates high-level resistance to serum-mediated killing and phagocytosis and is therefore thought to be responsible for the propensity to produce **bacteremia.** *C. jejuni* and *C. coli* are generally sensitive to serum-mediated killing, but serum-resistant variants exist. It has been suggested that these serum-resistant variants may be more capable of systemic dissemination.

Campylobacter infections can be followed by Guillain-Barré syndrome, reactive arthritis, and erythema nodosum. Such complications are thought to be from molecular mimicry between nerve tissue and *Campylobacter* surface antigens. Most *Campylobacter* infections are not followed by immunoreactive complications, indicating that host conditions as well as other factors, in addition to molecular mimicry, are required for these complications. There is some evidence of an association between *Campylobacter* infection and irritable bowel syndrome. It is proposed that low-grade inflammation caused by *Campylobacter,* below the threshold that can be detected by endoscopy, results in crosstalk with gut nerves, leading to symptoms.

CLINICAL MANIFESTATIONS

There are a variety of clinical presentations of *Campylobacter* infections, depending on host factors such as age, immunocompetence, and underlying conditions. Infection presents most commonly as gastroenteritis, but also as bacteremia, neonatal infections, and, occasionally, extraintestinal infections.

Acute Gastroenteritis

Diarrhea is most commonly caused by *C. jejuni* (90-95%) or *C. coli,* and rarely by *C. lari, Campylobacter hyointestinalis,* or *C. upsaliensis.* The average incubation period is 3 days (range: 1-7 days). One-third of symptomatic patients can have a prodrome with fever, headache, dizziness, and myalgias; 1-3 days later, they develop cramping abdominal pain and loose, watery stools or, less commonly, bloody, mucus-containing stools. In severe cases (approximately 15%), blood appears in the stools 2-4 days after the onset of symptoms. In younger children, more than 50% may develop blood in their stools. Some patients do not develop diarrhea at all, most commonly children 6-15 yr old. Fever may be the only manifestation initially and is most pronounced in patients older than 1 yr of age. Febrile seizures can also occur in this age group. Sixty percent to 90% of older children also complain of

abdominal pain. The abdominal pain is most commonly periumbilical and sometimes persists after the stools return to normal. The abdominal pain can mimic appendicitis, colitis, or intussusception. Nausea is common, with up to 25% of adults developing vomiting. Vomiting tends to be more common the younger the patient and is most frequent in infants.

Diarrhea lasts around 7 days and will resolve spontaneously. More mild disease can last 1-2 days; 20-30% of patients will have symptoms for 2 wk and 5-10% are symptomatic for longer than 2 wk. Relapse can occur in 5-10% of patients. Persistent or recurrent *Campylobacter* gastroenteritis has been reported in immunocompetent patients, in patients with hypogammaglobulinemia (both congenital and acquired), and in patients with AIDS. Persistent infection can mimic chronic inflammatory bowel disease; therefore, *Campylobacter* infection should also be considered when evaluating for inflammatory bowel disease. There is some suggestion that infection may also be the trigger for the development of inflammatory bowel disease. Fecal shedding of the organisms in untreated patients usually lasts for 2-3 wk, with a range from a few days to several months. Shedding tends to occur longer in young children. Acute appendicitis, mesenteric lymphadenitis, and ileocolitis have been reported in patients who have had appendectomies during *C. jejuni* infection.

Bacteremia

Transient bacteremia has been shown in early acute infection in 0.1-1% of patients. With the exception of bacteremia caused by *C. fetus*, bacteremia with *Campylobacter* occurs most often among malnourished children, patients with chronic illnesses or immunodeficiency, such as HIV, and in the very old and very young. Bacteremia can also occur in patients without underlying disease. The majority of cases of bacteremia are asymptomatic. *C. fetus* causes bacteremia in adults with or without identifiable focal infection, usually in the setting of underlying conditions such as malignancy or diabetes mellitus. When symptomatic, *C. jejuni* bacteremia is associated with fever, headache, malaise, and abdominal pain. Relapsing or intermittent fever is associated with night sweats, chills, and weight loss when the illness is prolonged. Lethargy and confusion can occur, but focal neurologic signs are unusual without cerebrovascular disease or meningitis. A cough is present occasionally, without additional evidence of pulmonary involvement. Moderate leukocytosis may be found. Variable presentations, including transient asymptomatic bacteremia, rapidly fatal septicemia, and prolonged bacteremia of 8-13 wk, have been described.

Focal Extraintestinal Infections

Focal infections caused by *C. jejuni* are rare and occur mainly among neonates and immunocompromised patients. Multiple sites have been reported including meningitis, pneumonia, thrombophlebitis, pancreatitis, cholecystitis, ileocecitis, urinary tract infection, arthritis, peritonitis, myocarditis, pericarditis, and endocarditis. *C. fetus* shows a predilection for vascular endothelium, leading to endocarditis, pericarditis, thrombophlebitis, and mycotic aneurysms. *C. hyointestinalis* has been associated with proctitis; *C. upsaliensis* has been associated with breast abscesses; *Campylobacter rectus* has been associated with periodontitis.

Perinatal Infections

Perinatal infections are most often acquired at birth from a mother infected with or shedding *Campylobacter*. Maternal *C. fetus* and *C. jejuni* infections may be asymptomatic and can result in abortion, stillbirth, premature delivery, or neonatal infection with sepsis and meningitis. Severe perinatal infections are uncommon and are caused most often by *C. fetus* and rarely by *C. jejuni*. Neonatal infection with *C. jejuni* is associated with diarrhea that may be bloody. Nosocomial infections in nurseries have also been described.

DIAGNOSIS

The clinical presentation of *Campylobacter* enteritis can be similar to that of enteritis caused by other bacterial pathogens. The differential diagnosis includes *Shigella, Salmonella, Escherichia coli*, *Yersinia enterocolitica, Aeromonas, Vibrio parahaemolyticus,* and amebiasis. Fecal leukocytes are found in as many as 75% of cases, and fecal blood is present in 50% of cases. *Campylobacter* should be considered in patients with bloody stools, fever, and abdominal pain.

The diagnosis of *Campylobacter* enteritis is usually confirmed by identification of the organism in cultures of stool or rectal swabs. Isolation is most likely from selective media such as CAMPY-agar grown in microaerophilic conditions (5-10% oxygen), 1-10% carbon dioxide, with some hydrogen. Some *C. jejuni* grow best at 42°C (107.6°F). Growth on solid media results in small (0.5-1.0 mm), slightly raised, smooth colonies. Organisms can be identified from stool under the microscope in approximately 50% of known *Campylobacter* cases. Gram stain is even less sensitive. Stool culture is greater than 90% sensitive and is the standard method of diagnosis. Visible growth on stool culture is most often present in 1-2 days. Visible growth in blood cultures is often not apparent until 5-14 days after inoculation.

Routine culture may be adequate for isolation of *C. jejuni* because of the large numbers of bacteria that are often present. However, because campylobacters grow more slowly under routine conditions than do other enteric bacteria, routine culture can result in failure because of overgrowth of other enteric bacteria. Culture for campylobacters can be enhanced, when necessary, with selective media. However, selective culture media developed to enhance isolation of *C. jejuni* may inhibit the growth of other *Campylobacter* species. Filtration methods are available and can preferentially enrich for *Campylobacter* by selecting for their small size. These methods allow subsequent culture of the enriched sample on antibiotic free media, enhancing rates of isolation of *Campylobacter* organisms inhibited by the antibiotics included in standard selective media. Isolation of *Campylobacter* from normally sterile sites does not require enhancement procedures. Clinically, it is not necessary to speciate *Campylobacter,* as clinical disease is the same. Speciation can be done, when needed, and specialized labs can perform strain typing when required for epidemiologic purposes.

For rapid diagnosis of *Campylobacter* enteritis, direct carbol fuchsin stain of fecal smear, indirect fluorescence antibody test, dark-field microscopy, or latex agglutination can be used. Enzyme immunoassay and polymerase chain reaction have been tested and used in research studies but are not currently available in the clinical setting. These tests are quite sensitive. However, there continues to be concern regarding the specificity of these tests. In a recent study published in 2013, enzyme immunoassay had a positive predictive value of 91% in verification studies, which dropped to 42% in routine diagnostic studies. Polymerase chain reaction seems to be more specific and currently is being studied regarding differentiation of species. At this time, the recommendation remains to confirm all positive rapid tests with culture. Serologic diagnosis is also possible. This is especially important in patients with late-onset reactive arthritis or Guillain-Barré syndrome, as these patients may have negative stool cultures.

COMPLICATIONS

Severe, prolonged *C. jejuni* infection can occur in patients with immunodeficiencies, including hypogammaglobulinemia and malnutrition. In patients with AIDS, increased frequency and severity of *C. jejuni* infection have been reported; severity correlates inversely with CD4 count. Complications can include acute complications, as described earlier, and late onset complications that may present after the acute infection has resolved. The most common late-onset complications include reactive arthritis and Guillain-Barré syndrome.

Reactive Arthritis

Reactive arthritis can accompany *Campylobacter* enteritis in adolescents and adults, especially in patients who are positive for HLA-B27. Reactive arthritis occurs in up to 3% of patients, though up to 13% may have joint symptoms. This manifestation appears most commonly 1-2 wk after the onset of diarrhea, but has been seen 5-40 days later. It involves mainly large joints and resolves without sequelae. The arthritis is typically migratory and occurs without fever. Synovial fluid lacks bacteria. The arthritis responds well to nonsteroidal antiinflammatory

drugs and typically resolves after 1 wk to several months. Reactive arthritis with conjunctivitis, urethritis, and rash (including erythema nodosum) also occurs, but is less common.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is an acute demyelinating disease of the peripheral nervous system characterized clinically by acute flaccid paralysis and is the most common cause of neuromuscular paralysis worldwide. GBS carries a mortality rate of approximately 2%, and approximately 20% of patients with this disease develop major neurologic sequelae. *C. jejuni* has been identified as the trigger in up to 45% of patients with GBS and is most closely linked to the serotypes Penner O19 and O14. It has been reported 1-12 wk after *C. jejuni* gastroenteritis in 1 of every 1,000 *C. jejuni* infections. Stool cultures obtained from patients with GBS at the onset of neurologic symptoms have yielded *C. jejuni* in greater than 25% of the cases. Serologic studies suggest that 20-45% of patients with GBS have evidence of recent *C. jejuni* infection. Molecular mimicry between nerve tissue GM_1 ganglioside and *Campylobacter* surface antigens may be the triggering factor in *Campylobacter*-associated GBS. The Miller-Fisher variant, which more commonly affects cranial nerves, is characterized by ataxia, areflexia, and ophthalmoplegia, and is linked to cross-reacting antibodies to the GQ1b ganglioside found in cranial nerve myelin. The next common serotype is Penner O2. When associated with *Campylobacter,* GBS is more likely to be the axonal form and has a worse prognosis with slower recovery and more neurologic disability. The management of GBS includes supportive care, intravenous immunoglobulin, and plasma exchange.

Other Complications

Immunoglobulin A nephropathy and immune complex glomerulonephritis with *C. jejuni* antigens in the kidneys have been reported. *Campylobacter* infection has also been associated with hemolytic anemia.

TREATMENT

Fluid replacement, correction of electrolyte imbalance, and supportive care are the mainstays of treatment of children with *Campylobacter* gastroenteritis. Antimotility agents can cause prolonged or fatal disease and should not be used. The need for antibiotic therapy in patients with uncomplicated gastroenteritis is controversial. Data suggest a shortened duration of symptoms (by an average of 1.3 days) and intestinal shedding of organisms if antibiotics are initiated early in the disease.

Most *Campylobacter* isolates are susceptible to macrolides, fluoroquinolones, aminoglycosides, chloramphenicol, tetracyclines, and clindamycin, and are resistant to cephalosporins, rifampin, penicillins, trimethoprim, and vancomycin. Resistance to tetracyclines, macrolides, and fluoroquinolones has been described. Antibiotic resistance among *C. jejuni* has become a serious worldwide problem. Macrolide resistance is increased in areas such as Thailand and Ireland, whereas fluoroquinolone resistance has been reported in Spain, Hungary, and multiple developing countries in greater than 50% of cultured *Campylobacter*. Fluoroquinolone resistance continues to increase in the United States and is related to the use of quinolones in veterinary medicine and food products, as well as acquisition from travelers. Erythromycin-resistant *Campylobacter* isolates are uncommon; therefore, erythromycin or azithromycin is the drug of choice if therapy is required. Drug sensitivities should be determined for patients who do not respond to therapy. Antibiotics are recommended for patients with bloody stools, high fever, or a severe course, and for children who are immunosuppressed or have underlying diseases. Sepsis is treated with parenteral antibiotics such as an aminoglycoside, meropenem, or imipenem. Extraintestinal infections should also be treated with antibiotics. For extraintestinal infection caused by *C. fetus*, prolonged therapy is advised. *C. fetus* isolates resistant to erythromycin have been reported.

PROGNOSIS

Although *Campylobacter* gastroenteritis is usually self-limited, immunosuppressed children (including children with AIDS) can experience a protracted or severe course. Septicemia in newborns and immunocompromised hosts has a poor prognosis, with an estimated mortality rate of 30-40%. Additional prognosis is based upon the secondary sequelae that may develop.

PREVENTION

Most human *Campylobacter* infections are sporadic and are acquired from infected animals or contaminated foods. Interventions to minimize transmission include cooking meats thoroughly, preventing recontamination after cooking by not using the same surfaces, utensils, or containers for both uncooked and cooked food, and avoiding unpasteurized dairy products. Also, it is important to ensure that water sources are not contaminated and that water is kept in clean containers. Contact with infected animals should be avoided. No specific isolation is required; standard precautions are sufficient. However, children in diapers should be kept out of daycare until the diarrhea resolves. Breastfeeding appears to decrease symptomatic *Campylobacter* disease but does not reduce colonization.

Several approaches at immunization have been studied, including the use of live-attenuated organisms, subunit vaccines, and killed whole-cell vaccines. No vaccine is currently available.

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Chapter 203
Yersinia

Ramia Zakhour, Gloria P. Heresi, and James R. Murphy

The genus *Yersinia* is a member of the family Enterobacteriaceae and comprises more than 14 named species, 3 of which are established as human pathogens. *Yersinia enterocolitica* is by far the most common *Yersinia* species causing human disease and it produces fever, abdominal pain that can mimic appendicitis, and diarrhea. *Yersinia pseudotuberculosis* is most often associated with mesenteric lymphadenitis. *Yersinia pestis* is the agent of plague and most commonly causes an acute febrile lymphadenitis (bubonic plague) and less commonly occurs as septicemic, pneumonic, pharyngeal, or meningeal plague. Other *Yersinia* organisms are uncommon causes of infections of humans, and their identification is often an indicator of immunodeficiency. *Yersinia* is enzootic and can colonize pets. Infections in humans are incidental and most often result from contact with infected animals or their tissues; ingestion of contaminated water, milk, or meat; or, for *Y. pestis,* the bite of infected fleas. Association with human disease is less clear for *Yersinia frederiksenii, Yersinia intermedia, Yersinia kristensenii*, *Yersinia aldovae, Yersinia bercovieri, Yersinia mollaretii, Yersinia rohdei,* and *Yersinia ruckeri*. Some *Yersinia* isolates replicate at low temperatures (1-4°C [33.8-39.2°F]) or survive at high temperatures (50-60°C [122-140°F]). Thus, common food preparation and storage and common pasteurization methods might not limit the number of bacteria. Most are sensitive to oxidizing agents.

203.1 *Yersinia enterocolitica*

Ramia Zakhour, Gloria P. Heresi, and James R. Murphy

ETIOLOGY

Y. enterocolitica is a large, Gram-negative coccobacillus that exhibits little or no bipolarity when stained with methylene blue and carbol

fuchsin. It ferments glucose and sucrose but not lactose, is oxidase-negative, and reduces nitrate to nitrite. These facultative anaerobes grow well on common culture media and are motile at 22°C (71.6°F) but not at 37°C (98.6°F). Optimal growth temperature is 25-28°C (77-82.4°F); however, the organism can grow at refrigerator temperature. *Y. enterocolitica* includes pathogenic and nonpathogenic members. It has 6 different biotypes (1A, 1B, and 2-5). *Y. enterocolitica* relies on other bacteria for iron uptake, and conditions associated with iron overload increase risk of infection.

EPIDEMIOLOGY

This agent is transmitted to humans through food, water, animal contact, and contaminated blood products. Transmission can occur from mother to newborn. *Y. enterocolitica* appears to have a global distribution but is seldom a cause of tropical diarrhea. In 2010, incidence of culture-confirmed *Y. enterocolitica* infection in the United States was 0.3 per 100,000 population (52% decrease from incidence in 1996-1998). Infection may be more common in Northern Europe. Prevalence in fecal samples from asymptomatic humans of nonvirulent *Y. enterocolitica* biotype 1A was 1.1% in 1 study. Most infections occur among children younger than 5 yr of age (incidence: 1.6-1.9 per 100,000 population), with the majority among children younger than 1 yr of age. It is estimated that *Y. enterocolitica* accounts for 5% of illnesses secondary to major bacterial enteric pathogens in children younger than 5 yr old in the United States. Cases are more common in colder months and among males.

Natural reservoirs of *Y. enterocolitica* include pigs, rodents, rabbits, sheep, cattle, horses, dogs, and cats, with pigs being the major animal reservoir. A recent publication estimated direct or indirect contact with animals, including pets, other domesticated animals, as well as wild animals, to be responsible for <1% of cases of enteric illnesses caused by *Y. enterocolitica*. Culture and molecular techniques have found the organism in a variety of foods and beverages, including vegetable juice, pasteurized milk, carrots, and water. Consumption of contaminated water or food, specially undercooked pork, is the most common form of transmission to humans. A source of sporadic *Y. enterocolitica* infections is pig offal (chitterlings). In 1 study, 71% of human isolates were indistinguishable from the strains isolated from pigs. *Y. enterocolitica* is an occupational threat to butchers. There is evidence that under conventional farm conditions pigs can be raised free of *Y. enterocolitica*.

In part because of its capacity to multiply at refrigerator temperatures, *Y. enterocolitica* can be transmitted by intravenous injection of contaminated fluids, including blood products.

Patients with conditions leading to iron overload are at higher risk of developing *Yersinia* infections.

PATHOGENESIS

The organisms most often enter by the alimentary tract and cause mucosal ulcerations in the ileum. Necrotic lesions of Peyer patches and mesenteric lymphadenitis occur. If septicemia develops, suppurative lesions can be found in infected organs. Infection can trigger reactive arthritis and erythema nodosum.

Virulence traits of pathogenic biotypes (1B and 2-5) are encoded by chromosomal genes and a highly conserved 70 kb virulence plasmid (pYV/pCD). The chromosomal genes control the production of heat stable enterotoxins and the plasmid allows penetration through the intestinal wall. Adherence, invasion, and toxin production are the essential mechanisms of pathogenesis. The bacteria mainly invade the intestinal epithelium in the Peyer patches of the ileum. After invasion plasmid encoded type III secretion of 3 antiphagocytic proteins protects *Yersinia* against the immunologic response of local macrophages. From Peyer patches bacteria can disseminate to cause local or systemic disease. Motility appears to be required for *Y. enterocolitica* pathogenesis. Serogroups that predominate in human illness are O:3, O:8, O:9, and O:5,27. Yersinia does not produce siderophores and uses analogous siderophores from other bacteria or host-chelated iron stores to thrive, placing patients with iron overload as in hemochromatosis, thalassemia, and sickle cell disease at higher risk for infection.

CLINICAL MANIFESTATIONS

Disease occurs most often as enterocolitis with diarrhea, fever, and abdominal pain. Acute enteritis is more common among younger children, and mesenteric lymphadenitis that can mimic appendicitis may be found in older children and adolescents. Stools may be watery or contain leukocytes and, less commonly, frank blood and mucus. *Y. enterocolitica* is excreted in stool for 1-4 wk. Family contacts of a patient are often found to be asymptomatically colonized with *Y. enterocolitica*. *Y. enterocolitica* septicemia is less common and is most often found in very young children (<3 mo of age) and immunocompromised persons. Systemic infection can be associated with splenic and hepatic abscesses, osteomyelitis, septic arthritis, meningitis, endocarditis, and mycotic aneurysms. Exudative pharyngitis, pneumonia, empyema, lung abscess, and acute respiratory distress syndrome uncommonly occur.

Reactive complications include erythema nodosum, reactive arthritis, and rarely uveitis. These manifestations may be more common in selected populations (northern Europeans), in association with HLA-B27, and in girls.

DIAGNOSIS

Diagnosis is made usually through isolation of the organism usually from the stool. *Y. enterocolitica* is easily cultured from normally sterile sites but requires special procedures for isolation from stool, where other bacteria can outgrow it. Cold enrichment, where a sample is held in buffered saline, can result in preferential growth of *Yersinia*, but the procedure takes weeks. Polymerase chain reaction (PCR) and DNA microarray are more sensitive than culture, with DNA microarray more sensitive and accurate than multiplex PCR. Many laboratories do not routinely perform the procedures required to detect *Y. enterocolitica*. Procedures targeted to this organism must be specifically requested. A history indicating contact with environmental sources of *Yersinia* and detection of fecal leukocytes are helpful indicators of a need to test for *Y. enterocolitica*. The isolation of a *Yersinia* from stool should be followed by tests to confirm that the isolate is a pathogen. Serodiagnosis is possible but not readily available.

DIFFERENTIAL DIAGNOSIS

The clinical presentation is similar to other forms of bacterial enterocolitis. The most common considerations include *Shigella, Salmonella, Campylobacter, Clostridium difficile,* enteroinvasive *Escherichia coli, Y. pseudotuberculosis*, and, occasionally, *Vibrio*-related diarrheal disease. Amebiasis, appendicitis, Crohn disease, ulcerative colitis, diverticulitis, and pseudomembranous colitis should also be considered.

TREATMENT

Enterocolitis in an immunocompetent patient is a self-limiting disease, and no benefit from antibiotic therapy is established. Patients with systemic infection and very young children (in whom septicemia is common) should be treated. *Yersinia* organisms are typically susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), aminoglycosides, third-generation cephalosporins, and quinolones, although strains resistant to quinolones have been recently reported. *Y. enterocolitica* produces β-lactamases, which are responsible for resistance to penicillins and first-generation cephalosporins. TMP-SMX is the recommended empirical treatment in children for enterocolitis (generally a 5-day course), because it has activity against most strains and is well tolerated. In severe infections such as bacteremia, third-generation cephalosporins, with or without aminoglycosides, are effective, and usually a 3 wk course of therapy is administered with possible transition to oral therapy. Patients on deferoxamine should discontinue iron chelation therapy during treatment for *Y. enterocolitica,* especially if they have complicated gastrointestinal infection or extraintestinal infection.

COMPLICATIONS

Reactive arthritis, erythema nodosum, erythema multiforme, hemolytic anemia, thrombocytopenia, and systemic dissemination of bacteria have been reported in association with *Y. enterocolitica* infection.

Septicemia is more common in younger children, and reactive arthritis is more common in older patients. Arthritis appears to be mediated by immune complexes, which form as a result of antigenic mimicry, and viable organisms are not present in involved joints.

PREVENTION

Prevention centers on reducing contact with environmental sources of *Yersinia.* Breaking or sterilization of the chain from animal reservoirs to humans holds the greatest potential to reduce infections, and the techniques applied must be tailored to the reservoirs in each geographic area. There is no licensed vaccine.

Bibliography is available at Expert Consult.

203.2 *Yersinia pseudotuberculosis*

Ramia Zakhour, Gloria P. Heresi, and James R. Murphy

Y. pseudotuberculosis has a worldwide distribution; *Y. pseudotuberculosis* disease is less common than *Y. enterocolitica* disease. The most common form of disease is a mesenteric lymphadenitis that produces an appendicitis-like syndrome. *Y. pseudotuberculosis* is associated with a Kawasaki disease–like illness in approximately 8% of cases.

ETIOLOGY

Y. pseudotuberculosis is a small Gram-negative aerobic and facultative anaerobic coccobacillus. Like *Y. enterocolitica,* it ferments glucose and does not ferment lactose, is oxidase negative, is catalase producing, is urea splitting, and shares a number of morphologic and culture characteristics. It is differentiated biochemically from *Y. enterocolitica* on the basis of ornithine decarboxylase activity, fermentation of sucrose, sorbitol, and cellobiose, and other tests, although some overlap between species occurs. Antisera to somatic O antigens and sensitivity to *Yersinia* phages can also be used to differentiate the 2 species. Subspecies-specific DNA sequences that allow direct probe- and primer-specific differentiation of *Y. pestis, Y. pseudotuberculosis,* and *Y. enterocolitica* have been described. *Y. pseudotuberculosis* is more closely related phylogenetically to *Y. pestis* than to *Y. enterocolitica.*

EPIDEMIOLOGY

Y. pseudotuberculosis is zoonotic, with reservoirs in wild rodents, rabbits, deer, farm animals, various birds, and domestic animals, including cats and canaries. Transmission to humans is by consumption of or contact with contaminated animals or contact with an environmental source contaminated by animals (often water). Direct evidence of transmission of *Y. pseudotuberculosis* to humans by consumption of lettuce and raw carrots has been reported. The organism has a worldwide distribution; however, infections are more commonly reported in Europe, in boys, and in the winter. During 1996-2007 FoodNet reported 18 cases of infections secondary to *Y. pseudotuberculosis* in the United States, with an annual average incidence of 0.04 per 1,000,000 persons. When compared to *Y. enterocolitica* infections, those caused by *Y. pseudotuberculosis* are more likely to be invasive and occur in adolescents and adults. Iron-overloading conditions, HIV infection, and other debilitating diseases (including liver cirrhosis) may predispose to invasive *Y. pseudotuberculosis* infection.

PATHOGENESIS

Ileal and colonic mucosal ulceration and mesenteric lymphadenitis are hallmarks of the infection. Necrotizing epithelioid granulomas may be seen in the mesenteric lymph nodes, but the appendix is often grossly and microscopically normal. The mesenteric nodes are often the only source of isolation of the organism. *Y. pseudotuberculosis* antigens bind directly to human leukocyte antigen class II molecules and can function as superantigens, which might account for the clinical illness resembling Kawasaki disease.

CLINICAL MANIFESTATIONS

Pseudoappendicitis and mesenteric lymphadenitis with abdominal pain, right lower quadrant tenderness, fever, and leukocytosis is the most common clinical presentation. Enterocolitis and extraintestinal spread are uncommon. Iron overload, diabetes mellitus, and chronic liver disease are often found concomitantly with extraintestinal *Y. pseudotuberculosis* infection. Renal involvement with tubulointerstitial nephritis, azotemia, pyuria, and glucosuria can occur. *Y. pseudotuberculosis* can present as a Kawasaki disease-like illness with fever of 1-2 days duration; strawberry tongue; pharyngeal erythema; a scarlatiniform rash; cracked, red, swollen lips; conjunctivitis; sterile pyuria; periungual desquamation; and thrombocytosis. Other uncommon manifestations include septic arthritis, massive lower gastrointestinal bleeding, postaneurysmal prosthetic vascular infection, and acute encephalopathy.

DIAGNOSIS

PCR of involved tissue can be used to identify the organism; isolation by culture can require an extended interval. Involved mesenteric lymph nodes removed at appendectomy can yield the organism by culture. Abdominal CT scan or ultrasound examination of children with unexplained fever and abdominal pain can reveal a characteristic picture of enlarged mesenteric lymph nodes and thickening of the terminal ileum with or without peritoneal findings including appendiceal inflammation and periappendiceal fluid. *Y. pseudotuberculosis* is rarely recovered from stool. Serologic procedures are available, but not in most routine laboratories.

DIFFERENTIAL DIAGNOSIS

Appendicitis (most commonly), inflammatory bowel disease, and other intraabdominal infections should be considered. Kawasaki disease, staphylococcal or streptococcal disease, leptospirosis, Stevens-Johnson syndrome, and collagen vascular diseases, including acute-onset juvenile rheumatoid arthritis, can mimic the syndrome with prolonged fever and rash. *C. difficile* colitis, meningitis, encephalitis, enteropathic arthropathies, acute pancreatitis, sarcoidosis, toxic shock syndrome, typhoid fever, and ulcerative colitis may also be considered.

TREATMENT

Uncomplicated mesenteric lymphadenitis caused by *Y. pseudotuberculosis* is a self-limited disease, and antimicrobial therapy is not required. Few data exist on optimal treatment and duration of therapy. Infections with *Y. pseudotuberculosis* can generally be managed same as those caused by *Y. enterocolitica*. Culture-confirmed bacteremia should be treated with an aminoglycoside, ampicillin, TMP-SMX, a third-generation cephalosporin, a fluoroquinolones, or chloramphenicol.

COMPLICATIONS

Erythema nodosum and reactive arthritis can follow infection. Coronary aneurysm formation has been described with disease presenting as Kawasaki-like illness. Rare local complications of gastrointestinal disease include perforation, obstruction, and intussusception.

PREVENTION

Avoiding exposure to potentially infected animals and good food-handling practices can prevent infection. The sporadic nature of the disease makes application of targeted prevention measures difficult.

Bibliography is available at Expert Consult.

203.3 Plague *(Yersinia pestis)*

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ETIOLOGY

Y. pestis is a Gram-negative, facultative anaerobe that is a pleomorphic nonmotile, non-spore-forming coccobacillus and is a potential agent

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of bioterrorism. It evolved from *Y. pseudotuberculosis* through acquisition of chromosomal changes and plasmid-associated factors that are essential to its virulence and survival in mammalian hosts and fleas. *Y. pestis* shares bipolar staining appearance with *Y. pseudotuberculosis* and can be differentiated by biochemical reactions, serology, phage sensitivity, and molecular techniques. The *Y. pestis* genome has been determined and is approximately 4,600,000 base pairs in size. *Y. pestis* exists in 3 biovars: Antigua (Africa), Medievalis (central Asia), and Orientalis (widespread).

EPIDEMIOLOGY

Plague is endemic in at least 24 countries. Approximately 3,000 cases are reported worldwide per year, with 100-200 deaths. Plague is uncommon in the United States (0-40 reported cases/yr); most of these cases occur west of a line from east Texas to east Montana, with 80% of cases in New Mexico, Arizona, and Colorado. The epidemic form of disease killed approximately 25% of the population of Europe in the Middle Ages in one of a number of epidemics and pandemics. The epidemiology of epidemic plague involves extension of infection from the zoonotic reservoirs to urban rats, *Rattus rattus* and *Rattus norvegicus,* and from fleas of urban rats to humans. Epidemics are no longer seen. Selective pressure exerted by plague pandemics in medieval Europe is hypothesized for enrichment of a deletion mutation in the gene encoding CCR5 (CCR5-Δ32). The enhanced frequency of this mutation in European populations endows approximately 10% of European descendants with resistance to HIV-1.

The most common mode of transmission of *Y. pestis* to humans is through flea bites. Historically, most human infections are thought to have resulted from bites of fleas that acquired infection from feeding on infected urban rats. Less commonly, infection is caused by contact with infectious body fluids or tissues or inhalation of respiratory secretions of infected animals. Nowadays most cases of plague secondary to direct animal contact or inhalation of animal secretions are related to domestic cats. Direct transmission from human to human through droplet inhalation is possible but extremely rare. Laboratory transmission of *Y. pestis* has been described as well. Sylvatic plague can exist as a stable enzootic infection or as an epizootic disease with high host mortality. Ground squirrels, rock squirrels, prairie dogs, rats, mice, bobcats, cats, rabbits, and chipmunks may be infected. Transmission among animals is usually by flea bite or by ingestion of contaminated tissue. *Xenopsylla cheopis* is the flea most commonly associated with transmission to humans, but more than 30 species of fleas have been demonstrated as vector competent, and *Pulex irritans,* the human flea, can transmit plague and might have been an important vector in some historical epidemics. Both sexes are similarly affected by plague, and transmission is more common in colder regions and seasons, possibly because of temperature effects on *Y. pestis* infections in vector fleas.

PATHOGENESIS

In the most common form of plague, infected fleas regurgitate organisms into a patient's skin during feeding. The bacteria translocate via lymphatics to regional lymph nodes, where *Y. pestis* replicates, resulting in bubonic plague. In the absence of rapidly implemented specific therapy, bacteremia can occur, resulting in purulent, necrotic, and hemorrhagic lesions in many organs. Both plasmid and chromosomal genes are required for full virulence. Pneumonic plague can be secondary to bacteremia or primary when infected material is inhaled. The organism is highly transmissible from persons with pneumonic plague and from domestic cats with pneumonic infection. This high transmissibility and high morbidity and mortality have provided an impetus for attempts to use *Y. pestis* as a biologic weapon.

CLINICAL MANIFESTATIONS

Y. pestis infection can manifest as several clinical syndromes; infection can also be subclinical. The 3 principal clinical presentations of plague are bubonic, septicemic, and pneumonic. **Bubonic plague** is the most common form and accounts for 80-90% of cases in the United States. From 2-8 days after a flea bite, lymphadenitis develops in lymph nodes closest to the inoculation site, including the inguinal (most common), axillary, or cervical region. These buboes are remarkable for tenderness. Fever, chills, weakness, prostration, headache, and the development of septicemia are common. The skin might show insect bites or scratch marks. Purpura and gangrene of the extremities can develop as a result of disseminated intravascular coagulation. These lesions may be the origin of the name Black Death. Untreated plague results in death in more than 50% of symptomatic patients. Death can occur within 2-4 days after onset of symptoms.

Occasionally, *Y. pestis* establishes systemic infection and induces the systemic symptoms seen with bubonic plague without causing a bubo **(primary septicemic plague).** Because of the delay in diagnosis linked to the lack of the bubo, septicemic plague carries a higher case fatality rate than bubonic plague. In some regions, bubo-free septicemic plague accounts for 25% of cases.

Pneumonic plague is the least common but most dangerous and lethal form of the disease. Pneumonic plague can result from hematogenous dissemination, or, rarely, as primary pneumonic plague after inhalation of the organism from a human or animal with plague pneumonia or potentially from a biologic attack. Signs of pneumonic plague include severe pneumonia with high fever, dyspnea, and hemoptysis.

Plague meningitis, tonsillitis, or gastroenteritis can occur. Meningitis tends to be a late complication following inadequate treatment. Tonsillitis and gastroenteritis can occur with or without apparent bubo formation or lymphadenopathy.

DIAGNOSIS

Plague should be suspected in patients with fever and history of exposure to small animals in endemic areas. Thus, bubonic plague is suspected in a patient with a painful swollen lymph node, fever, and prostration who has been exposed to fleas or rodents in the western United States. A history of camping or the presence of flea bites increases the index of suspicion.

Y. pestis is readily transmitted to humans by some routine laboratory manipulations. Thus, *it is imperative to clearly notify a laboratory* when submitting a sample suspected of containing *Y. pestis.* Laboratory diagnosis is based on bacteriologic culture or direct visualization using Gram, Giemsa, or Wayson stains of lymph node aspirates, blood, sputum, or exudates. *Y. pestis* grows slowly under routine culture conditions and best at temperatures that differ from those used for routine cultures in many clinical laboratories. Enzyme-linked immunosorbent assay and PCR are available but are not in routine clinical use. A rapid antigen test detecting *Y. pestis* F1 antigen in sputum and serum samples exists as well. Suspected isolates of *Y. pestis* should be forwarded to a reference laboratory for confirmation. Special containment shipping precautions are required. Cases of plague should be reported to local and state health departments and the Centers for Disease Control and Prevention (CDC).

DIFFERENTIAL DIAGNOSIS

The Gram stain of *Y. pestis* may be confused with *Enterobacter agglomerans.* Mild and subacute forms of bubonic plague may be confused with other disorders causing localized lymphadenitis and lymphadenopathy. Septicemic plague may be indistinguishable from other forms of overwhelming bacterial sepsis like tularemia and cat-scratch disease.

Pulmonary manifestations of plague are similar to those of anthrax, Q fever, and tularemia, all agents with bioterrorism and biological warfare potential. Thus, the presentation of a suspected case, and especially any cluster of cases, requires immediate reporting. Additional information on this aspect of plague and procedures can be found at http://www.bt.cdc.gov/agent/plague/.

TREATMENT

Patients with suspected plague should be placed on droplet isolation until pneumonia is ruled out, sputum cultures are negative, and antibiotic treatment has been administered for 48 hr. The treatment of choice for bubonic plague historically has been streptomycin (30 mg/kg/day, maximum 2 g/day, divided every 12 hr IM for 10 days). Intramuscular streptomycin is inappropriate for septicemia because absorption may be erratic when perfusion is poor. The poor central nervous

system penetration of streptomycin makes this an inappropriate drug for meningitis. Furthermore, streptomycin might not be widely and immediately available. Gentamicin (children, 7.5 mg/kg IM or IV divided every 8 hr; adults, 5 mg/kg IM or IV once daily) has been shown to be as efficacious as streptomycin. Alternative treatments include doxycycline (in children who weigh <45 kg: 2-5 mg/kg/day every 12 hr IV, maximum 200 mg/day; not recommended for children <8 yr of age; in children who weigh ≥45 kg, 100 mg every 12 hr PO), ciprofloxacin (30 mg/kg/day divided every 12 hr, maximum 400 mg every 12 hr IV), and chloramphenicol (50-100 mg/kg/day IV divided every 6 hr). Meningitis is usually treated with chloramphenicol or a fluoroquinolone. Resistance to these agents and relapses are rare. *Y. pestis* is susceptible to fluoroquinolones in vitro, which are effective in treating experimental plague in animals. *Y. pestis* is susceptible to penicillin in vitro, but penicillin is ineffective in treatment of human disease. Mild disease may be treated with oral chloramphenicol or tetracycline in children older than 8 yr of age. Clinical improvement is noted within 48 hr of initiating treatment. Typical duration of therapy is 7-10 days or a few days following clinical improvement.

Postexposure prophylaxis should be given to close contacts of patients with pneumonic plague. Antimicrobial prophylaxis is recommended within 7 days of exposure for persons with direct, close contact with patient with pneumonic plague or those exposed to an accidental or terrorist-induced aerosol. Recommended regimens include a 7-day course of tetracycline, doxycycline, or TMP-SMX. Contacts of cases of uncomplicated bubonic plague do not require prophylaxis. *Y. pestis* is a potential agent of bioterrorism that can require mass casualty prophylaxis.

PREVENTION

Avoidance of exposure to infected animals and fleas is the best method of prevention of infection. In the United States, special care is required in environments inhabited by rodent reservoirs of *Y. pestis* and their ectoparasites. Patients with plague should be isolated if they have pulmonary symptoms, and infected materials should be handled with extreme care. There is currently no available licensed vaccine for *Y. pestis* in the United States. Several vaccine development trials are underway, and recombinant subunit vaccines based on rF1 and rV antigens seem to be the most promising. Using baits containing live vaccines for oral immunization of wild animals may be a helpful alternative for control of epidemics.

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Chapter 204
Aeromonas and *Plesiomonas*

Amanda N. Shaw and Gloria P. Heresi

Aeromonas and *Plesiomonas* are Gram-negative bacilli that include species capable of causing enteritis and less frequently cause skin and soft-tissue infections and septicemia. They are common in fresh and brackish water and colonize animals and plants in these environments.

204.1 *Aeromonas*

Amanda N. Shaw and Gloria P. Heresi

ETIOLOGY

Aeromonas is a member of the Aeromonadaceae family and are oxidase-positive, facultative anaerobic, Gram-negative bacilli that ferment glucose. At least 24 phenotypic species are known, though there is controversy regarding species differentiation. Eleven are recognized as clinically significant human pathogens. *Aeromonas hydrophila, Aeromonas veronii* biotype sobria, and *Aeromonas caviae* are the species most often associated with human infection. *Aeromonas trota* continues to be isolated with increasing frequency from human stool. *A. hydrophila* strain ATCC 7966 has been sequenced and contains 5,195 predicted protein-encoding genes identified.

Aeromonas infects many cold- and warm-blooded animals. There are 2 major groups of *Aeromonas* isolates: the nonmotile psychrophilic organisms that infect cold-blooded animals, most commonly fish (optimal growth 22-25°C [71.6-77°F]), and the motile mesophilic organisms that infect humans and other warm-blooded animals (optimal growth 35-37°C [95-98.6°F]).

EPIDEMIOLOGY

Aeromonas organisms are ubiquitous and are found in fresh and brackish aquatic sources, including rivers and streams, well water, both treated and bottled drinking water, and sewage. They are most often cultivated from aquatic sources during warm weather months, when they are able to attain large populations. The prevalence of human infection tends to exhibit seasonality, depending on local conditions. For example, *Aeromonas* are isolated with increased frequency from May to October in the northern hemisphere. Some species can resist chlorination of water and show tolerance to high salt. *Aeromonas* has been isolated from meats, milk, seafood, seaweed, and vegetables consumed by humans. Most human infections with *Aeromonas* are associated with exposure to contaminated water. A systematic review of cases of traveler's diarrhea worldwide implicated *Aeromonas* in 0.8-3.3% of infections, with highest frequencies in travelers to Southeast Asia and Africa. A study in India of 3,500 stool samples from patients hospitalized with diarrhea found 4.7% positive for *Aeromonas*. *Aeromonas* infections have also been acquired at various sites of natural disasters. Following the 2004 Thailand tsunami, 305 survivors with skin and soft-tissue infections were found to have *Aeromonas*, making it the most common bacterial pathogen causing skin infections following this disaster. Asymptomatic colonization occurs in humans and is more common in inhabitants of tropical regions.

PATHOGENESIS

Clinical and epidemiologic data seem to support that *Aeromonas* organisms are enteric pathogens, although this is not universally accepted. Reasons for uncertainty include a lack of outbreaks with colonially distinct isolates, infrequent person to person transmission, absence of a good animal model, and overlapping prevalence in symptomatic and asymptomatic patients. Adult volunteers can ingest 10^4-10^{10} colony-forming units without developing diarrhea or becoming colonized.

Aeromonas isolates possess a variety of potential virulence factors, including: constitutive polar and inducible lateral flagella, fimbriae, outer membrane proteins, an S-layer, endotoxin (lipopolysaccharide), capsules, collagenase, elastase, nuclease, gelatinase, lipase, chitinase, enterotoxins, hemolysins, and multiple secretion systems. Polar flagella provide motility in liquid media, and lateral flagella act as adhesins. There are various hemolysins and heat labile- and heat-stable enterotoxins. *Aeromonas* cytotoxic enterotoxin (aerolysin) is secreted by a type II secretion system and is able to lyse erythrocytes, inhibit phagocytosis, and induce cytotoxicity in eukaryotic cells. *Aeromonas* also has a type III secretion system with an effector protein that causes actin reorganization and eventual apoptosis in vitro. A type VI secretion system has been identified in a clinical isolate and is being studied further. *Aeromonas sobria* is the most enterotoxic among clinical isolates, and cytotoxic activity with cytopathic and intracellular effects is found in 89% of isolates. A few strains produce *Shiga* toxin. *Aeromonas* has serine proteases that can cause a cascade of inflammatory mediators leading to vascular leakage, and in vitro studies show induction of apoptosis in murine macrophages by human isolates of *Aeromonas*. *Aeromonas* also has enzyme systems and efflux pumps that enable it to develop resistance to antibiotics. There are limited data on identified quorum-sensing molecules, which coordinate gene expression according to local density and may be involved in biofilm production or population control.

Human serum generally promotes phagocytosis and intracellular killing of *Aeromonas.* Absence of this serum action has been associated with a poor prognosis.

CLINICAL MANIFESTATIONS

Colonization with *Aeromonas* may be asymptomatic or cause illness, including enteritis, focal invasive infection, and septicemia. Although apparently immunologically normal individuals may present with any manifestation, invasive disease is more common among immunocompromised persons.

Enteritis

The most common clinical manifestation of infection with *Aeromonas* is enteritis, which occurs primarily among children younger than 3 yr of age. *Aeromonas* is the 3rd or 4th most common cause of childhood bacterial diarrhea and has been isolated from 2-10% of patients with diarrhea and 1-5% of asymptomatic control subjects. One study showed isolation from hospitalized neonates with diarrhea at rates of 0-19% depending on season. Diarrhea is often watery and self-limited, although a dysentery-like syndrome with blood and mucus in the stool has also been described. Fever, abdominal pain, and vomiting are common in children. Enteritis caused by *A. hydrophila* and *A. sobria* tends to be acute and self-limited, whereas 30% of the patients with *A. caviae* enteritis have chronic or intermittent diarrhea that may last 4-6 wk. *A. sobria* and *A. caviae* are most frequently associated with traveler's diarrhea. Complications of *Aeromonas* enteritis include intussusception, failure to thrive, hemolytic-uremic syndrome, bacteremia, and strangulated intestinal hernia. *A. caviae* infection may mimic inflammatory bowel disease.

Skin and Soft-Tissue Infections

Skin and soft-tissue infections are the second most common presentation of *Aeromonas.* Predisposing factors include local trauma and exposure to contaminated fresh water. *Aeromonas* soft-tissue infections have been reported following animal bites, including alligator, tiger, bear, and snake bites, as well as tick bites. It has also been reported following sports injuries and following medicinal leech therapy. Antibiotic prophylaxis is currently used in conjunction with medicinal leech therapy because of the presence of symbiotic *A. hydrophila*. The spectrum of skin and soft-tissue infections is broad, ranging from a localized skin nodule to life-threatening necrotizing fasciitis, myonecrosis, and gas gangrene. Soft-tissue infections are most commonly found on the extremities and are 3 times more likely in men than in women. *Aeromonas* cellulitis, the most common skin manifestation, clinically presents like any other bacterial cellulitis but should be suspected in wounds following contact with a water source, especially during the summer.

Septicemia

Aeromonas septicemia is the third most frequent presentation of infection and is associated with a mortality rate of 27-73%. Patients often present with fever and gastrointestinal symptoms including abdominal pain, nausea, vomiting, and diarrhea. Multiple pediatric cases of septicemia from *A. hydrophila* have been reported; symptoms include diarrhea, pneumonia, and acute renal failure. *Aeromonas* septicemia usually occurs in patients with underlying conditions, such as hepatobiliary disease or malignancy, but may occur in apparently immunocompetent persons. *Aeromonas* may be the only organism isolated or may be part of a polymicrobial bacteremic illness. The source of the infection is frequently not identified, and in these cases is most likely from the gastrointestinal tract. *A. sobria* bacteremia has resulted in disseminated intravascular gas production and subsequent acute death in the absence of any underlying condition.

Other Infections

Aeromonas is a rare cause of gastrointestinal infections such as necrotizing gastroenteritis, peritonitis, cholecystitis, appendicitis, and liver and pancreas abscess formation, cardiovascular infections including endocarditis and septic embolism, and pulmonary infections including tracheobronchitis, pneumonia, empyema, and abscess formation. *Aeromonas* is also associated with musculoskeletal infections, including osteomyelitis, pyogenic arthritis, pyomyositis, and necrotizing fasciitis, as well as ear, nose and throat infections, including endophthalmitis, keratitis, orbital cellulitis, otitis media, and epiglottitis. Other infections include meningitis, urinary tract infection, pelvic inflammatory disease, lymphadenitis, hot tub folliculitis, and surgical wound infections. *Aeromonas* is associated with tracheobronchitis and aspiration pneumonia after near-drowning.

DIAGNOSIS

Diagnosis is established by culture isolation of *Aeromonas.* The organism is easily grown on standard media when the source material is normally sterile. Isolation of the organism from samples containing numerous bacteria is more difficult, possibly because competing bacteria outgrow *Aeromonas.* Often, *Aeromonas* is not identified by typical lab protocols for examining stool specimens. If *Aeromonas* is suspected, the yield will increase if the lab is notified prior to testing. Previously suggested use of ampicillin containing agars is no longer recommended, because a significant number of *A. caviae* and all *A. trota* are sensitive to ampicillin and will not grow. Most (~90%) strains produce β-hemolysis on blood agar. However, lack of hemolysis is not a reliable indicator of lack of hemolysin in the isolate. Lactose-fermenting strains of *Aeromonas* may not be identified if the clinical laboratory does not routinely perform oxidase tests on lactose fermenters isolated on MacConkey agar. Automated identification systems are more routinely being used and can identify most *Aeromonas* as a group. More specific identification is not done as often, and when it is done, is often incomplete or erroneous.

TREATMENT

Aeromonas enteritis is usually self-limited, and antimicrobial therapy may not be indicated. Nevertheless, data from uncontrolled trials suggest that antimicrobial therapy shortens the course of the illness. Antimicrobial therapy is reasonable to consider in patients with protracted diarrhea, dysentery-like illness, or underlying conditions such as hepatobiliary disease or an immunocompromised state. Antibiotic sensitivity varies between species. Therefore, it is important to identify the species and sensitivities when antibiotics are used. Most species produce an inducible β-lactamase which may not be detected by automated systems. There is near-uniform resistance to penicillins. Septicemia should be treated with a third-generation cephalosporin or an aminoglycoside. Other options include imipenem, meropenem, chloramphenicol, trimethoprim-sulfamethoxazole (TMP-SMZ), quinolones, and tetracyclines. Many species have developed multidrug resistance, especially to quinolones. Sensitivities vary by geographic region. For example, in Taiwan there is increasing resistance to TMP-SMZ, so travel history should be taken into consideration when planning treatment. There are no clinic trial data available to guide duration of treatment. As a consequence, treatment is typically guided by clinical response. In general, diarrhea is treated for 3 days, wound infections for 7-10 days, and bacteremia for 14 days.

PREVENTION

Reducing contact with contaminated environmental fresh and brackish water and contaminated foods should reduce the risk for *Aeromonas* infections. *Aeromonas* expresses LamB-like outer membrane proteins that facilitate bacterial adherence to extracellular matrix components. Outer membrane proteins are strongly immunogenic and have been target antigens for vaccine development.

Bibliography is available at Expert Consult.

204.2 *Plesiomonas shigelloides*

Amanda N. Shaw and Gloria P. Heresi

ETIOLOGY

Plesiomonas shigelloides is most commonly associated with acute enteritis and rarely with extraintestinal infections. The organism is a facultative anaerobic, Gram-negative non–spore-forming bacillus with more

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than 100 serotypes. It is catalase- and oxidase-positive, able to ferment xylose, and motile, with 2-5 polar flagellae.

P. shigelloides is the only oxidase positive member of the Enterobacteriaceae family. A high level of diversity has been recognized within *P. shigelloides* strains, reflecting the frequency of homologous recombination and differing from other members of the Enterobacteriaceae.

EPIDEMIOLOGY

P. shigelloides is ubiquitous in fresh water and can be found in estuarine water. Historically, it has been found most often in warmer and tropical waters or during warmer months, although there are increasing reports of isolation from surface water in colder climates. *P. shigelloides* colonizes numerous cold- and warm-blooded animals, has been isolated from fish and seafood, and may cause disease in cats. Infection of humans is thought to be the result of consumption of contaminated water or raw seafood and possibly through contact with colonized animals. There have also been cases of immunocompromised patients who are injured in fresh water. A majority of symptomatic patients in North America have known exposure to potentially contaminated water or seafood or have traveled abroad. In general, enteric infections with *Plesiomonas* occur more commonly in areas where development and hygiene are inadequate and have been associated with large outbreaks.

PATHOGENESIS

Epidemiologic evidence indicates that *P. shigelloides* is an enteropathogen. However, the pathogenic capacity of *P. shigelloides* has not been confirmed when volunteers have been fed the organism. The mechanism of enteritis is not known, but it appears that the species can commonly cause secretory and less commonly invasive disease. In vitro studies show that isolates of *P. shigelloides* are capable of invading and inducing apoptosis in cells of enteric origin. Most strains of *P. shigelloides* secrete a β-hemolysin, which is thought to be a major virulence factor. They also produce a β-lactamase, which renders them resistant to the penicillins. Studies show evidence of modulation of host defenses through inhibition of cathepsins involved in antigen processing and presentation.

CLINICAL MANIFESTATIONS

Clinical disease in humans generally begins 24-48 hr after exposure to the organism, although there have been cases 4 days after exposure. Diarrhea is commonly secretory or watery and less-often presents as invasive dysentery. In 13% of cases, diarrhea can last more than 2 wk and has been noted to last as long as 3 mo. The frequency of secretory vs dysenteric presentation seems to cluster by individual outbreak, suggesting that either the human populations or bacterial populations involved associate with their particular presentation. Symptoms include diarrhea (84-100%), vomiting (70%), fever (8-50%), headache, abdominal cramping (more common in adults), nausea, and transient arthralgias. Frequently, diarrhea is mild and watery without significant dehydration. Blood, mucus, or both may be passed with stool, and white blood cells may be visualized in stained preparations of stool.

Extraintestinal infections are rare and usually occur in patients with underlying conditions, such as immunodeficiency (including HIV), malignancy, sickle cell disease, thalassemia, splenectomy, or hepatobiliary disease. Traumatic wounds sustained in aquatic environments less commonly contain *P. shigelloides*. Rarely, bacteremia accompanying enteritis has been documented in apparently otherwise normal children. Extraintestinal disease includes septicemia, pneumonia, meningitis, osteomyelitis, septic arthritis, reactive arthritis, cellulitis with abscess formation, endophthalmitis, cholecystitis, pseudoappendicitis, pseudomembranous colitis, proctitis, epididymo-orchitis, and pyosalpinx. Early onset neonatal sepsis and meningitis are rare but make up most of the reported cases of *P. shigelloides* meningitis and have a very high mortality rate (80%). Septicemia has a high mortality rate in adults.

DIAGNOSIS

A history of foreign travel, ingestion of raw seafood, or exposure to contaminated water or an animal with diarrhea suggests possible *P. shigelloides* infection. Mixed infection with *Salmonella, Aeromonas,* rotavirus, or other enteric pathogens may occur in 30-50% of patients. *P. shigelloides* is a nonlactose fermenter and grows well on traditional enteric media, although selective techniques may be required to isolate the organism from mixed cultures and to differentiate *P. shigelloides* from *Shigella* species. Many strains cross react with *Shigella* on serologic testing, but can be differentiated easily as oxidase positive organisms. It may be underrecognized by clinical laboratories that do not routinely perform an oxidase test. Rapid identification systems are fairly accurate when identifying *P. shigelloides*.

TREATMENT

Enteritis caused by *P. shigelloides* is usually mild and self-limited. In cases associated with dehydration, patients respond favorably to oral rehydration solution. Antimicrobial therapy is reserved for those patients with prolonged or bloody diarrhea, those who are immunocompromised, the very old, and the very young. Data from uncontrolled studies suggest that antimicrobial therapy decreases the duration of symptoms, although no difference was found in an exclusively pediatric study. Most strains of *P. shigelloides* are susceptible to TMP-SMZ, cephalosporins, carbapenems, and fluoroquinolones. *P. shigelloides* is commonly resistant to broad-spectrum penicillins, aminoglycosides, and tetracyclines. In some strains resistance has also been found to TMP-SMZ and fluoroquinolones. Resistance to gentamicin, chloramphenicol, and nalidixic acid has been demonstrated in strains of *P. shigelloides* isolated from tilapia.

Antibiotics are essential for therapy of extraintestinal disease. Empirical therapy with a third-generation cephalosporin is often first-line management, because most isolates are susceptible in vitro. Alternatives include imipenem, aztreonam, β-lactam/β-lactamase inhibitor combinations, and quinolones. Definitive therapy should be guided by the susceptibility of the individual isolate. Duration of therapy ranges from 1-2 wk, but may be extended depending on underlying chronic conditions and clinical response.

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Chapter 205

Pseudomonas, Burkholderia, and *Stenotrophomonas*

205.1 *Pseudomonas aeruginosa*

Thomas S. Murray and Robert S. Baltimore

ETIOLOGY

Pseudomonas aeruginosa is a Gram-negative rod and is a strict aerobe. It can multiply in a great variety of environments that contain minimal amounts of organic compounds. Strains from clinical specimens do not ferment lactose, are oxidase positive, and may produce β-hemolysis on blood agar. Many strains produce pigments, including pyocyanin, pyoverdin, and pyorubrin, that diffuse into and color the surrounding medium. Strains of *P. aeruginosa* are differentiated for epidemiologic purposes by a variety of genotyping methods, including restriction fragment length polymorphisms using pulsed-field gel electrophoresis and multilocus sequence typing.

EPIDEMIOLOGY

P. aeruginosa is a classic opportunist. It rarely causes disease in people who do not have a predisposing risk factor. Compromised host defense mechanisms owing to trauma, neutropenia, mucositis, immunosuppression, or impaired mucociliary transport explain the predominant role of this organism in producing opportunistic infections. One series of neonatal intensive care unit infections reported that 33/862 (3.8%) episodes of neonatal bacteremia from 1989-2003 were caused by *P. aeruginosa*. Another children's hospital reported 232 episodes of *P. aeruginosa* bacteremia over a 10 yr period, with half the infected children diagnosed with an underlying malignancy. *P. aeruginosa* and other pseudomonads frequently enter the hospital environment on the clothes, skin, or shoes of patients or hospital personnel, with plants or vegetables brought into the hospital, and in the gastrointestinal tracts of patients. Colonization of any moist or liquid substance may ensue; the organisms may be found growing in any water reservoir, including distilled water, and in hospital kitchen sinks and laundries, some antiseptic solutions, and equipment used for respiratory therapy and urinary procedures. Colonization of skin, throat, stool, and nasal mucosa of patients is low at admission to the hospital but increases to as high as 50-70% with prolonged hospitalization and with the use of broad-spectrum antibiotics, chemotherapy, mechanical ventilation, and urinary catheters. Patients' intestinal microbial flora may be altered by the use of broad-spectrum antibiotics, which reduces resistance to colonization and permits *P. aeruginosa* in the environment to populate the gastrointestinal tract. Intestinal mucosal breakdown associated with medications, especially cytotoxic agents, and nosocomial enteritis may provide a pathway by which *P. aeruginosa* spreads to the lymphatics or bloodstream.

PATHOLOGY

The pathologic manifestations of *P. aeruginosa* infections depend on the site and type of infection. Because of its elaboration of toxins and invasive factors, the organism can often be seen invading blood vessels and causing vascular necrosis. In some infections there is spread through tissues with necrosis and microabscess formation. In patients with cystic fibrosis, focal and diffuse bronchitis/bronchiolitis leading to bronchiolitis obliterans has been reported.

Pathogenesis

Invasiveness of *P. aeruginosa* is mediated by a host of virulence factors. Bacterial attachment is facilitated by pili that adhere to epithelium damaged by prior injury or infection. Extracellular proteins, proteases, elastases, and cytotoxin disrupt cell membranes, and in response, host-produced cytokines cause capillary vascular permeability and induce an inflammatory response. Dissemination and bloodstream invasion follow extension of local tissue damage and are facilitated by the antiphagocytic properties of endotoxin, the exopolysaccharide, and protease cleavage of immunoglobulin G. *P. aeruginosa* also produces numerous exotoxins, including **exotoxin A,** which causes local necrosis and facilitates systemic bacterial invasion. *P. aeruginosa* possesses a type III secretion system that is important for virulence in multiple animal models. This needle structure inserts into host cell membranes and allows secretion of exotoxins directly into host cells. *P. aeruginosa* strains with the gene encoding the type III secretion system–dependent phospholipase ExoU are associated with increased mortality compared with ExoU-negative strains in retrospective studies of patients with *P. aeruginosa* ventilator-associated pneumonia. The host responds to infection with a robust inflammatory response, recruiting neutrophils to the infection site and by producing antibodies to *P. aeruginosa* proteins such as exotoxin A and endotoxin. There is a lack of convincing data that these antibodies are protective against the establishment of infection.

In addition to acute infection, *P. aeruginosa* is also capable of chronic persistence thought to be partly a result of the formation of biofilms, organized communities of bacteria encased in an extracellular matrix that protects the organisms from the host immune response and the effects of antibiotics. Biofilm formation requires pilus-mediated attachment to a surface, proliferation of the organism, and production of exopolysaccharide as the main component of the extracellular matrix. A mature biofilm can persist despite an intense host immune response, is resistant to many antimicrobials, and is difficult to eradicate with current therapies.

CLINICAL MANIFESTATIONS

Most clinical patterns (Table 205-1) are related to opportunistic infections in immunocompromised hosts (see Chapter 178) or are

Table 205-1 *Pseudomonas aeruginosa* Infections

INFECTION	COMMON CLINICAL CHARACTERISTICS
Endocarditis	Native right-sided (tricuspid) valve disease with intravenous drug abuse
Pneumonia	Compromised local (lung) or systemic host defense mechanisms; nosocomial (respiratory), bacteremic (malignancy), or abnormal mucociliary clearance (cystic fibrosis) may be pathogenetic; cystic fibrosis is associated with mucoid *P. aeruginosa* organisms producing capsular slime
Central nervous system infection	Meningitis, brain abscess; contiguous spread (mastoiditis, dermal sinus tracts, sinusitis); bacteremia or direct inoculation (trauma, surgery)
External otitis	Swimmer's ear; humid warm climates, swimming pool contamination
Malignant otitis externa	Invasive, indolent, febrile toxic, destructive necrotizing lesion in young infants, immunosuppressed neutropenic patients, or diabetic patients; associated with 7th nerve palsy and mastoiditis
Chronic mastoiditis	Ear drainage, swelling, erythema; perforated tympanic membrane
Keratitis	Corneal ulceration; contact lens keratitis
Endophthalmitis	Penetrating trauma, surgery, penetrating corneal ulceration; fulminant progression
Osteomyelitis/septic arthritis	Puncture wounds of foot and osteochondritis; intravenous drug abuse; fibrocartilaginous joints, sternum, vertebrae, pelvis; open fracture osteomyelitis; indolent pyelonephritis and vertebral osteomyelitis
Urinary tract infection	Iatrogenic, nosocomial; recurrent urinary tract infections in children, instrumented patients, and those with obstruction or stones
Intestinal tract infection	Immunocompromised, neutropenia, typhlitis, rectal abscess, ulceration, rarely diarrhea; peritonitis in peritoneal dialysis
Ecthyma gangrenosum	Metastatic dissemination; hemorrhage, necrosis, erythema, eschar, discrete lesions with bacterial invasion of blood vessels; also subcutaneous nodules, cellulitis, pustules, deep abscesses
Primary and secondary skin infections	Local infection; burns, trauma, decubitus ulcers, toe web infection, green nail (paronychia); whirlpool dermatitis; diffuse, pruritic, folliculitis, vesiculopustular or maculopapular, erythematous lesions

Figure 205-1 Round, nontender skin lesion on 2 yr old female's buttock. Note the black ulcerated center of the lesion and its red margin. *(From Ghanaiem H, Engelhard D: A healthy 2-year-old child with a round black skin lesion.* J Pediatr *163:1225, 2013.)*

associated with shunts and indwelling catheters (see Chapter 179). *P. aeruginosa* may be introduced into a minor wound of a healthy person as a secondary invader, and cellulitis and a localized abscess that exudes green or blue pus may follow. The characteristic skin lesions of *P. aeruginosa,* **ecthyma gangrenosum,** whether caused by direct inoculation or a metastatic focus secondary to septicemia, begin as pink macules and progress to hemorrhagic nodules and eventually to ulcers with ecchymotic and gangrenous centers with eschar formation, surrounded by an intense red areola (Fig. 205-1).

Outbreaks of dermatitis and urinary tract infections caused by *P. aeruginosa* have been reported in healthy persons after use of pools or hot tubs. Skin lesions of folliculitis develop several hours to 2 days after contact with these water sources. Skin lesions may be erythematous, macular, papular, or pustular. Illness may vary from a few scattered lesions to extensive truncal involvement. In some children, malaise, fever, vomiting, sore throat, conjunctivitis, rhinitis, and swollen breasts may be associated with dermal lesions. Urinary tract infections caused by *P. aeruginosa* are most often nosocomial and are commonly associated with the presence of an indwelling urinary catheter, urinary tract malformations, and previous antibiotic use. Urinary tract infections may be minimized or prevented by prompt removal of the catheter and by early identification and corrective surgery of obstructive lesions when present.

Burns and Wound Infection

The surfaces of burns or wounds are frequently populated by *P. aeruginosa* and other Gram-negative organisms; this initial colonization with a low number of adherent organisms is a necessary prerequisite to invasive disease. *P. aeruginosa* colonization of a burn site may develop into burn wound sepsis, which has a high mortality rate when the density of organisms reaches a critical concentration. Administration of antibiotics may diminish the susceptible microbiologic flora, permitting strains of relatively resistant *P. aeruginosa* to flourish. Multiplication of organisms in devitalized tissues or associated with prolonged use of intravenous or urinary catheters increases the risk for septicemia with *P. aeruginosa,* a major problem in burned patients (see Chapter 75).

Cystic Fibrosis

P. aeruginosa is common in children with cystic fibrosis, with a prevalence that increases with increasing age and severity of pulmonary disease (see Chapter 403). Initial infection is caused by **nonmucoid environmental strains** of *P. aeruginosa,* but after a variable period of time, **mucoid strains** of *P. aeruginosa* that produce the antiphagocytic exopolysaccharide alginate, which are rarely encountered in other conditions, predominate. Repeated isolation of mucoid *P. aeruginosa* from the sputum is associated with increased morbidity and mortality. The infection begins insidiously or even asymptomatically, and the progression has a highly variable pace. In children with cystic fibrosis, antibody does not eradicate the organism and antibiotics are only partially effective; thus, after infection becomes chronic, it cannot be completely eradicated. Repeated courses of antibiotics select for *P. aeruginosa* strains that are resistant to multiple antibiotics.

Immunocompromised Persons

Children with leukemia or other malignancies, particularly those who are receiving immunosuppressive therapy and who are neutropenic, typically with intravascular catheters, are extremely susceptible to septicemia caused by invasion of the bloodstream by *P. aeruginosa* that is colonizing the respiratory or gastrointestinal tract. Signs of sepsis are often accompanied by a generalized vasculitis, and hemorrhagic necrotic lesions may be found in all organs, including the skin (ecthyma gangrenosum) (see Fig. 205-1). Hemorrhagic or gangrenous perirectal cellulitis or abscesses may occur, associated with ileus and profound hypotension.

Nosocomial Pneumonia

Although not a frequent cause of community-acquired pneumonia in children, *P. aeruginosa* is an increasingly important cause of community-acquired pneumonia in adults and of nosocomial pneumonia, especially ventilator-associated pneumonia, in patients of all ages. *P. aeruginosa* has historically been found to contaminate ventilators, tubing, and humidifiers. Such contamination is uncommon because of disinfection practices and routine changing of equipment. Nevertheless, colonization of the upper respiratory tract and the gastrointestinal tract may be followed by aspiration of *P. aeruginosa*–contaminated secretions, resulting in severe pneumonia. Prior use of broad-spectrum antibiotics is a risk factor for colonization with antibiotic-resistant strains of *P. aeruginosa.* One of the most challenging situations is distinguishing between colonization and pneumonia in intubated patients. This distinction can often only be resolved by using invasive culture techniques such as quantitative bronchoalveolar lavage.

Infants

P. aeruginosa is an occasional cause of nosocomial bacteremia in newborns and accounts for 2-5% of positive blood culture results in neonatal intensive care units. A frequent focus preceding bacteremia is **conjunctivitis.** Older infants may occasionally present with community-acquired sepsis due to *P. aeruginosa,* but this circumstance is uncommon. In the few reports describing community-acquired sepsis, preceding conditions included ecthyma-like skin lesions, virus-associated transient neutropenia, and prolonged contact with contaminated bath water or a hot tub.

DIAGNOSIS

P. aeruginosa infection is rarely clinically distinctive. Diagnosis depends on recovery of the organism from the blood, cerebrospinal fluid, urine, or needle aspirate of the lung, or from purulent material obtained by aspiration of subcutaneous abscesses or areas of cellulitis. In the appropriate clinical setting the recovery of *P. aeruginosa* from a coughed or suctioned sputum may represent infection; but it also may only represent colonization and clinical judgment is required. Rarely, skin lesions that resemble *P. aeruginosa* infection may follow septicemia caused by *Aeromonas hydrophila,* other Gram-negative bacilli, and *Aspergillus.* When *P. aeruginosa* is recovered from nonsterile sites such as skin, mucous membranes, voided urine, quantitative cultures may be useful to differentiate colonization from invasive infection. In general, ≥100,000 colony forming units/mL of fluid or gram of tissue is evidence suggestive of invasive infection. Quantitative cultures of tissue and skin are not routine and may require consultation with the clinical microbiology laboratory.

TREATMENT

Systemic infections with *P. aeruginosa* should be treated promptly with an antibiotic to which the organism is susceptible in vitro. Response to treatment may be limited, and prolonged treatment may be necessary for systemic infection in immunocompromised hosts.

Septicemia and other aggressive infections should be treated with either 1 or 2 bactericidal agents. Although the number of agents required is controversial, the evidence continues to suggest that the benefit of adding a second agent is questionable, even when studies have included immunosuppressed patients. Whether the use of 2 agents delays the development of resistance is also controversial, with evidence both for and against. Appropriate antibiotics for single-agent therapy include ceftazidime, cefepime, ticarcillin-clavulanate, and piperacillin-tazobactam. Gentamicin or another aminoglycoside may be used concomitantly for synergistic effect.

Ceftazidime has proved to be extremely effective in patients with cystic fibrosis (150-250 mg/kg/day divided every 6-8 hr IV to a maximum of 6 g/day). Piperacillin or piperacillin-tazobactam (300-450 mg/kg/day divided every 6-8 hr IV to a maximum of 12 g/day) also has proven to be effective therapy for susceptible strains of *P. aeruginosa* when combined with an aminoglycoside. Additional effective antibiotics include imipenem-cilastatin, meropenem, and aztreonam. Ciprofloxacin is an effective outpatient therapy and while commonly used in children with cystic fibrosis, it is not approved in the United States for persons younger than 18 yr of age except for oral treatment of urinary tract infections or when there are no other agents to which the organism is susceptible. Inhaled therapy with either tobramycin or aztreonam is also used for chronic pulmonary infection with inhaled colistin reserved for the treatment of resistant pseudomonads. It is important to base continued treatment on the results of susceptibility tests because antibiotic resistance of *P. aeruginosa* to 1 or more antibiotics is increasing. Macrolide therapy decreases pulmonary exacerbations in patients with chronic lung disease and *P. aeruginosa* infection Although the mechanism is not entirely clear, it likely relates to altering the virulence properties of *P. aeruginosa* rather than direct bacterial killing.

P. aeruginosa displays intrinsic and acquired resistance to antibiotics. It has many mechanisms for resistance to multiple classes of antibiotics, including but not limited to genetic mutation, production of β-lactamases, and drug efflux pumps. Critical care units throughout the United States have documented a rising rate of resistance of *P. aeruginosa* to all of the major classes of antibiotics.

Meningitis can occur from spread from a contiguous focus, as a secondary focus when there is bacteremia, or after invasive procedures. *P. aeruginosa* meningitis is best treated with ceftazidime in combination with an aminoglycoside such as gentamicin, both given intravenously. Concomitant intraventricular or intrathecal treatment with gentamicin may be required when intravenous therapy fails but is not recommended for routine use.

SUPPORTIVE CARE

P. aeruginosa infections vary in severity from superficial to intense septic presentations. With severe infections there is often multisystem involvement and a systemic inflammatory response. Supportive care is similar to care for severe sepsis caused by other Gram-negative bacilli and requires support of blood pressure, oxygenation, and appropriate fluid management.

PROGNOSIS

The prognosis is dependent primarily on the nature of the underlying factors that predisposed the patient to *P. aeruginosa* infection. In severely immunocompromised patients, the prognosis for patients with *P. aeruginosa* sepsis is poor unless susceptibility factors such as neutropenia or hypogammaglobulinemia can be reversed. The overall mortality rate was 12.3% in 1 series of 232 children with *P. aeruginosa* bacteremia, with 3% dying within 48 hr of admission. Resistance of the organism to first-line antibiotics also decreases the chance of survival. The outcome may be improved when there is a urinary tract portal of entry, absence of neutropenia or recovery from neutropenia, and drainage of local sites of infection.

P. aeruginosa is recovered from the lungs of most children who die of cystic fibrosis and adds to the slow deterioration of these patients. The prognosis for normal development is poor in the few infants who survive *P. aeruginosa* meningitis.

PREVENTION

Prevention of infections is dependent on limiting contamination of the healthcare environment and preventing transmission to patients. Effective hospital infection control programs are necessary to identify and eradicate sources of the organism as quickly as possible. In hospitals, infection can be transmitted to children by the hands of personnel, from washbasin surfaces, from catheters and other hospital equipment, and from solutions used to rinse suction catheters.

Strict attention to hand hygiene before and between contacts with patients may prevent or interdict epidemic disease. Meticulous care and sterile procedures in suctioning of endotracheal tubes, insertion and maintenance of indwelling catheters, and removal of catheters as soon as medically reasonable greatly reduce the hazard of extrinsic contamination by *P. aeruginosa* and other Gram-negative organisms. Prevention of follicular dermatitis caused by *P. aeruginosa* contamination of whirlpools or hot tubs is possible by maintaining pool water at a pH of 7.2-7.8.

Infections in burned patients may be minimized by protective isolation, debridement of devitalized tissue, and topical applications of bactericidal cream. Administration of intravenous immunoglobulin may be used. Approaches under investigation to prevent infection include development of a *P. aeruginosa* vaccine. No vaccine is currently licensed in the United States.

Bibliography is available at Expert Consult.

205.2 *Burkholderia cepacia* Complex

Thomas S. Murray and Robert S. Baltimore

Burkholderia cepacia is a filamentous Gram-negative rod now recognized to be a group of related species or genomovars. It is ubiquitous in the environment but may be difficult to isolate from respiratory specimens in the laboratory, requiring an enriched, selective media oxidation fermentation base supplemented with polymyxin B–bacitracin-lactose agar (OFPBL) and as long as 3 days of incubation.

B. cepacia is a classic opportunist that rarely infects normal tissue but can be a pathogen for individuals with preexisting damage to respiratory epithelium, especially persons with cystic fibrosis or with immune dysfunction such as chronic granulomatous disease. *B. cepacia* has multiple virulence factors, including lipopolysaccharide and a type III secretion system that promotes invasion of respiratory epithelial cells. Resistance to many antibiotics and disinfectants appears to be a factor in the emergence of *B. cepacia* as a nosocomial pathogen. In critical care units it may colonize the tubing used to ventilate patients with respiratory failure. In some patients this colonization may lead to invasive pneumonia and septic shock. Although *B. cepacia* is found throughout the environment, human-to-human spread among patients with cystic fibrosis occurs either directly by inhalation of aerosols or indirectly from contaminated equipment or surfaces, accounting for the practice of cohorting patients with cystic fibrosis in some clinics, hospital wards, and social gatherings on the basis of *B. cepacia* colonization. *B. cepacia* infections in persons with cystic fibrosis may represent chronic infection in some patients but others, especially those with *Burkholderia cenocepacia*, genomovar III, can develop an acute respiratory syndrome of fever, leukocytosis, and progressive respiratory failure, and more rapid decline in pulmonary function and lower survival rate.

Treatment in hospitals should include standard precautions and avoidance of placing colonized and uncolonized patients in the same room. Patients with cystic fibrosis who are colonized with *B. cepacia* are asked not to attend events where other persons with cystic fibrosis will be present. The use of antibiotics is guided by susceptibility studies of a patient's isolates, because the susceptibility pattern of this species is quite variable and multiply resistant strains are common. Trimethoprim-sulfamethoxazole and doxycycline or minocycline are potential oral therapies for *B. cepacia complex*. For intravenous therapy meropenem along with a second agent such as trimethoprim-sulfamethoxazole, doxycycline, minocycline, ceftazidime, or amikacin

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are potential options. Even though there is primary resistance to aminoglycosides, these agents may be useful in combination with other antibiotics. Treatment with 2 or more agents may be necessary to control the infection and avoid the development of resistance. No vaccine is currently available.

BURKHOLDERIA MALLEI (GLANDERS)

Glanders is a severe infectious disease of horses and other domestic and farm animals that is caused by *Burkholderia mallei,* a nonmotile Gram-negative bacillus that is occasionally transmitted to humans. It is acquired by inoculation into the skin, usually at the site of a previous abrasion, or by inhalation of aerosols. Laboratory workers may acquire it from clinical specimens. The disease is relatively common in Asia, Africa, and the Middle East. The clinical manifestations include septicemia, acute or chronic pneumonitis, and hemorrhagic necrotic lesions of the skin, nasal mucous membranes, and lymph nodes. The diagnosis is usually made by recovery of the organism in cultures of affected tissue. Glanders is treated with sulfadiazine, tetracyclines, or chloramphenicol and streptomycin over a period of many months. The disease has been eliminated from the United States, but interest in this organism has increased because of the possibility of its use as a bioterrorism agent (see Chapter 723). Although standard precautions are appropriate when caring for hospitalized infected patients, biosafety level 3 precautions are required for laboratory staff working with *B. mallei.* No vaccine is available.

BURKHOLDERIA PSEUDOMALLEI (MELIOIDOSIS)

Melioidosis is an important disease of Southeast Asia and northern Australia and occurs in the United States mainly in persons returning from endemic areas. The causative agent is *Burkholderia pseudomallei,* an inhabitant of soil and water in the tropics. It is ubiquitous in endemic areas, and infection follows inhalation of dust, ingestion, or direct contamination of abrasions or wounds. Human-to-human transmission has only rarely been reported. Serologic surveys demonstrate that asymptomatic infection occurs in endemic areas. The disease may remain latent and appear when host resistance is reduced, sometimes years after the initial exposure. Diabetes mellitus is a risk factor for severe melioidosis.

Melioidosis may present as a single **primary skin lesion** (vesicle, bulla, or urticaria). Pulmonary infection may be subacute and mimic tuberculosis or may present as an acute necrotizing pneumonia. Occasionally, septicemia occurs and numerous abscesses are noted in various organs of the body. Myocarditis, pericarditis, endocarditis, intestinal abscess, cholecystitis, acute gastroenteritis, urinary tract infections, septic arthritis, paraspinal abscess, osteomyelitis, mycotic aneurysm, and generalized lymphadenopathy all have been observed. Melioidosis may also present as an encephalitic illness with fever and seizures. It is also an agent of severe wound infections following contact with contaminated water following a tsunami.

Diagnosis is based on visualization of characteristic small Gram-negative rods in exudates or growth on laboratory media such as eosin–methylene blue or MacConkey agar. Serologic tests are available, and diagnosis can be established by a 4-fold or greater increase in antibody titer in an individual with an appropriate syndrome. It has been recognized as a possible agent of bioterrorism (see Chapter 723).

B. pseudomallei is susceptible to many antimicrobial agents, and the Centers for Disease Control and Prevention (CDC) recommends meropenem or ceftazidime as intravenous therapies and trimethoprim-sulfamethoxazole or doxycycline as oral therapy. Other choices include aminoglycosides, tetracycline, chloramphenicol, and amoxicillin-clavulanate. Therapy should be guided by antimicrobial susceptibility tests; 2 or 3 agents such as ceftazidime or meropenem plus either trimethoprim-sulfamethoxazole, sulfisoxazole, or an aminoglycoside are usually chosen for severe or septicemic disease. For severe disease, prolonged treatment for 2-6 mo is recommended to prevent relapses. Appropriate antibiotic therapy generally results in recovery.

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205.3 *Stenotrophomonas*

Thomas S. Murray and Robert S. Baltimore

Stenotrophomonas maltophilia (formerly *Xanthomonas maltophilia* or *P. maltophilia*) is a short to medium-sized straight Gram-negative bacillus. It is ubiquitous in nature and can be found in the hospital environment, especially in tap water or standing water, and may contaminate sinks and hospital equipment such as nebulizers. Strains isolated in the laboratory may be contaminants, may be a commensal from the colonized surface of a patient, or may represent an invasive pathogen. The species is an opportunist and is often recovered from immunosuppressed patients and patients with cystic fibrosis after multiple courses of antimicrobial therapy. Serious infections usually occur among those requiring intensive care, including neonatal intensive care, typically patients with ventilator-associated pneumonia or catheter-associated infections. Prolonged antibiotic exposure appears to be a frequent factor in nosocomial *S. maltophilia* infections, probably because of its endogenous antibiotic resistance pattern. Common types of infection include pneumonia following airway colonization and aspiration, bacteremia, soft-tissue infections, endocarditis, and osteomyelitis. *S. maltophilia* bacteremia is a nosocomial infection associated with the presence of a central venous catheter.

Strains vary as to antibiotic susceptibility, and the treatment of *S. maltophilia* can be difficult because of inherent antimicrobial resistance. Data are lacking on whether there is clinical benefit to treat *S. maltophilia* recovered from the respiratory tract of a patient with cystic fibrosis. For invasive infections, trimethoprim-sulfamethoxazole is the treatment of choice and is the only antimicrobial for which susceptibility is routinely reported. Mean inhibitory concentration testing is available for other antibiotics, such as ticarcillin-clavulanate, and reserved for trimethoprim-sulfamethoxazole resistant isolates. For resistant organisms or for patients who cannot tolerate sulfa drugs, other options based on clinical outcome include ciprofloxacin, and ceftazidime alone, or in combination with other agents such as aminoglycosides. Tigecycline is a newer agent reported to have efficacy for treating a highly resistant isolate.

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Chapter 206

Tularemia *(Francisella tularensis)*

Gordon E. Schutze and Richard F. Jacobs

Tularemia is a zoonotic infection caused by the Gram-negative bacterium *Francisella tularensis*. Tularemia is primarily a disease of wild animals; human disease is incidental and usually results from contact with blood-sucking insects or live or dead wild animals. The illness caused by *F. tularensis* is manifested by different clinical syndromes, the most common consisting of an ulcerative lesion at the site of inoculation with regional lymphadenopathy or lymphadenitis. *F. tularensis* is also a potential agent of bioterrorism (see Chapter 723).

ETIOLOGY

F. tularensis is a small, nonmotile, pleomorphic, Gram-negative coccobacillus that can be classified into 4 main subspecies, namely *F. tularensis tularensis* [type A], *F. tularensis holarctica* [type B],

F. tularensis mediasiatica, and *F. tularensis novicida*. Type A can be further subdivided into 4 distinct genotypes designated A1a, A1b, A2a, and A2b, with A1b appearing to produce more serious disease in humans. Type A is found exclusively in North America and is associated with wild rabbits, ticks, and tabanid flies (e.g., deer flies), whereas type B is found in North America, Europe, and Asia and is associated with semiaquatic rodents, hares, mosquitoes, ticks, tabanid flies, water (e.g., ponds, rivers), and marine animals. Human infections with type B are usually milder and have lower mortality rates compared to infections with type A.

EPIDEMIOLOGY

During 2001-2010, a total of 1,208 cases of tularemia were reported in the United States from 47 states, averaging 126.5 cases (range: 90-154) per year (Fig. 206-1). Six states accounted for 59% of all reported cases: Missouri, 231 cases (19%); Arkansas, 162 cases (13%); Oklahoma, 108 cases (9%); Massachusetts, 84 cases (7%); South Dakota, 65 cases (5%); and Kansas, 59 cases (5%).

Transmission

Of all the zoonotic diseases, tularemia is unusual because of the different modes of transmission of disease. A large number of animals serve as a reservoir for this organism, which can penetrate both intact skin and mucous membranes. Transmission can occur through the bite of infected ticks or other biting insects, by contact with infected animals or their carcasses, by consumption of contaminated foods or water, or through inhalation, as might occur in a laboratory setting. However, this organism is not transmitted from person to person. In the United States, rabbits and ticks are the principal reservoirs. Most disease caused by rabbit exposure occurs in the winter, and disease from tick exposure occurs in the warmer months (April-September). *Amblyomma americanum* (Lone Star tick), *Dermacentor variabilis* (dog tick), and *Dermacentor andersoni* (wood tick) are the most common tick vectors. These ticks usually feed on infected small rodents and later feed on humans. Taking that blood meal through a fecally contaminated field transmits the infection.

PATHOGENESIS

The most common portal of entry for human infection is through the skin or mucous membrane. Entry may occur through the bite of an infected insect or by way of unapparent abrasions. Inhalation or ingestion of *F. tularensis* can also result in infection. Usually $>10^8$ organisms are required to produce infection if they are ingested, but as few as 10 organisms may cause disease if they are inhaled or injected into the skin. Within 48-72 hr after injection into the skin, an erythematous, tender, or pruritic papule may appear at the portal of entry. This papule may enlarge and form an ulcer with a black base, followed by regional lymphadenopathy. Once *F. tularensis* reaches the lymph nodes, the

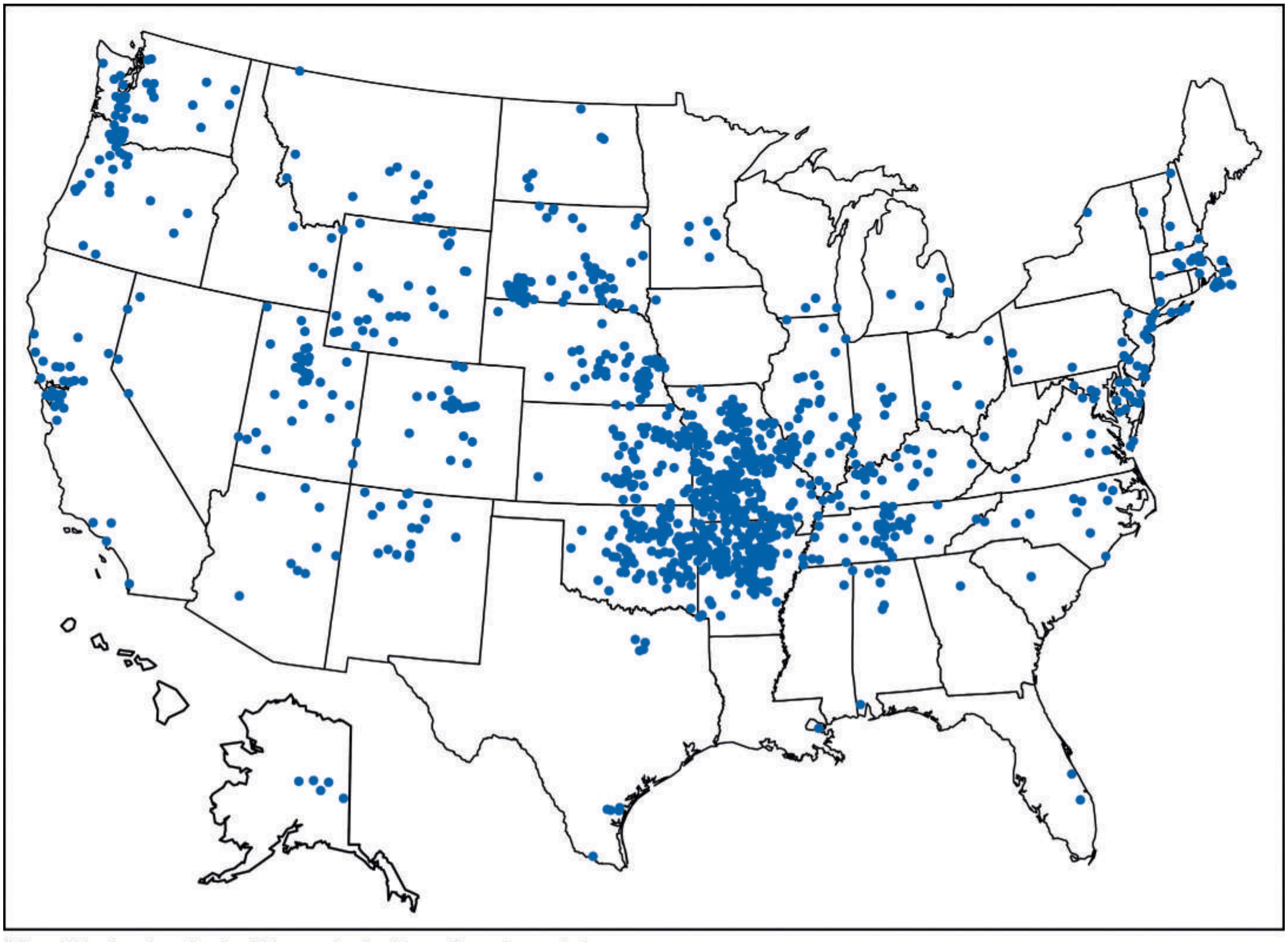

* One dot is placed randomly within county of residence for each reported case.

Figure 206-1 Reported cases of tularemia—United States, 2001–2010. *(From Centers for Disease Control and Prevention (CDC): Tularemia—United States, 2001-2010.* MMWR Morb Mortal Wkly Rep *62(47):963–966, 2013.)*

organism may multiply and form granulomas. Bacteremia may also be present and is most commonly associated with involvement of the reticuloendothelial system, although any organ of the body may be involved.

Conjunctival inoculation may result in infection of the eye with preauricular lymphadenopathy. Inhalation or hematogenous spread of the organisms can result in pneumonia. Chest roentgenograms of such patients may reveal patchy infiltrates rather than areas of consolidation. Pleural effusions may also be present and may contain blood. In pulmonary infections, mediastinal adenopathy may be present; in oropharyngeal disease, patients may develop cervical lymphadenopathy. Typhoidal tularemia is a term used to describe severe bacteremic disease, regardless of the mode of transmission or portal of entry.

Infection with *F. tularensis* stimulates the host to produce antibodies, which have only recently been recognized as important in the immune response to this organism. The body is most dependent on cell-mediated immunity to contain and eradicate *F. tularensis*. Tularemia is usually followed by specific protection; thus, chronic infection or reinfection is unlikely.

CLINICAL MANIFESTATIONS

Although it may vary, the average incubation period from infection until clinical symptoms is 3 days (range: 1-21 days). A sudden onset of fever with other associated symptoms is common (Table 206-1). Physical examination may include lymphadenopathy, hepatosplenomegaly, or skin lesions. Various skin lesions have been described, including erythema multiforme and erythema nodosum. Approximately 20% of patients may develop a generalized maculopapular rash that occasionally becomes pustular. These clinical manifestations of tularemia have been divided into various syndromes (Table 206-2).

Table 206-1 Common Clinical Manifestations of Tularemia in Children

SIGN OR SYMPTOM	FREQUENCY (%)
Lymphadenopathy	96
Fever (>38.3°C [100.9°F])	87
Ulcer/eschar/papule	45
Pharyngitis	43
Myalgias/arthralgias	39
Nausea/vomiting	35
Hepatosplenomegaly	35

Table 206-2 Clinical Syndromes of Tularemia in Children

CLINICAL SYNDROME	FREQUENCY (%)
Ulceroglandular	45
Glandular	25
Pneumonia	14
Oropharyngeal	4
Oculoglandular	2
Typhoidal	2
Other*	6

*Includes meningitis, pericarditis, hepatitis, peritonitis, endocarditis, and osteomyelitis.

Ulceroglandular and glandular disease are the 2 most common forms of tularemia diagnosed in children. The most common glands involved are the cervical or posterior auricular nodes owing to a tick bite on the head or neck. If an ulcer is present, it is erythematous and painful and may last from 1-3 wk. The ulcer is located at the portal of entry. After the ulcer develops, regional lymphadenopathy ensues. These nodes may vary in size from 0.5-10 cm and may appear singly or in clusters. These affected nodes may become fluctuant and drain spontaneously, but usually resolve with treatment. Late suppuration of the involved nodes has been described in 25-30% of patients despite effective therapy. Examination of this material from such lymph nodes usually reveals sterile necrotic material.

Pneumonia caused by *F. tularensis* usually presents as variable parenchymal infiltrates that are unresponsive to β-lactam antimicrobial agents. Inhalation-related infection has been described in laboratory workers who are working with the organism and results in a relatively high mortality rate. Aerosols from farming activities involving rodent contamination (haying, threshing) or animal carcass destruction with lawn mowers have been reported to cause pneumonia as well. Patchy parenchymal infiltrates can also be demonstrated in other forms of tularemia. Patchy segmental infiltrates, hilar adenopathy, and pleural effusions are the most common abnormalities demonstrated on chest roentgenograms. Patients may also complain of a nonproductive cough, dyspnea, or pleuritic chest pain.

Oropharyngeal tularemia results from consumption of poorly cooked meats or contaminated water. This syndrome is characterized by acute pharyngitis, with or without tonsillitis, and cervical lymphadenitis. Infected tonsils may become large and develop a yellowish-white membrane that may resemble the membranes associated with diphtheria. Gastrointestinal disease may also occur and usually presents with mild, unexplained diarrhea but may progress to rapidly fulminant and fatal disease.

Oculoglandular tularemia is uncommon, but when it does occur, the portal of entry is the conjunctiva. Contact with contaminated fingers or debris from crushed insects is the most common way of applying the organisms to the conjunctiva. The conjunctiva is painful and inflamed, with yellowish nodules and pinpoint ulcerations. Purulent conjunctivitis with ipsilateral preauricular or submandibular lymphadenopathy is referred to as **Parinaud oculoglandular syndrome.**

Typhoidal tularemia is usually associated with a large inoculum of organisms and usually presents with fever, headaches, and signs or symptoms of endotoxemia. Patients typically are critically ill, and symptoms mimic those with other forms of sepsis. Clinicians practicing in tularemia-endemic regions must always consider this diagnosis in critically ill children.

DIAGNOSIS

The history and physical examination of the patient may suggest the diagnosis of tularemia, especially if the patient lives in or has visited an endemic region. A history of animal or tick exposure may be especially helpful. Hematologic blood tests are nondiagnostic. Results of routine cultures and smears are positive in only approximately 10% of cases. *F. tularensis* can be cultured in the microbiology laboratory on cysteine–glucose–blood agar, but care should be taken to alert the personnel in the laboratory if this is attempted so that they can take the proper precautions to protect themselves from acquiring infection.

The diagnosis of tularemia is most commonly established through the use of a standard and highly reliable serum agglutination test. In the standard tube agglutination test, a single titer of ≥1 : 160 in a patient with a compatible history and physical findings can establish the diagnosis. A 4-fold increase in titer from paired serum samples collected 2-3 wk apart is also diagnostic. False-negative serologic responses can be obtained early in the infection, and as many as 30% of individuals require longer than 3 wk before testing positive. Once infected, patients may have a positive agglutination test result (1 : 20 to 1 : 80) that may persist for life.

Other testing techniques available include a microagglutination test, enzyme-linked immunosorbent assay, analysis of urine for tularemia

antigen, and polymerase chain reaction. These techniques may become more popular in the future but at this time have a limited role in establishing the diagnosis of tularemia.

Differential Diagnosis

The differential diagnosis of ulceroglandular or glandular tularemia includes cat scratch disease *(Bartonella henselae);* infectious mononucleosis; Kawasaki syndrome; lymphadenopathy caused by *Staphylococcus aureus,* group A streptococcus, *Mycobacterium tuberculosis, Toxoplasma gondii,* nontuberculous mycobacteria, or *Sporothrix schenckii;* plague; anthrax; melioidosis; and rat-bite fever. Oculoglandular disease may also occur with other infectious agents, such as *B. henselae, Treponema pallidum, Coccidioides immitis,* herpes simplex virus, adenoviruses, and the bacterial agents responsible for purulent conjunctivitis. Oropharyngeal tularemia must be differentiated from the same diseases that cause ulceroglandular/glandular disease and from cytomegalovirus, herpes simplex, adenovirus, and other viral or bacterial etiologies. Pneumonic tularemia must be differentiated from the other non–β-lactam-responsive organisms such as *Mycoplasma, Chlamydophila,* mycobacteria, fungi, and rickettsia. Typhoidal tularemia must be differentiated from other forms of sepsis as well as from enteric fever (typhoid and paratyphoid fever) and brucellosis.

TREATMENT

All strains of *F. tularensis* are susceptible to gentamicin and streptomycin. Gentamicin (5 mg/kg/day divided bid or tid IV or IM) is the drug of choice for the treatment of tularemia in children because of the limited availability of streptomycin (30-40 mg/kg/day divided bid IM) and the fewer adverse effects of gentamicin. Therapy is typically continued for 7-10 days, but in mild cases, 5-7 days may be sufficient. Chloramphenicol and tetracyclines have been used, but the high relapse rate has limited their use in children. Early data suggested that *F. tularensis* is susceptible to the third-generation cephalosporins (cefotaxime, ceftriaxone), but clinical case reports demonstrate a nearly universal failure rate with these agents. Fluoroquinolones have been used with success in cases of illness caused by the subspecies *holarctica*. Ciprofloxacin (15-20 mg/kg/day in 2 divided doses for 10-14 days) has been used in children, but the lack of treatment data for the subspecies *tularensis* and the issues related to the use of fluoroquinolones in patients younger than 18 yr of age limit the use of this group of medications in North American children at this time.

Patients typically have defervescence within 24-48 hr after starting therapy, and relapses are uncommon if gentamicin or streptomycin is used. Patients who have not started on appropriate therapy early may respond more slowly to antimicrobial therapy. Late suppuration of involved lymph nodes may occur despite adequate therapy.

PROGNOSIS

Poor outcomes are associated with a delay in recognition and treatment, but with rapid recognition and treatment, fatalities are exceedingly rare. The mortality rate for severe untreated disease (e.g., pneumonia, typhoidal disease) can be as high as 30% in these situations, but in general, the overall mortality rate is <1%.

PREVENTION

Prevention of tularemia is based on avoiding exposure. Children living in tick-endemic regions should be taught to avoid tick-infested areas, and families should have a tick control plan for their immediate environment and for their pets. Protective clothing should be worn when entering a tick-infested area. Insect repellents for use on the skin (e.g., DEET [*N,N*-diethyl-3-methylbenzamide] or picaridin) can be used safely in infants and children. If skin repellents are used, they should be used sparingly on the exposed skin, avoiding the hands and face on children younger than 1 yr of age. The repellent should be washed off completely after leaving the high-risk region. Clothing repellents that use permethrin have been demonstrated to be an effective addition to the use of protective clothing. Infants and young children should not be allowed to chew or suck on permethrin impregnated clothing. Children should undergo frequent tick checks during and after their time in tick-infested areas. If ticks are found on the child, forceps should be used to pull the tick straight out. The skin should be cleansed before and after this procedure.

Children should also be taught to avoid sick and dead animals. Dogs and cats are most likely to bring these animals to a child's attention. Children should be encouraged to wear gloves while cleaning wild game. Prophylactic antimicrobial agents are not effective in preventing tularemia and should not be used after exposure. No tularemia vaccine is currently available for the general public.

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Chapter 207

Brucella

Gordon E. Schutze and Richard F. Jacobs

Human brucellosis is caused by organisms of the genus *Brucella* and continues to be a major public health problem worldwide. Humans are accidental hosts and acquire this zoonotic disease from direct contact with an infected animal or consumption of products of an infected animal. Although brucellosis is widely recognized as an occupational risk among adults working with livestock, much of the brucellosis in children is foodborne and is associated with consumption of unpasteurized milk products. *Brucella* spp. are also potential agents of bioterrorism (see Chapter 723).

ETIOLOGY

Brucella abortus (cattle), *Brucella melitensis* (goat/sheep), *Brucella suis* (swine), and *Brucella canis* (dog) are the most common organisms responsible for human disease. These organisms are small, aerobic, non–spore-forming, nonmotile, Gram-negative coccobacillary bacteria that are fastidious in their growth but can be grown on various laboratory media, including blood and chocolate agars.

EPIDEMIOLOGY

Because of improved sanitation, brucellosis has become rare in industrialized countries. Brucellosis exists worldwide and is especially prevalent in the Mediterranean basin, Persian Gulf, Indian subcontinent, and parts of Mexico and Central and South America. In industrialized countries, recreational or occupational exposure to infected animals is a major risk factor for the development of disease. In the United States, more than 50% of cases occur in California, Florida, and Texas, and hunting feral swine in these states is a recently recognized risk factor. Among children, geographic locations that are endemic for *B. melitensis* remain areas of increased risk for the development of infection. In such locations, unpasteurized milk from goats or camels may be used to feed children, thus leading to the development of brucellosis. A history of travel to endemic regions or consumption of exotic food or unpasteurized dairy or dairy products may be an important clue to the diagnosis of human brucellosis.

PATHOGENESIS

Routes of infection for these organisms include inoculation through cuts or abrasions in the skin, inoculation of the conjunctival sac of the eye, inhalation of infectious aerosols, or ingestion of contaminated meat or dairy products. The risk for infection depends on the nutritional and immune status of the host, the route of inoculum, and the species of *Brucella.* For reasons that remain unclear, it has been suggested that *B. melitensis* and *B. suis* are more virulent than *B. abortus* or *B. canis.*

The major virulence factor for *Brucella* appears to be its cell wall lipopolysaccharide. Strains containing smooth lipopolysaccharide have been demonstrated to have greater virulence and are more resistant to killing by polymorphonuclear leukocytes. These organisms are facultative intracellular pathogens that can survive and replicate within the mononuclear phagocytic cells (monocytes, macrophages) of the reticuloendothelial system. Even though *Brucella* are chemotactic for entry of leukocytes into the body, the leukocytes are less efficient at killing these organisms than other bacteria despite the assistance of serum factors such as complement.

Organisms that are not phagocytosed by the leukocytes are ingested by the macrophages and become localized within the reticuloendothelial system. Specifically, they reside within the liver, spleen, lymph nodes, and bone marrow and result in **granuloma** formation. Antibodies are produced against the lipopolysaccharide and other cell wall antigens, providing a means of diagnosis and probably playing a role in long-term immunity. The major factor in recovery from infection appears to be development of a cell-mediated response resulting in macrophage activation and enhanced intracellular killing. Specifically, sensitized T lymphocytes release cytokines (e.g., interferon-γ and tumor necrosis factor-α), which activate the macrophages and enhance their intracellular killing capacity.

CLINICAL MANIFESTATIONS

Brucellosis is a systemic illness that can be very difficult to diagnose in children without a history of animal or food exposure. Symptoms can be acute or insidious in nature and are usually nonspecific, beginning 2-4 wk after inoculation. Although the clinical manifestations vary, the classic triad of fever, arthralgia/arthritis, and hepatosplenomegaly can be demonstrated in most patients. Some present as a fever of unknown origin. Other associated symptoms include abdominal pain, headache, diarrhea, rash, night sweats, weakness/fatigue, vomiting, cough, and pharyngitis. A common constellation of symptoms in children is refusal to eat, lassitude, refusal to bear weight, and failure to thrive. Besides hepatosplenomegaly, the physical findings on examination are usually few, with the exception of arthritis. The fever pattern can vary widely, and virtually any organ or tissue can be involved.

If abnormalities are demonstrated on physical examination, monoarticular arthritis of the knees and hips in children and of the sacroiliac joint in adolescents and adults can be found. Although headache, mental inattention, and depression may be demonstrated in patients with brucellosis, invasion of the nervous system occurs in only approximately 1% of cases. Neonatal and congenital infections with these organisms have also been described, resulting from transmission transplacentally, from breast milk, and through blood transfusions. The signs and symptoms associated with brucellosis are vague and not pathognomonic.

DIAGNOSIS

Routine laboratory examinations of the blood are not helpful; thrombocytopenia, neutropenia, anemia, or pancytopenia may occur. A history of exposure to animals or ingestion of unpasteurized dairy products may be more helpful. A definitive diagnosis is established by recovering the organisms in the blood, bone marrow, or other tissues. Although automated culture systems and the use of the lysis-centrifugation method have shortened the isolation time from weeks to days, it is prudent to alert the clinical microbiology laboratory that brucellosis is suspected. Isolation of the organism still may require as long as 4 wk from a blood culture sample unless the laboratory is using an automated culture system such as the lysis centrifugation method where the organism can be recovered in <5 days. Bone marrow cultures may be superior to blood cultures when evaluating patients with previous antimicrobial therapy. Caution is advised when using automated bacterial identification systems, because isolates have been misidentified as other Gram-negative organisms (*Haemophilus influenzae* type b).

In the absence of positive culture results, various serologic tests have been applied to the diagnosis of brucellosis. The serum agglutination test is the most widely used and detects antibodies against *B. abortus, B. melitensis,* and *B. suis.* This method does not detect antibodies against *B. canis* because this organism lacks the smooth lipopolysaccharide. No single titer is ever diagnostic, but most patients with acute infections have titers of ≥1 : 160. Low titers may be found early in the course of the illness, requiring the use of acute and convalescent sera testing to confirm the diagnosis. Because patients with active infection have both an immunoglobulin (Ig) M and an IgG response and the serum agglutination test measures the total quantity of agglutinating antibodies, the total quantity of IgG is measured by treatment of the serum with 2-mercaptoethanol. This fractionation is important in determining the significance of the antibody titer because low levels of IgM can remain in the serum for weeks to months after the infection has been treated. It is important to remember that all titers must be interpreted in light of a patient's history and physical examination. False-positive results resulting from crossreacting antibodies to other Gram-negative organisms, such as *Yersinia enterocolitica, Francisella tularensis,* and *Vibrio cholerae,* can occur. In addition, the prozone effect can give false-negative results in the presence of high titers of antibody. To avoid this issue, serum that is being tested should be diluted to ≥1 : 320.

Among newer tests, the enzyme immunoassay should only be used for suspected cases with negative serum agglutination tests or for the evaluation of patients in the following situations: (1) complicated cases; (2) suspected chronic brucellosis; (3) reinfection. Polymerase chain reaction assays have been developed but are not available in most clinical laboratories.

Differential Diagnosis

Brucellosis may be confused with other infections such as tularemia, cat scratch disease, typhoid fever, histoplasmosis, blastomycosis, and coccidioidomycosis. Infections caused by *Mycobacterium tuberculosis,* atypical mycobacteria, rickettsiae, and *Yersinia* can present in a similar fashion to brucellosis.

TREATMENT

Many antimicrobial agents are active in vitro against the *Brucella* species, but the clinical effectiveness does not always correlate with these results. Doxycycline is the most useful antimicrobial agent and, when combined with an aminoglycoside, is associated with the fewest relapses (Table 207-1). Treatment failures with β-lactam antimicrobial agents, including the third-generation cephalosporins, may be because of the intracellular nature of the organism. Agents that provide intracellular killing are required for eradication of this infection. Similarly, it is apparent that prolonged treatment is the key to preventing disease relapse. Relapse is confirmed by isolation of *Brucella* within weeks to months after therapy has ended and is usually not associated with antimicrobial resistance.

The onset of initial antimicrobial therapy may precipitate a Jarisch-Herxheimer–like reaction, presumably because of a large antigen load. It is rarely severe enough to require corticosteroid therapy.

PROGNOSIS

Before the use of antimicrobial agents, the course of brucellosis was often prolonged and may have led to death. Since the institution of specific therapy, most deaths are a result of specific organ system involvement (e.g., endocarditis) in complicated cases. The prognosis after specific therapy is excellent if patients are compliant with the prolonged therapy (see Table 207-1).

PREVENTION

Prevention of brucellosis is dependent on effective eradication of the organism from cattle, goats, and swineherds, as well as from other animals. Pasteurization of milk and dairy products for human consumption remains an important aspect of prevention. It should be noted that certification of raw milk does not eliminate the risk of brucellosis acquisition. No vaccine currently exists for use in children and, therefore, education of the public continues to have a prominent role in prevention of this disease.

Bibliography is available at Expert Consult.

Table 207-1 Recommended Therapy for the Treatment of Brucellosis				
AGE AND CONDITION	**ANTIMICROBIAL AGENT**	**DOSE**	**ROUTE**	**DURATION**
≥8 yr	Doxycycline	2-4 mg/kg/day; maximum: 200 mg/day	PO	6 wk
	+			
	Rifampin	15-20 mg/kg/day; maximum: 600-900 mg/day	PO	6 wk
	Alternative:			
	Doxycycline	2-4 mg/kg/day; maximum: 200 mg/day	PO	6 wk
	+			
	Streptomycin	15-30 mg/kg/day; maximum: 1 g/day	IM	2-3 wk
	or			
	Gentamicin	3-5 mg/kg/day	IM/IV	1-2 wk
<8 yr	Trimethoprim-sulfamethoxazole (TMP-SMZ)	TMP (10 mg/kg/day; maximum: 480 mg/day) and SMZ (50 mg/kg/day; maximum: 2.4 g/day)	PO	4-8 wk
	+			
	Rifampin	15-20 mg/kg/day	PO	6 wk
Meningitis, osteomyelitis, endocarditis	Doxycycline	2-4 mg/kg/day; maximum: 200 mg/day	PO	4-6 mo
	+			
	Gentamicin	3-5 mg/kg/day	IV	1-2 wk
	±			
	Rifampin	15-20 mg/kg/day; maximum: 600-900 mg/day	PO	4-6 mo

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Chapter 208

Legionella

Lucy S. Tompkins and Elizabeth V. Robilotti

Legionellosis comprises **Legionnaires disease** (*Legionella* pneumonia), other invasive extrapulmonary *Legionella* infections, and an acute flu-like illness known as **Pontiac fever.** In contrast to the syndromes associated with invasive disease, Pontiac fever is a self-limited illness that develops after aerosol exposure and may represent a toxic or hypersensitivity response to *Legionella.*

ETIOLOGY

Legionellaceae are aerobic, non–spore-forming, unencapsulated Gram-negative bacilli that stain poorly with Gram stain when performed on smears from clinical specimens. Microorganisms in tissue can be better visualized with the Gimenez or silver stains (Dieterle or Warthin-Starry). Stained smears of *Legionella pneumophila* taken from colonial growth resemble *Pseudomonas.* Unlike other *Legionella* species, *Legionella micdadei* stains acid fast. Although more than 30 species of the genus have now been identified, the majority (90%) of clinical infections are caused by *L. pneumophila,* and most of the remainder are caused by *L. micdadei, Legionella bozemanii, Legionella dumoffii,* and *Legionella longbeachae.*

The organisms are fastidious and require L-cysteine, ferric ion, and α-keto acids for growth. Colonies develop within 3-5 days on buffered charcoal yeast extract agar, which may contain selected antibiotics to inhibit overgrowth by other microorganisms; *Legionella* rarely grows on routine laboratory media.

EPIDEMIOLOGY

The environmental reservoir of *Legionella* in nature is fresh water (lakes, streams, thermally polluted waters, potable water), and invasive pneumonia (Legionnaires disease) is related to exposure to potable water or to aerosols containing the bacteria. Growth of *Legionella* occurs more readily in warm water, and exposure to warm water sources is an important risk factor for disease. *Legionella* organisms are facultative intracellular parasites and grow inside protozoans present in biofilms consisting of organic and inorganic material found in plumbing and water storage tanks and various other bacterial species. Epidemic and sporadic cases of community-acquired Legionnaires disease can be attributed to potable water in the local environment of the patient. Risk factors for acquisition of sporadic community-acquired pneumonia include exposure to cooling towers, nonmunicipal water supply, residential plumbing repairs, and lower water heater temperatures, which facilitate growth of bacteria or lead to release of a bolus of biofilm containing *Legionella* into potable water. The mode of transmission may be by way of inhalation of aerosols or by microaspiration. Outbreaks of Legionnaires disease have been associated with protozoans in the implicated water source; replication within these eukaryotic cells presumably amplifies and maintains *Legionella* within the potable water distribution system or in cooling towers. Outbreaks of community-acquired pneumonia and some nosocomial outbreaks have been linked to common sources, including potable hot water heaters, evaporative condensers, cooling towers, whirlpool baths, humidifiers, and nebulizers. Travel-associated Legionnaires disease and Pontiac fever are increasingly recognized in major outbreaks.

Hospital-acquired infections are most often linked to potable water. Exposure may occur through 3 general mechanisms: (1) inhalation of contaminated water vapor through artificial ventilation; (2) aspiration of ingested microorganisms, including those in gastric feedings that are mixed with contaminated tap water; and (3) inhalation of aerosols from showers, sinks and fountains. Extrapulmonary legionellosis may occur through topical application of contaminated tap water into surgical or traumatic wounds. In contrast to Legionnaires disease, Pontiac fever outbreaks have occurred through exposure to aerosols from whirlpool baths and ventilation systems.

The incidence of legionellosis in the United States increased from 1,100 cases in 2000 to 3,522 cases in 2009 for a national incidence rate of 1.15 per 100,000 persons based on passive reporting to the Centers for Disease Control and Prevention (CDC) through the National Notifiable Disease Surveillance System. Legionellosis demonstrates geographic differences, and the vast majority of cases are classified as Legionnaires disease (99.5%) vs a small fraction as Pontiac fever (0.5%). *Legionella* infections are reported most frequently in fall and summer, and recent studies show an association with total monthly rainfall and humidity. Approximately 0.5-5.0% of those exposed to a common source develop pneumonia, whereas the attack rate in Pontiac fever outbreaks is very high (85-100%). Although *Legionella* is associated with 2-9% of pneumonia cases in adults, it is a rare cause of disease in pediatric populations, accounting for fewer than 1% of cases. Taken together, *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *L. pneumophila* have been identified in 3-23% of children studied with atypical pneumonia. These pathogens show a specific age distribution, with *M. pneumoniae* more commonly isolated in older children and *C. pneumoniae* more frequently recovered from infants. *Legionella* remains a rare cause of community-acquired pneumonia in those younger than 19 yr of age. Acquisition of antibodies to *L. pneumophila*

in healthy children occurs progressively over time, although these antibodies presumably reflect subclinical infection or mild respiratory disease or antibodies that crossreact with other bacterial species. Community-acquired Legionnaires disease in children is increasingly reported (1.7% of reported cases), and most cases occur in children ages 15-19 yr, followed by infants age younger than 1 yr. The incidence in infants is reported to be 0.11 per 100,000. It is likely that legionellosis is significantly underreported, both in children and adults.

As estimated by seroconversion to *L. pneumophila* among children hospitalized with pneumonia, the Legionnaires disease rate is quite low. Most nosocomial infections have been reported as case reports; consequently, the true incidence of disease in children is unknown. Nosocomial infection rates in adults are difficult to determine, because many hospital laboratories do not attempt to isolate *Legionella* by culture. Hospital-acquired legionellosis in children is associated with clinical risk factors and with environmental exposure.

PATHOGENESIS

Although *Legionella* can be grown on artificial media, the intracellular environment of eukaryotic cells provides the definitive site of growth. *Legionella* organisms are facultative intracellular parasites of eukaryotic cells. In nature, *Legionella* replicate within protozoans found in fresh water. In humans, the main target cell for *Legionella* is the alveolar macrophage, although other cell types may also be invaded. After entry, virulent strains of *L. pneumophila* stimulate the formation of a special phagosome that permits bacterial replication to proceed. The phagosome consists of components of the endoplasmic reticulum and escapes the degradative lysosomal pathway. Growth in macrophages occurs to the point of cell death, followed by reinfection of new cells, until these cells are activated and can subsequently kill intracellular microorganisms. Acute, severe infection of the lung provokes an acute inflammatory response and necrosis; early on, more bacteria are found in extracellular spaces as a result of intracellular replication, lysis, and release of bacteria. Subsequently, macrophage activation and other immune responses produce intense infiltration of tissue by macrophages that contain intracellular bacteria, ultimately leading to control of bacterial replication and killing. Corticosteroid therapy poses a high risk for infection by interfering with T-cell and macrophage function. Although community-acquired Legionnaires disease may occur in healthy, immunocompetent patients without other comorbid conditions, those who have defects in cellular-mediated immunity are at high risk for infection. As in other diseases caused by facultative intracellular microorganisms, the outcome is critically dependent on the specific and nonspecific immune responses of the host, particularly macrophage and T-cell responses.

CLINICAL MANIFESTATIONS

Legionnaires disease was originally believed to cause atypical pneumonia associated with extrapulmonary signs and symptoms, including diarrhea, confusion, hyponatremia, hypophosphatemia, abnormal results of liver function tests, and renal dysfunction. Although a subset of patients may exhibit these classic manifestations, *Legionella* infection typically causes pneumonia that is indistinguishable from disease produced by other infectious agents. Fever, cough, and chest pain are common presenting symptoms; the cough may be productive of purulent sputum or may be nonproductive. Although the classic chest radiographic appearance demonstrates rapidly progressive alveolar filling infiltrates, in usual cases of pneumonia the chest radiographic appearance is widely variable, appearing as tumor-like shadows, evidence of nodular infiltrates, unilateral or bilateral infiltrates, or cavitation, although cavitation is rarely seen in immunocompetent patients. This picture overlaps substantially with disease caused by *Streptococcus pneumoniae.* Although pleural effusion is less commonly associated with Legionnaires disease, its frequency varies so widely that neither the presence nor absence of effusion is helpful in differential diagnosis. If present, pleural fluid should be obtained for culture.

A few clinical features may help to differentiate *Legionella* pneumonia from other causes. *Legionella* pneumonia produces an acute-onset febrile illness and radiographic evidence of alveolar filling infiltrates, and usually there is no clinical response to broad-spectrum β-lactam (penicillins and cephalosporins) or aminoglycoside antibiotics.

Concomitant infection with other pathogens, including *M. pneumoniae* and *C. pneumoniae*, occurs in 5-10% of cases of Legionnaires disease; therefore, detection of another potential pulmonary pathogen does not preclude the diagnosis of legionellosis.

Most reports of nosocomial *Legionella* pneumonia in children demonstrate the following clinical features: rapid onset, temperature greater than 38.5°C (101.3°F), cough, pleuritic chest pain, tachypnea, and dyspnea. Abdominal pain, headache, and diarrhea are also common. Chest radiographs reveal lobar consolidations or diffuse bilateral infiltrates, and pleural effusions may be noted.

Risk factors for Legionnaires disease in adults include chronic diseases of the lung (smoking, bronchitis), older age, diabetes and renal failure, immunosuppression associated with organ transplantation, corticosteroid therapy, and episodes of aspiration. In surveys of community-acquired infection, a significant number of adults have no identified risk factors. The number of reported cases of community-acquired Legionnaires disease in children is small. Among these, immunocompromised status, especially corticosteroid treatment, coupled with exposure to contaminated potable water is the major risk factor. Infection in a few children with chronic pulmonary disease without immune deficiency has also been reported, but infection in children lacking any risk factors is very uncommon. The modes of transmission of community-acquired disease in children include exposure to mists, fresh water, water coolers, and other aerosol-generating apparatuses. Nosocomial *Legionella* infection occurs more frequently than community-acquired disease in children and occurs most commonly in those who are immunocompromised, although Legionnaires disease has been seen in immunocompetent children who are postoperative receiving artificial ventilation or exposed to other aerosols. The modes of acquisition include microaspiration, frequently associated with nasogastric tubes, and aerosol inhalation. Bronchopulmonary *Legionella* infections are reported in patients with cystic fibrosis and have been associated with aerosol therapy or mist tents. Legionnaires disease is also reported in pediatric patients with asthma and tracheal stenosis. Chronic corticosteroid therapy for asthma is a reported risk factor for *Legionella* infections in children. Molecular fingerprinting of strains has demonstrated that potable water serves as the major reservoir and source of nosocomial infection.

Pontiac fever in adults and children is characterized by high fever, myalgia, headache, and extreme debilitation, lasting for a few days. Cough, breathlessness, diarrhea, confusion, and chest pain may occur, but there is no evidence for invasive infection. The disease is self-limited without sequelae. Virtually all exposed individuals seroconvert to *Legionella* antigens. A very large outbreak in Scotland that affected 35 children was attributed to *L. micdadei,* which was isolated from a whirlpool spa. The onset of illness was 1-7 days (median: 3 days), and all exposed children developed significant titers of specific antibodies to *L. micdadei.* The pathogenesis of Pontiac fever is not known. In the absence of evidence of true infection, the most likely hypothesis is that this syndrome is caused by a toxic or hypersensitivity reaction to microbial, or protozoan, antigens.

DIAGNOSIS

Culture of *Legionella* from sputum, other respiratory tract specimens, blood, or tissue is the gold standard against which indirect methods of detection should be compared. Specimens obtained from the respiratory tract that are contaminated with oral flora must be treated and processed to reduce contaminants and plated onto selective media. Because these are costly and time-consuming methods, many laboratories do not process specimens for culture. The urinary antigen assay that detects *L. pneumophila* serogroup I has revolutionized the diagnosis of *Legionella* infection and has 80% sensitivity and 99% specificity. The assay is a useful method in the prompt diagnosis of Legionnaires disease caused by this serogroup, which accounts for the majority of symptomatic infections. In the United States, this test is frequently used because it is widely available in reference laboratories. Where available, polymerase chain reaction is used to identify *L. pneumophila* from bronchoscopic lavage and other clinical specimens to the exclusion of other respiratory pathogens. Other methods, including direct immunofluorescence, have low sensitivity and are generally not employed. Retrospective diagnosis can be made serologically using the enzyme-linked

immunosorbent assay or enzyme immunoassay to detect specific antibody production. Seroconversion may not occur for several weeks after onset of infection, and the available serologic assays do not detect all strains of *L. pneumophila* or all species. In view of the low sensitivity of direct detection and the slow growth of the microorganism in culture, the diagnosis of legionellosis should be pursued actively when there is suggestive clinical evidence, including the lack of response to usual antibiotics, even when results of other laboratory studies are negative.

TREATMENT

In community-acquired pneumonia in adults who are hospitalized, guidelines recommend empirical treatment with a broad-spectrum cephalosporin plus a macrolide or quinolone so as to treat atypical microorganisms *(Legionella, Chlamydophila pneumoniae, M. pneumoniae)*. Evidence-based guidelines for management of community-acquired pneumonia in children do not yet include *Legionella* in the differential diagnosis or empiric treatment recommendations. Effective treatment of Legionnaires disease is based in part on the intracellular concentration of antibiotics. Erythromycin (40 mg/kg/day PO or IV) with or without rifampin (15 mg/kg/day) was considered effective therapy many years ago. Azithromycin (10 mg/kg on day 1, not to exceed 500 mg/day, and then 5 mg/kg daily for 4 days PO) and clarithromycin (15 mg/kg/day PO) and the quinolones (ciprofloxacin and levofloxacin) have generally replaced erythromycin as therapy for patients with diagnosed *Legionella* infection. Quinolones are not approved for children younger than 18 yr of age and should be avoided in those who have not achieved growth maturity. In serious infections or in high-risk patients, parenteral therapy is recommended initially; a switch to oral therapy can be made when a patient has had a clinical response. The duration of oral azithromycin therapy for Legionnaires disease in adults is 4 days, although therapy is usually continued for 10-14 days in more seriously ill or immunocompromised patients. Acute reversible hearing loss is associated with high-dose parenteral macrolide therapy. Treatment of extrapulmonary infections, including prosthetic valve endocarditis and sternal wound infections, may require prolonged therapy. Trimethoprim-sulfamethoxazole (TMP-SMZ; 15 mg TMP/kg/day and 75 mg SMZ/kg/day) is used as an alternative.

PROGNOSIS

The mortality rate for community-acquired Legionnaires disease in adults who are hospitalized is approximately 15% but may exceed 50% in immunocompromised patients. The prognosis depends on underlying host factors and possibly on the duration of illness before initiation of appropriate therapy. Despite appropriate antibiotic therapy, patients may succumb to respiratory complications, such as acute respiratory distress syndrome, associated with artificial ventilation and intubation. A high mortality rate is noted in case reports of premature infants and children, virtually all of whom have been immunocompromised. Delay in diagnosis is also associated with increased mortality. Consequently, *Legionella* should be considered in the differential diagnosis of both community-acquired and nosocomial pneumonia in children, especially in those refractory to empiric therapy or with epidemiologic risk factors for legionellosis.

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Chapter 209
Bartonella
Barbara W. Stechenberg

The spectrum of disease resulting from human infection with *Bartonella* species includes the association of bacillary angiomatosis and cat-scratch disease (CSD) with *Bartonella henselae.* There are more than 30 validated species of *Bartonella*; however, 6 major species are pathogenic for humans: *B. henselae, Bartonella quintana, Bartonella bacilliformis, Bartonella elizabethae, Bartonella vinsonii,* and *Bartonella clarridgeiae* (Table 209-1). Several other *Bartonella* species have been found in animals, particularly rodents and moles.

Members of the genus *Bartonella* are Gram-negative, oxidase-negative, fastidious aerobic rods that ferment no carbohydrates. *B. bacilliformis* is the only species that is motile, achieving motility by means of polar flagella. Optimal growth is obtained on fresh media containing 5% or more sheep or horse blood in the presence of 5% carbon dioxide. The use of lysis centrifugation for specimens from blood on chocolate agar for extended periods (2-6 wk) enhances recovery.

Bibliography is available at Expert Consult.

209.1 Cat-Scratch Disease *(Bartonella henselae)*
Barbara W. Stechenberg

The most common presentation of *Bartonella* infection is CSD, which is a subacute, regional lymphadenitis caused by *B. henselae.* It is the most common cause of chronic lymphadenitis that persists for longer than 3 wk.

ETIOLOGY
B. henselae can be cultured from the blood of healthy cats. *B. henselae* organisms are the small pleomorphic Gram-negative bacilli visualized with Warthin-Starry stain in affected lymph nodes from patients with CSD. Development of serologic tests that showed prevalence of antibodies in 84-100% of cases of CSD, culturing of *B. henselae* from CSD nodes, and detection of *B. henselae* by polymerase chain reaction in the majority of lymph node samples and pus from patients with CSD, confirmed the organism as the cause of CSD. Occasional cases of CSD may be caused by other organisms; 1 report described a veterinarian with CSD caused by *B. clarridgeiae.*

EPIDEMIOLOGY
CSD is common, with more than 24,000 estimated cases per year in the United States. It is transmitted by cutaneous inoculation. Most (87-99%) patients have had contact with cats, many of which are kittens younger than 6 mo of age, and more than 50% of patients have a definite history of a cat scratch or bite. Cats have high-level *Bartonella* bacteremia for months without any clinical symptoms; kittens are more frequently bacteremic than adult cats. Transmission between cats occurs via the cat flea, *Ctenocephalides felis.* In temperate zones, the majority of cases occur between September and March, perhaps in relation to the seasonal breeding of domestic cats or to the close proximity of family pets in the fall and winter. In tropical zones, there is no seasonal prevalence. Distribution is worldwide, and infection occurs in all races.

Cat scratches appear to be more common among children, and boys are affected more often than girls. CSD is a sporadic illness; usually only 1 family member is affected, even though many siblings play with the same kitten. However, clusters do occur, with family cases within weeks of one another. Anecdotal reports have implicated other sources, such as dog scratches, wood splinters, fishhooks, cactus spines, and porcupine quills.

PATHOGENESIS
The pathologic findings in the primary inoculation **papule** and affected lymph nodes are similar. Both show a central avascular necrotic area with surrounding lymphocytes, giant cells, and histiocytes. Three stages of involvement occur in affected nodes, sometimes simultaneously in the same node. The 1st stage consists of generalized enlargement with thickening of the cortex and hypertrophy of the germinal center and with a predominance of lymphocytes. Epithelioid granulomas with Langhans giant cells are scattered throughout the node. The middle stage is characterized by granulomas that increase in density, fuse, and become infiltrated with polymorphonuclear leukocytes, with

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beginning central necrosis. In the final stage, necrosis progresses with formation of large pus-filled sinuses. This purulent material may rupture into surrounding tissue. Similar granulomas have been found in the liver, spleen, and osteolytic lesions of bone when those organs are involved.

CLINICAL MANIFESTATIONS

After an incubation period of 7-12 days (range: 3-30 days), 1 or more 3-5 mm red papules develop at the site of cutaneous inoculation, often reflecting a linear cat scratch. These lesions are often overlooked because of their small size but are found in at least 65% of patients when careful examination is performed (Fig. 209-1). Lymphadenopathy is generally evident within a period of 1-4 wk (Fig. 209-2). Chronic regional lymphadenitis is the hallmark, affecting the 1st or 2nd set of nodes draining the entry site. Affected lymph nodes in order of frequency include the axillary, cervical, submandibular, preauricular, epitrochlear, femoral, and inguinal nodes. Involvement of more than 1 group of nodes occurs in 10-20% of patients, although at a given site, half the cases involve several nodes.

Nodes involved are usually tender and have overlying erythema but without cellulitis. They usually range between 1 and 5 cm in size, although they can become much larger. Between 10% and 40% eventually suppurate. The duration of enlargement is usually 1-2 mo, with persistence up to 1 yr in rare cases. Fever occurs in approximately 30% of patients, usually 38-39°C (100.4-102.2°F). Other nonspecific symptoms, including malaise, anorexia, fatigue, and headache, affect less than one-third of patients. Transient rashes, which may occur in approximately 5% of patients, are mainly truncal maculopapular rashes. Erythema nodosum, erythema multiforme, and erythema annulare are also reported.

CSD is usually a self-limited infection that spontaneous resolves within a few weeks to months. The most common atypical presentation is **Parinaud oculoglandular syndrome,** which is unilateral conjunctivitis followed by preauricular lymphadenopathy and occurs in 2-17% of patients with CSD (Fig. 209-3). Direct eye inoculation as a result of rubbing with the hands after cat contact is the presumed mode of spread. A conjunctival granuloma may be found at the inoculation site. The involved eye is usually not painful and has little or no discharge but may be quite red and swollen. Submandibular or cervical lymphadenopathy may also occur.

More severe, disseminated illness occurs in a small percentage of patients and is characterized by presentation with high fever, often persisting for several weeks. Other prominent symptoms include significant abdominal pain and weight loss. **Hepatosplenomegaly** may occur, although hepatic dysfunction is rare (Fig. 209-4). Granulomatous changes may be seen in the liver and spleen. Another common site of dissemination is bone, with the development of **granulomatous osteolytic lesions,** associated with localized pain but without erythema, tenderness, or swelling. Other uncommon manifestations are neuroretinitis with papilledema and stellate macular exudates, encephalitis, fever of unknown origin, and atypical pneumonia.

DIAGNOSIS

In most cases, the diagnosis can be strongly suspected on clinical grounds in a patient with history of exposure to a cat. The U.S. Centers for Disease Control and Prevention (CDC) has developed

Table 209-1 *Bartonella* Species Causing Human Disease

DISEASE	ORGANISM	VECTOR	PRIMARY RISK FACTOR
Bartonellosis	*B. bacilliformis*	Sandfly *(Lutzomyia verrucarum)*	Living in endemic areas (Andes Mountains)
Cat-scratch disease	*B. henselae* *B. clarridgeiae* (1 case)	Cat	Cat scratch or bite
Trench fever	*B. quintana*	Human body louse	Body louse infestation during outbreak
Bacteremia, endocarditis	*B. henselae* *B. quintana* *B. elizabethae* *B. vinsonii*	Cat for *B. henselae* Human body louse for *B. quintana*	Severe immunosuppression
Bacillary angiomatosis	*B. henselae* *B. quintana*	Cat for *B. henselae* Human body louse for *B. quintana*	Severe immunosuppression
Peliosis hepatis	*B. henselae* *B. quintana*	Cat for *B. henselae* Human body louse for *B. quintana*	Severe immunosuppression

Figure 209-1 A child with typical cat-scratch disease demonstrating the original scratch injuries and the primary papule that soon thereafter developed proximal to the middle finger. *(Courtesy of Dr. V.H. San Joaquin, University of Oklahoma Health Sciences Center, Oklahoma City.)*

Figure 209-2 Right axillary lymphadenopathy followed the scratches and development of a primary papule in this child with typical cat-scratch disease. *(From Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases, *ed 6. Philadelphia, 2006, Elsevier, p. 2737.)*

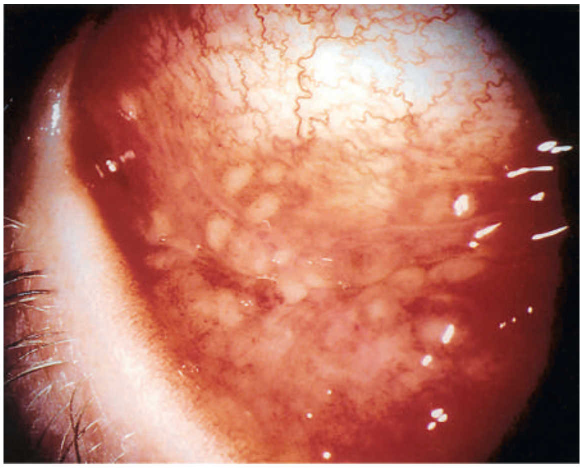

Figure 209-3 The granulomatous conjunctivitis of Parinaud oculoglandular syndrome is associated with ipsilateral local lymphadenopathy, usually preauricular and less commonly submandibular. *(From Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases, *ed 6. Philadelphia, 2006, Elsevier, p. 2739.)*

Figure 209-4 In this CT scan of a patient with hepatic involvement of cat-scratch disease, the absence of enhancement of the multiple lesions after contrast infusion is consistent with the granulomatous inflammation of this entity. Treated empirically with various antibiotics without improvement before establishment of this diagnosis, the patient subsequently recovered fully with no further antimicrobial therapy. *(Courtesy of Dr. V.H. San Joaquin, University of Oklahoma Health Sciences Center, Oklahoma City.)*

an indirect immunofluorescent assay that shows good correlation with disease. Other immunofluorescent assay and enzyme-linked immunoassay tests are commercially available, although little comparative data are available. Most patients have elevated antibody titers at presentation; however, the timing of immunoglobulin G and immunoglobulin M response to *B. henselae* can be quite variable. There is crossreactivity among *Bartonella* species, particularly *B. henselae* and *B. quintana*.

If tissue specimens are obtained, bacilli may be visualized with Warthin-Starry and Brown-Hopps tissue stains. *Bartonella* DNA can be identified through polymerase chain reaction analysis of tissue specimens. Culturing of the organism is not generally practical for clinical diagnosis.

Differential Diagnosis

The differential diagnosis of CSD includes virtually all causes of lymphadenopathy (see Chapter 490). The more-common entities include pyogenic (suppurative) lymphadenitis, primarily from staphylococcal or streptococcal infections, atypical mycobacterial infections, and malignancy. Less-common entities are tularemia, brucellosis, and sporotrichosis. Epstein-Barr virus, cytomegalovirus, and *Toxoplasma gondii* infections usually cause more generalized lymphadenopathy.

LABORATORY FINDINGS

Routine laboratory tests are not helpful. The erythrocyte sedimentation rate is often elevated. The white blood cell count may be normal or mildly elevated. Hepatic transaminases are often normal, but may be elevated in systemic disease. Ultrasonography or CT may reveal many granulomatous nodules in the liver and spleen; the nodules appear as hypodense round irregular lesions.

TREATMENT

Antibiotic treatment of CSD is not always needed and is not clearly beneficial. For most patients, treatment consists of conservative symptomatic care and observation. Studies show a significant discordance between in vitro activity of antibiotics and clinical effectiveness. For many patients, diagnosis is considered in the context of failure to respond to β-lactam antibiotic treatment of presumed staphylococcal lymphadenitis.

A small prospective study of oral azithromycin (500 mg on day 1, and then 250 mg on days 2-5; for smaller children, 10 mg/kg/24 hr on day 1 and 5 mg/kg/24 hr on days 2-5) showed a decrease in initial lymph node volume in 50% of patients during the 1st 30 days, but after 30 days there was no difference in lymph node volume. No other clinical benefit was found. For the majority of patients, CSD is self-limited, and resolution occurs over weeks to months without antibiotic treatment. Azithromycin, clarithromycin, trimethoprim-sulfamethoxazole, rifampin, ciprofloxacin, and gentamicin appear to be the best agents if treatment is considered.

Suppurative lymph nodes that become tense and extremely painful should be drained by needle aspiration, which may need to be repeated. Incision and drainage of nonsuppurative nodes should be avoided because chronic draining sinuses may result. Surgical excision of the node is rarely necessary.

Children with hepatosplenic CSD appear to respond well to rifampin at a dose of 20 mg/kg for 14 days, either alone or in combination with trimethoprim-sulfamethoxazole.

COMPLICATIONS

Encephalopathy, which can occur in as many as 5% of patients with CSD, typically manifests 1-3 wk after the onset of lymphadenitis as the sudden onset of neurologic symptoms, which often include seizures, combative or bizarre behavior, and altered level of consciousness. Imaging studies are generally normal. The cerebrospinal fluid is normal or shows minimal pleocytosis and protein elevation. Recovery occurs without sequelae in nearly all patients but may take place slowly over many months.

Other neurologic manifestations include peripheral facial nerve paralysis, myelitis, radiculitis, compression neuropathy, and cerebellar ataxia. One patient has been reported to have encephalopathy with persistent cognitive impairment and memory loss.

Stellate macular retinopathy is associated with several infections, including CSD. Children and young adults present with unilateral or rarely bilateral loss of vision with central scotoma, optic disc swelling, and macular star formation from exudates radiating out from the macula. The findings usually resolve completely, with recovery of vision, generally within 2-3 mo. The optimal treatment for the neuroretinitis is unknown, although treatment of adults with doxycycline and rifampin for 4-6 wk has had good results.

Hematologic manifestations include hemolytic anemia, thrombocytopenic purpura, nonthrombocytopenic purpura, and eosinophilia. **Leukocytoclastic vasculitis,** similar to Henoch-Schönlein purpura, has been reported in association with CSD in 1 child. A systemic presentation of CSD with pleurisy, arthralgia or arthritis, mediastinal masses, enlarged nodes at the head of the pancreas, and atypical pneumonia also has been reported.

PROGNOSIS

The prognosis for CSD in a normal host is generally excellent, with resolution of clinical findings over weeks to months. Recovery is occasionally slower and may take as long as a year.

PREVENTION

Person-to-person spread of *Bartonella* infections is not known. Isolation of the affected patient is not necessary. Prevention would require elimination of cats from households, which is not practical or necessarily desirable. Awareness of the risk of cat (and particularly kitten) scratches should be emphasized to parents. Cat scratches or bites should be washed immediately. Cat flea control is helpful.

Bibliography is available at Expert Consult.

209.2 Bartonellosis *(Bartonella bacilliformis)*

Barbara W. Stechenberg

The first human *Bartonella* infection described was bartonellosis, a geographically distinct disease caused by *B. bacilliformis.* There are 2 predominant forms of illness caused by *B. bacilliformis*: **Oroya fever,** a severe, febrile hemolytic anemia, and **verruca peruana** (verruga peruana), an eruption of hemangioma-like lesions. *B. bacilliformis* also causes asymptomatic infection. Bartonellosis is also called **Carrión disease**.

ETIOLOGY

B. bacilliformis is a small, motile, Gram-negative organism with a brush of 10 or more unipolar flagella, which appear to be important components for invasiveness. An obligate aerobe, it grows best at 28°C (82.4°F) in semisolid nutrient agar containing rabbit serum and hemoglobin.

EPIDEMIOLOGY

Bartonellosis is a zoonosis found only in mountain valleys of the Andes Mountains in Peru, Ecuador, Colombia, Chile, and Bolivia at altitudes and environmental conditions favorable for the vector, which is the sandfly, *Lutzomyia verrucarum.*

PATHOGENESIS

After the sandfly bite, *Bartonella* organisms enter the endothelial cells of blood vessels, where they proliferate. Found throughout the reticuloendothelial system, they then re-enter the bloodstream and parasitize erythrocytes. They bind on the cells, deform the membranes, and then enter intracellular vacuoles. The resultant **hemolytic anemia** may involve as many as 90% of circulating erythrocytes. Patients who survive this acute phase may or may not experience the cutaneous manifestations, which are nodular hemangiomatous lesions or verrucae ranging in size from a few millimeters to several centimeters.

CLINICAL MANIFESTATIONS

The incubation period is 2-14 wk. Patients may be totally asymptomatic or may have nonspecific symptoms such as headache and malaise without anemia.

Oroya fever is characterized by fever with rapid development of anemia. Clouding of the sensorium and delirium are common symptoms and may progress to overt psychosis. Physical examination demonstrates signs of severe hemolytic anemia, including icterus and pallor, sometimes in association with generalized lymphadenopathy.

In the preeruptive stage of **verruca peruana** (Fig. 209-5), patients may complain of arthralgias, myalgias, and paresthesias. Inflammatory reactions such as phlebitis, pleuritis, erythema nodosum, and encephalitis may develop. The appearance of verrucae is pathognomonic of the eruptive phase. Lesions vary greatly in size and number.

Figure 209-5 A single, large lesion of verruca peruana on the leg of an inhabitant of the Peruvian Andes. Such lesions are prone to superficial ulceration, and their vascular nature may lead to copious bleeding. Ecchymosis of the skin surrounding the lesion is also evident. *(Courtesy of Dr. J.M. Crutcher, Oklahoma State Department of Health, Oklahoma City.)*

DIAGNOSIS

The diagnosis is established on clinical grounds in conjunction with a blood smear demonstrating organisms or with blood culture. The anemia is macrocytic and hypochromic, with reticulocyte counts as high as 50%. *B. bacilliformis* may be seen on Giemsa stain preparation as red-violet rods in the erythrocytes. In the recovery phase, organisms change to a more coccoid form and disappear from the blood. In the absence of anemia, the diagnosis depends on blood cultures. In the eruptive phase, the typical verruca confirms the diagnosis. Antibody testing has been used to document infection.

TREATMENT

B. bacilliformis is sensitive to many antibiotics, including rifampin, tetracycline, and chloramphenicol. Treatment is very effective in rapidly diminishing fever and eradicating the organism from the blood. Chloramphenicol (50-75 mg/kg/day) is considered the drug of choice, because it is also useful in the treatment of concomitant infections such as *Salmonella.* Fluoroquinolones are used successfully as well. Blood transfusions and supportive care are critical in patients with severe anemia. Antimicrobial treatment for verruca peruana is considered when there are more than 10 cutaneous lesions, if the lesions are erythematous or violaceous, or if the onset of the lesions was <1 mo before presentation. Oral rifampin is effective in the healing of lesions. Surgical excision may be needed for lesions that are large and disfiguring or that interfere with function.

PREVENTION

Prevention depends on avoidance of the vector, particularly at night, by the use of protective clothing and insect repellents (see Chapter 175).

Bibliography is available at Expert Consult.

209.3 Trench Fever *(Bartonella quintana)*

Barbara W. Stechenberg

ETIOLOGY

The causative agent of trench fever was first designated *Rickettsia quintana,* was then assigned to the genus *Rochalimaea,* and now has been reassigned as *B. quintana.*

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EPIDEMIOLOGY

Trench fever was first recognized as a distinct clinical entity during World War I, when more than a million troops in the trenches were infected. The disease became quiescent until World War II, when it again was epidemic. It is extremely rare in the United States.

Humans are the only known reservoir. No other animal is naturally infected, and usual laboratory animals are not susceptible. The human **body louse,** *Pediculus humanus* var. *corporis,* is the vector and is capable of transmission to a new host 5-6 days after feeding on an infected person. Lice excrete the organism for life; transovarian passage does not occur. Humans may have prolonged asymptomatic bacteremia for years.

CLINICAL MANIFESTATIONS

The incubation period for trench fever averages about 22 days (range: 4-35 days). The clinical presentation is highly variable. Symptoms can be very mild and brief. About half of infected persons have a single febrile illness with abrupt onset lasting 3-6 days. In other patients, prolonged, sustained fever may occur. More commonly, patients have periodic febrile illness with 3-8 episodes lasting 4-5 days each, sometimes occurring over a period of a year or more. This form is reminiscent of malaria or relapsing fever *(Borrelia recurrentis).* Afebrile bacteremia can occur.

Clinical findings usually consist of fever (typically with a temperature of 38.5-40°C [101.3-104°F]), malaise, chills, sweats, anorexia, and severe headache. Common findings include marked conjunctival injection, tachycardia, myalgias, arthralgias, and severe pain in the neck, back, and legs. **Crops of erythematous macules** or **papules** may occur on the trunk on as many as 80% of patients. Splenomegaly and mild liver enlargement may be noted.

DIAGNOSIS

In nonepidemic situations, it is impossible to establish a diagnosis of trench fever on clinical grounds, because the findings are not distinctive. A history of body louse infection or having been in an area of epidemic disease should heighten suspicions. *B. quintana* can be cultured from the blood with modification to include culture on epithelial cells. Serologic tests for *B. quintana* are available, but there is cross reaction with *B. henselae.*

TREATMENT

There are no controlled trials of treatment, but patients with trench fever typically show dramatic response to tetracycline or chloramphenicol, with rapid defervescence.

209.4 Bacillary Angiomatosis and Bacillary Peliosis Hepatis (*Bartonella henselae* and *Bartonella quintana*)

Barbara W. Stechenberg

Both *B. henselae* and *B. quintana* cause vascular proliferative disease called **bacillary angiomatosis** and **bacillary peliosis** in severely immunocompromised persons, primarily adult patients with AIDS or cancer and organ transplant recipients. Subcutaneous and lytic bone lesions are strongly associated with *B. quintana,* whereas peliosis hepatis is associated exclusively with *B. henselae.*

BACILLARY ANGIOMATOSIS

Lesions of cutaneous bacillary angiomatosis, also known as *epithelioid angiomatosis*, are the most easily identified and recognized form of *Bartonella* infection in immunocompromised hosts. They are found primarily in patients with AIDS who have very low CD4 counts. The clinical appearance can be quite diverse. The vasoproliferative lesions of bacillary angiomatosis may be cutaneous or subcutaneous and may resemble the vascular lesions (verruca peruana) of *B. bacilliformis* in immunocompetent persons, characterized by erythematous papules on an erythematous base with a collarette of scale. They may enlarge to form large pedunculated lesions and may ulcerate. Trauma may result in profuse bleeding.

Bacillary angiomatosis may be clinically indistinguishable from Kaposi sarcoma. Other considerations in the differential diagnosis are pyogenic granuloma and verruca peruana *(B. bacilliformis).* Deep soft-tissue masses caused by bacillary angiomatosis may mimic a malignancy.

Osseous bacillary angiomatosis lesions commonly involve the long bones. These lytic lesions are very painful and highly vascular and are occasionally associated with an overlying erythematous plaque. The high degree of vascularity produces a very positive result on a technetium-Tc 99m methylene diphosphonate bone scan, resembling that of a malignant lesion.

Lesions can be found in virtually any organ, producing similar vascular proliferative lesions. They may appear raised, nodular, or ulcerative when seen on endoscopy or bronchoscopy. They may be associated with enlarged lymph nodes with or without an obvious local cutaneous lesion. Brain parenchymal lesions have been described.

BACILLARY PELIOSIS

Bacillary peliosis affects the reticuloendothelial system, primarily the liver **(peliosis hepatis)** and less frequently the spleen and lymph nodes. It is a vasoproliferative disorder characterized by random proliferation of venous lakes surrounded by fibromyxoid stroma harboring numerous bacillary organisms. Clinical findings include fever and abdominal pain in association with abnormal results of liver function tests, particularly a markedly increased alkaline phosphatase level. Cutaneous bacillary angiomatosis with splenomegaly may be associated with thrombocytopenia or pancytopenia. The vascular proliferative lesions in the liver and spleen appear on CT scan as hypodense lesions scattered throughout the parenchyma. The differential diagnosis includes hepatic Kaposi sarcoma, lymphoma, and disseminated infection with *Pneumocystis carinii* or *Mycobacterium avium* complex.

BACTEREMIA AND ENDOCARDITIS

B. henselae, B. quintana, B. vinsonii, and *B. elizabethae* all are reported to cause bacteremia or endocarditis. They are associated with symptoms such as prolonged fevers, night sweats, and profound weight loss. A cluster of cases in Seattle in 1993 occurred in a homeless population with chronic alcoholism. These patients with high fever or hypothermia were thought to represent "urban trench fever," but no body louse infestation was associated. Some cases of culture-negative endocarditis may represent *Bartonella* endocarditis. One report described central nervous system involvement with *B. quintana* infection in 2 children.

DIAGNOSIS

Diagnosis of bacillary angiomatosis is made initially by biopsy. The characteristic small vessel proliferation with mixed inflammatory response and the staining of bacilli by Warthin-Starry silver staining distinguish bacillary angiomatosis from pyogenic granuloma or Kaposi sarcoma (see Chapter 257). Travel history can usually preclude verruca peruana.

Culture is impractical for CSD but is the diagnostic procedure for suspected bacteremia or endocarditis. Use of the lysis centrifugation technique or fresh chocolate or heart infusion agar with 5% rabbit blood with prolonged incubation may increase the yield of culture. Polymerase chain reaction can also be a useful tool.

TREATMENT

Bartonella infections in immunocompromised hosts caused by both *B. henselae* and *B. quintana* have been treated successfully with antimicrobial agents. Bacillary angiomatosis responds rapidly to erythromycin, azithromycin, and clarithromycin, which are the drugs of choice. Alternative choices are doxycycline or tetracycline. Severely ill patients with peliosis hepatis, endocarditis, or osteomyelitis may be treated initially with intravenous erythromycin or doxycycline and the addition of rifampin or gentamicin. The use of an aminoglycoside for a minimum of 2 wk is associated with improved prognosis in

endocarditis. A Jarisch-Herxheimer reaction may occur. Relapses may follow, and prolonged treatment for several months may be necessary.

PREVENTION

Immunocompromised persons should consider the potential risks of cat ownership because of the risks for *Bartonella* infections as well as toxoplasmosis and enteric infections. Those who elect to obtain a cat should adopt or purchase a cat >1 yr of age and in good health. Prompt washing of any wounds from cat bites or scratches is essential.

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Section 6

Anaerobic Bacterial Infections

Chapter 210

Botulism *(Clostridium botulinum)*

Stephen S. Arnon

Three naturally occurring forms of human botulism are known: infant (intestinal toxemia) botulism (the most common in the United States), foodborne (classic) botulism, and wound botulism. Two other forms, both human-made, also occur: inhalational botulism from inhaling accidentally aerosolized toxin and iatrogenic botulism from overdosage of therapeutic or cosmetic use of botulinum toxin.

ETIOLOGY

Botulism is the acute, flaccid paralysis caused by the neurotoxin produced by *Clostridium botulinum* or, infrequently, an equivalent neurotoxin produced by rare strains of *Clostridium butyricum* and *Clostridium baratii*. *C. botulinum* is a Gram-positive, spore-forming, obligate anaerobe whose natural habitat worldwide is soil, dust, and marine sediments. The organism is found in a wide variety of fresh and cooked agricultural products. Spores of some *C. botulinum* strains endure boiling for several hours, enabling the organism to survive efforts at food preservation. In contrast, botulinum toxin is heat labile and easily destroyed by heating at ≥85°C (185°F) for 5 min. Neurotoxigenic *C. butyricum* has been isolated from a soybean food and from soils near Lake Weishan in China, the site of foodborne botulism outbreaks associated with this organism. Little is known about the ecology of neurotoxigenic *C. baratii.*

Botulinum toxin is a simple dichain protein consisting of a 100 kDa heavy chain that contains the neuronal attachment sites and a 50 kDa light chain that is taken into the cell after binding. Botulinum toxin is the most poisonous substance known, the parenteral human lethal dose being estimated at 10^{-6} mg/kg. The toxin blocks neuromuscular transmission and causes death through airway and respiratory muscle paralysis. Eight antigenic toxin types, designated by letters A-H, are distinguished by the inability of neutralizing antibody against 1 toxin type to protect against a different toxin type. Toxin types are further differentiated into subtypes by differences in the nucleotide sequences of their toxin genes. Like the gene for tetanus toxin, the gene for botulinum toxin for some toxin types and subtypes resides on a plasmid.

The 8 toxin types serve as convenient clinical and epidemiologic markers. Toxin types A, B, E, and F are well-established causes of human botulism, whereas types C and D cause illness in other animals. Neurotoxigenic *C. butyricum* strains produce a type E toxin, whereas neurotoxigenic *C. baratii* strains produce a type F toxin. Type G toxin has not been established as a cause of either human or animal disease. Type H toxin is a novel toxin that was discovered in 2013 and sickened an infant patient. The phenomenal potency of the botulinum toxins occurs because their 8 light chains are zinc endopeptidases whose substrates are 1 or 2 proteins of the docking complex by which synaptic vesicles fuse with the terminal neuronal cell membrane and release acetylcholine into the synaptic cleft.

EPIDEMIOLOGY

Infant botulism has been reported from all inhabited continents except Africa. Notably, the infant is the only family member who is ill. The most striking epidemiologic feature of infant botulism is its age distribution, with 95% of cases involving infants between 3 wk and 6 mo of age, with a broad peak from 2-4 mo of age. Cases have been recognized in infants as young as 1.5 days or as old as 382 days at onset. The male : female ratio of hospitalized cases is approximately 1 : 1, and cases have occurred in most racial and ethnic groups.

Although infant botulism is an uncommon and often unrecognized illness, it is the most common form of human botulism in the United States, with 80-120 hospitalized cases diagnosed annually. The full clinical spectrum of infant botulism includes mild outpatient cases and fulminant sudden death cases. Approximately 40% of U.S. hospitalized cases have been reported from California. Consistent with the known asymmetric soil distribution of *C. botulinum* toxin types, most cases west of the Mississippi River have been caused by type A strains, whereas most cases east of the Mississippi River have been caused by type B strains. One case each in New Mexico, Washington, Ohio, California, Iowa, and Colorado has been caused by *C. baratii* and type F toxin. Four cases in Italy have resulted from *C. butyricum* and type E toxin. Identified risk factors for the illness include breastfeeding, the ingestion of honey, a slow intestinal transit time (<1 stool/day), and ingestion of untreated well-water. Breastfeeding may provide protection against fulminant sudden death from infant botulism. Under rare circumstances of altered intestinal anatomy, physiology, and microflora, older children and adults may contract infant-type botulism.

Foodborne botulism results from the ingestion of a food in which *C. botulinum* has multiplied and produced its toxin. Outbreaks in North America have been associated with baked potatoes, sautéed onions, and chopped garlic served in restaurants, revising the traditional view of foodborne botulism as resulting mainly from home-canned foods. Other outbreaks in the United States have occurred from commercial foods sealed in plastic pouches that relied solely on refrigeration to prevent outgrowth of *C. botulinum* spores. Uncanned foods responsible for foodborne botulism cases include peyote tea, the hazelnut flavoring added to yogurt, sweet cream cheese, sautéed onions in "patty melt" sandwiches, potato salad, and fresh and dried fish. A trend toward a single case per outbreak or of cases manifesting separately in different cities or hospitals portends that physicians cannot rely on the temporal and geographic clustering of cases to suggest the diagnosis.

Most types of preserved foods have been implicated in foodborne botulism, but the usual offenders in the United States are the "low-acid" (pH ≥ 6.0) home-canned foods such as jalapeño peppers, asparagus, olives, and beans. The potential for foodborne botulism exists throughout the world, but outbreaks occur most commonly in the temperate zones rather than the tropics, where preservation of fruits, vegetables, and other foods is less common.

Approximately 5-10 outbreaks and 15-25 cases of foodborne botulism occur annually in the United States. Most of the continental U.S. outbreaks resulted from proteolytic type A or type B strains, which produce a strongly putrefactive odor in the food that some people find necessary to verify by tasting. In contrast, in Alaska and Canada, most foodborne outbreaks have resulted from nonproteolytic type E strains

in Native American foods, such as fermented salmon eggs and seal flippers, which do not exhibit signs of spoilage. A further hazard of type E strains is their ability to grow at the temperatures maintained by household refrigerators (5°C [41°F]).

Wound botulism is an exceptionally rare disease, with fewer than 400 cases reported worldwide, but it is important to pediatrics because adolescents and children may be affected. Although many cases have occurred in young, physically active males who are at greatest risk for traumatic injury, wound botulism also occurs with crush injuries in which no break in the skin is evident. In the past 15 yr, wound botulism from injection has become increasingly common in adult heroin abusers in the western United States and in Europe, not always with evident abscess formation or cellulitis.

A single outbreak of **inhalational botulism** was reported in 1962 in which 3 laboratory workers in Germany were exposed unintentionally to aerosolized botulinum toxin. Some patients in the United States have been hospitalized by accidental overdose of therapeutic or cosmetic botulinum toxin.

PATHOGENESIS

All forms of botulism produce disease through a final common pathway. Botulinum toxin is carried by the bloodstream to peripheral cholinergic synapses, where it binds irreversibly, blocking acetylcholine release and causing impaired neuromuscular and autonomic transmission. **Infant botulism** is an infectious disease that results from ingesting the spores of any of the 3 botulinum toxin-producing clostridial strains, with subsequent spore germination, multiplication, and production of botulinum toxin in the large intestine. **Foodborne botulism** is an intoxication that results when preformed botulinum toxin contained in an improperly preserved or inadequately cooked food is swallowed. **Wound botulism** results from spore germination and colonization of traumatized tissue by *C. botulinum;* it is the analog of tetanus. **Inhalational botulism** occurs when aerosolized botulinum toxin is inhaled. A bioterrorist attack could result in large or small outbreaks of inhalational or foodborne botulism (see Chapter 723).

Botulinum toxin is not a cytotoxin and does not cause overt macroscopic or microscopic pathology. Secondary pathologic changes (pneumonia, petechiae on intrathoracic organs) may be found at autopsy. No diagnostic technique is available to identify botulinum toxin bound at the neuromuscular junction. The healing process in botulism consists of sprouting of new terminal unmyelinated motor neurons. Movement resumes when these new twigs locate noncontracting muscle fibers and reinnervate them by inducing formation of a new motor end plate. In experimental animals, this process takes about 4 wk.

CLINICAL MANIFESTATIONS

Botulinum toxin is distributed hematogenously. Because relative blood flow and density of innervation are greatest in the bulbar musculature, all forms of botulism manifest neurologically as a symmetric, descending, flaccid paralysis beginning with the cranial nerve musculature. It is not possible to have botulism without having multiple bulbar palsies, yet in infants, such symptoms as poor feeding, weak suck, feeble cry, drooling, and even obstructive apnea are often not recognized as bulbar in origin (Fig. 210-1). Patients with evolving illness may already have generalized weakness and hypotonia in addition to bulbar palsies when first examined. In contrast to botulism caused by *C. botulinum,* a majority of the rare cases caused by intestinal colonization with *C. butyricum* are associated with a Meckel diverticulum accompanying abdominal distention, often leading to misdiagnosis as an acute abdomen. The also rare *C. baratii* type F infant botulism cases have been characterized by very young age at onset, rapidity of onset, and greater severity but shorter duration of paralysis.

In older children with **foodborne** or **wound botulism,** the onset of neurologic symptoms follows a characteristic pattern of diplopia, blurred vision, ptosis, dry mouth, dysphagia, dysphonia, and dysarthria, with decreased gag and corneal reflexes. Importantly, because the toxin acts only on motor nerves, paresthesias are not seen in botulism, except when a patient hyperventilates from anxiety. The sensorium remains clear, but this fact may be difficult to ascertain because of the slurred speech.

Figure 210-1 A 3 mo old infant with mild infant botulism showing signs of ptosis, an expressionless face, and hypotonia of the neck, trunk, and limbs. The additional bulbar palsies—ophthalmoplegia, weak cry, weak sucking, and dysphagia (drooling)—are not apparent in the photograph. *(From Arnon SS, Schechter R, Maslanka SE, et al: Human botulism immune globulin for the treatment of infant botulism,* N Engl J Med *354: 462–471, 2006.)*

Foodborne botulism begins with gastrointestinal symptoms of nausea, vomiting, or diarrhea in approximately 30% of cases. These symptoms are thought to result from metabolic by-products of growth of *C. botulinum* or from the presence of other toxic contaminants in the food, because gastrointestinal distress is rarely observed in wound botulism. Constipation may occur in foodborne botulism once flaccid paralysis becomes evident. Illness usually begins 12-36 hr after ingestion of the contaminated food but can range from as little as 2 hr to as long as 8 days. The incubation period in **wound botulism** is 4-14 days. Fever may be present in wound botulism but is absent in foodborne botulism unless a secondary infection (often pneumonia) is present. All forms of botulism display a wide spectrum of clinical severity, from the very mild, with minimal ptosis, flattened facial expression, minor dysphagia, and dysphonia, to the fulminant, with rapid onset of extensive paralysis, frank apnea, and fixed, dilated pupils. Fatigability with repetitive muscle activity is the clinical hallmark of botulism.

Infant botulism differs in apparent initial symptoms of illness only because the infant cannot verbalize them. Usually, the first indication of illness is a decreased frequency or even absence of defecation, although this sign is frequently overlooked. Parents typically notice inability to feed, lethargy, weak cry, and diminished spontaneous movement. Dysphagia may be evident as secretions drooling from the mouth. Gag, suck, and corneal reflexes diminish as the paralysis advances. Oculomotor palsies may be evident only with sustained observation. Paradoxically, the pupillary light reflex may be unaffected until the child is severely paralyzed, or it may be initially sluggish. Loss of head control is typically a prominent sign. Respiratory arrest may occur suddenly from airway occlusion by unswallowed secretions or

from obstructive flaccid pharyngeal musculature. Occasionally, the diagnosis of infant botulism is suggested by a respiratory arrest that occurs after the infant is curled into position for lumbar puncture.

In mild cases or in the early stages of illness, the physical signs of infant botulism may be subtle and easily missed. Eliciting cranial nerve palsies and fatigability of muscular function requires careful examination. Ptosis may not be seen unless the head of the child is kept erect.

DIAGNOSIS

Clinical diagnosis of botulism is confirmed by specialized laboratory testing that requires hours to days to complete. Therefore, clinical diagnosis is the foundation for early recognition of and response to all forms of botulism. Routine laboratory studies, including those of the cerebrospinal fluid, are normal in botulism unless dehydration, undernourishment (metabolic acidosis and ketosis), or secondary infection is present.

The **classic triad of botulism** is the acute onset of a symmetric flaccid descending paralysis with clear sensorium, no fever, and no paresthesias. Suspected botulism represents a medical and public health emergency that is immediately reportable by telephone in most U.S. health jurisdictions. State health departments (first call) and the U.S. Centers for Disease Control and Prevention (CDC; telephone 770-488-7100 at any time) can arrange for diagnostic testing, epidemiologic investigation, and provision of equine antitoxin.

The diagnosis of botulism is unequivocally established by demonstration of the presence of botulinum toxin in serum or of *C. botulinum* toxin or organisms in wound material, enema fluid, or feces. *C. botulinum* is not part of the normal resident intestinal flora of humans, and its presence in the setting of acute flaccid paralysis is diagnostic. An epidemiologic diagnosis of food-borne botulism can be established when *C. botulinum* organisms and toxin are found in food eaten by patients.

Electromyography can sometimes distinguish between causes of acute flaccid paralysis, although results may be variable, including normal, in patients with botulism. The distinctive electromyography finding in botulism is facilitation (potentiation) of the evoked muscle action potential at high-frequency (50 Hz) stimulation. In infant botulism, a characteristic pattern, known by the acronym **BSAP** (brief, small, abundant motor unit action potentials), is present only in clinically weak muscles. Nerve conduction velocity and sensory nerve function are normal in botulism.

Infant botulism requires a high index of suspicion for early diagnosis (Table 210-1). "Rule out sepsis" remains the most common admission diagnosis. If a previously healthy infant (commonly 2-4 mo of age) demonstrates weakness with difficulty in sucking, swallowing, crying, or breathing, infant botulism should be considered a likely diagnosis. A careful cranial nerve examination is then very helpful. Rare instances of coinfection with *Clostridium difficile*, respiratory syncytial virus, or influenza virus have occurred.

Differential Diagnosis

Botulism is frequently misdiagnosed, most often as a polyradiculoneuropathy (Guillain-Barré or Miller Fisher syndrome), myasthenia gravis, or a disease of the central nervous system (see Tables 210-1 and 210-2). In the United States, botulism is more likely than Guillain-Barré syndrome, intoxication, or poliomyelitis to cause a cluster of cases of acute flaccid paralysis. Botulism differs from other flaccid paralyses in its prominent cranial nerve palsies disproportionate to milder weakness and hypotonia below the neck, in its symmetry, and in its absence of sensory nerve damage. Spinal muscular atrophy may closely mimic infant botulism at presentation.

Additional diagnostic procedures may be useful in rapidly excluding botulism as the cause of paralysis. The cerebrospinal fluid is unchanged in botulism but is abnormal in many central nervous system diseases. Although the cerebrospinal fluid protein concentration is eventually elevated in Guillain-Barré syndrome, it may be normal early in illness. Imaging of the brain, spine, and chest may reveal hemorrhage, inflammation, or neoplasm. A test dose of edrophonium chloride briefly reverses paralytic symptoms in many patients with myasthenia gravis and, reportedly, in some with botulism. A close inspection of the skin, especially the scalp, may reveal an attached tick that is causing paralysis. Possible organophosphate intoxication should be pursued aggressively because specific antidotes (oximes) are available and because the patient may be part of a commonly exposed group, some of whom have yet to demonstrate illness. Other tests that require days for results include stool culture for *Campylobacter jejuni* as a precipitant of Guillain-Barré syndrome, spinal muscular atrophy and other genetic (including mitochondrial) disorders, and assays for the autoantibodies that cause myasthenia gravis, Lambert-Eaton syndrome, and Guillain-Barré syndrome.

TREATMENT

Human botulism immune globulin, given intravenously (BIG-IV), is licensed for the treatment of infant botulism caused by type A or B botulinum toxin. Treatment with BIG-IV consists of a single intravenous infusion of 50-100 mg/kg (see package insert) that should be given as soon as possible after infant botulism is suspected so as to

Table 210-1 Diagnoses Considered in Subsequently Laboratory-Confirmed Cases of Infant Botulism

ADMISSION DIAGNOSIS	SUBSEQUENTLY CONSIDERED DIAGNOSES
Suspected sepsis, meningitis	Guillain-Barré syndrome
Pneumonia	Myasthenia gravis
Dehydration	Disorders of amino acid metabolism
Viral syndrome	Hypothyroidism
Hypotonia of unknown etiology	Drug ingestion Organophosphate poisoning
Constipation	Brainstem encephalitis
Failure to thrive	Heavy metal poisoning (Pb, Mg, As)
Spinal muscular atrophy type 1 (Werdnig-Hoffmann disease)	Poliomyelitis Viral polyneuritis Hirschsprung disease Metabolic encephalopathy Medium chain acetyl–coenzyme A dehydrogenase deficiency

Table 210-2 Diagnoses Considered in Foodborne and Wound Botulism

Acute gastroenteritis
Myasthenia gravis
Guillain-Barré syndrome
Organophosphate poisoning
Meningitis
Encephalitis
Psychiatric illness
Cerebrovascular accident
Poliomyelitis
Hypothyroidism
Aminoglycoside-associated paralysis
Tick paralysis
Hypocalcemia
Hypermagnesemia
Carbon monoxide poisoning
Hyperemesis gravidarum
Laryngeal trauma
Diabetic complications
Inflammatory myopathy
Overexertion

immediately end the toxemia that is the cause of the illness. Treatment should not be delayed for laboratory confirmation. In the United States, BIG-IV may be obtained from the California Department of Public Health (24-hr telephone 510-231-7600; http://www.infantbotulism.org). The use of BIG-IV shortens mean hospital stay from approximately 6 wks to 2 wks. Most of the decrease in length of hospital stay results from the reduced time that the patient requires ventilation and intensive care. Hospital costs are reduced by more than $100,000 per case (in 2012 dollars).

Older patients with suspected food, wound, or inhalational botulism may be treated with 1 vial of licensed equine heptavalent (A-G) botulinum antitoxin, available in the United States through the Centers for Disease Control and Prevention (CDC) by way of state and local health departments.

Antibiotic therapy is not part of the treatment of uncomplicated infant or foodborne botulism, because the toxin is primarily an intracellular molecule that is released into the intestinal lumen with vegetative bacterial cell death and lysis. Antibiotics are reserved for the treatment of secondary infections, and in the absence of antitoxin therapy, a nonclostridiocidal antibiotic such as trimethoprim-sulfamethoxazole is preferred. Aminoglycoside antibiotics should be avoided because they may potentiate the blocking action of botulinum toxin at the neuromuscular junction. Wound botulism requires aggressive treatment with antibiotics and antitoxin in a manner analogous to that for tetanus (see Chapter 211).

SUPPORTIVE CARE

Management of botulism rests on the following 3 principles: (1) fatigability with repetitive muscle activity is the clinical hallmark of the disease; (2) complications are best avoided by anticipating them; and (3) meticulous supportive care is a necessity. The first principle applies mainly to feeding and breathing. Correct positioning is imperative to protect the airway and improve respiratory mechanics. The patient is placed face up on a rigid-bottomed crib (or bed), the head of which is tilted at 30 degrees. A small cloth roll is placed under the cervical vertebrae to tilt the head back so that secretions drain to the posterior pharynx and away from the airway. In this tilted position, the abdominal viscera pull the diaphragm down, thereby improving respiratory mechanics. The patient's head and torso should not be elevated by bending the middle of the bed; in such a position, the hypotonic thorax would slump into the abdomen and breathing would be compromised.

About half of patients with infant botulism require endotracheal intubation, which is best done prophylactically. The indications include diminished gag and cough reflexes and progressive airway obstruction by secretions. With meticulous management techniques (especially proper tube diameter), monitoring, and positioning, patients have tolerated months of intubation without subglottic stenosis or need for tracheostomy.

Feeding should be done by a nasogastric or nasojejunal tube until sufficient oropharyngeal strength and coordination enable feeding by breast or bottle. Expressed breast milk is the most desirable food for infants, in part because of its immunologic components (e.g., secretory immunoglobulin A, lactoferrin, leukocytes). Tube feeding also assists in the restoration of peristalsis, a nonspecific but probably essential part of eliminating *C. botulinum* from the intestinal flora. Intravenous feeding (hyperalimentation) is discouraged because of the potential for infection and the advantages of tube feeding.

Because sensation remains intact, providing auditory, tactile, and visual stimuli is beneficial. Maintaining strong central respiratory drive is essential, so sedatives and central nervous system depressants are best avoided. Full hydration and stool softeners such as lactulose may mitigate the protracted constipation. Cathartics are not recommended. Patients with foodborne and infant botulism excrete *C. botulinum* toxin and organisms in their feces, often for many weeks, and care should be taken in handling their excreta. When bladder palsy occurs in severe cases, gentle suprapubic pressure with the patient in the sitting position with the head supported may help attain complete voiding and reduce the risk for urinary tract infection. Families of affected patients may require emotional and financial support, especially when the paralysis of botulism is prolonged.

Table 210-3 Complications of Infant Botulism
Acute respiratory distress syndrome
Aspiration
Clostridium difficile enterocolitis
Hypotension
Inappropriate antidiuretic hormone secretion
Long bone fractures
Misplaced or plugged endotracheal tube
Nosocomial anemia
Otitis media
Pneumonia
Pneumothorax
Recurrent atelectasis
Seizures secondary to hyponatremia
Sepsis
Subglottic stenosis
Tracheal granuloma
Tracheitis
Transfusion reaction
Urinary tract infection

COMPLICATIONS

Almost all of the complications of botulism are nosocomial, and a few are iatrogenic (Table 210-3). Some critically ill, toxin-paralyzed patients who must spend weeks or months on ventilators in intensive care units inevitably experience some of these complications. Suspected "relapses" of infant botulism usually reflect premature hospital discharge or an inapparent underlying complication such as pneumonia, urinary tract infection, or otitis media.

PROGNOSIS

When the regenerating nerve endings have induced formation of a new motor end plate, neuromuscular transmission is restored. In the absence of complications, particularly those related to hypoxia, the prognosis in infant botulism is for full and complete recovery. Hospital stay in untreated infant botulism averages 5.7 wk but differs significantly by toxin type, with patients with untreated type B disease being hospitalized a mean of 4.2 wk and those with untreated type A disease being hospitalized a mean of 6.7 wk.

In the United States, the case fatality ratio for hospitalized cases of infant botulism is <1%. After recovery, patients with untreated infant botulism appear to have an increased incidence of strabismus that requires timely screening and treatment.

The case fatality ratio in foodborne and wound botulism varies by age, with younger patients having the best prognosis. Some adults with botulism have reported chronic weakness and fatigue for more than 1 yr as sequelae.

PREVENTION

Foodborne botulism is best prevented by adherence to safe methods of home canning (pressure cooker and acidification), by avoiding suspicious foods, and by heating all home canned foods to 85°C (185°F) for ≥5 min. Wound botulism is best prevented by not using illicit drugs and by treatment of contaminated wounds with thorough cleansing, surgical debridement, and provision of appropriate antibiotics.

Most patients with infant botulism probably inhaled and then swallowed airborne clostridial spores; these cases cannot be prevented. The 1 identified, avoidable source of botulinum spores for infants is honey. *Honey is an unsafe food for any child younger than 1 yr.* Corn syrups were once thought to be a possible source of botulinum spores, but evidence indicates otherwise. Breastfeeding appears to slow the onset of infant botulism and to diminish the risk for sudden death in infants in whom the disease develops.

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Chapter 211

Tetanus *(Clostridium tetani)*

Stephen S. Arnon

ETIOLOGY

Tetanus is an acute, spastic paralytic illness historically called **lockjaw** that is caused by the neurotoxin produced by *Clostridium tetani,* a motile, Gram-positive, spore-forming obligate anaerobe whose natural habitat worldwide is soil, dust, and the alimentary tracts of various animals. *C. tetani* forms spores terminally, producing a drumstick or tennis racket appearance microscopically. Tetanus spores can survive boiling but not autoclaving, whereas the vegetative cells are killed by antibiotics, heat, and standard disinfectants. Unlike many clostridia, *C. tetani* is not a tissue-invasive organism and instead causes illness through the effects of a single toxin, **tetanospasmin,** more commonly referred to as **tetanus toxin**. Tetanospasmin is the second most poisonous substance known, surpassed in potency only by botulinum toxin. The human lethal dose of tetanus toxin is estimated to be 10^{-5} mg/kg.

EPIDEMIOLOGY

Tetanus occurs worldwide and is endemic in approximately 90 developing countries, although its incidence varies considerably. The most common form, **neonatal (or umbilical) tetanus,** kills approximately 300,000 infants each year, with approximately 80% of deaths in just 12 tropical Asian and African countries. It occurs in infants whose mothers are not immunized. In addition, an estimated 15,000-30,000 unimmunized women worldwide die each year of **maternal tetanus,** which results from postpartum, postabortal, or postsurgical wound infection with *C. tetani.* Approximately 50 cases of tetanus are reported each year in the United States, mostly in persons older than 60 yr of age, although cases also occur in toddlers and neonates. Approximately 20% of children in the United States 10-16 yr of age lack a protective antibody level. The majority of childhood cases of tetanus in the United States have occurred in unimmunized children whose parents objected to vaccination.

Most nonneonatal cases of tetanus are associated with a traumatic injury, often a penetrating wound inflicted by a dirty object such as a nail, splinter, fragment of glass, or unsterile injection. Tetanus occurring after illicit drug injection is becoming more common. The disease also occurs after the use of contaminated suture material and after intramuscular injection of medicines, most notably quinine for chloroquine-resistant falciparum malaria. The disease may also occur in association with animal bites, abscesses (including dental abscesses), ear and other body piercing, chronic skin ulceration, burns, compound fractures, frostbite, gangrene, intestinal surgery, ritual scarification, infected insect bites, and female circumcision. Rare cases have no history of trauma.

PATHOGENESIS

Tetanus occurs after introduced spores germinate, multiply, and produce tetanus toxin in the low oxidation-reduction potential of an infected injury site. A plasmid carries the toxin gene. Toxin is released after vegetative bacterial cell death and lysis. Tetanus toxin (and the botulinum toxins) is a 150 kDa simple protein consisting of a heavy chain (100 kDa) and a light (50 kDa) chain joined by a single disulfide bond. Tetanus toxin binds at the neuromuscular junction and enters the motor nerve by endocytosis, after which it undergoes retrograde axonal transport to the cytoplasm of the α-motoneuron. In the sciatic nerve, the transport rate was found to be 3.4 mm/hr. The toxin exits the motoneuron in the spinal cord and next enters adjacent spinal inhibitory interneurons, where it prevents release of the neurotransmitters glycine and γ-aminobutyric acid. Tetanus toxin thus blocks the normal inhibition of antagonistic muscles on which voluntary coordinated movement depends; as a consequence, affected muscles sustain maximal contraction and cannot relax. The autonomic nervous system is also rendered unstable in tetanus.

The phenomenal potency of tetanus toxin is enzymatic. The light chain of tetanus toxin (and of several botulinum toxins) is a zinc-containing endoprotease whose substrate is synaptobrevin, a constituent protein of the docking complex that enables the synaptic vesicle to fuse with the terminal neuronal cell membrane. The heavy chain of the toxin contains its binding and internalization domains.

Because *C. tetani* is not an invasive organism, its toxin-producing vegetative cells remain where introduced into the wound, which may display local inflammatory changes and a mixed bacterial flora.

CLINICAL MANIFESTATIONS

Tetanus is most often generalized but may also be localized. The incubation period typically is 2-14 days but may be as long as months after the injury. In **generalized tetanus,** the presenting symptom in about half of cases is **trismus** (masseter muscle spasm, or lockjaw). Headache, restlessness, and irritability are early symptoms, often followed by stiffness, difficulty chewing, dysphagia, and neck muscle spasm. The so-called **sardonic smile of tetanus (risus sardonicus)** results from intractable spasms of facial and buccal muscles. When the paralysis extends to abdominal, lumbar, hip, and thigh muscles, the patient may assume an arched posture of extreme hyperextension of the body, or **opisthotonos,** with the head and the heels bent backward and the body bowed forward with only the back of the head and the heels touching the supporting surface. Opisthotonos is an equilibrium position that results from unrelenting total contraction of opposing muscles, all of which display the typical board-like rigidity of tetanus. Laryngeal and respiratory muscle spasm can lead to airway obstruction and asphyxiation. Because tetanus toxin does not affect sensory nerves or cortical function, the patient unfortunately remains conscious, in extreme pain, and in fearful anticipation of the next tetanic seizure. The seizures are characterized by sudden, severe tonic contractions of the muscles, with fist clenching, flexion, and adduction of the arms and hyperextension of the legs. Without treatment, the seizures range from a few seconds to a few minutes in length with intervening respite periods, but as the illness progresses, the spasms become sustained and exhausting. The smallest disturbance by sight, sound, or touch may trigger a tetanic spasm. Dysuria and urinary retention result from bladder sphincter spasm; forced defecation may occur. Fever, occasionally as high as 40°C (104°F), is common because of the substantial metabolic energy consumed by spastic muscles. Notable autonomic effects include tachycardia, dysrhythmias, labile hypertension, diaphoresis, and cutaneous vasoconstriction. The tetanic paralysis usually becomes more severe in the 1st wk after onset, stabilizes in the 2nd wk, and ameliorates gradually over the ensuing 1-4 wk.

Neonatal tetanus, the infantile form of generalized tetanus, typically manifests within 3-12 days of birth as progressive difficulty in feeding (sucking and swallowing), associated hunger, and crying. Paralysis or diminished movement, stiffness and rigidity to the touch, and spasms, with or without opisthotonos, are characteristic. The umbilical stump may hold remnants of dirt, dung, clotted blood, or serum, or it may appear relatively benign.

Localized tetanus results in painful spasms of the muscles adjacent to the wound site and may precede generalized tetanus. **Cephalic tetanus** is a rare form of localized tetanus involving the bulbar musculature that occurs with wounds or foreign bodies in the head, nostrils, or face. It also occurs in association with chronic otitis media. Cephalic tetanus is characterized by retracted eyelids, deviated gaze, trismus, risus sardonicus, and spastic paralysis of the tongue and pharyngeal musculature.

DIAGNOSIS

The picture of tetanus is one of the most dramatic in medicine, and the diagnosis may be established clinically. The typical setting is an

unimmunized patient (and/or mother) who was injured or born within the preceding 2 wk, who presents with trismus, other rigid muscles, and a clear sensorium.

Results of routine laboratory studies are usually normal. A peripheral leukocytosis may result from a secondary bacterial infection of the wound or may be stress induced from the sustained tetanic spasms. The cerebrospinal fluid is normal, although the intense muscle contractions may raise intracranial pressure. Neither the electroencephalogram nor the electromyogram shows a characteristic pattern. *C. tetani* is not always visible on Gram stain of wound material and is isolated in only approximately 30% of cases.

DIFFERENTIAL DIAGNOSIS

Fully developed, generalized tetanus cannot be mistaken for any other disease. However, trismus may result from parapharyngeal, retropharyngeal, or dental abscesses or, rarely, from acute encephalitis involving the brainstem. Either rabies or tetanus may follow an animal bite, and rabies may manifest as trismus with seizures. Rabies may be distinguished from tetanus by hydrophobia, marked dysphagia, predominantly clonic seizures, and pleocytosis (see Chapter 274). Although strychnine poisoning may result in tonic muscle spasms and generalized seizure activity, it seldom produces trismus, and unlike in tetanus, general relaxation usually occurs between spasms. Hypocalcemia may produce tetany that is characterized by laryngeal and carpopedal spasms, but trismus is absent. Occasionally, epileptic seizures, narcotic withdrawal, or other drug reactions may suggest tetanus.

TREATMENT

Management of tetanus requires eradication of *C. tetani* and the wound environment conducive to its anaerobic multiplication, neutralization of all accessible tetanus toxin, control of seizures and respiration, palliation, provision of meticulous supportive care, and, finally, prevention of recurrences.

Surgical wound excision and debridement are often needed to remove the foreign body or devitalized tissue that created anaerobic growth conditions. Surgery should be performed promptly after administration of **human tetanus immunoglobulin (TIG)** and antibiotics. Excision of the umbilical stump in the neonate with tetanus is no longer recommended.

Tetanus toxin cannot be neutralized by TIG after it has begun its axonal ascent to the spinal cord. TIG should be given as soon as possible so as to neutralize toxin that diffuses from the wound into the circulation before the toxin can bind at distant muscle groups. The optimal dose of TIG has not been determined. A single intramuscular injection of 500 units of TIG is sufficient to neutralize systemic tetanus toxin, but total doses as high as 3,000-6,000 units are also recommended. Infiltration of TIG into the wound is now considered unnecessary. If TIG is unavailable, use of human intravenous immunoglobulin may be necessary. Intravenous immunoglobulin contains 4-90 units/mL of TIG; the optimal dosage of intravenous immunoglobulin for treating tetanus is not known, and its use is not approved for this indication. Another alternative is equine- or bovine-derived tetanus antitoxin (TAT). The usual dose of TAT is 50,000-100,000 units, with half given intramuscularly and half intravenously, but as little as 10,000 units may be sufficient. TAT is not available in the United States. Approximately 15% of patients given the usual dose of TAT experience serum sickness. When TAT is used, it is essential to check for possible sensitivity to horse serum; desensitization may be needed. The human-derived immunoglobulins are much preferred because of their longer half-lives (30 days) and the virtual absence of allergic and serum sickness adverse effects. Intrathecal TIG, given to neutralize tetanus toxin in the spinal cord, is not effective.

Penicillin G (100,000 units/kg/day divided every 4-6 hr IV for 10-14 days) remains the antibiotic of choice because of its effective clostridiocidal action and its diffusibility, which is an important consideration because blood flow to injured tissue may be compromised. Metronidazole (500 mg every 8 hr IV for adults) appears to be equally effective. Erythromycin and tetracycline (for persons >8 yr of age) are alternatives for penicillin-allergic patients.

All patients with generalized tetanus need muscle relaxants. Diazepam provides both relaxation and seizure control. The initial dose of 0.1-0.2 mg/kg every 3-6 hr given intravenously is subsequently titrated to control the tetanic spasms, after which the effective dose is sustained for 2-6 wk before a tapered withdrawal. Magnesium sulfate, other benzodiazepines (midazolam), chlorpromazine, dantrolene, and baclofen are also used. Intrathecal baclofen produces such complete muscle relaxation that apnea often ensues; like most other agents listed, baclofen should be used only in an intensive care unit setting. The highest survival rates in generalized tetanus are achieved with neuromuscular blocking agents such as vecuronium and pancuronium, which produce a general flaccid paralysis that is then managed by mechanical ventilation. Autonomic instability is regulated with standard α- or β- (or both) blocking agents; morphine has also proved useful.

SUPPORTIVE CARE

Meticulous supportive care in a quiet, dark, secluded setting is most desirable. Because tetanic spasms may be triggered by minor stimuli, the patient should be sedated and protected from all unnecessary sounds, sights, and touch, and all therapeutic and other manipulations must be carefully scheduled and coordinated. Endotracheal intubation may not be required, but it should be done to prevent aspiration of secretions before laryngospasm develops. A tracheostomy kit should be immediately at hand for unintubated patients. Endotracheal intubation and suctioning easily provoke reflex tetanic seizures and spasms, so early tracheostomy should be considered in severe cases not managed by pharmacologically induced flaccid paralysis. Therapeutic botulinum toxin has been used for this purpose, that is, to overcome trismus.

Cardiorespiratory monitoring, frequent suctioning, and maintenance of the patient's substantial fluid, electrolyte, and caloric needs are fundamental. Careful nursing attention to mouth, skin, bladder, and bowel function is needed to avoid ulceration, infection, and obstipation. Prophylactic subcutaneous heparin may be of value but must be balanced with the risk for hemorrhage.

COMPLICATIONS

The seizures and the severe, sustained rigid paralysis of tetanus predispose the patient to many complications. Aspiration of secretions and pneumonia may have begun before the first medical attention was received. Maintaining airway patency often mandates endotracheal intubation and mechanical ventilation with their attendant hazards, including pneumothorax and mediastinal emphysema. The seizures may result in lacerations of the mouth or tongue, in intramuscular hematomas or rhabdomyolysis with myoglobinuria and renal failure, or in long bone or spinal fractures. Venous thrombosis, pulmonary embolism, gastric ulceration with or without hemorrhage, paralytic ileus, and decubitus ulceration are constant hazards. Excessive use of muscle relaxants, which are an integral part of care, may produce iatrogenic apnea. Cardiac arrhythmias, including asystole, unstable blood pressure, and labile temperature regulation reflect disordered autonomic nervous system control that may be aggravated by inattention to maintenance of intravascular volume needs.

PROGNOSIS

Recovery in tetanus occurs through regeneration of synapses within the spinal cord and thereby the restoration of muscle relaxation. However, because an episode of tetanus does not result in the production of toxin-neutralizing antibodies, active immunization with tetanus toxoid at discharge with provision for completion of the primary series is mandatory.

The most important factor that influences outcome is the quality of supportive care. Mortality is highest in the very young and the very old. A favorable prognosis is associated with a long incubation period, absence of fever, and localized disease. An unfavorable prognosis is associated with onset of trismus <7 days after injury and with onset of generalized tetanic spasms <3 days after onset of trismus. Sequelae of hypoxic brain injury, especially in infants, include cerebral palsy,

diminished mental abilities, and behavioral difficulties. Most fatalities occur within the 1st wk of illness. Reported case fatality rates for generalized tetanus are 5-35%, and for neonatal tetanus they extend from <10% with intensive care treatment to >75% without it. Cephalic tetanus has an especially poor prognosis because of breathing and feeding difficulties.

PREVENTION

Tetanus is an entirely preventable disease. A serum antibody titer of ≥0.01 units/mL is considered protective. Active immunization should begin in early infancy with combined diphtheria toxoid–tetanus toxoid–acellular pertussis (DTaP) vaccine at 2, 4, 6 and 15-18 mo of age, with boosters at 4-6 yr (DTaP) and 11-12 yr (Tdap) of age and at 10 yr intervals thereafter throughout adult life with tetanus and reduced diphtheria toxoid (Td). Immunization of women with tetanus toxoid prevents neonatal tetanus, and pregnant women should receive 1 dose of reduced diphtheria and pertussis toxoids (Tdap) during each pregnancy, preferably at 27-36 wk gestation. Recommended immunization schedules are regularly updated; the most current versions may be found at http://www.cdc.gov/vaccines/schedules.

Arthus reactions (type III hypersensitivity reactions), a localized vasculitis associated with deposition of immune complexes and activation of complement, are reported rarely after tetanus vaccination. Mass immunization campaigns in developing countries have occasionally provoked a widespread hysterical reaction.

Wound Management

Tetanus prevention measures after trauma consist of inducing active immunity to tetanus toxin and of passively providing antitoxic antibody (Table 211-1). Tetanus prophylaxis is an essential part of all wound management, but specific measures depend on the nature of the injury and the immunization status of the patient. Regrettably, prevention of tetanus must now be included in planning for the consequences of bombings and other possible civilian mass-casualty events.

Tetanus toxoid should always be given after a dog or other animal bite, even though *C. tetani* is infrequently found in canine mouth flora.

Table 211-1 Tetanus Prophylaxis in Routine Wound Management

	Clean, Minor Wounds		All Other Wounds*	
HISTORY OF ABSORBED TETANUS TOXOID	TDAP OR TD†	TIG‡	TDAP OR TD†	TIG‡
Uncertain or <3 doses	Yes	No	Yes	Yes
3 or more doses	No§	No	No‖	No

*Such as, but not limited to, wounds contaminated with dirt, feces, and saliva; puncture wounds; avulsions; wounds resulting from missiles, crushing, burns, and frostbite.

†For children younger than 7 yr of age, DTaP is preferred to tetanus toxoid alone if <3 doses of DTaP have been previously given. If pertussis vaccine is contraindicated, DT is given. For persons 7 yr of age or older, Td (or Tdap for adolescents 11-18 yr of age) is preferred to tetanus toxoid alone. Tdap is preferred to Td for adolescents 11-18 yr of age who have never received Tdap. Td is preferred to tetanus toxoid for adolescents who received Tdap previously or when Tdap is not available.

‡TIG should be administered for tetanus-prone wounds in HIV-infected patients regardless of the history of tetanus immunizations.

§Yes, if 10 yr or longer since the last tetanus toxoid–containing vaccine dose.

‖Yes, if 5 yr or longer since the last tetanus toxoid–containing vaccine dose. (More frequent boosters are not needed and can accentuate adverse events.)

DT, diphtheria and tetanus toxoid vaccine; DTaP, combined diphtheria toxoid–tetanus toxoid–acellular pertussis vaccine; Td, tetanus toxoid and reduced diphtheria toxoid vaccine; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; TIG, tetanus immune globulin.

Adapted from the Centers for Disease Control and Prevention (CDC): Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR Morbid Mortal Wkly Rep *55:1–43, 2006.*

All nonminor wounds require human TIG except those in a fully immunized patient. In any other circumstance (e.g., patients with an unknown or incomplete immunization history; crush, puncture, or projectile wounds; wounds contaminated with saliva, soil, or feces; avulsion injuries; compound fractures; or frostbite), TIG 250 units should be given intramuscularly, with 500 units for highly tetanus-prone wounds (i.e., unable to be debrided, with substantial bacterial contamination, or longer than 24 hr since injury). If TIG is unavailable, use of human intravenous immunoglobulin may be considered. If neither of these products is available, then 3,000-5,000 units of equine- or bovine-derived TAT may be given intramuscularly after testing for hypersensitivity. Even at this dose, serum sickness may occur.

The wound should undergo immediate, thorough surgical cleansing and debridement to remove foreign bodies and any necrotic tissue in which anaerobic conditions might develop. Tetanus toxoid should be given to stimulate active immunity and may be administered concurrently with TIG (or TAT) if given in separate syringes at widely separated sites. A tetanus toxoid booster (preferably Td or Tdap) is administered to all persons with any wound if the tetanus immunization status is unknown or incomplete. A booster is administered to injured persons who have completed the primary immunization series if (1) the wound is clean and minor but 10 or more years have passed since the last booster or (2) the wound is more serious and 5 or more years have passed since the last booster. Persons who experienced an Arthus reaction after a dose of tetanus toxoid–containing vaccine should not receive Td more frequently than every 10 yr, even for tetanus prophylaxis as part of wound management. In a situation of delayed wound care, active immunization should be started at once. Although fluid tetanus toxoid produces a more rapid immune response than the absorbed or precipitated toxoids, the absorbed toxoid results in a more durable titer.

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Chapter 212

Clostridium difficile Infection

Ethan A. Mezoff and Mitchell B. Cohen

Clostridium difficile **infection** (CDI), also known as *pseudomembranous colitis* or *C. difficile*–associated diarrhea, refers to gastrointestinal colonization with *C. difficile* resulting in a diarrheal illness. An increase in inpatient and outpatient acquisition of CDI has been observed and new risk factors identified, fueling the development of new therapeutic options.

ETIOLOGY

C. difficile is a Gram-positive, anaerobic bacillus capable of forming a spore that is resistant to killing by alcohol. Organisms causing symptomatic disease produce 1 or both of the following: **toxin A** and **toxin B**. These toxins affect intracellular signaling pathways, resulting in inflammation and cell death. The cytotoxic **binary toxin**, an AB toxin, is not present in the majority of strains but has been detected in epidemic strains.

EPIDEMIOLOGY

Once thought to be an infrequent infection of chronically ill and hospitalized patients, the incidence of CDI is increasing and the setting of acquisition is changing. The incidence in pediatric patients increased 48%, from 2.5 to 3.7 cases per 1,000 admissions between 2001 and 2006. A population-based cohort study over a similar time period found that 75% of cases were community-acquired and 16% had no

preceding hospitalization or antibiotic exposure. In addition to an overall increase in all strains, a hypervirulent strain, denoted NAP1/BI/027 (also called BI), has emerged and is estimated to cause approximately 10-20% of pediatric infections. This strain produces binary toxin and exhibits 16- and 23-fold increases in the production of toxins A and B, respectively. The specific role of this hypervirulent strain in the changing epidemiology of CDI is not completely understood.

Asymptomatic carriage occurs with potentially pathogenic strains; this is common in neonates and infants 1 year of age and younger. A carrier frequency rate of 50% may occur in children younger than age 1 yr, but the rate declines by age 3 yr. Carriers can infect other susceptible individuals.

Risk factors for CDI include the use of broad-spectrum antibiotics, hospitalization (particularly if the prior room occupant was infected), gastrointestinal surgery, inflammatory bowel disease, chemotherapy, enteral tube feeding, proton pump–inhibitor use, and chronic illness.

PATHOGENESIS

Disease is caused by gastrointestinal infection with a toxin-producing strain. Any process that disrupts normal flora, impairs the acid barrier defense, alters the normal gastrointestinal immune response (e.g., inflammatory bowel disease), or inhibits intestinal motility may lead to infection. Normal bowel flora appears to be protective, conferring "colonization resistance."

By affecting intracellular signaling pathways and cytoskeletal organization, toxins induce an inflammatory response and cell death, leading to diarrhea and pseudomembrane formation. Antibodies against toxin A have been shown to confer protection against symptomatic disease, and failure of antibody production has been shown to occur in patients with recurrent disease.

CLINICAL MANIFESTATIONS

Infection with toxin-producing strains of *C. difficile* leads to a spectrum of disease ranging from mild, self-limited diarrhea to explosive, watery diarrhea with occult blood or mucous, to pseudomembranous colitis, and even death. **Pseudomembranous colitis** describes a bloody diarrhea with accompanying fever, abdominal pain/cramps, nausea, and vomiting. Rarely, small gut involvement, bacteremia, abscess formation, toxic megacolon, and even death can occur.

Symptoms of CDI generally begin less than a week after colonization and may develop during or weeks after antibiotic exposure. They are generally more severe in certain populations, including patients receiving chemotherapy, patients with chronic gastrointestinal disease (e.g., inflammatory bowel disease), and some patients with cystic fibrosis.

DIAGNOSIS

CDI is diagnosed by the detection of a *C. difficile* **toxin** in the stool of a symptomatic patient. Most patients present with a history of recent antibiotic use, but the absence of antibiotic exposure should not dissuade the astute clinician from considering this diagnosis and ordering the appropriate test. Conversely, high carriage rates among infants should prompt careful consideration when testing and treating children younger than the age of 3 yr.

The cell culture cytotoxicity assay was replaced as the standard test for toxin detection by the enzyme immunoassay, a same-day test for 1 or both toxins with sufficient specificity (94-100%) but less-than-ideal sensitivity (88-93%). Nucleic acid amplification tests are used by some laboratories to supplement or supplant the immunoassay with the goal of improving sensitivity.

Culture for organism isolation is a sensitive test but is labor intensive, taking several days. Culture alone is not specific, as it does not differentiate between toxin-producing and non–toxin-producing strains. Pseudomembranous nodules and characteristic plaques may be seen on colonoscopy or sigmoidoscopy.

TREATMENT

Initial treatment of CDI involves discontinuation of any nonvital antibiotic therapy and administration of fluid/electrolyte replacement. For mild cases, this treatment may be curative. Persistent symptoms or moderate to severe disease warrants antimicrobial therapy directed against *C. difficile*.

Oral metronidazole (20-40 mg/kg/day PO divided every 6-8 hr for 7-10 days) works well in mild to moderate infection. Orally administered vancomycin (40 mg/kg/day PO divided every 6 hr for 7-10 days) is approved by the U.S. Food and Drug Administration for use against infection with *C. difficile*. Vancomycin exhibits ideal pharmacologic properties for treatment of this enteric pathogen, as it is not absorbed in the gut. This agent is suggested as a first-line agent for severe disease as manifested by hypotension, peripheral leukocytosis, or severe pseudomembranous colitis. Concern for the emergence of vancomycin-resistant enterococci and cost limit its use as first-line therapy in mild to moderate disease. Fidaxomicin, a second-line agent not yet approved for pediatric use, is a narrow spectrum macrolide antibiotic with non-inferior efficacy to vancomycin but superior recurrence prevention. The cost of a course of fidaxomicin can be twice that of vancomycin and 125-fold higher than that of metronidazole. Reports have demonstrated a high success treatment efficacy for donor (unaffected) fecal therapy (transplant) (see below for recurrences).

PROGNOSIS

The response rate to initial treatment of CDI is greater than 95%; however, both the treatment failure rate and the recurrence rate have increased since the late 1990s. Additionally, the risk of subsequent reappearance increases with each recurrence.

Initial recurrence rates are between 5% and 20%, are diagnosed clinically and generally occur within 4 wk of treatment. Some recurrences are a result of incomplete eradication of the original strain and others are because of reinfection with a different strain. Treatment for the initial reoccurrence involves retreatment with the original antibiotic course.

Recurrences of CDI may be a consequence of a suboptimal immune response, failure to kill organisms that have sporulated, or failure of delivery of antibiotic to the site of infection in the case of ileus or toxic megacolon. In the case of the 1st 2 causes, treatment with pulsed or tapered vancomycin decreases recurrence rates. In addition to this approach, other antibiotics (rifaximin or nitazoxanide), toxin-binding polymers (Tolevamer), and probiotics (*Saccharomyces boulardii* or *Lactobacillus* GG) have been used as adjunctive therapy. Although not well studied in children, *S. boulardii* significantly decreases recurrence rates when used as an adjunct to vancomycin therapy in adults. Because failure to manifest an adequate antitoxin immune response is associated with a higher frequency of recurrent CDI, intravenous immune globulin has been used to treat recurrent disease. In the case of ileus or toxic megacolon, an enema of vancomycin may be used to directly place the antibiotic at the site of infection, although most often intravenous therapy is first attempted in this circumstance.

Fecal microbial transplantation has been used to address the disruption in normal gut flora felt to allow colonization with *C. difficile*. Transplantation involves the instillation of fecal material from a healthy donor into the patient's gastrointestinal tract by nasoenteric tube, enema, capsules, or colonoscopy. Initial reports indicate an overall success rate of approximately 90% in patients with recurrent CDI.

It is important to recognize that postinfectious diarrhea may be from other causes. Examples are postinfectious irritable bowel syndrome, microscopic colitis, and inflammatory bowel disease. A test of cure is not recommended in the asymptomatic patient, and a positive test for recurrence is not useful until at least 4 wk after the initial test.

PREVENTION

Strategies for prevention of CDI include recognition of common sites of acquisition (hospitals, childcare settings, extended care facilities); effective environmental cleaning (i.e., use of chlorinated cleaning solutions); appropriate antibiotic and proton-pump inhibitor prescription practices; cohorting of infected patients; and proper handwashing with soap and water. There is moderate evidence that probiotics may reduce the incidence of *C. difficile*–associated diarrhea.

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Chapter 213

Other Anaerobic Infections

Michael J. Chusid

Anaerobic bacteria are among the most numerous organisms colonizing humans. Anaerobes are present in soil and are normal inhabitants of all living animals, but infections caused by anaerobes are relatively uncommon. Anaerobes are relatively or entirely intolerant of exposure to oxygen. Most are **facultative anaerobes,** being able to survive in the presence of oxygen but growing better in reduced oxygen tensions. **Obligate anaerobes** cannot survive any exposure to oxygen.

Infections with anaerobes frequently occur adjacent to mucosal surfaces, often as **mixed infections** with aerobes. Conditions of reduced oxygen tension provide the optimal conditions for proliferation of anaerobes. Traumatized areas, devascularized areas, and areas of crush injury are all ideal sites for anaerobic infection. Often both aerobic and anaerobic organisms are inoculated in devitalized areas, with local extension and bacteremia most often caused by the more virulent aerobes. Abscess formation evolves over days to weeks and generally involves both aerobes and anaerobes. Examples of such infections include appendicitis and periappendiceal, pelvic, perirectal, peritonsillar, retropharyngeal, parapharyngeal, pulmonary, and dental abscesses. Septic thrombophlebitis, as a consequence of appendicitis, chronic sinusitis, pharyngitis, and otitis media, provides a route for hematogenous spread of anaerobic infection to parenchymal organs such as the liver, brain, and lungs.

Anaerobic infection is usually caused by endogenous flora. Combinations of impaired physical barriers to infection, compromised tissue viability, alterations in normal flora, impaired host immunity, and anaerobic bacterial virulence factors contribute to infection with normal anaerobic inhabitants of mucous membranes. Virulence factors include capsules, toxins, enzymes, and fatty acids.

CLINICAL MANIFESTATIONS

Anaerobic infections occur in a variety of sites throughout the body (Table 213-1). Anaerobes often coexist synergistically with aerobes. Infections with anaerobes are usually polymicrobial and also include aerobes.

Bacteremia

Anaerobes account for approximately 1% of bloodstream bacterial isolates in adults, but the rate is lower in children. Isolation of anaerobes from the blood is often an indication of a serious primary anaerobic infection. The most common blood isolates of anaerobic bacteria in children are *Bacteroides fragilis*, *Peptostreptococcus* spp., *Clostridium* spp., and *Fusobacterium* spp. As with aerobes, the cell walls of Gram-negative anaerobes may contain endotoxin and can be associated with the development of hypotension and shock when present in the circulatory system. Clostridia produce hemolysins, and the presence of these organisms in the blood can result in massive hemolysis and cardiovascular collapse.

Central Nervous System

Anaerobic meningitis is rare but can occur in neonates and as a complication of infections of the ear and neck or because of anatomic defects of meninges (sinus tracts). Brain abscess and subdural empyema are usually polymicrobial, with anaerobes commonly involved (see Chapter 604). Brain abscess usually occurs as a result of spread from infected sinuses, middle ear, or lung.

Upper Respiratory Tract

The respiratory tract is colonized by both aerobes and anaerobes. Anaerobic bacteria are involved in chronic sinusitis, chronic otitis media, peritonsillar infections, parapharyngeal and retropharyngeal abscesses, and periodontal infections. Anaerobic periodontal disease is most common in patients with poor dental hygiene or who are receiving drugs that provide hypertrophy of the gums. **Vincent angina,** also known as **acute necrotizing ulcerative gingivitis** or **trench mouth,** is an acute, fulminating, mixed anaerobic bacterial-spirochetal infection of the gingival margin and floor of the mouth. It is characterized by gingival pain, foul breath, and pseudomembrane formation. **Ludwig angina** is an acute, life-threatening cellulitis of dental origin of the sublingual and submandibular spaces. Infection spreads rapidly in the neck and may cause sudden airway obstruction.

Lemierre syndrome, or **postanginal sepsis,** is a suppurative infection of the lateral pharyngeal space, of increasing prevalence, that often begins as pharyngitis (see Chapter 381). It may complicate Epstein-Barr virus or other viral and bacterial infections of the pharynx. It usually manifests as a unilateral septic thrombophlebitis of the jugular venous system with septic pulmonary embolization. Clinical signs include unilateral painful neck swelling, trismus, and dysphagia, culminating with signs of sepsis and respiratory distress. *Fusobacterium necrophorum* is the most commonly isolated organism, although polymicrobial infection may occur. Metastatic infections involving muscles, bones, and solid organs can occur as a complication of Lemierre syndrome.

Lower Respiratory Tract

Anaerobic lung abscess, empyema, and anaerobic pneumonia are most common in children who have disordered swallowing or seizures or in whom an inhaled foreign body is occluding a bronchus. Children and adults can aspirate oral contents during sleep, seizure, or periods of unconsciousness. In most cases, lung cilia and phagocytes clear particulate matter and microbes. If the aspiration is of increased volume or frequency or a foreign body blocks normal ciliary clearance, normal pulmonary clearance mechanisms are overcome and infection ensues. In unusual cases, particularly in patients with poor dental hygiene, aspirated mouth contents may contain the anaerobe *Actinomyces israelii*, resulting in pulmonary actinomycosis (see Chapter 189). This anaerobic pneumonitis is remarkable for traversing tissues planes, and affected patients often have fistulas extruding distinctive particulate matter, called sulfur granules, from the chest wall overlying areas of intrathoracic infection.

Intraabdominal Infection

The entire digestive tract is heavily colonized by anaerobes. The density of organisms is highest in the colon, where anaerobes outnumber aerobes 1,000 : 1. Perforation of the gut leads to leakage of gut flora into the peritoneum, resulting in peritonitis involving both aerobes and anaerobes. Secondary sepsis caused by aerobes often occurs early. As the peritoneal infection is walled off, an abscess containing both aerobes and anaerobes often evolves. Secondary hepatic abscesses may then develop as complications of appendicitis, intestinal perforation, inflammatory bowel disease, or biliary tract disease. In children with malignancies who are receiving chemotherapy, the intestinal mucosa is often damaged, leading to translocation of bacteria and focal invasion of bowel flora. **Typhlitis** is a mixed infection of the gut wall usually beginning in the ileocecum and characterized by abdominal pain, diarrhea, fever, and abdominal distention in neutropenic patients. Empiric antimicrobial therapy of fever and neutropenia may not be optimal against the anaerobes involved in typhlitis (see Chapter 178). Similarly, a mixed aerobic–anaerobic infection of the intestinal wall and peritoneum may develop in a small infant as a complication of **necrotizing enterocolitis**, believed to be a result of the relative vascular insufficiency of the gut and hypoxia (see Chapter 102.2).

Genital Tract

Pelvic inflammatory disease and tuboovarian abscesses are frequently caused by mixed aerobic anaerobic infection. Vaginitis can be caused

Table 213-1 Infections Associated with Anaerobic Bacteria

SITE AND INFECTION	MAJOR RISK FACTORS	ANAEROBIC BACTERIA*
CENTRAL NERVOUS SYSTEM		
Cerebral abscess	Cyanotic heart disease Cystic fibrosis Penetrating trauma	Polymicrobial
Epidural and subdural empyemas, meningitis	Direct extension from contiguous sinusitis, otitis media, mastoiditis, or anatomic defect involving the dura	*Bacteroides fragilis*† *Fusobacterium* *Peptostreptococcus* *Veillonella*
UPPER RESPIRATORY TRACT		
Dental abscess	Poor periodontal hygiene	*Peptostreptococcus*
Ludwig angina (cellulitis of sublingual-submandibular space)	Drugs producing gingival hypertrophy	*Fusobacterium*
Necrotizing gingivitis (Vincent stomatitis)		*Prevotella melaninogenica*
Chronic otitis-mastoiditis-sinusitis	Tympanic perforation Tympanostomy tubes	
Peritonsillar abscess	Streptococcal pharyngitis	
Retropharyngeal abscess	Penetrating injury	
Lemierre syndrome	Preexisting viral or bacterial pharyngitis	*Fusobacterium*
LOWER RESPIRATORY TRACT		
Aspiration pneumonia Necrotizing pneumonitis Lung abscess	Periodontal disease Bronchial obstruction Altered gag or consciousness Aspirated foreign body Sequestered lobe Vascular anomaly	Polymicrobial *P. melaninogenica* *Bacteroides intermedius* *Fusobacterium* *Peptostreptococcus*, *Eubacterium* *B. fragilis*, *Veillonella*
Septic pulmonary emboli		*Fusobacterium*
INTRAABDOMINAL		
Abscess	Appendicitis	Polymicrobial
Secondary peritonitis	Penetrating trauma (especially of the colon)	*Bacteroides* spp. *Clostridium* *Peptostreptococcus* *Eubacterium* *Fusobacterium*
FEMALE GENITAL TRACT		
Bartholin abscess Tuboovarian abscess Endometritis Pelvic thrombophlebitis Salpingitis Chorioamnionitis	Vaginosis Intrauterine device	*B. fragilis* *Bacteroides bivius* *Peptostreptococcus* *Clostridium* *Mobiluncus* *Actinomyces*
Septic abortion		*Clostridium*
SKIN AND SOFT TISSUE		
Cellulitis	Decubitus ulcers	Varies with site and contamination with oral or enteric flora
Perirectal cellulitis	Abdominal wounds	*Clostridium perfringens* (myonecrosis)
Myonecrosis (gas gangrene)	Pilonidal sinus	*Bacteroides* *Clostridia*
Necrotizing fasciitis and synergistic gangrene	Trauma Human and animal bites Immunosuppressed or neutropenic patients Varicella	*Fusobacterium* *Clostridium tertium* *Clostridium septicum* Anaerobic streptococci
BLOOD		
Bacteremia	Intraabdominal infection, abscesses, myonecrosis, necrotizing fasciitis	*B. fragilis* *Clostridium* *Peptostreptococcus* *Fusobacterium*

*Infections may also be from or may involve aerobic bacteria as the sole agent or as part of a mixed infection; brain abscess may contain microaerophilic streptococci; intraabdominal infections may contain Gram-negative enteric organisms and enterococci; and salpingitis may contain *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

†*Bacteroides fragilis* is usually isolated from infections below the diaphragm except for brain abscesses.

by overgrowth of anaerobic flora. Anaerobes frequently contribute to chorioamnionitis and premature labor and may result in anaerobic bacteremia of the newborn. Although these bacteremias are often transient, anaerobes occasionally cause invasive disease in the newborn, including central nervous system infection.

Skin and Soft Tissue

Anaerobic skin infections occur in the setting of bites, foreign bodies, and skin and tissue ulceration because of pressure necrosis or lack of adequate blood supply. Animal bites and human bites inoculate oral and skin flora into damaged and hypoxic cutaneous tissue. The extent

of the infection depends on the depth of the bite and the associated crush injury to the tissues. In immunocompromised patients, unusual oral anaerobes such as *Capnocytophaga canimorsus* can cause life-threatening infection.

Clostridial myonecrosis, or **gas gangrene,** is a rapidly progressive infection of deep soft tissues, primarily muscles, associated with *Clostridium perfringens.* **Necrotizing fasciitis** is a more superficial, polymicrobial infection of the subcutaneous space with acute onset and rapid progression that has significant morbidity and mortality (see Chapter 665.2). Group A streptococcus, known in the popular press as "the flesh-eating bacteria," and *Staphylococcus aureus* are occasionally the causative pathogens. Commonly, necrotizing fasciitis is produced by combined infection of *S. aureus* or Gram-negative bacilli and anaerobic streptococci, termed **synergistic gangrene**. This infection is often seen as a complication of varicella following secondary infection of cutaneous vesicles. Diabetic patients may have a particularly aggressive and destructive synergistic gangrene of the inguinal area and adjacent scrotum or vulva known as **Fournier gangrene**. Early recognition with aggressive surgical debridement and antimicrobial therapy is necessary to limit disfiguring morbidity and mortality.

Other Sites

Occasionally, the bone adjacent to an anaerobic infection becomes infected by direct extension from a contiguous infection or by direct inoculation associated with trauma. Anaerobic infections of the kidneys (renal and perirenal abscesses) and heart (pericarditis) are rare. **Enteritis necroticans (pigbel)** is a rare but often fatal gastrointestinal infection that most commonly follows ingestion of a large meal in a previously starved child or adult. Anaerobic osteomyelitis, particularly of fingers and toes, can complicate any process capable of producing hypoxic necrosis, including diabetes, neuropathies, vasculopathies, and coagulopathies.

DIAGNOSIS

The diagnosis of anaerobic infection requires a high index of suspicion and the collection of appropriate and adequate specimens for anaerobic culture (Table 213-2). Culture specimens should be obtained in a manner that protects them from contamination with mucosal bacteria and from exposure to ambient oxygen. Swab samples from mucosal surfaces, nasal secretions, respiratory specimens, and stool should not be sent for anaerobic culture, because these sites normally harbor many anaerobes. Aspirates of infected sites, abscess material, and biopsy specimens are appropriate for anaerobic culturing. Specimens must be protected from oxygen and transported to the laboratory immediately. Anaerobic **transport medium** is used to increase the likelihood of recovery of obligate anaerobes. Gram staining of abscess fluid from suspected anaerobic infections is useful because even if the organisms do not grow in culture, they can be seen on the smear. The use of DNA probe technology in the near future is likely to increase the sensitivity of microbiologic confirmation of an anaerobic infection. Methods for susceptibility testing exist but may not be routinely available. A rapid and simple screening test for antibiotic susceptibility can be used to detect β-lactamase production and presumptive penicillin resistance.

Table 213-2 Clues to Presumptive Diagnosis of Anaerobic Infections*
Infection contiguous to or near a mucosal surface colonized with anaerobic bacteria (oropharynx, intestinal–genitourinary tract)
Putrid odor
Severe tissue necrosis, abscesses, gangrene, or fasciitis
Gas formation in tissues (crepitus on exam or visible on plain radiograph)
Failure to recover organisms using conventional aerobic microbiologic methods, despite the presence of mixed pleomorphic organisms on smears
Failure of organisms to grow after pretreatment with antibiotics effective against anaerobes
Failure of clinical response to antibiotic therapy poorly effective against anaerobic bacteria (e.g., aminoglycosides)
Toxin-mediated syndromes: botulism, tetanus, gas gangrene, food poisoning, pseudomembranous colitis
Infections associated with anaerobic bacteria (see Table 213-1)
Septic thrombophlebitis
Septicemic syndrome with jaundice or intravascular hemolysis
Typical appearance on Gram stain:
Bacteroides species—small, delicate, pleomorphic, pale, Gram-negative bacilli
Fusobacterium nucleatum—thin Gram-negative bacilli with fusiform shape, pointed ends
Fusobacterium necrophorum—pleomorphic Gram-negative bacilli with rounded ends
Peptostreptococcus—Gram-positive chained cocci similar to aerobic cocci
Clostridium perfringens—large, short, fat (boxcar-shaped), Gram-positive bacilli

*Suspicion of anaerobic infection is critical before specimens are sampled for culture, so as to ensure optimal microbiologic techniques and prompt, appropriate therapy.

TREATMENT

Treatment of anaerobic infections usually requires adequate drainage and appropriate antimicrobial therapy. Antibiotic therapy varies depending on the suspected or proven anaerobe involved. Many oral anaerobic bacterial species are susceptible to penicillins, although some strains may produce a β-lactamase. Drugs that are active against such strains include metronidazole, penicillins combined with β-lactamase inhibitors (ampicillin-sulbactam, ticarcillin-clavulanate, and piperacillin-tazobactam), carbapenems (imipenem and meropenem), clindamycin, and cefoxitin. Penicillin and vancomycin are active against the Gram-positive anaerobes.

Aerobes are usually present with the anaerobes, necessitating broad-spectrum antibiotic combinations for empirical therapy. Specific therapy is based on culture results and clinical course.

For soft-tissue infections, providing adequate perfusion to the area is critical. At times, a muscle flap or skin flap procedure is needed to ensure that nutrients and antimicrobial agents are brought to the affected area and adequate oxygen tension is maintained. Drainage of infected areas is often necessary for cure. Bacteria may survive in abscesses because of high bacterial inoculum, lack of bactericidal activity, and local conditions that facilitate bacterial proliferation. Aspiration is sometimes effective for small collections, whereas incision and drainage may be required for larger abscesses. Extensive debridement and resection of all devitalized tissue are needed to control fasciitis and myonecrosis. The therapeutic benefit of hyperbaric oxygen therapy remains uncertain.

COMMON ANAEROBIC PATHOGENS

Clostridium

Strains of *Clostridium* cause disease by proliferation and often by production of toxins. Of the more than 60 species that have been identified, only a few cause infections in humans. The most frequently implicated species are *Clostridium difficile* (see Chapter 212), *C. perfringens*, *Clostridium botulinum* (see Chapter 210), *Clostridium tetani* (see Chapter 211), *Clostridium butyricum, Clostridium septicum, Clostridium sordellii, Clostridium tertium,* and *Clostridium histolyticum.*

C. perfringens produces a variety of toxins and virulence factors. Strains of *C. perfringens* are designated A through E. **Alpha toxin** is a phospholipase that hydrolyzes sphingomyelin and lecithin and is produced by all strains. This toxin causes hemolysis, platelet lysis, increased capillary permeability, and hepatotoxicity. **Beta toxin,** produced by strains B and C, causes hemorrhagic necrosis of the small bowel. **Epsilon toxin** is produced by B and D strains and injures vascular endothelial cells, leading to increased vascular permeability, edema, and organ dysfunction. **Iota toxin,** produced by E strains, causes dermal edema. An enterotoxin is produced by type A and some type

C and D strains. Hemolysins and a variety of enzymes are produced by many *C. perfringens* strains.

Clostridium species commonly invade the bloodstream shortly before, during, or just after death, leading to contamination of tissues that may be donated for transplantation. A large outbreak of *Clostridium* infections in tissue graft recipients was reported in 14 patients who received musculoskeletal grafts processed at a single tissue bank. As a result of this outbreak, recommendations for tissue processing now include a processing method that kills bacterial spores.

Myonecrosis (Gas Gangrene)

C. perfringens is the major etiologic cause of myonecrosis, a rapidly progressive anaerobic soft-tissue infection. In immunocompromised persons, especially patients receiving cancer chemotherapy, *C. septicum* is a classic cause of rapidly fatal gas gangrene. A clue to the diagnosis is pain out of proportion to the clinical appearance of the wound. Infection progresses rapidly with edema, swelling, myonecrosis, and sometimes crepitation of soft tissues. Hypotension, mental confusion, shock, and renal failure are common. A characteristic sweet odor is present in the serosanguineous discharge. Gram staining of the exudate reveals Gram-positive bacilli but few leukocytes. Early and complete debridement with excision of necrotic tissue is key to controlling the infection. Repeated, frequent assessment of tissue viability in the operating room is required. High-dose penicillin (250,000 units/kg/day divided every 4-6 hr IV) or clindamycin (25-40 mg/kg/day divided every 6-8 hr IV) should be started immediately. Amputation of affected limbs is often required. The role of hyperbaric oxygen remains unclear but has been reported to be beneficial in several studies. Unfortunately, the prognosis for patients with myonecrosis is poor, even with early, aggressive therapy.

Food Poisoning

C. perfringens type A produces an enterotoxin that causes food poisoning (see Chapter 340). This intoxication results in the acute onset of watery diarrhea and crampy abdominal pain. The usual foods containing toxin are improperly prepared or stored meats and gravies. A specific etiologic diagnosis is rarely made in children with food poisoning. Therapy consists of rehydration and electrolyte replacement if necessary. The illness resolves spontaneously within 24 hr of onset. Prevention requires the maintenance of hot food at a temperature ≥74°C (165.2°F).

Bacteroides and *Prevotella*

B. fragilis is one of the more virulent anaerobic pathogens and is most frequently recovered from blood cultures and cultures of tissue or pus. The most common *B. fragilis* infection in children occurs as a complication of appendicitis. The organism is part of normal colonic flora but is not common in the mouth or respiratory tract. *B. fragilis* is usually found as part of polymicrobial appendiceal and other intraabdominal abscesses and is often involved in genital tract infections such as pelvic inflammatory disease and tuboovarian abscess. *Prevotella* organisms are normal oral flora, and infection with them typically involves gums, teeth, tonsils, and parapharyngeal spaces. Both *B. fragilis* and *Prevotella* may be involved in aspiration pneumonitis and lung abscess.

Strains of *B. fragilis* and *Prevotella melaninogenica* produce β-lactamase and are resistant to penicillins. Recommended treatment is with ticarcillin-clavulanate, piperacillin-tazobactam, cefoxitin, metronidazole, clindamycin, imipenem, or meropenem. Because infections involving these organisms are usually polymicrobial, therapy should include antimicrobial agents active against likely concomitant aerobic pathogens. Drainage of any abscesses and debridement of necrotic tissue are often required for control of these infections.

Fusobacterium

Fusobacterium organisms inhabit the intestine, respiratory tract, and female genital tracts. These organisms, which are more virulent than most of the normal anaerobic flora, cause bacteremia and a variety of rapidly progressive infections. **Lemierre syndrome,** bone and joint infections, and abdominal and genital tract infections are most common. Some strains produce a β-lactamase and are resistant to penicillins, requiring therapy with drugs like ampicillin-sulbactam and clindamycin.

Veillonella

Veillonella organisms are normal flora of the mouth, upper respiratory tract, intestine, and vagina. These anaerobes rarely cause infection. Strains are recovered as part of the polymicrobial flora causing abscess, chronic sinusitis, empyema, peritonitis, and wound infection. *Veillonella* organisms are susceptible to penicillins, cephalosporins, clindamycin, metronidazole, and carbapenems.

Anaerobic Cocci

Peptostreptococcus species are normal flora of the skin, respiratory tract, and gut. These organisms are often present in brain abscesses, chronic sinusitis, chronic otitis, and lung abscesses. Such infections are often polymicrobial, and therapy is aimed at the accompanying aerobes as well as the anaerobes. Most of the Gram-positive cocci are susceptible to penicillin, cephalosporins, carbapenems, and vancomycin.

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Section 7

Mycobacterial Infections

Chapter 214

Principles of Antimycobacterial Therapy

Stacene R. Maroushek

The treatment of mycobacterial infection and disease can be challenging. Patients require therapy with multiple agents, the offending pathogens commonly exhibit complex drug resistance patterns, and patients often have underlying conditions that affect drug choice and monitoring. Several of the drugs have not been well studied in children, and current recommendations are extrapolated from the experience in adults.

Single-drug therapy of *Mycobacterium tuberculosis* and nontuberculous mycobacteria is not recommended because of the high likelihood of developing antimicrobial resistance. Susceptibility testing of mycobacterial isolates often can aid in therapeutic decision making.

AGENTS USED AGAINST *MYCOBACTERIUM TUBERCULOSIS*

Commonly Used Agents

Isoniazid

Isoniazid (INH) is a hydrazide form of isonicotinic acid and is bactericidal for rapidly growing *M. tuberculosis.* The primary target of INH involves the INH A gene, which encodes the enoyl ACP (acyl carrier

Table 214-1 Recommended Treatment Regimens for Drug-Susceptible Tuberculosis in Infants, Children, and Adolescents

INFECTION OR DISEASE CATEGORY	REGIMEN	REMARKS
LATENT TUBERCULOSIS INFECTION*		
Isoniazid susceptible	9 mo of isoniazid, once a day	If daily therapy is not possible, DOT twice a week can be used for 9 mo
Isoniazid resistant	6 mo of rifampin, once a day	If daily therapy is not possible, DOT twice a week can be used for 6 mo
Isoniazid-rifampin resistant‡	Consult a tuberculosis specialist	
PULMONARY AND EXTRAPULMONARY INFECTION		
Except meningitis	2 mo of isoniazid, rifampin, pyrazinamide, and ethambutol daily, followed by 4 mo of isoniazid and rifampin† by DOT§ for drug-susceptible *Mycobacterium tuberculosis* 9-12 mo of isoniazid and rifampin for drug-susceptible *Mycobacterium bovis*	If possible drug resistance is a concern (see text), another drug (ethambutol or an aminoglycoside) is added to the initial 3 drug therapy until drug susceptibilities are determined; DOT is highly desirable If hilar adenopathy only, a 6-mo course of isoniazid and rifampin is sufficient Drugs can be given 2 or 3×/wk under DOT in the initial phase if nonadherence is likely
Meningitis	2 mo of isoniazid, rifampin, pyrazinamide, and an aminoglycoside or ethambutol or ethionamide, once a day, followed by 7-10 mo of isoniazid and rifampin, once a day or twice a week (9-12 mo total) for drug-susceptible *M. tuberculosis* ≥12 mo of therapy without pyrazinamide for drug-susceptible *M. bovis*	A 4th drug, such as an aminoglycoside, is given with initial therapy until drug susceptibility is known For patients who might have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin can be used instead of streptomycin

*Positive TST or IGRA result, no disease.
†Duration of therapy is longer for human immunodeficiency virus (HIV)-infected people, and additional drugs may be indicated.
‡Medications should be administered daily for the 1st 2 wk to 2 mo of treatment and then can be administered 2-3×/wk by DOT.
§If initial chest radiograph shows cavitary lesions and sputum after 2 mo of therapy remains positive, duration of therapy is extended to 9 mo.
DOT, directly observed therapy; IGRA, interferon-γ release assay; TST, tuberculin skin test.
From American Academy of Pediatrics: Tuberculosis. In Pickering LK, Baker CJ, Kimberlin DW, Long SS, editors: Red book 2012: report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

protein) reductase needed for the last step of the mycolic acid biosynthesis pathway of cell wall production. Resistance to INH occurs following mutations in the INH A gene or in other genes encoding enzymes that activate INH, such as kat G.

INH is indicated for the treatment of *M. tuberculosis, Mycobacterium kansasii,* and *Mycobacterium bovis.* The pediatric dosage is 10-15 mg/kg/day PO in a single dose not to exceed 300 mg/day. The adult dosage is 5 mg/kg/day PO in a single dose not to exceed 300 mg/day. Alternative pediatric dosing is 20-30 mg/kg PO in a single dose not to exceed 900 mg/dose given twice weekly under **directly observed therapy,** in which patients are observed to ingest each dose of antituberculosis medication to maximize the likelihood of completing therapy. The duration of treatment depends on the disease being treated (Table 214-1). INH needs to be taken 1 hr before or 2 hr after meals because food decreases absorption. It is available in liquid, tablet, IV (not approved by the FDA), and IM preparations.

Major **adverse events** include hepatotoxicity in 1% of children and approximately 3% of adults (increasing with age) and dose-related peripheral neuropathy. Pyridoxine can prevent the peripheral neuropathy and is indicated for breastfeeding infants and their mothers, children and youth on milk- or meat-deficient diets, pregnant adolescents, and symptomatic HIV-infected children. Minor adverse events include rash, worsening of acne, epigastric pain with occasional nausea and vomiting, decreased vitamin D levels, and dizziness. The liquid formulation of INH contains sorbitol, which often causes diarrhea and stomach upset.

INH is accompanied by significant drug–drug interactions (Table 214-2). The metabolism of INH is by acetylation. Acetylation rates have little effect on efficacy, but **slow acetylators** have an increased risk for hepatotoxicity, especially when used in combination with rifampin. Routine baseline liver function testing or monthly monitoring is only indicated for persons with underlying hepatic disease or on concomitant hepatotoxic drugs, including other antimycobacterial agents, acetaminophen, and alcohol. Monthly clinic visits while on INH alone are encouraged to monitor adherence, adverse effects, and worsening of infection.

Table 214-2 Isoniazid Drug–Drug Interactions

DRUG USED WITH ISONIAZID	EFFECTS
Acetaminophen, alcohol, rifampin	Increased hepatotoxicity of isoniazid or listed drugs
Aluminum salts (antacids)	Decreased absorption of isoniazid
Carbamazepine, phenytoin, theophylline, diazepam, warfarin	Increased level, effect, or toxicity of listed drugs due to decreased metabolism
Itraconazole, ketoconazole, oral hypoglycemic agents	Decreased level or effect of listed drugs due to increased metabolism
Cycloserine, ethionamide	Increased central nervous system adverse effects of cycloserine and ethionamide
Prednisolone	Increased isoniazid metabolism

Rifamycins

The rifamycins (rifampin, rifabutin, rifapentine) are a class of macrolide antibiotics developed from *Streptomyces mediterranei.* Rifampin is a synthetic derivative of rifamycin B, and rifabutin is a derivative of rifamycin S. Rifapentine is a cyclopentyl derivative. The rifamycins inhibit the DNA-dependent RNA polymerase of mycobacteria, resulting in decreased RNA synthesis. They are generally bactericidal at treatment doses, but they may be bacteriostatic at lower doses.

Resistance is from a mutation in the DNA-dependent RNA polymerase gene (RpoB) that is often induced by previous incomplete therapy. Cross-resistance between rifampin and rifabutin has been demonstrated.

Rifampin is active against *M. tuberculosis, Mycobacterium leprae, M. kansasii,* and *Mycobacterium avium* complex. Rifampin is an integral drug in standard combination treatment of active *M. tuberculosis* disease and can be used as an alternative to INH in the treatment of latent tuberculosis infection in children who cannot tolerate INH. Rifabutin has a similar spectrum, with increased activity against *M. avium* complex. Rifapentine is undergoing pediatric clinical trials and appears to have activity similar to the activity of rifampin. The pediatric dosage of rifampin is 10-15 mg/kg/day PO in a single dose, not to exceed 600 mg/day. The adult dosage of rifampin is 5-10 mg/kg/day PO in a single dose, not to exceed 600 mg/day. Commonly used rifampin preparations include 150 and 300 mg capsules and a suspension that is usually formulated at a concentration of 10 mg/mL. The shelf life of rifampin suspension is short (approximately 4 wk), so it should not be compounded with other antimycobacterial agents. An intravenous form of rifampin is also available for initial treatment of patients who cannot take oral preparations. Dosage adjustment is needed for patients with liver failure. Other rifamycins (rifabutin and rifapentine) have been poorly studied in children and are not recommended for use in children.

Rifampin can be associated with **adverse events** such as transient elevations of liver enzymes; gastrointestinal (GI) upset with cramps, nausea, vomiting, and anorexia; headache; dizziness; and immunologically mediated fever and flu-like symptoms. Thrombocytopenia and hemolytic anemias can also occur. Rifabutin has a similar spectrum of toxicities, except for an increased incidence of rash (4%) and neutropenia (2%). Rifapentine has fewer adverse effects but is associated with hyperuricemia and cytopenias, especially lymphopenia and neutropenia. All rifamycins can turn urine and other secretions (tears, saliva, stool, sputum) orange, which can stain contact lenses. Patients and families should be warned about this common but otherwise innocuous adverse effect.

Rifamycins induce the hepatic cytochrome P450 isoenzyme system and are associated with the increased metabolism and decreased level of several drugs when administered concomitantly. These drugs include digoxin, corticosteroids such as prednisone and dexamethasone, dapsone, fluconazole, phenytoin, oral contraceptives, warfarin, and many antiretroviral agents, especially protease inhibitors and nonnucleoside reverse transcriptase inhibitors. Rifabutin has less of an effect on lowering protease inhibitor levels.

The use of pyrazinamide in combination with rifampin for short-course latent tuberculosis therapy has been associated with serious liver dysfunction and death. This combination has never been well studied or recommended for pediatric patients and should not be used.

No routine laboratory monitoring for rifamycins is indicated unless the patient is symptomatic. In patients with signs of toxicity, complete blood count (CBC) and kidney and liver function tests are indicated.

Pyrazinamide

Pyrazinamide (PZA) is a synthetic pyrazide analog of nicotinamide that is bactericidal against intracellular *M. tuberculosis* organisms in acidic environments, such as within macrophages or inflammatory lesions. A bacteria-specific enzyme (pyrazinamidase) converts PZA to pyrazinoic acid, which leads to low pH levels not tolerated by *M. tuberculosis.* Resistance is poorly understood but can arise from bacterial pyrazinamidase alterations.

PZA is indicated for the initial treatment phase of active tuberculosis in combination with other antimycobacterial agents. The pediatric dosage is 15-30 mg/kg/day PO in a single dose, not to exceed 2,000 mg/day. Twice weekly dosing with directly observed therapy only is with 50 mg/kg/day PO in a single dose, not to exceed 4,000 mg/day. It is available in a 500 mg tablet and can be made into a suspension of 100 mg/mL.

Adverse events include GI upset (e.g., nausea, vomiting, poor appetite) in approximately 4% of children, dosage-dependent hepatotoxicity, and elevated serum uric acid levels that can precipitate gout in susceptible adults. Approximately 10% of pediatric patients have elevated uric acid levels but with no associated clinical sequelae. Minor reactions include arthralgias, fatigue, and, rarely, fever.

Use of PZA in combination with rifampin for short-course treatment of latent tuberculosis is associated with serious liver dysfunction and death, and this combination should be avoided.

No routine laboratory monitoring for PZA is required, but monthly visits to reinforce the importance of therapy are desirable.

Ethambutol

Ethambutol is a synthetic form of ethylenedi-imino-di-1-butanol dihydrochloride that inhibits RNA synthesis needed for cell wall formation. At standard dosages it is bacteriostatic, but at dosages of >25 mg/kg ethambutol has bactericidal activity. The mechanism of resistance to ethambutol is unknown, but resistance develops rapidly when ethambutol is used as a single agent against *M. tuberculosis.*

Ethambutol is indicated for the treatment of infections caused by *M. tuberculosis, M. kansasii, M. bovis,* and *M. avium* complex. Ethambutol should only be used as part of a combination treatment regimen for *M. tuberculosis.* Daily dosing is 15-20 mg/kg PO in a single dose, not to exceed 2,500 mg/day. Twice-weekly dosing is with 50 mg/kg PO in a single dose, not to exceed 2,500 mg/day. Dosage adjustment is needed in renal insufficiency. Ethambutol is available in 100 and 400 mg tablets.

The **major adverse** effect with ethambutol is optic neuritis, and thus ethambutol should generally be reserved for children old enough to have visual acuity and color discrimination reliably monitored. Visual changes are usually dosage dependent and reversible. Other adverse events include headache, dizziness, confusion, hyperuricemia, GI upset, peripheral neuropathy, hepatotoxicity, and cytopenias, especially neutropenia and thrombocytopenia.

Routine laboratory monitoring includes baseline and periodic visual acuity and color discrimination testing, CBC, serum uric acid levels, and kidney and liver function tests.

Less Commonly Used Agents

Aminoglycosides

The aminoglycosides used for mycobacterial infections include streptomycin, amikacin, kanamycin, and capreomycin. Streptomycin is isolated from *Streptomyces griseus* and was the first drug used to treat *M. tuberculosis.* Capreomycin, a cyclic polypeptide from *Streptomyces capreolus,* and amikacin, a semisynthetic derivative of kanamycin, are newer agents that are recommended when streptomycin is unavailable. Aminoglycosides act by binding irreversibly to the 30S subunit of ribosomes and inhibiting subsequent protein synthesis. Streptomycin exhibits concentration-dependent bactericidal activity, and capreomycin is bacteriostatic. Resistance results from mutation in the binding site of the 30S ribosome, by decreased transport into cells, or by inactivation by bacterial enzymes. Cross-resistance between aminoglycosides has been demonstrated.

The aminoglycosides are indicated for the treatment of *M. tuberculosis* and *M. avium* complex. All are considered second-line drugs in the treatment of *M. tuberculosis* and should be used only when resistance patterns are known. Aminoglycosides are poorly absorbed orally and are administered by IM injection. Pediatric dosing ranges for streptomycin are 20 mg/kg/day if given daily and 20-40 mg/kg/day if given twice weekly; dosing is IM in a single daily dose. Capreomycin, amikacin, and kanamycin dosages are 15-30 mg/kg/day IM in a single dose, not to exceed 1 g/day. Dosage adjustment is necessary in renal insufficiency.

Aminoglycosides have **adverse effects** on proximal renal tubules, the cochlea, and the vestibular apparatus of the ear. Nephrotoxicity and ototoxicity account for most of the significant adverse events. Rarely, patients exhibit fever or rash with the administration of aminoglycosides. Concomitant use of other nephrotoxic or ototoxic agents should be avoided, because adverse effects may be additive. An infrequent but

serious, synergistic, dosage-dependent, aminoglycoside effect with nondepolarizing neuromuscular blockade agents can result in respiratory depression or paralysis.

Hearing and kidney function should be monitored at baseline and periodically. Early signs of ototoxicity include tinnitus, vertigo, and hearing loss. Ototoxicity appears to be irreversible, but early kidney damage may be reversible. As with other aminoglycosides, peak and trough drug levels are helpful in dosing and managing early toxicities.

Cycloserine

Cycloserine, derived from *Streptomyces orchidaceus* or *Streptomyces garyphalus,* is a synthetic analog of the amino acid D-alanine that interferes with bacterial cell wall synthesis via competitive inhibition of D-alanine components to be incorporated into the cell wall. It is bacteriostatic, and the mechanism of resistance is unknown.

Cycloserine is used to treat *M. tuberculosis* and *M. bovis*. The dosage is 10-20 mg/kg/day PO divided into 2 doses, not to exceed 1g/day. It is available in a 250 mg capsule.

The major **adverse event** is neurotoxicity with significant psychologic disturbance, including seizures, acute psychosis, headache, confusion, depression, and personality changes. The neurotoxic effects are additive with ethionamide and INH. It has also been associated with megaloblastic anemia. Cycloserine must be dosage adjusted with kidney impairment. It should be used with caution in patients with underlying psychiatric illness.

Routine laboratory monitoring includes kidney and hepatic function, CBC, and cycloserine levels. Psychiatric symptoms are less common at blood levels of <30 μg/mL.

Ethionamide

Ethionamide is structurally related to INH and is an ethyl derivative of thioisonicotinamide that inhibits peptide synthesis by an unclear mechanism thought to involve nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate dehydrogenase disruptions. Ethionamide is bacteriostatic at most therapeutic levels. Resistance develops quickly if ethionamide used as a single-agent therapy, although the mechanism is unknown.

Ethionamide is used as an alternative to streptomycin or ethambutol in the treatment of *M. tuberculosis* and has some activity against *M. kansasii* and *M. avium* complex. A metabolite, ethionamide sulfoxide, is bactericidal against *M. leprae.* Ethionamide has been shown to have good central nervous system (CNS) penetration and has been used as a 4th drug in combination with rifampin, INH, and PZA. The pediatric dosing is 15-20 mg/kg/day PO in 2 divided doses, not to exceed 1 g/day. It is available as a 250 mg tablet.

GI upset is common, and other **adverse effects** include neurologic disturbances (anxiety, dizziness, peripheral neuropathy, seizures, acute psychosis), hepatic enzyme elevations, hypothyroidism, hypoglycemia, and hypersensitivity reaction with rash and fever. It should be used with caution in patients with underlying psychiatric or thyroid disease. The psychiatric adverse effects can be potentiated with concomitant use of cycloserine.

In addition to close assessment of mood, routine monitoring includes thyroid and liver function tests. In diabetic patients, blood glucose levels should be monitored.

Fluoroquinolones

The fluoroquinolones are fluorinated derivatives of the quinolone class of antibiotics. Ciprofloxacin is a first-generation fluoroquinolone, and levofloxacin is the more active l-isomer of ofloxacin. Moxifloxacin and gatifloxacin are agents with emerging use in pediatric mycobacterial disease. Fluoroquinolones are not indicated for use in children younger than 18 yr of age, but studies of their use in pediatric patients continue to indicate that they may be used in special circumstances. Fluoroquinolones are bactericidal and exert their effect via inhibition of DNA gyrase. The alterations in DNA gyrase result in relaxation of supercoiled DNA and breaks in double-stranded DNA. The mechanism of resistance is not well defined but likely involves mutations in the DNA gyrase.

Levofloxacin is an important second-line drug in the treatment of multidrug-resistant *M. tuberculosis.* Ciprofloxacin has activity against *Mycobacterium fortuitum* complex and against *M. tuberculosis.* The pediatric dosage of ciprofloxacin is 20-30 mg/kg/day PO or IV, not to exceed 1.5 mg/day PO or 800 mg/day IV. The adult dosage of ciprofloxacin is 500-750 mg/dose PO divided into 2 doses or 200-400 mg/dose IV every 12 hr. Ciprofloxacin is available in 100, 250, 500, and 750 mg tablets and can be made in 5% (50 mg/mL) or 10% (100 mg/mL) suspensions. The dosage of levofloxacin for children is 5-10 mg/kg/day given once daily either PO or IV, not to exceed 1,000 mg/day, and for adults it is 500-1,000 mg/day PO or IV, not to exceed 1,000 mg/day. Levofloxacin is available in 250, 500, and 750 mg tablets, and a 50 mg/mL suspension can be extemporaneously compounded. The suspension has a shelf life of only 8 wk.

The most common **adverse effect** of fluoroquinolones is GI upset, with nausea, vomiting, abdominal pain, and diarrhea, including pseudomembranous colitis. Other less-common adverse effects include bone marrow depression, CNS effects (e.g., lowered seizure threshold, confusion, tremor, dizziness, headache), elevated liver transaminases, photosensitivity, and arthropathies. The potential for arthropathies (e.g., tendon ruptures, arthralgias, tendinitis) is the predominant reason that fluoroquinolones are not recommended for pediatric use. The mechanism of injury appears to involve the disruption of extracellular matrix of cartilage and depletion of collagen, a particular concern related to the bone and joint development of children.

Fluoroquinolones induce the cytochrome P450 isoenzymes that can increase the concentrations of dually administered theophylline and warfarin. Nonsteroidal antiinflammatories can potentiate the CNS effects of fluoroquinolones and should be avoided while taking a fluoroquinolone. Both ciprofloxacin and levofloxacin should be dosage adjusted in patients with significant renal dysfunction.

While taking fluoroquinolones, patients should be monitored for hepatic and renal dysfunction, arthropathies, and hematologic abnormalities.

Linezolid

Linezolid is a synthetic oxazolidinone derivative. This drug is not currently approved for use against mycobacterial infection in pediatric or adult patients but has activity against some mycobacterial species. Studies on efficacy of treatment of mycobacterial infections are under way. Linezolid inhibits translation by binding to the 23S ribosomal component of the 50S ribosome subunit, preventing coupling with the 70S subunit. Resistance is thought to be from a point mutation at the binding site but is poorly studied because only a few cases of resistance have been reported.

The approved indications for linezolid are for bacterial infections other than mycobacteria, but studies reveal in vitro activity against rapidly growing mycobacteria (*M. fortuitum* complex, *Mycobacterium chelonae, Mycobacterium abscessus*), *M. tuberculosis,* and *M. avium* complex. The dosage for 0-11 yr old children is 10 mg/kg/day PO or IV in divided doses every 8-12 hr. For persons older than 12 yr of age, the dosage is 600 mg PO or IV every 12 hr. Linezolid is available in 400 and 600 mg tablets and as a 20 mg/mL suspension.

Adverse effects of linezolid include GI upset (e.g., nausea, vomiting, diarrhea), CNS disturbances (e.g., dizziness, headache, insomnia, peripheral neuropathy), lactic acidosis, fever, myelosuppression, and pseudomembranous colitis. Linezolid is a weak inhibitor of monoamine oxidase A, and patients are advised to avoid foods with high tyramine content. Linezolid should be used cautiously in patients with preexisting myelosuppression.

In addition to monitoring for GI upset and CNS perturbations, routine laboratory monitoring includes CBC at least weekly.

Paraaminosalicylic Acid

Paraaminosalicylic acid (PAS) is a structural analog of paraaminobenzoic acid (PABA). It is bacteriostatic and acts by competitively inhibiting the synthesis of folic acid similar to the action of sulfonamides. Resistance mechanisms are poorly understood.

PAS acts against *M. tuberculosis.* The dosage is 150 mg/kg/day PO in 2 or 3 divided doses. PAS is dispensed in 4 g packets, and the granules should be mixed with liquid and swallowed whole.

Common **adverse events** include GI upset, and less-common events include hypokalemia, hematuria, albuminuria, crystalluria, and elevations of hepatic transaminases. PAS can decrease the absorption of rifampin, and coadministration with ethionamide potentiates the adverse effects of PAS.

In addition to monitoring for weight loss, routine laboratory monitoring includes liver and kidney function tests.

Bedaquiline Fumarate

This oral diarylquinoline has been recommended for the treatment of multidrug resistant tuberculosis. It should be used as part of combination therapy and administered by direct observation. Although approved for patients 18 yr of age and older, it may be considered for children on a case-by-case basis. Serious side effects include hepatotoxicity and a prolonged Qt interval.

AGENTS USED AGAINST *MYCOBACTERIUM LEPRAE*

Dapsone

Dapsone is a sulfone antibiotic with characteristics similar to sulfonamides. Similar to other sulfonamides, dapsone acts as a competitive antagonist of PABA, which is needed for the bacterial synthesis of folic acid. Dapsone is bacteriostatic against *M. leprae.* Resistance is not well understood but is thought to occur after alterations at the PABA-binding site.

Dapsone is used in the treatment of *M. leprae* in combination with other antileprosy agents (rifampin, clofazimine, ethionamide). The pediatric dosage is 1-2 mg/kg/day PO as a single dose, not to exceed 100 mg/day for a duration of 3-10 yr. The adult dosage is 100 mg/day PO as a single dose. Dapsone is available in 25 and 100 mg scored tablets and as an oral suspension of 2 mg/mL. The dosage should be adjusted in renal insufficiency.

Dapsone has many reported **adverse events,** including dosage-related hemolytic anemia, especially in patients with glucose-6-phosphate dehydrogenase deficiency, pancreatitis, renal complications (acute tubular necrosis, acute renal failure, albuminuria), increased liver enzymes, psychosis, tinnitus, peripheral neuropathy, photosensitivity, and a hypersensitivity syndrome with fever, rash, hepatic damage, and malaise. A **lepra reaction** may occur with treatment, which is a nontoxic, paradoxical worsening of lepromatous leprosy with the initiation of therapy. This hypersensitivity reaction is not an indication to discontinue therapy. Dapsone should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency or taking other folic acid antagonists. Dapsone levels can decrease with concomitant rifampin and can increase with concomitant clotrimazole.

Routine laboratory monitoring includes CBC weekly during the 1st mo of therapy, weekly through 6 mo of therapy, and then every 6 mo thereafter. Other periodic assessments include kidney function with creatine levels and urinalysis and liver function tests.

Clofazimine

Clofazimine is a synthetic phendimetrazine tartrate derivative that acts by binding to the mycobacterial DNA at guanine sites. It has a slow bactericidal activity against *M. leprae.* Mechanisms of resistance are not well studied. No cross-resistance between clofazimine and dapsone or rifampin has been shown.

Clofazimine is indicated as part of a combination therapy for the treatment of *M. leprae.* It appears there may be some activity against other mycobacteria such as *M. avium* complex, although treatment failures are common. Safety and efficacy of clofazimine are poorly studied in children. The pediatric dosage is 1 mg/kg/day PO as a single dose, not to exceed 100 mg/day in combination with dapsone and rifampin for 2 yr and then additionally as a single agent for longer than 1 yr. The adult dosage is 100 mg/day PO. It should be taken with food to increase absorption.

The most common **adverse effect** is a dosage-related, reversible pink to tan-brown discoloration of the skin and conjunctiva. Other adverse effects include a dry, itchy skin rash, headache, dizziness, abdominal pain, diarrhea, vomiting, peripheral neuropathy, and elevated hepatic transaminases.

Routine laboratory monitoring includes periodic liver function tests.

AGENTS USED AGAINST NONTUBERCULOUS MYCOBACTERIA

Cefoxitin

Cefoxitin, a cephamycin derivative, is a second-generation cephalosporin that, like other cephalosporins, inhibits cell wall synthesis by linking with penicillin-binding proteins to create an unstable bacterial cell wall. Resistance develops by alterations in penicillin-binding proteins.

Cefoxitin is often used in combination therapy for mycobacterial disease (Table 214-3). Pediatric dosing is based on disease severity, with a range of 80-160 mg/kg/day divided every 4-8 hr, not to exceed 12 g/day. Adult dosages are 1-2 g/day, not to exceed 12 g/day. Cefoxitin is available in IV or IM formulations. Increased dosing intervals are needed with renal insufficiency.

Adverse effects are primarily hematologic (eosinophilia, granulocytopenia, thrombocytopenia, hemolytic anemia), GI (nausea, vomiting, diarrhea with possible pseudomembranous colitis), and CNS-related (dizziness, vertigo). Potential additive adverse effects can occur when cefoxitin is used with aminoglycosides.

Routine laboratory monitoring with long-term use includes CBC and liver and renal function tests.

Doxycycline

Doxycycline is in the tetracycline family of antibiotics and has limited use in pediatrics. Like other tetracyclines, doxycycline acts to decrease protein synthesis by binding to the 30S ribosome and to transfer RNA. It can also cause alterations to the cytoplasmic membrane of susceptible bacteria.

Doxycycline is used to treat *M. fortuitum* (see Table 214-3). Although it can be used to treat *Mycobacterium marinum,* adult treatment failures have occurred. Pediatric dosing is based on age and weight. For children older than 8 yr of age who weigh <45 kg, the dosage is 4.4 mg/kg/day divided twice daily. Dosing for larger children and adults is 100 mg twice daily. Doxycycline is available as 50 and 100 mg capsules or tablets and in 25 mg/5 mL and 50 mg/5 mL suspensions.

Doxycycline use in children is limited by a permanent tooth discoloration, which becomes worse with long-term use. Other **adverse effects** include photosensitivity, liver and kidney dysfunction, and esophagitis, which can be minimized by dosing with large volumes of liquid. Doxycycline can decrease the effectiveness of oral contraceptives. Rifampin, carbamazepine, and phenytoin can decrease the concentration of doxycycline.

Routine laboratory monitoring with long-term use includes kidney and liver function tests as well as CBC.

Macrolides

Clarithromycin and azithromycin belong to the macrolide family of antibiotics. Clarithromycin is a methoxy derivative of erythromycin. Macrolides act by binding the 50S subunit of ribosomes, subsequently inhibiting protein synthesis. Resistance mechanisms for mycobacteria are not well understood but might involve binding site alterations. Clarithromycin appears to have synergistic antimycobacterial activity when combined with rifamycins, ethambutol, or clofazimine.

Clarithromycin is widely used for the prophylaxis and treatment of *M. avium* complex disease and also has activity against *Mycobacterium abscessus, M. fortuitum,* and *M. marinum.* Azithromycin has significantly different pharmacokinetics compared with other macrolide agents and has not been studied and is not indicated for mycobacterial infections. The pediatric dosage of clarithromycin for primary

Table 214-3 Treatment of Nontuberculous Mycobacteria Infections in Children

ORGANISM	DISEASE	TREATMENT
SLOWLY GROWING SPECIES		
Mycobacterium avium complex (MAC); *Mycobacterium haemophilum; Mycobacterium lentiflavum*	Lymphadenitis	Complete excision of lymph nodes; if excision is incomplete or disease recurs, clarithromycin or azithromycin plus ethambutol or rifampin (or rifabutin)
	Pulmonary infection	Clarithromycin or azithromycin plus ethambutol with rifampin or rifabutin (pulmonary resection in some patients who fail to respond to drug therapy). For severe disease, an initial course of amikacin or streptomycin often is included. Clinical data in adults support that 3×/wk therapy is as effective as daily therapy, with less toxicity. For patients with advanced disease, drugs should be given daily
	Disseminated	See text
Mycobacterium kansasii	Pulmonary infection	Rifampin plus ethambutol with isoniazid
	Osteomyelitis	Surgical debridement and prolonged antimicrobial therapy using rifampin plus ethambutol with isoniazid
Mycobacterium marinum	Cutaneous infection	Trimethoprim-sulfamethoxazole, clarithromycin, or doxycycline for mild disease; ethambutol with clarithromycin or rifampicin for extensive disease; extensive lesions might require surgical debridement.
Mycobacterium ulcerans	Cutaneous and bone infections	Daily intramuscular streptomycin and oral rifampin × 8 wk; excision of tissue
RAPIDLY GROWING SPECIES		
Mycobacterium fortuitum group	Cutaneous infection	Initial therapy for serious disease is amikacin plus cefoxitin or imipenem IV, followed by clarithromycin, doxycycline,* or trimethoprim-sulfamethoxazole or ciprofloxacin, orally, on the basis of in vitro susceptibility testing; might require surgical excision
	Catheter infection	Catheter removal and amikacin plus cefoxitin or imipenem, IV; clarithromycin, trimethoprim-sulfamethoxazole, or ciprofloxacin, orally, on the basis of in vitro susceptibility testing
Mycobacterium abscessus	Otitis media	Clarithromycin plus initial course of amikacin plus cefoxitin or imipenem; might require surgical debridement. Base regimen on in vitro susceptibility testing (50% are amikacin resistant)
	Pulmonary infection (in cystic fibrosis)	Serious disease, clarithromycin, amikacin, and cefoxitin on the basis of susceptibility testing; might require surgical resection
Mycobacterium chelonae	Catheter infection	Catheter removal and tobramycin (initially) plus clarithromycin
	Disseminated cutaneous infection	Tobramycin and ciprofloxacin or linezolid (initially) plus clarithromycin

*Doxycycline should not be given to children younger than 8 yr of age unless the benefits of therapy are greater than the risks of dental staining. Only 50% of isolates of *Mycobacterium marinum* are susceptible to doxycycline.

From American Thoracic Society/Infectious Disease Society of America Statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175:367-416, 2007.

prophylaxis of *M. avium* complex infections is 7.5 mg/kg/dose PO given twice daily, not to exceed 500 mg/day. This dosage is used for recurrent *M. avium* complex disease in combination with ethambutol and rifampin. The adult dosage is 500 mg PO twice daily to be used as a single agent for primary prophylaxis or as part of combination therapy with ethambutol and rifampin. Dosage adjustment is needed for renal insufficiency but not liver failure. Clarithromycin is available in 250 and 500 mg tablets and suspensions of 125 mg/5 mL and 250 mg/5 mL.

The primary **adverse effect** of clarithromycin is GI upset, including vomiting (6%), diarrhea (6%), and abdominal pain (3%). Other adverse effects include taste disturbances, headache, and QT prolongation if used with inhaled anesthetics, clotrimazole, antiarrhythmic agents, or azoles. Clarithromycin should be used cautiously in patients with renal insufficiency or liver failure.

Routine laboratory monitoring with prolonged use of clarithromycin includes periodic liver enzyme tests. Diarrhea is an early sign of pseudomembranous colitis.

Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP-SMX) is formulated in a fixed ratio of 1 part TMP to 5 parts SMX. SMX is a sulfonamide that inhibits synthesis of dihydrofolic acid by competitively inhibiting PABA, similar to dapsone. TMP blocks production of tetrahydrofolic acid and downstream biosynthesis of nucleic acids and protein by reversibly binding to dihydrofolate reductase. The combination of the 2 agents is synergistic and often bactericidal.

TMP-SMX is often used in combination therapy for mycobacterial disease (see Table 214-3). Oral or IV dosing for pediatric patients is TMP 15-20 mg/kg/day divided every 6-8 hr for serious infections and TMP 6-12 mg/kg/day divided every 12 hr for mild infections. The adult dosage is 160 mg TMP and 800 mg SMX every 12 hr. Dosage reduction may be needed in renal insufficiency. TMP-SMX is available in single-strength tablets (80/400 mg TMP/SMX) and double-strength tablets (160/800 mg TMP/SMX) and in a suspension of 40 mg TMP and 200 mg SMX per 5 mL.

The most common **adverse effect** with TMP-SMX is myelosuppression. It must be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency. Other adverse effects include renal abnormalities, rash, aseptic meningitis, GI disturbances (e.g., pancreatitis, diarrhea), and prolonged QT interval if coadministered with inhaled anesthetics, azoles, or macrolides.

Routine laboratory monitoring includes monthly CBC and periodic electrolytes and creatinine to monitor renal function.

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Chapter 215

Tuberculosis (*Mycobacterium tuberculosis*)

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Tuberculosis has caused human disease for more than 4,000 yr and is one of the most important infectious diseases worldwide. Tuberculosis was first recognized as a clinical entity in the early 19th century by Schönlein, who used the term *tuberculosis* in 1830, which was derived from the English term "tubercle," or lesion of consumption.

ETIOLOGY

There are 5 closely related mycobacteria in the *Mycobacterium tuberculosis* complex: *M. tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti,* and *Mycobacterium canetti. M. tuberculosis* is the most important cause of tuberculosis disease in humans. The tubercle bacilli are non-spore-forming, nonmotile, pleomorphic, weakly Gram-positive curved rods 1-5 µm long, typically slender and slightly bent. They can appear beaded or clumped under microscopy. They are obligate aerobes that grow in synthetic media containing glycerol as the carbon source and ammonium salts as the nitrogen source (Löwenstein-Jensen culture media). These mycobacteria grow best at 37-41°C (98.6-105.8°F), produce niacin, and lack pigmentation. A lipid-rich cell wall accounts for resistance to the bactericidal actions of antibody and complement. A hallmark of all mycobacteria is **acid fastness**—the capacity to form stable mycolate complexes with arylmethane dyes (crystal violet, carbolfuchsin, auramine, and rhodamine). They resist decoloration with ethanol and hydrochloric or other acids.

Mycobacteria grow slowly, with a generation time of 12-24 hr. Isolation from clinical specimens on solid synthetic media usually takes 3-6 wk, and drug susceptibility testing requires an additional 2-4 wk. Growth can be detected in 1-3 wk in selective liquid medium using radiolabeled nutrients (e.g., the BACTEC radiometric system), and drug susceptibilities can be determined in an additional 3-5 days. Once mycobacterial growth is detected, the species of mycobacteria present can be determined within hours using high-pressure liquid chromatography analysis (identifying the mycolic acid fingerprint of each species) or DNA probes. Restriction fragment length polymorphism profiling of mycobacteria is a helpful tool to study the epidemiology of tuberculosis strain relatedness in both outbreaks and routine epidemiology of tuberculosis in a community.

TERMINOLOGY: EXPOSURE, INFECTION, DISEASE

There are 3 major clinical stages of tuberculosis: exposure, infection, and disease. Exposure means a child has had significant contact ("shared the air") with an adult or adolescent with infectious tuberculosis but lacks proof of infection. In this stage, the tuberculin skin test (TST) or interferon-γ release assay (IGRA) result is negative, the chest radiograph is normal, the physical examination is normal, and the child lacks signs or symptoms of disease. However, the child may be infected and develop tuberculosis disease rapidly, as there may not have been enough time for the TST or IGRA to turn positive. Infection occurs when the individual inhales droplet nuclei containing *M. tuberculosis,* which survive intracellularly within the lung and associated lymphoid tissue. The hallmark of tuberculosis infection is a positive TST or IGRA result. In this stage, the child has no signs or symptoms, a normal physical examination is normal, and the chest radiograph is either normal or reveals only granuloma or calcifications in the lung parenchyma. Disease occurs when signs or symptoms or radiographic manifestations caused by *M. tuberculosis* become apparent. Not all infected individuals have the same risk of developing disease. An immunocompetent adult with untreated tuberculosis infection has approximately a 5-10% **lifetime** risk of developing disease. In contrast, an infected child younger than 1 yr of age has a 40% chance of developing disease within 9 mo.

EPIDEMIOLOGY

The World Health Organization estimates that tuberculosis remains the second leading cause of death from an infectious disease worldwide (after HIV) and that almost one-third of the world's population (2.5 billion people) is infected with *M. tuberculosis.* Approximately 95% of tuberculosis cases occur in the developing world. The highest numbers of cases are in Asia, Africa, and the eastern Mediterranean region. An estimated 8.7 million incident cases, 12 million prevalent cases, and 1.4 million deaths from tuberculosis occurred worldwide in 2013 (Fig. 215-1). The World Health Organization estimates that in 2013, there were 550,000 childhood cases and 80,000 tuberculosis-associated deaths among non–HIV-infected children; no estimates were given for HIV-infected children who likely bear an even greater burden of tuberculosis. The global burden of tuberculosis is influenced by several factors including: the HIV pandemic; the development of multidrug-resistant (MDR) tuberculosis; and the disproportionate access of populations in low-resource settings worldwide to both diagnostic tests and effective medical therapy.

In the United States, tuberculosis case rates decreased steadily during the first half of the 20th century, long before the advent of antituberculosis drugs, as a result of improved living conditions and, likely, genetic selection favoring persons resistant to developing disease. A resurgence of tuberculosis in the late 1980s was associated primarily with the HIV epidemic; transmission of the organism in congregate settings including healthcare institutions; disease occurring in recent immigrants; and poor conduct of community tuberculosis control. Since 1992, the number of reported cases of tuberculosis has decreased each year, reaching a record low of 9,582 cases (a rate of 3.0 cases per 100,000 persons) in 2013 (Fig. 215-2). Of the cases in 2011, 786 (6.1%) occurred in children younger than 15 yr of age (rate 1.3 per 100,000 population). Despite the overall declining rates nationwide, racial and ethnic minorities and foreign-born persons are disproportionately affected by tuberculosis in the United States. In 2011, the Centers for Disease Control and Prevention (CDC) reported that 84% of all tuberculosis cases were among ethnic minority populations. The tuberculosis case rate among Asians, blacks, and Hispanics were 25.0, 7.3, and 6.6 times as high as among non-Hispanic whites, respectively. The tuberculosis rate among foreign-born persons in the United States was 11.5 times higher than among U.S.-born persons and accounted for 62% of all tuberculosis cases in 2011 (Fig. 215-3). In the non-Hispanic white population tuberculosis rates are highest among the elderly who acquired the infection decades ago. In contrast, among nonwhite populations, tuberculosis is most common in young adults and children younger than 5 yr of age. The age range of 5-14 yr is often called the "favored age"; in all human populations, this group has the lowest rate of tuberculosis disease. Among adults, two-thirds of cases occur in men, but in children there is no significant difference by gender.

Among children in the United States, being born in a country with a high rate of tuberculosis and being a household contact to a domestic case of tuberculosis are the most important risk factors for having tuberculosis infection. Most children are infected with *M. tuberculosis* in their home by someone close to them, but outbreaks of childhood tuberculosis also have occurred in elementary and high schools, nursery schools, daycare centers and homes, churches, school buses, and sports teams. HIV-infected adults with tuberculosis can transmit *M. tuberculosis* to children, and children with HIV infection are at increased risk for developing tuberculosis after infection. Specific groups are at high risk for acquiring tuberculosis infection and progressing from latent tuberculosis infection (LTBI) to tuberculosis (Table 215-1).

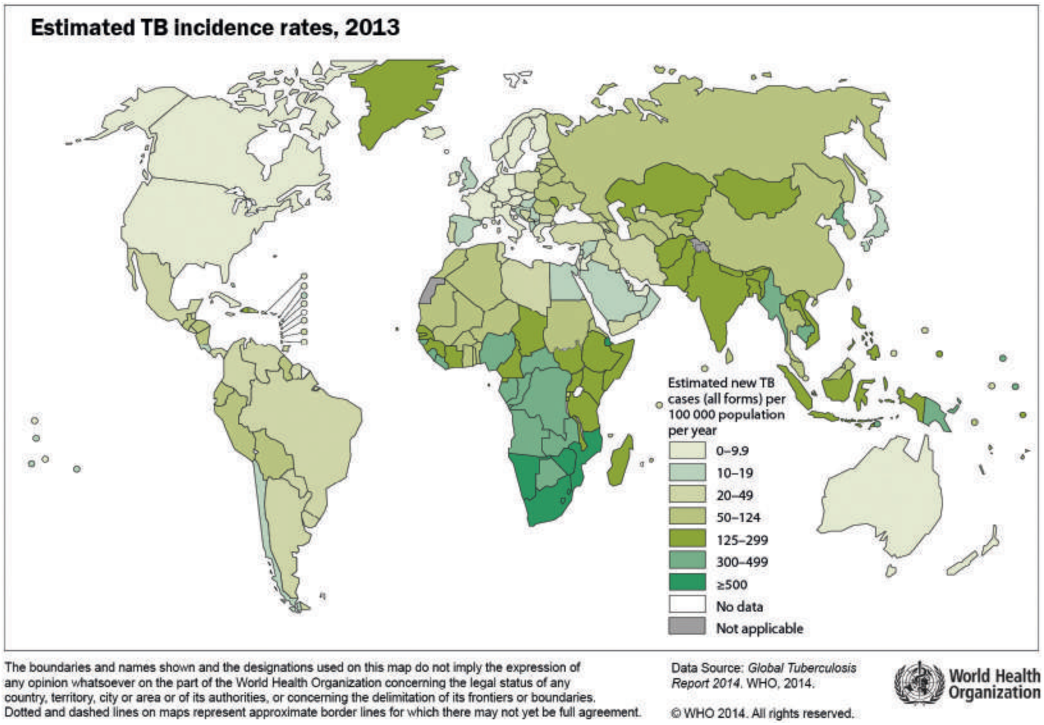

Figure 215-1 Estimated 2013 tuberculosis incidence rates. *(From The World Health Organization:* Global tuberculosis report 2014. *Geneva, 2014, World Health Organization.)*

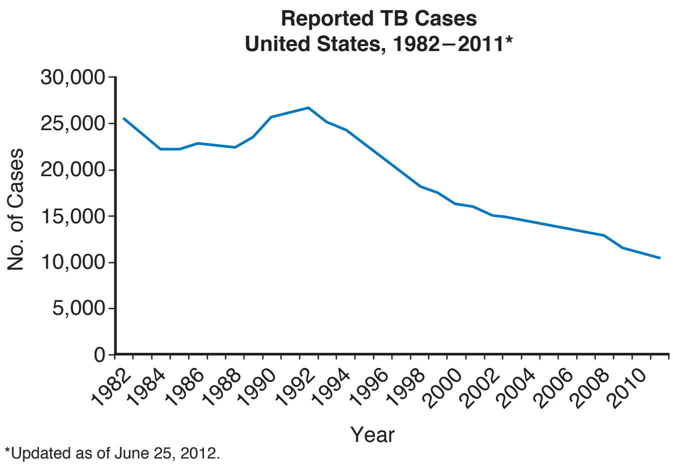

Figure 215-2 Reported tuberculosis cases in the United States for the years 1982-2011. *(From National Tuberculosis Surveillance System Highlights from 2011 an accompaniment to: Centers for Disease Control and Prevention:* Reported tuberculosis in the United States, 2011. *Atlanta, 2011, U.S. Department of Health and Human Services.)*

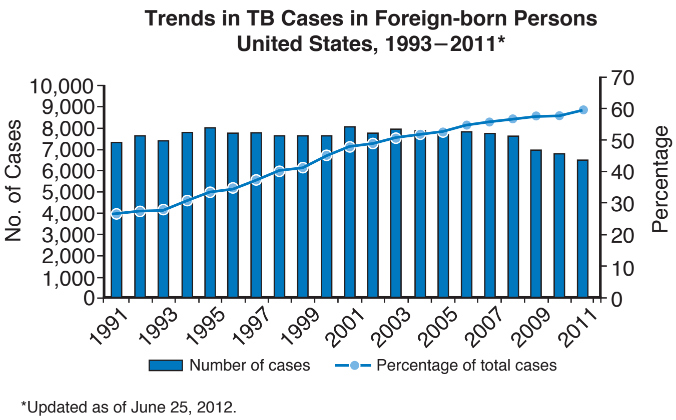

Figure 215-3 Tuberculosis cases, percentages, and case rates per 100,000 by Hispanic ethnicity and non-Hispanic race in the United States during the years 1991-2011. *(From the Centers for Disease Control and Prevention:* Reported tuberculosis in the United States, 2011. *Atlanta, 2011, U.S. Department of Health and Human Services.)*

The incidence of **drug-resistant** tuberculosis has increased dramatically throughout the world. The estimate for MDR tuberculosis is 4% globally, but rates as high as 26% have been reported in countries formerly part of the Soviet Union. A total of 127 cases of MDR tuberculosis were reported in the United States in 2011; of those, 85.8% were foreign-born (Fig. 215-4). MDR-TB is defined as resistance to at least isoniazid and rifampin; extensively drug-resistant tuberculosis includes MDR-TB plus resistance to any fluoroquinolone and at least 1 of 3 injectable drugs (kanamycin, capreomycin, amikacin).

TRANSMISSION

Transmission of *M. tuberculosis* is usually by inhalation of airborne mucus droplet nuclei, particles 1-5 µm in diameter that contain *M. tuberculosis.* Transmission rarely occurs by direct contact with an infected discharge or a contaminated fomite. The chance of transmission increases when the patient has a positive acid-fast smear of sputum, an extensive upper lobe infiltrate or cavity, copious production of thin sputum, and severe and forceful cough. Environmental factors such as poor air circulation enhance transmission. Most adults no longer transmit the organism within several days to 2 wks after beginning adequate chemotherapy, but some patients remain infectious for many weeks. Young children with tuberculosis rarely infect other children or adults. Tubercle bacilli are sparse in the endobronchial secretions of children with pulmonary tuberculosis, and cough is often absent or lacks the tussive force required to suspend infectious particles of the correct size. Children and adolescents with adult-type cavitary or endobronchial pulmonary tuberculosis can transmit the organism.

Airborne transmission of *M. bovis* and *M. africanum* also occurs. *M. bovis* can penetrate the gastrointestinal mucosa or invade the lymphatic tissue of the oropharynx when large numbers of the organism are ingested. Human infection with *M. bovis* is rare in developed countries as a result of the pasteurization of milk and effective tuberculosis-control programs for cattle. Approximately 30% of culture-proven childhood tuberculosis cases in San Diego, California, since 1990, have been caused by *M. bovis,* likely acquired by children when visiting Mexico or another country with suboptimal veterinary tuberculosis control programs.

PATHOGENESIS

The primary complex (or Ghon complex) of tuberculosis includes local infection at the portal of entry and the regional lymph nodes that drain the area. The lung is the portal of entry in >98% of cases. The tubercle bacilli multiply initially within alveoli and alveolar ducts. Most of the bacilli are killed, but some survive within nonactivated macrophages, which carry them through lymphatic vessels to the regional lymph nodes. When the primary infection is in the lung, the hilar lymph nodes usually are involved, although an upper lobe focus can drain into paratracheal nodes. The tissue reaction in the lung parenchyma and lymph nodes intensifies over the next 2-12 wk as the organisms grow in number and tissue **hypersensitivity** develops. The parenchymal portion of the primary complex often heals completely by fibrosis or calcification after undergoing caseous necrosis and encapsulation (Fig. 215-5). Occasionally, this portion continues to enlarge, resulting in focal pneumonitis and pleuritis. If caseation is intense, the center of the lesion liquefies and empties into the associated bronchus, leaving a residual cavity.

The foci of infection in the regional lymph nodes develop some fibrosis and encapsulation, but healing is usually less complete than in the parenchymal lesion. Viable *M. tuberculosis* can persist for decades within these foci. In most cases of initial tuberculosis infection, the lymph nodes remain normal in size. However, hilar and paratracheal lymph nodes that enlarge significantly as part of the host inflammatory reaction can encroach on a regional bronchus (Figs. 215-6 and 215-7).

Table 215-1	Groups at High Risk for Acquiring Tuberculosis Infection and Developing Disease in Countries with Low Incidence
RISK FACTORS FOR TUBERCULOSIS INFECTION	
Children exposed to high-risk adults	
Foreign-born persons from high-prevalence countries	
Homeless persons	
Persons who inject drugs	
Present and former residents or employees of correctional institutions, homeless shelters, and nursing homes	
Healthcare workers caring for high-risk patients (if infection control is not adequate)	
RISK FACTORS FOR PROGRESSION OF LATENT TUBERCULOSIS INFECTION TO TUBERCULOSIS DISEASE	
Infants and children ≤4 yr of age, especially those <2 yr of age	
Adolescents and young adults	
Persons coinfected with HIV	
Persons with skin test conversion in the past 1-2 yr	
Persons who are immunocompromised, especially in cases of malignancy and solid organ transplantation, immunosuppressive medical treatments including anti–tumor necrosis factor therapies, diabetes mellitus, chronic renal failure, silicosis, and malnutrition	
RISK FACTORS FOR DRUG-RESISTANT TUBERCULOSIS	
Personal or contact history of treatment for tuberculosis	
Contacts of patients with drug-resistant tuberculosis	
Birth or residence in a country with a high rate of drug resistance	
Poor response to standard therapy	
Positive sputum smears (acid-fast bacilli) or culture ≥2 mo after initiating appropriate therapy	

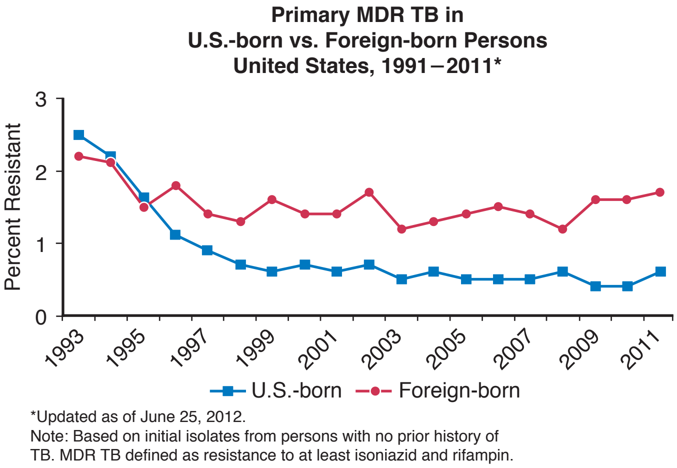

Figure 215-4 Primary isoniazid resistance in U.S.-born vs foreign-born persons in the United States during the years 1993-2011. *(From National Tuberculosis Surveillance System Highlights from 2011 an accompaniment to: Centers for Disease Control and Prevention:* Reported tuberculosis in the United States, 20011. *Atlanta, 2011, U.S. Department of Health and Human Services.)*

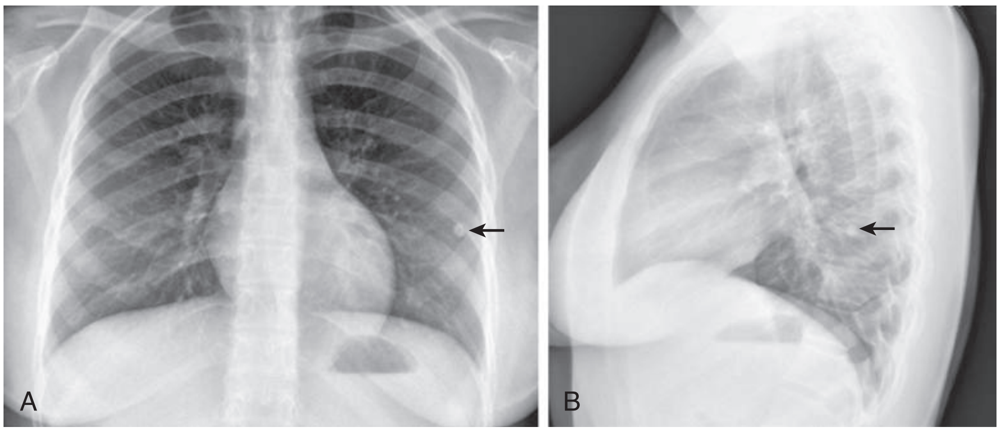

Figure 215-5 **A** and **B,** Posteroanterior and lateral chest radiograph images of an adolescent showing a 7 mm calcified granuloma in the left lower lobe *(arrows). (From Lighter J, Rigaud M: Diagnosing childhood tuberculosis: traditional and innovative modalities,* Curr Probl Pediatr Adolesc Health Care *39:55–88, 2009.)*

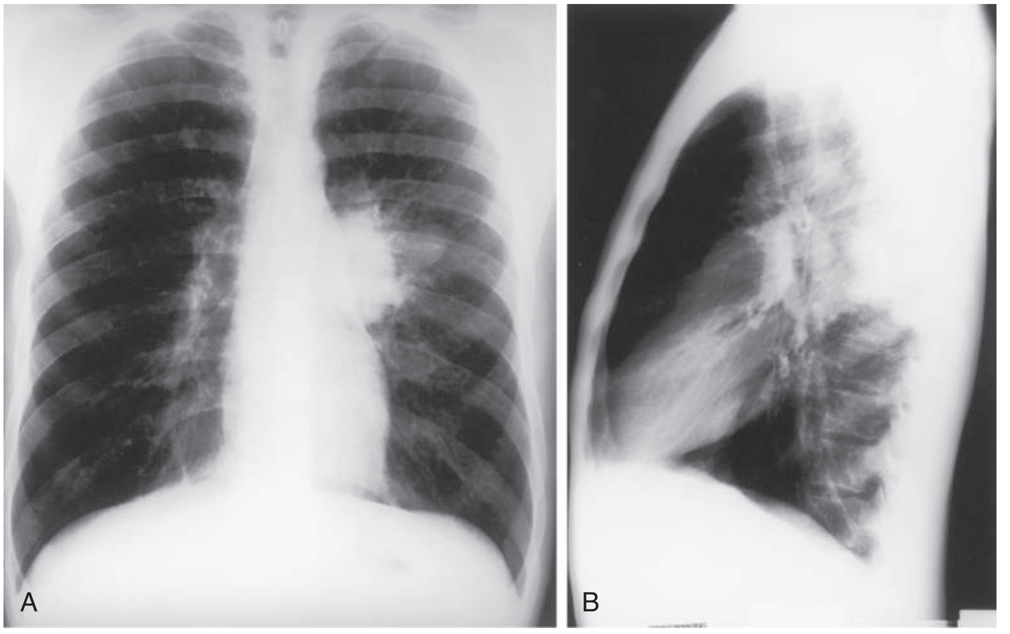

Figure 215-6 A 14 yr old child with proven primary tuberculosis. Frontal **(A)** and lateral **(B)** views of the chest show hyperinflation, prominent left hilar lymphadenopathy, and alveolar consolidation involving the posterior segment of the left upper lobe as well as the superior segment of the left lower lobe. *(From Hilton SVW, Edwards DK, editors:* Practical pediatric radiology*, ed 3, Philadelphia, 2003, Saunders, p. 334.)*

Figure 215-7 An 8 yr old child with a history of cough. A single frontal view of the chest shows marked right hilar and paratracheal lymphadenopathy with alveolar disease involving the right middle and lower lung fields. This was also a case of primary tuberculosis. *(From Hilton SVW, Edwards DK, editors:* Practical pediatric radiology*, ed 3, Philadelphia, 2003, Saunders, p. 335.)*

Figure 215-8 Right-sided hilar lymphadenopathy and collapse-consolidation lesions of primary tuberculosis in a 4 yr old child.

Partial obstruction of the bronchus caused by external compression can cause hyperinflation in the distal lung segment. Complete obstruction results in atelectasis. Inflamed caseous nodes can attach to the bronchial wall and erode through it, causing endobronchial tuberculosis or a fistula tract. The caseum causes complete obstruction of the bronchus. The resulting lesion is a combination of pneumonitis and atelectasis and has been called a **collapse-consolidation** or **segmental lesion** (Fig. 215-8).

During the development of the **primary complex** tubercle bacilli are carried to most tissues of the body through the blood and lymphatic vessels. Although seeding of the organs of the reticuloendothelial system is common, bacterial replication is more likely to occur in organs with conditions that favor their growth, such as the lung apices, brain, kidneys, and bones. **Disseminated tuberculosis** occurs if the number of circulating bacilli is large and the host's cellular immune response is inadequate. More often the number of bacilli is small, leading to clinically inapparent metastatic foci in many organs. These remote foci usually become encapsulated, but they may be the origin of both extrapulmonary tuberculosis and reactivation pulmonary tuberculosis.

The time between initial infection and clinically apparent disease is variable. Disseminated and meningeal tuberculosis are early manifestations, often occurring within 2-6 mo of acquisition. Significant lymph node or endobronchial tuberculosis usually appears within 3-9 mo. Lesions of the bones and joints take several years to develop, whereas renal lesions become evident decades after infection. Extrapulmonary manifestations are more common in children than adults and develop in 25-35% of children with tuberculosis, compared to approximately 10% of immunocompetent adults.

Pulmonary tuberculosis that occurs more than 1 yr after the primary infection is usually caused by endogenous regrowth of bacilli persisting in partially encapsulated lesions. This reactivation tuberculosis is rare

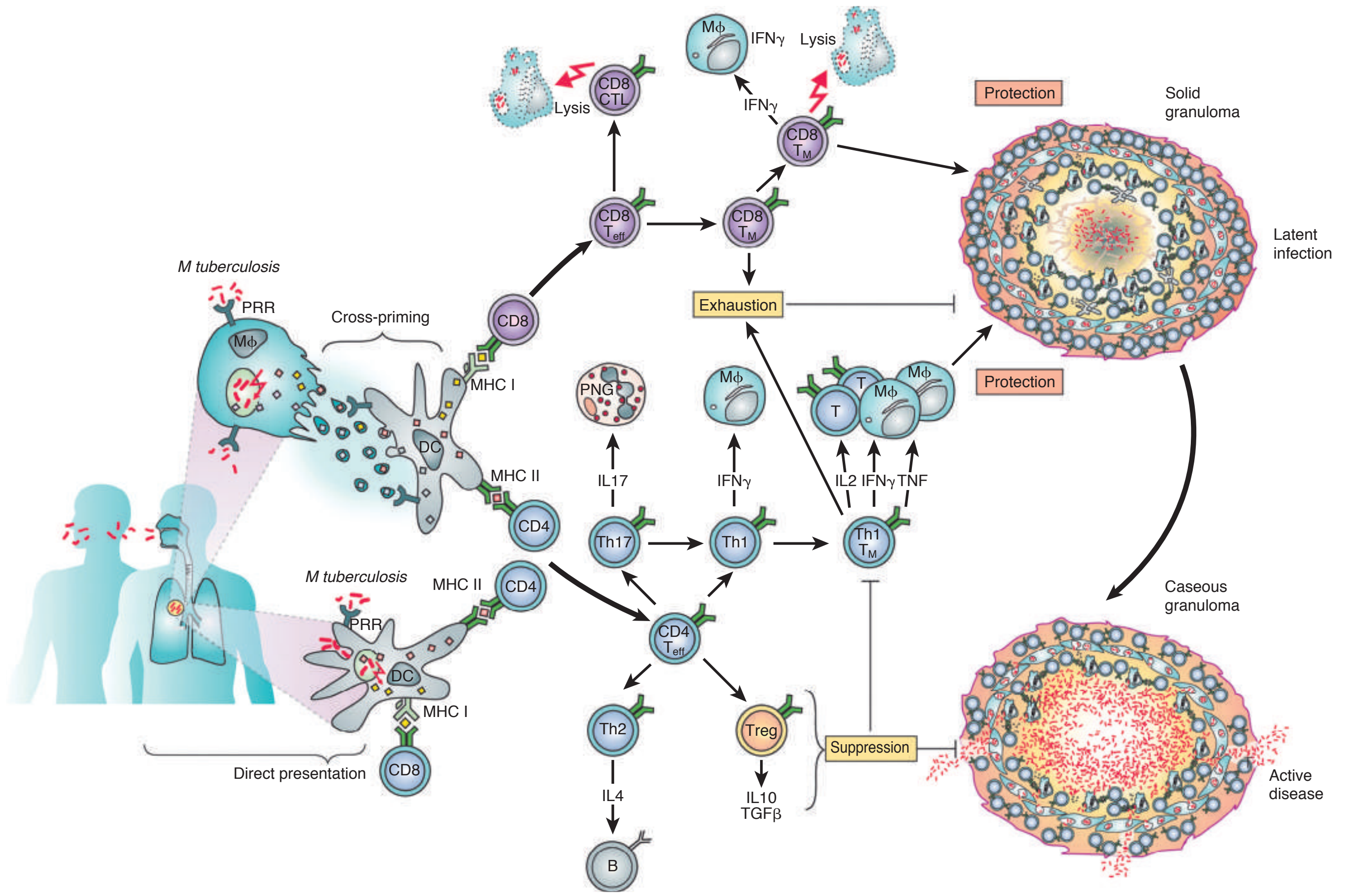

Figure 215-9 Overview of the immune response in tuberculosis. Control of *Mycobacterium tuberculosis* is mainly the result of productive teamwork between T-cell populations and macrophages (Mϕ). *M. tuberculosis* survives within macrophages and dendritic cells (DCs) inside the phagosomal compartment. Gene products of major histocompatibility complex (MHC) class II are loaded with mycobacterial peptides that are presented to CD4 T cells. CD8 T-cell stimulation requires loading of MHC I molecules by mycobacterial peptides in the cytosol, either by egression of mycobacterial antigens into the cytosol or cross-priming, by which macrophages release apoptotic bodies carrying mycobacterial peptides. These vesicles are taken up by DCs and peptides presented. The CD4 T-helper (Th) cells polarize into different subsets. DCs and macrophages express pattern recognition receptors (PRRs), which sense molecular patterns on pathogens. Th1 cells produce interleukin (IL)-2 for T-cell activation, interferon-γ (IFN-γ), or tumor necrosis factor (TNF) for macrophage activation. Th17 cells, which activate polymorphonuclear granulocytes (PNGs), contribute to the early formation of protective immunity in the lung after vaccination. Th2 cells and regulatory T cells (Treg) counterregulate Th1-mediated protection via IL4, transforming growth factor β (TGF-β), or IL-10. CD8 T cells produce IFN-γ and TNF, which activate macrophages. They also act as cytolytic T lymphocytes (CTL) by secreting perforin and granulysin, which lyse host cells and directly attack *M. tuberculosis*. These effector T cells (Teff) are succeeded by memory T cells T_M. T_M cells produce multiple cytokines, notably IL2, IFN-γ, and TNF. During active containment in solid granuloma, *M. tuberculosis* recesses into a dormant stage and is immune to attack. Exhaustion of T cells is mediated by interactions between T cells and DCs through members of the programmed death 1 system. Treg cells secrete IL-10 and TGF-β, which suppress Th1. This process allows resuscitation of *M. tuberculosis*, which leads to granuloma caseation and active disease. B, B cell. *(From Kaufman SHE, Hussey G, Lambert PH: New vaccines for tuberculosis.* Lancet *375:2110–2118, 2010.)*

in children but is common among adolescents and young adults. The most common form is an infiltrate or cavity in the apex of the upper lobes, where oxygen tension and blood flow are highest.

The risk for dissemination of *M. tuberculosis* is very high in HIV-infected persons. Reinfection also can occur in persons with advanced HIV or AIDS. In immunocompetent persons the response to the initial infection with *M. tuberculosis* usually provides protection against reinfection when a new exposure occurs. However, exogenous reinfection has been reported to occur in adults and children without immune compromise in highly endemic areas.

Immunity

Conditions that adversely affect cell-mediated immunity predispose to progression from tuberculosis infection to disease. Rare specific genetic defects associated with deficient cell-mediated immunity in response to mycobacteria include interleukin 12 receptor B1 deficiency and complete and partial interferon-γ (IFN-γ) receptor 1 chain deficiencies. Tuberculosis infection is associated with a humoral antibody response, which plays little known role in host defense. Shortly after infection, tubercle bacilli replicate in both free alveolar spaces and inactivated alveolar macrophages. Sulfatides in the mycobacterial cell wall inhibit fusion of the macrophage phagosome and lysosomes, allowing the organisms to escape destruction by intracellular enzymes. **Cell-mediated immunity** develops 2-12 wk after infection, along with tissue hypersensitivity (Fig. 215-9). After bacilli enter macrophages, lymphocytes that recognize mycobacterial antigens proliferate and secrete lymphokines and other mediators that attract other lymphocytes and macrophages to the area. Certain lymphokines activate macrophages, causing them to develop high concentrations of lytic enzymes that enhance their mycobactericidal capacity. A discrete subset of regulator helper and suppressor lymphocytes modulates the immune response. Development of specific cellular immunity prevents progression of the initial infection in most persons.

The pathologic events in the initial tuberculosis infection seem to depend on the balance among the mycobacterial antigen load; cell-mediated immunity, which enhances intracellular killing; and tissue

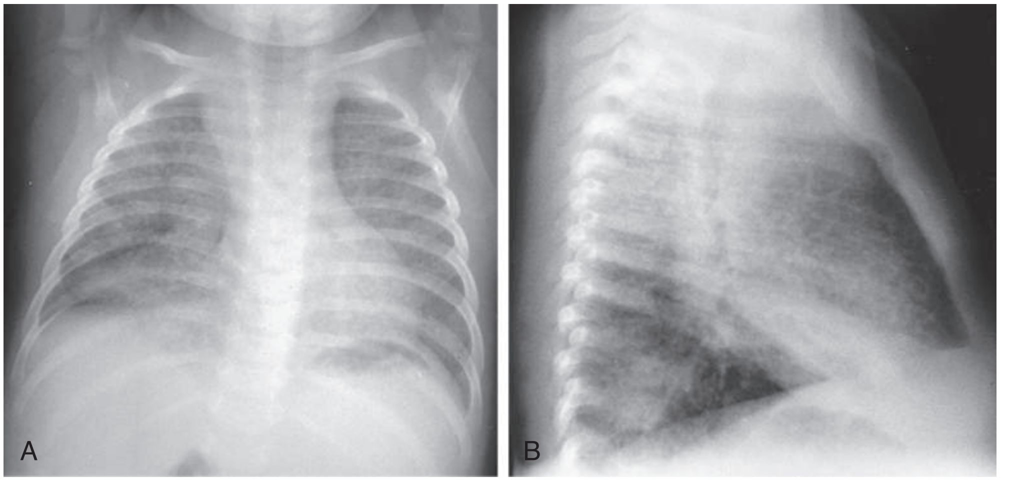

Figure 215-10 Posteroanterior (A) and lateral (B) chest radiographs of an infant with miliary tuberculosis. The child's mother had failed to complete treatment for pulmonary tuberculosis twice within 3 yr of this child's birth.

hypersensitivity, which promotes extracellular killing. When the antigen load is small and the degree of tissue sensitivity is high, granuloma formation results from the organization of lymphocytes, macrophages, and fibroblasts. When both antigen load and the degree of sensitivity are high, granuloma formation is less organized. Tissue necrosis is incomplete, resulting in formation of caseous material. When the degree of tissue sensitivity is low, as is often the case in infants or immunocompromised persons, the reaction is diffuse and the infection is not well contained, leading to dissemination and local tissue destruction. Tumor necrosis factor and other cytokines released by specific lymphocytes promote cellular destruction and tissue damage in susceptible persons.

CLINICAL MANIFESTATIONS

Primary Pulmonary Disease

The **primary complex** includes the parenchymal pulmonary focus and the regional lymph nodes. Approximately 70% of lung foci are subpleural, and localized pleurisy is common. The initial parenchymal inflammation usually is not visible on chest radiograph, but a localized, nonspecific infiltrate may be seen before the development of tissue hypersensitivity. All lobar segments of the lung are at equal risk for initial infection. Two or more primary foci are present in 25% of cases. The hallmark of primary tuberculosis in the lung is the relatively large size of the regional lymphadenitis compared with the relatively small size of the initial lung focus (see Figs. 215-6 to 215-8). As delayed-type hypersensitivity develops, the hilar lymph nodes continue to enlarge in some children, especially infants, compressing the regional bronchus and causing obstruction. The usual sequence is hilar lymphadenopathy, focal hyperinflation, and then atelectasis. The resulting radiographic shadows have been called collapse-consolidation or segmental tuberculosis (see Fig. 215-8). Rarely, inflamed caseous nodes attach to the endobronchial wall and erode through it, causing endobronchial tuberculosis or a fistula tract. The caseum causes complete obstruction of the bronchus, resulting in extensive infiltrate and collapse. Enlargement of the subcarinal lymph nodes can cause compression of the esophagus and, rarely, a bronchoesophageal fistula.

Most cases of tuberculous bronchial obstruction in children resolve fully with appropriate treatment. Occasionally, there is residual calcification of the primary focus or regional lymph nodes. The appearance of calcification implies that the lesion has been present for at least 6-12 mo. Healing of the segment can be complicated by scarring or contraction associated with cylindrical bronchiectasis, but this is rare.

Children can have lobar pneumonia without impressive hilar lymphadenopathy. If the primary infection is progressively destructive, liquefaction of the lung parenchyma can lead to formation of a thin-walled primary tuberculosis cavity. Rarely, bullous tuberculous lesions occur in the lungs and lead to pneumothorax if they rupture. Erosion of a parenchymal focus of tuberculosis into a blood or lymphatic vessel can result in dissemination of the bacilli and a **miliary pattern,** with small nodules evenly distributed on the chest radiograph (Fig. 215-10).

The symptoms and physical signs of primary pulmonary tuberculosis in children are surprisingly meager considering the degree of radiographic changes often present. When active case finding is performed, up to 50% of infants and children with radiographically moderate to severe pulmonary tuberculosis have no physical findings. Infants are more likely to experience signs and symptoms. Nonproductive cough and mild dyspnea are the most common symptoms. Systemic complaints such as fever, night sweats, anorexia, and decreased activity occur less often. Some infants have difficulty gaining weight or develop a true failure-to-thrive syndrome that often does not improve significantly until several months of effective treatment have been taken. Pulmonary signs are even less common. Some infants and young children with bronchial obstruction have localized wheezing or decreased breath sounds that may be accompanied by tachypnea or, rarely, respiratory distress. These pulmonary symptoms and signs are occasionally alleviated by antibiotics, suggesting bacterial superinfection.

Progressive Primary Pulmonary Disease

A rare but serious complication of tuberculosis in a child occurs when the primary focus enlarges steadily and develops a large caseous center. Liquefaction can cause formation of a primary cavity associated with large numbers of tubercle bacilli. The enlarging focus can slough necrotic debris into the adjacent bronchus, leading to further intrapulmonary dissemination. Significant signs or symptoms are common in locally progressive disease in children. High fever, severe cough with sputum production, weight loss, and night sweats are common. Physical signs include diminished breath sounds, rales, and dullness or egophony over the cavity. The prognosis for full recovery is excellent with appropriate therapy.

Reactivation Tuberculosis

Pulmonary tuberculosis in adults usually represents endogenous reactivation of a site of tuberculosis infection established previously in the body. This form of tuberculosis is rare in childhood but can occur in adolescence. Children with a healed tuberculosis infection acquired when they were younger than 2 yr of age rarely develop chronic reactivation pulmonary disease, which is more common in those who acquire the initial infection when they are older than 7 yr of age. The most common pulmonary sites are the original parenchymal focus, lymph nodes, or the apical seedings **(Simon foci)** established during the hematogenous phase of the early infection. This form of

tuberculosis disease usually remains localized in the lungs, as the established immune response prevents further extrapulmonary spread. The most common radiographic findings are extensive infiltrates or thick-walled cavities in the upper lobes.

Older children and adolescents with reactivation tuberculosis are more likely to experience fever, anorexia, malaise, weight loss, night sweats, productive cough, hemoptysis, and chest pain than children with primary pulmonary tuberculosis. However, physical examination findings usually are minor or absent, even when cavities or large infiltrates are present. Most signs and symptoms improve within several weeks of starting effective treatment, although the cough can last for several months. This form of tuberculosis may be highly contagious if there is significant sputum production and cough. The prognosis for full recovery is excellent with appropriate therapy.

Pleural Effusion

Tuberculous pleural effusions, which can be local or general, originate in the discharge of bacilli into the pleural space from a subpleural pulmonary focus or caseated lymph node. Asymptomatic local pleural effusion is so common in primary tuberculosis that it is considered as part of the primary complex. Larger and clinically significant effusions occur months to years after the primary infection. Tuberculous pleural effusion is uncommon in children younger than 6 yr of age and rare in children younger than 2 yr of age. Effusions are usually unilateral but can be bilateral. They are rarely associated with a segmental pulmonary lesion and are uncommon in disseminated tuberculosis. Often the radiographic abnormality is more extensive than would be suggested by physical findings or symptoms (Fig. 215-11).

Clinical onset of tuberculous pleurisy is often sudden, characterized by low to high fever, shortness of breath, chest pain on deep inspiration, and diminished breath sounds. The fever and other symptoms can last for several weeks after the start of antituberculosis chemotherapy. The TST is positive in only 70-80% of cases. The prognosis is excellent, but radiographic resolution often takes months. Scoliosis is a rare complication from a long-standing effusion.

Examination of pleural fluid and the pleural membrane is important to establish the diagnosis of tuberculous pleurisy. The pleural fluid is usually yellow and only occasionally tinged with blood. The specific gravity is usually 1.012-1.025, the protein level is usually 2-4 g/dL, and the glucose concentration may be low, although it is usually in the low-normal range (20-40 mg/dL). Typically there are several hundred to several thousand white blood cells per microliter, with an early predominance of polymorphonuclear cells followed by a high percentage of lymphocytes. Acid-fast smears of the pleural fluid are rarely positive. Cultures of the fluid are positive in <30% of cases. Biopsy of the pleural membrane is more likely to yield a positive acid-fast stain or culture, and granuloma formation can be demonstrated.

Figure 215-11 Pleural tuberculosis in a 16 yr old girl.

Pericardial Disease

The most common form of cardiac tuberculosis is pericarditis. It is rare, occurring in 0.5-4% of tuberculosis cases in children. Pericarditis usually arises from direct invasion or lymphatic drainage from subcarinal lymph nodes. The presenting symptoms are nonspecific, including low-grade fever, malaise, and weight loss. Chest pain is unusual in children. A pericardial friction rub or distant heart sounds with pulsus paradoxus may be present. The pericardial fluid is typically serofibrinous or hemorrhagic. Acid-fast smear of the fluid rarely reveals the organism, but cultures are positive in 30-70% of cases. The culture yield from pericardial biopsy may be higher, and the presence of granulomas often suggests the diagnosis. Partial or complete pericardiectomy may be required when constrictive pericarditis develops.

Lymphohematogenous (Disseminated) Disease

Tubercle bacilli are disseminated to distant sites, including liver, spleen, skin, and lung apices, in all cases of tuberculosis infection. Lymphohematogenous spread is usually asymptomatic. Rare patients experience protracted hematogenous tuberculosis caused by the intermittent release of tubercle bacilli as a caseous focus erodes through the wall of a blood vessel in the lung. The clinical picture subsequent to lymphohematogenous dissemination depends on the burden of organisms released from the primary focus to distant sites and the adequacy of the host's immune response. Although the clinical picture may be acute, more often it is indolent and prolonged, with spiking fever accompanying the release of organisms into the bloodstream. Multiple organ involvement is common, leading to hepatomegaly, splenomegaly, lymphadenitis in superficial or deep nodes, and papulonecrotic tuberculids appearing on the skin. Bones and joints or kidneys also can become involved. Meningitis occurs only late in the course of the disease. Early pulmonary involvement is surprisingly mild, but diffuse involvement becomes apparent with prolonged infection.

The most clinically significant form of disseminated tuberculosis is **miliary disease,** which occurs when massive numbers of tubercle bacilli are released into the bloodstream, causing disease in 2 or more organs. Miliary tuberculosis usually complicates the primary infection, occurring within 2-6 mo of the initial infection. Although this form of disease is most common in infants and young children, it is also found in adolescents and older adults, resulting from the breakdown of a previously healed primary pulmonary lesion. The clinical manifestations of miliary tuberculosis are protean, depending on the number of organisms that disseminate and where they lodge. Lesions are often larger and more numerous in the lungs, spleen, liver, and bone marrow than other tissues. Because this form of tuberculosis is most common in infants and malnourished or immunosuppressed patients, the host's immune incompetence likely plays a role in pathogenesis.

Rarely, the onset of miliary tuberculosis is explosive, and the patient can become gravely ill in several days. More often, the onset is insidious, with early systemic signs, including anorexia, weight loss, and low-grade fever. At this time, abnormal physical signs are usually absent. Generalized lymphadenopathy and hepatosplenomegaly develop within several weeks in approximately 50% of cases. The fever can then become higher and more sustained, although the chest radiograph usually is normal and respiratory symptoms are minor or absent. Within several more weeks, the lungs can become filled with tubercles, and dyspnea, cough, rales, or wheezing occur. The lesions of miliary tuberculosis are usually smaller than 2-3 mm in diameter when first visible on chest radiograph (see Fig. 215-10). The smaller lesions coalesce to form larger lesions and sometimes extensive infiltrates. As the pulmonary disease progresses, an alveolar-air block syndrome can result in frank respiratory distress, hypoxia, and pneumothorax, or pneumomediastinum. Signs or symptoms of meningitis or peritonitis are found in 20-40% of patients with advanced disease. Chronic or

recurrent headache in a patient with miliary tuberculosis usually indicates the presence of meningitis, whereas the onset of abdominal pain or tenderness is a sign of tuberculous peritonitis. **Cutaneous lesions** include papulonecrotic tuberculids, nodules, or purpura. Choroid tubercles occur in 13-87% of patients and are highly specific for the diagnosis of miliary tuberculosis. Unfortunately, the TST is nonreactive in up to 40% of patients with disseminated tuberculosis.

Diagnosis of disseminated tuberculosis can be difficult, and a high index of suspicion by the clinician is required. Often the patient presents with fever of unknown origin. Early sputum or gastric aspirate cultures have a low sensitivity. Biopsy of the liver or bone marrow with appropriate bacteriologic and histologic examinations more often yields an early diagnosis. The most important clue is usually history of recent exposure to an adult with infectious tuberculosis.

The resolution of miliary tuberculosis is slow, even with proper therapy. Fever usually declines within 2-3 wk of starting chemotherapy, but the chest radiographic abnormalities might not resolve for many months. Occasionally, corticosteroids hasten symptomatic relief, especially when air block, peritonitis, or meningitis is present. The prognosis is excellent with early diagnosis and adequate chemotherapy.

Upper Respiratory Tract Disease

Tuberculosis of the upper respiratory tract is rare in developed countries but is still observed in developing countries. Children with laryngeal tuberculosis have a croup-like cough, sore throat, hoarseness, and dysphagia. Most children with laryngeal tuberculosis have extensive upper lobe pulmonary disease, but occasional patients have primary laryngeal disease with a normal chest radiograph. Tuberculosis of the middle ear results from aspiration of infected pulmonary secretions into the middle ear or from hematogenous dissemination in older children. The most common signs and symptoms are painless unilateral otorrhea, tinnitus, decreased hearing, facial paralysis, and a perforated tympanic membrane. Enlargement of lymph nodes in the preauricular or anterior cervical chains can accompany this infection. Diagnosis is difficult, because stains and cultures of ear fluid are often negative, and histology of the affected tissue often shows a nonspecific acute and chronic inflammation without granuloma formation.

Lymph Node Disease

Tuberculosis of the superficial lymph nodes, often referred to as **scrofula,** is the most common form of extrapulmonary tuberculosis in children (Fig. 215-12). Historically, scrofula was usually caused by drinking unpasteurized cow's milk laden with *M. bovis.* Most current cases occur within 6-9 mo of initial infection by *M. tuberculosis,* although some cases appear years later. The tonsillar, anterior cervical, submandibular, and supraclavicular nodes become involved secondary to extension of a primary lesion of the upper lung fields or abdomen. Infected nodes in the inguinal, epitrochlear, or axillary regions result from regional lymphadenitis associated with tuberculosis of the skin or skeletal system. The nodes usually enlarge gradually in the early stages of lymph node disease. They are discrete, nontender, and firm but not hard. The nodes often feel fixed to underlying or overlying tissue. Disease is most often **unilateral,** but bilateral involvement can occur because of the crossover drainage patterns of lymphatic vessels in the chest and lower neck. As infection progresses, multiple nodes are infected, resulting in a mass of matted nodes. Systemic signs and symptoms other than a low-grade fever are usually absent. The TST is usually reactive, but the chest radiograph is normal in 70% of cases. The onset of illness is occasionally more acute, with rapid enlargement, tenderness, and fluctuance of lymph nodes and with high fever. The initial presentation is rarely a fluctuant mass with overlying cellulitis or skin discoloration.

Lymph node tuberculosis can resolve if left untreated but more often progresses to caseation and necrosis. The capsule of the node breaks down, resulting in the spread of infection to adjacent nodes. Rupture of the node usually results in a draining sinus tract that can require surgical removal. Tuberculous lymphadenitis can usually be diagnosed by fine-needle aspiration of the node and responds well to antituberculosis therapy, although the lymph nodes do not return to normal size

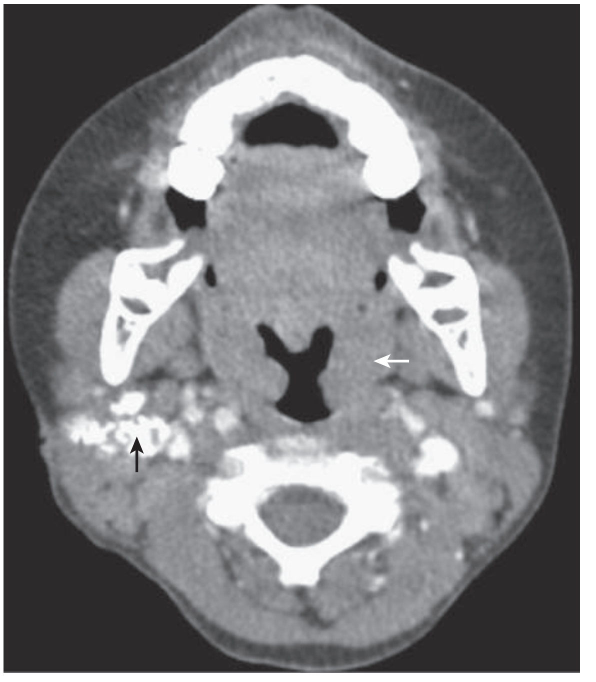

Figure 215-12 Axial CT image of the neck in an 8 yr old boy shows calcified right cervical lymphadenopathy *(black arrow)* with tonsillar swelling *(white arrow). (From Lighter J, Rigaud M: Diagnosing childhood tuberculosis: traditional and innovative modalities,* Curr Probl Pediatr Adolesc Health Care *39:55–88, 2009.)*

for months or even years. Surgical removal is not usually necessary and must be combined with antituberculosis medication, as the lymph node disease is only 1 part of a systemic infection.

A definitive diagnosis of tuberculous adenitis usually requires histologic or bacteriologic confirmation, which is best accomplished by fine-needle aspiration for culture, stain, and histology. If fine-needle aspiration is not successful in establishing a diagnosis, excisional biopsy of the involved node is indicated. Culture of lymph node tissue yields the organism in only approximately 50% of cases. Many other conditions can be confused with tuberculous adenitis, including infection caused by nontuberculous mycobacteria (NTM), cat-scratch disease *(Bartonella henselae),* tularemia, brucellosis, toxoplasmosis, pyogenic infection, or noninfectious causes, including tumor, branchial cleft cyst, and cystic hygroma. The most common problem is distinguishing infection caused by *M. tuberculosis* from lymphadenitis caused by NTM in geographic areas where NTM are common. Both conditions are usually associated with a normal chest radiograph and a reactive TST. An important clue to the diagnosis of tuberculous adenitis is an epidemiologic link to an adult with infectious tuberculosis. In areas where both diseases are common, culture of the involved tissue may be necessary to establish the exact cause of the disease.

Central Nervous System Disease

Tuberculosis of the central nervous system (CNS) is the most serious complication in children and is fatal without prompt and appropriate treatment. Tuberculous meningitis usually arises from the formation of a metastatic caseous lesion in the cerebral cortex or meninges that develops during the lymphohematogenous dissemination of the primary infection. This initial lesion increases in size and discharges small numbers of tubercle bacilli into the subarachnoid space. The resulting gelatinous exudate infiltrates the corticomeningeal blood vessels, producing inflammation, obstruction, and subsequent infarction of cerebral cortex. The brainstem is often the site of greatest involvement, which accounts for the commonly associated dysfunction of cranial nerves III, VI, and VII. The exudate also interferes with the normal flow of cerebrospinal fluid (CSF) in and out of the ventricular

system at the level of the basilar cisterns, leading to a communicating hydrocephalus. The combination of vasculitis, infarction, cerebral edema, and hydrocephalus results in the severe damage that can occur gradually or rapidly. Profound abnormalities in electrolyte metabolism from salt wasting or the syndrome of inappropriate antidiuretic hormone secretion also contribute to the pathophysiology of tuberculous meningitis.

Tuberculous meningitis complicates approximately 0.3% of untreated tuberculosis infections in children. It is most common in children between 6 mo and 4 yr of age. Occasionally, tuberculous meningitis occurs many years after the infection, when rupture of 1 or more of the subependymal tubercles discharges tubercle bacilli into the subarachnoid space. The clinical progression of tuberculous meningitis may be rapid or gradual. Rapid progression tends to occur more often in infants and young children, who can experience symptoms for only several days before the onset of acute hydrocephalus, seizures, and cerebral edema. More commonly, the signs and symptoms progress slowly over weeks and are divided into 3 stages.

The **1st stage** typically lasts 1-2 wk and is characterized by nonspecific symptoms such as fever, headache, irritability, drowsiness, and malaise. Focal neurologic signs are absent, but infants can experience a stagnation or loss of developmental milestones. The **2nd stage** usually begins more abruptly. The most common features are lethargy, nuchal rigidity, seizures, positive Kernig and Brudzinski signs, hypertonia, vomiting, cranial nerve palsies, and other focal neurologic signs. The accelerating clinical illness usually correlates with the development of hydrocephalus, increased intracranial pressure, and vasculitis. Some children have no evidence of meningeal irritation but can have signs of encephalitis, such as disorientation, movement disorders, or speech impairment. The **3rd stage** is marked by coma, hemi- or paraplegia, hypertension, decerebrate posturing, deterioration of vital signs, and eventually death.

The prognosis of tuberculous meningitis correlates most closely with the clinical stage of illness at the time treatment is initiated. The majority of patients in the 1st stage have an excellent outcome, whereas most patients in the 3rd stage who survive have permanent disabilities, including blindness, deafness, paraplegia, diabetes insipidus, or mental retardation. The prognosis for young infants is generally worse than for older children. It is imperative that antituberculosis treatment be considered for any child who develops basilar meningitis and hydrocephalus, cranial nerve palsy, or stroke with no other apparent etiology. Often the key to the correct diagnosis is identifying an adult who has infectious tuberculosis and is in contact with the child. Because of the short incubation period of tuberculous meningitis, the illness has not yet been diagnosed in the adult in many cases.

The diagnosis of tuberculous meningitis can be difficult early in its course, requiring a high degree of suspicion on the part of the clinician. The TST is nonreactive in up to 50% of cases, and 20-50% of children have a normal chest radiograph. The most important laboratory test for the diagnosis of tuberculous meningitis is examination and culture of the lumbar CSF. The CSF leukocyte count usually ranges from 10-500 cells/μL. Polymorphonuclear leukocytes may be present initially, but lymphocytes predominate in the majority of cases. The CSF glucose is typically <40 mg/dL but rarely <20 mg/dL. The protein level is elevated and may be markedly high (400-5,000 mg/dL) secondary to hydrocephalus and spinal block. Although the lumbar CSF is grossly abnormal, ventricular CSF can have normal chemistries and cell counts because this fluid is obtained from a site proximal to the inflammation and obstruction. During early stage 1, the CSF can resemble that of viral aseptic meningitis only to progress to the more-severe CSF profile over several weeks. The success of the microscopic examination of acid-fast–stained CSF and mycobacterial culture is related directly to the volume of the CSF sample. Examinations or culture of small amounts of CSF are unlikely to demonstrate *M. tuberculosis.* When 5-10 mL of lumbar CSF can be obtained, the acid-fast stain of the CSF sediment is positive in up to 30% of cases and the culture is positive in 50-70% of cases. Polymerase chain reaction (PCR) testing of the CSF can improve diagnosis. Cultures of other body fluids can help confirm the diagnosis.

Figure 215-13 MRI of brain of a 3 yr old child showing multiple pontine tuberculomas.

Radiographic studies can aid in the diagnosis of tuberculous meningitis. CT or MRI of the brain of patients with tuberculous meningitis may be normal during early stages of the disease. As disease progresses, basilar enhancement and communicating hydrocephalus with signs of cerebral edema or early focal ischemia are the most common findings. Some small children with tuberculous meningitis have one or several clinically silent tuberculomas, occurring most often in the cerebral cortex or thalamic regions.

Another manifestation of CNS tuberculosis is the **tuberculoma,** a tumor-like mass resulting from aggregation of caseous tubercles that usually manifests clinically as a brain tumor. Tuberculomas account for up to 30% of brain tumors in some areas of the world but are rare in North America. In adults tuberculomas are most often supratentorial, but in children they are often infratentorial, located at the base of the brain near the cerebellum (Fig. 215-13). Lesions are most often singular but may be multiple. The most common symptoms are headache, fever, focal neurologic findings, and convulsions. The TST is usually reactive, but the chest radiograph is usually normal. Surgical excision is sometimes necessary to distinguish tuberculoma from other causes of brain tumor. However, surgical removal is not necessary because most tuberculomas resolve with medical management. Corticosteroids are usually administered during the 1st few wk of treatment or in the immediate postoperative period to decrease cerebral edema. On CT or MRI of the brain, tuberculomas usually appear as discrete lesions with a significant amount of surrounding edema. Contrast medium enhancement is often impressive and can result in a ring-like lesion. Since the advent of CT, the paradoxical development of tuberculomas in patients with tuberculous meningitis who are receiving ultimately effective chemotherapy has been recognized. The cause and nature of these tuberculomas are poorly understood, but they do not represent failure of antimicrobial treatment. This phenomenon should be considered whenever a child with tuberculous meningitis deteriorates or develops focal neurologic findings while on treatment. Corticosteroids can alleviate the occasionally severe clinical signs and symptoms that occur. These lesions can persist for months or years.

Cutaneous Disease

Cutaneous tuberculosis is rare in the United States, but occurs worldwide and accounts for 1-2% of tuberculosis (see Chapter 665).

Bone and Joint Disease

Bone and joint infection complicating tuberculosis is most likely to involve the vertebrae. The classic manifestation of tuberculous spondylitis is progression to Pott disease, in which destruction of the vertebral bodies leads to gibbus deformity and kyphosis (see Chapter 679.4). Skeletal tuberculosis is a late complication of tuberculosis and has become a rare entity since the availability of antituberculosis therapy but is more likely to occur in children than in adults. Tuberculous bone lesions can resemble pyogenic and fungal infections or bone tumors. Multifocal bone involvement can occur. A bone biopsy is essential to confirm the diagnosis. Surgical intervention is generally not necessary for cure and prognosis is excellent with adequate medical treatment.

Abdominal and Gastrointestinal Disease

Tuberculosis of the oral cavity or pharynx is quite unusual. The most common lesion is a painless ulcer on the mucosa, palate, or tonsil with enlargement of the regional lymph nodes. Tuberculosis of the parotid gland has been reported rarely in endemic countries. Tuberculosis of the esophagus is rare in children but may be associated with a tracheoesophageal fistula in infants. These forms of tuberculosis are usually associated with extensive pulmonary disease and swallowing of infectious respiratory secretions. They can occur in the absence of pulmonary disease, by spread from mediastinal or peritoneal lymph nodes.

Tuberculous peritonitis occurs most often in young men and is uncommon in adolescents and rare in children. Generalized peritonitis can arise from subclinical or miliary hematogenous dissemination. Localized peritonitis is caused by direct extension from an abdominal lymph node, intestinal focus, or genitourinary tuberculosis. Rarely, the lymph nodes, omentum, and peritoneum become matted and can be palpated as a doughy irregular nontender mass. Abdominal pain or tenderness, ascites, anorexia, and low-grade fever are typical manifestations. The TST is usually reactive. The diagnosis can be confirmed by paracentesis with appropriate stains and cultures, but this procedure must be performed carefully to avoid entering a bowel that is adherent to the omentum.

Tuberculous enteritis is caused by hematogenous dissemination or by swallowing tubercle bacilli discharged from the patient's own lungs. The jejunum and ileum near Peyer patches and the appendix are the most common sites of involvement. The typical findings are shallow ulcers that cause pain, diarrhea or constipation, weight loss, and low-grade fever. Mesenteric adenitis usually complicates the infection. The enlarged nodes can cause intestinal obstruction or erode through the omentum to cause generalized peritonitis. The clinical presentation of tuberculous enteritis is nonspecific, mimicking other infections and conditions that cause diarrhea. The disease should be suspected in any child with chronic gastrointestinal complaints and a reactive TST or positive IGRA. Biopsy, acid-fast stain, and culture of the lesions are usually necessary to confirm the diagnosis.

Genitourinary Disease

Renal tuberculosis is rare in children, because the incubation period is several years or longer. Tubercle bacilli usually reach the kidney during lymphohematogenous dissemination. The organisms often can be recovered from the urine in cases of miliary tuberculosis and in some patients with pulmonary tuberculosis in the absence of renal parenchymal disease. In true renal tuberculosis, small caseous foci develop in the renal parenchyma and release *M. tuberculosis* into the tubules. A large mass develops near the renal cortex that discharges bacteria through a fistula into the renal pelvis. Infection then spreads locally to the ureters, prostate, or epididymis. Renal tuberculosis is often clinically silent in its early stages, marked only by sterile pyuria and microscopic hematuria. Dysuria, flank or abdominal pain, and gross hematuria develop as the disease progresses. Superinfection by other bacteria is common and can delay recognition of the underlying tuberculosis. Hydronephrosis or ureteral strictures can complicate the disease. Urine cultures for *M. tuberculosis* are positive in 80-90% of cases, and acid-fast stains of large volumes of urine sediment are positive in 50-70% of cases. The TST is nonreactive in up to 20% of patients. A pyelogram or CT scan often reveals mass lesions, dilation of the proximal ureters, multiple small filling defects, and hydronephrosis if ureteral stricture is present. Disease is most often unilateral.

Tuberculosis of the genital tract is uncommon in prepubescent boys and girls. This condition usually originates from lymphohematogenous spread, although it can be caused by direct spread from the intestinal tract or bone. Adolescent girls can develop genital tract tuberculosis during the primary infection. The fallopian tubes are most often involved (90-100% of cases), followed by the endometrium (50%), ovaries (25%), and cervix (5%). The most common symptoms are lower abdominal pain and dysmenorrhea or amenorrhea. Systemic manifestations are usually absent, and the chest radiograph is normal in the majority of cases. The TST is usually reactive. Genital tuberculosis in adolescent boys causes epididymitis or orchitis. The condition usually manifests as a unilateral nodular painless swelling of the scrotum. Involvement of the glans penis is extremely rare. Genital abnormalities and a positive TST in an adolescent boy or girl suggest genital tract tuberculosis.

Pregnancy and the Newborn

Pulmonary and particularly extrapulmonary tuberculosis other than lymphadenitis in a pregnant woman is associated with increased risk for prematurity, fetal growth retardation, low birthweight, and perinatal mortality. Congenital tuberculosis is rare because the most common result of female genital tract tuberculosis is infertility. Primary infection in the mother just before or during pregnancy is more likely to cause congenital infection than is reactivation of a previous infection. Congenital transmission usually occurs from a lesion in the placenta through the umbilical vein, when tubercle bacilli infect the fetal liver, where a primary focus with periportal lymph node involvement can occur. Organisms pass through the liver into the main fetal circulation and infect many organs. The bacilli in the lung usually remain dormant until after birth, when oxygenation and pulmonary circulation increase significantly. Congenital tuberculosis can also be caused by aspiration or ingestion of infected amniotic fluid. However, the most common route of infection for the neonate is postnatal airborne transmission from an adult with infectious pulmonary tuberculosis.

Perinatal Disease

Symptoms of congenital tuberculosis may be present at birth but more commonly begin by the 2nd or 3rd wk of life. The most common signs and symptoms are respiratory distress, fever, hepatic or splenic enlargement, poor feeding, lethargy or irritability, lymphadenopathy, abdominal distention, failure to thrive, ear drainage, and skin lesions. The clinical manifestations vary in relation to the site and size of the caseous lesions. Many infants have an abnormal chest radiograph, most often with a miliary pattern. Some infants with no pulmonary findings early in the course of the disease later develop profound radiographic and clinical abnormalities. Hilar and mediastinal lymphadenopathy and lung infiltrates are common. Generalized lymphadenopathy and meningitis occur in 30-50% of patients.

The clinical presentation of tuberculosis in newborns is similar to that caused by bacterial sepsis and other congenital infections, such as syphilis, toxoplasmosis, and cytomegalovirus. The diagnosis should be suspected in an infant with signs and symptoms of bacterial or congenital infection whose response to antibiotic and supportive therapy is poor and in whom evaluation for other infections is unrevealing. The most important clue for rapid diagnosis of congenital tuberculosis is a maternal or family history of tuberculosis. Often, the mother's disease is discovered only after the neonate's diagnosis is suspected. The infant's TST is negative initially but can become positive in 1-3 mo. A positive acid-fast stain of an early morning gastric aspirate from a newborn usually indicates tuberculosis. Direct acid-fast stains on middle-ear discharge, bone marrow, tracheal aspirate, or biopsy tissue (especially liver) can be useful. The CSF should be examined, cultured and sent for PCR testing. The mortality rate of congenital tuberculosis remains very high because of delayed diagnosis; many children have a complete recovery if the diagnosis is made promptly and adequate chemotherapy is started.

Disease in HIV-Infected Children

Most cases of tuberculosis in HIV-infected children are seen in developing countries. However, the rate of tuberculosis disease in untreated HIV-infected children is 30 times higher than in non–HIV-infected children in the United States. Establishing the diagnosis of tuberculosis in an HIV-infected child may be difficult, because TST reactivity can be absent (also with a negative IGRA), culture confirmation is difficult, and the clinical features of tuberculosis are similar to many other HIV-related infections and conditions. Tuberculosis in HIV-infected children is often more severe, progressive, and likely to occur in extrapulmonary sites. Radiographic findings are similar to those in children with normal immune systems, but lobar disease and lung cavitation are more common. Nonspecific respiratory symptoms, fever, and weight loss are the most common complaints. Rates of drug-resistant tuberculosis tend to be higher in HIV-infected adults and probably are also higher in HIV-infected children. Recurrent disease and relapse occur more frequently in HIV-infected children. The prognosis generally is good if tuberculosis disease is not far advanced at diagnosis and appropriate antituberculosis drugs are available.

The mortality rate of HIV-infected children with tuberculosis is high, especially as the CD4 lymphocyte numbers decrease. In adults, the host immune response to tuberculosis infection appears to enhance HIV replication and accelerate the immune suppression caused by HIV. Increased mortality rates are attributed to progressive HIV infection rather than tuberculosis. Therefore, HIV-infected children with potential exposures and/or recent infection should be promptly evaluated and treated for tuberculosis. Conversely, all children with tuberculosis disease should be tested for HIV infection.

Children with HIV infection who are given highly active antiretroviral therapy (HAART) are at high risk of developing immune reconstitution inflammatory syndrome (IRIS). IRIS should be suspected in patients who experience a worsening of tuberculosis symptoms while on antituberculosis therapy (paradoxical IRIS) or who develop new-onset tuberculosis symptoms and radiographic findings after initiation of HAART (unmasking IRIS). Factors suggesting IRIS are temporal association (within 3 mo of starting HAART), unusual clinical manifestations, unexpected clinical course, exclusion of alternative explanations, evidence of preceding immune restoration (rise in CD4 lymphocyte count), and fall in HIV viral load.

The most common clinical manifestations of IRIS in children are fever, cough, new skin lesions, enlarging lymph nodes in the thorax or neck, and appearance or enlargement of tuberculomas in the brain, with or without accompanying meningitis. The treatment of IRIS in HIV-positive children with tuberculosis should be undertaken by a clinician with specific expertise in the treatment of tuberculosis.

DIAGNOSTIC TOOLS

Tuberculin Skin Testing

The development of delayed-type hypersensitivity in most persons infected with the tubercle bacillus makes the TST a useful diagnostic tool. The **Mantoux TST** is the intradermal injection of 0.1 mL purified protein derivative stabilized with Tween 80. T cells sensitized by prior infection are recruited to the skin, where they release lymphokines that induce induration through local vasodilation, edema, fibrin deposition, and recruitment of other inflammatory cells to the area. The amount of induration in response to the test should be measured by a trained person 48-72 hr after administration. In some patients, the onset of induration is longer than 72 hr after placement; this is also a positive result. Immediate hypersensitivity reactions to tuberculin or other constituents of the preparation are short-lived (<24 hr) and not considered a positive result. Tuberculin sensitivity develops 3 wk to 3 mo (most often in 4-8 wk) after inhalation of organisms.

Host-related factors, including very young age, malnutrition, immunosuppression by disease or drugs, viral infections (measles, mumps, varicella, influenza), vaccination with live-virus vaccines, and overwhelming tuberculosis, can depress the skin test reaction in a child infected with *M. tuberculosis*. Corticosteroid therapy can decrease the reaction to tuberculin, but the effect is variable. TST done at the time of initiating corticosteroid therapy is usually reliable. Approximately 10% of immunocompetent children with tuberculosis disease (up to 50% of those with meningitis or disseminated disease) do not react initially to purified protein derivative; most become reactive after several months of antituberculosis therapy. False-positive reactions to tuberculin can be caused by cross-sensitization to antigens of NTM, which generally are more prevalent in the environment as one approaches the equator. These crossreactions are usually transient over months to years and produce <10-12 mm of induration. Previous vaccination with bacille Calmette-Guérin (BCG) also can cause a reaction to a TST, especially if a person has received 2 or more BCG vaccinations. Approximately 50% of the infants who receive a BCG vaccine never develop a reactive TST, and the reactivity usually wanes in 2-3 yr in those with initially positive skin test results. Older children and adults who receive a BCG vaccine are more likely to develop tuberculin reactivity, but most lose the reactivity by 5-10 yr after vaccination. When skin test reactivity is present, it usually causes <10 mm of induration, although larger reactions occur in some persons.

The appropriate size of induration indicating a positive Mantoux TST result varies with related epidemiologic and risk factors. In children with no risk factors for tuberculosis, skin test reactions are usually false-positive results. The American Academy of Pediatrics and the CDC discourage routine testing of all children and recommend targeted tuberculin testing of children at risk identified through periodic screening questionnaires (see Tables 215-1 and 215-2). Possible exposure to an adult with or at high risk for infectious pulmonary

Table 215-2	Tuberculin Skin Test Recommendations for Infants, Children, and Adolescents*

CHILDREN FOR WHOM IMMEDIATE TST OR IGRA IS INDICATED†:

- Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation)
- Children with radiographic or clinical findings suggesting tuberculosis disease
- Children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries from the former Soviet Union), including international adoptees
- Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries‡
- Children who should have annual TST or IGRA:
  - Children infected with HIV

CHILDREN AT INCREASED RISK FOR PROGRESSION OF LTBI TO TUBERCULOSIS DISEASE

Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, and congenital or acquired immunodeficiencies deserve special consideration. Without recent exposure, these children are not at increased risk of acquiring tuberculosis infection. Underlying immunodeficiencies associated with these conditions theoretically would enhance the possibility for progression to severe disease. Initial histories of potential exposure to tuberculosis should be included for all of these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST should be considered. **An initial TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged steroid administration, use of tumor necrosis factor-α antagonists, or immunosuppressive therapy in any child requiring these treatments.**

*Bacille Calmette-Guérin immunization is not a contraindication to a TST.
†Beginning as early as 3 mo of age.
‡If the child is well and has no history of exposure, the TST or IGRA should be delayed up to 10 wk after return.
HIV, human immunodeficiency virus; IGRA indicates interferon-γ release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 740.*

Table 215-3	Definitions of Positive Tuberculin Skin Test Results in Infants, Children, and Adolescents*
INDURATION ≥5 MM	
Children in close contact with known or suspected contagious people with tuberculosis disease	
Children suspected to have tuberculosis disease:	
• Findings on chest radiograph consistent with active or previously tuberculosis disease	
• Clinical evidence of tuberculosis disease[†]	
Children receiving immunosuppressive therapy[‡] or with immunosuppressive conditions, including HIV infection	
INDURATION ≥10 MM	
Children at increased risk of disseminated tuberculosis disease:	
• Children younger than 4 yr of age	
• Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition (see Table 215-2)	
Children with increased exposure to tuberculosis disease:	
• Children born in high-prevalence regions of the world	
• Children often exposed to adults who are HIV infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized, or migrant farm workers	
• Children who travel to high-prevalence regions of the world	
INDURATION ≥15 MM	
Children ≥4 yr of age without any risk factors	

*These definitions apply regardless of previous bacille Calmette-Guérin (BCG) immunization; erythema at TST site does not indicate a positive test result. Tests should be read at 48-72 hr after placement.
[†]Evidence by physical examination or laboratory assessment that would include tuberculosis in the working differential diagnosis (e.g., meningitis).
[‡]Including immunosuppressive doses of corticosteroids or tumor necrosis factor-α antagonists.
HIV, human immunodeficiency virus; TST, tuberculin skin test.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 737.*

tuberculosis is the most crucial risk factor for children. Reaction size limits for determining a positive tuberculin test result vary with the person's risk for infection (Table 215-3). In those at highest risk of progression to tuberculosis disease, TST sensitivity is most important whereas specificity is more important for persons at low risk of progression.

Interferon-γ Release Assays

Two blood tests (T-SPOT.*TB* and QuantiFERON-TB) detect IFN-γ generation by the patient's T cells in response to specific *M. tuberculosis* antigens (ESAT-6, CFP-10, and TB7.7). The QuantiFERON-TB test measures whole blood concentrations of IFN-γ, and the T-SPOT.*TB* test measures the number of lymphocytes/monocytes producing IFN-γ. The test antigens are not present on *M. bovis*–BCG and *Mycobacterium avium* complex, the major group of environmental mycobacteria, so one would expect higher specificity compared with the TST and fewer false-positive results. Both IGRAs have internal positive and negative controls. Like the TST, IGRAs cannot differentiate between tuberculosis infection and disease. Two clear advantages of the IGRAs are the need for only 1 patient encounter (vs 2 with the TST) and the lack of crossreaction with BCG vaccination and most other mycobacteria.

IGRAs should be interpreted with caution when used for children younger than 5 yr of age and immunocompromised patients owing to the relative lack of data and the increased propensity for indeterminate results in these groups, making TSTs preferred in these populations. IGRAs are preferred and TSTs are considered acceptable in the BCG-immunized older child (≥5 yr) and in those ≥5 yr who are unlikely to return for TST reading. Both TST and IGRA testing should be obtained in children with an indeterminate initial and repeat IGRA testing; in

Table 215-4	Recommendations for Use of the Tuberculin Skin Test and an Interferon-γ Release Assay in Children
TST preferred, IGRA acceptable	
• Children <5 yr of age*	
IGRA preferred, TST acceptable	
• Children >5 yr of age who have received the BCG vaccine	
• Children >5 yr of age who are unlikely to return for TST reading	
TST and IGRA should be considered when:	
• The initial and repeat IGRA are indeterminate	
• The initial test (TST or IGRA) is negative and:	
• Clinical suspicion for tuberculosis disease is moderate to high[†]	
• Risk of progression and poor outcome is high[†]	
• The initial TST is positive and:	
• >5 yr of age and history of BCG vaccination	
• Additional evidence needed to increase compliance	
• Nontuberculous mycobacterial disease is suspected	

*Positive result of either test is considered significant in these groups.
[†]IGRAs should not be used in children younger than 2 yr of age unless tuberculosis disease is suspected. In children 2-4 yr of age, there are limited data about the usefulness of IGRAs in determining tuberculosis infection, but IGRA testing can be performed if tuberculosis disease is suspected.
IGRA indicates interferon-γ release assay; TST, tuberculin skin test.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 744.*

those in whom initial TST or IGRA testing is negative and the suspicion for tuberculosis disease or risk of progression to disease is high; in those ≥5 yr who have a positive TST and have received the BCG vaccine; in those whose family is reluctant to treat infection based on a TST result alone; and in those in whom nontuberculous mycobacterial disease is suspected (Table 215-4). As most studies have not shown a consistent, significant difference between the IGRAs, the CDC recommends that the assays may be used interchangeably.

MYCOBACTERIAL SAMPLING, SUSCEPTIBILITY AND CULTURE

The most specific confirmation of pulmonary tuberculosis is isolation of *M. tuberculosis* from a clinical sample. Sputum specimens for culture should be collected from adolescents and older children who are able to expectorate. Induced sputum with a jet nebulizer, inhaled saline and chest percussion followed by nasopharyngeal suctioning is effective in children as young as 1 yr of age. Sputum induction provides samples for both culture and acid-fast bacilli staining. The traditional culture specimen in young children is the early morning gastric acid obtained before the child has arisen and peristalsis has emptied the stomach of the pooled respiratory secretions that have been swallowed overnight. However, even under optimal conditions, 3 consecutive morning gastric aspirates yield the organisms in <50% of cases. The culture yield from bronchoscopy is even lower, but this procedure can demonstrate the presence of endobronchial disease or a fistula. Negative cultures never exclude the diagnosis of tuberculosis in a child. The presence of a positive TST or IGRA, an abnormal chest radiograph consistent with tuberculosis, and history of exposure to an adult with infectious tuberculosis is adequate for the probable diagnosis of tuberculosis disease. If a likely adult source case has been identified, drug susceptibility test results of the isolate from the adult source can be used to determine the best therapeutic regimen for the child. Cultures should be obtained from the child whenever the source case is unknown, there are multiple possible source cases, or the source case has possible or confirmed drug-resistant tuberculosis.

Confirmation of extrapulmonary tuberculosis is best achieved with a positive culture. However, for many forms of tuberculosis, the culture yield is only 25-50%, and probable diagnosis is by a combination of clinical signs and symptoms, analysis of body fluids when possible, radiographic or histopathologic evidence of tuberculosis, and elimination of other possible diagnoses.

Nucleic Acid Amplification

The main form of nucleic acid amplification studied in children with tuberculosis is PCR, which uses specific DNA sequences as markers for microorganisms. Evaluation of PCR in childhood tuberculosis has been limited. Compared with a clinical diagnosis of pulmonary tuberculosis in children, the sensitivity of PCR has varied from 25-83%, and specificity has varied from 80-100%. A negative PCR result never eliminates the diagnosis of tuberculosis, and the diagnosis is not confirmed by a positive PCR result.

Gene Xpert MTB/RIF is a real-time PCR assay for *M. tuberculosis* that simultaneously detects rifampin resistance, which is often used as a proxy for MDR tuberculosis. This assay uses a self-contained cartridge system, which yields results from direct specimens in 2 hr and is less operator dependent than traditional PCR detection methods. Sensitivity and specificity were 72-77% and 99% in smear-negative adults and 98-99% and 99-100% in smear-positive adults, respectively. Pediatric studies reveal that compared to smear microscopy, this technology has superior diagnostic capability on direct sputum and gastric aspirates. Although cartridges for the Xpert system are expensive, it offers advantages in rapid detection of MDR tuberculosis and is especially useful in settings lacking laboratory infrastructure. Xpert should never replace mycobacterial cultures.

TREATMENT

The basic principles of management of tuberculosis disease in children and adolescents are the same as those in adults. Several drugs are used to affect a relatively rapid cure and prevent the emergence of secondary drug resistance during therapy (Tables 215-5 and 215-6). The choice of regimen depends on the extent of tuberculosis disease, the host, and the likelihood of drug resistance (see Chapter 214 and Table 214-1). The standard therapy of intrathoracic tuberculosis (pulmonary disease and/or hilar lymphadenopathy) in children, as recommended by the CDC and American Academy of Pediatrics, is a 6 mo regimen of isoniazid and rifampin supplemented in the 1st 2 mo of treatment by pyrazinamide and ethambutol. Several clinical trials have shown that this regimen yields a success rate approaching 100%, with an incidence of clinically significant adverse reactions of <2%. Nine-month regimens of only isoniazid and rifampin are also highly effective for drug-susceptible tuberculosis, but the necessary length of treatment, the need for good adherence by the patient, and the relative lack of protection against possible initial drug resistance have led to the favoring of treatment regimens with additional drugs for a short time period. Most experts recommend that all drug administration be directly observed, meaning that a healthcare worker is physically present when the medications are administered to the patients. When **directly observed therapy** is used, intermittent (twice or thrice weekly) administration of drugs after an initial period as short as 2 wk of daily therapy is as effective in children as daily therapy for the entire course.

Extrapulmonary tuberculosis is usually caused by small numbers of mycobacteria. In general, the treatment for most forms of extrapulmonary tuberculosis in children, including cervical lymphadenopathy, is the same as for pulmonary tuberculosis. Exceptions are bone and joint, disseminated, and CNS tuberculosis, for which there are inadequate data to recommend 6 mo of therapy. These conditions are treated for 9-12 mo. Surgical débridement in bone and joint disease and ventriculoperitoneal shunting in CNS disease may be necessary adjuncts to medical therapy.

The optimal treatment of tuberculosis in HIV-infected children has not been established. HIV-seropositive adults with tuberculosis can be treated successfully with standard regimens that include isoniazid, rifampin, pyrazinamide, and ethambutol. The total duration of therapy should be 6-9 mo, or 6 mo after culture of sputum becomes sterile, whichever is longer. Data for children are limited to relatively small series. Most experts believe that HIV-infected children with drug-susceptible tuberculosis should receive the standard 4-drug regimen for the 1st 2 mo followed by isoniazid and rifampin for a total duration of at least 9 mo. Children with HIV infection appear to have more frequent adverse reactions to antituberculosis drugs and must be monitored closely during therapy. Coadministration of rifampin and some antiretroviral agents results in subtherapeutic blood levels of protease inhibitors and nonnucleoside reverse transcriptase inhibitors and toxic levels of rifampin. Concomitant administration of these drugs is not recommended. Treatment of HIV-infected children is often empiric based on epidemiologic and radiographic information, because the radiographic appearance of other pulmonary complications of HIV in children, such as lymphoid interstitial pneumonitis and bacterial pneumonia, may be similar to that of tuberculosis. Therapy should be considered when tuberculosis cannot be excluded.

Table 215-5 Commonly Used Drugs for the Treatment of Tuberculosis in Infants, Children, and Adolescents

DRUG	DOSAGE FORMS	DAILY DOSAGE, mg/kg	TWICE A WEEK DOSAGE, mg/kg PER DOSE	MAXIMUM DOSE	ADVERSE REACTIONS
Ethambutol	Tablets: 100 mg 400 mg	20	50	2.5 g	Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity
Isoniazid*	Scored tablets: 100 mg 300 mg Syrup: 10 mg/mL	10-15†	20-30	Daily, 300 mg Twice a week, 900 mg	Mild hepatic enzyme elevation, hepatitis,† peripheral neuritis, hypersensitivity
Pyrazinamide*	Scored tablets: 500 mg	30-40	50	2 g	Hepatotoxic effects, hyperuricemia, arthralgias, gastrointestinal tract upset
Rifampin*	Capsules: 150 mg 300 mg Syrup formulated from capsules	10-20	10-20	600 mg	Orange discoloration of secretions or urine, staining of contact lenses, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus; oral contraceptives may be ineffective

*Rifamate is a capsule containing 150 mg of isoniazid and 300 mg of rifampin. Two capsules provide the usual adult (i.e., person weighing >50 kg) daily doses of each drug. Rifater, in the United States, is a capsule containing 50 mg of isoniazid, 120 mg of rifampin, and 300 mg of pyrazinamide. Isoniazid and rifampin also are available for parenteral administration.

†When isoniazid in a dosage exceeding 10 mg/kg per day is used in combination with rifampin, the incidence of hepatotoxic effects may be increased.

From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 746.*

Table 215-6 Less-Commonly Used Drugs for Treating Drug-Resistant Tuberculosis in Infants, Children, and Adolescents*

DRUGS	DOSAGE, FORMS	DAILY DOSAGE, mg/kg	MAXIMUM DOSE	ADVERSE REACTIONS
Amikacin†	Vials: 500 mg, 1 g	15-30 (IV or IM administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects
Capreomycin†	Vials: 1 g	15-30 (IM administration)	1 g	Auditory and vestibular toxicity and nephrotoxic effects
Cycloserine	Capsules: 250 mg	10-20, given in 2 divided doses	1 g	Psychosis, personality changes, seizures, rash
Ethionamide	Tablets: 250 mg	15-20, given in 2-3 divided doses	1 g	Gastrointestinal tract disturbances, hepatotoxic effects, hypersensitivity reactions, hypothyroidism
Kanamycin	Vials: 75 mg/2 mL 500 mg/2 mL 1 g/3 mL	15-30 (IM or IV administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects
Levofloxacin‡	Tablets: 250 mg 500 mg 750 mg Vials: 25 mg/mL	Adults: 750-1000 mg (once daily) Children: 15 mg/kg daily	1 g	Theoretic effect on growing cartilage, gastrointestinal tract disturbances, rash, headache, restlessness, confusion
Ofloxacin	Tablets: 200 mg 300 mg 400 mg Vials: 20 mg/mL 40 mg/mL	Adults and adolescents: 800 mg Children 15-20 mg/kg daily	800 mg	Arthropathy, arthritis
Moxifloxacin	Tablets: 400 mg IV solution: 400 mg/250 mL in 0.8% saline	Adults and adolescents: 400 mg Children: 7.5-10 mg/kg daily	400 mg	Arthropathy, arthritis
Paraaminosalicylic acid (PAS)	Packets: 3 g	200-300 (2-4 times a day)	10 g	Gastrointestinal tract disturbances, hypersensitivity, hepatotoxic effects
Streptomycin†	Vials: 1 g 4 g	20-40 (IM administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects, rash

*These drugs should be used in consultation with a specialist in tuberculosis.
†Dose adjustment in renal insufficiency.
‡Levofloxacin currently is not approved for use in children younger than 18 yr of age; its use in younger children necessitates assessment of the potential risks and benefits.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 748.*

Drug-Resistant Tuberculosis

The incidence of drug-resistant tuberculosis is increasing in many areas of the world, including North America. There are two major types of drug resistance. **Primary resistance** occurs when a person is infected with *M. tuberculosis* that is already resistant to a particular drug. **Secondary resistance** occurs when drug-resistant organisms emerge as the dominant population during treatment. The major causes of secondary drug resistance are poor adherence to the medication by the patient or inadequate treatment regimens prescribed by the physician. Nonadherence to 1 drug is more likely to lead to secondary resistance than is failure to take all drugs. Secondary resistance is rare in children because of the small size of their mycobacterial population. Consequently, most drug resistance in children is primary, and patterns of drug resistance among children tend to mirror those found among adults in the same population. The main predictors of drug-resistant tuberculosis among adults are history of previous antituberculosis treatment, coinfection with HIV, and exposure to another adult with infectious drug-resistant tuberculosis.

Treatment of drug-resistant tuberculosis is successful only when at least 2 bactericidal drugs are given to which the infecting strain of *M. tuberculosis* is susceptible. When a child has possible drug-resistant tuberculosis, usually 4 or 5 drugs should be administered initially until the susceptibility pattern is determined and a more-specific regimen can be designed. The specific treatment plan must be individualized for each patient according to the results of susceptibility testing on the isolates from the child or the adult source case. Treatment duration of 9 mo with rifampin, pyrazinamide, and ethambutol is usually adequate for isoniazid-resistant tuberculosis in children. When resistance to isoniazid and rifampin is present, the total duration of therapy often must be extended to 12-24 mo, and intermittent regimens should not be used. The prognosis of single- or multidrug-resistant tuberculosis in children is usually good if the drug resistance is identified early in the treatment, appropriate drugs are administered under directly observed therapy, adverse reactions from the drugs are minor, and the child and family are in a supportive environment. The treatment of drug-resistant tuberculosis in children always should be undertaken by a clinician with specific expertise in the treatment of tuberculosis.

Corticosteroids

Corticosteroids are useful in treating some children with tuberculosis disease. They are most beneficial when the host inflammatory reaction contributes significantly to tissue damage or impairment of organ function. There is convincing evidence that corticosteroids decrease

mortality rates and long-term neurologic sequelae in some patients with **tuberculous meningitis** by reducing vasculitis, inflammation, and, ultimately, intracranial pressure. Lowering the intracranial pressure limits tissue damage and favors circulation of antituberculosis drugs through the brain and meninges. Short courses of corticosteroids also may be effective for children with **endobronchial tuberculosis** that causes respiratory distress, localized emphysema, or segmental pulmonary lesions. Several randomized clinical trials have shown that corticosteroids can help relieve symptoms and constriction associated with acute tuberculous **pericardial effusion.** Corticosteroids can cause dramatic improvement in symptoms in some patients with tuberculous pleural effusion and shift of the mediastinum. However, the long-term course of disease is probably unaffected. Some children with severe **miliary tuberculosis** have dramatic improvement with corticosteroid therapy if the inflammatory reaction is so severe that alveolocapillary block is present. There is no convincing evidence to support a specific corticosteroid preparation. The most commonly used regimen is prednisone, 1-2 mg/kg/day in 1-2 divided doses orally for 4-6 wk, followed by a taper.

Supportive Care

Children receiving treatment should be followed carefully to promote adherence to therapy, to monitor for toxic reactions to medications, and to ensure that the tuberculosis is being adequately treated. Adequate nutrition is important. Patients should be seen at monthly intervals and should be given just enough medication to last until the next visit. Anticipatory guidance with regard to the administration of medications to children is crucial. The physician should foresee difficulties that the family might have in introducing several new medications in inconvenient dosage forms to a young child. The clinician must report all cases of suspected tuberculosis in a child to the local health department to be sure that the child and family receive appropriate care and evaluation.

Nonadherence to treatment is the major problem in tuberculosis therapy. The patient and family must know what is expected of them through verbal and written instructions in their primary language. Approximately 30-50% of patients taking long-term treatment are significantly nonadherent with self-administered medications, and clinicians are usually not able to determine in advance which patients will be nonadherent. Preferably, directly observed therapy should be instituted by the local health department.

Latent *Mycobacterium tuberculosis* Infection

The following aspects of the natural history and treatment of LTBI in children must be considered in the formulation of recommendations about therapy: (1) infants and children younger than 5 yr of age with LTBI have been infected recently; (2) the risk for progression to disease is high; (3) untreated infants with LTBI have up to a 40% chance of development of tuberculosis disease; (4) the risk for progression decreases gradually through childhood, until adolescence when the risk increases; (5) infants and young children are more likely to have life-threatening forms of tuberculosis, including meningitis and disseminated disease; and (6) children with LTBI have more years at risk for development of disease than adults. Because of these factors, and the excellent safety profile of isoniazid in children, there is a tendency to err on the side of overtreatment in infants, young children and adolescents.

Isoniazid therapy for LTBI appears to be more effective for children than adults, with several large clinical trials demonstrating risk reduction of 70-90%. The risk of isoniazid-related hepatitis is minimal in infants, children, and adolescents, who tolerate the drug better than adults.

The recommended regimen for treatment of LTBI in United States children is a 9 mo course of isoniazid as self-administered daily therapy or by twice-weekly directly observed therapy. Analysis of data from several studies demonstrates that the efficacy decreased significantly if isoniazid was taken for <9 mo. However, the international standard is 6 mo treatment with isoniazid. Isoniazid given twice weekly has been used extensively to treat LTBI in children, especially schoolchildren and close contacts of case patients. Directly observed therapy should be considered when it is unlikely that the child and family will adhere to daily self-administration, or if the child is at increased risk for rapid development of disease (newborns and infants, recent contacts, immunocompromised children). For healthy children taking isoniazid but no other potentially hepatotoxic drugs, routine biochemical monitoring and supplementation with pyridoxine are not necessary. A 3 mo regimen of rifampin and isoniazid has been used in Europe, with programmatic data suggesting that the regimen is effective, but this regimen is not recommended in the United States. Rifampin alone for 4-6 mo has been used for the treatment of LTBI in infants, children, and adolescents when isoniazid could not be tolerated or the child has had contact with a source case infected with an isoniazid-resistant but rifamycin-susceptible organism. However, no controlled clinical trials have been conducted. Rifapentine is a rifamycin with a very long half-life, allowing for weekly administration in conjunction with isoniazid. Studies have demonstrated that 12 doses of once weekly isoniazid and rifapentine are as effective for treating LTBI and as safe as 9 mo of daily isoniazid, and this regimen is recommended by the American Academy of Pediatrics and the CDC for treatment of LTBI in patients 12 yr of age and older. Given the risk of selecting for drug-resistant isolates by missing intermittent doses of rifamycins, this treatment regimen currently is recommended only under directly observed therapy under the supervision of local health departments.

For children with multidrug-resistant tuberculosis infection, the regimen will depend on the drug-susceptibility profile of the contract case's organism; an expert in tuberculosis should be consulted.

Few controlled studies have been published regarding the efficacy of any form of treatment for LTBI in HIV-infected children. A 9-mo course of daily isoniazid is recommended. Most experts recommend that routine monitoring of serum hepatic enzyme concentrations be performed and pyridoxine be given when HIV-infected children are treated with isoniazid. The optimal duration of rifampin therapy in children with LTBI is not known, but many experts recommend at least a 6 mo course.

Isoniazid should be given to children younger than 5 yr of age who have a negative TST or IGRA result but who have known recent exposure to an adult with potentially contagious tuberculosis disease. This practice is often referred to as **window prophylaxis**. By the time delayed hypersensitivity develops (2-3 mo), an untreated child already may have developed severe tuberculosis. For these children, tuberculin skin or IGRA testing is repeated 3 mo after contact with the source case for tuberculosis has been broken (*broken contact* is defined as physical separation or adequate initial treatment of the source case). If the second test result is positive, isoniazid therapy is continued for 9 mo, but if the result is negative, treatment can be stopped.

PREVENTION

The highest priority of any tuberculosis control program should be case finding and treatment, which interrupts transmission of infection between close contacts. All children and adults with symptoms suggestive of tuberculosis disease and those in close contact with an adult with suspected infectious pulmonary tuberculosis should be tested for tuberculosis infection (by TST or IGRA) and examined as soon as possible. On average, 30-50% of household contacts to infectious cases are infected, and 1% of contacts already have overt disease. This scheme relies on effective and adequate public health response and resources. Children, particularly young infants, should receive high priority during contact investigations, because their risk for infection is high and they are more likely to rapidly develop severe forms of tuberculosis.

Mass testing of large groups of children for tuberculosis infection is an inefficient process. When large groups of children at low risk for tuberculosis are tested, the vast majority of TST reactions are actually false-positive reactions because of biologic variability or cross sensitization with NTM. However, testing of high-risk groups of adults or children should be encouraged, because most of these persons with positive TST or IGRA results have tuberculosis infection. Testing

should take place only if effective mechanisms are in place to ensure adequate evaluation and treatment of the persons who test positive.

Bacille Calmette-Guérin Vaccination

The only available vaccine against tuberculosis is the BCG vaccine. The original vaccine organism was a strain of *M. bovis* attenuated by subculture every 3 wk for 13 yr. This strain was distributed to dozens of laboratories that continued to subculture the organism on different media under various conditions. The result has been production of many BCG vaccines that differ widely in morphology, growth characteristics, sensitizing potency, and animal virulence.

The administration route and dosing schedule for the BCG vaccines are important variables for efficacy. The preferred route of administration is intradermal injection with a syringe and needle, because it is the only method that permits accurate measurement of an individual dose.

The BCG vaccines are extremely safe in immunocompetent hosts. Local ulceration and regional suppurative adenitis occur in 0.1-1% of vaccine recipients. Local lesions do not suggest underlying host immune defects and do not affect the level of protection afforded by the vaccine. Most reactions are mild and usually resolve spontaneously, but chemotherapy is needed occasionally. Surgical excision of a suppurative draining node is rarely necessary and should be avoided if possible. Osteitis is a rare complication of BCG vaccination that appears to be related to certain strains of the vaccine that are no longer in wide use. Systemic complaints such as fever, convulsions, loss of appetite, and irritability are extraordinarily rare after BCG vaccination. Profoundly immunocompromised patients can develop disseminated BCG infection after vaccination. Children with HIV infection appear to have rates of local adverse reactions to BCG vaccines that are comparable with rates in immunocompetent children. However, the incidence in these children of disseminated infection months to years after vaccination is currently unknown.

Recommended vaccine schedules vary widely among countries. The official recommendation of the World Health Organization is a single dose administered during infancy, in populations where the risk for tuberculosis is high. However, infants with known HIV infection should not receive a BCG vaccination. In some countries repeat vaccination is universal, although no clinical trials support this practice. In others, it is based on either TST or the absence of a typical scar. The optimal age for administration and dosing schedule are unknown because adequate comparative trials have not been performed.

Although dozens of BCG trials have been reported in various human populations, the most useful data have come from several controlled trials. The results of these studies have been disparate. Some demonstrated a great deal of protection from BCG vaccines, but others showed no efficacy at all. A meta-analysis of published BCG vaccination trials suggested that BCG is 50% effective in preventing pulmonary tuberculosis in adults and children. The protective effect for disseminated and meningeal tuberculosis appears to be slightly higher, with BCG preventing 50-80% of cases. A variety of explanations for the varied responses to BCG vaccines have been proposed, including methodologic and statistical variations within the trials, interaction with NTM that either enhances or decreases the protection afforded by BCG, different potencies among the various BCG vaccines, and genetic factors for BCG response within the study populations. BCG vaccination administered during infancy has little effect on the ultimate incidence of tuberculosis in adults, suggesting waning protection with time.

BCG vaccination has worked well in some situations but poorly in others. Clearly, BCG vaccination has had little effect on the ultimate control of tuberculosis throughout the world, because more than 5 billion doses have been administered but tuberculosis remains epidemic in most regions. BCG vaccination does not substantially influence the chain of transmission, because cases of contagious pulmonary tuberculosis in adults that can be prevented by BCG vaccination constitute a small fraction of the sources of infection in a population. The best use of BCG vaccination is to prevent life-threatening forms of tuberculosis in infants and young children.

BCG vaccination has never been adopted as part of the strategy for the control of tuberculosis in the United States. Widespread use of the vaccine would render subsequent TSTs less useful. However, BCG vaccination can contribute to tuberculosis control in selected population groups. BCG is recommended for TST-negative, HIV-negative infants and children who are at high risk for intimate and prolonged exposure to persistently untreated or ineffectively treated adults with infectious pulmonary tuberculosis and who cannot be removed from the source of infection or placed on long-term preventive therapy. It also is recommended for those who are continuously exposed to persons with tuberculosis who have bacilli that are resistant to isoniazid and rifampin. Any child receiving BCG vaccination should have a documented negative TST before receiving the vaccine. After receiving the vaccine, the child should be separated from the possible sources of infection until it can be demonstrated that the child has had a vaccine response, demonstrated by tuberculin reactivity, which usually develops within 1-3 mo.

Active research to develop new tuberculosis vaccines has led to the creation and preliminary testing of several vaccine candidates based on attenuated strains of mycobacteria, subunit proteins, or DNA. The genome of *M. tuberculosis* has been sequenced, allowing researchers to further study and better understand the pathogenesis and host immune responses to tuberculosis.

Prevention of Perinatal Tuberculosis

The most effective way of preventing tuberculosis infection and disease in the neonate or young infant is through appropriate testing and treatment of the mother and other family members. High-risk pregnant women should be tested with a TST or IGRA, and those with a positive test result should receive a chest radiograph with appropriate abdominal shielding. If the mother has a negative chest radiograph and is clinically well, no separation of the infant and mother is needed after delivery. The child needs no special evaluation or treatment if the child remains asymptomatic. **Other household members should undergo testing for tuberculosis infection and further evaluation as indicated.**

If the mother has suspected tuberculosis at the time of delivery, the newborn should be separated from the mother until the chest radiograph is obtained. If the mother's chest radiograph is abnormal, separation should be maintained until the mother has been evaluated thoroughly, including examination of the sputum. If the mother's chest radiograph is abnormal but the history, physical examination, sputum examination, and evaluation of the radiograph show no evidence of current active tuberculosis, it is reasonable to assume that the infant is at low risk for infection. The mother should receive appropriate treatment, and she and her infant should receive careful follow-up care.

If the mother's chest radiograph or acid-fast sputum smear shows evidence of current tuberculosis disease, additional steps are necessary to protect the infant. Isoniazid therapy for newborns has been so effective that separation of the mother and infant is no longer considered mandatory. Separation should occur only if the mother is ill enough to require hospitalization, has been or is expected to become nonadherent to treatment, or has suspected drug-resistant tuberculosis. Isoniazid treatment for the infant should be continued until the mother is sputum culture negative for ≥3 mo. At that time, a Mantoux TST should be placed on the child. If the test is positive, isoniazid is continued for a total duration of 9-12 mo; if the test is negative, isoniazid can be discontinued. Once the mother and child are taking adequate therapy, it is usually safe for the mother to breastfeed, as the medications, although found in milk, are present in low concentrations. If isoniazid resistance is suspected or the mother's adherence to medication is in question, continued separation of the infant from the mother should be considered. The duration of separation must be at least as long as is necessary to render the mother noninfectious. An expert in tuberculosis should be consulted if the young infant has potential exposure to the mother or another adult with tuberculosis disease caused by an isoniazid-resistant strain of *M. tuberculosis*.

Although isoniazid is not thought to be teratogenic, the treatment of pregnant women who have asymptomatic tuberculosis infection is

often deferred until after delivery. However, symptomatic pregnant women or those with radiographic evidence of tuberculosis disease should be appropriately evaluated. Because pulmonary tuberculosis is harmful to both the mother and the fetus and represents a great danger to the infant after delivery, tuberculosis in pregnant women always should be treated. The most common regimen for drug-susceptible tuberculosis is isoniazid, rifampin, and ethambutol. The aminoglycosides and ethionamide should be avoided because of their teratogenic effect. The safety of pyrazinamide in pregnancy has not been established.

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Chapter 216
Hansen Disease (*Mycobacterium leprae*)

Monica I. Ardura and Asuncion Mejias

Leprosy is a heterogeneous, chronic mycobacterial infection that primarily affects the upper airway, skin, and peripheral nerves. Disease manifestations are determined by the host's immunopathologic response to infection, resulting in a wide clinical spectrum. Hansen disease (HD) is currently the accepted designation of leprosy. Contrary to historical folklore, HD is not highly transmissible and is treatable. In addition, the associated morbidity and disability can be prevented with early diagnosis and appropriate treatment.

ETIOLOGY

Mycobacterium leprae, the etiologic agent of leprosy, is an obligate intracellular acid-fast Gram-positive bacillus of the family Mycobacteriaceae measuring 1-8 µm in length. It grows optimally at 27-33°C (80.6-91.4°F) yet cannot be cultured in vitro. Natural infection occurs in humans and possibly in armadillos, although mice and certain primates can be infected with *M. leprae* in the laboratory. Based on assays in footpads of immunodeficient mice, the doubling time of *M. leprae* is estimated to be 11-13 days. The incubation period between natural infection and overt clinical disease in humans ranges from 3 mo to 20 yr, with a mean of 4 yr for tuberculoid leprosy and 10 yr for lepromatous leprosy. The infectiousness of patients with HD becomes negligible within 24 hr of the first administration of effective multidrug therapy.

EPIDEMIOLOGY

The World Health Organization's goal to eliminate leprosy as a public health problem, defined as reduction in the prevalence of leprosy to less than 1 case per 10,000 population, was achieved at the global level in 2000. Yet, despite an overall decline in reported prevalence since the introduction of effective antimycobacterial therapy in the early 1980s, HD continues to afflict more than 2 million people worldwide. Approximately 245,000 new cases were reported globally in 2009, with more than 80% of cases occurring in Southeast Asia, Africa, and South America. In the United States, HD is a notifiable disease with 12,685 new HD cases since 1894. In 2009, there were 213 new U.S. cases, with 65% of them occurring in Texas, Louisiana, Hawaii, California, Florida, New York, Massachusetts, and Puerto Rico. Seventy-four percent of cases were among immigrants, with the largest proportion identifying themselves as Asian or South Pacific islanders. Less than 4% of U.S. cases in 2009 occurred in children younger than 16 yr of age. Although infection in infants is rare, the youngest patient reported in the literature is a 3 mo old.

The likelihood of developing HD is determined by several variables: age (with 2 incidence peaks: 10-14 yr and 30 yr), gender (male : female 2 : 1), and contact with a patient with multibacillary disease. Approximately 5% of people are genetically susceptible to infection with *M. leprae*. Whole-genome sequencing has allowed identification of genes and polymorphisms associated with increased susceptibility to leprosy. HD in immunocompromised hosts has been reported in solid-organ and bone marrow transplant recipients and patients receiving tumor necrosis factor (TNF)-blocking monoclonal antibodies. Patients with HIV infection do not appear to be at increased risk of acquiring leprosy, to have increased disease severity, or to have a poor response to treatment. However, clinicians should be aware that concomitant HIV infection and leprosy can result in worsening of symptoms of leprosy during HIV treatment as a result of an immune reconstitution inflammatory syndrome.

The exact mechanism of transmission is not fully understood but is thought to occur primarily via the respiratory route. Up to 10^7 viable bacilli per day can be shed in the respiratory secretions of patients with multibacillary leprosy. Type of disease (multibacillary) and proximity to contact cases are important determinants of human-to-human transmission; the relative risk for developing disease in household contacts is 8-10 for lepromatous disease and 2-4 for the tuberculoid form. Transmissions via breast milk and entry through broken skin have been reported. Autochthonous cases of leprosy have also been reported in the southern Gulf Coast area of the United States and represent a probable zoonosis from armadillos, though the transmission risk is low.

PATHOGENESIS

M. leprae is the only bacterium known to infect nerves. The mechanism of mycobacterial dissemination from the respiratory tract to the skin and nerves is thought to occur hematogenously but has not been completely elucidated. *M. leprae* has been shown to colonize the perineural space and gain entry into the endoneural space. The organism then binds to the laminin-2 glycoprotein present in the basal lamina of Schwann cells in peripheral nerves. It is then taken up inside the Schwann cell, where it replicates slowly intracellularly over several years. Specific T cells recognize the mycobacterial antigens within the nerve and initiate a chronic inflammatory response. In addition to the direct nerve invasion by *M. leprae*, the immune response to infection also contributes to nerve damage. Schwann cells express human leukocyte antigen class 2 molecules and play an important role in the immunologic reaction by presenting mycobacterial peptides to the human leukocyte antigen class 2–restricted CD4-positive T cells. This likely explains the nerve damage seen in paucibacillary disease and in reversal reactions. Swelling within the perineurium leads to ischemia, further nerve damage, and eventually to fibrosis and axonal death.

CLINICAL MANIFESTATIONS

Skin and serologic studies suggest that up to 90% of infected people develop immunity after exposure, without manifesting clinical disease. In susceptible individuals with sufficient exposure to become infected, the spectrum of clinical manifestations reflects *M. leprae*'s unique tropism for peripheral nerves, the host's immunologic response to infection, and disease subtype. Classic manifestations of leprosy include hypopigmented, erythematous, or infiltrative skin lesions with or without neurologic symptoms such as hypoesthesia or anesthesia, weakness, autonomic dysfunction, and peripheral nerve thickening.

Skin Involvement

Examination of the skin should ideally be performed in natural sunlight and be tested for hypoesthesia to light touch, pin prick, temperature, and anhidrosis. The most common skin lesions are macules or plaques. Diffuse infiltrative lesions and subcutaneous nodules are less common. Initial lesions are insidious hypopigmented macules, although they may appear erythematous on pale skin. Lesions may involve any area of the body, are more pronounced in cooler areas (for

example the earlobes and nose), and occur less frequently on the scalp, axillae, or perineum. Approximately 70% of skin lesions have reduced sensation; the degree of hypoesthesia depends on the location and size of the lesion and degree of Th1 immune response. Patients with tuberculous leprosy generally have 1-3 well-demarcated macules or plaques with elevated borders (Fig. 216-1) and reduced or absent sensation. In the lepromatous form, multiple lesions are present but are not all hypoesthetic or anesthetic.

Nerve Involvement

The skin lesions overlying a nerve trunk distribution predict the involvement of nerves in the vicinity. Peripheral nerves are most commonly affected early in the disease course and should be palpated for thickness (Fig. 216-2) and tenderness and evaluated for both motor and sensory function (particularly temperature and light touch). The posterior tibial nerve (medial malleolus) is the most common nerve affected, followed by the ulnar (elbow), median (wrist), lateral popliteal (fibular neck), and facial nerves. There is a pure neuritic form of leprosy, occurring most commonly in India and Nepal, in which patients present with asymmetrical neuropathy, but lack skin lesions. A nerve biopsy (usually of the sural nerve) is required to demonstrate granulomatous histopathology, thereby confirming the diagnosis.

Figure 216-1 A patient with tuberculous leprosy with a single skin lesion with a raised border and flattened center.

Figure 216-2 Thickened, superficial peroneal nerve of leprosy.

Other Involvement

Ocular involvement leading to vision loss results from both direct bacillary invasion of the eye and optic nerve damage. Lagophthalmos occurs when there is destruction of the facial nerve. Facial skin lesions are associated with a 10-fold higher risk of facial nerve damage. Damage to the trigeminal nerve causes anesthesia of the cornea and conjunctiva, leading to abrasions. Systemic involvement of other organs is seen mainly in patients with lepromatous leprosy where a high bacillary burden leads to infiltration of the nasal mucosa, bones, and testes. Renal involvement and amyloidosis are rare findings.

Patients may also present with leprosy reactions. Leprosy reactions are acute clinical exacerbations reflecting disturbances of the immunologic balance to *M. leprae* infection occurring in 30-50% of all leprosy patients. These sudden changes occur most commonly during the initial years after infection and in patients with borderline and multibacillary leprosy, but can occur before, during, or after completion of treatment. Three types of leprosy reactions have been described and require immediate treatment so as to prevent complications.

1. Type 1 reactions (also known as reversal reactions) occur in one-third of patients with borderline disease and are caused by a spontaneous increase in T-cell–mediated reactivity to mycobacterial antigens. This increase in the Th1 cellular immune response causes local production and increased infiltration of interferon-γ and TNF-α–secreting CD4+ lymphocytes into cutaneous and neural sites. Reversal reactions are characterized by acute edema and increased erythema, warmth, and painful inflammation of preexisting cutaneous plaques or nodules with acute swelling and tenderness of peripheral nerves that can quickly progress to cause nerve abscesses and necrosis. There may be a peripheral lymphocytosis and an increased cytokine response, but systemic symptoms are uncommon. Rapid and sustained reversal of the inflammatory process using corticosteroids is essential to prevent continued nerve damage.
2. Type 2 reactions (erythema nodosum leprosum [ENL]) occur in borderline lepromatous and lepromatous forms, as these patients have the highest levels of *M. leprae* antigens and antibodies, most commonly in the 1st 2 yr after starting therapy. ENL is distinguished from reversal reactions by the development of new painful, erythematous subcutaneous nodules with an accompanying systemic inflammatory response. ENL is accompanied by high circulating concentrations of TNF-α. Patients develop high fever and signs of systemic toxicity, and in severe cases, ENL can be life-threatening, presenting with features similar to septic shock. Patients present with either a single, acute episode, a relapsing form comprised of multiple acute episodes, or a chronic, continuous form. Deposition of extravascular immune complexes leads to neutrophil infiltration and activation of complement in the skin and other organs. Tender, erythematous dermal papules or nodules (resembling erythema nodosum) occur in clusters, typically on extensor surfaces of the lower extremities and face. Immune complex deposition also contributes to migrating polyarthralgias, painful swelling of lymph nodes and spleen, iridocyclitis, vasculitis, orchitis, and, rarely, nephritis.
3. Lucio's phenomenon (erythema necroticans) is an uncommon, but potentially fatal reaction distinct from type 1 or 2 reactions that occurs in patients with untreated lepromatous leprosy, most commonly from Mexico. It is a necrotizing vasculitis caused by *M. leprae* directly invading the endothelium. Clinically, patients develop violaceous or hemorrhagic plaques, followed by ulcerations in the absence of systemic complaints. Secondary bacterial infections are common.

DIAGNOSIS

The diagnosis of HD requires high clinical suspicion and should be considered in any patient with a hypoesthetic or anesthetic skin rash, especially if they have resided in an endemic region. Patients are considered to have HD if they have one or more of the 3 cardinal signs: loss of sensation in a localized skin lesion, thickened peripheral nerve with loss of sensation or weakness of muscles enervated by that nerve, or the presence of acid-fast bacilli on biopsy. The positive predictive value for the diagnosis of leprosy in patients meeting all 3 criteria is 98%. Histopathologic examination of full-thickness biopsies taken of active lesions is considered the gold standard for establishing the diagnosis and allows for precise disease classification. Two classification schemas are frequently applied:

A. The World Health Organization classification is a simple field classification based on the number of skin lesions.
   1. Paucibacillary, single lesion
   2. Paucibacillary (2-5 patches)
   3. Multibacillary (≥6 patches)
B. The Ridley-Jopling scale is commonly used in the United States and describes the 5 types of leprosy, according to clinical spectrum of disease, bacillary load, and findings on histopathology.
   1. Tuberculoid form: Patients usually have a vigorous and specific cellular immune response to *M. leprae* antigens and have a small number of skin lesions. The lesions are infiltrated by T-helper type 1 T cells producing abundant interferon-γ and TNF-α, forming well-demarcated granulomas, with few, if any bacilli found within the lesions.
   2. Borderline tuberculoid form
   3. Borderline
   4. Borderline lepromatous
   5. Lepromatous form: Patients have an absence of specific cellular immunity to *M. leprae* but intact immunity to *Mycobacterium tuberculosis*. Patients with lepromatous form have the most severe form of the disease, characterized by many skin lesions, clinically apparent infiltration of peripheral nerves and skin lesions, and a high load of bacilli in the absence of an effective cell mediated immune response. They also have involvement of the nasal mucosa causing nasal congestion and epistaxis. Skin biopsies reveal extensive infiltration of the skin and nerves, containing messenger RNA for T-helper type 2–like cytokines such as interleukin-4 and interleukin-10, poorly formed granulomas, and uncontrolled proliferation of bacilli within foamy macrophages. A large amount of circulating antibody to *M. leprae* is present but does not confer protective immunity. Over time, patients with the lepromatous form develop symmetrical peripheral nerve involvement and a diffuse infiltrative dermopathy that includes thickening of the facial skin with accentuation of the skin creases and hair loss of the eyelashes and eyebrows (madarosis), leading to the classic presentation of the "leonine facies."

Patients with the extremes of the disease (tuberculoid and lepromatous forms) are considered to have stable cell-mediated immunity, as their disease manifestations do not change much over time. In contrast, patients with borderline disease (borderline tuberculoid, borderline, borderline lepromatous) have unstable cell-mediated immunity and demonstrate changes in their clinical manifestations over time toward the polar forms or sudden reversal reactions. From borderline tuberculoid to borderline lepromatous forms, there is a progressive reduction in cellular immune responses, an increase in bacillary load, more frequent hypopigmented skin lesions (Fig. 216-3) and nerve involvement, and higher antibody titers.

Indeterminate leprosy is the earliest form of leprosy in which patients have a single hypopigmented macule with poorly defined borders, without erythema or induration. Anesthesia is minimal or absent, especially if the lesion is on the face. The diagnosis is usually one of exclusion in the setting of a contact investigation. Tissue biopsies show diagnostic evidence of leprosy but do not meet sufficient criteria for classification. Up to 50-75% of the lesions will heal spontaneously, while the rest will progress to another form of leprosy.

Figure 216-3 A patient with borderline leprosy with numerous, hypopigmented lesions with poorly defined borders.

To confirm the diagnosis, a full-thickness skin biopsy should be taken from the most active skin lesion, entirely within the lesion and including the active margin. *M. leprae* is best identified in tissue using the Fite stain. Lesions from patients with the lepromatous form reveal numerous acid fast bacilli in clumps (globi), whereas patients with the tuberculoid form of the disease rarely have mycobacteria identified but demonstrate well-formed noncaseating granulomas and nerve involvement. The presence of neural inflammation differentiates leprosy from other granulomatous disorders. Hematoxylin-and-eosin staining and immunohistochemistry may also contribute to the diagnosis. Mycobacterial culture of lesions is performed to exclude *M. tuberculosis* and nontuberculous cutaneous infections. Antibodies to *M. leprae* are present in 90% of patients with untreated lepromatous disease, 40-50% with paucibacillary disease, and 1-5% of healthy controls. Serologic testing is insensitive, however, and is not used for diagnosis.

In endemic countries with few medical resources, diagnosis is based primarily on clinical evidence. In areas with laboratory access, a slit-skin smear may be performed in lieu of a biopsy. The slit-skin procedure involves making a small incision in the dermis of a suspected lesion, scraping the dermal surface and edge of the lesion, smearing the scraping on a glass slide, heat fixing, and staining (Fite) the specimen to detect the mycobacteria. Although slit-skin smears have high specificity, they have low sensitivity, as only 30% of patients are smear positive, usually patients with the lepromatous form. The bacterial index can range from 0 (no bacilli in 100 oil-immersion fields), as is generally seen in paucibacillary disease, to 6+ (>1,000 bacilli/field), as can be seen in multibacillary disease.

Diagnostic and histopathologic consultation in the United States is available through the National Hansen's Disease Programs (NHDP; http://www.hrsa.gov/hansens or 800-642-2477). Specimens (formalin or paraffin embedded) can be sent to the NHDP for pathologic analysis free of charge. A polymerase chain reaction (PCR) test for *M. leprae* is

not readily available in clinical practice but may be performed at the NHDP. In nonendemic areas, PCR may be useful for diagnosis when acid-fast bacilli are discernable in tissue, but clinical and histopathologic features are not typical. *M. leprae* DNA is detectable by PCR in 95% of multibacillary disease (sensitivity >90%) and 55% of paucibacillary disease (sensitivity of 34-80%). PCR has also allowed detection of the organism in nasal secretions from asymptomatic people. Molecular testing for mutations causing drug resistance is also available through the NHDP.

TREATMENT

In the United States, clinical providers considering a diagnosis and treatment of a patient with HD should obtain consultation from the NHDP. The primary goal of treatment is early antimicrobial therapy to prevent permanent neuropathy. Effective treatment of leprosy requires multidrug therapy (MDT) with dapsone, clofazimine, and rifampin. Combination therapy is employed to prevent antimicrobial resistance. The recommended combination MDT can be obtained free of charge in the United States from the NHDP (Table 216-1) and in other countries, from the World Health Organization (Table 216-2).

Before starting combination MDT, patients should be tested for glucose-6-phosphate dehydrogenase deficiency, have a baseline complete blood cell count and liver function testing, and be evaluated for evidence of concomitant tuberculosis infection. The latter is imperative so as to avoid giving rifampin monotherapy to someone with active tuberculosis. Darkening of the skin is a common adverse reaction to clofazimine; this generally resolves 6-12 mo after completing therapy. Bone marrow suppression and hepatotoxicity have been reported and should be monitored every 3 mo during therapy. Yearly, a screening urinalysis should be performed. Other reactions such as methemoglobinemia and hypersensitivity reactions to dapsone are rare.

Response to therapy is seen clinically as flattening or disappearance of skin lesions and improvement in nerve function, usually within 1-2 mo after initiating MDT. Complete resolution or improvement may take 6-12 mo, depending on the severity of infection. Most skin lesions heal without scarring. A large number of dead bacilli may remain in the tissue for years before they are eliminated. After completion of MDT, annual follow up for ≥5 yr for paucibacillary and ≥10 yr for multibacillary disease is warranted. Relapse of the disease after completion of MDT is rare (0.01-4.0%) and must be distinguished from the more common leprosy immunologic reactions. Patients who have a bacillary index of ≥4 pre-MDT or ≥3 at the completion of MDT have the highest risk of relapse. When relapse occurs, it is usually within 5-10 yr of MDT completion and a result of reactivation of drug-susceptible mycobacteria, thus patients are treated with the same MDT regimen. Resistance to dapsone and rifampicin has been documented, although it rarely occurs with combination therapy. Minocycline, clarithromycin, rifapentine, diarylquinoline, and some fluoroquinolones (ofloxacin, moxifloxacin) have been shown to be bactericidal against *M. leprae*. Given limited data, these alternative antimicrobials are used in selected cases of intolerance to the routine combination MDT regimen or for documented resistance. It is important to note that some patients who have been adequately treated for HD may later show evidence of chronic reversal reactions and late neuropathies but are bacillus negative, thus they should not be considered relapses. In these patients, low-dose clofazimine (50-100 mg thrice weekly) is generally employed until all signs of the reaction have abated.

Treatment of leprosy reactions can be complicated and requires expert consultation. Generally, continuation of antimycobacterial drugs, effective and prolonged antiinflammatory therapy, and adequate analgesia and physical support is essential for patients with active neuritis to prevent nerve damage. For type 1 reactions, the addition of

Table 216-1 NHDP Recommended Multidrug Therapy Regimens for Hansen Disease in the United States

TYPE OF LEPROSY	ANTIMICROBIAL THERAPY	ADULT DOSING (GIVEN ORALLY)	PEDIATRIC DOSING* (GIVEN ORALLY)	DURATION OF THERAPY
MULTIBACILLARY LEPROSY (LL, BL, BB)				
	Dapsone *and*	100 mg/day	1 mg/kg/day	24 months
	Rifampin *and*	600 mg/day	10-20 mg/kg/day	24 months
	Clofazimine	50 mg/day	1 mg/kg/day[†]	24 months
PAUCIBACILLARY LEPROSY (TT, BT)				
	Dapsone *and*	100 mg/day	1-2 mg/kg/day	12 months
	Rifampin	600 mg/day	10-20 mg/kg/day	12 months

NHDP multidrug therapy therapy is daily and of longer duration than World Health Organization recommended regimen.
*Daily pediatric mg/kg dose should not exceed adult daily maximum.
[†]Clofazimine is only available through NHDP Investigational New Drug (IND) program; minimum formulation is 50 mg and capsules should not be cut. Alternative dosing includes: clofazimine 2 mg/kg every other day *or* clarithromycin 7.5 mg/kg/day.
BB, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; NHDP, National Hansen's Disease Program; TT, tuberculoid.

Table 216-2 World Health Organization Recommended Multidrug Therapy Regimens for Hansen Disease

TYPE OF LEPROSY		Antimicrobial Therapy: MONTHLY (SUPERVISED)	Antimicrobial Therapy: DAILY (SELF-ADMINISTERED)	DURATION OF THERAPY
Multibacillary (LL, BL, BB)	Adult	Rifampicin 600 mg *and* clofazimine 300 mg	Dapsone 100 mg *and* clofazimine 50 mg	12-24 months
	Pediatric*	Rifampicin 450 mg *and* clofazimine 150 mg	Dapsone 50 mg *and* clofazimine 50 mg *every other day*	
Paucibacillary (TT, BT)	Adult	Rifampicin 600 mg	Dapsone 100 mg	6-12 months
	Pediatric*	Rifampicin 450 mg	Dapsone 50 mg	6 months
Paucibacillary (single lesion)[†]		Rifampicin 600 mg *and* ofloxacin 400 mg *and* minocycline 100 mg		One time, single dose

*In children younger than 10 yr of age, dosages of multidrug therapy should be in mg/kg, not to exceed the adult daily maximum: rifampicin 10 mg/kg once monthly, dapsone 2 mg/kg/day, clofazimine 1 mg/kg on alternate days.
[†]Paucibacillary single-lesion, one-time single-dose therapy may be less effective than the 6 mo paucibacillary multidrug therapy regimen.
BB, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; TT, tuberculoid.

prednisone 1 mg/kg/day orally (40-60 mg) with a slow taper (decreasing by 5 mg every 2-4 wk after evidence of improvement over 3-6 mo) is recommended in addition to standard MDT. If there is evidence of peripheral nerve deterioration, higher doses and longer tapers may be needed. Nerve function improves after corticosteroid treatment in 60-70% of patients who did not have preexisting neuritis. For type 2 reactions in patients older than 12 yr of age with systemic symptoms, thalidomide (100 mg/day for 4 days) is the drug of choice. Given the teratogenicity of thalidomide, the drug is only available from the Celgene Corporation under the System for Thalidomide Education and Prescribing Safety (STEPS) program (http://www.celgene.com; 888-771-0141). In younger patients or pregnant females in whom thalidomide is contraindicated or in older patients with thalidomide-refractory ENL, corticosteroids may be used in daily doses of 1 mg/kg for 12 wk. Monitoring and management of the deleterious side effects of chronic corticosteroid therapy is challenging in chronic cases. Clofazimine (300 mg/day tapering to <100 mg/day for 12 mo) has been useful in managing patients with chronic ENL as well. Lucio's phenomenon is managed with corticosteroids and treatment of underlying infections.

In regards to care of the exposed contacts of index patients, standard isolation precautions are recommended in the hospital setting. Hand hygiene is recommended for all people in contact with a patient with lepromatous leprosy. Disinfection of nasal secretions and handkerchiefs should be performed until treatment is established. Household contacts of patients, particularly patients with multibacillary disease, should be examined at baseline and then yearly for 5 yr. Any suspected or newly diagnosed case of leprosy in the United States should be reported to local and state public health departments, the Centers for Disease Control and Prevention, and the NHDP.

In endemic countries, close monitoring of household contacts of HD patients, particularly those with multibacillary disease and either chemoprophylaxis or early treatment to contacts with evidence of early HD are effective control strategies. A single dose of bacilli Calmette-Guérin (BCG) vaccine gives variable protective efficacy against leprosy ranging from 28-80%; an additional dose demonstrated increased protection. A heat-killed leprosy vaccine, given as an immunotherapeutic adjuvant along with combination MDT, is approved for use in India. In nonendemic areas, disease presenting in the contacts of patients with HD is rare. Chemoprophylaxis after contact is not routinely recommended in the United States, but local public health departments should be contacted for consultation on individual cases. There are no leprosy vaccines available or recommended for use in the United States.

LONG-TERM COMPLICATIONS

Serious consequences of leprosy occur from the mycobacterium's direct effect on skin and nerve involvement as well as from immune reactions. Indeed, leprosy is a leading cause of permanent physical disability among communicable diseases worldwide. The major chronic complications and deformities of leprosy are caused by segmental demyelination and permanent nerve injury. The prognosis for arresting progression of tissue and nerve damage is good if therapy is started early, but recovery of lost sensory and motor function is variable and frequently incomplete. Nerve impairment may be purely sensory, motor, or autonomic, or may be a combination. Sensory deficits lead to undetected trauma, ulceration, and osteomyelitis. Motor deficits result in muscle paralysis, atrophy, and limb deformities, especially of small muscles of the hand and foot (claw hand or foot, foot drop). Autonomic deficits can lead to skin drying and cracking. The most chronic residual deformity is that of an insensitive foot and requires frequent, routine surveillance of the plantar aspect of both feet. Painful neuropathy is also observed. Nerve function impairment can occur before diagnosis, during MDT, or after MDT and can develop during a reaction or without overt signs of skin or nerve inflammation (silent neuropathy). Patients at highest risk of nerve impairment are those with multibacillary leprosy and preexisting nerve damage. These patients should undergo regular monthly surveillance during therapy and for at least 2 yr from the time of diagnosis. From 3-10% of children will develop deformities, with the risk being 6.1 times higher in children with nerve enlargement as compared with children who do not have nerve enlargement. Other factors contributing to risk of deformities include increasing age of children, delay in accessing medical care, multiple skin lesions, multibacillary disease, smear positivity, multiple nerve involvement, and leprosy reaction at the time of presentation. An ophthalmologist should routinely examine all patients with HD because ocular complications, such as lagophthalmos and blindness, can occur. Given the proclivity for testicular invasion in multibacillary leprosy with resultant testicular dysfunction and infertility, males should be screened for elevated follicle-stimulating hormone or luteinizing hormone concentrations and decreased testosterone levels.

PREVENTION

Patient education is key to the successful management of HD. Patients should be encouraged to be compliant with MDT, educated about the signs and symptoms of neuritis, and advised to practice self-examination and seek prompt medical care should they develop neuritis or other symptoms of clinical exacerbations or leprosy reactions. Surgery and rehabilitation therapies such as physical and occupational therapy as well as counseling for the social and psychologic effects of the disease may also be required for optimal outcomes. Patient reassurance of the ability to lead a normal and productive social life and education of the community, including refuting myths and social stigma, are important parts of management.

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Chapter 217

Nontuberculous Mycobacteria

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Nontuberculous mycobacteria (NTM), also referred to as **atypical mycobacteria** or **mycobacteria other than tuberculosis**, are all members of the genus *Mycobacterium* other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*. The NTM constitute a highly diverse group of bacteria that differ from *M. tuberculosis* complex bacteria in their pathogenicity, interhuman transmissibility, nutritional requirements, ability to produce pigments, enzymatic activity, and drug susceptibility. In contrast to the *M. tuberculosis* complex, NTM are acquired from environmental sources and not by person-to-person spread, although the latter is now under debate, especially in patients with cystic fibrosis. Their omnipresence in our environment implies that the clinical relevance of NTM isolation from clinical specimens is often unclear; a positive culture might reflect occasional presence or contamination rather than true NTM disease. NTM are associated with pediatric lymphadenitis, otomastoiditis, serious lung infections, and, albeit rarely, disseminated disease. Treatment is long-term and cumbersome and often requires adjunctive surgical intervention. Guidelines on diagnosis and treatment are provided by the American and British Thoracic Societies.

ETIOLOGY

NTM are ubiquitous in the environment all over the world, existing as saprophytes in soil and (tap) water, environmental niches that are the supposed sources of human infections. Owing to the introduction of molecular identification tools such as 16S recombinant DNA gene sequencing, the number of identified NTM species has grown to more than 150; the clinical relevance (i.e., the percentage of isolates that are causative agents of true NTM disease, rather than occasional presence) differs significantly by species.

Mycobacterium avium complex (MAC; i.e., *M. avium*, *Mycobacterium intracellulare* and several closely related but more rare species) and *Mycobacterium kansasii* are most often isolated from clinical samples, yet the isolation frequency of these species differs significantly by geographic area. MAC bacteria have been commonly isolated from natural and synthetic environments, and cases of MAC disease have been successfully linked to home exposure to shower and tap water. Although the designation *M. avium* suggests that human *M. avium* infections are acquired from birds (*avium* being Latin for "of birds"), molecular typing has established that *M. avium* strains that cause pediatric lymphadenitis and adult pulmonary disease represent the *M. avium hominissuis* subgrouping that is mainly found in humans and pigs and not in birds.

Some NTM have well-defined ecologic niches that help explain infection patterns. The natural reservoir for *Mycobacterium marinum* is fish and other cold-blooded animals, and the "fish-tank granuloma," a localized skin infection caused by *M. marinum*, follows skin injury in an aquatic environment. *Mycobacterium fortuitum* complex bacteria and *Mycobacterium chelonae* are ubiquitous in water and have caused clusters of nosocomial surgical wound and venous catheter–related infections. *Mycobacterium ulcerans* is associated with severe, chronic skin infections (**Buruli ulcer disease**) and is endemic mainly in West Africa and Australia, although other foci exist. Its incidence is highest in children younger than 15 yr old. *M. ulcerans* had been commonly detected in environmental samples by polymerase chain reaction but was only recently recovered by culture from a Water Strider (*Gerris* sp.) from Benin.

EPIDEMIOLOGY

Humans are exposed to NTM on a daily basis. In rural counties in the United States, where *M. avium* is prevalent in swamps, the **prevalence** of asymptomatic infections with *M. avium* complex, as measured by skin test sensitization, approaches 70% by adulthood. Still, the incidence and prevalence of the various NTM disease types remain largely unknown, especially for pediatric NTM disease. In Australian children, the overall **incidence** of NTM infection is 0.84 per 100,000, with lymphadenitis accounting for two-thirds of cases. The incidence of pediatric NTM disease in the Netherlands is estimated at 0.77 infections per 100,000 children per year, with lymphadenitis making up 92% of all infections.

In comparison, estimations of the prevalence of NTM from respiratory samples in adults are 5-15 per 100,000 persons per year, with important differences between countries or regions. Because pulmonary NTM disease progresses slowly, over years rather than months, and usually takes several years to cure, the prevalence of pulmonary NTM disease is much higher than incidence rates would suggest.

The paradigm that NTM disease is a rare entity limited to developed countries is changing. In recent studies in African countries with a high prevalence of HIV infection, it has been found that NTM might play a much larger role as a cause of tuberculosis-like disease of children and adults than previously assumed and thus confuse the diagnosis of tuberculosis.

Although it is generally believed that NTM infections are contracted from environmental sources, recent whole genome sequence analysis of *Mycobacterium abscessus* strains of patients in a cystic fibrosis clinic in the United Kingdom has raised the possibility of nosocomial transmission among patients with cystic fibrosis.

PATHOGENESIS

The histologic appearances of lesions caused by *M. tuberculosis* and NTM are often indistinguishable. The classic pathologic lesion consists of **caseating granulomas.** Compared to *M. tuberculosis* infections, NTM infections are more likely to result in granulomas that are **noncaseating,** ill defined (nonpalisading), irregular or serpiginous or even absent, with only chronic inflammatory changes observed. The histology likely reflects the immune status of the patient.

In patients with AIDS and disseminated NTM infection, the inflammatory reaction is usually scant and tissues are filled with large numbers of histiocytes packed with acid-fast bacilli. These disseminated NTM infections typically occur only after the number of CD4 T-lymphocytes has fallen below 50/μL, suggesting that specific T-cell products or activities are required for immunity to mycobacteria.

The pivotal roles of interferon-γ, interleukin (IL)-12, and tumor necrosis factor-α in disease pathogenesis are demonstrated by the high incidence of mostly disseminated NTM disease in children with interferon-γ and IL-12 pathway deficiencies and in persons treated with agents that neutralize tumor necrosis factor-α.

Observed differences in pathogenicity, clinical relevance, and spectrum of clinical disease associated with the various NTM species emphasize the importance of bacterial factors in the pathogenesis of NTM disease, although exact virulence factors remain largely unknown.

CLINICAL MANIFESTATIONS

Lymphadenitis of the superior anterior cervical or submandibular lymph nodes is the most common manifestation of NTM infection in children (Table 217-1). Preauricular, posterior cervical, axillary, and inguinal nodes are involved occasionally. Lymphadenitis is most

Table 217-1 Diseases Caused by Nontuberculous Mycobacterial Species

CLINICAL DISEASE	COMMON SPECIES	LESS-COMMON SPECIES
Cutaneous infection	*Mycobacterium chelonae, Mycobacterium fortuitum, Mycobacterium abscessus, Mycobacterium marinum*	*Mycobacterium ulcerans**
Lymphadenitis	MAC	*Mycobacterium kansasii, Mycobacterium haemophilum, Mycobacterium malmoense*†
Otologic infection	*M. abscessus*, MAC	*M. fortuitum*
Pulmonary infection	MAC, *M. kansasii, M. abscessus*	*Mycobacterium xenopi, Mycobacterium malmoense,*† *Mycobacterium szulgai, M. fortuitum, Mycobacterium simiae*
Catheter-associated infection	*M. chelonae, M. fortuitum*	*M. abscessus*
Skeletal infection	MAC, *M. kansasii, M. fortuitum*	*M. chelonae, M. marinum, M. abscessus, M. ulcerans**
Disseminated	MAC	*M. kansasii, Mycobacterium genavense, M. haemophilum, M. chelonae*

*Endemic in West Africa and Australia, minor foci in East Asia and Latin America.
†Found primarily in Northern Europe.
MAC, *Mycobacterium avium* complex.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 761.*

Figure 217-1 An enlarging cervical lymph node infected with *Mycobacterium avium* complex infection. The node is firm, painless, freely movable, and not erythematous.

Figure 217-3 A ruptured cervical lymph node infected with *Mycobacterium avium* complex, which resembles the classic scrofula of tuberculosis.

Figure 217-2 A suppurating cervical lymph node infected with *Mycobacterium avium* complex.

common in children 1-5 yr of age and has been related to soil exposure (e.g., playing in sandpits) and teething, although exact predisposing conditions have not been found. Given the constant environmental exposure to NTM, the occurrence of these infections might also reflect an atypical immune response of a subset of the infected children during or after their first contact with NTM.

Affected children usually lack constitutional symptoms and present with a unilateral subacute and slowly enlarging lymph node or group of closely approximated nodes >1.5 cm in diameter that are firm, painless, freely movable, and not erythematous (Fig. 217-1). The involved nodes occasionally resolve without treatment, but most undergo rapid suppuration after several weeks (Fig. 217-2). The center of the node becomes fluctuant, and the overlying skin becomes erythematous and thin. Eventually, the nodes rupture and form cutaneous sinus tracts that drain for months or years, resembling the classic scrofula of tuberculosis (Fig. 217-3).

In the United States and Western Europe, *M. avium* complex accounts for approximately 80% of NTM lymphadenitis in children. Birds are an unlikely source of these *M. avium* complex infections, as molecular typing has shown that the lymphadenitis-associated *M. avium* bacteria are of the human or porcine subtype rather than the bird type. *M. kansasii* accounts for most other cases of lymphadenitis in the United States. *Mycobacterium malmoense* and *Mycobacterium haemophilum* have also been described as causative agents of lymphadenitis. The former is only common in Northwestern Europe; for the latter, underestimation of its importance is likely because the bacteria require specific culture conditions (hemin-enriched media, low incubation temperatures). On the basis of polymerase chain reaction analysis of lymph node samples from lymphadenitis cases in the Netherlands, *M. haemophilum* is the second most common cause of this infection after *M. avium* complex. One study suggests that children with *M. avium* complex lymphadenitis are significantly younger than those infected by *M. haemophilum*, possibly related to age-specific environmental exposures.

Cutaneous disease caused by NTM is rare in children (see Table 217-1). Infection usually follows percutaneous inoculation with fresh or salt water contaminated by *M. marinum*. Within 2-6 wk after exposure, an erythematous papule develops at the site of minor abrasions on the elbows, knees, or feet (**swimming pool granuloma**) and on the hands and fingers of fish tank owners, mostly inflicted during tank cleaning (**fish tank granuloma**). These lesions are usually nontender and enlarge over 3-5 wk to form violaceous plaques. Nodules or pustules can develop and occasionally will ulcerate, resulting in a serosanguineous discharge. The lesions sometimes resemble sporotrichosis, with satellite lesions near the site of entry, extending along the superficial lymphatics. Lymphadenopathy is usually absent. Although most infections remain localized to skin, penetrating *M. marinum* infections can result in tenosynovitis, bursitis, osteomyelitis, or arthritis.

M. ulcerans infection is the third most common mycobacterial infection in immunocompetent patients, after *M. tuberculosis* and *M. leprae* infection, and causes cutaneous disease in children living in tropical regions of Africa, South America, Asia, and parts of Australia. In some communities in West Africa, up to 16% of people have been affected. Infection follows percutaneous inoculation from minor trauma, such as pricks and cuts from plants or insect bites. After an incubation period of approximately 3 mo, lesions appear as an erythematous nodule, most commonly on legs or arms. The lesion undergoes central necrosis and ulceration. The lesion, often called a **Buruli ulcer** after the region in Uganda where a large number of cases was reported, has a characteristic undermined edge, expands over several weeks, and can result in extensive, deep soft-tissue destruction or bone involvement. Lesions are typically painless, and constitutional symptoms are unusual. Lesions might heal slowly over 6-9 mo or might continue to spread, leading to deformities and contractures.

Skin and soft-tissue infections caused by rapidly growing mycobacteria, such as *M. fortuitum, M. chelonae,* or *M. abscessus,* are rare in children and usually follow percutaneous inoculation from puncture or surgical wounds, minor abrasions, or following tattooing. Clinical disease usually arises after a 4-6 wk incubation period and manifests as localized cellulitis, painful nodules, or a draining abscess. *M. haemophilum* can cause painful subcutaneous nodules, which often ulcerate and suppurate in immunocompromised patients, particularly after kidney transplantation.

NTM are an uncommon cause of **catheter-associated infections** but are becoming increasingly recognized in this respect. Infections caused

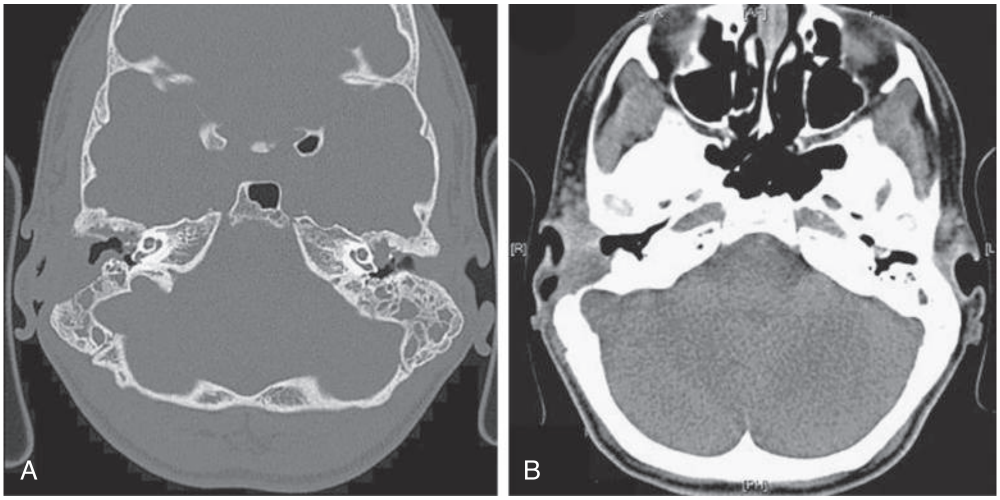

Figure 217-4 Computed tomography images of the middle ear of a 6 yr old child infected with *Mycobacterium abscessus* demonstrating extensive bone destruction in the right mastoid and associated right-sided mucosal swelling. **A,** Bone tissue window setting. **B,** Soft-tissue window setting.

by *M. fortuitum, M. chelonae,* or *M. abscessus* can manifest as bacteremia or localized catheter tunnel infections.

Otomastoiditis, or chronic otitis media, is a rare extrapulmonary NTM disease type that specifically affects children with tympanostomy tubes and a history of topical antibiotic or steroid use. *M. abscessus* is the most common causative agent, followed by *M. avium* complex (see Table 217-1). Patients present with painless, chronic otorrhea resistant to antibiotic therapy. CT imaging can reveal destruction of the mastoid bone with mucosal swelling (Fig. 217-4). Delayed or unsuccessful treatment can result in permanent hearing loss. In unusual circumstances, NTM causes other **bone** and **joint infections** that are indistinguishable from those produced by *M. tuberculosis* or other bacterial agents. Such infections usually result from operative incision or accidental puncture wounds. *M. fortuitum* infections from puncture wounds of the foot resemble infections caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Pulmonary infections are the most common form of NTM illness in adults but are rare in children. *M. avium* complex bacteria, the most commonly identified organisms (see Table 217-1), are capable of causing acute pneumonitis, chronic cough, or wheezing associated with paratracheal or peribronchial lymphadenitis and airway compression in normal children. Associated constitutional symptoms such as fever, anorexia, and weight loss occur in 60% of these children. Chest radiographic findings are very similar to those for primary tuberculosis, with unilateral infiltrates and hilar lymphadenopathy (Fig. 217-5). Pleural effusion is uncommon. Rare cases of progression to endobronchial granulation tissue have been reported.

Pulmonary infections usually occur in adults with underlying chronic lung disease. The onset is insidious and consists of cough and fatigue, progressing to weight loss, night sweats, low-grade fever, and generalized malaise in severe cases. Thin-walled cavities with minimal surrounding parenchymal infiltrates are characteristic, but radiographic findings can resemble those of tuberculosis. A separate disease manifestation occurs in postmenopausal women and is radiologically characterized by bronchiectasis and nodular lesions, often affecting the middle lobe and lingula.

Chronic pulmonary infections specifically affect children with **cystic fibrosis** and are generally caused by *M. abscessus* and *M. avium* complex. *M. abscessus* primarily affects children, and *M. avium* complex is most common among adults. The percentage of patients with cystic fibrosis with at least 1 sputum culture positive for NTM is 6-8.1% overall and increases with age; in cystic fibrosis patients younger than 12 yr of age, a prevalence of 3.9% has been reported. The strong representation of *M. abscessus* in these patients is remarkable, because this bacterium is an uncommon isolate in other categories of patients.

Figure 217-5 Chest radiograph of a 2 yr old child infected with *Mycobacterium avium* complex demonstrating a left upper lobe infiltrate and left hilar lymphadenopathy.

There are indications that NTM infections in patients with cystic fibrosis further accelerate the decline in lung function; antimycobacterial therapy can result in weight gain and improved lung function in affected patients.

Disseminated disease is usually associated with *M. avium* complex infection and occurs in immunocompromised children. The first category of patients with disseminated disease includes persons with mutations in genes coding for the interferon-γ receptor (IFNGR) or the IL-12 receptor, or for IL-12 production. Patients with complete **IFNGR deficiency** have severe disease that is difficult to treat. Those with partial IFNGR deficiency or IL-12 pathway mutations have milder disease that can respond to interferon-γ and antimycobacterial therapy. **Multifocal osteomyelitis** is particularly prevalent in persons with the IFNGR1 818del4 mutation. Recurrences, even years after a course of treatment, and multiple infections are well documented. The second

category of patients affected by **disseminated disease** is patients with **AIDS**. Disseminated NTM disease in patients with AIDS usually appears when CD4 cell counts are <50 cells/μL; in younger children (especially those <2 yr of age) these infections occur at higher CD4 cell counts. The most recent estimate of the incidence of disseminated NTM disease is 0.14-0.2 episodes per 100 person-years, a 10-fold decrease from its incidence before highly active antiretroviral therapy (HAART) was available.

Colonization of the respiratory or gastrointestinal tract probably precedes disseminated *M. avium* complex infections, but screening studies of respiratory secretions or stool samples are not useful to predict dissemination. Continuous high-grade bacteremia is common, and multiple organs are infected, most commonly including lymph nodes, liver, spleen, bone marrow, and gastrointestinal tract. Thyroid, pancreas, adrenal gland, kidney, muscle, and brain can also be involved. The most common signs and symptoms of disseminated *M. avium* complex infections in patients with AIDS are fever, night sweats, chills, anorexia, marked weight loss, wasting, weakness, generalized lymphadenopathy, and hepatosplenomegaly. Jaundice, elevated alkaline phosphatase or lactate dehydrogenase levels, anemia, and neutropenia can occur. Imaging studies usually demonstrate massive lymphadenopathy of hilar, mediastinal, mesenteric, or retroperitoneal nodes. The survival in children with AIDS has improved considerably with the availability of HAART therapy.

Disseminated disease in children without any apparent immunodeficiency is exceedingly rare.

DIAGNOSIS

For infections of lymph nodes, skin, bone, and soft tissues, isolation of the causative NTM bacteria by *Mycobacterium* **culture**, preferably with histologic confirmation of granulomatous inflammation, normally suffices for diagnosis. The differential diagnosis of NTM lymphadenitis includes acute bacterial lymphadenitis, tuberculosis, cat scratch disease (*Bartonella henselae*), mononucleosis, toxoplasmosis, brucellosis, tularemia, and malignancies, especially lymphomas. Differentiation between NTM and *M. tuberculosis* may be difficult, but children with NTM lymphadenitis usually have a Mantoux tuberculin skin test reaction of <15 mm induration, unilateral anterior cervical node involvement, a normal chest x-ray, and no history of exposure to adult tuberculosis. Definitive diagnosis requires excision of the involved nodes for culture and histology. Fine-needle aspiration for **polymerase chain reaction** and culture can enable earlier diagnosis, before excisional biopsy.

The diagnosis of **pulmonary NTM infection** in children is difficult because many species of NTM, including *M. avium* complex, are omnipresent in our environment and can contaminate, or occasionally be present in, clinical samples. As a result, isolation of these bacteria from nonsterile specimens (respiratory and digestive tract) does not necessarily reflect true disease. To determine the clinical relevance of isolation of NTM, the diagnostic criteria of the American and British Thoracic Societies are an important support. These criteria take into consideration clinical features and radiologic, pathologic, and microbiologic findings. The hallmark of these criteria is the need for **multiple positive cultures** yielding the same NTM species to make a definitive diagnosis of pulmonary NTM disease. In children, definitive diagnosis often requires invasive procedures such as bronchoscopy and pulmonary or endobronchial biopsy; in patients with cystic fibrosis, more-aggressive sample pretreatment is necessary to prevent overgrowth by other species, especially *Pseudomonas* spp. The chance that isolation of NTM is clinically relevant differs significantly by species; some species are more likely causative agents of true pulmonary disease (*M. avium*, *M. kansasii*, *M. abscessus*, *M. malmoense*), whereas others are most likely contaminants (*Mycobacterium gordonae*, *M. fortuitum*, *M. chelonae*).

Blood cultures are 90-95% sensitive in AIDS patients with disseminated infection. *M. avium* complex may be detected within 7-10 days of inoculation in nearly all patients by automated blood culture systems. In adults, liver biopsy cultures and stains have, in some studies, shown to be more sensitive than blood culture or bone marrow biopsy work-up. Commercially available DNA probes differentiate NTM from *M. tuberculosis*. If DNA probes cannot identify the causative mycobacteria, DNA sequencing of bacterial housekeeping genes will always yield a clue to the identity of these NTM. Identification of histiocytes containing numerous acid-fast bacilli from bone marrow and other biopsy tissues provides a rapid presumptive diagnosis of disseminated mycobacterial infection.

TREATMENT

Therapy for NTM infections is long-term and cumbersome; **expert consultation** is advised. Therapy involves medical, surgical, or combined treatment (see Chapter 214 and Table 214-3). Isolation of the infecting strain followed by **drug-susceptibility testing** is ideal, because it provides a baseline for drug susceptibility. Important discrepancies exist between in vitro drug susceptibility and in vivo response to treatment, explained in part by synergism, mainly among first-line antituberculosis drugs. In vitro, slow growers (*M. kansasii, M. marinum, Mycobacterium xenopi, M. ulcerans,* and *M. malmoense*) are usually susceptible to the first-line antituberculosis drugs rifampicin and ethambutol; *M. avium* complex bacteria are often resistant to these drugs alone but susceptible to the combination and have variable susceptibility to other antibiotics, most importantly the macrolides. Rapid growers (*M. fortuitum, M. chelonae, M. abscessus*) are highly resistant to antituberculosis drugs and often have inducible macrolide resistance mechanisms. Susceptibility to macrolides, aminoglycosides, carbapenems, tetracyclines, and glycylcyclines are most relevant for therapy guidance. In all NTM infections, multiple-drug therapy is essential to avoid development of resistance.

The preferred treatment of NTM lymphadenitis is complete **surgical excision;** clinical trials revealed that it is more effective than antibiotic treatment (see Table 214-3 in Chapter 214). Nodes should be removed while still firm and encapsulated. Excision is more difficult if extensive caseation with extension to surrounding tissue has occurred, and complications of facial nerve damage or recurrent infection are more likely in such cases. Incomplete surgical excision is not advised, because chronic drainage can develop. If there is concern for possible *M. tuberculosis* infection, therapy with isoniazid, rifampin, ethambutol, and pyrazinamide should be administered until cultures confirm the cause to be NTM (see Chapter 215). If for some reason surgery of NTM lymphadenitis cannot be performed, removal of infected tissue is incomplete, or recurrence or chronic drainage develops, a 3 mo trial of chemotherapy is warranted. Clarithromycin or azithromycin combined with rifabutin or ethambutol are the most commonly reported therapy regimens (see Table 214-3 in Chapter 214). In selected cases, a wait-and-see approach can be chosen, as the disease can resolve spontaneously.

Posttraumatic cutaneous NTM lesions in immunocompetent patients usually heal spontaneously after incision and drainage without other therapy (see Table 214-3 in Chapter 214). ***M. marinum*** is susceptible to rifampin, amikacin, ethambutol, sulfonamides, trimethoprim-sulfamethoxazole, and tetracycline. Therapy with a combination of these drugs, particularly clarithromycin and ethambutol, may be given for until 1 month after the lesion has disappeared. Corticosteroid injections should not be used. Superficial infections with *M. fortuitum* or *M. chelonae* usually resolve after surgical incision and open drainage, but deep-seated or catheter-related infections require removal of infected central lines and therapy with parenteral amikacin plus cefoxitin, ciprofloxacin, or clarithromycin.

Some localized forms of *M. ulcerans* skin disease (**Buruli ulcer**) can heal spontaneously; for most forms, excisional surgery with primary closure or skin grafting is recommended. Provisional guidelines by the World Health Organization recommend treatment with rifampin and streptomycin, with or without surgery. Currently, all-oral regimens of rifampicin and fluoroquinolones or macrolides are tested in clinical trials. In clinical experience, a drug treatment duration of 8 wk generally leads to low recurrence levels. Physiotherapy after surgery is essential to prevent contractures and functional disabilities.

Pulmonary infections should be treated initially with isoniazid, rifampin, ethambutol, and pyrazinamide pending culture identification

and drug-susceptibility testing. For slow-growing NTM, a combination of rifampin or rifabutin, ethambutol, and clarithromycin is recommended; exceptions are *M. kansasii*, for which a regimen of isoniazid, rifampicin, and ethambutol is advised, and *M. simiae*, for which no effective regimen is known and regimens are usually designed on the basis of in vitro drug susceptibilities. After culture conversion, treatment should be continued for at least 1 yr. For pulmonary disease caused by rapidly growing NTM, a combination of macrolides, fluoroquinolones, aminoglycosides, cefoxitin, and carbapenems is the optimal therapy; 3 or 4 drug regimens are selected on the basis of drug-susceptibility testing results. In patients with cystic fibrosis, there may be a role for inhaled antibiotics.

Patients with disseminated *M. avium* complex and IL-12 pathway defects or IFNGR deficiency should be treated for at least 12 mo with clarithromycin or azithromycin combined with rifampin or rifabutin and ethambutol. In vitro susceptibility testing for clarithromycin is important to guide therapy. Once the clinical illness has resolved, lifelong daily prophylaxis with azithromycin or clarithromycin is advisable to prevent recurrent disease. The use of interferon adjunctive therapy is determined by the specific genetic defect.

In children with **AIDS**, **prophylaxis** with azithromycin or clarithromycin is indicated to prevent infection with *M. avium* complex. Although few pediatric studies exist, the U.S. Public Health Service recommends either azithromycin (20 mg/kg once weekly PO; maximum: 1,200 mg/dose) or clarithromycin (7.5 mg/kg/dose twice daily PO; maximum:500 mg/dose) for HIV-infected children with significant immune deficiency as defined by the CD4 count (children ≥6 yr, CD4 count <50/µL; 2-6 yr, CD4 count <75/µL; 1-2 yr, CD4 count <500/µL; <1 yr, CD4 count <750/µL). Prophylaxis may be safely discontinued in children older than 2 yr of age receiving stable HAART for longer than 6 mo and experiencing sustained (>3 mo) CD4 cell recovery well above the age-specific target for initiation of prophylaxis: >100 cells/µL for children ≥6 yr of age and >200 cells/µL for children 2-5 yr of age. For children younger than 2 yr of age, no specific recommendations for discontinuing MAC prophylaxis exist.

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Section 8

Spirochetal Infections

Chapter 218

Syphilis *(Treponema pallidum)*

Maria Jevitz Patterson and H. Dele Davies

Syphilis is a chronic systemic sexually transmitted infection that can be easily treated if detected early but manifests with protean clinical symptoms and significant morbidity if left unchecked.

ETIOLOGY

Syphilis is caused by *Treponema pallidum,* a delicate, tightly spiraled, motile spirochete with finely tapered ends belonging to the family Spirochaetaceae. The pathogenic members of this genus include *T. pallidum* subspecies *pallidum* (venereal syphilis), *T. pallidum* subspecies *pertenue* (yaws), *T. pallidum* subspecies *endemicum* (bejel or endemic syphilis), and *T. pallidum* subspecies *carateum* (pinta). Because these microorganisms stain poorly and are below the detection limits of conventional light microscopy, detection in clinical specimens requires dark-field or phase contrast microscopy or direct immunofluorescent staining. *T. pallidum* cannot be cultured in vitro.

EPIDEMIOLOGY

In addition to presentation at sexually transmitted disease clinics, patients with syphilis are increasingly seen by primary care providers in private practice settings. Two forms of syphilis occur in children and adolescents.

Acquired syphilis is transmitted almost exclusively by sexual contact, including vaginal, anal, and oral exposure. Less-common modes of transmission include transfusion of contaminated blood or direct contact with infected tissues. After an epidemic resurgence of primary and secondary syphilis in the United States that peaked in 1989, the annual rate declined 90% by 2000. The total number of cases of primary and secondary syphilis has subsequently increased since 2000, particularly among men who have sex with men. Despite a decrease among women for almost a decade, their rates increased every year from 2004-2008. Cases of congenital syphilis rose in the same time period, but have fallen from 2008 through 2011, reflecting the slight decrease among women (Fig. 218-1). Rates in the southern United States, in some urban areas, and among non-Hispanic blacks remain disproportionately high.

Congenital syphilis results from transplacental transmission of spirochetes or during birth by contact with infectious lesions. Women with primary and secondary syphilis and spirochetemia are more likely to transmit infection to the fetus than are women with latent infection. Transmission can occur at any stage of pregnancy, resulting in early fetal loss, preterm or low birthweight infants, stillbirths, neonatal deaths, or infants born with congenital disease. The incidence of congenital infection in offspring of untreated or inadequately treated infected women remains highest during the 1st 4 yr after acquisition of primary infection, secondary infection, and early latent disease. Maternal factors associated with congenital syphilis are limited access to healthcare, late or no prenatal care, drug use, multiple sex partners, unprotected sexual contact, work in the sex trade, and inadequate treatment of syphilis during pregnancy (Fig. 218-2). Confirmed cases of both acquired and congenital syphilis must be reported to the local health department.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Many persons infected with syphilis are asymptomatic for years or do not recognize the early signs of disease or seek treatment. The Centers for Disease Control and Prevention (CDC) recommends selective testing of adolescents, based on lesions or risk factors (those with other sexually transmitted diseases, men who have sex with men,

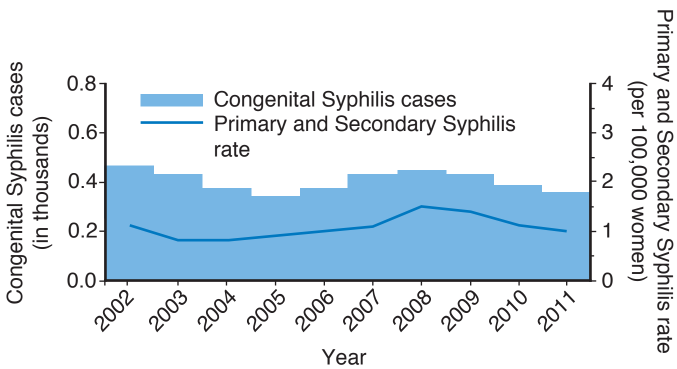

Figure 218-1 Congenital syphilis—reported cases among infants by year of birth and rates of primary and secondary syphilis among women, United States, 2002-2011. *(From Centers for Disease Control and Prevention [CDC]: 2011 Sexually transmitted disease surveillance. Available at: http://www.cdc.gov/std/stats11/figures/50.htm)*

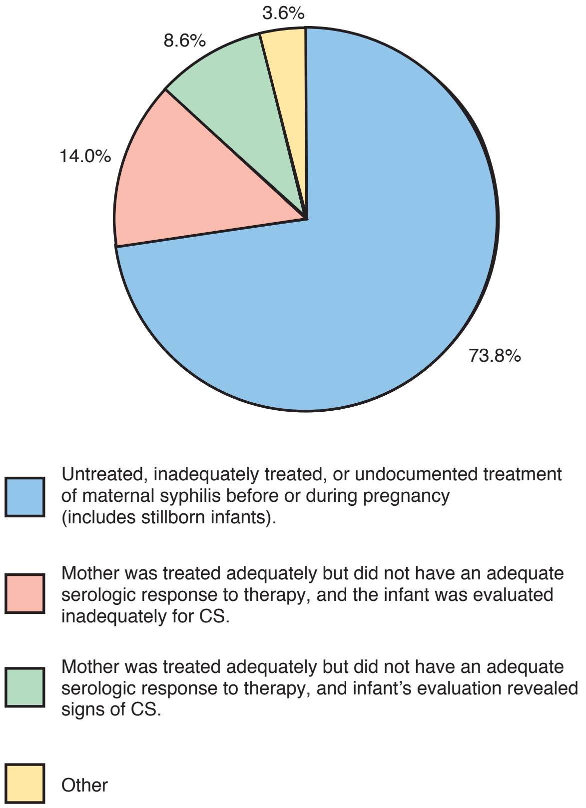

Figure 218-2 Diagnoses of congenital syphilis in the United States, 2002. *(From Centers for Disease Control and Prevention [CDC]: Primary and secondary syphilis—United States, 2002,* MMWR Morb Mortal Wkly Rep *52:1117–1120, 2003.)*

incarcerated individuals, or persons who exchange sex for money or drugs). **Primary syphilis** is characterized by a chancre and regional lymphadenitis. A **painless papule** appears at the site of entry (usually the genitals) 2-6 wk after inoculation and develops into a clean, painless, but highly contagious ulcer with raised borders (**chancre**) containing abundant *T. pallidum*. Extragenital chancres can occur at other sites of primary entry and pose a diagnostic challenge. Oral lesions can be mistaken for aphthous ulcers or herpes. Lesions on the nipple can be confused with cellulitis or eczema. Adjacent lymph nodes are generally enlarged and nontender. The chancre heals spontaneously within 4-6 wk, leaving a thin scar.

Untreated patients develop manifestations of **secondary syphilis** related to spirochetemia 2-10 wk after the chancre heals. Manifestations of secondary syphilis include a generalized nonpruritic maculopapular rash, notably involving the palms and soles (Fig. 218-3). Pustular lesions can also develop. **Condylomata lata,** gray-white to erythematous wart-like plaques, can occur in moist areas around the anus and vagina, and white plaques (**mucous patches)** may be found in mucous membranes. Secondary syphilis should be considered in the differential diagnosis of virtually any rash of unknown etiology. A **flu-like illness** with low-grade fever, headache, malaise, anorexia, weight loss, sore throat, myalgias, arthralgias, and generalized lymphadenopathy is often present. Renal, hepatic, and ophthalmologic manifestations may be present. Meningitis occurs in 30% of patients with secondary syphilis and is characterized by cerebrospinal fluid (CSF) pleocytosis and elevated protein level. Patients with meningitis might not show neurologic symptoms. Even without treatment, secondary infection becomes **latent** within 1-2 mo after onset of rash. Relapses with secondary manifestations can occur during the 1st yr of latency (the **early latent period). Late syphilis** follows and may be either asymptomatic (**late latent**) or symptomatic (**tertiary**). Tertiary disease follows in about one-third of untreated cases and is marked by neurologic, cardiovascular, and **gummatous lesions** (nonsuppurative granulomas

Figure 218-3 Secondary syphilis. Ham-colored palmar macules on an adolescent with secondary syphilis. *(From Weston WL, Lane AT, Morelli JG:* Color textbook of pediatric dermatology, *ed 3. St. Louis, 2002, Mosby.)*

of the skin, bone, and liver, resulting from the host cytotoxic T-cell response). The clinical course of syphilis and its tissue manifestations reflect the immunopathobiology of the host humoral and delayed-type hypersensitivity responses.

Congenital Infection

Untreated syphilis during pregnancy has a vertical transmission rate approaching 100%, with profound effects on pregnancy outcome. Fetal or perinatal death occurs in 40% of affected infants. Premature delivery can also occur. Neonates can also be infected at delivery by contact with an active genital lesion. Most infected infants are asymptomatic at birth and are identified only by routine prenatal screening. In the absence of treatment, symptoms develop within weeks or months. Among infants symptomatic at birth or in the 1st few mo of life, manifestations have traditionally been divided into early and late stages. All stages of congenital syphilis are characterized by a vasculitis, with progression to necrosis and fibrosis. The **early signs** appear during the 1st 2 yr of life, and the **late signs** appear gradually during the 1st 2 decades. Early manifestations vary and involve multiple organ systems, resulting from transplacental spirochetemia and are analogous to the secondary stage of acquired syphilis (Table 218-1). Hepatosplenomegaly, jaundice, and elevated liver enzymes are common. Histologically, liver involvement includes bile stasis, fibrosis, and extramedullary hematopoiesis. Lymphadenopathy tends to be diffuse and resolve spontaneously, although shotty nodes can persist.

Coombs-negative hemolytic anemia is characteristic. Thrombocytopenia is often associated with platelet trapping in an enlarged spleen. Characteristic osteochondritis and periostitis (Fig. 218-4) and a mucocutaneous rash (Fig. 218-5*A* and *B*) manifesting with erythematous maculopapular or vesiculobullous lesions followed by desquamation involving hands and feet (Fig. 218-5*C*) are common. Mucous patches, persistent rhinitis (**snuffles**), and condylomatous lesions (Fig. 218-6) are highly characteristic features of mucous membrane involvement containing abundant spirochetes. Blood and moist open lesions from infants with congenital syphilis and children with acquired primary or secondary syphilis are infectious until 24 hr of appropriate treatment.

Bone involvement is common. Roentgenographic abnormalities include **Wimberger lines** (metaphyseal demineralization of the medial aspect of the proximal tibia), multiple sites of osteochondritis at the wrists, elbows, ankles, and knees, and periostitis of the long bones and rarely the skull. The osteochondritis is painful, often resulting in irritability and refusal to move the involved extremity (**pseudoparalysis of Parrot**).

Congenital neurosyphilis is often asymptomatic in the neonatal period although CSF abnormalities can occur even in such infants.

Table 218-1 Late Manifestations of Congenital Syphilis

SYMPTOM/SIGN	DESCRIPTION/COMMENTS
Olympian brow	Bony prominence of the forehead caused by persistent or recurrent periostitis
Clavicular or Higoumenakia sign	Unilateral or bilateral thickening of the sternoclavicular third of the clavicle
Saber shins	Anterior bowing of the midportion of the tibia
Scaphoid scapula	Convexity along the medial border of the scapula
Hutchinson teeth	Peg-shaped upper central incisors; they erupt during 6th yr of life with abnormal enamel, resulting in a notch along the biting surface
Mulberry molars	Abnormal 1st lower (6 yr) molars characterized by small biting surface and excessive number of cusps
Saddle nose*	Depression of the nasal root, a result of syphilitic rhinitis destroying adjacent bone and cartilage
Rhagades	Linear scars that extend in a spoke-like pattern from previous mucocutaneous fissures of the mouth, anus, and genitalia
Juvenile paresis	Latent meningovascular infection; it is rare and typically occurs during adolescence with behavioral changes, focal seizures, or loss of intellectual function
Juvenile tabes	Rare spinal cord involvement and cardiovascular involvement with aortitis
Hutchinson triad	Hutchinson teeth, interstitial keratitis, and 8th nerve deafness
Clutton joint	Unilateral or bilateral painless joint swelling (usually involving knees) from synovitis with sterile synovial fluid; spontaneous remission usually occurs after several weeks
Interstitial keratitis	Manifests with intense photophobia and lacrimation, followed within weeks or months by corneal opacification and complete blindness
8th nerve deafness	May be unilateral or bilateral, appears at any age, manifests initially as vertigo and high-tone hearing loss, and progresses to permanent deafness

*A perforated nasal septum may be an associated abnormality.

Figure 218-4 Osteochondritis and periostitis in a newborn with congenital syphilis.

Failure to thrive, chorioretinitis, nephritis, and nephrotic syndrome can also be seen. Manifestations of renal involvement include hypertension, hematuria, proteinuria, hypoproteinemia, hypercholesterolemia, and hypocomplementemia, probably related to glomerular deposition of circulating immune complexes. Less-common clinical manifestations of early congenital syphilis include gastroenteritis, peritonitis, pancreatitis, pneumonia, eye involvement (glaucoma and chorioretinitis), nonimmune hydrops, and testicular masses.

Late manifestations (children >2 yr of age) are rarely seen in developed countries. These result primarily from chronic granulomatous inflammation of bone, teeth, and central nervous system and are summarized in Table 218-1. Skeletal changes are caused by persistent or recurrent periostitis and associated thickening of the involved bone. Dental abnormalities, such as **Hutchinson teeth** (Fig. 218-7), are common. Defects in enamel formation lead to repeated caries and eventual tooth destruction. S**addle nose** (Fig. 218-8) is a depression of the nasal root and may be associated with a perforated nasal septum.

Other late manifestations of congenital syphilis can manifest as hypersensitivity phenomena. These include unilateral or bilateral interstitial keratitis and the **Clutton joint** (see Table 218-1). Other common ocular manifestations include choroiditis, retinitis, vascular occlusion, and optic atrophy. Soft-tissue gummas (identical to those of acquired disease) and paroxysmal cold hemoglobinuria are rare hypersensitivity phenomena.

DIAGNOSIS

Fundamental limitations of the currently available tests for syphilis are vexing, but results must always be interpreted in the context of patient history and physical examination. Physicians should treat presumptively when syphilis is suspected by clinical and epidemiologic data. Diagnosis of primary syphilis is confirmed when *T. pallidum* is demonstrated by darkfield microscopy or direct fluorescent antibody testing on specimens from skin lesions, placenta, or umbilical cord. Nucleic acid–based amplification assays, such as polymerase chain reaction, are not commercially available. Despite the absence of a true gold standard serologic assay, serologic testing for syphilis remains the principal means for diagnosis and traditionally involves screening

Figure 218-5 **A** and **B,** Papulosquamous plaques in 2 infants with syphilis. **C,** Desquamation on the palm of a newborn's hand. *(**A** and **B** from Eichenfeld LF, Frieden IJ, Esterly NB, editors:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 196. **C** courtesy of Dr. Patricia Treadwell.)*

Figure 218-6 Perianal condylomata lata. *(From Karthikeyan K, Thappa DM: Early congenital syphilis in the new millennium,* Pediatr Dermatol *19:275–276, 2002.)*

Figure 218-7 Hutchinson teeth as a late manifestation of congenital syphilis.

Figure 218-8 Saddle nose in a newborn with congenital syphilis.

with a nontreponemal test followed by a confirmatory treponemal test (Fig. 218-9*A*).

The **Venereal Disease Research Laboratory (VDRL)** and **rapid plasma reagin (RPR)** tests are sensitive **nontreponemal tests** that detect antibodies against phospholipid antigens on the treponeme surface that crossreact with cardiolipin-lecithin-cholesterol antigens of damaged host cells. The quantitative results of these tests are helpful both in screening and in monitoring therapy. Titers increase with active disease, including treatment failure or reinfection, and decline with adequate treatment (Fig. 218-10). Nontreponemal tests usually become nonreactive within 1 yr of adequate therapy for primary syphilis and within 2 yr of adequate treatment for secondary disease. Uncommonly some patients become **serofast** (nontreponemal titers persisting at low levels for long periods). In congenital infection, these tests become nonreactive within a few months after adequate treatment. Certain conditions such as infectious mononucleosis and other viral infections, autoimmune diseases, and pregnancy can give false-positive VDRL results. False-positive results are less common with the use of purified cardiolipin-lecithin-cholesterol antigen. All pregnant women should be screened early in pregnancy and at delivery. All positive maternal serologic tests for syphilis, regardless of titer, necessitate thorough investigation. Antibody excess can give a false-negative reading unless the serum is diluted **(prozone effect).** False-negative results can also occur in early primary syphilis, in latent syphilis of long duration, and in late congenital syphilis.

Treponemal tests traditionally are used to confirm diagnosis and measure specific *T. pallidum* antibodies (immunoglobulin [Ig] G, IgM and IgA), which appear earlier than nontreponemal antibodies. These treponemal tests include the *T. pallidum* particle agglutination test, the *T. pallidum* hemagglutination assay, and the fluorescent treponemal antibody absorption test. Treponemal antibody titers become positive soon after initial infection and usually remain positive for life, even with adequate therapy (see Fig. 218-10). These antibody titers do not correlate with disease activity. Traditionally they are useful for diagnosis of a first episode of syphilis and for distinguishing false-positive results of nontreponemal antibody tests but cannot accurately identify length of time of infection, response to therapy, or reinfection.

There is limited crossreactivity of treponemal antibody tests with other spirochetes, including the causative organisms of Lyme disease

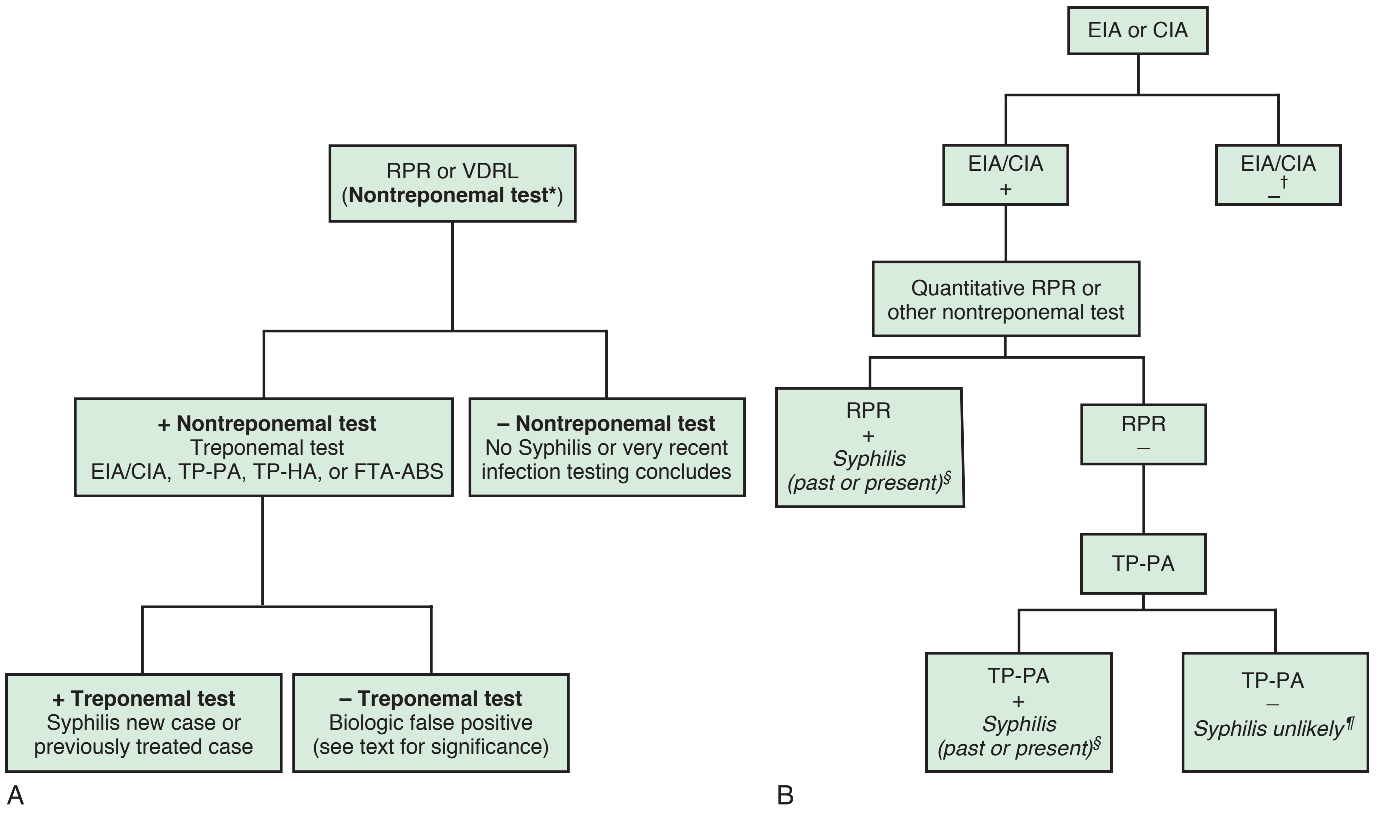

Figure 218-9 **A,** Traditional laboratory testing algorithm for syphilis. **B,** CDC-recommended algorithm for reverse sequence syphilis screening (treponemal test screening followed by nontreponemal test confirmation). Despite these recommendations for reverse sequence screening, the CDC continues to recommend the traditional algorithm with reactive nontreponemal tests confirmed by treponemal testing. *EIA/CIA*, enzyme immunoassay/chemiluminescence immunoassay; *FTA-ABS*, fluorescent treponemal antibody absorption; *RPR*, rapid plasma reagin; *TP-HA*, *Treponema pallidum* hemagglutination; *TP-PA*, Treponema pallidum particle agglutination; *VDRL*, Venereal Disease Research Laboratory. *If nontreponemal test is positive qualitatively, a titer is then quantitated. †If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units intramuscularly in a single dose. §Evaluate clinically, determine whether treated for syphilis in the past, assess risk for infection, and administer therapy according to CDC's 2010 STD Treatment Guidelines (available at http://www.cdc.gov/std/treatment/2010). ¶If at risk for syphilis, repeat RPR in several weeks. *(**A** based on data from Workowski KA, Berman S; Centers for Diseases Control and Prevention [CDC]: Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 59[RR-12]:1-110, 26-29, 2010; **B** from Centers for Disease Control and Prevention [CDC]: Discordant results from reverse sequence syphilis screening—five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep 60(5):133-137, 2011.)*

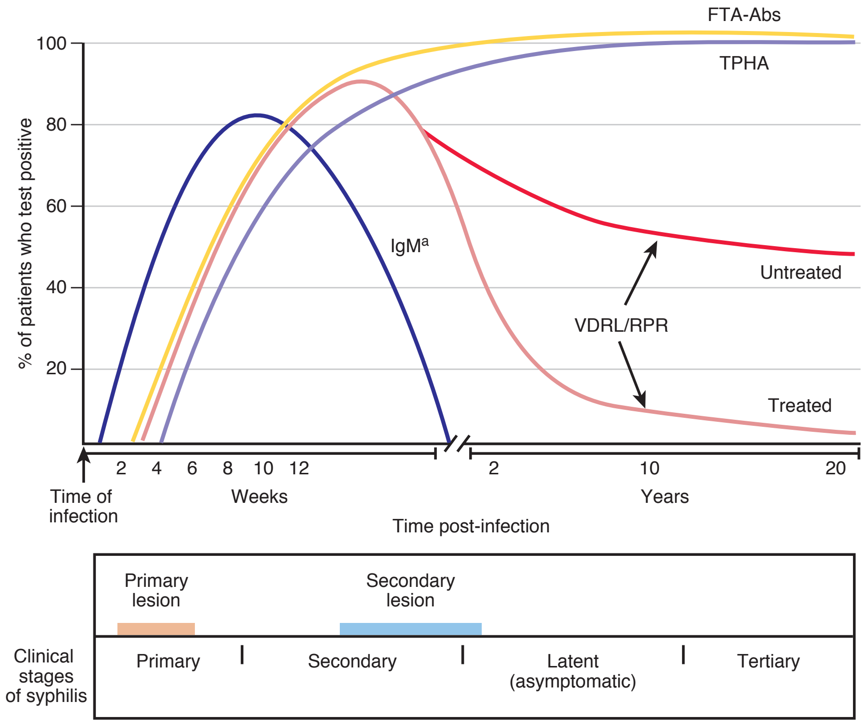

[a]IgM by ELISA or FTA-ABS 195 or immunoblot

Figure 218-10 **Common patterns of serologic reactivity in syphilis patients.** *FTA-Abs*, fluorescent treponemal antibody absorption (test); *RPR*, rapid plasma reagin (test); *TPHA*, *Treponema pallidum* hemagglutination assay; *VDRL*, Venereal Disease Research Laboratory (test). *(From Peeling RW, Ye H: Diagnostic tools for preventing and managing maternal and congenital syphilis: an overview,* Bull World Health Organ *82:439–446, 2004.)*

(Borrelia burgdorferi), yaws, endemic syphilis, and pinta. Only venereal syphilis and Lyme disease are found in the United States. Nontreponemal tests (VDRL, RPR) are uniformly nonreactive in Lyme disease.

Enzyme immunoassays and chemiluminescence immunoassays to detect treponemal IgG and IgM have been developed. These assays have increased sensitivity and are amenable to automation and high volume use. Such assays should allow developing countries quality screening programs at the point-of-service because the World Health Organization currently relies on syndromic management of sexually transmitted infections, where patients are treated for all likely causes of their constellation of signs and symptoms. In the United States, use of enzyme immunoassays has confounded screening because it switches the traditional algorithm: the treponemal-specific testing is done before the nontreponemal testing. Because the former remain positive for life, clinical and epidemiologic data are required to provide clear guidelines to distinguish cured disease, early syphilis, untreated late latent disease, and true false-positive tests. The benefits of reverse screening are increased detection of transmissible early syphilis and of late latent disease to afford monitoring for tertiary disease. Although the CDC continues to recommend the traditional screen (see Fig. 218-9*A*) they have provided guidelines for interpretation of the reverse screening algorithm (see Fig. 218-9*B*). Interpretation of nontreponemal and treponemal serologic tests in the newborn can be confounded by maternal IgG antibodies transferred to the fetus. Passively acquired antibody is suggested by a neonatal titer at least 4-fold (i.e., a 2 tube dilution) less than the maternal titer. This conclusion can be verified by gradual decline in antibody in the infant, usually becoming undetectable by 3-6 mo of age.

The diagnosis of neurosyphilis remains difficult but is often established by demonstrating pleocytosis and increased protein in the CSF and a positive CSF VDRL test along with neurologic symptoms. The CSF VDRL test is specific but relatively insensitive (22-69%) for neurosyphilis. CSF polymerase chain reaction (polymerase chain reaction) and IgM immunoblot tests are under development to assist in diagnosis of neurosyphilis.

Darkfield microscopy of scrapings from primary lesions or congenital or secondary lesions can reveal *T. pallidum,* often before serology becomes positive, but this technique is usually not available in clinical practice. Placental examination by gross and microscopic techniques can be useful in the diagnosis of congenital syphilis. The disproportionately large placentas are characterized histologically by focal proliferative villitis, endovascular and perivascular arteritis, and focal or diffuse immaturity of placental villi.

Congenital Syphilis

Diagnosis of congenital syphilis requires thorough review of maternal history of syphilis treatment preconception and testing, treatment, and the dynamics of response during the current pregnancy. Regardless of maternal treatment and the presence/absence of symptoms in the infant, proactive evaluation and treatment of exposed neonates is critical (Fig. 218-11 and Table 218-2). Symptomatic infants should be thoroughly evaluated and treated. Table 218-3 describes the guidelines for

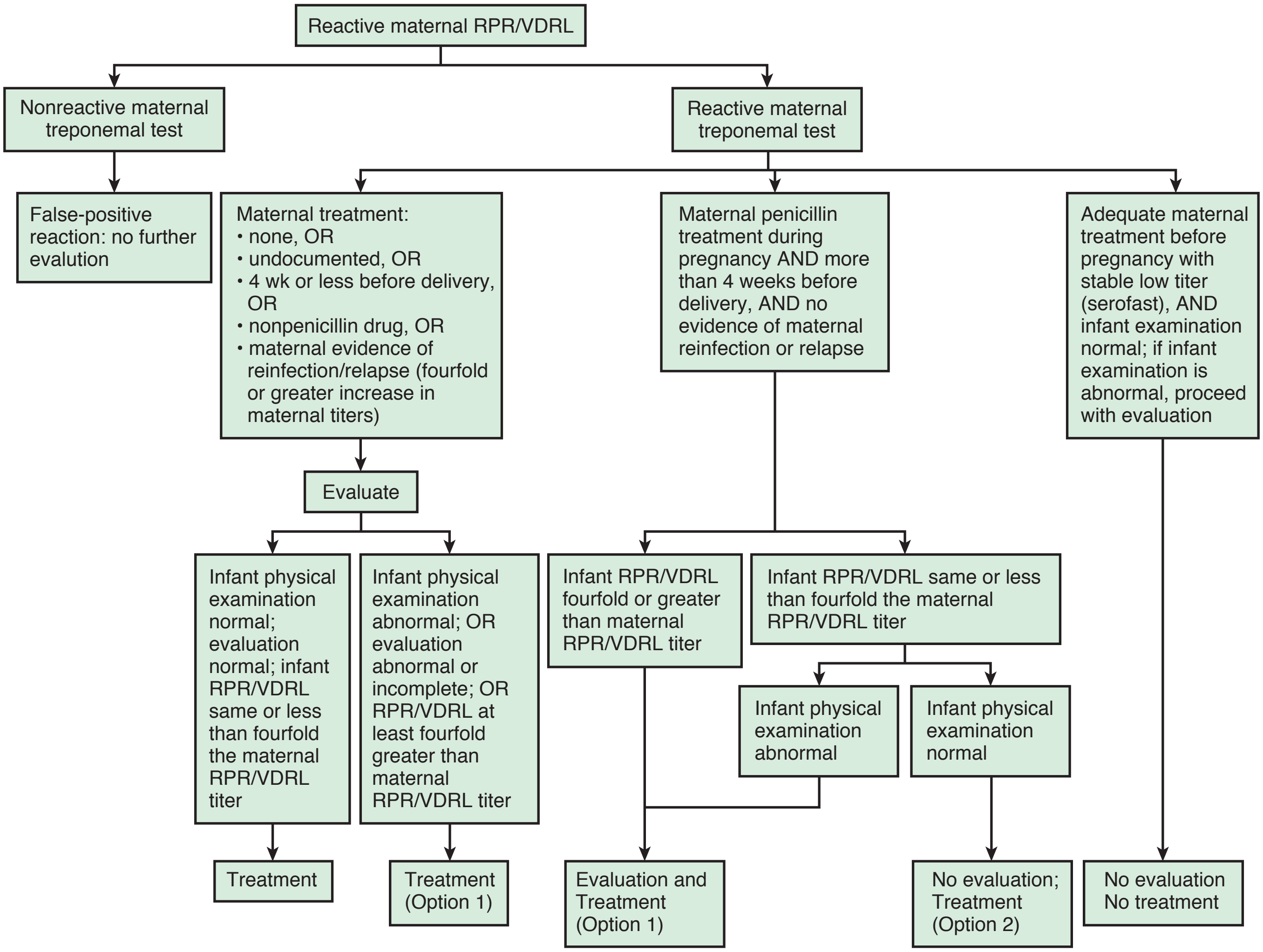

Figure 218-11 Algorithm for evaluating and treating infants born to mothers with reactive serologic tests for syphilis. *(From American Academy of Pediatrics:* Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics,* Fig. 3-7, *p. 695.)*

Table 218-2 Clues That Suggest a Diagnosis of Congenital Syphilis*

EPIDEMIOLOGIC BACKGROUND	CLINICAL FINDINGS
Untreated early syphilis in the mother Untreated latent syphilis in the mother An untreated mother who has contact with a known syphilitic during pregnancy Mother treated for syphilis during pregnancy with a drug other than penicillin Mother treated for syphilis during pregnancy without follow-up to demonstrate 4-fold change in titer Mother coinfected with HIV	Osteochondritis, periostitis Snuffles, hemorrhagic rhinitis Condylomata lata Bullous lesions, palmar or plantar rash Mucous patches Hepatomegaly, splenomegaly Jaundice Nonimmune hydrops fetalis Generalized lymphadenopathy Central nervous system signs; elevated cell count or protein in cerebrospinal fluid Hemolytic anemia, diffuse intravascular coagulation, thrombocytopenia Pneumonitis Nephrotic syndrome Placental villitis or vasculitis (unexplained enlarged placenta) Intrauterine growth restriction

*Arranged in decreasing order of confidence of diagnosis.
Modified from Remington JS, Klein JO, Wilson CB, et al, editors: Infectious diseases of the fetus and newborn infant, *ed 6. Philadelphia, 2006, WB Saunders, p. 556.*

Table 218-3 Recommended Management of Neonates (≤1 Month of Age) Born to Mothers with Serologic Tests for Syphilis

CLINICAL STATUS	EVALUATION (IN ADDITION TO PHYSICAL EXAMINATION AND QUANTITATIVE NONTREPONEMAL TESTING)	ANTIMICROBIAL THERAPY*
Proven or highly probable disease†	CSF analysis for VDRL, cell count, and protein CBC and platelet count Other tests as clinically indicated (e.g., long-bone radiography, liver function tests, ophthalmologic examination)	Aqueous crystalline penicillin G, 100,000-150,000 units/kg/day, administered as 50,000 units/kg/dose IV q12hr during the 1st 7 days of life and 18 hr thereafter for a total of 10 days *or* Penicillin G procaine, 50,000 units/kg/day IM in a single dose × 10 days
NORMAL PHYSICAL EXAMINATION AND SERUM QUANTITATIVE NONTREPONEMAL TITER ≤4 TIMES THE MATERNAL TITER:		
(a) (i) Mother was not treated or inadequately treated or has no documented treatment; (ii) mother was treated with erythromycin or other nonpenicillin regimen; (iii) mother received treatment ≤4 wk before delivery; (iv) maternal evidence of reinfection or relapse (<4-fold decrease in titers)	CSF analysis for VDRL, cell count, and protein§ CBC and platelet count§ Long-bone radiography§	Aqueous crystalline penicillin G IV × 10 days§ *or* Penicillin G procaine‡ 50,000 units/kg IM in a single dose × 10 days§ *or* Penicillin G benzathine‡ 50,000 units/kg IM in a single dose§
(b) (i) Adequate maternal therapy given >4 wk before delivery; (ii) mother has no evidence of reinfection or relapse	None	Clinical, serologic follow-up, and penicillin G benzathine 50,000 units/kg IM in a single dose‖
(c) Adequate therapy before pregnancy and mother's nontreponemal serologic titer remained low and stable during pregnancy and at delivery	None	None¶

*If more than 1 day of therapy is missed, the entire course should be restarted.
†Abnormal physical examination, serum quantitative nontreponemal titer that is 4-fold greater than the mother's titer, or positive result of darkfield or fluorescent antibody test of body fluid(s).
‡Penicillin G benzathine and penicillin G procaine are approved for IM administration only.
§A complete evaluation (CSF analysis, bone radiography, CBC) is not necessary if 10 days of parenteral therapy is administered, but it may be useful to support a diagnosis of congenital syphilis. If a single dose of penicillin G benzathine is used, then the infant must be evaluated fully, results of the full evaluation must be normal, and follow-up must be certain. If any part of the infant's evaluation is abnormal or not performed or if the CSF analysis is uninterpretable, the 10-day course of penicillin is required.
‖Some experts would not treat the infant but would provide close serologic follow-up.
¶Some experts would treat with penicillin G benzathine, 50,000 units/kg, as a single IM injection, if follow-up is uncertain.
CBC, complete blood cell count; CSF, cerebrospinal fluid; VDRL, Venereal Disease Research Laboratory.
From American Academy of Pediatrics: Red book: 2009 report of the Committee on Infectious Diseases, *28/e. Elk Grove Village, IL, 2009, American Academy of Pediatrics, p. 645.*

evaluating and managing asymptomatic infants who are considered at risk for congenital syphilis because the maternal nontreponemal and treponemal serology is positive. Internationally adopted children should also be screened.

Diagnosis of neurosyphilis in the newborn with syphilitic infection is confounded by poor sensitivity of the CSF VDRL test in this age group and lack of CSF abnormalities. A positive CSF VDRL test in a newborn warrants treatment for neurosyphilis, even though it might reflect passive transfer of antibodies from serum to CSF. It is now accepted that all infants with a presumptive diagnosis of congenital syphilis should be treated with regimens effective for neurosyphilis because central nervous system involvement cannot be reliably excluded. Diagnosis of syphilis beyond early infancy should lead to consideration of possible child abuse.

For infants with proven or highly probable disease or abnormal physical findings, complete evaluation including serologic tests (RPR or VDRL), complete blood count with differential and platelet count, liver function tests, long-bone radiographs, ophthalmology examination, auditory brainstem response, and other tests as indicated should be performed. For infants with a positive VDRL or RPR test result and normal physical examination whose mothers were inadequately treated, further evaluation is not necessary if 10 days of parenteral therapy is administered.

TREATMENT

T. pallidum remains extremely sensitive to penicillin, with no evidence of emerging penicillin resistance, and thus penicillin remains the treatment drug of choice (see Tables 218-3 and 218-4 and http://www.cdc.gov/std/treatment). Parenteral penicillin G is the only documented effective treatment for congenital syphilis, syphilis during pregnancy, and neurosyphilis. Aqueous crystalline penicillin G is preferred over procaine penicillin, because it better achieves and sustains the minimum concentration of 0.018 µg/mL (0.03 units/mL) needed for 7-10 days to achieve treponemicidal levels. Although nonpenicillin regimens are available to the penicillin-allergic patient, desensitization followed by standard penicillin therapy is the most reliable strategy. An acute systemic febrile reaction called the **Jarisch-Herxheimer reaction** (caused by massive release of endotoxin-like antigens during bacterial lysis) occurs in 15-20% of patients with acquired or congenital syphilis treated with penicillin. It is not an indication for discontinuing penicillin therapy.

Acquired Syphilis

Primary, secondary, and early latent disease is treated with a single dose of benzathine penicillin G (50,000 units/kg IM, maximum 2.4 million units). Persons with late latent or tertiary disease require 3 doses at 1 wk intervals. Nonpregnant penicillin-allergic patients without neurosyphilis may be treated with either doxycycline (100 mg PO twice daily for 2 wk) or tetracycline (500 mg PO 4 times daily for 2 wk). Emerging azalide and macrolide resistance has been documented in several U.S. cities, compromising the effective use of these antibiotics. Careful serologic follow-up is always necessary. Less than a 4-fold decline in titer reflects treatment failure.

The CDC recommends that all persons with syphilis be tested for HIV. Patients coinfected with HIV are at increased risk for neurologic complications and higher rates of treatment failure. CDC guidelines recommend the same treatment of primary and secondary syphilis as for patients who are not infected with HIV, but some experts recommend 3 weekly doses of benzathine penicillin G. HIV-infected patients with late latent syphilis or latent syphilis of unknown duration should have a CSF evaluation for neurosyphilis before treatment.

Sex partners of infected persons of any stage should be evaluated and treated. Persons exposed for 90 days or less preceding diagnosis in a sex partner should be treated presumptively even if seronegative. Persons exposed for more than 90 days before the diagnosis in a sex partner should be treated if seropositive or if serologic tests are not available. Follow-up serology should be performed on treated patients to establish adequacy of therapy, and all patients should be tested for other sexually transmitted diseases, including HIV.

Table 218-4 Recommended Treatment for Syphilis in Patients Older Than 1 Month of Age

STATUS	CHILDREN	ADULTS
Congenital syphilis	Aqueous crystalline penicillin G 200,000-300,000 units/kg/day IV administered as 50,000 units/kg q4-6hr × 10 days*	
Primary, secondary, and early latent syphilis†	Penicillin G benzathine,‡ 50,000 units/kg, IM, up to the adult dose of 2.4 million units in a single dose	Penicillin G benzathine,‡ 2.4 million units IM in a single dose *or* *If allergic to penicillin and not pregnant,* doxycycline 100 mg PO bid × 14 days *or* Tetracycline 500 mg PO qid × 14 days
Late latent syphilis§ or syphilis of unknown duration	Penicillin G benzathine,‡ 50,000 units/kg IM up to the adult dose of 2.4 million units, administered as 3 single doses at 1 wk intervals (total 150,000 units/kg, up to the adult dose of 7.2 million units)	Penicillin G benzathine‡ 7.2 million units total administered as 3 doses of 2.4 million units IM, each at 1 wk intervals *or* *If allergic to penicillin and not pregnant,* doxycycline 100 mg PO bid × 4 wk *or* Tetracycline 500 mg PO qid × 4 wk
Tertiary syphilis		Penicillin G benzathine‡ 7.2 million units total, administered as 3 doses of 2.4 million units IM at 1 wk intervals *If allergic to penicillin and not pregnant, same as for late latent syphilis*
Neurosyphilis‖	Aqueous crystalline penicillin G 200,000-300,000 units/kg/day q4-6hr × 10-14 days in doses not to exceed the adult dose	Aqueous crystalline penicillin G 18-24 million units/day administered as 3-4 million units IV q4hr × 10-14 days¶ *or* Penicillin G procaine,‡ 2.4 million units IM once daily *plus* probenecid 500 mg PO qid, both × 10-14 days¶

*If the patient has no clinical manifestations of disease, the CSF examination is normal, and the CSF VDRL result is negative, some experts would treat with up to 3 weekly doses of penicillin G benzathine 50,000 units/kg IM. Some experts also suggest giving these patients a single dose of penicillin G benzathine 50,000 units/kg IM after the 10-day course of IV aqueous penicillin.

†Early latent syphilis is defined as being acquired within the preceding year.

‡Penicillin G benzathine and penicillin G procaine are approved for IM administration only.

§Late latent syphilis is defined as syphilis beyond 1 year's duration.

‖Patients who are allergic to penicillin should be desensitized.

¶Some experts administer penicillin G benzathine 2.4 million units IM, once per week for up to 3 wk after completion of these neurosyphilis treatment regimens.

CSF, cerebrospinal fluid; VDRL, Venereal Disease Research Laboratory.

From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 698, Table 3.72.*

Syphilis in Pregnancy

When clinical or serologic findings suggest active infection or when diagnosis of active syphilis cannot be excluded with certainty, treatment is indicated. Patients should be treated with the penicillin regimen appropriate for the woman's stage of syphilis. Women who have been adequately treated in the past do not require additional therapy unless quantitative serology suggests evidence of reinfection (**4-fold elevation in titer**). Doxycycline and tetracycline should not be administered during pregnancy, and macrolides do not effectively prevent fetal infection. Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin.

Congenital Syphilis

Adequate maternal therapy should eliminate the risk for congenital syphilis. All infants born to mothers with syphilis should be followed until nontreponemal serology is negative. The infant should be treated if there is any uncertainty about the adequacy of maternal treatment. Any infant at risk of congenital syphilis should be evaluated for HIV.

Congenital syphilis is treated with aqueous penicillin G (100,000-150,000 units/kg/24 hr divided every 12 hr IV for the 1st wk of life, and every 8 hr thereafter) or procaine penicillin G (50,000 units/kg IM once daily) given for 10 days. Both penicillin regimens are recognized as adequate therapy for congenital syphilis, but higher concentrations of penicillin are achieved in the CSF of infants treated with intravenous aqueous penicillin G than in those treated with intramuscular procaine penicillin. Treated infants should be followed every 2-3 mo to confirm at least a 4-fold decrease in nontreponemal titers. Treated infants with congenital neurosyphilis should undergo clinical and CSF evaluation at 6-mo intervals until CSF is normal. In a very-low-risk neonate who is asymptomatic and whose mother was treated appropriately, without evidence of relapse or reinfection, but with a low and stable VDRL titer (serofast), no evaluation is necessary. Some specialists would treat such an infant with a single dose of benzathine penicillin G 50,000 units/kg IM.

PREVENTION

Syphilis, including congenital syphilis, is a reportable disease in all 50 states and the District of Columbia. Testing is indicated at any time for persons with suspicious lesions, a history of recent sexual exposure to a person with syphilis, or diagnosis of another sexually transmitted infection, including HIV infection. Timely treatment lessens risk of community spread. Vaccine prevention remains elusive, confounded by the treponeme's ability to evade the immune system.

Congenital Syphilis

Congenital syphilis is a preventable disease, with primary prevention tied to prevention of syphilis in women of childbearing age and secondary prevention being early diagnosis and prompt treatment of women and their partners. Routine prenatal screening for syphilis remains the most important factor in identifying infants at risk for developing congenital syphilis. Screening all women at the beginning of prenatal care is an evidence-based standard of care and legally required in all states. In pregnant women without optimal prenatal care, serologic screening for syphilis should be performed at the time pregnancy is diagnosed. Any woman who is delivered of a stillborn infant at 20 wk or fewer of gestation should be tested for syphilis. In communities and populations with a high prevalence of syphilis and in patients at high risk, testing should be performed at least 2 additional times: at the beginning of the 3rd trimester (28 wk) and at delivery. Some states mandate repeat testing at delivery for all women, underscoring the importance of preventive screening. Women at high risk for syphilis should be screened even more frequently, either monthly or pragmatically in the case of inconsistent prenatal care, at every medical encounter because they can have repeat infections during pregnancy or reinfection late in pregnancy. Follow-up serologic testing of all treated women should be done after treatment to document titer decline, relapse, or reinfection.

No newborn should leave the hospital without the maternal serologic status having been determined at least once during pregnancy. In states conducting newborn screening for syphilis, both the mother's and infant's serologic results should be known before discharge. In addition, all previously uninvestigated infants of an infected mother should be screened.

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Chapter 219

Nonvenereal Treponemal Infections

Stephen K. Obaro and H. Dele Davies

Nonvenereal treponemal infections—yaws, bejel (endemic syphilis), and pinta—are caused by different subspecies of *Treponema pallidum* and occur in tropical and subtropical areas. The causative agents of nonvenereal treponematoses—*T. pallidum pertenue, T. pallidum* subspecies *endemicum,* and *Treponema carateum*—cannot be distinguished from *T. pallidum pallidum* by morphologic or serologic tests.

In general, nonvenereal treponematoses have prominent cutaneous manifestations and relapsing courses, as in venereal syphilis, but they are not found in urban centers, they are not sexually transmitted, and they are not congenitally acquired. Transmission is primarily through body contact, poor hygiene, crowded conditions, and poor access to healthcare. Children also serve as the primary reservoirs for these organisms, spreading infection via skin-to-skin and skin-to-mucous membrane contact, and possibly via fomites as well.

Penicillin remains the treatment of choice for syphilis and nonvenereal treponemal infections.

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219.1 Yaws *(Treponema pertenue)*

Stephen K. Obaro and H. Dele Davies

Yaws is the most prevalent nonvenereal treponematosis. The causative agent, *Treponema pertenue* bears very close genomic resemblance to *T. pallidum*. The *T. pallidum pertenue* genome was sequenced in 2010 and compared with *T. pallidum pallidum* strains; the overall sequence identity between the 2 genomes was 99.8%. It is a contagious, chronic, relapsing infection involving the skin and bony structures caused by the spirochete *T. pertenue,* which is identical to *T. pallidum* microscopically and serologically. It occurs in tropical regions with heavy rainfall and annual temperatures ≥27°C (80°F). Almost all cases occur in children in tropical and subtropical countries. It is also referred to as "framboesia," "pian," "parangi," and "bouba." A high percentage of the population is infected in endemic areas.

T. pertenue is transmitted by direct contact from an infected lesion through a skin abrasion or laceration. Transmission is facilitated by overcrowding and poor personal hygiene in the rain forest areas of the world. Yaws predominantly affects children, with approximately 75% of cases being reported in children younger than 15 yr of age. This population also constitutes the reservoir for disease transmission. The initial papular lesion, which constitutes **primary yaws**, also described as the **"mother yaw,"** occurs 2-8 wk after inoculation. This lesion typically involves the buttocks or lower extremities. The papule develops

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into a raised, raspberry-like papilloma and is often accompanied by regional lymphadenopathy. The skin pathology is very similar to that of venereal syphilis, consisting of epidermal hyperplasia and papillomatosis. Healing of the mother yaw leaves a hypopigmented scar. The **secondary stage** lesions can erupt anywhere on the body before or after the healing of the mother yaw and may be accompanied by lymphadenopathy, anorexia, and malaise. Multiple cutaneous lesions (daughter yaws, pianomas, or frambesias) appear, spread diffusely, ulcerate, and are covered by exudates containing treponemes. Secondary lesions heal without scarring. Recurrent lesions are common within 5 yr after the primary lesion.

The lesions are often associated with bone pain resulting from underlying periostitis or osteomyelitis, especially of the fingers, nose, and tibia. The initial period of clinical activity is followed by a 5-10 yr period of latency. The appearance of tertiary stage lesions develops in approximately 10% of infected patients, with onset typically at puberty with solitary and destructive lesions. These lesions occur as painful papillomas on the hands and feet, gummatous skin ulcerations, or osteitis. Bony destruction and deformity, juxtaarticular nodules, depigmentation, and painful hyperkeratosis **("dry crab yaws")** of the palms and soles are common. Approximately 10% of patients may progress and develop tertiary stage lesions after 5 yr or more of untreated infection, although this is now rare.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Darkfield examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of crossreactivity, are used to confirm the diagnosis. The nontreponemal agglutination tests such as the rapid plasma reagin and Venereal Diseases Research Laboratory tests are positive in untreated cases, and these tests can be used for test of cure, because they revert to negative following treatment. However, the treponemal tests (*T. pallidum* hemagglutination assay, *T. pallidum* particle agglutination assay, and fluorescent treponemal antibody absorption) are more specific and remain positive for life. New immunochromatographic test strips that can be applied for testing both whole blood and serum were developed. These are simple, cheap, and easy to use and do not require refrigeration.

Differential diagnosis includes other conditions with similar cutaneous manifestations such as eczema, psoriasis, excoriated chronic scabies, tungiasis, leishmaniasis, tropical ulcer cutaneous mycoses, and verrucae. Involvement of the bone may mimic dactylitis that is commonly associated with sickle cell disease

Treatment of yaws consists of a single dose of the long-acting benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 yr) for index patients and all contacts. Patients allergic to penicillin may be treated with erythromycin, doxycycline, or tetracycline at appropriate doses for venereal syphilis (see Chapter 218). One oral dose of azithromycin (30 mg/kg; maximum: 2 g) is as effective as benzathine penicillin. Treatment cures the lesions of active yaws, renders them noninfectious, and prevents relapse. Family members, contacts, and patients with latent infection should receive the same dose as those with active disease. Eradication of yaws from some endemic areas has been accomplished by treating the entire population with penicillin or azithromycin.

219.2 Bejel (Endemic Syphilis; *Treponema pallidum endemicum*)

Stephen K. Obaro and H. Dele Davies

Bejel, or endemic syphilis, affects children in remote rural communities living in poor hygienic conditions. Bejel, unlike yaws, can occur in temperate as well as dry, hot climates. Infection with *T. pallidum* subspecies *endemicum* follows penetration of the spirochete through traumatized skin or mucous membranes. In experimental infections, a primary papule forms at the inoculation site after an incubation period of 3 wk. A primary lesion is almost never visualized in human infections; however, primary ulcers have been described surrounding the nipples of nursing mothers with infected children.

The clinical manifestations of the **secondary stage** typically occurs 3-6 mo after inoculation and are confined to the skin and mucous membranes. They consist of highly infectious mucous patches on the oral mucosa and condyloma-like lesions on the moist areas of the body, especially the axilla and anus. These mucocutaneous lesions resolve spontaneously over a period of several months, but recurrences are common. The secondary stage is followed by a variable latency period before the onset of late or tertiary bejel. The tertiary stage can occur as early as 6 mo or as late as several years after resolution of initial symptoms. The lesions in the tertiary stage are identical to those of yaws and include gumma formation in skin, subcutaneous tissue, and bone, resulting in painful destructive ulcerations, swelling, and deformity.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Dark-field examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of crossreactivity, are used to confirm the diagnosis.

Differentiation from venereal syphilis is extremely difficult in an endemic area. Bejel is distinguished by the absence of a primary chancre and lack of involvement of the central nervous system and cardiovascular system during the late stage.

Treatment of early infection consists of a single dose of benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 yr). Late infection is treated with 3 injections of the same dosage at intervals of 7 days. Patients allergic to penicillin may be treated with erythromycin or tetracycline.

219.3 Pinta *(Treponema carateum)*

Stephen K. Obaro and H. Dele Davies

Pinta is a chronic, nonvenereally transmitted infection caused by *T. pallidum* subsp. *carateum,* a spirochete morphologically and serologically indistinguishable from other human treponemes. This is perhaps the mildest of the nonvenereal treponematoses. The disease is endemic in Mexico, Central America, South America, and parts of the West Indies and largely affects children younger than 15 yr of age.

Infection follows direct inoculation of the treponeme through abraded skin. After a variable incubation period of days, the **primary** lesion appears at the inoculation site as a small asymptomatic erythematous papule resembling localized psoriasis or eczema. The regional lymph nodes are often enlarged. Spirochetes can be visualized on darkfield examination of skin scrapings or from biopsy of the involved lymph nodes. After a period of enlargement, the primary lesion disappears. Unlike primary yaws, the lesion does not ulcerate but can expand with central depigmented resolution. **Secondary** lesions follow within 6-8 mo and consist of small macules and papules on the face, scalp, and other sun-exposed portions of the body. These pigmented, highly infectious lesions are scaly and nonpruritic and can coalesce to form large plaque-like elevations resembling psoriasis. In the late or **tertiary** stage, atrophic and depigmented lesions develop on the hands, wrists, ankles, feet, face, and scalp. Hyperkeratosis of palms and soles is uncommon.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Darkfield examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of crossreactivity, are used to confirm the diagnosis.

Treatment consists of a single dose of benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 yr). Tetracycline and erythromycin are alternatives for patients allergic to penicillin. Treatment campaigns and improvement of standards of living are necessary for reduction and elimination of disease.

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Chapter 220

Leptospira

H. Dele Davies and Kari A. Simonsen

Leptospirosis is a common and widespread zoonosis caused by aerobic, motile spirochetes of the genus *Leptospira.*

ETIOLOGY

Pathogenic leptospires belong to 9 species, which include more than 300 antigenically distinct serovars. A single serovar can produce a variety of distinct syndromes, and a single clinical manifestation may be caused by multiple serotypes.

EPIDEMIOLOGY

Most human cases of leptospirosis occur in tropical and subtropical countries, but the distribution is worldwide. Leptospires survive for days to weeks in warm and damp environmental conditions, including water and moist soil. In the United States, Hawaii reports approximately 50% of all cases, with Pacific coastal states and Southern states having higher incidence than the remainder of the country. Leptospires infect many species of animals, including rats, mice, moles, livestock (such as cattle, goats, sheep, horses, and pigs), wild mammals like raccoons or opossums, and domestic dogs. Infected animals excrete spirochetes in their urine for prolonged periods. Worldwide, most human cases result from occupational exposure to water or soil contaminated with rat urine; however, the major animal reservoir in the United States is the dog. Groups at high risk for leptospirosis include persons exposed occupationally or recreationally to contaminated soil, water, or infected animals, including agricultural workers, veterinarians, abattoir workers, meat inspectors, rodent control workers, laboratory workers, and military personnel. Transmission via animal bites and directly from person to person has been rarely reported.

PATHOLOGY AND PATHOGENESIS

Leptospires enter humans through mucous membranes (primarily eyes, nose, and mouth) or abraded skin or by ingestion of contaminated water. After penetration, they circulate in the bloodstream to all body organs, causing endothelial lining damage of small blood vessels with secondary ischemic damage to end organs.

CLINICAL MANIFESTATIONS

The spectrum of human leptospirosis ranges from asymptomatic infection (most cases) to severe disease with multiorgan dysfunction and death. The onset is usually abrupt, and the illness tends to follow a biphasic course (Fig. 220-1). After an incubation period of 7-12 days, there is an **initial** or **septicemic phase** lasting 2-7 days, during which leptospires can be isolated from the blood, cerebrospinal fluid (CSF), and other tissues. This phase may be followed by a brief period of well-being before onset of a second symptomatic **immune** or **leptospiruric phase**. This phase is associated with the appearance of circulating immunoglobulin M antibody, disappearance of organisms from the blood and CSF, and appearance of signs and symptoms associated with localization of leptospires in the tissues. Despite the presence of circulating antibody, leptospires can persist in the kidney, urine, and aqueous humor. The immune phase can last for several weeks. Symptomatic infection may be anicteric or icteric.

Anicteric Leptospirosis

The **septicemic phase** of anicteric leptospirosis has an abrupt onset with flu-like symptoms of fever, shaking chills, lethargy, severe headache, malaise, nausea, vomiting, and severe debilitating myalgia most prominent in the lower extremities, lumbosacral spine, and abdomen. Bradycardia and hypotension can occur, but circulatory collapse is uncommon. Conjunctival suffusion with photophobia and orbital pain (in the absence of chemosis and purulent exudate), generalized lymphadenopathy, and hepatosplenomegaly may also be present. A transient (<24 hr) erythematous maculopapular, urticarial, petechial, purpuric, or desquamating rash occurs in 10% of cases. Rarer manifestations include pharyngitis, pneumonitis, arthritis, carditis, cholecystitis, and orchitis. The **second** or **immune phase** can follow a brief asymptomatic interlude and is characterized by recurrence of fever and aseptic meningitis. Although 80% of infected children have abnormal CSF profiles, only 50% have clinical meningeal manifestations. CSF abnormalities include a modest elevation in pressure, pleocytosis with early polymorphonuclear leukocytosis followed by mononuclear predominance rarely exceeding 500 cells/µL, normal or slightly elevated protein levels, and normal glucose values. Encephalitis, cranial and peripheral neuropathies, papilledema, and paralysis are uncommon. A self-limited unilateral or bilateral uveitis can occur during this phase, rarely resulting in permanent visual impairment. Central nervous system symptoms usually resolve spontaneously within 1 wk, with almost no mortality.

Icteric Leptospirosis (Weil Syndrome)

Weil syndrome is a rare (<10% of cases) severe form of leptospirosis seen more commonly in adults (>30 yr) than in children. The initial manifestations are similar to those described for anicteric leptospirosis. The immune phase, however, is characterized by jaundice, renal failure, thrombocytopenia, and, in fulminant cases, hemorrhage and cardiovascular collapse. Hepatic involvement leads to right upper quadrant pain, hepatomegaly, direct and indirect hyperbilirubinemia, and

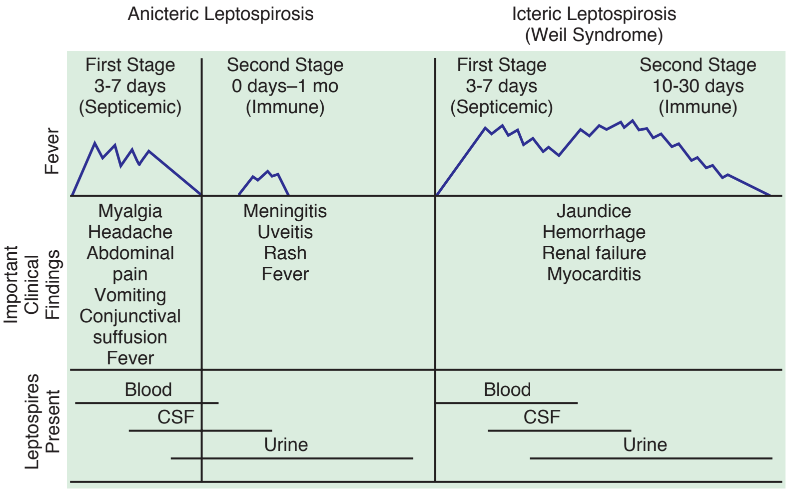

Figure 220-1 Stages of anicteric and icteric leptospirosis. Correlation between clinical findings and presence of leptospires in body fluids. CSF, cerebrospinal fluid. *(Reprinted with permission from Feigin RD, Anderson DC: Human leptospirosis,* CRC Crit Rev Clin Lab Sci *5:413–467, 1975. Copyright CRC Press, Inc, Boca Raton, FL.)*

modestly elevated serum levels of hepatic enzymes. Liver function usually returns to normal after recovery. All patients have abnormal findings on urinalysis (hematuria, proteinuria, and casts), and azotemia is common, often associated with oliguria or anuria. Acute kidney failure occurs in 16-40% of cases and is the principal cause of death. Abnormal electrocardiograms are present in 90% of cases, but congestive heart failure is uncommon. Transient thrombocytopenia occurs in >50% of cases. Rarely, hemorrhagic manifestations occur, including epistaxis, hemoptysis, and pulmonary, gastrointestinal, and adrenal hemorrhage. The mortality rate is 5-15%.

DIAGNOSIS

Leptospirosis should be considered in the differential diagnosis of acute flu-like febrile illnesses with a history of direct contact with animals or with soil or water contaminated with animal urine. This disease may be difficult to distinguish clinically from dengue or malaria.

The diagnosis is most often confirmed by serologic testing and less often by isolation of the infecting organism from clinical specimens. The "gold-standard" diagnostic method is the **microscopic agglutination test,** a serogroup-specific assay using live antigen suspension of leptospiral serovars and dark-field microscopy for agglutination. A 4-fold or greater increase in titer in paired sera confirms the diagnosis. Agglutinins usually appear by the 12th day of illness and reach a maximum titer by the 3rd wk. Low titers can persist for years. Approximately 10% of infected persons do not have detectable agglutinins, presumably because available antisera do not identify all *Leptospira* serotypes. Additionally, enzyme-linked immunosorbent assay methods, latex agglutination, and immunochromatography are commercially available, and DNA polymerase chain reaction diagnostics have been developed but are not in common clinical usage. Phase-contrast and darkfield microscopy are insensitive for spirochete detection, but organisms may be identified using Warthin-Starry silver stain or fluorescent antibody staining of tissue or body fluids. Unlike other pathogenic spirochetes, leptospires can be recovered from the blood or CSF during the 1st 10 days of illness and from urine after the 2nd wk by repeated culture of small inoculum (i.e., 1 drop of blood or CSF in 5 mL of medium) on commercially available selective media. However, the inoculum in clinical specimens is small, and growth can take up to 13 wk.

TREATMENT

Despite in vitro sensitivity of *Leptospira* to penicillin and tetracyclines, the effectiveness of these antibiotics in treating human leptospirosis is unclear because of the naturally high spontaneous recovery rates. Some studies suggest that initiation of treatment before the 7th day shortens the clinical course and decreases the severity of the infection; thus treatment with penicillin G, cefotaxime, or doxycycline (in children ≥8 yr of age) should be instituted early when the diagnosis is suspected. Parenteral penicillin G (6-8 million units/m^2/day divided every 4 hr IV for 7 days) is recommended, with doxycycline 2 mg/kg/day divided in 2 doses with maximum of 100 mg twice daily as an alternative for patients allergic to penicillin. Azithromycin was evaluated in a randomized, nonblinded clinical trial and shown to be as effective as doxycycline and can be used as an alternative in patients for whom doxycycline is contraindicated. In severe illness, supportive care with specific attention given to cardiopulmonary status, renal function, coagulopathy, and fluid and electrolyte balance is warranted.

PREVENTION

Prevention of human leptospirosis infection is facilitated by instituting rodent control measures and avoiding contaminated water and soil. Immunization of livestock and domestic dogs is recommended as a means of reducing animal reservoirs. Attempts at a human vaccine have been challenging, and the diversity of *Leptospira* serovars and their geographic distributions are important considerations in vaccine design. Protective clothing (i.e., boots, gloves, and goggles) should be worn by persons at risk for occupational exposure. In hospital settings, standard precautions are recommended, with contact precautions for exposure to, or handling of infected urine. Leptospirosis was successfully prevented in American soldiers stationed in the tropics by administering prophylactic doxycycline (200 mg PO once a week). This approach may be similarly effective for travelers to highly endemic areas for short periods; however, there are no specific pediatric data to support any prophylaxis regimen.

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Chapter 221

Relapsing Fever *(Borrelia)*

H. Dele Davies and Stephen K. Obaro

Relapsing fever is characterized by recurring fevers and "flu-like symptoms" such as headaches, myalgia, arthralgia, and rigors.

ETIOLOGY

It is an arthropod (lice or ticks)-transmitted infection caused by spirochetes of the genus *Borrelia*.

Louse-borne (epidemic) relapsing fever is caused by *Borrelia recurrentis* and is transmitted from person to person by *Pediculus humanus,* the human body louse. Human infection occurs as a result of crushing lice during scratching, facilitating entry of infected hemolymph through abraded or normal skin or mucous membranes.

Tick-borne (endemic) relapsing fever is caused by several species of *Borrelia* and is transmitted to humans by *Ornithodoros* ticks. *Borrelia hermsii* and *Borrelia turicatae* are the common species in the western United States, while *Borrelia dugesii* is the major cause of disease in Mexico and Central America. Human infection occurs when saliva, coxal fluid, or excrement is released by the tick during feeding, thereby permitting spirochetes to penetrate the skin and mucous membranes.

EPIDEMIOLOGY

Louse-borne relapsing fever tends to occur in epidemics associated with war, poverty, famine, and poor personal hygiene, often in association with typhus. This form of relapsing fever is no longer seen in the United States but is endemic in parts of East Africa. Up to 20.5% of all unexplained fever in the horn of Africa, including northwestern Morocco where the population traditionally lives in mud huts, is caused by tickborne relapsing fever using 16sRNA polymerase chain reaction assays for molecular detection, making this the most common cause of bacterial infections.

Ornithodoros ticks, which transmit endemic relapsing fever and are distributed worldwide, including in the western United States, prefer warm, humid environments and high altitudes, and are found in rodent burrows, caves, and other nesting sites (Fig. 221-1). Rodents (e.g., squirrels and chipmunks) are the principal reservoirs. Infected ticks gain access to human dwellings on the rodent host. Human contact is often unnoticed because these soft ticks have a painless bite, and detach immediately after a short blood meal.

PATHOLOGY AND PATHOGENESIS

Relapsing fever is cyclical because the *Borrelia* organisms undergo antigenic (phase) variation. Multiple variants evolve simultaneously during the first relapse, with 1 type becoming predominant. Spirochetes isolated during the primary febrile episode differ antigenically from those recovered during a subsequent relapse. During febrile episodes, spirochetes enter the bloodstream, induce the development of specific immunoglobulins M and G antibodies, and undergo

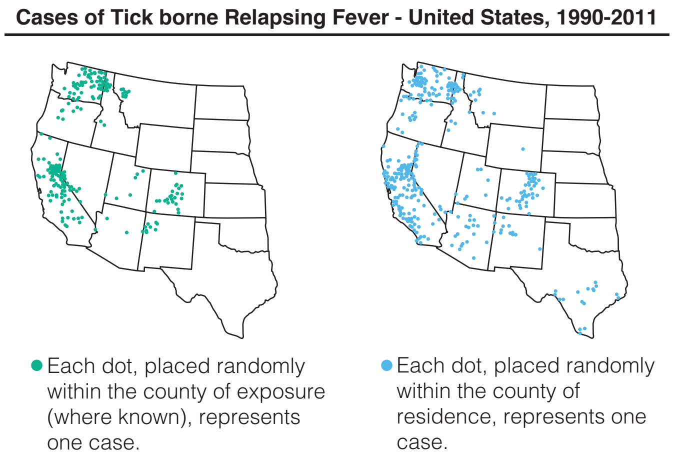

Figure 221-1 Cases of tickborne relapsing fever–United States, 1990-2011. During the years 1990-2011, 483 cases of tickborne relapsing fever were reported in the western United States, with infections being transmitted most frequently in California, Washington, and Colorado. *(From Centers for Disease Control and Prevention [CDC]: Tick-borne relapsing fever: distribution. Available at: http://www.cdc.gov/relapsing-fever/distribution)*

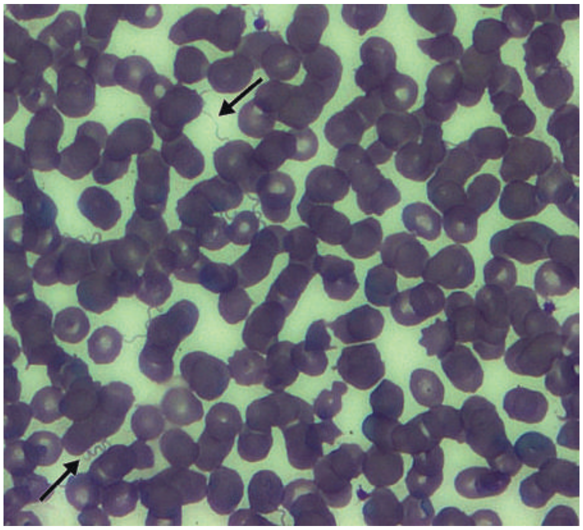

Figure 221-2 Stained thin smear of a newborn's peripheral blood, showing the presence of numerous spirochetes (indicated by *black arrows*) at ×63 magnification—Colorado, 2011. *(From Centers for Disease Control and Prevention [CDC]: Tickborne relapsing fever in a mother and newborn child–Colorado, 2011.* MMWR Morb Mortal Wkly Rep *61:174–176, 2012.)*

agglutination, immobilization, lysis, and phagocytosis. During remission, *Borrelia* spirochetes may remain in the bloodstream, but spirochetemia is insufficient to produce symptoms. The number of relapses in untreated patients depends on the number of antigenic variants of the infecting strain.

CLINICAL MANIFESTATIONS

Relapsing fever is characterized by febrile episodes lasting 2-9 days, separated by afebrile intervals of 2-7 days. Louse-borne disease has an incubation period of 2-14 days, longer periods of pyrexia, fewer relapses, and longer remission periods than tickborne disease. The incubation period of tickborne disease is usually 7 days (range: 2-9 days). Each form of relapsing fever is characterized by sudden onset of high fever, lethargy, headache, photophobia, nausea, vomiting, myalgia, and arthralgia. Additional symptoms may appear later and include abdominal pain, a productive cough, mild respiratory distress and bleeding manifestations, including epistaxis, hemoptysis, hematuria, and hematemesis. During the end of the primary febrile episode, a diffuse, erythematous, macular, or petechial rash lasting up to 2 days may develop over the trunk and shoulders. There may also be lymphadenopathy, pneumonia, and splenomegaly. Hepatic tenderness associated with hepatomegaly is a common sign, with jaundice in half of affected children. Central nervous system manifestations include lethargy, stupor, meningismus, convulsions, peripheral neuritis, focal neurologic deficits, and cranial nerve paralysis and may be the principal feature of late relapses in tickborne disease. Severe manifestations include myocarditis, hepatic failure, and disseminated intravascular coagulopathy.

The initial symptomatic period characteristically ends with a crisis in 2-9 days, marked by abrupt diaphoresis, hypothermia, hypotension, bradycardia, profound muscle weakness, and prostration. In untreated patients, the first relapse occurs within 1 wk, followed by usually 3 but up to 10 relapses, with symptoms during each relapse becoming milder and shorter as the afebrile remission period lengthens.

DIAGNOSIS

Diagnosis depends on demonstration of spirochetes by darkfield microscopy or in thin or thick blood smears stained with Giemsa or Wright stain and by blood culture (Fig. 221-2). During afebrile remissions, spirochetes are not found in the blood. Serologic tests have not been standardized, are generally not available, and produce crossreactions with other spirochetes, including *Borrelia burgdorferi,* the agent of Lyme disease. Molecular methods, including nested polymerase chain reaction or 16sRNA polymerase chain reaction assays, have been used for detection of tickborne and louse-borne recurrent fever and have been found to have improved sensitivity and specificity compared to blood smears. However, these assays are not yet routinely available for commercial use.

TREATMENT

Oral or parenteral tetracycline or doxycycline is the drug of choice for louse-borne and tickborne relapsing fever. For children older than 8 yr of age and young adults, tetracycline 500 mg PO every 6 hr or doxycycline 100 mg PO every 12 hr for 10 days is effective. Single-dose treatment with tetracycline (500 mg PO) or erythromycin is efficacious in adults, but experience in children is limited. In children younger than 8 yr of age, erythromycin (50 mg/kg/day divided every 6 hr PO) for a total of 10 days is recommended. Penicillin and chloramphenicol are also effective.

Resolution of each febrile episode either by natural crisis or as a result of antimicrobial treatment is often accompanied by the Jarisch-Herxheimer reaction, which is caused by massive antigen release. Corticosteroid or antipyretic pretreatment do not prevent the reaction.

PROGNOSIS

With adequate therapy, the mortality rate for relapsing fever is <5%. A majority of patients recover from their illness with or without treatment after the appearance of anti-*Borrelia* antibodies, which agglutinate, kill, or opsonize the spirochete. However, pregnant women and their neonates are at increased risk for tickborne recurrent fever-associated complications, including adult respiratory distress syndrome, Jarisch-Herxheimer reaction, and precipitous or premature delivery. Neonates have up to a 33% case-fatality rate.

PREVENTION

No vaccine is available. Disease control requires avoidance or elimination of the arthropod vectors. In epidemics of louse-borne disease, good personal hygiene and delousing of persons, dwellings, and clothing with commercially available insecticides can prevent dissemination. The risk for tickborne disease can be minimized in endemic areas by maintaining rodent-free dwellings. Giving prophylactic doxycycline for 4 days after a tick bite may prevent tickborne relapsing fever caused by *Borrelia persica.*

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Chapter 222

Lyme Disease *(Borrelia burgdorferi)*

Stephen C. Eppes

Lyme disease is the most common vector-borne disease in the United States and is an important public health problem.

ETIOLOGY

Lyme disease is caused by the spirochete *Borrelia burgdorferi* sensu lato (broad sense). In North America, *B. burgdorferi* sensu stricto (strict sense) causes virtually all cases, and in Europe, the species *Borrelia afzelii* and *Borrelia garinii* also cause disease. The 3 major outer-surface proteins, called OspA, OspB, and OspC (which are highly charged basic proteins of molecular weights of about 31, 34, and 23 kDa, respectively), and the 41 kDa flagellar protein are important targets for the immune response. Differences in the molecular structure of the different species are associated with differences in the clinical manifestations of Lyme borreliosis in Europe and the United States. These differences include the greater incidence of radiculoneuritis in Europe.

EPIDEMIOLOGY

Lyme disease has been reported from more than 50 countries. In the United States, more than 30,000 cases were reported in 2011; however, because of incomplete reporting of cases, it is estimated that the actual number of cases is much higher. In 2011, 93% of cases occurred in 13 states: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Vermont, Virginia, and Wisconsin (Fig. 222-1). In endemic areas, the reported annual incidence ranges from 20-100 cases per 100,000 population, although this figure may be as high as 600 cases per 100,000 population in hyperendemic areas. In Europe, most cases occur in the Scandinavian countries and in central Europe, especially Germany, Austria, and Switzerland. The reported incidence is highest among children 5-9 yr of age, with a second peak of disease activity in middle-age adults. In the United States, Lyme disease is diagnosed in boys slightly more often than in girls, and 94% of patients are of European descent. Early Lyme disease (described later) usually occurs from spring to early fall, corresponding to deer tick activity. Late disease (chiefly arthritis) occurs year round. Among adults, outdoor occupation and leisure activities are risk factors; for children, location of residence in an endemic area is the most important risk for infection.

TRANSMISSION

Lyme disease is a zoonosis caused by the transmission of *B. burgdorferi* to humans through the bite of an infected tick of the *Ixodes* genus. In the eastern and midwestern United States, the vector is *Ixodes scapularis,* the black-legged tick that is commonly known as the deer tick, which is responsible for most cases of Lyme disease in the United States. The vector on the Pacific Coast is *Ixodes pacificus,* the western black-legged tick. *Ixodes* ticks have a 2 yr, 3 stage life cycle. The larvae hatch in the early summer and are usually uninfected with *B. burgdorferi.* The tick can become infected at any stage of its life cycle by feeding on a host, usually a small mammal such as the white-footed mouse (*Peromyscus leucopus*), which is a natural reservoir for *B. burgdorferi.* The larvae overwinter and emerge the following spring in the nymphal stage, which is the stage of the tick most likely to transmit the infection. The nymphs molt to adults in the fall, and then adults spend the second winter attached to white-tailed deer (*Odocoileus virginianus*). The females lay their eggs the following spring before they die, and the 2 yr life cycle begins again.

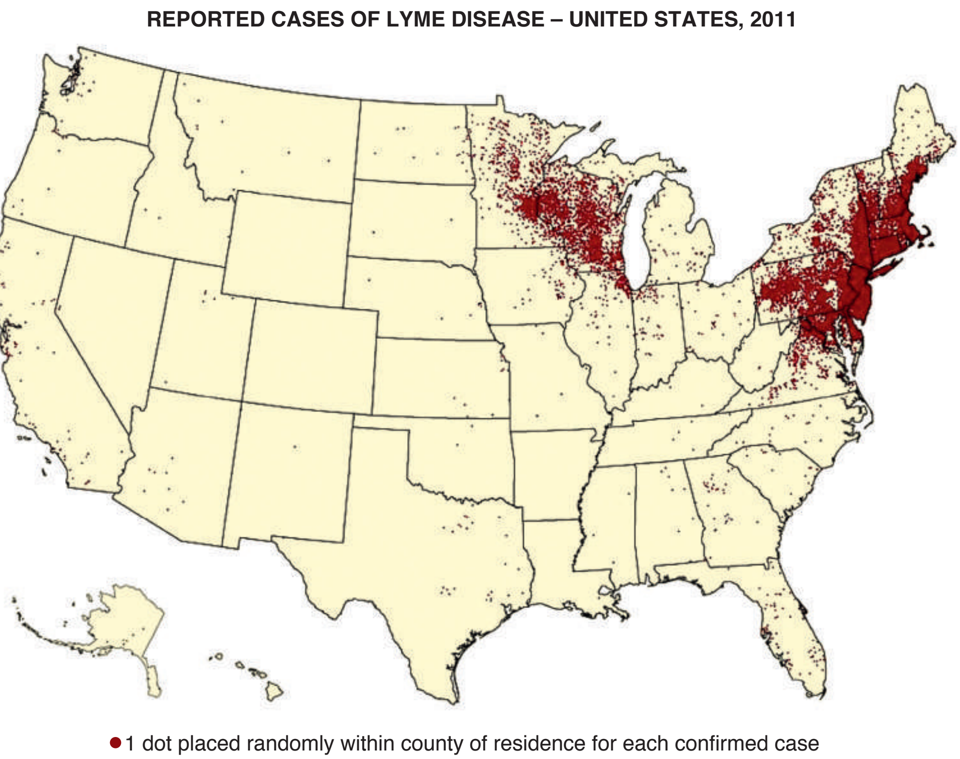

Figure 222-1 **The approximate distribution of predicted risk for Lyme disease in the United States.** The risk varies by the distribution of *Ixodes scapularis* and *Ixodes pacificus*, the proportion of ticks that are infected at each stage of the tick's life cycle, and the presence of grassy or wooded locations favored by white-tailed deer. *(From the Centers for Disease Control and Prevention [CDC]: Reported cases of Lyme disease—United States, 2011. Available at: http://www.cdc.gov/lyme/stats/maps/map2011.html)*

Several factors are associated with increased risk for transmission of *B. burgdorferi* from ticks to humans. The proportion of infected ticks varies by geographic area and by stage of the tick's life cycle. In endemic areas in the northeastern and midwestern United States, 15-25% of nymphal ticks and 35-50% of adult ticks are infected with *B. burgdorferi.* By contrast, *I. pacificus* often feeds on lizards, which are not a competent reservoir for *B. burgdorferi,* reducing the chance that these ticks will be infected. The risk for transmission of *B. burgdorferi* from infected *Ixodes* ticks is related to the duration of feeding. Experiments in animals show that infected nymphal ticks must feed for 36-48 hr, and infected adults must feed for 48-72 hr, before the risk for transmission of *B. burgdorferi* becomes substantial. If the tick is recognized and removed promptly, transmission of *B. burgdorferi* will not occur.

I. scapularis also transmits other microorganisms, namely *Anaplasma phagocytophilum* and *Babesia microti.* Simultaneous transmission can result in coinfections with these organisms and *B. burgdorferi.*

PATHOLOGY AND PATHOGENESIS

Similar to other spirochetal infections, untreated Lyme disease is characterized by asymptomatic infection, clinical disease that can occur in stages, and a propensity for cutaneous and neurologic manifestations.

The skin is the initial site of infection by *B. burgdorferi.* Inflammation induced by *B. burgdorferi* leads to the development of the characteristic rash, **erythema migrans**. Early disseminated Lyme disease results from the spread of spirochetes through the bloodstream to tissues throughout the body. The spirochete adheres to the surfaces of a wide variety of different types of cells, but the principal target organs are skin, central and peripheral nervous system, joints, heart, and eyes. Because the organism can persist in tissues for prolonged periods, symptoms can appear very late after initial infection.

The symptoms of early disseminated and late Lyme disease are a result of inflammation mediated by interleukin-1 and other lymphokines in response to the presence of the organism. It is likely that relatively few organisms actually invade the host, but cytokines serve to amplify the inflammatory response and lead to much of the tissue damage. Lyme disease is characterized by inflammatory lesions that contain both T and B lymphocytes, macrophages, plasma cells, and mast cells. The refractory symptoms of late Lyme disease can have an immunogenetic basis. Persons with certain HLA-DR allotypes may be genetically predisposed to develop chronic Lyme arthritis. An autoinflammatory response in the synovium can result in clinical symptoms long after the bacteria have been killed by antibiotics.

CLINICAL MANIFESTATIONS

The clinical manifestations of Lyme disease are divided into early and late stages (Table 222-1). Early Lyme disease is further classified as early localized or early disseminated disease. Untreated patients can progressively develop clinical symptoms of each stage of the disease, or they can present with early disseminated or with late disease without apparently having had any symptoms of the earlier stages of Lyme disease.

Early Localized Disease

The first clinical manifestation of Lyme disease in most patients is erythema migrans (Fig. 222-2). Although it usually occurs 7-14 days

Table 222-1 Clinical Stages of Lyme Disease

DISEASE STAGE	TIMING AFTER TICK BITE	TYPICAL CLINICAL MANIFESTATIONS
Early localized	3-30 days	Erythema migrans (single), variable constitutional symptoms (headache, fever, myalgia, arthralgia, fatigue)
Early disseminated	3-12 wk	Erythema migrans (single or multiple), worse constitutional symptoms, cranial neuritis, meningitis, carditis, ocular disease
Late	>2 mo	Arthritis

Figure 222-2 Skin manifestations of Lyme borreliosis. **A,** Erythema migrans on the upper leg, showing central clearing. **B,** Erythema migrans of the arm showing "bulls-eye" appearance. (***A*** *from Stanek G, Strle F: Lyme borreliosis.* Lancet *362:1639–1647, 2003).*

after the bite, the onset of the rash has been reported from 3-30 days later. The initial lesion occurs at the site of the bite. The rash is generally either uniformly erythematous or a target lesion with central clearing; rarely, there are vesicular or necrotic areas in the center of the rash. Occasionally the rash is itchy or painful, although usually it is asymptomatic. The lesion can occur anywhere on the body, although the most common locations are the axilla, periumbilical area, thigh, and groin. It is not unusual for the rash to occur on the neck or face, especially in young children. Without treatment, the rash gradually expands (hence the name *migrans*) to an average diameter of 15 cm and typically remains present for 1-2 wk. Erythema migrans may be associated with systemic features, including fever, myalgia, headache, or malaise. Coinfection with *B. microti* or *A. phagocytophilum* during early infection with *B. burgdorferi* is associated with more severe systemic symptoms. Powassan virus, *Borrelia miyamotoi*, and Wisconsin *Ehrlichia* species are also possible coinfections. Coinfections should be suspected with unusual features of Lyme disease, poor response to treatment, and prolonged fever, anemia, leukopenia, or thrombocytopenia.

Early Disseminated Disease

In the United States, approximately 20% of patients with acute *B. burgdorferi* infection develop secondary (multiple) erythema migrans lesions, a common manifestation of early disseminated Lyme disease, caused by hematogenous spread of the organisms to multiple skin sites (Fig. 222-3). The secondary lesions, which can develop several days or weeks after the first lesion, are usually smaller than the primary lesion, and are often accompanied by more-severe constitutional symptoms. The most common early neurologic manifestations are peripheral facial nerve palsy and meningitis. Lyme meningitis usually has an indolent onset with days to weeks of symptoms that can include headache, neck pain and stiffness, and fatigue. Fever is variably present.

The clinical findings of optic neuritis, cranial neuropathy (especially cranial nerve VII), and erythema migrans, which are present individually or together in 90% of cases, help differentiate Lyme from viral meningitis, in which these findings are rarely present. Lyme aseptic meningitis can be accompanied by significant elevations of intracranial pressure, which can sometimes last weeks or even months. All of the cranial nerves except the olfactory have been reported to be involved with Lyme disease, but the most common are VI and especially VII. In endemic areas, Lyme disease is the leading cause of peripheral facial nerve palsy. It is often the initial or the only manifestation of Lyme disease and is sometimes bilateral. Cerebrospinal fluid findings indicating meningitis are present in more than half of the cases of peripheral facial nerve palsy. The facial paralysis usually lasts 2-8 wk and resolves completely in most cases. Radiculoneuritis and other peripheral neuropathies can occur but are more common in Europe.

Figure 222-3 Multiple erythema migrans in a boy with early disseminated Lyme disease.

Cardiac involvement occurs in 5-15% of early disseminated Lyme disease and usually takes the form of heart block, which can be 1st, 2nd, or 3rd degree, and the rhythm can fluctuate rapidly. Rarely, myocardial dysfunction can occur. Patients presenting with suspected or proven early disseminated Lyme disease should have a careful cardiac examination, and electrocardiography should be strongly considered. Lyme carditis is a treatable condition and is the only manifestation of Lyme disease that has been fatal.

Of the ocular conditions reported in Lyme disease, papilledema and uveitis are most common.

Late Disease

Arthritis is the usual manifestation of late Lyme disease and begins weeks to months after the initial infection. Arthritis typically involves the large joints, especially the knee, which is affected in 90% of cases; involvement is usually monoarticular. The hallmark of Lyme arthritis is joint swelling, which is a result of synovial effusion and sometimes synovial hypertrophy. The swollen joint may be only mildly symptomatic or it may be painful and tender, although patients usually do not experience the severe pain and systemic toxicity that are common in pyogenic arthritis. If untreated, the arthritis can last several weeks, resolve, and then be followed by recurrent attacks in the same or other joints.

Late manifestations of Lyme disease involving the central nervous system, sometimes termed *late neuroborreliosis*, are rarely reported in children. In adults, chronic encephalitis and polyneuritis have been attributed to Lyme disease. The term *Lyme encephalopathy* has been used to describe chronic encephalitis (demonstrable by objective measures), but other literature has also used this term in reference to memory loss and other cognitive sequelae after Lyme disease has been treated. At times, the vague term *chronic Lyme disease* has been used to describe symptomatology in persons who might have never had well-documented infection with *B. burgdorferi* at all, have serologic evidence of prior infection but current symptoms not consistent with Lyme disease, or have persistent symptoms after having received appropriate antibiotic therapy. Post–Lyme disease syndrome is now the preferred term for this last group.

Congenital Lyme Disease

In endemic areas, infection can occur during pregnancy, although congenital infection appears to be a rare event. *B. burgdorferi* has been identified from several abortuses and from a few liveborn children with congenital anomalies; however, the tissues in which the spirochete has been identified usually have not shown histologic evidence of inflammation. Severe skin and cardiac manifestations have been described in a few cases, but no consistent pattern of fetal damage has been identified to suggest a clinical syndrome of congenital infection. Furthermore, studies conducted in endemic areas have indicated that there is no difference in the prevalence of congenital malformations among the offspring of women with serum antibodies against *B. burgdorferi* and the offspring of those without such antibodies.

LABORATORY FINDINGS

Standard laboratory tests rarely are helpful in diagnosing Lyme disease because any associated laboratory abnormalities usually are nonspecific. The peripheral white blood cell count may be either normal or elevated. The erythrocyte sedimentation rate may be mildly elevated. Liver transaminases are occasionally mildly elevated. In Lyme arthritis, the white blood cell count in joint fluid can range from 25,000 to 100,000/mL, often with a preponderance of polymorphonuclear cells. A lower erythrocyte sedimentation rate and a peripheral blood absolute neutrophil count of less than 10,000 may help to differentiate Lyme from septic arthritis. When meningitis is present, there usually is a low-grade pleocytosis with a lymphocytic and monocytic predominance. The cerebrospinal fluid (CSF) protein level may be elevated, but the glucose concentration usually is normal. Gram stain and routine bacterial cultures are negative. Imaging of the central nervous system

(e.g., MRI and single-photon emission computed tomography) occasionally reveals abnormalities, but there is no definitive pattern in Lyme disease. The main role of imaging is to exclude other diagnoses.

DIAGNOSIS

In the appropriate epidemiologic setting, typical erythema migrans is virtually pathognomonic. Occasionally, the diagnosis of erythema migrans may be difficult because the rash initially can be confused with nummular eczema, tinea corporis, granuloma annulare, an insect bite, southern tick-associated rash illness, or cellulitis. The relatively rapid expansion of erythema migrans helps distinguish it from these other skin lesions. The other clinical manifestations of Lyme disease are less specific and may be confused with other conditions; the monoarticular or pauciarticular arthritis sometimes is confused with a septic joint or other causes of arthritis in children, such as juvenile rheumatoid arthritis or rheumatic fever; the facial nerve palsy caused by Lyme disease is clinically indistinguishable from idiopathic Bell palsy, although bilateral involvement is much more common with Lyme disease; Lyme meningitis generally occurs in the warmer months, the same period that enteroviral meningitis is prevalent. Therefore, for all disease manifestations other than erythema migrans, it is recommended to have laboratory confirmation of infection with *B. burgdorferi.*

Although *B. burgdorferi* has been isolated from blood, skin, CSF, myocardium, and the synovium of patients with Lyme disease, the organism is difficult to isolate in culture (cultivation is largely relegated to research laboratories). Infection is usually identified by the detection of antibody in serum. Although some laboratories offer polymerase chain reaction as a diagnostic test for Lyme disease, its sensitivity may be poor because of the low concentrations of bacteria in many sites, especially CSF. Other antigen-based tests, including a test for *B. burgdorferi* antigens in urine, are unreliable. Clinicians should be aware that some laboratories use alternative diagnostic tests and/or alternative interpretive criteria that are not evidence based, leading to a false diagnosis of Lyme disease.

Serology

Following the transmission of *B. burgdorferi* from a tick bite, specific immunoglobulin (Ig) M antibodies appear first, usually within 2 wk, peak at 6-8 wk, and subsequently decline. Sometimes a prolonged elevation of IgM antibodies occurs despite effective antimicrobial treatment. (For that reason, the results of tests for specific IgM antibodies alone should not be used as a reliable indicator of either active or recent infection.) Specific IgG antibodies usually appear between 2 and 6 wk, peak after 4-6 mo, and can remain elevated for years, particularly in patients with arthritis. The antibody response to *B. burgdorferi* may be blunted in patients with early Lyme disease who are treated promptly with an effective antimicrobial agent. Serodiagnosis during the 1st 4 wk of infection is not sensitive and may need to be repeated.

By far the most common method used to detect IgG and IgM antibodies is the **enzyme-linked immunosorbent assay (ELISA)**. *This method is sensitive but not optimally specific*. The ELISA sometimes produces false-positive results because of antibodies that crossreact with other spirochetal infections (e.g., syphilis, leptospirosis, or relapsing fever), or certain viral infections (e.g., Epstein-Barr virus or parvovirus B19), or that occur in certain autoimmune diseases (e.g., systemic lupus erythematosus). The positive predictive value of the ELISA result depends primarily on the plausibility that the patient has Lyme disease based on the clinical and epidemiologic history and the physical examination (**the pretest probability**). For patients who have been in endemic areas with opportunities for *Ixodes* tick exposure and who have typical clinical manifestations of Lyme disease, the pretest probability is high and positive ELISA results are usually true positives. For patients who are from nonendemic areas and/or who have little risk for *Ixodes* tick exposures and/or have nonspecific symptoms (low pretest probability), rates of false-positive results are high.

Western immunoblotting is well standardized, and there are accepted criteria for interpretation. Five of 10 IgG bands and 2 of 3 IgM bands are considered reactive. The Western blot is not as sensitive as ELISA, especially in early infection, but it is highly specific. Any positive or equivocal ELISA should be confirmed with Western blotting. This 2-tier testing is the recommended laboratory evaluation of most cases of Lyme disease and is associated with a high degree of sensitivity and specificity when used appropriately.

Clinicians should be aware that Lyme disease might not be the cause of a patient's symptoms despite the presence of antibodies to *B. burgdorferi*. The test result may be falsely positive (as described for ELISA), or the patient might have been infected previously. Antibodies to *B. burgdorferi* that develop with infection can persist for many years despite adequate treatment and clinical cure of the disease. In addition, because some people who become infected with *B. burgdorferi* are asymptomatic, the background rate of seropositivity among patients who have never had clinically apparent Lyme disease may be substantial in endemic areas. Finally, because antibodies against *B. burgdorferi* persist after successful treatment, there is no reason to obtain follow-up serologic tests.

TREATMENT

Table 222-2 provides treatment recommendations. Most patients can be treated with an oral regimen of antibiotic therapy. Young children are generally treated with amoxicillin. Doxycycline has the advantages of good central nervous system penetration and activity against *A. phagocytophilum*, which may be transmitted at the same time as *B. burgdorferi* in certain geographic areas. In general, children younger than 8 yr of age should not be treated with doxycycline because of the risk of permanent staining of the teeth (although courses of ≤2 wk are usually safe in this regard). Patients who are treated with doxycycline should be alerted to the risk for developing photosensitivity in sun-exposed areas while taking the medication; long sleeves, long pants, and hat are recommended for activities in direct sunlight. The only oral cephalosporin proved to be effective for the treatment of Lyme disease is cefuroxime axetil, which is an alternative for persons who cannot take doxycycline or who are allergic to penicillin. Macrolide antibiotics, including azithromycin, appear to have limited activity.

Table 222-2 Recommended Treatment of Lyme Disease

DRUG	PEDIATRIC DOSING
Amoxicillin	50 mg/kg/day in 3 divided doses (max: 1,500 mg/day)
Doxycycline	4 mg/kg/day in 2 divided doses (max: 200 mg/day) (see text regarding doxycycline use in children)
Cefuroxime axetil	30 mg/kg/day in 2 divided doses (max: 1,000 mg/day)
Ceftriaxone (IV)*†	50-75 mg/kg/day once daily (max: 2,000 mg/day)
RECOMMENDED THERAPY BASED ON CLINICAL MANIFESTATION	
Erythema migrans	Oral regimen, 14-21 days
Meningitis	Ceftriaxone, 10-28 days
Cranial nerve palsy	Oral regimen, 14-21 days (see text regarding possible need for lumbar puncture)
Cardiac disease	Oral regimen or ceftriaxone, 14-21 days (see text for specifics)
Arthritis‡	Oral regimen, 28 days
Late neurologic disease	Ceftriaxone, 14-28 days

*Cefotaxime and penicillin G are alternative parenteral agents.
†Doses of 100 mg/kg/day should be used for meningitis.
‡Persistent arthritis can be treated with a second oral regimen or ceftriaxone.
From Wormser GP, Dattwyler RJ, Shapiro ED, et al: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America, Clin Infect Dis *43:1089–1134, 2006.*

Parenteral therapy is recommended for patients with central nervous system infection and higher degrees of heart block. Patients with arthritis that fails to resolve after an initial course of oral therapy can be retreated with an oral regimen or can receive intravenous antibiotic therapy. Ceftriaxone is usually favored because of its excellent anti-*Borrelia* activity, tolerability, and once-daily dosing regimen, which can usually be done on an outpatient basis.

Peripheral facial nerve palsy can be treated using an oral antibiotic. However, many of these patients have concomitant meningitis; patients with meningitis should receive a parenteral antibiotic. Experts are divided on whether every patient with Lyme-associated facial palsy should have a CSF analysis, but clinicians should consider lumbar puncture for patients with significant headache, neck pain or stiffness, or papilledema.

Patients with symptomatic cardiac disease, 2nd- or 3rd-degree heart block, or significantly prolonged PR interval should be hospitalized and monitored closely. These patients should receive a parenteral antibiotic. Patients with mild 1st-degree heart block can be treated with an oral antibiotic.

Some patients develop a **Jarisch-Herxheimer reaction** soon after treatment is initiated; this results from lysis of the *Borrelia*. The manifestations of this reaction are low-grade fever and achiness. These symptoms resolve spontaneously within 24-48 hr, although administration of nonsteroidal antiinflammatory drugs often is beneficial. Nonsteroidal antiinflammatory drugs also may be useful in treating symptoms of early Lyme disease and of Lyme arthritis. Coinfections with other pathogens transmitted by *Ixodes* ticks should be treated according to standard recommendations.

Criteria for the post–Lyme disease syndrome have been proposed by the Infectious Disease Society of America. There is no clear evidence that this condition is related to persistence of the organism. Studies in adults show little benefit associated with prolonged or repeated treatment with oral or parenteral antibiotics.

PROGNOSIS

There is a widespread misconception that Lyme disease is difficult to cure and that chronic symptoms and clinical recurrences are common. The most likely reason for apparent treatment failure is an incorrect diagnosis of Lyme disease.

The prognosis for children treated for Lyme disease is excellent. Children treated for erythema migrans rarely progress to late Lyme disease. The long-term prognosis for patients who are treated beginning in the later stages of Lyme disease also is excellent. Although chronic and recurrent arthritis does occur rarely, especially among patients with certain human leukocyte antigen allotypes (an autoimmune process), most children who are treated for Lyme arthritis are cured and have no sequelae. Although there are rare reports of adults who have developed late neuroborreliosis, usually among persons with Lyme disease in whom treatment was delayed for months or years; similar cases in children are rare.

PREVENTION

The best way to avoid Lyme disease is to avoid tick-infested areas. Children should be examined for deer ticks after known or potential exposure (although many people are not able to identify the species or the stage of the tick). If a tick attachment is noted, the tick should be grasped at the mouthparts with a forceps or tweezers; if these are not available, the tick should be covered with a tissue. The recommended method of tick removal is to pull directly outward without twisting; infection is usually preventable if the tick is removed before 48 hr of attachment. The overall risk for acquiring Lyme disease after a tick bite is low (1-3%) in most endemic areas. Patients and families can be advised to watch the area for development of erythema migrans and to seek medical attention if the rash or constitutional symptoms occur. If infection develops, early treatment of the infection is highly effective. Although a study of prophylaxis after a tick bite found that a single dose of doxycycline in adults (200 mg PO) was 87% effective in preventing Lyme disease, data in children using this strategy are lacking. For these various reasons, **routine** administration of antimicrobial prophylaxis is **not recommended.** The routine testing of ticks that have been removed from humans for evidence of *B. burgdorferi* is not recommended, because the value of a positive test result for predicting infection in the human host is unknown.

Personal protective measures that may be effective in reducing the chance of tick bites include wearing protective clothing (long pants tucked into socks, long-sleeved shirts) when entering tick-infested areas, checking for and promptly removing ticks, and using tick repellents such as *N,N*-diethyl-3-methylbenzamide (DEET). This chemical can safely be used on pants, socks, and shoes; care must be used with heavy or repeated application on skin, particularly in infants, because of the risk of systemic absorption and toxicity.

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Section 9

Mycoplasmal Infections

Chapter 223

Mycoplasma pneumoniae

Asuncion Mejias and Octavio Ramilo

Among the 7 *Mycoplasma* species isolated from the human respiratory tract, *Mycoplasma pneumoniae* remains the most common species causing respiratory infections in school-age children and young adults.

THE ORGANISM

Mycoplasmas are the smallest self-replicating prokaryotes known to cause disease in humans. Their size of 150-250 nm is more on the order of viruses than bacteria. *M. pneumoniae* is a fastidious double-stranded DNA bacterium that is distinguished by a small genome (800,000 base pairs) and a long doubling time, which makes culturing of *Mycoplasma* a slow process (5-20 days) compared to other bacteria. Like other mycoplasmas, *M. pneumoniae* is distinguished by the complete absence of a cell wall that results (1) in their dependence to host cells for obtaining essential nutrients, (2) the intrinsic resistance to β-lactam agents, and (3) their pleomorphic shape and lack of visibility on Gram staining.

EPIDEMIOLOGY

M. pneumoniae infections occur worldwide and throughout the year. This organism is a frequent cause of community-acquired pneumonia (CAP) in school-age children and adults, accounting for 7-40% of all CAP in children 3-15 yr of age.

In contrast to the acute, short-lived epidemics of some respiratory viruses, *M. pneumoniae* infection is endemic in larger communities, with epidemic outbreaks occurring every 4-7 yr, usually beginning in the fall. Infection occurs through the respiratory route by large droplet spread during close contact with a symptomatic person. Community outbreaks have been described in closed settings (colleges, summer camps, military bases) and can spread largely through school contacts. High transmission rates have been documented within families with up to 40% of household contacts developing mycoplasma lower respiratory tract infection. In contrast to many other respiratory infections the incubation period is 2-3 wk; hence, the course of infection in a specific population (family) may last several weeks.

The occurrence of mycoplasmal illness is related, in part, to age and preexposure immunity. Overt illness is less common before 3 yr of age but can occur. Children younger than 5 yr of age appear to have mild

illness associated with upper respiratory tract involvement, vomiting, and diarrhea. Immunity after infection is not long lasting. Recurrent infections occur infrequently but are well documented in adults at intervals of 4-7 yr. Asymptomatic carriage after infection can last up to 4 mo despite antibiotic therapy and may contribute to prolonged outbreaks.

PATHOLOGY AND PATHOGENESIS

The pathogenicity of *M. pneumoniae* is dependent upon its extracellular attachment and the initiation of the host cell immune response. Cells of the ciliated respiratory epithelium are the target cells of *M. pneumoniae* infection. The organism is an elongated snake-like structure with a one-end organelle, which mediates the attachment to the ciliary membrane through different adherence-accessory proteins (P1, P30, P65, P116, and HMW1-3). *M. pneumoniae* rarely invades beyond the respiratory tract basement membrane. Virulent organisms attach to ciliated respiratory epithelial cell surfaces located in the bronchi, bronchioles, alveoli, and possibly upper respiratory tract and burrow down between cells, resulting in ciliostasis and eventual sloughing of the cells. In addition, *M. pneumoniae* causes cytolytic injury to the host cells in part by the production of hydrogen peroxide and possibly through an adenosine diphosphate–ribosylating and vacuolating toxin termed CARDS: community-acquired respiratory distress syndrome. This toxin is associated with more severe or even fatal disease.

Once *M. pneumoniae* reaches the lower respiratory tract, promotes the polyclonal activation of B-lymphocytes and CD4+ T-cells, and amplifies the immune response with the production of various proinflammatory and antiinflammatory cytokines and chemokines such as tumor necrosis factor-α, interferon-γ, and granulocyte-macrophage colony-stimulating factor.

Although it is well documented that specific cell-mediated immunity and antibody titers against *M. pneumoniae* increase with age (and therefore probably follow repeated infections), the immune mechanisms that protect against or clear the infection are not well defined. The high prevalence of infection in children, adolescents, and young adults, but the frequently mild disease in young children suggests the possible role of immune-mediated mechanisms associated with reinfections causing disease in older patients. Patients with congenital immunodeficiencies such as hypogammaglobulinemia as well as those with sickle cell disease or sickle-related hemoglobinopathies can have more severe forms of *Mycoplasma* pneumonia. *M. pneumoniae* is a common infectious cause of acute chest syndrome in sickle cell disease, and in patients with hypogammaglobulinemia it can persist for years in the respiratory tract despite multiple courses of antibiotics. On the other hand, *M. pneumoniae* does not seem to be a common opportunistic agent in patients with AIDS.

M. pneumoniae has been detected by polymerase chain reaction (PCR) in many nonrespiratory sites. The mechanisms of extrapulmonary disease associated with *M. pneumoniae* are unclear. The identification of *M. pneumoniae* by PCR from blood, pleural fluid, cerebrospinal fluid, or synovial fluid in some cases indicates that direct dissemination rather than an immune-mediated mechanism may occur.

CLINICAL MANIFESTATIONS

Respiratory Tract Disease

Tracheobronchitis and pneumonia are the most commonly recognized clinical syndromes associated with *M. pneumoniae* infection. This agent is responsible for up to 20% of all cases of pneumonia. Although the onset of illness may be abrupt, it is usually characterized by gradual onset of headache, malaise, fever, and sore throat, followed by progression of lower respiratory symptoms, including hoarseness and nonproductive cough. Coryza or gastrointestinal complaints are unusual with *M. pneumoniae* pneumonia and usually suggest a viral etiology. Although the clinical course in untreated patients is variable, cough, the clinical hallmark of *M. pneumoniae* infection, usually worsens during the 1st wk of illness, and symptoms generally resolve within 2 wk. Cough can last up to 4 wk and may be accompanied by wheezing. Patients generally recover without complications.

Chest exam is often unrevealing, even in patients with severe cough. There may be no auscultative or percussive findings or only minimum dry rales. Clinical findings are often less severe than suggested by the patient chest radiograph, explaining why the term "walking pneumonia" is often used to describe CAP caused by *M. pneumoniae*. Radiographic findings are variable and nonspecific, not allowing differentiation from viral or bacterial pathogens. Pneumonia is usually described as interstitial or bronchopneumonic, and involvement is most common in the lower lobes. Bilateral diffuse infiltrates, lobar pneumonia or hilar lymphadenopathy can occur in up to 30% of patients. Although unusual, large pleural effusions associated with lobar infiltrates and necrotizing pneumonia have been described in patients with sickle cell disease, immunodeficiencies, Down syndrome, and chronic cardiopulmonary disease. The white blood cell and differential counts are usually normal, whereas the erythrocyte sedimentation rate is often elevated.

Other respiratory illnesses caused occasionally by *M. pneumoniae* include undifferentiated upper respiratory tract infections, pharyngitis (usually without marked cervical lymphadenopathy), sinusitis, croup, and bronchiolitis. *M. pneumoniae* is a common trigger of wheezing in asthmatic children and can cause chronic colonization in the airways, resulting in lung dysfunction in adolescents and adult asthmatic patients. Otitis media and bullous myringitis, which also occur with other viral and bacterial infections, have been described but are rare, and their absence should not rule out the diagnosis of *M. pneumoniae*.

Extrapulmonary Disease

Despite the reportedly rare isolation of *M. pneumoniae* from nonrespiratory sites, the improved sensitivity of PCR for *M. pneumoniae* DNA detection has led to increasing identification of *M. pneumoniae* in nonrespiratory sites, particularly the central nervous system (CNS). Patients with or without respiratory symptoms can have involvement of the skin, CNS, blood, heart, gastrointestinal tract, and joints. Nonrespiratory manifestations of *M. pneumoniae* include:

1. ***CNS disease***, which may be the most common extrapulmonary site associated with *M. pneumoniae* infection and includes encephalitis, transverse myelitis, aseptic meningitis, Guillain-Barré syndrome, ataxia, Bell palsy, postinfectious demyelination, peripheral neuropathy, and acute disseminated encephalomyelitis. CNS disease manifestations occur 3-23 days (mean: 10 days) after onset of respiratory illness but may not be preceded by any signs of respiratory infection in up to 20% of cases. Encephalitis occurring within 5 days of the onset of prodromal symptoms may be caused by direct invasion of *M. pneumoniae* in the CNS, although cerebrospinal fluid (CSF) PCR is positive in <5% of cases. Encephalitis occurring more than 7 days after onset of prodromal symptoms is more likely to be caused by an autoimmune response to *M. pneumoniae* and accounts for up to 5-15% of all forms of childhood encephalitis. Involvement of the brainstem can result in severe dystonia and movement disorders. Concomitant infection with other pathogens such as enteroviruses or respiratory viruses is found in approximately 10% of children. The CSF may be normal or have mild mononuclear pleocytosis. Diagnosis is confirmed with positive CSF PCR, positive PCR from a throat swab, or the presence of definitive serum antibody titers. Findings on MRI include focal ischemic changes, ventriculomegaly, diffuse edema, or multifocal white matter inflammatory lesions consistent with postinfectious demyelinating encephalomyelitis. Long-term sequelae are not uncommon and have been reported in 23-64% of cases.
2. ***Dermatologic disease,*** which includes a variety of exanthemas, most notably maculopapular rash urticaria, and erythema multiforme or Stevens-Johnson syndrome (SJS). Gianotti-Crosti syndrome and erythema nodosum are also associated with *M. pneumoniae* infections. Approximately 10% of children with *M. pneumoniae* CAP will exhibit a maculopapular rash. *M. pneumoniae* is the most common infectious agent associated with SJS and has a male predominance. SJS usually develops

Figure 223-1 Lip changes found in Stevens-Johnson-like syndrome associated with *Mycoplasma pneumoniae* infection.

Figure 223-2 Classic erythema multiforme skin lesions found in Stevens-Johnson-like syndrome associated with *Mycoplasma pneumoniae* infection.

3-21 days after initial respiratory symptoms, lasts less than 14 days, and is rarely associated with severe complications (Figs. 223-1 and 223-2). *M. pneumoniae* is linked to atypical SJS with oral mucositis but absence of rash.

3. ***Hematologic abnormalities,*** which include mild degrees of hemolysis with a positive Coombs test and minor reticulocytosis 2-3 wk after the onset of illness. Severe hemolysis is associated with high titers of cold hemagglutinins (≥1 : 512) and occurs rarely. Thrombocytopenia, aplastic anemia, and coagulation defects occur occasionally.
4. ***Arthritis,*** which appears to be less common in children than adults, but monoarthritis, polyarthritis, and migratory arthritis have been described.
5. ***Other conditions,*** such as mild hepatitis, pancreatitis, acute glomerulonephritis, and cardiac complication (pericarditis, myocarditis, and rheumatic fever-like syndrome, most commonly seen in adults), are also described. Fatal *M. pneumoniae* infections are rare.

DIAGNOSIS

No specific clinical, epidemiologic, or laboratory parameters allow for a definite diagnosis of *M. pneumoniae* infection early in the clinical course. Nevertheless, pneumonia in school-age children and young adults with cough as a prominent finding suggests *M. pneumoniae* infection. The best method of diagnosis is a combination of PCR from respiratory samples and serology (acute and convalescent).

Cultures on special media (SP4 agar media) of the throat or sputum might demonstrate the classic *M. pneumoniae* "mulberry" colonies, but growth generally requires incubation for 1-3 wk, and few commercial laboratories maintain the capability of culturing *M. pneumoniae*. The fastidious nutritional requirements of *Mycoplasma* make cultures slow and impractical.

Serologic tests (immunofluorescence tests or enzyme-linked immune assays) to detect serum immunoglobulin (Ig) M and IgG antibodies against *M. pneumoniae* are commercially available. IgM antibodies have a high rate of false-positive and false-negative results. In most cases, IgM antibodies are not detected within the 1st wk after onset of symptoms or in children with recurrent infections and may be positive for up to 6-12 mo after infection. A 4-fold or greater increase in IgG antibody titers against *M. pneumoniae* between acute and convalescent sera obtained 10 days to 3 wk apart is diagnostic.

Cold hemagglutinins (cold-reacting antibodies against red blood cells) can be detected in approximately 50% of patients with *M. pneumoniae* atypical pneumonia. These antibodies are nonspecific, especially at titers <1 : 64, as modest increases in cold hemagglutinin can be observed in other viral infections. Cold agglutinin antibodies should not be used for the diagnosis of *M. pneumoniae* infections if other methods are available. Nonetheless the PCR may be positive in some asymptomatic patients.

PCR-based tests for *M. pneumoniae* have replaced other diagnostic tests. PCR of a nasopharyngeal or throat swab (doing both increases sensitivity) for *M. pneumoniae* DNA carries a sensitivity and a specificity of 80% to >97%. Different primers have been used to identify gene sequences of the P1 cytoadhesin protein or the ribosomal (r)RNA. PCR allows a more rapid diagnosis in acutely ill patients and can be positive earlier in the course of infection than serologic tests. Identification of *M. pneumoniae* by PCR (or culture) from a patient with compatible clinical manifestations suggests causation.

The diagnosis of extrapulmonary disease associated with *M. pneumoniae* is challenging. Although small case series identified *M. pneumoniae* by PCR in the CSF of children with encephalitis, there are currently no reliable tests for the diagnosis of CNS or other nonrespiratory sites associated with *M. pneumoniae.*

TREATMENT

M. pneumoniae illness is usually mild, and most cases of pneumonia can be managed without the need for hospitalization. Because mycoplasmas lack a cell wall, they inherently are resistant to β-lactam agents that act by inhibiting the cell wall synthesis.

Antimicrobial Therapy

M. pneumoniae is typically sensitive to macrolides (erythromycin, clarithromycin, azithromycin), the tetracyclines, and quinolones in vitro. Data from observational studies showed that macrolide treatment of children with *M. pneumoniae* CAP markedly shortened the course of illness. Treatment may be more effective when started within 3-4 days of illness onset. Although macrolides do not have bactericidal activity, they are preferred in children younger than 8 yr of age. Two multicenter studies of pediatric CAP demonstrated comparable clinical and bacteriologic success rates between erythromycin and clarithromycin or azithromycin. However, the newer macrolides were better tolerated. The recommended treatment is clarithromycin (15 mg/kg/day divided into 2 doses PO for 10 days) or azithromycin (10 mg/kg once PO on day 1 and 5 mg/kg once daily PO on days 2-5). In addition to the antibacterial effect, macrolides have immunomodulatory properties, but the relevance of the anti-inflammatory properties of macrolides for the treatment of *M. pneumoniae* CAP is not known. Tetracyclines (doxycycline 100 mg twice a day for 7-14 days) are also effective and may be used for children older than 8 yr of age. Fluoroquinolones such as levofloxacin (500 mg once a day for 7-14 days) are effective but are less active than macrolides and are not recommended as a first-line therapy in children.

Macrolide-resistant strains, mostly associated with mutations in the 23S rRNA, have been reported in Asia (>40% in Japan and 80-90% in China) and are also present in Europe and the United States (with rates ranging from 8-20%). Although not routinely done at commercial laboratories, identification of macrolide-resistant strains can be performed by sequencing and identification of specific mutations at the 23S rRNA gene. The tetracycline minocycline (for children > 8 yr) and the quinolone tosufloxacin (for children < 8 yr) are approved in Japan for pediatric use to treat macrolide-resistant *M. pneumoniae* infections. For patients with severe mycoplasma pneumonia not responding to macrolide therapy, the possibility of macrolide-resistant *M. pneumoniae* strains should be considered, and switching to a nonmacrolide antimicrobial agent might be prudent.

Adjunctive Therapy

There is no evidence that treatment of upper respiratory tract or nonrespiratory tract disease with antimicrobial agents alters the course of illness. However, patients with severe manifestations of extrapulmonary disease may benefit from antimicrobial treatment combined with immunotherapy. In this regard, corticosteroids with or without intravenous immunoglobulin are the most commonly used agents in the management of severe *M. pneumoniae* extrapulmonary manifestations, particularly with CNS involvement. Although definitive data are lacking, case studies suggest associated clinical benefit of steroids used in the management of severe lung disease, SJS, and hemolytic anemia.

PREVENTION

Trials with inactivated and live attenuated vaccines for *M. pneumoniae* have been conducted with disappointing results. In hospitalized patients standard and droplet precautions are recommended for the duration of symptoms. It is important to emphasize that *Mycoplasma* infection remains contagious as long as cough persists and despite successful antibiotic therapy. Prophylaxis with tetracyclines or azithromycin substantially reduces the secondary attack rates in institutional outbreaks and family close contacts. Antimicrobial prophylaxis is not recommended routinely; however, it can be considered in patients at high risk for severe disease, such as children with sickle cell disease.

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Chapter 224

Genital Mycoplasmas (*Mycoplasma Hominis, Mycoplasma Genitalium,* and *Ureaplasma Urealyticum*)

Rebecca Wallihan and Asuncion Mejias

ETIOLOGY

Mycoplasma species are small pleomorphic bacteria that typically lack a cell wall. These ubiquitous organisms are difficult to cultivate and belong to the family Mycoplasmataceae in the class Mollicutes and represent the smallest self-replicating organisms known to date. The family Mycoplasmataceae is composed of 2 genera responsible for human infection: *Mycoplasma* and *Ureaplasma*. Of those, *Mycoplasma hominis, Mycoplasma genitalium,* and *Ureaplasma* spp., which includes *Ureaplasma urealyticum (biovar 2)* and *Ureaplasma parvum (biovar 1),* are considered human urogenital pathogens and are reviewed in this chapter. Genital mycoplasmas are often associated with sexually transmitted infections such as cervicitis and nongonococcal urethritis (NGU) or with puerperal infections such as endometritis. *M. hominis* and *Ureaplasma* spp. commonly colonize the female genital tract and can cause chorioamnionitis, colonization of neonates, and perinatal infections. Two other genital *Mycoplasma* species, *Mycoplasma fermentans* and *Mycoplasma penetrans,* have been identified in respiratory or genitourinary secretions primarily in HIV-infected patients.

EPIDEMIOLOGY

M. hominis and *Ureaplasma* spp. are commensal organisms in the lower genital and urinary tracts of postpubertal women and men. Colonization rates are directly related to sexual activity and are highest among individuals with multiple sexual partners. Female colonization is maximal in the vagina and less in the endocervix, urethra, and endometrium, with rates varying from 40-80% for *Ureaplasma* spp. and 21-70% for *M. hominis* among sexually active asymptomatic women. Male colonization is less common and occurs primarily in the urethra. Among prepubertal children and sexually inactive adults, colonization rates are <10%. *M. genitalium* is implicated in approximately 25% of NGU cases in men and plays a role in cervicitis and pelvic inflammatory disease in women. Studies using polymerase chain reaction (PCR) show that colonization of the female lower urogenital tract with *M. genitalium* is less common than with *M. hominis* or *Ureaplasma* spp.

TRANSMISSION

Genital mycoplasmas are transmitted by sexual contact or by vertical transmission from mother to infant. As with other perinatal infections, vertical transmission can occur through ascending intrauterine infection, hematogenous spread from placental infection, or through a colonized birth canal at the time of delivery. Transmission rates among neonates born to women colonized with *Ureaplasma* spp. range from 18-88%. Neonatal colonization rates are higher among infants who weigh <1,000 g, are born in the presence of chorioamnionitis, or are born to mothers of lower socioeconomic status. Organisms may be recovered from the newborn's throat, vagina, rectum, and, occasionally, conjunctiva for as long as 3 mo after birth.

PATHOLOGY AND PATHOGENESIS

Genital mycoplasmas can cause chronic inflammation of the genitourinary tract and amniotic membranes. *Ureaplasma* spp. can infect the amniotic sac early in gestation without rupturing the amniotic membranes, resulting in a clinically silent, chronic chorioamnionitis characterized by an intense inflammatory response. Attachment to fetal human tracheal epithelium can cause ciliary disarray, clumping, and loss of epithelial cells. In vitro studies show that *Ureaplasma* spp. stimulates macrophage production of interleukin-6 and tumor necrosis factor-α. In addition, high concentrations of proinflammatory cytokines possibly associated with development of chronic lung disease (CLD) of prematurity, such as monocyte chemoattractant protein-1 and interleukin-8, have been found in tracheal secretions from very-low-birthweight infants colonized with *Ureaplasma* spp. Immunity appears to require serotype-specific antibody. Thus, lack of maternal antibodies might account for a higher disease risk in premature newborns.

CLINICAL MANIFESTATIONS

Intrauterine and Neonatal Infections

Genital mycoplasmas are associated with a variety of fetal and neonatal infections. *Ureaplasma* spp. can cause clinically inapparent chorioamnionitis resulting in spontaneous abortion, increased fetal death, or premature delivery. *Ureaplasma* spp. can also be recovered from tracheal, blood, cerebrospinal fluid (CSF), or lung biopsy specimens in up

to 50% of sick infants younger than 34 wk of gestational age. In a study of 351 preterm infants born between 23 and 32 wk of gestational age, isolation of *Ureaplasma* spp. or *M. hominis* from cord blood correlated with the development of systemic inflammatory response syndrome. The role of these organisms causing severe respiratory insufficiency, the need for mechanical ventilation, the development of CLD, or death remains controversial. Meta-analyses of published studies have identified respiratory colonization with *Ureaplasma* spp. as an independent risk factor for the development of CLD. However, trials of erythromycin therapy in high-risk preterm infants with tracheobronchial colonization of *U. urealyticum* have failed to show any difference in the development of CLD in treated vs nontreated infants.

M. hominis and *Ureaplasma* spp. have been isolated from the CSF of premature and, less commonly, full-term infants. However, the clinical significance of recovering these bacteria from the CSF is uncertain. Simultaneous isolation of other pathogens is unusual, and most infants have no overt signs of central nervous system (CNS) disease. Overall, CSF pleocytosis is not consistent, and spontaneous clearance of mycoplasmas has been documented without specific therapy. *Ureaplasma* spp. meningitis has been associated with intraventricular hemorrhage and hydrocephalus. Limited data suggest that meningitis caused by *M. hominis* can be associated with significant morbidity and mortality. In a review of 29 reported neonatal cases with *M. hominis* meningitis, 8 (28%) neonates died and 8 (28%) developed neurologic sequelae. The age of onset of meningitis ranges from 1 to 196 days of life, and organisms can persist in the CSF without therapy for days to weeks. Pachymeningitis may be evident on MRI scans. *M. hominis* and *Ureaplasma* spp. have also been associated with neonatal conjunctivitis, lymphadenitis, pharyngitis, pneumonitis, osteomyelitis, brain abscess, pericarditis, meningoencephalitis, and scalp abscess.

Genitourinary Infections

In sexually active adolescents and adults, genital mycoplasmas are associated with sexually transmitted diseases and are rarely associated with focal infections outside the genital tract. *Ureaplasma* spp. and *M. genitalium* are recognized etiologic agents of NGU. Approximately 30% of NGU in males may be caused by these organisms either alone or associated with *Chlamydia trachomatis* (see Chapter 226). *Ureaplasma* spp. are also associated with the development of urinary calculi. Disease is most common in young adults but is also prevalent in sexually active adolescents. The average incubation period is 2-3 wk, with symptoms typically consisting of scant mucoid-white urethral discharge, dysuria, and penile discomfort. The discharge is often evident only in the morning or after the urethra is stripped. Rare complications of NGU include epididymitis and proctitis. Approximately 20-60% of patients with *M. genitalium* NGU develop recurrent or chronic urethritis despite 1-2 wk of treatment with doxycycline.

Nongenital Infections

Extragenital *Ureaplasma* spp. infections are rarely described but include pneumonia, osteomyelitis, arthritis, meningitis, mediastinitis, infection of aortic grafts, and postcesarean wound infections. Patients with hypogammaglobulinemia appear to be at higher risk for chronic arthritis caused by various *Mycoplasma* spp. On the other hand, *M. hominis* is associated with septicemia, endocarditis, wound infections, osteomyelitis, lymphadenitis, pneumonia, meningitis, brain abscesses, arthritis, amnionitis, and postpartum fever. There are reports of life-threatening mediastinitis, sternal wound infections, pleuritis, peritonitis, and pericarditis with high mortality rates in patients following organ transplantation.

DIAGNOSIS

All Mollicutes lack a cell wall and are therefore not visible on Gram stain. *M. hominis* and *Ureaplasma* spp. can grow in cell-free media and require sterols for growth, producing characteristic colonies on agar. Colonies of *M. hominis* are 200-300 µm in diameter with a "fried-egg" appearance, while colonies of *Ureaplasma* spp. are smaller (16-60 µm in diameter). Although these organisms can grow in culture, PCR assays have a greater sensitivity. Assays for both *Ureaplasma* spp. and *M. hominis* are available at research and reference laboratories in the United States. *M. genitalium* is a fastidious organism and can be isolated with difficulty in cell culture systems; however, PCR provides a more practical method for detection.

Genital Tract Infection

Confirmation of genital tract infection is challenging because of the high colonization rates in the vagina and urethra. NGU is typically defined as new-onset urethral discharge or dysuria with Gram stain of urethral discharge showing ≥5 polymorphonuclear leukocytes per oil-immersion field in the absence of Gram-negative diplococci (i.e., *Neisseria gonorrhoeae*). A urethral swab or exudate can be cultured for *C. trachomatis* and *Ureaplasma* spp. Detection of *Ureaplasma* spp. or *M. hominis* by PCR is available for a variety of specimens, including urine, amniotic fluid, placental tissue, respiratory specimens, synovial fluid, and swabs of the cervix, urethra, and vagina. *M. genitalium* is often identified by PCR testing of first-void urine specimens in men and vaginal swabs in women.

Neonates

Ureaplasma spp. and *M. hominis* have been isolated from urine, blood, CSF, tracheal aspirates, pleural fluid, abscesses, and lung tissue. Premature neonates who are clinically ill with pneumonitis, focal abscesses, or CNS disease (particularly progressive hydrocephalus with or without pleocytosis) for whom bacterial cultures are negative or in whom there is no improvement with standard antibiotic therapy warrant cultures/PCR for genital mycoplasmas. Isolation requires special media, and clinical specimens must be cultured immediately or frozen at −70°C (−94°F) to prevent loss of organisms. When inoculated into broth containing arginine (for *M. hominis*) or urea (for *Ureaplasma* spp.), growth is indicated by an alkaline pH. Identification of *Ureaplasma* spp. on agar requires 1-2 days of growth and visualization with the dissecting microscope, whereas *M. hominis* is apparent to the eye but can require 1 wk to grow. Cultures from the upper respiratory tract may be less specific owing to high colonization rates. Cultures of the lower respiratory tract through endotracheal aspirate or biopsy are essential.

TREATMENT

These organisms lack a cell wall, and thus β-lactam agents are not effective. These bacteria are also resistant to sulfonamides and trimethoprim because they do not produce folic acid. Rifamycins do not have activity against Mollicutes. *M. hominis* is resistant to macrolides but generally susceptible to clindamycin and quinolones. Most *Ureaplasma* spp. are susceptible to macrolides and advanced generation quinolones, such as moxifloxacin, but often resistant to ciprofloxacin and clindamycin. Susceptibility to tetracyclines is variable for both organisms, with increasing resistance being reported. *M. genitalium* is typically susceptible to macrolides and moxifloxacin, with variable resistance to tetracyclines and clindamycin.

Adolescents and Adults

Recommended treatment for NGU in males is azithromycin (1 g PO as a single dose) and doxycycline (100 mg PO twice daily for 7 days). Recurrent NGU after completion of treatment suggests the presence of azithromycin-resistant *M. genitalium*. Retreatment with moxifloxacin may be most effective. Sexual partners should also be treated to avoid recurrent disease in the index case. Nongenital mycoplasmal infections may require surgical drainage and prolonged antibiotic therapy.

Neonates

Therapy for neonates with genital mycoplasma infections is indicated if infections are associated with pure growth of the organism or if the organism is detected by PCR from a normally sterile site in conjunction with compatible disease manifestations to assure the treatment of an infectious process rather than merely colonization. The role of preventive therapy for the possible role of genital mycoplasmas in the genesis of CLD in very-low-birthweight infants awaits results of further studies. Treatment is based on predictable antimicrobial sensitivities,

because susceptibility testing is not readily available for individual isolates. For infants with symptomatic CNS infection, cures have been described with chloramphenicol, doxycycline, and moxifloxacin. The long-term consequences of asymptomatic CNS infection associated with genital mycoplasmas, especially in the absence of pleocytosis, are unknown. Because mycoplasmas can spontaneously clear from the CSF, therapy should involve minimal risks.

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Section 10
Chlamydial Infections

Chapter 225
Chlamydia (Chlamydophila) pneumoniae

Stephan A. Kohlhoff and
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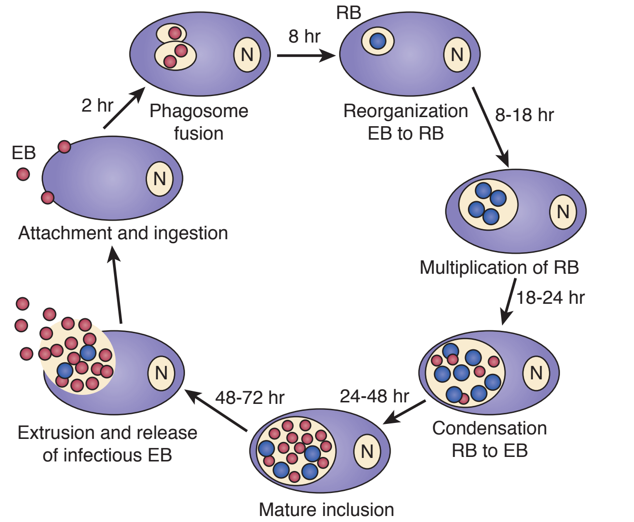

Figure 225-1 Life cycle of chlamydiae in epithelial cells. *EB,* elementary body; *RB,* reticulate body. *(From Hammerschlag MR: Infections due to* Chlamydia trachomatis *and* Chlamydia pneumoniae *in children and adolescents.* Pediatr Rev *25:43–50, 2004.)*

Chlamydia pneumoniae is a common cause of lower respiratory tract diseases, including pneumonia in children and bronchitis and pneumonia in adults.

ETIOLOGY
Chlamydiae are obligate intracellular pathogens that have established a unique niche in host cells. Chlamydiae cause a variety of diseases in animal species at virtually all phylogenic levels. The most significant human pathogens are *C. pneumoniae* and *Chlamydia trachomatis* (see Chapter 226). *Chlamydia psittaci* is the cause of psittacosis, an important zoonosis (see Chapter 227).

Chlamydiae have a Gram-negative envelope without detectable peptidoglycan, although recent genomic analysis has revealed that both *C. pneumoniae* and *C. trachomatis* encode proteins forming a nearly complete pathway for synthesis of peptidoglycan, including penicillin-binding proteins. Chlamydiae also share a group-specific lipopolysaccharide antigen and use host adenosine triphosphate for the synthesis of chlamydial proteins. Although chlamydiae are auxotrophic for 3 of 4 nucleoside triphosphates, they encode functional glucose-catabolizing enzymes that can be used to generate adenosine triphosphate. As with peptidoglycan synthesis, for some reason these genes are turned off. All chlamydiae also encode an abundant surface exposed protein called the *major outer membrane protein.* The major outer membrane protein is the major determinant of the serologic classification of *C. trachomatis* and *C. psittaci* isolates.

EPIDEMIOLOGY
C. pneumoniae is primarily a human respiratory pathogen. The organism has also been isolated from nonhuman species, including horses, koalas, reptiles, and amphibians, where it also causes respiratory infection, although the role that these infections might play in transmission to humans is unknown. *C. pneumoniae* appears to affect individuals of all ages. The proportion of community-acquired pneumonias associated with *C. pneumoniae* infection is 2-19%, varying with geographic location, the age group examined, and the diagnostic methods used. Several studies of the role of *C. pneumoniae* in lower respiratory tract infection in pediatric populations have found evidence of infection in 0-18% of patients based on serology or culture for diagnosis. In 1 study, almost 20% of the children with *C. pneumoniae* infection were coinfected with *Mycoplasma pneumoniae. C. pneumoniae* may also be responsible for 10-20% of episodes of acute chest syndrome in children with sickle cell disease, up to 10% of asthma exacerbations, 10% of episodes of bronchitis, and 5-10% episodes of pharyngitis in children. Asymptomatic infection appears to be common based on epidemiologic studies.

Transmission probably occurs from person to person through respiratory droplets. Spread of the infection appears to be enhanced by close proximity, as is evident from localized outbreaks in enclosed populations, such as military recruits and in nursing homes.

PATHOGENESIS
Chlamydiae are characterized by a unique developmental cycle (Fig. 225-1) with morphologically distinct infectious and reproductive forms: the elementary body (EB) and reticulate body (RB). Following infection, the infectious EBs, which are 200-400 µm in diameter, attach to the host cell by a process of electrostatic binding and are taken into the cell by endocytosis that does not depend on the microtubule system. Within the host cell, the EB remains within a membrane-lined phagosome. The phagosome does not fuse with the host cell lysosome. The inclusion membrane is devoid of host cell markers, but lipid markers traffic to the inclusion, which suggests a functional interaction with the Golgi apparatus. The EBs then differentiate into RBs that undergo binary fission. After approximately 36 hr, the RBs differentiate into EBs. At approximately 48 hr, release can occur by cytolysis or by a process of exocytosis or extrusion of the whole inclusion, leaving the host cell intact. Chlamydiae can also enter a persistent state after treatment with certain cytokines such as interferon-γ, treatment with antibiotics, or restriction of certain nutrients. While chlamydiae are in the persistent state, metabolic activity is reduced. The ability to cause prolonged, often subclinical, infection is one of the major characteristics of chlamydiae.

CLINICAL MANIFESTATIONS
Infections caused by *C. pneumoniae* cannot be readily differentiated from those caused by other respiratory pathogens, especially *M. pneumoniae.* The pneumonia usually occurs as a classic atypical (or nonbacterial) pneumonia characterized by mild to moderate constitutional symptoms, including fever, malaise, headache, cough, and often pharyngitis. Severe pneumonia with pleural effusions and empyema has

been described. Milder respiratory infections have been described, which can manifest as a pertussis-like illness.

C. pneumoniae can serve as an infectious trigger for asthma, can cause pulmonary exacerbations in patients with cystic fibrosis, and produce acute chest syndrome in patients with sickle cell anemia. *C. pneumoniae* has been isolated from middle ear aspirates of children with acute otitis media, most of the time as co-infection with other bacteria. Asymptomatic respiratory infection has been documented in 2-5% of adults and children and can persist for 1 yr or longer.

DIAGNOSIS

It is not possible to differentiate *C. pneumoniae* from other causes of atypical pneumonia on the basis of clinical findings. Auscultation reveals the presence of rales and often wheezing. The chest radiograph often appears worse than the patient's clinical status would indicate and can show mild, diffuse involvement or lobar infiltrates with small pleural effusions. The complete blood count may be elevated with a left shift but is usually unremarkable.

Specific diagnosis of *C. pneumoniae* infection is based on isolation of the organism in tissue culture. *C. pneumoniae* grows best in cycloheximide-treated HEp-2 and HL cells. The optimum site for culture is the posterior nasopharynx; the specimen is collected with wire-shafted swabs in the same manner as that used for *C. trachomatis*. The organism can be isolated from sputum, throat cultures, bronchoalveolar lavage fluid, and pleural fluid, but few laboratories perform such cultures because of technical difficulties. BioFire Technologies (formerly Idaho Technologies) has a nucleic acid amplification testing assay (Film Array) for the detection of 17 viruses and some of the atypical agents of pneumonia, including *C. pneumoniae*, *M. pneumoniae,* and *Bordetella pertussis*. This assay received FDA clearance in July 2012. The Film Array system combines nucleic acid extraction, nested polymerase chain reaction, detection, and data analysis.

Serologic diagnosis can be accomplished using the microimmunofluorescence (MIF) or the complement fixation tests. The complement fixation test is genus specific and is also used for diagnosis of lymphogranuloma venereum (see Chapter 226.4) and psittacosis (see Chapter 227). Its sensitivity in hospitalized patients with *C. pneumoniae* infection and children is variable. The Centers for Disease Control and Prevention (CDC) has proposed modifications in the serologic criteria for diagnosis. Although the MIF test was considered to be the only currently acceptable serologic test, the criteria were made significantly more stringent. Acute infection, using the MIF test, was defined by a 4-fold increase in immunoglobulin (Ig) G titer or an IgM titer of ≥16; use of a single elevated IgG titer was discouraged. An IgG titer of ≥16 was thought to indicate past exposure, but neither elevated IgA titers nor any other serologic marker was thought to be a valid indicator of persistent or chronic infection. Because diagnosis would require paired sera, this would be a retrospective diagnosis. The CDC did not recommend the use of any enzyme-linked immune assay for detection of antibody to *C. pneumoniae* because of concern about the inconsistent correlation of these results with culture results. Studies of *C. pneumoniae* infection in children with pneumonia and asthma show that more than 50% of children with culture-documented infection have no detectable MIF antibody.

TREATMENT

The optimum dose and duration of antimicrobial therapy for *C. pneumoniae* infections remain uncertain. Most treatment studies have used only serology for diagnosis, and thus microbiologic efficacy cannot be assessed. Prolonged therapy for 2 wk or longer is required for some patients, because recrudescent symptoms and persistent positive cultures have been described following 2 wk of erythromycin and 30 days of tetracycline or doxycycline.

Tetracyclines, erythromycin, the macrolides (azithromycin and clarithromycin), and quinolones show in vitro activity. Like *C. psittaci, C. pneumoniae* is resistant to sulfonamides. The results of treatment studies have shown that erythromycin (40 mg/kg/day PO divided twice a day for 10 days), clarithromycin (15 mg/kg/day PO divided twice a day for 10 days), and azithromycin (10 mg/kg PO on day 1, and then 5 mg/kg/day PO on days 2-5) are effective for eradication of *C. pneumoniae* from the nasopharynx of children with pneumonia in approximately 80% of cases.

PROGNOSIS

Clinical response to antibiotic therapy varies. Coughing often persists for several weeks even after therapy.

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Chapter 226

Chlamydia trachomatis

Margaret R. Hammerschlag

Chlamydia trachomatis is subdivided into 2 biovars: lymphogranuloma venereum (LGV) and trachoma, which is the agent of human oculogenital diseases other than LGV. Although the strains of both biovars have almost complete DNA homology, they differ in growth characteristics and virulence in tissue culture and animals. In developed countries, *C. trachomatis* is the most prevalent sexually transmitted disease, causing urethritis in men, cervicitis and salpingitis in women, and conjunctivitis and pneumonia in infants.

226.1 Trachoma

Margaret R. Hammerschlag

Trachoma is the most important preventable cause of **blindness** in the world. It is caused primarily by the A, B, Ba, and C serotypes of *C. trachomatis.* It is endemic in the Middle East and Southeast Asia and among Navajo Indians in the southwestern United States. In areas that are endemic for trachoma, such as Egypt, genital chlamydial infection is caused by the serotypes responsible for oculogenital disease: D, E, F, G, H, I, J, and K. The disease is spread from eye to eye. Flies are a common vector.

Trachoma begins as a **follicular conjunctivitis,** usually in early childhood. The follicles heal, leading to conjunctival scarring that can result in an entropion, with the eyelid turning inward so that the lashes abrade the cornea. It is the corneal ulceration secondary to the constant trauma that leads to scarring and blindness. Bacterial superinfection can also contribute to scarring. Blindness occurs years after the active disease.

Trachoma can be diagnosed clinically. The World Health Organization suggests that at least 2 of 4 criteria must be present for a diagnosis of trachoma: lymphoid follicles on the upper tarsal conjunctivae, typical conjunctival scarring, vascular pannus, and limbal follicles. The diagnosis is confirmed by culture or staining tests for *C. trachomatis* performed during the active stage of disease. Serologic tests are not helpful clinically because of the long duration of the disease and the high seroprevalence in endemic populations.

Poverty and lack of sanitation are important factors in the spread of trachoma. As socioeconomic conditions improve, the incidence of the disease decreases substantially. Endemic trachoma has been controlled in most instances by administering topical tetracyclines (or, rarely, erythromycin ointment) daily for periods of 6-10 wk or intermittently over a 6 mo period. Oral doxycycline is effective but is contraindicated in children younger than 8 yr of age. Oral erythromycin requires frequent dosing, which is impractical in the control of endemic trachoma.

Several studies have reported that 1-6 doses of oral azithromycin are equivalent to 30 days of treatment with topical oxytetracycline/polymyxin ointment. The World Health Organization recommends single-dose azithromycin (20 mg/kg; maximum: 1 g) for the treatment of trachoma in children. Mass treatment with a single dose of azithromycin to all the residents of a village dramatically reduced the prevalence and intensity of infection. This effect continued for 2 yr after treatment, probably by interrupting the transmission of ocular *C. trachomatis* infection.

Bibliography is available at Expert Consult.

226.2 Genital Tract Infections

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EPIDEMIOLOGY

There are an estimated 3 million new cases of chlamydial sexually transmitted infections each year in the United States. *C. trachomatis* is a major cause of epididymitis and is the cause of 23-55% of all cases of nongonococcal urethritis, although the proportion of chlamydial nongonococcal urethritis has been gradually declining. As many as 50% of men with gonorrhea may be coinfected with *C. trachomatis*. The prevalence of chlamydial cervicitis among sexually active women is 2-35%. Rates of infection among girls 15-19 yr of age exceed 20% in many urban populations but can be as high as 15% in suburban populations as well.

Children who have been sexually abused can acquire anogenital *C. trachomatis* infection, which is usually asymptomatic. However, because perinatally acquired rectal and vaginal *C. trachomatis* infections can persist for 3 yr or longer, the detection of *C. trachomatis* in the vagina or rectum of a young child is not absolute evidence of sexual abuse.

CLINICAL MANIFESTATIONS

The trachoma biovar of *C. trachomatis* causes a spectrum of disease in sexually active adolescents and adults. Up to 75% of women with *C. trachomatis* have no symptoms of infection. *C. trachomatis* can cause urethritis (acute urethral syndrome), epididymitis, cervicitis, salpingitis, proctitis, and pelvic inflammatory disease. The symptoms of chlamydial genital tract infections are less acute than those of gonorrhea, consisting of a discharge that is usually mucoid rather than purulent. Asymptomatic urethral infection is common in sexually active men. Autoinoculation from the genital tract to the eyes can lead to concomitant inclusion conjunctivitis.

DIAGNOSIS

Definitive diagnosis of genital chlamydial infection is accomplished by isolation of the organism in tissue culture and confirmed by microscopic identification of the characteristic inclusions using fluorescent antibody staining in culture specimens obtained from the urethra in men and the endocervix in women. Care should be taken to obtain epithelial cells, not only discharge. *C. trachomatis* can be cultured in cycloheximide-treated HeLa, McCoy, and HEp-2 cells. Chlamydia culture has been further defined by the Centers for Disease Control and Prevention (CDC) as isolation of the organism in tissue culture and as confirmation of the characteristic intracytoplasmic inclusions by fluorescent antibody staining.

Alternatively, a nonculture method, specifically a nucleic acid amplification test (NAAT) can be used. These tests have high sensitivity, perhaps even detecting 10-20% greater than culture, while retaining high specificity. Currently, 4 FDA-approved NAATs are commercially available for detecting *C. trachomatis*: polymerase chain reaction (PCR; Amplicor Chlamydia test, Roche Molecular Diagnostics, Nutley, NJ), strand displacement amplification (ProbeTec, BD Diagnostic Systems, Sparks, MD), transcription-mediated amplification (Amp CT, Gen-Probe, San Diego, CA) and GeneXpert CT/NG assay (Cepheid, Sunnyvale, CA). PCR and strand displacement amplification are DNA amplification tests that use primers that target gene sequences on the cryptogenic *C. trachomatis* plasmid that are present at approximately 10 copies in each infected cell. Transcription-mediated amplification is a ribosomal RNA amplification assay. GeneXpert is an on-demand qualitative real-time PCR. All these assays are also available as coamplification tests for simultaneously detecting *C. trachomatis* and *Neisseria gonorrhoeae.*

The currently available commercial NAATs are FDA approved for cervical swabs from adolescent girls and women, urethral swabs from adolescent boys and men, and urine from adolescents and adults. The latest version of transcription-mediated amplification was approved for use with vaginal swabs in adolescents and adults. Use of urine avoids the necessity for a clinical pelvic examination and can greatly facilitate screening in certain populations, especially adolescents, although several studies have now demonstrated that endocervical specimens and vaginal swabs are superior to urine for NAAT. Self-collected vaginal specimens appear to be as reliable as specimens obtained by a healthcare professional.

Data on use of NAATs for vaginal specimens or urine from children are very limited and insufficient to allow making a recommendation for their use. The CDC recommends that NAATs be used as an alternative to culture only if confirmation is available. Confirmation tests should consist of a second FDA-approved NAAT that targets a different gene sequence from the initial test.

The etiology of most cases of nonchlamydial nongonococcal urethritis is unknown, although *Ureaplasma urealyticum* and possibly *Mycoplasma genitalium* are implicated in up to one-third of cases (see Chapter 224). Proctocolitis may develop in individuals who have a rectal infection with an LGV strain (see Chapter 226.4).

TREATMENT

The first-line treatment regimens recommended by the CDC for uncomplicated *C. trachomatis* genital infection in men and nonpregnant women include azithromycin (1 g PO as a single dose) and doxycycline (100 mg PO twice a day for 7 days). Alternative regimens are erythromycin base (500 mg PO 4 times a day for 7 days), erythromycin ethylsuccinate (800 mg PO 4 times a day for 7 days), ofloxacin (300 mg PO twice a day for 7 days), and levofloxacin (500 mg PO once daily for 7 days). The high erythromycin dosages might not be well tolerated. Doxycycline and quinolones are contraindicated in pregnant women, and quinolones are contraindicated in persons younger than 18 yr. For pregnant women, the recommended treatment regimen is azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days). Alternative regimens for pregnant women are erythromycin base (250 mg PO 4 times a day for 14 days), and erythromycin ethylsuccinate (800 mg PO 4 times a day for 7 days or 400 mg PO 4 times a day for 14 days).

Empirical treatment without microbiologic diagnosis is recommended only for patients at high risk for infection who are unlikely to return for follow-up evaluation, including adolescents with multiple sex partners. These patients should be treated empirically for both *C. trachomatis* and gonorrhea.

Sex partners of patients with nongonococcal urethritis should be treated if they have had sexual contact with the patient during the 60 days preceding the onset of symptoms. The most recent sexual partner should be treated even if the last sexual contact was more than 60 days from onset of symptoms.

COMPLICATIONS

Complications of genital chlamydial infections in women include perihepatitis (Fitz-Hugh-Curtis syndrome) and salpingitis. Of women with untreated chlamydial infection who develop pelvic inflammatory disease, up to 40% will have significant sequelae; approximately 17% will suffer from chronic pelvic pain, approximately 17% will become infertile, and approximately 9% will have an ectopic (tubal) pregnancy. Adolescent girls may be at higher risk for developing complications, especially salpingitis, than older women. Salpingitis in adolescent girls is also more likely to lead to tubal scarring, subsequent obstruction with secondary infertility, and increased risk for ectopic pregnancy. Approximately 50% of neonates born to pregnant women with untreated chlamydial infection will acquire *C. trachomatis* infection

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(see Chapter 226.3). Women with *C. trachomatis* infection have a 3-5–fold increased risk for acquiring HIV infection.

PREVENTION

Timely treatment of sex partners is essential for decreasing risk for reinfection. Sex partners should be evaluated and treated if they had sexual contact during the 60 days preceding onset of symptoms in the patient. The most recent sex partner should be treated even if the last sexual contact was >60 days. Patients and their sex partners should abstain from sexual intercourse until 7 days after a single-dose regimen or after completion of a 7 day regimen.

Annual routine screening for *C. trachomatis* is recommended for all sexually active female adolescents, for all women 20-25 yr of age, and for older women with risk factors such as new or multiple partners or inconsistent use of barrier contraceptives. Sexual risk assessment might indicate more frequent screening of some women.

Bibliography is available at Expert Consult.

226.3 Conjunctivitis and Pneumonia in Newborns

Margaret R. Hammerschlag

EPIDEMIOLOGY

Chlamydial genital infection is reported in 5-30% of pregnant women, with a risk for vertical transmission at parturition to newborn infants of approximately 50%. The infant may become infected at 1 or more sites, including the conjunctivae, nasopharynx, rectum, and vagina. Transmission is rare following cesarean section with intact membranes. The introduction of systematic prenatal screening for *C. trachomatis* infection and treatment of pregnant women has resulted in a dramatic decrease in the incidence of neonatal chlamydial infection in the United States. However, in countries where prenatal screening is not done, such as the Netherlands, *C. trachomatis* remains an important cause of neonatal infection, accounting for >60% of neonatal conjunctivitis.

Inclusion Conjunctivitis

Approximately 30-50% of infants born to mothers with active, untreated chlamydial infection develop clinical conjunctivitis. Symptoms usually develop 5-14 days after delivery, or earlier in infants born after prolonged rupture of membranes. The presentation is extremely variable and ranges from mild conjunctival injection with scant mucoid discharge to severe conjunctivitis with copious purulent discharge, chemosis, and pseudomembrane formation. The conjunctiva may be very friable and might bleed when stroked with a swab. Chlamydial conjunctivitis must be differentiated from gonococcal ophthalmia, which is sight threatening. At least 50% of infants with chlamydial conjunctivitis also have nasopharyngeal infection.

Pneumonia

Pneumonia caused by *C. trachomatis* can develop in 10-20% of infants born to women with active, untreated chlamydial infection. Only approximately 25% of infants with nasopharyngeal chlamydial infection develop pneumonia. *C. trachomatis* pneumonia of infancy has a very characteristic presentation. Onset usually occurs between 1 and 3 mo of age and is often insidious, with persistent cough, tachypnea, and absence of fever. Auscultation reveals rales; wheezing is uncommon. The absence of fever and wheezing helps to distinguish *C. trachomatis* pneumonia from respiratory syncytial virus pneumonia. A distinctive laboratory finding is the presence of peripheral eosinophilia (>400 cells/µL). The most consistent finding on chest radiograph is hyperinflation accompanied by minimal interstitial or alveolar infiltrates.

Infections at Other Sites

Infants born to mothers with *C. trachomatis* can develop infection in the rectum or vagina. Although infection in these sites appears to be totally asymptomatic, it can cause confusion if it is identified at a later date. Perinatally acquired rectal, vaginal, and nasopharyngeal infections can persist for 3 yr or longer. *Chlamydia pneumoniae* can also be confused with *C. trachomatis* infection in nasopharyngeal cultures if a genus-specific monoclonal antibody is used to confirm the culture.

DIAGNOSIS

Definitive diagnosis is achieved by isolation of *C. trachomatis* in cultures of specimens obtained from the conjunctiva or nasopharynx. Nonculture methods including direct fluorescent antibody and NAATs are available, but only the direct fluorescent antibody is currently approved for diagnosis of chlamydial conjunctivitis with sensitivities of ≥90% and specificities of ≥95% for conjunctival specimens compared with culture. Accuracy for nasopharyngeal specimens is not as good. Data on use of NAATs for diagnosis of *C. trachomatis* in children are limited. Limited data suggest that PCR may be equivalent to culture for detecting *C. trachomatis* in the conjunctiva of infants with conjunctivitis.

TREATMENT

The recommended treatment regimens for *C. trachomatis* conjunctivitis or pneumonia in infants are erythromycin (base or ethylsuccinate, 50 mg/kg/day divided 4 times a day PO for 14 days) and azithromycin suspension (20 mg/kg/day once daily PO for 3 days). The rationale for using oral therapy for conjunctivitis is that 50% or more of these infants have concomitant nasopharyngeal infection or disease at other sites, and studies demonstrate that topical therapy with sulfonamide drops and erythromycin ointment is not effective. The failure rate with oral erythromycin remains 10-20%, and some infants require a second course of treatment. Mothers (and their sexual contacts) of infants with *C. trachomatis* infections should be empirically treated for genital infection. An association between treatment with oral erythromycin and infantile hypertrophic pyloric stenosis has been reported in infants younger than 6 wk of age who were given the drug for prophylaxis after nursery exposure to pertussis.

PREVENTION

Neonatal gonococcal prophylaxis with topical erythromycin ointment does not prevent chlamydial ophthalmia or nasopharyngeal colonization with *C. trachomatis* or chlamydial pneumonia. *The most effective method of controlling perinatal chlamydial infection is screening and treatment of pregnant women.* For treatment of *C. trachomatis* infection in pregnant women, the CDC currently recommends either azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days) as first-line regimens. Erythromycin base (250 mg PO 4 times a day for 14 days) and erythromycin ethylsuccinate (800 mg 4 times a day for 7 days, or 400 mg PO 4 times a day for 14 days) are listed as alternative regimens. Reasons for failure of maternal treatment to prevent infantile chlamydial infection include poor compliance and reinfection from an untreated sexual partner.

Bibliography is available at Expert Consult.

226.4 Lymphogranuloma Venereum

Margaret R. Hammerschlag

LGV is a systemic sexually transmitted disease caused by the L_1, L_2, and L_3 serotypes of the LGV biovar of *C. trachomatis.* Unlike strains of the trachoma biovar, LGV strains have a predilection for lymphoid tissue. Less than 1,000 cases are reported in adults in the United States annually. There has been a resurgence of LGV infections among men who have sex with men in Europe and the United States. Many of the men were HIV infected and used illicit drugs, specifically methamphetamines. To our knowledge, cases in the pediatric population have not been reported since the emergence of the new clusters of HIV-associated cases in 2003. We reported a case of a 16 yr old boy who presented with LGV proctocolitis after having receptive unprotected anal intercourse with a 30 yr old man he met on the Internet. This history was obtained after the boy was found to be HIV-positive. The

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diagnosis of LGV, particularly when it presents with proctocolitis, relies on a high index of suspicion that would lead to emphasizing certain aspects of the history and ordering the pertinent diagnostic tests. Many pediatricians and pediatric gastroenterologists might not be very familiar with the entity and might not entertain it as a diagnostic consideration in the pediatric patients. The diagnosis can be further suggested by *C. trachomatis* testing: culturing the organism or, more commonly by NAATs. Currently available NAATs will not differentiate LGV from other *C. trachomatis* serovars. NAATs for *C. trachomatis* are also not FDA-cleared for testing rectal specimens. Trying to ascertain the *C. trachomatis* serovar for confirmation of LGV has therapeutic implications as a single-dose of azithromycin is unlikely to eradicate the infection and a 3 wk course of doxycycline is the preferred treatment.

CLINICAL MANIFESTATIONS

The 1st stage of LGV is characterized by the appearance of the primary lesion, a painless, usually transient papule on the genitals. The 2nd stage is characterized by usually unilateral femoral or inguinal lymphadenitis with enlarging, painful buboes. The nodes may break down and drain, especially in men. In women, the vulvar lymph drains to the retroperitoneal nodes. Fever, myalgia, and headache are common. The 3rd stage is a genitoanorectal syndrome with rectovaginal fistulas, rectal strictures, and urethral destruction. Among men who have sex with men, rectal infection with LGV can produce a severe, acute proctocolitis, which can be confused with inflammatory bowel disease or malignancy.

DIAGNOSIS

LGV can be diagnosed by serologic testing or by culture of *C. trachomatis* or molecular testing for *C. trachomatis* from a specimen aspirated from a bubo. Most patients with LGV have complement-fixing antibody titers of >1 : 16. Chancroid and herpes simplex virus can be distinguished clinically from LGV by the concurrent presence of painful genital ulcers. Syphilis can be differentiated by serologic tests. However, co-infections can occur.

TREATMENT

Doxycycline (100 mg PO bid for 21 days) is the recommended treatment. The alternative regimen is erythromycin base (500 mg PO 4 times/day for 21 days). Azithromycin (1 g PO once weekly for 3 wk) may also be effective but clinical data are lacking. Sex partners of patients with LGV should be treated if they have had sexual contact with the patient during the 30 days preceding the onset of symptoms.

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Chapter 227

Psittacosis *(Chlamydia psittaci)*

Stephan A. Kohlhoff and
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Chlamydia psittaci, the agent of psittacosis (also known as **parrot fever** and **ornithosis**), is primarily an animal pathogen and causes human disease uncommonly. In birds, *C. psittaci* infection is known as *avian chlamydiosis*.

ETIOLOGY

C. psittaci affects both psittacine birds (e.g., parrots, parakeets, macaws) and nonpsittacine birds (ducks, turkeys); the known host range includes 130 avian species. The life cycle of *C. psittaci* is the same as for *Chlamydia pneumoniae* (see Chapter 217). Strains of *C. psittaci* have been analyzed by patterns of pathogenicity, inclusion morphology in tissue culture, DNA restriction endonuclease analysis, and monoclonal antibodies, which indicate that there are 7 avian serovars. Two of the avian serovars, psittacine and turkey, are of major importance in the avian population of the United States. Each is associated with important host preferences and disease characteristics.

EPIDEMIOLOGY

From 1988-2003 there were 935 reported cases of psittacosis in the United States. Of these, 85% of these cases were associated with exposure to birds, including 70% following exposure to caged pet birds, which were usually psittacine birds, including cockatiels, parakeets, parrots, and macaws. Chlamydiosis among caged nonpsittacine birds occurs most often in pigeons, doves, and mynah birds. Persons at highest risk for acquiring psittacosis include bird fanciers and owners of pet birds (43% of cases) and pet shop employees (10% of cases). Reported cases most likely underestimate the number of actual infections owing to a lack of awareness.

Inhalation of aerosols from feces, fecal dust, and nasal secretions of animals infected with *C. psittaci* is the primary route of infection. *Source birds are either asymptomatic or have anorexia, ruffled feathers, lethargy, and watery green droppings*. Psittacosis is uncommon in children, in part because children may be less likely to have close contact with infected birds. One high-risk activity is cleaning the cage. Several major outbreaks of psittacosis have occurred in turkey-processing plants; workers exposed to turkey viscera are at the highest risk for infection.

CLINICAL MANIFESTATIONS

Infection with *C. psittaci* in humans ranges from clinically inapparent to severe disease, including pneumonia and multiorgan involvement. The mean incubation period is 15 days after exposure, with a range of 5-21 days. Onset of disease is usually abrupt, with fever, cough, headache, myalgia, and malaise. The fever is high and is often associated with rigors and sweats. The headache can be so severe that meningitis is considered. The cough is usually nonproductive. Gastrointestinal symptoms are occasionally reported. Crackles may be heard on auscultation. Chest radiographs are usually abnormal and are characterized by the presence of variable infiltrates, sometimes accompanied by pleural effusions. The white blood cell count is usually normal but is sometimes mildly elevated. Elevated levels of aspartate aminotransferase, alkaline phosphatase, and bilirubin are common.

DIAGNOSIS

Psittacosis can be difficult to diagnose because of the varying clinical presentations. A history of exposure to birds or association with an active case can be important clues, but as many as 20% of patients with psittacosis have no known contact. Person-to-person spread has been suggested but not proved. Other infections that cause pneumonia with high fever, unusually severe headache, and myalgia include routine bacterial and viral respiratory infections as well as *Coxiella burnetii* infection (Q fever), *Mycoplasma pneumoniae* infection, *C. pneumoniae* infection, tularemia, tuberculosis, fungal infections, and Legionnaires disease.

The Centers for Disease Control and Prevention and the Council of State and Territorial Epidemiologists have established national case definitions for epidemiologic surveillance of psittacosis. A patient is considered to have a confirmed case of psittacosis if clinical illness is compatible with psittacosis and the case is laboratory confirmed by either: isolation of *C. psittaci* from respiratory specimens (e.g., sputum, pleural fluid, or tissue) or blood, or 4-fold or greater increase in antibody (immunoglobulin G) against *C. psittaci* by complement fixation or microimmunofluorescence between paired acute- and convalescent-phase serum specimens obtained at least 2-4 wk apart. A patient is considered to have a probable case of psittacosis if the

clinical illness is compatible with psittacosis and 1 of the 2 following laboratory results is present: supportive serology (*e.g., C. psittaci* antibody titer [Immunoglobulin M] of greater ≥32 in at least 1 serum specimen obtained after onset of symptoms), or detection of *C. psittaci* DNA in a respiratory specimen (e.g., sputum, pleural fluid or tissue) via amplification of a specific target by polymerase chain reaction assay.

Although microimmunofluorescence has greater specificity to *C. psittaci* than complement fixation, crossreactions with other *Chlamydia* species can occur. Therefore acute- and convalescent-phase serum specimens should be analyzed at the same time in the same laboratory. False-negative microimmunofluorescence results can occur in acutely ill patients. Early treatment of psittacosis with tetracycline can abrogate the antibody response.

Although *C. psittaci* will grow in the same culture systems used for isolation of *Chlamydia trachomatis* and *C. pneumoniae,* very few laboratories culture for *C. psittaci,* mainly because of the potential biohazard. Real-time polymerase chain reaction assays have been developed for use in the detection of *C. psittaci* in respiratory specimens. These assays can distinguish *C. psittaci* from other chlamydial species and identify different *C. psittaci* genotypes. However, polymerase chain reaction–based tests have not been cleared by the FDA for use as diagnostic tests in humans samples.

TREATMENT

Recommended treatment regimens for psittacosis are doxycycline (100 mg PO twice daily) or tetracycline (500 mg PO 4 times a day) for at least 10-14 days after the fever abates. The initial treatment of severely ill patients is doxycycline hyclate (4.4 mg/kg/day divided every 12 hr IV; maximum: 100 mg/dose). Erythromycin (500 mg PO 4 times a day) and azithromycin (10 mg/kg PO day 1, not to exceed 500 mg, followed by 5 mg/kg PO on days 2-5, not to exceed 250 mg) are alternative drugs if tetracyclines are contraindicated (e.g., children <8 yr of age and pregnant women) but may be less effective. Remission is usually evident within 48-72 hr. Initial infection does not appear to be followed by long-term immunity. Reinfection and clinical disease can develop within 2 mo of treatment.

PROGNOSIS

The mortality rate of psittacosis is 15-20% with no treatment but is <1% with appropriate treatment. Severe illness leading to respiratory failure and fetal death has been reported among pregnant women.

PREVENTION

Several control measures are recommended to prevent transmission of *C. psittaci* from birds. Bird fanciers should be cognizant of the potential risk. *C. psittaci* is susceptible to heat and to most disinfectants and detergents but is resistant to acid and alkali. Accurate records of all bird-related transactions aid in identifying sources of infected birds and potentially exposed persons. Newly acquired birds, including birds that have been to shows, exhibitions, fairs, or other events, should be isolated for 30-45 days or tested or treated prophylactically before adding them to a group of birds. Care should be taken to prevent transfer of fecal material, feathers, food, or other materials between birdcages. Birds with signs of avian chlamydiosis (e.g., ocular or nasal discharge, watery green droppings, or low body weight) should be isolated and should not be sold or purchased. Their handlers should wear protective clothing and a disposable surgical cap and use a respirator with an N95 or higher efficiency rating (not a surgical mask) when handling them or cleaning their cages. Infected birds should be isolated until fully treated, which is generally 45 days.

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Section 11

Rickettsial Infections

Chapter 228

Spotted Fever Group Rickettsioses

J. Stephen Dumler and Megan E. Reller

Rickettsia species were classically divided into "spotted fever" and "typhus" groups based on serologic reactions and later on the presence or absence of the outer membrane protein A (*ompA*) gene. Sequencing of at least 45 complete genomes has refined distinctions. However, there is controversy regarding phylogeny and some data suggest that diversity and pathogenicity are the result of gene loss and lateral gene transfer from other prokaryotes or even eukaryotes, which further obscures accurate taxonomic classification. One proposal is to divide existing species into spotted fever and "transitional" groups based on genetic relatedness; both include pathogenic species and species not now known to cause human disease (Table 228-1). Although increasingly more is understood about the molecular basis by which these bacteria cause human illness, an alternative classification system based on pathogenetic mechanisms has not been defined. The list of pathogens and potential pathogens in the spotted fever group has expanded dramatically in recent years. Among them are the tickborne agents *Rickettsia rickettsii,* the cause of Rocky Mountain or Brazilian spotted fever (RMSF); *Rickettsia conorii,* the cause of Mediterranean spotted fever (MSF) or boutonneuse fever; *Rickettsia sibirica,* the cause of North Asian tick typhus; *Rickettsia japonica,* the cause of Oriental spotted fever; *Rickettsia honei,* the cause of Flinders Island spotted fever or Thai tick typhus; *Rickettsia africae,* the cause of African tick bite fever; *Rickettsia akari,* the cause of mite-transmitted rickettsialpox; *Rickettsia felis*, the cause of cat flea–transmitted typhus; and *Rickettsia australis,* the cause of tick-transmitted Queensland tick typhus. One proposal creates subspecies of *R. conorii*, including subsp. *conorii* (classical MSF), subsp. *indica* (Indian tick typhus), subsp. *caspia* (Astrakhan fever), and subsp. *israelensis* (Israeli spotted fever). The recognition that *Rickettsia parkeri* and "*Rickettsia philippi*" (*Rickettsia* 364D) both cause mild spotted fever in North America and the association of high seroprevalence for spotted fever group *Rickettsia* infections in humans where *Amblyomma* ticks frequently contain *Rickettsia amblyommii* suggest that the full range of agents that can cause spotted fever is still to be discerned.

Infections with other members of the spotted fever and transitional groups are clinically similar to MSF, with fever, maculopapular rash, and eschar at the site of the tick bite. Israeli spotted fever is generally associated with a more severe course, including death, in children. African tick bite fever is relatively mild, can include a vesicular rash, and often manifests with multiple eschars. New potentially pathogenic rickettsial species have been identified, including *Rickettsia slovaca,* the cause of tickborne lymphadenopathy or *Dermacentor*-borne necrosis and lymphadenopathy. *Rickettsia aeschlimannii, Rickettsia heilongjiangensis, Rickettsia helvetica, Rickettsia massiliae,* and *Rickettsia raoultii* are all reported to cause mild to moderate illnesses in humans, although few cases have been described. Fortunately, the vast majority of infections respond well to doxycycline treatment if instituted early in illness; however, this is a significant challenge.

Table 228-1 Summary of Rickettsial Diseases of Humans, Including *Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia,* and *Coxiella*

GROUP OR DISEASE AGENT		ARTHROPOD VECTOR, TRANSMISSION HOSTS		GEOGRAPHIC DISTRIBUTION	PRESENTING CLINICAL FEATURES*	COMMON LAB ABNORMALITIES	DIAGNOSTIC TESTS	TREATMENT†
SPOTTED FEVER GROUP								
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Tick bite: *Dermacentor* species (wood tick, dog tick) *Rhipicephalus sanguineus* (brown dog tick)	Dogs Rodents	Western hemisphere	Fever, headache, rash,* emesis, diarrhea, myalgias	AST, ALT $\downarrow$Na (mild) $\downarrow$Platelets ±Leukopenia Left shift	Early: IH, DFA, PCR After 1st wk: IFA	**Doxycycline** Tetracycline Chloramphenicol
Mediterranean spotted fever (Boutonneuse fever)	*Rickettsia conorii*	Tick bite: *R. sanguineus* (brown dog tick)	Dogs Rodents	Africa, Mediterranean, India, Middle East	Painless eschar (tache noir) with regional lymphadenopathy, fever, headache, rash,* myalgias	AST, ALT $\downarrow$Na (mild) $\downarrow$Platelets ±Leukopenia Left shift	Early: IH, DFA, PCR After 1st wk: IFA	**Doxycycline** Tetracycline Chloramphenicol Azithromycin Clarithromycin Fluoroquinolones
African tick-bite fever	*Rickettsia africae*	Tick bite	Cattle Goats?	Sub-Saharan Africa, Caribbean	Fever, single or multiple eschars, regional lymphadenopathy, rash* (can be vesicular)	AST, ALT $\downarrow$Platelets	Early: IH, DFA After 1st wk: IFA	**Doxycycline**
Tickborne lymphadenopathy (TIBOLA); Dermacentor-borne necrosis and lymphadenopathy (DEBONEL)	*Rickettsia slovaca*	Tick bite: *Dermacentor*	?	Europe	Eschar (scalp), painful lymphadenopathy	?	PCR	**Doxycycline**
Rickettsia sp, 364D genotype	"*Rickettsia philippi*"	*Dermacentor occidentalis* (Pacific coast tick)		California	Eschar, fever, headache, lymphadenopathy malaise	Unremarkable	PCR	Doxycycline
TRANSITIONAL GROUP								
Rickettsialpox	*Rickettsia akari*	Mite bite	Mice	North America, Russia, Ukraine, Adriatic, Korea, South Africa	Painless eschar, ulcer or papule; tender regional lymphadenopathy, fever, headache, rash* (can be vesicular)	$\downarrow$WBC	Early: IH, DFA After 1st wk: IFA	**Doxycycline** Chloramphenicol
Cat flea typhus	*Rickettsia felis*	Flea bite	Opossums Cats Dogs	Western hemisphere, Europe	Fever, rash,* headache	?	Early: PCR After 1st wk: IFA	**Doxycycline**
TYPHUS GROUP								
Murine typhus	*Rickettsia typhi*	Flea feces	Rats Opossums	Worldwide	Fever, headache, rash,* myalgias, emesis, lymphadenopathy, hepatosplenomegaly	AST, ALT $\downarrow$Na (mild) $\downarrow$WBC $\downarrow$ Platelets	Early: DFA After 1st wk: IFA	**Doxycycline** Chloramphenicol
Epidemic (louse-borne) typhus (recrudescent form: Brill-Zinsser disease)	*Rickettsia prowazekii*	Louse feces	Humans	South America, Central America, Mexico, Africa, Asia, Eastern Europe	Fever, headache, abdominal pain, rash,* CNS involvement	AST, ALT $\downarrow$Platelets	Early: none After 1st wk: IgG/IgM, IFA	**Doxycycline** Tetracycline Chloramphenicol
Flying squirrel (sylvatic) typhus	*Rickettsia prowazekii*	Louse feces? Flea feces or bite?	Flying squirrels	Eastern United States	Same as above (often milder)	AST, ALT $\downarrow$Platelets	Early: none After 1st wk: IFA	**Doxycycline** Tetracycline Chloramphenicol

SCRUB TYPHUS								
Scrub typhus	*Orientia tsutsugamushi*	Chigger bite: *Leptotrombidium*	Rodents?	South Asia, Japan, Indonesia, Korea, China, Russia, Australia	Fever, rash,* headache, painless eschar, hepatosplenomegaly, gastrointestinal symptoms	↓Platelets AST, ALT	Early: none After 1st wk: IFA	**Doxycycline** Tetracycline Chloramphenicol *If doxycycline resistant:* rifampicin Azithromycin
EHRLICHIOSIS AND ANAPLASMOSIS								
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	Tick bite: *Amblyomma americanum* (lone star tick)	Deer Dogs	United States Europe? Africa? Asia?	Fever, headache, malaise, myalgias, rash*[‡], hepatosplenomegaly,[‡] swollen hands/feet[‡]	AST, ALT ↓WBC ↓Platelets ↓Na (mild)	Early: PCR After 1st wk: IFA	**Doxycycline** Tetracycline
Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	Tick bite: *Ixodes* species	Rodents Deer Ruminants	United States, Europe, Asia	Fever, headache, malaise, myalgias	AST, ALT ↓WBC, ↓ANC ↓Platelets ↓Na (mild)	Early: PCR, blood smear After 1st wk: IFA	**Doxycycline** Tetracycline Rifampin
Ewingii ehrlichiosis	*Ehrlichia ewingii*	Tick bite: *Amblyomma americanum* (lone star tick)	Dogs Deer	United States (south-central, southeast)	Fever, headache, malaise, myalgias	AST, ALT, ↓WBC ↓Platelets ↓Na (mild)	Early: PCR After 1st wk: IFA	**Doxycycline** Tetracycline
Ehrlichia muris–like agent (EMLA) infection	*Ehrlichia muris*–like agent	*Ixodes scapularis*	?	Minnesota, Wisconsin	Fever, headache, malaise, myalgias	AST, ALT ↓WBC, ↓Platelets	Early: PCR After 1st wk: IFA	**Doxycycline**
Sennetsu ehrlichiosis	*Neorickettsia sennetsu*	Ingestion of fish helminth?	?	Japan Malaysia	Fever, "mononucleosis" symptoms, postauricular and posterior cervical lymphadenopathy	Atypical lymphocytosis	Early: none After 1st wk: IFA	**Doxycycline** Tetracycline
Q FEVER								
Q Fever: acute (for chronic, see text)	*Coxiella burnetii*	Inhalation of infected aerosols: contact with parturient animals, abattoir, contaminated cheese and milk, ?ticks	Cattle Sheep Goats Cats Rabbits	Worldwide	Fever, headache, arthralgias, myalgias, gastrointestinal symptoms, cough, pneumonia, rash (children)	AST, ALT WBC ↓ Platelets Interstitial infiltrate	Early: PCR After 1st wk: IFA	**Doxycycline** Tetracycline Fluoroquinolones Trimethoprim-sulfamethoxazole

*Rash is infrequently present at initial presentation but appears during the 1st wk of illness.
[†]Preferred treatment is in **bold**.
[‡]Often present in children but not adults.
ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CNS, central nervous system; DFA, direct fluorescent antibody; IFA, indirect fluorescent antibody; IgG, immunoglobulin G; IgM, immunoglobulin M; IH, immunohistochemistry; PCR, polymerase chain reaction; WBC, white blood cell count.

228.1 Rocky Mountain Spotted Fever *(Rickettsia rickettsii)*

Megan E. Reller and J. Stephen Dumler

RMSF is the most frequently identified and most severe rickettsial disease in the United States. It is also the most common vector-borne disease in the United States after Lyme disease. Although considered uncommon, RMSF is believed to be greatly underdiagnosed and underreported. RMSF should be considered in the differential diagnosis of fever, headache, and rash in the summer months, especially after tick exposure. Because fulminant disease and death are associated with delays in treatment, patients in whom the illness is clinically suspected should be treated promptly.

ETIOLOGY

RMSF results from systemic infection of endothelial cells by the obligate intracellular bacterium *Rickettsia rickettsii.*

EPIDEMIOLOGY

The term **Rocky Mountain spotted fever** is historical, because the agent was discovered in the Bitterroot Range of the Rocky Mountains of Montana. Few cases are now reported from this region. Cases have been reported throughout the continental United States (except Vermont and Maine), southwestern Canada, Mexico, Central America, and South America, but not from outside of the Western Hemisphere. In 2010, the Centers for Disease Control and Prevention (CDC) reporting criteria for "Rocky Mountain spotted fever" changed to **spotted fever group rickettsiosis** because serology often does not distinguish *R. rickettsii* from infection by other spotted fever group *Rickettsia*. Additionally, cases detected by enzyme immunoassay were classified as probable. Thus, in 2012, 2,802 confirmed and probable cases of spotted fever rickettsiosis were reported in Morbidity and Mortality Weekly Reports Summary of Notifiable Diseases. Unlike in prior years, most cases were reported from the west south-central states, especially from Arkansas, Oklahoma, and Missouri; high numbers of cases were also reported from North Carolina, Tennessee, Virginia, New Jersey, Georgia, Alabama, as well as Arizona. The incidence of RMSF cycles over 25-35 yr intervals but has generally increased over the past decades. The mean number of cases reported each year to the CDC has steadily increased (515 during 1993-1998, 946 during 1999-2004, and 2,068 cases in 2005-2010). Habitats favored by ticks, including wooded areas or coastal grassland and salt marshes, and, in the Southwestern United States and Mexico, shaded areas where dogs congregate are associated with disease. Foci of intense infection are found both in rural and urban areas. Clustering of cases within families likely reflects shared environmental exposures. In the United States, 90% of cases occur between April and September, months in which humans spend the most time outdoors. The highest age-specific incidence of RMSF among children is seen in those older than 5 yr of age, with boys outnumbering girls.

TRANSMISSION

Ticks are the natural hosts, reservoirs, and vectors of *R. rickettsii* and maintain the infection in nature by transovarial transmission (passage of the organism from infected ticks to their progeny). Ticks harboring rickettsiae are substantially less fecund than uninfected ticks; thus, horizontal transmission (acquisition of rickettsiae by taking a blood meal from transiently rickettsemic hosts such as small mammals or dogs) contributes to maintenance of rickettsial infections in ticks. Uninfected ticks that simultaneously feed (cofeed) with infected transmitting ticks easily become infected, even if feeding on an immune host and are also likely to be major contributors to natural transmission and maintenance. Ticks transmit the infectious agent to mammalian hosts (including humans) via infected saliva during feeding. The pathogen *R. rickettsii* in ticks becomes virulent after exposure to blood or increased temperature; thus, the longer the tick is attached, the greater the risk of transmission. The principal tick hosts of *R. rickettsii* are *Dermacentor variabilis* (the American dog tick) in the eastern United States and Canada, *Dermacentor andersoni* (the wood tick) in the western United States and Canada, *Rhipicephalus sanguineus* (the common brown dog tick) in the southwestern United States and in Mexico, and *Amblyomma cajennense* and *Amblyomma aureolatum* in Central and South America (Fig. 228-1).

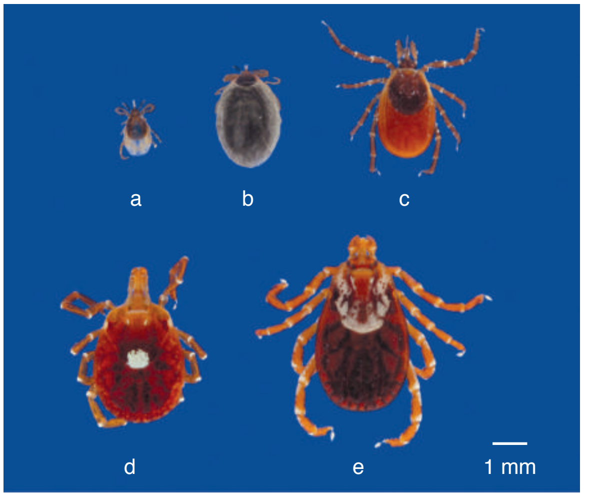

Figure 228-1 Tick vectors of agents of human rickettsial diseases. An unengaged nymph **(A),** engorged nymph **(B),** and adult female **(C)** of *Ixodes scapularis* (deer tick), the vector of *Anaplasma phagocytophilum* and *Ehrlichia muris*–like agent (EMLA), the causes of human granulocytic anaplasmosis and EMLA ehrlichiosis, respectively. An adult female **(D)** of *Amblyomma americanum* (lone star tick), the vector of *Ehrlichia chaffeensis* and *Ehrlichia ewingii*, the causes of human monocytic ehrlichiosis and ewingii ehrlichiosis, respectively. An adult female **(E)** of *Dermacentor variabilis* (American dog tick), the vector of *Rickettsia rickettsii*, the cause of Rocky Mountain spotted fever.

Dogs can serve as reservoir hosts for *R. rickettsii,* can develop RMSF themselves, and can bring infected ticks into contact with humans. Serologic studies suggest that many patients with RMSF likely acquired the illness from ticks carried by the family dog.

Humans can also become infected when trying to remove an attached tick, because *R. rickettsii*–containing tick fluids or feces can be rubbed into the open wound at the bite site or into the conjunctivae by contaminated fingers. Finally, inhalation of aerosolized rickettsiae has caused severe infections and deaths in laboratory workers.

PATHOLOGY AND PATHOGENESIS

Systemic infection is most obvious on the skin (rash), but nearly all organs and tissues are affected. Following inoculation of tick saliva into the dermis, rickettsial outer surface proteins bind to the vascular endothelial cell surface proteins, which signals focal cytoskeletal changes that lead to endocytosis. Thereafter, rickettsia phospholipase-mediated dissolution of the endosomal membranes allows escape into the cytosol. Members of the spotted fever group actively nucleate actin polymerization on one pole to achieve directional movement, allowing some rickettsiae to propel into neighboring cells despite minimal initial damage to its host cell. The rickettsiae proliferate and damage the host cells by oxidative membrane alterations, protease activation, or continued phospholipase activity. It is likely that some aspects of intracellular infection are mediated by rickettsial protein effectors delivered into the host cell by a type 4 secretion system.

The histologic correlate of the initial macular or maculopapular rash is perivascular infiltration of lymphoid and histiocytic cells with edema but without significant endothelial damage. Proliferation of rickettsiae within the cytoplasm of infected endothelial cells leads to endothelial injury and **lymphohistiocytic or leukocytoclastic vasculitis** of small venules and capillaries, which allows extravasation of intravascular erythrocytes into the dermis and manifests as a petechial rash. This process is systemic and ultimately results in widespread microvascular

leakage, tissue hypoperfusion, and possibly end-organ ischemic injury. Infrequently, inflammation leads to nonocclusive thrombi. Very rarely, small and large vessels become completely obliterated by thrombi, leading to tissue infarction or hemorrhagic necrosis. Interstitial pneumonitis and vascular leakage in the lungs can lead to noncardiogenic pulmonary edema, and meningoencephalitis can cause significant cerebral edema and herniation.

The presence of the infectious agent initiates an inflammatory cascade, including release of cytokines and chemokines such as tumor necrosis factor-α, interleukin-1β, and interferon-γ, and RANTES (regulated upon activation, normal T-cell expressed and secreted). Infection of endothelial cells by *R. rickettsii* induces surface E-selectin expression and procoagulant activity followed by chemokine recruitment of lymphocytes, macrophages, and, occasionally, neutrophils. Local inflammatory and immune responses are suspected to contribute to the vascular injury; however, the benefits of effective inflammation and immunity are greater. Blockade of tumor necrosis factor-α and interferon-γ action in animal models diminishes survival and increases morbidity; reactive oxygen intermediates, nitric oxide expression, and sequestration of tryptophan from rickettsiae are mechanisms by which rickettsiae are killed within cells. Direct contact of infected endothelial cells with perforin-producing CD8 T lymphocytes and interferon-γ–producing natural killer cells, accompanied by rickettsia antibody, helps control the infection. The timing and balance between rickettsia-mediated increases in vascular permeability and the benefits of induction of innate and adaptive immunity are likely the major determinants of severity and outcome.

CLINICAL MANIFESTATIONS

The incubation period of RMSF in children varies from 2-14 days (median: 7 days). In 49% of cases, patients or their parents report a history of removing an attached tick, although the site of the tick bite is usually inapparent. Epidemiologic clues include living in or visiting an endemic area, playing or hiking in the woods, typical season, similar illness in family members, and close contact with a dog. In patients presenting for care, the illness is initially nonspecific, and most patients are not diagnosed during their first visit with a healthcare practitioner. Manifestations often (>50%) include fever, rash, nausea and vomiting, and headache, and less often (<50%) myalgias, abdominal pain, diarrhea, conjunctival injection, altered mental status, lymphadenopathy, and peripheral edema. Pain and tenderness of calf muscles are particularly common in children.

The typical **clinical triad of fever, headache, and rash** is observed in 58% of pediatric patients overall, but is present in only 3% of all patients at presentation. Fever and headache persist if the illness is untreated. Fever can exceed 40°C (104°F) and may be persistently elevated or can fluctuate dramatically. Headache is severe, unremitting, and unresponsive to analgesics.

Rash usually appears after only 1-2 days of illness, and an estimated 3-5% of children never develop a rash that is recognized. Initially, discrete, pale, rose-red blanching macules or maculopapules appear; characteristically this initial rash is observed on the extremities, including the wrists, ankles, or lower legs (Fig. 228-2). In 65% of patients, the initial rash spreads rapidly to involve the entire body, including the soles and palms. The rash can become petechial or even hemorrhagic, sometimes with palpable purpura. In severe disease, the petechiae can enlarge into ecchymoses, which can become necrotic. Severe vascular obstruction secondary to the rickettsial vasculitis and thrombosis is uncommon but can result in gangrene of the digits, earlobes, scrotum, nose, or an entire limb.

Central nervous system infection usually manifests as changes in mental status (33%) or as photophobia (18%), seizure (17%), or meningismus (16%). Patients can also manifest ataxia, coma, or auditory deficits. Cerebrospinal fluid parameters are usually normal, but one-third have pleocytosis (<10-300 cells/µL), either mononuclear or less often neutrophil-dominated. Some (20%) have elevated protein (<200 mg/dL) in the cerebrospinal fluid; hypoglycorrhachia is rare. Neuroimaging studies generally reveal only subtle abnormalities that do not alter treatment. Cerebral edema, meningeal enhancement, and prominent perivascular spaces have been observed in patients with severe disease.

Figure 228-2 Rocky Mountain spotted fever. *(Courtesy of Debra Karp Skopocki, MD.)*

Other

Pulmonary disease occurs more often in adults than in children. However, 33% of children examined have a chest radiograph interpreted as an infiltrate or pneumonia. The clinical presentation in these cases can manifest as rales, infiltrates, and noncardiogenic pulmonary edema. Other findings can include conjunctival suffusion, periorbital edema, dorsal hand and foot edema, and hepatosplenomegaly. Severe disease can include myocarditis, acute renal failure, and vascular collapse.

Persons with glucose-6-phosphate dehydrogenase deficiency are at increased risk for fulminant RMSF, defined as death from *R. rickettsii* infection within 5 days. The clinical course of fulminant RMSF is characterized by profound coagulopathy and extensive thrombosis leading to kidney, liver, and respiratory failure. Features associated with increased risk of death include altered mental status, admission to an intensive care unit, need for inotropic support, coma, and need for rapidly administered intravenous fluid.

Occasionally, clinical signs and symptoms suggest a localized process such as appendicitis or cholecystitis. Thorough evaluation usually reveals evidence of a systemic process and unnecessary surgical interventions are avoided.

LABORATORY FINDINGS

Laboratory abnormalities are common but nonspecific. Thrombocytopenia occurs in 60%, and the total white blood cell count is most often normal, with leukocytosis in 24% and leukopenia in 9%. Other characteristic abnormalities include a left-shifted leukocyte differential, anemia (33%), hyponatremia (<135 mEq/mL in 52%), and elevated serum aminotransferase levels (50%).

DIAGNOSIS

Delays in diagnosis and treatment are associated with severe disease and death. Because no reliable diagnostic test is available to confirm RMSF during acute illness, the decision to treat must be based on compatible epidemiologic, clinical, and laboratory features. RMSF should be considered in patients presenting spring through fall with an acute febrile illness accompanied by headache and myalgia (particularly if they report exposure to ticks or contact with a dog or have been in forested or tick-infested rural areas). A history of tick exposure, a rash (especially if on the palms or soles), a normal or low leukocyte count with a marked left shift, a relatively low or decreasing platelet count, and a low serum sodium concentration are all clues that can support a diagnosis of RMSF. In patients without a rash or in dark-skinned patients in whom a rash can be difficult to appreciate, the diagnosis can be exceptionally elusive and delayed. One half of pediatric deaths occur within 9 days of onset of symptoms. Thus, treatment

should not be withheld pending definitive laboratory results for a patient with clinically suspected illness. Further, prompt response to early treatment is diagnostically helpful.

If a rash is present, a vasculotropic rickettsial infection can be diagnosed as early as day 1 or 2 of illness with biopsy of a petechial lesion and immunohistochemical or immunofluorescent demonstration of specific rickettsial antigen in the endothelium. Although very specific, the sensitivity of this method is probably 70% at most. Furthermore, it can be adversely influenced by prior antimicrobial therapy, suboptimal selection of skin lesions for biopsy, and examination of insufficient tissue because of the focal nature of the infection. Tissue or blood can also be evaluated for *R. rickettsii* nucleic acids by polymerase chain reaction (PCR) at the CDC and selected public health or reference laboratories; PCR on blood is less sensitive than PCR on tissue and of similar sensitivity to tissue immunohistology, probably because the level of rickettsemia is generally very low (<6 rickettsiae/mL).

Definitive diagnosis is most often accomplished by serology, which is retrospective, because a rise in titer is not seen until after the 1st wk of illness. The gold standard for the diagnosis of RMSF is a 4-fold increase in immunoglobulin G antibody titer by indirect fluorescent antibody assay between acute and convalescent (at 2-4 wk) sera or demonstration of seroconversion. A single titer is neither sensitive (patients can die before seroconversion) nor specific (an elevated titer can represent prior infection); despite the historic role of immunoglobulin M testing, its role in early diagnosis has recently become controversial and cannot be advocated. With current serologic methods, RMSF cannot be reliably distinguished from other spotted fever group rickettsiae infections. Cross-reactions with typhus group rickettsiae also occur, but titers may be lower for the typhus group. Cross-reactions are not seen with *Ehrlichia* or *Anaplasma* infections. Weil-Felix antibody testing should not be performed, because it lacks both sensitivity and specificity. RMSF and other spotted fever group rickettsioses are reportable diseases in the United States.

DIFFERENTIAL DIAGNOSIS

Other rickettsial infections are easily confused with RMSF, especially all forms of human ehrlichiosis and murine typhus and novel spotted fever group rickettsioses that result from *R. parkeri* or "*R. philippii*" infections. RMSF can also mimic a variety of other diseases, such as meningococcemia and enteroviral infections. Negative blood cultures can exclude meningococcemia. PCR can differentiate enterovirus from *R. rickettsii* in patients with aseptic meningitis and a lymphocytic cerebrospinal fluid pleocytosis. Other diseases in the differential diagnosis are typhoid fever, secondary syphilis, Lyme disease, leptospirosis, rat-bite fever, scarlet fever, toxic shock syndrome, rheumatic fever, rubella, parvovirus infection, Kawasaki disease, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Henoch-Schönlein purpura, hemolytic uremic syndrome, aseptic meningitis, acute gastrointestinal illness, acute abdomen, hepatitis, infectious mononucleosis, hemophagocytic syndromes, dengue fever, and drug reactions.

TREATMENT

The time-proven effective therapies for RMSF are tetracyclines and chloramphenicol. The treatment of choice for suspected RMSF in patients of all ages, including for young children, is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day) is an alternative. Chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/day) should be reserved for patients with doxycycline allergy and for pregnant women, because chloramphenicol is an independent risk factor for increased mortality vs tetracyclines. If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 μg/mL. Chloramphenicol is preferred for pregnant women because of potential adverse effects of doxycycline on fetal teeth and bone and maternal liver function. Although tetracycline and doxycycline can be associated with tooth discoloration in children younger than 8 yr of age, RMSF is a life-threatening illness for which prompt therapy is imperative. Furthermore, tooth discoloration with tetracyclines is dose dependent and is unlikely to occur in children prescribed short-course therapy. Chloramphenicol is rarely associated with aplastic anemia and is no longer available as an oral preparation in the United States. An additional benefit of doxycycline over chloramphenicol is its effectiveness against potential concomitant ehrlichia infection. Sulfonamides should not be used, because they are associated with greater morbidity and mortality with all rickettsial infections. Other antibiotics, including penicillins, cephalosporins, and aminoglycosides, are not effective. The use of alternative antimicrobial agents, such as fluoroquinolones and the macrolides (azithromycin and clarithromycin), has not been evaluated.

Therapy should be continued for a minimum of 5-7 days and until the patient has been afebrile for at least 3 days to avoid relapse, especially in patients treated early. Treated patients usually defervesce within 48 hr, so the duration of therapy is usually <10 days.

SUPPORTIVE CARE

Most infections resolve rapidly with appropriate antimicrobial therapy and do not require hospitalization or other supportive care. Infection requires intensive care in 36% of cases. Particular attention to hemodynamic status is mandatory in severely ill children, because iatrogenic pulmonary or cerebral edema could be easily precipitated owing to diffuse microvascular injury of the lungs, meninges, and brain. Judicious use of corticosteroids for meningoencephalitis has been advocated by some, but no controlled trials have been conducted.

COMPLICATIONS

Complications of RMSF include noncardiogenic pulmonary edema from pulmonary microvascular leakage, cerebral edema from meningoencephalitis, and multiorgan damage (hepatitis, pancreatitis, cholecystitis, epidermal necrosis, and gangrene) mediated by rickettsial vasculitis and/or the accumulated effects of hypoperfusion and ischemia (acute renal failure). Long-term neurologic sequelae can occur in any child with RMSF but are more likely to occur in those hospitalized for ≥2 wk. Examples of neurologic sequelae include speech or swallowing disorders; global encephalopathy; cerebellar, vestibular, and motor dysfunction; hearing loss; and cortical blindness. Learning disabilities and behavioral problems are the most common neurologic sequelae among children who have survived severe disease.

PROGNOSIS

Delays in diagnosis and therapy are significant factors associated with death or severe illness. Before the advent of effective antimicrobial therapy for RMSF, the case fatality rate was 10% for children and 30% for adults. Although overall case fatality rate decreased to an historic low (0.3%) during 2003-2007, the case fatality rate of children 5-9 yr of age was 2.4%, and rates as high as 8.5% and 11.8% were documented in Texas (1986 through 1996) and in Arizona (1999-2007), respectively. Diagnosis based on serology alone underestimates the true mortality of RMSF, because death often occurs within 14 days (before developing a serologic response). Deaths occur despite the availability of effective therapeutic agents, indicating the need for clinical vigilance and a low threshold for early empiric therapy. Even with administration of appropriate antimicrobials, delayed therapy can lead to irreversible vascular or end-organ damage and long-term sequelae or death. Early therapy in uncomplicated cases usually leads to rapid defervescence within 1-3 days and recovery within 7-10 days. A slower response may be seen if therapy is delayed. In those who survive despite no treatment, fever subsides in 2-3 wks.

PREVENTION

No vaccines are available. Prevention of RMSF is best accomplished by preventing or treating tick infestation in dogs, avoiding areas where ticks reside, using insect repellents containing N,*N*-diethyl-3-methylbenzamide (DEET), wearing protective clothing, and carefully inspecting children after play in areas where they are potentially exposed to ticks. Recovery from infection yields lifelong immunity.

Prompt and complete removal of attached ticks helps reduce the risk for transmission because rickettsiae in the ticks need to be reactivated

to become virulent, and this requires at least several hours to days of exposure to body heat or blood. Contrary to popular belief, the application of petroleum jelly, 70% isopropyl alcohol, fingernail polish, or a hot match are not effective in removing ticks. A tick can be safely removed by grasping the mouth parts with a pair of forceps at the site of attachment to the skin and applying gentle and steady pressure to achieve retraction without twisting, thereby removing the entire tick and its mouth parts. The site of attachment should then be disinfected. Ticks should not be squeezed or crushed, because their fluids may be infectious. The removed tick should be soaked in alcohol or flushed down the toilet, and hands should be washed to avoid accidental inoculation into conjunctivae, mucous membranes, or breaks in skin. Typically, prophylactic antimicrobial therapy is not recommended because tetracyclines and chloramphenicol are only rickettsiostatic; however, the evidence to support this position is meager.

228.2 Mediterranean Spotted Fever or Boutonneuse Fever *(Rickettsia conorii)*

Megan E. Reller and J. Stephen Dumler

Boutonneuse fever is caused by *R. conorii* and its related subspecies; it is also called MSF, Kenya tick typhus, Indian tick typhus, Israeli spotted fever, and Astrakhan fever. It is a moderately severe vasculotropic rickettsiosis in adults, and comparatively mild in children, that is often initially associated with an eschar at the site of the tick bite. Minor differences in clinical presentation could be associated with genetic diversity of the rickettsial subspecies.

ETIOLOGY

MSF is caused by systemic endothelial cell infection by the obligate intracellular bacterium *R. conorii.* Similar species are distributed globally, such as *R. sibirica* and *Rickettsia mongolotimonae* in Russia, China, Mongolia, and Pakistan; *R. australis* and *R. honei* in Australia; *R. japonica* in Japan; and *R. africae* in South Africa (see Table 220-1). Analysis of antigens and related DNA sequences show that all are closely related within a genetic clade that includes spotted fever group *Rickettsia* species such as *R. rickettsii*, the cause of RMSF.

EPIDEMIOLOGY

R. conorii is distributed over a large geographic region, including India, Pakistan, Russia, Ukraine, Georgia, Israel, Morocco, southern Europe, Ethiopia, Kenya, and South Africa. Reported cases of MSF in southern Europe have steadily increased since 1980, and the seroprevalence is 11-26% in some areas. The peak in reported cases occurs during July and August in the Mediterranean basin; in other regions it occurs during warm months when ticks are active.

TRANSMISSION

Transmission occurs after the bite of the brown dog tick, *R. sanguineus,* or other tick species such as *Dermacentor, Haemaphysalis, Amblyomma, Hyalomma,* and *Ixodes.* Clustering of human cases of boutonneuse fever, infected ticks, and infected dogs implicate the household dog as a potential vehicle for transmission.

PATHOLOGY AND PATHOGENESIS

The underlying pathology seen with MSF is nearly identical to that of RMSF, except that eschars are often present at the site of tick bite where inoculation of rickettsiae occurs. The histopathology of the resultant lesion includes necrosis of dermal and epidermal tissues with a superficial crust; a dermis densely infiltrated by lymphocytes, histiocytes, and scattered neutrophils; and damaged capillaries and venules in the dermis. Immunohistochemical stains and nucleic acid amplification tests confirm that the lesions contain rickettsia-infected endothelial cells, but the vascular structure might not be apparent owing to extensive inflammation and necrosis. The necrosis results from both direct rickettsia-mediated vasculitis and resultant extensive local inflammation. Rickettsiae thus have ready access to lymphatics and venous blood and disseminate to cause systemic disease.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Typical findings in children include fever (93-100%), a maculopapular rash that appears 3-5 days after onset of fever (94-100%), hepatosplenomegaly (20-66%), myalgias and arthralgias (10-42%), headache (29-63%), and nausea, vomiting, or diarrhea (5-28%). In 60-90% of patients, a painless eschar or **tache noire** appears at the site of the tick bite, often on the scalp, with accompanying regional lymphadenopathy (50-60%). Although previously considered self-limited, this infection can be severe, mimicking RMSF. Findings can include seizures, purpuric skin lesions, neurologic deficits, respiratory and/or acute renal failure, and severe thrombocytopenia. Even though the case fatality rate can be as high as 10% in adults and severe infections occur in approximately 9% of children, pediatric deaths are rare. As with RMSF, a particularly severe form occurs in patients with glucose-6-phosphate dehydrogenase deficiency and in patients with underlying conditions such as alcoholic liver disease or diabetes mellitus.

DIAGNOSIS

Laboratory diagnosis of MSF and related spotted fever group rickettsioses is the same as that for RMSF. Cases can be confirmed by immunohistologic or immunofluorescent or demonstration of or amplification of nucleic acids from rickettsiae in skin biopsies, in vitro cultivation via centrifugation-assisted shell vial tissue culture, or demonstration of seroconversion or accompanied by a 4-fold rise in serum antibody titer to spotted fever group rickettsiae between acute and convalescent sera. Antibodies to spotted fever group antigens crossreact, so RMSF or other spotted fever group rickettsiosis in the United States or MSF in Europe, Africa, and Asia cannot be distinguished by these methods.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes conditions also associated with single eschars, such as anthrax, bacterial ecthyma, brown recluse spider bite, rat-bite fever (caused by *Spirillum minus*), and other rickettsioses (such as rickettsialpox, African tick-bite fever, and scrub typhus). The spotted fever group rickettsia *R. africae* causes African tick-bite fever, a milder illness than MSF that is often associated with multiple eschars and occasionally a vesicular rash. African tick bite fever can be contracted in North Africa, where MSF also occurs and is a common infection of travelers to sub-Saharan Africa who encounter bush or high grasslands on safari.

TREATMENT AND SUPPORTIVE CARE

In adults, MSF is effectively treated with tetracycline, doxycycline, chloramphenicol, ciprofloxacin, ofloxacin, levofloxacin, azithromycin, or clarithromycin. For children, the treatment of choice is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Tetracycline and chloramphenicol are alternatives, as for RMSF. Azithromycin (10 mg/kg/day once daily PO for 3 days) and clarithromycin (15 mg/kg/day divided twice daily PO for 7 days) are also used. Specific fluoroquinolone regimens effective for children have not been established, although recent reports suggest the use of fluoroquinolones is associated with increased disease severity as compared with doxycycline. Intensive care may be required.

COMPLICATIONS

The complications of MSF are similar to those of RMSF. The case fatality rate is approximately 2%. Particularly severe infections have been noted in patients with underlying medical conditions, including glucose-6-phosphate dehydrogenase deficiency and diabetes mellitus.

PREVENTION

MSF is transmitted by tick bites, and prevention is the same as recommended for RMSF. No vaccine is currently available.

228.3 Rickettsialpox *(Rickettsia akari)*

Megan E. Reller and J. Stephen Dumler

Rickettsialpox is caused by *R. akari,* a transitional group *Rickettsia* species that is transmitted by the mouse mite, *Allodermanyssus sanguineus.* The mouse host for this mite is widely distributed in cities in the United States, Europe, and Asia. Seroepidemiologic studies suggest a high prevalence of this infection in urban settings. The disease is uncommon and is usually mild. Unlike the situation with most forms of rickettsiosis, the macrophage is an important target cell for *R. akari.*

Rickettsialpox is best known because of its association with a varicelliform rash. In fact, this rash is a modified form of an antecedent typical macular or maculopapular rash like those seen in other vasculotropic rickettsioses, and is occasionally seen with other rickettsioses such as African tick bite fever. Clinical descriptions in children are infrequent. At presentation, most patients have fever, headache, and chills. In up to 90% of cases, there is a painless papular or ulcerative lesion or eschar at the initial site of inoculation, which may be associated with regional lymphadenopathy that is often tender. In some patients, the maculopapular rash becomes vesicular, involving the trunk, head, and extremities. The infection generally resolves spontaneously and does not require therapy. However, a short course of doxycycline hastens resolution and is sometimes used in patients older than 8 yr of age and in young children with relatively severe illness. Complications and fatalities are rare; however, clear examples of severe disease in children like that observed with RMSF are described.

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Chapter 229

Scrub Typhus *(Orientia tsutsugamushi)*

Megan E. Reller and J. Stephen Dumler

Scrub typhus is an important cause of acute febrile illness in South and East Asia and the Pacific. The causative agent is distinct from, but related to, *Rickettsia* species. The infection is transmitted via chigger (larval mite) bites and involves many antigenically diverse strains of *Orientia tsutsugamushi*, hampering vaccine development.

ETIOLOGY

The causative agent of scrub typhus, or tsutsugamushi fever, is *O. tsutsugamushi,* which is distinct from other spotted fever and typhus group rickettsiae (see Table 228-1 in Chapter 228). *O. tsutsugamushi* lacks both lipopolysaccharide and peptidoglycan in its cell wall. Like other vasculotropic rickettsiae, *O. tsutsugamushi* infects endothelial cells and causes vasculitis, the predominant clinicopathologic feature of the disease. However, the organism also infects macrophages and cardiac myocytes. A new Candidatus species, *Orientia chuto*, was isolated from a patient in the Middle East, suggesting a wider range for scrub typhus and related infections.

EPIDEMIOLOGY

Approximately 1 million infections occur each year, and it is estimated that more than 1 billion people are at risk. Scrub typhus occurs mostly in Asia, including areas delimited by Korea, Pakistan, and northern Australia. Outside these tropical and subtropical regions, the disease occurs in Japan, the Primorye of far eastern Russia, Tajikistan, Nepal, and nontropical China, including Tibet. Cases imported to the United States and other parts of the world are reported. Most infections in children are acquired in rural areas. In Thailand and Sri Lanka, scrub typhus is the cause of 1-8% of acute fevers of unknown origin. Infections are most common during rainy months, usually June through November. Reported cases in boys are higher than in girls.

TRANSMISSION

O. tsutsugamushi is transmitted via the bite of the larval stage (chigger) of a trombiculid mite *(Leptotrombidium),* which serves as both vector and reservoir. Transovarial transmission (passage of the organism from infected mites to their progeny) is the major mechanism for maintenance in nature. Because only the larval stage takes blood meals, a role for horizontal transmission from infected rodent hosts to uninfected mites has not been proved, but transmission among cofeeding larval mites is a possibility. Multiple serotypes of *O. tsutsugamushi* are recognized, and some share antigenic cross reactivity; however, they do not stimulate protective cross-immunity.

PATHOLOGY AND PATHOGENESIS

The pathogenesis of scrub typhus is uncertain. Recent studies suggest that the process is stimulated by widespread infection of vascular endothelial cells, which corresponds to the distribution of disseminated vasculitic and perivascular inflammatory lesions observed in histopathologic examinations. In autopsy series, the major result of the vascular injury appears to be hemorrhage. However, data support the concept that vascular injury initiated by the infection is sustained by immune-mediated inflammation that together cause significant vascular leakage. The net result is significant vascular compromise and ensuing end-organ injury, most often manifested in the brain and lungs, as with other vasculotropic rickettsioses.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Scrub typhus can be mild or severe in children. Most patients present with fever for 9-11 days (range: 1-30 days) before seeking medical care. Regional or generalized lymphadenopathy is reported in 23-93% of patients, hepatomegaly in about two-thirds, and splenomegaly in about one-third of children with scrub typhus. Gastrointestinal symptoms, including abdominal pain, vomiting, and diarrhea, occur in up to 40% of children at presentation. A single painless eschar with an erythematous rim at the site of the chigger bite is seen in 7-68% of cases, and a maculopapular rash is present in <30%; both can be absent. Hemophagocytic lymphohistiocytosis has been described. Leukocyte and platelet counts are most commonly within normal ranges, although thrombocytopenia occurs in one-quarter to one-third of children, and leukocytosis is observed in approximately 40%.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Owing to the potential for severe complications, diagnosis and decision to initiate treatment should be based on clinical suspicion and confirmed by *O. tsutsugamushi* serologic tests such as indirect fluorescent antibody or immunoperoxidase assays. The indirect fluorescent antibody assay is approximately 90% sensitive with 11 days or more of fever. Although the rickettsiae can be cultivated using tissue culture methods, polymerase chain reaction tests are not highly sensitive, and these diagnostic methods are not widely available. The differential diagnosis includes fever of unknown origin, enteric fever, typhoid fever, dengue hemorrhagic fever, other rickettsioses, tularemia, anthrax, dengue, leptospirosis, malaria, and infectious mononucleosis.

TREATMENT AND SUPPORTIVE CARE

The recommended treatment regimen for scrub typhus is doxycycline (4 mg/kg/day PO or IV divided every 12 hr; maximum: 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day PO divided every 6 hr; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/24 hr). If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 μg/mL. Therapy should be continued for a minimum of 5 days and until the patient has been afebrile for at least 3 days to avoid

relapse. However, a single dose of oral doxycycline was reported effective for all 38 children treated with this regimen in a large series of children with scrub typhus from Thailand. Most children respond rapidly to doxycycline or chloramphenicol within 1-2 days (range: 1-5 days). Strains of *O. tsutsugamushi* with modestly higher doxycycline minimal inhibitory concentrations are reported in some regions of Thailand. Clinical trials showed that azithromycin could be as effective and that rifampicin is superior to doxycycline in such cases and may have a role as an alternative therapy, especially for pregnant women. The use of ciprofloxacin in pregnant women resulted in an adverse outcome in 5 of 5 pregnancies among Indian women. Intensive care may be required for hemodynamic management of severely affected patients.

COMPLICATIONS

Serious complications include pneumonitis in 20-35% and meningoencephalitis in approximately 10% of children. Acute renal failure, myocarditis, and a septic shock–like syndrome occur much less often. Cerebrospinal fluid examination shows a mild mononuclear pleocytosis with normal glucose levels. Chest radiographs reveal transient perihilar or peribronchial interstitial infiltrates in most children who are examined. The case fatality rate in untreated patients may be as high as 30%, although deaths in children are uncommon.

PREVENTION

Prevention is based on avoidance of the chiggers that transmit *O. tsutsugamushi.* Protective clothing is the next most useful mode of prevention. Infection provides immunity to reinfection by homologous but not heterologous strains; however, because natural strains are highly heterogeneous, infection does not always provide complete protection against reinfection. No vaccines are currently available.

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Chapter 230
Typhus Group Rickettsioses

Megan E. Reller and J. Stephen Dumler

Members of the typhus group of rickettsiae (see Table 228-1 in Chapter 228) include *Rickettsia typhi,* the cause of murine typhus, and *Rickettsia prowazekii,* the cause of louse-borne or epidemic typhus. *R. typhi* is transmitted to humans by fleas, and *R. prowazekii* is transmitted in the feces of body lice. Louse-borne or epidemic typhus is widely considered to be the most virulent of the rickettsial diseases, with a high case fatality rate even with treatment. Murine typhus is moderately severe and likely underreported worldwide. The genomes of both *R. typhi* and *R. prowazekii* are similar. *Rickettsia felis* is often considered within the typhus group because of flea transmission; however, phylogenetic studies place it more closely to the spotted fever group or within a "transitional" group in the *Rickettsia* genus.

230.1 Murine (Endemic or Flea-Borne) Typhus *(Rickettsia typhi)*

Megan E. Reller and J. Stephen Dumler

ETIOLOGY

Murine typhus is caused by *R. typhi,* a rickettsia transmitted from infected fleas to rats, other rodents, or opossums and back to fleas. Transovarial transmission (passage of the organism from infected fleas to their progeny) in fleas is inefficient. Transmission depends on infection from the flea to uninfected mammals that then sustain transient rickettsemia and serve as sources of the bacterium for uninfected fleas that bite during the period of rickettsemia.

R. felis is a species identified as a cause of a murine typhus-like illness worldwide. This rickettsia is genetically a member of a transitional *Rickettsia* group and is capable of highly efficient transovarial transmission in cat fleas. This organism is found in cat fleas obtained from areas endemic for murine typhus in the United States and increasingly worldwide.

EPIDEMIOLOGY

Murine typhus has a worldwide distribution and occurs especially in warm coastal ports, where it is maintained in a cycle involving rat fleas (*Xenopsylla cheopis*) and rats (*Rattus* species). Peak incidence occurs when rat populations are highest during spring, summer, and fall. Sentinel surveillance studies suggest that travel-acquired murine typhus occurs most often in those visiting Southeast Asia and Africa. In the United States, the disease is recognized most often in south Texas and southern California. However, seroprevalence studies among children indicate that murine typhus is acquired across the southeast and south-central United States, thus expanding the endemic areas in which pediatricians must be alert for this infection. In the coastal areas of south Texas and in Southern California, the disease is seen predominantly from March through June and is associated with a "sylvatic" cycle involving opossums and cat fleas (*Ctenocephalides felis*).

TRANSMISSION

R. typhi normally cycles between rodents or midsize animals such as opossums and their fleas. Human acquisition of murine typhus occurs when rickettsiae-infected flea feces contaminate flea bite wounds. Direct inoculation via flea bite is possible, but inefficient.

PATHOLOGY AND PATHOGENESIS

R. typhi is a vasculotropic rickettsia that causes disease in a manner similar to *Rickettsia rickettsii* (see Chapter 228.1). *R. typhi* organisms in flea feces deposited on the skin as part of the flea feeding reflex are inoculated into the pruritic flea bite wound. After an interval for local proliferation, the rickettsiae spread systemically via lymphatics to infect the endothelium in many tissues. As with spotted fever group rickettsiae, typhus group rickettsiae infect endothelial cells, but unlike the spotted fever group rickettsiae, they polymerize intracellular actin poorly, have limited intracellular mobility, and probably cause cellular injury by either enzymatic membrane or mechanical lysis after accumulating in large numbers within the endothelial cell cytoplasm. Intracellular infection leads to endothelial cell damage, recruitment of inflammatory cells, and vasculitis. The inflammatory cell infiltrates bring in a number of effector cells, including macrophages that produce proinflammatory cytokines, and CD4, CD8, and natural killer lymphocytes, which can produce immune cytokines such as interferon-γ or participate in cell-mediated cytotoxic responses. Intracellular rickettsial proliferation of typhus group rickettsiae is inhibited by cytokine-mediated mechanisms and nitric oxide–dependent and –independent mechanisms.

Pathologic findings include systemic vasculitis in response to rickettsiae within endothelial cells. This manifests as interstitial pneumonitis, meningoencephalitis, interstitial nephritis, myocarditis, and mild hepatitis with periportal lymphohistiocytic infiltrates. As vasculitis and inflammatory damage accumulate, multiorgan damage can ensue.

CLINICAL MANIFESTATIONS

Murine typhus is a moderately severe infection that is similar to other vasculotropic rickettsioses. The incubation period varies from 1-2 wk. The initial presentation is often nonspecific and mimics typhoid fever; fever of undetermined origin is the most common presentation. Pediatric patients with murine typhus exhibit symptoms classically attributed to other vasculotropic rickettsioses, such as rash (48-80%), myalgias (29-57%), vomiting (29-45%), cough (15-40%), headache (19-77%), and diarrhea or abdominal pain (10-40%). A petechial rash

is observed in <15% of children, and the usual appearance is that of macules or maculopapules distributed on the trunk and extremities. The rash can involve both the soles and palms. Lymphadenopathy and hepatosplenomegaly are reported often among children with murine typhus in Europe. Murine-typhus associated hemophagocytic syndrome was recently described. Although neurologic involvement is a common finding in adults with murine typhus, photophobia, confusion, stupor, coma, seizures, meningismus, and ataxia are seen in <20% of hospitalized children and <6% of infected children treated as outpatients.

LABORATORY FINDINGS

Although nonspecific, laboratory findings that could be helpful include mild leukopenia (36-40%) with a moderate left shift, mild to marked thrombocytopenia (43-60%), hyponatremia (20-66%), hypoalbuminemia (46-87%), and elevated aspartate aminotransferase (82%) and alanine aminotransferase (38%). Elevations in serum urea nitrogen are usually a result of prerenal mechanisms.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

As for other vasculotropic rickettsioses, delays in diagnosis and therapy are associated with increased morbidity and mortality; thus, diagnosis must be based on clinical suspicion. Occasionally, patients present with findings suggesting pharyngitis, bronchitis, hepatitis, gastroenteritis, or sepsis; thus, the differential diagnosis may be extensive.

Confirmation of the diagnosis is usually accomplished by comparing acute and convalescent-phase antibody titers obtained with the indirect fluorescent antibody assay to demonstrate a 4-fold rise in titer. Research tools now being evaluated include polymerase chain reaction amplification of rickettsial nucleic acids in acute-phase blood, rickettsial culture by the centrifugation-assisted shell vial assay, and immunohistology on skin biopsy.

TREATMENT

Therapy for murine typhus includes tetracyclines or chloramphenicol, similar to treatment for Rocky Mountain spotted fever. No controlled trials of other antimicrobial agents have been performed. Clinical studies show that ciprofloxacin is as effective as doxycycline and chloramphenicol to treat murine typhus; however, treatment failures have been reported. In vitro experiments suggest that minimal inhibitory concentrations of azithromycin and clarithromycin for *R. typhi* should be easily achieved.

The time-honored recommended treatment for murine typhus is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/day). Therapy should be continued for a minimum of 5 days and until the patient has been afebrile for at least 3 days to avoid relapse, especially in patients treated early.

SUPPORTIVE CARE

Although disease is usually mild, 7% of children with murine typhus require intensive care to manage complications such as meningoencephalitis or a disseminated intravascular coagulation–like condition. As for other rickettsial infections with significant systemic vascular injury, careful hemodynamic management is mandatory to avoid pulmonary or cerebral edema.

COMPLICATIONS

Complications of murine typhus in pediatric patients are uncommon; however, relapse, stupor, facial edema, dehydration, splenic rupture, and meningoencephalitis are reported. Predominance of abdominal pain has led to surgical exploration to exclude a perforated viscus.

PREVENTION

Control of murine typhus was dependent on elimination of the flea reservoir and control of flea hosts, and this remains important. However, with the recognition of cat fleas as potentially significant reservoirs and vectors, the presence of these flea vectors and their mammalian hosts in suburban areas where close human exposures occur poses increasingly difficult control problems. It is not known with certainty if infection confers protective immunity; reinfection appears to be rare.

230.2 Epidemic (Louse-Borne) Typhus (*Rickettsia prowazekii*)

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ETIOLOGY

Humans are considered the principal reservoir of *R. prowazekii*, the causative agent of epidemic or louse-borne typhus and its recrudescent form, Brill-Zinsser disease. Another reservoir exists in flying squirrels, their ectoparasites, and potentially ticks, in a sylvatic cycle with small rodents. *R. prowazekii* is the most pathogenic member of the genus *Rickettsia* and multiplies to very large intracellular quantities before rupture of infected endothelial cells.

EPIDEMIOLOGY

The infection is characteristically seen in winter or spring and especially during times of poor hygienic practices associated with crowding, war, famine, extreme poverty, and civil strife. A cause of some sporadic cases of a mild, typhus-like illness in the United States is confirmed as *R. prowazekii;* such cases are associated with exposure to flying squirrels harboring infected lice or fleas. *R. prowazekii* organisms isolated from these squirrels appear to be genetically similar to isolates obtained during typical outbreaks.

Most cases of louse-borne typhus in the developed world are sporadic, but outbreaks have been identified in Africa (Ethiopia, Nigeria, and Burundi), Mexico, Central America, South America, Eastern Europe, Afghanistan, Russia, northern India, and China within the past 25 yr. Following the Burundi Civil War in 1993, 35,000-100,000 cases of epidemic typhus were diagnosed in displaced refugees, resulting in an estimated 6,000 deaths.

TRANSMISSION

Human body lice *(Pediculus humanus corporis)* become infected by feeding on persons who have rickettsiae circulating in their blood owing to endothelial infection. The ingested rickettsiae infect the midgut epithelial cells of the lice and are passed into the feces, which, in turn, are introduced into a susceptible human host through abrasions or perforations in the skin, through the conjunctivae, or rarely through inhalation as fomites in clothing, bedding, or furniture.

CLINICAL MANIFESTATIONS

Louse-borne typhus can be mild or severe in children. The incubation period is usually <14 days. The typical clinical manifestations include fever, severe headache, abdominal tenderness, and rash in most patients, as well as chills (82%), myalgias (70%), arthralgias (70%), anorexia (48%), nonproductive cough (38%), dizziness (35%), photophobia (33%), nausea (32%), abdominal pain (30%), tinnitus (23%), constipation (23%) meningismus (17%), visual disturbances (15%), vomiting (10%), and diarrhea (7%). However, investigation of recent African outbreaks has shown a lower incidence of rash (25%) and a high incidence of delirium (81%) and cough associated with pneumonitis (70%). The rash is initially pink or erythematous and blanches. In one-third of patients, red, nonblanching macules and petechiae appear predominantly on the trunk. Infections identified during the preantibiotic era typically produced a variety of central nervous system findings, including delirium (48%), coma (6%), and seizures (1%). Estimates of case fatality rates range between 3.8% and 20% in outbreaks.

Brill-Zinsser disease is a form of typhus that becomes recrudescent months to years after the primary infection, thus rarely affecting children. When bacteremic with rickettsiae, these infected patients can transmit the agent to lice, potentially providing the initial event that triggers an outbreak if hygienic conditions permit.

TREATMENT

Recommended treatment regimens for louse-borne or sylvatic typhus are identical to those used for murine typhus. The treatment of choice is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Alternative treatments include tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/day). Therapy should be continued for a minimum of 5 days and until the patient is afebrile for at least 3 days to avoid relapse, especially in patients treated early. Good evidence exists that doxycycline as a single 200 mg oral dose (4.4 mg/kg if <45 kg) is also efficacious.

PREVENTION

Immediate destruction of vectors with an insecticide is important in the control of an epidemic. Lice live in clothing rather than on the skin; thus, searches for ectoparasites should include examination of clothes. For epidemic typhus, antibiotic therapy and delousing measures interrupt transmission, reduce the prevalence of infection in the human reservoir, and diminish the impact of an outbreak. Dust containing excreta from infected lice is stable and capable of transmitting typhus, and care must be taken to prevent its inhalation. Infection confers solid protective immunity. However, recrudescence can occur years later with Brill-Zinsser disease, implying that immunity is not complete.

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Chapter 231

Ehrlichiosis and Anaplasmosis

J. Stephen Dumler and Megan E. Reller

ETIOLOGY

Ehrlichiosis in humans was first described in 1987, when clusters of bacteria confined within cytoplasmic vacuoles of circulating leukocytes (morulae), particularly mononuclear leukocytes, were detected in the peripheral blood of a patient with suspected Rocky Mountain spotted fever (RMSF). The etiologic agent, *Ehrlichia chaffeensis,* was cultivated from blood of an infected patient in 1990 and identified as the predominant cause of "human ehrlichiosis." Investigations showed that infection by *E. chaffeensis* is transmitted by *Amblyomma americanum* ticks and occurs more often than RMSF in some geographic areas. By 1994, other cases in which morulae were found only in neutrophils and lacked serologic evidence for *E. chaffeensis* infection led to the recognition of the species now classified as *Anaplasma phagocytophilum*, which encompasses several previously described veterinary pathogens on at least 2 different continents.

Since these first discoveries in humans, additional species in the *Anaplasmataceae* family have been identified as human pathogens, including: (1) *Ehrlichia ewingii* in 1996, a veterinary pathogen of canine neutrophils transmitted by *A. americanum* ticks; (2) the *Ixodes scapularis*–transmitted *Ehrlichia muris*–like agent in 2009, discovered in molecular screening tests for *E. chaffeensis*, *E. ewingii*, and *A. phagocytophilum* infections and only present so far in patients from Minnesota and Wisconsin in the United States; and (3) human infections by *Candidatus* Neoehrlichia mikurensis, presumably transmitted by *Ixodes* spp. or *Haemaphysalis concinna* ticks, first recognized in 2010 as a cause of sepsis-like infections of immune compromised patients in Europe, and also as a cause of mild febrile illness in healthy individuals in China. The latter 2 infections have not yet been identified in pediatric patients.

Although these infections are caused by bacteria assigned to various genera, the name ehrlichiosis has been applied to all and the etiologic agents are all classified within the Anaplasmataceae family. **Human monocytic ehrlichiosis (HME)** is used to describe disease characterized by infection of predominantly monocytes caused by *E. chaffeensis*, **human granulocytic anaplasmosis (HGA)** to describe disease of where circulating neutrophils are infected by *Anaplasma phagocytophilum*, and **ewingii ehrlichiosis** caused by *E. ewingii* (see Table 228-1 in Chapter 228).

All of these organisms are tick-transmitted, small, obligate intracellular bacteria with Gram-negative–type cell walls. *Neorickettsia sennetsu* is another related bacterium that rarely causes human disease and is not transmitted by ticks. *E. chaffeensis* alters host signaling and transcription once inside the cell. It survives in an endosome that enters a receptor recycling pathway to avoid phagosome-lysosome fusion and growth into a "**morula,**" an intravacuolar aggregate of bacteria. *A. phagocytophilum* survives in a unique vacuole that becomes decorated by microbial proteins which prevent endosomal maturation and lysosome fusion. Little is known about the vacuoles in which *E. ewingii* and *E. muris*–like agent grow. These bacteria are pathogens of phagocytic cells in mammals, and characteristically each species has a specific host cell affinity: *E. chaffeensis* infects mononuclear phagocytes, and *A. phagocytophilum* and *E. ewingii* infect neutrophils. Infection leads to direct modifications in function, in part the result of changes in intracellular signal transduction or epigenetic modulation of transcription of the host cell that diminish host defenses toward the bacterium; yet, host immune and inflammatory reactions are still activated and in part account for many of the clinical manifestations in ehrlichiosis.

EPIDEMIOLOGY

Infections with *E. chaffeensis* occur across the southeastern, south central, and mid-Atlantic states of the United States in a distribution that parallels that of RMSF; cases have also been reported in northern California. Suspected cases with appropriate serologic and occasionally molecular evidence have been reported in Europe, Africa, South America, and the Far East, including China and Korea. Human infections with *E. ewingii* have only been identified in the United States in areas where *E. chaffeensis* also exists, perhaps owing to the shared tick vector. Canine infections are documented in both sub-Saharan Africa and in South America.

Although the median age of patients with HME and HGA is generally older (>51 yr), many infected children have been identified, and for HME the case fatality rate is higher in those 5-9 yr of age. Little is known about the epidemiology of *E. ewingii* infections, although many patients have also been children. All infections are strongly associated with tick exposure and tick bites and are identified predominantly during May through September. Although both nymphal and adult ticks can transmit infection, nymphs are more likely to transmit disease, because they are most active during the summer.

TRANSMISSION

The predominant tick species that harbors *E. chaffeensis* and *E. ewingii* is *A. americanum,* the Lone Star tick (see Fig. 228-1D in Chapter 228). The tick vectors of *A. phagocytophilum* are *Ixodes* spp., including *I. scapularis* (black-legged or deer tick) in the eastern United States (see Fig. 228-1 in Chapter 228), *Ixodes pacificus* (western black-legged tick) in the western United States, *Ixodes ricinus* (sheep tick) in Europe, and *Ixodes persulcatus* in Eurasia. These ticks also transmit *Borrelia burgdorferi, Babesia microti,* and tickborne encephalitis-associated flaviviruses in Europe, Powassan viruses in North America. Coinfections with these agents and *A. phagocytophilum* have been documented in children and adults.

Ehrlichia and *Anaplasma* species are maintained in nature predominantly by horizontal transmission (tick to mammal to tick), because the organisms are not transmitted to the progeny of infected adult female ticks (transovarial transmission). The major reservoir for *E. chaffeensis* is the white-tailed deer (*Odocoileus virginianus*), which is found abundantly in many parts of the United States. A reservoir for

A. phagocytophilum in the eastern United States appears to be the white-footed mouse, *Peromyscus leucopus.* Deer or domestic ruminants may also have persistent asymptomatic infections, but the genetic variants in these reservoirs might not be infectious for humans. Efficient transmission requires persistent infections of mammals. Although *E. chaffeensis* and *A. phagocytophilum* can cause persistent infections in animals, documentation of chronic infections in humans is exceedingly rare. Transmission of *Ehrlichia* can occur within hours of tick attachment, in contrast to the 1-2 days of attachment required for transmission of *B. burgdorferi* to occur. Transmission of *A. phagocytophilum* is via the bite of the small nymphal stage of *Ixodes* spp., including *I. scapularis* (see Fig. 228-1A in Chapter 228), which is very active during late spring and early summer in the eastern United States.

PATHOLOGY AND PATHOGENESIS

Although HME and anaplasmosis often clinically mimic RMSF or typhus, vasculitis is rare. Pathologic findings include mild, diffuse perivascular lymphohistiocytic infiltrates; Kupffer cell hyperplasia and mild lobular hepatitis with infrequent apoptotic hepatocytes and less frequently centrilobular necrosis, cholestasis and steatosis; infiltrates of mononuclear phagocytes in the spleen, lymph nodes, and bone marrow with occasional erythrophagocytosis; granulomas of the liver and bone marrow in patients with *E. chaffeensis* infections; and hyperplasia of one or more bone marrow hematopoietic lineages.

The exact pathogenetic mechanisms are poorly understood, but histopathologic examinations suggest diffuse macrophage activation and poorly regulated host immune and inflammatory reactions. This activation results in moderate to profound leukopenia and thrombocytopenia despite a hypercellular bone marrow, and deaths often are related to severe hemorrhage or secondary opportunistic infections. Hepatic and other organ-specific injury occurs by a mechanism that appears to be triggered by the bacterium but more closely related to induction of innate and adaptive immune effectors. Meningoencephalitis with a mononuclear cell pleocytosis in the cerebrospinal fluid (CSF) occurs with HME, but is rare with HGA.

CLINICAL MANIFESTATIONS

The clinical manifestations of HME, HGA, and ewingii ehrlichiosis are similar. Many well-characterized infections of HME and HGA of variable severity have been reported in children, including deaths. Children with ehrlichiosis are often ill for 4-12 days, shorter than in adults. In series of children with HME, most required hospitalization and many (25%) required intensive care; these statistics might represent preferential reporting of severe cases. However, review of case reports and electronic surveillance of HGA to the Centers for Disease Control and Prevention identified that 42% of patients 5-9 yr of age required hospitalization. Population-based studies document that seroconversion often occurs in children who are well or who have only a mild illness. Fewer pediatric cases of *E. ewingii* infection are reported, so the clinical manifestations related to this infection are less-well characterized. However, in adults *E. ewingii* is clinically similar to HME, yet less severe. The incubation period (time from last tick bite or exposure) appears to range from 2 days to 3 wk. Nearly 25% of patients do not report a tick bite.

Clinically, ehrlichioses are undifferentiated febrile illnesses. In HME, fever (~100%), headache (77%), and myalgia (77%) are most common, but many patients also report abdominal pain, nausea, and vomiting. Altered mental status accompanied by other signs of central nervous system involvement is present in 36%. Rash is a common feature (~60%) in children. The rash is usually macular or maculopapular, but petechial lesions can occur. Photophobia, conjunctivitis, pharyngitis, arthralgias, and lymphadenopathy can occur but are less consistently present. Lymphadenopathy, hepatomegaly, and splenomegaly are detected in nearly 50% of children with ehrlichiosis. Edema of the face, hands, and feet occurs more commonly in children than in adults, but arthritis is uncommon in both groups.

Similar but less severe manifestations occur with HGA in children, including fever (93%), headache (73%), myalgia (73%), rigors (60%); nausea, vomiting, abdominal pain, and anorexia occur in 30% or less. Cough is present in 20%; rash is very infrequent and most often is erythema migrans that results from concurrent Lyme disease.

Meningoencephalitis with a lymphocyte-predominant CSF pleocytosis is an uncommon but potentially severe complication of HME that appears to be rare with HGA. CSF protein may be elevated and glucose may be mildly depressed in adults with HME meningoencephalitis, but CSF protein and glucose in affected children are typically normal. In 1 series, 19% of adult patients with central nervous system symptoms and abnormal CSF died despite normal CTs of the brain.

Chronic or persistent disease with low or absent fever is very unlikely to be any form of ehrlichiosis.

LABORATORY FINDINGS

Characteristically, most children with HME and HGA present with leukopenia (57-80%) and thrombocytopenia (38-93%); cytopenias reach a nadir several days into the illness. Lymphopenia is common in both HME and HGA, and neutropenia is reported in adults with HGA. Leukocytosis can also occur, but usually after the 1st wk of illness or with effective antimicrobial treatment. Adults with pancytopenia often have a cellular or reactive bone marrow examination, and in nearly 75% of bone marrow specimens from adults with HME, granulomas and granulomatous inflammation are present; this finding is not a feature of adults with HGA. Mild to severely elevated serum hepatic transaminase levels are frequent in both HME (85-92%) and HGA (40-50%). Hyponatremia (<135 mEq/L) is present in most cases. A clinical picture similar to disseminated intravascular coagulopathy has also been reported.

DIAGNOSIS

Any delays in diagnosis or treatment are major contributors to increased morbidity or mortality in adults, where those not started on doxycycline at hospital admission are much more likely to require intensive care and a significantly longer course of illness and hospitalization. Thus, treatment must begin as early as possible based on clinical suspicion. Because both HME and anaplasmosis can be fatal, therapy should not be withheld while waiting for the results of confirmatory testing. In fact, prompt response to therapy supports the diagnosis.

While several reports document pediatric patients with *E. chaffeensis* infection diagnosed based on typical *Ehrlichia* morulae in peripheral blood leukocytes (Fig. 231-1*A*), this finding is too infrequent to be considered a useful diagnostic approach. In contrast, HGA in adults presents with a small but significant percentage (1-40%) of circulating neutrophils (Fig. 231-1*B*) containing typical morulae in 20-60% of patients.

E. chaffeensis and *A. phagocytophilum* infections can be confirmed by demonstrating a 4-fold change in immunoglobulin G titer by indirect immunofluorescence assay between paired sera *or* detection of specific DNA by polymerase chain reaction *or* demonstration of specific antigen in a tissue sample by immunohistochemistry *or* isolation of the organism in cell culture. A single specific titer of ≥64 or identification of morulae in monocytes or macrophages for *E. chaffeensis* or in neutrophils or eosinophils for *A. phagocytophilum* by microscopy is suggestive. *E. ewingii* infection can only be confirmed by polymerase chain reaction, because it has not been cultured and serologic antigens are not available. *E. ewingii* antibodies cross react with *E. chaffeensis* in routine serologic tests. Up to 15% of patients with HGA have serologic cross-reactions with *E. chaffeensis;* thus, serodiagnosis depends on testing with both *E. chaffeensis* and *A. phagocytophilum* antigens and demonstrating a 4-fold or higher difference between titers. During the acute phase of illness when antibodies are often not detected, polymerase chain reaction amplification of *E. chaffeensis* or *A. phagocytophilum* DNA is sensitive in >86% of cases. Although *E. chaffeensis* and *A. phagocytophilum* can be cultivated in tissue culture, this method is not timely or widely available.

DIFFERENTIAL DIAGNOSIS

Because of the nonspecific presentation, ehrlichiosis mimics other arthropod-borne infections such as RMSF, tularemia, babesiosis, Lyme

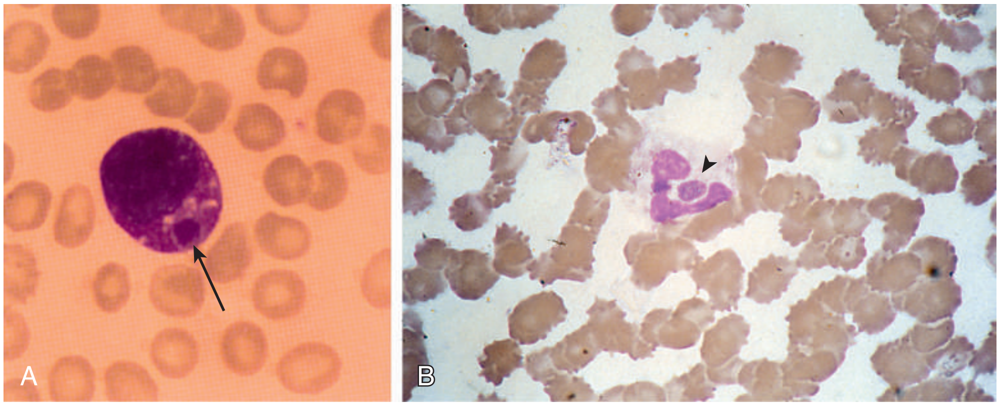

Figure 231-1 Morulae in peripheral blood leukocytes in patients with human monocytic ehrlichiosis and human granulocytic anaplasmosis. **A,** A morula *(arrow)* containing *Ehrlichia chaffeensis* in a monocyte. **B,** A morula *(arrowhead)* containing *Anaplasma phagocytophilum* in a neutrophil. Wright stains, original magnifications ×1,200. *E. chaffeensis* and *A. phagocytophilum* have similar morphologies but are serologically and genetically distinct.

disease, murine typhus, relapsing fever, and Colorado tick fever. Other potential diagnoses often considered include otitis media, streptococcal pharyngitis, infectious mononucleosis, Kawasaki disease, endocarditis, respiratory or gastrointestinal viral syndromes, hepatitis, leptospirosis, Q fever, collagen–vascular diseases, hemophagocytic syndromes, and leukemia. If rash and disseminated intravascular coagulopathy predominate, meningococcemia, bacterial sepsis, and toxic shock syndrome are also suspected. Meningoencephalitis might suggest aseptic meningitis caused by enterovirus or herpes simplex virus, bacterial meningitis, or RMSF. Severe respiratory disease may be confused with bacterial, viral, and fungal causes of pneumonia.

TREATMENT

Both HME and HGA are effectively treated with tetracyclines, especially doxycycline, and the majority of patients improve within 48 hr. In vitro tests document that both *E. chaffeensis* and *A. phagocytophilum* have minimal inhibitory concentrations to chloramphenicol above blood levels that can be safely achieved. Therefore, a short course of doxycycline is the recommended regimen. Doxycycline is used safely in children younger than 8 yr of age because tooth discoloration is dose dependent and the need for multiple courses is unlikely. Few data exist to recommend alternative therapies; however, both *E. chaffeensis* and *A. phagocytophilum* are susceptible in vitro to rifampin, which has been used successfully to treat HGA in pregnant women and children.

The recommended regimen for patients of all ages with severe or complicated HME and HGA is doxycycline (for those who weigh <45 kg, 4 mg/kg/day PO or IV divided every 12 hr; maximum: dose 100 mg/dose). An alternative regimen is tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day). For children who weigh more than 45 kg, the adult dose, 100 mg twice daily by oral or intravenous route can be used. Therapy should be continued for ≥5 days and until the patient has been afebrile for ≥2-4 days.

Other broad-spectrum antibiotics, including penicillins, cephalosporins, aminoglycosides, and macrolides, are not effective. In vitro studies suggest that fluoroquinolones are active against *A. phagocytophilum*, although at least 1 patient relapsed when levofloxacin was discontinued. *E. chaffeensis* is naturally resistant to fluoroquinolones owing to a single nucleotide change in *gyrA,* which suggests that *A. phagocytophilum* could also become resistant to fluoroquinolones rapidly.

COMPLICATIONS AND PROGNOSIS

Fatal HME is reported in at least 1 pediatric patient, where the findings were initially dominated by pulmonary involvement with respiratory failure complicated by nosocomial bacterial pneumonia. The pattern of severe pulmonary involvement culminating in diffuse alveolar damage and acute respiratory distress syndrome and secondary nosocomial or opportunistic infections is now well-documented with HME and HGA in adults. One child with HGA died after 3 wk of fever, thrombocytopenia, and lymphadenopathy suspected to be a hematologic malignancy. Other severe complications include a toxic shock–like illness, meningoencephalitis with long-term neurologic sequelae, brachial plexopathy, demyelinating polyneuropathy, myocarditis, rhabdomyolysis, and renal failure. Hemophagocytic lymphohistiocytosis is increasingly reported in children with both HME and HGA. Patients who are immunocompromised (e.g., HIV infection, high-dose corticosteroid therapy, cancer chemotherapy, immunosuppression for organ transplantation) are at high risk for fulminant *E. chaffeensis* infection, and severe HGA has been reported after stem cell transplantation in pediatric oncology.

PREVENTION

HME, HGA, and ewingii ehrlichiosis are tickborne diseases, and any activity that increases exposure to ticks increases risk. Avoiding tick-infested areas, wearing appropriate light-colored clothing, spraying tick repellents on clothing, carefully inspecting for ticks after exposure, and promptly removing any attached ticks diminish the risk. The interval between tick attachment and transmission of the agents may be as short as 4 hr; thus, attached ticks should be removed promptly. A role of prophylactic therapy for ehrlichiosis and anaplasmosis after tick bites has not been investigated. It is not known if infection confers protective immunity; however, reinfection appears to be exceedingly rare.

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Chapter 232

Q Fever *(Coxiella burnetii)*

Megan E. Reller and J. Stephen Dumler

Q fever (for **query fever,** the name given following an outbreak of febrile illness in an abattoir in Queensland, Australia) is rarely reported in children but is probably underdiagnosed. Symptomatic patients can have acute or chronic disease.

ETIOLOGY

Although previously classified within the order Rickettsiales, *Coxiella burnetii* (the causative agent of Q fever) is genetically distinct from the

genera *Rickettsia, Orientia*, *Ehrlichia,* and *Anaplasma*. Hence, based on small genome analysis, it best aligns within the order Legionellales, family Coxiellaceae. *C. burnetii* is highly infectious for both humans and animals; even a single organism can cause infection. The agent has been nationally notifiable since 1999 and is listed as a Category B agent of bioterrorism by the Centers for Disease Control and Prevention (CDC). Unlike *Rickettsia,* the organism can enter a sporogenic differentiation cycle, which renders it highly resistant to chemical and physical treatments.

C. burnetii resides intracellularly within macrophages. In vitro, the organism undergoes lipopolysaccharide phase variation similar to that described for smooth and rough strains of Enterobacteriaceae. Unlike *Ehrlichia, Anaplasma,* and *Chlamydia, C. burnetii* survives and proliferates within acidified phagosomes to form aggregates of >100 bacteria.

EPIDEMIOLOGY

The disease is reported worldwide, except in New Zealand. Although seroepidemiologic studies suggest that infection occurs just as often in children as in adults, children less often present with clinical disease than do adults. During the large outbreak of Q fever in the Netherlands in 2007-2009, only 3.5% of those diagnosed with Q fever were age 19 yr or younger. Although infections are recognized more often in men than in women, reported cases in boys and girls are equal. Approximately 60% of infections are asymptomatic, and only 5% of symptomatic patients require hospitalization. Seroprevalence surveys show that 6-70% of children in endemic European and African communities have evidence of past infection. In France, the overall incidence of Q fever is estimated to be 50 cases per 100,000 persons. A similar estimate is not available for Africa, where cases are likely misdiagnosed as malaria. The seroprevalence of Q fever in the United States is estimated to be 3.1%. Reported cases of Q fever in the United States, which have been received from every state, increased by greater than 9-fold from 17 cases in 2000 to 167 cases in 2008, which might reflect an increase in incidence, increased reporting after September 11, 2001, improved diagnostic tools, or a combination of factors. Reported cases in Asia and Australia have also increased. Most infections in children are identified during the lamb birthing season in Europe (January through June), following farm visits, or after exposure to placentas of dogs, cats, and rabbits. The largest (~4,000 human cases) community outbreak ever described occurred in the Netherlands in 2007-2010 and was associated with intensive farming of dairy goats and dairy sheep. In 2011, the first multistate outbreak of Q fever in humans was linked to interstate sale of infected goats; an outbreak of unknown source was also reported. From 2000-2010, 60% of cases reported to CDC occurred in those without reported exposure to livestock. More than 20% of cases of clinically recognized acute or chronic Q fever occur in immunosuppressed hosts or in persons with prosthetic valves or damaged native valves or vessels. These findings highlight the need for considering Q fever in those with clinically compatible illness, especially but not exclusively in those with likely exposures and in vulnerable hosts.

TRANSMISSION

In contrast to other rickettsial infections, humans usually acquire *C. burnetii* by inhaling infectious aerosols (e.g., contaminated barnyard dust) or ingesting (and likely aspirating) contaminated foods. Ticks are rarely implicated. Cattle, sheep, and goats are the primary reservoirs, but infection in other livestock and domestic pets is also described. Organisms are excreted in milk, urine, and feces of infected animals, but especially in amniotic fluids and the placenta. An increase in incidence is associated with the seasonal mistral winds in France that coincide with lamb birthing season and with consumption of cheese among children in Greece. In Nova Scotia and Maine, exposure to newborn animals, especially kittens, has been associated with small outbreaks of Q fever in families. Exposure to domestic ruminants is the major risk in Europe and Australia, although many urban dwellers in France also acquire Q fever without such an exposure. Person-to-person transmission is possible but rare. Clinical Q fever during pregnancy can result from primary infection or reactivation of latent infection and is associated with miscarriage, intrauterine growth retardation, and premature births. Obstetricians and other related healthcare workers are at risk for acquiring infection because of the quantity of *C. burnetii* sequestered in the placenta. Sexual transmission and cases attributable to blood transfusion or bone marrow transplantation are also reported.

PATHOLOGY AND PATHOGENESIS

The pathology of Q fever depends on the mode of transmission, route of dissemination, specific tissues involved, and course of the infection. When acquired via inhalation, a mild interstitial lymphocytic pneumonitis and macrophage- and organism-rich intraalveolar exudates are often seen. When the liver is involved, a mild to moderate lymphocytic lobular hepatitis can be seen. Inflammatory pseudotumors can develop in the pulmonary parenchyma or other tissues. Classic fibrin-ring ("doughnut") granulomas, generally associated with acute, self-limited infections, are occasionally identified in liver, bone marrow, meninges, and other organs. Typically, infected tissues are also infiltrated by lymphocytes and histiocytes.

Recovery from symptomatic or asymptomatic acute infection can result in persistent subclinical infection and possibly maintained by dysregulated cytokine responses. The persistence of *C. burnetii* in tissue macrophages at sites of preexisting tissue damage elicits low-grade chronic inflammation and, depending on the site of involvement, can result in irreversible cardiac valve damage, persistent vascular injury, or osteomyelitis. Endocarditis of native or prosthetic valves is characterized by infiltrates of macrophages and lymphocytes in necrotic fibrinous valvular vegetations and an absence of granulomas.

CLINICAL MANIFESTATIONS AND COMPLICATIONS

Only approximately 40-50% of people infected with *C. burnetii* develop symptoms. Two forms of symptomatic disease occur. **Acute Q fever** is more common and usually manifests as self-limited undifferentiated fever or an influenza-like illness with interstitial pneumonitis. **Chronic Q fever** in adults usually involves native heart valves, prosthetic valves, or other endovascular prostheses. Q fever osteomyelitis is less common but proportionally more common in children.

Acute Q Fever

Acute Q fever develops approximately 3 wk (range: 14-39 days) after exposure to the causative agent. The severity of illness in children ranges from subclinical infection to a systemic illness of sudden onset characterized by high fever, severe frontal headache, nonproductive cough, chest pain, vomiting, diarrhea, abdominal pain, arthralgias, and myalgias. Approximately 40% of children with acute Q fever present with fever, 25% with pneumonia or an influenza-like illness, >10% with meningoencephalitis, and >10% with myocarditis. Other manifestations include pericarditis, hepatitis, hemophagocytosis, rhabdomyolysis, and a hemolytic uremic–like syndrome. Rash, ranging from maculopapular to purpuric lesions, is an unusual finding in adults with Q fever but is observed in approximately 50% of pediatric patients. Rigors and night sweats are common in adults with Q fever and occur less often in children. Prominent clinical findings that can create diagnostic confusion include fatigue, vomiting, abdominal pain, and meningismus. Hepatomegaly and splenomegaly may be detected in some patients.

Routine laboratory investigations in pediatric acute Q fever are usually normal but can reveal mild leukocytosis and thrombocytopenia. Up to 85% of children have modestly elevated serum hepatic transaminase levels that usually normalize within 10 days. Hyperbilirubinemia is uncommon in the absence of complications. C-reactive protein is uniformly elevated in pediatric Q fever. Chest radiographs are abnormal in 27% of all patients; in children, the most common findings include single or multiple bilateral infiltrates with reticular markings in the lower lobes.

Acute Q fever in children is usually a self-limited illness, with fever persisting for only 7-10 days compared with 2-3 wk in adults. However, severe manifestations of acute illness, such as myocarditis requiring cardiac transplantation, meningoencephalitis, pericarditis, and hemophagocytosis, as well as a relapsing febrile illness lasting for several months have been reported.

Chronic Q Fever

The risk for developing chronic Q fever is strongly correlated with advancing age and underlying conditions such as cardiac valve damage or immunosuppression; chronic Q fever is rarely diagnosed in children. A review identified only 5 cases of chronic Q fever endocarditis and 6 cases of osteomyelitis among children, none of whom had known predisposing immune deficiencies. Four of the 5 cases of endocarditis occurred in children with underlying congenital heart abnormalities and involved the aortic, pulmonary, and tricuspid valves. Four of the 6 children with Q fever osteomyelitis had a prior diagnosis or clinical course consistent with idiopathic chronic recurrent multifocal osteomyelitis. A long interval before diagnosis and lack of high fever are common in pediatric cases of chronic Q fever.

Although Q fever endocarditis often results in death (23-65% of cases) in adults, mortality has not been reported for children. Endocarditis associated with chronic Q fever can occur months to years after acute infection and can occur in the absence of recognized acute Q fever. Chronic hepatitis has also been reported.

LABORATORY FINDINGS

Laboratory features in children with chronic Q fever are poorly documented; adult patients often have an erythrocyte sedimentation rate of >20 mm/hr (80% of cases), hypergammaglobulinemia (54%), and hyperfibrinogenemia (67%). In children, the presence of rheumatoid factor in >50% of cases and circulating immune complexes in nearly 90% suggest an autoimmune process, as do antiplatelet antibodies, anti–smooth muscle antibodies, antimitochondrial antibodies, circulating anticoagulants, and positive direct Coombs tests.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Although uncommonly diagnosed, Q fever should be considered in children who have fever of unknown origin, atypical pneumonia, myocarditis, meningoencephalitis, culture-negative endocarditis, or recurrent osteomyelitis and who live in rural areas or who are in close contact with domestic livestock, cats, or animal products.

The diagnosis of Q fever is most easily and commonly confirmed by testing acute and convalescent sera (2-4 wk apart), which show a 4-fold increase in indirect fluorescent immunoglobulin G antibody titers to phase II *C. burnetii* antigens. The phase II antibody response to *C. burnetii* appears first and is higher than the phase I antibody response. Phase II immunoglobulin G antibodies can remain elevated for months to years regardless of initial symptoms or lack thereof. In contrast chronic Q fever is characterized by the rise of phase I immunoglobulin G antibodies and an antibody titer greater than 800 raises the suspicion of Q fever endocarditis in patients with valvular heart disease or other sites of chronic, active Q fever infection. Cross-reactions with antibodies to *Legionella* and *Bartonella* can occur.

Although culture has been considered the gold standard, sensitivity (compared with a composite standard including serology and polymerase chain reaction) is low. *C. burnetii* has been cultivated in tissue culture cells, which can become positive within 48 hr, but isolation and antimicrobial susceptibility testing of *C. burnetii* should be attempted only in specialized biohazard facilities. Testing by polymerase chain reaction can be performed on blood, serum, and tissue samples and is available only in some public health, reference, or research laboratories. Although polymerase chain reaction has been helpful in patients with equivocal titers, sensitivity has been improved by real-time methods and use of repeated sequences as targets. Immunohistochemical staining has also been used, but is not readily available.

The differential diagnosis depends on the clinical presentation. In patients with respiratory disease, *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* legionellosis, psittacosis, and Epstein-Barr virus infection should be considered. In patients with granulomatous hepatitis, tuberculous and nontuberculous mycobacterial infections, salmonellosis, visceral leishmaniasis, toxoplasmosis, Hodgkin disease, monocytic ehrlichiosis, granulocytic anaplasmosis, brucellosis, cat scratch disease (*Bartonella henselae*), or autoimmune disorders such as sarcoidosis should be considered. Culture-negative endocarditis suggests infection with *Brucella, Bartonella,* or HACEK organisms *(Haemophilus, Aggregatibacter, Cardiobacterium hominis, Eikenella corrodens, Kingella)*, partially treated bacterial endocarditis, or nonbacterial endocarditis.

TREATMENT

Selection of an appropriate antimicrobial regimen for children is difficult owing to the lack of rigorous studies, the limited therapeutic window for drugs that are known to be efficacious, and the potential length of therapy required to preclude relapse.

Most pediatric patients with Q fever have a self-limited illness that is identified only on retrospective serologic evaluation. However, to prevent potential complications, treatment should be considered for patients who present with acute Q fever within 3 days of onset of symptoms, because therapy started more than 3 days after onset of illness has little effect on the course of acute Q fever. Because confirmatory testing in early acute infection is not possible and because tetracycline and doxycycline can be associated with tooth discoloration in children younger than 9 yr of age, empirical therapy is warranted in those with clinically suspected Q fever who are 8 yr of age or older or at high risk for severe illness. Doxycycline (4 mg/kg/day PO or IV divided every 12 hr; maximum: 200 mg/day) is the drug of choice; the usual course is 2 wk. Children at high risk include those hospitalized or with severe illness; those diagnosed after prolonged (>2 wk) unremitting symptoms; and those with preexisting valvular heart disease or who are immunocompromised. Because tooth discoloration is both dose and duration dependent and few children require multiple courses, younger children with mild Q fever could be treated with 5 days of doxycycline followed by 14 days of trimethoprim-sulfamethoxazole if symptoms persist. During pregnancy, Q fever is best treated with trimethoprim-sulfamethoxazole. The fluoroquinolones are also effective, and success with a combination of a fluoroquinolone and rifampin is also achieved with prolonged therapy (16-21 days). Macrolides, including erythromycin and clarithromycin, are less-effective alternatives.

For chronic Q fever, especially endocarditis and mostly in adults, therapy for 18-36 mo is mandatory. The current recommended regimen for chronic Q fever endocarditis is a combination of doxycycline and hydroxychloroquine for 18 mo or longer. For patients with heart failure, valve replacement could be necessary. Interferon-γ therapy has been used as adjunct therapy for intractable Q fever.

PREVENTION

Recognition of the disease in livestock or other domestic animals should alert communities to the risk for human infection. Milk from infected herds must be pasteurized at temperatures sufficient to destroy *C. burnetii. C. burnetii* is resistant to significant environmental conditions but can be inactivated with a solution of 1% Lysol, 1% formaldehyde, or 5% hydrogen peroxide. Special isolation measures are not required because person-to-person transmission is rare, except when others are exposed to the placenta of an infected patient. A vaccine is available and provides protection against Q fever for at least 5 yr in abattoir workers. Because the vaccine is strongly reactogenic and no trials in children have been conducted, it should only be used when extreme risk is judged to exist. Clusters of cases resulting from intense natural exposures, such as in slaughterhouses or on farms, are well documented. Clusters of cases that occur in the absence of such an exposure should be investigated as potential sentinel events for bioterrorism.

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Section 12
Fungal Infections

Chapter 233
Principles of Antifungal Therapy

William J. Steinbach, Michael Cohen-Wolkowiez, and Daniel K. Benjamin Jr.

As a result of advances in aggressive antineoplastic agents and organ transplantation, invasive fungal infections are a major cause of morbidity and mortality in children. Fortunately, the therapeutic armamentarium for invasive fungal infections has markedly increased since the 1990s (Table 233-1).

POLYENES
Amphotericin B
The prototype of the oldest antifungal class, the polyene macrolides, is amphotericin B deoxycholate. Amphotericin B was once the preferred treatment for invasive fungal infections as well as the standard of comparison for all newer antifungal agents. Amphotericin B is so named because it is amphoteric, forming soluble salts in both acidic and basic environments. However, because of its insolubility in water, amphotericin B for clinical use is actually amphotericin B mixed with the detergent deoxycholate. Amphotericin B binds to ergosterol, the major sterol found in fungal cytoplasmic membranes, and acts by creating transmembrane channels. The fungicidal activity is the result of a damaged barrier and subsequent cell death through leakage of essential nutrients from the fungal cell.

Amphotericin B is released from its carrier and distributes very efficiently with lipoproteins, taken up preferentially by organs of the reticuloendothelial system. Following an initial 24-48 hr distributional half-life there is very slow release and a subsequent terminal elimination half-life of up to 15 days. In addition to conventional amphotericin B deoxycholate, 3 fundamentally different lipid-associated formulations have been developed that offer the advantage of an increased daily dosage of the parent drug, better delivery to the primary reticuloendothelial organs (lungs, liver, spleen), and reduced toxicity. Amphotericin B lipid complex is a tightly packed ribbon-like structure of a bilayered membrane, amphotericin B colloidal dispersion is composed of disk-like structures of cholesteryl sulfate complexed with amphotericin B, and liposomal amphotericin B (L-amphotericin B) consists of small uniformly sized vesicles of a lipid bilayer of amphotericin B. Lipid formulations of amphotericin B generally have a slower onset of action, presumably owing to the required disassociation of free amphotericin B from the lipid vehicle. The ability to safely administer higher daily doses of the parent drugs improves their efficacy, comparing favorably with amphotericin B deoxycholate but with less toxicity. Lipid formulations have the added benefit of increased tissue concentrations compared to conventional amphotericin B, specifically in the liver, lungs, and spleen. However, it is not entirely clear if these higher concentrations in tissue are truly available to the microfoci of infection.

Tolerance to amphotericin B deoxycholate is limited by its acute and chronic toxicities. In addition to interacting with fungal ergosterol, the drug also interacts with cholesterol in human cell membranes, likely accounting for its toxicity. Up to 80% of patients receiving amphotericin B develop either infusion-related toxicity or nephrotoxicity, especially with concomitant therapy with nephrotoxic drugs such as aminoglycosides, vancomycin, cyclosporine, or tacrolimus. Renal function usually returns to normal after cessation of amphotericin B, although permanent renal impairment is common after larger doses. Amphotericin B nephrotoxicity is generally less severe in infants and children than in adults, likely because of the more rapid clearance of the drug in children. Lipid formulations appear to stabilize amphotericin B in a self-associated state so that it is not available to interact with the cholesterol of human cellular membranes.

Unlike older guidelines, there is no total dosage of amphotericin B recommended, and the key to success is to give high dosages in the initial phase of therapy and to reduce the dosage if toxicity develops. There are no data or consensus opinions among authorities indicating improved efficacy of any new amphotericin B lipid formulation over conventional amphotericin B deoxycholate. One exception is that

Table 233-1 Suggested Dosing of Antifungal Agents in Children and Neonates

DRUG	FORMULATIONS	SUGGESTED PEDIATRIC DOSAGE	COMMENTS
Amphotericin B deoxycholate	IV	1 mg/kg/day	Generally less toxicity in children than adults; do not start with smaller test doses
Lipid amphotericin B formulations	IV	5 mg/kg/day	Generally all lipid formulations are dosed the same; there is no clear indication of one formulation over another for clinical efficacy
Fluconazole	IV, PO	12 mg/kg/day	Loading dose (25 mg/kg) is suggested based on pharmacokinetic simulations, but insufficiently studied
Itraconazole	IV, PO	2.5 mg/kg/dose bid	Divide dosage twice daily in children; follow trough levels
Voriconazole	IV, PO	8 mg/kg/dose bid IV maintenance; 9 mg/kg/dose bid oral maintenance	Linear pharmacokinetics in children requires higher dosing than in adults; 9 mg/kg/dose bid IV loading, followed by maintenance dosing; follow trough levels
Posaconazole	PO	12-24 mg/kg/day divided tid	Dosage unclear in children at present In adults, max dosage is 800 mg/day, and optimally divide this into 2 or 3 doses; follow trough levels
Micafungin	IV	2-10 mg/kg/day	Highest dosages in neonates (10 mg/kg/day), and lower dosages in children; older than 8 yr of age, use adult dosage
Anidulafungin	IV	1.5 mg/kg/day	Loading dose of 3 mg/kg/day
Caspofungin	IV	50 mg/m^2/day	Load with 70 mg/m^2/day, then 50/mg/m^2/day as maintenance dosage

L-amphotericin B shows fewer infusion-related adverse events than the other lipid formulations or conventional amphotericin B.

PYRIMIDINE ANALOGS

5-Fluorocytosine

5-Fluorocytosine is a fluorinated analog of cytosine, and its antifungal activity results from the rapid conversion into 5-fluorouracil (5-FU) within susceptible fungal cells. Clinical and microbiologic antifungal resistance appears to develop quickly to 5-fluorocytosine (5-FC) monotherapy, so clinicians have reserved it for combination approaches to augment other, more potent antifungals. Fungistatic 5-FC is thought to enhance the antifungal activity of amphotericin B, especially in anatomic sites where amphotericin B penetration is often suboptimal, such as cerebrospinal fluid (CSF), heart valves, and the vitreal body. 5-FC penetrates well into most body sites because it is small, highly water soluble, and not bound by serum proteins to any great extent. One explanation for the synergism detected with the combination of amphotericin B plus 5-FC is that the membrane-permeabilizing effects of low concentrations of amphotericin B facilitate penetration of 5-FC to the cell interior. 5-FC is only available as an oral formulation in the United States, and the correct dosage is 150 mg/kg/day in 4 divided doses.

5-FC can exacerbate myelosuppression in patients with neutropenia, and toxic levels can develop when used in combination with amphotericin B owing to nephrotoxicity of the amphotericin B and decreased renal clearance of 5-FC. Routine serum 5-FC level monitoring is warranted in high-risk patients, because peak serum concentrations of ≥100 μg/mL (2 hr after dose) are associated with bone marrow aplasia. Toxicities can include azotemia, renal tubular acidosis, leukopenia, thrombocytopenia, and others and appear in approximately 50% of patients in the 1st 2 wk of therapy.

Nearly all clinical studies involving 5-FC are combination antifungal protocols for cryptococcal meningitis, owing to the inherently rather weak antifungal activity of 5-FC monotherapy. The use of 5-FC in premature neonates is discouraged. A study evaluating risk factors and mortality rates of neonatal candidiasis among extremely premature infants showed that infants with *Candida* meningitis who received amphotericin B in combination with 5-FC had a prolonged time to sterilization of the CSF compared to infants receiving amphotericin B monotherapy.

AZOLES

The azole antifungals inhibit the fungal cytochrome $P450_{14DM}$ (also known as lanosterol 14α-demethylase), which catalyzes a late step in fungal cell membrane ergosterol biosynthesis. Of the older first-generation triazoles, itraconazole has activity against *Aspergillus* but fluconazole is ineffective against *Aspergillus* and other molds. Second-generation triazoles (voriconazole and posaconazole) are modifications of prior triazoles with an expanded antifungal spectrum of activity, including activity against molds, and generally greater in vitro antifungal activity.

Fluconazole

Fluconazole is fungistatic, and this activity is not influenced by concentration once the maximal fungistatic concentration is surpassed (concentration independent), in contrast to the concentration-dependent fungicidal activity of amphotericin B. Fluconazole is available as either an oral or intravenous form, and oral administration has a bioavailability of approximately 90% relative to intravenous administration. Fluconazole passes into tissues and fluids very rapidly, probably because of its relatively low lipophilicity and limited degree of binding to plasma proteins. Concentrations of fluconazole are 10-20–fold higher in the urine than blood, making it an ideal agent for treating fungal urinary tract infections. Concentrations in the CSF and vitreous humor of the eye are approximately 80% of those found simultaneously in blood.

It is clear that simple conversion of the corresponding adult dosage of fluconazole on a weight basis is inappropriate for pediatric patients. Fluconazole clearance is generally more rapid in children than adults, with a mean plasma half-life of approximately 20 hr in children and approximately 30 hr in adult patients. Therefore, to achieve comparable exposure in pediatric patients, the daily fluconazole dosage needs to be essentially doubled. Correct pediatric fluconazole dosages should be proportionately higher than adult dosages, generally 12 mg/kg/day. In neonates the volume of distribution is significantly greater and more variable than in infants and children, and doubling the dosage for neonatal patients is necessary to achieve comparable plasma concentrations. The increased volume of distribution is thought to be from the larger amount of body water found in the total body volume of neonates. A pharmacokinetic study in premature infants suggests that maintenance fluconazole dosages of 12 mg/kg/day are necessary to achieve exposures similar to those in older children and adults. In addition, a loading dose of 25 mg/kg would achieve steady-state concentrations sooner than the traditional dosing scheme. Side effects of fluconazole are uncommon but generally include gastrointestinal upset (vomiting, diarrhea, nausea) and skin rash.

Fluconazole plays an important role in the treatment of invasive candidiasis. The latest guidelines suggest use of the fungistatic fluconazole in patients who have invasive candidiasis but who are not critically ill or neutropenic. Although most isolates of *Candida albicans* remain susceptible to fluconazole, for certain *Candida* species fluconazole is not an ideal agent: *Candida krusei* is generally resistant and *Candida glabrata* is often resistant. In treating infection caused by these *Candida* species, it is critical to treat with an echinocandin or amphotericin B rather than fluconazole. There is no confirmed role for combination antifungal therapy with fluconazole and another antifungal against invasive candidiasis.

Prophylaxis with fluconazole to prevent neonatal candidiasis in premature infants remains a controversial topic. In a prospective, randomized double-blind trial over a 30 mo period of 100 infants with birth weights <1,000 g, infants who received fluconazole for 6 wk had a decrease in fungal colonization (22% vs 60%) and a decrease in the development of invasive fungal infection (0% vs 20%) compared to placebo. Other studies have yielded similarly encouraging results and have demonstrated that use of fluconazole prophylaxis for 4-6 wk in high-risk infants does not increase the incidence of fungal colonization and infections caused by natively fluconazole-resistant *Candida* species. The universal implementation of such a strategy across nurseries is discouraged, because the rate of *Candida* infections varies greatly among centers and there are insufficient neurodevelopmental follow-up data in these infants to justify prophylaxis.

Itraconazole

Compared to fluconazole, itraconazole has the benefit of antifungal activity against *Aspergillus* species but comes with several practical constraints, such as erratic oral absorption in high- risk patients and significant drug interactions. These pharmacokinetic concerns have been addressed with both an intravenous formulation and a better-absorbed oral solution to replace the capsules used earlier. Itraconazole has a high volume of distribution and accumulates in tissues, and tissue-bound levels are probably more clinically relevant to infection treatment than serum levels. Dissolution and absorption of itraconazole are affected by gastric pH. Patients with achlorhydria or taking H_2-receptor antagonists might demonstrate impaired absorption, and coadministration of the capsule with acidic beverages such as colas or cranberry juice can enhance absorption. Administration with food significantly increases the absorption of the capsule formulation, but the oral suspension with a cyclodextrin base is better absorbed on an empty stomach.

Side effects are relatively few and include nausea and vomiting (10%), elevated transaminases (5%), and peripheral edema. There are reports in adults of development of cardiomyopathy. Itraconazole also is associated with important drug interactions, and prior or concurrent use of rifampin, phenytoin, carbamazepine, and phenobarbital should be avoided.

Itraconazole has a role in treating less-serious infections with endemic mycoses (histoplasmosis, coccidioidomycosis, and blastomycosis), as well as use in prophylaxis against invasive fungal infections

in high-risk patients. The plethora of drug interactions make itraconazole a concern in complex patients receiving other medications, and itraconazole serum levels (to achieve ≥0.5 μg/mL) are recommended to confirm appropriate dosing. Itraconazole is no longer recommended for primary therapy of invasive aspergillosis.

Voriconazole

Voriconazole is a second-generation triazole and a synthetic derivative of fluconazole. Voriconazole generally has the spectrum of activity of itraconazole but the better bioavailability than fluconazole. Importantly, it is fungicidal against *Aspergillus* and fungistatic against *Candida*. It is extensively metabolized by the liver and has approximately 90% oral bioavailability. The cytochrome P450 2C19 (CYP2C19) enzyme appears to play a major role in the metabolism of voriconazole, and polymorphisms in CYP2C19 are associated with slow voriconazole metabolism. As many as 20% of non-Indian Asians have low CYP2C19 activity and develop voriconazole levels as much as 4-fold higher than those in homozygous subjects, leading to potentially increased toxicity.

Voriconazole is available as an oral tablet, an oral suspension, and an intravenous solution. In adults, voriconazole exhibits nonlinear pharmacokinetics, has a variable half-life of approximately 6 hr with large interpatient variation in blood levels, and achieves good CSF penetration. In contrast to the situation in adults, elimination of voriconazole is linear in children. A multicenter safety, population pharmacokinetic study of intravenous voriconazole dosages in immunocompromised pediatric patients showed that body weight was more influential than age in accounting for the observed variability in voriconazole pharmacokinetics, and voriconazole needs to be dosed higher in pediatric patients than adult patients. Adult patients load with 6 mg/kg/dose and then transition to a maintenance dosage of 4 mg/kg/dose, but children should begin and continue with 9 mg/kg/dose intravenously (see Table 233-1) and continue maintenance dosing at 8 mg/kg/dose. This need for an increased dosage in treating children is crucial to understand and is mandated by the fundamentally different pharmacokinetics of this drug in pediatric patients. Obtaining voriconazole serum levels (to achieve ≥1-2 μg/mL) is critical for therapeutic success. Oral voriconazole is best absorbed on an empty stomach. Generally a trough level greater than the minimum inhibitory concentration of the infecting organism is preferred, and very high voriconazole levels have been associated with toxicity (generally >7 μg/mL). The main side effects of voriconazole include reversible dosage-dependent visual disturbances (increased brightness, blurred vision) in as many as one-third of treated patients, elevated hepatic transaminases with increasing dosages, and occasional skin reactions likely caused by photosensitization.

The largest prospective clinical trial of voriconazole as primary therapy for invasive aspergillosis compared initial randomized therapy with voriconazole vs amphotericin B and demonstrated improved response and survival with voriconazole over amphotericin B. Voriconazole is guideline-recommended as the preferred primary therapy against invasive aspergillosis. Voriconazole also has a role in treating candidiasis, but its fungistatic nature makes it often less than ideal for treating critically ill or neutropenic patients where the fungicidal echinocandin antifungals are preferred.

Posaconazole

Posaconazole is a second-generation triazole that is a derivative of itraconazole and is currently available as an intravenous formulation, an extended-release oral tablet, and an oral suspension. The antimicrobial spectrum of posaconazole is similar to that of voriconazole; however, the former is active against *Zygomycetes* such as mucormycosis, and voriconazole is not active against these particular mold infections. When administered with a nonfat or high-fat diet, posaconazole exposure and maximum concentration are 3-4 times higher than when administered in the fasting state, emphasizing the importance of diet to increase serum levels of posaconazole (the opposite of voriconazole). Posaconazole exposure is maximized with acidic beverages, administration in divided doses, and the absence of proton pump inhibitors. Posaconazole causes transient hepatic reactions, including mild to moderate elevations in liver transaminases, alkaline phosphatase, and total bilirubin.

The correct pediatric dosage of posaconazole is not known, because initial studies are still ongoing. In adult patients, dosages >800 mg/day do not result in increased serum levels, and division of daily dosing into 3 or 4 doses/day results in greater serum levels than a once- or twice-daily dosing scheme. Similar to itraconazole and voriconazole, posaconazole should be monitored with trough levels (to achieve ≥0.7 μg/mL).

In an international randomized, single-blinded study of posaconazole vs fluconazole or itraconazole in neutropenic patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes, posaconazole was superior in preventing invasive fungal infections. Fewer patients in the posaconazole group had invasive aspergillosis, and survival was significantly longer among recipients of posaconazole than among recipients of fluconazole or itraconazole. Another multisite international randomized, double-blinded study in patients with allogeneic hematopoietic stem-cell transplantation and graft-versus-host disease showed that posaconazole was not inferior to fluconazole in the prevention of invasive fungal infections. Posaconazole is approved for prophylaxis against invasive fungal infections but has shown great efficacy in clinical experience with recalcitrant mold infections.

In patients with chronic granulomatous disease and proven invasive fungal infection refractory to standard therapy, posaconazole proved to be well tolerated and quite effective. This agent might prove to be very useful in this patient population where long-term therapy with an oral agent is required.

ECHINOCANDINS

The echinocandins are a class of antifungals and interfere with cell wall biosynthesis by noncompetitive inhibition of 1,3-β-D-glucan synthase, an enzyme present in fungi but absent in mammalian cells. 1,3-β-D-Glucan is an essential cell wall polysaccharide and provides structural integrity for the fungal cell wall. Echinocandins are generally fungicidal in vitro against *Candida* species, although not as rapidly as amphotericin B, and are fungistatic against *Aspergillus*. As a class these agents are not metabolized through the CYP enzyme system, lessening some of the drug interactions and side effects seen with the azole class. The echinocandins appear to have a prolonged and dosage-dependent fungicidal antifungal effect on *C. albicans*, compared to the fungistatic fluconazole. Three compounds in this class (caspofungin, micafungin, and anidulafungin) are FDA approved for use. Owing to the large size of the molecules, the current echinocandins are only available in an intravenous formulation. Because 1,3-β-D-glucan is a selective target present only in fungal cell walls and not in mammalian cells, this eliminates much of the drug mechanism–based toxicity for the echinocandins, and there appears to be no apparent myelotoxicity or nephrotoxicity with the agents.

Caspofungin

At present there is no known maximum tolerated dosage and no toxicity-determined maximum length of therapy for caspofungin. The usual course is to begin with a loading dose followed by a lesser daily maintenance dosage, which is 70 mg followed by 50 mg daily in adult patients. Much of the dosage accumulation is achieved in the 1st wk of dosing, and renal insufficiency has little effect on the pharmacokinetics of caspofungin. Caspofungin has been evaluated at double the recommended dosage (100 mg/day in adults) with no adverse effects, and it is unclear if higher dosage of this relatively safe agent results in greater clinical efficacy.

Pharmacokinetics are slightly different in children, with caspofungin levels lower in smaller children and with a reduced half-life. A study evaluated the pharmacokinetics of caspofungin in children with neutropenia and showed that in patients receiving 50 mg/m^2/day (maximum: 70 mg/day), the levels were similar to those in adults receiving 50 mg/day and were consistent across age ranges. In this study, weight-based dosing (1 mg/kg/day) was suboptimal when

compared to body surface area regimens, so caspofungin should be appropriately dosed in children as a loading dose of 70 mg/m^2/day, followed by daily maintenance dosing of 50 mg/m^2/day.

Caspofungin was approved for refractory aspergillosis or intolerance to other therapies and for candidemia and various other sites of invasive *Candida* infections. In the pivotal clinical study, patients with acute invasive aspergillosis underwent “salvage” therapy after failing primary therapy, and recipients had a 41% favorable response with caspofungin. In a multicenter trial of patients with invasive candidiasis, 73% of patients who received caspofungin had a favorable response at the end of therapy, compared to 62% in the amphotericin B group. Importantly, caspofungin treatment performed equally well to amphotericin B treatment for all the major *Candida* species, but other studies show that some infections with *Candida parapsilosis* do not clear as effectively with an echinocandin. Current guideline recommendations state that infection with *C. parapsilosis* should be treated initially with fluconazole or amphotericin B for this reason. Caspofungin was also evaluated against L-amphotericin B in the empirical treatment of patients with persistent fever and neutropenia and was not inferior to liposomal amphotericin B in more than 1,000 patients.

Caspofungin in children is reported to be safe. Caspofungin pharmacokinetics were evaluated in older infants and toddlers at 50 mg/m^2/day and found to be similar to adults receiving the standard 50 mg daily dose. Caspofungin in newborns has been used as single or adjuvant therapy for refractory cases of disseminated candidiasis. Neonates with invasive candidiasis are at high risk for central nervous system involvement; it is not known if the dosages of caspofungin studied provide sufficient exposure to penetrate the central nervous system at levels necessary to cure infection. Therefore, caspofungin is not recommended as monotherapy in neonatal candidiasis.

Micafungin

The pharmacokinetics of micafungin have been evaluated in children and young infants. An inverse relation between age and clearance was observed, where mean systemic clearance was significantly greater and mean half-life was significantly shorter in patients 2-8 yr of age compared to patients 9-17 yr of age. Therefore, dosing of micafungin in children is age-related and needs to be higher in children younger than 8 yr old. To achieve micafungin exposures equivalent to exposures in adults receiving 100, 150, and 200 mg daily, as evidenced by simulation profiles, children require dosages >3 mg/kg.

Several pharmacokinetic studies of micafungin in term and preterm infants show that micafungin in infants has a shorter half-life and a more rapid rate of clearance compared with published data in older children and adults. These results suggest that young infants should receive 10 mg/kg daily of micafungin if used to treat invasive candidiasis.

The safety profile of micafungin is optimal when compared to other antifungal agents. Clinical trials including those of micafungin used for treatment of localized and invasive candidiasis as well as prophylaxis studies in patients following stem cell transplantation have demonstrated fewer adverse events compared to liposomal amphotericin B and fluconazole. The most common adverse events experienced by these patients are related to the gastrointestinal tract (nausea, diarrhea). Hypersensitivity reactions associated with micafungin have been reported, and liver enzymes are elevated in 5% of patients receiving this agent. Hyperbilirubinemia, renal impairment, and hemolytic anemia related to micafungin use have also been identified in postmarketing surveillance of the drug.

An open-label, noncomparative, multinational study in adult and pediatric patients with a variety of diagnoses evaluated the use of micafungin monotherapy and combination therapy in 225 patients with invasive aspergillosis. Of those only treated with micafungin, favorable responses were seen in 50% of the primary and 41% of the salvage therapy group.

Micafungin at dosages of 100 and 150 mg daily was also noninferior to caspofungin in an international, randomized, double-blinded study of adults with candidemia or invasive candidiasis and was found to be superior to fluconazole in the prevention of invasive fungal infections in a randomized study of adults undergoing hematopoietic stem cell transplantation.

Of the 3 drugs within the echinocandin class, micafungin has been the one most extensively studied in children, including several pharmacokinetic studies in neonates. A pediatric substudy as part of a double-blind, randomized, multinational trial comparing micafungin (2 mg/kg/day) with liposomal amphotericin B (3 mg/kg/day) as first-line treatment for invasive candidiasis showed similar success for micafungin and liposomal amphotericin B. In general, micafungin was better tolerated than liposomal amphotericin B as evidenced by fewer adverse events leading to discontinuation of therapy. Micafungin doses up to 15 mg/kg/day have been evaluated in small cohorts of premature infants and found to be well tolerated; doses of 8-10 mg/kg/day achieve exposures comparable to adults in this population.

Anidulafungin

Anidulafungin has the longest half-life of all the echinocandins (approximately 18 hr). In a study of 25 neutropenic children receiving anidulafungin as empirical therapy, 4 patients in the group receiving 0.75 mg/kg/day experienced adverse events such as facial erythema and rash, elevation in serum blood urea nitrogen, and fever and hypotension. In a pharmacokinetic study in neonates and young infants, anidulafungin exposures comparable to adults were achieved with doses of 1.5 mg/kg/day (3 mg/kg loading dose). One infant in this cohort supported by extracorporeal membrane oxygenation achieved the lowest exposure, which suggests that dose adjustments are required in this population.

A randomized, double-blind study in adult patients without neutropenia with invasive candidiasis showed that anidulafungin was not inferior to fluconazole in the treatment of invasive candidiasis. In this study, the incidence and types of adverse events were similar in the 2 groups, and all-cause mortality was 31% in the fluconazole group and 23% in the anidulafungin group. No clinical studies of anidulafungin in pediatric patients are currently available.

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Chapter 234

Candida

Jessica Ericson, P. Brian Smith, and Daniel K. Benjamin Jr.

Candidiasis encompasses many clinical syndromes that may be caused by several species of *Candida*. Invasive candidiasis (*Candida* infections of the blood and other sterile body fluids) is a leading cause of infection-related mortality in hospitalized immunocompromised patients.

Candida exists in 3 morphologic forms: oval to round **blastospores or yeast cells** (3-6 mm in diameter); double-walled **chlamydospores** (7-17 mm in diameter), which are usually at the terminal end of a pseudohypha; and **pseudomycelium,** which is a mass of pseudohyphae and represents the tissue phase of *Candida.* **Pseudohyphae** are filamentous processes that elongate from the yeast cell without the cytoplasmic connection of a true hypha. *Candida* grows aerobically on routine laboratory media but can require several days of incubation for visible growth.

Candida albicans accounts for most human infections, but *Candida parapsilosis, Candida tropicalis, Candida krusei, Candida lusitaniae, Candida glabrata,* and several other species are commonly isolated from hospitalized children. *C. albicans* forms a germ tube when suspended in rabbit or human serum and incubated for 1-2 hr; consequently, a rapid germ tube test should be performed before further

identification tests are conducted. The other clinically important *Candida* species can be identified within 48 hr on the basis of biochemical test results. Differentiation and susceptibility testing are important owing to increasing frequency of fluconazole resistance.

Treatment of invasive *Candida* infections is complicated by the emergence of non-*albicans* strains. Amphotericin B deoxycholate is inactive against approximately 20% of strains of *C. lusitaniae.* Fluconazole is useful for many *Candida* infections but is inactive against all strains of *C. krusei* and 5-25% of strains of *C. glabrata.* Susceptibility testing of these clinical isolates is recommended.

234.1 Neonatal Infections

Jessica Ericson, P. Brian Smith, and Daniel K. Benjamin Jr.

Candida is a common cause of oral mucous membrane infections **(thrush)** and perineal skin infections **(*Candida* diaper dermatitis)** in young infants. Rare presentations include **congenital cutaneous candidiasis,** caused by an ascending infection into the uterus during gestation, and **invasive fungal dermatitis,** a postnatal skin infection resulting in positive blood cultures. Invasive candidiasis is a common infectious complication in the neonatal intensive care unit (NICU) because of improved survival of extremely preterm infants.

EPIDEMIOLOGY

Candida species are the third most common cause of bloodstream infection in premature infants. The cumulative incidence is <0.3% among infants >2,500 g birthweight admitted to the NICU. The cumulative incidence increases to 8% for infants <750 g birthweight. In addition, the incidence varies greatly by individual NICU. Among centers in the National Institutes of Health-sponsored Neonatal Research Network, the cumulative incidence of candidiasis among infants <1,000 g birthweight ranges from 2-28%. Colonization is associated with a significantly increased risk of future invasive *Candida* infection. Up to 10% of full-term infants are colonized as the result of vertical transmission from the mother at birth, with slightly higher rates of colonization in premature infants. Colonization rates increase to >50% among infants admitted to the NICU by 1 mo of age. Histamine-2 blockers and broad-spectrum antibiotics facilitate *Candida* colonization and overgrowth.

Significant risk factors for neonatal invasive candidiasis include prematurity, low birthweight, exposure to broad-spectrum antibiotics, abdominal surgery, and presence of a central venous catheter.

PATHOGENESIS

Immunologic immaturity along with an underdeveloped layer of skin, need for invasive measures (endotracheal tubes, central venous catheters), and exposure to broad-spectrum antibiotics places preterm infants at great risk for invasive candidiasis. Premature infants are also at high risk for spontaneous intestinal perforations and necrotizing enterocolitis. Both conditions require abdominal surgery, prolonged exposure to broad-spectrum antibiotics, and total parenteral nutrition administration requiring placement of central venous catheters. Each of these factors increases the risk of invasive candidiasis by decreasing the physiologic barriers that protect against invasive infection.

CLINICAL MANIFESTATIONS

The manifestations of neonatal candidiasis vary in severity from oral thrush and *Candida* diaper dermatitis (see Chapter 234.2) to invasive candidiasis that can manifest with overwhelming sepsis (see Chapter 234.3). Signs of invasive candidiasis among premature infants are often nonspecific and include temperature instability, lethargy, apnea, hypotension, respiratory distress, abdominal distention, and thrombocytopenia.

Central nervous system involvement is common and is most accurately described as meningoencephalitis. *Candida* infections involving the central nervous system often result in abscesses leading to unremarkable cerebrospinal fluid parameters (white blood cell count, glucose, protein) even though central nervous system infection is present. Endophthalmitis is an uncommon complication affecting <5% of infants with invasive candidiasis. In addition, candidemia is associated with an increased risk of severe retinopathy of prematurity. Renal involvement commonly complicates neonatal invasive candidiasis. Renal involvement may be limited to candiduria or can manifest with diffuse infiltration of *Candida* throughout the renal parenchyma or the presence of *Candida* and debris within the collecting system. Other affected organs include the heart, bones, joints, liver, and spleen.

DIAGNOSIS

Mucocutaneous infections are most often diagnosed by direct clinical exam. Scrapings of skin lesions may be examined with a microscope after Gram staining or suspension in KOH. Definitive diagnosis of invasive disease requires histologic demonstration of the fungus in tissue specimens or recovery of the fungus from normally sterile body fluids. Hematologic parameters are sensitive but not specific. Thrombocytopenia occurs in more than 80% of premature infants with invasive candidiasis, but also occurs in 75% of premature infants with Gram-negative bacterial sepsis and nearly 50% of infants with Gram-positive bacterial sepsis. Blood cultures have very low sensitivity for invasive candidiasis. In a study of autopsy-proven candidiasis in adult patients, the sensitivity of multiple blood cultures for detecting single-organ disease was 28%. Blood culture volumes in infants are often only 0.5-1 mL, making the sensitivity in this population almost certainly lower. Blood culture volume should be maximized as much as possible to increase sensitivity. Fungal-specific media can improve sensitivity when *Candida* is present as a coinfection with bacteria and can also decrease the time to positivity leading to more rapid diagnosis.

Further assessment of infants in the presence of documented candidemia should include ultrasound or computerized tomography of the head to evaluate for abscesses; ultrasound of the liver, kidney, and spleen; cardiac echocardiography; ophthalmologic exam; lumbar puncture; and urine culture. These tests are necessary to determine if more than 1 body system is infected, which is commonly the case.

PROPHYLAXIS

NICUs with a high incidence of invasive candidiasis should consider prophylaxis with fluconazole in infants <1,000 g birthweight. Twice-weekly fluconazole at 3 and 6 mg/kg/dose decreases rates of both colonization with *Candida* species and invasive fungal infections. Use of this dosing strategy has not been shown to increase the frequency of infections caused by fluconazole-resistant strains, but use of an alternative antifungal class for cases of breakthrough infection is suggested.

TREATMENT

In the absence of systemic manifestations, topical antifungal therapy is the treatment of choice for congenital cutaneous candidiasis in full-term infants. Congenital cutaneous candidiasis in preterm infants can progress to systemic disease, and therefore systemic therapy is warranted.

Every attempt should be made to remove or replace central venous catheters once the diagnosis of candidemia is confirmed. Delayed removal has been consistently associated with increased mortality and morbidity including poor neurodevelopmental outcomes.

Although no well-powered randomized, controlled trials exist to guide length and type of therapy, 21 days of systemic antifungal therapy from the last positive *Candida* culture is recommended in infants. Antifungal therapy should be targeted based on susceptibility testing. Amphotericin B deoxycholate has been the mainstay of therapy for systemic candidiasis and is active against both yeast and mycelial forms. Nephrotoxicity, hypokalemia, and hypomagnesemia are common, but amphotericin B deoxycholate is better tolerated in infants than in adult patients. *C. lusitaniae*, an uncommon pathogen in infants, is often resistant to amphotericin B deoxycholate. Liposomal amphotericin is associated with worse outcomes in infants and should be used only when urinary tract involvement can reliably be excluded. Fluconazole is often used instead of amphotericin B deoxycholate for treatment of invasive neonatal *Candida* infections because of its effectiveness and low incidence of side effects. It is particularly useful for urinary

Table 234-1 Dosing of Antifungal Agents in Infants* and Number of Infants Younger Than 1 Yr of Age Studied with Reported Pharmacokinetic Parameters

DRUG	INFANTS STUDIED	SUGGESTED DOSE
Amphotericin B deoxycholate	27	1 mg/kg/day
Amphotericin B lipid complex	28	5 mg/kg/day
Liposomal amphotericin B	17	5 mg/kg/day
Amphotericin B colloidal dispersion	0	5 mg/kg/day
Fluconazole†	65	12 mg/kg/day
Micafungin‡	120	10 mg/kg/day
Caspofungin§	22	50 mg/m^2/day
Anidulafungin‡	15	1.5 mg/kg/day

*Voriconazole dosing has not been investigated in the nursery.
†A loading dose of 25 mg/kg of fluconazole is necessary to achieve therapeutic serum concentrations in the early days of therapy.
‡Micafungin has been studied in infants <120 days of life at this dosage.
§Caspofungin and anidulafungin should generally be avoided because dosing sufficient to penetrate brain tissue has not been studied.

tract infections, obtaining high concentrations in the urine. A loading dose should be given to obtain therapeutic serum concentrations in a timely manner. Fluconazole is inactive against all strains of *C. krusei* and some isolates of *C. glabrata.* Additionally, in centers where fluconazole prophylaxis is used, another agent, such as amphotericin B deoxycholate, should be used for treatment. The echinocandins have excellent activity against most *Candida* species and have been used successfully in patients with resistant organisms or in whom other therapies have failed. Several studies have described the pharmacokinetics of antifungals in infants (Table 234-1).

PROGNOSIS

Mortality following invasive candidiasis in premature infants has been consistently reported to be around 20% in large studies. Candidiasis is also associated with poor neurodevelopmental outcomes, chronic lung disease, and severe retinopathy of prematurity.

Bibliography is available at Expert Consult.

234.2 Infections in Immunocompetent Children and Adolescents

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ORAL CANDIDIASIS

Oral thrush is a superficial mucous membrane infection that affects approximately 2-5% of normal neonates. *C. albicans* is the most commonly isolated species. Oral thrush can develop as early as 7-10 days of age. The use of antibiotics, especially in the 1st yr of life, can lead to recurrent or persistent thrush. It is characterized by pearly white, curdish material visible on the tongue, palate, and buccal mucosa. Oral thrush may be asymptomatic or can cause pain, fussiness, and decreased feeding, leading to inadequate nutritional intake and dehydration. It is uncommon after 1 yr of age but can occur in older children treated with antibiotics. Persistent or recurrent thrush with no obvious predisposing reason, such as recent antibiotic treatment, warrants investigation of an underlying immunodeficiency, especially vertically transmitted HIV infection or a primary congenital genetic immune defect.

Treatment of mild cases might not be necessary. When treatment is warranted, the most commonly prescribed antifungal agent is nystatin. For recalcitrant or recurrent infections, a single dose of fluconazole may be useful. In breastfed infants, simultaneous treatment of infant and mother with topical nystatin or oral fluconazole may be indicated.

DIAPER DERMATITIS

Diaper dermatitis is the most common infection caused by *Candida* (see Chapter 666) and is characterized by a confluent erythematous rash with satellite pustules. *Candida* diaper dermatitis often complicates other noninfectious diaper dermatitides and often occurs following a course of oral antibiotics.

A common practice is to presumptively treat any diaper rash that has been present for longer than 3 days with topical antifungal therapy such as nystatin, clotrimazole, or miconazole. If significant inflammation is present, the addition of hydrocortisone 1% may be useful for the 1st 1-2 days, but topical corticosteroids should be used cautiously in infants because the relatively potent topical corticosteroid can lead to adverse effects. Frequent diaper changes and short periods without diapers are important adjunctive treatments.

UNGUAL AND PERIUNGUAL INFECTIONS

Paronychia and onychomycosis may be caused by *Candida,* although *Trichophyton* and *Epidermophyton* are more common causes (see Chapter 663). *Candida* onychomycosis differs from tinea infections by its propensity to involve the fingernails and not the toenails, and by the associated paronychia. *Candida* paronychia often responds to treatment consisting of keeping the hands dry and using a topical antifungal agent. Psoriasis and immune dysfunction, including HIV and primary immunodeficiencies, predispose to *Candida* ungual infections. Ungual infections often require systemic antifungal therapy. Once-weekly fluconazole for 4-12 mo is an effective treatment strategy with fairly low toxicity.

VULVOVAGINITIS

Vulvovaginitis is a common *Candida* infection of pubertal and postpubertal female patients (see Chapter 549). Predisposing factors include pregnancy, use of oral contraceptives, and use of oral antibiotics. Prepubertal girls with *Candida* vulvovaginitis usually have a predisposing factor such as diabetes mellitus or prolonged antibiotic treatment. Clinical manifestations can include pain or itching, dysuria, vulvar or vaginal erythema, and an opaque white or cheesy exudate. More than 80% of cases are caused by *C. albicans.*

Candida vulvovaginitis can be effectively treated with either vaginal creams or troches of nystatin, clotrimazole, or miconazole. Oral therapy with a single dose of fluconazole is also effective.

Bibliography is available at Expert Consult.

234.3 Infections in Immunocompromised Children and Adolescents

Jessica Ericson, P. Brian Smith, and Daniel K. Benjamin Jr.

ETIOLOGY

C. albicans is the most common cause of invasive candidiasis among immunocompromised pediatric patients and is associated with higher rates of mortality and end-organ involvement than are non-*albicans* species.

CLINICAL MANIFESTATIONS

HIV-Infected Children

Oral thrush and diaper dermatitis are the most common *Candida* infections in HIV-infected children. Besides oral thrush, 3 other types of oral *Candida* infections can occur in HIV-infected children: atrophic candidiasis, which manifests as a fiery erythema of the mucosa or loss of papillae of the tongue; chronic hyperplastic candidiasis, which presents with oral symmetric white plaques; and angular cheilitis, in which there is erythema and fissuring of the angles of the mouth. Topical antifungal therapy may be effective, but systemic treatment

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with fluconazole or itraconazole is usually necessary. Symptoms of dysphagia or poor oral intake can indicate progression to *Candida* esophagitis, requiring systemic antifungal therapy. In HIV patients, esophagitis can also be caused by cytomegalovirus, herpes simplex virus, reflux, or lymphoma; *Candida* is the most common cause, and *Candida* esophagitis can occur in the absence of thrush.

Candida dermatitis and onychomycosis are more common in HIV-infected children. These infections are generally more severe than they are in immunocompetent children and can require systemic antifungal therapy.

Cancer and Transplant Patients

Fungal infections, especially *Candida* and *Aspergillus* infections, are a significant problem in oncology patients with chemotherapy-associated neutropenia (see Chapter 178). Greater than 5 days of fever during a neutropenic episode is associated with presence of an invasive fungal infection. Accordingly, empirical antifungal therapy should be started if fever and neutropenia persist for 5 or more days. Fluconazole can be used if the patient is not critically ill and the drug is not already being used for prophylaxis. An echinocandin or liposomal amphotericin B should be used when these conditions are not met. High-risk oncology patients warrant prophylaxis against invasive *Candida* infection. Both fluconazole and echinocandins are used for this indication; lower doses are typically used for this purpose than those used for treatment.

Bone marrow transplant recipients have a much higher risk of fungal infections because of the dramatically prolonged duration of neutropenia. Voriconazole prophylaxis decreases the incidence of candidemia in bone marrow transplant recipients with the additional benefit over fluconazole of mold prophylaxis. The use of myelopoietic colony-stimulating factor reduces the duration of neutropenia after chemotherapy and is associated with decreased risk for candidemia. When *Candida* infection occurs in this population, the lung, spleen, kidney, and liver are involved in more than 50% of cases.

Solid-organ transplant recipients are also at increased risk for superficial and invasive *Candida* infections. Studies in liver transplant recipients demonstrate the utility of antifungal prophylaxis with amphotericin B deoxycholate, fluconazole, voriconazole, or caspofungin in high-risk patients (those with prolonged surgical time, comorbidities, recent antibiotic exposure, or bile leak).

Catheter-Associated Infections

Central venous catheter infections occur most often in oncology patients but can affect any patient with a central catheter (see Chapter 179). Neutropenia, use of broad-spectrum antibiotics, and parenteral alimentation are associated with increased risk for *Candida* central catheter infection. Treatment typically requires removing or replacing the catheter followed by a 2-3 wk course of systemic antifungal therapy. Removal of the central catheter in place at time of positive blood culture and use of a peripheral IV or enteral support for at least 48 hr prior to obtaining central access is advocated. Removal of the original catheter followed by immediate replacement with a new central catheter in a different anatomic location is acceptable if an interval without central access is not feasible.

DIAGNOSIS

The diagnosis is often presumptive in neutropenic patients with prolonged fever because positive blood cultures for *Candida* occur only in a minority of patients who are later found to have disseminated infection. If isolated, *Candida* grows readily on routine blood culture media, with ≥90% of positive cultures identified within 72 hr. CT may demonstrate findings consistent with invasive fungal infection but also is limited by nonspecific findings and false negatives. The role of screening by CT scan has not been well defined.

TREATMENT

Echinocandins are favored as empirical therapy for moderately or severely ill children; fluconazole is acceptable for those who are infected with a susceptible organism and are less critically ill; amphotericin B products are also acceptable. Definitive antifungal selection should be made based on susceptibility testing results. Fluconazole is not effective against *C. krusei* and some isolates of *C. glabrata. C. parapsilosis* has occasional resistance to the echinocandins, but the overall rate is still low. Amphotericin B deoxycholate is inactive against approximately 20% of the strains of *C. lusitaniae,* and therefore susceptibility testing should be performed for all strains (Table 234-2).

Table 234-2 Dosing of Antifungal Agents in Children Older Than 1 Year of Age for Treatment of Invasive Disease

DRUG	SUGGESTED DOSAGE
Amphotericin B deoxycholate	1 mg/kg/day
Amphotericin B lipid complex	5 mg/kg/day
Liposomal amphotericin B	5 mg/kg/day
Amphotericin B colloidal dispersion	5 mg/kg/day
Fluconazole†	12 mg/kg/day
Voriconazole	8 mg/kg every 12 hr
Micafungin*	2-4 mg/kg/day
Caspofungin	50 mg/m^2/day
Anidulafungin	1.5 mg/kg/day

*Use adult dosages in children older than 8 yr of age.

†Loading doses should be used for fluconazole (25 mg/kg), voriconazole (9 mg/kg q 12 × 24 hr), caspofungin (70 mg/m^2), and anidulafungin (3 mg/kg).

PRIMARY IMMUNE DEFECTS

Chronic mucocutaneous candidiasis involves *Candida* infections of the oral cavity, esophagus, and/or genital mucosa, as well as involvement of skin and nails, that is recurrent or persistent and difficult to treat. There is a broad spectrum of genetic immune defects associated with chronic mucocutaneous candidiasis mostly related to severe T-cell defects or disorders of interleukin-17 production (see Chapter 125). Genes or disorders associated with chronic mucocutaneous candidiasis include severe combined immunodeficiency syndrome, NEMO or IKBG deficiency, DOCK8 deficiency, STAT3 deficiency (autosomal dominant hyperimmunoglobulin E syndrome), autoimmune polyendocrinopathy type 1, CARD9 deficiency, *STAT1* gain of function mutations, and *IL17RA* mutations.

Primary immunodeficiencies associated with an increased risk of invasive *Candida* infections include severe congenital neutropenia, CARD 9 deficiency, chronic granulomatous disease, and leukocyte adhesion deficiency type 1.

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Chapter 235

Cryptococcus neoformans

Jane M. Gould and Stephen C. Aronoff

ETIOLOGY

Cryptococcosis is an invasive fungal disease caused by a monomorphic, encapsulated yeast. *Cryptococcus neoformans* var. *neoformans* is the most common etiologic agent worldwide and is the predominant pathogenic fungal infection among persons infected with HIV.

EPIDEMIOLOGY

C. neoformans var. *neoformans* (serotypes A, D, and AD) is distributed in temperate climates predominantly in soil contaminated with droppings from certain avian species, including pigeons, canaries, and cockatoos. It may also be found on fruits and vegetables and may be carried by cockroaches. *C. neoformans* var. *gattii* (serotypes B and C) is found in the tropics and subtropics and is associated with several species of eucalyptus trees. This species causes endemic disease primarily in immunologically competent hosts living in the tropics and is associated with the formation of large granulomas known as **cryptococcomas**. The distribution and ecology of *C. gattii* seem to be changing, and this organism can now be found in association with a wide range of trees, including firs and oaks. *C. gattii* has caused disease in approximately 24 patients residing in Oregon and Washington, most occurring since 2006. Pulmonary disease with or without meningoencephalitis was the most common manifestation. *C. gattii* is believed to be more virulent clinically than *C. neoformans*. It is critical to distinguish between the 2 cryptococcal species because *C. gattii* is less susceptible to fluconazole. *Cryptococcus laurentii* is occasionally reported as a cause of invasive fungal disease, usually in immunocompromised patients and most recently in the premature neonatal population.

C. neoformans exposure is much more common than previously thought. Seroprevalence studies in temperate urban environments have shown that most children older than 2 yr of age and nearly all adults have been exposed to this organism. Despite this high prevalence, clinical disease is unusual in immunocompetent persons and is rare in children. Pigeon breeders and laboratory personnel who work with *Cryptococcus* are at greatest risk. Cryptococcosis is also rare (<1%) among HIV-infected children but occurs in 5-10% of HIV-infected adults, with higher rates of infection reported from developing countries. Pediatric cases of cryptococcosis are evenly divided among immunocompetent and immunocompromised persons. Cryptococcosis is the third most common invasive fungal infection after candidiasis and aspergillosis in solid organ transplant patients. Other risk factors for cryptococcal infection include diabetes mellitus, renal failure, cirrhosis, and use of corticosteroids, chemotherapy agents, and monoclonal antibodies such as etanercept, infliximab, and alemtuzumab. Children with primary immunodeficiency diseases are at increased risk for infection; these include those with autoantibodies to granulocyte-macrophage colony-stimulating factor or interferon-γ, CD40 ligand deficiency, and monoMAC syndrome (monocytopenia, B and natural killer cell lymphopenia). Interestingly organ transplant recipients who are receiving calcineurin-inhibitor–based immunosuppression are less likely to have cryptococcal central nervous system (CNS) infection and more likely to have disease limited to the lung, because these agents have antifungal activity in vivo.

PATHOGENESIS

In most cases *C. neoformans* is acquired by inhalation of fungal spores (<5-10 µm), which are engulfed by alveolar macrophages. Local inoculation leads to cutaneous or ophthalmic infection rarely. An additional portal of entry can be seen with organ transplantation of infected tissue. Direct entry through the gastrointestinal tract can also occur. After entry into the body, either latent infection or acute disease is produced. Cell-mediated immunity is the most important host defense for producing granulomatous inflammation and thus containing cryptococcal infection. Patients with compromised cell-mediated immunity have the highest risk for developing cryptococcal disease. In most immunocompetent persons, infection is limited to the lung. When the immune system fails to contain the infection, dissemination follows, with potential involvement of the brain, meninges, skin, eyes, prostate, and skeletal system.

In immunocompetent patients, *C. neoformans* can produce both a suppurative and granulomatous tissue reaction or a granulomatous reaction alone with varying degrees of necrosis. Healing is characterized by fibrosis usually without calcification. In immunocompromised patients tissue reactions may be minimal or absent, leading to the proliferation of yeast and the development of mucoid cystic lesions. Pulmonary cryptococcosis produces granulomas that are often subpleural in location and contain yeast forms. Cystic cryptococcomas occur in the CNS of 20% of non–HIV-infected patients with disseminated disease and may be found in the absence of overt meningitis. Granulomas and microabscesses containing yeast occur in patients with skin and bone infection.

CLINICAL MANIFESTATIONS

The manifestations of cryptococcal infection reflect the route of inoculation and the immunocompetence of the host. Sites of infection include lung, CNS, blood, skin, bone, and mucous membranes.

Pneumonia

Pneumonia is the most common form of cryptococcosis. Asymptomatic pulmonary infections occur often, especially among pigeon breeders, bird fanciers, and laboratory workers. Asymptomatic carriage can occur in persons with underlying chronic lung disease. Progressive pulmonary disease is symptomatic with fever, cough, pleuritic chest pain, and constitutional symptoms. In a 2006 review of 24 patients with pulmonary cryptococcosis, cough was the most common symptom. Pulmonary disease often precedes disseminated infection in immunocompromised persons. Chest radiographs can demonstrate a poorly localized bronchopneumonia, nodular changes, or lobar consolidations; cavities and pleural effusions are rare. Immunocompromised patients can have alveolar and interstitial infiltrates that can mimic *Pneumocystis* pneumonia. In adults with HIV infection, cryptococcal pneumonia is usually asymptomatic, although >90% of patients have concomitant CNS infection.

Disseminated Infection

Disseminated infection usually follows primary pulmonary disease, especially among immunocompromised persons. Advanced HIV infection is the most common predisposing factor for disseminated cryptococcosis. Other major predisposing conditions include lymphoproliferative disorders, corticosteroid therapy, primary immunodeficiencies affecting both T- and B-cell lineages, and immunosuppressive therapy for rheumatic disorders, celiac disease, and organ transplantation.

Meningitis

Subacute or chronic meningitis is the most common clinical manifestation of disseminated cryptococcal infection. The clinical presentation is variable and prognostic. Good outcomes are associated with headache as the initial symptom, normal mental status, absence of a predisposing condition, normal cerebrospinal fluid (CSF) opening pressure, normal CSF glucose, negative India ink stain, absence of extraneural infection by culture, and cryptococcal antigen titers in CSF and serum of <1 : 32. Overt symptoms of meningitis and HIV infection predict a poor outcome. HIV-infected patients typically present with unexplained fevers, headache, and malaise; cryptococcal antigen titers in these patients are often >1 : 1,024. Computed tomography of the brain identifies cryptococcomas in as many as 30% of patients with disseminated infection, even with no clinical signs of CNS involvement. The mortality rate for cryptococcal meningitis is 15-30%, and most deaths occur within several weeks of diagnosis. The fatality rates are higher among HIV-infected patients, who had relapse rates of >50% before the use of lifelong maintenance highly active antiretroviral therapy (HAART). In adults, relapse rates have decreased to <5% with daily fluconazole therapy. Relapse is unusual in adequately treated immunocompetent persons. Postinfectious sequelae are common and include hydrocephalus, decreased visual acuity, deafness, cranial nerve palsies, seizures, and ataxia.

Sepsis Syndrome

Sepsis syndrome is a rare manifestation of cryptococcosis and occurs almost exclusively among HIV-infected patients. Fever is followed by respiratory distress and multiorgan system disease that is often fatal.

Cutaneous Infection

Cutaneous disease most commonly follows disseminated cryptococcosis and rarely local inoculation. Early lesions are erythematous, may be single or multiple, and are variably indurated and tender. Lesions often become ulcerated with central necrosis and raised borders. Cutaneous cryptococcosis in immunocompromised patients can resemble molluscum contagiosum.

Skeletal Infection

Skeletal infection occurs in approximately 5% of patients with disseminated infection but rarely in HIV-infected patients. The onset of symptoms is insidious and chronic. Bone involvement is typified by soft tissue swelling and tenderness, and arthritis is characterized by effusion, erythema, and pain on motion. Skeletal disease is unifocal in approximately 75% of cases. The vertebrae are the most common sites of infection, followed by the tibia, ileum, rib, femur, and humerus. Concomitant bone and joint disease results from contiguous spread.

Ocular Infection

Chorioretinitis is rare, occurs primarily in adults, and is usually a manifestation of disseminated disease, although direct inoculation of the eye has been described. Eye infection is characterized by the acute loss of visual acuity, eye pain, visual floaters, and photophobia. Examination usually reveals choroiditis with or without retinitis. Retinal and vitreal masses and anterior uveitis are seen less commonly. Eye disease is often a manifestation of disseminated infection and is associated with a mortality rate of >20%. Only 15% of survivors recover full vision.

Lymph Nodes

Lymphonodular disease has been reported in 2 children, 1 of whom had an underlying immunodeficiency. Lymphonodular cryptococcosis is characterized by disseminated lymphadenopathy including thoracic and abdominal nodes, subcutaneous lesions, liver granulomas, and concomitant pulmonary disease.

DIAGNOSIS

Recovery of the fungus by culture or demonstration of the fungus in histologic sections of infected tissue is definitive. A latex agglutination test, which detects cryptococcal antigen in serum and CSF, is the most useful diagnostic test. Titers of >1 : 4 in bodily fluid strongly suggest infection, and titers of >1 : 1,024 reflect high burden of yeast, poor host immune response, and greater likelihood of therapeutic failure. India ink preparations of CSF are useful prognostically but are less sensitive than culture and antigen detection. Skin test antigens are poorly characterized, and the sensitivity and specificity of this test are unknown. Serum cryptococcal antibody tests have poor sensitivity and specificity and are generally not helpful in diagnosing cryptococcosis. Cryptococci can grow easily on standard fungal and bacterial culture media. Colonies can be seen within 48-72 hr when grown aerobically at standard temperatures. Polymerase chain reaction tests are in development.

TREATMENT

The choice of treatment depends on the sites of involvement and the host immune status. The immunocompetent patient with asymptomatic or mild disease limited to the lungs may be closely observed without therapy or, alternatively, treated with oral fluconazole (pediatric dose 6-12 mg/kg/day and adult dose 200-400 mg/day) or itraconazole (pediatric dose 5-10 mg/kg/day divided every 12 hr and adult dose 200-400 mg/day) for 3-12 mo, with the duration dependent on clinical response.

Patients with cryptococcemia or severe symptoms and non–HIV-immunocompromised hosts with lung disease with cryptococcal antigen titers of >1 : 8 or with CNS, urinary tract, or cutaneous disease should be treated in a staged approach, because these factors suggest disseminated disease. In general, these patients receive induction therapy with amphotericin B (0.7-1 mg/kg/day) plus flucytosine (100-150 mg/kg/day divided every 6 hr assuming normal kidney function) for a minimum of 2 wk, keeping serum flucytosine concentrations between 40 and 60 µg/mL. Depending on the clinical response, induction therapy may be continued as long as 6-10 wk.

Induction is followed by a consolidation phase with oral fluconazole or itraconazole for 6-12 mo. Itraconazole does not penetrate well into CSF, so consolidation therapy for CNS disease should be accomplished with fluconazole. Lifelong maintenance therapy may be required for children who remain immunocompromised. Lipid-complex amphotericin B (3-6 mg/kg/day) is recommended for patients intolerant of the deoxycholate amphotericin, although experience with this agent in children with cryptococcosis is limited. The current echinocandins do not have clinical activity against cryptococcal infections. Effectiveness of anticryptococcal therapy is monitored by serial cryptococcal antigen testing. Serum or CSF values of ≥1 : 8 predict relapse. Ventriculoperitoneal shunts may be required for patients with hydrocephalus, and aggressive medical management of increased intracranial pressure might also be required.

Because of the high rate of relapse, pulmonary, CNS, or disseminated cryptococcal infections in HIV-infected patients require induction, consolidation, and maintenance therapy. Patients with pulmonary disease most often require lifelong therapy with fluconazole or itraconazole. For those with CNS disease, the most commonly used regimen is amphotericin B (0.7 mg/kg/day) and flucytosine (100 mg/kg/day) for a minimum of 2 wk and as long as 6-10 wk (induction), followed by fluconazole for a minimum of 8-10 wk (consolidation). Fluconazole should be continued for life (maintenance therapy) after the completion of consolidation therapy. Itraconazole should be used only in cases where the patient is intolerant or has failed fluconazole therapy due to the higher relapse rates with itraconazole. Cessation of maintenance therapy in children whose HIV infection is well controlled with HAART has not been well studied to date.

Cutaneous infections are usually treated medically, although surgical biopsy may be required for diagnosis. Skeletal infections generally require surgical debridement in addition to systemic antifungal therapy. Chorioretinitis also requires systemic antifungal therapy with amphotericin B and either fluconazole or flucytosine, both of which achieve high drug concentrations in the vitreous.

PREVENTION

Persons at high risk should avoid exposures such as bird droppings. Effective HAART for persons with HIV infection reduces the risk of cryptococcal disease. Fluconazole prophylaxis is effective for preventing cryptococcosis in patients with AIDS and $CD4^+$ lymphocyte counts <100/µL. A cryptococcal glucuronoxylomannan–tetanus toxoid conjugate vaccine has been developed that elicits protective antibodies in mice but awaits clinical trials in children. Passive immunization with protective monoclonal antibodies has yet to be studied in children.

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Chapter 236

Malassezia

Ashley M. Maranich and Martin E. Weisse

Members of the genus *Malassezia* include the causative agents of **tinea versicolor** (also pityriasis versicolor) (Fig. 236-1) and are associated with other dermatologic conditions and with fungemia in patients with indwelling catheters. *Malassezia* species are commensal lipophilic yeasts with a predilection for the sebum-rich areas of the skin. They are considered a part of the normal skin flora, with presence established by 3-6 mo of age.

The history of *Malassezia* nomenclature is complex and can be confusing. Because the yeast forms may be oval or round, these organisms were formally designated *Pityrosporum ovale* and *Pityrosporum*

Figure 236-1 A young adult with tinea versicolor. Notice the characteristic hypopigmented scaling macules. The asymmetric pattern seen in this patient is not characteristic of all patients with this infection. *(Photo courtesy of Navin S. Arora, DO.)*

orbiculare. Newer technologies have allowed an improved classification system, with 13 recognized species. Only *Malassezia pachydermatis*, a zoophilic yeast that causes dermatitis in dogs, is not lipophilic.

Transformation of the yeast form to a hyphal form facilitates invasive disease. The clusters of thick-walled blastospores together with the hyphae produce the characteristic **spaghetti-and-meatballs** appearance of *Malassezia* species.

Malassezia globosa, *Malassezia sympodialis*, *Malassezia restricta*, and *Malassezia furfur* are the major causes of tinea versicolor (see Chapter 666). *Malassezia* organisms are also increasingly associated with other dermatologic conditions. *M. sympodialis* and *M. globosa* are implicated in neonatal acne, and *M. globosa* and *M. restricta* are most closely associated with seborrheic dermatitis and dandruff. *Malassezia* are also causally associated with scalp psoriasis, *Pityrosporum* folliculitis, and head and neck atopic dermatitis. *Malassezia* may be isolated from sebum-rich areas of asymptomatic persons, emphasizing that demonstration of the fungus does not equate with infection.

The traditional primary **therapy for tinea versicolor** is topical selenium sulfide 2.5% applied daily for at least 10 min for a week, followed by weekly to monthly applications for several months to prevent relapse. Additional topical agents that have efficacy include terbinafine, clotrimazole, and topical azoles. *Malassezia*-associated skin diseases limited to the head and neck can be managed with either 1% ciclopirox, ketoconazole, or zinc pyrithione shampoos.

Oral therapy for tinea versicolor with fluconazole, itraconazole, or ketoconazole is easier to administer but is more expensive, has higher side effect risks, and may be less effective than topical therapy. Various dosing regimens have been used with success, including ketoconazole 200 mg daily for 10 days, fluconazole 300 mg weekly for 2-4 wk, and itraconazole 200 mg daily for 3-7 days or 100 mg daily for 2 wk. Single-dose therapy with 400 mg of ketoconazole has also been used but with lower success rates. Regardless of the regimen chosen, patients should be encouraged to exercise while taking these medications so as to increase the skin concentration of the drug through sweating.

Despite successful treatment, repigmentation might not occur for several months. Relapses are common and can require repeat or alternative therapies.

M. furfur is the species most commonly causing **fungemia**, and *M. pachydermatis* has been implicated in several outbreaks in neonatal intensive care units. The use of lipid emulsions containing medium-chain triglycerides inhibits the growth of *Malassezia* and can prevent infection. Infection is most common in premature infants, although immunocompromised patients, especially those with malignancies, can also be infected. Symptoms of catheter-associated fungemia are indistinguishable from other causes of catheter-associated infections (see Chapter 179) but should be suspected in patients, especially neonates, receiving intravenous lipid infusions. Compared with other causes of fungal sepsis, it is unusual for catheter-related *Malassezia* fungemia to be associated with secondary focal infection.

Malassezia species do not grow readily on standard fungal media, and successful culture requires overlaying the agar with olive oil. Recovery of *Malassezia* from blood culture is optimized by supplementing the medium with olive oil or palmitic acid.

Fungemia caused by *M. furfur* or other species can be successfully treated in most cases by immediately discontinuing the lipid infusion and removing the involved catheter. For persistent or invasive infections, amphotericin B (deoxycholate or lipid-complex formulations), fluconazole, and itraconazole are effective. Flucytosine has no activity against *Malassezia*.

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Chapter 237

Aspergillus

William J. Steinbach

The aspergilli are ubiquitous fungi whose normal ecologic niche is that of a soil saprophyte that recycles carbon and nitrogen. The genus *Aspergillus* contains approximately 185 species, but most human disease is caused by *Aspergillus fumigatus*, *A. flavus*, *A. niger*, *A. terreus,* and *A. nidulans*. Invasive disease is most commonly caused by *A. fumigatus*. *Aspergillus* reproduces asexually via production of spores (conidia). Most cases of *Aspergillus* disease **(aspergillosis)** are a result of inhalation of airborne conidia that subsequently germinate into fungal hyphae and invade host tissue. People are likely exposed to conidia on a daily basis. When inhaled by an immunocompetent person, conidia are rarely deleterious, presumably because they are efficiently cleared by phagocytic cells. Macrophage- and neutrophil-mediated host defenses are required for resistance to invasive disease.

Aspergillus is a relatively unusual pathogen in that it can create very different disease states depending on the host characteristics, including allergic (hypersensitivity), saprophytic (noninvasive), chronic, or invasive disease. Immunodeficient hosts are at risk for invasive disease, whereas immunocompetent hosts tend to develop allergic disease. Disease manifestations include primary allergic reactions; colonization of the lungs or sinuses; localized infection of the lung or skin; chronic infection; invasive pulmonary disease; or widely disseminated disease of the lungs, brain, skin, eye, bone, heart, and other organs. Clinically, these syndromes often manifest with mild, nonspecific, and late-onset symptoms, particularly in the immunosuppressed host, complicating accurate diagnosis and timely treatment. Immunocompromised patients, at risk for invasive disease, include those treated for malignancies with myelosuppressing chemotherapy but may also include those with primary immunodeficiency syndromes. Genetic disorders of immune regulation in the latter group of patients include those with chronic granulomatous disease, STAT3 deficiency (autosomal dominant hyperimmunoglobulin E syndrome), severe congenital neutropenia, monoMAC syndrome (monocytopenia, B and natural killer cell lymphopenia), and leukocyte adhesion deficiency type 1.

237.1 Allergic Disease (Hypersensitivity Syndromes)

William J. Steinbach

ASTHMA

Attacks of atopic asthma can be triggered by inhalation of *Aspergillus* conidia, producing allergic responses and subsequent bronchospasm.

Exposure to fungi, especially *Aspergillus*, needs to be considered as a trigger in a patient with an asthma flare, especially in those patients with severe asthma.

EXTRINSIC ALVEOLAR ALVEOLITIS

Extrinsic alveolar alveolitis is a hypersensitivity pneumonitis that occurs from repetitive inhalational exposure to inciting materials, including *Aspergillus* conidia. Symptoms typically occur shortly after exposure and include fever, cough, and dyspnea. Neither blood nor sputum eosinophilia is present. Chronic exposure to the triggering material can lead to pulmonary fibrosis.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disease resulting from immunologic sensitization to *Aspergillus* antigens. It is primarily seen in patients with asthma or cystic fibrosis. Inhalation of conidia produces noninvasive colonization of the bronchial airways, resulting in persistent inflammation and development of hypersensitivity inflammatory responses. Disease manifestations are a result of abnormal immunologic responses to *A. fumigatus* antigens and include wheezing, pulmonary infiltrates, bronchiectasis, and even fibrosis.

There are 7 primary diagnostic criteria for ABPA: episodic bronchial obstruction, peripheral eosinophilia, immediate cutaneous reactivity to *Aspergillus* antigen, precipitating antibodies to *Aspergillus* antigen, elevated immunoglobulin (Ig) E, pulmonary infiltrates, and central bronchiectasis. Secondary diagnostic criteria include repeated detection of *Aspergillus* from sputum by identification of morphologically consistent fungal elements or direct culture, coughing brown plugs or specks, elevated *Aspergillus* antigen–specific IgE antibodies, and late skin reaction to *Aspergillus* antigen. Radiologically, bronchial wall thickening, pulmonary infiltrates, and central bronchiectasis can be seen.

Treatment depends on relieving inflammation via an extended course of systemic corticosteroids. Addition of oral antifungal agents, such as itraconazole or voriconazole, is used to decrease the fungal burden and diminish the inciting stimulus for inflammation. Because disease activity is correlated with serum IgE levels, these levels are used as 1 marker to define duration of therapy. An area of research interest is the utility of anti-IgE antibody therapy in the management of ABPA.

ALLERGIC *ASPERGILLUS* SINUSITIS

Allergic *Aspergillus* sinusitis is thought to be similar in etiology to ABPA. It has been primarily described in young adult patients with asthma and may or may not be seen in combination with ABPA. Patients often present with symptoms of chronic sinusitis or recurrent acute sinusitis, such as congestion, headaches, and rhinitis, and are found to have nasal polyps and opacification of multiple sinuses on imaging. Laboratory findings can include elevated IgE levels, precipitating antibodies to *Aspergillus* antigen, and immediate cutaneous reactivity to *Aspergillus* antigen. Sinus tissue specimens might contain eosinophils, Charcot-Leyden crystals, and fungal elements consistent with *Aspergillus* species. Surgical drainage is an important aspect of treatment, often accompanied by courses of either systemic or inhaled steroids. Use of an antifungal agent may also be considered.

Bibliography is available at Expert Consult.

237.2 Saprophytic (Noninvasive) Syndromes

William J. Steinbach

PULMONARY ASPERGILLOMA

Aspergillomas are masses of fungal hyphae, cellular debris, and inflammatory cells that proliferate without vascular invasion, generally in the setting of preexisting cavitary lesions or ectatic bronchi. These cavitary lesions can occur as a result of infections such as tuberculosis, histoplasmosis, or resolved abscesses, or secondary to congenital or acquired defects such as pulmonary cysts or bullous emphysema. Patients may be asymptomatic, with diagnosis made through imaging for other reasons, or they might present with hemoptysis, cough, or fever. On imaging, there may be thickening of the walls of a cavity initially, or later, a solid round mass separated from the cavity wall, as the fungal ball develops. Detection of *Aspergillus* antibody in the serum suggests this diagnosis. Treatment is indicated for control of complications, such as hemoptysis. Surgical resection is the definitive treatment but has been associated with significant risks. Systemic antifungal treatment with azole-class agents may be indicated in certain patients.

CHRONIC PULMONARY ASPERGILLOSIS

Chronic aspergillosis can occur in patients with normal immune systems or mild degrees of immunosuppression, including intermittent corticosteroids. Three categories have been proposed to describe different manifestations of chronic aspergillosis. The first is chronic cavitary pulmonary aspergillosis, which is similar to aspergilloma, except that multiple cavities form and expand with occupying fungal balls. The second is chronic fibrosing pulmonary aspergillosis, where the multiple individual lesions progress to significant pulmonary fibrosis. The third is chronic necrotizing pulmonary aspergillosis, also known as *subacute invasive* or *semiinvasive pulmonary aspergillosis*, a slowly progressive subset found in patients with mild to moderate immune impairment.

Management of chronic cavitary pulmonary aspergillosis can sometimes be via surgical resection, although long-term antifungal therapy is indicated. Management of chronic necrotizing pulmonary aspergillosis is similar to that of invasive pulmonary aspergillosis; however, the disease is more indolent, and thus there is a greater emphasis on oral therapy. Direct instillation of antifungals into the lesion cavity has been employed with some success.

SINUSITIS

Sinus aspergillosis typically manifests with chronic sinus symptoms that are refractory to antibacterial treatment. Imaging can demonstrate mucosal thickening in the case of *Aspergillus* sinusitis or a single mass within the maxillary or ethmoid sinus in the case of sinus aspergilloma. If untreated, sinusitis can progress and extend into the ethmoid sinuses and orbits. Therapy of sinusitis depends on surgical debridement and drainage, including surgical removal of the fungal mass in cases of sinus aspergilloma.

OTOMYCOSIS

Aspergillus can colonize the external auditory canal, with possible extension to the middle ear and mastoid air spaces if the tympanic membrane is disrupted by concurrent bacterial infection. Symptoms include pain, itching, decreased unilateral hearing, or otorrhea. Otomycosis is more often seen in patients with impaired mucosal immunity, such as patients with hypogammaglobulinemia, diabetes mellitus, chronic eczema, or HIV and those using chronic steroids. Treatments have not been well studied, but topical treatment with acetic or boric acid instillations or azole creams as well as oral azoles, such as voriconazole, itraconazole, and posaconazole, have been described.

Bibliography is available at Expert Consult.

237.3 Invasive Disease

William J. Steinbach

Invasive aspergillosis (IA) occurs after conidia enter the body, escape immunologic control mechanisms, and germinate into fungal hyphae that subsequently invade tissue parenchyma and vasculature. The invasion of the vasculature can result in thrombosis and localized necrosis and facilitates hematogenous dissemination. The incidence of IA increased over the last 2 decades, likely as a result of more use of

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severely immunosuppressive therapies for a widening array of underlying diseases and better management of other infections found in the at-risk populations. The most common site of primary infection is the lung, but primary infection is also seen in the sinuses and skin, and rarely elsewhere. Secondary infection can be seen after hematogenous spread, often to the skin, central nervous system (CNS), eye, bone, and heart.

IA is primarily a disease of immunocompromised hosts, and common risk factors include cancer or chemotherapy-induced neutropenia, particularly if severe and/or prolonged; hematopoietic stem cell transplantation, especially during the initial preengraftment phase or if complicated by graft-versus-host disease; neutrophil or macrophage dysfunction such as occurs in severe combined immunodeficiency or chronic granulomatous disease (CGD); prolonged high-dose steroid use; solid organ transplantation; and, rarely, HIV. Studies in the pediatric age group have identified similar risk factors for IA, but a well-defined incidence of IA among pediatric patients has not been determined to date.

INVASIVE PULMONARY ASPERGILLOSIS

Invasive pulmonary aspergillosis is the most common form of aspergillosis. It plays a significant role in morbidity and mortality in the patient populations mentioned at increased risk for IA. Presenting symptoms can include fever despite initiation of empirical broad-spectrum antibacterial therapy, cough, chest pain, hemoptysis, and pulmonary infiltrates. Patients on high-dose steroids are less likely to present with fever. Symptoms in these immunocompromised patients can be very vague, and thus maintaining a high index of suspicion when confronted with a high-risk patient is essential.

Diagnosis

Imaging can be helpful, although no finding is pathognomonic for invasive pulmonary aspergillosis. Characteristically, multiple, ill-defined nodules can be seen, though lobar or diffuse consolidation is not uncommon and normal chest radiographs do not rule out disease. Classic radiologic signs on CT during neutropenia include the **halo sign,** when angioinvasion produces a hemorrhagic nodule surrounded by ischemia. Early on there is a rim of ground-glass opacification surrounding a nodule. Over time, these lesions evolve into cavitary lesions or lesions with an **air crescent** when the lung necroses around the fungal mass, often seen during recovery from neutropenia. Unfortunately, these findings are not specific to invasive pulmonary aspergillosis and can also be seen in other pulmonary fungal infections, as well as pulmonary hemorrhage and organizing pneumonia. In addition, several reviews of imaging results of pediatric aspergillosis cases suggest that cavitation and air crescent formation are less common among these patients than among adult patients. Computed tomographic pulmonary angiography demonstrates interruption or invasion of arterial vessels and may enhance the diagnosis of invasive pulmonary aspergillosis (Fig. 237-1). On MRI, the typical finding for

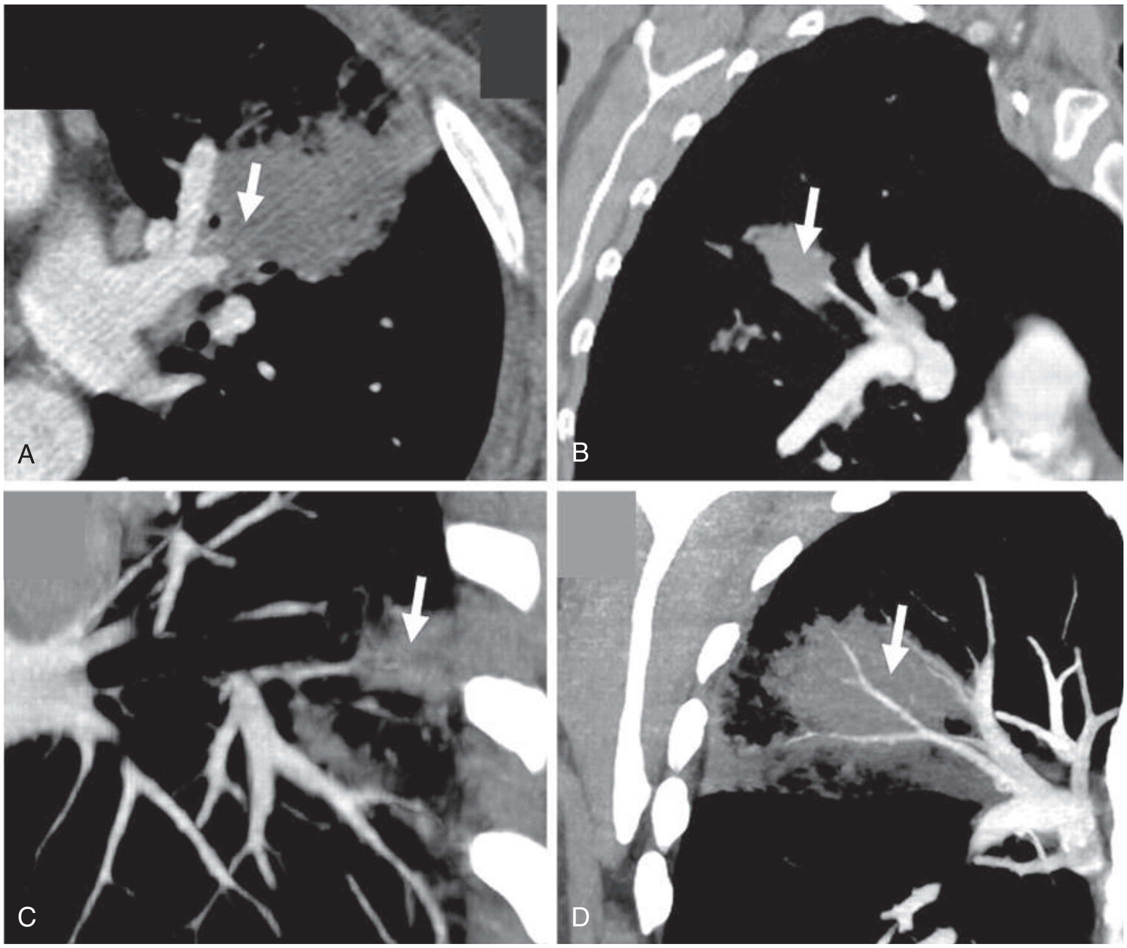

Figure 237-1 **A** and **B,** Representative high-resolution computed tomographic findings for patients with positive CT pulmonary angiographic (CTPA) findings and proven invasive mold disease. **C,** False-positive CTPA findings for a patient with *Staphylococcus aureus* pneumonia with septic emboli. **D,** Negative CTPA findings for a patient with bacterial pneumonia. *Arrows* indicate areas of vessel interruption **(A-C)** or lack of vessel interruption **(D).** *(From Stanzani M, Battista G, Sassi C, et al: Computed tomographic pulmonary angiography for diagnosis of invasive mold diseases in patients with hematological malignancies.* Clin Infect Dis *54:610–616, 2012, Fig.1.)*

pulmonary disease is the **target sign,** in which a nodule has a central signal that is lower than that of the rim-enhancing periphery.

Diagnosis of IA can be complicated for a number of reasons. Conclusive diagnosis requires culture of *Aspergillus* from a normally sterile site and histologic identification of tissue invasion by fungal hyphae consistent with *Aspergillus* morphology. However, obtaining tissue specimens is often impractical in critically ill, often thrombocytopenic, patients. In addition, depending on the specimen type, a positive result from culture can represent colonization rather than infection; however, this should be interpreted conservatively in high-risk patients. Isolation of *Aspergillus* from blood cultures is uncommon, likely because fungemia is low-level and intermittent.

Serology can be useful in the diagnosis of allergic *Aspergillus* syndromes as well as aspergilloma but is of low yield for invasive disease, likely because of deficient immune responses in the high-risk immunocompromised population. Bronchoalveolar lavage can be useful, but negative culture results cannot be used to rule out disease, owing to inadequate sensitivity. Addition of molecular biologic assays such as antigen detection and polymerase chain reaction can improve the diagnostic yield of bronchoalveolar lavage for aspergillosis. An enzyme-linked immunosorbent assay–based assay for galactomannan, one of the components of the *Aspergillus* cell wall, is useful for the diagnosis of IA in serum, bronchoalveolar lavage fluid, and cerebrospinal fluid. This molecular test is best used in serial monitoring for development of infection and is the most sensitive in detecting disease in cancer patients or hematopoietic stem cell transplant recipients, with less utility in solid organ transplant recipients. Earlier reports of increased false-positive reactions in children vs adults have been refuted, and the galactomannan assay is effective in diagnosing IA in children. This test does possess high rates of false negativity in patients with congenital immunodeficiency (e.g., CGD) and invasive *Aspergillus* infections. Another molecular assay, the β-glucan assay, is a fungal-nonspecific assay that detects the major component of the fungal cell wall and has been used to diagnose IA. Unlike the galactomannan assay, which is specific for *Aspergillus*, despite some cross reactivity with other fungi, the β-glucan assay will not discriminate which fungal infection is infecting the patient. Polymerase chain reaction–based assays are in development for the diagnosis of aspergillosis but are still being optimized and are not yet commercially available.

Treatment

Successful treatment of IA hinges on the ability to reconstitute normal immune function and use of effective antifungal agents until immune recovery can be achieved. Therefore, lowering overall immunosuppression, specifically via cessation of corticosteroid use, is vital to improve the ultimate outcome. In 2008, new treatment guidelines for *Aspergillus* infections were published by the Infectious Diseases Society of America, marking a major shift in management recommendations. In the past, first-line therapy was amphotericin B, notable for low response rates and significant infusion reactions and drug toxicity. Liposomal formulations of amphotericin B exist, which are associated with decreased toxicity and may still have a role as first-line therapy for invasive infection in certain patients.

Primary therapy is now the azole-class antifungal voriconazole, based on multiple studies showing both improved response rates and survival in patients receiving voriconazole when compared to amphotericin B. In addition, voriconazole is better tolerated than amphotericin B and can be given orally as well as intravenously. Azoles are metabolized through the cytochrome P450 system, and thus medication interactions can be a significant complication, specifically some contraindications with chemotherapeutic agents. Other triazole antifungals are also available, including posaconazole, which is approved for antifungal prophylaxis and may be an alternative agent for first-line treatment of IA. Although the dosing of itraconazole and voriconazole are established for pediatric patients, the pharmacokinetic studies for posaconazole are not yet complete. Importantly, the dose of voriconazole used in children is higher than that used in adults (see Chapter 233).

The echinocandin class of antifungals may also a play a role in treatment of IA, but to date, these agents are generally employed as second-line medications, particularly for salvage therapy. Combination antifungal therapy has revealed disparate results in anecdotal studies, and currently there are no firm recommendations for combination antifungal therapy. However, it is possible that combination therapy may be beneficial to certain specific patient groups. Unfortunately, even with newer antifungals, complete or partial response rates for treatment of IA are only approximately 50%. To augment antifungal therapies, patients have been treated with growth factors to increase neutrophil counts, granulocyte transfusions, interferon-γ, and surgery.

Special Populations

Patients with CGD represent a pediatric population at particular risk for pulmonary aspergillosis. Invasive pulmonary aspergillosis can be the first serious infection identified in these patients, and the lifetime risk of development is estimated to be 33%. Unlike classical IA in cancer patients, the onset of symptoms is often gradual, with slow development of fever, fatigue, pneumonia, and elevated sedimentation rate. The neutrophils of patients with CGD surround the collections of fungal elements but cannot kill them, thereby permitting local invasion with extension of disease to the pleura, ribs, and vertebrae, although angioinvasion is not seen. Imaging in these patients is much less likely to reveal the halo sign, infarcts, or cavitary lesions and instead generally shows areas of tissue destruction due to the ongoing inflammatory processes.

CUTANEOUS ASPERGILLOSIS

Cutaneous aspergillosis can occur as a primary disease or as a consequence of hematogenous dissemination or spread from underlying structures. Primary cutaneous disease classically occurs at sites of skin disruption, such as intravenous access device locations, adhesive dressings, or sites of injury or surgery. Premature infants are particularly at risk, given their immature skin and need for multiple access devices. Cutaneous disease in transplant recipients tends to reflect hematogenous distribution from a primary site of infection, often the lungs. Lesions are erythematous indurated papules that progress to painful, ulcerated, necrotic lesions. Treatment depends on the combination of surgical debridement and antifungal therapy, with systemic voriconazole recommended as primary therapy.

INVASIVE SINONASAL DISEASE

Invasive *Aspergillus* sinusitis represents a difficult diagnosis because the clinical presentation tends to be highly variable. Patients can present with congestion, rhinorrhea, epistaxis, headache, facial pain or swelling, orbital swelling, fever, or abnormal appearance of the nasal turbinates. Because noninvasive imaging can be normal, diagnosis rests on direct visualization via endoscopy and biopsy. Sinus mucosa may be pale, discolored, granulating, or necrotic depending on the stage and extent of disease. The infection can invade adjacent structures, including the eye and brain. This syndrome is difficult to distinguish clinically from other types of invasive fungal disease of the sinuses such as mucormycosis, rendering obtaining specimens for culture and histology extremely important. *If the diagnosis is confirmed, treatment should be with voriconazole, similar to invasive pulmonary disease. Because voriconazole is not active against mucormycosis, amphotericin B formulations should be considered in invasive fungal sinusitis pending definitive identification.*

CENTRAL NERVOUS SYSTEM

The primary site of *Aspergillus* infection tends to be the lungs, but as the hyphae invade the vasculature, fungal elements can dislodge and travel through the bloodstream, permitting establishment of secondary infection sites. One site commonly involved in disseminated disease is the CNS. Cerebral aspergillosis can also arise secondary to local extension of sinus disease. The presentation of cerebral aspergillosis is highly variable but can include changes in mental status, seizures, paralysis,

coma, and ophthalmoplegia. As the hyphae invade the CNS vasculature, hemorrhagic infarcts develop that convert to abscesses. Biopsy is required for definitive diagnosis, but patients are often too ill to tolerate surgery. Imaging can be helpful for diagnosis, and MRI is preferred. Lesions tend to be multiple, located in the basal ganglia, have intermediate intensity with no enhancement, and have no mass effect. CT shows hypodense, well-demarcated lesions, sometimes with ring enhancement and edema. Diagnosis often depends on characteristic imaging findings in a patient with known aspergillosis at other sites. Galactomannan assay testing of cerebrospinal fluid has been studied and may become a future methodology to confirm the diagnosis. In general, the prognosis for CNS aspergillosis is extremely poor, likely owing to the late onset at presentation. Reversal of immunosuppression is extremely important. Surgical resection of lesions may be useful. *Voriconazole, usually at high doses, is the best therapy, and itraconazole, posaconazole, and liposomal formulations of amphotericin B are alternative options.*

EYE

Fungal endophthalmitis and keratitis may be seen in patients with disseminated *Aspergillus* infection. Pain, photophobia, and decreased visual acuity may be present, though many patients are asymptomatic. Emergent ophthalmologic evaluation is important when these entities are suspected. Endophthalmitis is treated with intravitreal injection of either amphotericin B or voriconazole along with surgical intervention and systemic antifungal therapy with voriconazole. Keratitis requires topical and systemic antifungal therapy.

BONE

Aspergillus osteomyelitis can occur, most commonly in the vertebrae. Rib involvement occurs owing to extension of disease in patients with CGD and is most often caused by *A. nidulans*. Treatment depends on the combination of surgical débridement and systemic antifungals. Arthritis can develop owing to hematogenous dissemination or local extension, and treatment depends on joint drainage combined with antifungal therapy. Amphotericin B has been the most commonly employed agent in the past, although voriconazole is the preferred first-line therapy now.

HEART

Cardiac infection can occur as a result of surgical contamination, secondary to disseminated infection, or as a result of direct extension from a contiguous focus of infection and includes endocarditis, myocarditis, and pericarditis. Treatment requires surgical intervention in the case of endocarditis and pericarditis, along with systemic antifungals, sometimes lifelong because of the possibility of recurrent infection.

EMPIRICAL ANTIFUNGAL THERAPY

Because the diagnosis of invasive *Aspergillus* infections is often complicated and delayed, empirical initiation of antifungal therapy is often considered in high-risk patients. At present, antifungal coverage with amphotericin B (conventional or liposomal), voriconazole, itraconazole, or the echinocandin caspofungin or micafungin should be considered in patients at risk for prolonged neutropenia or with findings suggesting invasive fungal infections. At this time, our ability to diagnose and treat infections caused by *Aspergillus* remains suboptimal. Additional study of antigen detection assays based on galactomannan and other *Aspergillus* cell wall components, as well as standardization of polymerase chain reaction–based assays, will facilitate diagnosis. The optimal treatment remains another challenging question, because current therapeutic regimens tend to produce complete or partial response only approximately half of the time. Novel antifungals currently under development offer a future with hopefully improved survival, but immune reconstitution remains of paramount importance.

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Chapter 238

Histoplasmosis (*Histoplasma capsulatum*)

Jane M. Gould and Stephen C. Aronoff

ETIOLOGY

Histoplasmosis is caused by *Histoplasma capsulatum,* a dimorphic fungus found in the environment as a saprophyte in the mycelial (mold) form and in tissues in the parasitic form as yeast.

EPIDEMIOLOGY

The saprophytic form is found in soil throughout the midwestern United States, primarily along the Ohio and Mississippi rivers. Sporadic cases of human and animal histoplasmosis have been reported from 31 of the 48 contiguous states. In parts of Kentucky and Tennessee, almost 90% of the population older than 20 yr of age have positive skin test results for histoplasmin. *Histoplasma* is endemic to parts of the Caribbean islands, Central and South America, certain areas of Southeast Asia, and the Mediterranean. *H. capsulatum* thrives in soil rich in nitrates such as areas that are heavily contaminated with bird or bat droppings or decayed wood. Fungal spores are often carried on the wings of birds. Focal outbreaks of histoplasmosis have been reported after aerosolization of microconidia resulting from construction in areas previously occupied by starling roosts or chicken coops or by chopping decayed wood or burning bamboo exposed to a blackbird roost. Unlike birds, bats are actively infected with *Histoplasma.* Focal outbreaks of histoplasmosis have also been reported after intense exposure to bat guano in caves and along bridges frequented by bats. Person-to-person transmission does not occur.

PATHOGENESIS

Inhalation of microconidia (fungal spores) is the initial stage of human infection. The conidia reach the alveoli, germinate, and proliferate as yeast. Alternatively, spores can remain as mold with the potential for activation. Most infections are asymptomatic or self-limited. When disseminated disease occurs, any organ system can be involved. The initial infection is a bronchopneumonia. As the initial pulmonary lesion ages, giant cells form, followed by formation of caseating or noncaseating granulomas and central necrosis. Granulomas contain viable yeast, and disease can relapse. At the time of spore germination, yeast cells are phagocytosed by alveolar macrophages, where they replicate and gain access to the reticuloendothelial system via the pulmonary lymphatic system and hilar lymph nodes. Dissemination with splenic involvement typically follows the primary pulmonary infection. In normal hosts, specific cell-mediated immunity follows in approximately 2 wk, enabling sensitized T cells to activate macrophages and kill the organism. The initial pulmonary lesion resolves within 2-4 mo but may undergo calcification resembling the Ghon complex of tuberculosis. Alternatively, "buckshot" calcifications involving the lung and spleen may be seen. Unlike tuberculosis, reinfection with *H. capsulatum* occurs and can lead to exaggerated host responses in some cases.

Children with certain primary congenital immune defects are at increased risk of histoplasmosis; these include interferon-γR1 deficiency, interleukin-12Rβ1 deficiency, *STAT1* gain-of-function mutations, idiopathic CD4 lymphopenia, DOCK8 deficiency, X-linked CD4OL deficiency, and monoMAC syndrome (monocytopenia, B-cell and natural killer cell lymphoma).

CLINICAL MANIFESTATIONS

There are 3 forms of human histoplasmosis: acute pulmonary infection, chronic pulmonary histoplasmosis, and progressive disseminated histoplasmosis.

Acute pulmonary histoplasmosis follows initial or recurrent respiratory exposure to microconidia. The majority of patients are asymptomatic. Symptomatic disease occurs more often in young children; in older patients, symptoms follow exposure to large inocula in closed spaces (e.g., chicken coops or caves) or prolonged exposure (e.g., camping on contaminated soil, chopping decayed wood). The median incubation time is 14 days. The prodrome is not specific and usually consists of flu-like symptoms including headache, fever, chest pain, cough, and myalgias. Hepatosplenomegaly occurs more often in infants and young children. Symptomatic infections may be associated with significant respiratory distress and hypoxia and can require intubation, ventilation, and steroid therapy. Acute pulmonary disease can also manifest with a prolonged illness (10 days to 3 wk) consisting of weight loss, dyspnea, high fever, asthenia, and fatigue. In 10% of patients, infection is a sarcoid-like disease with arthritis or arthralgia, erythema nodosum, keratoconjunctivitis, iridocyclitis, and pericarditis. Pericarditis, with effusions both pericardial and pleural, is a self-limited benign condition that develops as a result of an inflammatory reaction to adjacent mediastinal disease. The effusions are exudative, and the organism is rarely culturable from fluid. Most children with acute pulmonary disease have normal chest radiographs. Patients with symptomatic disease typically have a patchy bronchopneumonia; hilar lymphadenopathy is variably present (Fig. 238-1). In young children, the pneumonia can coalesce. Focal or buckshot calcifications are convalescent findings in patients with acute pulmonary infection.

Exaggerated host responses to fungal antigens within the lung parenchyma or hilar lymph nodes produce thoracic complications of acute pulmonary histoplasmosis. Histoplasmomas are of parenchymal origin and are usually asymptomatic. These fibroma-like lesions are often concentrically calcified and single. Rarely, these lesions produce broncholithiasis associated with "stone spitting," wheezing, and hemoptysis. In endemic regions, these lesions can mimic parenchymal tumors and are occasionally diagnosed at lung biopsy. Mediastinal granulomas form when reactive hilar lymph nodes coalesce and mat together. Although these lesions are usually asymptomatic, huge granulomas can compress the mediastinal structures, producing symptoms of esophageal, bronchial, or vena caval obstruction. Local extension and necrosis can produce pericarditis or pleural effusions. Mediastinal fibrosis is a rare complication of mediastinal granulomas and represents an uncontrolled fibrotic reaction arising from the hilar nodes. Structures within the mediastinum become encased within a fibrotic mass, producing obstructive symptomatology. Superior vena cava syndrome, pulmonary venous obstruction with a mitral stenosis–like syndrome, and pulmonary artery obstruction with congestive heart failure have been described. Dysphagia accompanies esophageal entrapment, and a syndrome of cough, wheeze, hemoptysis, and dyspnea accompanies bronchial obstruction.

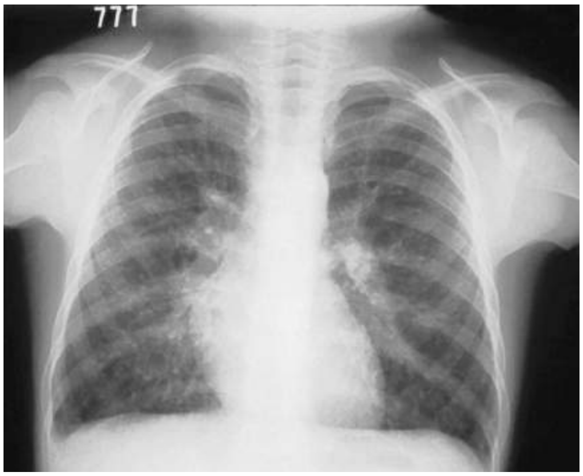

Figure 238-1 Radiograph of an 8 yr old child with acute pulmonary histoplasmosis showing hilar enlargement with bilateral infiltrates. *(From Fischer GB, Mocelin H, Severo CB, et al: Histoplasmosis in children.* Paediatr Respir Rev *10:172–177, 2009, Fig. 1.)*

Chronic pulmonary histoplasmosis is an opportunistic infection in adult patients with centrilobular emphysema. This entity is rare in children.

Progressive disseminated histoplasmosis accounts for 10% of histoplasmosis cases and affects infants and immunocompromised patients. Disseminated disease of childhood occurs almost exclusively in children younger than 2 yr of age because of a relatively immature cellular immune system and follows primary pulmonary infection. The mortality of progressive disseminated histoplasmosis without therapy is 100%. Fever is the most common finding and can persist for weeks to months before the condition is diagnosed. The majority of patients have hepatosplenomegaly, lymphadenopathy, anemia, and thrombocytopenia. Pneumonia and pancytopenia are variably present. Some patients develop mucous membrane ulcerations and skin findings such as nodules, ulcers, or molluscum-like papules. Half of the infected infants have transient T-cell deficiencies, and many experience transient hyperglobulinemia. Elevated acute-phase reactants and hypercalcemia are typically seen but are not specific for disseminated histoplasmosis. Although chest radiographs are normal in more than half of these children, the yeast can often be identified on bone marrow examination.

Children who are immunosuppressed (cancer patients, organ transplant recipients, patients with HIV infection) are at increased risk for disseminated histoplasmosis. In children who are not infected with HIV, disseminated disease manifests with unexplained fevers, weight loss, lymphadenopathy, and interstitial pulmonary disease. Extrapulmonary infection is a characteristic of disseminated disease and can include destructive bony lesions, oropharyngeal ulcers, Addison disease, meningitis, multifocal chorioretinitis, cutaneous infection, and endocarditis. Elevated liver function test results and high serum concentrations of angiotensin-converting enzyme may be observed.

Disseminated histoplasmosis in an HIV-infected patient is an AIDS-defining illness. Disseminated disease is often preceded or followed by another opportunistic infection in this patient population. HIV-infected patients at greatest risk for acquiring disseminated histoplasmosis are those with a history of exposure to avian excreta or bat guano, no prior history of antiretroviral therapy, or no history of previous antifungal prophylaxis. Fever and weight loss occur in most patients. In the majority of patients, pulmonary disease develops; hepatosplenomegaly, lymphadenopathy, skin rashes, and meningoencephalitis are variably present. A sepsis-like syndrome has been identified in a small number of HIV-infected patients with disseminated histoplasmosis and is characterized by the rapid onset of shock, multiorgan failure, and coagulopathy. Reactive hemophagocytic syndrome has been described in immunocompromised patients with severe disseminated histoplasmosis. Transplacental transmission of *H. capsulatum* has been reported in immunocompromised mothers.

DIAGNOSIS

Histoplasma typically grows within 6 wk on Sabouraud agar at 25°C (77°F). Identification of tuberculate macroconidia allows for only a presumptive diagnosis, because *Sepedonium* species form similar structures. A confirmatory test using a chemiluminescent DNA probe for *H. capsulatum* is necessary to establish a definitive identification. Recovery of *H. capsulatum* by culture differs with the form of infection. In normal hosts with symptomatic or asymptomatic acute pulmonary histoplasmosis, sputum cultures are rarely obtained and are variably positive; cultures of bronchoalveolar lavage fluid appear to have a slightly higher yield than sputum cultures. Sputum cultures are positive in 60% of adults with chronic pulmonary histoplasmosis. The yeast can be recovered from blood or bone marrow in >90% of patients with progressive disseminated histoplasmosis. Blood cultures are sterile in patients with acute pulmonary histoplasmosis, and cultures from any source are typically sterile in patients with the sarcoid form of the

disease. Yeast forms may be demonstrated histologically in tissue from patients with complicated forms of acute pulmonary disease (histoplasmoma, mediastinal granuloma, and mediastinal fibrosis). Tissue should be stained with methenamine silver or periodic acid–Schiff stains, and yeast can be found within or outside of macrophages. Wright stain of peripheral blood can demonstrate fungal elements within leukocytes. Real-time polymerase chain reaction has been used on formalin-fixed, paraffin-embedded biopsy tissue and has an analytical sensitivity of at least 6 pg/µL from tissue-extracted DNA and a clinical sensitivity and specificity of 88.9% and 100%, respectively. Although not widely available, molecular methods may ultimately provide a more timely and accurate diagnosis.

Detection of fungal polysaccharide antigen by radioimmunoassay is the most widely available diagnostic study for patients with suspected progressive disseminated histoplasmosis. In HIV-infected patients as well as others at risk for disseminated disease, histoplasma-associated antigen can be demonstrated in the urine, blood, or bronchoalveolar lavage fluid in more than 90% of cases. Antigenuria has been shown to correlate with severity of disseminated histoplasmosis. The likelihood of hospitalization was 2.75 and need for intensive care was 3.11 if the antigen was ≥19 ng/mL. Additionally, antigenuria was present in 83% of patients with acute disease and 30% of patients with subacute pulmonary disease. False-positive results on urinary antigen testing can occur in patients with *Blastomyces dermatitidis, Coccidioides immitis* and *Coccidioides posadasii, Paracoccidioides brasiliensis,* and *Penicillium marneffei*. False-positive results on serum antigen testing can occur in the presence of rheumatoid factor and following treatment with rabbit antithymocyte globulin. Antigen detection by enzyme immunoassay has comparable sensitivity and improved specificity but limited availability; however, both the radioimmunoassay and the enzyme immunoassay are more sensitive when urine is tested rather than serum. Serum, urine, and bronchoalveolar lavage fluid from patients with acute or chronic pulmonary infections are variably antigen positive. Sequential measurement of antigen in patients with disseminated disease is useful for monitoring response to therapy.

Seroconversion continues to be useful for the diagnosis of acute pulmonary histoplasmosis, its complications, and chronic pulmonary disease. Serum antibody to yeast and mycelium-associated antigens is classically measured by complement fixation. Although titers of >1 : 8 are found in more than 80% of patients with histoplasmosis, titers of ≥1 : 32 are most significant for the diagnosis of recent infection. Complement-fixation antibody titers are often not significant early in the infection and do not become positive until 4-6 wk after exposure. A 4-fold increase in either yeast or mycelial-phase titers or a single titer of ≥1 : 32 is presumptive evidence of active infection. Complement-fixation titers may be falsely positive in patients with other systemic mycoses such as *B. dermatitidis* and *C. immitis* and may be falsely negative in immunocompromised patients. Antibody detection by immunodiffusion is less sensitive but more specific than complement fixation and is used to confirm questionably positive complement-fixation titers. The highest sensitivity for antibody testing can be achieved by combining complement fixation and immunodiffusion testing. Skin testing is useful only for epidemiologic studies because cutaneous reactivity is lifelong, and intradermal injection can elicit an immune response in otherwise seronegative persons.

TREATMENT

Antifungal therapy is not warranted for persons with asymptomatic or mildly symptomatic acute pulmonary histoplasmosis. Oral itraconazole or fluconazole should be considered in patients with acute pulmonary infections who fail to improve clinically within 1 mo. Itraconazole is superior to fluconazole in treatment of histoplasmosis in adults. Patients with primary or reexposure pulmonary histoplasmosis who become hypoxemic or require ventilatory support should receive amphotericin B (0.7-1.0 mg/kg/day) or amphotericin B lipid complex (3-5 mg/kg/day) until improved; continued therapy with oral itraconazole (5-10 mg/kg/day in 2 divided doses, not to exceed 400 mg daily) for a minimum of 12 wk is also recommended. The lipid preparations of amphotericin are not preferred. Patients with severe obstructive symptoms caused by granulomatous mediastinal disease may be treated sequentially with amphotericin B followed by itraconazole for 6-12 mo. Patients with milder mediastinal disease may be treated with oral itraconazole alone. Some experts recommend that surgery be reserved for patients who fail to improve after 1 mo of intensive amphotericin B therapy. Sarcoid-like disease with or without pericarditis may be treated with nonsteroidal antiinflammatory agents for 2-12 wk.

Amphotericin B continues to be the cornerstone of therapy for infants with progressive disseminated histoplasmosis. In one study, sequential therapy with amphotericin B and oral ketoconazole for 3 mo was curative in 88% of patients. Alternatively, amphotericin B (1 mg/kg/day) or its lipid complex may be given acutely for 4-6 wk or amphotericin B (1 mg/kg/day) may be given for 2-4 wk followed by oral itraconazole (5-10 mg/kg/day in 2 divided doses) as maintenance therapy for 3 mo, depending on *Histoplasma* antigen status. Longer therapy may be needed in patients with severe disease, immunosuppression, or primary immunodeficiency syndromes. It is recommended to monitor blood levels of itraconazole during treatment, aiming for a concentration of ≥1 µg/mL but <10 µg/mL to avoid potential drug toxicity. It is also recommended to monitor urine antigen levels during therapy and for 12 mo after therapy has ended to ensure cure. In general, amphotericin B lipid complex may be substituted in severely ill children who are intolerant of the classic drug preparation. The newer azoles (voriconazole and posaconazole) have not been well studied in the treatment of histoplasmosis and are currently not recommended.

Relapses in HIV-infected patients with progressive disseminated histoplasmosis are common. Currently, induction therapy with amphotericin B or lipid complex amphotericin B is recommended. Lifelong suppressive therapy with daily itraconazole (5 mg/kg/day up to adult dose of 200 mg/day) is also required. For severely immunocompromised HIV-infected children living in endemic regions, itraconazole (2-5 mg/kg every 12-24 hr) may be used prophylactically. Care must be taken to avoid interactions between antifungal azoles and protease inhibitors.

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Chapter 239

Blastomycosis (*Blastomyces dermatitidis*)

Gregory M. Gauthier and Bruce S. Klein

ETIOLOGY

Blastomyces dermatitidis belongs to a group of fungi that exhibit thermal dimorphism. In the soil (22-25°C [71.6-77°F]), these fungi grow as mold and produce spores, which are the infectious particles. Following soil disruption, aerosolized mycelial fragments and spores inhaled into the lungs (37°C [98.6°F]) convert into pathogenic yeast and cause infection.

EPIDEMIOLOGY

B. dermatitidis causes disease in immunocompetent and immunocompromised children. Only 2-13% of blastomycosis cases occur in the pediatric population (average age: 9.1-11.5 yr; range: 19 days to 18 yr). Blastomycosis of newborns and infants is rare. In North America, the geographic distribution of blastomycosis cases is restricted to the Midwest, South-Central, and Southeastern United States and parts of

Canada bordering the Great Lakes and Saint Lawrence River Valley. In these geographic regions, several areas are hyperendemic for blastomycosis (e.g., Marathon and Vilas Counties, Wisconsin; Washington Parish, Louisiana; central and south-central Mississippi; Kenora, Ontario). Outside of North America, autochthonous infections have been reported from Africa (~100 cases) and India (<12 cases). *B. dermatitidis* is not endemic to the Middle East, Central America, South America, Europe, Asia, or Australia. In North America, *B. dermatitidis* grows in an ecologic niche characterized by forested, sandy soils with an acidic pH that have decaying vegetation and are near water. Most *B. dermatitidis* infections are sporadic; however, 15 outbreaks have been reported and most have involved pediatric patients. Outbreaks are associated with outdoor activities (camping, hiking, fishing); nonetheless some outbreaks have no identifiable risk factors other than geography. The severity of infection is influenced by the size of the inhaled inoculum and the integrity of the patient's immune system. Those immunosuppressed by solid organ transplantation, AIDS, and tumor necrosis factor-α inhibitors are at risk for developing severe or disseminated infection.

PATHOGENESIS

The ability of mycelial fragments and spores to convert to yeast in the lung is a crucial event in the pathogenesis of infection with *B. dermatitidis* and other dimorphic fungi. This conversion, which is known as the phase transition, enables *B. dermatitidis* to evade the host immune system and establish infection. In the yeast form, *B. dermatitidis* produces BAD1 (B*lastomyces ad*hesin-1; formerly WI-1), an essential virulence factor that is secreted into the extracellular milieu and binds back to chitin on the fungal cell wall. BAD1 promotes binding of yeast to macrophages in lung alveoli, blocks the deposition of complement on the yeast surface, binds calcium, and suppresses the production of proinflammatory cytokines such as tumor necrosis factor-α in the host.

The phase transition from mold to yeast is a complex event that involves alteration in cell wall composition, metabolism, intracellular signaling, and gene expression. In *B. dermatitidis*, this transition is regulated, in part, by a histidine kinase known as *DRK1* (*d*imorphism *r*egulating *k*inase-1). This sensor kinase controls not only the conversion of mold to yeast but also spore production, cell wall composition, and *BAD-1* expression; the loss of *DRK1* expression through gene disruption renders *B. dermatitidis* avirulent in a murine model of blastomycosis.

The phase transition is reversible and following a drop in temperature from 37°C (98.6°F) to 22°C (71.6°F), *B. dermatitidis* yeast convert to sporulating mold. Growth as mold promotes survival in the soil, allows for sexual reproduction to enhance genetic diversity, and facilitates transmission to new hosts. The transition from yeast to mold is influenced by *SREB* (siderophore biosynthesis repressor in *Blastomyces*), which encodes a transcription factor. Deletion of *SREB* results in the failure of *B. dermatitidis* yeast to complete the conversion to mold.

Innate and adaptive immune systems are required to effectively control *B. dermatitidis* infection; humoral immunity is dispensable. Macrophages and neutrophils are capable of ingesting and killing *B. dermatitidis* conidia. In contrast, yeast are poorly killed by nonactivated macrophages, are resistant to reactive oxygen species, and suppress nitric oxide production. Adaptive immunity is mediated by T lymphocytes (Th1 and Th17), which activate macrophages and neutrophils to facilitate clearance of infection. Following infection, cell-mediated immunity against *B. dermatitidis* can last for at least 2 yr.

CLINICAL MANIFESTATIONS

The clinical manifestations of blastomycosis are diverse and include subclinical infection, symptomatic pneumonia, and disseminated disease. Clinical disease develops 3 wk to 3 mo following exposure to *B. dermatitidis*. Asymptomatic or subclinical infections are estimated to occur in 50% of patients.

The most common clinical manifestation of blastomycosis is pneumonia, which can range from acute to chronic. Acute symptoms resemble community-acquired pneumonia and include fever, dyspnea, cough, chest pain, and malaise. Respiratory failure, including acute respiratory distress syndrome, can occur in patients with an overwhelming burden of infection. Chest imaging typically demonstrates air space consolidation, which can involve the upper or lower lobes. Other radiographic features include nodular, reticulonodular, and miliary patterns. Hilar adenopathy and pleural effusions are uncommon. Because the clinical and radiographic features can mimic bacterial pneumonia, patients can be mistakenly treated with antibiotics, resulting in disease progression. Patients with subacute or chronic pneumonia also present with fevers, chills, night sweats, cough, weight loss, hemoptysis, dyspnea, and chest pain. Air space consolidation, mass lesions, or cavitary disease can be present on chest roentgenography. These features can mimic tuberculosis or malignancy.

Extrapulmonary blastomycosis most often affects the skin or bone but can involve almost any organ. The incidence of extrapulmonary disease in children ranges from 38-50%, which is similar to rates in adult patients (25-40%). The skin is the most common site for extrapulmonary blastomycosis, which is usually the result of hematogenous dissemination. Direct inoculation of *B. dermatitidis* into the skin from trauma or a laboratory accident can result in primary cutaneous blastomycosis. Skin manifestations include plaques, papules, ulcers, nodules, and verrucous lesions. Erythema nodosum is rare in blastomycosis. Dissemination of *B. dermatitidis* to the bone results in lytic destruction, pain, soft tissue swelling, sinus tract formation, and ulceration. The ribs, skull, spine, and long bones are most commonly affected. Patients with osteomyelitis often have pulmonary or cutaneous involvement. Vertebral osteomyelitis can be complicated by paraspinal abscess, psoas abscess, and vertebral body collapse. Extension of long bone osteomyelitis can result in pathologic fracture or septic arthritis. Genitourinary blastomycosis occurs in 10-30% of adults but is rare in children.

Blastomycosis of the central nervous system occurs in <10% of immunocompetent patients and can result in brain abscess or meningitis. Some patients with central nervous system blastomycosis have widely disseminated disease. Symptoms include headache, altered mental status, memory loss, seizure, cranial nerve deficits, and focal neurologic deficits. Complications include hydrocephalus, cerebral herniation, infarction, panhypopituitarism, residual weakness, and poor functioning in school. Lumbar puncture demonstrates leukocytosis with a neutrophil or lymphocyte predominance, elevated protein, and low glucose. Growth of *B. dermatitidis* in culture from cerebral spinal fluid occurs in less than 50% of affected patients.

Blastomycosis can complicate pregnancy, and clinical information is limited to case reports. Disseminated infection involving the lungs, skin, and bone is common. Spread of infection to the placenta has been documented by histopathology; however, the frequency of placental blastomycosis remains unknown. Transmission of *B. dermatitidis* to the fetus may involve transplacental transmission or aspiration of infected vaginal secretions. Although clinical data are limited, blastomycosis during pregnancy does not appear to increase the risk for congenital malformations.

DIAGNOSIS

The diagnosis of blastomycosis requires a high index of suspicion, because the clinical and radiographic manifestations can mimic other diseases including community-acquired pneumonia, tuberculosis, and malignancy. Blastomycosis should be included in the differential diagnosis for patients with pneumonia who live in or visit areas in which this pathogen is endemic, fail to respond to antibiotics, or have chronic skin lesions or osteomyelitis. A detailed medical history regarding exposure risks (e.g., canoeing, hiking, fishing, playing in outdoor forts, beaver dam exploration, home remodeling, nearby road or commercial construction, use of a woodpile for a wood burning stove) should be obtained. In addition, the health of family pets such as dogs should also be ascertained, as **canine disease** may be a harbinger of human infection. The incidence of blastomycosis in dogs is 10-fold higher than in humans, and canine infection suggests a common source of exposure.

Growth of *B. dermatitidis* in culture from sputum, skin, bone, or other clinical specimens provides a definitive diagnosis. Sputum specimens should be stained with 10% potassium hydroxide or calcofluor white. Histopathology shows neutrophilic infiltration with noncaseating granulomas (pyogranulomas). *B. dermatitidis* yeast in tissue samples can be visualized using Gomori methenamine silver or peri-

odic acid–Schiff stains. Yeasts are 8-20 µm in size, have a double refractile cell wall, and display broad-based budding.

Nonculture diagnostic techniques should be used in conjunction with fungal smears and cultures to facilitate the diagnosis of blastomycosis. The development of a *Blastomyces* antigen test has supplanted insensitive serologic methods such as complement fixation and immunodiffusion. Urine, serum, cerebrospinal fluid, and bronchoalveolar fluid specimens can be collected for the *Blastomyces* antigen test. Sensitivity of the urine antigen test ranges from 85.1-92.9% and is influenced by the burden of infection. The antigen test can crossreact with other dimorphic fungi including *Histoplasma capsulatum, Paracoccidioides brasiliensis,* and *Penicillium marneffei*, which decreases the specificity to 76.9-79%. An antibody test against the BAD1 protein has been developed with a sensitivity of 87.8% and a specificity of 94-99%. Combination antigen and BAD1 antibody testing can increase diagnostic sensitivity to 97.6%.

TREATMENT

Antifungal therapy is influenced by the severity of the infection, involvement of the central nervous system, the integrity of the host's immune system, and pregnancy. All persons diagnosed with blastomycosis should receive antifungal therapy. Newborns with blastomycosis should be treated with amphotericin B deoxycholate 1 mg/kg/day. Children with mild to moderately severe infection can be treated with itraconazole 10 mg/kg/day (maximum: 400 mg/day) for 6-12 mo. Children with severe disease or underlying immunodeficiency or immunosuppression should be treated with amphotericin B deoxycholate 0.7-1.0 mg/kg/day or lipid amphotericin B 3-5 mg/kg/day until there is clinical improvement, generally 7-14 days, and then itraconazole 10 mg/kg/day (maximum: 400 mg/day) for a total of 12 mo. Central nervous system blastomycosis requires therapy with lipid amphotericin B 5 mg/kg/day for 4-6 wk followed by itraconazole, fluconazole, or voriconazole for ≥12 mo.

All pediatric patients of childbearing age should undergo pregnancy testing prior to initiation of azole antifungals. Itraconazole can increase the risk for spontaneous abortion and fluconazole can cause craniofacial defects resembling Antley-Bixler syndrome. Voriconazole and posaconazole cause skeletal abnormalities in animal models. Treatment of blastomycosis in pregnant patients consists of lipid amphotericin B 3-5 mg/kg/day.

For patients receiving itraconazole, the oral antifungal of choice, serum drug levels need to be measured 14 days into therapy (goal ≥1 µg/mL) and liver function tests should be monitored periodically. The newest azole antifungal drugs, voriconazole and posaconazole, have activity against *B. dermatitidis*; however, clinical experience with these drugs remains limited. The echinocandins (caspofungin, micafungin, and anidulafungin) should not be used to treat blastomycosis. Serial measurement of urine antigen levels to assess response to therapy appears promising, but the clinical usefulness of this strategy remains to be determined.

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Chapter 240
Coccidioidomycosis (*Coccidioides* Species)

Martin B. Kleiman

ETIOLOGY

Coccidioidomycosis (valley fever, San Joaquin fever, desert rheumatism, coccidioidal granuloma) is caused by *Coccidioides* spp., a soil-dwelling dimorphic fungi. *Coccidioides* spp. grow in the environment as spore-bearing (arthroconidia-bearing) mycelial forms. In their parasitic form, they appear as unique, endosporulating spherules in infected tissue. The 2 recognized species, *C. immitis* and *C. posadasii,* cause similar illnesses.

EPIDEMIOLOGY

Coccidioides spp. inhabit soil in arid regions. *C. immitis* is primarily found in California's San Joaquin Valley. *C. posadasii* is endemic to southern regions of Arizona, Utah, Nevada, New Mexico, western Texas and regions of Mexico and Central and South America.

Population migrations into endemic areas and increasing numbers of immunosuppressed persons have caused coccidioidomycosis to become an important health problem. Infection rates increased from 2000-2007. Approximately 150,000 newly reported infections occur annually in the United States. Coccidioidin skin test positivity in 5-7 yr old students in a highly endemic area demonstrated a decline from 10% to 2% in a 58 yr period ending in 2000. During 2002, 153 children required hospitalization for coccidioidomycosis, and infection was fatal in 9% of cases.

Infection results from inhalation of aerosolized spores. Incidence increases during windy, dry periods that follow rainy seasons. Seismic events, archaeologic excavations, and other activities that disturb contaminated sites have caused outbreaks. Person-to-person transmission does not occur. Rarely, infections result from spores that contaminate fomites or grow beneath casts or wound dressings of infected patients. Infection has also resulted from transplantation of organs from infected donors and from mother to fetus or newborn. Visitors to endemic areas can acquire infections, and diagnosis may be delayed when they are evaluated in nonendemic areas. Spores are highly virulent, and *Coccidioides* spp. are potential agents of bioterrorism (see Chapter 723).

PATHOGENESIS

Inhaled spores reach terminal bronchioles, where they transform into septated spherules that resist phagocytosis and within which many endospores develop. Released endospores transform into new spherules, and the process results in an acute focus of infection. Endospores can also disseminate lymphohematogenously. Eventually, a granulomatous reaction predominates. Both recovery and protection upon reexposure depend on effective cellular immunity.

Children with congenital primary immunodeficiency disorders may be at increased risk for infection; these disorders include interleukin-12Rβ1 deficiency, interferon-γR1 deficiency, and *STAT1* gain-of-function mutations.

CLINICAL MANIFESTATIONS

The clinical spectrum (Fig. 240-1) encompasses pulmonary and extrapulmonary disease. Pulmonary infection occurs in 95% of cases and can be divided into primary, complicated, and residual infections. Approximately 60% of infections are asymptomatic. Symptoms in children are milder than those in adults. The incidence of extrapulmonary dissemination in children approaches that of adults.

Primary Coccidioidomycosis

The incubation period is 1-4 wk, with an average of 10-16 days. Early symptoms include malaise, chills, fever, and night sweats. Chest

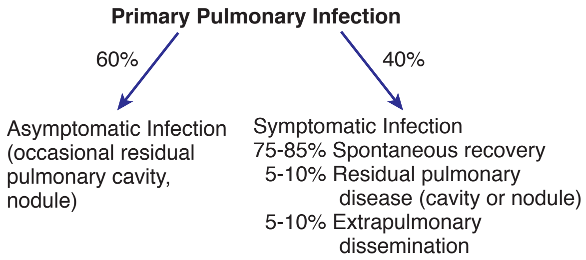

Figure 240-1 Natural history of coccidioidomycosis.

Figure 240-2 Chest radiograph of a 19 yr old man with acute primary coccidioidomycosis. There is prominent hilar lymphadenopathy and mediastinal widening.

discomfort occurs in 50-70% of patients and varies from mild tightness to severe pain. Headache and/or backache are sometimes reported. An evanescent, generalized, fine macular erythematous or urticarial eruption may be seen within the 1st few days of infection. Erythema nodosum can occur (more often in women) and is sometimes accompanied by an erythema multiforme rash, usually 3-21 days after the onset of symptoms. The clinical constellation of erythema nodosum, fever, chest pain, and arthralgias (especially knees and ankles) has been termed *desert rheumatism* and *valley fever*. The chest examination is often normal even if radiographic findings are present. Dullness to percussion, friction rub, or fine rales may be present. Pleural effusions can occur and can become large enough to compromise respiratory status. Hilar and mediastinal lymphadenopathy are common (Fig. 240-2).

Complicated Pulmonary Infection

Complicated infections include severe and persistent pneumonia, progressive primary coccidioidomycosis, progressive fibrocavitary disease, transient cavities that develop in areas of pulmonary consolidation, and empyema that follows rupture of a cavity into the pleural space. Some cavities persist, are thin walled and peripheral, and cause no symptoms; occasionally there is mild hemoptysis, and rarely there is serious hemorrhage. Rarely, acute respiratory insufficiency occurs following intense exposure; this is associated with high mortality rates.

Residual Pulmonary Coccidioidomycosis

Residual pulmonary coccidioidomycosis includes fibrosis as well as persisting pulmonary nodules. Nodules are present in 5-7% of infections and sometimes require differentiation from malignancy.

Disseminated (Extrapulmonary) Infection

Clinically apparent dissemination occurs in 0.5% of patients. Its incidence is increased in infants; men; persons of Filipino, African, and Latin American ancestry; and persons from other Asian backgrounds. Primary or acquired disorders of cellular immunity (Table 240-1) markedly increase the risk of dissemination.

Table 240-1	Risk Factors for Poor Outcome in Patients with Active Coccidioidomycosis
PRIMARY INFECTIONS	
Severe, prolonged (≥6 wk), or progressive infection	
RISK FACTORS FOR EXTRAPULMONARY DISSEMINATION	
Primary or acquired cellular immune dysfunction (including patients receiving tumor necrosis factor inhibitors)	
Neonates, infants, the elderly	
Male sex (adult)	
Filipino, African, Native American, or Latin American ethnicity	
Late-stage pregnancy and early postpartum period	
Standardized complement fixation antibody titer >1 : 16 or increasing titer with persisting symptoms	
Blood group B	
Human leukocyte antigen (HLA) class II allele-DRBI*1301	

Symptoms usually occur within 6 mo of primary infection. Prolonged fever, toxicity, skin lesions, subcutaneous and/or osseous cold abscesses, and laryngeal lesions can herald the onset. Organism-specific skin lesions have a predilection for the nasolabial area and appear initially as papules, which evolve to form pustules, plaques, abscesses, and verrucous plaques. Biopsy of these lesions demonstrates spherules. Basilar meningitis is the most common manifestation and may be accompanied by ventriculitis, ependymitis, cerebral vasculitis, abscess, and syringomyelia. Headache, vomiting, meningismus, and cranial nerve dysfunction are often present. Untreated meningitis is almost invariably fatal. Bone infections account for 20-50% of extrapulmonary manifestations, are often multifocal, and can affect adjacent structures. Miliary dissemination and peritonitis can mimic tuberculosis.

DIAGNOSIS

Nonspecific tests have limited usefulness. The complete blood count might show an elevated eosinophil count, and marked eosinophilia can accompany dissemination.

Culture, Histopathologic Findings, and Antigen Detection

Although diagnostic, culture is positive in only 8.3% of respiratory tract specimens and in only 3.2% of all other sites. *Coccidioides* is isolated from clinical specimens as the spore-bearing mold form, and thus the laboratory should be informed and use special precautions when the diagnosis is suspected. The observation of endosporulating spherules in histopathologic specimens is also diagnostic.

A quantitative enzyme immunoassay (EIA) (MiraVista Diagnostics) that detects coccidioidal galactomannan in urine has excellent specificity and is positive in 70% of patients with severe infections. Although the EIA can cross react with other endemic mycoses, interpretation is often straightforward because there is negligible geographic overlap with areas endemic for other mycoses.

Cerebrospinal fluid (CSF) analysis should be performed in patients with suspected dissemination. The findings in meningitis are similar to those seen with tuberculous meningitis (see Chapter 215). Eosinophilic pleocytosis may be present. Fungal stains and culture are usually negative. Volumes of 10 mL in adults have improved the yield of culture.

Serology

Serologic tests provide valuable diagnostic information but may be falsely negative early in self-limited infections and in immunocompromised patients. Three major methods are used, including EIA, complement fixation (CF), and immunodiffusion. EIA and CF tests are best done in experienced reference laboratories.

Immunoglobulin (Ig) M–specific antibody becomes measurable in 50% of infected patients 1 wk after onset and in 90% of infected patients by 3 wk. EIA is sensitive and can detect IgM and IgG antibody; it is less specific than other methods, and confirmation with immunodiffusion or CF may be needed. IgG antibodies measured by CF appear between the 2nd and 3rd wk but can take several months; follow-up testing is needed if tests are negative and clinical suspicion persists. In the presence of CF titers of 1:2 or 1:4, a positive immunodiffusion test can help corroborate significance. IgG-specific antibody can persist for months, with titers elevated in proportion to the severity of illness. CF titers >1:16 are suggestive of dissemination. Direct comparison of the results of CF (IgG) antibody tests measured by different methodologies should be interpreted with caution. IgG antibody titers used to monitor disease activity should be tested concurrently with serum samples taken earlier in the illness using the same methodology.

C. immitis antibody is present in CSF in 95% of patients with meningitis and is usually diagnostic. Rarely, "spillover" in patients without meningitis but with high IgG titers in serum can be present in CSF. Isolation of *Coccidioides* from CSF culture of patients with meningitis is uncommon, although culture of large volumes of CSF may improve sensitivity.

Imaging Procedures

During primary infection, chest radiography may be normal or demonstrate consolidation, single or multiple circumscribed lesions, or soft pulmonary densities. Hilar and subcarinal lymphadenopathy is often present (see Fig. 240-2). Cavities tend to be thin walled (Fig. 240-3). Pleural effusions vary in size. The presence of miliary or reticulonodular lesions is prognostically unfavorable. Isolated or multiple osseous lesions are usually lytic and often affect cancellous bone. Lesions can affect adjacent structures, and vertebral lesions can impact the spinal cord.

TREATMENT

Based on the few rigorous clinical trials performed in adults and the opinions of experts in the management of coccidioidomycosis, consensus treatment guidelines have been developed (Table 240-2). Consultation with experts in an area of endemicity should be considered when formulating a plan of management.

Patients should be followed closely because late relapse can occur, especially in patients who are immunosuppressed or have severe manifestations. Treatment is recommended for all HIV-infected patients

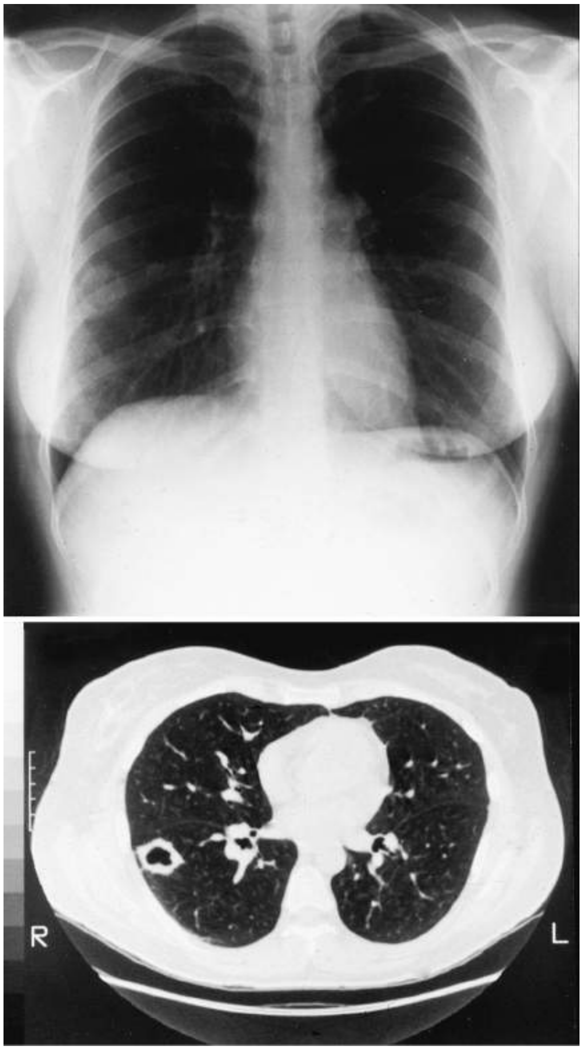

Figure 240-3 **Top,** Chest radiograph revealing a chronic cavitary lesion in the right lung of a woman with coccidioidomycosis. **Bottom,** CT showing the same cavity in the right lung.

Table 240-2 Indications for Treatment of Coccidioidomycosis in Adults

INDICATION	TREATMENT
Acute pneumonia, mild	Observe without antifungal treatment at 1-3 mo intervals for ≥1 yr; some experts recommend antifungal treatment
Weight loss >10%; sweats >3 wk; infiltrates at least half of 1 lung or parts of both lungs; prominent or persistent hilar lymphadenopathy; complement fixation titers >1:16; inability to work, symptoms >2 mo	Treat with an azole daily for 3-6 mo, with follow-up at 1-3 mo intervals for ≥1 yr
Uncomplicated acute pneumonia, special circumstances: immunosuppression, late pregnancy, Filipino or African ancestry, age >55 yr, other chronic diseases (diabetes, cardiopulmonary disease), symptoms >2 mo	Treat with an azole daily for 3-6 mo, with follow-up at 1-3 mo intervals for ≥1 yr Treat with amphotericin B if in late pregnancy
Diffuse pneumonia: reticulonodular or miliary infiltrates suggest underlying immunodeficiency and possible fungemia, pain	Treat initially with amphotericin B if significant hypoxia or rapid deterioration, followed by an azole for ≥1 yr In mild cases, an azole for ≥1 yr
Chronic pneumonia	Treat with an azole for ≥1 yr
Disseminated disease, nonmeningeal	Treat with an azole for ≥1 yr except in severe or rapidly worsening cases, for which amphotericin B is recommended
Disseminated disease, meningeal	Treat with fluconazole (some add intrathecal amphotericin B) and treat indefinitely

with active coccidioidomycosis and CD4 counts <250/µL. Following successful treatment, antifungals may be stopped if the CD4 count exceeds 250/µL. Treatment should be continued if the CD4 count remains less than 250/µL and should be given indefinitely in all HIV-infected patients with coccidioidal meningitis.

First-line agents include oral and intravenous preparations of fluconazole (6-12 mg/kg/day IV or PO) and itraconazole (5-10 mg/kg/day). Serum levels of itraconazole should be monitored.

Amphotericin B is preferred for initial treatment of severe infections. Amphotericin B deoxycholate is less costly than lipid formulations and is often well tolerated in children. Once a daily dose of amphotericin B deoxycholate of 1-1.5 mg/kg/day is achieved, the frequency of administration can be reduced to 3 times weekly. The recommended total dosage ranges from 15 mg/kg to 45 mg/kg and is determined by the clinical response. Lipid formulations of amphotericin are recommended for patients with impaired renal function, patients receiving other nephrotoxic agents, or if amphotericin B deoxycholate is not tolerated. Some experts prefer liposomal amphotericin to treat central nervous system infections because it achieves higher levels in brain parenchyma. Amphotericin B preparations do not cross the blood–brain barrier to effectively treat *Coccidioides* spp., but they can mask the signs of meningitis. Infections during pregnancy should be treated with amphotericin B, because the azoles are potentially teratogenic. Voriconazole and posaconazole have been used successfully as salvage therapy in infections failing the standard agents.

Primary Pulmonary Infection

Primary pulmonary coccidioidomycosis resolves in 95% of patients without risk factors for dissemination; antifungal therapy does not lessen the frequency of dissemination or pulmonary residua. When it is elected to defer antifungal therapy, visits are recommended at 3-6 mo intervals for 2 yr and as needed.

Patients with significant or prolonged symptoms are more likely to incur benefit from antifungal agents, but there are no established criteria upon which to base the decision. Table 240-2 summarizes commonly used indicators in adults. A treatment trial in adults with primary respiratory infections examined outcomes of antifungal therapy prescribed on the basis of severity and compared them to an untreated group with less-severe symptoms; complications occurred only in patients in the treatment group and only in those in whom treatment was stopped. If treatment is elected, a 3-6 mo course of fluconazole (6-12 mg/kg/day) or itraconazole (5-10 mg/kg/day) is recommended.

Diffuse Pneumonia

Diffuse reticulonodular densities or miliary infiltrates, sometimes accompanied by severe illness, can occur in dissemination or follow exposure to a large fungal inoculum. In this setting, amphotericin B is recommended for initial treatment, followed thereafter by extended treatment with high-dose fluconazole (see Table 240-2).

Disseminated (Extrapulmonary) Infection

For **nonmeningeal infection** (see Table 240-2), oral fluconazole and itraconazole are effective for treating disseminated coccidioidomycosis that is not extensive, is not progressing rapidly, and has not affected the central nervous system. Some experts recommend higher doses for adults than were used in clinical trials. A subgroup analysis showed a tendency for improved response of skeletal infections that were treated with itraconazole. Amphotericin B deoxycholate is used as an alternative, especially if there is rapid worsening and lesions are in critical locations. Voriconazole has been used successfully as salvage therapy. The optimal duration of therapy with the azoles has not been clearly defined. Late relapses have occurred after lengthy treatment and favorable clinical response.

Meningitis

Therapy with oral fluconazole is currently preferred for coccidioidal meningitis. In adults, a dosage >400 mg/day is recommended by some experts. Itraconazole at a dosage of 400-600 mg/day in adults is reported to have a comparable effect. Some experts use intrathecal, intraventricular, or intracisternally administered amphotericin B in addition to an azole, believing that the clinical response may be faster. Patients who respond to the azole should continue treatment indefinitely. Hydrocephalus is a common occurrence and is not necessarily a marker of treatment failure. In the event of treatment failure with azoles, intrathecal therapy with amphotericin B deoxycholate is indicated, with or without the azole treatment. Cerebral vasculitis can occur and can predispose to cerebral ischemia, infarction, or hemorrhage. The efficacy of steroids in high dosage is unresolved. Salvage therapy with voriconazole has been found to be effective.

Surgical Management

If a cavity is located peripherally or there is recurrent bleeding or pleural extension, excision may be needed. Infrequently, bronchopleural fistula or recurrent cavitation occurs as a surgical complication; rarely, dissemination can result. Perioperative intravenous therapy with amphotericin B may be considered. Drainage of cold abscesses, synovectomy, and curettage or excision of osseous lesions is sometimes needed. Local and systemic administration of amphotericin B can be used to treat coccidioidal articular disease.

PREVENTION

Prevention relies on education about ways to reduce exposure. Physicians practicing in nonendemic regions should incorporate careful travel histories when evaluating patients with symptoms compatible with coccidioidomycosis.

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Chapter 241

Paracoccidioides brasiliensis

Jane M. Gould and Stephen C. Aronoff

ETIOLOGY

Paracoccidioidomycosis (South American or Brazilian blastomycosis, Lutz-Splendore-Almeida disease) is an uncommon fungal infection endemic in South America, with cases reported in Central America and Mexico. Brazil accounts for more than 80% of all reported cases. The etiologic agent, *Paracoccidioides brasiliensis,* is a thermally dimorphic fungus found in the environment in the mycelial (mold) form and in tissues as yeast.

EPIDEMIOLOGY

P. brasiliensis, a soil-inhabiting microorganism, is ecologically unique to Central and South America. Endemic outbreaks occur mainly in the tropical rain forests of Brazil, with cases scattered in Argentina, Colombia, and Venezuela. There is an increased incidence in areas with moderately high altitude, with high humidity and rainfall, and where coffee and tobacco are grown. Armadillos appear to be a natural reservoir for *P. brasiliensis.* The most common route of infection is by inhalation of conidia. The disease is not usually thought to be contagious, and person-to-person transmission has not been confirmed. Paracoccidioidomycosis is more common among boys after puberty because of the role of estrogen in preventing the transition of conidia to the yeast form. Children account for <10% of the total number of cases.

PATHOGENESIS

The entry route into the body is via the respiratory tract, and the lungs are the site of primary infection, although not all patients have respiratory symptoms. Once the conidia reach the alveoli, yeast

transformation takes place. The infection then spreads to the mucous membranes of the nose, mouth, and gastrointestinal tract. Cell-mediated immunity, specifically a T-helper type 2–type response, is crucial to containing the infection. Tumor necrosis factor-α and interferon-γ activated macrophages are responsible for intracellular killing of *P. brasiliensis*. The yeast can disseminate by the lymphohematogenous route to skin, lymph nodes, and other organs and remain dormant in lymph nodes, producing a latent infection with reactivation occurring later on in life. There are cases of patients who developed disease 30 or more years after leaving an endemic region.

Histopathologically, the yeast-like cells are round, with the parent cell being quite large and surrounded by small buds, giving it the appearance of a ship's wheel. A mixed suppurative and granulomatous inflammatory reaction with areas of necrosis is seen in pulmonary infections. In chronic infections fibrosis and calcification may be seen. Mucocutaneous infections are typified by ulceration and pseudoepitheliomatous hyperplasia.

CLINICAL MANIFESTATIONS

There are 2 clinical forms of disease. The **acute** form is rare, occurs almost exclusively in children and persons with impaired immunity, and targets the reticuloendothelial system. Pulmonary symptoms may be absent, although chest radiographs often show patchy, confluent, or nodular densities. Patients typically present acutely with fever, malaise, wasting, lymphadenopathy, and abdominal enlargement from intraabdominal lymphadenopathy. Hepatomegaly and splenomegaly are nearly constant. Localized bony lesions have been reported in children and can progress to systemic disease. Multifocal osteomyelitis, arthritis, and pericardial effusions can also occur. Nonspecific laboratory findings include anemia, eosinophilia, and hypergammaglobulinemia. Acute paracoccidioidomycosis has a 25% mortality rate.

Adults develop a **chronic,** progressive illness that manifests initially with flu-like symptoms, fever, and weight loss. Pulmonary infection develops with dyspnea, cough, chest pain, and hemoptysis. Findings on physical examination are scant, although chest radiographs can show infiltrates that are disproportionate with mild clinical findings. Mucositis involving the mouth and its structures as well as the nose can manifest as localized pain, change in voice, or dysphagia. Lesions can extend beyond the oral cavity onto the skin. Generalized lymphadenopathy, hepatosplenomegaly, and adrenal involvement (seen in 15-50% of cases) can lead to Addison disease. Meningoencephalitis and central nervous system granulomas can occur as presenting or secondary symptoms. Adults with extensive exposure to soil, such as farmers, are most likely to develop the chronic form of the disease.

DIAGNOSIS

Demonstration of the fungus by direct wet mount (potassium hydroxide) preparation of sputum, exudate, or pus supports the diagnosis in many cases. Histopathologic examination of biopsy specimens using special fungal staining techniques is also diagnostic. Immunohistochemistry using monoclonal antibodies to specific glycoproteins can also be done on tissue sections. Culture of the fungus on Sabouraud-dextrose or yeast extract agar confirms the diagnosis. Antibodies to *P. brasiliensis* can be demonstrated in most patients. Serial antibody titers and lymphocyte proliferative responses to fungal antigens are useful for monitoring the response to therapy. The 43 kDa glycoprotein (gp43) is present in sera of more than 90% of patients with paracoccidioidomycosis by immunodiffusion (the most commonly used diagnostic test) and in 100% by immunoblotting. A latex particle agglutination test using pooled crude fungal exoantigens is being developed for the detection of anti–*P. brasiliensis* antibodies and has shown 92% agreement with the double immunodiffusion test. Newer diagnostic methods that might prove to be very useful in the future include polymerase chain reaction, detection of gp43, and capture enzyme-linked immunosorbent assay to detect specific immunoglobulin E in patient sera. Skin testing with paracoccidioidin is not reliable, because 30-50% of patients with active disease are nonreactive initially and a positive test indicates previous exposure but not necessarily active disease.

TREATMENT

Itraconazole (5-10 mg/kg/day with maximum dosage of 400 mg/day) orally for 6 mo is the treatment of choice for paracoccidioidomycosis. Fluconazole has also been used, but high doses (≥600 mg/day) and longer treatment periods are required. Terbinafine, an allylamine, has potent in vitro activity against *P. brasiliensis* and has been used for successful treatment of paracoccidioidomycosis unresponsive to treatment with trimethoprim-sulfamethoxazole (TMP-SMX) (8-10 mg/kg/day). Amphotericin B is recommended for disseminated disease and if other therapies fail. Therapy with sulfonamide compounds, including sulfadiazine, TMP-SMX, and dapsone, have been used historically and are generally less expensive than the newer azoles and allylamines. The primary disadvantage is that the treatment course is very long, lasting months to years, depending on the agent selected. Relapse can occur following any form of therapy, including with amphotericin B.

Two therapies currently under investigation include the use of curcumin, an antioxidant found in the Indian spice turmeric, and the calcineurin inhibitor cyclosporine. Curcumin was found to have more antifungal activity than fluconazole against *P. brasiliensis* when studied in vitro using human buccal epithelial cells. Cyclosporine blocks the thermodimorphism of *P. brasiliensis*. Animal models demonstrate that fungal whole cells, purified antigens, peptides, and DNA vaccines have great potential toward the development of a vaccine for use in humans.

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Chapter **242**

Sporotrichosis *(Sporothrix schenckii)*

Beth Moughan and Stephen C. Aronoff

ETIOLOGY

Sporotrichosis is a rare fungal infection that occurs worldwide both sporadically and in outbreaks. The etiologic agent, *Sporothrix schenckii,* exhibits temperature dimorphism, existing as a mold at environmental temperatures (25-30°C [77-86°F]) and as a yeast in vivo (37°C [98.6°F]).

EPIDEMIOLOGY

S. schenckii is found throughout the world, but most cases of sporotrichosis are reported from North and South America and Japan. In the United States, the majority of cases have occurred in the Midwest, particularly in areas along the Mississippi and Missouri rivers. The fungus is found in decaying vegetation and has been isolated most commonly from sphagnum moss, rosebushes, barberry, straw, and some types of hay. Sporotrichosis can occur as an occupational disease among farmers, gardeners, veterinarians, and laboratory workers. Transmission from bites and scratches of animals, most commonly cats and armadillos, has occurred. Reports of human-to-human transmission are rare. Sporotrichosis has rarely been reported in infants. The mechanism of transmission in children may be zoonotic but usually is unclear. In 1 endemic area of Peru, the incidence of infection in children is greater than adults; risk factors for infection in these children were playing in crop fields, living in houses with dirt floors, and owning a cat.

PATHOGENESIS

Disease in humans usually follows cutaneous inoculation of the fungus into a minor wound. Pulmonary infection can result from the

inhalation of large numbers of spores. Disseminated infection is unusual but can occur in immunocompromised patients following ingestion or inhalation of spores. The cellular immune response to *S. schenckii* infection is both neutrophilic and monocytic. Histologically, the coexistence of noncaseating granulomas and microabscess formation is characteristic. T-cell–mediated immunity appears to be important in limiting infection, and antibody does not protect against infection. As a result of the paucity of organisms, it is usually difficult to demonstrate the fungi in biopsy specimens.

CLINICAL MANIFESTATIONS

Cutaneous sporotrichosis is the most common form of disease in all age groups. Cutaneous disease may either be lymphocutaneous or fixed cutaneous, the former being much more common. Lymphocutaneous sporotrichosis accounts for more than 75% of reported cases in children and occurs after traumatic subcutaneous inoculation. After a variable and often prolonged incubation period (1-12 wk), an isolated, painless erythematous papule develops at the inoculation site. The initial lesion is usually on an extremity in adults but is often on the face in children. The original papule enlarges and ulcerates. Although the infection might remain limited to the inoculation site (fixed cutaneous form), satellite lesions follow lymphangitic spread and appear as multiple tender subcutaneous nodules tracking along the lymphatic channels that drain the lesion. These secondary nodules are subcutaneous granulomas that adhere to the overlying skin and subsequently ulcerate. Sporotrichosis does not heal spontaneously, and these ulcerative lesions can persist for years if they are untreated. Systemic signs and symptoms are uncommon.

Extracutaneous sporotrichosis is rare in children, and most cases are reported in adults with underlying medical conditions, including AIDS and other immunosuppressing diseases. The most common form of extracutaneous sporotrichosis involves infection of the bones and joints. Pulmonary sporotrichosis usually manifests as a chronic pneumonitis similar to the presentation of pulmonary tuberculosis.

DIAGNOSIS

Cutaneous and lymphocutaneous sporotrichosis must be differentiated from other causes of nodular lymphangitis, including atypical mycobacterial infection, nocardiosis, leishmaniasis, tularemia, melioidosis, cutaneous anthrax, and other systemic mycoses, including coccidioidomycosis. Definitive diagnosis requires isolation of the fungus from the site of infection by culture. Special histologic staining such as periodic acid–Schiff and methenamine silver is required to identify yeast forms in tissues. In spite of special staining techniques, diagnostic yield from biopsy specimens is low because of the small number of organisms present in the tissues. In cases of disseminated disease, demonstration of serum antibody against *S. schenckii*–related antigens can be diagnostically useful. Serologic testing is not commercially available, but it is offered by specialized laboratories including the Centers for Disease Control and Prevention in the United States.

TREATMENT

Although comparative trials and extensive experience in children are not available, itraconazole is the recommended treatment of choice for infections outside the central nervous system. The recommended dosage for children is 5-10 mg/kg/day orally, with a target of 200 mg daily. Dosing may be increased up to 400 mg daily if there is no initial response. Alternatively, younger children with cutaneous disease only may be treated with a saturated solution of potassium iodide given orally once daily beginning at 5-10 drops 3 times per day. The dose is gradually advanced to 25-40 drops 3 times per day for children or 40-50 drops 3 times per day for adolescents and adults. Adverse reactions, usually in the form of nausea and vomiting, should be managed with temporary cessation of therapy and reinstitution at a lower dosage. Therapy is continued until the cutaneous lesions have resolved, which usually takes 6-12 wk. Terbinafine, an allylamine, also has been used successfully to treat cutaneous sporotrichosis. Further clinical efficacy data are needed to routinely recommend its use. Amphotericin B is the treatment of choice for pulmonary infections, disseminated infections, central nervous system disease, and infections in immunocompromised persons.

Therapy with azoles or a saturated solution of potassium iodide should not be used in pregnant women. Amphotericin B can safely be used for cases of pulmonary or disseminated disease in pregnancy. Pregnant patients with cutaneous disease can be treated with local hyperthermia, or therapy can be delayed until the pregnancy is completed. Hyperthermia, in which the affected area is heated to 42-45°C (107.6-113°F) using water baths or heating pads, inhibits growth of the fungus. Dissemination to the fetus does not occur, and the disease is not worsened by pregnancy. Surgical debridement has a role in the treatment of some cases of sporotrichosis, particularly in osteoarticular disease.

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Chapter 243

Zygomycosis (Mucormycosis)

Jane M. Gould and Stephen C. Aronoff

ETIOLOGY

Zygomycosis refers to a group of opportunistic fungal infections caused by dimorphic fungi of the class Zygomycetes, which are primitive, fast-growing fungi that are largely saprophytic and ubiquitous. These organisms are found commonly in soil, in decaying plant and animal matter, and on moldy cheese, fruit, and bread.

This class is subdivided into 2 orders, Mucorales and Entomophthorales, each containing human pathogens. The term **mucormycosis** refers only to infections caused by Mucorales, which includes the genera *Absidia, Apophysomyces, Mucor, Rhizomucor,* and *Rhizopus* and represents the more-common cause of zygomycosis in humans. Infections caused by organisms of the genera *Cunninghamella, Saksenaea,* and *Cokeromyces* are seen less often. Mucorales disease in humans is characterized by a rapidly evolving course, tissue necrosis, and blood vessel invasion in addition to subcutaneous infection. These infections are most acute and fulminant in debilitated patients. Genera of the order Entomophthorales causing infection in humans include *Conidiobolus* and *Basidiobolus*. These agents typically cause indolent sinus or subcutaneous infections in immunocompetent persons.

EPIDEMIOLOGY

Zygomycosis is primarily a disease of persons with underlying conditions that impair host immunity. Predisposing factors include diabetes, hematologic malignancies, persistent acidosis, corticosteroid or deferoxamine therapy, organ transplantation, prematurity, and, less commonly, AIDS. Fungi that are pathogenic in humans grow on almost any carbohydrate substrate and are able to grow at temperatures >37°C (98.6°F). Acidosis diminishes the phagocytic and chemotactic ability of neutrophils while increasing the availability of unbound iron. Deferoxamine-bound iron can also be used by the fungus to enhance its growth.

PATHOGENESIS

Macrophages and neutrophils are the main host defense against Zygomycetes and other filamentous fungi and provide almost complete immunity against Zygomycetes by phagocytosis and oxidative killing

of spores, perhaps explaining the predilection for zygomycosis in patients with neutropenia or neutrophil dysfunction. Many of the Zygomycetes have virulence mechanisms that scavenge iron, an element essential for cell growth, from the host. The primary route of infection from Zygomycetes is inhalation of spores from the environment. In immunocompromised persons, if spores are not cleared by macrophages they germinate into hyphae, resulting in local invasion and tissue destruction. Cutaneous or percutaneous routes of infection can lead to cutaneous and subcutaneous zygomycosis. Ingestion of contaminated food or drinks has been linked to gastrointestinal disease. Typically these infections are characterized by extensive angioinvasion resulting in thrombosis, infarction, and tissue necrosis, which can limit the delivery of antifungal agents and leukocytes to the site of infection and contribute to dissemination of the organism to other organs.

CLINICAL MANIFESTATIONS

There are no unique signs or symptoms of zygomycosis. It can occur as any of several clinical syndromes, including sinus/rhinocerebral, pulmonary, gastrointestinal, disseminated, or cutaneous or subcutaneous disease.

Sinus and rhinocerebral infection are the most common forms of zygomycosis and occur primarily in persons with diabetes mellitus or who are immunocompromised. Infection typically originates in the paranasal sinuses. Initial symptoms are consistent with sinusitis and include headache, retroorbital pain, fever, and nasal discharge. Infection can evolve rapidly or be slowly progressive. Orbital involvement manifesting as periorbital edema, proptosis, ptosis, and ophthalmoplegia can occur early in the disease. The nasal discharge is often dark and bloody; examination of the nasal mucosa reveals the hallmark finding of black, necrotic areas; however, its absence does not exclude the diagnosis. Extension beyond the nasal cavity into the mouth is common. Involved tissues become red, then violaceous, and then black as vessel thrombosis and tissue necrosis occur. Direct bony involvement is common as a result of contiguous pressure effects or because of direct invasion and infarction. Destructive paranasal sinusitis with intracranial extension can be demonstrated by CT or MRI. Cases complicated by cavernous sinus thrombosis and thrombosis of the internal carotid artery have been reported. Brain abscesses can occur in patients with rhinocerebral infection that extends directly from the nasal cavity and sinuses, usually to the frontal or frontotemporal lobes. In patients with disseminated disease, abscesses can involve the occipital lobe or brainstem.

Pulmonary zygomycosis infection usually occurs in severely neutropenic patients and is characterized by fever, tachypnea, and productive cough with pleuritic chest pain and hemoptysis. A wide range of pulmonary radiologic findings, including solitary pulmonary nodule, segmental or lobar consolidation, and cavitary and bronchopneumonic changes, are recognized.

Gastrointestinal zygomycosis is uncommon. Often the diagnosis is delayed; only 25% of cases are diagnosed antemortem, and the subsequent mortality is as high as 85%. It can occur as a complication of disseminated disease or as an isolated intestinal infection in diabetics, immunosuppressed or malnourished children, or preterm infants. Any part of the gastrointestinal tract can be involved, with the stomach followed by colon and ileum being the most commonly affected. Abdominal pain and distention with hematemesis, hematochezia, or melena can occur. Stomach or bowel wall perforation is not uncommon.

Disseminated zygomycosis is associated with a very high mortality rate, especially among immunocompromised persons. Pulmonary involvement is most common, but infection can originate from any of the primary sites of infection. A metastatic skin lesion is an important clue to early diagnosis.

Cutaneous and soft tissue zygomycosis can complicate burns or surgical wounds. An outbreak occurred among preterm infants following the use of contaminated wooden tongue depressors to immobilize the extremities. Primary cutaneous disease may be invasive locally, progressing through all tissue layers, including muscle, fascia, and bone. Necrotizing fasciitis may occur. Infection manifests as an erythematous papule that ulcerates, leaving a black necrotic center. The skin lesions are painful, and affected patients may be febrile. Cutaneous lesions from hematogenous seeding tend to be nodular, with minimal destruction of the epidermis.

DIAGNOSIS

The diagnosis relies on direct morphologic identification of mycotic elements and recovery of Zygomycetes in culture or by biopsy identification in specimens obtained at the site of presumed involvement. To identify the fungus from scrapings, sputum, and exudates under direct microscopy, the use of calcofluor white or 10% potassium hydroxide and Parker ink is recommended. In lung and other tissue biopsy specimens, demonstration of fungal elements with fungal specific stains is recommended. Mucorales appear as broad (5-25 µm in diameter), infrequently septate, thin-walled hyphae, branching irregularly at right angles when stained with Gomori methenamine silver or hematoxylin and eosin. Secondary to their thin-walled structure and lack of regular septation, they often appear twisted, collapsed, or folded. Angiotropism is a hallmark of zygomycosis. The fungi can be cultured on standard laboratory media from sputum, bronchoalveolar lavage fluid, skin lesions, or biopsy material. Mucorales are common culture contaminants. Serologic tests for detecting zygomycosis are not clinically useful. Real-time quantitative polymerase chain reaction assay targeting the 28S rRNA gene has been tested in a rabbit model of experimental pulmonary zygomycosis and shows great promise as a rapid, sensitive, and specific diagnostic test. Additionally, direct sequencing of cultured organisms or formalin fixed tissue and fluorescent in situ hybridization are methods that show great promise to increase the sensitivity, specificity, and speed of laboratory-based diagnostics.

TREATMENT

All forms of the disease can be aggressive and difficult to treat, with high fatality rates. The optimal therapy for zygomycosis in children requires early diagnosis and prompt institution of medical therapy combined with extensive surgical debridement of all devitalized tissue. Correction of the underlying disease, if possible, is an essential component of management. Use of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor to reverse immunosuppression is recommended in conjunction with antifungal agents.

Amphotericin B deoxycholate (1-1.5 mg/kg/day to a total dose of 70 mg/kg or 3-4 g over several weeks) or amphotericin B lipid complex (3-5 mg/kg/day) has been successful in treating infection. Anecdotal reports suggest that higher total doses of amphotericin B lipid complex (15-20 mg/kg/day) are associated with better outcomes in invasive infection. Pulmonary and cutaneous disease has been successfully treated with intermediate dosages of amphotericin B (30 mg/kg total dose).

Surveillance in the United States suggests an association between use of voriconazole prophylaxis and the emergence of zygomycosis in transplant patients, which might represent increased patient survival or selection of resistant organisms. Voriconazole is inactive against the Zygomycetes. Posaconazole appears to be active against most of the Zygomycetes both in vitro and in vivo and together with surgery has been associated with dramatic clinical responses and holds promise as a therapeutic agent for mucormycosis. Caspofungin has limited or no in vitro activity against Zygomycetes; however, when combined with amphotericin lipid complex, caspofungin has been found to be more active than lipid complex alone or caspofungin alone for the treatment of experimental zygomycosis in diabetic mice. Caspofungin has been shown to uncover β-glucan in the cell wall of *Rhizopus,* which results in an increase in neutrophil activity. Hyperbaric oxygen has been used anecdotally as an adjunctive therapy, and iron chelation with deferasirox has been tried as salvage therapy in refractory mucormycosis.

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Chapter 244

Pneumocystis jiroveci

Francis Gigliotti and Terry W. Wright

Pneumocystis jiroveci pneumonia (interstitial plasma cell pneumonitis) in an immunocompromised person is a life-threatening infection. Primary infection in the immunocompetent person is usually subclinical and goes unrecognized. The disease most likely results from new or repeat acquisition of the organism rather than reactivation of latent organisms. Even in the most severe cases, with rare exceptions, the organisms remain localized to the lungs.

ETIOLOGY

P. jiroveci is a common extracellular parasite found worldwide in the lungs of mammals. The taxonomic placement of this organism has not been unequivocally established, but nucleic acid homologies place it closest to fungi despite sharing morphologic features and drug susceptibility with protozoa. Detailed studies of the basic biology of the organism are not possible because of the inability to maintain *P. jiroveci* in culture. Phenotypic and genotypic analyses demonstrate that each mammalian species is infected by a unique strain (or possibly species) of *Pneumocystis*. A biologic correlate of these differences is evidenced by animal experiments that have shown organisms are not transmissible from one mammalian species to another. These observations have led to the suggestion that organisms be renamed, with those infecting humans renamed *P. jiroveci*. Alternative acceptable nomenclature retains the use of *Pneumocystis carinii* but uses the annotation *forma specialis* to designate the host of origin such that *P. carinii* infecting humans, rats, or mice would carry the *forma specialis* designation *hominis, ratti,* or *muris,* respectively. Both nomenclatures appear in the medical literature.

EPIDEMIOLOGY

Serologic surveys show that most humans are infected with *P. jiroveci* before 4 yr of age. In the immunocompetent child, these infections are usually asymptomatic. *P. jiroveci* DNA can occasionally be detected in nasopharyngeal aspirates of normal infants. Pneumonia caused by *P. jiroveci* occurs almost exclusively in severely immunocompromised hosts, including those with congenital or acquired immunodeficiency disorders, malignancies, or transplanted organs. Patients with primary immunodeficiency diseases at risk for infection include severe immunodeficiency disease, X-linked CD40 ligand deficiency, major histocompatibility complex class II deficiency, nuclear factor kappa B essential modulator deficiency, dedicator of cytokinesis 8 deficiency, Wiskott-Aldrich syndrome, and caspase recruitment domain 11 deficiency. Small numbers of *P. jiroveci* can be found in the lungs of infants who have died with the diagnosis of sudden infant death syndrome. This observation could indicate a cause-and-effect relationship or simply that there is overlap in the timing of the primary infection with *P. jiroveci* and sudden infant death syndrome.

Without chemoprophylaxis, approximately 40% of infants and children with AIDS, 70% of adults with AIDS, 12% of children with leukemia, and 10% of patients with organ transplants experience *P. jiroveci* pneumonia. Epidemics that occurred among debilitated infants in Europe during and after World War II are attributed to malnutrition. The use of new biologic immunosuppressive agents has expanded at-risk populations. The addition of tumor necrosis factor-α inhibitors to the management of patients with inflammatory bowel disease has resulted in a demonstrable increase in *P. jiroveci* pneumonia in this patient population as has the use of rituximab in patients with hematologic malignancies.

The natural habitat and mode of transmission to humans are unknown, but animal studies clearly demonstrate airborne transmission. Animal-to-human transmission is unlikely because of the host specificity of *P. jiroveci*. Thus, person-to-person transmission is likely but has not been conclusively demonstrated.

PATHOGENESIS

Two forms of *P. jiroveci* are found in the alveolar spaces: cysts, which are 5-8 µm in diameter and contain up to 8 pleomorphic intracystic sporozoites (or intracystic bodies), and extracystic trophozoites (or trophic forms), which are 2-5 µm cells derived from excysted sporozoites. The terminology of sporozoite and trophozoite is based on the morphologic similarities to protozoa, because there are no exact correlates for these forms of the organism among the fungi. *P. jiroveci* attaches to type I alveolar epithelial cells, possibly by adhesive proteins such as fibronectin and or mannose-dependent ligands.

Control of infection depends on intact cell-mediated immunity. Studies in patients with AIDS show an increased incidence of *P. jiroveci* pneumonia with markedly decreased $CD4^+$ T-lymphocyte counts. The $CD4^+$ cell count provides a useful indicator in both older children and adults of the need for prophylaxis for *P. jiroveci* pneumonia. Although normally functioning $CD4^+$ T cells are central to controlling infection by *P. jiroveci,* the final effector pathway for destruction of *P. jiroveci* is poorly understood but likely depends on alveolar macrophages. A role for $CD4^+$ T cells could be to provide help for the production of specific antibody that is then involved in the clearance of organisms through interaction with complement, phagocytes, or T cells or through direct activation of alveolar macrophages.

In the absence of an adaptive immune response, as can be modeled in severe combined immunodeficient mice, infection with *P. jiroveci* produces little alteration in lung histology or function until late in the course of the disease. If functional lymphocytes are given to severe combined immunodeficient mice infected with *P. jiroveci,* there is a rapid onset of an inflammatory response that results in an intense cellular infiltrate, markedly reduced lung compliance, and significant hypoxia, which are the characteristic changes of *P. jiroveci* pneumonia in humans. These inflammatory changes are also associated with marked disruption of surfactant function. T-cell subset analysis has shown that $CD4^+$ T cells produce an inflammatory response that clears the organisms but also results in lung injury. $CD8^+$ T cells are ineffective in the eradication of *P. jiroveci.* $CD8^+$ T cells do help modulate the inflammation produced by $CD4^+$ T cells, but in the absence of $CD4^+$ T cells the ineffectual inflammatory response of $CD8^+$ T cells contributes significantly to lung injury. These various T-cell effects are likely responsible for the variations in presentation and outcome of *P. jiroveci* pneumonia observed in different patient populations.

PATHOLOGY

The histopathologic features of *P. jiroveci* pneumonia are of 2 types. The first type is infantile interstitial plasma cell pneumonitis, which was seen in epidemic outbreaks in debilitated infants 3-6 mo of age. Extensive infiltration with thickening of the alveolar septum occurs, and plasma cells are prominent. The second type is a diffuse desquamative alveolar pneumonitis found in immunocompromised children and adults. The alveoli contain large numbers of *P. jiroveci* in a foamy exudate with alveolar macrophages active in the phagocytosis of organisms. The alveolar septum is not infiltrated to the extent it is in the infantile type, and plasma cells are usually absent.

CLINICAL MANIFESTATIONS

There are at least 3 distinct clinical presentations of *P. jiroveci* pneumonia. In patients with profound congenital immunodeficiency or in AIDS patients with very few $CD4^+$ T cells, the onset of hypoxia and symptoms is subtle, with tachypnea progressing to nasal flaring, often without fever; intercostal, suprasternal, and infrasternal retractions; and cyanosis in severe cases. In cases of *P. jiroveci* pneumonia occurring in children and adults with immunodeficiency resulting from immunosuppressive medications, the onset of hypoxia and symptoms is often more abrupt, with fever, tachypnea, dyspnea, and cough, progressing to severe respiratory compromise. This type accounts for the

majority of cases, although the severity of clinical expression can vary. Rales are usually not detected on physical examination. The third pattern of disease is seen in severely immunocompromised patients with *P. jiroveci* pneumonia who appear to be responding to therapy but then have an acute and seemingly paradoxical deterioration thought to be associated with return of immune function. This condition is referred to as *immune restitution inflammatory syndrome* and is most commonly seen in patients with newly diagnosed AIDS who present with *P. jiroveci* pneumonia and who have a rapid response to antiretroviral therapy that is instituted at the same time as anti-*Pneumocystis* therapy. It can also occur in stem cell transplant recipients who engraft while infected with *P. jiroveci.*

LABORATORY FINDINGS

The chest radiograph reveals bilateral diffuse alveolar disease with a granular pattern. The earliest densities are perihilar, and progression proceeds peripherally, sparing the apical areas until last. The arterial oxygen tension ($Pa{O_2}$) is invariably decreased. The major role of the laboratory in establishing a diagnosis of *P. jiroveci* pneumonia is in identifying organisms in lung specimens by a variety of methods. Once obtained, the specimens are typically stained with 1 of 4 commonly used stains: Grocott-Gomori silver stain and toluidine blue stain for the cyst form, polychrome stains such as Giemsa stain for the trophozoites and sporozoites, and the fluorescein-labeled monoclonal antibody stains for both trophozoites and cysts. Polymerase chain reaction analysis of respiratory specimens offers promise as a rapid diagnostic method, but a standardized system for clinical use has not been established.

DIAGNOSIS

Definitive diagnosis requires demonstration of *P. jiroveci* in the lung in the presence of clinical signs and symptoms of the infection. Organisms can be detected in specimens collected by bronchoalveolar lavage (BAL), tracheal aspirate, transbronchial lung biopsy, bronchial brushings, percutaneous transthoracic needle aspiration, and open lung biopsy. Hypertonic saline–induced sputum samples are helpful if *P. jiroveci* is found, but the absence of the organisms in induced sputum does not exclude the infection and BAL should be performed. Open lung biopsy is the most reliable method, although BAL is more practical in most cases. Estimates of the diagnostic yield of the various specimens are 20-40% for induced sputum, 50-60% for tracheal aspirate, 75-95% for BAL, 75-85% for transbronchial biopsy, and 90-100% for open lung biopsy.

TREATMENT

The recommended therapy for *P. jiroveci* pneumonia is trimethoprim-sulfamethoxazole (TMP-SMX) (15-20 mg TMP and 75-100 mg SMX/kg/day in 4 divided doses) administered intravenously, or orally if there is mild disease and no malabsorption or diarrhea. The duration of treatment is 3 wk for patients with AIDS and 2 wk for other patients. Unfortunately, adverse reactions often occur with TMP-SMX, especially rash and neutropenia in patients with AIDS. For patients who cannot tolerate or who fail to respond to TMP-SMX after 5-7 days, pentamidine isethionate (4 mg/kg/day as a single dose IV) may be used. Adverse reactions are frequent and include renal and hepatic dysfunction, hyperglycemia or hypoglycemia, rash, and thrombocytopenia. Atovaquone (750 mg twice daily with food, for patients >13 yr of age) is an alternative treatment that has been used primarily in adults with mild to moderate disease. Limited experience is available for younger children. Pharmacokinetic studies of atovaquone show that a dose of 30 mg/kg/day PO in 2 divided doses for children 0-3 mo of age and older than 2 yr of age is adequate and safe; a dose of 45 mg/kg/day PO in 2 divided doses is needed for children between 4 mo and 2 yr of age. Other effective therapies include trimetrexate glucuronate or combinations of trimethoprim plus dapsone or clindamycin plus primaquine.

Some studies in adults suggest that administration of corticosteroids as adjunctive therapy to suppress the inflammatory response increases the chances for survival in moderate and severe cases of *P. jiroveci* pneumonia. The recommended regimen of corticosteroids for adolescents older than 13 yr of age and for adults is oral prednisone, 80 mg/day PO in 2 divided doses on days 1-5, 40 mg/day PO once daily on days 6-10, and 20 mg/day PO once daily on days 11-21. A reasonable regimen for children is oral prednisone, 2 mg/kg/day for the 1st 7-10 days, followed by a tapering regimen for the next 10-14 days.

SUPPORTIVE CARE

Basic supportive care is dictated by the condition of the patient, with careful attention to maintain appropriate hydration and oxygenation. Only 5-10% of AIDS patients require mechanical ventilation compared to 50-60% of patients without AIDS, consistent with the hypothesis that the patient's ability to mount an inflammatory response correlates with severity and outcome. There are anecdotal reports of giving surfactant to children with severe *P. jiroveci* pneumonia, although the use of surfactant to treat adult-type respiratory distress syndrome is controversial.

COMPLICATIONS

Most complications occur as adverse events associated with the drugs used or the mechanical ventilation used for treatment. The most severe pulmonary complication of *P. jiroveci* pneumonia is adult-type respiratory distress syndrome. Rarely, *P. jiroveci* infection affects extrapulmonary sites (e.g., retina, spleen, and bone marrow), but such infections are usually not symptomatic and also respond to treatment.

PROGNOSIS

Without treatment, *P. jiroveci* pneumonitis is fatal in almost all immunocompromised hosts within 3-4 wk of onset. The mortality rate varies with patient population and is related to inflammatory response rather than organism burden. AIDS patients have a mortality rate of 5-10%, and patients with other diseases such as malignancies have mortality rates as high as 20-25%. Patients who require mechanical ventilation have mortality rates of 60-90%. Patients remain at risk for *P. jiroveci* pneumonia as long as they are immunocompromised. Continuous prophylaxis should be initiated or reinstituted at the end of therapy for patients with AIDS (see Chapter 276).

PREVENTION

Patients at high risk for *P. jiroveci* pneumonia should be placed on chemoprophylaxis. Prophylaxis in infants born to HIV-infected mothers and for HIV-infected infants and children is based on age and CD4 cell counts (see Chapter 276). Patients with severe combined immunodeficiency syndrome, patients receiving intensive immunosuppressive therapy for cancer or other diseases, and organ transplant recipients are also candidates for prophylaxis. TMP-SMX (5 mg/kg TMP and 25 mg SMX/kg PO once daily or divided into 2 doses daily) is the drug of choice and may be given for 3 consecutive days each week, or, alternatively, each day. Alternatives for prophylaxis include dapsone (2 mg/kg/day PO, maximum: 100 mg/dose; or 4 mg/kg PO once weekly, maximum: 200 mg/dose), atovaquone (30 mg/kg/day PO for infants 1-3 mo and ≥24 mo of age; 45 mg/kg/day for infants and toddlers 4-23 mo of age), and aerosolized pentamidine (300 mg monthly by Respirgard II nebulizer), but all of these agents are inferior to TMP-SMX. Finally, limited clinical experience suggests that pentamidine can be given intravenously once monthly to prevent *P. jiroveci* pneumonia. Prophylaxis must be continued as long as the patient remains immunocompromised. Some AIDS patients who reconstitute adequate immune response during highly active antiretroviral therapy may have prophylaxis withdrawn.

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Section 13

Viral Infections

Chapter 245

Principles of Antiviral Therapy

Mark R. Schleiss

Antiviral chemotherapy typically requires a delicate balance between targeting critical steps in viral replication without interfering with host cellular function. Because viruses require cellular functions to complete replication, many antiviral agents exert significant host cellular toxicity, a limitation that has hindered antiviral drug development. In spite of this limitation, a number of agents are licensed for use against viruses, particularly herpesviruses, respiratory viruses, and hepatitis viruses (Table 245-1).

In making the decision to commence antiviral drugs, it is important for the clinician to obtain appropriate diagnostic specimens, which can help clarify the antiviral of choice. The choice of a specific antiviral is based on the recommended agent of choice for a particular clinical condition, pharmacokinetics, toxicities, cost, and the potential for development of resistance (Table 245-2). Intercurrent conditions in the patient, such as renal insufficiency, should also be considered. Clinicians must monitor antiviral therapy closely for adverse events or toxicities, both anticipated and unanticipated.

In vitro sensitivity testing of virus isolates to antiviral compounds usually involves a complex tissue culture system. The potency of an antiviral is determined by the **50% inhibitory dose (ID_{50}),** which is the antiviral concentration required to inhibit the growth in cell culture of a standardized viral inoculum by 50%. Because of the complexity of these assays, the results vary widely, and the actual relationship between antiviral sensitivity testing and antiviral therapy outcomes is sometimes unclear. Moreover, these assays are often not readily available and take considerable time to complete, limiting their utility and value in clinical practice. Fortunately, **genotypic analysis** of antiviral resistance mutations is increasingly available for clinical testing, based on identification by molecular techniques of known mutations associated with antiviral resistance.

Knowledge of the precise status of a patient's immune system, particularly cell-mediated immunity, is important in the decision making for using an antiviral agent. Treatment of cytomegalovirus (CMV) infection in an immunocompetent patient is seldom necessary, whereas antiviral therapy may be lifesaving when administered to an immunocompromised solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT) patient. Antivirals can be employed with a variety of clinical goals in mind. Antivirals can be used for **treatment** of active end-organ disease, as **prophylaxis** to prevent viral infection or disease, or as **preemptive therapy** of viral infection to prevent viral disease. In preemptive therapy, a patient will demonstrate evidence of an active infection, usually by molecular means such as polymerase chain reaction–based identification of viral nucleic acids in clinical samples (blood or body fluids), but may have no symptoms. However, SOT and HSCT patients are at high risk of developing disease in this setting (particularly CMV infection), a scenario that warrants preemptive

Table 245-1 Currently Licensed Antiviral Drugs*

ANTIVIRAL	TRADE NAME	MECHANISM OF ACTION
Acyclovir	Zovirax	Inhibits viral DNA polymerase
Adefovir	Hepsera	Nucleotide reverse transcriptase inhibitor
Amantadine	Symmetrel	Blocks M2 protein ion channel
Cidofovir	Vistide	Inhibits viral DNA polymerase
Famciclovir	Famvir	Inhibits viral DNA polymerase
Fomivirsen	Vitravene	Phosphorothioate oligonucleotide inhibits viral replication via antisense mechanism
Foscarnet	Foscavir	Inhibits viral DNA polymerase and reverse transcriptase at pyrophosphate-binding site
Ganciclovir	Cytovene	Inhibits viral DNA polymerase
Idoxuridine	Herplex	Inhibits viral DNA polymerase
Interferon-α	Intro-A (interferon-α2b) Roferon-A (interferon-α2a) Infergen (interferon alfacon-1)	Produces multiple effector proteins that exert antiviral effects; also directly interacts with immune system components
Interferon-α2b plus ribavirin	Rebetron	Not established
Lamivudine	Epivir	Inhibits viral DNA polymerase and reverse transcriptase
Oseltamivir	Tamiflu	Neuraminidase inhibitor; interference with deaggregation and release of viral progeny
Pegylated interferon	PEG-Intron (α2b), Pegasys (α2a)	Same as interferon
Penciclovir	Denavir	Inhibits viral DNA polymerase
Ribavirin	Virazole, Rebetol, Copegus	Interference with viral messenger RNA
Rimantadine	Flumadine	Blocks M2 protein ion channel
Trifluridine	Viroptic	Inhibits viral DNA polymerase
Valacyclovir	Valtrex	Same as acyclovir
Valganciclovir	Valcyte	Same as ganciclovir
Vidarabine	ara-A	Inhibits viral DNA polymerase (and to lesser extent, cellular DNA polymerase)
Zanamivir	Relenza	Neuraminidase inhibitor; interference with deaggregation and release of viral progeny
FDA-APPROVED COMBINATION THERAPIES		
Interferon-α2b + ribavirin	Rebetron (Intron-A plus Rebetol)	
Interferon-α2a + ribavirin	Roferon-A + ribavirin	
Pegylated interferon-α2b + ribavirin	PEG-Intron + Rebetol	
Pegylated interferon-α2a + ribavirin	Pegasys + Copegus	

*See Chapter 276 for antiretroviral drugs.

Table 245-2 Antiviral Therapies for Non-HIV Clinical Conditions

VIRUS	CLINICAL SYNDROME	ANTIVIRAL AGENT OF CHOICE	ALTERNATIVE ANTIVIRAL AGENTS
Influenza A	Treatment	Oseltamivir (>1 yr old)	Rimantadine Amantadine
	Prophylaxis	Oseltamivir (>1 yr old)	Amantadine Rimantadine Zanamivir (>7 yr old)
Influenza B	Treatment	Oseltamivir	Zanamivir (>7 yr old)
Respiratory syncytial virus	Bronchiolitis or pneumonia in high-risk host	Ribavirin aerosol	
Cytomegalovirus (CMV)	Congenital CMV infection	Ganciclovir (IV)	Valganciclovir (if oral therapy appropriate; long-term oral valganciclovir investigational but may improve developmental and hearing outcomes)
	Retinitis in AIDS patients	Valganciclovir	Ganciclovir Cidofovir Foscarnet Ganciclovir ocular insert
	Pneumonitis, colitis; esophagitis in immunocompromised patients	Ganciclovir (IV)	Foscarnet Cidofovir Valganciclovir
Herpes simplex virus (HSV)	Neonatal herpes	Acyclovir (IV)	
	Suppressive therapy following neonatal herpes with central nervous system involvement	Acyclovir (PO)	
	HSV encephalitis	Acyclovir (IV)	
	HSV gingivostomatitis	Acyclovir (PO)	Acyclovir (IV)
	First episode genital infection	Acyclovir (PO)	Valacyclovir Famciclovir Acyclovir (IV) (severe disease)
	Recurrent genital herpes	Acyclovir (PO)	Valacyclovir Famciclovir
	Suppression of genital herpes	Acyclovir (PO)	Valacyclovir Famciclovir
	Cutaneous HSV (whitlow, herpes gladiatorum)	Acyclovir (PO)	Penciclovir (topical)
	Eczema herpeticum	Acyclovir (PO)	Acyclovir (IV) (severe disease)
	Mucocutaneous infection in immunocompromised host (mild)	Acyclovir (IV)	Acyclovir (PO) (if outpatient therapy acceptable)
	Mucocutaneous infection in immunocompromised host (moderate to severe)	Acyclovir (IV)	
	Prophylaxis in bone marrow transplant recipients	Acyclovir (IV)	Valacyclovir Famciclovir
	Acyclovir-resistant HSV	Foscarnet	Cidofovir
	Keratitis or keratoconjunctivitis	Trifluridine	Vidarabine
Varicella-zoster virus	Chickenpox, healthy child	Supportive care	Acyclovir (PO)
	Chickenpox, immunocompromised child	Acyclovir (IV)	
	Zoster (not ophthalmic branch of trigeminal nerve), healthy child	Supportive care	Acyclovir (PO)
	Zoster (ophthalmic branch of trigeminal nerve), healthy child	Acyclovir (IV)	
	Zoster, immunocompromised child	Acyclovir (IV)	Valacyclovir

Modified from Kimberlin DW: Antiviral therapies in children: Has their time arrived? Pediatr Clin North Am *52:837–867, 2005.*

treatment with an antiviral agent. In contrast, prophylaxis is administered to seropositive patients who are at risk to reactivate latent viral infection but do not yet have evidence of active viral replication or shedding.

A fundamental concept important in the understanding of the mechanism of action of most antivirals is that viruses must use host cell components to replicate. Thus, mechanisms of action for antiviral compounds must be selective to virus-specific functions whenever possible, and antiviral agents may have significant toxicities to the host if these compounds impact cellular physiology. Many of the approved antiviral drugs active against the herpesviruses are analogs of deoxynucleosides and subsequently inhibit viral DNA polymerase. Some of the more commonly targeted sites of action for antiviral agents include viral entry, absorption, penetration, and uncoating (amantadine, rimantadine); transcription or replication of the viral genome (acyclovir, valacyclovir, cidofovir, famciclovir, penciclovir, foscarnet, ganciclovir, valganciclovir, ribavirin, trifluridine); viral protein synthesis (interferons); and viral assembly, release, or deaggregation (oseltamivir, zanamivir, interferons).

An understudied and underappreciated issue in antiviral therapy is emergence of resistance, particularly in the setting of high viral load, high intrinsic viral mutation rate, and prolonged or repeated courses of antiviral therapy. Resistant viruses are more likely to develop in or be selected for immunocompromised patients, because these patients are more likely to have multiple or long-term exposures to an antiviral agent.

ANTIVIRALS USED FOR HERPESVIRUSES

The herpesviruses are important pediatric pathogens, particularly in newborns and immunocompromised children. Most of the licensed antivirals are nucleoside analogs that inhibit viral DNA polymerase,

inducing premature chain termination during viral DNA synthesis in infected cells.

Acyclovir

Acyclovir is a safe and effective therapy for herpes simplex virus (HSV) infections. The favorable safety profile of acyclovir derives from its requirement for activation to its active form via phosphorylation by a viral enzyme, thymidine kinase (TK). Thus, acyclovir can only be activated in cells already infected with HSV that express the viral TK enzyme, a strategy that maximizes selectivity and reduces the potential for cellular toxicity in uninfected cells. Acyclovir is most active against HSV and also is active against varicella-zoster virus (VZV); therapy is indicated for infections with these viruses in a variety of clinical settings. Activity of acyclovir against CMV is less pronounced, and activity against Epstein-Barr virus is modest, both in vitro and clinically. Therefore, under most circumstances acyclovir should not be used to treat CMV or Epstein-Barr virus infections.

The biggest impact of acyclovir in clinical practice is in the treatment of primary and recurrent genital HSV infections. Oral nucleoside therapy plays an important role in the management of acute primary genital herpes, treatment of episodic symptomatic reactivations, and prophylaxis against reactivation. Acyclovir is also indicated in the management of suspected or proven HSV encephalitis in patients of all ages, and for treatment of neonatal HSV infection, with or without central nervous system (CNS) involvement. With respect to neonatal HSV infection, the routine use of acyclovir as empiric therapy against HSV infection in infants admitted with fever of unknown origin in the 1st 4-8 wk of life is controversial. Acyclovir should be routinely empirically used in infants born to women with risk factors for primary genital herpes or infants presenting with any combination of vesicular lesions, seizures, meningoencephalitis, hepatitis, pneumonia, or disseminated intravascular coagulation. Some advocate initiation of acyclovir in all febrile infants pending the collection and analysis of viral culture and polymerase chain reaction studies. Others have argued that a selective approach based on the history and physical exam is more appropriate when making decisions about the use of acyclovir in febrile infants. Given the safety of the drug, prudence would dictate the use of acyclovir in such patients if HSV infection cannot be excluded. In neonates with HSV infection including CNS involvement, the use of suppressive therapy with oral acyclovir for 6 mo has been demonstrated to improve neurodevelopmental outcome.

Acyclovir is indicated for the treatment of primary HSV gingivostomatitis and for primary genital HSV infection. Long-term suppressive therapy for genital HSV and for recurrent oropharyngeal infections (herpes labialis) is also effective. Acyclovir is also recommended for less-commonly encountered HSV infections, including herpetic whitlow, *eczema herpeticum*, and *herpes gladiatorum*. In addition, acyclovir is commonly used for prophylaxis against HSV reactivation in SOT and HSCT transplant patients. Severe end-organ HSV disease, including disseminated infection, is occasionally encountered in immunocompromised or pregnant patients, representing another clinical scenario where acyclovir therapy is warranted.

Acyclovir modifies the course of primary VZV infection, although the effect is modest. Acyclovir or another nucleoside analog should always be used in localized or disseminated VZV infections, such as pneumonia, particularly in immunocompromised patients. Primary VZV infection in pregnancy is another setting where acyclovir is indicated; this is a high-risk scenario and can be associated with a substantial risk of maternal mortality, particularly if pneumonia is present.

Acyclovir is available in topical, parenteral, and oral formulations, including an oral suspension formulation for pediatric use. Topical therapy has little role in pediatric practice and should be avoided in favor of alternative modes of delivery, particularly in infants with vesicular lesions compatible with herpetic infection; indeed, neonatal infection represents a setting in which topical therapy should never be used. The bioavailability of oral formulations is modest, with only 15-30% of the oral formulation being absorbed. There is widespread tissue distribution following systemic administration, and high concentrations of drug are achieved in the kidneys, lungs, liver, myocardium, and skin vesicles. Cerebrospinal fluid concentrations are approximately 50% of plasma concentrations. Acyclovir crosses the placenta, and breast milk concentrations are approximately 3 times plasma concentrations, although there are no data on efficacy of in utero therapy or impact of acyclovir therapy on nursing infants. Acyclovir therapy in a nursing mother is not a contraindication to breastfeeding. The main route of elimination is renal, and dosage adjustments are necessary for renal insufficiency. Hemodialysis also eliminates acyclovir.

Acyclovir has an exceptional safety profile. Toxicity is observed typically only in exceptional circumstances: for example, if administered by rapid infusion to a dehydrated patient or a patient with underlying renal insufficiency, acyclovir can crystallize in renal tubules and produce a reversible obstructive uropathy. High doses of acyclovir are associated with neurotoxicity, and prolonged use can cause neutropenia. The favorable safety profile of acyclovir is underscored by recent studies of its safe use during pregnancy, and suppressive therapy in pregnant women with histories of recurrent genital HSV infection, typically with valacyclovir (see "Valacyclovir" below), has become standard of care among many obstetricians. One uncommon but important complication of long-term use of acyclovir is the selection for acyclovir-resistant HSV strains, which usually occurs from mutations in the HSV TK gene. Resistance is rarely observed in pediatric practice but should be considered in any patient who has been on long-term antiviral therapy and who has an HSV or VZV infection that fails to clinically respond to acyclovir therapy.

Valacyclovir

Valacyclovir is the L-valyl ester of acyclovir and is rapidly converted to acyclovir following oral administration. This agent has a safety and activity profile similar to that of acyclovir, but it has a bioavailability of >50%, 3-5–fold greater than that of acyclovir. Plasma concentrations approach those observed with intravenous acyclovir. Valacyclovir is only available for oral administration. A suspension formulation is not commercially available, but an oral suspension (25 mg/mL or 50 mg/mL) may be prepared extemporaneously from 500-mg caplets for use in pediatric patients for whom a solid dosage form is not appropriate. Suppressive therapy with valacyclovir is commonly prescribed in the 2nd and 3rd trimesters of pregnancy in women who have a clinical history of recurrent genital herpes. It is important to be aware that perinatal transmission of HSV can occur, leading to symptomatic disease in spite of maternal antenatal antiviral prophylaxis. In such settings, the possibility of emergence of acyclovir-resistant virus should be considered.

Penciclovir and Famciclovir

Penciclovir is an acyclic nucleoside analog that, like acyclovir, inhibits the viral DNA polymerase following phosphorylation to its active form. Compared with acyclovir, penciclovir has a substantially longer intracellular half-life, which in theory can confer superior antiviral activity at the intracellular level: however, there is no evidence that this effect confers clinical superiority. Penciclovir is licensed only as a topical formulation (1% penciclovir cream), and this formulation is indicated for therapy of cutaneous HSV infections. Topical therapy for primary or recurrent herpes labialis or cutaneous HSV infection is an appropriate use of penciclovir in children older than 2 yr of age.

Famciclovir is the prodrug formulation (diacetyl ester) of penciclovir. In contrast to penciclovir, famciclovir may be administered orally and has bioavailability of approximately 70%. Following oral administration, famciclovir is deacetylated to the parent drug, penciclovir. The efficacy of famciclovir for HSV and VZV infections appears equivalent to that of acyclovir, although the pharmacokinetic profile is more favorable. Famciclovir is indicated for oral therapy of HSV and VZV infections. There is currently no liquid or suspension formulation available. The toxicity profile is identical to that of acyclovir. In a clinical trial, valacyclovir was found to be superior to famciclovir in prevention of reactivation and reduction of viral shedding in the setting of recurrent genital HSV infection.

Ganciclovir

Ganciclovir is a nucleoside analog with structural similarity to acyclovir. Like acyclovir, ganciclovir must be phosphorylated for antiviral activity, which is targeted against the viral polymerase. The gene responsible for

ganciclovir phosphorylation is not *TK* but rather the virally encoded UL97 phosphotransferase gene. Antiviral resistance in CMV can be observed with prolonged use of nucleoside antivirals, and resistance should be considered in patients on long-term therapy who appear to fail to respond clinically and virologically. Ganciclovir is broadly active against many herpesviruses, including HSV and VZV, but its greatest value is derived from its activity against CMV. Ganciclovir was the first antiviral agent licensed specifically to treat and prevent CMV infection. It is indicated for prophylaxis against and therapy of CMV infections in high-risk patients, including HIV-infected patients and SOT or HSCT recipients. Of particular importance is the use of ganciclovir in the management of CMV retinitis, a sight-threatening complication of HIV infection. Ganciclovir is also of benefit for newborns with symptomatic congenital CMV infection and may be of value in partially ameliorating the sensorineural hearing loss and developmental disabilities that are common complications of congenital CMV infection.

Ganciclovir is supplied as parenteral and oral formulations. Ganciclovir ocular implants are also available for the management of CMV retinitis. The bioavailability of oral ganciclovir is poor, <10%. An oral prodrug, valganciclovir, is well absorbed from the gastrointestinal tract and quickly converted to ganciclovir by intestinal or hepatic metabolism. Bioavailability of ganciclovir (from valganciclovir) is approximately 60% from tablet and solution formulations. Significant concentrations are found in aqueous humor, subretinal fluid, cerebrospinal fluid, and brain tissue (enough to inhibit susceptible strains of CMV). Subretinal concentrations are comparable to plasma concentrations, but intravitreal concentrations are lower. Drug concentrations in the CNS range from 24-70% of plasma concentrations. The main route of elimination is renal, and dosage adjustments are necessary for renal insufficiency. Dose reduction is proportional to the creatinine clearance. Hemodialysis efficiently eliminates ganciclovir, so administration of additional doses after dialysis is necessary.

Ganciclovir has several important toxicities. Reversible myelosuppression is the most important toxicity associated with ganciclovir therapy and commonly requires either discontinuation of therapy or the intercurrent administration of granulocyte colony-stimulating factor. There are also the theoretical risks for carcinogenicity and gonadal toxicity; although these effects have been observed in some animal models, they have never been observed in patients. The decision to administer ganciclovir to a pediatric patient is complex and should be made in consultation with a pediatric infectious diseases specialist.

Foscarnet

Foscarnet has a unique profile, insofar as it is not a nucleoside analog but rather a pyrophosphate analog. The drug has broad activity against most herpesviruses. Like the nucleoside analogs, foscarnet inhibits viral DNA polymerase. On the other hand, foscarnet does not require phosphorylation to exert its antiviral activity, thus differing from the nucleoside analogs. It binds to a different site on the viral DNA polymerase to exert its antiviral effect and therefore retains activity against strains of HSV and CMV that are resistant to nucleoside analogs. Its clinical utility is as a second-line agent for management of CMV infections in high-risk patients who cannot tolerate ganciclovir and as an alternative for patients with persistent or refractory HSV, CMV, or VZV disease with suspected or documented antiviral drug resistance.

Foscarnet is only available as a parenteral formulation and is a toxic agent that must be administered cautiously. Nephrotoxicity is common, and reversible renal insufficiency is often observed, as evidenced by an increase in serum creatinine. Abnormalities in calcium and phosphorus homeostasis are common, and electrolytes and renal function must be monitored carefully during treatment.

Cidofovir

Cidofovir is an acyclic nucleotide analog that requires phosphorylation to its active form, cidofovir diphosphate, to exert its antiviral effect. Analogous to penciclovir, it has an extended intracellular half-life that contributes to its prolonged antiviral activity. Cidofovir is active against HSV, VZV, and CMV. In contrast to most of the other agents with activity against herpesviruses, cidofovir also exhibits broad-spectrum activity against other DNA viruses, most notably the poxviruses. Cidofovir has activity against the BK virus, a polyomavirus, and therapy may be warranted in some settings of BK reactivation post-HSCT and SOT. Cidofovir is also useful in the management of CMV disease caused by strains with documented ganciclovir resistance.

Cidofovir is administered intravenously and is cleared renally by tubular secretion. Extensive prehydration and coadministration of probenecid are recommended. Nephrotoxicity is commonly encountered, even with appropriate prehydration; cidofovir must be coadministered with other nephrotoxic medications with care. Other potential toxicities include reproductive toxicity and carcinogenesis.

Trifluridine

Trifluridine is a pyrimidine nucleoside analog with activity against HSV, CMV, and adenovirus. It is formulated as a 1% ophthalmic solution and approved for topical use in the treatment of HSV keratitis and keratoconjunctivitis. Trifluridine is the treatment of choice for HSV keratitis, a disease that should always be managed in consultation with an ophthalmologist.

Vidarabine

Vidarabine is a nucleoside analog that has activity against HSV. It was the first parenteral antiviral agent for HSV infection, although it is no longer available for intravenous administration. A topical preparation remains available to treat HSV keratitis and is considered a second-line agent for this indication.

Fomivirsen

Fomivirsen is a novel anti-CMV compound that is used as a second-line agent for CMV retinitis by direct injection into the vitreous space. It is an antisense 21-mer DNA oligonucleotide that binds directly to complementary messenger RNA. This agent was the first antisense antiviral agent approved by the FDA. The standard dosage is 330 µg via intravitreal injection every 2 wk for 2 doses followed by maintenance therapy of 330 µg every 4 wk. There is no systemic absorption following intravitreal injection.

New Agents

There is a major need for development of new, nontoxic antivirals for HSV infection. Two new agents are approaching licensure that will be very useful in the management of HSCT and SOT patients. The oral lipid conjugate prodrug of cidofovir, **CMX001**, has improved activity against herpesviruses compared to parenterally administered cidofovir and a markedly reduced risk of nephrotoxicity. Another novel agent, letermovir (AIC246), is highly orally bioavailable and has a novel mechanism of action, exerting its antiviral effect by interfering with the viral terminase complex. This agent demonstrates substantial promise as an alternative to more toxic antivirals in patients at high risk for CMV disease, particularly in the transplantation setting. It is also active against BK virus and poxviruses.

ANTIVIRALS USED FOR RESPIRATORY VIRAL INFECTIONS

Antiviral therapies are available for many respiratory pathogens, including respiratory syncytial virus (RSV), influenza A, and influenza B. Antiviral therapy for respiratory viral infections is of particular value for infants, children with chronic lung disease, and immunocompromised children.

Ribavirin

Ribavirin is a guanosine analog that has broad-spectrum activity against a variety of viruses, particularly RNA viruses. Its precise mechanism of action is incompletely understood but is probably related to interference with viral messenger RNA processing and translation. Ribavirin is available in oral, parenteral, and aerosolized formulations. Although intravenous ribavirin is highly effective in the management of Lassa fever and other hemorrhagic fevers, this formulation is not licensed for use in the United States. The only licensed formulations in the United States are an aqueous formulation for aerosol administration (indicated for RSV infection) and an oral formulation that is combined with interferon-α for the treatment of hepatitis C. (For more information about antivirals

for hepatitis, see Chapter 358.) Administration of ribavirin by aerosol should be considered for serious RSV lower respiratory tract disease in immunocompromised children, young infants with serious RSV-associated illness, and high-risk infants and children (children with chronic lung disease or cyanotic congenital heart disease). In vitro testing and uncontrolled clinical studies also suggest efficacy of aerosolized ribavirin for parainfluenza, influenza, and measles infections.

Ribavirin is generally nontoxic, particularly when administered by aerosol. Ribavirin and its metabolites concentrate in red blood cells and can persist for several weeks and, in rare instances, may be associated with anemia. Conjunctivitis and bronchospasm have been reported following exposure to aerosolized drug. Care must be taken when using aerosolized ribavirin in children undergoing mechanical ventilation to avoid precipitation of particles in ventilator tubing; the drug is not formally approved for use in the mechanically ventilated patient, although there is published experience with this approach and it can be considered for mechanically ventilated patients, particularly in a "high-dose, short-duration" regimen. Concerns regarding potential teratogenicity from animal studies have not been borne out in clinical practice, although care should be taken to prevent inadvertent exposure to aerosolized drug in pregnant healthcare providers.

Amantadine and Rimantadine

Amantadine and rimantadine are tricyclic amines that are highly similar to each other, both structurally and functionally. Both are indicated for the prophylaxis and therapy of influenza A, and neither has discernible activity against influenza B or any other respiratory viruses. For maximal therapeutic efficacy, therapy should begin as soon as possible and within 48 hr of the onset of symptoms. Influenza immunization is a greatly preferred method of disease control, but these agents can be useful for prophylaxis, particularly in unimmunized, high-risk persons during annual seasonal epidemics of influenza.

The mechanism of action of the tricyclic amines against influenza A virus is unclear, but they appear to exert their antiviral effect at the level of uncoating of the virus. Both agents are extremely well absorbed after oral administration and are eliminated via the kidneys (90% of the dose is unchanged), necessitating dosage adjustments for renal insufficiency. The toxicities of the tricyclic amines are modest and include CNS adverse effects such as anxiety, difficulty concentrating, and lightheadedness and gastrointestinal adverse effects such as nausea and loss of appetite. Adverse effects are less common with rimantadine than with amantadine.

Oseltamivir, Zanamivir, and Peramivir

Oseltamivir and zanamivir are active against both influenza A and B, although the importance of this broader spectrum of antiinfluenza activity in disease control is modest because influenza B infection is typically a much milder illness. Emerging strains of influenza, including H5N1 and the 2009-2010 pandemic strain, H1N1 (swine flu), are susceptible to oseltamivir and zanamivir but resistant to amantadine. Therefore, these agents are emerging as the antivirals of choice for influenza infection. Neither agent has appreciable activity against other respiratory viruses. The mechanism of antiviral activity of these agents is via inhibition of the influenza neuraminidase.

Zanamivir has poor oral bioavailability and is licensed only for inhalational administration. With inhaled administration, >75% of the dose is deposited in the oropharynx and much of it is swallowed. The actual amount distributed to the airways and lungs depends on factors such as the patient's inspiratory flow. Approximately 13% of the dose appears to be distributed to the airways and lungs, with approximately 10% of the inhaled dose distributed systemically. Local respiratory mucosal drug concentrations greatly exceed the drug concentration needed to inhibit influenza A and B viruses. Elimination is via the kidneys, and no dosage adjustment is necessary with renal insufficiency, because the amount that is systemically absorbed is low.

Oseltamivir is administered as an esterified prodrug that has high oral bioavailability. It is eliminated by tubular secretion, and dosage adjustment is required for patients with renal insufficiency. Gastrointestinal adverse effects, including nausea and vomiting, are occasionally observed. The drug is indicated for both treatment and prophylaxis. The usual adult dosage for treatment of influenza is 75 mg twice daily for 5 days. Treatment should be initiated within 2 days of the appearance of symptoms. Recommended treatment dosages for children vary by age and weight. The recommended dose for children younger than 1 yr of age is 3 mg/kg/dose twice a day. For children older than 1 yr of age, doses are 30 mg twice a day for children weighing ≤15 kg, 45 mg twice a day for children weighing 15-23 kg, 60 mg twice a day for those weighing 23-40 kg, and 75 mg twice a day for children weighing ≥40 kg. Dosages for chemoprophylaxis are the same for each weight group in children older than 1 yr of age, but the drug should be administered only once daily rather than twice daily. Oseltamivir is FDA-approved for therapy of influenza A and B treatment in children 2 wk of age and older, whereas zanamivir is recommended for treatment of children 7 yr of age and older. Current treatment and dosage recommendations for treatment of influenza in children and for chemoprophylaxis are available at: http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Oseltamivir has been described to produce neuropsychiatric (narcolepsy) and psychologic (suicidal events) side effects in some patient populations; the drug should be discontinued if behavioral or psychiatric side effects are observed. In late 2014 the FDA approved another neuraminidase inhibitor, peramivir, for treatment of influenza. It is available as a single-dose, intravenous option. The standard adult dose is 600 mg IV in a single, one-time dose. The drug is currently approved for use only in adults.

ANTIVIRAL IMMUNE GLOBULINS

Immune globulins are useful adjuncts in the management of viral disease. However, they are most useful when administered as prophylaxis against infection and disease in high-risk patients; their value as therapeutic agents in the setting of established infection is less clear. **Varicella-zoster immune globulin (human)** is valuable for prophylaxis against VZV in high-risk children, particularly newborns and immunocompromised children (see Chapter 253). **Cytomegalovirus immune globulin** is warranted for children at high risk for CMV disease, particularly SOT and HSCT patients, and can play a role in preventing injury to the infected fetus when administered to the pregnant patient (see Chapter 255). **Palivizumab,** a monoclonal antibody with anti-RSV activity, is effective for preventing severe RSV lower respiratory tract disease in high-risk premature infants and has replaced **RSV immune globulin** (see Chapter 260). **Hepatitis B immune globulin** is indicated in infants born to hepatitis B surface antigen-positive mothers (see Chapter 358).

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Chapter 246

Measles

Wilbert H. Mason

Measles is highly contagious but owing to widespread vaccination, endemic transmission has been interrupted in the United States; indigenous or imported cases (in children or adults) have occasionally resulted in epidemics in the United States in unimmunized or partially immunized American or foreign-born children (adopted children, refugees, returning tourists). In some areas of the world, measles remains a serious threat to children.

ETIOLOGY

Measles virus is a single-stranded, lipid-enveloped RNA virus in the family Paramyxoviridae and genus *Morbillivirus*. Other members of the genus *Morbillivirus* affect a variety of mammals, such as rinderpest virus in cattle and distemper virus in dogs, but humans are

the only host of measles virus. Of the 6 major structural proteins of measles virus, the 2 most important in terms of induction of immunity are the hemagglutinin (H) protein and the fusion (F) protein. The neutralizing antibodies are directed against the H protein, and antibodies to the F protein limit proliferation of the virus during infection. Small variations in genetic composition have also been identified that result in no effect on protective immunity but provide molecular markers that can distinguish between viral types. Related genotypes have been grouped by clades, and the World Health Organization recognizes 8 clades, A-H, and 23 genotypes. These markers have been useful in the evaluation of endemic and epidemic spread of measles.

EPIDEMIOLOGY

The measles vaccine has changed the epidemiology of measles dramatically. Once worldwide in distribution, endemic transmission of measles has been interrupted in many countries where there is widespread vaccine coverage. Historically, measles caused universal infection in childhood in the United States, with 90% of children acquiring the infection before 15 yr of age. Morbidity and mortality associated with measles decreased prior to the introduction of the vaccine as a result of improvements in healthcare and nutrition. However, the incidence declined dramatically following the introduction of the measles vaccine in 1963. The attack rate fell from 313 cases per 100,000 population in 1956-1960 to 1.3 cases per 100,000 in 1982-1988.

A nationwide indigenous measles outbreak occurred in the United States in 1989-1991, resulting in more than 55,000 cases, 11,000 hospitalizations, and 123 deaths, demonstrating that the infection had not yet been conquered. This resurgence was attributed to vaccine failure in a small number of school-age children, low coverage of preschool-age children, and more rapid waning of maternal antibodies in infants born to mothers who had never experienced wild-type measles infection. Implementation of the 2 dose vaccine policy and more intensive immunization strategies resulted in interruption of endemic transmission in the United States in 1993. The current rate is <1 case per 1,000,000 population.

Measles continues to be imported into the United States from abroad; therefore, continued maintenance of >90% immunity through vaccination is necessary to prevent widespread outbreaks from occurring (Fig. 246-1).

In 2011, 222 cases of measles were reported to the U.S. Centers for Disease Control and Prevention (CDC), an incidence rate of 0.7 per 1,000,000 population. There were 17 outbreaks reported compared to a median of 4 outbreaks reported annually during 2001-2010. Of the 222 cases, 200 were associated with importations from other countries (returning tourists, adoptees, refugees) and 112 were associated with outbreaks. Measles rates remain high in the World Health Organization European Region, which reported more than 30,000 cases in

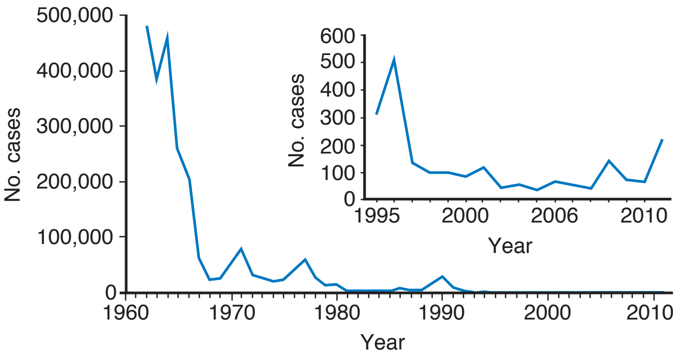

Figure 246-1 Number of measles cases—United States, 1962–2011. Measles data provided were reported voluntarily to Centers for Disease Control and Prevention (CDC) from state health departments. *(From McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS; Centers for Disease Control and Prevention: Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep *62(RR-04):1–34, 2013, Fig. 1.)*

2011. Almost half of the measles importations to the United States were from this World Health Organization region.

High measles vaccination coverage rates early in life are essential to maintain the endemic spread of measles in the United States (>90% 1 dose coverage at 12-15 mo and >95% 2 dose coverage in school-age children.) While measles-mumps-rubella coverage was high (median: 94.8%) in the 2011-2012 school year, pockets of lower coverage rates exist because of reluctance of parents to vaccinate their children because of personal beliefs. This variability in vaccination has contributed to outbreaks among school-age children in recent years. In addition, measles may occur more often in children receiving the first dose at age 12-13 mo when compared to those immunized at age 15 mo and older.

TRANSMISSION

The portal of entry of measles virus is through the respiratory tract or conjunctivae following contact with large droplets or small-droplet aerosols in which the virus is suspended. Patients are infectious from 3 days before to up to 4-6 days after the onset of rash. Approximately 90% of exposed susceptible individuals experience measles. Face-to-face contact is not necessary, because viable virus may be suspended in air for as long as 1 hr after the patient with the source case leaves a room. Secondary cases from spread of aerosolized virus have been reported in airplanes, physicians' offices, and hospitals.

PATHOLOGY

Measles infection causes necrosis of the respiratory tract epithelium and an accompanying lymphocytic infiltrate. Measles produces a small-vessel vasculitis on the skin and on the oral mucous membranes. Histology of the rash and exanthem reveals intracellular edema and dyskeratosis associated with formation of epidermal syncytial giant cells with up to 26 nuclei. Viral particles have been identified within these giant cells. In lymphoreticular tissue, lymphoid hyperplasia is prominent. Fusion of infected cells results in multinucleated giant cells, the **Warthin-Finkeldey giant cells** that are pathognomonic for measles, with up to 100 nuclei and intracytoplasmic and intranuclear inclusions.

PATHOGENESIS

Measles consists of 4 phases: incubation period, prodromal illness, exanthematous phase, and recovery. During incubation, measles virus migrates to regional lymph nodes. A primary viremia ensues that disseminates the virus to the reticuloendothelial system. A secondary viremia spreads virus to body surfaces. The prodromal illness begins after the secondary viremia and is associated with epithelial necrosis and giant cell formation in body tissues. Cells are killed by cell-to-cell plasma membrane fusion associated with viral replication that occurs in many body tissues, including cells of the central nervous system. Virus shedding begins in the prodromal phase. With onset of the rash, antibody production begins, and viral replication and symptoms begin to subside. Measles virus also infects $CD4^+$ T cells, resulting in suppression of the Th1 immune response and a multitude of other immunosuppressive effects.

Recent research has clarified the pathogenesis of disease caused by measles virus. Unlike other Paramyxoviridae members that utilize sialic acid molecules on the virus surface to enter cells, measles virus attaches to specific cell receptors to infect host cells. Studies in primates show that the initial targets for measles virus are alveolar macrophages, dendritic cells, and lymphocytes. The cell receptor used appears to be the signaling lymphocyte activating molecule or more properly CD150. Subsequently, respiratory epithelial cells become infected but do not express CD150. The mechanism of infection of respiratory tissues is attachment to the PVRL4 receptor (Nectin4) that is expressed on cells in the trachea, oral mucosa, nasopharynx, and lungs. These 2 receptors, CD150 and PVRL4, account for the lymphotropic and epitheliotropic nature of natural measles virus infection, and along with the prolonged immunosuppressive effects of measles, suggest that it is more characteristic of human immunodeficiency virus infection than a respiratory illness.

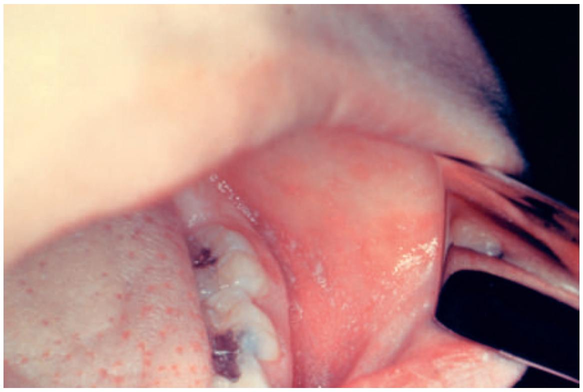

Figure 246-2 Koplik spots on the buccal mucosa during the 3rd day of rash. *(From Centers for Disease Control and Prevention (CDC): Public health image library, image #4500. Available at: http://phil.cdc.gov/phil/details.asp)*

CLINICAL MANIFESTATIONS

Measles is a serious infection characterized by high fever, an enanthem, cough, coryza, conjunctivitis, and a prominent exanthem. After an incubation period of 8-12 days, the prodromal phase begins with a mild fever followed by the onset of conjunctivitis with photophobia, coryza, a prominent cough, and increasing fever. **Koplik spots** represent the enanthem and are the pathognomonic sign of measles, appearing 1-4 days prior to the onset of the rash (Fig. 246-2). They first appear as discrete red lesions with bluish white spots in the center on the inner aspects of the cheeks at the level of the premolars. They may spread to involve the lips, hard palate, and gingiva. They also may occur in conjunctival folds and in the vaginal mucosa. Koplik spots have been reported in 50-70% of measles cases but probably occur in the great majority.

Symptoms increase in intensity for 2-4 days until the 1st day of the rash. The rash begins on the forehead (around the hairline), behind the ears, and on the upper neck as a red maculopapular eruption. It then spreads downward to the torso and extremities, reaching the palms and soles in up to 50% of cases. The exanthem frequently becomes confluent on the face and upper trunk (Fig. 246-3).

With the onset of the rash, symptoms begin to subside. The rash fades over about 7 days in the same progression as it evolved, often leaving a fine desquamation of skin in its wake. Of the major symptoms of measles, the cough lasts the longest, often up to 10 days. In more-severe cases, generalized lymphadenopathy may be present, with cervical and occipital lymph nodes especially prominent.

INAPPARENT MEASLES INFECTION

In individuals with passively acquired antibody, such as infants and recipients of blood products, a subclinical form of measles may occur. The rash may be indistinct, brief, or, rarely, entirely absent. Likewise, some individuals who have received vaccine, when exposed to measles, may have a rash but few other symptoms. Persons with inapparent or subclinical measles do not shed measles virus and do not transmit infection to household contacts.

LABORATORY FINDINGS

The diagnosis of measles is almost always based on clinical and epidemiologic findings. Laboratory findings in the acute phase include reduction in the total white blood cell count, with lymphocytes decreased more than neutrophils. Absolute neutropenia has been known to occur, however. In measles not complicated by bacterial infection, the erythrocyte sedimentation rate and C-reactive protein level are normal.

DIAGNOSIS

In the absence of a recognized measles outbreak, confirmation of the clinical diagnosis is often recommended. Serologic confirmation is most conveniently made by identification of immunoglobulin (Ig) M antibody in serum. IgM antibody appears 1-2 days after the onset of the rash and remains detectable for about 1 mo. If a serum specimen is collected <72 hr after onset of rash and is negative for measles antibody, a second specimen should be obtained. Serologic confirmation may also be made by demonstration of a 4-fold rise in IgG antibodies in acute and convalescent specimens collected 2-4 wk apart. Viral isolation from blood, urine, or respiratory secretions can be accomplished by culture at the CDC or local or state laboratories. Molecular detection by polymerase chain reaction is available through some state and local health departments and through the CDC.

Figure 246-3 A child with measles displaying the characteristic red blotchy pattern on his face and body. *(From Kremer JR, Muller CP: Measles in Europe—there is room for improvement,* Lancet *373:356–358, 2009.)*

DIFFERENTIAL DIAGNOSIS

Typical measles is unlikely to be confused with other illnesses, especially if Koplik spots are observed. Measles in the later stages or inapparent or subclinical infections may be confused with a number of other exanthematous immune-mediated illnesses and infections, including rubella, adenovirus infection, enterovirus infection, and Epstein-Barr virus infection. Exanthem subitum (in infants) and erythema infectiosum (in older children) may also be confused with measles. *Mycoplasma pneumoniae* and group A streptococcus may also produce rashes similar to that of measles. Kawasaki syndrome can cause many of the same findings as measles but lacks discrete intraoral lesions (Koplik spots) and a severe prodromal cough, and typically leads to elevations of neutrophils and acute-phase reactants. In addition, the characteristic thrombocytosis of Kawasaki syndrome is absent in measles (see Chapter 166). Drug eruptions may occasionally be mistaken for measles.

COMPLICATIONS

Complications of measles are largely attributable to the pathogenic effects of the virus on the respiratory tract and immune system (Table 246-1). Several factors make complications more likely. Morbidity and mortality from measles are greatest in patients younger than 5 yr of age (especially <1 yr of age) and older than 20 yr of age. In developing countries, higher case fatality rates have been associated with crowding, possibly attributable to larger inoculum doses after household exposure. Severe malnutrition in children results in a suboptimal

Table 246-1 Complications By Age for Reported Measles Cases, United States, 1987-2000

COMPLICATION	OVERALL (67,032 CASES WITH AGE INFORMATION)	No. (%) of Persons with Complication by Age Group				
		<5 YR (N = 28,730)	5-9 YR (N = 6,492)	10-19 YR (N = 18,580)	20-29 YR (N = 9,161)	<30 YR (N = 4,069)
Any	19,480 (29.1)	11,883 (41.4)	1,173 (18.1)	2,369 (12.8)	2,656 (29.0)	1,399 (34.4)
Death	177 (0.3)	97 (0.3)	9 (0.1)	18 (0.1)	26 (0.3)	27 (0.7)
Diarrhea	5,482 (8.2)	3,294 (11.5)	408 (6.3)	627 (3.4)	767 (8.4)	386 (9.5)
Encephalitis	97 (0.1)	43 (0.2)	9 (0.1)	13 (0.1)	21 (0.2)	11 (0.3)
Hospitalization	12,876 (19.2)	7,470 (26.0)	612 (9.4)	1,612 (8.7)	2,075 (22.7)	1,107 (27.2)
Otitis media	4,879 (7.3)	4,009 (14.0)	305 (4.7)	338 (1.8)	157 (1.7)	70 (1.7)
Pneumonia	3,959 (5.9)	2,480 (8.6)	183 (2.8)	363 (2.0)	554 (6.1)	379 (9.3)

From Perry RT, Halsey NA: The clinical significance of measles: a review, Clin Infect Dis *189(Suppl 1):S4–S16, 2004.*

immune response and higher morbidity and mortality with measles infection. Low serum retinol levels in children with measles are associated with higher measles morbidity and mortality in developing countries and in the United States. Measles infection lowers serum retinol concentrations, so subclinical cases of hyporetinolemia may be made symptomatic during measles. Measles infection in immunocompromised persons is associated with increased morbidity and mortality. Among patients with malignancy in whom measles develops, pneumonitis occurs in 58% and encephalitis occurs in 20%.

Pneumonia is the most common cause of death in measles. It may manifest as **giant cell pneumonia** caused directly by the viral infection or as superimposed bacterial infection. The most common bacterial pathogens are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus*. Following severe measles pneumonia, the final common pathway to a fatal outcome is often the development of bronchiolitis obliterans.

Croup, tracheitis, and bronchiolitis are common complications in infants and toddlers with measles. The clinical severity of these complications frequently requires intubation and ventilatory support until the infection resolves.

Acute otitis media is the most common complication of measles and was of particularly high incidence during the epidemic of the late 1980s and early 1990s because of the relatively young age of affected children. Sinusitis and mastoiditis also occur as complications. Viral and/or bacterial tracheitis is seen and can be life-threatening. Retropharyngeal abscess has also been reported.

Measles infection is known to suppress skin test responsiveness to purified tuberculin antigen. There may be a higher rate of activation of pulmonary tuberculoses in populations of individuals infected with *Mycobacterium tuberculosis* who are then exposed to measles.

Diarrhea and vomiting are common symptoms associated with acute measles, and diffuse giant cell formation is found in the epithelium in the gastrointestinal tract. Dehydration is a common consequence, especially in young infants and children. Appendicitis or abdominal pain may occur from obstruction of the appendiceal lumen by lymphoid hyperplasia.

Febrile seizures occur in <3% of children with measles. Encephalitis following measles is a long-associated complication, often with an unfavorable outcome. Rates of 1-3 per 1,000 cases of measles have been reported, with greater numbers occurring in adolescents and adults than in preschool- or school-age children. Encephalitis is a postinfectious, immunologically mediated process and is not the result of a direct effect by the virus. Clinical onset begins during the exanthem and manifests as seizures (56%), lethargy (46%), coma (28%), and irritability (26%). Findings in cerebrospinal fluid include lymphocytic pleocytosis in 85% of cases and elevated protein concentrations. Approximately 15% of patients with measles encephalitis die. Another 20-40% of patients suffer long-term sequelae, including mental retardation, motor disabilities, and deafness.

Measles encephalitis in immunocompromised patients results from direct damage to the brain by the virus. Subacute measles encephalitis manifests 1-10 mo after measles in immunocompromised patients, particularly those with AIDS, lymphoreticular malignancies, and immunosuppression. Signs and symptoms include seizures, myoclonus, stupor, and coma. In addition to intracellular inclusions, abundant viral nucleocapsids and viral antigen are seen in brain tissue. Progressive disease and death almost always occur.

A severe form of measles rarely seen now is **hemorrhagic measles** or **"black measles."** It manifested as a hemorrhagic skin eruption and was often fatal. Keratitis, appearing as multiple punctate epithelial foci, resolved with recovery from the infection. Thrombocytopenia sometimes occurred following measles.

Myocarditis is a rare complication of measles. Miscellaneous bacterial infections have been reported, including bacteremia, cellulitis, and toxic shock syndrome. Measles during pregnancy is associated with high rates of maternal morbidity, fetal wastage, and stillbirths with and congenital malformations in 3% of liveborn infants.

Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a chronic complication of measles with a delayed onset and an outcome that is nearly always fatal. It appears to result from a persistent infection with an altered measles virus that is harbored intracellularly in the central nervous system for several years. After 7-10 yr the virus apparently regains virulence and attacks the cells in the central nervous system that offered the virus protection. This "slow virus infection" results in inflammation and cell death, leading to an inexorable neurodegenerative process.

SSPE is a rare disease and generally follows the prevalence of measles in a population. The incidence in the United States in 1960 was 0.61 cases per million persons younger than age 20 yr. By 1980 the rate had fallen to 0.06 cases per million. Between 1956 and 1982 a total of 634 cases of SSPE had been reported to the national SSPE registry. After 1982 approximately 5 cases/yr were reported annually in the United States, and only 2-3 cases/yr were reported in the early 1990s. However, between 1995 and 2000, reported cases in the United States increased and 13 cases were reported in 2000. Nine of the 13 cases occurred in foreign-born individuals. This "resurgence" may be the result of an increased incidence of measles between 1989 and 1991. Although the age of onset ranges from <1 yr to <30 yr, the illness is primarily one of children and adolescents. Measles at an early age favors the development of SSPE: 50% of patients with SSPE had primary measles before 2 yr of age, and 75% had measles before 4 yr of age. Males are affected twice as often as females, and there appear to be more cases reported from rural than urban populations. Recent observations from the registry indicate a higher prevalence among children of Hispanic origin.

The pathogenesis of SSPE remains enigmatic. Factors that seem to be involved include defective measles virus and interaction with a defective or immature immune system. The virus isolated from brain tissue of patients with SSPE is missing 1 of the 6 structural proteins, the matrix or M protein. This protein is responsible for assembly, orientation, and alignment of the virus in preparation for budding during

viral replication. Immature virus may be able to reside, and possibly propagate, within neuronal cells for long periods. The fact that most patients with SSPE were exposed at a young age suggests that immune immaturity is involved in pathogenesis. In addition, the intracellular location of the virus sequesters it from the immune system, especially from humoral immunity.

Clinical manifestations of SSPE begin insidiously 7-13 yr after primary measles infection. Subtle changes in behavior or school performance appear, including irritability, reduced attention span, and temper outbursts. This initial phase (stage I) may at times be missed because of brevity or mildness of the symptoms. Fever, headache, and other signs of encephalitis are absent. The hallmark of the 2nd stage is massive myoclonus, which coincides with extension of the inflammatory process site to deeper structures in the brain, including the basal ganglia. Involuntary movements and repetitive myoclonic jerks begin in single muscle groups but give way to massive spasms and jerks involving both axial and appendicular muscles. Consciousness is maintained. In the 3rd stage, involuntary movements disappear and are replaced by choreoathetosis, immobility, dystonia, and lead pipe rigidity that result from destruction of deeper centers in the basal ganglia. The sensorium deteriorates into dementia, stupor, and then coma. The 4th stage is characterized by loss of critical centers that support breathing, heart rate, and blood pressure. Death soon ensues. Progression through the clinical stages may follow courses characterized as acute, subacute, or chronic progressive.

The diagnosis of SSPE can be established through documentation of a compatible clinical course and at least 1 of the following supporting findings: (1) measles antibody detected in cerebrospinal fluid, (2) characteristic electroencephalographic findings, and (3) typical histologic findings in and/or isolation of virus or viral antigen from brain tissue obtained by biopsy or postmortem examination.

Cerebrospinal fluid analysis reveals normal cells but elevated IgG and IgM antibody titers in dilutions >1 : 8. Electroencephalographic patterns are normal in stage I, but in the myoclonic phase, suppression-burst episodes are seen that are characteristic of, but not pathognomonic for, SSPE. Brain biopsy is no longer routinely indicated for diagnosis of SSPE.

Management of SSPE is primarily supportive and similar to care provided to patients with other neurodegenerative diseases. Clinical trials using isoprinosine with or without interferon suggest significant benefit (30-34% remission rate) compared to patients without treatment (5-10% with spontaneous remissions).

It is recognized that carbamazepine is of significant benefit in the control of myoclonic jerks in the early stages of the illness.

Virtually all patients eventually succumb to SSPE. Most die within 1-3 yr of onset from infection or loss of autonomic control mechanisms. Prevention of SSPE depends on prevention of primary measles infection through vaccination. SSPE has been described in patients who have no history of measles infection and only exposure to the vaccine virus. However, wild-type virus, not vaccine virus, has been found in brain tissue of at least some of these patients, suggesting that they had had subclinical measles previously.

TREATMENT

Management of measles is supportive. Antiviral therapy is not effective in the treatment of measles in otherwise normal patients. Maintenance of hydration, oxygenation, and comfort are goals of therapy. Antipyretics for comfort and fever control are useful. For patients with respiratory tract involvement, airway humidification and supplemental oxygen may be of benefit. Respiratory failure from croup or pneumonia may require ventilatory support. Oral rehydration is effective in most cases, but severe dehydration may require intravenous therapy. Prophylactic antimicrobial therapy to prevent bacterial infection is not indicated.

Measles infection in immunocompromised patients is highly lethal. Ribavirin is active in vitro against measles virus. Anecdotal reports of ribavirin therapy with or without intravenous gamma globulin suggest some benefit in individual patients. However, no controlled trials have been performed, and ribavirin is not licensed in the United States for treatment of measles.

Vitamin A

Vitamin A deficiency in children in developing countries has long been known to be associated with increased mortality from a variety of infectious diseases, including measles. In the United States, studies in the early 1990s documented that 22-72% of children with measles had low retinol levels. In addition, 1 study demonstrated an inverse correlation between the level of retinol and severity of illness. Several randomized controlled trials of vitamin A therapy in the developing world and the United States have demonstrated reduced morbidity and mortality from measles. Vitamin A therapy is indicated for all patients with measles. Vitamin A should be administered once daily for 2 days at doses of 200,000 IU for children 12 mo of age or older; 100,000 IU for infants 6 mo through 11 mo of age; and 50,000 IU for infants younger than 6 mo of age.

In children with signs and symptoms of vitamin A deficiency, a 3rd age-appropriate dose is recommended 2 through 4 wk after the 2nd dose.

PROGNOSIS

In the early 20th century, deaths from measles in the United States varied between 2,000 and 10,000 per year, or about 10 deaths per 1,000 cases of measles. With improvements in healthcare and antimicrobial therapy, better nutrition, and decreased crowding, the death : case ratio fell to 1 per 1,000 cases. Between 1982 and 2002, the CDC estimated that there were 259 deaths caused by measles in the United States, with a death : case ratio of 2.5-2.8 per 1,000 cases of measles. Pneumonia and encephalitis were complications in most of the fatal cases, and immunodeficiency conditions were identified in 14-16% of deaths. In 2011, of the 222 cases reported in the United States, 70 (32%) were hospitalized, including 17 (24%) with diarrhea, 15 (21%) with dehydration, and 12 (17%) with pneumonia. No cases of encephalitis or deaths were reported.

PREVENTION

Patients shed measles virus from 7 days after exposure to 4-6 days after the onset of rash. Exposure of susceptible individuals to patients with measles should be avoided during this period. In hospitals, standard and airborne precautions should be observed for this period. Immunocompromised patients with measles will shed virus for the duration of the illness, so isolation should be maintained throughout the disease.

Vaccine

Measles vaccine in the United States is available as a monovalent preparation or combined with the measles-rubella or measles-mumps-rubella vaccine, the last of which is the recommended form in most circumstances (Table 246-2). Following the measles resurgence of 1989-1991, a 2nd dose of measles vaccine was added to the schedule. The current recommendations include a 1st dose at 12-15 mo of age, followed by a 2nd dose at 4-6 yr of age. Seroconversion is slightly lower in children who receive the 1st dose before or at 12 mo of age (87% at 9 mo, 95% at 12 mo, and 98% at 15 mo) because of persisting maternal antibody. For children who have not received 2 doses by 11-12 yr of age, a 2nd dose should be provided. Infants who receive a dose before 12 mo of age should be given 2 additional doses at 12-15 mo and 4-6 yr of age.

Adverse events from the measles-mumps-rubella vaccine include fever (usually 6-12 days following vaccination), rash in approximately 5% of vaccinated persons, and, rarely, transient thrombocytopenia. Children prone to febrile seizures may experience an event following vaccination, so the risks and benefits of vaccination should be discussed with parents. Encephalopathy and autism have not been shown to be causally associated with the measles-mumps-rubella vaccine or vaccine constituents.

A review of the effect of measles vaccination on the epidemiology of SSPE has demonstrated that measles vaccination protects against SSPE and does not accelerate the course of SSPE or trigger the disease in those already infected with wild measles virus.

Passively administered immune globulin may inhibit the immune response to live measles vaccine, and administration should be delayed for variable amounts of time based on the dose of immune globulin (Table 246-3).

Table 246-2 Recommendations for Measles Immunization

CATEGORY	RECOMMENDATIONS
Unimmunized, no history of measles (12-15 mo of age)	A 2 dose schedule (with MMR) is recommended The 1st dose is recommended at 12-15 mo of age; the 2nd is recommended at 4-6 yr of age
Children 6-11 mo of age in epidemic situations or prior to international travel	Immunize with MMR vaccine, but this dose is not considered valid, and 2 valid doses administered on or after the 1st birthday are required, The 1st valid dose should be administered at 12-15 mo of age. The 2nd valid dose is recommended at least 28 days later and is given at 4 through 6 yr of age
Students in kindergarten or elementary, middle, and high school who have received 1 dose of measles vaccine at 12 mo of age or older	Administer the 2nd dose
Students in college and other post–high school institutions who have received 1 dose of measles vaccine at ≥12 mo of age	Administer the 2nd dose
History of immunization before the 1st birthday	Do not consider valid and immunize (2 doses)
History of receipt of inactivated measles vaccine or unknown type of vaccine, 1963-1967	Do not consider valid and immunize (2 doses)
Further attenuated or unknown vaccine given with Ig	Do not consider valid and immunize (2 doses)
Allergy to eggs	Immunize; no reactions likely
Neomycin allergy, nonanaphylactic	Immunize; no reactions likely
Severe hypersensitivity (anaphylaxis) to neomycin or gelatin	Avoid immunization
Tuberculosis	Immunize; if patient has untreated tuberculosis disease, start antituberculosis therapy before immunizing
Measles exposure	Immunize and/or give Ig, depending on circumstances
HIV-infected	Immunize (2 doses) unless severely immunocompromised, and give Ig if exposed to measles
Personal or family history of seizures	Immunize; advise parents of slightly increased risk of seizures
Ig or blood recipient	Immunize at the appropriate interval (see Table 246-3)

Ig, immunoglobulin; MMR, measles-mumps-rubella vaccine.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 494.*

Table 246-3 Suggested Intervals Between Immunoglobulin Administration and Measles Immunization*

		Dose		
INDICATION FOR IMMUNOGLOBULIN	ROUTE	UNITS (U) OR MILLILITERS (mL)	mg IgG/kg	INTERVAL (mo)†
Tetanus (as tetanus Ig)	IM	250 U	10	3
Hepatitis A prophylaxis (as Ig):				
Contact prophylaxis	IM	0.02 mL/kg	3.3	3
International travel	IM	0.06 mL/kg	10	3
Hepatitis B prophylaxis (as hepatitis B Ig)	IM	0.06 mL/kg	10	3
Rabies prophylaxis (as rabies Ig)	IM	20 IU/kg	22	4
Varicella prophylaxis (as VariZIG)	IM	125 U/10 kg (maximum 625 U)	20-40	5
Measles prophylaxis (as Ig):				
Standard	IM	0.25 mL/kg	40	5
Immunocompromised host	IM	0.50 mL/kg	80	6
Respiratory syncytial virus prophylaxis (palivizumab monoclonal antibody)‡	IM	—	15 mg/kg (monoclonal)	None
Cytomegalovirus immune globulin	IV	3 mL/kg	150	6
Blood transfusion:				
Washed RBCs	IV	10 mL/kg	Negligible	0
RBCs, adenine-saline added	IV	10 mL/kg	10	3
Packed RBCs	IV	10 mL/kg	20-60	5
Whole blood	IV	10 mL/kg	80-100	6
Plasma or platelet products	IV	10 mL/kg	160	7

Continued

Table 246-3	Suggested Intervals Between Immunoglobulin Administration and Measles Immunization*—cont'd			
		Dose		
INDICATION FOR IMMUNOGLOBULIN	ROUTE	UNITS (U) OR MILLILITERS (mL)	mg IgG/kg	INTERVAL (mo)†
Replacement (or therapy) of immune deficiencies (as IVIG)	IV	—	300-400	8
ITP (as IVIG)	IV	—	400	8
ITP	IV	—	1,000	10
ITP or Kawasaki disease	IV	—	1,600-2,000	11

*Immunization in the form of measles-mumps-rubella (MMR), measles-mumps-rubella-varicella (MMRV), or monovalent measles vaccine.

†These intervals should provide sufficient time for decreases in passive antibodies in all children to allow for an adequate response to measles vaccine. Physicians should not assume that children are fully protected against measles during these intervals. Additional doses of Ig or measles vaccine may be indicated after exposure to measles (see text).

‡Monoclonal antibodies, such as palivizumab, do not interfere with the immune response to vaccines.

Ig, immunoglobulin; IgG, immunoglobulin G; ITP, immune (formerly termed "idiopathic") thrombocytopenic purpura; IVIG, intravenous Ig; RBCs, red blood cells.

From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, Fig. 1-9.*

Live vaccines should not be administered to pregnant women or to immunodeficient or immunosuppressed patients. However, patients with HIV who are not severely immunocompromised should be immunized. Because measles virus may suppress the cutaneous response to tuberculosis antigen, skin testing for tuberculosis should be performed before or at the same time as administration of the vaccine. Individuals infected with *M. tuberculosis* should be receiving appropriate treatment at the time of administration of measles vaccine.

Postexposure Prophylaxis

Susceptible individuals exposed to measles may be protected from infection by either vaccine administration or immunization with immune globulin. The vaccine is effective in prevention or modification of measles if given within 72 hr of exposure. Immune globulin may be given up to 6 days after exposure to prevent or modify infection. Immunocompetent children should receive 0.25 mL/kg intramuscularly, and immunocompromised children should receive 0.5 mL/kg (maximum dose in both cases is 15 mL/kg). Immune globulin is indicated for susceptible household contacts of measles patients, especially infants younger than 6 mo of age, pregnant women, and immunocompromised persons.

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Chapter 247
Rubella

Wilbert H. Mason

Rubella (**German measles** or **3 day measles**) is a mild, often exanthematous disease of infants and children that is typically more severe and associated with more complications in adults. Its major clinical significance is transplacental infection and fetal damage as part of the **congenital rubella syndrome (CRS).**

ETIOLOGY

Rubella virus is a member of the family Togaviridae and is the only species of the genus *Rubivirus.* It is a single-stranded RNA virus with a lipid envelope and 3 structural proteins, including a nucleocapsid protein that is associated with the nucleus and 2 glycoproteins, E1 and E2, that are associated with the envelope. The virus is sensitive to heat, ultraviolet light, and extremes of pH but is relatively stable at cold temperatures. Humans are the only known host.

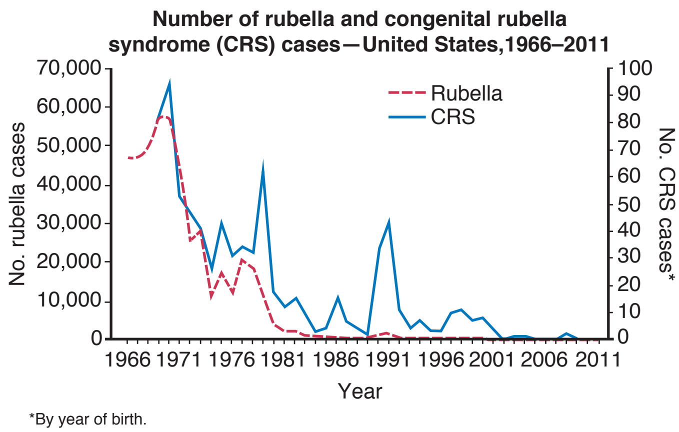

Figure 247-1 Number of rubella and congenital rubella syndrome cases—United States, 1966-2011. Rubella and CRS data provided were reported voluntarily to Centers for Disease Control and Prevention (CDC) from state health departments. *(From McLean HQ, Fiebelkorn AP, Temte JL, Wallace GH: Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013,* MMWR Recomm Rep *62(RR-04): 1–34, 2013.)*

EPIDEMIOLOGY

In the prevaccine era, rubella appeared to occur in major epidemics every 6-9 yr, with smaller peaks interspersed every 3-4 yr, and was most common in preschool-age and school-age children. During the rubella epidemic of 1964-1965 there were an estimated 12.5 million cases of rubella associated with 2,000 cases of encephalitis, more than 13,000 abortions or perinatal deaths, and 20,000 cases of CRS. Following introduction of the rubella vaccine in 1969, the incidence of rubella fell 78% by 1976 and CRS cases fell 69% (Fig. 247-1). Further decline in rubella and CRS cases occurred when certain at-risk populations were added to those for whom rubella immunization is indicated, including adolescents and college students. After years of decline, a resurgence of rubella and CRS cases occurred during 1989-1991 in association with the epidemic of measles during that period (Fig. 247-1). Subsequently, a 2 dose recommendation for rubella vaccine was implemented and resulted in a decrease in incidence of rubella from 0.45 per 100,000 population in 1990 to 0.1 per 100,000 in 1999 and a corresponding decrease of CRS, with an average of 6 infants with CRS reported annually from 1992-2004. Mothers of these infants tended to be young, Hispanic, or foreign born. The number of reported cases of rubella continued to decline through the 1990s and first decade of this century.

The endemic spread of rubella has been eliminated in the United States; elimination of transmission of rubella in the Americas also may have been achieved. However, cases of rubella continue to be imported

into the United States from countries where it remains endemic. From 2004-2012 there were 79 cases of rubella and 6 cases of CRS, all of which were imported cases of unknown source. Three of the CRS cases were acquired in Africa. Between January 1 and May 1, 2013, 5,442 cases of rubella and 10 cases of CRS were reported, demonstrating that the elimination of rubella internationally has not been achieved and continued vigilance and maintenance of high levels of immunity in the United States are necessary.

PATHOLOGY

Little information is available on the pathologic findings in rubella occurring postnatally. The few reported studies of biopsy or autopsy material from cases of rubella revealed only nonspecific findings of lymphoreticular inflammation and mononuclear perivascular and meningeal infiltration. The pathologic findings for CRS are often severe and may involve nearly every organ system (Table 247-1).

PATHOGENESIS

The viral mechanisms for cell injury and death in postnatal or congenital rubella are not well understood. Following infection, the virus replicates in the respiratory epithelium and then spreads to regional lymph nodes (Fig. 247-2). Viremia ensues and is most intense from 10-17 days after infection. Viral shedding from the nasopharynx begins approximately 10 days after infection and may be detected up to 2 wk following onset of the rash. The period of highest communicability is from 5 days before to 6 days after the appearance of the rash.

The most important risk factor for severe congenital defects is the stage of gestation at the time of infection. Maternal infection during the 1st 8 wk of gestation results in the most severe and widespread defects. The risk for congenital defects has been estimated at 90% for maternal infection before 11 wk of gestation, 33% at 11-12 wk, 11% at 13-14 wk, and 24% at 15-16 wk. Defects occurring after 16 wk of gestation are uncommon, even if fetal infection occurs.

Causes of cellular and tissue damage in the infected fetus may include tissue necrosis due to vascular insufficiency, reduced cellular multiplication time, chromosomal breaks, and production of a protein inhibitor causing mitotic arrests in certain cell types. The most distinctive feature of congenital rubella is chronicity. Once the fetus is infected early in gestation, the virus persists in fetal tissue until well beyond delivery. Persistence suggests the possibility of ongoing tissue damage and reactivation, most notably in the brain.

CLINICAL MANIFESTATIONS

Postnatal infection with rubella is a mild disease not easily discernible from other viral infections, especially in children. Following an incubation period of 14-21 days, a prodrome consisting of low-grade fever, sore throat, red eyes with or without eye pain, headache, malaise, anorexia, and lymphadenopathy begins. Suboccipital, postauricular, and anterior cervical lymph nodes are most prominent. In children, the first manifestation of rubella is usually the rash, which is variable and not distinctive. It begins on the face and neck as small, irregular pink macules that coalesce, and it spreads centrifugally to involve the torso and extremities, where it tends to occur as discrete macules (Fig. 247-3). About the time of onset of the rash, examination of the oropharynx may reveal tiny, rose-colored lesions (**Forchheimer spots**)

Table 247-1 Pathologic Findings in Congenital Rubella Syndrome

SYSTEM	PATHOLOGIC FINDINGS
Cardiovascular	Patent ductus arteriosus Pulmonary artery stenosis Ventriculoseptal defect Myocarditis
Central nervous system	Chronic meningitis Parenchymal necrosis Vasculitis with calcification
Eye	Microphthalmia Cataract Iridocyclitis Ciliary body necrosis Glaucoma Retinopathy
Ear	Cochlear hemorrhage Endothelial necrosis
Lung	Chronic mononuclear interstitial pneumonitis
Liver	Hepatic giant cell transformation Fibrosis Lobular disarray Bile stasis
Kidney	Interstitial nephritis
Adrenal gland	Cortical cytomegaly
Bone	Malformed osteoid Poor mineralization of osteoid Thinning cartilage
Spleen, lymph node	Extramedullary hematopoiesis
Thymus	Histiocytic reaction Absence of germinal centers
Skin	Erythropoiesis in dermis

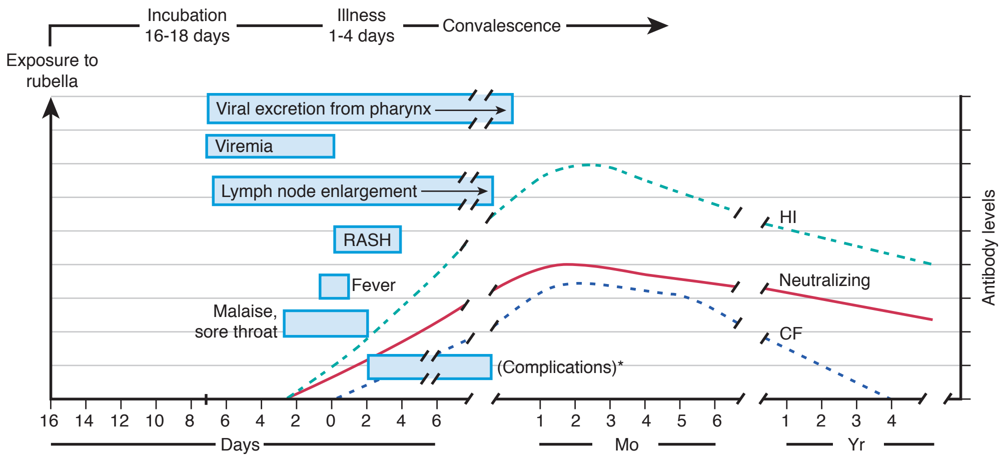

Figure 247-2 Pathophysiologic events in postnatally acquired rubella virus infection. *Possible complications include arthralgia and/or arthritis, thrombocytopenic purpura, and encephalitis. CF, complement fixation titer; HI, hemagglutination-inhibition titer. *(From Lamprecht CL: Rubella virus. In Beshe RB, editor:* Textbook of human virology, *ed 2, Littleton, MA, 1990, PSG Publishing, p. 685.)*

Figure 247-3 Rash of rubella.

Table 247-2 Clinical Manifestations of Congenital Rubella Syndrome in 376 Children Following Maternal Rubella*	
MANIFESTATION	RATE (%)
Deafness	67
Ocular	71
Cataracts	29
Retinopathy	39
Heart disease†	48
Patent ductus arteriosus	78
Right pulmonary artery stenosis	70
Left pulmonary artery stenosis	56
Valvular pulmonic stenosis	40
Low birthweight	60
Psychomotor retardation	45
Neonatal purpura	23
Death	35

*Other findings: hepatitis, linear streaking of bone, hazy cornea, congenital glaucoma, delayed growth.

†Findings in 87 patients with congenital rubella syndrome and heart disease who underwent cardiac angiography.

From Cooper LZ, Ziring PR, Ockerse AB, et al: Rubella: clinical manifestations and management, Am J Dis Child *118:18–29, 1969.*

or petechial hemorrhages on the soft palate. The rash fades from the face as it extends to the rest of the body so that the whole body may not be involved at any one time. The duration of the rash is generally 3 days, and it usually resolves without desquamation. Subclinical infections are common, and 25-40% of children may not have a rash.

LABORATORY FINDINGS

Leukopenia, neutropenia, and mild thrombocytopenia have been described during postnatal rubella.

DIAGNOSES

A specific diagnosis of rubella is important for epidemiologic reasons, for diagnosis of infection in pregnant women, and for confirmation of the diagnosis of congenital rubella. The most common diagnostic test is rubella immunoglobulin (Ig) M enzyme immunosorbent assay. As with any serologic test, the positive predictive value of testing decreases in populations with low prevalence of disease. Tests should be performed in the context of a supportive history of exposure or consistent clinical findings. The relative sensitivity and specificity of commercial kits used in most laboratories range from 96-99% and 86-97%, respectively. A caveat for testing of congenitally infected infants early in infancy is that false-negative results may occur owing to competing IgG antibodies circulating in these patients. In such patients, an IgM capture assay, reverse transcriptase polymerase chain reaction test, or viral culture should be performed for confirmation.

DIFFERENTIAL DIAGNOSES

Rubella may manifest as distinctive features suggesting the diagnosis. It is frequently confused with other infections because it is uncommon, similar to other viral exanthematous diseases, and demonstrates variability in the presence of typical findings. In severe cases, it may resemble measles. The absence of Koplik spots and a severe prodrome as well as a shorter course allow for differentiation from measles. Other diseases frequently confused with rubella include infections caused by adenoviruses, parvovirus B19 (erythema infectiosum), Epstein-Barr virus, enteroviruses, and *Mycoplasma pneumoniae.*

COMPLICATIONS

Complications following postnatal infection with rubella are infrequent and generally not life-threatening.

Postinfectious **thrombocytopenia** occurs in approximately 1 in 3,000 cases of rubella and occurs more frequently among children and in girls. It manifests about 2 wk following the onset of the rash as petechiae, epistaxis, gastrointestinal bleeding, and hematuria. It is usually self-limited.

Arthritis following rubella occurs more commonly among adults, especially women. It begins within 1 wk of onset of the exanthem and classically involves the small joints of the hands. It also is self-limited and resolves within weeks without sequelae. There are anecdotal reports and some serologic evidence linking rubella with rheumatoid arthritis, but a true causal association remains speculative.

Encephalitis is the most serious complication of postnatal rubella. It occurs in 2 forms: a postinfectious syndrome following acute rubella and a rare progressive panencephalitis manifesting as a neurodegenerative disorder years following rubella.

Postinfectious encephalitis is uncommon, occurring in 1 in 5,000 cases of rubella. It appears within 7 days after onset of the rash, consisting of headache, seizures, confusion, coma, focal neurologic signs, and ataxia. Fever may recrudesce with the onset of neurologic symptoms. Cerebrospinal fluid may be normal or have a mild mononuclear pleocytosis and/or elevated protein concentration. Virus is rarely, if ever, isolated from cerebrospinal fluid or brain, suggesting a noninfectious pathogenesis. Most patients recover completely, but mortality rates of 20% and long-term neurologic sequelae have been reported.

Progressive rubella panencephalitis (PRP) is an extremely rare complication of either acquired rubella or CRS. It has an onset and course similar to those of the subacute sclerosing panencephalitis associated with measles (see Chapter 246). Unlike in the postinfectious form of rubella encephalitis, however, rubella virus may be isolated from brain tissue of the patient with PRP, suggesting an infectious pathogenesis, albeit a "slow" one. The clinical findings and course are undistinguishable from those of subacute sclerosing panencephalitis and transmissible spongiform encephalopathies (see Chapter 278). Death occurs 2-5 yr after onset.

Other neurologic syndromes rarely reported with rubella include Guillain-Barré syndrome and peripheral neuritis. Myocarditis is a rare complication.

Congenital Rubella Syndrome

In 1941, an ophthalmologist first described a syndrome of cataracts and congenital heart disease that he correctly associated with rubella infections in the mothers during early pregnancy (Table 247-2). Shortly after the first description, hearing loss was recognized as a common

Figure 247-4 Bilateral cataracts in infant with congenital rubella syndrome.

finding often associated with microcephaly. In 1964-1965 a pandemic of rubella occurred, with 20,000 cases reported in the United States, leading to more than 11,000 spontaneous or therapeutic abortions and 2,100 neonatal deaths. From this experience emerged the expanded definition of CRS that includes numerous other transient or permanent abnormalities.

Nerve deafness is the single most common finding among infants with CRS. Most infants have some degree of intrauterine growth restriction. Retinal findings described as **salt-and-pepper retinopathy** are the most common ocular abnormality but have little early effect on vision. Unilateral or bilateral cataracts are the most serious eye finding, occurring in about a third of infants (Fig. 247-4). Cardiac abnormalities occur in half of the children infected during the 1st 8 wk of gestation. Patent ductus arteriosus is the most frequently reported cardiac defect, followed by lesions of the pulmonary arteries and valvular disease. Interstitial pneumonitis leading to death in some cases has been reported. Neurologic abnormalities are common and may progress following birth. Meningoencephalitis is present in 10-20% of infants with CRS and may persist for up to 12 mo. Longitudinal follow-up through 9-12 yr of infants without initial retardation revealed progressive development of additional sensory, motor, and behavioral abnormalities, including hearing loss and autism. PRP has also been recognized rarely after CRS. Subsequent postnatal growth retardation and ultimate short stature have been reported in a minority of cases. Rare reports of immunologic deficiency syndromes have also been described.

A variety of late-onset manifestations of CRS have been recognized. In addition to PRP, they include diabetes mellitus (20%), thyroid dysfunction (5%), and glaucoma and visual abnormalities associated with the retinopathy, which had previously been considered benign.

TREATMENT

There is no specific treatment available for either acquired rubella or CRS.

SUPPORTIVE CARE

Postnatal rubella is generally a mild illness that requires no care beyond antipyretics and analgesics. Intravenous immunoglobulin or corticosteroids can be considered for severe, nonremitting thrombocytopenia.

Management of children with CRS is more complex and requires pediatric, cardiac, audiologic, ophthalmologic, and neurologic evaluation and follow-up because many manifestations may not be readily apparent initially or may worsen with time. Hearing screening is of special importance, because early intervention may improve outcomes in children with hearing problems caused by CRS.

PROGNOSIS

Postnatal infection with rubella has an excellent prognosis. Long-term outcomes of CRS are less favorable and somewhat variable. In an Australian cohort evaluated 50 yr after infection, many had chronic conditions but most were married and had made good social adjustments. A cohort from New York from the mid-1960s epidemic had less-favorable outcomes, with 30% leading normal lives, 30% in dependent situations but functional, and 30% requiring institutionalization and continuous care.

Reinfection with wild virus occurs postnatally in both individuals who were previously infected with wild-virus rubella and in vaccinated individuals. Reinfection is defined serologically as a significant increase in IgG antibody level and/or an IgM response in an individual who has a documented preexisting rubella-specific IgG above an accepted cutoff. Reinfection may result in an anamnestic IgG response, an IgM and IgG response, or clinical rubella. There are 29 reports of CRS following maternal reinfection in the literature. Reinfection with serious adverse outcomes to adults or children is rare and of unknown significance.

PREVENTION

Patients with postnatal infection should be isolated from susceptible individuals for 7 days after onset of the rash. Standard plus droplet precautions are recommended for hospitalized patients. Children with CRS may excrete the virus in respiratory secretions up to 1 yr of age, so contact precautions should be maintained for them until then, unless repeated cultures of urine and pharyngeal secretions have negative results. Similar precautions apply to patients with CRS with regard to attendance in school and out-of-home childcare.

Exposure of susceptible pregnant women poses a potential risk to the fetus. For pregnant women exposed to rubella, a blood specimen should be obtained as soon as possible for rubella IgG-specific antibody testing; a frozen aliquot also should be saved for later testing. If the rubella antibody test result is positive, the mother is likely immune. If the rubella antibody test is negative, a 2nd specimen should be obtained 2-3 wk later and tested concurrently with the saved specimen. If both of these test negative, a 3rd specimen should be obtained 6 wk after exposure and tested concurrently with the saved specimen. If both the 2nd and 3rd specimens test negative, infection has not occurred. A negative 1st specimen and a positive test result in either the 2nd and 3rd specimen indicate that seroconversion has occurred in the mother, suggesting recent infection. Counseling should be provided about the risks and benefits of termination of pregnancy. The routine use of immunoglobulin for susceptible pregnant women exposed to rubella is not recommended and is considered only if termination of pregnancy is not an option because of maternal preferences. In such circumstances, immunoglobulin 0.55 mL/kg IM may be given with the understanding that prophylaxis may reduce the risk for clinically apparent infection but does not guarantee prevention of fetal infection.

VACCINATION

Rubella vaccine in the United States consists of the attenuated Wistar RA 27/3 strain that is usually administered in combination with measles and mumps (MMR) or also with varicella (MMRV) in a 2 dose regimen at 12-15 mo and 4-6 yr of age. It theoretically may be effective as postexposure prophylaxis if administered within 3 days of exposure. Vaccine should not be administered to severely immunocompromised patients (e.g., transplant recipients). Patients with HIV infection who are not severely immunocompromised may benefit from vaccination. Fever is not a contraindication, but if a more serious illness is suspected, immunization should be delayed. Immunoglobulin preparations may inhibit the serologic response to the vaccine (see Chapter 172). Vaccine should not be administered during pregnancy. If pregnancy occurs within 28 days of immunization, the patient should be counseled on the theoretical risks to the fetus. Studies of more than 200 women who had been inadvertently immunized with rubella vaccine during pregnancy showed that none of their offspring developed CRS. Therefore, interruption of pregnancy is probably not warranted.

Following a single dose of rubella RA 27/3 vaccine, 95% of persons 12 mo of age and older develop serologic immunity, and after 2 doses 99% have detectable antibody. Rubella RA 27/3 vaccine is highly protective as 97% of those vaccinated are protected from clinical disease after

1 dose. Detectable antibodies remain for 15 yr in most individuals vaccinated following 1 dose, and 91% to 100% had antibodies after 12-15 yr after 2 doses. Although antibody levels may wane, especially after 1 dose of vaccine, increased susceptibility to rubella disease does not occur.

Adverse reactions to rubella vaccination are uncommon in children. MMR administration is associated with fever in 5-15% of vaccinees and with rash in approximately 5% of vaccinees. Arthralgia and arthritis are more common following rubella vaccination in adults. Approximately 25% of postpubertal women experience arthralgia, and 10% experience arthritis. Peripheral neuropathies and transient thrombocytopenia may also occur.

As part of the worldwide effort to eliminate endemic rubella virus transmission and occurrence of CRS, maintaining high population immunity through vaccination coverage and high-quality integrated measles-rubella surveillance have been emphasized as being vital to its success.

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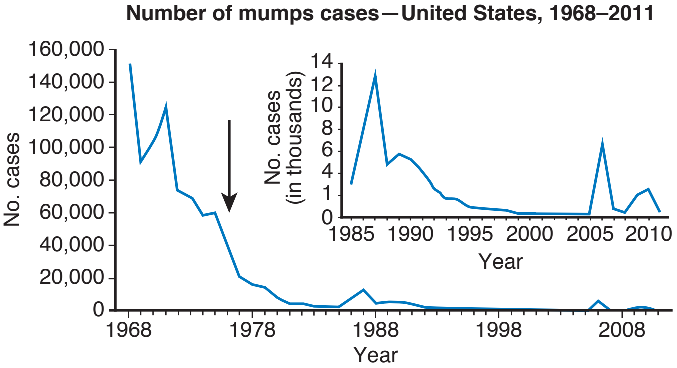

Figure 248-1 Mumps cases in the United States from 1967, when the live mumps vaccine was introduced, to 2011. There was a steady decline following introduction of the vaccine and recommendation for routine vaccination in 1977 *(arrow)*. Note national increases in activity in 1986-1987 and 2006. Mumps data provided were reported voluntarily to Centers for Disease Control and Prevention from state health departments. *(From McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS: Prevention of measles, rubella, congenital rubella syndrome and mumps, 2013,* MMWR Recomm Rep *62(RR-04):1–34, 2013.)*

Chapter 248

Mumps

Wilbert H. Mason

Mumps is an acute self-limited infection that was once commonplace but is now unusual in developed countries because of widespread use of vaccination. It is characterized by fever, bilateral or unilateral parotid swelling and tenderness, and the frequent occurrence of meningoencephalitis and orchitis. Although no longer common in countries with extensive vaccination programs, mumps remains endemic in the rest of the world, warranting continued vaccine protection.

ETIOLOGY

Mumps virus is in the family Paramyxoviridae and the genus *Rubulavirus*. It is a single-stranded pleomorphic RNA virus encapsulated in a lipoprotein envelope and possessing 7 structural proteins. Surface glycoproteins called HN (hemagglutinin-neuraminidase) and F (fusion) mediate absorption of the virus to host cells and penetration of the virus into cells, respectively. Both of these proteins stimulate production of protective antibodies. Mumps virus exists as a single immunotype, and humans are the only natural host.

EPIDEMIOLOGY

In the prevaccine era, mumps occurred primarily in young children between the ages of 5 and 9 yr and in epidemics about every 4 yr. Mumps infection occurred more often in the winter and spring months. In 1968, just after the introduction of the mumps vaccine, 185,691 cases were reported in the United States. Following the recommendation for routine use of mumps vaccine in 1977, the incidence of mumps fell dramatically in young children (Fig. 248-1) and shifted instead to older children, adolescents, and young adults. Outbreaks continued to occur *even in highly vaccinated* populations as a result of vaccine failure and also because of undervaccination of susceptible persons. After implementation of the 2 dose recommendation for the measles-mumps-rubella (MMR) vaccine for measles control in 1989, the number of mumps cases declined further. During 2001-2003, fewer than 300 mumps cases were reported each year. In 2006, the largest mumps epidemic in the last 20 yr occurred in the United States. A total of 6,584 cases occurred, 85% of them in 8 midwestern states. Twenty-nine percent of the cases occurred in patients 18-24 yr old, most of whom were attending college. An analysis of 4,039 patients with mumps seen in the 1st 7 mo of the epidemic indicated that 63% had received more than 2 doses of the MMR vaccine. Subsequently, several outbreaks of mumps have been documented in highly vaccinated populations in the Northeast United States, in a large public university in the Western United States, and in Guam.

Mumps is spread from person to person by respiratory droplets. Virus appears in the saliva from up to 7 days before to as long as 7 days after onset of parotid swelling. The period of maximum infectiousness is 1-2 days before to 5 days after onset of parotid swelling. Viral shedding before onset of symptoms and in asymptomatic infected individuals impairs efforts to contain the infection in susceptible populations. The U.S. Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the Health Infection Control Practices Advisory Committee recommend an isolation period of 5 days after onset of parotitis for patients with mumps in both community and healthcare settings.

PATHOLOGY AND PATHOGENESIS

Mumps virus targets the salivary glands, central nervous system (CNS), pancreas, testes, and, to a lesser extent, thyroid, ovaries, heart, kidneys, liver, and joint synovia.

Following infection, initial viral replication occurs in the epithelium of the upper respiratory tract. Infection spreads to the adjacent lymph nodes by the lymphatic drainage, and viremia ensues, spreading the virus to targeted tissues. Mumps virus causes necrosis of infected cells and is associated with a lymphocytic inflammatory infiltrate. Salivary gland ducts are lined with necrotic epithelium, and the interstitium is infiltrated with lymphocytes. Swelling of tissue within the testes may result in focal ischemic infarcts. The cerebrospinal fluid (CSF) frequently contains a mononuclear pleocytosis, even in individuals without clinical signs of meningitis.

CLINICAL MANIFESTATIONS

The incubation period for mumps ranges from 12-25 days but is usually 16-18 days. Mumps virus infection may result in clinical presentation ranging from asymptomatic or nonspecific symptoms to the typical illness associated with parotitis with or without complications involving several body systems. The typical patient presents with a prodrome lasting 1-2 days and consisting of fever, headache, vomiting, and achiness. Parotitis then appears and may be unilateral initially but becomes bilateral in approximately 70% of cases (Fig. 248-2). The parotid gland is tender, and parotitis may be preceded or accompanied by ear pain on the ipsilateral side. Ingestion of sour or acidic foods or liquids may enhance pain in the parotid area. As swelling progresses, the angle of the jaw is obscured and the ear lobe may be lifted upward and outward (Figs. 248-2 and 248-3). The opening of the Stensen duct may be red and edematous. The parotid swelling peaks in approximately 3 days and then gradually subsides over 7 days. Fever and the

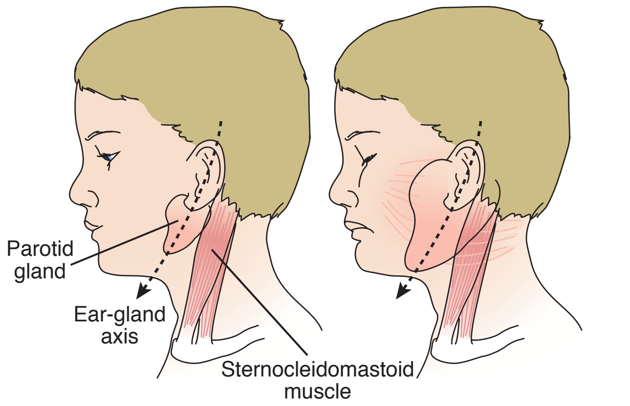

Figure 248-2 Schematic of a parotid gland infected with mumps *(right)* compared with a normal gland *(left).* An imaginary line bisecting the long axis of the ear divides the parotid gland into 2 equal parts. These anatomic relationships are not altered in the enlarged gland. An enlarged cervical lymph node is usually posterior to the imaginary line. *(From Mumps [epidemic parotitis]. In Krugman S, Ward R, Katz SL, editors:* Infectious diseases in children, *ed 6, St. Louis, 1977, Mosby, p. 182.)*

Figure 248-3 A child with mumps showing parotid swelling. *(From the Centers for Disease Control and Prevention [CDC]: Public health image library [PHIL], image #4491. Available at: http://phil.cdc.gov/phil/home.asp)*

other systemic symptoms resolve in 3-5 days. A morbilliform rash is rarely seen. Submandibular salivary glands may also be involved or may be enlarged without parotid swelling. Edema over the sternum as a result of lymphatic obstruction may also occur.

DIAGNOSIS

When mumps was highly prevalent, the diagnosis could be made on the basis of a history of exposure to mumps infection, an appropriate incubation period, and development of typical clinical findings. Confirmation of the presence of parotitis could be made with demonstration of an elevated serum amylase value. Leukopenia with a relative lymphocytosis was a common finding. Today, in patients with parotitis lasting longer than 2 days and of unknown cause, a specific diagnosis of mumps should be confirmed or ruled out by virologic or serologic means. This step may be accomplished by isolation of the virus in cell culture, detection of viral antigen by direct immunofluorescence, or identification of nucleic acid by reverse transcriptase polymerase chain reaction. Virus can be isolated from upper respiratory tract secretions, CSF, or urine during the acute illness. Serologic testing is usually a more convenient and available mode of diagnosis. A significant increase in serum mumps immunoglobulin G antibody between acute and convalescent serum specimens as detected by complement fixation, neutralization hemagglutination, or enzyme immunoassay tests establishes the diagnosis. Mumps immunoglobulin G antibodies may cross react with antibodies to parainfluenza virus in serologic testing. More commonly, an enzyme immunoassay for mumps immunoglobulin M antibody is used to identify recent infection. Skin testing for mumps is neither sensitive nor specific and should not be used.

DIFFERENTIAL DIAGNOSIS

Parotid swelling may be caused by many other infectious and noninfectious conditions. Viruses that cause parotitis include parainfluenza 1 and parainfluenza 3 viruses, influenza A virus, cytomegalovirus, Epstein-Barr virus, enteroviruses, lymphocytic choriomeningitis virus, and HIV. Purulent parotitis, usually caused by *Staphylococcus aureus,* is unilateral, is extremely tender, is associated with an elevated white blood cell count, and may involve purulent drainage from the Stensen duct. Submandibular or anterior cervical adenitis from a variety of pathogens may also be confused with parotitis. Other noninfectious causes of parotid swelling include obstruction of the Stensen duct, collagen vascular diseases such as Sjögren syndrome, systemic lupus erythematosus, and tumor.

COMPLICATIONS

The most common complications of mumps are meningitis, with or without encephalitis, and gonadal involvement. Uncommon complications include conjunctivitis, optic neuritis, pneumonia, nephritis, pancreatitis, and thrombocytopenia.

Maternal infection with mumps during the 1st trimester of pregnancy results in increased fetal wastage. No fetal malformations have been associated with intrauterine mumps infection. However, perinatal mumps disease has been reported in infants born to mothers who acquired mumps late in gestation.

Meningitis and Meningoencephalitis

Mumps virus is neurotropic and is thought to enter the CNS via the choroid plexus and infect the choroidal epithelium and ependymal cells, both of which can be found in CSF along with mononuclear leukocytes. Symptomatic CNS involvement occurs in 10-30% of infected individuals, but CSF pleocytosis has been found in 40-60% of patients with mumps parotitis. The meningoencephalitis may occur before, along with, or following the parotitis. It most commonly manifests 5 days after the parotitis. Clinical findings vary with age. Infants and young children have fever, malaise, and lethargy, whereas older children, adolescents, and adults complain of headache and demonstrate meningeal signs. In 1 series of children with mumps and meningeal involvement, findings were fever in 94%, vomiting in 84%, headache in 47%, parotitis in 47%, neck stiffness in 71%, lethargy in 69%, and seizures in 18%. In typical cases, symptoms resolve in 7-10 days. CSF in mumps meningitis has a white blood cell pleocytosis of 200-600/μL with a predominance of lymphocytes. The CSF glucose content is normal in most patients, but a moderate hypoglycorrhachia (glucose content 20-40 mg/dL) may be seen in 10-20% of patients. The CSF protein content is normal or mildly elevated.

Less-common CNS complications of mumps include transverse myelitis, aqueductal stenosis, and facial palsy. Sensorineural hearing loss is rare and has been estimated to occur in 0.5-5.0 in 100,000 cases of mumps. There is some evidence that this sequela is more likely in patients with meningoencephalitis.

Orchitis and Oophoritis

In adolescent and adult males, orchitis is second only to parotitis as a common finding in mumps. Involvement in prepubescent boys is extremely rare, but after puberty, orchitis occurs in 30-40% of males. It begins within days following onset of parotitis in the majority of cases and is associated with moderate to high fever, chills, and exquisite pain and swelling of the testes. In 30% or less of cases, the orchitis is bilateral. Atrophy of the testes may occur, but sterility is rare even with bilateral involvement.

Oophoritis is uncommon in postpubertal females but may cause severe pain and may be confused with appendicitis when located on the right side.

Pancreatitis

Pancreatitis may occur in mumps with or without parotid involvement. Severe disease is rare, but fever, epigastric pain, and vomiting are suggestive. Epidemiologic studies have suggested that mumps may be associated with the subsequent development of diabetes mellitus, but a causal link has not been established.

Cardiac Involvement

Myocarditis has been reported in mumps, and molecular studies have identified mumps virus in heart tissue taken from patients with endocardial fibroelastosis.

Arthritis

Arthralgia, monoarthritis, and migratory polyarthritis have been reported in mumps. Arthritis is seen with or without parotitis and usually occurs within 3 wk of onset of parotid swelling. It is generally mild and self-limited.

Thyroiditis

Thyroiditis is rare following mumps. It has not been reported without parotitis and may occur weeks after the acute infection. Most cases resolve, but some become relapsing and result in hypothyroidism.

TREATMENT

No specific antiviral therapy is available for mumps. Management should be aimed at reducing the pain associated with meningitis or orchitis and maintaining adequate hydration. Antipyretics may be given for fever.

PROGNOSIS

The outcome of mumps is nearly always excellent, even when the disease is complicated by encephalitis, although fatal cases from CNS involvement or myocarditis have been reported.

PREVENTION

Immunization with the live mumps vaccine is the primary mode of prevention used in the United States. It is given as part of the MMR 2 dose vaccine schedule, at 12-15 mo of age for the 1st dose and 4-6 yr of age for the 2nd dose. If not given at 4-6 yr, the 2nd dose should be given before children enter puberty. Antibody develops in 94% (range: 89-97%) of vaccinees after 1 dose. Antibody levels achieved following vaccination are lower than following natural infection.

The median vaccine effectiveness of mumps vaccine after 1 dose of vaccine is 78% (range: 49-92%) and after 2 doses is 88% (range: 66-95%). Duration of effectiveness is ≥10 yr after 1 dose and ≥15 yr after 2 doses.

As a live-virus vaccine, MMR should not be administered to pregnant women or to severely immunodeficient or immunosuppressed individuals. HIV-infected patients who are not severely immunocompromised may receive the vaccine, because the risk for severe infection with mumps outweighs the risk for serious reaction to the vaccine. Individuals with anaphylactoid reactions to egg or neomycin may be at risk for immediate-type hypersensitivity reactions to the vaccine. Persons with other types of reactions to egg or reactions to other components of the vaccine are not restricted from receiving the vaccine.

In 2006, in response to the multistate outbreak in the United States, evidence of immunity to mumps through vaccination was redefined. Acceptable presumptive evidence of immunity to mumps now consists of 1 of the following: (1) documentation of adequate vaccination at age 12 mo or older, (2) laboratory evidence of immunity, (3) birth before 1957, and (4) documentation of physician-diagnosed mumps. Evidence of immunity through documentation of adequate vaccination is now defined as 1 dose of a live mumps virus vaccine for preschool-age children and adults not at high risk and 2 doses for school-age children (i.e., grades K-12) and for adults at high risk (e.g., healthcare workers, international travelers, and students at post–high school educational institutions).

All persons who work in healthcare facilities should be immune to mumps. Adequate mumps vaccination for healthcare workers born during or after 1957 consists of 2 doses of a live mumps virus vaccine. Healthcare workers with no history of mumps vaccination and no other evidence of immunity should receive 2 doses, with >28 days between doses. Healthcare workers who have received only 1 dose previously should receive a 2nd dose. Because birth before 1957 is only presumptive evidence of immunity, healthcare facilities should consider recommending 1 dose of a live mumps virus vaccine for unvaccinated workers born before 1957 who do not have a history of physician-diagnosed mumps or laboratory evidence of mumps immunity. During an outbreak, healthcare facilities should strongly consider recommending 2 doses of a live mumps virus vaccine to unvaccinated workers born before 1957 who do not have evidence of mumps immunity.

Adverse reactions to mumps virus vaccine are rare. Parotitis and orchitis have been reported rarely. Other reactions, such as febrile seizures, deafness, rash, purpura, encephalitis, and meningitis, may not be causally related to the strain of mumps vaccine virus used for immunization in the United States. Higher rates of aseptic meningitis following vaccination for mumps are associated with vaccine strains used elsewhere in the world, including the Leningrad 3 and Urabe Am 9 strains. Transient suppression of reactivity to tuberculin skin testing has been reported after mumps vaccination.

In 2005, the quadrivalent measles, mumps, rubella, and varicella vaccine (MMRV) was made available. However, in 2010 studies showed a greater risk of febrile seizures in children 12-23 mo of age 5-12 days following administration of the vaccine. No increased risk of seizures was seen in children receiving the 1st dose of the MMRV at older than 48 mo of age. As a result, the American Academy of Pediatrics currently recommends either the MMR vaccine and separate varicella vaccine or the MMRV vaccine in children 12 through 47 mo of age. After 48 mo of age, the MMRV is generally preferred.

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Chapter 249

Polioviruses

Eric A.F. Simões

ETIOLOGY

The polioviruses are nonenveloped, positive-stranded RNA viruses belonging to the Picornaviridae family, in the genus *Enterovirus,* and consist of 3 antigenically distinct serotypes (types 1, 2, and 3). Polioviruses spread from the intestinal tract to the central nervous system (CNS), where they cause aseptic meningitis and poliomyelitis, or polio. The polioviruses are extremely hardy and can retain infectivity for several days at room temperature.

EPIDEMIOLOGY

The most devastating result of poliovirus infection is paralysis, although 90-95% of infections are inapparent but induce protective immunity. Clinically apparent but nonparalytic illness occurs in approximately 5% of all infections, with paralytic polio occurring in approximately 1 in 1,000 infections among infants to approximately 1 in 100 infections among adolescents. In developed countries prior to universal vaccination, epidemics of paralytic poliomyelitis occurred primarily in adolescents. Conversely, in developing countries with poor sanitation, infection early in life results in infantile paralysis. Improved sanitation explains the virtual eradication of polio from the United States in the early 1960s, when only approximately 65% of the population was immunized with the Salk vaccine, which contributed to the disappearance of circulating wild-type poliovirus in the United States and

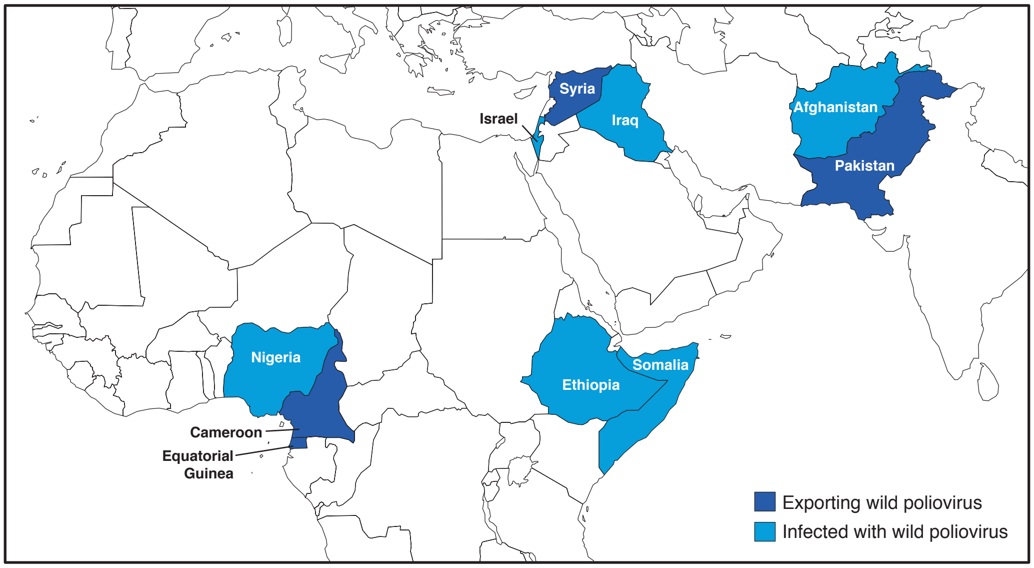

As of June 30, 2014.

Figure 249-1 Countries identified by the World Health Organization as exporting wild poliovirus and those in which wild poliovirus infection is currently found, worldwide, 2014. *(From Wallace GS, Seward JF, Pallansch MA; Centers for Disease Control and Prevention: Interim CDC guidelines for polio vaccination for travel to and from countries affected by wild poliovirus.* MMWR Morb Mortal Wkly Rep *63:591–594, 2014.)*

Europe. Poor sanitation and crowding have permitted the continued transmission of poliovirus in certain poor countries in Africa and Asia, despite massive global efforts to eradicate polio, which in some areas involve an average of 12-13 doses of polio vaccine administered to children in the 1st 5 yr of life (Fig. 249-1).

TRANSMISSION

Humans are the only known reservoir for the polioviruses, which are spread by the fecal-oral route. Poliovirus has been isolated from feces for longer than 2 wk before paralysis to several weeks after the onset of symptoms.

PATHOGENESIS

Polioviruses infect cells by adsorbing to the genetically determined **poliovirus receptor.** The virus penetrates the cell, is uncoated, and releases viral RNA. The RNA is translated to produce proteins responsible for replication of the RNA, shutoff of host cell protein synthesis, and synthesis of structural elements that compose the capsid. Mature virus particles are produced in 6-8 hr and are released into the environment by disruption of the cell.

In the contact host, wild-type and vaccine strains of polioviruses gain host entry via the gastrointestinal tract. The primary site of replication is in the M cells lining the mucosa of the small intestine. Regional lymph nodes are infected, and primary viremia occurs after 2-3 days. The virus seeds multiple sites, including the reticuloendothelial system, brown fat deposits, and skeletal muscle. Wild-type poliovirus probably accesses the CNS along peripheral nerves. Vaccine strains of polioviruses do not replicate in the CNS, a feature that accounts for the safety of the live-attenuated vaccine. Occasional **revertants** (by nucleotide substitution) of these vaccine strains develop a neurovirulent phenotype and cause **vaccine-associated paralytic poliomyelitis (VAPP).** Reversion occurs in the small intestine and probably accesses the CNS via the peripheral nerves. Because poliovirus replicates in endothelial cells, the theory of viremic spread to the CNS was favored; however, poliovirus has almost never been cultured from the cerebrospinal fluid (CSF) of patients with paralytic disease, and patients with aseptic meningitis caused by poliovirus never have paralytic disease. With the first appearance of non-CNS symptoms, a secondary viremia probably occurs as a result of enormous viral replication in the reticuloendothelial system.

The exact mechanism of entry into the CNS is not known. However, once entry is gained the virus may traverse neural pathways, and multiple sites within the CNS are often affected. The effect on motor and vegetative neurons is most striking and correlates with the clinical manifestations. Perineuronal inflammation, a mixed inflammatory reaction with both polymorphonuclear leukocytes and lymphocytes, is associated with extensive neuronal destruction. Petechial hemorrhages and considerable inflammatory edema also occur in areas of poliovirus infection. The poliovirus primarily infects motor neuron cells in the spinal cord (**the anterior horn cells**) and the medulla oblongata (the cranial nerve nuclei). Because of the overlap in muscle innervation by 2-3 adjacent segments of the spinal cord, clinical signs of weakness in the limbs develop when more than 50% of motor neurons are destroyed. In the medulla, less-extensive lesions cause paralysis, and involvement of the reticular formation that contains the vital centers controlling respiration and circulation may have a catastrophic outcome. Involvement of the intermediate and dorsal areas of the horn and the dorsal root ganglia in the spinal cord results in hyperesthesia and myalgias that are typical of acute poliomyelitis. Other neurons affected are the nuclei in the roof and vermis of the cerebellum, the substantia nigra, and, occasionally, the red nucleus in the pons; there may be variable involvement of thalamic, hypothalamic, and pallidal nuclei and the motor cortex.

Apart from the histopathology of the CNS, inflammatory changes occur generally in the reticuloendothelial system. Inflammatory edema and sparse lymphocytic infiltration are prominently associated with hyperplastic lymphocytic follicles.

Infants acquire immunity transplacentally from their mothers. Transplacental immunity disappears at a variable rate during the 1st 4-6 mo of life. Active immunity after natural infection is probably lifelong but protects against the infecting serotype only; infections with other serotypes are possible. Poliovirus neutralizing antibodies develop within several days after exposure as a result of replication of the virus in the M cells in the intestinal tract and deep lymphatic tissues. This early production of circulating immunoglobulin (Ig) G antibodies protects against CNS invasion. Local (mucosal) immunity, conferred mainly by secretory IgA, is an important defense against subsequent reinfection of the gastrointestinal tract.

CLINICAL MANIFESTATIONS

The incubation period of poliovirus from contact to initial clinical symptoms is usually considered to be 8-12 days, with a range of 5-35 days. Poliovirus infections with wild-type virus may follow 1 of several courses: **inapparent infection,** which occurs in 90-95% of cases and causes no disease and no sequelae; abortive poliomyelitis; nonparalytic

poliomyelitis; or paralytic poliomyelitis. Paralysis, if it occurs, appears 3-8 days after the initial symptoms. The clinical manifestations of paralytic polio caused by wild or vaccine strains are comparable, although the incidence of abortive and nonparalytic paralysis with vaccine-associated poliomyelitis is unknown.

Abortive Poliomyelitis

In approximately 5% of patients, a nonspecific influenza-like syndrome occurs 1-2 wk after infection, which is termed *abortive poliomyelitis*. Fever, malaise, anorexia, and headache are prominent features, and there may be sore throat and abdominal or muscular pain. Vomiting occurs irregularly. The illness is short lived, lasting up to 2-3 days. The **physical examination** may be normal or may reveal nonspecific pharyngitis, abdominal or muscular tenderness, and weakness. Recovery is complete, and no neurologic signs or sequelae develop.

Nonparalytic Poliomyelitis

In approximately 1% of patients infected with wild-type poliovirus, signs of abortive poliomyelitis are present, as are more intense headache, nausea, and vomiting, as well as soreness and stiffness of the posterior muscles of the neck, trunk, and limbs. Fleeting paralysis of the bladder and constipation are frequent. Approximately two thirds of these children have a short symptom-free interlude between the 1st phase (**minor illness**) and the 2nd phase (CNS disease or **major illness**). Nuchal rigidity and spinal rigidity are the basis for the diagnosis of nonparalytic poliomyelitis during the second phase.

Physical examination reveals nuchal-spinal signs and changes in superficial and deep reflexes. Gentle forward flexion of the occiput and neck elicits nuchal rigidity. The examiner can demonstrate head drop by placing the hands under the patient's shoulders and raising the patient's trunk. Although normally the head follows the plane of the trunk, in poliomyelitis it often falls backward limply, but this response is not attributable to true paresis of the neck flexors. In struggling infants it may be difficult to distinguish voluntary resistance from clinically important true nuchal rigidity. The examiner may place the infant's shoulders flush with the edge of the table, support the weight of the occiput in the hand, and then flex the head anteriorly. True nuchal rigidity persists during this maneuver. When open, the anterior fontanel may be tense or bulging.

In the early stages the reflexes are normally active and remain so unless paralysis supervenes. Changes in reflexes, either increased or decreased, may precede weakness by 12-24 hr. The superficial reflexes, the cremasteric and abdominal reflexes, and the reflexes of the spinal and gluteal muscles are usually the first to diminish. The spinal and gluteal reflexes may disappear before the abdominal and cremasteric reflexes. Changes in the deep tendon reflexes generally occur 8-24 hr after the superficial reflexes are depressed and indicate impending paresis of the extremities. Tendon reflexes are absent with paralysis. Sensory defects do not occur in poliomyelitis.

Paralytic Poliomyelitis

Paralytic poliomyelitis develops in approximately 0.1% of persons infected with poliovirus, causing 3 clinically recognizable syndromes that represent a continuum of infection differentiated only by the portions of the CNS most severely affected. These are (1) spinal paralytic poliomyelitis, (2) bulbar poliomyelitis, and (3) polioencephalitis.

Spinal paralytic poliomyelitis may occur as the 2nd phase of a biphasic illness, the 1st phase of which corresponds to abortive poliomyelitis. The patient then appears to recover and feels better for 2-5 days, after which severe headache and fever occur with exacerbation of the previous systemic symptoms. Severe muscle pain is present, and sensory and motor phenomena (e.g., paresthesia, hyperesthesia, fasciculations, and spasms) may develop. On physical examination the distribution of paralysis is characteristically spotty. Single muscles, multiple muscles, or groups of muscles may be involved in any pattern. Within 1-2 days, asymmetric flaccid paralysis or paresis occurs. Involvement of one leg is most common, followed by involvement of one arm. The proximal areas of the extremities tend to be involved to a greater extent than the distal areas. To detect mild muscular weakness, it is often necessary to apply gentle resistance in opposition to the muscle group being tested. Examination at this point may reveal nuchal stiffness or rigidity, muscle tenderness, initially hyperactive deep tendon reflexes (for a short period) followed by absence or diminution of reflexes, and paresis or flaccid paralysis. In the spinal form, there is weakness of some of the muscles of the neck, abdomen, trunk, diaphragm, thorax, or extremities. Sensation is intact; sensory disturbances, if present, suggest a disease other than poliomyelitis.

The paralytic phase of poliomyelitis is extremely variable; some patients progress during observation from paresis to paralysis, whereas others recover, either slowly or rapidly. The extent of paresis or paralysis is directly related to the extent of neuronal involvement; paralysis occurs if >50% of the neurons supplying the muscles are destroyed. The extent of involvement is usually obvious within 2-3 days; only rarely does progression occur beyond this interval. Bowel and bladder dysfunction ranging from transient incontinence to paralysis with constipation and urinary retention often accompany paralysis of the lower limbs.

The onset and course of paralysis are variable in developing countries. The biphasic course is rare; typically the disease manifests in a single phase in which prodromal symptoms and paralysis occur in a continuous fashion. In developing countries, where a history of intramuscular injections precedes paralytic poliomyelitis in approximately 50-60% of patients, patients may present initially with fever and paralysis (**provocation paralysis**). The degree and duration of muscle pain are also variable, ranging from a few days usually to a week. Occasionally spasm and increased muscle tone with a transient increase in deep tendon reflexes occur in some patients, whereas in most patients, flaccid paralysis occurs abruptly. Once the temperature returns to normal, progression of paralytic manifestations stops. Little recovery from paralysis is noted in the 1st days or weeks, but, if it is to occur, it is usually evident within 6 mo. The return of strength and reflexes is slow and may continue to improve for as long as 18 mo after the acute disease. Lack of improvement from paralysis within the 1st several weeks or months after onset is usually evidence of permanent paralysis. Atrophy of the limb, failure of growth, and deformity are common and are especially evident in the growing child.

Bulbar poliomyelitis may occur as a clinical entity without apparent involvement of the spinal cord. Infection is a continuum, and designation of the disease as bulbar implies only dominance of the clinical manifestations by dysfunctions of the cranial nerves and medullary centers. The clinical findings seen with bulbar poliomyelitis with respiratory difficulty (other than paralysis of extraocular, facial, and masticatory muscles) include (1) nasal twang to the voice or cry caused by palatal and pharyngeal weakness (hard-consonant words such as "cookie" and "candy" bring this feature out best); (2) inability to swallow smoothly, resulting in accumulation of saliva in the pharynx, indicating partial immobility (holding the larynx lightly and asking the patient to swallow will confirm such immobility); (3) accumulated pharyngeal secretions, which may cause irregular respirations that appear interrupted and abnormal even to the point of falsely simulating intercostal or diaphragmatic weakness; (4) absence of effective coughing, shown by constant fatiguing efforts to clear the throat; (5) nasal regurgitation of saliva and fluids as a result of palatal paralysis, with inability to separate the oropharynx from the nasopharynx during swallowing; (6) deviation of the palate, uvula, or tongue; (7) involvement of vital centers in the medulla, which manifest as irregularities in rate, depth, and rhythm of respiration; as cardiovascular alterations, including blood pressure changes (especially increased blood pressure), alternate flushing and mottling of the skin, and cardiac arrhythmias; and as rapid changes in body temperature; (8) paralysis of 1 or both vocal cords, causing hoarseness, aphonia, and, ultimately, asphyxia unless the problem is recognized on laryngoscopy and managed by immediate tracheostomy; and (9) the **rope sign,** an acute angulation between the chin and larynx caused by weakness of the hyoid muscles (the hyoid bone is pulled posteriorly, narrowing the hypopharyngeal inlet).

Uncommonly, bulbar disease may culminate in an ascending paralysis (Landry type), in which there is progression cephalad from initial involvement of the lower extremities. Hypertension and other

autonomic disturbances are common in bulbar involvement and may persist for a week or more or may be transient. Occasionally, hypertension is followed by hypotension and shock and is associated with irregular or failed respiratory effort, delirium, or coma. This kind of bulbar disease may be rapidly fatal.

The course of bulbar disease is variable; some patients die as a result of extensive, severe involvement of the various centers in the medulla; others recover partially but require ongoing respiratory support, and others recover completely. Cranial nerve involvement is seldom permanent. Atrophy of muscles may be evident, patients immobilized for long periods may experience pneumonia, and renal stones may form as a result of hypercalcemia and hypercalciuria secondary to bone resorption.

Polioencephalitis is a rare form of the disease in which higher centers of the brain are severely involved. Seizures, coma, and spastic paralysis with increased reflexes may be observed. Irritability, disorientation, drowsiness, and coarse tremors are often present with peripheral or cranial nerve paralysis that coexists or ensues. Hypoxia and hypercapnia caused by inadequate ventilation due to respiratory insufficiency may produce disorientation without true encephalitis. The manifestations are common to encephalitis of any cause and can be attributed to polioviruses only with specific viral diagnosis or if accompanied by flaccid paralysis.

Paralytic poliomyelitis with ventilatory insufficiency results from several components acting together to produce ventilatory insufficiency resulting in hypoxia and hypercapnia. It may have profound effects on many other systems. Because respiratory insufficiency may develop rapidly, close continued clinical evaluation is essential. Despite weakness of the respiratory muscles, the patient may respond with so much respiratory effort associated with anxiety and fear that overventilation may occur at the outset, resulting in respiratory alkalosis. Such effort is fatiguing and contributes to respiratory failure.

There are certain characteristic patterns of disease. Pure spinal poliomyelitis with respiratory insufficiency involves tightness, weakness, or paralysis of the respiratory muscles (chiefly the diaphragm and intercostals) without discernible clinical involvement of the cranial nerves or vital centers that control respiration, circulation, and body temperature. The cervical and thoracic spinal cord segments are chiefly affected. Pure bulbar poliomyelitis involves paralysis of the motor cranial nerve nuclei with or without involvement of the vital centers. Involvement of the 9th, 10th, and 12th cranial nerves results in paralysis of the pharynx, tongue, and larynx with consequent airway obstruction. Bulbospinal poliomyelitis with respiratory insufficiency affects the respiratory muscles and results in coexisting bulbar paralysis.

The clinical findings associated with involvement of the respiratory muscles include (1) anxious expression; (2) inability to speak without frequent pauses, resulting in short, jerky, "breathless" sentences; (3) increased respiratory rate; (4) movement of the ala nasi and of the accessory muscles of respiration; (5) inability to cough or sniff with full depth; (6) paradoxical abdominal movements caused by diaphragmatic immobility caused by spasm or weakness of 1 or both leaves; and (7) relative immobility of the intercostal spaces, which may be segmental, unilateral, or bilateral. When the arms are weak, and especially when deltoid paralysis occurs, there may be impending respiratory paralysis because the phrenic nerve nuclei are in adjacent areas of the spinal cord. Observation of the patient's capacity for thoracic breathing while the abdominal muscles are splinted manually indicates minor degrees of paresis. Light manual splinting of the thoracic cage helps assess the effectiveness of diaphragmatic movement.

DIAGNOSIS

Poliomyelitis should be considered in any unimmunized or incompletely immunized child with paralytic disease. While this guideline is most applicable in poliomyelitis endemic countries (Afghanistan, Pakistan, and Nigeria), the spread of polio in 2013 from endemic countries to many nonendemic countries (Niger, Chad, Cameroon, Ethiopia, Kenya, Somalia, and Syria) and the isolation of wild poliovirus type 1 in Israel suggest that the diagnosis of polio should still be entertained in all countries. VAPP should be considered in any child with paralytic disease occurring 7-14 days after receiving the orally administered polio vaccine (OPV). VAPP can occur at later times after administration and should be considered in any child with paralytic disease in countries or regions where wild-type poliovirus has been eradicated and the OPV has been administered to the child or a contact. The combination of fever, headache, neck and back pain, asymmetric flaccid paralysis without sensory loss, and pleocytosis does not regularly occur in any other illness.

The World Health Organization (WHO) recommends that the laboratory diagnosis of poliomyelitis be confirmed by isolation and identification of poliovirus in the stool, with specific identification of wild-type and vaccine-type strains. In suspected cases of acute flaccid paralysis, 2 stool specimens should be collected 24-48 hr apart as soon as possible after the diagnosis of poliomyelitis is suspected. Poliovirus concentrations are high in the stool in the 1st wk after the onset of paralysis, which is the optimal time for collection of stool specimens. Polioviruses may be isolated from 80-90% of specimens from acutely ill patients, whereas <20% of specimens from such patients may yield virus within 3-4 wk after onset of paralysis. Because most children with spinal or bulbospinal poliomyelitis have constipation, rectal straws may be used to obtain specimens; ideally a minimum of 8-10 g of stool should be collected. In laboratories that can isolate poliovirus, isolates should be sent to either the U.S. Centers for Disease Control and Prevention or to one of the WHO-certified poliomyelitis laboratories where DNA sequence analysis can be performed to distinguish between wild poliovirus and neurovirulent, revertant OPV strains. With the current WHO plan for global eradication of poliomyelitis, most regions of the world (the Americas, Europe, Australia) have been certified wild-poliovirus free; in these areas, poliomyelitis is most often caused by vaccine strains. Hence it is critical to differentiate between wild-type and revertant vaccine-type strains.

The CSF is often normal during the minor illness and typically contains a pleocytosis with 20-300 cells/μL with CNS involvement. The cells in the CSF may be polymorphonuclear early during the course of the disease but shift to mononuclear cells soon afterward. By the 2nd wk of major illness, the CSF cell count falls to near-normal values. In contrast, the CSF protein content is normal or only slightly elevated at the outset of CNS disease but usually rises to 50-100 mg/dL by the 2nd wk of illness. In polioencephalitis, the CSF may remain normal or show minor changes. Serologic testing demonstrates seroconversion or a 4-fold or greater increase in antibody titers from the acute phase of illness to 3-6 wk later.

DIFFERENTIAL DIAGNOSIS

Poliomyelitis should be considered in the differential diagnosis of any case of paralysis, and is only 1 of many causes of acute flaccid paralysis in children and adults. There are numerous other causes of acute flaccid paralysis (Table 249-1). In most conditions, the clinical features are sufficient to differentiate between these various causes, but in some cases nerve conduction studies and electromyograms, in addition to muscle biopsies, may be required.

The possibility of polio should be considered in any case of acute flaccid paralysis, even in countries where polio has been eradicated. The diagnoses most often confused with polio are VAPP, West Nile virus infection, infections caused by other enteroviruses, as well as Guillain-Barré syndrome, transverse myelitis, and traumatic paralysis. In Guillain-Barré syndrome, which is the most difficult to distinguish from poliomyelitis, the paralysis is characteristically symmetric, and sensory changes and pyramidal tract signs are common, contrasting with poliomyelitis. Fever, headache, and meningeal signs are less notable, and the CSF has few cells but an elevated protein content. Transverse myelitis progresses rapidly over hours to days, causing an acute symmetric paralysis of the lower limbs with concomitant anesthesia and diminished sensory perception. Autonomic signs of hypothermia in the affected limbs are common, and there is bladder dysfunction. The CSF is usually normal. Traumatic neuritis occurs from a few hours to a few days after the traumatic event, is asymmetric, is acute, and affects only 1 limb. Muscle tone and deep tendon reflexes are reduced or absent in the affected limb with pain in the gluteus. The CSF is normal.

Table 249-1 Differential Diagnosis of Acute Flaccid Paralysis

SITE, CONDITION, FACTOR, OR AGENT	CLINICAL FINDINGS	ONSET OF PARALYSIS	PROGRESSION OF PARALYSIS	SENSORY SIGNS AND SYMPTOMS	REDUCTION OR ABSENCE OF DEEP TENDON REFLEXES	RESIDUAL PARALYSIS	PLEOCYTOSIS
ANTERIOR HORN CELLS OF SPINAL CORD							
Poliomyelitis (wild and vaccine-associated paralytic poliomyelitis)	Paralysis	Incubation period 7-14 days (range: 4-35 days)	24-48 hr to onset of full paralysis; proximal → distal, asymmetric	No	Yes	Yes	Aseptic meningitis (moderate polymorphonuclear leukocytes at 2-3 days)
Nonpolio enteroviruses	Hand-foot-and-mouth disease, aseptic meningitis, acute hemorrhagic conjunctivitis, possibly idiopathic epidemic flaccid paralysis	As in poliomyelitis	As in poliomyelitis	No	Yes	Yes	As in poliomyelitis
West Nile virus	Meningitis encephalitis	As in poliomyelitis	As in poliomyelitis	No	Yes	Yes	Yes
OTHER NEUROTROPIC VIRUSES							
Rabies virus		Month–year	Acute, symmetric, ascending	Yes	Yes	No	±
Varicella-zoster virus	Exanthematous vesicular eruptions	Incubation period 10-21 days	Acute, symmetric, ascending	Yes	±	±	Yes
Japanese encephalitis virus		Incubation period 5-15 days	Acute, proximal, asymmetric	±	±	±	Yes
GUILLAIN-BARRÉ SYNDROME							
Acute inflammatory polyradiculoneuropathy	Preceding infection, bilateral facial weakness	Hours to 10 days	Acute, symmetric, ascending (days to 4 wk)	Yes	Yes	±	No
Acute motor axonal neuropathy	Fulminant, widespread paralysis, bilateral facial weakness, tongue involvement	Hours to 10 days	1-6 days	No	Yes	±	No

ACUTE TRAUMATIC SCIATIC NEURITIS							
Intramuscular gluteal injection	Acute, asymmetric	Hours to 4 days	Complete, affected limb	Yes	Yes	±	No
Acute transverse myelitis	Preceding *Mycoplasma pneumoniae*, *Schistosoma*, other parasitic or viral infection	Acute, symmetric hypotonia of lower limbs	Hours to days	Yes	Yes, early	Yes	Yes
Epidural abscess	Headache, back pain, local spinal tenderness, meningismus	Complete		Yes	Yes	±	Yes
Spinal cord compression; trauma		Complete	Hours to days	Yes	Yes	±	±
NEUROPATHIES							
Exotoxin of *Corynebacterium diphtheriae*	In severe cases, palatal paralysis, blurred vision	Incubation period 1-8 wk (paralysis 8-12 wk after onset of illness)		Yes	Yes		±
Toxin of *Clostridium botulinum*	Abdominal pain, diplopia, loss of accommodation, mydriasis	Incubation period 18-36 hr	Rapid, descending, symmetric	±	No		No
Tick bite paralysis	Ocular symptoms	Latency period 5-10 days	Acute, symmetric, ascending	No	Yes		No
DISEASES OF THE NEUROMUSCULAR JUNCTION							
Myasthenia gravis	Weakness, fatigability, diplopia, ptosis, dysarthria		Multifocal	No	No	No	No
DISORDERS OF MUSCLE							
Polymyositis	Neoplasm, autoimmune disease	Subacute, proximal → distal	Weeks to months	No	Yes		No
Viral myositis		Pseudoparalysis	Hours to days	No	No		No
METABOLIC DISORDERS							
Hypokalemic periodic paralysis		Proximal limb, respiratory muscles	Sudden postprandial	No	Yes	±	No
INTENSIVE CARE UNIT WEAKNESS							
Critical illness polyneuropathy	Flaccid limbs and respiratory weakness	Acute, following systemic inflammatory response syndrome/sepsis	Hours to days	±	Yes	±	No

Modified from Marx A, Glass JD, Sutter RW: Differential diagnosis of acute flaccid paralysis and its role in poliomyelitis surveillance, Epidemiol Rev *22:298–316, 2000.*

Conditions causing pseudoparalysis do not present with nuchal-spinal rigidity or pleocytosis. These causes include unrecognized trauma, transient (toxic) synovitis, acute osteomyelitis, acute rheumatic fever, scurvy, and congenital syphilis (pseudoparalysis of Parrot).

TREATMENT

There is no specific antiviral treatment for poliomyelitis. The management is supportive and aimed at limiting progression of disease, preventing ensuing skeletal deformities, and preparing the child and family for the prolonged treatment required and for permanent disability if this seems likely. Patients with the nonparalytic and mildly paralytic forms of poliomyelitis may be treated at home. All intramuscular injections and surgical procedures are contraindicated during the acute phase of the illness, especially in the 1st wk of illness, because they might result in progression of disease.

Abortive Poliomyelitis

Supportive treatment with analgesics, sedatives, an attractive diet, and bed rest until the child's temperature is normal for several days is usually sufficient. Avoidance of exertion for the ensuing 2 wk is desirable, and careful neurologic and musculoskeletal examinations should be performed 2 mo later to detect any minor involvement.

Nonparalytic Poliomyelitis

Treatment for the nonparalytic form is similar to that for the abortive form; in particular, relief is indicated for the discomfort of muscle tightness and spasm of the neck, trunk, and extremities. Analgesics are more effective when they are combined with the application of hot packs for 15-30 min every 2-4 hr. Hot tub baths are sometimes useful. A firm bed is desirable and can be improvised at home by placing table leaves or a sheet of plywood beneath the mattress. A footboard or splint should be used to keep the feet at a right angle to the legs. Because muscular discomfort and spasm may continue for some weeks, even in the nonparalytic form, hot packs and gentle physical therapy may be necessary. Patients with nonparalytic poliomyelitis should also be carefully examined 2 mo after apparent recovery to detect minor residual effects that might cause postural problems in later years.

Paralytic Poliomyelitis

Most patients with the paralytic form of poliomyelitis require hospitalization with complete physical rest in a calm atmosphere for the 1st 2-3 wk. Suitable body alignment is necessary for comfort and to avoid excessive skeletal deformity. A neutral position with the feet at right angles to the legs, the knees slightly flexed, and the hips and spine straight is achieved by use of boards, sandbags, and, occasionally, light splint shells. The position should be changed every 3-6 hr. Active and passive movements are indicated as soon as the pain has disappeared. Moist hot packs may relieve muscle pain and spasm. Opiates and sedatives are permissible only if no impairment of ventilation is present or impending. Constipation is common, and fecal impaction should be prevented. When bladder paralysis occurs, a parasympathetic stimulant such as bethanechol may induce voiding in 15-30 min; some patients show no response to this agent, and others respond with nausea, vomiting, and palpitations. Bladder paresis rarely lasts more than a few days. If bethanechol fails, manual compression of the bladder and the psychologic effect of running water should be tried. If catheterization must be performed, care must be taken to prevent urinary tract infections. An appealing diet and a relatively high fluid intake should be started at once unless the patient is vomiting. Additional salt should be provided if the environmental temperature is high or if the application of hot packs induces sweating. Anorexia is common initially. Adequate dietary and fluid intake can be maintained by placement of a central venous catheter. An orthopedist and a physiatrist should see patients as early in the course of the illness as possible and should assume responsibility for their care before fixed deformities develop.

The management of pure bulbar poliomyelitis consists of maintaining the airway and avoiding all risk of inhalation of saliva, food, and vomitus. Gravity drainage of accumulated secretions is favored by using the head-low (foot of bed elevated 20-25 degrees) prone position with the face to one side. Patients with weakness of the muscles of respiration or swallowing should be nursed in a lateral or semiprone position. Aspirators with rigid or semirigid tips are preferred for direct oral and pharyngeal aspiration, and soft, flexible catheters may be used for nasopharyngeal aspiration. Fluid and electrolyte equilibrium is best maintained by intravenous infusion because tube or oral feeding in the 1st few days may incite vomiting. In addition to close observation for respiratory insufficiency, the blood pressure should be measured at least twice daily because hypertension is not uncommon and occasionally leads to hypertensive encephalopathy. Patients with pure bulbar poliomyelitis may require tracheostomy because of vocal cord paralysis or constriction of the hypopharynx; most patients who recover have little residual impairment, although some exhibit mild dysphagia and occasional vocal fatigue with slurring of speech.

Impaired ventilation must be recognized early; mounting anxiety, restlessness, and fatigue are early indications for preemptive intervention. Tracheostomy is indicated for some patients with pure bulbar poliomyelitis, spinal respiratory muscle paralysis, or bulbospinal paralysis because such patients are generally unable to cough, sometimes for many months. Mechanical respirators are often needed.

COMPLICATIONS

Paralytic poliomyelitis may be associated with numerous complications. Acute gastric dilation may occur abruptly during the acute or convalescent stage, causing further respiratory embarrassment; immediate gastric aspiration and external application of ice bags are indicated. Melena severe enough to require transfusion may result from single or multiple superficial intestinal erosions; perforation is rare. Mild hypertension for days or weeks is common in the acute stage and probably related to lesions of the vasoregulatory centers in the medulla and especially to underventilation. In the later stages, because of immobilization, hypertension may occur along with hypercalcemia, nephrocalcinosis, and vascular lesions. Dimness of vision, headache, and a lightheaded feeling associated with hypertension should be regarded as premonitory of a frank convulsion. Cardiac irregularities are uncommon, but electrocardiographic abnormalities suggesting myocarditis occur with some frequency. Acute pulmonary edema occurs occasionally, particularly in patients with arterial hypertension. Hypercalcemia occurs because of skeletal decalcification that begins soon after immobilization and results in hypercalciuria, which in turn predisposes the patient to urinary calculi, especially when urinary stasis and infection are present. High fluid intake is the only effective prophylactic measure.

PROGNOSIS

The outcome of inapparent, abortive poliomyelitis and aseptic meningitis syndromes is uniformly good, with death being exceedingly rare and with no long-term sequelae. The outcome of paralytic disease is determined primarily by degree and severity of CNS involvement. In severe bulbar poliomyelitis, the mortality rate may be as high as 60%, whereas in less-severe bulbar involvement and/or spinal poliomyelitis, the mortality rate varies from 5-10%, death generally occurring from causes other than the poliovirus infection.

Maximum paralysis usually occurs 2-3 days after the onset of the paralytic phase of the illness, with stabilization followed by gradual return of muscle function. The recovery phase lasts usually about 6 mo, beyond which persisting paralysis is permanent. Generally, paralysis is more likely to develop in male children and female adults. Mortality and the degree of disability are greater after the age of puberty. Pregnancy is associated with an increased risk for paralytic disease. Tonsillectomy and intramuscular injections may enhance the risk for acquisition of bulbar and localized disease, respectively. Increased physical activity, exercise, and fatigue during the early phase of illness have been cited as factors leading to a higher risk for paralytic disease. Finally, it has been clearly demonstrated that type 1 poliovirus has the greatest propensity for natural poliomyelitis, and type 3 poliovirus has a predilection for producing VAPP.

Postpolio Syndrome

After an interval of 30-40 yr, as many as 30-40% of persons who survived paralytic poliomyelitis in childhood may experience muscle pain

and exacerbation of existing weakness or development of new weakness or paralysis. This entity, referred to as postpolio syndrome, has been reported only in persons who were infected in the era of wild-type poliovirus circulation. Risk factors for postpolio syndrome include increasing length of time since acute poliovirus infection, presence of permanent residual impairment after recovery from acute illness, and female sex.

PREVENTION

Vaccination is the only effective method of preventing poliomyelitis. Hygienic measures help limit the spread of the infection among young children, but immunization is necessary to control transmission among all age groups. Both the inactivated polio vaccine (IPV), which is currently produced using better methods than those for the original vaccine and is sometimes referred to as enhanced IPV, and the live-attenuated OPV have established efficacy in preventing poliovirus infection and paralytic poliomyelitis. Both vaccines induce production of antibodies against the 3 strains of poliovirus. IPV elicits higher serum IgG antibody titers, but the OPV also induces significantly greater mucosal IgA immunity in the oropharynx and gastrointestinal tract, which limits replication of the wild poliovirus at these sites. Transmission of wild poliovirus by fecal spread is limited in OPV recipients. The immunogenicity of IPV is not affected by the presence of maternal antibodies, and IPV has no adverse effects. Live vaccine may undergo reversion to neurovirulence as it multiplies in the human intestinal tract and may cause VAPP in vaccinees or in their contacts. The overall risk for recipients varies from 1 case per 750,000 immunized infants in the United States to 1 in 143,000 immunized infants in India. The risk for paralysis in the B-cell–immunodeficient recipient may be as much as 6,800 times that in normal subjects. HIV infection has not been found to result in long-term excretion of virus. As of January 2000, the IPV-only schedule is recommended for routine polio vaccination in the United States. All children should receive 4 doses of IPV, at 2 mo, 4 mo, 6-18 mo, and 4-6 yr of age.

In 1988, the World Health Assembly resolved to eradicate poliomyelitis globally by 2000, and remarkable progress had been made toward reaching this target. To achieve this goal, the WHO used 4 basic strategies: routine immunization, National Immunization Days, acute flaccid paralysis surveillance, and “mop-up” immunization. This strategy has resulted in a >99% decline in poliomyelitis cases; in early 2002, there were only 10 countries in the world endemic for poliomyelitis. In 2012, there were the fewest cases of poliomyelitis ever, and the virus was endemic in only 3 countries (Afghanistan, Pakistan, and Nigeria). India has not had a child paralyzed with wild poliovirus type 2 since February 2011. The last case of wild poliovirus type 3 infection occurred in Nigeria in 2012, and the last case of wild poliovirus type 2 infection occurred in India in 1999. This progress prompted the WHO assembly, in May 2013, to recommend the development of a *Polio Eradication and Endgame Strategic Plan 2013-2018*. This plan includes the withdrawal of trivalent OPV with bivalent OPV (bOPV) in all countries by 2016 and the introduction of initially one dose of IPV followed by the replacement of bivalent OPV with IPV in all countries of the world by 2019. As long as the OPV is being used, there is the potential that vaccine-derived poliovirus will acquire the neurovirulent phenotype and transmission characteristics of the wild-type polioviruses. Vaccine-derived poliovirus emerges from the OPV because of continuous replication in immunodeficient persons or by circulation in populations with low vaccine coverage (cVDPVs). The risk appears to be highest with the type 2 strain. Currently, 90% of all cVDPV outbreaks are caused by type 2 strains (Fig. 249-2). Outbreaks of cVDPV2 occurred in Hispaniola, the Philippines, and Madagascar in 2001, and endemic cVDPV2 circulation occurred in Egypt from 1983-1993. As of 2012, 5 outbreaks of cVDPV2 were detected in the 3 polio endemic countries and in Chad, Democratic Republic of Congo, Kenya, Somalia, and China.

Several countries are global priorities because they face challenges in eradication of the disease (see Fig. 249-1). Polioviruses are endemic in Pakistan, Afghanistan, and Nigeria. Twenty previously polio-free countries were infected by importations of wild poliovirus type 1 originating from Nigeria, and 3 polio-free African countries experienced

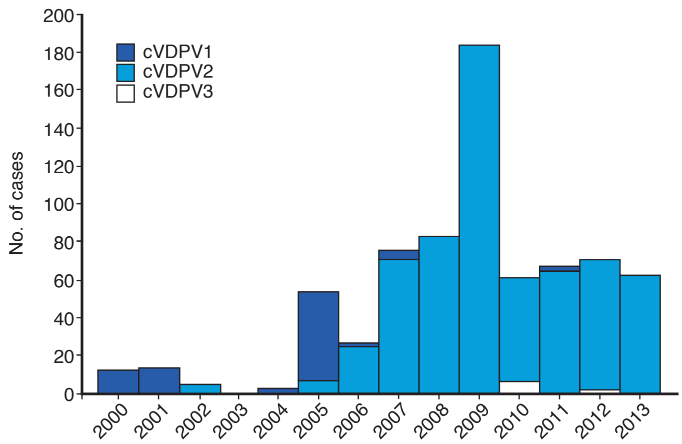

Figure 249-2 Circulating vaccine-derived poliovirus (cVDPV) cases detected worldwide, by serotype and year—2000–2013. *(From Diop OM, Burns CC, Wassilak SG, Kew OM; Centers for Disease Control and Prevention (CDC): Update on vaccine-derived polioviruses–worldwide, July 2012-December 2013.* MMWR Morb Mortal Wkly Rep *63:242–248, 2014.)*

infections with wild poliovirus type 1 imported from India. For the 3 countries with uninterrupted outbreaks, there are 2 main reasons for the failure to eradicate polio. The suboptimal campaign quality in Nigeria, parts of Pakistan and southern Afghanistan, and the countries with prolonged transmission of imported virus as well as security-compromised areas in parts of Afghanistan and Pakistan are still the main difficulties faced in 2014. Of the 416 wild poliovirus cases in 2012, 160 cases were in the 3 endemic countries and 256 were in nonendemic countries. There have been importations from Nigeria into the horn of Africa and the Middle East (Cameroon, Ethiopia, Kenya, Somalia, and Syrian Arab Republic). However, since December 2014 this ratio has changed, and the number of cases in endemic countries (especially Nigeria and Afghanistan) has increased to 306, mostly in Pakistan (276). Equally worrisome to the strategy of switching completely to IPV is the detection of a Pakistani strain of wild poliovirus type 1 in Israel and the West Bank, first in sewage, and now found in up to 4% of children and adults. Israel has used IPV exclusively for the past 10 yr and has introduced bOPV as a single continuous supplementary immunization activity (SIA). bOPV is included in routine immunization, following at least 1 dose of IPV. This follows the experience in the United States that reported no VAPP following a sequential use of IPV followed by OPV. Global synchronous cessation of OPV will need to be coordinated by the WHO, but the recent experiences in the horn of Africa and Israel/West Bank suggest that stopping transmission of wild poliovirus type 1 in the 3 endemic countries is of the utmost urgency, if we are ever going to be able to stop using OPV.

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Chapter 250

Nonpolio Enteroviruses

Mark J. Abzug

The genus *Enterovirus* contains a large number of agents that produce a broad range of illnesses. The genus name reflects the importance of the gastrointestinal tract as the primary site of invasion and replication and the source for transmission. Viremic spread to distant sites accounts for the majority of clinical manifestations.

Table 250-1	Classification of Human Enteroviruses
Family	Picornaviridae
Genus	*Enterovirus*
Subgroups*	Poliovirus serotypes 1-3 Coxsackie A virus serotypes 1-22, 24 (23 **reclassified** as echovirus 9) Coxsackie B virus serotypes 1-6 Echovirus serotypes 1-9, 11-27, 29-33 (echoviruses 10 and 28 **reclassified** as nonenteroviruses; echovirus 34 **reclassified** as a variant of coxsackie A virus 24; echoviruses 22 and 23 **reclassified** within the genus *Parechovirus*) Numbered enterovirus serotypes (enterovirus 72 **reclassified** as hepatitis A virus)

*The human enteroviruses have been alternatively classified on the basis of nucleotide and amino acid sequences into 5 species (polioviruses and human enteroviruses A-D).

ETIOLOGY

Enteroviruses are nonenveloped, single-stranded, positive-sense viruses in the Picornaviridae ("small RNA virus") family, which also includes the genera *Rhinovirus, Hepatovirus* (hepatitis A virus), and *Parechovirus* and genera containing related animal viruses. The original human enterovirus subgroups—polioviruses (see Chapter 249), coxsackieviruses (named after Coxsackie, New York, where they were discovered), and echoviruses (*e*nteric *c*ytopathic *h*uman *o*rphan *viruses*)—were differentiated by their replication patterns in tissue culture and animals (Table 250-1). The human enteroviruses have been reclassified on the basis of genetic similarity into 5 species, polioviruses and human enteroviruses A-D. Enterovirus types are distinguished by antigenic and genetic sequence differences; newer enteroviruses are classified by numbering. Although more than 100 types have been described, 10-15 account for the majority of disease. No disease is uniquely associated with any specific serotype, although certain manifestations are preferentially associated with specific serotypes. It has been observed that human parechoviruses can manifest clinical presentations similar to those of enteroviruses.

EPIDEMIOLOGY

Enterovirus infections are common and have a worldwide distribution. In temperate climates there is an annual epidemic peak in summer/fall, although some transmission occurs year-round. Enteroviruses are responsible for 33-65% of acute febrile illnesses and 55-65% of hospitalizations for suspected sepsis in infants during the summer and fall in the United States, and 25% year-round. In tropical and semitropical areas, enteroviruses circulate year-round. In general, only a few serotypes circulate simultaneously. Infections by different serotypes can occur within the same season. Factors associated with increased incidence and/or severity include young age, male sex, exposure to children, poor hygiene, overcrowding, and low socioeconomic status; >25% of symptomatic infections occur in children younger than 1 yr of age. Breastfeeding reduces the risk for infection, likely via enterovirus-specific antibodies.

Humans are the only known reservoir for human enteroviruses, although some nonhuman primates can be infected. Virus is primarily spread person to person, by the fecal-oral and respiratory routes, although types causing acute hemorrhagic conjunctivitis may be spread via airborne transmission. Virus can be transmitted vertically prenatally or in the peripartum period, or, possibly, via breastfeeding. Enteroviruses can survive on environmental surfaces, permitting transmission via fomites. Enteroviruses also can frequently be isolated from water sources and sewage and can survive for months in wet soil. Although environmental contamination (of drinking water, swimming pools and ponds, and hospital water reservoirs) may occasionally be responsible for transmission, it is often considered the result, rather than the cause, of human infection. Transmission occurs within families (≥50% risk of spread to nonimmune household contacts), daycare centers, playgrounds, summer camps, orphanages, and hospital nurseries; severe secondary infections may occur in nursery outbreaks. Transmission risk is increased by diaper changing and decreased by handwashing. Tickborne transmission has been suggested.

Large enterovirus outbreaks have included echovirus meningitis epidemics in numerous countries (echoviruses 4, 6, 9, 13, and 30 commonly); epidemics of hand-foot-and-mouth disease with severe central nervous system (CNS) and/or cardiopulmonary disease caused by enterovirus 71 in Asia and Australia; outbreaks of atypical hand-foot-and-mouth disease caused by coxsackievirus A6 in the United States and United Kingdom; outbreaks of human enterovirus 68 producing respiratory illness and possibly acute flaccid paralysis in the United States, Europe, and Asia; outbreaks of acute hemorrhagic conjunctivitis caused by enterovirus 70, coxsackievirus A24, and coxsackievirus A24 variant in tropical and temperate regions; and community outbreaks of uveitis. Reverse transcription polymerase chain reaction (RT-PCR), restriction fragment length polymorphism analysis, single-strand conformation polymorphism analysis, heteroduplex mobility analysis, and genomic sequencing help identify outbreaks and allow phylogenetic analyses that demonstrate, depending on the outbreak, commonality of outbreak strains, differences among epidemic strains and older prototype strains, changes in circulating viral subgroups over time, cocirculation of multiple genetic lineages, coinfections with different enterovirus serotypes, and associations between specific genogroups and/or substitutions at specific genetic loci and epidemiologic and clinical characteristics. Genetic analyses have demonstrated recombination and genetic drift that lead to evolutionary changes in genomic sequence and antigenicity and extensive genetic diversity. Rapid genetic evolution and recombination events associated with emergence of new subgenotypes and genetic lineages of enterovirus 71 may contribute to sequential outbreaks and increases in viral circulation.

The incubation period is typically 3-6 days, except for a 1-3 day incubation period for acute hemorrhagic conjunctivitis. Infected children, both symptomatic and asymptomatic, frequently shed cultivable enteroviruses from the respiratory tract for <1-3 wk, whereas fecal shedding continues for as long as 7-11 wk. Enterovirus RNA can be shed from mucosal sites for comparable, and, possibly, longer periods.

PATHOGENESIS

Following oral or respiratory acquisition, initial replication occurs in the pharynx and intestine, possibly within mucosal M cells. The absence of an envelope favors survival in the gastrointestinal tract. Cell surface macromolecules, including poliovirus receptor, integrin very-late-activation antigen (VLA)-2, decay-accelerating factor/complement regulatory protein (DAF/CD55), intercellular adhesion molecule-1 (ICAM-1), and coxsackievirus-adenovirus receptor, serve as receptors, as do sialic acid for enterovirus 68, enterovirus 70, and coxsackievirus A24 variants and human scavenger receptor class B2 (SCARB2), human P-selectin glycoprotein ligand-1, and DC-SIGN for enterovirus 71. Two or more enteroviruses may invade and replicate in the gastrointestinal tract simultaneously, but replication of 1 type often hinders growth of the heterologous type (**interference**).

After the virus attaches to a cell surface receptor, a conformational change in surface capsid proteins facilitates penetration and uncoating with release of viral RNA in the cytoplasm. Translation of the positive-sense RNA produces a polyprotein that undergoes cleavage by proteinases encoded in the polyprotein. Several proteins produced guide synthesis of negative-sense RNA that serves as a template for

replication of new positive-sense RNA. The genome is approximately 7,500 nucleotides long and includes a highly conserved 5′ noncoding region important for replication efficiency and a highly conserved 3′ polyA region, which flank a continuous region encoding viral proteins. The 5′ end is covalently linked to a small viral protein (VPg) necessary for initiation of RNA synthesis. There is significant variation within genomic regions encoding the structural proteins (with corresponding variability in antigenicity). Replication is followed by further cleavage of proteins and assembly into 30 nm icosahedral virions. Of the 4 structural proteins (VP1-VP4) in the capsid (additional regulatory proteins such as an RNA-dependent RNA polymerase and proteases are also present in the virion), VP1 is the most important determinant of serotype specificity. Approximately 10^4-10^5 virions are released from an infected cell by lysis within 5-10 hr of infection.

Initial replication in the pharynx and intestine is followed within days by multiplication in lymphoid tissue such as tonsils, Peyer patches, and regional lymph nodes. A primary, transient viremia (**minor viremia**) results in spread to distant parts of the reticuloendothelial system, including the liver, spleen, bone marrow, and distant lymph nodes. Host immune responses may limit replication and progression beyond the reticuloendothelial system, resulting in subclinical infection. Clinical infection occurs if replication proceeds in the reticuloendothelial system and virus spreads via a secondary, sustained viremia (**major viremia**) to target organs such as the CNS, heart, and skin. Tropism to target organs is determined in part by the infecting serotype.

Enteroviruses can damage a wide variety of organs and systems, including the CNS, heart, liver, lungs, pancreas, kidneys, muscle, and skin. Damage is mediated by necrosis and the inflammatory response. CNS infections are often associated with mononuclear pleocytosis of the cerebrospinal fluid (CSF), composed of macrophages and activated T lymphocytes, and a mixed meningeal inflammatory response. Parenchymal involvement may affect the cerebral white and gray matter, cerebellum, basal ganglia, brainstem, and spinal cord with perivascular and parenchymal mixed or lymphocytic inflammation, gliosis, cellular degeneration, and neuronophagocytosis. Encephalitis during enterovirus 71 epidemics has been characterized by severe involvement of the brainstem, spinal cord gray matter, hypothalamus, and subthalamic and dentate nuclei, and frequently complicated by pulmonary edema, hemorrhage and/or interstitial pneumonitis and cardiopulmonary failure, presumed secondary to brainstem damage, sympathetic hyperactivity, autonomic dysfunction, and CNS and systemic inflammatory responses (including cytokine and chemokine overexpression), and, only occasionally, myocarditis. Immunologic cross-reactivity with brain tissue has been postulated as one mechanism responsible for neurologic damage and sequelae following enterovirus 71 infection.

Enterovirus myocarditis is characterized by perivascular and interstitial mixed inflammatory infiltrates and myocyte damage, possibly mediated by viral cytolytic (e.g., cleavage of dystrophin or serum response factor) and innate and adaptive immune-mediated mechanisms. Chronic inflammation may persist after viral clearance.

The potential for enteroviruses to cause persistent infection is controversial. Persistent infection has been implicated in dilated cardiomyopathy and in myocardial infarction, with enteroviral RNA sequences and/or antigens demonstrated in cardiac tissues in some, but not other, series. Infections with enteroviruses such as coxsackievirus B4, during gestation or subsequently, have been implicated as a trigger for development of β-cell autoantibodies and/or type 1 diabetes in genetically susceptible hosts. Persistent infection in the pancreas, intestine, or peripheral blood mononuclear cells, with downstream immunomodulatory effects, has also been suggested, but data are inconsistent. Similarly, persistent infection is implicated in amyotrophic lateral sclerosis, Sjögren syndrome, and gastrointestinal tract tumors, and evidence of chronic infection has been described in some studies of chronic fatigue syndrome but not in others.

Severe **neonatal infections** can manifest as hepatic necrosis, hemorrhage, inflammation, endotheliitis, and venoocclusive disease; myocardial mixed inflammatory infiltrates, edema, and necrosis; meningeal and brain inflammation, hemorrhage, gliosis, necrosis, and white matter damage; inflammation, hemorrhage, thrombosis, and necrosis in the lungs, pancreas, and adrenal glands; and disseminated intravascular coagulation. In utero infections are characterized by placentitis and infection of multiple fetal organs such as heart, lung, and brain.

Development of type-specific neutralizing antibodies appears to be the most important immune defense, mediating prevention against and recovery from infection. Immunoglobulin (Ig) M antibodies, followed by long-lasting IgA and IgG antibodies, and secretory IgA, mediating mucosal immunity, are produced. Although local reinfection of the gastrointestinal tract can occur, replication is usually limited and not associated with disease. In vitro and animal experiments suggest that heterotypic antibody may enhance disease caused by a different serotype. Evidence also suggests that subneutralizing concentrations of serotype-specific antibody may lead to antibody-dependent enhancement of enterovirus 71 infection. Innate and cellular defenses (macrophages and cytotoxic T lymphocytes) may play important roles in recovery from infection. Altered cellular responses to enterovirus 71, including T lymphocyte and natural killer cell depletion, were associated with severe meningoencephalitis ± pulmonary edema.

Hypogammaglobulinemia and agammaglobulinemia predispose to severe, often chronic enterovirus infections. Similarly, perinatally infected neonates lacking maternal type-specific antibody to the infecting virus are at risk for severe disease. Enterovirus 71 disease increases after 6 mo of age, when maternal serotype-specific antibody levels have declined. Other risk factors for significant illness include young age, immune suppression (posttransplantation and lymphoid malignancy), and, according to animal models and/or epidemiologic observations, exercise, cold exposure, malnutrition, and pregnancy. Specific human leukocyte antigen genes, immune response gene (e.g., interleukin-10 and interferon-γ) polymorphisms, and low vitamin A levels have been linked to enterovirus 71 susceptibility and severe disease.

CLINICAL MANIFESTATIONS

Manifestations are protean, ranging from asymptomatic infection or undifferentiated febrile or respiratory illnesses in the majority, to, less frequently, severe diseases such as meningoencephalitis, myocarditis, and neonatal sepsis. A majority of individuals are asymptomatic or have very mild illness, yet may serve as significant sources for spread of infection. Symptomatic disease is generally more common in young children.

Nonspecific Febrile Illness

Nonspecific febrile illnesses are the most common symptomatic manifestations, especially in infants and young children. These are difficult to clinically differentiate from serious infections such as bacteremia and bacterial meningitis, necessitating diagnostic testing, presumptive therapy, and hospitalizations for suspected bacterial infection in young infants.

Illness usually begins abruptly with fever of 38.5-40°C (101-104°F), malaise, and irritability. Other symptoms are lethargy, anorexia, diarrhea, nausea, vomiting, abdominal discomfort, rash, sore throat, and respiratory symptoms, and, in older children, headache and myalgia. Findings are generally nonspecific and may include mild conjunctivitis, pharyngeal injection, and cervical lymphadenopathy. Meningitis may be present, but, in infants, specific clinical features distinguishing those with meningitis are often lacking. Fever lasts a mean of 3 days and, occasionally, is biphasic. Duration of illness is usually 4-7 days but can range from 1 day to >1 wk. White blood cell (WBC) count and results of routine laboratory tests are generally normal, although transient neutropenia can be seen. Concomitant enterovirus and bacterial infection has been observed in a small number of infants.

Enterovirus illnesses may be associated with a wide variety of skin manifestations, including macular, maculopapular, urticarial, vesicular, and petechial eruptions. Rare cases of idiopathic thrombocytopenic purpura have been reported. Enteroviruses have also been implicated in pityriasis rosea. In general, the frequency of cutaneous manifestations is inversely related to age. Serotypes commonly associated with rashes are echoviruses 9, 11, 16, and 25; coxsackie A viruses 2, 4, 6, 9, and 16; coxsackie B viruses 3-5; and enterovirus 71. Virus can occasionally be recovered from vesicular skin lesions.

Figure 250-1 **A,** Oval blisters of the palms in a child with hand-foot-and-mouth disease (coxsackievirus A16 infection). **B,** Oval blisters on the feet of a child with hand-foot-and-mouth disease. **C,** Erosion of the tongue in a child with hand-foot-and-mouth disease. *(From Weston WL, Lane AT, Morelli JG:* Color textbook of pediatric dermatology, *ed 3, St. Louis, 2002, Mosby, p. 109.)*

Hand-Foot-and-Mouth Disease

Hand-foot-and-mouth disease, one of the more distinctive rash syndromes, is most frequently caused by coxsackievirus A16, sometimes in large outbreaks, and can also be caused by enterovirus 71; coxsackie A viruses 5, 6, 7, 9, and 10; coxsackie B viruses 2 and 5; and some echoviruses. It is usually a mild illness, with or without low-grade fever. The oropharynx is inflamed and contains scattered vesicles on the tongue, buccal mucosa, posterior pharynx, palate, gingiva, and/or lips (Fig. 250-1). These may ulcerate, leaving 4-8 mm shallow lesions with surrounding erythema. Maculopapular, vesicular, and/or pustular lesions may occur on the hands and fingers, feet, and buttocks and groin; the hands are more commonly involved than the feet (see Fig. 250-1). Lesions on the hands and feet are usually tender, 3-7 mm vesicles that occur more commonly on dorsal surfaces but frequently also on palms and soles. Vesicles resolve in about 1 wk. Buttock lesions do not usually progress to vesiculation. Disseminated vesicular rashes may complicate preexisting eczema. Hand-foot-and-mouth disease caused by enterovirus 71 is frequently more severe than coxsackievirus A16 disease, with high rates of neurologic and cardiopulmonary involvement, especially in young children (see "Neurologic Manifestations" below). Coxsackievirus A16 also can occasionally be associated with complications such as encephalitis, acute flaccid paralysis, myocarditis, pericarditis, and shock. Coxsackievirus A6 is also responsible for atypical hand-foot-and-mouth disease (and herpangina), notable for affecting adults and children and causing relatively severe disease, including fever, generalized rash (face, proximal extremities, and trunk, in addition to hands, feet, and buttocks), pain, dehydration, and desquamation of palms and soles. **Onychomadesis** (nail shedding) has been observed following coxsackievirus A6 and other coxsackievirus infections.

Herpangina

Herpangina is characterized by sudden onset of fever, sore throat, dysphagia, and lesions in the posterior pharynx. Temperatures range from normal to 41°C (106°F); fever tends to be greater in younger patients. Headache and backache may occur in older children, and vomiting and abdominal pain occur in 25% of cases. Characteristic lesions, present on the anterior tonsillar pillars, soft palate, uvula, tonsils, posterior pharyngeal wall, and, occasionally, the posterior buccal surfaces, are discrete 1-2 mm vesicles and ulcers that enlarge over 2-3 days to 3-4 mm and are surrounded by erythematous rings that vary in size up to 10 mm. Typically, approximately 5 lesions are present, with a range of 1 to >15. The remainder of the pharynx appears normal or minimally erythematous. Most cases are mild and have no complications; however, some are associated with meningitis or more severe illness. Fever generally lasts 1-4 days, and resolution of symptoms occurs in 3-7 days. A variety of enteroviruses cause herpangina, including enterovirus 71, although coxsackie A viruses are implicated most often.

Respiratory Manifestations

Symptoms such as sore throat and coryza frequently accompany and sometimes dominate enterovirus illnesses. Other respiratory findings may include wheezing, exacerbation of asthma, apnea, respiratory distress, pneumonia, otitis media, bronchiolitis, croup, parotitis, and pharyngotonsillitis, which may occasionally be exudative. Lower respiratory tract infection may be significant in immunocompromised patients. Clusters and outbreaks of cases of severe respiratory disease, including pneumonia and wheezing (both in children with a history of asthma and those unaffected by asthma), have been observed in association with multiple lineages of enterovirus 68.

Pleurodynia (**Bornholm disease**), caused most frequently by coxsackie B viruses 3, 5, 1, and 2 and echoviruses 1 and 6, is an epidemic or sporadic illness characterized by paroxysmal thoracic pain, due to myositis involving chest and abdominal wall muscles and, possibly, pleural inflammation. In epidemics, children and adults are affected, but most cases occur in persons younger than age 30 yr. Malaise, myalgias, and headache are followed by sudden onset of fever and spasmodic, pleuritic pain in the chest or upper abdomen aggravated by coughing, sneezing, deep breathing, or other movement. During spasms, which last from a few minutes to several hours, pain may be severe and respirations are usually rapid, shallow, and grunting, suggesting pneumonia or pleural inflammation. A pleural friction rub may be noted during pain episodes. Chest radiographs are generally normal but can demonstrate pulmonary infiltrates or pleural effusions. Pain localized to the abdomen may suggest colic, intestinal obstruction, appendicitis, or peritonitis. Illness usually lasts 3-6 days, and, occasionally, up to 2 wk. It is frequently biphasic and is rarely associated with recurrent episodes over a few weeks, with less prominent fever during recurrences. Pleurodynia may be associated with meningitis, orchitis, myocarditis, or pericarditis.

Life-threatening pulmonary edema, hemorrhage, and/or interstitial pneumonitis may occur in patients with enterovirus 71 encephalitis.

Ocular Manifestations

Epidemics of **acute hemorrhagic conjunctivitis,** primarily caused by enterovirus 70 and coxsackievirus A24/A24 variant, are explosive, spreading mainly via eye-hand-fomite-eye transmission. School-age children, teenagers, and adults 20-50 yr of age have the highest attack rates. Sudden onset of severe eye pain is associated with photophobia, blurred vision, lacrimation, conjunctival erythema and congestion, lid edema, preauricular lymphadenopathy, and, in some cases, subconjunctival hemorrhages and superficial punctate keratitis. Eye discharge is initially serous but becomes mucopurulent with secondary bacterial infection. Systemic symptoms including fever are rare, although manifestations suggestive of pharyngoconjunctival fever occasionally occur. Recovery is usually complete within 1-2 wk. Polyradiculoneuropathy or paralytic disease following enterovirus 70 disease occurs

occasionally. Other enteroviruses have occasionally been implicated as causes of keratoconjunctivitis.

Epidemic and sporadic uveitis in infants caused by subtypes of enteroviruses 11 and 19 can be associated with severe complications, including destruction of the iris, cataracts, and glaucoma. Enteroviruses have been implicated in cases of chorioretinitis, uveoretinitis, optic neuritis, and unilateral acute idiopathic maculopathy.

Myocarditis and Pericarditis

Enteroviruses account for approximately 25-35% of cases of myocarditis and pericarditis with proven cause (see Chapters 440 and 441). Coxsackie B viruses are most commonly implicated, although coxsackie A viruses and echoviruses also may be causative. Adolescents and young adults, especially males, are disproportionately affected. Myopericarditis may be the dominant feature or it may be part of disseminated disease, as in neonates. Disease ranges from relatively mild to severe. Upper respiratory symptoms frequently precede fatigue, dyspnea, chest pain, congestive heart failure, and dysrhythmias. Presentations may mimic myocardial infarction; sudden death may also occur (including apparent sudden infant death syndrome). A pericardial friction rub indicates pericardial involvement. Chest radiography often demonstrates cardiac enlargement. Electrocardiography frequently reveals ST segment, T wave, and/or rhythm abnormalities, and echocardiography may confirm cardiac dilation, reduced contractility, and/or pericardial effusion. Myocardial enzyme serum concentrations may be elevated. The acute mortality of enterovirus myocarditis is 0-4%. Recovery is complete without residual disability in the majority. Occasionally, chronic cardiomyopathy, inflammatory ventricular microaneurysms, or constrictive pericarditis may result. The role of persistent infection in chronic dilated cardiomyopathy is controversial. Enteroviruses have also been implicated in late adverse cardiac events following heart transplantation and in acute coronary events, including myocardial infarction, endocarditis, and peripartum cardiomyopathy. Myocardial dysfunction observed in enterovirus 71 epidemics most commonly has occurred without evidence of myocarditis and may be of neurogenic origin; however, true myocarditis has also been described.

Gastrointestinal and Genitourinary Manifestations

Symptoms such as emesis (especially with meningitis), diarrhea (rarely severe), and abdominal pain are frequent but generally not dominant. Diarrhea, hematochezia, pneumatosis intestinalis, and necrotizing enterocolitis have occurred in premature infants during nursery outbreaks. Enterovirus infection has been implicated in acute and chronic gastritis, intussusception, chronic intestinal inflammation in hypogammaglobulinemic patients, sporadic hepatitis in normal children, severe hepatitis in neonates, and pancreatitis, which may result in transient exocrine pancreatic insufficiency.

Coxsackie B viruses are second only to mumps as causes of orchitis. The illness is frequently biphasic; fever and pleurodynia or meningitis are followed, in approximately 2 wk, by orchitis, often with epididymitis. Enteroviruses have also been implicated in cases of nephritis and IgA nephropathy.

Neurologic Manifestations

Enteroviruses are the most common cause of viral meningitis in mumps-immunized populations, accounting for up to 90% or more of cases in which a cause is identified. Meningitis is particularly common in infants, especially in those younger than 3 mo of age, often in community epidemics. Frequently implicated serotypes include coxsackie B viruses 2-5; echoviruses 4, 6, 7, 9, 11, 13, 16, and 30; and enteroviruses 70 and 71. Most cases in infants and young children are mild and lack specific signs and symptoms. Fever is present in 50-100%, accompanied by irritability, malaise, headache, photophobia, nausea, emesis, anorexia, lethargy, hypotonia, rash, cough, rhinorrhea, pharyngitis, diarrhea, and/or myalgia. Nuchal rigidity is apparent in more than half of children older than 1-2 yr of age. Some cases are biphasic, with fever and nonspecific symptoms for a few days followed by return of fever with meningeal signs several days later. Fever usually resolves in 3-5 days, and other symptoms in infants and young children usually resolve within 1 wk. Symptoms tend to be more severe and longer lasting in adults. CSF findings include pleocytosis (generally <500 but occasionally as high as 1,000-8,000 WBCs/μL; often predominantly polymorphonuclear cells in the 1st 48 hr before becoming mostly mononuclear); normal or slightly low glucose content (10% <40 mg/dL); and normal or mildly increased protein content (generally <100 mg/dL). CSF can have normal parameters despite positive viral culture or polymerase chain reaction (PCR) results, particularly in the 1st few months of life and early after illness onset. Complications occur in approximately 10% of young children, including simple and complex seizures, obtundation, increased intracranial pressure, syndrome of inappropriate antidiuretic hormone secretion, ventriculitis, transient cerebral arteriopathy, and coma. The prognosis for most children is good.

Enteroviruses are also responsible for ≥10-20% of cases of encephalitis with an identified cause. Frequently implicated serotypes include echoviruses 3, 4, 6, 9, and 11; coxsackie B viruses 2, 4, and 5; coxsackie A virus 9; and enterovirus 71. After initial nonspecific symptoms, there is progression to confusion, weakness, lethargy, and/or irritability. Depression is usually generalized, although focal findings, including focal motor seizures, hemichorea, acute cerebellar ataxia, aphasia, extrapyramidal symptoms, and/or focal imaging abnormalities, may occur. Manifestations range from altered mental status to coma to decerebrate status. Long-term sequelae, including epilepsy, weakness, cranial nerve palsy, spasticity, psychomotor retardation, and hearing loss, or death may follow severe disease. Persistent or recurrent cases have been observed rarely.

Neurologic disorders have been prominent in recent epidemics in Asia and Australia of enterovirus 71, and, to a lesser extent, coxsackievirus A16 disease. The majority of affected children had hand-foot-and-mouth disease, some had herpangina, and others had no mucocutaneous manifestations. Neurologic syndromes in a fraction of children included meningitis, meningoencephalomyelitis, poliomyelitis-like acute flaccid paralysis, Guillain-Barré syndrome, transverse myelitis, cerebellar ataxia, opsoclonus-myoclonus syndrome, benign intracranial hypertension, and brainstem encephalitis (**rhombencephalitis** involving the midbrain, pons, and medulla). The last is characterized by altered consciousness, myoclonus, vomiting, ataxia, nystagmus, tremor, cranial nerve abnormalities, autonomic dysfunction, and MRI demonstrating lesions in the brainstem, thalamus, and cerebellum. Although the disease was mild and reversible in some children, others had rapid progression to neurogenic pulmonary edema and hemorrhage, cardiopulmonary failure, shock, and coma. High mortality rates have been reported in children younger than 5 yr of age, especially in those younger than 1 yr of age. Deficits such as central hypoventilation, bulbar dysfunction, neurodevelopmental delay, cerebellar defects, attention deficit/hyperactivity–related symptoms, and limb weakness and atrophy have been observed among survivors, especially those who experienced cardiopulmonary failure during their acute illness. Although the most severe cases have been associated with enterovirus 71, similar clinical pictures have been produced by other enterovirus serotypes (e.g., coxsackieviruses A16 and B5, echovirus 7).

Patients with **antibody or combined immunodeficiencies** (including human immunodeficiency virus infection, acute lymphocytic leukemia, and transplantation) and patients receiving anti-CD20 antibody therapy are at risk for acute or, more commonly, **chronic meningoencephalitis.** The latter is characterized by persistent CSF abnormalities, viral detection by culture or PCR for years, and recurrent encephalitis and/or progressive neurologic deterioration, including insidious intellectual or personality deterioration, altered mental status, seizures, motor weakness, and increased intracranial pressure. Although disease may wax and wane, deficits generally become progressive and ultimately are frequently fatal or lead to long-term sequelae. A **dermatomyositis-like syndrome,** hepatitis, arthritis, myocarditis, or disseminated infection may also occur. Chronic enterovirus meningoencephalitis has become less common with high-dose intravenous immunoglobulin replacement.

A variety of nonpoliovirus enteroviruses, including enteroviruses 70 and 71, coxsackie A viruses 7 and 24, coxsackie B viruses, several

echoviruses, and possibly enterovirus 68, can cause poliomyelitis-like acute flaccid paralysis with motor weakness because of spinal cord anterior horn cell involvement. Disease tends to be milder than that caused by poliovirus, with less bulbar involvement and less persistent weakness. Other neurologic syndromes include cerebellar ataxia; transverse myelitis; Guillain-Barré syndrome, axonal polyneuropathy, and Miller-Fisher syndrome; acute disseminated encephalomyelitis; peripheral neuritis; optic neuritis; sudden hearing loss, tinnitus, and inner ear disorders such as vestibular neuritis; and other cranial neuropathies.

Myositis and Arthritis

Although myalgia is common, direct evidence of muscle involvement, including rhabdomyolysis, muscle swelling, focal myositis, and polymyositis, has uncommonly been reported. A dermatomyositis-like syndrome and arthritis can be seen in enterovirus-infected hypogammaglobulinemic patients. Enteroviruses are a rare cause of arthritis in normal hosts.

Neonatal Infections

Neonatal infections are relatively common, with a disease incidence comparable to or greater than that of neonatal herpes simplex virus, cytomegalovirus, and group B streptococcus disease. Infection frequently is caused by coxsackie B viruses 2-5 and echoviruses 6, 9, 11, and 19, although many serotypes have been implicated, including, in more recent years, coxsackie B virus 1 and echovirus 30. Enteroviruses may be acquired vertically before, during, or after delivery, including possible transmission via breast milk; horizontally from family members; or by sporadic or epidemic transmission in nurseries. In utero infection can lead to fetal demise, nonimmune hydrops fetalis, or neonatal illness. Additionally, maternal and intrauterine infections have been speculatively linked to congenital anomalies; prematurity, low birthweight, and intrauterine growth retardation; neurodevelopmental sequelae; unexplained neonatal illness and death; and increased risk of type 1 diabetes.

Neonatal infection may range from asymptomatic (the majority) to benign febrile illness to severe multisystem disease. Most affected newborns are full term and previously well; maternal history often reveals a recent viral illness, including fever and, frequently, abdominal pain. Neonatal symptoms may occur as early as day 1 of life, with onset of severe disease generally within the 1st 2 wk of life. Frequent findings include fever or hypothermia, irritability, lethargy, anorexia, rash (usually maculopapular, occasionally petechial or papulovesicular), jaundice, respiratory symptoms, apnea, hepatomegaly, abdominal distention, emesis, diarrhea, and decreased perfusion. Most patients have benign courses, with resolution of fever in an average of 3 days and of other symptoms in about 1 wk. A biphasic course may occur occasionally. A minority have severe disease dominated by any combination of sepsis, meningoencephalitis, myocarditis, hepatitis, coagulopathy, and/or pneumonitis. Meningoencephalitis may be manifested by focal or complex seizures, bulging fontanelle, nuchal rigidity, or reduced level of consciousness. Myocarditis, most often associated with coxsackie B virus infection, may be suggested by tachycardia, dyspnea, cyanosis, and cardiomegaly. Hepatitis and pneumonitis are associated with echovirus infection, although they may occur with coxsackie B viruses. Gastrointestinal manifestations may predominate in premature neonates. Laboratory and radiographic evaluation may reveal leukocytosis, thrombocytopenia, CSF pleocytosis, CNS white matter damage, elevations of serum transaminases and bilirubin, coagulopathy, pulmonary infiltrates, and electrocardiographic changes.

Complications of severe neonatal disease include CNS necrosis and generalized or focal neurologic compromise; arrhythmias, congestive heart failure, myocardial infarction, and pericarditis; hepatic necrosis and failure; intracranial or other bleeding; adrenal necrosis and hemorrhage; and rapidly progressive pneumonitis and pulmonary hypertension. Myositis, arthritis, necrotizing enterocolitis, inappropriate antidiuretic hormone secretion, hemophagocytic lymphohistiocytosis-like presentation, bone marrow failure, and sudden death are rare events. Mortality with severe disease is significant and most often associated with hepatitis and bleeding complications, myocarditis, or pneumonitis.

Survivors of severe neonatal disease may have gradual resolution of hepatic and cardiac dysfunction, although persistent hepatic dysfunction and residual cardiac impairment, chronic calcific myocarditis, and ventricular aneurysm can occur. Meningoencephalitis may be associated with speech and language impairment; cognitive deficits; spasticity, hypotonicity, or weakness; seizure disorders; microcephaly or hydrocephaly; and ocular abnormalities. However, many survivors appear not to have long-term sequelae. Risk factors for severe disease include illness onset in the 1st few days of life, maternal illness just prior to or at delivery, prematurity, male sex, infection by echovirus 11 or a coxsackie B virus, positive serum viral culture, absence of neutralizing antibody to the infecting virus, and evidence of severe hepatitis and/or multisystem disease.

Transplant Recipients and Patients with Malignancies

Enterovirus infections in stem cell and solid organ transplant recipients may be severe and/or prolonged, causing progressive pneumonia, severe diarrhea, pericarditis, heart failure, meningoencephalitis, and disseminated disease. Enterovirus-associated hemophagocytic lymphohistiocytosis, meningitis, encephalitis, and myocarditis have been reported in children with malignancies and patients treated with anti-CD20 monoclonal antibody. Infections in these groups are associated with high fatality rates.

DIAGNOSIS

Clues to enterovirus infection include characteristic findings such as hand-foot-and-mouth disease or herpangina lesions, consistent seasonality, known community outbreak, and exposure to enterovirus-compatible disease. In the neonate, history of maternal fever, malaise, and/or abdominal pain near delivery during enterovirus season is suggestive.

Enterovirus infection can be confirmed with viral culture using a combination of cell lines. Sensitivity ranges from 50-75% and can be increased by sampling of multiple sites (e.g., CSF plus throat and rectum in children with meningitis). In neonates, yields of 30-70% are achieved when blood, urine, CSF, and mucosal swabs are cultured. A major limitation is the inability of most coxsackie A viruses to grow in culture. Yield may also be limited by neutralizing antibody in patient specimens, improper specimen handling, or insensitivity of the cell lines used. Culture is relatively slow, with 3-8 days usually required to detect growth. Centrifugation-enhanced antigen detection coupled with culture (shell vial techniques) can shorten the time to detection, but the sensitivity of this method has been limiting. Although cultivation of an enterovirus from any site can generally be considered evidence of recent infection, isolation from the rectum or stool can reflect more remote shedding. Similarly, recovery from a mucosal site may suggest an association with an illness, whereas recovery from a normally sterile site (e.g., CSF, blood, or tissue) is more conclusive evidence of causation. Serotype identification by type-specific antibody staining or neutralization of a viral isolate is generally required only for investigation of an outbreak or an unusual disease manifestation, surveillance, or to distinguish nonpoliovirus enteroviruses from vaccine or wild-type polioviruses.

Direct testing for nucleic acid overcomes the imperfect sensitivity and delayed results of culture. RT-PCR detection of highly conserved areas of the enterovirus genome can detect the majority of enteroviruses, including coxsackie A viruses (but generally *not* the parechoviruses) in CSF; serum; urine; conjunctival, nasopharyngeal, throat, tracheal, rectal, and stool specimens; dried blood spots; and tissues such as myocardium, liver, and brain. Sensitivity and specificity of RT-PCR are high, with results in as short as 2-3 hr. Real-time, quantitative PCR assays and nested PCR assays with enhanced sensitivity have been developed, as have enterovirus-containing multiplex PCR assays, nucleic acid sequence–based amplification assays, reverse transcription-loop-mediated isothermal amplification, culture-enhanced PCR assays, and PCR-based microarray assays. PCR testing of CSF from children with meningitis and from hypogammaglobulinemic patients with chronic meningoencephalitis is frequently positive despite negative cultures. Routine application of CSF PCR for infants and young children with

suspected meningitis decreases the number of diagnostic tests, duration of hospital stay, antibiotic use, and overall costs. PCR testing of tracheal aspirates of children with myocarditis has good concordance with testing of myocardial specimens. In ill neonates and young infants, PCR testing of serum and urine has higher yields than culture. Viral load in blood of neonates is correlated with disease severity, and viral nucleic acid may persist in blood of severely ill newborns for up to 2 mo.

Sequence analysis of amplified nucleic acid can be used for serotype identification and phylogenetic analysis and to establish a transmission link among cases. Serotype-specific (e.g., enterovirus 71 and coxsackie A virus 16) PCR assays have been developed, including assays that can be used in resource-poor regions. For enterovirus 71, the yield of specimens other than CSF and blood (throat, nasopharyngeal, rectal, and vesicle swabs and CNS tissue) is greater (by PCR or culture) than the yield of CSF and blood, which are infrequently positive. Antigen detection assays that target specific serotypes such as enterovirus 71 with monoclonal antibodies have also been developed.

Enterovirus infections can be detected serologically by a rise, in serum or CSF, of neutralizing, complement fixation, enzyme-linked immunosorbent assay, or other type-specific antibody or by detection of serotype-specific IgM antibody. However, serologic testing requires presumptive knowledge of the infecting serotype or an assay with sufficiently broad cross-reactivity. Sensitivity and specificity may be limiting, and cross-reactivity among serotypes may occur. Except for epidemiologic studies or cases characteristic of specific serotypes (e.g., enterovirus 71), serology is generally less useful than culture or nucleic acid detection.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of enterovirus infections varies with the clinical presentation (Table 250-2).

Human parechoviruses, members of the *Picornaviridae* family, produce many manifestations similar to the nonpolio enteroviruses. Human parechoviruses are small RNA viruses that were once mistakenly classified as echoviruses. Infections in older children are often unrecognized or cause nonspecific acute and benign febrile illnesses with very few specific findings. Neonates and young infants are often more severely affected, demonstrating aseptic meningitis, encephalitis, a sepsis-like picture, and hepatitis. The viral sepsis and the encephalitic presentations are the most common serious manifestations, often requiring intensive care treatment for shock, seizures, and other signs of encephalitis. Epidemics occur in the same season as enterovirus infections; in contrast to the enteroviruses there is a higher incidence of MRI abnormalities in those with encephalitis.

More frequently than with enteroviruses, those affected by parechovirus may have no CSF pleocytosis despite the presence of CNS infection. The diagnosis is confirmed by human parechovirus-specific PCR on CSF, stool, and nasopharyngeal secretions. Infants suspected of having an enteroviral infection should also be considered as possibly having a parechovirus infection because the two may be indistinguishable; nonetheless, parechovirus infections appear to be less common.

TREATMENT

In the absence of a proven antiviral agent for enterovirus infections, supportive care is the mainstay of treatment. Newborns and young infants with nonspecific febrile illnesses and children with meningitis frequently require diagnostic evaluations for bacterial and herpes simplex virus infection and hospitalization for presumptive treatment until tests rule out these diagnoses. Neonates with severe disease and infants and children with myocarditis or concerning neurologic diseases (e.g., enterovirus 71 neurologic and/or cardiopulmonary disease) may require intensive supportive care, including cardiorespiratory and blood product support. Milrinone has been suggested as a useful agent in severe enterovirus 71 cardiopulmonary disease. Liver and cardiac transplantation have been performed for neonates with progressive end-organ failure.

Immunoglobulin has been utilized to treat enterovirus infections based on the importance of the humoral immune response to enterovirus infection and the observation that absence of neutralizing antibody is a risk factor for symptomatic infection. Immunoglobulin products contain neutralizing antibodies to many commonly circulating serotypes, although titers vary with serotype and among products and lots. Anecdotal and retrospective, uncontrolled use of intravenous immunoglobulin or infusion of maternal convalescent plasma to treat newborns with severe disease has been associated with varying outcomes. The one randomized, controlled trial was too small to demonstrate significant clinical benefits, although neonates who received immunoglobulin containing high neutralizing titers to their own isolates had shorter periods of viremia and viruria. Immunoglobulin has been administered intravenously and intraventricularly to treat hypogammaglobulinemic patients with chronic enterovirus meningoencephalitis and intravenously in transplant and oncology patients with severe infections, with variable success. Intravenous immunoglobulin and corticosteroids have been used for patients with neurologic disease caused by enterovirus 71 and other enteroviruses; modulation of cytokine profiles after administration of intravenous immunoglobulin for enterovirus 71–associated brainstem encephalitis has been demonstrated. High-titer enterovirus 71 immunoglobulin appeared promising in animal models, and clinical trials in regions with epidemic enterovirus 71 disease are underway. Development of anti–enterovirus 71 monoclonal antibodies is also being pursued. A retrospective study suggested that treatment of presumed viral myocarditis with immunoglobulin was associated with improved outcome; however, virologic diagnoses were not made. Evaluation of corticosteroids and

Table 250-2 Differential Diagnosis of Enterovirus Infections

CLINICAL MANIFESTATION	BACTERIAL PATHOGENS	VIRAL PATHOGENS
Nonspecific febrile illness	*Streptococcus pneumoniae, Haemophilus influenzae* type b, *Neisseria meningitidis*	Influenza viruses, human herpesviruses 6 and 7, human parechoviruses
Exanthems/enanthems	Group A streptococcus, *Staphylococcus aureus, N. meningitidis*	Herpes simplex virus, adenoviruses, varicella-zoster virus, Epstein-Barr virus, measles virus, rubella virus, human herpesviruses 6 and 7, human parechoviruses
Respiratory illness/conjunctivitis	*S. pneumoniae, H. influenzae* (nontypeable and type b), *N. meningitidis, Mycoplasma pneumoniae, Chlamydia pneumoniae*	Adenoviruses, influenza viruses, respiratory syncytial virus, parainfluenza viruses, rhinoviruses, human metapneumovirus, coronaviruses
Myocarditis/pericarditis	*S. aureus, H. influenzae* type b, *M. pneumoniae*	Adenoviruses, influenza virus, parvovirus, cytomegalovirus
Meningitis/encephalitis	*S. pneumoniae, H. influenzae* type b, *N. meningitidis, Mycobacterium tuberculosis, Borrelia burgdorferi, M. pneumoniae, Bartonella henselae, Listeria monocytogenes*	Herpes simplex virus, West Nile virus, influenza viruses, adenoviruses, Epstein-Barr virus, mumps virus, lymphocytic choriomeningitis virus, arboviruses, human parechoviruses
Neonatal infections	Group B streptococcus, Gram-negative enteric bacilli, *L. monocytogenes, Enterococcus*	Herpes simplex virus, adenoviruses, cytomegalovirus, rubella virus, human parechoviruses

cyclosporine and other immunosuppressive therapy for myocarditis has been inconclusive. Successful treatment of enterovirus myocarditis with interferon-α has been reported anecdotally, and interferon-β treatment was associated with viral clearance, improved cardiac function, and survival in chronic cardiomyopathy associated with persistence of enterovirus (or adenovirus) genome. Activity of interferon-α against enterovirus 71 has been demonstrated in in vitro and in animal models, but potency varies with interferon-α type.

Antiviral agents that act at various steps in the enterovirus life cycle—attachment, penetration, uncoating, translation, polyprotein processing, protease activity, replication, and assembly—are being evaluated. Candidates include pharmacologically active chemical compounds, small interfering RNAs and DNA-like antisense agents, purine nucleoside analogs, synthetic peptides, enzyme inhibitors of signal transduction pathways, interferon-inducers, and herbal compounds. **Pleconaril**, an inhibitor of attachment and uncoating, was associated with benefit in some controlled studies of enterovirus meningitis and picornavirus upper respiratory tract infections, and uncontrolled experience suggested possible benefits in high-risk infections; however, application for licensure was denied because of concern about potential medication interactions. A randomized, controlled trial of pleconaril in neonates with severe hepatitis, coagulopathy, and/or myocarditis suggested possible virologic and clinical benefits of treatment.

Design and evaluation of candidate agents active against enterovirus 71 is a priority. Of currently available agents, lactoferrin and ribavirin have demonstrated activity in vitro and/or in animal models. Challenges to development of antivirals for enterovirus 71 include limited cross-genotypic activity of candidate compounds and high viral mutagenicity that favors emergence of resistance.

COMPLICATIONS AND PROGNOSIS

The prognosis in the majority of enterovirus infections is excellent. Morbidity and mortality are associated primarily with myocarditis, neurologic disease, severe neonatal infections, and infections in immune compromised hosts.

PREVENTION

The first line of defense is hygiene, such as handwashing, to prevent fecal-oral and respiratory spread within families, schools, and institutional settings; avoidance of sharing utensils and drinking containers and other potential fomites; disinfection of contaminated surfaces; and avoiding community settings where exposures are likely to occur. Chlorination of drinking water and swimming pools may be important. Infection control techniques such as cohorting have proven effective in limiting nursery outbreaks. Prophylactic administration of immunoglobulin or convalescent plasma has been used in nursery epidemics; simultaneous use of infection control interventions makes it difficult to determine efficacy.

Pregnant women near term should avoid contact with individuals ill with possible enterovirus infections. If a pregnant woman experiences a suggestive illness, it is advisable not to proceed with emergency delivery unless there is concern for fetal compromise or obstetric emergencies cannot be excluded. Rather, it may be advantageous to extend pregnancy, allowing the fetus to passively acquire protective antibodies. A strategy of prophylactically administering immunoglobulin to neonates born to mothers with enterovirus infections is untested.

Maintenance antibody replacement with high-dose intravenous immunoglobulin for patients with hypogammaglobulinemia has reduced the incidence of chronic enterovirus meningoencephalitis, although breakthrough infections occur. Vaccines for nonpoliovirus enteroviruses are not available, but candidates for virulent serotypes such as enterovirus 71 are being investigated. Approaches include inactivated vaccines; VP1 capsid protein-based subunit, DNA, and vector vaccines; combined peptide vaccines; live-attenuated vaccines; virus-like particles; breast milk enriched with VP1 capsid protein or lactoferrin; and interferon-γ–expressing recombinant viral vectors. Several enterovirus 71 candidate vaccines have demonstrated protection in animal models and human clinical trials. Circulation of multiple enterovirus 71 types, antigenic drift, viral recombination, and potential immunologic cross-reactivity with brain tissue may pose challenges to vaccine development.

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Chapter 251

Parvoviruses

William C. Koch

The parvoviruses are small, single-stranded DNA viruses. They are common infectious agents of a variety of animal species, including mammals, birds, and insects. Parvoviruses as a group include a number of important animal pathogens. There are now 4 different types of parvoviruses known to infect humans: the dependoviruses also called adeno-associated viruses (AAVs), parvovirus B19 (B19), human bocaviruses (HBoV), and parvovirus 4. B19 and HBoV are the only 2 parvoviruses known to be pathogenic in humans. B19 is the most well studied and clinically important of the human parvoviruses and the cause of **erythema infectiosum** or **fifth disease**. *The more recently described human bocavirus is an emerging human pathogen.*

ETIOLOGY

The 4 human parvoviruses are distinct enough from each other to represent 4 different genera within the Parvoviridae family. B19 is a member of the genus *Erythrovirus*. The virus is composed of an icosahedral protein capsid without an envelope and contains a single-stranded DNA genome of approximately 5.5 kb. It is relatively heat and solvent resistant. It is antigenically distinct from other mammalian parvoviruses and has only 1 known serotype. The relatively short parvovirus genome does not encode a DNA polymerase, so all parvoviruses require either host cell factors present in late S phase or coinfection with another virus to replicate their DNA. B19 can be propagated effectively in vitro only in $CD36^+$ erythroid progenitor cells derived from human bone marrow, umbilical cord blood, or peripheral blood.

HBoV is a member of the genus *Bocavirus*. HBoV was first isolated from nasopharyngeal specimens from children with respiratory tract infection in 2005. It was identified using random polymerase chain reaction (PCR) amplification and sequencing methods specifically designed to detect previously unknown viral sequences. Analysis of the gene sequences showed similarities to both bovine and canine parvoviruses, and thus the virus was named human bocavirus. Later, 3 other HBoVs were identified in stool samples and named HBoV types 2, 3, and 4, with the initial respiratory isolate called HBoV1. The HBoV capsid structure and genome size are similar to those of B19, but the genomic organization and replication are different (though not fully characterized to date). HBoVs cannot be propagated in conventional cell culture but have been grown in a pseudostratified human airway epithelial cell culture system.

The AAVs are members of the genus *Dependovirus* and were the first parvoviruses to be found in humans. They were originally identified as contaminants in adenovirus preparations, resulting in the designation "adeno-associated viruses." They were later isolated directly from human tissue samples, and now several AAV serotypes are known to commonly infect humans. AAVs have a unique life cycle that can take 1 of 2 paths: (1) a lytic infection with replication of viral DNA and production of new virus, or (2) viral integration into the host cell DNA. In the presence of a "helper" virus, usually an adenovirus or a herpesvirus, AAV can replicate its DNA, produce capsids, and release new virions by cell lysis. In the absence of a helper virus infection, the AAV genome becomes integrated into the host cell DNA. This feature has drawn interest in AAVs as potential vectors for gene therapy. Although

human infection with AAVs is common, there is no known disease association and no evidence of pathogenicity, so this virus will not be discussed further in this chapter.

Parvovirus 4 was initially identified in 2005 from the blood of an adult patient with "acute viral syndrome," who was also an intravenous drug user coinfected with hepatitis C. Subsequently, this virus has been found in blood donors and donated plasma pools in many different countries. It appears to be present in approximately 3% of blood donors in the United States and 4% of plasma pools. There is, as of this writing, no known disease association or clinical symptoms associated with infection. The virus has not yet been assigned to a parvovirus genus and may represent a new genus once its virology is better characterized. The full epidemiology and clinical relevance of this virus await further study, and the reader is referred to the bibliography for further information.

EPIDEMIOLOGY

Parvovirus B19

Infections with B19 are common and occur worldwide. Clinically apparent infections, such as the rash illness of erythema infectiosum and transient aplastic crisis, are most prevalent in school-age children (70% of cases occur in patients between 5 and 15 yr of age). Seasonal peaks occur in the late winter and spring, with sporadic infections throughout the year. Seroprevalence increases with age, 40-60% of adults having evidence of prior infection.

Transmission of B19 is by the respiratory route, presumably via large-droplet spread from nasopharyngeal viral shedding. The transmission rate is 15-30% among susceptible household contacts, and mothers are more commonly infected than fathers. In outbreaks of erythema infectiosum in elementary schools, the secondary attack rates range from 10-60%. Nosocomial outbreaks also occur, with secondary attack rates of 30% among susceptible healthcare workers.

Although respiratory spread is the primary mode of transmission, B19 is also transmissible in blood and blood products, as documented among children with hemophilia receiving pooled-donor clotting factor. Given the resistance of the virus to solvents, fomite transmission could be important in childcare centers and other group settings, but this mode of transmission has not been established.

Human Bocaviruses

The majority of studies published have used molecular methods to detect HBoV DNA in respiratory secretions, fecal samples, blood, and other tissues. HBoV DNA (HBoV1) can be found commonly in respiratory secretions from children hospitalized with acute lower respiratory tract infections (LRTIs). It is more prevalent in children younger than 2 yr of age and seems to be associated with wheezing respiratory illness. However, it can be isolated from respiratory secretions from asymptomatic children and can often be found as a coinfection with other common respiratory pathogens of children this age, including respiratory syncytial virus, human metapneumovirus, and rhinoviruses. This has caused some confusion as to the pathogenic role of HBoV in acute LRTI, including whether it can persist in secretions long after a subclinical infection or requires a helper virus. A limited number of seroepidemiologic studies have been performed, and these suggest that infection is common in children younger than 5 yr of age. The most recent studies provide evidence that the virus is in fact pathogenic, especially in children younger than 2 with wheezing and LRTI, as HBoV1 is more likely to be the only virus isolated in these patients and more likely to have an acute antibody response when coupled with antibody testing. When quantitative PCR is used, the virus is found to be much higher in titer in these symptomatic cases.

HBoV DNA (HBoV2, HBoV3, and HBoV4) has also been found in fecal samples in studies from various countries, but its role as a cause of viral gastroenteritis is still undetermined.

PATHOGENESIS

Parvovirus B19

The primary target of B19 infection is the erythroid cell line, specifically erythroid precursors near the pronormoblast stage. Viral infection produces cell lysis, leading to a progressive depletion of erythroid precursors and a transient arrest of erythropoiesis. The virus has no apparent effect on the myeloid cell line. The tropism for erythroid cells is related to the erythrocyte P blood group antigen, which is the primary cell receptor for the virus and is also found on endothelial cells, placental cells, and fetal myocardial cells. Thrombocytopenia and neutropenia are often observed clinically, but the pathogenesis of these abnormalities is unexplained.

Experimental infection of normal volunteers with B19 revealed a biphasic illness. From 7-11 days after inoculation, subjects had viremia and nasopharyngeal viral shedding with fever, malaise, and rhinorrhea. Reticulocyte counts dropped to undetectable levels but resulted in only a mild, clinically insignificant fall in serum hemoglobin. With the appearance of specific antibodies, symptoms resolved and serum hemoglobin returned to normal. Several subjects experienced a rash associated with arthralgia 17-18 days after inoculation. Some manifestations of B19 infection, such as transient aplastic crisis, appear to be a direct result of viral infection, whereas others, including the exanthem and arthritis, appear to be **postinfectious phenomena** related to the immune response. Skin biopsy of patients with erythema infectiosum reveals edema in the epidermis and a perivascular mononuclear infiltrate compatible with an immune-mediated process.

Individuals with **chronic hemolytic anemia** and increased red blood cell (RBC) turnover are very sensitive to minor perturbations in erythropoiesis. Infection with B19 leads to a transient arrest in RBC production and a precipitous fall in serum hemoglobin, often requiring transfusion. The reticulocyte count drops to undetectable levels, reflecting the lysis of infected erythroid precursors. Humoral immunity is crucial in controlling infection. Specific immunoglobulin (Ig) M appears within 1-2 days of infection and is followed by anti-B19 IgG, which leads to control of the infection, restoration of reticulocytosis, and a rise in serum hemoglobin.

Individuals with **impaired humoral immunity** are at increased risk for more serious or persistent infection with B19, which usually manifests as chronic RBC aplasia, although neutropenia, thrombocytopenia, and marrow failure are also described. Children undergoing chemotherapy for leukemia or other forms of cancer, transplant recipients, and patients with congenital or acquired immunodeficiency states (including AIDS) are at risk for chronic B19 infections.

Infections in the **fetus** and **neonate** are somewhat analogous to infections in immunocompromised persons. B19 is associated with nonimmune fetal hydrops and stillbirth in women experiencing a primary infection but does not appear to be teratogenic. Like most mammalian parvoviruses, B19 can cross the placenta and cause fetal infection during primary maternal infection. Parvovirus cytopathic effects are seen primarily in erythroblasts of the bone marrow and sites of extramedullary hematopoiesis in the liver and spleen. Fetal infection can presumably occur as early as 6 wk of gestation, when erythroblasts are first found in the fetal liver; after the 4th mo of gestation, hematopoiesis switches to the bone marrow. In some cases, fetal infection leads to profound fetal anemia and subsequent high-output cardiac failure (see Chapter 103). **Fetal hydrops** ensues and is often associated with fetal death. There may also be a direct effect of the virus on myocardial tissue that contributes to the cardiac failure. However, most infections during pregnancy result in normal deliveries at term. Some of the asymptomatic infants from these deliveries have been reported to have chronic postnatal infection with B19 that is of unknown significance.

Human Bocaviruses

Mechanisms of HBoV replication and pathogenesis are poorly characterized to date. Growth of HBoV1 in tissue culture is difficult, though the virus has been cultured in primary respiratory epithelial cells as noted above. The primary site of viral replication appears to be the respiratory tract, as the virus has been detected most frequently and in highest copy numbers here. HBoV1 has also been found occasionally in the serum, suggesting the potential for systemic spread. HBoV1 has also been detected in stool, but copy numbers are very low. In contrast, HBoV types 2-4 are found predominantly in the stool, but host cell types are not known.

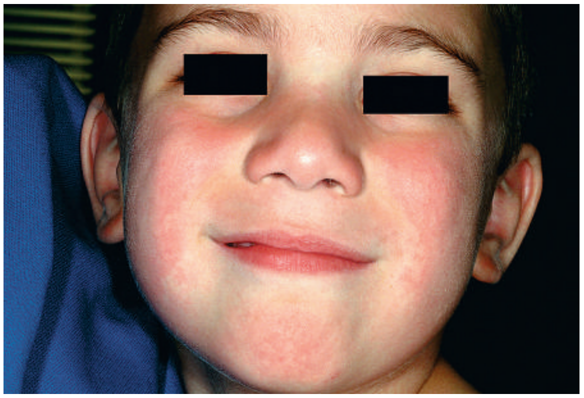

Figure 251-1 **Erythema infectiosum.** Erythema of the bilateral cheeks, which has been likened to a "slapped cheek" appearance. *(From Paller AS, Macini AJ:* Hurwitz clinical pediatric dermatology, *ed 3. Philadelphia, 2006, WB Saunders, p. 431.)*

CLINICAL MANIFESTATIONS

Parvovirus B19

Many infections are clinically inapparent. Infected children characteristically demonstrate the rash illness of erythema infectiosum. Adults, especially women, frequently experience acute polyarthropathy with or without a rash.

Erythema Infectiosum (Fifth Disease)

The most common manifestation of parvovirus B19 is erythema infectiosum, also known as *fifth disease*, which is a benign, self-limited exanthematous illness of childhood.

The incubation period for erythema infectiosum is 4-28 days (average: 16-17 days). The prodromal phase is mild and consists of low-grade fever in 15-30% of cases, headache, and symptoms of mild upper respiratory tract infection. The hallmark of erythema infectiosum is the characteristic rash, which occurs in 3 stages that are not always distinguishable. The initial stage is an erythematous facial flushing, often described as a **"slapped-cheek" appearance** (Fig. 251-1). The rash spreads rapidly or concurrently to the trunk and proximal extremities as a diffuse macular erythema in the 2nd stage. Central clearing of macular lesions occurs promptly, giving the rash a **lacy, reticulated appearance** (Fig. 251-2). The rash tends to be more prominent on extensor surfaces, sparing the palms and soles. Affected children are afebrile and do not appear ill. Some have petechiae. Older children and adults often complain of mild pruritus. The rash resolves spontaneously without desquamation, but tends to wax and wane over 1-3 wk. It can recur with exposure to sunlight, heat, exercise, and stress. Lymphadenopathy and atypical papular, purpuric, vesicular rashes are also described.

Arthropathy

Arthritis and arthralgia may occur in isolation or with other symptoms. Joint symptoms are much more common among adults and older adolescents with B19 infection. Females are affected more frequently than males. In 1 large outbreak of fifth disease, 60% of adults and 80% of adult women reported joint symptoms. Joint symptoms range from diffuse polyarthralgia with morning stiffness to frank arthritis. The joints most often affected are the hands, wrists, knees, and ankles, but practically any joint may be affected. The joint symptoms are self-limited and, in the majority of patients, resolve within 2-4 wk. Some patients may have a prolonged course of many months, suggesting rheumatoid arthritis. Transient rheumatoid factor positivity is reported in some of these patients but with no joint destruction.

Transient Aplastic Crisis

The transient arrest of erythropoiesis and absolute reticulocytopenia induced by B19 infection leads to a sudden fall in serum hemoglobin in individuals with chronic hemolytic conditions. This B19-induced RBC aplasia or transient aplastic crisis occurs in patients with all types of chronic hemolysis and/or rapid RBC turnover, including sickle cell disease, thalassemia, hereditary spherocytosis, and pyruvate kinase deficiency. In contrast to children with erythema infectiosum only, patients with aplastic crisis are ill with fever, malaise, and lethargy and have signs and symptoms of profound anemia, including pallor, tachycardia, and tachypnea. Rash is rarely present. The incubation period for transient aplastic crisis is shorter than that for erythema infectiosum because the crisis occurs coincident with the viremia. Children with sickle cell hemoglobinopathies may also have a concurrent vaso-occlusive pain crisis, further confusing the clinical presentation.

Figure 251-2 **Erythema infectiosum.** Reticulate erythema on the upper arm of a patient with erythema infectiosum. *(From Paller AS, Macini AJ:* Hurwitz clinical pediatric dermatology, *ed 3. Philadelphia, 2006, WB Saunders, p. 431.)*

Immunocompromised Persons

Persons with impaired humoral immunity are at risk for chronic parvovirus B19 infection. Chronic anemia is the most common manifestation, sometimes accompanied by neutropenia, thrombocytopenia, or complete marrow suppression. Chronic infections occur in persons receiving cancer chemotherapy or immunosuppressive therapy for transplantation and persons with congenital immunodeficiencies, AIDS, and functional defects in IgG production who are thereby unable to generate neutralizing antibodies.

Fetal Infection

Primary maternal infection is associated with nonimmune fetal hydrops and intrauterine fetal demise, with the risk for fetal loss after infection estimated at <5%. The mechanism of fetal disease appears to be a viral-induced RBC aplasia at a time when the fetal erythroid fraction is rapidly expanding, leading to profound anemia, high-output cardiac failure, and fetal hydrops. Viral DNA has been detected in infected abortuses. The 2nd trimester seems to be the most sensitive period, but fetal losses are reported at every stage of gestation. If maternal B19 infection is suspected, fetal ultrasonography and measurement of the peak systolic flow velocity of the middle cerebral artery are sensitive,

noninvasive procedures to diagnose fetal anemia and hydrops. Most infants infected in utero are born normally at term, including some who have had ultrasonographic evidence of hydrops. A small subset of infants infected in utero may acquire a chronic or persistent postnatal infection with B19 that is of unknown significance. Congenital anemia associated with intrauterine B19 infection has been reported in a few cases, sometimes following intrauterine hydrops. This process may mimic other forms of congenital hypoplastic anemia (e.g., Diamond-Blackfan syndrome). Fetal infection with B19 has been associated with bone lesions but has not been associated with other birth defects. B19 is only 1 of many causes of hydrops fetalis (see Chapter 103.2).

Myocarditis

B19 infection has been associated with myocarditis in fetuses, infants, children, and a few adults. Diagnosis has often been based on serologic findings suggestive of a concurrent B19 infection, but in many cases B19 DNA has been demonstrated in cardiac tissue. B19-related myocarditis is plausible because fetal myocardial cells are known to express P antigen, the cell receptor for the virus. In the few cases in which histology is reported, a predominantly lymphocytic infiltrate is described. Outcomes have varied from complete recovery to chronic cardiomyopathy to fatal cardiac arrest. Although B19-associated myocarditis seems to be a rare occurrence, there appears to be enough evidence to consider B19 as a potential cause of lymphocytic myocarditis, especially in infants and immunocompromised persons.

Other Cutaneous Manifestations

A variety of atypical skin eruptions have been reported with B19 infection. Most of these are petechial or purpuric in nature, often with evidence of vasculitis on biopsy. Among these rashes, the ***papular-purpuric "gloves-and-socks" syndrome (PPGSS)*** is well established in the dermatologic literature as distinctly associated with B19 infection (Fig. 251-3). PPGSS is characterized by fever, pruritus, and painful edema and erythema localized to the distal extremities in a distinct "gloves-and-socks" distribution, followed by acral petechiae and oral lesions. The syndrome is self-limited and resolves within a few weeks. Although PPGSS was initially described in young adults, a number of reports of the disease in children have since been published. In those cases linked to B19 infection, the eruption is accompanied by serologic evidence of acute infection.

Figure 251-3 Photographs revealing the petechial rash on the extremities **(A),** that was sharply demarcated on the ankles **(B)** in a 6 yr old child. *(From Parez N, Dehee A, Michel Y, et al: Papular-purpuric gloves and socks syndrome associated with B19V infection in a 6-year-old child.* J Clin Virol *44:167–169, 2009, Fig. 1.)*

Human Bocaviruses

Many studies have reported an association between respiratory tract infection and HBoV1 infection as detected by PCR of respiratory secretions, primarily nasopharyngeal secretions. Clinical manifestations in these studies have ranged from mild upper respiratory symptoms to pneumonia. However, the role of HBoV1 as a pathogen has been challenged by the detection of the virus in asymptomatic children and by the frequent detection of other respiratory viruses in the same samples. Nonetheless, studies that have included some combination of quantitative PCR, serum PCR, and serology have been more convincing about HBoV1 as a human pathogen. The use of a quantitative PCR method also seems to differentiate between HBoV1 infection (and wheezing) and prolonged viral shedding, as patients with higher viral titers were more likely to be symptomatic, to be viremic, and to have HBoV1 isolated without other viruses.

HBoV type 2 DNA has been found in the stool of 3-25% of children with gastroenteritis, but often with another enteric virus. DNA of HBoV types 2, 3, and 4 has also been found in the stool of healthy, asymptomatic individuals. At present, there are few data linking HBoV2, HBoV3, or HBoV4 to gastroenteritis or any clinical illness. Further studies are required to determine if any of the HBoVs are associated with some cases of childhood gastroenteritis.

DIAGNOSIS

Parvovirus B19 Infection

The diagnosis of erythema infectiosum is usually based on clinical presentation of the typical rash and rarely requires virologic confirmation. Similarly, the diagnosis of a typical transient aplastic crisis in a child with sickle cell disease is generally made on clinical grounds without specific virologic testing.

Serologic tests for the diagnosis of B19 infection are available. B19-specific IgM develops rapidly after infection and persists for 6-8 wk. Anti-B19 IgG serves as a marker of past infection or immunity. Determination of anti-B19 IgM is the best marker of recent/acute infection on a single serum sample; seroconversion of anti-B19 IgG antibodies in paired sera can also be used to confirm recent infection. Demonstration of anti-B19 IgG in the absence of IgM, even in high titer, is not diagnostic of recent infection.

Serologic diagnosis is unreliable in immunocompromised persons; diagnosis in these patients requires methods to detect viral DNA. Because the virus cannot be isolated by standard cell culture, methods to detect viral particles or viral DNA, such as PCR and nucleic acid hybridization, are necessary to establish the diagnosis. These tests are not widely available outside of research centers or reference laboratories. Prenatal diagnosis of B19-induced fetal hydrops can be accomplished by detection of viral DNA in fetal blood or amniotic fluid by these methods.

Human Bocavirus Infections

HBoV1 infections cannot be differentiated from other viral respiratory infections on clinical grounds. HBoV DNA can be readily detected by PCR methods and is now included in several commercially available multiplex respiratory virus PCR assays. As noted above, quantitative

PCR is useful to differentiate acute infection from persistent viral shedding, as higher viral copy numbers (>10(4) HBoV1 genomes/mL) correlate with acute illness, but this test is not widely available. Likewise, serologic methods to detect specific IgM and IgG antibodies have been developed, but these too are not routinely available and there are problems with cross-reactivity among antibodies to the various HBoV types. The most reliable method to diagnose HBoV1 infection would include detection of viral DNA in serum by PCR, and in respiratory tract samples by quantitative PCR, with concurrent detection of IgM or a diagnostic IgG response in paired samples.

DIFFERENTIAL DIAGNOSIS

Parvovirus B19

The rash of erythema infectiosum must be differentiated from rubella, measles, enteroviral infections, and drug reactions. Rash and arthritis in older children should prompt consideration of juvenile rheumatoid arthritis, systemic lupus erythematosus, serum sickness, and other connective tissue disorders.

Human Bocavirus

Respiratory illness and wheezing caused by HBoV1 cannot clinically be differentiated from other common viral respiratory infections, especially respiratory syncytial virus, human metapneumovirus, rhinoviruses, enterovirus 68, and parainfluenza viruses. HBoV1 infection in young children seems to most closely resemble that of respiratory syncytial virus and human metapneumovirus, as the clinical symptoms and age ranges will overlap.

TREATMENT

Parvovirus B19

There is no specific antiviral therapy for B19 infection. Commercial lots of intravenous immunoglobulin (IVIG) have been used with some success to treat B19-related episodes of anemia and bone marrow failure in immunocompromised children. Specific antibody may facilitate clearance of the virus; it is not always necessary, however, because cessation of cytotoxic chemotherapy with subsequent restoration of immune function often suffices. In patients whose immune status is not likely to improve, such as patients with AIDS, administration of IVIG may give only a temporary remission, and periodic reinfusions may be required. In patients with AIDS, clearance of B19 infection has been reported after initiation of highly active antiretroviral therapy without the use of IVIG.

No controlled studies have been published regarding dosing of IVIG for B19-induced RBC aplasia. Doses reported with good results in a limited number of cases include 200 mg/kg/day for 5-10 days and 1 g/kg/day for 3 days. IVIG should not be used for treatment of B19-induced arthropathy.

B19-infected fetuses with anemia and hydrops have been managed successfully with intrauterine RBC transfusions, but this procedure has significant attendant risks. Once fetal hydrops is diagnosed, regardless of the suspected cause, the mother should be referred to a fetal therapy center for further evaluation because of the high risk for serious complications (see Chapter 103.2).

Human Bocavirus

There is no specific antiviral therapy available. Appropriate supportive treatment for viral LRTI and pneumonia is recommended, as directed by clinical severity. For children with wheezing illness specifically caused by HBoV1 infection, there are no data examining their response to bronchodilator therapy.

COMPLICATIONS

Parvovirus B19

Erythema infectiosum is often accompanied by arthralgias or arthritis in adolescents and adults that may persist after resolution of the rash. B19 may rarely cause thrombocytopenic purpura. Neurologic conditions, including aseptic meningitis, encephalitis, and peripheral neuropathy, have been reported in both immunocompromised and healthy individuals in association with B19 infection. The incidence of stroke may be increased in children with sickle cell disease following B19-induced transient aplastic crisis. B19 is also a cause of infection-associated hemophagocytic syndrome, usually in immunocompromised persons.

Human Bocavirus

There are no studies reporting on complications of HBoV1 infection. Complications of wheezing and viral pneumonia would be possible, including hypoxemia and secondary bacterial infection, among others.

PREVENTION

Parvovirus B19

Children with erythema infectiosum are not likely to be infectious at presentation because the rash and arthropathy represent immune-mediated, postinfectious phenomena. Isolation and exclusion from school or child care are unnecessary and ineffective after diagnosis.

Children with B19-induced RBC aplasia, including the transient aplastic crisis, are infectious upon presentation and demonstrate a more intense viremia. Most of these children require transfusions and supportive care until their hematologic status stabilizes. They should be isolated in the hospital to prevent spread to susceptible patients and staff. Isolation should continue for at least 1 wk and until after resolution of fever. Pregnant caregivers should not be assigned to these patients. Exclusion of pregnant women from workplaces where children with erythema infectiosum may be present (e.g., primary and secondary schools) is not recommended as a general policy because it is unlikely to reduce their risk. There are no data to support the use of IVIG for postexposure prophylaxis in pregnant caregivers or immunocompromised children. No vaccine is currently available, though this is a topic of ongoing research.

Human Bocavirus

There are no studies that have addressed the prevention of transmission of this infection. In the hospital setting, standard precautions should be observed to limit spread of the virus. Since HBoV1 causes respiratory infection and can be detected in respiratory secretions sometimes in very high titer, measures to limit contact with respiratory secretions should be considered, including contact and droplet isolation for severely symptomatic young children. No vaccine is available, and no other preventive measures have been reported.

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Chapter 252

Herpes Simplex Virus

Lawrence R. Stanberry

The 2 closely related herpes simplex viruses (HSVs), HSV type 1 (HSV-1) and HSV type 2 (HSV-2), cause a variety of illnesses, depending on the anatomic site where the infection is initiated, the immune state of the host, and whether the symptoms reflect primary or recurrent infection. Common infections involve the skin, eye, oral cavity, and genital tract. Infections tend to be mild and self-limiting, except in the immunocompromised patient and newborn infant, in whom they may be severe and life-threatening.

Primary infection occurs in individuals who have not been infected previously with either HSV-1 or HSV-2. Because these individuals are HSV seronegative and have no preexisting immunity to HSV, primary infections can be severe. **Nonprimary 1st infection** occurs in individuals previously infected with 1 type of HSV (e.g., HSV-1) who have become infected for the 1st time with the other type of HSV (in this case, HSV-2). Because immunity to 1 HSV type provides some cross-protection against disease caused by the other HSV type, nonprimary 1st infections tend to be less severe than true primary infections.

During primary and nonprimary initial infections, HSV establishes latent infection in regional sensory ganglion neurons. Virus is maintained in this latent state for the life of the host but periodically can reactivate and cause **recurrent infection.** Symptomatic recurrent infections tend to be less severe and of shorter duration than 1st infections. Asymptomatic recurrent infections are extremely common. They cause no physical distress, although patients with recurrent infections are contagious and can transmit the virus to susceptible individuals. Reinfection with a new strain of either HSV-1 or HSV-2 at a previously infected anatomic site (e.g., the genital tract) can occur but is relatively uncommon, suggesting that host immunity, perhaps site-specific local immunity, resulting from the initial infection affords protection against exogenous reinfection. This observation suggests that it might be feasible to develop effective HSV vaccines.

ETIOLOGY

HSVs contain a double-stranded DNA genome of approximately 152 kb that encodes at least 84 proteins. The DNA is contained within an icosadeltahedral capsid, which is surrounded by an outer envelope composed of a lipid bilayer containing at least 12 viral glycoproteins. These glycoproteins are the major targets for humoral immunity, whereas other nonstructural proteins are important targets for cellular immunity. Two encoded proteins, viral DNA polymerase and thymidine kinase, are targets for antiviral drugs. HSV-1 and HSV-2 have a similar genetic composition with extensive DNA and protein homology. One important difference in the 2 viruses is their glycoprotein G genes, which have been exploited to develop a new generation of commercially available, accurate, type-specific serologic tests that can be used to discriminate whether a patient has been infected with HSV-1 or HSV-2, or both.

EPIDEMIOLOGY

HSV infections are ubiquitous, and there are no seasonal variations in risk for infection. The only natural host is humans, and the mode of transmission is direct contact between mucocutaneous surfaces. There are no documented incidental transmissions from inanimate objects such as toilet seats.

All infected individuals harbor latent infection and experience recurrent infections, which may be symptomatic or may go unrecognized, and thus are periodically contagious. This information helps explain the widespread prevalence of HSV.

HSV-1 and HSV-2 are equally capable of causing initial infection at any anatomic site but differ in their capacity to cause recurrent infections. HSV-1 has a greater propensity to cause recurrent oral infections, whereas HSV-2 has a greater proclivity to cause recurrent genital infections. For this reason, HSV-1 infection typically results from contact with contaminated oral secretions, whereas HSV-2 infection most commonly results from anogenital contact.

HSV seroprevalence rates are highest in developing countries and among lower socioeconomic groups, although high rates of HSV-1 and HSV-2 infections are found in developed nations and among persons of the highest socioeconomic strata. Incident HSV-1 infections are more common during childhood and adolescence but are also found throughout later life. Data from the U.S. population–based National Health and Nutrition Examination Survey conducted between 1999 and 2004 showed a consistent increase of HSV-1 prevalence with age, which rose from 39% in adolescents 14-19 yr of age to 65% among those 40-49 yr of age. HSV-1 seroprevalence was not influenced by gender but rates were highest in Mexican-Americans (80.8%), intermediate in non-Hispanic blacks (68.3%), and lowest in non-Hispanic whites (50.1%). The National Health and Nutrition Examination Survey study conducted between 2005 and 2008 found an overall HSV-2 prevalence of 16.2% with a steady increase with age from 1.4% in the 14-19 yr old age group to 26.1% in the 40-49 yr old group. The rate was higher among females than males (20.9% and 11.5%, respectively) and varied by race and ethnic group, with an overall seroprevalence of 39.2% in blacks, 10.1% in Mexican-Americans, and 12.3% in whites. Modifiable factors that predict HSV-2 seropositivity include less education, poverty, cocaine use, and a greater lifetime number of sexual partners. Studies show that only approximately 10-20% of HSV-2–seropositive subjects report a history of genital herpes, emphasizing the asymptomatic nature of most HSV infections.

A 3 yr longitudinal study of Midwestern adolescent girls 12-15 yr of age found that 44% were seropositive for HSV-1 and 7% for HSV-2 at enrollment. At the end of the study, 49% were seropositive for HSV-1 and 14% for HSV-2. The attack rates, based on the number of cases per 100 person-years, were 3.2 for HSV-1 infection among all girls and 4.4 for HSV-2 infection among girls who reported being sexually experienced. Findings of this study indicate that sexually active young women have a high attack rate for genital herpes and suggest that genital herpes should be considered in the differential diagnosis of any young woman who reports recurrent genitourinary complaints. In this study, participants with preexisting HSV-1 antibodies had a significantly lower attack rate for HSV-2 infection, and those who became infected were less likely to have symptomatic disease than girls who were HSV seronegative when they entered the study. Prior HSV-1 infection appears to afford adolescent girls some protection against becoming infected with HSV-2; in adolescent girls infected with HSV-2, the preexisting HSV-1 immunity appears to protect against development of symptomatic genital herpes.

Neonatal herpes is an uncommon but potentially fatal infection of the fetus or more likely the newborn. It is not a reportable disease in most states, and therefore there are no solid epidemiologic data regarding its frequency in the general population. In King County, Washington, the estimated incidence of neonatal herpes was 2.6 cases per 100,000 live births in the late 1960s, 11.9 cases per 1000,000 live births from 1978-1981, and 31 cases per 1,000,000 live births from 1982-1999. This increase in neonatal herpes cases parallels the increase in cases of genital herpes. The estimated rate of neonatal herpes is 1 per 3,000-5,000 live births, which is higher than reported for the reportable perinatally acquired sexually transmitted infections such as congenital syphilis and gonococcal ophthalmia neonatorum. More than 90% of the cases are the result of maternal-fetal transmission. The risk for transmission is greatest during a primary or nonprimary 1st infection (30-50%) and much lower when the exposure is during a recurrent infection (<2%). HSV viral suppression therapy in mothers does not consistently eliminate the possibility of neonatal infection. Infants born to mothers dually infected with HIV and HSV-2 are also at higher risk for acquiring HIV than infants born to HIV-positive mothers who are not HSV-2 infected. It is estimated that approximately 25% of pregnant women are HSV-2 infected and that approximately 2% of pregnant women acquire HSV-2 infection during pregnancy.

HSV is a leading cause of sporadic, fatal encephalitis in children and adults. In the United States it is estimated that there are 1,250 cases annually of HSV encephalitis.

PATHOGENESIS

In the immunocompetent host the pathogenesis of HSV infection involves viral replication in skin and mucous membranes followed by replication and spread in neural tissue. Viral infection typically begins at a cutaneous **portal of entry** such as the oral cavity, genital mucosa, ocular conjunctiva, or breaks in keratinized epithelia. Virus replicates locally, resulting in the death of the cell, and sometimes produces clinically apparent inflammatory responses that facilitate the development of characteristic herpetic vesicles and ulcers. Virus also enters nerve endings and spreads beyond the portal of entry to sensory ganglia by intraneuronal transport. Virus replicates in some sensory neurons, and the progeny virions are sent via intraneuronal transport mechanisms back to the periphery, where they are released from nerve endings and replicate further in skin or mucosal surfaces. It is virus moving through this neural arc that is primarily responsible for the development of characteristic herpetic lesions, although most HSV infections do not reach a threshold necessary to cause clinically recognizable disease. Although many sensory neurons become productively infected during the initial infection, some infected neurons do not initially support viral replication. It is in these neurons that the virus establishes a **latent infection,** a condition in which the viral genome persists within the neuronal nucleus in a largely metabolically inactive state. Intermittently throughout the life of the host, undefined changes can occur in latently infected neurons that trigger the virus to begin to replicate.

This replication occurs despite the host's having established a variety of humoral and cellular immune responses that successfully controlled the initial infection. With reactivation of the latent neuron, progeny virions are produced and transported within nerve fibers back to cutaneous sites somewhere in the vicinity of the initial infection, where further replication occurs and causes recurrent infections. Recurrent infections may be symptomatic (with typical or atypical herpetic lesions) or asymptomatic. In either case, virus is shed at the site where cutaneous replication occurs and can be transmitted to susceptible individuals who come in contact with the site or with contaminated secretions. Latency and reactivation are the mechanisms by which the virus is successfully maintained in the human population.

Viremia, or hematogenous spread of the virus, does not appear to play an important role in HSV infections in the immunocompetent host but can occur in neonates, individuals with eczema, and severely malnourished children. It is also seen in patients with depressed or defective cell-mediated immunity, such as occurs with HIV infection or some immunosuppressive therapies. Viremia can result in dissemination of the virus to visceral organs, including the liver and adrenals. Hematogenous dissemination of virus to the central nervous system appears to only occur in neonates.

The pathogenesis of HSV infection in newborns is complicated by their relative immunologic immaturity. The source of virus in neonatal infections is typically but not exclusively the mother. Transmission generally occurs during delivery, although it is well documented to occur even with cesarean delivery with intact fetal membranes. The most common portals of entry are the conjunctiva, mucosal epithelium of the nose and mouth, and breaks or abrasions in the skin that occur with scalp electrode use or forceps delivery. With prompt antiviral therapy, virus replication may be restricted to the site of inoculation (the skin, eye, or mouth). However, virus may also extend from the nose to the respiratory tract to cause pneumonia, move via intraneuronal transport to the central nervous system to cause encephalitis, or spread by hematogenous dissemination to visceral organs and the brain. Factors that may influence neonatal HSV infection include the virus type, portal of entry, inoculum of virus to which the infant is exposed, gestational age of the infant, and presence of maternally derived antibodies specific to the virus causing infection. Latent infection is established during neonatal infection, and survivors may experience recurrent cutaneous and neural infections. Persistent central nervous system infection may impact the neurodevelopment of the infant.

CLINICAL MANIFESTATIONS

The hallmarks of common HSV infections are skin vesicles and shallow ulcers. Classic infections manifest as small, 2-4 mm vesicles that may be surrounded by an erythematous base. These may persist for a few days before evolving into shallow, minimally erythematous ulcers. The vesicular phase tends to persist longer when keratinized epithelia is involved and is generally brief and sometimes just fleeting when moist mucous membranes are the site of infection. Because HSV infections are common and their natural history is influenced by many factors, including portal of entry, immune status of the host, and whether it is an initial or recurrent infection, the typical manifestations are seldom classic. Most infections are asymptomatic or unrecognized, and nonclassic presentations, such as small skin fissures and small erythematous nonvesicular lesions, are common.

Acute Oropharyngeal Infections

Herpes gingivostomatitis most often affects children 6 mo to 5 yr of age but is seen across the age spectrum. It is an extremely painful condition with sudden onset, pain in the mouth, drooling, refusal to eat or drink, and fever of up to 40.0-40.6°C (104-105.1°F). The gums become markedly swollen, and vesicles may develop throughout the oral cavity, including the gums, lips, tongue, palate, tonsils, pharynx, and perioral skin (Fig. 252-1). The vesicles may be more extensively distributed than typically seen with enteroviral herpangina. During the initial phase of the illness there may be tonsillar exudates suggestive of bacterial pharyngitis. The vesicles are generally present only a few days before progressing to form shallow indurated ulcers that may be covered with a yellow-gray membrane. Tender submandibular, submaxillary, and cervical lymphadenopathy is common. The breath may be foul as a result of overgrowth of anaerobic oral bacteria. Untreated, the illness resolves in 7-14 days, although the lymphadenopathy may persist for several weeks.

Figure 252-1 Clustered perioral vesicles and erosions in an infant with primary herpetic gingivostomatitis. *(From Schachner LA, Hansen RC, editors:* Pediatric dermatology, *ed 3. Philadelphia, 1988, Mosby, p. 1078.)*

In older children, adolescents, and college students, the initial HSV oral infection may manifest as pharyngitis and tonsillitis rather than gingivostomatitis. The vesicular phase is often over by the time the patient presents to a healthcare provider, and signs and symptoms may be indistinguishable from those of streptococcal pharyngitis, consisting of fever, malaise, headache, sore throat, and white plaques on the tonsils. The course of illness is typically longer than for untreated streptococcal pharyngitis.

Herpes Labialis

Fever blisters (cold sores) are the most common manifestation of recurrent HSV-1 infections. The most common site of herpes labialis is the vermilion border of the lip, although lesions sometimes occur on the nose, chin, cheek, or oral mucosa. Older patients report experiencing burning, tingling, itching, or pain 3-6 hr (rarely as long as 24-48 hr) before the development of the herpes lesion. The lesion generally begins as a small grouping of erythematous papules that over a few hours progress to create a small, thin-walled vesicle. The vesicles may form shallow ulcers or become pustular. The short-lived ulcer dries and develops a crusted scab. Complete healing without scarring occurs with reepithelialization of the ulcerated skin, usually within 6-10 days. Some patients experience local lymphadenopathy but no constitutional symptoms.

Cutaneous Infections

In the healthy child or adolescent, cutaneous HSV infections are generally the result of skin trauma with macro or micro abrasions and

Figure 252-2 Herpes simplex infection of finger (whitlow). *(From Schachner LA, Hansen RC, editors:* Pediatric dermatology, *ed 3. Philadelphia, 1988, Mosby, p. 1079.)*

exposure to infectious secretions. This situation most often occurs in play or contact sports such as wrestling (**herpes gladiatorum**) and rugby (**scrum pox**). As with other HSV infections, an initial cutaneous infection establishes a latent infection that can subsequently result in recurrent infections at or near the site of the initial infection. Pain, burning, itching, or tingling often precedes the herpetic eruption by a few hours to a few days. Like herpes labialis, lesions begin as grouped, erythematous papules that progress to vesicles, pustules, ulcers, and crusts and then heal without scarring in 6-10 days. Although herpes labialis typically results in a single lesion, a cutaneous HSV infection results in multiple discrete lesions and involves a larger surface area. Regional lymphadenopathy may occur but systemic symptoms are uncommon. Recurrences are sometimes associated with local edema and lymphangitis or local neuralgia.

Herpes whitlow is a term generally applied to HSV infection of fingers or toes, although strictly speaking it refers to HSV infection of the paronychia. Among children, this condition is most commonly seen in infants and toddlers who suck the thumb or fingers and who are experiencing either a symptomatic or a subclinical oral HSV-1 infection (Fig. 252-2). An HSV-2 herpes whitlow occasionally develops in an adolescent as a result of exposure to infectious genital secretions. The onset of the infection is heralded by itching, pain, and erythema 2-7 days after exposure. The cuticle becomes erythematous and tender and may appear to contain pus, although if it is incised, little fluid is present. Incising the lesion is discouraged, as this maneuver typically prolongs recovery and increases the risk for secondary bacterial infection. Lesions and associated pain typically persist for about 10 days, followed by rapid improvement and complete recovery in 18-20 days. Regional lymphadenopathy is common, and lymphangitis and neuralgia may occur. Unlike other recurrent herpes infections, recurrent herpetic whitlows are often as painful as the primary infection but are generally shorter in duration.

Cutaneous HSV infections can be severe or life-threatening in patients with disorders of the skin such as eczema (eczema herpeticum), pemphigus, burns, and Darier disease, and following laser skin resurfacing. The lesions are frequently ulcerative and nonspecific in appearance, although typical vesicles may be seen in adjacent normal skin (Fig. 252-3). If untreated, these lesions can progress to disseminated infection and death. Recurrent infections are common but generally less severe than the initial infection.

Figure 252-3 Widespread cutaneous herpes infection in a child with underlying eczema (eczema herpeticum).

Genital Herpes

Genital HSV infection is common in sexually experienced adolescents and young adults, but up to 90% of infected individuals are unaware they are infected. Infection may result from genital-genital transmission (usually HSV-2) or oral-genital transmission (usually HSV-1). Symptomatic and asymptomatic individuals periodically shed virus from anogenital sites and hence can transmit the infection to sexual partners or, in the case of pregnant women, to their newborns. Classic primary genital herpes may be preceded by a short period of local burning and tenderness before vesicles develop on genital mucosal surfaces or keratinized skin and sometimes around the anus or on the buttocks and thighs. Vesicles on mucosal surfaces are short lived and rupture to produce shallow, tender ulcers covered with a yellowish gray exudate and surrounded by an erythematous border. Vesicles on keratinized epithelium persist for a few days before progressing to the pustular stage and then crusting.

Patients may experience urethritis and dysuria severe enough to cause urinary retention and bilateral, tender inguinal and pelvic lymphadenopathy. Women may experience a watery vaginal discharge, and men may have a clear mucoid urethral discharge. Significant local pain and systemic symptoms such as fever, headache, and myalgia are common. Aseptic meningitis develops in an estimated 15% of cases. The course of classic primary genital herpes from onset to complete healing is 2-3 wk.

Most patients with symptomatic primary genital herpes experience at least 1 recurrent infection in the following year. Recurrent genital herpes is usually less severe and of shorter duration than the primary infection. Some patients experience a sensory prodrome with pain, burning, and tingling at the site where vesicles subsequently develop. Asymptomatic recurrent anogenital HSV infections are common, and all HSV-2–seropositive individuals appear to periodically shed virus from anogenital sites. Most sexual transmissions and maternal-neonatal transmissions of virus result from asymptomatic shedding episodes.

Genital infections caused by HSV-1 and HSV-2 are indistinguishable, but HSV-1 causes significantly fewer subsequent episodes of recurrent infection; hence, knowing which virus is causing the infection has important prognostic value. Genital HSV infection increases the risk for acquiring HIV infection.

Rarely, genital HSV infections are identified in young children and preadolescents. Although genital disease in children should raise concerns about possible sexual abuse, there are documented cases of autoinoculation, in which a child has inadvertently transmitted virus from contaminated oral secretions to his or her own genitalia.

Ocular Infections

HSV ocular infections may involve the conjunctiva, cornea, or retina and may be primary or recurrent. Conjunctivitis or keratoconjunctivitis is usually unilateral and is often associated with blepharitis and tender preauricular lymphadenopathy. The conjunctiva appears edematous but there is rarely purulent discharge. Vesicular lesions may be seen on the lid margins and periorbital skin. Patients typically have fever. Untreated infection generally resolves in 2-3 wk. Obvious corneal involvement is rare, but when it occurs it can produce ulcers that are described as appearing dendritic or geographic. Extension to the stroma is uncommon although more likely to occur in patients inadvertently treated with corticosteroids. When it occurs, it may be associated with corneal edema, scarring, and corneal perforation. Recurrent infections tend to involve the underlying stroma and can cause progressive corneal scarring and injury that can lead to blindness.

Retinal infections are rare and are more likely among infants with neonatal herpes and immunocompromised persons with disseminated HSV infections.

Central Nervous System Infections

HSV encephalitis is the leading cause of sporadic, nonepidemic encephalitis in children and adults in the United States. It is an acute necrotizing infection generally involving the frontal and/or temporal cortex and the limbic system and, beyond the neonatal period, is almost always caused by HSV-1. The infection may manifest as nonspecific findings, including fever, headache, nuchal rigidity, nausea, vomiting, generalized seizures, and alteration of consciousness. Injury to the frontal or temporal cortex or limbic system may produce findings more indicative of HSV encephalitis, including anosmia, memory loss, peculiar behavior, expressive aphasia and other changes in speech, hallucinations, and focal seizures. The untreated infection progresses to coma and death in 75% of cases. Examination of the cerebrospinal fluid (CSF) typically shows a moderate number of mononuclear cells and polymorphonuclear leukocytes, a mildly elevated protein concentration, a normal or slightly decreased glucose concentration, and often a moderate number of erythrocytes.

HSV is also a cause of aseptic meningitis and is the most common cause of recurrent aseptic meningitis (**Mollaret meningitis**).

Infections in Immunocompromised Persons

Severe, life-threatening HSV infections can occur in patients with compromised immune functions, including neonates, the severely malnourished, those with primary or secondary immunodeficiency diseases, including AIDS, and those receiving some immunosuppressive regimens, particularly for cancer and organ transplantation. Mucocutaneous infections, including mucositis and esophagitis, are most common, although their presentations may be atypical and can result in lesions that slowly enlarge, ulcerate, become necrotic, and extend to deeper tissues. Other HSV infections include tracheobronchitis, pneumonitis, and anogenital infections. Disseminated infection can result in a sepsis-like presentation, with liver and adrenal involvement, disseminated intravascular coagulopathy, and shock.

Perinatal Infections

HSV infection may be acquired in utero, during the birth process, or during the neonatal period. Intrauterine and postpartum infections are well described but occur infrequently. Postpartum transmission may be from the mother or another adult with a nongenital (typically HSV-1) infection such as herpes labialis. Most cases of neonatal herpes result from maternal infection and transmission, usually during passage through an infected birth canal of a mother with asymptomatic genital herpes. Transmission is well documented in infants delivered by cesarean section. Fewer than 30% of mothers of an infant with neonatal herpes have a history of genital herpes. The risk for infection is higher in infants born to mothers with primary genital infection (>30%) than with recurrent genital infection (<2%). Use of scalp electrodes may also increase risk. There also have been rare cases of neonatal herpes associated with Jewish ritual circumcisions, but only with ritual oral contact with the circumcision site.

Neonatal HSV infection is thought to never be asymptomatic. Its clinical presentation reflects timing of infection, portal of entry, and extent of spread. Infants with intrauterine infection typically have skin vesicles or scarring, eye findings including chorioretinitis and keratoconjunctivitis, and microcephaly or hydranencephaly that are present at delivery. Few infants survive without therapy, and those who do generally have severe sequelae. Infants infected during delivery or the postpartum period present with 1 of the following 3 patterns of disease: (1) disease localized to the skin, eyes, or mouth; (2) encephalitis with or without skin, eye, and mouth disease; and (3) disseminated infection involving multiple organs, including the brain, lungs, liver, heart, adrenals, and skin.

Infants with **skin, eye, and mouth disease** generally present at 5-11 days of life and typically demonstrate a few small vesicles, particularly on the presenting part or at sites of trauma such as sites of scalp electrode placement. If untreated, skin, eye, and mouth disease in infants may progress to encephalitis or disseminated disease.

Infants with encephalitis typically present at 8-17 days of life with clinical findings suggestive of bacterial meningitis, including irritability, lethargy, poor feeding, poor tone, and seizures. Fever is relatively uncommon, and skin vesicles occur in only approximately 60% of cases (Fig. 252-4). If untreated, 50% of infants with HSV encephalitis die and most survivors have severe neurologic sequelae.

Infants with disseminated HSV infections generally become ill at 5-11 days of life. Their clinical picture is similar to that of infants with bacterial sepsis, consisting of hyperthermia or hypothermia, irritability, poor feeding, and vomiting. They may also exhibit respiratory distress, cyanosis, apneic spells, jaundice, purpuric rash, and evidence of central nervous system infection; seizures are common. Skin vesicles

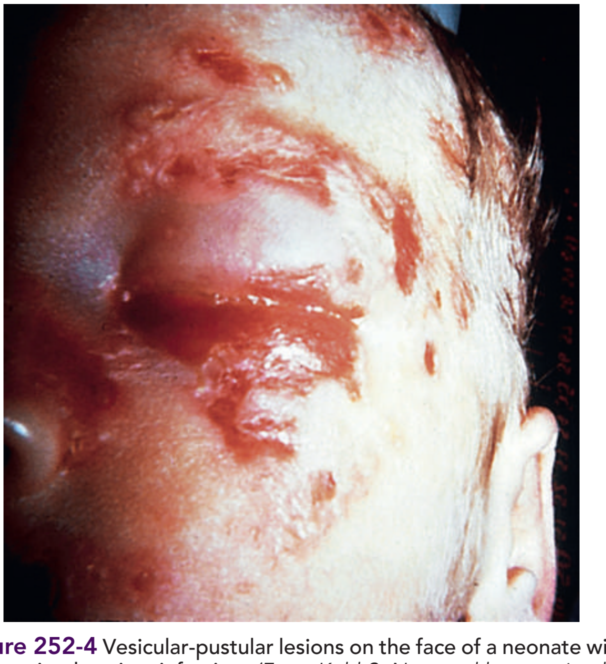

Figure 252-4 Vesicular-pustular lesions on the face of a neonate with herpes simplex virus infection. *(From Kohl S: Neonatal herpes simplex virus infection,* Clin Perinatol *24:129–150, 1997.)*

are seen in approximately 75% of cases. If untreated, the infection causes shock and disseminated intravascular coagulation; approximately 90% of these infants die, and most survivors have severe neurologic sequelae.

Infants with neonatal herpes whose mothers received antiherpes antiviral drugs in the weeks prior to delivery may present later than their untreated counterparts; whether the natural history of the infection in these infants is different is an unanswered question.

DIAGNOSIS

The clinical diagnosis of HSV infections, particularly life-threatening infections and genital herpes, should be confirmed by laboratory test, preferably isolation of virus or viral DNA detection by polymerase chain reaction (PCR). Histologic findings or imaging studies may support the diagnosis but should not substitute for virus-specific tests. HSV immunoglobulin M tests are notoriously unreliable, and the demonstration of a 4-fold or greater rise in HSV-specific immunoglobulin G titers between acute and convalescent serum samples is useful only in retrospect.

Virus culture remains the gold standard for diagnosing HSV infections. The highest yield comes from rupturing a suspected herpetic vesicle and vigorously rubbing the base of the lesion to collect fluid and cells. Culturing dried, crusted lesions is generally of low yield. Although not as sensitive as viral culture, direct detection of HSV antigens in clinical specimens can be done rapidly and has very good specificity. The use of PCR for detection of HSV DNA is highly sensitive and specific and in some instances can be performed rapidly. It is the test of choice in examining CSF in cases of suspected HSV encephalitis.

Evaluation of the neonate with suspected HSV infection should include cultures of suspicious lesions as well as eye and mouth swabs and PCR of CSF and blood. In neonates testing for elevation of liver enzymes may provide indirect evidence of HSV dissemination to visceral organs. Culture or antigen detection should be used in evaluating lesions associated with suspected acute genital herpes. HSV-2 type-specific antibody tests are useful for evaluating sexually experienced adolescents or young adults who have a history of unexplained recurrent nonspecific urogenital signs and symptoms, but these tests are less useful for general screening in populations in which HSV-2 infections are of low prevalence.

Because most HSV diagnostic tests take at least a few days to complete, treatment should not be withheld but rather initiated promptly so as to ensure the maximum therapeutic benefit.

LABORATORY FINDINGS

Most self-limited HSV infections cause few changes in routine laboratory parameters. Mucocutaneous infections may cause a moderate polymorphonuclear leukocytosis. In HSV meningoencephalitis there can be an increase in mononuclear cells and protein in CSF, the glucose content may be normal or reduced, and red blood cells may be present. The electroencephalogram and MRI of the brain may show temporal lobe abnormalities in HSV encephalitis beyond the neonatal period. Encephalitis in the neonatal period tends to be more global and not limited to the temporal lobe (Fig. 252-5). Disseminated infection may cause elevated liver enzymes, thrombocytopenia, and abnormal coagulation.

TREATMENT

See Chapter 245 for more information about principles of antiviral therapy.

Three antiviral drugs are available in the United States for the management of HSV infections, namely acyclovir, valacyclovir, and

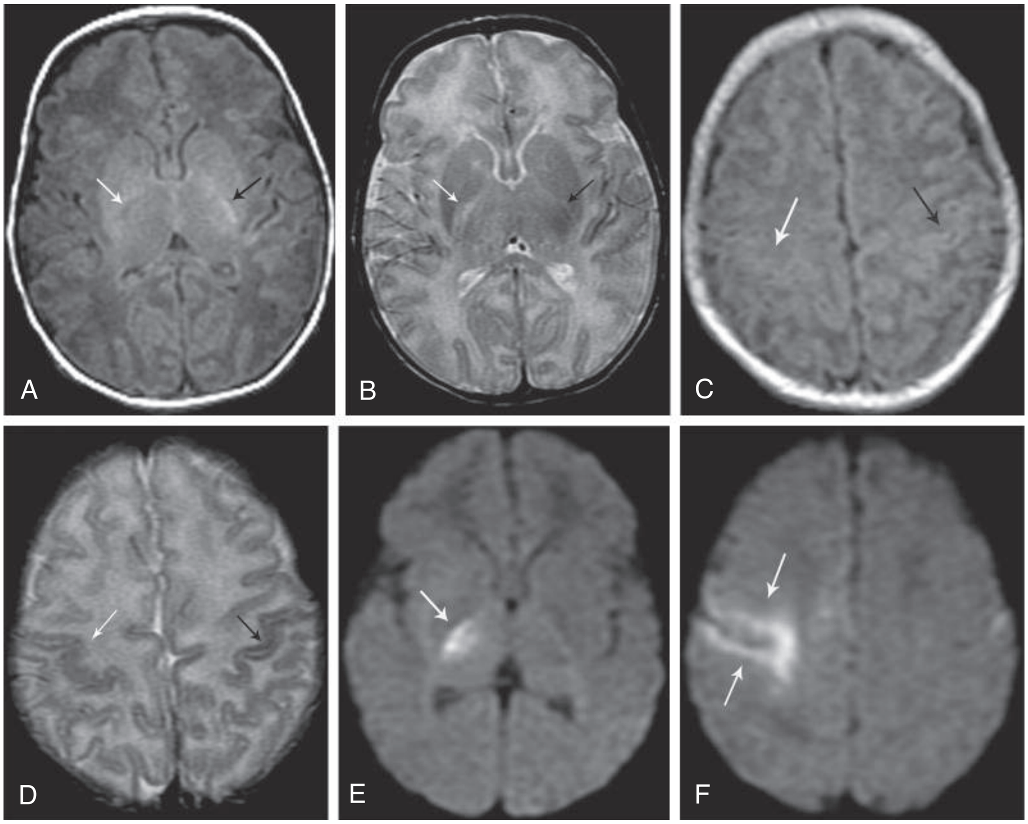

Figure 252-5 Involvement of corticospinal tract and thalamus in a 2 wk old infant. **A,** MRI with axial T1-weighted image demonstrating subtle loss of T1 hyperintensity corresponding to myelination in the posterior limb of the right internal capsule *(white arrow)*. T1 hyperintensity in the left posterior limb of the internal capsule is maintained *(black arrow)*. **B,** T2-weighted image showing findings similar to those seen on T1-weighted imaging. **C,** Axial T1- and **(D)** T2-weighted images through the vertex demonstrating subtle indistinct margins of the cortex around the right central sulcus *(white arrow)* compared with the normal appearance on the left side *(black arrow)*. **E** and **F,** Diffusion-weighted images with more extensive diffusion restriction in the posterior limb of the right internal capsule and lateral thalamus *(arrows)*, and in the right pre- and postcentral gyrus *(arrows)*. *(From Bajaj M, Mody S, Natarajan G: Clinical and neuroimaging findings in neonatal herpes simplex virus infection.* J Pediatr *165:404–407, 2014, Fig. 1.)*

famciclovir. All 3 are available in oral form, but only acyclovir is available in a suspension form. Acyclovir has the poorest bioavailability and hence requires more frequent dosing. Valacyclovir, a prodrug of acyclovir, and famciclovir, a prodrug of penciclovir, both have very good oral bioavailability and are dosed once or twice daily. Acyclovir and penciclovir are also available in a topical form but these provide limited or no benefit to patients with recurrent mucocutaneous HSV infections. Only acyclovir has an intravenous formulation. Early initiation of therapy results in the maximal therapeutic benefit. All 3 drugs have exceptional safety profiles and are safe to use in pediatric patients. Doses should be modified in patients with renal impairment.

Resistance to acyclovir and penciclovir is rare in immunocompetent persons but does occur in immunocompromised persons. Virus isolates from immunocompromised persons whose HSV infection is not responding or is worsening with acyclovir therapy should be tested for drug sensitivities. Foscarnet and cidofovir have been used in the treatment of HSV infections caused by acyclovir-resistant mutants.

Topical trifluorothymidine, vidarabine, and idoxuridine are used in the treatment of herpes keratitis.

Patients with genital herpes also require counseling to address psychosocial issues, including possible stigma, and to help them understand the natural history and management of this chronic infection.

Acute Mucocutaneous Infections

For gingivostomatitis, oral acyclovir (15 mg/kg/dose 5 times a day PO for 7 days; maximum: 1 g/day) started within 72 hr of onset reduces the severity and duration of the illness. Pain associated with swallowing may limit oral intake of infants and children, putting them at risk for dehydration. Intake should be encouraged through the use of cold beverages, ice cream, and yogurt.

For **herpes labialis,** oral treatment is superior to topical antiviral therapy. For treatment of a recurrence in adolescents, oral valacyclovir (2,000 mg bid PO for 1 day), acyclovir (200-400 mg 5 times daily PO for 5 days), or famciclovir (1,500 mg once daily PO for 1 day) shortens the duration of the episode. Long-term daily use of oral acyclovir (400 mg bid PO) or valacyclovir (500 mg once daily PO) has been used to prevent recurrences in individuals with frequent or severe recurrences.

Anecdotal reports suggest that treatment of adolescents with **herpes gladiatorum** with oral acyclovir (200 mg 5 times daily PO for 7-10 days) or valacyclovir (500 mg bid PO for 7-10 days) at the first signs of the outbreak can shorten the course of the recurrence. For patients with a history of recurrent herpes gladiatorum, chronic daily prophylaxis with valacyclovir (500-1,000 mg daily) has been reported to prevent recurrences.

There are no clinical trials assessing the benefit of antiviral treatment for **herpetic whitlow.** High-dose oral acyclovir (1,600-2,000 mg/day divided in 2-3 doses PO for 10 days) started at the first signs of illness has been reported to abort some reoccurrences and reduce the duration of others in adults.

A clinical trial in adults has established the effectiveness of oral acyclovir (200 mg 5 times a day PO for 5 days) in the treatment of **eczema herpeticum;** however, serious infections should be treated with intravenous acyclovir. Oral-facial HSV infections can reactivate after cosmetic facial laser resurfacing, causing extensive disease and scarring. Treatment of adults beginning the day before the procedure with either valacyclovir (500 mg twice daily PO for 10-14 days) or famciclovir (250-500 mg bid PO for 10 days) has been reported to be effective in preventing the infections. HSV infections in **burn patients** can be severe or life-threatening and have been treated with intravenous acyclovir (10-20 mg/kg/day divided every 8 hr IV).

Antiviral drugs are not effective in the treatment of HSV-associated **erythema multiforme,** but their daily use as for herpes labialis prophylaxis prevents reoccurrences of erythema multiforme.

Genital Herpes

Pediatric patients, usually adolescents or young adults, with suspected 1st-episode genital herpes should be treated with antiviral therapy. Treatment of the initial infection reduces the severity and duration of the illness but has no effect on the frequency of subsequent recurrent infections. Treatment options for adolescents include acyclovir (400 mg tid PO for 7-10 days), famciclovir (250 mg tid PO for 7-10 days), or valacyclovir (1,000 mg bid PO for 7-10 days). The twice-daily valacyclovir option avoids treatment during school hours. For smaller children, acyclovir suspension can be used at a dose of 10-20 mg/kg/dose 4 times daily not to exceed the adult dose. The 1st episode of genital herpes can be extremely painful, and use of analgesics is generally indicated. All patients with genital herpes should be offered counseling to help them deal with psychosocial issues and understand the chronic nature of the illness.

There are 3 strategic options regarding the management of recurrent infections. The choice should be guided by several factors, including the frequency and severity of the recurrent infections, the psychologic impact of the illness on the patient, and concerns regarding transmission to a susceptible sexual partner. Option 1 is no therapy; option 2 is episodic therapy; and option 3 is long-term suppressive therapy. For **episodic therapy,** treatment should be initiated at the first signs of an outbreak. Recommended choices for episodic therapy in adolescents include famciclovir (1,000 mg bid PO for 1 day), acyclovir (800 mg tid PO for 2 days), or valacyclovir (500 mg bid PO for 3 days or 1,000 mg once daily for 5 days). Long-term suppressive therapy offers the advantage that it prevents most outbreaks, improves patient quality of life in terms of the psychosocial impact of genital herpes, and, with daily valacyclovir therapy, also reduces (but does not eliminate) the risk for sexual transmission to a susceptible sexual partner. Options for **long-term suppressive therapy** are acyclovir (400 mg bid PO), famciclovir (250 mg bid PO), and valacyclovir (500 or 1,000 mg qd PO).

Ocular Infections

HSV ocular infections can result in blindness. Management should involve consultation with an ophthalmologist.

Central Nervous System Infections

Patients older than neonates who have herpes encephalitis should be promptly treated with intravenous acyclovir (10 mg/kg every 8 hr given as a 1 hr infusion for 14-21 days). Treatment for increased intracranial pressure, management of seizures, and respiratory compromise may be required.

Infections in Immunocompromised Persons

Severe mucocutaneous and disseminated HSV infections in immunocompromised patients should be treated with intravenous acyclovir (5-10 mg/kg or 250 mg/m^2 every 8 hr) until there is evidence of resolution of the infection. Oral antiviral therapy with acyclovir, famciclovir, or valacyclovir has been used for treatment of less-severe HSV infections and for suppression of recurrences during periods of significant immunosuppression. Drug resistance does occur occasionally in immunocompromised patients, and in individuals whose HSV infection does not respond to antiviral drug therapy, viral isolates should be tested to determine sensitivity. Acyclovir-resistant viruses are often also resistant to famciclovir but may be sensitive to foscarnet or cidofovir.

Perinatal Infections

All infants with proven or suspected neonatal HSV infection should be treated immediately with high-dose intravenous acyclovir (60 mg/kg/day divided every 8 hr IV). Treatment may be discontinued in infants shown by laboratory testing not to be infected. Infants with HSV disease limited to skin, eyes, and mouth should be treated for 14 days, whereas those with disseminated or central nervous system disease should receive 21 days of therapy. Patients receiving high-dose therapy should be monitored for neutropenia.

Suppressive oral acyclovir therapy for 6 mo after completion of the intravenous therapy has been shown to improve the neurodevelopment of infants with central nervous system infection and to prevent cutaneous recurrences in infants regardless of disease pattern. Infants should receive 300 mg/m^2 per dose 3 times daily for 6 mo. The absolute

neutrophil count should be measured at weeks 2 and 4 after initiation treatment and then monthly.

PROGNOSIS

Most HSV infections are self-limiting, last from a few days (for recurrent infections) to 2-3 wk (for primary infections), and heal without scarring. Recurrent oral-facial herpes in a patient who has undergone dermabrasion or laser resurfacing can be severe and lead to scarring. Because genital herpes is a sexually transmitted infection, it can be stigmatizing, and its psychologic consequences may be much greater than its physiologic effects. Some HSV infections can be severe and may have grave consequences without prompt antiviral therapy. Life-threatening conditions include neonatal herpes, herpes encephalitis, and HSV infections in immunocompromised patients, burn patients, and severely malnourished infants and children. Recurrent ocular herpes can lead to corneal scarring and blindness.

PREVENTION

Transmission of infection occurs through exposure to virus either as the result of skin-to-skin contact or from contact with contaminated secretions. Good handwashing and, when appropriate, the use of gloves provide healthcare workers with excellent protection against HSV infection in the workplace. Healthcare workers with active oral-facial herpes or herpes whitlow should take precautions, particularly when caring for high-risk patients such as newborns, immunocompromised individuals, and patients with chronic skin conditions. Patients and parents should be advised about good hygienic practices, including handwashing and avoiding contact with lesions and secretions, during active herpes outbreaks. Schools and daycare centers should clean shared toys and athletic equipment such as wrestling mats at least daily after use. Athletes with active herpes infections who participate in contact sports such as wrestling and rugby should be excluded from practice or games until the lesions are completely healed. Genital herpes can be prevented by avoiding genital-genital and oral-genital contact. The risk for acquiring genital herpes can be reduced but not eliminated through the correct and consistent use of condoms. Male circumcision is associated with a reduced risk of acquiring genital HSV infection. The risk for transmitting genital HSV-2 infection to a susceptible sexual partner can be reduced but not eliminated by the daily use of oral valacyclovir by the infected partner.

For **pregnant women** with **active genital herpes** at the time of delivery, the risk for mother-to-baby transmission can be reduced but not eliminated by delivering the baby via a cesarean section (within 4-6 hr of rupture of membranes). The risk for recurrent genital herpes, and therefore the need for cesarean delivery, can be reduced but not eliminated in pregnant women with a history of genital herpes by the daily use of oral acyclovir, valacyclovir, or famciclovir during the last 4 wk of gestation, which is recommended by the American College of Obstetrics and Gynecology. There are documented cases of neonatal herpes occurring in infants delivered by cesarean section, as well as in infants born to mothers who have been appropriately treated with antiherpes antiviral drugs for the last month of gestation. Hence a history of cesarean delivery or antiviral treatment at term does not rule out consideration of neonatal herpes.

Infants delivered vaginally to women with 1st-episode genital herpes are at very high risk for acquiring HSV infection. The nasopharynx, mouth, conjunctivae, rectum, and umbilicus should be cultured (some add PCR surface testing) at delivery and on day 1-2 of life. Some also recommend HSV-PCR on blood. Some authorities recommend that these infants receive anticipatory acyclovir therapy for at least 2 wk, and others treat such infants if signs develop or if the 48 hr cultures have positive results. Infants delivered to women with a history of recurrent genital herpes are at low risk for development of neonatal herpes. In this setting, parents should be educated about the signs and symptoms of neonatal HSV infection and should be instructed to seek care without delay at the first suggestion of infection. When the situation is in doubt, infants should be evaluated and tested with surface culture (and PCR) for neonatal herpes as well as with PCR on blood *and* CSF; intravenous acyclovir is begun until culture results are negative or until another explanation can be found for the signs and symptoms.

Recurrent genital HSV infections can be prevented by the daily use of oral acyclovir, valacyclovir, or famciclovir, and these drugs have been used to prevent recurrences of oral-facial (labialis) and cutaneous (gladiatorum) herpes. Oral and intravenous acyclovir has also been used to prevent recurrent HSV infections in immunocompromised patients. Use of sun blockers is reported to be effective in preventing recurrent oral-facial herpes in patients with a history of sun-induced recurrent disease.

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Chapter 253

Varicella-Zoster Virus

Philip S. LaRussa and Mona Marin

Varicella-zoster virus (VZV) causes primary, latent, and recurrent infections. The primary infection is manifested as varicella **(chickenpox)** and results in establishment of a lifelong latent infection of sensory ganglion neurons. Reactivation of the latent infection causes herpes zoster **(shingles).** Although often a mild illness of childhood, varicella can cause substantial morbidity and mortality in otherwise healthy children. Morbidity and mortality are higher in immunocompetent infants, adolescents, and adults as well as in immunocompromised persons. Varicella predisposes to severe group A *Streptococcus* and *Staphylococcus aureus* infections. A clinically modified disease can occur among vaccinated persons (breakthrough varicella), usually with milder presentation. Varicella and herpes zoster can be treated with antiviral drugs. Primary clinical disease can be prevented by immunization with live-attenuated VZV vaccine (varicella vaccine). Herpes zoster vaccine (zoster vaccine), which contains the same VZV strain used in the varicella vaccine but with a higher potency, is available for persons 50 yr of age and older to boost their immunity to VZV and prevent herpes zoster and its major complication, painful postherpetic neuralgia.

ETIOLOGY

VZV is a neurotropic human herpesvirus with similarities to herpes simplex virus. These enveloped viruses contain double-stranded DNA genomes that encode more than 70 proteins, including proteins that are targets of cellular and humoral immunity.

EPIDEMIOLOGY

Before the introduction of varicella vaccine in 1996, varicella was an almost universal communicable infection of childhood in the United States. Most children were infected by 15 yr of age, with fewer than 5% of adults remaining susceptible. This pattern of infection at younger ages remains characteristic in all countries in temperate climates. In contrast, in tropical areas, children acquire varicella at older ages and a higher proportion of young adults remain susceptible leading to a higher proportion of cases occurring among adults. In the United States, prior to introduction of varicella vaccination, annual varicella epidemics occurred in winter and spring, and there were about 4 million cases of varicella, 11,000-15,000 hospitalizations, and 100-150 deaths every year. Varicella is a more serious disease in young infants, adults, and immunocompromised persons, in whom there are higher rates of complications and deaths than in healthy children. Within households, transmission of VZV to susceptible individuals occurs at a rate of 65-86%; more casual contact, such as occurs in a

school classroom, is associated with lower attack rates among susceptible children. Persons with varicella are contagious 24-48 hr before the rash is evident and until vesicles are crusted, usually 3-7 days after onset of rash. Susceptible persons may also acquire varicella after close, direct contact with adults or children who have herpes zoster.

Since implementation of the varicella vaccination program in 1996, there have been substantial declines in varicella morbidity and mortality in the United States. By 2006, prior to implementation of the 2 dose program, 1 dose vaccination coverage had reached 90% and varicella incidence had declined 90-91% since 1995 in sites where active surveillance was being conducted; varicella-related hospitalizations had declined 84% from prevaccine years. Varicella-related deaths decreased by 88% from 1990-1994 to 2005-2007; in persons younger than 20 yr of age there was a 97% decline in deaths. Declines in morbidity and mortality were seen in all age groups, including infants younger than 12 mo of age who were not eligible for vaccination, indicating protection from exposure by indirect vaccination effects. Although the age-specific incidence has declined in all age groups, the median age at infection has increased, and cases occur predominantly in children in upper elementary school rather than in the preschool years. This change in varicella epidemiology highlights the importance of offering vaccine to every susceptible child, adolescent, and adult. The continued occurrence of breakthrough infections and of outbreaks in settings with high 1-dose varicella vaccine coverage, together with the evidence that 1 dose is only approximately 85% effective against all varicella, prompted adoption in 2006 of a routine 2 dose childhood varicella vaccination program with catch-up vaccination of all individuals without evidence of immunity. Between 2006 and 2010, varicella incidence declined further by approximately 70% and fewer outbreaks were reported.

Herpes zoster is caused by the reactivation of latent VZV. It is not common in childhood and shows no seasonal variation in incidence. Zoster is not caused by exposure to a patient with varicella; in fact, exposures to varicella boost the cell-mediated immune response to VZV in individuals with prior infection, decreasing the likelihood of reactivation of latent virus. The lifetime risk for herpes zoster for individuals with a history of varicella is 20-30%, with 75% of cases occurring after 45 yr of age. Herpes zoster is very rare in healthy children younger than 10 yr of age, with the exception of those infected with VZV in utero or in the 1st yr of life, who have an increased risk for development of zoster in the 1st few yr of life. Herpes zoster in children tends to be milder than herpes zoster in adults, is less frequently associated with acute pain, and postherpetic neuralgia generally does not occur in healthy children. In children receiving immunosuppressive therapy for malignancy or other diseases and in those who have HIV infection, herpes zoster occurs more frequently, occasionally multiple times, and may be severe. The attenuated VZV in the varicella vaccine can establish latent infection and reactivate as herpes zoster. However, the evidence to date indicates that the risk for development of subsequent herpes zoster is lower after vaccination than after natural VZV infection among both healthy and immunocompromised children. Vaccinated children who do develop zoster may have disease resulting from vaccine or wild-type VZV.

PATHOGENESIS

VZV is transmitted by contact with oropharyngeal secretions and the fluid of skin lesions of infected individuals, either by airborne spread or through direct contact. Primary infection (varicella) results from inoculation of the virus onto the mucosa of the upper respiratory tract and tonsillar lymphoid tissue. During the early part of the 10-21 day incubation period, virus replicates in the local lymphoid tissue, and then a brief subclinical viremia spreads the virus to the reticuloendothelial system. Widespread cutaneous lesions occur during a 2nd viremic phase that lasts 3-7 days. Peripheral blood mononuclear cells carry infectious virus, generating new crops of vesicles during this period of viremia. VZV is also transported back to the mucosa of the upper respiratory tract and oropharynx during the late incubation period, permitting spread to susceptible contacts 1-2 days before the appearance of rash. Host immune responses limit viral replication and facilitate recovery from infection. In the immunocompromised child, the failure of immune responses, especially cell-mediated immune responses, results in continued viral replication that may lead to prolonged and/or disseminated infection with resultant complications in the lungs, liver, brain, and other organs. Virus is transported in a retrograde manner through sensory axons to the dorsal root ganglia throughout the spinal cord, where the virus establishes latent infection in the neurons and satellite cells associated with these axons. Virus may also reach the ganglia by the hematogenous route. Subsequent **reactivation** of latent virus causes **herpes zoster,** a vesicular rash that usually is dermatomal in distribution. During herpes zoster, necrotic changes may be produced in the neurons and surrounding satellite cells in associated ganglia. The skin lesions of varicella and herpes zoster have identical histopathology, and infectious VZV is present in both. Varicella elicits humoral and cell-mediated immunity that is highly protective against symptomatic reinfection. Suppression of cell-mediated immunity to VZV correlates with an increased risk for VZV reactivation as herpes zoster.

CLINICAL MANIFESTATIONS

Varicella is an acute febrile rash illness that was common in children in the United States before the universal childhood vaccination program. It has variable severity but is usually self-limited. It may be associated with severe complications, including staphylococcal and streptococcal superinfection, pneumonia, encephalitis, bleeding disorders, congenital infection, and life-threatening perinatal infection. Herpes zoster, not common in children, causes localized cutaneous symptoms, but may disseminate in immunocompromised patients.

Varicella in Unvaccinated Individuals

The illness usually begins 14-16 days after exposure, although the incubation period can range from 10-21 days. Subclinical varicella is rare; almost all exposed, susceptible persons experience a rash, albeit so mild in some cases that it may go unnoticed. Prodromal symptoms may be present, particularly in older children and adults. Fever, malaise, anorexia, headache, and occasionally mild abdominal pain may occur 24-48 hr before the rash appears. Temperature elevation is usually 37.8-38.9°C (100-102°F) but may be as high as 41.1°C (106°F); fever and other systemic symptoms usually resolve within 2-4 days after the onset of the rash.

Varicella lesions often appear first on the scalp, face, or trunk. The initial exanthem consists of intensely pruritic erythematous macules that evolve through the papular stage to form clear, fluid-filled vesicles. Clouding and umbilication of the lesions begin in 24-48 hr. While the initial lesions are crusting, new crops form on the trunk and then the extremities; the simultaneous presence of lesions in various stages of evolution is characteristic of varicella (Fig. 253-1). The distribution of the rash is predominantly central or centripetal with the greatest concentration on the trunk and proximally on the extremities. Ulcerative lesions involving the mucosa of the oropharynx and vagina are also common; many children have vesicular lesions on the eyelids and conjunctivae, but corneal involvement and serious ocular disease are rare. The average number of varicella lesions is about 300, but healthy children may have fewer than 10 to more than 1,500 lesions. In cases resulting from secondary household spread and in older children, more lesions usually occur, and new crops of lesions may continue to develop for more than 7 days. The exanthem may be much more extensive in children with skin disorders, such as eczema or recent sunburn. Hypopigmentation or hyperpigmentation of lesion sites persists for days to weeks in some children, but severe scarring is unusual unless the lesions were secondarily infected.

The **differential diagnosis** of varicella includes vesicular rashes caused by other infectious agents, such as herpes simplex virus, enterovirus, monkey pox, rickettsial pox, and *S. aureus;* drug reactions; disseminated herpes zoster; contact dermatitis; and insect bites (especially for breakthrough varicella). Severe varicella was the most common illness confused with smallpox before the eradication of smallpox.

Varicelliform Rashes in Vaccinated Individuals

Varicelliform rashes that occur after vaccination could be a result of wild-type VZV, vaccine strain VZV, or other etiologies (e.g., insect bites, coxsackievirus). During days 0-42 after vaccination, the

Figure 253-1 **A,** Varicella lesions in unvaccinated persons display the characteristic "cropping" distribution, or manifest themselves in clusters; the simultaneous presence of lesions in various stages of evolution is characteristic. **B,** Breakthrough varicella lesions are predominantly maculopapular, and vesicles are less common; the illness is most commonly mild with <50 lesions. *(**A** courtesy of the Centers for Disease Control and Prevention [CDC]; **B** courtesy of the CDC and Dr. John Noble, Jr.)*

likelihood of rash from wild-type or vaccine strain VZV varies depending on the stage of a country's vaccination program. In the early stages of a vaccine program, rash within 1-2 wk is still most commonly caused by wild-type VZV, reflecting exposure to varicella before vaccination could provide protection. Rash occurring 14-42 days after vaccination is a result of either wild-type or vaccine strains, reflecting exposure and infection before protection from vaccination or an adverse event of vaccination (vaccine-associated rash), respectively. As wild-type varicella continues to decline as a consequence of the vaccination program, VZV circulation will also decline and rashes in the interval 0-42 days after vaccination will be less commonly caused by wild-type VZV.

Breakthrough varicella is disease that occurs in a person vaccinated more than 42 days before rash onset and is caused by **wild-type** virus**.** One dose of varicella vaccine is >97% effective in preventing moderate and severe varicella and is 85% (median; range: 44-100%) effective in preventing all disease after exposure to wild-type VZV. This means that after close exposure to VZV, as may occur in a household or an outbreak setting in a school or daycare center, about 1 of every 5 children who received one dose of vaccine may experience breakthrough varicella. Exposure to VZV may also result in asymptomatic infection in the previously immunized child. The rash in breakthrough disease is frequently atypical and predominantly maculopapular, vesicles are seen less commonly. The illness is most commonly mild with <50 lesions, shorter duration of rash, fewer complications, and little or no fever. However, approximately 25-30% of breakthrough cases in vaccinees who received one dose are not mild, with clinical features more similar to those of wild-type infection. Breakthrough cases are overall **less contagious** than wild-type infections within household settings, but contagiousness varies proportionally with the number of lesions; typical breakthrough cases (<50 lesions) is about one third as contagious as disease in unvaccinated cases, whereas breakthrough cases with ≥50 lesions are as contagious as wild-type cases. Consequently, children with breakthrough disease should be considered potentially infectious and excluded from school until lesions have crusted or, if there are no vesicles present, until no new lesions are occurring. Transmission has been documented to occur from breakthrough cases in household, childcare, and school settings.

Fewer studies have evaluated the performance of the 2 dose varicella vaccine regimen. One clinical trial estimated the 2 dose vaccine effectiveness for preventing all disease at 98%; the estimate is 95% (median; range: 88-98%) in conditions of everyday clinical practice. Breakthrough cases have been reported among 2 dose vaccinees, although recipients of 2 doses of varicella vaccine are less likely to have breakthrough disease than those who received 1 dose. Additionally, data suggest that disease may be further attenuated among 2 dose vaccine recipients.

Neonatal Varicella

Mortality is particularly high in neonates born to susceptible mothers who contracted varicella around the time of delivery. Infants whose mothers demonstrate varicella in the period from 5 days prior to delivery to 2 days afterward are at high risk for severe varicella. These infants acquire the infection transplacentally as a result of maternal viremia, which may occur up to 48 hr prior to onset of maternal rash. The infant's rash usually occurs toward the end of the 1st wk to the early part of the 2nd wk of life (although it may be as soon as 2 days). Because the mother has not yet developed a significant antibody response, the infant receives a large dose of virus without the moderating effect of maternal anti-VZV antibody. If the mother demonstrates varicella more than 5 days prior to delivery, she still may pass virus to the soon-to-be-born child, but infection is attenuated because of transmission of maternal VZV-specific antibody across the placenta. This moderating effect of maternal antibody is present if delivery occurs after about 30 wk of gestation, when maternal immunoglobulin (Ig) G is able to cross the placenta in significant amounts. The recommendations for use of human varicella-zoster immunoglobulin (VZIG) differ based on when the infant is exposed to varicella. Newborns whose mothers develop varicella during the period of 5 days before to 2 days after delivery should receive VZIG as soon as possible. Although neonatal varicella may occur in about half of these infants despite administration of VZIG, it is usually milder than in the absence of VZIG administration. All premature infants born <28 wk of gestation to a mother with active varicella at delivery (even if the maternal rash has been present for >1 wk) should receive VZIG. If VZIG is not available, intravenous immunoglobulin (IVIG) may provide some protection, although varicella-specific antibody titers may vary from lot to lot. Because perinatally acquired varicella may be life threatening, the infant should be treated with acyclovir (10 mg/kg every 8 hr IV) when lesions develop. Some experts might initiate treatment with oral acyclovir in infants who received VZIG. Neonatal varicella can also follow a postpartum exposure of an infant delivered to a mother who was susceptible to VZV, although the frequency of complications declines rapidly in the weeks after birth. Recommendations for VZIG administration for these infants are presented in the postexposure prophylaxis section. Neonates with community-acquired varicella who experience severe varicella, especially those who have a complication such as pneumonia, hepatitis, or encephalitis, should also receive treatment with intravenous acyclovir (10 mg/kg every 8 hr). Infants with neonatal varicella who receive prompt antiviral therapy have an excellent prognosis.

Congenital Varicella Syndrome

In utero transmission of VZV can occur; however, because most adults in temperate climates are immune, pregnancy complicated by varicella is unusual in these settings. When pregnant women do contract

varicella early in pregnancy, experts estimate that as many as 25% of the fetuses may become infected. Fortunately, clinically apparent disease in the infant is uncommon: The congenital varicella syndrome occurs in approximately 0.4% of infants born to women who have varicella during pregnancy before 13 wk of gestation and in approximately 2% of infants born to women with varicella between 13 and 20 wk of gestation. Rarely, cases of congenital varicella syndrome have been reported in infants of women infected after 20 wk of pregnancy, the latest occurring at 28 wk of gestation. Before availability of varicella vaccine in the United States, 44 cases of congenital varicella syndrome were estimated to occur each year. The congenital varicella syndrome is characterized by cicatricial skin scarring in a zoster-like distribution; limb hypoplasia; and abnormalities of the neurologic system (e.g., microcephaly, cortical atrophy, seizures, and mental retardation), eye (e.g., chorioretinitis, microphthalmia, and cataracts), renal system (e.g., hydroureter and hydronephrosis), and autonomic nervous system (neurogenic bladder, swallowing dysfunction, and aspiration pneumonia). Low birthweight is common among infants with congenital varicella syndrome. Most of the stigmata can be attributed to virus-induced injury to the nervous system, although there is no obvious explanation why certain regions of the body are preferentially infected during fetal VZV infection. The characteristic cutaneous lesion has been called a cicatrix, a zigzag scarring, in a **dermatomal** distribution, often associated with atrophy of the affected limb (Fig. 253-2). Many infants with severe manifestations of congenital varicella syndrome (atrophy and scarring of a limb) have significant neurologic deficiencies. Alternatively, there may be neither skin nor limb abnormalities but the infant may show cataracts or even extensive aplasia of the entire brain.

There are rare case reports of fetal abnormalities following the development of herpes zoster in the mother; whether or not these cases truly represent the congenital varicella syndrome is unclear. If it does occur, the congenital syndrome acquired as a result of maternal herpes zoster is exceedingly rare. Maternal herpes zoster was associated with typical congenital varicella syndrome in 1 case, but the mother had disseminated herpes zoster (at 12 wk of gestation).

The diagnosis of VZV fetopathy is based mainly on the history of gestational varicella combined with the presence of characteristic abnormalities in the newborn infant. Virus cannot be cultured from the affected newborn, but viral DNA may be detected in tissue samples by polymerase chain reaction (PCR). VZV-specific IgM antibody is detectable in the cord blood sample in some infants, although the IgM titer drops quickly in the postpartum period and can be nonspecifically positive. Chorionic villus sampling and fetal blood collection for the detection of viral DNA, virus, or antibody have been used in an attempt to diagnose fetal infection and embryopathy. The usefulness of these tests for patient management and counseling has not been defined. Because these tests may not distinguish between infection and disease, their utility may primarily be that of reassurance when the result is negative. A persistently positive VZV IgG antibody titer at 12-18 mo of age is a reliable indicator of prenatal infection in the asymptomatic child, as is the development of zoster in the 1st yr of life without evidence of postnatal infection.

Figure 253-2 Newborn with congenital varicella syndrome. The infant had severe malformations of both lower extremities and cicatricial scarring over his left abdomen.

VZIG has often been administered to the susceptible mother exposed to varicella to modify maternal disease severity; it is uncertain whether this step modifies infection in the fetus, although some evidence suggests that it may be beneficial for the fetus too. Similarly, acyclovir treatment may be given to the mother with severe varicella. A prospective registry of acyclovir use in the 1st trimester demonstrated that the occurrence of birth defects approximates that found in the general population. Acyclovir is a class B drug for pregnancy and should be considered when the benefit to the mother outweighs the potential risk to the fetus. The efficacy of acyclovir treatment of the pregnant woman in preventing or modifying the severity of congenital varicella is not known, but its use should be considered to protect the mother from severe disease. Because the damage caused by fetal VZV infection does not progress in the postpartum period, antiviral treatment of infants with congenital VZV syndrome is not indicated.

COMPLICATIONS

The complications of VZV infection occur with varicella or with reactivation of infection, more commonly in immunocompromised patients. In the otherwise healthy child, mild varicella hepatitis is relatively common but rarely clinically symptomatic. Mild thrombocytopenia occurs in 1-2% of children with varicella and may be associated with transient petechiae. Purpura, hemorrhagic vesicles, hematuria, and gastrointestinal bleeding are rare complications that may have serious consequences. Other complications of varicella, some of them rare, include acute cerebellar ataxia, encephalitis, pneumonia, nephritis, nephrotic syndrome, hemolytic-uremic syndrome, arthritis, myocarditis, pericarditis, pancreatitis, orchitis, and acute retinal necrosis. A reduction in the number and rates of varicella-related complications is seen with the use of the vaccine. Reports of serious varicella-related complications in vaccinated persons (breakthrough) have been rare (meningitis, 1 case of acute transverse myelitis, 1 fatal case of VZV encephalitis in an apparently immunocompetent child, and 4 fatal cases of breakthrough disease, 3 of which involved high-dose steroids or an underlying immunocompromising condition).

Declines in varicella-related hospitalizations and deaths in the United States since implementation of the varicella vaccination program provide supporting evidence that varicella vaccine reduces severe complications from varicella. Approximately 100 deaths (with varicella listed as the underlying cause of death) occurred in the United States annually before the introduction of the varicella vaccine; during 2005-2007 the annual average number of varicella deaths was 15. In both the pre- and postvaccine era, the majority of deaths (>80%) have been among persons without high-risk preexisting conditions.

Bacterial Infections

Secondary bacterial infections of the skin, usually caused by group A *Streptococcus* and *S. aureus,* may occur in up to 5% of children with varicella. These range from impetigo to cellulitis, lymphadenitis, and subcutaneous abscesses. An early manifestation of secondary bacterial infection is erythema of the base of a new vesicle. Recrudescence of fever 3-4 days after the initial exanthem may also herald a secondary bacterial infection. Varicella is a well-described risk factor for serious invasive infections caused by group A *Streptococcus*, which can have a fatal outcome. The more invasive infections, such as varicella gangrenosa, bacterial sepsis, pneumonia, arthritis, osteomyelitis, cellulitis, and necrotizing fasciitis, account for much of the morbidity and

mortality of varicella in otherwise healthy children. Bacterial toxin–mediated diseases (e.g., toxic shock syndrome) also may complicate varicella. A substantial decline in varicella-related invasive bacterial infections is associated with the use of the varicella vaccine.

Encephalitis and Cerebellar Ataxia

Encephalitis (1 per 50,000 cases of varicella in unvaccinated children) and acute cerebellar ataxia (1 per 4,000 cases of varicella in unvaccinated children) are well-described neurologic complications of varicella; morbidity from central nervous system complications is highest among patients younger than 5 yr and older than 20 yr. Nuchal rigidity, altered consciousness, and seizures characterize meningoencephalitis. Patients with cerebellar ataxia have a gradual onset of gait disturbance, nystagmus, and slurred speech. Neurologic symptoms usually begin 2-6 days after the onset of the rash but may occur during the incubation period or after resolution of the rash. Clinical recovery is typically rapid, occurring within 24-72 hr, and is usually complete. Although severe hemorrhagic encephalitis, analogous to that caused by herpes simplex virus, is very rare in children with varicella, the consequences are similar to those of herpes encephalitis. Reye syndrome (hepatic dysfunction with hypoglycemia and encephalopathy) associated with varicella and other viral illnesses such as influenza is rare now that salicylates are no longer used as antipyretics in these situations (see Chapter 361).

Pneumonia

Varicella pneumonia is a severe complication that accounts for most of the increased morbidity and mortality from varicella in adults and other high-risk populations, but pneumonia may also complicate varicella in young children. Respiratory symptoms, which may include cough, dyspnea, cyanosis, pleuritic chest pain, and hemoptysis, usually begin within 1-6 days after the onset of the rash. Smoking has been described as a risk factor for severe pneumonia complicating varicella. The frequency of varicella pneumonia may be greater in the parturient.

Progressive Varicella

Progressive varicella, with visceral organ involvement, coagulopathy, severe hemorrhage, and continued vesicular lesion development after 7 days, is a severe complication of primary VZV infection. Severe abdominal pain, which may reflect involvement of mesenteric lymph nodes or the liver, or the appearance of hemorrhagic vesicles in otherwise healthy adolescents and adults, immunocompromised children, pregnant women, and newborns, may herald severe, and potentially fatal, disease. Although rare in healthy children, the risk for progressive varicella is highest in children with congenital cellular immune deficiency disorders and those with malignancy, particularly if chemotherapy, and especially corticosteroids, had been given during the incubation period and the absolute lymphocyte count is <500 cells/µL. The mortality rate for children who acquired varicella while undergoing treatment for malignancy and who were not treated with antiviral therapy approached 7%; varicella-related deaths usually occurred within 3 days after the diagnosis of varicella **pneumonia.** Children who acquire varicella after organ transplantation are also at risk for progressive VZV infection. Children undergoing long-term, low-dose systemic or inhaled corticosteroid therapy are not considered to be at higher risk for severe varicella, but progressive varicella does occur in patients receiving high-dose corticosteroids. There are case reports in patients receiving inhaled corticosteroids as well as in asthmatic patients receiving multiple short courses of systemic corticosteroid therapy. Unusual clinical findings of varicella, including lesions that develop a hyperkeratotic appearance and continued new lesion formation for weeks or months, have been described in children with untreated, late-stage **HIV infection.** Immunization of HIV-infected children who have a $CD4^+$ T-lymphocyte percent ≥15%, as well as children with leukemia and solid organ tumors who are in remission and whose chemotherapy can be interrupted for 2 wk around the time of immunization or has been terminated, have reduced frequency of severe disease. Moreover, since the advent of the universal immunization program in the United States, many children who would become immunocompromised later in life because of disease or treatment are protected before the immunosuppression occurs; also, as a result of reductions in varicella incidence, immunocompromised children are less likely to be exposed to varicella.

Figure 253-3 Herpes zoster involving the lumbar dermatome. *(From Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases, *ed 6. Philadelphia, 2005, Elsevier, p. 1783.)*

Figure 253-4 Many groups of blisters occurring over the arm in a child with herpes zoster. *(From Weston WL, Lane AT, Morelli JG:* Color textbook of pediatric dermatology, *ed 3. Philadelphia, 2002, Mosby, Fig. 8-28.)*

Herpes Zoster

Herpes zoster manifests as vesicular lesions clustered within 1 or, less commonly, 2 adjacent dermatomes (Fig. 253-3). In the elderly, herpes zoster typically begins with burning pain followed by clusters of skin lesions in a dermatomal pattern. Almost half of the elderly with herpes zoster experience complications; the most frequent complication is postherpetic neuralgia, a painful condition that affects the nerves despite resolution of the skin lesions. Approximately 4% of patients suffer a 2nd episode of herpes zoster; 3 or more episodes are rare. Unlike herpes zoster in adults, zoster in children is infrequently associated with localized pain, hyperesthesia, pruritus, low-grade fever, or complications. In children, the rash is mild, with new lesions appearing for a few days (Fig. 253-4); symptoms of acute neuritis are minimal; and complete resolution usually occurs within 1-2 wk. Unlike in adults, postherpetic neuralgia is unusual in children. An increased risk for herpes zoster early in childhood has been described in children who acquire infection with VZV in utero or in the 1st yr of life.

Immunocompromised children may have more severe herpes zoster, similar to the situation in adults, including postherpetic neuralgia. Immunocompromised patients may also experience disseminated cutaneous disease that mimics varicella, with or without initial dermatomal rash, as well as visceral dissemination with pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy. Severely immunocompromised children, particularly those with advanced HIV infection, may have unusual, chronic, or relapsing cutaneous disease,

retinitis, or central nervous system disease without rash. The finding of a lower risk for herpes zoster among vaccinated children with leukemia than in those who have had varicella suggested that the vaccine virus reactivates less commonly than wild-type VZV. Studies to date indicate that the risk for herpes zoster in healthy children who have received one dose of vaccine is lower than in children who had wild-type varicella. Many more years of follow-up are needed to determine whether this lower risk is maintained among older persons who are at greatest risk for herpes zoster. The risk for herpes zoster in healthy children following 2 doses of varicella vaccine has not been evaluated.

DIAGNOSIS

Varicella and herpes zoster have been diagnosed primarily by their clinical appearance. Laboratory evaluation has not been considered necessary for diagnosis or management. However, as varicella disease has declined to low levels, laboratory confirmation has become increasingly useful. The atypical nature of breakthrough varicella, with a higher proportion of papular rather than vesicular rash, poses both clinical and laboratory diagnostic challenges.

Leukopenia is typical during the 1st 72 hr after onset of rash; it is followed by a relative and absolute lymphocytosis. Results of liver function tests are also usually (75%) mildly elevated. Patients with neurologic complications of varicella or uncomplicated herpes zoster have a mild lymphocytic pleocytosis and a slight to moderate increase in protein content of the cerebrospinal fluid; the cerebrospinal fluid glucose concentration is usually normal.

Rapid laboratory diagnosis of VZV is often important in high-risk patients and can be important for infection control, especially for breakthrough cases that have mild or atypical presentations. Confirmation of VZV infections can be accomplished by many referral hospital laboratories and all state health laboratories. VZV can be identified quickly by direct fluorescence assay of cells from cutaneous lesions (vesicular fluid) in 15-20 min, by PCR amplification testing (vesicular fluid, crusts) in hours to days, depending on availability, and by rapid culture with specific immunofluorescence staining (shell vial technique) in 48-72 hr. In the absence of vesicles or scabs, scrapings of maculopapular lesions can be collected for PCR or direct fluorescence assay testing. Infectious virus may be recovered by means of tissue culture methods; such methods require specific expertise, and virus may take days to weeks to grow. Of available tests, PCR is the most sensitive and allows for differentiation of wild-type and vaccine strains. Direct fluorescence assay is specific and less sensitive than PCR but when available allows for rapid diagnosis. Although multinucleated giant cells can be detected with nonspecific stains (Tzanck smear), they have poor sensitivity and do not differentiate VZV from herpes simplex virus infections. Strain identification (genotyping) can distinguish wild-type VZV from the vaccine strain in a vaccinated child; however, genotyping is available only at specialized reference laboratories. Laboratory tests of lesions cannot be used to distinguish between varicella and disseminated herpes zoster. VZV IgG antibodies can be detected by several methods, and a 4-fold or greater rise in IgG antibodies is confirmatory of acute infection (although this requires a 2-3 wk delay to collect a convalescent specimen); in vaccinated persons, commercially available tests are not sufficiently sensitive to always detect antibody following vaccination and a 4-fold rise in IgG antibody may not occur. VZV IgG antibody tests can also be valuable to determine the immune status of individuals whose clinical history of varicella is unknown or equivocal. Testing for VZV IgM antibodies is not useful for routine confirmation or ruling out of varicella because commercially available methods are unreliable and the kinetics of the IgM response have not been well defined. Reliable VZV-specific IgM assays are available in certain reference laboratories, including a capture-IgM assay available at the national VZV laboratory at the Centers for Disease Control and Prevention. Serologic tests are not useful for the initial diagnosis of herpes zoster, but a large rise in IgG titer in convalescent titer in the presence of an atypical zoster rash is confirmatory. As with any laboratory tests, a negative varicella test should be considered in the context of the clinical presentation. Clinicians should use clinical judgment to decide on the best course of therapy.

TREATMENT

Antiviral treatment modifies the course of both varicella and herpes zoster. Antiviral drug resistance is rare but has occurred, primarily in children with HIV infection and other immunocompromising conditions where frequent relapse of VZV infections has resulted in multiple courses of antiviral therapy. Foscarnet and cidofovir may be useful for the treatment of acyclovir-resistant VZV infections, but consultation of an infectious disease specialist is recommended.

Varicella

The only antiviral drug available in liquid formulation that is licensed for treatment of varicella for pediatric use is acyclovir. Given the safety profile of acyclovir and its demonstrated efficacy in the treatment of varicella, treatment of all children, adolescents, and adults with varicella is acceptable. However, acyclovir therapy is not recommended routinely by the American Academy of Pediatrics for treatment of uncomplicated varicella in the otherwise healthy child because of the marginal benefit, the cost of the drug, and the low risk for complications of varicella. Oral therapy with acyclovir (20 mg/kg/dose; maximum: 800 mg/dose) given as 4 doses/day for 5 days can be used to treat uncomplicated varicella in individuals at increased risk for moderate to severe varicella: nonpregnant individuals older than 12 yr of age and individuals older than 12 mo of age with chronic cutaneous or pulmonary disorders; individuals receiving short-term, intermittent, or aerosolized corticosteroid therapy; individuals receiving long-term salicylate therapy; and possibly secondary cases among household contacts. To be most effective, treatment should be initiated as early as possible, preferably within 24 hr of the onset of the exanthem. There is less clinical benefit if treatment is initiated more than 72 hr after onset of the exanthem. Acyclovir therapy does not interfere with the induction of VZV immunity. Acyclovir has been used to treat varicella in pregnant women; its safety for the fetus has not been established (see congenital varicella syndrome section). Some experts recommend the use of famciclovir or valacyclovir in older children who can swallow tablets. These drugs are highly active against VZV by the same mechanism as acyclovir and are better absorbed by the oral route than acyclovir. Valacyclovir (20 mg/kg/dose; maximum: 1,000 mg/dose, administered 3 times daily for 5 days) is licensed for treatment of varicella in children 2 to <18 yr of age, and both valacyclovir and famciclovir are approved for treatment of herpes zoster in adults.

Intravenous therapy is indicated for severe disease and for varicella in immunocompromised patients (even if begun more than 72 hr after onset of rash). Any patient who has signs of disseminated VZV, including pneumonia, severe hepatitis, thrombocytopenia, or encephalitis, should receive immediate treatment. IV acyclovir therapy (500 mg/m^2 every 8 hr) initiated within 72 hr of development of initial symptoms decreases the likelihood of progressive varicella and visceral dissemination in high-risk patients. Treatment is continued for 7-10 days or until no new lesions have appeared for 48 hr. Delaying antiviral treatment in high-risk individuals until it is obvious that prolonged new lesion formation is occurring is not advisable because visceral dissemination occurs during the same period.

Acyclovir-resistant VZV has been identified primarily in children infected with HIV. These children may be treated with intravenous foscarnet (120 mg/kg/day divided every 8 hr for up to 3 wk). The dose should be modified in the presence of renal insufficiency. Resistance to foscarnet has been reported with prolonged use. Cidofovir is also useful in this situation. Because of the increased toxicity profile of foscarnet and cidofovir, these 2 drugs should be initiated in collaboration with an infectious disease specialist.

Herpes Zoster

Antiviral drugs are effective for treatment of herpes zoster. In healthy adults, acyclovir (800 mg 5 times a day PO for 5-7 days), famciclovir (500 mg tid PO for 7 days), and valacyclovir (1,000 mg tid PO for 7 days) reduce the duration of the illness and the risk for development of postherpetic neuralgia. In otherwise healthy children, herpes zoster is a less-severe disease, and postherpetic neuralgia usually does not occur. Therefore, treatment of uncomplicated herpes zoster in the child

with an antiviral agent may not always be necessary, although some experts would treat with oral acyclovir (20 mg/kg/dose; maximum: 800 mg/dose) to shorten the duration of the illness. It is important to start antiviral therapy as soon as possible. Delay beyond 72 hr from onset of rash limits its effectiveness.

In contrast, herpes zoster in **immunocompromised** children can be severe, and disseminated disease may be life-threatening. Patients at high risk for disseminated disease should receive IV acyclovir (500 mg/m^2 or 10 mg/kg every 8 hr). Oral acyclovir, famciclovir, and valacyclovir are options for immunocompromised patients with uncomplicated herpes zoster, who are considered at low risk for visceral dissemination. Neuritis with herpes zoster should be managed with appropriate analgesics.

Use of corticosteroids in the treatment of herpes zoster in children is not recommended.

PROGNOSIS

Primary varicella has a mortality rate of 2-3 per 100,000 cases, with the lowest case fatality rates among children 1-9 yr of age (~1 death per 100,000 cases). Compared with these age groups, infants have a 4 times greater risk of dying and adults have a 25 times greater risk of dying. The most common complications among people who died from varicella were pneumonia, central nervous system complications, secondary infections, and hemorrhagic conditions. The mortality rate of untreated primary infection is 7-14% in immunocompromised children and may approach 50% in untreated adults with pneumonia.

Herpes zoster among healthy children has an excellent prognosis and is usually self-limited. Severe presentation with complications and sometimes fatalities can occur in immunocompromised children.

PREVENTION

VZV transmission is difficult to prevent, especially from persons with varicella, because a person with varicella is contagious for 24-48 hr before the rash is apparent. Herpes zoster is less infectious than varicella; nonetheless, transmission has been reported even in the absence of direct contact with the patient. Infection control practices, including caring for patients with varicella in isolation rooms with filtered air systems, are essential. All healthcare workers should have evidence of varicella immunity (Table 253-1). Unvaccinated healthcare workers without other evidence of immunity who have had a close exposure to VZV should be furloughed for days 8-21 after exposure because they are potentially infectious during this period.

Table 253-1	Evidence of Immunity to Varicella

Evidence of immunity to varicella consists of any of the following:

- Documentation of age-appropriate vaccination with a varicella vaccine:
  - Preschool-age children (i.e., age ≥12 mo): 1 dose
  - School-age children, adolescents, and adults: 2 doses*
- Laboratory evidence of immunity† or laboratory confirmation of disease
- Birth in the United States before 1980§
- Diagnosis or verification of a history of varicella disease by a healthcare provider¶
- Diagnosis or verification of a history of herpes zoster by a healthcare provider

*For children who received their 1st dose at younger than age 13 yr and for whom the interval between the 2 doses was 28 or more days, the 2nd dose is considered valid.

†Commercial assays can be used to assess disease-induced immunity, but they lack sensitivity to always detect vaccine-induced immunity (i.e., they might yield false-negative results).

§For healthcare personnel, pregnant women, and immunocompromised persons, birth before 1980 should not be considered evidence of immunity.

¶Verification of history or diagnosis of typical disease can be provided by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, or physician). For persons reporting a history of, or reporting with, atypical or mild cases, assessment by a physician or his/her designee is recommended, and 1 of the following should be sought: (1) an epidemiologic link to a typical varicella case or to a laboratory-confirmed case or (2) evidence of laboratory confirmation if it was performed at the time of acute disease. When such documentation is lacking, persons should not be considered as having a valid history of disease, because other diseases might mimic mild atypical varicella.

Vaccine

Varicella is a vaccine-preventable disease. Varicella vaccine contains live, attenuated VZV (Oka strain) and is indicated for subcutaneous administration. In the United States, varicella vaccine is recommended for routine administration as a 2 dose regimen to healthy children at ages 12-15 mo and 4-6 yr. Catch-up vaccination with the 2nd dose is recommended for children and adolescents who received only 1 dose. Vaccination with 2 doses is recommended for all persons without evidence of immunity. The minimum interval between the 2 doses is 3 mo for persons 12 yr of age or younger and 4 wk for older children, adolescents, and adults. Administration of varicella vaccine within 4 wk of measles-mumps-rubella (MMR) vaccination is associated with a higher risk for breakthrough disease; therefore, it is recommended that the varicella and MMR vaccines either be administered simultaneously at different sites or be given at least 4 wk apart. Varicella vaccine can be administered as a monovalent vaccine (for all healthy persons ≥12 mo of age) or as the quadrivalent measles-mumps- rubella-varicella (MMRV) vaccine (for children age 12 mo through 12 yr only).

Varicella vaccine is contraindicated for persons who have a history of anaphylactic reaction to any component of the vaccine; pregnant women; persons with cell-mediated immune deficiencies, including those with leukemia, lymphoma, and other malignant neoplasms affecting the bone marrow or lymphatic systems; persons receiving immunosuppressive therapy; and persons who have a family history of congenital or hereditary immunodeficiency in 1st-degree relatives unless the immune competence of the potential vaccine recipient is demonstrated. Children with isolated humoral immunodeficiencies may receive varicella vaccine. The monovalent varicella vaccine has been studied in clinical trial settings in children with acute lymphocytic leukemia and certain solid tumors who are in remission. Protocols are available that define the timing of vaccination in terms of the length of time a patient has been in remission while receiving maintenance chemotherapy; when to interrupt maintenance chemotherapy, including therapy with corticosteroids, before and after vaccination; and the minimal acceptable lymphocyte and platelet counts at the time of vaccination. Because of the risk of severe vaccine-related complications, use of the vaccine in these specific populations of children should only be considered in settings where these protocols can be followed, antiviral therapy with acyclovir is readily available, and physicians have expertise with use of the vaccine in these populations.

The vaccine should be considered for HIV-infected children with a $CD4^+$ T-lymphocyte percentage ≥15%. These children should receive 2 doses of vaccine, 3 mo apart. Specific guidelines for immunizing these children should be reviewed before vaccination. Data indicate that varicella vaccine is 100% effective in preventing herpes zoster among children infected with HIV. MMRV should not be administered as a substitute for the component vaccines in HIV-infected children.

Zoster vaccine is licensed for use as a single immunization for prevention of herpes zoster and to decrease the frequency of postherpetic neuralgia among individuals 50 yr of age and older. It is not indicated for the treatment of zoster or postherpetic neuralgia.

Vaccine-Associated Adverse Events

Varicella vaccine is safe and well tolerated. The incidence of injection site complaints observed ≤3 days after vaccination was slightly higher after dose 2 (25%) than after dose 1 (22%). A mild vaccine-associated varicelliform rash was reported in approximately 1-5% of healthy vaccinees, consisting of 6-10 papular-vesicular, erythematous lesions with peak occurrence 8-21 days after vaccination. Serious adverse reactions confirmed to be caused by the vaccine strain are rare and include pneumonia, hepatitis, meningitis, recurrent herpes zoster, severe rash, and 2 deaths. Transmission of vaccine virus to susceptible contacts is a very rare event (9 documented occurrences from healthy vaccine recipients, all in the presence of a rash in the vaccine recipient). MMRV vaccine is associated with a greater risk for febrile seizures 5-12 days after the 1st dose among children 12-23 mo of age compared with

simultaneous MMR and varicella vaccines (1 extra febrile seizure for every 2,500 children vaccinated).

Postexposure Prophylaxis

Vaccine given to healthy children within 3 or 5 days after exposure (as soon as possible is preferred) is effective in preventing or modifying varicella. Varicella vaccine is now recommended for postexposure use and for outbreak control. Oral acyclovir administered late in the incubation period may modify subsequent varicella in the healthy child; however, its use in this manner is not recommended until it can be further evaluated.

High-titer anti-VZV immune globulin as postexposure prophylaxis is recommended for immunocompromised children, pregnant women, and newborns exposed to varicella. Since 2012 the product licensed for use in the United States is VariZIG. VariZIG is distributed in the United States by FFF Enterprises, Temecula, California (1-800-843-7477) or ASD Healthcare, Frisco Texas (800-746-6273). The recommended dose is 1 vial (125 units) for each 10 kg increment of body weight (maximum: 625 units), except for infants weighing ≤2 kg who should receive 0.5 vial. VariZIG should be given intramuscularly as soon as possible but may be efficacious up to 10 days after exposure.

Newborns whose mothers demonstrate varicella 5 days before to 2 days after delivery should receive VariZIG (0.5 vial for those weighing ≤2 kg and 1 vial for those weighing >2 kg). VariZIG is also indicated for pregnant women and immunocompromised persons without evidence of varicella immunity; hospitalized premature infants born at <28 wks of gestation (or weight <1,000 g) who were exposed to varicella, regardless of maternal varicella immunity; and hospitalized premature infants born at ≥28 wk of gestation who were exposed to varicella and whose mothers have no evidence of varicella immunity. If possible, adults should be tested for VZV IgG antibodies before VariZIG administration, because many adults with no clinical history of varicella are immune. Anti-VZV antibody prophylaxis may ameliorate disease but does not eliminate the possibility of progressive disease and does not ensure that varicella is not transmitted to close susceptible contacts; patients should be monitored and treated with acyclovir if necessary once lesions develop.

Close contact between a susceptible high-risk patient and a patient with herpes zoster is also an indication for VariZIG prophylaxis. Passive antibody administration or treatment does not reduce the risk for herpes zoster or alter the clinical course of varicella or herpes zoster when given after the onset of symptoms.

Although licensed pooled IVIG preparations contain anti-VZV antibodies, the titer varies from lot to lot. In situations in which administration of VariZIG does not appear possible, IVIG can be administered (400 mg/kg administered once within 10 days of exposure). Immunocompromised patients who have received high-dose IVIG (>400 mg/kg) for other indications within 2-3 wk before VZV exposure can be expected to have serum antibodies to VZV.

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Chapter 254

Epstein-Barr Virus

Hal B. Jenson

Infectious mononucleosis is the best-known clinical syndrome caused by Epstein-Barr virus (EBV). It is characterized by systemic somatic complaints consisting primarily of fatigue, malaise, fever, sore throat, and generalized lymphadenopathy. Originally described as **glandular fever,** it derives its name from the mononuclear lymphocytosis with atypical-appearing lymphocytes that accompany the illness. Other infections may cause infectious mononucleosis-like illnesses.

ETIOLOGY

EBV is a double-stranded DNA virus that is a member of the γ-herpesviruses and causes >90% of cases of infectious mononucleosis. Two distinct types of EBV, **type 1 and type 2 (also called type A and type B),** have been characterized and have 70-85% sequence homology. EBV-1 is more prevalent worldwide, although EBV-2 is more common in Africa than in the United States and Europe. Both types lead to persistent, lifelong, latent infection. Dual infections with both types have been documented among immunocompromised persons. EBV-1 induces in vitro growth transformation of B cells more efficiently than does EBV-2, but no type-specific disease manifestations or clinical differences have been identified. Coacquisition of multiple EBV genotypes has been shown by heteroduplex tracking assays to occur commonly in otherwise healthy patients with infectious mononucleosis. However, only a single genotype tends to be cultured. It is unknown if this represents isolation of a predominant strain or if the strains that are not able to be cultured, using the transformation assay, are defective.

As many as 5-10% of **infectious mononucleosis–like illnesses** are caused by primary infection with cytomegalovirus, *Toxoplasma gondii*, adenovirus, hepatitis virus, primary HIV, and possibly rubella virus. In the majority of EBV-negative infectious mononucleosis-like illnesses, the exact cause remains unknown.

EPIDEMIOLOGY

EBV infects more than 95% of the world's population. It is transmitted primarily via oral secretions and may be transmitted via penetrative sexual intercourse. Among children, transmission may occur by exchange of saliva from child to child, such as occurs between children in out-of-home childcare. Nonintimate contact, environmental sources, or fomites do not contribute to spread of EBV.

EBV is shed in oral secretions consistently for more than 6 mo after acute infection and then intermittently for life. As many as 20-30% of healthy EBV-infected persons excrete virus at any particular time. Immunosuppression permits reactivation of latent EBV; 60-90% of EBV-infected immunosuppressed patients shed the virus. EBV is also found in male and female genital secretions and, especially for EBV-2, is spread through sexual contact.

Infection with EBV in developing countries and among socioeconomically disadvantaged populations of developed countries usually occurs during infancy and early childhood. In central Africa, almost all children are infected by 3 yr of age. Among more affluent populations in industrialized countries, half of the population is infected by 6-8 yr of age with approximately 30% of infections during adolescence and young adulthood. In the United States, seroprevalence increases with age, from approximately 54% for 6-8 yr olds to 83% for 18-19 yr olds. Seroprevalence at each age is substantially higher for Mexican-Americans and non-Hispanic blacks than non-Hispanic whites. Large differences are seen by family income, with highest seroprevalence in children of families with lowest income.

The epidemiology of the illness of infectious mononucleosis is related to the age of acquisition of EBV infection. Primary infection with EBV during childhood is usually asymptomatic or mild and indistinguishable from other childhood infections; the clinical syndrome of infectious mononucleosis is practically unknown in undeveloped regions of the world. Primary EBV infection in adolescents and adults manifests in 30-50% of cases as the **classic triad** of fatigue, pharyngitis, and generalized lymphadenopathy, which constitute the major clinical manifestations of infectious mononucleosis. This syndrome may be seen at all ages but is rarely apparent in children younger than 4 yr of age, when most EBV infections are asymptomatic, or in adults older than 40 yr of age, when most individuals have already been infected by EBV. The true incidence of the syndrome of infectious mononucleosis is unknown but is estimated to occur in 20-70 per 100,000 persons/yr; in young adults, the incidence increases to approximately 100 per 100,000 persons/yr. The prevalence of serologic evidence of past EBV infection increases with age; almost all adults in the United States are seropositive.

PATHOGENESIS

After acquisition in the oral cavity, EBV initially infects crypt epithelial cells, which may contribute to the symptoms of pharyngitis. After

intracellular viral replication and cell lysis with release of new virions, virus spreads to contiguous structures such as the salivary glands, with eventual viremia and infection of B lymphocytes in the peripheral blood and the entire lymphoreticular system, including the liver and spleen. The atypical lymphocytes that are characteristic of infectious mononucleosis are CD8 T lymphocytes, which exhibit both suppressor and cytotoxic functions that develop in response to the infected B lymphocytes. This relative as well as absolute increase in CD8 lymphocytes results in a transient reversal of the normal 2 : 1 CD4/CD8 (helper/suppressor) T-lymphocyte ratio. Many of the clinical manifestations of infectious mononucleosis may result, at least in part, from cytokine release from the host immune response, which is effective in reducing the EBV load to <1 copy/105 circulating B lymphocytes, equivalent to <10 copies/µg of DNA from whole blood. The EBV load is more variable among immunocompromised persons and can be >4,000 copies/µg of DNA.

Epithelial cells of the uterine cervix may become infected by sexual transmission of the virus, although local symptoms have been described after sexual transmission. EBV is consistently found intracellularly in smooth muscle cells of leiomyosarcomas of immunocompromised persons, but not in leiomyosarcomas of immunocompetent persons.

EBV, like the other herpesviruses, establishes lifelong latent infection after the primary illness. The latent virus is carried in oropharyngeal epithelial cells and systemically in memory B lymphocytes as multiple episomes in the nucleus. The viral episomes replicate with cell division and are distributed to both daughter cells. Viral integration into the cell genome is not typical. Only a few viral proteins, including the EBV-determined nuclear antigens (EBNAs), are produced during latency. These proteins are important in maintaining the viral episome during the latent state. Progression to viral replication begins with production of EBV early antigens (EAs), proceeds to viral DNA replication, is followed by production of viral capsid antigen (VCA), and culminates in cell death and release of mature virions. Reactivation with viral replication occurs at a low rate in populations of latently infected cells and is responsible for intermittent viral shedding in oropharyngeal secretions of infected individuals. Reactivation is apparently asymptomatic and not recognized to be accompanied by distinctive clinical symptoms.

ONCOGENESIS

EBV was the first human virus to be associated with malignancy. EBV infection may result in a spectrum of proliferative disorders ranging from self-limited, usually benign disease such as infectious mononucleosis to aggressive, nonmalignant proliferations such as the virus-associated hemophagocytic syndrome to lymphoid and epithelial cell malignancies. Benign EBV-associated proliferations include oral hairy leukoplakia, primarily in adults with AIDS, and lymphoid interstitial pneumonitis, primarily in children with AIDS. Malignant EBV-associated proliferations include nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease, lymphoproliferative disorders, and leiomyosarcoma in immunodeficient states, including AIDS. There is no firm evidence of development of EBV quasispecies that would contribute to the pathogenesis of EBV-positive malignancies.

Nasopharyngeal carcinoma occurs worldwide but is 10 times more common in persons in southern China, where it is the most common malignant tumor among adult men. It is also common among whites in North Africa and Inuits in North America. Patients usually present with cervical lymphadenopathy, eustachian tube blockage, and nasal obstruction with epistaxis. All malignant cells of undifferentiated nasopharyngeal carcinoma contain a high copy number of EBV episomes. Persons with undifferentiated and partially differentiated, nonkeratinizing nasopharyngeal carcinomas have elevated EBV antibody titers that are both diagnostic and prognostic. High levels of immunoglobulin (Ig) A antibody to EA and VCA may be detected in asymptomatic individuals and can be used to follow response to tumor therapy (Table 254-1). Cells of well-differentiated, keratinizing nasopharyngeal carcinoma contain a low number of or no EBV genomes; these persons have EBV serologic patterns similar to those of the general population.

CT and MR images are helpful in both identifying and defining masses in the head and neck. The diagnosis is established by biopsy of the mass or of a suspicious cervical lymph node. Surgery is important for staging and diagnosis. Radiation therapy is effective for control of the primary tumor and regional nodal metastases. Chemotherapy with 5-fluorouracil, cisplatin, and methotrexate is effective but not always curative. The prognosis is good if the tumor is localized.

Endemic (African) Burkitt lymphoma, often found in the jaw, is the most common childhood cancer in equatorial East Africa and New

Table 254-1 Correlation of Clinical Status and Serologic Responses to Epstein-Barr Virus Infection

	Serologic Response					
		EBV-Specific Antibody				
CLINICAL STATUS	HETEROPHILE ANTIBODIES (QUALITATIVE TEST)	IgM-VCA	IgG-VCA	EA-D	EA-R	EBNA
Negative reaction	–	<1 : 8*	<1 : 10*	<1 : 10*	<1 : 10*	<1 : 2.5*
Susceptible	–	–	–	–	–†	–
Acute primary infection: infectious mononucleosis	+	1 : 32 to 1 : 256	1 : 160 to 1 : 640	1 : 40 to 1 : 160	–†	– to 1 : 2.5
Recent primary infection: infectious mononucleosis	±	– to 1 : 32	1 : 320 to 1 : 1,280	1 : 40 to 1 : 160	–†	1 : 5 to 1 : 10
Remote infection	–	–	1 : 40 to 1 : 160	–‡	– to 1 : 40	1 : 10 to 1 : 40
Reactivation: immunosuppressed or immunocompromised	–	–	1 : 320 to 1 : 1,280	–‡	1 : 80 to 1 : 320	– to 1 : 160
Burkitt lymphoma	–	–	1 : 320 to 1 : 1,280	–‡	1 : 80 to 1 : 320	1 : 10 to 1 : 80
Nasopharyngeal carcinoma	–	–	1 : 320 to 1 : 1,280	1 : 40 to 1 : 160	–§	1 : 20 to 1 : 160

The data were obtained from numerous studies. Individual responses outside the characteristic range may occur.

*Or the lowest test dilution.

†In young children and adults with asymptomatic seroconversion, the anti–early antigen response may be mainly to the EA-R component.

‡A minority of individuals will have the anti–early antigen response mainly to the EA-D component.

§A minority of individuals will have the anti–early antigen response mainly to the EA-R component.

–, Negative; +, positive; EA-D, diffuse staining component of early antigen; EA-R, cytoplasmic restricted component of early antigen; EBNA, EBV-determined nuclear antigens; EBV, Epstein-Barr virus; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen.

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Guinea (see Chapter 496.2). The median age at onset is 5 yr. These regions are holoendemic for *Plasmodium falciparum* malaria and have a high rate of EBV infection early in life. The constant malarial exposure acts as a B-lymphocyte mitogen that contributes to the polyclonal B-lymphocyte proliferation with EBV infection, impairs T-lymphocyte surveillance of EBV-infected B lymphocytes, and increases the risk for developing Burkitt lymphoma. Approximately 98% of cases of endemic Burkitt lymphoma contain the EBV genome compared with only 20% of nonendemic (sporadic or American) Burkitt lymphoma cases. Individuals with Burkitt lymphoma have unusually and characteristically high levels of antibody to VCA and EA that correlate with the risk for developing tumor (see Table 254-1).

All cases of Burkitt lymphoma, including those that are EBV-negative, are monoclonal and demonstrate chromosomal translocation of the c-*myc* protooncogene to the constant region of the immunoglobulin heavy-chain locus, t(8;14), to the κ constant light-chain locus, t(2;8), or to the λ constant light-chain locus, t(8;22). This results in the deregulation and constitutive transcription of the c-*myc* gene with overproduction of a normal c-*myc* product that autosuppresses c-*myc* production on the untranslocated chromosome.

The incidence of **Hodgkin disease** peaks in childhood in developing countries and in young adulthood in developed countries. Levels of EBV antibodies are consistently elevated preceding development of Hodgkin disease; only a small minority of patients is seronegative for EBV. Infection with EBV increases the risk for Hodgkin disease by a factor of 2-4, with the risk of developing Hodgkin disease peaking at 2.4 yr following infectious mononucleosis. EBV is associated with more than half of cases of mixed cellularity Hodgkin disease and approximately one quarter of cases of the nodular sclerosing subtype, and is rarely associated with lymphocyte-predominant Hodgkin disease. Immunohistochemical studies have localized EBV to the Reed-Sternberg cells and their variants, the pathognomonic malignant cells of Hodgkin disease.

Failure to control EBV infection may result from host immunologic deficits. The prototype is the **X-linked lymphoproliferative syndrome (Duncan syndrome),** an X chromosome–linked recessive disorder of the immune system associated with severe, persistent, and sometimes fatal EBV infection (see Chapter 123). Approximately 65% of these male patients die of disseminated and fulminating lymphoproliferation involving multiple organs at the time of primary EBV infection. Surviving patients acquire hypogammaglobulinemia, B-cell lymphoma, or both. Most patients die by 10 yr of age.

Numerous congenital and acquired immunodeficiency syndromes are associated with an increased incidence of EBV-associated B-lymphocyte lymphoma, especially central nervous system lymphoma, and leiomyosarcoma. The incidence of lymphoproliferative syndromes parallels the degree of immunosuppression. A decline in T-cell function evidently permits EBV to escape from immune surveillance. Congenital immunodeficiencies predisposing to EBV-associated lymphoproliferation include the X-linked lymphoproliferative syndrome, common-variable immunodeficiency, ataxia-telangiectasia, Wiskott-Aldrich syndrome, and Chédiak-Higashi syndrome. Individuals with acquired immunodeficiencies resulting from anticancer chemotherapy, immunosuppression after solid organ or bone marrow transplantation, or HIV infection have a significantly increased risk for EBV-associated lymphoproliferation. The lymphomas may be focal or diffuse and are usually histologically polyclonal but may become monoclonal. Their growth is not reversed on cessation of immunosuppression.

EBV is found intracellularly in all of the smooth muscle cells of leiomyosarcomas occurring in immunocompromised persons, including HIV-infected patients and transplant recipients, but not in leiomyosarcomas occurring in immunocompetent persons.

EBV is also associated with carcinoma of the salivary glands. Other tumors putatively associated with EBV include some T-lymphocyte lymphomas (including lethal midline), angioimmunoblastic lymphadenopathy-like lymphoma, thymomas and thymic carcinomas derived from thymic epithelial cells, supraglottic laryngeal carcinomas, lymphoepithelial tumors of the respiratory tract and gastrointestinal tract, and gastric adenocarcinoma. The precise contribution of EBV to these various malignancies is not well defined.

CLINICAL MANIFESTATIONS

The incubation period of infectious mononucleosis in adolescents is 30-50 days. In children, it may be shorter. The majority of cases of primary EBV infection in infants and young children are clinically silent. In older patients, the onset of illness is usually insidious and vague. Patients may complain of malaise, fatigue, acute or prolonged (>1 wk) fever, headache, sore throat, nausea, abdominal pain, and myalgia. This prodromal period may last 1-2 wk. Lytic infection of B lymphocytes and crypt epithelial cells results in high salivary levels and oral shedding. The complaints of sore throat and fever gradually increase until patients seek medical care. Splenic enlargement may be rapid enough to cause left upper quadrant abdominal discomfort and tenderness, which may be the presenting complaint.

The classic physical examination findings are generalized lymphadenopathy (90% of cases), splenomegaly (50% of cases), and hepatomegaly (10% of cases). Lymphadenopathy occurs most commonly in the anterior and posterior cervical nodes and the submandibular lymph nodes and less commonly in the axillary and inguinal lymph nodes. Epitrochlear lymphadenopathy is particularly suggestive of infectious mononucleosis. Symptomatic hepatitis or jaundice is uncommon, but elevated liver enzymes are very common. Splenomegaly to 2-3 cm below the costal margin is typical (15-65% of cases) and is seen in most cases by ultrasonography; massive enlargement is uncommon.

The sore throat is often accompanied by moderate to severe pharyngitis with marked tonsillar enlargement, occasionally with exudates (Fig. 254-1). Palatal petechiae at the junction of the hard and soft palate are frequently seen. The pharyngitis resembles that caused by streptococcal infection. Other clinical findings may include rashes and edema of the eyelids.

Rashes are usually maculopapular and have been reported in 3-15% of patients. Patients with infectious mononucleosis treated with ampicillin or amoxicillin may experience **"ampicillin rash,"** which may occur with other β-lactam antibiotics. This morbilliform, vasculitic rash is probably immune mediated and resolves without specific treatment. EBV is also associated with **Gianotti-Crosti syndrome,** a symmetric rash on the cheeks with multiple erythematous papules, which may coalesce into plaques and persist for 15-50 days. The rash has the appearance of atopic dermatitis and may appear on the extremities and buttocks.

Infants coinfected with HIV acquire EBV infection at an earlier age, have higher EBV plasma loads that are slower to resolve, and more frequently develop pneumonia and hepatosplenomegaly and require hospitalization compared to HIV-negative infants.

DIAGNOSIS

The diagnosis of infectious mononucleosis implies primary EBV infection. A presumptive diagnosis may be made by the presence of typical clinical symptoms with atypical lymphocytosis in the peripheral blood.

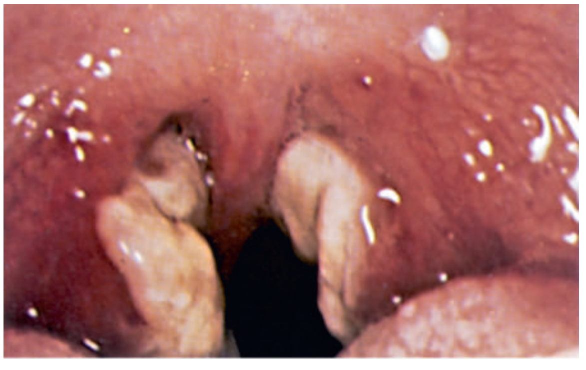

Figure 254-1 Tonsillitis with membrane formation in infectious mononucleosis. *(Courtesy of Alex J. Steigman, MD.)*

The diagnosis is usually confirmed by serologic testing, either for heterophile antibody or specific EBV antibodies.

Culture of EBV is tedious and requires 4-6 wk. The culture method is the **transformation assay,** which is performed by cocultivating oropharyngeal or genital secretions, peripheral blood (10-30 mL), or tumor with human umbilical cord lymphocytes. The cultures are observed for 6 wk for signs of **cell transformation:** proliferation and rapid growth, mitotic figures, large vacuoles, granular morphology, and cell aggregation. EBV **immortalizes** the umbilical cord cells, resulting in cell lines that harbor the EBV strain isolated from the patient and can be maintained in vitro in perpetuity.

Differential Diagnosis

Infectious mononucleosis-like illnesses may be caused by primary infection with cytomegalovirus, *T. gondii,* adenovirus, hepatitis virus, HIV, or possibly rubella virus. Cytomegalovirus infection is a particularly common cause in adults. Streptococcal pharyngitis may cause sore throat and cervical lymphadenopathy indistinguishable from that of infectious mononucleosis but is not associated with hepatosplenomegaly. Approximately 5% of cases of EBV-associated infectious mononucleosis have positive throat cultures for group A *Streptococcus*, representing pharyngeal streptococcal carriage. Failure of a patient with streptococcal pharyngitis to improve within 48-72 hr should evoke suspicion of infectious mononucleosis. The most serious problem in the diagnosis of acute illness arises in the occasional patient with extremely high or low white blood cell counts, moderate thrombocytopenia, and even hemolytic anemia. In these patients, bone marrow examination and hematologic consultation are warranted to exclude the possibility of leukemia.

Laboratory Tests

In >90% of cases there is leukocytosis of 10,000-20,000 cells/µL, of which at least two thirds are lymphocytes; atypical lymphocytes usually account for 20-40% of the total number. The atypical cells are mature T lymphocytes that have been antigenically activated. Compared with regular lymphocytes microscopically, **atypical lymphocytes** are larger overall, with larger, eccentrically placed indented and folded nuclei with a lower nuclear-to-cytoplasm ratio. Although atypical lymphocytosis may be seen with many of the infections usually causing lymphocytosis, the highest degree of atypical lymphocytes is classically seen with EBV infection. Other syndromes associated with atypical lymphocytosis include acquired cytomegalovirus infection (in contrast to congenital cytomegalovirus infection), toxoplasmosis, viral hepatitis, rubella, roseola, mumps, tuberculosis, typhoid, *Mycoplasma* infection, and malaria, as well as some drug reactions. Mild thrombocytopenia to 50,000-200,000 platelets/µL occurs in more than 50% of patients, but only rarely is associated with purpura. Mild elevation of hepatic transaminases occurs in approximately 50% of uncomplicated cases, but is usually asymptomatic without jaundice.

Heterophile Antibody Test

Heterophile antibodies agglutinate cells from species different from those in the source serum. The transient heterophile antibodies seen in infectious mononucleosis, also known as **Paul-Bunnell antibodies**, are IgM antibodies detected by the Paul-Bunnell-Davidsohn test for sheep red cell agglutination. The heterophile antibodies of infectious mononucleosis agglutinate sheep or, for greater sensitivity, horse red cells but not guinea pig kidney cells. This adsorption property differentiates this response from the heterophile response found in patients with serum sickness, rheumatic diseases, and some normal individuals. Titers of >1 : 28 or >1 : 40, depending on the dilution system used, after absorption with guinea pig cells are considered positive.

Heterophile antibody tests are positive in 75% of cases in the 1st wk and 90-95% of cases in the 2nd wk. Results of the sheep red cell agglutination test are often positive for several months after infectious mononucleosis; those of the horse red cell agglutination test may be positive for as long as 2 yr. The most widely used method is the qualitative rapid slide test using horse erythrocytes. It detects heterophile antibody in 90% of cases of EBV-associated infectious mononucleosis in adolescents and adults but in only up to 50% of cases in children younger than 4 yr of age because they typically develop a lower titer. From 5-10% of cases of infectious mononucleosis syndromes are not caused by EBV and are not uniformly associated with a heterophile antibody response. The false-positive rate is <10%, usually resulting from erroneous interpretation. If the heterophile test result is negative and an EBV infection is suspected, EBV-specific antibody testing is indicated. Nonetheless, a positive heterophile test, together with classic clinical manifestations of mononucleosis, helps confirm the diagnosis in adolescents and adults. Primary HIV infection may also be associated with a positive heterophile test and a mononucleosis-like clinical picture.

SPECIFIC EPSTEIN-BARR VIRUS ANTIBODIES

EBV-specific antibody testing is useful to confirm acute EBV infection, especially in heterophile-negative cases, or to confirm past infection and determine susceptibility to future infection. Several distinct EBV antigen systems have been characterized for diagnostic purposes (Fig. 254-2 and see Table 254-1). The EBNA, EA, and VCA antigen systems are most useful for diagnostic purposes. The acute phase of infectious mononucleosis is characterized by rapid IgM and IgG antibody responses to VCA in all cases and an IgG response to EA in most cases. The IgM response to VCA is transient but can be detected for at least 4 wk and occasionally up to 3 mo. The laboratory must take steps to remove rheumatoid factor, which may cause a false-positive IgM VCA result. The IgG response to VCA usually peaks late in the acute phase, declines slightly over the next several weeks to months, and then persists at a relatively stable level for life.

Anti-EA antibodies are usually detectable for several months but may persist or be detected intermittently at low levels for many years. Antibodies to the diffuse-staining component of EA, EA-D, are found transiently in 80% of patients during the acute phase of infectious mononucleosis and reach high titers in patients with nasopharyngeal carcinoma. Antibodies to the cytoplasmic-restricted component of EA, EA-R, emerge transiently in the convalescence from infectious mononucleosis and often attain high titers in patients with EBV-associated Burkitt lymphoma, which in the terminal stage of the disease may be exceeded by antibodies to EA-D. High levels of antibodies to EA-D or EA-R may be found also in immunocompromised patients with persistent EBV infections and active EBV replication. Anti-EBNA antibodies are the last to develop in infectious mononucleosis and gradually

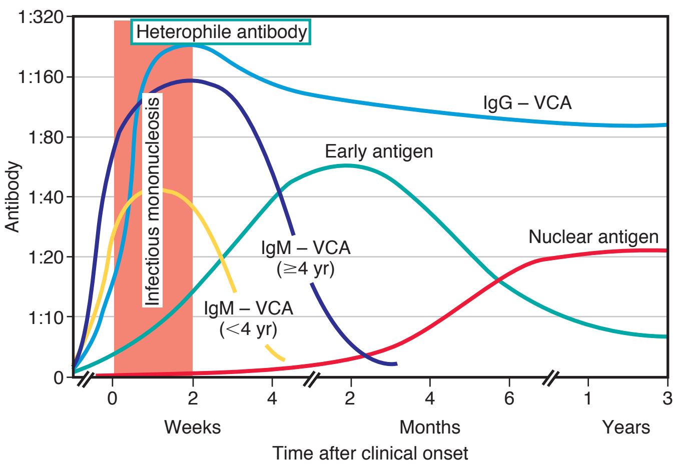

Figure 254-2 Schematic of the development of antibodies to various Epstein-Barr virus antigens in patients with infectious mononucleosis. Antibody titers are calculated as geometric mean values expressed as reciprocals of the serum dilution. The immunoglobulin M (IgM) response to viral capsid antigen (VCA) is divided because of the significant differences noted according to age of the patient. *IgG,* immunoglobulin G. *(Reprinted with permission from Jenson HB: Epstein-Barr virus. In Detrick B, Hamilton RG, Folds JD, editors:* Manual of molecular and clinical laboratory immunology, *ed 7. Washington, DC, 2006, American Society for Microbiology.)*

appear 3-4 mo after the onset of illness and remain at low levels for life. Absence of anti-EBNA when other antibodies are present implies recent infection, whereas the presence of anti-EBNA implies infection occurring more than 3-4 mo previously. The wide range of individual antibody responses and the various laboratory methods used can occasionally make interpretation of an antibody profile difficult. The detection of IgM antibody to VCA is the most valuable and specific serologic test for the diagnosis of acute EBV infection and is generally sufficient to confirm the diagnosis.

TREATMENT

There is no specific treatment for infectious mononucleosis. The mainstays of management are rest, encouraging adequate fluid and nutrition intake, and symptomatic treatment with acetaminophen or nonsteroidal antiinflammatory agents to manage fever, throat discomfort, and malaise. Bed rest is necessary only when the patient has debilitating fatigue. As soon as there is definite symptomatic improvement, the patient should be allowed to begin resumption of normal activities. Because blunt abdominal trauma may predispose patients to splenic rupture, it is customary and prudent to advise against participation in contact sports and strenuous athletic activities during the 1st 2-3 wk of illness or while splenomegaly is present.

Short courses of corticosteroids (<2 wk) may be helpful for selected complications of infectious mononucleosis, but this use has not been evaluated critically. Some appropriate indications include incipient airway obstruction, thrombocytopenia with hemorrhaging, autoimmune hemolytic anemia, seizures, and meningitis. A recommended regimen is prednisone 1 mg/kg/day (maximum: 60 mg/day) or equivalent for 7 days and tapered over another 7 days. There are no controlled data showing efficacy of corticosteroids in any of these conditions. In view of the potential and unknown hazards of immunosuppression for a virus infection with oncogenic complications, corticosteroids should not be used in uncomplicated cases of infectious mononucleosis.

Antiviral therapy is not recommended. Therapy with high doses of acyclovir, with or without corticosteroids, decreases viral replication and oropharyngeal shedding during the period of administration but does not reduce the severity or duration of symptoms or alter the eventual outcome.

COMPLICATIONS

Very few patients with infectious mononucleosis experience complications. The most feared complication is subcapsular splenic hemorrhage or splenic rupture, which occurs most frequently during the 2nd wk of the disease at a rate of <0.5% of cases in adults; the rate in children is unknown but is probably much lower. Rupture is commonly related to trauma, which is often mild, and is rarely fatal. Swelling of the tonsils and oropharyngeal lymphoid tissue may be substantial and may cause airway obstruction that manifests as drooling, stridor, and interference with breathing. Airway compromise with progressive symptoms occurs in <5% of cases and is a common indication for hospitalization with infectious mononucleosis. It may be managed by elevating the head of the bed, intravenous hydration, humidified air, and systemic corticosteroids. Respiratory distress with incipient or actual airway occlusion should be managed by tonsilloadenoidectomy and endotracheal intubation for 12-24 hr in an intensive care setting.

Many uncommon and unusual neurologic conditions are reported to be associated with EBV infectious mononucleosis. Headache is present in about half of cases, with severe neurologic manifestations, such as seizures and ataxia, in 1-5% of cases. Perceptual distortions of sizes, shapes, and spatial relationships, known as the **Alice-in-Wonderland syndrome (metamorphopsia),** may be a presenting symptom. There may be meningitis with nuchal rigidity and mononuclear cells in the cerebrospinal fluid, facial nerve palsy, transverse myelitis, and encephalitis. Most patients with encephalitis from EBV, however, do not demonstrate the common symptoms of infectious mononucleosis.

Guillain-Barré syndrome or Reye syndrome may follow acute illness. Hemolytic anemia, often with a positive Coombs test result and with cold agglutinins specific for red cell antigen i, occurs in 3% of cases. The onset is typically in the 1st 2 wk of illness and lasts for <1 mo. Aplastic anemia is a rare complication that usually presents 3-4 wk after the onset of illness, usually with recovery in 4-8 days, but some cases do require bone marrow transplantation. Mild thrombocytopenia and neutropenia are common, but severe thrombocytopenia (<20,000 platelets/µL) or severe neutropenia (<1,000 neutrophils/µL) is rare. Myocarditis or interstitial pneumonia may occur, both resolving in 3-4 wk. Other rare complications include pancreatitis, parotitis, and orchitis.

PROGNOSIS

The prognosis for complete recovery is excellent. The major symptoms typically last 2-4 wk followed by gradual recovery within 2 mo of onset of symptoms. Individuals often harbor multiple strains of EBV and second infections with a different type of EBV (type 1 or type 2) have been demonstrated in immunocompromised persons, but symptoms or second clinical episodes of infectious mononucleosis have not been documented. Cervical lymphadenopathy and fatigue may resolve more slowly. Prolonged and debilitating fatigue, malaise, and some disability that may wax and wane for several weeks to 6 mo are common complaints even in otherwise unremarkable cases. Occasional persistence of fatigue for a few years after infectious mononucleosis is well recognized. There is no convincing evidence linking EBV infection or EBV reactivation to chronic fatigue syndrome (see Chapter 121).

PREVENTION

It is impractical to try to prevent EBV infection because the virus is ubiquitous and the majority of the population is EBV-positive. A recombinant EBV subunit glycoprotein 350 candidate vaccine in a 3 dose regimen shows promise to prevent infectious mononucleosis and potentially EBV-associated malignancies as well.

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Chapter 255

Cytomegalovirus

William J. Britt

Human cytomegalovirus (CMV) is ubiquitous in the population, and once infected, individuals remain persistently infected for life with intermittent excretion of infectious virus. Although CMV rarely causes symptoms in normal individuals, it is an important cause of morbidity, and in some cases death, in immunocompromised hosts. CMV remains a well-recognized cause of disease in the newborn infant following intrauterine infection (congenital CMV) and the allograft recipients undergoing posttransplantation immunosuppression. CMV has emerged as the most common opportunistic infection in HIV/AIDS patients prior to the advent of highly active retroviral therapy. Case reports also indicate that invasive CMV infections can be observed in patients treated with immunosuppressive biologics such as anti–tumor necrosis factor antibodies. In each of these clinical situations, the association of disease with CMV infection has been linked to high levels of virus replication and end-organ disease, usually following virus dissemination. In contrast, there is likely another group of disease states associated with chronic effects of persistent CMV infection that reflects the robust inflammatory response induced by this virus. Such associations have included coronary artery disease, transplant vasculopathy and cardiac allograft loss, tubular sclerosis and renal allograft loss, exacerbations of inflammatory bowel disease, and possibly some cancers such as glioblastoma.

THE VIRUS AND ITS INTERACTION WITH THE HOST

CMV is the largest of the human herpesvirus with an estimated size of 190 nm. The 230-kb double-stranded DNA genome is approximately

50% larger than the herpes simplex virus genome and encodes more than 100 unique virion proteins and an unknown number of nonstructural proteins. Viral DNA replication takes place in the nucleus of the infected cell followed by virus assembly in both the nucleus and cytoplasm. The structure of the virus is typical of herpesviruses and includes a complex envelope composed of host cell–derived membrane studded with virion glycoproteins, an amorphous area between the envelope and the capsid called the tegument layer, and an icosahedral capsid that contains the virion DNA. The tegument layer is highly immunogenic and induces strong adaptive immune responses, including CMV-specific $CD8^+$ cytotoxic T lymphocytes that are thought to play a pivotal role in controlling CMV replication in the infected host. Likewise, the protein components of the viral envelope are also immunogenic and believed to induce protective antibody responses that can be most closely correlated with virus neutralization. In vivo, CMV appears to replicate in nearly all tissue and cell types, whereas in vitro productive virus replication (production of infectious progeny) occurs in primary cells derived from epithelial tissue and the dermis. Literature from nearly 3 decades ago suggested that each strain of CMV isolated from epidemiologically unrelated individuals was genetically unique, a finding suggesting that an infinite number of distinct viruses existed in the human population. New evidence suggests that CMV exists as genetically diverse swarms within an individual because CMV DNA synthesis is fraught with error rates that are much higher than has been thought; alternately an individual may acquire a library of CMV variants during each exposure and infection. An important finding supportive of this latter possibility is that reinfection of previously infected individuals with new strains of CMV is commonplace. These observations have led many to argue that CMV must express an armamentarium of immune evasion functions that allow it to remain hidden from protective host immunity. This relationship between host and virus is best illustrated by the finding that a persistently infected individual over years can maintain a stable virus load, unwavering antiviral antibody responses, and, in some cases, up to 15% of a total peripheral blood $CD8^+$ cytotoxic T-lymphocyte activity dedicated to recognition of CMV-infected cells.

EPIDEMIOLOGY

CMV infections are acquired through several settings: (1) community exposure, (2) nosocomial transmission, and (3) intrauterine infection. Community acquisition occurs throughout life and is linked by exposure to CMV present in saliva and urine. Peaks in exposure occur during childhood and in adolescents and young adults, presumably in the latter cases secondary to sexual activity. Common routes of infection of the young infant include perinatal exposure to infected genital secretions during birth and ingestion of breast milk containing CMV. Breastfeeding is the most common route of CMV infection in early childhood. Ingestion of breast milk from seropositive women results in a rate of infection of approximately 60-70% in infants. Infection is most common during the 1st 6 mo of breastfeeding, but the risk continues for the duration of breastfeeding. Infants infected through breast milk excrete virus in the saliva and urine for prolonged periods of time measured in months to years and thus serve as a reservoir of virus for spread to other infants, children, and adults. After this period of intense exposure to CMV during the 1st yr of life, infection in the remainder of childhood and early teenage years depends on specific exposures, such as enrollment in group childcare facilities and/or exposure to infected, similarly aged siblings. Up to 50% of young infants and children attending group care facilities can be excreting CMV, a source of virus that can result in infection of uninfected children enrolled in the facility, and in some cases, the workers in the facility. Furthermore, once infected, infants can then readily transmit virus to their parents and siblings. Throughout childhood and early adulthood, CMV is transmitted by exposure to saliva and urine. However, in adolescence and early adulthood there is a spike in infection possibly associated with sexual exposure. CMV is considered a sexually transmitted infection.

Nosocomial infections with CMV are well described and follow exposure to blood products containing CMV and less commonly through allograft transplantation following transplantation of an organ from a CMV infected donor. Prior to improvements in blood banking that limited the number of leukocytes in red blood transfusions, transmission of CMV by blood transfusion was not uncommon and was closely related to the volume of blood that was transfused. Transfusion-acquired CMV infections often resulted in symptomatic illness, with laboratory findings including hepatitis and thrombocytopenia in children and adults. In newborn infants lacking antibodies to CMV secondary to being born to women without seroimmunity to CMV or extreme prematurity, severe, sometimes fatal infections have developed. Similarly, immunocompromised patients who received CMV containing blood were also at risk for severe infection. Current methodologies of leukocyte depletion and the use of blood products from CMV seronegative donors have greatly decreased the incidence of transfusion-associated CMV infections. Finally, CMV transmission through infected allografts is well described, and infections arising from CMV transferred in the allograft are a major cause of morbidity in the early and late period after transplantation. Severe infections and graft loss are more often associated with mismatches between the donor and recipient, for instance, if the donor has a history of CMV infection (and is therefore positive for CMV) and the recipient has not been exposed to CMV (and is therefore negative for CMV), there is a D+/R– mismatch. Even with effective antiviral therapy, CMV infection remains linked to long-term graft dysfunction and graft loss, a particularly important problem in cardiac and lung transplant recipients.

Congenital CMV infection (present at birth) occurs following intrauterine transmission of CMV. Rates of congenital infection between 0.5-1.0% have been routinely reported in the United States. Rates as high as 2% in some areas in Asia and Africa have also been described. CMV is thought to be transferred to the developing fetus following hematogenous spread of the virus to the placenta, presumably followed by cell-free transfer of virus to the fetal blood system. The rate of transmission to the fetus is approximately 30% in women undergoing primary infection during pregnancy, whereas in utero infections also occur in previously immune women (nonprimary infection) albeit at a reduced rate on the order of 1-2%. This later rate is an estimate because a precise rate following nonprimary maternal infection has not been established. It is important to note that although the rate of transmission of CMV is more frequent following primary maternal infection, the absolute number of congenitally infected infants born to women with nonprimary infections in most populations outnumber those resulting from primary maternal infection by 3-4–fold. This is particularly true in Africa, South America, and Asia, where maternal seroimmunity to CMV often exceeds 95%. Interestingly, these populations also have the highest rates of congenital CMV infections. The source of nonprimary infection is also somewhat controversial. Older reports suggested it followed reactivation (recurrence) of virus infection in seroimmune women, whereas more recent literature has demonstrated that reinfection by genetically distinct strains of CMV occurs in previously infected women and that these strains can be transmitted to the developing fetus. In some studies, the reinfection rates are approximately 15-20% with annualized rates as high as 25%. Thus, immunity to CMV is far from protective, although it appears to decrease the risk of transmission to the developing fetus.

Mechanisms of Disease Associated with Cytomegalovirus Infections

The mechanism(s) of disease associated with CMV infections remain undefined for most clinical syndromes that follow CMV infection. Several reasons have contributed to the overall lack of understanding of the pathogenesis of CMV infections and include (1) the asymptomatic nature of infections in almost all normal individuals, (2) the complexity of the underlying disease processes in immunocompromised hosts that often confounds the assignment of specific manifestations of CMV infection, (3) limitations of observational studies in humans, and (4) the species-specific tropism of human CMV. Although CMV replicates in a limited number of cell types in vitro, CMV inclusions, antigens, and nucleic acids can be demonstrated in almost organ systems and cell types in individuals with severe, disseminated infections. The virus does

not exhibit specific cellular or organ system tropism in vivo. Hematogenous dissemination is usually associated with cell-associated virus, and significant levels of plasma virus are usually detected only in severely immunocompromised hosts. Virus and viral DNA can be recovered from neutrophils, monocytes, and endothelial cells. High levels of virus replication can result in end-organ disease, presumably secondary to direct virus-mediated cellular damage. These manifestations of CMV infections are thought to result from uncontrolled virus replication and dissemination secondary to deficits in innate and adaptive immune responses to CMV. In some cases, clinical disease has been observed in patients without significant levels of virus replication, a finding suggesting indirect mechanisms of disease such as immunopathologic responses to CMV. Such a mechanism was clearly operative in patients with immune recovery vitreitis, a pathologic T-lymphocyte–mediated response to CMV in HIV/AIDS patients with CMV retinitis that closely followed the reconstitution of their virus-specific T-lymphocyte responses following active retroviral therapy. Likewise, the level of virus replication has not been closely correlated with several chronic diseases thought to be linked to CMV, an observation that is consistent with indirect mechanisms of disease such as immunopathologic responses.

From early observations in patients with invasive CMV infections in allograft recipients it was apparent that immunosuppressive therapies that resulted in altered T-lymphocyte function predisposed these patients to severe infections. Definitive evidence consistent with this mechanism was provided by a clinical study that demonstrated that in vitro expanded, CMV-specific cytotoxic T lymphocytes could limit invasive infection in hematopoietic cell transplant recipients. Invasive infections such as retinitis and colitis in HIV/AIDS patients with very low $CD4^+$ T-lymphocyte counts also clearly demonstrated the importance of T-lymphocyte responses and invasive CMV infections. Other studies in solid organ transplant recipients have demonstrated that the passive transfer of immune globulins containing high titers of anti-CMV antibodies could provide some degree of protection from invasive disease, a finding that was consistent with the proposed role of antiviral antibodies in limiting CMV dissemination and disease in animal models of invasive CMV infections. The importance of innate immune responses such as natural killer cells and γΔ T lymphocytes in limiting invasive infections has been well documented in representative animal models, but definitive evidence for a key role in resistance to CMV infections in humans is limited. Lastly, effector molecules such as γ-interferon appear to a play an important role in controlling local CMV infections in animal models, but evidence of a similar role in humans has not been shown experimentally.

The control of acute CMV infection is clearly dependent on an effective adaptive immune response; however, even a vigorous T-lymphocyte response is not sufficient to eliminate CMV from the infected host as CMV persists for the lifetime of the host either as a low-level chronic infection or as a latent infection with limited expression of its genome. The inability of the host to clear CMV remains incompletely understood, but the large array of immune evasion functions encoded by this virus likely contributes to the blunted innate and adaptive immune response. These functions include inhibition of apoptotic functions of infected cells, inhibition of interferon-regulated responses, inhibition of natural killer cell activation, downregulation of class I major histocompatibility complex expression, inhibition of class II major histocompatibility complex function, and mechanisms to limit antibody recognition of envelope proteins such as carbohydrate masking of antibody recognition sites and extensive variation in amino acid sequences in virion envelope proteins. Although each of these functions by itself could be expected to have limited effects on virus clearance by the immune system, when acting in concert they likely provide the virus an advantage that leads to its persistence.

CLINICAL MANIFESTATIONS

In the overwhelming majority of normal patients with acute CMV infections there are no specific symptoms or clinical findings. In patients with symptomatic, acute CMV infection, clinical findings are consistent with a mononucleosis-like syndrome, with fatigue and occasionally cervical adenopathy. Up to 20% of heterophile antibody negative cases of mononucleosis could be attributed to CMV. Laboratory findings could include mild elevation of hepatic transaminases and decreased platelet counts.

Immunocompromised Host

The clinical presentation of CMV infection in immunocompromised hosts often reflects the magnitude of the immunodeficiency. Profoundly immunocompromised hosts such as hematopoietic cell allograft recipients can present with disseminated infection and clinical manifestations reflecting the involvement of multiple organ systems including liver, lung, gastrointestinal tract, and rarely the central nervous system. Organ-threatening and life-threatening disease is not infrequent. In less-immunocompromised patients such as most solid organ transplant recipients, CMV infection can present with fever, hematologic abnormalities including leukopenia and thrombocytopenia, and mild hepatocellular dysfunction. In contrast to renal and liver solid organ transplant recipients, heart–lung and lung transplant recipients are at high risk for severe manifestations from CMV infection, presumably because the transplanted organ is a site of virus replication and disease. Prior to the use of antivirals for prophylaxis of allograft recipients, clinical disease usually developed between 30 and 60 days posttransplantation. More recently, prolonged antiviral prophylaxis has nearly eliminated CMV disease in most solid-organ transplants but late manifestations of CMV disease can be seen after discontinuation of the antiviral prophylaxis. These late manifestations are most worrisome in hematopoietic cell recipients, as they may signal deficits in graft function leading to invasive CMV infections. Finally, long-term graft function has been reported to be influenced by CMV infection. This has been most well studied in the renal allograft recipients but has been seen perhaps most dramatically in heart transplant recipients, where CMV is believed to play a major role in transplant vascular sclerosis, a vasculopathy of the coronary arteries in the allograft, leading to loss of the transplanted heart.

Congenital Infection

Congenital infection with CMV can present with symptomatic infections (Table 255-1) in approximately 10% of infected newborns, whereas 90% of infected infants will have no clinical manifestations of infection in the newborn period. Severe multiorgan disease is

Table 255-1 Findings in Infants with Symptomatic Congenital Cytomegalovirus Infection Identified Through Newborn Screening Program*

	PERCENTAGE (%) OF INFANTS
CLINICAL FINDINGS	
Prematurity (<37 wk)	24
Jaundice (direct bilirubin >2 mg/dL)	42
Petechiae	54
Hepatosplenomegaly	19
Purpura	3
Microcephaly	35
Small gestational age	28
1 Clinical finding	41
2 Clinical findings	59
LABORATORY FINDINGS	
Elevated alanine aminotransferase (>80 IU/mL)	71
Thrombocytopenia (<100,000/µL)	43
Direct hyperbilirubinemia (>2 mg/dL)	54
Head CT abnormalities	42

*Findings in 70 infants with symptomatic congenital CMV infection identified during the newborn screening program for infants with congenital CMV infection performed at the University of Alabama Hospitals over an approximate 20 yr interval.

infrequent and occurs in less than 5% of infants with congenital CMV infections. The clinical findings of infants with symptomatic congenital CMV infections can include hepatosplenomegaly, petechial rashes, jaundice, and in some cases microcephaly. These findings were utilized for natural history studies to classify infants as having symptomatic or asymptomatic infections; however, several authors have included intrauterine growth restriction as a finding of symptomatic congenital CMV infection. Laboratory findings include direct hyperbilirubinemia, elevation of hepatic transaminases, thrombocytopenia, anemia, and abnormal findings on cranial ultrasonography. If cerebrospinal fluid is obtained, there can be evidence of encephalitis with elevation of mononuclear cell number and in some cases, elevation of cerebrospinal fluid protein. A small number of symptomatically infected infants (<10%) will be found to have chorioretinitis. Finally, because hearing loss is the most common long-term sequela associated with congenital CMV infection, the failure of an infant to pass a newborn hearing screening exam should raise the possibility of congenital CMV infection. Hearing loss in the older infant and young child should also alert the clinician to the possibility of congenital CMV infection, as approximately 50% of infants with hearing loss associated with congenital CMV infection will pass an initial hearing screening exam but develop hearing loss in later infancy and early childhood.

An organized plan for follow-up is an important aspect in the clinical management of infants with congenital CMV infection. Because permanent sequelae are limited to disorders of the nervous system, long-term follow-up should include appropriate assessment of development and neuromuscular function in infected infants, with referral to specialized care if necessary. Hearing loss will develop in approximately 11% of infected infants, and in some infants hearing loss will progress during infancy. Thus, audiologic testing and follow-up are mandatory in these patients. Other sequelae such as vision loss are infrequent, but vision testing and comprehensive eye examinations should be included in the care plan.

Perinatal Infection

Perinatal infections can be acquired during birth or following ingestion of CMV-containing breast milk. In almost all cases, perinatal infections are not associated with any clinical manifestations of infection and, perhaps more importantly, have not been associated with any long-term sequelae. In rare cases, such as is seen in breast milk transmission of CMV to extremely premature infants or infants born to nonimmune women, perinatal infection can result in severe, disseminated infections associated with end-organ disease and death. These more severe infections are thought to develop in infants who lack transplacentally acquired antiviral antibodies either secondary to extreme prematurity or being the product of a mother lacking anti-CMV antibodies.

DIAGNOSIS

In the nonimmunocompromised individual, diagnosis of CMV infection requires evidence of a primary infection. Serologic reactivity for CMV is lifelong following primary infection; therefore, the presence of immunoglobulin (Ig) G antibody to CMV does not provide evidence of infection. In addition, IgM reactivity for CMV can be detected for prolonged periods after acute infection and cannot be used to reliably to estimate the duration of infection. Furthermore, recovery of virus from body fluids such as saliva or urine does not in itself permit diagnosis of CMV infection, because persistently infected individuals can intermittently shed virus. In the immunocompromised host, CMV can frequently be recovered from patients in the absence of evidence of invasive CMV infection. Thus, assignment of CMV as a cause of disease in this patient population must be made carefully, and other potential causes of symptoms and clinical findings in these patients must also be considered. Serologic assays are of limited value in the transplant recipient secondary to impact of immunosuppression on antibody responses in the allograft recipient. Furthermore, IgM antibodies can be produced following a nonprimary infection in these patients. Sequential viral load measurements by polymerase chain reaction in relevant body fluids such as blood and measurements of CMV DNA in biopsy tissue can be of great value in establishing CMV as a cause of disease in allograft recipients.

Congenital Infections

The diagnosis of congenital CMV infections requires the recovery of replicating virus and/or viral nucleic acids within the 1st 3 wk of life. Sources of virus and viral nucleic acids include urine, saliva, and blood. Methods of detection include routine virus culture combined with immunofluorescence and polymerase chain reaction. Although quantification of virus in various specimens can suggest the likelihood of long-term sequelae such as hearing loss for a population of infected newborns, the predictive value for the individual patient is limited. A considerable amount of effort has been devoted to identifying screening assays that would be suitable for populations of newborn infants. Newborn screening using saliva has proven sensitive and specific and is now performed for newborn screening in some institutions.

Early studies suggested that congenitally infected newborn infants could be identified by CMV-specific IgM reactivity and that elevated levels of CMV-specific IgM correlated with severity of disease. Subsequent studies have demonstrated that although of some value, the limited sensitivity of most assays employed to detect newborn IgM also limit their clinical utility.

Noncongenital Infections

In nonimmunocompromised patients, demonstration of CMV-specific IgG seroconversion or the presence of CMV-specific IgM antibodies represents evidence of a newly acquired CMV infection. IgM anti-CMV antibody reactivity can persist for months depending on the sensitivity of the particular assay. The use of the IgG avidity assays in which CMV-specific binding antibodies are eluted with increasing concentrations of chaotropic agents such as urea can be used to estimate the duration of infection. This assay has been used almost exclusively in the management of CMV infections during pregnancy to aid in defining primary maternal infections. Detection of CMV in urine, saliva, and blood and in tissue specimens obtained at biopsy can be most reliably accomplished by polymerase chain reaction–based methods, and because findings can be quantified, treatment responses can be monitored. However, conventional culture of CMV using human dermal fibroblasts often combined with immunofluorescence detection of CMV-encoded immediate early antigens also remains standard in many institutions. Routine histologic stains allow detection of characteristic nuclear (and cytoplasmic) inclusions (owl-eye inclusions) in tissue specimens.

TREATMENT

Treatment of immunocompromised hosts with invasive CMV disease limits both the morbidity and mortality in the patient with disseminated CMV infections with end-organ disease. This has been shown in allograft transplant recipients and patients with HIV/AIDS. Similarly, antiviral prophylaxis can limit the development of clinically important CMV disease in allograft recipients. Several agents are currently licensed for CMV infections, including ganciclovir and foscarnet. In some transplant centers, high-titered CMV immunoglobulins are included as a component of prophylaxis. Treatment with CMV immunoglobulins alters the natural history of CMV infection in renal and liver allograft recipients. Currently, the effectiveness of antiviral agents in prophylaxis has resulted in less-frequent use of these biologics.

Treatment of congenitally (symptomatic and asymptomatic but at risk for hearing loss) infected infants with ganciclovir has been studied in clinical trials; many infected infants have been treated off-label with this agent because of severe CMV infections. The study conducted by the Collaborative Antiviral Study Group sponsored by the National Institutes of Health suggested that 6 wk of ganciclovir treatment could limit hearing loss and possibly improve developmental outcome in symptomatically infected infants. In addition, infants with severe perinatal CMV infection following breast milk ingestion have been successfully treated with ganciclovir. Preliminary evidence suggests

that 6 mo of oral valganciclovir may be more effective and less toxic than intravenous ganciclovir in infants with symptomatic CMV infection.

PREVENTION

Passive Immunoprophylaxis

Passive transfer of anti-CMV antibodies has been utilized to limit disease but not infection in allograft recipients. A similar approach has also been considered for prevention of intrauterine disease. An uncontrolled trial of human immunoglobulin suggested that passive transfer of anti-CMV antibodies to pregnant women undergoing primary CMV infection may limit transmission and disease. Unfortunately, another study that was controlled failed to confirm this first study.

Active Immunoprophylaxis

A number of different vaccine platforms have been explored, including replicating attenuated CMV as vaccines, protein-based vaccines, heterologous virus vectored CMV vaccines, and DNA vaccines. In all cases, some level of immunity was induced in volunteers. Larger-scale trials have been carried out using replication competent, attenuated CMV vaccines and adjuvant recombinant protein vaccines. However, there has been little evidence that current approaches will be adequate to attenuate a replicating CMV and yet retain sufficient immunogenicity to induce protective responses. More progress has been made in use of adjuvant recombinant proteins. An adjuvant recombinant glycoprotein B, a major protein component of the envelope and target of neutralizing antibodies, has been shown to induce virus-neutralizing antibodies and $CD4^+$ T-lymphocyte proliferative responses. Moreover, this vaccine reduced virus acquisition by approximately 50% in a small trial carried out in young women. However, closer examination of this vaccine trial revealed that protection was very short-lived and that the effectiveness of the vaccine, although statistically significant, was not convincingly demonstrated because of the small numbers of subjects in the trial. Yet, this was perhaps the first evidence that active immunization could effect some level of protection. Because of the potentially large population that may be targeted by a successful vaccine, it should be anticipated that more candidate vaccines will be tested in the near future. Finally, a major question that will face all vaccine programs is whether existing immunity in seropositive women can be augmented to a level to prevent damaging infection in their offspring. The maternal population with existing immunity to CMV prior to childbearing age is responsible for the greatest number of congenitally infected infants in almost all regions of the world.

Counseling

Studies of the natural history of CMV repeatedly demonstrate that transmission requires close, often direct, contact with infected material, such as secretions from the oral or genitourinary tract. Although only limited data suggest that it can be transmitted on fomites, infectivity can persist for hours on surfaces such as toys. Limiting exposure to such secretions and attention to hygiene such as handwashing can drastically limit acquisition of CMV. Counseling is very effective in the prevention of CMV infection in women of childbearing age. In fact, counseling programs are more effective in limiting CMV infection during pregnancy than any vaccine that has been tested to date. Sexual transmission is an important route of infection, and CMV is considered to be a sexually transmitted infection. Limiting sexual transmission through education and counseling should be considered in sexually active individuals.

Acquisition of CMV by hospital workers and other healthcare providers was shown to be less than that of age-matched individuals in the general public. Importantly, these studies were carried out prior to universal precautions that are in place in most hospitals today. Thus, patient education with an emphasis on describing the sources of infectious virus in communities and attention to general hygiene could dramatically reduce CMV spread in the community.

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Chapter 256

Roseola (Human Herpesviruses 6 and 7)

Mary T. Caserta

Human herpesvirus 6 (HHV-6A and HHV-6B) and human herpesvirus 7 (HHV-7) cause ubiquitous infection in infancy and early childhood. HHV-6B is responsible for the majority of cases of **roseola infantum (exanthema subitum** or **sixth disease**) and is associated with other diseases, including encephalitis, especially in immunocompromised hosts. A small percentage of children with roseola have primary infection with HHV-7.

ETIOLOGY

HHV-6A, HHV-6B, and HHV-7 are the sole members of the *Roseolovirus* genus in the Betaherpesvirinae subfamily of human herpesviruses. Human cytomegalovirus, the only other β-herpesvirus, shares limited sequence homology with HHV-6 and HHV-7. Morphologically all human herpesviruses are composed of an icosahedral nucleocapsid, protein-dense tegument, and lipid envelope. Within the nucleocapsid, HHV-6 and HHV-7 both contain large, linear, double-stranded DNA genomes that encode more than 80 unique proteins.

Initially, 2 strain groups of HHV-6 were recognized, HHV-6 variant A and HHV-6 variant B. Despite sharing highly conserved genomes with approximately 90% sequence identity, the 2 variants could be distinguished by restriction fragment length polymorphisms, reactivity with monoclonal antibodies, differential cell tropism, and epidemiology. Because of these differences, the 2 were reclassified as separate species in the genus *Roseolovirus* by the International Committee on the Taxonomy of Viruses in 2012.

Although the frequency of detection of HHV-6A DNA differs among studies, HHV-6B is the overwhelmingly predominant virus found in both normal and immunocompromised hosts by both culture and polymerase chain reaction (PCR). Primary infection with HHV-6A has been detected by PCR in children in Africa. It is not clear whether the differences in the detection of HHV-6A DNA and HHV-6B DNA relate to different tissue tropism, differences in mode or age of acquisition, differences in the ability to cause human disease, or geographic location of the population studied.

EPIDEMIOLOGY

Primary infection with HHV-6B is acquired rapidly by essentially all children following the loss of maternal antibodies in the 1st few mo of infancy, 95% of children being infected with HHV-6 by 2 yr of age. The peak age of primary HHV-6B infection is 6-9 mo of life, with infections occurring sporadically and without seasonal predilection or contact with other ill individuals. Infection with HHV-7 is also widespread but occurs later in childhood and at a slower rate; only 50% of children have evidence of prior infection with HHV-7 by 3 yr of age. Seroprevalence reaches 75% at 3-6 yr of age. In a small study of children with primary HHV-7 infection, the mean age of the patients was 26 mo, significantly older than that of children with primary HHV-6 infection.

Preliminary data suggest that the majority of children acquire primary infection with HHV-6 from the saliva or respiratory droplets of asymptomatic adults or older children. However, congenital infection with HHV-6 occurs in 1% of newborns. Two mechanisms of vertical transmission of HHV-6 have been identified, transplacental infection and chromosomal integration. HHV-6 is unique among the human herpesviruses in that it is integrated at the telomere end of human chromosomes at a frequency of 0.2-2.2% of the population and is passed from parent to child via the germline. Chromosomal

integration has been identified as the major mechanism by which HHV-6 is vertically transmitted, accounting for 86% of congenital infections, with one third resulting from HHV-6A, a percentage much higher than in primary infection in the United States. The clinical consequences of chromosomal integration or transplacental infection with HHV-6 have yet to be determined. In 1 series of infants identified with HHV-6 congenital infection, no evidence of disease was present in the early neonatal period. Congenital infection with HHV-7 has not been demonstrated, and primary infection is presumed to be spread by the saliva of asymptomatic individuals. DNA of both HHV-6 and HHV-7 has been identified in the cervical secretions of pregnant women, suggesting an additional role for sexual or perinatal transmission of these viruses. Breast milk does not appear to play a role in transmission of either HHV-6 or HHV-7.

PATHOLOGY/PATHOGENESIS

Primary HHV-6B infection causes a viremia that can be demonstrated by coculture of the patient's peripheral blood mononuclear cells with mitogen-stimulated cord blood mononuclear cells. HHV-6 has a recognizable cytopathic effect, consisting of the appearance of large refractile mononucleated or multinucleated cells with intracytoplasmic and/or intranuclear inclusions. Infected cells exhibit a slightly prolonged life span in culture; however, lytic infection predominates. HHV-6 infection also induces apoptosis of T cells and may lead to cell expiration via loss of mitochondrial membrane potential as well as alteration of interferon and retinoic acid–induced cell death signals. In vitro, HHV-6 can infect a broad range of cell types, including primary T cells, monocytes, natural killer cells, dendritic cells, and astrocytes. HHV-6 has also been documented to infect B-cell, megakaryocytic, endothelial, and epithelial cell lines. Human astrocytes, oligodendrocytes, and microglia have been infected with HHV-6 ex vivo. The broad tropism of HHV-6 is consistent with the recognition that CD46, a complement regulatory protein present on the surface of all nucleated cells, is a cellular receptor for HHV-6. Recent data also suggest that CD134 is a selective receptor for HHV-6B and may explain some of the differences in tissue tropism noted between HHV-6A and HHV-6B. The CD4 molecule has been identified as a receptor for HHV-7. HHV-7 has been demonstrated to reactivate HHV-6 from latency in vitro. Whether this phenomenon occurs in vivo is not clear.

Primary infection with HHV-6 and HHV-7 is followed by lifelong latency or persistence of virus at multiple sites. HHV-6 exists in a true state of viral latency in monocytes and macrophages. The detection of replicating HHV-6 in cultures of primary $CD34^+$ hematopoietic stem cells has also been described, suggesting that cellular differentiation is a trigger of viral reactivation. This observation is clinically significant because HHV-6 may cause either primary or reactivated infection during hematopoietic stem cell transplantation (HSCT). Additionally, HHV-6 and HHV-7 infection may be persistent in salivary glands, and DNA of both HHV-6 and HHV-7 can be routinely detected in the saliva of both adults and children. HHV-7 can also be isolated in tissue culture from saliva, but HHV-6 cannot. HHV-6 DNA has been identified in the cerebrospinal fluid (CSF) of children, both during and subsequent to primary infection, as well as in brain tissue from immunocompetent adults at autopsy, implicating the central nervous system as an additional important site of either viral latency or persistence. HHV-7 DNA has also been found in adult brain tissue but at a significantly lower frequency.

CLINICAL MANIFESTATIONS

Roseola infantum (**exanthem subitum**, or **sixth disease**) is an acute, self-limited disease of infancy and early childhood. It is characterized by the abrupt onset of high fever, which may be accompanied by fussiness. The fever usually resolves acutely after 72 hr ("crisis") but may gradually fade over a day ("lysis") coincident with the appearance of a faint pink or rose-colored, nonpruritic, 2-3 mm morbilliform rash on the trunk (Fig. 256-1). The rash usually lasts 1-3 days but is often described as evanescent and may be visible only for hours, spreading

Figure 256-1 Roseola infantum. Erythematous, blanching macules and papules **(A)** in an infant who had high fever for 3 days preceding development of the rash. On closer inspection **(B),** some lesions reveal a subtle peripheral halo of vasoconstriction. *(From Paller AS, Mancinin AJ, editors:* Hurwitz clinical pediatric dermatology, *ed 3. Philadelphia, 2006, Elsevier, p. 434.)*

from the trunk to the face and extremities. Because the rash is variable in appearance, location, and duration, it is not distinctive. Associated signs are few but can include mild injection of the pharynx, palpebral conjunctivae, or tympanic membranes and enlarged suboccipital nodes. In Asian countries, ulcers at the uvulopalatoglossal junction (**Nagayama spots**) are commonly reported in infants with roseola.

High fever (mean: 39.7°C [103.5°F]) is the most consistent finding associated with primary HHV-6B infection. Rash detected either during the illness or following defervescence has been reported in approximately 20% of infected children in the United States. Additional symptoms and signs include irritability, inflamed tympanic membranes, rhinorrhea and congestion, gastrointestinal complaints, and encephalopathy. Symptoms of lower respiratory tract involvement such as cough are identified significantly less frequently in children with primary HHV-6B infection than in children with other febrile illnesses. The mean duration of illness caused by primary HHV-6B infection is 6 days, with 15% of children having fever for 6 or more days. Primary infection with HHV-6B accounts for a significant burden of illness on the healthcare system; 1 study found that 24% of visits to emergency departments by infants between 6 and 9 mo of age were because of primary HHV-6B infection. A population-based study of primary HHV-6B infection confirmed that 93% of infants had symptoms and were more likely to visit a physician than noninfected infants. Fever was less likely to be present with HHV-6B infection in children younger than 6 mo of age but was significantly more common in older infants and children.

Much less is known about the clinical manifestations of HHV-7 infection. Primary infection with HHV-7 has been identified in a small number of children with roseola in whom the illness is indistinguishable from that caused by HHV-6B. Secondary cases of roseola caused by infection with HHV-7 have also been reported. Additionally, primary infection with HHV-7 may be asymptomatic or may cause a nonspecific febrile illness lasting approximately 3 days.

LABORATORY FINDINGS

The most characteristic laboratory findings noted in children with primary HHV-6B infection are lower mean numbers of total white blood cells (8,900/µL), lymphocytes (3,400/µL), and neutrophils (4,500/µL), than in febrile children without primary HHV-6B infection. Similar hematologic findings have been reported during primary infection with HHV-7. Thrombocytopenia, elevated serum transaminase values, and atypical lymphocytes have also been noted sporadically in children with primary HHV-6B infection.

Results of CSF analyses reported in patients with encephalitis thought to be caused by HHV-6 have been normal or demonstrated only minimal CSF pleocytosis with mild elevations of protein, especially early in the course of the disease, which may progress with time. Areas of hyperintense signal on T2-weighted and fluid attenuation inversion recovery images of the hippocampus, uncus, and amygdala have been found on MRI, as well as increased metabolism within the hippocampus on positron emission tomography scanning.

DIAGNOSIS

Although roseola is generally a benign self-limited disease, its diagnosis can exclude other, more serious disorders that cause fever and rash. A history of 3 days of high fever in an otherwise nontoxic 10 mo old infant with a blanching maculopapular rash on the trunk suggests a diagnosis of roseola. Likewise, a specific diagnosis of HHV-6 is not usually necessary except in situations in which the manifestations of the infection are severe or unusual and might benefit from antiviral therapy.

The diagnosis of primary infection with either HHV-6 or HHV-7 is confirmed by demonstrating the presence of actively replicating virus in the patient's blood sample coupled with seroconversion. Viral culture is the gold standard method to document active viral replication. Unfortunately, culture is expensive, time-consuming, and available only in research laboratories. Two other methods used to identify active HHV-6 replication are the detection of viral DNA by PCR on *acellular fluids* such as plasma or reverse transcriptase PCR on peripheral blood mononuclear cell samples designed to detect viral transcription and protein production. Quantitative PCR for HHV-6 genome copy numbers on various specimens is also frequently reported and is commercially available. However, the role of this methodology is not clear, as a specific value of DNA that can discriminate between patients with viremia and those who are culture negative has not been determined. *Complicating the use of molecular assays for the detection of active replication of HHV-6 is the recognition that individuals with chromosomally integrated HHV-6 have persistent HHV-6 DNA in plasma, peripheral blood mononuclear cells, and CSF in the absence of disease and replicating virus.*

Serologic methods including indirect immunofluorescence assays, enzyme-linked immunosorbent assays, neutralization assays, and immunoblot have been described for the measurement of concentrations of antibodies to HHV-6 and HHV-7 in serum or plasma and are commercially available. Although immunoglobulin M antibody is produced early in infection with HHV-6, assays designed to measure this response have not proved useful in the diagnosis of primary or reactivated infection. The absence of immunoglobulin G antibody in an infant older than 6 mo of age combined with the presence of replicating virus is strong evidence of primary infection with either HHV-6 or HHV-7. Alternatively, the demonstration of seroconversion between acute and convalescent samples also confirms primary infection but is not clinically useful in the acute care setting. Unfortunately, serologic assays have not been found reliable in the detection of HHV-6 reactivation and cannot be used to differentiate between infection with HHV-6A and HHV-6B. Additionally, limited antibody cross-reactivity has been demonstrated between HHV-6 and HHV-7, complicating the interpretation of serologic assays, especially if low titers are reported.

Differential Diagnosis

Primary infection with either HHV-6B or HHV-7 usually causes an undifferentiated febrile illness that may be very difficult to distinguish from other common viral infections of childhood. This difficulty also applies to the early stages of roseola, before the development of rash. Once the rash is present, roseola may be confused with other exanthematous diseases of childhood, especially measles and rubella. Children with **rubella** often have a prodrome characterized by mild illness with low-grade fever, sore throat, arthralgia, and gastrointestinal complaints, unlike those with roseola. On physical examination, suboccipital and posterior auricular lymph nodes are prominent up to 1 wk before the rash of rubella is evident and persist during the exanthematous phase. Additionally, the rash of rubella usually begins on the face and spreads to the chest, like that in measles. The associated symptoms of **measles** virus infection include cough, coryza, and conjunctivitis, with high fever coincident with the development of rash, unlike in roseola. Roseola may also be confused with scarlet fever, though the latter is rare in children younger than 2 yr of age and causes a characteristic sandpaper-like rash concurrent with fever.

Roseola may be confused with illness caused by enterovirus infections, especially in the summer and fall months. Drug hypersensitivity reactions may also be difficult to distinguish from roseola. Antibiotics are frequently prescribed for children with fever from roseola before the appearance of rash. A child who then demonstrates rash after the resolution of fever may erroneously be labeled as being drug allergic.

COMPLICATIONS

Convulsions are the most common complication of roseola and are recognized in up to one third of patients. Seizures are also the most common complication of children with primary HHV-6B infection, occurring in approximately 15%, with a peak age of 12-15 mo. Children with primary HHV-6B infection are also reported to have a higher frequency of partial seizures, prolonged seizures, postictal paralysis, and repeated seizures than are children with febrile seizures

not associated with HHV-6. In a study limited to children with primary HHV-6B infection and seizures, 30% of patients had prolonged seizures, 29% had focal seizures, and 38% had repeated seizures. A prospective study of children 2-35 mo of age with suspected encephalitis or severe febrile illness with convulsions found that 17% had primary infection with either HHV-6 or HHV-7, and status epilepticus was the most common presentation. Among children with febrile status epilepticus (FSE), primary or reactivated infection with HHV-6B or HHV-7 has been identified in approximately one third.

An association between recurrent seizures and reactivated or persistent infection of the central nervous system by HHV-6 has also been suggested. Studies evaluating brain tissue specimens implicate HHV-6 in as many as 35% of patients with temporal lobe epilepsy, high viral loads being found in the hippocampus or lateral temporal lobe regions. HHV-6 protein production has also been identified in a small number of resected tissue specimens. Primary astrocytes obtained from these samples had undetectable levels of a glutamate transporter, suggesting the loss of ability to control glutamate levels as a possible mechanism for the development of recurrent seizures. Contrary to these findings, limited clinical data suggest that there may be a decreased risk of recurrent seizures after primary infection with HHV-6 and febrile seizures than of febrile seizures from other causes. Additionally, children with FSE associated with HHV-6B and HHV-7 had similar seizure characteristics and a similar proportion of electroencephalography and MRI hippocampal abnormalities as children with FSE not associated with HHV-6B or HHV-7, suggesting a shared pathogenesis to other etiologies of FSE. Further study is needed to determine if there is a link between HHV-6 and HHV-7 infection and epilepsy.

Case reports and small patient series have described additional complications in children with primary HHV-6B infection, including encephalitis, acute disseminated demyelination, autoimmune encephalitis, acute cerebellitis, hepatitis, and myocarditis. Late-developing long-term sequelae, including developmental disabilities and autistic-like features, are reported rarely in children who have central nervous system symptoms during primary HHV-6B infection.

Reactivation of HHV-6 has been reported in several different populations with and without disease with the use of various methods of detection. The best documentation of HHV-6 reactivation has been in immunocompromised hosts, especially those patients who have undergone HSCT. Such reactivation occurs in approximately 50% of patients, typically at 2-4 wk after transplantation. Many of the clinical complications seen following HSCT have been associated with HHV-6B reactivation, including fever, rash, delayed engraftment of platelets or monocytes, and graft-versus-host disease with variable degrees of support in the literature for each.

HHV-6B reactivation has also been reported as a cause of encephalitis in both normal and immunocompromised hosts. A distinct syndrome of *posttransplant acute limbic encephalitis (PALE)* has been described primarily in patients following HSCT, especially cord blood stem cell transplantation; it is characterized by short-term memory dysfunction, confusion, and insomnia with seizures noted either clinically or on prolonged electroencephalography monitoring. HHV-6B DNA has been identified in the CSF in the majority of these patients with additional evidence of reactivation by detection of HHV-6B DNA in plasma. HHV-6 proteins were identified in the astrocytes of the hippocampus in 1 postmortem specimen, consistent with active HHV-6B infection at the time of death. The development of PALE is associated with increased mortality and long-term neurocognitive sequelae.

TREATMENT

Supportive care is usually all that is needed for infants with roseola. Parents should be advised to maintain hydration and may use antipyretics if the child is especially uncomfortable with the fever. Specific antiviral therapy is not recommended for routine cases of primary HHV-6B or HHV-7 infection. Unusual or severe manifestations of primary or presumed reactivated HHV-6B infection such as encephalitis/PALE, especially in immunocompromised patients, may benefit from treatment. Ganciclovir, foscarnet, and cidofovir all demonstrate inhibitory activity against HHV-6 in vitro similar to their activity against cytomegalovirus. Case reports suggest that all 3 drugs, alone or in combination, can decrease HHV-6 viral replication, as evidenced by decreased viral loads in plasma and CSF. However, clinical data regarding efficacy are sparse and contradictory, with no randomized trials to guide use. Additionally, in vitro resistance of HHV-6 to all 3 drugs has been described. Despite these drawbacks, treatment with ganciclovir or foscarnet as first-line agents has been recommended for a minimum of 3 wk in patients with PALE. Foscarnet appears to be most likely to have activity against HHV-7 on the basis of in vitro testing, but no clinical data are available.

PROGNOSIS

Roseola is generally a self-limited illness associated with complete recovery. The majority of children with primary infections with HHV-6B and HHV-7 also recover uneventfully without sequelae. Although seizures are a common complication of primary infection with HHV-6B and HHV-7, the risk of recurrent seizures does not appear to be higher than that associated with other causes of simple febrile seizures.

PREVENTION

Primary infections with HHV-6 and HHV-7 are widespread throughout the human population with no current means of interrupting transmission.

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Chapter 257

Human Herpesvirus 8

Mary T. Caserta

Human herpesvirus 8 (HHV-8) was first identified in tissue specimens from patients with **Kaposi sarcoma (KS)**. Because of this association, it is also known as **Kaposi sarcoma–associated herpesvirus**. HHV-8 has since been recognized as the etiologic agent of 2 additional lymphoproliferative disorders: **primary effusion–based lymphoma (PEL)** and **multicentric Castleman disease**.

ETIOLOGY

HHV-8 is a γ_2-human herpesvirus similar to Epstein-Barr virus. The virus contains a large DNA genome encoding 85-95 unique proteins. Infection is followed by both lytic and latent viral states with different degrees of viral replication associated with distinct disease manifestations.

EPIDEMIOLOGY

The prevalence of infection with HHV-8 varies both geographically and by population and roughly matches the epidemiology of KS. HHV-8 infection is endemic in Africa and parts of South America, with infection rates of up to 30-60% by adolescence. Seroprevalence >20% has also been found in regions bordering the Mediterranean. In contrast, infection rates <5% are noted in North America, central Europe, and Asia. However, within geographic regions, the prevalence

of infection varies with risk behaviors, rates of 30-75% being found among men who have sex with men in North America and Europe. HHV-8 DNA can be detected in saliva, blood, and tissues. Based upon large-scale epidemiologic studies, the current consensus is that saliva is the major mode of transmission. Other less-common routes of HHV-8 transmission include blood transfusion, bone marrow transplantation, and solid organ transplantation. Vertical transmission may occur in regions where HHV-8 is highly endemic, but the risk appears low.

PATHOLOGY AND PATHOGENESIS

HHV-8 contains multiple genes that impact cell-cycle regulation and the host immune response. Viral proteins interfere with the function of the tumor suppressor molecules p53 and retinoblastoma protein, induce the expression of proangiogenesis factors vascular endothelial growth factor A and vascular endothelial growth factor receptor-2, and lead to upregulation of the human mammalian target of rapamycin pathway, which is instrumental in the control of cell growth and metabolism. HHV-8 also encodes a homolog of human interleukin-6, which can bind and activate cytokine receptors and serve as a host cell autocrine growth factor. Additionally, viral proteins are associated with the constitutive expression of the transcription factor nuclear factor-κB. All of these proteins may be potential targets for therapeutic intervention.

CLINICAL MANIFESTATIONS

Although subclinical infection appears to be common, symptomatic primary HHV-8 infection has been described in immunocompetent children. Patients commonly had fever and a maculopapular rash or a mononucleosis-like syndrome, with full recovery the rule. In immunocompromised patients, primary infection has been associated with fever, rash, splenomegaly, pancytopenia, and lymphoid hyperplasia, and may be quite severe. Additionally, preliminary data suggest that transfusion-associated primary infection with HHV-8 is associated with an increased risk of mortality.

KS has several different clinical forms; each includes multifocal, angiogenic lesions arising from vascular endothelial cells infected with HHV-8. Classic KS is an indolent disorder seen in elderly men with limited involvement of the skin of the lower extremities. Endemic KS is more aggressive, occurring in children and young people, primarily in Africa, and can include visceral involvement as well as widespread cutaneous lesions (patches, plaques, or nodules). Posttransplantation KS and AIDS-related KS are the most severe forms, with disseminated lesions, often in the gastrointestinal tract and lungs, in addition to the skin.

Primary effusion–based lymphoma is a rare disease caused by HHV-8 that is seen most commonly in HIV-infected individuals. It consists of lymphomatous invasion of the serosal surfaces of the pleura, pericardium, and peritoneum. Similarly, **multicentric Castleman disease** is an unusual lymphoproliferative disorder characterized by anemia, thrombocytopenia, generalized lymphadenopathy, and constitutional symptoms and frequently associated with HHV-8 infection and a high degree of viral replication.

DIAGNOSIS

Serologic assays, including immunofluorescence and enzyme-linked immunosorbent assays, are the primary methods of diagnosing infection with HHV-8. However, testing has limited sensitivity, specificity, and reproducibility and is primarily a research tool with no universally recognized standard assays. Additionally, the loss of antibodies over time, referred to as *seroreversion,* has been described, further complicating serodiagnosis. Immunohistochemistry and molecular methods are available for the detection of the HHV-8 genome in tissue samples and are utilized in the diagnosis of KS, PEL, and multicentric Castleman disease.

TREATMENT

Treatment for KS, PEL, and multicentric Castleman disease is multifaceted and includes attempts to control malignant proliferations with traditional chemotherapeutic regimens and biologic agents as well as agents aimed at specific cellular pathways targeted by HHV-8 proteins. Highly active antiretroviral treatment (HAART) is a mainstay of both prevention and therapy for HHV-8 related disease in HIV-infected patients. In HIV associated KS, treatment with HAART alone is often used for the control of mild disease, while HAART plus chemotherapy is utilized for more severe disease. In transplantation-associated KS, the first line of treatment includes decreasing immunosuppression, often in association with a switch from calcineurin inhibitors to sirolimus (rapamycin) to block the mammalian target of rapamycin pathway. Severe disease frequently requires the use of traditional chemotherapy as well. The role of specific antiherpesvirus antiviral treatment is unclear. Oral valganciclovir decreases both the quantity and frequency of detection of HHV-8 in saliva, and ganciclovir treatment has been associated with decreased rates of development of KS in HIV-infected individuals. However, results of using antivirals in the treatment of established disease have been generally disappointing. The prognosis for PEL tends to be poor despite the use of traditional chemotherapy, while rituximab (anti-CD20) shows promise in the treatment of multicentric Castleman disease, both alone and in combination with chemotherapy. Rituximab treatment may worsen concurrent KS.

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Chapter 258

Influenza Viruses

Fiona P. Havers and Angela J.P. Campbell

Influenza viral infections cause a broad array of respiratory illnesses that are responsible for significant morbidity and mortality in children. Influenza A viruses also have the potential to cause periodic global pandemics with even higher penetrance of illness than seasonal epidemics.

ETIOLOGY

Influenza viruses are large, single-stranded RNA viruses belonging to the family Orthomyxoviridae, which includes 3 genera (or types): A, B, and C. Influenza A and B viruses are the primary human pathogens, causing seasonal epidemics, while influenza virus type C is a sporadic cause of predominantly mild upper respiratory tract illness. Influenza A viruses are further divided into subtypes based on 2 surface proteins that project as spikes from the lipid envelope, the hemagglutinin (HA) and neuraminidase (NA) proteins (Fig. 258-1). Strain variants are identified by antigenic differences in their HA and NA and are designated by the geographic area from which they were originally isolated, isolate number, and year of isolation—for example, influenza A/Victoria/361/2011(H3N2). The HA and NA antigens from influenza B and C viruses do not receive subtype designations, as there is less variation among influenza B and C antigens.

EPIDEMIOLOGY

Influenza has generally been thought to be transmitted primarily via respiratory droplets, but transmission via contact with secretions and small-particle aerosols may also occur. The incubation period is short, ranging from 12-72 hr. Seasonal influenza incidence peaks during colder months in temperate climates and circulates throughout

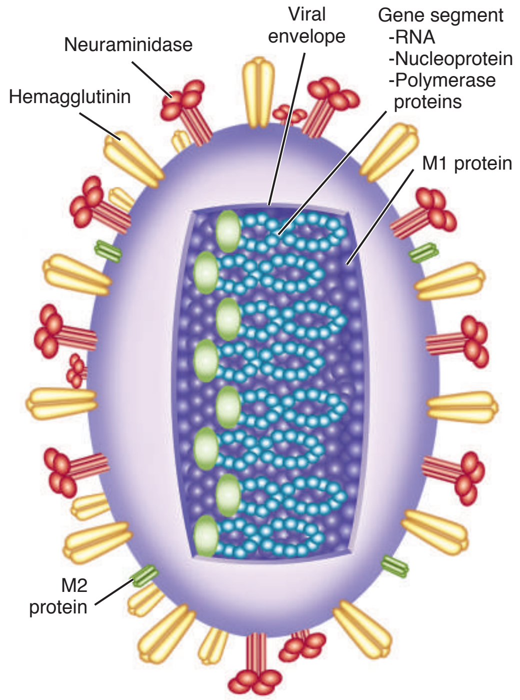

Figure 258-1 Schematic of influenza A virus. *(From Treanor JJ: Influenza viruses, including avian influenza and swine influenza. In Mandell GL, Bennet JE, Dolin R, editors:* Mandell, Douglas, and Bennet's principles and practice of infectious diseases, *ed 7. Philadelphia, 2009, WB Saunders,* Fig. 165-2.*)*

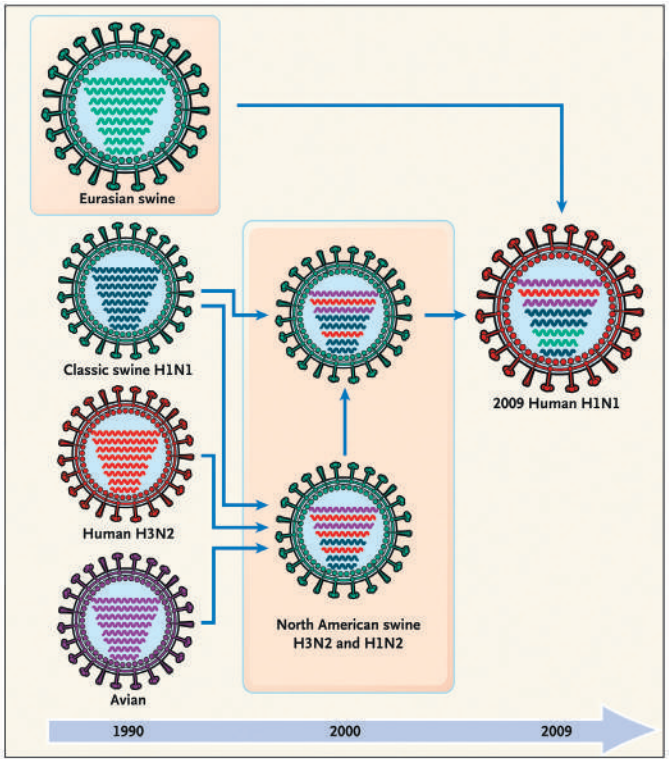

Figure 258-2 History of reassortment events in the evolution of the 2009 influenza A (H1N1) virus. The 8 segments shown within each virus code for the following proteins of the influenza A virus *(top to bottom):* polymerase PB2, polymerase PB1, polymerase PA, hemagglutinin, nuclear protein, neuraminidase, matrix proteins, and nonstructural proteins. The segments of the human 2009 influenza A (H1N1) virus have coexisted in swine influenza A virus strains for more than 10 yr. *(From Trifonov V, Khiabanian H, Rabadan R. Geographic dependence, surveillance, and origins of the 2009 influenza A [H1N1] virus.* N Engl J Med *361(2):115–119, 2009, Fig. 1.)*

the year in the tropics. Transmission through a community is rapid, with the highest incidence of illness occurring within 2-3 wk of introduction.

Antigenic Variation

Influenza A and B viruses contain a genome consisting of 8 single-strand RNA segments. Minor changes within a subtype continually occur through point mutations during viral replication, particularly in the HA gene, and result in new influenza strains of the same HA type. This phenomenon, termed *antigenic drift*, occurs in both influenza A and B viruses. Variation in antigenic composition of influenza virus surface proteins occurs almost yearly, which confers a selective advantage to a new strain and results in annual epidemics.

Major changes in subtype, less frequent but more dramatic, can occur through reassortment of viral gene segments when there is simultaneous infection by more than 1 strain of influenza in a single host. This process is called *antigenic shift,* and can occur in humans or animal hosts, resulting in emergence of novel subtypes. This occurs in influenza A viruses, which have multiple avian and mammalian hosts acting as reservoirs for diverse strains.

Through the process of reassortment, potentially any of 18 HA and 10 NA proteins currently known to reside in influenza A viruses of nonhuman hosts could be introduced into humans, who may have little existing immunologic cross protection to emerging viruses. A global pandemic can result if an influenza A virus with a novel HA or NA enters a nonimmune human population and acquires the capacity for sustained and efficient transmission between people. In the last 100 yr, 4 major global pandemics have occurred: in 1918 (caused by an influenza A[H1N1] virus), 1957 (A[H2N2]), 1968 (A[H3N2]), and 2009 (caused by an influenza A[H1N1] virus designated (A[H1N1]pdm09). The most severe pandemic in recorded history occurred in 1918, when the virus was estimated to have killed an estimated 50 million people. The 1918 pandemic virus was likely the result of direct adaptation of an avian influenza virus to the human host, rather than from reassortment. The 2009 pandemic stemmed from reassortment of genes from swine, avian, and human viruses (Fig. 258-2). This resulted in the emergence of a novel influenza A(H1N1) virus that spread quickly from North America across the globe, and has replaced the previously circulating seasonal H1N1 viruses.

In addition to the 2009 H1N1 pandemic, several other novel influenza strains, all originating in animals, have recently caused outbreaks of human infections. Avian influenza A(H5N1), a virulent avian influenza strain that was first identified in 1997, has caused more than 600 documented cases in 15 countries, with a 60% mortality rate. Another novel avian influenza, A(H7N9)—which first caused an outbreak of human infections in China during the spring of 2013 and second larger outbreak beginning fall 2014—also appears highly virulent; it has been fatal in more than one third of cases. In addition, a novel influenza A(H3N2v) virus caused more than 300 confirmed human infections in the United States from 2011-2013. Influenza viruses that normally circulate in swine are designated variant ("v") viruses when detected in humans. In contrast to avian influenza A(H5N1) and A(H7N9), this H3N2v influenza virus caused generally mild illness, primarily in children with swine contact at agricultural fairs. However, none of these viruses has exhibited sustained, efficient human-to-human transmission.

Seasonal Influenza

An estimated 20,000 children younger than 5 yr of age are hospitalized annually in the United States as a result of seasonal influenza-associated

complications, with hospitalization and mortality rates greatest in infants. Since 2004, the annual number of reported influenza-associated pediatric deaths in the United States has ranged from 34-149 during regular influenza seasons (it was 348 during the 2009 H1N1 pandemic). Influenza disproportionately affects children with specific chronic conditions, such as underlying pulmonary, cardiac, or neurologic and neuromuscular disorders. Very young children, especially those younger than 2 yr of age, and children with chronic medical conditions are more likely to develop severe influenza-related complications, including viral and bacterial pneumonia, respiratory failure, and death. However, while children with underlying medical conditions are at higher risk of complications, many healthy children are hospitalized with influenza, and nearly half of pediatric influenza-associated deaths are in children that have no known underlying medical condition.

Hospitalizations represent a small fraction of influenza-associated healthcare use; the proportion of outpatient visits resulting from influenza ranges from 10-25% annually in children younger than 5 yr of age. Influenza may also be underdiagnosed. Many who seek medical care for influenza do not have laboratory testing performed and do not receive a diagnosis of influenza. Children with primary influenza infection have higher influenza viral loads and more prolonged viral shedding than adults, making children extremely effective transmitters of infection. Nosocomial outbreaks of influenza can cause significant morbidity.

Every year, 3-4 influenza virus types or subtypes typically cocirculate, including H3N2, H1N1, and B viruses. Although 1 subtype usually predominates in any given season, it is difficult to predict which will be predominant. Thus, the influenza vaccine varies annually and contains 3 or 4 antigens representing the expected circulating types.

PATHOGENESIS

Influenza viruses infect the respiratory tract epithelium, primarily the ciliated columnar epithelial cells, by using the HA to attach to sialic acid residues. Virus is then adsorbed and virus replication occurs, usually within 4-6 hr. Infectious virus is then released, infecting neighboring cells and allowing the virus to spread rapidly. Influenza virus is rarely detected in extrapulmonary sites. With primary infection, virus replication continues for 10-14 days. Influenza virus causes a lytic infection of the respiratory epithelium with loss of ciliary function, decreased mucus production, and desquamation of the epithelial layer. These changes permit secondary bacterial invasion, either directly through the epithelium or, in the case of the middle ear space, through obstruction of the normal drainage through the eustachian tube.

The exact immune mechanisms involved in termination of primary infection and protection against reinfection are complex. Induction of cytokines that inhibit viral replication, such as interferon and tumor necrosis factor, as well as other host defenses, such as cell-mediated immune responses and local and humoral antibody defenses, all likely play a role. Secretory antibodies produced by the respiratory mucosa immunoglobulin A antibodies are thought to be an effective and immediate response generated during influenza infection. Serum antibody levels inhibiting HA activity can usually be detected by the 2nd wk after infection. These antibodies are also generated by vaccines, and high HA inhibition titers correlate with protection.

CLINICAL MANIFESTATIONS

The onset of influenza illness is often abrupt, with a predominance of systemic symptoms including fever, myalgias, chills, headache, malaise, and anorexia. Coryza, pharyngitis, and dry cough are also usually present at the onset of illness but may be less prominent than systemic symptoms. Respiratory manifestations can include isolated upper respiratory tract illness, including croup, or progression to lower tract disease, such as bronchiolitis or pneumonia. More than any other respiratory virus, influenza virus causes systemic manifestations such as high temperature, myalgia, malaise, and headache.

Abdominal pain, vomiting, and diarrhea may also occur in children; in some studies, diarrhea was reported to be more often associated with 2009 H1N1 compared with seasonal influenza. Influenza is a less-distinct illness in younger children and infants. The infected young infant or child may be highly febrile and toxic in appearance, prompting a full diagnostic work-up. The typical duration of the febrile illness is 2-4 days. Cough may persist for longer periods, and evidence of small airway dysfunction is often found weeks later. Owing to the high transmissibility of influenza, other family members or close contacts of an infected person often experience a similar illness.

COMPLICATIONS

Otitis media and pneumonia are common complications of influenza in young children. Acute otitis media may be seen in up to 25% of cases of documented influenza. Pneumonia accompanying influenza may be a primary viral process or a secondary bacterial infection (usually *Staphylococcus aureus*) facilitated through damaged respiratory epithelium. Unusual clinical manifestations of influenza include acute myositis seen with influenza type B, marked by muscle weakness and pain, particularly in the calf muscles, and myoglobinuria. Influenza types A and B are reported to cause myocarditis. Toxic shock syndrome can be associated with toxin-producing staphylococcal colonization. Central nervous system complications, such as encephalitis, myelitis, and Guillain-Barré syndrome, can occur and are seen more commonly in children than adults. Although it has essentially disappeared in the United States, Reye syndrome can result with the use of salicylates during influenza type B infection (see Chapter 361). Influenza is particularly severe in children with underlying cardiopulmonary disease, including congenital and acquired valvular disease, cardiomyopathy, bronchopulmonary dysplasia, asthma, cystic fibrosis, and neuromuscular diseases affecting the accessory muscles of breathing. Pregnant women are at special risk for severe influenza. In children receiving cancer chemotherapy and children with immunodeficiency, virus is shed for longer periods, with higher risk of complications.

LABORATORY FINDINGS

The clinical laboratory abnormalities associated with influenza are nonspecific. Relative leukopenia is frequently seen. Chest radiographs may show evidence of atelectasis or infiltrate.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of influenza depends on epidemiologic, clinical, and laboratory considerations. In the context of an epidemic, the clinical diagnosis of influenza in a young child who has fever without a focus, malaise, and respiratory symptoms may be made with some certainty; however, clinical presentation is often indistinguishable from other respiratory viruses, including respiratory syncytial virus, parainfluenza virus, human metapneumovirus, adenovirus, and even rhinovirus. Although confirmation of influenza virus infection by diagnostic testing is not required for clinical decisions to prescribe antiviral medications, prompt suspicion or diagnosis of influenza may allow for early antiviral therapy to be initiated and may reduce inappropriate use of antibiotics. A number of diagnostic tests may be used for laboratory confirmation of influenza (Table 258-1).

Although rapid influenza diagnostic tests are often employed because of their ease of use and fast results, they can have suboptimal sensitivity to detect influenza virus infection, particularly for novel influenza viruses. Sensitivities of rapid diagnostic tests are generally 50-70%, although a range of 10-80% has been reported, compared to viral culture or reverse-transcription polymerase chain reaction. Specificities are higher, approximately 95-100%. Therefore, false-negative results occur more often than false-positive results. The interpretation of negative results should take into account the clinical characteristics and the patient's risk for complications. If there is clinical suspicion for influenza in a patient at high risk for complications (Table 258-2), early empiric treatment should be given regardless of a negative rapid diagnostic test result, and another type of test (e.g., reverse-transcription

Table 258-1 Influenza Virus Testing Methods

METHOD	ACCEPTABLE SPECIMENS	TEST TIME	COMMENTS
Rapid influenza diagnostic tests	Nasopharyngeal (NP) swab, throat swab, nasal wash, nasal aspirate	<30 min	Rapid turnaround; suboptimal sensitivity
Immunofluorescence, direct (DFA) or indirect (IFA) antibody staining	NP swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hr	Relatively rapid turnaround; requires laboratory expertise and experience
RT-PCR* (single and multiplex; real-time and other RNA-based) and other molecular assays	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	Varied (generally 1-6 hr)	Excellent sensitivity, relatively rapid turnaround
Rapid cell culture (shell vials culture)	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	1-3 days	Culture isolates important for strain information and antiviral resistance monitoring
Viral cell culture (conventional)	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 days	
Serologic tests (antibody detection)	Paired acute and convalescent sera	N/A (not performed during acute infection)	Not generally recommended for routine patient diagnosis

*Reverse transcription polymerase chain reaction

Adapted from Centers for Disease Control and Prevention (CDC): Rapid diagnostic testing for influenza: information for health care professionals*; available at http://www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm#table*

Table 258-2 Children and Adolescents Who Are at Higher Risk for Influenza Complications*

Children younger than 2 yr of age†
Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
Persons with immunosuppression, including that caused by medications or by HIV infection
Adolescents who are pregnant or postpartum (within 2 wk after delivery)
Persons younger than 19 yr of age who are receiving long-term aspirin therapy
American Indians/Alaska Natives
Persons who are morbidly obese
Residents of long-term care facilities

Current for 2014-2015 influenza season.

*Antiviral treatment is recommended for high-risk children with confirmed or suspected influenza; antivirals are also recommended for children who are hospitalized or have severe or progressive disease.

†Although all children younger than 5 yr of age are considered at higher risk for complications from influenza, the highest risk is for those younger than 2 yr of age, with the highest hospitalization and death rates among infants younger than 6 mo of age.

Adapted from Centers for Disease Control and Prevention (CDC): Influenza antiviral medications: summary for clinicians. *Available at http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. For current details, consult annually updated recommendations at http://www.cdc.gov/flu*

polymerase chain reaction, direct fluorescent antibody, or viral culture) may be performed for confirmation.

TREATMENT

Two classes of antiviral drugs are licensed for treatment of influenza in children. The NA inhibitors, oseltamivir and zanamivir, may be used for treatment of children from the ages of 2 wk and 7 yr, respectively (Table 258-3). These drugs are generally given either by inhalation (zanamivir) or oral administration (oseltamivir). In December 2012, the FDA approved the use of oseltamivir for the treatment of influenza in infants as young as 2 wk of age, and the Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics recommend its use in all infants. Investigational intravenous zanamivir is also available for compassionate use under an emergency investigational new drug request.

The second class of drugs, adamantanes, includes amantadine and rimantadine, which are effective only against influenza A viruses. These 2 antivirals are not effective against influenza type B strains and are not approved for use in children younger than 5 yr of age. Genetic mutations have conferred widespread adamantane resistance among circulating influenza A (H3N2) and A(H1N1)pdm09 viruses; therefore, this class of antivirals is not currently recommended for use. Many H5N1 viruses and the H7N9 avian influenza viruses detected in 2013 and 2014 are also resistant to amantadine and rimantadine. It is important to review annual recommendations and updates published by the CDC before prescribing influenza antiviral medications.

When initiated early in the course of uncomplicated influenza illness, antiviral agents can reduce the duration of symptoms and the likelihood of complications. Among hospitalized patients, observational studies suggest that early treatment reduces disease severity and mortality. Most data regarding potential benefit are for adults; however, a few studies support the use of antiviral agents in children. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hr of influenza illness onset. Although early treatment is desired, treatment as early as possible, even more than 48 hr from onset, is recommended for hospitalized patients, patients with complicated or progressive illness, and patients at high risk for

Table 258-3 Centers for Disease Control and Prevention Recommended Dosage and Schedule of Influenza Antiviral Medications for Treatment and Chemoprophylaxis

ANTIVIRAL AGENT	USE	CHILDREN	ADULTS*
Oseltamivir (Tamiflu)	Treatment (5 days)	**If child is younger than 1 yr old†:** 3 mg/kg/dose twice daily‡ **If child is 1 yr or older, dose varies by child's weight:** 15 kg or less, the dose is 30 mg **twice** a day >15-23 kg, the dose is 45 mg **twice** a day >23-40 kg, the dose is 60 mg **twice** a day >40 kg, the dose is 75 mg **twice** a day	75 mg twice daily
	Chemoprophylaxis (7 days)	If child is younger than 3 mo old, use of oseltamivir for chemoprophylaxis is not recommended unless situation is judged critical because of limited data in this age group **If child's age is 3 mo or older and younger than 1 yr old†:** 3 mg/kg/dose **once** daily‡ **If child is 1 yr or older, dose varies by child's weight:** 15 kg or less, the dose is 30 mg **once** a day >15-23 kg, the dose is 45 mg **once** a day >23-40 kg, the dose is 60 mg **once** a day >40 kg, the dose is 75 mg **once** a day	75 mg once daily
Zanamivir¶ (Relenza)	Treatment (5 days)	**For children age 7 yr and older:** 10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) **twice** daily
	Chemoprophylaxis (7 days)	**For children age 5 yr and older:** 10 mg (two 5-mg inhalations) once daily	10 mg (two 5-mg inhalations) **once** daily

Current for 2013-2014 influenza season, United States.

*Intravenous peramivir (Rapivab) was approved on December 19, 2014, for use in the treatment of acute uncomplicated influenza in people 18 years and older.

†Oral oseltamivir is approved by the FDA for treatment of acute uncomplicated influenza with twice-daily dosing in persons older than 14 days of age, and for prophylaxis with once-daily dosing in persons 1 yr and older. Although not part of the FDA-approved indications, use of oral oseltamivir for treatment of influenza in infants younger than 14 days old, and for prophylaxis in infants 3 mo to 1 yr of age, is recommended by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics.

‡This is the FDA-approved oral and CDC-recommended oseltamivir treatment dose for infants 14 days and older and less than 1 yr old, and provides oseltamivir exposure in children similar to that achieved by the approved dose of 75 mg orally twice daily for adults, as shown in 2 studies of oseltamivir pharmacokinetics. The American Academy of Pediatrics recommends an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants ages 9-11 mo for the 2013-2014 season, on the basis of data that indicated that the higher dose of 3.5 mg/kg was needed to achieve the protocol-defined targeted exposure for this cohort as defined in the Collaborative Antiviral Study Group (CASG) 114 study. It is unknown whether this higher dose will improve efficacy or prevent the development of antiviral resistance. However, there is no evidence that the 3.5 mg/kg dose is harmful or causes more adverse events to infants in this age group.

¶Inhaled zanamivir is approved for treatment of acute uncomplicated influenza with twice-daily dosing in persons age 7 yr and older, and for prophylaxis with once-daily dosing in persons age 5 yr and older.

Adapted from Centers for Disease Control and Prevention (CDC): Influenza antiviral medications: summary for clinicians. *Available at http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. For current details, consult annually updated recommendations at http://www.cdc.gov/flu*

influenza complications (see Table 258-2). **Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza.** Currently, for hospitalized patients and patients with severe or complicated illness, treatment with oral or enterically administered oseltamivir (and not inhaled zanamivir) is recommended. The recommended treatment course for uncomplicated influenza is 2 doses per day of an NA inhibitor medication for 5 days; however, the optimal duration and dose are uncertain for severe or complicated influenza and longer courses of treatment (e.g., 10 days of treatment) may be considered.

Clinical judgment, on the basis of the patient's disease severity, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important when making antiviral treatment decisions for outpatients at high risk for complications. Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hr of illness onset.

Drug resistance can develop commonly during a course of amantadine or rimantadine therapy and has also been reported to emerge in patients receiving oseltamivir treatment. Antiviral medications should be considered an adjunct to vaccination.

SUPPORTIVE CARE

Adequate fluid intake and rest are important components in the management of influenza. Bacterial superinfections are relatively common and should be appropriately treated with antibiotic therapy. Bacterial superinfection should be suspected with recrudescence of fever, prolonged fever, or deterioration in clinical status. With uncomplicated influenza, children should start to feel better after the 1st 48-72 hr of symptoms.

PROGNOSIS

The prognosis for recovery from uncomplicated influenza is generally excellent, although full return to normal level of activity and freedom from cough usually requires weeks rather than days. Fatigue may also persist for weeks. However, severe influenza disease can be associated with hospitalizations and death, even among previously healthy children.

PREVENTION

Influenza vaccination is the best means of preventing severe disease caused by influenza. In studies of children who are fully vaccinated, influenza vaccine was approximately 50-80% effective in reducing the risk of laboratory-confirmed influenza illness. Vaccine effectiveness can vary from year to year and among different age and risk groups. Recommendations for use of the influenza vaccine have broadened as the impact of influenza is appreciated in such groups as *pregnant women* and *young infants*. Starting in the 2008-2009 influenza season, the Advisory Committee on Immunization Practices (ACIP) recommended that all children from 6 mo to 18 yr of age be vaccinated for influenza unless they have a specific contraindication to receiving the

vaccine. In 2012, the Department of Health in the United Kingdom announced plans to extend their influenza vaccination program at no charge to include all children between the ages of 2 and 17 yr. In addition, household contacts and out-of-home caregivers of children 0-6 mo of age are a targeted group so as to protect infants who are too young to receive vaccine. Chemoprophylaxis with antiviral medications is a secondary means of prevention, and not a substitute for vaccination.

Vaccines

There are 2 main categories of seasonal influenza vaccines available for children, inactivated influenza vaccine (IIV) and live-attenuated influenza vaccine (LAIV). Previously referred to as the trivalent inactivated vaccine, IIV is given intramuscularly; it uses killed virus components and cannot cause influenza virus infection. The LAIV vaccine uses weakened influenza virus and is administered as an intranasal spray. Starting in 2014-2015, ACIP and CDC recommended the use of the LAIV nasal spray vaccine for healthy children 2 through 8 yr of age, when it is immediately available and when no contraindications or precautions to that vaccine exist. LAIV is not recommended for children younger than 2 yr of age or children who are at higher risk of developing influenza complications. In addition, special vaccination instructions for children 6 mo to 8 yr of age should be followed: depending on vaccination history, some children will require 2 doses of seasonal influenza vaccine (administered a minimum of 4 wk apart) to optimize immune response (Fig. 258-3). Influenza vaccines have an excellent safety profile, with the most common side effects being soreness, redness, tenderness, or swelling from the injection, and nasal congestion after the nasal spray.

Inactivated and live-attenuated seasonal influenza vaccines become available in the late summer and early fall of each year. The formulation reflects the strains of influenza viruses that are expected to circulate in the coming winter. Beginning in the 2013-2014 season, IIVs were available in both trivalent and quadrivalent formulations. The trivalent vaccine (IIV3) contains 2 influenza A strains and 1 influenza B strain; the quadrivalent vaccine (IIV4) contains a second influenza B strain of an antigenically distinct lineage. In addition to IIV and LAIV vaccines, a third vaccine category, recombinant hemagglutinin influenza vaccine, became available as a trivalent formulation in the 2013-2014 season.

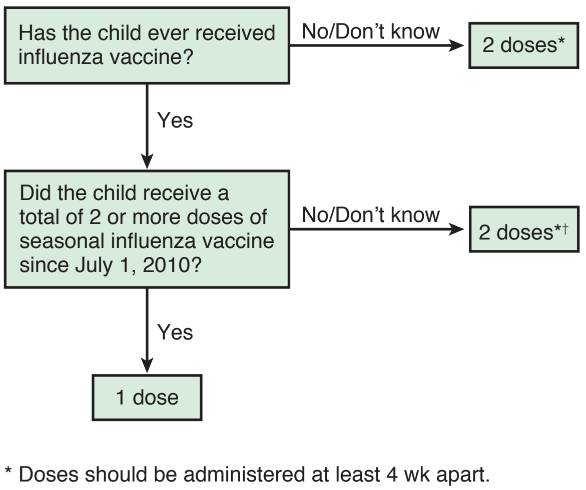

Figure 258-3 Influenza vaccine dosing algorithm for children 6 mo through 8 yr of age. *(From Centers for Disease Control and Prevention (CDC):* Summary recommendations: prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices–United States, 2014-15. *Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6332a3.htm.)*

Vaccination should be given as soon as vaccine is available, preferably before the onset of influenza circulation in the community, so that there is time for antibodies to reach protective levels. The ACIP publishes guidelines for vaccine use each year when the vaccines are formulated and released. These guidelines are widely publicized but appear initially in the *Morbidity and Mortality Weekly Report* published by the CDC.

Chemoprophylaxis

Routine use of antiviral medications for chemoprophylaxis is not recommended. Examples for which the use of chemoprophylaxis may be considered to prevent influenza after exposure to an infectious person include (1) unvaccinated persons at high risk of influenza complications, (2) persons for whom vaccine is contraindicated or expected to have low effectiveness, and (3) residents/patients in care facilities during institutional influenza outbreaks. NA inhibitors or adamantanes may be used for chemoprophylaxis of influenza; however, adamantanes are not currently recommended because of widespread adamantane resistance. Table 258-3 shows the recommendations for dosage and duration of treatment and chemoprophylaxis for the 2012-2013 influenza season, but updated recommendations from the ACIP and CDC should be consulted every season (http://www.cdc.gov/flu). In general, if chemoprophylaxis can be started within 48 hr of exposure to an infectious person, postexposure chemoprophylaxis for persons at high risk of influenza complications (see Table 258-2) is recommended for at least 7 days after the most recent exposure. An alternative to chemoprophylaxis for some persons after a suspected exposure is close monitoring and early initiation of antiviral treatment if symptoms develop. For control of outbreaks with seasonal influenza in long-term care facilities and hospitals, antiviral chemoprophylaxis should be considered for exposed vaccinated and unvaccinated high-risk patients, as well as unvaccinated healthcare providers. The CDC and the Infectious Disease Society of America recommend chemoprophylaxis for a minimum of 2 wk and up to 1 wk after the last known case is identified, whichever is longer.

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Chapter 259

Parainfluenza Viruses

Angela J.P. Campbell

Parainfluenza viruses (PIVs) are common causes of acute respiratory illness in infants and children and are important causes of lower respiratory tract disease in young children and immunocompromised persons. These viruses cause a spectrum of upper and lower respiratory tract illnesses but are particularly associated with croup (laryngotracheitis or laryngotracheobronchitis), bronchiolitis, and pneumonia.

ETIOLOGY

The PIVs are members of the Paramyxoviridae family. Four PIVs cause illness in humans, classified as types 1-4, with diverse manifestations of infection. Type 4 is divided into 2 antigenic subgroups, A and B. PIVs have a nonsegmented, single-stranded RNA genome with a lipid-containing envelope derived from budding through the cell membrane. The major antigenic moieties are the HN and F envelope spike glycoproteins, which exhibit hemagglutinin-neuraminidase and fusion functions, respectively.

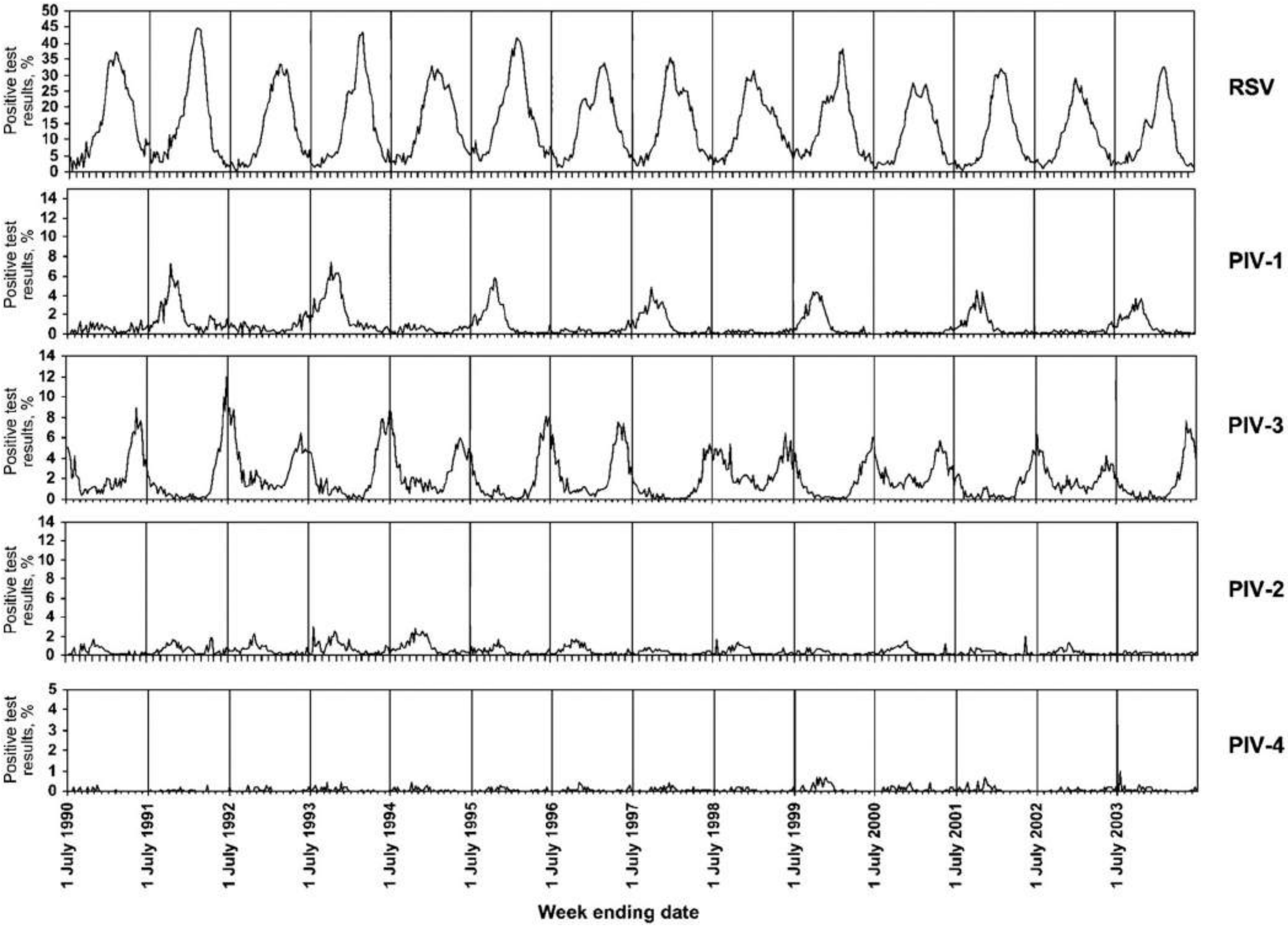

Figure 259-1 The percentage of tests positive for parainfluenza virus (PIV) serotypes 1, 3, 2, and 4 reported to the National Respiratory and Enteric Viruses Surveillance System (NREVSS), by week, July 1990-June 2004. The percentage of antigen detection tests positive for respiratory syncytial virus (RSV) reported to NREVSS is shown for comparison. (Note that RSV and PIV-4 have different axis scales than the other human PIV serotypes.) *(From Fry AM, Curns AT, Harbour K, Hutwagner L, Holman RC, Anderson LJ. Seasonal trends of human parainfluenza viral infections: United States, 1990-2004.* Clin Infect Dis *43:1016–1022, 2006, Fig. 1.)*

EPIDEMIOLOGY

By 5 yr of age, most children have experienced primary infection with PIV types 1, 2, and 3. PIV-3 infections often occur in the 1st 6 mo of life, with half of children estimated to be infected by age 1 year, and 90-100% by age 5 yr. PIV-1 and PIV-2 are more common after infancy, with 60-75% infected by age 5 yr. Although PIV-4 is not recognized as often, about half of children have antibody by the age of 5 yr. In the United States and temperate climates, PIV-1 has typically been reported to have biennial epidemics in the fall, sometimes noted to alternate years in which the serotype is most prevalent with PIV-2 (Fig. 259-1). PIV-2 has also been reported to cause yearly outbreaks. PIV-3 is endemic throughout the year but typically peaks in late spring. In years with less PIV-1 activity, the PIV-3 season has been observed to extend longer or to have a second peak in the fall (Fig. 259-1). The epidemiology of PIV-4 is less-well defined, because it is difficult to grow in tissue culture and was often excluded from previous studies, but newer studies show it to have an irregular epidemic pattern.

PIVs are spread primarily from the respiratory tract by inhalation of large respiratory droplets or contact with infected secretions. PIVs are notable for causing outbreaks of respiratory infections in hospital wards, clinics, neonatal nurseries, and other institutional settings. The incubation period from exposure to symptom onset is 2-6 days. Children are likely to excrete virus from the oropharynx for 2-3 wk, but excretion can be more prolonged even in immunocompetent children; in immunocompromised patients, excretion may persist for months. Primary infection does not confer permanent immunity, and reinfections are common throughout life. Reinfections are generally mild and self-limited.

PATHOGENESIS

PIVs replicate in the respiratory epithelium. The propensity to cause illness in the upper large airways is presumably related to preferential replication in the larynx, trachea, and bronchi in comparison with other viruses. Some PIVs induce cell-to-cell fusion. During the budding process, cell membrane integrity is lost, and viruses can induce cell death through the process of apoptosis. In children, the most severe illness coincides with the time of maximal viral shedding. However, disease severity is likely related to the host immune response to infection as much as to direct cytopathic effects of the virus.

Virus-specific immunoglobulin A antibody levels correlate with protection from PIV infection. Circulating serum antibody is also likely to play a role in protection against PIV acquisition and progression to severe infection. Patients with compromised cellular immunity have severe, prolonged disease, suggesting that T cells are critical to controlling and terminating PIV infection.

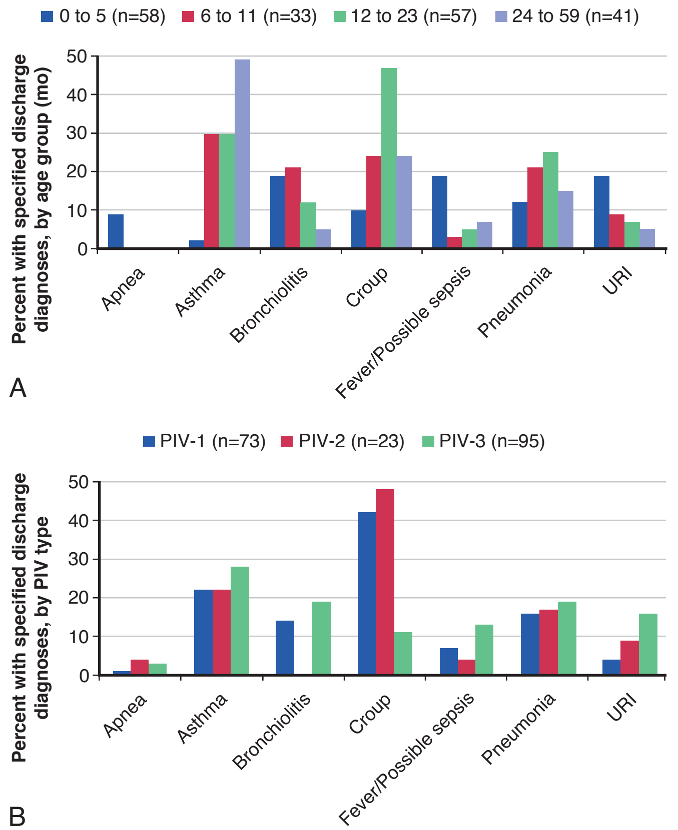

Figure 259-2 Selected discharge diagnoses of hospitalized children with parainfluenza (PIV) infection, by **(A)** age in months and **(B)** virus type. *(Adapted with data from Weinberg GA, Hall CB, Iwane MK, et al. Parainfluenza virus infection of young children: estimates of the population-based burden of hospitalization.* J Pediatr *154:694–699, 2009, Table II.)*

CLINICAL MANIFESTATIONS

The most common type of illness caused by PIV infection consists of some combination of low-grade fever, rhinorrhea, cough, pharyngitis, and hoarseness, and may be associated with vomiting or diarrhea. Rarely, PIV infection is associated with parotitis. Illness usually lasts 4-5 days. The generally mild illness pattern is belied by a spectrum of rarer but more serious illnesses that result in hospitalization (Fig. 259-2). PIVs account for 50% of hospitalizations for croup and at least 15% of cases of bronchiolitis and pneumonia. PIV-1, and to a lesser extent PIV-2, cause more cases of croup, whereas PIV-3 is more likely to infect the small air passages and cause pneumonia, bronchiolitis, or bronchitis. PIV-4 causes a similar range of illness as the other PIV types. Any PIV can cause lower respiratory tract disease, particularly during primary infection or in immunosuppressed patients. In children and adult patients with hematologic malignancies and undergoing hematopoietic stem cell transplantation, lymphopenia has repeatedly been shown to be an independent risk factor for progression from upper to lower respiratory tract disease.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of PIV infection in children is often based only on clinical and epidemiologic criteria. Croup is a clinical diagnosis and must be distinguished from foreign body aspiration, epiglottitis, pharyngeal abscess, and subglottic hemangioma. Although the radiographic "steeple sign," consisting of progressive narrowing of the subglottic region, is characteristic of croup, differential considerations include acute epiglottitis, thermal injury, angioedema, and bacterial tracheitis. Manifestation of PIV lower respiratory tract disease may be similar to that of a number of other respiratory viral infections; therefore, identification of virus should be specifically sought by the most sensitive diagnostic means available for certain severe illnesses, such as pneumonia in immunocompromised children.

Conventional laboratory diagnosis of infection is accomplished by PIV isolation in tissue culture. Direct immunofluorescent staining is available in some centers for rapid identification of virus antigen in respiratory secretions. Many laboratories now use sensitive and specific multiplex polymerase chain reaction assays, which greatly increase sensitivity of PIV detection. For immunocompromised patients, these highly sensitive platforms provide the critical ability to make a diagnosis by detecting a wide range of viral pathogens, including PIVs, thus allowing for early implementation of infection prevention measures and potential treatment.

TREATMENT

There are no specific antiviral medications approved for the treatment of PIV infections. For croup, the possibility of rapid respiratory compromise should influence the acuity of care given (see Chapter 385). Humidified air has not been shown to be effective. Corticosteroids, including dexamethasone orally or by injection and budesonide via nebulizer, improve symptoms within 6 hr after treatment, lessen the need for other medications, and shorten hospital stays. *In general, because of its safety, efficacy, and cost-effectiveness, a single dose of oral dexamethasone (0.6 mg/kg) is preferred as part of the management of croup in the office or emergency room setting.* A single dose of intramuscular dexamethasone or budesonide (2 mg [2 mL solution] via nebulizer) may provide an alternative to dexamethasone for children with severe respiratory distress or vomiting. The dose may be repeated, but this should not necessary on a routine basis, and there are no guidelines to compare outcomes of single- and multiple-dose treatment schedules. Moderate to severe symptoms that persist for more than a few days should prompt investigation for other causes of airway obstruction.

For obstructive airway symptoms associated with moderate to severe croup, nebulized epinephrine (either racemic epinephrine 2.25%, 0.5 mL in 2.5 mL of saline, or L-epinephrine, 1:1,000 dilution in 5 mL of saline) is recommended and may also provide temporary symptomatic improvement. Children should be observed for at least 2 hr after receiving epinephrine treatment for return of obstructive symptoms. Repeated treatments may be provided, depending on the duration of symptoms. Oxygen should be administered for hypoxia, and supportive care with analgesics and antipyretics is reasonable for fever and discomfort associated with PIV infections. The indications for antibiotics are limited to well-documented secondary bacterial infections of the middle ear(s) or lower respiratory tract.

Ribavirin has some antiviral activity against PIVs in vitro and in animal models. Inhaled ribavirin has been given to severely immunocompromised children with PIV pneumonia, although the majority of data indicate that it is not effective, particularly for PIV pneumonia when given late in the course of illness. It is unclear whether treatment given early to prevent progression to pneumonia may be beneficial, although there have been anecdotal reports of successful use of aerosolized ribavirin for this purpose in children with severe combined immunodeficiency and transplant recipients. DAS181, a novel sialidase fusion protein inhibitor, has shown clinical potential when used for treatment of PIV lower respiratory tract disease among solid organ and hematopoietic stem cell transplant recipients, with reported improvement in viral load and symptoms following initiation of therapy. Other promising strategies for drug development include hemagglutinin-neuraminidase inhibitors, transcription inhibitors, and synthetic small interfering RNAs.

COMPLICATIONS

Eustachian tube obstruction can lead to secondary bacterial invasion of the middle ear space and acute otitis media in 30-50% of PIV

infections. Similarly, obstruction of the paranasal sinuses can lead to sinusitis. The destruction of cells in the upper airways can lead to secondary bacterial invasion and resultant bacterial tracheitis, and antecedent PIV infection of lower airways may predispose to bacterial pneumonia. Nonrespiratory complications of PIV are rare but include aseptic meningitis, encephalitis, acute disseminated encephalomyelitis, rhabdomyolysis, myocarditis, and pericarditis.

PROGNOSIS

The prognosis for full recovery from PIV infection in the normal child is excellent, with no long-term pulmonary sequelae.

PREVENTION

Vaccine development has focused largely on live-attenuated intranasal PIV-3 vaccines. The candidates include a cold-adapted virus of human origin (cp45), an attenuated bovine PIV-3, and newer constructs using the bovine PIV-3 vaccine with insertion of human PIV-3 HN and F genes and the F and G proteins of respiratory syncytial virus. Reverse genetics technology has led to development of a live-attenuated investigational PIV-3 vaccine virus (rcp45) derived from complementary DNA, as well as complementary DNA–derived chimeric bovine/human PIV-3 virus constructs; these candidates are well tolerated and immunogenic in infants and young children. Although less advanced, candidate PIV-1 and PIV-2 vaccines have been developed and are undergoing phase 1 clinical studies in children (www.clinicaltrials.gov). The measure of protection afforded by vaccines will be difficult to assess, because symptomatic reinfection occurs and the frequency of serious infection in the general population is low. Nonetheless, it is clear that prevention of acute respiratory illness caused by PIVs, particularly lower respiratory tract infections among infants and young children, is a worthwhile goal.

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Chapter 260

Respiratory Syncytial Virus

James E. Crowe Jr.

Respiratory syncytial virus (RSV) is the major cause of bronchiolitis (see Chapter 391) and viral pneumonia in children younger than 1 yr of age and is the most important respiratory tract pathogen of early childhood.

ETIOLOGY

RSV is an enveloped RNA virus with a single-stranded negative-sense genome that replicates entirely in the cytoplasm of infected cells and matures by budding from the apical surface of the cell membrane. Because this virus has a nonsegmented genome, it cannot undergo antigenic shift by reassortment like the influenza viruses do. The virus belongs to the family Paramyxoviridae, along with parainfluenza and measles viruses, and is in the subfamily Pneumovirinae, which also contains the human metapneumovirus (see Chapter 261). It is the only member of the genus *Pneumovirus* that infects humans. There are 2 antigenic subgroups of RSV, distinguished based primarily on variation in 1 of the 2 surface proteins, the G glycoprotein that is responsible for attachment. This antigenic variation caused by point mutations from infidelity of the virus RNA polymerase may to some degree contribute to the frequency with which RSV reinfects children and adults.

RSV replicates in a wide variety of cell line monolayer cultures in vitro, and in HeLa or HEp-2 cells produces characteristic syncytial cytopathology, from which the virus derives its name. Interestingly, it is now known that the virus does not cause large syncytia in polarized epithelial cells in vitro, and it is not clear whether syncytium formation occurs to any significant degree in vivo.

EPIDEMIOLOGY

RSV is distributed worldwide and appears in yearly epidemics. In temperate climates, these epidemics occur each winter over 4-5 mo. During the remainder of the year, infections are sporadic and much less common. In the Northern hemisphere, epidemics usually peak in January, February, or March, but peaks have been recognized as early as December and as late as June. Some areas in the United States, such as Florida, report a moderate incidence year-round. In the Southern hemisphere, outbreaks also occur during winter months in that hemisphere. RSV outbreaks often overlap with outbreaks of influenza and human metapneumovirus but are generally more consistent from year to year and result in more disease overall, especially among infants younger than 6 mo of age. In the tropics, the epidemic pattern is less clear. This pattern of widespread annual outbreaks and the high incidence of infection during the 1st 3-4 mo of life are unique among human viruses.

Transplacentally acquired anti-RSV maternal immunoglobulin G serum antibodies, if present in high concentration, appear to provide partial but incomplete protection. These immunoglobulin Gs may account for the lower severity of RSV infections during the 1st 4-6 wk of life, except among infants born prematurely, who receive less maternal immunoglobulin. Breastfeeding provides substantial protection against severe disease, an effect that may pertain only to female infants and not male infants. RSV is one of the most contagious viruses that affect humans. Infection is nearly universal among children by their 2nd birthday. Reinfection occurs at a rate of at least 10-20% per epidemic throughout childhood, with a lower frequency among adults. In situations of high exposure, such as daycare centers, attack rates are nearly 100% among previously uninfected infants and 60-80% for second and subsequent infections.

Reinfection may occur as early as a few weeks after recovery, but usually takes place during subsequent annual outbreaks. Antigenic variation is not required for reinfection, as shown by the fact that a proportion of adults inoculated repeatedly with the same experimental preparation of wild-type virus could be reinfected multiple times. The immune response of infants is poor in quality, magnitude, and durability. The severity of illness during reinfection in childhood is usually lower and appears to be a function of partial acquired immunity, more robust airway physiology, and increased age.

Asymptomatic RSV infection is unusual in young children. Most infants experience coryza and pharyngitis, often with fever and frequently with otitis media caused by a virus in the middle ear or bacterial superinfection following eustachian tube dysfunction. The lower respiratory tract is involved to a varying degree with bronchiolitis and bronchopneumonia in about a third of children. The hospitalization rate for RSV infection in otherwise healthy infants is typically 0.5-4%, depending on region, gender, socioeconomic status, exposure to cigarette smoke, gestational age, and family history of atopy. The admitting diagnosis is usually bronchiolitis with hypoxia, although this condition is often indistinguishable from RSV pneumonia in infants, and, indeed, the 2 processes frequently coexist. All RSV diseases of the lower respiratory tract (excluding croup) have their highest incidence at 6 wk to 7 mo of age and decrease in frequency thereafter. The syndrome of bronchiolitis is much less common after the 1st birthday. The terminology used for diagnosis of virus-associated wheezing illnesses in toddlers is confusing, as these illnesses are variably termed *wheezing-associated respiratory infection, "wheezy bronchitis," exacerbation of reactive airways disease,* or *asthma attack*. Because many toddlers wheeze during RSV infection but do not go on to have lifelong asthma, it is best to use the diagnostic term *asthma* only later in life. Acute viral

pneumonia is a recurring problem throughout childhood, although RSV becomes less prominent as the etiologic agent after the 1st yr. RSV plays a causative role in an estimated 40-75% of cases of hospitalized bronchiolitis, 15-40% of cases of childhood pneumonia, and 6-15% of cases of croup.

Bronchiolitis and pneumonia resulting from RSV are more common in boys than in girls by a ratio of approximately 1.5 : 1. Other risk factors with similar impact include 1 or more siblings in the home, white race, rural residence, maternal smoking, and maternal education <12 yr. The medical factors in infants associated with highest risk are chronic lung disease of prematurity, congenital heart disease, immunodeficiency, and prematurity. Still, most infants admitted to the hospital because of RSV infection do not have strong, easily identifiable risk factors. Therefore, any strategy for prophylaxis focused only on individuals with strong risk factors probably could prevent only approximately 10% of hospitalizations, even if the prophylaxis was 100% effective in treated high-risk individuals.

The incubation period from exposure to first symptoms is approximately 3-5 days. The virus is excreted for variable periods, probably depending on severity of illness and immunologic status. Most infants with lower respiratory tract illness shed infectious virus for 1-2 wk after hospital admission. Excretion for 3 wk, and even longer, has been documented. Spread of infection occurs when large, infected droplets, either airborne or conveyed on hands or other fomites, are inoculated in the nasopharynx of a susceptible subject. RSV is probably introduced into most families by young schoolchildren undergoing reinfection. Typically, in the space of a few days, 25-50% of older siblings and 1 or both parents acquire upper respiratory tract infections, but infants become more severely ill with fever, otitis media, or lower respiratory tract disease.

Nosocomial infection during RSV epidemics is an important concern. Virus is usually spread from child to child on the hands of caregivers or other fomites. Adults undergoing reinfection also have been implicated in spread of the virus. Contact precautions are sufficient to prevent spread when compliance is meticulous, as the virus is not usually spread by small particle aerosol. In practice, however, adherence to isolation procedures by caregivers often is not complete.

PATHOGENESIS

Bronchiolitis is caused by obstruction and collapse of the small airways during expiration. Infants are particularly apt to experience small airway obstruction because of the small size of their normal bronchioles; airway resistance is proportional to 1/radius^4. There has been relatively little pathologic examination of RSV disease in the lower airways of otherwise healthy subjects. Airway narrowing likely is caused by virus-induced necrosis of the bronchiolar epithelium, hypersecretion of mucus, and round-cell infiltration and edema of the surrounding submucosa. These changes result in formation of mucus plugs obstructing bronchioles, with consequent hyperinflation or collapse of the distal lung tissue. In interstitial pneumonia, the infiltration is more generalized, and epithelial shedding may extend to both the bronchi and the alveoli. In older subjects, smooth muscle hyperreactivity may contribute to airway narrowing, but the airways of young infants typically do not exhibit a high degree of reversible smooth muscle hyperreactivity during RSV infection.

Several facts suggest that elements of the host response may cause inflammation and contribute to tissue damage. The immune response required to eliminate virus-infected cells is a double-edged sword, reducing the cells producing virus but causing host cell death in the process. A large number of soluble factors, such as cytokines, chemokines, and leukotrienes, are released in the process, and skewing of the patterns of these responses may predispose some individuals to more severe disease. There is also evidence that genetic factors may predispose to more severe bronchiolitis.

Children who received a formalin-inactivated, parenterally administered RSV vaccine in the 1960s experienced more severe and more frequent bronchiolitis upon subsequent natural exposure to wild-type RSV than did their age-matched controls. Several children died during naturally acquired RSV infection after vaccination. This event has greatly inhibited progress in RSV vaccine development, because of both an incomplete understanding of the mechanism and a reluctance to test new experimental vaccines that might induce the same type of response.

Some studies have identified the presence of both RSV and human metapneumovirus viral RNA in airway secretions in a significant proportion of infants requiring assisted ventilation and intensive care. It may be that coinfection is associated with more severe disease. Positive results of polymerase chain reaction (PCR) analysis must be interpreted carefully because this positivity can remain for prolonged periods after infection, even when infectious virus can no longer be detected.

It is not clear how often superimposed bacterial infection plays a pathogenic role in RSV lower respiratory tract disease. RSV bronchiolitis in infants is probably exclusively a viral disease, although there is evidence that bacterial pneumonia can be triggered by respiratory viral infection, including with RSV. A large clinical study of pneumococcal vaccine showed that childhood vaccination reduced the incidence of viral pneumonia by approximately 30%, suggesting viral-bacterial interactions that we currently do not fully understand.

CLINICAL MANIFESTATIONS

Typically, the first sign of infection in infants with RSV is rhinorrhea. Cough may appear simultaneously but more often does so after an interval of 1-3 days, at which time there may also be sneezing and a low-grade fever. Soon after the cough develops, the child who experiences bronchiolitis begins to wheeze audibly. If the disease is mild, the symptoms may not progress beyond this stage. Auscultation often reveals diffuse fine inspiratory crackles and expiratory wheezes. Rhinorrhea usually persists throughout the illness, with intermittent fever. Chest radiograph findings at this stage are frequently normal.

If the illness progresses, cough and wheezing worsen and air hunger ensues, with increased respiratory rate, intercostal and subcostal retractions, hyperexpansion of the chest, restlessness, and peripheral cyanosis. Signs of severe, life-threatening illness are central cyanosis, tachypnea of >70 breaths/min, listlessness, and apneic spells. At this stage, the chest may be significantly hyperexpanded and almost silent to auscultation because of poor air movement.

Chest radiographs of infants hospitalized with RSV bronchiolitis have normal findings in approximately 30% of cases, with the other 70% showing hyperexpansion of the chest, peribronchial thickening, and interstitial infiltrates. Segmental or lobar consolidation is unusual and pleural effusion is rare.

In some infants, the course of the illness may resemble that of pneumonia, the prodromal rhinorrhea and cough being followed by dyspnea, poor feeding, and listlessness, with a minimum of wheezing and hyperexpansion. Although the clinical diagnosis is pneumonia, wheezing is often present intermittently and the chest radiographs may show air trapping.

Fever is an inconstant sign in RSV infection. In young infants, particularly those who were born prematurely, periodic breathing and apneic spells have been distressingly frequent signs, even with relatively mild bronchiolitis. Apnea is not necessarily caused by respiratory exhaustion, but rather appears to be a consequence of alterations in central control of breathing.

RSV infections in profoundly immunocompromised hosts may be severe at any age of life. The mortality rates associated with RSV pneumonia in the 1st few wk after hematopoietic stem cell or solid organ transplantation in both children and adults are high. RSV infection does not seem to be more severe in HIV-infected patients with reasonable control of HIV disease, although these patients may shed virus for prolonged periods.

DIAGNOSIS

Bronchiolitis is a clinical diagnosis. RSV can be suspected with varying degrees of certainty on the basis of the season of the year and the presence of the virus in the community. Other epidemiologic features that

may be helpful are the presence of colds in older household contacts and the age of the child. The other respiratory viruses that attack infants frequently during the 1st few mo of life are parainfluenza virus type 3, human metapneumovirus, enteroviruses, coronaviruses, and influenza viruses. Rhinovirus is frequently found in the respiratory tract of children, and there is growing evidence that this virus may contribute significantly to lower respiratory tract disease.

Routine laboratory tests are of minimal diagnostic use in most cases of bronchiolitis or pneumonia caused by RSV. The white blood cell count is normal or elevated, and the differential cell count may be normal with either a neutrophilic or mononuclear predominance. Hypoxemia as measured by pulse oximetry or arterial blood gas analysis is frequent and tends to be more marked than anticipated from the clinical findings. A normal or elevated blood CO_2 value in a patient with a markedly elevated respiratory rate is a sign of respiratory failure.

The most important diagnostic concern is to identify bacterial or chlamydial involvement. When bronchiolitis is not accompanied by infiltrates on chest radiographs, there is little likelihood of a bacterial component. In infants 1-4 mo of age, interstitial pneumonitis may be caused by *Chlamydia trachomatis* (see Chapter 226). With *C. trachomatis* pneumonia there may be a history of conjunctivitis, and the illness tends to be of subacute onset. Coughing and inspiratory crackles may be prominent; wheezing is not. Fever is usually absent.

Lobar consolidation without other signs or with pleural effusion should be considered of bacterial etiology until proved otherwise. Other signs suggesting bacterial pneumonia are neutrophilia, neutropenia in the presence of severe disease, ileus or other abdominal signs, high temperature, and circulatory collapse. In such instances, antibiotics should be initiated.

Definitive diagnosis of RSV infection is based on the detection in respiratory secretions of live virus by cell culture. The presence of viral RNA (detected by a molecular diagnostic test using reverse transcription PCR) or viral antigens (detected by a rapid diagnostic test, usually a membrane blotting test incorporating antibody detection of viral proteins) is strongly supportive in the right clinical setting. The antigen test is less sensitive than culture, whereas reverse transcription PCR analysis is more sensitive than culture. An aspirate of mucus or a nasopharyngeal wash from the child's posterior nasal cavity is the optimal specimen. Nasopharyngeal or throat swabs are less preferable but acceptable. A tracheal aspirate is unnecessary, but endotracheal tube lavage fluid from patients intubated for mechanical ventilation can be tested. The specimen should be placed on ice, taken directly to the laboratory, and processed immediately for culture, antigen detection, or PCR analysis. The virus is thermolabile, so it degrades over relatively short periods of time unless frozen at a low temperature such as −80°C (−112°F) in freezers used in research settings.

TREATMENT

The treatment of uncomplicated cases of bronchiolitis is symptomatic. Humidified oxygen and suctioning are usually indicated for hospitalized infants who are hypoxic. Many infants are slightly to moderately dehydrated, and therefore fluids should be carefully administered in amounts somewhat greater than those for maintenance. Often, intravenous or tube feeding is helpful when sucking is difficult because of tachypnea.

There is disagreement among experts regarding the usefulness of aerosolized saline or hypertonic saline, epinephrine or β_2-agonists in RSV bronchiolitis. Most patients do not receive lasting benefit from prolonged therapy, which is associated with a relatively high frequency of side effects. Corticosteroid therapy is not indicated except in older children with an established diagnosis of asthma, because its use is associated with prolonged virus shedding and is of no proven clinical benefit.

In nearly all instances of bronchiolitis, antibiotics are not useful, and their inappropriate use contributes to development of antibiotic resistance. Interstitial pneumonia in infants 1-4 mo old may be caused by *C. trachomatis,* and macrolide therapy may be indicated for that infection.

Ribavirin is an antiviral agent delivered through an oxygen hood, face mask, or endotracheal tube with use of a small-particle aerosol generator most of the day for 3-5 days. Early small trials of its use suggested a modest beneficial effect on the course of RSV pneumonia, with some reduction in the duration of both mechanical ventilation and hospitalization. However, subsequent studies failed to document a clear beneficial effect of ribavirin, and therefore this drug is no longer used for routine therapy of RSV disease. The monoclonal antibody palivizumab is licensed for prophylaxis in high-risk infants during the RSV season, and does prevent about half of the expected hospitalizations in that population. Small clinical trials using the palivizumab as a therapy during established infection have not shown benefit to date.

PROGNOSIS

The mortality rate of hospitalized infants with RSV infection of the lower respiratory tract is very low in the developed world. Almost all deaths occur among young, premature infants or infants with underlying disease of the neuromuscular, pulmonary, cardiovascular, or immunologic system. It is estimated, however, that more than 100,000 children worldwide in resource-poor settings die each year from RSV. In addition, thousands of elderly patients die of RSV infection each year in the United States.

Many children with asthma have a history of bronchiolitis in infancy. There is recurrent wheezing in 30-50% of children with severe RSV bronchiolitis in infancy. The likelihood of recurrence is increased in the presence of an allergic diathesis (e.g., eczema, hay fever, or a family history of asthma). With a clinical presentation of bronchiolitis in a patient older than 1 yr of age, there is an increasing probability that, although the episode may be virus induced, this is likely the first of multiple wheezing attacks that will later be diagnosed as hyperreactive airways disease or asthma. Asthma is difficult to diagnose in the 1st yr of life. It is not fully clear at this time whether early, severe RSV wheezing disease causes some cases of asthma or whether subjects destined to suffer asthma present with symptoms first when provoked by RSV infection during infancy. However, results from a recent long-term follow-up study of infants who received palivizumab prophylaxis suggested that prevention of severe RSV infection reduces the incidence of reactive airways disease later in life.

PREVENTION

In the hospital, the most important preventive measures are aimed at blocking nosocomial spread. During RSV season, high-risk infants should be separated from all infants with respiratory symptoms. Gowns, gloves, and careful handwashing should be used for the care of all infants with suspected or established RSV infection. A high level of compliance with contact isolation is essential. Viral laboratory tests are adequate for diagnosis in the setting of acute disease when levels of virus are high, but they are not designed to detect low levels of virus. Therefore, contact precaution isolation should be observed for most patients admitted for acute disease assigned for the duration of hospitalization; rapid antigen tests should not be used to determine whether or not a patient still requires isolation. Ideally, patients with RSV or metapneumovirus infections are housed separately, because coinfection may be associated with more severe disease.

Passive Immunoprophylaxis

Administration of palivizumab (15 mg/kg IM once a month), a neutralizing humanized murine monoclonal antibody against RSV, is recommended for protecting high-risk children against serious complications from RSV disease. Immunoprophylaxis reduces the frequency and total days of hospitalization for RSV infections in high-risk infants in about half of cases. Palivizumab is administered monthly from the beginning to the end of the RSV season. The American Academy of Pediatrics Committee on Infectious Diseases issued "Modified Recommendations for Use of Palivizumab for Prevention of Respiratory Syncytial Virus Infections" in 2014. Palivizumab prophylaxis may be considered for the following infants and children

- Infants born before 29 wk of gestation in the 1st yr of life
- Infants born before 32 wk of gestation, who have chronic lung disease of prematurity (required >21% F_{IO_2} [fraction of inspired oxygen] for ≥28 days after birth), in the 1st yr of life

- Infants younger than 1 yr of age with hemodynamically significant congenital heart disease
- Children 24 mo of age or younger with profound immunocompromising conditions during RSV season
- Infants in the 1st yr of life who have either congenital abnormalities of the airway or neuromuscular disease that compromises handling of respiratory secretions
- Administration in the 2nd yr of life is recommended for children who required 28 or more days of oxygen after birth and who have ongoing treatment for chronic pulmonary disease (oxygen, steroids, diuretics)

The American Academy of Pediatrics 2012 *Red Book* recommendations also give the following specific guidelines on implementation of prophylaxis. Recommendations for initiation and termination of prophylaxis reflect current descriptions from the Centers for Disease Control and Prevention of RSV seasonality in different geographic locations within the United States. Typically, prophylaxis is initiated July 1 in southeast Florida, September 15 in north-central and southwest Florida, and November 1 in most other areas of the United States. Regardless of the month in which the 1st dose is administered, the recommendation for a maximal number of 5 doses for all geographic locations is emphasized for infants with hemodynamically significant congenital heart disease, chronic lung disease of prematurity, or birth before 32 wk, 0 days of gestation. A maximal number of 3 doses is recommended for infants with a gestational age of 32 wk, 0 days to 34 wk, 6 days without hemodynamically significant congenital heart disease or chronic lung disease of prematurity who qualify for prophylaxis. Infants born from 32 wk, 0 days through 34 wk, 6 days of gestation who qualify for prophylaxis under the new recommendations should receive prophylaxis only until they reach 90 days of age or a maximum of 3 doses (whichever comes first).

Vaccine

There is no licensed vaccine against RSV. The challenge for development of live virus vaccines has been to produce attenuated vaccine strains that infect infants in the nasopharynx after topical inoculation without producing unacceptable symptoms, that remain genetically stable during shedding, and that induce protection against severe disease following reinfection. The most promising live-attenuated virus candidates have been engineered in the laboratory from cold-passaged strains of RSV, according to a basic strategy that yielded the live poliovirus and influenza virus vaccine strains. A variety of nonreplicating experimental vaccines are being tested in early clinical trials. Plans are underway to study some of the new vaccine candidates in maternal immunization trials. The rationale of such studies is to test whether boosting the serum level of RSV-neutralizing antibodies in the mother can enhance immunity in neonates following transplacental transfer of maternal antibodies to the infant.

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Chapter 261

Human Metapneumovirus

James E. Crowe Jr.

Human metapneumovirus (HMPV) is a respiratory virus that was first identified in 2001 and has emerged as one of the most common causes of serious lower respiratory tract illness in children throughout the world.

ETIOLOGY

HMPV is an enveloped, single-stranded nonsegmented negative-sense RNA genome of the Paramyxoviridae family, which is divided into 2 subfamilies, Pneumovirinae and Paramyxovirinae. The Pneumovirinae subfamily includes the 2 genera *Metapneumovirus* and *Pneumovirus,* which includes respiratory syncytial virus (RSV). HMPV and the avian pneumoviruses are highly related and are separated into the separate genus *Metapneumovirus* because the gene order in the nonsegmented genome is slightly altered and because avian pneumoviruses/HMPVs lack the genes for 2 nonstructural proteins, NS1 and NS2, that are encoded at the 3′ end of RSV genomes. These proteins are thought to counteract host type I interferons. The absence of NS1/NS2 in the metapneumoviruses may contribute to an overall slightly reduced pathogenicity relative to wild-type RSV strains.

Full-length sequences of a number of HMPV genomes have been determined. The genome encodes 9 proteins in the order 3′-N-P-M-F-M2-(orf1 and 2)-SH-G-L-5′. The genome also contains noncoding 3′ leader, 5′ trailer, and intergenic regions, consistent with the organization of most paramyxoviruses, with a viral promoter contained in the 3′ end of the genome. The F (fusion), G (glycosylated), and SH (short hydrophobic) proteins are integral membrane proteins on the surfaces of infected cells and virion particles. The F protein is a classic type I integral membrane viral fusion protein that contains 2 heptad repeats in the extracellular domain that facilitate membrane fusion. There is a predicted protein cleavage site near a hydrophobic fusion peptide that likely is cleaved by an extracellular protease, activating the F protein for fusion. The predicted attachment (G) protein of HMPV exhibits the basic features of a glycosylated type II mucin-like protein. The HMPV G protein differs from the RSV G protein in that it lacks a cysteine noose structure. This protein may inhibit innate immune responses. The internal proteins of the virus appear similar in function to those of other paramyxoviruses.

EPIDEMIOLOGY

HMPV outbreaks occur in annual epidemics during late winter and early spring in temperate climates, often overlapping with the second half of the annual RSV epidemic (Fig. 261-1). Sporadic infections occur year round. The usual period of viral shedding is likely to be many days or even several weeks after primary infection in infants. The incubation period is approximately 3-5 days. Humans are the only source of virus, as there is no known animal or environmental reservoir. Transmission occurs by close or direct contact with contaminated secretions involving large-particle aerosols, droplets, or contaminated surfaces. Nosocomial infections have been reported, and contact isolation with excellent handwashing for healthcare providers is critical in medical settings. This virus affects the elderly, immunocompromised patients, and patients with reactive airways disease more severely than otherwise healthy individuals.

PATHOLOGY

Infection is usually limited to the superficial layer of airway epithelial cells and is associated with a local inflammatory infiltrate consisting of lymphocytes and macrophages. Immunocompromised individuals have evidence of both acute and organizing injuries during prolonged infection.

PATHOGENESIS

Infection occurs via inoculation of the upper respiratory tract. Infection can spread rapidly to the lower respiratory tract, but it is not clear whether the dissemination is mediated by cell-to-cell spread or aspiration of infected materials from the upper tract. Severe lower respiratory tract illness, especially wheezing, occurs mainly during the 1st yr of life, at a time when the airways are of a small diameter and high resistance. Maternal serum neutralizing antibodies that cross the placenta may afford a relative protection against severe disease for several weeks or months after birth. Once infection is established, it is likely that cytotoxic T cells recognize and eliminate virus-infected cells, thus terminating the infection but also causing some cytopathology. The virus appears to have specific mechanisms for inhibiting T-cell responses during acute infection. Individuals with an underlying predisposition to reactive airways disease (including adults) are susceptible to severe wheezing during reinfection later in life, suggesting that HMPV may cause smooth muscle hyperactivity, inflammation, or increased mucus

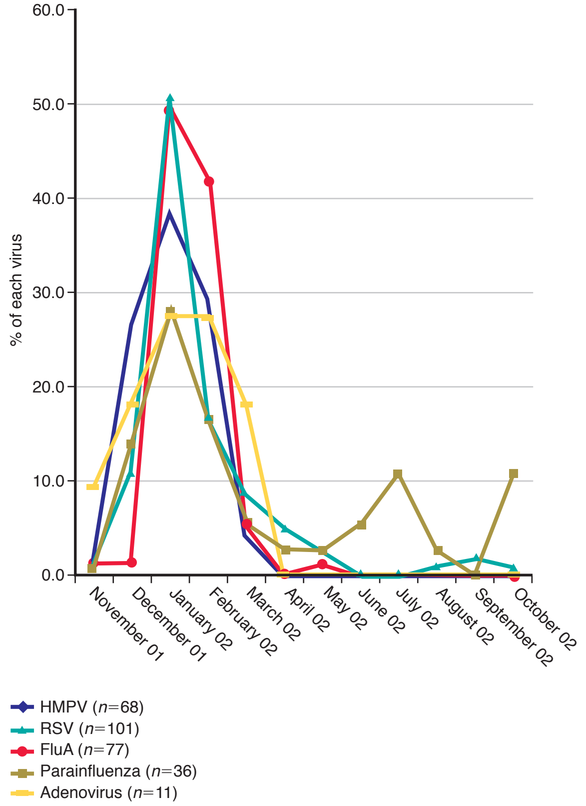

Figure 261-1 Temporal distribution of respiratory viruses among children hospitalized with lower respiratory tract infections from November 2001 through October 2002. Data are displayed as the proportion of each virus detected monthly. *FluA*, influenza A; *HMPV*, human metapneumovirus; *RSV*, respiratory syncytial virus. *(From Wolf DG, Greenberg D, Kalkstein D, et al: Comparison of human metapneumovirus, respiratory syncytial virus and influenza A virus lower respiratory tract infections in hospitalized young children,* Pediatr Infect Dis J *25:320–324, 2006.)*

production in such individuals. Infection in otherwise healthy individuals resolves without apparent long-term consequences in most cases. HMPV infection is associated with exacerbations of asthma later in life.

CLINICAL MANIFESTATIONS

HMPV is associated with the common cold (complicated by otitis media in approximately 30% of cases) and with lower respiratory tract illnesses such as bronchiolitis, pneumonia, croup, and exacerbation of reactive airways disease. The profile of signs and symptoms caused by HMPV is very similar to that caused by RSV (Table 261-1). Approximately 5-10% of outpatient lower respiratory tract illnesses in otherwise healthy young children is associated with HMPV infection, which is second in incidence only to RSV. Children with RSV or HMPV infection require supplemental oxygen and medical intensive care at similar frequencies.

About half of the cases of HMPV lower respiratory tract illness in children occur in the 1st 6 mo of life, suggesting that young age is a major risk factor for severe disease. Both young adults and the elderly can have HMPV infection that requires medical care including hospitalization, but severe disease occurs at much lower frequencies in adults than in young children. Severe disease in older subjects is most common in immunocompromised patients and can be fatal. A significant number of both adult and pediatric patients with asthma exacerbations have HMPV infection; it is not clear whether the virus causes long-term wheezing. RSV and HMPV coinfections have been reported; coinfections may be more severe than infection with a single virus, resulting in pediatric intensive care unit admissions. It is difficult to define true coinfections because these viral genomes can be detected

Table 261-1 Clinical Manifestations of Human Metapneumovirus in Children
COMMON (>50%)
Fever >38°C (100.4°F)
Cough
Rhinitis, coryza
Wheezing
Tachypnea, retractions
Hypoxia (O_2 saturation <94%)
Chest radiograph demonstration of infiltrates or hyperinflation
LESS COMMON
Otitis media
Pharyngitis
Rales
RARE
Conjunctivitis
Hoarseness
Encephalitis
Fatal respiratory failure in immunocompromised children

by reverse transcriptase polymerase chain reaction (PCR) in respiratory secretions for at least several weeks after illness, even when virus shedding has terminated.

LABORATORY FINDINGS

The virus can be visualized only with electron microscopy. The virus grows in primary monkey kidney cells or LLC-MK2 cell or Vero cell-line monolayer cultures, but efficient isolation of the virus requires an experienced laboratory technician. Conventional bright-field microscopy of infected cell monolayer cultures often reveals cytopathic effect only after multiple passages in cell culture. The characteristics of the cytopathic effect are not sufficiently distinct to allow identification of the virus on this basis alone, even by a trained observer. Direct antigen tests for identification of HMPV antigens in nasopharyngeal secretions are available but are less efficient than nucleic acid–based detection. Some laboratories have success with the use of immunofluorescence staining with monoclonal or polyclonal antibodies to detect HMPV in nasopharyngeal secretions and shell vial cultures or in monolayer cultures in which virus has been cultivated. The most sensitive test for identification of HMPV in clinical samples is reverse transcriptase PCR, usually performed with primers directed to conserved viral genes. Detection by this modality is also available in some multiplex PCR tests for panels of respiratory viruses. Real-time reverse transcriptase PCR tests offer enhanced sensitivity and specificity, including assays designed to detect viruses from the 4 known genetic lineages.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In temperate areas, the diagnosis should be suspected during the late winter in infants or young children with wheezing or pneumonia and a negative RSV diagnostic test result. The diseases caused by RSV and HMPV cannot be distinguished clinically. Many other common respiratory viruses, such as parainfluenza viruses, influenza viruses, adenoviruses, rhinoviruses, enteroviruses, and coronaviruses, can cause similar disease in young children. Some of these viruses can be identified by PCR genetic testing or conventional cell culture means.

COMPLICATIONS

Bacterial superinfection of the lower airways is unusual but does occur. The local complication of otitis media is common, likely a result of eustachian tube dysfunction caused by the virus.

TREATMENT

There is no specific treatment at this time for HMPV infection. Management consists of supportive care. The rate of bacterial lung infection or bacteremia associated with HMPV infection is not fully defined but is suspected to be low. Antibiotics are usually not indicated in treatment of infants hospitalized for HMPV bronchiolitis or pneumonia.

SUPPORTIVE CARE

Treatment is supportive and includes careful attention to hydration, monitoring of respiratory status by physical examination and measurement of oxygen saturation, use of supplemental oxygen, and, if necessary, mechanical ventilation.

PROGNOSIS

Most infants and children recover from acute HMPV infection without apparent long-term consequences. Many experts believe an association exists between severe HMPV infections in infancy and risk for recurrent wheezing or the development of asthma; however, it is not clear whether the virus causes these conditions or precipitates their first manifestations.

PREVENTION

The only method of prevention of HMPV infection is reduction of exposure. Contact precautions are recommended for the duration of HMPV-associated illness among hospitalized infants and young children. Patients known to have HMPV infection should be housed in single rooms or with a cohort of HMPV-infected patients. When feasible, it is wise to care for patients with RSV infection in a separate cohort from HMPV-infected patients, so as to prevent coinfection. Preventive measures include limiting exposure to contagious settings during annual epidemics (such as daycare centers) as much as possible and emphasis on hand hygiene in all settings, including the home, especially during periods when the contacts of high-risk children have respiratory infections. However, providers should keep in mind that infection is universal in the 1st several years of life. Therefore, reduction of exposure makes most sense during the 1st 6 mo of life, when infants are at highest risk for severe disease.

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Table 262-1	Adenovirus Types with Associated Infections	
SPECIES	TYPE	PREFERRED SITE OF INFECTION
A	12, 18, 31	Gastrointestinal
B1	3, 7, 16, 21, 50	Respiratory
B2	11, 14, 34, 35	Renal/urinary tract epithelium
C	1, 2, 5, 6	Respiratory
D	8, 9, 10, 13, 15, 17, 19a, 19p, 20, 22-30, 32, 33, 36, 37, 38, 39, 42-48, 49, 51	Ocular
E	4	Respiratory
F	40, 41	Gastrointestinal
G	52	Gastrointestinal

Chapter 262

Adenoviruses

Jason B. Weinberg and John V. Williams

Human adenoviruses (HAdVs) are a common cause of human disease. Conjunctivitis is a familiar illness associated with HAdVs, but these viruses also cause upper and lower respiratory disease, pharyngitis, gastroenteritis, and hemorrhagic cystitis. HAdVs can cause severe disease in immunocompromised hosts. Outbreaks of HAdV infection occur in communities and closed populations, notably the military. No specific antivirals that are highly effective against HAdVs are available. Vaccines are available for HAdV types 4 and 7, but are used only for military populations.

ETIOLOGY

Adenoviruses were first isolated from human adenoidal surgical specimens in 1953. They are nonenveloped viruses with an icosahedral protein capsid. The double-stranded DNA genome is contained within the particle complexed with several viral proteins. Antigenic variability in surface proteins of the virion defines more than 50 serotypes grouped into 8 species. Species differ in their tissue tropism and target organs, causing distinct clinical infections (Table 262-1). HAdVs can be shed from the gastrointestinal tract for prolonged periods and can establish chronic low-level infection of the tonsils and adenoids.

EPIDEMIOLOGY

HAdVs circulate worldwide and cause endemic infections year-round in immunocompetent hosts. Asymptomatic infections are also common. Only about one third of all known HAdV types are associated with clinically apparent disease. The most prevalent types in recent surveillance studies are HAdV types 3, 2, 1, and 5. Epidemics of conjunctivitis (often severe), pharyngitis, and respiratory disease occur, especially in schools and military settings. Outbreaks of febrile respiratory illness caused by HAdV-4 and HAdV-7 are a major source of morbidity in military barracks, with attack rates ranging from 25% to >90%. Spread of HAdV occurs by respiratory and fecal-oral routes. An important factor in HAdV transmission, especially in epidemics, is the ability of the nonenveloped particle to survive on inanimate objects in the environment. Nosocomial outbreaks have been reported.

PATHOGENESIS

HAdVs bind to cell surface receptors and trigger internalization by endocytosis. Acidification of the endosome induces conformational changes in the capsid, leading to eventual translocation of the genome to the cell nucleus. Viral messenger RNA transcription and genomic replication occur in the nucleus. Progeny virion particles assemble in the nucleus. Lysis of the cell releases new infectious particles and causes damage to epithelial mucosa, sloughing of cell debris, and inflammation. Host responses to HAdV infection include the recruitment of neutrophils, macrophages, and natural killer cells to the site of infection and the elaboration by these cells of a number of cytokines and chemokines. This host immune response is likely to contribute to the symptoms of HAdV infection, but specific mechanisms of pathogenesis are poorly understood. The strict species specificity of the adenoviruses precludes the development of an animal model for HAdVs; consequently, mouse adenovirus is used to study adenovirus pathogenesis using a murine model.

CLINICAL MANIFESTATIONS

HAdVs cause a variety of common clinical syndromes in both immunocompetent and immunocompromised hosts. These syndromes are difficult to distinguish reliably from similar illnesses caused by other pathogens, such as respiratory syncytial virus, human metapneumovirus, human rhinovirus, rotavirus, group A streptococcus, and other common viral and bacterial pathogens.

Acute Respiratory Disease

Respiratory tract infections are common manifestations of HAdV infections in children and adults. HAdVs cause an estimated 5-10% of all childhood respiratory disease. Primary infections in infants may manifest as bronchiolitis or pneumonia. HAdV pneumonia may manifest as features more typical of bacterial disease (lobar infiltrates, high fever, parapneumonic effusions). HAdV-14 has recently emerged as a significant cause of severe acute respiratory disease in military and civilian populations, in some cases leading to hospitalization and death. Pharyngitis caused by HAdV typically includes symptoms of coryza, sore throat, and fever. The virus can be identified in 15-20% of

children with isolated pharyngitis, mostly in preschool children and infants.

Ocular Infections

Common follicular conjunctivitis caused by HAdV is self-limiting and requires no specific treatment. A more severe form, called *epidemic keratoconjunctivitis*, involves the cornea and conjunctiva. Pharyngoconjunctival fever is a distinct syndrome that includes a high temperature, pharyngitis, nonpurulent conjunctivitis, and preauricular and cervical lymphadenopathy.

Gastrointestinal Infections

HAdV can be detected in the stools of 5-10% of children with acute diarrhea. Most cases of acute diarrhea are self-limiting, although severe disease can occur. Enteric infection with HAdV is often asymptomatic, so the causative role in these episodes is frequently uncertain. HAdV may also cause mesenteric adenitis.

Hemorrhagic Cystitis

Hemorrhage cystitis consists of a sudden onset of hematuria, dysuria, frequency, and urgency with negative urine bacterial culture results. Urinalysis may show sterile pyuria in addition to red blood cells. This illness occurs more frequently in young males and typically resolves on its own in 1-2 wk.

Other Complications

Rarely, HAdVs are associated with myocarditis, hepatitis, or meningoencephalitis in immunocompetent individuals.

Adenoviruses in Immunocompromised Patients

Immunocompromised persons are at high risk for severe disease caused by HAdV, particularly recipients of hematopoietic stem cell transplants (HSCTs) and solid organ transplants. These patients may experience primary HAdV infection, but reactivation of endogenous virus in a transplant recipient, as well as transmission of virus from a donor organ, may also occur. Organ failure as a consequence of pneumonia, hepatitis, gastroenteritis, and disseminated infection occurs primarily in these patients. HAdV infection in HSCT recipients commonly manifests as pulmonary or disseminated disease and is most likely to occur in the 1st 100 days after transplantation. Hemorrhagic cystitis can be severe in HSCT recipients. Infections caused by HAdV in solid organ transplant recipients usually involve the transplanted organ. Immunocompromised children are at greater risk than immunocompromised adults for complicated HAdV infection, presumably because of a lack of preexisting immunity. Additional risk factors are T-cell–depleted grafts, high-level immunosuppression, and presence of graft-versus-host disease. Some experts advocate a preemptive screening approach to detect and treat HAdV infection early in immunocompromised patients, with the intent to prevent dissemination and severe illness in this vulnerable population.

DIAGNOSIS

HAdV may be suspected as the etiology of an illness on the basis of epidemiologic or clinical features; neither of these categories is specific enough to firmly establish the diagnosis. The frequency of asymptomatic shedding of HAdV makes assigning causality to this pathogen difficult at times. Most HAdV serotypes grow well in culture, although this method requires 2-7 days and thus is not helpful for early identification. Cells from respiratory or ocular specimens can be tested using immunofluorescent staining with antibodies to detect HAdV protein. Commercially available enzyme-linked immunoassays can be used to rapidly detect HAdV in patient specimens, usually in stool. Molecular techniques, such as polymerase chain reaction, offer rapid, sensitive, and specific diagnosis of HAdV infections and are most useful clinically for the management of suspected HAdV infections in immunocompromised hosts. In these patients, measurement of *HAdV genome copy number* using quantitative real-time polymerase chain reaction can facilitate diagnosis, and repeated measurements can aid in assessing a patient's response to treatment. Serology is generally useful only in epidemiologic investigations.

COMPLICATIONS

HAdV pneumonia can lead to respiratory failure requiring mechanical ventilation, especially in the immunocompromised patient. Secondary bacterial pneumonias do not appear to be as common following HAdV infection as they are after influenza infection, but data for this issue are limited. Severe HAdV pneumonia has been linked to chronic lung disease and bronchiolitis obliterans in a minority of cases. Epidemic keratoconjunctivitis is a sight-threatening form of HAdV infection. Nearly any form of HAdV infection can be fatal in an HSCT or solid organ transplant recipient. Refractory severe anemia requiring repeated blood transfusions can develop in HSCT recipients with hemorrhagic cystitis. Mortality rates of up to 60-80% have been reported in transplant recipients with disseminated HAdV or HAdV pneumonia.

TREATMENT

Supportive care is the mainstay of HAdV treatment in most cases. Patients with severe HAdV conjunctivitis should be referred for ophthalmologic consultation. No specific antiviral therapy produces a definite clinical benefit against HAdV infection. The nucleoside analog cidofovir has in vitro activity against most HAdV serotypes. Cidofovir is used topically to treat epidemic keratoconjunctivitis, often in conjunction with topical steroids or other immunosuppressive agents to limit the inflammatory component. Cidofovir may be used intravenously for HAdV infections in immunocompromised patients. Cidofovir is highly nephrotoxic; however, prehydration, concomitant administration of probenecid, and weekly dosing may alleviate renal toxicity. Clinical studies suggest benefit from cidofovir, but there are no prospective, randomized controlled trials of cidofovir for HAdV. In addition, no formal guidelines or recommendations for treatment exist. There are anecdotal descriptions of benefit from intravenous immunoglobulin. Adoptive immunotherapy involving the infusion of HAdV-specific T cells may also provide some benefit for immunocompromised patients with life-threatening HAdV infections, but this intervention is not yet considered standard therapy.

PREVENTION

Environmental and fomite transmission of HAdV occurs readily; therefore, simple measures such as handwashing and cleaning reduce spread. Live-attenuated HAdV-4 and HAdV-7 vaccines were used effectively in the United States military from the 1970s until 1999. Cessation of their use led to widespread outbreaks in barracks, and these vaccines have been reintroduced into military use. HAdVs are highly immunogenic and have been used as gene therapy vectors and vaccine vectors for other pathogens, including malaria and HIV, but no HAdV-specific vaccines are commercially available.

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Chapter 263

Rhinoviruses

E. Kathryn Miller and John V. Williams

Human rhinoviruses (HRVs) are the most frequent cause of the **common cold** in both adults and children. Although rhinoviruses were once thought to cause only the common cold, it is now known that they are associated with lower respiratory infections in adults and children. Many HRVs do not grow in culture; studies using molecular diagnostic tools such as polymerase chain reaction (PCR) have revealed that HRVs are leading causes of both mild and serious respiratory illnesses in children.

ETIOLOGY

HRVs are members of the Picornaviridae family ("pico" = small; "rna" = RNA genome). Traditional methods of virus typing using immune

antiserum have identified approximately 100 serotypes, classified into HRVA and HRVB species on the basis of genetic sequence similarity. A novel group of HRVs, designated HRVCs, has been detected by reverse transcriptase PCR but has not been cultivated using conventional methods. Virus gene sequence analysis demonstrates that HRVCs are a genetically distinct and diverse species. The increased proportions of HRV reported in recent PCR-based studies are likely the result of detection of these previously unknown HRVC viruses in addition to improved detection of known HRVA and HRVB strains.

EPIDEMIOLOGY

Rhinoviruses are distributed worldwide. There is no proven correlation between serotypes and epidemiologic or clinical characteristics, although several studies suggest that HRVC may be more strongly associated with lower respiratory infection and asthma than other HRVs. Multiple serotypes circulate in a community simultaneously, and particular HRV strains may be isolated during consecutive epidemic seasons, suggesting persistence in a community over an extended period. In temperate climates the incidence of HRV infection peaks in fall, with another peak in spring, but HRV infections occur year-round. HRVC appears to circulate with seasonal variation, exchanging dominance with HRVA. Rhinoviruses are the major infectious trigger for asthma among young children, and numerous studies have described a sharp increase in asthmatic attacks in this age group when school opens in the fall. Peak HRV incidence in the tropics occurs during the rainy season, from June to October.

Rhinoviruses are present in high concentrations in nasal secretions and can be detected in the lower airways. Rhinovirus particles are nonenveloped and quite hardy, persisting for hours to days in secretions on hands or other surfaces such as telephones, light switches, doorknobs, and stethoscopes. Transmission occurs when infected secretions carried on contaminated fingers are rubbed onto the nasal or conjunctival mucosa. Rhinoviruses are present in aerosols produced by talking, coughing, and sneezing. Children are the most important reservoir of the virus.

PATHOGENESIS

The majority of HRVs infect respiratory epithelial cells via intercellular adhesion molecule-1, but some HRV strains utilize the low-density lipoprotein receptor. The receptor for HRVCs is not known. Infection begins in the nasopharynx and spreads to the nasal mucosa and, in some cases, to bronchial epithelial cells in the lower airway. Rhinoviruses do not appear to cause significant direct cellular damage, so it is thought that many of the pathogenic effects are produced by the host immune response. Rhinovirus infection of bronchial epithelial cells in vitro induces the secretion of many inflammatory chemokines and cytokines. Both innate and adaptive immune mechanisms are important in HRV pathogenesis and clearance. HRV-specific nasal immunoglobulin (Ig) A can be detected on day 3 after infection, followed by the production of serum IgM and IgG after 7-8 days. Neutralizing IgG to HRVs may prevent or limit the severity of illness following reinfection. Cross protection between antibodies to different HRV serotypes is limited in breadth and duration. Both allergen exposure and elevated IgE values predispose patients with asthma to more severe respiratory symptoms in response to HRV infection. Abnormalities in the host cellular response to HRV infection that result in impaired apoptosis and increased viral replication may be responsible for the severe and prolonged symptoms in individuals with asthma.

CLINICAL MANIFESTATIONS

Most HRV infections produce clinical symptoms, but approximately 15% are asymptomatic. Typical symptoms of sneezing, nasal congestion, rhinorrhea, and sore throat develop following an incubation period of 1-4 days. Cough and hoarseness are present in one third of cases. Fever is less common with HRV than with other common respiratory viruses, including influenza virus, respiratory syncytial virus, and human metapneumovirus. Symptoms are frequently more severe and last longer in children, with 70% of children still reporting symptoms by day 10, compared with 20% of adults. Virus can be shed for as long as 3 wk.

HRVs are the most prevalent agents associated with acute wheezing, otitis media, and hospitalization for respiratory illness in children and are an important cause of severe pneumonia and exacerbation of asthma or chronic obstructive pulmonary disease in adults. HRV-associated hospitalizations are more frequent in young infants than in older children and in children with a history of wheezing or asthma. HRV infection in immunocompromised hosts may be life threatening. Certain strains or species of HRV, namely HRVC, may be more pathogenic than others.

DIAGNOSIS

Culturing HRV is labor intensive and of relatively low yield; HRVC has only been cultivated in polarized primary airway epithelial cell culture, a highly specialized method. Sensitive and specific diagnostic methods based on reverse transcriptase PCR are commercially available. However, because reverse transcriptase PCR tests do not identify the HRV types, it can be difficult to distinguish prolonged shedding from newly acquired infection. An important caveat of HRV detection is the fact that HRV infection can be asymptomatic, and thus the presence of the virus does not prove causality in all cases. Serology is impractical because of the great number of HRV serotypes. Presumptive clinical diagnosis based on symptoms and seasonality is not specific, because many other viruses cause similar clinical illnesses. Bacterial culture or antigen testing may exclude streptococcal pharyngitis. Rapid detection techniques for HRV might lessen the use of unnecessary antibiotics or procedures.

COMPLICATIONS

Possible complications of HRV infection include sinusitis, otitis media, asthma exacerbation, bronchiolitis, pneumonia, and, rarely, death. HRV-associated wheezing during infancy is a significant risk factor for the development of childhood asthma. This effect appears to remain until adulthood, but the mechanisms have not been elucidated. One large study determined that genetic variants at the 17q21 locus were associated with asthma in children who had experienced HRV wheezing illnesses during infancy. Further studies are required to determine the likely multiple genetic and environmental factors that contribute to HRV-related asthma.

TREATMENT

Supportive care is the mainstay of HRV treatment. The symptoms of HRV infection are commonly treated with analgesics, decongestants, antihistamines, or antitussives. Data are limited on the effectiveness of such nonprescription cold medications for children. If bacterial superinfections are highly suspected or diagnosed, antibiotics may be appropriate. Antibiotics are not indicated for uncomplicated viral upper respiratory infection. Vaccines have not been successfully developed because of the numerous HRV serotypes and limited cross protection between serotypes.

PREVENTION

Good handwashing remains the mainstay of prevention of HRV infection and should be reinforced frequently, especially in young children, the predominant "vectors" for disease.

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Chapter 264

Coronaviruses

Megan Culler Freeman and Mark R. Denison

Coronaviruses are increasingly recognized as important human pathogens. They cause up to 15% of common colds and have been implicated in more serious diseases, including croup, asthma exacerbations, bronchiolitis, and pneumonia. Evidence also suggests that coronaviruses may cause enteritis or colitis in neonates and infants and may be

underappreciated as agents of meningitis or encephalitis. Four coronaviruses are endemic in humans: human coronaviruses **(HCoVs) 229E**, **OC43**, **NL63**, and **HKU1**. In addition, 2 epidemics of previously unknown coronaviruses caused significant respiratory distress and high mortality rates among infected individuals. The discoveries of **SARS-associated coronavirus (SARS-CoV)** in 2003, the cause of **severe acute respiratory syndrome (SARS)**, and of **Middle East respiratory syndrome coronavirus (MERS-CoV)** in 2012, support the potential for coronaviruses to emerge from animal hosts such as bats and become important human pathogens.

ETIOLOGY

Coronaviruses are enveloped viruses of medium to large size (80-220 nm) that possess the largest known single-stranded positive-sense RNA genomes. These viruses encode the protein nsp14-ExoN, which is the first known RNA proofreading enzyme and is likely responsible for the evolution of the large and complex coronavirus genome. Coronaviruses derive their name from the characteristic surface projections of spike protein, which give a corona or crown-like appearance on negative-stain electron microscopy. Coronaviruses are organized taxonomically by a lettering system based on genomic phylogenetic relationships. Alphacoronaviruses include human coronavirus 229E (HCoV-229E) and HCoV-NL63. Betacoronaviruses include 4 human pathogens and are commonly divided into 4 lineages, without formal taxonomic recognition. HCoV-OC43 and the HCoV-HKU1 are in lineage A, while SARS-CoV falls in lineage B. Lineages C and D were exclusively comprised of bat coronaviruses until the discovery of MERS-CoV, which aligns with lineage C. Gammacoronaviruses and deltacoronaviruses presently include exclusively nonhuman pathogens.

In 2002-2003, coronaviruses received international attention during the SARS outbreak, which was responsible for more than 800 deaths in 30 countries. SARS-CoV, a novel coronavirus at the time of the epidemic, was found to be the causative agent of SARS. The detection of SARS-like coronaviruses in a live animal market in the Guangdong province in Southern China, along with serologic evidence of exposure in food handlers in the same market, suggest that these markets may have facilitated the spread of SARS-CoV to humans from an animal reservoir. Subsequent studies identified SARS-like coronaviruses in fecal specimens from asymptomatic Chinese horseshoe bats that are very closely related, but not direct precursors to, SARS-CoV. Thus, although bats are thought to be a reservoir for SARS-like precursors, the precise antecedent to SARS-CoV remains to be identified.

In June 2012, another novel coronavirus, **MERS-CoV**, was isolated from a man with acute pneumonia and renal failure in Saudi Arabia. To date, more than 500 cases have been confirmed in Saudi Arabia, Qatar, Jordan, United Arab Emirates, Oman, Kuwait, Yemen, United States (imported), and the United Kingdom; 145 of these patients died from their infection. **MERS-CoV** differs from SARS in that it seems to be less communicable, although human-to-human transmission has been confirmed. **MERS-CoV** has been shown to use dipeptidyl peptidase 4 as its cellular receptor, a difference compared to SARS-CoV, which utilizes ACE-2. With this receptor specificity, **MERS-CoV** is able to infect cells from several animal lineages, including human, pig, and bat, suggesting the possibility of movement between multiple species.

EPIDEMIOLOGY

Seroprevalence studies have demonstrated that antibodies against 229E and OC43 increase rapidly during early childhood, so that by adulthood 90-100% of persons are seropositive. Although less information is available for HKU1 and NL63, available studies demonstrate similar patterns of seroconversion to these viruses during early childhood. Although some degree of strain-specific protection may be afforded by recent infection, reinfections are common and occur despite the presence of strain-specific antibodies. Attack rates are similar in different age groups. Although infections occur throughout the year, there is a peak during the winter and early spring for each of these HCoVs. In the United States, outbreaks of OC43 and 229E have occurred in 2- to 3-yr alternating cycles. Independent studies of viral etiologies of upper and lower respiratory infections during the same period, but from different countries, have confirmed that all known HCoVs have a worldwide distribution. Studies using both viral culture and polymerase chain reaction (PCR) multiplex assays demonstrate that coronaviruses often occur as coinfections with other respiratory viruses, including respiratory syncytial virus, adenovirus, rhinovirus, or human metapneumovirus. Volunteer studies demonstrated that OC43 and 229E are transmitted predominantly through the respiratory route. Droplet spread appears to be most important, although aerosol transmission may also occur.

There have been no identified natural or laboratory-acquired cases of SARS-CoV since 2004, but the mechanisms of introduction, spread, and disease remain important for potential animal-to-human transmission and disease. The primary mode of SARS-CoV transmission occurred through direct or indirect contact of mucous membranes with infectious droplets or fomites. Aerosol transmission was less common, occurring primarily in the setting of endotracheal intubation, bronchoscopy, or treatment with aerosolized medications. Fecal-oral transmission did not appear to be an efficient mode of transmission, but may have occurred because of the profuse diarrhea observed in some patients. The seasonality of SARS-CoV remains unknown. SARS-CoV is not highly infectious, with generally only 2-4 secondary cases resulting from a single infected adult. During the SARS epidemic, a small number of infected individuals, "superspreaders," transmitted infection to a much larger number of persons, but the mechanism for this high degree of spread remains unknown. In contrast, persons with mild disease, such as children younger than 12 yr of age, rarely transmitted the infection to others. Infectivity correlated with disease stage; transmission occurred almost exclusively during symptomatic disease. During the 2003 outbreak, most individuals with SARS-CoV infection were hospitalized within 3-4 days of symptom onset. Consequently, most subsequent infections occurred within hospitals and involved either healthcare workers or other hospitalized patients. MERS-CoV may begin in an animal vector (camel, bat); although person-to-person contagion has been reported, it is thought to be a minor mechanism for acquisition of the MERS-CoV.

PATHOGENESIS

Coronaviruses are reported to cause minimal cytopathology. Studies with SARS-CoV in human airway epithelial cell cultures indicate that ciliated cells are principal targets for infection and that infected ciliated cells may be directly extruded or lost from the infected monolayer. Thus, the cytopathology from other HCoVs may be from direct cell infection and loss, although symptoms may also be from the host immune response. Infection with OC43 and 229E is associated with the elaboration of cytokines, including interleukin-8 and interferon-γ. In experimentally infected volunteers, serum-specific immunoglobulin A and immunoglobulin G antibody levels peak 12-14 days after infection but decline rapidly thereafter. At 1 year following experimental infection, there is only partial protection against reinfection with the homologous strain, suggesting a challenge for the development of successful vaccines against HCoVs.

CLINICAL MANIFESTATIONS

While all known HCoVs cause respiratory disease, the role of HCoVs in gastrointestinal and neurologic disease is less clear and remains to be proven. In addition to causing severe respiratory pathology, both SARS-CoV and MERS-CoV can cause renal failure, although this symptom is observed less frequently during SARS-CoV infections.

Respiratory Infections

Even though up to 50% of respiratory tract infections with OC43 and 229E are asymptomatic, coronaviruses are still responsible for up to 15% of common colds. Cold symptoms caused by HCoVs are indistinguishable from those caused by rhinoviruses and other respiratory viruses. The average incubation period is 2-4 days, with symptoms typically lasting 4-7 days. Rhinorrhea, cough, sore throat, malaise, and headache are the most common symptoms. Fever occurs in up to 60% of cases. Coronavirus NL63 is a cause of croup in children younger than 3 yr of age. Coronavirus infections are linked to episodes of wheezing in asthmatic children, albeit at a lower frequency and

severity than observed with rhinovirus and respiratory syncytial virus infections. Lower respiratory tract infections, including bronchiolitis and pneumonia, are also reported in immunocompetent and immunocompromised children and adults. As with respiratory syncytial virus or rhinovirus, coronavirus detection in upper respiratory infections is frequently associated with acute otitis media and can be isolated from middle ear fluid.

Nonrespiratory Sequelae

There is some evidence to support a role for coronaviruses in human gastrointestinal disease, particularly in young children. Coronavirus-like particles have been detected by electron microscopy in the stools of infants with nonbacterial gastroenteritis. In addition, several outbreaks in neonatal intensive care units of gastrointestinal disease characterized by diarrhea, bloody stools, abdominal distention, bilious gastric aspirates, and classic necrotizing enterocolitis have also been associated with the presence of coronavirus-like particles in stools. In older children and adults, coronavirus-like viruses have been observed with similar frequency in symptomatic and asymptomatic individuals, making it difficult to discern if they are pathogenic in the gastrointestinal tract. Coronaviruses are well-known causes of neurologic disease in animals, including demyelinating encephalitis, but their role in causing human neurologic disease remains unclear. They have been detected by culture, in situ hybridization, and reverse transcriptase PCR (RT-PCR) in brain tissue from a few patients with multiple sclerosis. However, coronavirus RNA has also been recovered from the spinal fluid and brain tissue of adults without neurologic disease. HCoV-OC43 has been detected by RT-PCR in the spinal fluid and nasopharynx of one child with acute disseminated encephalomyelitis.

Severe Acute Respiratory Syndrome–Associated Coronavirus

SARS-CoV infections in teenagers and adults included a viral replication phase and an immunologic phase. During the viral replication phase there was a progressive increase in viral load that reached its peak during the 2nd wk of illness. The appearance of specific antibodies coincided with peak viral replication. The clinical deterioration that typified the 2nd and 3rd wk of illness was characterized by a decline in the viral load and evidence of tissue injury likely from cytokine-mediated immunity. The explanation for milder clinical disease in children younger than 12 yr of age has not been determined. Seroepidemiologic studies suggest that asymptomatic SARS-CoV infections were uncommon. The incubation period ranged from 1-14 days, with a median of 4-6 days. The clinical manifestations were nonspecific, most commonly consisting of fever, cough, malaise, coryza, chills or rigors, headache, and myalgia. Coryza was more common in children younger than 12 yr of age, whereas systemic symptoms were seen more often in teenagers. Some young children had no respiratory symptoms. Gastrointestinal symptoms, including diarrhea and nausea or vomiting, occurred in up to one third of cases. The clinical course of SARS-CoV infection varied with age. Adults were most severely affected, with initial onset of fever, cough, chills, myalgia, malaise, and headache. Following an initial improvement at the end of the 1st wk, fever recurred and respiratory distress developed, with dyspnea, hypoxemia, and diarrhea. These symptoms progressed in 20% of patients to acute respiratory distress syndrome and respiratory failure. Acute renal failure with histologic acute tubular necrosis was present in 6.9% of patients, likely a result of hypoxic kidney damage. Of SARS patients, 28.8% had abnormal urinalysis, with viral genome detectable by quantitative RT-PCR. In contrast, children younger than 12 yr of age had a relatively mild nonspecific illness, with only a minority experiencing significant lower respiratory tract disease and illness typically lasting less than 5 days. There were no deaths or acute respiratory distress syndrome in children younger than 12 yr of age from SARS-CoV infection. Adolescents manifested increasing severity in direct correlation to increasing age; respiratory distress and hypoxemia were observed in 10-20% of patients, one third of whom required ventilator support. The case fatality rate from SARS-CoV infection during the 2003 outbreak was 10-17%. No pediatric deaths were reported. The estimated case fatality rate according to age varied from <1% for those younger than 20 yr of age to >50% for those older than 65 yr of age.

Middle East Respiratory Syndrome Coronavirus

The incubation period of HCoV-EMC infection is thought to be approximately 10 days. Because most healthcare workers caring for patients with HCoV-EMC infection have not been infected, this virus is considered to be less transmissible from person to person than SARS-CoV. Two clusters of patients have been diagnosed with confirmed cases, although it is difficult to determine if their infections were spread from person to person or if they shared a common environmental exposure. A third cluster in the United Kingdom confirmed person-to-person transmission, as only 1 of the individuals had traveled to the Arabian Peninsula. Because the method of transmission is presently unknown, appropriate airborne and contact precautions are required when treating infected patients. Patients have presented with acute respiratory infection, a fever higher than 38°C (100.4°F), cough, and pulmonary parenchymal disease such as pneumonia or acute respiratory distress syndrome. Lymphopenia, neutrophilia, and late thrombocytopenia occurred in the index-case patient. This patient also had progressive renal impairment, beginning on the ninth day of symptoms which continued to progress until the patient's death at day 11. The case fatality rate is presently >65% for the limited number of confirmed cases. Most patients have been adults, although children as young as 1 yr of age have been infected. Approximately 65% of patients have severe disease requiring hospitalization; approximately 5% had mild disease, and the remainder may have been asymptomatic.

DIAGNOSIS

In the past, specific diagnostic tests for coronavirus infections were not available in most clinical settings. The use of conserved PCR primers for coronaviruses in multiplex RT-PCR viral diagnostic panels now allows widely available and sensitive detection of the viruses. Virus culture of primary clinical specimens remains a challenge for HCoVs HKU1, OC43, 229E, and NL63, even though both SARS-CoV and MERS-CoV can successfully be grown in culture from respiratory samples. Serodiagnosis with complement fixation, neutralization, hemagglutination inhibition, enzyme immunoassay, and Western blots have been used in the research setting. The diagnosis of SARS-CoV infection can be confirmed by serologic testing, detection of viral RNA using RT-PCR, or isolation of the virus in cell culture. Even though serology for SARS-CoV has sensitivity and specificity approaching 100%, antibodies are not detectable until 10 days after the onset of symptoms, and immunoglobulin G seroconversion may be delayed for up to 4 wk. In addition, the SARS epidemic resulted in the inclusion of coronavirus-conserved primers in many diagnostic PCR multiplex assays such that coronaviruses may be more readily detected. For emerging coronaviruses, such as HCoV-EMC, highly conserved primers were used for initial detection, with confirmatory assays using specific primers. Thus, the mainstay of early diagnosis is RT-PCR. For all known endemic and emerging HCoVs, respiratory specimens (nasopharyngeal swabs or aspirates) are most likely to be positive, but in a setting of a possible novel coronavirus, serum or stool may be positive. Two highly sensitive real-time RT-PCR assays are currently available for testing for MERS-CoV RNA in addition to utilizing immunofluorescence microscopy for the detection of antibody response.

TREATMENT AND PREVENTION

Coronavirus infections of humans are acute and self-limited, although persistent infection and shedding may occur in multiple animal models in the setting of minimal or no symptomology. There are no available antiviral agents for clinical use against coronaviruses, although strategies targeting conserved coronavirus proteases have been shown to block replication of the virus in vitro. Challenges for development of effective vaccines targeted against OC43, 229E, HKU1, and NL63 include the fact that infections are rarely life-threatening and reinfection is the rule, even in the presence of natural immunity from previous infections. Treatment of SARS-CoV and MERS-CoV infections is primarily supportive. The role of antiviral and immune-modulating

agents remains inconclusive, largely because none of these therapies have been evaluated in properly conducted randomized controlled trials. Ribavirin was extensively used during the 2003 SARS-CoV outbreak, but is of questionable benefit given its poor in vitro activity against SARS-CoV at clinically relevant concentrations. The identification of the proofreading nsp14-exonuclease suggests that this activity may be important in resistance to antiviral nucleosides and RNA mutagens such as ribavirin. Systemic corticosteroid therapy was temporally associated with clinical improvement in some patients. In another small, open-label, nonrandomized pilot study, interferon-α was associated with more rapid resolution of oxygen requirements and radiographic abnormalities. Human monoclonal antibodies derived from SARS patients demonstrate broad neutralization against early and late epidemic strains of SARS-CoV and could potentially be therapeutic.

An effective vaccine for SARS-CoV and MERS-CoV is highly desirable but not yet available. A potential vaccine target is the viral spike protein, which could be delivered as a recombinant protein or via viral or DNA vectors. This approach appears to be effective against closely related strains of SARS-CoV but not necessarily early animal or human variants. A SARS-CoV vaccine approach that recently has shown success in animal models utilized a live-engineered SARS-CoV mutant with inactivated ExoN, demonstrating attenuation and protection in a variety of aged, immunocompromised mice. Approaches for rapid development of stably attenuated live viruses or broadly immunogenic and cross-protective protein immunogens continues to be a key area for future research. Although SARS-CoV demonstrated characteristics of symptomatic transmission that made it controllable by public health measures like quarantine, these characteristics cannot be assumed for future novel HCoVs. The recent outbreak of MERS-CoV serves as a reminder that coronavirus emergence is both likely and unpredictable, making it very important to continue studies of the coronavirus replication, emergence, and transmission of coronaviruses. Additionally, strategies for rapid recovery, testing, and development of vaccines and neutralizing human monoclonal antibodies may be essential to prevent the high morbidity and mortality associated with previous epidemics.

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Chapter 265
Rotaviruses, Caliciviruses, and Astroviruses

Dorsey M. Bass

Diarrhea is a leading cause of childhood mortality in the world, accounting for 5-10 million deaths/yr. In early childhood, the single most important cause of severe dehydrating diarrhea is rotavirus infection. Rotavirus and other gastroenteric viruses not only are major causes of pediatric mortality but also lead to significant morbidity. Children in the United States, before vaccine was available, were estimated to have a risk of hospitalization for rotavirus diarrhea of 1:43, corresponding to 80,000 hospitalizations annually.

ETIOLOGY

Rotaviruses, astroviruses, caliciviruses such as the **Norwalk agent,** and enteric adenoviruses are the medically important pathogens of human viral gastroenteritis (see Chapter 340).

Rotaviruses are in the Reoviridae family and cause disease in virtually all mammals and birds. These viruses are wheel-like, triple-shelled icosahedrons containing 11 segments of double-stranded RNA. The diameter of the particles on electron microscopy is approximately 80 nm. Rotaviruses are classified by serogroup (A, B, C, D, E, F, and G) and subgroup (I or II). Rotavirus strains are species specific and do not cause disease in heterologous hosts. Group A includes the common human pathogens as well as a variety of animal viruses. Group B rotavirus is reported as a cause of severe disease in infants and adults in China only. Occasional human outbreaks of group C rotavirus are reported. The other serogroups infect only nonhumans.

Subgrouping of rotaviruses is determined by the antigenic structure of the inner capsid protein, VP6. Serotyping of rotaviruses, described for group A only, is determined by classic cross-neutralization testing and depends on the outer capsid glycoproteins, VP7 and VP4. The VP7 serotype is referred to as the *G type* (for glycoprotein). There are 10 G serotypes, of which 4 cause most illness and vary in occurrence from year to year and region to region. The VP4 serotype is referred to as the P type. There are 11 P serotypes. Although both VP4 and VP7 elicit neutralizing immunoglobulin G antibodies, the relative role of these systemic antibodies compared with that of mucosal immunoglobulin A antibodies and cellular responses in protective immunity remains unclear.

Caliciviruses, which constitute the Caliciviridae family, are small 27-35 nm viruses that are the most common cause of gastroenteritis outbreaks in older children and adults. Caliciviruses also cause a rotavirus-like illness in young infants. They are positive-sense, single-stranded RNA viruses with a single structural protein. Human caliciviruses are divided into 2 genera, the noroviruses and sapoviruses. Caliciviruses have been named for locations of initial outbreaks: Norwalk, Snow Mountain, Montgomery County, Sapporo, and others. Caliciviruses and astroviruses are sometimes referred to as **small, round viruses** on the basis of appearance on electron microscopy.

Astroviruses, which constitute the Astroviridae family, are important agents of viral gastroenteritis in young children, with a high incidence in both the developing and developed worlds. Astroviruses are positive-sense, single-stranded RNA viruses. They are small particles, approximately 30 nm in diameter, with a characteristic central 5- or 6-pointed star when viewed on electron microscopy. The capsid consists of 3 structural proteins. There are 8 known human serotypes.

Enteric adenoviruses are a common cause of viral gastroenteritis in infants and children. Although many adenovirus serotypes exist and are found in human stool, especially during and after typical upper respiratory tract infections (see Chapter 262), only serotypes 40 and 41 cause gastroenteritis. These strains are very difficult to grow in tissue culture. The virus consists of an 80 nm-diameter icosahedral particle with a relatively complex double-stranded DNA genome.

Aichi virus is a picornavirus that is associated with gastroenteritis and was initially described in Asia. Several other viruses that may cause diarrheal disease in animals have been postulated but are not well established as human gastroenteritis viruses. These include coronaviruses, toroviruses, and pestiviruses. The **picobirnaviruses** are an unclassified group of small (30 nm), single-stranded RNA viruses that have been found in 10% of patients with HIV-associated diarrhea.

EPIDEMIOLOGY

Worldwide, rotavirus is estimated to cause more than 111 million cases of diarrhea annually in children younger than 5 yr of age. Of these, 18 million cases are considered at least moderately severe, with approximately 500,000 deaths per year. Rotavirus causes 3 million cases of diarrhea, 80,000 hospitalizations, and 20-40 deaths annually in the United States.

Rotavirus infection is most common in winter months in temperate climates. In the United States, the annual winter peak historically spread from west to east. Unlike the spread of other winter viruses, such as influenza, this wave of increased incidence was not caused by a single prevalent strain or serotype. Since widespread adoption of vaccine, this geographic phenomenon has vanished. Typically, several serotypes predominate in a given community for 1 or 2 seasons, while nearby locations may harbor unrelated strains. Disease tends to be most severe in patients 3-24 mo of age, although 25% of the cases of severe disease occur in children older than 2 yr of age, with serologic evidence of infection developing in virtually all children by 4-5 yr of age. Infants younger than 3 mo are relatively protected by transplacental antibody and possibly breastfeeding. Infections in neonates and in adults in close

contact with infected children are generally asymptomatic. Some rotavirus strains have stably colonized newborn nurseries for years, infecting virtually all newborns without causing any overt illness.

Rotavirus and the other gastrointestinal viruses spread efficiently via a fecal-oral route, and outbreaks are common in children's hospitals and childcare centers. The virus is shed in stool at very high concentration before and for days after the clinical illness. Very few infectious virions are needed to cause disease in a susceptible host.

The epidemiology of **astroviruses** is not as thoroughly studied as that of rotavirus, but these viruses are a common cause of mild to moderate watery winter diarrhea in children and infants and an uncommon pathogen in adults. Hospital outbreaks are common. **Enteric adenovirus** gastroenteritis occurs year-round, mostly in children younger than 2 yr of age. Nosocomial outbreaks occur but are less common than with rotavirus and astrovirus. **Calicivirus** is best known for causing large, explosive outbreaks among older children and adults, particularly in settings such as schools, cruise ships, and hospitals. Often a single food, such as shellfish or water used in food preparation, is identified as a source. Like astrovirus and rotavirus, caliciviruses are also commonly found in winter infantile gastroenteritis.

PATHOGENESIS

Viruses that cause human diarrhea selectively infect and destroy villus tip cells in the small intestine. Biopsies of the small intestines show variable degrees of villus blunting and round cell infiltrate in the lamina propria. Pathologic changes may not correlate with the severity of clinical symptoms and usually resolve before the clinical resolution of diarrhea. The gastric mucosa is not affected despite the commonly used term *gastroenteritis,* although delayed gastric emptying has been documented during Norwalk virus infection.

In the small intestine, the upper villus enterocytes are differentiated cells, which have both digestive functions, such as hydrolysis of disaccharides, and absorptive functions, such as the transport of water and electrolytes via glucose and amino acid cotransporters. Crypt enterocytes are undifferentiated cells that lack the brush-border hydrolytic enzymes and are net secretors of water and electrolytes. Selective viral infection of intestinal villus tip cells thus leads to (1) decreased absorption of salt and water and an imbalance in the ratio of intestinal fluid absorption to secretion, and (2) diminished disaccharidase activity and malabsorption of complex carbohydrates, particularly lactose. Most evidence supports altered absorption as the more important factor in the genesis of viral diarrhea. It has been proposed that a rotavirus nonstructural protein (NSP4) functions as an enterotoxin.

Viremia may occur often in severe, primary infections, but symptomatic **extraintestinal infection** is extremely rare in immunocompetent persons—although immunocompromised patients may rarely experience hepatic and renal involvement. The increased vulnerability of infants (compared with older children and adults) to severe morbidity and mortality from gastroenteritis viruses may relate to a number of factors, including decreased intestinal reserve function, lack of specific immunity, and decreased nonspecific host defense mechanisms such as gastric acid and mucus. Viral enteritis greatly enhances intestinal permeability to luminal macromolecules and has been postulated to increase the risk for food allergies.

CLINICAL MANIFESTATIONS

Rotavirus infection typically begins after an incubation period of <48 hr (range: 1-7 days) with mild to moderate fever as well as vomiting, followed by the onset of frequent, watery stools. All 3 symptoms are present in about 50-60% of cases. Vomiting and fever typically abate during the 2nd day of illness, but diarrhea often continues for 5-7 days. The stool is without gross blood or white blood cells. Dehydration may develop and progress rapidly, particularly in infants. The most severe disease typically occurs among children 4-36 mo of age. Malnourished children and children with underlying intestinal disease, such as short-bowel syndrome, are particularly likely to acquire severe rotavirus diarrhea. Rarely, immunodeficient children experience severe and prolonged illness. Although most newborns infected with rotavirus are asymptomatic, some outbreaks of necrotizing enterocolitis have been associated with the appearance of a new rotavirus strain in the affected nurseries.

The clinical course of **astrovirus** infection appears to be similar to that of rotavirus gastroenteritis, with the notable exception that the disease tends to be milder, with less significant dehydration. **Adenovirus enteritis** tends to cause diarrhea of longer duration, often 10-14 days. The **Norwalk virus** has a short (12-hr) incubation period. Vomiting and nausea tend to predominate in illness associated with the Norwalk virus, and the duration is brief, usually consisting of 1-3 days of symptoms. The clinical and epidemiologic picture of Norwalk virus often closely resembles so-called food poisoning from preformed toxins such as *Staphylococcus aureus* and *Bacillus cereus.*

DIAGNOSIS

In most cases, a satisfactory diagnosis can be made on the basis of the clinical and epidemiologic features. Enzyme-linked immunosorbent assays, which offer >90% specificity and sensitivity, are available for detection of group A rotavirus, caliciviruses, and enteric adenovirus in stool samples. Latex agglutination assays are also available for group A rotavirus and are less sensitive than enzyme-linked immunosorbent assay. Research tools include electron microscopy of stools, RNA polymerase chain reaction analysis to identify G and P antigens, and culture. The diagnosis of viral gastroenteritis should always be questioned in patients with persistent or high fever, blood or white blood cells in the stool, or persistent severe or bilious vomiting, especially in the absence of diarrhea.

LABORATORY FINDINGS

Isotonic dehydration with acidosis is the most common finding in children with severe viral enteritis. The stools are free of blood and leukocytes. Although the white blood cell count may be moderately elevated secondary to stress, the marked left shift seen with invasive bacterial enteritis is absent.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other infectious causes of enteritis, such as bacteria and protozoa. Occasionally, surgical conditions such as appendicitis, bowel obstruction, and intussusception may initially mimic viral gastroenteritis.

TREATMENT

Avoiding and treating dehydration are the main goals in treatment of viral enteritis. A secondary goal is maintenance of the nutritional status of the patient (see Chapters 58 and 340).

There is no routine role for antiviral drug treatment of viral gastroenteritis. Controlled studies show no benefit from antiemetics or antidiarrheal drugs, and there is a significant risk for serious side effects with both types of agents. Antibiotics are similarly of no benefit. Immunoglobulins have been administered orally to both normal and immunodeficient patients with severe rotavirus gastroenteritis, but this treatment is currently considered experimental. Therapy with probiotic organisms such as *Lactobacillus* species has been shown to be helpful only in mild cases and not in dehydrating disease.

Supportive Treatment

Rehydration via the oral route can be accomplished in most patients with mild to moderate dehydration (see Chapters 58 and 340). Severe rehydration requires immediate intravenous therapy followed by oral rehydration. Modern oral rehydration solutions containing appropriate quantities of sodium and glucose promote optimum absorption of fluid from the intestine. There is no evidence that a particular carbohydrate source (rice) or addition of amino acids improves the efficacy of these solutions for children with viral enteritis. Other clear liquids, such as flat soda, fruit juice, and sports drinks, are inappropriate for rehydration of young children with significant stool loss. Rehydration via the oral (or nasogastric) route should be done over 6-8 hr, and feedings should be initiated immediately thereafter. Providing the rehydration fluid at a slow, steady rate, typically 5 mL/min, reduces vomiting and improves the success of oral therapy. Rehydration

solution should be continued as a supplement to make up for ongoing excessive stool loss. Initial intravenous fluids are required for the infant in shock or the occasional child with intractable vomiting.

After rehydration has been achieved, resumption of a normal diet for age has been shown to result in a more rapid recovery from viral gastroenteritis. Prolonged (>12 hr) administration of exclusive clear liquids or dilute formula is without clinical benefit and actually prolongs the duration of diarrhea. Breastfeeding should be continued even during rehydration. Selected infants may benefit from lactose-free feedings (such as soy formula and lactose-free cow's milk) for several days, although this step is not necessary for most children. Hypocaloric diets low in protein and fat such as BRAT (*b*ananas, *r*ice, cereal, *a*pplesauce, and *t*oast) have not been shown to be superior to a regular diet.

PROGNOSIS

Most fatalities occur in infants with poor access to medical care and are attributed to dehydration. Children may be infected with rotavirus each year during the 1st 5 yr of life, but each subsequent infection decreases in severity. Primary infection results in a predominantly serotype-specific immune response, whereas reinfection, which is usually with a different serotype, induces a broad immune response with cross-reactive heterotypic antibody. After the initial natural infection, children have limited protection against subsequent asymptomatic infection (38%) and greater protection against mild diarrhea (73%) and moderate to severe diarrhea (87%). After the second natural infection, protection increases against subsequent asymptomatic infection (62%) and mild diarrhea (75%) and is complete (100%) against moderate to severe diarrhea. After the third natural infection, there is even higher protection against subsequent asymptomatic infection (74%) and near-complete protection against even mild diarrhea (99%).

PREVENTION

Good hygiene reduces the transmission of viral gastroenteritis, but even in the most hygienic societies, virtually all children become infected as a result of the efficiency of infection of the gastroenteritis viruses. Good handwashing and isolation procedures can help control nosocomial outbreaks. The role of breastfeeding in prevention or amelioration of rotavirus infection may be small, given the variable protection observed in a number of studies. Vaccines offer the best hope for control of these ubiquitous infections.

Vaccines

A trivalent rotavirus vaccine was licensed in the United States in 1998 and was subsequently linked to an increased risk for intussusception, especially during the 3-14 day period after the 1st dose and the 3-7 day period after the 2nd dose. The vaccine was withdrawn from the market in 1999. Subsequently 2 new live, oral rotavirus vaccines have been approved in the United States after extensive safety and efficacy testing.

A live, oral, pentavalent rotavirus vaccine was approved in 2006 for use in the United States. The vaccine contains 5 reassortant rotaviruses isolated from human and bovine hosts. Four of the reassortant rotaviruses express 1 serotype of the outer protein VP7 (G1, G2, G3, or G4), and the 5th expresses the protein P1A (genotype P[8]) from the human rotavirus parent strain. The pentavalent vaccine protects against rotavirus gastroenteritis when administered as a 3 dose series at 2, 4, and 6 mo of age. The 1st dose should be administered between 6 and 12 wk of age, with all 3 doses completed by 32 wk of age. The vaccine provides substantial protection against rotavirus gastroenteritis, with primary efficacy of 98% against severe rotavirus gastroenteritis caused by G1-G4 serotypes and 74% efficacy against rotavirus gastroenteritis of any severity through the first rotavirus season after vaccination. It provides a 96% reduction in hospitalizations for rotavirus gastroenteritis through the 1st 2 yr after the 3rd dose. In a study of more than 70,000 infants, the pentavalent vaccine did not increase the risk for intussusception, although other studies suggest a slight increased risk.

Another new monovalent rotavirus vaccine was licensed in the United States and also appears to be safe and effective. It is an attenuated monovalent human rotavirus and is administered as 2 oral doses at 2 and 4 mo of age. The vaccine has 85% efficacy against severe gastroenteritis and was found to reduce hospital admissions for all diarrhea by 42%. Despite being monovalent, the vaccine is effective in prevention of all 4 common serotypes of human rotavirus.

Preliminary surveillance data on rotavirus incidence from the U.S. Centers for Disease Control and Prevention suggest that rotavirus vaccination greatly reduced the disease burden in the United States during the 2007-2008 rotavirus season. Given the incomplete vaccine coverage during this period, the results suggest a degree of "herd immunity" from rotavirus immunization. Studies from several developed countries show greater than 90% protection against severe rotavirus disease. Studies from developing countries show 50-60% protection from severe disease. Vaccine-associated disease has been reported in vaccine recipients who have severe combined immunodeficiency disease (a contraindication). In addition, vaccine-derived virus may undergo reassortment and become more virulent, producing diarrhea in unvaccinated siblings.

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Chapter 266

Human Papillomaviruses

Anna-Barbara Moscicki

See also Chapter 667.

Human papillomaviruses (HPVs) cause a variety of proliferative cutaneous and mucosal lesions, including common skin warts, benign and malignant anogenital tract lesions, oral pharyngeal cancers, and life-threatening respiratory papillomas. Most HPV-related infections in children and adolescents are benign.

ETIOLOGY

The papillomaviruses are small (55 nm), DNA-containing viruses that are ubiquitous in nature, infecting most mammalian and many non-mammalian animal species. Strains are almost always species specific. More than 100 different types of HPVs have been identified through comparison of sequence homologies. The different HPV types typically cause disease in specific anatomic sites; more than 30 HPV types have been identified from genital tract specimens.

EPIDEMIOLOGY

HPV infections of the skin are common, and most individuals are probably infected with 1 or more HPV types at some time. There are no animal reservoirs for HPV; all transmission is presumably from person to person. There is little evidence to suggest that HPV is transmitted by fomites. Common warts, including palmar and plantar warts, are frequently seen in children and adolescents and typically infect the hands and feet, common areas of frequent minor trauma.

Human papillomavirus is the most prevalent viral sexually transmitted infection in the United States. Up to 80% of sexually active women will acquire HPV through sexual transmission; most have their first infection within 3 yr of beginning sexual intercourse. The greatest risks for HPV in sexually active adolescents is exposure to new sexual partners or having more than 1 partner, underscoring the ease of transmission of this virus through sexual contact. It is estimated that after 11 acts of sexual intercourse 100% of all HPV types will be transmitted to the other sexual partner. Couple studies show that there is high concordance in the genital area as well as between the hand and the genital area in the other partner. Whether the DNA detected in the hand is capable of transmitting infectious particles is unknown. Unlike other sexually transmitted infections, female-to-male transmission appears greater than male-to-female transmission. This may be because males in general have superficial transient infections or deposition. In turn, males do not develop an adequate immune response, so reinfections

are quite common. The prevalence of HPV in women decreases with time, suggesting immune protection, whereas in men, the prevalence of HPV remains high across all ages.

As with many other genital pathogens, perinatal transmission to newborns also occurs, but infections appear transient. Transmission from caregiver to the child during the early childhood years has also been documented but is generally transient, as with perinatal detection. It remains unclear whether these HPV DNA detections are simply deposition of caregiver DNA or true infections. Detection of HPV DNA in older preadolescent children is rare. HPV DNA detection in nonsexually active adolescents has been reported, but the reports of no sexual activity in adolescent populations can be difficult to confirm. If lesions are detected in a child older than 3 yr of age, the possibility of sexual transmission should be raised.

In adolescents, HPV DNA is most commonly detected without evidence of any lesion. Some of these detections are thought to be the result of partner deposition and hence do not represent a true infection. In older women, detection of HPV DNA is more commonly associated with a lesion. This is because the HPV DNA detected in older women reflects those HPV infections that became established persistent infections. Persistence is now the known necessary prerequisite for the development of significant precancerous lesions and cervical cancer. Approximately 15-20% of sexually active adolescents have detectable HPV at any given time and have normal cytologic findings. External genital warts are much less common, occurring in <1% of adolescents. The most common clinically detected lesion in adolescent women is the cervical lesion termed **low-grade squamous intraepithelial lesion (LSIL)** (Table 266-1). LSILs can be found in 25-30% of adolescents infected with HPV. LSIL is a cytologic and histologic term to reflect the benign changes caused by an active viral infection and is likely present in most, if not all, women with HPV infection. The majority of women, however, have very minute or subtle lesions not easily detected by cytology. As with HPV DNA detection, most LSILs regress spontaneously in young women and do not require any intervention or therapy. Less commonly, HPV can induce more severe cellular changes, termed **high-grade squamous intraepithelial lesions (HSILs)** (see Chapter 553).

Although HSILs are considered precancerous lesions, they rarely progress to invasive cancer. HSILs occur in approximately 0.4-3% of sexually active women, whereas invasive cervical cancer occurs in 8 cases per 100,000 adult women. In true virginal populations, including children who are not sexually abused, rates of clinical disease are close to zero. In the United States, there are approximately 12,000 new cases and 3,700 deaths from cervical cancer each year. Worldwide, cervical cancer is the second most common cause of cancer deaths among women.

Some infants may acquire papillomaviruses during passage through an infected birth canal, leading to recurrent **juvenile laryngeal papillomatosis** (also referred to as *respiratory papillomatosis*). Cases also have been reported after cesarean section. The incubation period for emergence of clinically apparent lesions (genital warts or laryngeal papillomas) after perinatally acquired infection is unknown but is estimated to be around 3-6 mo (see Chapter 390.2). It may be that infections can also occur during hygienic care from an infected parent.

Genital warts appearing in childhood may result from sexual abuse, with HPV transmission during the abusive contact. Genital warts may represent a sexually transmitted infection even in some very young children. Their presence is cause to suspect that possibility. A child with genital warts should therefore be provided with a complete evaluation for evidence of possible abuse (see Chapter 40.1), including the presence of other sexually transmitted infections (see Chapter 120). Presence of genital warts in a child does not confirm sexual abuse, because perinatally transmitted genital warts may go undetected until the child is older. Typing for specific genital HPV types in children is not helpful in diagnosis or to confirm sexual abuse status, because the same genital types occur in both perinatal transmission and abuse.

PATHOGENESIS

Initial HPV infection of the cervix is thought to begin by viral invasion of the basal cells of the epithelium, a process that is enhanced by disruption of the epithelium caused by trauma or inflammation. It is thought that the virus initially remains relatively dormant because virus is present without any evidence of clinical disease. The life cycle of HPV depends on the differentiation program of keratinocytes. The pattern of HPV transcription varies throughout the epithelial layer as well as through different stages of disease (LSIL, HSIL, invasive cancer). Understanding of HPV transcription enhances understanding of its ability to behave as an oncovirus. Early region proteins, E6 and E7, function as transactivating factors that regulate cellular transformation. Complex interactions between E6- and E7-transcribed proteins and host proteins result in the perturbation of normal processes that regulate cellular DNA synthesis. The perturbations caused by E6 and E7 are primarily disruption of the antioncoprotein p53 and retinoblastoma protein (Rb), respectively, contributing to the development of anogenital cancers. Disruption of these proteins results in continued cell proliferation, even under the circumstances of DNA damage, which leads to basal cell proliferation, chromosomal abnormalities,

Table 266-1 Terminology for Reporting Cervical Cytology and Histology

DESCRIPTIVE DIAGNOSIS OF EPITHELIAL CELL ABNORMALITIES	EQUIVALENT TERMINOLOGY
SQUAMOUS CELL	
Atypical squamous cells of undetermined significance (ASC-US)	Squamous atypia
Atypical squamous cells, cannot exclude HSIL (ASC-H)	
Low-grade squamous intraepithelial lesion (LSIL)	Mild dysplasia, condylomatous atypia, HPV-related changes, koilocytic atypia, cervical intraepithelial neoplasia (CIN) 1
High-grade squamous intraepithelial lesion (HSIL)	Moderate dysplasia, CIN 2, severe dysplasia, CIN 3, carcinoma in situ
GLANDULAR CELL	
Endometrial cells, cytologically benign, in a postmenopausal woman	
Atypical	
• Endocervical cells, NOS	
• Endometrial cells, NOS	
• Glandular cells, NOS	
• Endocervical cells, favor neoplastic	
• Glandular cells, favor neoplastic	
Endocervical adencocarinoma in situ	
Adenocarcinoma	
• Endocervical	
• Endometrial	
• Extrauterine	
• NOS	

NOS, not otherwise specified.

and aneuploidy, hallmarks of squamous intraepithelial lesion (SIL) development.

Evidence of productive viral infection occurs in benign lesions such as external genital warts and LSILs, with the abundant expression of viral capsid proteins in the superficial keratinocytes. The appearance of the HPV-associated koilocyte is a result of the expression of E4, a structural protein that causes collapse of the cytoskeleton. Low-level expression of E6 and E7 proteins results in cell proliferation seen in the basal cell layer of LSILs. LSILs are a manifestation of active viral replication and protein expression. In HSILs, expression of E6 and E7 predominates throughout the epithelium with little expression of the structural proteins L1 and L2. This results in the chromosomal abnormalities and aneuploidy characteristic of the higher-grade lesions. The critical events that lead to cancer have not been verified; however, several mechanisms are thought to be critical, including viral integration into the host chromosome and activation of telomerase to lengthen chromosomes and avoid physiologic cell senescence. Over 150 HPV types have been documented and are classified by extent of their DNA homology into 5 genera, with the different types having different life-cycle and disease characteristics. The predominant group is α HPV types, which are associated with cutaneous and mucosal anogenital infections and cancers. β, γ, μ, and ν cause predominantly benign cutaneous lesions but can be difficult to manage in severely immunocompromised individuals. β Types are commonly detected on the skin without any apparent lesions but are associated with the development of skin cancers in those with epidermodysplasia verruciformis or other forms of immunodeficiencies. Genital lesions caused by the α HPV types may be broadly grouped into those with little to no malignant potential (low risk) and those with greater malignant potential (high risk). **Low-risk HPV types** 6 and 11 are most commonly found in genital warts and are rarely found isolated in malignant lesions. **High-risk HPV types are those types that are associated with anogenital cancers, specifically cervical cancer. HPV 16 and 18 are thought to be more oncogenic than other HPV types because they comprise 70% of cervical cancers, whereas each of the other 13 high-risk types** (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73) **contributes less than 1-9%.** HPV 16 appears to be even more important in anal and HPV-associated oropharyngeal cancers, comprising close to 90% of these cancers. HPV 16 is also commonly found in women without lesions or in those with LSILs, making the connection with cancer confusing. Genital warts and SIL are commonly associated with the detection of multiple HPV types, including a combination of low- and high-risk HPV types. Recent data show that it is likely that a single lesion arises from a single HPV type. Detection of multiple HPV types reflects the presence of cervical and anal coexisting lesions. Almost all (95%) incident low-risk and high-risk HPV DNA detection, with or without detectable SIL, will spontaneously resolve within 1-3 yr. Although HPV 16 has a slower rate of regression than some of the other high-risk types, the majority of incident HPV 16 detection also will resolve. Data suggest that clearance of an HPV type results in natural immune protection against reinfection with that same type. Redetections of the same type are not common and when found are often associated with a history of a new sexual partner, suggesting that these are not reactivated infections but are due to new exposures. These redetections rarely result in high-grade disease. Persistent high-risk–type infections are associated with increased risk for development of HSILs and invasive cancer. Progression of HSIL to invasive cancer is still rare, with only 5-15% showing progression. Approximately 50% of HPV 16–associated HSILs and 80% of non–HPV 16 HSILs will spontaneously regress in young women. Genital and common warts in general also resolve without therapy but may take years to do so. Genital warts in only extremely rare conditions can become malignant.

Most infants with recognized genital warts are infected with the low-risk types. In contrast, children with a history of sexual abuse have a clinical picture more like that of adult genital warts, consisting of mixed low- and high-risk types. There are rare reports of HPV-associated genital malignancies occurring in preadolescent children and adolescents. On the other hand, precancerous HSILs do occur in sexually active adolescents. There is a concern that younger age of sexual debut has contributed to the increase in invasive cervical cancers seen in women younger than 50 yr of age in the United States, specifically cervical adenocarcinomas. Persistent HPV infections are considered necessary but not sufficient for the development of invasive cancers. Other risk factors for which there is relatively strong suggestive evidence of association include smoking cigarettes, prolonged oral contraceptive use, greater parity, and *Chlamydia trachomatis* and herpes simplex virus infections.

CLINICAL MANIFESTATIONS

The clinical findings in HPV infection depend on the site of epithelial infection.

Skin Lesions

The typical HPV-induced lesions of the skin are proliferative, papular, and hyperkeratotic. Common warts are raised circinate lesions with a keratinized surface (Fig. 266-1). Plantar and palmar warts are practically flat. Multiple warts are common and may create a mosaic pattern. Flat warts appear as small (1-5 mm), flat, flesh-colored papules.

Genital Warts

Genital warts may be found throughout the perineum around the anus, vagina, and urethra, as well as in the cervical, intravaginal, and intraanal areas (Fig. 266-2). Intraanal warts occur predominantly in patients who have had receptive anal intercourse, in contrast with perianal warts, which may occur in men and women without a history of anal sex. Although rare, lesions caused by genital genotypes can also be found on other mucosal surfaces, such as the conjunctivae, tongue, gingivae, and nasal mucosa. They may be single or multiple lesions and are frequently found in multiple anatomic sites, including the cervix. External genital warts can be flat, dome shaped, keratotic, pedunculated, and cauliflower shaped and may occur singly, in clusters, or as plaques. On mucosal epithelium, the lesions are softer. Depending on the size and anatomic location, lesions may be pruritic and painful, may cause burning with urination, may be friable and bleed, or may become superinfected. Adolescents are frequently disturbed by the development of genital lesions. Other rarer lesions caused by HPV of the external genital area include Bowen disease, bowenoid papulosis, squamous cell carcinomas, Buschke-Löwenstein tumors, and vulvar intraepithelial neoplasias.

Squamous Intraepithelial Lesions and Cancers

Squamous intraepithelial lesions detected with cytology are usually invisible to the naked eye and require the aid of colposcopic magnification and acetic acid. With aid, the lesions appear white and show evidence of neovascularity. SILs can occur on the cervix, vagina, vulva, penis, and intraanus. Invasive cancers tend to be more exophytic, with aberrant-appearing vasculature. These lesions are rarely found in non–sexually active individuals.

Figure 266-1 Common warts of the left hand and the chest wall. *(From Meneghini CL, Bonifaz E:* An atlas of pediatric dermatology, *Chicago, 1986, Year Book Medical Publishers, p. 45.)*

Figure 266-2 Common warts of the hand in a mother and perianal condylomata acuminata in her son. *(From Meneghini CL, Bonifaz E: An atlas of pediatric dermatology, Chicago, 1986, Year Book Medical Publishers, p. 44.)*

Laryngeal Papillomatosis

The median age at diagnosis of recurrent laryngeal papillomatosis is 3 yr. Children present with hoarseness, an altered cry, and sometimes stridor. Rapid growth of respiratory papillomas can occlude the upper airway, causing respiratory compromise. These lesions may recur within weeks of removal, requiring frequent surgery. The lesions do not become malignant unless treated with irradiation.

DIAGNOSIS

The diagnosis of external genital warts and common warts may be reliably determined by visual inspection of a lesion by an experienced observer and does not require additional tests for confirmation. A biopsy should be considered if the diagnosis is uncertain, the lesions do not respond to therapy, or the lesions worsen during therapy.

Screening for cervical cancer in young women begins with cytology, which is either performed by Papanicolaou smear or liquid-based cytology. Screening guidelines, which were updated in 2012 by the American Cancer Society and the U.S. Preventive Services Task Force, recommend to start screening at age 21 yr. Screening earlier is more likely to result in unnecessary referrals for colposcopy, because most lesions, both LSILs and HSILs in this group, are likely to regress. Updated guidelines now recommend screening with cytology every 3 yr. At 30 yr of age, screening can also include cotesting with HPV DNA. This is not recommended earlier, because HPV infections are extremely common in young women, resulting in a very-low positive-predictive value in this age group. The recommended terminology used for cytologic evaluation is based on the Bethesda system (see Table 266-1). Recent updates to terminology used for histology uses similar terms. Many clinicians still prefer the World Health Organization terminology using cervical intraepithelial neoplasia (CIN) 1, 2, and 3 (see Table 266-1). Although the purpose of screening is to identify CIN 3+ lesions, the majority of these lesions are found in women who were referred for **atypical squamous cells of undetermined significance (ASC-US)** or LSILs on cytology. On the other hand, few CIN 3 or cancers exist in women younger than 24 yr of age. For women 21-24 yr of age, ASC-US and LSILs are treated the same. The current preferred recommendation for young women with ASC-US or LSILs is to repeat cytology every 12 mo for up to 24 mo. For persistent ASC-US or LSILs at 2 yr of follow-up, referral for colposcopy is recommended. Women 21-24 yr of age with HSIL at any visit should be referred for colposcopy and biopsy. In adult women, HSIL can be treated without histologic confirmation. However, this approach should be avoided in those 21-24 yr of age, because HSIL is often misdiagnosed in this group or will resolve spontaneously.

In women older than 21 yr of age, high-risk HPV testing is acceptable to assist in ASC-US triage. This recommendation is based on the observations that adult women with ASC-US and a positive HPV test result for high-risk types are more likely to have CIN 2/3 than women with a negative HPV test result. However, in women with ASC-US and a positive HPV test for high-risk types, repeat cytology is recommended. In women 21-24 yr of age referred for colposcopy and found to have no lesion or biopsy-confirmed LSIL after ASC-US or LSIL cytology, repeat cytology is recommended at 12 mo intervals. If ASC-US or LSIL has persisted after 2 yr or if HSIL is present at any time, referral for colposcopy is recommended. In women with biopsy-confirmed LSIL after atypical squamous cells of high grade (ASC-H) or HSIL, observation with cytology and colposcopy is recommended at 6 mo intervals for up to 2 yr. For persistent ASC-H or HSIL at 2 yr or progression at any time, treatment is recommended. Any young woman with histology-confirmed HSIL can be followed by colposcopy and cytology at 6 mo intervals if the patient is compliant. If HSIL continues to persist after 2 yr of follow-up, treatment is recommended. When CIN 3 is specified, treatment is recommended. These guidelines and updates can be found at http://www.asccp.org.

Very sensitive tests for the presence of HPV DNA, RNA, and proteins are becoming generally available, although they are not required for the diagnosis of external genital warts or related conditions. There are no indications for HPV DNA testing in women younger than 21 yr of age or children. HPV DNA testing is not recommended in women 21-24 yr of age but is acceptable for ASC-US triage.

Diagnosis of juvenile laryngeal papillomatosis (JRP) is made based on laryngeal examination.

DIFFERENTIAL DIAGNOSIS

A number of other conditions should be considered in the differential diagnosis of genital warts, including condyloma latum, seborrheic keratoses, dysplastic and benign nevi, molluscum contagiosum, pearly penile papules, neoplasms, Bowen disease, bowenoid papulosis, Buschke-Löwenstein tumors, and vulvar intraepithelial neoplasias.

Condyloma latum is caused by secondary syphilis and can be diagnosed with darkfield microscopy and standard serologic tests for syphilis. Seborrheic keratoses are common, localized, hyperpigmented lesions that are rarely associated with malignancy. Molluscum contagiosum is caused by a poxvirus, is highly infectious, and is often umbilicated. Pearly penile papules occur at the penile corona and are normal variants that require no treatment.

TREATMENT

Most common (plantar, palmar, skin) warts eventually resolve spontaneously (see Chapter 667). Symptomatic lesions should be removed. Removal includes a variety of self-applied therapies, including salicylic acid preparations and provider-applied therapies (cryotherapy, laser therapy, electrosurgery). Genital warts are benign and usually remit, but only over an extended period. It is recommended that genital lesions be treated if the patient or the parent requests therapy. Treatments for genital warts are categorized into self-applied and provider-applied. No one therapy has been shown to be more efficacious than any other. Recommended patient-applied treatment regimens for external genital warts include topical podofilox, imiquimod, and sinecatechins. Podofilox 0.5% solution (using a cotton swab) or gel (using a finger) is applied to visible warts in a cycle of applications twice a day for 3 days followed by 4 days of no therapy, repeated for up to a total of 4 cycles. Imiquimod 5% cream is applied at bedtime, 3 times a week, every other day, for up to 16 wk; the treated area should be washed with mild soap and water 6-10 hr after treatment. Sinecatechins (15% ointment) is a topical product from green tea extract used for external genital wart treatment that can be used 3 times daily for up to 16 wk. Provider-applied therapies include surgical treatments (electrosurgery, surgical excision, laser surgery) and office-based treatment (cryotherapy with liquid nitrogen or a cryoprobe, podophyllin resin 10-25%, and bichloroacetic or trichloroacetic acid). Office-based treatments are usually applied once a week for 3-6 wk. Podophyllin resins have lost favor to other methods because of the variability in preparations. Intralesional interferon is associated with significant adverse effects and is reserved for treatment of recalcitrant cases.

Many therapies are painful, and children should not undergo painful genital treatments unless adequate pain control is provided. Parents and

patients should not be expected to apply painful therapies themselves. None of the patient-applied therapies are approved for use during pregnancy, and podophyllin resin is contraindicated in pregnancy. For any of the nonsurgical treatments, prescription is contraindicated in a patient with any history of hypersensitivity to any product constituents.

If HPV exposure as a result of sexual abuse is suspected or known, the clinician should ensure that the child's safety has been achieved and is maintained.

When indicated, the most common treatments for CIN 2/3 are ablative and excisional treatments, including cryotherapy, laser, and loop electrosurgical excisional procedures. Once confirmed by histology with CIN 1, LSILs can be observed indefinitely. The decision to treat a persistent CIN 1 rests between the provider and patient. Risks of treatment, including premature delivery in a future pregnancy, should be discussed prior to any treatment decision. Treatment in pregnancy is not recommended unless invasive cancer is present.

JRP is commonly treated with surgical removal of lesions, but laser and microdebriders are also used.

COMPLICATIONS

The presence of HPV lesions in the genital area may be a cause of profound embarrassment to a child or parent. Complications of therapy are uncommon; chronic pain (vulvodynia) or hypoesthesia may occur at the treatment site. Lesions may heal with hypopigmentation or hyperpigmentation and less commonly with depressed or hypertrophic scars. Surgical therapies can lead to infection and scarring. Premature delivery and low birthweight in future pregnancies are complications of excisional therapy for CIN.

It is estimated that 5-15% of untreated CIN 3 lesions will progress to cervical cancer. Most cancer is prevented by early detection and treatment of these lesions. Despite screening, cervical cancer develops rapidly in a few adolescents and young women. The reason for the rapid development of cancer in these rare cases remains unknown, but host genetic defects are likely underlying causes. Juvenile laryngeal papillomas rarely become malignant, unless they have been treated with irradiation. Vulvar condylomas rarely become cancerous. HPV-associated cancers of the vagina, vulva, anus, penis, and oral cavity are much rarer than cervical tumors, and therefore screening for them is not currently recommended. However, anal, vaginal, and vulvar cancers are more common in women with cervical cancer; hence, it is recommended to screen women with cervical cancer for these tumors with visual and/or digital inspection.

PROGNOSIS

With all forms of therapy, genital warts commonly recur, and approximately half of children and adolescents require a 2nd or 3rd treatment. Recurrence is also evident in patients with Juvenile laryngeal papillomatosis. Patients and parents should be warned of this likelihood. Combination therapy for genital warts (imiquimod and podofilox) does not improve response and may increase complications. Prognosis of cervical disease is better, with 85-90% cure rates after a single treatment with the loop electrosurgical excision procedure. Cryotherapy has a slightly lower cure rate. Recalcitrant disease should prompt an evaluation and is common in immunocompromised individuals, specifically men and women infected with HIV.

PREVENTION

The only means of preventing HPV infection is to avoid direct contact with lesions. Condoms may reduce the risk for HPV transmission; condoms also prevent other sexually transmitted infections, which are risk factors associated with SIL development. In addition, condoms appear to hasten the regression of LSILs in women. Avoiding smoking cigarettes is important in preventing cervical cancer. Prolonged oral contraceptive use and parity have been shown to be risks for cervical cancer. However, the mechanisms associated with these factors have not been identified, and consequently no change in counseling is recommended.

HPV vaccines show efficacy against type-specific persistence and development of type-specific disease, including the cervix, vagina, vulva, and anus. A quadrivalent HPV vaccine containing types 6, 11, 16, and 18 was licensed in the United States in 2006, and a bivalent HPV vaccine containing types 16 and 18 was licensed in the United States in 2009. A 9-valent vaccine containing types 6, 11, 16, 18, 31, 33, 45, 52, and 58 has recently been approved. The efficacy of these vaccines is mediated by the development of neutralizing antibodies. Data from Sweden and Australia show a decrease in national rates of genital warts within 4 yr of implementing vaccination programs. Vaccination in the United States is recommended routinely for all girls at 11-12 yr of age and is administered intramuscularly in the deltoid region in a 3 dose series at 0, 1-2, and 6 mo. It is important that vaccination take place in children before they become sexually active, because the rate of HPV acquisition is high shortly after the onset of sexual activity. Vaccine can be given to girls as young as 9 yr of age, and a catch-up vaccination is recommended in girls 13-26 yr. Individuals who are already infected with 1 or more vaccine-related HPV types prior to vaccination are protected from clinical disease caused by the remaining vaccine HPV types. However, the vaccines are not therapeutic. The quadrivalent vaccine is also licensed to be administered in a 3 dose series to males 9 through 26 yr of age to reduce their likelihood of acquiring genital warts and developing anal dysplasia and cancer. Two doses of the vaccines have shown similar levels of immunogenicity as 3 doses. A vaccine that will cover 9 HPV high-risk types has been approved.

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Chapter 267

Arboviral Infections in North America

Scott B. Halstead

The arthropod-borne viral infections in North America are a group of mosquito-transmitted pathogens of several taxa causing neurologic infections or acute viral exanthems. Neuroviruses are transmitted during warmer weather in overlapping regions across most the United States and much of southern Canada.

ETIOLOGY

The principal causes of the arthropod-borne infections (with or without encephalitis) of North America are West Nile encephalitis (WNE), St. Louis encephalitis (StLE), Powassan (POW), a complex of California encephalitis group viruses, and, less frequently, western equine encephalitis (WEE), eastern equine encephalitis (EEE), and Colorado tick fever. Chikungunya virus is an emerging pathogen in the Western Hemisphere including the United States. The etiologic agents belong to different viral taxa: alphaviruses of the family Togaviridae (chikungunya virus, EEE, and WEE), Flaviviridae (WNE, STLE, POW), the California complex of the family Bunyaviridae (California encephalitis), and Reoviridae (Colorado tick fever virus). Alphaviruses are 69 nm, enveloped, positive-sense RNA viruses that evolved from a common Venezuelan equine encephalitis–like viral ancestor in the Western hemisphere. Flaviviruses are 40-50 nm, enveloped, positive-sense RNA viruses that evolved from a common ancestor. They are mosquito-borne (WNE, STLE) and tick-borne (POW) agents, globally distributed, and responsible for many important human viral diseases. The California serogroup, 1 of 16 Bunyavirus groups, are 75-115 nm enveloped viruses possessing a 3-segment, negative-sense RNA genome. Reoviruses are 60-80 nm double-stranded RNA viruses.

EPIDEMIOLOGY

Eastern Equine Encephalitis

In the United States, EEE is a very low incidence disease, with a median of 8 cases occurring annually in the Atlantic and Gulf States from 1964-2007 (Fig. 267-1). Transmission occurs often in focal endemic

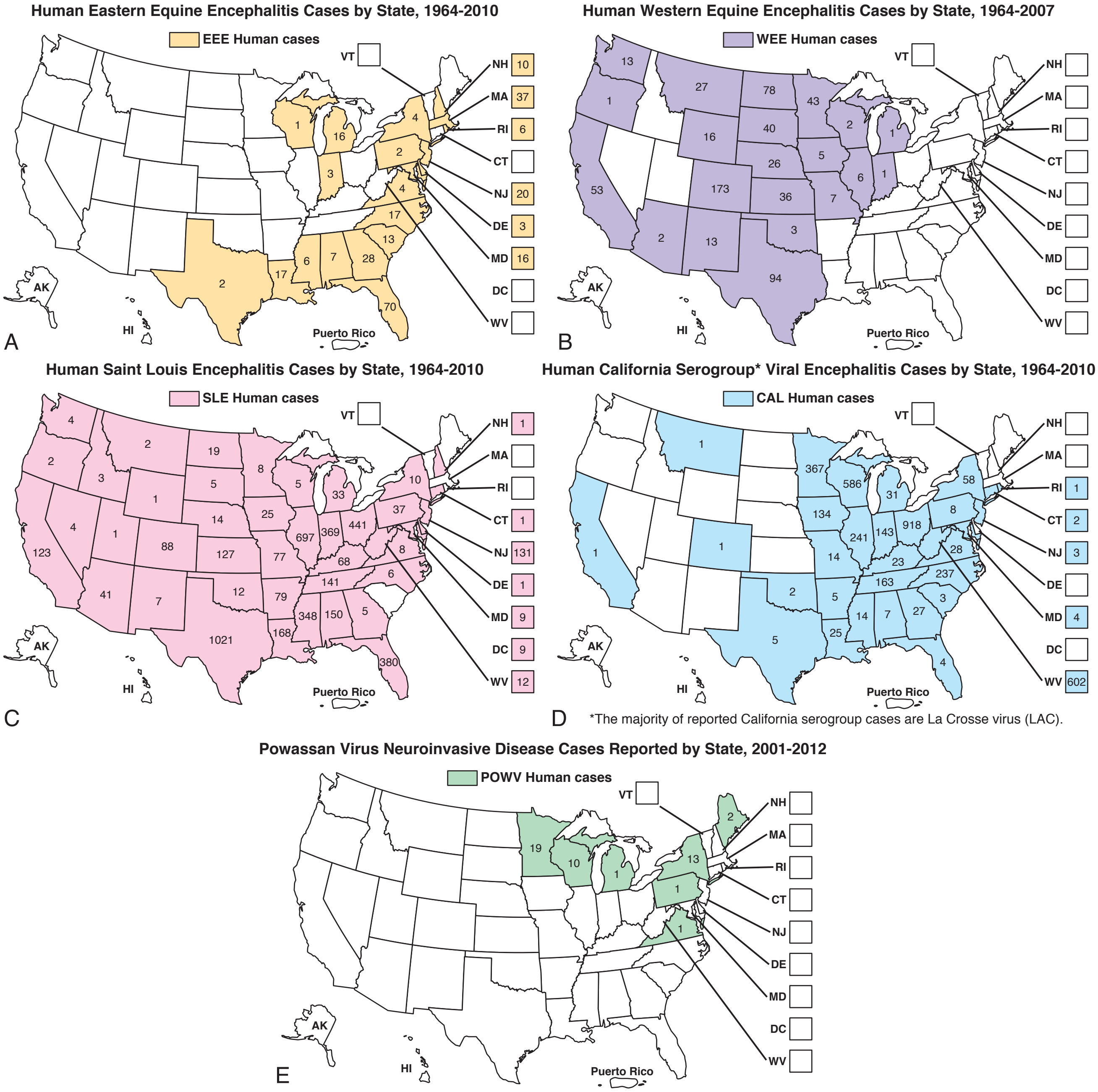

Figure 267-1 The distribution and incidence of reported cases of eastern equine encephalitis **(A),** western equine encephalitis **(B),** St. Louis encephalitis **(C),** California serogroup encephalitis **(D),** and Powassan encephalitis **(E)** reported by state to the Centers for Disease Control and Prevention, 1964–2010. *(From Division of Vector-Borne Diseases, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/ncidod/dvbid/arbor/arbocase/htm)*

areas of the coast of Massachusetts, the 6 southern counties of New Jersey, and northeastern Florida. In North America, the virus is maintained in freshwater swamps in a zoonotic cycle involving *Culiseta melanura* and birds. Various other mosquito species obtain viremic meals from birds and transmit the virus to horses and humans. Virus activity varies markedly from year to year in response to still unknown ecologic factors. Most infections in birds are silent, but infections in pheasants are often fatal, and epizootics in these species are used as sentinels for periods of increased viral activity. Cases have been recognized on Caribbean islands. The case : infection ratio is lowest in children (1 : 8) and somewhat higher in adults (1 : 29).

Western Equine Encephalitis

WEE infections occur principally in the United States and Canada west of the Mississippi River (see Fig. 267-1), mainly in rural areas where water impoundments, irrigated farmland, and naturally flooded land provide breeding sites for *Culex tarsalis.* The virus is transmitted in a cycle involving mosquitoes, birds, and other vertebrate hosts. Humans and horses are susceptible to encephalitis. The case : infection ratio varies by age, having been estimated at 1 : 58 in children younger than 4 yr of age and 1 : 1,150 in adults. Infections are most severe at the extremes of life; one third of cases occur in children younger than 1 yr of age. Recurrent human epidemics have been reported from the Yakima Valley in Washington State and the Central Valley of California; the largest outbreak on record resulted in 3,400 cases and occurred in Minnesota, North and South Dakota, Nebraska, and Montana as well as Alberta, Manitoba, and Saskatchewan, Canada. Epizootics in horses precede human epidemics by several weeks. For the past 20 yr, only 3 cases of WEE have been reported, presumably reflecting successful mosquito abatement.

St. Louis Encephalitis

Cases of STLE are reported from nearly all states; the highest attack rates occur in the Gulf and central states (see Fig. 267-1). Epidemics frequently occur in urban and suburban areas; the largest, in 1975, involved 1,800 persons living in Houston, Chicago, Memphis, and Denver. Cases often cluster in areas where there is ground water or septic systems, which support mosquito breeding. The principal vectors are *Culex pipiens* and *Culex quinquefasciatus* in the central Gulf States, *Culex nigripalpus* in Florida, and *C. tarsalis* in California. STLE virus is maintained in nature in a bird–mosquito cycle. Viral amplification occurs in bird species abundant in residential areas (e.g., sparrows, blue jays, and doves). Virus is transmitted in the late summer and early fall. The case : infection ratio may be as high as 1 : 300. Age-specific attack rates are lowest in children and highest in individuals older than age 60 yr. The most recent small outbreaks were in Florida in 1990 and Louisiana in 2001. For the past 15 yr there have been a mean of 18 cases annually.

West Nile Encephalitis

West Nile (WN) virus has been implicated as the cause of sporadic summertime cases of human encephalitis and meningitis in Israel, India, Pakistan, Romania, Russia, and the United States. All American WN viruses are genetically similar and are related to a virus recovered from a goose in Israel in 1998. WN virus was imported into the United States in 1999 and now survives in a broad enzootic cycle across the United States. Every state in the continental United States plus 9 provinces in Canada have reported mosquito, bird, mammalian, or human WN virus infection, most frequently during the summer or fall months (Fig. 267-2). Through the end of 2012, 35,941 total cases had been reported, 40-50% of which were neuroinvasive, with 1,439 deaths. WN virus transmission cycles appear to resemble those of Japanese encephalitis with large epizootics and human cases every 5-10 yr. WN virus has entered the blood supply through asymptomatic viremic potential blood donors. Blood banks screen for WN virus RNA. In 2012, 597 viremic potential blood donors were identified and the donation was rejected (Fig. 267-2). WN virus has also been transmitted to humans via the placenta, breast milk, and organ transplantation. Throughout its range, the virus is maintained in nature by transmission between mosquitoes of the *Culex* genus and various species of birds. In the United States, human infections are largely acquired from *C. pipiens.* Horses are the nonavian vertebrates most likely to exhibit disease with WN virus infection. During the 2002 transmission season, 14,000 equine cases were reported, with a mortality rate of 30%. Disease occurs predominantly in individuals >50 yr of age.

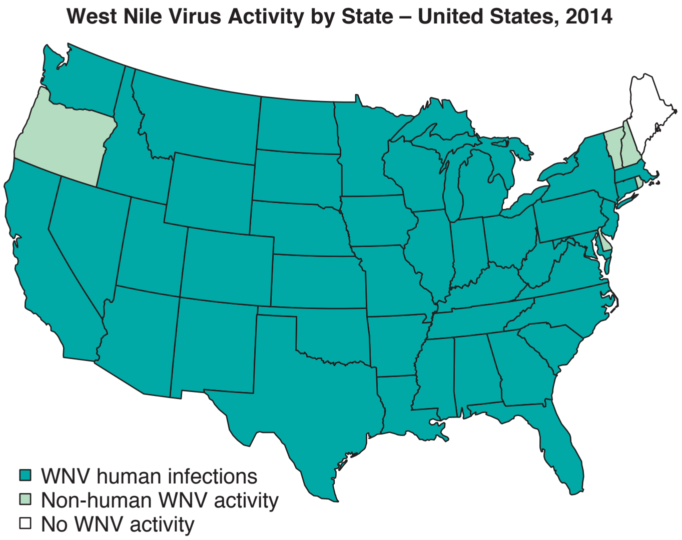

Figure 267-2 West Nile virus activity reported to ArboNET by state, United States, 2014. (Preliminary data as of October 28, 2014.) *(From ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/westnile/statsMaps/preliminaryMapsData/activitystatedate.html)*

Powassan Encephalitis

POW virus is transmitted by *Ixodes cookei* among small mammals in eastern Canada and the United States; it has been responsible for 39 deaths in the United States since 2008 (see Fig. 267-1). Other ticks may transmit the virus in a wider geographic area, and there is some concern that *Ixodes scapularis* (also called *Ixodes dammini*), a competent vector in the laboratory, may become involved as it becomes more prominent in the United States.

La Crosse/California Encephalitis

La Crosse viral infections are endemic in the United States, occurring annually from July to September, principally in the north-central and central states (see Fig. 267-1). Infections occur in peridomestic environments as the result of bites from *Aedes triseriatus* mosquitoes, which often breed in tree holes. The virus is maintained vertically in nature by transovarial transmission and can be spread between mosquitoes by copulation and amplified in mosquito populations by viremic infections in various vertebrate hosts. Amplifying hosts include chipmunks, squirrels, foxes, and woodchucks. A case : infection ratio of 1 : 22-300 has been surmised. La Crosse encephalitis is principally a disease of children, who may account for up to 75% of cases. A mean of 100 cases has been reported annually for the past 10 yr.

Colorado Tick Fever

Colorado tick fever virus is transmitted by the wood tick *Dermacentor andersoni,* which inhabits high-elevation areas of states extending from the central plains to the Pacific coast. The tick is infected with the virus at the larval stage and remains infected for life. Squirrels and chipmunks serve as primary reservoirs. Human infections typically occur in hikers and campers in indigenous areas during the spring and early summer.

Chikungunya Virus

Chikungunya virus is endemic in Africa and Asia as well as parts of Latin America. It is an emerging pathogen in areas of the United States inhabited by day biting mosquitos (*Aedes aegyti, Aedes albopictus*).

CLINICAL MANIFESTATIONS

The arboviruses produce symptoms of viral meningitis or encephalitis. WN virus and Colorado tick fever illnesses more commonly manifest as flulike diseases and only occasionally as encephalitides.

Eastern Equine Encephalitis

EEE virus infections result in fulminant encephalitis with a rapid progression to coma and death in one third of cases. In infants and children, abrupt onset of fever, irritability, and headache are followed by lethargy, confusion, seizures, and coma. High temperature, bulging fontanel, stiff neck, and generalized flaccid or spastic paralysis are observed. There may be a brief prodrome of fever, headache, and dizziness. Unlike most other viral encephalitides, the peripheral white blood cell count usually demonstrates a marked leukocytosis, and the cerebrospinal fluid (CSF) may show marked pleocytosis. Pathologic changes are found in the cortical and gray matter, with viral antigens localized to neurons. There is necrosis of neurons, neutrophilic infiltration, and perivascular cuffing by lymphocytes.

Western Equine Encephalitis

In WEE, there may be a prodrome with symptoms of an upper respiratory tract infection. The onset is usually sudden with chills, fever, dizziness, drowsiness, increasing headache, malaise, nausea and vomiting, stiff neck, and disorientation. Infants typically present with the sudden cessation of feeding, fussiness, fever, and protracted vomiting. Convulsions and lethargy develop rapidly. On physical examination, patients are somnolent, exhibit meningeal signs, and have generalized motor weakness and reduced deep tendon reflexes. In infants, a bulging fontanel, spastic paralysis, and generalized convulsions may be observed. On pathologic examination, disseminated small focal abscesses, small focal hemorrhages, and patchy areas of demyelination are distinctive.

St. Louis Encephalitis

Clinical manifestations of STLE vary from a mild flulike illness to fatal encephalitis. There may be a prodrome of nonspecific symptoms with subtle changes in coordination or mentation of several days to 1 wk in duration. Early signs and symptoms include fever, photophobia, headache, malaise, nausea, vomiting, and neck stiffness. About half of patients exhibit abrupt onset of weakness, incoordination, disturbed sensorium, restlessness, confusion, lethargy, and delirium or coma. The peripheral white blood cell count is modestly elevated, with 100-200 cells/µL found in the CSF. On autopsy, the brain shows scattered foci of neuronal damage and perivascular inflammation.

West Nile Encephalitis

WNE may be asymptomatic, but when clinical features appear, they include an abrupt onset of high fever, headache, myalgias, and nonspecific signs of emesis, rash, abdominal pain, or diarrhea. Most infections manifest as a flulike febrile illness, whereas a minority of patients demonstrate meningitis or encephalitis, or both. Rarely there may be cardiac dysrhythmias, myocarditis, rhabdomyolysis, optic neuritis, uveitis, retinitis, orchitis, pancreatitis, or hepatitis. WN virus disease in the United States has been accompanied by prolonged lymphopenia and an acute asymmetric polio-like paralytic illness with CSF pleocytosis involving the anterior horn cells of the spinal cord. A striking but uncommon feature has been parkinsonism and movement disorders (with tremor and myoclonus). WN virus infections have been shown to lead to chronic kidney disease in a small group of patients.

Powassan Encephalitis

POW encephalitis has occurred mostly in adults living in enzootic areas with vocational or recreational exposure; it is associated with significant long-term morbidity and has a case-fatality rate of 10-15%.

Lacrosse/California Encephalitis

The clinical spectrum includes a mild febrile illness, aseptic meningitis, and fatal encephalitis. Children typically present with a prodrome of 2-3 days with fever, headache, malaise, and vomiting. The disease evolves with clouding of the sensorium, lethargy, and, in severe cases, focal or generalized seizures. On physical examination, children are lethargic but not disoriented. Focal neurologic signs, including weakness, aphasia, and focal or generalized seizures, have been reported in 16-25% of cases. CSF shows low to moderate leukocyte counts. On autopsy, the brain shows focal areas of neuronal degeneration, inflammation, and perivascular cuffing.

Colorado Tick Fever

Colorado tick fever begins with the abrupt onset of a flulike illness, including high temperature, malaise, arthralgia and myalgia, vomiting, headache, and decreased sensorium. Rash is uncommon. The symptoms rapidly disappear after 3 days of illness. However, in approximately half of patients, a second identical episode reoccurs 24-72 hr after the first, producing the typical "saddleback" temperature curve of Colorado tick fever. Complications, including encephalitis, meningoencephalitis, and a bleeding diathesis, develop in 3-7% of infected persons and may be more common in children younger than 12 yr of age.

Chikungunya Virus

Clinical manifestations begin 3-7 days after a mosquito bite and begin abruptly with high fever and severe joint symptoms (hands, feet, ankles, wrists) that include symmetric bilateral polyarthralgia or arthritis. Most patients are symptomatic, and all ages are vulnerable. In addition, there may be headache, myalgias, conjunctivitis, weakness, lymphopenia, and a maculopapular rash. Mortality is rare; some develop prolonged joint symptoms (tenosynovitis, arthritis) lasting over a year. The acute episode lasts 7-10 days. The differential diagnosis includes dengue, West Nile, enterovirus diseases, leptospirosis, rickettsial disease, measles, parvovirus disease, rheumatologic diseases, and other alphavirus diseases in endemic areas. Figure 267-3 lists the diagnostic criteria.

DIAGNOSIS

The etiologic diagnosis of a specific arboviral infection is established by testing an acute-phase serum ≥5 days after onset of illness for the presence of virus-specific immunoglobulin (Ig) M antibodies using an indirect immunofluorescence test or an enzyme-linked immunosorbent assay IgM capture test. Alternatively, acute and convalescent sera can be tested for a 4-fold or greater increase in enzyme-linked immunosorbent assay, hemagglutination inhibition, or neutralizing IgG antibody titers. Commercial serologic diagnostic kits are marketed, especially for WN viral infections. Serum and CSF should be tested for WN virus–specific IgM. However, IgM may reflect past infection, because it may be present up to 12 mo after infection. The diagnosis may also be established by isolation in cell cultures of virus in brain tissue, obtained by brain biopsy or at autopsy, or by identification of viral RNA reverse transcriptase polymerase chain reactions.

The diagnosis of encephalitis may be aided by CT or MRI and by electroencephalography. Focal seizures or focal findings on CT or MRI or electroencephalography should suggest the possibility of herpes simplex encephalitis, which should be treated with acyclovir (see Chapter 252).

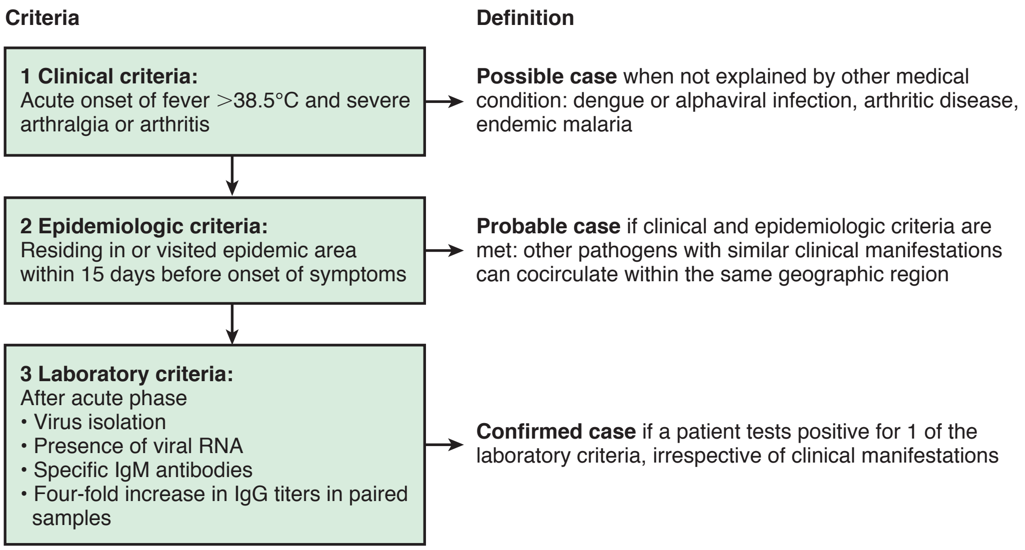

Figure 267-3 Diagnostic criteria for chikungunya virus fever. *(From Burt FJ, Rolph MS, Rulli NE, et al: Chikungunya: a re-emerging virus,* Lancet *379:662–668, 2012, Fig. 6.)*

TREATMENT

There is no specific treatment for arboviral encephalitides, although oral ribavirin may have been of benefit in a case of La Crosse encephalitis. The treatment of acute arboviral encephalitis is intensive supportive care (see Chapter 67), including control of seizures (see Chapter 593).

PROGNOSIS

Fatalities occur with all arboviral encephalitides. With the exception of EEE, most resolve without residua.

Eastern Equine Encephalitis

The prognosis in EEE is better for patients with a prolonged prodrome; the occurrence of convulsions conveys a poor prognosis. Patient fatality rates are 33-75% and are highest in the elderly. Residual neurologic defects are common, especially in children.

Western Equine Encephalitis

Patient fatality rates in WEE are 3-9% and highest in the elderly. Major neurologic sequelae have been reported in up to 13% of cases and may be as high as 30% in infants. Parkinsonian syndrome has been reported as a residual in adult survivors.

St. Louis Encephalitis

The principal risk factor for fatal outcome of STLE is advanced age, with patient fatality rates being as high as 80% in early outbreaks. In children, mortality rates are 2-5%. In adults, underlying hypertensive cardiovascular disease has been a risk factor for fatal outcome. Recovery from STLE is usually complete, but the rate of serious neurologic sequelae has been reported to be as high as 10% in children.

West Nile Encephalitis

Cases and deaths caused by WNE occur mainly in the elderly, although many serologic surveys show that persons of all ages are infected. In 2012, among a total of 5,387 human cases, 2,734 were neuroinvasive disease, which resulted in 243 deaths, an 8.9% mortality rate (Fig. 267-4). Paralysis may result in permanent weakness.

Powassan Encephalitis

In a limited experience, POW encephalitis has occurred mainly in adults with vocational or recreational exposure and has a high fatality rate.

La Crosse or California Encephalitis

Recovery from California encephalitis is usually complete. The case fatality rate is approximately 1%.

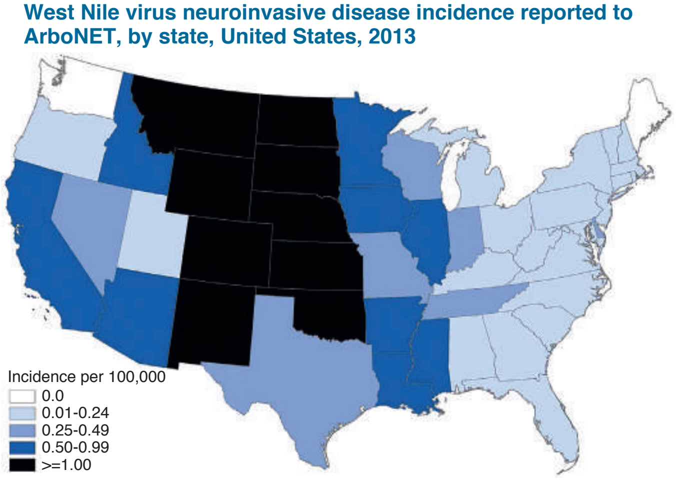

Figure 267-4 West Nile virus neuroinvasive disease incidence reported to ArboNET by state, United States, 2013. *(From ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/westnile/statsMaps/finalMapsData/data/2013StateIncidenceMap.pdf)*

Colorado Tick Fever

Recovery from Colorado tick fever is usually complete. Three deaths have been reported, all in persons with hemorrhagic signs.

Chikungunya

The incidence of febrile convulsions is high in infants. Prognosis is generally good, although in large outbreaks in Africa and India severe disease and deaths have been attributed to chikungunya infections, predominantly in adults.

PREVENTION

Killed EEE, WEE, and WNE vaccines are available for horses, and an experimental killed vaccine is administered to human laboratory workers who handle EEE virus. Flocks of sentinel chickens or pheasants have been stationed at various locations along the Atlantic coast during the late summer or early fall to obtain early warning of increased transmission of EEE virus. No human vaccine is licensed for arboviral encephalitides, although several WNE vaccines are in late-stage development. Killed WNE vaccines are licensed for veterinary use. Protection against CHIK is attained by avoiding bites by vector mosquitoes. These bite during daytime hours in and around human habitations (see Chapter 269).

Extensive water management and mosquito abatement programs in California have reduced transmission of WEE and the incidence of human infections. Urban WNE and STLE outbreaks in the eastern United States, Texas, and the Midwest have been controlled by the application of ultra-low-volume adulticide chemicals applied from trucks or low-flying aircraft. Because mosquito biting may occur in and around residential areas, sealing mosquito breeding sites, using insect repellents, and instructing children to play in open, sunny areas away from forest fringe may help prevent disease.

Because there is no vaccine or specific therapy for POW encephalitis, the best means of prevention is protection from tick bite. This includes using insect repellents, wearing light-colored clothing with long sleeves and pants tucked into socks or boots, avoiding or clearing brushy areas, and removing ticks before they attach or soon after attachment. Checking family pets also can prevent ticks from entering the home. Because *I. cookei* are often found on woodchucks and skunks and may be the primary vector of POW virus, reducing human contact with small and medium-sized mammals may reduce risk of exposure to POW virus-infected ticks. Areas around homes in enzootic areas should be kept clear of brush, weeds, trash, and other elements that could support small and medium-sized mammals. When removing rodent nests, avoid direct contact with nesting materials and use sealed plastic bags for disposal and to prevent direct contact with ticks.

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Chapter 268

Arboviral Infections Outside North America

Scott B. Halstead

Globally, the principal causes of arboviral encephalitis are Venezuelan equine encephalitis (VEE), Japanese encephalitis (JE), West Nile fever (WN), and tickborne encephalitis (TBE) (Table 268-1). Other widespread arboviral infections include chikungunya (CHIK) and dengue (DEN) (see Chapter 269).

Table 268-1 Vectors and Geographic Distribution of Arboviral Encephalitis Outside North America

GENUS	VIRUS AND DISEASE	VECTOR	GEOGRAPHIC DISTRIBUTION
Flavivirus	Japanese encephalitis	*Culex tritaeniorhynchus*	Asia/Japan to Sri Lanka
	Murray Valley encephalitis	*Culex annulirostris*	Eastern Australia
	Rocio	*Psorophora* or *Aedes*	Sao Paulo, Brazil
	West Nile	*Culex* and others	Europe to Australia
	Tick-borne encephalitis	*Ixodes ricinus*	Europe
		Ixodes persulcatus	Russia
Togavirus	Venezuelan equine encephalitis	*Culex* and others	Northern South America

268.1 Venezuelan Equine Encephalitis

Scott B. Halstead

The VEE virus was isolated from an epizootic in Venezuelan horses in 1938. Human cases were first identified in 1943. Hundreds of thousands of equine and human cases have occurred over the past 70 yr. During 1971, epizootics moved through Central America and Mexico to southern Texas. After 2 decades of quiescence, epizootic disease emerged again in Venezuela and Colombia in 1995.

ETIOLOGY

VEE is an alphavirus of the family Togaviridae. VEE circulates in nature in 6 subtypes. Virus types I and III have multiple antigenic variants. Types IAB and IC have caused epizootics and human epidemics.

EPIDEMIOLOGY

The majority of epizootics resulting from types IAB and IC have occurred in Venezuela and Colombia. The virus resides in ill-defined sylvatic reservoirs in the South American rain forests. Known hosts include rodents and aquatic birds with transmission by *Culex melanoconion* species. Vectors for horse-to-horse and horse-to-human transmission include *Aedes taeniorhynchus* and *Psorophora confinnis.* Epizootics move rapidly, up to several miles per day. Human cases are proportional to and follow epizootic occurrences. Viremia levels in human blood are high enough to infect mosquitoes. Because virus can be recovered from human pharyngeal swabs, and household attack rates are often as high as 50%, it is widely believed that person-to-person transmission occurs, although direct evidence is lacking. Virus types II-VI are restricted to relatively small foci; each has a unique vector–host relationship and rarely results in human infections.

CLINICAL MANIFESTATIONS

The incubation period is 2-5 days, followed by the abrupt onset of fever, chills, headache, sore throat, myalgia, malaise, prostration, photophobia, nausea, vomiting, and diarrhea. In 5-10% of cases, there is a biphasic illness; the 2nd phase is heralded by seizures, projectile vomiting, ataxia, confusion, agitation, and mild disturbances in consciousness. There is cervical lymphadenopathy and conjunctival suffusion. Cases of meningoencephalitis may demonstrate **cranial nerve palsy,** motor weakness, paralysis, seizures, and coma. Microscopic examination of tissues reveals inflammatory infiltrates in lymph nodes, spleen, lung, liver, and brain. Lymph nodes show cellular depletion, necrosis of germinal centers, and lymphophagocytosis. The liver shows patchy hepatocellular degeneration, the lungs demonstrate a diffuse interstitial pneumonia with intraalveolar hemorrhages, and the brain shows patchy cellular infiltrates.

DIAGNOSIS

The etiologic diagnosis of VEE is established by testing an acute-phase serum collected early in the illness for the presence of virus-specific immunoglobulin (Ig) M antibodies or, alternatively, demonstrating a 4-fold or greater increase in IgG antibody titers by testing paired acute and convalescent sera. The virus can also be identified by isolation in tissue cultures or recovery of viral RNA by polymerase chain reaction.

TREATMENT

There is no specific treatment for VEE. The treatment is intensive supportive care (see Chapter 67), including control of seizures (see Chapter 593).

PROGNOSIS

In patients with VEE meningoencephalitis, the fatality rate ranges from 10-25%. Sequelae include nervousness, forgetfulness, recurrent headache, and easy fatigability.

PREVENTION

Several veterinary vaccines are available to protect equines. VEE virus is highly infectious in laboratory settings, and biosafety level 3 containment should be used. An experimental vaccine is available for use in laboratory workers. Several vaccine constructs are in the pipeline for potential use in humans.

Bibliography is available at Expert Consult.

268.2 Japanese Encephalitis

Scott B. Halstead

Epidemics of encephalitis were reported in Japan from the late 1800s.

ETIOLOGY

JE virus is a positive-sense, single-stranded RNA virus of the family Flaviviridae.

EPIDEMIOLOGY

JE is a mosquito-borne viral disease of humans as well as horses, swine, and other domestic animals that causes human infections and acute disease in a vast area of Asia, northern Japan, Korea, China, Taiwan, the Philippines, and the Indonesian archipelago and from Indochina through the Indian subcontinent. *Culex tritaeniorhynchus summarosus,* a night-biting mosquito that feeds preferentially on large domestic animals and birds but only infrequently on humans, is the principal vector of zoonotic and human JE in northern Asia. A more complex ecology prevails in southern Asia. From Taiwan to India, *C. tritaeniorhynchus* and members of the closely related *Culex vishnui* group are vectors. Before the introduction of JE vaccine, summer outbreaks of JE occurred regularly in Japan, Korea, China, Okinawa, and Taiwan. Over the past decade, there has been a pattern of steadily enlarging recurrent seasonal outbreaks in Vietnam, Thailand, Nepal, and India, with small outbreaks in the Philippines, Indonesia, and the northern tip of Queensland, Australia. Seasonal rains are accompanied by increases in mosquito populations and JE transmission. Pigs serve as an amplifying host.

The annual incidence in endemic areas ranges from 1-10 per 10,000 population. Children younger than 15 yr of age are principally affected, with nearly universal exposure by adulthood. The case : infection ratio for JE virus has been variously estimated at 1 : 25 to 1 : 1,000. Higher ratios have been estimated for populations indigenous to enzootic areas. JE occurs in travelers visiting Asia; therefore, a travel history in the diagnosis of encephalitis is critical.

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CLINICAL MANIFESTATIONS

After a 4-14 day incubation period, cases typically progress through the following 4 stages: prodromal illness (2-3 days), acute stage (3-4 days), subacute stage (7-10 days), and convalescence (4-7 wk). Onset may be characterized by abrupt onset of fever, headache, respiratory symptoms, anorexia, nausea, abdominal pain, vomiting, and sensory changes, including psychotic episodes. Grand mal seizures are seen in 10-24% of children with JE; parkinsonian-like nonintention tremor and cogwheel rigidity are seen less frequently. Particularly characteristic are **rapidly changing central nervous system** signs (e.g., hyperreflexia followed by hyporeflexia or plantar responses that change). The sensory status of the patient may vary from confusion through disorientation and delirium to somnolence, progressing to coma. There is usually a mild pleocytosis (100-1,000 leukocytes/µL) in the cerebrospinal fluid, initially polymorphonuclear but in a few days predominantly lymphocytic. Albuminuria is common. Fatal cases usually progress rapidly to coma, and the patient dies within 10 days.

DIAGNOSIS

JE should be suspected in patients reporting exposure to night-biting mosquitoes in endemic areas during the transmission season. The etiologic diagnosis of JE is established by testing acute-phase serum collected early in the illness for the presence of virus-specific IgM antibodies or, alternatively, demonstrating a fourfold or greater increase in IgG antibody titers by testing paired acute and convalescent sera. The virus can also be identified by polymerase chain reaction.

TREATMENT

There is no specific treatment for JE. The treatment is intensive supportive care (see Chapter 67), including control of seizures (see Chapter 593).

PROGNOSIS

Patient fatality rates for JE are 24-42% and are highest in children 5-9 yr of age and in adults older than 65 yr of age. The frequency of sequelae is 5-70% and is directly related to the age of the patient and severity of disease. Sequelae are most common in patients younger than 10 yr at the onset of disease. The more common sequelae are mental deterioration, severe emotional instability, personality changes, motor abnormalities, and speech disturbances.

PREVENTION

Travelers to endemic countries who plan to be in rural areas of the endemic region during the expected period of seasonal transmission and travelers in rural areas experiencing endemic transmission should receive JE vaccine. An inactivated vaccine manufactured in Japan by intracerebral injection of young mice and available throughout the world has been taken off the market owing to a high incidence of adverse events. In 2008-2009, tissue culture–based JE vaccine (Ixiaro) was licensed in Europe, Australia, and the United States. In the United States, this vaccine (also called IC51) is licensed for use in children and adults and is distributed by Novartis (Basel). For this vaccine, JE virus is grown in Vero cells, then formalin inactivated and administered intramuscularly as 2 doses of 0.5 mL each, 28 days apart. The final dose should be completed at least 1 wk prior to the patient's expected arrival in a JE endemic area. This vaccine contains alum and protamine sulfate and has exhibited only mild adverse events. A highly efficacious live-attenuated single-dose JE vaccine developed in China for children is licensed and marketed in some Asian countries. This vaccine can be coadministered with live-attenuated measles vaccine without altering the immune responses to either vaccine. In humans, prior dengue virus infection provides partial protection from clinical JE.

Personal measures should be taken to reduce exposure to mosquito bites, especially for short-term residents in endemic areas. They consist of avoiding evening outdoor exposure, using insect repellents, covering the body with clothing, and using bed nets or house screening.

Commercial pesticides, widely used by rice farmers in Asia, are effective in reducing populations of *C. tritaeniorhynchus.* Fenthion, fenitrothion, and phenthoate are effectively adulticidal and larvicidal. Insecticides may be applied from portable sprayers or from helicopters or light aircraft.

Bibliography is available at Expert Consult.

268.3 Tickborne Encephalitis

Scott B. Halstead

TBE is widespread in Europe, where it has also been identified as the cause of milkborne encephalitis.

ETIOLOGY

TBE virus is a positive-sense, single-stranded RNA virus of the family Flaviviridae.

EPIDEMIOLOGY

TBE refers to neurotropic tick-transmitted flaviviral infections occurring across the Eurasian land mass. In the Far East, the disease is called *Russian spring-summer encephalitis*; the milder, often biphasic form in Europe is simply called TBE. TBE is found in all countries of Europe except Portugal and the Benelux countries. The incidence is particularly high in Austria, Poland, Hungary, Czech Republic, Slovakia, former Yugoslavia, and Russia. The incidence tends to be very focal. Seroprevalence is as high as 50% in farm and forestry workers. The majority of cases occur in adults, but even young children may be infected while playing in the woods or on picnics or camping trips. The seasonal distribution of cases is midsummer in southern Europe, with a longer season in Scandinavia and the Russian Far East. TBE can be excreted from the milk of goats, sheep, or cows. Before World War II, when milk was consumed unpasteurized, milkborne cases of TBE were common.

Viruses are transmitted principally by hard ticks of *Ixodes ricinus* in Europe and *Ixodes persulcatus* in the Far East. Viral circulation is maintained by a combination of transmission from ticks to birds, rodents, and larger mammals and transtadial transmission from larval to nymphal and adult stages. In some parts of Europe and Russia, ticks feed actively during the spring and early fall, giving rise to the name "spring-summer encephalitis."

CLINICAL MANIFESTATIONS

After an incubation period of 7-14 days, the European form begins as an acute nonspecific febrile illness that is followed in 5-30% of cases by meningoencephalitis. The Far Eastern variety more often results in encephalitis with higher case fatality and sequelae rates. The 1st phase of illness is characterized by fever, headache, myalgia, malaise, nausea, and vomiting for 2-7 days. Fever disappears and after 2-8 days may return accompanied by vomiting, photophobia, and signs of meningeal irritation in children and more severe encephalitic signs in adults. This phase rarely lasts more than 1 wk.

DIAGNOSIS

The diagnosis of TBE should be suspected in any patient reporting a tick bite in an endemic area during the transmission season. The etiologic diagnosis of TBE is established by testing acute-phase serum collected early in the illness for the presence of virus-specific IgM antibodies or, alternatively, demonstrating a 4-fold or greater increase in IgG antibody titers by testing paired acute and convalescent sera. The virus can also be identified by polymerase chain reaction. With widespread use of vaccines, an IgM titer of >500 arbitrary units in early convalescent serum has been recommended for the diagnosis of acute TBE.

TREATMENT

There is no specific treatment for TBE. The treatment is intensive supportive care (see Chapter 67), including control of seizures (see Chapter 593).

PROGNOSIS

The main risk for fatal outcome is advanced age; the fatality rate in adults is approximately 1%, but sequelae in children are rare. Transient

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unilateral paralysis of an upper extremity is a common finding in adults. Common sequelae include chronic fatigue, headache, sleep disorders, and emotional disturbances.

PREVENTION

Specific immunoglobulin has been given to persons with seasonal tick bite exposure, although efficacy of this preventive therapy is not well studied. Effective inactivated vaccines for human use, made from virus grown in tissue culture, are licensed in Russia and Europe. They are administered in a 3 dose series.

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268.4 West Nile Encephalitis

See Chapter 267.

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Chapter 269

Dengue Fever and Dengue Hemorrhagic Fever

Scott B. Halstead

Dengue fever is a benign syndrome caused by several arthropod-borne viruses and is characterized by biphasic fever, myalgia or arthralgia, rash, leukopenia, and lymphadenopathy. **Dengue hemorrhagic fever** (Philippine, Thai, or Singapore hemorrhagic fever; hemorrhagic dengue; acute infectious thrombocytopenic purpura) is a severe, often fatal, febrile disease caused by 1 of 4 dengue viruses. It is characterized by capillary permeability, abnormalities of hemostasis, and, in severe cases, a protein-losing shock syndrome **(dengue shock syndrome),** which is thought to have an immunopathologic basis.

ETIOLOGY

There are at least 4 distinct antigenic types of dengue virus (dengue 1, 2, 3, and 4), members of the family Flaviviridae. In addition, 3 other arthropod-borne viruses (arboviruses) cause similar or identical febrile diseases with rash (Table 269-1).

EPIDEMIOLOGY

Dengue viruses are transmitted by mosquitoes of the Stegomyia family. *Aedes aegypti,* a daytime biting mosquito, is the principal vector, and all 4 virus types have been recovered from it. In most tropical areas, *A. aegypti* is highly urbanized, breeding in water stored for drinking or bathing and in rainwater collected in any container. Dengue viruses have also been recovered from *Aedes albopictus,* as in the 2001 Hawaiian epidemic, whereas outbreaks in the Pacific area have been attributed to several other *Aedes* species. These species breed in water trapped in vegetation. In Southeast Asia and West Africa, dengue virus may be maintained in a cycle involving canopy-feeding jungle monkeys and *Aedes* species, which feed on monkeys.

Epidemics were common in temperate areas of the Americas, Europe, Australia, and Asia until early in the 20th century. Dengue fever and dengue-like disease are now endemic in tropical Asia, the South Pacific Islands, northern Australia, tropical Africa, the Arabian Peninsula, the Caribbean, and Central and South America. Dengue fever occurs frequently among travelers to these areas. Locally acquired disease has been reported in Florida and Texas, and imported cases in the United States occur in travelers to endemic areas. More than 390 million dengue infections occur annually; approximately 96 million have clinical disease.

Dengue outbreaks in urban areas infested with *A. aegypti* may be explosive; up to 70-80% of the population may be involved. Most overt disease occurs in older children and adults. Because *A. aegypti* has a limited flight range, spread of an epidemic occurs mainly through viremic human beings and follows the main lines of transportation. Sentinel cases may infect household mosquitoes; a large number of nearly simultaneous secondary infections give the appearance of a contagious disease. Where dengue is endemic, children and susceptible foreigners may be the only persons to acquire overt disease, as adults have become immune.

Table 269-1 Vectors and Geographic Distribution of Dengue-Like Diseases

VIRUS	GENUS AND DISEASE	VECTOR	GEOGRAPHIC DISTRIBUTION
Togavirus	Chikungunya	*Aedes aegypti* *Aedes africanus* *Aedes albopictus*	Africa, India, Southeast Asia, Latin America, United States
Togavirus	O'nyong-nyong	*Anopheles funestus*	East Africa
Flavivirus	West Nile fever	*Culex molestus* *Culex univittatus*	Europe, Africa, Middle East, India

Dengue-Like Diseases

Dengue-like diseases may occur in epidemics. Epidemiologic features depend on the vectors and their geographic distribution (see Table 269-1). Chikungunya virus is enzootic throughout much of West, Central, and South Africa as well as Central America and recently the southern United States. Periodic introductions of virus into the urban transmission cycle have led to pandemics, resulting in widespread endemicity in the most populous areas of Asia. In Asia, *A. aegypti* is the principal vector; in Africa, other Stegomyia species may be important vectors. In Southeast Asia, dengue and chikungunya outbreaks occur concurrently. Outbreaks of o'nyong-nyong fever usually involve villages or small towns, in contrast to the urban outbreaks of dengue and chikungunya. West Nile virus is enzootic in Africa. Chikungunya is now endemic in urban cycles in tropical countries throughout the world. Intense transmission in Caribbean countries presages emergence of chikungunya into the United States.

Dengue Hemorrhagic Fever

Dengue hemorrhagic fever occurs where multiple types of dengue virus are simultaneously or sequentially transmitted. It is endemic in all of tropical America and Asia, where warm temperatures and the practices of water storage in homes plus outdoor breeding sites result in large, permanent populations of *A. aegypti.* Under these conditions, infections with dengue viruses of all types are common. A first infection, referred to as a primary infection, may be followed by infection with a different dengue virus, referred to as a secondary infection. In areas of high endemicity secondary infections are frequent.

Secondary dengue infections are relatively mild in the majority of instances, ranging from an inapparent infection through an undifferentiated upper respiratory tract or dengue-like disease, but may also progress to dengue hemorrhagic fever. Nonimmune foreigners, both adults and children, who are exposed to dengue virus during outbreaks of hemorrhagic fever have classic dengue fever or even milder disease. The differences in clinical manifestations of dengue infections between natives and foreigners in Southeast Asia are related more to immunologic status than to racial susceptibility. Dengue hemorrhagic fever can occur during primary dengue infections, most frequently in infants whose mothers are immune to dengue. Dengue hemorrhagic fever or severe dengue occurs rarely in individuals of African ancestry because of an as yet

undiscovered resistance gene that would explain the low incidence of severe dengue throughout much of Africa and among African populations in the American tropics despite high rates of dengue infection.

PATHOGENESIS

Fatalities with chikungunya and West Nile fever infections are not common but have been ascribed to viral encephalitis.

The pathogenesis of dengue hemorrhagic fever is incompletely understood, but epidemiologic studies suggest that it is usually associated with second heterotypic infections with dengue types 1-4. Retrospective studies of sera from human mothers whose infants acquired dengue hemorrhagic fever and prospective studies in children acquiring sequential dengue infections have shown that the circulation of infection-enhancing antibodies at the time of infection is the strongest risk factor for development of severe disease. Absence of cross-reactive neutralizing antibodies and presence of enhancing antibodies from passive transfer or active production are the best correlates of risk for dengue hemorrhagic fever. Monkeys that are infected sequentially or are receiving small quantities of enhancing antibodies have enhanced viremias. In humans studied early during the course of secondary dengue infections, viremia levels directly predicted disease severity. When dengue virus immune complexes attach to macrophage Fc receptors, a signal is sent that suppresses innate immunity, resulting in enhanced viral production. In the Americas, dengue hemorrhagic fever and dengue shock syndrome have been associated with dengue types 1-4 strains of recent Southeast Asian origin. Recent occurrences of sizable dengue hemorrhagic fever outbreaks in India, Pakistan, and Bangladesh also appear to be related to imported dengue strains.

Early in the acute stage of secondary dengue infections, there is rapid activation of the complement system. Shortly before or during shock, blood levels of soluble tumor necrosis factor receptor, interferon-γ, and interleukin-2 are elevated. C1q, C3, C4, C5-C8, and C3 proactivators are depressed, and C3 catabolic rates are elevated. These factors, the virus itself, or viral nonstructural protein 1 (NS1) may interact with endothelial cells, blood clotting factors, and platelets to produce increased vascular permeability. The blood clotting and fibrinolytic systems are activated, and levels of factor XII (Hageman factor) are depressed. The mechanism of bleeding in dengue hemorrhagic fever is not known, but a mild degree of disseminated intravascular coagulopathy, liver damage, and thrombocytopenia may operate synergistically. Capillary damage allows fluid, electrolytes, small proteins, and, in some instances, red blood cells to leak into extravascular spaces. This internal redistribution of fluid, together with deficits caused by fasting, thirsting, and vomiting, results in hemoconcentration, hypovolemia, increased cardiac work, tissue hypoxia, metabolic acidosis, and hyponatremia.

Usually no pathologic lesions are found to account for death. In rare instances, death may be a result of gastrointestinal or intracranial hemorrhages. Minimal to moderate hemorrhages are seen in the upper gastrointestinal tract, and petechial hemorrhages are common in the interventricular septum of the heart, on the pericardium, and on the subserosal surfaces of major viscera. Focal hemorrhages are occasionally seen in the lungs, liver, adrenals, and subarachnoid space. The liver is usually enlarged, often with fatty changes. Yellow, watery, and at times blood-tinged effusions are present in serous cavities in approximately 75% of patients at autopsy.

Dengue virus is frequently absent in tissues at the time of death; viral antigens or RNA have been localized to hepatocytes and macrophages in liver, spleen, lung, and lymphatic tissues.

CLINICAL MANIFESTATIONS

Dengue Fever

The incubation period is 1-7 days. The clinical manifestations are variable and are influenced by the age of the patient. In infants and young children, the disease may be undifferentiated or characterized by fever for 1-5 days, pharyngeal inflammation, rhinitis, and mild cough. A majority of infected older children and adults experience sudden onset of fever, with temperature rapidly increasing to 39.4-41.1°C (103-106°F), usually accompanied by frontal or retroorbital pain, particularly when pressure is applied to the eyes. Occasionally, severe back pain precedes the fever (back-break fever). A transient, macular, generalized rash that blanches under pressure may be seen during the 1st 24-48 hr of fever. The pulse rate may be slow relative to the degree of fever. Myalgia and arthralgia occur soon after the onset of fevers and increase in severity over time. Joint symptoms may be particularly severe in patients with chikungunya or o'nyong-nyong infection. From the 2nd-6th day of fever, nausea and vomiting are apt to occur, and generalized lymphadenopathy, cutaneous hyperesthesia or hyperalgesia, taste aberrations, and pronounced anorexia may develop.

Approximately 1-2 days after defervescence, a generalized, morbilliform, maculopapular rash appears that spares the palms and soles. It disappears in 1-5 days; desquamation may occur. Rarely there is edema of the palms and soles. About the time this second rash appears, the body temperature, which has previously decreased to normal, may become slightly elevated and demonstrate the characteristic biphasic temperature pattern.

Dengue Hemorrhagic Fever

Differentiation between dengue fever and dengue hemorrhagic fever is difficult early in the course of illness. A relatively mild 1st phase with abrupt onset of fever, malaise, vomiting, headache, anorexia, and cough may be followed after 2-5 days by rapid clinical deterioration and collapse. In this 2nd phase, the patient usually has cold, clammy extremities, a warm trunk, flushed face, diaphoresis, restlessness, irritability, midepigastric pain, and decreased urinary output. Frequently, there are scattered petechiae on the forehead and extremities; spontaneous ecchymoses may appear, and easy bruising and bleeding at sites of venipuncture are common. A macular or maculopapular rash may appear, and there may be circumoral and peripheral cyanosis. Respirations are rapid and often labored. The pulse is weak, rapid, and thready, and the heart sounds are faint. The liver may enlarge to 4-6 cm below the costal margin and is usually firm and somewhat tender. Approximately 20-30% of cases of dengue hemorrhagic fever are complicated by shock (dengue shock syndrome). Dengue shock can be subtle, arising in patients who are fully alert, and is accompanied by increased peripheral vascular resistance and raised diastolic blood pressure. Shock is not from congestive heart failure but from venous pooling. With increasing cardiovascular compromise, diastolic pressure rises toward the systolic level and the pulse pressure narrows. Fewer than 10% of patients have gross ecchymosis or gastrointestinal bleeding, usually after a period of uncorrected shock. After a 24-36 hr period of crisis, convalescence is fairly rapid in the children who recover. The temperature may return to normal before or during the stage of shock. Bradycardia and ventricular extrasystoles are common during convalescence.

DIAGNOSIS

A clinical diagnosis of dengue fever derives from a high index of suspicion and knowledge of the geographic distribution and environmental cycles of causal viruses. Because clinical findings vary and there are many possible causative agents, the term *dengue-like disease* should be used until a specific diagnosis is established. A case is confirmed by isolation of the virus, viral antigen, or genome by polymerase chain reaction analysis, as well as demonstration of a 4-fold or greater increase in antibody titers. A probable case is a typical acute febrile illness with supportive serology and occurrence at a location where there are confirmed cases.

The World Health Organization criteria for **dengue hemorrhagic fever** are fever (2-7 days in duration or biphasic), minor or major hemorrhagic manifestations, thrombocytopenia (≤100,000/µL), and objective evidence of increased capillary permeability (hematocrit increased by ≥20%), pleural effusion or ascites (by chest radiography or ultrasonography), or hypoalbuminemia. **Dengue shock syndrome** criteria include those for dengue hemorrhagic fever as well as hypotension, tachycardia, narrow pulse pressure (≤20 mm Hg), and signs of poor perfusion (cold extremities).

In 2009, the World Health Organization promulgated new guidelines for the diagnosis of probable dengue, dengue with warning signs, and a category called "severe dengue." Occurrence of warning signs in an individual with probable dengue should alert the physician to the need for hospitalization. Severe dengue is a mixture of syndromes associated

with dengue infection. This includes classical dengue hemorrhagic fever and dengue shock syndrome, but also rare instances of encephalitis or encephalopathy associated with dengue infection. Severe dengue also includes respiratory distress that may be a harbinger of pulmonary edema caused by overhydration, an all too common outcome of inexpert treatment (see "Treatment" and "Complications" sections).

Virologic diagnosis can be established by serologic tests, by detection of viral proteins or viral RNA, or by the isolation of the virus from blood leukocytes or acute-phase serum. Following primary and secondary dengue infections, there is a relatively transient appearance of antidengue (immunoglobulin [Ig] M) antibodies. These disappear after 6-12 wk, a feature that can be used to time a dengue infection. In secondary dengue infections, most antibody is of the IgG class. Serologic diagnosis depends on a 4-fold or greater increase in IgG antibody titer in paired sera by hemagglutination inhibition, complement fixation, enzyme immunoassay, or neutralization test. Carefully standardized IgM and IgG capture enzyme commercial immunoassays are now widely used to identify acute-phase antibodies from patients with primary or secondary dengue infections in single-serum samples. Usually such samples should be collected not earlier than 5 days and not later than 6 wk after onset. It may not be possible to distinguish the infecting virus by serologic methods alone, particularly when there has been prior infection with another member of the same arbovirus group. Virus can be recovered from acute-phase serum after inoculating tissue culture or living mosquitoes. Viral RNA can be detected in blood or tissues by specific complementary RNA probes or amplified first by polymerase chain reaction or by real-time polymerase chain reaction. A viral nonstructural protein, NS1, is released by infected cells into the circulation and can be detected in acute-stage blood samples using monoclonal or polyclonal antibodies. The detection of NS1 is the basis of commercial tests, including rapid lateral flow tests. These tests offer reliable point of care diagnosis of acute dengue infection.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of dengue fever includes dengue-like diseases, viral respiratory and influenza-like diseases, the early stages of malaria, mild yellow fever, scrub typhus, viral hepatitis, and leptospirosis.

Four arboviral diseases have dengue-like courses but without rash: Colorado tick fever, sandfly fever, Rift Valley fever, and Ross River fever. Colorado tick fever occurs sporadically among campers and hunters in the western United States; sandfly fever in the Mediterranean region, the Middle East, southern Russia, and parts of the Indian subcontinent; and Rift Valley fever in North, East, Central, and South Africa. Ross River fever is endemic in much of eastern Australia, with epidemic extension to Fiji. In adults, Ross River fever often produces protracted and crippling arthralgia involving weight-bearing joints.

Because meningococcemia, yellow fever (see Chapter 270), other viral hemorrhagic fevers (see Chapter 271), many rickettsial diseases, and other severe illnesses caused by a variety of agents may produce a clinical picture similar to dengue hemorrhagic fever, the etiologic diagnosis should be made only when epidemiologic or serologic evidence suggests the possibility of a dengue infection.

LABORATORY FINDINGS

In dengue fever, pancytopenia may develop after the 3-4 days of illness. Neutropenia may persist or reappear during the latter stage of the disease and may continue into convalescence, with white blood cell counts <2,000/μL. Platelet counts rarely fall below 100,000/μL. Venous clotting, bleeding and prothrombin times, and plasma fibrinogen values are within normal ranges. The tourniquet test result may be positive. Mild acidosis, hemoconcentration, increased transaminase values, and hypoproteinemia may occur during some primary dengue virus infections. The electrocardiogram may show sinus bradycardia, ectopic ventricular foci, flattened T waves, and prolongation of the P-R interval.

The most common hematologic abnormalities during dengue hemorrhagic fever and dengue shock syndrome are hemoconcentration with an increase of >20% in hematocrit, thrombocytopenia, prolonged bleeding time, and a moderately decreased prothrombin level that is seldom <40% of control. Fibrinogen levels may be subnormal, and fibrin split-product values are elevated. Other abnormalities include moderate elevations of serum transaminase levels, consumption of complement, mild metabolic acidosis with hyponatremia, occasionally hypochloremia, slight elevation of serum urea nitrogen, and hypoalbuminemia. Roentgenograms of the chest reveal pleural effusions (right > left) in nearly all patients with dengue shock syndrome. Ultrasongraphy can be used to detect serosal effusions of the thorax or abdomen. Thickening of gallbladder wall and presence of perivesicular fluid are characteristic signs of increased vascular permeability.

TREATMENT

Treatment of uncomplicated dengue fever is supportive. Bed rest is advised during the febrile period. Antipyretics should be used to keep body temperature <40°C (104°F). Analgesics or mild sedation may be required to control pain. Aspirin is contraindicated and should not be used because of its effects on hemostasis. Fluid and electrolyte replacement is required for deficits caused by sweating, fasting, thirsting, vomiting, and diarrhea.

Dengue Hemorrhagic Fever and Dengue Shock Syndrome

Dengue shock syndrome is a medical emergency that may occur in any child with a recent travel history to a tropical destination. Management begins with diagnostic suspicion and the understanding that shock often occurs during defervescence. Detailed instructions for case management are available at the Geneva or New Delhi World Health Organization websites: http://www.who.int/csr/don/archive/disease/dengue_fever/dengue.pdf. Management of dengue hemorrhagic fever and dengue shock syndrome includes immediate evaluation of vital signs and degrees of hemoconcentration, dehydration, and electrolyte imbalance. Close monitoring is essential for at least 48 hr, because shock may occur or recur precipitously early in the disease. Patients who are cyanotic or have labored breathing should be given oxygen. Rapid intravenous replacement of fluids and electrolytes can frequently sustain patients until spontaneous recovery occurs. Normal saline is more effective than the more expensive Ringer lactated saline in treating shock. When pulse pressure is ≤10 mm Hg or when elevation of the hematocrit persists after replacement of fluids, plasma or colloid preparations are indicated.

Care must be taken to avoid overhydration, which may contribute to cardiac failure. Transfusions of fresh blood or platelets suspended in plasma may be required to control bleeding; they should not be given during hemoconcentration but only after evaluation of hemoglobin or hematocrit values. Salicylates are contraindicated because of their effect on blood clotting.

Sedation may be required for children who are markedly agitated. Use of vasopressors has not resulted in a significant reduction of mortality over that observed with simple supportive therapy. Disseminated intravascular coagulation may require treatment (see Chapter 483). Corticosteroids do not shorten the duration of disease or improve prognosis in children receiving careful supportive therapy.

COMPLICATIONS

Hypervolemia during the fluid reabsorptive phase may be life-threatening and is heralded by a decrease in hematocrit with wide pulse pressure. Diuretics and digitalization may be necessary.

Primary infections with dengue fever and dengue-like diseases are usually self-limited and benign. Fluid and electrolyte losses, hyperpyrexia, and febrile convulsions are the most frequent complications in infants and young children. Epistaxis, petechiae, and purpuric lesions are uncommon but may occur at any stage. Blood from epistaxis that is swallowed, vomited, or passed by rectum may be erroneously interpreted as gastrointestinal bleeding. In adults and possibly in children, underlying conditions may lead to clinically significant bleeding. Convulsions may occur during high temperature, especially with chikungunya fever. Infrequently, after the febrile stage, prolonged asthenia, mental depression, bradycardia, and ventricular extrasystoles may occur in children.

In endemic areas, dengue hemorrhagic fever should be suspected in children with a febrile illness suggestive of dengue fever who experience hemoconcentration and thrombocytopenia.

PROGNOSIS

Dengue Fever

The prognosis is good. Care should be taken to avoid use of drugs that suppress platelet activity.

Dengue Hemorrhagic Fever

The prognosis of dengue hemorrhagic fever is adversely affected by late diagnosis and delayed or improper treatment. Death has occurred in 40-50% of patients with shock, but with adequate intensive care, deaths should occur in <1% of cases. Infrequently, there is residual brain damage as a consequence of prolonged shock or occasionally of intracranial hemorrhage. Many fatalities are caused by overhydration.

PREVENTION

Several types of dengue type 1-4 vaccines are under development, and a killed vaccine for chikungunya is efficacious but not licensed. Large-scale Phase III clinical evaluations of a chimeric yellow fever/dengue tetravalent vaccine manufactured by Sanofi Pasteur reveal only moderate protection against individual dengue viruses but a reduction in hospitalization and severe disease. Other major vaccine manufacturers, GlaxoSmithKline, Takeda and Merck, have other tetravalent dengue vaccines in human clinical trials. Sanofi plans to license their vaccine first in dengue-endemic countries. The possibility exists that incomplete dengue immunization may sensitize recipients, with the potential that ensuing dengue infections could result in dengue hemorrhagic fever. Prophylaxis consists of avoiding daytime household-based **mosquito bites** through the use of insecticides, repellents, body covering with clothing, screening of houses, and destruction of *A. aegypti* breeding sites. If water storage is mandatory, a tight-fitting lid or a thin layer of oil may prevent egg laying or hatching. A larvicide, such as Abate (O,O′-[thiodi-*p*-phenylene] O,O,O,O′-tetramethyl phosphorothioate), available as a 1% sand-granule formation and effective at a concentration of 1 ppm, may be added safely to drinking water. Ultra-low-volume spray equipment effectively dispenses the adulticide malathion from truck or airplane for rapid intervention during an epidemic. Only mosquito repellants and other personal antimosquito measures are effective against mosquitoes in the field, forest, or jungle.

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Chapter 270
Yellow Fever

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Yellow fever is an acute infection characterized in its most severe form by fever, jaundice, proteinuria, and hemorrhage. The virus is mosquito-borne and occurs in epidemic or endemic form in South America and Africa. Seasonal epidemics occurred in cities located in temperate areas of Europe and the Americas until 1900, and epidemics continue in West, Central, and East Africa.

ETIOLOGY

Yellow fever is the prototype of the *Flavivirus* genus of the family Flaviviridae, which are enveloped single-stranded RNA viruses 35-50 nm in diameter.

Yellow fever circulates zoonotically as 5 genotypes: type IA in West Central Africa, type IB in South America, type II in West Africa, type III in East Central Africa, and type IV in East Africa. Types IA and IB virus are capable of urban transmission between human beings by *Aedes aegypti*. Sometime in the 1600s yellow fever virus was brought to the American tropics through the African slave trade. Subsequently, yellow fever caused enormous coastal and riverine epidemics in the Atlantic and Caribbean basins until the 20th century, when the virus and its urban and sylvan mosquito cycles were identified, mosquito control methods were perfected, and a vaccine was developed. The East and East/Central African genotypes have not fully entered the urban cycle and have not spread to the East Coast of Africa or to the countries of Asia.

EPIDEMIOLOGY

Human and nonhuman primate hosts acquire the yellow fever infection by the bite of infected mosquitoes. After an incubation period of 3-6 days, virus appears in the blood and may serve as a source of infection for other mosquitoes. The virus must replicate in the gut of the mosquito and pass to the salivary gland before the mosquito can transmit the virus. Yellow fever virus is transmitted in an urban cycle—human to *A. aegypti* to human—and a jungle cycle—monkey to jungle mosquitoes to monkey. Classic yellow fever epidemics in the United States, South America, the Caribbean, and parts of Europe were of the urban variety. Since 2000, West Africa has experienced 5 urban epidemics, including in the capital cities of Abidjan (Cote d'Ivoire), Conakry (Guinea), and Dakar (Senegal). In 2012-2013, large outbreaks of East and East/Central yellow fever occurred across a large, predominantly rural area of war-ravaged Darfur in southwestern Sudan and in adjacent areas of northern Uganda. Most of the approximately 200 cases reported each year in South America are jungle yellow fever. In colonial times, urban yellow fever attack rates in white adults were very high, suggesting that subclinical infections are uncommon in this age group. Yellow fever may be less severe in children, with subclinical infection : clinical case ratios ≥2 : 1. In areas where outbreaks of urban yellow fever are common, most cases involve children because many adults are immune. Transmission in West Africa is highest during the rainy season, from July to November. The migration of nonimmune laborers into endemic regions is a significant factor in some outbreaks.

In tropical forests, yellow fever virus is maintained in a transmission cycle involving monkeys and tree hole–breeding mosquitoes (*Haemagogus* in Central and South America; the *Aedes africanus* complex in Africa). In the Americas, most cases involve tourists, campers, and men who work in forested areas and are exposed to infected mosquitoes. In Africa, the virus is prevalent in moist savanna and savanna transition areas, where other tree hole–breeding *Aedes* vectors transmit the virus between monkeys and humans and between humans.

PATHOGENESIS

Pathologic changes seen in the liver include: (1) coagulative necrosis of hepatocytes in the midzone of the liver lobule, with sparing of cells around the portal areas and central veins; (2) eosinophilic degeneration of hepatocytes **(Councilman bodies);** (3) microvacuolar fatty change; and (4) minimal inflammation. The kidneys show acute tubular necrosis. In the heart, myocardial fiber degeneration and fatty infiltration are seen. The brain may show edema and petechial hemorrhages. Direct viral injury to the liver results in impaired ability to perform functions of biosynthesis and detoxification; this is the central pathogenic event of yellow fever. Hemorrhage is postulated to result from decreased synthesis of vitamin K–dependent clotting factors and, in some cases, disseminated intravascular clotting. However, because the pathogenesis of shock in patients with yellow fever appears similar to that described for dengue shock syndrome and the other viral hemorrhagic fevers, viral damage to platelets and endothelial cells resulting in release of prohemorrhagic factors may be the central mechanism of hemorrhage in yellow fever.

Renal dysfunction has been attributed to hemodynamic factors (prerenal failure progressing to acute tubular necrosis).

CLINICAL MANIFESTATIONS

In Africa, inapparent, abortive, or clinically mild infections are frequent; some studies suggest that children experience a milder disease than adults do. Abortive infections, characterized by fever and headache, may be unrecognized except during epidemics.

In its classic form, yellow fever begins with sudden onset of fever, headache, myalgia, lumbosacral pain, anorexia, nausea, and vomiting. Physical findings during the early phase of illness, when virus is present in the blood, include prostration, conjunctival injection, flushing of

face and neck, reddening of the tongue at the tip and edges, and relative bradycardia. After 2-3 days, there may be a brief period of remission, followed in 6-24 hr by reappearance of fever with vomiting, epigastric pain, jaundice, dehydration, gastrointestinal and other hemorrhages, albuminuria, hypotension, renal failure, delirium, convulsions, and coma. Death may occur after 7-10 days, with the fatality rate in severe cases approaching 50%. Some patients who survive the acute phase of illness later succumb to renal failure or myocardial damage. Laboratory abnormalities include leukopenia; prolonged clotting, prothrombin, and partial thromboplastin times; thrombocytopenia; hyperbilirubinemia; elevated serum transaminase values; albuminuria; and azotemia. Hypoglycemia may be present in severe cases. Electrocardiogram abnormalities such as bradycardia and ST-T changes are described.

DIAGNOSIS

Yellow fever should be suspected when fever, headache, vomiting, myalgia, and jaundice appear in residents of enzootic areas or in unimmunized visitors who have recently traveled (within 2 wk before onset of symptoms) to endemic areas. Clinically, yellow fever is quite similar to dengue hemorrhagic fever. In contrast to the gradual onset of acute viral hepatitis resulting from hepatitis A, B, C, D, or E virus, jaundice in yellow fever appears after 3-5 days of high temperature and is often accompanied by severe prostration. Mild yellow fever is dengue-like and cannot be distinguished from a wide variety of other infections. Jaundice and fever may occur in any of several other tropical diseases, including malaria, viral hepatitis, louse-borne relapsing fever, leptospirosis, typhoid fever, rickettsial infections, certain systemic bacterial infections, sickle cell crisis, Rift Valley fever, Crimean-Congo hemorrhagic fever, and other viral hemorrhagic fevers. Outbreaks of yellow fever always include cases with severe gastrointestinal hemorrhage.

Specific diagnosis depends on detection of virus or viral antigen in acute-phase blood samples or antibody assays. The immunoglobulin M enzyme immunoassay is particularly useful. Sera obtained during the 1st 10 days after onset of symptoms should be kept in an ultra-low-temperature freezer (−70°C [−94°F]) and shipped on dry ice for virus testing. Convalescent-phase samples for antibody tests are managed by conventional means. In handling acute-phase blood specimens, medical personnel must take care to avoid contaminating themselves or others on the evacuation trail (laboratory personnel and others). Postmortem diagnosis is based on virus isolation from liver or blood, identification of Councilman bodies in liver tissue, or detection of antigen or viral genome in liver tissue.

TREATMENT

It is customary to keep patients with yellow fever in a mosquito-free area, with use of mosquito nets if necessary. Patients are viremic during the febrile phase of the illness. Although there is no specific treatment for yellow fever, medical care is directed at maintaining physiologic status with the following measures: (1) sponging and acetaminophen to reduce high temperature, (2) vigorous fluid replacement of losses resulting from fasting, thirsting, vomiting, or plasma leakage, (3) correcting acid–base imbalance, (4) maintaining nutritional intake to lessen the severity of hypoglycemia, and (5) avoiding drugs that are either metabolized by the liver or toxic to the liver, kidney, or central nervous system.

COMPLICATIONS

Complications of acute yellow fever include severe hemorrhage, liver failure, and acute renal failure. Bleeding should be managed by transfusion of fresh whole blood or fresh plasma with platelet concentrates if necessary. Renal failure may require peritoneal dialysis or hemodialysis.

PREVENTION

Yellow fever 17D is a live-attenuated vaccine with a long record of safety and efficacy. It is administered as a single 0.5 mL subcutaneous injection at least 10 days before arrival in a yellow fever–endemic area. With the exceptions noted later, individuals traveling to endemic areas in South America and Africa should be considered for vaccination, but length of stay, exact locations to be visited, and environmental or occupational exposure may determine the specific risk and individual need for vaccination. Persons traveling from yellow fever–endemic to yellow fever–receptive countries may be required by national authorities to obtain a yellow fever vaccine (e.g., from South America or Africa to India). Usually countries that require travelers to obtain a yellow fever immunization do not issue a visa without a valid immunization certificate. Vaccination is valid for 10 yr for international travel certification, although immunity lasts at least 40 yr and probably for life. Immunoglobulin M antibodies circulate for years after administration of yellow fever vaccine.

Since 1996, there have been a number of reports of **yellow fever vaccine–associated viscerotropic disease** with higher risk in elderly vaccine recipients and in persons with previous thymectomies. Yellow fever vaccine should not be administered to persons who have symptomatic immunodeficiency diseases, are taking immunosuppressant drugs, or have a history of thymectomy. A recent study has shown that individuals on maintenance corticosteroids may be successfully vaccinated. Although the vaccine is not known to harm fetuses, its administration during pregnancy is not advised. The vaccine virus may be rarely transmitted through breastfeeding. In very young children, there is a small risk of encephalitis and death after yellow fever 17D vaccination. The 17D vaccine should not be administered to infants younger than 4 mo. Residence in or travel to areas of known or anticipated yellow fever activity (e.g., forested areas in the Amazon basin), which puts an individual at high risk, warrants immunization of infants 4-9 mo of age. Immunization of children 9 mo of age and older is routinely recommended before entry into endemic areas. Immunization of persons older than 60 yr of age should be weighed against their risk for sylvatic yellow fever in the American tropics and for urban or sylvatic yellow fever in Africa. Vaccination should be avoided in persons with a history of egg allergy. Alternatively, a skin test can be performed to determine whether a serious allergy exists that would preclude vaccination.

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Chapter 271

Ebola and Other Viral Hemorrhagic Fevers

Scott B. Halstead

Viral hemorrhagic fevers are a loosely defined group of clinical syndromes in which hemorrhagic manifestations are either common or especially notable in severe illness. Both the etiologic agents and clinical features of the syndromes differ, but disseminated intravascular coagulopathy may be a common pathogenetic feature.

ETIOLOGY

Six of the viral hemorrhagic fevers are caused by arthropod-borne viruses (arboviruses) (Table 271-1). Four are caused by togaviruses of the family Flaviviridae: Kyasanur Forest disease, Omsk hemorrhagic fever, dengue (see Chapter 269), and yellow fever (see Chapter 270) viruses. Three are caused by viruses of the family Bunyaviridae: Congo fever, Hantaan fever, and Rift Valley fever (RVF) viruses. Four are caused by viruses of the family Arenaviridae: Junin fever, Machupo fever, Guanarito fever, and Lassa fever. Two are caused by viruses of the family Filoviridae: Ebola and Marburg disease. The Filoviridae are enveloped, filamentous RNA viruses that are sometimes branched, unlike any other known virus.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

With some exceptions, the viruses causing viral hemorrhagic fevers are transmitted to humans via a nonhuman entity. The specific ecosystem

Table 271-1 Viral Hemorrhagic Fevers

MODE OF TRANSMISSION	DISEASE	VIRUS
Tick-borne	Crimean-Congo hemorrhagic fever (HF)*	Congo
	Kyasanur Forest disease	Kyasanur Forest disease
	Omsk HF	Omsk
Mosquito-borne†	Dengue HF	Dengue (4 types)
	Rift Valley fever	Rift Valley fever
	Yellow fever	Yellow fever
Infected animals or materials to humans	Argentine HF	Junin
	Bolivian HF	Machupo
	Lassa fever*	Lassa
	Marburg disease*	Marburg
	Ebola HF*	Ebola
	HF with renal syndrome	Hantaan

*Patients may be contagious; nosocomial infections are common.
†Chikungunya virus is associated infrequently with petechiae and epistaxis. Severe hemorrhagic manifestations have been reported in some cases.

required for viral survival determines the geographic distribution of disease. Although it is commonly thought that all viral hemorrhagic fevers are arthropod borne, 7 may be contracted from environmental contamination caused by animals or animal cells or from infected humans (see Table 271-1). Laboratory and hospital infections have occurred with many of these agents. Lassa fever and Argentine and Bolivian hemorrhagic fevers are reportedly milder in children than in adults.

Crimean-Congo Hemorrhagic Fever

Sporadic human infection with Crimean-Congo hemorrhagic fever in Africa provided the original virus isolation. Natural foci are recognized in Bulgaria, western Crimea, and the Rostov-on-Don and Astrakhan regions; disease occurs in Central Asia from Kazakhstan to Pakistan. Index cases were followed by nosocomial transmission in Pakistan and Afghanistan in 1976, in the Arabian Peninsula in 1983, and in South Africa in 1984. In the Russian Federation, the vectors are ticks of the species *Hyalomma marginatum* and *Hyalomma anatolicum,* which, along with hares and birds, may serve as viral reservoirs. Disease occurs from June to September, largely among farmers and dairy workers.

Kyasanur Forest Disease

Human cases of Kyasanur Forest disease occur chiefly in adults in an area of Mysore State, India. The main vectors are 2 Ixodidae ticks, *Haemaphysalis turturis* and *Haemaphysalis spinigera.* Monkeys and forest rodents may be amplifying hosts. Laboratory infections are common.

Omsk Hemorrhagic Fever

Omsk hemorrhagic fever occurs throughout south-central Russia and northern Romania. Vectors may include *Dermacentor pictus* and *Dermacentor marginatus,* but direct transmission from moles and muskrats to humans seems well established. Human disease occurs in a spring-summer-autumn pattern, paralleling the activity of vectors. This infection occurs most frequently in persons with outdoor occupational exposure. Laboratory infections are common.

Rift Valley Fever

The virus causing RVF is responsible for epizootics involving sheep, cattle, buffalo, certain antelopes, and rodents in North, Central, East, and South Africa. The virus is transmitted to domestic animals by *Culex theileri* and several *Aedes* species. Mosquitoes may serve as reservoirs by transovarial transmission. An epizootic in Egypt in 1977-1978 was accompanied by thousands of human infections, principally among veterinarians, farmers, and farm laborers. Smaller outbreaks occurred in Senegal in 1987, Madagascar in 1990, and Saudi Arabia and Yemen in 2000-2001. Humans are most often infected during the slaughter or skinning of sick or dead animals. Laboratory infection is common.

Argentine Hemorrhagic Fever

Before introduction of vaccine, hundreds to thousands of cases of Argentine hemorrhagic fever occurred annually from April through July in the maize-producing area northwest of Buenos Aires that reaches to the eastern margin of the Province of Cordoba. Junin virus has been isolated from the rodents *Mus musculus, Akodon arenicola,* and *Calomys laucha laucha.* It infects migrant laborers who harvest the maize and who inhabit rodent-contaminated shelters.

Bolivian Hemorrhagic Fever

The recognized endemic area of Bolivian hemorrhagic fever consists of the sparsely populated province of Beni in Amazonian Bolivia. Sporadic cases occur in farm families who raise maize, rice, yucca, and beans. In the town of San Joaquin, a disturbance in the domestic rodent ecosystem may have led to an outbreak of household infection caused by Machupo virus transmitted by chronically infected *Calomys callosus,* ordinarily a field rodent. Mortality rates are high in young children.

Venezuelan Hemorrhagic Fever

In 1989, an outbreak of hemorrhagic illness occurred in the farming community of Guanarito, Venezuela, 200 miles south of Caracas. Subsequently, in 1990-1991, there were 104 cases reported with 26 deaths caused by Guanarito virus. Cotton rats *(Sigmodon alstoni)* and cane rats *(Zygodontomys brevicauda)* have been implicated as likely reservoirs of Venezuelan hemorrhagic fever.

Lassa Fever

Lassa virus has an unusual potential for human-to-human spread, which has resulted in many small epidemics in Nigeria, Sierra Leone, and Liberia. In 2012, an outbreak of more than 1,000 cases of Lassa fever occurred in east-central Nigeria. Medical workers in Africa and the United States have also contracted the disease. Patients with acute Lassa fever have been transported by international aircraft, necessitating extensive surveillance among passengers and crews. The virus is probably maintained in nature in a species of African peridomestic rodent, *Mastomys natalensis.* Rodent-to-rodent transmission and infection of humans probably operate via mechanisms established for other arenaviruses.

Marburg Disease

Until recently, the world experience of Marburg disease had been limited to 26 primary and 5 secondary cases in Germany and Yugoslavia in 1967, and to small outbreaks in Zimbabwe in 1975, Kenya in 1980 and 1988, and South Africa in 1983. However, in 1999 a large outbreak occurred in Congo Republic and in 2005 a still larger outbreak occurred in Uige Province, Angola, with 252 cases and 227 deaths. In laboratory and clinical settings, transmission occurs by direct contact with tissues of the African green monkey or with infected human blood or semen. A reservoir in bats has been demonstrated. It appears that the virus is transmitted by close contact between fructivorous bats and from bats by aerosol to humans.

Ebola Hemorrhagic Fever

Ebola virus was isolated in 1976 from a devastating epidemic involving small villages in northern Zaire and southern Sudan; smaller outbreaks have occurred subsequently. Outbreaks have initially been nosocomial. Attack rates have been highest in the birth-1 yr old and 15-50 yr old age groups. The virus is closely related to Marburg virus. Ebola virus epidemics have occurred in Kikwit, Zaire, in 1995, followed by scattered outbreaks in Uganda and Central and West Africa. The virus has been recovered from chimpanzees, and antibodies have been found in other subhuman primates, which apparently acquire infection from a zoonotic reservoir in bats. The mode of transmission to humans is unknown. Reston virus, related to Ebola virus, has been recovered from Philippine monkeys and pigs and has caused subclinical infections in workers in monkey colonies in the United States.

West Africa in 2014 has experienced the largest number of cases of Ebola virus disease (EVD), with more than 17,900 cases reported as of December 2014 (Fig. 271-1). Countries primarily affected are Liberia, Sierra Leone, and Guinea, with imported cases reported in Nigeria,

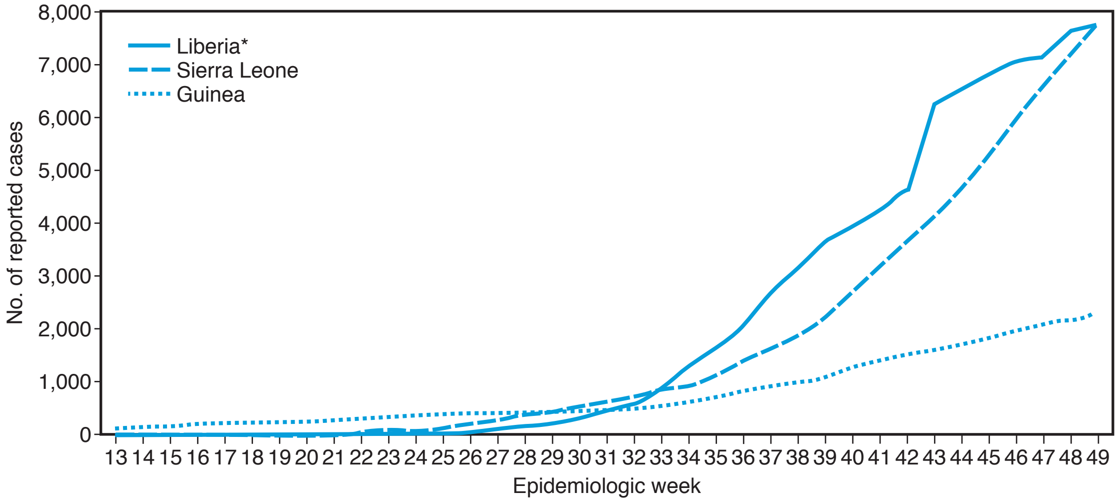

Figure 271-1 Cumulative number of Ebola virus disease cases reported—three countries, West Africa, March 29–September 20, 2014. The highest reported case counts were from Sierra Leone (7,897 cases) and Liberia (7,719), followed by Guinea (2,292). *A change in reporting source data at week 43 resulted in an adjustment of cumulative cases in Liberia. *(From Centers for Disease Control and Prevention (CDC): Ebola virus disease epidemic–West Africa, December 2014.* MMWR *63:1199–1201, 2014.)*

Mali, and Senegal as well as Europe and the United States. Of the 3 strains of EVD (Zaire, Sudan, Bundibugyo), the new strain in Zaire has a mortality rate of approximately 55-65%.

EVD may occur following exposure to fruit bats or bushmeat but most often occurs through exposure to body fluids (blood, sweat, saliva, vomitus, diarrhea, and less often human milk or semen). Patients are infectious once they are symptomatic; the incubation period is 2-21 days (mean: 11 days). The age range in the West African epidemic is broad but most patients are between 15 and 44 yr old.

Manifestations of EVD may come in stages, but most EVD begins with the sudden onset of fever accompanied by fatigue, weakness, myalgias, headache, and sore throat. This is followed by gastrointestinal involvement including anorexia, nausea, abdominal pain, vomiting, and diarrhea. Hemorrhage (defined by any evidence of bleeding) is seen in more than 50% and is a serious later phase often accompanied by vascular leakage, multiorgan failure, and death. Those who survive improve on approximately days 6-11 of EVD.

The diagnosis is confirmed by enzyme-linked immunosorbent assay immunoglobulin M and polymerase chain reaction (which may need to be repeated if initially negative). The differential diagnosis includes malaria, typhoid, Lassa fever, influenza, and meningococcemia. Criteria to aid in the diagnosis of EVD include temperature >38.6°C (101.5°F) plus symptoms; contact with an affected patient, the patient's body fluids, or the funeral; residence in or travel to an endemic region; or a history of handling bats, rodents, or primates from an endemic area.

Treatment of EVD often requires an intensive care unit and management of multiorgan system dysfunction, including fluid replacement and ventilation support. Convalescent serum and monoclonal antibodies have been employed on an experimental basis. Strict isolation and appropriate barrier protection of healthcare workers is mandatory. There is no vaccine, and epidemic control measures, isolation, and quarantine have been used to attempt to decrease the spread of the West African epidemic.

Hemorrhagic Fever with Renal Syndrome

The endemic area of hemorrhagic fever with renal syndrome (HFRS), also known as *epidemic hemorrhagic fever* and *Korean hemorrhagic fever*, includes Japan, Korea, far eastern Siberia, north and central China, European and Asian Russia, Scandinavia, Czechoslovakia, Romania, Bulgaria, Yugoslavia, and Greece. Although the incidence and severity of hemorrhagic manifestations and the mortality are lower in Europe than in northeastern Asia, the renal lesions are the same. Disease in Scandinavia, **nephropathia epidemica,** is caused by a different although antigenically related virus, Puumala virus, associated with the bank vole, *Clethrionomys glareolus*. Cases occur predominantly in the spring and summer. There appears to be no age factor in susceptibility, but because of occupational hazards, young adult men are most frequently attacked. Rodent plagues and evidence of rodent infestation have accompanied endemic and epidemic occurrences. Hantaan virus has been detected in lung tissue and excreta of *Apodemus agrarius coreae*. Antigenically related agents have been detected in laboratory rats and in urban rat populations around the world, including Prospect Hill virus in the wild rodent *Microtus pennsylvanicus* in North America and *sin nombre* virus in the deer mouse in the southern and southwestern United States; these viruses are causes of hantavirus pulmonary syndrome (see Chapter 273). Rodent-to-rodent and rodent-to-human transmission presumably occurs via the respiratory route.

CLINICAL MANIFESTATIONS

Dengue hemorrhagic fever (see Chapter 269) and yellow fever (see Chapter 270) cause similar syndromes in children in endemic areas.

Crimean-Congo Hemorrhagic Fever

The incubation period of 3-12 days is followed by a febrile period of 5-12 days and a prolonged convalescence. Illness begins suddenly with fever, severe headache, myalgia, abdominal pain, anorexia, nausea, and vomiting. After 1-2 days, fever may subside until the patient experiences an erythematous facial or truncal flush and injected conjunctivae. A second febrile period of 2-6 days then develops, with a hemorrhagic enanthem on the soft palate and a fine petechial rash on the chest and abdomen. Less frequently, there are large areas of purpura and bleeding from the gums, nose, intestines, lungs, or uterus. Hematuria and proteinuria are relatively rare. During the hemorrhagic stage, there is usually tachycardia with diminished heart sounds and occasionally hypotension. The liver is usually enlarged, but there is no icterus. In protracted cases, central nervous system signs include delirium, somnolence, and progressive clouding of consciousness. Early in the disease, leukopenia with relative lymphocytosis, progressively worsening thrombocytopenia, and gradually increasing anemia occur. In convalescence there may be hearing and memory loss. The mortality rate is 2-50%.

Kyasanur Forest Disease and Omsk Hemorrhagic Fever

After an incubation period of 3-8 days, both Kyasanur Forest disease and Omsk hemorrhagic fever begin with sudden onset of fever and headache. Kyasanur Forest disease is characterized by severe myalgia, prostration, and bronchiolar involvement; it often manifests without hemorrhage but occasionally with severe gastrointestinal bleeding. In Omsk hemorrhagic fever, there is moderate epistaxis, hematemesis,

and a hemorrhagic enanthem but no profuse hemorrhage; bronchopneumonia is common. In both diseases, severe leukopenia and thrombocytopenia, vascular dilation, increased vascular permeability, gastrointestinal hemorrhages, and subserosal and interstitial petechial hemorrhages occur. Kyasanur Forest disease may be complicated by acute degeneration of renal tubules and focal liver damage. In many patients, recurrent febrile illness may follow an afebrile period of 7-15 days. This 2nd phase takes the form of a meningoencephalitis.

Rift Valley Fever

Most RVF infections have occurred in adults with signs and symptoms resembling those of dengue fever (see Chapter 269). Onset is acute, with fever, headache, prostration, myalgia, anorexia, nausea, vomiting, conjunctivitis, and lymphadenopathy. The fever lasts 3-6 days and is often biphasic. Convalescence is often prolonged. In the 1977-1978 outbreak many patients died after showing signs that included purpura, epistaxis, hematemesis, and melena. RVF affects the uvea and posterior chorioretina; macular scarring, vascular occlusion, and optic atrophy occur, resulting in permanent visual loss in a high proportion of patients with mild to severe RVF. At autopsy extensive eosinophilic degeneration of the parenchymal cells of the liver has been observed.

Argentine, Venezuelan, and Bolivian Hemorrhagic Fevers and Lassa Fever

The incubation period in Argentine, Venezuelan, and Bolivian hemorrhagic fevers and Lassa fever is commonly 7-14 days; the acute illness lasts for 2-4 wk. Clinical illnesses range from undifferentiated fever to the characteristic severe illness. **Lassa fever** is most often clinically severe in white persons. Onset is usually gradual, with increasing fever, headache, diffuse myalgia, and anorexia (Table 271-2). During the 1st wk, signs frequently include a sore throat, dysphagia, cough, oropharyngeal ulcers, nausea, vomiting, diarrhea, and pains in the chest and abdomen. Pleuritic chest pain may persist for 2-3 wk. In Argentine and Bolivian hemorrhagic fevers and less frequently in Lassa fever, a petechial enanthem appears on the soft palate 3-5 days after onset and at about the same time on the trunk. The tourniquet test may be positive. The clinical course of Venezuelan hemorrhagic fever has not been well described.

In 35-50% of all patients, these diseases may become severe, with persistent high temperature, increasing toxicity, swelling of the face or neck, microscopic hematuria, and frank hemorrhages from the stomach, intestines, nose, gums, and uterus. A syndrome of **hypovolemic shock** is accompanied by pleural effusion and renal failure. **Respiratory distress** resulting from airway obstruction, pleural effusion, or congestive heart failure may occur. A total of 10-20% of patients experience late neurologic involvement, characterized by intention tremor of the tongue and associated speech abnormalities. In severe cases, there may be intention tremors of the extremities, seizures, and delirium. The cerebrospinal fluid is normal. In Lassa fever, nerve deafness occurs in early convalescence in 25% of cases.

Table 271-2 Clinical Stages of Lassa Fever

STAGE	SYMPTOMS
1 (days 1-3)	General weakness and malaise. High fever, >39°C (102.2°F), constant with peaks of 40-41°C (104-105.8°F)
2 (days 4-7)	Sore throat (with white exudative patches) very common; headache; back, chest, side, or abdominal pain; conjunctivitis; nausea and vomiting; diarrhea; productive cough; proteinuria; low blood pressure (systolic <100 mm Hg); anemia
3 (after 7 days)	Facial edema; convulsions; mucosal bleeding (mouth, nose, eyes); internal bleeding; confusion or disorientation
4 (after 14 days)	Coma and death

From Richmond JK, Baglole DJ: Lassa fever: epidemiology, clinical features, and social consequences, BMJ *327: 1271–1275, 2003.*

Prolonged convalescence is accompanied by alopecia and, in Argentine and Bolivian hemorrhagic fevers, by signs of autonomic nervous system lability, such as postural hypotension, spontaneous flushing or blanching of the skin, and intermittent diaphoresis.

Laboratory studies reveal marked leukopenia, mild to moderate thrombocytopenia, proteinuria, and, in Argentine hemorrhagic fever, moderate abnormalities in blood clotting, decreased fibrinogen, increased fibrinogen split products, and elevated serum transaminases. There is focal, often extensive eosinophilic necrosis of liver parenchyma, focal interstitial pneumonitis, focal necrosis of the distal and collecting tubules, and partial replacement of splenic follicles by amorphous eosinophilic material. Usually bleeding occurs by diapedesis with little inflammatory reaction. The mortality rate is 10-40%.

Marburg Disease and Ebola Hemorrhagic Fever

After an incubation period of 4-7 days, illness begins abruptly with severe frontal headache, malaise, drowsiness, lumbar myalgia, vomiting, nausea, and diarrhea. A **maculopapular** eruption begins 5-7 days later on the trunk and upper arms. It becomes generalized and often hemorrhagic and exfoliates during convalescence. The exanthem is accompanied by a dark red enanthem on the hard palate, conjunctivitis, and scrotal or labial edema. Gastrointestinal hemorrhage occurs as the severity of illness increases. Late in the illness, the patient may become tearfully depressed with marked hyperalgesia to tactile stimuli. In fatal cases, patients become hypotensive, restless, and confused and lapse into coma. Convalescent patients may experience alopecia and may have paresthesias of the back and trunk. There is a marked leukopenia with necrosis of granulocytes. **Disseminated intravascular coagulopathy** and thrombocytopenia are universal and correlate with severity of disease; there are moderate abnormalities in concentrations of clotting proteins and elevations of serum transaminases and amylase. Pregnant women and young children are at high risk of severe disease with fatal outcome. The mortality rate of Marburg disease is 25-85%, and the mortality rate of Ebola hemorrhagic fever 50-90%. High viral loads in acute-phase blood samples convey a poor prognosis.

Hemorrhagic Fever with Renal Syndrome

In most cases, HFRS is characterized by fever, petechiae, mild hemorrhagic phenomena, and mild proteinuria, followed by relatively uneventful recovery. In 20% of recognized cases, the disease may progress through 4 distinct phases. The febrile phase is ushered in with fever, malaise, and facial and truncal flushing. It lasts 3-8 days and ends with thrombocytopenia, petechiae, and proteinuria. The hypotensive phase, of 1-3 days, follows defervescence. Loss of fluid from the intravascular compartment may result in marked hemoconcentration. Proteinuria and ecchymoses increase. The oliguric phase, usually 3-5 days in duration, is characterized by a low output of protein-rich urine, increasing nitrogen retention, nausea, vomiting, and dehydration. Confusion, extreme restlessness, and hypertension are common. The diuretic phase, which may last for days or weeks, usually initiates clinical improvement. The kidneys show little concentrating ability, and rapid loss of fluid may result in severe dehydration and shock. Potassium and sodium depletion may be severe. Fatal cases manifest as abundant protein-rich retroperitoneal edema and marked hemorrhagic necrosis of the renal medulla. The mortality rate is 5-10%.

DIAGNOSIS

Diagnosis of these viral hemorrhagic fevers depends on a high index of suspicion in endemic areas. In nonendemic areas, histories of recent travel, recent laboratory exposure, or exposure to an earlier case should evoke suspicion of a viral hemorrhagic fever.

In all viral hemorrhagic fevers, the viral agent circulates in the blood at least transiently during the early febrile stage. Togaviruses and bunyaviruses can be recovered from acute-phase serum samples by inoculation into tissue culture or living mosquitoes. Argentine, Bolivian, and Venezuelan hemorrhagic fever viruses can be isolated from acute-phase blood or throat washings by intracerebral inoculation into guinea pigs, infant hamsters, or infant mice. Lassa virus may be isolated from acute-phase blood or throat washings by inoculation into tissue cultures. For Marburg disease and Ebola hemorrhagic fever,

acute-phase throat washings, blood, and urine may be inoculated into tissue culture, guinea pigs, or monkeys. The viruses are readily identified on electron microscopy, with a filamentous structure differentiating them from all other known agents. Specific complement-fixing and immunofluorescent antibodies appear during convalescence. The virus of HFRS is recovered from acute-phase serum or urine by inoculation into tissue culture. A variety of antibody tests using viral subunits is becoming available. Serologic diagnosis depends on demonstration of seroconversion or a 4-fold or greater increase in immunoglobulin G antibody titer in acute and convalescent serum specimens collected 3-4 wk apart. Viral RNA may also be detected in blood or tissues with use of reverse transcriptase polymerase chain reaction analysis.

Handling blood and other biologic specimens is hazardous and must be performed by specially trained personnel. Blood and autopsy specimens should be placed in tightly sealed metal containers, wrapped in absorbent material inside a sealed plastic bag, and shipped on dry ice to laboratories with biocontainment safety level 4 facilities. Even routine hematologic and biochemical tests should be done with extreme caution.

Differential Diagnosis

Mild cases of hemorrhagic fever may be confused with almost any self-limited systemic bacterial or viral infection. More severe cases may suggest typhoid fever; epidemic, murine, or scrub typhus; leptospirosis; or a rickettsial spotted fever, for which effective chemotherapeutic agents are available. Many of these disorders may be acquired in geographic or ecologic locations endemic for a viral hemorrhagic fever.

TREATMENT

Ribavirin administered intravenously is effective in reducing mortality rates in Lassa fever and HFRS. Further information and advice about management, control measures, diagnosis, and collection of biohazardous specimens can be obtained from the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Special Pathogens Branch, Atlanta, Georgia 30333 (404-639-1115).

The therapeutic principle involved in all of these diseases, especially HFRS, is the reversal of dehydration, hemoconcentration, renal failure, and protein, electrolyte, or blood losses. The contribution of disseminated intravascular coagulopathy to the hemorrhagic manifestations is unknown, and the management of hemorrhage should be individualized. Transfusions of fresh blood and platelets are frequently given. Good results have been reported in a few patients after the administration of clotting factor concentrates. The efficacy of corticosteroids, ε-aminocaproic acid, pressor amines, and α-adrenergic blocking agents has not been established. Sedatives should be selected with regard to the possibility of kidney or liver damage. The successful management of HFRS may require renal dialysis.

Although whole-blood transfusions from Ebola virus–immune donors are thought to be therapeutic, studies in a monkey model were unable to confirm this outcome.

Patients suspected of having Lassa fever, Ebola fever, Marburg fever, or Congo Crimean hemorrhagic fever should be placed in a private room on standard contact and droplet precautions. Caretakers should use barrier precautions to prevent skin or mucous membrane exposure. All persons entering the patient's room should wear gloves and gowns and face shields. Before exiting the patient's room, caretakers should safely remove and dispose of all protective gear and should clean and disinfect shoes. Protocols require two-person clinical care teams, one observer and one caregiver. (see CDC website: www.cdc.gov/vhf/ebola/hcp).

PREVENTION

A live-attenuated vaccine (Candid-I) for Argentine hemorrhagic fever (Junin virus) is highly efficacious. A form of inactivated mouse brain vaccine is reported to be effective in preventing Omsk hemorrhagic fever. Inactivated RVF vaccines are widely used to protect domestic animals and laboratory workers. HFRS inactivated vaccine is licensed in Korea, and killed and live-attenuated vaccines are widely used in China. A vaccinia-vector glycoprotein vaccine provides protection against Lassa fever in monkeys. A single dose of a recombinant vesicular stomatitis virus vaccine containing surface glycoproteins from Ebola and Marburg viruses is effective in preventing virus hemorrhagic fevers due to several strains of filovirus in a monkey model.

Prevention of **mosquito-borne** and **tick-borne infections** includes use of repellents, wearing of tight-fitting clothing that fully covers the extremities, and careful examination of the skin after exposure, with removal of any vectors found. Diseases transmitted from a rodent-infected environment can be prevented through methods of rodent control; elimination of refuse and breeding sites is particularly successful in urban and suburban areas.

Patients should be isolated until they are virus-free or for 3 wk after illness. Patient urine, sputum, blood, clothing, and bedding should be disinfected. Disposable syringes and needles should be used. Prompt and strict enforcement of barrier nursing may be lifesaving. The mortality rate among medical workers contracting these diseases is 50%. A few entirely asymptomatic Ebola infections result in strong antibody production.

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Chapter 272

Lymphocytic Choriomeningitis Virus

Daniel J. Bonthius

Lymphocytic choriomeningitis virus (LCMV) is a prevalent human pathogen and an important cause of meningitis in children and adults. Capable of crossing the placenta and infecting the fetus, LCMV is also an important cause of neurologic birth defects and encephalopathy in the newborn.

ETIOLOGY

LCMV is a member of the family Arenaviridae, which are enveloped, negative-sense single-stranded RNA viruses. The name of the arenaviruses is derived from *arenosus*, the Latin word for "sandy," because of the fine granularities observed within the virion on ultrathin electron microscopic sections.

EPIDEMIOLOGY

Like all arenaviruses, LCMV utilizes rodents as its reservoir. The common house mouse, *Mus musculus,* is both the natural host and primary reservoir for the virus, which is transferred vertically from 1 generation of mice to the next via intrauterine infection. Hamsters and guinea pigs are also potential reservoirs. Although heavily infected with LCMV, rodents that acquire the virus transplacentally often remain asymptomatic because congenital infection provides rodents with immunologic tolerance for the virus. Infected rodents shed the virus in large quantities in nasal secretions, urine, feces, saliva, and milk throughout their lives.

Humans typically acquire LCMV by contacting fomites contaminated with infectious virus or by inhaling aerosolized virus. Most human infections occur during the fall and early winter, when mice move into human habitations. Humans can also acquire the virus via organ transplantation. Congenital LCMV infection occurs when a woman acquires a primary LCMV infection during pregnancy. The virus passes through the placenta to the fetus during maternal viremia. The fetus may also acquire the virus during passage through the birth canal from exposure to infected vaginal secretions. Outside of organ transplantation and vertical transmission during pregnancy, there have been no cases of human-to-human transmission of LCMV.

LCMV is prevalent in the environment, has a great geographic range, and infects large numbers of humans. The virus is found throughout the world's temperate regions and probably occurs wherever the genus *Mus* has been introduced (which is every continent but

Antarctica). An epidemiologic study found that 9% of house mice are infected and that substantial clustering occurs, where the prevalence is higher. Serologic studies demonstrate that approximately 5% of adult humans possess antibodies to LCMV, indicating prior exposure and infection.

PATHOGENESIS

LCMV is not a cytolytic virus. Thus, unlike many other nervous system pathogens that directly damage the brain by killing host brain cells, LCMV pathogenesis involves other underlying mechanisms. Furthermore, the pathogenic mechanisms are different in postnatal (acquired) infection than in prenatal (congenital) infection. A critical difference in the pathogenesis of postnatal vs prenatal infection is that the virus infects brain parenchyma in the case of prenatal infection, but is restricted to the meninges and choroid plexus in postnatal cases.

In postnatal infections, LCMV replicates to high titers in the choroid plexus and meninges. Viral antigen within these tissues becomes the target of an acute mononuclear cell infiltration driven by $CD8^+$ T lymphocytes. The presence of lymphocytes in large numbers within the meninges and cerebrospinal fluid leads to the symptoms of meningitis that mark acquired LCMV infection. As the lymphocytes clear the virus from the meninges and cerebrospinal fluid, the density of lymphocytes declines, and the symptoms of meningitis resolve. Thus, symptoms of acquired (postnatal) LCMV infection are immune mediated and are a result of the presence of large numbers of lymphocytes.

Prenatal infection likewise inflames the tissues surrounding the brain parenchyma, and this inflammation leads to some of the signs of congenital LCMV. In particular, within the ventricular system, congenital LCMV infection often leads to ependymal inflammation, which may block the egress of cerebrospinal fluid (CSF) at the cerebral aqueduct and lead to hydrocephalus. However, unlike postnatal cases, prenatal infection with LCMV includes infection of the substance of the brain rather than just the meninges or ependyma. This infection of brain parenchyma leads to the substantial neuropathologic changes typically accompanying congenital LCMV infection. In particular, LCMV infects the mitotically active neuroblasts, located at periventricular sites. Through an unknown mechanism, presence of the virus kills these periventricular cells, leading to periventricular calcifications, a radiographic hallmark of this disorder. Within the fetal brain, LCMV infection of neurons and glial cells also disrupts neuronal migration, leading to abnormal gyral patterns, and interferes with neuronal mitosis, leading to microcephaly and cerebellar hypoplasia.

CLINICAL MANIFESTATIONS

The clinical manifestations of LCMV infection depend on whether the infection occurs prenatally or postnatally. Congenital infection with LCMV is unique, as it involves both the postnatal infection of a pregnant woman and the prenatal infection of a fetus.

Acquired (Postnatal) Lymphocytic Choriomeningitis Virus Infection

LCMV infection during postnatal life (during childhood or adulthood) typically consists of a brief febrile illness, from which the patient fully recovers. The illness classically consists of 2 clinical phases. In the 1st phase, the symptoms are those of a nonspecific viral syndrome and include fever, myalgia, malaise, nausea, anorexia, and vomiting. These symptoms usually resolve after several days but are followed by a 2nd phase, consisting of central nervous system disease. The symptoms of this 2nd phase are those of aseptic meningitis, including headache, fever, nuchal rigidity, photophobia, and vomiting. The entire course of the biphasic disease is typically 1-3 wk.

The clinical spectrum of LCMV infection is broad. One third of postnatal infections are asymptomatic. Other patients develop extraneural disease that extends beyond the usual symptoms and may include orchitis, pneumonitis, myocarditis, parotitis, dermatitis, alopecia, and pharyngitis. In others, the neurologic disease may be considerably more severe than usual and may include transverse myelitis, Guillain-Barré syndrome, hydrocephalus, and encephalitis. Recovery from acquired LCMV infection is usually complete, but fatalities occasionally occur.

LCMV infections acquired via solid organ transplantation always induce severe disease. Several weeks posttransplantation, recipients of infected organs develop fever, leukopenia, and lethargy. Following these nonspecific symptoms, the course of disease rapidly progresses to multiorgan system failure and shock. These cases are almost always fatal.

Congenital Lymphocytic Choriomeningitis Virus Infection

LCMV infection during pregnancy can kill the fetus and induce spontaneous abortion. Among surviving fetuses, the 2 clinical hallmarks of congenital LCMV infection are vision impairment and brain dysfunction.

The vision impairment in congenital LCMV infection is a result of chorioretinitis and the formation of chorioretinal scars. The scarring is usually bilateral and most commonly located in the periphery of the fundus, but involvement of the macula also occurs.

Although the retinal injuries from congenital LCMV infection are often severe, it is the *brain* effects that cause the greatest disability. Prenatal infection with LCMV commonly induces either macrocephaly or microcephaly. Macrocephaly following LCMV infection is almost invariably caused by noncommunicating hydrocephalus, stemming from inflammation within the ventricular system. Microcephaly is a result of virus-induced failure of brain growth. In addition to disturbances of head size, periventricular calcifications are also cardinal features of congenital LCMV infection.

Although hydrocephalus, microencephaly, and periventricular calcifications are by far the most commonly observed abnormalities of the brain in congenital LCMV, other forms of neuropathology, alone or in combination, can also occur. These include periventricular cysts, porencephalic cysts, encephalomalacia, intraparenchymal calcifications, cerebellar hypoplasia, and neuronal migration disturbances.

Infants with congenital LCMV infection typically present during the newborn period with evidence of brain dysfunction. The most common signs are lethargy, seizures, irritability, and jitteriness.

Within the fetus, LCMV has a specific tropism for the brain. Thus, unlike many other congenital infections, LCMV usually does not induce systemic manifestations. Birthweight is typically appropriate for gestational age. Skin rashes and thrombocytopenia, which are common in several other prominent congenital infections, are unusual in congenital LCMV infection. Hepatosplenomegaly is only rarely observed, and serum liver enzyme levels are usually normal. Auditory deficits are unusual.

LABORATORY FINDINGS

In acquired (postnatal) LCMV infection, the hallmark laboratory abnormality occurs during the 2nd (central nervous system) phase of the disease and is CSF pleocytosis. The CSF typically contains hundreds to thousands of white blood cells, almost all of which are lymphocytes. However, CSF eosinophilia may also occur. Mild elevations of CSF protein and hypoglycorrhachia are common.

In congenital LCMV infection, laboratory findings in the newborn depend on whether the infant is still infected or not. If the infant still harbors the infection, then examination of the CSF may reveal a lymphocytic pleocytosis. Unlike many other congenital infections, LCMV does not typically induce elevations in liver enzymes, thrombocytopenia, or anemia. In many cases, the most reliably abnormal test is the head CT scan, which typically reveals a combination of microencephaly, hydrocephalus, and periventricular calcifications (Fig. 272-1).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Acute LCMV infections can be diagnosed by isolating the virus from CSF. Polymerase chain reaction has also been used to detect LCMV RNA in patients with active infections. However, by the time of birth, a baby prenatally infected with LCMV may no longer harbor the virus. Thus, congenital LCMV infection is more commonly diagnosed by serologic testing. The immunofluorescent antibody test detects both immunoglobulin (Ig) M and IgG and has greater sensitivity than the more widely available complement fixation method. The immunofluorescent antibody test is commercially available, and its specificity and sensitivity make it an acceptable diagnostic tool. A more sensitive test for detecting congenital LCMV infection is the enzyme-linked

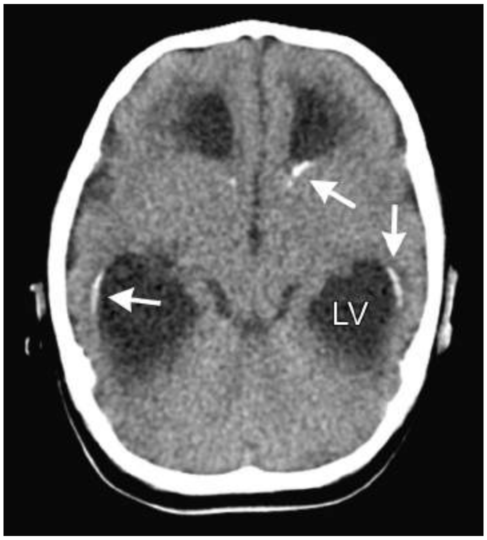

Figure 272-1 Head CT scan from a 2 mo old microcephalic baby with congenital lymphocytic choriomeningitis virus infection. The scan reveals enlargement of the lateral ventricles *(LV)* and periventricular calcifications *(arrows).*

immunosorbent assay, which measures titers of LCMV IgG and IgM and is performed at the Centers for Disease Control and Prevention.

For acquired (postnatal) LCMV infection, the principal items in the differential diagnosis are the other infectious agents that can induce meningitis. These include bacteria, fungi, viruses, and some other forms of pathogens. The most common viral causes of meningitis are the enteroviruses, including coxsackieviruses and echoviruses, and the arboviruses, including La Crosse encephalitis virus and equine encephalitis virus. Unlike LCMV, which is most common in winter, the enteroviruses and arboviruses are most commonly acquired in summer and early fall.

The principal items in the differential diagnosis of congenital LCMV infection are the other infectious pathogens that can cross the placenta and damage the developing fetus. These infectious agents are linked by the acronym "TORCHS" and include *Toxoplasma gondii*, rubella virus, cytomegalovirus, herpes simplex virus, and syphilis. Toxoplasmosis and cytomegalovirus infection are particularly difficult to differentiate from LCMV because all 3 of these infectious agents can produce microcephaly, intracerebral calcifications, and chorioretinitis. Although clinical clues may aid in distinguishing 1 congenital infection from another, definitive identification of the causative infectious agent usually requires laboratory data, including cultures and serologic studies.

COMPLICATIONS

Complications in children with congenital LCMV infection are nonspecific and include the medical problems that commonly arise in scenarios involving ventriculoperitoneal shunts, severe seizure disorders, and static encephalopathy. These complications include shunt failure or infection, aspiration pneumonia, injuries from falls, and joint contractures.

TREATMENT

There is no specific treatment for acquired or congenital LCMV infection. An effective antiviral therapy for LCMV infection has not yet been developed. Ribavirin is active against LCMV and other arenaviruses in vitro, but its utility in vivo is unproven. Immunosuppressive therapy, if present, should be reduced.

SUPPORTIVE CARE

Children with hydrocephalus from congenital LCMV infection often require placement of a ventriculoperitoneal shunt during infancy for treatment of hydrocephalus. Seizures often begin during early postnatal life, are often difficult to control, and require administration of multiple antiepileptic medications. The mental retardation induced by congenital LCMV infection is often profound. In most cases, affected children should be referred for educational intervention during early life. The spasticity accompanying congenital LCMV infection is often severe. Although physical therapy can help to maintain range of motion and minimize painful spasms and contractures, implantation of a baclofen pump is often helpful.

PROGNOSIS

The great majority of patients with postnatally acquired LCMV infection have a full recovery with no permanent sequelae. Rarely, postnatal infections induce hydrocephalus and require shunting. Rarer yet, postnatal LCMV infection is fatal.

In contrast to the usual benign outcome of postnatal infections, prenatal infections typically lead to severe and permanent disability. In children with congenital LCMV infection, brain function is nearly always impaired and chorioretinitis is invariably present. Mental retardation, cerebral palsy, ataxia, epilepsy, and blindness are common neurologic sequelae. However, children with congenital LCMV infection have diverse outcomes. All children with the combination of microencephaly and periventricular calcifications are profoundly neurologically impaired. Blindness, medically refractory epilepsy, spastic quadriparesis, and mental retardation are typical of this group. However, other children with congenital LCMV infection who do not have the combination of microencephaly and periventricular calcifications often have a more favorable outcome, with less severe motor, mental, and vision impairments. Children with isolated cerebellar hypoplasia may be ataxic but have only mild or moderate mental retardation and vision loss.

PREVENTION

No vaccine exists to prevent LCMV infection. However, measures can be taken to reduce the risk of infection. Because rodents, especially house mice, are the principal reservoir of LCMV, people can reduce their risk of contracting LCMV by minimizing their exposure to the secretions and excretions of mice. This can be accomplished most effectively by eliminating cohabitation with mice. Congenital LCMV infection will not occur unless a woman contracts a primary infection with LCMV during pregnancy. Thus, women should be especially careful to avoid contact or cohabitation with mice during pregnancy. Pregnant women should also avoid contact with pet rodents, especially mice and hamsters. These facts should be stressed during prenatal visits.

Acquisition of LCMV from solid organ transplantation represents a substantial risk to organ recipients. Prospective donors with LCMV meningitis or encephalitis pose a clear risk for transmitting a fatal infection to recipients. Healthcare providers, transplantation centers, and organ procurement organizations should be aware of the risks posed by LCMV and should consider LCMV in any potential donor with signs of aseptic meningitis but no identified infectious agent. The risks and benefits of offering and receiving organs from donors with possible LCMV infection should be carefully considered.

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Chapter 273

Hantavirus Pulmonary Syndrome

Scott B. Halstead

The hantavirus pulmonary syndrome (HPS) is caused by multiple closely related hantaviruses that have been identified from the western United States, with sporadic cases reported from the eastern United States (Fig. 273-1) and Canada and important foci of disease in several countries in South America. HPS is characterized by a febrile

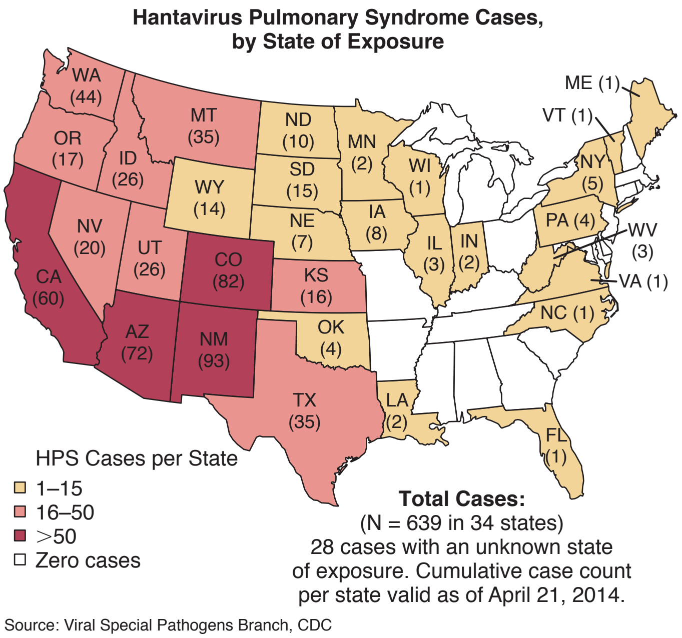

Figure 273-1 Total number of confirmed cases of Hantavirus pulmonary syndrome, by state of exposure—United States, 1993-2014. N = 639 as of April 21, 2014. *(From Viral Special Pathogens Branch, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/hantavirus/surveillance/reporting-state.html).*

prodrome followed by the rapid onset of noncardiogenic pulmonary edema and hypotension or shock. Sporadic cases in the United States caused by related viruses may manifest with renal involvement. Cases in Argentina and Chile sometimes include severe gastrointestinal hemorrhaging; nosocomial transmission has been documented in this geographic region only.

ETIOLOGY

Hantaviruses are a genus in the family Bunyaviridae, which are lipid-enveloped viruses with a negative-sense RNA genome composed of 3 unique segments. Several pathogenic viruses that have been recognized within the genus include Hantaan virus, which causes the most severe form of hemorrhagic fever with renal syndrome (HFRS) seen primarily in mainland Asia (see Chapter 271); Dobrava virus, which causes the most severe form of HFRS seen primarily in the Balkans; Puumala virus, which causes a milder form of HFRS with a high proportion of subclinical infections and is prevalent in northern Europe; and Seoul virus, which results in moderate HFRS and is transmitted predominantly in Asia by urban rats or worldwide by laboratory rats. Prospect Hill virus, a hantavirus that is widely disseminated in meadow voles in the United States, is not known to cause human disease. There are an increasing number of case reports of European hantaviruses causing HPS.

HPS is associated with *sin nombre* virus, isolated from deer mice, *Peromyscus maniculatus,* in New Mexico. Multiple HPS-like agents in the American hemisphere isolated to date belong to a single genetic group of hantaviruses and are associated with rodents of the family Muridae, subfamily Sigmodontinae. These rodent species are restricted to the Americas, suggesting that HPS may be a Western hemisphere disease.

EPIDEMIOLOGY

Persons acquiring HPS generally have a history of recent outdoor exposure or live in an area with large populations of deer mice. Clusters of cases have occurred among individuals who have cleaned houses that were rodent infested. *P. maniculatus* is one of the most common North American mammals and, where found, is frequently the dominant member of the rodent community. About half of the average of 30+ cases seen annually occurs between the months of May and July. Patients are almost exclusively 12-70 yr of age; 60% of patients are 20-39 yr of age. Rare cases are reported in children younger than 12 yr of age. Two thirds of patients are male, probably reflecting their greater outdoor activities. It is not known whether almost complete absence of disease in young children is a reflection of innate resistance or simply lack of exposure. Evidence of human-to-human transmission has been reported in Argentine outbreaks.

Hantaviruses do not cause apparent illness in their reservoir hosts, which remain asymptomatically infected for life. Infected rodents shed virus in saliva, urine, and feces for many weeks, but the duration of shedding and the period of maximum infectivity are unknown. The presence of infectious virus in saliva, the sensitivity of these animals to parenteral inoculation with hantaviruses, and field observations of infected rodents indicate that biting is important for rodent-to-rodent transmission. Aerosols from infective saliva or excreta of rodents are implicated in the transmission of hantaviruses to humans. Persons visiting animal care areas housing infected rodents have been infected after exposure for as little as 5 min. It is possible that hantaviruses are spread through contaminated food and breaks in skin or mucous membranes; transmission to humans has occurred by rodent bites. Person-to-person transmission is distinctly uncommon but has been documented in Argentina.

PATHOGENESIS

HPS is characterized by sudden and catastrophic pulmonary edema, resulting in anoxia and acute heart failure. The virus is detected in pulmonary capillaries, suggesting that pulmonary edema is the consequence of T-cell attack on virus-infected capillaries. Disease severity is predicted by the level of acute-phase viremia titer. A useful hamster model of HPS is available.

CLINICAL MANIFESTATIONS

HPS is characterized by a prodrome and a cardiopulmonary phase. The mean duration after the onset of prodromal symptoms to hospitalization is 5.4 days. The mean duration of symptoms to death is 8 days (median: 7 days; range: 2-16 days). The most common **prodromal symptoms** are fever and myalgia (100%); cough or dyspnea (76%); gastrointestinal symptoms, including vomiting, diarrhea, and midabdominal pain (76%); and headache (71%). The **cardiopulmonary phase** is heralded by progressive cough and shortness of breath. The most common initial physical findings are tachypnea (100%), tachycardia (94%), and hypotension (50%). Rapidly progressive acute pulmonary edema, hypoxia, and shock develop in most severely ill patients. Pulmonary vascular permeability is complicated by cardiogenic shock associated with increased vascular resistance. The clinical course of the illness in patients who die is characterized by pulmonary edema accompanied by severe hypotension, frequently terminating in sinus bradycardia, electromechanical dissociation, ventricular tachycardia, or fibrillation. Hypotension may be progressive even with adequate oxygenation. HPS virus is excreted in the urine during the acute illness phase, and survivors may demonstrate evidence of chronic renal damage.

DIAGNOSIS

The diagnosis of HPS should be considered in a previously healthy patient presenting with a febrile prodrome and acute respiratory distress. Occurrence of thrombocytopenia with the febrile prodrome and outdoor exposure in the spring and summer months are strongly suggestive of HPS. Specific diagnosis of HPS is made by serologic tests that detect hantavirus immunoglobulin M antibodies. Early appearance of immunoglobulin G antibodies signals probable recovery. Hantavirus antigen can be detected in tissue by immunohistochemistry and amplification of hantavirus nucleotide sequences detected by reverse transcriptase polymerase chain reaction. The state health department or the Centers for Disease Control and Prevention should be consulted to assist in diagnosis, epidemiologic investigations, and outbreak control.

Laboratory Findings

Laboratory findings include leukocytosis (median: 26,000 cells/µL), elevated hematocrit resulting from hemoconcentration, thrombocytopenia (median: 64,000 cells/µL), prolonged prothrombin and partial

thromboplastin times, elevated serum lactate dehydrogenase concentration, decreased serum protein concentrations, proteinuria, and microscopic hematuria. Patients who die often experience disseminated intravascular coagulopathy including frank hemorrhage and exceptionally high leukocyte counts.

Differential Diagnosis

The differential diagnosis includes adult respiratory distress syndrome, pneumonic plague, psittacosis, severe mycoplasmal pneumonia, influenza, leptospirosis, inhalation anthrax, rickettsial infections, pulmonary tularemia, atypical bacterial and viral pneumonial diseases, legionellosis, meningococcemia, and other sepsis syndromes. The key determinant in the diagnosis of HPS is thrombocytopenia.

TREATMENT

Management of patients with hantavirus infection requires maintenance of adequate oxygenation and careful monitoring and support of cardiovascular function. The pathophysiology of HPS somewhat resembles that of dengue shock syndrome (see Chapter 269). Pressor or inotropic agents, such as dobutamine, should be administered in combination with judicious volume replacement to treat symptomatic hypotension or shock while avoiding exacerbation of the pulmonary edema. Intravenous ribavirin, which is lifesaving if given early in the course of HFRS and is effective in preventing death in the hamster model, has not yet been demonstrated to be of value in HPS.

Further information and advice about management, control measures, diagnosis, and collection of biohazardous specimens can be obtained from the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Special Pathogens Branch, Atlanta, Georgia 30333 (404-639-1115).

PROGNOSIS

In some geographic areas fatality rates for HPS have been 50%. Severe abnormalities in hematocrit, white blood cell count, lactate dehydrogenase value, and partial thromboplastin time, and a high viral load predict death with high specificity and sensitivity. Early appearance of immunoglobulin G antibodies may signal a hopeful prognosis.

PREVENTION

Avoiding contact with rodents is the only preventive strategy against HPS. Rodent control in and around the home is important. Barrier nursing is advised, and biosafety level 3 facilities and practices are recommended for laboratory handling of blood, body fluids, and tissues from suspect patients or rodents, because the virus may be aerosolized.

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Chapter 274

Rabies

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Rabies virus is a bullet-shaped, negative-sense, single-stranded, enveloped RNA virus from the family Rhabdoviridae, genus *Lyssavirus*. There currently are 12 known genotypes of *Lyssavirus*, and more are under taxonomic consideration. The classic rabies virus (genotype 1) is distributed worldwide and naturally infects a large variety of animals. The other 6 genotypes are more geographically confined, with none found in the Americas. Seven *Lyssavirus* genotypes are associated with rabies in humans, although genotype 1 accounts for the great majority of cases. Within genotype 1, a number of genetic variants have been defined. Each variant is specific to a particular animal reservoir, although cross-species transmission can occur.

EPIDEMIOLOGY

Rabies is present on all continents except Antarctica. Rabies predominantly afflicts underaged, poor, and geographically isolated populations. Approximately 50,000 cases of human rabies occur in Africa and Asia annually. Theoretically, rabies virus can infect any mammal (which then can transmit disease to humans), but true animal reservoirs that maintain the presence of rabies virus in the population are limited to terrestrial carnivores and bats. Worldwide, transmission from dogs accounts for >90% of human cases. In Africa and Asia, other animals serve as prominent reservoirs, such as jackals, mongooses, and raccoon dogs. In industrialized nations, canine rabies has been largely controlled through the routine immunization of pets. In the United States, raccoons are the most commonly infected wild animal along the eastern seaboard. Three phylogenies of skunk rabies are endemic in the Midwest (north and south) and California, and gray foxes harbor rabies in Arizona and Texas and mongooses in Puerto Rico. Rabies occurs infrequently in livestock. Among American domestic pets, infected cats outnumber infected dogs, probably because cats frequently prowl unsupervised and are not uniformly subject to vaccine laws. Rabies is rare in small mammals, including mice, squirrels, and rabbits; to date, no animal-to-human transmission from these animals has been documented.

The epidemiology of human rabies in the United States is dominated by cryptogenic bat rabies. Bats are migratory in the spring and fall; rabid bats are identified in every state of the union except Hawaii. In 1 study, the largest proportion of cases of human rabies were infected with a bat variant, and in almost all cases of bat-associated human rabies there was no history of a bat bite. Among inhabitants of the Peruvian Amazon region who have exposure to rabies infected vampire bats, there are some who have rabies virus neutralizing antibodies and have survived. Antibody-positive patients remember bat bites but do not recall symptoms of rabies.

In the United States, 30,000 episodes of rabies postexposure prophylaxis (PEP) occur annually. Between 1 and 3 endemic human cases are diagnosed annually, half postmortem. There have been 3 outbreaks of rabies associated with solid-organ and corneal transplantations.

TRANSMISSION

Rabies virus is found in large quantities in the saliva of infected animals, and transmission occurs almost exclusively through inoculation of the infected saliva through a bite or scratch from a rabid mammal. Approximately 35-50% of people bitten by a known rabies-infected animal and receiving no PEP contract rabies. The transmission rate is increased if the victim has suffered multiple bites and if the inoculation occurs in highly innervated parts of the body such as the face and the hands. Infection does not occur after exposure of intact skin to infected secretions, but virus may enter the body through intact mucous membranes. Claims that spelunkers may experience rabies after inhaling bat excreta have come under doubt, although inhalational exposure can occur during laboratory accidents.

No case of nosocomial transmission to a healthcare worker has been documented to date, but caregivers of a patient with rabies are advised to use full barrier precautions. The virus is rapidly inactivated in the environment, and contamination of fomites is not a mechanism of spread.

PATHOGENESIS

After inoculation, rabies virus replicates slowly and at low levels in muscle or skin. This slow initial step likely accounts for the disease's long incubation period. Virus then enters the peripheral motor nerve, utilizing the nicotinic acetylcholine receptor and possibly several other receptors for entry. Once in the nerve, the virus travels by fast axonal transport, crossing synapses roughly every 12 hr. Rapid dissemination occurs throughout the brain and spinal cord before symptoms appear. Infection of the dorsal root ganglia is apparently futile but causes characteristic radiculitis. Infection concentrates in the brainstem, accounting for autonomic dysfunction and relative sparing of cognition. Despite severe neurologic dysfunction with rabies, histopathology reveals limited damage, inflammation, or apoptosis. The pathologic

hallmark of rabies, the Negri body, is composed of clumped viral nucleocapsids that create cytoplasmic inclusions on routine histology. Negri bodies can be absent in documented rabies virus infection. Rabies may be a metabolic disorder of neurotransmission; tetrahydrobiopterin deficiency in human rabies causes severe deficiencies in dopamine, norepinephrine, and serotonin metabolism.

After infection of the central nervous system, the virus travels anterograde through the peripheral nervous system to virtually all innervated organs. It is through this route that the virus infects the salivary glands. Many victims of rabies die from uncontrolled cardiac dysrhythmia.

Deficiency of tetrahydrobiopterin, an essential cofactor for neuronal nitric oxide synthase, is predicted to lead to spasm of the basilar arteries. Onset of vasospasm has been confirmed in a few patients within 5-8 days of first hospitalization, at about the time coma supervenes in the natural history. Increased intracranial pressure is regularly measured early in rabies in association with elevated *N*-acetylaspartate in cerebrospinal fluid (CSF), but is rarely radiologically apparent. Metabolites in CSF consistent with ketogenesis are associated with demise.

CLINICAL MANIFESTATIONS

The incubation period for rabies is 1-3 mo, but is variable. In severe wounds to the head, symptoms may occur within 5 days after exposure, and occasionally the incubation period can extend to longer than 6 mo. Rabies has 2 principal clinical forms. **Encephalitic** or **"furious" rabies** begins with nonspecific symptoms, including fever, sore throat, malaise, headache, nausea and vomiting, and weakness. These symptoms are often accompanied by paresthesia and pruritus at or near the site of the bite that then extend along the affected limb. Soon thereafter the patient begins to demonstrate symptoms of encephalitis, with agitation, depressed mentation, and, occasionally, seizures. Characteristically, patients with rabies encephalitis initially have periods of lucidity alternating with periods of profound encephalopathy. Hydrophobia and aerophobia are the cardinal signs of rabies; they are unique to humans and are not universal or specific. Phobic spasms are manifested by agitation and fear created by being offered a drink or fanning of air in the face, which in turn produce choking and aspiration through spasms of the pharynx, neck, and diaphragm. The illness is relentlessly progressive. There is a dissociation of electrophysiologic or encephalographic activity with findings of brainstem coma caused by anterograde denervation. Death almost always occurs within 1-2 days of hospitalization in developing countries and by 18 days of hospitalization with intensive care.

A second form of rabies known as **paralytic** or **"dumb" rabies** is seen much less frequently and is characterized principally by fevers and ascending motor weakness affecting both the limbs and the cranial nerves. Most patients with paralytic rabies also have some element of encephalopathy as the disease progresses subacutely.

Case reports suggest that milder forms of rabies encephalitis may exist, and 16 rabies survivors are known. Rabies should be considered earlier and more frequently in the diagnosis than current practice.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of rabies encephalitis includes all forms of severe cerebral infections, tetanus, and some intoxications and envenomations. Rabies can be confused with autoimmune (anti–*N*-methyl-D-aspartate receptor) encephalitis, other infectious encephalitis, psychiatric illness, drug abuse, and conversion disorders. Paralytic rabies is most frequently confused with Guillain-Barré syndrome. The diagnosis of rabies is frequently delayed in Western countries because of its rarity and the unfamiliarity of the medical staff with the infection. These considerations highlight the need to pursue a history of contact with an animal belonging to 1 of the known reservoirs for rabies or to establish a travel history to a rabies-endemic region.

DIAGNOSIS

The Centers for Disease Control and Prevention (CDC) require a number of tests to confirm a clinically suspected case of rabies. Reverse transcription polymerase chain reaction is the most sensitive available assay for the diagnosis of rabies when done iteratively. Rabies virus RNA has been detected in saliva, skin, and brain by the reverse transcription polymerase chain reaction. The virus can be grown both in cell culture and after animal injection, but identification of rabies by these methods is slow. Rabies antigen is detected through immunofluorescence of saliva or biopsies of hairy skin or brain. Corneal impressions are not recommended. Rabies-specific antibody can be detected in serum or CSF samples, but most patients die while seronegative. Antirabies antibodies are present in the sera of patients who have received an incomplete course of the rabies vaccine, precluding a meaningful interpretation in this setting. Antibody in CSF is rarely detected after vaccination and is considered diagnostic of rabies regardless of immunization status. CSF abnormalities in cell count, glucose, and protein content are minimal and are not diagnostic. MRI findings in the brain are late.

TREATMENT AND PROGNOSIS

Rabies is generally fatal. Conventional critical care yielded 1 survivor from 74 attempts since 1990. Five of 16 patients survived without use of critical care (including 3 milder cases) and 7 with use of the Milwaukee Protocol (http://www.mcw.edu/rabies). Survival using the Milwaukee Protocol is estimated at 20%; neurologic outcomes are poor in one third of patients. Neither rabies immunoglobulin (RIG) nor rabies vaccine provides benefit once symptoms have appeared. Among 11 survivors of rabies after use of biologics, 6 had poor neurologic outcomes. Among 5 vaccine-naïve survivors, 1 had a poor outcome. Antiviral treatments have not been effective. Ribavirin delays the immune response and should be avoided during early management. In contrast, appearance of the normal antibody response by 7 days is associated with clearance of salivary viral load and survival.

PREVENTION

Primary prevention of rabies infection includes vaccination of domestic animals and education to avoid wild animals, stray animals, and animals with unusual behavior.

Immunization and Fertility Control of Animal Reservoirs

The introduction of routine rabies immunization for domestic pets in the United States and Europe during the middle of the 20th century virtually eliminated infection in dogs, which prior to that time had been the principal transmitter of rabies to humans in developed, as well as nonindustrialized, countries. In the 1990s, control efforts in Europe and North America shifted to immunization of wildlife reservoirs of rabies, where rabies was newly emerging. These programs employed bait laced with either an attenuated rabies vaccine or a recombinant rabies surface glycoprotein inserted into vaccinia, distributed by air or hand into areas inhabited by rabid animals. Human contact with vaccine-laden bait has been infrequent. Adverse events after such contact have been rare, but the vaccinia vector poses a threat to the same population at risk for vaccinia itself, namely, pregnant women, immunocompromised patients, and people with atopic dermatitis. Mass culling of endemic reservoirs has never worked; vaccination and fertility control stop outbreaks. Bats are ubiquitous and very important for insect control. Less than 1% of free-flying bats but >8% of downed bats and bats found in dwellings are rabid.

Postexposure Prophylaxis

The relevance of rabies for most pediatricians centers on evaluating whether an animal exposure warrants PEP (Table 274-1). No case of rabies has been documented in a person receiving the recommended schedule of PEP since introduction of modern cellular vaccines in the 1970s.

Given the incubation period for rabies, PEP is a medical urgency, not emergency. Algorithms have been devised to aid practitioners in deciding when to initiate rabies PEP (Fig. 274-1). The decision to proceed ultimately depends on the local epidemiology of animal rabies

as determined by active surveillance programs, information that can be obtained from local and state health departments. In general, bats, raccoons, skunks, coyotes, and foxes should be considered rabid unless proven otherwise through euthanasia and testing of brain tissue, whereas bites from small herbivorous animals (squirrels, hamsters, gerbils, chipmunks, rats, mice, and rabbits) can be discounted. The response to bites from a pet, particularly a dog, cat, or ferret, depends on local surveillance statistics and on whether the animal is available for observation.

The approach to nonbite bat exposures is controversial. In response to the observation that most cases of rabies in the United States have been caused by bat variants and that the majority of affected patients had no recollection of a bat bite, the CDC has recommended that rabies PEP be considered after any physical contact with bats and when a bat is found in the same room as persons who may not be able to accurately report a bite, assuming that the animal is unavailable for testing. Such people include young children, the mentally disabled, and intoxicated individuals. Other nonbite contacts (e.g., handling a carcass, exposure to an animal playing with a carcass, or coming into contact with blood or excreta from a potentially rabid animal) usually do not require PEP.

In all instances of a legitimate exposure, effort should be made to recover the animal for quarantine and observation or brain examination after euthanasia. Testing obviates the need for PEP more than half the time. In most instances, PEP can be deferred until the results of observation or brain histology are known. In dogs, cats, and ferrets, symptoms of rabies always occur within several days of viral shedding; therefore, in these animals a 10-day observation period is sufficient to eliminate the possibility of rabies.

No duration of time between exposure and onset of symptoms should preclude rabies prophylaxis. Rabies PEP is most effective when applied expeditiously. Nevertheless, the series should be initiated in the asymptomatic person as soon as possible, regardless of the length of time since the bite. *The vaccine and RIG are contraindicated once symptoms develop.*

The first step in rabies PEP is to cleanse the wound thoroughly. Soapy water is sufficient to inactivate an enveloped virus, and its effectiveness is supported by broad experience. Other commonly used

Table 274-1 Rabies Postexposure Prophylaxis Guide

ANIMAL TYPE	EVALUATION AND DISPOSITION OF ANIMAL	POSTEXPOSURE PROPHYLAXIS RECOMMENDATIONS
Dogs, cats, and ferrets	Healthy and available for 10 days of observation Rabid or suspected of being rabid[†] Unknown (escaped)	Prophylaxis only if animal shows signs of rabies* Immediate immunization and RIG Consult public health officials for advice
Bats, skunks, raccoons, foxes, and most other carnivores; woodchucks	Regarded as rabid unless geographic area is known to be free of rabies or until animal proven negative by laboratory tests[†]	Immediate immunization and RIG
Livestock, rodents, and lagomorphs (rabbits, hares, and pikas)	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice and other rodents, rabbits, hares, and pikas almost never require antirabies treatment

*During the 10-day observation period, at the first sign of rabies in the biting dog, cat, or ferret, treatment of the exposed person with RIG (human) and vaccine should be initiated. The animal should be euthanized immediately and tested.

[†]The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended. Immunization is discontinued if immunofluorescent test result for the animal is negative.

RIG, rabies immunoglobulin.

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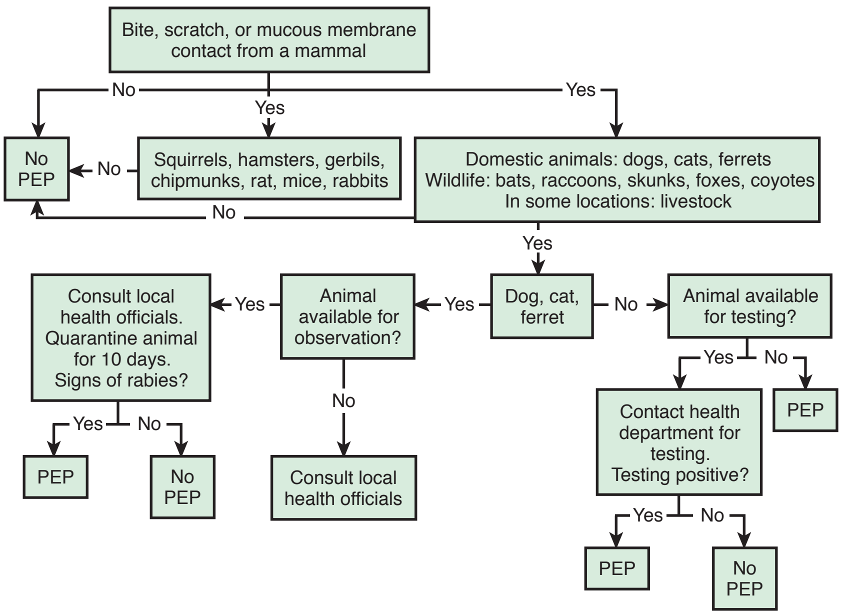

Figure 274-1 Algorithm for evaluating a child for rabies postexposure prophylaxis. This and any other algorithm should be used in concert with local epidemiologic information regarding the incidence of animal rabies in any given location.

disinfectants, such as iodine-containing preparations, are virucidal and should be used in addition to soap when available. Probably the most important aspect of this component is that the wound is cleansed with copious volumes of disinfectant. Primary closure is avoided; wounds may be bacterially infected as well, so cosmetic repair should follow. Antibiotics and tetanus prophylaxis (see Chapter 211) should be applied with the use of usual wound care criteria.

The second component of rabies PEP consists of passive immunization with RIG. Most failures of PEP are attributed to not using RIG. Human RIG, the formulation used in industrialized countries, is administered at a dose of 20 IU/kg. As much of the dose is infused around the wound as possible, and the remainder is injected intramuscularly in a limb distant from the 1 injected with the killed vaccine. Like other immunoglobulin preparations, RIG interferes with the take of live viral vaccines for at least 4 mo after administration of the RIG dose. Human RIG is not available in many parts of the developing world. Equine RIG serves as a substitute for the human immunoglobulin preparation in some areas. Modern preparations of equine RIG are associated with fewer side effects than prior products composed of crude horse serum. Regrettably, for a large segment of the world's population, no passive immunization product is available at all. Monoclonal antibody products are in clinical trials and may alleviate this deficiency.

The third component of rabies PEP is immunization with inactivated vaccine. In most of the world, cell-based vaccines have replaced previous preparations. Two formulations currently are available in the United States, namely, RabAvert (Chiron Behring Vaccines, Maharashtra, India), a purified chick-embryo cell cultivated vaccine, and Imovax Rabies (Aventis Pasteur, Bridgewater, NJ), cultivated in human diploid cell cultures. In both children and adults, both vaccines are administered intramuscularly in a 1 mL volume in the deltoid or anterolateral thigh on days 0, 3, 7, and 14 after presentation. Injection into the gluteal area is associated with a blunted antibody response, so this area should not be used. The rabies vaccines can be safely administered during pregnancy. In most persons the vaccine is well tolerated; most adverse effects are related to booster doses. Pain and erythema at the injection site occur commonly, and local adenopathy, headache, and myalgias occur in 10-20% of patients. Approximately 5% of patients who receive the human diploid cell vaccine experience an immune complex–mediated allergic reaction, including rash, edema, and arthralgias, several days after a booster dose. The World Health Organization has approved schedules using smaller amounts of vaccine, administered intradermally, that are immunogenic and protective (http://www.who.int/rabies/human/postexp/en/), but none is approved for use in the United States. Other cell culture–derived rabies virus vaccines are available in the developing world. A few countries still produce nerve tissue–derived vaccines; these preparations are poorly immunogenic, and cross reactivity with human nervous tissue may occur with their use, producing severe neurologic symptoms even in the absence of rabies infection.

Preexposure Prophylaxis

The killed rabies vaccine can be given to prevent rabies in persons at high risk for exposure to wild-type virus, including laboratory personnel working with rabies virus, veterinarians, and others likely to be exposed to rabid animals as part of their occupation. Preexposure prophylaxis should be considered for persons traveling to a rabies-endemic region where there is a credible risk for a bite or scratch from a rabies-infected animal, particularly if there is likely to be a shortage of RIG or cell culture–based vaccine (see Chapter 175). Rabies vaccine as part of the routine vaccine series is under investigation in some countries. The schedule for preexposure prophylaxis consists of 3 intramuscular injections on days 0, 7, and 21 or 28. PEP in the patient who has received preexposure prophylaxis or a prior full schedule of PEP consists of 2 doses of vaccine (1 each on days 0 and 3) and does not require RIG. Immunity from preexposure prophylaxis wanes after several years and requires boosting if the potential for exposure to rabid animals recurs.

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Chapter 275

Polyomaviruses

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The polyomaviruses are small (45 nm), nonenveloped, circular, double-stranded DNA viruses with genomes of approximately 5,000 bp. Because of the association of animal polyomaviruses with tumors in the animals they infect, there has also been concern for a relationship to neoplasia in humans; however, the only virus for which there is strong evidence for an etiologic role in neoplasia is Merkel cell polyomavirus (see below). Among the polyomaviruses, the traditional human pathogens are JC virus and BK viruses. In recent years the number of human polyomaviruses has expanded dramatically, with discovery in humans of 10 additional viruses. Two of the newer polyomaviruses, designated KI virus and WU virus, can be detected in respiratory samples from children; however, a pathogenic role for these viruses has not been proven to date. Merkel cell polyomavirus is associated with Merkel cell carcinoma, an unusual neuroectodermal tumor of the skin that occurs primarily in elderly and immunocompromised individuals. Clonal integration of Merkel cell polyomavirus DNA is present in Merkel cell carcinoma cells, supporting an etiologic role for the virus in the development of the tumor. Another human polyomavirus has been isolated from patients with the dermatologic condition trichodysplasia spinulosa and has been named trichodysplasia spinulosa–associated polyomavirus. Trichodysplasia spinulosa is a condition of the skin that occurs in immunocompromised individuals and involves the development of follicular papules and keratin spines, usually involving the face. Two other viruses, designated human polyomaviruses 6 and 7, have also been found in human skin samples, but are not presently known to cause disease. Human polyomavirus 9 was detected in serum from a renal transplant recipient. The most recently discovered viruses, named Malawi virus and St. Louis virus, were first detected in stool samples, but a role in gastrointestinal or other disease has not been established at this time.

JC and BK viruses are tropic for renal epithelium; JC virus also infects brain oligodendrocytes and is the etiologic agent of **progressive multifocal leukoencephalopathy,** a rare and fatal demyelinating disease of immunocompromised persons, especially those with AIDS. Progressive multifocal leukoencephalopathy is now known to occur in individuals receiving the immunomodulatory agents natalizumab (Tysabri), used to treat multiple sclerosis and Crohn disease, and efalizumab (Raptiva), used to treat psoriasis. It has also been reported in individuals receiving the anti-CD20 monoclonal antibody rituximab (Rituxan) and the anti-CD52 monoclonal antibody alemtuzumab (Campath). BK virus is the cause of transplant nephropathy in renal transplant recipients and of hemorrhagic cystitis in hematopoietic stem cell and bone marrow transplant recipients. Several million persons in the United States were exposed to simian virus 40 (SV40), an oncogenic polyomavirus of Asian macaques, from contaminated poliovirus vaccines administered during 1955-1963. There were no recognized sequelae and no demonstrable increased risk for cancer.

Seroepidemiologic studies have shown that infection with all of the human polyomaviruses appears to be widespread, often occurring during childhood. Primary infection with these viruses is not recognized clinically. Approximately half of children in the United States are infected with BK virus by 3-4 yr of age and with JC virus by 10-14 yr of age, and approximately 60-80% of adults are seropositive for 1 or both viruses. Infection with polyomaviruses is thought to persist throughout life, with JC and BK viruses remaining latent in renal epithelium, oligodendrocytes, and peripheral blood mononuclear cells. The site of latency of the other human polyomaviruses is not currently known. Approximately 30-50% of healthy persons have detectable BK or JC virus in renal tissue at autopsy. Reactivation and viruria occur

with increased frequency with advancing age and are more common in immunocompromised persons. On the basis of polymerase chain reaction results, BK and JC viruria occur in 2.6% and 13.2%, respectively, of persons younger than 30 yr of age and in approximately 9% and 50%, respectively, of persons older than 60 yr of age.

Reactivation of BK and JC viruses with asymptomatic viruria occurs in 10-50% of hematopoietic stem cell and bone marrow transplant recipients and in 30% of renal transplant recipients. Of those renal transplant recipients who demonstrate BK viruria, approximately one third also have plasma viremia. Recipients with plasma viremia are at risk for development of nephropathy, which can clinically mimic allograft rejection and can result in failure of the allograft. Reduction of immunosuppression has been effective in preventing progression from viremia to nephropathy, and thus posttransplantation monitoring of either urine or plasma by polymerase chain reaction is important. It is particularly important to distinguish BK nephropathy from rejection because the treatments are different—increase in immunosuppression for rejection but decrease in immunosuppression for BK nephropathy.

Polymerase chain reaction is the preferred means to detect the BK and JC viruses. The high seroprevalence in the general population and lack of clear relationship to clinical illness limit the usefulness of serologic testing. There are no proven antiviral treatments for BK or JC virus infection, although cidofovir may be effective in some cases of BK-related transplant nephropathy. Effective treatment of AIDS with antiretroviral therapy can prevent the progression of progressive multifocal leukoencephalopathy.

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Chapter 276

Acquired Immunodeficiency Syndrome (Human Immunodeficiency Virus)

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Advances in research and major improvements in the treatment and management of HIV infection have brought about a substantial decrease in the incidence of new HIV infections and AIDS in children. Globally, there has been an estimated 58% decline in newly infected children since 2001, largely the result of antiretroviral treatment of HIV-infected pregnant women for the prevention of mother-to-child transmission. More than 90% of adults and children with HIV infection live in sub-Saharan Africa, where the disease continues to have a devastating impact (Fig. 276-1). Children experience more rapid disease progression than adults, with up to half of untreated children dying within the 1st 2 yr of life. This rapid progression is correlated with a higher viral burden and faster depletion of infected CD4 lymphocytes in infants and children than in adults. Accurate diagnostic tests and the early initiation of potent drugs to inhibit HIV replication have dramatically increased the ability to prevent and control this disease.

ETIOLOGY

HIV-1 and HIV-2 are members of the Retroviridae family and belong to the *Lentivirus* genus, which includes cytopathic viruses causing diverse diseases in several animal species. The HIV-1 genome contains 2 copies of single-stranded RNA that is 9.2 kb in size. At both ends of the genome there are identical regions, called **long terminal repeats,** which contain the regulation and expression genes of HIV. The remainder of the genome includes 3 major sections: the **GAG** region, which encodes the viral core proteins (p24 [capsid protein: CA], p17 [matrix protein: MA], p9, and p6, which are derived from the precursor p55); the **POL** region, which encodes the viral enzymes (i.e., reverse transcriptase [p51], protease [p10], and integrase [p32]); and the **ENV** region, which encodes the viral envelope proteins (gp120 and gp41, which are derived from the precursor gp160). Other regulatory proteins, such as transactivator of transcription (tat: p14), regulator of virion (rev: p19), negative regulatory factor (nef: p27), viral protein r (vpr: p15), viral infectivity factor (vif: p23), viral protein u (vpu in HIV-1: P16), and viral protein x (vpx in HIV-2: P15) are involved in transactivation, viral messenger RNA expression, viral replication, induction of cell cycle arrest, promotion of nuclear import of viral reverse transcription complexes, downregulation of CD4 receptors and class I major histocompatibility complex, proviral DNA synthesis, and virus release and infectivity (Fig. 276-2).

The HIV tropism to the target cell is determined by its envelope glycoprotein (Env). Env consists of 2 components, namely the surface heavily glycosylated subunit gp120 protein and the associated transmembrane subunit glycoprotein gp41. Both gp120 and gp41 are produced from the precursor protein gp160. The glycoprotein gp41 is very immunogenic and is used to detect HIV-1 antibodies in diagnostic assays; gp120 is a complex molecule that includes the highly variable **V3 loop.** This region is immunodominant for neutralizing antibodies. The heterogeneity of gp120 presents major obstacles in establishing an effective HIV vaccine. The gp120 glycoprotein also carries the binding site for the CD4 molecule, the most common host cell surface receptor of T lymphocytes. This tropism for $CD4^+$ T cells is beneficial to the virus because of the resulting reduction in the effectiveness of the host immune system. Other CD4-bearing cells include macrophages and microglial cells. The observations that $CD4^-$ cells are also infected by HIV and that some $CD4^+$ T cells are resistant to such infections suggests that other cellular attachment sites are needed for the interaction between HIV and human cells. Several chemokines serve as coreceptors for the envelope glycoproteins, permitting membrane fusion and entry into the cell. Most HIV strains have a specific tropism for 1 of the chemokines, including the fusion-inducing molecule **CXCR-4**, which acts as a coreceptor for HIV attachment to lymphocytes, and **CCR-5**, a β chemokine receptor that facilitates HIV entry into macrophages. Several other chemokine receptors (CCR-3) have also been shown in vitro to serve as virus co-receptors. Other mechanisms of attachment of HIV to cells use nonneutralizing antiviral antibodies and complement receptors. The Fab portion of these antibodies attaches to the virus surface, and the Fc portion binds to cells that express Fc receptors (macrophages, fibroblasts), thus facilitating virus transfer into the cell. Other cell-surface receptors, such as mannose-binding protein on macrophages or DC-specific C-type lectin (DC-SIGN) on dendritic cells, also bind to the HIV-1 envelope glycoprotein and increase the efficiency of viral infectivity. Cell-to-cell transfer of HIV without formation of fully formed particles is a more rapid mechanism of spreading the infection to new cells than is direct infection by the virus.

Following viral attachment, gp120 and the CD4 molecule undergo conformational changes, and gp41 interacts with the fusion receptor on the cell surface (Fig. 276-3). Viral fusion with the cell membrane allows entry of viral RNA into the cell cytoplasm. This process involves accessory viral proteins (nef, vif) and binding of cyclophilin A (a host cellular protein) to the capsid protein (p24). The p24 protein is involved in virus uncoating, recognition by restriction factors, and nuclear importation and integration of the newly created viral DNA. Viral DNA copies are then transcribed from the virion RNA through viral reverse transcriptase enzyme activity, which builds the 1st DNA strand from the viral RNA and then destroys the viral RNA and builds a 2nd DNA strand to produce double-stranded circular DNA. The HIV-1 reverse transcriptase is error prone and lacks error-correcting mechanisms. Thus, many mutations arise, creating wide genetic variation in

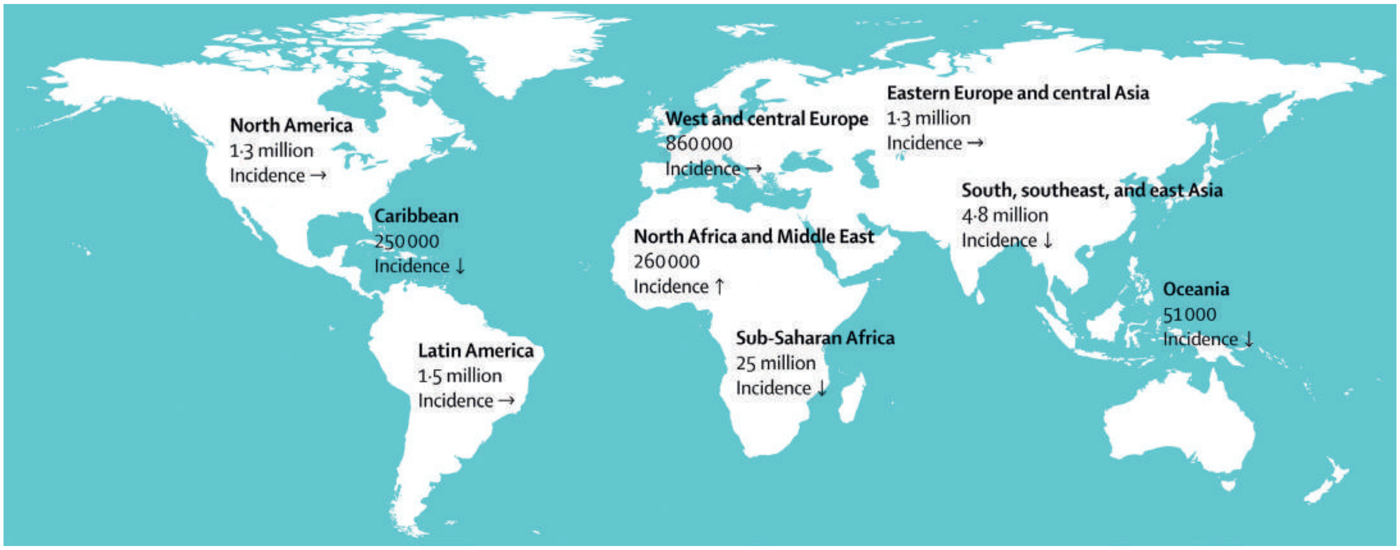

Figure 276-1 Estimated number of people living with HIV in 2012 and trends in the incidence of new infections from 2001 to 2012 by global region. Data from UNAIDS 2013 report. *(From Maartens G, Celum C, Lewin SR: HIV infection: epidemiology, pathogenesis, treatment, and prevention.* Lancet *384:258–268, 2014, Fig. 1).*

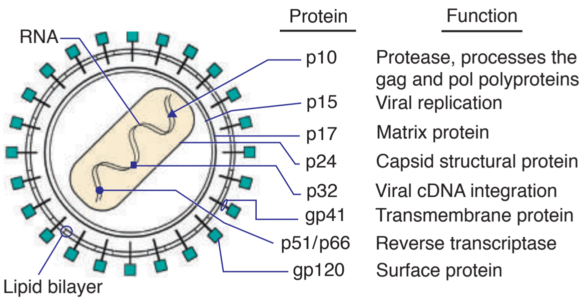

Figure 276-2 The human immunodeficiency virus and associated proteins and their functions.

HIV-1 isolates even within an individual patient. Many of the drugs used to fight HIV infection were designed to block the reverse transcriptase action. The circular DNA is transported into the cell nucleus, using viral accessory proteins like vpr, where it is integrated (with the help of the virus integrase) into the host chromosomal DNA and referred to as the *provirus*. The provirus has the advantage of latency, as it can remain dormant for extended periods, making it extremely difficult to eradicate. The infected $CD4^+$ T cells that survive long enough to revert to resting memory state become the HIV latent reservoir where the virus persists indefinitely even in patients who respond favorably to potent antiretroviral therapy. The molecular mechanisms of this latency are complex and involve unique biologic properties of the latent provirus (e.g., absence of tat, epigenetic changes inhibiting HIV gene expression) and the nature of the cellular host (e.g., absence of transcription factors like nuclear factor κB). Integration usually occurs near active genes, which allow a high level of viral production in response to various external factors such as an increase in inflammatory cytokines (by infection with other pathogens) and cellular activation. Anti-HIV drugs that block the integrase enzyme activity have been developed. Depending on the relative expression of the viral regulatory genes (tat, rev, nef), the proviral DNA may encode production of the viral RNA genome, which, in turn, leads to production of viral proteins necessary for viral assembly.

HIV-1 transcription is followed by translation. A capsid polyprotein is cleaved to produce, the virus-specific protease (p10), among other products. This enzyme is critical for HIV-1 assembly because it cleaves the long polyproteins into the proper functional pieces. Several HIV-1 antiprotease drugs have been developed, targeting the increased sensitivity of the viral protease, which differs from the cellular proteases. The regulatory protein vif is active in virus assembly and Gag processing. The RNA genome is then incorporated into the newly formed viral capsid that requires zinc finger domains (p7) and the matrix protein (MA: p17). The matrix protein forms a coat on the inner surface of the viral membrane, which is essential for the budding of the new virus from the host cell's surface. As new virus is formed, it buds through specialized membrane areas, known as *lipid rafts*, and is released. The virus release is facilitated by the viroporin vpu, which induces rapid degradation of newly synthesized CD4 molecules that impede viral budding. In addition, vpu counteracts host innate immunity (e.g., hampering natural killer T-cell activity).

Full-length sequencing of the HIV-1 genome demonstrated 3 different groups (M [main], O [outlier], and N [non-M, non-O]), probably occurring from multiple zoonotic infections from primates in different geographic regions. The same technique identified 8 groups of HIV-2 isolates. Group M diversified to 9 subtypes (or clades A to D, F to H, J and K). In each region of the world, certain clades predominate, for example, clade A in Central Africa, clade B in the United States and South America, clade C in South Africa, clade E in Thailand, and clade F in Brazil. Although some subtypes were identified within group O, none was found in any of the HIV-2 groups. Clades are mixed in some patients as a result of HIV recombination, and some crossing between groups (i.e., M and O) has been reported.

HIV-2 has a similar life cycle to HIV-1 and is known to cause infection in several monkey species. Subtypes A and B are the major causes of infection in humans, but rarely cause infection in children. HIV-2 differs from HIV-1 in its accessory genes (e.g., it has no *vpu* gene but contains the *vpx* gene, which is not found in HIV-1). It is most prevalent in western Africa, but increasing numbers of cases are reported from Europe and southern Asia. The diagnosis of HIV-2 infection is more difficult because of major differences in the genetic sequences between HIV-1 and HIV-2. Thus, several of the standard confirmatory assays (immunoblot), which are HIV-1 specific, may give indeterminate results with HIV-2 infection. If HIV-2 infection is suspected, a combination screening test that detects antibody to HIV-1 and HIV-2 peptides should be used. In addition, the rapid HIV detection tests have been less reliable in patients suspected to be dually infected with HIV-1 and HIV-2, because of lower antibody concentrations against HIV-2.

EPIDEMIOLOGY

The World Health Organization (WHO) estimated that in 2013, 3.2 million children younger than 15 yr of age worldwide were living with

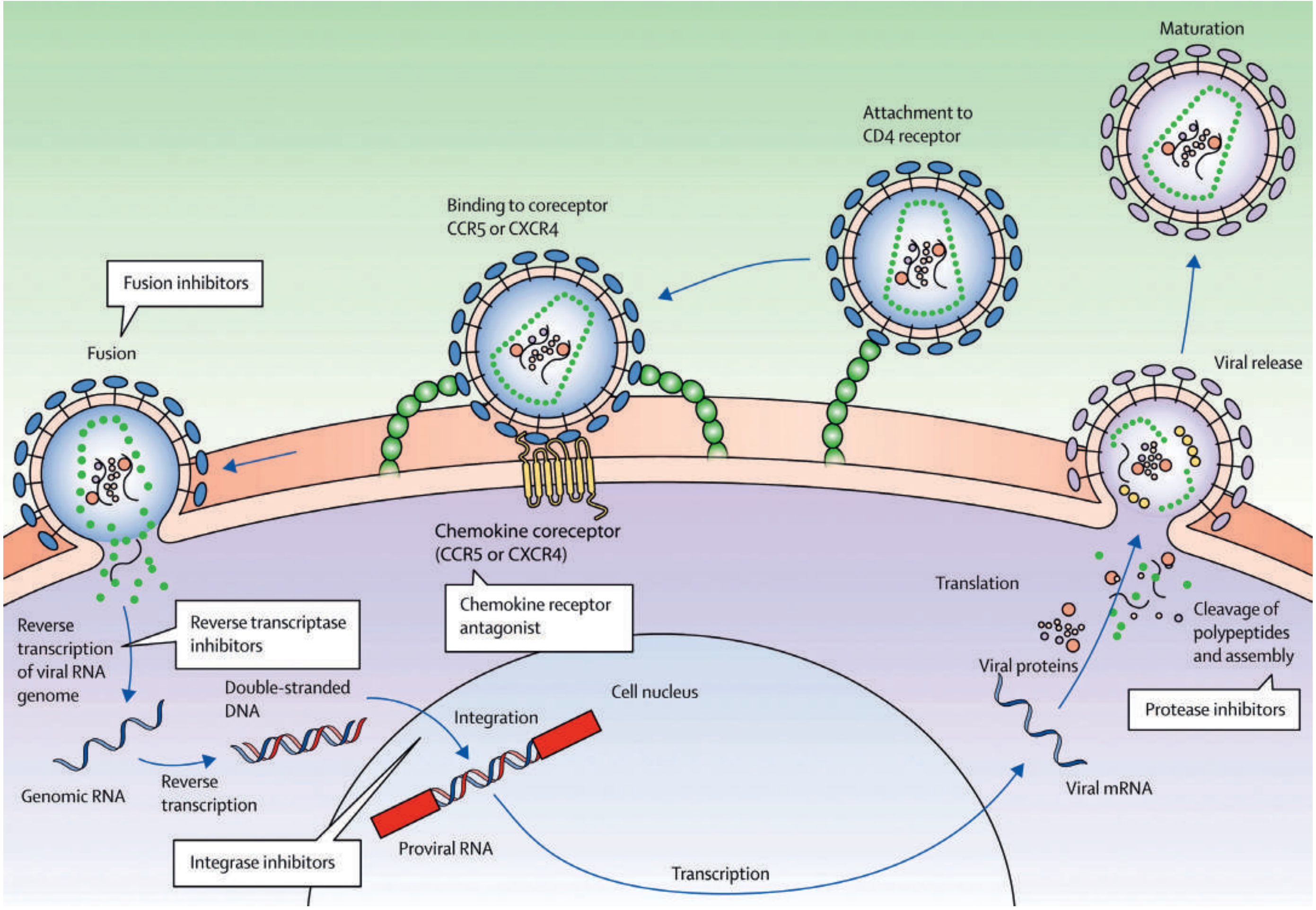

Figure 276-3 HIV life cycle showing the sites of action and different classes of antiretroviral drugs. *(Adapted from Walker BN, Colledge NR, Ralston SH, Penman I, editors:* Davidson's principles and practice of medicine, *ed 22. London, 2014, Churchill Livingstone.)*

HIV-1 infection, 90% of whom were from sub-Saharan Africa. Although the number of children born with HIV in this region decreased by 43% between 2009 and 2013, still 199,000 children were newly infected with HIV in 2013 alone. These trends reflect the slow but steady expansion of services to prevent perinatal transmission of HIV to infants. Unfortunately, through 2011, an estimated 16.6 million children have been orphaned by AIDS, defined as having 1 or both parents die from AIDS.

The vast majority of HIV infections in childhood are the result of **vertical transmission** from an HIV-infected mother. In the United States, approximately 10,800 children, adolescents, or young adults were reported to be living with perinatally acquired HIV infection in 2010. The number of U.S. children with AIDS diagnosed each year increased from 1984-1992 but then declined by more than 95% to <100 cases annually by 2003, largely from the success of prenatal screening and perinatal antiretroviral treatment of HIV-infected mothers and infants. Children of racial and ethnic minority groups are disproportionately overrepresented, particularly non-Hispanic African-Americans and Hispanics. Race and ethnicity are not risk factors for HIV infection but more likely reflect other social factors that may be predictive of increased risk for HIV infection, such as lack of educational and economic opportunities. New York, Florida, Texas, and California are the states with the highest number of cases of HIV in children in the United States.

Although adolescents (13-24 yr of age) represent a minority of U.S. AIDS cases (approximately 4%), they constitute a growing population of newly infected individuals; in 2011, almost 10,500 new cases of HIV were diagnosed in this age group, representing 21% of all new HIV infections in the United States. In 2009, 69% of all new youth infections occurred in young males who have sex with males (MSM), with a 48% increase in new infections in black MSM between 2006 and 2009. More than 50% of HIV-positive youth report being unaware of their diagnosis. Considering the long latency period between the time of infection and the development of clinical symptoms, reliance on AIDS case definition surveillance data significantly underrepresents the impact of the disease in adolescents. Based on a median incubation period of 8-12 yr, it is estimated that 15-20% of all AIDS cases were acquired between 13 and 19 yr of age.

Risk factors for HIV infection vary by gender in adolescents. For example, 91-93% of males between the ages of 13 and 24 yr with HIV acquire infection through sex with males. In contrast, 91-93% of adolescent females with HIV are infected through heterosexual contact. As in the pediatric population, adolescent racial and ethnic minority populations are overrepresented, especially among females.

Transmission

Transmission of HIV-1 occurs via sexual contact, parenteral exposure to blood, or vertical transmission from mother to child. The primary route of infection in the pediatric population is vertical transmission. Rates of transmission of HIV from mother to child have varied in high- and low-resource countries; the United States and Europe have documented transmission rates in untreated women between 12% and 30%, whereas transmission rates in Africa and Haiti have been higher (25-52%), likely because of more advanced maternal disease and the presence of coinfections. Perinatal treatment of HIV-infected pregnant women with antiretroviral drugs has dramatically decreased the rate to <2%.

Vertical transmission of HIV can occur before **(intrauterine),** during **(intrapartum),** or after delivery (through **breastfeeding**). Although intrauterine transmission has been suggested by identification of HIV by culture or polymerase chain reaction (PCR) in fetal tissue as early as 10 wk, statistical modeling data suggest that the majority of in utero transmissions likely occur in late gestation, when the vascular integrity of the placenta weakens and microtransfusions across the maternal–fetal circulation occur. It is generally accepted that 20-30% of infected newborns are infected in utero, because this percentage of infants has laboratory evidence of infection (positive viral culture or PCR) within the 1st wk of life. Some studies have found that viral detection soon after birth also correlates with early onset of symptoms and rapid progression to AIDS, consistent with more long-standing infection during gestation.

A higher percentage of HIV-infected children acquire the virus intrapartum, evidenced by the fact that 70-80% of infected infants do not demonstrate detectable virus until after 1 wk of age. The mechanism of transmission appears to be mucosal exposure to infected blood and cervicovaginal secretions in the birth canal, and intrauterine contractions during active labor/delivery could also increase the risk of late microtransfusions. Breastfeeding is the least-common route of vertical transmission in industrialized nations, but is responsible for as much as 40% of perinatal infections in resource-limited countries. Both free and cell-associated viruses have been detected in breast milk from HIV-infected mothers. The risk for transmission through breastfeeding is approximately 9-16% in women with established infection, but is 29-53% in women who acquire HIV postnatally, suggesting that the viremia experienced by the mother during primary infection at least triples the risk for transmission. Where replacement feeding is readily available and safe, it seems reasonable for women to substitute infant formula for breast milk if they are known to be HIV infected or are at risk for ongoing sexual or parenteral exposure to HIV. However, the WHO recommends that in low-resource countries where other diseases (diarrhea, pneumonia, malnutrition) substantially contribute to a high infant mortality rate, the benefit of breastfeeding outweighs the risk for HIV transmission, and HIV-infected women in developing countries should breastfeed their infants for at least the 1st 6 mo of life (see "Prevention" below).

Several risk factors influence the rate of vertical transmission: maternal viral load at delivery, preterm delivery (<34 wk gestation), and low maternal antenatal CD4 count. The most important variable appears to be the level of maternal viremia; the odds of transmission may be increased more than 2-fold for every $\log_{10}$ increase in viral load at delivery. Elective cesarean delivery was shown to decrease transmission by 87% if used in conjunction with zidovudine therapy in the mother and infant. However, because these data predated the advent of **combined antiretroviral therapy (cART, also called HAART),** the additional benefit of cesarean section appears to be negligible if the mother's viral load is <1,000 copies/mL. It should be noted that rarely (≤0.1%) transmission may occur with maternal viral loads <50 copies/mL.

Transfusions of infected blood or blood products have accounted for 3-6% of all pediatric AIDS cases. The period of highest risk was between 1978 and 1985, before the availability of HIV antibody-screened blood products. Whereas the prevalence of HIV infection in individuals with hemophilia treated before 1985 was as high as 70%, heat treatment of factor VIII concentrate and HIV antibody screening of donors has virtually eliminated HIV transmission in this population. Donor screening has dramatically reduced, but not eliminated, the risk for blood transfusion–associated HIV infection: nucleic acid amplification testing of "minipools" (pools of 16-24 donations) performed on antibody-nonreactive blood donations (to identify donations made during the window period before seroconversion) reduced the residual risk of transfusion-transmitted HIV-1 to approximately 1 in 2 million blood units. However, in many resource-limited countries, screening of blood is not uniform, and the risk for transmitting HIV infection via transfusion remains.

Although HIV can be isolated rarely from saliva, it is in very low titers (<1 infectious particle/mL) and has not been implicated as a transmission vehicle. Studies of hundreds of household contacts of HIV-infected individuals have found that the risk for household HIV transmission is practically nonexistent. Only a few cases have been reported in which urine or feces (possibly devoid of visible blood) have been proposed as a possible vehicle of HIV transmission.

In the pediatric population, sexual transmission is infrequent, but a small number of cases resulting from sexual abuse have been reported. Sexual contact is a major route of transmission in the adolescent population, accounting for most of the cases.

PATHOGENESIS

HIV infection affects most of the immune system and disrupts its homeostasis (see Fig. 276-3). In most cases, the initial infection is caused by low amounts of a single virus. Therefore, disease may be prevented by prophylactic drug(s) or vaccine. When the mucosa serves as the portal of entry for HIV, the 1st cells to be affected are the dendritic cells. These cells collect and process antigens introduced from the periphery and transport them to the lymphoid tissue. HIV does not infect the dendritic cell but binds to its DC-SIGN surface molecule, allowing the virus to survive until it reaches the lymphatic tissue. In the lymphatic tissue (e.g., lamina propria, lymph nodes), the virus selectively binds to cells expressing CD4 molecules on their surface, primarily helper T lymphocytes ($CD4^+$ T cells) and cells of the monocyte-macrophage lineage. Other cells bearing CD4, such as microglia, astrocytes, oligodendroglia, and placental tissue containing villous Hofbauer cells, may also be infected by HIV. Additional factors (coreceptors) are necessary for HIV fusion and entry into cells. These factors include the chemokines CXCR4 (fusion) and CCR5. Other chemokines (CCR1, CCR3) may be necessary for the fusion of certain HIV strains. Several host genetic determinants affect the susceptibility to HIV infection, the progression of disease, and the response to treatment. These genetic variants vary in different populations. A deletion in the CCR5 gene that is protective against HIV infection (CCR5Δ32) is relatively common in whites but is rare in blacks. Several other genes that regulate chemokine receptors, ligands, the histocompatibility complex, and cytokines also influence the outcome of HIV infection. Usually, $CD4^+$ lymphocytes migrate to the lymphatic tissue in response to viral antigens and then become activated and proliferate, making them highly susceptible to HIV infection. This antigen-driven migration and accumulation of CD4 cells within the lymphoid tissue may contribute to the generalized lymphadenopathy characteristic of the acute retroviral syndrome in adults and adolescents. HIV preferentially infects the very cells that respond to it (HIV-specific memory CD4 cells), accounting for the progressive loss of these cells and the subsequent loss of control of HIV replication. The continued destruction of memory $CD4^+$ cells in the gastrointestinal tract leads to reduced integrity of the gastrointestinal epithelium followed by leakage of bacterial particles into the blood and increased inflammatory response, which cause further $CD4^+$ cell loss. When HIV replication reaches a threshold (usually within 3-6 wk from the time of infection), a burst of plasma viremia occurs. This intense viremia causes **flu or mononucleosis-like symptoms** (fever, rash, lymphadenopathy, arthralgia) in 50-70% of infected adults. With establishment of a cellular and humoral immune response within 2-4 mo, the viral load in the blood declines substantially, and patients enter a phase characterized by a lack of symptoms and a return of CD4 cells to only moderately decreased levels.

The HIV rapidly responds to the immune system pressure by developing a genetically complex population (quasispecies) that successfully evade it. In addition, inappropriate use of antiretroviral treatment increases the ability of the virus to diverge even further. Early HIV-1 replication in children has no apparent clinical manifestations. Whether tested by virus isolation or by PCR for viral nucleic acid sequences, fewer than 40% of HIV-1–infected infants demonstrate evidence of the virus at birth. The virus load increases by 1-4 mo, and almost all HIV-infected infants have detectable HIV-1 in peripheral blood by 4 mo of age.

In adults, the long period of clinical latency (8-12 yr) is not indicative of viral latency. In fact, there is a very high turnover of virus and CD4 lymphocytes (more than a billion cells per day), gradually causing deterioration of the immune system, marked by depletion of CD4 cells.

Several mechanisms for the depletion of CD4 cells in adults and children have been suggested, including HIV-mediated single cell killing, formation of multinucleated giant cells of infected and uninfected CD4 cells **(syncytia formation),** virus-specific immune responses (natural killer cells, antibody-dependent cellular cytotoxicity), superantigen-mediated activation of T cells (rendering them more susceptible to infection with HIV), autoimmunity, and programmed cell death (apoptosis). The viral burden is greater in the lymphoid organs than in the peripheral blood during the asymptomatic period. As HIV virions and their immune complexes migrate through the lymph nodes, they are trapped in the network of dendritic follicular cells. Because the ability of HIV to replicate in T cells depends on the state of activation of the cells, the immune activation that takes place within the microenvironment of the lymph nodes in HIV disease serves to promote infection of new CD4 cells as well as subsequent viral replication within these cells. Monocytes and macrophages can be productively infected by HIV yet resist the cytopathic effect of the virus and, with their long lifespan, explain their role as reservoirs of HIV and as effectors of tissue damage in organs such as the brain. In addition, they reside in anatomic viral sanctuaries where current treatment agents are less effective.

The innate immune system responds almost immediately following HIV infection by recognizing the viral nucleic acids, once the virus fuses into the infected cell, by the toll-like receptor 7. This engagement leads to activation of proinflammatory cytokines and interferon (IFN-α), which blocks virus replication and spread. The virus uses its Nef protein to downregulate the expression of major histocompatibility complex (MHC) and non-MHC ligands to reduce the natural killing (NK) cell–mediated anti-HIV activity. It also modulates NK cell differentiation and maturation, dysregulates cytokine production, and increases apoptosis. While the mechanism by which the innate system triggers the adaptive immune responses is not yet fully understood, cell-mediated and humoral responses occur early in the infection. CD8 T cells play an important role in containing the infection. These cells produce various ligands (macrophage inflammatory proteins 1α and 1β, RANTES), which suppress HIV replication by blocking the binding of the virus to the coreceptors (CCR5). HIV-specific cytotoxic T lymphocytes (CTLs) develop against both the structural (ENV, POL, GAG) and regulatory (tat) viral proteins. The CTLs appear at the end of the acute infection, as viral replication is controlled by killing HIV-infected cells before new viruses are produced and by secreting potent antiviral factors that compete with the virus for its receptors (CCR5). Neutralizing antibodies appear later in the infection and seem to help in the continued suppression of viral replication during clinical latency. There are at least 2 possible mechanisms that control the steady-state viral load level during the chronic clinical latency. One mechanism may be the limited availability of activated CD4 cells, which prevent further increase in viral load. The other mechanism is development of an active immune response, which is influenced by the amount of viral antigen and limits viral replication at a steady state. There is no general consensus about which of these 2 mechanisms is more important. The CD4 cell limitation mechanism accounts for the effect of antiretroviral therapy, whereas the immune response mechanism emphasizes the importance of immune modulation treatment (cytokines, vaccines) to increase the efficiency of immune-mediated control. A group of cytokines that includes tumor necrosis factor TNF-α, TNF-β, interleukin IL-1, IL-2, IL-3, IL-6, IL-8, IL-12, IL-15, granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor plays an integral role in upregulating HIV expression from a state of quiescent infection to active viral replication. Other cytokines such as IFN-γ, IFN-β, and IL-13 exert a suppressive effect on HIV replication. Certain cytokines (IL-4, IL-10, IFN-γ, transforming growth factor-β) reduce or enhance viral replication depending on the infected cell type. The interactions among these cytokines influence the concentration of viral particles in the tissues. Plasma concentrations of cytokines need not be elevated for them to exert their effect, because they are produced and act locally in the tissues. The activation of virtually all the cellular components of the immune system (i.e., T and B cells, natural killer cells, and monocytes) plays a significant role in the pathologic aspects of HIV infection. Further understanding of their interactions during the infection will expand our treatment options. Commonly, HIV isolated during the clinical latency period grows slowly in culture and produces low titers of reverse transcriptase. These isolates use CCR5 as their coreceptor. By the late stages of clinical latency, the isolated virus is phenotypically different. It grows rapidly and to high titers in culture and uses CXCR4 as its coreceptor. The switch from CCR5 receptor to CXCR4 receptor increases the capacity of the virus to replicate, to infect a broader range of target cells (CXCR4 is more widely expressed on resting and activated immune cells), and to kill T cells more rapidly and efficiently. As a result, the clinical latency phase is over and progression toward AIDS is noted. The **progression of disease** is related temporally to the gradual disruption of lymph node architecture and degeneration of the follicular dendritic cell network with loss of its ability to trap HIV particles. The virus is freed to recirculate, producing high levels of viremia and an increased disappearance of CD4 T cells during the later stages of disease.

The clinical course of the HIV infection shows a substantial heterogenicity. This variation is determined by both viral and host factors. HIV viruses that use coreceptor CXCR4 in the course of the infection are associated with an accelerated deterioration of the immune system and more rapid progression to AIDS. In addition, several host genetic determinants (e.g., variants in the human leukocyte antigen region, polymorphisms in the CCR5 region like CCR5Δ32) were already identified as affecting the disease course. **Three distinct patterns of disease** were described in children. Approximately 15-25% of HIV-infected newborns in developed countries present with a **rapid disease course**, with onset of AIDS and symptoms during the 1st few months of life and a median survival time of 6-9 mo if untreated. In resource-poor countries, the majority of HIV-infected newborns will have this rapidly progressing disease. It has been suggested that if intrauterine infection coincides with the period of rapid expansion of CD4 cells in the fetus, the virus could effectively infect the majority of the body's immunocompetent cells. The normal migration of these cells to the marrow, spleen, and thymus would result in efficient systemic delivery of HIV, unchecked by the immature immune system of the fetus. Thus, infection would be established before the normal ontogenic development of the immune system, causing more-severe impairment of immunity. Most children in this group have a positive HIV-1 culture and/or detectable virus in the plasma (median level: 11,000 copies/mL) in the 1st 48 hr of life. This early evidence of viral presence suggests that the newborn was infected in utero. The viral load rapidly increases, peaking by 2-3 mo of age (median: 750,000 copies/mL) and staying high for at least the 1st 2 yr of life.

From 60-80% of perinatally infected newborns in developed countries present with a much **slower progression** of disease, with a median survival time of 6 yr representing the 2nd pattern of disease. Many patients in this group have a negative viral culture or PCR in the 1st wk of life and are therefore considered to be infected intrapartum. In a typical patient, the viral load rapidly increases, peaking by 2-3 mo of age (median: 100,000 copies/mL) and then slowly declines over a period of 24 mo. The slow decline in viral load is in sharp contrast to the rapid decline after primary infection seen in adults. This observation can be explained only partially by the immaturity of the immune system in newborns and infants.

The 3rd pattern of disease occurs in <5% of perinatally infected children, referred to as **long-term survivors,** who have minimal or no progression of disease with relatively normal CD4 counts and very low viral loads for longer than 8 yr. Mechanisms for the delay in disease progression include effective humoral immunity and/or CTL responses, host genetic factors (e.g., human leukocyte antigen profile), and infection with attenuated (defective gene) virus. A subgroup of the long-term survivors called "elite survivors" has no detectable viruses in the blood and may reflect different or greater mechanisms of protection from disease progression.

HIV-infected children have changes in the immune system that are similar to those in HIV-infected adults. CD4 cell depletion may be less dramatic because infants normally have a relative lymphocytosis. A value of 1,500 CD4 cells/μL in children younger than 1 yr of age is indicative of severe CD4 depletion and is comparable to <200 CD4

cells/μL in adults. Lymphopenia is relatively rare in perinatally infected children and is usually only seen in older children or those with end-stage disease. Although cutaneous anergy is common during HIV infection, it is also frequent in healthy children younger than 1 yr of age, and thus its interpretation is difficult in infected infants. The depletion of CD4 cells also decreases the response to soluble antigens such as in vitro mitogens phytohemagglutinin and concanavalin A.

Polyclonal activation of B cells occurs in most children early in the infection, as evidenced by elevation of immunoglobulin (Ig) A, IgM, IgE, and particularly IgG (**hypergammaglobulinemia**), with high levels of anti–HIV-1 antibody. This response may reflect both dysregulation of T-cell suppression of B-cell antibody synthesis and active CD4 enhancement of B-lymphocyte humoral response. As a result, antibody response to routine childhood vaccinations may be abnormal. The B-cell dysregulation precedes the CD4 depletion in many children, and may serve as a surrogate marker of HIV infection in symptomatic children in whom specific diagnostic tests (PCR, culture) are not available or are too expensive. Despite the increased levels of immunoglobulins, some children lack specific antibodies or protective antibodies. Hypogammaglobulinemia is very rare (<1%).

Central nervous system (CNS) involvement is more common in pediatric patients than in adults. Macrophages and microglia play an important role in HIV neuropathogenesis, and data suggest that astrocytes may also be involved. Although the specific mechanisms for encephalopathy in children are not yet clear, the developing brain in young infants is affected by at least 2 mechanisms. The virus itself may directly infect various brain cells or cause indirect damage to the nervous system by the release of cytokines (IL-1α, IL-1β, TNF-α, IL-2) or reactive oxygen from HIV-infected lymphocytes or macrophages.

Appropriate therapy with antiretroviral agents may result in **immune reconstitution inflammatory syndrome (IRIS)**, which is characterized by an increased inflammatory response from the recovered immune system to subclinical opportunistic infections (e.g., *Mycobacterium*, herpes simplex virus [HSV] infection, toxoplasmosis, cytomegalovirus [CMV] infection, *Pneumocystis*, cryptococcal infection). This condition is more commonly observed in patients with progressive disease and severe CD4$^+$ T-lymphocyte depletion. Patients with IRIS develop fever and worsening of the clinical manifestations of the opportunistic infection or new manifestations (e.g., enlargement of lymph nodes, pulmonary infiltrates), typically within the 1st few weeks after initiation of antiretroviral therapy. Determining whether the symptoms represent IRIS, worsening of a current infection, a new opportunistic infection, or drug toxicity is often very difficult. If the syndrome does represent IRIS, adding nonsteroidal antiinflammatory agents or corticosteroids may alleviate the inflammatory reaction, although the use of corticosteroids is controversial. The inflammation may take weeks or months to subside. In most cases, continuation of anti-HIV treatment while treating the opportunistic infection (with or without antiinflammatory agents) is sufficient. If opportunistic infection is suspected prior to initiation of antiretroviral therapy, appropriate antimicrobial treatment should be given 1st.

CLINICAL MANIFESTATIONS

The clinical manifestations of HIV infection vary widely among infants, children, and adolescents. In most infants, physical examination at birth is normal. Initial symptoms may be subtle, such as lymphadenopathy and hepatosplenomegaly, or nonspecific, such as failure to thrive, chronic or recurrent diarrhea, respiratory symptoms, or oral thrush and may be distinguishable only by their persistence. Whereas systemic and pulmonary findings are common in the United States and Europe, chronic diarrhea, pneumonia, wasting, and severe malnutrition predominate in Africa. Clinical manifestations found more commonly in children than adults with HIV infection include recurrent bacterial infections, chronic parotid swelling, lymphocytic interstitial pneumonitis (LIP), and early onset of progressive neurologic deterioration.

The CDC Surveillance Case Definition for HIV infection was revised in 2014 and has consolidated the staging system for children with adolescents and adults. It is based on age-specific CD4$^+$ T-lymphocyte count or CD4$^+$ T-lymphocyte percentage of total lymphocytes (Table 276-1), except when a stage 3-defining opportunistic illness (Table 276-2) supersedes the CD4 data. Age adjustment of the absolute CD4 count is necessary because counts that are relatively high in normal infants decline steadily until age 6 yr, when they reach adult norms. The CD4 count takes precedence over the CD4 T-lymphocyte percentage, and the percentage is considered only if the count is missing.

Infections

Approximately 20% of AIDS-defining illnesses in children are recurrent bacterial infections caused primarily by encapsulated organisms such as *Streptococcus pneumoniae* and *Salmonella* as a result of disturbances in humoral immunity. Other pathogens, including *Staphylococcus, Enterococcus, Pseudomonas aeruginosa, Haemophilus influenzae,* and other Gram-positive and Gram-negative organisms, may also be seen. The most common serious infections in HIV-infected children are bacteremia, sepsis, and bacterial pneumonia, accounting for more than 50% of infections in these patients. Meningitis, urinary tract infections, deep-seated abscesses, and bone/joint infections occur less frequently. Milder recurrent infections, such as otitis media, sinusitis, and skin and soft tissue infections, are very common and may be chronic with atypical presentations.

Opportunistic infections are generally seen in children with severe depression of the CD4 count. In adults, these infections usually represent reactivation of a latent infection acquired early in life. In contrast, young children generally have primary infection and often have a more fulminant course of disease reflecting the lack of prior immunity. This principle is best illustrated by *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia, the most common opportunistic infection in the pediatric population (see Chapter 244). The peak incidence of *Pneumocystis* pneumonia occurs at age 3-6 mo in the setting of undiagnosed perinatally acquired disease, with the highest mortality rate in children younger than 1 yr of age. Aggressive approaches to treatment have improved the outcome substantially. While the overall

Table 276-1 HIV Infection Stage* Based on Age-Specific CD4$^+$ T-Lymphocyte Count or CD4$^+$ T-Lymphocyte Percentage of Total Lymphocytes

	Age on Date of CD4$^+$ T-Lymphocyte Test					
	<1 Yr		1-5 Yr		≥6 Yr	
Stage	**CELLS/μL**	**%**	**CELLS/μL**	**%**	**CELLS/μL**	**%**
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750-1,499	26-33	500-999	22-29	200-499	14-25
3	<750	<26	<500	<22	<200	<14

*Stage is based primarily on the CD4$^+$ T-lymphocyte count. The CD4$^+$ T-lymphocyte count takes precedence over the CD4$^+$ T-lymphocyte percentage, and the percentage is considered only if the count is missing.

From Centers for Disease Control and Prevention: Revised surveillance case definition for HIV infection—United States, 2014. MMWR 63(No RR-3):1-10, 2014.

Table 276-2	Stage 3—Defining Opportunistic Illnesses in HIV Infection

Bacterial infections, multiple or recurrent*
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive†
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 mo duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 mo
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV‡
Herpes simplex: chronic ulcers (>1 mo duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 mo)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 mo duration)
Kaposi sarcoma
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary,† disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jiroveci (previously known as *Pneumocystis carinii*) pneumonia
Pneumonia, recurrent†
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 mo
Wasting syndrome attributed to HIV‡

*Only among children aged <6 yr.
†Only among adults, adolescents, and children aged ≥6 yr.
‡Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references: Centers for Disease Control and Prevention: 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 43(No. RR-12), 1994. Centers for Disease Control and Prevention: 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 41(No. RR-17), 1992.
From Centers for Disease Control and Prevention: Revised surveillance case definition for HIV infection—United States, 2014. MMWR 63(No RR-3):1-10, 2014.

incidence of opportunistic infections has markedly declined since the era of combination antiretroviral therapy, opportunistic infections still occur in patients with severe immunodepletion as the result of unchecked viral replication, which often accompanies poor antiretroviral therapy adherence.

The classic clinical presentation of *Pneumocystis* pneumonia includes acute onset of fever, tachypnea, dyspnea, and marked hypoxemia; in some children, more indolent development of hypoxemia may precede other clinical or x-ray manifestations. Chest x-ray findings most commonly consist of interstitial infiltrates or diffuse alveolar disease, which rapidly progresses. Nodular lesions, streaky or lobar infiltrates, or pleural effusions may occasionally be seen. Diagnosis is established by demonstration of *P. jiroveci* with appropriate staining of induced sputum or bronchoalveolar fluid lavage; rarely, an open lung biopsy is necessary.

The 1st-line therapy for *Pneumocystis* pneumonia is intravenous trimethoprim-sulfamethoxazole (TMP-SMZ) (15-20 mg/kg/day of the TMP component every 6 hr IV) with adjunctive corticosteroids if the Pao_2 is <70 mm Hg while breathing room air. When the patient has improved, therapy with oral TMP-SMZ should be continued for a total of 21 days while the corticosteroids are weaned. Alternative therapy for *Pneumocystis* pneumonia includes intravenous administration of pentamidine (4 mg/kg/day). Other regimens such as TMP plus dapsone, clindamycin plus primaquine, or atovaquone are used as alternatives in adults but have not been widely used in children to date.

Nontuberculous mycobacterial infection, with *Mycobacterium avium-intracellulare* complex (MAC), may cause disseminated disease in HIV-infected children who are severely immunosuppressed. The incidence of MAC infection in antiretroviral therapy–naïve children with <100 CD4 cells/mm^3 is estimated to be as high as 10%, but effective cART that results in viral suppression makes MAC infections rare. Disseminated MAC infection is characterized by fever, malaise, weight loss, and night sweats; diarrhea, abdominal pain, and, rarely, intestinal perforation or jaundice (a result of biliary tract obstruction by lymphadenopathy) may also be present. Diagnosis is made by isolation of MAC from blood, bone marrow, or tissue; the isolated presence of MAC in the stool does not confirm a diagnosis of disseminated MAC. Treatment can reduce symptoms and prolong life but is at best only capable of suppressing the infection if severe CD4 depletion persists. Therapy should include at least 2 drugs: clarithromycin or azithromycin and ethambutol. A 3rd drug (rifabutin, rifampin, ciprofloxacin, levofloxacin, or amikacin) is generally added to decrease the emergence of drug-resistant isolates. Careful consideration of possible drug interactions with antiretroviral agents is necessary before initiation of disseminated MAC therapy. Drug susceptibilities should be ascertained, and the treatment regimen should be adjusted accordingly in the event of inadequate clinical response to therapy. Because of the great potential for toxicity with most of these medications, surveillance for adverse effects should be ongoing.

Oral candidiasis is the most common **fungal infection** seen in HIV-infected children. Oral nystatin suspension (2-5 mL qid) is often effective. Clotrimazole troches or fluconazole (3-6 mg/kg PO qd) are an effective alternative. Oral thrush progresses to involve the esophagus in as many as 20% of children with severe CD4 depletion, presenting with symptoms such as anorexia, dysphagia, vomiting, and fever. Treatment with oral fluconazole for 7-14 days generally results in rapid improvement in symptoms. Fungemia rarely occurs, usually in the setting of indwelling venous catheters, and up to 50% of cases may be caused by non–albicans species. Disseminated histoplasmosis, coccidioidomycosis, and cryptococcosis are rare in pediatric patients but may occur in endemic areas. Parasitic infections such as intestinal cryptosporidiosis and microsporidiosis and rarely isosporiasis or giardiasis are other opportunistic infections that cause significant morbidity. Although these intestinal infections are usually self-limiting in healthy hosts, they cause severe chronic diarrhea in HIV-infected children with low CD4 counts, often leading to malnutrition. Nitazoxanide therapy is partially effective at improving cryptosporidia diarrhea, but immune reconstitution with cART is the most important factor for clearance of the infection. Albendazole has been reported to be effective against some microsporidia, and TMP-SMZ appears to be effective for isosporiasis.

Viral infections, especially with the herpesvirus group, pose significant problems for HIV-infected children. HSV causes recurrent gingivostomatitis, which may be complicated by local and distant cutaneous dissemination. Primary varicella-zoster virus infection (chickenpox) may be prolonged and complicated by bacterial infections or visceral dissemination, including pneumonitis. Recurrent, atypical, or chronic episodes of herpes zoster are often debilitating and require prolonged therapy with acyclovir; in rare instances, varicella-zoster virus has developed resistance to acyclovir, requiring the use of foscarnet. Disseminated CMV infection occurs in the setting of severe CD4 depletion (<50 CD4 cells/µL) and may involve single or multiple organs. Retinitis, pneumonitis, esophagitis, gastritis with pyloric obstruction, hepatitis, colitis, and encephalitis have been reported, but these complications are rarely seen if cART is given. Ganciclovir (6 mg/kg bid IV) and foscarnet (60 mg/kg tid IV) are the drugs of choice and are often given together in children with sight-threatening CMV retinitis. Intraocular injections of foscarnet or intraocular ganciclovir implants plus oral valganciclovir have also been efficacious in adults and older children with CMV retinitis. Measles may occur despite immunization and may present without the typical rash. It often disseminates to the lung or brain with a high mortality rate.

Respiratory viruses such as respiratory syncytial virus and adenovirus may present with prolonged symptoms and persistent viral shedding. In parallel with the increased prevalence of genital tract human papillomavirus infection, cervical intraepithelial neoplasia and anal intraepithelial neoplasia also occur with increased frequency among HIV-1–infected adult women compared with HIV-seronegative women. The relative risk for cervical intraepithelial neoplasia is 5-10 times higher for HIV-1 seropositive women. Multiple modalities are used to treat human papillomavirus infection (see Chapter 266), although none is uniformly effective and the recurrence rate is high among HIV-1–infected persons.

Central Nervous System

The incidence of CNS involvement in perinatally infected children is as high as 50-90% in resource-limited countries but significantly lower in developed countries, with a median onset at 19 mo of age. Manifestations may range from subtle developmental delay to progressive encephalopathy with loss or plateau of developmental milestones, cognitive deterioration, impaired brain growth resulting in acquired microcephaly, and symmetric motor dysfunction. **Encephalopathy** may be the initial manifestation of the disease or may present much later when severe immune suppression occurs. With progression, marked apathy, spasticity, hyperreflexia, and gait disturbance may occur, as well as loss of language and oral, fine, and/or gross motor skills. The encephalopathy may progress intermittently, with periods of deterioration followed by transiently stable plateaus. Older children may exhibit behavioral problems and learning disabilities. Associated abnormalities identified by neuroimaging techniques include cerebral atrophy in up to 85% of children with neurologic symptoms, increased ventricular size, basal ganglia calcifications, and, less frequently, leukomalacia.

Fortunately, since the advent of cART, the incident rate of encephalopathy has dramatically declined to as low as 0.08% in 2006. However, as HIV-infected children progress through adolescence and young adulthood, other subtle manifestations of CNS disease are evident, such as cognitive deficits, attention problems, and psychiatric disorders. Living with a chronic, often stigmatizing, disease, parental loss, and the requirement for lifelong pristine medication adherence compounds these issues, making it challenging for these youth as they inherit responsibility for managing their disease as adults.

Focal neurologic signs and seizures are unusual and may imply a comorbid pathologic process such as a CNS tumor, opportunistic infection, or stroke. **CNS lymphoma** may present with new onset focal neurologic findings, headache, seizures, and mental status changes. Characteristic findings on neuroimaging studies include a hyperdense or isodense mass with variable contrast enhancement or a diffusely infiltrating contrast-enhancing mass. **CNS toxoplasmosis** is exceedingly rare in young infants, but may occur in HIV-infected adolescents and is typically associated with serum antitoxoplasma IgG as a marker of infection. Other opportunistic infections of the CNS are rare and include infection with CMV, JC virus **(progressive *multifocal leukoencephalopathy*)**, HSV, *Cryptococcus neoformans*, and *Coccidioides immitis.* Although the true incidence of cerebrovascular disorders (both hemorrhagic and nonhemorrhagic strokes) is unclear, 6-10% of children from large clinical series have been affected.

Respiratory Tract

Recurrent upper respiratory tract infections such as otitis media and sinusitis are very common. Although the typical pathogens *(S. pneumoniae, H. influenzae, Moraxella catarrhalis)* are most common, unusual pathogens such as *P. aeruginosa,* yeast, and anaerobes may be present in chronic infections and result in complications such as invasive sinusitis and mastoiditis.

LIP is the most common chronic lower respiratory tract abnormality reported to the Centers for Disease Control and Prevention (CDC); historically this occurred in approximately 25% of HIV-infected children, although the incidence has declined in the cART era. LIP is a chronic process with nodular lymphoid hyperplasia in the bronchial and bronchiolar epithelium, often leading to progressive alveolar capillary block over months to years. It has a characteristic chronic diffuse reticulonodular pattern on chest radiography rarely accompanied by hilar lymphadenopathy, allowing a presumptive diagnosis to be made radiographically before the onset of symptoms. There is an insidious onset of tachypnea, cough, and mild to moderate hypoxemia with normal auscultatory findings or minimal rales. Progressive disease presents with symptomatic hypoxemia, which usually resolves with oral corticosteroid therapy, accompanied by digital clubbing. Several studies suggest that LIP is a lymphoproliferative response to a primary Epstein-Barr virus infection in the setting of HIV infection.

Most symptomatic HIV-infected children experience at least 1 episode of pneumonia during the course of their disease. *S. pneumoniae* is the most common bacterial pathogen, but *P. aeruginosa* and other Gram-negative bacterial pneumonias may occur in end-stage disease and are often associated with acute respiratory failure and death. Rarely, severe recurrent bacterial pneumonia results in bronchiectasis. *Pneumocystis* pneumonia is the most common opportunistic infection, but other pathogens, including CMV, *Aspergillus, Histoplasma,* and *Cryptococcus,* can cause pulmonary disease. Infection with common respiratory viruses, including respiratory syncytial virus, parainfluenza, influenza, and adenovirus, may occur simultaneously and have a protracted course and period of viral shedding from the respiratory tract. Pulmonary and extrapulmonary tuberculosis (TB) has been reported with increasing frequency in HIV-infected children in low-resource countries, although it is considerably more common in HIV-infected adults. Because of drug interactions between rifampin and ritonavir-based antiretroviral therapy and poor tolerability of the combination of multiple drugs required, treatment of TB/HIV coinfection is particularly challenging in children.

Cardiovascular System

Cardiac dysfunction, including left ventricular hypertrophy, left ventricular dilation, reduced left ventricular fractional shortening, and/or heart failure occurred in 18-39% of HIV-infected children in the pre-cART era; among those affected, lower nadir CD4 percent and a higher viral load were associated with lower cardiac function. However, a more recent evaluation of HIV-infected children taking long-term cART found that echocardiographic findings were closer to normal and none had symptomatic heart disease, suggesting that cART has a cardioprotective effect. What is still unclear is whether an increased rate of premature cardiovascular disease that has been seen in adults will be seen in children who have disease- or treatment-related hyperlipidemia, and prospective studies will be needed to assess this risk.

Gastrointestinal and Hepatobiliary Tract

Oral manifestations of HIV disease include erythematous or pseudomembranous candidiasis, periodontal disease (e.g., ulcerative gingivitis or periodontitis), salivary gland disease (i.e., swelling, xerostomia), and rarely ulcerations or oral hairy leukoplakia. Gastrointestinal tract involvement is common in HIV-infected children. A variety of pathogens can cause gastrointestinal disease, including bacteria (*Salmonella, Campylobacter,* MAC), protozoa (*Giardia, Cryptosporidium, Isospora,* microsporidia), viruses (CMV, HSV, rotavirus), and fungi *(Candida).* MAC and the protozoal infections are most severe and protracted in patients with severe CD4 cell depletion. Infections may be localized or disseminated and affect any part of the gastrointestinal tract from the oropharynx to the rectum. Oral or esophageal ulcerations, either viral in origin or idiopathic, are painful and often interfere with eating. AIDS enteropathy, a syndrome of malabsorption with partial villous atrophy not associated with a specific pathogen, has been postulated to be a result of direct HIV infection of the gut. Disaccharide intolerance is common in HIV-infected children with chronic diarrhea.

The most common symptoms of gastrointestinal disease are chronic or recurrent diarrhea with malabsorption, abdominal pain, dysphagia, and failure to thrive. Prompt recognition of weight loss or poor growth velocity in the absence of diarrhea is critical. Linear growth impairment often correlates with the level of HIV viremia. Supplemental enteral feedings should be instituted, either by mouth or with nighttime nasogastric tube feedings in cases associated with more severe chronic

growth problems; placement of a gastrostomy tube for nutritional supplementation may be necessary in severe cases. The wasting syndrome, defined as a loss of >10% of body weight, is not as common as failure to thrive in pediatric patients, but the resulting malnutrition is associated with a grave prognosis. Chronic liver inflammation evidenced by fluctuating serum levels of transaminases with or without cholestasis is relatively common, often without identification of an etiologic agent. Cryptosporidial cholecystitis is associated with abdominal pain, jaundice, and elevated γ-glutamyltransferase. In some patients, chronic hepatitis caused by CMV, hepatitis B, hepatitis C, or MAC may lead to portal hypertension and liver failure. Several of the antiretroviral drugs or other drugs such as didanosine, protease inhibitors, nevirapine, and dapsone may also cause reversible elevation of transaminases.

Pancreatitis with increased pancreatic enzymes with or without abdominal pain, vomiting, and fever may be the result of drug therapy (e.g., with pentamidine, didanosine, or lamivudine) or, rarely, opportunistic infections such as MAC or CMV.

Renal Disease

Nephropathy is an unusual presenting symptom of HIV infection, more commonly occurring in older symptomatic children. A direct effect of HIV on renal epithelial cells has been suggested as the cause, but immune complexes, hyperviscosity of the blood (secondary to hyperglobulinemia), and nephrotoxic drugs are other possible factors. A wide range of histologic abnormalities has been reported, including focal glomerulosclerosis, mesangial hyperplasia, segmental necrotizing glomerulonephritis, and minimal change disease. Focal glomerulosclerosis generally progresses to renal failure within 6-12 mo, but other histologic abnormalities in children may remain stable without significant renal insufficiency for prolonged periods. Nephrotic syndrome is the most common manifestation of pediatric renal disease, with edema, hypoalbuminemia, proteinuria, and azotemia with normal blood pressure. Cases resistant to steroid therapy may benefit from cyclosporine therapy. Polyuria, oliguria, and hematuria have also been observed in some patients.

Skin Manifestations

Many cutaneous manifestations seen in HIV-infected children are inflammatory or infectious disorders that are not unique to HIV infection. These disorders tend to be more disseminated and respond less consistently to conventional therapy than in the uninfected child. Seborrheic dermatitis or eczema that is severe and unresponsive to treatment may be an early nonspecific sign of HIV infection. Recurrent or chronic episodes of HSV, herpes zoster, molluscum contagiosum, flat warts, anogenital warts, and candidal infections are common and may be difficult to control.

Allergic drug eruptions are also common, in particular related to nonnucleoside reverse transcription inhibitors, and generally respond to withdrawal of the drug but also may resolve spontaneously without drug interruption: rarely, progression to Stevens-Johnson syndrome has been reported. Epidermal hyperkeratosis with dry, scaling skin is frequently observed, and sparse hair or hair loss may be seen in the later stages of the disease.

Hematologic and Malignant Diseases

Anemia occurs in 20-70% of HIV-infected children, more commonly in children with AIDS. The anemia may be a result of chronic infection, poor nutrition, autoimmune factors, virus-associated conditions (hemophagocytic syndrome, parvovirus B19 red cell aplasia), or the adverse effect of drugs (zidovudine).

Leukopenia occurs in almost 30% of untreated HIV-infected children, and neutropenia often occurs. Multiple drugs used for treatment or prophylaxis for opportunistic infections, such as *Pneumocystis* pneumonia, MAC, and CMV, or antiretroviral drugs (zidovudine) may also cause leukopenia and/or neutropenia. In cases in which therapy cannot be changed, treatment with subcutaneous granulocyte colony-stimulating factor may be necessary.

Thrombocytopenia has been reported in 10-20% of patients. The etiology may be immunologic (i.e., circulating immune complexes or antiplatelet antibodies) or, less commonly, from drug toxicity, or the cause may be unknown. Antiretroviral (ARV) therapy may also reverse thrombocytopenia in ARV-naïve patients. In the event of sustained severe thrombocytopenia (<10,000 platelets/μL), treatment with intravenous immunoglobulin or anti-D offers temporary improvement in most patients already taking ARVs. If ineffective, a course of steroids may be an alternative, but consultation with a hematologist should be sought. Deficiency of clotting factors (factors II, VII, IX) is not rare in children with advanced HIV disease and is often easy to correct with vitamin K. A novel disease of the thymus has been observed in a few HIV-infected children. These patients were found to have characteristic anterior mediastinal multilocular thymic cysts without clinical symptoms. Histologic examination shows focal cystic changes, follicular hyperplasia, and diffuse plasmacytosis and multinucleated giant cells. Treatment with cART may result in resolution, or spontaneous involution occurs in some cases.

In contrast to the more frequent occurrence in adults, malignant diseases have been reported infrequently in HIV-infected children, representing only 2% of AIDS-defining illnesses. Non-Hodgkin lymphoma, primary CNS lymphoma, and leiomyosarcoma are the most commonly reported neoplasms among HIV-infected children. Epstein-Barr virus is associated with most lymphomas and with all leiomyosarcomas (see Chapter 254). Kaposi sarcoma, which is caused by human herpesvirus 8, occurs frequently among HIV-infected adults but is exceedingly uncommon among HIV-infected children in resource-rich countries (see Chapter 257).

DIAGNOSIS

All infants born to HIV-infected mothers test antibody-positive at birth because of passive transfer of maternal HIV antibody across the placenta during gestation. Most uninfected infants without ongoing exposure (i.e., who are not breastfed) lose maternal antibody between 6 and 12 mo of age and are known as **seroreverters.** Because a small proportion of uninfected infants continue to test HIV antibody-positive for up to 18 mo of age, positive IgG antibody tests, including the rapid tests, cannot be used to make a definitive diagnosis of HIV infection in infants younger than this age. The presence of IgA or IgM anti-HIV in the infant's circulation can indicate HIV infection, because these immunoglobulin classes do not cross the placenta; however, IgA and IgM anti-HIV assays have been both insensitive and nonspecific and therefore are not valuable for clinical use. In any child older than 18 mo of age, demonstration of IgG antibody to HIV by a repeatedly reactive enzyme immunoassay and confirmatory Western blot test establishes the diagnosis of HIV infection. Breastfed infants should have antibody testing performed 12 wk following cessation of breastfeeding to identify those who became infected at the end of lactation by the HIV-infected mother. Certain diseases (e.g., syphilis, autoimmune diseases) may cause false-positive or indeterminate results. In such cases specific viral diagnostic tests (see later) have to be done.

Several rapid HIV tests are currently available with sensitivity and specificity better than those of the standard enzyme immunoassay. Many of these tests require only a single step that allows test results to be reported within less than 30 min. Incorporating rapid HIV testing during delivery or immediately after birth is crucial for the care of HIV-exposed newborns whose HIV status was unknown during pregnancy. A positive rapid test has to be confirmed by Western blot testing. However, if 2 different rapid tests (testing different HIV-associated antibodies) are positive, there is no need for further verification with Western blot testing. In infants who are at risk of exposure to HIV-2 infection (e.g., born to an HIV-infected woman from West Africa), a rapid test that can detect both HIV-1 and HIV-2 should be used. However, if the HIV testing is negative or the Western blot test reveals an unusual pattern, further diagnostic tests should be considered. In addition, they should be tested with HIV-2 specific DNA PCR assay.

Viral diagnostic assays, such as HIV DNA or RNA PCR or HIV culture, are considerably more useful in young infants, allowing a definitive diagnosis in most infected infants by 1-6 mo of age (Table 276-3). By 3-4 mo of age, the HIV culture and/or PCR identifies all infected infants. HIV DNA PCR is the preferred virologic assay in

Table 276-3 Laboratory Diagnosis of HIV Infection

TEST	COMMENT
HIV DNA PCR	Preferred test to diagnose HIV-1 subtype B infection in infants and children younger than 18 mo of age; highly sensitive and specific by 2 wk of age and available; performed on peripheral blood mononuclear cells. False negatives can occur in non-B subtype HIV-1 infections
HIV culture	Expensive, not easily available, requires up to 4 wk to do test; not recommended
HIV RNA PCR	Preferred test to identify non-B subtype HIV-1infections. Similar sensitivity and specificity to HIV DNA PCR in infants and children younger than 18 mo of age, but DNA PCR is generally preferred because of greater clinical experience with that assay

PCR, polymerase chain reaction.

Data from American Academy of Pediatrics, Committee of Pediatric AIDS: Diagnosis of HIV-1 infection in children younger than 18 months in the United States, Pediatrics *120:e1547–e1562, 2007.*

developed countries. Almost 40% of infected newborns have positive test results in the 1st 2 days of life, with >90% testing positive by 2 wk of age. Plasma HIV RNA assays, which detect viral replication, are as sensitive as the DNA PCR for early diagnosis. HIV culture has similar sensitivity to HIV DNA PCR but is more technically complex and expensive, and results are often not available for several weeks compared with 2-3 days for PCR. The commercially available HIV-1 assays are not designed for quantification of HIV-2 RNA and thus should not be used to monitor patients with this infection.

Viral diagnostic testing should be performed within the 1st 12-24 hr of life. Almost 40% of HIV-infected children can be identified at this time. It seems that many of these children have a more rapid progression of their disease and deserve more aggressive therapy. Data suggest that if anti-HIV treatment will start at this point, the outcome will be much better. In exposed children with negative virologic testing at 1-2 days of life, additional testing should be done at 1-2 mo of age and at 4-6 mo of age; some also favor testing at age 14 days as almost 90% of the infected infants can be identified and ARV therapy can be initiated earlier. A positive virologic assay (i.e., detection of HIV by PCR, culture, or p24 antigen) suggests HIV infection and should be confirmed by a repeat test on a second specimen as soon as possible. A diagnosis of HIV infection can be made with 2 positive virologic test results obtained from different blood samples.

The perinatal use of ARV prophylaxis (either single drug or combination) to prevent vertical transmission has not affected the predictive value of viral diagnostic testing. In addition, the intensive antiviral combinations (protease inhibitors) in pregnant women do not affect the DNA PCR; however, these combinations may have an effect on the RNA PCR. HIV infection can be reasonably excluded if an infant has had at least 2 negative virologic test results with at least 1 test performed at ≥4 mo of age. In some parts of the world where non–subtype B strains are common (i.e., outside of the United States), interpretation of a negative PCR test result should be done with caution because the assay may not detect the particular subtype (e.g., group O). Close clinical monitoring with serologic testing (by 18 mo of age) or culture (if possible) is recommended. In older infants, 2 or more negative HIV antibody tests performed at least 1 mo apart past 6 mo of age in the absence of hypogammaglobulinemia or clinical evidence of HIV disease can reasonably exclude HIV infection. The infection can be excluded definitively if the same parameters are met when the infant is at least 18 mo of age.

Few surrogate markers (e.g., neopterin, β_2-microglobin) were shown to improve the predictive information of $CD4^+$ T-cell counts. These markers may be useful in places where $CD4^+$ T-cell counts are not available. Neopterin is an early marker of HIV infection and its level rises further as the disease progress to AIDS. β_2-Microglobin, which can be measured both in blood and urine, spikes in the acute phase of the disease, declines during the asymptomatic phase, and rises again as the disease progresses.

TREATMENT

The currently available therapy does not eradicate the virus and cure the patient; instead it suppresses the virus for extended periods of time and changes the course of the disease to a chronic process. Decisions about ARV therapy for pediatric HIV-infected patients are based on the magnitude of viral replication (viral load), CD4 lymphocyte count or percentage, and clinical condition. Because ARV therapy changes as new drugs become available, decisions regarding therapy should be made in consultation with an expert in pediatric HIV infection. Plasma viral load monitoring and measurement of CD4 values have made it possible to implement rational treatment strategies for viral suppression as well as to assess the efficacy of a particular drug combination. The following principles form the basis for ARV treatment: (1) uninterrupted HIV replication causes destruction of the immune system and progression to AIDS; (2) the magnitude of the viral load predicts the rate of disease progression, and the CD4 cell count reflects the risk of opportunistic infections and HIV infection complications; (3) cART, which includes at least 3 drugs with at least 2 different mechanisms of action, should be the initial treatment. Potent combination therapy that suppresses HIV replication to an undetectable level restricts the selection of ARV-resistant mutants; drug-resistant strains are the major factor limiting successful viral suppression and delay of disease progression; (4) the goal of sustainable suppression of HIV replication is best achieved by the simultaneous initiation of combinations of ARV agents to which the patient has not been exposed previously and that are not crossresistant to drugs with which the patient has been treated previously; (5) drug-related interactions and toxicities should be minimal; and (6) adherence to the complex drug regimens is crucial for a successful outcome.

Combination Therapy

As of 2014, 21 ARV drugs were approved by the FDA for use in HIV-infected adults and adolescents and 19 of them (Table 276-4) for the pediatric population (most of them available as liquid, powder, or small tablet/capsules). ARV drugs are categorized by their mechanism of action, such as preventing viral entrance into $CD4^+$ T cells, inhibiting the HIV reverse transcriptase or protease enzymes, or inhibiting integration of the virus into the human DNA. Within the reverse transcriptase inhibitors, a further subdivision can be made: **nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs)** and **nonnucleoside reverse transcriptase inhibitors (NNRTIs)** (see Fig. 276-3). The NRTIs have a similar structure to the building blocks of DNA (e.g., thymidine, cytosine). When incorporated into DNA, they act like chain terminators and block further incorporation of nucleosides, preventing viral DNA synthesis. Among the NRTIs, thymidine analogs (e.g., stavudine, zidovudine [ZDV]) are found in higher concentrations in activated or dividing cells producing >99% of the HIV virions population) and nonthymidine analogs (e.g., didanosine, lamivudine) have more activity in resting cells, which account for <1% of the HIV virions but may serve as a reservoir for HIV. Suppression of replication in both populations is thought to be an important component of long-term viral control. NNRTIs (i.e., nevirapine, efavirenz, etravirine, rilpivirine) act differently than the NRTIs. They attach to the reverse transcriptase and restrict its motility, reducing the activity of the enzyme. The **protease inhibitors** are potent agents that act farther along the viral replicative cycle. They bind to the site where the viral long polypeptides are cut to individual, mature, and functional core proteins that produce the infectious virions before they leave the cell. The virus entry into the cell is a complex process that involves several cellular receptors and fusion. Several drugs have been developed to prevent this process. The **fusion inhibitor,** enfuvirtide, which binds to viral gp41, causes conformational changes that prevent fusion of the virus with the $CD4^+$ cell and entry into the cell. Maraviroc is an example of a selective CCR5 coreceptor antagonist that blocks the attachment of the virus to this chemokine (an essential process in the viral binding and fusion to the

Text continued on p. 1660

Table 276-4 Summary of Antiretroviral Therapies Available in 2014

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS		Class adverse effects: Lactic acidosis with hepatic steatosis	
Abacavir (ABC) Ziagen, ABC Tablet: 300 mg Oral solution: 20 mg/mL Trizivir: combination of zidovudine (ZDV), lamivudine, ABC (300, 150, 300 mg) Epzicom: combination of lamivudine, ABC (300, 600 mg)	Children: ≥3 mo to 13 yr: 8 mg/kg bid (maximum dose 300 mg bid) >30 kg: 300 mg bid Children with viral load <40 copies/mm^3:16 mg/kg once daily (max 600 mg) Adolescents >16 yr and adults: 600 mg once daily Trizivir (>40 kg): 1 tablet bid Epzicom (>16 yr of age): 1 tablet bid	Common: nausea, vomiting, anorexia, fever, headache, diarrhea, rash Less common: hypersensitivity, lactic acidosis with hepatic steatosis, pancreatitis, elevated triglycerides, myocardial infarction	Can be given with food Genetic screening for HLAB*5701 is recommended prior to initiation of ABC-containing treatment. If test is positive avoid ABC. Do not restart ABC in patients who had hypersensitivity-like symptoms (e.g., flu-like symptoms)
Didanosine Videx, ddI Powder for oral solution (prepared with solution containing antacid): 10 mg/mL	2 wk to <3 mo: 50 mg/m^2 bid 3-8 mo: 100 mg/m^2 bid >8 mo: 120 mg/m^2 (maximum 200 mg per dose) bid Adolescents (>13 yr) and adults <60 kg: 250 mg once daily >60 kg: 400 mg once daily (to increase adherence) If combined with tenofovir <60 kg–200 mg once daily >60 kg–250 mg once daily	Common: diarrhea, abdominal pain, nausea, vomiting Less common: pancreatitis, peripheral neuropathy, electrolyte abnormalities, lactic acidosis with hepatic steatosis, hepatomegaly, retinal depigmentation	Food decreases bioavailability up to 50%. Take 30 min before or 2 hr after meal. Tablets dissolved in water are stable for 1 hr (4 hr in buffered solution) Drug interactions: antacids/gastric acid antagonists may increase bioavailability; possible decreased absorption of fluoroquinolones, ganciclovir, ketoconazole, itraconazole, dapsone, and some protease inhibitors. Combination with d4T enhances toxicity, also common if combined with tenofovir
Videx EC Capsule, delayed release: 125, 200, 250, 400 mg Generic: 200, 250, 400 mg	Children: not established 20-25 kg: 200 mg once daily 25-60 kg: 250 mg once daily ≥60 kg: 400 mg once daily	Same as for ddI	Same as for ddI
Emtricitabine Emtriva, FTC Capsules: 200 mg Oral solution: 10 mg/mL Truvada: combination FTC, tenofovir disoproxil fumarate (TDF) (200, 300 mg) Atripla: Combination FTC, TDF, efavirenz (EFV) (200, 300, 600 mg) Complera: combination of FTC, TDF, rilpivirine (RPV) (200, 300, 25mg) Stribild: combination of FTC, TDF, elvitegravir (EVG), cobicistat (COBI) (200, 300, 150, 150 mg)	Infants: 0-3 mo: 3 mg/kg once daily Children ≥3 mo to 17 yr: 6 mg/kg (maximum 240 mg) once daily >33 kg, adolescent and adult: 200 mg capsule or 240 mg solution once daily Truvada or Atripla or Complera or Stribild adult dose: 1 tablet once daily	Common: headache, insomnia, diarrhea, nausea, skin discoloration Less common: lactic acidosis with hepatic steatosis, neutropenia	Closely monitor patients with hepatitis B coinfection Can be given without regard to food. Oral solution should be refrigerated if temperature above 25°C (77°F)
Lamivudine Epivir, Epivir HBV, 3TC Tablet: 150 (scored), 300 mg (Epivir) 100 mg (Epivir HBV) Solution: 5 mg/mL (Epivir HBV), 10 mg/mL (Epivir) Combivir: combination of ZDV, lamivudine (300, 150 mg) Trizivir and Epzicom combination (see abacavir)	Neonates (<30 days): 2 mg/kg bid >1 mo: 4 mg/kg bid (maximum 150 mg bid) ≥30 kg: 150 mg bid or 300 mg once daily Children with VL <40 copies/mL: 8-10 mg/kg qd Combivir, Trizivir (>30 kg): 1 tablet bid Epzicom (>16 yr): 1 tablet qd	Common: headache, nausea Less common: pancreatitis, peripheral neuropathy, lactic acidosis with hepatic steatosis, lipodystrophy	No food restrictions Combination with ZDV may prevent ZDV resistance. Patient should be screened for hepatitis B virus (HBV) and if positive watched for HBV exacerbation when lamivudine is discontinued
Stavudine Zerit, d4T Capsule: 15, 20, 30, 40 mg Solution: 1 mg/mL	Neonates (0-13 days): 0.5 mg/kg bid 14 days to 30 kg: 1 mg/kg bid >30 kg: 30 mg bid	Common: headache, nausea, hyperlipidemia, fat maldistribution Less common: peripheral neuropathy, pancreatitis, lactic acidosis, hepatic steatosis	No food restrictions. Should not be administered with ZDV because of virologic antagonism. Higher incidence of lactic acidosis. Increased toxicity if combined with ddI

Continued

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Tenofovir Viread, TDF Tablet: 150, 200, 250, 300 mg Powder: 40 mg per 1 gr powder Truvada: combination of FTC, TDF (200, 300 mg) Atripla: Combination of FTC, TDF, EFV (200, 300, 600 mg) Complera: combination of FTC, TDF, RPV (200, 300, 25 mg) Stribild: combination of FTC, TDF, EVG, COBI (200, 300, 150, 150 mg)	2 to <12 yr: 8 mg/kg qd >12 yr and 35 kg, adolescent >12 yr and 35 kg and adult: 300 mg once daily Truvada, Atripla, Complera, and Stribild (see FTC)	Common: nausea, vomiting, diarrhea Less common: lactic acidosis with hepatic steatosis, hepatomegaly, reduced bone density, renal toxicity	High-fat meal increases absorption; coadministration with ddI may increase ddI toxicity, decrease atazanavir (ATV) levels (therefore boosting ATV with ritonavir is required). ATV and lopinavir (LPV) increase TDF levels and potential toxicity. Screen for HBV before TDF given, as exacerbation of hepatitis may occur when TDF is discontinued
Zidovudine Retrovir, AZT, ZDV Capsule: 100 mg Tablet: 300 mg Syrup: 10 mg/mL Injection: 10 mg/mL Combivir: combination of ZDV, lamivudine (300, 150 mg) Trizivir: Combination of ZDV, lamivudine, ABC (300, 150, 300 mg)	**Prophylaxis:** 0-6 wk: Premature infants: 1.5 mg/kg IV every 12 hr *or* 2 mg/kg orally every 12 hr for 2 wk (for gestational age 30 to 35 wk) or 4 wk (for gestational age <30 wk); then increase to 3 mg/kg every 12 hr to complete 6 wk (if needed) For gestational age >35 wk: 3 mg/kg/dose IV every 12 hr *or* 4 mg/kg orally every 12 hr **Treatment:** 6 wk to 18 yr: 240 mg/m^2 every 12 hr *or* 4 kg to <9 kg: 12 mg/kg bid 9 kg to <30 kg: 9 mg/kg bid >30 kg, adolescent and adult: 200 mg tid or 300 mg bid Combivir *or* Trizivir: 1 tablet bid	Common: bone marrow suppression (e.g., macrocytic anemia, leukopenia), headache, nausea, vomiting, anorexia Less common: liver toxicity, lactic acidosis with hepatic steatosis, myopathy, fat redistribution	No food restrictions Drug interactions: should not be given with d4T or doxorubicin Rifampin may increase metabolism Cimetidine, fluconazole, valproic acid may decrease metabolism Ganciclovir, IFN-α, ribavirin increase ZDV toxicity
NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		Class adverse effects: Rash is mild to severe, usually within 1st 6 wk. Discontinue the drug if severe rash (with blistering, desquamation, muscle involvement, or fever)	
Efavirenz Sustiva, EFV Capsule: 50, 200 mg Tablet: 600 mg Atripla combination of EFV, FTC, TDF (600, 200, 300 mg)	Children <3 yr: consult with expert Children ≥3 yr: 10 to <15 kg: 200 mg qd 15 to <20 kg: 250 mg qd 20 to <25 kg: 300 mg qd 25 to <32.5 kg: 350 mg qd 32.5 to <40 kg: 400 mg qd ≥40 kg: 600 mg qd or 370 mg/m^2 body surface area Atripla (see FTC)	Common: skin rashes, CNS abnormalities (e.g., abnormal dreams, impaired concentration, insomnia, depression, hallucination) Less common: increased liver enzymes; potentially teratogenic	Capsules can be opened for mixing in food. Can be given without regard to food except fatty foods (because absorption is increased 50%) Drug interactions: Efavirenz induces/inhibits CYP3A4 enzymes. Increase clearance of drugs metabolized by this pathway (e.g., antihistamines, sedatives and hypnotics, cisapride, ergot derivatives, warfarin, ethinyl estradiol) and several other ARVs (i.e., protease inhibitors). Drugs that induce CYP3A4 (e.g., phenobarbital, rifampin, rifabutin) decrease efavirenz levels. Clarithromycin levels decrease with EFV and azithromycin should be considered
Etravirine (ETR), Intelence, ETR, tablet: 25, 100, 200 mg	Children <6 yr: consult with expert 16 to <20 kg: 100 mg bid 20 to <25 kg: 125 mg bid 25 to <30 kg: 150 mg bid >30 kg, adolescent and adult: 200 mg bid	Common: nausea, rash, diarrhea Less common: hypersensitivity reactions	Given only with food. Tablets can be dispensed in water Inducer of CYP3A4 enzymes and inhibitor of CYP2C9 and CYP2C19, causing multiple interactions that should be checked before initiating ETR. Should not be given in combination with TPV, Fos-APV, ATZ, or other nonnucleoside reverse transcriptase inhibitors

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Nevirapine Viramune, NVP Tablet: 200 mg Extended-release (XR) tablet: 100, 400 mg Suspension: 10 mg/mL	**Prophylaxis:** For infant of woman with no antepartum ARV treatment: 2 mg/kg birth to 48 hr 2 mg/kg 48 hr after 1st dose 2 mg/kg 96 hr after 2nd dose **Treatment:** <8 yr: 200 mg/m^2 once daily for 14 days; then same dose bid (maximum 200 mg per dose) or XR 400 mg qd >8 yr: 120-150 mg/m^2 once daily for 14 days; then bid (maximum 200 mg per dose) Adolescent and adult: 200 mg once daily for 14 days; then 200 mg bid *or* XR 400 mg qd	Common: skin rash, headache, fever, nausea, abnormal liver function tests Less common: hepatotoxicity (rarely life-threatening), hypersensitivity reactions	No food restrictions Drug interactions: induces hepatic CYP450A enzymes (including CYP3A and CYP2B6) activity and decreases protease inhibitor concentrations (e.g., IND, SQV, LPV). Should not be given with ATV. Reduces ketoconazole concentrations (fluconazole should be used as an alternative). Rifampin decreases nevirapine serum levels. Anticonvulsants and psychotropic drugs using same metabolic pathways as NVP should be monitored. Oral contraceptives may also be affected
Rilpivirine Edurant, RPV Tablet: 25 mg Complera combination of RPV, FTC, TDF (25, 200, 300 mg)	Pediatrics: consult with expert Adolescent (>18 yr) and adult: 25 mg	Headache, insomnia, rash, depression, mood changes	Given with food only Should not be used if viral load >100,000 copies/mm^3 or drugs that induce CYP3A or with proton pump inhibitors
PROTEASE INHIBITORS		Class adverse effects: hyperglycemia, hyperlipidemia (except atazanavir), lipodystrophy, increased transaminases, increased bleeding disorders in hemophiliacs. Can induce metabolism of ethinyl estradiol; use alternate contraception (other than estrogen-containing oral contraceptives). All undergo hepatic metabolism, mostly by CYP3A4, with many drug interactions	
Atazanavir Reyataz, ATV Capsules: 100, 150, 200, 300 mg	<6 yr: consult with expert 6-18 yr: 15 to <20 kg: 150 mg + 100 RTV qd 20 to 40 kg: 200 mg + 100 RTV qd >40 kg, adolescent and adult: 300 mg + 100 RTV qd *or* 400 mg if unboosted with food If given with EFV (600 mg) or TDF (300 mg): 400 mg + 100 RTV qd	Common: elevation of indirect bilirubin; headache, arthralgia, depression, insomnia, nausea, vomiting, diarrhea, paresthesias Less common: prolongation of PR interval on electrocardiogram (ECG); rash, rarely Stevens-Johnson syndrome, diabetes mellitus, nephrolithiasis	Administer with food to increase absorption. Review drug interactions before initiating because ATV inhibits CYP3A4, CYP1A2,CYP2C9, and UGT1A1 enzymes. Use with caution with cardiac conduction disease or liver impairment. Combination with EFV should not be used in treatment-experienced patients because it decreases ATV levels. TDF, antacids, H_2-receptor antagonists, and proton-pump inhibitors decreases ATV concentrations. Patients taking buffered ddI should take it at least 2 hr before ATV
Darunavir Prezista, DRV Tablets: 75, 150, 400, 600, 800 mg Suspension: 100 mg/mL	<3 yr: consult with expert 3 to <18 yr: 10 to <15 kg: 20 mg/kg DRV + 3 mg/kg RTV 15 to <30 kg: 375 mg DRV + 50 mg RTV bid 30 to <40 kg: 450 DRV mg + 100 mg RTV bid >40 kg, adolescent and adult: 600 mg DRV + 100 mg RTV bid *or* Adolescent (>12 yr and 40 kg) and adult: 800 mg DRV + 100 mg RTV qd with food If any DRV resistance is found: 600 mg DRV = 100 mg RTV bid	Common: diarrhea, nausea, vomiting, abdominal pain, fatigue, headache Less common: skin rashes (including Stevens-Johnson syndrome), lipid and liver enzyme elevations, hyperglycemia, fat maldistribution	DRV should not be given without food. Contraindicated for concurrent therapy with cisapride, ergot alkaloids, benzodiazepines, pimozide, or any major CYP3A4 substrates. Use with caution in patients taking strong CYP3A4 inhibitors, or moderate/strong CYP3A4 inducers. Adjust dose with concurrent rifamycin therapy. Contains sulfa moiety: potential for cross-sensitivity with sulfonamide class

Continued

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Fosamprenavir Lexiva, FPV Tablets: 700 mg Suspension: 50 mg/mL	6 mo to 18 yr: <11 kg: 45 mg/kg FPV + 7 mg/kg RTV bid 11 to <15 kg: 30 mg/kg + 3 mg/kg RTV bid 15 to <20 kg: 23 mg/kg + 3 mg/kg RTV bid >20 kg: 18 mg/kg (max 700 mg) + 3 mg/kg (max: 100 mg) RTV bid Adolescent >18 yr and adult: FPV 700 mg + RTV 100 mg bid *or* FPV 1,400 mg + RTV 200 mg qd For protease inhibitor (PI)-experienced, the once daily dose is not recommended	Common: nausea, vomiting, perioral paresthesias, headache, rash, lipid abnormalities Less common: Stevens-Johnson syndrome, fat redistribution, neutropenia, elevated creatine kinase, hyperglycemia, diabetes mellitus, elevated liver enzymes, angioedema, nephrolithiasis	Should be given with food. FPV is an inhibitor of the CYP450 system and an inducer, inhibitor, and substrate of CYP3A4, which can cause multiple drug interactions. Use with caution in sulfa-allergic individuals
Indinavir Crixivan, IDV Capsule: 100, 200, 400 mg	Infants: not approved Children: 500 mg/m^2 every 8 hr (max dose: 800 mg per dose) *or* 400 mg/m^2 + RTV 100 mg/m^2 bid Adolescent and adult: 800 mg IDV + 100 *or* 200 mg RTV bid	Common: nausea, abdominal pain, hyperbilirubinemia, headache, dizziness, lipid abnormalities, nephrolithiasis, metallic taste Less common: fat redistribution, hyperglycemia, diabetes mellitus, hepatitis, acute hemolytic anemia	Administer on empty stomach if given without RTV. Reduce dose (600 mg IDV every 8 hr) with mild to moderate liver dysfunction. Adequate hydration (at least 48 oz fluid/day in adults) necessary to minimize risk of nephrolithiasis. IDV is cytochrome P450 3A4 inhibitor and substrate, which can cause multiple drug interactions: rifampin reduces levels; ketoconazole, ritonavir, and other protease inhibitors increase IDV levels. Do not coadminister with EFV, astemizole cisapride, terfenadine
Lopinavir/Ritonavir Kaletra, LPV/r Tablets: 100/25 mg, 200/50 mg Solution: 80/20 mg per/mL (contains 42% alcohol)	14 days to 18 yr: 300 mg/m^2 LPV +75 mg/m^2 RTV bid Adolescent (>18 yr) and adult: 400 mg LPV +100 mg RTV bid *or* 800 mg LPV +200 mg RTV qd If taken with NVP, EFV, FPV, or NFV: LPV 600 mg + RTV 150 mg bid	Common: diarrhea, headache, nausea and vomiting, lipid elevation Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation	No food restrictions. High-fat meal and flavoring of solution to increase palpability are recommended if oral solution is used. Interacts with drugs using CYP3A4, which can cause multiple drug interactions
Nelfinavir Viracept, NFV Tablet: 250, 625 mg	<2 yr: not recommended Children 2-13 yr: 45-55 mg/kg bid Adolescents and adults: 1,250 mg bid	Common: diarrhea asthenia, abdominal pain, skin rashes, lipid abnormalities Less common: exacerbation of liver disease, fat redistribution, hyperglycemia, diabetes mellitus, elevation of liver enzymes	Administer with a meal to optimize absorption; avoid acidic food or drink (e.g., orange juice). Tablet can be crushed or dissolved in water to administer as a solution Drug interactions: Nelfinavir inhibits CYP3A4 activity, which may cause multiple drug interactions. Rifampin, phenobarbital, and carbamazepine reduce levels. Ketoconazole, ritonavir, indinavir, and other protease inhibitors increase levels. Do not coadminister astemizole, cisapride, terfenadine. RTV boosting has no effect. Because of very high variation in plasma levels, TDM should be used for dose adjustment

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Ritonavir Norvir, RTV Capsule: 100 mg Tablet: 100 mg Solution: 80 mg/mL (contains 43% alcohol)	Only use is to enhance other PIs; dose varies (see information for specific PI)	Common: nausea, headache, vomiting, abdominal pain, diarrhea, taste aversion, lipid abnormalities, perioral paresthesias Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation, allergic reactions	Administration with food enhances bioavailability and reduces gastrointestinal symptoms. RTV solution should not be refrigerated RTV is potent inhibitor of CYP3A4 and CYP2D6 and inducer of CYP3A4 and CYP1A2 that leads to many drug interactions (e.g., protease inhibitors, antiarrhythmics, antidepressants, cisapride). Use cautiously with inhaled steroids
Saquinavir Invirase, SQV Hard gel: 200 mg Film-coated tablets: 500 mg	Infants and children <2 yr: not established SQV must be boosted with RTV >2 yr: 5 to <15 kg: 50 mg/kg + 3 mg/kg RTV bid 15-40 kg: 50 mg/kg + 2.5 mg/kg RTV bid >40: 50 mg/kg + 100 RTV bid Adolescent and adult: SQV 1,000 mg + 100 mg RTV bid	Common: diarrhea, abdominal pain, headache, nausea, skin rashes, lipid abnormalities Less common: exacerbation of chronic liver disease, diabetes mellitus, pancreatitis, elevated liver transaminases, fat maldistribution, increase in both QT and PR in ECG	Administration with a high-fat meal to enhance bioavailability. Use only in combination with ritonavir boosting dose. SQV is metabolized by CYP3A4, which may cause many drug interactions): rifampin, phenobarbital, and carbamazepine decrease serum levels. Saquinavir may decrease metabolism of calcium channel antagonists, azoles (e.g., ketoconazole), macrolides
Tipranavir Aptivus, TPV Capsule: 250 mg Solution 100 mg/mL (contains 116 IU vitamin E/mL)	<2 yr: not established. 2-18 yr: 375 mg/m^2 TPV + 150 mg/m^2 RTV (maximum 500 mg TPV + 200 mg RTV) bid *or* 14 mg TPV + 6 mg RTV per kg (maximum-same) bid Adolescent (>18 yr) and adult: 500 mg TPV +200 mg RTV bid	Common: diarrhea, nausea, vomiting, fatigue, headache, skin rashes, elevated liver enzymes, lipid abnormalities Less common: fat redistribution, hepatitis, hyperglycemia, diabetes mellitus, intracranial hemorrhage	No food restrictions. Better tolerated with meal. TPV must be boosted with RTV. Can inhibit human platelet aggregation: use with caution in patients at risk for increased bleeding (trauma, surgery, etc.) or in patients receiving concurrent medications that may increase the risk of bleeding. TPV is metabolized by CYP3A4, which may cause many drug interactions. Contraindicated in patients with hepatic insufficiency or receiving concurrent therapy with amiodarone, cisapride, ergot alkaloids, benzodiazepines, pimozide. TPV contains sulfonamide moiety and caution should be taken in patients with sulfonamide allergy
FUSION INHIBITORS			
Enfuvirtide Fuzeon, ENF Injection: lyophilized powder of 108 mg reconstituted in 1.1 mL of sterile water delivers 90 mg/mL	<6 yr: not established Children >6 yr to 16 yr: 2 mg/kg SQ (maximum 90 mg) bid Adolescent and adult: 90 mg SQ bid	Common: Local injection site reactions in 98% (e.g., erythema, induration nodules, cysts, ecchymoses) Less common: increased incidence of bacterial pneumonia, hypersensitivity, fever, nausea, vomiting, chills, elevated liver enzymes, hypotension, immune-mediated reactions (e.g., glomerulonephritis, Guillain-Barré syndrome, respiratory distress)	Must be given subcutaneously. Severity of reactions increased if given intramuscularly. Apply ice after injection and massage the area to reduce local reactions. Injection sites should be rotated

Continued

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
ENTRY INHIBITORS			
Maraviroc Selzentry, MVC Tablets: 150, 300 mg	Not approved for children or adolescents <16 yr Adolescents >16 yr and adults: 150 mg bid if given with potent CYP3A inhibitor (e.g., protease inhibitor except TPV) 300 mg bid if given with not potent CYP3A4 inhibitors (e.g., NRTI, TPV, NVP, ENF, RAL) 600 mg bid if given with potent CYP3A4 inducer (e.g., EFV, ETR, rifampin, phenobarbital)	Common: fever, upper respiratory infection–like symptoms, rash, abdominal pain, musculoskeletal symptoms, dizziness Less common: cardiovascular abnormalities, cholestatic jaundice, rhabdomyolysis, myositis, osteonecrosis	No food restrictions. MVC is a CYP3A4 and P-glycoprotein (Pgp) substrate, which may cause many drug interactions Tropism assay to exclude the presence of CXCR4 HIV is required before using MVC. Caution should be used when given to patients with hepatic impairment or cardiac disease or receiving CYP3A4 or Pgp modulating drugs
INTEGRASE INHIBITORS			
Dalutegravir Tivicay, DTG Tablet: 50 mg	Children <12 yr: consult with expert >12 yr and 40 kg, adolescents, and adults: 50 mg qd If taken with EFV, FPV, TPV, or rifampin: 50 mg bid	Insomnia Headache	No food restrictions UGT1A1 and CYP450 (CYP) 3A substrate Should be taken 2 hr before or 6 hr after taking laxatives, sucralfate, iron or calcium supplements, or buffered medications
Elvitegravir EVG Only as Stribild combination of EVG, FTC, TDF, cobicistat (COBI) (150, 200, 300, 150 mg)	Children and adolescents (<18 yr): not established Adolescent (>18 yr) and adult: 1 tablet qd	Common: nausea, diarrhea Less common: increased serum creatinine, urea, and phosphate, decreased bone density; lactic acidosis, hepatomegaly with stenosis	Administer with food EVG is metabolized by CYP3A4 and modestly induces CYP2D6 that can cause multiple drug interactions. Cautiously use with nephrotoxic drugs. Stribild should not be used with ritonavir
Raltegravir Isentress, RAL Film-coated tablet: 400 mg Chewable tablet: 25, 100 mg Solution: 20 mg/ml	Oral solution: 3 to <4 kg: 20 mg bid 4 to <6 kg: 30 mg bid 6 to <8 kg: 40 mg bid 8 to <11 kg: 60 mg bid 11 to <14 kg: 80 mg bid 14 to <20 kg: 100 mg bid Chewable tablet: 10 to <14 kg: 75 mg bid 14 to <20 kg: 100 mg bid 20 to <28 kg: 150 mg bid 28 to <40 kg: 200 mg bid Adolescent (>12 yr) and adult: 400 mg bid	Common: nausea, headache, dizziness, diarrhea, fatigue Less common: abdominal pain, vomiting, itching, creatine phosphokinase elevation, myopathy, rhabdomyolysis, depression, hypersensitivity	No food restrictions Film-coated tablet and chewable tablet are not interchangeable RAL is metabolized by UGT1A1 glucuronidation, and inducers of this system (e.g., rifampin, TPV) will reduce RGV levels, whereas inhibitors (e.g., ATV) will increase it

Antiretroviral drugs often have significant drug–drug interactions, with each other and with other classes of medicines, which should be reviewed before initiating any new medication.

The information in this table is not all-inclusive. Updated and additional information on dosing, drug–drug interactions, and toxicities is available on the AIDSinfo website at http://www.aidsinfo.nih.gov

Modified from the Guidelines for use of antiretroviral agents in pediatric HIV infection. *http://aidsinfo.nih.gov/contentFiles/PediatricGuidelines.pdf*

CD4+ cells). **Integrase inhibitors** like raltegravir block the enzyme that catalyzes the incorporation of the viral genome into the host's DNA.

While the principal site of viral replication is lymphoid tissue, sanctuary sites such as the CNS may harbor residual virions with the potential to be a source of local or persistent disease. Impaired penetration of drugs to these compartments could result in development of resistance. Although data on CNS penetration of antiviral agents are presently limited, ZDV, stavudine, and lamivudine appear to achieve inhibitory concentrations in the CNS. Nevirapine and efavirenz also penetrate the cerebrospinal fluid, but protease inhibitors are actively transported out of the CNS, thereby limiting their potential efficacy at this site.

By targeting different points in the viral life cycle and stages of cell activation and by delivering drug to all tissue sites, maximal viral suppression may be feasible. Combinations of 3 drugs, a thymidine analog NRTI (abacavir or ZDV) and a nonthymidine analog NRTI (lamivudine) to suppress replication in both active and resting cells and a protease inhibitor (atazanavir or lopinavir/ritonavir) or an NNRTI (efavirenz) produce prolonged viral suppression. Less-potent combinations, such as triple NRTIs (abacavir, zidovudine, lamivudine), may be considered in special situations (e.g., children <3 yr with concomitant tuberculosis when nevirapine-based cART is unacceptable or in rare cases when there are concerns about significant drug interactions or adherence to a complex drug regimen). The use of 3 drugs from 3 different classes should be avoided as it has the potential to cause resistance to 3 drug classes. Combination treatment increases the rate of toxicities (see Table 276-4), and complex drug–drug interactions exist among many of the antiretroviral drugs. Many protease inhibitor drugs are inducers or inhibitors of the cytochrome P450 system and are therefore likely to have serious interactions with multiple drug classes, including nonsedating antihistamines and psychotropic, vasoconstrictor, antimycobacterial, cardiovascular, analgesic, and gastrointestinal drugs (cisapride). Whenever new medications are added

to an antiretroviral treatment regimen, especially a protease inhibitor–containing regimen, a pharmacist and/or HIV specialist should be consulted to address possible drug interactions. The inhibitory effect of ritonavir (a protease inhibitor) on the cytochrome P450 system has been exploited, and small doses of the drug are added to several other protease inhibitors (e.g., lopinavir, tipranavir, atazanavir, darunavir) to slow their metabolism by the P450 system and to improve their pharmacokinetic profile. This strategy provides more effective drug levels with less toxicity and less-frequent dosing. Recently, the development of cobicistat provides an alternative to ritonavir. Although cobicistat is a potent inhibitor of cytochrome P450 3A, it is a weak inhibitor of CYP2D6 and other CYP isoforms (e.g., CYP1A2), making pharmacologic interactions with many drugs more predictable than for ritonavir, which is also active against these isoforms. Preliminary studies with cobicistat suggest that it has a good tolerability profile and less effect on adipocytes (resulting in milder accumulation of lipid and response to insulin). The better solubility of cobicistat compared to ritonavir may foster the availability of more single-tablet combination regimens with cobicistat.

Adherence

Adherence to the medication schedules and dosages is fundamental to ARV therapy success. Therefore, assessment of the likelihood of adherence to treatment is an important factor in deciding whether and when to initiate therapy. Numerous studies show that compliance of <90% results in less-successful suppression of the viral load. In addition, several studies document that almost half of the pediatric patients surveyed were nonadherent to their regimen. Poor adherence to prescribed medication regimens results in subtherapeutic drug concentrations and enhances development of resistance. Several barriers to adherence are unique to children with HIV infection. Combination antiretroviral regimens are often unpalatable and require extreme dedication on the part of the caregiver and child; a reluctance to disclose the child's disease to others reduces social support; there may be a tendency to skip doses if the caregiver is not around or when the child is in school. Adolescents have other issues that reduce adherence. Denial and/or fear of their infection, unstructured lifestyle, conduct or emotional disorder, wishing to be the same as their peers, depression, fatigue from taking a lifelong regimen, anxiety, and alcohol and substance abuse are just a few of the barriers for a long-term adherence in this growing population. These and other barriers make participation of the family in the decision to initiate therapy essential. Intensive education on the relationship of drug adherence to viral suppression, training on drug administration, frequent follow-up visits, peer support, pager messaging, and commitment of the caregiver and the patient (despite the inconvenience of adverse effects, dosing schedule) are critical for successful antiviral treatment. Multiple methods such as viral load response, self-reporting of missed doses during the last 3-7 days, and pharmacy/pill counting or monitoring drugs' concentrations in the blood should be used to assess adherence.

Initiation of Therapy

The decision on when to initiate cART is controversial and keeps evolving. Even the recent adult guidelines that recommend initiation of cART in individuals with CD4 cell counts <500 cells/µL acknowledges that treatment of individuals with higher CD4 cell counts may be beneficial. Therefore, the following recommendations for pediatric patients are only accurate for the time they were written (August 2014), and physicians providing care to few HIV-exposed or infected children should periodically consult physicians with expertise in pediatric HIV infection as well as the U.S. pediatric guidelines for treatment of HIV-infected children found at http://aidsinfo.nih.gov.

Children younger than 1 yr of age are at high risk for disease progression, and immunologic and virologic tests to identify those likely to develop rapidly progressive disease are less predictive than in older children. Therefore, HIV-infected infants younger than 1 yr of age should be treated with ARV agents as soon as the diagnosis of HIV infection has been confirmed, regardless of clinical or immunologic status or viral load. Data suggest that HIV-infected infants who are treated before the age of 3 mo control their HIV infection better than infants whose ARV therapy started later than 3 mo of age. Some of these infants even become HIV seronegative and lose their HIV specific immune response.

There is still a debate on when to start therapy in children older than 1 yr of age. The 2014 U.S. Pediatric Guidelines Panel recommends, with varying strength of the recommendations, treating all children ≥1 year of age with Stage 3 CD4 counts, significant clinical symptoms, or HIV RNA >100,000 copies/mL. Children 1-<6 years of age should be treated with CD4 counts between 500-999 cells/mm^3, and treatment should be considered if the child has minimal/no symptoms and a CD4 count ≥1000 cells/mm^3. Children ≥6 years of age should be treated with CD4 counts between 200-499 cells/mm^3, and treatment should be considered if the child has minimal/no symptoms and a CD4 count ≥500 cells/mm^3. These guidelines are reviewed yearly, and care providers should check for revisions at http://aidsinfo.nih.gov. Some clinicians advocate treating all HIV-infected children regardless of their clinical stage, viral load, or CD4$^+$ T-cell status to prevent the inevitable immunologic deterioration that will otherwise occur.

Dosing

Children are usually treated with higher doses (per kg weight) than adults because of reduced absorption or increased elimination. Data on ARV drug dosages for neonates, especially premature infants, are often limited. Because of the immaturity of the neonatal liver, there must often be an increase in the dosing interval of drugs primarily cleared through hepatic glucuronidation. In addition, drug absorption from the gastrointestinal tract may be problematic. Therefore, monitoring of drugs plasma levels should be considered, if available.

Adolescents should have ARV dosages prescribed on the basis of Tanner staging of puberty rather than on the basis of age. Pediatric dosing ranges should be used during early puberty (Tanner stages I, II, and III), whereas adult dosing schedules should be followed in adolescents in late puberty (Tanner stages IV and V). Efavirenz should be avoided in females who may become pregnant and do not use effective contraception because of its potential teratogenicity. Because some protease inhibitors may change the metabolism of oral contraceptives and decrease their effectiveness, monthly injections of medroxyprogesterone (DMPA) or use of an intrauterine device should be considered, or the protease inhibitor can be changed, if needed, to an integrase inhibitor, which has no interaction with estrogen-based contraceptives.

Changing Antiretroviral Therapy

Therapy should be changed when the current regimen is judged ineffective as evidenced by increase in viral load, deterioration of the CD4 cell count, or clinical progression. Development of toxicity or intolerance to drugs is another reason to consider a change in therapy. When a change is considered, the patient and family should be reassessed for adherence problems. Because adherence is a major issue in this population, resistance testing (while on ARV medications) is important in identifying adherence issues (e.g., detectable virus sensitive to current drugs will suggest lack of adherence) or development of resistance (e.g., evidence of resistance mutations to given drugs). In both situations, other contributing factors such as poor absorption, incorrect dose, or drug–drug interactions should be carefully reviewed. While considering possible new drug choices, potential cross-resistance should be addressed. In addition, few patients who have virologic failure may still demonstrate improved CD4 cell counts (discordant response). Impaired replication ability of the resistant virus (also called reduced viral fitness) and enhanced CTL effects are some of the reasons for this discordant response. In these patients, delay in changing therapy should be considered as long as the immunologic benefit is evident. Ideally, when a decision is made to change the ARV therapy, all drugs should be changed. However, in many situations (previous ARV experience, intolerance, toxicity) this is not possible, thus at least 2 drugs should be changed based on the resistance mutation genotype or phenotype (if available) or evaluation of the drugs used in the previous regimen.

Monitoring Antiretroviral Therapy

To ensure proper monitoring, the CD4 cells count, viral load, complete blood count, chemistries, urinalysis, and serum lipids should be done before initiation or change in cART to have a baseline for comparisons while on treatment. Children need to be seen within 1-2 wk after initiation of new ARV therapy to ensure compliance and to screen for potential side effects. Virologic and immunologic surveillance (using HIV RNA copy number and CD4 lymphocyte count or percentage) as well as clinical assessment should be performed regularly during ARV therapy. Initial virologic response (i.e., at least a 5-fold [0.7 $\log_{10}$] reduction in viral load) should be achieved within 4-8 wk of initiating antiretroviral therapy. The maximum response to therapy usually occurs within 12-16 wk, but may be later (24 wk) in very young infants. Thus, HIV RNA levels should be measured at 4 wk and 3-4 mo after therapy initiation. Once an optimal response has occurred, viral load should then be measured at least every 3-6 mo. If the response is unsatisfactory, another viral load should be performed as soon as possible to verify the results before a change in therapy is considered. The CD4 cells respond more slowly to successful treatment and, therefore, can be monitored less frequently. Potential toxicity should be monitored closely for the 1st 8-12 wk (including complete blood count, serum chemistries, urinalysis, and lipids), and if no clinical or laboratory toxicity is documented, a follow-up visit every 3-4 mo is adequate. Monitoring for potential toxicity should be tailored to the drugs taken. These toxicities include but are not limited to hematologic complications (e.g., ZDV); hypersensitivity rash (e.g., efavirenz); lipodystrophy (e.g., redistribution of body fat seen with NRTIs, protease inhibitors); hyperlipidemia (elevation of cholesterol and triglyceride concentrations); hyperglycemia, and insulin resistance (e.g., protease inhibitors); mitochondrial toxicity leading to severe lactic acidosis (e.g., stavudine, didanosine); electrocardiogram abnormalities (e.g., atazanavir, lopinavir); abnormal bone mineral metabolism (e.g., tenofovir); and hepatic toxicity, including severe hepatomegaly with steatosis.

Resistance to Antiretroviral Therapy

Young children usually are at greater risk than adults for developing resistance because they have higher viral loads than adults and are more limited by which ARV options are available. The high mutation rate of HIV (mainly as a result of the absence of error-correcting mechanisms) severely impairs the success of ARV therapy. Failure to reduce the viral load to <40 copies/mL increases the risk for developing resistance. Even effectively treated patients do not completely suppress viral replication, and persistence of HIV transcription and evolution of envelope sequences continues in the latent cellular reservoirs. The accumulation of resistance mutations progressively diminishes the potency of the ARV therapy and challenges the physician to find new regimens. For some drugs (e.g., nevirapine, lamivudine) a single mutation is associated with resistance, whereas for other drugs (e.g., ZDV, lopinavir) several mutations are needed before resistance develops. Testing for drug resistance, especially when devising a new regimen, is becoming the standard of care. Two types of tests are available: (1) The **phenotypic assay** measures the virus susceptibility in various concentrations of the drug that allows calculation of the drug concentration that inhibits viral replication by 50% (IC_{50}). The ratio of the IC_{50} and a reference virus IC_{50} is reported as fold resistance change. (2) The **genotypic assay** predicts the virus susceptibility from mutations identified in the HIV genome isolated from the patient. Several online sites (e.g., http://hivdb.stanford.edu) can assist in interpreting the test's results. Several studies show that treatment success is higher in patients whose ARV therapy was guided by genotype or phenotype testing. Neither method may detect drug resistance if the amount of the resistant virus is <10% of the circulating population or if it is present only in the latent reservoir.

It is recommended to test for drug resistance before initiating therapy and before changing treatment because of failure. When changing therapy, the resistance test results should be considered in the context of previous resistance tests results, if done, and drugs used in previous regimens.

Supportive Care

Even before ARV drugs were available, a significant impact on the quality of life and survival of HIV-infected children was achieved when supportive care was given. A multidisciplinary team approach is desirable for successful management. Following initiation or change of cART, more frequent visits or contacts with the patient/caregivers for support and education will help in their acceptance and adjustment to the new regimen and will contribute to a better adherence. Close attention should be paid to nutritional status, which is often delicately balanced and may require aggressive supplementation. Painful oropharyngeal lesions and dental caries may interfere with eating, and thus routine dental evaluations and careful attention to oral hygiene should be encouraged. Paradoxically, an increasing number of adolescents with perinatally acquired or behavioral risk-acquired disease are obese. Some teens experience ARV-related central lipo-accumulation, but others have poor dietary habits and inactivity as the cause of their obesity, in parallel to epidemic obesity in the United States. Development should be evaluated regularly with provision of necessary physical, occupational, and/or speech therapy. Recognition of pain in the young child may be difficult, and effective nonpharmacologic and pharmacologic protocols for pain management should be instituted.

All infants born to HIV-infected mothers should receive ZDV prophylaxis for 4-6 wk. Additional ARV therapy should be considered if the risk of acquiring HIV by the newborn is high. For example, if the mother has not received cART during pregnancy, 3 doses of nevirapine (at birth, 48 hr, and 144 hr of life) should be added. If the mother's HIV status is unknown, rapid HIV-testing of either the mother or the newborn should be done immediately after delivery and if positive, ARV prophylaxis should be started as soon as possible without waiting for the confirmatory test results. Guidelines for prophylaxis in newborns are updated at least yearly and can be accessed at http://www.aidsinfo.nih.gov. A complete blood count, differential leukocyte count, and platelet count should be performed at 4 wk of age to monitor ZDV toxicity. These tests should be continued every 1-3 mo to assess the hematologic effect of ZDV and prophylactic trimethoprim-sulfamethoxazole (TMP-SMZ), if given. If the child is found to be HIV infected, baseline laboratory assessment (e.g., CD4 count, HIV RNA, complete blood count, chemistries) should be done and cART should be started as soon as possible. Viral load and CD4 lymphocyte counts should be performed at 1 and 3 mo of age and should be repeated every 3 mo. All HIV-exposed and infected children should receive standard pediatric immunizations. In general, live oral polio vaccine should not be given (Fig. 276-4). The risk and benefits of rotavirus vaccination should be considered in infants born to HIV-infected mothers. Because <1% of these infants in resource-rich countries will develop HIV infection, the vaccine should be given. In other situations, the considerable attenuation of the vaccine's strains should be taken into account and unless the infant has clinical symptoms of AIDS or CD4 <15%, vaccination seems to be appropriate. Other live bacterial vaccines (e.g., bacillus Calmette-Guérin) should be avoided because of the high incidence of bacillus Calmette-Guérin–related disease in HIV-infected infants. Varicella and measles-mumps-rubella vaccines are recommended for children who are not severely immunosuppressed (i.e., CD4 cell percentage ≥15%), but these vaccines should not be given to severely immunocompromised children (i.e., CD4 cell <15%). Of note, prior immunizations do not always provide protection, as evidenced by outbreaks of measles and pertussis in immunized HIV-infected children. Durability of vaccine-induced titers is often short, especially if vaccines are administered when the child's CD4 cell is <15%, and re-immunization when the CD4 count has increased (i.e., >15%) may be indicated.

Prophylactic regimens are integral for the care of HIV-infected children. All infants between 4-6 wk and 1 yr of age who are proven to be HIV-infected should receive prophylaxis to prevent *P. carinii (*also called *P. jiroveci*) infection regardless of the CD4 count or percentage (Tables 276-5 and 276-6). Infants exposed to HIV-infected mothers should receive the same prophylaxis until they are proven to be noninfected; however, prophylaxis does not have to be initiated if there is strong presumptive evidence of noninfection (i.e., non–breastfed

Vaccine	Birth	1 mo	2 mo	4 mo	6 mo	12 mo	15 mo	18 mo	24 mo	4-6 yr	11-12 yr	14-16 yr
Hepatitis B	Hep B	Hep B			Hep B							
Measles, Mumps, Rubella*						MMR†	MMR†					
Influenza					Influenza‡							
Pneumococcal Conjugate and Hemophilus b			PCV Hib	PCV Hib	PCV Hib	PCV Hib					Pneumococcal§	
Diphtheria, Tetanus, Pertussis			DTap	DTap	DTap		DTap					
Polio (inactivated)			Polio	Polio	Polio							
Varicella						Varicella						
Hepatitis A						Hep A◊						
Rotavirus*			RV¶	RV	RV							

* See text.
† Contraindicated in children with AIDS or CD4$^+$ <15%. Give 2 doses 1-3 mo apart.
‡ Revaccination is recommended every year. Attenuated vaccine can be used >2 yr of age only if CD4$^+$ >15%.
§ Revaccination with pneumococcal polysaccharide vaccine (PPV) every 5 yr.
◊ Two doses at least 6 mo apart.
¶ First dose 6 through 14 wk of age and final dose no later than 8 mo 0 days of age. If using Rotarix, only 2 doses (2 and 4 mo) are needed.

Figure 276-4 Routine childhood immunization schedule for HIV-infected children.

Table 276-5 Recommendations for PCP Prophylaxis and CD4 Monitoring for HIV-Exposed Infants and HIV-Infected Children, by Age and HIV Infection Status

AGE/HIV INFECTION STATUS	PCP PROPHYLAXIS	CD4 MONITORING
Birth to 4-6 wk, HIV exposed	No prophylaxis	None
HIV infection reasonably excluded*	No prophylaxis	None
<1 yr, HIV-infected or indeterminate	Prophylaxis regardless of CD4 count or percentage	According to local practice for initiation or follow-up of cART
1-5 yr, HIV infected	Prophylaxis if: CD4 <500 cells/µL or <15%†	According to local practice for initiation or follow-up of cART
>6 yr, HIV infected	Prophylaxis if: CD4 <200 cells/µL or <15%†‡	According to local practice for initiation or follow-up of cART

The National Perinatal HIV Hotline (1-888-448-8765) provides consultation on all aspects of perinatal HIV care.
*See text.
†More frequent monitoring (e.g., monthly) is recommended for children whose CD4 counts or percentages are approaching the threshold at which prophylaxis is recommended.
‡Prophylaxis should be considered on a case-by-case basis for children who might otherwise be at risk for PCP, such as children with rapidly declining CD4 counts or percentages or children with category C conditions. Children who have had PCP should receive PCP prophylaxis until their CD4 count is >20% (for >6 yr of age) or >25% (for 2-5 yr of age) on continuous cART.
cART, combined antiretroviral therapy; PCP, *Pneumocystis carinii* (also called *P. jirovecii*) pneumonia.

infant with 2 negative HIV PCR tests at older than 14 days and 4 wk of age, respectively). When the HIV-infected child is older than 1 yr of age, prophylaxis should be given according to the CD4 lymphocyte count (Table 276-5). The best prophylactic regimen is 150 mg/m^2/day of TMP and 750 mg/m^2/day of SMZ (maximum: 320/1,600 mg) given as 1-2 daily doses 3 days (consecutively or every other day) per wk. For severe adverse reactions to TMP-SMZ, alternative therapies include dapsone, atovaquone, and aerosolized pentamidine.

Prophylaxis against MAC should be offered to HIV-infected children with advanced immunosuppression (i.e., CD4 lymphocyte count <750 cells/µL in children younger than 1 yr of age, <500 cells/µL in children 1-2 yr of age, <75 cells/µL in children 2-5 yr of age, and <50 cells/µL in children >6 yr of age) (see Table 276-6). The drugs of choice are azithromycin (20 mg/kg [maximum: 1,200 mg] once a week PO or 5 mg/kg [maximum: 250 mg] once daily PO) or clarithromycin (7.5 mg/kg bid PO). In rare situations, rifabutin 300 mg qd can be an alternative for children older than 6 yr of age.

Based on adult data, primary prophylaxis against opportunistic infections may be discontinued if patients have experienced sustained (>6 mo duration) immune reconstitution with cART, even if they had previous opportunistic infections such as *Pneumocystis* pneumonia or disseminated MAC. HIV-infected children are at higher risk for TB and thus should have tuberculin skin testing (5 tuberculin units purified protein derivation) for TB at least once per year; an induration of 5 mm or more should be considered positive. If the child is living in close contact with a person with TB, the child should be tested more frequently. Of note, the sensitivity of purified protein derivation is reduced in severely immunocompromised patients and other laboratory tests should be used. For example, assays that determine IFN-γ release from lymphocytes following stimulation by specific *Mycobacterium tuberculosis* antigens were found to be more specific than the skin testing in adults. Limited data suggest that they are less sensitive in diagnosing TB in children, and therefore caution should be used in interpreting negative results of such tests in children. The "Guidelines for Prevention and Treatment of

Table 276-6 Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States*

	Preventive Regimen		
PATHOGEN	**INDICATION**	**FIRST CHOICE**	**ALTERNATIVE**
STRONGLY RECOMMENDED AS STANDARD OF CARE			
Pneumocystis pneumonia[†]	HIV-infected or HIV-indeterminate infants aged 1-12 mo; HIV-infected children aged 1-5 yr with CD4 count of <500 cells/µL or CD4 percentage of <15%; HIV-infected children aged 6-12 yr with CD4 count of <200 cells/µL or CD4 percentage of <15%	**TMP-SMX**, 150/750 mg/m^2 body surface area per day (max: 320/1600 mg) orally qd or bid 3 times weekly on consecutive days *or* qd or bid orally 3 times weekly on alternate days	**Dapsone**: age ≥1 mo: 2 mg/kg (max: 100 mg) orally qd; *or* 4 mg/kg (max: 200 mg) orally once a week **Atovaquone**: age 1-3 mo and >24 mo: 30 mg/kg orally qd; age 4-24 mo: 45 mg/kg orally qd **Aerosolized pentamidine**: age ≥5 yr: 300 mg once a month by Respirgard II (Marquest, Englewood, CO) nebulizer **Doxycycline** age >8 yr: 2.2 mg/kg qd
Malaria	Living or traveling to area in which malaria is endemic	Same for HIV-infected and HIV-uninfected children. Refer to http://www.cdc.gov/malaria/ for the most recent recommendations. **Mefloquine**, 5 mg/kg orally 1 time weekly (max: 250 mg) **Atovaquone/proguanil** (Malarone) qd 11-20 kg: 62.5 mg/25 mg (1 pediatric tablet) 21-30 kg: 2 pediatric tablets 31-40 kg: 3 pediatric tablets >40 kg: 1 adult tablet (250 mg/100 mg)	**Doxycycline**, 100 mg orally qd for children >8 yr **Chloroquine,** 5 mg/kg base (equal 7.5 mg/kg chloroquine phosphate) orally up to 300 mg weekly (only for regions where the parasite is sensitive)
Mycobacterium tuberculosis			
Isoniazid-sensitive	TST reaction ≥5 mm *or* Prior positive TST result without treatment *or* Close contact with any person who has contagious TB. TB disease must be excluded before start of treatment	**Isoniazid,** 10-15 mg/kg body weight (max: 300 mg) qd for 9 mo *or* 20-30 mg/kg body weight (max: 900 mg) orally 2 times weekly for 9 mo	**Rifampin,** 10-20 mg/kg body weight (max: 600 mg) orally daily for 4-6 mo
Isoniazid-resistant	Same as previous pathogen; increased probability of exposure to isoniazid-resistant TB	**Rifampin,** 10-20 mg/kg body weight (max: 600 mg) orally daily for 4-6 mo	Uncertain
Multidrug-resistant (isoniazid and rifampin)	Same as previous pathogen; increased probability of exposure to multidrug-resistant TB	Choice of drugs requires consultation with public health authorities and depends on susceptibility of isolate from source patient	
Mycobacterium avium complex[‡]	For children age ≥6 yr with CD4 count of <50 cells/µL; age 2-5 yr with CD4 count of <75 cells/µL; age 1-2 yr with CD4 count of <500 cells/µL; age <1 yr with CD4 count of <750 cells/µL	**Clarithromycin,** 7.5 mg/kg (max: 500 mg) orally bid *or* **Azithromycin,** 20 mg/kg (max: 1,200 mg) orally once a week	**Azithromycin,** 5 mg/kg body weight (max: 250 mg) orally qd *or* Children age ≥6 yr *or* **Rifabutin**, 300 mg orally qd
Varicella-zoster virus[§]	Exposure to varicella or shingles with no history of varicella *or* Zoster or seronegative status for VZV *or* Lack of evidence for age-appropriate vaccination	Varicella-zoster immunoglobulin (VariZIG), 125 IU per 10 kg (max: 625 IU) IM, administered within 96 hr after exposure[‖]	If VariZIG is not available and <96 hr from exposures, **acyclovir** 20 mg/kg (max: 800 mg) 4 times a day for 5-7 days *or* IVIG, 400 mg/kg, administered once
Vaccine-preventable pathogens	Standard recommendations for HIV-exposed and HIV-infected children	Routine vaccinations (see Fig. 276-3)	

Table 276-6 Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States—cont'd

PATHOGEN	Preventive Regimen		
	INDICATION	FIRST CHOICE	ALTERNATIVE
USUALLY RECOMMENDED			
Toxoplasma gondii[¶]	Seropositive IgG to *Toxoplasma* and severe immunosuppression: age <6 yr with CD4 <15%; age ≥6 yr with CD4 <100 cells/µL	TMP-SMZ, 150/750 mg/m^2 orally bid *or* Same dosage qd 3 times weekly on consecutive days *or* bid 3 times weekly on alternate days	**Dapsone,** age ≥1 mo: 2 mg/kg or 15 mg/m^2 (max: 25 mg) orally qd *plus* **Pyrimethamine,** 1 mg/kg (max: 25 mg) orally qd *plus* **Leucovorin,** 5 mg orally twice a week *or* **Atovaquone,** age 1-3 mo and >24 mo, 30 mg/kg orally qd; children age 4-24 mo, 45 mg/kg orally qd with or without **pyrimethamine,** 1 mg/kg (or 15 mg/m^2) (max: 25 mg) qd *plus* **Leucovorin,** 5 mg orally twice a week (3 days apart)
Invasive bacterial infections	Hypogammaglobulinemia (i.e., IgG <400 mg/dL)	IVIG 400 mg/kg body weight every 2-4 wk	
Cytomegalovirus	CMV antibody positivity and severe immunosuppression (CD4 <50 cells/µL)	**Valganciclovir,** 900 mg orally qd with food for older children who can receive adult dosing	

*Information in these guidelines might not represent FDA approval or FDA-approved labeling for products or indications. Specifically, the terms "safe" and "effective" might not be synonymous with the FDA-defined legal standards for product approval.

[†]Daily trimethoprim-sulfamethoxazole (TMP-SMZ) reduces the frequency of certain bacterial infections. Compared with weekly dapsone, daily dapsone is associated with lower incidence of PCP but higher hematologic toxicity and mortality. Patients receiving therapy for toxoplasmosis with sulfadiazine-pyrimethamine are protected against PCP and do not need TMP-SMZ. TMP-SMZ, dapsone-pyrimethamine, and possibly atovaquone (with or without pyrimethamine) protect against toxoplasmosis; however, data have not been prospectively collected.

[‡]Substantial drug interactions can occur between rifamycins (i.e., rifampin and rifabutin) and protease inhibitors and nonnucleoside reverse transcriptase inhibitors. A specialist should be consulted.

[§]Children routinely being administered intravenous immunoglobulin (IVIG) should receive VariZIG if the last dose of IVIG was administered more than 21 days before exposure.

[‖]As of 2007, VariZIG can be obtained only under a treatment Investigational New Drug protocol (1-800-843-7477, FFF Enterprises, Temecula, CA).

[¶]Protection against toxoplasmosis is provided by the preferred anti-*Pneumocystis* regimens and possibly by atovaquone.

CMV, cytomegalovirus; FDA, U.S. Food and Drug Administration; HIV, human immunodeficiency virus IgG, immunoglobulin G; IM, intramuscularly; IVIG, intravenous immunoglobulin; PCP, *Pneumocystis* pneumonia; TMP-SMZ, trimethoprim-sulfamethoxazole; TB, tuberculosis; TST, tuberculin skin test;; VZV, varicella-zoster virus.

From Centers for Disease Control and Prevention (CDC): Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children, MMWR Recomm Rep *58(RR-11):127–128, 2009, Table 1.*

Opportunistic Infections Among HIV-Exposed and HIV-Infected Children" (http://aidsinfo.nih.gov) should be consulted for these and other opportunistic infections that may occur in these populations. To reduce the incidence of opportunistic infections, parents should be counseled about (1) the importance of good hand washing, (2) avoiding raw or undercooked food *(Salmonella)*, (3) avoiding drinking or swimming in lake or river water or being in contact with young farm animals *(Cryptosporidium)*, and (4) the risk of playing with pets (*Toxoplasma* and *Bartonella* from cats, *Salmonella* from reptiles).

PROGNOSIS

The improved understanding of the pathogenesis of HIV infection in children and the availability of more effective antiretroviral drugs has changed the prognosis considerably. The earlier cART is started, the better the prognosis; a clinical trial aims to start treatment as close to delivery as possible will test the possibility of curing perinatally infected newborns. In settings with ready access to early diagnosis and antiretroviral therapy, progression of the disease to AIDS has significantly diminished. Since the advent of cART in the mid-1990s, mortality in perinatally infected children has declined more than 90% and many of the children survive to adolescence and adulthood. Even with only partial reduction of viral load, children may have both significant immunologic and clinical benefits. In general, the best prognostic indicators are the sustained suppression of plasma viral load and restoration of a normal CD4$^+$ lymphocyte count. If determinations of viral load and CD4 lymphocytes are available, the results can be used to evaluate prognosis. It is unusual to see rapid progression in an infant with a viral load <100,000 copies/mL. In contrast, a high viral load (>100,000 copies/mL) over time is associated with greater risk for disease progression and death. CD4 lymphocyte percentage is another prognostic indicator, and the mortality rate is higher in patients with a CD4 lymphocyte percentage <15%. To define prognosis more accurately, the use of changes in both markers (CD4 lymphocyte percentage and plasma viral load) is recommended.

Even in resource-limited countries where ARV therapy and molecular diagnostic tests are less available, the use of cART had a substantial benefit on the survival of HIV-infected children and reduced the hazard of mortality by 75%. Children with opportunistic infections (e.g., *Pneumocystis* pneumonia, MAC), encephalopathy and regressing developmental milestones, or wasting syndrome have the worst prognosis, with 75% dying before 3 yr of age. A higher risk of mortality was documented in children who did not receive TMP-SMZ preventive therapy. Persistent fever and/or oral thrush, serious bacterial infections (meningitis, pneumonia, sepsis), hepatitis, persistent anemia (<8 g/dL), and/or thrombocytopenia (<100,000/µL) also suggest a poor outcome, with >30% of such children dying before 3 yr of age. In contrast, lymphadenopathy, splenomegaly, hepatomegaly, lymphoid interstitial pneumonitis, and parotitis are indicators of a better prognosis.

PREVENTION

Use of antiretroviral therapy for interruption of perinatal transmission from mother-to-child has been one of the greatest achievements of HIV research. Maternal cART is documented to decrease the rate of

perinatal HIV-1 transmission to <2%, and <1% if the mother's viral RNA level is <1,000 copies/mL at delivery. Therefore, it is recommended that **all** pregnant women be tested for HIV and if positive, treated with a cART regimen, irrespective of viral load or CD4 count during pregnancy. This should be in conjunction with 4-6 wk of ZDV prophylaxis for the infant and with collaboration between the HIV-specialist and the obstetrician. Cesarean section (C-section) as a prevention strategy was examined in a multinational meta-analysis, which showed that the combination of elective C-section and maternal ZDV treatment reduced transmission by 87%. However, these data were obtained prior to the advent of cART, and the additional benefit of elective C-section to the cART-treated mother whose viral load is <1,000 copies/mL is negligible. Thus, elective C-section at 38 wk of gestation should be considered only for women whose viral load is >1,000 copies/mL in late gestation, to further reduce the risk of vertical transmission.

A multinational randomized, controlled trial in non-breastfed neonates whose mothers received no ARVs during pregnancy showed that prophylaxis with a two- or three-drug ARV regimen is superior to ZDV alone for the prevention of intrapartum HIV transmission. Based on these data, the U.S. Guidelines Panel recommends that infants born to HIV-infected women who have received no antepartum or only intrapartum ARVs, or who have HIV RNA >1000 copies/mL near delivery, should receive prophylaxis with ZDV for 6 wk combined with three doses of NVP in the 1st wk of life (i.e., at birth, 48 hr later, and 96 hr after the second dose), begun as soon after birth as possible (see Table 276-4).

The WHO recommends that all pregnant women receive a cART regimen appropriate for their own health, which should be continued at least throughout breastfeeding (in resource-limited areas) and for the remainder of their lives. This approach has the potential to reduce transmission during breastfeeding and future pregnancies, lowers the transmission risk to sexual partners, improves maternal survival, and promotes simplified universal treatment regimens. Breastfed infants should receive NVP for 6 wk if the mother is receiving cART, or NVP for the duration of breastfeeding if the mother is not on therapy. Formula-fed infants in resource-limited countries should receive ZDV bid or NVP qd for 6 wk.

Although the most effective way to prevent postpartum transmission of HIV is to eliminate breastfeeding altogether and substitute replacement feeding, there is evidence that early weaning may not be safe in resource-limited settings because of the high risk of malnutrition and diarrhea in formula-fed infants without a consistent source of clean water. Furthermore, exclusive breastfeeding (no additional solids or fluids other than water) results in less transmission than mixed feeding. Guidelines have evolved to recommend that HIV-infected mothers living in resource-limited settings should breastfeed their infants until at least 12 mo of age, with exclusive breastfeeding for the 1st 6 mo, and ARVs should continue to be provided, either to the mother or to the infant, at least until 1 wk after all breastfeeding has ceased. In settings where there are safe alternatives to breastfeeding, formula feeding is recommended. U.S. guidelines for prevention of mother-to-child transmission are regularly updated at http://aidsinfo.nih.gov/ and the international guidelines are regularly updated at the WHO website (http://www.who.int/hiv/topics/mtct/en/).

Now that it is clear that perinatal transmission can be reduced dramatically by treating pregnant mothers, a compelling argument can be made for prenatal identification of HIV-1 infection in the mother. The benefit of therapy both for the mother's health and to prevent transmission to the infant cannot be overemphasized. The recommended universal prenatal HIV-1 counseling and HIV-1 testing for all pregnant women has reduced the number of new infections dramatically in many areas of the United States and Europe. For women not tested during pregnancy, the use of rapid HIV antibody testing during labor or on the 1st day of the infant's life is a way to provide perinatal prophylaxis to an additional group of at-risk infants.

Prevention of sexual transmission involves avoiding the exchange of bodily fluids. In sexually active adolescents, condoms should be an integral part of programs to reduce sexually transmitted diseases, including HIV-1. Unprotected sex with older partners or with multiple partners and use of recreational drugs is common among HIV-1–infected adolescents, increasing their risk. Educational efforts about avoidance of risk factors are essential for older school-age children and adolescents and should begin before the onset of sexual activity. In addition, promising research for sexually active adults may translate to increased prevention for adolescents. Three African trials demonstrated that male circumcision was associated with a 50-60% reduction in risk of HIV acquisition in young men. For women, use of a 1% vaginal gel formulation of tenofovir during intercourse was found to reduce HIV acquisition by nearly 40%. Other topical microbicides are being investigated. A double-blind study of preexposure prophylaxis in MSM using once daily dosing of coformulated tenofovir and emtricitabine resulted in a 44% reduction in the incidence of HIV (95% confidence interval, 15-63; P = 0.005). Of interest, the incidence of HIV transmission was reduced by 73% when participants took the drug on 90% or more days. In addition, a large randomized multinational clinical trial of HIV serodiscordant adults demonstrated that effective ARV therapy in the HIV-infected partner reduced secondary transmission to an uninfected sexual partner by 96%. However, none of the studies that have shown promise for prevention in at-risk populations has included adequate representation in youth, making it difficult to interpret the effect on this population.

Despite prolonged suppression of viremia, it is obvious that cART may not fully restore health and may be associated with long-term toxicity. In addition, adherence is a major challenge and constrained resources will limit the ability to expand cART to all patients who need it. However, recent discoveries of new antiretroviral drugs, new vaccines, and advances in our understanding of HIV latency are encouraging developments on the long road to a cure.

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Chapter 277

Human T-Lymphotropic Viruses (1 and 2)

Hal B. Jenson

ETIOLOGY

Human T-lymphotropic viruses 1 (HTLV-1) and 2 (HTLV-2) are members of the *Deltaretrovirus* genus of the Retroviridae family, which are single-stranded RNA viruses that encode reverse transcriptase, an RNA-dependent DNA polymerase that transcribes the single-stranded viral RNA into a double-stranded DNA copy. HTLV-1 was the first human retrovirus to be associated with cancer, as the cause of adult T-cell leukemia/lymphoma (ATL).

HTLV-1 and -2 share a genome homology of approximately 65% and infect T cells, B cells, and synovial cells via the ubiquitous glucose transporter type 1, which serves as the virus receptor. The genome contains *gag, pol,* and *env* genes and the pX region, which encodes nonstructural proteins. The nonstructural proteins include the Tax and Rex regulatory proteins, the novel proteins essential for virus spread (p30, p12, and p13), and the antisense-encoded HTLV-1 basic leucine zipper factor. Circular viral DNA is transported into the nucleus where it is integrated into chromosomal DNA (provirus), evading the typical mechanisms of immune surveillance and facilitating lifelong infection. The host response is mediated by cytotoxic T lymphocytes, resulting in lysis of infected cells. An exuberant inflammatory response with overproduction of cytokines contributes to developing nonmalignant disease.

EPIDEMIOLOGY

HTLV-1 infects 15-20 million persons globally. It is endemic in southwestern Japan (where >10% of adults are seropositive), areas of the

Caribbean, including Jamaica and Trinidad (up to 6%), and in parts of sub-Saharan Africa (up to 5%). Lower seroprevalence rates are found in South America (up to 2%) and Taiwan (0.1-1%). There is microclustering with marked variability within geographic regions.

The seroprevalence of HTLV-1 and HTLV-2 in the United States in the general population is 0.01-0.03% for each virus, with higher rates with increasing age. The prevalence of HTLV-1 infection is highest in babies born in endemic areas or in persons who have had sexual contact with persons from endemic areas. The prevalence of HTLV-2 infection correlates with intravenous illicit drug use. A prevalence of approximately 18% was found in a study of illicit drug users in the United States, often with concomitant HIV infection.

HTLV-1 and -2 are transmitted as cell-associated viruses by **vertical transmission** from mother to child and **horizontal transmission** through genital secretions, contaminated blood products, and intravenous illicit drug use. Higher maternal HTLV-1 proviral load may be associated with greater risk of vertical transmission, which occurs primarily via breastfeeding from infected mothers with a 3-fold increased risk of transmission with breastfeeding for longer than 6 mo. Intrauterine and intrapartum transmissions account for <5% of vertical transmissions. In Japan, approximately 20-25% of children born to infected mothers become infected, and more than 90% of HTLV-1–infected children have HTLV-1–infected mothers. HTLV-2 may also be transmitted via breastfeeding, but it has a slightly lower reported transmission rate via breast milk of approximately 14%.

DIAGNOSIS

HTLV-1 and HTLV-2 infections are diagnosed by screening using 2nd-generation enzyme immunoassay with confirmation by immunoblot, indirect immunofluorescence, or line immunoassays. Polymerase chain reaction can also be used to distinguish HTLV-1 from HTLV-2 infection.

CLINICAL MANIFESTATIONS

The lifetime risk of disease associated with HTLV-1 infection is estimated at 5-10% and is highest following vertical transmission. HTLV-1 is associated with ATL and several nonmalignant conditions, including the neurodegenerative disorder HTLV-1–associated myelopathy (HAM), also known as tropical spastic paraparesis and sometimes termed HAM/tropical spastic paraparesis. The geographic epidemiologic characteristics of ATL and HAM are similar. **HTLV-1–associated arthropathy** mimics rheumatoid arthritis, including a positive rheumatoid factor. Treatment is with antiinflammatory agents. **HTLV-1–associated uveitis** may be unilateral or bilateral, is more common among women, and resolves spontaneously, although it often recurs within 1-3 yr. Topical corticosteroids hasten recovery. **HTLV-1–associated infective dermatitis** is a chronic and recurrent eczematous disease occurring during childhood and adolescence. HTLV-1 infection predisposes to disseminated and recurrent *Strongyloides stercoralis* infection, increased risk of developing tuberculosis disease following latent infection, and severe scabies.

Adult T-Cell Leukemia/Lymphoma

The age distribution of ATL peaks at approximately 50 yr, underscoring the long latent period of HTLV-1 infection. HTLV-1–infected persons remain at risk for ATL even if they move to an area of low HTLV-1 prevalence, with a lifetime risk for ATL of 2-4%. Most cases of ATL are associated with monoclonal integration of HTLV-1 provirus into the cellular genome of CD4 lymphocytes, resulting in unchecked proliferation of CD4 T cells. There is a spectrum of disease that is categorized into different forms: acute, lymphomatous, chronic, primary cutaneous smoldering, and primary cutaneous tumoral. The acute form of ATL comprises 55-75% of all cases. Smoldering, subclinical lymphoproliferation may spontaneously resolve, in approximately half of cases, or progress to chronic leukemia or lymphomatous or even acute ATL. **Chronic, low-grade, HTLV-1–associated lymphoproliferation (pre-ATL)** may persist for years with abnormal lymphocytes with or without peripheral lymphadenopathy before progressing to the acute form. Acute ATL is characterized by hypercalcemia, lytic bone lesions, lymphadenopathy that spares the mediastinum, hepatomegaly, splenomegaly, cutaneous lymphomas, and opportunistic infections. Leukemia may develop with circulating polylobulated malignant lymphocytes, called **flower cells**, possessing mature T-cell markers. Cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) is often the initial therapy for ATL, although chemotherapy is not curative and relapses are common. The median survival after diagnosis is 6-13 mo.

Human T-Cell Lymphotropic Virus-1–Associated Myelopathy

HAM is more common in women than in men and has a relatively short incubation period after HTLV-1 infection, of 1-4 yr compared with 40-60 yr for ATL. HAM occurs in up to 4% of persons with HTLV-1 infection, usually developing during middle age. It is characterized by infiltration of mononuclear cells into the gray and white matter of the thoracic spinal cord, leading to severe white matter degeneration and fibrosis. HTLV-1 is found near but not directly within the lesions, suggesting that reactive inflammation is a major mechanism of disease. The cerebrospinal fluid typically shows a mildly elevated protein and a modest monocytic pleocytosis, along with anti–HTLV-1 antibodies. Neuroimaging studies are normal or show periventricular lesions in the white matter. Clinical manifestations include gradual onset of slowly progressive, symmetric neurologic degeneration of the corticospinal tracts and, to a lesser extent, the sensory system that leads to lower-extremity spasticity or weakness, lower back pain, and hyperreflexia of the lower extremities with an extensor plantar response. The bladder and intestines may become dysfunctional, and men may become impotent. Some patients develop dysesthesias of the lower extremities with diminished sensation to vibration and pain. Upper-extremity function and sensation, cranial nerves, and cognitive function are usually preserved. Treatment regimens have included corticosteroids, danazol, interferon, plasmapheresis, high-dose vitamin C, and antivirals, all with minimal effects.

Human T-Cell Lymphotropic Virus-2

HTLV-2 was originally identified in patients with hairy cell leukemia, although most patients with hairy cell leukemia are seronegative for HTLV-2 infection. HTLV-2 has been rarely isolated from patients with leukemias or with myelopathies resembling HAM, and there is limited evidence of disease specifically associated with HTLV-2 infection.

PREVENTION

Routine antibody testing of all blood products using HTLV-1 viral lysate began in the United States in 1988 and missed 30-58% of HTLV-2 infections. Combination HTLV-1/2 antibody testing was implemented in 1997. Formula feeding in lieu of breastfeeding of infants of HTLV-1–infected mothers is an effective means of controlling endemic HTLV-1 transmission. No vaccine is available.

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Chapter 278

Transmissible Spongiform Encephalopathies

David M. Asher

The transmissible spongiform encephalopathies (TSEs) are slow infections of the human nervous system, consisting of at least 4 diseases of humans (Table 278-1): kuru; Creutzfeldt-Jakob disease (CJD) with its variants—sporadic CJD (sCJD), familial CJD (fCJD), iatrogenic CJD (iCJD), and new-variant or variant CJD (vCJD); Gerstmann-Sträussler-Scheinker syndrome (GSS); and fatal familial insomnia (FFI), or the even more rare sporadic fatal insomnia syndrome. TSEs also affect

Table 278-1 Clinical and Epidemiologic Features of Human Transmissible Spongiform Encephalopathies (Prion Diseases)

DISEASE	CLINICAL FEATURES	SOURCE OF INFECTION	GEOGRAPHIC DISTRIBUTION AND PREVALENCE	USEFUL ANCILLARY TESTS	DURATION OF ILLNESS
sCJD	Dementia, myoclonus, ataxia	Unknown	Worldwide; ≈1/1 million/yr; 85-95% of all CJD cases in U.S.	EEG—PSWCs; CSF 14-3-3; MRI/DWI	1-24 mo (mean: 4-6 mo)
fCJD	Dementia, myoclonus, ataxia	Genetic association (*PRNP* mutations) ?? Possible exogenous source of infection	Worldwide—geographic clusters; >100 known families; 5-15% of CJD cases	Gene testing; EEG—PSWC rare; MRI/DWI (?)	Mean ≈15 mo
iCJD	Incoordination, dementia (late)	Cadaver dural grafts, human pituitary hormones, corneal transplantation, neurosurgical instruments, EEG depth electrodes	≈1% of CJD cases in toto (cadaver dural grafts), >100 cases (human pituitary hormones), >100 cases; corneal transplantation 3 cases; neurosurgical instruments, 6 cases, including 2 from cortical depth electrodes; RBC transfusions, 4 cases of vCJD infection, 3 clinical, 1 preclinical (U.K.); human plasma–derived factor VIII, 1 preclinical case of vCJD (U.K.)		1 mo-10 yr
vCJD	Mood and behavioral abnormalities, paresthesias, dementia	Linked to BSE in cattle, transfusion plasma products	>220 clinical cases (see iatrogenic vCJD above)	Tonsil biopsy may show PrP^{TSE} MRI/FLAIR	8-36 mo (mean 14 mo)
Kuru	Incoordination, ataxia, tremors, dementia (late)	Linked to cannibalism	Fore people of Papua New Guinea (≈2,600 known cases)	EEG—no PSWCs; CSF 14-3-3 often negative; MRI (?)	3-24 mo
GSS	Incoordination, chronic progressive ataxia, corticospinal tract signs, dementia (late), myoclonus (rare)	90% genetic (*PRNP* mutations)	Worldwide; >50 families; ≈1-10/100 million/yr	*PRNP* gene sequencing	2-12 yr (mean ≈ 57 mo)
FFI	Disrupted sleep, intractable insomnia; autonomic hyperactivation; myoclonus, ataxia; corticospinal tract signs; dementia	*PRNP* gene mutation (D 178L); very rare sporadic cases	≈27 families in Europe, U.K., U.S., Finland, Australia, China, Japan	EEG—PSWCs only rarely positive; MRI—no DWI abnormalities; CSF 14-3-3 positive in ≈ 50%	8 mo–6 yr (mean: *PRNP* 129 MM 12 ± 4 mo 129 MV 21 ± 15 mo)

BSE, bovine spongiform encephalopathy; CSF, cerebrospinal fluid; CJD, Creutzfeldt-Jakob disease; DWI, diffusion-weighted image; EEG, electroencephalography; fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; FLAIR, fluid attenuation inversion recovery MRI; GSS, Gerstmann-Sträussler-Scheinker syndrome; iCJD, iatrogenic Creutzfeldt-Jakob disease; *PRNP*, prion protein encoding gene; PrP^{TSE}, abnormal prion protein; PSWCs, periodic sharp wave complexes; RBC, red blood cell; sCJD, sporadic Creutzfeldt-Jakob disease; vCJD, variant Creutzfeldt-Jakob disease.

NOTE: PRNP 129 MM, homozygous, encoding the amino acid methionine at both codons 129 of the prion-protein-encoding (PRNP) gene on chromosome 20; 129 MV, heterozygous at PRNP codon 129, encoding methionine on one chromosome 20 and valine on the other.

Modified from Mandell GL, Bennett JE, Dolin R, editors: Principles and practice of infectious diseases, *vol 2, ed 6, Philadelphia, 2005, Elsevier, p. 2222; Love S, Louis DN, Ellison DW, editors:* Greenfield's neuropathology, *vol 2, ed 8, London, 2008, Hodder Arnold, p. 1239.*

animals; the most common and best-known TSEs of animals are scrapie in sheep, bovine spongiform encephalopathy (BSE or mad cow disease) in cattle, and a chronic wasting disease (CWD) of deer, elk, and moose found in parts of the United States and Canada. All TSEs have similar clinical manifestations and histopathology, and all are "slow" infections with very long asymptomatic incubation periods (often years), durations of several months or more, and overt disease affecting only the nervous system. TSEs are relentlessly progressive after illness begins and invariably fatal. The most striking neuropathologic change that occurs in each TSE, to a greater or lesser extent, is spongy degeneration of the cerebral cortical gray matter.

ETIOLOGY

The TSEs are transmissible to susceptible animals by inoculation of tissues from affected subjects. Although the infectious agents replicate in some cell cultures, they do not achieve the high titers of infectivity found in brain tissues or cause recognizable cytopathic effects in cultures. Most studies of TSE agents have used in vivo assays, relying on the transmission of typical neurologic disease to animals as evidence that the agent was present and intact. Inoculation of susceptible recipient animals with small amounts of infectious TSE agent results, months later, in the accumulation in tissues of large amounts of agent with the same physical and biologic properties as the original agent. The TSE agents display a spectrum of extreme resistance to inactivation by a variety of chemical and physical treatments that is unknown among conventional pathogens. This characteristic, as well as their partial sensitivity to protein-disrupting treatments and their consistent association with abnormal isoforms of a normal host-encoded protein (prion protein or PrP), stimulated the hypothesis that the TSE agents are probably subviral in size, composed of protein, and devoid of nucleic acid.

The term **prion** (for proteinaceous infectious agent) is now widely used for such agents. The prion hypothesis proposes that the molecular mechanism by which the pathogen-specific information of TSE agents is propagated involves a self-replicating change in the folding host-encoded PrP associated with a transition from an α-helix–rich structure in the native protease-sensitive conformation (cellular PrP or

PrP^C) to a β-sheet–rich structure in the protease-resistant conformation associated with infectivity. The existence of a second host-encoded protein—termed "protein X"—that participates in the transformation was also postulated to explain certain otherwise puzzling findings but never identified.

The prion hypothesis is still not universally accepted; it relies on the postulated existence of a genome-like coding mechanism based on differences in protein folding that have not been satisfactorily explained at a molecular level. In addition, it has yet to account convincingly for the many biologic strains of TSE agent that have been observed, although strain-specific differences in the abnormal forms of the PrP have been found and proposed as providing a plausible molecular basis for the coding. It fails to explain why pure PrP uncontaminated with nucleic acid from an infected host has not transmitted a convincingly typical spongiform encephalopathy associated with a serially self-propagating agent. Also troubling, in several experimental models and human illnesses, abnormal PrP and infectivity were not consistently associated. Particularly problematic is the finding that some illnesses associated with mutations in the *PRNP* gene and accompanied by abnormal PrP failed to transmit infection to animals. If the TSE agents ultimately prove to consist of protein and only protein, without any obligatory nucleic acid component, then the term *prion* will indeed be appropriate and the early proponents of the prion hypothesis will prove to have been prescient. If the agents are ultimately found to contain small nucleic acid genomes, then they might better be considered atypical viruses, for which the term *virino* has been suggested. Until the actual molecular structure of the infectious TSE pathogens and the presence or absence of a nucleic acid genome are rigorously established, it seems less contentious to continue calling them TSE agents, although many authorities now use the term *prion* (sometimes referring to the agent of a TSE and sometimes to the abnormal protein, even when nontransmissible).

The earliest evidence that abnormal proteins are associated with the TSE was morphologic: scrapie-associated fibrils were found in extracts of tissues from patients and animals with spongiform encephalopathies but not in normal tissues. Scrapie-associated fibrils resemble but are distinguishable from the amyloid fibrils that accumulate in the brains of patients with Alzheimer disease. A group of antigenically related protease-resistant proteins (PrPs) proved to be components of scrapie-associated fibril and to be present in the amyloid plaques found in the brains of patients and animals with TSEs. The abnormal forms of PrP are variously designated PrP^{Sc} (scrapie-type PrP), PrP-res (protease-resistant PrP), PrP^{TSE} (TSE-associated PrP), or PrP^D (disease-associated PrP) by different authorities.

It remains unclear whether abnormal PrP constitutes the complete infectious particle of spongiform encephalopathies, is a component of those particles, or is a pathologic host protein not usually separated from the actual infectious entity by currently used techniques. The demonstration that PrP is encoded by a normal host gene seemed to favor the last possibility. Several studies suggest that agent-specific pathogenic information can be transmitted and replicated by different conformations of a protein with the same primary amino acid sequence in the absence of agent-specific nucleic acids. Properties of 2 fungal proteins were found to be heritable without encoding in nucleic acid, although those properties have not been transmitted to recipient fungi as infectious elements. Whatever its relationship to the actual infectious TSE particles, PrP clearly plays a central role in susceptibility to infection, because the normal PrP must be expressed in mice and cattle if they are to acquire a TSE or to sustain replication of the infectious agents. Furthermore, inherited normal variations in PrP phenotype are associated with increased susceptibility to vCJD and (to a lesser extent) to sCJD and with occurrence of fCJD.

PrPs are glycoproteins; protease-resistant PrPs, when aggregated, have the physical properties of amyloid proteins. The PrPs of different species of animals are very similar in their amino acid sequences and antigenicity but are not identical in structure. The primary structure of PrP is encoded by the host and is not altered by the source of the infectious agent provoking its formation. The function of the ubiquitous protease-sensitive PrP precursor (designated PrP^C, for "cellular" PrP, or PrP-sen, for protease-sensitive PrP) in normal cells is unknown; it binds copper and may play some role in normal synaptic transmission, but it is not required for life or for relatively normal cerebral function in mice and cattle. As noted, expression of PrP is required both for development of scrapie disease and for replication of the transmissible scrapie agent in animals. The degree of homology between amino acid sequences of PrPs in different animal species may correlate with the "species barrier" that affects susceptibility of animals of 1 species to infection with a TSE agent adapted to grow in another species.

Attempts to find particles resembling those of viruses or virus-like agents in brain tissues of humans or animals with spongiform encephalopathies have been unsuccessful. Peculiar tubulovesicular structures reminiscent of some viruses have been seen in thin sections of TSE-infected brain tissues and cultured cells but not in normal cells. It has never been convincingly established that those structures are associated with infectivity.

EPIDEMIOLOGY

Kuru once affected many children of both sexes ≥4 yr of age, adolescents, and young adults (mainly women) living in 1 limited area of Papua New Guinea. The complete disappearance of kuru among people born after 1957 suggests that the practice of ritual cannibalism (thought to have ended that year) was probably the only mechanism by which the infection was spread in Papua New Guinea.

CJD, the most common human spongiform encephalopathy, was formerly thought to occur only in older adults; however, iCJD and, much more rarely, sCJD (to date, 7 reports in adolescents—1 a 14 yr old girl) have affected young people. A single case of sporadic fatal insomnia was recognized in a U.S. adolescent. GSS has not been diagnosed in children or adolescents. vCJD, however, has a peculiar predilection for younger people. Of 174 cases of vCJD reported through 2010 in the United Kingdom, all except 23 were in people younger than 40 yr of age and 22 were younger than 20 yr of age; the youngest age at onset was 12 yr. sCJD has been recognized worldwide, at yearly rates of 0.25-2 cases/million population (not age-adjusted), with CJD foci of considerably higher incidence among Libyan Jews in Israel, in isolated villages of Slovakia, and in other limited areas. Sporadic CJD has not been convincingly linked to any common exposure, and the source of infection remains unknown. Proponents of the prion hypothesis are convinced that PrP can spontaneously misfold, becoming self-replicating and causing sCJD; skeptics favor infection with some ubiquitous TSE agent which, fortunately, has a very low attack rate except in persons with certain mutations in the *PRNP* gene. Neither of those possible etiologies has been proven. Person-to-person spread has been confirmed only for iatrogenic cases. Spouses and household contacts of patients are at very low risk of acquiring CJD, although 2 instances of conjugal CJD have been reported. However, medical personnel exposed to brains of patients with CJD may be at some increased risk; at least 20 healthcare workers have been recognized with the disease.

The striking resemblance of CJD to scrapie prompted a concern that infected sheep tissues might be a source of spongiform encephalopathy in humans. No reliable epidemiologic evidence suggests that exposure to potentially scrapie-contaminated animals, meat, meat products, or experimental preparations of the scrapie agent have transmitted a TSE to humans. The potential of the CWD agent to infect human beings has also not been demonstrated but remains under investigation; deer, elk, and moose in 15 U.S. states and 2 Canadian provinces have been naturally infected; monkeys have been experimentally infected by injections with deer tissues containing the CWD agent. Exposure to contaminated meat, including venison from animals infected with the CWD agent, has not been implicated as a risk factor for sCJD.

The outbreak of BSE among cattle (possibly infected by eating scrapie-agent–contaminated meat-and-bone meal added to feed) was first recognized in the United Kingdom in 1986 and later reported in native cattle of 24 other countries, including Canada and the United States. The finding of a new TSE in ungulate and feline animals in British zoos and later in domestic cats raised a fear that some TSE agent (probably a strain of the scrapie agent), having crossed the species barrier from sheep to cattle, had acquired a broadened range

of susceptible hosts, posing a potential danger for humans. That remains a plausible explanation for the occurrence of vCJD, first described in adolescents in Britain in 1996 and as of November 2013 affecting at least 177 people in the United Kingdom (not counting a disturbing number of people with evidence of possible asymptomatic or "preclinical" vCJD infection) and more than 50 in other countries: 27 in France, 5 in Spain, 4 in Ireland, 3 in the Netherlands, 2 each in Italy and Portugal, and single cases in Japan and Saudi Arabia. Variant CJD has also occurred in former U.K. residents living in Ireland (2 cases), France (1 case), Canada (1 case), Taiwan (1 case), and the United States (2 cases); 2 additional cases of vCJD—1 in the United States and 1 in Canada—have been reported in former long-time residents of Saudi Arabia, a country that has not recognized BSE but might have imported contaminated meat products from the United Kingdom. A third case of vCJD was previously confirmed in a Saudi citizen residing in Saudi Arabia. Examination of resected appendixes in the United Kingdom for evidence of subclinical infection with prions suggested that many more people than expected had subclinical infection than those recognized with actual vCJD.

Iatrogenic transmissions of CJD have been recognized for more than 30 yr (Table 278-2). Such accidental transmissions of CJD have been attributed to use of contaminated neurosurgical instruments (no case reported since 1980) or operating facilities, use of cortical electrodes contaminated during epilepsy surgery, injections of human cadaveric pituitary growth hormone and gonadotropin (no longer marketed in the United States), and transplantation of contaminated corneas and allografts of human dura mater used as a surgical patching material. Pharmaceuticals and tissue grafts derived from or contaminated with human neural tissues, particularly when obtained from unselected donors and large pools of donors, pose special risks.

Studies of animals experimentally infected with TSE agents first suggested that blood and blood components from humans with preclinical CJD infections might pose a risk of transmitting disease to recipients, and since the 1980s such blood components have been withdrawn as a precaution in the United States when a donor was later found to have CJD and blood products were still in-date. While no epidemiologic study identified any subject exposed to such products obtained from donors later diagnosed with sporadic or fCJD, a surveillance program in the United Kingdom has already reported vCJD in 3 recipients of nonleukoreduced red blood cells from donors later diagnosed with vCJD; there was autopsy evidence of a preclinical vCJD infection in a fourth red cell recipient who died of another disease. Evidence of a preclinical vCJD infection was also found at autopsy in a patient with hemophilia A who was treated with human plasma–derived coagulation factor VIII to which at least 1 vCJD-infected donor contributed; the coagulation factor involved was never licensed in the United States.

Table 278-2 Iatrogenic Transmission of Creutzfeldt-Jakob Disease by Products of Human Origin

PRODUCT	NO. OF PATIENTS	INCUBATION TIME	
		Mean	Range
Cornea	3	17 mo	16-18 mo
Dura mater allograft	>100	7.4 yr	1.3-16 yr
Pituitary extract			
Growth hormone	>100*	12 yr	5-38.5 yr
Gonadotropin	4	13 yr	12-16 yr
Red blood cells	4	? 6 yr	6.3-8.5 yr[†]
Plasma-derived coagulation factor VIII	1	? > 11 yr[‡]	

*There have been 28 cases reported among approximately 8,000 recipients of human cadaveric growth hormone in the United States; the remaining cases have been reported in other countries.

[†]The second transfusion-transmitted case of vCJD (Peden AH, Head MW, Ritchie DL, et al: Preclinical vCJD after blood transfusion in a *PRNP* codon 129 heterozygous patient, *Lancet* 364:527–529, 2004) died of unrelated causes about 5 yr after transfusion but was found to have accumulations of abnormal PrP in spleen and cervical lymph node—a finding unique to vCJD and interpreted as probable preclinical infection.

[‡]The diagnosis of vCJD infection attributed to treatment with human plasma–derived coagulation factor VIII (UK Health Protection Agency vCJD abnormal prion protein found in a patient with haemophilia at post mortem. Press release 17 February 2009. http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1234859690542?p=1231252394302) was also supported by immunohistochemical testing for abnormal PrP in the spleen of a person who died of other causes. Both patients with "preclinical" infections are thought to have died during the asymptomatic incubation period of vCJD.

PATHOGENESIS AND PATHOLOGY

The probable portal of entry for the TSE agent in kuru is thought to have been either through the gastrointestinal tract or lesions in the mouth or integument incidentally exposed to the agent during cannibalism. Patients with vCJD (and animals with BSE and BSE-related TSEs) are thought to have been similarly infected with the BSE agent through exposure to a contaminated beef product, possibly through the intestinal tract. Except after direct introduction into the nervous system, the first site of replication of TSE agents appears to be in tissues of the reticuloendothelial system. TSE agents have been detected in low titers in blood of experimentally infected animals (mice, monkeys, hamsters, and sheep and in the blood of persons with vCJD and perhaps sCJD); infectivity was mainly associated with nucleated cells, although plasma contained a substantial portion of total infectivity in blood. Circulating lymphoid cells seem to be required to infect mice by peripheral routes. Limited evidence suggests that TSE agents also spread to the central nervous system by ascending peripheral nerves. Several researchers claim to have developed tests that detected the CJD agent in human blood, although most attempts have failed. To date no blood-based test has been validated for antemortem testing of either humans or animals.

In human kuru, it seems probable that the only portal of exit of the agent from the body, at least in quantities sufficient to infect others, was through infected tissues exposed during cannibalism. In iatrogenically transmitted CJD, the brains and eyes of patients with CJD have been the probable sources of contamination. Experimental transmission of the agent to animals from kidney, liver, lung, lymph node, and spleen showed that those tissues as well as cerebrospinal fluid (CSF) sometimes contain the CJD agent; none of those sources has been implicated in accidental transmission of CJD to humans. At no time during the course of any TSE have antibodies or cell-mediated immunity to the infectious agents been convincingly demonstrated in either patients or animals. However, mice must be immunologically competent to be infected with the scrapie agent by peripheral routes of inoculation.

Typical changes in TSE include vacuolation and loss of neurons with hypertrophy and proliferation of glial cells, most pronounced in the cerebral cortex in patients with CJD and in the cerebellum in those with kuru. The central nervous system lesions are usually most severe in or even confined to gray matter, at least early in the disease. Loss of myelin appears to be secondary to degeneration of neurons. There generally is no inflammation, but a marked increase in the number and size of astrocytes is usual. Spongiform changes are not a striking autopsy finding in patients with FFI, and neuronal degeneration and gliosis are largely restricted to thalamic nuclei.

Amyloid plaques are found in the brains of all patients with GSS and in at least 70% of those with kuru. These plaques are less common in patients with CJD. Amyloid plaques are most common in the cerebellum but occur elsewhere in the brain as well. In brains of patients with vCJD, plaques surrounded by halos of vacuoles (described as flower-like or florid plaques) have been a consistent finding. TSE amyloid plaques react with antiserum prepared against PrP. Even in the absence of plaques, extracellular PrP can be detected in the brain parenchyma by immunostaining.

CLINICAL MANIFESTATIONS

Kuru, no longer seen, is a progressive degenerative disease of the cerebellum and brainstem with less obvious involvement of the cerebral cortex. The first sign of kuru was usually cerebellar ataxia followed by progressive incoordination. Coarse, shivering tremors were characteristic. Variable abnormalities in cranial nerve function appeared, frequently with impairment in conjugate gaze and swallowing. Patients died of inanition and pneumonia or of burns from cooking fires, usually within 1 yr after onset. Although changes in mentation were common, there was no frank dementia or progression to coma, as in CJD. There were no signs of acute encephalitis such as fever, headaches, and convulsions.

CJD occurs throughout the world. Patients initially have either sensory disturbances (most often visual) or confusion and inappropriate behavior, progressing over weeks or months to frank dementia, akinetic mutism, and ultimately coma. Some patients have cerebellar ataxia early in disease, and most patients experience myoclonic jerking movements. Mean survival of patients with sCJD has been <1 yr from the earliest signs of illness, although approximately 10% live for 2 yr. Variant CJD (Table 278-3) differs from the more common sCJD: patients with vCJD are much younger at onset (as young as 12 yr) and more often present with complaints of dysesthesia and subtle behavioral changes, often mistaken for psychiatric illness. Severe mental deterioration occurs later in the course of vCJD. Patients with vCJD have survived substantially longer than those with sCJD. (Attempts have been made to subclassify cases of CJD based on electrophoretic differences in PrP^{TSE} and variation in its sensitivity to digestion with the proteolytic enzyme proteinase (PK); the different variants are said to have somewhat different clinical features, including duration of illness, though all are ultimately fatal.)

GSS is a familial disease resembling CJD but with more prominent cerebellar ataxia and amyloid plaques. Dementia may appear only late in the course, and the average duration of illness is longer than typical sCJD. Progressively severe insomnia and dysautonomia as well as ataxia, myoclonus, and other signs resembling those of CJD and GSS characterize FFI and sporadic fatal insomnia. A case of sporadic fatal insomnia has been described in a young adolescent. GSS has not been diagnosed in children or adolescents.

A novel “prion disease” has been reported that is expressed in several generations with an autosomal dominant pattern associated with a unique mutation in the *PRNP* gene. The affected persons were middle-aged with a history of chronic diarrhea for years plus autonomic neuropathy and modest mental impairment but without full-blown dementia; PK-resistant PrP deposits with amyloid properties occurred in the brain, lymphoid tissues, kidney, spleen, and intestinal tract. The disease was not successfully transmitted to 3 lines of mice susceptible to several TSEs. It is not clear that such a syndrome—not a spongiform encephalopathy and apparently not associated with an infectious agent—should be lumped together with TSEs. It might well result from the abnormal *PRNP* gene product itself; if so, it would not pose the same potential threat to public health as do the TSEs.

DIAGNOSIS

Diagnosis of spongiform encephalopathies is most often determined on clinical grounds after excluding other diseases. The presence of 14-3-3 protein (see “Laboratory Findings”) in CSF may aid in distinguishing between CJD and Alzheimer disease, although this is not a consideration in children. Elevations of 14-3-3 protein levels in CSF are not specific to TSEs and are common in viral encephalitis and other conditions causing rapid necrosis of brain tissue. Brain biopsy may be diagnostic of CJD, but it can be recommended only if a potentially treatable disease remains to be excluded or if there is some other compelling reason to make an antemortem diagnosis. Definitive diagnosis usually requires microscopic examination of brain tissue obtained at autopsy. The demonstration of protease-resistant PrP proteins in brain extracts can be useful to augment histopathologic diagnosis. Accumulation of the abnormal PrP in lymphoid tissues, even before the onset of neurologic signs, is typical of vCJD. Tonsil biopsy may avoid the need for brain biopsy when antemortem diagnosis of vCJD is indicated. Transmission of disease to susceptible animals by inoculation of brain suspension must be reserved for cases of special research interest.

LABORATORY FINDINGS

Virtually all patients with typical sporadic, iatrogenic, and familial forms of CJD have abnormal electroencephalograms (EEGs) as the disease progresses; the background becomes slow and irregular with diminished amplitude. A variety of paroxysmal discharges such as slow waves, sharp waves, and spike-and-wave complexes may also appear, and these may be unilateral or focal or bilaterally synchronous. Paroxysmal discharges may be precipitated by loud noise. Many patients have typical periodic suppression-burst complexes of high-voltage slow activity on EEG at some time during the illness. Patients with vCJD have had only generalized slowing, without periodic bursts of high-voltage discharges on EEG. CT or MRI may show cortical atrophy and large ventricles late in the course of CJD. Many patients with vCJD have an increase in density of the pulvinar on MRI. Reliable interpretation of the images might best be left to experienced radiologists.

Table 278-3 Clinical and Histopathologic Features of Patients with Variant and Typical Sporadic Creutzfeldt-Jakob Disease

FEATURE	VARIANT CJD (FIRST 10 PATIENTS)	SPORADIC CJD (185 PATIENTS)
Years of age at death* (range)	29 (19-74)	65
Duration of illness, mo (range)	12 (8-23)	4
Presenting signs	Abnormal behavior, dysesthesia	Dementia
Later signs	Dementia, ataxia, myoclonus	Ataxia, myoclonus
Periodic complexes on EEG	Rare	Most
PRNP 129 Met/Met	All tested (except 1 transfusion-transmitted case, 1 plasma-derivative transmitted case; 1 possible clinical case in United Kingdom where no tissue was available to confirm)	83%
Histopathologic changes	Vacuolation, neuronal loss, astrocytosis, plaques (100%)	Vacuolation, neuronal loss, astrocytosis, plaques (≤15%)
Florid PrP plaques†	100%	0
PrP^{TSE} glycosylation pattern	BSE-like‡	Not BSE-like

*Median age and duration for variant CJD; averages for typical sporadic CJD.

†Dense plaques with a pale periphery of surrounding vacuolated cells.

‡Characterized by an excess of high molecular mass band (diglycosylated) and 19 kDa nonglycosylated band glycoform of PrP-res (Collinge J, Sidle KC, Meads J, et al: Molecular analysis of prion strain variation and the aetiology of “new variant” CJD, *Nature* 383:685–690, 1996).

BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; EEG, electroencephalogram; Met, codon 129 of one *PRNP* gene encoding for methionine; *PRNP*, prion protein–encoding gene; PrP, prion protein.

Modified from Will RG, Ironside JW, Zeidler M, et al: A new variant of Creutzfeldt-Jakob disease in the UK, Lancet *347:921–925, 1996.*

There may be modest elevation of CSF protein content in patients with TSE. Unusual protein spots were observed in CSF specimens after 2-dimensional separation in gels and silver staining; the spots were identified as 14-3-3 proteins, normal proteins (not related to PrP) abundant in neurons but not ordinarily detected in CSF. However, the finding of 14-3-3 protein in CSF has also been detected in CSF specimens from some patients with acute viral encephalitides and recent cerebral infarctions, and thus is not specific to CJD. Finding the 14-3-3 protein in CSF is neither sensitive nor specific but has been of some help in confirming the diagnosis of vCJD, especially when accompanied by increases in other cellular proteins. Diagnosis usually rests on recognizing the typical constellation of clinical findings, clinical course, and testing (CSF examination, CT or MRI, EEG), confirmed by histopathology and detection of PrP^{TSE} in brain tissues at autopsy (or, less often, by tonsil or brain biopsy).

TREATMENT

No treatment has proven effective. Studies of cell cultures and rodents experimentally infected with TSE agents suggested that treatment with chlorpromazine, quinacrine, and tetracyclines might be of benefit, especially during the incubation period. Early reports of clinical trials based on those studies have been discouraging, and it seems unlikely that the severe brain damage found in late disease can be reversed by such treatment. Infusions with pentosan polysulfate directly into the cerebral ventricles appear to have delayed the progression of vCJD in a least 1 patient but did not reverse earlier brain damage. Appropriate supportive care should be provided to all CJD patients as for other progressive fatal neurologic diseases. On the basis of experimental studies in animals, several prophylactic postexposure treatment regimens have been suggested, but none has been widely accepted.

GENETIC COUNSELING

TSE sometimes occurs in families in a pattern consistent with an autosomal dominant mode of inheritance. In patients with a family history of CJD, the clinical and histopathologic findings are similar to those seen in sporadic cases. In the United States, only approximately 10% of cases of CJD are familial. GSS and FFI are always familial. In some affected families, approximately 50% of siblings and children of a patient with a familial TSE eventually acquire the disease; in other families, the "penetrance" of illness may be less.

The gene coding for PrP is closely linked if not identical to that controlling the incubation periods of scrapie in sheep and both scrapie and CJD in mice. The gene encoding PrP in humans is designated the *PRNP* gene and is located on the short arm of chromosome 20. It has an open reading frame of about 759 nucleotides (253 codons), in which more than 20 different point mutations and a variety of inserted sequences encoding extra tandem-repeated octapeptides are linked to the occurrence of spongiform encephalopathy in families with a pattern consistent with autosomal dominance of variable penetrance.

The same nucleotide substitution at codon 178 of the *PRNP* gene associated with CJD in some families has been found in all patients with FFI. Homozygosity for valine and especially for methionine at codon 129 seems to increase susceptibility to iCJD and sCJD. Almost all patients with vCJD to be genotyped have been homozygous for methionine at codon 129 of the *PRNP* gene. A few probable preclinical vCJD infections and 1 clinically typical case of vCJD have been reported in persons with other genotypes. It is of interest that when the *PRNP* genes from appendices containing accumulations of what appears to be PrP^{TSE} in the United Kingdom were sequenced, a surprising number were homozygous for valine—the genotype of only approximately 10% of U.K. subjects and never found in a case of vCJD. The significance of this finding is not clear. U.K. authorities have adopted the precautionary assumption that some persons with PrP^{TSE} in lymphoid tissues may have latent infections. Whether the blood and tissues of such persons are infectious is unknown.

Although the interpretation of these findings in regard to the prion hypothesis is in dispute, persons from families with CJD or GSS who have the associated mutations in the *PRNP* gene have a high probability of eventually acquiring spongiform encephalopathy. The significance of mutations in the *PRNP* genes of individuals from families with no history of spongiform encephalopathy is not known. It seems wise to avoid alarming those from unaffected families who have miscellaneous mutations in the *PRNP* gene, because the implications are not yet clear; in the United States, such persons are deferred from donating blood if a blood relative has been diagnosed with a TSE.

PROGNOSIS

The prognosis of all spongiform encephalopathies is uniformly poor. Approximately 10% of patients may survive for longer than 1 yr, but the quality of life is poor.

FAMILY SUPPORT

The CJD Foundation (http://www.cjdfoundation.org), organized and maintained by family members and friends of patients with CJD and related disorders, working closely with the Centers for Disease Control and Prevention (http://www.cdc.gov/ncidod/dvrd/prions) and with the National Prion Disease Pathology Surveillance Center, Case Western Reserve University, Cleveland, Ohio (http://www.cjdsurveillance.com), is a support and educational group and a useful source of information regarding available resources for those dealing with the diseases.

PREVENTION

Exposure to the BSE agent in meat products clearly poses a special danger. Authorities in Canada, the United States, and other countries have responded by implementing progressively more stringent agricultural and public health measures during the past 20 yr, with elimination of most bovine-derived materials from animal feeds probably the most effective measure. Three cases of BSE in native cattle have been recognized in the United States since 2004—the last in 2012; a case was also recognized in a Canadian cow imported into the United States in 2003. Canada found 19 native cattle with BSE between 2003 and 2010 (and imported a case from the United Kingdom in 1993). In spite of encouraging epidemiologic studies that failed to implicate exposure to scrapie or CWD agents in human TSEs, it seems prudent to avoid exposing children to meat and other products likely to be contaminated with any TSE agent.

The safety of human blood, blood components, and plasma derivatives in the United States and Canada is protected by deferring those donors with histories suggesting an increased risk of TSEs: persons treated with cadaveric pituitary hormones (no longer used) or dura mater allografts, patients with a family history of CJD (unless sequencing shows that the TSE-affected blood relative or the donor has revealed no TSE-related mutation in either *PRNP* gene), and persons who spent substantial periods of time in specified countries during years when BSE was prevalent. Persons transfused with blood in the United Kingdom and France after 1980 should be deferred from donating blood (similar deferral policies are in place for donors of human cells and tissues). U.K. authorities have warned persons treated with U.K.-sourced pooled coagulation factor concentrates or antithrombin between 1989 and 2001 that they may be "at risk of vCJD for public health purposes" and that "special infection control precautions" apply to them.

In principle, it would be better to identify the few blood and tissue donors actually infected with a TSE rather than deferring all those at increased risk of exposure, because most of them are unlikely to have been infected. Accordingly, antemortem donor screening tests that might identify persons with preclinical TSE infections are currently under development but have not been clinically validated. Another attractive approach would be to remove TSE agents from blood. Along these lines, a committee of expert advisors to the U.K. government recommended considering the use of an investigational device to filter red cells intended to transfuse children, because some unknown but possibly substantial number of U.K. blood donors might be incubating vCJD; authorities in the United Kingdom (and Ireland) evaluated, but have not adopted, that advice.

Standard precautions should be used to handle all human tissues, blood, and body fluids. Materials and surfaces contaminated with tissues or fluids from patients suspected of having CJD must be treated with great care. Whenever possible, discard contaminated instruments

by careful packaging and incineration. Contaminated tissues and biologic products probably cannot be completely freed of infectivity without destroying their structural integrity and biologic activity; therefore, the medical and family histories of individual tissue donors should be carefully reviewed to exclude a diagnosis of TSE. Histopathologic examination of brain tissues of cadaveric donors and testing for abnormal PrP might be performed where feasible to provide an additional assurance of safety. Although no method of sterilization can be relied on to remove all infectivity from contaminated surfaces, exposures to moist heat, sodium hydroxide, chlorine bleach, concentrated formic acid, acidified detergent, and guanidine salts markedly reduced infectivity in experimental studies.

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Section 14

Antiparasitic Therapy

Chapter 279

Principles of Antiparasitic Therapy

Mark R. Schleiss

Parasites are divided into 2 main groups taxonomically: **protozoans,** which are unicellular, and **helminths**, which are multicellular. Chemotherapeutic agents appropriate for 1 group may not be appropriate for the other, and not all drugs are readily available (Table 279-1). Some drugs are available only from the manufacturer, some are not available in the United States, and some are available through the Centers for Disease Control and Prevention (CDC). Availability of drugs can be ascertained by contacting the Parasitic Diseases Public Inquiries Branch (1-404-718-4745; e-mail INTER REF chagas@cdc.gov). For after-hours emergencies, practitioners can contact the CDC Emergency Operations Center (770-488-7100) and ask for the on-call parasitic diseases physician. For assistance in the management of malaria, healthcare should call the CDC Malaria Hotline: 770-488-7788 or 855-856-4713 toll-free (M-F, 9 AM-5 PM, Eastern time). For emergency consultation after hours, clinicians can phone 770-488-7100 and request to speak with a CDC Malaria Branch clinician.

SELECTED ANTIPARASITIC DRUGS FOR PROTOZOANS

Nitazoxanide (Alinia)

Nitazoxanide is a nitrothiazole benzamide, initially developed as a veterinary anthelmintic. Nitazoxanide inhibits pyruvate-ferredoxin oxidoreductase, which is an enzyme necessary for anaerobic energy metabolism. In humans, nitazoxanide is effective against many protozoans and helminths. Nitazoxanide is approved for the treatment of diarrhea caused by *Cryptosporidium* species in children 1-11 yr of age and by *Giardia intestinalis* in children 1 yr of age and older.

Nitazoxanide is available as an oral suspension, which has a pink color and strawberry flavor. The bioavailability is doubled with food. The drug is well absorbed from the gastrointestinal tract. One third is excreted in urine, and two thirds is excreted in feces as the active metabolite, tizoxanide. Although in vitro metabolism studies have not demonstrated cytochrome P450 enzyme effects, no pharmacokinetic studies have been performed yet in patients with compromised renal or hepatic function. In addition, no studies have been performed in pregnant or lactating women. Common adverse effects include abdominal pain, diarrhea, and nausea. Rare side effects include anorexia, flatulence, increased appetite, fever, pruritus, and dizziness. Intriguingly, nitazoxanide has activity against both hepatitis C and rotavirus, although the use of the agent against these viruses is investigational.

Tinidazole (Tindamax)

Tinidazole is a synthetic nitroimidazole with a chemical structure similar to metronidazole. It is FDA approved for treatment of trichomoniasis and for giardiasis and amebiasis in children 3 yr of age and older. In the treatment of giardiasis, it has the advantages of very few side effects and only requiring a single dose. Its mechanism of action against *Trichomonas* may be secondary to the generation of free nitro radicals by the protozoan. The mechanism of action against *Giardia lamblia* and *Entamoeba histolytica* is unknown. After oral administration, tinidazole is rapidly and completely absorbed and distributes into almost all tissues and body fluids, including crossing the blood–brain barrier and placental barrier. It is excreted via urine and feces. Hemodialysis increases clearance of drug. No studies have been performed for patients undergoing peritoneal dialysis or for patients with compromised hepatic function. Tinidazole carries a pregnancy category C classification and can be detected in breast milk. Breastfeeding should be interrupted during treatment and for 3 days after treatment.

Atovaquone/Proguanil (Malarone)

Atovaquone is a hydroxynaphthoquinone and has been used in the past predominantly against *Pneumocystis* pneumonia in AIDS patients. Its mechanism of action is via disruption of mitochondria membrane potential through interaction with cytochrome B. Atovaquone can also effectively inhibit liver stages of all *Plasmodium* species.

Proguanil is approved for use in the United States. Its mechanism of action is inhibition of the parasite dihydrofolate reductase enzyme by the active form, cycloguanil. When used alone, it has poor efficacy for prophylaxis.

Proguanil acts in synergy with atovaquone on the cytochrome B enzyme in *Plasmodia* mitochondria. The exact mechanism of synergy is unknown. In 2000, the FDA approved atovaquone/proguanil for the prevention and treatment of acute, uncomplicated *Plasmodium falciparum* malaria. Atovaquone alone and in combination with proguanil is the only drug to completely inhibit the liver stage, which provides the advantage of only needing to use the drug for 7 days after departing a malaria-endemic area (compared to several weeks).

Two double-blind, randomized clinical trials assessing malaria prophylaxis demonstrated that atovaquone/proguanil was at least comparable to (and perhaps better than) chloroquine plus proguanil, and that atovaquone/proguanil was comparable to mefloquine. Atovaquone/proguanil was better tolerated than chloroquine plus proguanil and mefloquine. Atovaquone/proguanil treatment of acute uncomplicated *P. falciparum* infection has demonstrated higher or comparable cure rates when compared with other *P. falciparum* treatment drugs. Compared with other antimalaria treatment therapies, atovaquone/proguanil treatment has the highest cost.

Artemisinin Derivatives and Artemether/Lumefantrine (Coartem, Artemether, Artesunate)

Artemisinin is a sesquiterpene lactone isolated from the weed *Artemisia annua.* It was developed in China where it is known as qinghaosu. Artemisinins act very rapidly against *Plasmodium vivax* as well as chloroquine-sensitive and chloroquine-resistant *P. falciparum.* Artemisinins are also rapidly eliminated. Emerging resistance to artemisinins has been seen in Cambodia, but not all of Southeast Asia. Coartem is the first artemisinin-containing drug approved for use by the FDA. It is a fixed-dose combination of 2 novel antimalarials, artemether (20 mg) and lumefantrine (120 mg). It is a highly effective 3 day malaria treatment with cure rates of >96%, even in areas of multidrug resistance.

Text continued on p. 1687

Table 279-1 Drugs for Parasitic Infections

Parasitic infections are found throughout the world. With increasing travel, immigration, use of immunosuppressive drugs, and the spread of AIDS, physicians anywhere may see infections caused by previously unfamiliar parasites. The table below lists first-choice and alternative drugs for most parasitic infections.

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Acanthamoeba keratitis			
Drug of choice:	See footnote 1		
Amebiasis *(Entamoeba histolytica)*			
Asymptomatic			
Drug of choice:	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day (max 2 g) in 3 doses PO × 20 days
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Alternative:	Diloxanide furoate[2]	500 mg tid PO × 10 days	20 mg/kg/day PO in 3 doses × 10 days
Mild to moderate intestinal disease[3]			
Drug of choice[4]:	Metronidazole	500-750 mg tid PO × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole[5]	2 g PO once daily × 3 days	50 mg/kg/day PO (max 2 g) in 1 dose × 3 days
Either followed by:	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Severe intestinal and extraintestinal disease[3]			
Drug of choice:	Metronidazole	750 mg PO tid × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole[5]	2 g PO once daily × 5 days	50 mg/kg/day PO (max 2 g) × 5 days
Either followed by:	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Amebic meningoencephalitis, primary and granulomatous			
Naegleria			
Drug of choice:	Amphotericin B[6,7]	1.5 mg/kg/day IV in 2 doses × 3 days, then 1.5 mg/kg/day IV × 6 days	1.5 mg/kg/day IV in 2 doses × 3 days, then 1 mg/kg/d IV × 6 days
or		1 mg/kg IV once/day plus 0.5 mg/day intraventricularly (max of 1.5 mg/kg by both routes)	1 mg/kg IV once/daily plus 0.5 mg/d intraventricularly (max of 1.5 mg/kg by both routes)
or	Rifampin Fluconazole Azithromycin	10 mg/kg IV once/daily (max 600 mg/d) 12 mg/kg IV once/daily 500 mg IV once/daily	10 mg/kg IV once/daily (max 600 mg/d) 12 mg/kg IV once/daily 20 mg/kg IV once/daily (max 500 mg/d)
Acanthamoeba			
Drug of choice:	See footnote 8		

[1]For treatment of keratitis caused by *Acanthamoeba*, concurrent topical use of 0.1% propamidine isethionate (Brolene) plus neomycin-polymyxin B-gramicidin ophthalmic solution has been successful (Hargrave SL, et al: *Ophthalmology* 106:952, 1999). In some European countries, propamidine is not available and hexamidine (Desmodine) has been used (Seal DV: *Eye* 17:893, 2003). In addition, 0.02% topical polyhexamethylene biguanide (PHMB) and/or chlorhexidine has been used successfully in a large number of patients (Tabin G, et al: *Cornea* 20:757, 2001; Wysenbeek YS, et al: *Cornea* 19:464, 2000). PHMB is available from Leiter's Park Avenue Pharmacy, San Jose, CA (800-292-6773; www.leiterrx.com). The combination of chlorhexidine, natamycin (pimaricin), and debridement also has been successful (Kitagawa K, et al: *Jpn J Ophthalmol* 47:616, 2003).

[2]The drug is not available commercially, but as a service can be compounded by Panorama Compounding Pharmacy, 6744 Balboa Blvd, Van Nuys, CA 91406 (800-247-9767) or Medical Center Pharmacy, New Haven, CT (203-688-6816).

[3]Treatment should be followed by a course of iodoquinol or paromomycin in the dosage used to treat asymptomatic amebiasis.

[4]Nitazoxanide is FDA approved as a pediatric oral suspension for treatment of *Cryptosporidium* in immunocompetent children younger than 12 yr old and for *Giardia* (*Med Lett* 2003;45:29). It may also be effective for mild to moderate amebiasis (Diaz E, et al: *Am J Trop Med Hyg* 68:384, 2003). Nitazoxanide is available in 500 mg tablets and an oral suspension; it should be taken with food.

[5]A nitroimidazole similar to metronidazole, tinidazole was recently approved by the FDA and appears to be as effective and better tolerated than metronidazole. It should be taken with food to minimize GI adverse effects. For children and patients unable to take tablets, a pharmacist may crush the tablets and mix them with cherry syrup (Humco, and others). The syrup suspension is good for 7 days at room temperature and must be shaken before use. Ornidazole, a similar drug, is also used outside the United States.

[6]*Naegleria* infection has been treated successfully with intravenous and intrathecal use of both amphotericin B and miconazole plus rifampin and with amphotericin B, rifampin, and ornidazole (Seidel J, et al: *N Engl J Med* 306:346, 1982; Jain R, et al: *Neurol India* 50:470, 2002). Other reports of successful therapy are less-well documented.

[7]An approved drug, but considered investigational for this condition by the FDA.

[8]Strains of *Acanthamoeba* isolated from fatal granulomatous amebic encephalitis are usually susceptible in vitro to pentamidine, ketoconazole, flucytosine, and (less so) to amphotericin B. Chronic *Acanthamoeba* meningitis has been successfully treated in 2 children with a combination of oral trimethoprim-sulfamethoxazole, rifampin, and ketoconazole (Singhal T, et al: *Pediatr Infect Dis J* 20:623, 2001), and in an AIDS patient with fluconazole, sulfadiazine, and pyrimethamine combined with surgical resection of the CNS lesion (Seijo Martinez M, et al: *J Clin Microbiol* 38:3892, 2000). Disseminated cutaneous infection in an immunocompromised patient has been treated successfully with IV pentamidine isethionate, topical chlorhexidine, and 2% ketoconazole cream, followed by oral itraconazole (Slater CA, et al: *N Engl J Med* 331:85, 1994).

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Balamuthia mandrillaris			
Drug of choice:	See footnote 9		
Sappinia diploidea			
Drug of choice:	See footnote 10		
Ancylostoma caninum (eosinophilic enterocolitis)			
Drug of choice:	Albendazole[7]	400 mg PO once	400 mg PO once
or	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days
or	Pyrantel pamoate[7]	11 mg/kg PO (max 1 g) × 3 days	11 mg/kg PO (max 1 g) × 3 days
or	Endoscopic removal		
Ancylostoma duodenale, see Hookworm			
Angiostrongyliasis *(Angiostrongylus cantonensis, Angiostrongylus costaricensis)*			
Drug of choice:	See footnote 11		
Anisakiasis (*Anisakis* spp.)			
Treatment of choice[12]:	Surgical or endoscopic removal		
Ascariasis (*Ascaris lumbricoides,* roundworm)			
Drug of choice:	Albendazole[7]	400 mg PO once	400 mg PO once
or	Mebendazole	100 mg PO bid × 3 days or 500 mg PO once	100 mg PO bid × 3 days or 500 mg PO once
or	Ivermectin[7]	150-200 µg/kg PO once	150-200 µg/kg PO once
Babesiosis *(Babesia microti)*			
Drugs of choice[13]:	Atovaquone[7] **plus** azithromycin[7]	750 mg PO bid × 7-10 days 600 mg PO daily × 7-10 days	20 mg/kg PO bid × 7-10 days 10 mg/kg PO on day 1 (max 500 mg/dose), then 5 mg/kg/d (max 250 mg/dose) PO days 2-10
or	Clindamycin[7] **plus** quinine[7]	300-600 mg IV qid or 600 mg tid PO × 7-10 days 650 mg tid PO × 7-10 days	20-40 mg/kg/day IV or PO in 3 or 4 doses × 7-10 days (max 600 mg/dose) 24 mg/kg/day PO in 3 doses × 7-10 days
Balamuthia mandrillaris, see Amebic meningoencephalitis, primary			
Balantidiasis *(Balantidium coli)*			
Drug of choice:	Tetracycline[7,14]	500 mg PO qid × 10 days	40 mg/kg/day PO (max 2 g) in 4 doses × 10 days
Alternatives:	Metronidazole[7] Iodoquinol[7]	750 mg PO tid × 5 days 650 mg PO tid × 20 days	35-50 mg/kg/day PO in 3 doses × 5 days 40 mg/kg/day PO in 3 doses × 20 days

[9]A free-living leptomyxid ameba that causes subacute to fatal granulomatous CNS disease. Several cases of *Balamuthia* encephalitis have been successfully treated with flucytosine, pentamidine, fluconazole, and sulfadiazine plus either azithromycin or clarithromycin (phenothiazines were also used) combined with surgical resection of the CNS lesion (Deetz TR, et al: *Clin Infect Dis* 37:1304, 2003; Jung S, et al: *Arch Pathol Lab Med* 128:466, 2004). Miltefosine is another option currently being evaluated but it is not approved for any indication in the United States at this time. Case reports and in vitro data suggest it may have some antiamebic activity (AC Aichelburg et al., *Emerg Infect Dis* 2008; 14:1743; DY Martinez et al., *Clin Infect Dis* 2010; 51:e7; FL Schuster et al., *J Eukaryot Microbiol* 2006; 53:121). Miltefosine (Impavido) is manufactured in 10 or 50 mg capsules by Paladin (Canada) and is available in the United States from the CDC for treatment of infections with free-living amebas.

[10]A free-living ameba not previously known to be pathogenic to humans. It has been successfully treated with azithromycin, IV pentamidine, itraconazole, and flucytosine combined with surgical resection of the CNS lesion (Gelman BB, et al: *J Neuropathol Exp Neurol* 62:990, 2003).

[11]Most patients have a self-limited course and recover completely. Analgesics, corticosteroids, and careful removal of CSF at frequent intervals can relieve symptoms from increased intracranial pressure (Lo Re V III, Gluckman SJ: *Am J Med* 114:217, 2003). No anthelmintic drug is proven to be effective, and some patients have worsened with therapy (Slom TJ, et al: *N Engl J Med* 346:668, 2002). Mebendazole or albendazole and a corticosteroid appeared to shorten the course of infection (K Sawanyawisuth and K Sawanyawisuth, *Trans R Soc Trop Med Hyg* 2008; 102:990; V Chotmongkol et al. *Am J Trop Med Hyg* 2009;81:443).

[12](Repiso Ortega A, et al: *Gastroenterol Hepatol* 26:341, 2003.) Successful treatment of a patient with *Anisakiasis* with albendazole has been reported (Moore DA, et al *Lancet* 360:54, 2002).

[13]Exchange transfusion has been used in severely ill patients and those with high (>10%) parasitemia (Hatcher JC, et al *Clin Infect Dis* 32:1117, 2001). In patients who were not severely ill, combination therapy with atovaquone and azithromycin was as effective as clindamycin and quinine and may have been better tolerated (Krause PJ, et al: *N Engl J Med* 343:1454, 2000). Highly immunosuppressed patients should be treated for a minimum of 6 wk and at least 2 wk past the last positive smear (PJ Krause et al., *Clin Infect Dis* 2008; 46:370). High doses of azithromycin (600-1,000 mg) have been used in combination with atovaquone for the treatment of immunocompromised patients (LM Weiss et al., *N Engl J Med* 2001; 344:773). Resistance to atovaquone plus azithromycin has been reported in immunocompromised patients treated with a single subcurative course of this regimen (GP Wormser et al., *Clin Infect Dis* 2010; 50:381).

[14]Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Baylisascariasis *(Baylisascaris procyonis)*			
Drug of choice:	See footnote 15		
Blastocystis hominis infection			
Drug of choice:	See footnote 16		
Capillariasis *(Capillaria philippinensis)*			
Drug of choice:	Mebendazole[7]	200 mg PO bid × 20 days	200 mg PO bid × 20 days
Alternatives:	Albendazole[7]	400 mg PO daily × 10 days	400 mg PO daily × 10 days
Chagas disease, see Trypanosomiasis			
Clonorchis sinensis, see Fluke infection			
Cryptosporidiosis *(Cryptosporidium)*			
Immunocompetent			
Drug of choice:	Nitazoxanide[4]	500 mg PO bid × 3 days[7]	1-3 yr: 100 mg PO bid × 3 days
			4-11 yr: 200 mg PO bid × 3 days
HIV infected			
Drug of choice:	See footnote 17		
Cutaneous larva migrans (creeping eruption, dog and cat hookworm)			
Drug of choice[18]:	Albendazole[7]	400 mg PO daily × 3 days	400 mg PO daily × 3 days
or	Ivermectin[7]	200 µg/kg PO daily × 1-2 days	200 µg/kg PO daily × 1-2 days
Alternative:	Thiabendazole	Topically	Topically
Cyclosporiasis *(Cyclospora cayetanensis)*			
Drug of choice[19]:	Trimethoprim-sulfamethoxazole (TMP-SMX)[7]	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 7-10 days	TMP 5 mg/kg, SMX 25 mg/kg bid PO × 7-10 days
Alternative:	Ciprofloxacin	500 mg PO bid × 7 days	-
Cysticercosis, see Tapeworm infection			
Drug of choice:			
Cystoisosporiasis *(Cystoisospora belli, formerly known as Isospora)*			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)[7]	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 10 days	TMP 5 mg/kg, SMX 25 mg/kg PO bid × 10 days
Dientamoeba fragilis infection[20]			
	Paromomycin[7]	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
or	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day PO (max 2 g) in 3 doses × 20 days
or	Metronidazole	500-750 mg tid × 10 days	20-40 mg/kg/day in 3 doses × 10 days
Diphyllobothrium latum, see Tapeworm infection			

[15]No drugs have been consistently demonstrated to be effective. The combination of albendazole 37 mg/kg/d PO and high-dose steroids has been used successfully (JM Peters et al., *Pediatrics* 2012; 129:e806; S Haider, *Emerg Infect Dis* 2012; 18:347). Albendazole 25 mg/kg/d PO × 20 d started as soon as possible (up to 3 d after possible infection) might prevent clinical disease and is recommended for children with known exposure, such as in the setting of ingestion of raccoon stool or contaminated soil (WJ Murray and KR Kazacos, *Clin Infect Dis* 2004; 39:1484). Mebendazole, levamisole, or ivermectin could be tried if albendazole is not available. Ocular baylisascariasis has been treated successfully using laser photocoagulation therapy to destroy the intraretinal larvae.

[16]Clinical significance of these organisms is controversial; metronidazole 750 mg tid × 10 days, iodoquinol 650 mg tid × 20 days or trimethoprim-sulfamethoxazole 1 DS tab bid × 7 days have been reported to be effective (Stenzel DJ, Borenam PFL: *Clin Microbiol Rev* 9:563, 1996; Ok UZ, et al: *Am J Gastroenterol* 94:3245, 1999). Metronidazole resistance may be common (Haresh K, et al: *Trop Med Int Health* 4:274, 1999). Nitazoxanide has been effective in children (Diaz E, et al: *Am J Trop Med Hyg* 68:384, 2003).

[17]Nitazoxanide has not consistently been shown to be superior to placebo in HIV-infected patients (Amadi B, et al: *Lancet* 360;1375, 2002). For HIV-infected patients, potent antiretroviral therapy (ART) is the mainstay of treatment. Nitazoxanide (treatment duration of 5-21 days), paromomycin, or a combination of paromomycin and azithromycin may be tried to decrease diarrhea and recalcitrant malabsorption of antimicrobial drugs, which can occur with chronic cryptosporidiosis (B Pantenburg et al., *Expert Rev Anti Infect Ther* 2009; 7:385).

[18]Albanese G, et al: *Int J Dermatol* 40:67, 2001.

[19]HIV-infected patients may need higher dosage and long-term maintenance (Kansouzidou A, et al: *J Trav Med* 11:61, 2004).

[20]Norberg A, et al: *Clin Microbiol Infect* 9:65, 2003.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Dracunculus medinensis (guinea worm) infection			
Drug of choice:	See footnote 21		
Echinococcus, see Tapeworm Infection			
Entamoeba histolytica, see Amebiasis			
Enterobius vermicularis (pinworm) infection			
Drug of choice[22]:	Albendazole[7]	400 mg PO once; repeat in 2 wk	400 mg PO once; repeat in 2 wk
or	Mebendazole	100 mg PO once; repeat in 2 wk	100 mg PO once; repeat in 2 wk
or	Pyrantel pamoate	11 mg/kg base PO once (max 1 g); repeat in 2 wk	11 mg/kg base PO once (max 1 g); repeat in 2 wk
Fasciola hepatica, see Fluke infection			
Filariasis[23]			
Wuchereria bancrofti, Brugia malayi, Brugia timori			
Drug of choice[24]:	Diethylcarbamazine	6 mg/kg PO in 3 doses × 14 days[25]	6 mg/kg PO in 3 doses × 14 days[25]
Loa loa			
Drug of choice[26]:	Diethylcarbamazine	9 mg/kg PO in 3 doses × 14 days[25]	9 mg/kg PO in 3 doses × 14 days[25]
Mansonella ozzardi			
Drug of choice:	See footnote 27		
Mansonella perstans			
Drug of choice:	Doxycycline[7,14]	100 mg bid PO × 7 days	4 mg/kg/day in 2 doses PO × 7 days
Mansonella streptocerca[28]			
Drug of choice:	Diethylcarbamazine Ivermectin[7]	6 mg/kg/day PO × 14 days 150 µg/kg PO once	6 mg/kg/day PO × 14 days 150 µg/kg PO once
Tropical pulmonary eosinophilia (TPE)[29]			
Drug of choice:	Diethylcarbamazine	6 mg/kg/day in 3 doses × 12-21 days	6 mg/kg/day in 3 doses × 12-21 days
Onchocerca volvulus (river blindness)			
Drug of choice:	Invermectin[30]	150 µg/kg PO once, repeated every 6-12 mo until asymptomatic	150 µg/kg PO once, repeated every 6-12 mo until asymptomatic
Fluke, hermaphroditic, infection			

[21]Treatment of choice is slow extraction of worm combined with wound care (*MMWR Morbid Mortal Wkly Rep* 2011; 60:1450). 10 days' treatment with metronidazole 250 mg tid in adults and 25 mg/kg/day in 3 doses in children is not curative, but decreases inflammation and facilitates removal of the worm. Mebendazole 400-800 mg/day × 6 days has been reported to kill the worm directly.

[22]Since all family members are usually infected, treatment of the entire household is recommended.

[23]Antihistamines or corticosteroids may be required to decrease allergic reactions due to disintegration of microfilariae from treatment of filarial infections, especially those caused by *Loa loa*. Endosymbiotic *Wolbachia* bacteria may have a role in filarial development and host response, and may represent a new target for therapy. Treatment with doxycycline 100 or 200 mg/day × 4-6 wk in lymphatic filariasis and onchocerciasis has resulted in substantial loss of *Wolbachia* with subsequent block of microfilariae production and absence of microfilaria when followed for 24 mo after treatment (Hoerauf A, et al: *Med Microbiol Immunol* 192:211, 2003; Hoerauf A, et al: *BMJ* 326:207, 2003).

[24]Most symptoms caused by adult worm. Single-dose combination of albendazole (400 mg) with either ivermectin (200 µg/kg) or diethylcarbamazine (6 mg/kg) is effective for reduction or suppression of *Wuchereria bancrofti* microfilaria but does not kill the adult forms (Addiss D, et al: *Cochrane Database Syst Rev* 2004;CD003753).

[25]For patients with microfilaria in the blood, *Medical Letter* consultants would start with a lower dosage and scale up: day 1, 50 mg; day 2, 50 mg tid; day 3, 100 mg tid; day 4-14, 6 mg/kg in 3 doses (for *Loa loa* day 4-14, 9 mg/kg in 3 doses). Multidose regimens have been shown to provide more rapid reduction in microfilaria than single-dose diethylcarbamazine, but microfilaria levels are similar 6-12 mo after treatment (Andrade LD, et al: *Trans R Soc Trop Med Hyg* 89:319, 1995; Simonsen PE, et al: *Am J Trop Med Hyg* 53:267, 1995). A single dose of 6 mg/kg is used in endemic areas for mass treatment (Figueredo-Silva J, et al: *Trans R Soc Trop Med Hyg* 90:192, 1996; Noroes J, et al: *Trans R Soc Trop Med Hyg* 91:78, 1997).

[26]In heavy infections with *Loa loa*, rapid killing of microfilariae can provoke an encephalopathy. Apheresis has been reported to be effective in lowering microfilarial counts in patients heavily infected with *Loa loa* (Ottesen ES: *Infect Dis Clin North Am* 7:619, 1993). Albendazole or ivermectin have also been used to reduce microfilaremia; albendazole is preferred because of its slower onset of action and lower risk for encephalopathy (Klion AD, et al: *J Infect Dis* 168:202, 1993; Kombila M, et al: *Am J Trop Med Hyg* 58:458, 1998). Albendazole may be useful for treatment of loiasis when diethylcarbamazine is ineffective or cannot be used, but repeated courses may be necessary (Klion AD, et al: *Clin Infect Dis* 29:680, 1999). Diethylcarbamazine, 300 mg once/wk, has been recommended for prevention of loiasis (Nutman TB, et al: *N Engl J Med* 319:752, 1988).

[27]Diethylcarbamazine has no effect. Ivermectin 200 µg/kg once has been effective.

[28]Diethylcarbamazine is potentially curative because of activity against both adult worms and microfilariae. Ivermectin is only active against microfilariae. (The Medical Letter: *Drugs for parasitic infections*, ed 2, 2010).

[29]Relapse occurs and can be treated with diethylcarbamazine.

[30]Annual treatment with ivermectin, 150 µg/kg, can prevent blindness from ocular onchocerciasis (Mabey D, et al: *Ophthalmology* 103:1001, 1996). Diethylcarbamazine should not be used for treatment of this disease.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Clonorchis sinensis (Chinese liver fluke)			
Drug of choice:	Praziquantel	75 mg/kg/day PO in 3 doses × 1 day	75 mg/kg/day PO in 3 doses × 1 day
or	Albendazole[7]	10 mg/kg PO × 7 days	10 mg/kg PO × 7 days
Fasciola hepatica (sheep liver fluke)			
Drug of choice[31]:	Triclabendazole	10 mg/kg PO once or twice[32]	10 mg/kg PO once or twice[32]
Alternative:	Bithionol	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
or	Nitazoxanide	500 mg PO bid × 7 days	1-3 yr: 100 mg PO bid 4-11 yr: 200 mg PO bid
Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai (intestinal flukes)			
Drug of choice:	Praziquantel[7]	75 mg/kg/day PO in 3 doses × 1 day	75 mg/kg/day PO in 3 doses × 1 day
Metorchis conjunctus (North American liver fluke)[33]			
Drug of choice:	Praziquantel[7]	75 mg/kg/day PO in 3 doses × 1 day	75 mg/kg/day PO in 3 doses × 1 day
Nanophyetus salmincola			
Drug of choice:	Praziquantel[7]	60 mg/kg/day PO in 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day
Opisthorchis viverrini (Southeast Asian liver fluke)			
Drug of choice:	Praziquantel	75 mg/kg/day PO in 3 doses × 2 days	75 mg/kg/day PO in 3 doses × 2 days
or	Albendazole	10 mg/kg/day PO × 7 days	10 mg/kg/day PO × 7 days
Paragonimus westermani (lung fluke)			
Drug of choice:	Praziquantel[7]	75 mg/kg/day PO in 3 doses × 2 days	75 mg/kg/day PO in 3 doses × 2 days
or[34]	Bithionol	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
or	Triclabendazole	10 mg/kg PO once or twice	10 mg/kg PO once or twice
Giardiasis *(Giardia duodenalis)*			
Drugs of choice:	Metronidazole[7] Nitazoxanide[4] Tinidazole[5]	250 mg PO tid × 5 days 500 mg PO bid × 3 days 2 g PO once	15 mg/kg/day PO in 3 doses × 5 days 1-3 yr: 100 mg PO every 12 hr × 3 days 4-11 yr: 200 mg PO every 12 hr × 3 days 50 mg/kg PO once (max 2 g)
Alternatives[35]:	Paromomycin[7,36] Furazolidone Quinacrine[2]	25-35 mg/kg/day PO in 3 doses × 7 days 100 mg PO qid × 7-10 days 100 mg PO tid × 5 days	25-35 mg/kg/day PO in 3 doses × 7 days 6 mg/kg/day PO in 4 doses × 7-10 days 2 mg/kg tid PO × 5 days (max 300 mg/day)
Gnathostomiasis *(Gnathostoma spinigerum)*			
Treatment of choice[37]:	Albendazole[7]	400 mg PO bid × 21 days	400 mg PO bid × 21 days
or	Ivermectin[7]	200 μg/kg/day PO × 2 days	200 μg/kg/day PO × 2 days
±	Surgical removal		
Gongylonemiasis (*Gongylonema* sp.)[38]			
Treatment of choice:	Surgical removal		
or	Albendazole[7]	10 mg/kg/day PO × 3 days	10 mg/kg/day PO × 3 days

[31]Unlike infections with other flukes, *Fasciola hepatica* infections may not respond to praziquantel. Triclabendazole (Egaten, Novartis) may be safe and effective but data are limited (Graham CS, et al: *Clin Infect Dis* 33:1, 2001). It is available from Victoria Pharmacy, Zurich, Switzerland (www.pharmaworld.com; 41-1-211-24-32) and should be given with food for better absorption. A single study has found that nitazoxanide has limited efficacy for treating fascioliasis in adults and children (Favennec L, et al: *Aliment Pharmacol Ther* 17:265, 2003).

[32]Richter J, et al: *Curr Treat Options Infect Dis* 2002;4:313.

[33]MacLean JD, et al: *Lancet* 347:154, 1996.

[34]Triclabendazole may be effective in a dosage of 5 mg/kg once/day × 3 days or 10 mg/kg bid + 1 day (Calvopiña M, et al: *Trans R Soc Trop Med Hyg* 92:566, 1998). See footnote 31 for availability.

[35]Albendazole 400 mg daily × 5 days alone or in combination with metronidazole may also be effective (Hall A, Nahar Q: *Trans R Soc Trop Med Hyg* 87:84, 1993; Dutta AK, et al: *Indian J Pediatr* 61:689, 1994; Cacopardo B, et al: *Clin Ter* 146:761, 1995). Combination treatment with standard doses of metronidazole and quinacrine given for 3 wk has been effective for a small number of refractory infections (Nash TE, et al: *Clin Infect Dis* 33:22, 2001). In 1 study, nitazoxanide was used successfully in high doses to treat a case of *Giardia* resistant to metronidazole and albendazole (Abboud P, et al: *Clin Infect Dis* 32:1792, 2001).

[36]Not absorbed; may be useful for treatment of giardiasis in pregnancy.

[37]de Gorgolas M, et al: *J Travel Med* 10:358, 2003. All patients should be treated with a medication regardless of whether surgery is attempted.

[38]Eberhard ML, Busillo C: *Am J Trop Med Hyg* 61:51, 1999; Wilson ME, et al: *Clin Infect Dis* 32:1378, 2001.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Hookworm infection *(Ancylostoma duodenale, Necator americanus)*			
Drug of choice:	Albendazole[7]	400 mg PO once	400 mg PO once
or	Mebendazole	100 mg PO bid × 3 days or 500 mg once	100 mg PO bid × 3 days or 500 mg once
or	Pyrantel pamoate[7]	11 mg/kg (max 1 g) PO × 3 days	11 mg/kg (max 1 g) PO × 3 days
Hydatid cyst, see Tapeworm infection			
Hymenolepis nana, see Tapeworm infection			
Leishmania **infection**			
Visceral[39, 40]			
Drugs of choice:	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 28 days[41]	20 mg Sb/kg/day IV or IM × 28 days[41]
or	Meglumine antimonate	20 mg pentavalent antimony/kg/day IV or IM × 28 days[41]	20 mg pentavalent antimony/kg/day IV or IM × 28 days[41]
or	Amphotericin B[7]	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk
or	Liposomal amphotericin B[42]	3 mg/kg/day IV (days 1-5) followed by 3 mg/kg/day on days 14 and 21[43]	3 mg/kg/day IV (days 1-5) followed by 3 mg/kg/day on days 14 and 21[43]
or	Miltefosine	2.5 mg/kg/day PO (max 150 mg/day) × 28 days	2.5 mg/kg/day PO (max 150 mg/day) × 28 days
Alternative[44]:	Pentamidine[7]	4 mg/kg IV or IM daily or every 2 days for 15-30 doses	4 mg/kg IV or IM daily or every 2 days for 15-30 doses
Cutaneous[45]			
Drugs of choice:	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 20 days[41]	20 mg Sb/kg/day IV or IM × 20 days[41]
or	Meglumine antimonate	20 mg pentavalent antimony/kg/day IV or IM × 20 days[41]	20 mg pentavalent antimony/kg/day IV or IM × 20 days[41]
or	Miltefosine	2.5 mg/kg/day PO (max 150 mg/day) × 28 days	2.5 mg/kg/day PO (max 150 mg/day) × 28 days
Alternatives[46]:	Pentamidine[7]	2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses[47]	2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses[47]
or	Paromomycin[7,48]	Topically 2×/day × 10-20 days	Topically 2×/day × 10-20 days

[39]Consultation with physicians experienced in management of this disease is recommended. To maximize effectiveness and minimize toxicity, the choice of drug, dosage and duration of therapy should be individualized based on the region of disease acquisition, likely infecting species, number, significance and location of lesions, and host factors such as immune status (HW Murray, Lancet 2005; 366:1561). Some of the listed drugs and regimens are effective only against certain *Leishmania* species/strains and only in certain areas of the world (S Sundar and J Chakravarty, Expert Opin Pharmacother 2013; 14:53).

[40]Visceral infection is most commonly caused by the Old World species *Leishmania donovani* (kala-azar) and *Leishmania infantum* and the New World species. *Leishmania chagasi*. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[41]May be repeated or continued; a longer duration may be needed for some patients (Herwaldt BL: *Lancet* 354:1191, 1999).

[42]Three lipid formulations of amphotericin B have been used for treatment of visceral leishmaniasis. Largely based on clinical trials in patients infected with *Leishmania infantum,* the FDA approved liposomal amphotericin B (AmBisome) for treatment of visceral leishmaniasis (Meyerhoff A, *Clin Infect Dis* 1999;28:42). Amphotericin B lipid complex (Abelcet) and amphotericin B cholesteryl sulfate (Amphotec) have also been used with good results but are considered investigational for this condition by the FDA.

[43]The FDA-approved dosage regimen for immunocompromised patients (e.g., HIV infected) is 4 mg/kg/day (days 1-5) and 4 mg/kg/day on days 10, 17, 24, 31, and 38. The relapse rate is high; maintenance therapy may be indicated, but there is no consensus as to dosage or duration. (Russo R, Nigro LC, Minniti S, et al: Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B [AmBisome], *J Infect* 32:133-137, 1996).

[44]For treatment of kala-azar in adults in India, oral miltefosine 100 mg/day (~205 mg/kg/day) for 3-4 wk was 97% effective after 6 mo (Jha TK, et al: *N Engl J Med* 341:1795, 1999; Sangraula H, et al: *J Assoc Physicians India* 51:686, 2003). Gastrointestinal adverse effects are common, and the drug is contraindicated in pregnancy. The dose of miltefosine in an open-label trial in children in India was 2.5 mg/kg/day × 28 days (Bhattacharya SK, et al: *Clin Infect Dis* 38:217, 2004). Miltefosine (Impavido) is available from the manufacturer (Zentaris, Frankfurt, Germany at Impavido@zentaris.de).

[45]Cutaneous infection is most commonly caused by the Old World species *Leishmania major* and *Leishmania tropica* and the New World species *Leishmania mexicana, Leishmania (Viannia) braziliensis* and others. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[46]In a placebo-controlled trial in patients 12 yr old and older, oral miltefosine was effective for the treatment of cutaneous leishmaniasis caused by *Leishmania (Viannia) panamensis* in Colombia but not *L. (V.) braziliensis* in Guatemala at a dosage of about 2.5 mg/kg/day for 28 days. "Motion sickness," nausea, headache and increased creatinine were the most frequent adverse effects (Soto J, et al: *Clin Infect Dis* 38:1266, 2004). See footnote 44 regarding miltefosine availability. For treatment of *L. major* cutaneous lesions, a study in Saudi Arabia found that oral fluconazole, 200 mg once/day × 6 wk, appeared to speed healing (Alrajhi AA, et al: *N Engl J Med* 346:891, 2002).

[47]At this dosage pentamidine has been effective against leishmaniasis in Colombia where the likely organism was *L. (V.) panamensis* (Soto-Mancipe J, et al: *Clin Infect Dis* 16:417, 1993; Soto J, et al: *Am J Trop Med Hyg* 50:107, 1994); its effect against other species is not well established.

[48]Topical paromomycin should be used only in geographic regions where cutaneous leishmaniasis species have low potential for mucosal spread. A formulation of 15% paromomycin/12% methylbenzethonium chloride (Leshcutan) in soft white paraffin for topical use has been reported to be partially effective in some patients against cutaneous leishmaniasis due to *L. major* in Israel and against *L. mexicana* and *L. (V.) braziliensis* in Guatemala, where mucosal spread is very rare (Arana BA, et al: *Am J Trop Med Hyg* 65:466, 2001). The methylbenzethonium is irritating to the skin; lesions may worsen before they improve.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Mucosal[49]			
Drugs of choice:	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 28 days[41]	20 mg Sb/kg/day IV or IM × 28 days[41]
or	Meglumine antimonate	20 mg pentavalent antimony/kg/day IV or IM × 28 days[41]	20 mg pentavalent antimony/kg/day IV or IM × 28 days[41]
or	Amphotericin B[7]	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk
or	Miltefosine	2.5 mg/kg/day PO (max 150 mg/day) × 28 days	2.5 mg/kg/day PO (max 150 mg/day) × 28 days
Lice infestation *(Pediculus humanus, Pediculus capitis, Phthirus pubis)*[50]			
Drugs of choice:	0.5% Malathion[51]	Topically	Topically
or	1% Permethrin[52]	Topically	Topically
or	Pyrethrins with piperonyl butoxide[52]	Topically	Topically
or	0.5% Ivermectin lotion	Topically, once	Topically, once
or	0.9% Spinosad susp	Topically, 2 × at least 7 days apart	Topically, 2 × at least 7 days apart
or	Ivermectin[7,53]	200 µg/kg PO × 3 doses, on days 1, 2, and 10	200 µg/kg PO × 3 doses, on days 1, 2, and 10
Loa loa, see Filariasis			
Malaria, treatment of *(Plasmodium falciparum, Plasmodium ovale, Plasmodium vivax,* and *Plasmodium malariae)*			
P. falciparum[54] acquired in areas of **chloroquine resistance**			
Oral[55]			
Drugs of choice:	Atovaquone/ proguanil[56]	2 adult tabs PO bid[58] or 4 adult tabs PO once daily × 3 days	<5 kg: not indicated 5-8 kg: 2 pediatric tabs PO once/day × 3 days 9-10 kg: 3 pediatric tabs PO once/day × 3 days 11-20 kg: 1 adult tab PO once/day × 3 days 21-30 kg: 2 adult tabs PO once/day × 3 days 31-40 kg: 3 adult tabs PO once/day × 3 days >40 kg: 4 adult tabs PO once/day × 3 days
or	Quinine sulfate	650 mg PO every 8 hr × 3-7 days[57]	30 mg/kg/day PO in 3 doses × 3-7 days[57]
	plus doxycycline[7,14]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 doses × 7 days
	or plus tetracycline[7,14]	250 mg PO qid × 7 days	6.25 mg/kg PO qid × 7 days
	or plus clindamycin[7,59]	20 mg/kg/day PO in 3 doses × 7 days[60]	20 mg/kg/day PO in 3 doses × 7 days

[49]Mucosal infection is most commonly due to the New World species *L. (V.) braziliensis, L. (V.) panamensis,* or *L. (V.) guyanensis*. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[50]For infestation of eyelashes with *Phthirus pubis* lice, use petrolatum; TMP-SMX has also been used (Meinking TL: *Curr Probl Dermatol* 24:157, 1996). For pubic lice, treat with 5% permethrin or ivermectin as for scabies. TMP-SMX has also been effective together with permethrin for head lice (Hipolito RB, et al: *Pediatrics* 107:E30, 2001).

[51]Yoon KS, et al: *Arch Dermatol* 139:994, 2003.

[52]A second application is recommended 1 wk later to kill hatching progeny. Some lice are resistant to pyrethrins and permethrin (Meinking et al: *Arch Dermatol* 2002;138:220).

[53]Ivermectin is effective against adult lice but has no effect on nits (Jones KN, JC English III: *Clin Infect Dis* 36:1355, 2003).

[54]Chloroquine-resistant *P. falciparum* occurs in all malarious areas except Central America west of the Panama Canal Zone, Mexico, Haiti, the Dominican Republic, and most of the Middle East (chloroquine resistance has been reported in Yemen, Oman, Saudi Arabia, and Iran). For treatment of multidrug-resistant. *P. falciparum* in Southeast Asia, especially Thailand, where resistance to mefloquine is frequent, atovaquone/proguanil, artesunate plus mefloquine, or artemether plus mefloquine may be used (Luxemburger JC, et al: *Trans R Soc Trop Med Hyg* 88:213, 1994; Karbwang J, et al: *Trans R Soc Trop Med Hyg* 89:296, 1995).

[55]Uncomplicated or mild malaria may be treated with oral drugs.

[56]Atovaquone/proguanil is available as a fixed-dose combination tablet: adult tablets (Malarone; atovaquone 250 mg/proguanil 100 mg) and pediatric tablets (Malarone Pediatric; atovaquone 62.5 mg/proguanil 25 mg). To enhance absorption and reduce nausea and vomiting, it should be taken with food or a milky drink. Safety in pregnancy is unknown and use is generally not recommended. In a few small studies outcomes were normal in women treated with the combination in the 2nd and 3rd trimester (B Paternak et al., *Arch Intern Med* 2011; 171:259; AK Boggild et al., *Am J Trop Med Hyg* 2007; 76:208). The drug should not be given to patients with severe renal impairment (creatinine clearance <30 mL/min). There have been isolated case reports of resistance in *P. falciparum* in Africa, but *Medical Letter* consultants do not believe there is a high risk for acquisition of Malarone-resistant disease (E Schwartz et al., *Clin Infect Dis* 2003; 37:450; A Farnert et al., *BMJ* 2003; 326:628; S Kuhn et al., *Am J Trop Med Hyg* 2005; 72:407; CT Happi et al., *Malar J* 2006; 5:82).

[57]In Southeast Asia, relative resistance to quinine has increased and treatment should be continued for 7 days.

[58]Although approved for once daily dosing, *Medical Letter* consultants usually divide the dose in 2 to decrease nausea and vomiting.

[59]For use in pregnancy.

[60]Lell B, Kremsner PG: *Antimicrob Agents Chemother* 46:2315, 2002.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Coartem (Artemether-lumefantrine)	1 tablet = 20 mg artemether and 120 mg lumefantrine A 3 day treatment schedule with a total of six oral doses is recommended for both adult and pediatric patients based on weight. These six doses should be administered over 3 days (4 tabs/dose at 0, 8, 24, 36, 48, and 60 hr)	5 to <15 kg: 1 tablet PO per dose 15 to <25 kg: 2 tablets PO per dose 25 to <35 kg: 3 tablets per dose ≥35 kg: 4 tablets PO per dose
Alternative:	Mefloquine[61,62]	750 mg PO followed 12 hr later by 500 mg	15 mg/kg PO followed 12 hr later by 10 mg/kg
***P. vivax*[63] acquired in areas of chloroquine resistance**			
Oral[55]			
Drug of choice:	Quinine sulfate	650 mg PO every 8 hr × 3-7 days[57]	30 mg/kg/day PO in 3 doses × 3-7 days[57]
	plus doxycycline[7,14]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 doses × 7 days
	plus primaquine[64]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
or	Mefloquine[61]	750 mg PO followed 12 hr later by 500 mg PO	15 mg/kg PO followed 12 hr later by 10 mg/kg PO
Alternatives:	Chloroquine	25 mg base/kg PO in 3 doses over 48 hr	25 mg base/kg PO in 3 doses over 48 hr
	plus primaquine[64]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
All *Plasmodium* except chloroquine-resistant *P. falciparum*[54] and chloroquine-resistant *P. vivax*[63] (areas without chloroquine resistance)			
Oral[55]			
Drug of choice:	Chloroquine phosphate[65]	1 g (600 mg base), then 500 mg (300 mg base) 6 hr later PO, then 500 mg (300 mg base) at 24 and 48 hr	10 mg base/kg (max 600 mg base), then 5 mg base/kg 6 hr later PO, then 5 mg base/kg at 24 and 48 hr
All *Plasmodium*			
Parenteral (severe infection; chloroquine-sensitive and resistant)			
Drugs of choice[66]:	Quinidine gluconate[67]	10 mg/kg IV loading dose (max 600 mg) in normal saline over 1-2 hr, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started	10 mg/kg IV loading dose (max 600 mg) in normal saline over 1-2 hr, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started
or	Quinine dihydrochloride[67]	20 mg/kg IV loading dose in 5% dextrose over 4 hr, followed by 10 mg/kg over 2-4 hr every 8 hr (max 1,800 mg/day) until PO therapy can be started	20 mg/kg IV loading dose in 5% dextrose over 4 hr, followed by 10 mg/kg over 2-4 hr every 8 hr (max 1,800 mg/day) until PO therapy can be started

[61]At this dosage, adverse effects including nausea, vomiting, diarrhea, dizziness, disturbed sense of balance, toxic psychosis, and seizures can occur. Mefloquine should not be used for treatment of malaria in pregnancy unless there is no other treatment option because of increased risk for stillbirth (Nosten F, et al: *Clin Infect Dis* 28:808, 1999). It should be avoided for treatment of malaria in persons with active depression or with a history of psychosis or seizures and should be used with caution in persons with psychiatric illness. Mefloquine can be given to patients taking β blockers if they do not have an underlying arrhythmia; it should not be used in patients with conduction abnormalities. Mefloquine should not be given together with quinine, quinidine, or halofantrine, and caution is required in using quinine, quinidine, or halofantrine to treat patients with malaria who have taken mefloquine for prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders and in the Amazon basin, where 25 mg/kg should be used. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

[62]*P. falciparum* with resistance to mefloquine is a significant problem in the malarious areas of Thailand and in areas of Myanmar and Cambodia that border on Thailand. It has also been reported on the borders between Myanmar and China, Laos and Myanmar, and in Southern Vietnam. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

[63]*P. vivax* with decreased susceptibility to chloroquine is a significant problem in Papua New Guinea and Indonesia. There are also a few reports of resistance from Myanmar, India, the Solomon Islands, Vanuatu, Guyana, Brazil, Colombia, and Peru.

[64]Primaquine phosphate can cause hemolytic anemia, especially in patients whose red cells are deficient in glucose-6-phosphate dehydrogenase (G6PD). This deficiency is most common in African, Asian, and Mediterranean peoples. Patients should be screened for G6PD deficiency before treatment. Primaquine should not be used during pregnancy.

[65]If chloroquine phosphate is not available, hydroxychloroquine sulfate is as effective; 400 mg of hydroxychloroquine sulfate is equivalent to 500 mg of chloroquine phosphate.

[66]Exchange transfusion has been helpful for some patients with high-density (>10%) parasitemia, altered mental status, pulmonary edema, or renal complications (Miller KD, et al: *N Engl J Med* 321:65, 1989).

[67]Continuous ECG, blood pressure, and glucose monitoring are recommended, especially in pregnant women and young children. For problems with quinidine availability, call the manufacturer (Eli Lilly, 800-545-5979) or the CDC Malaria Hotline (770-488-7788). Quinidine may have greater antimalarial activity than quinine. The loading dose should be decreased or omitted in those patients who have received quinine or mefloquine. If more than 48 hr of parenteral treatment is required, the quinine or quinidine dose should be reduced by 30-50%.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Alternative:	Artesunate[68] Plus a second oral drug	2.4 mg/kg/dose IV × 3 days, at 0, 12, 24, 48, and 72 hr	2.4 mg/kg/dose IV × 3 days, at 0, 12, 24, 48, and 72 hr
Prevention of relapses: *P. vivax* and *P. ovale* only			
Drug of choice:	Primaquine phosphate[64]	30 mg base/day PO × 14 days	0.6 mg base/kg/day PO × 14 days
Malaria, prevention of[69]			
Chloroquine-sensitive areas[54]			
Drug of choice	Chloroquine phosphate[70,71]	500 mg (300 mg base), PO once/wk[72]	5 mg/kg base once/wk, up to adult dose of 300 mg base[72]
Chloroquine-resistant areas[54]			
Drug of choice:	Atovaquone/ proguanil[56,71]	1 adult tab PO q day[73]	11-20 kg: 1 pediatric tab PO/day[56,73] 21-30 kg: 2 pediatric tabs PO/day[56,73] 31-40 kg: 3 pediatric tabs PO/day[56,73] >40 kg: 1 adult tab PO/day[56,73]
or	Mefloquine[61,71,74]	250 mg PO once/wk[72]	<9 kg: 5 mg/kg salt once/wk[72] 9-19 kg: ¼ tab once/wk[72] 19-30 kg: ½ tab once/wk[72] 31-45 kg: ¾ tab once/wk[72] >45 kg: 1 tab once/wk[72]
or	Doxycycline[7,71]	100 mg PO daily[75]	2 mg/kg/day, up to 100 mg/day[75]
Alternatives:	Primaquine[7]	30 mg base PO daily[76]	0.6 mg/kg base daily
Malaria, self-presumptive treatment[77]			
Drug of choice:	Atovaquone/ proguanil[7,56,78]	4 adult tabs PO daily × 3 days	<5 kg: not indicated 5-8 kg: 2 pediatric tabs PO once/day × 3 days 9-10 kg: 3 pediatric tabs PO once/day × 3 days 11-20 kg: 1 adult tab PO once/day × 3 days 21-30 kg: 2 adult tabs PO once/day × 3 days 31-40 kg: 3 adult tabs PO once/day × 3 days >40 kg: 4 adult tabs PO once/day × 3 days

[68]Oral artesunate is not available in the United States; the IV formulation is available through the CDC Malaria branch under an investigational new drug (IND) for patients with severe disease who do not have timely access or cannot tolerate, or fail to respond to IV quinidine (*Med Lett Drugs Ther* 2008; 50:37). To avoid development of resistance, adults treated with artesunate must also receive oral treatment doses of either atovaquone/proguanil, doxycycline, clindamycin, or mefloquine; children should take either atovaquone/proguanil, clindamycin, or mefloquine (F Nosten et al., *Lancet* 2000; 356:297; M van Vugt, *Clin Infect Dis* 2002; 35:1498; F Smithuis et al., *Trans R Soc Trop Med Hyg* 2004; 98:182). If artesunate is given IV, oral medication should be started when the patient is able to tolerate it (SEAQUAMAT group, *Lancet* 2005; 366:717; PE Duffy and CH Sibley, *Lancet* 2005;366:1908). Reduced susceptibility to artesunate characterized by slow parasitic clearance has been reported in Cambodia (WO Rogers et al., *Malar J* 2009; 8:10; AM Dundorp et al., *N Engl J Med* 2009; 361:455).

[69]No drug regimen guarantees protection against malaria. If fever develops within a year (particularly within the first 2 mo) after travel to malarious areas, travelers should be advised to seek medical attention. Insect repellents, insecticide-impregnated bed nets, and proper clothing are important adjuncts for malaria prophylaxis (*Med Lett* 45:41, 2003). Malaria in pregnancy is particularly serious for both mother and fetus; therefore, prophylaxis is indicated if exposure cannot be avoided.

[70]In pregnancy, chloroquine prophylaxis has been used extensively and safely.

[71]For prevention of attack after departure from areas where *P. vivax* and *P. ovale* are endemic, which includes almost all areas where malaria is found (except Haiti), some experts prescribe in addition primaquine phosphate 30 mg base/day or, for children, 0.6 mg base/kg/day during the last 2 wk of prophylaxis. Others prefer to avoid the toxicity of primaquine and rely on surveillance to detect cases when they occur, particularly when exposure was limited or doubtful. See also footnote 64.

[72]Beginning 1-2 wk before travel and continuing weekly for the duration of stay and for 4 wk after leaving malarious zone. Most adverse events occur within 3 doses. Some *Medical Letter* consultants favor starting mefloquine 3 wk prior to travel and monitoring the patient for adverse events; this allows time to change to an alternative regimen if mefloquine is not tolerated. Mefloquine should not be taken on an empty stomach; it should be taken with at least 8 oz of water. For pediatric doses less than ½ tablet, it is advisable to have a pharmacist crush the tablet, estimate doses by weighing, and package them in gelatin capsules. There are no data for use in children weighing <5 kg, but based on dosages in other weight groups, a dose of 5 mg/kg can be used.

[73]Beginning 1-2 days before travel and continuing for the duration of stay and for 1 wk after leaving. In 1 study of malaria prophylaxis, atovaquone/proguanil was better tolerated than mefloquine in nonimmune travelers (Overbosch D, et al: *Clin Infect Dis* 33:1015, 2001).

[74]Mefloquine has not been approved for use during pregnancy. However, it has been reported to be safe for prophylactic use during the 2nd or 3rd trimester of pregnancy and possibly during early pregnancy as well. Mefloquine is not recommended for patients with cardiac conduction abnormalities, and patients with a history of depression, seizures, psychosis, or psychiatric disorders should avoid mefloquine prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders; in these areas, atovaquone/proguanil or doxycycline should be used for prophylaxis.

[75]Beginning 1-2 days before travel and continuing for the duration of stay and for 4 wk after leaving. Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old. Doxycycline can cause gastrointestinal disturbances, vaginal moniliasis, and photosensitivity reactions.

[76]Studies have shown that daily primaquine beginning 1 day before departure and continued until 3-7 days after leaving the malaria area provides effective prophylaxis against chloroquine-resistant *P. falciparum* (Baird JK, et al: *Clin Infect Dis* 37:1659, 2003). Some studies have shown less efficacy against *P. vivax*. Nausea and abdominal pain can be diminished by taking with food.

[77]A traveler can be given a course of atovaquone/proguanil, mefloquine, or quinine plus doxycycline for presumptive self-treatment of febrile illness. The drug given for self-treatment should be different from that used for prophylaxis. This approach should be used only in very rare circumstances when a traveler cannot promptly get to medical care.

[78]Beginning 1-2 days before travel and continuing for the duration of stay and for 1 wk after leaving malarious zone. In 1 study of malaria prophylaxis, atovaquone/proguanil was better tolerated than mefloquine in nonimmune travelers (D Overbosch et al., *Clin Infect Dis* 2001; 33:1015). The protective efficacy of Malarone against *P. vivax* is variable ranging from 84% in Indonesian New Guinea (J Ling et al., *Clin Infect Dis* 2002; 35:825) to 100% in Colombia (J Soto et al., *Am J Trop Med Hyg* 2006; 75:430). Some *Medical Letter* consultants prefer alternate drugs if traveling to areas where *P. vivax* predominates.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Quinine sulfate plus doxycycline[7,14]	650 mg PO every 8 hr × 3-7 days[57] 100 mg bid PO × 7 days	30 mg/kg/day PO in 3 doses × 3-7 days[57] 4 mg/kg/day in 2 PO doses × 7 days
or	Mefloquine[61]	750 mg PO followed 12 hr later by 500 mg	15 mg/kg followed 12 hr later by 10 mg/kg
Microsporidiosis			
Ocular *(Encephalitozoon hellem, Encephalitozoon cuniculi, Vittaforma corneae [Nosema corneum])*			
Drug of choice:	Albendazole[7] **plus** fumagillin[79]	400 mg PO bid	
Intestinal *(Enterocytozoon bieneusi, Encephalitozoon [Septata] intestinalis)*			
E. bieneusi[80]			
Drug of choice:	Fumagillin	60 mg/day PO × 14 days in 3 divided doses	
E. intestinalis			
Drug of choice	Albendazole[7]	400 mg PO bid × 21 days	
Disseminated (*E. hellem, E. cuniculi, E. intestinalis, Pleistophora* sp., *Trachipleistophora* sp., and *Brachiola vesicularum*)			
Drug of choice[81]:	Albendazole[7]	400 mg PO bid	
Mites, see Scabies			
Moniliformis *moniliformis* infection			
Drug of choice:	Pyrantel pamoate[7]	11 mg/kg PO once, repeat twice, 2 wk apart	11 mg/kg PO once, repeat twice, 2 wk apart
***Naegleria* species,** see Amebic meningoencephalitis, primary			
Necator americanus, see Hookworm infection			
Oesophagostomum *bifurcum*			
Drug of choice:	See footnote 82		
Onchocerca volvulus, see Filariasis			
Opisthorchis viverrini, see Fluke infection			
Paragonimus westermani, see Fluke infection			
Pediculus capitis, Pediculus humanus, Phthirus pubis, see Lice			
Pinworm, see *Enterobius*			
Pneumocystis jiroveci (formerly *Pneumocystis carinii*) pneumonia (PCP)[83]			
Moderate to severe disease			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	TMP 15-20 mg/kg/day, SMX 75-100 mg/kg/day, PO or IV (change to PO after clinical improvement) in 3 or 4 doses × 21 days	TMP 15-20 mg/kg/day, SMX 75-100 mg/kg/day, PO or IV (change to PO after clinical improvement) in 3 or 4 doses × 21 days
Alternatives:	Pentamidine *or* Primaquine **plus** clindamycin[7]	3-4 mg IV daily × 21 days 30 mg base PO daily × 21 days 600-900 mg IV tid or qid × 21 days, or 300-450 mg PO tid or qid × 21 days (change to PO after clinical improvement)	3-4 mg IV daily × 21 days 0.3 mg/kg base PO (max 30 mg) daily × 21 days 15-25 mg/kg IV tid or qid × 21 days, or 10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days (change to PO after clinical improvement)

[79]Ocular lesions caused by *E. hellem* in HIV-infected patients have responded to fumagillin eyedrops prepared from Fumidil-B (bicyclohexyl ammonium fumagillin) used to control a microsporidial disease of honey bees (Diesenhouse MC: *Am J Ophthalmol* 115:293, 1993), available from Leiter's Park Avenue Pharmacy (see footnote 1). For lesions caused by *V. corneae,* topical therapy is generally not effective and keratoplasty may be required (Davis RM, et al: *Ophthalmology* 97:953, 1990).

[80]Oral fumagillin (Sanofi Recherche, Gentilly, France) has been effective in treating *E. bieneusi* (Molina J-M, et al: *N Engl J Med* 346:1963, 2002), but has been associated with thrombocytopenia. HAART may lead to microbiologic and clinical response in HIV-infected patients with microsporidial diarrhea (Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, *MMWR Recomm Rep* 53([RR-15]:1-112, 2004). Octreotide (Sandostatin) has provided symptomatic relief in some patients with large-volume diarrhea.

[81]Molina J-M, et al: *J Infect Dis* 171:245, 1995. There is no established treatment for *Pleistophora*. For disseminated disease caused by *Trachipleistophora* or *Brachiola,* itraconazole 400 mg PO once/day plus albendazole may also be tried (Coyle CM, et al: *N Engl J Med* 351:42, 2004).

[82]Albendazole or pyrantel pamoate may be effective (Ziem JB, et al: *Ann Trop Med Parasitol* 98:385, 2004).

[83]*Pneumocystis* has been reclassified as a fungus. In severe disease with room air PO_2 ≤70 mm Hg or A-aO_2 gradient ≥35 mm Hg, prednisone should also be used (Gagnon S, et al: *N Engl J Med* 323:1444, 1990; Caumes E, et al: *Clin Infect Dis* 18:319, 1994).

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Mild to moderate disease			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	2 DS tablets (160 mg/800 mg each) PO tid × 21 days	TMP 15-20 mg/kg/day SMX 75-100 mg/kg/day PO in 3 or 4 doses × 21 days
Alternative:	Dapsone	100 mg PO daily × 21 days	2 mg/kg/day (max 100 mg) PO × 21 days
	plus trimethoprim	15 mg/kg/day PO in 3 doses	15 mg/kg/day PO in 3 doses
	or primaquine	30 mg base PO daily × 21 days	0.3 mg/kg base PO daily (max 30 mg) × 21 days
	plus clindamycin	300-450 mg PO tid or qid × 21 days	10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days
	or atovaquone	750 mg PO bid × 21 days	1-3 mo: 30 mg/kg/day PO in 2 doses × 21 days 4-24 mo: 45 mg/kg/day PO in 2 doses × 21 days >24 mo: 30 mg/kg/day PO in 2 doses × 21 days
Primary and secondary prophylaxis[84]			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	1 tab (single or double strength) PO daily or 1 DS tab PO 3 doses/wk	TMP 150 mg/m^2, SMX 750 mg/m^2 PO in 2 doses on 3 consecutive days per wk
Alternatives[85]:	Dapsone[7]	50 mg PO bid, or 100 mg PO daily	2 mg/kg/day (max 100 mg) PO or 4 mg/kg (max 200 mg) PO each wk
or	Dapsone[7] **plus** pyrimethamine[86]	50 mg PO daily or 200 mg PO each wk 50 mg PO or 75 mg PO each wk	
or	Pentamidine aerosol	300 mg inhaled monthly via *Respirgard II* nebulizer	≥5 yr: 300 mg inhaled monthly via *Respirgard II* nebulizer
or	Atovaquone[7]	1,500 mg/d PO in 1 or 2 doses	1-3 mo: 30 mg/kg/day PO 4-24 mo: 45 mg/kg/day PO >24 mo: 30 mg/kg/day PO
Roundworm, see Ascariasis			
Sappinia diploidea, see Amebic meningoencephalitis, primary			
Scabies *(Sarcoptes scabiei)*			
Drug of choice:	5% Permethrin	Topically, 2× at least 7 days apart[87]	Topically, 2× at least 7 days apart[87]
Alternatives[88]:	Ivermectin[7,89] 10% Crotamiton	200 µg/kg PO 2× at least 7 days apart [87] Topically overnight on days 1, 2, 3, 8	200 µg/kg PO 2× at least 7 days apart [87] Topically overnight on days 1, 2, 3, 8
Schistosomiasis *(Bilharziasis)*			
Schistosoma haematobium			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day
Schistosoma intercalatum			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day
Schistosoma japonicum			
Drug of choice:	Praziquantel	60 mg/kg/day PO in 2 or 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day

[84]Primary/secondary prophylaxis in patients with HIV can be discontinued after CD4 count increases to >200 × 10^6/L for longer than 3 mo.

[85]An alternative trimethoprim-sulfamethoxazole regimen is 1 DS tab 3×/wk. Weekly therapy with sulfadoxine 500 mg/pyrimethamine 25 mg/leucovorin 25 mg was effective *Pneumocystis carinii* pneumonia (PCP) prophylaxis in liver transplant patients (Torre-Cisneros J, et al: *Clin Infect Dis* 29:771, 1999).

[86]Plus leucovorin 25 mg with each dose of pyrimethamine.

[87]In some cases, treatment may need to be repeated in 10-14 days. BJ Currie and JS McCarthy, *N Engl J Med* 2010; 362:717. A second ivermectin dose taken 2 wk later increased the cure rate to 95%, which is equivalent to that of 5% permethrin (V Usha et al., *J Am Acad Dermatol* 2000; 42:236). Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (P del Giudice, *Curr Opin Infect Dis* 2004; 15:123).

[88]Lindane (γ-benzene hexachloride; Kwell) should be reserved as a second-line agent. The FDA has recommended it should not be used for immunocompromised patients, young children, the elderly, and patients who weigh <50 kg.

[89]Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (del Giudice P: *Curr Opin Infect Dis* 15:123, 2004). The safety of oral ivermectin in pregnancy and young children has not been established.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Schistosoma mansoni			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day
Alternative:	Oxamniquine[90]	15 mg/kg PO once[91]	20 mg/kg/day PO in 2 doses × 1 day[91]
Schistosoma mekongi			
Drug of choice:	Praziquantel	60 mg/kg/day PO in 2 or 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day
Sleeping sickness, see Trypanosomiasis			
Strongyloidiasis *(Strongyloides stercoralis)*			
Drug of choice[92]:	Ivermectin	200 µg/kg/day PO × 2 days	200 µg/kg/day PO × 2 days
Alternative:	Albendazole[7, 93]	400 mg PO bid × 7 days	400 mg bid PO × 7 days
Tapeworm infection			
Adult (intestinal stage)			
Diphyllobothrium latum **(fish),** ***Taenia saginata*** **(beef),** ***Taenia solium*** **(pork),** ***Dipylidium caninum*** **(dog)**			
Drug of choice:	Praziquantel[7]	5-10 mg/kg PO once	5-10 mg/kg PO once
Alternative:	Niclosamide	2 g PO once	50 mg/kg PO once
Hymenolepis nana **(dwarf tapeworm)**			
Drug of choice:	Praziquantel[7]	25 mg/kg PO once	25 mg/kg PO once
Alternative:	Niclosamide	2 g PO daily × 7 days	11-34 kg: 1 g PO on day 1 then 500 mg/day PO × 6 days[94] >34 kg: 1.5 g PO on day 1 then 1 g/d PO × 6 days[94]
Larval (tissue stage)			
Echinococcus granulosus (hydatid cyst)			
Drug of choice[95]:	Albendazole	400 mg PO bid × 1-6 mo	15 mg/kg/day PO (max 800 mg) × 1-6 mo
Echinococcus multilocularis			
Treatment of choice:	See footnote 96		
Taenia solium (cysticercosis)			
Treatment of choice		See footnote 97	
Alternative:	Albendazole	400 mg bid PO × 8-30 days; can be repeated as necessary	15 mg/kg/day PO (max 800 mg) in 2 doses × 8-30 days; can be repeated as necessary
or	Praziquantel[7]	50 mg/kg/day PO in 3 doses × 15 days	50 mg/kg/day PO × 15 day
Toxocariasis, see Visceral larva migrans			

[90]Oxamniquine has been effective in some areas in which praziquantel is less effective (Stelma FF, et al: *J Infect Dis* 176:304, 1997). Oxamniquine is contraindicated in pregnancy.

[91]In East Africa, the dose should be increased to 30 mg/kg, and in Egypt and South Africa to 30 mg/kg/day × 2 days. Some experts recommend 40-60 mg/kg over 2-3 days in all of Africa (Shekhar KC: *Drugs* 42:379, 1991).

[92]In immunocompromised patients or disseminated disease, it may be necessary to prolong or repeat therapy, or to use other agents. Veterinary parenteral and enema formulations of ivermectin have been used in severely ill patients unable to take oral medications (Chiodini PL, et al: *Lancet* 355:43, 2000; Orem J, et al: *Clin Infect Dis* 37:152, 2003; Tarr PE: *Am J Trop Med Hyg* 68:453, 2003).

[93]Albendazole must be taken with food; a fatty meal increases oral bioavailability.

[94]Niclosamide must be thoroughly chewed or crushed and swallowed with a small amount of water. Nitazoxanide may be an alternative (JJ Ortiz et al., *Trans R Soc Trop Med Hyg* 2002; 96:193; JC Chero et al., *Trans R Soc Trop Med Hyg* 2007; 101:203; E Diaz et al., *Am J Trop Med Hyg* 2003; 68:384).

[95]Patients may benefit from surgical resection or percutaneous drainage of cysts. Praziquantel is useful preoperatively or in case of spillage of cyst contents during surgery. Percutaneous aspiration-injection-reaspiration (PAIR) with ultrasound guidance plus albendazole therapy has been effective for management of hepatic hydatid cyst disease (Smego RA Jr, et al: *Clin Infect Dis* 37:1073, 2003).

[96]Surgical excision is the only reliable means of cure. Reports have suggested that in nonresectable cases use of albendazole or mebendazole can stabilize and sometimes cure infection (Craig P: *Curr Opin Infect Dis* 16:437, 2003).

[97]Initial therapy for patients with inflamed parenchymal cysticercosis should focus on symptomatic treatment with antiseizure medication. Treatment of parenchymal cysticerci with albendazole or praziquantel is controversial (Maguire JM: *N Engl J Med* 350:215, 2004). Patients with live parenchymal cysts who have seizures should be treated with albendazole together with steroids (6 mg dexamethasone or 40-60 mg prednisone daily) and an antiseizure medication (Garcia HH, et al: *N Engl J Med* 350:249, 2004). Patients with subarachnoid cysts or giant cysts in the fissures should be treated for at least 30 days (Proaño JV, et al: *N Engl J Med* 345:879, 2001). Surgical intervention or CSF diversion is indicated for obstructive hydrocephalus; prednisone 40 mg/day may be given with surgery. Arachnoiditis, vasculitis, or cerebral edema is treated with prednisone 60 mg/day or dexamethasone 4-6 mg/day together with albendazole or praziquantel (White Jr AC: *Annu Rev Med* 51:187, 2000). Any cysticercocidal drug may cause irreparable damage when used to treat ocular or spinal cysts, even when corticosteroids are used. An ophthalmic exam should always precede treatment to rule out intraocular cysts.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Toxoplasmosis *(Toxoplasma gondii)*[98]			
Drugs of choice[99,100]:	Pyrimethamine[101]	200 mg PO × 1, then 50-75 mg/day × 3-6 wk	2 mg/kg/d × 3 days, then 1 mg/kg/day (max 25 mg/day) × 4 wk[102]
	plus Sulfadiazine	1-1.5 g PO qid × 3-6 wk	100-200 mg/kg/day × 3-4 wk
	or **plus** Clindamycin	1.8-2.4 g/day IV or PO in 3 or 4 doses	5-7.5 mg/kg/day IV or PO in 3 or 4 doses (max 600 mg/dose)
	or **plus** Atovaquone	1,500 mg PO bid	1,500 mg PO bid
Alternative:	Trimethoprim-sulfamethoxazole (TMP-SMX)	TMP 15-20 mg/kg/day; SFX 75-100 mg/kg/day PO or IV in 3 or 4 doses	TMP 15-20 mg/kg/day; SFX 75-100 mg/kg/day PO or IV in 3 or 4 doses
Trichinellosis *(Trichinella spiralis)*			
Drugs of choice:	Steroids for severe symptoms	Prednisone 30-60 mg PO daily × 10-15 days	
	plus Albendazole[7]	400 mg PO bid × 8-14 days	400 mg PO bid × 8-14 days
Alternative:	Mebendazole[7]	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days
Trichomoniasis *(Trichomonas vaginalis)*			
Drug of choice[103]:	Metronidazole	2 g PO once or 500 mg PO bid × 7 days	15 mg/kg/day PO in 3 doses × 7 days
or	Tinidazole[5]	2 g PO once	50 mg/kg PO once (max 2 g)
Trichostrongylus infection			
Drug of choice:	Pyrantel pamoate[7]	11 mg/kg base PO once (max 1 g)	11 mg/kg PO once (max 1 g)
Alternative:	Mebendazole[7]	100 mg PO bid × 3 days	100 mg PO bid × 3 days
or	Albendazole[7]	400 mg PO once	400 mg PO once
Trichuriasis (*Trichuris trichiura*, whipworm)			
Drug of choice:	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days
Alternative:	Albendazole[7] Ivermectin[7]	400 mg PO × 3 days 200 µg/kg PO × 3 days	400 mg PO × 3 days 200 µg/kg PO × 3 days
Trypanosomiasis[104]			
Trypanosoma cruzi (American trypanosomiasis, Chagas disease)			
Drug of choice:	Benznidazole	5-7 mg/kg/day PO in 2 divided doses × 60 days	≤12 yr: 10 mg/kg/day PO in 2 or 3 doses × 60 days
or	Nifurtimox[105]	8-10 mg/kg/day PO in 3-4 doses × 90 days	1-10 yr: 15-20 mg/kg/day PO in 4 doses × 90 days 11-16 yr: 12.5-15 mg/kg/day in 4 doses × 90 days

[98]In ocular toxoplasmosis with macular involvement, corticosteroids are recommended in addition to antiparasitic therapy for an antiinflammatory effect.

[99]To treat CNS toxoplasmosis in HIV-infected patients, some clinicians have used pyrimethamine 50-100 mg/day (after a loading dose of 200 mg) with sulfadiazine and, when sulfonamide sensitivity developed, have given clindamycin 1.8-2.4 g/day in divided doses instead of the sulfonamide. Atovaquone plus pyrimethamine appears to be an effective alternative in sulfa-intolerant patients (Chirgwin K, et al: *Clin Infect Dis* 34:1243, 2002). Treatment is followed by chronic suppression with lower-dosage regimens of the same drugs. For primary prophylaxis in HIV patients with <100 × 10^6/L CD4 cells, either trimethoprim-sulfamethoxazole, pyrimethamine with dapsone, or atovaquone with or without pyrimethamine can be used. Primary or secondary prophylaxis may be discontinued when the CD4 count increases to >200 × 10^6/L for more than 3 mo (Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, *MMWR Recomm Rep* 53([RR-15]:1-112, 2004).

[100]Women who develop toxoplasmosis during the 1st trimester of pregnancy can be treated with spiramycin (3-4 g/day). After the 1st trimester, if there is no documented transmission to the fetus, spiramycin can be continued until term. If transmission has occurred in utero, therapy with pyrimethamine and sulfadiazine should be started (Montoya JG, Liesenfeld O: *Lancet* 363:1965, 2004). Pyrimethamine is a potential teratogen and should be used only after the 1st trimester.

[101]Plus leucovorin 10-25 mg with each dose of pyrimethamine.

[102]Congenitally infected newborns should be treated with pyrimethamine every 2 or 3 days and a sulfonamide daily for about 1 yr (Remington JS, Klein JO, editors: *Infectious disease of the fetus and newborn infant,* ed 5, Philadelphia, 2001, WB Saunders, p. 290).

[103]Sexual partners should be treated simultaneously. Metronidazole-resistant strains have been reported and can be treated with higher doses of metronidazole (2-4 g/day × 7-14 days) or with tinidazole (Hager WD: *Sex Transm Dis* 31:343, 2004).

[104]Barrett MP, et al: *Lancet* 362:1469, 2003.

[105]The addition of γ-interferon to nifurtimox for 20 days in experimental animals and in a limited number of patients appears to shorten the acute phase of Chagas disease (McCabe RE, et al: *J Infect Dis* 163:912, 1991).

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Trypanosoma brucei gambiense (West African trypanosomiasis, sleeping sickness)			
Hemolymphatic stage			
Drug of choice[106]:	Pentamidine isethionate[7]	4 mg/kg/day IM × 7 days	4 mg/kg/day IM or IV × 7 days
Alternative:	Suramin	100-200 mg (test dose) IV, then 1 g IV on days 1, 3, 5, 14, and 21	2 mg/kg (test dose) IV, then 20 mg/kg IV on days 1, 3, 5, 14, and 21
Late disease with CNS involvement			
Drug of choice:	Melarsoprol[107]	2.2 mg/kg/day IV × 10 days	2.2 mg/kg/day IV × 10 days
or	Eflornithine[108]	400 mg/kg/day IV in 4 doses × 14 d	400 mg/kg/day in 4 doses × 14 days
Trypanosoma brucei rhodesiense (East African trypanosomiasis, sleeping sickness)			
Hemolymphatic stage			
Drug of choice:	Suramin	100-200 mg (test dose) IV, then 1 g IV on days 1, 3, 5, 14, and 21	2 mg/kg (test dose), then 20 mg/kg IV on days 1, 3, 5, 14, and 21
Late disease with CNS involvement			
Drug of choice:	Melarsoprol[107]	2.2 mg/kg/day × 10 days	2.2 mg/kg/day × 10 days
Visceral larva migrans[109] (Toxocariasis)			
Drugs of choice:	Albendazole[7] Mebendazole[7]	400 mg PO bid × 5 days 100-200 mg PO bid × 5 days	400 mg PO bid × 5 days 100-200 mg PO bid × 5 days
Whipworm, see Trichuriasis			
Wuchereria bancrofti, see Filariasis			

[106]For treatment of *T. b. gambiense,* pentamidine and suramin have equal efficacy but pentamidine is better tolerated.

[107]In frail patients, begin with as little as 18 mg and increase the dose progressively. Pretreatment with suramin has been advocated for debilitated patients. Corticosteroids have been used to prevent arsenical encephalopathy (Pepin J, et al: *Trans R Soc Trop Med Hyg* 89:92, 1995). Up to 20% of patients with *T. b. gambiense* fail to respond to melarsoprol (Barrett MP: *Lancet* 353:1113, 1999).

[108]Eflornithine is highly effective in *T. b. gambiense* but not against *T. b. rhodesiense* infections. It is available in limited supply only from the WHO and the CDC. Eflornithine dose may be reduced to 400 mg/kg IV in 2 doses for 7 d when used in conjunction with nifurtimox at a dose of 15 mg/kg/d PO in 3 doses × 10 d.

[109]Optimum duration of therapy is not known; some *Medical Letter* consultants would treat for 20 days. For severe symptoms or eye involvement, corticosteroids can be used in addition.

CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; DS, double strength; ECG, electrocardiography; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HAART, highly active antiretroviral therapy; SMX, sulfamethoxazole; TMP, trimethoprim; WHO, World Health Organization.

From: Drugs for parasitic infection. Med Lett *11(Suppl):e1-e23, 2013. Available at* http://www.medicalletter.org.

SELECTED ANTIPARASITIC DRUGS FOR HELMINTHS

Albendazole (Albenza)

Albendazole is a benzimidazole carbamate structurally related to mebendazole and has similar anthelmintic activity. Its absorption from the gastrointestinal tract is poor but improved with a concomitant high-fat meal. Albendazole sulfoxide, the principal metabolite with anthelmintic activity, has a plasma half-life of 8.5 hr. It is widely distributed in the body, including the bile and cerebrospinal fluid. It is eliminated by bile. Albendazole is FDA approved for treatment of neurocysticercosis and hydatid diseases *(Echinococcus granulosus).* It is not FDA approved but is used for *Ancylostoma caninum,* ascariasis, Chinese liver fluke, cutaneous larva migrans, pinworms, filariasis, gnathostomiasis, hookworms, microsporidiosis, and visceral larva migrans. Albendazole is generally well tolerated. Common adverse effects include headache, nausea, vomiting, and abdominal pain. Serious adverse effects include elevated liver enzymes and leukopenia, which have occurred in a few patients with treatment of hydatid disease. Rare adverse effects include acute renal failure, pancytopenia, granulocytopenia, and thrombocytopenia.

Ivermectin (Stromectol, Mectizan)

Ivermectin is a semisynthetic derivative of 1 of the avermectins, which is a group of macrocyclic lactones produced by *Streptomyces avermitilis.* After oral administration, ivermectin has peak plasma concentrations after approximately 4 hr and a plasma elimination half-life of approximately 12 hr. It is excreted as metabolites over a 2 wk period via feces. It is FDA approved for treatment of onchocerciasis and intestinal strongyloidiasis. It may have some effect in treating cutaneous larva migrans, intestinal nematode infections, loiasis, lymphatic filariasis, *Mansonella* infections, and scabies. Combination therapies of ivermectin with albendazole or diethylcarbamazine are being used to treat lymphatic filariasis. Common adverse events include dizziness, headache, pruritus, and gastrointestinal effects. Serious adverse events include Mazzotti reactions, including arthralgia, synovitis, enlarged lymph nodes, rash, and fever secondary to microfilaria death in patients with onchocerciasis.

Praziquantel (Biltricide)

Praziquantel achieves its antiparasitic activity via the pyrazino isoquinoline ring system and was originally synthesized as a potential tranquillizer. After oral administration, praziquantel is rapidly absorbed with peak levels in 1-2 hr and plasma half-life of about 1-3 hr. Elimination via the urine and feces is >80% complete after 24 hr. Praziquantel is metabolized in the liver by the microsomal cytochrome P450 (especially 2B1 and 3A). Bioavailability of praziquantel is increased with concomitant administration of agents that inhibit cytochrome P450. Praziquantel is FDA approved for treatment of Chinese liver fluke, Southeast Asian liver fluke, and schistosomiasis. It is used for treatment of intestinal flukes, North American liver fluke, *Nanophyetus salmincola,* lung fluke, and tapeworm infections but is not FDA approved for these indications. Adverse effects can be seen in 30-60% of patients,

although most are mild and disappear within 24 hr. Common adverse effects include headache, abdominal pain, dizziness, and malaise. Serious but rare adverse effects include arrhythmias, heart block, and convulsions.

Section 15
Protozoan Diseases

Chapter 280
Primary Amebic Meningoencephalitis

Matthew D. Eberly and Martin E. Weisse

Naegleria, Acanthamoeba, Balamuthia, and *Sappinia* are small, free-living amebas that cause human amebic meningoencephalitis, which has 2 distinct clinical presentations. The more common is an acute, fulminant, and usually fatal **amebic meningitis** caused by *Naegleria* that occurs in previously healthy children and young adults. **Granulomatous amebic meningoencephalitis,** which is caused by *Acanthamoeba, Balamuthia,* and *Sappinia,* is a more indolent infection that typically occurs in immunocompromised hosts.

ETIOLOGY
Naegleria is an ameboflagellate that can exist as cysts, trophozoites, and transient flagellate forms. Temperature and environmental nutrient and ion concentrations are the major factors that determine the stage of the ameba. Trophozoites are the only stages that are invasive, although cysts are potentially infective, because they can convert to the vegetative form very quickly under the proper environmental stimuli. Although there are some 30 species of *Naegleria,* only *Naegleria fowleri* has been shown to be pathogenic for humans.

Acanthamoeba exist in cyst and motile trophozoite forms; only the trophozoite form is invasive. Cases of *Acanthamoeba* **keratitis** usually follow incidents of trivial corneal trauma followed by flushing with contaminated tap water. Infections can also occur among contact lens wearers who come in contact with contaminated water during swimming or using contact lenses cleaned or stored in contaminated tap water. Granulomatous amebic encephalitis from *Acanthamoeba* occurs worldwide and is associated with an immunocompromising condition such as HIV infection, diabetes mellitus, chronic liver disease, renal failure, immunosuppressive therapy, or radiation therapy.

Balamuthia mandrillaris has been implicated as an etiology of granulomatous amebic encephalitis. Although the clinical presentation is similar to infection with *Acanthamoeba,* most patients are not immunocompromised.

Other free-living amebas can also cause infection, as illustrated by case reports of *Sappinia diploidea* granulomatous encephalitis.

EPIDEMIOLOGY
The free-living amebas have a worldwide distribution. *Naegleria* species have been isolated from a variety of freshwater sources, including ponds and lakes, domestic water supplies, hot springs and spas, thermal discharge of power plants, groundwater, and, occasionally, from the nasal passages of healthy children. *Acanthamoeba* species have been isolated from soil, mushrooms, vegetables, brackish water, and seawater, as well as most of the freshwater sources for *Naegleria.* It can also be found in tap water, as chlorination does not kill *Acanthamoeba. Balamuthia* is present in soil and may be transmitted by inhalation or contamination of preexisting skin lesions.

Naegleria meningoencephalitis has been reported from every continent. Most of the cases occur during the summer months in previously healthy individuals who have a history of swimming in or contact with freshwater before their illness. Only 1-2 cases are reported in the United States per year, but 8 cases were reported in 2001-2002, and 6 cases were reported in 2007. Most of the reports have come from the southern and southwestern states, particularly Florida and Texas, with occasional infections occurring in the Midwest and East. Of note, 2 cases from Louisiana in 2011 were linked to sinus irrigation with neti pots, which contained contaminated tap water.

PATHOGENESIS
The free-living amebas enter the nasal cavity by inhalation or aspiration of dust or water contaminated with trophozoites or cysts. *Naegleria* gains access to the central nervous system through the olfactory epithelium and migrates via the olfactory nerve to the olfactory bulbs located in the subarachnoid space and bathed by the cerebrospinal fluid (CSF). This space is richly vascularized and is the route of spread to other areas of the central nervous system. Grossly, there is widespread cerebral edema and hyperemia of the meninges. The olfactory bulbs are necrotic, hemorrhagic, and surrounded by a purulent exudate. Microscopically, the gray matter is the most severely affected, with severe involvement in all cases. Fibrinopurulent exudate may be found throughout the cerebral hemispheres, brainstem, cerebellum, and upper portions of the spinal cord. Pockets of trophozoites may be seen in necrotic neural tissue, usually in the perivascular spaces of arteries and arterioles.

The route of invasion and penetration in cases of granulomatous amebic meningoencephalitis caused by *Acanthamoeba* and *Balamuthia* may be by direct spread through olfactory epithelium or hematogenous from a primary focus in the skin or lungs. Pathologic examination reveals granulomatous encephalitis, with multinucleated giant cells mainly in the posterior fossa structures, basal ganglia, bases of the cerebral hemispheres, and cerebellum. Both trophozoites and cysts may be found in the central nervous system lesions, primarily located in the perivascular spaces and invading blood vessel walls. The olfactory bulbs and spinal cord are usually spared. The single case of *Sappinia* encephalitis followed a sinus infection, and evaluation revealed a solitary 2 cm temporal lobe mass with mild ring enhancement.

CLINICAL MANIFESTATIONS
The incubation of ***Naegleria* infection** may be as short as 2 days or as long as 15 days. Symptoms have an acute onset and progress rapidly. Infection is characterized by a sudden onset of severe headache, fever, pharyngitis, nasal congestion or discharge, and nausea and vomiting, followed by altered mental status, confusion, somnolence, seizures, and ultimately coma. Most cases end in death within 3-10 days after onset of symptoms.

Granulomatous amebic meningoencephalitis may occur weeks to months after initial infection. The presenting signs and symptoms are often those of single or multiple central nervous system space-occupying lesions and include hemiparesis, ataxia, personality changes, seizures, and drowsiness. Altered mental status is often a prominent symptom. Headache and fever occur only sporadically, but stiff neck is seen in a majority of cases. Cranial nerve palsies, especially of cranial nerves III and VI, may be present. There is also 1 report of acute hydrocephalus and fever with *Balamuthia.* Granulomatous amebic meningoencephalitis is usually fatal after 4-6 wk of illness. Results of neuroimaging studies of the brain usually demonstrate multiple low-density lesions resembling infarcts or enhancing lesions of granulomas (Fig. 280-1).

DIAGNOSIS
The CSF in *Naegleria* infection may mimic that of herpes simplex encephalitis early in the disease and that of acute bacterial meningitis later in the disease, with a neutrophilic pleocytosis, elevated protein level, and hypoglycorrhachia. Motile amebas may be visualized on a wet mount of freshly drawn CSF using Wright or Giemsa stains, but are often mistaken for lymphocytes or macrophages. Because *Naegleria* are the only amebas that differentiate into the flagellate state in a

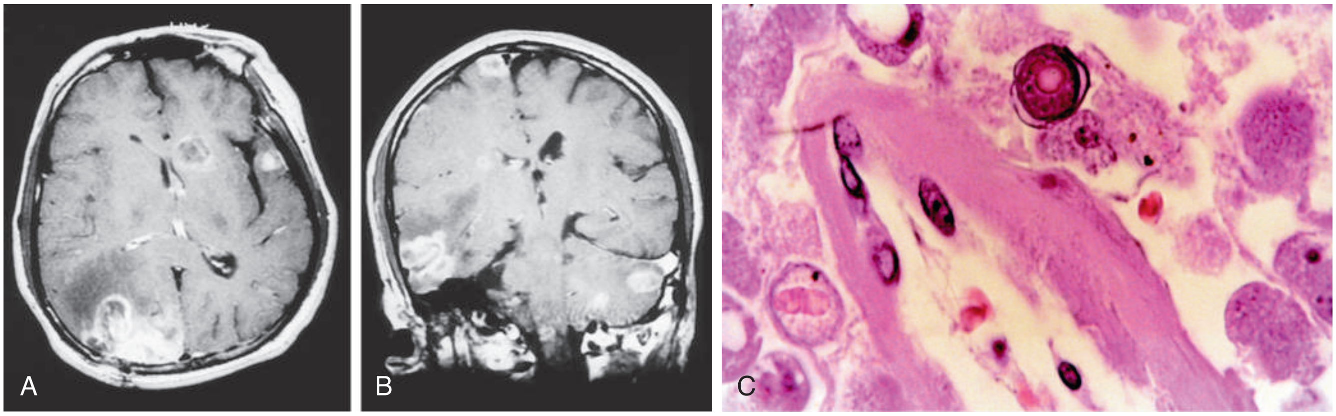

Figure 280-1 **A** and **B,** MRIs of the brain of a patient with *Balamuthia mandrillaris* granulomatous amebic encephalitis. Multiple enhancing lesions are seen in the right hemisphere, left cerebellum, midbrain, and brainstem. **C,** Photomicrograph of the brain lesion from the same patient showing perivascular amebic trophozoites. A round amebic cyst with a characteristic double wall is seen in the top center (hematoxylin-and-eosin, original magnification ×100). *(From Deol I, Robledo L, Meza A, et al: Encephalitis due to a free-living amoeba* [Balamuthia mandrillaris]: *case report with literature review,* Surg Neurol *53:611–616, 2000.)*

hypotonic environment, placing a drop of fresh CSF in 1 mL of distilled water and watching for development of swimming flagellates after 1-2 hr can confirm the diagnosis of *Naegleria*. *Naegleria* can also be grown on a nonnutrient agar plate coated with *Escherichia coli*, on which they feed.

The diagnosis of granulomatous amebic meningoencephalitis relies on the isolation or histologic identification of *Acanthamoeba* trophozoites or cysts from brain tissue specimens. The CSF findings of granulomatous meningoencephalitis reveal lymphocytic pleocytosis, moderately elevated protein, and low glucose concentrations. Motile trophozoites of *Acanthamoeba,* however, are more difficult to isolate than *Naegleria* and the CSF is typically sterile. *Acanthamoeba* may be cultured from the same agar used for growing *Naegleria,* but *Balamuthia* must be grown on mammalian cell cultures. Pediatric cases of *Balamuthia* meningoencephalitis have been diagnosed antemortem by brain biopsy as well as postmortem. Immunofluorescence staining of brain tissue can differentiate *Acanthamoeba* and *Balamuthia.*

TREATMENT

Naegleria infection is nearly always fatal, and early recognition and early treatment are crucial to successful therapy. There are several reports of treatment survivors, most of whom recovered fully. *Naegleria* infections have been successfully treated using amphotericin B, either alone or in combination with rifampin, chloramphenicol, fluconazole, or ketoconazole. The early use of dexamethasone may be considered, as steroid treatment was used in the few cases of survivors (as well as nonsurvivors). The optimal duration of treatment is unknown, but at least 10 days of therapy has been used in survivors. In 2013, the U.S. Centers for Disease Control and Prevention made available miltefosine for the treatment of primary amebic meningoencephalitis. In 2013, two children with *Naegleria* infection survived; both received miltefosine as part of their treatment; one received therapeutic hypothermia.

The optimal therapy for granulomatous amebic meningoencephalitis is also uncertain. Miltefosine has been used to successfully treat patients with *Balamuthia* and disseminated *Acanthamoeba* infections. Strains of *Acanthamoeba* isolated from fatal cases are usually susceptible in vitro to pentamidine, ketoconazole, flucytosine, and less so to amphotericin B. One patient was successfully treated with sulfadiazine and fluconazole, and another was successfully treated with intravenous pentamidine followed by oral itraconazole. *Acanthamoeba* keratitis responds to long courses of topical propamidine–polymyxin B sulfate or topical polyhexamethylene biguanide or chlorhexidine gluconate, and antifungal azoles plus topical steroids. Limited success has been demonstrated in *Balamuthia* infection with systemic azole therapy combined with flucytosine. More recently, the combination of flucytosine, pentamidine, fluconazole, sulfadiazine, a macrolide, and phenothiazines resulted in the survival of 2 patients with *Balamuthia* meningoencephalitis, although both were left with mild neuromotor and cognitive impairment. Corticosteroids prior to initiating effective therapy appear to have a detrimental effect, contributing to rapid progression of disease.

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Chapter 281

Amebiasis

Edsel Maurice T. Salvana and Robert A. Salata

Entamoeba species infects or colonizes up to 10% of the world's population, particularly in resource-limited settings. In most infected individuals, *Entamoeba histolytica* or a related species parasitizes the lumen of the gastrointestinal tract and causes few symptoms or sequelae. *E. histolytica* is the only invasive species and can cause **amebic colitis** with parasitic invasion of the intestinal mucosa and **amebic liver abscess** with dissemination of the parasite to the liver.

ETIOLOGY

Three morphologically identical but genetically distinct species of *Entamoeba* commonly infect humans. *Entamoeba dispar,* the most prevalent species, does not cause symptomatic disease. *Entamoeba moshkovskii*, previously thought to be nonpathogenic, has been shown to cause diarrhea in infants. *E. histolytica,* the main pathogenic species, causes a spectrum of disease and can become invasive in 4-10% of infected patients. Patients previously described as asymptomatic carriers of *E. histolytica* based on microscopy findings were likely harboring *E. dispar.* Four other species of nonpathogenic *Entamoeba* are known to colonize the human gastrointestinal tract: *E. coli, E. hartmanni, E. gingivalis,* and *E. polecki.*

Infection is acquired through the ingestion of parasite cysts, which measure 10-18 µm in diameter and contain 4 nuclei. Cysts are resistant to harsh environmental conditions, including chlorine concentrations commonly used in water purification, but can be killed by heating to 55°C (131°F). After ingestion, cysts are resistant to gastric acidity and digestive enzymes and germinate in the small intestine to form trophozoites. These large, actively motile organisms colonize the lumen of the large intestine and may invade the mucosal lining. Infection is not

usually transmitted by trophozoites, as these rapidly degenerate outside the body and are unable to survive the low pH of the stomach if swallowed.

EPIDEMIOLOGY

Prevalence of infection with *E. histolytica* varies greatly depending on region and socioeconomic status. Most prevalence studies have not distinguished between *E. histolytica* and *E. dispar,* and thus the true prevalence of *E. histolytica* infection is not known. It is estimated that infection with *E. histolytica* leads to 50 million cases of symptomatic disease and 40,000-110,000 deaths annually. Amebiasis is the second leading parasitic cause of death worldwide, after malaria. Prospective studies show that 4-10% of individuals infected with *E. histolytica* develop amebic colitis and that <1% of infected individuals develop disseminated disease, including amebic liver abscess. These numbers vary by region; for example, in South Africa and Vietnam, liver abscesses form a disproportionately large number of the cases of invasive disease caused by *E. histolytica.* Amebic liver abscesses are rare in children and occur equally in male and female children; in adults, amebic liver abscesses occur predominantly in men.

Amebiasis is endemic to Africa, Latin America, India, and Southeast Asia. In the United States, amebiasis is seen most frequently in immigrants from and in travelers to developing countries. Residents of mental health institutions and men who have sex with men are also at increased risk for invasive amebiasis. Food or drink contaminated with *Entamoeba* cysts and oral-anogenital sex are the most common means of infection. Untreated water and night soil (human feces used as fertilizer) are important sources of infection. Food handlers shedding amebic cysts play a role in spreading infection. Direct contact with infected feces can also result in person-to-person transmission.

PATHOGENESIS

Trophozoites are responsible for tissue invasion and destruction. These attach to colonic epithelial cells by a galactose and *N*-acetyl-ᴅ-galactosamine–specific lectin. This lectin is also thought to be responsible for resistance to complement-mediated lysis. Once attached to the colonic mucosa, amebas release proteases that allow for penetration through the epithelial layer. Host cells are destroyed by cytolysis and apoptosis. Cytolysis is mediated by trophozoite release of **amoebapores** (pore-forming proteins), phospholipases, and hemolysins. Amoebapores, which cause a massive influx of extracellular calcium, may also be partially responsible for the induction of apoptosis that occurs with amebic liver disease and colitis. Once host cells are partially digested by amebic proteases, the degraded material is internalized through phagocytosis. Early invasive amebiasis produces significant inflammation, due in part to parasite-mediated activation of nuclear factor-κB. Once *E. histolytica* trophozoites invade the intestinal mucosa, the organisms multiply and spread laterally underneath the intestinal epithelium to produce the characteristic **flask-shaped ulcers.** Amebas produce similar lytic lesions if they reach the liver. These lesions are commonly called *abscesses*, although they contain no granulocytes. Well-established ulcers and amebic liver abscesses demonstrate little local inflammatory response.

Immunity to infection is associated with a mucosal secretory IgA response against the galactose/*N*-acetyl-ᴅ-galactosamine lectin. Neutrophils appear to be important in initial host defense, but *E. histolytica*–induced epithelial cell damage releases neutrophil chemoattractants, and *E. histolytica* is able to kill neutrophils, which then release mediators that further damage epithelial cells. The disparity between the extent of tissue destruction by amebas and the absence of a local host inflammatory response in the presence of systemic humoral (antibody) and cell-mediated responses may reflect both parasite-mediated apoptosis and the ability of the trophozoite to kill not only epithelial cells but neutrophils, monocytes, and macrophages. Studies show a protective role of the hormone leptin in mucosal resistance. A malnourished state, in which leptin levels are low, and a genetic polymorphism in the leptin receptor can increase susceptibility to invasive disease.

The sequencing of the *E. histolytica* genome has led to further insights into the pathogenesis of *E. histolytica* disease. The genome is functionally tetraploid and contains evidence of lateral gene transfer from bacteria. It has been demonstrated that the **amoebapore-A** *(Ap-A)* gene, along with other important genes, can be epigenetically silenced using plasmids with specifically engineered sequences or short hairpin RNAs. Transcriptional profiling using proteomics and microarrays has likewise identified several candidate virulence factors. Several classes of proteases that may be associated with pathogenesis have been identified, including the cysteine proteases binding family proteins (CPBF8), which modulate lysosome and phagosome function, and M8 metalloprotease EhMSP-1, which likely has a key role in amebic invasion and is notably absent in *E. dispar*.

CLINICAL MANIFESTATIONS

Clinical presentations range from asymptomatic cyst passage to amebic colitis, amebic dysentery, ameboma, and extraintestinal disease. Up to 10% of infected persons develop invasive disease within a year. Thus, asymptomatic carriers should be treated. Severe disease is more common in young children, pregnant women, malnourished individuals, and persons taking corticosteroids, and invasive disease is more common in men. Extraintestinal disease usually involves the liver, but less common extraintestinal manifestations include amebic brain abscess, pleuropulmonary disease, ulcerative skin, and genitourinary lesions.

Amebic Colitis

Amebic colitis may occur within 2 wk of infection or may be delayed for months. The onset is usually gradual, with colicky abdominal pains and frequent bowel movements (6-8/day). Diarrhea is frequently associated with tenesmus. Almost all stool is heme-positive, but most patients do not present with grossly bloody stools. Generalized constitutional symptoms and signs are characteristically absent, with fever documented in only one third of patients. Amebic colitis affects all age groups but is strikingly common in children 1-5 yr of age. Severe amebic colitis in infants and young children tends to be rapidly progressive with more frequent extraintestinal involvement and high mortality rates, particularly in tropical countries. Amebic dysentery can result in dehydration and electrolyte disturbances.

Amebic Liver Abscess

Amebic liver abscess, a serious manifestation of disseminated infection, is uncommon in children. Although diffuse liver enlargement has been associated with intestinal amebiasis, liver abscesses occur in <1% of infected individuals and may appear in patients with no clear history of intestinal disease. Amebic liver abscess may occur months to years after exposure, so obtaining a careful travel history is critical. In children, fever is the hallmark of amebic liver abscess and is frequently associated with abdominal pain, abdominal distention, and enlargement and tenderness of the liver. Changes at the base of the right lung, such as elevation of the diaphragm and atelectasis or effusion, may also occur.

Men Who Have Sex with Men and HIV Coinfection

Epidemiologic studies from both developed and developing countries have shown an increased risk for *E. histolytica* infection among men who have sex with men. This risk is further increased in HIV because of increased host susceptibility, and is particularly pronounced in men who have sex with men with HIV infection.

LABORATORY FINDINGS

Laboratory examination findings are often unremarkable in uncomplicated amebic colitis. Laboratory findings in amebic liver abscess are a slight leukocytosis, moderate anemia, high erythrocyte sedimentation rate, and elevations of hepatic enzyme (particularly alkaline phosphatase) levels. Stool examination for amebas is negative in more than half of patients with documented amebic liver abscess. Ultrasonography, CT, or MRI can localize and delineate the size of the abscess cavity (Fig. 281-1). The most common finding is a single abscess in the right hepatic lobe in about one half of these cases. Higher-resolution

ultrasound and CT studies show that left lobe abscess and multiple abscesses occur more often than previously recognized.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A diagnosis of amebic colitis is made in the presence of compatible symptoms with detection of *E. histolytica* antigens in stool. This approach has a >95% sensitivity and specificity and coupled with a positive serology test is the most accurate means of diagnosis in developed countries. The *E. histolytica* II stool antigen detection test (TechLab, Blacksburg, VA) is able to distinguish *E. histolytica* from *E. dispar* infection. Microscopic examination of stool samples has a sensitivity of 60%. Sensitivity can be increased to 85-95% by examining 3 stools, as excretion of cysts can be intermittent. However, microscopy cannot differentiate between *E. histolytica* and *E. dispar* unless phagocytosed erythrocytes (specific for *E. histolytica*) are seen. In highly endemic areas, trophozoites without phagocytosed erythrocytes may reflect coinfection with *E. dispar* in a patient with another cause of colitis, such as shigellosis. Endoscopy and biopsies of suspicious areas should be performed when stool sample results are negative and suspicion for amebiasis remains high.

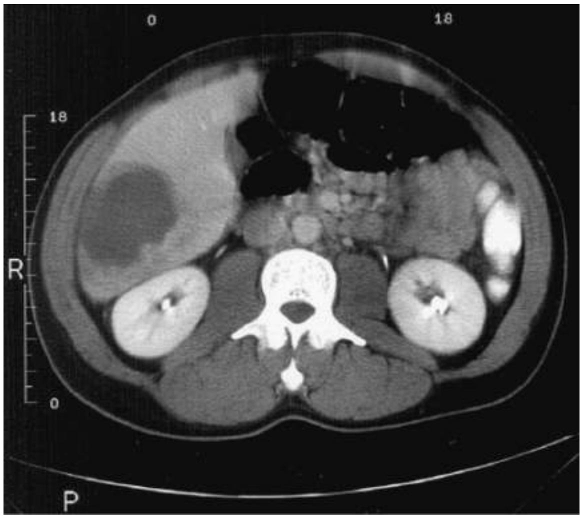

Figure 281-1 Abdominal CT scan of a patient with an amebic liver abscess. *(From Miller Q, Kenney JM, Cotlar AM: Amebic abscess of the liver presenting as acute cholecystitis,* Curr Surg *57:476–479, 2000, Fig. 1, p. 477.)*

Various serum antiamebic antibody tests are available. Serologic results are positive in 70-80% of patients with invasive disease (colitis or liver abscess) at presentation and in >90% of patients after 7 days of disease symptoms. The most sensitive serologic test, indirect hemagglutination, yields a positive result even years after invasive infection. Therefore, many uninfected adults and children in highly endemic areas demonstrate antibodies to *E. histolytica.* Polymerase chain reaction detection in stool of *E. histolytica* is also able to distinguish *E. histolytica* from *E. dispar* but is less sensitive (72%) than the stool antigen test. Rapid antigen and antibody tests for bedside diagnosis in the developing world have been developed and are currently being tested. A high-throughput Luminex technique for simultaneous detection and differentiation of *Entamoeba* species has also been developed. In addition, a loop-mediated isothermal amplification assay that can be optimized for field use is under development.

The **differential diagnosis** for amebic colitis includes colitis caused by bacterial (*Shigella, Salmonella,* enteropathogenic *Escherichia coli, Campylobacter, Yersinia, Clostridium difficile*), mycobacterial (tuberculosis and atypical mycobacteria), and viral (cytomegalovirus) pathogens, as well as noninfectious causes such as inflammatory bowel disease. Pyogenic liver abscess from bacterial infection, hepatoma, and echinococcal cysts are in the differential diagnosis for amebic liver abscess. However, echinococcal cysts are rarely associated with systemic symptoms such as fever unless there is cyst rupture or leakage.

COMPLICATIONS

Complications of amebic colitis include acute necrotizing colitis, ameboma, toxic megacolon, extraintestinal extension, or local perforation and peritonitis. Less commonly, a chronic form of amebic colitis develops, often recurring over several years. Amebomas are nodular foci of proliferative inflammation that sometimes develop in the wall of the colon. Chronic amebiasis should be excluded before initiating corticosteroid treatment for inflammatory bowel disease, as corticosteroid therapy given during active amebic colitis is associated with high mortality rates.

An amebic liver abscess may rupture into the peritoneum, pleural cavity, skin, and pericardium. Cases of amebic abscesses in extrahepatic sites, including the lung and brain, have been reported.

TREATMENT

Invasive amebiasis is treated with a nitroimidazole such as **metronidazole** or **tinidazole** and then a **luminal amebicide** (Table 281-1).

Table 281-1 Drug Treatment for Amebiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
INVASIVE DISEASE		
Metronidazole	Colitis or liver abscess: 750 mg tid for 7-10 days	Colitis or liver abscess: 35-50 mg/kg/day in 3 divided doses for 7-10 days
or		
Tinidazole	Colitis: 2 g once daily for 3 days Liver abscess: 2 g once daily for 3-5 days	Colitis: 50 mg/kg/day once daily for 3 days Liver abscess: 50 mg/kg/day once daily for 3-5 days
Followed by:		
Paromomycin (preferred)	500 mg tid for 7 days	25-35 mg/kg/day in 3 divided doses for 7 days
or		
Diloxanide furoate†	500 mg tid for 10 days	20 mg/kg/day in 3 divided doses for 7 days
or		
Iodoquinol	650 mg tid for 20 days	30-40 mg/kg/day in 3 divided doses for 20 days
ASYMPTOMATIC INTESTINAL COLONIZATION		
Paromomycin (preferred)	As for invasive disease	As for invasive disease
or		
Diloxanide furoate†		
or		
Iodoquinol		

*All pediatric dosages are up to a maximum of the adult dose.
†Not available in the United States.

Tinidazole has similar efficacy to metronidazole with shorter and simpler dosing and less-frequent adverse effects. These adverse effects include nausea, abdominal discomfort, and a metallic taste that disappears after completion of therapy. Therapy with a nitroimidazole should be followed by treatment with a luminal agent, such as paromomycin (which is preferred) or iodoquinol. Diloxanide furoate can also be used in children older than 2 yr of age, but it is no longer available in the United States. Paromomycin should not be given concurrently with metronidazole or tinidazole, because diarrhea is a common side effect of paromomycin and may confuse the clinical picture. Asymptomatic intestinal infection with *E. histolytica* should be treated preferably with paromomycin or alternatively with either iodoquinol or diloxanide furoate. For fulminant cases of amebic colitis, some experts suggest adding dehydroemetine (1 mg/kg/day subcutaneously or IM, never IV), available only through the Centers for Disease Control and Prevention. Patients should be hospitalized for monitoring if dehydroemetine is administered. Dehydroemetine should be discontinued if tachycardia, T-wave depression, arrhythmia, or proteinuria develops.

Broad-spectrum antibiotic therapy may be indicated in fulminant colitis to cover possible spillage of intestinal bacteria into the peritoneum and translocation into the bloodstream. Intestinal perforation and toxic megacolon are indications for surgery. In amebic liver abscess, image-guided aspiration of large lesions or left lobe abscesses may be necessary if rupture is imminent or if the patient shows a poor clinical response 4-6 days after administration of amebicidal drugs. A Cochrane metaanalysis comparing metronidazole and metronidazole plus aspiration in uncomplicated amebic liver abscess showed that there is insufficient evidence to make any recommendation for or against this approach. Chloroquine, which concentrates in the liver, may also be a useful adjunct to nitroimidazoles in the treatment of amebic liver abscess. To confirm cure, stool examination should be repeated every 2 wk following completion of therapy until clear.

PROGNOSIS

Most infections evolve to either an asymptomatic carrier state or eradication. Extraintestinal infection carries about a 5% mortality rate.

PREVENTION

Control of amebiasis can be achieved by exercising proper sanitation and avoiding fecal-oral transmission. Regular examination of food handlers and thorough investigation of diarrheal episodes may help identify the source of infection. No prophylactic drug or vaccine is currently available for amebiasis. Immunization with a combination of galactose/*N*-acetyl-D-galactosamine lectin and CpG oligodeoxynucleotides is protective against amebic trophozoite challenge in animals, and an intranasal galactose-lectin subunit vaccine is protective in baboons.

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Chapter 282

Giardiasis and Balantidiasis

282.1 *Giardia lamblia*

Chandy C. John

Giardia lamblia is a flagellated protozoan that infects the duodenum and small intestine. Infection results in clinical manifestations that range from asymptomatic colonization to acute or chronic diarrhea and malabsorption. Infection is more prevalent in children than in adults. *Giardia* is endemic in areas of the world with poor levels of sanitation. It is also an important cause of morbidity in developed countries, where it is associated with urban childcare centers, residential institutions for the developmentally delayed, and waterborne and foodborne outbreaks. *Giardia* is a particularly significant pathogen in people with malnutrition, certain immunodeficiencies, and cystic fibrosis.

ETIOLOGY

The life cycle of *G. lamblia* (also known as *Giardia intestinalis* or *Giardia duodenalis*) is composed of 2 stages: trophozoites and cysts. *Giardia* infects humans after ingestion of as few as 10-100 cysts (which measure 8-10 µm in diameter). Each ingested cyst produces 2 trophozoites in the duodenum. After excystation, trophozoites colonize the lumen of the duodenum and proximal jejunum, where they attach to the brush border of the intestinal epithelial cells and multiply by binary fission. The body of the trophozoite is teardrop shaped, measuring 10-20 µm in length and 5-15 µm in width. *Giardia* trophozoites contain 2 oval nuclei anteriorly, a large ventral disk, a curved median body posteriorly, and 4 pairs of flagella. As detached trophozoites pass down the intestinal tract, they encyst to form oval cysts that contain 4 nuclei. Cysts are passed in stools of infected individuals and may remain viable in water for as long as 2 mo. Their viability often is not affected by the usual concentrations of chlorine used to purify water for drinking.

Giardia strains that infect humans are diverse biologically, as shown by differences in antigens, restriction endonuclease patterns, DNA fingerprinting, isoenzyme patterns, and pulsed-field gel electrophoresis. Studies suggest that different *Giardia* genotypes may cause unique clinical manifestations, but these findings appear to vary according to the geographic region tested.

EPIDEMIOLOGY

Giardia occurs worldwide and is the most common intestinal parasite identified in public health laboratories in the United States, where it is estimated that up to 2 million cases of giardiasis occur annually. *Giardia* infection usually occurs sporadically, but *Giardia* is a frequently identified etiologic agent of outbreaks associated with drinking water. The age-specific prevalence of giardiasis is high during childhood and begins to decline after adolescence. The asymptomatic carrier rate of *G. lamblia* in the United States is as high as 20-30% in children younger than 36 mo of age attending childcare centers. Asymptomatic carriage may persist for several months.

Transmission of *Giardia* is common in certain high-risk groups, including children and employees in childcare centers, consumers of contaminated water, travelers to certain areas of the world, men who have sex with men, and persons exposed to certain animals. The major reservoir and vehicle for spread of *Giardia* appears to be water contaminated with *Giardia* cysts, but foodborne transmission occurs. The seasonal peak in age-specific case reports coincides with the summer recreational water season and might be a result of the extensive use of communal swimming venues by young children, the low infectious dose, and the extended periods of cyst shedding that can occur. In addition, *Giardia* cysts are relatively resistant to chlorination and to ultraviolet light irradiation. Boiling is effective for inactivating cysts.

Person-to-person spread also occurs, particularly in areas of low hygiene standards, frequent fecal-oral contact, and crowding. Individual susceptibility, lack of toilet training, crowding, and fecal contamination of the environment all predispose to transmission of enteropathogens, including *Giardia,* in childcare centers. Childcare centers play an important role in transmission of urban giardiasis, with secondary attack rates in families as high as 17-30%. Children in childcare centers may pass cysts for several months. Campers who drink untreated stream or river water, particularly in the western United States, and residents of institutions for the developmentally delayed are also at increased risk for infection.

Humoral immunodeficiencies, including common variable hypogammaglobulinemia and X-linked agammaglobulinemia, predispose

humans to chronic symptomatic *Giardia* infection, suggesting the importance of humoral immunity in controlling giardiasis. Selective immunoglobulin A deficiency is also associated with *Giardia* infection. Although many individuals with AIDS have relatively mild *Giardia* infections, some reports suggest that severe *Giardia* infection, often refractory to treatment, may occur in a subset of individuals with AIDS. There is a higher incidence of *Giardia* infection in patients with cystic fibrosis, probably owing to local factors such as the increased amount of mucus, which may protect the organism against host factors in the duodenum. Human milk contains glycoconjugates and secretory immunoglobulin A antibodies that may provide protection to nursing infants against *Giardia*.

CLINICAL MANIFESTATIONS

The incubation period of *Giardia* infection usually is 1-2 wk but may be longer. A broad spectrum of clinical manifestations occurs, depending on the interaction between *G. lamblia* and the host. Children who are exposed to *G. lamblia* may experience asymptomatic excretion of the organism, acute infectious diarrhea, or chronic diarrhea with persistent gastrointestinal tract signs and symptoms, including failure to thrive and abdominal pain or cramping. *Giardia* was the cause of 15% of nondysenteric diarrhea illnesses in children examined in U.S. outpatient clinics in 1 study. Most infections in both children and adults are asymptomatic. There usually is no extraintestinal spread, but occasionally trophozoites may migrate into bile or pancreatic ducts.

Symptomatic infections occur more frequently in children than in adults. Most symptomatic patients usually have a limited period of acute diarrheal disease with or without low-grade fever, nausea, and anorexia; in a small proportion of patients, an intermittent or more protracted course characterized by diarrhea, abdominal distention and cramps, bloating, malaise, flatulence, nausea, anorexia, and weight loss develops (Table 282-1). Stools initially may be profuse and watery and later become greasy and foul smelling and may float. Stools do not contain blood, mucus, or fecal leukocytes. Varying degrees of malabsorption may occur. Abnormal stool patterns may alternate with periods of constipation and normal bowel movements. Malabsorption of sugars, fats, and fat-soluble vitamins is well documented and may be responsible for substantial weight loss. *Giardia* has been associated with iron deficiency in internationally adopted children. Giardiasis has been associated with growth stunting, and repeated *Giardia* infections correlate with a decrease in cognitive function in children in endemic areas.

Table 282-1 Clinical Signs and Symptoms of Giardiasis

SYMPTOM	FREQUENCY (%)
Diarrhea	64-100
Malaise, weakness	72-97
Abdominal distention	42-97
Flatulence	35-97
Abdominal cramps	44-81
Nausea	14-79
Foul-smelling, greasy stools	15-79
Anorexia	41-73
Weight loss	53-73
Vomiting	14-35
Fever	0-28
Constipation	0-27

DIAGNOSIS

Giardiasis should be considered in children who have acute nondysenteric diarrhea, persistent diarrhea, intermittent diarrhea and constipation, malabsorption, chronic crampy abdominal pain and bloating, failure to thrive, or weight loss. It should be particularly high in the differential diagnosis of children in child care, children in contact with an index case, children with a history of recent travel to an endemic area, and children with humoral immunodeficiencies. Testing for giardiasis should be standard for internationally adopted children from *Giardia*-endemic areas, and screening for iron deficiency should be considered in internationally adopted children with giardiasis.

Stool enzyme immunoassay (EIA) or direct fluorescent antibody tests for *Giardia* antigens are the tests of choice for giardiasis in most situations. EIA is less reader dependent and more sensitive for detection of *Giardia* than microscopy. Some studies report that a single stool is sufficiently sensitive for detection of *Giardia* by EIA, whereas others suggest that sensitivity is increased with testing of 2 samples. A diagnosis of giardiasis was traditionally established by microscopy documentation of trophozoites or cysts in stool specimens, but 3 stool specimens are required to achieve a sensitivity of >90% using this approach. In patients in whom other parasitic intestinal infections are in the differential diagnosis, microscopy examination of stool allows evaluation for these infections in addition to *Giardia*. Laboratories can reduce reagent and personnel costs by pooling specimens submitted for detection of *Giardia* before evaluation by microscopy or EIA. Polymerase chain reaction and gene probe–based detection systems specific for *Giardia* have been used in environmental monitoring but at present remain research tools. Multiplex polymerase chain reaction testing for multiple parasitic pathogens may become a viable option for testing in the future.

In patients with chronic symptoms in whom giardiasis is suspected but in whom testing of stool specimens for *Giardia* yields a negative result, aspiration or biopsy of the duodenum or upper jejunum should be considered. In a fresh specimen, trophozoites usually can be visualized by direct wet mount. An alternate method of directly obtaining duodenal fluid is the commercially available Entero-Test (Hedeco Corp, Mountain View, CA), but this method is less sensitive than aspiration or biopsy. The biopsy can be used to make touch preparations and tissue sections for identification of *Giardia* and other enteric pathogens and also to visualize changes in histology. Biopsy of the small intestine should be considered in patients with characteristic clinical symptoms, negative stool and duodenal fluid specimen findings, and 1 or more of the following: abnormal radiographic findings (such as edema and segmentation in the small intestine); abnormal lactose tolerance test result; absent secretory immunoglobulin A level; hypogammaglobulinemia; and achlorhydria. Duodenal biopsy may show findings consistent with chronic inflammation, including eosinophilic infiltration of the lamina propria.

Radiographic contrast studies of the small intestine may show nonspecific findings such as irregular thickening of the mucosal folds. Blood cell counts usually are normal. Giardiasis is not tissue invasive and is not associated with peripheral blood eosinophilia.

TREATMENT

Children with acute diarrhea in whom *Giardia* organisms are identified should receive therapy. In addition, children who manifest failure to thrive or exhibit malabsorption or gastrointestinal tract symptoms such as chronic diarrhea should be treated.

Asymptomatic excreters generally are not treated except in specific instances such as outbreak control, prevention of household transmission by toddlers to pregnant women and patients with hypogammaglobulinemia or cystic fibrosis, and situations requiring oral antibiotic treatment where *Giardia* may produce malabsorption of the antibiotic.

The FDA has approved tinidazole and nitazoxanide for the treatment of *Giardia* in the United States. Both medications have been used to treat *Giardia* in thousands of patients in other countries and have excellent safety and efficacy against *Giardia* (Table 282-2). Tinidazole

Table 282-2 Drug Treatment for Giardiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
RECOMMENDED		
Tinidazole	2 g once	>3 yr: 50 mg/kg once
Nitazoxanide	500 mg bid for 3 days	1-3 yr: 100 mg (5 mL) bid for 3 days 4-11 yr: 200 mg (10 mL) bid for 3 days >12 yr: 500 mg bid for 3 days
Metronidazole	250 mg tid for 5-7 days	15 mg/kg/day in 3 divided doses for 5-7 days
ALTERNATIVE		
Albendazole	400 mg once a day for 5 days	>6 yr: 400 mg once a day for 5 days
Paromomycin	25-35 mg/kg/day in 3 divided doses for 5-10 days	Not recommended
Quinacrine[†]	100 mg tid for 5-7 days	6 mg/kg/day in 3 divided doses for 5 days

*All pediatric dosages are up to a maximum of the adult dose.
[†]Not commercially available. Can be compounded by Medical Center Pharmacy in New Haven, CT (203-688-6816) or Panorama Compounding Pharmacy in Van Nuys, CA (800-247-9767).

has the advantage of single-dose treatment and very high efficacy (>90%), while nitazoxanide has the advantage of a suspension form, high efficacy (80-90%), and very few adverse effects. Metronidazole, though never approved by the FDA for treatment of *Giardia,* is also highly effective (80-90% cure rate), and the generic form is considerably less expensive than tinidazole or nitazoxanide. Frequent adverse effects are seen with metronidazole therapy, and it requires 3 times a day dosing for 5-7 days. Suspension forms of tinidazole and metronidazole must be compounded by a pharmacy; neither drug is sold in suspension form.

Second-line alternatives for the treatment of patients with giardiasis include albendazole, paromomycin, and quinacrine (see Table 282-2). Albendazole may be of similar efficacy to metronidazole. Albendazole has few adverse effects and is effective against many helminths, making it useful for treatment when multiple intestinal parasites are identified or suspected. Paromomycin is a nonabsorbable aminoglycoside and is less effective than other agents but is recommended for treatment of pregnant women with giardiasis because of potential teratogenic effects of other agents. Quinacrine is effective and inexpensive but is not available commercially and must be obtained from compounding pharmacies (see Table 282-2). Quinacrine can also rarely have serious side effects, including hallucinations and psychosis. Refractory cases of giardiasis have been successfully treated with nitazoxanide, prolonged courses of tinidazole, or a 3 wk course of metronidazole and quinacrine.

PROGNOSIS

Symptoms recur in some patients in whom reinfection cannot be documented and in whom an immune deficiency such as an immunoglobulin abnormality is not present, despite use of appropriate therapy. Several studies have demonstrated that variability in antimicrobial susceptibility exists among strains of *Giardia,* and in some instances resistant strains have been demonstrated. Combined therapy may be useful for infection that persists after single-drug therapy, assuming reinfection has not occurred and the medication was taken as prescribed.

PREVENTION

Infected persons and persons at risk should practice strict handwashing after any contact with feces. This point is especially important for caregivers of diapered infants in childcare centers, where diarrhea is common and *Giardia* organism carriage rates are high.

Methods to purify public water supplies adequately include chlorination, sedimentation, and filtration. Inactivation of *Giardia* cysts by chlorine requires the coordination of multiple variables such as chlorine concentration, water pH, turbidity, temperature, and contact time. These variables cannot be appropriately controlled in all municipalities and are difficult to control in swimming pools. Individuals, especially children in diapers, should avoid swimming if they have diarrhea. Individuals should also avoid swallowing recreational water and drinking untreated water from shallow wells, lakes, springs, ponds, streams, and rivers.

Travelers to endemic areas are advised to avoid uncooked foods that might have been grown, washed, or prepared with water that was potentially contaminated. Purification of drinking water can be achieved by a filter with a pore size of <1 µm or that has been National Sanitation Foundation rated for cyst removal, or by brisk boiling of water for at least 1 min. Treatment of water with chlorine or iodine is less effective but may be used as an alternate method when boiling or filtration is not possible.

Bibliography is available at Expert Consult.

282.2 Balantidiasis

Chandy C. John

Balantidium coli is a ciliated protozoan and is the largest protozoan that parasitizes humans. Both trophozoites and cysts may be identified in feces. Disease caused by this organism is uncommon in the United States and generally is reported where there is a close association of humans with pigs, which are the natural hosts of *B. coli.* Because the organism infects the large intestine, symptoms are consistent with large bowel disease, similar to those associated with amebiasis and trichuriasis, and include nausea, vomiting, lower abdominal pain, tenesmus, and bloody diarrhea. Symptoms associated with chronic infection include abdominal cramps, watery diarrhea with mucus, occasionally bloody diarrhea, and colonic ulcers similar to those associated with *Entamoeba histolytica.* Extraintestinal spread of *B. coli* is rare and usually occurs only in immunocompromised patients. Most infections are asymptomatic.

Diagnosis using direct saline mounts is established by identification of trophozoites (50-100 µm long) or spherical or oval cysts (50-70 µm in diameter) in stool specimens. Trophozoites usually are more numerous than cysts. The recommended treatment regimen is metronidazole (45 mg/kg/day divided tid PO; maximum: 750 mg/dose) for 5 days, or tetracycline (40 mg/kg/day divided qid PO; maximum: 500 mg/dose) for 10 days for persons older than 8 yr of age. An alternative is iodoquinol (40 mg/kg/day divided tid PO; maximum: 650 mg/dose) for 20 days. Prevention of contamination of the environment by pig feces is the most important means for control.

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Chapter 283

Cryptosporidium, Isospora, Cyclospora, and Microsporidia

Patricia M. Flynn

The spore-forming intestinal protozoa *Cryptosporidium, Isospora,* and *Cyclospora* are important intestinal pathogens in both immunocompetent and immunocompromised hosts. *Cryptosporidium, Isospora,* and *Cyclospora* are coccidian parasites that predominantly infect the epithelial cells lining the digestive tract. Microsporidia were formerly considered spore-forming protozoa but have been reclassified as fungi. Microsporidia are ubiquitous, obligate intracellular parasites that infect many other organ systems in addition to the gastrointestinal tract and cause a broader spectrum of disease.

CRYPTOSPORIDIUM

Cryptosporidium is recognized as a leading protozoal cause of diarrhea in children worldwide and is a common cause of outbreaks in childcare centers; it is also a significant pathogen in immunocompromised patients.

Etiology

Cryptosporidium hominis and *Cryptosporidium parvum* cause most cases of cryptosporidiosis in humans. Disease is initiated by ingestion of infectious oocysts that release 4 sporozoites that invade enterocytes, primarily in the small intestine. The cysts are immediately infectious to other hosts or can reinfect the same host.

Epidemiology

Cryptosporidiosis is associated with diarrheal illness worldwide and is more prevalent in developing countries and among children younger than 2 yr of age. It has been implicated as an etiologic agent of persistent diarrhea in the developing world and as a cause of significant morbidity and mortality from malnutrition, including permanent effects on growth.

Transmission of *Cryptosporidium* to humans can occur by close association with infected animals, via person-to-person transmission, or from environmentally contaminated water. Although zoonotic transmission, especially from cows, occurs in persons in close association with animals, person-to-person transmission is probably responsible for cryptosporidiosis outbreaks within hospitals and childcare centers where transmission rates as high as 67% have been reported. Recommendations to prevent outbreaks in childcare centers include strict handwashing, use of protective clothes or diapers capable of retaining liquid diarrhea, and separation of diapering and food-handling areas and responsibilities.

Outbreaks of cryptosporidial infection are associated with contaminated community water supplies and recreational waters, including lakes and chlorinated swimming pools. Wastewater in the form of raw sewage and runoff from dairies and grazing lands can contaminate both drinking and recreational water sources. It is estimated that *Cryptosporidium* oocysts are present in 65-97% of the surface water in the United States. The organism's small size (4-6 µm in diameter), resistance to chlorination, and ability to survive for long periods outside a host creates problems in public water supplies.

Clinical Manifestations

The incubation period is 2-14 days. Infection with *Cryptosporidium* is associated with profuse, watery, nonbloody diarrhea that can be accompanied by diffuse crampy abdominal pain, nausea, vomiting, and anorexia. Although less common in adults, vomiting occurs in more than 80% of children with cryptosporidiosis. Nonspecific symptoms such as myalgia, weakness, and headache also may occur. Fever occurs in 30-50% of cases. Malabsorption, lactose intolerance, dehydration, weight loss, and malnutrition often occur in severe cases. Recently, the clinical spectrum and disease severity has been linked with both the infecting species and host human leukocyte antigen class I and class II alleles.

In immunocompetent persons, the disease is usually self-limiting, typically 5-10 days, although diarrhea may persist for several weeks and oocyst shedding may persist many weeks after symptoms resolve. Chronic diarrhea is common in individuals with immunodeficiency, such as congenital hypogammaglobulinemia or HIV infection. Symptoms and oocyst shedding can continue indefinitely and may lead to severe malnutrition, wasting, anorexia, and even death.

Cryptosporidiosis in **immunocompromised hosts** is often associated with biliary tract disease, characterized by fever, right upper quadrant pain, nausea, vomiting, and diarrhea. It also is associated with pancreatitis. Respiratory tract disease, with symptoms of cough, shortness of breath, wheezing, croup, and hoarseness, is very rare.

Diagnosis

Infection can be diagnosed by microscopy using modified acid-fast stain or polymerase chain reaction, but immunodetection of antigens on the surface of the organism in stool samples using monoclonal antibody–based assays is the current diagnostic method of choice. In stool, oocysts appear as small, spherical bodies (2-6 µm) and stain red with modified acid-fast staining. Because *Cryptosporidium* does not invade below the epithelial layer of the mucosa, fecal leukocytes are not found in stool specimens. Oocyst shedding in feces can be intermittent, and several fecal specimens (at least 3 for an immunocompetent host) should be collected for microscopic examination. Serologic diagnosis is not helpful in acute cryptosporidiosis.

In tissue sections, *Cryptosporidium* organisms can be found along the microvillus region of the epithelia that line the gastrointestinal tract. The highest concentration usually is detected in the jejunum. Histologic section results reveal villus atrophy and blunting, epithelial flattening, and inflammation of the lamina propria.

Treatment

Often the diarrheal illness attributable to cryptosporidiosis is self-limited in immunocompetent patients and requires no specific antimicrobial therapy. Treatment should focus on supportive care, including rehydration orally or, if fluid losses are severe, intravenously. Nitazoxanide (100 mg bid PO for 3 days for children 1-3 yr of age; 200 mg bid PO for children 4-11 yr of age; 500 mg bid PO for children ≥12 yr of age) is approved for treatment of diarrhea caused by *Cryptosporidium.* Clinical studies have not definitively demonstrated that nitazoxanide is superior to placebo in trials of HIV-infected (with low CD4 counts) or immunocompromised patients. However, given the severity of the infection in these populations, nitazoxanide treatment is usually initiated. In patients with HIV infection, treatment with combination antiretroviral therapy should also be administered to improve immune function. Other agents that have been suggested for treatment in clinical reports or small studies include orally administered human serum immunoglobulin or bovine colostrum, paromomycin, spiramycin, azithromycin, and roxithromycin or a combination of antibiotics.

ISOSPORA

Like *Cryptosporidium, Isospora belli* (also called *Cystoisospora*) is implicated as a cause of diarrhea in institutional outbreaks and in travelers and has also been linked with contaminated water and food. *Isospora* appears to be more common in tropical and subtropical climates and in developing areas, including South America, Africa, and Southeast Asia. *Isospora* has not been associated with animal contact. It is also an infrequent cause of diarrhea in patients with AIDS in the United States but may infect up to 15% of AIDS patients in Haiti.

The life cycle and pathogenesis of infection with *Isospora* species are similar to those of *Cryptosporidium* organisms except that oocysts excreted in the stool are not immediately infectious and must undergo further maturation at temperatures below 37°C (98.6°F). Thus, direct person-to-person transmission is unlikely. The most common clinical manifestation is watery, nonbloody diarrhea. Symptoms of infection are indistinguishable from those of cryptosporidiosis, although fever may be a more common finding. Eosinophilia may be present in up to 50% of cases, contrasting with other enteric protozoan infections. The diagnosis is established by detecting the oval, 22-33 µm long by 10-19 µm wide, oocysts by using modified acid-fast staining of the stool. Each oocyst contains 2 sporocysts with 4 sporozoites in each. Fecal leukocytes are not detected. Oocysts are shed in low number, underscoring the need for repeated stool examinations. Presence of oocysts in the gastrointestinal track is almost always associated with clinical symptoms. Histologic appearance of gastrointestinal epithelium reveals blunting and atrophy of the villi, acute and chronic inflammation, and crypt hyperplasia.

Isosporiasis responds promptly to **treatment** with oral trimethoprim-sulfamethoxazole (TMP-SMZ) (5 mg TMP and 25 mg SMZ/kg/dose; maximum: 160 mg TMP and 800 mg SMZ/dose bid for 10 days). In patients with AIDS, relapses are common and often necessitate higher doses of trimethoprim-sulfamethoxazole and/or maintenance therapy. Combination antiretroviral therapy associated with immune recovery may also result in improved symptoms. Ciprofloxacin, nitazoxanide, or a regimen of pyrimethamine alone or with folinic acid is effective in patients intolerant of sulfonamide drugs.

CYCLOSPORA

Cyclospora cayetanensis is a coccidian parasite similar to but larger than *Cryptosporidium.* The organism infects both immunocompromised and immunocompetent individuals and is more common in children younger than 18 mo of age. The pathogenesis and pathologic findings of cyclosporiasis are similar to those of isosporiasis. Asymptomatic carriage of the organism has been found, but travelers who harbor the organism almost always have diarrhea. Outbreaks of cyclosporiasis are linked with contaminated food and water. Implicated foods include raspberries, lettuce, snow peas, basil, and other fresh food items. After fecal excretion, the oocysts must sporulate outside the host to become infectious. This finding explains the lack of person-to-person transmission.

The **clinical manifestations** of cyclosporiasis are similar to those of cryptosporidiosis and isosporiasis and follow an incubation period of approximately 7 days. Moderate *Cyclospora* illness is characterized by a median of 6 stools/day with a median duration of 10 days (range: 3-25 days). The duration of diarrhea in immunocompetent persons is characteristically longer in cyclosporiasis than in the other intestinal protozoan illnesses. Associated symptoms frequently include anorexia; fatigue; abdominal bloating or gas; abdominal cramps or pain; nausea; muscle, joint, or body aches; low-grade fever; chills; headache; and weight loss. Vomiting may occur. Bloody stools are uncommon. Biliary disease has been reported. Intestinal pathology includes inflammation with villus blunting.

The diagnosis is established by identification of oocysts in the stool. Oocysts are wrinkled spheres, measure 8-10 µm in diameter, and resemble large *Cryptosporidium* organisms. Each oocyst contains 2 sporocysts, each with 2 sporozoites. The organisms can be seen by using modified acid-fast, auramine-phenol, or modified trichrome staining, but stain less consistently than *Cryptosporidium.* They can also be detected with phenosafranin stain and by autofluorescence using strong green or intense blue under ultraviolet epifluorescence. Multiple stool samples enhance identification of the pathogen. New molecular diagnostic testing, including real-time polymerase chain reaction, is currently under investigation. Fecal leukocytes are not present.

The **treatment** of choice for cyclosporiasis is TMP-SMZ (5 mg TMP and 25 mg SMZ/kg/dose bid PO for 7 days; maximum: 160 mg TMP and 800 mg SMZ/dose). Ciprofloxacin or nitazoxanide is effective in patients intolerant of sulfonamide drugs.

MICROSPORIDIA

Microsporidia are ubiquitous and infect most animal groups, including humans. They are classified as fungi and multiple species of the phylum Microsporidia have been linked with human disease in both immunocompetent and immunocompromised hosts. The species most commonly associated with gastrointestinal disease are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis.*

Although still not definitive, the source of human infections is likely zoonotic. Like *Cryptosporidium,* there is concern for waterborne transmission through occupational and recreational contact with contaminated water sources. There is also the potential for foodborne outbreaks; the organisms have been identified on vegetables as a consequence of contaminated irrigation water. Vector-borne transmission is hypothesized because 1 species, *Brachiola algerae*, typically infects mosquitoes. Finally, transplacental transmission has been reported in animals but not in humans. Once infected, intracellular division produces new spores that can spread to nearby cells, disseminate to other host tissues, or be passed into the environment via feces. Spores also have been detected in urine and respiratory epithelium, suggesting that some body fluids may also be infectious. Once in the environment, microsporidial spores remain infectious for up to 4 mo.

Initially, microsporidial intestinal infection had been almost exclusively reported in patients with AIDS, but there is increasing evidence that immunocompetent individuals are also commonly infected. Microsporidia-associated diarrhea is intermittent, copious, watery, and nonbloody. Abdominal cramping and weight loss may be present; fever is unusual. Stromal keratitis and encephalitis may also be associated with microsporidia infections. Disseminated disease involving most organs, including liver, heart, kidney, bladder, biliary tract, lung, bone, skeletal muscle, and sinuses, has been reported.

Microsporidia stain with modified trichrome, hematoxylin-eosin, Giemsa, Gram, periodic acid–Schiff, and acid-fast stains, but are often overlooked because of their small size (1-5 µm) and the absence of associated inflammation in surrounding tissues. Electron microscopy remains the reference method of detection. Multiple research laboratories report success with polymerase chain reaction technology in detecting microsporidia, both in human and environmental samples.

There is no proven **therapy** for microsporidial intestinal infections. Albendazole (adult dose 400 mg bid PO for 3 wk) is usually effective against *E. intestinalis* infection, but is ineffective against infection caused by some microsporidial species. Fumagillin (adult dose 20 mg tid PO for 2 wk) was effective in a small controlled study of adults with *E. bieneusi* infection and topical therapy with this agent was also demonstrated to be effective in HIV-infected adults with keratoconjunctivitis. Supportive care with hydration, correction of electrolyte imbalances, and nutrition should be used in gastrointestinal infection when clinically indicated. Improvement in underlying HIV infection with combination antiretroviral therapy also improves microsporidiosis symptoms.

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Chapter 284

Trichomoniasis (*Trichomonas vaginalis*)

Edsel Maurice T. Salvana and Robert A. Salata

Trichomoniasis, caused by the protozoan parasite *Trichomonas vaginalis,* is the most common nonviral sexually transmitted disease worldwide. It primarily causes vulvovaginitis in women but has been implicated in pelvic inflammatory disease, adverse outcomes in pregnancy, chronic prostatitis, and an increased risk of transmission of HIV.

EPIDEMIOLOGY

More than 170 million new cases of trichomoniasis occur yearly, the majority in resource-limited settings. Prevalence and incidence rates are likely underestimated, as most men and up to 30% of women are asymptomatic. Diagnostic accuracy using wet mount microscopy, the mainstay of diagnosis, is less sensitive than previously assumed. While the disease is easily treated, sequelae of untreated infection remain a significant cause of morbidity as a result of high reinfection rates from untreated partners, underrecognition of asymptomatic cases, and insensitive diagnostics.

Trichomoniasis is the most common parasitic infection in the United States, with approximately 7.4 million cases occurring each year. A population-based study conducted in 2005 showed a prevalence of 2.8% in women and 1.7% in men, and an overall prevalence of 2.3%. The incidence of trichomoniasis is highest among females with multiple sexual partners and in groups with the highest rates of other sexually transmitted infections. *T. vaginalis* is recovered from more than 60% of female partners of infected men and 70% of male sexual partners of infected women. Vaginal trichomoniasis is rare until menarche. Its presence in a younger child should raise the possibility of **sexual abuse.**

Trichomoniasis may be transmitted to neonates during passage through an infected birth canal. Infection in this setting is usually self-limited, but rare cases of neonatal vaginitis and respiratory infection have been reported.

PATHOGENESIS

T. vaginalis is an anaerobic, flagellated protozoan parasite. Infected vaginal secretions contain 10^1 to 10^5 or more protozoa/mL. *T. vaginalis* is pear shaped and exhibits characteristic twitching motility in wet mount (Fig. 284-1). Reproduction is by binary fission. It exists only as **vegetative cells;** cyst forms have not been described. *T. vaginalis* damages host cells and tissues by a number of mechanisms. Adhesion molecules allow attachment of *T. vaginalis* to host cells, and hydrolases, proteases, and cytotoxic molecules act to destroy or impair the integrity of host cells. An iron-upregulated cysteine proteinase legumain-1 (TvLEGU-1) has been characterized as a major factor in cytoadherence. There is increasing evidence that *T. vaginalis* is associated with low levels of *Lactobacillus* spp. and high levels of *Mycoplasma* spp. in the vaginal microbiota. However, whether trichomoniasis alters the bacterial flora or whether altered bacterial flora predisposes to trichomoniasis is uncertain. Parasite-specific antibodies and lymphocyte priming occur in response to infection, but durable protective immunity does not occur.

CLINICAL MANIFESTATIONS

The **incubation period** in females is 5-28 days. Symptoms may begin or exacerbate with menses. Most infected women eventually develop symptoms, although up to one third remain asymptomatic. Common signs and symptoms include a copious malodorous gray, frothy vaginal discharge, vulvovaginal irritation, dysuria, and dyspareunia. Physical examination may reveal a frothy discharge with vaginal erythema and cervical hemorrhages ("strawberry cervix"). The discharge usually has a pH of >4.5. Abdominal discomfort is unusual and should prompt evaluation for pelvic inflammatory disease (see Chapter 120).

Most infections in males are asymptomatic. Symptomatic males usually have dysuria and scant urethral discharge. Trichomonads occasionally cause epididymitis, prostatic involvement, and superficial penile ulceration. Infection is often self-limited, spontaneously resolving in 36% of men. *Trichomonas* has been implicated as a cause of recurrent or relapsing urethritis and can be isolated in 3-20% of men with **nongonococcal urethritis.** Treatment failures with standard therapy for gonorrhea and *Chlamydia* are frequently treated with antitrichomonal therapy.

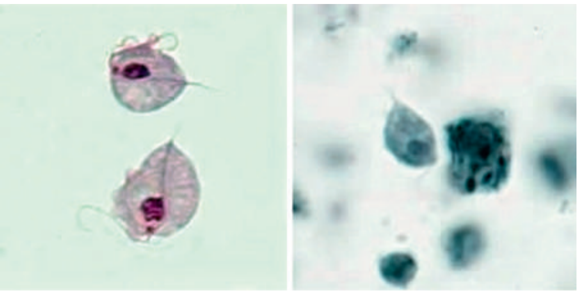

Figure 284-1 *Trichomonas vaginalis* trophozoites stained with Giemsa *(left)* and iron hematoxylin *(right). (From the Centers for Disease Control and Prevention [CDC]: Laboratory identification of parasites of public health concern. Trichomoniasis. Available at:* http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Trichomoniasis_il.htm*)*

DIAGNOSIS

Trichomonads may be recognized in vaginal secretions by using the wet mount technique. This technique has been estimated to have a sensitivity of 60-70%; studies using more sensitive assays with nucleic acid probes and polymerase chain reaction suggest that this is closer to 35-60%. Although *Trichomonas* is sometimes seen on Papanicolaou smears and in urine, these methods are not considered reliable tests for disease. Wet mount examination of material obtained by platinum loop from the anterior urethra may reveal the organism in 50-90% of infected men. Microscopic examination of urine sediment after prostatic massage is also useful in infected men. Culture of the organism is the gold standard for detection, and commercial culture media are available. Enzyme-linked immunosorbent assay and direct fluorescent antigen testing of vaginal secretions are more sensitive than wet mount testing but less sensitive than culture for detection of *T. vaginalis* infection. In women, DNA immunoblot and polymerase chain reaction testing of vaginal secretions have similar sensitivity and specificity to culture. In men, these methods appear to be more sensitive at detection of infection than culture. Nucleic acid amplification testing and immunologic diagnostic kits for diagnosis of *Trichomonas* alone and in combination with other gynecologic diseases, such as *Candida* and *Gardnerella,* have been evaluated by multiple studies and have been found to be accurate and easy to use. The APTIMA TV (Gen-Probe Incorporated, CA) assay is an FDA-approved commercial nucleic acid amplification test that is highly sensitive and specific, particularly in asymptomatic patients. Two point-of-care kits for rapid testing, Affirm VP III (BD Diagnostic Systems, Sparks, MD) and OSOM *Trichomonas* Rapid Test (Genzyme Diagnostics, Cambridge, MA), have received approval by the FDA but are less sensitive than the APTIMA TV. Patients with *T. vaginalis* should be screened for other sexually transmitted infections, including *Chlamydia* and gonorrhea.

COMPLICATIONS

Untreated trichomoniasis is associated with pelvic inflammatory disease, premature delivery, low birthweight, tubal infertility, and vaginal cuff cellulitis. *T. vaginalis* infection increases the risk of acquisition and transmission of HIV. *Trichomonas*-induced inflammation of the genital mucosa recruits greater numbers of $CD4^+$ cells in the epithelium and provides greater access to the bloodstream for HIV. In HIV-infected individuals, trichomoniasis is associated with higher viral loads in cervical secretions and semen, as well as higher levels of infected lymphocytes in urogenital fluids. HIV-1 shedding in vaginal fluids decreases following treatment for trichomoniasis.

TREATMENT

In the United States, **metronidazole** and **tinidazole** are used; in other countries ornidazole is also used. Both metronidazole (single-dose regimen of 2 g orally as a single dose for adolescents and adults; alternative regimen, 500 mg orally bid for 7 days) and tinidazole (single 2 g dose orally in adolescents and adults) are used as first-line treatment. For children infected prior to adolescence, the recommended regimen is metronidazole 15 mg/kg/day divided in 3 doses orally for 7 days; tinidazole is not approved for dosing in younger children. Topical metronidazole gel is not efficacious when used as the sole therapy for *T. vaginalis* infection, but it may decrease symptoms in individuals with severe infection when used in conjunction with oral therapy. Sexual partners should be treated simultaneously to prevent reinfection. Multiple head-to-head trials comparing the efficacy between single-dose/short courses of metronidazole and single-dose tinidazole have shown either noninferiority or superior efficacy for tinidazole. A Cochrane metaanalysis demonstrated that single dose tinidazole was superior compared to short-course metronidazole in clinical efficacy and parasitologic cure rates and had significantly fewer side effects. Tinidazole is more expensive than metronidazole and is generally reserved for treatment failures or metronidazole intolerance.

Treatment failures have been reported with metronidazole, although poor response can usually be overcome by higher doses of drugs. Second-line treatment recommendations include either a 7-day course of metronidazole 500 mg twice daily or a single dose of tinidazole. If this treatment fails, either metronidazole or tinidazole at 2 g daily for 5 days is recommended. Further treatment failure should be referred to an infectious diseases specialist and may require susceptibility testing, which is available from the Centers for Disease Control and Prevention. Metronidazole has not been shown to be teratogenic during pregnancy in humans but is currently classified as a category C drug. A Cochrane metaanalysis showed an association (RR = 1.78 [1.19, 2.66]) between premature births with metronidazole treatment of asymptomatic *T. vaginalis* infection in pregnancy. Further studies are needed to confirm this finding. Treatment of symptomatic trichomoniasis in pregnancy should be weighed against possible risks, while treatment of asymptomatic disease should be delayed as much as possible to near term.

PREVENTION

Prevention of *T. vaginalis* infection is best accomplished by treatment of all sexual partners of an infected person and by programs aimed at prevention of all sexually transmitted infections (see Chapter 120). No vaccine is available, and drug prophylaxis is not recommended.

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Chapter 285

Leishmaniasis (*Leishmania*)

Peter C. Melby

The leishmaniases are a diverse group of diseases caused by intracellular protozoan parasites of the genus *Leishmania,* which are transmitted by phlebotomine sand flies. Multiple species of *Leishmania* are known to cause human disease involving the skin and mucosal surfaces and the visceral reticuloendothelial organs. Cutaneous disease is generally mild but may cause cosmetic disfigurement. Mucosal and visceral leishmaniasis is associated with significant morbidity and mortality.

ETIOLOGY

Leishmania organisms are members of the Trypanosomatidae family and include 2 subgenera, *Leishmania (Leishmania)* and *Leishmania (Viannia)*. The parasite is dimorphic, existing as a flagellate promastigote in the insect vector and as an aflagellate amastigote that resides and replicates within mononuclear phagocytes of the vertebrate host. Within the sandfly vector, the promastigote changes from a noninfective procyclic form to an infective metacyclic stage. Fundamental to this transition are changes that take place in the terminal polysaccharides of the surface lipophosphoglycan, which allow forward migration of the infective parasites from the sandfly midgut to the mouth parts and inoculation of the host during a blood meal. Metacyclic lipophosphoglycan also plays an important role in the entry and survival of *Leishmania* in the mammalian host by conferring complement resistance and by facilitating entry into the macrophage by way of multiple receptors, including complement receptors 1 and 3. Once within the macrophage, the promastigote transforms to an amastigote and resides and replicates within a phagolysosome. The parasite is resistant to the acidic, hostile environment of the macrophage and eventually ruptures the cell and goes on to infect other macrophages. Infected macrophages have a diminished capacity to initiate and respond to an inflammatory response, thus providing a safe haven for the intracellular parasite.

EPIDEMIOLOGY

The leishmaniases are estimated to affect 10-20 million people in endemic tropical and subtropical regions on all continents except Australia and Antarctica. The different forms of the disease are distinct in their causes, epidemiologic characteristics, transmission, and geographic distribution. The leishmaniases may occur sporadically throughout an endemic region or may occur in epidemic focuses. With only rare exceptions, the *Leishmania* organisms that primarily cause cutaneous disease do not cause visceral disease.

Localized cutaneous leishmaniasis (LCL) in the Old World is caused by *L. (Leishmania) major* and *L. (L.) tropica* in North Africa, the Middle East, central Asia, and the Indian subcontinent. *L. (L.) aethiopica* is a cause of LCL and diffuse cutaneous leishmaniasis (DCL) in Kenya and Ethiopia. **Visceral leishmaniasis (VL)** in the Old World is caused by *L. (L.) donovani* in Kenya, Sudan, India, Pakistan, and China and by *L. (L.) infantum* in the Mediterranean basin, Middle East, and central Asia. *L. infantum* is also a cause of LCL (without visceral disease) in this same geographic distribution. *L. tropica* also has been recognized as an uncommon cause of visceral disease in the Middle East and India. In the New World, *L. (L.) mexicana* causes LCL in a region stretching from southern Texas through Central America. *L. (L.) amazonensis, L. (L.) pifanoi, L. (L.) garnhami,* and *L. (L.) venezuelensis* cause LCL in South America, the Amazon basin, and northward. Members of the *Viannia* subgenus (*L. [V.] braziliensis, L. [V.] panamensis, L. [V.] guyanensis,* and *L. [V.] peruviana*) cause LCL from the northern highlands of Argentina northward to Central America.

Members of the *Viannia* subgenus also cause **mucosal leishmaniasis (ML)** in a similar geographic distribution. VL in the New World is caused by *L. (L.) chagasi* (now considered to be the same organism as *L. infantum*), which is distributed from Mexico (rare) through Central and South America. *L. infantum/chagasi* can also cause LCL in the absence of visceral disease.

The maintenance of *Leishmania* in most endemic areas is through a zoonotic transmission cycle. In general, the dermotropic strains in both the Old and New Worlds are maintained in rodent reservoirs, and the domestic dog is the usual reservoir for *L. infantum/chagasi.* The transmission between reservoir and sandfly is highly adapted to the specific ecologic characteristics of the endemic region. Human infections occur when human activities bring them in contact with the zoonotic cycle. Anthroponotic transmission, in which humans are the presumed reservoir, occurs with *L. tropica* in some urban areas of the Middle East and Central Asia, and with *L. donovani* in India and Sudan. Congenital transmission of *L. donovani* or *L. infantum/chagasi* has been reported.

There is a resurgence of leishmaniasis in long-standing endemic areas as well as in new foci. Tens of thousands of cases of LCL occurred in an outbreak in Kabul, Afghanistan, and severe epidemics with more than 100,000 deaths from VL have occurred in India and Sudan. VL is most prevalent among the poorest of the poor, with substandard housing contributing to the vector-borne transmission and undernutrition leading to increased host susceptibility. The emergence of the leishmaniases in new areas is the result of (1) movement of a susceptible population into existing endemic areas, usually because of agricultural or industrial development or timber harvesting; (2) increase in vector and/or reservoir populations as a result of agriculture development projects; (3) increase in anthroponotic transmission owing to rapid urbanization in some focuses; and (4) increase in sandfly density resulting from a reduction in vector control programs.

PATHOLOGY

Histopathologic analysis of the LCL lesion shows intense chronic granulomatous inflammation involving the epidermis and dermis. Occasionally, neutrophils and even microabscesses can be seen. The lesions of DCL are characterized by dense infiltration with vacuolated macrophages containing abundant amastigotes. ML is characterized by an intense granulomatous reaction with prominent tissue necrosis, which may include adjacent cartilage or bone. In VL there is prominent reticuloendothelial cell hyperplasia in the liver, spleen, bone marrow, and lymph nodes. Amastigotes are abundant in the histiocytes and Kupffer cells. Late in the course of disease, splenic infarcts are common, centrilobular necrosis and fatty infiltration of the liver occur, the normal marrow elements are replaced by parasitized histiocytes, and erythrophagocytosis is present.

PATHOGENESIS

Cellular immune mechanisms determine resistance or susceptibility to infection with *Leishmania.* Resistance is mediated by interleukin (IL)-12–driven generation of a T helper 1 cell response, with interferon-γ inducing classical macrophage (M1) activation and parasite killing. Susceptibility is associated with expansion of IL-4–producing Th2 cells and/or the production of IL-10 and transforming growth factor-β, which are inhibitors of macrophage-mediated parasite killing, and the generation of regulatory T cells and alternatively activated (M2) macrophages. Patients with ML exhibit a hyperresponsive cellular immune reaction that may contribute to the prominent tissue destruction seen in this form of the disease. Patients with DCL or active VL demonstrate reduced or altered *Leishmania*-specific cellular immune responses, with prominent generation of IL-10, but these responses recover after successful therapy.

Within endemic areas, people who have had a subclinical infection can be identified by a positive delayed-type hypersensitivity skin response to leishmanial antigens **(Montenegro skin test)** or by antigen-induced production of interferon-γ in a whole blood assay**.** Subclinical infection occurs considerably more frequently than does active cutaneous or visceral disease. Host factors (genetic background, concomitant disease, nutritional status), parasite factors (virulence, size of the inoculum), and possibly vector-specific factors (vector genotype, immunomodulatory salivary constituents) influence the expression as either subclinical infection or active disease. Within endemic areas the prevalence of skin test result positivity increases with age and the incidence of clinical disease decreases with age, indicating that immunity is acquired in the population over time. Individuals with prior active disease or subclinical infection are usually immune to a subsequent clinical infection; however, latent infection can lead to active disease if the patient is immunosuppressed.

CLINICAL MANIFESTATIONS

The different forms of the disease are distinct in their causes, epidemiologic features, transmission, and geographic distribution.

Localized Cutaneous Leishmaniasis

LCL **(Oriental sore)** can affect individuals of any age, but children are the primary victims in many endemic regions. It may present as 1 or a few papular, nodular, plaquelike, or ulcerative lesions that are usually located on exposed skin, such as the face and extremities (Fig. 285-1). Rarely, more than 100 lesions have been recorded. The lesions typically begin as a small papule at the site of the sandfly bite, which enlarges to 1-3 cm in diameter and may ulcerate over the course of several weeks to months. The shallow ulcer is usually nontender and surrounded by a sharp, indurated, erythematous margin. There is no drainage unless a bacterial superinfection develops. Lesions caused by *L. major* and *L. mexicana* usually heal spontaneously after 3-6 mo, leaving a depressed scar. Lesions on the ear pinna caused by *L. mexicana,* called **chiclero ulcer** because they were common in chicle harvesters in Mexico and Central America, often follow a chronic, destructive course. In general, lesions caused by *L. (Viannia)* species tend to be larger and more chronic. Regional lymphadenopathy and palpable subcutaneous nodules or lymphatic cords, the so-called sporotrichoid appearance, are also more common when the patient is infected with organisms of the *Viannia* subgenus. If lesions do not become secondarily infected, there are usually no complications aside from the residual cutaneous scar.

Diffuse Cutaneous Leishmaniasis

DCL is a rare form of leishmaniasis caused by organisms of the *L. mexicana* complex in the New World and *L. aethiopica* in the Old World. DCL manifests as large nonulcerating macules, papules,

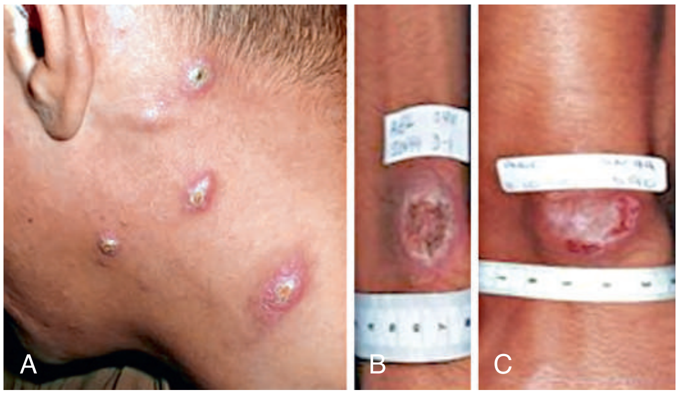

Figure 285-1 Cutaneous disease. **A,** Old World infection *(Leishmania major)* acquired in Iraq; note 5 papular and nodular lesions on neck. **B,** New World infection *(Leishmania panamensis)* in Colombia; purely ulcerative lesion is characteristic of New World disease. **C,** Healed infection in patient shown in **B** 70 days after 20 days of meglumine antimonate treatment; note paper-thin scar tissue over flat reepithelialized skin. (***A*** *courtesy of P. Weina.* ***B*** *courtesy of J. Soto.* ***A-C*** *modified from Murray HW, Berman JD, Davies CR, et al: Advances in leishmaniasis,* Lancet *366:1561–1577, 2005.)*

nodules, or plaques that often involve large areas of skin and may resemble lepromatous leprosy. The face and extremities are most commonly involved. Dissemination from the initial lesion usually takes place over several years. It is thought that an immunologic defect underlies this severe form of cutaneous leishmaniasis.

Mucosal Leishmaniasis

ML **(espundia)** is an uncommon but serious manifestation of leishmanial infection resulting from hematogenous metastases to the nasal or oropharyngeal mucosa from a cutaneous infection. It is usually caused by parasites in the *L. (Viannia)* complex. Approximately half of the patients with mucosal lesions have had active cutaneous lesions within the preceding 2 yr, but ML may not develop until many years after resolution of the primary lesion. ML occurs in <5% of individuals who have, or have had, LCL caused by *L. (V.) braziliensis.* Patients with ML most commonly have nasal mucosal involvement and present with nasal congestion, discharge, and recurrent epistaxis. Oropharyngeal and laryngeal involvement is less common but associated with severe morbidity. Marked soft tissue, cartilage, and even bone destruction occurs late in the course of disease and may lead to visible deformity of the nose or mouth, nasal septal perforation, and tracheal narrowing with airway obstruction.

Visceral Leishmaniasis

VL **(kala-azar)** typically affects children younger than 5 yr of age in the New World and Mediterranean region (*L. infantum/chagasi*) and older children and young adults in Africa and Asia (*L. donovani*). After inoculation of the organism into the skin by the sandfly, the child may have a completely asymptomatic infection or an oligosymptomatic illness that either resolves spontaneously or evolves into active kala-azar. Children with asymptomatic infection are transiently seropositive but show no clinical evidence of disease. Children who are oligosymptomatic have mild constitutional symptoms (malaise, intermittent diarrhea, poor activity tolerance) and intermittent fever; most will have a mildly enlarged liver. In most of these children the illness will resolve without therapy, but in approximately 25% it will evolve to active kala-azar within 2-8 mo. Extreme incubation periods of several years have rarely been described. During the first few wk to months of disease evolution the fever is intermittent, there is weakness and loss of energy, and the spleen begins to enlarge. The classic clinical features of high fever, marked splenomegaly, hepatomegaly, and severe cachexia typically develop approximately 6 mo after the onset of the illness, but a rapid clinical course over 1 mo has been noted in up to 20% of patients in some series (Fig. 285-2). At the terminal stages of kala-azar the hepatosplenomegaly is massive, there is gross wasting, the pancytopenia is profound, and jaundice, edema, and ascites may be present. Anemia may be severe enough to precipitate heart failure. Bleeding episodes, especially epistaxis, are frequent. The late stage of the illness is often complicated by secondary bacterial infections, which frequently are a cause of death. A younger age at the time of infection and underlying malnutrition may be risk factors for the development and more rapid evolution of active VL. Death occurs in more than 90% of patients without specific antileishmanial treatment.

VL is an opportunistic infection associated with HIV infection. Most cases have occurred in southern Europe and Brazil, often as a result of needle sharing associated with illicit drug use, with the potential for many more cases as the endemic regions for HIV and VL converge. Leishmaniasis may also result from reactivation of a longstanding subclinical infection. Frequently there is an atypical clinical presentation of VL in HIV-infected individuals with prominent involvement of the gastrointestinal tract and absence of the typical hepatosplenomegaly.

A small percentage of patients previously treated for VL develop diffuse skin lesions, a condition known as **post–kala-azar dermal leishmaniasis.** These lesions may appear during or shortly after therapy (Africa) or up to several years later (India). The lesions of post–kala-azar dermal leishmaniasis are hypopigmented, erythematous, or nodular and commonly involve the face and torso. They may persist for several months or for many years.

LABORATORY FINDINGS

Patients with cutaneous leishmaniasis or ML generally do not have abnormal laboratory results unless the lesions are secondarily infected with bacteria. Laboratory findings associated with classic kala-azar include anemia (hemoglobin 5-8 mg/dL), thrombocytopenia, leukopenia (2,000-3,000 cells/µL), elevated hepatic transaminase levels, and hyperglobulinemia (>5 g/dL) that is mostly immunoglobulin G.

DIFFERENTIAL DIAGNOSIS

Diseases that should be considered in the differential diagnosis of LCL include sporotrichosis, blastomycosis, chromomycosis, lobomycosis, cutaneous tuberculosis, atypical mycobacterial infection, leprosy, ecthyma, syphilis, yaws, and neoplasms. Infections such as syphilis, tertiary yaws, histoplasmosis, paracoccidioidomycosis, as well as sarcoidosis, Wegener granulomatosis, midline granuloma, and carcinoma may have clinical features similar to those of ML. VL should be strongly suspected in the patient with prolonged fever, weakness, cachexia, marked splenomegaly, hepatomegaly, cytopenias, and hypergammaglobulinemia who has had potential exposure in an endemic area. The clinical picture may also be consistent with that of malaria, typhoid

Figure 285-2 Visceral leishmaniasis *(Leishmania donovani)* in Bihar State, India. **A,** Hepatosplenomegaly and wasting in a young man. **B,** Children with burn marks over enlarged spleen or liver—local shaman's unsuccessful remedy. (***A*** *courtesy of D. Sacks.* ***B*** *courtesy of R. Kenney.* ***A*** *and* ***B*** *modified from Murray HW, Berman JD, Davies CR, et al: Advances in leishmaniasis,* Lancet *366:1561–1577, 2005.)*

fever, miliary tuberculosis, schistosomiasis, brucellosis, amebic liver abscess, infectious mononucleosis, lymphoma, and leukemia.

DIAGNOSIS

The development of 1 or several slowly progressive, nontender, nodular, or ulcerative lesions in a patient who had potential exposure in an endemic area should raise suspicion of LCL.

Serologic tests for diagnosis of ML or LCL generally have low sensitivity and specificity and offer little for diagnosis. Serologic testing by enzyme immunoassay, indirect fluorescence assay, or direct agglutination is very useful in VL because of the very high level of antileishmanial antibodies. An immunochromatographic strip test using a recombinant antigen (K39) has a diagnostic sensitivity and specificity for VL of 80-90% and 95%, respectively. Serodiagnostic tests have positive findings in only about half of the patients who are coinfected with HIV.

Definitive diagnosis of leishmaniasis is established by the demonstration of amastigotes in tissue specimens or isolation of the organism by culture. Amastigotes can be identified in Giemsa-stained tissue sections, aspirates, or impression smears in about half of the cases of LCL but only rarely in the lesions of ML. Culture of a tissue biopsy or aspirate, best performed by using Novy-McNeal-Nicolle biphasic blood agar medium, yields a positive finding in only approximately 65% of cases of cutaneous leishmaniasis. Identification of parasites in impression smears, histopathologic sections, or culture medium is more readily accomplished in DCL than in LCL. In patients with VL, smears or cultures of material from splenic, bone marrow, or lymph node aspirations are usually diagnostic. In experienced hands, **splenic aspiration** has a higher diagnostic sensitivity, but it is rarely performed in the United States because of the risk for bleeding complications. A positive culture result allows speciation of the parasite, usually by isoenzyme analysis by a reference laboratory, which may have therapeutic and prognostic significance.

TREATMENT

Specific antileishmanial therapy is not routinely indicated for uncomplicated LCL caused by strains that have a high rate of spontaneous resolution and self-healing *(L. major, L. mexicana)*. Lesions that are extensive, severely inflamed, or located where a scar would result in disability (near a joint) or cosmetic disfigurement (face or ear), that involve the lymphatics, or that do not begin healing within 3-4 mo should be treated. Cutaneous lesions suspected or known to be caused by members of the *Viannia* subgenus (New World) should be treated because of the low rate of spontaneous healing and the potential risk for development of mucosal disease. Similarly, patients with lesions caused by *L. tropica* (Old World), which are typically chronic and nonhealing, should be treated. All patients with VL or ML should receive therapy.

The pentavalent antimony compounds (sodium stibogluconate [Pentostam, GlaxoSmithKline, Uxbridge, UK] and meglumine antimoniate [Glucantime, Aventis, Strasbourg, France]) have been the mainstay of antileishmanial chemotherapy for more than 40 yr. These drugs have similar efficacies, toxicities, and treatment regimens. Currently, for sodium stibogluconate (available in the United States from the Centers for Disease Control and Prevention, Atlanta, Georgia), the recommended regimen is 20 mg/kg/day intravenously or intramuscularly for 20 days (for LCL and DCL) or 28 days (for ML and VL). Repeated courses of therapy may be necessary in patients with severe cutaneous lesions, ML, or VL. An initial clinical response to therapy usually occurs in the 1st wk of therapy, but complete clinical healing (reepithelialization and scarring for LCL and ML, and regression of splenomegaly and normalization of cytopenias for VL) is usually not evident for weeks to a few months after completion of therapy. Cure rates with this regimen of 90-100% for LCL, 50-70% for ML, and 80-100% for VL were common in the 1990s, but treatment failures, especially in children, have become common in parts of India, East Africa, and Latin America. Relapses are common in patients who do not have an effective antileishmanial cellular immune response (DCL or HIV coinfection). Adverse effects of antimony therapy are dose and duration dependent and commonly include fatigue, arthralgias and myalgias (50%), abdominal discomfort (30%), elevated hepatic transaminase level (30-80%), elevated amylase and lipase levels (almost 100%), mild hematologic changes (slightly decreased leukocyte count, hemoglobin level, and platelet count) (10-30%), and nonspecific T-wave changes on electrocardiography (30%). Sudden death from cardiac toxicity has rarely been reported with use of very high doses of pentavalent antimony.

Amphotericin B desoxycholate and the amphotericin lipid formulations are very useful in the treatment of VL or ML and in some regions have replaced antimony as first-line therapy. However, the prohibitively high cost of these drugs precludes their use in many resource-poor regions of the world. Amphotericin B desoxycholate at doses of 0.5-1.0 mg/kg every day or every other day for 14-20 doses achieved a cure rate for VL of close to 100%, but the renal toxicity associated with amphotericin B was common. The lipid formulations of amphotericin B are especially attractive for treatment of leishmaniasis because the drugs are concentrated in the reticuloendothelial system and are less nephrotoxic. Liposomal amphotericin B is highly effective, with a 90-100% cure rate for VL in immunocompetent children, some of whom were refractory to antimony therapy. Liposomal amphotericin B (AmBisome, Gilead Sciences, Foster City, CA) is approved by the U.S. Food and Drug Administration for treatment of VL at a recommended dose for immunocompetent patients of 3 mg/kg on days 1-5, 14, and 21 and should be considered for first-line therapy in the United States. Therapy for immunocompromised patients may need to be prolonged. A single high dose of liposomal amphotericin B (10 mg/kg) was found to be noninferior to conventional amphotericin (15 doses of 1 mg/kg) in India and offers a less-cost-prohibitive approach. Parenteral treatment of VL with the aminoglycoside paromomycin (aminosidine) has efficacy (~95%) similar to that of amphotericin B in India. Miltefosine, a membrane-activating alkylphospholipid, has been approved as the first oral treatment for VL and has a cure rate of 80-90% in Indian patients with VL when administered orally at 50-100 mg/day (or 2.5 mg/kg for children younger than 12 yr of age) for 28 days. Miltefosine is indicated for cutaneous infection caused by *L. braziliensis*, *L. guyanensis,* and *L. panamensis*; mucosal disease caused by *L. braziliensis*; and visceral disease caused by *L. donovani*. Gastrointestinal adverse effects were frequent but did not require discontinuation of the drug. An increased rate of relapse (up to 20%) has been seen in children treated with miltefosine. Dose-sparing combination regimens are being actively investigated for treatment of VL. Treatment of LCL with oral drugs has had only modest success. Ketoconazole has been effective in treating adults with LCL caused by *L. major, L. mexicana,* and *L. panamensis,* but not *L. tropica* or *L. braziliensis*. Fluconazole in high doses (up to 8 mg/kg/day) for 4-8 wk was demonstrated to be effective in treating LCL in studies in both the Old and New World; however, the experience in young children is limited. Miltefosine 2.5 mg/kg/day orally for 20-28 days was effective in 70-90% of patients with LCL in the Americas. Topical treatment of LCL with paromomycin ointment has been effective in selected areas in the both Old and New World. Enhanced drug development efforts and clinical trials of new drugs are clearly needed, especially in children.

PREVENTION

Personal protective measures should include avoidance of exposure to the nocturnal sandflies and, when necessary, the use of insect repellent and permethrin-impregnated mosquito netting. Where peridomiciliary transmission is present, community-based residual insecticide spraying has had some success in reducing the prevalence of leishmaniasis, but long-term effects are difficult to maintain. Control or elimination of infected reservoir hosts (e.g., seropositive domestic dogs) has had limited success. Where anthroponotic transmission is thought to occur, early recognition and treatment of cases are essential. Several vaccines have been demonstrated to have efficacy in experimental models, and vaccination of humans or domestic dogs may have a role in the control of the leishmaniases in the future.

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Chapter 286

African Trypanosomiasis (Sleeping Sickness; *Trypanosoma brucei* Complex)

Edsel Maurice T. Salvana and Robert A. Salata

Seventy million people in 36 countries are at risk for infection with *Trypanosoma brucei* complex, the causative agent of sleeping sickness. Also known as **human African trypanosomiasis (HAT)**, this disease is restricted to sub-Saharan Africa, the range of the tsetse fly vector. It is a disease of extreme poverty, with an increased burden observed in remote rural areas. HAT comes in 2 geographically and clinically distinct forms. *T. brucei gambiense* causes a chronic infection lasting years and mostly affects people who live in Western and Central Africa **(West African sleeping sickness, Gambian trypanosomiasis).** *T. brucei rhodesiense* is a zoonosis that presents as an acute illness lasting several weeks and usually occurs in residents of eastern and southern Africa **(East African sleeping sickness, Rhodesian trypanosomiasis).**

ETIOLOGY

HAT is a vector-borne disease caused by parasitic, flagellated kinetoplastid protozoans of 2 subspecies of *T. brucei*. It is transmitted to humans through the bite of *Glossina*, commonly known as the **tsetse fly.**

The vector feeds on the blood of humans and wild game animals and penetrates intact mucous membranes and skin. Humans usually contract East African HAT when they venture from towns to rural areas to visit woodlands or livestock, highlighting the importance of zoonotic reservoirs in this disease. West African HAT is contracted closer to settlements and only requires a small vector population, making it difficult to eradicate. Low rates of infection in tsetse flies of this form necessitates close and repeated contact between humans and insects to permit frequent biting. While animal reservoirs occur, these are less important than for East African HAT, and the main source of infection remains chronically infected human hosts.

LIFE CYCLE

T. brucei undergoes several stages of development in the insect and mammalian host. Upon ingestion with a blood meal, nonproliferative stumpy forms of the parasite, which are optimally adapted to surviving in *Glossina,* transform into procyclic forms in the insect's midgut. These procyclic forms proliferate and undergo further development into epimastigotes, which then become infective metacyclic forms that migrate to the insect's salivary glands. The life cycle within the tsetse fly takes 15-35 days. On inoculation into the mammalian host, the metacyclic stage transforms into proliferative long and slender forms in the bloodstream and the lymphatics, eventually penetrating the central nervous system. These slender forms appear in waves in the peripheral blood, with each wave followed by a febrile crisis and heralding the formation of a new antigenic variant. The slender forms transform into intermediate forms, which become nonproliferative stumpy forms that are ingested by *Glossina* and start the cycle anew.

Direct transmission to humans has been reported, either mechanically through contact with the contaminated mouth parts of tsetse flies with viable slender forms during feeding or vertically to infants.

EPIDEMIOLOGY

HAT is a major public health problem in sub-Saharan Africa. It occurs in the region between latitudes 14 degrees north and 29 degrees south, corresponding roughly to the area where the annual rainfall creates optimal climatic conditions for *Glossina* flies to thrive. More than 70% of reported cases are from the Democratic Republic of Congo. In 2009, as a result of intensive control efforts spearheaded by the World Health Organization (WHO), the number of new HAT cases annually fell below 10,000 for the first time in 50 yr. In 2011, this further fell to 6,743 cases. As a result, the disease has been targeted by the international community for elimination as a public health problem.

T. brucei rhodesiense infection is restricted to the eastern third of the endemic area in tropical Africa, stretching from Ethiopia to the northern boundaries of South Africa. *T. brucei gambiense*, which accounts for 97% of HAT cases, occurs mainly in the western half of the continent's endemic region. *Glossina* captured in endemic foci show a low rate of infection, usually <5%. Rhodesian HAT, which has an acute and often fatal course, greatly reduces chances of transmission to tsetse flies. The ability of *T. brucei rhodesiense* to multiply rapidly in the bloodstream and infect other species of mammals helps maintain its life cycle. The insect vector is able to transmit disease for up to 6 mo.

PATHOGENESIS

The initial entry site of the organisms develops a hard, painful, red nodule known as a trypanosomal **chancre.** It contains long, thin trypanosomes multiplying beneath the dermis and is surrounded by a lymphocytic cellular infiltrate. Dissemination into the blood and lymphatic systems follows, with subsequent localization to the central nervous system (CNS). Histopathologic findings in the brain are consistent with meningoencephalitis, with lymphocytic infiltration and perivascular cuffing of the membranes. The appearance of **morular** cells (large, strawberry-like cells, supposedly derived from plasma cells) is a characteristic finding in chronic disease.

Antigenic variation of **variant surface glycoproteins** on the trypanosome's surface enables evasion of acquired immunity during infection. Both *T. brucei gambiense* and *T. brucei rhodesiense* have acquired resistance to trypanolytic factors in human serum, the most well-studied of which is **apolipoprotein L-1** (APOL1), through the expression of a protein known as *serum resistance-associated protein*. A frameshift mutation in the APOL1 gene in 1 patient enabled infection with a nonhuman trypanosome, *Trypanosoma evansi*, and treatment with recombinant APOL1 restored trypanolytic activity. Mechanisms underlying virulence in HAT are still incompletely understood, although severity of disease seems to be dependent on the host inflammatory response, particularly interferon-γ production in the CNS and blood.

CLINICAL MANIFESTATIONS

Clinical presentations vary not only because of the 2 subspecies of organisms but also because of differences in host response in the indigenous population of endemic areas and in newcomers or visitors. Visitors usually suffer more from the acute symptoms, but in untreated cases death is inevitable for natives and visitors alike. Symptoms usually occur within 1-4 wk of infection. The clinical syndromes of HAT are trypanosomal chancre, hemolymphatic stage, and meningoencephalitic stage.

Trypanosomal Chancre

The site of the tsetse fly bite may be the first presenting feature. A nodule or chancre develops in 2-3 days and becomes a painful, hard, red nodule surrounded by an area of erythema and swelling within 1 wk. Nodules are commonly seen on the lower limbs and sometimes also on the head. They subside spontaneously in about 2 wk, leaving no permanent scar.

Hemolymphatic Stage (Stage 1)

The most common presenting features of acute HAT occur at the time of invasion of the bloodstream by the parasites, 2-3 wk after infection.

Patients usually present with irregular episodes of fever, each lasting up to 7 days, accompanied by headache, sweating, and generalized lymphadenopathy. Attacks may be separated by symptom-free intervals of days or even weeks. Painless, nonmatted lymphadenopathy, most commonly of the posterior cervical and supraclavicular nodes, is one of the most constant signs, particularly in the Gambian form. A common feature of trypanosomiasis in Caucasians is the presence of blotchy, irregular, nonpruritic, erythematous macules, which may appear any time after the first febrile episode, usually within 6-8 wk. The majority of macules have a normal central area, giving the rash a circinate outline. This rash is seen mainly on the trunk and is evanescent, fading in 1 place only to appear at another site. Examination of the blood during this stage may show anemia, leukopenia with relative monocytosis, and elevated levels of immunoglobulin M. Cardiac manifestations of HAT have also been reported but are generally limited to nonspecific ST-T wave electrocardiographic abnormalities. Histopathologic characterization shows a lymphomonohistiocytic infiltrate in the interstitium and no penetration of the myocardial cells, unlike that for American trypanosomiasis (see Chapter 287). Progression of cardiac pathology to congestive heart failure has not been reported, and the perimyocarditis is usually self-limited and/or readily resolves with treatment.

Meningoencephalitic Stage (Stage 2)

Neurologic symptoms and signs are nonspecific, including irritability, insomnia, and irrational and inexplicable anxieties with frequent changes in mood and personality. Neurologic symptoms may precede invasion of the CNS by the organisms. In untreated *T. brucei rhodesiense* infections, CNS invasion occurs within 3-6 wk and is associated with recurrent bouts of headache, fever, weakness, and signs of acute toxemia. Tachycardia may be evidence of myocarditis. Death occurs in 6-9 mo as a result of secondary infection or cardiac failure.

In Gambian HAT, cerebral symptoms appear within 2 yr after the acute symptoms. An increase in drowsiness during the day and insomnia at night reflect the continuous progression of infection and may be accompanied by anemia, leukopenia, and muscle wasting. Patients are also at increased risk for infection.

The chronic, diffuse meningoencephalitis without localizing symptoms is the form referred to as **sleeping sickness.** Drowsiness and an uncontrollable urge to sleep are the major features of this stage of the disease and become almost continuous in the terminal stages. Tremor or rigidity with stiff and ataxic gait, suggest involvement of the basal ganglia. Psychotic changes occur in almost one third of untreated patients. Although untreated disease has been thought to be uniformly fatal, there is prospective evidence that, in rare cases, some individuals remain asymptomatic, are able to clear parasitemia, and occasionally become seronegative.

DIAGNOSIS

Definitive diagnosis can be established during the early stages by examination of a fresh, thick blood smear, which permits visualization of the motile active forms (Fig. 286-1). HAT can also be detected from blood using a variety of sensitive techniques: quantitative buffy coat smears and mini anion exchange resins are common examples. The **card agglutination trypanosomiasis test** is of value for epidemiologic purposes and in screening for *T. brucei gambiense.* Dried, Giemsa-stained smears should be examined for the detailed morphologic features of the organisms. If a thick blood or buffy coat smear is negative, concentration techniques may help. Aspiration of an enlarged lymph node can also be used to obtain material for parasitologic examination. If positive, cerebrospinal fluid should also be examined for the organisms. The presence of trypanosomes, or 5 white blood cells/µL, or both, is indicative of stage 2 disease. If trypanosomes are absent in the cerebrospinal fluid, some authorities use a count of 20 white blood cells/µL as a cutoff for diagnosing late-stage disease. Because the white blood cell count in the cerebrospinal fluid is critical in making treatment decisions, methods for improving cell counting, such as the use of disposable cell counters and combining multiple counts, have been proposed.

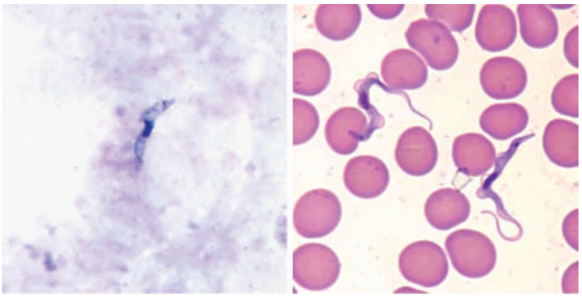

Figure 286-1 *Trypanosoma brucei* sp. trypomastigotes in thick blood smear stained with Giemsa *(left)* and thin blood smear stained with Wright-Giemsa *(right). (From the Centers for Disease Control and Prevention [CDC]: Laboratory identification of parasites of public health concern. Trypanosomiasis, African. Available at: http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/TrypanosomiasisAfrican_il.htm)*

Polymerase chain reaction–based tests have been shown to be highly sensitive and specific, but these require advanced laboratory facilities. Field-based loop-mediated isothermal amplification tests have been developed but need further validation. Low cost, stable, but highly specific rapid tests such as the HAT Sero-Strip and HAT Sero-K-SeT that detect trypanosome-specific antibodies have been developed, and may prove to be useful for point-of-care diagnosis as the focus shifts from control to elimination.

TREATMENT

The choice of chemotherapeutic agents for treatment is dependent upon the stage of the infection and the causative organisms.

Stage 1 Treatment

Hematogenous forms of both Rhodesian and Gambian HAT can be treated with either suramin or pentamidine, which are better tolerated than drugs for stage 2 or CNS disease but are associated with substantial risks of toxicity. **Suramin** is a polysulphonated symmetrical naphthalene derivative given as a 10% solution for intravenous administration. A **test dose** (10 mg for children; 100-200 mg for adults) is initially administered to detect rare idiosyncratic reactions of shock and collapse. The dose for subsequent IV injections is 20 mg/kg (maximum: 1 g) administered on days 1, 3, 7, 14, and 21. Suramin is nephrotoxic, and thus a urinalysis should be performed before each dose. Marked proteinuria, blood, or casts is a contraindication to continuation of suramin. Resistance is rare but has been reported.

Pentamidine isethionate (4 mg/kg/day IM for 7-10 days daily or on alternate days) concentrates to high levels in trypanosomes and is highly trypanocidal. It is better tolerated than suramin but carries significant risk of hypoglycemia, nephrotoxicity, hypotension, leukopenia, and liver enzyme elevation. Because of its potency, long half-life, and toxicity, short course treatment is desirable and is being investigated.

Stage 2 Treatment

The treatment of late stage *T. brucei gambiense* has substantially changed as a result of programmatic efforts of the WHO and the donation of large quantities of trypanosomicidal drugs, including eflornithine, pentamidine, suramin, and nifurtimox. **Combination eflornithine and nifurtimox** is the treatment of choice for *T. brucei gambiense* CNS infection. This regimen is noninferior to eflornithine monotherapy, and the duration of treatment is shorter. For combination therapy eflornithine is given at 400 mg/kg/day every 12 hr IV for 7 days, along with nifurtimox 15 mg/kg/day every 8 hr PO for 10 days. If nifurtimox is unavailable, eflornithine monotherapy can be given at a dose of 400 mg/kg/day, every 6 hr IV for 14 days. Adverse reactions to these regimens include fever, hypertension and seizures, with combination eflornithine and nifurtimox having less-frequent events.

Melarsoprol is an arsenical compound and is the only effective treatment for late *T. brucei rhodesiense* disease. Treatment of children is initiated at 0.36 mg/kg once daily IV, with gradually escalating doses every 1-5 days to 3.6 mg/kg once daily IV; treatment is usually 10 doses (18-25 mg/kg total dose). Treatment of adults is with melarsoprol 2-3.6 mg/kg once daily IV for 3 days; and after 1 wk, 3.6 mg/kg once daily IV for 3 days, which is repeated after 10-21 days. An alternative regimen is 2.2 mg/kg once daily for 10 days. Guidelines recommend 18-25 mg/kg total over 1 mo. Reactions such as fever, abdominal pain, and chest pain are rare but may occur during or shortly after administration. Serious toxic effects include encephalopathy and exfoliative dermatitis.

Because of the inherent logistic difficulties in administering intravenous therapy for late stage HAT, an active area of research is finding effective oral agents for late-stage HAT. Several promising agents are due to enter phase 2 trials. Efforts to decrease the toxicity of melarsoprol by making it more water soluble are also underway.

PREVENTION

A vaccine or consistently effective prophylactic therapy is not available and is particularly challenging because of the antigenic variation resulting from variant surface glycoproteins. A single injection of pentamidine (3-4 mg/kg IM) provides protection against Gambian trypanosomiasis for at least 6 mo, but the effectiveness against the Rhodesian form is uncertain.

While the progress in controlling HAT has been impressive, the increasing cost of treatment per case as the overall number of patients decline may lead to premature termination of intensive control efforts. Underreporting of cases remains a challenge. Vector control programs to control *Glossina* have been essential in controlling disease, coupled with the use of screens, traps, and sanitary measures. Encouraging neutral-colored clothing that is not attractive to the tsetse fly may reduce bites.

Using serology and parasitologic methods, mobile medical surveillance of the population at risk by specialized staff has been done, and strong collaboration between WHO, Medecins sans Frontieres, and African governments has shifted the burden of treatment to well-organized and funded national control programs. Ground spraying of insecticides, aerial spraying, and the use of cloth and live animal baits have proven successful. Transgenic techniques to restrict the ability of the tsetse fly to survive and transmit pathogens are also being developed.

The full genome of *T. brucei* with approximately 9,000 genes has been sequenced. Approximately 10% of these genes encode variant surface glycoproteins. This advance has helped identify genes relevant to the disease and its possible prevention, as well as the design of new antitrypanosomal drugs, including those that target specific metabolic pathways.

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Chapter 287

American Trypanosomiasis (Chagas Disease; *Trypanosoma cruzi*)

Edsel Maurice T. Salvana and Robert A. Salata

American trypanosomiasis or Chagas disease is a vector-borne disease caused by the protozoan *Trypanosoma cruzi*. Its natural vectors are the bloodsucking insects of the family Reduviidae. It can also be transmitted orally from contaminated food, vertically from mother to child, and through blood transfusion and organ transplantation. While acute American trypanosomiasis usually manifests as a nonspecific febrile illness, chronic Chagas disease is associated with cardiomyopathy and severe gastrointestinal abnormalities.

ETIOLOGY

American trypanosomiasis is a caused by *T. cruzi*, a parasitic, flagellated kinetoplastid protozoan (Fig. 287-1). The main vectors for *T. cruzi* are insects of the order Triatominae, which includes *Triatoma infestans* (free roaming kissing bugs), *Rhodnius prolixus,* and *Panstrongylus megistus.*

LIFE CYCLE

T. cruzi has 3 recognizable morphogenetic phases: amastigotes, trypomastigotes, and epimastigotes (see Figs. 287-1 and 287-2). **Amastigotes** are intracellular forms found in mammalian tissues that are spherical and have a short flagellum but form clusters of oval shapes (pseudocysts) within infected tissues. **Trypomastigotes** are spindle-shaped, extracellular, nondividing forms that are found in blood and are responsible for both transmission of infection to the insect vector and cell-to-cell spread of infection. **Epimastigotes** are found in the midgut of the vector insect and multiply in the midgut and rectum of arthropods, differentiating into **metacyclic trypomastigotes.** Metacyclic trypomastigotes are the infectious form for humans and are released onto the skin of a human when the insect defecates close to the site of a bite, entering via the damaged skin or mucous membranes. Once in the host, these multiply intracellularly as amastigotes and are

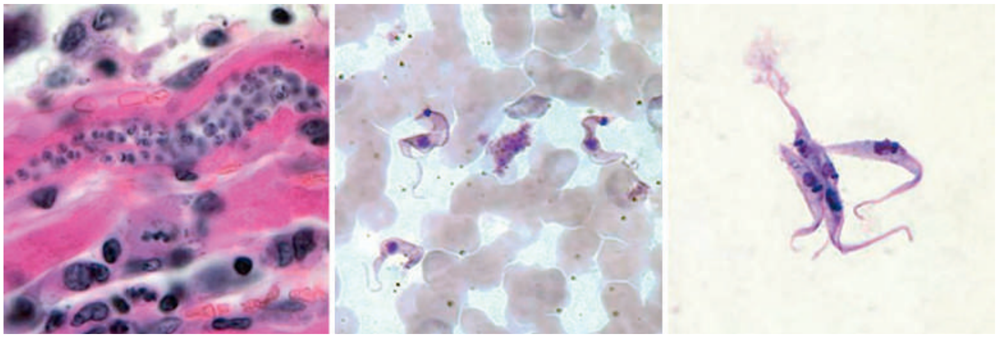

Figure 287-1 Stages of *Trypanosoma cruzi.* From *left* to *right:* amastigote, trypomastigote, and epimastigote. *(From the Centers for Disease Control and Prevention [CDC]: Laboratory identification of parasites of public health concern. Trypanosomiasis, American. Available at: http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/TrypanosomiasisAmerican_il.htm)*

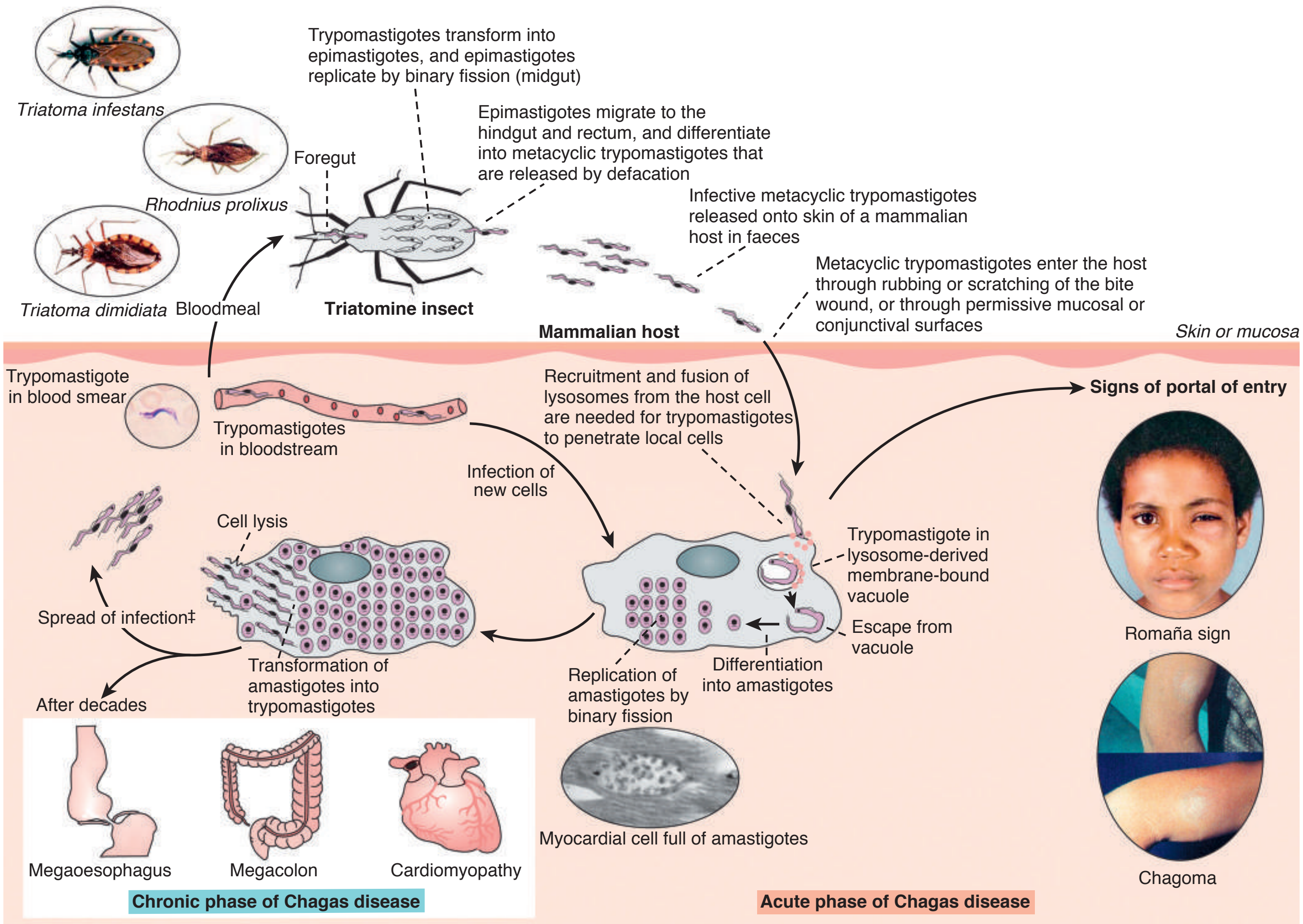

Figure 287-2 Vector-borne transmission and life cycle of *Trypanosoma cruzi*. *(From Rassi A Jr, Rassi A, Marin-Neto JA: Chagas disease,* Lancet *375:1388–1400, 2010, Fig. 1, p. 1389.)*

released into the circulation when the cell dies. Bloodborne trypomastigotes circulate until they enter another host cell or are taken up by the bite of another insect, completing the life cycle.

EPIDEMIOLOGY

Chagas disease is found only in the Western hemisphere, specifically the Americas, particularly in southern Patagonia (Fig. 287-3). Natural transmission only occurs within this region, but the disease may arise elsewhere as a consequence of migration and transmission through contaminated blood. Multilateral efforts coordinated by the World Health Organization and the Pan-American Health Organization in large-scale vector control, blood donor screening to prevent transmission through transfusion, and case-finding and treatment of chronically infected mothers and newborn infants have effectively halted transmission in a number of areas of South America. In the Brazilian Amazon, vectorial transmission from *T. infestans* has been effectively interrupted through multicountry programs involving vector control, housing design improvements, and health education. The number of cases has dropped from a peak of 24 million in 1984 to a current estimate of 8-10 million. Vectorial transmission continues to drop in other regions, although challenges remain, including the emergence of disease in new areas thought to be Chagas-free, along with occasional re-emergence in previously controlled areas.

Infection is divided into 3 main phases: acute (Table 287-1), indeterminate, and chronic. Acute infection is the most amenable to treatment. Indeterminate infection is asymptomatic but associated with a positive antibody titer. Up to 30% of infected persons proceed to chronic *T. cruzi* infection and develop symptoms. While it was initially believed that chronic infection without treatment does not clear, at least 3 well-documented cases of spontaneous resolution without treatment have been reported. It is still unclear how this parasitic protozoan escapes the immune system because, unlike African trypanosomiasis (see Chapter 286), antigenic variation is not observed. The *T. cruzi* genome has been fully sequenced and contains 12,000 genes, the most widely expanded among trypanosomatids, possibly reflect the ability of *T. cruzi* to invade a wide variety of host tissues. Significant strain-to-strain genome variability and extensive epigenetic modification of surface proteins have been found, likely contributing to immune evasion.

T. cruzi infection is primarily a zoonosis, and humans are incidental hosts. *T. cruzi* has a large sylvan reservoir and has been isolated from numerous animal species. The presence of reservoirs and vectors of *T. cruzi* and the socioeconomic and educational levels of the population are the most important risk factors for vector-borne transmission to humans. The arthropod vectors for *T. cruzi* are the **reduviid insects** or **triatomines,** variably known as **wild bedbugs, assassin bugs,** or **kissing bugs.** Insect vectors are found in rural, wooded areas and acquire infection through ingestion of blood from humans or animals with circulating trypomastigotes. Free roaming kissing bugs in the southwestern United States have been found to have fed on humans; some bugs contained *T. cruzi*.

Housing conditions are very important in the transmission chain. Incidence and prevalence of infection depends on the adaptation of the triatomines to human dwellings as well as the vector capacity of the species. Animal reservoirs of reduviid bugs include dogs, cats, rats, opossums, guinea pigs, monkeys, bats, and raccoons. Humans often

Figure 287-3 **Estimated number of immigrants with *Trypanosoma cruzi* infection living in nonendemic countries.** Data are supplied for Canada, Australia, and Japan in 2006; the United States in 2005; Spain in 2008; and other European countries in 2004–2006. *(From Rassi A Jr, Rassi A, Marin-Neto JA: Chagas disease,* Lancet *375:1388–1400, 2010, Fig. 2, p. 1391.)*

become infected when land in enzootic areas is developed for agricultural or commercial purposes. Although reduviid insects can be found in warmer regions of the United States as far north as Maryland, Chagas disease is extremely rare owing to the higher standard of domestic housing. Most acute cases in the United States are associated with laboratory accidents. An estimated 300,000 immigrants from endemic countries living in the United States are likely infected with *T. cruzi,* 30,000 to 45,000 of whom have cardiomyopathy.

Humans can be infected transplacentally, occurring in 10.5% of infected mothers and causing congenital Chagas disease. Transplacental infection is associated with premature birth, fetal wastage, and placentitis. Previously, up to 1,000 neonates infected with *T. cruzi* were born every year in Argentina; this number has substantially decreased since widespread control programs were initiated. Disease transmission can occur through blood transfusions in endemic areas from asymptomatic blood donors. Seropositivity rates in endemic areas are as high as 20%. The risk for transmission through a single blood transfusion from a chagasic donor is 13-23%. Blood screening for Chagas disease in the United States was started in 2006 and has demonstrated a prevalence of slightly over 1 in 13,000 donors. Risk factors in these donors were consistent with exposure to Chagas disease, including travel to endemic areas and a history of a reduviid bug bite.

Percutaneous injection as a result of laboratory accidents is also a documented mode of transmission. Oral transmission through contaminated food is an increasingly important method of transmission as vector transmission is successfully interrupted by control programs. Although breastfeeding is a very uncommon mode of transmission, women with acute infections should not nurse until they have been treated.

PATHOGENESIS

Acute Disease

At the site of entry or puncture site, neutrophils, lymphocytes, macrophages, and monocytes infiltrate. *T. cruzi* organisms are engulfed by macrophages and are sequestered in membrane-bound vacuoles. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, and replicate. A local tissue reaction, the **chagoma,** develops, and the process extends to a local lymph node (see Fig. 287-2). Blood forms appear, and the process disseminates. Initial immune recognition of parasites is through innate pathways involving activation of multiple Toll-like receptors (TLRs) by different parasite substrates, including TLR 2/6, TLR 4, and TLR 9. Adaptive immunity is mediated by interferon-γ and interleukin-12 activation of T-cells and is modulated by interleukin-10 and transforming growth factor-β, which downregulates macrophage activity. The interplay of these cytokines is probably responsible, in part, for the variability in disease manifestations and the progression to chronic disease. Acute myocarditis likely occurs in all patients with acute disease but is frequently asymptomatic and may only be apparent on biopsy.

Chronic Disease

The pathophysiology of chronic Chagas disease is incompletely understood. Two main mechanisms are likely involved, although other factors may come into play. The first mechanism involves direct tissue destruction by low-level parasite persistence mediated by lymphocytic infiltration and fibrosis. The second mechanism involves molecular mimicry of host antigens by the parasite, resulting in autoantibodies that produce (1) an inflammatory reaction associated with direct damage to host tissue, and/or (2) direct stimulation of adrenergic and muscarinic cholinergic receptors associated with dysautonomia and increased risk of arrhythmia.

T. cruzi strains demonstrate selective parasitism for certain tissues. Most strains are myotropic and invade smooth, skeletal, and heart muscle cells. Attachment is mediated by specific receptors on the trypomastigotes that attach to complementary glycoconjugates on the host cell surface. Attachment to cardiac muscle results in inflammation of the endocardium and myocardium, edema, focal necrosis in the contractile and conducting systems, periganglionitis, and lymphocytic inflammation. The heart becomes enlarged, and endocardial thrombosis or aneurysm may result. Right bundle-branch block is also common. Trypanosome parasites also attach to neural cells and reticuloendothelial cells. In patients with gastrointestinal tract involvement, myenteric plexus destruction leads to pathologic organ dilation. Immunologic mechanisms for control of parasitism and resistance are not fully

Table 287-1 Vector-Borne Transmission and Life Cycle of *Trypanosoma Cruzi*

	GEOGRAPHICAL DISTRIBUTION	PREDOMINANT POPULATION	INCUBATION TIME	CLINICAL PRESENTATION	DIAGNOSIS	MORTALITY
Vectorial	Endemic countries	Children and adolescents	1-2 wk	Asymptomatic; fever, malaise, lymphadenopathy, hepatosplenomegaly, subcutaneous edema; signs of portal of entry (Romaña sign, chagoma); myocarditis, meningoencephalitis	Parasite detection by microscopy; fresh blood specimen; stained blood smears; buffy coat preparation (microhematocrit technique); or serum precipitate (Strout technique)	Low (<5-10%*)
Transfusion-based	Endemic and nonendemic countries	Adults	8-120 days	Same as for vectorial but excluding signs of portal of entry	Same as for vectorial	Variable†
Congenital	Endemic and nonendemic countries	Neonates and children younger than 1 yr	Up to a few weeks	Asymptomatic; abortion, neonatal death, prematurity, low birthweight, low Apgar score; hypotonicity, fever, hepatosplenomegaly, respiratory distress, anemia; myocarditis, meningoencephalitis, megaviscera, edema	Microhematocrit with cord blood or peripheral blood from neonate; 2 or more samples in the 1st mo of life; immunoglobulin G serology at 6-9 mo of age is microhematocrit negative or not done	Unknown
Oral	Amazon basin and regional outbreaks	Individuals of any age from the same family or community	3-22 days	Same as for transfusion-based plus headache, myalgia, vomiting, abdominal pain, jaundice, diarrhea, and digestive hemorrhage	Same as for vectorial	High (8-35%)
Reactivation-based	Endemic and nonendemic countries	Patients with associated immunosuppressive states	Variable	Same as for transfusion-based plus panniculitis, subcutaneous parasite-containing nodules, and skin ulcers	Same as for vectorial, and parasites can also be detected in tissues by microscopy or polymerase chain reaction	Variable†

*Refers to symptomatic cases; because 95% of acute infections from vectorial transmission are asymptomatic and 5-10% of patients with acute symptoms die, estimated mortality in this phase of infection is between 1 in 200 and 1 in 400.

†Depends on the underlying disease and the patient's clinical condition.

From Rassi A Jr, Rassi A, Marin-Neto JA: Chagas disease, Lancet *375:1388–1400, 2010, Table 2, p. 1393.*

understood. Despite strong acquired immunity, parasitologic cure in chronic infection is exceedingly rare. Antibodies involved with resistance to *T. cruzi* are related to the phase of infection. Immunoglobulin G antibodies, probably to several major surface antigens, mediate immunophagocytosis of *T. cruzi* by macrophages. Conditions that depress cell-mediated immunity increase the severity of *T. cruzi* infection. There is increasing evidence that host genetic factors play a significant role in progression and severity of chronic disease.

CLINICAL MANIFESTATIONS

Acute Chagas disease in children is usually asymptomatic or is associated with a mild febrile illness characterized by malaise, facial edema, and lymphadenopathy (see Table 287-1). Infants often demonstrate local signs of inflammation at the site of parasite entry, which is then referred to as a **chagoma.** Approximately 50% of children come to medical attention with the **Romaña sign** (unilateral, painless eye swelling), conjunctivitis, and preauricular lymphadenitis. Patients complain of fatigue and headache. Fever can persist for 4-5 wk. More severe systemic presentations can occur in children younger than 2 yr old and may include lymphadenopathy, hepatosplenomegaly, and meningoencephalitis. A cutaneous morbilliform eruption can accompany the acute syndrome. Anemia, lymphocytosis, hepatitis, and thrombocytopenia have also been described.

The heart, central nervous system, peripheral nerve ganglia, and reticuloendothelial system are often heavily parasitized. The heart is the primary target organ. The intense parasitism can result in acute inflammation and in 4-chamber cardiac dilation. Diffuse myocarditis and inflammation of the conduction system can lead to the development of fibrosis. Histologic examination reveals the characteristic **pseudocysts,** which are the intracellular aggregates of amastigotes.

Intrauterine infection in pregnant women can cause spontaneous abortion or premature birth. In children with congenital infection, severe anemia, hepatosplenomegaly, jaundice, and convulsions can mimic congenital cytomegalovirus infection, toxoplasmosis, and erythroblastosis fetalis. *T. cruzi* can be visualized in the cerebrospinal fluid in meningoencephalitis. Children usually undergo spontaneous remission in 8-12 wk and enter an indeterminate phase with lifelong low-grade parasitemia and development of antibodies to many *T. cruzi* cell

surface antigens. The mortality rate is 5-10%, with deaths caused by acute myocarditis with resultant heart failure, or meningoencephalitis. Acute Chagas disease should be differentiated from malaria, schistosomiasis, visceral leishmaniasis, brucellosis, typhoid fever, and infectious mononucleosis.

Autonomic dysfunction and peripheral neuropathy can occur. Central nervous system involvement in Chagas disease is uncommon. If granulomatous encephalitis occurs in the acute infection, it is usually fatal.

Chronic Chagas disease may be asymptomatic or symptomatic. The most common presentation of chronic *T. cruzi* infection is **cardiomyopathy,** manifested by congestive heart failure, arrhythmia, and thromboembolic events. Electrocardiographic abnormalities include partial or complete atrioventricular block and right bundle-branch block. Left bundle-branch block is unusual. Pathologic examination of infected heart muscle reveals muscle atrophy, myonecrosis, myocytolysis, fibrosis, and lymphocytic infiltration. Myocardial infarction has been reported and may be secondary to left apical aneurysm embolization or necrotizing arteriolitis of the microvasculature. Left ventricular apical aneurysms are pathognomonic of chronic chagasic cardiomyopathy.

Gastrointestinal manifestations of chronic Chagas disease occur in 8-10% of patients and involve a diminution in the Auerbach plexus and Meissner plexus. There are also preganglionic lesions and a reduction in the number of dorsal motor nuclear cells of the vagus nerve. Characteristically, this involvement presents clinically as **megaesophagus** and **megacolon.** Sigmoid dilation, volvulus, and fecalomas are often found in megacolon. Loss of ganglia in the esophagus results in abnormal dilation; the esophagus can reach up to 26 times its normal weight and hold up to 2 L of excess fluid. Megaesophagus presents as dysphagia, odynophagia, and cough. Esophageal body abnormalities occur independently of lower esophageal dysfunction. Megaesophagus can lead to esophagitis and cancer of the esophagus. Aspiration pneumonia and pulmonary tuberculosis are also more common in patients with megaesophagus.

Immunocompromised Persons

T. cruzi infections in immunocompromised persons may be caused by transmission from an asymptomatic donor of blood products or reactivation of prior infection. Organ donation to allograft recipients can result in a devastating form of the illness. Cardiac transplantation for Chagas cardiomyopathy has resulted in reactivation, despite prophylaxis and postoperative treatment with benznidazole. HIV infection also leads to reactivation in approximately 20% of cases; cerebral lesions are more common in these patients and can mimic those of toxoplasmic encephalitis. Myocarditis is also commonly observed, and secondary prophylaxis may be of benefit in some HIV coinfected patients. In immunocompromised patients at risk for reactivation, serologic testing and close monitoring are necessary.

DIAGNOSIS

A careful history with attention to geographic origin and travel is important. A **peripheral blood smear** or a Giemsa-stained smear during the acute phase of illness may show motile trypanosomes, which is diagnostic for Chagas disease (see Fig. 287-1). These are only seen in the 1st 6-12 wk of illness. Buffy coat smears may improve yield.

Most persons seek medical attention during the chronic phase of the disease, when parasites are not found in the bloodstream and clinical symptoms are not diagnostic. Serologic testing is used for diagnosis, most commonly enzyme-linked immunosorbent assay, indirect hemagglutination, and indirect fluorescent antibody testing. No single serology test is sufficiently reliable to make the diagnosis, so repeat or parallel testing using a different method or antigen is required to confirm the result of an initial positive serologic test. In the case of discordant results, a third test may be employed. Confirmatory tests used typically include the radiologic immunoprecipitation assay (used as a confirmatory test in blood donors in the United States) and Western blot assays based on trypomastigote excreted-secreted antigens.

Nonimmunologic methods of diagnosis are also available. Mouse inoculation and xenodiagnosis (allowing uninfected reduviid bugs to feed on a patient's blood and examining the intestinal contents of those bugs 30 days after the meal) are quite sensitive. Parasites may also be cultured in Novy-MacNeal-Nicolle media. Polymerase chain reaction of nuclear and kinetoplast DNA sequences have been developed and can be highly sensitive in acute disease, but are less reliable for the detection of chronic disease. Polymerase chain reaction is not sufficiently sensitive for blood screening and was only positive in 1 of 22 radiologic immunoprecipitation assay–confirmed donors in the United States. Moreover, there is significant variability among methods and parasite strains. An international collaborative study has validated 4 methods that have the best performance characteristics for widespread use. Diagnosis of congenital transmission in newborns cannot be made at birth with serology because of the presence of maternal antibodies in the 1st 6 mo of life. Microscopic examination, parasite culture, or polymerase chain reaction can be used. However, a serologic test at 6-12 mo is recommended to completely exclude infection.

TREATMENT

Biochemical differences between the metabolism of American trypanosomes and that of mammalian hosts have been exploited for chemotherapy. Trypanosomes are very sensitive to oxidative radicals and do not possess catalase or glutathione reductase/glutathione peroxidase, which are key enzymes in scavenging free radicals. All trypanosomes also have an unusual reduced nicotinamide adenine dinucleotide phosphate–dependent disulfide reductase. Drugs that stimulate H_2O_2 generation or prevent its use are potential trypanosomicidal agents. Other biochemical pathways that have been targeted include ergosterol synthesis using azole compounds and the hypoxanthine-guanine phosphoribosyltransferase pathway using allopurinol.

Drug treatment for *T. cruzi* infection is currently limited to nifurtimox and benznidazole. Both are effective against trypomastigotes and amastigotes and have been used to eradicate parasites in the acute stages of infection. Treatment responses vary according to the phase of Chagas disease, duration of treatment, dose, age of the patient, and geographic origin of the patient. For acute disease, the average cure rate is approximately 60-80%, while for chronic cases, the cure rate is less than 20%. Neither drug is safe in pregnancy.

Benznidazole is a nitroimidazole derivative that may be slightly more effective than nifurtimox. Although benznidazole is capable of inducing the production of free oxide radicals, the dose at which it is given is not effective for this mode of action. Instead, its nitro reduction intermediates may form covalent bonds or interact in other ways with parasitic DNA, lipids, and proteins and cause damage to parasite components. The recommended treatment regimen for children younger than 12 yr of age is 10 mg/kg/day divided twice daily PO for 60 days, and for those older than 12 yr of age, it is 5-7 mg/kg/day divided twice daily PO for 60 days. This drug is associated with significant toxicity, including rash, photosensitivity, peripheral neuritis, granulocytopenia, and thrombocytopenia.

Nifurtimox generates highly toxic oxygen metabolites through the action of nitroreductases, which produce unstable nitro anion radicals, which, in turn, react with oxygen to produce peroxide and superoxide free radicals. The treatment regimen for children 1-10 yr of age is 15-20 mg/kg/day divided 4 times a day PO for 90 days; for children 11-16 yr of age, 12.5-15 mg/kg/day divided 4 times a day PO for 90 days; and for children older than 16 yr of age, 8-10 mg/kg/day divided 3 or 4 times a day PO for 90-120 days. Nifurtimox is associated with weakness, anorexia, gastrointestinal disturbances, toxic hepatitis, tremors, and seizures (hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency).

Although treatment is generally recommended for acute Chagas disease and is effective in the early stages of infection, the treatment of asymptomatic (or indeterminate) infection and symptomatic chronic disease is controversial. Multiple trials with long-term follow-up have yielded mixed results, with an estimated response rate of 6-20% for chronic disease. The definition of response in itself is

problematic, and parasitologic cure is nearly impossible to demonstrate given the limitations of the sensitivity and specificity of detection methods. Instead, serologic conversion is seen as an appropriate treatment response, although some patients who achieve this still eventually develop symptoms. Recommendations from authorities are mixed, with some advocating for treatment regardless of disease phase and others recommending against treatment because of uncertain benefit and the toxicity of the drugs involved. Proponents of the latter approach instead advocate symptomatic treatment of disease manifestations.

Treatment of congestive heart failure is generally in line with recommendations for management of dilated cardiomyopathy from other causes. β-Blockers have been validated in the management of these patients. Digitalis toxicity occurs frequently in patients with Chagas cardiomyopathy. Pacemakers may be necessary in cases of severe heart block. Although cardiac transplantation has been used successfully in chagasic patients, it is reserved for those with the most severe disease manifestations. Plasmapheresis to remove antibodies with adrenergic activity has been proposed for refractory patients, as this approach has been tried and has worked in patients with dilated cardiomyopathy from other causes. However, its application to Chagas disease is unproven.

A light, balanced diet is recommended for megaesophagus. Surgery or dilation of the lower esophageal sphincter treats megaesophagus; pneumatic dilation is the superior mode of therapy. Nitrates and nifedipine have been used to reduce lower esophageal sphincter pressure in patients with megaesophagus. Treatment of megacolon is surgical and symptomatic. Treatment of meningoencephalitis is also supportive.

In accidental infection when parasitic penetration is certain, treatment should be initiated immediately and continued for 10-15 days. Blood is usually collected and tested for seroconversion at 15, 30, and 60 days.

PREVENTION

Massive coordinated vector control programs under the auspices of the World Health Organization and Pan-American Health Organization and the institution of widespread blood donor screening and targeted surveillance of chronically infected mothers and infants at risk have effectively eliminated or at least drastically reduced transmission in most endemic countries. As Chagas disease remains linked to poverty, improvement of living conditions is likewise essential to successful control and eradication. Education of residents in endemic areas, use of bed nets, use of insecticides, and destruction of adobe houses that harbor reduviid bugs are effective methods to control the bug population. Synthetic pyrethroid insecticides help keep houses free of vectors for up to 2 yr and have low toxicity for humans. Paints incorporating insecticides have also been used. A therapeutic vaccine composed of bivalent recombinant *T. cruzi* antigens has been shown to be effective in preclinical proof-of-concept animal models and is currently undergoing further development.

Blood transfusions in endemic areas are a significant risk. Gentian violet, an amphophilic cationic agent that acts photodynamically, has been used to kill the parasite in blood. Photoirradiation of blood containing gentian violet and ascorbate generates free radicals and superoxide anions that are trypanosomicidal. Mepacrine and maprotiline have also been used to eradicate the parasite in blood transfusions.

Because immigrants can carry this disease to nonendemic areas, serologic testing should be performed in blood and organ donors from endemic areas. Potential seropositive donors can be identified by determining whether they have been or have spent extensive time in an endemic area. Questionnaire-based screening of potentially infected blood and organ donors from areas endemic for infection can reduce the risk for transmission. Seropositivity should be considered a contraindication to organ donation, particularly for heart transplantation.

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Chapter 288

Malaria *(Plasmodium)*

Chandy C. John

Malaria is an acute and chronic illness characterized by paroxysms of fever, chills, sweats, fatigue, anemia, and splenomegaly. It has played a major role in human history, causing harm to more people than perhaps any other infectious disease. Malaria is of overwhelming importance in the developing world today, with an estimated 300-500 million cases and more than 1 million deaths each year. Most malarial deaths occur among infants and young children. Although malaria is not endemic in the United States, approximately 1,000 imported cases are recognized in the United States each year. Physicians practicing in nonendemic areas should consider the diagnosis of malaria in any febrile child who has returned from a malaria-endemic area within the previous year, because delay in diagnosis and treatment can result in severe illness or death.

ETIOLOGY

Malaria is caused by intracellular *Plasmodium* protozoa transmitted to humans by female *Anopheles* mosquitoes. Prior to 2004, only 4 species of *Plasmodium* were known to cause malaria in humans: *P. falciparum, P. malariae, P. ovale*, and *P. vivax*. In 2004 *P. knowlesi* (a primate malaria species) was also shown to cause human malaria, and cases of *P. knowlesi* infection have been documented in Malaysia, Indonesia, Singapore, and the Philippines. Malaria also can be transmitted through blood transfusion, use of contaminated needles, and transplacentally from a pregnant woman to her fetus. The risk for blood transmission is small and decreasing in the United States, but may occur by way of whole blood, packed red blood cells, platelets, leukocytes, and organ transplantation.

EPIDEMIOLOGY

Malaria is a major worldwide problem, occurring in more than 100 countries with a combined population of more than 1.6 billion people (Fig. 288-1). The principal areas of transmission are Africa, Asia, and South America. *P. falciparum* and *P. malariae* are found in most malarious areas. *P. falciparum* is the predominant species in Africa, Haiti, and New Guinea. *P. vivax* predominates in Bangladesh, Central America, India, Pakistan, and Sri Lanka. *P. vivax* and *P. falciparum* predominate in Southeast Asia, South America, and Oceania. *P. ovale* is the least-common species and is transmitted primarily in Africa. Transmission of malaria has been eliminated in most of North America (including the United States), Europe, and the Caribbean, as well as Australia, Chile, Israel, Japan, Korea, Lebanon, and Taiwan.

Most cases of malaria in the United States occur among previously infected visitors to the United States from endemic areas and among U.S. citizens who travel to endemic areas without appropriate chemoprophylaxis. The most common regions of acquisition of the 10,100 cases of malaria reported to the Centers for Disease Control and Prevention (CDC) among U.S. citizens between 1985 and 2001 were sub-Saharan Africa (58%), Asia (18%), and the Caribbean and Central or South America (16%). Most of the fatal cases were caused by *P. falciparum* (94% or 66 of the 70 cases), of which 47 (71%) were acquired in sub-Saharan Africa. More than 60% of imported cases of *P. vivax* come from Asia; the remaining species usually come from Africa, Rare cases of apparent locally transmitted malaria have been reported since the 1950s. These cases are likely a result of transmission from untreated and often asymptomatic infected individuals from malaria endemic countries who travel to the United States and infect local mosquitoes or to infected mosquitoes from malaria endemic areas that are transported to the United States on airplanes.

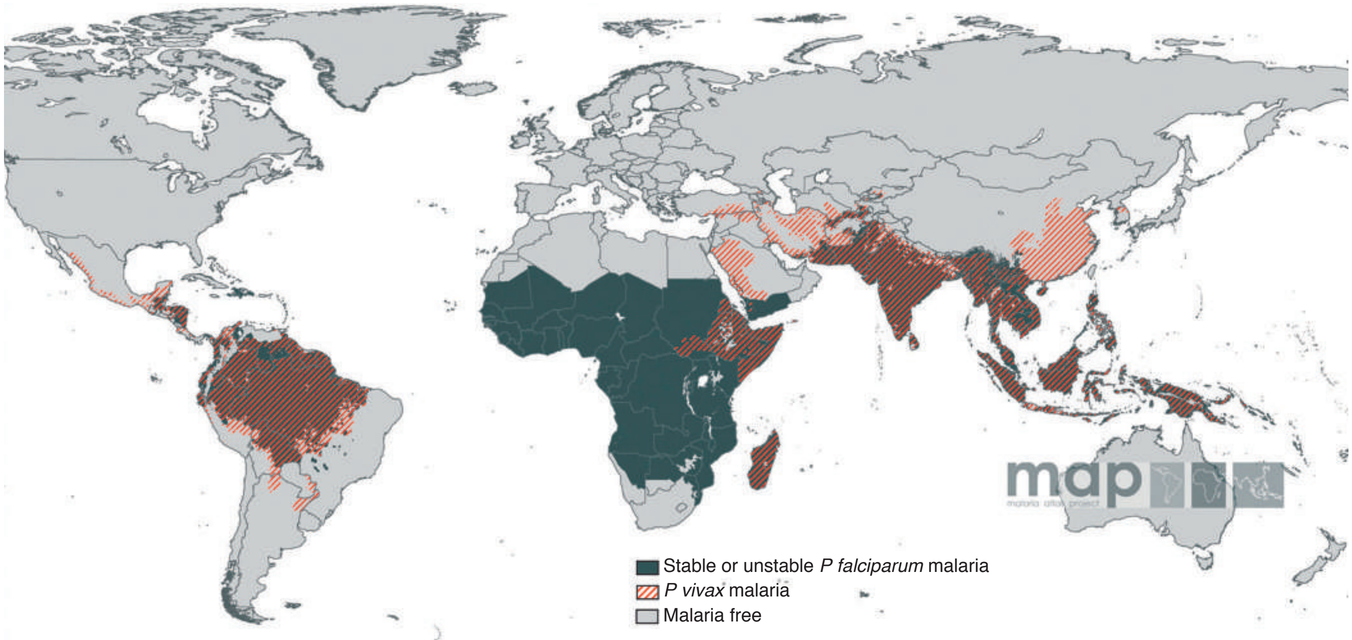

Figure 288-1 Global spatial distribution of *Plasmodium falciparum* malaria in 2007 and preliminary global distribution of *Plasmodium vivax* malaria. *(From Crawley J, Chu C, Mtove G, et al: Malaria in children,* Lancet *375:1468–1478, 2010, Fig. 1, p. 1469.)*

PATHOGENESIS

Plasmodium species exist in a variety of forms and have a complex life cycle that enables them to survive in different cellular environments in the human host (asexual phase) and the mosquito (sexual phase) (Fig. 288-2). A marked amplification of *Plasmodium*, from approximately 10^2 to as many as 10^{14} organisms, occurs during a 2-step process in humans, with the first phase in hepatic cells (exoerythrocytic phase) and the second phase in the red cells (erythrocytic phase). The **exoerythrocytic phase** begins with inoculation of sporozoites into the bloodstream by a female *Anopheles* mosquito. Within minutes, the sporozoites enter the hepatocytes of the liver, where they develop and multiply asexually as a schizont. After 1-2 wk, the hepatocytes rupture and release thousands of merozoites into the circulation. The tissue schizonts of *P. falciparum, P. malariae,* and apparently *P. knowlesi* rupture once and do not persist in the liver. There are 2 types of tissue schizonts for *P. ovale* and *P. vivax*. The primary type ruptures in 6-9 days, and the secondary type remains dormant in the liver cell for weeks, months, or as long as 5 yr before releasing merozoites and causing relapse of infection. The **erythrocytic phase** of *Plasmodium* asexual development begins when the merozoites from the liver penetrate erythrocytes. Once inside the erythrocyte, the parasite transforms into the **ring form,** which then enlarges to become a **trophozoite.** These latter 2 forms can be identified with Giemsa stain on blood smear, the primary means of confirming the diagnosis of malaria (Fig. 288-3). The trophozoite multiplies asexually to produce a number of small erythrocytic **merozoites** that are released into the bloodstream when the erythrocyte membrane ruptures, which is associated with fever. Over time, some of the merozoites develop into male and female gametocytes that complete the *Plasmodium* life cycle when they are ingested during a blood meal by the female anopheline mosquito. The male and female gametocytes fuse to form a **zygote** in the stomach cavity of the mosquito. After a series of further transformations, sporozoites enter the salivary gland of the mosquito and are inoculated into a new host with the next blood meal.

Four important pathologic processes have been identified in patients with malaria: fever, anemia, immunopathologic events, and tissue anoxia. Fever occurs when erythrocytes rupture and release merozoites into the circulation. Anemia is caused by hemolysis, sequestration of erythrocytes in the spleen and other organs, and bone marrow suppression. Immunopathologic events that have been documented in patients with malaria include excessive production of proinflammatory cytokines, such as tumor necrosis factor, that may be responsible for most of the pathology of the disease, including tissue anoxia; polyclonal activation resulting in both hypergammaglobulinemia and the formation of immune complexes; and immunosuppression. Cytoadherence of infected erythrocytes to vascular endothelium occurs in *P. falciparum* malaria and may lead to obstruction of blood flow and capillary damage, with resultant vascular leakage of blood, protein, and fluid and tissue anoxia. In addition, hypoglycemia and lactic acidemia are caused by anaerobic metabolism of glucose. The cumulative effects of these pathologic processes may lead to cerebral, cardiac, pulmonary, intestinal, renal, and hepatic failure.

Immunity after *Plasmodium* species infection is incomplete, preventing severe disease but still allowing future infection. In some cases, parasites circulate in small numbers for a long time but are prevented from rapidly multiplying and causing severe illness. Repeated episodes of infection occur because the parasite has developed a number of immune evasive strategies, such as intracellular replication, vascular cytoadherence that prevents infected erythrocytes from circulating through the spleen, rapid antigenic variation, and alteration of the host immune system resulting in partial immune suppression. The human host response to *Plasmodium* infection includes natural immune mechanisms that prevent infection by other *Plasmodium* species, such as those of birds or rodents, as well as several alterations in erythrocyte physiology that prevent or modify malarial infection. Erythrocytes containing hemoglobin S (sickle erythrocytes) resist malaria parasite growth, erythrocytes lacking Duffy blood group antigen are resistant to *P. vivax*, and erythrocytes containing hemoglobin F (fetal hemoglobin) and ovalocytes are resistant to *P. falciparum*. In hyperendemic areas, newborns rarely become ill with malaria, in part because of passive maternal antibody and high levels of fetal hemoglobin. Children 3 mo to 2-5 yr of age have little specific immunity to malaria species and therefore suffer yearly attacks of debilitating and potentially fatal disease. Immunity is subsequently acquired, and severe cases of malaria become less common. Severe disease may occur during pregnancy, particularly first pregnancies or after extended residence outside the endemic region. In general, extracellular *Plasmodium* organisms are targeted by antibody, whereas intracellular organisms are targeted by cellular defenses such as T lymphocytes, macrophages, polymorphonuclear leukocytes, and the spleen.

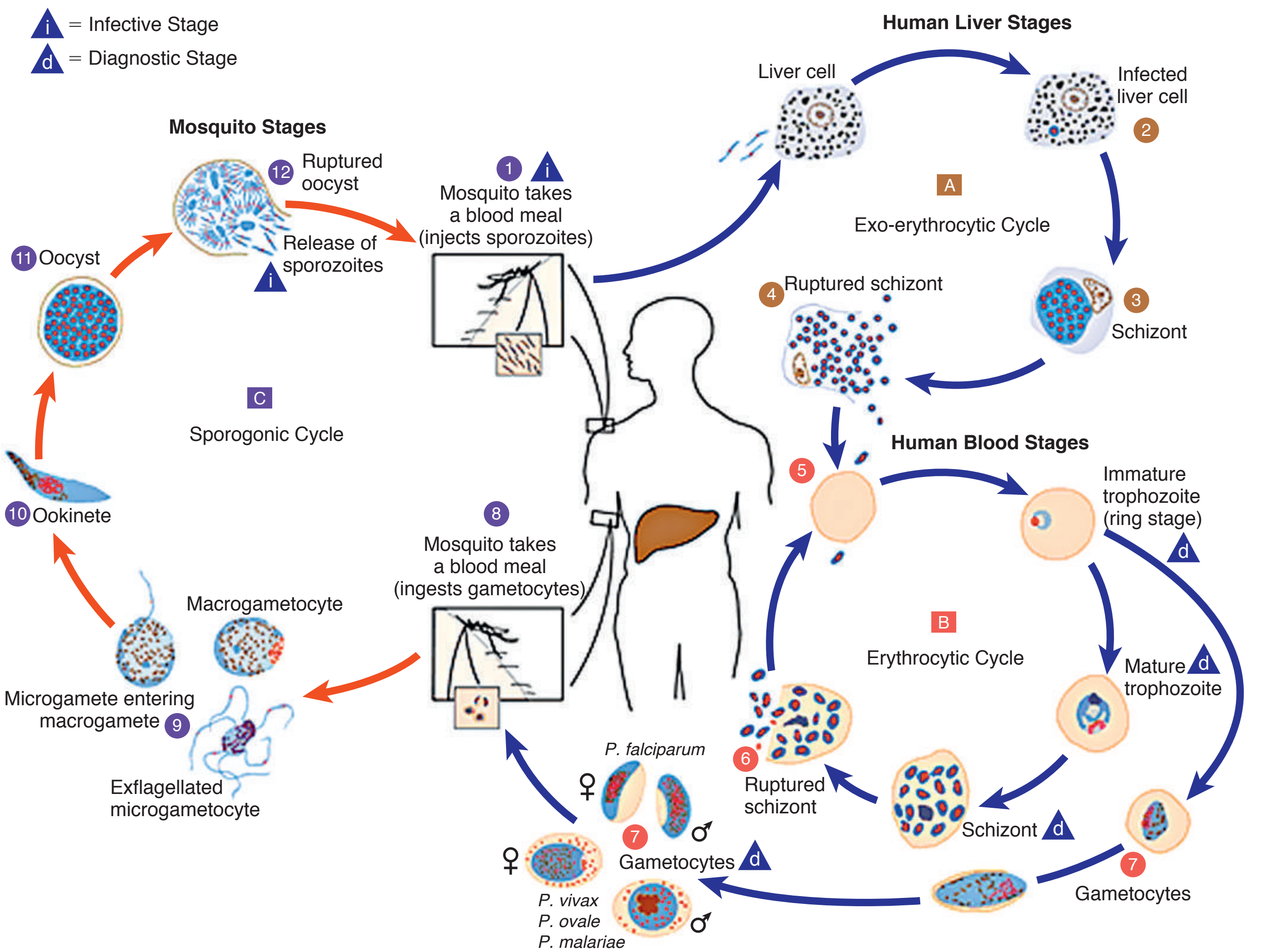

Figure 288-2 Life cycle of *Plasmodium* spp. *(From Centers for Disease Control and Prevention [CDC]: Laboratory diagnosis of malaria:* Plasmodium *spp. Available at: http://www.dpd.cdc.gov/dpdx/HL/ImageLibrary/M-R/Malaria/body_Malaria_il1.h)*

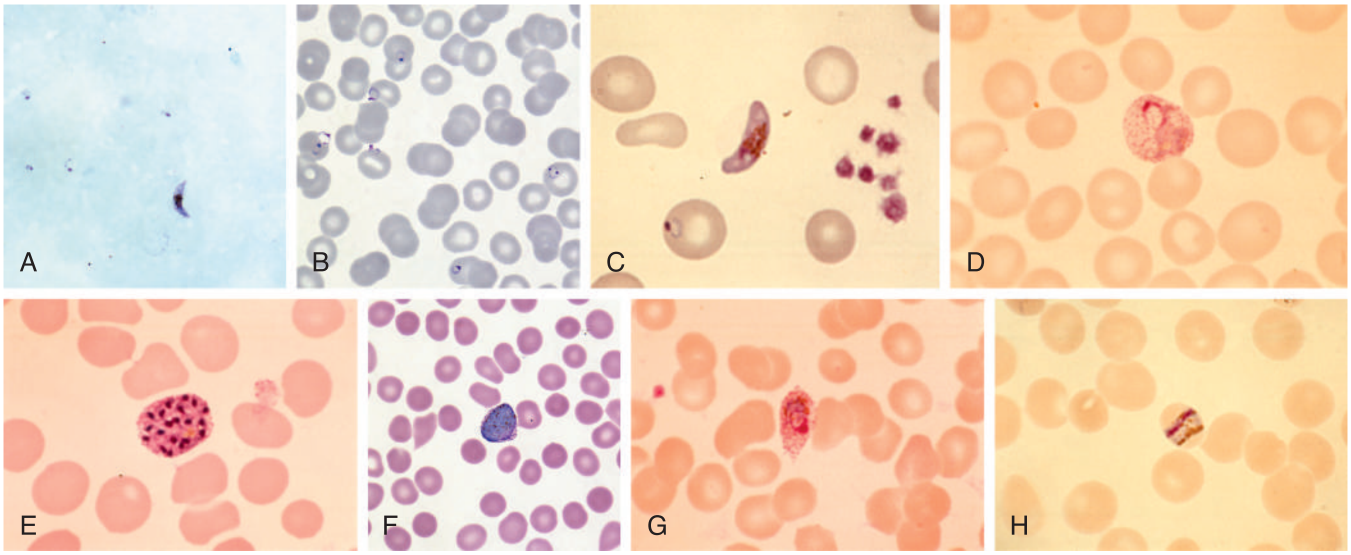

Figure 288-3 Giemsa-stained thick **(A)** and thin **(B-H)** smears used for the diagnosis of malaria and the speciation of *Plasmodium* parasites. **A,** Multiple signet-ring *Plasmodium falciparum* trophozoites, which are visualized outside erythrocytes. **B,** A multiply infected erythrocyte containing signet-ring *P. falciparum* trophozoites, including an accolade form positioned up against the inner surface of the erythrocyte membrane. **C,** Banana-shaped gametocyte unique to *P. falciparum*. **D,** Ameboid trophozoite characteristic of *Plasmodium vivax*. Both *P. vivax*– and *Plasmodium ovale*–infected erythrocytes exhibit Schüffner dots and tend to be enlarged compared with uninfected erythrocytes. **E,** *P. vivax* schizont. Mature *P. falciparum* parasites, by contrast, are rarely seen on blood smears because they sequester in the systemic microvasculature. **F,** *P. vivax* spherical gametocyte. **G,** *P. ovale* trophozoite. Note Schüffner dots and ovoid shapes of the infected erythrocyte. **H,** Characteristic band form trophozoite of *Plasmodium malariae*, containing intracellular pigment hemozoin. *(***A, B,** *and* **F** *from Centers for Disease Control and Prevention [CDC]: DPDx: laboratory identification of parasites of public health concern. Available at: http://www.dpd.cdc.gov/dpdx/.* **C, D, E, G,** *and* **H** *courtesy of David Wyler, Newton Centre, MA.)*

CLINICAL MANIFESTATIONS

Children and adults are asymptomatic during the initial phase of infection, the incubation period of malaria infection. The usual incubation periods are 9-14 days for *P. falciparum*, 12-17 days for *P. vivax*, 16-18 days for *P. ovale,* and 18-40 days for *P. malariae*. The incubation period can be as long as 6-12 mo for *P. vivax* and can also be prolonged for patients with partial immunity or incomplete chemoprophylaxis. A prodrome lasting 2-3 days is noted in some patients before parasites are detected in the blood. Prodromal symptoms include headache, fatigue, anorexia, myalgia, slight fever, and pain in the chest, abdomen, and joints.

The classic presentation of malaria is seldom noted with other infectious diseases and consists of **paroxysms** of fever alternating with periods of fatigue but otherwise relative wellness. Febrile paroxysms are characterized by high fever, sweats, and headache, as well as myalgia, back pain, abdominal pain, nausea, vomiting, diarrhea, pallor, and jaundice. Paroxysms coincide with the rupture of schizonts that occurs every 48 hr with *P. vivax* and *P. ovale,* resulting in fever spikes every other day. Rupture of schizonts occurs every 72 hr with *P. malariae*, resulting in fever spikes every third or fourth day. Periodicity is less apparent with *P. falciparum* and mixed infections and may not be apparent early on in infection, when parasite broods have not yet synchronized. Patients with primary infection, such as travelers from nonendemic regions, also may have irregular symptomatic episodes for 2-3 days before regular paroxysms begin. Children with malaria often lack typical paroxysms and have nonspecific symptoms, including fever (may be low-grade but is often greater than 40°C [104°F]), headache, drowsiness, anorexia, nausea, vomiting, and diarrhea. Distinctive physical signs may include splenomegaly (common), hepatomegaly, and pallor as a consequence of anemia. Typical laboratory findings include anemia, thrombocytopenia, and a normal or low leukocyte count. The erythrocyte sedimentation rate is often elevated.

P. falciparum is the most severe form of malaria and is associated with higher density parasitemia and a number of complications (Fig. 288-4). The most common serious complication is severe anemia, which also is associated with other malaria species. Serious complications that appear unique to *P. falciparum* include cerebral malaria, acute renal failure, respiratory distress from metabolic acidosis, algid malaria and bleeding diatheses (see "Complications of *Plasmodium falciparum* Malaria" below and Table 288-1). The diagnosis of *P. falciparum* malaria in a nonimmune individual constitutes a medical emergency. Severe complications and death can occur if appropriate therapy is not instituted promptly. In contrast to malaria caused by *P. ovale, P. vivax,* and *P. malariae,* which usually results in parasitemias of less than 2%, malaria caused by *P. falciparum* can be associated with parasitemia levels as high as 60%. The differences in parasitemia reflect the fact that *P. falciparum* infects both immature and mature erythrocytes, whereas *P. ovale* and *P. vivax* primarily infect immature erythrocytes and *P. malariae* infects only mature erythrocytes. Like *P. falciparum, P. knowlesi* has a 24 hr replication cycle and can also lead to very-high-density parasitemia.

P. vivax malaria has long been considered less severe than *P. falciparum* malaria, but recent reports suggest that in some areas of Indonesia it is as frequent a cause of severe disease and death as *P. falciparum*. Severe disease and death from *P. vivax* are usually a consequence of severe anemia and sometimes of splenic rupture. *P. ovale* malaria is the least-common type of malaria. It is similar to *P. vivax* malaria and commonly is found in conjunction with *P. falciparum* malaria. *P. malariae* is the mildest and most chronic of all malaria infections. Nephrotic syndrome is a rare complication of *P. malariae* infection that is not observed with any other human malaria species. Nephrotic syndrome associated with *P. malariae* infection is poorly responsive to steroids. Low-level, undetected *P. malariae* infection may be present for years and is sometimes unmasked by immunosuppression or physiologic stress such as splenectomy or corticosteroid treatment.

Recrudescence after a primary attack may occur from the survival of erythrocyte forms in the bloodstream. Long-term relapse is caused by release of merozoites from an exoerythrocytic source in the liver, which occurs with *P. vivax* and *P. ovale*, or from persistence within the

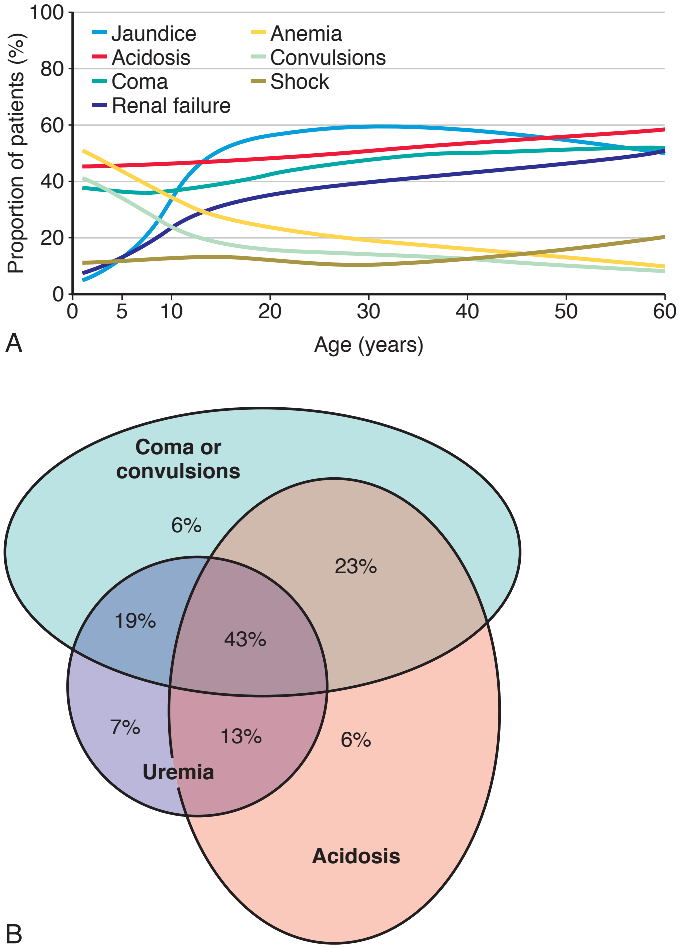

Figure 288-4 Manifestations of severe falciparum malaria by age **(A)** and mortality in children associated with central nervous system involvement, acidosis, and uremia **(B).** Data from 3,228 prospectively studied African children with severe falciparum malaria. Uremia here is defined as a blood urea nitrogen higher than 7.14 mmol/L. Surface areas denote the relative prevalence of the different severity signs, which frequently coexist. The percentages denote the observed mortality associated with the presenting signs. *(From White NJ, Pukrittayakamee S, Hien TT, et al: Malaria.* Lancet *383:723–735, 2014; based on data from von Seidlein L, Olaosebikan R, Hendriksen ICE, et al: Predicting the clinical outcome of severe falciparum malaria in African children: findings from a large randomized trial.* Clin Infect Dis *54:1080–1090, 2012.)*

Table 288-1	World Health Organization Criteria for Severe Malaria, 2000
Impaired consciousness	
Prostration	
Respiratory distress	
Multiple seizures	
Jaundice	
Hemoglobinuria	
Abnormal bleeding	
Severe anemia	
Circulatory collapse	
Pulmonary edema	

erythrocyte, which occurs with *P. malariae* and rarely with *P. falciparum*. A history of typical symptoms in a person more than 4 wk after return from an endemic area is therefore more likely to be *P. vivax, P. ovale,* or *P. malariae* infection than *P. falciparum* infection. In the most recent survey of malaria in the United States among individuals in whom a malaria species was identified, 48.6% of cases were caused by *P. falciparum,* 22.1% by *P. vivax,* 3.5% by *P. malariae,* and 2.5% by *P. ovale*. Ninety-four percent of *P. falciparum* infections were diagnosed within 30 days of arrival in the United States, and 99% within 90 days of arrival. In contrast, 50.7% of *P. vivax* cases occurred more than 30 days after arrival in the United States.

Congenital malaria is acquired from the mother prenatally or perinatally and is a serious problem in tropical areas but is rarely reported in the United States. In endemic areas, congenital malaria is an important cause of abortions, miscarriages, stillbirths, premature births, intrauterine growth retardation, and neonatal deaths. Congenital malaria usually occurs in the offspring of a nonimmune mother with *P. vivax* or *P. malariae* infection, although it can be observed with any of the human malaria species. The first sign or symptom most commonly occurs between 10 and 30 days of age (range: 14 hr to several months of age). Signs and symptoms include fever, restlessness, drowsiness, pallor, jaundice, poor feeding, vomiting, diarrhea, cyanosis, and hepatosplenomegaly. Malaria is often severe during pregnancy and may have an adverse effect on the fetus or neonate, resulting in intrauterine growth retardation and low birthweight, even in the absence of transmission from mother to child.

DIAGNOSIS

Any child who presents with fever or unexplained systemic illness and has traveled or resided in a malaria-endemic area within the previous year should be assumed to have life-threatening malaria until proven otherwise. Malaria should be considered regardless of the use of chemoprophylaxis. Important criteria that suggest *P. falciparum* malaria include symptoms occurring less than 1 mo after return from an endemic area, more than 2% parasitemia, ring forms with double chromatin dots, and erythrocytes infected with more than 1 parasite.

The diagnosis of malaria is established by identification of organisms on Giemsa-stained smears of peripheral blood (see Fig. 288-3) or by rapid immunochromatographic assay (rapid diagnostic test). Giemsa stain is superior to Wright stain or Leishman stain. Both thick and thin blood smears should be examined. The concentration of erythrocytes on a **thick smear** is 20-40 times that on a thin smear and is used to quickly scan large numbers of erythrocytes. The **thin smear** allows for positive identification of the malaria species and determination of the percentage of infected erythrocytes and is useful in following the response to therapy. Identification of the species is best made by an experienced microscopist and checked against color plates of the various *Plasmodium* species (see Fig. 288-3). Morphologically it is impossible to distinguish *P. knowlesi* from *P. malariae*, so polymerase chain reaction detection by a reference lab or the CDC is required. Although *P. falciparum* is most likely to be identified from blood just after a febrile paroxysm, the timing of the both thick and thin smears is less important than their being obtained several times a day over a period of 3 successive days. A single negative blood smear does not exclude malaria. Most symptomatic patients with malaria will have detectable parasites on thick blood smears within 48 hr. For nonimmune persons, symptoms typically occur 1-2 days before parasites are detectable on blood smear.

The BinaxNOW Malaria test is approved by the FDA for rapid diagnosis of malaria. This immunochromatographic test for *P. falciparum* histidine-rich protein (HRP2) and aldolase is approved for testing for *P. falciparum* and *P. vivax*. Aldolase is present in all 5 of the malaria species that infect humans. Thus, a positive result for *P. vivax* could be because of *P. ovale* or *P. malariae* infection. Sensitivity and specificity for *P. falciparum* (94-99% and 94-99%, respectively) and *P. vivax* (87-93% and 99%, respectively) are good, but sensitivity for *P. ovale* and *P. malariae* is lower. Sensitivity for *P. falciparum* decreases at lower levels of parasitemia, so microscopy is still advised in areas where expert microscopy is available. The test is simple to perform and can be done in the field or laboratory in 10 min. Polymerase chain reaction is even more sensitive than microscopy but is technically more complex. It is available in some reference laboratories, but the time delay in availability of results generally precludes its use for acute diagnosis of malaria.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of malaria is broad and includes viral infections such as influenza and hepatitis, sepsis, pneumonia, meningitis, encephalitis, endocarditis, gastroenteritis, pyelonephritis, babesiosis, brucellosis, leptospirosis, tuberculosis, relapsing fever, typhoid fever, yellow fever, viral hemorrhagic fevers, amebic liver abscess, Hodgkin disease, and collagen vascular disease.

TREATMENT

Physicians caring for patients with malaria or traveling to endemic areas need to be aware of current information regarding malaria because resistance to antimalarial drugs has complicated therapy and prophylaxis. The best source for such information is the CDC Malaria webpage (http://www.cdc.gov/malaria/diagnosis_treatment/treatment.hl), which provides up-to-date guidelines for malaria treatment, and an algorithm for an approach to malaria treatment (Fig. 288-5). In cases in which treatment is unclear or complex, the CDC Malaria Hotline, which is available to physicians 24 hr a day (770-488-7788 from 8:00 AM to 4:30 PM Eastern Standard Time [EST] and 770-488-7100 from 4:30 PM to 8:00 AM EST, and on weekends and holidays; ask the operator to page the person on call for the Malaria Epidemiology Branch), is an excellent resource.

Fever without an obvious cause in any patient who has left a *P. falciparum* endemic area within 30 days and is nonimmune should be considered a medical emergency. Thick and thin blood smears should be obtained immediately, and all children with symptoms of severe disease should be hospitalized. If blood films are negative, they should be repeated every few hours. If the patient is severely ill, antimalarial therapy should be initiated immediately. Outpatient therapy generally is not given to nonimmune children but may be considered in immune or semi-immune children who have low-level parasitemia (<1%), no evidence of complications defined by the World Health Organization, no vomiting, and a lack of toxic appearance; who are able to contact the physician or emergency department at any time; and in whom follow-up within 24 hr is assured.

Plasmodium Falciparum Malaria

Malarious regions considered chloroquine-sensitive include Central America west of the Panama Canal, Haiti, the Dominican Republic, and most of the Middle East except Iran, Oman, Saudi Arabia, and Yemen. The CDC website (http://www.cdc.gov/MALARIA/) should be consulted for updated information on chloroquine susceptibility in an area, and current treatment options. Individuals traveling from areas with chloroquine-susceptible *P. falciparum* can be treated with chloroquine if they do not have severe malaria. Malaria acquired in *P. falciparum* areas with chloroquine resistance or where there is any doubt about chloroquine sensitivity after conferring with the CDC should be treated with drugs other than chloroquine (Table 288-2). Trials in Asia and Africa have definitively proven that artesunate treatment of severe malaria is associated with decreased mortality when compared to quinine treatment. However, artesunate is still not FDA approved in the United States for treatment of malaria, or available outside of special request indications from the CDC, so intravenous quinidine gluconate remains first-line therapy for severe malaria in the United States (Table 288-2). Monotherapy with artesunate agents is discouraged because of the development of resistance and treatment failures. Nonetheless in endemic countries, artesunate derivatives in combination with other antimalarial agents have become the treatment of choice (Tables 288-3 and 288-4). Children with severe malaria should be admitted to the intensive care unit for monitoring of complications, plasma quinidine levels, and adverse effects during quinidine administration. During administration of quinidine, blood pressure monitoring for hypotension and cardiac monitoring for widening of the QRS

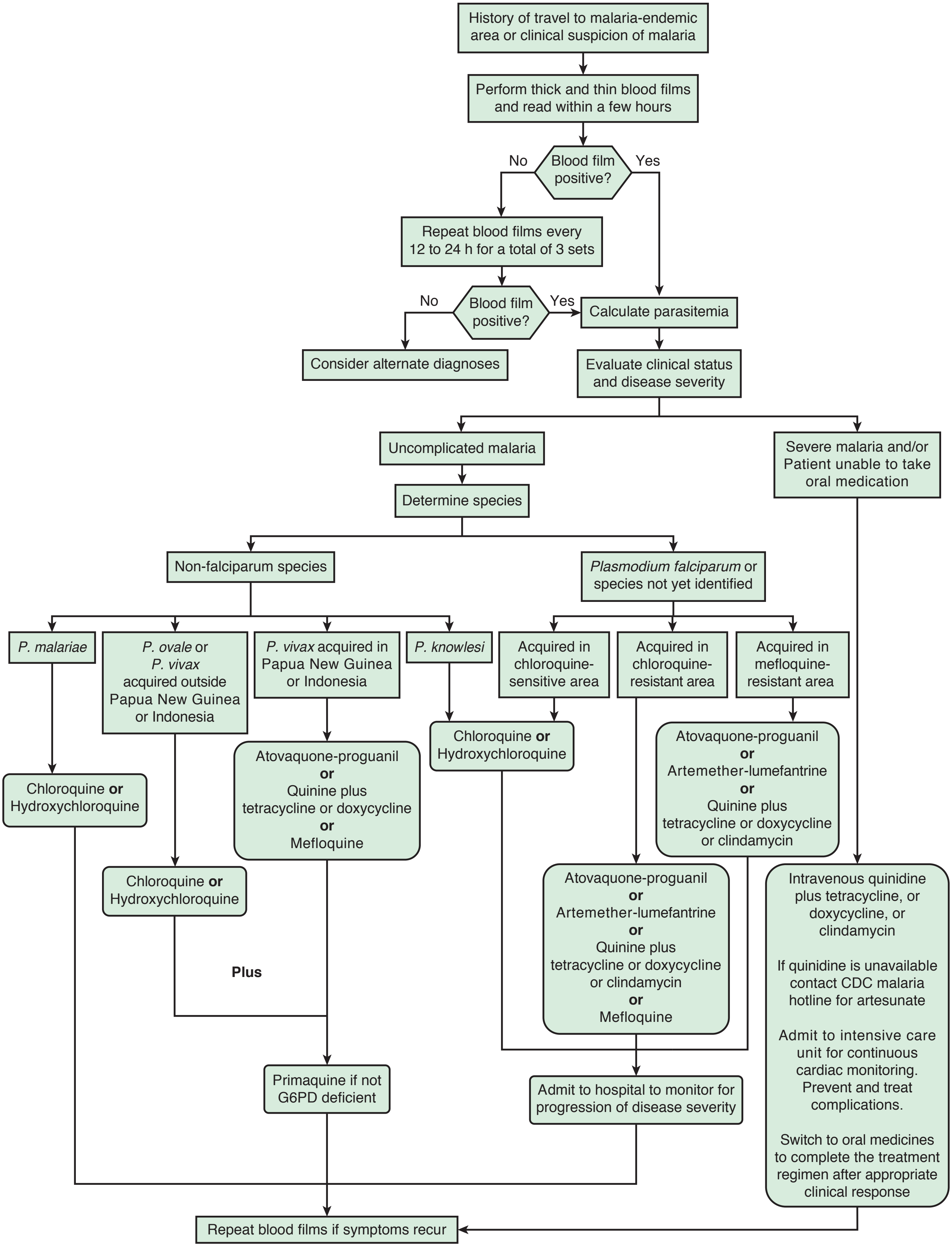

Figure 288-5 Algorithm for approach to patient with malaria in the United States. *(From Centers for Disease Control and Prevention [CDC]. Available at: http://www.cdc.gov/malaria/resources/pdf/algorithm.pdf)*

Table 288-2 CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States–Updated July 1, 2013)

(CDC Malaria Hotline: [770] 488-7788 or [855] 856-4713 toll-free Monday-Friday 9 AM to 5 PM EST; [770] 488-7100 after hours, weekends, and holidays)

CLINICAL DIAGNOSIS/ *PLASMODIUM* SPECIES	REGION INFECTION ACQUIRED	RECOMMENDED DRUG AND ADULT DOSE[1]	RECOMMENDED DRUG AND PEDIATRIC DOSE[1] PEDIATRIC DOSE SHOULD *NEVER* EXCEED ADULT DOSE
Uncomplicated malaria/ *P. falciparum* *or* Species not identified If "species not identified" is subsequently diagnosed as *P. vivax* or *P. ovale:* see *P. vivax* and *P. ovale* (below) regarding treatment with primaquine	Chloroquine-resistant or unknown resistance[2] (All malarious regions except those specified as chloroquine-sensitive listed in the box below)	A. Atovaquone-proguanil (Malarone)[3] Adult tab = 250 mg atovaquone/100 mg proguanil 4 adult tabs PO qd × 3 days	A. Atovaquone-proguanil (Malarone)[3] Adult tab = 250 mg atovaquone/100 mg proguanil Pediatric (ped) tab = 62.5 mg atovaquone/25 mg proguanil 5-8 kg: 2 ped tabs PO qd × 3 days 9-10 kg: 3 ped tabs PO qd × 3 days 11-20 kg: 1adult tab PO qd × 3 days 21-30 kg: 2 adult tabs PO qd × 3 days 31-40 kg: 3 adult tabs PO qd × 3 days > 40 kg: 4 adult tabs PO qd × 3 days
		B. Artemether-lumefantrine (Coartem)[3] 1 tablet = 20 mg artemether and 120 mg lumefantrine A 3 day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hr later, then 1 dose PO bid for the following 2 days 5-<15 kg: 1 tablet per dose 15-<25 kg: 2 tablets per dose 25-<35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose	
		C. Quinine sulfate plus 1 of the following: doxycycline, tetracycline, or clindamycin **Quinine sulfate:** 542 mg base (=650 mg salt)[4] PO tid × 3 or 7 days[5] **Doxycycline:** 100 mg PO bid × 7 days **Tetracycline:** 250 mg PO qid × 7 days **Clindamycin:** 20 mg base/kg/day PO divided tid × 7 days	C. Quinine sulfate[4] plus 1 of the following: doxycycline[6], tetracycline,[6] or clindamycin **Quinine sulfate:** 8.3 mg base/kg (=10 mg salt/kg) PO tid × 3 or 7 days[5] **Doxycycline:** 2.2 mg/kg PO every 12 hr × 7 days **Tetracycline:** 25 mg/kg/day PO divided qid × 7 days **Clindamycin:** 20 mg base/kg/day PO divided tid × 7 days
		D. Mefloquine (Lariam and generics)[7] 684 mg base (=750 mg salt) PO as initial dose, followed by 456 mg base (=500 mg salt) PO given 6-12 hr after initial dose Total dose = 1,250 mg salt	D. Mefloquine (Lariam and generics)[7] 13.7 mg base/kg (=15 mg salt/kg) PO as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) PO given 6-12 hr after initial dose. Total dose = 25 mg salt/kg
Uncomplicated malaria/ *P. falciparum* *or* Species not identified	Chloroquine-sensitive (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)	Chloroquine phosphate (Aralen and generics)[8] 600 mg base (=1,000 mg salt) PO immediately, followed by 300 mg base (=500 mg salt) PO at 6, 24, and 48 hr Total dose: 1,500 mg base (=2,500 mg salt) *or* Hydroxychloroquine (Plaquenil and generics) 620 mg base (=800 mg salt) PO immediately, followed by 310 mg base (=400 mg salt) PO at 6, 24, and 48 hr Total dose: 1,550 mg base (=2,000 mg salt)	Chloroquine phosphate (Aralen and generics)[8] 10 mg base/kg PO immediately, followed by 5 mg base/kg PO at 6, 24, and 48 hr Total dose: 25 mg base/kg *or* Hydroxychloroquine (Plaquenil and generics) 10 mg base/kg PO immediately, followed by 5 mg base/kg PO at 6, 24, and 48 hr Total dose: 25 mg base/kg

[1]If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use 1 of the other options instead.

[2]NOTE: There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum*. Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin.

[3]Take with food or whole milk. If patient vomits within 30 min of taking a dose, then patient should repeat the dose.

[4]U.S. manufactured quinine sulfate capsule is in a 324 mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult because of unavailability of noncapsule forms of quinine.

[5]For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.

[6]Doxycycline and tetracycline are not indicated for use in children younger than 8 yr old. For children younger than 8 yr old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children younger than 8 yr old with chloroquine-resistant *P. vivax*, mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.

[7]Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia as a consequence of drug resistance.

[8]When treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available, more convenient, or preferred.

Continued

Table 288-2 CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States–Updated July 1, 2013)—cont'd

CLINICAL DIAGNOSIS/ *PLASMODIUM* SPECIES	REGION INFECTION ACQUIRED	RECOMMENDED DRUG AND ADULT DOSE[1]	RECOMMENDED DRUG AND PEDIATRIC DOSE[1] PEDIATRIC DOSE SHOULD *NEVER* EXCEED ADULT DOSE
Uncomplicated malaria/*P. malariae* or *P. knowlesi*	All regions	**Chloroquine phosphate:**[8] treatment as above *or* **Hydroxychloroquine:** treatment as above	**Chloroquine phosphate:**[8] treatment as above *or* **Hydroxychloroquine:** treatment as above
Uncomplicated malaria/*P. vivax* or *P. ovale*	All regions Note: for suspected chloroquine-resistant *P. vivax,* see row below	Chloroquine phosphate[8] plus primaquine phosphate[9] **Chloroquine phosphate:** treatment as above **Primaquine phosphate:** 30 mg base PO qd × 14 days *or* Hydroxychloroquine plus primaquine phosphate[9] **Hydroxychloroquine:** treatment as above **Primaquine phosphate:** 30 mg base PO qd × 14 days	Chloroquine phosphate[8] plus primaquine phosphate[9] **Chloroquine phosphate:** treatment as above **Primaquine:** 0.5 mg base/kg PO qd × 14 days *or* Hydroxychloroquine plus primaquine phosphate[9] **Hydroxychloroquine:** treatment as above **Primaquine phosphate:** 0.5 mg base/kg PO qd × 14 days
Uncomplicated malaria/*P. vivax*	Chloroquine-resistant[10] (Papua New Guinea and Indonesia)	A. Quinine sulfate plus either doxycycline or tetracycline plus primaquine phosphate[9] **Quinine sulfate:** treatment as above **Doxycycline or tetracycline:** Treatment as above **Primaquine phosphate:** treatment as above B. Atovaquone-proguanil plus primaquine phosphate[9] **Atovaquone-proguanil:** treatment as above **Primaquine phosphate:** treatment as above C. Mefloquine plus primaquine phosphate[9] **Mefloquine:** treatment as above **Primaquine phosphate:** treatment as above	A. Quinine sulfate plus either doxycycline[6] or tetracycline[6] plus primaquine phosphate[9] **Quinine sulfate:** treatment as above **Doxycycline or tetracycline:** treatment as above **Primaquine phosphate:** treatment as above B. Atovaquone-proguanil plus primaquine phosphate[9] **Atovaquone-proguanil:** treatment as above **Primaquine phosphate:** treatment as above C. Mefloquine plus primaquine phosphate[9] **Mefloquine:** treatment as above **Primaquine phosphate:** treatment as above
Uncomplicated malaria: alternatives for pregnant women[11-13]	Chloroquine-sensitive (See uncomplicated malaria sections above for chloroquine-sensitive species by region)	**Chloroquine phosphate:** treatment as above *or* **Hydroxychloroquine:** treatment as above	Not applicable
	Chloroquine-resistant (See sections above for regions with chloroquine-resistant *P. falciparum and P. vivax*)	Quinine sulfate plus clindamycin **Quinine sulfate:** treatment as above **Clindamycin:** treatment as above *or* **Mefloquine:** treatment as above	Not applicable

[9]Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally 1 time per week for 8 wk; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.

[10]NOTE: There are 3 options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax*. High treatment failure rates as a result of chloroquine-resistant *P. vivax* are well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P. vivax* are also documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant *P. vivax* infections, options A, B, and C are equally recommended.

[11]For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

[12]Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the 1st trimester because of a lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.

[13]For *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

Table 288-2 CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States–Updated July 1, 2013)—cont'd

CLINICAL DIAGNOSIS/ *PLASMODIUM* SPECIES	REGION INFECTION ACQUIRED	RECOMMENDED DRUG AND ADULT DOSE[1]	RECOMMENDED DRUG AND PEDIATRIC DOSE[1] PEDIATRIC DOSE SHOULD *NEVER* EXCEED ADULT DOSE
Severe malaria[14-16]	All regions	Quinidine gluconate[14] plus 1 of the following: doxycycline, tetracycline, or clindamycin **Quinidine gluconate:** 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1-2 hr, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hr. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 hr, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hr every 8 hr, starting 8 hr after the loading dose (see package insert). Once parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinidine/quinine course = 7 days in Southeast Asia; =3 days in Africa or South America **Doxycycline:** treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 hr and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days **Tetracycline:** treatment as above **Clindamycin:** treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hr. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days *Investigational new drug (contact CDC for information):* Artesunate followed by 1 of the following: atovaquone-proguanil (Malarone), doxycycline (clindamycin in pregnant women), or mefloquine	Quinidine gluconate[14] plus one of the following: doxycycline[4], tetracycline[4], or clindamycin **Quinidine gluconate:** same mg/kg dosing and recommendations as for adults **Doxycycline:** treatment as above. If patient not able to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 hr and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication. For children >45 kg, use same dosing as for adults. For IV use, avoid rapid administration. Treatment course = 7 days **Tetracycline:** treatment as above **Clindamycin:** treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hr. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. *Investigational new drug (contact CDC for information):* **Artesunate followed by 1 of the following: atovaquone-proguanil (Malarone), clindamycin, or mefloquine**

[14]Persons with a positive blood smear *or* history of recent possible exposure and no other recognized pathology who have 1 or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of >5%) are considered to have manifestations of more severe disease. Severe malaria is most often caused by *P. falciparum*.

[15]Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 hr or if they have received mefloquine within the preceding 12 hr. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion.

[16]Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy.

From the Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf

complex or lengthening of the QTc interval should be performed continuously, and blood glucose monitoring for hypoglycemia should be performed periodically. Cardiac adverse events may require temporary discontinuation of the drug or slowing of the intravenous infusion. Parenteral therapy should be continued until the parasitemia is less than 1%, which usually occurs within 48 hr, and the patient can tolerate oral medication. Quinidine gluconate (United States) or quinine sulfate (other countries) is administered for a total of 3 days for malaria acquired in Africa or South America and for 7 days for malaria acquired in Southeast Asia. Doxycycline, tetracycline, or clindamycin is then given orally to complete the therapeutic course (see Tables 288-2 and 288-4). Although there are no data to support the use of sequential quinine and atovaquone-proguanil, the difficulty of maintaining compliance with oral quinine has led many clinicians to complete oral therapy after IV quinine with a complete course of atovaquone-proguanil.

Parenterally administered artesunate or artemether can be substituted for quinine for treatment of severe malaria in children and adults (see Table 288-2). Artesunate is now available on special request from the CDC (770-488-7788) for treatment of severe malaria, but empirical therapy should not be delayed while awaiting delivery of artesunate. Children who do receive artesunate can follow up with

Table 288-3 Treatment of Uncomplicated Malaria

	REGIMENS
All *Plasmodium falciparum* malaria	Artemether-lumefantrine 1.5 mg/kg-9 mg/kg twice daily for 3 days with food or milk Artesunate 4 mg/kg daily for 3 days and mefloquine 25 mg base per kg (8 mg/kg/daily for 3 days*)[†] Dihydroartemisinin-piperaquine 2.5 mg/kg-20 mg/kg daily for 3 days
Sensitive *P. falciparum* malaria	Artesunate 4 mg/kg daily for 3 days and a single dose of sulfadoxine-pyrimethamine 25 mg/kg-1.25 mg/kg Artesunate 4 mg/kg and amodiaquine* 10 mg base per kg daily for 3 days
Chloroquine-sensitive *Plasmodium vivax*[‡], *Plasmodium malariae*[‡], *Plasmodium ovale*[‡], *Plasmodium knowlesi*[‡]	Chloroquine 10 mg base per kg immediately, followed by 10 mg/kg at 24 hr and 5 mg/kg at 48 hr

*World Health Organization prequalified fixed dose formulations are preferable to loose tablets. A taste masked dispersible pediatric tablet formulation of artemether-lumefantrine is available.

[†]High failure rates with artesunate-mefloquine have been reported on the Thailand–Myanmar border.

[‡]Any of the artemisinin combination treatments can be given except for artesunate-sulfadoxine-pyrimethamine where *P. vivax* is resistant. Patients with *P. vivax* or *P. ovale* infections should also be given a 14 day course of primaquine to eradicate hypnozoites (radical cure). However, severe glucose-6-phosphate dehydrogenase deficiency is a contraindication because a 14 day course of primaquine can cause severe hemolytic anemia in this group.

From White NJ, Pukrittayakamee S, Hien TT, et al: Malaria. Lancet *383:723–732, 2014.*

Table 288-4 Treatment of Severe Malaria in Adults and Children

- Artesunate 2·4 mg/kg by intravenous or intramuscular* injection, followed by 2.4 mg/kg at 12 hr and 24 hr; continue injection once daily if necessary[†]
- Artemether 3.2 mg/kg by immediate intramuscular* injection, followed by 1.6 mg/kg daily
- Quinine dihydrochloride 20 mg salt per kg infused during 4 hr, followed by maintenance of 10 mg salt per kg infused during 2-8 hr every 8 hr (can also be given by intramuscular injection* when diluted to 60-100 mg/mL)

Artesunate is the treatment of choice. Artemether should only be used if artesunate is unavailable. Quinine dihydrochloride should be given only when artesunate and artemether are unavailable.

*Intramuscular injections should be given to the anterior thigh.

[†]Young children with severe malaria have lower exposure to artesunate and its main biologically active metabolite dihydroartemisinin than do older children and adults. Revised dose regimens to ensure similar drug exposures have been suggested.

From White NJ, Pukrittayakamee S, Hien TT, et al: Malaria. Lancet *383:723–732, 2014.*

artemether-lumefantrine oral therapy. Oral and rectal administration of these artemisinin-based antimalarial drugs is effective in treatment of malaria, but such formulations are not indicated or approved in the United States.

Patients from areas with chloroquine-resistant *P. falciparum* who have mild infection, parasitemia less than 1%, no evidence of complications, and no vomiting and who can take oral medication can be considered for oral therapy with either oral atovaquone-proguanil (Malarone), oral artemether-lumefantrine (Coartem), or oral quinine plus doxycycline, tetracycline, or clindamycin (see Table 288-2). However, as noted in Figure 288-5, all children with clinical malaria, even those started on oral therapy, should be admitted to evaluate for progression of disease. Coartem is approved by the FDA for the treatment of uncomplicated malaria and is an appealing choice because it is highly effective and well-tolerated. Pediatric dosing is well established, but pediatric dispersible tablets, available in some other countries, are not yet available in the United States. Coartem should not be used in children with known QT interval prolongation. Patients who acquire *P. falciparum* in Thailand, Myanmar, or Cambodia should receive 7 days of quinine therapy if they are prescribed quinine. Mefloquine is contraindicated for use in patients with a known hypersensitivity to mefloquine or with a history of epilepsy or severe psychiatric disorders. Mefloquine is not recommended for persons with cardiac conduction abnormalities but may be administered to persons concurrently receiving β-blockers if they have no underlying arrhythmia. Quinidine or quinine may exacerbate the adverse effects of mefloquine and should generally not be given to patients who have received mefloquine unless there are no other alternatives.

Patients with uncomplicated *P. falciparum* malaria acquired in areas without chloroquine resistance should be treated with oral chloroquine phosphate. If the parasite count does not drop rapidly (within 24-48 hr) and become negative after 4 days, chloroquine resistance should be assumed and the patient started on a different antimalarial regimen.

Supportive therapy is very important and may include red blood cell transfusion(s) to maintain the hematocrit at more than 20%, exchange transfusion in *P. falciparum* malaria with parasitemia greater than 10% and evidence of severe complications (e.g., severe malarial anemia, cerebral malaria), supplemental oxygen and ventilatory support for pulmonary edema or cerebral malaria, careful intravenous rehydration for severe malaria, intravenous glucose for hypoglycemia, anticonvulsants for cerebral malaria with seizures, and dialysis for renal failure. Exchange transfusion is thought to be useful in severe malaria with high-level parasitemia, but no randomized clinical trial has ever been conducted to assess its utility, and some groups, including the Centers for Disease Control and Prevention, no longer advocate its use for severe malaria. Corticosteroids are not recommended for cerebral malaria.

Plasmodium Vivax, P. Ovale, P. Malariae, or P. Knowlesi Malaria

Uncomplicated infection caused by *P. vivax*, *P. ovale*, or *P. malariae* can usually be treated with chloroquine (see Table 288-2). Chloroquine remains the initial drug of choice for *P. vivax* malaria in the absence of good data on drug alternatives. Indications for using alternative therapy are worsening or new symptoms, persistent *P. vivax* parasitemia after 72 hr, and possibly acquisition of infection in Oceania or India. Patients with *P. vivax* or *P. ovale* malaria should also be given primaquine once daily for 14 days to prevent relapse from the hypnozoite forms that remain dormant in the liver. Some strains may require 2 courses of primaquine. Testing for glucose-6-phosphate dehydrogenase deficiency must be performed before initiation of primaquine, because it can cause hemolytic anemia in such patients. Unfortunately, no alternatives to primaquine currently exist for eradication of the hypnozoite forms of *P. vivax* or *P. ovale*. Patients with any type of malaria must be monitored for possible recrudescence with repeat blood smears at the end of therapy because recrudescence may occur more than 90 days after therapy with low-grade resistant organisms. If vomiting precludes oral administration, chloroquine can be given by nasogastric tube. Based on limited evidence, chloroquine plus sulfadoxine-pyrimethamine should be used to treat *P. knowlesi* infections. For cases of severe malaria caused by any *Plasmodium* species, intravenous quinidine or quinine along with a second drug (clindamycin, doxycycline, or tetracycline) should be used, as for *P. falciparum*. Patients with any type of malaria must be monitored for possible recrudescence with repeat blood smears at the end of therapy, because recrudescence may occur more than 90 days after therapy with low-grade resistant organisms. For children living in endemic areas, mothers should be encouraged to seek evaluation for malaria any time the child has a fever, as many clinics in endemic areas now have accurate rapid diagnostic tests available. If such children are severely ill, they should be given the same therapy as nonimmune children.

COMPLICATIONS OF *PLASMODIUM FALCIPARUM* MALARIA

The World Health Organization has identified 10 complications of *P. falciparum* malaria that define severe malaria (see Table 288-1 and Fig. 288-4). The most common complications in children are severe anemia, impaired consciousness (including cerebral malaria), respiratory distress (a result of metabolic acidosis), multiple seizures, prostration, and jaundice.

Severe malarial anemia (hemoglobin level <5 g/dL) is the most common severe complication of malaria in children and is the leading cause of anemia leading to hospital admission in African children. Anemia is associated with hemolysis, but removal of infected erythrocytes by the spleen and impairment of erythropoiesis likely play a greater role than hemolysis in the pathogenesis of severe malarial anemia. The primary treatment for severe malarial anemia is blood transfusion. With appropriate and timely treatment, severe malarial anemia usually has a relatively low mortality (~1%).

Cerebral malaria is defined as the presence of coma in a child with *P. falciparum* parasitemia and an absence of other reasons for coma. Children with altered mental status who are not in coma fall into the larger category of impaired consciousness. Cerebral malaria is most common in children in areas of midlevel transmission and in adolescents or adults in areas of very low transmission. It is less frequently seen in areas of very high transmission. Cerebral malaria often develops after the patient has been ill for several days but may develop precipitously. Cerebral malaria has a fatality rate of 15-20% and is associated with long-term cognitive impairment in children. Repeated seizures are frequent in children with cerebral malaria. Hypoglycemia is common, but children with true cerebral malaria fail to arouse from coma even after receiving a dextrose infusion that normalizes their glucose level. Physical findings may include high fever, seizures, muscular twitching, rhythmic movement of the head or extremities, contracted or unequal pupils, retinal hemorrhages, hemiplegia, absent or exaggerated deep tendon reflexes, and a positive Babinski sign. Lumbar puncture reveals increased pressure and cerebrospinal fluid protein with no pleocytosis and normal glucose and protein concentrations. Studies suggest that funduscopic findings of malaria retinopathy (retinal hemorrhages, peripheral whitening, macular whitening, vessel changes) are specific for cerebral malaria and may identify children in whom malaria is the reason for coma, as opposed to children with coma and incidental *P. falciparum* parasitemia. Treatment of cerebral malaria other than antimalarial medications is largely supportive and includes evaluation of and treatment of seizures and hypoglycemia. Although increased intracranial pressure has been documented in some children with cerebral malaria, treatment with mannitol and corticosteroids has not improved outcomes in these children.

Respiratory distress is a poor prognostic indicator in severe malaria and appears to be caused by metabolic acidosis rather than intrinsic pulmonary disease. To date, no successful interventions for treatment of metabolic acidosis in children with severe malaria have been described, but trials of dichloroacetate treatment and fluid expansion are ongoing.

Seizures are a common complication of severe malaria, particularly cerebral malaria. Benzodiazepines are first-line therapy for seizures, and intrarectal diazepam has been used successfully in children with malaria and seizures. Many seizures resolve with a single dose of diazepam. For persistent seizures, phenobarbital or phenytoin are the standard medications used. Phenytoin may be preferred for seizure treatment, particularly in hospitals or clinics where ventilatory support is not available. However, no comparative trials of the 2 drugs have been performed, and phenytoin is considerably more expensive than phenobarbital. There are currently no drugs recommended for seizure prophylaxis in children with severe malaria. Phenobarbital prophylaxis decreased seizure activity but increased mortality in 1 major study of children with severe malaria, probably because of the respiratory depression associated with phenobarbital that may have been exacerbated by benzodiazepine therapy.

Hypoglycemia is a complication of malaria that is more common in children, pregnant women, and patients receiving quinine therapy. Patients may have a decreased level of consciousness that can be confused with cerebral malaria. Any child with impaired consciousness and malaria should have a glucose level checked, and if glucometers are not available, an empirical bolus of dextrose should be given. Hypoglycemia is associated with increased mortality and neurologic sequelae.

Circulatory collapse (**algid malaria**) is a rare complication that manifests as hypotension, hypothermia, rapid weak pulse, shallow breathing, pallor, and vascular collapse. Death may occur within hours. Severe malaria is occasionally accompanied by bacteremia, which may have been the cause of some of the cases previously referred to as algid malaria. Any child with severe malaria and hypotension or hypoperfusion should have a blood culture obtained and be treated empirically for bacterial sepsis.

Long-term cognitive impairment occurs in 25% of children with cerebral malaria and also occurs in children with repeated episodes of uncomplicated disease. Prevention of attacks in these children improves educational attainment.

Tropical splenomegaly syndrome is a chronic complication of *P. falciparum* malaria in which massive splenomegaly persists after treatment of acute infection. The syndrome is characterized by marked splenomegaly, hepatomegaly, anemia, and an elevated immunoglobulin M level. Tropical splenomegaly syndrome is thought to be caused by an impaired immune response to *P. falciparum* antigens. Prolonged antimalarial prophylaxis (for at least several years) is required to treat this syndrome if the child remains in a malaria endemic area. Spleen size gradually regresses on antimalarial prophylaxis but often increases again if prophylaxis is stopped.

Other complications in children include jaundice, which is associated with a worse outcome, and prostration. Prostration is defined as the inability to sit, stand, or eat without support, in the absence of impaired consciousness. Prostration also has been associated with increased mortality in some studies, but the pathophysiology of this process is not well understood. Uncommon complications include hemoglobinuria, abnormal bleeding, pulmonary edema, and renal failure. These are uncommon complications in children with severe malaria and are more common in adults, particularly pulmonary edema and renal failure. Although frank renal failure is uncommon in children, uremia (when defined as an elevation in blood urea nitrogen levels) is not, particularly in older children. It remains unclear whether BUN elevation reflects a degree of renal failure or primarily dehydration.

PREVENTION

Malaria prevention consists of reducing exposure to infected mosquitoes and chemoprophylaxis. The most accurate and current information on areas in the world where malaria risk and drug resistance exist can be obtained by contacting local and state health departments or the CDC or consulting *Health Information for International Travel*, which is published by the U.S. Public Health Service.

Travelers to endemic areas should remain in well-screened areas from dusk to dawn, when the risk for transmission is highest. They should sleep under permethrin-treated mosquito netting and spray insecticides indoors at sundown. During the day the travelers should wear clothing that covers the arms and legs, with trousers tucked into shoes or boots. Mosquito repellent should be applied to thin clothing and exposed areas of the skin, with applications repeated every 1-2 hr. A child should not be taken outside from dusk to dawn, but if at risk for exposure, a solution with 25-35% *N,N*-diethyl-3-methylbenzamide (DEET) (not greater than 40%) should be applied to exposed areas except for the eyes, mouth, or hands. Hands are excluded because they are often placed in the mouth. DEET should then be washed off as soon as the child comes back inside. The American Academy of Pediatrics recommends that DEET solutions be avoided in children less than 2 mo of age. Adverse reactions to DEET include rashes, toxic encephalopathy, and seizures, but these reactions occur almost exclusively with inappropriate application of high concentrations of DEET. Picaridin is an alternative and sometimes better tolerated repellent. Even with these precautions, a child should be taken to a physician immediately if the child develops illness when traveling to a malarious area.

Table 288-5 Chemoprophylaxis of Malaria for Children

AREA	DRUG	DOSAGE (ORAL)	ADVANTAGES	DISADVANTAGES	BEST USE
Chloroquine-resistant area	Mefloquine[*,†]	<10 kg: 4.6 mg base (5 mg salt)/kg/wk 10-19 kg: $\frac{1}{4}$ tab/wk 20-30 kg: $\frac{1}{2}$ tab/wk 31-45 kg: $\frac{3}{4}$ tab/wk >45 kg: 1 tab/wk (228 mg base)	Once weekly dosing	Bitter taste No pediatric formulation Side effects of sleep disturbance, vivid dreams	Children going to malaria endemic area for 4 wk or more Children unlikely to take daily medication
	Doxycycline[‡]	2 mg/kg daily (max 100 mg)	Inexpensive	Cannot give to children <8 yr Daily dosing Must take with food or causes stomach upset Photosensitivity	Children going to area for <4 wk who cannot take or cannot obtain atovaquone-proguanil
	Atovaquone/proguanil[§] (Malarone)	Pediatric tabs: 62.5 mg atovaquone/25 mg proguanil Adult tabs: 250 mg proguanil/100 mg proguanil 5-8 kg: pediatric tab once daily (off-label) 9-10 kg: pediatric tab once daily (off-label) 11-20 kg: 1 pediatric tab once daily 21-30 kg: 2 pediatric tabs once daily 31-40 kg: 3 pediatric tabs once daily >40 kg: 1 adult tab once daily	Pediatric formulation Generally well tolerated	Daily dosing Expensive Can cause stomach upset	Children going to malaria endemic area for <4 wk
Chloroquine-susceptible area	Chloroquine phosphate	5 mg base/kg/wk (max: 300 mg base)	Once weekly dosing Inexpensive Generally well tolerated	Bitter taste No pediatric formulation	Best medication for children traveling to areas with *Plasmodium falciparum* or *Plasmodium vivax* that is chloroquine susceptible
	Drugs used for chloroquine-resistant areas can also be used in chloroquine-susceptible areas				

*Chloroquine and mefloquine should be started 1-2 wk prior to departure and continued for 4 wk after last exposure.
[†]Mefloquine resistance exists in western Cambodia and along the Thailand–Cambodia and Thailand–Myanmar borders. Travelers to these areas should take doxycycline or atovaquone-proguanil. See text for precautions about mefloquine use.
[‡]Doxycycline should be started 1-2 days prior to departure and continued for 4 wk after last exposure. Do not use in children younger than 8 yr of age or in pregnant women.
[§]Atovaquone/proguanil (Malarone) should be started 1-2 days prior to departure and continued for 7 days after last exposure. Should be taken with food or a milky drink. Not recommended in pregnant women, children weighing <5 kg, and women breastfeeding infants who weigh <5 kg. Contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min).

Chemoprophylaxis is necessary for all visitors to and residents of the tropics who have not lived there since infancy, including children of all ages (Table 288-5). Healthcare providers should consult the latest information on resistance patterns before prescribing prophylaxis for their patients. Chloroquine is given in the few remaining areas of the world free of chloroquine-resistant malaria strains. In areas where chloroquine-resistant *P. falciparum* exists, atovaquone-proguanil, mefloquine, or doxycycline may be given as chemoprophylaxis. Atovaquone-proguanil is generally recommended for shorter trips (up to 2 wk) because it must be taken daily. Pediatric tablets are available and are generally well tolerated, although the taste is sometimes unpleasant to very young children. For longer trips, mefloquine is preferred, as it is given only once a week. Mefloquine does not have a pediatric formulation and has an unpleasant taste that usually requires that the cut tablet be "disguised" in another food, such as chocolate syrup. Mefloquine should not be given to children if they have a known hypersensitivity to mefloquine, are receiving cardiotropic drugs, have a history of convulsive or certain psychiatric disorders, or travel to an area where mefloquine resistance exists (the borders of Thailand with Myanmar and Cambodia, the western provinces of Cambodia, and the eastern states of Myanmar). Atovaquone-proguanil is started 1-2 days before travel, and mefloquine is started 2 wk before travel. It is important that these doses are given, both to allow therapeutic levels of the drugs to be achieved and to be sure that the drugs are tolerated. Doxycycline is an alternative for children older than 8 yr of age. It must be given daily and should be given with food. Side effects of doxycycline include photosensitivity and vaginal yeast infections. Primaquine is a daily prophylaxis option for children who cannot tolerate any of the other options, but it should be provided in consultation with a travel medicine specialist if needed, and all children should be checked for glucose-6-phosphate dehydrogenase deficiency prior to prescribing this medication, which is contraindicated in children with glucose-6-phosphate dehydrogenase deficiency. Provision of medication can be considered in individuals who refuse to take prophylaxis or will be in very remote areas without accessible medical care. Provision of medication for self-treatment of malaria should be done in

consultation with a travel medicine specialist, and the medication provided should be different than that used for prophylaxis.

A number of other efforts are currently underway to prevent malaria in malaria endemic countries. Some have been highly successful, leading to a significant decrease in malaria incidence in many countries in Africa, Asia, and South America in the last decade. These interventions include the use of insecticide-treated bed nets (which have decreased all-cause mortality in children under 5 yr of age in several highly malaria endemic areas by ~20%), indoor residual spraying with long-lasting insecticides, and the use of artemisinin-combination therapy for first-line malaria treatment. The first malaria vaccine to have any degree of efficacy is the RTS,S vaccine, which is based on the circumsporozoite protein of *P. falciparum*. In various clinical trials, this vaccine has shown an efficacy of 17-56% against uncomplicated malaria and 38-50% against severe malaria in young children in malaria endemic areas for periods as long as 48 mo after vaccination. The vaccine is in large phase III trials. Given the relatively low efficacy of this vaccine, it is unclear if it will be implemented as part of a combination strategy that includes the already successful interventions mentioned. Numerous other vaccines are also in current clinical trials, and it is hoped that future vaccines will improve upon the efficacy of the RTS,S vaccine. There is currently no vaccine with sufficient efficacy to be considered for prevention of malaria in travelers.

Intermittent prevention treatment during infancy has been particularly successful in reducing the incidence of malaria in sub Saharan Africa. Sulfadoxine-pyrimethamine given to infants at the second and third doses of the diphtheria, tetanus toxoid, and pertussis and measles vaccinations is safe and relatively effective. Intermittent prevention treatment has also been given to pregnant women; 3 doses of sulfadoxine-pyrimethamine have resulted in a reduction of low birthweight infants.

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Chapter 289

Babesiosis *(Babesia)*

Peter J. Krause

Babesiosis is an emerging disease caused by intraerythrocytic protozoa that are transmitted by hard body (ixodid) ticks. The clinical manifestations of babesiosis range from subclinical illness to fulminant disease resulting in death.

ETIOLOGY

There are more than 100 species of *Babesia* that infect a wide variety of wild and domestic animals throughout the world. Only a few of these species have been reported to infect humans, including *Babesia microti* (and *B. microti*-like species), *Babesia divergens* (and *B. divergens*-like species), *Babesia duncani*, *Babesia venatorum*, and KO1.

EPIDEMIOLOGY

Babesia are transmitted to humans from vertebrate reservoir hosts by the *Ixodes* species of ticks. *B. microti* is the most common cause of babesiosis in humans. The primary reservoir for *B. microti* is the white-footed mouse, *Peromyscus leucopus*, and the primary vector is *Ixodes scapularis*, the black legged tick. *I. scapularis* ticks also transmit the causative agents of Lyme disease, human granulocytic anaplasmosis, *Borrelia miyamotoi*, and Powassan virus and may simultaneously transmit 2 or more microorganisms. White-tailed deer (*Odocoileus virginianus*) serve as the host on which adult ticks most abundantly feed but are incompetent reservoirs. Babesiosis may be transmitted through blood transfusion, and *B. microti* is the most frequently reported transfusion-transmitted microbial agent in the United States. Rarely, babesiosis is acquired by transplacental transmission.

Human *B. microti* infection is endemic (most cases occurring in June, July, and August) in the northeastern and upper midwestern United States and has been sporadically reported in China, Taiwan, and Europe (Fig. 289-1). Human babesial infections caused by the cattle parasite, *B. divergens*, have been described in many countries in Europe, while *B. divergens*-like infections have been described in Kentucky, Missouri, and Washington State. *B. duncani* infects humans along the northern Pacific coast. *B. venatorum* infects people in Austria, Germany, China, and Italy. Human babesiosis cases also have been documented in Africa, Australia, and South America.

In certain sites and in certain years of high transmission, babesiosis constitutes a significant public health burden. On Nantucket Island, case rates as high as 280 per 100,000 population have been recorded, placing the community burden of disease in a category with gonorrhea as "moderately common." Comparable incidence rates have been described elsewhere on the southern New England coast.

PATHOGENESIS

The pathogenesis of human babesiosis is not well understood. Cytoadherence and lysis of infected erythrocytes and excessive production of proinflammatory cytokines such as tumor necrosis factor and interleukin-1 may account for most of the clinical manifestations and complications of the disease. The spleen has an important role in clearing parasitemia as do T and B cells, macrophages, polymorphonuclear leukocytes, cytokines, antibody, and complement.

CLINICAL MANIFESTATIONS

The clinical severity of babesiosis ranges from subclinical infection to fulminating disease and death. In clinically apparent cases, symptoms of babesiosis begin after an incubation period of 1-4 wk from the beginning of tick feeding or 1 wk to 6 mo after transfusion. Typical symptoms in moderate to severe infection include intermittent fever to as high as 40.9°C (105.6°F) accompanied by any combination of fatigue, chills, sweats, myalgias, headache, and anorexia. Less commonly noted are emotional lability, hyperesthesia, headache, sore throat, abdominal pain, conjunctival injection, photophobia, weight loss, and nonproductive cough. The findings on physical examination generally are minimal, often consisting only of fever. Splenomegaly, hepatomegaly, or both are noted occasionally, but rash seldom is reported. Abnormal laboratory findings include moderately severe hemolytic anemia, elevated reticulocyte count, thrombocytopenia, proteinuria, and elevated bilirubin, blood urea nitrogen, and creatinine levels. The leukocyte count is normal to slightly decreased, with increased bands. Babesiosis symptoms usually last for 1 to 2 weeks, with prolonged recovery of up to a year or more in severe cases. Complications include respiratory failure, disseminated intravascular coagulation, congestive heart failure, renal failure, liver failure, and coma. A prolonged relapsing course of illness has been described in highly immunocompromised hosts, such as those with cancer, with asplenia, and on treatment with immunosuppressive agents, even though they received multiple courses of antibabesial therapy. About a quarter of these patients died, while the remainder were cured after an average of 3 mo (range: 1-24 mo) of antibabesial therapy.

Risk factors for severe disease include anatomic or functional asplenia, concomitant malignancy or HIV infection, immunosuppressive drugs, age of more than 50 yr, acquisition of infection through blood transfusion, or infection with *B. divergens* or *B. duncani*. Concurrent babesiosis and Lyme disease occurs in 3-11% of patients experiencing Lyme disease depending upon location in southern New England and the northern Midwest. Such coinfection results in more severe acute Lyme disease illness. Moderate to severe babesiosis may occur in children, but infection generally is less severe than in adults. About half of infected children are asymptomatic or experience minimal symptoms. Neonates may develop severe illness and usually are infected from blood transfusion.

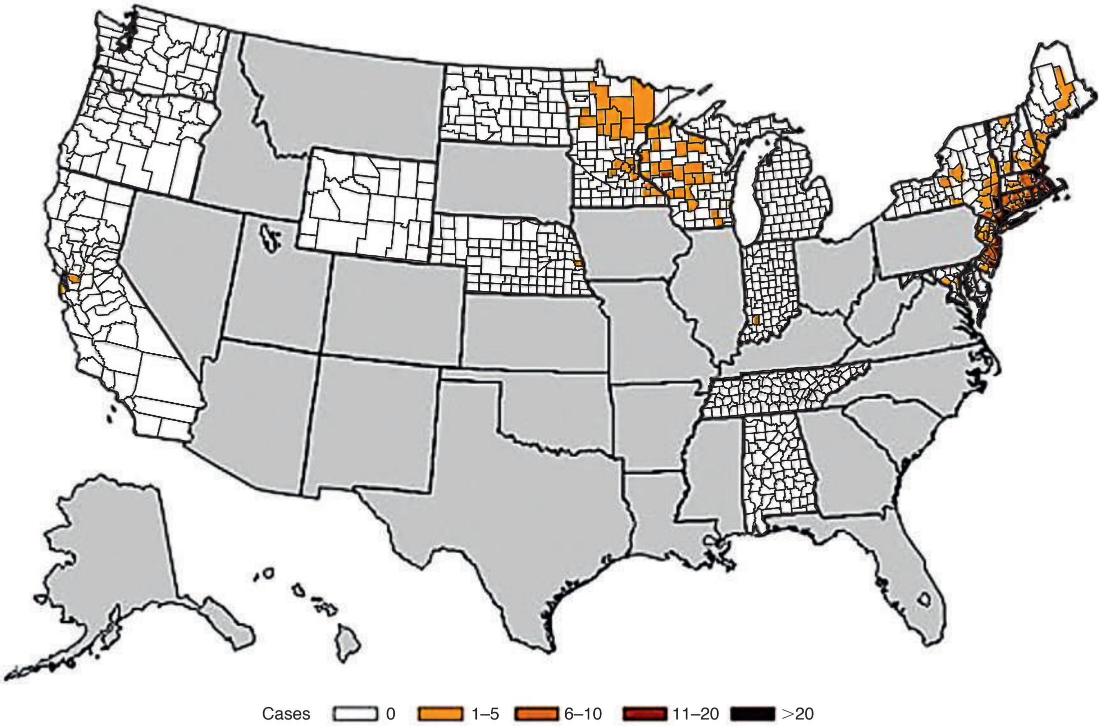

N = 1,750; county of residence was unknown for 12 of the 1,762 patients. Cases are mapped to the patients' county of residence, which was notnecessarily where they became infected.

For 2013, 22 of the 27 states that conducted surveillance for babesiosis reported at least 1 case: California, Connecticut, Delaware, Indiana, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Nebraska, New Hampshire, New Jersey, New York, North Dakota, Rhode Island, South Carolina, South Dakota, Texas, Vermont, Washington, and Wisconsin. Five (5) states reported 0 cases: Alabama, Oregon, Tennessee, West Virginia, and Wyoming. In 2013, babesiosis was not a reportable disease in the gray states, and health departments in those states did not notify CDC of cases.

Figure 289-1 Number of reported cases of babesiosis, by county of residence–27 states, 2013. *(Adapted from Centers for Disease Control and Prevention, Data and Statistics, Babesiosis: http://www.cdc.gov/parasites/babesiosis/data-statistics/index.html.)*

DIAGNOSIS

The diagnosis of babesiosis should be considered in any patient with an unexplained febrile illness who has resided in or traveled to an endemic area within the previous 2 mo or received a blood transfusion within the previous 6 mo. The diagnosis is confirmed by microscopic identification of parasites on blood smear or amplifiable Babesia DNA in blood and antibacterial antibody in serum. Babesia are identified on blood smear using Giemsa or Wright staining. Parasitemia may be exceedingly low, especially early in the course of illness. Thick blood smears may be examined, but the organisms may be mistaken for stain precipitate or iron inclusion bodies. The polymerase chain reaction is a sensitive and specific test for detection of *Babesia* DNA. Subinoculation of blood into hamsters or gerbils and in vitro cultivation are too specialized for all but the most experienced laboratories. Serologic testing is useful, particularly for diagnosing *B. microti* infection. The indirect immunofluorescence serologic assay for both immunoglobulin G and immunoglobulin M antibodies is sensitive and specific and can help confirm a diagnosis of babesiosis when parasites are scarce or undetectable. The diagnosis of active babesial infection based on seropositivity alone is unreliable.

TREATMENT

The combination of clindamycin (7-10 mg/kg given every 6-8 hr [up to a maximum of 600 mg per dose] intravenously or orally) and quinine (8 mg/kg given every 8 hr [up to a maximum of 650 mg per dose] orally) for 7-10 days was the first effective therapeutic combination for the treatment of babesiosis and remains the treatment of choice for severe disease. Adverse reactions are common, however, especially tinnitus and abdominal distress. The combination of atovaquone (20 mg/kg every 12 hr [up to a maximum of 750 mg per dose]) and azithromycin (10 mg/kg per day once per day on day 1 [up to a maximum of 500 mg per dose] and 5 mg/kg once per day [up to a maximum of 250 mg per dose] thereafter orally) for 7-10 days is as effective as clindamycin and quinine but has fewer adverse effects. Combination atovaquone and azithromycin has been used successfully to treat babesiosis in infants and should be considered for initial use in children experiencing mild to moderate infection. Treatment failure with clindamycin and quinine and with atovaquone and azithromycin may occur in highly immunocompromised hosts. Consultation with an infectious diseases expert is recommended in these cases. Exchange blood transfusion can decrease parasitemia rapidly and remove toxic by-products of infection. It should be considered for all patients experiencing severe babesiosis.

PROGNOSIS

Moderate to severe disease is frequently observed in some highly endemic areas. The case fatality rate was estimated at 5% in a retrospective study of 136 New York cases but may be as high as 21% in immunocompromised hosts. Immunity is sometimes incomplete with low-level asymptomatic parasitemia persisting for as long as 26 mo after symptoms have resolved or with relapsing symptomatic disease in immunocompromised hosts.

PREVENTION

Prevention of babesiosis can be accomplished by avoiding areas where ticks, deer, and mice are known to thrive. Use of clothing that covers the lower part of the body and that is sprayed or impregnated with diethyltoluamide (DEET), dimethyl phthalate, or permethrin (Permanone) is recommended for those who travel in the foliage of endemic areas. A search for ticks on people and pets should be carried out and the ticks removed using tweezers. Prospective blood donors with a history of babesiosis are excluded from giving blood to prevent transfusion-related cases.

Bibliography is available at Expert Consult.

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Chapter 290

Toxoplasmosis (*Toxoplasma gondii*)

Rima Mcleod, Christine VanTubbergen, and Kenneth M. Boyer

Toxoplasma gondii, an obligate intracellular protozoan, is acquired perorally, transplacentally, or, rarely, parenterally in laboratory accidents; by transfusion; or from a transplanted organ. In immunologically normal children, acute acquired infection may be asymptomatic, cause lymphadenopathy, or affect almost any organ. Once acquired, latent encysted organisms persist in the host throughout life. In immunocompromised persons either initial acquisition or recrudescence of latent organisms often causes signs or symptoms related to the central nervous system (CNS) and can result in systemic disease in bone marrow transplant recipients. If untreated, congenital infection often causes disease either perinatally or later in life, most frequently chorioretinitis and CNS lesions. Other manifestations, such as intrauterine growth retardation, prematurity, being small for gestational age, cognitive and motor deficits, fever, lymphadenopathy, rash, hearing loss, pneumonitis, hepatitis, thrombocytopenia, and cerebrospinal fluid (CSF) inflammatory changes such as pleocytosis, elevated CSF protein, and low CSF glucose, may also occur. Congenital toxoplasmosis in infants with HIV infection may be fulminant.

ETIOLOGY

T. gondii is a coccidian protozoan that multiplies only in living cells. The tachyzoites are oval or crescent-like, measuring 2-4 × 4-7 µm. Tissue cysts, which are 10-100 µm in diameter, may contain thousands of parasites, and will remain in tissues, especially the CNS and skeletal and heart muscle, for the life of the host. *Toxoplasma* can multiply in all tissues of mammals and birds.

Newly infected cats and other Felidae species excrete infectious *Toxoplasma* oocysts in their feces. *Toxoplasma* organisms are transmitted to cats by ingestion of infected meat containing encysted bradyzoites or by ingestion of oocysts excreted by other recently infected cats. The parasites then multiply through schizogonic and gametogonic cycles in the distal ileal epithelium of the cat intestine. Oocysts containing 2 sporocysts are excreted, and, under proper conditions of temperature and moisture, each sporocyst matures into 4 sporozoites. For approximately 2 wk the cat excretes 10^5-10^7 oocysts/day, which may retain their viability for longer than 1 yr in a suitable environment. Oocysts sporulate 1-5 days after excretion and are then infectious. Oocysts are killed by drying or boiling but not exposure to bleach. Oocysts have been isolated from soil and sand frequented by cats, and outbreaks associated with contaminated food and water have been reported. Oocysts and tissue cysts are sources of animal and human infections (Fig. 290-1). There are genetically distinct types of *T. gondii* that have different virulence for mice (and perhaps for humans) and form different numbers of cysts in the brains of outbred mice. In the United States, there are 4 predominant clonal lineages called types I, II, III, and IV (haplogroup XII) in addition to atypical, recombinant types. Virulence differs based on parasite genetics. There is 1 predominant clonal type in France, Austria, and Poland, and nonarchetypal parasites in Brazil, Guyana, French Guiana, and Central America.

EPIDEMIOLOGY

Toxoplasma infection is ubiquitous in animals and is one of the most common latent infections of humans throughout the world. Incidence varies considerably among people and animals in different geographic areas. In many areas of the world, approximately 3-35% of pork, 7-60% of lamb, and 0-9% of beef contain *T. gondii* organisms. Significant antibody titers are detected in 50-80% of residents of some localities, such as France, Brazil, and Central America, and in <5% in other areas. There is a higher prevalence of infection in warmer, more humid climates. Non-II genetic type parasites are more common in mothers of congenitally infected infants in warm, moist southern climates, in rural areas with lower socioeconomic status, and in places with Hispanic ethnicity in the United States.

Human infection is usually acquired orally by eating undercooked or raw meat that contains cysts or food or other material contaminated with oocysts from acutely infected cats. Freezing meat to −20°C (−4°F) or heating meat to 66°C (150.8°F) renders the cysts noninfectious. Outbreaks of acute acquired infection have occurred in families, at social gatherings, and in restaurants where people have consumed the same infected food. *Toxoplasma* organisms are not known to be transmitted from person to person except for transplacental infection from mother to fetus and, rarely, by organ transplantation or transfusion.

Seronegative transplant recipients who receive an organ or bone marrow from seropositive donors have experienced life-threatening illness requiring therapy. Seropositive recipients may have increased serologic titers without associated disease. Laboratory accidents have resulted in infections, including fatalities.

Congenital Toxoplasmosis

Transmission to the fetus usually follows acquisition of primary infection by an immunologically normal pregnant woman during gestation. Congenital transmission from mothers infected before pregnancy is extremely rare except for immunocompromised women who are chronically infected. The incidence of congenital infection in the United States ranges from 1 in 1,000 to 1 in 8,000 live births. The incidence of infection among pregnant women depends on the general risk for infection in the specific locale and the proportion of the population that has not been infected previously.

PATHOGENESIS

T. gondii is acquired by children and adults from ingesting food that contains cysts or that is contaminated with oocysts from acutely infected cats. Oocysts also may be transported to food by flies and cockroaches or be carried on the fur of dogs. When the organism is ingested, bradyzoites are released from cysts or sporozoites from oocysts. The organisms enter gastrointestinal cells where they multiply, rupture cells, infect contiguous cells, enter the lymphatics, and disseminate hematogenously throughout the body. Tachyzoites proliferate, producing necrotic foci surrounded by a cellular reaction. With development of a normal immune response that is both humoral and cell mediated, tachyzoites disappear from tissues. In immunocompromised persons and also some apparently immunocompetent persons, acute infection progresses and may cause potentially lethal disease, including pneumonitis, myocarditis, or encephalitis.

Alterations of T-lymphocyte populations during acute *T. gondii* infection are common and include lymphocytosis, increased CD8 count, and decreased CD4:CD8 ratio. Depletion of CD4 cells in patients with AIDS may contribute to severe manifestations of toxoplasmosis. Characteristic lymph node changes include reactive follicular hyperplasia with irregular clusters of epithelioid histiocytes that encroach on and blur margins of germinal centers, and focal distention of sinuses with monocytoid cells.

Cysts form as early as 7 days after infection and remain for the life of the host. During latent infection they produce little or no inflammatory response but can cause recrudescent disease in immunocompromised persons. Recrudescent chorioretinitis occurs in children with postnatal infection and in older children and adults with congenital infection. Host and parasite genetics influence outcome.

Congenital Toxoplasmosis

When a mother acquires infection during gestation, organisms may disseminate hematogenously to the placenta. Infection may be transmitted to the fetus transplacentally or during vaginal delivery. Of

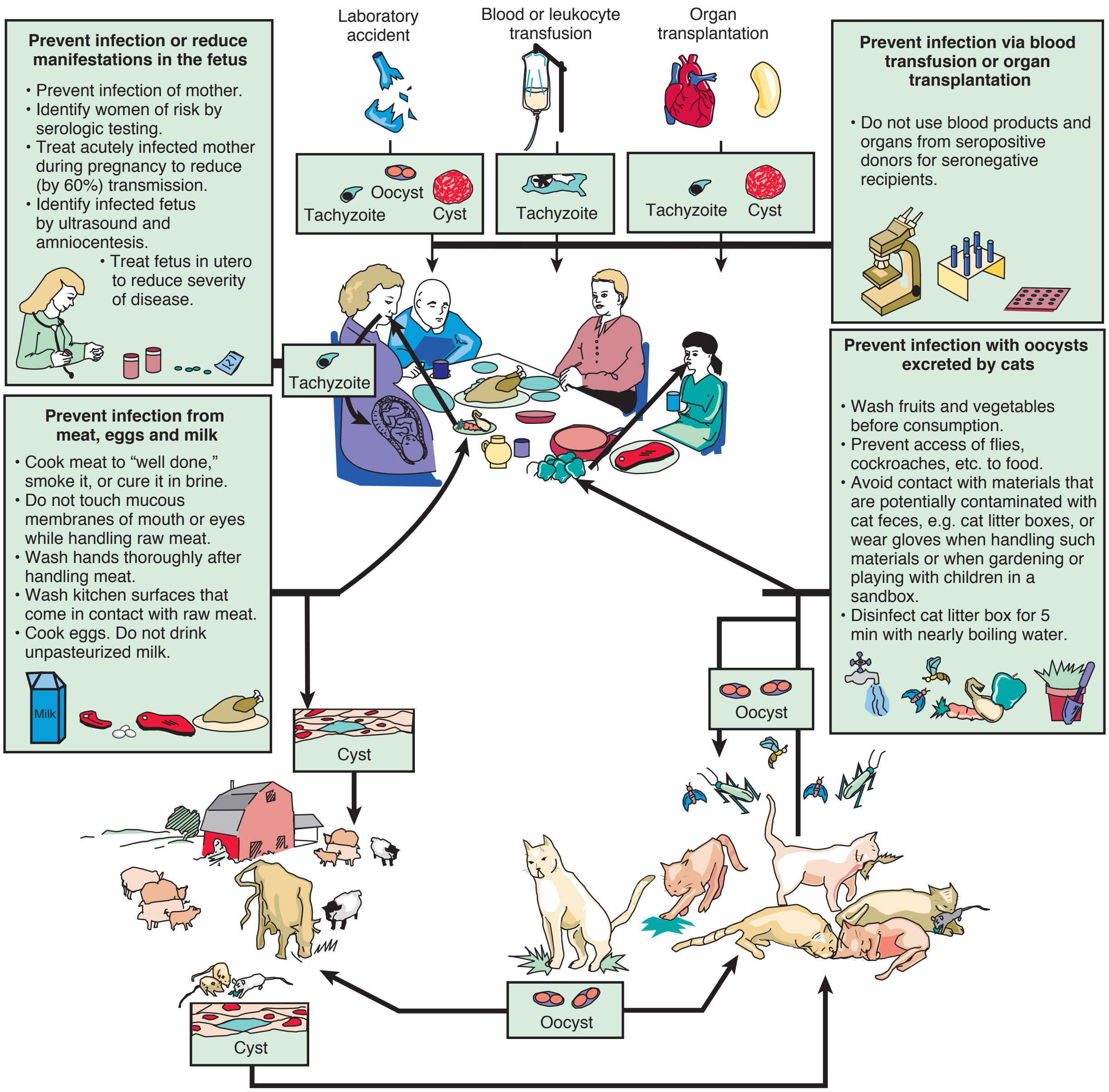

Figure 290-1 Life cycle of *Toxoplasma gondii* and prevention of toxoplasmosis by interruption of transmission to humans.

untreated maternal infections acquired in the 1st trimester, approximately 17% of fetuses are infected, usually with severe disease. Of untreated maternal infection acquired in the 3rd trimester, approximately 65% of fetuses are infected, usually with disease that is more mild or inapparent at birth. These different rates of transmission and outcomes are most likely related to placental blood flow, virulence, inoculum of *T. gondii,* and immunologic capacity of the mother and fetus to limit parasitemia.

Examination of the placenta of infected newborns may reveal chronic inflammation and cysts. Tachyzoites can be seen with Wright or Giemsa stains but are best demonstrated with immunoperoxidase technique. Tissue cysts stain well with periodic acid–Schiff and silver stains as well as with the immunoperoxidase technique. Gross or microscopic areas of necrosis may be present in many tissues, especially the CNS, choroid and retina, heart, lungs, skeletal muscle, liver, and spleen. Areas of calcification occur in the brain.

Almost all congenitally infected individuals who are not treated manifest signs or symptoms of infection, such as chorioretinitis, by adolescence. Some severely involved infants with congenital infection appear to have *Toxoplasma* antigen–specific cell-mediated anergy, which may be important in the pathogenesis of disease.

CLINICAL MANIFESTATIONS

Manifestations of primary infection with *T. gondii* are highly variable and are influenced primarily by host immunocompetence. There may be no signs or symptoms or severe disease. Reactivation of previously asymptomatic congenital toxoplasmosis usually manifests as ocular toxoplasmosis.

Acquired Toxoplasmosis

Immunocompetent children who acquire infection postnatally generally do not have clinically recognizable symptoms. When clinical manifestations are apparent, they may include almost any combination of fever, stiff neck, myalgia, arthralgia, maculopapular rash that spares the palms and soles, localized or generalized lymphadenopathy, hepatomegaly, hepatitis, reactive lymphocytosis, meningitis, brain abscess, encephalitis, confusion, malaise, pneumonia, polymyositis, pericarditis, pericardial effusion, and myocarditis. Chorioretinitis is usually

unilateral and is estimated to occur in approximately 1% of cases in the United States. Approximately 10% of mothers of congenitally infected infants also have eye lesions. Acquired chorioretinal lesions cannot be distinguished from congenital infection based on their appearance. In some areas of Brazil, 80% of the population is infected and, of these, 20% have retinal involvement. Ocular symptoms may be present for a few days only or may persist for many months. The most common manifestation of acute acquired toxoplasmosis is enlargement of 1 or a few cervical lymph nodes. Cases of *Toxoplasma* lymphadenopathy can resemble infectious mononucleosis, lymphoma, or other lymphadenopathies (see Chapter 490). In the pectoral area in older girls and women, enlarged nodes may be confused with breast neoplasms. Mediastinal, mesenteric, and retroperitoneal lymph nodes may be involved. Involvement of intraabdominal lymph nodes may be associated with fever, mimicking appendicitis. Nodes may be tender but do not suppurate. Lymphadenopathy may wax and wane for as long as 1-2 yr. However, almost all patients with lymphadenopathy recover spontaneously without antimicrobial therapy. Significant organ involvement in immunologically normal persons is uncommon, although some individuals have suffered significant morbidity, including rare cases of encephalitis, brain abscesses, hepatitis, myocarditis, pericarditis, and polymyositis. In persons acquiring *T. gondii* in Guyana and along Amazon tributaries, a severe form of multivisceral involvement with fever has occurred.

Ocular Toxoplasmosis

In the United States and Western Europe, *T. gondii* is estimated to cause 35% of cases of chorioretinitis (Fig. 290-2). In Brazil, *T. gondii* retinal lesions are common. Clinical manifestations include blurred vision, visual floaters, photophobia, epiphora, and, with macular involvement, loss of central vision. Ocular findings of congenital toxoplasmosis also include strabismus, microphthalmia, microcornea, cataracts, anisometropia, nystagmus, glaucoma, optic neuritis, and optic atrophy. Episodic recurrences are common, but precipitating factors have not been defined. Recurrent, active disease occurs most commonly at school-entry age and during adolescence. Anecdotally, stress or trauma seems to precipitate symptoms. Recurrences are most common closest to the time of acquisition of infection, and treatment leads to resolution of activity.

Immunocompromised Persons

Disseminated *T. gondii* infection among older children who are immunocompromised by AIDS, malignancy, cytotoxic therapy, corticosteroids, or immunosuppressive drugs given for organ transplantation involves the CNS in 50% of cases and may also involve the heart, lungs, and gastrointestinal tract. Stem cell transplant recipients present a special problem, because active infection is difficult to diagnose serologically. After transplantation, *T. gondii*-specific antibody levels may remain the same, increase, or decrease, and can even become undetectable. Toxoplasmosis in transplantation patients almost always results from transplantation from a seropositive donor to a seronegative recipient. Active infection is often fulminant and rapidly fatal without treatment.

Congenital *T. gondii* infection in infants with HIV infection is rare and can be a severe and fulminant disease with substantial CNS involvement. Alternatively, it may be more indolent in presentation, with focal neurologic deficits or systemic manifestations such as pneumonitis occurring with CD4 depletion.

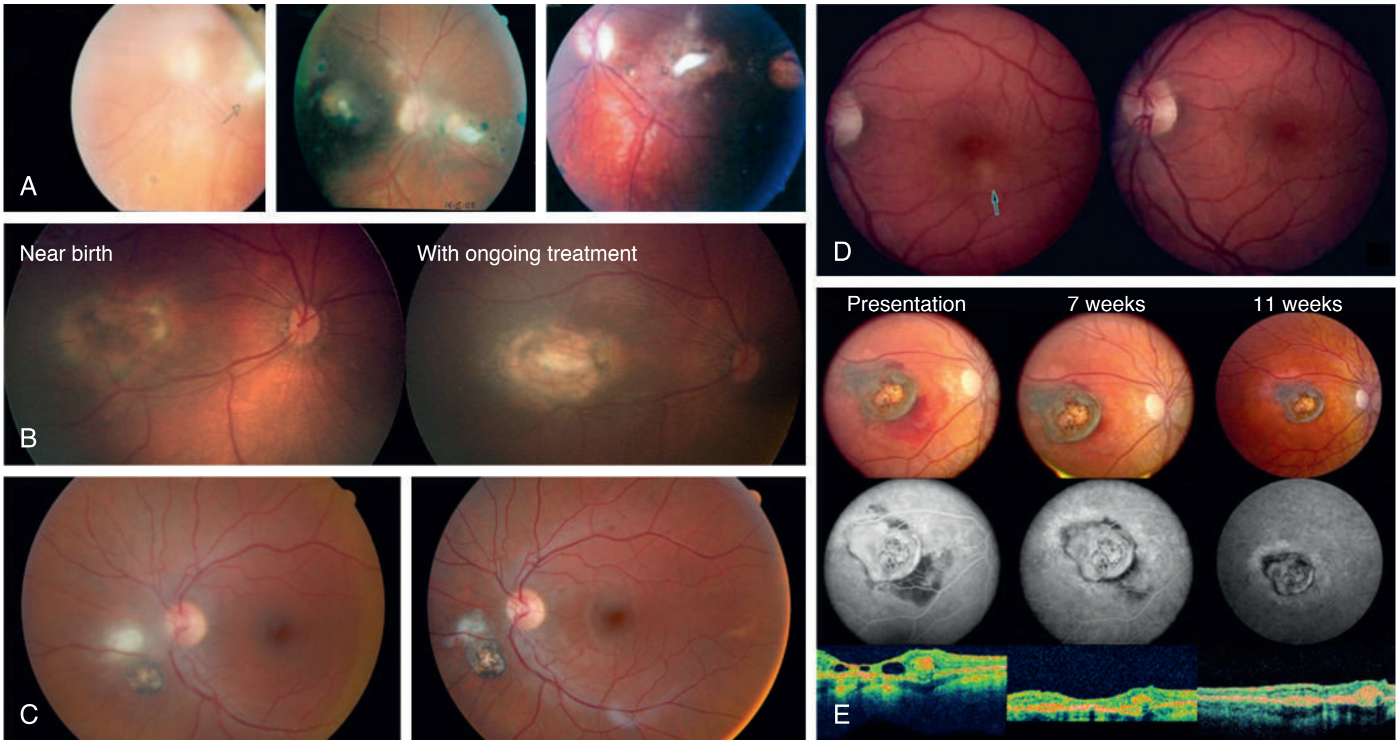

Figure 290-2 Toxoplasmic chorioretinitis. **A,** Retinal photographs of a child with severe vitreitis that is less intense than the classic "headlight in fog" appearance *(left)*. Resolving vitreitis caused by underlying active lesion *(middle)*. Resolved healed lesion without vitreitis *(right)*. **B,** Retina photographs for a newborn infant with active vitreitis (*left,* labeled "near birth") with clearing of vitreitis and marked, but not complete, resolution of activity of the lesion 3 wk later (*right,* labeled "with ongoing treatment"). **C,** Retinal photographs of a child showing an active lesion at presentation *(left)*, and scarred lesion *(right)*. **D,** Retinal photographs showing an active retinal lesion before treatment *(left)* and a completely resolved normal appearing retina within 1 mo of initiating treatment *(right)*. **E,** Example of active choroidal neovascular membranes (CNVMs) in a child. Fundus photographs *(top row)*, fluorescein angiogram (FA; *middle row*), and ocular coherence tomography (OCT; *bottom row*) of a child at presentation *(first column)*, 7 wk after first ranibizumab (Lucentis, antibody to VEGF) injection *(second column)*, and 11 wk after first ranibizumab injection *(third column)*. (***A** to **D** adapted from Delair E, Latkany P, Noble AG, et al: Clinical manifestations of ocular toxoplasmosis,* Ocul Immunol Inflamm *19:91–102, 2011;* ***E** adapted from Benevento JD, Jager RD, Noble AG, et al: Toxoplasmosis-associated neovascular lesions treated successfully with ranibizumab and antiparasitic therapy,* Arch Ophthalmol *126:1152–1156, 2008.)*

From 25-50% of persons with *T. gondii* antibodies and **HIV infection** without antiretroviral treatment eventually experience toxoplasmic encephalitis, which is fatal if not treated. Highly active antiretroviral therapy and trimethoprim-sulfamethoxazole prophylaxis have diminished the incidence of toxoplasmosis in patients with HIV infection, but toxoplasmic encephalitis remains a presenting manifestation in adult patients with AIDS. Typical findings include fever, headache, altered mental status, psychosis, cognitive impairment, seizures, and focal neurologic defects, including hemiparesis, aphasia, ataxia, visual field loss, cranial nerve palsies, and dysmetria or movement disorders. In adult patients with AIDS, toxoplasmic retinal lesions are often large with diffuse necrosis and contain many organisms but little inflammatory cellular infiltrate. Diagnosis of presumptive toxoplasmic encephalitis based on neuroradiologic studies in patients with AIDS necessitates a prompt therapeutic trial of medications effective against *T. gondii.* Clear clinical improvement within 7-14 days and improvement of neuroradiologic findings within 3 wk makes the presumptive diagnosis almost certain.

Congenital Toxoplasmosis

Congenital toxoplasmosis usually occurs when a woman acquires primary infection while pregnant. Most often, maternal infection is asymptomatic or without specific symptoms or signs. As with other adults with acute toxoplasmosis, lymphadenopathy is the most common symptom.

In monozygotic twins the clinical pattern of involvement is most often similar, whereas in dizygotic twins the manifestations often differ, including cases of congenital infection in only 1 twin. The major histocompatibility complex class II gene DQ3 appears to be more frequent among HIV-infected persons seropositive for *T. gondii* who develop toxoplasmic encephalitis, and in children with congenital toxoplasmosis who develop hydrocephalus. These findings suggest that the presence of HLA-DQ3 is a risk factor for severity of toxoplasmosis. Other allelic variants of genes, including *COL2A*, *ABC4R*, *P2X7R*, *NALP1*, *TLR9*, and *ERAAP*, are also associated with susceptibility.

Congenital infection may present as a mild or severe neonatal disease. It may also present with sequelae or relapse of a previously undiagnosed and untreated infection later in infancy or even later in life. There is a wide variety of manifestations of congenital infection, ranging from hydrops fetalis and perinatal death to small size for gestational age, prematurity, peripheral retinal scars, persistent jaundice, mild thrombocytopenia, CSF pleocytosis, and the characteristic triad of chorioretinitis, hydrocephalus, and cerebral calcifications. More than 50% of congenitally infected infants are considered normal in the perinatal period, but almost all such children develop ocular involvement later in life if they are not treated during infancy. Neurologic signs such as convulsions, setting-sun sign with downward gaze, and hydrocephalus with increased head circumference may be associated with substantial cerebral damage or with relatively mild inflammation obstructing the aqueduct of Sylvius. If affected infants are treated and shunted promptly, signs and symptoms may resolve and development may be normal.

The spectrum and frequency of neonatal manifestations of 210 newborns with congenital *Toxoplasma* infection identified by a serologic screening program of pregnant women were described in 1984. In this study, 10% had severe congenital toxoplasmosis with CNS involvement, eye lesions, and general systemic manifestations; 34% had mild involvement with normal clinical examination results other than retinal scars or isolated intracranial calcifications; and 55% had no detectable manifestations. These numbers represent an underestimation of the incidence of severe congenital infection for several reasons: the most-severe cases, including most of those individuals who died, were not referred; therapeutic abortion sometimes was performed when acute acquired infection of the mother was diagnosed early during pregnancy; in utero spiramycin therapy prevented or diminished the severity of infection; only 13 of the 210 congenitally infected newborns had brain CT, and only 77% of these 210 infants had a CSF examination. Routine newborn examinations often yield normal findings for congenitally infected infants, but more careful evaluations may

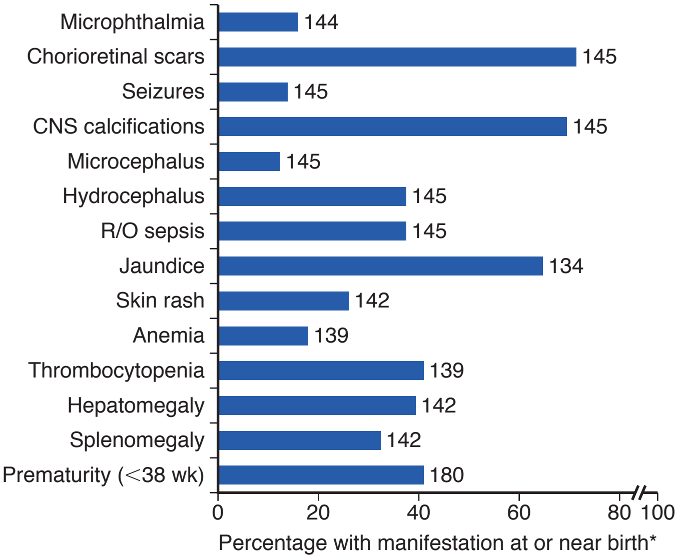

Figure 290-3 Manifestations at presentation, National Collaborative Chicago-Based Congenital Toxoplasmosis Study (NCCCTS) (1981-2009). *Infants diagnosed with congenital toxoplasmosis in the newborn period and referred to the NCCCTS during the first yr of life. Number in parenthesis represents number of infants with this manifestation and is based on information in birth records; R/O, rule out sepsis. Sample size dependent on available birth records/diagnoses at birth. *(Adapted from McLeod R, Boyer KM, Lee D, et al: Prematurity and severity are associated with* Toxoplasma gondii *alleles [NCCCTS, 1981-2009],* Clin Infect Dis *54:1595-1605, 2012.)*

reveal significant abnormalities. In a 2012 analysis of the National Collaborative Chicago-Based Congenital Toxoplasmosis Study (NCCCTS) (1981-2009) data, it was found that 72% of children at or near birth had chorioretinal scars, 70% had CNS calcifications, 12% had microcephalus, 37% had hydrocephalus, 41% had thrombocytopenia, 39% had hepatomegaly, 32% had splenomegaly, and 41% were born prematurely (Fig. 290-3). In 1 study of 28 infants identified by a universal state-mandated serologic screening program for *T. gondii*–specific immunoglobulin (Ig) M, 26 had normal findings on routine newborn examination but 14 had significant abnormalities detected with more careful evaluation. The abnormalities included retinal scars (7 infants), active chorioretinitis (3 infants), and CNS abnormalities (8 infants). In Fiocruz, Belo Horizonte, Brazil, infection is common, occurring in 1 in 600 live births. Half of these infected infants have active chorioretinitis at birth. When the infection is acquired in utero and the fetus is treated by treatment of the pregnant woman with pyrimethamine, sulfadiazine, and leucovorin, signs and symptoms in the infant may be prevented. The newborn infant may appear normal with no CSF abnormalities and no brain or eye disease. In utero treatment initiated rapidly results in a reduction of ocular and neurologic sequelae.

There is also a wide spectrum of symptoms of untreated congenital toxoplasmosis that presents later in the 1st yr of life (Table 290-1). More than 80% of these children have IQ scores of <70, and many have convulsions and severely impaired vision.

SYSTEMIC SIGNS

From 25% to >50% of infants with clinically apparent disease at birth are born prematurely. Parasite clonal types other than type II are more often associated with prematurity and more-severe disease. Intrauterine growth retardation, low Apgar scores, and temperature instability are common. Other manifestations may include lymphadenopathy, hepatosplenomegaly, myocarditis, pneumonitis, nephrotic syndrome, vomiting, diarrhea, and feeding problems. Bands of metaphyseal lucency and irregularity of the line of provisional calcification at the epiphyseal plate may occur without periosteal reaction in the ribs, femurs, and vertebrae. Congenital toxoplasmosis may be confused with erythroblastosis fetalis resulting from isosensitization, although

Table 290-1 Signs and Symptoms Occurring Before Diagnosis or During the Course of Untreated Acute Congenital Toxoplasmosis in 152 Infants (A) and in 101 of These Same Children After They Had Been Followed 4 Yr or More (B)

SIGNS AND SYMPTOMS	Frequency of Occurrence in Patients with "Neurologic" Disease*	"Generalized" Disease†
A. INFANTS	**108 PATIENTS (%)**	**44 PATIENTS (%)**
Chorioretinitis	102 (94)	29 (66)
Abnormal cerebrospinal fluid	59 (55)	37 (84)
Anemia	55 (51)	34 (77)
Convulsions	54 (50)	8 (18)
Intracranial calcification	54 (50)	2 (4)
Jaundice	31 (29)	35 (80)
Hydrocephalus	30 (28)	0 (0)
Fever	27 (25)	34 (77)
Splenomegaly	23 (21)	40 (90)
Lymphadenopathy	18 (17)	30 (68)
Hepatomegaly	18 (17)	34 (77)
Vomiting	17 (16)	21 (48)
Microcephalus	14 (13)	0 (0)
Diarrhea	7 (6)	11 (25)
Cataracts	5 (5)	0 (0)
Eosinophilia	6 (4)	8 (18)
Abnormal bleeding	3 (3)	8 (18)
Hypothermia	2 (2)	9 (20)
Glaucoma	2 (2)	0 (0)
Optic atrophy	2 (2)	0 (0)
Microphthalmia	2 (2)	0 (0)
Rash	1 (1)	11 (25)
Pneumonitis	0 (0)	18 (41)
B. CHILDREN ≥4 YR OF AGE	**70 PATIENTS (%)**	**31 PATIENTS (%)**
Mental retardation	62 (89)	25 (81)
Convulsions	58 (83)	24 (77)
Spasticity and palsies	53 (76)	18 (58)
Severely impaired vision	48 (69)	13 (42)
Hydrocephalus or microcephalus	31 (44)	2 (6)
Deafness	12 (17)	3 (10)
Normal	6 (9)	5 (16)

*Patients with otherwise undiagnosed central nervous system disease in the 1st yr of life.

†Patients with otherwise undiagnosed nonneurologic diseases during the 1st 2 mo of life.

Adapted from Eichenwald H: A study of congenital toxoplasmosis. In Slim JC, editor: Human toxoplasmosis, *Copenhagen, 1960, Munksgaard, pp. 41–49. Study performed in 1947. The most severely involved institutionalized patients were not included in the later study of 101 children.*

the Coombs test result is usually negative with congenital *T. gondii* infection.

Skin

Cutaneous manifestations among newborn infants with congenital toxoplasmosis include rashes and jaundice and/or petechiae secondary to thrombocytopenia, but ecchymoses and large hemorrhages secondary to thrombocytopenia also occur. Rashes may be fine punctate, diffuse maculopapular, lenticular, deep blue-red, sharply defined macular, or diffuse blue and papular. Macular rashes involving the entire body including the palms and soles, exfoliative dermatitis, and cutaneous calcifications have been described. Jaundice with hepatic involvement and/or hemolysis, cyanosis due to interstitial pneumonitis from congenital infection, and edema secondary to myocarditis or nephrotic syndrome may be present. Jaundice and conjugated hyperbilirubinemia may persist for months.

Endocrine Abnormalities

Endocrine abnormalities may occur secondary to hypothalamic or pituitary involvement or end-organ involvement but are not common. Occasionally reported endocrinopathies include myxedema, persistent hypernatremia with vasopressin-sensitive diabetes insipidus, sexual precocity, and partial anterior hypopituitarism.

Central Nervous System

Neurologic manifestations of congenital toxoplasmosis vary from massive acute encephalopathy to subtle neurologic syndromes. Toxoplasmosis should be considered as a potential cause of any undiagnosed neurologic disease in children younger than 1 yr of age, especially if retinal lesions are present.

Hydrocephalus may be the sole clinical neurologic manifestation of congenital toxoplasmosis and almost always requires shunt placement. Hydrocephalus may present prenatally and progress during the perinatal period, or, much less commonly, may present later in life. Patterns of seizures are protean and have included focal motor seizures, petit and grand mal seizures, muscular twitching, opisthotonus, and hypsarrhythmia. Spinal or bulbar involvement may be manifested by paralysis of the extremities, difficulty swallowing, and respiratory distress. Microcephaly usually reflects severe brain damage, but some children with microcephaly caused by congenital toxoplasmosis who have been treated have normal or superior cognitive function. Untreated congenital toxoplasmosis that is symptomatic in the 1st yr of life can cause substantial diminution in cognitive function and developmental delay. Intellectual impairment also occurs in some children with subclinical infection without or despite treatment with pyrimethamine and sulfonamides. Seizures and focal motor defects may become apparent after the newborn period, even when infection is subclinical at birth.

CSF abnormalities occur in at least 50% of infants with congenital toxoplasmosis. A CSF protein level of >1 g/dL is characteristic of severe CNS toxoplasmosis and is usually accompanied by hydrocephalus. Local production of *T. gondii*–specific IgG and IgM antibodies may be demonstrated. CT of the brain is useful to detect calcifications, determine ventricular size, and demonstrate porencephalic cystic structures (Fig. 290-4). Calcifications occur throughout the brain, but there is a propensity for development of calcifications in the caudate nucleus and basal ganglia, choroid plexus, and subependyma. MRI and contrast-enhanced CT brain scans are useful for detecting active inflammatory lesions. MRIs that take only a brief time (<45 sec) for imaging or ultrasonography may be useful for following ventricular size. Treatment in utero and in the 1st yr of life results in improved neurologic outcomes.

Eyes

Almost all untreated congenitally infected infants develop chorioretinal lesions by adulthood, and may have severe visual impairment. *T. gondii* causes a focal necrotizing retinitis in congenitally infected individuals (see Fig. 290-2). Retinal detachment may occur. Any part of the retina may be involved, either unilaterally or bilaterally, including the maculae. The optic nerve may be involved, and toxoplasmic lesions that involve projections of the visual pathways in the brain or the visual cortex also may lead to visual impairment. In association with severe retinal lesions and vitreitis, secondary anterior uveitis may develop and occasionally lead to erythema of the external eye. Other ocular findings include cells and protein in the anterior chamber, large keratic precipitates, posterior synechiae, nodules on the iris, and neovascular formation on the surface of the iris, sometimes with increased intraocular pressure and glaucoma. Rarely, the extraocular musculature may also be involved directly. Other manifestations include strabismus, nystagmus, visual impairment, and microphthalmia. Enucleation has been required for a blind, phthisic, painful eye. The differential diagnosis of ocular toxoplasmosis includes congenital coloboma and inflammatory lesions caused by cytomegalovirus, *Treponema pallidum, Mycobacterium tuberculosis,* or vasculitis. Ocular toxoplasmosis may be a recurrent and progressive disease that requires multiple courses of therapy.

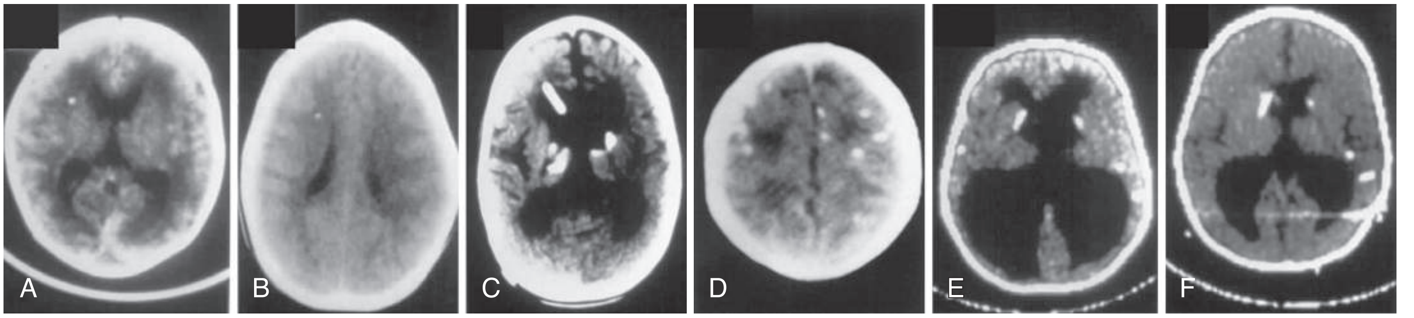

Figure 290-4 **Head CT scans of infants with congenital toxoplasmosis. A,** CT scan at birth that shows areas of hypolucency, mildly dilated ventricles, and small calcifications. **B,** CT scan of the same child at 1 yr of age (after antimicrobial therapy for 1 yr). This scan is normal with the exception of 2 small calcifications. This child's Mental Development Index (MDI) at 1 yr of age was 140 by the Bayley Scale of Infant Development. **C,** CT scan from a 1 yr old infant who was normal at birth. His meningoencephalitis became symptomatic in the 1st few wk of life but was not diagnosed correctly and remained untreated during his 1st 3 mo of life. At 3 mo of age, development of hydrocephalus and bilateral macular chorioretinitis led to the diagnosis of congenital toxoplasmosis, and antimicrobial therapy was initiated. This scan shows significant residual atrophy and calcifications. This child had substantial motor dysfunction, development delays, and visual impairment. **D,** CT scan obtained during the 1st mo of life of a microcephalic child. Note the numerous calcifications. This child's IQ scores using the Stanford-Binet Intelligence Scale for children when she was 3 yr of age and the Wechsler Preschool and Primary Scale Intelligence when she was 5 yr of age were 100 and 102, respectively. She received antimicrobial therapy during her 1st yr of life. **E,** CT scan with hydrocephalus owing to aqueductal obstruction, before shunt. **F,** Scan from the same patient as the scan in **E,** after shunt. This child's IQ scores using the Stanford-Binet Intelligence Scale for children were approximately 100 when she was 3 and 6 yr of age. *(**A** to **F** adapted from McAuley J, Boyer K, Patel D, et al: Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial,* Clin Infect Dis *18:38–72, 1994.)*

Limited data suggest that occurrence of lesions in the early years of life may be prevented by instituting antimicrobial treatment with pyrimethamine and sulfonamides during the 1st yr of life and that treatment of the infected fetus in utero followed by treatment in the 1st yr of life with pyrimethamine, sulfadiazine, and leucovorin reduces the incidence and the severity of the retinal disease.

Ears

Sensorineural hearing loss, both mild and severe, may occur. It is not known whether this is a static or progressive disorder. Treatment in the 1st yr of life is associated with decreased frequency of hearing loss.

DIAGNOSIS

Diagnosis of acute *Toxoplasma* infection can be established by a number of methods (Table 290-2). For example, isolation of *T. gondii* from blood or body fluids; identification of tachyzoites in sections or preparations of tissues and body fluids, amniotic fluid, or placenta; identification of cysts in the placenta or tissues of a fetus or newborn; and characteristic lymph node histologic features establish the diagnosis. Serologic tests are very useful for diagnosis. Polymerase chain reaction (PCR) is useful to identify *T. gondii* DNA in CSF and amniotic fluid, and has been reported to be useful with infant peripheral blood and urine to definitively establish the diagnosis.

Isolation

Organisms are isolated by inoculation of body fluids, leukocytes, or tissue specimens into mice or tissue cultures. Body fluids should be processed and inoculated immediately, but *T. gondii* has been isolated from tissues and blood that have been stored overnight or even for 4-5 days at 4°C (39.2°F). Freezing or treatment of specimens with formalin kills *T. gondii.* From 6-10 days after inoculation into mice, or earlier if mice die, peritoneal fluids should be examined for tachyzoites. If inoculated mice survive for 6 wk and seroconvert, definitive diagnosis is made by visualization of *Toxoplasma* cysts in mouse brain. If cysts are not seen, subinoculations of mouse tissue into other mice are performed.

Microscopic examination of tissue culture inoculated with *T. gondii* shows necrotic, heavily infected cells with numerous extracellular tachyzoites. Isolation of *T. gondii* from blood or body fluids reflects acute infection. Except in the fetus or neonate, it is usually not possible to distinguish acute from past infection by isolation of *T. gondii* from tissues such as skeletal muscle, lung, brain, or eye obtained by biopsy or at autopsy.

Diagnosis of acute infection can be established by visualization of tachyzoites in biopsy tissue sections, bone marrow aspirate, or body fluids such as CSF or amniotic fluid. Immunofluorescent antibody and immunoperoxidase staining techniques may be necessary, because it is often difficult to distinguish the tachyzoite using ordinary stains. Tissue cysts are diagnostic of infection but do not differentiate between acute and chronic infection, although the presence of many cysts suggests recent acute infection. Cysts in the placenta or tissues of the newborn infant establish the diagnosis of congenital infection. Characteristic histologic features strongly suggest the diagnosis of toxoplasmic lymphadenitis.

Serologic Testing

Serologic tests are useful in establishing the diagnosis of congenital or acutely acquired *Toxoplasma* infection. Each laboratory that reports serologic test results must have established values for their tests that diagnose infection in specific clinical settings, provide interpretation of their results, and ensure appropriate quality control before therapy is based on serologic test results. Serologic test results used as the basis for therapy should be confirmed in a reference laboratory.

The **Sabin-Feldman dye test** is sensitive and specific. It measures primarily IgG antibodies. Results should be expressed in international units (IU/mL), based on international standard reference sera available from the World Health Organization.

The **IgG indirect fluorescent-antibody (IgG-IFA) test** measures the same antibodies as the dye test, and the titers tend to be parallel. These antibodies usually appear 1-2 wk after infection, reach high titers (≥1 : 1,000) after 6-8 wk, and then decline over months to years. Low titers (1 : 4 to 1 : 64) usually persist for life. Antibody titer does not correlate with severity of illness.

An **agglutination test** (Bio-Mérieux, Lyon, France) that is available commercially in Europe uses formalin-preserved whole parasites to detect IgG antibodies. This test is accurate, simple to perform, and inexpensive.

The **IgM-IFA test** is useful for the diagnosis of acute acquired infection with *T. gondii* in the older child because IgM antibodies appear earlier, often by 5 days after infection, and diminish more quickly than IgG antibodies. In most instances, IgM antibodies rise rapidly (1 : 50 to <1 : 1,000) and then fall to low titers (1 : 10 or 1 : 20) or disappear after weeks or months. However, some patients continue to have positive IgM results with low titers for several years. The IgM-IFA test detects *Toxoplasma*-specific IgM in only approximately 25% of congenitally infected infants at birth. IgM antibodies may not be present in sera of

Table 290-2 Generalizations Concerning Clinical Presentations, *Toxoplasma*-Specific Diagnostic Tests, and Treatment

CLINICAL SETTING & MANIFESTATION	SAMPLE SOURCE	***Toxoplasma*-Specific Diagnostic Tests**								**Treatment**				
		G	**M**	**A**	**E**	**AV**	**AC/HS**	**PCR**	**SUBINOCULATION**	**SP**	**PSL***	**CO**	**LU**	**NONE**
PRENATAL														
Acute infection in pregnant woman ≤18 wk gestation *and* no clinical evidence of fetal infection	Mother	+	+	+	+	L	Acute	AF (17-18 wk)	NS					
Acute infection in pregnant woman ≤18 wk gestation *and* signs of fetal infection	Mother	+	+	+	+	L	Acute	AF (may not be necessary)	NS		†No P 1st trimester			
Acute infection in pregnant woman at >21 wk gestation	Mother	+	+	+	+	L	Acute	AF	NS					
Congenital infection in infant	Infant	+	+	+	+	L	Acute	Placenta/buffy coat	placenta/buffy coat			‡		
POSTNATAL														
Acute, symptomatic	Child	+	+	+	+	L	Acute	NS	NS					
Acute, self-limited symptoms														
Chronic, asymptomatic	Child	+	–	–	–	H	Chronic	NS	NS					
Acute, severely symptomatic	Child	+	+	+	+	L	Acute	§	Body fluids/buffy coat					
Immune compromised¶	Child	+/–	+/–	+/–	+/–	+/–	+/–	§	Body fluids/buffy coat					
Laboratory accident‖	Child	+/–	+/–	+/–	+/–	+/–	+/–	NS	NS		‖			
Eye Disease														
Quiescent scar**	Child	+	+/–	+/–	+/–	+/–	+/–	NS	NS					
Active chorioretinitis**	Child	+	+/–	+/–	+/–	+/–	+/–	NS	NS					
Active CNVM**	Child	+	+/–	+/–	+/–	+/–	+/–	NS	NS				††	

*Pyrimethamine and leucovorin should be adjusted for granulocytopenia; complete blood counts, including platelets, should be monitored each Monday and Thursday. If there is sulfonamide allergy, alternative medicines include clindamycin, azithromycin, or clarithromycin in place of sulfadiazine.

†*DO NOT* use pyrimethamine in the 1st 14 wk gestation.

‡Occasionally, corticosteroids (prednisone) have been used when CSF protein is ≥1 g/dL or when active chorioretinitis threatens vision and should be continued until signs of inflammation or active chorioretinitis that threatens vision have subsided; then dosage can be tapered and the steroids discontinued.

§Utility of PCR depends on clinical setting. For example, the following may be useful to establish the diagnosis: PCR of body fluids such as amniotic fluid or CSF; cells from bronchoalveolar lavage from a patient with pneumonia; or tissue such as placenta where presence of parasites or parasite DNA would support a diagnosis of infection.

¶In some cases, in immune compromised persons, there is no detectable serologic response to *T. gondii*. However, if clinical presentation is indicative of infection in the absence of positive serologic results, then CSF, buffy coat of peripheral blood, histopathology of tissue samples, or body fluids tested with PCR or subinoculation may be useful. If PCR demonstrates the presence of *T. gondii* DNA in the sample, it is useful for diagnosis. However, the sensitivity of PCR has been variable in this setting. In some circumstances, presumptive treatment may be warranted.

‖Whether a person should be treated for a laboratory accident depends on the nature of the accident, the serology of the person before the accident, and other factors. When there is risk of infection, treatment is given.

**Serologic results depend on whether infection is acute (recently acquired) or chronic. When testing serum from persons with ocular toxoplasmosis, *T. gondii*-specific IgG may be demonstrable only in an undiluted serum sample.

††Corticosteroids (prednisone) are used if inflammation or edema due to infection threatens vision and should be continued until signs of inflammation or active chorioretinitis that threatens vision have subsided; then dosage can be tapered and the steroids discontinued.

+, positive; –, negative; +/–, equivocal; A, *T. gondii*–specific IgA; AC/HS, direct agglutination; AF, amniotic fluid; Av, *T. gondii*–specific IgG avidity; CNVM, choroidal neovascular membrane; Co, corticosteroids (prednisone); CSF, cerebrospinal fluid; E, *T. gondii*–specific IgE; G, *T. gondii*–specific IgG; IG, immunoglobulin; Lu, Lucentis (antibody to vascular endothelial growth factor); M, *T. gondii*–specific IgM; NS, not standard to obtain; PCR, polymerase chain reaction; PSL, pyrimethamine, sulfadiazine, leucovorin (folinic acid); Sp, spiramycin.

Adapted from Remington JS, McLeod R, et al: Toxoplasmosis. In Remington JS, Klein JO, editors: Infectious diseases of the fetus and newborn infant, *ed 6, Philadelphia, 2006, WB Saunders.*

immunocompromised patients with acute toxoplasmosis or in patients with reactivation of ocular toxoplasmosis. The IgM-IFA test may yield false-positive results as a result of rheumatoid factor.

The **double-sandwich IgM enzyme-linked immunosorbent assay (IgM-ELISA)** is also useful for detection of *Toxoplasma* IgM antibodies. In the older child, serum IgM-ELISA *Toxoplasma* antibodies of >2 (a value of 1 reference laboratory; each laboratory must establish its own value for positive results) indicates that *Toxoplasma* infection most likely has been acquired recently. The IgM-ELISA identifies approximately 50-75% of infants with congenital infection. IgM-ELISA avoids both the false-positive results from rheumatoid factor and the false-negative results from high levels of passively transferred maternal

IgG antibody in fetal serum, as may occur in the IgM-IFA test. Results obtained with commercial kits must be interpreted with caution, because false-positive reactions are not infrequent. Care must also be taken to determine whether kits have been standardized for diagnosis of infection in specific clinical settings, such as in the newborn infant. The **IgA-ELISA** also is a sensitive test for detection of maternal and congenital infection, and results may be positive when those of the IgM-ELISA are not.

The **immunosorbent agglutination assay (ISAGA)** combines trapping of a patient's IgM to a solid surface and use of formalin-fixed organisms or antigen-coated latex particles. It is read as an agglutination test. There are no false-positive results from rheumatoid factor or antinuclear antibodies. The IgM-ISAGA is more sensitive than the IgM-ELISA and may detect specific IgM antibodies before and for longer periods than the IgM-ELISA.

At present, the IgM-ISAGA and the **IgA-ELISA** are the most useful tests for diagnosis of congenital infection in the newborn. The **IgE-ELISA** and **IgE-ISAGA** are also sometimes useful in establishing the diagnosis of congenital toxoplasmosis or acute acquired *T. gondii* infection. The presence of IgM antibodies in the older child or adult can never be used alone to diagnose acute acquired infection.

The **differential agglutination test (HS/AC)** compares antibody titers obtained with formalin-fixed tachyzoites **(HS antigen)** with titers obtained using acetone- or methanol-fixed tachyzoites **(AC antigen)** to differentiate recent and remote infections in adults and older children. This method may be particularly useful in differentiating remote infection in pregnant women, because levels of IgM and IgA antibodies detectable by ELISA or ISAGA may remain elevated for months to years in adults and older children.

The **avidity test** can be helpful to establish time of acquisition of infection. A high-avidity test result indicates that infection began more than 12-16 wk earlier, which is especially useful in determining time of acquisition of infection in the 1st or final 16 wk of gestation. A low-avidity test result may be present for many months and is not diagnostic of recent acquisition of infection.

A relatively higher level of *Toxoplasma* antibody in the aqueous humor or in CSF demonstrates local production of antibody during active ocular or CNS toxoplasmosis. This comparison is performed, and a coefficient [C] is calculated as follows:

$$C = \frac{\text{Antibody titer in body fluid}}{\text{Antibody titer in serum}} \times \frac{\text{Concentration of IgG in serum}}{\text{Concentration of IgG in body fluid}}$$

Significant coefficients [C] are >8 for ocular infection, >4 for CNS for congenital infection, and >1 for CNS infection in patients with AIDS. If the serum dye test titer is >300 IU/mL, it is not possible to demonstrate significant local antibody production using this formula with either the dye test or the IgM-IFA test titer. IgM antibody may be detectable in CSF.

Comparative **Western immunoblot** tests of sera from a mother and infant may detect congenital infection. Infection is suspected when the mother's serum and her infant's serum contain antibodies that react with different *Toxoplasma* antigens.

The **enzyme-linked immunofiltration assay** using micropore membranes permits simultaneous study of antibody specificity by immunoprecipitation and characterization of antibody isotypes by immunofiltration with enzyme-labeled antibodies. This method is capable of detecting 85% of cases of congenital infection in the 1st few days of life.

PCR is used to amplify the DNA of *T. gondii,* which then can be detected by using a DNA probe. Detection of repetitive *T. gondii* genes, the B1 or 529 bp, 300 copy gene, in amniotic fluid is the PCR target of choice for establishing the diagnosis of congenital *Toxoplasma* infection in the fetus. Sensitivity and specificity of this test in amniotic fluid obtained to diagnose infections acquired between 17 and 21 wk of gestation are approximately 95%. Before and after that time, PCR with the 529 bp, 300 copy repeat gene as the template is 92% sensitive and 100% specific for detection of congenital infection. PCR of vitreous or aqueous fluids also has been used to diagnose ocular toxoplasmosis. PCR of peripheral white blood cells, CSF, and urine has been reported to detect congenital infection.

Lymphocyte blastogenesis to *Toxoplasma* antigens has been used to diagnose congenital toxoplasmosis when the diagnosis is uncertain and other test results are negative. However, a negative result does not exclude the diagnosis because peripheral blood lymphocytes of infected newborns may not respond to *T. gondii* antigens.

Acquired Toxoplasmosis

Recent infection is diagnosed by seroconversion from a negative to a positive IgG antibody titer (in the absence of transfusion); a 2 tube increase in *Toxoplasma*-specific IgG titer when serial sera are obtained 3 wk apart and tested in parallel; or the detection of *Toxoplasma*-specific IgM antibody in conjunction with other tests, but never alone.

Ocular Toxoplasmosis

IgG antibody titers of 1 : 4 to 1 : 64 are usual in older children with active *Toxoplasma* chorioretinitis. Even the presence of antibodies measurable only when serum is tested undiluted is helpful in establishing the diagnosis. The diagnosis is likely with characteristic retinal lesions and positive serologic tests. PCR of aqueous or vitreous fluid has been used to diagnose ocular toxoplasmosis but is infrequently performed because of the risks associated with obtaining intraocular fluid.

Immunocompromised Persons

IgG antibody titers may be low, and *Toxoplasma*-specific IgM is often absent in immunocompromised stem cell transplant recipients, but not in kidney or heart transplant recipients with toxoplasmosis. Demonstration of *Toxoplasma* DNA in serum, blood, and CSF may identify disseminated *Toxoplasma* infection in immunocompromised persons. Resolution of CNS lesions during a therapeutic trial of pyrimethamine and sulfadiazine has been useful to diagnose toxoplasmic encephalitis in patients with AIDS. Brain biopsy has been used to establish the diagnosis if there is no response to a therapeutic trial and to exclude other likely diagnoses such as CNS lymphoma.

Congenital Toxoplasmosis

Fetal ultrasound examination, performed every 2 wk during gestation, beginning at the time acute acquired infection is diagnosed in a pregnant woman, and PCR analysis of amniotic fluid are used for prenatal diagnosis. *T. gondii* may also be isolated from the placenta at delivery.

Serologic tests are also useful in establishing a diagnosis of congenital toxoplasmosis. Either persistent or rising titers in the dye test or IFA test, or a positive IgM-ELISA or IgM-ISAGA result is diagnostic of congenital toxoplasmosis. The half-life of IgM is approximately 2 days, so if there is a placental leak, the level of IgM antibodies in the infant's serum decreases significantly, usually within 1 wk. Passively transferred maternal IgG antibodies may require many months to a year to disappear from the infant's serum, depending on the magnitude of the original titer. The half-life of passively transferred maternal IgG is approximately 30 days, so the titer diminishes by half each 30 days. Synthesis of *Toxoplasma* antibody is usually demonstrable by the 3rd mo of life if the infant is untreated, although the rate of IgG synthesis varies considerably in infants younger than 1 year of age. If the infant is treated, synthesis may be delayed for as long as the 9th mo of life and, infrequently, may not occur at all. When an infant begins to synthesize IgG antibody, infection may be documented serologically even without demonstration of IgM antibodies by an increase in the ratio of specific serum IgG antibody titer to the total IgG, whereas the ratio will decrease if the specific IgG antibody has been passively transferred from the mother.

Newborns suspected of having congenital toxoplasmosis should be evaluated by general, ophthalmologic, and neurologic examinations; head CT scan; attempt to isolate *T. gondii* from the placenta and infant's leukocytes from peripheral blood buffy coat; measurement of serum *Toxoplasma*-specific IgG, IgM, IgA, and IgE antibodies, and the levels

of total serum IgM and IgG; lumbar puncture including analysis of CSF for cells, glucose, protein, *Toxoplasma*-specific IgG and IgM antibodies, and level of total IgG; and testing of CSF for *T. gondii* by PCR and inoculation into mice. Presence of *Toxoplasma*-specific IgM in CSF that is not contaminated with blood or confirmation of local antibody production of *Toxoplasma*-specific IgG antibody in CSF establishes the diagnosis of congenital *Toxoplasma* infection.

Many manifestations of congenital toxoplasmosis are similar to findings that occur in other perinatal infections, especially congenital cytomegalovirus infection. Thus, neither cerebral calcification nor chorioretinitis is pathognomonic. The clinical picture in the newborn infant may also be compatible with sepsis, aseptic meningitis, syphilis, or hemolytic disease. Some children younger than 5 yr of age with chorioretinitis have postnatally acquired *T. gondii* infection.

TREATMENT

Pyrimethamine and sulfadiazine act synergistically against *Toxoplasma,* and combination therapy is indicated for many of the forms of toxoplasmosis. Use of pyrimethamine is contraindicated during the 1st trimester of pregnancy. Spiramycin should be used to attempt to prevent vertical transmission of infection to the fetus of acutely infected pregnant women. Pyrimethamine inhibits the enzyme dihydrofolate reductase, and thus the synthesis of folic acid, and therefore produces a dose-related, reversible, and usually gradual depression of the bone marrow. Neutropenia is most common but rarely treatment has been reported to result in thrombocytopenia and anemia. Reversible neutropenia is the most common adverse effect in treated infants. All patients treated with pyrimethamine should have platelet and leukocyte counts twice weekly. Seizures may occur with overdosage of pyrimethamine. Folinic acid, as calcium leucovorin, should always be administered concomitantly and for 1 wk after treatment with pyrimethamine is discontinued to prevent bone marrow suppression. Potential toxic effects of sulfonamides (e.g., crystalluria, hematuria, and rash) should be monitored. Hypersensitivity reactions occur, especially in patients with AIDS.

Acquired Toxoplasmosis

Patients with acquired toxoplasmosis and lymphadenopathy usually do not need specific treatment unless they have severe and persistent symptoms or evidence of damage to vital organs (see Table 290-2). If such signs and symptoms occur, treatment with pyrimethamine, sulfadiazine, and leucovorin should be initiated. Patients who appear to be immunocompetent but have severe and persistent symptoms or damage to vital organs (e.g., chorioretinitis, myocarditis) need specific therapy until these specific symptoms resolve, followed by therapy for an additional 2 wk. Therapy often is administered for at least 4-6 wk. The optimal duration of therapy is unknown. A loading dose of pyrimethamine for older children is 2 mg/kg/day divided bid (maximum: 50 mg/bid), given for the 1st 2 days of treatment. The maintenance dose begins on the 3rd day and is 1 mg/kg/day (maximum: 50 mg/day). Sulfadiazine is administered at a dosage of 100 mg/kg/day divided bid (maximum: 4 g/day). Leucovorin is administered orally at a dosage of 5-20 mg 3 times a week (or even daily depending on the leukocyte count).

Ocular Toxoplasmosis

Patients with active ocular toxoplasmosis are treated with pyrimethamine, sulfadiazine, and leucovorin (see Table 290-2). They are treated while disease is active and then for approximately 1 wk after the lesion has developed a quiescent appearance (i.e., sharp borders, pigmentation at margins of the lesion, and resolution of associated inflammatory cells in the vitreous), which usually occurs in 2-4 wk when treatment is initiated promptly. Within 7-10 days the borders of the retinal lesions sharpen, and visual acuity usually returns to that noted before development of the acute lesion. Systemic corticosteroids have been administered concomitantly with antimicrobial treatment when lesions involve the macula, optic nerve head, or papillomacular bundle. Corticosteroids are never given alone and are begun after loading doses of pyrimethamine and sulfadiazine have been administered (2 days). With recurrences, new lesions often appear contiguous to old ones. Very rarely, vitrectomy and removal of the lens are needed to restore visual acuity. Suppressive treatment has prevented frequent recurrences of vision-threatening lesions.

Active choroidal neovascular membranes as a result of toxoplasmic chorioretinitis have been treated successfully in children with intravitreal injection of antibody to vascular endothelial growth factor in addition to oral anti-*Toxoplasma* medicines.

Immunocompromised Persons

Serologic evidence of acute infection in an immunocompromised patient, regardless of whether signs and symptoms of infection are present or tachyzoites are demonstrated in tissue, are indications for therapy similar to that described for immunocompetent persons with symptoms of organ injury (see Table 290-2). It is important to establish the diagnosis as rapidly as possible and institute treatment early. In immunocompromised patients other than those with AIDS, therapy should be continued for at least 4-6 wk beyond complete resolution of all signs and symptoms of active disease and resolution of cause for immune suppression. Careful follow-up observation of these patients is imperative because relapse may occur, requiring prompt reinstitution of therapy. Relapse used to be frequent in patients with AIDS without antiretroviral treatment, and suppressive therapy with pyrimethamine and sulfonamides, or trimethoprim-sulfamethoxazole, was continued for life. Now it is possible to discontinue maintenance therapy when the CD4 count remains at >200 cells/µL for 4 mo and all lesions have resolved. Therapy usually induces a beneficial response clinically, but it does not eradicate cysts. Treatment of *T. gondii*–seropositive patients with AIDS should be continued as long as CD4 counts remain at <200 cells/µL. Prophylactic treatment with trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia significantly reduces the incidence of toxoplasmosis in patients with AIDS.

Congenital Toxoplasmosis

All fetuses and newborns infected with *T. gondii* should be treated whether or not they have clinical manifestations of the infection because treatment may be effective in interrupting acute disease that damages vital organs (see Table 290-2 and Fig. 290-5). The fetus is treated by treating the pregnant woman with pyrimethamine and sulfadiazine (with leucovorin). Infants should be treated for 1 yr with pyrimethamine (2 mg/kg/day divided bid for 2 days, then beginning on the 3rd day, 1 mg/kg/day for 2 or 6 mo, and then 1 mg/kg given on Monday, Wednesday, and Friday, PO), sulfadiazine (100 mg/kg/day divided bid PO), and leucovorin (5-10 mg given on Monday, Wednesday, and Friday, or more often depending on neutrophil count, PO). The relative efficacy in reducing sequelae of infection and the safety of treatment with 2 vs 6 mo of the higher dosage of pyrimethamine are being compared in the U.S. National Collaborative Study. Updated information about this study and these regimens is available from Dr. Rima McLeod (773-834-4131). Pyrimethamine and sulfadiazine are available only in tablet form and can be prepared as suspensions. Prednisone (1 mg/kg/day divided bid PO) has been used in addition when active chorioretinitis involves the macula or otherwise threatens vision or the CSF protein is >1,000 mg/dL at birth, but the efficacy is not established. Prednisone is continued only for as long as the active inflammatory process in the posterior pole of the eye is vision threatening or CSF protein is >1,000 mg/dL and then tapered rapidly if the duration of treatment has been brief.

Pregnant Women with *Toxoplasma gondii* Infection

The immunologically normal pregnant woman who acquired *T. gondii* more than 6 mo before conception does not need treatment to prevent congenital infection of her fetus. Although data are not available to allow for a definitive time interval, if infection occurs during or shortly before the pregnancy, it is reasonable to evaluate the fetus by use of PCR with amniotic fluid and ultrasonography and treat to prevent congenital infection in the fetus (see Table 290-2).

Treatment of a pregnant woman who acquires infection at any time during pregnancy reduces the chance of congenital infection in her

Oral Suspension Formulations	
Sulfadiazine 100mg/mL suspension 1. Crush ten 500mg sulfadiazine tablets in a mortar to a fine powder 2. Add enough sterile water to make a smooth paste 3. Slowly triturate syrup vehicle close to 50mL final volume 4. Transfer mixture to an amber bottle 5. Add enough syrup vehicle to q.s. to 50mL final volume 6. Shake very well. 7. Label and give a 7 day expiration 8. Store refrigerated	**Pyrimethamine** 2mg/mL suspension 1. Crush four 25mg pyrimethamine tablets in a mortar to a fine powder 2. Add 10cc of syrup vehicle 3. Transfer mixture to an amber bottle 4. Rinse motor with 10cc sterile water and transfer to bottle 5. Add enough syrup vehicle to q.s. to 50mL final volume 6. Shake very well. 7. Label and give 7 day expiration 8. Store refrigerated

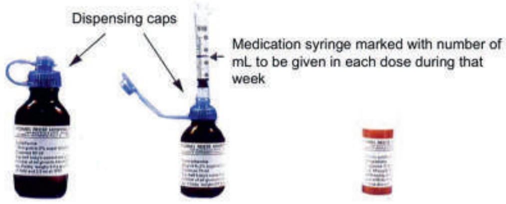

Medication:	Sulfadiazine	Pyrimethamine	Folinic acid (calcium leukovorin)
Concentration:	100mg/mL	2mg/mL	5mg tablets
Dispense:	50mL*	25mL*	30 tablets
Dosage:	Half of infant's current weight in kg equals number of mL given in AM and PM†	Half of infant's current weight in kg equals number of mL given once daily‡§	10mg (two 5mg tablets) on Monday, Wednesday, and Friday. Crush and give with formula, water, milk, or juice in one dosage. May adjust based on neutrophil count.

* Suspended in 2% sugar solution. Suspension at usual concentration must be made each week. Store refrigerated.
† e.g. If infant weighs 5kg, give 2.5mL at 7AM and 7 PM.
‡ e.g. If infant weighs 5kg, give 2.5mL daily.
§ *For pyrimethamine*, first loading dose is 1mg/kg given BID for 2 days. Beginning third day, dose is 1mg/kg per day.

Figure 290-5 Compounding and administration of medications to treat congenital toxoplasmosis in infants. *(Adapted from Remington JS, McLeod R, et al: Toxoplasmosis. In Remington JS, Klein JO, editors:* Infectious diseases of the fetus and newborn infant, *ed 6, Philadelphia, 2006, WB Saunders; and McAuley J, Boyer K, Patel D, et al: Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial,* Clin Infect Dis *18:38–72, 1994.)*

infant. Spiramycin (1 g every 8 hr PO without food) is recommended for prevention of fetal infection if the mother develops acute toxoplasmosis during pregnancy. Spiramycin is available in the United States upon an "emergency use" request by a physician through the FDA Division of Anti-Infective Drugs (301-796-1400) after the diagnosis of acute infection is confirmed in a reference laboratory (Palo Alto Medical Facility Toxoplasma Serology Lab 650-853-4828). With this approval, the physician can then contact the spiramycin manufacturer, Sanofi Pasteur (1-800-822-2463), to obtain spiramycin for the patient. Adverse reactions are infrequent and include paresthesia, rash, nausea, vomiting, and diarrhea. Following a loading dose of pyrimethamine (50 mg divided bid) for 2 days, beginning on the 3rd day, pyrimethamine is administered at a dose of 50 mg once daily. Beginning on the 1st day of treatment with pyrimethamine, sulfadiazine (1.5-2.0 g bid PO), and leucovorin (10 mg once daily PO) are recommended for treatment of the pregnant woman whose fetus has confirmed or probable fetal infection except in the 1st trimester. In the 1st trimester, when there is definite infection, sulfadiazine alone is recommended because pyrimethamine is potentially teratogenic at that time. Spiramycin treatment is used for infection acquired early in gestation when it is uncertain whether there is fetal infection. Treatment of the mother of an infected fetus with pyrimethamine and sulfadiazine reduces infection in the placenta and the severity of disease in the newborn. Delay in maternal treatment during gestation results in greater brain and eye disease in the infant. Diagnostic amniocentesis should be performed at >17-18 wk of gestation in pregnancies when there is high suspicion of fetal infection. Overall sensitivity of PCR for amniotic fluid is at 85% between 17 and 21 wk of gestation. The sensitivity of PCR using amniotic fluid for diagnosis of fetal infection is 92% in early and late gestation when amniotic fluid is tested for presence of the 529 bp, 300 copy gene. After 24 wk gestation, incidence of transmission is relatively high and pregnant women who are infected acutely after that time are treated with pyrimethamine and sulfadiazine to treat the fetus.

The approach in France to congenital toxoplasmosis includes systematic serologic screening of all women of childbearing age and again intrapartum each month during gestation beginning at ≤11 wk gestational age, at birth, and 1 mo after birth. Mothers with acute infection early in gestation and without evidence of involvement of the fetus are treated with spiramycin, which decreases the transmission. Ultrasonography and amniocentesis for PCR at approximately 18 wk of gestation are used for fetal diagnosis and have 97% sensitivity and 100% specificity. Confidence intervals for sensitivity are largest early and late in gestation. Fetal infection is treated with pyrimethamine and sulfadiazine. Termination of pregnancy is very rare at present. Prompt initiation of treatment with pyrimethamine and sulfadiazine during pregnancy usually has an excellent outcome, with normal development of children. Only 19% have subtle findings of congenital infection, including intracranial calcifications (13%) and chorioretinal scars (6%), although 39% have chorioretinal scars detected at follow-up observation during later childhood. Several studies have demonstrated improved outcomes with shorter times between diagnosis and initiation of treatment.

Chronically infected pregnant women who are immunocompromised have transmitted *T. gondii* to their fetuses. Such women should be treated with spiramycin throughout gestation. The optimal management for prevention of congenital toxoplasmosis in the fetus of a pregnant woman with HIV infection with a CD4 count <200 cells/µL and inactive *T. gondii* infection is unknown. If the pregnancy is not terminated, some investigators suggest that the mother should be treated with spiramycin during the 1st 14 wk of gestation and thereafter with pyrimethamine and sulfadiazine until term. There are no universally accepted guidelines at present. In a study of adult patients with AIDS and toxoplasmic encephalitis, pyrimethamine (75 mg once daily PO) combined with high dosages of intravenously administered clindamycin (1,200 mg every 6 hr IV) appeared equal in efficacy to sulfadiazine and pyrimethamine in the treatment of the toxoplasmic encephalitis. Other experimental agents include the macrolides clarithromycin and azithromycin.

PROGNOSIS

Early institution of specific treatment for congenitally infected infants usually cures the active manifestations of toxoplasmosis, including active chorioretinitis, meningitis, encephalitis, hepatitis, splenomegaly, and thrombocytopenia. Rarely, hydrocephalus resulting from aqueductal obstruction may develop or become worse during therapy. Treatment appears to reduce the incidence of some sequelae such as diminished cognitive and abnormal motor function. Without therapy and in some treated patients as well, chorioretinitis often recurs. Children with extensive involvement at birth may function normally later in life or have mild to severe impairment of vision, hearing, cognitive

function, and other neurologic functions. Delays in diagnosis and therapy, perinatal hypoglycemia, hypoxia, hypotension, repeated shunt infections, and severe visual impairment are associated with a poorer prognosis. The prognosis is not necessarily poor for infected babies. It should be understood, however, that treatment with pyrimethamine and sulfadiazine does not eradicate encysted parasites.

Studies in Lyon and Paris, France, demonstrated that outcome of treated fetal toxoplasmosis, even when infection is acquired early in gestation, is usually favorable if no hydrocephalus is detected on ultrasound, and treatment with pyrimethamine and sulfadiazine is initiated promptly. The SYROCOT (Systematic Review on Congenital Toxoplasmosis) study in Europe indicated that neurologic outcome is improved with shorter times between diagnosis and initiation of treatment of fetal toxoplasmosis. Work in Lyon, France, has indicated a low incidence of recurrent eye disease in children with congenital toxoplasmosis who had been treated in utero and in their 1st yr of life. The National Collaborative Chicago-Based Congenital Toxoplasmosis Study (NCCCTS) (1981-2004) in the United States found that neurologic, developmental, audiologic, and ophthalmologic outcomes are considerably better for most, but not all, children who were treated in their 1st yr of life with pyrimethamine and sulfadiazine (with leucovorin) when compared to children who had not been treated or were treated for only 1 mo in earlier decades described in the literature. The mean age of the children in this study was 10.8 yr at the time of this analysis, when most of the children had not yet entered their teenage years. Recurrent disease, if it occurs, appears most commonly during adolescence.

PREVENTION

Counseling pregnant women about the methods of preventing transmission of *T. gondii* (see Fig. 290-1) during pregnancy can reduce acquisition of infection during gestation. Women who do not have specific antibody to *T. gondii* before pregnancy should only eat well-cooked meat during pregnancy and avoid contact with oocysts excreted by cats. Cats that are kept indoors, maintained on prepared food, and not fed fresh, uncooked meat should not contact encysted *T. gondii* or shed oocysts. Serologic screening, ultrasound monitoring, and treatment of pregnant women during gestation can also reduce the incidence and manifestations of congenital toxoplasmosis. No protective vaccine is available.

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Section 16
Helminthic Diseases

Chapter 291
Ascariasis (*Ascaris lumbricoides*)

Arlene E. Dent and James W. Kazura

ETIOLOGY

Ascariasis is caused by the nematode, or roundworm, *Ascaris lumbricoides*. Adult worms of *A. lumbricoides* inhabit the lumen of the small intestine and have a life span of 10-24 mo. The reproductive potential of *Ascaris* is prodigious; a gravid female worm produces 200,000 eggs per day. The fertile ova are oval in shape with a thick mammillated covering measuring 45-70 µm in length and 35-50 µm in breadth (Fig. 291-1). After passage in the feces, the eggs embryonate and become infective in 5-10 days under favorable environmental conditions. Adult worms can live for 12-18 mo (Fig. 291-2).

Figure 291-1 Soil-transmitted helminth eggs. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm,* Lancet *367:1521–1532, 2006.)*

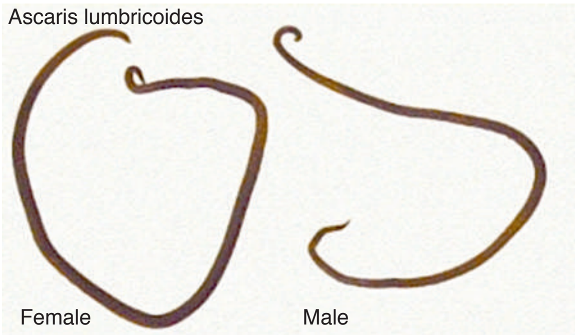

Figure 291-2 Adult male and female soil-transmitted helminths. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm,* Lancet *367:1521–1532, 2006.)*

EPIDEMIOLOGY

Ascariasis occurs globally and is the most prevalent human helminthiasis in the world. It is most common in tropical areas of the world where environmental conditions are optimal for maturation of ova in the soil. Approximately 1 billion persons are estimated to be infected. Although the number of cases in the United States is not known precisely, the highest prevalence is thought to be in high poverty areas of the South and Appalachia. Pig farming in Maine is also associated with *Ascaris* species. Key factors linked with a higher prevalence of infection include poor socioeconomic conditions, use of human feces as fertilizer, and geophagia. Even though infection can occur at any age, the highest rate is in preschool or early school-age children. Transmission is primarily hand to mouth, but may also involve ingestion of contaminated raw fruits and vegetables. Transmission is enhanced by the high output of eggs by fecund female worms and resistance of ova to the outside environment. *Ascaris* eggs can remain viable at 5-10°C (41-50°F) for as long as 2 yr.

PATHOGENESIS

Ascaris ova hatch in the small intestine after ingestion by the human host. Larvae are released, penetrate the intestinal wall, and migrate to

the lungs by way of the venous circulation. The parasites then cause **pulmonary ascariasis** as they enter into the alveoli and migrate through the bronchi and trachea. They are subsequently swallowed and return to the intestines, where they mature into adult worms. Female *Ascaris* begin depositing eggs in 8-10 wk.

CLINICAL MANIFESTATIONS

The clinical presentation depends on the intensity of infection and the organs involved. Most individuals have low to moderate worm burdens and have no symptoms or signs. The most common clinical problems are from **pulmonary disease** and **obstruction of the intestinal or biliary tract**. Larvae migrating through these tissues may cause allergic symptoms, fever, urticaria, and granulomatous disease. The pulmonary manifestations resemble Loeffler syndrome and include transient respiratory symptoms such as cough and dyspnea, pulmonary infiltrates, and blood eosinophilia. Larvae may be observed in the sputum. Vague abdominal complaints have been attributed to the presence of adult worms in the small intestine, although the precise contribution of the parasite to these symptoms is difficult to ascertain. A more serious complication occurs when a large mass of worms leads to acute bowel obstruction. Children with heavy infections may present with vomiting, abdominal distention, and cramps. In some cases, worms may be passed in the vomitus or stools. *Ascaris* worms occasionally migrate into the biliary and pancreatic ducts, where they cause cholecystitis or pancreatitis. Worm migration through the intestinal wall can lead to peritonitis. Dead worms can serve as a nidus for stone formation. Studies show that chronic infection with *A. lumbricoides* (often coincident with other helminth infections) impairs growth, physical fitness, and cognitive development.

DIAGNOSIS

Microscopic examination of fecal smears can be used for diagnosis because of the high number of eggs excreted by adult female worms (see Fig. 291-1). A high index of suspicion in the appropriate clinical context is needed to diagnose pulmonary ascariasis or obstruction of the gastrointestinal tract. Ultrasound examination of the abdomen is capable of visualizing intraluminal adult worms.

TREATMENT

Although several chemotherapeutic agents are effective against ascariasis, none has documented utility during the pulmonary phase of infection. Treatment options for gastrointestinal ascariasis include albendazole (400 mg PO once, for all ages), mebendazole (100 mg PO bid for 3 days or 500 mg once for all ages), or ivermectin (150-200 µg/kg PO once). Piperazine citrate (75 mg/kg/day for 2 days; maximum: 3.5 g/day), which causes neuromuscular paralysis of the parasite and rapid expulsion of the worms, is the treatment of choice for intestinal or biliary obstruction and is administered as syrup through a nasogastric tube. Surgery may be required for cases with severe obstruction. Nitazoxanide (100 mg PO bid for 3 days for children 1-3 yr of age, 200 mg bid for 3 days for children 4-11 yr, and 500 mg bid for 3 days for adolescents and adults) produces cure rates comparable to single-dose albendazole. Drug resistance has not been reported, but repeated treatment for ascariasis may be necessary because reinfection is common.

PREVENTION

Although ascariasis is the most prevalent worm infection in the world, little attention has been given to its control. Anthelmintic chemotherapy programs can be implemented in 1 of 3 ways: (1) offering universal treatment to all individuals in an area of high endemicity; (2) offering treatment targeted to groups with high frequency of infection, such as children attending primary school; or (3) offering individual treatment based on intensity of current or past infection. Improving education about and practices of sanitary conditions and sewage facilities, discontinuing the practice of using human feces as fertilizer, and education are the most effective long-term preventive measures.

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Chapter 292

Hookworms (*Necator americanus* and *Ancylostoma* Spp.)

Peter J. Hotez

ETIOLOGY

Two major genera of hookworms, which are nematodes or roundworms, infect humans. *Necator americanus,* the only representative of its genus, is a major anthropophilic hookworm and is the most common cause of human hookworm infection. Hookworms of the genus *Ancylostoma* include the anthropophilic hookworm *Ancylostoma duodenale* that also causes classic hookworm infection and the less common zoonotic species *Ancylostoma ceylanicum, Ancylostoma caninum,* and *Ancylostoma braziliense.* Human zoonotic infection with the dog hookworm *A. caninum* is associated with an eosinophilic enteritis syndrome. The larval stage of *A. braziliense,* whose definitive hosts include dogs and cats, is the principal cause of cutaneous larva migrans.

The infective larval stages of the anthropophilic hookworms live in a developmentally arrested state in warm, moist soil. Larvae infect humans either by penetrating through the skin (*N. americanus* and *A. duodenale*) or when they are ingested *(A. duodenale).* Larvae entering the human host by skin penetration undergo **extraintestinal migration** through the venous circulation and lungs before they are swallowed, whereas orally ingested larvae may undergo extraintestinal migration or remain in the gastrointestinal tract. Larvae returning to the small intestine undergo 2 molts to become adult, sexually mature, male and female worms ranging in length from 5-13 mm. The buccal capsule of the adult hookworm is armed with cutting plates *(N. americanus)* or teeth *(A. duodenale)* to facilitate attachment to the mucosa and submucosa of the small intestine. Hookworms can remain in the intestine for 1-5 yr, where they mate and produce eggs. Although up to 2 mo is required for the larval stages of hookworms to undergo extraintestinal migration and develop into mature adults, *A. duodenale* larvae may remain developmentally arrested for many months before resuming development in the intestine. Mature *A. duodenale* female worms produce about 30,000 eggs per day; daily egg production by *N. americanus* is <10,000/day (Fig. 292-1). The eggs are thin shelled and ovoid, measuring approximately 40-60 µm. Eggs that are deposited on soil with adequate moisture and shade develop into first-stage larvae and hatch. Over the ensuing several days and under appropriate conditions, the larvae molt twice to the infective stage. Infective larvae are developmentally arrested and nonfeeding. They migrate vertically in the soil until they either infect a new host or exhaust their lipid metabolic reserves and die.

EPIDEMIOLOGY

Hookworm infection is one of the most prevalent infectious diseases of humans, affecting an estimated 600-700 million individuals worldwide. New information from the Global Burden of Disease 2010 Study indicates that hookworm infection leads all neglected tropical diseases in years lost through disability. In the case of hookworm infection, all of the years lost through disability are attributed to anemia from intestinal blood loss.

Because of the requirement for adequate soil moisture, shade, and warmth, hookworm infection is usually confined to rural areas, especially where human feces are used for fertilizer or where sanitation is inadequate. Hookworm is an infection associated with economic underdevelopment and poverty throughout the tropics and subtropics. Sub-Saharan Africa, East Asia, and tropical regions of the Americas

Figure 292-1 Adult male and female soil-transmitted helminths. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm,* Lancet *367:1521–1532, 2006.)*

Figure 292-2 Soil-transmitted helminth eggs. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm,* Lancet *367:1521–1532, 2006.)*

have the highest prevalence of hookworm infection. High rates of infection are often associated with cultivation of certain agricultural products such as tea in India; sweet potato, corn, cotton, and mulberry trees in China; coffee in Central and South America; and rubber in Africa. It is not uncommon to find dual *N. americanus* and *A. duodenale* infections. *N. americanus* predominates in Central and South America as well as in southern China and southeast Asia, whereas *A. duodenale* predominates in North Africa, in northern India, in China north of the Yangtze River, and among aboriginal people in Australia. The ability of *A. duodenale* to withstand somewhat harsher environmental and climatic conditions may reflect its ability to undergo arrested development in human tissues. *A. ceylanicum* infection occurs in India and Southeast Asia.

Eosinophilic enteritis caused by *A. caninum* was first described in Queensland, Australia, with 2 reported cases in the United States. Because of its global distribution in dogs, it was initially anticipated that human *A. caninum* infections would be identified in many locales, but this has not been found.

PATHOGENESIS

The major morbidity of human hookworm infection is a direct result of intestinal blood loss. Adult hookworms adhere tenaciously to the mucosa and submucosa of the proximal small intestine by using their cutting plates or teeth and a muscular esophagus that creates negative pressure in their buccal capsules. At the attachment site, host inflammation is downregulated by the release of antiinflammatory polypeptides by the hookworm. Rupture of capillaries in the lamina propria is followed by blood extravasation, with some of the blood ingested directly by the hookworm. After ingestion, the blood is anticoagulated, the red blood cells are lysed, and the hemoglobin released and digested. Each adult *A. duodenale* hookworm causes loss of an estimated 0.2 mL of blood/day; blood loss is less for *N. americanus.* Individuals with light infections suffer from very little blood loss and, consequently, may have hookworm infection but not hookworm disease. There is a direct correlation between the number of adult hookworms in the gut and the volume of fecal blood loss. Hookworm disease results only when individuals with moderate and heavy infections experience sufficient blood loss to develop iron deficiency and anemia. Hypoalbuminemia and consequent edema and anasarca from the loss of intravascular oncotic pressure can also occur. These features depend heavily on the dietary reserves of the host.

CLINICAL MANIFESTATIONS

Chronically infected children with moderate and heavy hookworm infections suffer from intestinal blood loss that results in **iron deficiency** and can lead to **anemia** as well as protein malnutrition. Prolonged iron deficiency associated with hookworms in childhood can lead to physical growth retardation and cognitive and intellectual deficits.

Anthropophilic hookworm larvae elicit dermatitis sometimes referred to as **ground itch** when they penetrate human skin. The vesiculation and edema of ground itch are exacerbated by repeated infection. Infection with a zoonotic hookworm, especially *A. braziliense,* can result in lateral migration of the larvae to cause the characteristic cutaneous tracts of **cutaneous larva migrans** (see Chapter 292.1). Cough subsequently occurs in *A. duodenale* and *N. americanus* hookworm infection when larvae migrate through the lungs to cause laryngotracheobronchitis, usually about 1 wk after exposure. Pharyngitis also can occur. The onset of eosinophilia coincides with the entry of hookworm larvae into the gastrointestinal tract. Upper abdominal pain can occur during this period, but it eventually subsides.

Chronic intestinal hookworm infection is not typically associated with specific gastrointestinal complaints, although pain, anorexia, and diarrhea have been attributed to the presence of hookworms. The major clinical manifestations are related to intestinal blood loss. Heavily infected children exhibit all of the signs and symptoms of iron deficiency anemia and protein malnutrition. In some cases, children with chronic hookworm disease acquire a yellow-green pallor known as **chlorosis.**

An infantile form of ancylostomiasis resulting from heavy *A. duodenale* infection has been described. Affected infants experience diarrhea, melena, failure to thrive, and profound anemia. Infantile ancylostomiasis has significant mortality.

Eosinophilic enteritis caused by *A. caninum* is associated with colicky abdominal pain that begins in the epigastrium and radiates outward and is usually exacerbated by food. Extreme cases may mimic acute appendicitis.

DIAGNOSIS

Children with hookworm release eggs that can be detected by direct fecal examination (Fig. 292-2). Quantitative methods are available to determine whether a child has a heavy worm burden that can cause hookworm disease. The eggs of *N. americanus* and *A. duodenale* are morphologically indistinguishable. Species identification typically requires egg hatching and differentiation of third-stage infective larvae; newer methods using polymerase chain reaction methods have been developed but are not generally used in clinical practice.

In contrast, eggs are generally not present in the feces of patients with eosinophilic enteritis caused by *A. caninum.* Eosinophilic enteritis is often diagnosed by demonstrating ileal and colonic ulcerations by colonoscopy in the presence of significant blood eosinophilia. An adult canine hookworm may occasionally be recovered during colonoscopic biopsy. Patients with this syndrome develop immunoglobulin G and immunoglobulin E serologic responses.

TREATMENT

The goal of **deworming** is removal of the adult hookworms with an anthelmintic drug. The benzimidazole anthelmintics, mebendazole and albendazole, are effective at eliminating hookworms from the

intestine, although multiple doses are sometimes required. Albendazole (400 mg PO once, for all ages) usually achieves high cure rates, although *N. americanus* adult hookworms are sometimes more refractory and require additional doses. Mebendazole (100 mg bid PO for 3 days, for all ages) is also effective. In many developing countries, mebendazole is administered as a single dose of 500 mg; however, the cure rates with this regimen can be as low as 10% or less. According to the World Health Organization, children should be encouraged to chew tablets of albendazole or mebendazole because forcing very young children to swallow large tablets may cause choking or asphyxiation. Mebendazole is recommended for *A. caninum*–associated eosinophilic enteritis, although recurrences are common. Because the benzimidazoles have been reported to be embryotoxic and teratogenic in laboratory animals, their safety during pregnancy and in young children is a potential concern and the risks vs benefits must be carefully considered. The World Health Organization currently support the use of benzimidazoles in infected children ≥1 yr of age but at a reduced dose (200 mg for albendazole) in the youngest age group (1-2 yr old). Pyrantel pamoate (11 mg/kg PO once daily for 3 days; maximum dose: 1 g) is available in liquid form and is an effective alternative to the benzimidazoles. Replacement therapy with oral iron is not usually required to correct hookworm-associated iron deficiency in children.

PREVENTION

In 2001, the World Health Assembly urged its member states to implement programs of periodic deworming so as to control the morbidity of hookworm and other soil-transmitted helminth infections. Although anthelmintic drugs are effective at eliminating hookworms from the intestine, the high rates of drug failure from single-dose mebendazole and posttreatment reinfection among children suggest that mass drug administration alone is not effective for controlling hookworm in highly endemic areas. Moreover, data suggest that the efficacy of mebendazole decreases with frequent, periodic use, leading to concerns about the possible emergence of anthelmintic drug resistance. To reduce the reliance exclusively on anthelmintic drugs, a recombinant human hookworm vaccine has been developed and is undergoing clinical testing. Economic development and associated improvements in sanitation, health education, and avoidance of human feces as fertilizer remain critical for reducing hookworm transmission and endemicity.

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292.1 Cutaneous Larva Migrans

Peter J. Hotez

ETIOLOGY

Cutaneous larva migrans **(creeping eruption)** is caused by the larvae of several nematodes, primarily hookworms, which are not usually parasitic for humans. *A. braziliense,* a hookworm of dogs and cats, is the most common cause, but other animal hookworms may also produce the disease.

EPIDEMIOLOGY

Cutaneous larva migrans is usually caused by *A. braziliense,* which is endemic to the southeastern United States and Puerto Rico. Travelers account for a significant percentage of the cases.

CLINICAL MANIFESTATIONS

After penetrating the skin, larvae localize at the epidermal-dermal junction and migrate in this plane, moving at a rate of 1-2 cm/day. The response to the parasite is characterized by raised, erythematous, serpiginous tracks, which occasionally form bullae (Fig. 292-3). These lesions may be single or numerous and are usually localized to an extremity, although any area of the body may be affected. As the organism migrates, new areas of involvement may appear every few days. Intense localized pruritus, without any systemic symptoms, may be associated with the lesions. Bacterial superinfection can occur.

Figure 292-3 Creeping eruption of cutaneous larva migrans. *(From Korting GW:* Hautkrankheiten bei kindern und jugendlichen, *Stuttgart, Germany, 1969, FK Schattauer Verlag.)*

DIAGNOSIS

Cutaneous larva migrans is diagnosed by clinical examination of the skin. Patients are often able to recall the exact time and location of exposure, because the larvae produce intense itching at the site of penetration. Eosinophilia may occur but is uncommon.

TREATMENT

If left untreated, the larvae die, and the syndrome resolves within a few weeks to several months. Treatment with ivermectin (200 µg/kg daily PO for 1-2 days; considered the drug of choice by some investigators), albendazole (400 mg daily PO for 3 days, for all ages), or topical thiabendazole hastens resolution, if symptoms warrant treatment. Nausea and vomiting frequently preclude repeated administration of oral thiabendazole. The safety of ivermectin in young children (weighing <15 kg) and pregnant women remains to be established. Ivermectin should be taken on an empty stomach with water, whereas albendazole should be taken with a fatty meal.

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Chapter 293

Trichuriasis *(Trichuris trichiura)*

Arlene E. Dent and James W. Kazura

ETIOLOGY

Trichuriasis is caused by the **whipworm,** *Trichuris trichiura,* a nematode, or roundworm, that inhabits the cecum and ascending colon. The principal hosts of *T. trichiura* are humans who acquire infection by ingesting embryonated, barrel-shaped eggs (Fig. 293-1). The larvae escape from the shell in the upper small intestine and penetrate the intestinal villi. The worms slowly move toward the cecum, where the

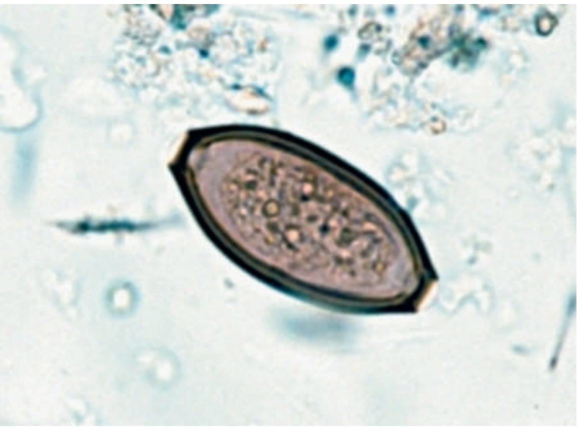

Figure 293-1 ***Trichuris trichiura.*** Soil-transmitted helminth eggs. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm,* Lancet *367: 1521–1532, 2006.)*

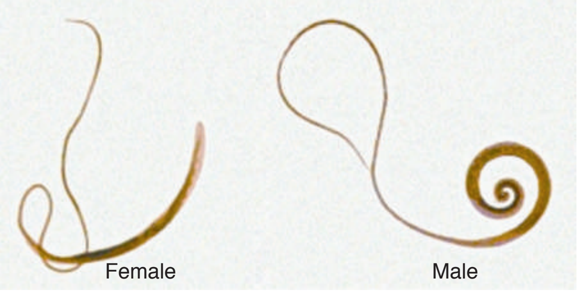

Figure 293-2 ***Trichuris trichiura.*** Adult male and female soil-transmitted helminths. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm,* Lancet *367:1521–1532, 2006.)*

anterior three quarters whiplike portion remains within the superficial mucosa and the short posterior end is free in the lumen (Fig. 293-2). In 1-3 mo, the adult female worm begins producing 5,000-20,000 eggs per day. After excretion in the feces, embryonic development occurs in 2-4 wk with optimal temperature and soil conditions. The adult worm life span is approximately 2 yr.

EPIDEMIOLOGY

Trichuriasis occurs throughout the world and is especially common in poor rural communities with inadequate sanitary facilities and soil contaminated with human or animal feces. Trichuriasis is one of the most prevalent human helminthiases, with an estimated 1 billion infected individuals worldwide. In many parts of the world, where protein-energy malnutrition and anemia are common, the prevalence of *T. trichiura* infection can be as high as 95%. Although trichuriasis occurs in the rural southeastern United States, its prevalence has not been reported. The highest rate of infection occurs among children 5-15 yr of age. Infection develops after ingesting embryonated ova by direct contamination of hands, food (raw fruits and vegetables fertilized with human feces), or drink. Transmission can also occur indirectly through flies or other insects.

CLINICAL MANIFESTATIONS

Most persons harbor low worm burdens and do not have symptoms. Some individuals may have a history of right-lower-quadrant or vague periumbilical pain. Adult *Trichuris* suck approximately 0.005 mL of blood per worm per day. Children, who are most likely to be heavily infected, frequently suffer from disease. Clinical manifestations include chronic dysentery, rectal prolapse, anemia, poor growth, as well as developmental and cognitive deficits. There is no significant eosinophilia, even though a portion of the worm is embedded in the mucosa of the large bowel.

DIAGNOSIS

Because egg output is so high, fecal smears frequently reveal the characteristic barrel-shaped ova of *T. trichiura.*

TREATMENT

Albendazole (400 mg PO for 3 days for all ages) is the drug of choice and is safe and effective, in part because it is poorly absorbed from the gastrointestinal tract. It reduces egg output by 90-99% and has cure rates of 70-90%, although reinfection and resumption of egg production by live worms that presumably survive after treatment may occur. Alternatives include mebendazole (100 mg PO bid for 3 days) and ivermectin (200 µg/kg PO for 3 days). Single-day treatment with albendazole, nitazoxanide, or albendazole plus nitazoxanide lead to cure rates that are low and short-lived. Combination treatment with oxantel pamoate (20 mg/kg) plus 400 mg albendazole on consecutive days may have the highest cure rate.

PREVENTION

Disease can be prevented by personal hygiene, improved sanitary conditions, and eliminating the use of human feces as fertilizer.

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Chapter 294

Enterobiasis *(Enterobius vermicularis)*

Arlene E. Dent and James W. Kazura

ETIOLOGY

The cause of enterobiasis, or **pinworm** infection, is *Enterobius vermicularis,* which is a small (1 cm in length), white, threadlike nematode, or roundworm, that typically inhabits the cecum, appendix, and adjacent areas of the ileum and ascending colon. Gravid females migrate at night to the perianal and perineal regions, where they deposit up to 15,000 eggs. Ova are convex on 1 side and flattened on the other and have diameters of approximately 30 × 60 µm. Eggs embryonate within 6 hr and remain viable for 20 days. Human infection occurs by the fecal-oral route typically by ingestion of embryonated eggs that are carried on fingernails, clothing, bedding, or house dust. After ingestion, the larvae mature to form adult worms in 36-53 days.

EPIDEMIOLOGY

Enterobiasis infection occurs in individuals of all ages and socioeconomic levels. It is prevalent in regions with temperate climates and is the most common helminth infection in the United States. It infects 30% of children worldwide, and humans are the only known host. Infection occurs primarily in institutional or family settings that include children. The prevalence of pinworm infection is highest in children 5-14 yr of age. It is common in areas where children live, play, and sleep close together, thus facilitating egg transmission. Because the life span of the adult worm is short, chronic parasitism is likely due to repeated cycles of reinfection. Autoinoculation can occur in individuals who habitually put their fingers in their mouth.

Figure 294-1 Eggs of *Enterobius vermicularis*. *(From Guerrant RL, Walker DH, Weller PF, et al:* Tropical infectious diseases, *Philadelphia, 2006, Churchill Livingstone, p. 1248.)*

PATHOGENESIS

Enterobius infection may cause symptoms by mechanical stimulation and irritation, allergic reactions, and migration of the worms to anatomic sites where they become pathogenic. *Enterobius* infection has been associated with concomitant *Dientamoeba fragilis* infection, which causes diarrhea.

CLINICAL MANIFESTATIONS

Pinworm infection is innocuous and rarely causes serious medical problems. The most common complaints include itching and restless sleep secondary to nocturnal perianal or perineal pruritus**.** The precise cause and incidence of pruritus are unknown but may be related to the intensity of infection, psychologic profile of the infected individual and his or her family, or allergic reactions to the parasite. Eosinophilia is not observed in most cases, because tissue invasion does not occur. Aberrant migration to ectopic sites occasionally may lead to appendicitis, chronic salpingitis, pelvic inflammatory disease, peritonitis, hepatitis, and ulcerative lesions in the large or small bowel.

DIAGNOSIS

A history of nocturnal perianal pruritus in children strongly suggests enterobiasis. Definitive diagnosis is established by identification of parasite eggs or worms. Microscopic examination of adhesive cellophane tape pressed against the perianal region early in the morning frequently demonstrates eggs (Fig. 294-1). Repeated examinations increase the chance of detecting ova; a single examination detects 50% of infections, 3 examinations 90%, and 5 examinations 99%. Worms seen in the perianal region should be removed and preserved in 75% ethyl alcohol until microscopic examination can be performed. Digital rectal examination may also be used to obtain samples for a wet mount. Routine stool samples rarely demonstrate *Enterobius* ova.

TREATMENT

Anthelmintic drugs should be administered to infected individuals and their family members. Albendazole (400 mg PO with a repeat dose 2 wk later for all age groups) is the treatment of choice and results in cure rates exceeding 90%. Alternatives include mebendazole (100 mg PO with a repeat dose 2 wk later) and pyrantel pamoate (11 mg/kg base PO 3 times for 1 day up to a maximum of 1 g; repeat at 2 wk). Morning bathing removes a large portion of eggs. Frequent changing of underclothes, bed clothes, and bed sheets decreases environmental egg contamination and may decrease the risk for autoinfection.

PREVENTION

Household contacts can be treated at the same time as the infected individual. Repeated treatments every 3-4 mo may be required in circumstances with repeated exposure, such as with institutionalized children. Good hand hygiene is the most effective method of prevention.

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Chapter 295

Strongyloidiasis (*Strongyloides stercoralis*)

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ETIOLOGY

Strongyloidiasis is caused by the nematode, or roundworm, *Strongyloides stercoralis.* Only adult female worms inhabit the small intestine. The nematode reproduces in the human host by parthenogenesis and releases eggs containing mature larvae into the intestinal lumen. Rhabditiform larvae immediately emerge from the ova and are passed in feces, where they can be visualized by stool examination. Rhabditiform larvae either differentiate into free-living adult male and female worms or metamorphose into the infectious filariform larvae. Sexual reproduction occurs only in the free-living stage. Humans are usually infected through skin contact with soil contaminated with infectious larvae. Larvae penetrate the skin, enter the venous circulation and then pass to the lungs, break into alveolar spaces, and migrate up the bronchial tree. They are then swallowed and pass through the stomach, and adult female worms develop in the small intestine. Egg deposition begins approximately 28 days after initial infection.

The **hyperinfection syndrome** occurs when large numbers of larvae transform into infective organisms during their passage in feces and then reinfect (autoinfect) the host by way of the lower gastrointestinal tract or perianal region. This cycle may be accelerated in immunocompromised persons, particularly those with depressed T-cell function.

EPIDEMIOLOGY

S. stercoralis infection is prevalent in tropical and subtropical regions of the world and is endemic in several areas of Europe, the southern United States, and Puerto Rico. Transmission requires appropriate environmental conditions, particularly warm, moist soil. Poor sanitation and crowded living conditions are conducive to high levels of transmission. Dogs and cats can act as reservoirs. The highest prevalence of infection in the United States (4% of the general population) is in impoverished rural areas of Kentucky and Tennessee. Infection may be especially common among residents of mental institutions, veterans who were prisoners of war in areas of high endemicity, and refugees and immigrants. Because of internal autoinfection, individuals may remain infected for decades. Infection may be transmitted by organ transplantation. Individuals with hematologic malignancies, autoimmune diseases, malnutrition, and drug-induced immunosuppression (especially corticosteroids) are at high risk for the **hyperinfection syndrome**. Patients with AIDS may experience a rapid course of disseminated strongyloidiasis with a fatal outcome.

PATHOGENESIS

The initial host immune response to infection is production of immunoglobulin E and eosinophilia in blood and tissues, which presumably prevents dissemination and hyperinfection in the immunocompetent host. Adult female worms in otherwise healthy and asymptomatic individuals may persist in the gastrointestinal tract for years. If infected persons become immunocompromised, the reduction in cellular and humoral immunity may lead to an abrupt and dramatic increase in parasite load with systemic dissemination.

CLINICAL MANIFESTATIONS

Approximately 30% of infected individuals are asymptomatic. The remaining patients have symptoms that correlate with the 3 stages of infection: invasion of the skin, migration of larvae through the lungs, and parasitism of the small intestine by adult worms. **Larva currens** is

the manifestation of an allergic reaction to filariform larvae that migrate through the skin, where they leave pruritic, tortuous, urticarial tracks. The lesions may recur and are typically found over the lower abdominal wall, buttocks, or thighs, resulting from larval migration from defecated stool. Pulmonary disease secondary to larval migration through the lung rarely occurs and may resemble **Loeffler syndrome** (cough, wheezing, shortness of breath, transient pulmonary infiltrates accompanied by eosinophilia). Gastrointestinal strongyloidiasis is characterized by indigestion, crampy abdominal pain, vomiting, diarrhea, steatorrhea, protein-losing enteropathy, protein-caloric malnutrition, and weight loss. Edema of the duodenum with irregular mucosal folds, ulcerations, and strictures can be seen radiographically. Infection may be chronic in nature and is associated with **eosinophilia.**

Strongyloidiasis is potentially lethal because of the ability of the parasite to replicate within the host and cause overwhelming hyperinfection in immunocompromised persons. The **hyperinfection syndrome** is characterized by an exaggeration of the clinical features that develop in symptomatic immunocompetent individuals. The onset is usually sudden, with generalized abdominal pain, distention, and fever. Multiple organs can be affected as massive numbers of larvae disseminate throughout the body and introduce bowel flora. The latter may result in bacteremia and septicemia. Cutaneous manifestations may include petechiae and purpura. Cough, wheezing, and hemoptysis are indicative of pulmonary involvement. Whereas eosinophilia is a prominent feature of strongyloidiasis in immunocompetent persons, this sign may be absent in immunocompromised persons. Because of the low incidence of strongyloidiasis in industrialized countries, it is often misdiagnosed, resulting in a significant delay in treatment.

DIAGNOSIS

Intestinal strongyloidiasis is diagnosed by examining feces or duodenal fluid for the characteristic larvae (Fig. 295-1). Several stool samples should be examined either by direct smear, the Koga agar plate method, or the Baermann test. Alternatively, duodenal fluid can be sampled by the **enteric string test** (Entero-Test) or aspiration via endoscopy. In children with the hyperinfection syndrome, larvae may be found in sputum, gastric aspirates, and, rarely, in small intestinal biopsy specimens. An enzyme-linked immunosorbent assay for immunoglobulin G antibody to *Strongyloides* may be more sensitive than parasitologic methods for diagnosing intestinal infection in the immunocompetent host. The utility of the assay in diagnosing infection in immunocompromised subjects with the hyperinfection syndrome has not been determined. Eosinophilia is common.

TREATMENT

Treatment is directed at eradication of infection. Ivermectin (200 µg/kg/day once daily PO for 2 days) is the drug of choice for uncomplicated strongyloidiasis. Alternatively, albendazole (400 mg PO twice daily for 7 days) may be used. Patients with the hyperinfection syndrome should be treated with ivermectin for 7-10 days and may require repeated courses. Reducing the dose of immunosuppressive therapy and treatment of concomitant bacterial infections are essential in the management of the hyperinfection syndrome. Close follow-up with repeated stool examination is necessary to ensure complete elimination of the parasite. *Strongyloides* antibodies decrease within 6 mo after successful treatment.

PREVENTION

Sanitary practices designed to prevent soil and person-to-person transmission are the most effective control measures. Wearing shoes is a main preventive strategy. Reduction in transmission in institutional settings can be achieved by decreasing fecal contamination of the environment such as by the use of clean bedding. Because infection is uncommon in most settings, case detection and treatment are advisable. Individuals who will be given prolonged high-dose corticosteroids, immunosuppressive drugs before organ transplantation, or cancer chemotherapy should have a screening examination for *S. stercoralis.* If infected, they should be treated before immunosuppression is initiated.

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Figure 295-1 Larvae of intestinal strongyloidiasis.

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Chapter 296

Lymphatic Filariasis (*Brugia malayi, Brugia timori,* and *Wuchereria bancrofti*)

Arlene E. Dent and James W. Kazura

ETIOLOGY

The filarial worms *Brugia malayi* **(Malayan filariasis),** *Brugia timori,* and *Wuchereria bancrofti* **(bancroftian filariasis)** are threadlike nematodes that cause similar infections. Infective larvae are introduced into humans during blood feeding by the mosquito vector. Over a period of 4-6 mo, the larval forms develop into sexually mature adult worms. Once an adequate number of male and female worms accumulate in the afferent lymphatic vessels, adult female worms release large numbers of microfilariae that circulate in the bloodstream. The life cycle of the parasite is completed when mosquitoes ingest microfilariae

in a blood meal, which molt to form infective larvae over a period of 10-14 days. Adult worms have a 5-7 yr life span.

EPIDEMIOLOGY

More than 120 million people living in tropical Africa, Asia, and Latin America are infected; approximately 10-20% of these individuals have clinically significant morbidity attributable to filariasis. *W. bancrofti* is transmitted in Africa, Asia, and Latin America and accounts for 90% of lymphatic filariasis. *B. malayi* is restricted to the South Pacific and Southeast Asia, and *B. timori* is restricted to several islands of Indonesia. Travelers from nonendemic areas of the world who spend brief periods of time in endemic areas are rarely infected. Global elimination has been targeted for 2020.

CLINICAL MANIFESTATIONS

The clinical manifestations of *B. malayi, B. timori,* and *W. bancrofti* infection are similar; manifestations of acute infection include transient, recurrent lymphadenitis and lymphangitis. The early signs and symptoms include episodic fever, lymphangitis of an extremity, lymphadenitis (especially the inguinal and axillary areas), headaches, and myalgias that last a few days to several weeks. These symptoms are caused by an acute inflammatory response triggered by death of adult worms. Initial damage to lymphatic vessels may remain subclinical for years. The syndrome is most frequently observed in persons 10-20 yr of age. Manifestations of chronic lymphatic filariasis occur mostly in adults 30 yr of age or older and result from anatomic and functional obstruction to lymph flow. This obstruction results in lymphedema of the legs, arms, breasts, and/or genitalia. Male genital involvement, such as hydrocele, is very common in *W. bancrofti* infection, but uncommon in *Brugia* species infection. Chronic lymphedema predisposes affected extremities to bacterial superinfections, sclerosis, and verrucous skin changes, resulting in elephantiasis, which may involve 1 or more limbs, the breasts, or genitalia. It is uncommon for children to have overt signs of chronic filariasis.

Tropical Pulmonary Eosinophilia

The presence of microfilariae in the body has no apparent pathologic consequences except in persons with tropical pulmonary eosinophilia, a syndrome of filarial etiology in which microfilariae are found in the lungs and lymph nodes but not the bloodstream. It occurs only in individuals who have lived for years in endemic areas. Men 20-30 yr of age are most likely to be affected, although the syndrome occasionally occurs in children. The presentation includes paroxysmal nocturnal cough with dyspnea, fever, weight loss, and fatigue. Rales and rhonchi are found on auscultation of the chest. The x-ray findings may occasionally be normal, but increased bronchovascular markings, discrete opacities in the middle and basal regions of the lung, or diffuse miliary lesions are usually present (Fig. 296-1). Recurrent episodes may result in interstitial fibrosis and chronic respiratory insufficiency in untreated individuals. Hepatosplenomegaly and generalized lymphadenopathy are often seen in children. The diagnosis is suggested by residence in a filarial endemic area, eosinophilia (>2,000/µL), compatible clinical symptoms, increased serum immunoglobulin E (>1,000 IU/mL), and high titers of antimicrofilarial antibodies in the absence of microfilaremia. Although microfilariae may be found in sections of lung or lymph node, biopsy of these tissues is unwarranted in most situations. The clinical response to diethylcarbamazine (2 mg/kg/dose tid PO for 12-21 days) is the final criterion for diagnosis; the majority of patients improve with this therapy. If symptoms recur, a second course of the anthelmintic should be administered. Patients with chronic symptoms are less likely to show improvement than those who have been ill for a short time.

DIAGNOSIS

Demonstration of microfilariae in the blood is the primary means for confirming the diagnosis of lymphatic filariasis. Because microfilaremia is **nocturnal** in most cases, blood samples should be obtained between 10 PM and 2 AM Anticoagulated blood is passed through a Nuclepore filter that is stained and examined microscopically for microfilariae. Adult worms or microfilariae can be identified in tissue specimens obtained at biopsy. Infection with *W. bancrofti* in the absence of bloodborne microfilariae may be diagnosed by detection of parasite antigen in the serum. Adult worms in lymphatic vessels can be visualized by ultrasonography.

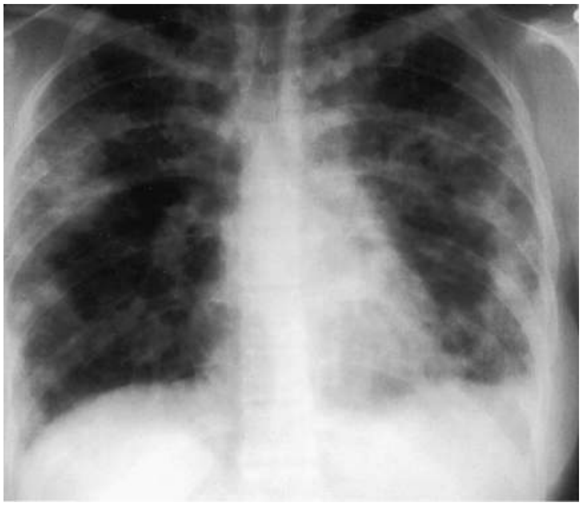

Figure 296-1 Chest radiograph of a woman with tropical pulmonary eosinophilia. Reticulonodular opacities are scattered throughout both lungs. *(From Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases, *vol 2, ed 6, Philadelphia, 2006, Elsevier, p. 3274.)*

TREATMENT

The use of antifilarial drugs in the management of acute lymphadenitis and lymphangitis is controversial. No controlled studies demonstrate that administration of drugs such as diethylcarbamazine modifies the course of acute lymphangitis. Diethylcarbamazine may be given to asymptomatic microfilaremic persons to lower the intensity of parasitemia. The drug also kills a proportion of the adult worms. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypotension, and even death may occur, especially with high microfilarial levels, the dose of diethylcarbamazine should be increased gradually (children: 1 mg/kg PO as a single dose on day 1, 1 mg/kg tid PO on day 2, 1-2 mg/kg tid PO on day 3, and 6 mg/kg/day divided tid PO on days 4-14; adults: 50 mg PO on day 1, 50 mg tid PO on day 2, 100 mg tid PO on day 3, and 6 mg/kg/day divided tid PO on days 4-14). For patients with no microfilaria in the blood, the full dose (6 mg/kg/day divided tid PO) can be given beginning on day 1. Repeat doses may be necessary to further reduce the microfilaremia and kill lymph-dwelling adult parasites. *W. bancrofti* is more sensitive than *B. malayi* to diethylcarbamazine.

Global programs to control and ultimately eradicate lymphatic filariasis from endemic populations currently recommend a single annual dose of diethylcarbamazine (6 mg/kg PO once) in combination with albendazole (400 mg PO once) for 5 yr (mass drug administration). In coendemic areas of filariasis and onchocerciasis, mass drug applications with single-dose ivermectin (150 µg/kg PO once) and albendazole are used because of severe adverse reactions with diethylcarbamazine in onchocerciasis-infected individuals. Five years of annual mass treatment is thought to be necessary to stop transmission. Adjuvant medicines (e.g., doxycycline) that target endosymbiont bacteria *(Wolbachia)* in filarial parasites may accelerate eradication.

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Chapter 297

Other Tissue Nematodes

Arlene E. Dent and James W. Kazura

ONCHOCERCIASIS *(ONCHOCERCA VOLVULUS)*

Infection with *Onchocerca volvulus* leads to onchocerciasis or **river blindness.** Onchocerciasis occurs primarily in West Africa but also in Central and East Africa and is the world's second leading infectious cause of blindness. There have been scattered foci in Central and South America, but the infection is now thought to be eliminated in the Americas with the exception of isolated populations living in the border area of Venezuela and Brazil. *O. volvulus* larvae are transmitted to humans by way of the bite of *Simulium* black flies that breed in fast-flowing streams. The larvae penetrate the skin and migrate through the connective tissue and eventually develop into adult worms that can be found tangled in fibrous tissue. Adult worms can live in the human body for up to 14 yr. Female worms produce large numbers of microfilariae that migrate through the skin, connective tissue, and eye. Most infected individuals are asymptomatic. In heavily infected subjects, clinical manifestations are a result of localized host inflammatory reactions to dead or dying microfilariae and subcutaneous adult worms surrounded by a palpable fibrous capsule. Cutaneous and ocular reactions to microfilaria produce pruritic dermatitis, punctate keratitis, corneal pannus formation, and chorioretinitis. Adult worms in **subcutaneous nodules** are not painful and tend to occur over bony prominences of the hip. The **diagnosis** can be established by obtaining snips of skin covering the scapulae, iliac crests, buttocks, or calves. The snips are immersed in saline for several hours and examined microscopically for microfilariae that have emerged into the fluid. The diagnosis can also be established by demonstrating microfilariae in the cornea or anterior chamber on slit-lamp examination or finding adult worms on a nodule biopsy specimen. Ophthalmology consultation should be obtained before treatment of eye lesions. A single dose of ivermectin (150 µg/kg PO) is the drug of choice and clears *O. volvulus* microfilariae from the skin for several months but has no effect on the adult worm. Treatment with ivermectin should be repeated every 6-12 mo until the patient is asymptomatic or has no evidence of eye infection. Adverse effects of ivermectin therapy include fever, urticaria, and pruritus, which are more frequent in individuals not born in endemic areas who acquired the infection following periods of intense exposure, such as Peace Corps volunteers. Patients with concurrent high-density microfilaremia from loiasis may develop encephalopathy with ivermectin therapy. Treatment with ivermectin should be withheld until *Loa loa* microfilaremia can be reduced by cytapheresis or the use of doxycycline, which kills endosymbiont bacteria *(Wolbachia)* of *O. volvulus*. Personal protection includes avoiding areas where biting flies are numerous, wearing protective clothing, and using insect repellent. Programs of mass treatment with ivermectin have been implemented in Africa in an effort to reduce the prevalence of onchocerciasis.

Although an etiologic link has not been established, epidemiologic studies have reported an association between onchocerciasis and a nodding syndrome of children living in focal areas of Uganda, Tanzania and South Sudan. The syndrome is characterized by the head dropping forward, convulsions, and periods of staring. A meta-analysis suggests an association between *O. volvulus* infection and epilepsy.

LOIASIS *(LOA LOA)*

Loiasis is caused by infection with the tissue nematode *Loa loa*. The parasite is transmitted to humans via diurnally biting flies *(Chrysops)* that live in the rain forests of West and Central Africa. Migration of adult worms through skin, subcutaneous tissue, and subconjunctival area can lead to transient episodes of pruritus, erythema, and localized edema known as **Calabar swellings,** which are nonerythematous areas of subcutaneous edema 10-20 cm in diameter typically found around joints such as the wrist or the knee (Fig. 297-1). They resolve over several days to wk and may recur at the same or different sites. Lifelong residents of *L. loa* endemic regions may have microfilaremia and eosinophilia but are often asymptomatic. In contrast, travelers to endemic regions may have a hyperreactive response to *L. loa* infection characterized by frequent recurrences of swelling, high level eosinophilia, debilitation, and serious complications such as glomerulonephritis and encephalitis. Diagnosis is usually established on clinical grounds, often assisted by the infected individual reporting a worm being seen crossing the conjunctivae. Microfilariae may be detected in blood smears collected between 10 AM and 2 PM. Adult worms should be surgically excised when possible. Diethylcarbamazine is the agent of choice for eradication of microfilaremia, but the drug does not kill adult worms. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypertension, and even death may occur, especially with high microfilaria levels, the dose of diethylcarbamazine should be increased gradually in such cases (children: 1 mg/kg PO on day 1, 1 mg/kg tid on day 2, 1-2 mg/kg tid on day 3, 6 mg/kg in 3 doses on days 4-21; adults: 50 mg PO on day 1, 50 mg tid on day 2, 100 mg tid on day 3, 6 mg/kg in 3 doses on days 4-21). Full doses can be instituted on day 1 in persons without microfilaremia (9 mg/kg/day PO divided tid for 12 days). A single dose of ivermectin (150 µg/kg) decreases microfilarial densities in the blood in persons with high density microfilaremia. A 3 wk course of albendazole can also be used to slowly reduce *L. loa* microfilarial levels as a result of embryotoxic effects on the adult worms. Antihistamines or corticosteroids may be used to limit allergic reactions secondary to killing of microfilariae. Personal protective measures include avoiding areas where biting flies are present, wearing protective clothing, and using insect repellents. Diethylcarbamazine (300 mg PO once weekly) prevents infection in travelers who spend prolonged periods of time in endemic areas. *L. loa* do not harbor *Wolbachia* endosymbionts, and therefore doxycycline has no effect on infection.

Figure 297-1 Calabar swelling of the right hand. *(From Guerrant RL, Walker DH, Weller PF, et al:* Tropical infectious diseases, *Philadelphia, 2006, Churchill Livingstone, p. 1165.)*

INFECTION WITH ANIMAL FILARIAE

The most commonly recognized zoonotic filarial infections are caused by members of the genus *Dirofilaria*. The worms are introduced into humans by the bites of mosquitoes containing third-stage larvae. The most common filarial zoonosis in the United States is *Dirofilaria tenuis,* a parasite of raccoons. In Europe, Africa, and Southeast Asia, infections are most commonly caused by the dog parasite *Dirofilaria repens*. The **dog heartworm,** *Dirofilaria immitis,* is the second most commonly

encountered filarial zoonosis worldwide. Other genera, including *Dipetalonema*-like worms, *Onchocerca,* and *Brugia,* are rare causes of zoonotic filarial infections.

Animal filariae do not undergo normal development in the human host. The clinical manifestations and pathologic findings correspond to the anatomic site of infection and can be categorized into 4 major groups: subcutaneous, lung, eye, and lymphatic. Pathologic examination of affected tissue reveals a localized foreign-body reaction around a dead or dying parasite. The lesion consists of granulomas with eosinophils, neutrophils, and tissue necrosis. *D. tenuis* does not leave the subcutaneous tissues, whereas *Brugia beaveri* eventually localizes to superficial lymph nodes. Infections may be present for up to several months. *D. immitis* larvae migrate for several months in subcutaneous tissues and most frequently result in a well-circumscribed coinlike lesion in a single lobe of the lung. The chest x-ray typically reveals a solitary pulmonary nodule 1-3 cm in diameter. Definitive diagnosis and cure depend on surgical excision and identification of the nematode within the surrounding granulomatous response. *D. tenuis* and *B. beaveri* infections present as painful 1-5 cm rubbery nodules in the skin of the trunk, of the extremities, and around the orbit. Patients often report having been engaged in activities predisposing to exposure to infected mosquitoes, such as working or hunting in swampy areas. Diagnosis and management is by surgical excision.

ANGIOSTRONGYLUS CANTONENSIS

Angiostrongylus cantonensis, the **rat lungworm,** is the most common cause of eosinophilic meningitis worldwide. Rats are the definitive host. Human infection follows ingestion of third-stage larvae in raw or undercooked intermediate hosts such as snails and slugs, or transport hosts such as freshwater prawns, frogs, and fish. Most cases are sporadic, but clusters have been reported, including clusters related to consumption of lettuce contaminated with intermediate or transport hosts. Even though most infections have been described in Southeast Asia, the South Pacific, and Taiwan, shipboard travel of infected rats has spread the parasite to Madagascar, Africa, the Caribbean, and, most recently, Australia and North America. Larvae penetrate the vasculature of the intestinal tract and migrate to the meninges, where they usually die but induce eosinophilic aseptic meningitis. Patients present 2-35 days after ingestion of larvae with severe headache, neck pain or nuchal rigidity, hyperesthesias and paresthesias (often migrating), fatigue, fever, rash, pruritus, nausea, and vomiting. Neurologic involvement varies from asymptomatic to paresthesias, severe pain, weakness, and focal neurologic findings such as cranial nerve palsies. Symptoms can last for several weeks to months, especially headache. Coma and death from hydrocephalus occur rarely in heavy infections. Peripheral blood eosinophilia is not always present on initial examination but peaks about 5 wk after exposure, often when symptoms are improving. Cerebrospinal fluid analysis reveals pleocytosis with >10% eosinophils in more than half of patients, with mildly elevated protein, a normal glucose level, and an elevated opening pressure. Head CT or MRI is usually unremarkable. The diagnosis is established clinically with supporting travel and diet history. A sensitive and specific enzyme-linked immunosorbent assay is available on a limited basis from the Centers for Disease Control and Prevention for testing either cerebrospinal fluid or serum. Treatment is primarily supportive because the majority of infections are mild and most patients recover within 2 mo without neurologic sequelae. Analgesics should be given for headache. Careful, repeated lumbar punctures should be performed to relieve hydrocephalus. Anthelmintic drugs have not been shown to influence the outcome and may exacerbate neurologic symptoms. The use of corticosteroids may shorten the duration of persistent and severe headaches. There is a higher incidence of permanent neurologic sequelae and mortality among children than among adults. Infection can be avoided by not eating raw or undercooked crabs, prawns, or snails.

ANGIOSTRONGYLUS COSTARICENSIS

Angiostrongylus costaricensis is a nematode that infects several species of rodents and causes abdominal angiostrongyliasis, which has been described predominantly in Latin America and the Caribbean. The mode of transmission to humans, who are accidental hosts, is unknown. It is speculated that infectious larvae from a molluscan intermediate host, such as the slug *Vaginulus plebeius,* contaminate water or vegetation that is inadvertently consumed (chopped up in salads or on vegetation contaminated with the slug's mucus secretions). Although this slug is not indigenous to the continental United States, it has been found on imported flowers and produce. The incubation period for abdominal angiostrongyliasis is unknown, but limited data suggest that it ranges from 2 wk to several months after ingestion of larvae. Third-stage larvae migrate from the gastrointestinal tract to the mesenteric arteries, where they mature into adults. These eggs degenerate and elicit an eosinophilic granulomatous reaction. The clinical findings of abdominal angiostrongyliasis **mimic appendicitis,** although the former are typically more indolent. Children can have fever, right lower quadrant pain, a tumor-like mass, abdominal rigidity, and a painful rectal examination. Most patients have leukocytosis with eosinophilia. Radiologic examination may show bowel wall edema, spasticity, or filling defects in the ileocecal region and the ascending colon. Examination of stool for ova and parasites is not useful for *A. costaricensis* but is useful for evaluating the presence of other intestinal parasites. An enzyme-linked immunosorbent assay is available for diagnosis on a limited basis from the Centers for Disease Control and Prevention, but the test has a low specificity and is known to cross react with *Toxocara, Strongyloides,* and *Paragonimus.* Many patients undergo laparotomy for suspected appendicitis and are found to have a mass in the terminal ileum to the ascending colon. No specific treatment is known for abdominal angiostrongyliasis. Even though the use of anthelmintic therapy has not been studied systematically, thiabendazole or diethylcarbamazine has been suggested. The prognosis is generally good. Most cases are self-limited, although surgery may be required in some patients. Cornerstones of prevention include avoidance of slugs and not ingesting raw food and water that may be contaminated with imperceptible slugs or slime from slugs. Rat control is also important in preventing the spread of infection.

DRACUNCULIASIS *(DRACUNCULUS MEDINENSIS)*

Dracunculiasis is caused by the guinea worm, *Dracunculus medinensis.* The World Health Organization has targeted dracunculiasis for eradication. As of 2012, the transmission of the infection was confined to Chad, Ethiopia, Mali, and South Sudan. Humans become infected by **drinking contaminated stagnant water** that contains immature forms of the parasite in the gut of tiny crustaceans (copepods or water fleas). Larvae are released in the stomach, penetrate the mucosa, mature, and mate. Approximately 1 yr later, the adult female worm (1-2 mm in diameter and up to 1 m long) migrates and partially emerges through the human host skin, usually of the legs. Thousands of immature larvae are released when the affected body part is immersed in the water. The cycle is completed when larval forms are ingested by the crustaceans. Infected humans have no symptoms until the worm reaches the subcutaneous tissue, causing a **stinging papule** that may be accompanied by urticaria, nausea, vomiting, diarrhea, and dyspnea. The lesion vesiculates, ruptures, and forms a painful ulcer in which a portion of the worm is visible. Diagnosis is established clinically. Larvae can be identified by microscopic examination of the discharge fluid. Metronidazole (25 mg/kg/day PO divided into 3 doses for 10 days; maximum dose: 750 mg) decreases local inflammation. Although the drug does not kill the worm, it facilitates its removal. The worm must be physically removed by rolling the slowly emerging 1 m long parasite onto a thin stick over a week. Topical corticosteroids shorten the time to complete healing while topical antibiotics decrease the risk of secondary bacterial infection. Dracunculiasis can be prevented by boiling or chlorinating drinking water or passing the water through a cloth sieve before consumption. Eradication is dependent on behavior modification and education.

GNATHOSTOMA SPINIGERUM

Gnathostoma spinigerum is a dog and cat nematode endemic to Southeast Asia, Japan, China, Bangladesh, and India, but has been identified

in Mexico and parts of South America. Infection is acquired by ingesting intermediate hosts containing larvae of the parasite such as raw or undercooked freshwater fish, chickens, pigs, snails, or frogs. Penetration of the skin by larval forms and prenatal transmission has also been described. Nonspecific signs and symptoms such as generalized malaise, fever, urticaria, anorexia, nausea, vomiting, diarrhea, and epigastric pain develop 24-48 hr after ingestion of *G. spinigerum*. Ingested larvae penetrate the gastric wall and migrate through soft tissue for up to 10 yr. Moderate to severe eosinophilia can develop. Cutaneous gnathostomiasis manifests as intermittent episodes of localized, migratory nonpitting edema associated with pain, pruritus, or erythema. Central nervous system involvement in gnathostomiasis is suggested by focal neurologic findings, initially neuralgia followed within a few days by paralysis or changes in mental status. Multiple cranial nerves may be involved, and the cerebrospinal fluid may be xanthochromic but typically shows an eosinophilic pleocytosis. Diagnosis of gnathostomiasis is based on clinical presentation and epidemiologic background. Brain and spinal cord lesions may be seen on CT or MRI. Serologic testing varies in sensitivity and specificity and is available through the Centers for Disease Control and Prevention. There is no well-documented effective chemotherapy, although albendazole (400 mg PO bid for 21 days) as first-line therapy or ivermectin (200 µg/kg for 2 days) as an alternative is recommended without or with surgical removal. Multiple courses may be needed. Corticosteroids have been used to relieve focal neurologic deficits. Surgical resection of the *Gnathostoma* is the major mode of therapy and the treatment of choice. Blind surgical resection of subcutaneous areas of diffuse swelling is not recommended because the worm can rarely be located. Prevention through the avoidance of ingestion of poorly cooked or raw fish, poultry, or pork should be emphasized for individuals living in or visiting endemic areas.

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Chapter 298
Toxocariasis (Visceral and Ocular Larva Migrans)

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ETIOLOGY

Most cases of human toxocariasis are caused by the **dog roundworm,** *Toxocara canis.* Adult female *T. canis* worms live in the intestinal tracts of young puppies and their lactating mothers. Large numbers of eggs are passed in the feces of dogs and embryonate under optimal soil conditions. *Toxocara* eggs can survive relatively harsh environmental conditions and are resistant to freezing and extremes of moisture and pH. Humans ingest embryonated eggs contaminating soil, hands, or fomites. The larvae hatch and penetrate the intestinal wall and travel via the circulation to the liver, lung, and other tissues. Humans do not excrete *T. canis* eggs because the larvae are unable to complete their maturation to adult worms in the intestine. The **cat roundworm,** *Toxocara cati,* is responsible for far fewer cases of visceral larva migrans (VLM) than *T. canis.* Ingestion of infective larvae of the raccoon ascarid *Baylisascaris procyonis* rarely leads to VLM but can cause neural larva migrans resulting in fatal eosinophilic meningitis. Ingestion of larvae from the opossum ascarid *Lagochilascaris minor* leads to VLM rarely.

EPIDEMIOLOGY

Human *T. canis* infections have been reported in nearly all parts of the world, primarily in temperate and tropical areas where dogs are popular household pets. Young children are at highest risk because of their unsanitary play habits and tendency to place fingers in the mouth. Other behavioral risk factors include pica, contact with puppy litters, and institutionalization. In North America, the highest prevalences of infection are in the southeastern United States and Puerto Rico, particularly among socially disadvantaged African-American and Hispanic children. In the United States, serosurveys show that 4.6-7.3% of children are infected. Assuming an unrestrained and untreated dog population, toxocariasis is prevalent in settings where other geohelminth infections, such as ascariasis, trichuriasis, and hookworm infections, are common.

PATHOGENESIS

T. canis larvae secrete large amounts of immunogenic glycosylated proteins. These antigens induce immune responses that lead to eosinophilia and polyclonal and antigen-specific immunoglobulin E production. The characteristic histopathologic lesions are granulomas containing eosinophils, multinucleated giant cells (histiocytes), and collagen. Granulomas are typically found in the liver but may also occur in the lungs, central nervous system, and ocular tissues. Clinical manifestations reflect the intensity and chronicity of infection, anatomic localization of larvae, and host granulomatous responses.

CLINICAL MANIFESTATIONS

There are 3 major clinical syndromes associated with human toxocariasis: VLM, ocular larva migrans (OLM), and covert toxocariasis (Table 298-1). The classic presentation of VLM includes eosinophilia, fever, and hepatomegaly, and occurs most commonly in toddlers with a history of pica and exposure to puppies. The findings include fever, cough, wheezing, bronchopneumonia, anemia, hepatomegaly, leukocytosis, eosinophilia, and positive *Toxocara* serology. Cutaneous manifestations such as pruritus, eczema, and urticaria can be present. OLM tends to occur in older children without signs or symptoms of VLM. Presenting symptoms include unilateral visual loss, eye pain, white pupil, or strabismus that develops over a period of weeks. Granulomas occur on the posterior pole of the retina and may be mistaken for retinoblastoma. Serologic testing for *Toxocara* has allowed the identification of individuals with less obvious or covert symptoms of infection. These children may have nonspecific complaints that do not constitute a recognizable syndrome. Common findings include hepatomegaly, abdominal pain, cough, sleep disturbance, failure to thrive, and headache with elevated *Toxocara* antibody titers. Eosinophilia may be present in only 50-75% of cases. The prevalence of positive *Toxocara* serology in the general population supports the notion that most children with *T. canis* infection are asymptomatic and will not develop overt clinical sequelae over time. A correlation between positive *Toxocara* serology and allergic asthma has also been described.

DIAGNOSIS

A presumptive diagnosis can be established in a young child with **eosinophilia** (>20%), leukocytosis, hepatomegaly, fevers, wheezing, and a history of geophagia and exposure to puppies or unrestrained dogs. Supportive laboratory findings include hypergammaglobulinemia and elevated isohemagglutinin titers to A and B blood group antigens. Most patients with VLM have an absolute eosinophil count of >500/µL. Eosinophilia is less common in subjects with OLM. Biopsy confirms the diagnosis. When biopsies cannot be obtained, an enzyme-linked immunosorbent assay using excretory-secretory proteins harvested from *T. canis* larvae maintained in vitro is the standard serologic test used to confirm toxocariasis. A titer of 1 : 32 is associated with a sensitivity of approximately 78% and a specificity of approximately 92%. The sensitivity for OLM is significantly less. The diagnosis of OLM can be established in patients with typical clinical findings of a retinal or peripheral pole granuloma or endophthalmitis with elevated antibody titers. Vitreous and aqueous humor fluid anti-*Toxocara* titers are usually greater than serum titers. The diagnosis of covert toxocariasis should be considered in individuals with chronic weakness, abdominal pain, or allergic signs with eosinophilia and increased immunoglobulin E. In temperate regions of the world, nonparasitic causes of eosinophilia that should be considered in the differential diagnosis include allergies,

Table 298-1 Clinical Syndromes of Human Toxocariasis

SYNDROME	CLINICAL FINDINGS	AVERAGE AGE	INFECTIOUS DOSE	INCUBATION PERIOD	LABORATORY FINDINGS	ELISA
Visceral larva migrans	Fevers, hepatomegaly, asthma	5 yr	Moderate to high	Weeks to months	Eosinophilia, leukocytosis, elevated IgE	High (≥1 : 16)
Ocular larva migrans	Visual disturbances, retinal granulomas, endophthalmitis, peripheral granulomas	12 yr	Low	Months to years	Usually none	Low
Covert toxocariasis	Abdominal pain, gastrointestinal symptoms, weakness, hepatomegaly, pruritus, rash	School-age to adult	Low to moderate	Weeks to years	±Eosinophilia, ±elevated IgE	Low to moderate

ELISA, enzyme-linked immunosorbent assay; IgE, immunoglobulin E; ±, with or without.

Adapted from Liu LX: Toxocariasis and larva migrans syndrome. In Guerrant RL, Walker DH, Weller PF, editors: Tropical infectious diseases: principles, pathogens & practice*, Philadelphia, 2006, Churchill-Livingstone, p. 1209.*

drug hypersensitivity, lymphoma, vasculitis, and the idiopathic hypereosinophilic syndrome (see Chapter 129).

TREATMENT

Most cases do not require treatment because signs and symptoms are mild and subside over a period of weeks to months. Several anthelmintic drugs have been used for symptomatic cases, often with adjunctive corticosteroids to limit inflammatory responses that presumably result from release of *Toxocara* antigens by dying parasites. Albendazole (400 mg PO bid for 5 days for all ages) has demonstrated efficacy in both children and adults. Mebendazole (100-200 PO mg bid for 5 days for all ages) is also useful. Anthelmintic treatment of central nervous system and ocular disease should be extended (3-4 wk). Even though there are no clinical trials regarding therapy of OLM, a course of oral corticosteroids such as prednisone (1 mg/kg/day PO for 2-4 wk) has been recommended to suppress local inflammation while treatment with anthelmintic agents is initiated.

PREVENTION

Transmission can be minimized by public health measures that prevent dog feces from contaminating the environment. These include keeping dogs on leashes and excluding pets from playgrounds and sandboxes that toddlers use. Children should be discouraged from putting dirty fingers in their mouth and eating dirt. Vinyl covering of sandboxes reduces the viability of *T. canis* eggs. Widespread veterinary use of broad-spectrum anthelmintics effective against *Toxocara* may lead to a decline in parasite transmission to humans.

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Chapter 299
Trichinellosis *(Trichinella spiralis)*

Arlene E. Dent and James W. Kazura

ETIOLOGY

Human trichinellosis (also called trichinosis) is caused by consumption of meat containing encysted larvae of *Trichinella spiralis,* a tissue-dwelling nematode with a worldwide distribution. After ingestion of raw or inadequately cooked meat from pigs (or other commercial meat sources such as horses) containing viable *Trichinella* larvae, the organisms are released from the cyst by acid-pepsin digestion of the cyst walls in the stomach and then pass into the small intestine. The larvae invade the small intestine columnar epithelium at the villi base and develop into adult worms. The adult female worm produces about 500 larvae over 2 wk and is then expelled in the feces. The larvae enter the bloodstream and seed striated muscle by burrowing into individual muscle fibers. Over a period of 3 wk, they coil as they increase about 10 times in length and become capable of infecting a new host if ingested. The larvae eventually become encysted and can remain viable for years. Sylvatic *Trichinella* spp. (*T. brivoti, T. nativa, T. pseudospiralis,* and *T. murrelli*) present in traditional native foods such as walrus meat and game meat may also cause disease similar to that caused by *T. spiralis*.

EPIDEMIOLOGY

Despite public health efforts to control trichinellosis by eliminating the practice of feeding garbage to domestic swine, epidemics and isolated cases of *Trichinella* spp. infection continue to be a health problem in many areas of the world. It is most common in Asia, Latin America, and Central Europe. Swine fed with garbage may become infected when given uncooked trichinous scraps, usually pig meat, or when the carcasses of infected wild animals such as rats are eaten. Prevalence rates of *T. spiralis* in domestic swine range from 0.001% in the United States to ≥25% in China. The resurgence of this disease can be attributed to translocations of animal populations, human travel, and export of food as well as ingestion of sylvatic *Trichinella* (*T. brivoti, T. nativa, T. pseudospiralis,* and *T. murrelli*) through game meat. In the United States from 1997 to 2001, wild game meat (especially bear meat) was the most common source of infection. Most outbreaks occur from the consumption of *T. spiralis*–infected pork (or horse meat in areas of the world where horse is eaten) obtained from a single source.

PATHOGENESIS

During the 1st 2-3 wk after infection, pathologic reactions to infection are limited to the gastrointestinal tract and include a mild, partial villous atrophy with an inflammatory infiltrate of neutrophils, eosinophils, lymphocytes, and macrophages in the mucosa and submucosa. Larvae are released by female worms and disseminate over the next several weeks. Skeletal muscle fibers show the most striking changes with edema and basophilic degeneration. The muscle fiber may contain the typical coiled worm, the cyst wall derived from the host cell, and the surrounding lymphocytic and eosinophilic infiltrate.

CLINICAL MANIFESTATIONS

The development of symptoms depends on the number of viable larvae ingested. Most infections are asymptomatic or mild, and children often show milder symptoms than adults who consumed the same amount of infected meat. Watery diarrhea is the most common symptom corresponding to maturation of the adult worms in the gastrointestinal tract, which occurs during the 1st 1-2 wk after ingestion. Patients may also complain of abdominal discomfort and vomiting. Fulminant

enteritis may develop in individuals with extremely high worm burdens. The classic symptoms of facial and periorbital edema, fever, weakness, malaise, and myalgia peak approximately 2-3 wk after the infected meat is ingested as the larvae migrate and then encyst in the muscle. Headache, cough, dyspnea, dysphagia, subconjunctival and splinter hemorrhages, and a macular or petechial rash may occur. Patients with high-intensity infection may die from myocarditis, encephalitis, or pneumonia. In symptomatic patients, eosinophilia is common and may be dramatic.

DIAGNOSIS

The Centers for Disease Control and Prevention diagnostic criteria for trichinellosis require positive serology or muscle biopsy for *Trichinella* with 1 or more compatible clinical symptoms (eosinophilia, fever, myalgia, facial or periorbital edema). To declare a discrete outbreak, at least 1 person must have positive serology or muscle biopsy. Antibodies to *Trichinella* are detectable approximately 3 wk after infection. Severe muscle involvement results in elevated serum creatine phosphokinase and lactic dehydrogenase levels. Muscle biopsy is not usually necessary, but if needed, a sample should be obtained from a tender swollen muscle. A history of eating undercooked meat supports the diagnosis. The cysts may calcify and be visible by radiograph.

TREATMENT

Recommended treatment of trichinellosis diagnosed at the gastrointestinal phase is albendazole (400 mg PO bid for 8-10 days for all ages) to eradicate the adult worms if a patient has ingested contaminated meat within the previous 1 wk. An alternative regimen is mebendazole (200-400 mg PO tid for 3 days followed by 400-500 mg tid for 10 days). There is no consensus for treatment of muscle-stage trichinellosis. Corticosteroids may be used, although evidence for efficacy is anecdotal.

PREVENTION

Trichinella larvae can be killed by cooking meat (≥55°C [131°F]) until there is no trace of pink fluid or flesh, or by storage in a freezer (−15°C [5°F]) for ≥3 wk. Freezing to kill larvae should only be applied to pork meat, as larvae in horse, wild boar, or game meat can remain viable even after 4 wk of freezing. Smoking, salting, and drying meat are unreliable methods of killing *Trichinella.* Strict adherence to public health measures, including garbage feeding regulations, stringent rodent control, prevention of exposure of pigs and other livestock to animal carcasses; constructing barriers between livestock, wild animals, and domestic pets; and proper handling of wild animal carcasses by hunters, can reduce infection with *Trichinella.* Current meat inspection for trichinellosis is by direct digestion and visualization of encysted larvae in meat samples. Serologic testing does not have a role in meat inspection.

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Chapter 300
Schistosomiasis (*Schistosoma*)

Charles H. King and Amaya L. Bustinduy

The term *schistosomiasis* **(bilharzia)** encompasses the acute and chronic inflammatory disorders caused by human infection with *Schistosoma* spp. parasites. Disease is related to both the systemic and focal effects of schistosome infection and its consequent host immune responses triggered by parasite eggs deposited in the tissues. For the affected individuals, this frequently manifests as disabling chronic morbidity.

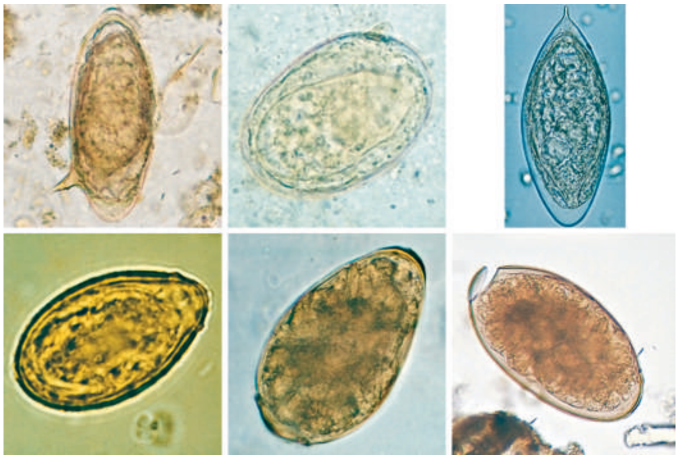

Figure 300-1 Eggs of common human trematodes. Clockwise from upper left: *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma haematobium*, *Clonorchis sinensis*, *Paragonimus westermani*, and *Fasciola hepatica* (note the partially open operculum). *(From Centers for Disease Control and Prevention [CDC]:* DPDx: laboratory identification of parasites of public health concern. *Available at: http://www.cdc.gov/dpdx/az.html)*

ETIOLOGY

Schistosoma organisms are the trematodes, or flukes, that parasitize the bloodstream. Five schistosome species infect humans: *Schistosoma haematobium, S. mansoni, S. japonicum, S. intercalatum,* and *S. mekongi*. Humans are infected through contact with water contaminated with cercariae, the free-living infective stage of the parasite. These motile, forked-tail organisms emerge from infected snails and are capable of penetrating intact human skin. As they reach maturity, adult worms migrate to specific anatomic sites characteristic of each schistosome species: *S. haematobium* adults are found in the perivesical and periureteral venous plexus, *S. mansoni* in the inferior mesenteric veins, and *S. japonicum* in the superior mesenteric veins. *S. intercalatum* and *S. mekongi* are usually found in the mesenteric vessels. Adult schistosome worms (1-2 cm long) are clearly adapted for an intravascular existence. The female accompanies the male in a groove formed by the lateral edges of its body. On fertilization, female worms begin oviposition in the small venous tributaries. The eggs of the 3 main schistosome species have characteristic morphologic features: *S. haematobium* has a terminal spine, *S. mansoni* has a lateral spine, and *S. japonicum* has a smaller size with a short, curved spine (Fig. 300-1). Parasite eggs provoke a significant granulomatous inflammatory response, which allows them to ulcerate through host tissues to reach the lumen of the urinary tract or intestines. They are carried to the outside environment in urine or feces (depending on the species), where they will hatch if deposited in freshwater. Motile miracidia emerge, infect specific freshwater snail intermediate hosts, and divide asexually. After 4-12 wk, the infective cercariae are released by the snails into the contaminated water.

EPIDEMIOLOGY

Schistosomiasis infects more than 207 million people worldwide, primarily children and young adults. Prevalence is increasing in many areas as population density increases and new irrigation projects provide broader habitats for vector snails. Humans are the main definitive hosts for the 5 clinically important species of schistosomes, although *S. japonicum* is also a zoonosis, infecting animals such as dogs, rats, pigs, and cattle. *S. haematobium* is prevalent in Africa and the Middle East; *S. mansoni* is prevalent in Africa, the Middle East, the Caribbean, and South America; and *S. japonicum* is prevalent in China, the Philippines, and Indonesia, with some sporadic foci in parts of Southeast Asia. The other 2 species are less prevalent. *S. intercalatum*

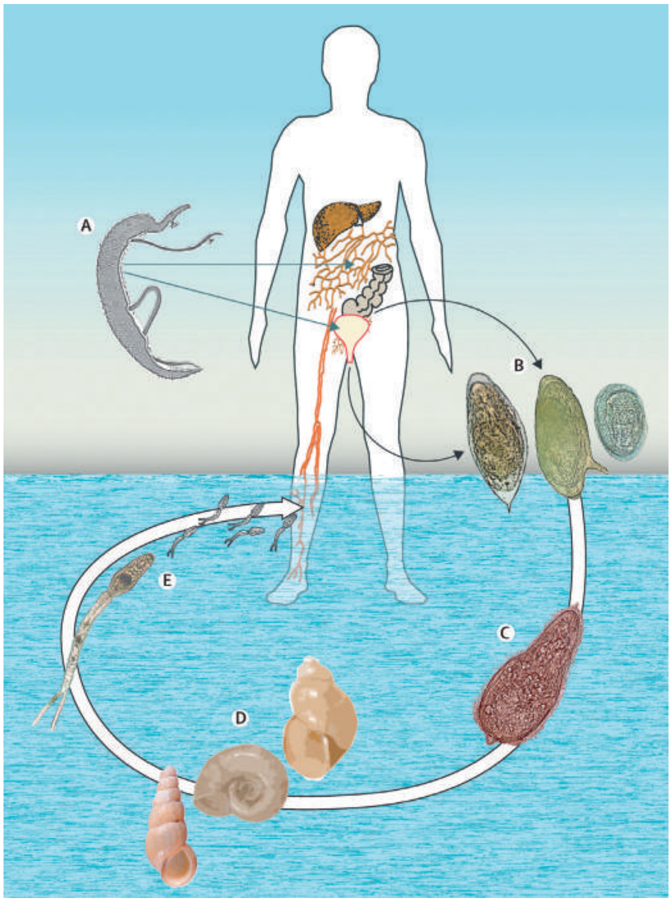

Figure 300-2 Lifecycles of *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*. *A*, Paired adult worms (larger male enfolding slender female). *B*, Eggs *(left to right, S. haematobium, S. mansoni, S. japonicum)*. *C*, Ciliated miracidium. *D*, Intermediate host snails *(left to right, Oncomelania, Biomphalaria, Bulinus)*. *E*, Cercariae. *(From Colley DG, Bustinduy AL, Secor WE, King CH: Human schistosomiasis.* Lancet *383:2253–2264, 2014, Fig. 1.)*

is found in West and Central Africa, and *S. mekongi* is found only along the upper Mekong River in the Far East.

Transmission depends on disposal of excreta, the presence of specific intermediate snail hosts, and the patterns of water contact and social habits of the population (Fig. 300-2). The distribution of infection in endemic areas shows that prevalence increases with age, to a peak at 10-20 yr of age. Exposure to infected water starts early in life for children living in endemic areas. Passive water contact by infants (accompanying mothers in their daily household activities) evolves to more active water contact as school age children pursue recreational activities such as swimming and wading.

Measuring intensity of infection (by quantitative egg count in urine or feces) demonstrates that the heaviest worm loads are found in school-age and adolescent children. Therefore, schistosomiasis is most prevalent and most severe in children and young adults, who are at maximal risk for suffering from its acute and chronic sequelae.

PATHOGENESIS

Both the early and late manifestations of schistosomiasis are immunologically mediated. Acute schistosomiasis, known as snail fever or Katayama syndrome, is a febrile illness that represents an immune complex disease associated with early infection and oviposition. The major pathology of infection occurs later, with chronic schistosomiasis, in which retention of eggs in the host tissues is associated with chronic granulomatous injury. Eggs may be trapped at sites of deposition (urinary bladder, ureters, intestine) or be carried by the bloodstream to other organs, most commonly the liver and less often the lungs and central nervous system. The host response to these eggs involves local as well as systemic manifestations. The cell-mediated immune response leads to granulomas composed of lymphocytes, macrophages, and eosinophils that surround the trapped eggs and add significantly to the degree of tissue destruction. Granuloma formation in the bladder wall and at the ureterovesical junction results in the major disease manifestations of schistosomiasis haematobia: hematuria, dysuria, and obstructive uropathy. Intestinal as well as hepatic granulomas underlie the pathologic sequelae of the other schistosome infections: ulcerations and fibrosis of intestinal wall, hepatosplenomegaly, and portal hypertension due to presinusoidal obstruction of blood flow. In terms of systemic disease, antischistosome inflammation increases circulating levels of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6, associated with elevated levels of C-reactive protein. These responses are associated with hepcidin-mediated inhibition of iron uptake and use, leading to anemia of chronic inflammation. Schistosomiasis-related undernutrition may be the result of similar pathways of chronic inflammation. Acquired partial protective immunity against schistosomiasis has been demonstrated in some animal species and may occur in humans.

CLINICAL MANIFESTATIONS

Most chronically infected individuals experience mild symptoms and may not seek medical attention; the more severe symptoms of schistosomiasis occur mainly in those who are heavily infected or who have been infected over longer periods of time. In addition to organ-specific morbidities, infected patients frequently demonstrate anemia, chronic pain, diarrhea, exercise intolerance, and chronic undernutrition manifesting as growth stunting. Cercarial penetration of human skin may result in a papular pruritic rash known as schistosomal dermatitis or swimmer's itch. It is more pronounced in previously exposed individuals and is characterized by edema and intense cellular infiltrates in the dermis and epidermis. Acute schistosomiasis, Katayama syndrome, may occur, particularly in heavily infected individuals 4-8 wk after exposure; this is a serum sickness–like syndrome manifested by the acute onset of fever, cough, chills, sweating, abdominal pain, lymphadenopathy, hepatosplenomegaly, and eosinophilia. Acute schistosomiasis most commonly presents in first-time visitors to endemic areas who experience primary infection at an older age.

Symptomatic children with chronic schistosomiasis haematobia usually complain of frequency, dysuria, and hematuria. Urine examination shows erythrocytes, parasite eggs, and occasional eosinophiluria. In endemic areas, moderate to severe pathologic lesions have been demonstrated in the urinary tract of >20% of infected children. The extent of disease correlates with the intensity of infection, but significant morbidity can occur even in lightly infected children. The advanced stages of schistosomiasis haematobia are associated with chronic renal failure, secondary infections, and cancer of the bladder.

An important complication of *S. haematobium* infection is female genital schistosomiasis. Eggs migrate from the vesical plexus to lodge in the female genital tract where they induce a granulomatous inflammatory response that can manifest as contact bleeding, pain, and eventual infertility. Symptoms start as early as 10 yr of age with an apparent 3-4–fold greater risk of HIV transmission. Pathognomonic lesions can be visualized in the cervix by photocolposcopy.

Children with chronic schistosomiasis *mansoni, japonica, intercalatum*, or *mekongi* may have intestinal symptoms; colicky abdominal pain and bloody diarrhea are the most common. However, the intestinal phase may remain subclinical, and the late syndrome of hepatosplenomegaly, portal hypertension, ascites, and hematemesis may then be the first clinical presentation. Liver disease is caused by granuloma formation and subsequent fibrosis; no appreciable liver cell injury occurs, and hepatic function may be preserved for a long time. Schistosome eggs may escape into the lungs, causing pulmonary hypertension and cor pulmonale. *S. japonicum* worms may migrate to the brain vasculature and produce localized lesions that cause seizures. Transverse myelitis, spinal compression, and other central nervous system involvement (meningoencephalitis) are rare but well known

complications in children or young adults with either acute or chronic *S. haematobium* or *S. mansoni* infection.

Although end-organ scarring is pathognomonic, affected children may also have persistent long-term systemic effects of infection, including poor growth, anemia, decreased aerobic capacity, and cognitive impairment.

DIAGNOSIS

Schistosome eggs are found in the excreta of infected individuals; quantitative methods should be used to provide an indication of the burden of infection. For diagnosis of schistosomiasis haematobia, a volume of 10 mL of urine should be collected around midday, which is the time of maximal egg excretion, and filtered for microscopic examination. Stool examination by the Kato-Katz thick smear procedure and detection of parasite antigen in patient serum or urine are the methods of choice for diagnosis and quantification of other schistosome infections.

TREATMENT

Treatment of children with schistosomiasis should be based on an appreciation of the intensity of infection and the extent of disease. The recommended treatment for schistosomiasis is praziquantel (40 mg/kg/day divided bid PO for 1 day for schistosomiasis *haematobia, mansoni,* and *intercalatum*; 60 mg/kg/day divided tid PO for 1 day for schistosomiasis *japonica* and *mekongi*). For *S. mansoni*, oxamniquine has been effective in some areas where praziquantel has been less effective.

PREVENTION

Transmission in endemic areas may be decreased by reducing the parasite load in the human population. The availability of oral, single-dose, effective chemotherapeutic agents may help achieve this goal. When added to national control drug-based programs, other measures such as improved sanitation, focal application of molluscicidals, and animal vaccination may prove useful in breaking the cycle of transmission. Ultimately, control of schistosomiasis is closely linked to economic and social development.

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Chapter 301

Flukes (Liver, Lung, and Intestinal)

Charles H. King and Amaya L. Bustinduy

Several different trematodes, or flukes, can parasitize humans and cause disease. Flukes are endemic worldwide but are more prevalent in the less-developed parts of the world. They include *Schistosoma,* or the blood flukes (see Chapter 300), as well as fluke species that cause infection in the human biliary tree, lung tissue, and intestinal tract. These latter trematodes are characterized by complex life cycles (Fig. 301-1). Sexual reproduction of adult worms in the definitive host produces eggs that are passed in the stool. Larvae, called **miracidia**, develop in freshwater. These, in turn, infect certain species of mollusks (aquatic snails or clams), in which asexual multiplication by parasite larvae produces **cercariae**. Cercariae then seek a second intermediate host, such as an insect, crustacean, or fish, or attach to vegetation to produce infectious **metacercariae**. Humans acquire liver, lung, and intestinal fluke infections by eating uncooked, lightly cooked, pickled, or smoked foods containing these infectious parasite cysts. The "alternation of generations" requires that flukes parasitize more than 1 host (often 3) to complete their life cycle. Because parasitic flukes are dependent on these nonhuman species for transmission, the distribution of human fluke infection closely matches the ecologic range of the flukes' intermediate hosts.

LIVER FLUKES

Fascioliasis *(Fasciola Hepatica)*

Fasciola hepatica, the sheep liver fluke, infects cattle, other ungulates, and occasionally humans. This infection affects approximately 17 million people worldwide and has been reported in many different

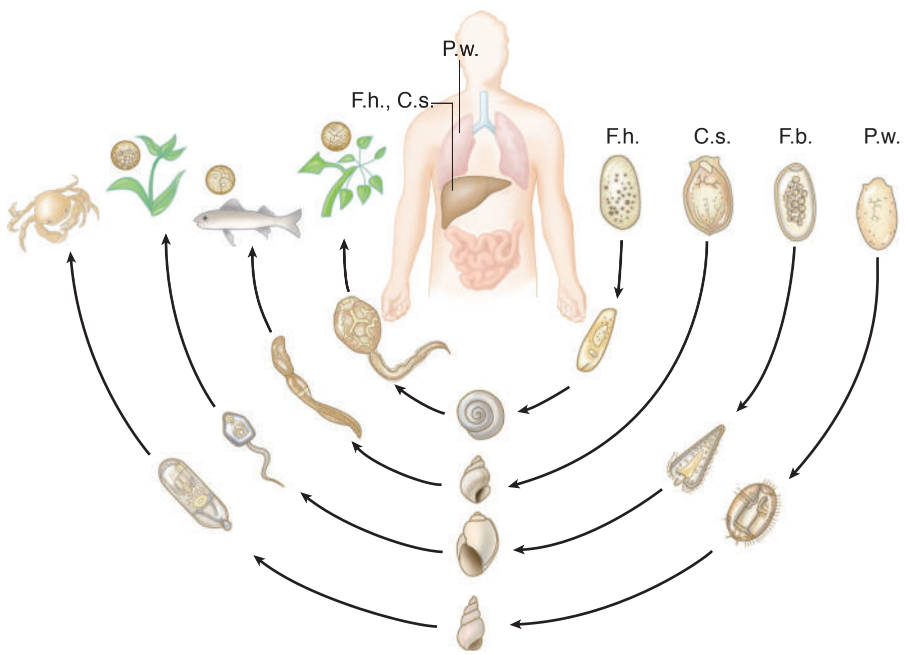

Figure 301-1 Life cycle of parasitic liver, lung, and intestinal flukes. *(Adapted from Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases*, ed 7. Philadelphia, 2010, Elsevier, Fig. 289-2.)*

parts of the world, particularly South America, Europe, Africa, China, Australia, and Cuba. Although *F. hepatica* is enzootic in North America, reported cases are extremely rare. Humans are infected by ingestion of metacercariae attached to vegetation, especially wild watercress, lettuce, and alfalfa. In the duodenum, the parasites excyst and penetrate the intestinal wall, liver capsule, and parenchyma. They wander for a few weeks before entering the bile ducts, where they mature. Adult *F. hepatica* (1-2.5 cm) commence oviposition approximately 12 wk after infection; the eggs are large (75-140 µm) and operculated. They pass to the intestines with bile and exit the body in the feces (see Fig. 301-1). On reaching freshwater, the eggs mature and hatch into miracidia, which infect specific snail intermediate hosts to multiply into many cercariae. These then emerge from infected snails and encyst on aquatic grasses and plants.

Clinical manifestations usually occur either during the liver migratory phase of the parasites or after their arrival at their final habitat in upper bile ducts. Fever, right upper quadrant pain, and hepatosplenomegaly characterize the first phase of illness. Peripheral blood eosinophilia is usually marked. As the worms enter bile ducts, most of the acute symptoms subside. On rare occasions, patients may suffer from obstructive jaundice or biliary cirrhosis, with signs of cholestasis, ascending cholangitis, cholelithiasis and jaundice with elevation in liver enzymes, direct bilirubin, and γ-glutamyl transpeptidase. *F. hepatica* infection is diagnosed by identifying the characteristic eggs in fecal smears or duodenal aspirates. Diagnosis can be suggested by positive serology and imaging that reveals acute hypodense liver lesions that change over time. Presentation can be dramatic in children, with features including generalized edema, hepatic cirrhosis with esophageal varices, and, in severe cases, death from generalized organ failure.

The recommended treatment of fascioliasis is triclabendazole (10 mg/kg once or twice PO) or bithionol (30-50 mg/kg once daily PO on alternate days for a total of 10-15 doses). In the United States, bithionol is available from the Centers for Disease Control and Prevention (telephone: 404-639-3670).

Clonorchiasis *(Clonorchis Sinensis)*

Infection of bile passages with *Clonorchis sinensis,* the Chinese or oriental liver fluke, is endemic in China, other parts of East Asia, and Japan, affecting more than 35 million people. Humans acquire infection by ingestion of raw or inadequately cooked freshwater fish carrying the encysted metacercariae of the parasite under their scales or skin. Metacercariae excyst in the duodenum and pass through the ampulla of Vater to the common bile duct and bile capillaries, where they mature into hermaphroditic adult worms (3-15 mm). *C. sinensis* worms deposit small operculated eggs (14-30 µm), which are discharged by way of the bile duct to the intestine and feces (see Fig. 301-1). The eggs mature and hatch outside the body, releasing motile miracidia into local freshwater streams, rivers, or ponds. If these are taken up by the appropriate snails, they develop into cercariae, which are in turn released from the snail to encyst under the skin or scales of freshwater fish.

Most individuals with *C. sinensis* infection, particularly those with few organisms, are minimally symptomatic. In heavily infected individuals, who tend to be older (>30 yr of age), localized obstruction of a bile duct results from repeated local trauma and inflammation. In these cases, cholangitis and cholangiohepatitis may lead to liver enlargement and jaundice. In Hong Kong, Korea, and other parts of Asia, cholangiocarcinoma is associated with chronic *C. sinensis* infection.

Clonorchiasis is diagnosed by examination of feces or duodenal aspirates for the parasite eggs. The recommended treatment of clonorchiasis is praziquantel (75 mg/kg/day divided tid PO for 2 days). An alternative, used in adults, is albendazole (10 mg/kg once daily PO for 7 days).

Opisthorchiasis (*Opisthorchis* Spp.)

Infections with species of *Opisthorchis* are clinically similar to those caused by *C. sinensis. Opisthorchis felineus* and *Opisthorchis viverrini* are liver flukes of cats and dogs that infect humans through ingestion of metacercariae in freshwater fish. Infection with *O. felineus* is endemic in Eastern Europe and Southeast Asia, and *O. viverrini* is found mainly in Thailand, affecting an estimated 10 million people. Most individuals are minimally symptomatic; liver enlargement, relapsing cholangitis, and jaundice may occur in heavily infected individuals. Diagnosis is based on recovering eggs from stools or duodenal aspirates. The recommended treatment of opisthorchiasis is praziquantel (75 mg/kg/day divided tid PO for 2 days).

LUNG FLUKES

Paragonimiasis (*Paragonimus* Spp.)

Human infection by the lung fluke *Paragonimus westermani,* and less frequently other species of *Paragonimus,* occurs throughout the Far East, in localized areas of West Africa, and in several parts of Central and South America, affecting approximately 20 million people. The highest incidence of paragonimiasis occurs in older children and adolescents 11-15 yr of age. Although *P. westermani* is found in many carnivores, human cases are relatively rare and seem to be associated with specific dietary habits, such as eating raw freshwater crayfish or crabs. These crustaceans contain the infective metacercariae in their tissues. After ingestion, the metacercariae excyst in the duodenum, penetrate the intestinal wall, and migrate to their final habitat in the lungs. Adult worms (5-10 mm) encapsulate within the lung parenchyma and deposit brown operculated eggs (60-100 µm), which pass into the bronchioles and are expectorated by coughing (see Fig. 301-1). Ova can be detected in the sputum of infected individuals or in their feces. If eggs reach freshwater, they hatch and undergo asexual multiplication in specific snails. The cercariae encyst in the muscles and viscera of crayfish and freshwater crabs.

Most individuals infected with *P. westermani* harbor low or moderate worm loads and are minimally symptomatic. The clinical manifestations include cough, production of rust-colored sputum, and hemoptysis (mimicking tuberculosis), which is the principal manifestation and occurs in 98% of symptomatic children. There are no characteristic physical findings, but laboratory examination usually demonstrates marked eosinophilia. Chest x-rays often reveal small patchy infiltrates or radiolucencies in the middle lung fields; however, radiographs may appear normal in one-fifth of infected individuals. In rare circumstances, lung abscess, pleural or pericardial effusion, or bronchiectasis may develop. Extrapulmonary localization of *P. westermani* in the brain, peritoneum, intestines, or pericardium may rarely occur. Cerebral paragonimiasis occurs primarily in heavily infected individuals living in highly endemic areas of the Far East. The clinical presentation resembles Jacksonian epilepsy or the symptoms of cerebral tumors.

Definitive diagnosis of paragonimiasis is established by identification of eggs in fecal or sputum smears. The recommended treatment of paragonimiasis is praziquantel (75 mg/kg/day divided tid PO for 2 days). Triclabendazole can also be used (5 mg/kg PO daily for 3 days).

INTESTINAL FLUKES

Several wild and domestic animal intestinal flukes, including *Fasciolopsis buski, Nanophyetus salmincola,* and *Heterophyes heterophyes,* may accidentally infect humans who eat uncooked or undercooked fish or water plants. For example, *F. buski* is endemic in the Far East, where humans who ingest metacercariae encysted on aquatic plants become infected. These develop into large flukes (1-5 cm) that inhabit the duodenum and jejunum. Mature worms produce operculated eggs that pass with feces; the organism completes its life cycle through specific snail intermediate hosts. Individuals with *F. buski* infection are usually asymptomatic; heavily infected subjects complain of abdominal pain and diarrhea and show signs of malabsorption. Diagnosis of fasciolopsiasis and other intestinal fluke infections is established by fecal examination and identification of the eggs (see Fig. 301-1). As for other fluke infections, praziquantel (75 mg/kg/day divided tid PO for 2 days) is the drug of choice.

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Chapter 302

Adult Tapeworm Infections

Philip R. Fischer and A. Clinton White Jr.

Tapeworms are adult forms of cestodes, multicellular helminth parasites, that live in human intestines and cause non–life-threatening illness. Invasive larval forms of cestodes are associated with cysts that lead to severe human disease such as neurocysticercosis (*Taenia solium*, discussed in Chapter 303) and echinococcosis (mostly *Echinococcus granulosa* and *Echinococcus multilocularis*, discussed in Chapter 304). The worms are flat and multisegmented, varying in length from 8 mm to 10 meters. Table 302-1 summarizes the key features of tapeworms that affect children.

ETIOLOGY

The **beef tapeworm** *(Taenia saginata)*, the **pork tapeworm** *(T. solium)*, and the Asian tapeworm *(Taenia asiatica)* are long worms (4-10 m) named for their intermediate hosts (*T. saginata*, *T. solium*) or geographic distribution (*T. asiatica*; larval host is the pig). The adult worms are found only in the human intestine. Like the adult stage of all tapeworms, their body is a series of hundreds or thousands of flattened segments **(proglottids)** with an anterior attachment organ **(scolex)** that anchors the parasite to the bowel wall. New segments arise from the distal aspect of the scolex with progressively more mature segments attached distally. The gravid terminal segments contain 50,000-100,000 eggs, and the eggs or even detached intact proglottids pass out of the child via the anus (with or separate from defecation). These tapeworms differ most significantly in that the intermediate stage of the pork tapeworm (cysticercus) can also infect humans and cause significant morbidity (see Chapter 303), whereas the larval stage of *T. saginata* does not cause human disease. *T. asiatica* is similar to and often confused with the beef tapeworm.

EPIDEMIOLOGY

The pork and beef tapeworms are distributed worldwide, with the highest risk for infection in Central America, Africa, India, Southeast Asia, and China where the relevant intermediate host is raised domestically. The prevalence in adults may not reflect the prevalence in young children, because cultural practices may dictate how well meat is cooked and how much is served to children.

PATHOGENESIS

When children ingest raw or undercooked meat containing larval cysts, gastric acid and bile facilitate release of immature scolices that attach to the lumen of the small intestine. The parasite grows, adding new segments at the base of the scolex. The terminal segments mature and after 2-3 mo produce eggs that are released in stool. The surface of proglottids serves as an absorptive organ to "steal" nutritional elements from the child's small bowel for use by the parasite. There is sometimes a transient eosinophilia prior to the parasite maturing enough to release eggs.

CLINICAL MANIFESTATIONS

Nonspecific abdominal symptoms have been reported with beef and pork tapeworm infections, but the most bothersome symptom is the psychologic distress caused by seeing proglottids in the stool or undergarments. The released segments of the worms are motile (especially those of *T. saginata)* and sometimes lead to anal pruritus. The adult beef and pork tapeworms are only rarely associated with other symptoms.

DIAGNOSIS

Identification of the infecting tapeworm species facilitates understanding of risk for invasive disease. Carriers of adult pork tapeworms are at increased risk for transmitting eggs with the pathogenic intermediate stage **(cysticercus)** to themselves or others, whereas children infected with the beef tapeworm or *T. asiatica* are a risk only to livestock. Because proglottids are generally passed intact, visual examination for gravid proglottids in the stool is a sensitive test; these segments may be used to identify species. Eggs, by contrast, are often absent from stool and cannot distinguish between *T. saginata* and *T. solium* (Fig. 302-1). If the parasite is completely expelled, the scolex of each species is diagnostic. The scolex of *T. saginata* has only a set of 4 anteriorly oriented suckers, whereas *T. solium* is armed with a double row of hooks in addition to suckers. The proglottids of *T. saginata* have more than 20 branches from a central uterine structure, and those of *T. solium* have 10 or fewer. Expelled proglottid segments are usually about 0.5 × 1-2 × 0.1 cm in size. Molecular methods can distinguish *T. saginata* from *T. asiatica*. Antigen detection tests are increasingly available.

Table 302-1 Key Features of Common Tapeworms in Children

PARASITE SPECIES	GEOGRAPHY	SOURCE	SYMPTOMS	TREATMENT
Taenia saginata	Asia, Africa, Latin America	Cysts in beef	Abdominal discomfort, motile proglottid migration, passing segments	Praziquantel or niclosamide, possibly nitazoxanide
Taenia solium	Asia, Africa, Latin America	Cysticerci in pork	Minimal, proglottids in stool	Praziquantel or niclosamide, possibly nitazoxanide
Taenia asiatica	Asia	Pigs	Minimal	Praziquantel or niclosamide, possibly nitazoxanide
Diphyllobothrium species	Worldwide, often northern areas	Plerocercoid cysts in fresh water fish	Usually minimal; with prolonged or heavy infection with *Diphyllobothrium latum*, vitamin B_{12} deficiency	Praziquantel or niclosamide
Hymenolepis	Worldwide, often northern areas	Infected humans, rodents	Mild abdominal discomfort	Praziquantel, niclosamide, or nitazoxanide
Dipylidium caninum	Worldwide	Domestic dogs and cats	Eosinophilia, anal pruritus confused with pinworm, proglottids in stool	Praziquantel or niclosamide

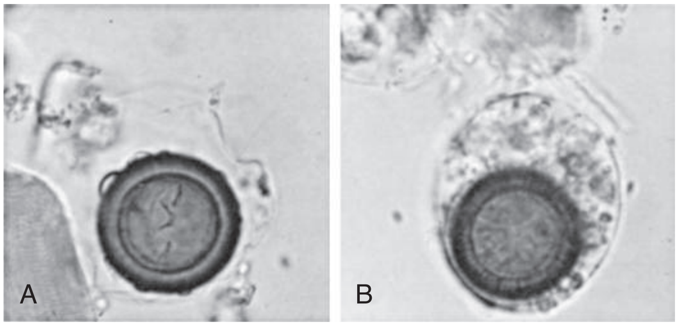

Figure 302-1 **A** and **B,** Eggs of *Taenia saginata* recovered from feces (original magnification ×400). The eggs are generally bile stained, dark, and prismatic. There is occasionally some surrounding cellular material from the proglottid in which the egg develops, which is more evident in **B** than in **A.** The larva within the egg shows 3 pairs of hooklets **(A),** which may occasionally be observed in motion.

DIFFERENTIAL DIAGNOSIS

Anal pruritus may mimic symptoms of pinworm *(Enterobius vermicularis)* infection. *Diphyllobothrium latum* and *Ascaris lumbricoides* (a long round worm) may be mistaken for *T. saginata* or *T. solium* in stools.

TREATMENT

Infections with all adult tapeworms respond to praziquantel (25 mg/kg PO once). When available, an alternative treatment for taeniasis is niclosamide (50 mg/kg PO once for children, 2 g PO once for adults). Nitazoxanide is sometimes effective as well. The parasite is usually expelled on the day of administration. Treatment with electrolyte-polyethylene glycol bowel preparations can increase the yield of passage of scolices.

PREVENTION

Prolonged freezing or thorough cooking of beef and pork kills the larval cystic forms of the parasite. Appropriate human sanitation can interrupt transmission by preventing infection in livestock.

DIPHYLLOBOTHRIASIS (*DIPHYLLOBOTHRIUM* SPECIES)

Etiology

The **fish tapeworms** of the genus *Diphyllobothrium* are the longest human tapeworms, reaching more than 10 meters in length, and have an anatomic organization similar to that of other adult cestodes. An elongated scolex equipped with slits **(bothria)** along each side but no suckers or hooks is followed by thousands of segments looped in the small bowel. Gravid terminal proglottids detach periodically but tend to disintegrate before expulsion, thus releasing eggs rather than intact worm segments in the feces. In contrast to taeniids, the life cycle of *Diphyllobothrium* species requires 2 intermediate hosts. Small fresh water crustaceans (copepods) take up the larvae that hatch from parasite eggs. The parasite passes up the food chain as small fish eat the copepods and are in turn eaten by larger fish. In this way, the juvenile parasite becomes concentrated in pike, walleye, perch, burbot, and perhaps salmon associated with aquaculture of this species. Consumption of raw or undercooked fish leads to human infection with adult fish tapeworms.

Epidemiology

The fish tapeworm is most prevalent in the temperate climates of Europe, North America, and Asia but may be found along the Pacific coast of South America and in Africa. In North America, the prevalence is highest in Alaska, Canada, and northern areas of continental United States. The tapeworm is found in fish from those areas that are then taken to market. Persons who prepare raw fish for home or commercial use or who sample fish before cooking are particularly at risk for infection.

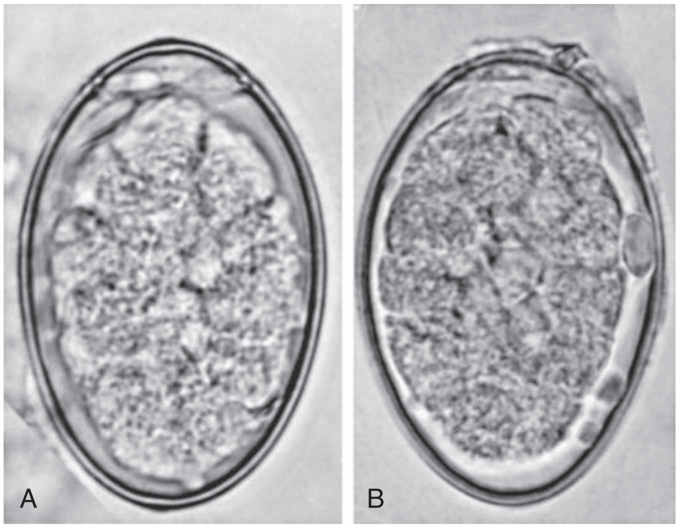

Figure 302-2 **A** and **B,** Eggs of *Diphyllobothrium latum* as seen in feces (original magnification ×400). The caplike operculum is at the upper end of the egg here.

Pathogenesis

The adult worm of *D. latum* (found in northern Europe) has high affinity receptors and efficiently scavenges vitamin B_{12} for its own use in the constant production of large numbers of segments and as many as 1 million eggs per day. As a result, diphyllobothriasis causes megaloblastic anemia in 2-9% of infections. Interestingly, other *Diphyllobothrium* species do not out-compete the host for vitamin B_{12}. Children with other causes of vitamin B_{12} or folate deficiency, such as chronic infectious diarrhea, celiac disease, or congenital malabsorption, are more likely to develop symptomatic infection.

Clinical Manifestations

Infection is largely asymptomatic. Segments may be noted in stool. Those who develop vitamin B_{12} or folate deficiency present with megaloblastic anemia with leukopenia, thrombocytopenia, glossitis, and/or signs of spinal cord posterior column dysfunction (loss of vibratory sense, proprioception, and coordination).

Diagnosis

Parasitologic examination of the stool is useful because eggs are abundant in the feces and have morphology distinct from that of all other tapeworms. The eggs are ovoid and have an operculum, which is a cap structure at 1 end that opens to release the embryo (Fig. 302-2). The worm itself has a distinct scolex and proglottid morphology; however, these are not likely to be passed spontaneously.

Differential Diagnosis

A segment or a whole section of the worm might be confused with *Taenia* or *Ascaris* after it is passed. Pernicious anemia, bone marrow toxins, and dietary restriction may contribute to or mimic the nutritional deficiencies associated with diphyllobothriasis.

Treatment

As with all adult tapeworms, *D. latum* infections respond to praziquantel (5-10 mg/kg PO once). Niclosamide (50 mg/kg in a single oral dose) is also effective.

Prevention

The intermediate stage is easily killed by brief cooking or prolonged freezing of fish prior to ingestion. Because humans are the major reservoir for adult worms, health education is one of the most important tools for preventing transmission, together with improved human sanitation.

HYMENOLEPIASIS *(HYMENOLEPIS)*

Infection with *Hymenolepis nana,* the **dwarf tapeworm,** is very common in developing countries. It is a major cause of eosinophilia, and although it rarely causes overt disease, the presence of *H. nana* eggs in stool may serve as a marker for exposure to poor hygienic conditions and the risk of additional fecal-oral contamination. The intermediate stage of *Hymenolepis diminuta* develop in various hosts (e.g., rodents, ticks, and fleas), but the entire life cycle of *H. nana* is completed in humans. Therefore, hyperinfection with thousands of small adult worms in a single child may occur. A similar infection may occur less commonly with the species *H. diminuta.* Eggs but not segments may be found in the stool. *H. nana* infection responds to praziquantel (25 mg/kg PO once). Nitazoxanide is effective in about three-fourths of children (100 mg by mouth twice daily for 3 days for children 1-3 yr of age, 200 mg by mouth twice daily for 3 days for children 4-11 yr of age, and 500 mg by mouth twice daily for 3 days for older children).

DIPYLIDIASIS *(DIPYLIDIUM CANINUM)*

Dipylidium caninum is a common tapeworm of domestic dogs and cat. Human infection is relatively rare. Direct transmission between pets and humans does not occur; human infection requires ingestion of the parasite's intermediate host, the dog or cat flea. Infants and small children are particularly susceptible because of their level of hygiene, generally more intimate contact with pets, and activities in areas where fleas can be encountered. Thus, children are most at risk of inadvertent ingestion of fleas infected with the larvae. The most common symptoms is passage of proglottids in stool. The proglottids are similar in size and shape to white rice grains. Anal pruritus, vague abdominal pain, and diarrhea have at times been associated with dipylidiasis, which is thus sometimes confused with pinworm *(E. vermicularis).* Dipylidiasis responds to treatment with praziquantel (5-10 mg/kg PO once) and niclosamide (50 mg/kg orally as a single dose). Deworming of pets and flea control are the best preventive measures.

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Chapter 303

Cysticercosis

A. Clinton White Jr. and Philip R. Fischer

ETIOLOGY

Taenia solium, also known as the **pork tapeworm**, causes 2 different infections in children. In its normal lifecycle, children can acquire the tapeworm form by ingestion of undercooked pork containing the larvae cysts (see Chapter 302). In the intestines, the cyst converts into the tapeworm form. Children are also susceptible to infection by the eggs shed by tapeworm carriers. After the eggs are ingested, the larvae are released from the eggs, invade through the intestines, and migrate through the bloodstream to the muscles (and other organs), where they form tissue cysts (0.2-2.0 cm fluid-filled bladders containing a single invaginated **scolex**). Infection with the cystic form is termed cysticercosis, and involvement of the central nervous system is termed **neurocysticercosis.** The tapeworm form only develops after ingestion of undercooked pork. Ingestion of pork is not necessary to develop cysticercosis, but individuals harboring an adult worm may infect themselves with the eggs by the fecal-oral route.

EPIDEMIOLOGY

The pork tapeworm is widely distributed wherever pigs are raised and have contact with human fecal material. Intense transmission occurs in Central and South America, southern and Southeast Asia, and much of sub-Saharan Africa. In these areas, approximately 30% of cases of seizures may be a result of cysticercosis. Most cases of cysticercosis in the United States are imported; however local transmission has been rarely documented.

PATHOGENESIS

Living, intact cystic stages usually suppress the host immune and inflammatory responses. Intact cysts can be associated with disease when they obstruct the flow of cerebrospinal fluid. Most cysts remain asymptomatic for a few years. Symptoms typically develop as the cysticerci begin to degenerate, associated with a host inflammatory response. The natural history of cysts is to eventually resolve by complete resorption or calcification, but this process make take years. Cysticerci can also present as subcutaneous nodules, ocular infection, or spinal lesions with myelopathy or radiculopathy.

CLINICAL MANIFESTATIONS

Seizures are the presenting finding in the vast majority of children with neurocysticercosis. Less-common manifestations include hydrocephalus, diffuse cerebral edema, or focal neurologic findings. It is important to classify neurocysticercosis as parenchymal, intraventricular, subarachnoid, spinal, or ocular on the basis of anatomic location, clinical presentation, and radiologic appearance since the prognosis and management vary with location.

Parenchymal neurocysticercosis typically presents with seizures. The seizures are usually focal, but often generalize. Children may present with a single seizure or recurrent epilepsy. Mild neurocognitive defects have been documented from cysticerci alone, but are more commonly associated with poorly controlled seizures. A fulminant encephalitis-like presentation may rarely occur, after a massive initial infection associated with cerebral edema. Intraventricular neurocysticercosis (up to 20% of cases) is associated with obstructive hydrocephalus and acute, subacute, or intermittent signs of increased intracranial pressure, usually without localizing signs. Subarachnoid neurocysticercosis is rare in children. It can be associated with basilar arachnoiditis that can present with signs of meningeal irritation, communicating hydrocephalus, cerebral infarction, or spinal disease with radiculitis or transverse myelitis. Cysticerci in the tissues may present with focal findings from mass effect. Ocular neurocysticercosis causes decreased visual acuity because of cysticerci in the retina or vitreous, retinal detachment, or iridocyclitis.

DIAGNOSIS

Neurocysticercosis should be suspected in a child with onset of seizures or hydrocephalus and who also has a history of residence in an endemic area or a care provider from an endemic area. The most useful diagnostic study for parenchymal disease is MRI of the head. MRI provides the most information about cyst location, viability, and associated inflammation. The protoscolex is sometimes visible within the cyst, which provides a pathognomonic sign for cysticercosis (Fig. 303-1*A*). The MRI also better detects basilar arachnoiditis (Fig. 303-1*B*), intraventricular cysts (Fig. 303-1*C*), and cysts in the spinal cord. CT is best for identifying calcifications. A solitary parenchymal cyst, with or without contrast enhancement, and central nervous system calcifications are the most common findings in children (Fig. 303-2). Plain films may reveal calcifications in muscle or brain consistent with cysticercosis. In children from endemic regions, the presentation with a single enhancing lesion that is round and <2 cm in diameter, absence of symptoms or signs of other diseases (e.g., no fever or lymph nodes), no focal findings, and no evidence of increased intracranial pressure is highly specific for neurocysticercosis.

Serologic diagnosis using the enzyme-linked immunotransfer blot is available commercially in the United States and through the Centers for Disease Control and Prevention. Serum antibody testing is highly specific, but is frequently negative in children with single lesions or just calcifications. Antigen-detection assays and polymerase chain reaction assays show promise as diagnostic procedures but are currently not commercially available.

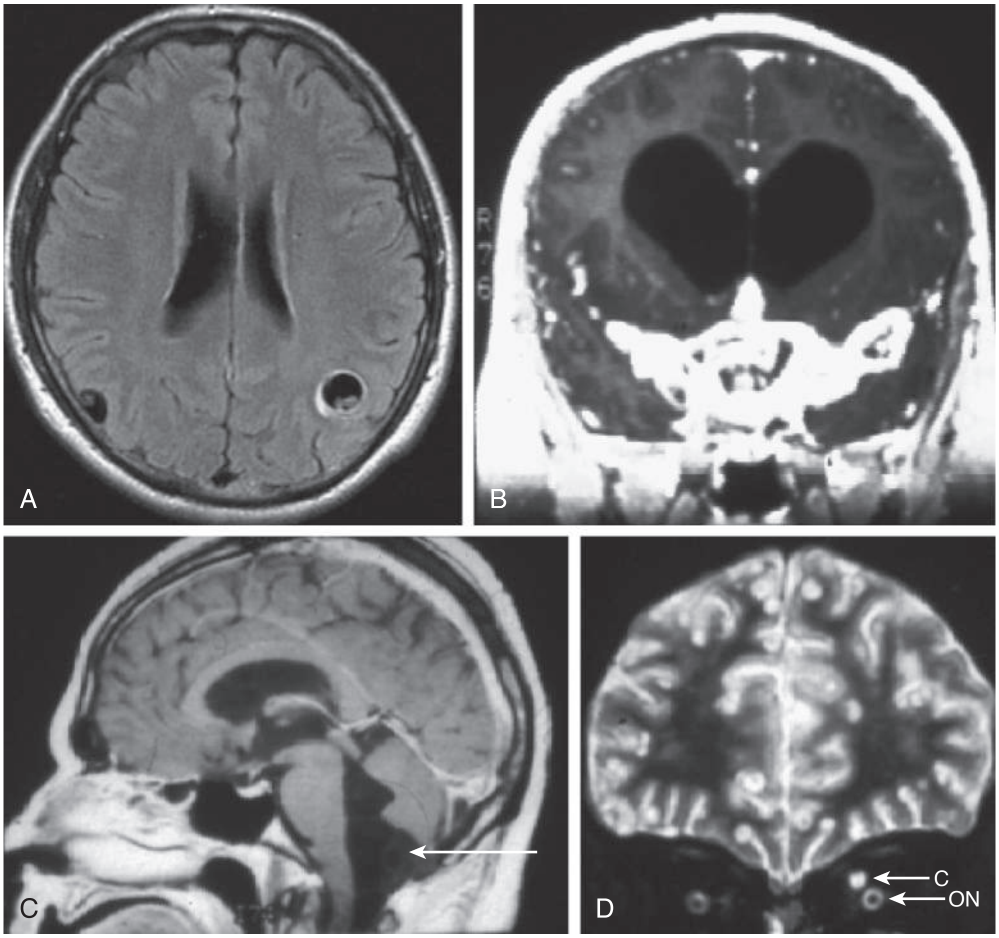

Figure 303-1 **A,** MRI (T1 weighted) demonstrating 2 parenchymal cysts with protoscoleces. **B,** MRI (T1 weighted) of cysticercal basilar arachnoiditis. **C,** MRI (T1 weighted) showing a cyst below the fourth ventricle *(arrow)*. **D,** MRI (T2 weighted) showing a cysticercus **(C)** above the optic nerve *(ON)*.

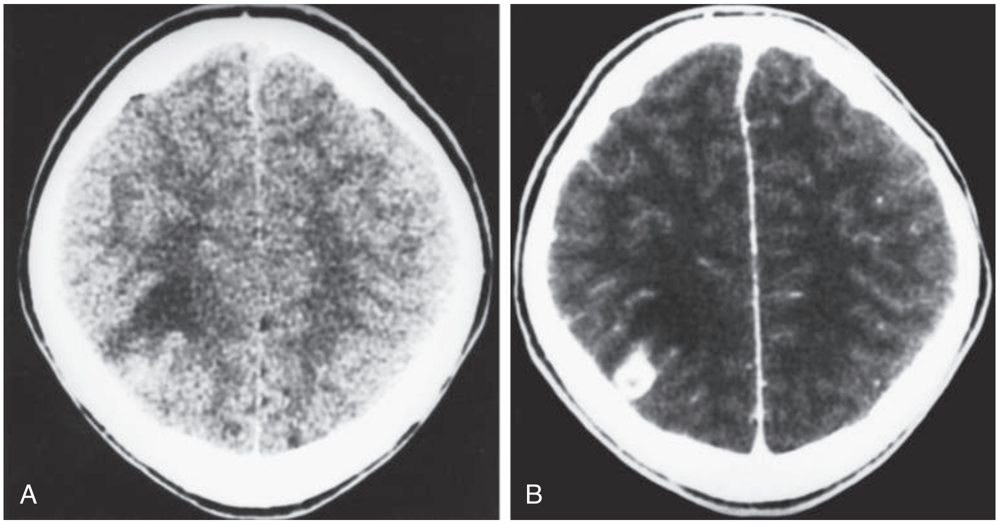

Figure 303-2 CT image of a solitary lesion of neurocysticercosis with **(A)** and without **(B)** contrast, showing contrast enhancement. *(Courtesy of Dr. Wendy G. Mitchell and Dr. Marvin D. Nelson, Children's Hospital, Los Angeles.)*

DIFFERENTIAL DIAGNOSIS

Neurocysticercosis is often confused clinically with other seizure disorders. Clinical suspicion is based on travel history, a history of contact with an individual who might carry an adult tapeworm, or suggestive imaging studies. The imaging appearance can be confused with brain abscess, granulomas (including tuberculomas, fungal infections, Langerhans histiocytosis, and toxoplasmosis), and tumors.

TREATMENT

The initial management of cysticercosis should focus on symptomatic therapy for seizures and/or hydrocephalus. Seizures can usually be controlled using standard antiepileptic drugs. If the lesions resolve, antiepileptic drugs can often be tapered off. Frequent seizures or the development of calcified lesions are risk factors for recurrent seizures and indications for prolonged or lifelong antiepileptic therapy.

The natural history of parenchymal lesions is to resolve spontaneously with or without antiparasitic drugs, but this process is often prolonged (months to years). Solitary parenchymal cysts resolve slightly more rapidly with antiparasitic therapy. Antiparasitic drugs also decrease the frequency of recurrent seizures. Other forms of the disease are less common in children. In adults with cystic lesions, randomized, controlled trials suggested an overall 2-fold decrease in recurrence of generalized seizures with albendazole treatment. The benefit to children was significantly less, perhaps because most of these infections were with only 1-2 cysts. Corticosteroids likely also decrease seizure frequency.

Albendazole is the most commonly used antiparasitic (15 mg/kg/day PO divided bid). It can be taken with a fatty meal to improve absorption. The most common duration of therapy is 7 days for parenchymal lesions. However, longer duration (months), higher doses (up to 30 mg/kg/day), or combination therapy with praziquantel is often required for multiple lesions or subarachnoid disease. Praziquantel (50-100 mg/kg/day PO divided tid for 28 days) can be used with albendazole or as an alternative to it. First-pass metabolism is common with corticosteroids or antiepileptic drugs. Cimetidine can be used in conjunction with praziquantel to blunt the first-pass metabolism. A worsening of symptoms can follow the use of either drug based on the host's inflammatory response to the dying parasite. Patients should be medicated with prednisone 1-2 mg/kg per day or oral dexamethasone 0.15 mg/kg per day beginning before the first dose of antiparasitic drugs and continuing for at least 2 wk. Methotrexate can be used as a steroid-sparing agent in patients requiring prolonged antiinflammatory therapy

Most patients with hydrocephalus require neurosurgical interventions. Some cases require emergent placement of a ventriculostomy, but most can be managed by cystectomy alone. For obstructive hydrocephalus caused by ventricular cysticercosis, many patients can be cured by minimally invasive surgery. Neuroendoscopy is the preferred approach to cysticerci in the lateral or third ventricle. Cysticerci in the fourth ventricle can be removed by either flexible endoscopy or via a suboccipital craniotomy Adherent cysticerci that cannot be removed can be treated by placement of a ventriculoperitoneal shunt. However, there is a high rate of shunt failure, which can be minimized somewhat by treatment with antiparasitic drugs plus corticosteroids.

Subarachnoid disease has a poor prognosis. However, recent studies suggest that the prognosis is much improved by aggressive therapy, including antiparasitic drugs, antiinflammatory treatment, and neurosurgical procedures for hydrocephalus (e.g., placement of a ventriculoperitoneal shunt). However, the dose and duration of antiparasitic and antiinflammatory therapy often need to be prolonged. Ocular cysticercosis is usually treated surgically, although there are reports of cure using medical therapy alone.

PREVENTION

In areas with evolved public health systems, cysticercosis can largely be eliminated by meat inspection, condemnation of infected meat, and thorough cooking of pork. This approach has not worked in countries where most meat is butchered informally. Mass chemotherapy for tapeworm carriers, mass treatment of pigs, and improved personal hygiene have decreased or eliminated transmission in some areas. Screening family members and those preparing food for index cases for cysticercosis has a very low yield, in part because of the poor sensitivity of current tests. Those who have noted passing material consistent with taeniasis should be treated with praziquantel regardless of the results of stool studies. Veterinary vaccines for several cestode infections have a high degree of efficacy and have a potential role in decreasing parasite transmission.

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Chapter 304

Echinococcosis (*Echinococcus granulosus* and *Echinococcus multilocularis*)

Philip R. Fischer, Miguel M. Cabada, and A. Clinton White Jr.

ETIOLOGY

Echinococcosis (**hydatid disease** or **hydatidosis**) is a widespread, serious human cestode infection (Fig. 304-1). Two major *Echinococcus* groups of species are responsible for distinct clinical presentations. *Echinococcus granulosus* and related species cause **cystic hydatid disease.** The organisms were, until recently, thought to be a single species, but recent molecular data have confirmed that there are a number of different species and genotypes in what was formally thought to be a single species. *Echinococcus multilocularis* causes **alveolar hydatid disease.** The adult parasites are a small (2-7 mm) tapeworm with only 2-6 segments that inhabit the intestines of dogs, wolves, dingoes, jackals, coyotes, and foxes. These carnivores pass the eggs in their stool, which contaminates the soil, pasture, and water, as well as their own fur. Domestic animals, such as sheep, goats, cattle, and camels, ingest *E. granulosus* complex eggs while grazing. Humans are also infected by consuming eggs by direct contact with infected dogs or from ova in the environment. The larvae hatch, penetrate the gut, and are carried by the vascular or lymphatic systems to the liver, lungs, and less commonly bones, brain, or heart.

The different species within the *E. granulosus* complex show significant variation in both ecology and genetics. One distinct variant is found in a sylvatic wolf/moose cycle in North America and Siberia. For *E. multilocularis*, the main intermediate hosts are small rodents. The rodents are consumed by foxes, wolves, and other natural predators. In Europe, contamination of gardens by fox excrement is a major risk factor for transmission. Ingestion of infected rodents by dogs can also facilitate transmissions to children.

EPIDEMIOLOGY

There is potential for transmission of this parasite to humans wherever dogs are allowed to ingest the entrails of herd animals. Cysts have been detected in up to 10% of the human population in northern Kenya and western China. Disease is highly endemic in the Middle East and Central Asia. In South America, the disease is prevalent in sheepherding areas of the Andes, the beef-herding areas of the Brazilian/Argentine Pampas, and Uruguay. Among developed countries, the disease is recognized in Italy, Greece, Portugal, Spain, and Australia,

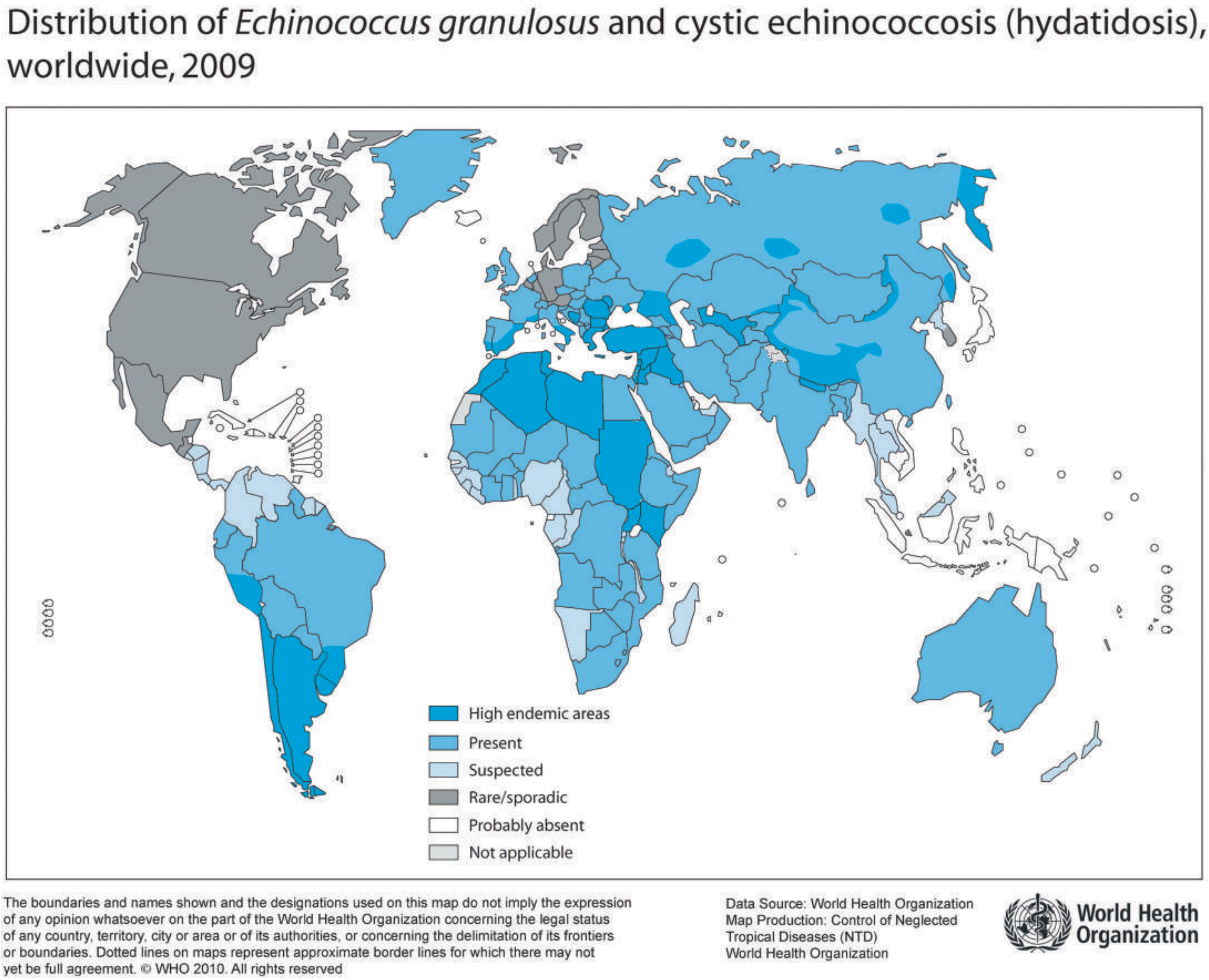

Figure 304-1 Worldwide distribution of cystic echinococcosis. *(From Control of Neglected Tropical Diseases. © World Health Organization, 2011. Available at: http://gamapserver.who.int/mapLibrary/Files/Maps/Global_echinococcosis_2009.png)*

and is reemergent in dogs in Great Britain. In North America, transmission rarely occurs through a sylvatic cycle in the Arctic, as well as in foci of the domestic cycle in sheep raising areas of western United States.

Transmission of *E. multilocularis* occurs primarily in Central Europe, Siberia, Turkey, and China. Transmission is now rare in the Arctic regions of North America. Separate species, *Echinococcus vogel* and *Echinococcus oligarthurus,* cause polycystic disease similar to alveolar hydatidosis in northern South America.

PATHOGENESIS

E. granulosus complex parasites are often acquired in childhood, but liver cysts require many years to become large enough to detect or cause symptoms. In children, the lung is a common site, whereas in adults 70% of cysts develop in the liver. Cysts can also develop in bone, the genitourinary system, spleen, subcutaneous tissues, and brain. The host surrounds the primary cyst with a tough, fibrous capsule. Inside this capsule, the parasite produces a thick lamellar layer with the consistency of a soft-boiled egg white. Inside of the lamellar layer is the thin germinal layer of cells responsible for production of thousands of **protoscoleces** that remain attached to the wall or float free in the cyst fluid (Video 304-1). Smaller internal daughter cysts may develop within the primary cyst capsule. The fluid in a healthy cyst is clear, colorless, and watery. Rupture of the cyst, which can occur with trauma or during surgery, can be associated with an anaphylactic reaction. Protoscoleces released into the tissues can also develop into new cysts.

E. multilocularis almost always involves the liver. The lesions grow very slowly and rarely present in children. The secondary reproductive units bud externally and are not confined within a single well-defined structure. Thus, the lesions are often confused with a malignancy. Furthermore, the cyst tissues are poorly demarcated from those of the host, making surgical removal difficult. The secondary cysts are also capable of distant metastatic spread. The growing cyst mass eventually replaces a significant portion of the liver and compromises adjacent tissues and structures.

CLINICAL MANIFESTATIONS

In the liver, cysts may remain asymptomatic, may regress spontaneously, or may produce nonspecific symptoms. Symptomatic cysts can cause increased abdominal girth, hepatomegaly, a palpable mass, vomiting, or abdominal pain. Serious complications result from compression of adjacent structures or spillage of cyst contents. Mass effects can be noted in the brain and bone. Anaphylaxis can occur with cyst rupture or spontaneous spillage, from trauma or intraoperatively.

Spillage can also be catastrophic long-term, because each protoscolex can form a new cyst. Jaundice from cystic hydatid disease is rare. In the lung, cysts produce chest pain, cough, or hemoptysis. Fluid from partially ruptured cysts is often noted to be salty.

In alveolar hydatid disease, the proliferating mass may compromise hepatic tissue or the biliary system and causes progressive obstructive jaundice and hepatic failure. Symptoms also occur from expansion of extrahepatic foci.

DIAGNOSIS

Symptoms and signs are usually nonspecific (e.g., hepatomegaly or a palpable abdominal mass). Ultrasonography is the most valuable tool for both the diagnosis and treatment of cystic hydatid disease of the liver. The presence of internal membranes or echogenic cyst material (**protoscoleces,** termed **hydatid sand**) can be observed in real time to aid in the diagnosis. Ultrasonography can also be used for disease staging used to define optimal therapy (Fig. 304-2). Chest radiographs frequently reveal characteristic rounded masses (Fig. 304-3). Alveolar disease resembles a diffuse solid tumor. CT findings are similar to those of ultrasonography and may at times be useful in distinguishing alveolar from cystic hydatid disease in geographic regions where both occur (Fig. 304-4). CT or MRI is also important in planning a surgical intervention. Lung hydatid disease is usually apparent on chest radiograph (Fig. 304-3).

Serologic studies may be useful in confirming a diagnosis of cystic echinococcosis. The sensitivity is high for hepatic or bone disease, but the false-negative rate may be >50% with pulmonary or central nervous system infection.

DIFFERENTIAL DIAGNOSIS

Benign hepatic cysts are common but can be distinguished from cystic hydatid disease by the absence of a distinct wall, internal membranes, and hydatid sand. The density of bacterial hepatic abscesses is distinct from the watery cystic fluid characteristic of *E. granulosus* infection, but hydatid cysts may also be complicated by secondary bacterial infection. Alveolar echinococcosis is often confused with hepatoma or metastatic tumor.

TREATMENT

Management of cystic hydatid disease should be individualized and guided by disease stage. Approaches range from surgical resection for complicated disease to watchful waiting for cysts that are already degenerating. For small cystic lesions (cystic echinococcosis [CE] types 1 or 3; see Fig. 304-2) that are <5 cm in diameter, albendazole chemotherapy alone (15 mg/kg/day divided bid PO for 1-6 mo; maximum: 800 mg/day) may result in a high rate of cure. Adverse effects include occasional alopecia, mild gastrointestinal disturbance, and elevated transaminases on prolonged use. Because of leukopenia, the FDA recommends that blood counts be monitored at the beginning and every 2 wk during therapy. Chemotherapy may also be used for cysts that are not suitable to **PAIR** (***p***ercutaneous ***a***spiration, ***i***nstillation, and ***r***easpiration) or operative management.

For larger CE1 and CE3 lesions, ultrasound- or CT-guided PAIR is the preferred therapy. Compared with surgical treatment alone, PAIR plus albendazole results in similar cyst disappearance with fewer adverse events and fewer days in the hospital. Spillage with PAIR is surprisingly uncommon, but prophylactic albendazole therapy is routinely administered more than 1 wk prior to PAIR and should be continued for at least 1 mo afterward. PAIR is contraindicated in pregnancy and for bile-stained cysts, which should not be injected with a scolicidal agent because of increased risk for biliary complications. In experienced centers, cysts with thick internal septation (CE2) can be managed using a trochar to break up the membranes and external drainage or with surgery.

Surgery is the treatment of choice for complicated cysts, including ruptured cysts, cysts communicating with the biliary tract, large pulmonary cysts, or cysts of the central nervous system or bones.

For conventional surgery, the inner cyst wall (only laminate and germinal layers are of parasite origin) can be easily peeled from the

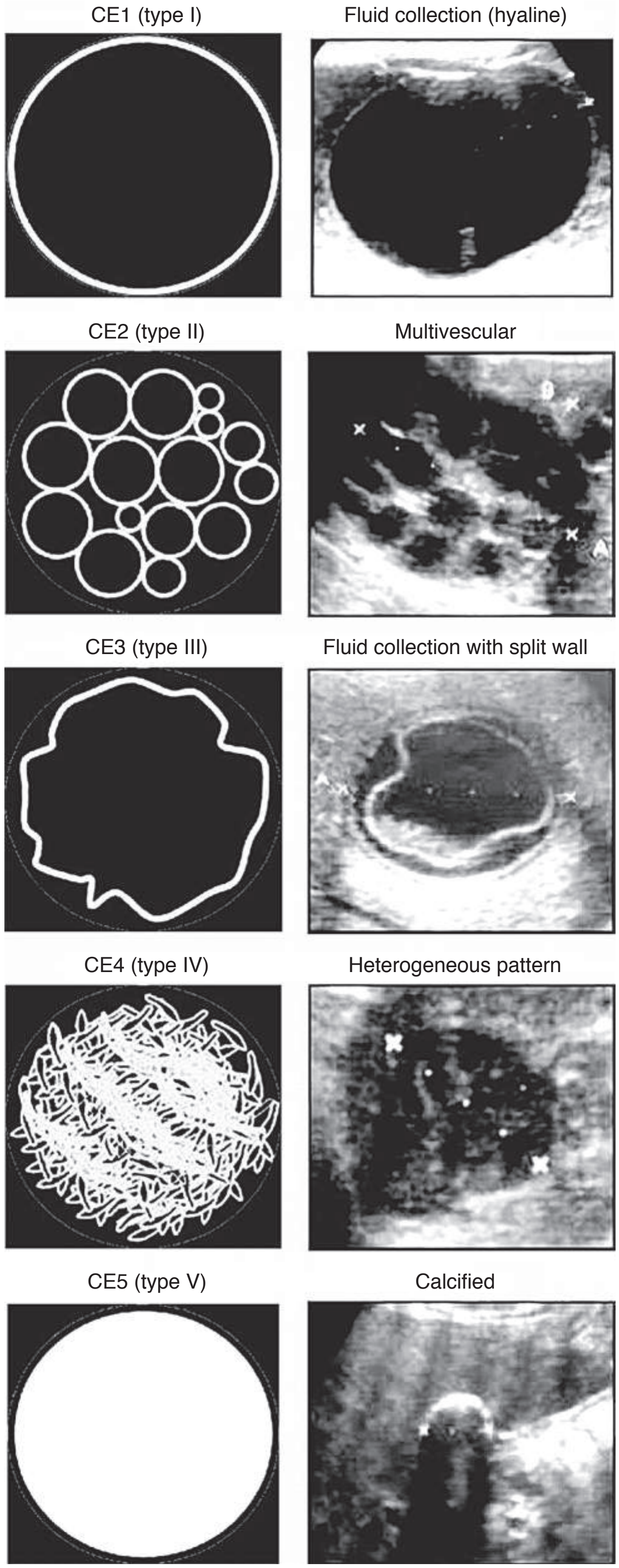

Figure 304-2 **Ultrasound classification of cystic echinococcosis (CE) cysts.** The WHO informal working group on echinococcosis classification differs from that of Gharbi and colleagues by the addition of a "cystic lesion" (CL) stage (undifferentiated) (not shown), and by reversing the order of CE types 2 and 3. CE3 transitional cysts may be differentiated into CE3a (with detached endocyst) and CE3b (predominantly solid with daughter vesicles). CE1 and CE3a are early stage cysts and CE4 and CE5 late stage cysts. *(From McManus DP, Gray DJ, Zhang W, Yang Y: Diagnosis, treatment, and management of echinococcosis.* BMJ *344:e3866, 2012, Fig. 4.)*

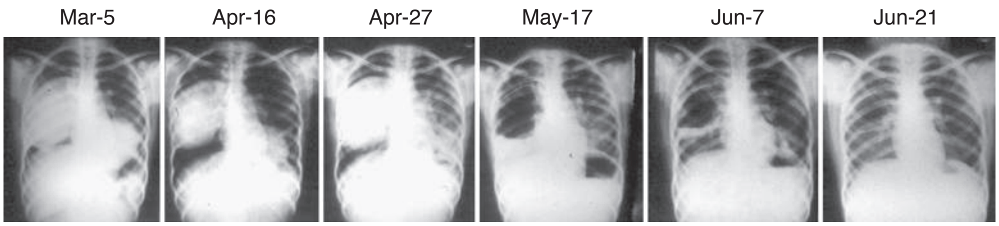

Figure 304-3 Serial chest x-rays of a young Kenyan woman with bilateral hydatid cysts. After 2 mo of albendazole therapy, sudden rupture of the right cyst was associated with massive aspiration and acute respiratory distress.

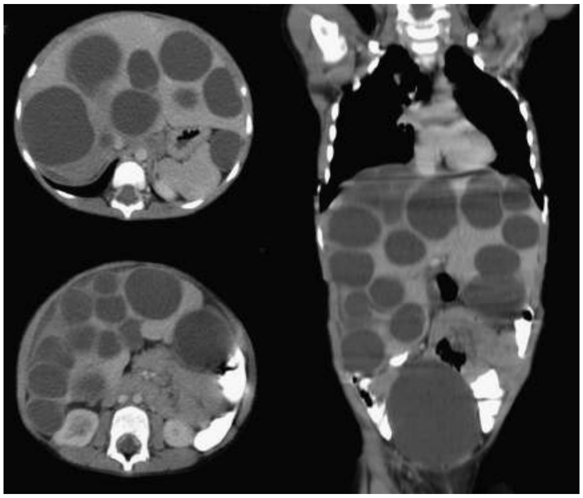

Figure 304-4 Abdominal CT revealed hepatomegaly and multiple (>20) liver cysts. *(From Ben-Shimol S, Zelcer I: Liver hydatid cysts. J Pediatr 163:1792, 2013.)*

fibrous layer, although some studies suggest that removal of the whole capsule has a better outcome. Considerable care must be taken to avoid spillage of cyst contents and surgical drapes should be soaked in hypertonic saline because cyst fluid contains viable protoscoleces, each capable of producing secondary cysts. An additional risk is anaphylaxis because of spilled cyst fluid, making it useful to employ a surgeon experienced in this surgery. For hepatic cysts, patients should begin therapy with albendazole (ideally in combination with praziquantel) for several days to weeks preoperatively. Antiparasitic drugs should be continued for 6-8 wk postoperatively. CE4 and CE5 cysts are in the process of degeneration and usually do not require specific therapy. They can be managed with serial imaging studies to document resolution (watch and wait). Small thoracic cysts may resolve with chemotherapy, but most cysts require operative removal.

Alveolar hydatidosis frequently requires radical surgery, including partial hepatectomy, lobectomy, or liver transplantation. Medical therapy with albendazole should be continued for 2 yr after presumably curative surgery. In patients who are not operative candidates or whose lesions are not amenable to surgical cure, albendazole long-term suppressive therapy should be used to slow the progression, but the infection generally recurs if albendazole is stopped.

PROGNOSIS

Factors predictive of success with chemotherapy are age of the cyst (<2 yr), low internal complexity of the cyst, and small size. The site of the cyst is not important, although cysts in bone respond poorly. For alveolar hydatidosis, if surgical removal is unsuccessful, the average mortality is 92% by 10 yr after diagnosis.

PREVENTION

Important measures to interrupt transmission include, above all, thorough handwashing, avoiding contact with dogs in endemic areas, boiling or filtering water when camping, proper disposal of animal carcasses, and proper meat inspection. Strict procedures for proper disposal of refuse from slaughterhouses must be instituted and followed so that dogs and wild carnivores do not have access to entrails. Other useful measures are control or treatment of the feral dog population and regular praziquantel treatment of pets and working dogs in endemic areas. Vaccines have been developed to prevent infection in grazing animals but are not widely used.

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The Digestive System

PART XVIII

Section 1

Clinical Manifestations of Gastrointestinal Disease

Chapter 305

Normal Digestive Tract Phenomena

Chris A. Liacouras

Gastrointestinal function varies with maturity; what is a physiologic event in a newborn or infant might be a pathologic symptom at an older age. A fetus can swallow amniotic fluid as early as 12 wk of gestation, but nutritive sucking in neonates first develops at about 34 wk of gestation. The coordinated oral and pharyngeal movements necessary for swallowing solids develop within the 1st few mo of life. Before this time, the tongue thrust is upward and outward to express milk from the nipple, instead of a backward motion, which propels solids toward the esophageal inlet. By 1 mo of age, infants appear to show preferences for sweet and salty foods. Infants' interest in solids increases at approximately 4 mo of age. The recommendation to begin solids at 6 mo of age is based on nutritional and cultural concepts rather than maturation of the swallowing process (see Chapter 45). Infants swallow air during feeding, and burping is encouraged to prevent gaseous distention of the stomach.

A number of normal anatomic variations may be noted in the mouth. A **short lingual frenulum** ("tongue-tie") may be worrisome to parents but only rarely interferes with eating or speech, generally requiring no treatment. **Surface furrowing** of the tongue (a geographic or scrotal tongue) is usually a normal finding. A **bifid uvula** may be normal or associated with a submucous cleft of the soft palate.

Regurgitation, the result of gastroesophageal reflux, occurs commonly in the 1st yr of life. Effortless regurgitation can dribble out of an infant's mouth but also may be forceful. In an otherwise healthy infant with regurgitation, volumes of emesis are commonly approximately 15-30 mL but occasionally are larger. Most often, the infant remains happy, although possibly hungry, after an episode of regurgitation. Episodes can occur from one to several times per day. Regurgitation gradually resolves in 80% of infants by 6 mo of age and in 90% by 12 mo. If complications develop or regurgitation persists, gastroesophageal reflux is considered pathologic rather than merely developmental and deserves further evaluation and treatment. Complications of gastroesophageal reflux include failure to thrive, pulmonary disease (apnea or aspiration pneumonitis), and esophagitis with its sequelae (see Chapters 323 and 324).

Infants and young children may be erratic eaters; this may be a worry to parents. A toddler might eat insatiably or refuse to consume food during a meal. Toddlers and young children also tend to eat only a limited variety of foods. Parents should be encouraged to view nutritional intake over several days and not be overly concerned about individual meals. Infancy and adolescence are periods of rapid growth; high nutrient requirements for growth may be associated with voracious appetites. The reduced appetite of toddlers and preschool children is often a worry to parents who are used to the relatively greater dietary intake during infancy. Demonstration of age-appropriate growth on a growth curve is reassuring.

The number, color, and consistency of stools can vary greatly in the same infant and between infants of similar age without apparent explanation. The earliest stools after birth consist of meconium, a dark, viscous material that is normally passed within the 1st 48 hr of life. With the onset of feeding, meconium is replaced by green-brown transition stools, often containing curds, and, after 4-5 days, by yellow-brown milk stools. **Stool frequency** is extremely variable in normal infants and can vary from none to 7 per day. Breastfed infants can have frequent small, loose stools early (transition stools), and then after 2-3 wk can have very infrequent soft stools. Some nursing infants might not pass any stool for 1-2 wk and then have a normal soft bowel movement. The color of stool has little significance except for the presence of blood or absence of bilirubin products (white-gray rather than yellow-brown). The presence of vegetable matter, such as peas or corn, in the stool of an older infant or toddler ingesting solids is normal and suggests poor chewing and not malabsorption. A pattern of intermittent loose stools, known as **toddler's diarrhea,** occurs commonly between 1 and 3 yr of age. These otherwise healthy growing children often drink excessive carbohydrate-containing beverages. The stools typically occur during the day and not overnight. The volume of fluid intake is often excessive; limiting sugar and unabsorbable carbohydrate-containing beverages and increasing fat in the diet often leads to resolution of the pattern of loose stools.

A protuberant abdomen is often noted in infants and toddlers, especially after large feedings. This can result from the combination of weak abdominal musculature, relatively large abdominal organs, and lordotic stance. In the 1st yr of life, it is common to palpate the liver 1-2 cm below the right costal margin. The normal liver is soft in consistency and percusses to normal size for age. A Riedel lobe is a thin projection of the right lobe of the liver that may be palpated low in the right lateral abdomen. A soft spleen tip might also be palpable as a normal finding. In thin young children, the vertebral column is easily palpable, and an overlying structure may be mistaken for a mass. Pulsation of the aorta can be appreciated. Normal stool can often be palpated in the left lower quadrant in the descending or sigmoid colon.

Blood loss from the gastrointestinal tract is never normal, but swallowed blood may be misinterpreted as gastrointestinal bleeding. Maternal blood may be ingested at the time of birth or later by a nursing infant if there is bleeding near the mother's nipple. Nasal or oropharyngeal bleeding is occasionally mistaken for gastrointestinal bleeding (see Chapter 103.4). Red dyes in foods or drinks can turn the stool red but do not produce a positive test result for occult blood.

Jaundice is common in neonates, especially among premature infants, and usually results from the inability of an immature liver to conjugate bilirubin, leading to an elevated indirect component (see Chapter 102.4). Persistent elevation of indirect bilirubin levels in nursing infants may be a result of breast milk jaundice, which is usually a benign entity in full-term infants. An elevated direct bilirubin is not normal and suggests liver disease, although in infants it may be a result of extrahepatic infection (urinary tract infection). The direct bilirubin fraction should account for no more than 15-20% of the total serum bilirubin. Elevations in direct bilirubin levels can follow indirect hyperbilirubinemia as the liver converts excessive indirect to direct bilirubin and the rate-limiting step in bilirubin excretion shifts from the glucuronidation of bilirubin to excretion of direct bilirubin into the bile canaliculus. Indirect hyperbilirubinemia, which occurs commonly in normal newborns, tends to tint the sclerae and skin golden yellow, whereas direct hyperbilirubinemia produces a greenish yellow hue.

Chapter 306

Major Symptoms and Signs of Digestive Tract Disorders

Raman Sreedharan and Chris A. Liacouras

Disorders of organs outside the gastrointestinal (GI) tract can produce symptoms and signs that mimic digestive tract disorders and should be considered in the differential diagnosis (Table 306-1). In children with normal growth and development, treatment may be initiated without a formal evaluation based on a presumptive diagnosis after taking a history and performing a physical examination. Poor weight gain or weight loss is often associated with a significant pathologic process and usually necessitates a more formal evaluation.

DYSPHAGIA

Difficulty in swallowing is termed *dysphagia*. Painful swallowing is termed **odynophagia**. **Globus** is the sensation of something stuck in the throat without a clear etiology. Swallowing is a complex process that starts in the mouth with mastication and lubrication of food that is formed into a bolus. The bolus is pushed into the pharynx by the tongue. The pharyngeal phase of swallowing is rapid and involves protective mechanisms to prevent food from entering the airway. The epiglottis is lowered over the larynx while the soft palate is elevated against the nasopharyngeal wall; respiration is temporarily arrested while the upper esophageal sphincter opens to allow the bolus to enter the esophagus. In the esophagus, peristaltic coordinated muscular contractions push the food bolus toward the stomach. The lower esophageal sphincter relaxes shortly after the upper esophageal sphincter, so liquids that rapidly clear the esophagus enter the stomach without resistance.

Dysphagia is classified as oropharyngeal dysphagia and esophageal dysphagia. **Oropharyngeal dysphagia** occurs when the transfer of the food bolus from the mouth to the esophagus is impaired (also termed *transfer dysphagia*). The striated muscles of the mouth, pharynx, and upper esophageal sphincter are affected in oropharyngeal dysphagia. Neurologic and muscular disorders can give rise to oropharyngeal dysphagia (Table 306-2). The most serious complication of oropharyngeal dysphagia is life-threatening aspiration.

A complex sequence of neuromuscular events is involved in the transfer of foods to the upper esophagus. Abnormalities of the muscles involved in the ingestion process and their innervation, strength, or coordination are associated with transfer dysphagia in infants and children. In such cases, an oropharyngeal problem is usually part of a more generalized neurologic or muscular problem (botulism, diphtheria, neuromuscular disease). Painful oral lesions, such as acute viral stomatitis or trauma, occasionally interfere with ingestion. If the nasal air passage is seriously obstructed, the need for respiration causes severe distress when suckling. Although severe structural, dental, and salivary abnormalities would be expected to create difficulties, ingestion proceeds relatively well in most affected children if they are hungry.

Esophageal dysphagia occurs when there is difficulty in transporting the food bolus down the esophagus. Esophageal dysphagia can result from neuromuscular disorders or mechanical obstruction (Table 306-3). Primary motility disorders causing impaired peristaltic function and dysphagia are rare in children. Achalasia is an esophageal motility disorder with associated inability of relaxation of the lower esophageal sphincter, and it rarely occurs in children. Motility of the distal esophagus is disordered after surgical repair of tracheoesophageal fistula or achalasia. Abnormal motility can accompany collagen vascular disorders. Mechanical obstruction can be intrinsic or extrinsic. Intrinsic structural defects cause a fixed impediment to the passage of food bolus because of a narrowing within the esophagus, as in a stricture, web, or tumor. Extrinsic obstruction is

Table 306-1	Some Nondigestive Tract Causes of Gastrointestinal Symptoms in Children
ANOREXIA	
Systemic disease: inflammatory, neoplastic	
Cardiorespiratory compromise	
Iatrogenic: drug therapy, unpalatable therapeutic diets	
Depression	
Anorexia nervosa	
VOMITING	
Inborn errors of metabolism	
Medications: erythromycin, chemotherapy, nonsteroidal anti-inflammatory drugs	
Increased intracranial pressure	
Brain tumor	
Infection of the urinary tract	
Labyrinthitis	
Adrenal insufficiency	
Pregnancy	
Psychogenic	
Abdominal migraine	
Toxins	
Renal disease	
DIARRHEA	
Infection: otitis media, urinary	
Uremia	
Medications: antibiotics, cisapride	
Tumors: neuroblastoma	
Pericarditis	
Adrenal insufficiency	
CONSTIPATION	
Hypothyroidism	
Spina bifida	
Developmental delay	
Dehydration: diabetes insipidus, renal tubular lesions	
Medications: narcotics	
Lead poisoning	
Infant botulism	
ABDOMINAL PAIN	
Pyelonephritis, hydronephrosis, renal colic	
Pneumonia (lower lobe)	
Pelvic inflammatory disease	
Porphyria	
Angioedema	
Endocarditis	
Abdominal migraine	
Familial Mediterranean fever	
Sexual or physical abuse	
Systemic lupus erythematosus	
School phobia	
Sickle cell crisis	
Vertebral disk inflammation	
Psoas abscess	
Pelvic osteomyelitis or myositis	
Medications	
ABDOMINAL DISTENTION OR MASS	
Ascites: nephrotic syndrome, neoplasm, heart failure	
Discrete mass: Wilms tumor, hydronephrosis, neuroblastoma, mesenteric cyst, hepatoblastoma, lymphoma	
Pregnancy	
JAUNDICE	
Hemolytic disease	
Urinary tract infection	
Sepsis	
Hypothyroidism	
Panhypopituitarism	

Table 306-2 Causes of Oropharyngeal Dysphagia

NEUROMUSCULAR DISORDERS
Cerebral palsy
Brain tumors
Cerebrovascular accidents
Polio and postpolio syndromes
Multiple sclerosis
Myositis
Dermatomyositis
Myasthenia gravis
Muscular dystrophies
Acquired or inherited dystonia syndrome
Dysautonomia
METABOLIC AND AUTOIMMUNE DISORDERS
Hyperthyroidism
Systemic lupus erythematosus
Sarcoidosis
Amyloidosis
INFECTIOUS DISEASE
Meningitis
Botulism
Diphtheria
Lyme disease
Neurosyphilis
Viral infection: polio, Coxsackievirus, herpes, cytomegalovirus
STRUCTURAL LESIONS
Inflammatory: abscess, pharyngitis
Congenital web
Cricopharyngeal bar
Dental problems
Bullous skin lesions
Plummer-Vinson syndrome
Zenker diverticulum
Extrinsic compression: osteophytes, lymph nodes, thyroid swelling
OTHER
Corrosive injury
Side effects of medications
After surgery
After radiation therapy

Adapted from Gasiorowska A, Faas R: Current approach to dysphagia, Gastroenterol Hepatol *5(4):269–279, 2009.*

caused by compression from vascular rings, mediastinal lesions, or vertebral abnormalities. Structural defects typically cause more problems in swallowing solids than liquids. In infants, esophageal web, tracheobronchial remnant, or vascular ring can cause dysphagia. An esophageal stricture secondary to esophagitis (chronic gastroesophageal reflux, eosinophilic esophagitis, chronic infections) occasionally has dysphagia as the first manifestation. An esophageal foreign body or a stricture secondary to a caustic ingestion also causes dysphagia. A Schatzki ring, a thin ring of mucosal tissue near the lower esophageal sphincter, is another mechanical cause of recurrent dysphagia, and again is rare in children.

When dysphagia is associated with a delay in passage through the esophagus, the patient may be able to point to the level of the chest where the delay occurs, but esophageal symptoms are usually referred to the suprasternal notch. When a patient points to the suprasternal notch, the impaction can be found anywhere in the esophagus.

REGURGITATION

Regurgitation is the effortless movement of stomach contents into the esophagus and mouth. It is not associated with distress, and infants with regurgitation are often hungry immediately after an episode. The lower esophageal sphincter prevents reflux of gastric contents into the esophagus. Regurgitation is a result of gastroesophageal reflux through an incompetent or, in infants, immature lower esophageal sphincter. This is often a developmental process, and regurgitation or "spitting" resolves with maturity. Regurgitation should be differentiated from

Table 306-3 Causes of Esophageal Dysphagia

NEUROMUSCULAR DISORDERS
GERD
Achalasia cardia
Diffuse esophageal spasm
Scleroderma
MECHANICAL
Intrinsic Lesions
Foreign bodies including pills
Esophagitis: GERD, eosinophilic esophagitis
Stricture: corrosive injury, pill induced, peptic
Esophageal webs
Esophageal rings
Esophageal diverticula
Neoplasm
Extrinsic Lesions
Vascular compression
Mediastinal lesion
Cervical osteochondritis
Vertebral abnormalities

GERD, gastroesophageal reflux disease.
Adapted from Gasiorowska A, Faas R: Current approach to dysphagia, Gastroenterol Hepatol *5(4):269–279, 2009.*

vomiting, which denotes an active reflex process with an extensive differential diagnosis (Table 306-4).

ANOREXIA

Anorexia means prolonged lack of appetite. Hunger and satiety centers are located in the hypothalamus; it seems likely that afferent nerves from the GI tract to these brain centers are important determinants of the anorexia that characterizes many diseases of the stomach and intestine (see Chapter 47). Satiety is stimulated by distention of the stomach or upper small bowel, the signal being transmitted by sensory afferents, which are especially dense in the upper gut. Chemoreceptors in the intestine, influenced by the assimilation of nutrients, also affect afferent flow to the appetite centers. Impulses reach the hypothalamus from higher centers, possibly influenced by pain or the emotional disturbance of an intestinal disease. Other regulatory factors include hormones, ghrelin, leptin, and plasma glucose, which, in turn, reflect intestinal function (see Chapter 47).

VOMITING

Vomiting is a highly coordinated reflex process that may be preceded by increased salivation and begins with involuntary retching. Violent descent of the diaphragm and constriction of the abdominal muscles with relaxation of the gastric cardia actively force gastric contents back up the esophagus. This process is coordinated in the medullary vomiting center, which is influenced directly by afferent innervation and indirectly by the chemoreceptor trigger zone and higher central nervous system (CNS) centers. Many acute or chronic processes can cause vomiting (see Tables 306-1 and 306-4).

Vomiting caused by obstruction of the GI tract is probably mediated by intestinal visceral afferent nerves stimulating the vomiting center (Table 306-5). If obstruction occurs below the second part of the duodenum, vomitus is usually bile stained. Emesis can also become bile stained with repeated vomiting in the absence of obstruction when duodenal contents are refluxed into the stomach. Nonobstructive lesions of the digestive tract can also cause vomiting; this includes diseases of the upper bowel, pancreas, liver, or biliary tree. CNS or metabolic derangements can lead to severe, persistent emesis.

Cyclic vomiting is a syndrome with numerous episodes of vomiting interspersed with well intervals. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition consensus statement on the diagnosis and management of cyclic vomiting criteria are listed in Table 306-6. Rome III criteria for functional GI disorders have 2 criteria for cyclic vomiting in children, and both these criteria have to

Table 306-4 Differential Diagnosis of Emesis During Childhood

INFANT	CHILD	ADOLESCENT
COMMON		
Gastroenteritis	Gastroenteritis	Gastroenteritis
Gastroesophageal reflux	Systemic infection	GERD
Overfeeding	Gastritis	Systemic infection
Anatomic obstruction*	Toxic ingestion	Toxic ingestion
Systemic infection†	Pertussis syndrome	Gastritis
Pertussis syndrome	Medication	Sinusitis
Otitis media	Reflux (GERD)	Inflammatory bowel disease
	Sinusitis	Appendicitis
	Otitis media	Migraine
	Anatomic obstruction*	Pregnancy
	Eosinophilic esophagitis	Medications
		Ipecac abuse, bulimia
		Concussion
RARE		
Adrenogenital syndrome	Reye syndrome	Reye syndrome
Inborn errors of metabolism	Hepatitis	Hepatitis
Brain tumor (increased intracranial pressure)	Peptic ulcer	Peptic ulcer
Subdural hemorrhage	Pancreatitis	Pancreatitis
Food poisoning	Brain tumor	Brain tumor
Rumination	Increased intracranial pressure	Increased intracranial pressure
Renal tubular acidosis	Middle ear disease	Concussion
Ureteropelvic junction obstruction	Chemotherapy	Middle ear disease
Pseudoobstruction	Achalasia	Chemotherapy
	Cyclic vomiting (migraine)	Cyclic vomiting (migraine)
	Esophageal stricture	Biliary colic
	Duodenal hematoma	Renal colic
	Inborn error of metabolism	Diabetic ketoacidosis
	Pseudoobstruction	Pseudoobstruction
		Intestinal tumor
		Achalasia

*Includes malrotation, pyloric stenosis, intussusception, Hirschsprung disease.
†Meningitis, sepsis.
GERD, gastroesophageal reflux disease, inguinal hernia.

Table 306-5 Causes of Gastrointestinal Obstruction

ESOPHAGUS
Congenital
Esophageal atresia
Vascular rings
Schatzki ring
Tracheobronchial remnant
Acquired
Esophageal stricture
Foreign body
Achalasia
Chagas disease
Collagen vascular disease

STOMACH
Congenital
Antral webs
Pyloric stenosis
Acquired
Bezoar, foreign body
Pyloric stricture (ulcer)
Chronic granulomatous disease of childhood
Eosinophilic gastroenteritis
Crohn disease
Epidermolysis bullosa

SMALL INTESTINE
Congenital
Duodenal atresia
Annular pancreas
Malrotation/volvulus
Malrotation/Ladd bands
Ileal atresia
Meconium ileus
Meckel diverticulum with volvulus or intussusception
Inguinal hernia
Internal hernia
Intestinal duplication
Pseudoobstruction
Acquired
Postsurgical adhesions
Crohn disease
Intussusception
Distal ileal obstruction syndrome (cystic fibrosis)
Duodenal hematoma
Superior mesenteric artery syndrome

COLON
Congenital
Meconium plug
Hirschsprung disease
Colonic atresia, stenosis
Imperforate anus
Rectal stenosis
Pseudoobstruction
Volvulus
Colonic duplication
Acquired
Ulcerative colitis (toxic megacolon)
Chagas disease
Crohn disease
Fibrosing colonopathy (cystic fibrosis)

be present for a diagnosis of cyclic vomiting: 2 or more periods of intense nausea and unremitting vomiting or retching lasting hours to days and return to usual state of health lasting weeks to months.

The onset of cyclic vomiting is usually between 2 and 5 yr of age but has been observed in infants and adults. The frequency of vomiting episodes is variable (average of 12 episodes per yr) with each episode typically lasting 2-3 days and 4 or more emesis episodes per hour. The episodes usually occur in the early hours of the morning or upon wakening. Patients can have a prodrome of nausea, pallor, intolerance of noise or light, lethargy, and headache. Epigastric pain, abdominal pain, diarrhea, and fever are seen in many patients, making the diagnosis difficult. Precipitants include infection, physical stress, and psychologic stress.

Several theories have been proposed as causative factors, including a migraine-related mechanism, mitochondrial disorders, and autonomic dysfunction. More than 80% of affected children have a 1st-degree relative with migraines; many patients develop migraines later in life. Many children show evidence for sympathetic autonomic dysfunction of sudomotor systems. The differential diagnosis includes GI anomalies (malrotation, duplication cysts, choledochal cysts, recurrent intussusceptions), CNS disorders (neoplasm, epilepsy, vestibular pathology), nephrolithiasis, cholelithiasis, hydronephrosis, metabolic-endocrine disorders (urea cycle, fatty acid metabolism, Addison disease, porphyria, hereditary angioedema, familial Mediterranean fever), chronic appendicitis, and inflammatory bowel disease. Laboratory evaluation is based on a careful history and physical examination and may include, if indicated, endoscopy, contrast GI radiography, brain MRI, and metabolic studies (lactate, organic acids, ammonia). Treatment includes hydration and antiemetics (e.g., ondansetron). Prevention may be possible with lifestyle changes and prophylactic medications (cyproheptadine, propranolol, amitriptyline, phenobarbital) based on the patient's age.

Potential complications of emesis are noted in Table 306-7. Broad management strategies for vomiting in general and specific causes of emesis are noted in Tables 306-8 and 306-9.

Table 306-6 Criteria for Cyclical Vomiting Syndrome

All of the criteria must be met for the consensus definition of cyclical vomiting syndrome:

- At least 5 attacks in any interval, or a minimum of 3 episodes during a 6-mo period
- Recurrent episodes of intense vomiting and nausea lasting 1 hr to 10 days and occurring at least 1 wk apart
- Stereotypical pattern and symptoms in the individual patient
- Vomiting during episodes occurs ≥4 times/hr for ≥1 hr
- Return to baseline health between episodes
- Not attributed to another disorder

Li, B UK, Lefevre F, Chelimsky GG, et al: North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome, J Pediatr Gastroenterol Nutr *47:379–393, 2008.*

DIARRHEA

Diarrhea is best defined as excessive loss of fluid and electrolyte in the stool. Acute diarrhea is defined as sudden onset of excessively loose stools of >10 mL/kg/day in infants and >200 g/24 hr in older children, which lasts <14 days. When the episode lasts longer than 14 days, it is called *chronic* or *persistent diarrhea.*

Normally, a young infant has approximately 5 mL/kg/day of stool output; the volume increases to 200 g/24 hr in an adult. The greatest volume of intestinal water is absorbed in the small bowel; the colon concentrates intestinal contents against a high osmotic gradient. The small intestine of an adult can absorb 10-11 L/day of a combination of ingested and secreted fluid, whereas the colon absorbs approximately 0.5 L. Disorders that interfere with absorption in the small bowel tend to produce voluminous diarrhea, whereas disorders compromising colonic absorption produce lower-volume diarrhea. **Dysentery** (small-volume, frequent bloody stools with mucus, tenesmus, and urgency) is the predominant symptom of colitis.

The basis of all diarrheas is disturbed intestinal solute transport and water absorption. Water movement across intestinal membranes is passive and is determined by both active and passive fluxes of solutes, particularly sodium, chloride, and glucose. The pathogenesis of most episodes of diarrhea can be explained by secretory, osmotic, or motility abnormalities or a combination of these (Table 306-10).

Secretory diarrhea occurs when the intestinal epithelial cell solute transport system is in an active state of secretion. It is often caused by a secretagogue, such as cholera toxin, binding to a receptor on the

Table 306-7 Complications of Vomiting

COMPLICATION	PATHOPHYSIOLOGY	HISTORY, PHYSICAL EXAMINATION, AND LABORATORY STUDIES
Metabolic	Fluid loss in emesis HCl loss in emesis Na, K loss in emesis Alkalosis → • Na into cells	Dehydration Alkalosis; hypochloremia Hyponatremia; hypokalemia
Nutritional	Emesis of calories and nutrients Anorexia for calories and nutrients	Malnutrition; "failure to thrive"
Mallory-Weiss tear	Retching → tear at lesser curve of gastroesophageal junction	Forceful emesis → hematemesis
Esophagitis	Chronic vomiting → esophageal acid exposure	Heartburn; Hemoccult + stool
Aspiration	Aspiration of vomitus, especially in context of obtundation	Pneumonia; neurologic dysfunction
Shock	Severe fluid loss in emesis or in accompanying diarrhea Severe blood loss in hematemesis	Dehydration (accompanying diarrhea can explain acidosis?) Blood volume depletion
Pneumomediastinum, pneumothorax	Increased intrathoracic pressure	Chest x-ray
Petechiae, retinal hemorrhages	Increased intrathoracic pressure	Normal platelet count

From Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p 318.*

Table 306-8 Pharmacologic Therapies for Vomiting Episodes

THERAPEUTIC DRUG CLASS	DRUG	DOSAGE
REFLUX		
Dopamine antagonist	Metoclopramide (Reglan)	0.1-0.2 mg/kg PO or IV qid
GASTROPARESIS		
Dopamine antagonist	Metoclopramide (Reglan)	0.1-0.2 mg/kg PO or IV qid
Motilin agonist	Erythromycin	3-5 mg/kg PO or IV tid-qid
INTESTINAL PSEUDOOBSTRUCTION		
Stimulation of intestinal migratory myoelectric complexes	Octreotide (Sandostatin)	1 µg/kg SC bid-tid
CHEMOTHERAPY		
Dopamine antagonist	Metoclopramide	0.5-1.0 mg/kg IV qid, with antihistamine prophylaxis of extrapyramidal side effects
Serotoninergic 5-HT_3 antagonist	Ondansetron (Zofran)	0.15-0.3 mg/kg IV or PO tid
Phenothiazines (extrapyramidal, hematologic side effects)	Prochlorperazine (Compazine)	≈0.3 mg/kg PO bid-tid
	Chlorpromazine (Thorazine)	>6 mo of age: 0.5 mg/kg PO or IV tid-qid
Steroids	Dexamethasone (Decadron)	0.1 mg/kg PO tid
Cannabinoids	Tetrahydrocannabinol (Nabilone)	0.05-0.1 mg/kg PO bid-tid
POSTOPERATIVE		
	Ondansetron, phenothiazines	See under chemotherapy
MOTION SICKNESS, VESTIBULAR DISORDERS		
Antihistamine	Dimenhydrinate (Dramamine)	1 mg/kg PO tid-qid
Anticholinergic	Scopolamine (Transderm Scop)	Adults: 1 patch/3 days
ADRENAL CRISIS		
Steroids	Cortisol	2 mg/kg IV bolus followed by 0.2-0.4 mg/kg/hr IV (±1 mg/kg IM)
CYCLIC VOMITING SYNDROME		
Supportive		
Analgesic	Meperidine (Demerol)	1-2 mg/kg IV or IM q 4-6 hr
Anxiolytic, sedative	Lorazepam (Ativan)	0.05-0.1 mg/kg IV q 6 hr
Antihistamine, sedative	Diphenhydramine (Benadryl)	1.25 mg/kg IV q 6 hr
Abortive		
Serotoninergic 5-HT_3 antagonist	Ondansetron	See above
	Granisetron (Kytril)	10 µg/kg IV q 4-6 hr
Nonsteroidal antiinflammatory agent (GI ulceration side effect)	Ketorolac (Toradol)	0.5-1.0 mg/kg IV q 6-8 hr
Serotoninergic 5-HT_{1D} agonist	Sumatriptan (Imitrex)	>40 kg: 20 mg intranasally or 25 mg PO, 1 time only
PROPHYLACTIC*		
Antimigraine, β-adrenergic blocker	Propranolol (Inderal)	0.5-2.0 mg/kg PO bid
Antimigraine, antihistamine	Cyproheptadine (Periactin)	0.25-0.5 mg/kg/day PO ÷ bid-tid
Antimigraine, tricyclic antidepressant	Amitriptyline (Elavil)	0.33-0.5 mg/kg PO tid, and titrate to maximum of 3.0 mg/kg/day as needed Obtain baseline ECG at start of therapy, and consider monitoring drug levels
Antimigraine antiepileptic	Phenobarbital (Luminal)	2-3 mg/kg qhs
	Erythromycin (see above)	
Low-estrogen oral contraceptives	Consider for catamenial CVS episodes	

*If >1 CVS bout/mo or symptoms are extremely disabling; taken daily.
CVS, cyclic vomiting syndrome; ECG, electrocardiogram; GI, gastrointestinal.
From Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p 317.*

surface epithelium of the bowel and thereby stimulating intracellular accumulation of cyclic adenosine monophosphate or cyclic guanosine monophosphate. Some intraluminal fatty acids and bile salts cause the colonic mucosa to secrete through this mechanism. Diarrhea not associated with an exogenous secretagogue can also have a secretory component (congenital microvillus inclusion disease). Secretory diarrhea is usually of large volume and persists even with fasting. The stool osmolality is predominantly indicated by the electrolytes and the ion gap is 100 mOsm/kg or less. The ion gap is calculated by subtracting the concentration of electrolytes from total osmolality:

$$\text{Ion gap} = \text{Stool osmolality} - [(\text{Stool Na} + \text{stool K}) \times 2]$$

Osmotic diarrhea occurs after ingestion of a poorly absorbed solute. The solute may be one that is normally not well absorbed (magnesium, phosphate, lactulose, or sorbitol) or one that is not well absorbed because of a disorder of the small bowel (lactose with lactase deficiency or glucose with rotavirus diarrhea). Malabsorbed carbohydrate is fermented in the colon, and short-chain fatty acids are produced. Although short-chain fatty acids can be absorbed in the colon and used as an energy source, the net effect is increase in the osmotic solute load. This form of diarrhea is usually of lesser volume than a secretory diarrhea and stops with fasting. The osmolality of the stool will not be explained by the electrolyte content, because another osmotic component is present and so the anion gap is >100 mOsm.

Table 306-9 Supportive and Nonpharmacologic Therapies for Vomiting Episodes

DISEASE	THERAPY
All	Treat cause • Obstruction: operate • Allergy: change diet (±steroids) • Metabolic error: Rx defect • Acid peptic disease: H2RAs, PPIs, etc.
COMPLICATIONS	
Dehydration	IV fluids, electrolytes
Hematemesis	Transfuse, correct coagulopathy
Esophagitis	H_2RAs, PPIs
Malnutrition	NG or NJ drip feeding useful for many chronic conditions
Meconium ileus	Gastrografin enema
DIOS	Gastrografin enema; balanced colonic lavage solution (e.g., GoLYTELY)
Intussusception	Barium enema; air reduction enema
Hematemesis	Endoscopic: injection sclerotherapy or banding of esophageal varices; injection therapy, fibrin sealant application, or heater probe electrocautery for selected upper GI tract lesions
Sigmoid volvulus	Colonoscopic decompression
Reflux	Positioning; dietary measures (infants: rice cereal, 1 tbs/oz of formula)
Psychogenic components	Psychotherapy; tricyclic antidepressants; anxiolytics (e.g., diazepam: 0.1 mg/kg PO tid-qid)

DIOS, distal intestinal obstruction syndrome; GI, gastrointestinal; H_2RA, H_2-receptor antagonist; NG, nasogastric; NJ, nasojejunal; PPIs, proton pump inhibitors; tbs, tablespoon.

From Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p 319.*

Table 306-10 Mechanisms of Diarrhea

PRIMARY MECHANISM	DEFECT	STOOL EXAMINATION	EXAMPLES	COMMENT
Secretory	Decreased absorption, increased secretion, electrolyte transport	Watery, normal osmolality with ion gap < 100 mOsm/kg	Cholera, toxigenic *Escherichia coli*; carcinoid, VIP, neuroblastoma, congenital chloride diarrhea, *Clostridium difficile*, cryptosporidiosis (AIDS)	Persists during fasting; bile salt malabsorption can also increase intestinal water secretion; no stool leukocytes
Osmotic	Maldigestion, transport defects ingestion of unabsorbable substances	Watery, acidic, and reducing substances; increased osmolality with ion gap > 100 mOsm/kg	Lactase deficiency, glucose-galactose malabsorption, lactulose, laxative abuse	Stops with fasting; increased breath hydrogen with carbohydrate malabsorption; no stool leukocytes
Increased motility	Decreased transit time	Loose to normal-appearing stool, stimulated by gastrocolic reflex	Irritable bowel syndrome, thyrotoxicosis, postvagotomy dumping syndrome	Infection can also contribute to increased motility
Decreased motility	Defect in neuromuscular unit(s) stasis (bacterial overgrowth)	Loose to normal-appearing stool	Pseudoobstruction, blind loop	Possible bacterial overgrowth
Decreased surface area (osmotic, motility)	Decreased functional capacity	Watery	Short bowel syndrome, celiac disease, rotavirus enteritis	Might require elemental diet plus parenteral alimentation
Mucosal invasion	Inflammation, decreased colonic reabsorption, increased motility	Blood and increased WBCs in stool	*Salmonella, Shigella* infection; amebiasis; *Yersinia, Campylobacter* infection	Dysentery evident in blood, mucus, and WBCs

VIP, vasoactive intestinal peptide; WBC, white blood cell.

From Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p 274.*

Motility disorders can be associated with rapid or delayed transit and are not generally associated with large-volume diarrhea. Slow motility can be associated with bacterial overgrowth leading to diarrhea. The differential diagnosis of common causes of acute and chronic diarrhea is noted in Table 306-11.

CONSTIPATION

Any definition of constipation is relative and depends on stool consistency, stool frequency, and difficulty in passing the stool. A normal child might have a soft stool only every 2nd or 3rd day without difficulty; this is not constipation. A hard stool passed with difficulty every 3rd day should be treated as constipation. Constipation can arise from defects either in filling or emptying the rectum (Table 306-12).

A nursing infant might have very infrequent stools of normal consistency; this is usually a normal pattern. True constipation in the neonatal period is most likely secondary to Hirschsprung disease, intestinal pseudoobstruction, or hypothyroidism.

Defective rectal filling occurs when colonic peristalsis is ineffective (in cases of hypothyroidism or opiate use and when bowel obstruction is caused either by a structural anomaly or by Hirschsprung disease).

Table 306-11 Differential Diagnosis of Diarrhea

INFANT	CHILD	ADOLESCENT
ACUTE		
Common		
Gastroenteritis (viral > bacterial > protozoal)	Gastroenteritis (viral > bacterial > protozoal)	Gastroenteritis (viral > bacterial > protozoal)
Systemic infection	Food poisoning	Food poisoning
Antibiotic associated	Systemic infection	Antibiotic associated
Overfeeding	Antibiotic associated	
Rare		
Primary disaccharidase deficiency	Toxic ingestion	Hyperthyroidism
Hirschsprung toxic colitis	Hemolytic uremic syndrome	Appendicitis
Adrenogenital syndrome	Intussusception	
Neonatal opiate withdrawal		
CHRONIC		
Common		
Postinfectious secondary lactase deficiency	Postinfectious secondary lactase deficiency	Irritable bowel syndrome
Cow's milk or soy protein intolerance (allergy)	Irritable bowel syndrome	Inflammatory bowel disease
Chronic nonspecific diarrhea of infancy	Celiac disease	Lactose intolerance
Excessive fruit juice (sorbitol) ingestion	Cystic fibrosis	Giardiasis
Celiac disease	Lactose intolerance	Laxative abuse (anorexia nervosa)
Cystic fibrosis	Excessive fruit juice (sorbitol) ingestion	Constipation with encopresis
AIDS enteropathy	Giardiasis	
	Inflammatory bowel disease	
	AIDS enteropathy	
Rare		
Primary immune defects	Primary and acquired immune defects	Secretory tumor
Autoimmune enteropathy	Secretory tumors	Primary bowel tumor
IPEX and IPEX-like syndromes	Pseudoobstruction	Parasitic infections and venereal diseases
Glucose-galactose malabsorption	Sucrase-isomaltase deficiency	Appendiceal abscess
Microvillus inclusion disease (microvillus atrophy)	Eosinophilic gastroenteritis	Addison disease
Congenital transport defects (chloride, sodium)	Secretory tumors	
Primary bile acid malabsorption		
Factitious syndrome by proxy		
Hirschsprung disease		
Shwachman syndrome		
Secretory tumors		
Acrodermatitis enteropathica		
Lymphangiectasia		
Abetalipoproteinemia		
Eosinophilic gastroenteritis		
Short bowel syndrome		

From Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p 272.*

The resultant colonic stasis leads to excessive drying of stool and a failure to initiate reflexes from the rectum that normally trigger evacuation. Emptying the rectum by spontaneous evacuation depends on a defecation reflex initiated by pressure receptors in the rectal muscle. Stool retention, therefore, can also result from lesions involving these rectal muscles, the sacral spinal cord afferent and efferent fibers, or the muscles of the abdomen and pelvic floor. Disorders of anal sphincter relaxation can also contribute to fecal retention.

Constipation tends to be self-perpetuating, whatever its cause. Hard, large stools in the rectum become difficult and even painful to evacuate; thus, more retention occurs and a vicious circle ensues. Distention of the rectum and colon lessens the sensitivity of the defecation reflex and the effectiveness of peristalsis. Fecal impaction is common and leads to other problems. Eventually, watery content from the proximal colon might percolate around hard retained stool and pass per rectum unperceived by the child. This involuntary **encopresis** may be mistaken for diarrhea. Constipation itself does not have deleterious systemic organic effects, but urinary tract stasis can accompany severe long-standing cases and constipation can generate anxiety, having a marked emotional impact on the patient and family.

ABDOMINAL PAIN

There is considerable variation among children in their perception and tolerance for abdominal pain. This is one reason the evaluation of chronic abdominal pain is difficult. A child with **functional abdominal pain** (no identifiable organic cause) may be as uncomfortable as one with an organic cause. It is very important to distinguish between organic and nonorganic (functional) abdominal pain because the approach for the management is based on this. Normal growth and physical examination (including a rectal examination) and the absence of anemia or hematochezia are reassuring in a child who is suspected of having functional pain.

A specific cause may be difficult to find, but the nature and location of a pain-provoking lesion can usually be determined from the clinical description. Two types of nerve fibers transmit painful stimuli in the abdomen. In skin and muscle, A fibers mediate sharp localized pain; C fibers from viscera, peritoneum, and muscle transmit poorly localized, dull pain. These afferent fibers have cell bodies in the dorsal root ganglia, and some axons cross the midline and ascend to the medulla, midbrain, and thalamus. Pain is perceived in the cortex of the postcentral gyrus, which can receive impulses arising from both sides of the body. In the gut, the usual stimulus provoking pain is tension or stretching. Inflammatory lesions can lower the pain threshold, but the mechanisms producing pain of inflammation are not clear. Tissue metabolites released near nerve endings probably account for the pain caused by ischemia. Perception of these painful stimuli can be modulated by input from both cerebral and peripheral sources. Psychologic factors are particularly important. Tables 306-13 and 306-14 list features of abdominal pain. Pain that suggests a potentially serious organic etiology is associated with age younger than 5 yr; fever; weight loss;

Table 306-12 Causes of Constipation

NONORGANIC (FUNCTIONAL)—RETENTIVE
ANATOMIC
Anal stenosis, atresia with fistula
Imperforate anus
Anteriorly displaced anus
Intestinal stricture (postnecrotizing enterocolitis)
Anal stricture
ABNORMAL MUSCULATURE
Prune-belly syndrome
Gastroschisis
Down syndrome
Muscular dystrophy
INTESTINAL NERVE OR MUSCLE ABNORMALITIES
Hirschsprung disease
Pseudoobstruction (visceral myopathy or neuropathy)
Intestinal neuronal dysplasia
Spinal cord defects
Tethered cord
Spinal cord trauma
Spina bifida
DRUGS
Anticholinergics
Narcotics
Methylphenidate
Phenytoin
Antidepressants
Chemotherapeutic agents (vincristine)
Pancreatic enzymes (fibrosing colonopathy)
Lead
Vitamin D intoxication
METABOLIC DISORDERS
Hypokalemia
Hypercalcemia
Hypothyroidism
Diabetes mellitus, diabetes insipidus
INTESTINAL DISORDERS
Celiac disease
Cow's milk protein intolerance
Cystic fibrosis (meconium ileus equivalent)
Inflammatory bowel disease (stricture)
Tumor
Connective tissue disorders
Systemic lupus erythematosus
Scleroderma
PSYCHIATRIC DIAGNOSIS
Anorexia nervosa

bile or blood-stained emesis; jaundice; hepatosplenomegaly; back or flank pain or pain in a location other than the umbilicus; awakening from sleep in pain; referred pain to shoulder, groin or back; elevated erythrocyte sedimentation rate, white blood cell count, or C-reactive protein; anemia; edema; hematochezia, or a strong family history of inflammatory bowel disease or celiac disease.

Visceral pain tends to be dull and aching and is experienced in the dermatome from which the affected organ receives innervations. So, most often, the pain and tenderness is not felt over the site of the disease process. Painful stimuli originating in the liver, pancreas, biliary tree, stomach, or upper bowel are felt in the epigastrium; pain from the distal small bowel, cecum, appendix, or proximal colon is felt at the umbilicus; and pain from the distal large bowel, urinary tract, or pelvic organs is usually suprapubic. The pain from the cecum, ascending colon, and descending colon sometimes is felt at the site of the lesion because of the short mesocecum and corresponding mesocolon. The pain caused by appendicitis is initially felt in the periumbilical region, and pain from the transverse colon is usually felt in the supra pubic region. The shifting (localization) of pain is a pointer toward diagnosis; for example, periumbilical pain of a few hours localizing to the right lower quadrant suggests appendicitis. Radiation of pain can be helpful in diagnosis; for example, in biliary colic the radiation of pain is toward the inferior angle of the right scapula, pancreatic pain radiated to the back, and the renal colic pain is radiated to the inguinal region on the same side.

Somatic pain is intense and is usually well localized. When the inflamed viscus comes in contact with the somatic organ like the parietal peritoneum or the abdominal wall, pain is localized to that site. Peritonitis gives rise to generalized abdominal pain with rigidity, involuntary guarding, rebound tenderness, and cutaneous hyperesthesia on physical examination.

Referred pain from extraintestinal locations, from shared central projections with the sensory pathway from the abdominal wall, can give rise to abdominal pain, as in pneumonia when the parietal pleural pain is referred to the abdomen.

GASTROINTESTINAL HEMORRHAGE

Bleeding can occur anywhere along the GI tract, and identification of the site may be challenging (Table 306-15). Bleeding that originates in the esophagus, stomach, or duodenum can cause **hematemesis.** When exposed to gastric or intestinal juices, blood quickly darkens to resemble coffee grounds; massive bleeding is likely to be red. Red or maroon blood in stools, **hematochezia,** signifies either a distal bleeding site or massive hemorrhage above the distal ileum. Moderate to mild bleeding from sites above the distal ileum tends to cause blackened stools of tarry consistency **(melena);** major hemorrhages in the duodenum or above can also cause melena.

Erosive damage to the mucosa of the GI tract is the most common cause of bleeding, although variceal bleeding secondary to portal hypertension occurs often enough to require consideration. Prolapse gastropathy producing subepithelial hemorrhage and Mallory-Weiss lesions secondary to mucosal tears associated with emesis are causes of upper intestinal bleeds. Vascular malformations are a rare cause in children; they are difficult to identify. Upper intestinal bleeding is evaluated with esophagogastroduodenoscopy. Evaluation of the small intestine is facilitated by capsule endoscopy. The capsule-sized imaging device is swallowed in older children or placed endoscopically in younger children. Lower GI bleeding is investigated with a colonoscopy. In brisk intestinal bleeding of unknown location, a tagged red blood cell scan is helpful in locating the site of the bleeding. Occult blood in stool is usually detected by using commercially available fecal occult blood testing cards, which are based on a chemical reaction between the chemical guaiac and oxidizing action of a substrate (hemoglobin), giving a blue color. The guaiac test is very sensitive, but random testing can miss chronic blood loss, which can lead to iron-deficiency anemia. GI hemorrhage can produce hypotension and tachycardia but rarely causes GI symptoms; brisk duodenal or gastric bleeding can lead to nausea, vomiting, or diarrhea. The breakdown products of intraluminal blood might tip patients into hepatic coma if liver function is already compromised and can lead to elevation of serum bilirubin.

ABDOMINAL DISTENTION AND ABDOMINAL MASSES

Enlargement of the abdomen can result from diminished tone of the wall musculature or from increased content: fluid, gas, or solid. Ascites, the accumulation of fluid in the peritoneal cavity, distends the abdomen both in the flanks and anteriorly when it is large in volume. This fluid shifts with movement of the patient and conducts a percussion wave. Ascitic fluid is usually a transudate with a low protein concentration resulting from reduced plasma colloid osmotic pressure of hypoalbuminemia and/or from raised portal venous pressure. In cases of portal hypertension, the fluid leak probably occurs from lymphatics on the liver surface and from visceral peritoneal capillaries, but ascites does not usually develop until the serum albumin level falls. Sodium excretion in the urine decreases greatly as the ascitic fluid accumulates and, thus, additional dietary sodium goes directly to the peritoneal space, taking with it more water. When ascitic fluid contains a high protein

Table 306-13 Chronic Abdominal Pain in Children

DISORDER	CHARACTERISTICS	KEY EVALUATIONS
NONORGANIC		
Functional abdominal pain	Nonspecific pain, often periumbilical	Hx and PE; tests as indicated
Irritable bowel syndrome	Intermittent cramps, diarrhea, and constipation	Hx and PE
Nonulcer dyspepsia	Peptic ulcer–like symptoms without abnormalities on evaluation of the upper GI tract	Hx; esophagogastroduodenoscopy
GASTROINTESTINAL TRACT		
Chronic constipation	Hx of stool retention, evidence of constipation on examination	Hx and PE; plain x-ray of abdomen
Lactose intolerance	Symptoms may be associated with lactose ingestion; bloating, gas, cramps, and diarrhea	Trial of lactose-free diet; lactose breath hydrogen test
Parasite infection (especially *Giardia*)	Bloating, gas, cramps, and diarrhea	Stool evaluation for O&P; specific immunoassays for *Giardia*
Excess fructose or sorbitol ingestion	Nonspecific abdominal pain, bloating, gas, and diarrhea	Large intake of apples, fruit juice, or candy or chewing gum sweetened with sorbitol
Crohn disease	See Chapter 336	
Peptic ulcer	Burning or gnawing epigastric pain; worse on awakening or before meals; relieved with antacids	Esophagogastroduodenoscopy, upper GI contrast x-rays, or MRI enteroscopy
Esophagitis	Epigastric pain with substernal burning	Esophagogastroduodenoscopy
Meckel diverticulum	Periumbilical or lower abdominal pain; may have blood in stool (usually painless)	Meckel scan or enteroclysis
Recurrent intussusception	Paroxysmal severe cramping abdominal pain; blood may be present in stool with episode	Identify intussusception during episode or lead point in intestine between episodes with contrast studies of GI tract
Internal, inguinal, or abdominal wall hernia	Dull abdomen or abdominal wall pain	PE, CT of abdominal wall
Chronic appendicitis or appendiceal mucocele	Recurrent RLQ pain; often incorrectly diagnosed, may be rare cause of abdominal pain	Barium enema, CT
GALLBLADDER AND PANCREAS		
Cholelithiasis	RUQ pain, might worsen with meals	Ultrasound of gallbladder
Choledochal cyst	RUQ pain, mass ± elevated bilirubin	Ultrasound or CT of RUQ
Recurrent pancreatitis	Persistent boring pain, might radiate to back, vomiting	Serum amylase and lipase ± serum trypsinogen; ultrasound, CT, or MRI-ERCP of pancreas
GENITOURINARY TRACT		
Urinary tract infection	Dull suprapubic pain, flank pain	Urinalysis and urine culture; renal scan
Hydronephrosis	Unilateral abdominal or flank pain	Ultrasound of kidneys
Urolithiasis	Progressive, severe pain; flank to inguinal region to testicle	Urinalysis, ultrasound, IVP, CT
Other genitourinary disorders	Suprapubic or lower abdominal pain; genitourinary symptoms	Ultrasound of kidneys and pelvis; gynecologic evaluation
MISCELLANEOUS CAUSES		
Abdominal migraine	See text; nausea, family Hx migraine	Hx
Abdominal epilepsy	Might have seizure prodrome	EEG (can require > 1 study, including sleep-deprived EEG)
Gilbert syndrome	Mild abdominal pain (causal or coincidental?); slightly elevated unconjugated bilirubin	Serum bilirubin
Familial Mediterranean fever	Paroxysmal episodes of fever, severe abdominal pain, and tenderness with other evidence of polyserositis	Hx and PE during an episode, DNA diagnosis
Sickle cell crisis	Anemia	Hematologic evaluation
Lead poisoning	Vague abdominal pain ± constipation	Serum lead level
Henoch-Schönlein purpura	Recurrent, severe crampy abdominal pain, occult blood in stool, characteristic rash, arthritis	Hx, PE, urinalysis
Angioneurotic edema	Swelling of face or airway, crampy pain	Hx, PE, upper GI contrast x-rays, serum C1 esterase inhibitor
Acute intermittent porphyria	Severe pain precipitated by drugs, fasting, or infections	Spot urine for porphyrins

EEG, electroencephalogram; GI, gastrointestinal; Hx, history; IVP, intravenous pyelography; O&P, ova and parasites; PE, physical exam; RLQ, right lower quadrant; RUQ, right upper quadrant.

Table 306-14 Distinguishing Features of Acute Gastrointestinal Tract Pain in Children

DISEASE	ONSET	LOCATION	REFERRAL	QUALITY	COMMENTS
Pancreatitis	Acute	Epigastric, left upper quadrant	Back	Constant, sharp, boring	Nausea, emesis, tenderness
Intestinal obstruction	Acute or gradual	Periumbilical-lower abdomen	Back	Alternating cramping (colic) and painless periods	Distention, obstipation, emesis, increased bowel sounds
Appendicitis	Acute	Periumbilical, then localized to lower right quadrant; generalized with peritonitis	Back or pelvis if retrocecal	Sharp, steady	Anorexia, nausea, emesis, local tenderness, fever with peritonitis
Intussusception	Acute	Periumbilical-lower abdomen	None	Cramping, with painless periods	Hematochezia, knees in pulled-up position
Urolithiasis	Acute, sudden	Back (unilateral)	Groin	Sharp, intermittent, cramping	Hematuria
Urinary tract infection	Acute	Back	Bladder	Dull to sharp	Fever, costovertebral angle tenderness, dysuria, urinary frequency

Table 306-15 Differential Diagnosis of Gastrointestinal Bleeding in Childhood

INFANT	CHILD	ADOLESCENT
COMMON		
Bacterial enteritis	Bacterial enteritis	Bacterial enteritis
Milk protein allergy intolerance	Anal fissure	Inflammatory bowel disease
Intussusception	Colonic polyps	Peptic ulcer/gastritis
Swallowed maternal blood	Intussusception	Prolapse (traumatic) gastropathy secondary to emesis
Anal fissure	Peptic ulcer/gastritis	Mallory-Weiss syndrome
Lymphonodular hyperplasia	Swallowed epistaxis	Colonic polyps
	Prolapse (traumatic) gastropathy secondary to emesis	Anal fissure
	Mallory-Weiss syndrome	
RARE		
Volvulus	Esophageal varices	Hemorrhoids
Necrotizing enterocolitis	Esophagitis	Esophageal varices
Meckel diverticulum	Meckel diverticulum	Esophagitis
Stress ulcer, gastritis	Lymphonodular hyperplasia	Pill ulcer
Coagulation disorder (hemorrhagic disease of newborn)	Henoch-Schönlein purpura	Telangiectasia-angiodysplasia
Esophagitis	Foreign body	Graft-vs-host disease
	Hemangioma, arteriovenous malformation	Duplication cyst
	Sexual abuse	
	Hemolytic-uremic syndrome	
	Inflammatory bowel disease	
	Coagulopathy	
	Duplication cyst	

concentration, it is usually an exudate caused by an inflammatory or neoplastic lesion.

When fluid distends the gut, either obstruction or imbalance between absorption and secretion should be suspected. The factors causing fluid accumulation in the bowel lumen often cause gas to accumulate, too. The result may be audible gurgling noises. The source of gas is usually swallowed air, but endogenous flora can increase considerably in malabsorptive states and produce excessive gas when substrate reaches the lower intestine. Gas in the peritoneal cavity (pneumoperitoneum) is usually caused by a perforated viscus and can cause abdominal distention depending on the amount of gas leak. A tympanitic percussion note, even over solid organs such as the liver, indicates a large collection of gas in the peritoneum.

An abdominal organ can enlarge diffusely or be affected by a discrete mass. In the digestive tract, such discrete masses can occur in the lumen, wall, omentum, or mesentery. In a constipated child, mobile, nontender fecal masses are often found. Congenital anomalies, cysts, or inflammatory processes can affect the wall of the gut. Gut wall neoplasms are extremely rare in children. The pathologic enlargement of liver, spleen, bladder, and kidneys can give rise to abdominal distention.

JAUNDICE

See Chapters 102.3 and 356.

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Section 2
The Oral Cavity

Chapter 307
Development and Developmental Anomalies of the Teeth

Norman Tinanoff

INITIATION

The primary teeth form in dental crypts that arise from a band of epithelial cells incorporated into each developing jaw. By 12 wk of fetal life, each of these epithelial bands **(dental laminae)** has 5 areas of rapid growth on each side of the maxilla and the mandible, seen as rounded, bud-like enlargements. Organization of adjacent mesenchyme takes place in each area of epithelial growth, and the 2 elements together are the beginning of a tooth.

After the formation of these crypts for the 20 primary teeth, another generation of tooth buds forms lingually (toward the tongue); these will develop into the succeeding permanent incisors, canines, and premolars that eventually replace the primary teeth. This process takes place from approximately 5 mo of gestation for the central incisors to approximately 10 mo of age for the 2nd premolars. The permanent 1st, 2nd, and 3rd molars, on the other hand, arise from extension of the dental laminae distal to the 2nd primary molars; buds for these teeth develop at approximately 4 mo of gestation, 1 yr of age, and 4-5 yr of age, respectively.

HISTODIFFERENTIATION–MORPHODIFFERENTIATION

As the epithelial bud proliferates, the deeper surface invaginates and a mass of mesenchyme becomes partially enclosed. The epithelial cells differentiate into the ameloblasts that lay down an organic matrix that forms enamel; the mesenchyme forms the dentin and dental pulp.

CALCIFICATION

After the organic matrix has been laid down, the deposition of the inorganic mineral crystals takes place from several sites of calcification that later coalesce. The characteristics of the inorganic portions of a tooth can be altered by disturbances in formation of the matrix, decreased availability of minerals, or the incorporation of foreign materials. Such disturbances can affect the color, texture, or thickness of the tooth surface. Calcification of primary teeth begins at 3-4 mo in utero and concludes postnatally at approximately 12 mo with mineralization of the 2nd primary molars (Table 307-1).

Table 307-1 Calcification, Crown Completion, and Eruption

TOOTH	FIRST EVIDENCE OF CALCIFICATION	CROWN COMPLETED	ERUPTION
PRIMARY DENTITION			
Maxillary			
Central incisor	3-4 mo in utero	4 mo	7.5 mo
Lateral incisor	4.5 mo in utero	5 mo	8 mo
Canine	5.5 mo in utero	9 mo	16-20 mo
First molar	5 mo in utero	6 mo	12-16 mo
Second molar	6 mo in utero	10-12 mo	20-30 mo
Mandibular			
Central incisor	4.5 mo in utero	4 mo	6.5 mo
Lateral incisor	4.5 mo in utero	4¼ mo	7 mo
Canine	5 mo in utero	9 mo	16-20 mo
First molar	5 mo in utero	6 mo	12-16 mo
Second molar	6 mo in utero	10-12 mo	20-30 mo
PERMANENT DENTITION			
Maxillary			
Central incisor	3-4 mo	4-5 yr	7-8 yr
Lateral incisor	10 mo	4-5 yr	8-9 yr
Canine	4-5 mo	6-7 yr	11-12 yr
First premolar	1.5-1¾ yr	5-6 yr	10-11 yr
Second premolar	2-2¼ yr	6-7 yr	10-12 yr
First molar	At birth	2.5-3 yr	6-7 yr
Second molar	2.5-3 yr	7-8 yr	12-13 yr
Third molar	7-9 yr	12-16 yr	17-21 yr
Mandibular			
Central incisor	3-4 mo	4-5 yr	6-7 yr
Lateral incisor	3-4 mo	4-5 yr	7-8 yr
Canine	4-5 mo	6-7 yr	9-10 yr
First premolar	1¾-2 yr	5-6 yr	10-12 yr
Second premolar	2¼-2.5 yr	6-7 yr	11-12 yr
First molar	At birth	2.5-3 yr	6-7 yr
Second molar	2.5-3 yr	7-8 yr	11-13 yr
Third molar	8-10 yr	12-16 yr	17-21 yr

Modified from Logan WHG, Kronfeld R: Development of the human jaws and surrounding structures from birth to age 15 years, J Am Dent Assoc 20:379, 1993.

ERUPTION

At the time of tooth bud formation, each tooth begins a continuous movement toward the oral cavity. Table 307-1 lists the times of eruption of the primary and permanent teeth.

ANOMALIES ASSOCIATED WITH TOOTH DEVELOPMENT

Both failures and excesses of tooth initiation are observed. Developmentally missing teeth can result from environmental insult, a genetic defect involving only teeth, or the manifestation of a syndrome. **Anodontia,** or absence of teeth, occurs when no tooth buds form (ectodermal dysplasia, or familial missing teeth) or when there is a disturbance of a normal site of initiation (the area of a palatal cleft). The teeth that are most commonly absent are the 3rd molars, the maxillary lateral incisors, and the mandibular 2nd premolars.

If the dental lamina produces more than the normal number of buds, **supernumerary teeth** occur, most often in the area between the maxillary central incisors. Because they tend to disrupt the position and eruption of the adjacent normal teeth, their identification by radiographic examination is important. Supernumerary teeth also occur with cleidocranial dysplasia (see Chapter 311) and in the area of cleft palates.

Twinning, in which 2 teeth are joined together, is most often observed in the mandibular incisors of the primary dentition. It can result from gemination, fusion, or concrescence. **Gemination** is the result of the division of 1 tooth germ to form a bifid crown on a single root with a common pulp canal; an extra tooth appears to be present in the dental arch. **Fusion** is the joining of incompletely developed teeth that, owing to pressure, trauma, or crowding, continue to develop as 1 tooth. Fused teeth are sometimes joined along their entire length; in other cases, a single wide crown is supported on 2 roots. **Concrescence** is the attachment of the roots of closely approximated adjacent teeth by an excessive deposit of cementum. This type of twinning, unlike the others, is found most often in the maxillary molar region.

Disturbances during differentiation can result in alterations in dental morphology, such as **macrodontia** (large teeth) or **microdontia** (small teeth). The maxillary lateral incisors can assume a slender, tapering shape **(peg-shaped laterals).**

Figure 307-1 **Amelogenesis imperfecta, hypoplastic type.** The enamel defect results in areas of missing or thin enamel as well as grooves and pits.

Figure 307-2 **Dentinogenesis imperfecta.** The bluish, opalescent sheen on several of these teeth results from genetically defective dentin. This condition may be associated with osteogenesis imperfecta. *(From Nazif MM, Martin BS, McKibben DH, et al: Oral disorders. In Zitelli BJ, Davis HW, editors:* Atlas of pediatric physical diagnosis, *ed 4, Philadelphia, 2002, Mosby, p. 703.)*

Amelogenesis imperfecta represents a group of hereditary conditions that manifest in enamel defects of the primary and permanent teeth without evidence of systemic disorders (Fig. 307-1). The teeth are covered by only a thin layer of abnormally formed enamel through which the yellow underlying dentin is seen. The primary teeth are generally affected more than the permanent teeth. Susceptibility to caries is low, but the enamel is subject to destruction from abrasion. Complete coverage of the crown may be indicated for dentin protection, to reduce tooth sensitivity, and for improved appearance.

Dentinogenesis imperfecta, or hereditary opalescent dentin, is a condition analogous to amelogenesis imperfecta in which the odontoblasts fail to differentiate normally, resulting in poorly calcified dentin (Fig. 307-2). This autosomal dominant disorder can also occur in patients with **osteogenesis imperfecta.** The enamel-dentin junction is altered, causing enamel to break away. The exposed dentin is then susceptible to abrasion, in some cases worn to the gingiva. The teeth are opaque and pearly, and the pulp chambers are generally obliterated by calcification. Both primary and permanent teeth are usually involved. If there is excessive wear of the teeth, selected complete coverage of the teeth may be indicated to prevent further tooth loss and improve appearance.

Localized disturbances of calcification that correlate with periods of illness, malnutrition, premature birth, or birth trauma are common. **Hypocalcification** appears as opaque white patches or horizontal lines on the tooth; **hypoplasia** is more severe and manifests as pitting or areas devoid of enamel. Systemic conditions, such as renal failure and cystic fibrosis, are associated with enamel defects. Local trauma to the primary incisors can also affect calcification of permanent incisors.

Fluorosis (mottled enamel) can result from systemic fluoride consumption > 0.05 mg/kg/day during enamel formation. This high fluoride consumption can be caused by residing in an area of high fluoride content of the drinking water (>2.0 ppm), swallowing excessive fluoridated toothpaste, or inappropriate fluoride prescriptions. Excessive fluoride during enamel formation affects ameloblastic function, resulting in inconspicuous white, lacy patches on the enamel to severe brownish discoloration and hypoplasia. The latter changes are usually seen with fluoride concentrations in the drinking water > 5.0 ppm.

Discolored teeth can result from incorporation of foreign substances into developing enamel. Neonatal hyperbilirubinemia can produce blue to black discoloration of the primary teeth. Porphyria produces a red-brown discoloration. Tetracyclines are extensively incorporated into bones and teeth and, if administered during the period of formation of enamel, can result in brown-yellow discoloration and hypoplasia of the enamel. Such teeth fluoresce under ultraviolet light. The period at risk extends from approximately 4 mo of gestation to 7 yr of life. Repeated or prolonged therapy with tetracycline carries the highest risk.

Delayed eruption of the 20 primary teeth can be familial or indicate systemic or nutritional disturbances such as hypopituitarism, hypothyroidism, cleidocranial dysplasia, trisomy 21, and multiple syndromes. Failure of eruption of single or small groups of teeth can arise from local causes such as malpositioned teeth, supernumerary teeth, cysts, or retained primary teeth. Premature loss of primary teeth is most commonly caused by premature eruption of the permanent teeth. If the entire dentition is advanced for age and sex, precocious puberty or hyperthyroidism should be considered.

Natal teeth are observed in approximately 1 in 2,000 newborn infants usually in the position of the mandibular central incisors. Natal teeth are present at birth, whereas **neonatal teeth** erupt in the 1st mo of life. Attachment of natal and neonatal teeth is generally limited to the gingival margin, with little root formation or bony support. They may be a supernumerary or a prematurely erupted primary tooth. A radiograph can easily differentiate between the two conditions. Natal teeth are associated with cleft palate, Pierre Robin syndrome, Ellis-van Creveld syndrome, Hallermann-Streiff syndrome, pachyonychia congenita, and other anomalies. A family history of natal teeth or premature eruption is present in 15-20% of affected children.

Natal or neonatal teeth occasionally result in pain and refusal to feed and can produce maternal discomfort because of abrasion or biting of the nipple during nursing. If the tooth is mobile there is a danger of detachment, with aspiration of the tooth. Because the tongue lies between the alveolar processes during birth, it can become lacerated **(Riga-Fede disease).** Decisions regarding extraction of prematurely erupted primary teeth must be made on an individual basis.

Exfoliation failure occurs when a primary tooth is not shed before the eruption of its permanent successor. Most often the primary tooth exfoliates eventually, but in some cases, the primary tooth needs to be extracted. This occurs most commonly in the mandibular incisor region.

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Chapter 308

Disorders of the Oral Cavity Associated with Other Conditions

Norman Tinanoff

Disorders of the teeth and surrounding structures can occur in isolation or in combination with other systemic conditions (Table 308-1). Most commonly, medical conditions that occur during tooth development can affect tooth formation or appearance. Damage to teeth during their development is permanent.

Table 308-1 Dental Problems Associated with Selected Medical Conditions

MEDICAL CONDITION	COMMON ASSOCIATED DENTAL OR ORAL FINDINGS
Cleft lip and palate	Missing teeth, extra (supernumerary) teeth, shifting of arch segments, feeding difficulties, speech problems
Kidney failure	Mottled enamel (permanent teeth), facial dysmorphology
Cystic fibrosis	Stained teeth with extensive medication, mottled enamel
Immunosuppression	Oral candidiasis with potential for systemic candidiasis, cyclosporine-induced gingival hyperplasia
Low birthweight	Palatal groove, narrow arch with prolonged oral intubation; enamel defects of primary teeth
Heart defects with susceptibility to bacterial endocarditis	Bacteremia from dental procedures or trauma
Neutrophil chemotactic deficiency	Juvenile periodontitis (loss of supporting bone around teeth)
Juvenile diabetes (uncontrolled)	Juvenile periodontitis
Neuromotor dysfunction	Oral trauma from falling; malocclusion (open bite); gingivitis from lack of hygiene
Prolonged illness (generalized) during tooth formation	Enamel hypoplasia of crown portions forming during illness
Seizures	Gingival enlargement if phenytoin is used
Maternal infections	Syphilis: abnormally shaped teeth
Vitamin D–dependent rickets	Enamel hypoplasia

Chapter 309

Malocclusion

Norman Tinanoff

The oral cavity is essentially a masticatory instrument. The purpose of the anterior teeth is to bite off portions of large amounts of food. The posterior teeth reduce foodstuff to a soft, moist bolus. The cheeks and tongue force the food onto the areas of tooth contact. Establishing a proper relationship between the mandibular and maxillary teeth is important for physiologic and cosmetic reasons.

VARIATIONS IN GROWTH PATTERNS

Growth patterns are classified into 3 main types of occlusion, determined when the jaws are closed and the teeth are held together (Fig. 309-1). According to the Angle Classification of Malocclusion, in **class I occlusion** (normal), the cusps of the posterior mandibular teeth interdigitate ahead of and inside of the corresponding cusps of the opposing maxillary teeth. This relationship provides a normal facial profile.

In **class II malocclusion,** "buck teeth," the cusps of the posterior mandibular teeth are behind and inside the corresponding cusps of the maxillary teeth. This common occlusal disharmony is found in ~45% of the population. The facial profile can give the appearance of a "receding chin" (retrognathia) (mandibular deficiency) or protruding front teeth. The resultant increased space between upper and lower anterior teeth encourage finger sucking and tongue-thrust habits. Additionally, children with pronounced class II malocclusions are at greater risks of damage to the incisors as a consequence of trauma. Treatment includes orthodontic retraction of the maxilla or stimulation of the mandible.

In **class III malocclusion,** "underbite," the cusps of the posterior mandibular teeth interdigitate a tooth or more ahead of their opposing maxillary counterparts. The anterior teeth appear in cross bite with the mandibular incisors protruding beyond the maxillary incisors. The facial profile gives the appearance of a "protruding chin" **(prognathia)** with or without an appearance of maxillary deficiency. If necessary, treatment includes mandibular excess reduction osteotomy or orthodontic maxillary facial protrusion.

CROSSBITE

Normally, the mandibular teeth are in a position just inside the maxillary teeth, so that the outside mandibular cusps or incisal edges meet the central portion of the opposing maxillary teeth. A reversal of this relation is referred to as a crossbite. Crossbites can be anterior, involving the incisors; can be posterior, involving the molars; or can involve single or multiple teeth.

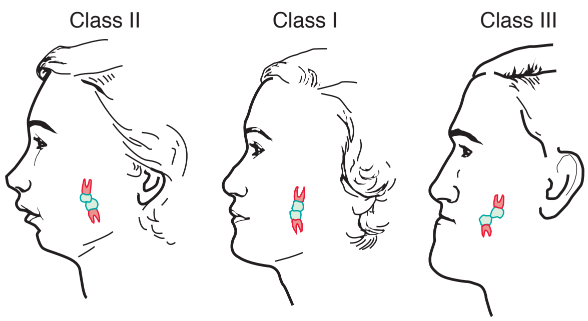

Figure 309-1 **Angle classification of occlusion.** The typical correspondence between the facial-jaw profile and molar relationship is shown.

OPEN AND CLOSED BITES

If the posterior mandibular and maxillary teeth make contact with each other, but the anterior teeth are still apart, the condition is called an *open bite*. Open bites can result from skeletal growth pattern or digit sucking. If digit sucking is terminated before skeletal and dental growth is complete, the open bite might resolve naturally. If mandibular anterior teeth occlude inside the maxillary anterior teeth in an overclosed position, the condition is referred to as a *closed* or *deep bite*.

Treatment of open and closed bites consists of orthodontic correction, generally performed in the preteen or teenage years. Some cases require orthognathic surgery to position the jaws optimally in a vertical direction.

DENTAL CROWDING

Overlap of incisors can result when the jaws are too small or the teeth are too large for adequate alignment of the teeth. Growth of the jaws is mostly in the posterior aspects of the mandible and maxilla, and therefore inadequate space for the teeth at 7 or 8 yr of age will not resolve with growth of the jaws. Spacing in the primary dentition is normal and favorable for adequate alignment of successor teeth.

DIGIT SUCKING

Various and conflicting etiologic theories and recommendations for correction have been proposed for digit sucking in children. Prolonged digit sucking can cause flaring of the maxillary incisor teeth, an open bite, and a posterior crossbite. The prevalence of digit sucking decreases steadily from the age of 2 yr to ≈10% by the age of 5 yr. The earlier the habit is discontinued after the eruption of the permanent maxillary incisors (age 7-8 yr), the greater the likelihood that there will be lessening effects on the dentition.

A variety of treatments have been suggested, from behavioral modification to insertion of an appliance with extensions that serves as a reminder when the child attempts to insert the digit. The greatest likelihood of success occurs in cases in which the child desires to stop. Stopping of the habit will not rectify a malocclusion caused by a prior deviant growth pattern.

Chapter 310

Cleft Lip and Palate

Norman Tinanoff

Clefts of the lip and palate are distinct entities closely related embryologically, functionally, and genetically. It is thought that cleft of the lip appears because of hypoplasia of the mesenchymal layer, resulting in a failure of the medial nasal and maxillary processes to join. Cleft of the palate appears to represent failure of the palatal shelves to approximate or fuse.

INCIDENCE AND EPIDEMIOLOGY

The incidence of cleft lip with or without cleft palate is approximately 1 in 750 white births; the incidence of cleft palate alone is approximately 1 in 2,500 white births. Clefts of the lip are more common in males. Possible causes include maternal drug exposure, a syndrome-malformation complex, or genetic factors. Although clefts of lips and palates appear to occur sporadically, the presence of susceptible genes appears important. There are approximately 400 syndromes associated with cleft lip and palates. There are families in which a cleft lip or palate, or both, is inherited in a dominant fashion (**van der Woude syndrome**), and careful examination of parents is important to distinguish this type from others, because the recurrence risk is 50%. Ethnic factors also affect the incidence of cleft lip and palate; the incidence is highest among Asians (~1 in 500) and Native Americans (~1 in 300), and lowest among blacks (~1 in 2,500). Cleft lip may be associated with other cranial facial anomalies, whereas cleft palate may be associated with central nervous system anomalies.

CLINICAL MANIFESTATIONS

Cleft lip can vary from a small notch in the vermilion border to a complete separation involving skin, muscle, mucosa, tooth, and bone. Clefts of the lip may be unilateral (more often on the left side) or bilateral and can involve the alveolar ridge (Fig. 310-1).

Isolated cleft palate occurs in the midline and might involve only the uvula or can extend into or through the soft and hard palates to the incisive foramen. When associated with cleft lip, the defect can involve the midline of the soft palate and extend into the hard palate on one or both sides, exposing one or both of the nasal cavities as a unilateral or bilateral cleft palate. The palate can also have a submucosal cleft indicated by a bifid uvula, partial separation of muscle with intact mucosa, or a palpable notch at the posterior of the palate.

TREATMENT

A complete program of habilitation for the child with a cleft lip or palate can require years of special treatment by a team consisting of a pediatrician, plastic surgeon, otolaryngologist, oral and maxillofacial surgeon, pediatric dentist, prosthodontist, orthodontist, speech therapist, geneticist, medical social worker, psychologist, and public health nurse.

The immediate problem in an infant born with a cleft lip or palate is feeding. Although some advocate the construction of a plastic obturator to assist in feedings, most believe that with the use of soft artificial nipples with large openings, a squeezable bottle, and proper instruction, feeding of infants with clefts can be achieved.

Surgical closure of a cleft lip is usually performed by 3 mo of age, when the infant has shown satisfactory weight gain and is free of any oral, respiratory, or systemic infection. Modification of the Millard rotation–advancement technique is the most commonly used technique; a staggered suture line minimizes notching of the lip from retraction of scar tissue. The initial repair may be revised at 4 or 5 yr of age. Corrective surgery on the nose may be delayed until adolescence. Nasal surgery can also be performed at the time of the lip repair. Cosmetic results depend on the extent of the original deformity, healing potential of the individual patient, absence of infection, and the skill of the surgeon.

Because clefts of the palate vary considerably in size, shape, and degree of deformity, the timing of surgical correction should be individualized. Criteria such as width of the cleft, adequacy of the existing palatal segments, morphology of the surrounding areas (width of the oropharynx), and neuromuscular function of the soft palate and pharyngeal walls affect the decision. The goals of surgery are the union of the cleft segments, intelligible and pleasant speech, reduction of nasal regurgitation, and avoidance of injury to the growing maxilla.

In an otherwise healthy child, closure of the palate is usually done before 1 yr of age to enhance normal speech development. When surgical correction is delayed beyond the 3rd yr, a contoured speech bulb can be attached to the posterior of a maxillary denture so that contraction of the pharyngeal and velopharyngeal muscles can bring tissues into contact with the bulb to accomplish occlusion of the nasopharynx and help the child develop intelligible speech.

A cleft palate usually crosses the alveolar ridge and interferes with the formation of teeth in the maxillary anterior region. Teeth in the cleft area may be displaced, malformed, or missing. Missing teeth or teeth that are nonfunctional are replaced by prosthetic devices.

POSTOPERATIVE MANAGEMENT

During the immediate postoperative period, special nursing care is essential. Gentle aspiration of the nasopharynx minimizes the chances of the common complications of atelectasis or pneumonia. The primary considerations in postoperative care are maintenance of a clean suture line and avoidance of tension on the sutures. The infant is fed with a

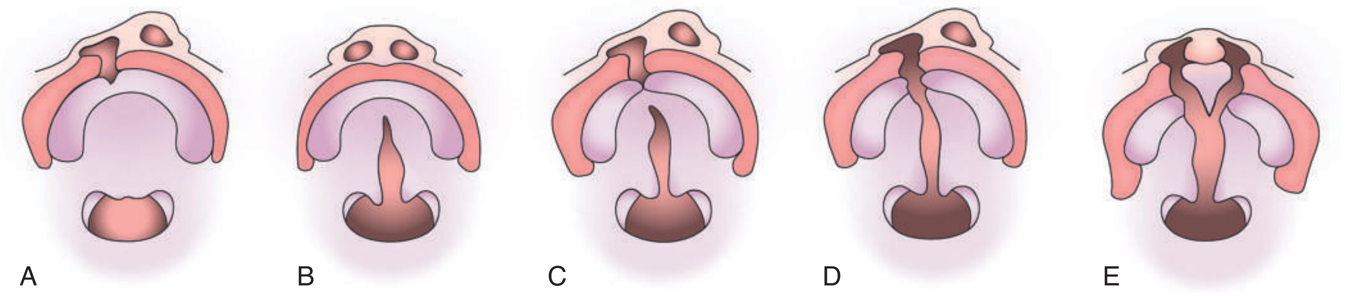

Figure 310-1 Nonsyndromic orofacial clefts. **A,** Cleft lip and alveolus. **B,** Cleft palate. **C,** Incomplete unilateral cleft lip and palate. **D,** Complete unilateral cleft lip and palate. **E,** Complete bilateral cleft lip and palate. *(From Shaw WC:* Orthodontics and occlusal management, *Oxford, England, 1993, Butterworth-Heinemann.)*

Mead Johnson bottle and the arms are restrained with elbow cuffs. A fluid or semifluid diet is maintained for 3 wk. The patient's hands, toys, and other foreign bodies must be kept away from the surgical site.

SEQUELAE

Recurrent otitis media and subsequent hearing loss are frequent with cleft palate. Displacement of the maxillary arches and malposition of the teeth usually require orthodontic correction. Misarticulations and velopharyngeal dysfunction are often associated with cleft lip and palate and may be present or persist because of physiologic dysfunction, anatomic insufficiency, malocclusion, or inadequate surgical closure of the palate. Such speech is characterized by the emission of air from the nose and by a hypernasal quality with certain sounds or by compensatory misarticulations (glottal stops). Before and sometimes after palatal surgery, the speech defect is caused by inadequacies in function of the palatal and pharyngeal muscles. The muscles of the soft palate and the lateral and posterior walls of the nasopharynx constitute a valve that separates the nasopharynx from the oropharynx during swallowing and in the production of certain sounds. If the valve does not function adequately, it is difficult to build up enough pressure in the mouth to make such explosive sounds as p, b, d, t, h, y, or the sibilants s, sh, and ch, and such words as "cats," "boats," and "sisters" are not intelligible. After operation or the insertion of a speech appliance, speech therapy is necessary.

VELOPHARYNGEAL DYSFUNCTION

The speech disturbance characteristic of the child with a cleft palate can also be produced by other osseous or neuromuscular abnormalities where there is an inability to form an effective seal between oropharynx and nasopharynx during swallowing or phonation. In a child who has the potential for abnormal speech, adenoidectomy can precipitate overt hypernasality. If the neuromuscular function is adequate, compensation in palatopharyngeal movement might take place and the speech defect might improve, although speech therapy is necessary. In other cases, slow involution of the adenoids can allow gradual compensation in palatal and pharyngeal muscular function. This might explain why a speech defect does not become apparent in some children who have a submucous cleft palate or similar anomaly predisposing to palatopharyngeal incompetence.

Clinical Manifestations

Although clinical signs vary, the symptoms of velopharyngeal dysfunction are similar to those of a cleft palate. There may be hypernasal speech (especially noted in the articulation of pressure consonants such as p, b, d, t, h, v, f, and s); conspicuous constricting movement of the nares during speech; inability to whistle, gargle, blow out a candle, or inflate a balloon; loss of liquid through the nose when drinking with the head down; otitis media; and hearing loss. Oral inspection might reveal a cleft palate or a relatively short palate with a large oropharynx; absent, grossly asymmetric, or minimal muscular activity of the soft palate and pharynx during phonation or gagging; or a submucous cleft.

Velopharyngeal dysfunction may also be demonstrated radiographically. The head should be carefully positioned to obtain a true lateral view; one film is obtained with the patient at rest and another during continuous phonation of the vowel u as in "boom." The soft palate contacts the posterior pharyngeal wall in normal function, whereas in velopharyngeal dysfunction such contact is absent.

In selected cases of velopharyngeal dysfunction, the palate may be retropositioned or pharyngoplasty may be performed using a flap of tissue from the posterior pharyngeal wall. Dental speech appliances have also been used successfully. The type of surgery used is best tailored to the findings on nasoendoscopy.

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Chapter 311

Syndromes with Oral Manifestations

Norman Tinanoff

Many syndromes have distinct or accompanying facial, oral, and dental manifestations (see Apert syndrome, Chapter 591.12; Crouzon disease, Chapter 591.12; Down syndrome, Chapter 81.2).

Osteogenesis imperfecta is often accompanied by effects on the teeth, termed dentinogenesis **imperfecta** (see Chapter 307, Fig. 307-2). Depending on the severity of presentation, treatment of the dentition varies from routine preventive and restorative monitoring to covering affected posterior teeth with stainless steel crowns, to prevent further tooth loss and improve appearance. Dentinogenesis imperfecta can also occur in isolation without the bony effects.

Another syndrome, **cleidocranial dysplasia,** has orofacial features such as frontal bossing, hypoplastic maxilla and supernumerary teeth. The primary teeth can be over retained and the permanent teeth remain unerupted. Supernumerary teeth are common, especially in the premolar area. Extensive dental rehabilitation may be needed to correct severe tooth crowding, unerupted and supernumerary teeth.

Ectodermal dysplasias (see Chapter 649) are a heterogeneous group of conditions in which oral manifestations range from little or no involvement (the dentition is completely normal) to cases in which the teeth can be totally or partially absent or malformed. Because alveolar bone does not develop in the absence of teeth, the alveolar processes can be either totally or partially absent, and the resultant overclosure of the mandible causes the lips to protrude. Facial development is otherwise not disturbed. Teeth, when present, can range from normal to small and conical. If aplasia of the buccal and labial salivary glands

Figure 311-1 Pierre Robin syndrome. *(From Clark DA:* Atlas of neonatology, *ed 7, Philadelphia, 2000, WB Saunders, p. 144.)*

is present, dryness and irritation of the oral mucosa can occur. People with ectodermal dysplasia might need partial or full dentures, even at a very young age. The vertical height between the jaws is thus restored, improving the position of the lips and facial contours as well as restoring masticatory function.

Pierre Robin syndrome consists of micrognathia usually accompanied by a high arched or cleft palate (Fig. 311-1). The tongue is usually of normal size, but the floor of the mouth is foreshortened. The air passages can become obstructed, particularly on inspiration, usually requiring treatment to prevent suffocation. The infant should be maintained in a prone or partially prone position so that the tongue falls forward to relieve respiratory obstruction. Some patients require tracheostomy. Mandibular distraction procedures in the neonate can improve mandibular size, enhance respiration, and facilitate oral feedings.

Sufficient spontaneous mandibular growth can take place within a few months to relieve the potential airway obstruction. Often the growth of the mandible achieves a normal profile in 4-6 yr. Of children with Pierre Robin syndrome, 30-50% have **Stickler syndrome**, an autosomal dominant condition that includes other findings such as prominent joints, arthritis, hypotonia, hypermobile joints, mitral valve prolapse, hearing loss, and ocular problems (myopia, glaucoma, cataracts, retinal detachment). Mutations are noted in the genes that produce types II, IX, and XI collagen in many, but not all, patients with Stickler syndrome. Other syndromes are associated with Pierre Robin syndrome including 22Q11.2 deletion syndrome (Velocardio facial syndrome).

Mandibulofacial dysostosis (Treacher Collins syndrome or Franceschetti syndrome) is an autosomal dominant syndrome that primarily affects the face. The facial appearance varies but is characterized by downward sloping palpebral fissures, colobomas of the lower eyelids, sunken cheekbones, blind fistulas opening between the angles of the mouth and the ears, deformed pinnae, atypical hair growth extending toward the cheeks, receding chin, and large mouth. Facial clefts, abnormalities of the ears, and deafness are common. The mandible is usually hypoplastic; the ramus may be deficient, and the coronoid and condylar processes are flat or even aplastic. The palatal vault may be either high or cleft. Dental malocclusions are common. The teeth may be missing, hypoplastic, or displaced or be in an open bite position. Initially, the primary concern is breathing and feeding problems. Surgery to restore normal structure of the face can be performed, which may include repair of cleft palate, zygomatic and orbit reconstruction, reconstruction of the lower eyelid, external ear reconstruction, and orthognathic surgery.

Hemifacial microsomia presentation can be quite variable but is usually characterized by unilateral hypoplasia of the mandible and can be associated with partial paralysis of the facial nerve, underdeveloped ear, and blind fistulas between the angles of the mouth and the ears. Severe facial asymmetry and malocclusion can develop because of the absence or hypoplasia of the mandibular condyle on the affected side. Congenital condylar deformity tends to increase with age. Early craniofacial surgery may be indicated to minimize the deformity. This disorder can be associated with ocular and vertebral anomalies (oculo-auriculo-vertebral spectrum, including Goldenhar syndrome); therefore, radiographs of the vertebrae and ribs should be considered to determine the extent of skeletal involvement.

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Chapter 312

Dental Caries

Norman Tinanoff

ETIOLOGY

The development of dental caries depends on interrelationships among the tooth surface, dietary carbohydrates, and specific oral bacteria. Organic acids produced by bacterial fermentation of dietary carbohydrates reduce the pH of dental plaque adjacent to the tooth to a point where demineralization occurs. The initial demineralization appears as an opaque **white spot lesion** on the enamel, and with progressive loss of tooth mineral, cavitation of the tooth occurs (Fig. 312-1).

The group of microorganisms, mutans streptococci, is associated with the development of dental caries. These bacteria have the ability to adhere to enamel, produce abundant acid, and survive at low pH. Once the enamel surface cavitates, other oral bacteria (lactobacilli) can colonize the tooth, produce acid, and foster further tooth demineralization. Demineralization from bacterial acid production is determined by the frequency of carbohydrate consumption and by the type of carbohydrate. Sucrose is the most cariogenic sugar because one of its by-products during bacterial metabolism is glucan, a polymer that enables bacteria to adhere more readily to tooth structures. Dietary behaviors, such as consuming sweetened beverages in a nursing bottle or frequently consuming sticky candies, increase the cariogenic potential of foods because of the long retention of sugar in the mouth.

EPIDEMIOLOGY

The incidence of dental caries has decreased in developed countries in the past 30 yr but has not decreased and remains highly prevalent among low-income children and children from developing countries. More than half of the children in the United States have dental caries, with most of those having caries primarily in the pits and fissures of the occlusal (biting) surfaces of the molar teeth.

CLINICAL MANIFESTATIONS

Dental caries of the primary dentition usually begins in the pits and fissures. Small lesions may be difficult to diagnose by visual inspection,

Figure 312-1 Initial carious lesions (white spot lesions) around the necks of the maxillary central incisors.

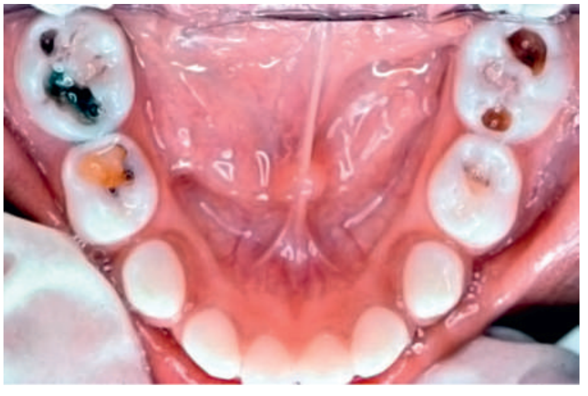

Figure 312-2 Rampant caries in a 3 yr old child. Note darkened and cavitated lesions on the fissure surfaces of mandibular molars.

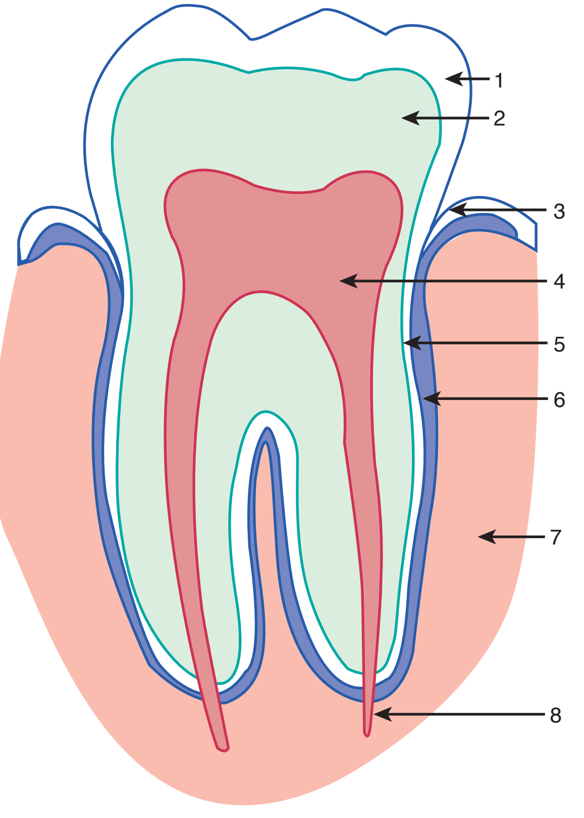

Figure 312-3 Basic dental anatomy: **1,** enamel; **2,** dentin; **3,** gingival margin; **4,** pulp; **5,** cementum; **6,** periodontal ligament; **7,** alveolar bone; **8,** neurovascular bundle.

but larger lesions are evident as darkened or cavitated lesions on the tooth surfaces (Fig. 312-2). Rampant dental caries in infants and toddlers, referred to as **early childhood caries**, is the result of early colonization of the child with cariogenic bacteria and the frequent ingestion of sugar, either in the bottle or in solid foods. The carious process in this situation is initiated earlier and consequently can affect the maxillary incisors first and then progress to the molars as they erupt.

The prevalence of early childhood caries is 30-50% in children from low socioeconomic backgrounds and as high as 70% in some Native American groups. Besides high frequency of sugar consumption and colonization with cariogenic bacteria, other enabling factors include low socioeconomic status of the family, other family member with carious teeth, recent immigrant status of the child, and the visual presence of dental plaque on the child's teeth. Children who develop caries at a young age are known to be at high risk for developing further caries as they get older. Therefore, the appropriate prevention of early childhood caries can result in the elimination of major dental problems in toddlers and less decay in later childhood.

COMPLICATIONS

Left untreated, dental caries usually destroy most of the tooth and invade the dental pulp (Fig. 312-3), leading to an inflammation of the pulp **(pulpitis)** and significant pain. Pulpitis can progress to pulp necrosis, with bacterial invasion of the alveolar bone causing a dental abscess (Fig. 312-4). Infection of a primary tooth can disrupt normal development of the successor permanent tooth. In some cases, this process leads to sepsis and infection of the facial space.

TREATMENT

The age at which dental caries occurs is important in dental management. Children younger than 3 yr of age lack the developmental ability

Figure 312-4 Facial swelling from an abscessed primary molar. Resolution of the inflammation can be achieved by a course of antibiotics, followed by either extraction or root canal of the offending tooth.

to cooperate with dental treatment and often require sedation, or general anesthesia to repair carious teeth. After age 4 yr, children can generally cope with dental restorative care with the use of local anesthesia.

Dental treatment, using silver amalgam, plastic composite, or stainless steel crowns, can restore most teeth affected with dental caries. If caries involves the dental pulp, a partial removal of the pulp (pulpotomy) or complete removal of the pulp (pulpectomy) may be required. If a tooth requires extraction, a space maintainer may be indicated to prevent migration of teeth, which subsequently leads to malposition of permanent successor teeth.

Clinical management of the pain and infection associated with untreated dental caries varies with the extent of involvement and the medical status of the patient. Dental infection localized to the dentoalveolar unit can be managed by local measures (extraction, pulpectomy). Oral antibiotics are indicated for dental infections associated with fever, cellulitis, and facial swelling, or if it is difficult to anesthetize the tooth in the presence of inflammation. Penicillin is the antibiotic of choice, except in patients with a history of allergy to this agent. Clindamycin and erythromycin are suitable alternatives. Oral analgesics, such as ibuprofen, are usually adequate for the pain control.

PREVENTION

Because they are seeing infants and toddlers on a periodicity schedule, physicians have an important role in screening children younger than 3 yr of age for dental caries; providing preventive instructions; applying preventive measures, such as fluoride varnish; and referring the child to a dentist if problems exist.

Fluoride

The most effective preventive measure against dental caries is communal water supplies with optimal fluoride content. Water fluoridation at the level of 0.7-1.2 mg fluoride per liter (ppm F) was introduced in the United States in the 1940s. Because fluoride from water supplies is now one of several sources of fluoride, the Department of Health and Human Services proposes to not have a fluoride range, but instead to limit the recommendation to the lower limit of 0.7 ppm F. The rationale is to balance the benefits of preventing dental caries with reducing the chance of fluorosis. Children who reside in areas with fluoride-deficient water supplies and are at risk for caries benefit from dietary fluoride supplements (Table 312-1). If the patient uses a private water supply, it is necessary to get the water tested for fluoride levels before prescribing fluoride supplements. To avoid potential overdoses, no fluoride prescription should be written for more than a total of 120 mg of fluoride. However, because of confusion regarding fluoride supplements among practitioners and parents, association of supplements with fluorosis, and lack of parent compliance with the daily administration, supplements may no longer be the first-line approach for preventing caries in preschool-aged children.

Topical fluoride on a daily basis can be achieved by using fluoridated toothpaste. Supervised use of less than a "pea-sized" amount of toothpaste (approximately 0.25 g) on the toothbrush in children younger than 6 yr of age reduces the risk of fluorosis. Children younger than 4 yr of age should brush with less than a "smear or grain-sized" amount of fluoridated toothpaste. Professional topical fluoride applications performed semiannually reportedly reduce caries by approximately 30%. Fluoride varnish is ideal for professional applications in preschool children because of ease of use, even with non–dental health providers, and its safety because of single-dose dispensers. Products that are available now come in containers of 0.25, 0.4, or 0.6 mL of varnish, corresponding to 5.6, 9.0, and 13.6 mg fluoride, respectively. Fluoride varnish should be administered twice a year for preschool children at moderate caries risk and 4 times a year for children at high caries risk.

Oral Hygiene

Daily brushing, especially with fluoridated toothpaste, helps prevent dental caries. Most children younger than 8 yr of age do not have the coordination required for adequate tooth brushing. Accordingly, parents should assume responsibility for the child's oral hygiene, with the degree of parental involvement appropriate to the child's changing abilities.

Diet

Frequent consumption of sweetened fruit drinks is not generally recognized by parents for its high cariogenic potential. Consuming sweetened beverages in a nursing bottle or sippy cup should be discouraged, and special efforts made to instruct parents that their child should only consume sweetened beverages at meal times and not exceed 6 oz per day.

Dental Sealant

Plastic dental sealants have been shown to be effective in preventing caries on the pit and fissure of the primary and permanent molars. Sealants are most effective when placed soon after teeth erupt and used in children with deep grooves and fissures in the molar teeth.

Bibliography is available at Expert Consult.

Table 312-1 Supplemental Fluoride Dosage Schedule

AGE	FLUORIDE IN HOME WATER		
	<0.3 (ppm)	0.3-0.6 (ppm)	>0.6 (ppm)
6 mo-3 yr	0.25*	0	0
3-6 yr	0.50	0.25	0
6-16 yr	1.00	0.50	0

*Milligrams of fluoride per day.

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Chapter 313
Periodontal Diseases

Norman Tinanoff

The periodontium includes the gingiva, alveolar bone, cementum, and periodontal ligament (see Fig. 312-3).

GINGIVITIS

Poor oral hygiene results in the accumulation of dental plaque at the tooth–gingival interface that activates an inflammatory response, expressed as localized or generalized reddening and swelling of the gingiva. More than half of American school children experience gingivitis. In severe cases, the gingiva spontaneously bleeds and there is oral malodor. Treatment is proper oral hygiene (careful tooth brushing and flossing); complete resolution can be expected. Fluctuations in hormonal levels during the onset of puberty can increase inflammatory response to plaque. Gingivitis in healthy children is unlikely to progress to periodontitis (inflammation of the periodontal ligament resulting in loss of alveolar bone).

AGGRESSIVE PERIODONTITIS IN CHILDREN (PREPUBERTAL PERIODONTITIS)

Periodontitis in children before puberty is a rare disease that often begins between the time of eruption of the primary teeth and the age of 4 or 5 yr. The disease occurs in localized and generalized forms. There is rapid bone loss, often leading to premature loss of primary teeth. It is often associated with systemic problems, including

neutropenia, leukocyte adhesion or migration defects, hypophosphatasia, Papillon-Lefèvre syndrome, leukemia, and histiocytosis X. In many cases, however, there is no apparent underlying medical problem. Nonetheless, diagnostic work-ups are necessary to rule out underlying systemic disease.

Treatment includes aggressive professional teeth cleaning, strategic extraction of affected teeth, and antibiotic therapy. There are few reports of long-term successful treatment to reverse bone loss surrounding primary teeth.

AGGRESSIVE PERIODONTITIS IN ADOLESCENTS (LOCALIZED JUVENILE PERIODONTITIS)

Aggressive periodontitis in adolescents is characterized by rapid alveolar bone loss, especially around the permanent incisors and 1st molars. Overall prevalence in the United States is <1%, but the prevalence among African-Americans is reportedly 2.5%. This form of periodontitis is associated with a strain of *Aggregatibacter (Actinobacillus)* bacteria. In addition, the neutrophils of patients with aggressive periodontitis can have chemotactic or phagocytic defects. If left untreated, affected teeth lose their attachment and can exfoliate. Treatment varies with the degree of involvement. Patients whose disease is diagnosed at onset are usually managed by surgical or nonsurgical debridement in conjunction with antibiotic therapy. Prognosis depends on the degree of initial involvement and compliance with therapy.

TEETHING

Teething can lead to intermittent localized discomfort in the area of erupting primary teeth, irritability, low-grade fevers, and excessive salivation; many children have no apparent difficulties. Treatment of symptoms includes oral analgesics and ice rings for the child to "gum." Similar manifestations can also arise when the 1st permanent molars erupt at about age 6 yr.

CYCLOSPORINE- OR PHENYTOIN-INDUCED GINGIVAL OVERGROWTH

The use of cyclosporine to suppress organ rejection or phenytoin for anticonvulsant therapy, and in some cases calcium channel blockers, is associated with generalized enlargement of the gingiva. Phenytoin and its metabolites have a direct stimulatory action on gingival fibroblasts, resulting in accelerated synthesis of collagen. Phenytoin induces less gingival hyperplasia in patients who maintain meticulous oral hygiene.

Gingival hyperplasia occurs in 10-30% of patients treated with phenytoin. Severe manifestations can include gross enlargement of the gingiva, sometimes covering the teeth; edema and erythema of the gingiva; secondary infection, resulting in abscess formation; migration of teeth; and inhibition of exfoliation of primary teeth and subsequent impaction of permanent teeth. Treatment should be directed toward prevention and, if possible, discontinuation of cyclosporine or phenytoin. Patients undergoing long-term treatment with these drugs should receive frequent dental examinations and oral hygiene care. Severe forms of gingival overgrowth are treated by gingivectomy, but the lesion recurs if drug use is continued.

ACUTE PERICORONITIS

Acute inflammation of the flap of gingiva that partially covers the crown of an incompletely erupted tooth is common in mandibular permanent molars. Accumulation of debris and bacteria between the gingival flap and tooth precipitates the inflammatory response. A variant of this condition is a gingival abscess caused by entrapment of bacteria because of orthodontic bands or crowns. Trismus and severe pain may be associated with the inflammation. Untreated cases can result in facial space infections and facial cellulitis.

Treatment includes local debridement and irrigation, warm saline rinses, and antibiotic therapy. When the acute phase has subsided, resection of the gingival flap prevents recurrence. Early recognition of the partial impaction of mandibular 3rd molars and their subsequent extraction prevents these areas from developing pericoronitis.

NECROTIZING PERIODONTAL DISEASE (ACUTE NECROTIZING ULCERATIVE GINGIVITIS)

Necrotizing periodontal disease, in the past sometimes referred to as "trench mouth," is a distinct periodontal disease associated with oral spirochetes and fusobacteria. It is not clear, however, whether bacteria initiate the disease or are secondary. It rarely develops in healthy children in developed countries, with a prevalence in the United States of <1%, but is seen more often in children and adolescents from developing areas of Africa, Asia, and South America. In certain African countries, where affected children usually have protein malnutrition, the lesion can extend into adjacent tissues, causing necrosis of facial structures (cancrum oris, or noma).

Clinical manifestations of necrotizing periodontal disease include necrosis and ulceration of gingiva between the teeth, an adherent grayish pseudomembrane over the affected gingiva, oral malodor, cervical lymphadenopathy, malaise, and fever. The condition may be mistaken for acute herpetic gingivostomatitis. Dark-field microscopy of debris obtained from necrotizing lesions demonstrates dense spirochete populations.

Treatment of necrotizing periodontal disease is divided into an acute management with local debridement, oxygenating agents (direct application of 10% carbamide peroxide in anhydrous glycerol qid), and analgesics. Dramatic resolution usually occurs within 48 hr. If a patient is febrile, antibiotics (penicillin or metronidazole) may be an important adjunctive therapy. A second phase of treatment may be necessary if the acute phase of the disease has caused irreversible morphologic damage to the periodontium. The disease is not contagious.

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Chapter 314

Dental Trauma

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Traumatic oral injuries may be categorized into 3 groups: injuries to teeth, injuries to soft tissue (contusions, abrasions, lacerations, punctures, avulsions, and burns), and injuries to jaw (mandibular and/or maxillary fractures).

INJURIES TO TEETH

Approximately 10% of children between 18 mo and 18 yr of age sustain significant tooth trauma. There appear to be 3 age periods of greatest predilection: toddlers (1-3 yr), usually from falls or child abuse; school-age children (7-10 yr), usually from bicycle and playground accidents; and adolescents (16-18 yr), often the result of fights, athletic injuries, and automobile accidents. Injuries to teeth are more common among children with protruding front teeth. Children with craniofacial abnormalities or neuromuscular deficits are also at increased risk for dental injury. Injuries to teeth can involve the hard dental tissues, the dental pulp (nerve), and injuries to the periodontal structure (surrounding bone and attachment apparatus) (Fig. 314-1 and Table 314-1).

Fractures of teeth may be uncomplicated (confined to the hard dental tissues) or complicated (involving the pulp). Exposure of the pulp results in its bacterial contamination, which can lead to infection and pulp necrosis. Such pulp exposure complicates therapy and can lower the likelihood of a favorable outcome.

The teeth most often affected are the maxillary incisors. Uncomplicated crown fractures are treated by covering exposed dentin and by placing an aesthetic restoration. Complicated crown fractures involving the tooth pulp usually require **endodontic therapy** (root canal). Crown-root fractures and root fractures usually require extensive

dental therapy. Such injuries in the primary dentition can interfere with normal development of the permanent dentition, and therefore significant injuries of the primary incisor teeth are usually managed by extraction.

Traumatic oral injuries should be referred to a dentist as soon as possible. Even when the teeth appear intact, a dentist should promptly evaluate the patient. Baseline data (radiographs, mobility patterns, responses to specific stimuli) enable the dentist to assess the likelihood of future complications.

INJURIES TO PERIODONTAL STRUCTURES

Trauma to teeth with associated injury to periodontal structures that hold the teeth usually manifests as mobile or displaced teeth. Such injuries are more common in the primary than in the permanent dentition. Categories of trauma to the periodontium include concussion, subluxation, intrusive luxation, extrusive luxation, and avulsion.

Concussion

Injuries that produce minor damage to the periodontal ligament are termed *concussions.* Teeth sustaining such injuries are not mobile or displaced but react markedly to percussion (gentle hitting of the tooth with an instrument). This type of injury usually requires no therapy and resolves without complication. Primary incisors that sustain concussion can change color, indicating pulpal degeneration, and should be evaluated by a dentist.

Subluxation

Subluxated teeth exhibit mild to moderate horizontal mobility and/or vertical mobility. Hemorrhage is usually evident around the neck of the tooth at the gingival margin. There is no displacement of the tooth. Many subluxated teeth need to be immobilized by splints to ensure adequate repair of the periodontal ligament. Some of these teeth develop pulp necrosis.

Intrusion

Intruded teeth are pushed up into their socket, sometimes to the point where they are not clinically visible. Intruded primary incisors can give the false appearance of being avulsed (knocked out). To rule out avulsion, a dental radiograph is indicated (Figs. 314-2 and 314-3).

Extrusion

Extrusion injury is characterized by displacement of the tooth from its socket. The tooth is usually displaced to the lingual (tongue) side, with fracture of the wall of the alveolar socket. These teeth need immediate treatment; the longer the delay, the more likely the tooth will be fixed in its displaced position. Therapy is directed at reduction (repositioning the tooth) and fixation (splinting). The pulp of such teeth often becomes necrotic and requires endodontic therapy. Extrusive luxation in the primary dentition is usually managed by extraction because

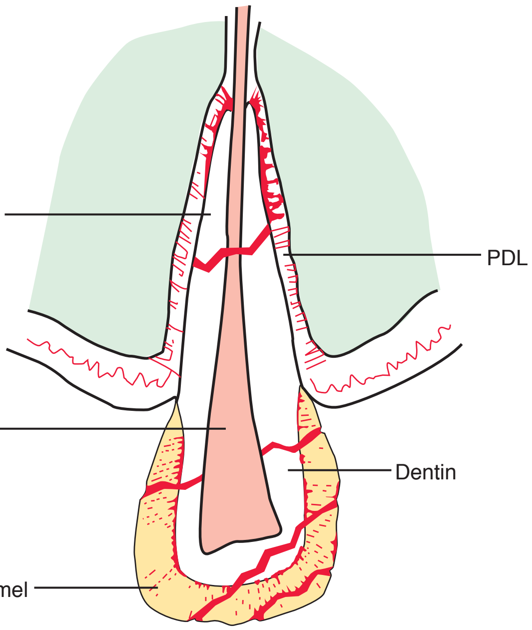

Figure 314-1 Tooth fractures can involve enamel, dentin, or pulp and can occur in the crown or root of a tooth. *PDL,* periodontal ligament. *(From Pinkham JR:* Pediatric dentistry: infancy through adolescence, *Philadelphia, 1988, WB Saunders, p. 172.)*

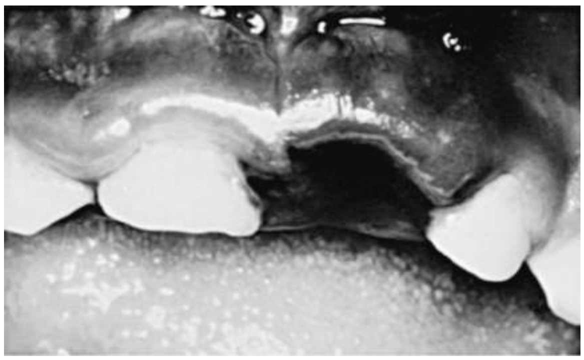

Figure 314-2 Intruded primary incisor that appears avulsed (knocked out).

Table 314-1 Injuries to Crowns of Teeth

TYPE OF TRAUMA	DESCRIPTION	TREATMENT AND REFERRAL
Enamel infraction (crazing)	Incomplete fracture of enamel without loss of tooth structure	Initially might not require therapy but should be assessed periodically by dentist
Enamel fractures	Fracture of only the tooth enamel	Tooth may be smoothed or treated to replace fragment
Enamel and dentin fracture	Fracture of enamel and dentinal layer of the tooth. Tooth may be sensitive to cold or air. Pulp may become necrotic, leading to periapical abscess	Refer as soon as possible. Area should be treated to preserve the integrity of the underlying pulp
Enamel, dentin fracture involving the pulp	Bacterial contamination can lead to pulpal necrosis and periapical abscess. The tooth might have the appearance of bleeding or might display a small red spot	Refer immediately. The dental therapy of choice depends on the extent of injury, the condition of the pulp, the development of the tooth, time elapsed from injury, and any other injuries to the supporting structures. Therapy is directed toward minimizing contamination in an effort to improve the prognosis

From Josell SD, Abrams RG: Managing common dental problems and emergencies, Pediatr Clin North Am *38:1325–1342, 1991.*

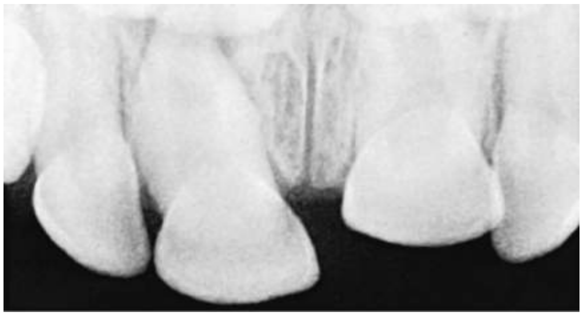

Figure 314-3 Occlusal radiograph documents intrusion of "missing tooth" presented in Figure 314-2.

complications of reduction and fixation can result in problems with development of permanent teeth.

Avulsion

If avulsed permanent teeth are replanted as soon as possible after injury, there is a good chance that normal reattachment will follow and the tooth will have a good prognosis. However, if the tooth is in a dry environment for longer than 1 hr, the ligament that holds the tooth in place has little chance for survival and failure (root resorption, ankylosis) is common. Parents confronted with this emergency situation can be instructed to do the following:

- Find the tooth.
- Briefly rinse the tooth. (Do not scrub the tooth. Do not touch the root. After plugging the sink drain, hold the tooth by the crown and rinse it under running tap water.)
- Insert the tooth into the socket. (Gently place it back into its normal position. Do not be concerned if the tooth extrudes slightly. If the parent or child is too apprehensive for replantation of the tooth, the tooth should be placed in cold cow's milk or other cold isotonic solution.)
- Go directly to the dentist. (In transit, the child should hold the tooth in its socket with a finger. The parent should buckle a seatbelt around the child and drive safely.)

After the tooth is replanted, it must be immobilized to facilitate reattachment; endodontic therapy is always required. The initial signs of complications associated with replantation can appear as early as 1 wk after trauma or as late as several years later. Close dental follow-up is indicated for at least 1 yr.

PREVENTION

To minimize the likelihood of dental injuries:

- Every child or adolescent who engages in contact sports should wear a mouth guard, which may be constructed by a dentist or purchased at any athletic goods store.
- Helmets with face guards should be worn by children or adolescents with neuromuscular problems or seizure disorders to protect the head and face during falls.
- Helmets should also be used during biking, skiing, skating, and skateboarding.
- All children or adolescents with protruding incisors should be evaluated by a pediatric dentist or orthodontist.

ADDITIONAL CONSIDERATIONS

Children who experience dental trauma might also have sustained head or neck trauma, and therefore neurologic assessment is warranted. Tetanus prophylaxis should be considered with any injury that disrupts the integrity of the oral tissues. The possibility of child abuse should always be considered.

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Chapter 315

Common Lesions of the Oral Soft Tissues

Norman Tinanoff

OROPHARYNGEAL CANDIDIASIS

Oropharyngeal infection with *Candida albicans* (thrush, moniliasis) (see Chapter 234.1) is common in neonates from contact with the organism in the birth canal or breast. The lesions of oropharyngeal candidiasis (OPC) appear as white plaques covering all or part of the oropharyngeal mucosa. These plaques are removable from the underlying surface, which is characteristically inflamed and has pinpoint hemorrhages. The diagnosis is confirmed by direct microscopic examination on potassium hydroxide smears and culture of scrapings from lesions. OPC is usually self-limited in the healthy newborn infant, but topical application of nystatin to the oral cavity of the baby and to the nipples of breastfeeding mothers will hasten recovery.

OPC is also a major problem during myelosuppressive therapy. **Systemic candidiasis**, a major cause of morbidity and mortality during myelosuppressive therapy, develops almost exclusively in patients who have had prior oropharyngeal, esophageal, or intestinal candidiasis. This observation implies that prevention of OPC should reduce the incidence of systemic candidiasis. The use of oral rinses of 0.2% chlorhexidine solution plus systemic antifungals may be effective in preventing OPC, systemic candidiasis, or candidal esophagitis.

APHTHOUS ULCERS

The aphthous ulcer (canker sore) is a distinct oral lesion, prone to recurrence; Table 315-1 notes the differential diagnosis. Aphthous ulcers are reported to develop in 20% of the population. Their etiology is unclear, but allergic or immunologic reactions, emotional stress, genetics, and injury to the soft tissues in the mouth have been implicated. Aphthous-like lesions may be associated with inflammatory bowel disease, Behçet disease, gluten-sensitive enteropathy, periodic fever-aphthae-pharyngitis-adenitis syndrome, Sweet syndrome, HIV infection (especially if ulcers are large and slow to heal), and cyclic neutropenia. Clinically, these ulcers are characterized by well-circumscribed, ulcerative lesions with a white necrotic base surrounded by a red halo. The lesions last 10-14 days and heal without scarring. Nonprescription palliative therapies, such as benzocaine and topical lidocaine, are effective, as are topical steroids. Tetracycline has benefit with severe outbreaks, but caution is necessary in pregnant women and young children to prevent tetracycline tooth staining during a child's tooth development.

HERPETIC GINGIVOSTOMATITIS

After an initial incubation period of approximately 1 wk, the initial infection with herpes simplex virus manifests as fever and malaise, usually in a child younger than 5 yr (see Chapter 252). The oral cavity can show various expressions, including the gingiva becoming erythematous, mucosal hemorrhages, and clusters of small vesicles erupting throughout the mouth. There is often involvement of the mucocutaneous margin and perioral skin (Fig. 315-1). The oral symptoms generally are accompanied by fever, lymphadenopathy, and difficulty eating and drinking. The symptoms usually regress within 2 wk without scarring. Fluids should be encouraged because the child may become dehydrated. Analgesics and anesthetic rinses can make the child more comfortable. Oral acyclovir if taken within the 1st 3 days of symptoms may be beneficial in shortening the duration of

symptoms. Caution should be exercised to prevent autoinoculation or transmission of infection to the eyes.

RECURRENT HERPES LABIALIS

Approximately 90% of the population develops antibodies to herpes simplex virus. In periods of quiescence, the virus is thought to remain latent in sensory neurons. Unlike primary herpetic gingivostomatitis, which manifests as multiple painful vesicles on the lips, tongue, palate, gingiva, and mucosa, recurrent herpes is generally limited to the lips. Other than the annoyance of causing pain and an unattractive appearance, there are generally no systemic symptoms. Reactivation of the virus is thought to be the result of exposure to ultraviolet light, tissue trauma, stress, or fevers. There is little advantage of antiviral therapy over palliative therapies in an otherwise healthy patient affected by recurrent herpes.

Table 315-1 Differential Diagnosis of Oral Ulceration

CONDITION	COMMENT
COMMON	
Aphthous (canker sore)	Painful, circumscribed lesions; recurrences
Traumatic	Accidents, chronic cheek biter, or after dental local anesthesia
Hand, foot, mouth disease	Painful; lesions on tongue, anterior oral cavity, hands, and feet
Herpangina	Painful; lesions confined to soft palate and oropharynx
Herpetic gingivostomatitis	Vesicles on mucocutaneous borders; painful, febrile
Recurrent herpes labialis	Vesicles on lips; painful
Chemical burns	Alkali, acid, aspirin; painful
Heat burns	Hot food, electrical
UNCOMMON	
Neutrophil defects	Agranulocytosis, leukemia, cyclic neutropenia; painful
Systemic lupus erythematosus	Recurrent, may be painless
Behçet syndrome	Resembles aphthous lesions; associated with genital ulcers, uveitis
Necrotizing ulcerative gingivostomatitis	Vincent stomatitis; painful
Syphilis	Chancre or gumma; painless
Oral Crohn disease	Aphthous-like; painful
Histoplasmosis	Lingual
Pemphigus	May be isolated to the oral cavity
Stevens-Johnson syndrome	May be isolated or appear initially in the oral cavity

Figure 315-1 **Herpetic gingivostomatitis.** Lip erosions with multiple perioral herpetic lesions involving the mucotaneous borders. *(From Paller AS, Mancini AJ, editors:* Hurwitz clinical pediatric dermatology, *ed 3, Philadelphia, 2006, WB Saunders, p. 398.)*

BOHN NODULES

Bohn nodules are small developmental anomalies located along the buccal and lingual aspects of the mandibular and maxillary ridges and in the hard palate of the neonate. These lesions arise from remnants of mucous gland tissue. Treatment is not necessary, because the nodules disappear within a few weeks.

DENTAL LAMINA CYSTS

Dental lamina cysts are small cystic lesions located along the crest of the mandibular and maxillary ridges of the neonate. These lesions arise from epithelial remnants of the dental lamina. Treatment is not necessary; they disappear within a few weeks.

FORDYCE GRANULES

Almost 80% of adults have multiple yellow-white granules in clusters or plaque-like areas on the oral mucosa, most commonly on the buccal mucosa or lips. They are aberrant sebaceous glands. The glands are present at birth, but they can hypertrophy and first appear as discrete yellowish papules during the preadolescent period in approximately 50% of children. No treatment is necessary.

PARULIS

The parulis (gum boil) is a soft reddish papule located adjacent to the root of a chronically abscessed tooth. It occurs at the end-point of a draining dental sinus tract. Treatment consists of diagnosing which tooth is abscessed and extracting it or performing root canal on the offending tooth.

CHEILITIS

This dryness of the lips followed by scaling and cracking and accompanied by a characteristic burning sensation is common in children. Cheilitis may be caused by sensitivity to contact substances, lip licking, vitamin deficiency, weakened immune system, or fungal or bacterial infections. Cheilitis often occurs in association with fever. Treatment may include antifungal or antibacterial agents and frequent application of petroleum jelly.

ANKYLOGLOSSIA

Ankyloglossia or "tongue-tie" is characterized by an abnormally short lingual frenum that can hinder the tongue movement but rarely interferes with feeding or speech. The frenum might spontaneously lengthen as the child gets older. If the extent of the ankyloglossia is severe, speech may be affected and surgical correction may be indicated.

GEOGRAPHIC TONGUE

Geographic tongue (migratory glossitis) is a benign and asymptomatic lesion and is characterized by 1 or more smooth, bright red patches, often showing a yellow, gray, or white membranous margin on the dorsum of an otherwise normally roughened tongue. The condition has no known cause, and no treatment is indicated (see Chapter 664).

FISSURED TONGUE

The fissured tongue (scrotal tongue) is a malformation manifested clinically by numerous small furrows or grooves on the dorsal surface (see Chapter 664). If the tongue is painful, brushing the tongue or irrigating with water can reduce the bacteria in the fissures.

Chapter 316

Diseases of the Salivary Glands and Jaws

Norman Tinanoff

With the exception of mumps (see Chapter 248), disease of the salivary glands is rare in children. Bilateral enlargement of the submaxillary glands can occur in AIDS, cystic fibrosis, Epstein-Barr virus infection, and malnutrition, and, transiently, during acute asthmatic attacks. Chronic vomiting can be accompanied by enlargement of the parotid glands. Benign salivary gland hypertrophy has been associated with endocrinopathies: thyroid disease, diabetes, and Cushing syndrome. Infiltrative disease or tumors are uncommon; red flags include facial nerve palsy, rapid growth, fixed skin, paresthesias, ulceration, or a history of radiation to the head or neck region.

PAROTITIS

Acute parotitis is often caused by blockage, with further inflammation due to bacterial infection. The blockage may be due to a salivary stone or mucous plug. Stones can be removed by physical manipulation, surgery, or lithotripsy. **Recurrent parotitis** is an idiopathic swelling of the parotid gland that can occur in otherwise healthy children. The swelling is usually unilateral, but both glands can be involved simultaneously or alternately. There is little pain; the swelling is limited to the gland and usually lasts 2-3 wk. Treatment may include local heat, massaging the gland, and antibiotics. **Suppurative parotitis** is usually caused by *Staphylococcus aureus*. It is usually unilateral and may be accompanied by fever. The gland becomes swollen, tender, and painful. Suppurative parotitis responds to antibacterial therapy based on culture obtained from the Stensen duct or by surgical drainage. Viral causes of parotitis include mumps (often in epidemics), EBV, human herpes virus 6, enteroviruses, and HIV.

RANULA

A ranula is a cyst associated with a major salivary gland in the sublingual area. It is a large, soft, mucus-containing swelling in the floor of the mouth. It occurs at any age, including infancy. The cyst should be excised, and the severed duct should be exteriorized.

MUCOCELE

Mucocele is a salivary gland lesion caused by a blockage of a salivary gland duct. It is most common on the lower lip and has the appearance of a fluid-filled vesicle or a fluctuant nodule with the overlying mucosa normal in color. Treatment is surgical excision, with removal of the involved accessory salivary gland.

CONGENITAL LIP PITS

Congenital lip pits are caused by fistulous tracts that lead to embedded mucous glands in the lower lip. They leak saliva, especially with salivary stimulation. Lip pits can be isolated anomalies, or they can be found in patients with cleft lip or palate. Treatment is surgical excision of the glandular tissue.

ERUPTION CYST

Eruption cyst is a smooth, painless swelling over the erupting tooth. If bleeding occurs in the cyst space, it may appear blue or blue-black. In most cases, no treatment is indicated and the cyst resolves with the full eruption of the tooth.

XEROSTOMIA

Also known as dry mouth, xerostomia may be associated with fever, dehydration, anticholinergic drugs, chronic graft-versus-host disease, Mikulicz disease (leukemia infiltrates), Sjögren syndrome, or tumoricidal doses of radiation when the salivary glands are within the field. Long-term xerostomia is a high-risk factor for dental caries.

SALIVARY GLAND TUMORS

See Chapter 500.

HISTIOCYTIC DISORDERS

See Chapter 507.

TUMORS OF THE JAW

Ossifying fibroma is a common benign tumor of the jaw. It is often asymptomatic, being discovered on routine radiographic examinations. Treatment is resection because of the possibility of recurrence. **Central giant cell granuloma** is another common lesion thought to be reactive rather than neoplastic. Although usually asymptomatic, it can be expansile, with or without resorption of the roots of teeth and perforation of the cortical plate. Treatment is complete curettage or surgical excision. **Dentigerous cysts** are common lesions associated with the crown of an impacted or unerupted tooth. Although usually asymptomatic, they can become large and destructive. Treatment is surgical removal.

The malignant primary tumors of the jaw in children include Burkitt lymphoma, osteogenic sarcoma, lymphosarcoma, ameloblastoma, and, more rarely, fibrosarcoma.

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Chapter 317

Diagnostic Radiology in Dental Assessment

Norman Tinanoff

The **panoramic radiograph** provides a single tomographic image of the upper and lower jaw, including all the teeth and supporting structures. The x-ray tube rotates about the patient's head with reciprocal movement of the film or image receptor during the exposure. The panoramic image shows the teeth, mandibular bodies, rami, and condyles; maxillary sinuses; and a majority of the facial buttresses. Such images are used to show abnormalities of tooth number, development and eruption pattern, cystic and neoplastic lesions, bone infections, and fracture, as well as dental caries and periodontal disease (Fig. 317-1).

Cephalometric radiographs are posteroanterior and lateral skull films that are taken using a **cephalostat** (head positioner) and employ techniques that clearly demonstrate the facial skeleton and soft facial tissues. Similar protocols for positioning children are used throughout the world. From these images, cranial and facial points and planes can be determined and compared with standards derived from thousands of images. A child's facial growth can be assessed serially when cephalometric radiographs are taken sequentially. Relationships among the maxilla, mandible, cranial base, and facial skeleton can be determined in a quantitative manner. Additionally, the alignment of the teeth and the relation of the teeth to the supporting bone can be serially measured.

Intraoral dental radiographs are highly detailed, direct-exposure films that demonstrate sections of the child's teeth and supporting bone structures. The film or image receptor is placed lingual to the teeth,

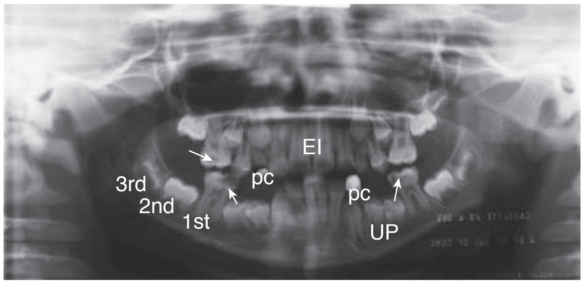

Figure 317-1 A panoramic radiograph of a 10 yr old child showing extensive dental caries of the 1st permanent molars *(arrows)*, as well as normal structures: erupted 1st permanent molar, unerupted 2nd molar, and unerupted 3rd molar; erupted incisors *(EI)*, unerupted premolars *(UP)*, and erupted primary canines *(pc)*.

and the x-ray beam is directed through the teeth and supporting structures. The resulting images are used to detect dental caries, loss of alveolar bone (periodontal disease), abscesses at the roots of the teeth, and trauma to the teeth and alveolar bone and to demonstrate the developmental status of permanent teeth within the bone.

Section 3

The Esophagus

Chapter 318

Embryology, Anatomy, and Function of the Esophagus

Seema Khan and Susan R. Orenstein

The esophagus is a hollow muscular tube, separated from the pharynx above and the stomach below by 2 tonically closed sphincters. Its primary function is to convey ingested material from the mouth to the stomach. Largely lacking digestive glands and enzymes, and exposed only briefly to nutrients, it has no active role in digestion.

EMBRYOLOGY

The esophagus develops from the postpharyngeal foregut and can be distinguished from the stomach in the 4 wk old embryo. At the same time, the trachea begins to bud just anterior to the developing esophagus; the resulting laryngotracheal groove extends and becomes the lung. Disturbance of this stage can result in congenital anomalies such as **tracheoesophageal fistula.** The length of the esophagus is 8-10 cm at birth and doubles in the 1st 2-3 yr of life, reaching approximately 25 cm in the adult. The abdominal portion of the esophagus is as large as the stomach in an 8 wk old fetus but gradually shortens to a few millimeters at birth, attaining a final length of approximately 3 cm by a few years of age. This intraabdominal location of both the distal esophagus and the **lower esophageal sphincter** (LES) is an important antireflux mechanism, because increases in intraabdominal pressure are also transmitted to the sphincter, augmenting its defense. Swallowing can be seen in utero as early as 16-20 wk of gestation, helping to circulate the amniotic fluid; **polyhydramnios** is a hallmark of lack of normal swallowing or of esophageal or upper gastrointestinal tract obstruction. Sucking and swallowing are not fully coordinated before 34 wk of gestation, a contributing factor for feeding difficulties in premature infants.

ANATOMY

The luminal aspect of the esophagus is covered by thick, protective, nonkeratinized stratified squamous epithelium, which abruptly changes to simple columnar epithelium at the stomach's upper margin at the **gastroesophageal junction (GEJ).** This squamous epithelium is relatively resistant to damage by gastric secretions (in contrast to the ciliated columnar epithelium of the respiratory tract), but chronic irritation by gastric contents can result in morphometric changes (thickening of the basal cell layer and lengthening of papillary ingrowth into the epithelium) and subsequent metaplasia of the cells lining the lower esophagus from squamous to columnar. Deeper layers of the esophageal wall are composed successively of lamina propria, muscularis mucosae, submucosa, and the 2 layers of muscularis propria (circular surrounded by longitudinal). The 2 delimiting sphincters of the esophagus, the **upper esophageal sphincter (UES)** at the cricopharyngeus muscle and the **LES** at the **GEJ,** constrict the esophageal lumen at its proximal and distal boundaries. The muscularis propria of the upper third of the esophagus is predominantly striated, and that of the lower two-thirds is smooth muscle. Clinical conditions involving striated muscle (cricopharyngeal dysfunction, cerebral palsy) affect the upper esophagus, whereas those involving smooth muscle (achalasia, reflux esophagitis) affect the lower esophagus. The muscular LES and the mucosal "Z-line" of the GEJ may be discrepant up to several centimeters.

FUNCTION

The esophagus can be divided into 3 areas: the UES, the esophageal body, and the LES. At rest, the tonic LES pressure is normally approximately 20 mm Hg; values <10 mm Hg are usually considered abnormal, although it seems that competence against retrograde flow of gastric material is maintained if the LES pressure is >5 mm Hg. The LES pressure rises during intragastric pressure amplifications, whether caused by gastric contractions, abdominal wall muscle contractions ("straining"), or external pressure applied to the abdominal wall. It also rises in response to cholinergic stimuli, gastrin, gastric alkalization, and certain drugs (bethanechol, metoclopramide, cisapride). The UES pressure is more variable and often higher than that of the LES; it decreases almost to zero during deep sleep and it increases markedly during stress and straining. The UES and LES relax briefly to allow material to pass through during swallowing, belching, reflux, and vomiting. They can contract in response to subthreshold levels of reflux (esophagoglottal closure reflex).

Swallowing is initiated by elevation of the tongue, propelling the bolus into the pharynx. The larynx elevates and moves anteriorly, pulling open the relaxing UES, while the opposed aryepiglottic folds close. The epiglottis drops back to cover the larynx and direct the bolus over the larynx and into the UES. The soft palate occludes the nasopharynx. The primary peristalsis thus initiated is a contraction originating in the oropharynx that clears the esophagus aborally (Fig. 318-1). The LES, tonically contracted as a barrier against gastroesophageal reflux (GER), relaxes as swallowing is initiated, at nearly the same time as the UES relaxation. The LES relaxation persists considerably longer, until the peristaltic wave traverses it and closes it. The normal esophageal peristaltic speed is approximately 3 cm/sec; the wave takes 4 sec or longer to traverse the 12 cm esophagus of a young infant and considerably longer in a larger child. Facial stimulation by a puff of air can induce swallowing and esophageal peristalsis in healthy young infants, a reflex termed the **Santmyer swallow.**

In addition to relaxing to move swallowed material past the GEJ into the stomach, the LES normally relaxes to vent swallowed air or to allow retrograde expulsion of material from the stomach. Perhaps as an extension of these functions, the normal LES also permits physiologic reflux episodes, brief events that occur approximately 5 times in the

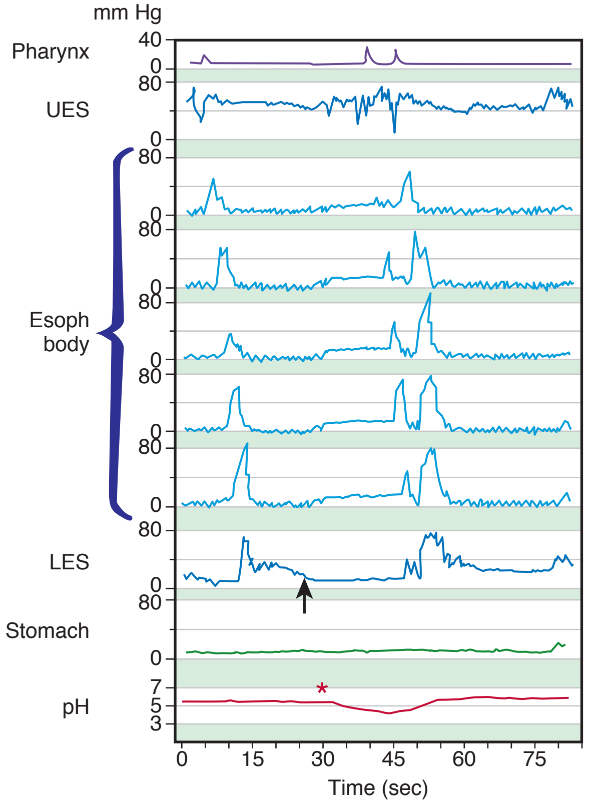

Figure 318-1 A continuous tracing of esophageal motility showing 2 swallows, as indicated by the pharyngeal contraction associated with relaxation of the upper esophageal sphincter (UES) and followed by peristalsis in the body of the esophagus. The lower esophageal sphincter (LES) also displays a transient relaxation *(arrow)* unassociated with a swallow. There is an episode of gastroesophageal reflux (*) recorded by a pH probe at the time of the transient LES relaxation. *(Courtesy of John Dent, FRACP, PhD, and Geoffrey Davidson, MD.)*

first postprandial hour, particularly in the awake state, but are otherwise uncommon. **Transient LES relaxation,** not associated with swallowing, is the major mechanism underlying **pathologic reflux** (see Fig. 318-1).

The close linkage of the anatomy of the upper digestive and respiratory tracts has mandated intricate functional protections of the respiratory tract during retrograde movement of gastric contents as well as during swallowing. The protective functions include the LES tone, the bolstering of the LES by the surrounding diaphragmatic crura, and the "backup protection" of the UES tone. Secondary peristalsis, akin to primary peristalsis but without an oral component, originates in the upper esophagus, triggered mainly by GER, and thereby also clears refluxed gastric contents from the esophagus. Another protective reflex is the "pharyngeal swallow" (initiated above the esophagus, but without lingual participation). Multiple levels of protection against aspiration include the rhythmic coordination of swallowing and breathing and a series of protective reflexes with esophagopharyngeal afferents and efferents that close the UES or larynx. These reflexes include the esophago-UES contractile reflex, the pharyngo-UES contractile reflex, the esophagoglottal closure reflex, and 2 pharyngoglottal adduction reflexes. The last 2 reflexes have chemoreceptors on the laryngeal surface of the epiglottis and mechanoreceptors on the aryepiglottic folds as their sites of stimulus. It is likely that interactions between the esophagus and the respiratory tract, which cause extraesophageal manifestations of gastroesophageal reflux disease (GERD), will be explained by subtle abnormalities in these protective reflexes.

Bibliography is available at Expert Consult.

318.1 Common Clinical Manifestations and Diagnostic Aids

Seema Khan and Susan R. Orenstein

COMMON CLINICAL MANIFESTATIONS

Manifestations of esophageal disorders include pain, obstruction or difficulty swallowing, abnormal retrograde movement of gastric contents (reflux, regurgitation, or vomiting), or bleeding; esophageal disease can also engender respiratory symptoms. Pain in the chest unrelated to swallowing **(heartburn)** can be a sign of esophagitis, but similar pain might also represent cardiac, pulmonary, or musculoskeletal disease or visceral hyperalgesia. Pain during swallowing **(odynophagia)** localizes the disease more discretely to the pharynx and esophagus and often represents inflammatory mucosal disease. Complete esophageal obstruction can be produced acutely by esophageal foreign bodies, including food impactions; can be congenital, as in esophageal atresia; or can evolve over time as a peptic stricture occludes the esophagus. Difficulty swallowing **(dysphagia)** can be produced by incompletely occlusive esophageal obstruction (by extrinsic compression, intrinsic narrowing, or foreign bodies) but can also result from dysmotility of the esophagus (whether primary/idiopathic or secondary to systemic disease). Inflammatory lesions of the esophagus without obstruction or dysmotility are a third cause of dysphagia; eosinophilic esophagitis, most often afflicting older boys, is relatively common.

The most common esophageal disorder in children is **GERD,** which is from retrograde return of gastric contents into the esophagus. **Esophagitis** can be caused by GERD, by eosinophilic disease, by infection, or by caustic substances. Esophageal **bleeding** can result from severe esophagitis that produces erosions or ulcerations and can manifest as anemia or Hemoccult-positive stools. More acute or severe bleeding can be from ruptured **esophageal varices.** The resulting hematemesis must be differentiated from more distal bleeding (gastric ulcer) and from more proximal bleeding (a nosebleed or hemoptysis). Respiratory symptoms of esophageal disease can result from luminal contents incorrectly being directed into the respiratory tract or to reflexive respiratory responses to esophageal stimuli.

DIAGNOSTIC AIDS

The esophagus can be evaluated by radiography, endoscopy, histology, scintigraphy, manometry, pH-metry (linked as indicated with other polysomnography), and multichannel intraluminal impedance. Contrast (usually barium) radiographic study of the esophagus usually incorporates fluoroscopic imaging over time so that motility and anatomy can be assessed. Although most often requested to evaluate for GERD, it is neither sensitive nor specific for this purpose; it can detect complications of GERD (stricture or hiatal hernia) or conditions mimicking GERD (pyloric stenosis or malrotation with intermittent volvulus).

Barium fluoroscopy is optimal for evaluating for structural anomalies, such as duplications, strictures, or external esophageal compression by an aberrant blood vessel, or for causes of dysmotility, such as achalasia. Modifications of the routine barium fluoroscopic study are used in special situations. When an "H-type" tracheoesophageal fistula is suspected, the test is most sensitive if the radiologist, with the patient prone, distends the esophagus with barium via a nasogastric tube. The videofluoroscopic evaluation of swallowing performed with varying consistencies of barium ("modified barium swallow," oropharyngeal videoesophagram, or "cookie swallow") optimally evaluates children with dysphagia by demonstrating incoordination of the pharyngeal and esophageal phases of swallowing and any associated aspiration.

In some centers, fiberoptic endoscopic evaluation of swallowing uses nasopharyngeal endoscopy to visualize the pharynx and larynx during swallowing of dye-enhanced foods when dysphagia, laryngeal penetration, or aspiration are suspected. This is often combined with sensory testing of the laryngeal adductor reflex in response to a calibrated puff of air through the endoscope to the arytenoids, generating the composite fiberoptic endoscopic evaluation of swallowing sensory testing

that examines the mechanisms of any aspiration that is present. Endoscopy allows direct visualization of esophageal mucosa and helps therapeutically in the removal of foreign bodies and treatment of esophageal varices. Endoscopy also allows biopsy samples to be taken, thus improving the diagnosis of "endoscopy-negative" GERD, differentiating GERD from eosinophilic esophagitis, and identifying viral or fungal causes of esophagitis.

Radionuclide scintigraphy scans are helpful in evaluating the efficiency of peristalsis and demonstrating reflux episodes. They can be specific, although not very sensitive, for aspiration and can quantify gastric emptying, thus hinting at a cause for GERD. The related radionuclide salivagram can demonstrate aspiration of even minute amounts of saliva.

Esophageal manometry evaluates for dysmotility from the pharynx to the stomach; by synchronized quantitative pressure measurements along the esophagus, it detects and characterizes dysfunctions sometimes missed radiographically. Manometry is often challenging in young infants, and sphincters are optimally evaluated with special Dent sleeves, rather than the simple ports available for the esophageal body.

Extended pH monitoring of the distal esophagus is a sensitive test for acidic GER episodes that can quantify duration and degree of acidity, but not volume, of the reflux episodes. It is linked with polysomnography (a "pneumogram") when GER is suspected to cause apnea or similar symptoms.

Multichannel intraluminal impedance is a method for pH-independent detection of bolus movements in the esophagus; with a pH probe incorporated, it can distinguish between acid and nonacid liquid and gaseous reflux, the proximal extent of reflux, and several aspects of esophageal function, such as direction of bolus flow, duration of bolus presence, and bolus clearance.

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Chapter 319

Congenital Anomalies

319.1 Esophageal Atresia and Tracheoesophageal Fistula

Seema Khan and Susan R. Orenstein

Esophageal atresia (EA) is the most common congenital anomaly of the esophagus, with a prevalence of 1.7 per 10,000 live births. Of these, >90% have an associated tracheoesophageal fistula (TEF). In the most common form of EA, the upper esophagus ends in a blind pouch and the TEF is connected to the distal esophagus (type C). Figure 319-1 shows the types of EA and TEF and their relative frequencies. The exact cause is still unknown; associated features include advanced maternal age, European ethnicity, obesity, low socioeconomic status, and tobacco smoking. This defect has survival rates of >90%, owing largely to improved neonatal intensive care, earlier recognition, and appropriate intervention. Infants weighing < 1,500 g at birth and those with severe cardiac anomalies have the highest risk for mortality. Fifty percent of infants are nonsyndromic without other anomalies, and the rest have associated anomalies, most often associated with the VATER or VACTERL (vertebral, anorectal, [cardiac], tracheal, esophageal, renal, radial, [limb]) syndrome. Cardiac and vertebral anomalies are seen in 32% and 24%, respectively. These syndromes generally are associated with normal intelligence. Despite low concordance among twins and the low incidence of familial cases, genetic factors have a role in the pathogenesis of TEF in some patients as suggested by discrete mutations in syndromic cases: Feingold syndrome *(N-MYC),* CHARGE syndrome (*c*oloboma of the eye, central nervous system anomalies; *h*eart defects; *a*tresia of the choanae; *r*etardation of growth and/or development; *g*enital and/or urinary defects [hypogonadism]; *e*ar anomalies and/or deafness) *(CHD7),* and anophthalmia-esophageal-genital syndrome *(SOX2).*

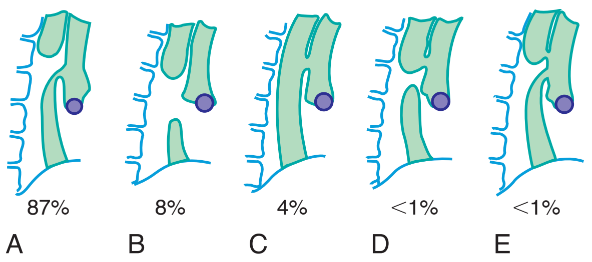

Figure 319-1 Diagrams of the 5 most commonly encountered forms of esophageal atresia and tracheoesophageal fistula, shown in order of frequency.

PRESENTATION

The neonate with EA typically has frothing and bubbling at the mouth and nose after birth as well as episodes of coughing, cyanosis, and respiratory distress. Feeding exacerbates these symptoms, causes regurgitation, and can precipitate aspiration. Aspiration of gastric contents via a distal fistula causes more damaging pneumonitis than aspiration of pharyngeal secretions from the blind upper pouch. The infant with an isolated TEF in the absence of EA ("H-type" fistula) might come to medical attention later in life with chronic respiratory problems, including refractory bronchospasm and recurrent pneumonias.

DIAGNOSIS

In the setting of early-onset respiratory distress, the inability to pass a nasogastric or orogastric tube in the newborn suggests EA. Perinatal radiographic findings of absence of the infant stomach bubble and maternal polyhydramnios might alert the physician to EA. Plain radiography in the evaluation of respiratory distress might reveal a coiled feeding tube in the esophageal pouch and/or an air-distended stomach, indicating the presence of a coexisting TEF (Fig. 319-2). Conversely, pure EA can manifest as an airless scaphoid abdomen. In isolated TEF (H type), an esophagogram with contrast medium injected under pressure can demonstrate the defect (Fig. 319-3). Alternatively, the orifice may be detected at bronchoscopy or when methylene blue dye injected into the endotracheal tube during endoscopy is observed in the esophagus during forced inspiration.

MANAGEMENT

Initially, maintaining a patent airway, pre-operative proximal pouch decompression to prevent aspiration of secretions and use of antibiotics to prevent consequent pneumonia are paramount. Prone positioning minimizes movement of gastric secretions into a distal fistula, and esophageal suctioning minimizes aspiration from a blind pouch. Endotracheal intubation with mechanical ventilation is to be avoided if possible because it can worsen distention of abdominal viscera. Surgical ligation of the TEF and primary end-to-end anastomosis of the esophagus via right-sided thoracotomy constitute the current standard surgical approach. In the premature or otherwise complicated infant, a primary closure may be delayed by temporizing with fistula ligation and gastrostomy tube placement. If the gap between the atretic ends of the esophagus is >3-4 cm, primary repair cannot be done; options include using gastric, jejunal, or colonic segments interposed as a neoesophagus. Careful search must be undertaken for the common associated cardiac and other anomalies. Thoracoscopic surgical repair is now considered feasible and associated with favorable long-term outcomes.

OUTCOME

The majority of children with EA and TEF grow up to lead normal lives, but complications are often challenging, particularly during the 1st 5 yr of life. Complications of surgery include anastomotic leak, refistulization, and anastomotic stricture. Gastroesophageal reflux

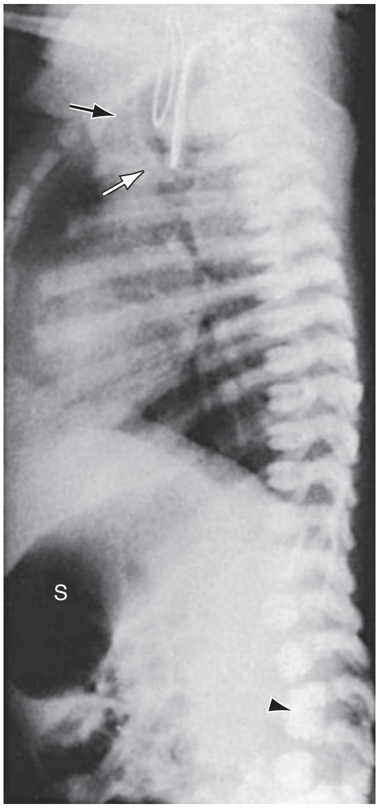

Figure 319-2 Tracheoesophageal fistula. Lateral radiograph demonstrating a nasogastric tube coiled *(arrows)* in the proximal segment of an atretic esophagus. The distal fistula is suggested by gaseous dilation of the stomach *(S)* and small intestine. The *arrowhead* depicts vertebral fusion, whereas a heart murmur and cardiomegaly suggest the presence of a ventricular septal defect. This patient demonstrated elements of the VATER (vertebral, anorectal, tracheal, esophageal, renal, radial) anomalad. *(From Balfe D, Ling D, Siegel M: The esophagus. In Putman CE, Ravin CE, editors:* Textbook of diagnostic imaging, *Philadelphia, 1988, WB Saunders.)*

disease, resulting from intrinsic abnormalities of esophageal function, often combined with delayed gastric emptying, contributes to management challenges in many cases. Gastroesophageal reflux disease contributes significantly to the respiratory disease **(reactive airway disease)** that often complicates EA and TEF and also worsens the frequent anastomotic strictures after repair of EA.

Many patients have an associated tracheomalacia that improves as the child grows.

Bibliography is available at Expert Consult.

319.2 Laryngotracheoesophageal Clefts

Seema Khan and Susan R. Orenstein

Laryngotracheoesophageal clefts are uncommon anomalies that result when the septum between the esophagus and trachea fails to develop fully, leading to a common channel defect between the pharyngoesophagus and laryngotracheal lumen, thus making the laryngeal closure incompetent during swallowing or reflux. Other developmental anomalies, such as EA and TEF, are seen in 20% of patients with clefts. The severity of presenting symptoms depends on the type of cleft; they are commonly classified as 4 types (I-IV) according to the inferior extent of the cleft. Early in life, the infant presents with stridor, choking, cyanosis, aspiration of feedings, and recurrent chest infections. The diagnosis is difficult and usually requires direct endoscopic visualization of the larynx and esophagus. When contrast radiography is used, material is often seen in the esophagus and trachea. Treatment is surgical repair, which can be complex if the defects are long.

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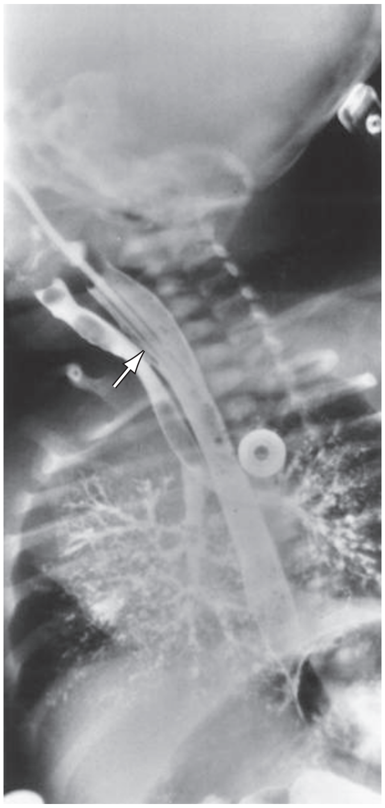

Figure 319-3 H-type fistula *(arrow)* demonstrated in an infant after barium swallow on frontal-oblique chest x-ray. The tracheal aspect of the fistula is characteristically superior to the esophageal aspect. Barium is seen to outline the tracheobronchial tree. *(From Wyllie R, Hyams JS, editors:* Pediatric gastrointestinal and liver disease, *ed 3, Philadelphia, 2006, Saunders Elsevier, p. 299.)*

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Chapter 320

Obstructing and Motility Disorders of the Esophagus

Seema Khan and Susan R. Orenstein

Obstructing lesions classically produce **dysphagia** to **solids** earlier and more noticeably than to liquids and can manifest when the infant liquid diet begins to incorporate solids; this is in contrast to **dysphagia** from **dysmotility,** in which swallowing of liquids is affected as early as, or earlier than, solids. In most instances of dysphagia, evaluation begins with fluoroscopy, which may include videofluoroscopic evaluation of swallowing, particularly if aspiration is a primary symptom. Secondary studies are often endoscopic if intrinsic obstruction is suspected or manometric if dysmotility is suspected; other imaging studies may be used in particular cases. Congenital lesions can require surgery, whereas

webs and peptic strictures might respond adequately to endoscopic (or bougie) dilation. Peptic strictures, once dilated, should prompt consideration of fundoplication for ongoing prophylaxis.

EXTRINSIC

Esophageal duplication cysts are the most commonly encountered foregut duplications. These cysts are lined by intestinal epithelium, have a well-developed smooth muscle wall, and are attached to the normal gastrointestinal tract. Most of these affect the distal half of the esophagus on the right side. The most common presentation is respiratory distress caused by compression of the adjacent airways. Dysphagia is a common symptom in older children. Upper gastrointestinal bleeding can occur as a result of acid-secreting gastric mucosa in the duplication wall. **Neuroenteric cysts** might contain glial elements and are associated with **vertebral anomalies.** Diagnosis is made using modalities, such as barium swallow, chest CT, and MRI, or endosonography. Treatment is surgical; laparoscopic approach to excision is also possible.

Enlarged mediastinal or subcarinal **lymph nodes,** caused by infection (tuberculosis, histoplasmosis) or neoplasm (lymphoma), are the most common external masses that compress the esophagus and produce obstructive symptoms. **Vascular anomalies** can also compress the esophagus; *dysphagia lusoria* is a term denoting the dysphagia produced by a developmental vascular anomaly, which is often an aberrant right subclavian artery or right-sided or double aortic arch (see Chapter 432.1).

INTRINSIC

Intrinsic narrowing of the esophageal lumen can be congenital or acquired. The etiology is suggested by the location, the character of the lesion, and the clinical situation. The lower esophagus is the most common location for peptic strictures, which are generally somewhat ragged and several cm long. Thin membranous rings, including the Schatzki ring at the squamocolumnar junction, can also occlude this area. In the midesophagus, congenital narrowing may be associated with the esophageal atresia–tracheoesophageal fistula complex, in which some of the lesions might incorporate cartilage and might be impossible to dilate safely; alternatively, reflux esophagitis can induce a ragged and extensive narrowing that appears more proximal than the usual peptic stricture, often because of an associated hiatal hernia. Congenital webs or rings can narrow the upper esophagus. The upper esophagus can also be narrowed by an inflammatory stricture occurring after a caustic ingestion or due to epidermolysis bullosa. Cricopharyngeal achalasia can appear radiographically as a cricopharyngeal "bar" posteriorly in the upper esophagus. **Eosinophilic esophagitis** is one of the most common causes for esophageal obstructive symptoms. Although the pathogenesis of obstructive eosinophilic esophagitis is not yet completely explained and seems to vary among individual patients, endoscopy or radiology demonstrates stricture formation in some children with eosinophilic esophagitis, and in others a noncompliant esophagus is evident, with thickened wall layers demonstrable by ultrasonography.

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Chapter 321
Dysmotility

Seema Khan and Susan R. Orenstein

UPPER ESOPHAGEAL AND UPPER ESOPHAGEAL SPHINCTER DYSMOTILITY (STRIATED MUSCLE)

Cricopharyngeal **achalasia** signifies a failure of complete relaxation of the upper esophageal sphincter (UES), whereas cricopharyngeal **incoordination** implies full relaxation of the UES but incoordination of the relaxation with the pharyngeal contraction. These entities are usually detected on videofluoroscopic evaluation of swallowing (sometimes accompanied by visible cricopharyngeal prominence, termed a *bar*), but often the most precise definition of the dysfunction is obtained with manometry. A self-limited form of cricopharyngeal incoordination occurs in infancy and remits spontaneously in the 1st yr of life if nutrition is maintained despite the dysphagia. In children, treatment options for non–self-limited cricopharyngeal achalasia consist of dilation, botox injection, and transcervical myotomy. It is important to evaluate such children thoroughly, including cranial MRI to detect **Arnold-Chiari malformations,** which can manifest in this way but are best treated by cranial decompression, rather than esophageal surgery. Cricopharyngeal spasm may be severe enough to produce posterior pharyngeal (Zenker) **diverticulum** above the obstructive sphincter; this entity occurs rarely in children.

Systemic causes of swallowing dysfunction that can affect the oropharynx, UES, and upper esophagus include cerebral palsy, Arnold-Chiari malformations, syringomyelia, bulbar palsy or cranial nerve defects (Möbius syndrome, transient infantile paralysis of the superior laryngeal nerve), transient pharyngeal muscle dysfunction, spinal muscular atrophy (including Werdnig-Hoffmann disease), muscular dystrophy, multiple sclerosis, infections (botulism, tetanus, poliomyelitis, diphtheria), inflammatory and autoimmune diseases (dermatomyositis, myasthenia gravis, polyneuritis, scleroderma), and familial dysautonomia. All of these can produce dysphagia. Medications (nitrazepam, benzodiazepines) and tracheostomy can adversely affect the function of the UES and thereby produce dysphagia.

LOWER ESOPHAGEAL AND LOWER ESOPHAGEAL SPHINCTER DYSFUNCTION (SMOOTH MUSCLE)

Causes of dysphagia resulting from more distal primary esophageal dysmotility include achalasia, diffuse esophageal spasm, nutcracker esophagus, and hypertensive lower esophageal sphincter (LES); all but achalasia are rare in children. Secondary causes include Hirschsprung disease, pseudoobstruction, inflammatory myopathies, scleroderma, and diabetes.

Achalasia is a primary esophageal motor disorder of unknown etiology characterized by loss of LES relaxation and loss of esophageal peristalsis, both contributing to a functional obstruction of the distal esophagus. Degenerative, autoimmune (antibodies to Auerbach plexus), and infectious (Chagas disease caused by *Trypanosoma cruzi*) factors are possible causes. In rare cases, achalasia is familial or part of the achalasia, alacrima, and adrenal insufficiency, known as triple A syndrome or **Allgrove syndrome**. *Pseudoachalasia* refers to achalasia caused by various forms of cancer via obstruction of the gastroesophageal junction, infiltration of the submucosa and muscularis of the LES, or as part of the paraneoplastic syndrome with formation of anti-Hu antibodies. Pathologically, in achalasia, inflammation surrounds ganglion cells, which are decreased in number. There is selective loss of postganglionic inhibitory neurons that normally lead to sphincter relaxation, leaving postganglionic cholinergic neurons unopposed. This imbalance produces high basal LES pressures and insufficient LES relaxation. The loss of esophageal peristalsis can be a secondary phenomenon.

Achalasia manifests with regurgitation and dysphagia for solids and liquids and may be accompanied by undernutrition or chronic cough; retained esophageal food can produce esophagitis. *The presentations of chronic regurgitation/vomiting with weight loss, and chronic cough have led to misdiagnoses of anorexia nervosa and asthma, respectively.* The mean age in children is 8.8 yr, with a mean duration of symptoms before diagnosis of 23 mo; it is uncommon before school age. Chest radiograph shows an air–fluid level in a dilated esophagus. **Barium fluoroscopy** reveals a smooth tapering of the lower esophagus leading to the closed LES, resembling a bird's beak (Fig. 321-1). Loss of primary peristalsis in the distal esophagus with retained food and poor emptying are often present. **Manometry** is the most sensitive diagnostic test; it reveals the defining features of aperistalsis in the

distal esophageal body and incomplete or absent LES relaxation, often accompanied by high pressure LES and low-amplitude esophageal body contractions.

The goals of achalasia therapy are relief of symptoms, improvement of esophageal emptying, and prevention of megaesophagus. The 2 most effective treatment options are pneumatic dilation and laparoscopic or surgical (Heller) myotomy. Pneumatic dilation is the initial treatment of choice, and does not preclude a future myotomy. Surgeons often supplement a myotomy with an antireflux procedure to prevent the gastroesophageal reflux disease that otherwise often ensues when the sphincter is rendered less competent. Laparoscopic myotomy is a particularly effective procedure in adolescent and young adult males. Peroral endoscopic myotomy may be a feasible, safe, and an effective alternative to the laparoscopic method. Calcium channel blockers (nifedipine) and phosphodiesterase inhibitors offer temporary relief of dysphagia. Endoscopic injection of the LES with **botulinum toxin** counterbalances the selective loss of inhibitory neurotransmitters by inhibiting the release of acetylcholine from nerve terminals and may be an effective therapy. Botulinum toxin is effective in 50-65% of patients and is expensive; half the patients might require a repeat injection within 1 yr. Most eventually require dilation or surgery.

Diffuse esophageal spasm causes chest pain and dysphagia and affects adolescents and adults. It is diagnosed **manometrically** and can be treated with nitrates or calcium-channel-blocking agents.

Gastroesophageal reflux disease constitutes the most common cause of nonspecific abnormalities of esophageal motor function, probably through the effect of the esophageal inflammation on the musculature.

Bibliography is available at Expert Consult.

Figure 321-1 **Barium esophagogram of a patient with achalasia demonstrating dilated esophagus and narrowing at the lower esophageal sphincter.** Note retained secretions layered on top of barium in the esophagus.

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Chapter 322

Hiatal Hernia

Seema Khan and Susan R. Orenstein

Herniation of the stomach through the esophageal hiatus can occur as a common sliding hernia (type 1), in which the gastroesophageal junction slides into the thorax, or it can be paraesophageal (type 2), in which a portion of the stomach (usually the fundus) is insinuated next to the esophagus inside the gastroesophageal junction in the hiatus (Figs. 322-1 and 322-2). A combination of sliding and paraesophageal types (type 3) is present in some patients. Sliding hernias are often associated with gastroesophageal reflux, especially in developmentally delayed children. The relationship to hiatal hernias in adults is unclear. Diagnosis is usually made by an upper gastrointestinal series and upper endoscopy. Medical treatment is not directed at the hernia but at the gastroesophageal reflux, unless failure of medical therapy prompts correction of the hernia at the time of fundoplication.

A paraesophageal hernia can be an isolated congenital anomaly or associated with gastric volvulus, or it may be encountered after fundoplication for gastroesophageal reflux, especially if the edges of a dilated esophageal diaphragmatic hiatus have not been approximated. Fullness after eating and upper abdominal pain are the usual symptoms. Infarction of the herniated stomach is rare.

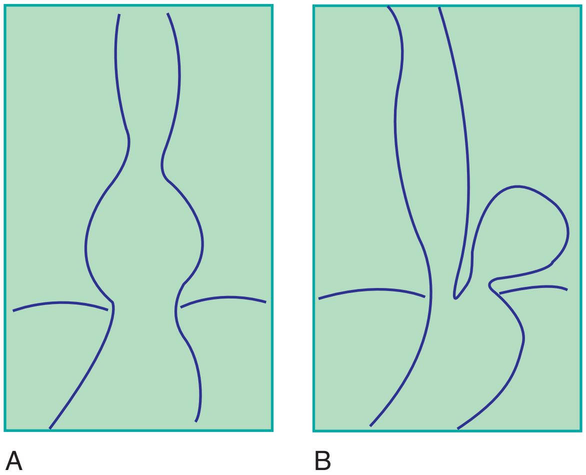

Figure 322-1 Types of esophageal hiatal hernia. **A,** Sliding hiatal hernia, the most common type. **B,** Paraesophageal hiatal hernia.

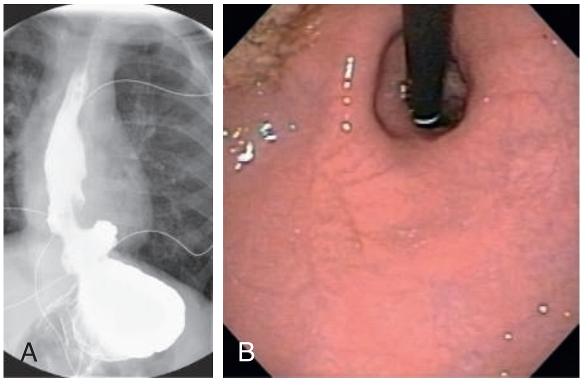

Figure 322-2 **A,** An upper gastrointestinal series shows a large hiatal hernia that extends above the diaphragm and impedes the exit of contrast from the esophagus into the stomach. Contrast is also noted to reflux to the upper esophagus. **B,** A retroflexed view of the hernia from the stomach during an upper endoscopy.

Chapter 323

Gastroesophageal Reflux Disease

Seema Khan and Susan R. Orenstein

Gastroesophageal reflux disease (GERD) is the most common esophageal disorder in children of all ages. Gastroesophageal reflux (GER) signifies the retrograde movement of gastric contents across the lower esophageal sphincter (LES) into the esophagus, which occurs physiologically every day in all infants, older children, and adults. Physiologic GER is exemplified by the effortless regurgitation of normal infants. The phenomenon becomes **pathologic GERD** in infants and children who manifest or report bothersome symptoms because of frequent or persistent GER, producing esophagitis-related symptoms, or extraesophageal presentations, such as respiratory symptoms or nutritional effects.

PATHOPHYSIOLOGY

Factors determining the esophageal manifestations of reflux include the duration of esophageal exposure (a product of the frequency and duration of reflux episodes), the causticity of the refluxate, and the susceptibility of the esophagus to damage. The LES, defined as a high-pressure zone by manometry, is supported by the crura of the diaphragm at the gastroesophageal junction, together with valve-like functions of the esophagogastric junction anatomy, form the antireflux barrier. In the context of even the normal intraabdominal pressure augmentations that occur during daily life, the frequency of reflux episodes is increased by insufficient LES tone, by abnormal frequency of LES relaxations, and by hiatal herniation that prevents the LES pressure from being proportionately augmented by the crura during abdominal straining. Normal intraabdominal pressure augmentations may be further exacerbated by straining or respiratory efforts. The duration of reflux episodes is increased by lack of swallowing (e.g., during sleep) and by defective esophageal peristalsis. Vicious cycles ensue because chronic esophagitis produces esophageal peristaltic dysfunction (low-amplitude waves, propagation disturbances), decreased LES tone, and inflammatory esophageal shortening that induces hiatal herniation, all worsening reflux.

Transient LES relaxation (TLESR) is the primary mechanism allowing reflux to occur, and is defined as simultaneous relaxation of both LES and the surrounding crura. TLESRs occur independent of swallowing, reduce LES pressure to 0-2 mm Hg (above gastric), and last 10-60 sec; they appear by 26 wk of gestation. A vagovagal reflex, composed of afferent mechanoreceptors in the proximal stomach, a brainstem pattern generator, and efferents in the LES, regulates TLESRs. Gastric distention (postprandially, or from abnormal gastric emptying or air swallowing) is the main stimulus for TLESRs. Whether GERD is caused by a higher frequency of TLESRs or by a greater incidence of reflux during TLESRs is debated; each is likely in different persons. Straining during a TLESR makes reflux more likely, as do positions that place the gastroesophageal junction below the air–fluid interface in the stomach. Other factors influencing gastric pressure–volume dynamics, such as increased movement, straining, obesity, large-volume or hyperosmolar meals, gastroparesis, a large sliding hiatal hernia, and increased respiratory effort (coughing, wheezing) can have the same effect.

EPIDEMIOLOGY AND NATURAL HISTORY

Infant reflux becomes evident in the 1st few mo of life, peaks at 4 mo, and resolves in up to 88% by 12 mo and in nearly all by 24 mo. Symptoms in **older children** tend to be chronic, waxing and waning, but completely resolving in no more than half, which resembles adult patterns (Table 323-1). The histologic findings of esophagitis persist in infants who have naturally resolving symptoms of reflux. GERD likely has genetic predispositions: family clustering of GERD symptoms, endoscopic esophagitis, hiatal hernia, Barrett esophagus, and adenocarcinoma have been identified. As a continuously variable and common disorder, complex inheritance involving multiple genes and environmental factors is likely. Genetic linkage is indicated by the strong evidence of GERD in studies with monozygotic twins. A pediatric autosomal dominant form with otolaryngologic and respiratory manifestations has been located to chromosome 13q14, and the locus is termed GERD1.

CLINICAL MANIFESTATIONS

Most of the common clinical manifestations of esophageal disease can signify the presence of GERD and are generally thought to be mediated by the pathogenesis involving acid GER (Table 323-2). Although less noxious for the esophageal mucosa, nonacid reflux events are recognized to play an important role in extraesophageal disease manifestations. **Infantile reflux** manifests more often with regurgitation (especially postprandially), signs of esophagitis (irritability, arching, choking, gagging, feeding aversion), and resulting failure to thrive; symptoms resolve spontaneously in the majority of infants by 12-24 mo. **Older children** can have regurgitation during the preschool years; this complaint diminishes somewhat as children age, and complaints of abdominal and chest pain supervene in later childhood and adolescence. Occasional children present with food refusal or neck contortions (arching, turning of head) designated **Sandifer syndrome.** The respiratory presentations are also age dependent: GERD in infants can manifest as obstructive apnea or as stridor or lower airway disease in which reflux complicates primary airway disease such as laryngomalacia or bronchopulmonary dysplasia. Otitis media, sinusitis, lymphoid hyperplasia, hoarseness, vocal cord nodules, and laryngeal edema have all been associated with GERD. Airway manifestations in older children are more commonly related to asthma or to otolaryngologic disease such as laryngitis or sinusitis. Despite the high prevalence of GERD symptoms in asthmatic children, data showing direction of causality are conflicting.

DIAGNOSIS

For most of the typical GERD presentations, particularly in older children, a thorough history and physical examination suffice initially to reach the diagnosis. This initial evaluation aims to identify the pertinent positives in support of GERD and its complications and the negatives that make other diagnoses unlikely. The history may be facilitated and standardized by questionnaires (e.g., the Infant Gastroesophageal Reflux Questionnaire, the I-GERQ, and its derivative, the I-GERQ-R), which also permit quantitative scores to be evaluated for their diagnostic discrimination and for evaluative assessment of improvement or worsening of symptoms. The clinician should be alerted to the possibility of other important diagnoses in the presence of any alarm or warning signs: bilious emesis, frequent projectile emesis, gastrointestinal bleeding, lethargy, organomegaly, abdominal distention, micro- or macrocephaly, hepatosplenomegaly, failure to thrive, diarrhea, fever, bulging fontanelle, and seizures. The important differential diagnoses to consider in the evaluation of an infant or a child with chronic vomiting are milk and other food allergies, eosinophilic esophagitis, pyloric stenosis, intestinal obstruction (especially malrotation with intermittent volvulus), nonesophageal inflammatory diseases, infections, inborn errors of metabolism, hydronephrosis, increased intracranial pressure, rumination, and bulimia. Focused diagnostic testing, depending on the presentation and the differential diagnosis, can then supplement the initial examination.

Most of the esophageal tests are of some use in particular patients with suspected GERD. **Contrast (usually barium) radiographic** study of the esophagus and upper gastrointestinal tract is performed in children with vomiting and dysphagia to evaluate for achalasia, esophageal strictures and stenosis, hiatal hernia, and gastric outlet or intestinal obstruction (Fig. 323-1). It has poor sensitivity and specificity in the diagnosis of GERD as a result of its limited duration and the inability

Table 323-1 Symptoms According to Age

MANIFESTATIONS	INFANTS	CHILDREN	ADOLESCENTS AND ADULTS
Impaired quality of life	+++	+++	+++
Regurgitation	++++	+	+
Excessive crying/irritability	+++	+	–
Vomiting	++	++	+
Food refusal/feeding disturbances/anorexia	++	+	+
Persisting hiccups	++	+	+
Failure to thrive	++	+	–
Abnormal posturing/Sandifer syndrome	++	+	–
Esophagitis	+	++	+++
Persistent cough/aspiration pneumonia	+	++	+
Wheezing/laryngitis/ear problems	+	++	+
Laryngomalacia/stridor/croup	+	++	–
Sleeping disturbances	+	+	+
Anemia/melena/hematemesis	+	+	+
Apnea/ALTE/desaturation	+	–	–
Bradycardia	+	?	?
Heartburn/pyrosis	?	++	+++
Epigastric pain	?	+	++
Chest pain	?	+	++
Dysphagia	?	+	++
Dental erosions/water brush	?	+	+
Hoarseness/globus pharyngeus	?	+	+
Chronic asthma/sinusitis	–	++	+
Laryngostenosis/vocal nodule problems	–	+	+
Stenosis	–	(+)	+
Barrett/esophageal adenocarcinoma	–	(+)	+

+++, Very common; ++ common; + possible; (+) rare; – absent; ? unknown; ALTE, apparent life-threatening event.
From Wyllie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, *ed 4, Philadelphia, 2011, WB Saunders, Table 22-3, p. 235.*

to differentiate physiologic GER from GERD. Furthermore, contrast radiography neither accurately assesses mucosal inflammation nor correlates with severity of GERD.

Extended **esophageal pH monitoring** of the distal esophagus, no longer considered the sine qua non of a GERD diagnosis, provides a quantitative and sensitive documentation of acidic reflux episodes, the most important type of reflux episodes for pathologic reflux. The distal esophageal pH probe is placed at a level corresponding to 87% of the nares-LES distance, based on regression equations using the patient's height, on fluoroscopic visualization, or on manometric identification of the LES. Normal values of distal esophageal acid exposure (pH < 4) are generally established as <5-8% of the total monitored time, but these quantitative normals are insufficient to establish or disprove a diagnosis of pathologic GERD. The most important indications for esophageal pH monitoring are for assessing efficacy of acid suppression during treatment, evaluating apneic episodes in conjunction with a pneumogram and perhaps impedance, and evaluating atypical GERD presentations such as chronic cough, stridor, and asthma. Dual pH probes, adding a proximal esophageal probe to the standard distal one, are used in the diagnosis of extraesophageal GERD, identifying upper esophageal acid exposure times of 1% of the total time as threshold values for abnormality.

Endoscopy allows diagnosis of erosive esophagitis (Fig. 323-2) and complications such as strictures or Barrett esophagus; esophageal biopsies can diagnose histologic reflux esophagitis in the absence of erosions while simultaneously eliminating allergic and infectious causes. Endoscopy is also used therapeutically to dilate reflux-induced strictures. Radionucleotide scintigraphy using technetium can demonstrate aspiration and delayed gastric emptying when these are suspected.

The multichannel **intraluminal impedance** is a cumbersome test, but with potential applications both for diagnosing GERD and for understanding esophageal function in terms of bolus flow, volume clearance, and (in conjunction with manometry) motor patterns associated with GERD. Owing to the multiple sensors and a distal pH sensor, it is possible to document acidic reflux (pH < 4), weakly acidic reflux (pH 4-7), and weakly alkaline reflux (pH > 7) with multichannel intraluminal impedance. It is an important tool in those with respiratory symptoms, particularly for the determination of nonacid reflux, but must be cautiously applied in routine clinical evaluation because of limited evidence-based parameters for GERD diagnosis and symptom association.

Laryngotracheobronchoscopy evaluates for visible airway signs that are associated with extraesophageal GERD, such as posterior laryngeal inflammation and vocal cord nodules; it can permit diagnosis of silent aspiration (during swallowing or during reflux) by bronchoalveolar lavage with subsequent quantification of lipid-laden macrophages in airway secretions. Detection of pepsin in tracheal fluid is a

marker of reflux-associated aspiration of gastric contents. Esophageal manometry permits evaluation for dysmotility, particularly in preparation for antireflux surgery.

Empirical antireflux therapy, using a time-limited trial of high-dose proton pump inhibitor (PPI), is a cost-effective strategy for diagnosis in adults; although not formally evaluated in older children, it has also been applied to this age group. Failure to respond to such empirical treatment, or a requirement for the treatment for prolonged periods, mandates formal diagnostic evaluation.

MANAGEMENT

Conservative therapy and lifestyle modifications that form the foundation of GERD therapy can be effectively implemented through education and reassurance for parents. Dietary measures for infants include normalization of any abnormal feeding techniques, volumes, and frequencies. Thickening of feeds or use of commercially prethickened formulas increases the percentage of infants with no regurgitation, decreases the frequency of daily regurgitation and emesis, and increases the infant's weight gain. However, caution should be exercised when managing preterm infants because of the possible association between xanthan gum-based thickened feeds and necrotizing enterocolitis. The evidence does not clearly favor 1 type of thickener over another; the addition of a Tbsp of rice cereal per oz of formula results in a greater caloric density (30 kcal/oz) and reduced crying time, although it might not modify the number of nonregurgitant reflux episodes. A short trial of a hypoallergenic diet in infants may be used to exclude milk or soy protein allergy before pharmacotherapy. A combination of modified feeding volumes, hydrolyzed infant formulas, proper positioning, and avoidance of smoke exposure satisfactorily improve GERD symptoms in 24-59% infants with GERD. Older children should be counseled to

Table 323-2	Symptoms and Signs That May Be Associated with Gastroesophageal Reflux
Symptoms	
Recurrent regurgitation with or without vomiting	
Weight loss or poor weight gain	
Irritability in infants	
Ruminative behavior	
Heartburn or chest pain	
Hematemesis	
Dysphagia, odynophagia	
Wheezing	
Stridor	
Cough	
Hoarseness	
Signs	
Esophagitis	
Esophageal stricture	
Barrett esophagus	
Laryngeal/pharyngeal inflammation	
Recurrent pneumonia	
Anemia	
Dental erosion	
Feeding refusal	
Dystonic neck posturing (Sandifer syndrome)	
Apnea spells	
Apparent life-threatening events	

From Wyllie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, *ed 4, Philadelphia, 2011, WB Saunders, Table 22-1, p. 235.*

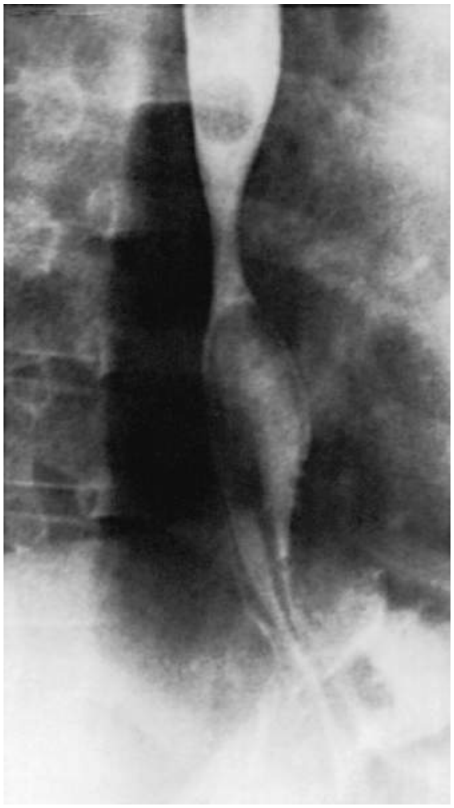

Figure 323-1 Barium esophagogram demonstrating free gastroesophageal reflux. Note stricture caused by peptic esophagitis. Longitudinal gastric folds above the diaphragm indicate the unusual presence of an associated hiatal hernia.

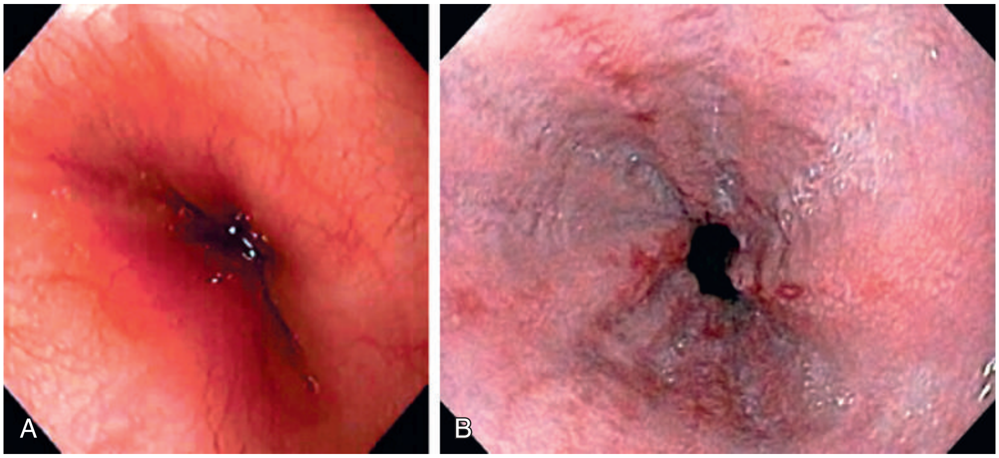

Figure 323-2 Endoscopic image of a normal esophagus **(A)** and erosive peptic esophagitis **(B).**

avoid acidic or reflux-inducing foods (tomatoes, chocolate, mint) and beverages (juices, carbonated and caffeinated drinks, alcohol). Weight reduction for obese patients and elimination of smoke exposure are other crucial measures at all ages.

Positioning measures are particularly important for infants, who cannot control their positions independently. Seated position worsens infant reflux and should be avoided in infants with GERD. Esophageal pH monitoring demonstrates more reflux episodes in infants in supine and side positions compared with the prone position, but evidence that the supine position reduces the risk of sudden infant death syndrome has led the American Academy of Pediatrics and the North American Society of Pediatric Gastroenterology and Nutrition to recommend supine positioning during sleep. When the infant is awake and observed, prone position and upright carried position can be used to minimize reflux. Lying in the flat supine position and semi-seated positions (e.g., car seats, infant carriers) in the postprandial period are considered provocative positions for GER and therefore should be avoided. The efficacy of positioning for older children is unclear, but some evidence suggests a benefit to left side position and head elevation during sleep. The head should be elevated by elevating the head of the bed, rather than using excess pillows, to avoid abdominal flexion and compression that might worsen reflux.

Pharmacotherapy is directed at ameliorating the acidity of the gastric contents or at promoting their aboral movement, and should be considered for those symptomatic infants and children who are either highly suspected or proven to have GERD. **Antacids** are the most commonly used antireflux therapy and are readily available over the counter. They provide rapid but transient relief of symptoms by acid neutralization. The long-term regular use of antacids cannot be recommended because of side effects of diarrhea (magnesium antacids) and constipation (aluminum antacids) and rare reports of more serious side effects of chronic use.

Histamine-2 receptor antagonists (H2RAs: cimetidine, famotidine, nizatidine, and ranitidine) are widely used antisecretory agents that act by selective inhibition of histamine receptors on gastric parietal cells. There is a definite benefit of H2RAs in treatment of mild-to-moderate reflux esophagitis. H2RAs have been recommended as first-line therapy because of their excellent overall safety profile, but they are superseded by PPIs in this role, as increased experience with pediatric use and safety, FDA approval, and pediatric formulations and dosing are available.

PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) provide the most potent antireflux effect by blocking the hydrogen–potassium adenosine triphosphatase channels of the final common pathway in gastric acid secretion. PPIs are superior to H2RAs in the treatment of severe and erosive esophagitis. Pharmacodynamic studies indicate that children require higher doses of PPIs than adults on a per-weight basis. The use of PPIs to treat infants and children deemed to have GERD on the basis of symptoms is now the standard of care. An important systematic review of the efficacy and safety of PPI therapy in pediatric GERD reveals no clear benefit for PPI over placebo use in suspected infantile GERD (crying, arching behavior). Limited pediatric data are available to draw definitive conclusions about potential complications implicated with PPI use, such as respiratory infections, *Clostridium difficile* infection, bone fractures (noted in adults), and hypomagnesemia.

Prokinetic agents available in the United States include metoclopramide (dopamine-2 and 5-HT_3 antagonist), bethanechol (cholinergic agonist), and erythromycin (motilin receptor agonist). Most of these increase LES pressure; some improve gastric emptying or esophageal clearance. None affects the frequency of TLESRs. The available controlled trials have not demonstrated much efficacy for GERD. In 2009, the FDA announced a black box warning for metoclopramide, linking its chronic use (longer than 3 mo) with tardive dyskinesia, the rarely reversible movement disorder. Baclofen is a centrally acting γ-aminobutyric acid agonist that decreases reflux by decreasing TLESRs in healthy adults and in a small number of neurologically impaired children with GERD. New agents of great interest include peripherally acting γ-aminobutyric acid agonists devoid of central side effects, and metabotropic glutamate receptor 5 antagonists that are reported to reduce TLESRs but are as yet inadequately studied for this indication in children.

Surgery, usually **fundoplication,** is effective therapy for intractable GERD in children, particularly those with refractory esophagitis or strictures and those at risk for significant morbidity from chronic pulmonary disease. It may be combined with a gastrostomy for feeding or venting. The availability of potent acid-suppressing medication mandates more-rigorous analysis of the relative risks (or costs) and benefits of this relatively irreversible therapy in comparison to long-term pharmacotherapy. Some of the risks of fundoplication include a wrap that is "too tight" (producing dysphagia or gas-bloat) or "too loose" (and thus incompetent). Surgeons may choose to perform a "tight" (360 degrees, Nissen) or variations of a "loose" (<360 degrees, Thal, Toupet, Boix-Ochoa) wrap, or to add a gastric drainage procedure (pyloroplasty) to improve gastric emptying, based on their experience and the patient's disease. Preoperative accuracy of diagnosis of GERD and the skill of the surgeon are 2 of the most important predictors of successful outcome. Long-term studies suggest that fundoplications often become incompetent in children, as in adults, with reflux recurrence rates of up to 14% for Nissen and up to 20% for loose wraps; this fact currently combines with the potency of PPI therapy that is now available to shift practice toward long-term pharmacotherapy in many cases. Fundoplication procedures may be performed as open operations, by laparoscopy, or by endoluminal (gastroplication) techniques. Pediatric experience is limited with endoscopic application of radiofrequency therapy (Stretta procedure) to a 2-3 cm area of the LES and cardia to create a high-pressure zone to reduce reflux.

Bibliography is available at Expert Consult.

323.1 Complications of Gastroesophageal Reflux Disease

Seema Khan and Susan R. Orenstein

ESOPHAGEAL: ESOPHAGITIS AND SEQUELAE—STRICTURE, BARRETT ESOPHAGUS, ADENOCARCINOMA

Esophagitis can manifest as irritability, arching, and feeding aversion in infants; chest or epigastric pain in older children; and, rarely, as hematemesis, anemia, or Sandifer syndrome at any age. Erosive esophagitis is found in approximately 12% of children with GERD symptoms and is more common in boys, older children, neurologically abnormal children, children with severe chronic respiratory disease, and in those with hiatal hernia. Prolonged and severe esophagitis leads to formation of strictures, generally located in the distal esophagus, producing dysphagia, and requiring repeated esophageal dilations and often fundoplication. Long-standing esophagitis predisposes to metaplastic transformation of the normal esophageal squamous epithelium into intestinal columnar epithelium, termed **Barrett esophagus,** a precursor of esophageal adenocarcinoma. A large multicenter prospective study of 840 consecutive children who underwent elective endoscopies reported a 25.7% prevalence for reflux esophagitis, and a mere 0.12% for Barrett esophagus in children without neurologic disorders or tracheoesophageal anomalies. Both Barrett esophagus and adenocarcinoma occur more in white males and in those with increased duration, frequency, and severity of reflux symptoms. This transformation increases with age to plateau in the 5th decade; adenocarcinoma is thus rare in childhood. Barrett esophagus, uncommon in children, warrants periodic surveillance biopsies, aggressive pharmacotherapy, and fundoplication for progressive lesions.

NUTRITIONAL

Esophagitis and regurgitation may be severe enough to induce failure to thrive because of caloric deficits. Enteral (nasogastric or nasojejunal, or percutaneous gastric or jejunal) or parenteral feedings are sometimes required to treat such deficits.

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EXTRAESOPHAGEAL: RESPIRATORY ("ATYPICAL") PRESENTATIONS

GERD should be included in the differential diagnosis of children with unexplained or refractory otolaryngologic and respiratory complaints. GERD can produce respiratory symptoms by direct contact of the refluxed gastric contents with the respiratory tract (aspiration, laryngeal penetration, or microaspiration) or by reflexive interactions between the esophagus and respiratory tract (inducing laryngeal closure or bronchospasm). Often, GERD and a primary respiratory disorder, such as asthma, interact and a vicious cycle between them worsens both diseases. Many children with these extraesophageal presentations do not have typical GERD symptoms, making the diagnosis difficult. These atypical GERD presentations require a thoughtful approach to the differential diagnosis that considers a multitude of primary otolaryngologic (infections, allergies, postnasal drip, voice overuse) and pulmonary (asthma, cystic fibrosis) disorders. Therapy for the GERD must be more intense (usually incorporating a PPI) and prolonged (usually at least 3-6 mo). Subspecialist assistance from the perspective of the airway disease (otolaryngology, pulmonology) and the reflux disease (gastroenterology) is often warranted for specialized diagnostic testing and for optimizing intensive management.

APNEA AND STRIDOR

These upper airway presentations have been linked with GERD in case reports and epidemiologic studies; temporal relationships between them and reflux episodes have been demonstrated in some patients by esophageal pH–multichannel intraluminal impedance studies, and a beneficial response to therapy for GERD provides further support in a number of case series. An evaluation of 1,400 infants with apnea attributed the apnea to GERD in 50%, but other studies have failed to find an association. Apnea and apparent life-threatening event caused by reflux is generally obstructive, owing to laryngospasm that may be conceived of as an abnormally intense protective reflex. At the time of such apnea, infants have often been provocatively positioned (supine or flexed seated), have been recently fed, and have shown signs of obstructive apnea, with unproductive respiratory efforts. *The evidence suggests that for the large majority of infants presenting with apnea and an apparent life-threatening event, GERD is not causal.* Stridor triggered by reflux generally occurs in infants anatomically predisposed toward stridor (laryngomalacia, micrognathia). Spasmodic croup, an episodic frightening upper airway obstruction, can be an analogous condition in older children. Esophageal pH probe studies might fail to demonstrate linkage of these manifestations with reflux owing to the buffering of gastric contents by infant formula and the episodic nature of the conditions. Pneumograms can fail to identify apnea if they are not designed to identify obstructive apnea by measuring nasal airflow.

Reflux laryngitis and other otolaryngologic manifestations (also known as laryngopharyngeal reflux) can be attributed to GERD. **Hoarseness,** voice fatigue, throat clearing, chronic cough, pharyngitis, sinusitis, otitis media, and a sensation of globus have been cited. Laryngopharyngeal signs of GERD include edema and hyperemia (of the posterior surface), contact ulcers, granulomas, polyps, subglottic stenosis, and interarytenoid edema. The paucity of well-controlled evaluations of the association contributes to the skepticism with which these associations may be considered. Other risk factors irritating the upper respiratory passages can predispose some patients with GERD to present predominantly with these complaints.

Many studies have reported a strong association between asthma and reflux as determined by history, pH–multichannel intraluminal impedance, endoscopy, and esophageal histology. **GERD symptoms are present in an average of 23% (19-80%) of children with asthma** as observed in a systematic review of 19 studies examining the prevalence of GERD in asthmatics. The review also reported abnormal pH results in 63%, and esophagitis in 35% of asthmatic children. However, this association does not clarify the direction of causality in individual cases and thus does not indicate which patients with asthma are likely to benefit from anti-GERD therapy. Children with asthma who are particularly likely to have GERD as a provocative factor are those with symptoms of reflux disease, those with refractory or steroid-dependent asthma, and those with nocturnal worsening of asthma. Endoscopic evaluation that discloses esophageal sequelae of GERD provides an impetus to embark on the aggressive (high dose and many months' duration) therapy of GERD.

Dental erosions constitute the most common oral lesion of GERD, the lesions being distinguished by their location on the lingual surface of the teeth. The severity seems to correlate with the presence of reflux symptoms and the presence of an acidic milieu as the result of reflux in the proximal esophagus and oral cavity. The other common factors that can produce similar dental erosions are juice consumption and bulimia.

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Chapter 324

Eosinophilic Esophagitis and Non–Gastroesophageal Reflux Disease Esophagitis

Seema Khan and Susan R. Orenstein

EOSINOPHILIC ESOPHAGITIS

Eosinophilic esophagitis (EoE) is a chronic esophageal disorder characterized by infiltration of the esophageal epithelium by eosinophils, typically in a density exceeding 15 per high-power field. While infants and toddlers present commonly with vomiting, feeding problems, and poor weight gain, older children and adolescents usually experience solid food dysphagia with occasional food impactions or strictures and may complain of chest or epigastric pain. Most patients are male. The mean age at diagnosis is 7 yr (range: 1-17 yr), and the duration of symptoms is 3 yr. Many patients have other atopic diseases (or a positive family history) and associated food allergies; laboratory abnormalities can include peripheral eosinophilia and elevated immunoglobulin E (IgE) levels. The pathogenesis involves mainly T-helper type 2 cytokine-mediated pathways leading to production of a potent eosinophil chemoattractant, eotaxin-3, by esophageal epithelium. Endoscopically, the esophagus presents a granular, furrowed, ringed, or exudative appearance (Fig. 324-1); esophageal histology reveals eosinophilia, with cutpoints for diagnosis variably chosen at 15-20/high-power field. Up to 30% children with EoE have grossly normal esophageal mucosa. EoE is differentiated from gastroesophageal reflux disease by its general lack of erosive esophagitis, its greater eosinophil density, and its normal esophageal pH-multichannel intraluminal impedance results. A favorable response to proton pump inhibitor therapy should no longer be considered diagnostic of gastroesophageal reflux disease, as a subgroup of EoE patients with normal esophageal pH-multichannel intraluminal impedance also demonstrate histologic response, and constitute a proton pump inhibitor–responsive EoE group. This response may be because of an antieosinophil effect of the proton pump inhibitor class that is mediated by inhibition of eotaxin-3 secretion. Gastroesophageal reflux disease may be an important coexisting diagnosis. Evaluation of EoE should include a thorough search for food and environmental allergies via skin prick (IgE mediated) and patch (non–IgE mediated) tests.

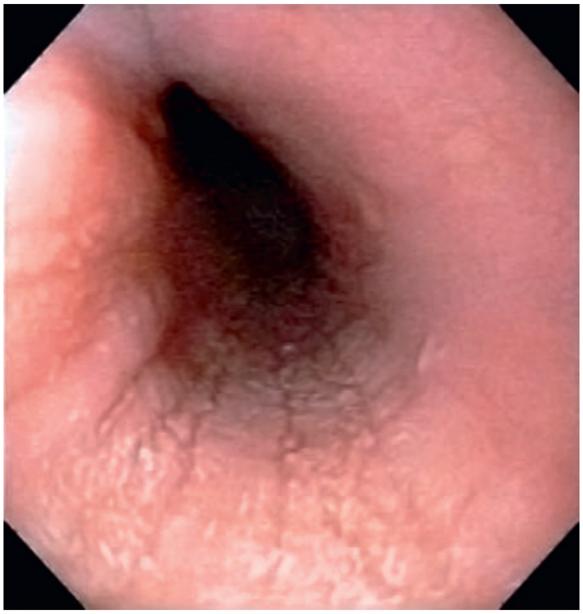

Figure 324-1 Endoscopic image of eosinophilic esophagitis with characteristic mucosal appearance of furrowing and white specks.

Treatment involves dietary restrictions that take one of 3 forms: elimination diets guided by circumstantial evidence and food allergy test results; "6 food elimination diet" removing the major food allergens (milk, soy, wheat, egg, peanuts and tree nuts, seafood); and elemental diet composed exclusively of an amino acid–based formula. Successful clinical and histologic remission is observed in 70-98% patients. Topical and systemic corticosteroids have been used successfully for nonresponders and for nonallergic ("primary") EoE, with symptomatic and histologic remission rates reaching 90%. Therapies under investigation include anti–interleukin-5 antibody (mepolizumab, reslizumab). Little is yet known about its natural history, but it seems that EoE is a chronic remitting and relapsing disorder with a potential for complications such as stricture formation.

INFECTIVE ESOPHAGITIS

Uncommon, and most often affecting immunocompromised children, infective esophagitis is caused by fungal agents, such as *Candida* and *Torulopsis glabrata;* viral agents, such as herpes simplex, cytomegalovirus, HIV, and varicella zoster; and, rarely, bacterial infections, including diphtheria and tuberculosis. The typical presenting signs and symptoms are odynophagia, dysphagia, and retrosternal pain; there may also be fever, nausea, and vomiting. Candida is the leading cause of infective esophagitis in immunocompetent and immunocompromised children, and presents with concurrent oropharyngeal infection in the majority of immunocompromised patients. Esophageal viral infections can also manifest in immunocompetent hosts as an acute febrile illness. Infectious esophagitis, like other forms of esophageal inflammation, occasionally progresses to esophageal stricture. Diagnosis of infectious esophagitis is made by endoscopy, usually notable for white plaques in candida, multiple superficial ulcers in herpes simplex virus, and single deep ulcer in cytomegalovirus, and histopathologic examination; adding polymerase chain reaction, tissue-viral culture, and immunocytochemistry enhances the diagnostic sensitivity and precision. Treatment is with appropriate antimicrobial agents, analgesics, and antacids.

"PILL" ESOPHAGITIS

This acute injury is produced by contact with a damaging agent. Medications implicated in "pill" esophagitis include tetracycline, potassium chloride, ferrous sulfate, nonsteroidal antiinflammatory medications, and alendronate. Most often the offending tablet is ingested at bedtime with inadequate water. This practice often produces acute discomfort followed by progressive retrosternal pain, odynophagia, and dysphagia. Endoscopy shows a focal lesion often localized to one of the anatomic narrowed regions of the esophagus or to an unsuspected pathologic narrowing. Treatment is supportive; lacking much evidence, antacids, topical anesthetics, and bland or liquid diets are often used.

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Chapter 325

Esophageal Perforation

Seema Khan and Susan R. Orenstein

The majority of esophageal perforations in children are from blunt trauma (automobile injury, gunshot wounds, child abuse) or are iatrogenic. Cardiac massage, the Heimlich maneuver, nasogastric tube placement, traumatic laryngoscopy or endotracheal intubation, excessively vigorous postpartum suctioning of the airway during neonatal resuscitation, difficult upper endoscopy, sclerotherapy of esophageal varices, esophageal compression by a cuffed endotracheal tube, and dilation for therapy of achalasia and strictures have all been implicated. Esophageal rupture has followed forceful vomiting in patients with anorexia and has followed esophageal injury due to caustic ingestion, foreign body ingestion, food impactions, pill esophagitis, or eosinophilic esophagitis. Drinking cold, carbonated beverages rapidly is also known to cause esophageal perforation.

Spontaneous esophageal rupture **(Boerhaave syndrome)** is less common and is associated with sudden increases in intraesophageal pressure wrought by situations such as vomiting, coughing, or straining at stool. Children and adults with eosinophilic esophagitis have also been described with Boerhaave syndrome in the setting of forceful emesis in the aftermath of esophageal food impaction. In older children, as in adults, the tear occurs on the distal left lateral esophageal wall, because the smooth muscle layer here is weakest; in neonates (neonatal Boerhaave syndrome), spontaneous rupture is on the right.

Symptoms of esophageal perforation include pain, neck tenderness, dysphagia, subcutaneous crepitus, fever, and tachycardia; several patients with cervical perforations have displayed cold water polydipsia in an attempt to soothe pain in the throat. Perforations in the proximal thoracic esophagus tend to create signs (pneumothorax, effusions) in the left chest, whereas the signs of distal tears are more often on the right. Cervical spine and chest radiographs are often diagnostic, showing mediastinal widening or paracervical free air. If these x-rays are normal, an esophagogram using water-soluble contrast media should be performed, but esophagograms miss >30% of cervical perforations. Therefore, a negative water-soluble contrast esophagogram should be followed by a barium study; the greater density of barium can better demonstrate a small defect, though with a higher risk of inflammatory mediastinitis. Endoscopy may also be useful but carries a 30% false-negative rate. CT of the chest can assist in difficult cases.

Treatment must be individualized. Small tears in contained perforations with minimal mediastinal contamination in hemodynamically stable patients can be treated conservatively with broad-spectrum antibiotics, nothing given orally, gastric drainage, and parenteral nutrition. Chest exploration and direct surgical repair is infrequently indicated these days. Mortality rates range between 20% and 28%, with poor prognosis correlated with delayed diagnosis and interventions.

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Chapter 326

Esophageal Varices

Seema Khan and Susan R. Orenstein

Esophageal varices form in adults with portal hypertension with hepatic venous pressure gradient above 10 mm Hg and pose a risk for bleeding at above 12 mm Hg (see Chapter 367). Spontaneous decompression of this hypertension through portosystemic collateral circulation via the coronary vein, in conjunction with the left gastric veins, gives rise to esophageal varices. Most esophageal varices are "uphill varices"; less commonly, those that arise in the absence of portal hypertension and with superior vena cava obstruction are "downhill varices." Their treatment is directed at the underlying cause of the superior vena cava abnormality. Hemorrhage from esophageal varices is the major cause of morbidity and mortality from portal hypertension. Presentation is with significant hematemesis and melena; whereas most patients have liver disease, some children with entities such as extrahepatic portal venous thrombosis might have been previously asymptomatic. Any child with hematemesis and splenomegaly should be presumed to have esophageal variceal bleeding until proved otherwise.

Upper endoscopy is the preferred diagnostic test for esophageal varices, as it provides definitive diagnosis and delineation of details that aid in predicting the risk for bleeding, as well as enabling therapy for acute bleeding episodes via either sclerotherapy or band ligation. A report comprising a large series of children with biliary atresia and portal hypertension described endoscopic findings of large varices, red marks, and the presence of gastric varices as predictive of bleeding. Non-invasive methods of evaluating varices include barium contrast studies, ultrasound, computerized tomography, magnetic resonance, and elastography, but they are not recommended for routine diagnostic evaluation because of suboptimal accuracy compared to endoscopy.

Primary prophylaxis with the goal of preventing an initial hemorrhage can decrease the incidence of esophageal bleeding; the various modalities used are nonselective β blockade (e.g., propranolol or nadolol), sclerotherapy, ligation, and portosystemic shunt surgery. Treated patients can bleed from congestive gastropathy, and no improvement in survival rate may be seen. Endoscopic variceal ligation in adults reduces the risk of first-time variceal bleeding when compared with untreated controls as well as patients treated with β blockade; a decrease in mortality is only noted in comparison to the control group (see Chapter 367). The management of acute variceal bleeding must include attention to hemodynamic stability through blood transfusion, vasoactive drugs (e.g., octreotide), short-term antibiotic use, and endoscopy to perform ligation or sclerotherapy, as needed. Transjugular intrahepatic portosystemic shunt should be considered for variceal bleeding refractory to medical and endoscopic therapy. Secondary prophylaxis to reduce recurrence of bleeding uses nonselective β blockade and obliteration of varices through serial treatment via ligation or sclerotherapy. The only randomized controlled pediatric study has shown superiority of ligation over sclerotherapy in reducing the risk for rebleeding and complications.

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Chapter 327 Ingestions

327.1 Foreign Bodies in the Esophagus

Seema Khan and Susan R. Orenstein

The majority (80%) of foreign-body ingestions occur in children, most of whom are between 6 mo and 3 yr of age. Older children and adolescents with developmental delays and those with psychiatric disorders are also at increased risk. The presentation of a foreign body lodged in the esophagus constitutes an emergency and is associated with significant morbidity and mortality because of the potential for perforation and sepsis. Coins and small toy items are the most commonly ingested foreign bodies. Food impactions are less common in children than in adults, and usually occur in children in association with eosinophilic esophagitis, repair of esophageal atresia, and Nissen fundoplication. Most esophageal foreign bodies lodge at the level of the cricopharyngeus (upper esophageal sphincter), the aortic arch, or just superior to the diaphragm at the gastroesophageal junction (lower esophageal sphincter).

At least 30% of children with esophageal foreign bodies may be totally asymptomatic, so any history of foreign body ingestion should be taken seriously and investigated. An initial bout of choking, gagging, and coughing may be followed by excessive salivation, dysphagia, food refusal, emesis, or pain in the neck, throat, or sternal notch regions. Respiratory symptoms such as stridor, wheezing, cyanosis, or dyspnea may be encountered if the esophageal foreign body impinges on the larynx or membranous posterior tracheal wall. Cervical swelling, erythema, or subcutaneous crepitations suggest perforation of the oropharynx or proximal esophagus.

Evaluation of the child with a history of foreign body ingestion starts with plain anteroposterior radiographs of the neck, chest, and abdomen, along with lateral views of the neck and chest. The flat surface of a coin in the esophagus is seen on the anteroposterior view and the edge on the lateral view (Fig. 327-1). The reverse is true for coins lodged in the trachea; here, the edge is seen anteroposteriorly and the flat side is seen

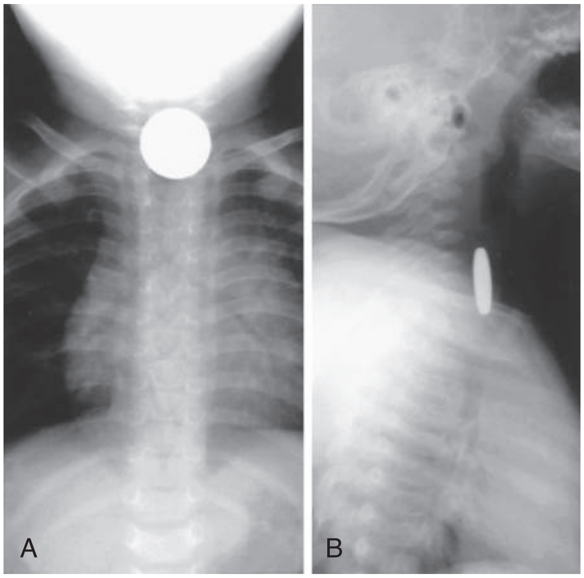

Figure 327-1 Radiographs of a coin in the esophagus. When foreign bodies lodge in the esophagus, the flat surface of the object is seen in the anteroposterior view **(A)** and the edge is seen in the lateral view **(B).** The reverse is true for objects in the trachea. *(Courtesy of Beverley Newman, MD.)*

laterally. Disk batteries can look like coins (Fig. 327-2) and have a much higher risk of burns and necrosis (Fig. 327-3). Materials such as plastic, wood, glass, aluminum, and bones may be radiolucent; failure to visualize the object with plain films in a symptomatic patient warrants urgent endoscopy. CT scan with 3-dimensional reconstruction may increase the sensitivity of imaging a foreign body. Although barium contrast studies may be helpful in the occasional asymptomatic patient with negative plain films, their use is to be discouraged because of the potential of aspiration as well as making subsequent visualization and object removal more difficult.

In managing the child with an esophageal foreign body, it is important to assess risk for airway compromise and to obtain a chest CT scan and surgical consultation in cases of suspected airway perforation. Treatment of esophageal foreign bodies usually merits endoscopic visualization of the object and underlying mucosa and removal of the object using an appropriately designed foreign-body-retrieving accessory instrument through the endoscope, and with an endotracheal tube protecting the airway. Sharp objects in the esophagus, disk button batteries, or foreign bodies associated with respiratory symptoms mandate urgent removal. Button (disk) batteries, in particular, must be expediently removed because they can induce mucosal injury in as little as 1 hr of contact time and involve all esophageal layers within 4 hr (see Fig. 327-3). Asymptomatic blunt objects and coins lodged in the esophagus can be observed for up to 24 hr in anticipation of passage into the stomach. If there are no problems in handling secretions, meat impactions can be observed for up to 12 hr. In patients without prior esophageal surgeries, glucagon (0.05 mg/kg IV) can sometimes be useful in facilitating passage of distal esophageal food boluses by decreasing the lower esophageal sphincter pressure. The use of meat tenderizers or gas-forming agents can lead to perforation and are not recommended. An alternative technique for removing esophageal coins impacted for <24 hr, performed most safely by experienced radiology personnel, consists of passage of a Foley catheter beyond the coin at fluoroscopy, inflating the balloon, and then pulling the catheter and coin back simultaneously with the patient in a prone oblique position. Concerns about the lack of direct mucosal visualization and, when tracheal intubation is not used, the lack of airway protection prompt caution in the use of this technique. Bougienage of esophageal coins toward the stomach in selected uncomplicated pediatric cases has been suggested to be an effective, safe, and economical modality where endoscopy might not be routinely available.

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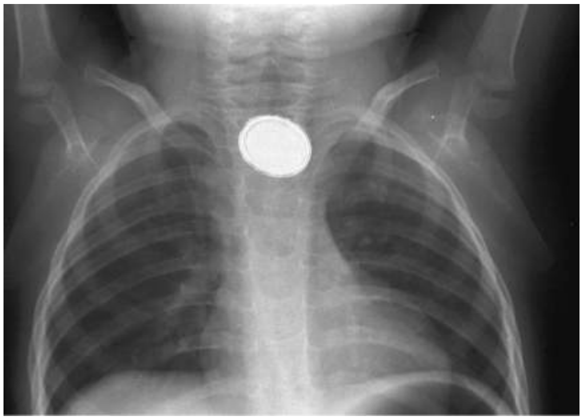

Figure 327-2 Disk battery impacted in esophagus. Note the double rim. *(From Wyllie R, Hyams JS, editors:* Pediatric gastrointestinal and liver disease, *ed 3, Philadelphia, 2006, Saunders.)*

327.2 Caustic Ingestions

Seema Khan and Susan R. Orenstein

Ingestion of caustic substances is a world-wide public health problem accounting for a significant burden on healthcare resources. According to an inpatient database of U.S. pediatric hospital discharges in 2009, the estimated number of caustic ingestions was 807 (95% CI, 731-882) cases, amounting to $22,900,000 in total hospital charges. The medical sequelae of caustic ingestions are esophagitis, necrosis, perforation, and stricture formation (see Chapter 63). Most cases (70%) are accidental ingestions of liquid alkali substances that produce severe, deep liquefaction necrosis; drain decloggers are most common, and because they are tasteless, more is ingested (Table 327-1). **Acidic agents** (20% of cases) are bitter, so less may be consumed; they produce coagulation necrosis and a somewhat protective thick eschar. They can produce severe gastritis, and volatile acids can result in respiratory symptoms. Children younger than 5 yr of age account for half of the cases of caustic ingestions, and boys are far more often involved than girls.

Caustic ingestions produce signs and symptoms such as vomiting, drooling, refusal to drink, oral burns, dysphagia, dyspnea, abdominal pain, hematemesis, and stridor. Twenty percent of patients develop esophageal strictures. Absence of oropharyngeal lesions does not exclude the possibility of significant esophagogastric injury, which can

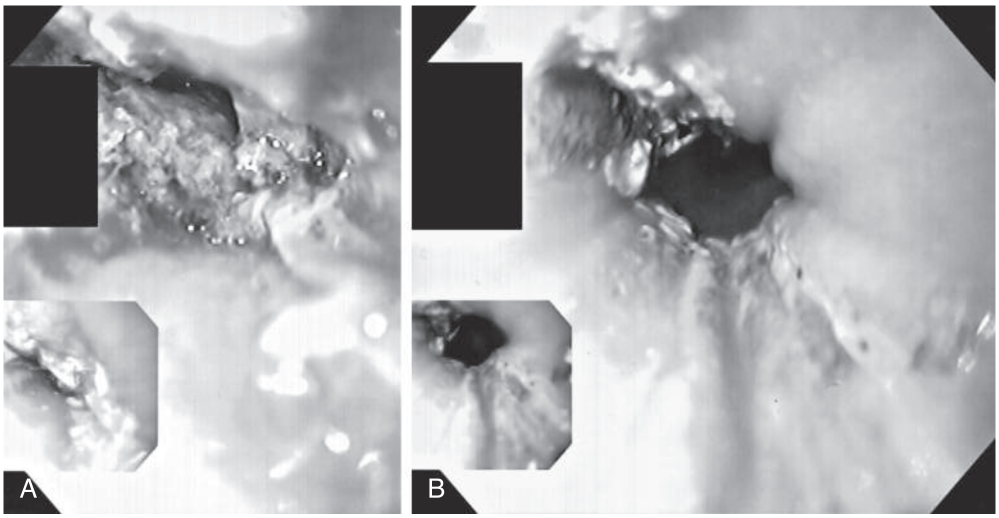

Figure 327-3 A, Disk battery in esophagus with necrotic debris at burn sites. **B,** Typical bilateral esophageal burn after removal of disk battery. *(From Wyllie R, Hyams JS, editors:* Pediatric gastrointestinal and liver disease, *ed 3, Philadelphia, 2006, Saunders.)*

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Table 327-1 Ingestible Caustic Materials Around the House

CATEGORY	MOST DAMAGING AGENTS	OTHER AGENTS
Alkaline drain cleaners, milking machine pipe cleaners	Sodium or potassium hydroxide	Ammonia Sodium hypochlorite Aluminum particles
Acidic drain openers	Hydrochloric acid Sulfuric acid	
Toilet cleaners	Hydrochloric acid Sulfuric acid Phosphoric acid Other acids	Ammonium chloride Sodium hypochlorite
Oven and grill cleaners	Sodium hydroxide Perborate (borax)	
Denture cleaners	Persulfate (sulfur) Hypochlorite (bleach)	
Dishwasher detergent • Liquid • Powdered • Packaged	Sodium hydroxide Sodium hypochlorite Sodium carbonate	
Bleach	Sodium hypochlorite	Ammonia salt
Swimming pool chemicals	Acids, alkalis, chlorine	
Battery acid (liquid)	Sulfuric acid	
Disk batteries	Electric current	Zinc or other metal salts
Rust remover	Hydrofluoric, phosphoric, oxalic, and other acids	
Household delimers	Phosphoric acid Hydroxyacetic acid Hydrochloric acid	
Barbeque cleaners	Sodium and potassium hydroxide	
Glyphosate surfactant (RoundUp) acid	Glyphosate herbicide	Surfactants
Hair relaxer	Sodium hydroxide	
Weed killer	Dichlorophenoxyacetate, ammonium phosphate, propionic acid	

Source: National Library of Medicine: Health and safety information on household products *(website).* http://householdproducts.nlm.nih.gov/
From Wylie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, *ed 4, Philadelphia, 2011, WB Saunders, Table 19-1, p. 198.*

Table 327-2 Classification of Caustic Injury

GRADE	VISIBLE APPEARANCE	CLINICAL SIGNIFICANCE
Grade 0	History of ingestion, but no visible damage or symptoms	Able to take fluids immediately
Grade 1	Edema, loss of normal vascular pattern, hyperemia, no transmucosal injury	Temporary dysphagia, able to swallow within 0-2 days, no long-term sequelae
Grade 2a	Transmucosal injury with friability, hemorrhage, blistering, exudate, scattered superficial ulceration	Scarring, no circumferential damage (no stenosis), no long-term sequelae
Grade 2b	Grade 2a plus discrete ulceration and/or circumferential ulceration	Small risk of perforation, scarring that may result in later stenosis
Grade 3a	Scattered deep ulceration with necrosis of the tissue	Risk of perforation, high risk of later stenosis
Grade 3b	Extensive necrotic tissue	High risk of perforation and death, high risk of stenosis

From Wylie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, *ed 4, Philadelphia, 2011, WB Saunders, Table 19-2, p. 199.*

lead to perforation or stricture. The absence of symptoms is usually associated with no or minimal lesions; hematemesis, respiratory distress, or presence of at least 3 symptoms predicts severe lesions. An upper endoscopy is recommended as the most efficient means of rapid identification of tissue damage and must be undertaken in all symptomatic children.

Dilution by water or milk is recommended as acute treatment, but neutralization, induced emesis, and gastric lavage are contraindicated. Treatment depends on the severity and extent of damage (Table 327-2). Stricture risk is increased by circumferential ulcerations, white plaques, and sloughing of the mucosa. Strictures can require treatment with dilation, and in some severe cases, surgical resection and colon or small bowel interposition are needed. Silicone stents (self-expanding) placed endoscopically after a dilation procedure can be an alternative and conservative approach to the management of strictures. Rare late cases of superimposed esophageal carcinoma are reported. The role of corticosteroids is controversial; they are not recommended in 1st-degree burns, but they can reduce the risk of strictures in more-advanced

caustic esophagitis. Some centers also use antibiotics in the initial treatment of caustic esophagitis on the premise that reducing superinfection in the necrotic tissue bed will, in turn, lower the risk of stricture formation. However, multiple studies examining the role of antibiotics in caustic esophagitis have not reported a clinically significant benefit even in those with grade 2 or greater severity of esophagitis.

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Section 4

Stomach and Intestines

Chapter 328

Normal Development, Structure, and Function

Chris A. Liacouras

DEVELOPMENT

The primitive gut is recognizable by the 4th wk of gestation and is composed of the foregut, midgut, and hindgut. The **foregut** gives rise to the upper gastrointestinal tract, which includes the esophagus, stomach, and duodenum to the level of the insertion of the common bile duct. The **midgut** gives rise to the rest of the small bowel and the large bowel to the level of the midtransverse colon. The **hindgut** forms the remainder of the colon and upper anal canal. The rapid growth of the midgut causes it to protrude out of the abdominal cavity through the umbilical ring during fetal development. The midgut subsequently returns to the peritoneal cavity and rotates counterclockwise until the cecum lies in the right lower quadrant. The process is normally complete by the 8th wk of gestation.

The liver derives from the hepatic diverticulum that evolves into parenchymal cells, bile ducts, vascular structures, and hematopoietic and Kupffer cells. The extrahepatic bile ducts and gallbladder develop first as solid cords that canalize by the 3rd mo of gestation. The dorsal and ventral pancreatic buds grow from the foregut by the 4th wk of gestation. The 2 buds fuse by the 6th wk. Exocrine secretory capacity is present by the 5th mo.

Cis-regulatory genomic sequences govern gene expression during development. Modules of *cis* sequences are linked and allow a cascade of gene regulation that controls functional development. Extrinsic factors have the capacity to influence gene expression. In the gut, several growth factors, including growth factor-β, insulin-like growth factor, and growth factors found in human colostrum (human growth factor and epidermal growth factor), influence gene expression.

Propulsion of food down the gastrointestinal tract relies on the coordinated action of muscles in the bowel wall. The contractions are regulated by the enteric nervous system under the influence of a variety of peptides and hormones. The enteric nervous system is derived from neural crest cells that migrate in a cranial to caudal fashion. Migration of the neural crest tissue is complete by the 24th wk of gestation. Interruption of the migration results in **Hirschsprung disease**. Newborn bowel motor patterns are different from adults. Normal fasting upper gastrointestinal motility is characterized by a triphasic pattern known as the migrating motor complex. Migrating motor complexes occur less often in neonates and they have more nonmigrating phasic activity. This leads to ineffective propulsion, particularly in premature infants. Motility in the fed state consists of a series of ring contractions that spread caudad over variable distances.

DIGESTION AND ABSORPTION

The wall of the stomach, small bowel, and colon consists of 4 layers: the mucosa, submucosa, muscularis, and serosa. Eighty-five percent of the gastric mucosa is lined by oxyntic glands containing cells that secrete hydrochloric acid, pepsinogen, and intrinsic factor, and mucous and endocrine cells that secrete peptides having paracrine and endocrine effects. Pepsinogen is a precursor of the proteolytic enzyme pepsin, and intrinsic factor is required for the absorption of vitamin B_{12}. Pyloric glands are located in the antrum and contain gastrin-secreting cells. Acid production and gastrin levels are inversely related to each other except in pathologic secretory states. Acid secretion is low at birth but increases dramatically by 24 hr. Acid and pepsin secretion peak in the 1st 10 days and decrease from 10-30 days after birth. Intrinsic factor secretion rises slowly in the 1st 2 wk of life.

The small bowel is approximately 270 cm long at birth in a term neonate and grows to an adult length of 450-550 cm by 4 yr of age. The mucosa of the small intestine is composed of villi, which are finger-like projections of the mucosa into the bowel lumen that significantly expand the absorptive surface area. The mucosal surface is further expanded by a brush border containing digestive enzymes and transport mechanisms for monosaccharides, amino acids, dipeptides and tripeptides, and fats. The cells of the villi originate in adjacent crypts and become functional as they migrate from the crypt up the villus. The small bowel mucosa is completely renewed in 4-5 days, providing a mechanism for rapid repair after injury, but in young infants or malnourished children, the process may be delayed. Crypt cells also secrete fluid and electrolytes. The villi are present by 8 wk of gestation in the duodenum and by 11 wk in the ileum.

Disaccharidase activities are measurable at 12 wk, but lactase activity does not reach maximal levels until 36 wk. Even premature infants usually tolerate lactose-containing formulas because of carbohydrate salvage by colonic bacteria. In children of African and Asian ethnicity, lactase levels may begin to fall at 4 yr of age, leading to intolerance to mammalian milk. Mechanisms to digest and absorb protein, including pancreatic enzymes and mucosal mechanisms to transport amino acids, dipeptides, and tripeptides, are in place by the 20th wk of gestation.

Carbohydrates, protein, and fat are normally absorbed by the upper half of the small intestine; the distal segments represent a vast reserve of absorptive capacity. Most of the sodium, potassium, chloride, and water are absorbed in the small bowel. Bile salts and vitamin B_{12} are selectively absorbed in the distal ileum, and iron is absorbed in the duodenum and proximal jejunum. Intraluminal digestion depends on the exocrine pancreas. Secretin and cholecystokinin stimulate synthesis and secretion of bicarbonate and digestive enzymes, which are released by the upper intestinal mucosa in response to various intraluminal stimuli, among them components of the diet.

Carbohydrate digestion is normally an efficient process that is completed in the distal duodenum. Starches are broken down to glucose, oligosaccharides, and disaccharides by pancreatic amylase. Residual glucose polymers are broken down at the mucosal level by glucoamylase. Lactose is broken down at the brush border by lactase, forming glucose and galactose; sucrose is broken down by sucrase-isomaltase to fructose and glucose. Galactose and glucose are primarily transported into the cell by a sodium- and energy-dependent process, whereas fructose is transported by facilitated diffusion.

Proteins are hydrolyzed by pancreatic enzymes, including trypsin, chymotrypsin, elastase, and carboxypeptidases, into individual amino acids and oligopeptides. The pancreatic enzymes are secreted as proenzymes, which are activated by release of the mucosal enzyme enterokinase. Oligopeptides are further broken down at the brush border by peptidases into dipeptides, tripeptides, and amino acids. Protein can enter the cell by separate noncompetitive carriers that can transport individual amino acids or dipeptides and tripeptides similar to those in the renal tubule. The human gut is capable of absorbing antigenic

intact proteins in the 1st few wk of life because of “leaky” junctions between enterocytes. Entry of potential protein antigens through the mucosal barrier might have a role in later food- and microbe-induced symptoms.

Fat absorption occurs in 2 phases. Dietary triglycerides are broken down into monoglycerides and free fatty acids by pancreatic lipase and colipase. The free fatty acids are subsequently emulsified by bile acids, forming micelles with phospholipids and other fat-soluble substances, and are transported to the cell membrane, where they are absorbed. The fats are re-esterified in the enterocyte, forming chylomicrons that are transported through the intestinal lymphatics to the thoracic duct. Medium-chain fats are absorbed more efficiently and can directly enter the cell. They are subsequently transported to the liver via the portal system. Fat absorption can be affected at any stage of the digestion and absorption process. Decreased pancreatic enzymes occur in cystic fibrosis, cholestatic liver disease leads to poor bile salt production and micelle formation, celiac disease affects mucosal surface area, abnormal chylomicron formation occurs in abetalipoproteinemia, and intestinal lymphangiectasia affects transport of the chylomicrons.

Fat absorption is less efficient in the neonate compared with adults. Premature infants can lose up to 20% of their fat calories compared with up to 6% in the adult. Decreased synthesis of bile acids and pancreatic lipase and decreased efficiency of ileal absorption are contributing factors. Fat digestion in the neonate is facilitated by lingual and gastric lipases. Bile salt–stimulated lipase in human milk augments the action of pancreatic lipase. Infants with malabsorption of fat are usually fed with formulas that have a greater percentage of medium-chain triglycerides, which are absorbed independently of bile salts.

The colon is a 75-100 cm sacculated tube formed by 3 strips of longitudinal muscle called *taenia coli* that traverse its length and fold the mucosa into haustra. Haustra and taenia appear by the 12th wk of gestation. The most common motor activity in the colon is nonpropulsive rhythmic segmentation that acts to mix the chyme and expose the contents to the colonic mucosa. Mass movement within the colon typically occurs after a meal. The colon extracts additional water and electrolytes from the luminal contents to render the stools partially or completely solid. The colon also acts to scavenge by-products of bacterial degradation of carbohydrates. Stool is stored in the rectum until distention triggers a defecation reflex that, when assisted by voluntary relaxation of the external sphincter, permits evacuation.

Chapter 329

Pyloric Stenosis and Other Congenital Anomalies of the Stomach

329.1 Hypertrophic Pyloric Stenosis

Anna K. Hunter and Chris A. Liacouras

Hypertrophic pyloric stenosis occurs in 1-3 per 1,000 infants in the United States. It is more common in whites of northern European ancestry, less common in blacks, and rare in Asians. Males (especially firstborns) are affected approximately 4-6 times as often as females. The offspring of a mother and, to a lesser extent, the father who had pyloric stenosis are at higher risk for pyloric stenosis. Pyloric stenosis develops in approximately 20% of the male and 10% of the female descendants of a mother who had pyloric stenosis. The incidence of pyloric stenosis is increased in infants with B and O blood groups. Pyloric stenosis is occasionally associated with other congenital defects, including tracheoesophageal fistula and hypoplasia or agenesis of the inferior labial frenulum.

ETIOLOGY

The cause of pyloric stenosis is unknown, but many factors have been implicated. Pyloric stenosis is usually not present at birth and is more concordant in monozygotic than dizygotic twins. It is unusual in stillbirths and probably develops after birth. Pyloric stenosis has been associated with eosinophilic gastroenteritis, Apert syndrome, Zellweger syndrome, trisomy 18, Smith-Lemli-Opitz syndrome, and Cornelia de Lange syndrome. An association has been found with the use of erythromycin in neonates with highest risk if the medication is given within the 1st 2 wk of life. There have also been reports of higher incidence of pyloric stenosis among mostly female infants of mothers treated with macrolide antibiotics during pregnancy and breastfeeding. Abnormal muscle innervation, elevated serum levels of prostaglandins, and infant hypergastrinemia has been implicated. Reduced levels of neuronal nitric oxide synthase have been found with altered expression of the neuronal nitric oxide synthase exon 1c regulatory region, which influences the expression of the neuronal nitric oxide synthase gene. Reduced nitric oxide might contribute to the pathogenesis of pyloric stenosis.

CLINICAL MANIFESTATIONS

Nonbilious vomiting is the initial symptom of pyloric stenosis. The vomiting may or may not be projectile initially but is usually progressive, occurring immediately after a feeding. Emesis might follow each feeding, or it may be intermittent. The vomiting usually starts after 3 wk of age, but symptoms can develop as early as the 1st wk of life and as late as the 5th mo. Approximately 20% have intermittent emesis from birth that then progresses to the classic picture. After vomiting, the infant is hungry and wants to feed again. As vomiting continues, a progressive loss of fluid, hydrogen ion, and chloride leads to hypochloremic metabolic alkalosis. Greater awareness of pyloric stenosis has led to earlier identification of patients with fewer instances of chronic malnutrition and severe dehydration and at times a subclinical self-resolving hypertrophy.

Hyperbilirubinemia is the most common clinical association of pyloric stenosis, also known as *icteropyloric syndrome*. Unconjugated hyperbilirubinemia is more common than conjugated and usually resolves with surgical correction. It may be associated with a decreased level of glucuronyl transferase as seen in approximately 5% of affected infants; mutations in the bilirubin uridine diphosphate glucuronosyltransferase gene *(UGT1A1)* have also been implicated. If conjugated hyperbilirubinemia is a part of the presentation, other etiologies need to be investigated. Other coexistent clinical diagnoses have been described, including eosinophilic gastroenteritis, hiatal hernia, peptic ulcer, congenital nephrotic syndrome, congenital heart disease, and congenital hypothyroidism.

The diagnosis has traditionally been established by palpating the pyloric mass. The mass is firm, movable, approximately 2 cm in length, olive shaped, hard, best palpated from the left side, and located above and to the right of the umbilicus in the midepigastrium beneath the liver's edge. The olive is easiest palpated after an episode of vomiting. After feeding, there may be a visible gastric peristaltic wave that progresses across the abdomen (Fig. 329-1).

Two imaging studies are commonly used to establish the diagnosis. Ultrasound examination confirms the diagnosis in the majority of cases. Criteria for diagnosis include pyloric thickness 3-4 mm, an overall pyloric length 15-19 mm, and pyloric diameter of 10-14 mm (Fig. 329-2). Ultrasonography has a sensitivity of approximately 95%. When contrast studies are performed, they demonstrate an elongated pyloric channel (string sign), a bulge of the pyloric muscle into the antrum (shoulder sign), and parallel streaks of barium seen in the narrowed channel, producing a "double tract sign" (Fig. 329-3).

DIFFERENTIAL DIAGNOSIS

Gastric waves are occasionally visible in small, emaciated infants who do not have pyloric stenosis. Infrequently, gastroesophageal reflux, with or without a hiatal hernia, may be confused with pyloric stenosis. Gastroesophageal reflux disease can be differentiated from pyloric stenosis by radiographic studies. Adrenal insufficiency from the adrenogenital syndrome can simulate pyloric stenosis, but the absence of a metabolic acidosis and elevated serum potassium and urinary sodium concentrations of adrenal insufficiency aid in differentiation (see Chapter 576). Inborn errors of metabolism can produce recurrent emesis with alkalosis (urea cycle) or acidosis (organic acidemia) and lethargy, coma, or seizures. Vomiting with diarrhea suggests gastroenteritis, but patients with pyloric stenosis occasionally have diarrhea. Rarely, a pyloric membrane or pyloric duplication results in projectile vomiting, visible peristalsis, and, in the case of a duplication, a palpable mass. Duodenal stenosis proximal to the ampulla of Vater results in the clinical features of pyloric stenosis but can be differentiated by the presence of a pyloric mass on physical examination or ultrasonography.

Figure 329-1 Gastric peristaltic wave in an infant with pyloric stenosis.

TREATMENT

The preoperative treatment is directed toward correcting the fluid, acid–base, and electrolyte losses. Correction of the alkalosis is essential to prevent postoperative apnea, which may be associated with anesthesia. Most infants can be successfully rehydrated within 24 hr. Vomiting usually stops when the stomach is empty, and only an occasional infant requires nasogastric suction.

The **surgical procedure of choice** is pyloromyotomy. The traditional Ramstedt procedure is performed through a short transverse skin incision. The underlying pyloric mass is cut longitudinally to the layer of the submucosa, and the incision is closed. Laparoscopic technique is equally successful and in one study resulted in a shorter time to full feedings and discharge from the hospital as well as greater parental satisfaction. The success of laparoscopy depends on the skill of the

Figure 329-3 **Barium in the stomach of an infant with projectile vomiting.** The attenuated pyloric canal is typical of congenital hypertrophic pyloric stenosis.

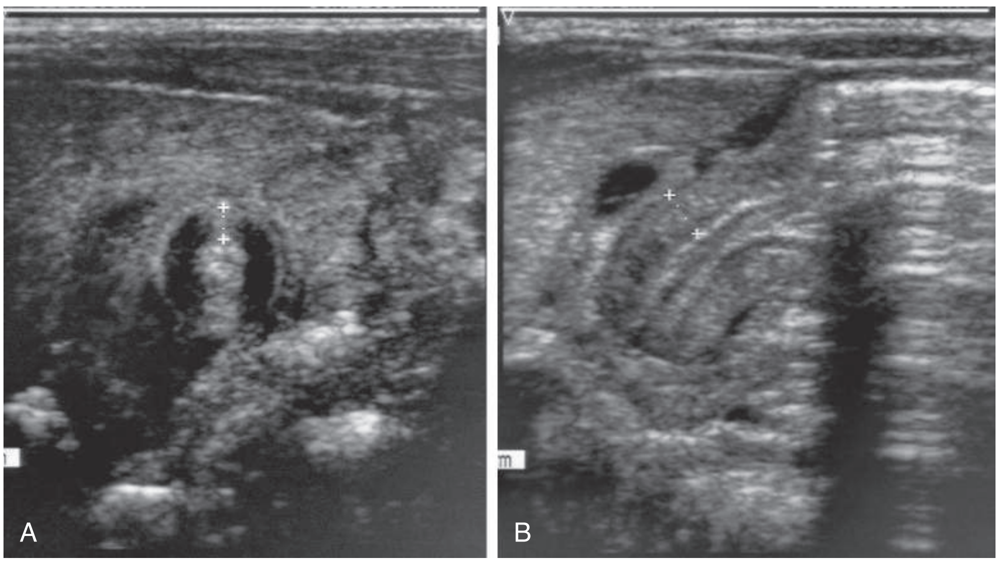

Figure 329-2 **A,** Transverse sonogram demonstrating a pyloric muscle wall thickness of >4 mm (distance between *crosses*). **B,** Horizontal image demonstrating a pyloric channel length >14 mm (wall thickness outlined between *crosses*) in an infant with pyloric stenosis.

surgeon. Postoperative vomiting occurs in half the infants and is thought to be secondary to edema of the pylorus at the incision site. In most infants, however, feedings can be initiated within 12-24 hr after surgery and advanced to maintenance oral feedings within 36-48 hr after surgery. Persistent vomiting suggests an incomplete pyloromyotomy, gastritis, gastroesophageal reflux disease, or another cause of the obstruction. The surgical treatment of pyloric stenosis is curative, with an operative mortality of 0-0.5%. Endoscopic balloon dilation has been successful in infants with persistent vomiting secondary to incomplete pyloromyotomy.

Conservative management with nasoduodenal feedings is advisable in patients who are not good surgical candidates. Oral and intravenous atropine sulfate (pyloric muscle relaxant) has also been described when surgical treatment is not available with 80% success rate described in some studies. In conservative protocols atropine is administered intravenously at a dose of 0.01 mg/kg 6 times a day 5 min before feeding. During atropine infusion, the heart rate needs to be continuously monitored by electrocardiography. Oral feeding is started at a volume of 10 mL formula, 6 times a day. The volume is increased day by day until patients tolerate 150 mL/kg/day unless vomiting occurs more than twice a day. When patients are able to tolerate the full volume of formula without vomiting more than twice a day, 0.02 mg/kg atropine is administered orally 6 times a day before feeding. As the conservative management takes longer and oral feedings may not be tolerated at first, worsening of the nutrition status may occur and total parenteral nutrition may be required. It was also postulated that surgical management is more time and cost effective.

Bibliography is available at Expert Consult.

329.2 Congenital Gastric Outlet Obstruction

Anna K. Hunter and Chris A. Liacouras

Gastric outlet obstruction resulting from pyloric atresia and antral webs is uncommon and accounts for <1% of all the atresias and diaphragms of the alimentary tract. The cause of the defects is unknown. Pyloric atresia has been associated with **epidermolysis bullosa** and usually presents in early infancy. The gender distribution is equal.

CLINICAL MANIFESTATIONS

Infants with pyloric atresia present with nonbilious vomiting, feeding difficulties, and abdominal distention during the 1st day of life. **Polyhydramnios** occurs in the majority of cases, and low birth weight is common. The gastric aspirate at birth is large (>20 mL fluid) and should be removed to prevent aspiration. Rupture of the stomach may occur as early as the 1st 12 hr of life. Infants with antral web may present with less dramatic symptoms, depending on the degree of obstruction. Older children with antral webs present with nausea, vomiting, abdominal pain, and weight loss.

DIAGNOSIS

The diagnosis of congenital gastric outlet obstruction is suggested by the finding of a large, dilated stomach on abdominal plain radiographs or in utero ultrasonography. Upper gastrointestinal (GI) contrast series is usually diagnostic and demonstrates a pyloric dimple. When contrast studies are performed, care must be taken to avoid possible aspiration. An antral web may appear as a thin septum near the pyloric channel. In older children, endoscopy has been helpful in identifying antral webs.

TREATMENT

The treatment of all causes of gastric outlet obstruction in neonates starts with the correction of dehydration and hypochloremic alkalosis. Persistent vomiting should be relieved with nasogastric decompression. Surgical or endoscopic repair should be undertaken when a patient is stable.

329.3 Gastric Duplication

Anna K. Hunter and Chris A. Liacouras

Gastric duplications are uncommon cystic or tubular structures that usually occur within the wall of the stomach. They account for 2-7% of all GI duplications. They are most commonly located on the greater curvature. Most are <12 cm in diameter and do not usually communicate with the stomach lumen; however, they do have common blood supply. Associated anomalies occur in as many as 35% of patients. Several hypotheses for the etiology of the duplication cysts have been developed including the splitting notochord theory, diverticulation, canalization defects, and caudal twinning.

The most common clinical manifestations are associated with partial or complete gastric outlet obstruction. In 33% of patients, the cyst may be palpable. Communicating duplications can cause gastric ulceration and be associated with hematemesis or melena.

Radiographic studies usually show a paragastric mass displacing stomach. Ultrasound can show the inner hyperechoic mucosal and outer hypoechoic muscle layers that are typical of GI duplications. Surgical excision is the treatment for symptomatic gastric duplications.

Bibliography is available at Expert Consult.

329.4 Gastric Volvulus

Anna K. Hunter and Chris A. Liacouras

The stomach is tethered longitudinally by the gastrohepatic, gastrosplenic, and gastrocolic ligaments. In the transverse axis, it is tethered by the gastrophrenic ligament and the retroperitoneal attachment of the duodenum. A volvulus occurs when one of these attachments is absent or elongated, allowing the stomach to rotate around itself. In some children, other associated defects are present, including intestinal malrotation, diaphragmatic defects, hiatal hernia, or adjacent organ abnormalities such as asplenia. Volvulus can occur along the longitudinal axis, producing organoaxial volvulus, or along the transverse axis, producing mesenteroaxial volvulus. Combined volvulus occurs if the stomach rotates around both organoaxial and mesenteroaxial axes.

The clinical presentation of gastric volvulus is nonspecific and suggests high intestinal obstruction. Gastric volvulus in infancy is usually associated with nonbilious vomiting and epigastric distention. It has also been associated with episodes of dyspnea and apnea in this age group. Acute volvulus can advance rapidly to strangulation and perforation. Chronic gastric volvulus is more common in older children; the children present with a history of emesis, abdominal pain and distention, early satiety, and failure to thrive.

The diagnosis is suggested in plain abdominal radiographs by the presence of a dilated stomach. Erect abdominal films demonstrate a double fluid level with a characteristic "beak" near the lower esophageal junction in mesenteroaxial volvulus. The stomach tends to lie in a vertical plane. In organoaxial volvulus, a single air–fluid level is seen without the characteristic beak with stomach lying in a horizontal plane. Upper GI series has also been used to aid the diagnosis.

Treatment of acute gastric volvulus is emergent surgery once a patient is stabilized. Laparoscopic gastropexy is the most common surgical approach. In selected cases of chronic volvulus in older patients, endoscopic correction has been successful.

Bibliography is available at Expert Consult.

329.5 Hypertrophic Gastropathy

Anna K. Hunter and Chris A. Liacouras

Hypertrophic gastropathy in children is uncommon and, in contrast to that in adults (Ménétrier disease), is usually a transient, benign, and self-limited condition.

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PATHOGENESIS

The condition is most often secondary to cytomegalovirus (CMV) infection, but other agents, including herpes simplex virus, *Giardia,* and *Helicobacter pylori,* are also implicated. The pathophysiologic mechanisms underlying the clinical picture are not completely understood but might involve widening of gap junctions between gastric epithelial cells with resultant fluid and protein losses. There is an association with increased expression of transforming growth factor-α in gastric mucosal tissue shown in CMV induced gastropathy. *H. pylori* infection can cause the elevation of serum glucagon-like peptide-2 levels, a mucosal growth-inducing gut hormone.

CLINICAL MANIFESTATIONS

Clinical manifestations include vomiting, anorexia, upper abdominal pain, diarrhea, edema (hypoproteinemic protein- losing enteropathy), ascites, and, rarely, hematemesis if ulceration occurs.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The mean age at diagnosis is 5 yr (range: 2 days-17 yr); the illness usually lasts 2-14 wk, with complete resolution being the rule. Endoscopy with biopsy and tissue CMV polymerase chain reaction is diagnostic. Endoscopy shows characteristic enlarged gastric folds. The upper GI series might show thickened gastric folds. The differential diagnosis includes eosinophilic gastroenteritis, gastric lymphoma or carcinoma, Crohn disease, and inflammatory pseudotumor.

TREATMENT

Therapy is supportive and should include adequate hydration, antisecretory agents (H_2 receptor blockade, acid suppression with proton pump inhibitors), and albumin replacement if the hypoalbuminemia is symptomatic. When *H. pylori* are detected, appropriate treatment is recommended. Ganciclovir in CMV-positive gastropathy is indicated only in severe cases. There are no official guidelines as far as the length of treatment. In practice, IV therapy is initiated for the 1st 24-48 hr. Treatment in continued with oral valganciclovir for a total of 3 wk. Complete recovery is the rule. Hypertrophic gastropathy should be considered in a previously healthy child with new onset edema and no other causes of protein losses. This is not a chronic condition in children. Disease tends to have much more severe course in adult patients.

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Chapter 330

Intestinal Atresia, Stenosis, and Malrotation

Christina Bales and Chris A. Liacouras

Approximately 1 in 1,500 children is born with intestinal obstruction. Obstruction may be partial or complete, and it may be characterized as simple or strangulating. Luminal contents fails to progress in an aboral direction in simple obstruction, whereas blood flow to the intestine is also impaired in strangulating obstruction. If strangulating obstruction is not promptly relieved, it can lead to bowel infarction and perforation.

Intestinal obstruction can be further classified as either intrinsic or extrinsic based on underlying etiology. Intrinsic causes include inherent abnormalities of intestinal innervation, mucus production, or tubular anatomy. Among these, congenital disruption of the tubular structure is most common and can manifest as obliteration (atresia) or narrowing (stenosis) of the intestinal lumen. More than 90% of intestinal stenosis and atresia occurs in the duodenum, jejunum, and ileum. Rare cases occur in the colon, and these may be associated with more proximal atresias.

Extrinsic causes of congenital intestinal obstruction involve compression of the bowel by vessels (e.g., preduodenal portal vein), organs (e.g., annular pancreas), and cysts (e.g., duplication, mesenteric). Abnormalities in intestinal rotation during fetal development also represent a unique extrinsic cause of congenital intestinal obstruction. Malrotation is associated with inadequate mesenteric attachment of the intestine to the posterior abdominal wall, which leaves the bowel vulnerable to autoobstruction as a result of intestinal twisting or volvulus. Malrotation is commonly accompanied by congenital adhesions that can compress and obstruct the duodenum as they extend from the cecum to the right upper quadrant.

Obstruction is typically associated with bowel distention, which is caused by an accumulation of ingested food, gas, and intestinal secretions proximal to the point of obstruction. As the bowel dilates, absorption of intestinal fluid is decreased and secretion of fluid and electrolytes is increased. This shift results in isotonic intravascular depletion, which is usually associated with hypokalemia. Bowel distention also results in a decrease in blood flow to the obstructed bowel. As blood flow is shifted away from the intestinal mucosa, there is loss of mucosal integrity. Bacteria proliferate in the stagnant bowel, with a predominance of coliforms and anaerobes. This rapid proliferation of bacteria, coupled with the loss of mucosal integrity, allows bacterial to translocate across the bowel wall and potentially lead to endotoxemia, bacteremia, and sepsis.

The clinical presentation of intestinal obstruction varies with the cause, level of obstruction, and time between the obstructing event and the patient's evaluation. Classic symptoms of obstruction in the neonate include vomiting, abdominal distention, and obstipation. Obstruction high in the intestinal tract results in large-volume, frequent, bilious emesis with little or no abdominal distention. Pain is intermittent and is usually relieved by vomiting. Obstruction in the distal small bowel leads to moderate or marked abdominal distention with emesis that is progressively feculent. Both proximal and distal obstructions are eventually associated with obstipation. However, meconium stools can be passed initially if the obstruction is in the upper part of the intestinal tract or if the obstruction developed late in intrauterine life.

The diagnosis of congenital bowel obstruction relies on a combination of history, physical examination, and radiologic findings. In certain cases, the diagnosis is suggested in the prenatal period. Routine prenatal ultrasound can detect polyhydramnios, which often accompanies high intestinal obstruction. The presence of polyhydramnios should prompt aspiration of the infant's stomach immediately after birth. Aspiration of more than 15-20 mL of fluid, particularly if it is bile stained, is highly indicative of proximal intestinal obstruction.

In the postnatal period, a plain radiograph is the initial diagnostic study and can provide valuable information about potential associated complications. With completely obstructing lesions, plain radiographs reveal bowel distention proximal to the point of obstruction. Upright or crosstable lateral views typically demonstrate a series of air–fluid levels in the distended loops. Caution must be exercised in using plain films to determine the location of intestinal obstruction. Because colonic haustra are not fully developed in the neonate, small and large bowel obstructions may be difficult to distinguish with plain films. In these cases, contrast studies of the bowel or computed tomography images may be indicated. Oral or nasogastric contrast medium may be used to identify obstructing lesions in the proximal bowel, and contrast enemas may be used to diagnose more-distal entities. Indeed, enemas may also play a therapeutic role in relieving distal obstruction caused by meconium ileus or meconium plug syndrome.

Initial treatment of infants and children with bowel obstruction must be directed at fluid resuscitation and stabilizing the patient. Nasogastric decompression usually relieves pain and vomiting. After appropriate cultures, broad-spectrum antibiotics are usually started in ill-appearing neonates with bowel obstruction and those with suspected strangulating infarction. Patients with strangulation must have

immediate surgical relief before the bowel infarcts, resulting in gangrene and intestinal perforation. Extensive intestinal necrosis results in short bowel syndrome (see Chapter 330.7). Nonoperative conservative management is usually limited to children with suspected adhesions or inflammatory strictures that might resolve with nasogastric decompression or anti-inflammatory medications. If clinical signs of improvement are not evident within 12-24 hr, then operative intervention is usually indicated.

Bibliography is available at Expert Consult.

330.1 Duodenal Obstruction

Christina Bales and Chris A. Liacouras

Congenital duodenal obstruction occurs in 2.5-10 per 100,000 live births. In most cases, it is caused by atresia, an intrinsic defect of bowel formation. It can also result from extrinsic compression by abnormal neighboring structures (e.g., annular pancreas, preduodenal portal vein), duplication cysts, or congenital bands associated with malrotation. Although intrinsic and extrinsic causes of duodenal obstruction occur independently, they can also coexist. Thus, a high index of suspicion for more than one underlying etiology may be critical to avoiding unnecessary reoperations in these infants.

Duodenal atresia complicates 1 per 10,000 live births and accounts for 25-40% of all intestinal atresias. In contrast to more-distal atresias, which likely arise from prenatal vascular accidents, duodenal atresia results from failed recanalization of the intestinal lumen during gestation. Throughout the 4th and 5th wk of normal fetal development, the duodenal mucosa exhibits rapid proliferation of epithelial cells. Persistence of these cells, which should degenerate after the 7th wk of gestation, leads to occlusion of the lumen (atresia) in approximately two-thirds of cases and narrowing (stenosis) in the remaining one-third. Duodenal atresia can take several forms, including a thin membrane that occludes the lumen, a short fibrous cord that connects 2 blind duodenal pouches, or a gap that spans 2 nonconnecting ends of the duodenum. The membranous form is most common, and it almost invariably occurs near the ampulla of Vater. In rare cases, the membrane is distensible and is referred to as a *windsock web*. This unusual form of duodenal atresia causes obstruction several centimeters distal to the origin of the membrane.

Approximately 50% of infants with duodenal atresia are premature. Concomitant congenital anomalies are common and include congenital heart disease (30%), malrotation (20-30%), annular pancreas (30%), renal anomalies (5-15%), esophageal atresia with or without tracheoesophageal fistula (5-10%), skeletal malformations (5%), and anorectal anomalies (5%). Of these anomalies, only complex congenital heart disease is associated with increased mortality. Annular pancreas is associated with increased late complications, including gastroesophageal reflux disease, peptic ulcer disease, pancreatitis, gastric outlet and recurrent duodenal obstruction, and gastric cancer. Thus, long-term follow-up of these patients into adulthood is warranted. Nearly half of patients with duodenal atresia have chromosome abnormalities; trisomy 21 is identified in up to one-third of patients.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The hallmark of duodenal obstruction is bilious vomiting without abdominal distention, which is usually noted on the 1st day of life. Peristaltic waves may be visualized early in the disease process. A history of polyhydramnios is present in half the pregnancies and is caused by inadequate absorption of amniotic fluid in the distal intestine. This fluid may be bile stained because of intrauterine vomiting. Jaundice is present in one-third of the infants.

The diagnosis is suggested by the presence of a "double-bubble" sign on a plain abdominal radiograph (Fig. 330-1). The appearance is caused by a distended and gas-filled stomach and proximal duodenum, which are invariably connected. Contrast studies are occasionally needed to exclude malrotation and volvulus because intestinal infarction can occur within 6-12 hr if the volvulus is not relieved. Contrast studies are generally not necessary and may be associated with aspiration. Prenatal diagnosis of duodenal atresia is readily made by fetal ultrasonography, which reveals a sonographic double-bubble. Prenatal identification of duodenal atresia is associated with decreased morbidity and fewer hospitalization days.

Figure 330-1 Abdominal radiograph of a newborn infant held upright. Note the "double-bubble" gas shadow above and the absence of gas in the distal bowel in this case of congenital duodenal atresia.

TREATMENT

The initial treatment of infants with duodenal atresia includes nasogastric or orogastric decompression and intravenous fluid replacement. Echocardiography, renal ultrasound, and radiology of the chest and spine should be performed to evaluate for associated anomalies. Definitive correction of the atresia is usually postponed until life-threatening anomalies are evaluated and treated.

The typical surgical repair for duodenal atresia is duodenoduodenostomy. This procedure is also preferred in cases of concomitant or isolated annular pancreas. In these instances, the duodenoduodenostomy is performed without dividing the pancreas. The dilated proximal bowel might have to be tapered to improve peristalsis. Postoperatively, a gastrostomy tube can be placed to drain the stomach and protect the airway. Intravenous nutritional support or a transanastomotic jejunal tube is needed until an infant starts to feed orally. Long-term prognosis is excellent, approaching 90% survival in most series.

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330.2 Jejunal and Ileal Atresia and Obstruction

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The primary etiologies of congenital small bowel obstruction involve intrinsic abnormalities in anatomic development (jejunoileal stenosis

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and atresia), mucus secretion (meconium ileus), and bowel wall innervation (long-segment Hirschsprung disease).

Jejunoileal atresias are generally attributed to intrauterine vascular accidents, which result in segmental infarction and resorption of the fetal intestine. Underlying events that potentiate vascular compromise include intestinal volvulus, intussusception, meconium ileus, and strangulating herniation through an abdominal wall defect associated with gastroschisis or omphalocele. Maternal behaviors that promote vasoconstriction, such as cigarette smoking and cocaine use, might also have a role. Only a few cases of familial inheritance have been reported. In these families, multiple intestinal atresias have occurred in an autosomal recessive pattern. Jejunoileal atresias have been linked with multiple births, low birthweight, and prematurity. Unlike atresia in the duodenum, they are not commonly associated with extraintestinal anomalies.

Five types of jejunal and ileal atresias are encountered (Fig. 330-2). In type I, a mucosal web occludes the lumen but continuity is maintained between the proximal and distal bowel. Type II involves a small-diameter solid cord that connects the proximal and distal bowel. Type III is divided into 2 subtypes. Type IIIa occurs when both ends of the bowel end in blind loops, accompanied by a small mesenteric defect. Type IIIb is similar, but it is associated with an extensive mesenteric defect and a loss of the normal blood supply to the distal bowel. The distal ileum coils around the ileocolic artery, from which it derives its entire blood supply, producing an "apple-peel" appearance. This anomaly is associated with prematurity, an unusually short distal ileum, and significant foreshortening of the bowel. Type IV involves multiple atresias. Types II and IIIa are the most common, each accounting for 30-35% of cases. Type I occurs in approximately 20% of patients. Types IIIb and IV account for the remaining 10-20% of cases, with IIIb being the least-common configuration.

Meconium ileus occurs primarily in newborn infants with cystic fibrosis, an exocrine gland defect of chloride transport that results in abnormally viscous secretions. Approximately 80-90% of infants with meconium ileus have cystic fibrosis, but only 10-15% of infants with cystic fibrosis present with meconium ileus. In simple cases, the distal 20-30 cm of ileum is collapsed and filled with pellets of pale stool. The proximal bowel is dilated and filled with thick meconium that resembles sticky syrup or glue. Peristalsis fails to propel this viscid material forward, and it becomes impacted in the ileum. In complicated cases, a volvulus of the dilated proximal bowel can occur, resulting in intestinal ischemia, atresia, and/or perforation. Perforation in utero results in meconium peritonitis, which can lead to potentially obstructing adhesions and calcifications.

Both intestinal atresia and meconium ileus must be distinguished from **long-segment Hirschsprung disease**. This condition involves congenital absence of ganglion cells in the myenteric and submucosal plexuses of the bowel wall. In a small subset (5%) of patients, the aganglionic segment includes the terminal ileum in addition to the entire length of the colon. Infants with long-segment Hirschsprung disease present with a dilated small intestine that is ganglionated but has hypertrophied walls, a funnel-shaped transitional hypoganglionic zone, and a collapsed distal aganglionic bowel.

CLINICAL MANIFESTATION AND DIAGNOSIS

Distal intestinal obstruction is less likely than proximal obstruction to be detected in utero. Polyhydramnios is identified in 20-35% of jejunoileal atresias, and it may be the first sign of intestinal obstruction. Abdominal distention is rarely present at birth, but it develops rapidly after initiation of feeds in the 1st 12-24 hr. Distention is often accompanied by vomiting, which is often bilious. Up to 80% of infants fail to pass meconium in the 1st 24 hr of life. Jaundice, associated with unconjugated hyperbilirubinemia, is reported in 20-30% of patients.

In patients with obstruction caused by jejunoileal atresia or long-segment Hirschsprung disease, plain radiographs typically demonstrate multiple air-fluid levels proximal to the obstruction in the upright or lateral decubitus positions (Fig. 330-3). These levels may be absent in patients with meconium ileus because the viscosity of the secretions in the proximal bowel prevents layering. Instead, a typical hazy or ground-glass appearance may be appreciated in the right lower quadrant. This haziness is caused by small bubbles of gas that become trapped in inspissated meconium in the terminal ileal region. If there is meconium peritonitis, patchy calcification may also be noted, particularly in the flanks. Plain films can reveal evidence of pneumoperitoneum due to intestinal perforation. Air may be seen in the subphrenic regions on the upright view and over the liver in the left lateral decubitus position.

Because plain radiographs do not reliably distinguish between small and large bowel in neonates, contrast studies are often required to localize the obstruction. Water-soluble enemas (Gastrografin, Hypaque) are particularly useful in differentiating atresia from meconium ileus and Hirschsprung disease. A small "microcolon" suggests disuse and the presence of obstruction proximal to the ileocecal valve. Abdominal ultrasound may be an important adjunctive study, which

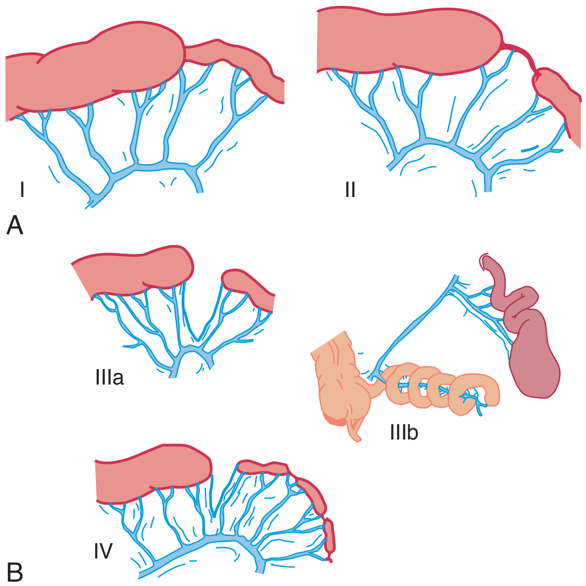

Figure 330-2 **A** and **B,** Classification of intestinal atresia. Type I: Mucosal obstruction caused by an intraluminal membrane with intact bowel wall and mesentery. Type II: Blind ends are separated by a fibrous cord. Type IIIa: Blind ends are separated by a V-shaped mesenteric defect. Type IIIb: "Apple-peel" appearance. Type IV: Multiple atresias. *(From Grosfeld J: Jejunoileal atresia and stenosis. In Welch KJ, Randolph JG, Ravitch MM, editors:* Pediatric surgery, *ed 4, Chicago, 1986, Year Book Medical Publishers.)*

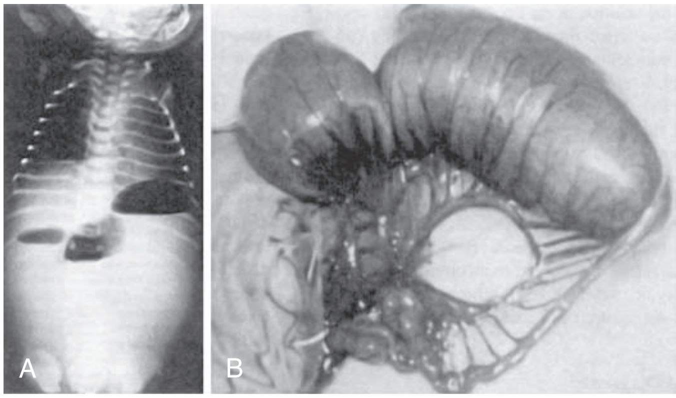

Figure 330-3 **A,** Abdominal radiograph in a neonate with bilious vomiting shows a few loops of dilated intestine with air–fluid levels. **B,** At laparotomy, a type I (mucosal) jejunal atresia was observed. *(From O'Neill JA Jr, Grosfeld JL, Fonkalsrud EW, et al, editors:* Principles of pediatric surgery, *ed 2, St. Louis, 2003, Mosby, p. 493.)*

can distinguish meconium ileus from ileal atresia and also identify concomitant intestinal malrotation.

TREATMENT

Patients with small bowel obstruction should be stable and in adequate fluid and electrolyte balance before operation or radiographic attempts at disimpaction unless volvulus is suspected. Documented infections should be treated with appropriate antibiotics. Prophylactic antibiotics are usually given before surgery.

Ileal or jejunal atresia requires resection of the dilated proximal portion of the bowel followed by end-to-end anastomosis. If a simple mucosal diaphragm is present, jejunoplasty or ileoplasty with partial excision of the web is an acceptable alternative to resection. In uncomplicated meconium ileus, Gastrografin enemas diagnose the obstruction and wash out the inspissated material. Gastrografin is hypertonic, and care must be taken to avoid dehydration, shock, and bowel perforation. The enema may have to be repeated after 8-12 hr. Resection after reduction is not needed if there have been no ischemic complications.

Approximately 50% of patients with simple meconium ileus do not adequately respond to water-soluble enemas and need laparotomy. Operative management is indicated when the obstruction cannot be relieved by repeated attempts at nonoperative management and for infants with complicated meconium ileus. The extent of surgical intervention depends on the degree of pathology. In simple meconium ileus, the plug can be relieved by manipulation or direct enteral irrigation with *N*-acetylcysteine following an enterotomy. In complicated cases, bowel resection, peritoneal lavage, abdominal drainage, and stoma formation may be necessary. Total parenteral nutrition is generally required.

Bibliography is available at Expert Consult.

330.3 Malrotation

Melissa Kennedy and Chris A. Liacouras

Malrotation is incomplete rotation of the intestine during fetal development and involves the intestinal nonrotation or incomplete rotation around the superior mesenteric artery. The gut starts as a straight tube from stomach to rectum. Intestinal rotation and attachment begins in the 5th wk of gestation when the midbowel (distal duodenum to midtransverse colon) begins to elongate and progressively protrudes into the umbilical cord until it lies totally outside the confines of the abdominal cavity. As the developing bowel rotates in and out of the abdominal cavity, the superior mesenteric artery, which supplies blood to this section of gut, acts as an axis. The duodenum, on reentering the abdominal cavity, moves to the region of the ligament of Treitz, and the colon that follows is directed to the left upper quadrant. The cecum subsequently rotates counterclockwise within the abdominal cavity and comes to lie in the right lower quadrant. The duodenum becomes fixed to the posterior abdominal wall before the colon is completely rotated. After rotation, the right and left colon and the mesenteric root become fixed to the posterior abdomen. These attachments provide a broad base of support to the mesentery and the superior mesenteric artery, thus preventing twisting of the mesenteric root and kinking of the vascular supply. Abdominal rotation and attachment are completed by the 12th wk of gestation.

Nonrotation occurs when the bowel fails to rotate after it returns to the abdominal cavity. The 1st and 2nd portions of the duodenum are in their normal position, but the remainder of the duodenum, jejunum, and ileum occupy the right side of the abdomen and the colon is located on the left. The most common type of malrotation involves failure of the cecum to move into the right lower quadrant (Fig. 330-4). The usual location of the cecum is in the subhepatic area. Failure of the cecum to rotate properly is associated with failure to form the normal broad-based adherence to the posterior abdominal wall. The mesentery, including the superior mesenteric artery, is tethered by a narrow stalk, which can twist around itself and produce a midgut volvulus. Bands of tissue **(Ladd bands)** can extend from the cecum to the right upper quadrant, crossing, and possibly obstructing, the duodenum.

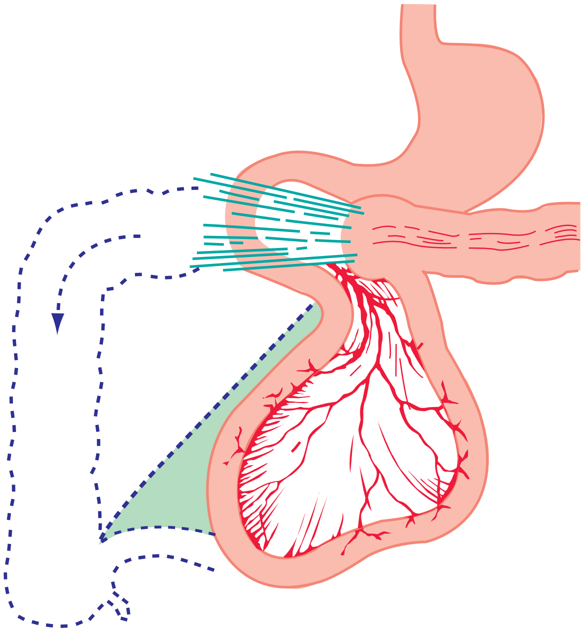

Figure 330-4 **The mechanism of intestinal obstruction with incomplete rotation of the midgut (malrotation).** The *dotted lines* show the course the cecum should have taken. Failure to rotate has left obstructing bands across the duodenum and a narrow pedicle for the midgut loop, making it susceptible to volvulus. *(From Nixon HH, O'Donnell B:* The essentials of pediatric surgery, *Philadelphia, 1961, JB Lippincott.)*

Malrotation and nonrotation are often associated with other anomalies of the abdominal wall such as diaphragmatic hernia, gastroschisis, and omphalocele. Malrotation is also associated with the heterotaxy syndrome, which is a complex of congenital anomalies including congenital heart malformations, malrotation, biliary atresia, and either asplenia or polysplenia (see Chapter 431.11).

CLINICAL MANIFESTATIONS

The reported incidence of malrotation is approximately 1 in 500 infant population. The majority, about 75-85% of patients, present in the 1st yr of life, and more than 50% present within the 1st mo of life, with symptoms of acute or chronic obstruction. Vomiting is the most common symptom in this age group. Infants often present in the 1st wk of life with **bilious emesis** and acute bowel obstruction. Older infants present with episodes of recurrent abdominal pain that can mimic colic and suggest intermittent volvulus. Malrotation in older children can manifest with recurrent episodes of vomiting and/or abdominal pain. Patients occasionally present with **malabsorption** or **protein-losing enteropathy** associated with bacterial overgrowth. Symptoms are caused by intermittent volvulus or duodenal compression by Ladd bands or other adhesive bands affecting the small and large bowel. Approximately 25-50% of adolescents with malrotation are asymptomatic. Adolescents who become symptomatic present with acute intestinal obstruction or history of recurrent episodes of abdominal pain or postprandial bloating and occasional vomiting. Patients of any age with a rotational anomaly can develop acute bowel-threatening volvulus without preexisting symptoms.

An acute presentation of small bowel obstruction in a patient without previous bowel surgery can be the result of **volvulus** associated with malrotation. This is a life-threatening complication of malrotation, which resembles an acute abdomen or sepsis and is the main reason that symptoms suggesting malrotation should always be investigated. Volvulus occurs when the small bowel twists around the

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superior mesenteric artery leading to vascular compromise of the bowel. The diagnosis may be suggested by ultrasound but is confirmed by contrast radiographic studies. The abdominal plain film is usually nonspecific but might demonstrate a gasless abdomen or evidence of duodenal obstruction with a double-bubble sign. Upper gastrointestinal series is the imaging test of choice and the gold standard in the evaluation and diagnosis of malrotation and volvulus. Normal rotation is indicates by the duodenal C-loop crossing the midline and a duodenojejunal junction located to the left of the spine. Upper gastrointestinal series is the best exam to visualize the malposition of the ligament of Treitz and can also reveal a corkscrew appearance of the small bowel or a duodenal obstruction with a "bird's beak" appearance of the duodenum. Barium enema usually demonstrates malposition of the cecum but is normal in up to 20% of patients. Ultrasonography can demonstrate the inversion of the superior mesenteric artery and vein. A superior mesenteric vein located to the left of the superior mesenteric artery suggests malrotation. Malrotation with volvulus is suggested by duodenal obstruction, thickened bowel loops to the right of the spine, the superior mesenteric vein coiling around the superior mesenteric artery, and free peritoneal fluid.

TREATMENT

Surgical intervention is recommended for any patient with a significant rotational abnormality, regardless of age. If a volvulus is present, surgery is done immediately as an acute emergency, the volvulus is reduced, and the duodenum and upper jejunum are freed of any bands and remain in the right abdominal cavity. The colon is freed of adhesions and placed in the right abdomen with the cecum in the left lower quadrant, usually accompanied by incidental appendectomy. The Ladd procedure may be done laparoscopically for malrotation without volvulus and if gut ischemia is not present, but it is generally done as an open procedure if volvulus is present. The purpose of surgical intervention is to minimize the risk of subsequent volvulus rather than to return the bowel to a normal anatomic configuration. Extensive intestinal ischemia from volvulus can result in short bowel syndrome (see Chapter 330.7).

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Chapter 331 Intestinal Duplications, Meckel Diverticulum, and Other Remnants of the Omphalomesenteric Duct

331.1 Intestinal Duplication

Chris A. Liacouras

Duplications of the intestinal tract are rare anomalies that consist of well-formed tubular or spherical structures firmly attached to the intestine with a common blood supply. The lining of the duplications resembles that of the gastrointestinal (GI) tract. Duplications are located on the mesenteric border and can communicate with the intestinal lumen. Duplications can be classified into 3 categories: localized duplications, duplications associated with spinal cord defects and vertebral malformations, and duplications of the colon. Occasionally (10-15% of cases), multiple duplications are found.

Localized duplications can occur in any area of the GI tract but are most common in the ileum and jejunum. They are usually cystic or tubular structures within the wall of the bowel. The cause is unknown, but their development has been attributed to defects in recanalization of the intestinal lumen after the solid stage of embryologic development. Duplication of the intestine occurring in association with **vertebral and spinal cord anomalies** (hemivertebra, anterior spina bifida, band connection between lesion and cervical or thoracic spine) is thought to arise from splitting of the notochord in the developing embryo. **Duplication of the colon** is usually associated with anomalies of the urinary tract and genitals. Duplication of the entire colon, rectum, anus, and terminal ileum can occur. The defects are thought to be secondary to caudal twinning, with duplication of the hindgut, genital, and lower urinary tracts.

CLINICAL MANIFESTATIONS

Symptoms depend on the size, location, and mucosal lining. Duplications can cause bowel obstruction by compressing the adjacent intestinal lumen, or they can act as the lead point of an intussusception or a site for a volvulus. If they are lined by acid-secreting mucosa, they can cause ulceration, perforation, and hemorrhage of or into the adjacent bowel. Patients can present with abdominal pain, vomiting, palpable mass, or acute GI hemorrhage. Intestinal duplications in the thorax **(neuroenteric cysts)** can manifest as respiratory distress. Duplications of the lower bowel can cause constipation or diarrhea or be associated with recurrent prolapse of the rectum.

The diagnosis is suspected on the basis of the history and physical examination. Radiologic studies such as barium studies, ultrasonography, CT, and MRI are helpful but usually nonspecific, demonstrating cystic structures or mass effects. Radioisotope technetium scanning can localize ectopic gastric mucosa. The treatment of duplications is surgical resection and management of associated defects.

331.2 Meckel Diverticulum and Other Remnants of the Omphalomesenteric Duct

Melissa Kennedy and Chris A. Liacouras

Meckel diverticulum is the most common congenital anomaly of the GI tract and is caused by the incomplete obliteration of the omphalomesenteric duct during the 7th wk of gestation. The omphalomesenteric duct connects the yolk sac to the gut in a developing embryo and provides nutrition until the placenta is established. Between the 5th and 7th wk of gestation, the duct attenuates and separates from the intestine. Just before this involution, the epithelium of the yolk sac develops a lining similar to that of the stomach. Partial or complete failure of involution of the omphalomesenteric duct results in various residual structures. Meckel diverticulum is the most common of these structures and is the most common congenital GI anomaly, occurring in 2-3% of all infants. A typical Meckel diverticulum is a 3-6 cm outpouching of the ileum along the antimesenteric border 50-75 cm (approximately 2 feet) from the ileocecal valve (Fig. 331-1). The distance from the ileocecal valve depends on the age of the patient. Meckel diverticulum has been conveniently referred to by the "rule of 2s," which explains the classic presentation of this congenital anomaly. Meckel diverticulum are found in approximately 2% of the general population, are usually located 2 feet proximal to the ileocecal valve and are approximately 2 inches in length, can contain 2 types of ectopic tissue (pancreatic or gastric), generally present before the age

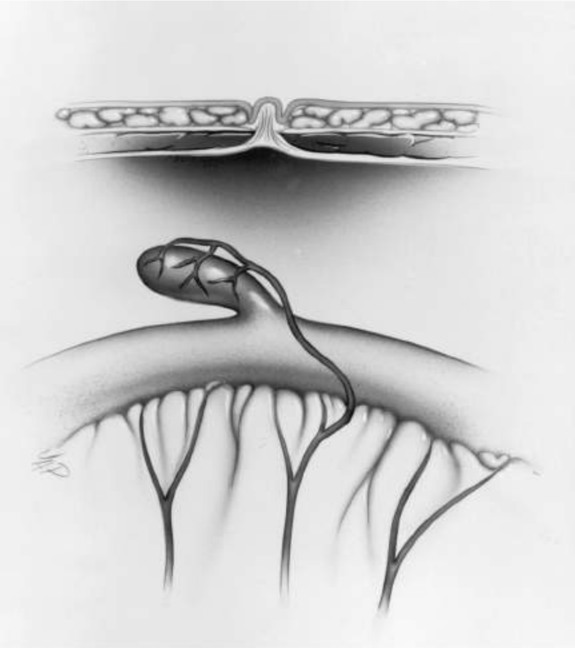

Figure 331-1 Typical Meckel diverticulum located on the antimesenteric border.

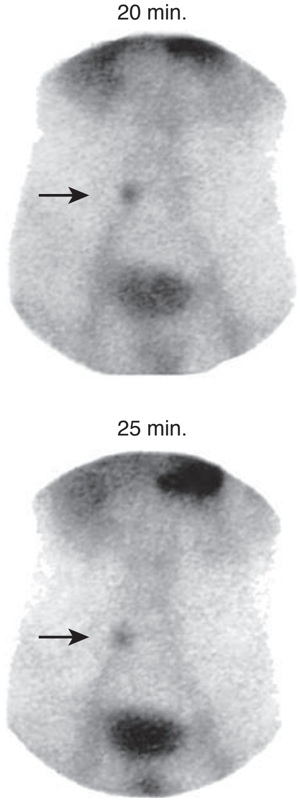

Figure 331-2 Meckel scan demonstrating accumulation of technetium in the stomach superior bladder (inferior) and in the acid-secreting mucosa of a Meckel diverticulum.

of 2 yr, and are found twice as commonly in females. Although intraabdominal in location, a rare presentation of a Meckel diverticulum is entrapment in an inguinal, umbilical, or femoral hernia (Littre hernia). Other omphalomesenteric duct remnants occur infrequently, including a persistently patent duct, a solid cord, or a cord with a central cyst or a diverticulum associated with a persistent cord between the diverticulum and the umbilicus.

CLINICAL MANIFESTATIONS

Symptoms of a Meckel diverticulum usually arise in the 1st or 2nd yr of life (average: 2.5 yr), but initial symptoms can occur in the 1st decade. The majority of symptomatic Meckel diverticula are lined by an ectopic mucosa, including an acid-secreting mucosa that causes intermittent painless rectal bleeding by ulceration of the adjacent normal ileal mucosa. This ectopic mucosa is most commonly of gastric origin, but it can also be pancreatic, jejunal, or a combination of these tissues. Unlike the upper duodenal mucosa, the acid is not neutralized by pancreatic bicarbonate.

The stool is typically described as brick colored or currant jelly colored. Bleeding can cause significant anemia but is usually self-limited because of contraction of the splanchnic vessels, as patients become hypovolemic. Bleeding from a Meckel diverticulum can also be less dramatic, with melanotic stools.

Less often, a Meckel diverticulum is associated with partial or complete bowel obstruction. The most common mechanism of obstruction occurs when the diverticulum acts as the lead point of an intussusception. The mean age of onset of obstruction is younger than that for patients presenting with bleeding. Obstruction can also result from intraperitoneal bands connecting residual omphalomesenteric duct remnants to the ileum and umbilicus. These bands cause obstruction by internal herniation or volvulus of the small bowel around the band. A Meckel diverticulum occasionally becomes inflamed **(diverticulitis)** and manifests similarly to acute appendicitis. These children are older, with a mean of 8 yr of age. Diverticulitis can lead to perforation and peritonitis.

DIAGNOSIS

The diagnosis of omphalomesenteric duct remnants depends on the clinical presentation. If an infant or child presents with significant painless rectal bleeding, the presence of a Meckel diverticulum should be suspected because Meckel diverticulum accounts for 50% of all lower GI bleeds in children younger than 2 yr of age.

Confirmation of a Meckel diverticulum can be difficult. Plain abdominal radiographs are of no value, and routine barium studies rarely fill the diverticulum. The most sensitive study is a Meckel radionuclide scan, which is performed after intravenous infusion of technetium-99m pertechnetate. The mucus-secreting cells of the ectopic gastric mucosa take up pertechnetate, permitting visualization of the Meckel diverticulum (Fig. 331-2). The uptake can be enhanced with various agents, including cimetidine, ranitidine, glucagon, and pentagastrin. The sensitivity of the enhanced scan is approximately 85%, with a specificity of approximately 95%. A false-negative scan may be seen in anemic patients; although false-positive results are uncommon, they have been reported with intussusception, appendicitis, duplication cysts, arteriovenous malformations, and tumors. Other methods of detection include radiolabeled tagged red blood cell scan (the patient must be actively bleeding), abdominal ultrasound, superior mesenteric angiography, abdominal CT scan, or exploratory laparoscopy. In patients who present with intestinal obstruction or a picture of appendicitis with omphalomesenteric duct remnants, the diagnosis is rarely made before surgery.

The treatment of a symptomatic Meckel diverticulum is surgical excision. A diverticulectomy can be performed safely as either a laparoscopic or open procedure, although most continue to be performed as open procedures. There is significant debate regarding the proper management of an asymptomatic Meckel's diverticulum and whether excision vs observation is appropriate. However, the risk of serious complications does seem to exceed the operative risk in children younger than 8 yr old.

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Chapter 332

Motility Disorders and Hirschsprung Disease

332.1 Chronic Intestinal Pseudoobstruction

Kristin N. Fiorino and Chris A. Liacouras

Chronic intestinal pseudoobstruction comprises a group of disorders characterized as a motility disorder with a primary defect of impaired peristalsis; symptoms are consistent with intestinal obstruction in the absence of mechanical obstruction. The natural history of pseudoobstruction is that of a primary progressive disorder, although there are occasional cases of secondary pseudoobstruction caused by conditions that can transiently or permanently alter bowel motility. The most common cause of acute pseudoobstruction is Ogilvie syndrome (acute pseudoobstruction of the colon). Pseudoobstruction represents a wide spectrum of pathologic disorders from abnormal myoelectric activity to abnormalities of the nerves (intestinal neuropathy) or musculature (intestinal myopathy) of the gut. The organs involved can include the entire gastrointestinal tract or be limited to certain components, although almost always include the small bowel. The distinctive pathologic abnormalities are considered together because of their clinical similarities.

Most congenital forms of pseudoobstruction occur sporadically, although autosomal dominant, autosomal recessive, X-linked, and familial patterns of inheritance have been identified. Patients with autosomal dominant forms of pseudoobstruction have variable expressions of the disease. Acquired pseudoobstruction can follow episodes of acute gastroenteritis, presumably resulting in injury to the myenteric plexus.

In congenital pseudoobstruction, abnormalities of the muscle or nerves can be demonstrated in the majority of cases. In myopathies, the smooth muscle is involved, in which the outer longitudinal muscle layer is replaced by fibrous material. The enteric nervous system is usually altered in neuropathies and may involve disorganized ganglia, hypoganglionosis, or hyperganglionosis. Abnormalities in the interstitial cells of Cajal, the intestinal pacemaker, are classified as mesenchymopathies. In others, mitochondrial defects have been identified. Genetic defects have been identified in the transcription factor *SOX10* and the DNA polymerase gamma gene (*POLG*) in mitochondriopathies.

CLINICAL MANIFESTATIONS

More than half the children with congenital pseudoobstruction experience symptoms in the 1st few mo of life. Two-thirds of the infants presenting in the 1st few days of life are born prematurely, and approximately 40% have malrotation of the intestine. In 75% of all affected children, symptoms occur in the 1st yr of life, while the remainder are usually symptomatic within the next several years. The most common symptoms are abdominal distention and vomiting, which are present in 75% of affected infants. Constipation, growth failure, and abdominal pain occur in approximately 60% of patients, and diarrhea in 30-40%. The symptoms wax and wane in the majority of the patients; poor nutrition, psychologic stress, and intercurrent illness tend to exacerbate symptoms. Urinary tract and bladder involvement occurs in 80% of children with myopathic pseudoobstruction and in 20% of those with neuropathic disease. Symptoms can manifest as recurrent urinary tract infection, megacystis, or obstructive symptoms.

Table 332-1 Findings in Pseudoobstruction

GI SEGMENT	FINDINGS*
Esophageal motility	Abnormalities in approximately half of CIPO, although in some series up to 85% demonstrate abnormalities Decreased LES pressure Failure of LES relaxation Esophageal body: low-amplitude waves, poor propagation, tertiary waves, retrograde peristalsis, occasionally aperistalsis
Gastric emptying	May be delayed
EGG	Tachygastria or bradygastria may be seen
ADM	Postprandial antral hypomotility is seen and correlates with delayed gastric emptying Myopathic subtype: low-amplitude contractions, <10-20 mm Hg Neuropathic subtype: contractions are uncoordinated, disorganized Absence of fed response Fasting MMC is absent, or MMC is abnormally propagated
Colonic	Absence of gastrocolic reflex because there is no increased motility in response to a meal
ARM	Normal rectoanal inhibitory reflex

*Findings can vary according to the segment(s) of the GI tract that are involved.

ADM, Antroduodenal manometry; ARM, anorectal manometry; CIPO, chronic intestinal pseudoobstruction; EGG, electrogastrography; GI, gastrointestinal; LES, lower esophageal sphincter; MMC, migrating motor complex.

From Steffen R: Gastrointestinal motility. In Wyllie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, *ed 3, Philadelphia, 2006, WB Saunders, p. 66.*

DIAGNOSIS

The diagnosis of pseudoobstruction is based on the presence of compatible symptoms in the absence of mechanical obstruction. Plain abdominal radiographs demonstrate air–fluid levels in the intestine. Neonates with evidence of obstruction at birth may have a microcolon. Contrast studies demonstrate slow passage of barium; water-soluble agents should be considered. Esophageal motility is abnormal in about half the patients. Antroduodenal (small intestinal) motility and gastric emptying studies have abnormal results if the upper gut is involved (Table 332-1). Manometric evidence of a normal migrating motor complex and postprandial activity should redirect the diagnostic evaluation. Anorectal motility is normal and differentiates pseudoobstruction from Hirschsprung disease. Full-thickness intestinal biopsy might show involvement of the muscle layers or abnormalities of the intrinsic intestinal nervous system.

The differential diagnosis is broad and includes such etiologies as Hirschsprung disease, mitochondrial neurogastrointestinal encephalomyopathy, other causes of mechanical obstruction, psychogenic constipation, neurogenic bladder, and superior mesenteric artery syndrome. Secondary causes of ileus or pseudoobstruction, such as hypothyroidism, opiates, scleroderma, Chagas disease, hypokalemia, diabetic neuropathy, amyloidosis, porphyria, angioneurotic edema, mitochondrial disorders, and radiation, must be excluded.

TREATMENT

Nutritional support is the mainstay of treatment for pseudoobstruction. Thirty percent to 50% of patients require partial or complete parenteral nutrition. Some patients can be treated with intermittent enteral supplementation, whereas others can maintain themselves on selective oral diets. Prokinetic drugs are generally used although studies have not shown definitive evidence of their efficacy. Isolated gastroparesis can follow episodes of viral gastroenteritis and spontaneously resolves, usually in 6-24 mo. Erythromycin, a motilin receptor agonist, and cisapride, a serotonin 5-HT_4 receptor agonist, can enhance

gastric emptying and proximal small bowel motility and may be useful in this select group of patients. Metoclopramide, a prokinetic and antinausea agent, is effective in gastroparesis, although side effects, such as tardive dyskinesia, limit its use. Domperidone, an antidopaminergic agent, is a prokinetic agent available though the government in special circumstances. Pain management is difficult and requires a multidisciplinary approach.

Symptomatic small bowel bacterial overgrowth is usually treated with rotated non-absorbable oral antibiotics and/or probiotics. Bacterial overgrowth can be associated with steatorrhea and malabsorption. Octreotide, a long-acting somatostatin analog, has been used in low doses to treat small bowel bacterial overgrowth. Patients with acid peptic symptoms are generally treated with acid suppression. Many benefit from a gastrostomy and some benefit from decompressive enterostomies. Colectomy with ileorectal anastomosis is beneficial if the large bowel is the primary site of the motility abnormality. Bowel transplantation may benefit selected patients.

Bibliography is available at Expert Consult.

332.2 Mitochondrial Neurogastrointestinal Encephalomyopathy

Kristin N. Fiorino and Chris A. Liacouras

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a multisystem autosomal recessive disease that initially presents with severe gastrointestinal disturbances; the neurologic manifestations usually occur later in the illness and may initially be subtle or asymptomatic.

MNGIE is caused by a mutation in the nuclear DNA *TYMP* gene encoding thymidine phosphorylase that results in abnormalities in intergenomic communication with resulting instability of mitochondrial DNA. There are at least 50 individual mutations with a poor genotype–phenotype correlation and varying manifestations within each family. Consanguinity is present in 30% of families.

MNGIE affects both males and females and is usually diagnosed in the 2nd and 3rd decade (average age: 18 yr; range: 5 mo-35 yr). Onset is usually around age 12 yr, but there is often a 5-10 yr delay in the diagnosis.

MNGIE initially presents with gastrointestinal symptoms. Severe intestinal dysmotility and gastroparesis is associated with early satiety, postprandial emesis, episodic pseudoobstruction, diarrhea, constipation and abdominal pain and cramping, which leads to significant cachexia. Because of the age of onset, emesis, early satiety, and cachexia patients are often misdiagnosed with an eating disorder.

Most often following the onset of gastrointestinal manifestations, ptosis, progressive external ophthalmoplegia, hearing loss and peripheral neuropathy may develop. The neuropathy is either demyelinating or a mixed axonal demyelinating type and manifests as weakness, decreased or absent deep tendon reflexes, and paresthesias. Leukoencephalopathy is initially asymptomatic and noted on MRI as patchy lesions predominantly in the cortex but also in the basal ganglia and brainstem. Eventually the central nervous system lesions become diffuse and confluent. A small number of patients develop cognitive impairment or dementia.

The diagnosis is suggested by the constellation of gastrointestinal and neurologic symptoms, lactic acidosis, ragged red fibers, and cytochrome C oxidase deficient fibers seen in most patients on muscle biopsy.

Treatment is focused on providing sufficient nutritional support and avoidance of infectious complications and of nutritional deficiencies. Stem cell transplantation has been successful in a small number of patients.

Overall the prognosis is poor with few surviving into the 4th or 5th decade.

Bibliography is available at Expert Consult.

332.3 Encopresis and Functional Constipation

Kristin N. Fiorino and Chris A. Liacouras

Constipation is defined as a delay or difficulty in defecation present for 2 wk or longer and significant enough to cause distress to the patient. Another approach to the definition is the Rome Criteria, outlined in Table 332-2. Functional constipation, also known as idiopathic constipation or fecal withholding, can usually be differentiated from constipation secondary to organic causes on the basis of a history and physical examination. Unlike anorectal malformations and Hirschsprung disease, functional constipation typically starts after the neonatal period. Usually, there is an intentional or subconscious withholding of stool. An acute episode usually precedes the chronic course. The acute episode may be a dietary change from human milk to cow's milk, secondary to the change in the protein and carbohydrate ratio or an allergy to cow's milk. The stool becomes firm, smaller, and difficult to pass, resulting in anal irritation and often an anal fissure. In toddlers, coercive or inappropriately early toilet training is a factor that can initiate a pattern of stool retention. In older children, retentive constipation can develop after entering a situation that makes stooling inconvenient such as school. Because the passage of bowel movements is painful, voluntary withholding of feces to avoid the painful stimulus develops.

CLINICAL MANIFESTATIONS

When children have the urge to defecate, typical behaviors include contracting the gluteal muscles by stiffening the legs while lying down, holding onto furniture while standing, or squatting quietly in corners, waiting for the call to stool to pass. The urge to defecate passes as the rectum accommodates to its contents. A vicious cycle of retention develops, as increasingly larger volumes of stool need to be expelled. Caregivers may misinterpret these activities as straining, but it is withholding behavior. There is often a history of blood in the stool noted with the passage of a large bowel movement. Findings suggestive of

Table 332-2	Chronic Constipation: Rome III Criteria
INFANTS AND TODDLERS	
Must include 1 mo of **at least 2** of the following in infants up to 4 yr of age: • ≤2 Defecations per week • ≥1 Episode of incontinence after the acquisition of toilet training skills • History of excessive stool retention • History of painful or hard bowel movements • Presence of a large fecal mass in the rectum • History of a large-diameter stool that might obstruct the toilet Accompanying symptoms may include irritability, decreased appetite, and/or early satiety. The accompanying symptoms disappear immediately following passage of a large stool.	
CHILDREN WITH A DEVELOPMENTAL AGE OF 4-18 YR	
Must include **2 or more** of the following in a child with a developmental age of at least 4 yr with insufficient criteria for diagnosis of irritable bowel syndrome*: • ≤2 Defecations per week • ≥1 Episode of fecal incontinence per week • History of retentive posturing or excessive volitional stool retention • History of painful or hard bowel movements • Presence of a large fecal mass in the rectum • History of a large-diameter stool that might obstruct the toilet	

*Criteria fulfilled at least once per week for at least 2 mo before diagnosis.

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underlying pathology include failure to thrive, weight loss, abdominal pain, vomiting, or persistent anal fissure or fistula.

In functional constipation, daytime encopresis is common. Encopresis is defined as voluntary or involuntary passage of feces into inappropriate places at least once a month for 3 consecutive months once a chronologic or developmental age of 4 yr has been reached. Encopresis is not diagnosed when the behavior is exclusively the result of the direct effects of a substance (e.g., laxatives) or a general medical condition (except through a mechanism involving constipation). Subtypes include retentive encopresis (with constipation and overflow incontinence) representing 65-95% of cases, and nonretentive encopresis (without constipation and overflow incontinence). **Nonretentive fecal incontinence** is defined as no evidence of fecal retention (impaction), ≥1 episodes per week in the previous 2 mo in a child at a developmental age >4 yr, defecation in places inappropriate to the social context and no evidence of anatomic, inflammatory, metabolic, endocrine, or neoplastic process that could explain the symptoms. Encopresis can persist from infancy onward (primary) or can appear after successful toilet training (secondary).

DIAGNOSIS

The physical examination often demonstrates a large volume of stool palpated in the suprapubic area; rectal examination demonstrates a dilated rectal vault filled with guaiac-negative stool. Children with encopresis often present with reports of underwear soiling, and many parents initially presume that diarrhea, rather than constipation, is the cause. In **retentive encopresis**, associated complaints of difficulty with defecation, abdominal or rectal pain, impaired appetite with poor growth, and urinary (day and/or night) incontinence are common. Children often have large bowel movements that obstruct the toilet. There may also be retentive posturing or recurrent urinary tract infections. **Nonretentive encopresis** is more likely to occur as a solitary symptom and have associated primary underlying psychological etiology. Children with encopresis can present with poor school performance and attendance that is triggered by the scorn and derision from schoolmates because of the child's offensive odor.

The presence of a hair tuft over the spine or spinal dimple, or failure to elicit a cremasteric reflex or anal wink suggests spinal pathology. A tethered cord is suggested by decreased or absent lower leg reflexes. Spinal cord lesions can occur with overlying skin anomalies. Urinary tract symptoms include recurrent urinary tract infection and enuresis. Children with no evidence of abnormalities on physical examination rarely require radiologic evaluation.

In refractory patients (intractable constipation), specialized testing should be considered to rule out conditions such as hypothyroidism, hypocalcemia, lead toxicity, celiac disease, and allergy testing. Colonic transit studies using radio-opaque markers or scintigraphy techniques may be useful. Selected children can benefit from MRI of the spine to identify an intraspinal process, motility studies to identify underlying myopathic or neuropathic bowel abnormalities, or a contrast enema to identify structural abnormalities. In patients with severe functional constipation, water-soluble contrast enema reveals the presence of a megarectosigmoid (Fig. 332-1). Anorectal motility studies can demonstrate a pattern of paradoxical contraction of the external anal sphincter during defecation, which can be treated by behavior modification and biofeedback. Colonic motility can guide therapy in refractory cases, demonstrating segmental problems that might require surgical intervention.

Complications of retentive encopresis include day and night urinary incontinence, urinary retention, urinary tract infection, megacystis, and rarely toxic megacolon.

TREATMENT

Therapy for functional constipation and encopresis includes patient education, relief of impaction, and softening of the stool. Caregivers must understand that soiling associated with overflow incontinence is associated with loss of normal sensation and not a willful act. There needs to be a focus on adherence with regular postprandial toilet sitting and adoption of a balanced diet. In addition, caregivers should be instructed not to respond to soiling with retaliatory or punitive measures, because children are likely to become angry, ashamed, and resistant to intervention. From the outset, parents should be actively encouraged to reward the child for adherence to a healthy bowel regimen and to avoid power struggles.

Figure 332-1 Barium enema in a 14 yr old boy with severe constipation. The enormous dilation of the rectum and distal colon is typical of acquired functional megacolon.

If an impaction is present on the initial physical examination, an enema is usually required to clear the impaction while stool softeners are started as maintenance medications. Typical regimens include the use of polyethylene glycol preparations, lactulose, or mineral oil (Tables 332-3 and 332-4). Prolonged use of stimulants such as senna or bisacodyl should be avoided.

Compliance can wane, and failure of this standard treatment approach sometimes requires more intensive intervention. In cases where behavioral or psychiatric problems are evident, involvement of a psychologist or behavioral management (e.g., behavior programs and/or biofeedback). Maintenance therapy is generally continued until a regular bowel pattern has been established and the association of pain with the passage of stool is abolished.

For children with chronic diarrhea and/or irritable bowel syndrome where stress and anxiety play a major role, stress reduction and learning effective coping strategies can play an important role in responding to the encopresis. Relaxation training, stress inoculation, assertiveness training, and/or general stress management procedures can be helpful. Children with spinal problems can be successfully managed with low volumes of fluid through a cecostomy or sigmoid tube.

Bibliography is available at Expert Consult.

Table 332-3 Suggested Medications and Dosages for Disimpaction

MEDICATION	AGE	DOSAGE
RAPID RECTAL DISIMPACTION		
Glycerin suppositories	Infants and toddlers	
Phosphate enema	<1 yr	60 mL
	>1 yr	6 mL/kg bodyweight, up to 135 mL twice
Milk of molasses enema	Older children	(1 : 1 milk : molasses) 200-600 mL
SLOW ORAL DISIMPACTION IN OLDER CHILDREN		
Over 2-3 Days		
Polyethylene glycol with electrolytes		25 mL/kg bodyweight/hr, up to 1000 mL/hr until clear fluid comes from the anus
Over 5-7 Days		
Polyethylene without electrolytes		1.5 g/kg bodyweight/day for 3 days
Milk of magnesia		2 mL/kg bodyweight twice/day for 7 days
Mineral oil		3 mL/kg bodyweight twice/day for 7 days
Lactulose or sorbitol		2 mL/kg bodyweight twice/day for 7 days

From Loening-Baucke V: Functional constipation with encopresis. In Wyllie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, *ed 3, Philadelphia, 2006, WB Saunders, p 183.*

Table 332-4 Suggested Medications and Dosages for Maintenance Therapy of Constipation

MEDICATION	AGE	DOSE
FOR LONG-TERM TREATMENT (YEARS)		
Milk of magnesia	>1 mo	1-3 mL/kg bodyweight/day, divided into 1-2 doses
Mineral oil	>12 mo	1-3 mL/kg bodyweight/day, divided into 1-2 doses
Lactulose or sorbitol	>1 mo	1-3 mL/kg bodyweight/day, divided into 1-2 doses
Polyethylene glycol 3350 (MiraLAX)	>1 mo	0.7 g/kg bodyweight/day, divided into 1-2 doses
FOR SHORT-TERM TREATMENT (MONTHS)		
Senna (Senokot) syrup, tablets	1-5 yr	5 mL (1 tablet) with breakfast, max 15 mL daily
	5-15 yr	2 tablets with breakfast, maximum 3 tablets daily
Glycerin enemas	>10 yr	20-30 mL/day (½ glycerin and ½ normal saline)
Bisacodyl suppositories	>10 yr	10 mg daily

From Loening-Baucke V: Functional constipation with encopresis. In Wyllie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, *ed 3, Philadelphia, 2006, WB Saunders, p. 185.*

332.4 Congenital Aganglionic Megacolon (Hirschsprung Disease)

Kristin N. Fiorino and Chris A. Liacouras

Hirschsprung disease, or congenital aganglionic megacolon, is a developmental disorder (neurocristopathy) of the enteric nervous system, characterized by the absence of ganglion cells in the submucosal and myenteric plexus. It is the most common cause of lower intestinal obstruction in neonates, with an overall incidence of 1 in 5,000 live births. The male : female ratio for Hirschsprung disease is 4 : 1 for short-segment disease, and approximately 2 : 1 with total colonic aganglionosis. Prematurity is uncommon.

There is an increased familial incidence in long-segment disease. Hirschsprung disease may be associated with other congenital defects, including trisomy 21, Joubert syndrome, Goldberg-Shprintzen syndrome, Smith-Lemli-Opitz syndrome, Shah-Waardenburg syndrome, cartilage-hair hypoplasia, multiple endocrine neoplasm 2 syndrome, neurofibromatosis, neuroblastoma, congenital hypoventilation (Ondine's curse), and urogenital or cardiovascular abnormalities. Hirschsprung disease has been seen in association with microcephaly, mental retardation, abnormal facies, autism, cleft palate, hydrocephalus, and micrognathia.

PATHOLOGY

Hirschsprung disease is the result of an absence of ganglion cells in the bowel wall, extending proximally and continuously from the anus for a variable distance. The absence of neural innervation is a consequence of an arrest of neuroblast migration from the proximal to distal bowel. Without the myenteric and submucosal plexus, there is inadequate relaxation of the bowel wall and bowel wall hypertonicity, which can lead to intestinal obstruction.

Hirschsprung disease is usually sporadic, although dominant and recessive patterns of inheritance have been demonstrated in family groups. Genetic defects have been identified in multiple genes that encode proteins of the RET signaling pathway *(RET, GDNF,* and *NTN)* and involved in the endothelin (EDN) type B receptor pathway *(EDNRB, EDN3,* and *EVE-1).* Syndromic forms of Hirschsprung disease have been associated with the *L1CAM, SOX10,* and *ZFHX1B* (formerly *SIP1*) genes.

The aganglionic segment is limited to the rectosigmoid in 80% of patients. Approximately 10-15% of patients have long-segment disease, defined as disease proximal to the sigmoid colon. Total bowel aganglionosis is rare and accounts for approximately 5% of cases. Observed histologically is an absence of Meissner's and Auerbach's plexuses and hypertrophied nerve bundles with high concentrations of acetylcholinesterase between the muscular layers and in the submucosa.

CLINICAL MANIFESTATIONS

Hirschsprung disease is usually diagnosed in the neonatal period secondary to a distended abdomen, failure to pass meconium, and/or bilious emesis or aspirates with feeding intolerance. In 99% of healthy full-term infants, meconium is passed within 48 hr of birth. Hirschsprung disease should be suspected in any full-term infant (the disease is unusual in preterm infants) with delayed passage of stool. Some neonates pass meconium normally but subsequently present with a history of chronic constipation. Failure to thrive with hypoproteinemia from protein-losing enteropathy is a less common presentation because Hirschsprung disease is usually recognized early in the course of the illness. Breastfed infants might not suffer disease as severe as formula-fed infants.

Failure to pass stool leads to dilation of the proximal bowel and abdominal distention. As the bowel dilates, intraluminal pressure

Table 332-5 Distinguishing Features of Hirschsprung Disease and Functional Constipation

VARIABLE	FUNCTIONAL	HIRSCHSPRUNG DISEASE
HISTORY		
Onset of constipation	After 2 yr of age	At birth
Encopresis	Common	Very rare
Failure to thrive	Uncommon	Possible
Enterocolitis	None	Possible
Forced bowel training	Usual	None
EXAMINATION		
Abdominal distention	Uncommon	Common
Poor weight gain	Rare	Common
Rectum	Filled with stool	Empty
Rectal examination	Stool in rectum	Explosive passage of stool
Malnutrition	None	Possible
INVESTIGATIONS		
Anorectal manometry	Relaxation of internal anal sphincter	Failure of internal anal sphincter relaxation
Rectal biopsy	Normal	No ganglion cells, increased acetylcholinesterase staining
Barium enema	Massive amounts of stool, no transition zone	Transition zone, delayed evacuation (>24 hr)

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increases, resulting in decreased blood flow and deterioration of the mucosal barrier. Stasis allows proliferation of bacteria, which can lead to enterocolitis (*Clostridium difficile, Staphylococcus aureus,* anaerobes, coliforms) with associated diarrhea, abdominal tenderness, sepsis and signs of bowel obstruction. Early recognition of Hirschsprung disease before the onset of enterocolitis is essential in reducing morbidity and mortality.

Hirschsprung disease in older patients must be distinguished from other causes of abdominal distention and chronic constipation (Table 332-5 and Fig. 332-2). The history often reveals constipation starting in infancy that has responded poorly to medical management. Fecal incontinence, fecal urgency, and stool-withholding behaviors are usually not present. The abdomen is tympanitic and distended, with a large fecal mass palpable in the left lower abdomen. Rectal examination demonstrates a normally placed anus that easily allows entry of the finger but feels snug. The rectum is usually empty of feces, and when the finger is removed, there may be an explosive discharge of foul-smelling feces and gas. The stools, when passed, can consist of small pellets, be ribbon-like, or have a fluid consistency, unlike the large stools seen in patients with functional constipation. Intermittent attacks of intestinal obstruction from retained feces may be associated with pain and fever. Urinary retention with enlarged balder or hydronephrosis can occur secondary to urinary compression.

In neonates, Hirschsprung disease must be differentiated from meconium plug syndrome, meconium ileus, and intestinal atresia. In older patients, the **Currarino triad** must be considered, which includes anorectal malformations (ectopic anus, anal stenosis, imperforate anus), sacral bone anomalies (hypoplasia, poor segmentation), and presacral anomaly (anterior meningoceles, teratoma, cyst).

Figure 332-2 Lateral view of a barium enema in a 3 yr old girl with Hirschsprung disease. The aganglionic distal segment is narrow, with distended normal ganglionic bowel above it.

DIAGNOSIS

Rectal suction biopsy is the gold standard for diagnosing Hirschsprung disease. The biopsy material should contain an adequate amount of submucosa to evaluate for the presence of ganglion cells. To avoid obtaining biopsies in the normal area of hypoganglionosis, which ranges from 3-17 mm in length, the suction rectal biopsy should be obtained no closer than 2 cm above the dentate line. The biopsy specimen should be stained for acetylcholinesterase to facilitate interpretation. Patients with aganglionosis demonstrate a large number of hypertrophied nerve bundles that stain positively for acetylcholinesterase with an absence of ganglion cells. Calretinin staining may provide a diagnosis of Hirschsprung disease when acetylcholinesterase staining may not be sufficient.

Anorectal manometry evaluates the internal anal sphincter while a balloon is distended in the rectum. In healthy individuals, rectal distention initiates relaxation of the internal anal sphincter in response to rectal distention. In patients with Hirschsprung disease, the internal anal sphincter fails to relax in response to rectal distention. Although the sensitivity and specificity can vary widely, in experienced hands, the test can be quite sensitive. The test, however, can be technically difficult to perform in young infants. A normal response in the course of manometric evaluation precludes a diagnosis of Hirschsprung disease; an equivocal or paradoxical response requires a repeat motility or rectal biopsy.

An unprepared contrast enema is most likely to aid in the diagnosis in children older than 1 mo of age because the proximal ganglionic segment might not be significantly dilated in the 1st few wk of life. Classic findings are based on the presence of an abrupt narrow transition zone between the normal dilated proximal colon and a smaller-caliber obstructed distal aganglionic segment. In the absence of this finding, it is imperative to compare the diameter of the rectum to that of the sigmoid colon, because a rectal diameter that is the same as or smaller than the sigmoid colon suggests Hirschsprung disease. Radiologic evaluation should be performed without preparation to prevent transient dilation of the aganglionic segment. As many as 10% of newborns with Hirschsprung disease have a normal contrast study. Twenty-four-hour delayed films are helpful in showing retained contrast (see Fig. 332-2). If significant barium is still present in the colon, it increases the suspicion of Hirschsprung disease even if a transition zone is not identified. Barium enema examination is useful in determining the extent of aganglionosis before surgery and in evaluating other diseases that manifest as lower bowel obstruction in a neonate. Full-thickness rectal biopsies can be performed at the time of surgery to confirm the diagnosis and level of involvement.

TREATMENT

Once the diagnosis is established, the definitive treatment is operative intervention. Previously, a temporary ostomy was placed and definitive surgery was delayed until the child was older. Currently, many infants undergo a primary pull-through procedure except if there is associated enterocolitis or other complications, when a decompressing ostomy is usually required.

There are 3 basic surgical options. The first successful surgical procedure, described by Swenson, was to excise the aganglionic segment and anastomose the normal proximal bowel to the rectum 1-2 cm above the dentate line. The operation is technically difficult and led to the development of 2 other procedures. Duhamel described a procedure to create a neorectum, bringing down normally innervated bowel behind the aganglionic rectum. The neorectum created in this procedure has an anterior aganglionic segment with normal sensation and a posterior ganglionic segment with normal propulsion. The endorectal pull-through procedure described by Soave involves stripping the mucosa from the aganglionic rectum and bringing normally innervated colon through the residual muscular cuff, thus bypassing the abnormal bowel from within. Advances in techniques have led to successful laparoscopic single-stage endorectal pull-through procedures, which are the treatment of choice.

In ultrashort-segment Hirschsprung disease, also known as anal achalasia, the aganglionic segment is limited to the internal sphincter. The clinical symptoms are similar to those of children with functional constipation. Ganglion cells are present on rectal suction biopsy, but the anorectal manometry is abnormal, with failure of relaxation of the internal anal sphincter in response to rectal distention. Current treatment, although controversial, includes anal botulism injection to relax the anal sphincter and anorectal myectomy if indicated.

Long-segment Hirschsprung disease involving the entire colon and, at times, part of the small bowel presents a difficult problem. Anorectal manometry and rectal suction biopsy demonstrate findings of Hirschsprung disease, but radiologic studies are difficult to interpret because a colonic transition zone cannot be identified. The extent of aganglionosis can be determined accurately by biopsy at the time of laparotomy. When the entire colon is aganglionic, often together with a length of terminal ileum, ileal-anal anastomosis is the treatment of choice, preserving part of the aganglionic colon to facilitate water absorption, which helps the stools to become firm.

The prognosis of surgically treated Hirschsprung disease is generally satisfactory; the great majority of patients achieve fecal continence. Long-term postoperative problems include constipation, recurrent enterocolitis, stricture, prolapse, perianal abscesses, and fecal soiling. Some children require myectomy or a redo pull-through procedure.

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332.5 Intestinal Neuronal Dysplasia

Kristin N. Fiorino and Chris A. Liacouras

Intestinal neuronal dysplasia (IND) describes different quantitative (hypo- or hyperganglionosis) and qualitative (immature or heterotropic ganglion cells) abnormalities of the myenteric and/or submucosal plexus. The typical histology is that of hyperganglionosis and giant ganglia. Type A occurs very rarely and is characterized by congenital aplasia or hypoplasia of the sympathetic innervation. Patients present early in the neonatal period with episodes of intestinal obstruction, diarrhea, and bloody stools. Type B, which accounts for more than 95% of cases, is characterized by malformation of the parasympathetic submucous and myenteric plexus with giant ganglia and thickened nerve fibers, increased acetylcholinesterase staining, and isolated ganglion cells in the lamina propria. IND type B mimics Hirschsprung disease, and patients present with chronic constipation.

Clinical manifestations include abdominal distention, constipation, and enterocolitis. Various lengths of bowel may be affected from segmental to the entire intestinal tract. IND has been observed in an isolated form and proximal to an aganglionic segment. Other intra- and extraintestinal manifestations are present in patients with IND. It has been reported in all age groups, most commonly in infancy, but is also seen in adults who have had constipation not dating back to childhood.

Associated diseases and conditions include Hirschsprung disease, prematurity, small left colon syndrome, and meconium plug syndrome. Studies have identified a deficiency in substance P in patients with IND. No mutations in the coding regions of the *RET*, *GDNF*, *EDNRB*, or *EDN3* genes have been identified.

Management includes that for functional constipation and, if unsuccessful, surgery is indicated.

Bibliography is available at Expert Consult.

332.6 Superior Mesenteric Artery Syndrome (Wilkie Syndrome, Cast Syndrome, Arteriomesenteric Duodenal Compression Syndrome)

Andrew Chu and Chris A. Liacouras

Superior mesenteric artery syndrome results from compression of the 3rd duodenal segment by the artery against the aorta. Malnutrition or catabolic states may cause mesenteric fat depletion, which collapses the duodenum within a narrowed aortomesenteric angle. Other etiologies include extraabdominal compression (e.g., body cast) and mesenteric tension, as can occur from ileoanal pouch anastomosis.

Symptoms include intermittent epigastric pain, anorexia, nausea, and vomiting. Risk factors include thin body habitus, prolonged bed rest, abdominal surgery, and exaggerated lumbar lordosis. Onset can be within weeks of a trigger, but some patients have chronic symptoms that evade diagnosis. A classic example is an underweight adolescent who begins vomiting 1-2 wk following scoliosis surgery. Recognition may be delayed in the context of an eating disorder.

The diagnosis is established radiologically by demonstrating a duodenal cutoff just right of midline along with proximal duodenal dilation, with or without gastric dilation. Although the upper gastrointestinal series remains a mainstay, modalities including CT, MR angiography, or ultrasound may be more appropriate if there is concern for other etiologies like malignancy. Upper endoscopy should be considered to rule out intraluminal pathology.

Treatment focuses on obstructive relief, nutritional rehabilitation, and correction of associated fluid and electrolyte abnormalities. Lateral or prone positioning can shift the duodenum away from obstructing structures and allow resumption of oral intake. In such cases, prokinetic agents (e.g., erythromycin) may be helpful. If repositioning is

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unsuccessful, patients require nasojejunal enteral nutrition past the obstruction or parenteral nutrition if this is not tolerated. Patients with refractory courses may require surgery to bypass the obstruction.

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Chapter 333
Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions

333.1 Ileus

Andrew Chu and Chris A. Liacouras

Ileus is the failure of intestinal peristalsis caused by loss of coordinated gut motility without evidence of mechanical obstruction. In children, it is most often associated with abdominal surgery or infection (gastroenteritis, pneumonia, peritonitis). Ileus also accompanies metabolic abnormalities (e.g., uremia, hypokalemia, hypercalcemia, hypermagnesemia, acidosis) or administration of certain drugs, such as opiates, vincristine, and antimotility agents such as loperamide when used during gastroenteritis.

Ileus manifests with nausea, vomiting, feeding intolerance, abdominal distention with associated pain, and delayed passage of stool and bowel gas. Bowel sounds are minimal or absent, in contrast to early mechanical obstruction, when they are hyperactive. Abdominal radiographs demonstrate multiple air–fluid levels throughout the abdomen. Serial radiographs usually do not show progressive distention as they do in mechanical obstruction. Contrast radiographs, if performed, demonstrate slow movement of barium through a patent lumen. Ileus after abdominal surgery generally resolves in within 72 hr.

Treatment involves correcting the underlying abnormality, supportive care of comorbidities, and mitigation of iatrogenic contributions. Electrolyte abnormalities should be identified and corrected, and narcotic agents, when used, should be weaned as tolerated. Nasogastric decompression can relieve recurrent vomiting or abdominal distention associated with pain; resultant fluid losses should be corrected with isotonic crystalloid solution. Prokinetic agents such as erythromycin are not routinely recommended. Selective peripheral opioid antagonists such as methylnaltrexone hold promise in decreasing postoperative ileus, but pediatric data are lacking.

Bibliography is available at Expert Consult.

333.2 Adhesions

Andrew Chu and Chris A. Liacouras

Adhesions are fibrous tissue bands that result from peritoneal injury. They can constrict hollow organs and are a major cause of postoperative small bowel obstruction. Most remain asymptomatic, but problems can arise anytime after the 2nd postoperative week to years after surgery, regardless of surgical extent. In one study, the 5-year readmission risk because of adhesions varied by operative region (2.1% for colon to 9.2% for ileum) and procedure (0.3% for appendectomy to 25% for ileostomy formation/closure). The overall risk was 5.3% excluding appendectomy and 1.1% when appendectomy was included.

The diagnosis is suspected in patients with abdominal pain, constipation, emesis, and a history of intraperitoneal surgery. Nausea and vomiting quickly follow onset of pain. Initially, bowel sounds are hyperactive, and the abdomen is flat. Subsequently, bowel sounds disappear, and bowel dilation can cause abdominal distention. Fever and leukocytosis suggest bowel necrosis and peritonitis. Plain radiographs demonstrate obstructive features, and a CT scan or contrast studies may be needed to define the etiology.

Management includes nasogastric decompression, intravenous fluid resuscitation, and broad-spectrum antibiotics in preparation for surgery. Nonoperative intervention is contraindicated unless a patient is stable with obvious clinical improvement. In children with repeated obstruction, fibrin-glued plication of adjacent small bowel loops can reduce the risk of recurrent problems. Long-term complications include female infertility, failure to thrive, and chronic abdominal and/or pelvic pain.

Bibliography is available at Expert Consult.

333.3 Intussusception

Melissa Kennedy and Chris A. Liacouras

Intussusception occurs when a portion of the alimentary tract is telescoped into an adjacent segment. It is the most common cause of intestinal obstruction between 5 mo and 3 yr of age and the most common abdominal emergency in children younger than 2 yr. Sixty percent of patients are younger than 1 yr of age, and 80% of the cases occur before age 24 mo; it is rare in neonates. The incidence varies from 1 to 4 per 1,000 live births. The male : female ratio is 3 : 1. Many small bowel–small bowel and a few small bowel–colonic intussusceptions reduce spontaneously; if left untreated, ileal–colonic intussusception may lead to intestinal infarction, perforation, peritonitis, and death.

ETIOLOGY AND EPIDEMIOLOGY

Approximately 90% of cases of intussusception in children are idiopathic. The seasonal incidence has peaks in fall and winter. Correlation with prior or concurrent respiratory adenovirus (type C) infection has been noted, and the condition can complicate otitis media, gastroenteritis, Henoch-Schönlein purpura, or other upper respiratory tract infections. The risk of intussusception was increased in infants 1 yr of age or younger after receiving a tetravalent rhesus-human reassortant rotavirus vaccine within 2 wk of immunization. The Advisory Committee on Immunization Practices no longer recommends this vaccine, and it is no longer available. Although rotavirus produces an enterotoxin, there is no association between wild-type human rotavirus and intussusception. The currently approved rotavirus vaccines are associated with a slightly increased risk of intussusception.

It is postulated that gastrointestinal infection or the introduction of new food proteins results in swollen Peyer patches in the terminal ileum. Lymphoid nodular hyperplasia is another related risk factor. Prominent mounds of lymph tissue lead to mucosal prolapse of the ileum into the colon, thus causing an intussusception. In 2-8% of patients, **recognizable lead points** for the intussusception are found, such as a Meckel diverticulum, intestinal polyp, neurofibroma, intestinal duplication cysts, inverted appendix stump, leiomyomas, hamartomas, ectopic pancreatic tissue, anastomotic suture line, enterostomy tube, posttransplant lymphoproliferative disease, hemangioma, or malignant conditions such as lymphoma, or Kaposi sarcoma. Lead points are more common in children older than 2 yr of age; the older the child, the higher the risk of a lead point. In adults, lead points are present in 90%. Intussusception can complicate mucosal hemorrhage, as in Henoch-Schönlein purpura, idiopathic thrombocytopenic purpura, or hemophilia. Cystic fibrosis, celiac disease, and Crohn disease are other risk factors. Postoperative intussusception is ileoileal and usually occurs within several days of an abdominal operation. Intrauterine intussusception may be associated with the development of intestinal atresia. Intussusception in premature infants is rare.

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Ileal–ileal intussusception may be more common than previously believed, is often idiopathic or associated with Henoch-Schönlein purpura, and usually resolves spontaneously.

PATHOLOGY

Intussusceptions are most often ileocolic, less commonly cecocolic, and occasionally ileal. Very rarely, the appendix forms the apex of an intussusception. The upper portion of bowel, the **intussusceptum,** invaginates into the lower, the **intussuscipiens,** pulling its mesentery along with it into the enveloping loop. Constriction of the mesentery obstructs venous return; engorgement of the intussusceptum follows, with edema, and bleeding from the mucosa leads to a bloody stool, sometimes containing mucus. The apex of the intussusception can extend into the transverse, descending, or sigmoid colon, even to and through the anus in neglected cases. This presentation must be distinguished from rectal prolapse. Most intussusceptions do not strangulate the bowel within the 1st 24 hr but can eventuate in intestinal gangrene and shock.

CLINICAL MANIFESTATIONS

In typical cases, there is sudden onset, in a previously well child, of severe paroxysmal colicky pain that recurs at frequent intervals and is accompanied by straining efforts with legs and knees flexed and loud cries. The infant may initially be comfortable and play normally between the paroxysms of pain; but if the intussusception is not reduced, the infant becomes progressively weaker and lethargic. At times, the **lethargy** is disproportionate to the abdominal signs. Eventually, a shock-like state, with fever and peritonitis, can develop. The pulse becomes weak and thready, the respirations become shallow and grunting, and the pain may be manifested only by moaning sounds. Vomiting occurs in most cases and is usually more frequent in the early phase. In the later phase, the vomitus becomes bile stained. Stools of normal appearance may be evacuated in the 1st few hr of symptoms. After this time, fecal excretions are small or more often do not occur, and little or no flatus is passed. Blood is generally passed in the 1st 12 hr, but at times not for 1-2 days, and infrequently not at all; 60% of infants pass a stool containing red blood and mucus, the currant jelly stool. Some patients have only irritability and alternating or progressive lethargy. The classic triad of pain, a palpable sausage-shaped abdominal mass, and bloody or currant jelly stool is seen in <30% of patients with intussusception. The combination of paroxysmal pain, vomiting and a palpable abdominal mass has a positive predictive value of >90%; the presence of rectal bleeding increases this to approximately 100%.

Palpation of the abdomen usually reveals a slightly tender sausage-shaped mass, sometimes ill defined, which might increase in size and firmness during a paroxysm of pain and is most often in the right upper abdomen, with its long axis cephalocaudal. If it is felt in the epigastrium, the long axis is transverse. Approximately 30% of patients do not have a palpable mass. The presence of bloody mucus on rectal examination supports the diagnosis of intussusception. Abdominal distention and tenderness develop as intestinal obstruction becomes more acute. On rare occasions, the advancing intestine prolapses through the anus. *This prolapse can be distinguished from prolapse of the rectum by the separation between the protruding intestine and the rectal wall, which does not exist in prolapse of the rectum.*

Ileoileal intussusception in children younger than 2 yr can have a less-typical clinical picture, the symptoms and signs being chiefly those of small intestinal obstruction; these often resolve without treatment. **Recurrent intussusception** is noted in 5-8% and is more common after hydrostatic than surgical reduction. Chronic intussusception, in which the symptoms exist in milder form at recurrent intervals, is more likely to occur with or after acute enteritis and can arise in older children as well as in infants.

DIAGNOSIS

When the clinical history and physical findings suggest intussusception, an ultrasound is typically performed. A plain abdominal radiograph might show a density in the area of the intussusception. Screening

Figure 333-1 Transverse image of an ileocolic intussusception. Note the loops within the loops of bowel.

ultrasounds for suspected intussusception increases the yield of diagnostic or therapeutic enemas and reduces unnecessary radiation exposure in children with negative ultrasound examinations. The diagnostic findings of intussusception on ultrasound include a tubular mass in longitudinal views and a doughnut or target appearance in transverse images (Fig. 333-1). Ultrasound has a sensitivity of approximately 98-100% and a specificity of approximately 98% in diagnosing intussusception. Air, hydrostatic (saline), and, less often, water-soluble contrast enemas have replaced barium examinations. Contrast enemas demonstrate a filling defect or cupping in the head of the contrast media where its advance is obstructed by the intussusceptum (Fig. 333-2). A central linear column of contrast media may be visible in the compressed lumen of the intussusceptum, and a thin rim of contrast may be seen trapped around the invaginating intestine in the folds of mucosa within the intussuscipiens (coiled-spring sign), especially after evacuation. Retrogression of the intussusceptum under pressure and visualized on x-ray or ultrasound documents successful reduction. Air reduction is associated with fewer complications and lower radiation exposure than traditional contrast hydrostatic techniques.

DIFFERENTIAL DIAGNOSIS

It may be particularly difficult to diagnose intussusception in a child who already has gastroenteritis; a change in the pattern of illness, in the character of pain, or in the nature of vomiting or the onset of rectal bleeding should alert the physician. The bloody stools and abdominal cramps that accompany enterocolitis can usually be differentiated from intussusception because in enterocolitis the pain is less severe and less regular, there is diarrhea, and the infant is recognizably ill between pains. Bleeding from a Meckel diverticulum is usually painless. Joint symptoms, purpura, or hematuria usually but not invariably accompany the intestinal hemorrhage of Henoch-Schönlein purpura. Because intussusception can be a complication of this disorder, ultrasonography may be needed to distinguish the conditions.

Figure 333-2 Intussusception in an infant. The obstruction is evident in the proximal transverse colon. Contrast material between the intussusceptum and the intussuscipiens is responsible for the coiled-spring appearance.

It is important in patients with cystic fibrosis to distinguish intussusception from distal intestinal obstruction syndrome. Distal intestinal obstruction syndrome requires antegrade treatment, which would be harmful if there was an intussusception.

TREATMENT

Reduction of an acute intussusception is an emergency procedure and should be performed immediately after diagnosis in preparation for possible surgery. In patients with prolonged intussusception and signs of shock, peritoneal irritation, intestinal perforation, or pneumatosis intestinalis, hydrostatic reduction should not be attempted.

The success rate of radiologic hydrostatic reduction under fluoroscopic or ultrasonic guidance is approximately 80-95% in patients with ileocolic intussusception. Spontaneous reduction of intussusception occurs in approximately 4-10% of patients. Bowel perforations occur in 0.5-2.5% of attempted barium and hydrostatic (saline) reductions. The perforation rate with air reduction is 0.1-0.2%. Surgical reduction is indicated in the presence of refractory shock, suspected bowel necrosis or perforation, peritonitis, and multiple recurrences (suspected lead point).

An **ileoileal intussusception** is best demonstrated by abdominal ultrasonography. Reduction by instillation of contrast agents, saline, or air might not be possible. Such intussusceptions can develop insidiously after bowel surgery and require reoperation if they do not spontaneously reduce. Ileoileal disease is common with Henoch-Schönlein purpura and other unidentifiable disorders and usually resolves without the need for any specific treatment. If manual operative reduction is impossible or the bowel is not viable, resection of the intussusception is necessary, with end-to-end anastomosis.

PROGNOSIS

Untreated intussusception in infants is usually fatal; the chances of recovery are directly related to the duration of intussusception before reduction. Most infants recover if the intussusception is reduced in the 1st 24 hr, but the mortality rate rises rapidly after this time, especially after the 2nd day. Spontaneous reduction during preparation for operation is not uncommon.

The **recurrence rate** after reduction of intussusceptions is approximately 10%, and after surgical reduction it is 2-5%; none has recurred after surgical resection. Most recurrences occur within 72 hr of reduction. Corticosteroids may reduce the frequency of recurrent intussusception. Repeated reducible episodes caused by lymphonodular hyperplasia may respond to treatment of identifiable food allergies if present. A single recurrence of intussusception can usually be reduced radiologically. In patients with multiple ileal–colonic recurrences, a lead point should be suspected and laparoscopic surgery considered. It is unlikely that an intussusception caused by a lesion such as lymphosarcoma, polyp, or Meckel diverticulum will be successfully reduced by radiologic intervention. With adequate surgical management, laparoscopic reduction carries a very low mortality.

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333.4 Closed-Loop Obstructions

Andrew Chu and Chris A. Liacouras

Closed-loop obstructions (i.e., **internal hernia**) result from bowel loops that enter windows created by mesenteric defects or adhesions and become trapped. Vascular engorgement of the strangulated bowel results in intestinal ischemia and necrosis unless promptly relieved. Prior abdominal surgery is an important risk factor. Symptoms include abdominal pain, distention, and bilious emesis. Symptoms can be intermittent if the herniated bowel slides in and out of the defect. Peritoneal signs suggest ischemic bowel. Plain radiographs demonstrate signs of small bowel obstruction or free air if the bowel has perforated. CT scan can identify and delineate internal hernias. Supportive management includes intravenous fluids, antibiotics, and nasogastric decompression. Prompt surgical relief of the obstruction is indicated to prevent bowel necrosis.

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Chapter 334
Foreign Bodies and Bezoars

334.1 Foreign Bodies in the Stomach and Intestine

Judith R. Kelsen and Chris A. Liacouras

Once in the stomach, 95% of all ingested objects pass without difficulty through the remainder of the gastrointestinal tract. Perforation after ingestion of a foreign body is estimated to be <1% of all objects ingested. Perforation tends to occur in areas of physiologic sphincters (pylorus, ileocecal valve), acute angulation (duodenal sweep), congenital gut malformations (webs, diaphragms, diverticula), or areas of previous bowel surgery.

Most patients who ingest foreign bodies are between the ages of 6 mo and 6 yr. Coins are the most commonly ingested foreign body in children, and meat or food impactions are the most common accidental foreign body in adolescents and adults. Patients with nonfood foreign bodies often describe a history of ingestion. Young children might have a witness to ingestion. Immediate concerns are what is the foreign body, location of the foreign body, what is the size of the foreign body, and the time that the ingestion occurred. Approximately 90% of foreign bodies are opaque. Radiologic examination is routinely performed to determine the type, number, and location of the suspected objects. Contrast radiographs may be necessary to demonstrate some objects, such as plastic parts or toys.

Conservative management is indicated for most foreign bodies that have passed through the esophagus and entered the stomach. Most objects pass though the intestine in 4-6 days, although some take as long as 3-4 wk. While waiting for the object to pass, parents are instructed to continue a regular diet and to observe the stools for the appearance of the ingested object. Cathartics should be avoided. Exceptionally long or sharp objects are usually monitored radiologically. Parents or patients should be instructed to report abdominal pain, vomiting, persistent fever, and hematemesis or melena immediately to their physicians. Failure of the object to progress within 3-4 wk seldom implies an impeding perforation but may be associated with a congenital malformation or acquired bowel abnormality.

Certain objects pose more risk than others. In cases of sharp foreign bodies, such as straight pins, weekly assessments are required. Surgical removal is necessary if the patient develops symptoms or signs of obstruction or perforation or if the foreign body fails to progress for several weeks. Small magnets used to secure earrings or parts of toys are associated with bowel perforation. Whereas a single magnet in the stomach may not require intervention in a asymptomatic child, a magnet in the esophagus requires immediate removal. When the multiple magnets disperse after ingestion, they may be attracted to each other across bowel wall, leading to pressure necrosis and perforation (Fig. 334-1). Inexpensive toy medallions containing lead can lead to **lead toxicity.** Newer coins can also decompose when subjected to prolonged acid exposure. Unless multiple coins are ingested; however, the metals released are unlikely to pose a clinical risk.

Ingestion of batteries rarely leads to problems, but symptoms can arise from leakage of alkali or heavy metal (mercury) from battery degradation in the gastrointestinal tract. Batteries can also generate electrical current and thereby cause low-voltage electrical burns to the intestine. If patients experience symptoms such as vomiting or abdominal pain, if a large-diameter battery (>20 mm in diameter) remains in the stomach for longer than 48 hr, or if a lithium battery is ingested, the battery should be removed. Batteries larger than 15 mm that do not pass the pylorus within 48 hr are less likely to pass spontaneously and generally require removal. In children younger than 6 yr of age, batteries larger than 15 mm are not likely to pass spontaneously and should be removed endoscopically. If the patient develops peritoneal signs, surgical removal is required. Batteries beyond the duodenum pass per rectum in 85% within 72 hr. The battery should be identified by size and imprint code or by evaluation of a duplicate measurement of the battery compartment. The National Button Battery Ingestion Hotline (202-625-3333) can be called for help in identification. The Poison Control Center (800-222-1222) can be called as well for ingestion of batteries and caustic materials. Lithium batteries result in more severe injury than a button alkali battery, with damage occurring in minutes. Button batteries in a symptomatic child should be removed, or if there are multiple batteries, they should be removed.

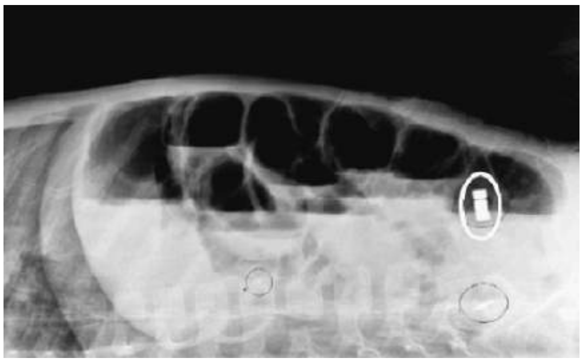

Figure 334-1 Abdominal radiograph of a boy aged 3 yr, noting 3 attached magnets that resulted in volvulus (i.e., twisting of the bowel) and multiple bowel perforations. *(Courtesy of the U.S. Consumer Product Safety Commission. From Centers for Disease Control and Prevention: Gastrointestinal injuries from magnet ingestion in children—United States, 2003–2006,* MMWR Morb Mortal Wkly Rep *55:1296–1300, 2006.)*

In older children and adults, oval objects larger than 5 cm in diameter or 2 cm in thickness tend to lodge in the stomach and should be endoscopically retrieved. Thin long objects >6 cm in length fail to negotiate the pylorus or duodenal sweep and should also be removed. In infants and toddlers, objects >3 cm in length or >20 mm in diameter do not usually pass through the pylorus and should be removed. An open safety pin presents a major problem and requires urgent endoscopic removal if within reach. Razor blades can be managed with a rigid endoscope by pulling the blade into instrument. The endoscopist can alternatively use a rubber hood on the head of the endoscope to protect the esophagus. Other sharp objects (needles, bones, pins) usually pass the stomach but complications may be as high as 35%; if possible they should be removed by endoscope if in the stomach or proximal duodenum. If sharp objects are not able to be removed but no progress is observed in location during 3 days, surgical removal is indicated. Drugs (aggregated iron pills, cocaine) may have to be surgically removed; initial management can include oral polyethylene glycol lavage. Drug body packing (heroin, cocaine) is usually seen on kidneys-ureters-bladder or CT imaging and often pass without incident. Endoscopic procedures may rupture the material causing severe toxicity. Surgery is indicated if toxicity develops or if the packages fail to progress or if there are signs of obstruction.

Ingestion of magnets poses a danger to children. The number of magnets is thought to be critical. If a single magnet is ingested, there is the least likelihood of complications. If 2 or more magnets are ingested, the magnetic poles are attracted to each other and create the risk of obstruction, fistula development, and perforation. Endoscopic retrieval is emergent after films are taken when multiple magnets are ingested. Abdominal pain or peritoneal signs require urgent surgical intervention. If all magnets are located in the stomach, immediate endoscopic removal is indicated. If the ingestion occurred greater than 12 hr prior to evaluation, General Surgery should be consulted. If the magnets are beyond the stomach and the patient is symptomatic, General Surgery should be consulted. If the patient is asymptomatic, endoscopic or colonoscopic removal may be considered along with a surgical evaluation.

Lead-based foreign bodies can cause symptoms from lead intoxication. Early endoscopic removal is indicated of an object suspected to contain lead. A lead level should be obtained.

Water-absorbing polymer balls (beads) can expand to approximately 400 times its starting size and if ingested may produce intestinal obstruction. Initially of a small diameter, they pass the pylorus only to rapidly enlarge in the small intestine. Surgical removal is indicated.

Children occasionally place objects in their rectum. Small blunt objects usually pass spontaneously, but large or sharp objects typically need to be retrieved. Adequate sedation is essential to relax the anal sphincter before attempted endoscopic or speculum removal. If the object is proximal to the rectum, observation for 12-24 hr usually allows the object to descend into the rectum.

Bibliography is available at Expert Consult.

334.2 Bezoars

Judith R. Kelsen and Chris A. Liacouras

A bezoar is an accumulation of exogenous matter in the stomach or intestine. They are predominantly composed of food or fiber. Most bezoars have been found in females with underlying personality problems or in neurologically impaired persons. Patients who have undergone abdominal surgery are at higher risk for the development of bezoars. The peak age at onset of symptoms is the 2nd decade of life.

Bezoars are classified on the basis of their composition. **Trichobezoars** are composed of the patient's own hair. It is most frequently it is a complication of the psychiatric disorders trichotillomania and the most severe form is known as Rapunzel syndrome. **Phytobezoars** are

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composed of a combination of plant and animal material, and gastric phytobezoars are the most common in patients with poor motility. **Lactobezoars** were previously found most often in premature infants and can be attributed to the high casein or calcium content of some premature formulas. Swallowed chewing gum can occasionally lead to a bezoar.

Trichobezoars can become large and form casts of the stomach; they can enter into the proximal duodenum. They manifest as symptoms of gastric outlet or partial intestinal obstruction including vomiting, anorexia, and weight loss. Patients might complain of abdominal pain, distention, and severe halitosis. Physical examination can demonstrate patchy baldness and a firm mass in the left upper quadrant. Patients occasionally have iron-deficiency anemia, hypoproteinemia, or steatorrhea caused by an associated chronic gastritis. Phytobezoars manifest in a similar manner. Detached segments of the bezoar or trichobezoar can migrate to the small intestine as a "satellite masses" and result in small bowel obstruction.

An abdominal plain film can suggest the presence of a bezoar, which can be confirmed on ultrasound or CT examination. On CT a bezoar appears a nonhomogeneous, nonenhancing mass within the lumen of the stomach or intestine. Oral contrast circumscribes the mass.

Bezoars in the stomach can usually be removed endoscopically. If endoscopy is unsuccessful, surgical intervention may be needed. Lactobezoars usually resolve when feedings are withheld for 24-48 hr. Coca-Cola has been used as a dissolution therapy for gastric phytobezoar and has been shown to be effective when used with endoscopy.

Sunflower seed bezoars are reported to cause rectal pain and constipation as a result of the seed shells being associated with fecal impaction. Endoscopic removal is indicated, as these bezoars are refractory to enema or lavage management.

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Table 335-1	Etiologic Classification of Peptic Ulcers
Positive for *Helicobacter pylori* infection	
Drug (NSAID)-induced	
H. pylori and NSAID-positive	
H. pylori and NSAID-negative*	
Acid hypersecretory state (Zollinger-Ellison syndrome)	
Anastomosis ulcer after subtotal gastric resection	
Tumors (cancer, lymphoma)	
Rare specific causes	
Crohn disease of the stomach or duodenum	
Eosinophilic gastroduodenitis	
Systemic mastocytosis	
Radiation damage	
Viral infections (cytomegalovirus or herpes simplex infection, particularly in immunocompromised patients)	
Colonization of stomach with *Helicobacter heilmannii*	
Severe systemic disease	
Cameron ulcer (gastric ulcer where a hiatal hernia passes through the diaphragmatic hiatus)	
True idiopathic ulcer	

*Requires search for other specific causes.
NSAID, nonsteroidal anti-inflammatory drug.
From Vakil N, Megraud F: Eradication therapy for Helicobacter pylori, Gastroenterology *133:985–1001, 2007.*

Chapter 335

Peptic Ulcer Disease in Children

Samra S. Blanchard and Steven J. Czinn

Peptic ulcer disease, the end result of inflammation caused by an imbalance between cytoprotective and cytotoxic factors in the stomach and duodenum, manifests with varying degrees of gastritis or frank ulceration. The pathogenesis of peptic ulcer disease is multifactorial, but the final common pathway for the development of ulcers is the action of acid and pepsin-laden contents of the stomach on the gastric and duodenal mucosa and the inability of mucosal defense mechanisms to allay those effects. Abnormalities in the gastric and duodenal mucosa can be visualized on endoscopy, with or without histologic changes. Deep mucosal lesions that disrupt the muscularis mucosa of the gastric or duodenal wall define **peptic ulcers.** Gastric ulcers are generally located on the lesser curvature of the stomach, and 90% of duodenal ulcers are found in the duodenal bulb. Despite the lack of large population-based pediatric studies, rates of peptic ulcer disease in childhood appear to be low. Large pediatric centers anecdotally report an incidence of 5-7 children with gastric or duodenal ulcers per 2,500 hospital admissions each year.

Ulcers in children can be classified as **primary** peptic ulcers, which are chronic and more often duodenal, or **secondary,** which are usually more acute in onset and are more often gastric (Table 335-1). Primary ulcers are most often associated with *Helicobacter pylori* infection; idiopathic primary peptic ulcers account for up to 20% of duodenal ulcers in children. Secondary peptic ulcers can result from stress caused by sepsis, shock, or an intracranial lesion (Cushing ulcer), or in response to a severe burn injury (Curling ulcer). Secondary ulcers are often the result of using aspirin or nonsteroidal antiinflammatory drugs (NSAIDs); hypersecretory states like Zollinger-Ellison syndrome (see Chapter 335.1), short bowel syndrome, and systemic mastocytosis are rare causes of peptic ulceration.

PATHOGENESIS

Acid Secretion

By 3-4 yr of age, gastric acid secretion approximates adult values. Acid initially secreted by the oxyntic cells of the stomach has a pH of approximately 0.8, whereas the pH of the stomach contents is 1-2. Excessive acid secretion is associated with a large parietal cell mass, hypersecretion by antral G cells, and increased vagal tone, resulting in increased or sustained acid secretion in response to meals and increased secretion during the night. The secretagogues that promote gastric acid production include acetylcholine released by the vagus nerve, histamine secreted by enterochromaffin cells, and gastrin released by the G cells of the antrum. Mediators that decrease gastric acid secretion and enhance protective mucin production include prostaglandins.

Mucosal Defense

A continuous layer of mucous gel that serves as a diffusion barrier to hydrogen ions and other chemicals covers the gastrointestinal (GI) mucosa. Mucus production and secretion are stimulated by prostaglandin E_2. Underlying the mucous coat, the epithelium forms a second-line barrier, the characteristics of which are determined by the biology of the epithelial cells and their tight junctions. Another important function of epithelial cells is to secrete chemokines when threatened by microbial attack. Secretion of bicarbonate into the mucous coat, which is regulated by prostaglandins, is important for neutralization of hydrogen ions. If mucosal injury occurs, active proliferation and migration of mucosal cells occurs rapidly, driven by epithelial growth factor, transforming growth factor-α, insulin-like growth factor, gastrin, and bombesin, and covers the area of epithelial damage.

CLINICAL MANIFESTATIONS

The presenting symptoms of peptic ulcer disease vary with the age of the patient. Hematemesis or melena is reported in up to half of the patients with peptic ulcer disease. School-age children and adolescents more commonly present with epigastric pain and nausea, presentations generally seen in adults. Dyspepsia, epigastric abdominal pain or fullness, is seen in older children. Infants and younger children usually

present with feeding difficulty, vomiting, crying episodes, hematemesis, or melena. In the neonatal period, gastric perforation can be the initial presentation.

The classic symptom of peptic ulceration, epigastric pain alleviated by the ingestion of food, is present only in a minority of children. Many pediatric patients present with poorly localized abdominal pain, which may be periumbilical. The vast majority of patients with periumbilical or epigastric pain or discomfort do not have a peptic ulcer, but rather a functional GI disorder, such as irritable bowel syndrome or nonulcer (functional) dyspepsia. Patients with peptic ulceration rarely present with acute abdominal pain from perforation or symptoms and signs of pancreatitis from a posterior penetrating ulcer. Occasionally, bright red blood per rectum may be seen if the rate of bleeding is brisk and the intestinal transit time is short. Vomiting can be a sign of gastric outlet obstruction.

The pain is often described as dull or aching, rather than sharp or burning, as in adults. It can last from minutes to hours; patients have frequent exacerbations and remissions lasting from weeks to months. Nocturnal pain waking the child is common in older children. A history of typical ulcer pain with prompt relief after taking antacids is found in <33% of children. Rarely, in patients with acute or chronic blood loss, penetration of the ulcer into the abdominal cavity or adjacent organs produces shock, anemia, peritonitis, or pancreatitis. If inflammation and edema are extensive, acute or chronic gastric outlet obstruction can occur.

DIAGNOSIS

Esophagogastroduodenoscopy is the method of choice to establish the diagnosis of peptic ulcer disease. It can be safely performed in all ages by experienced pediatric gastroenterologists. Endoscopy allows the direct visualization of esophagus, stomach, and duodenum, identifying the specific lesions. Biopsy specimens must be obtained from the esophagus, stomach, and duodenum for histologic assessment as well as to screen for the presence of *H. pylori* infection. Endoscopy also provides the opportunity for hemostatic therapy including injection and the use of a heater probe or electrocoagulation if necessary. Fecal enzyme immunoassay tests for *H. pylori* are available and have varying utility in children.

PRIMARY ULCERS

Helicobacter pylori Gastritis

H. pylori is among the most common bacterial infections in humans. *H. pylori* is a Gram-negative, S-shaped rod that produces urease, catalase, and oxidase, which might play a role in the pathogenesis of peptic ulcer disease. The mechanism of acquisition and transmission of *H. pylori* is unclear, although the most likely mode of transmission is fecal–oral or oral–oral. Viable *H. pylori* organisms can be cultured from the stool or vomitus of infected patients. Risk factors such as low socioeconomic status in childhood or affected family members also influence the prevalence. All children infected with *H. pylori* develop histologic chronic active gastritis but are often asymptomatic. In children, *H. pylori* infection can manifest with abdominal pain or vomiting and, less often, refractory iron deficiency anemia or growth retardation. *H. pylori* can be associated, though rarely, with chronic autoimmune thrombocytopenia. Chronic colonization with *H. pylori* can predispose children to a significantly increased risk of developing a duodenal ulcer, gastric cancer such as adenocarcinoma, or mucosa-associated lymphoid tissue lymphomas. The relative risk of gastric carcinoma is 2.3-8.7 times greater in infected adults as compared to uninfected subjects. *H. pylori* is classified by the World Health Organization as a group I carcinogen.

Anemia, idiopathic thrombocytopenic purpura, short stature, and sudden infant death syndrome (SIDS) have also been reported as extragastric manifestations of *H. pylori* infection. In one published study, *H. pylori* infection has been correlated with cases of SIDS, but there is no evidence to suggest that *H. pylori* plays a role in the pathogenesis of SIDS.

The **diagnosis** of *H. pylori* infection is made histologically by demonstrating the organism in the biopsy specimens (Fig. 335-1). Although

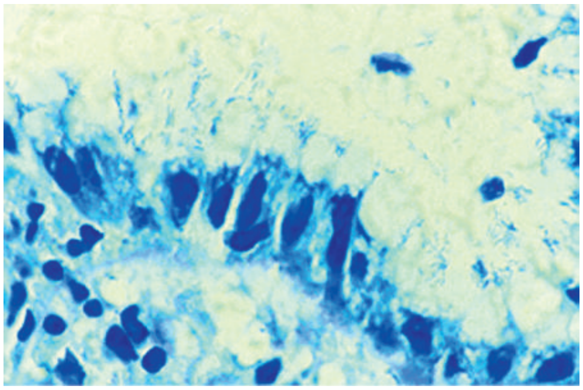

Figure 335-1 Appearance of *Helicobacter pylori* on the gastric mucosal surface with Giemsa stain (high-power view). *(From Campbell DI, Thomas JE:* Helicobacter pylori *infection in paediatric practice,* Arch Dis Child Educ Pract Ed *90:ep25–ep30, 2005.)*

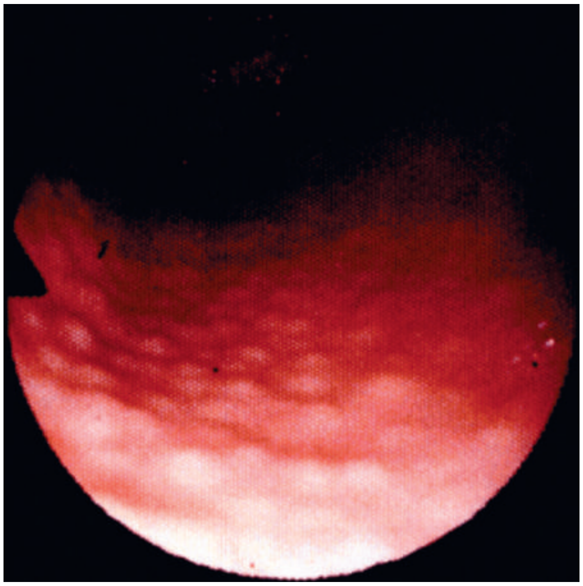

Figure 335-2 Endoscopic view of lymphoid modular hyperplasia of the gastric antrum. *(From Campbell DI, Thomas JE:* Helicobacter pylori *infection in paediatric practice,* Arch Dis Child Educ Pract Ed *90:ep25–ep30, 2005.)*

serologic assays using validated immunoglobulin G antibody detection may be helpful for screening children for the presence of *H. pylori,* they do not help predict active infection or assess the success of antimicrobial eradication therapy. ^{13}C-urea breath tests and stool antigen tests are also noninvasive methods of detecting *H. pylori* infection. Nonetheless, for children with suspected *H. pylori* infection, an initial upper endoscopy is recommended to evaluate and confirm *H. pylori* disease. The range of endoscopic findings in children with *H. pylori* infection varies from being grossly normal to the presence of nonspecific gastritis with prominent rugal folds, nodularity (Fig. 335-2), or ulcers. Because the antral mucosa appears to be endoscopically normal in a significant number of children with primary *H. pylori* gastritis, gastric biopsies should always be obtained from the body and antrum of the stomach regardless of the endoscopic appearance. If *H. pylori* is identified, even in a child with no symptoms, eradication therapy should be offered (Tables 335-2 and 335-3).

Idiopathic Ulcers

H. pylori–negative duodenal ulcers in children who have no history of taking NSAIDs represent 15-20% of pediatric duodenal ulcers. These patients do not have nodularity in the gastric antrum or histologic

Table 335-2 Recommended Eradication Therapies for *Helicobacter pylori*—Associated Disease in Children

MEDICATIONS	DOSE	DURATION OF TREATMENT
Amoxicillin	50 mg/kg/day in 2 divided doses	14 days
Clarithromycin	15 mg/kg/day in 2 divided doses	14 days
Proton pump inhibitor	1 mg/kg/day in 2 divided doses	1 mo
or		
Amoxicillin	50 mg/kg/day in 2 divided doses	14 days
Metronidazole	20 mg/kg/day in 2 divided doses	14 days
Proton pump inhibitor	1 mg/kg/day in 2 divided doses	1 mo
or		
Clarithromycin	15 mg/kg/day in 2 divided doses	14 days
Metronidazole	20 mg/kg/day in 2 divided doses	14 days
Proton pump inhibitor	1 mg/kg/day in 2 divided doses	1 mo

Adapted from Gold BD, Colletti RB, Abbott M, et al: Medical position statement: The North American Society for Pediatric Gastroenterology and Nutrition. Helicobacter pylori *infection in children: recommendations for diagnosis and treatment,* J Pediatr Gastroenterol Nutr *31:490–497, 2000.*

Table 335-3 Antisecretory Therapy with Pediatric Dosages

MEDICATION	PEDIATRIC DOSE	HOW SUPPLIED
H_2 RECEPTOR ANTAGONISTS		
Cimetidine	20-40 mg/kg/day Divided 2-4 × a day	Syrup: 300 mg/mL Tablets: 200, 300, 400, 800 mg
Ranitidine	4-10 mg/kg/day Divided 2 or 3 × a day	Syrup: 75 mg/5 mL Tablets: 75, 150, 300 mg
Famotidine	1-2 mg/kg/day Divided twice a day	Syrup: 40 mg/5 mL Tablets: 20, 40 mg
Nizatidine	5-10 mg/kg/day divided twice a day Older than 12 yr: 150 mg twice a day	Solution: 15 mg/ml Capsule 150, 300 Tablet: 75 mg
PROTON PUMP INHIBITORS		
Omeprazole	1.0-3.3 mg/kg/day weigh <20 kg: 10 mg/day weigh >20 kg: 20 mg/day Approved for use in those older than 2 yr	Capsules: 10, 20, 40 mg
Lansoprazole	0.8-4 mg/kg/day weigh <30 kg: 15 mg/day weigh >30 kg: 30 mg/day Approved for use in those older than 1 yr	Capsules: 15, 30 mg Powder packet: 15, 30 mg SoluTab: 15, 30 mg
Rabeprazole	1-11 yr(weigh <15 kg): 5 mg/day 1-11 yr (weigh >15 kg): 10 mg/day >12 yr: 20 mg tablet	Delayed release capsule: 5, 10 mg Delayed release tablet: 20 mg
Pantoprazole	1-5 yr:0.3-1.2 mg/kg/day (limited data) >5 yr of age: weigh >15 kg to <40 kg: 20 mg/day weigh >40 kg: 40 mg/day	Tablet: 20, 40 mg Powder pack: 40 mg
CYTOPROTECTIVE AGENTS		
Sucralfate	40-80 mg/kg/day	Suspension: 1,000 mg/5 mL Tablet: 1,000 mg

evidence of gastritis. In idiopathic ulcers, acid suppression alone is the preferred effective treatment. Either proton pump inhibitors (PPIs) or H_2 receptor antagonists may be used. Idiopathic ulcers have a high recurrence rate after discontinuing antisecretory therapy. These children should be followed closely, and if symptoms recur, antisecretory therapy should be restarted. In such cases, if the child is older than 1 yr, PPIs are preferred for maintenance therapy, because they have been shown to be superior to H_2 receptor antagonists in preventing recurrent ulcers.

SECONDARY ULCERS

Aspirin and Other Nonsteroidal Antiinflammatory Drugs

NSAIDs produce mucosal injury by direct local irritation and by inhibiting cyclooxygenase and prostaglandin formation. Prostaglandins enhance mucosal resistance to injury; therefore, a decrease in prostaglandin production increases the risk of mucosal injury. The severe erosive gastropathy produced by NSAIDs can ultimately result in bleeding ulcers or gastric perforations. The location of these ulcers is more common in the stomach than in the duodenum, and usually in the antrum.

"STRESS" ULCERATION

Stress ulceration usually occurs within 24 hr of onset of a critical illness in which physiologic stress is present. In many cases, the patients bleed from gastric erosions, rather than ulcers. Approximately 25% of the critically ill children in a pediatric intensive care unit have macroscopic evidence of gastric bleeding. Preterm and term infants in the neonatal intensive care unit can also develop gastric mucosal lesions and can present with upper GI bleeding or perforated ulcers. Although prophylactic measures to prevent stress ulcers in children are not standardized, drugs that inhibit gastric acid production are often used in the

pediatric intensive care unit to reduce the rate of gastric erosions or ulcers.

TREATMENT

The management of acute hemorrhage includes serial monitoring of pulse, blood pressure, and hematocrit to insure hemodynamic stability and avoid significant hypovolemia and anemia. Normal saline can be used to resuscitate a patient who has poor intravascular volume status. This can be followed by packed red blood cell transfusions for significant symptomatic anemia. The patient's blood should be typed and cross matched, and a large-bore catheter should be placed for fluid or blood replacement. A nasogastric tube should be placed to determine if the bleeding has stopped. Significant anemia can occur after fluid resuscitation as a consequence of equilibration or continued blood loss (which can also cause shock). In adults, a conservative threshold for transfusion (<7 g/dL vs 9 g hemoglobin) resulted in improved survival and fewer episodes of rebleeding. Fortunately, most acute peptic ulcer bleeding stops spontaneously.

Patients with suspected peptic ulcer hemorrhage should receive high-dose intravenous PPI therapy, which lowers the risk of rebleeding. Some centers also use octreotide, which lowers splanchnic blood flow and gastric acid production.

Once the patient is hemodynamically stable, endoscopy may be indicated to identify the source of bleeding and treat a potential bleeding site. Methods used for vessel hemostasis include pressure, laser, thermal or electric coagulation; clips; bands; and injections (epinephrine, saline).

Ulcer therapy has 2 goals: ulcer healing and elimination of the primary cause. Other important considerations are relief of symptoms and prevention of complications. The **first-line drugs** for the treatment of gastritis and peptic ulcer disease in children are PPIs and H_2 receptor antagonists (see Table 335-3). PPIs are more potent in ulcer healing. Cytoprotective agents can also be used as adjunct therapy if mucosal lesions are present. Antibiotics in combination with a PPI must be used for the treatment of *H. pylori*-associated ulcers (see Table 335-2).

H_2-receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine) competitively inhibit the binding of histamine at the H_2 subtype receptor of the gastric parietal cell. PPIs block the gastric parietal cell H^+/K^+–adenosine triphosphatase pump in a dose-dependent fashion, reducing basal and stimulated gastric acid secretion. Currently, 7 PPIs are available in the United States: omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole, dexlansoprazole, and omeprazole/sodium bicarbonate. Apart from the last 2, they are all approved in children and adolescents. They are well tolerated with only minor adverse effects, such as diarrhea (1-4%), headache (1-3%), and nausea (1%). When one considers therapeutic efficacy, the evidence suggests that all PPIs have comparable efficacy in treatment of peptic ulcer disease using standard doses and are superior to H_2-receptor antagonists. PPIs have their greatest effect when given before a meal. Pantoprazole and esomeprazole are the only PPI available in intravenous form in United States. Intravenous PPI should be used in acute upper GI bleeding. In adults, intravenous PPI in acute upper GI bleeding setting decreases the bleeding and need of intervention during endoscopy.

Treatment of *Helicobacter pylori*–Related Peptic Ulcer Disease

In pediatrics, antibiotics and bismuth salts have been used in combination with PPIs to treat *H. pylori* infection (see Table 335-2). Eradication rates in children range from 68-92% when the dual or triple therapy is used for 4-6 wk. The ulcer healing rate ranges from 91-100%. Triple therapy yields a higher cure rate than dual therapy. The optimal regimen for the eradication of *H. pylori* infection in children has yet to be established, but the use of a PPI in combination with clarithromycin and amoxicillin or metronidazole for 2 wk is a well-tolerated and recommended triple therapy (see Table 335-2). Although children younger than 5 yr of age can become reinfected, the most common reason for treatment failure is poor compliance or antibiotic resistance. *H. pylori* has become more resistant to clarithromycin or metronidazole as a consequence of the extensive use of these antibiotics for other infections. In the case of resistant *H. pylori* infection, sequential treatment or rescue therapy with different antibiotics is acceptable options. The sequential treatment regimen is a 10-day treatment consisting of a PPI and amoxicillin (both twice daily) administered for the 1st 5 days followed by triple therapy consisting of a PPI, clarithromycin, and metronidazole for the remaining 5 days. Levofloxacin, rifabutin, or furazolidone can be used with amoxicillin and bismuth as a rescue therapy depending on the age of the patient. Fidaxomicin has equivalent efficacy to vancomycin in adults. Knowledge of the community's *H. pylori* resistance pattern to clarithromycin or metronidazole might help chose the initial or rescue therapy.

Surgical Therapy

Since the discovery of *H. pylori* and the availability of modern medical management, peptic ulcer disease requiring surgical treatment has become extremely rare. The indications for surgery remain uncontrolled bleeding, perforation, and obstruction. Since the introduction of H_2-receptor antagonists, the recognition and treatment of *H. pylori,* and the use of PPIs, the incidence of surgery for bleeding and perforation has decreased dramatically.

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335.1 Zollinger-Ellison Syndrome

Samra S. Blanchard and Steven J. Czinn

Zollinger-Ellison syndrome is a rare syndrome characterized by refractory, severe peptic ulcer disease caused by gastric hypersecretion due to the autonomous secretion of gastrin by a neuroendocrine tumor, a gastrinoma. Clinical presentations are similar to those of peptic ulcer disease with the addition of diarrhea. The diagnosis is suspected by the presence of recurrent, multiple, or atypically located ulcers. More than 98% of patients have elevated fasting gastrin levels. Zollinger-Ellison syndrome is common in patients with **multiple endocrine neoplasia 1** and rare with **neurofibromatosis** and **tuberous sclerosis**. Prompt and effective management of increased gastric acid secretion is essential in the management. PPIs are the drug of choice due to their long duration of action and potency. H_2-receptor antagonists are also effective, but higher doses are required than those used in peptic ulcer disease.

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Chapter 336

Inflammatory Bowel Disease

Andrew B. Grossman and Robert N. Baldassano

The term *inflammatory bowel disease* (IBD) is used to represent 2 distinctive disorders of idiopathic chronic intestinal inflammation: Crohn disease and ulcerative colitis. Their respective etiologies are poorly understood, and both disorders are characterized by unpredictable exacerbations and remissions. The most common time of onset of IBD is during the preadolescent/adolescent era and young adulthood. A bimodal distribution has been shown with an early onset at 10-20 yr of age and a second, smaller peak at 50-80 yr of age. Approximately 25% of patients present before 20 yr of age. IBD may begin as early as the 1st yr of life, and an increased incidence among young children has

been observed since the turn of the century. Children with early-onset IBD are more likely to have colonic involvement. In developed countries, these disorders are the major causes of chronic intestinal inflammation in children beyond the 1st few yr of life. A third, less-common category, indeterminate colitis, represents approximately 10% of pediatric patients.

IBD may be classified according to age at onset: pediatric onset (<17 yr), early onset (<10 yr), very early onset (<6 yr), infant/toddler onset (0-2 yr), and neonatal onset IBD. Children with very early onset (representing ~1% of patients) and those <1 yr of age (0.2%), have a high incidence of monogenetic causes of IBD (see Table 336-5) rather than idiopathic and probably polygenetic-environmental causes of IBD.

Genetic and environmental influences are involved in the pathogenesis of IBD. The prevalence of Crohn disease in the United States is much lower for Hispanics and Asians than for whites and blacks. The risk of IBD in family members of an affected person has been reported in the range of 7-30%; a child whose parents both have IBD has a >35% chance of acquiring the disorder. Relatives of a patient with ulcerative colitis have a greater risk of acquiring ulcerative colitis than Crohn disease, whereas relatives of a patient with Crohn disease have a greater risk of acquiring this disorder; the 2 diseases can occur in the same family. The risk of occurrence of IBD among relatives of patients with Crohn disease is somewhat greater than for patients with ulcerative colitis.

The importance of genetic factors in the development of IBD is noted by a higher chance that both twins will be affected if they are monozygotic rather than dizygotic. The concordance rate in twins is higher in Crohn disease (36%) than in ulcerative colitis (16%). Genetic disorders that have been associated with IBD include Turner syndrome, the Hermansky-Pudlak syndrome, glycogen storage disease type Ib, and various immunodeficiency disorders. In 2001, the first IBD gene, *NOD2,* was identified through association mapping. A few months later, the IBD 5 risk haplotype was identified. These early successes were followed by a long period without notable risk factor discovery. Since 2006, the year of the first published genome wide array study on IBD, there has been an exponential growth in the set of validated genetic risk factors for IBD.

A perinuclear antineutrophil cytoplasmic antibody is found in approximately 70% of patients with ulcerative colitis compared with <20% of those with Crohn disease and is believed to represent a marker of genetically controlled immunoregulatory disturbance. Approximately 55% of those with Crohn disease are positive for anti–*Saccharomyces cerevisiae* antibody. Since the importance of these were first described, multiple other serologic and immune markers of Crohn disease and ulcerative colitis have been recognized.

IBD is caused by dysregulated or inappropriate immune response to environmental factors in a genetically susceptible host. An abnormality in intestinal mucosal immunoregulation may be of primary importance in the pathogenesis of IBD, involving activation of cytokines, triggering a cascade of reactions that results in bowel inflammation. These cytokines are recognized as known or potential targets for IBD therapies.

Multiple environmental factors are recognized to be involved in the pathogenesis of IBD, none more critical than the gut microbiota. The increasing incidence of IBD over time is likely in part attributable to alterations in the microbiome. Evidence includes association between IBD and residence in or immigration to industrialized nations, with a "Western" diet, increased use of antibiotics at a younger age, high rates of vaccination, and less exposure to microbes at a young age. While gut microbes likely play an important role in the pathogenesis of IBD, the exact mechanism needs to be elucidated further. Some environmental factors are disease specific; for example, cigarette smoking is a risk factor for Crohn disease but paradoxically protects against ulcerative colitis.

It is usually possible to distinguish between ulcerative colitis and Crohn disease by the clinical presentation and radiologic, endoscopic, and histopathologic findings (Table 336-1). It is not possible to make a definitive diagnosis in approximately 10% of patients with chronic colitis; this disorder is called *indeterminate colitis.* Occasionally, a child initially believed to have ulcerative colitis on the basis of clinical findings is subsequently found to have Crohn colitis. This is particularly true for the youngest patients, because Crohn disease in this patient population can more often manifest as exclusively colonic inflammation, mimicking ulcerative colitis. The medical treatments of Crohn disease and ulcerative colitis overlap.

Extraintestinal manifestations occur slightly more commonly with Crohn disease than with ulcerative colitis (Table 336-2). Growth retardation is seen in 15-40% of children with Crohn disease at diagnosis. Decrease in height velocity occurs in nearly 90% of patients with Crohn disease diagnosed in childhood or adolescence. Of the extraintestinal manifestations that occur with IBD, joint, skin, eye, mouth, and hepatobiliary involvement tend to be associated with colitis, whether ulcerative or Crohn. The presence of some manifestations, such as peripheral arthritis, erythema nodosum, and anemia, correlates with activity of the bowel disease. Activity of pyoderma gangrenosum correlates less well with activity of the bowel disease, whereas sclerosing cholangitis, ankylosing spondylitis, and sacroiliitis do not correlate with intestinal disease. Arthritis occurs in 3 patterns: migratory peripheral arthritis involving primarily large joints, ankylosing

Table 336-1 Comparison of Crohn Disease and Ulcerative Colitis

FEATURE	CROHN DISEASE	ULCERATIVE COLITIS
Rectal bleeding	Sometimes	Common
Diarrhea, mucus, pus	Variable	Common
Abdominal pain	Common	Variable
Abdominal mass	Common	Not present
Growth failure	Common	Variable
Perianal disease	Common	Rare
Rectal involvement	Occasional	Universal
Pyoderma gangrenosum	Rare	Present
Erythema nodosum	Common	Less common
Mouth ulceration	Common	Rare
Thrombosis	Less common	Present
Colonic disease	50-75%	100%
Ileal disease	Common	None except backwash ileitis
Stomach–esophageal disease	More common	Chronic gastritis can be seen
Strictures	Common	Rare
Fissures	Common	Rare
Fistulas	Common	Rare
Toxic megacolon	None	Present
Sclerosing cholangitis	Less common	Present
Risk for cancer	Increased	Greatly increased
Discontinuous (skip) lesions	Common	Not present
Transmural involvement	Common	Unusual
Crypt abscesses	Less common	Common
Granulomas	Common	None
Linear ulcerations	Uncommon	Common
Perinuclear antineutrophil cytoplasmic antibody–positive	<20%	70%

Table 336-2 Extraintestinal Complications of Inflammatory Bowel Disease

MUSCULOSKELETAL
Peripheral arthritis
Granulomatous monoarthritis
Granulomatous synovitis
Rheumatoid arthritis
Sacroiliitis
Ankylosing spondylitis
Digital clubbing and hypertrophic osteoarthropathy
Periosteitis
Osteoporosis, osteomalacia
Rhabdomyolysis
Pelvic osteomyelitis
Recurrent multifocal osteomyelitis
Relapsing polychondritis

SKIN AND MUCOUS MEMBRANES
Oral lesions
Cheilitis
Aphthous stomatitis, glossitis
Granulomatous oral Crohn disease
Inflammatory hyperplasia fissures and cobblestone mucosa
Peristomatitis vegetans

DERMATOLOGIC
Erythema nodosum
Pyoderma gangrenosum
Sweet syndrome
Metastatic Crohn disease
Psoriasis
Epidermolysis bullosa acquisita
Perianal skin tags
Polyarteritis nodosa

OCULAR
Conjunctivitis
Uveitis, iritis
Episcleritis
Scleritis
Retrobulbar neuritis
Chorioretinitis with retinal detachment
Crohn keratopathy
Posterior segment abnormalities
Retinal vascular disease

BRONCHOPULMONARY
Chronic bronchitis with bronchiectasis
Chronic bronchitis with neutrophilic infiltrates
Fibrosing alveolitis
Pulmonary vasculitis
Small airway disease and bronchiolitis obliterans
Eosinophilic lung disease
Granulomatous lung disease
Tracheal obstruction

CARDIAC
Pleuropericarditis
Cardiomyopathy
Endocarditis
Myocarditis

MALNUTRITION
Decreased intake of food
- Inflammatory bowel disease
- Dietary restriction

Malabsorption
- Inflammatory bowel disease
- Bowel resection
- Bile salt depletion
- Bacterial overgrowth

Intestinal losses
- Electrolytes
- Minerals
- Nutrients

Increased caloric needs
- Inflammation
- Fever

HEMATOLOGIC
Anemia: iron deficiency (blood loss)
Vitamin B_{12} (ileal disease or resection, bacterial overgrowth, folate deficiency)
Anemia of chronic inflammation
Anaphylactoid purpura (Crohn disease)
Hyposplenism
Autoimmune hemolytic anemia
Coagulation abnormalities
Increased activation of coagulation factors
Activated fibrinolysis
Anticardiolipin antibody
Increased risk of arterial and venous thrombosis with cerebrovascular stroke, myocardial infarction, peripheral arterial, and venous occlusions

RENAL AND GENITOURINARY
Metabolic
- Urinary crystal formation (nephrolithiasis, uric acid, oxylate)

Hypokalemic nephropathy
Inflammation
- Retroperitoneal abscess
- Fibrosis with ureteral obstruction
- Fistula formation

Glomerulitis
Membrane nephritis
Renal amyloidosis, nephrotic syndrome

PANCREATITIS
Secondary to medications (sulfasalazine, 6-mercaptopurine, azathioprine, parenteral nutrition)
Ampullary Crohn disease
Granulomatous pancreatitis
Decreased pancreatic exocrine function
Sclerosing cholangitis with pancreatitis

HEPATOBILIARY
Primary sclerosing cholangitis
Small duct primary sclerosing cholangitis (pericholangitis)
Carcinoma of the bile ducts
Fatty infiltration of the liver
Cholelithiasis
Autoimmune hepatitis

ENDOCRINE AND METABOLIC
Growth failure, delayed sexual maturation
Thyroiditis
Osteoporosis, osteomalacia

NEUROLOGIC
Peripheral neuropathy
Meningitis
Vestibular dysfunction
Pseudotumor cerebri
Cerebral vasculitis
Migraine

Modified from Kugathasan S: Diarrhea. In Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, WB Saunders, p. 285.*

spondylitis, and sacroiliitis. The peripheral arthritis of IBD tends to be nondestructive. Ankylosing spondylitis begins in the 3rd decade and occurs most commonly in patients with ulcerative colitis who have the human leukocyte antigen B27 phenotype. Symptoms include low back pain and morning stiffness; back, hips, shoulders, and sacroiliac joints are typically affected. Isolated sacroiliitis is usually asymptomatic but is common when a careful search is performed. Among the skin manifestations, erythema nodosum is most common. Patients with erythema nodosum or pyoderma gangrenosum have a high likelihood of having arthritis as well. Glomerulonephritis, uveitis, and a hypercoagulable state are other rare manifestations that occur in childhood. Cerebral thromboembolic disease has been described in children with IBD.

336.1 Chronic Ulcerative Colitis

Andrew B. Grossman and Robert N. Baldassano

Ulcerative colitis, an idiopathic chronic inflammatory disorder, is localized to the colon and spares the upper gastrointestinal (GI) tract. Disease usually begins in the rectum and extends proximally for a variable distance. When it is localized to the rectum, the disease is ulcerative proctitis, whereas disease involving the entire colon is pancolitis. Approximately 50-80% of pediatric patients have extensive colitis, and adults more commonly have distal disease. Ulcerative proctitis is less likely to be associated with systemic manifestations, although it may be less responsive to treatment than more-diffuse disease. Approximately 30% of children who present with ulcerative proctitis experience proximal spread of the disease. Ulcerative colitis has rarely been noted to present in infancy. Dietary protein intolerance can easily be misdiagnosed as ulcerative colitis in this age group. Dietary protein intolerance (cow's milk protein) is a transient disorder; symptoms are directly associated with the intake of the offending antigen.

The incidence of ulcerative colitis has remained relatively constant, in contrast to an increase in Crohn disease, but varies with country of origin. The age-specific incidence rates of pediatric ulcerative colitis in North America is 2 per 100,000 population. The prevalence of ulcerative colitis in northern European countries and the United States varies from 100-200 per 100,000 population. Men are slightly more likely to acquire ulcerative colitis than are women; the reverse is true for Crohn disease.

CLINICAL MANIFESTATIONS

Blood, mucus, and pus in the stool as well as diarrhea are the typical presentation of ulcerative colitis. Constipation may be observed in those with proctitis. Symptoms such as tenesmus, urgency, cramping abdominal pain (especially with bowel movements), and nocturnal bowel movements are common. The mode of onset ranges from insidious with gradual progression of symptoms to acute and fulminant (Table 336-3, Fig. 336-1). Fever, severe anemia, hypoalbuminemia, leukocytosis, and more than 5 bloody stools per day for 5 days define **fulminant colitis**. Chronicity is an important part of the diagnosis; it is difficult to know if a patient has a subacute, transient infectious colitis or ulcerative colitis when a child has had 1-2 wk of symptoms. Symptoms beyond this duration often prove to be secondary to IBD. Anorexia, weight loss, and growth failure may be present, although these complications are more typical of Crohn disease.

Extraintestinal manifestations that tend to occur more commonly with ulcerative colitis than with Crohn disease include pyoderma gangrenosum, sclerosing cholangitis, chronic active hepatitis, and ankylosing spondylitis. Iron deficiency can result from chronic blood loss as well as decreased intake. Folate deficiency is unusual but may be accentuated in children treated with sulfasalazine, which interferes with folate absorption. Chronic inflammation and the elaboration of a variety of inflammatory cytokines can interfere with erythropoiesis and result in the anemia of chronic disease. Secondary amenorrhea is common during periods of active disease.

The clinical course of ulcerative colitis is marked by remission and relapse, often without apparent explanation. After treatment of initial symptoms, approximately 5% of children with ulcerative colitis have a prolonged remission (longer than 3 yr). Approximately 25% of children presenting with severe ulcerative colitis require colectomy within 5 yr of diagnosis, compared with only 5% of those presenting with mild disease. It is important to consider the possibility of enteric infection with recurrent symptoms; these infections can mimic a flare-up or actually provoke a recurrence. The use of nonsteroidal antiinflammatory drugs is considered by some to predispose to exacerbation.

It is generally believed that the risk of colon cancer begins to increase after 8-10 yr of disease and can then increase by 0.5-1% per year. The risk is delayed by approximately 10 yr in patients with colitis limited to the descending colon. Proctitis alone is associated with virtually no increase in risk over the general population. Because colon cancer is usually preceded by changes of mucosal dysplasia, it is recommended that patients who have had ulcerative colitis for longer than 10 yr be screened with colonoscopy and biopsies every 1-2 yr. Although this is the current standard of practice, it is not clear if morbidity and mortality are changed by this approach. Two competing concerns about this

Table 336-3 Montreal Classification of Extent and Severity of Ulcerative Colitis

- E1 (proctitis): inflammation limited to the rectum
- E2 (left-sided; distal): inflammation limited to the splenic flexure
- E3 (pancolitis): inflammation extends to the proximal splenic flexure
- S0 (remission): no symptoms
- S1 (mild): 4 or less stools per day (with or without blood), absence of systemic symptoms, normal inflammatory markers
- S2 (moderate): 4 stools per day, minimum signs of systemic symptoms
- S3 (severe): 6 or more bloody stools per day, pulse rate of ≥90 beats per min, temperature ≥37.5°C (99.5°F), hemoglobin concentration <105 g/L, erythrocyte sedimentation rate ≥30 mm/hr

E, extent; S, severity.

From Ordàs I, Eckmann L, Talamini M, et al: Ulcerative colitis, Lancet *380:1606–1616, 2012 (Panel 2, p. 1610).*

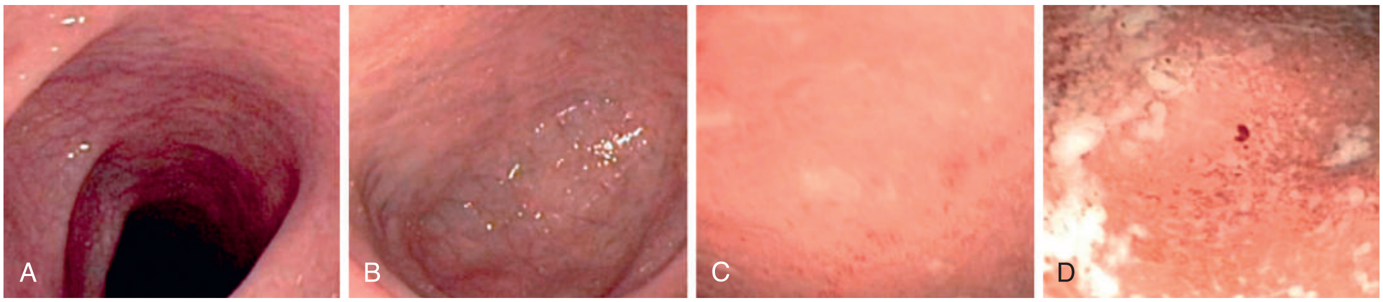

Figure 336-1 Mayo endoscopic score for ulcerative colitis. **A,** Score 0 = normal; endoscopic remission. **B,** Score 1 = mild; erythema, decreased vascular pattern, mild friability. **C,** Score 2 = moderate; marked erythema, absent vascular pattern, friability, erosions. **D,** Score 3 = severe; spontaneous bleeding, ulceration. *(Images courtesy of Elena Ricart. From Ordàs I, Eckmann L, Talamini M, et al: Ulcerative colitis,* Lancet *380:1606–1616, 2012, Fig. 2, p. 1610.)*

Table 336-4 Infectious Agents Mimicking Inflammatory Bowel Disease

AGENT	MANIFESTATIONS	DIAGNOSIS	COMMENTS
BACTERIAL			
Campylobacter jejuni	Acute diarrhea, fever, fecal blood, and leukocytes	Culture	Common in adolescents, may relapse
Yersinia enterocolitica	Acute → chronic diarrhea, right lower quadrant pain, mesenteric adenitis–pseudoappendicitis, fecal blood, and leukocytes Extraintestinal manifestations, mimics Crohn disease	Culture	Common in adolescents as fever of unknown origin, weight loss, abdominal pain
Clostridium difficile	Postantibiotic onset, watery → bloody diarrhea, pseudomembrane on sigmoidoscopy	Cytotoxin assay	May be nosocomial Toxic megacolon possible
Escherichia coli O157:H7	Colitis, fecal blood, abdominal pain	Culture and typing	Hemolytic uremic syndrome
Salmonella	Watery → bloody diarrhea, foodborne, fecal leukocytes, fever, pain, cramps	Culture	Usually acute
Shigella	Watery → bloody diarrhea, fecal leukocytes, fever, pain, cramps	Culture	Dysentery symptoms
Edwardsiella tarda	Bloody diarrhea, cramps	Culture	Ulceration on endoscopy
Aeromonas hydrophila	Cramps, diarrhea, fecal blood	Culture	May be chronic Contaminated drinking water
Plesiomonas shigelloides	Diarrhea, cramps	Culture	Shellfish source
Tuberculosis	Rarely bovine, now *Mycobacterium tuberculosis* Ileocecal area, fistula formation	Culture, purified protein derivative, biopsy	Can mimic Crohn disease
PARASITES			
Entamoeba histolytica	Acute bloody diarrhea and liver abscess, colic	Trophozoite in stool, colonic mucosal flask ulceration, serologic tests	Travel to endemic area
Giardia lamblia	Foul-smelling, watery diarrhea, cramps, flatulence, weight loss; no colonic involvement	"Owl"-like trophozoite and cysts in stool; rarely duodenal intubation	May be chronic
AIDS-ASSOCIATED ENTEROPATHY			
Cryptosporidium	Chronic diarrhea, weight loss	Stool microscopy	Mucosal findings not like inflammatory bowel disease
Isospora belli	As in *Cryptosporidium*		Tropical location
Cytomegalovirus	Colonic ulceration, pain, bloody diarrhea	Culture, biopsy	More common when on immunosuppressive medications

plan of management remain unresolved. The original studies may have overestimated the risk of colon cancer and, therefore, the need for surveillance has been overemphasized; and screening for dysplasia might not be adequate for preventing colon cancer in ulcerative colitis if some cancers are not preceded by dysplasia.

DIFFERENTIAL DIAGNOSIS

The major conditions to exclude are infectious colitis, allergic colitis, and Crohn colitis. Every child with a new diagnosis of ulcerative colitis should have stool cultured for enteric pathogens, stool evaluation for *Clostridium difficile*, ova and parasites, and perhaps serologic studies for amebae (Table 336-4). Cytomegalovirus infection can mimic ulcerative colitis or be associated with an exacerbation of existing disease, usually in immunocompromised patients. The most difficult distinction is from Crohn disease because the colitis of Crohn disease can initially appear identical to that of ulcerative colitis, particularly in younger children. The gross appearance of the colitis or development of small bowel disease eventually leads to the correct diagnosis; this can occur years after the initial presentation.

At the onset, the colitis of hemolytic uremic syndrome may be identical to that of early ulcerative colitis. Ultimately, signs of microangiopathic hemolysis (the presence of schistocytes on blood smear), thrombocytopenia, and subsequent renal failure should confirm the diagnosis of hemolytic-uremic syndrome. Although Henoch-Schönlein purpura can manifest as abdominal pain and bloody stools, it is not usually associated with colitis. Behçet disease can be distinguished by its typical features (see Chapter 161). Other considerations are radiation proctitis, viral colitis in immunocompromised patients, and ischemic colitis (Table 336-5). In infancy, dietary protein intolerance can be confused with ulcerative colitis, although the former is a transient problem that resolves on removal of the offending protein, and ulcerative colitis is extremely rare in this age group. Hirschsprung disease can produce an enterocolitis before or within months after surgical correction; this is unlikely to be confused with ulcerative colitis.

DIAGNOSIS

The diagnosis of ulcerative colitis or ulcerative proctitis requires a typical presentation in the absence of an identifiable specific cause (see Tables 336-4 and 336-5) and typical endoscopic and histologic findings (see Tables 336-1 and 336-2). One should be hesitant to make a diagnosis of ulcerative colitis in a child who has experienced symptoms for <2-3 wk until infection has been excluded. When the diagnosis is suspected in a child with subacute symptoms, the physician should make a firm diagnosis only when there is evidence of chronicity on colonic biopsy. Laboratory studies can demonstrate evidence of anemia (either iron deficiency or the anemia of chronic disease) or hypoalbuminemia. Although the sedimentation rate and C-reactive protein are often elevated, they may be normal even with fulminant colitis. An elevated white blood cell count is usually seen only with more-severe colitis. Fecal calprotectin levels are usually elevated and are increasingly recognized to be a more sensitive and specific marker of GI inflammation than typical laboratory parameters. Barium enema is suggestive but not diagnostic of acute (Fig. 336-2) or chronic burned-out disease (Fig. 336-3).

The diagnosis of ulcerative colitis must be confirmed by endoscopic and histologic examination of the colon (see Fig. 336-1). Classically, disease starts in the rectum with a gross appearance characterized by erythema, edema, loss of vascular pattern, granularity, and friability. There may be a "cutoff" demarcating the margin between inflammation and normal colon, or the entire colon may be involved. There may

Table 336-5 Chronic Inflammatory-Like Intestinal Disorders Including Monogenetic Diseases

INFECTION (see Table 336-4)
AIDS-Associated
Toxin
Immune–Inflammatory
Severe combined immunodeficiency diseases
Agammaglobulinemia
Chronic granulomatous disease
Wiskott-Aldrich syndrome
Common variable immunodeficiency diseases
Acquired immunodeficiency states
Dietary protein enterocolitis
Autoimmune polyendocrine syndrome type 1
Behçet disease
Lymphoid nodular hyperplasia
Eosinophilic gastroenteritis
Omenn syndrome
Graft-versus-host disease
IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndromes
Interleukin-10 signaling defects
Autoimmune enteropathy*
Microscopic colitis
Hyperimmunoglobulin M syndrome
Hyperimmunoglobulin E syndromes
Mevalonate kinase deficiency
Familial Mediterranean fever
Phospholipase Cγ_2 defects
Familial hemophagocytic lymphohistiocytosis type 5
X-linked lymphoproliferative syndromes types 1, 2
Congenital neutropenias
Leukocyte adhesion deficiency 1
VASCULAR–ISCHEMIC DISORDERS
Systemic vasculitis (systemic lupus erythematosus, dermatomyositis)
Henoch-Schönlein purpura
Hemolytic uremic syndrome
Granulomatosis with angiitis
OTHER
Glycogen storage disease type 1b
Dystrophic epidermolysis bullosa
X-linked ectodermal dysplasia and immunodeficiency
Dyskeratosis congenita
ADAM-17 deficiency
Prestenotic colitis
Diversion colitis
Radiation colitis
Neonatal necrotizing enterocolitis
Typhlitis
Sarcoidosis
Hirschsprung colitis
Intestinal lymphoma
Laxative abuse
Endometriosis
Hermansky-Pudlak syndrome
Trichohepatoenteric syndrome
PTEN hamartoma syndrome

*May be the same as IPEX.

be some variability in the intensity of inflammation even in those areas involved. Flexible sigmoidoscopy can confirm the diagnosis; colonoscopy can evaluate the extent of disease and rule out Crohn colitis. A colonoscopy should not be performed when fulminant colitis is suspected because of the risk of provoking *toxic megacolon* or causing a perforation during the procedure. The degree of colitis can be evaluated by the gross appearance of the mucosa. One does not generally see discrete ulcers, which would be more suggestive of Crohn colitis. The endoscopic findings of ulcerative colitis result from microulcers, which give the appearance of a diffuse abnormality. With very severe chronic colitis, pseudopolyps may be seen. Biopsy of involved bowel demonstrates evidence of acute and chronic mucosal inflammation. Typical histologic findings are cryptitis, crypt abscesses, separation of crypts by inflammatory cells, foci of acute inflammatory cells, edema, mucus depletion, and branching of crypts. The last finding is not seen in infectious colitis. Granulomas, fissures, or full-thickness involvement of the bowel wall (usually on surgical rather than endoscopic biopsy) suggests Crohn disease.

Perianal disease, with the exception of mild local irritation or anal fissures associated with diarrhea, should make the clinician think of Crohn disease. Plain radiographs of the abdomen might demonstrate loss of haustral markings in an air-filled colon or marked dilation with toxic megacolon. With severe colitis, the colon may become dilated; a diameter of >6 cm, determined radiographically, in an adult suggests toxic megacolon. If it is necessary to examine the colon radiologically in a child with severe colitis (to evaluate the extent of involvement or to try to rule out Crohn disease), it is sometimes helpful to perform an upper GI contrast series with small bowel follow-through and then look at delayed films of the colon. A barium enema is contraindicated in the setting of a potential toxic megacolon.

TREATMENT

Medical

A medical cure for ulcerative colitis is not available; treatment is aimed at controlling symptoms and reducing the risk of recurrence, with a secondary goal of minimizing steroid exposure. The intensity of treatment varies with the severity of the symptoms.

The first drug class to be used with mild or mild-to-moderate colitis is an aminosalicylate. Sulfasalazine is composed of a sulfur moiety linked to the active ingredient 5-aminosalicylate (5-ASA). This linkage prevents the premature absorption of the medication in the upper GI tract, allowing it to reach the colon, where the 2 components are separated by bacterial cleavage. The dose of sulfasalazine is 50-75 mg/kg/24 hr (divided into 2-4 doses). Generally, the dose is not more than 2-4 g/24 hr. Hypersensitivity to the sulfa component is the major side effect of sulfasalazine and occurs in 10-20% of patients. Because of poor tolerance, sulfasalazine is used less commonly than other, better tolerated 5-ASA preparations (mesalamine, 50-100 mg/kg/day; balsalazide 110-175 mg/kg/day). Sulfasalazine and the 5-ASA preparations effectively treat active ulcerative colitis and prevent recurrence. It is recommended that the medication be continued even when the disorder is in remission. These medications might also decrease the lifetime risk of colon cancer.

Approximately 5% of patients have an allergic reaction to 5-ASA, manifesting as rash, fever, and bloody diarrhea, which can be difficult to distinguish from symptoms of a flare of ulcerative colitis. 5-ASA can also be given in enema or suppository form and is especially useful for proctitis. Hydrocortisone enemas are used to treat proctitis as well, but they are probably not as effective. A combination of oral and rectal 5-ASA as well as monotherapy with rectal preparation has been shown to be more effective than just oral 5-ASA for distal colitis. Extended release budesonide may also induce remission in patients with mild to moderate ulcerative colitis.

Probiotics are effective in adults for maintenance of remission for ulcerative colitis, although they do not induce remission during an active flare. The most promising role for probiotics has been to prevent pouchitis, a common complication following colectomy and ileal–pouch anal anastomosis surgery.

Children with moderate to severe pancolitis or colitis that is unresponsive to 5-ASA therapy should be treated with corticosteroids, most commonly, prednisone. The usual starting dose of prednisone is 1-2 mg/kg/24 hr (40-60 mg maximum dose). This medication can be given once daily. With severe colitis, the dose can be divided twice daily and can be given intravenously. Steroids are considered an effective medication for acute flares, but they are not appropriate maintenance medications because of loss of effect and side effects, including growth retardation, adrenal suppression, cataracts, osteopenia, aseptic necrosis of the head of the femur, glucose intolerance, risk of infection, mood disturbance, and cosmetic effects.

For a hospitalized patient with persistence of symptoms despite intravenous steroid treatment for 3-5 days, escalation of therapy or

Figure 336-2 Ulcerative colitis. Double-contrast barium enema in a 5 yr old boy who had had intermittent intestinal and extraintestinal symptoms since the age of 3 yr. **A,** Small ulcerations are distributed uniformly about the colonic circumference and continuously from the rectum to the proximal transverse colon. This pattern of involvement is typical of ulcerative colitis. **B,** In this coned view of the sigmoid in the same patient, small ulcerations are represented by fine spiculation of the colonic contour in tangent and by fine stippling of the colon surface en face. *(From The child with diarrhea. In Hoffman AD, Hilton SW, Edwards DK, editors:* Practical pediatric radiology, *ed 2, Philadelphia, 1994, WB Saunders, p. 260.)*

Figure 336-3 Ulcerative colitis: late changes. This single-contrast barium enema shows the late changes of ulcerative colitis in a 15 yr old girl. The colon is featureless, reduced in caliber, and shortened. Dilation of the terminal ileum (backwash ileitis) is present. *(From The child with diarrhea. In Hoffman AD, Hilton SW, Edwards DK, editors:* Practical pediatric radiology, *ed 2, Philadelphia, 1994, WB Saunders, p 262.)*

surgical options should be considered. The validated pediatric ulcerative colitis activity index can be utilized to help determine current disease severity based on clinical factors, and help determine who is more likely to respond to steroids and those who will likely require escalation of therapy (Table 336-6).

With medical management, most children are in remission within 3 mo; however, 5-10% continue to have symptoms unresponsive to treatment beyond 6 mo. Many children with disease requiring frequent corticosteroid therapy are started on immunomodulators such as azathioprine (2.0-2.5 mg/kg/day) or 6-mercaptopurine (1-1.5 mg/kg/day). Uncontrolled data suggest a corticosteroid-sparing effect in many treated patients. This is not an appropriate choice in a steroid nonresponsive patient with acute severe colitis because of longer onset of action. Lymphoproliferative disorders are associated with thiopurine use. Cyclosporine, which is associated with improvement in some children with severe or fulminant colitis, is rarely used owing to its high side-effect profile, its inability to change the natural history of disease, and the increasing use of infliximab, a chimeric monoclonal antibody to tumor necrosis factor (TNF)-α, which is also effective in cases of fulminant colitis. Infliximab is effective for induction and maintenance therapy in adults with moderate to severe disease. TNF blocking agents are associated with an increased risk of infection (particularly tuberculosis) and malignancies (lymphoma, leukemia). Adalimumab is also approved for treatment of moderate to severe ulcerative colitis in adults. Vedolizumab, a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the gastrointestinal tract, is approved for the treatment of ulcerative colitis in adults. Tofacitinib, an oral Janus kinase inhibitor, is undergoing trials in adults with active moderate to severe ulcerative colitis.

Surgical

Colectomy is performed for intractable disease, complications of therapy, and fulminant disease that is unresponsive to medical management. No clear benefit of the use of total parenteral nutrition or a

Table 336-6 Pediatric Ulcerative Colitis Activity Index

ITEM	POINTS
(1) Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
(2) Rectal bleeding	
None	0
Small amount only, in <50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
(3) Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
(4) Number of stools per 24 h	
0-2	0
3-5	5
6-8	10
>8	15
(5) Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
(6) Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of Index (0-85)	

continuous enteral elemental diet in the treatment of severe ulcerative colitis has been noted. Nevertheless, parenteral nutrition is used if oral intake is insufficient so that the patient will be nutritionally ready for surgery if medical management fails. With any medical treatment for ulcerative colitis, the clinician should always weigh the risk of the medication or therapy against the fact that colitis can be successfully treated surgically.

Surgical treatment for intractable or fulminant colitis is total colectomy. The optimal approach is to combine colectomy with an endorectal pull-through, where a segment of distal rectum is retained and the mucosa is stripped from this region. The distal ileum is pulled down and sutured at the internal anus with a J pouch created from ileum immediately above the rectal cuff. This procedure allows the child to maintain continence. Commonly, a temporary ileostomy is created to protect the delicate anastomosis between the sleeve of the pouch and the rectum. The ileostomy is usually closed within several months, restoring bowel continuity. At that time, stool frequency is often increased but may be improved with loperamide. The major complication of this operation is *pouchitis,* which is a chronic inflammatory reaction in the pouch, leading to bloody diarrhea, abdominal pain, and, occasionally, low-grade fever. The cause of this complication is unknown, although it is more common when the ileal pouch has been constructed for ulcerative colitis than for other indications (e.g., familial polyposis coli). Pouchitis is seen in 30-40% of patients who had ulcerative colitis. It commonly responds to treatment with oral metronidazole or ciprofloxacin. Probiotics have also been shown to decrease the rate of pouchitis as well as the recurrence of pouchitis following antibiotic therapy.

Support

Psychosocial support is an important part of therapy for this disorder. This may include adequate discussion of the disease manifestations and management between patient and physician, psychologic counseling for the child when necessary, and family support from a social worker or family counselor. Patient support groups have proved helpful for some families. Children with ulcerative colitis should be encouraged to participate fully in age-appropriate activities; however, activity may need to be reduced during periods of disease exacerbation.

PROGNOSIS

The course of ulcerative colitis is marked by remissions and exacerbations. Most children with this disorder respond initially to medical management. Many children with mild manifestations continue to respond well to medical management and may stay in remission on a prophylactic 5-ASA preparation for long periods. An occasional child with mild onset, however, experiences intractable symptoms at a later time. Beyond the 1st decade of disease, the risk of development of colon cancer begins to increase rapidly. The risk of colon cancer may be diminished with surveillance colonoscopies beginning after 8-10 yr of disease. Detection of significant dysplasia on biopsy would prompt colectomy.

Bibliography is available at Expert Consult.

336.2 Crohn Disease (Regional Enteritis, Regional Ileitis, Granulomatous Colitis)

Andrew B. Grossman and Robert N. Baldassano

Crohn disease, an idiopathic, chronic inflammatory disorder of the bowel, involves any region of the alimentary tract from the mouth to the anus. Although there are many similarities between ulcerative colitis and Crohn disease, there are also major differences in the clinical course and distribution of the disease in the GI tract (see Table 336-1). The inflammatory process tends to be eccentric and segmental, often with skip areas (normal regions of bowel between inflamed areas). Although inflammation in ulcerative colitis is limited to the mucosa (except in toxic megacolon), GI involvement in Crohn disease is often transmural.

Compared to adult-onset disease, pediatric Crohn disease is more likely to have extensive anatomic involvement. At initial presentation, more than 50% of patients have disease that involves ileum and colon (ileocolitis), 20% have exclusively colonic disease, and upper GI involvement (esophagus, stomach, duodenum) is seen in up to 30% of children. Isolated small bowel disease is much less common in the pediatric population compared to adults. Isolated colonic disease is common in children younger than 8 yr of age and may be indistinguishable from ulcerative colitis. Anatomic location of disease tends to extend over time in children.

Crohn disease tends to have a bimodal age distribution, with the first peak beginning in the teenage years. The incidence of Crohn disease has been increasing, whereas that of ulcerative colitis has been stable. In the United States, the reported incidence of pediatric Crohn disease is 4.56 per 100,000 and the pediatric prevalence is 43 per 100,000 children.

CLINICAL MANIFESTATIONS

Crohn disease can be characterized as inflammatory, stricturing, or penetrating. Patients with small bowel disease are more likely to have an obstructive pattern (most commonly with right lower quadrant pain) characterized by fibrostenosis, and those with colonic disease are more likely to have symptoms resulting from inflammation (diarrhea, bleeding, cramping). Disease phenotypes often change as duration of disease lengthens (inflammatory becomes structuring and/or penetrating) (Fig. 336-4).

Systemic signs and symptoms are more common in Crohn disease than in ulcerative colitis. Fever, malaise, and easy fatigability are common. Growth failure with delayed bone maturation and delayed sexual development can precede other symptoms by 1 or 2 yr and is at least twice as likely to occur with Crohn disease as with ulcerative colitis. Children can present with growth failure as the only manifestation of Crohn disease. Decreased height velocity occurs in about 88% of prepubertal patients diagnosed with Crohn disease, and this often precedes GI symptoms. Causes of growth failure include inadequate caloric intake, suboptimal absorption or excessive loss of nutrients, the

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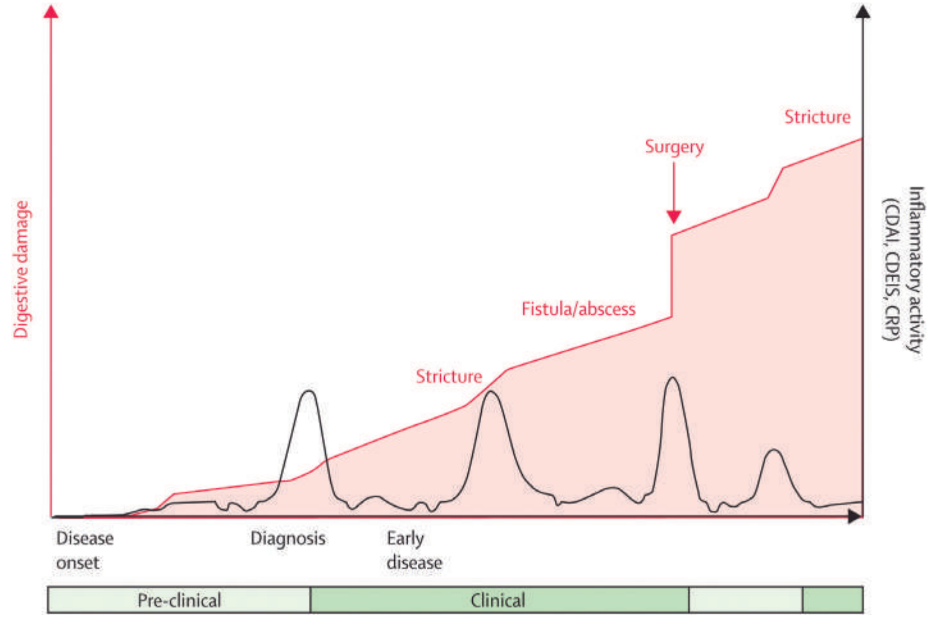

Figure 336-4 The Lémann Score. Exemplary visualization of the Lémann score, a new technique to score and study intestinal damage in Crohn disease. *CDAI*, Crohn disease activity index; *CDEIS*, Crohn disease of endoscopic severity; *CRP*, C-reactive protein. *(From Baumgart DC, Sandborn WJ: Crohn's disease. Lancet 380:1590–1602, 2012, Fig. 5, p. 1596.)*

effects of chronic inflammation on bone metabolism and appetite, and the use of corticosteroids during treatment. Primary or secondary amenorrhea and pubertal delay are common. In contrast to ulcerative colitis, perianal disease is common (tag, fistula, deep fissure, abscess). Gastric or duodenal involvement may be associated with recurrent vomiting and epigastric pain. Partial small bowel obstruction, usually secondary to narrowing of the bowel lumen from inflammation or stricture, can cause symptoms of cramping abdominal pain (especially with meals), borborygmus, and intermittent abdominal distention (Figs. 336-5 and 336-6). Stricture should be suspected if the child notes relief of symptoms in association with a sudden sensation of gurgling of intestinal contents through a localized region of the abdomen.

Penetrating disease is demonstrated by fistula formation. Enteroenteric or enterocolonic fistulas (between segments of bowel) are often asymptomatic but can contribute to malabsorption if they have high output or result in bacterial overgrowth (Fig. 336-7). Enterovesical fistulas (between bowel and urinary bladder) originate from ileum or sigmoid colon and appear as signs of urinary infection, pneumaturia, or fecaluria. Enterovaginal fistulas originate from the rectum, cause feculent vaginal drainage, and are difficult to manage. Enterocutaneous fistulas (between bowel and abdominal skin) often are caused by prior surgical anastomoses with leakage. Intraabdominal abscess may be associated with fever and pain but might have relatively few symptoms. Hepatic or splenic abscess can occur with or without a local fistula. Anorectal abscesses often originate immediately above the anus at the crypts of Morgagni. The patterns of perianal fistulas are complex because of the different tissue planes. Perianal abscess is usually painful, but perianal fistulas tend to produce fewer symptoms than anticipated. Purulent drainage is commonly associated with perianal fistulas. **Psoas abscess** secondary to intestinal fistula can present as hip pain, decreased hip extension (psoas sign), and fever.

Extraintestinal manifestations occur more commonly with Crohn disease than with ulcerative colitis; those that are especially associated with Crohn disease include oral aphthous ulcers, peripheral arthritis, erythema nodosum, digital clubbing, episcleritis, renal stones (uric acid, oxalate), and gallstones. Any of the extraintestinal disorders described in the section on IBD can occur with Crohn disease (see Table 336-2). The peripheral arthritis is nondeforming. The occurrence of extraintestinal manifestations usually correlates with the presence of colitis.

Extensive involvement of small bowel, especially in association with surgical resection, can lead to short bowel syndrome, which is rare in children. Complications of terminal ileal dysfunction or resection include bile acid malabsorption with secondary diarrhea and vitamin B_{12} malabsorption, with possible resultant deficiency. Chronic steatorrhea can lead to oxaluria with secondary renal stones. Increasing calcium intake can actually decrease the risk renal stones secondary to ileal inflammation. The risk of cholelithiasis is also increased secondary to bile acid depletion.

Figure 336-5 Stenotic Crohn disease. Severe stenosis of the terminal ileum is present in this 16 yr old boy. Inflammatory effacement of the mucosal folds and small ulcerations characterize the proximal nonstenotic segment. *(From The child with diarrhea. In Hoffman AD, Hilton SW, Edwards DK, editors:* Practical pediatric radiology, *ed 2, Philadelphia, 1994, WB Saunders, p. 267.)*

A disorder with this diversity of manifestations can have a major impact on an affected child's lifestyle. Fortunately, the majority of children with Crohn disease are able to continue with their normal activities, having to limit activity only during periods of increased symptoms.

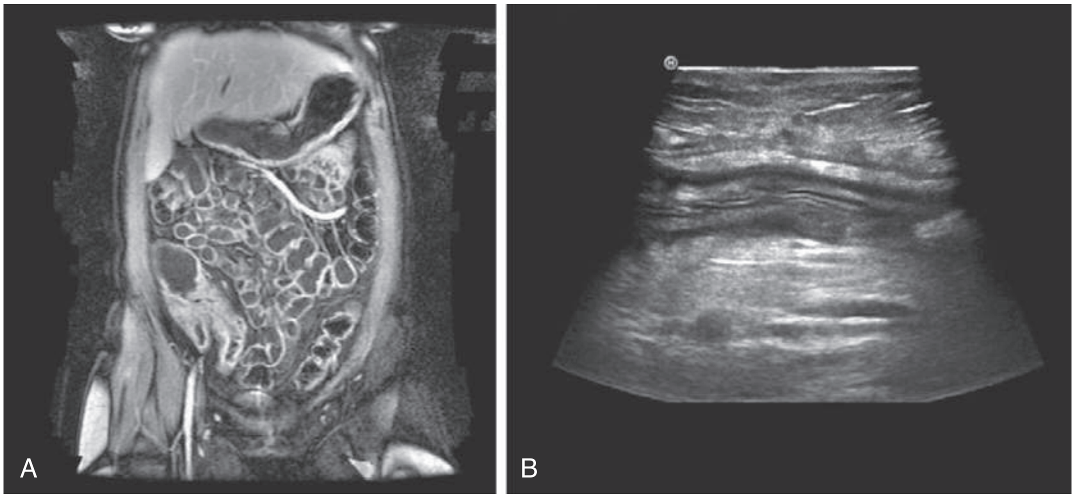

Figure 336-6 **Stenosis in Crohn disease. A,** MR enterography of Crohn disease restricted to the terminal ileum (Montreal category L1) with inflammatory stenosis. **B,** Ultrasound image of an intestinal stenosis in Crohn disease. *(From Baumgart DC, Sandborn WJ: Crohn's disease.* Lancet *380:1590–1602, 2012, Fig. 4, p. 1596.)*

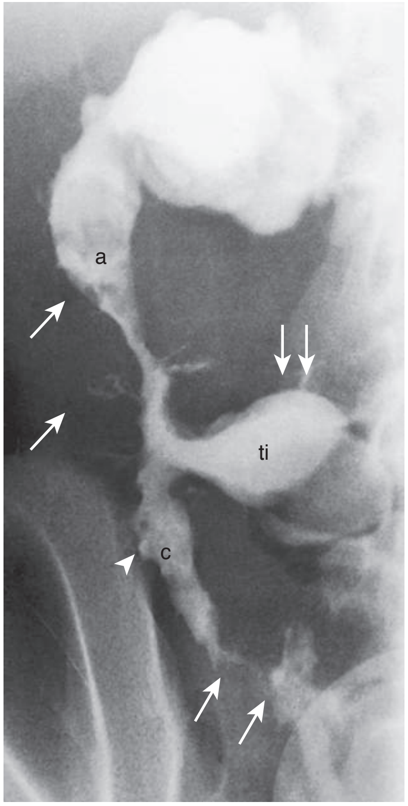

Figure 336-7 **Crohn disease: sinuses and fistula.** Severe ileocolitis has resulted in an ileocecal fistula *(single arrows, lower)* and sinus formation in the ascending colon *(a) (arrows on platform). c,* Cecum *(arrowhead); ti,* terminal ileum *(paired arrows). (From The child with diarrhea. In Hoffman AD, Hilton SW, Edwards DK, editors:* Practical pediatric radiology, *ed 2, Philadelphia, 1994, WB Saunders, p 268.)*

DIFFERENTIAL DIAGNOSIS

The most common diagnoses to be distinguished from Crohn disease are the infectious enteropathies (in the case of Crohn disease: acute terminal ileitis, infectious colitis, enteric parasites, and periappendiceal abscess) (see Tables 336-4, 336-5, and 336-7). *Yersinia* can cause many of the radiologic and endoscopic findings in the distal small bowel that are seen in Crohn disease. The symptoms of bacterial dysentery are more likely to be mistaken for ulcerative colitis than for Crohn disease. Celiac disease and *Giardia* infection have been noted to produce a Crohn-like presentation including diarrhea, weight loss, and protein-losing enteropathy. GI tuberculosis is rare but can mimic Crohn disease. Foreign-body perforation of the bowel (toothpick) can mimic a localized region with Crohn disease. Small bowel lymphoma can mimic Crohn disease but tends to be associated with nodular filling defects of the bowel without ulceration or narrowing of the lumen. Bowel lymphoma is much less common in children than is Crohn disease. Recurrent functional abdominal pain can mimic the pain of small bowel Crohn disease. *Lymphoid nodular hyperplasia* of the terminal ileum (a normal finding) may be mistaken for Crohn ileitis. Right lower quadrant pain or mass with fever can be the result of periappendiceal abscess. This entity is occasionally associated with diarrhea as well.

Growth failure may be the only manifestation of Crohn disease; other disorders such as growth hormone deficiency, gluten-sensitive enteropathy (celiac disease), Turner syndrome, or anorexia nervosa must be considered. If arthritis precedes the bowel manifestations, an initial diagnosis of juvenile idiopathic arthritis may be made. Refractory anemia may be the presenting feature and may be mistaken for a primary hematologic disorder. Chronic granulomatous disease of childhood can cause inflammatory changes in the bowel as well as perianal disease. Antral narrowing in this disorder may be mistaken for a stricture secondary to Crohn disease. Other immunodeficiencies or autoinflammatory conditions and monogenetic disorders may present with GI symptoms suggestive of IBD, particularly in very early or infant/toddler onset of disease (see Table 336-5).

DIAGNOSIS

Crohn disease can manifest as a variety of symptom combinations. At the onset, symptoms may be subtle (growth retardation, abdominal pain alone); this explains why the diagnosis might not be made until 1 or 2 yr after the start of symptoms. The diagnosis of Crohn disease depends on finding typical clinical features of the disorder (history, physical examination, laboratory studies, and endoscopic or radiologic findings), ruling out specific entities that mimic Crohn disease, and demonstrating chronicity. The history can include any combination of abdominal pain (especially right lower quadrant), diarrhea, vomiting, anorexia, weight loss, growth retardation, and extraintestinal manifestations. Only 25% initially have the triad of diarrhea, weight loss, and abdominal pain. Most do not have diarrhea, and only 25% have GI bleeding.

Children with Crohn disease often appear chronically ill. They commonly have weight loss and growth failure, and they are often

Table 336-7 Differential Diagnosis of Presenting Symptoms of Crohn Disease

PRIMARY PRESENTING SYMPTOM	DIAGNOSTIC CONSIDERATIONS
Right lower quadrant abdominal pain, with or without mass	Appendicitis, infection (e.g., *Campylobacter, Yersinia* spp.), lymphoma, intussusception, mesenteric adenitis, Meckel diverticulum, ovarian cyst
Chronic periumbilical or epigastric abdominal pain	Irritable bowel syndrome, constipation, lactose intolerance, peptic disease
Rectal bleeding, no diarrhea	Fissure, polyp, Meckel diverticulum, rectal ulcer syndrome
Bloody diarrhea	Infection, hemolytic-uremic syndrome, Henoch-Schönlein purpura, ischemic bowel, radiation colitis
Watery diarrhea	Irritable bowel syndrome, lactose intolerance, giardiasis, *Cryptosporidium* infection, sorbitol, laxatives
Perirectal disease	Fissure, hemorrhoid (rare), streptococcal infection, condyloma (rare)
Growth delay	Endocrinopathy
Anorexia, weight loss	Anorexia nervosa
Arthritis	Collagen vascular disease, infection
Liver abnormalities	Chronic hepatitis

From Kugathasan S: Diarrhea. In Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, WB Saunders, p. 287.*

malnourished. The earliest sign of growth failure is decreased height velocity, which can be present in up to 88% of prepubertal patients with Crohn disease and typically precedes symptoms. Children with Crohn disease often appear pale, with decreased energy level and poor appetite; the latter finding sometimes results from an association between meals and abdominal pain or diarrhea. There may be abdominal tenderness that is either diffuse or localized to the right lower quadrant. A tender mass or fullness may be palpable in the right lower quadrant. Perianal disease, when present, may be characteristic. Large anal skin tags (1-3 cm diameter) or perianal fistulas with purulent drainage suggest Crohn disease. Digital clubbing, findings of arthritis, and skin manifestations may be present.

A complete blood cell count commonly demonstrates anemia, often with a component of iron deficiency, as well as thrombocytosis. Although the erythrocyte sedimentation rate and C-reactive protein are often elevated, they may be unremarkable. The serum albumin level may be low, indicating small bowel inflammation or protein-losing enteropathy. Fecal calprotectin and lactoferrin are increasingly being utilized as more sensitive and specific markers of bowel inflammation as compared to serologic parameters, and these are often elevated. Multiple serologic, immune, and genetic markers can also be abnormal, although the best utilization of these remains to be determined.

The small and large bowel and the upper GI tract should be examined by both endoscopic and radiologic studies in the child with suspected Crohn disease. Esophagogastroduodenoscopy and ileocolonoscopy should be performed to properly assess the upper GI tract, terminal ileum, and entire colon. Findings on colonoscopy can include patchy, nonspecific inflammatory changes (erythema, friability, loss of vascular pattern), aphthous ulcers, linear ulcers, nodularity, and strictures. Findings on biopsy may be only nonspecific chronic inflammatory changes. Noncaseating granulomas, similar to those of sarcoidosis, are the most characteristic histologic findings, although often they are not present. Transmural inflammation is also characteristic but can be identified only in surgical specimens.

Radiologic studies are necessary to assess the entire small bowel and investigate for evidence of structuring or penetrating disease. A variety of findings may be apparent on radiologic studies. Plain films of the abdomen may be normal or might demonstrate findings of partial small bowel obstruction or thumbprinting of the colon wall. An upper GI contrast study with small bowel follow-through might show aphthous ulceration and thickened, nodular folds as well as narrowing or stricturing of the lumen. Linear ulcers can give a cobblestone appearance to the mucosal surface. Bowel loops are often separated as a result of thickening of bowel wall and mesentery. Other manifestations on radiographic studies that suggest more-severe Crohn disease are fistulas between bowel (enteroenteric or enterocolonic), sinus tracts, and strictures (see Figs. 336-5, 336-6, and 336-7).

An upper GI contrast examination with small bowel follow-through has typically been the study of choice for imaging of the small bowel, but CT and MR enterography and small bowel ultrasound are increasingly being used. MR and ultrasound have the advantage of not exposing the patient to ionizing radiation. CT and MR enterography can also assess for extraluminal findings such as abscesses and phlegmons. MR of the pelvis is also useful for delineating the extent of perianal involvement.

Video capsule endoscopy is another modality that allows for evaluation of the small bowel. This study can uncover mucosal inflammation or ulceration that might not have been detected by traditional imaging.

TREATMENT

Crohn disease cannot be cured by medical or surgical therapy. The aim of treatment is to relieve symptoms and prevent complications of chronic inflammation (anemia, growth failure), prevent relapse, minimize corticosteroid exposure, and, if possible, effect mucosal healing.

Medical

The specific therapeutic modalities used depend on geographic localization of disease, severity of inflammation, age of the patient, and the presence of complications (abscess). Traditionally, a "step-up" treatment paradigm has been utilized in the treatment of pediatric Crohn disease, whereby early disease is treated with steroids and less immunosuppressive medications. Escalation of therapy would occur if disease severity increased, the patient was refractory to current medications, or for steroid dependence. More recently, a "top-down" approach has been espoused, particularly in adults after multiple studies demonstrated superior efficacy. With this approach, patients with moderate to severe Crohn disease are treated initially with stronger, disease modifying agents, with the goal of achieving mucosal healing, or deep remission, early in the disease course. This is thought to increase the likelihood of long-term remission while decreasing corticosteroid exposure. The role for this approach in pediatrics is still being determined, but top down treatment is being increasingly utilized.

5-Aminosalicylates

For mild terminal ileal disease or mild Crohn disease of the colon, an initial trial of mesalamine (50-100 mg/kg/day, maximum 3-4 g) may be attempted. Specific pharmaceutical preparations have been formulated to release the active 5-ASA compound throughout the small bowel, in the ileum and colon, or exclusively in the colon. Rectal preparations are used for distal colonic inflammation.

Antibiotics/Probiotics

Antibiotics such as metronidazole (10-20 mg/kg/day) are used for infectious complications, are first-line therapy for perianal disease (although perianal disease usually recurs when antibiotic is discontinued), and they may be effective for treatment of mild to moderate Crohn disease. To date, probiotics have not been shown to be effective in induction or maintenance of remission for pediatric Crohn disease.

Corticosteroids

Corticosteroids are utilized for acute exacerbations of pediatric Crohn disease because they effectively suppress acute inflammation, rapidly relieving symptoms (prednisone, 1-2 mg/kg/day, maximum 40-60 mg). The goal is to taper dosing as soon as the disease becomes quiescent. Clinicians vary in their tapering schedules, and the disease can flare during this process. There is no role for continuing corticosteroids as maintenance therapy because, in addition to their side effects, tolerance develops and steroids do not change disease course or promote healing of mucosa. A special controlled ileal-release formulation of budesonide, a corticosteroid with local antiinflammatory activity on the bowel mucosa and high hepatic first-pass metabolism, is also used for mild to moderate ileal or ileocecal disease (adult dose: 9 mg daily). Ileal-release budesonide appears to be more effective than mesalamine in the treatment of active ileocolonic disease but is less effective than prednisone. Although less effective than traditional corticosteroids, budesonide does cause less steroid-related side effects.

Immunomodulators

Approximately 70% of patients require escalation of medical therapy within in the 1st yr of pediatric Crohn disease diagnosis. Immunomodulators such as azathioprine (2.0-2.5 mg/kg/day) or 6-mercaptopurine (1.0-1.5 mg/kg/day) may be effective in some children who have a poor response to prednisone or who are steroid dependent. Because a beneficial effect of these drugs can be delayed for 3-4 mo after starting therapy, they are not helpful acutely. The early use of these agents can decrease cumulative prednisone dosages over the 1st 1-2 yr of therapy. Genetic variations in an enzyme system responsible for metabolism of these agents (thiopurine *S*-methyltransferase) can affect response rates and potential toxicity. Lymphoproliferative disorders have developed from thiopurine use in patients with IBD. Other common toxicities include hepatitis, pancreatitis, increased risk of skin cancer, increased risk of infection, and slightly increased risk of lymphoma.

Methotrexate is another immunomodulator that is effective in the treatment of active Crohn disease and has been shown to improve height velocity in the 1st yr of administration. The advantages of this medication include once-weekly dosing by either subcutaneous or oral route (10-15 mg/m^2, adult dose 25 mg weekly) and a more-rapid onset of action (6-8 wk) than azathioprine or 6-mercaptopurine. Folic acid is usually administered concomitantly to decrease medication side effects. Administration of ondansetron prior to methotrexate has been shown to diminish the risk of the most common side effect of nausea. The most common toxicity is hepatitis. The immunomodulators are effective for the treatment of perianal fistulas.

Biologic Therapy

Therapy with antibodies directed against mediators of inflammation is used for patients with Crohn disease. Infliximab, a chimeric monoclonal antibody to TNF-α, is effective for the induction and maintenance of remission and mucosal healing in chronically active moderate to severe Crohn disease, healing of perianal fistulas, steroid sparing, and preventing postoperative recurrence. Pediatric data additionally support improved growth with the administration of this medication. The onset of action of infliximab is quite rapid and it is initially given as 3 infusions over a 6 wk period (0, 2, and 6 wk), followed by maintenance dosing beginning every 8 wk. The durability of response to infliximab is variable and dose escalation (higher dose and/or decreased interval) is often necessary. Measurement of serum trough infliximab level prior to an infusion can help guide dosing decisions. Side effects include infusion reactions, increased incidence of infections (especially reactivation of latent tuberculosis), increased risk of lymphoma, and the development of autoantibodies. The development of antibodies to infliximab is associated with an increased incidence of infusion reactions and decreased durability of response. Regularly scheduled dosing of infliximab, as opposed to episodic dosing on an as-needed basis, is associated with decreased levels of antibodies to infliximab. A purified protein derivative test for tuberculosis should be done before starting infliximab.

Adalimumab, a subcutaneously administered, fully humanized monoclonal antibody against TNF-α, is effective for the treatment of chronically active moderate to severe Crohn disease in adults and children. After a loading dose, this is typically administered once every 2 wk, although dose escalation is sometimes required with this medication. Vedolizumab, a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the gastrointestinal tract, was recently approved for the treatment of Crohn disease in adults. Antibodies against interleukins 12 and 23 antiselective adhesion molecules (ustekinumab), chemokine antagonists, and antagonist to Janus kinase 3 are currently being tested.

Enteral Nutritional Therapy

Exclusive enteral nutritional therapy, whereby all of a patient's calories are delivered via formula, is an effective primary as well as adjunctive treatment. The enteral nutritional approach is as rapid in onset of response and as effective as the other treatments. Pediatric studies have suggested similar efficacy to prednisone for improvement in clinical symptoms, but enteral nutritional therapy is superior to steroids for actual healing of mucosa. Because affected patients have poor appetite and these formulas are relatively unpalatable, they are often administered via a nasogastric or gastrostomy infusion, usually overnight. The advantages are that it is relatively free of side effects, avoids the problems associated with corticosteroid therapy, and simultaneously addresses the nutritional rehabilitation. Children can participate in normal daytime activities. A major disadvantage of this approach is that patients are not able to eat a regular diet because they are receiving all of their calories from formula. A novel approach where 80-90% of caloric needs are provided by formula, allowing children to have some food intake, has been successful. For children with growth failure, this approach may be ideal, however.

High-calorie oral supplements, although effective, are often not tolerated because of early satiety or exacerbation of symptoms (abdominal pain, vomiting, or diarrhea). Nonetheless, they should be offered to children whose weight gain is suboptimal even if they are not candidates for exclusive enteral nutritional therapy. The continuous administration of nocturnal nasogastric feedings for chronic malnutrition and growth failure has been effective with a much lower risk of complications than parenteral hyperalimentation.

Surgery

Surgical therapy should be reserved for very specific indications. Recurrence rate after bowel resection is high (>50% by 5 yr); the risk of requiring additional surgery increases with each operation. Potential complications of surgery include development of fistula or stricture, anastomotic leak, postoperative partial small bowel obstruction secondary to adhesions, and short bowel syndrome. Surgery is the treatment of choice for localized disease of small bowel or colon that is unresponsive to medical treatment, bowel perforation, fibrosed stricture with symptomatic partial small bowel obstruction, and intractable bleeding. Intraabdominal or liver abscess sometimes is successfully treated by ultrasonographic or CT-guided catheter drainage and concomitant intravenous antibiotic treatment. Open surgical drainage is necessary if this approach is not successful. Growth retardation was once considered an indication for resection; without other indications, trial of medical and/or nutritional therapy is currently preferred.

Perianal abscess often requires drainage unless it drains spontaneously. In general, perianal fistulas should be managed by a combined medical and surgical approach. Often, the surgeon places a seton through the fistula to keep the tract open and actively draining while

medical therapy is administered, to help prevent the formation of a perianal abscess. A severely symptomatic perianal fistula can require fistulotomy, but this procedure should be considered only if the location allows the sphincter to remain undamaged.

The surgical approach for Crohn disease is to remove as limited a length of bowel as possible. There is no evidence that removing bowel up to margins that are free of histologic disease has a better outcome than removing only grossly involved areas. The latter approach reduces the risk of short bowel syndrome. Laparoscopic approach is increasingly being used, with decreased postoperative recovery time. One approach to symptomatic small bowel stricture has been to perform a strictureplasty rather than resection. The surgeon makes a longitudinal incision across the stricture but then closes the incision with sutures in a transverse fashion. This is ideal for short strictures without active disease. The reoperation rate is no higher with this approach than with resection, whereas bowel length is preserved. Postoperative medical therapy with agents such as mesalamine, metronidazole, azathioprine, and, more recently, infliximab, is often given to decrease the likelihood of postoperative recurrence.

Severe perianal disease can be incapacitating and difficult to treat if unresponsive to medical management. Diversion of fecal stream can allow the area to be less active, but on reconnection of the colon, disease activity usually recurs.

Support

Psychosocial issues for the child with Crohn disease include a sense of being different, concerns about body image, difficulty in not participating fully in age-appropriate activities, and family conflict brought on by the added stress of this disease. Social support is an important component of the management of Crohn disease. Parents are often interested in learning about other children with similar problems, but children may be hesitant to participate. Social support and individual psychologic counseling are important in the adjustment to a difficult problem at an age that by itself often has difficult adjustment issues. Patients who are socially "connected" fare better. Ongoing education about the disease is an important aspect of management because children generally fare better if they understand and anticipate problems. The Crohn and Colitis Foundation of America has local chapters throughout the United States and supports several regional 1-wk camps for children with Crohn disease.

PROGNOSIS

Crohn disease is a chronic disorder that is associated with high morbidity but low mortality. Symptoms tend to recur despite treatment and often without apparent explanation. Weight loss and growth failure can usually be improved with treatment and attention to nutritional needs. Up to 15% of patients with early growth retardation secondary to Crohn disease have a permanent decrease in linear growth. Osteopenia is particularly common in those with chronic poor nutrition and frequent exposure to high doses of corticosteroids. Some of the extraintestinal manifestations can, in themselves, be major causes of morbidity, including sclerosing cholangitis, chronic active hepatitis, pyoderma gangrenosum, and ankylosing spondylitis.

The region of bowel involved and complications of the inflammatory process tend to increase with time and include bowel strictures, fistulas, perianal disease, and intra-abdominal or retroperitoneal abscess. A majority of patients with Crohn disease eventually require surgery for one of its many complications; the rate of reoperation is high. Surgery is unlikely to be curative and should be avoided except for the specific indications noted previously. An earlier, most aggressive medical treatment approach, with the goal of exacting mucosal healing may improve long-term prognosis, and this is an active area of investigation. The risk of colon cancer in patients with long-standing Crohn colitis approaches that associated with ulcerative colitis, and screening colonoscopy after 10 yr of colonic disease is indicated.

Despite these complications, most children with Crohn disease lead active, full lives with intermittent flare-up in symptoms.

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Chapter **337**

Eosinophilic Gastroenteritis

Andrew B. Grossman and Robert N. Baldassano

Eosinophilic gastroenteritis consists of a group of rare and poorly understood disorders that have in common gastric and small intestine infiltration with eosinophils and peripheral eosinophilia. The esophagus and large intestine may also be involved. Tissue eosinophilic infiltration can be seen in mucosa, muscularis, or serosa. The mucosal form is most common and is diagnosed by identifying large numbers of eosinophils in biopsy specimens of gastric antrum or small bowel. This condition clinically overlaps the dietary protein hypersensitivity disorders of the small bowel and colon. The differential diagnosis also includes celiac disease, chronic granulomatous disease, connective tissue disorders and vasculitides, multiple infections (particularly parasites), hypereosinophilic syndrome, early inflammatory bowel disease, and rarely malignancy. Many patients have allergies to multiple foods, seasonal allergies, atopy, eczema, and asthma. Serum immunoglobulin E is commonly elevated. Peripheral eosinophilia is present in approximately 5-70% of patients with this disorder. Other laboratory abnormalities can include hypoalbuminemia, iron deficiency anemia, and elevated liver enzymes.

The presentation of eosinophilic gastroenteritis is nonspecific. Clinical symptoms often correlate with which layers of the gastrointestinal tract are affected. Mucosal involvement can produce nausea, vomiting, diarrhea, abdominal pain, gastrointestinal bleeding, protein-losing enteropathy, or malabsorption. Involvement of the muscularis can produce obstruction (especially of the pylorus) or intussusception, whereas serosal activity produces abdominal distention and eosinophilic ascites. Presentation in infants can be similar to pyloric stenosis. Laboratory testing often reveals peripheral eosinophilia, elevated serum immunoglobulin E levels, hypoalbuminemia, and anemia.

The disease usually runs a chronic, debilitating course with sporadic severe exacerbations. Although almost always effective for the treatment of isolated eosinophilic esophagitis, elemental diets are not always successful for the treatment of eosinophilic gastroenteritis. Orally administered cromolyn sodium and montelukast are sometimes successful. A majority of patients require treatment with systemic corticosteroids, which are often effective.

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Chapter 338

Disorders of Malabsorption

David Branski

All disorders of malabsorption are associated with diminished intestinal absorption of one or more dietary nutrients. Malabsorption can result from a defect in the nutrient **digestion** in the intestinal lumen or from defective mucosal **absorption.** Malabsorption disorders can be categorized into generalized mucosal abnormalities usually

Table 338-1	Malabsorption Disorders and Chronic Diarrhea Associated with Generalized Mucosal Defect
Mucosal disorders	
Gluten-sensitive enteropathy (celiac disease)	
Cow's milk and other protein-sensitive enteropathies	
Eosinophilic enteropathy	
Protein-losing enteropathy	
Lymphangiectasia (congenital and acquired)	
Disorders causing bowel mucosal inflammation, Crohn disease	
Congenital bowel mucosal defects	
Microvillous inclusion disease	
Tufting enteropathy	
Carbohydrate-deficient glycoprotein syndrome	
Enterocyte heparan sulfate deficiency	
Enteric anendocrinosis (NEUROG 3 mutation)	
Tricho-hepatic-enteric syndrome	
Immunodeficiency disorders	
Congenital immunodeficiency disorders	
Selective immunoglobulin A deficiency (can be associated with celiac disease)	
Severe combined immunodeficiency	
Agammaglobulinemia	
X-linked hypogammaglobulinemia	
Wiskott-Aldrich syndrome	
Common variable immunodeficiency disease	
Chronic granulomatous disease	
Acquired immune deficiency	
HIV infection	
Immunosuppressive therapy and post–bone marrow transplantation	
Autoimmune enteropathy	
IPEX (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked inheritance)	
IPEX-like syndromes	
Autoimmune polyglandular syndrome type 1	
Miscellaneous	
Immunoproliferative small intestinal disease	
Short bowel syndrome	
Blind loop syndrome	
Radiation enteritis	
Protein–calorie malnutrition	
Crohn disease	
Pseudoobstruction	

resulting in malabsorption of multiple nutrients (Table 338-1) or malabsorption of specific nutrients (carbohydrate, fat, protein, vitamins, minerals, and trace elements) (Table 338-2). Almost all the malabsorption disorders are accompanied by chronic diarrhea which further worsens the malabsorption. (see Chapter 341).

CLINICAL APPROACH

The clinical features depend on the extent and type of the malabsorbed nutrient. The common presenting features, especially in toddlers with malabsorption, are diarrhea, abdominal distention, and failure to gain weight, with a fall in growth chart percentiles. Physical findings include abdominal distention, muscle wasting, and the disappearance of the subcutaneous fat, with subsequent loose skinfolds (Fig. 338-1). The nutritional consequences of malabsorption are more dramatic in toddlers because the limited energy reserves and higher proportion of calorie intake being used for weight gain and linear growth. In older children, malnutrition can result in growth retardation, as is commonly seen in children with late diagnosis of celiac disease. If malabsorption is left untreated, linear growth slows, and with prolonged malnutrition, death can follow (see Chapter 46). This extreme outcome is usually restricted to children living in the developing world, where resources to provide enteral and parenteral nutrition support may be limited. Specific findings on examination can guide toward a specific disorder; edema is usually associated with protein-losing enteropathy, digital clubbing with cystic fibrosis and celiac disease, perianal excoriation and gaseous abdominal distention with carbohydrate malabsorption, perianal and circumoral rash with acrodermatitis enteropathica, abnormal hair with Menkes syndrome, and the typical facial features diagnostic of the Johanson-Blizzard syndrome.

Table 338-2	Classification of Malabsorption Disorders and Chronic Diarrhea Based on the Predominant Nutrient Malabsorbed
CARBOHYDRATE MALABSORPTION	
Lactose malabsorption	
Congenital lactase deficiency	
Hypolactasia (adult type)	
Secondary lactase deficiency	
Congenital sucrase-isomaltase deficiency	
Glucose galactose malabsorption	
FAT MALABSORPTION	
Abetalipoproteinemia	
Lymphangiectasia	
Homozygous hypobetalipoproteinemia	
Chylomicron retention disease (Anderson disease)	
Cystic fibrosis	
Shwachman-Diamond syndrome	
Johanson-Blizzard syndrome	
Pearson syndrome	
Secondary exocrine pancreatic insufficiency	
Isolated enzyme deficiency	
Enterokinase deficiency	
Trypsinogen deficiency	
Lipase/colipase deficiency	
Chronic pancreatitis	
Protein–calorie malnutrition	
Decreased pancreozymin/cholecystokinin secretion	
Disrupted enterohepatic circulation of bile salts	
Cholestatic liver disease	
Bile acid synthetic defects	
Bile acid malabsorption (terminal ileal disease)	
PROTEIN/AMINO ACID MALABSORPTION	
Lysinuric protein intolerance (defect in dibasic amino acid transport)	
Hartnup disease (defect in free neutral amino acids)	
Blue diaper syndrome (isolated tryptophan malabsorption)	
Oasthouse urine disease (defect in methionine absorption)	
Lowe syndrome (lysine and arginine malabsorption)	
Enterokinase deficiency	
MINERAL AND VITAMIN MALABSORPTION	
Congenital chloride diarrhea	
Congenital sodium absorption defect	
Acrodermatitis enteropathica (zinc malabsorption)	
Menkes disease (copper malabsorption)	
Vitamin D–dependent rickets	
Folate malabsorption	
Congenital	
Secondary to mucosal damage (celiac disease)	
Vitamin B_{12} malabsorption	
Autoimmune pernicious anemia	
Decreased gastric acid (H_2 blockers or proton pump inhibitors)	
Terminal ileal disease (e.g., Crohn disease) or resection	
Inborn errors of vitamin B_{12} transport and metabolism	
Primary hypomagnesemia	
DRUG INDUCED	
Sulfasalazine: folic acid malabsorption	
Cholestyramine: calcium and fat malabsorption	
Anticonvulsant drugs such as phenytoin (causing vitamin D deficiency and folic acid and calcium malabsorption)	
Gastric acid suppression: vitamin B_{12}	
Methotrexate: mucosal injury	

Many children with malabsorption disorders have very good appetites as they try to compensate for the fecal protein and energy losses. In exocrine pancreatic insufficiency, fecal losses of up to 40% of ingested protein and energy do not lead to malnutrition, as long as they are compensated by an increased appetite. In conditions associated

Figure 338-1 An 18 mo old boy with active celiac disease. Note the loose skinfolds, marked proximal muscle wasting and distended abdomen. The child looks ill.

with villous atrophy or inflammation (celiac disease, postinfectious enteropathy), fecal protein and energy losses are usually modest, but associated anorexia and reduced food intake results in malnutrition.

The nutritional assessment is an important part of clinical evaluation in children with malabsorptive disorders (see Chapter 44). Long-term calcium and vitamin D malabsorption can lead to reduced bone mineral density and metabolic bone disease, with increased risk of bone fractures. Vitamin K malabsorption, irrespective of the underlying mechanism (fat malabsorption, mucosal atrophy), can result in coagulopathy. Severe protein-losing enteropathy is often associated with malabsorption syndromes (celiac disease, intestinal lymphangiectasia) and causes hypoalbuminemia and edema. Other nutrient deficiencies include iron malabsorption causing microcytic anemia and low reticulocyte count, low serum folate levels in conditions associated with mucosal atrophy, especially in the proximal part of the small intestinal tract and low serum vitamin A and vitamin E concentrations in fat malabsorption.

Clinical history alone might not be sufficient to make a specific diagnosis, but it can direct the pediatrician toward a more structured and rational investigative approach. Diarrhea is the main clinical expression of malabsorption. Onset of diarrhea in early infancy suggests a congenital defect (Tables 338-3 and 336-5). In secretory diarrhea caused by disorders such as congenital chloride diarrhea and microvillus inclusion disease, the stool is watery and voluminous and can be mistaken for urine. Onset of symptoms after introduction of a particular food into a child's diet can provide diagnostic clues, such as with sucrose in sucrase-isomaltase deficiency. The nature of the diarrhea may be helpful: explosive watery diarrhea suggests carbohydrate malabsorption; loose, bulky stools are associated with celiac disease; and pasty and yellowish offensive stools suggest an exocrine pancreatic insufficiency. Stool color is usually not helpful; green stool with undigested "peas and carrots" can suggest rapid intestinal transit in toddler's diarrhea, which is a self-limiting condition unassociated with failure to thrive.

Table 338-3 Diarrheal Diseases Appearing in the Neonatal Period

CONDITION	CLINICAL FEATURES
Microvillus inclusion disease	Secretory watery diarrhea
Tufting enteropathy	Secretory watery diarrhea
Congenital glucose-galactose malabsorption	Acidic diarrhea
Congenital lactase deficiency	Acidic diarrhea
Congenital chloride diarrhea	Hydramnion, secretory watery diarrhea Metabolic alkalosis
Congenital defective jejunal Na^+-H^+ exchange	Hydramnion, secretory watery diarrhea
Congenital bile acid malabsorption	Steatorrhea
Congenital enterokinase deficiency	Failure to thrive, edema
Congenital trypsinogen deficiency	Failure to thrive, edema
Congenital lipase and/or colipase deficiency	Failure to thrive, oily stool
Enteric anendocrinosis (NEUROG 3 mutation)	Hyperchloremic acidosis, failure to thrive
Immunodeficiency and autoinflammatory diseases (see Table 336-5)	Failure to thrive, opportunistic infections, eczema

Adapted from Schmitz J: Maldigestion and malabsorption. In Walker WA, Durie PR, Hamilton JR, et al, editors: Pediatric gastrointestinal disease, *ed 3, Hamilton, Ontario, 2000, BC Decker, p. 55.*

338.1 Evaluation of Children with Suspected Intestinal Malabsorption

Michael J. Lentze and David Branski

The investigation is guided by the history and physical examination. In a child presenting with chronic or recurrent diarrhea, the initial work-up should include stool cultures and antibody tests for parasites, stool microscopy for ova and parasites such as *Giardia*, and stool occult blood and leukocytes to exclude inflammatory disorders. Stool pH and reducing substances for carbohydrate malabsorption, and quantitative stool fat examination and α_1-antitrypsin to demonstrate fat and protein malabsorption, respectively, should also be determined. Fecal stool elastase-1 can determine exocrine pancreatic insufficiency.

A complete blood count including peripheral smear for microcytic anemia, lymphopenia (lymphangiectasia), neutropenia (Shwachman syndrome), and acanthocytosis (abetalipoproteinemia) is useful. If celiac disease is suspected, serum immunoglobulin (Ig) A and tissue transglutaminase (TG2) antibody levels should be determined. Depending on the initial test results, more-specific investigations can be planned.

INVESTIGATIONS FOR CARBOHYDRATE MALABSORPTION

Measurement of carbohydrate in the stool, using a Clinitest reagent that identifies reducing substances, is a simple screening test. An acidic stool with >2+ reducing substance suggests carbohydrate malabsorption. Sucrose or starch in the stool is not recognized as a reducing sugar until after hydrolysis with hydrochloric acid, which converts them to reducing sugars.

Breath hydrogen test is used to identify the specific carbohydrate that is malabsorbed. After an overnight fast, the suspected sugar (lactose, sucrose, fructose, or glucose) is administered as an oral solution (carbohydrate load 1-2 g/kg, maximum 50 g). In malabsorption,

the sugar is not digested or absorbed in the small bowel, passes on to the colon, and is metabolized by the normal bacteria flora. One of the products of this process is hydrogen gas, which is absorbed through the colon mucosa and excreted in the breath. Increased hydrogen concentration in the breath samples suggests carbohydrate malabsorption. A rise in breath hydrogen of 20 ppm above the baseline is considered a positive test. The child should not be on antibiotics at the time of the test, because colonic flora is essential for fermenting the sugar.

Small bowel mucosal biopsies can measure mucosal disaccharidase (lactase, sucrase, maltase, palatinase) concentrations directly. In primary enzyme deficiencies the mucosal enzyme levels are low and small bowel mucosal morphology is normal. Partial or total villous atrophy due to disorders such as celiac disease, or following rotavirus gastroenteritis can result in secondary disaccharidase deficiency and transient lactose intolerance. The disaccharidase levels revert to normal after mucosal healing.

INVESTIGATIONS FOR FAT MALABSORPTION

The presence of fat globules in the stool suggests fat malabsorption. The ability to assimilate fat varies with age; a premature infant can absorb only 65-75% of dietary fat, a full-term infant absorbs almost 90%, and an older child absorbs more than 95% of fat while on a regular diet. Quantitative determination of fat malabsorption requires a 3-day stool collection for evaluation of fat excretion and determination of the coefficient of fat absorption:

$$\text{Coefficient of fat absorption\%} = (\text{fat intake} - \text{fecal fat losses}/\text{fat intake}) \times 100$$

where fat intake and fat losses are in grams. Because fecal fat balance studies are cumbersome, expensive, and unpleasant to perform, simpler tests are often preferred. Among these stool tests, the acid steatocrit test is the most reliable. When bile acid deficiency is suspected of being the cause of fat malabsorption, the evaluation of bile acid levels in duodenal fluid aspirate may be useful.

Fat malabsorption and exocrine pancreatic insufficiency are usually associated with deficiencies of fat-soluble vitamins A, D, E, and K. Serum concentrations of vitamins A, D, and E can be measured. A prolonged prothrombin time is an indirect test to assess vitamin K deficiency.

INVESTIGATIONS FOR PROTEIN-LOSING ENTEROPATHY

Dietary and endogenous proteins secreted into the bowel are almost completely absorbed; <1 g of protein from these sources passes into the colon. The majority of the stool nitrogen is derived from gut bacterial proteins. Excessive bowel protein loss usually manifests as **hypoalbuminemia.** Because the most common cause of hypoalbuminemia in children is a renal disorder, urinary protein excretion must be determined. Other potential causes of hypoalbuminemia include liver disease (reduced production) and inadequate protein intake. Very rarely hypoalbuminemia can result from an extensive skin disorder causing protein loss via the skin. Measurement of stool **α_1-antitrypsin** is a useful screening test for protein-losing enteropathy. This serum protein has a molecular weight similar to albumin's; however, unlike albumin it is resistant to digestion in the gastrointestinal (GI) tract. Excessive α_1-antitrypsin excretion in the stool should prompt further investigations to identify the specific cause of gut or stomach (Menetrier disease) protein loss.

INVESTIGATIONS FOR EXOCRINE PANCREATIC FUNCTION (Fig. 338-2)

Cystic fibrosis is the most common cause of exocrine pancreatic insufficiency in children; therefore, a sweat chloride test must be performed before embarking on invasive tests to investigate possible exocrine pancreatic insufficiency. Many cases of cystic fibrosis are detected by neonatal genetic screening programs; occasional rare mutations are undetected.

Fecal elastase-1 estimation is a sensitive test to assess exocrine pancreatic function in chronic cystic fibrosis and pancreatitis. Elastase-1 is a stable endoprotease unaffected by exogenous pancreatic enzymes. One disadvantage of the fecal elastase-1 test is the lack of full differentiation between primary exocrine pancreatic insufficiency and exocrine pancreatic dysfunction secondary to intestinal villous atrophy. The proximal small bowel is the site for pancreozymin/cholecystokinin production; the latter is the hormone that stimulates enzyme secretion from the exocrine pancreas. Mucosal atrophy can lead to diminished pancreozymin/cholecystokinin secretion and subsequently to exocrine pancreatic insufficiency. Fecal elastase-1 can also give a false-positive result during acute episodes of diarrhea.

Serum trypsinogen concentration can also be used as a screening test for exocrine pancreatic insufficiency. In cystic fibrosis, the levels are greatly elevated early in life, and then they gradually fall, so that by 5-7 yr of age, most patients with cystic fibrosis with pancreatic insufficiency have subnormal levels. Patients with cystic fibrosis and adequate exocrine pancreatic function tend to have normal or elevated levels. In such patients, observing the trend in serial serum trypsinogen estimation may be useful in monitoring exocrine pancreatic function. In Shwachman syndrome, another condition associated with exocrine pancreatic insufficiency, the serum trypsinogen level is low.

Other tests for pancreatic insufficiency (nitroblue tetrazolium–paraaminobenzoic acid test and pancreolauryl test) measure urine or breath concentrations of substances released and absorbed across the mucosal surface following pancreatic digestion. These tests lack specificity and are rarely used in clinical practice.

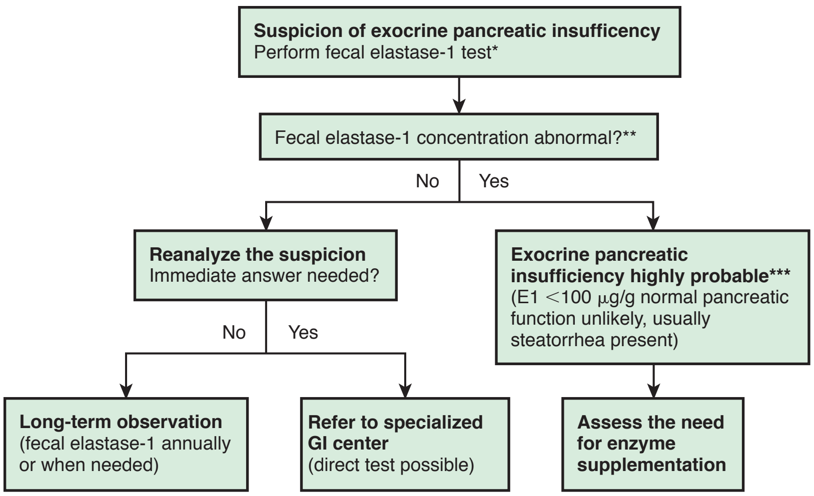

Figure 338-2 Algorithm for assessment of exocrine pancreatic function. *If not available, use other test. Perform appropriate imaging studies of the pancreas. **In case of borderline values, consider repeating the test with 3 independent samples. ***Consider differential diagnosis (especially consider mucosal villous atrophy and dilution effect of watery stool). GI, gastrointestinal. *(Adapted from Walkowiak J, Nousia-Arvanitakis S, Henker J, et al: Indirect pancreatic function tests in children.* J Pediatr Gastroenterol Nutr *40:107-114, 2005.)*

The gold standard test for exocrine pancreatic function is direct analysis of **duodenal aspirate** for volume, bicarbonate, trypsin, and lipase upon secretin, and pancreozymin/cholecystokinin stimulation. This involves duodenal intubation (see Chapter 348).

INVESTIGATIONS FOR INTESTINAL MUCOSAL DISORDERS

Establishing a specific diagnosis for malabsorption often requires histologic examination of small bowel mucosal biopsies. These are obtained during endoscopy, which allows multiple biopsies to be performed, because mucosal involvement can be patchy, especially in celiac disease. Periodic acid–Schiff (PAS) staining of mucosal biopsies and electron microscopy are necessary in congenital diarrhea to assess congenital microvillus atrophy. Bowel mucosal lesions can also be segmental in cases of intestinal lymphangiectasia. In these situations, radiographic small bowel series or repeated ultrasonographies can identify a region of thickened bowel responsible for protein loss. During endoscopy, mucosal biopsies can be obtained to measure mucosal disaccharidase activities. Duodenal aspirates can be performed to measure pancreatic enzyme concentration as well as quantitative bacterial cultures. Aspirates to demonstrate other infections and infestations such as *Giardia* may be useful.

IMAGING PROCEDURES

Plain radiographs and barium contrast studies might suggest a site and cause of intestinal motility disorders. Although flocculations of barium and dilated bowel with thickened mucosal folds have been attributed to diffuse malabsorptive lesions such as celiac disease, these abnormalities are nonspecific. Diffuse fluid-filled bowel loops during sonography also suggest malabsorption.

338.2 Celiac Disease (Gluten-Sensitive Enteropathy)

David Branski, Riccardo Troncone, and Alessio Fasano

ETIOLOGY AND EPIDEMIOLOGY

Celiac disease is an immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals and characterized by the presence of a variable combination of gluten-dependent clinical manifestations, celiac disease–specific antibodies, HLA-DQ2 or DQ8 haplotypes, and enteropathy. Celiac disease–specific antibodies comprise autoantibodies against **TG2,** including **endomysial antibodies (EMA)**, and antibodies against **deamidated forms of gliadin peptides**.

Celiac disease is triggered by the ingestion of wheat gluten and related prolamines from rye and barley. In most studies oats proved to be safe; however, a few celiac disease patients have oats prolamine–reactive mucosal T cells that can cause mucosal inflammation.

Celiac disease is a common disorder (1% prevalence of biopsy-proven disease). It is thought to be rare in Central Africa and East Asia. Environmental factors might affect the risk of developing celiac disease or the timing of its presentation. Neither the delayed introduction of gluten, or breastfeeding, or the introduction of small quantities of gluten prevents celiac disease in high-risk patients. Infectious agents have been hypothesized to play a role because frequent rotavirus infections are associated with an increased risk. It is plausible that the contact with gliadin at a time when there is ongoing intestinal inflammation, altered intestinal permeability, and enhanced antigen presentation can increase the risk of developing celiac disease, at least in a subset of persons (Fig. 338-3).

GENETICS AND PATHOGENESIS

A genetic predisposition is suggested by the family aggregation and the concordance in monozygotic twins, which approaches 100%. The strongest association is with human leukocyte antigen (HLA)-DQ2.5 (1 or 2 copies encoded by DQA1 *05 [for the chain] and DQB1*02 genes [for the chain]). Such a DQ molecule has been found to be present in more than 90% of celiac patients. The highly homologous DQ2.2 molecule confers a much lesser risk, while the data available on DQ2-negative celiac disease patients indicate that they almost invariably are HLA-DQ8–positive (DQA1*0301/DQB1*0302). A gene dosage effect has been suggested, and a molecular hypothesis for such a phenomenon has been proposed, based on the impact of the number and quality of the HLA-DQ2 molecules on gluten peptide presentation to T cells. Other non-HLA genes confer susceptibility to celiac disease. Genome-wide association studies have shown risk variants in genes controlling T-cell activation and recruitment, some being shared with type 1 diabetes and other autoimmune diseases. Interestingly, very few polymorphisms associated with celiac disease are in coding regions, as they often are in binding sites for transcription factors, then affecting gene expression.

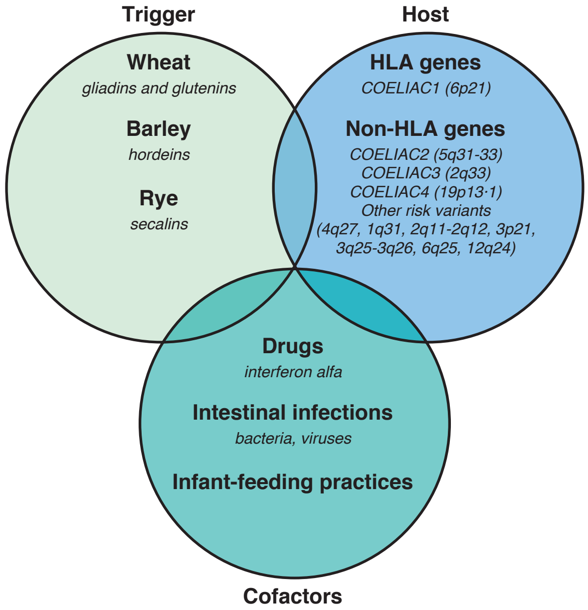

Figure 338-3 Causative factors in celiac disease. HLA, human leukocyte antigen. *(From Di Sabatino A, Corassa GR: Celiac disease.* Lancet *373:1480–1490, 2009.)*

Celiac disease is a T-cell–mediated chronic inflammatory disorder with an autoimmune component. Altered processing by intraluminal enzymes, changes in intestinal permeability and activation of innate immunity mechanisms precede the activation of the adaptive immune response. Immunodominant epitopes from gliadin are highly resistant to intraluminal and mucosal digestion; incomplete degradation favor the immunostimulatory and toxic effects of these sequences. Some gliadin peptides (p31-43) are able to activate innate immunity, in particular they induce interleukin (IL)-15. The latter, but also type 1 interferons, may alter the tolerogenic phenotype of dendritic cells, resulting in lamina propria T-cell activation by other peptides presented in the context of HLA-DQ2 or HLA-DQ8 molecules. Gliadin-specific T-cell responses are enhanced by the action of TG2; the enzyme converts particular glutamine residues into glutamic acid, which results in higher affinity of these gliadin peptides for HLA-DQ2 or HLA-DQ8. The pattern of cytokines produced following gliadin activation is clearly dominated by interferon-γ (T-helper type 1 skewed); IL-21 is also upregulated. Downstream T-cell activation, a complex remodeling of the mucosa takes place, involving increased levels of metalloproteinases and growth factors, which leads to the classical flat mucosa. A severe impairment of intraepitheleal lymphocytes (IELs) homeostasis is present in celiac disease. IL-15 is implicated in the expression of natural killer receptors CD94 and NKG2D, as well as in epithelial expression of stress molecules, thus enhancing cytotoxicity, cell apoptosis, and villous atrophy. The most evident expression of autoimmunity is the presence of serum antibodies to TG2. However, the

mechanisms leading to autoimmunity are largely unknown, as well as their pathogenetic significance. "Potential" celiac disease, in which TG2 antibodies can be detected in situ without any histologic abnormality, shows that the production of antibodies does not necessarily lead to intestinal damage. The finding of IgA deposits on extracellular TG2 in the liver, lymph nodes, and muscles indicates that TG2 is accessible to the gut-derived autoantibodies.

CLINICAL PRESENTATION AND ASSOCIATED DISORDERS

Clinical features of celiac disease vary considerably (Table 338-4). Intestinal symptoms are common in children whose disease is diagnosed within the 1st 2 yr of life; failure to thrive, chronic diarrhea, vomiting, abdominal distention, muscle wasting, anorexia, and irritability are present in most cases (see Fig. 338-1). Occasionally there is constipation, rectal prolapse, or intussusception. As the age at presentation of the disease shifts to later in childhood, and with the more liberal use of serologic screening tests, extraintestinal manifestations and associated disorders, without any accompanying digestive symptoms, have increasingly become recognized, affecting almost all organs (Table 338-5).

The most common extraintestinal manifestation of celiac disease is iron-deficiency anemia, unresponsive to iron therapy. Osteoporosis may be present; in contrast to the situation in adults, it can be reversed by a gluten-free diet, with restoration of normal peak bone densitometric values. Other extraintestinal manifestations include short stature, arthritis and arthralgia, epilepsy with bilateral occipital calcifications, peripheral neuropathies, cardiomyopathy, isolated hypertransaminasemia, dental enamel hypoplasia, aphthous stomatitis, and alopecia. The mechanisms responsible for the severity and the variety of clinical presentations remain obscure. Nutritional deficiencies or abnormal immune responses have been advocated.

Silent celiac disease is being increasingly recognized, mainly in asymptomatic 1st-degree relatives of celiac disease patients investigated during screening studies. However, small bowel biopsy in these people reveals severe mucosal damage consistent with celiac disease. Potential celiac disease is defined when patients have positive celiac disease–specific antibodies, but without documented small bowel damage. It is important to follow these patients because they can develop established celiac disease in the future (Table 338-6).

Some diseases, many with an autoimmune pathogenesis, are found with a higher-than-normal incidence in celiac disease patients. Among these are type 1 diabetes, autoimmune thyroid disease, Addison disease, Sjögren syndrome, autoimmune cholangitis, autoimmune hepatitis, primary biliary cirrhosis. Such associations have been interpreted as a consequence of the sharing of identical HLA haplotypes.

Table 338-4 Some Clinical Manifestations of Celiac Disease in Children and Adolescents

SYSTEM	MANIFESTATION	(POSSIBLE) CAUSE
Gastrointestinal	Diarrhea Distended abdomen Vomiting Anorexia Weight loss Failure to thrive Rectal prolapse Aphthous stomatitis Intussusception	Atrophy of the small bowel mucosa Malabsorption
Hematologic	Anemia	Iron malabsorption
Skeletal	Rickets Osteoporosis Enamel hypoplasia of the teeth	Calcium/vitamin D malabsorption
Muscular	Atrophy	Malnutrition
Neurologic	Peripheral neuropathy Epilepsy Irritability Cerebral calcifications Cerebellar ataxia	Thiamine/vitamin B_{12} deficiency
Endocrinologic	Short stature Pubertas tarda Secondary hyperparathyroidism	Malnutrition Calcium/vitamin D malabsorption
Dermatologic	Dermatitis herpetiformis Alopecia areata Erythema nodosum	Autoimmunity
Respiratory	Idiopathic pulmonary hemosiderosis	

Adapted from Mearin ML: Celiac disease among children and adolescents, Curr Probl Pediatr Adolesc Health Care *37:81–112, 2007.*

Table 338-5 Risk Groups for Celiac Disease Case-Finding

First-degree relatives
Dermatitis herpetiformis
Unexplained iron-deficiency anemia
Autoimmune thyroiditis
Type 1 diabetes
Unexplained infertility
Recurrent abortion
Dental enamel hypoplasia
Cryptic hypertransaminasemia
Autoimmune liver disease
Short stature
Delayed puberty
Down, Williams, and Turner syndromes
Irritable bowel syndrome
Unexplained osteoporosis
Sjögren syndrome
Epilepsy (poorly controlled) with occipital calcifications
Selective immunoglobulin A deficiency
Autoimmune endocrinopathies
Addison disease
Aphthous stomatitis
Ataxia
Alopecia
Polyneuropathy
Irritable bowel syndrome

Modified from Di Sabatino A, Corazza GR: Coeliac disease, Lancet *373:1480–1490, 2009.*

Table 338-6 Clinical Spectrum of Celiac Disease

SYMPTOMATIC
Frank malabsorption symptoms: chronic diarrhea, failure to thrive, weight loss
Extraintestinal manifestations: anemia, fatigue, hypertransaminasemia, neurologic disorders, short stature, dental enamel defects, arthralgia, aphthous stomatitis

SILENT
No apparent symptoms in spite of histologic evidence of villous atrophy
In most cases identified by serologic screening in at-risk groups (see Table 330-1)

LATENT
Subjects who have a normal histology, but at some other time, before or after, have shown a gluten-dependent enteropathy

POTENTIAL
Subjects with positive celiac disease serology but without evidence of altered jejunal histology
It might or might not be symptomatic

Table 338-7 Other Causes of Flat Mucosa

Other Causes of Flat Mucosa
Autoimmune enteropathy
Tropical sprue
Giardiasis
HIV enteropathy
Bacterial overgrowth
Crohn disease
Eosinophilic gastroenteritis
Cow's milk enteropathy
Soy protein enteropathy
Primary immunodeficiency
Graft-versus-host disease
Chemotherapy and radiation
Protein energy malnutrition
Tuberculosis
Lymphoma
Nongluten food intolerances

Modified from Di Sabatino A, Corazza GR: Coeliac disease, Lancet *373:1480–1490, 2009.*

The relation between celiac disease and other autoimmune diseases is poorly defined; once those diseases are established, they are not influenced by a gluten-free diet. Other associated conditions include selective IgA deficiency and Down, Turner, and Williams syndromes.

Patients with celiac disease show increased long-term mortality, the risk rising with delayed diagnosis and/or poor dietary compliance. Non-Hodgkin lymphoma is the main cause of death. Adult patients can develop complications such a refractory celiac disease, ulcerative jejunoileitis, or enteropathy-associated T-cell lymphoma.

DIAGNOSIS

The diagnosis of celiac disease is based on a combination of symptoms, antibodies, HLA, and duodenal histology (Table 338-7). The initial approach to symptomatic patients is to test for anti-TG2 IgA antibodies and in addition for total IgA in serum to exclude IgA deficiency. As an alternative for total IgA in serum direct testing for IgG anti–deamidated forms of gliadin peptides antibodies can be performed. If IgA anti-TG2 antibodies are negative and serum total IgA is normal for age (or IgG anti–deamidated forms of gliadin peptides antibodies are negative), celiac disease is unlikely to be the cause of the symptoms. If anti-TG2 antibody testing is positive the patients should be referred to a pediatric gastroenterologist for further diagnostic workup, which depends on the serum antibody levels. Patients with positive anti-TG2 antibody levels <10 × upper limits of normal should undergo upper endoscopy with multiple biopsies. In patients with positive anti-TG2 antibody levels at or >10 × upper limits of normal, blood should be drawn for HLA and EMA testing. If the patient is positive for EMA antibodies and positive for DQ2 or DQ8 HLA testing, the diagnosis of celiac disease is confirmed, a gluten-free diet is started and the patient is followed for improvement of symptoms and decline of antibodies. In the rare case of negative results for HLA and/or anti-EMA in a child with TG2 antibody titers ≥10 × upper limits of normal, the different possibilities for false-positive and false-negative test results need to be considered. In these circumstances, the diagnostic workup should be extended, including repeated testing and duodenal biopsies. In totally asymptomatic persons belonging to high-risk groups, celiac disease should always be diagnosed using duodenal biopsies. When biopsies are indicated at least 4 fragments should be obtained from the descending part of the duodenum and at least 1 from the duodenal bulb. The diagnosis is confirmed by an antibody decline and preferably a clinical response to a gluten-free diet. Gluten challenge and repetitive biopsies will only be necessary in selected cases in which diagnostic uncertainty remains.

TREATMENT

The only treatment for celiac disease is lifelong strict adherence to a gluten-free diet (Fig. 338-4). This requires a wheat-, barley-, and rye-free diet. Despite evidence that oats are safe for most patients with celiac disease, there is concern regarding the possibility of contamination of oats with gluten during harvesting, milling, and shipping. Nevertheless, it seems wise to add oats to the gluten-free diet only when the latter is well established, so that possible adverse reactions can be readily identified. There is a consensus that all celiac disease patients should be treated with a gluten-free diet regardless of the presence of symptoms. However, whereas it is relatively easy to assess the health improvement after treatment of celiac disease in patients with clinical symptoms of the disease, it proves difficult in persons with asymptomatic celiac disease. The nutritional risks, particularly osteopenia, are those mainly feared for subjects who have silent celiac disease and continue on a gluten-containing diet. Little is known about the health risks in untreated patients with minor enteropathy, which may be clinically silent. There are no guidelines concerning the need for a gluten-free diet in subjects with "potential" celiac disease (patients with positive celiac disease–associated serology but without enteropathy).

The Codex Alimentarius Guidelines define gluten-free as <20 ppm, but, although analytical methods for gluten detection have already reached a satisfactory degree of sensitivity, more information is needed on the daily gluten amount that may be tolerated by celiac disease patients. The data available so far seem to suggest that the threshold should be set to <50 mg/day, although individual variability makes it difficult to set a universal threshold.

It is important that an experienced dietician with specific expertise in celiac disease counseling educates the family and the child about dietary restriction. Compliance with a gluten-free diet can be difficult, especially in adolescents. It is recommended that children with celiac disease be monitored with periodic visits for assessment of symptoms, growth, physical examination, and adherence to the gluten-free diet. Periodic measurements of TG2 antibody levels to document reduction

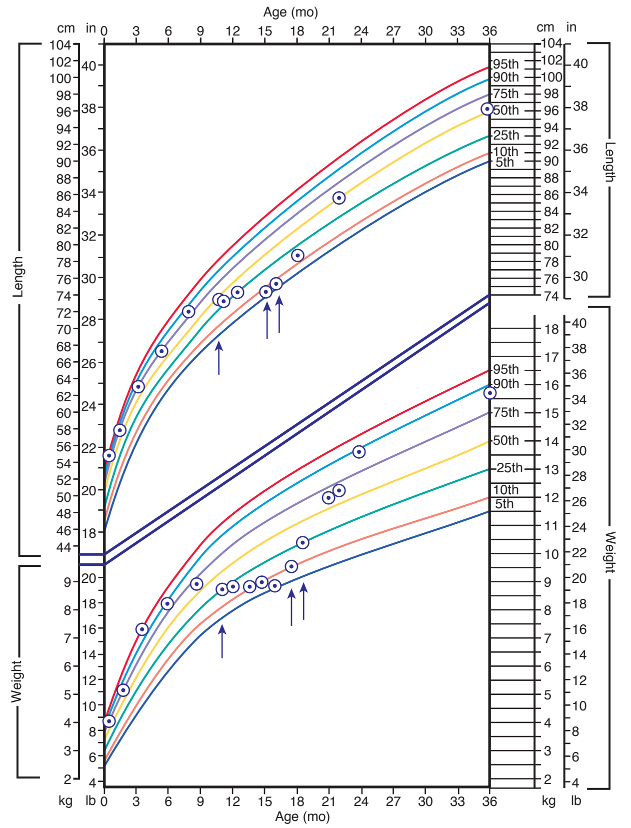

Figure 338-4 **Gluten-sensitive enteropathy.** Growth curve demonstrates initial normal growth from 0-9 mo, followed by onset of poor appetite with intermittent vomiting and diarrhea after initiation of gluten-containing diet *(single arrow)*. After biopsy conformed diagnosis and treatment with gluten-free diet *(double arrow)*, growth improves.

in antibody titers can be helpful as indirect evidence of adherence to a gluten-free diet, although they are inaccurate in detecting slight dietary transgressions.

NONCELIAC GLUTEN SENSITIVITY

Wheat-induced symptoms in patients who do not have celiac disease have been described in 2 groups. **IgE-mediated wheat allergy** may have overlapping symptoms with celiac disease but more often presents without an enteropathy but with symptoms of atopy (urticaria, angioedema, eczema, asthma, rhinitis) and is diagnosed by the presence of IgE antibodies to wheat (serum specific IgE or skin prick tests). In contrast to celiac disease and nonceliac gluten sensitivity, symptoms in IgE-mediated disease occur soon after ingestion of wheat products.

Gluten sensitivity has been defined as enteric (abdominal pain, bloating, diarrhea) and systemic (headache, fatigue, muscle aches, rash) after ingesting wheat in the absence of enteropathy or HLA risk factors and autoantibodies. Symptoms are often similar to patients with irritable bowel syndrome and some patients with irritable bowel syndrome respond positively to a gluten-free diet. This is an area of uncertainty in pediatrics because most studies have been performed in adults.

Bibliography is available at Expert Consult.

338.3 Other Malabsorptive Syndromes

Philip M. Sherman, David Branski, and Olivier Goulet

CONGENITAL INTESTINAL MUCOSAL DEFECTS

Microvillus Inclusion Disease (Congenital Microvillus Atrophy)

Microvillus inclusion disease (MVID) is an autosomal recessive disorder, which manifests *at birth* with **profuse watery secretory diarrhea**. It is the most severe cause of congenital diarrhea involving the development of intestinal mucosa. Light microscopy of the small bowel mucosa demonstrates diffuse thinning of the mucosa, with hypoplastic villus atrophy and no inflammatory infiltrate. Diagnosis may be easily performed with light microscopy using PAS and CD10 staining, which shows a very thin or absent brush border, together with positive PAS and CD10 intracellular inclusions. Electron microscopy shows enterocytes with absent or sparse microvilli. The apical cytoplasm of the enterocytes contains electron-dense secretory granules; the hallmark is presence of microvilli within involutions of the apical membrane. Polyhydramnios is not a classic presentation of MVID but is increasingly observed according to the progresses in prenatal follow up. Neonates usually present very early onset of severe watery diarrhea (up to 200-330 mL/kg/day) causing dehydration and failure to thrive. Despite parenteral nutrition, diarrhea continues and initial fluid management is difficult. The disease is fatal without long-term parenteral nutrition support. Most children die in infancy or early childhood. To date, no causal treatment exists for MVID. Trials with antiinflammatory drugs, including steroids and antisecretory medications (such as Sandostatin or loperamide), did not significantly change stool volumes over a prolonged period; colostrum and epidermal growth factor have failed as well, but octreotide has shown a partial improvement in 1 patient, supposedly via its ability to reduce intestinal fluids (see Chapter 339). Intestinal transplantation is the only definitive treatment for this rare disease. Many cases in the same family, frequently in a highly consanguineous union, gave the impression of an autosomic recessive transmission. Mutations of the *MYO5B* gene coding for a nonconventional motor protein, Myosin Vb, are associated with MVID in a cohort of patients suffering from early-onset MVID. Most early-onset MVID patients display a mutation in *MYO5B*, but there is a great allelic heterogeneity. These mutations result in a loss of function at the proteic level, with abnormal cell polarity, that would involve *MYO5B* protein in regulating intracellular protein trafficking as well as in the cytoskeleton organization.

It is likely that in very rare cases a milder phenotype may allow slow weaning from parenteral nutrition, allowing the patient to reach young adulthood and enjoy partial oral feeding.

Tufting Enteropathy (Congenital Tufting Enteropathy)

Tufting enteropathy (intestinal epithelial dysplasia) manifests in the 1st few wk of life with **persistent watery diarrhea** and accounts for a small fraction of infants with intractable diarrhea of infancy. The distinctive feature on small intestinal mucosal biopsy is focal epithelial “tufts” (teardrop-shaped groups of closely packed enterocytes with apical rounding of the plasma membrane) involving 80-90% of the epithelial surface. However, the typical pathology does not appear immediately after birth, and in other known enteropathies, tufts are seen on ≤15% of the epithelial surface. One difficulty comes from the mononuclear T cell’s infiltration of the lamina propria, which can guide wrongly to a disimmune enteropathy, especially when initially lacking tufts. The increased intestinal permeability caused by cell adhesion defect could be responsible for the inflammatory reaction. Colonic epithelium shows abnormalities that are more difficult to identify. Electron microscopy does not help in establishing the diagnosis.

The pathogenesis of this severe digestive disease is from a disorder of cell–cell and cell–matrix interactions, because there is an abnormal distribution of $\alpha_2\beta_1$-integrin along the crypt–villus axis, increased expression of desmoglein, and ultrastructural changes of desmosomes. Tufting enteropathy is often associated with *punctiform keratitis* and *conjunctival dysplasia* resembling typical pictures of tufts. The genetic basis of tufting enteropathy supports this speculation, because mutations in the *EPCAM* gene, encoding an epithelial cell adhesion molecule protein, have been described. The phenotype associated with mutations of *EPCAM* is usually an isolated congenital diarrhea without associated extradigestive symptoms, except in some patients with late-onset arthritis. A founder effect at the *EPCAM* locus in congenital tufting enteropathy (CTE) has been shown in the Arabic Gulf population.

In the **syndromic form** of CTE, diarrhea is associated with one or more of these same anomalies: superficial punctate keratitis, choanal, esophageal or intestinal atresia, anal imperforation, hair dysplasia, skin hyperlaxity, bone abnormalities, hexadactylia, and facial dysmorphism. Anomalies appear isolated for most, except for superficial punctate keratitis and choanal atresia that are consistently found in the population of patients with mutated *SPINT2* for conjunctival inflammation (100%) and in 50% of cases for choanal atresia; moreover, these anomalies are never found in the population of patients with *EPCAM* mutations.

No **treatment** has been effective, so management requires permanent parenteral nutrition with possible intestinal transplantation (see Chapter 339).

Enteric Anendocrinosis

Mutations of the *NEUROG3* gene produce generalized mucosal malabsorption, vomiting, diarrhea, failure to thrive, dehydration, and a hyperchloremic metabolic acidosis. Oral alimentation with anything other than water produces diarrhea. Villus-crypt architecture in small bowel biopsies is normal, but staining for neuroendocrine cells (e.g., employing antichromogranin antibodies) demonstrates a complete absence of this secretory cell lineage with preservation of goblet cells and Paneth cells. **Treatment** is with total parenteral nutrition and small bowel transplantation.

PROPROTEIN CONVERTASE 1/3 DEFICIENCY

Chronic watery, *neonatal onset diarrhea* is described in infants with hyperinsulinism, hypoglycemia, hypogonadism, and hypoadrenalism. Small bowel biopsy reveals a nonspecific enteropathy. A clue to the autosomal recessive condition is subsequent onset of marked obesity with hyperphagia in the toddler years in both affected probands and symptomatic siblings. Elevated serum levels of proinsulin are highly supportive of this underdiagnosed disorder, which is caused by loss-of-function mutations in the *PCSK1* gene.

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CARBOHYDRATE-DEFICIENT GLYCOPROTEIN SYNDROME AND ENTEROCYTE HEPARAN SULFATE DEFICIENCY

Congenital disorders of glycosylation (also carbohydrate-deficient glycoprotein [**CDG**]) are genetic disorders of assembly of *N*-glycans in the cytosol and endoplasmic reticulum, resulting in a variety of manifestations (see Chapter 87.6). The subtypes of CDG I are all associated with **protein-losing enteropathy.** Diagnosis can be established by isoelectric focusing of serum transferrin, enzyme analysis, and DNA analysis. Oral mannose can provide effective therapy in CDG Ib, so early identification of children presenting with hypoglycemia, hypothyroidism, and/or thyroid binding globulin deficiency is beneficial.

Congenital enterocyte heparan deficiency is a rare cause of intractable diarrhea with protein-losing enteropathy, which may be an unusual presentation of the CDG syndrome type 1 (also known as Jaeken syndrome) (see Chapter 87.6). Heparan sulfate is a glycosaminoglycan with multiple roles in the intestine, including restriction of charged macromolecules, such as albumin, in the vascular lumen.

SYNDROMIC DIARRHEA

Syndromic diarrhea (SD), also known as phenotypic diarrhea or **trichohepatoenteric** syndrome is a congenital enteropathy manifesting with *early onset* of severe diarrhea requiring parenteral nutrition. The estimated prevalence is approximately 1 per 300,000-400,000 live births in Western Europe. Patients are born small for gestational age and present with diarrhea starting in the 1st 6 mo of life (<1 mo of age in most cases). They have an abnormal phenotype, including facial dysmorphism with prominent forehead, broad nose, and hypertelorism and a distinct abnormality of hair, **trichorrhexis nodosa**. Hairs are woolly, easily removed, and poorly pigmented. Abnormal cutaneous spots including café-au-lait on the lower limbs may be observed. Liver disease affects about half of the patients with extensive fibrosis or cirrhosis. Cardiac abnormalities and colitis have been reported sporadically, as well as 1 case involving polyhydramnios, placental abnormalities, and congenital hemochromatosis. The patients have defective antibody responses despite normal serum immunoglobulin levels and defective antigen-specific skin tests despite positive proliferative responses in vitro. Microscopic analysis shows twisted hair (pili torti), aniso- and poilkilotrichosis, and trichorrhexis nodosa. Histopathologic analysis shows nonspecific villus atrophy with or without mononuclear cell infiltration of the lamina propria, and without specific histologic abnormalities involving the epithelium. The common association of the disorder with parental consanguinity and/or affected siblings indicates a genetic origin with autosomal recessive transmission. Mutations in the *TTC37* gene are the basis of the syndrome. *TTC37* encodes a protein known as Thespin, which is in many tissues (vascular endothelium, lymph, pituitary stalk, lung and intestine), but is not expressed in the liver. In patients with SD, with no mutation in *TTC37*, there are mutations in the *SKIV2L* gene. This gene encodes a protein of the Ski multiprotein complex that is involved in the control of RNA by the exosome, including the regulation of normal messenger RNA and the degradation of nonfunctional messenger RNA.

Prognosis of this type of intractable diarrhea of infancy is poor, with most patients having died between the ages of 2 and 5 yr, some of them with early-onset liver disease.

AUTOIMMUNE ENTEROPATHY

Symptoms of autoimmune enteropathy usually occur *after the 1st 6 mo of life,* presenting with chronic diarrhea, protein-losing enteropathy, malabsorption, and failure to thrive. The diagnosis is based on the endoscopic and histologic evaluation of the inflammation mainly of the small bowel but also of the colon. Histologic findings in the small bowel include partial or complete villous atrophy, crypt hyperplasia, and an increase in chronic inflammatory cells in the lamina propria. In contrast to gluten-sensitive enteropathy (celiac disease), there is no increased number in intraepithelial lymphocytes. Immunologic analyses indicate the presence of autoantibodies and, most importantly, of *anti–enterocyte antibodies*, as well as *anti–autoimmune enteropathy-75 kDa*. Specific serum antienterocyte antibodies can be identified in 50% or more of patients by indirect immunofluorescent staining of normal small bowel mucosa and kidney. In some patients *anti–goblet cell antibodies* also can be demonstrated.

Extraintestinal autoimmune disorders are usual and include arthritis, membranous glomerulonephritis, insulin-dependent diabetes, thrombocytopenia, autoimmune hepatitis, hypothyroidism, and hemolytic anemia. It is essential to exclude an underlying primary immune deficiency, particularly in boys with other autoimmune features (e.g., diabetes mellitus), because a proportion has underlying *i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked (**IPEX**) **syndrome** (see Chapter 126.5). Different phenotypes of IPEX syndrome patients, as well as IPEX-like forms of autoimmune enteropathy that are *FOXP3*-independent are described involving girls as well with or without extraintestinal autoimmune disorders. Contrary to classical IPEX, the cause of IPEX-like or type 2 autoimmune enteropathy is only partially elucidated on a molecular basis. However, in patients who do not show genetic defects in FOXP3 or CD25, abnormal functions of CD4+CD25 high-regulatory T cells should be documented. Autoimmune enteropathy is reported in cases of Schimke immunoosseous dysplasia.

Treatment options are rather limited and based on T-cell–suppressive immunomodulation. Upon initial stabilization using steroid pulse therapy and calcineurin-dependent immunosuppressive drugs, such as tacrolimus, most often patients are maintained on rapamycin with azathioprine, methotrexate or rituximab in few patients. A theoretic alternative treatment option could be in form of hematopoietic stem cell transplantation; this treatment option is preferable in patients with a molecular defect, such as previously shown for patients with classical IPEX syndrome.

BILE ACID MALABSORPTION

In primary bile acid malabsorption, mutation of the ileal sodium–bile acid cotransporter gene, *SLC10A2,* results in *congenital diarrhea*, steatorrhea, interruption of enterohepatic circulation of bile acids, and reduced plasma cholesterol levels. Bile acids are normally synthesized from cholesterol in the liver and secreted into the small intestine, where they facilitate absorption of fat, fat-soluble vitamins, and cholesterol. Bile acids are reabsorbed in the distal ileum, return to the liver via the portal venous circulation, and resecrete into bile. Normally, the enterohepatic circulation of bile acids is an extremely efficient process; only 10% of the intestinal bile acids escape reabsorption and are eliminated in feces. Bile acid secretion is largely autoregulated, but there is only a limited capacity to increase bile acid secretion. Reduction in the bile acid pool from bile acid malabsorption causes steatorrhea, which requires restriction of dietary fat. Unabsorbed bile acids stimulate chloride excretion in the colon, resulting in diarrhea, which responds to cholestyramine, an anion-binding resin. Secondary bile acid malabsorption can result from ileal disease, such as in Crohn disease, and following an ileal resection.

Chronic neonatal-onset diarrhea has also been described in autosomal recessive **cerebrotendinous xanthomatosis,** which is caused by an inborn error of bile acid synthesis resulting from 27-hydroxylase deficiency. These children also present with juvenile-onset cataracts and developmental delay. Neonatal cholestasis has also been described as a presenting feature. Tendon xanthomas develop in the second and third decades of life. The diagnosis is important to establish, because treatment is effective when employing oral chenodeoxycholic acid.

INTESTINAL LYMPHANGIECTASIA

Obstruction of the lymphatic drainage of the intestine can be caused by either congenital defects in lymphatic duct formation or by secondary causes (Table 338-8). The **congenital** form is often associated with lymphatic abnormalities elsewhere in the body, as occur with Turner, Noonan, and Klippel-Trenaunay-Weber syndromes. Causes of **secondary** lymphangiectasia include constrictive pericarditis, heart failure, retroperitoneal fibrosis, abdominal tuberculosis, and retroperitoneal malignancies. Lymph rich in proteins, lipids, and lymphocytes leak

Table 338-8 Causes of Protein-Losing Enteropathy
Mucosal inflammation
Infection
Cytomegalovirus
Bacterial overgrowth
Invasive bacterial infection
Clostridium difficile
Helicobacter pylori
Giardiasis
Measles
Strongyloides stercoralis
Gastric inflammation
Menetrier disease
Eosinophilic gastroenteropathy
Intestinal inflammation
Celiac disease
Crohn disease
Eosinophilic gastroenteropathy
Tropical sprue
Radiation enteritis
Primary intestinal lymphangiectasia
Secondary intestinal lymphangiectasia
Constrictive pericarditis
Congestive heart failure
Post-Fontan procedure
Malrotation
Lymphoma
Noonan syndrome
Sarcoidosis
Radiation therapy
Arsenic poisoning
Colonic inflammation
Inflammatory bowel diseases
Necrotizing enterocolitis
Congenital disorders of glycosylation
Enterocyte heparin sulfate deficiency

into the bowel lumen, resulting in protein-losing enteropathy, steatorrhea, and lymphocyte depletion. Hypoalbuminemia, hypogammaglobulinemia, edema, lymphopenia, malabsorption of fat and fat-soluble vitamins, and chylous ascites often occur. Intestinal lymphangiectasia can also manifest with ascites, peripheral edema and a low serum albumin.

The diagnosis is suggested by the typical findings in association with an elevated fecal α_1-antitrypsin clearance. Radiologic findings of uniform, symmetric thickening of mucosal folds throughout the small intestine are characteristic but nonspecific. Small bowel mucosal biopsy can show dilated lacteals with distortion of villi and no inflammatory infiltrate. A patchy distribution and deeper mucosal involvement on occasion causes false-negative results on small bowel histology. Video capsule endoscopy may reveal similar lesions (Figs. 338-5 and 338-6). **Treatment** of lymphangiectasia includes restricting the amount of long-chain fat ingested and administering a formula containing protein and medium-chain triglycerides (MCTs). Supplementing a low-fat diet with MCT oil in cooking is used in the management of older children with lymphangiectasia. Rarely, parenteral nutrition is required. If only a portion of the intestine is involved, surgical resection may be considered.

ABETALIPOPROTEINEMIA

Abetalipoproteinemia is a rare autosomal recessive disorder of lipoprotein metabolism (Bassen-Kornzweig syndrome) (see Chapter 86). It is associated with severe fat malabsorption from birth. Children fail to thrive during the 1st yr of life, with stools that are pale, foul smelling, and bulky. The abdomen is distended and deep tendon reflexes are absent as a result of peripheral neuropathy, which is secondary to vitamin E (fat-soluble vitamin) deficiency. Intellectual development tends to be slow. After 10 yr of age, intestinal symptoms are less severe, ataxia develops, and there is a loss of position and vibration sensation

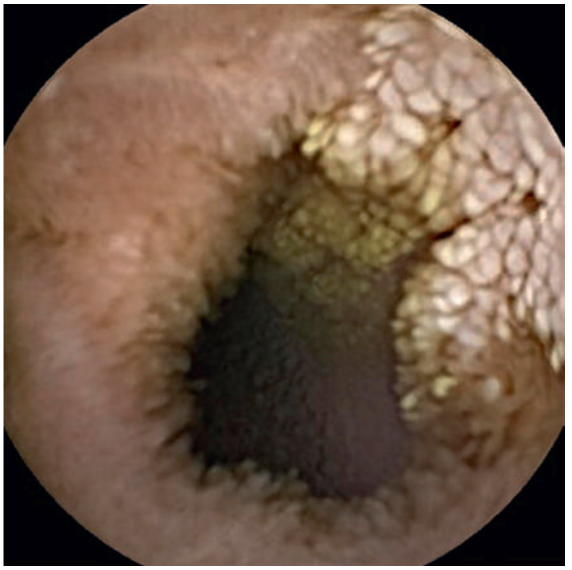

Figure 338-5 Swollen villi detected by videocapsule endoscopy in the proximal ileum. *(From Gortani G, Maschio M, Ventura A: A child with edema, lower limb deformity, and recurrent diarrhea.* J Pediatr *161:1177, 2012, Fig. 1.)*

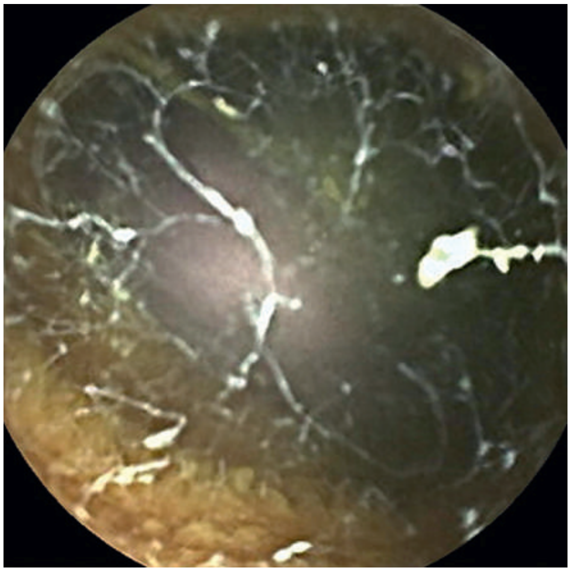

Figure 338-6 Protein-rich lymphatic fluid aggregates detected by videocapsule endoscopy in the intestinal lumen. *(From Gortani G, Maschio M, Ventura A: A child with edema, lower limb deformity, and recurrent diarrhea.* J Pediatr *161:1177, 2012, Fig. 2.)*

with the onset of intention tremors unless vitamin E levels are maintained in the normal range. These latter symptoms reflect involvement of the posterior columns, cerebellum, and basal ganglia. In adolescence, atypical retinitis pigmentosa develops without adequate supplemental of vitamin E; for instance, using a tocopheryl polyethylene glycol succinate (TPGS) formulation of the vitamin.

Diagnosis rests on the presence of acanthocytes in the peripheral blood smear and extremely low plasma levels of cholesterol (<50 mg/dL); triglycerides are also very low (<20 mg/dL). Chylomicrons and very-low-density lipoproteins are not detectable, and the low-density lipoprotein fraction is virtually absent from the circulation. Marked triglyceride accumulation in villus enterocytes occurs in the duodenal mucosa. Steatorrhea occurs in younger patients, but other processes of nutrient assimilation are intact. Rickets may be an unusual initial

manifestation of abetalipoproteinemia and hypobetalipoproteinemia. Rickets is caused by steatorrhea-induced calcium losses and vitamin D deficiency. Patients have mutations of the microsomal triglyceride transfer protein gene, resulting in absence of microsomal triglyceride transfer protein function in the small bowel. This protein is required for normal assembly and secretion of very low density lipoproteins and chylomicrons.

Specific **treatment** is not available. Large supplements of the fat-soluble vitamins A, D, E, and K should be given. Vitamin E (100-200 mg/kg/24 hr) appears to arrest neurologic and retinal degeneration. Limiting long-chain fat intake can alleviate intestinal symptoms; MCTs can be used to supplement fat intake.

HOMOZYGOUS HYPOBETALIPOPROTEINEMIA

Homozygous hypobetalipoproteinemia (see Chapter 86) is transmitted as an autosomal dominant trait. The homozygous form is indistinguishable from abetalipoproteinemia. The parents of these patients, as heterozygotes, have reduced plasma low-density lipoprotein and apoprotein-β concentrations, whereas the parents of patients with abetalipoproteinemia have normal levels. On transmission electron microscopy of small bowel biopsies, the size of lipid vacuoles in enterocytes differentiates between abetalipoproteinemia and hypobetalipoproteinemia: many small vacuoles are present in hypobetalipoproteinemia, and larger vacuoles are seen in abetalipoproteinemia.

CHYLOMICRON RETENTION DISEASE (ANDERSON DISEASE)

In chylomicron retention disease, a rare recessive disorder, there is a defect in chylomicron exocytosis from enterocytes. Sar1-guanosine triphosphate promotes the formation of endoplasmic reticulum to Golgi transport carriers, and *Sar1b* is defective in Anderson disease. These patients have severe intestinal symptoms with steatorrhea, chronic diarrhea, and failure to thrive. Acanthocytosis is rare and neurologic manifestations are less severe than those observed in abetalipoproteinemia. Plasma cholesterol levels are moderately reduced (<75 mg/dL) and fasting triglycerides are normal, but the fat-soluble vitamins, particularly A and E, are very low. Treatment is early aggressive therapy with fat-soluble vitamins and modification of dietary fat intake, as in the treatment of abetalipoproteinemia.

WOLMAN DISEASE

Wolman disease is a rare, lethal lipid storage disease that leads to lipid accumulation in multiple organs, including the small intestine. In addition to vomiting, severe diarrhea, and hepatosplenomegaly, patients have steatorrhea as a result of lymphatic obstruction. Deficiency of lysosomal acid lipase is the underlying cause of disease (see Chapter 80). Successful long-term bone marrow engraftment results in normalization of peripheral blood leukocyte lysosomal enzyme acid lipase activity, with subsequent resolution of diarrhea and the restoration of developmental milestones.

DGAT1 MUTATION

Two siblings in one family with severe protracted diarrhea starting at 3 days of age had loss-of-function homozygous splice mutations in the diacylglycerol acyltransferase (*DGAT1*) gene that catalyzes the final step in the synthesis of triglycerides.

Bibliography is available at Expert Consult.

338.4 Intestinal Infections and Infestations Associated with Malabsorption

Raanan Shamir and David Branski

Malabsorption is a rare consequence of primary intestinal infection and infestation in immunocompetent children. Malabsorption is mainly seen after infection with *Campylobacter, Shigella, Salmonella, Giardia*, cryptosporidium, coccidioidosis, and rotavirus. These infectious causes of malabsorption are more common in immunocompromised children.

POSTINFECTIOUS DIARRHEA

In infants and very young toddlers chronic diarrhea can appear following infectious enteritis, regardless of the nature of the pathogen. The pathogenesis of the diarrhea is not always clear and may be related to secondary lactase deficiency, food protein allergy, antibiotic-associated colitis (including pseudomembranous colitis caused by *Clostridium difficile* toxin), or a combination of these.

Treatment is supportive and may include a lactose-free diet in the presence of secondary lactase deficiency; infants might require a semi-elemental diet. The beneficial effect of specific probiotic products should await well-controlled clinical trials.

BACTERIAL OVERGROWTH

Bacteria are normally present in large numbers in the colon (10^{11}-10^{13} colony-forming units [CFU]/g of feces) and have a symbiotic relationship with the host, providing nutrients and protecting the host from pathogenic organisms. Bacteria are usually present only in a small number in the stomach and small bowel and excessive numbers of bacteria in the stomach or small bowel are harmful. Gastric acid pH prevents the ingested organisms from colonizing the small bowel. Small bowel motility and the migrating motor complex cleanse the small bowel between meals and at night; the ileocecal valve prevents colonic bacteria from refluxing into the ileum. Mucosal defenses such as mucin and immunoglobulins prevent bacterial overgrowth in the small bowel. Bacterial overgrowth can result from clinical conditions that alter the gastric pH or small bowel motility, including disorders such as partial bowel obstruction, diverticula, intestinal failure, intestinal duplications, diabetes mellitus, idiopathic intestinal pseudoobstruction syndrome, and scleroderma. Prematurity, immunodeficiency, and malnutrition are other factors associated with bacterial overgrowth of the small bowel.

Diagnosis of bacterial overgrowth can be made by culturing small bowel aspirate (>10^5 CFU/mL) or by lactulose hydrogen breath test. Lactulose is a synthetic disaccharide, which is not digested by mucosal brush border enzymes but can be fermented by bacteria. High baseline hydrogen and a quick rise in hydrogen in expired breath samples support the diagnosis of bacterial overgrowth, but false-positive tests are common.

Bacterial overgrowth leads to inefficient intraluminal processing of dietary fat and to steatorrhea due to bacterial deconjugation of bile salts, vitamin B_{12} malabsorption, and microvillus brush border damage with malabsorption. Bacterial consumption of vitamin B_{12} and enhanced synthesis of folate result in decreased vitamin B_{12} and increased folate serum levels. Overproduction of D-lactate (the isomer of L-lactate) can cause stupor, neurologic dysfunction, and shock from D-lactic acidosis. Lactic acidosis should be suspected in children at risk of bacterial overgrowth, who show signs of neurologic deterioration and a high anion gap metabolic acidosis not explained by measurable acids such as L-lactate. Measurement of D-lactate is required because standard lactate assay only measures the L-isomer.

Treatment of bacterial overgrowth focuses on correction of underlying causes such as partial obstruction. The oral administration of antibiotics is the mainstay of therapy. Initial treatment with 2-4 wk of metronidazole can provide relief for many months. Cycling of antibiotics including azithromycin, trimethoprim-sulfamethoxazole, ciprofloxacin, and metronidazole may be required. Other alternatives are oral nonabsorbable antibiotics such as aminoglycosides, nitazoxanide, or rifaximin. Occasionally, antifungal therapy is required to control fungal overgrowth of the bowel.

TROPICAL SPRUE

Natives and expatriates of certain tropical regions can present with a diffuse lesion of the small intestinal mucosa—tropical sprue, even long after emigration. The endemic regions include South India, the Philippines, and some islands in the Caribbean. It is uncommon in Africa, Jamaica, and Southeast Asia. The etiology of this disorder is unclear;

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because it follows outbreaks of acute diarrheal disease and improves with antibiotic therapy, an infectious etiology is suspected. The incidence is decreasing worldwide, possibly due to common use of antibiotics for gastroenteritis in developing countries. Yet, in 2011, tropical sprue was still the leading cause of malabsorption in a referral center in south India. Clinical symptoms include fever and malaise followed by watery diarrhea. After about a week the acute features subside, and anorexia, intermittent diarrhea, and chronic malabsorption result in severe malnutrition characterized by glossitis, stomatitis, cheilosis, night blindness, hyperpigmentation, and edema reflecting the various nutrient deficiencies. Muscle wasting is often marked, and the abdomen is often distended. Megaloblastic anemia results from folate and vitamin B_{12} deficiencies.

Diagnosis is made by small bowel biopsy, which shows villous flattening, crypt hyperplasia, and a chronic inflammatory cell infiltrate of the lamina propria with adjacent lipid accumulation in the surface epithelium.

Treatment requires nutritional supplementation, including supplementation of folate and vitamin B_{12}. To prevent recurrence, 6 mo of therapy with oral folic acid (5 mg) and tetracycline or sulfonamides is recommended. Relapses occur in 10-20% of patients who continue to reside in an endemic tropical region; additional courses of antibiotics may be necessary.

WHIPPLE DISEASE

Whipple disease is a chronic systemic infectious disorder. It is a rare disease, especially in childhood. The disease is caused by an infectious agent, *Tropheryma whipplei,* which can be cultured from a lymph node in the involved tissue.

The most common symptoms in Whipple disease are diarrhea, abdominal pain, weight loss, and joint pains. Malabsorption, lymphadenopathy, skin hyperpigmentation, and neurologic changes are also common. Neurologic manifestations and malabsorption are also common.

Involvement of other organs such as eyes, heart, and kidneys has been reported.

Diagnosis requires a high index of suspicion and is made upon demonstration of PAS-positive macrophage inclusions in the biopsy material, usually a duodenal biopsy. Positive identification using polymerase chain reaction for *T. whipplei confirms the diagnosis. It should not be done on stool specimens, because false-positive results were reported in healthy individuals.*

Treatment requires antibiotics such as cotrimoxazole for 1-2 yr. A 2-wk course of intravenous ceftriaxone or meropenem, followed by cotrimoxazole for 1 yr, is recommended.

Bibliography is available at Expert Consult.

338.5 Immunodeficiency Disorders

Ernest G. Seidman and David Branski

Malabsorption can occur with **congenital immunodeficiency** disorders, and chronic diarrhea with failure to thrive is often the mode of presentation. Defects of humoral and or cellular immunity may be involved, including selective IgA deficiency, agammaglobulinemia, common variable immunodeficiency disease (CVID), severe combined immunodeficiency, Wiskott-Aldrich syndrome, or chronic granulomatous disease. Although most patients with selective IgA deficiency are asymptomatic, malabsorption caused by giardiasis or nonspecific enteropathy with bacterial overgrowth can occur. Malabsorption syndrome or chronic noninfectious diarrhea has been reported in 60% of children with CVID, most often in the subgroup with low memory B cell counts. Malabsorption has also been reported in approximately 10% of patients with late-onset CVID, often secondary to giardiasis. Celiac disease is more common in patients with IgA deficiency and CVID. Paradoxically, it is more difficult to exclude the diagnosis of celiac disease because of the lack of reliability of IgA- and IgG-based serologic tests. Malabsorption as a result of chronic rotavirus, giardiasis, bacterial overgrowth, and protein-losing enteropathy are well-recognized complications of X-linked agammaglobulinemia. Malabsorption associated with immunodeficiency is exacerbated by villus atrophy and secondary disaccharidase deficiency. In chronic granulomatous disease, phagocytic function is impaired and granulomas develop throughout the GI tract, mimicking Crohn disease. In addition to failure to thrive, it is important to consider that malabsorption associated with immunodeficiency is often complicated by micronutrient deficiencies, including vitamins A, E, and B_{12}, and calcium, zinc, and iron.

Overall, immunodeficiencies such as hypogammaglobulinemia in the pediatric age group are more often secondary to other conditions such as cancer and chemotherapy, chronic infections, malabsorption, nephrotic syndrome, or cardiac disease. Malnutrition, diarrhea, and failure to thrive are common in untreated children with **HIV infection.** The risk of GI infection is related to the depression of the CD4 count. Opportunistic infections include *Cryptosporidium parvum,* cytomegalovirus, *Mycobacterium avium-intracellulare, Isospora belli, Enterocytozoon bieneusi, Candida albicans,* astrovirus, calicivirus, adenovirus, and the usual bacterial enteropathogens. In these patients, *Cryptosporidium* can cause a chronic secretory diarrhea.

Cancer chemotherapy can damage the bowel mucosa, leading to secondary malabsorption of disaccharides such as lactose. After bone marrow transplantation, mucosal damage from **graft-versus-host disease** can cause diarrhea and malabsorption. Small bowel biopsies show nonspecific villus atrophy, mixed inflammatory cell infiltrates, and increased apoptosis. Cancer chemotherapy and bone marrow transplantation are associated with pancreatic damage leading to exocrine pancreatic insufficiency.

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338.6 Immunoproliferative Small Intestinal Disease

Ernest G. Seidman and David Branski

Malignant lymphomas of the small intestine are categorized into 3 subtypes: Burkitt lymphoma, non-Hodgkin lymphomas, and Mediterranean lymphoma. Burkitt lymphoma, the most common form in children, characteristically involves the terminal ileum with extensive abdominal involvement. The relatively uncommon "Western" type of non-Hodgkin lymphomas (usually large B-cell type), can involve various parts of the small intestine. **Mediterranean lymphoma** predominantly involves the proximal small intestine. The World Health Organization recommended the term *immunoproliferative small intestinal disease* (IPSID) for the syndrome associated with Mediterranean lymphoma, because in its early stages it does not appear to be a truly malignant lymphoma. Many of the patients with "secretory" IPSID syndrome have variable levels of abnormal immunoglobulin in serum or other body fluids, identified as truncated α heavy chain. The World Health Organization classification lists IPSID with heavy chain diseases as a special variant of extranodal marginal zone B-cell small intestinal **mucosa-associated lymphoid tissue lymphoma.**

IPSID occurs most often in the proximal small intestine in older children and young adults in the Mediterranean basin, Middle East, Asia, and Africa. Poverty and frequent episodes of gastroenteritis during infancy are antecedent risk factors. The initial clinical presentation is intermittent diarrhea and abdominal pain. Later, chronic diarrhea with malabsorption (60-80%), protein-losing enteropathy, weight loss, digital clubbing, and growth failure ensue. Intestinal obstruction, abdominal masses, and ascites are common in advanced stages.

In contrast to primary nonimmunoproliferative small intestinal lymphomas, in which the pathology in the intestine is usually focal, involving specific segments of the intestine and leaving the segments between the involved areas free of disease, the pathology in IPSID is diffuse, with a mucosal cellular infiltrate involving large segments of

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the intestine and sometimes the entire length of the intestine, thus producing malabsorption. Molecular and immunohistochemical studies demonstrated an association with *Campylobacter jejuni* infection. The differential diagnosis includes chronic enteric infections (parasites, tropical sprue), celiac disease, and other lymphomas. Radiologic findings include multiple filling defects, ulcerations, strictures, and enlarged mesenteric lymph nodes on CT scan.

The diagnosis is usually established by endoscopic biopsies and/or laparotomy. Upper endoscopy shows thickening, erythema, and nodularity of the mucosal folds in the duodenum and proximal jejunum. As the disease progresses, tumors usually appear in the proximal small intestine and rarely in the stomach. The diagnosis requires multiple duodenal and jejunal mucosal biopsies showing dense mucosal infiltrates, consisting of centrocyte-like and plasma cells. Progression to higher-grade large-cell lymphoplasmacytic and immunoblastic lymphoma is characterized by increased plasmocytic atypia with formation of aggregates and later sheets of dystrophic plasma cells and immunoblasts invading the submucosa and muscularis propria. A serum marker of IgA, a heavy-chain paraprotein, is present in most cases.

Treatment of early-stage IPSID with antibiotics results in complete remission in 30-70% of cases. However, the majority of untreated IPSID cases progress to lymphoplasmacytic and immunoblastic lymphoma invading the intestinal wall and mesenteric lymph nodes and can metastasize to distant organs, requiring chemotherapy.

Bibliography is available at Expert Consult.

338.7 Short Bowel Syndrome

Jon A. Vanderhoof and David Branski

Short bowel syndrome results from congenital malformations or resection of the small bowel. Table 338-9 lists the causes of short bowel syndrome. Loss of >50% of the small bowel, with or without a portion of the large intestine, can result in symptoms of generalized malabsorption disorder or in specific nutrient deficiencies, depending on the region of the bowel resected. At birth, the length of small bowel is 200-250 cm; by adulthood, it grows to 300-800 cm. Bowel resection in an infant has a better prognosis than in an adult because of the potential for intestinal growth. An infant with as little as 15 cm of bowel with an ileocecal valve, or 20 cm without, has the potential to survive and be eventually weaned from total parenteral nutrition.

In addition to the length of the bowel, the anatomic location of the resection is also important. The jejunum has more circular folds and longer villi. The proximal 100-200 cm of jejunum is the main site for carbohydrate, protein, iron, and water-soluble vitamin absorption, whereas fat absorption occurs over a longer length of the small bowel. Depending on the region of the bowel resected, specific nutrient malabsorption can result. Vitamin B_{12} and bile salts are only absorbed in the distal ileum (Fig. 338-7). Jejunal resections are generally tolerated better than ileal resections because the ileum can adapt to absorb nutrients and fluids. Net sodium and water absorption is relatively much higher in the ileum. Ileal resection has a profound effect on fluid and electrolyte absorption due to malabsorption of sodium and water by the remaining ileum; ileal malabsorption of bile salts stimulates increased colonic secretion of fluid and electrolytes.

Table 338-9 Causes of Short Bowel Syndrome
CONGENITAL
Congenital short bowel syndrome
Multiple atresias
Gastroschisis
BOWEL RESECTION
Necrotizing enterocolitis
Volvulus with or without malrotation
Long segment Hirschsprung disease
Meconium peritonitis
Crohn disease
Trauma

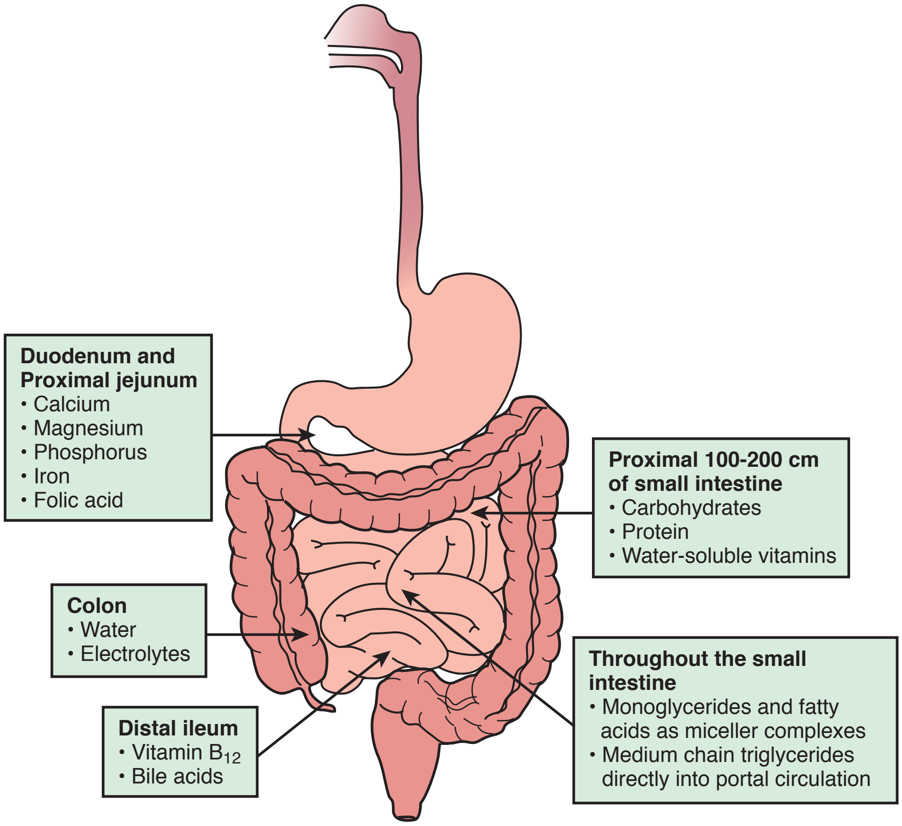

Figure 338-7 Absorption of nutrients in the small bowel varies with the region.

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TREATMENT

After bowel resection, treatment of short bowel syndrome is initially focused on repletion of the massive fluid and electrolyte losses while the bowel initially accommodates to absorb these losses. Nutritional support is often provided via parenteral nutrition. A central venous catheter should be inserted to provide parenteral fluid and nutrition support. The ostomy or stool output should be measured and fluid and electrolyte losses adequately replaced. Measurement of urinary Na^+ to assess body Na^+ stores is useful to prevent Na^+ depletion. Maintaining urinary Na^+ higher than K^+ ensures that Na^+ intake is adequate. Use of oral glucose electrolyte solutions improves intestinal sodium absorption, particularly in patients without a colon.

After the initial few weeks following resection, fluid and electrolyte losses stabilize, and the focus of therapy shifts to bowel rehabilitation with the gradual reintroduction of enteral feeds. Continuous small-volume trophic enteral feeding should be initiated with a an extensively hydrolyzed protein and MCT-enriched formula or mother's milk to stimulate gut hormones and promote mucosal growth. Enteral feeding also increases pancreatobiliary flow and reduces parenteral nutrition-induced hepatotoxicity. As soon as possible, the infant should be given a small amount of water and then formula or mother's milk by mouth to maintain an interest in oral feeding and minimize or avoid the development of **oral aversion.** As intestinal adaptation occurs, enteral feeding increases and parenteral supplementation decreases. The bowel mucosa proliferates and bowel lengthens with growth.

Approximately 50% of patients with short bowel syndrome achieve enteral autonomy within 5 yr of bowel resection. Many have initial successes but then require intermittent periods of parenteral nutrition. Enteral autonomy often requires years to achieve.

Patients may require repeat surgeries for obstruction or bowel lengthening procedures (longitudinal lengthening, serial transverse enteroplasties, or both).

After achieving the maximal increase in bowel absorptive capacity, management of specific micronutrient and vitamin deficiencies and treatment of transient problems such as postinfectious mucosal malabsorption are required. GI infections such as rotavirus or small bowel bacterial overgrowth can cause setbacks in the progression to full enteral feeding in patients with marginal absorptive function. A marked increase in stool output or evidence of carbohydrate malabsorption (stool pH <5.5 and positive test for reducing substances) contraindicate further increases in enteral feeds. Slow advancement of continuous enteral feeding rates continues until all nutrients are provided enterally. Then the feeds can be altered to include increased oral or bolus feeding volumes.

In patients with large stool output, the addition of soluble fiber and antidiarrheal agents such as loperamide and anticholinergics can be beneficial, although these drugs can increase the risk of bacterial overgrowth. Cholestyramine can be beneficial for patients with distal ileal resection, but its potential depletion of the bile acid pool can increase steatorrhea. Bacterial overgrowth is common in infants with a short bowel and can delay progression of enteral feedings. Empirical treatment with metronidazole or other antibiotics (nitazoxanide, rifaximine) is often useful. Diets high in fat and lower in carbohydrate may be helpful in reducing bacterial overgrowth as well as enhancing adaptation.

COMPLICATIONS

Long-term complications of short bowel syndrome include those of parenteral nutrition: central catheter infection, thrombosis, hepatic cholestasis and cirrhosis, and gallstones. Appropriate care of the central line to prevent infection and catheter-related thrombosis is extremely important. Sepsis is a leading cause of death, can occur any time after treatment is initiated (months to years later), and is most often bacterial (single organism more common than polymicrobial), although fungal infection may be noted in 20-25% of septic episodes.

Some patients need long-term parenteral nutritional support, and lack of central line access is potentially life-threatening; inappropriate removal or changes of central lines in the neonatal period should be avoided. Other complications of terminal ileal resection include vitamin B_{12} deficiency, which might not appear until 1-2 yr after parenteral nutrition is withdrawn. Long-term monitoring for deficiencies of vitamin B_{12}, folate, iron, fat-soluble vitamins, and trace minerals such as zinc and copper is important. **Renal stones** can occur as a result of hyperoxaluria secondary to steatorrhea (calcium binds to the excess fat and not to oxalate, so more oxalate is reabsorbed and excreted in the urine). Venous thrombosis and vitamin deficiency have been associated with hyperhomocystinemia in short bowel syndrome. Bloody diarrhea secondary to patchy, mild colitis can develop during the progression of enteral feedings. The pathogenesis of this "feeding colitis" is unknown, but it is usually benign and can improve with a hypoallergenic diet or treatment with mesalamine.

In patients who are unable to achieve full enteral feeding after several years of nutritional rehabilitation, surgical bowel lengthening procedures may be considered. In some children with complications of parenteral nutrition, especially impending liver failure, small intestinal and liver transplantation may be considered (see Chapter 331).

Bibliography is available at Expert Consult.

338.8 Chronic Malnutrition

Raanan Shamir and David Branski

Primary malnutrition (i.e., undernutrition) is very common in developing countries and is directly related to increased disease burden and mortality (see Chapter 46). In developed countries, chronic malnutrition occurs mainly as a result of decreased food intake, malabsorption syndromes, and increased nutritional needs in children with chronic diseases. Malnutrition is diagnosed in 11-50% of hospitalized children and recent reports from Europe suggest a prevalence of close to 20% in chronically ill children. Child neglect and improper preparation of formula can result in severe malnutrition. Malnutrition can be identified by evaluating dietary intake, by medical history (anorexia, vomiting, dysphagia, mood and behavioral changes, abdominal pain, diarrhea), by anthropometric measurements (e.g., reduced weight per age and weight per height, body mass index <5th percentile), and by clinical signs of nutrient deficiencies (atrophic tongue in iron-deficiency anemia or alopecia in zinc deficiency). Screening tools for malnutrition are used in adults to provide a simple and fast way of diagnosing those patients in need. Few such screening tools for the pediatric population were developed and are being studied.

Malnourished children suffer from impaired immunity, poor wound healing, muscle weakness, and diminished psychologic drive. Malnutrition has short-term consequences (increased disability, morbidity, and mortality) and long-term consequences (final adult size, lower IQ, economic productivity). Undernutrition in hospitalized children is related to increased infectious complications, delayed recovery, increased length of stay and costs, increased readmission rate, and increased mortality.

Nutritional rehabilitation in malnourished children is discussed in Chapter 46.

Chronic malnutrition complicated by diarrheal dehydration is a commonly observed phenomenon. Infectious diarrhea is common in tropical and subtropical countries, in the setting of poor hygiene practices, in immunocompromised hosts (e.g., HIV, congenital immunodeficiency), and when impairment of the immune response is due to chronic malnutrition itself. In children with chronic disorders, diarrhea may be related to the underlying disease that should be sought for. Examples include noncompliance with a gluten-free diet in celiac disease, noncompliance with pancreatic enzyme treatment in cystic fibrosis, and disease relapse in inflammatory bowel disease (IBD). In the case of IBD, relapse should be diagnosed only after infectious diarrhea and *C. difficile* infection have been ruled out. Malnutrition per se can lead to exocrine pancreatic insufficiency, which, in turn, aggravates malabsorption and diarrhea.

In infants and children with severe malnutrition, many of the signs normally used to assess the state of hydration or shock are unreliable.

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Severe malnutrition might be accompanied by sepsis; thus, children with septic shock might not have diarrhea, thirst, or sunken eyes but may be hypothermic, hypoglycemic, or febrile. The electrocardiogram often shows tachycardia, low amplitude, and flat or inverted T waves. Cardiac reserve seems lowered, and heart failure is a common complication.

Despite clinical signs of dehydration, urinary osmolality may be low in the chronically malnourished child. Renal acidifying ability is also limited in patients with malnutrition.

Management of the diarrhea in chronically malnourished children is based on 3 principles: oral rehydration to correct dehydration, rapid resumption of feeds with avoidance of periods of nothing by mouth, and treating the etiology of the diarrhea.

When treating the dehydration, it must be remembered that in dehydrated and malnourished infants there appears to be overexpansion of the extracellular space accompanied by extracellular and presumably intracellular hypoosmolality. Thus, reduced or hypotonic osmolarity oral rehydration solutions are indicated in this setting. When oral rehydration is not possible, the route of choice is nasogastric, and intravenous therapy should be avoided if possible.

Initial intravenous therapy in profound dehydration is designed to improve the circulation and expand extracellular volume. For patients with edema, the quality of fluid and the rate of administration might need to be readjusted from recommended levels to avoid over hydration and pulmonary edema. Blood should be given if the patient is in shock and is severely anemic. Potassium salts can be given early if urine output is good. Clinical and electrocardiogram improvement may be more rapid with magnesium therapy.

Children with chronic malnutrition are at risk for the refeeding syndrome. Therefore, initial calorie provision should not exceed the previous daily intake and is usually begun at 50-75% of estimated resting energy expenditure, with rapid increase to caloric goals once there are no severe abnormalities in sodium, potassium, phosphorus, calcium, or magnesium. Correction of malnutrition and catch-up growth are not part of the primary treatment of these children, but a nutrition rehabilitation plan is necessary.

Bibliography is available at Expert Consult.

338.9 Enzyme Deficiencies

Michael J. Lentze and David Branski

CARBOHYDRATE MALABSORPTION

Symptoms of carbohydrate malabsorption include loose watery diarrhea, flatulence, abdominal distention, and pain. Some children are asymptomatic unless the malabsorbed carbohydrate is consumed in large amounts. Disaccharidases are present on the brush border membrane of the small bowel. Disaccharidase deficiency can be caused by a genetic defect or secondarily by damage to the small bowel epithelium, as occurs with infection or inflammatory disorders.

Unabsorbed carbohydrates enter the large bowel and are fermented by intestinal bacteria, producing organic acids and gases such as methane and hydrogen. The gases can cause discomfort and the unabsorbed carbohydrate and the organic acids cause osmotic diarrhea characterized by an acidic pH and presence of either reducing or nonreducing sugars in the stool. Hydrogen gas can be detected in the breath as a sign of fermentation of unabsorbed carbohydrates (H_2-breath test).

LACTASE DEFICIENCY

Congenital lactase deficiency is rare and is associated with symptoms occurring on exposure to lactose in milk. Fewer than 50 cases have been reported worldwide. In patients with congenital lactase deficiency, 5 distinct mutations in the coding region of the *LCT* gene were found. In most patients (84%), homozygosity for a nonsense mutation, 4170T-A (Y1390X; OMIM 223000), designated Fin (major), was found.

Primary adult type-hypolactasia is caused by a physiologic decline in lactase actively that occurs following weaning in most mammals. The brush-border lactase is expressed at low levels during fetal life; activity increases in late fetal life and peaks from term to 3 yr, after which levels gradually decrease with age. This decline in lactase levels varies between ethnic groups. Lactase deficiency occurs in approximately 15% of white adults, 40% of Asian adults, and 85% of black adults in the United States. Lactase is encoded by a single gene *(LCT)* of approximately 50 kb located on chromosome 2q21. C/T (−13910) polymorphisms of the *MCM6* gene were found to be related to adult-type hypolactasia in most European populations. In 3 African populations—Tanzanians, Kenyans, and Sudanese—3 single-nucleotide polymorphisms, G/C (−14010), T/G(−13915), and C/G(−13907), were identified with lactase persistence and have derived alleles that significantly enhance transcription from the lactase gene promoter in vitro.

Secondary lactose intolerance follows small bowel mucosal damage (celiac disease, rotavirus infection) and is usually transient, improving with mucosal healing.

Lactase deficiency can be diagnosed by H_2-breath test or by measurement of lactase activity in mucosal tissue retrieved by small bowel biopsy. Diagnostic testing is not mandatory, and often simple dietary changes that reduce or eliminate lactose from the diet relieve symptoms.

Treatment of lactase deficiency consists of a milk-free diet. A lactose-free formula (based on either soy or cow's milk) can be used in infants. In older children, low-lactose milk can be consumed. Addition of lactase to dairy products usually abbreviates the symptoms.

Live-culture yogurt contains bacteria that produce lactase enzymes and is therefore tolerated in most patients with lactase deficiency. Hard cheeses have a small amount of lactose and are generally well tolerated.

FRUCTOSE MALABSORPTION

Children consuming a large quantity of juice rich in fructose, corn syrup, or natural fructose in fruit juices can present with diarrhea, abdominal distention, and slow weight gain. Restricting the amount of juice in the diet resolves the symptoms and helps avoid unnecessary investigations. Fructose H_2 breath test can be helpful in the diagnosis of fructose malabsorption. The reason for fructose malabsorption is the reduced abundance of GLUT-5 transporter on the surface of the intestinal brush-border membrane, which occurs in approximately 5% of the population.

SUCRASE–ISOMALTASE DEFICIENCY

Sucrase–isomaltase deficiency is a rare autosomal recessive disorder with a complete absence of sucrase and reduced maltase digestive activity. The sucrase–isomaltase complex is composed of 1,927 amino acids encoded by a 3,364 bp messenger RNA. The gene locus on chromosome 3 has 30 exons spanning 106.6 kb. The majority of sucrase–isomaltase mutations result in a lack of enzyme protein synthesis (null mutation). Posttranslational processing defects are also identified.

Approximately 2% of Europeans and Americans are mutant heterozygote. Sucrase deficiency is especially common in indigenous Greenlanders (estimated 5%) in whom it is often accompanied by lactase deficiency.

Symptoms of sucrase-isomaltase deficiency usually begin when the infant is exposed to sucrose or a glucose polymer diet. This can occur with ingestion of non–lactose-based infant formula or on the introduction of pureed food, especially fruits and sweets. Diarrhea, abdominal pain, and poor growth are observed. Occasional patients present with symptoms in late childhood or even adult life, but careful history often indicates that symptoms appeared earlier. Diagnosis of sucrase-isomaltase malabsorption requires acid hydrolysis of stool for reducing substances because sucrase is a nonreducing sugar. Alternatively, diagnosis can be achieved with hydrogen breath test or direct enzyme assay of small bowel biopsy.

The mainstay of **treatment** is lifelong dietary restriction of sucrose-containing foods. Enzyme replacement with a purified yeast

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enzyme, sacrosidase (Sucraid), is a highly effective adjunct to dietary restriction.

GLUCOSE–GALACTOSE MALABSORPTION

More than 30 different mutations of the sodium/glucose cotransporter gene *(SGLT1)* are identified. These mutations cause a rare autosomal recessive disorder of intestinal glucose and galactose/Na^+ cotransport system that leads to osmotic diarrhea. Because most dietary sugars are polysaccharides or disaccharides with glucose or galactose moieties, diarrhea follows the ingestion of glucose, breast milk, or conventional lactose-containing formulas. Dehydration and acidosis can be severe, resulting in death.

The stools are acidic and contain sugar. Patients with the defect have normal absorption of fructose, and their small bowel function and structure are normal in all other aspects. Intermittent or permanent glycosuria after fasting or after a glucose load is a common finding because of the transport defect also being present in the kidney. The presence of reducing substances in watery stools and slight glycosuria despite low blood sugar levels is highly suggestive of glucose–galactose malabsorption. Malabsorption of glucose and galactose is easily identified using the breath hydrogen test. It is safe to perform the first test with a dose of 0.5 g/kg of glucose; if necessary, a second test can be performed using 2 g/kg. Breath H_2 will rise more than 20 ppm. The small intestinal biopsy is useful to document a normal villous architecture and normal disaccharidase activities. The identification of mutations of *SGLT1* makes it possible to perform prenatal screening in families at risk for the disease.

Treatment consists of rigorous restriction of glucose and galactose. Fructose, the only carbohydrate that can be given safely, should be added to a carbohydrate-free formula at a concentration of 6-8%. Diarrhea immediately ceases when infants are given such a formula. Although the defect is permanent, later in life, limited amounts of glucose, such as starches or sucrose may be tolerated.

EXOCRINE PANCREATIC INSUFFICIENCY

Chapter 349 discusses disorders of exocrine pancreatic insufficiency. Cystic fibrosis is the most common congenital disorder associated with exocrine pancreatic insufficiency. Although rare, the next most common cause of pancreatic insufficiency in children is Shwachman-Diamond syndrome. Other rare disorders causing exocrine pancreatic insufficiency are Johanson-Blizzard syndrome (severe steatorrhea, aplasia of alae nasi, deafness, hypothyroidism, scalp defects), Pearson bone marrow syndrome (sideroblastic anemia, variable degree of neutropenia, thrombocytopenia), and isolated pancreatic enzyme deficiency (lipase, colipase and lipase–colipase, trypsinogen, amylase). Deficiency of enterokinase—a key enzyme that is produced in the proximal small bowel and is responsible for the activation of trypsinogen to trypsin—manifests clinically as exocrine pancreatic insufficiency.

Autoimmune polyendocrinopathy syndrome type 1, a rare autosomal recessive disorder, is caused by mutation in the autoimmune regulator gene *(AIRE)*. Chronic mucocutaneous candidiasis is associated with failure of parathyroid gland, adrenal cortex, pancreatic β cells, gonads, gastric parietal cells, and thyroid gland. Pancreatic insufficiency and steatorrhea are associated with this condition.

ENTEROKINASE (ENTEROPEPTIDASE) DEFICIENCY

Enterokinase (enteropeptidase) is a brush-border enzyme of the small intestine. It is responsible for the activation of trypsinogen into trypsin. Deficiency of this enzyme results in severe diarrhea, malabsorption, failure to thrive, and hypoproteinemic edema after birth.

Enterokinase deficiency is caused by mutation in the serine protease-7 gene *(PRSS7)* on chromosome 21q21. The diagnosis can be established by measuring the enzyme level in intestinal tissue. Treatment of this rare autosomal recessive disorder consists of replacement with pancreatic enzymes and administration of a protein hydrolyzed formula with added MCT oil in infancy.

TRYPSINOGEN DEFICIENCY

Trypsinogen deficiency is a rare syndrome with symptomatology similar to that of enterokinase deficiency. Enterokinase catalyzes the conversion of trypsinogen to trypsin, which, in turn, activates the various pancreatic proenzymes such as chymotrypsin, procarboxypeptidase, and proelastase for their active forms. Deficiency of trypsinogen results in severe diarrhea, malabsorption, failure to thrive, and hypoproteinemic edema soon after birth.

The trypsinogen gene is encoded on chromosome 7q35. Treatment is the same as for enterokinase deficiency, with pancreatic enzymes and protein hydrolysate formula with added MCT oil in infancy.

338.10 Liver and Biliary Disorders Causing Malabsorption

Anil Dhawan and David Branski

Absorption of fats and fat-soluble vitamins depends to a great extent on adequate bile flow providing bile acids to the small intestine. Most of the liver and biliary disorders lead to impairment of the bile flow, contributing to malabsorption of long-chain fatty acids and vitamins such as A, D, E, and K. Liver disorders that are associated with significant malabsorption and failure to thrive are: (1) progressive familial intrahepatic cholestasis (types 1, 2, and 3) and bile acid synthesis defects. Progressive familial intrahepatic cholestasis type 1 is also associated with chronic diarrhea caused by bile transport defect in the gut. It is not uncommon for these children to have symptomatic fat-soluble vitamin deficiencies like pathologic fractures and peripheral neuropathy. (2) Children with storage disorders such as Wolman disease also manifest with severe failure to thrive and multiple vitamin deficiencies. (3) Children with biliary disorders such as biliary atresia after a Kasai portoenterostomy, cystic fibrosis, neonatal sclerosing cholangitis, Alagille syndrome, and sclerosing cholangitis constitute another major group of disorders where malabsorption could be a significant problem. In addition, severe portal hypertension can lead to portal hypertensive enteropathy, resulting in poor absorption of the nutrients. Decompensated liver disease leads to anorexia and increased energy expenditures, further widening the gap between calorie intake and net absorption, leading to severe malnutrition. Adequate management of nutrition is essential to improve the outcome with or without liver transplantation. This is usually achieved by using MCT-rich milk formula, supplemental vitamins, and continuous or bolus enteral feed where oral intake is poor.

Vitamin D deficiency is commonly observed on biochemical tests, and children rarely present with pathologic fractures. Simultaneous administration of vitamin D with the water-soluble vitamin E preparation (TPGS 1,000 succinate) enhances absorption of vitamin D. In young infants, oral vitamin D_3 is given at a dose of 1,000 IU/kg/24 hr. After 1 mo, if the serum 25-hydroxyvitamin D level is low, the same dose of oral vitamin D is mixed with TPGS. 25-Hydroxyvitamin D is then monitored every 3 mo, with adjustment of doses as necessary.

Vitamin E deficiency in patients with chronic cholestasis is not usually symptomatic, but it can manifest as a progressive neurologic syndrome, which includes peripheral neuropathy (manifesting as loss of deep tendon reflexes and ophthalmoplegia), cerebellar ataxia, and posterior column dysfunction. Early in the course, findings are partially reversible with treatment; late features might not be reversible. It may be difficult to identify vitamin E deficiency because the elevated blood lipid levels in cholestatic liver disease can falsely elevate the serum vitamin E level. Therefore, it is important to measure the ratio of serum vitamin E to total serum lipids; the normal level for patients younger than 12 yr of age is >0.6, and for patients older than 12 yr it is >0.8. The neurologic disease can be prevented with the use of an oral water-soluble vitamin E preparation (TPGS, Liqui-E) at a dose of 25-50 IU/day in neonates and 1 IU/kg/day in children.

Vitamin K deficiency can occur as a result of cholestasis and poor fat absorption. In children with liver disease it is very important to

differentiate between the coagulopathy related to vitamin K malabsorption and one secondary to the synthetic failure of the liver. A single dose of vitamin K administered intravenously does not correct the prolonged prothrombin time in liver failure, but the deficiency state responds within a few hours. Easy bruising may be the first sign. In neonatal cholestasis, coagulopathy as a result of vitamin K deficiency can manifest with intracranial bleeds with devastating consequences, and prothrombin time should be routinely measured to monitor for deficiency in children with cholestasis. All children with cholestasis should receive vitamin K supplements.

Vitamin A deficiency is rare and is associated with night blindness, xerophthalmia, and increased mortality if patients contract measles. Serum vitamin A levels should be monitored and adequate supplementation considered.

338.11 Rare Inborn Defects Causing Malabsorption

Klaus-Peter Zimmer and David Branski

Some congenital (primary) malabsorption disorders originate from a defect of integral membrane proteins, which fulfill a transport function as receptor or channel across the apical or basolateral membrane of enterocytes for nutritional components. Histologic examination of the small and large bowel is typically normal. Most of these disorders are inherited in an autosomal recessive pattern. Most are rare, and patients present with a broad phenotypic heterogeneity as a result of modifier genes and nutritional and other secondary factors.

DISORDERS OF CARBOHYDRATE ABSORPTION

Patients with **Fanconi-Bickel syndrome** present with tubular nephropathy; rickets; hepatomegaly; glycogen accumulation in liver, kidney, and small bowel; failure to thrive; and fasting hypoglycemia. The disorder is caused by homozygous mutations of GLUT2, the facilitative glucose (and galactose) transporter at the basolateral membrane of enterocytes hepatocytes, renal tubules, pancreatic islet cells, and cerebral neurons. Because severe osmotic diarrhea is not a feature of Fanconi-Bickel syndrome, a GLUT2-independent basolateral transport for glucose is suggested. GLUT2 seems to modulate insulin secretion, renal reabsorption, and glucose uptake from the apical membrane of enterocytes in response to the (postprandial) sugar environment. Diagnostic signs are elevated galactose levels in the blood (found in the neonatal screening program), neonatal bilateral cataracts, marked glycosuria, generalized aminoaciduria, and excessive renal losses of phosphate and calcium. Liver and kidneys are enlarged. Therapy includes substitution of electrolyte losses and vitamin D and supplying uncooked cornstarch to prevent hypoglycemia. Patients who present in the neonatal period need frequent small meals and galactose-free milk.

DISORDERS OF AMINO ACID AND PEPTIDE ABSORPTION

Owing to their ontogenic origins, enterocytes and renal tubules express amino acid transporter in common. Their highest intestinal transporter activity is found in the jejunum. The transporters causing Hartnup disease, cystinuria, iminoglycinuria, and dicarboxylic aminoaciduria are located in the apical membrane, and those causing lysinuric protein intolerance (LPI) and blue diaper syndrome are anchored in the basolateral membrane of the intestinal epithelium.

Dibasic amino acids, including cystine, ornithine, lysine, and arginine are taken up by the Na-independent SLC3A1/SLC7A9, which is defective in **cystinuria**. The overall prevalence of the disease is 1 in 7,000 newborns. This disorder is not associated with any GI or nutritional consequences because of compensation by alternative transporter. However, hypersecretion of cystine in the urine leads to recurrent cystine stones, which account for up to 1% of all urinary tract stones. Ample hydration, urine alkalinization, and cystine-binding thiol drugs can increase the solubility of cystine. Cystinuria type I is inherited as an autosomal recessive trait, and the transmission of type II is autosomal dominant with incomplete penetrance. Cystinuria type I has been described in association with 2p21 deletion syndrome and hypotonia–cystinuria syndrome.

Hartnup disease is characterized by malabsorption of neutral amino acids, including the essential amino acid tryptophan, with aminoaciduria, photosensitive pellagra-like rash, headaches, cerebellar ataxia, delayed intellectual development, and diarrhea. The clinical spectrum ranges from asymptomatic patients to severely affected patients with progressive neurodegeneration leading to death by adolescence. SLC6A19, which is the major luminal sodium-dependent neutral amino acid transporter of small intestine and renal tubules, has been identified as the defective protein. Its association with collectrin and angiotensin-converting enzyme II is likely to be involved in the phenotypic heterogeneity of Hartnup disorder. Tryptophan is a precursor of nicotinamide adenine dinucleotide phosphate biosynthesis; therefore the disorder can be treated by nicotinamide in addition to a diet of 4 g protein/kg. The use of lipid-soluble esters of amino acids and tryptophan ethylester has also been reported.

In the **blue diaper syndrome** (**indicanuria, Drummond syndrome**) tryptophan is specifically malabsorbed and the defect is expressed only in the intestine and not in the kidney, in contrast to Hartnup disease. Intestinal bacteria convert the unabsorbed tryptophan to indican, which is responsible for the bluish discoloration of the urine after its hydrolysis and oxidation. Symptoms can include digestive disturbances such as vomiting, constipation, poor appetite, failure to thrive, hypercalcemia, nephrocalcinosis, fever, irritability, and ocular abnormalities. The molecular genetic defect of this disorder has not yet been characterized.

The underlying defect of **iminoglycinuria** is the malabsorption of proline, hydroxyproline, and glycine as a consequence of the proton amino acid transporter SLC36A2 defect, with a possible participation of modifier genes, one of which (SLC6A20) is present in the intestinal epithelium. This disorder is usually benign, but sporadic cases with encephalopathy, mental retardation, deafness, blindness, kidney stones, hypertension, and gyrate atrophy have been described.

The excitatory amino acid carrier SLC1A1 is affected in **dicarboxylic aminoaciduria**. This carrier is present in the small intestine, kidney, and brain, and transports the anionic acids L-glutamate, L- and D-aspartate, and L-cysteine. There are single case reports indicating that this disorder could be associated with hyperprolinemia and neurologic symptoms such as **POLIP** (polyneuropathy, ophthalmoplegia, leukoencephalopathy, intestinal pseudoobstruction syndrome).

A histidine-specific transport system has also been proposed. A few patients have been reported with an intestinal and renal defect of this carrier. It has not been confirmed that patients with **histidinuria**, who have low plasma histidine levels, in contrast to histidinemia, develop neurologic symptoms (e.g., hearing loss, myoclonic seizures).

A methionine-preferring transporter in the small intestine was suggested to be affected in **Smith-Strang disease** (**oasthouse urine disease**), which is characterized by purple, red-brown-colored urine with a cabbage-like odor, containing 2-hydroxybutyric acid, valine, and leucine. The potential symptoms of **methionine malabsorption** include neurologic signs, white hair, and diarrhea. Large amounts of methionine and branched-chain amino acids are present in the feces but not in the urine. A low-methionine diet is recommended to alleviate the symptoms.

Among the diseases (see the earlier discussion of cystinuria) with a membrane transport defect of cationic amino acids (lysine, arginine, ornithine), **LPI** is the second most common, with a prevalence in Finland of 1 in 60,000. The y^+LAT-1 (SLC7A7) carrier at the basolateral membrane of the intestinal and renal epithelium is affected, with failure to deliver cytosolic dibasic cationic amino acids into the paracellular space in exchange for Na^+ and neutral amino. This defect is not compensated by the SLC3A1/SLC7A9 transporter (at the apical membrane), the latter being affected in cystinuria. The symptoms of

LPI, which appear after weaning, include diarrhea, failure to thrive, hepatosplenomegaly, nephritis, respiratory insufficiency, alveolar proteinosis, pulmonary fibrosis, and osteoporosis. Abnormalities of bone marrow have also been described in a subgroup of LPI patients. The disorder is characterized by low plasma concentrations of dibasic amino acids (in contrast to high levels of citrulline, glutamine, and alanine) and massive excretion of lysine (as well as orotic acid, ornithine, and arginine in moderate excess) in the urine. Hyperammonemia and coma usually develop after episodic attacks of vomiting, after fasting, or following administration of large amounts of protein (or alanine load), possibly because of a deficiency of intramitochondrial ornithine. Some patients show moderate retardation. Cutaneous manifestations can include alopecia, perianal dermatitis, and sparse hair. Some patients avoid protein-containing food. Treatment includes orally administered citrulline (200 mg/kg/day), which is well absorbed from the intestine; dietary protein restriction (<1.5 g/kg/day); and carnitine supplementation. One patient with **isolated lysinuria** has been reported with growth failure, seizures, and mental retardation.

DISORDERS OF FAT TRANSPORT

Chapter 86 describes abetalipoproteinemia, hypobetalipoproteinemia, and chylomicron retention disease. The long-chain fatty acid (FATP4) and cholesterol transporters, the latter being called Niemann-Pick C1-like protein (NPC1L1), have been characterized at the intestinal brush-border in knockout mice models showing a hyperproliferative hyperkeratosis and an impaired fatty acid and cholesterol uptake. NPC1L1 is inhibited by ezetimibe, which is used to restrict the absorption of dietary cholesterol.

Tangier disease is characterized by the absence of high-density lipoprotein cholesterol, which is caused by mutations in the adenosine triphosphate–binding cassette transporter A1 (ABCA1) gene. The failure of intracellular phospholipids and cholesterol efflux to lipid-poor apolipoprotein acceptors such as high-density lipoprotein predisposes to premature coronary heart disease and accumulation of cholesterol in liver, spleen, lymph nodes (tonsils), and small intestine.

Features of Tangier disease include orange tonsils, hepatosplenomegaly, relapsing neuropathy, orange-brown spots on the colon and ileum, diarrhea in association with decreased plasma cholesterol levels (apolipoprotein A-I and A-II), and normal or elevated triglyceride levels. Specific therapy for Tangier disease has not yet been established.

In **sitosterolemia,** defective efflux of sterol leads to increased absorption of dietary sterols; normally, <5% are retained by the GI tract. Patients carry mutations of the ABCG5 (sterolin-1) and ABCG8 (sterolin-2) transporters. The disorder is associated with tendon xanthomas, increased atherosclerosis, and hemolysis. Plasma levels of phytosterols (mainly sitosterol) are typically >10 mg/dL.

Congenital diarrhea in newborns with hyperlipidemia may indicate impaired fat (bile) absorption and mutations of the microsomal enzyme acyl-coenzyme A:diacylglycerol acyltransferase 1 (DGAT1), which catalyzes the final step in triglyceride synthesis.

DISORDERS OF VITAMIN ABSORPTION

Transporters and receptors of the intestinal epithelium have been described for water-soluble but not fat-soluble vitamins, the latter being absorbed primarily by enterocytes, by passive diffusion after emulsification of fats by bile salts. Transfer proteins (retinol-binding protein, RBP4, and α-tocopherol transfer protein, TTP1) have been involved in deficiency states of vitamins E (spinocerebellar ataxia) and A (ophthalmologic signs), respectively.

Vitamin B_{12} (cobalamin) is used exclusively by microorganisms and is acquired mostly from meat and milk. Its absorption starts with the removal of cobalamin from dietary protein by gastric acidity and its binding to haptocorrin. In the duodenum, pancreatic proteases hydrolyze the cobalamin-haptocorrin complex, allowing the binding of cobalamin to intrinsic factor (IF), which originates from parietal cells. The receptor of the cobalamin-IF complex is located at the apical membrane of the ileal enterocytes and represents a heterodimer consisting of cubilin and amnionless, with endocytic uptake of this ligand into endosomes, where it binds to megalin and forms a cobalamin–transcobalamin-2 complex (after cleavage of IF) for further transcytosis. As a cofactor for methionine synthase, cobalamin converts homocysteine to methionine. Cobalamin deficiency can be caused by inadequate intake of the vitamin (e.g., breastfeeding by mothers on a vegetarian diet), primary or secondary achlorhydria including autoimmune gastritis, exocrine pancreatic insufficiency, bacterial overgrowth (see Chapter 338.4), ileal disease (Crohn disease, see Chapter 336), ileal (or gastric) resection, infections (fish tapeworm), and Whipple disease (see Chapter 341).

Clinical signs of congenital **cobalamin malabsorption**, which usually appear from a few mo to 14 yr of age, are pancytopenia including megaloblastic anemia, fatigue, failure to thrive, and neurologic symptoms, including developmental delay. Recurrent infections and bruising may be present. Laboratory evaluation indicates low serum cobalamin, hyperhomocysteinemia, methylmalonic acidemia, and mild proteinuria. The Schilling test is useful to differentiate between lack of IF and malabsorption of cobalamin. Three rare autosomal recessive disorders of congenital cobalamin deficiency affect absorption and transport of cobalamin (in addition to 7 other inherited defects of cobalamin metabolism). These include mutations of the gastric IF *(GIF)* gene with absence of IF (but normal acid secretion and lack of autoantibodies against IF or parietal cells), mutations of the amnionless *(AMN)* and cubilin *(CUBN)* genes (**Imerslund-Grasbeck syndrome**), and mutations in the transcobalamin 2 cDNA. These disorders require long-term parenteral cobalamin treatment: intramuscular injections of hydroxycobalamin 1 mg daily for 10 days and then once a month. High-dose substitution with oral cyanocobalamin (1 mg biweekly) does not seem to be sufficient for all patients with congenital cobalamin deficiency.

Folate is an essential vitamin required to synthesize methionine from homocysteine. It is found mainly in green leafy vegetables, legumes, and oranges. It is converted to 5- methyltetrahydrofolate after its uptake by enterocytes. Secondary folate deficiency is caused by insufficient folate intake, villous atrophy (e.g., celiac disease, IBD), treatment with phenytoin, and trimethoprim, among others (see Chapter 448.1). Several inherited disorders of folate metabolism and transport have been described.

Hereditary **folate malabsorption** is characterized by a defect of the proton-coupled folate transporter (formerly reported to be HCP1, a heme carrier) of the brush-border, leading to impaired absorption of folate in the upper small intestine as well as impaired transport of folate into the central nervous system. Mutations of the reduced folate carrier (RFC1, SLC19A1) have not been found in this entity. Sulfasalazine and methotrexate are potent inhibitors of proton-coupled folate transporter. Symptoms of congenital folate malabsorption are diarrhea, failure to thrive, megaloblastic anemia (in the 1st few mo of life), glossitis, infections *(Pneumocystis jiroveci)* with hypoimmunoglobulinemia, and neurologic abnormalities (seizures, mental retardation, and basal ganglia calcifications). Macrocytosis, with or without neutropenia, multilobulated polymorphonuclear cells, increased lactate dehydrogenase and bilirubin, increased saturation of transferrin, and decreased cholesterol can be found. Low levels of folate are present in serum and cerebrospinal fluid. Plasma homocysteine concentrations as well as urine excretion of formiminoglutamic acid and orotic acid are elevated. Long-lasting deficiency is best documented using red cell folate. Therapy involves large doses of oral (up to 100 mg/day) or systemic (intrathecal) folate.

The molecular basis of intestinal transport of other water-soluble vitamins such as **vitamin C** (Na^+-dependent vitamin C transporters 1 and 2), **pyridoxine/vitamin B_6**, and **biotin/vitamin B_5** (Na^+-dependent multivitamin transporter) have been described; however congenital defects of these transporter systems have not yet been found in humans. A **thiamine/vitamin B_1**-responsive megaloblastic anemia syndrome, which is associated with early-onset type 1 diabetes mellitus and sensorineural deafness, is caused by mutations of the thiamine transporter protein, THTR-1 (SLC19A2), present in the brush-border.

DISORDERS OF ELECTROLYTE AND MINERAL ABSORPTION

Congenital chloride diarrhea belongs to the more common causes of severe congenital diarrhea, with prevalence in Finland of 1:20,000. It is caused by a defect of the *SLC26A3* gene, which encodes a Na^+-independent Cl^-/HCO_3^- exchanger within the apical membrane of ileal and colonic epithelium. Founder mutations have been described in Finnish, Polish, and Arab patients: V317del, I675-676ins, and G187X, respectively. The Cl^-/HCO_3^- exchanger absorbs chloride originating from gastric acid and the cystic fibrosis transmembrane conductance regulator and secretes bicarbonate into the lumen, neutralizing the acidity of gastric secretion.

Prenatal clinical signs of this disorder are a dilated small bowel that can mislead to a diagnosis of intestinal obstruction. Newborns with congenital chloride diarrhea present with severe life-threatening secretory diarrhea during the 1st few wk of life. Laboratory findings are metabolic alkalosis, hypochloremia, hypokalemia, and hyponatremia (with high plasma renin and aldosterone activities). Fecal chloride concentrations are >90 mmol/L and exceed the sum of fecal sodium and potassium. Early diagnosis and aggressive lifelong enteral substitution of KCl in combination with NaCl (chloride doses of 6-8 mmol/kg/day for infants and 3-4 mmol/kg/day for older patients) prevent mortality and long-term complications (such as urinary infections, hyperuricemia with renal calcifications, renal insufficiency, and hypertension) and allow normal growth and development. Orally administered proton pump inhibitors, cholestyramine, and butyrate can reduce the severity of diarrhea. The diarrheal symptoms usually tend to regress with age. However, febrile diseases are likely to exacerbate symptoms as a consequence of severe dehydration and electrolyte imbalances. (See Chapter 52 for fluid and electrolyte management.)

The classic form of **congenital sodium diarrhea** manifests with polyhydramnios, massive secretory diarrhea, severe metabolic acidosis, alkaline stools (fecal pH >7.5) and hyponatremia as a result of fecal losses of Na^+ (fecal Na^+ >70 mmol/L). Urinary secretion of sodium is low to normal. There is partial villous atrophy. The molecular genetic defect could not be located in the Na^+-H^+ exchangers, which were thought to be impaired because they seem to be mainly responsible for Na^+ absorption in the small intestine. In addition, a syndromic form of congenital sodium diarrhea with choanal or anal atresia, hypertelorism, and corneal erosions has been related to mutations of *SPINT2,* encoding a serine–protease inhibitor, whose pathophysiologic action on intestinal Na^+ absorption is unclear. Some patients can be weaned from parenteral nutrition later in childhood but depend on oral sodium citrate supplementation.

The congenital form of **acrodermatitis enteropathica** manifests with severe deficiency of body zinc soon after birth in bottle-fed children or after weaning from breastfeeding. Clinical signs of this disorder are anorexia, diarrhea, failure to thrive, humoral and cell-mediated immunodeficiency (poor wound healing, recurrent infections), male hypogonadism, skin lesions (vesicobullous dermatitis on the extremities and perirectal, perigenital, and perioral regions, and alopecia), and neurologic abnormalities (tremor, apathy, depression, irritability, nystagmus, photophobia, night blindness, and hypogeusia). The genetic defect of acrodermatitis enteropathica is caused by a mutation in the Zrt-Irt-lik protein 4 (ZIP4, SLC39A4), normally expressed on the apical membrane, which enables the uptake of zinc into the cytosol of enterocytes. The zinc-dependent alkaline phosphatase and plasma zinc levels are low. Paneth cells in the crypt of the small intestinal mucosa show inclusion bodies. Acrodermatitis enteropathica requires long-term treatment with elemental zinc 1 mg/kg/day. Maternal zinc deficiency impairs embryonic, fetal, and postnatal development. Chapter 51 describes the acquired forms of zinc deficiency.

Menkes disease and **occipital horn syndrome** are both caused by mutations in the gene encoding Cu^{2+} transporting adenosine triphosphatase (ATPase), α-polypeptide (ATP7A), also called Menkes or MNK protein. ATP7A is mainly expressed by enterocytes, placental cells, and the central nervous system, and is localized in the *trans*-Golgi network for copper transfer to enzymes in the secretory pathway or to endosomes to facilitate copper efflux. Copper values in liver and brain are low in contrast to an increase in mucosal cells, including enterocytes and fibroblasts. Plasma copper and ceruloplasmin levels decline postnatally. Clinical features of Menkes disease are progressive cerebral degeneration (convulsions), feeding difficulties, failure to thrive, hypothermia, apnea, infections (urinary tract), peculiar facies, hair abnormalities (kinky hair), hypopigmentation, bone changes, and cutis laxa. Patients with the classic form of Menkes disease usually die before the age of 3 yr. A therapeutic trial with copper-histidinase should start before the age of 6 wk. In contrast to Menkes disease, occipital horn syndrome usually manifests during adolescence with borderline intelligence, craniofacial abnormalities, skeletal dysplasia (short clavicles, pectus excavatum, genu valgum), connective tissue abnormalities, chronic diarrhea, orthostatic hypotension, obstructive uropathy, and osteoporosis. It should be differentiated from Ehlers-Danlos syndrome type V.

Active **calcium** absorption is mediated by the transient receptor potential channel 6 (TRPV6) at the brush border membrane, calbindin, and the CaATPase, or the Na^+-Ca^{++} exchanger for calcium efflux at the basolateral membrane within the proximal small bowel. A congenital defect of these transporters has not yet been described.

Intestinal absorption of dietary magnesium, which occurs via the transient receptor potential channel TRPM6 at the apical membrane, is impaired in familial **hypomagnesemia with secondary hypocalcemia**, which manifests with neonatal seizures and tetany.

Intestinal iron absorption consists of several complex regulated processes starting with the uptake of heme-containing iron by heme carrier protein 1 (HCP1) and Fe^{2+} (after luminal reduction of oxidized Fe^{3+}) by the divalent metal transporter 1 (DMT1) at the apical membrane, followed by the efflux of Fe^{2+} by ferroportin 1 (also called iron-regulated transporter) at the basolateral membrane of duodenal enterocytes. Mutations of the ferroportin 1 gene have been found in the autosomal dominant form of **hemochromatosis type 4**. Mutations of HFE (Cys282 Tyr, His63Asn, Ser65Cys) of classic hemochromatosis reduce the endocytic uptake of diferric transferrin by the transferrin receptor-1 at the basolateral membrane of the intestinal epithelium. Hepcidin antimicrobial peptide encodes hepcidin, a hepatic peptide hormone, which inhibits the efflux of iron through ferroportin and can be induced by IL-6. It is the defective gene of juvenile hemochromatosis (type 2, subtype B).

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338.12 Malabsorption in Eosinophilic Gastroenteritis

Ernest G. Seidman and David Branski

Eosinophilic digestive diseases are a group of rare and heterogeneous conditions characterized by patchy or diffuse eosinophilic infiltration of GI tissue. The diagnosis of eosinophilic gastroenteritis is based on GI symptoms, GI eosinophilic infiltrates, and the absence of other causes such as parasitic infection (most commonly *Enterobius vermicularis* in children) or a specific allergic response. Peripheral eosinophilia and elevated serum IgE levels are variably present are not diagnostic criteria. The majority (50-70%) of patients have a history of other allergic disorders, and others might have associated connective tissue diseases. Approximately 10% of patients with this disorder have an immediate family member affected, suggesting that eosinophilic GI disorders stem from a genetic predisposition, common environmental factors, or, most likely, a combination. Hypersensitivity to specific food allergens has been postulated as an etiologic factor. Symptoms depend on the severity and location of eosinophilic inflammation. Any region or layer (mucosa, submucosa, and serosa) of the gut may be involved, alone or in combination.

Diagnosis requires pan-endoscopy with biopsies. Eosinophilic infiltrates dominate the histologic findings, and signs of other inflammatory diseases are absent; in particular, the crypt architecture remains normal, no parasites are identified, and no eggs or larvae are found.

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Table 338-10 Common Micronutrient Deficiencies in Inflammatory Bowel Disease

MICRONUTRIENT	CROHN DISEASE AND/OR ULCERATIVE COLITIS	MALABSORPTION	INTESTINAL LOSSES	INADEQUATE INTAKE
Iron	CD and UC	+ (CD)	+++	++
Vitamins A, D, E, K	CD > UC	++ (CD)		+++
Vitamin B_{12}	CD	+++		+
Vitamin B_1, B_2, B_6	CD > UC			++
Vitamin C, glutathione (antioxidants)	CD and UC		++	++
Folate	CD and UC	++		+
Calcium, magnesium, selenium, zinc	CD and UC	++	+++	+
Polyunsaturated fatty acids	CD	++		++

CD, Crohn disease; UC, ulcerative colitis.

An increase in mast cells and IgE-containing plasma cells may be observed. Mucosal biopsies will only establish the diagnosis in cases with mucosal involvement. Small bowel capsule endoscopy is often very useful in that it characteristically reveals denuded mucosal erythema with marked focal villous atrophy in areas out of reach of standard endoscopes. The most common sites of involvement are the stomach and small intestine.

Symptoms may include abdominal pain (90%), vomiting (60%), nausea (50%), and abdominal distention (50%). Diarrhea with weight loss because of malabsorption can occur if small bowel involvement with villous blunting is extensive. Other than peripheral eosinophilia, hypoalbuminemia as a result of protein-losing enteropathy and iron-deficiency anemia are the more common laboratory findings.

Nutritional exclusion (or elemental) diets and corticosteroids are the mainstay of treatment. Approximately 50% of cases are complex, characterized by unpredictable relapses and a chronic course. Less-well-documented treatments, such as mast cell stabilizers and leukotriene antagonists (montelukast), have been used in small, uncontrolled trials. Clinical trials using biological modalities such as monoclonal anti-IgE (omalizumab) and anti-IL-5 (SCH55700/reslizumab and mepolizumab) are anticipated for severe cases.

Bibliography is available at Expert Consult.

338.13 Malabsorption in Inflammatory Bowel Disease

Ernest G. Seidman and David Branski

Crohn disease and ulcerative colitis represent the 2 forms of chronic, immune-mediated IBD that commonly affect pediatric patients (see Chapter 336). Because the small bowel is involved in the majority of pediatric Crohn disease patients, malabsorption of nutrients is far more of a problem than in ulcerative colitis. At the time of diagnosis, significant weight loss is observed in up to 85% of pediatric patients with Crohn disease and in approximately 65% with ulcerative colitis, due to inadequate intake of energy and micronutrients as well as diarrhea and malabsorption. Consequently, growth failure as a consequence of chronic undernutrition is far more common in Crohn disease than in ulcerative colitis, affecting up to 40% of cases.

In addition to malabsorption, energy intake is lower in patients with Crohn disease compared to healthy controls, in part due to lesser appetite. Excessive levels of proinflammatory cytokines are implicated in causing the anorexia as well as in mediating impaired growth. The symptoms, including abdominal pain, nausea, vomiting, and diarrhea, can cause affected children to have a lower desire to eat, which can lead to reduced food intake. This can, in turn, negatively affect nutritional status during a child's critical period of growth and development. Patients with IBD are also at risk of developing nutritional deficiencies because of restrictive diets imposed by caregivers or by the patients themselves.

In children with active disease, inadequate intakes of energy and of a number of micronutrients have been observed. Reduced energy intake during active disease can contribute to poor weight gain and impaired growth. Patients with IBD, particularly Crohn disease, often have multiple nutritional deficiencies and may be in negative nitrogen balance because of decreased intake and malabsorption of macro- and micronutrients. Quantifying nutrient intake, determining micronutrient deficiencies, and ascertaining requirements for nutritional supplementation are essential components of successful management in pediatric IBD.

Optimizing nutritional status and growth are key priorities in the management of IBD in children and adolescents. Energy intake should meet the added costs of catch-up growth and are usually in the range of 40-70 kcal/kg ideal body weight per day. Protein requirements are higher in Crohn disease (1-1.5 g/kg/day). Bone mineral density deficit is common, even in pediatric patients who have not been exposed to systemic corticosteroid therapy. Osteoporosis or osteopenia is best assessed by bone densitometry, and levels of vitamin 25-hydroxyvitamin D should be monitored. Table 338-10 shows other micronutrient deficiencies that result from inadequate intake, malabsorption, and gut losses.

Bile acid malabsorption is common in ileal Crohn disease, especially after small bowel resection. This leads to diarrhea and also places patients at increased risk for urolithiasis and cholelithiasis. The prevalence of recurrent calcium-oxalate urolithiasis is up to 5-fold higher in Crohn disease. Increased urinary oxalate and decreased citrate excretion, resulting from bowel resection with mainly preserved colon, were identified as crucial risk factors for stone formation. The hyperoxaluria predominantly results from increased colonic permeability to oxalate due to disturbed bile acid metabolism.

Enteral nutrition support is favored over parenteral for all but Crohn disease patients with extreme short gut. To induce remission, exclusive nutritional therapy given orally was reported to be as effective as when continuously administered by enteral feeding tube. However, weight gain was significantly greater for the latter group. Patients requiring hospitalization for a severe relapse should receive nutrition support if they are already malnourished or their intake is likely to be severely curtailed for ≥1 wk. Preoperative nutrition support is essential to the prevention of morbidity and mortality. However, clinicians must be aware of the risk of the refeeding syndrome in patients with severe malnutrition. In ulcerative colitis, nutrition support is adjunctive therapy; there is no evidence that bowel rest or total parenteral nutrition parenteral nutrition influences the outcome of severe ulcerative colitis.

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Chapter 339

Intestinal Transplantation in Children with Intestinal Failure

Jorge D. Reyes and André A.S. Dick

The introduction of tacrolimus and the development of the abdominal multiorgan procurement techniques allowed the tailoring of various types of intestine grafts that can contain other intraabdominal organs, such as the liver, pancreas, and stomach; this has been critical to the application of this type of organ transplant. The understanding that the liver protects the intestine against rejection demonstrates the interaction between recipient and donor immunocytes (host-versus-graft and graft-versus-host) which under the cover of immunosuppression allows varying degrees of graft acceptance and eventual minimization of drug therapy. Over the past several years the number of patients placed on the list for and those undergoing intestinal transplantation has decreased, which may be a result of (1) improvements in the care of patients with intestinal failure under a multidisciplinary intestinal care team management, (2) the introduction of new lipid management strategies for the treatment of cholestatic liver disease, and (3) corrective surgery enhancing absorptive surface and motility.

INDICATIONS FOR INTESTINAL TRANSPLANT

Intestinal failure describes a patient who has lost the ability to maintain nutritional support and adequate fluid requirements, needed to sustain growth, with their own intestine and is permanently dependent on total parenteral nutrition (TPN). The majority of these patients have short bowels as a result of a congenital deficiency or acquired condition (see Chapter 338.7). In others, the cause of intestinal failure is a functional disorder of motility or absorption (Table 339-1). Rarely do patients receive intestinal transplants for benign neoplasms. The complications of intestinal failure include loss of venous access, life-threatening infections, and TPN-induced cholestatic liver disease.

Table 339-1 Causes of Intestinal Failure in Children Requiring Transplantation

SHORT BOWEL
- Congenital disorders
- Volvulus
- Gastroschisis
- Necrotizing enterocolitis
- Intestinal atresia
- Trauma

INTESTINAL DYSMOTILITY
- Intestinal pseudoobstruction
- Intestinal aganglionosis (Hirschsprung disease)

ENTEROCYTE DYSFUNCTION
- Microvillus inclusion disease
- Tufting enteropathy
- Autoimmune disorders
- Crohn disease

TUMORS
- Familial polyposis
- Inflammatory pseudotumor

Paucity of Venous Access

Administration of TPN requires the insertion of a centrally placed venous catheter, there being only 6 readily accessible sites (bilateral internal jugulars, subclavians, iliac veins). The loss of venous access generally occurs in the setting of recurrent catheter sepsis and thrombosis; clinical convention suggests that loss of 50% of these venous access sites places the patient at risk of not being able to be treated with TPN.

Life-Threatening Infections

Life-threatening infections are usually catheter-related; the absence of significant lengths of intestine may be associated with abnormal motility of the residual bowel (producing both delayed or rapid emptying), with varying degrees of bacterial overgrowth and possible bacterial or fungal translocation as a consequence of loss of intestinal barrier function and/or loss of gut immunity. This situation can produce cholestatic liver disease, multisystem organ failure, and metastatic infectious foci in lungs, kidneys, liver, and the brain.

Liver Disease

The development of cholestatic liver disease is the most serious complication of intestinal failure and may be a consequence of the toxic drug effects of TPN on hepatocytes, a disruption of bile flow and bile acid metabolism, and the frequent occurrence of bacterial translocation and sepsis with endotoxin release into the portal circulation. This complication varies in frequency depending on the patient's age and the etiology of the intestinal failure; it is most common in neonates with extreme short gut. The effects on the liver include fatty transformation, steatohepatitis and necrosis, fibrosis, and then cholestasis. The development of clinical jaundice (total bilirubin >3 mg/dL) and thrombocytopenia are significant risk factors for poor outcome, because these changes portend the development of portal hypertensive gastroenteropathy, hypersplenism, coagulopathy, and uncontrollable bleeding.

TRANSPLANTATION OPERATION

Donor Selection

Intestinal grafts are usually procured from hemodynamically stable, ABO-identical brain-dead donors who have minimal clinical or laboratory evidence suggesting intraabdominal ischemia; size matching varies according to age of the recipients; present surgical techniques allow for significant reductions of the graft in order to achieve abdominal closure. Human leukocyte antigen has been random, and cross-matching has not been a determinant of graft acceptance. Exclusion criteria include a history of malignancy and intraabdominal evidence of infection; systemic viral or bacterial infections are not excluded. Donor preparation has been limited to the administration of systemic and enteral antibiotics. Prophylaxis for graft-versus-host disease with graft pretreatment using irradiation or a monoclonal antilymphocyte antibody has varied over time. Grafts have been preserved with the University of Wisconsin solution, as is the case with other types of abdominal organs.

Types of Intestinal Grafts

Intestinal allografts are used in various forms, either alone (as an **isolated intestine graft**) or as a composite graft, which can include the liver, duodenum, and pancreas (**liver–intestine graft**); when this composite graft includes the stomach, and the recipient operation requires the removal of all of the patient's gastrointestinal tract (as with intestinal pseudoobstruction) and liver, then this replacement graft is known as a **multivisceral graft**.

The procurement of these various types of grafts focuses on the preservation of the arterial vessels of celiac and/or superior mesenteric arteries, as well as appropriate venous outflow, which would include the superior mesenteric vein or the hepatic veins in the composite grafts. The larger composite grafts inherently retain the celiac and superior mesenteric arteries; this includes multivisceral grafts, liver plus small bowel grafts, and "modified multivisceral grafts" in which the liver is excluded but the entire gastrointestinal tract is replaced,

including the stomach. The isolated intestine graft retains the superior mesenteric artery and vein; this graft can be accomplished with preservation of the vessels going to the pancreas, when that organ has been allocated to another recipient. The graft that is to be used in a particular recipient is dissected out in situ and then removed after cardiac arrest of the donor, with core cooling of the organs, using an infusion of preservation solution (Fig. 339-1).

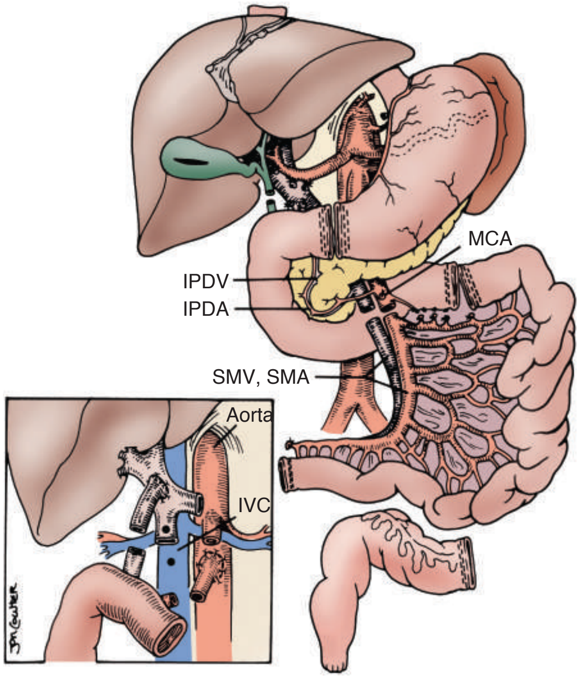

Figure 339-1 **The various abdominal organs can be dissected in situ, providing isolated or composite grafts to fit the individual patient's needs.** Separation of intestine and pancreas is feasible, with preservation of the inferior pancreaticoduodenal artery *(IPDA)* and vein *(IPDV)*. The use of vascular grafts from the donor allow connections to the superior mesenteric pedicle (artery *[SMA]* and vein *[SMV]*) to aorta and inferior vena cava *(IVC)* or portal vein *(inset)*. *(Reproduced with permission from Abu-Elmagd K, Fung J, Bueno J, et al: Logistics and technique for procurement of intestinal, pancreatic and hepatic grafts from the same donor,* Ann Surg *232:680–697, 2000.)*

Various modifications in these grafts have included the preservation of visceral ganglia at the base of the arteries, the inclusion of donor duodenum and pancreas for the liver and intestine graft, the inclusion of colon, the reduction of the liver graft (into left or right side) and variable reduction of the intestine graft, and the development of living donor intestine grafts.

The Recipient Operation

Because many children have had multiple previous abdominal operations, intestinal transplantation can be a formidable technical challenge; most children require replacement of the liver because of TPN-induced disease and often present with advanced liver failure. Transplantation of an isolated intestinal allograft involves exposure of the lower abdomen, infrarenal aorta, and inferior vena cava. Placement of vascular homografts using donor iliac artery and vein to these vessels allows arterialization and venous drainage of the intestinal graft. In patients who have retained their intestine and then undergo an enterectomy at the time of transplantation, use of the native superior mesenteric vessels is feasible.

Transplantation of a larger composite graft requires the removal and replacement of the native liver in the liver with intestine transplant, and complete abdominal exenteration in the multivisceral transplant. In a similar fashion, the infrarenal aorta is exposed for placement of an arterial conduit graft (donor thoracic aorta) for arterialization of the graft. The venous drainage is achieved to the retained hepatic veins, which are fashioned to a single conduit for anastomosis to the allograft liver.

The intestinal anastomosis to native proximal and distal bowel are performed, leaving an enterostomy of distal allograft ileum; this will be used for routine posttransplantation surveillance endoscopy and biopsy. This ostomy is closed 3-6 mo after transplantation (Fig. 339-2).

POSTOPERATIVE MANAGEMENT

Immunosuppression

Successful immunosuppression for intestinal transplantation is initiated with tacrolimus and corticosteroids. This required high levels of tacrolimus (in the nephrotoxic range), and although initial success rates were high they were followed by rejection rates of >80%, infection, and late drug toxicities, resulting in a gradual loss of grafts and patients. The next generation of protocols incorporated the addition of other agents, such as azathioprine, cyclophosphamide, induction with an interleukin-2 antibody antagonist, mycophenolate mofetil, and rapamycin. This modification resulted in a decreased incidence in the severity of initial rejection; the ability to decrease immunosuppression

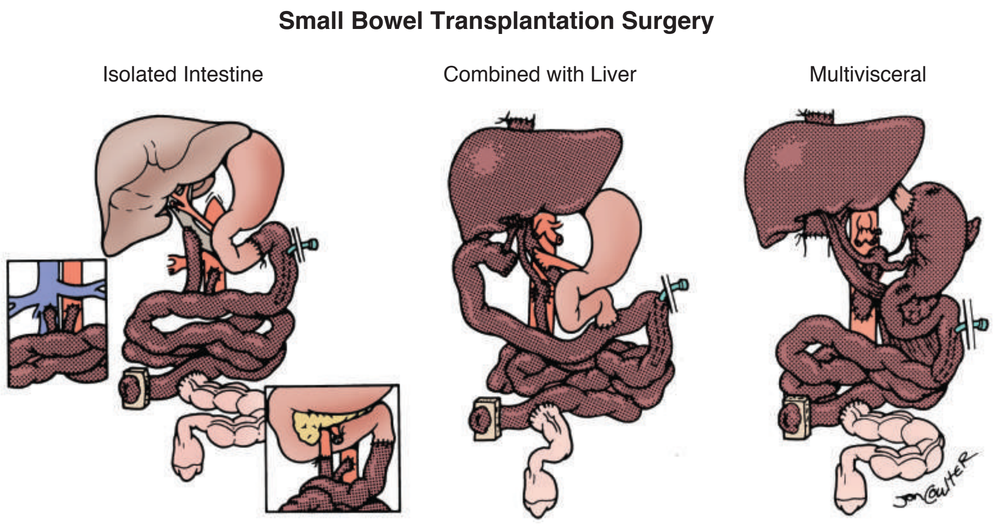

Figure 339-2 The 3 basic intestinal transplant procedures (the graft is *shaded*). With the isolated intestine, the venous outflow may be to the recipient portal vein *(main figure)*, inferior vena cava *(inset left)*, or superior mesenteric vein *(inset right)*. With the composite grafts, which include the liver, the arterialization is from the aorta with venous drainage out from the liver graft to the recipient inferior vena cava.

later did not allow for stabilization of long-term survival. The introduction of *recipient* pretreatment using antilymphocyte antibodies and the elimination of recipient therapy with steroids have resulted in improved transplant survival as a result of a significant decrease in the incidence of rejection and infection, permitting the gradual decrease of immunosuppressive drug therapy within 3 mo, and a decline in drug toxicity events. The most common initial maintenance regimen used is tacrolimus and prednisone dual therapy. By 1 yr the majority of patients are on tacrolimus monotherapy.

Allograft Assessment

There are no simple laboratory tools that allow assessment of the intestinal allograft. The gold standard for diagnosis of intestinal allograft rejection has been serial endoscopic surveillance and biopsies through the allograft ileostomy. Clinical signs and symptoms of rejection or infection of the allograft can overlap and mimic each other, producing either rapid diarrhea or complete ileus with pseudoobstruction syndromes, or gastrointestinal bleeding. Any changes in clinical status should warrant thorough evaluation for rejection with endoscopic biopsies and an evaluation for opportunistic infection, malabsorption, and other enteral infections.

The diagnosis of acute rejection is based on seeing destruction of crypt epithelial cells from apoptosis, in association with a mixed lymphocytic infiltrate. These histologic findings may or may not correlate with endoscopic evidence of injury, which varies from diffuse erythema and friability to ulcers and, in cases of severe rejection, exfoliation of the intestinal mucosa. Chronic rejection of the allograft can be diagnosed only through full thickness sampling of the intestine, which shows the typical vasculopathy that can result in progressive ischemia of the allograft.

Rejection and Graft-Versus-Host Disease

Acute rejection rates for the intestinal allograft are significantly higher than with any other organ, in the range of 80-90%, and severe rejection requiring the use of antilymphocyte antibody preparations may be as high as 30%. Triple-drug regimens and the use of interleukin-2 antibody inhibitors have resulted in significant decreases in rejection rates; nonetheless, the amount of immunosuppression was incompatible with improvements in long-term patient and graft survival. Rejection rates of 40% are achievable with the use of antilymphocyte globulin. These protocols induce varying degrees of "proper tolerance," which can eventually allow for minimization of immunosuppression, thus reducing the risk of drug toxicity and infection. Vascular rejection has been an uncommon occurrence, and chronic rejection has been seen in approximately 15% of cases. Graft-versus-host disease is infrequent but potentially life-threatening. The mortality rate exceeds 80% and most recipients die from infectious complications from bone marrow failure. The incidence seen in intestinal transplantation is 5–6%. Although no standard treatment is available, early diagnosis, prevention of infection, and initiation of treatment as soon as possible may improve outcomes.

Infections

Infectious complications are the most significant cause of morbidity and mortality after intestinal transplantation. The most common infections (bacterial, fungal, polymicrobial) occur as a result of the continuing need for venous catheter placement for as long as 1 yr posttransplantation. Infections as a consequence of immunosuppressive drug management are from cytomegalovirus (CMV) infection (22% incidence), Epstein-Barr virus (EBV)–induced infections (21% incidence), and adenovirus enteritis (40% incidence). Despite improvements in monitoring and preventative measures, CMV remains the most common viral infection post–intestinal transplantation. CMV may be acquired from blood transfusions, reactivation of endogenous viruses, or the donated allograft. The highest risk recipients for CMV infection are those who are immunologically naïve and receive an allograft from a donor who is seropositive. The 2 mainstay CMV prevention strategies commonly employed are universal prophylaxis and preemptive therapy. Current consensus guidelines recommend prophylaxis treatment for high-risk patients (donor+/recipient–). The preferred drugs for CMV prophylaxis are ganciclovir and oral valganciclovir.

Patients at the highest risk for EBV infection are similarly those who are seronegative at the time of transplantation and those requiring a high-burden immunosuppressive therapy to maintain their graft. EBV disease varies from asymptomatic viremia to posttransplant lymphoproliferative disorder (PTLD). The incidence of EBV-related PTLD is highest in patients receiving intestinal allografts compared to liver, heart, or kidney. Children have a higher incidence of PTLD compared to adults, and are most likely to have EBV+PTLD. Early diagnosis and prevention of PTLD is essential and the mainstay of therapy is to reduce immunosuppression, although some patients have required chemotherapy. The use of anti–B-cell monoclonal antibodies, such as the anti-CD20 antibody rituximab, in PTLD has been successful as noted in anecdotal reports. Successful management of these viral infections is achieved through early detection and preemptive therapy, for both CMV and EBV, before the development of a serious life-threatening infection. This approach has improved outcomes for CMV, eliminating the mortality in the pediatric patient population (see Chapters 178, 254, and 255).

Outcomes

Intestinal transplantation is the standard of care for children with intestinal failure who have significant complications of TPN and can no longer tolerate such therapy. Data from the Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) Annual Report 2011, and center-specific data reports have documented significant improvements with short- and long-term survivals for transplantations occurring principally in the last 10 yr; intestinal transplantation (liver-intestine and isolated intestinal transplants) graft failure rates for deceased donor transplants in 2010-2011 were 26% at 1 yr, 46% at 3 yr for transplants in 2008-2009, and 48% at 5 yr for transplants in 2006-2007 (Fig. 339-3). It is hoped that with the minimization strategies currently used the long-term survival will plateau as occurs with other organ transplants; rehabilitation and quality-of-life studies have shown that more than 80% of survivors reach total independence from TPN and have meaningful

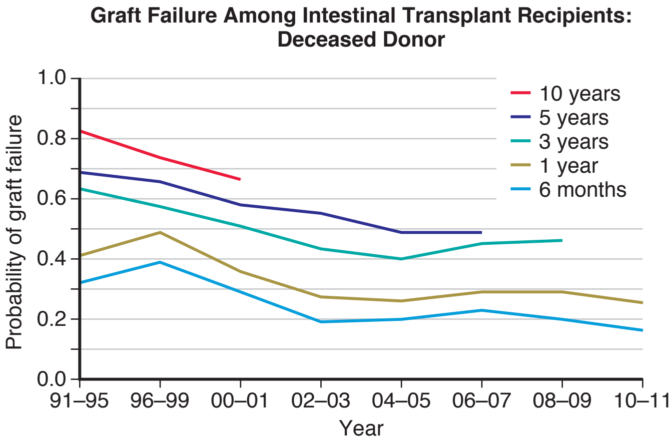

Figure 339-3 OPTN/SRTR Annual Report demonstrating that intestine graft survival has improved significantly with the application of better immunosuppressive strategies, infection surveillance and management, and perioperative care. Cox proportional hazards models reporting probability, adjusting for age, sex, and race. *(From Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR): OPTN/SRTR 2011 Annual Data Report. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2012. Available at* http://srtr.transplant.hrsa.gov/annual_reports/2011/default.aspx*)*

life activities. Consequently, there has been a shift in efforts to improve long-term outcomes and quality of life.

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Chapter 340

Acute Gastroenteritis in Children

Zulfiqar Ahmed Bhutta

The term *gastroenteritis* denotes infections of the gastrointestinal tract caused by bacterial, viral, or parasitic pathogens (Tables 340-1 to 340-3). Many of these infections are foodborne illnesses. The most common manifestations are diarrhea and vomiting, which can also be associated with systemic features such as abdominal pain and fever. The term **gastroenteritis** captures the bulk of infectious cases of diarrhea. The term **diarrheal disorders** is more commonly used to denote infectious diarrhea in public health settings, although several noninfectious causes of gastrointestinal illness with vomiting and/or diarrhea are well recognized (Table 340-4).

EPIDEMIOLOGY OF CHILDHOOD DIARRHEA

Diarrheal disorders in childhood account for a large proportion (9%) of childhood deaths, with an estimated 0.71 million deaths per year globally, making it the second most common cause of child deaths worldwide. Almost 1.731 billion episodes of diarrhea occurred in 2010 in children younger than 5 yr of age in developing countries, with more than 80% of the episodes occurring in Africa and South Asia (50.5% and 32.5%, respectively) and 36 million of the total episodes progress to severe episodes. Global mortality may be declining rapidly, but the overall incidence of diarrhea has only declined from 3.4 to approximately 2.9 episodes per child-year in the past 2 decades, and it is estimated to account for 23 million childhood disability-adjusted life years.

The decline in diarrheal mortality, despite the lack of significant changes in incidence, is the result of preventive rotavirus vaccination and improved case management of diarrhea, as well as improved nutrition of infants and children. These interventions have included widespread home- and hospital-based oral rehydration therapy and improved nutritional management of children with diarrhea.

In addition to the risk of mortality, persistently high rates of diarrhea, especially prolonged and persistent diarrhea among young children may be associated with long-term adverse outcomes. Diarrheal illnesses, especially early and repeated episodes among young children can be associated with malnutrition, micronutrient deficiencies, and significant deficits in psychomotor and cognitive development.

ETIOLOGY OF DIARRHEA

Gastroenteritis is the result of infection acquired through the fecal–oral route or by ingestion of contaminated food or water. Gastroenteritis is associated with poverty, poor environmental hygiene, and development indices. Enteropathogens that are infectious in a small inoculum (*Shigella,* enterohemorrhagic *Escherichia coli, Campylobacter jejuni,* noroviruses, rotavirus, *Giardia lamblia, Cryptosporidium parvum, Entamoeba histolytica*) can be transmitted by person-to-person contact, whereas others, such as cholera, are generally a consequence of contamination of food or water supply (see Tables 340-1 to 340-3).

In the United States, rotavirus and the noroviruses (small round viruses such as Norwalk-like virus and caliciviruses) are the most common viral agents, followed by sapoviruses, enteric adenoviruses, and astroviruses (see Table 340-2). Foodborne outbreaks in the United States are mostly caused by norovirus, accounting for 58% of all episodes, and by bacterial causes, which are most commonly *Salmonella, Clostridium perfringens, Campylobacter,* and *Staphylococcus aureus,* followed much less often by *E. coli, Clostridium botulinum, Shigella, Cryptosporidium, Yersinia, Listeria, Vibrio,* and *Cyclospora* species, in that order. Food sources include poultry, leafy vegetables, beef, fruits and nuts, vine-stalk vegetables, and many other foods.

Direct person-to-person contact outbreaks of gastroenteritis are usually caused by norovirus and *Shigella* species. Unknown agents are seen in 30-40%; other pathogens include *Salmonella*, rotavirus, *Giardia*, *Cryptosporidium*, *Clostridium difficile,* and *C. jejuni.*

The exact etiologic fractions of diarrhea among children in developing countries are a subject of much research, and our knowledge of the various pathogens that cause moderate to severe childhood diarrhea has grown considerably (Fig. 340-1; Table 340-5). There are indications that rates of hospitalization and deaths caused by *Shigella* infections, especially *Shigella dysenteriae* type 1, the most severe form of shigellosis, may be declining; however, it accounts for nearly 28,000 deaths annually. Enteropathogenic *E. coli* is responsible for 79,000 and enterotoxigenic *E. coli* (ETEC) may be responsible for 42,000 deaths annually among children younger than 5 yr. Rotavirus infections (the most common identifiable viral cause of gastroenteritis in all children) account for 197,000 deaths annually or 28% of all deaths caused by diarrhea among children younger than 5 yr of age.

PATHOGENESIS OF INFECTIOUS DIARRHEA

Pathogenesis and severity of bacterial disease depend on whether organisms have preformed toxins *(S. aureus, Bacillus cereus),* produce secretory (cholera, *E. coli*, *Salmonella*, *Shigella*) or cytotoxic (*Shigella*, *S. aureus*, *Vibrio parahaemolyticus*, *C. difficile*, *E. coli*, *C. jejuni*) toxins, or are invasive, and on whether they replicate in food. Enteropathogens can lead to either an inflammatory or noninflammatory response in the intestinal mucosa (Table 340-6).

Enteropathogens elicit **noninflammatory diarrhea** through **enterotoxin** production by some bacteria, destruction of villus (surface) cells by viruses, adherence by parasites, and adherence and/or translocation by bacteria. **Inflammatory diarrhea** is usually caused by bacteria that directly invade the intestine or produce cytotoxins with consequent fluid, protein, and cells (erythrocytes, leukocytes) that enter the intestinal lumen. Some enteropathogens possess more than 1 virulence property. Some viruses, such as rotavirus, target the microvillus tips of the enterocytes and can enter the cells by direct invasion or calcium-dependent endocytosis. This can result in villus shortening and loss of enterocyte absorptive surface through cell shortening and loss of microvilli (Fig. 340-2).

Most bacterial pathogens elaborate enterotoxins; the rotavirus protein NSP4 acts as a viral enterotoxin. Bacterial enterotoxins can selectively activate enterocyte intracellular signal transduction and can also affect cytoskeletal rearrangements with subsequent alterations in the water and electrolyte fluxes across enterocytes. In toxigenic diarrhea, enterotoxin produced by *Vibrio cholerae*, increased mucosal levels of cyclic adenosine monophosphate, inhibit electroneutral NaCl absorption but have no effect on glucose-stimulated Na^+ absorption. In inflammatory diarrhea (e.g., *Shigella* spp. or *Salmonella* spp.) there is extensive histologic damage, resulting in altered cell morphology and reduced glucose-stimulated Na^+ and electroneutral NaCl absorption. The role of 1 or more cytokines in this inflammatory response is critical. In secretory cells from crypts, Cl secretion is minimal in normal subjects and is activated by cyclic adenosine monophosphate in toxigenic and inflammatory diarrhea (Fig. 340-3).

ETEC colonizes and adheres to enterocytes of the small bowel via its surface fimbriae (pili) and induces hypersecretion of fluids and electrolytes into the small intestine through 1 of 2 toxins: the heat-labile enterotoxin or the heat-stable enterotoxin. Heat-labile enterotoxin is structurally similar to the *V. cholerae* toxin, and activates adenylate cyclase, resulting in an increase in intracellular cyclic guanosine monophosphate (Fig. 340-4). In contrast, *Shigella* spp. cause

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Table 340-1 Foodborne Bacterial Illnesses

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Bacillus anthracis	2 days to weeks	Nausea, vomiting, malaise, bloody diarrhea, acute abdominal pain	Weeks	Insufficiently cooked contaminated meat	Blood	Penicillin is first choice for naturally acquired GI anthrax but use beta lactams with high index of suspicion for resistance Ciprofloxacin is second option
Bacillus cereus (preformed enterotoxin)	1-6 hr	Sudden onset of severe nausea and vomiting Diarrhea may be present	24 hr	Improperly refrigerated cooked or fried rice, meats	Normally a clinical diagnosis Clinical laboratories do not routinely identify this organism If indicated, send stool and food specimens to reference laboratory for culture and toxin identification	Supportive care
Bacillus cereus (diarrheal toxin)	10-16 hr	Abdominal cramps, watery diarrhea, nausea	24-48 hr	Meats, stews, gravies, vanilla sauce	Testing not necessary, self-limiting Consider testing food and stool for toxin in outbreaks	Supportive care
Brucella abortus, Brucella melitensis, and *Brucella suis*	7-21 days	Fever, chills, sweating, weakness, headache, muscle and joint pain, diarrhea, bloody stools during acute phase	Weeks	Raw milk, goat cheese made from unpasteurized milk, contaminated meats	Blood culture and positive serology	Acute: Rifampin and doxycycline daily for ≥6 wk Infections with complications require combination therapy with rifampin, tetracycline, and an aminoglycoside
Campylobacter jejuni	2-5 days	Diarrhea, cramps, fever, and vomiting; diarrhea may be bloody	2-10 days	Raw and undercooked poultry, unpasteurized milk, contaminated water	Routine stool culture; *Campylobacter* requires special media and incubation at 42°C (107.6°F) to grow	Supportive care For severe cases, antibiotics, such as azithromycin and quinolones, may be indicated early in the diarrheal disease Guillain-Barré syndrome can be a sequela
Clostridium botulinum: children and adults (preformed toxin)	12-72 hr	Vomiting, diarrhea, blurred vision, diplopia, dysphagia, descending muscle weakness	Variable (days to months) Can be complicated by respiratory failure and death	Home-canned foods with a low acid content, improperly canned commercial foods, home-canned or fermented fish, herb-infused oils, baked potatoes in aluminium foil, cheese sauce, bottled garlic, foods held warm for extended periods (e.g., in a warm oven)	Stool, serum, and food can be tested for toxin Stool and food can also be cultured for the organism These tests can be performed at some state health department laboratories and CDC	Supportive care Botulism antitoxin is helpful if given early in the course of the illness. Antitoxin for children and adults is available through CDC Contact the state health department. The 24-hr number for CDC is (800) 232-4636 (800-CDC-INFO)
Clostridium botulinum: infants	3-30 days	In infants <12 mo, lethargy, weakness, poor feeding, constipation, hypotonia, poor head control, poor gag and sucking reflex	Variable	Honey, home-canned vegetables and fruits, corn syrup	Stool, serum, and food can be tested for toxin Stool and food can also be cultured for the organism These tests can be performed at some state health department laboratories and CDC	Supportive care Botulinum antitoxin for infants can be obtained from the Infant Botulism Prevention Program, Health and Human Services, California (510-540-2646)

Continued

Table 340-1 Foodborne Bacterial Illnesses—cont'd

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Clostridium perfringens toxin	8-16 hr	Watery diarrhea, nausea, abdominal cramps; fever is rare	24-48 hr	Meats, poultry, gravy, dried or precooked foods, time- and/or temperature-abused food	Stools can be tested for enterotoxin and cultured for organism Because *Clostridium perfringens* can normally be found in stool, quantitative cultures must be done: A count of at least 106 *C. perfringens* spores per gram of stool within 48 hr of when illness began is required to diagnose infection	Supportive care Antibiotics not indicated
Enterohemorrhagic *Escherichia coli* (EHEC) including *E. coli* O157:H7 and other *Shiga* toxin–producing *E. coli* (STEC)	1-8 days	Severe diarrhea that is often bloody, abdominal pain and vomiting Usually, little or no fever is present More common in children <4 yr old	5-10 days	Undercooked beef especially hamburger, unpasteurized milk and juice, raw fruits and vegetables (e.g., sprouts), salami (rarely), contaminated water	Stool culture; *E. coli* O157:H7 requires special media to grow. If *E. coli* O157:H7 is suspected, specific testing must be requested. Shiga toxin testing may be done using commercial kits; positive isolates should be forwarded to public health laboratories for confirmation and serotyping	Supportive care, monitor renal function, hemoglobin, and platelets closely. *E. coli* O157:H7 infection is also associated with hemolytic uremic syndrome (HUS), which can cause lifelong complications Studies indicate that antibiotics might promote the development of HUS. Antidiarrheal agents like Imodium may also increase the risk of developing HUS
Enterotoxigenic *E. coli* (ETEC)	1-3 days	Watery diarrhea, abdominal cramps, some vomiting	3 to >7 days	Water or food contaminated with human feces	Stool culture ETEC requires special laboratory techniques for identification that may not be widely available; consequently, physicians may make the diagnosis based on a patient's history and symptoms If ETEC is suspected, must alert microbiology laboratory that is testing the specimen	Supportive care Antibiotics are rarely needed except in severe cases Recommended antibiotics include quinolones although these are rarely required unless there is severe infection and should be administered early. Antimotility medications should be avoided by persons with high fevers or bloody diarrhea, and should be discontinued if diarrhea symptoms persist more than 48 hr. Bismuth subsalicylate compounds (e.g., Pepto-Bismol) can help reduce the number of bowel movements

Listeria monocytogenes	9-48 hr for GI symptoms, 2-6 wk for invasive disease	Fever, muscle aches, and nausea or diarrhea Pregnant women might have mild flu-like illness, and infection can lead to premature delivery or stillbirth Elderly or immunocompromised patients can have bacteremia or meningitis	Variable	Fresh soft cheeses, unpasteurized milk, inadequately pasteurized milk, ready-to-eat deli meats, hot dogs	Blood or cerebrospinal fluid cultures. Selective enrichment media improve rates of isolation from contaminated specimens Asymptomatic fecal carriage occurs; therefore, stool culture usually not helpful Antibody to listeriolysin *O* may be helpful to identify outbreak retrospectively	Supportive care and antibiotics; intravenous ampicillin, penicillin G, or TMP-SMX is recommended for invasive disease
	At birth and infancy	Infants infected from mother at risk for sepsis or meningitis				Higher dosages of ampicillin recommended for neonatal sepsis or meningitis
Salmonella spp.	1-3 days	Diarrhea, fever, abdominal cramps, vomiting *S. typhi* and *S. paratyphi* produce typhoid with insidious onset characterized by fever, headache, constipation, malaise, chills, and myalgia; diarrhea is uncommon, and vomiting is not usually severe	4-7 days	Contaminated eggs, poultry, unpasteurized milk or juice, cheese, contaminated raw fruits and vegetables (alfalfa sprouts, melons) *S. typhi* epidemics are often related to fecal contamination of water supplies or street-vended foods	Routine stool cultures	Supportive care Other than for *S. typhi* and *S. paratyphi*, antibiotics are not indicated unless there is extraintestinal spread, or the risk of extraintestinal spread of the infection Consider ampicillin, third-generation cephalosporins, or quinolones if indicated A vaccine exists for *S. typhi* but is not completely effective. Washing hands and avoiding suspicious foods is equally useful at preventing disease as vaccination
Shigella spp.	24-48 hr	Abdominal cramps, fever, diarrhea Stools might contain blood and mucus	4-7 days	Food or water contaminated with human fecal material Usually person-to-person spread, fecal–oral transmission Ready-to-eat foods touched by infected food workers, e.g., raw vegetables, salads, sandwiches	Routine stool cultures	Supportive care. Antibiotics are recommended for severe disease, bloody diarrhea, or compromised immune systems. Resistance to traditional first-line drugs like ampicillin and TMP-SMX is common. When susceptibility is unknown or when an ampicillin- or TMP-SMX–resistant strain is isolated, choices for therapy include fluoroquinolones, ceftriaxone, and azithromycin. Antidiarrheal agents such as Imodium or Lomotil can worsen the illness and should be avoided
Staphylococcus aureus (preformed enterotoxin)	1-6 hr	Sudden onset of severe nausea and vomiting Abdominal cramps Diarrhea and fever may be present	24-48 hr	Unrefrigerated or improperly refrigerated meats, potato and egg salads, cream pastries	Normally a clinical diagnosis Stool, vomitus, and food can be tested for toxin and cultured if indicated	Supportive care

Continued

Table 340-1 Foodborne Bacterial Illnesses—cont'd

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Vibrio cholerae (toxin)	24-72 hr	Profuse watery diarrhea and vomiting, which can lead to severe dehydration and death within hours	3-7 days Causes life-threatening dehydration	Contaminated water, fish, shellfish, street-vended food typically from Latin America or Asia	Stool culture *V. cholerae* requires special media to grow: Cary-Blair media is ideal for transport, and the selective thiosulfate–citrate–bile salts agar (TCBS) is ideal for isolation and identification. ; if *V. cholerae* is suspected, must request specific testing. Commercially available rapid test kits (e.g., Crystal VC dipstick) are useful in epidemic settings but do not test susceptibility or subtype so should not be used for routine diagnosis	Supportive care with aggressive oral and intravenous rehydration Doxycycline is recommended as first-line treatment for adults, whereas azithromycin is recommended as first-line treatment for children and pregnant women. Ciprofloxacin and doxycycline recommended as second-line drugs for children
Vibrio parahaemolyticus	2-48 hr	Watery diarrhea, abdominal cramps, nausea, vomiting	2-5 days	Undercooked or raw seafood, such as fish, shellfish	Stool cultures. *V. parahaemolyticus* requires special media (TCBS agar) to grow; must request specific testing	Supportive care There is no evidence that antibiotic treatment decreases the severity or the length of the illness. Antibiotics are recommended in severe or prolonged cases: tetracycline or ciprofloxacin can be used
Vibrio vulnificus	1-7 days	Vomiting, diarrhea, abdominal pain, bacteremia, and wound infections More common and potentially fatal in the immunocompromised or in patients with chronic liver disease (presenting with septic shock and hemorrhagic bullous skin lesions)	2-8 days	Undercooked or raw shellfish, especially oysters, other contaminated seafood, and open wounds exposed to seawater	Stool, wound, or blood cultures *V. vulnificus* requires special media (TCBS agar) to grow; if *V. vulnificus* is suspected, must request specific testing	Supportive care and antibiotics: doxycycline, and a third-generation cephalosporin such as ceftazidime is recommended
Yersinia enterocolitica and *Yersinia pseudotuberculosis*	24-48 hr	Appendicitis-like symptoms (diarrhea and vomiting, fever, abdominal pain) occur primarily in older children and young adults Might have a scarlatiniform rash or erythema nodosum with *Y. pseudotuberculosis*	1-3 wk, usually self-limiting	Undercooked pork, unpasteurized milk, tofu, contaminated water Infection has occurred in infants whose caregivers handled chitterlings	Stool, vomitus, or blood culture, throat, lymph nodes, joint fluid, urine, and bile *Yersinia* requires special media to grow; must request specific testing Serology is available in research and reference laboratories	Supportive care If septicemia or other invasive disease occurs, antibiotic therapy with aminoglycosides, doxycycline, TMP-SMX, or fluoroquinolones may be useful

CDC, Centers for Disease Control and Prevention; GI, gastrointestinal; TMP-SMX, trimethoprim-sulfamethoxazole.
From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, MMWR *53(RR-4):1-33, 2004.*

Table 340-2 Foodborne Viral Illnesses

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Hepatitis A	28 days average (15-50 days)	Diarrhea, dark urine, jaundice, and flu-like symptoms, i.e., fever, headache, nausea, and abdominal pain	Variable, 2 wk-3 mo	Shellfish harvested from contaminated waters, raw produce, contaminated drinking water, uncooked foods, and cooked foods that are not reheated after contact with infected food handler	Increase in ALT, bilirubin Positive IgM and anti–hepatitis A antibodies	Supportive care Prevention with immunization (vaccine available for persons 1 year and older)
Caliciviruses (including noroviruses and sapoviruses)	12-48 hr	Nausea, vomiting, abdominal cramping, diarrhea, fever, myalgia, and some headache Diarrhea is more prevalent in adults and vomiting is more prevalent in children Prolonged asymptomatic excretion possible	12-60 hr	Shellfish, fecally contaminated foods, ready-to-eat foods touched by infected food workers (salads, sandwiches, ice, cookies, fruit)	Routine RT-PCR. RT-PCR assays are the preferred laboratory method for detecting norovirus. Conventional RT-PCR followed by sequence analysis of the RT-PCR products is used for norovirus genotyping. Rapid commercial assays, such as enzyme immunoassays (EIAs), have poor sensitivity and are not recommended for establishing diagnosis Clinical diagnosis, negative bacterial cultures Stool is negative for WBCs	Supportive care such as rehydration. Avoid giving antimotility agents to children younger than 3 yr old. However, these agents may be helpful in older children and adults, particularly when used along with rehydration treatment Good hygiene
Rotavirus (groups A-C)	1-3 days	Vomiting, watery diarrhea, low-grade fever Temporary lactose intolerance can occur Infants and children, elderly, and immunocompromised are especially vulnerable	4-8 days	Fecally contaminated foods Ready-to-eat foods touched by infected food workers (salads, fruits)	Diagnosis may be made by rapid antigen detection of rotavirus in stool specimens.	Supportive care Severe diarrhea can require fluid and electrolyte replacement
Other viral agents (astroviruses, adenoviruses, parvoviruses)	10-70 hr	Nausea, vomiting, diarrhea, malaise, abdominal pain, headache, fever	2-9 days	Fecally contaminated foods Ready-to-eat foods touched by infected food workers Some shellfish	Identification of the virus in early acute stool samples Serology Commercial ELISA kits are available for adenoviruses and astroviruses	Supportive care, usually mild, self-limiting Good hygiene

ALT, alanine aminotransferase; ELISA, enzyme-linked immunosorbent assay; IgM, immunoglobulin M; RT-PCR, reverse transcriptase polymerase chain reaction; WBCs, white blood cells.
From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses. MMWR *53(RR-4):1-33, 2004.*

Table 340-3 Foodborne Parasitic Illnesses

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Angiostrongylus cantonensis	1 wk-≥1 mo	Severe headaches, nausea, vomiting, neck stiffness, paresthesias, hyperesthesias, seizures, and other neurologic abnormalities	Several weeks to several months	Raw or undercooked intermediate hosts (e.g., snails or slugs), infected paratenic (transport) hosts (e.g., crabs, freshwater shrimp), fresh produce contaminated with intermediate or transport hosts	No readily available blood tests. History is major guide to diagnosis. Examination of CSF for elevated pressure, protein, leukocytes, and eosinophils; serologic testing using ELISA to detect antibodies to *Angiostrongylus cantonensis*	Supportive care. There is no specific treatment. Repeat lumbar punctures and use of corticosteroid therapy may be used for more severely ill patients
Cryptosporidium	2-10 days	Diarrhea (usually watery), stomach cramps, upset stomach, slight fever	May be remitting and relapsing over weeks to months	Any uncooked food or food contaminated by an ill food handler after cooking; drinking water	Request specific examination of the stool for *Cryptosporidium*. Most often, stool specimens are examined microscopically using different techniques (e.g., acid-fast staining, direct fluorescent antibody [DFA], and/or enzyme immunoassays for detection of *Cryptosporidium* sp. antigens) May need to examine water or food	Supportive care, self-limited If severe, nitazoxanide can be prescribed for all patients 1 yr of age or older
Cyclospora cayetanensis	1-14 days, usually at ≥1 wk	Diarrhea (usually watery), loss of appetite, substantial loss of weight, stomach cramps, nausea, vomiting, fatigue	May be remitting and relapsing over weeks to months	Various types of fresh produce (imported berries, lettuce)	Request specific examination of the stool for *Cyclospora* May need to examine water or food	TMP-SMX for 7 days
Entamoeba histolytica	2-3 days–1-4 wk	Diarrhea (often bloody), frequent bowel movements, lower abdominal pain	May be protracted (several weeks to several months)	Any uncooked food or food contaminated by an ill food handler after cooking; drinking water	Examination of fresh stool for cysts and parasites; may need at least 3 samples Serology for long-term infections	For asymptomatic infections, paromomycin and iodoquinol are the drugs of choice. For symptomatic intestinal disease or extraintestinal infections (e.g., hepatic abscess), the drugs of choice are metronidazole and tinidazole, immediately followed by treatment with paromomycin or iodoquinol

Giardia lamblia	1-2 wk	Diarrhea, stomach cramps, gas, weight loss	Days to weeks	Any uncooked food or food contaminated by an ill food handler after cooking; drinking water	Examination of stool for ova and parasites; may need at least 3 samples	Metronidazole, tinidazole, or nitazoxanide. Alternatives to these medications include paromomycin, quinacrine, and furazolidone
Toxoplasma gondii	5-23 days	Generally asymptomatic, 20% develop cervical lymphadenopathy and/or a flu-like illness In immunocompromised patients: CNS disease, myocarditis, or pneumonitis is often seen	Months	Accidental ingestion of contaminated substances (e.g., soil contaminated with cat feces on fruits and vegetables), raw or partially cooked meat (especially pork, lamb, and venison)	The diagnosis of toxoplasmosis is typically made by serologic testing. however, IgM antibodies can persist for 6-18 mo and thus do not necessarily indicate recent infection PCR of bodily fluids Diagnosis can also be made by isolation of parasites from blood or other body fluids; observation of parasites in patient specimens via microscopy or histology Detection of organisms is rare	Asymptomatic healthy, but infected, persons do not require treatment Spiramycin or pyrimethamine plus sulfadiazine may be used for pregnant women Pyrimethamine plus sulfadiazine may be used for immunocompromised persons, in specific cases Pyrimethamine plus sulfadiazine (with or without steroids) may be given for ocular disease when indicated Folinic acid is given with pyrimethamine plus sulfadiazine to counteract bone marrow suppression
Toxoplasma gondii (congenital infection)	In infants at birth	Treatment of the mother can reduce severity and/or incidence of congenital infection Most infected infants have few symptoms at birth; later, they generally develop signs of congenital toxoplasmosis (mental retardation, severely impaired eyesight, cerebral palsy, seizures), unless the infection is treated	Months	Passed from mother (who acquired acute infection during pregnancy) to child	Isolation of *T. gondii* from placenta, umbilical cord, or infant blood; PCR of white blood cells, CSF, or amniotic fluid, or IgM and IgA serology, performed by a reference laboratory	
Trichinella spiralis	1-2 days for initial symptoms; others begin 2-8 wk after infection	Acute: nausea, diarrhea, vomiting, fatigue, fever, abdominal discomfort followed by muscle soreness, weakness, and occasional cardiac and neurologic complications	Months	Raw or undercooked contaminated meat, usually pork or wild game meat (e.g., bear or moose)	Positive serology or demonstration of larvae via muscle biopsy; increase in eosinophils	Supportive care plus mebendazole or albendazole. In addition to antiparasitic medication, treatment with steroids is sometimes required in more severe cases

CNS, central nervous system; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; IgA, immunoglobulin A; IgM, immunoglobulin M; PCR, polymerase chain reaction; TMP-SMX, trimethoprim-sulfamethoxazole.

From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses. MMWR *53(RR-4):1-33, 2004.*

Table 340-4 Foodborne Noninfectious Illnesses

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREATMENT
Antimony	5 min–8 hr usually <1 hr	Vomiting, metallic taste	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Arsenic	Few hours	Vomiting, colic, diarrhea	Several days	Contaminated food	Urine Can cause eosinophilia	Gastric lavage, BAL (dimercaprol)
Cadmium	5 min–8 hr usually <1 hr	Nausea, vomiting, myalgia, increase in salivation, stomach pain	Usually self-limited	Seafood, oysters, clams, lobster, grains, peanuts	Identification of metal in food	Supportive care
Ciguatera fish poisoning (ciguatera toxin)	2-6 hr 3 hr 2-5 days	GI: abdominal pain, nausea, vomiting, diarrhea Neurologic: paresthesias, reversal of hot or cold, pain, weakness Cardiovascular: bradycardia, hypotension, increase in T-wave abnormalities	Days to weeks to months	A variety of large reef fish: grouper, red snapper, amberjack, and barracuda (most common)	Radioassay for toxin in fish or a consistent history	Supportive care, IV mannitol Children more vulnerable
Copper	5 min–8 hr usually <1 hr	Nausea, vomiting, blue or green vomitus	Usually self-limited	Metallic container	Identification of metal in beverage or food	Supportive care
Mercury	1 wk or longer	Numbness, weakness of legs, spastic paralysis, impaired vision, blindness, coma Pregnant women and the developing fetus are especially vulnerable	May be protracted	Fish exposed to organic mercury, grains treated with mercury fungicides	Analysis of blood, hair	Supportive care
Mushroom toxins, short-acting (muscimol, muscarine, psilocybin, *Coprinus atramentaria*, ibotenic acid)	<2 hr	Vomiting, diarrhea, confusion, visual disturbance, salivation, diaphoresis, hallucinations, disulfiram-like reaction, confusion, visual disturbance	Self-limited	Wild mushrooms (cooking might not destroy these toxins)	Typical syndrome and mushroom identified or demonstration of the toxin	Supportive care
Mushroom toxins, long-acting (amanitin)	4-8 hr diarrhea; 24-48 hr liver failure	Diarrhea, abdominal cramps, leading to hepatic and renal failure	Often fatal	Mushrooms	Typical syndrome and mushroom identified and/or demonstration of the toxin	Supportive care, life-threatening, may need life support
Nitrite poisoning	1-2 hr	Nausea, vomiting, cyanosis, headache, dizziness, weakness, loss of consciousness, chocolate-brown blood	Usually self-limited	Cured meats, any contaminated foods, spinach exposed to excessive nitrification	Analysis of the food, blood	Supportive care, methylene blue

Pesticides (organophosphates or carbamates)	Few minutes to few hours	Nausea, vomiting, abdominal cramps, diarrhea, headache, nervousness, blurred vision, twitching, convulsions, salivation, meiosis	Usually self-limited	Any contaminated food	Analysis of the food, blood	Atropine; 2-PAM (pralidoxime) is used when atropine is not able to control symptoms; rarely necessary in carbamate poisoning
Puffer fish (tetrodotoxin)	<30 min	Paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure	Death usually in 4-6 hr	Puffer fish	Detection of tetrodotoxin in fish	Life-threatening, may need respiratory support
Scombroid (histamine)	1 min-3 hr	Flushing, rash, burning sensation of skin, mouth and throat, dizziness, urticaria, paresthesias	3-6 hr	Fish: bluefin, tuna, skipjack, mackerel, marlin, escolar, and mahi mahi	Demonstration of histamine in food or clinical diagnosis	Supportive care, antihistamines
Shellfish toxins (diarrheic, neurotoxic, amnesic)	Diarrheic shellfish poisoning: 30 min-2 hr	Nausea, vomiting, diarrhea, and abdominal pain accompanied by chills, headache, and fever	hr to 2-3 days	A variety of shellfish, primarily mussels, oysters, scallops, and shellfish from the Florida coast and the Gulf of Mexico	Detection of the toxin in shellfish; high-pressure liquid chromatography	Supportive care, generally self-limiting
	Neurotoxic shellfish poisoning: few minutes to hours	Tingling and numbness of lips, tongue, and throat, muscular aches, dizziness, reversal of the sensations of hot and cold, diarrhea, and vomiting				
	Amnesic shellfish poisoning: 24-48 hr	Vomiting, diarrhea, abdominal pain and neurologic problems such as confusion, memory loss, disorientation, seizure, coma				Elderly are especially sensitive to amnesic shellfish poisoning
Shellfish toxins (paralytic shellfish poisoning)	30 min-3 hr	Diarrhea, nausea, vomiting leading to paresthesias of mouth and lips, weakness, dysphasia, dysphonia, respiratory paralysis	Days	Scallops, mussels, clams, cockles	Detection of toxin in food or water where fish are located; high-pressure liquid chromatography	Life-threatening, may need respiratory support
Sodium fluoride	Few minutes to 2 hr	Salty or soapy taste, numbness of mouth, vomiting, diarrhea, dilated pupils, spasms, pallor, shock, collapse	Usually self-limited	Dry foods (e.g., dry milk, flour, baking powder, cake mixes) contaminated with NaF-containing insecticides and rodenticides	Testing of vomitus or gastric washings Analysis of the food	Supportive care
Thallium	Few hours	Nausea, vomiting, diarrhea, painful paresthesias, motor polyneuropathy, hair loss	Several days	Contaminated food	Urine, hair	Supportive care
Tin	5 min-8 hr usually <1 hr	Nausea, vomiting, diarrhea	Usually self-limited	Metallic container	Analysis of the food	Supportive care
Vomitoxin	Few minutes to 3 hr	Nausea, headache, abdominal pain, vomiting	Usually self-limited	Grains such as wheat, corn, barley	Analysis of the food	Supportive care
Zinc	Few hours	Stomach cramps, nausea, vomiting, diarrhea, myalgias	Usually self-limited	Metallic container	Analysis of the food, blood and feces, saliva or urine	Supportive care

BAL, bronchoalveolar lavage; GI, gastrointestinal.

From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, MMWR *53(RR-4):1-33, 2004.*

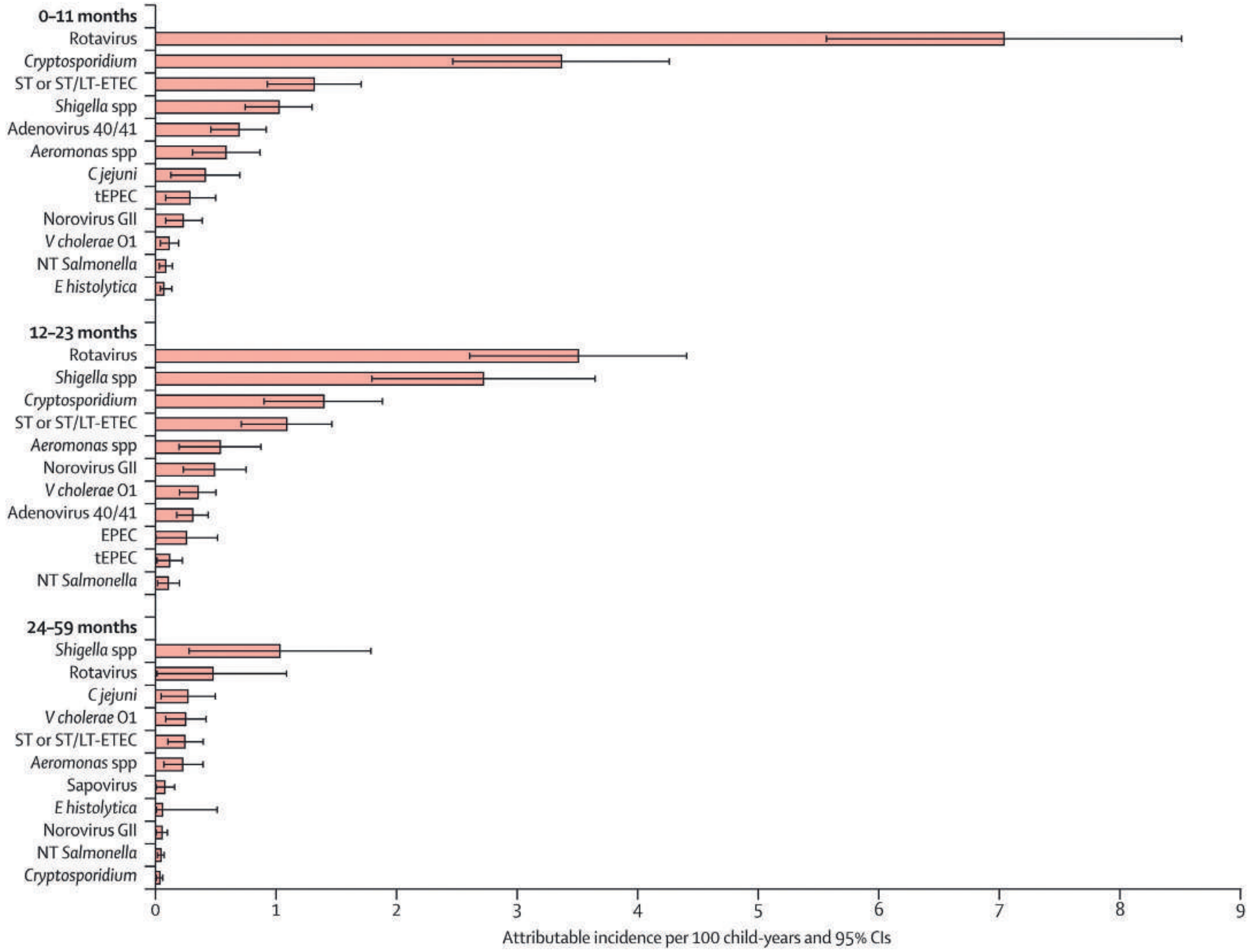

Figure 340-1 Attributable incidence of pathogen-specific moderate-to-severe diarrhea per 100 child-yr by age stratum, all sites combined. The bars show the incidence rates and the error bars show the 95% confidence intervals. *(From Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries [the Global Enteric Multicenter Study, GEMS]: a prospective, case-control study.* Lancet *382(9888):209–222, 2013, Fig. 4.)*

gastroenteritis via a superficial invasion of colonic mucosa, which they invade through M cells located over Peyer patches. After phagocytosis, a series of events occurs, including apoptosis of macrophages, multiplication and spread of bacteria into adjacent cells, release of inflammatory mediators (interleukin-1 and -8), transmigration of neutrophils into the lumen of the colon, neutrophil necrosis and degranulation, further breach of the epithelial barrier, and mucosal destruction (Fig. 340-5).

RISK FACTORS FOR GASTROENTERITIS

In developed countries, episodes of infectious diarrhea can occur through seasonal exposure to organisms such as rotavirus, or exposure to pathogens in settings of close contact (e.g., daycare centers). Major risks include environmental contamination and increased exposure to enteropathogens. Additional risks include young age, immunodeficiency, measles, malnutrition, and lack of exclusive or predominant breastfeeding. Malnutrition increases the risk of diarrhea and associated mortality, and moderate to severe stunting increases the odds of diarrhea-associated mortality. The fraction of such infectious diarrhea deaths that are attributable to nutritional deficiencies varies with the prevalence of deficiencies; the highest attributable fractions are in sub-Saharan Africa, south Asia, and Andean Latin America. The risks are particularly higher with micronutrient malnutrition; in children with **vitamin A deficiency,** and accounts for 157,000 deaths from diarrhea, measles, and malaria. **Zinc deficiency** is estimated to cause 116,000 deaths from diarrhea and pneumonia. Table 340-7 summarizes some of the key risk factors associated with childhood diarrhea globally.

The majority of cases of diarrhea resolve within the 1st wk of the illness. A smaller proportion of diarrheal illnesses fail to resolve and persist for longer than 2 wk. **Persistent diarrhea** is defined as episodes that began acutely but last for 14 or more days. Such episodes account for 3-19% of all diarrheal episodes in children younger than 5 yr of age and up to 50% of all diarrhea-related deaths; persistent diarrhea has a case fatality rate of 60%. Many children (especially infants and toddlers) in developing countries have frequent episodes of acute diarrhea. Although few individual episodes persist beyond 14 days, frequent episodes of acute diarrhea, as well as prolonged diarrhea (lasting between 7-13 days of age), can result in nutritional compromise and can predispose these children to develop persistent diarrhea, protein-calorie malnutrition, and secondary infections.

CLINICAL MANIFESTATION OF DIARRHEA

Most of the clinical manifestations and clinical syndromes of diarrhea are related to the infecting pathogen and the dose or inoculum (see Tables 340-1 to 340-3). Additional manifestations depend on the development of complications (e.g., dehydration and electrolyte imbalance)

Table 340-5 Weighted Annual Incidence (Per 100 Child-Years) of Moderate-to-Severe Diarrhea Attributable to a Specific Pathogen, with 95% Confidence Interval, By Age Stratum and Country

AGE GROUP	PATHOGEN	GAMBIA	MALI	MOZAMBIQUE	KENYA	INDIA	BANGLADESH	PAKISTAN
<12 mo	**VIRUSES**							
	Rotavirus	3.2 (1.7-4.6)	8.4 (3.5-13.3)	3.5 (1.5-5.4)	10.1 (5.4-14.8)	25.4 (14.7-36.2)	2.1 (1.0-3.2)	5.5 (2.6-8.5)
	Norovirus GII	1.2 (0.4-2.0)	–	–	–	–	–	–
	Adenovirus 40/41	0.3 (0.1-0.6)	0.7 (0.1-1.3)	0.3 (0.0-0.5)	–	3.7 (1.6-5.9)	0.5 (0.2-0.8)	0.5 (0.1-0.8)
	BACTERIA							
	ST-ETEC (ST-only or LT/ST)	0.7 (0.1-1.2)	1.4 (0.3-2.5)	–	3.6 (1.4-5.8)	2.8 (0.9-4.8)	0.2 (0.0-0.4)	1.7 (0.6-2.8)
	Shigella	0.5 (0.2-0.9)	–	–	2.3 (0.8-3.8)	1.9 (0.4-3.3)	1.7 (0.8-2.6)	1.9 (0.8-2.9)
	Aeromonas	–	–	–	–	–	1.2 (0.3-2.2)	2.8 (1.0-4.5)
	Campylobacter jejuni	–	–	–	–	–	1.1 (0.1-2.2)	1.7(0.0-3.3)
	Typical EPEC	–	–	–	2.7 (0.6-4.7)	–	–	–
	Nontyphoidal *Salmonella*	–	–	–	–	–	0.5 (0.2-0.9)	–
	Vibrio cholerae O1	–	–	–	–	–	–	0.8 (0.2-1.3)
	PROTOZOA							
	Cryptosporidium	1.6 (0.7-2.4)	5.4 (2.1-8.8)	1.8 (0.7-3.0)	4.6 (2.0-7.2)	11.1 (5.4-16.9)	0.7 (0.2-1.2)	1.4 (0.1-2.6)
	Entamoeba histolytica	–	–	–	–	–	0.5 (0.0-0.9)	–
12-23 mo	**VIRUSES**							
	Rotavirus	3.3 (1.3-5.2)	4.1 (1.0-7.1)	–	3.0 (1.6-4.3)	12.4 (7.1-17.7)	3.0 (1.1-4.9)	1.6 (0.6-2.7)
	Norovirus GII	1.7 (0.5-2.8)	–	–	–	2.3 (0.4-4.2)	–	–
	Adenovirus 40/41	0.4 (0.0-0.8)	–	–	–	2.2 (0.9-3.4)	–	0.4 (0.0-0.7)
	BACTERIA							
	ST-ETEC (ST-only or LT/ST)	1.5 (0.3-2.8)	0.8 (0.0-1.7)	0.7 (0.2-1.2)	1.5 (0.6-2.5)	2.8 (1.1-4.6)		0.9 (0.2-1.7)
	EAEC	–	–	–	–	–	1.6 (0.0-3.2)	–
	Shigella	2.5 (0.9-4.1)	0.8 (0.0-1.6)	0.5 (0.1-0.9)	1.0 (0.3-1.8)	3.5 (1.7-5.4)	8.5 (3.3-13.7)	2.1 (0.7-3.4)
	Aeromonas	–	–	–	–	–	1.9 (0.2-3.7)	1.6 (0.2-2.9)
	Campylobacter jejuni	–	–	–	–	–	–	–
	Typical EPEC	–	–	–	0.8 (0.0-1.5)	–	–	–
	Nontyphoidal *Salmonella*	–	–	–	0.7 (0.1-1.4)	–	–	–
	Vibrio cholerae O1	–	–	–	–	1.6 (0.6-2.7)	0.2 (0.0-0.5)	1.3 (0.4-2.1)
	PROTOZOA							
	Cryptosporidium	1.5 (0.4-2.5)	1.6 (0.0-3.3)	–	2.0 (0.9-3.0)	4.1 (1.2-6.9)	–	1.4 (0.4-2.4)
	Entamoeba histolytica	–	–	–	–	–	–	–
24–59 mo	**VIRUSES**							
	Rotavirus	0.4 (0.1-0.6)	0.4 (0.0-3.2)	–	0.3 (0.1-0.4)	3.5 (0.0-7.1)	–	–
	Norovirus GII	0.3 (0.0-0.5)	–	–	–	–	–	–
	Sapovirus	–	–	–	–	0.8 (0.0-1.8)	–	–
	Adenovirus 40/41	–	–	–	–	–	–	–
	BACTERIA							
	ST-ETEC (ST-only or LT/ST)	0.3 (0.0-0.5)	–	–	0.4 (0.1-0.6)	1.5 (0.0-3.1)	–	0.1 (0.0-0.3)
	EAEC	–	–	–	–	–	–	–
	Shigella	0.4 (0.1-0.7)	0.3 (0.0-2.9)	0.4 (0.0-0.9)	0.7 (0.4-1.1)	2.9 (0.0-5.9)	3.1 (0.0-6.3)	0.2 (0.0-0.4)
	Aeromonas	–	–	–	–	–	0.8 (0.0-1.8)	0.5 (0.2-0.9)
	Campylobacter jejuni	–	–	–	–	2.4 (0.0-5.0)	–	0.4 (0.0-0.7)
	Typical EPEC	–	–	–	–	–	–	–
	Nontyphoidal *Salmonella*	–	–	–	0.3 (0.1-0.5)	–	–	–
	Vibrio cholerae O1	–	–	0.2 (0.0-0.5)	–	1.8 (0.0-3.8)	0.1 (0.0-0.3)	–
	PROTOZOA							
	Cryptosporidium	–	–	–	0.2 (0.0-0.4)	–	–	–
	Entamoeba histolytica	–	0.3 (0.0-2.7)	–	–	–	–	–

EAEC, enteroadherent *Escherichia coli*; EPEC, enteropathogenic *Escherichia coli*; ETEC, enterotoxigenic *Escherichia coli*; LT, heat-labile; ST, heat stable.

Table 340-6 Comparison of 3 Types of Enteric Infection

PARAMETER	TYPE OF INFECTION I	II	III
Mechanism	Noninflammatory (enterotoxin or adherence/superficial invasion)	Inflammatory (invasion, cytotoxin)	Penetrating
Location	Proximal small bowel	Colon	Distal small bowel
Illness	Watery diarrhea	Dysentery	Enteric fever
Stool examination	No fecal leukocytes Mild or no ↑ lactoferrin	Fecal polymorphonuclear leukocytes ↑↑ Lactoferrin	Fecal mononuclear leukocytes
Examples	*Vibrio cholerae* *Escherichia coli* (ETEC, LT, ST) *Clostridium perfringens* *Bacillus cereus* *Staphylococcus aureus* Also[†]: *Giardia lamblia* *Rotavirus* *Norwalk-like viruses* *Cryptosporidium parvum* E. *coli (EPEC, EAEC)* *Microsporidia* *Cyclospora cayetanensis*	*Shigella* E. *coli* (EIEC, EHEC) *Salmonella enteritidis* *Vibrio parahaemolyticus* *Clostridium difficile* *Campylobacter jejuni* *Entamoeba histolytica**	*Salmonella typhi* *Yersinia enterocolitica* *?Campylobacter fetus*

*Although amebic dysentery involves tissue inflammation, the leukocytes are characteristically pyknotic or absent, having been destroyed by the virulent amebae.

[†]Although not typically enterotoxic, these pathogens alter bowel physiology via adherence, superficial cell entry, cytokine induction, or toxins that inhibit cell function.

EAEC, enteroaggregative *E. coli;* EHEC, enterohemorrhagic *E. coli;* EIEC, enteroinvasive *E. coli;* EPEC, enteropathogenic *E. coli;* ETEC, enterotoxigenic *E. coli;* LT, heat-labile; ST, heat-stable.

From Mandell GL, Bennett JE, Dolin R, editors: Principles and practices of infectious diseases, *ed 7, Philadelphia, 2010, Churchill Livingstone.*

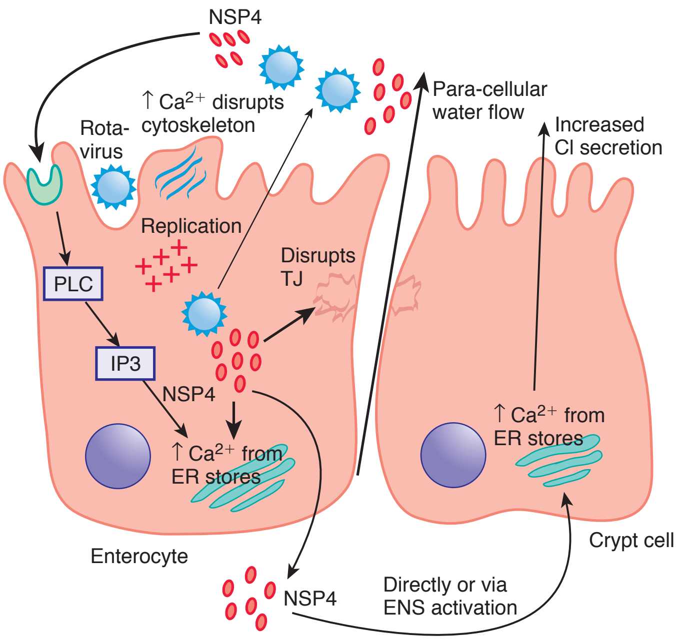

Figure 340-2 **Pathogenesis of rotavirus infection and diarrhea.** *ENS,* enteric nervous system; *ER,* endoplasmic reticulum; *PLC,* phospholipase C; *TJ,* tight junction. *(Adapted from Ramig RF: Pathogenesis of intestinal and systemic rotavirus infection,* J Virol *78:10213–10220, 2004.)*

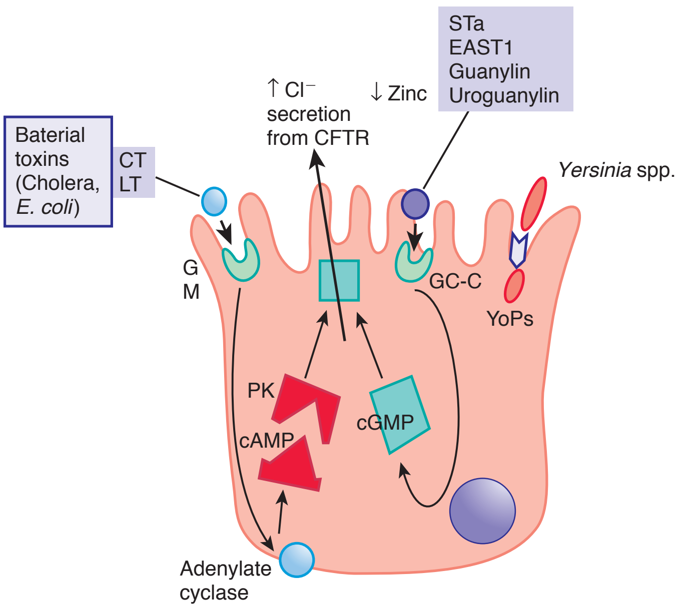

Figure 340-3 **Mechanism of cholera toxin.** *(Adapted from Thapar M, Sanderson IR: Diarrhoea in children: an interface between developing and developed countries,* Lancet *363:641–653, 2004; and Montes M, DuPont HL: Enteritis, enterocolitis and infectious diarrhea syndromes. In Cohen J, Powderly WG, Opal SM, et al, editors:* Infectious diseases, *ed 2, London, 2004, Mosby, pp. 31–52.)*

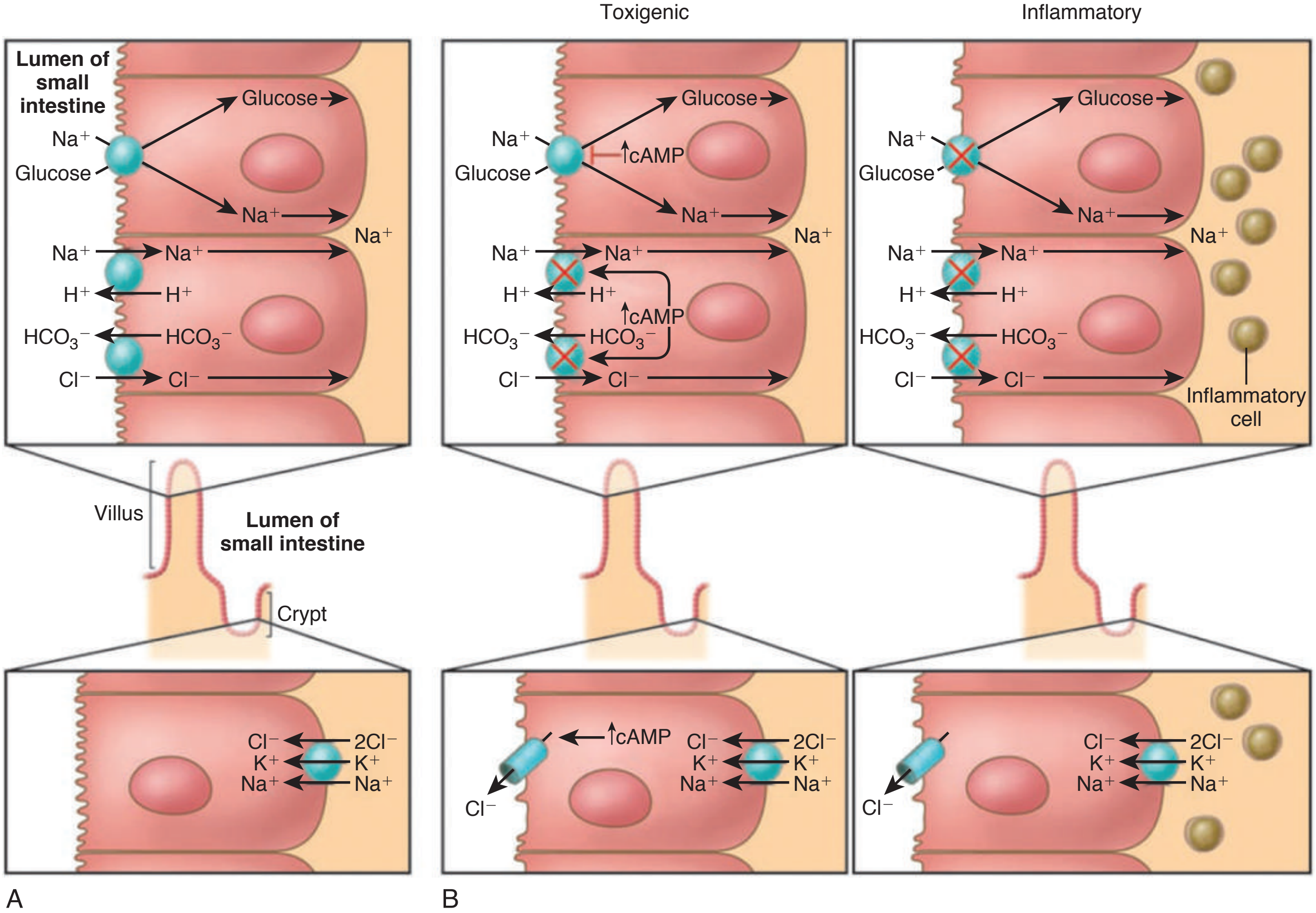

Figure 340-4 **Movement of Na^+ and Cl^- in the small intestine. A,** Movement in normal subjects. Na+ is absorbed by 2 different mechanisms in absorptive cells from villi: glucose-stimulated absorption and electroneutral absorption (which represents the coupling of Na^+/H^+ and Cl^-/HCO_3^- exchanges). **B,** Movement during diarrhea caused by a toxin and inflammation. *(From Petri WA, Miller M, Binder HJ, et al: Enteric infections, diarrhea and their impact on function and development,* J Clin Invest *118:1277–1290, 2008.)*

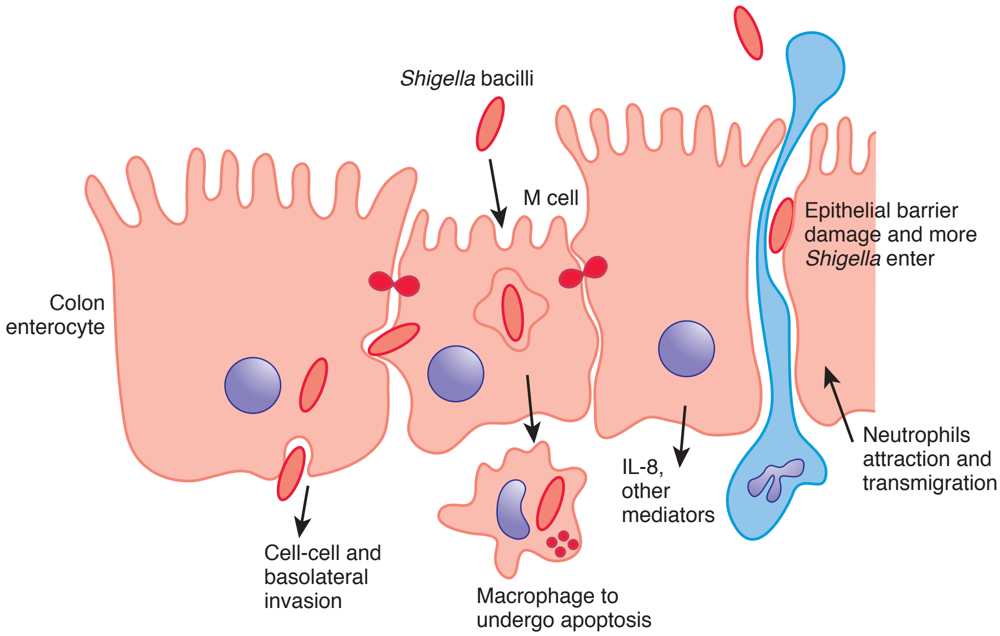

Figure 340-5 **Pathogenesis of *Shigella* infection and diarrhea.** *IL-8,* Interleukin-8. *(Adapted from Opal SM, Keusch GT: Host responses to infection. In Cohen J, Powderly WG, Opal SM, et al, editors:* Infectious diseases, *ed 2, London, 2004, Mosby, pp. 31–52.)*

Table 340-7 Proven Risk Factors with Direct Biologic Links to Diarrhea: Relative Risks (RR) or Odds Ratios (OR) and 95% Confidence Intervals

	DIARRHEA	
	MORBIDITY	**MORTALITY**
Lack of exclusive breastfeeding (0-5 mo)	RR = 2.65 (1.72-4.07) compared to not breastfed infants	RR = 10.52 (2.79-39.6) compared to not breastfed infants
No breastfeeding (6-23 mo)	RR = 1.32 (1.06-1.63)	RR = 2.18 (1.14-4.16)
Underweight	(<–2 WAZ) RR = 1.23 (1.12-1.35)	
–2 to <–1 WAZ		OR = 2.1 (1.6
–3 to <–2 WAZ		OR = 3.4 (2.7
<–3 WAZ		OR = 9.5 (5.5
Stunted		
–2 to <–1 HAZ		OR = 1.2 (0.9
–3 to <–2 HAZ		OR = 1.6 (1.1
<–3 HAZ		OR = 4.6 (2.7
Wasted		
–2 to <–1 WHZ		OR = 1.2 (0.7
–3 to <–2 WHZ		OR = 2.9 (1.8
<–3 WHZ		OR = 6.3 (2.7
Vitamin A deficiency	Inconsistent evidence	RR = 1.47 (1.25-175)
Zinc deficiency	RR = 0.87 (0.81-0.94)	RR = 0.82 (0.64-1.05)
Crowding (>8 persons/kitchen)		
Indoor air pollution		
Unwashed hands	RR = 0.58 (0.49–0.69)	Risk relationship suggested but studies of poor methodologic quality
Poor water quality	RR = 0.73 (0.53-1.01) Inconsistent evidence from blinded studies	Relationship suggested but few studies of sufficient quality
Inappropriate excreta disposal	Limited evidence suggests risk relationship	

HAZ, height-for-age Z-score; WAZ, weight-for-age Z score; WHZ, weight-for-height Z-score.
Adapted from Walker CL, Rudan I, Liu L, et al: Global burden of childhood pneumonia and diarrhoea. Lancet *381:1405–1416, 2013.*

and the nature of the infecting pathogen (Table 340-8). Usually the ingestion of preformed toxins (e.g., those of *S. aureus*) is associated with the rapid onset of nausea and vomiting within 6 hr, with possible fever, abdominal cramps, and diarrhea within 8-72 hr. Watery diarrhea and abdominal cramps after an 8-16 hr incubation period are associated with enterotoxin-producing *C. perfringens* and *B. cereus.* Abdominal cramps and watery diarrhea after a 16-48 hr incubation period can be associated with noroviruses, several enterotoxin-producing bacteria, *Cryptosporidium,* and *Cyclospora,* and also have been a notable feature of influenza virus H1N1 infections. Several organisms, including *Salmonella, Shigella, C. jejuni, Yersinia enterocolitica,* enteroinvasive or hemorrhagic (Shigatoxin-producing) *E. coli,* and *V. parahaemolyticus,* produce diarrhea that can contain blood as well as fecal leukocytes in association with abdominal cramps, tenesmus, and fever; these features suggest **bacterial dysentery** and fever (Table 340-8). Bloody diarrhea and abdominal cramps after a 72-120 hr incubation period are associated with infections from *Shigella* and also Shigatoxin-producing *E. coli,* such as *E. coli* O157:H7. Organisms associated with dysentery or hemorrhagic diarrhea can also cause watery diarrhea alone without fever or that precedes a more complicated course that results in dysentery.

Although many of the manifestations of acute gastroenteritis in children are nonspecific, some clinical features can help identify major categories of diarrhea and allow rapid triage for antibiotic or specific dietary therapy (see Tables 340-1 to 340-4). There is considerable overlap in the symptomatology. The positive predictive values for the features of dysentery are very poor; the negative predictability for bacterial pathogens is much better in the absence of signs of dysentery. If warranted and if facilities and resources permit, the etiology can be verified by appropriate laboratory testing.

COMPLICATIONS

Most of the complications associated with gastroenteritis are related to delays in diagnosis and delays in the institution of appropriate therapy. Without early and appropriate rehydration, many children with acute diarrhea would develop dehydration with associated complications (see Chapter 57). These can be life-threatening in infants and young children. Inappropriate therapy can lead to prolongation of the diarrheal episodes, with consequent malnutrition and complications such as secondary infections and micronutrient deficiencies (iron, zinc, vitamin A). In developing countries and HIV-infected populations, associated bacteremias are well-recognized complications in malnourished children with diarrhea.

Specific pathogens are associated with extraintestinal manifestations and complications. These are not pathognomonic of the infection, nor do they always occur in close temporal association with the diarrheal episode (Table 340-9).

DIAGNOSIS

The diagnosis of gastroenteritis is based on clinical recognition, an evaluation of its severity by rapid assessment and by confirmation by appropriate laboratory investigations, if indicated.

Table 340-8	Differential Diagnosis of Acute Dysentery and Inflammatory Enterocolitis
SPECIFIC INFECTIOUS PROCESSES	
Bacillary dysentery *(Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Shigella boydii;* invasive *Escherichia coli)*	
Campylobacteriosis *(Campylobacter jejuni)*	
Amebic dysentery *(Entamoeba histolytica)*	
Ciliary dysentery *(Balantidium coli)*	
Bilharzial dysentery *(Schistosoma japonicum, Schistosoma mansoni)*	
Other parasitic infections *(Trichinella spiralis)*	
Vibriosis *(Vibrio parahaemolyticus)*	
Salmonellosis *(Salmonella typhimurium)*	
Typhoid fever *(Salmonella typhi)*	
Enteric fever *(Salmonella choleraesuis, Salmonella paratyphi)*	
Yersiniosis *(Yersinia enterocolitica)*	
Spirillar dysentery (*Spirillum* spp.)	
PROCTITIS	
Gonococcal *(Neisseria gonorrhoeae)*	
Herpetic (herpes simplex virus)	
Chlamydial *(Chlamydia trachomatis)*	
Syphilitic *(Treponema pallidum)*	
OTHER SYNDROMES	
Necrotizing enterocolitis of the newborn	
Enteritis necroticans	
Pseudomembranous enterocolitis *(Clostridium difficile)*	
Typhlitis	
CHRONIC INFLAMMATORY PROCESSES	
Enteropathogenic and enteroaggregative *E. coli*	
Gastrointestinal tuberculosis	
Gastrointestinal mycosis	
Parasitic enteritis	
SYNDROMES WITHOUT KNOWN INFECTIOUS CAUSE	
Idiopathic ulcerative colitis	
Crohn disease	
Radiation enteritis	
Ischemic colitis	
Allergic enteritis	

From Mandell GL, Bennett JE, Dolin R, editors: Principles and practices of infectious diseases, *ed 7, Philadelphia, 2010, Churchill Livingstone.*

Clinical Evaluation of Diarrhea

The most common manifestations of gastrointestinal tract infection in children are diarrhea, abdominal cramps, and vomiting. Systemic manifestations are varied and associated with a variety of causes. The evaluation of a child with acute diarrhea includes:

- Assessing the degree of dehydration and acidosis and provide rapid resuscitation and rehydration with oral or intravenous fluids as required (Tables 340-10 and 340-11).
- Obtaining appropriate contact, travel, or exposure history. This includes information on exposure to contacts with similar symptoms, intake of contaminated foods or water, child-care center attendance, recent travel of patient or contact with a person who traveled to a diarrhea-endemic area, and use of antimicrobial agents.
- Clinically determining the etiology of diarrhea for institution of prompt antibiotic therapy, if indicated.

Although nausea and vomiting are nonspecific symptoms, they indicate infection in the upper intestine. Fever suggests an inflammatory process but also occurs as a result of dehydration or coinfection (e.g., urinary tract infection, otitis media). Fever is common in patients with inflammatory diarrhea. Severe abdominal pain and tenesmus indicate involvement of the large intestine and rectum. Features such as nausea and vomiting and absent or low-grade fever with mild to moderate periumbilical pain and watery diarrhea indicate small intestine involvement and also reduce the likelihood of a serious bacterial infection.

This clinical approach to the diagnosis and management of diarrhea in young children is a critical component of the **Integrated Management of Childhood Illnesses** package that is being implemented in developing countries that have a high burden of diarrhea mortality (Figs. 340-6 and 340-7).

Stool Examination

Microscopic examination of the stool and cultures can yield important information on the etiology of diarrhea. Stool specimens could be examined for mucus, blood, and leukocytes. Fecal leukocytes indicate bacterial invasion of colonic mucosa, although some patients with shigellosis have minimal leukocytes at an early stage of infection, as do patients infected with Shigatoxin-producing *E. coli* and *E. histolytica.* Recent advances in rapid molecular methods of diagnosis for bacterial and parasitic infections have made the role of traditional microscopy less important; however, this is still a useful test in developing countries. *XTAG GPP* is an FDA-approved gastrointestinal pathogen panel using multiplexed nucleic acid technology that detects *Campylobacter, C. difficile, toxin A/B, E. coli* 0157, enterotoxigenic *E. coli, Salmonella, Shigella,* Shiga-like toxin *E. coli,* norovirus, rotavirus A, *Giardia,* and *Cryptosporidium.* Stool cultures should be obtained as early in the course of disease as possible from children with **bloody diarrhea** in whom stool microscopy indicates **fecal leukocytes,** in **outbreaks** with suspected **hemolytic-uremic syndrome,** and in **immunosuppressed** children with diarrhea. Stool specimens for culture need to be transported and plated quickly; if the latter is not quickly available, specimens might need to be transported in special transport media. The yield and diagnosis of bacterial diarrhea is improved by using molecular diagnostic procedures such as real-time polymerase chain reaction. In most previously healthy children with uncomplicated watery diarrhea, no laboratory evaluation is needed except for epidemiologic purposes.

TREATMENT

The broad principles of management of acute gastroenteritis in children include oral rehydration therapy, enteral feeding and diet selection, zinc supplementation, and additional therapies such as probiotics.

Oral Rehydration Therapy

Children, especially infants, are more susceptible than adults to dehydration because of the greater basal fluid and electrolyte requirements per kg and because they are dependent on others to meet these demands. **Dehydration** must be evaluated rapidly and corrected in 4-6 hr according to the degree of dehydration and estimated daily requirements. A small minority of children, especially those in shock or unable to tolerate oral fluids, require initial intravenous rehydration, but oral rehydration is the preferred mode of rehydration and replacement of ongoing losses (see Tables 340-8 and 340-9). Risks associated with severe dehydration that might necessitate intravenous resuscitation include: age <6 mo; prematurity; chronic illness; fever >38°C (100.4°F) if younger than 3 mo or >39°C (102.2°F) if 3-36 mo of age; bloody diarrhea; persistent emesis; poor urine output; sunken eyes; and a depressed level of consciousness. The low-osmolality World Health Organization (WHO) oral rehydration solution (ORS) containing 75 mEq of sodium, 64 mEq of chloride, 20 mEq of potassium, and 75 mmol of glucose per liter, with total osmolarity of 245 mOsm/L, is now the global standard of care and more effective than home fluids, including decarbonated soda beverages, fruit juices, and tea. These are not suitable for rehydration or maintenance therapy because they have inappropriately high osmolalities and low sodium concentrations. Figure 340-7 and Tables 340-10 and 340-11 outline a clinical evaluation plan and management strategy for children with moderate to severe diarrhea. Oral rehydration should be given to infants and children slowly, especially if they have emesis. It can be given initially by a dropper, teaspoon, or syringe, beginning with as little as 5 mL at a time. The volume is increased as tolerated. Replacement for emesis or stool losses is noted in Table 340-11. Oral rehydration can also be given by a nasogastric tube if needed; this is not the usual route.

Limitations to oral rehydration therapy include shock, an ileus, intussusception, carbohydrate intolerance (rare), severe emesis, and

Table 340-9 Extraintestinal Manifestations of Enteric Infections

MANIFESTATION	ASSOCIATED ENTERIC PATHOGEN(S)	ONSET AND PROGNOSIS
Focal infections from systemic spread of bacterial pathogens, including vulvovaginitis, urinary tract infection, endocarditis, osteomyelitis, meningitis, pneumonia, hepatitis, peritonitis, chorioamnionitis, soft-tissue infection, and septic thrombophlebitis	All major pathogens can cause such direct extraintestinal infections, including *Salmonella, Shigella, Yersinia, Campylobacter, Clostridium difficile*	Onset usually during the acute infection but can occur subsequently Prognosis depends on infection site
Reactive arthritis	*Salmonella, Shigella, Yersinia, Campylobacter, Cryptosporidium, C. difficile*	Typically occurs 1-3 wk after infection Relapses after reinfection can develop in 15-50% of people, but most children recover fully within 2-6 mo after the first symptoms appear
Guillain-Barré syndrome	*Campylobacter*	Usually occurs a few weeks after the original infection Prognosis is good although 15-20% may have sequelae
Glomerulonephritis	*Shigella, Campylobacter, Yersinia*	Can be of sudden onset in acute, referring to a sudden attack of inflammation, or chronic, which comes on gradually In most cases, the kidneys heal with time
Immunoglobulin A (IgA) nephropathy	*Campylobacter*	Characterized by recurrent episodes of blood in the urine, this condition results from deposits of the protein IgA in the glomeruli. IgA nephropathy can progress for years with no noticeable symptoms Men seem more likely to develop this disorder than women
Erythema nodosum	*Yersinia, Campylobacter, Salmonella*	Although painful, is usually benign and more commonly seen in adolescents Resolves with 4-6 wk
Hemolytic uremic syndrome	*Shigella dysenteriae* 1, *Escherichia coli* O157:H7, others	Sudden onset, short-term renal failure In severe cases, renal failure requires several sessions of dialysis to take over the kidney function, but most children recover without permanent damage to their health
Hemolytic anemia	*Campylobacter, Yersinia*	Relatively rare complication and can have a chronic course

From Centers for Disease Control and Prevention: Managing acute gastroenteritis among children, MMWR Recomm Rep *53:1–33, 2004.*

Table 340-10 Symptoms Associated with Dehydration

SYMPTOM	MINIMAL OR NO DEHYDRATION (<3% LOSS OF BODY WEIGHT)	MILD TO MODERATE DEHYDRATION (3-9% LOSS OF BODY WEIGHT)	SEVERE DEHYDRATION (>9% LOSS OF BODY WEIGHT)
Mental status	Well; alert	Normal, fatigued or restless, irritable	Apathetic, lethargic, unconscious
Thirst	Drinks normally; might refuse liquids	Thirsty; eager to drink	Drinks poorly; unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, with bradycardia in most severe cases
Quality of pulses	Normal	Normal to decreased	Weak, thready, or impalpable
Breathing	Normal	Normal; fast	Deep
Eyes	Normal	Slightly sunken	Deeply sunken
Tears	Present	Decreased	Absent
Mouth and tongue	Moist	Dry	Parched
Skinfold	Instant recoil	Recoil in <2 sec	Recoil in >2 sec
Capillary refill	Normal	Prolonged	Prolonged; minimal
Extremities	Warm	Cool	Cold; mottled; cyanotic
Urine output	Normal to decreased	Decreased	Minimal

Adapted from Duggan C, Santosham M, Glass RI: The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy, MMWR Recomm Rep *41(RR-16):1–20, 1992; and World Health Organization:* The treatment of diarrhoea: a manual for physicians and other senior health workers, *Geneva, 1995, World Health Organization; Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses,* MMWR *53(RR-4):1-33, 2004.*

high stool output (>10 mL/kg/hr). Ondansetron (oral mucosal absorption preparation) reduces the incidence of emesis, thus permitting more effective oral rehydration and is well established in emergency management of acute gastroenteritis in developed countries.

Enteral Feeding and Diet Selection

Continued enteral feeding in diarrhea aids in recovery from the episode, and a continued age-appropriate diet after rehydration is the norm. Although intestinal brush-border surface and luminal enzymes can be affected in children with prolonged diarrhea, there is evidence that satisfactory carbohydrate, protein, and fat absorption can take place on a variety of diets. Once rehydration is complete, food should be reintroduced while oral rehydration is continued to replace ongoing losses from emesis or stools and for maintenance. Breastfeeding or nondiluted regular formula should be resumed as soon as possible. Foods with complex carbohydrates (rice, wheat, potatoes, bread, and cereals), lean meats, yogurt, fruits, and vegetables are also tolerated. Fatty foods or foods high in simple sugars (juices, carbonated sodas)

Table 340-11 Summary of Treatment Based on Degree of Dehydration

DEGREE OF DEHYDRATION	REHYDRATION THERAPY	REPLACEMENT OF LOSSES	NUTRITION
Minimal or no dehydration	Not applicable	<10 kg body weight: 60-120 mL ORS for each diarrheal stool or vomiting episode >10 kg body weight: 120-240 mL ORS for each diarrheal stool or vomiting episode	Continue breastfeeding or resume age-appropriate normal diet after initial hydration, including adequate caloric intake for maintenance*
Mild to moderate dehydration	ORS, 50-100 mL/kg body weight over 3-4 hr	Same	Same
Severe dehydration	Lactated Ringer solution or normal saline in 20 mL/kg body weight IV until perfusion and mental status improve; then administer 100 mL/kg body weight ORS over 4 hr or 5% dextrose normal saline IV at twice maintenance fluid rates	Same; if unable to drink, administer through nasogastric tube or administer 5% dextrose in normal saline with 20 mEq/L potassium chloride IV	Same

*Overly restricted diets should be avoided during acute diarrheal episodes. Breastfed infants should continue to nurse ad libitum even during acute rehydration. Infants too weak to eat can be given milk or formula through a nasogastric tube. Lactose-containing formulas are usually well tolerated. If lactose malabsorption appears clinically substantial, lactose-free formulas can be used. Complex carbohydrates, fresh fruits, lean meats, yogurt, and vegetables are all recommended. Carbonated drinks or commercial juices with a high concentration of simple carbohydrates should be avoided.

ORS, oral rehydration solution.

From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, MMWR *53(RR-4):1-33, 2004.*

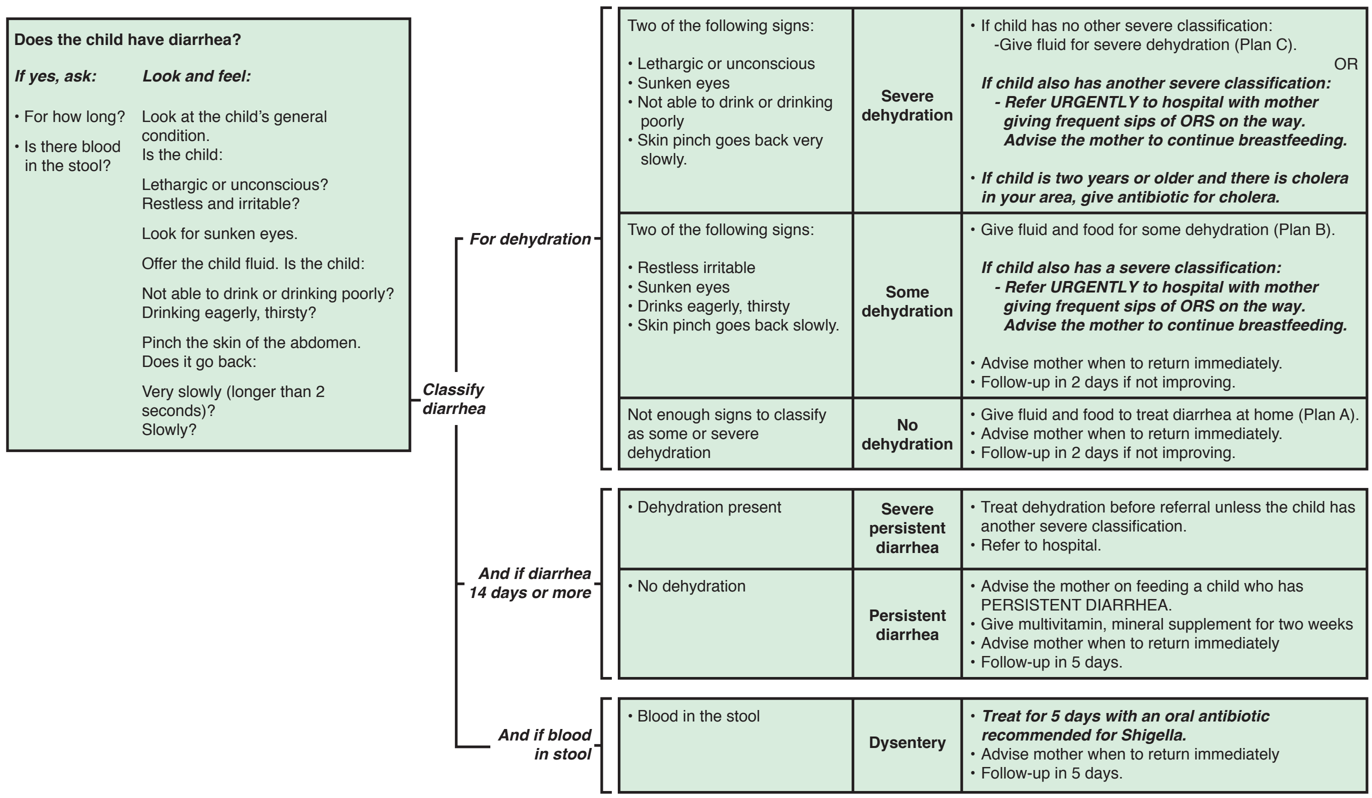

Figure 340-6 Integrated Management of Childhood Illnesses (IMCI) protocol for the recognition and management of diarrhea in developing countries. *ORS,* Oral rehydration solution.

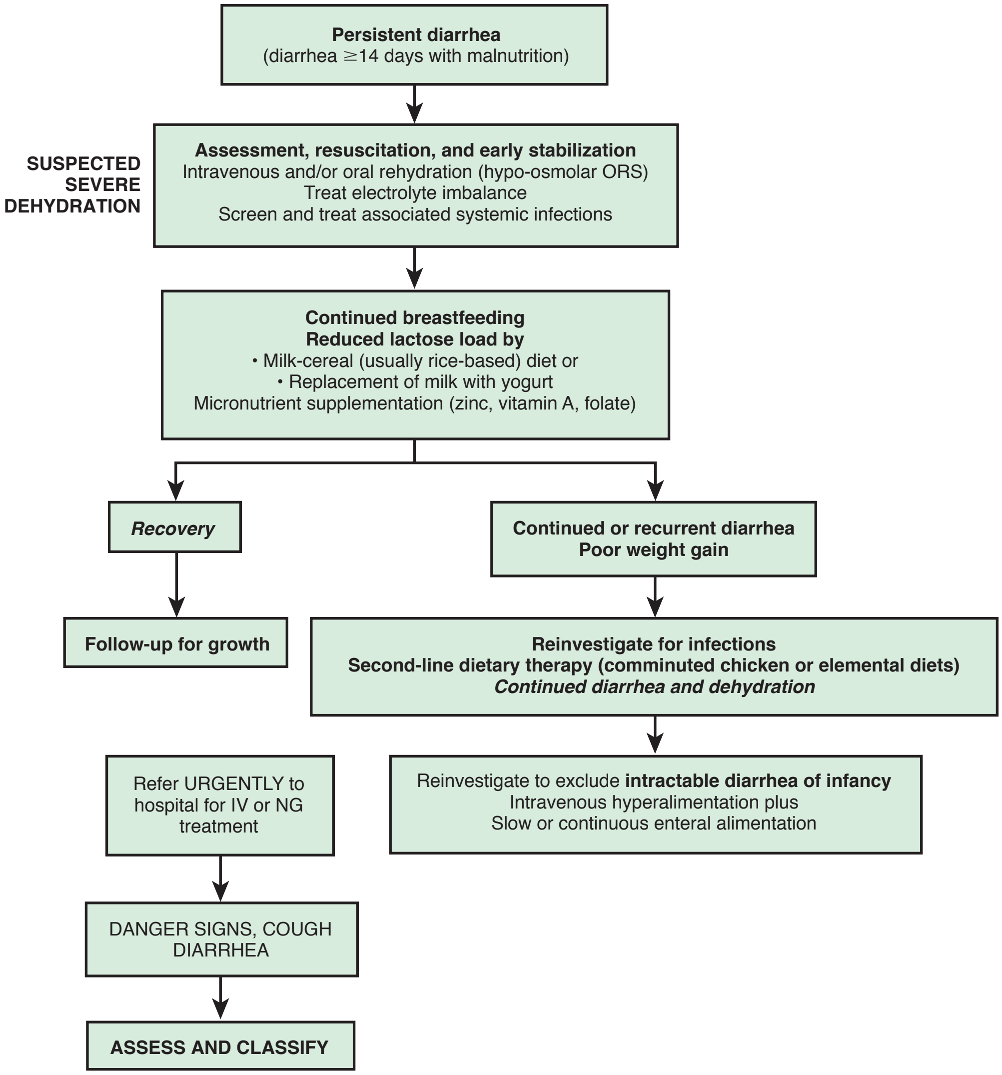

Figure 340-7 Management of persistent diarrhea. *IV,* Intravenous; *NG,* nasogastric tube; *ORS,* oral rehydration solution.

should be avoided. The usual energy density of any diet used for the therapy of diarrhea should be around 1 kcal/g, aiming to provide an energy intake of a minimum of 100 kcal/kg/day and a protein intake of 2-3 g/kg/day. In selected circumstances when adequate intake of energy-dense food is problematic, the addition of amylase to the diet through germination techniques can also be helpful.

With the exception of acute lactose intolerance in a small subgroup, most children with diarrhea are able to tolerate milk and lactose-containing diets. Withdrawal of milk and replacement with specialized (and expensive) lactose-free formulations are unnecessary. Although children with persistent diarrhea are not lactose intolerant, administration of a lactose load exceeding 5 g/kg/day may be associated with higher purging rates and treatment failure. Alternative strategies for reducing the lactose load while feeding malnourished children who have prolonged diarrhea include addition of milk to cereals and replacement of milk with fermented milk products such as yogurt.

Rarely, when dietary intolerance precludes the administration of cow's milk–based formulations or whole milk it may be necessary to administer specialized milk-free diets such as a comminuted or blenderized chicken-based diet or an elemental formulation. Although effective in some settings, the latter are unaffordable in most developing countries. In addition to rice-lentil formulations, the addition of green banana or pectin to the diet has also been shown to be effective in the treatment of persistent diarrhea. Figure 340-7 gives an algorithm for managing children with prolonged diarrhea in developing countries.

Among children in low- and middle-income countries, where the dual burden of diarrhea and malnutrition is greatest and where access to proprietary formulas and specialized ingredients is limited, the use of locally available age-appropriate foods should be promoted for the majority of acute diarrhea cases. Lactose intolerance is an important complication in some cases, but even among those children for whom lactose avoidance may be necessary, nutritionally complete diets comprised of locally available ingredients can be used at least as effectively as commercial preparations or specialized ingredients. These same conclusions may also apply to the dietary management of children with persistent diarrhea, but the evidence remains limited.

Zinc Supplementation

Zinc supplementation in children with diarrhea in developing countries leads to reduced duration and severity of diarrhea and could potentially prevent a large proportion of cases from recurring. Zinc administration for diarrhea management can significantly reduce all-cause mortality by 46% and hospital admission by 23%. In addition to improving diarrhea recovery rates, administration of zinc in community settings leads to increased use of ORS and reduction in the inappropriate use of antimicrobials. All children older than 6 mo of age with acute diarrhea in at-risk areas should receive oral zinc (20 mg/

day) in some form for 10-14 days during and continued after diarrhea. The role of zinc in well nourished, zinc replete populations in developed countries is less certain.

Additional Therapies

The use of probiotic nonpathogenic bacteria for prevention and therapy of diarrhea has been successful in some settings although the evidence is inconclusive to recommend their use in all settings. In addition to restoring beneficial intestinal flora, probiotics can enhance host protective immunity such as downregulation of proinflammatory cytokines and upregulation of anti inflammatory cytokines. A variety of organisms *(Lactobacillus, Bifidobacterium)* have a good safety record; therapy has not been standardized and the most effective (and safe) organism has not been identified. *Saccharomyces boulardii* is effective in antibiotic-associated and in *C. difficile* diarrhea, and there is some evidence that it might prevent diarrhea in daycare centers. *Lactobacillus rhamnosus GG* is associated with reduced diarrheal duration and severity, which reduction is more evident in cases of childhood rotavirus diarrhea.

Antimotility agents (loperamide) are contraindicated in children with dysentery and probably have no role in the management of acute watery diarrhea in otherwise healthy children. Similarly, **antiemetic** agents, such as the phenothiazines, are of little value and are associated with potentially serious side effects (lethargy, dystonia, malignant hyperpyrexia). Nonetheless, ondansetron is an effective and less-toxic antiemetic agent and as indicated previously, is a useful adjunct to the treatment of vomiting in ambulatory settings with reduced risk of intravenous fluid requirements and hospitalization. Because persistent vomiting can limit oral rehydration therapy, a single sublingual dose of an oral dissolvable tablet of ondansetron (4 mg 4-11 yr and 8 mg for children older than 11 yr [generally 0.2 mg/kg]) may be given. However, most children do not require specific antiemetic therapy; careful oral rehydration therapy is usually sufficient.

Racecadotril, an enkephalins inhibitor, has inconsistently been shown to reduce stool output in patients with diarrhea. Experience with this drug in children is limited, and for the average child with acute diarrhea it may be unnecessary.

Antibiotic Therapy

Timely antibiotic therapy in select cases of diarrhea related to bacterial infections can reduce the duration and severity of illness and prevent complications (Table 340-12). Although these agents are important to use in specific cases, their widespread and indiscriminate use leads to the development of antimicrobial resistance. **Nitazoxanide**, an antiinfective agent, is effective in the treatment of a wide variety of pathogens, including *C. parvum*, *G. lamblia*, *E. histolytica*, *Blastocystis hominis*, *C. difficile*, and rotavirus.

PREVENTION

In many developed countries, diarrhea caused by pathogens such as *C. botulinum, E. coli* O157:H7, *Salmonella, Shigella, V. cholerae, Cryptosporidium,* and *Cyclospora* is a notifiable disease and, thus, contact tracing and source identification is important in preventing outbreaks.

Many developing countries struggle with huge disease burdens of diarrhea where a wider approach to diarrhea prevention may be required. Preventive strategies may be of relevance to both developed and developing countries.

Promotion of Exclusive Breastfeeding

Exclusive breastfeeding (administration of no other fluids or foods for the 1st 6 mo of life) is not common, especially in many developed countries. Exclusive breastfeeding protects very young infants from diarrheal disease through the promotion of passive immunity and through reduction in the intake of potentially contaminated food and water. Breast milk contains all the nutrients needed in early infancy, and when continued during diarrhea, it also diminishes the adverse impact on nutritional status. Exclusive breastfeeding for the 1st 6 mo of life is widely regarded as one of the most effective interventions to reduce the risk of premature childhood mortality and the potential to prevent 12% of all deaths of children younger than 5 yr of age.

Improved Complementary Feeding Practices

There is a strong inverse association between appropriate, safe complementary feeding and mortality in children age 6-11 mo; malnutrition is an independent risk for the frequency and severity of diarrheal illness. Complementary foods should be introduced at 6 mo of age, and breastfeeding should continue for up to 2 yr. Complementary foods in developing countries are generally poor in quality and often are heavily contaminated, thus predisposing to diarrhea. Contamination of complementary foods can be potentially reduced through caregivers' education and improving home food storage. Improved vitamin A status has been shown to reduce the frequency of severe diarrhea. Vitamin A supplementation reduces all-cause childhood mortality by 25% (95% confidence interval [CI], 12-36%) and diarrhea-specific mortality by 30% (95% CI, 14-42%).

Rotavirus Immunization

Most infants acquire rotavirus diarrhea early in life; an effective rotavirus vaccine would have a major effect on reducing diarrhea mortality in developing countries. In 1998, a quadrivalent Rhesus rotavirus-derived vaccine was licensed in the United States but subsequently withdrawn because of an increased risk of intussusception. Subsequent development and testing of newer rotavirus vaccines have led to their introduction in most developed countries and approval by the WHO in 2009 for widespread use in developing countries. It is now clear that the introduction of these vaccines is associated with a significant reduction in severe diarrhea and associated mortality.

The institution of large-scale rotavirus vaccination programs has led to major reduction in the burden of disease and associated mortality. In an evaluation of large-scale rotavirus vaccine introduction, coverage rate of 74% was achieved in infants younger than 12 mo of age, with 41% reduction (95% CI, 36-47%) in diarrhea-related mortality. In an evaluation of the vaccine in Africa, overall protective efficacy against rotavirus gastroenteritis ranged from 49-61%, with 30% protective efficacy against all-cause severe gastroenteritis in infancy. Vaccine (live virus) associated rotavirus infection has been reported in children with severe combined immunodeficiency disease, but the vaccine has been shown to be safe in HIV-infected populations.

Other vaccines that could potentially reduce the burden of severe diarrhea and mortality in young children are vaccines against cholera, *Shigella*, and ETEC. Preventive use of cholera vaccines in endemic countries can reduce the risk of developing cholera by 52% (95% CI, 36-65%).

Improved Water and Sanitary Facilities and Promotion of Personal and Domestic Hygiene

Much of the reduction in diarrhea prevalence in the developed world is the result of improvement in standards of hygiene, sanitation, and water supply. Strikingly, an estimated 88% of all diarrheal deaths worldwide can be attributed to unsafe water, inadequate sanitation, and poor hygiene. Improving water quality can reduce the risk of diarrhea by 17%, whereas hand washing with soap and safe excreta disposal reduce the risk of diarrhea by 48% and 36%, respectively. Behavioral change strategies through promotion of handwashing indicate that handwashing promotion and access to soap reduces the burden of diarrhea in developing countries.

Improved Case Management of Diarrhea

Improved management of diarrhea through prompt identification and appropriate therapy significantly reduces diarrhea duration, its nutritional penalty, and risk of death in childhood. Improved management of acute diarrhea is a key factor in reducing the burden of prolonged episodes and persistent diarrhea. The WHO/UNICEF recommendations to use low-osmolality ORS and zinc supplementation for the management of diarrhea, coupled with selective and appropriate use of antibiotics, have the potential to reduce the number of diarrheal

Table 340-12 Antibiotic Therapy for Infectious Diarrhea

ORGANISM	DRUG OF CHOICE	DOSAGE AND DURATION OF TREATMENT
Shigella (severe dysentery and EIEC dysentery)	Ciprofloxacin, ampicillin, ceftriaxone, azithromycin, or TMP-SMX Most strains are resistant to several antibiotics	Ceftriaxone 50-100 mg/kg/day IV or IM, qd or bid × 7 days Ciprofloxacin 20-30 mg/kg/day PO bid × 7-10 days Ampicillin PO, IV 50-100 mg/kg/day qid × 7 days
EPEC, ETEC, EIEC	TMP-SMX or ciprofloxacin	TMP 10 mg/kg/day and SMX 50 mg/kg/day bid × 5 days Ciprofloxacin PO 20-30 mg/kg/day qid for 5-10 days
Salmonella	No antibiotics for uncomplicated gastroenteritis in normal hosts caused by nontyphoidal species **Treatment** indicated in infants younger than 3 mo, and patients with malignancy, chronic GI disease, severe colitis hemoglobinopathies, or HIV infection, and other immunocompromised patients Most strains are resistant to multiple antibiotics	See treatment of *Shigella*
Aeromonas/Plesiomonas	TMP-SMX Ciprofloxacin	TMP 10 mg/kg/day and SMX 50 mg/kg/day bid for 5 days Ciprofloxacin PO 20-30 mg/kg/day divided bid × 7-10 days
Yersinia spp.	Antibiotics are not usually required for diarrhea Deferoxamine therapy should be withheld for severe infections or associated bacteremia Treat sepsis as for immunocompromised hosts, using combination therapy with parenteral doxycycline, aminoglycoside, TMP-SMX, or fluoroquinolone	
Campylobacter jejuni	Erythromycin or azithromycin	Erythromycin PO 50 mg/kg/day divided tid × 5 days Azithromycin PO 5-10 mg/kg/day qid × 5 days
Clostridium difficile	Metronidazole (first line) Discontinue initiating antibiotic Vancomycin (second line)	PO 30 mg/kg/day divided qid × 5 days; max 2 g PO 40 mg/kg/day qid × 7 days, max 125 mg
Entamoeba histolytica	Metronidazole followed by iodoquinol or paromomycin	Metronidazole PO 30-40 mg/kg/day tid × 7-10 days Iodoquinol PO 30-40 mg/kg/day tid × 20 days Paromomycin PO 25-35 mg/kg/day tid × 7 days
Giardia lamblia	Furazolidone or metronidazole or albendazole or quinacrine	Furazolidone PO 25 mg/kg/day qid × 5-7 days Metronidazole PO 30-40 mg/kg/day tid × 7 days Albendazole PO 200 mg bid × 10 days
Cryptosporidium spp.	Nitazoxanide PO treatment may not be needed in normal hosts In immunocompromised, PO immunoglobulin + aggressively treat HIV, etc.	Children 1-3 yr: 100 mg bid × 3 days Children 4-11 yr: 200 mg bid
Isospora spp.	TMP-SMX	PO TMP 5 mg/kg/day and SMX 25 mg/kg/day, bid × 7-10 days
Cyclospora spp.	TMP/SMX	PO TMP 5 mg/kg/day and SMX 25 mg/kg/day bid × 7 days
Blastocystis hominis	Metronidazole or iodoquinol	Metronidazole PO 30-40 mg/kg/day tid × 7-10 days Iodoquinol PO 40 mg/kg/day tid × 20 days

EIEC, Enteroinvasive *Escherichia coli*; EPEC, enteropathogenic *E. coli*; ETEC, enterotoxigenic *E. coli*; GI, gastrointestinal; max, maximum; SMX, sulfamethoxazole; TMP, trimethoprim.

deaths among children through Community Case Management and Integrated Management of Childhood Illnesses.

Community-based interventions to diagnose and treat childhood diarrhea through community health workers leads to a significant rise in care seeking behaviors for diarrhea and are associated with significantly increased use of ORS and zinc at household level as well as reduction in the unnecessary use of antibiotics for diarrhea by 75%.

Bibliography is available at Expert Consult.

340.1 Traveler's Diarrhea

Zulfiqar Ahmed Bhutta

Traveler's diarrhea is a common complication of visitors to developing countries and is caused by a variety of pathogens, in part depending on the season and the region visited (see Table 340-12). Traveler's diarrhea has a high attack rate among travelers from higher-income countries visiting, during the summer, countries in a warmer climate that have a high prevalence of indigenous infectious diarrhea. Traveler's diarrhea can manifest with watery diarrhea or as dysentery. Without treatment, 90% will have resolved within a week and 98% within a month of onset. Some individuals develop more severe diarrhea and become dehydrated or unwell and may experience systemic complications that warrant further attention. Most cases of traveler's diarrhea resolve spontaneously and a simple stool culture may be the only investigation required. For those individuals with ongoing symptoms, further tests should be requested depending on the history and clinical presentation.

TREATMENT

Traveler's diarrhea is often self-limiting but requires particular attention to avoid dehydration. For infants and children, rehydration, as

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discussed in Chapter 340, is appropriate, followed by a standard diet. Adolescents and adults should increase their intake of electrolyte-rich fluids. Kaolin-pectin, anticholinergic agents, *Lactobacillus,* and bismuth salicylate have not been effective therapies. Loperamide, an antimotility and antisecretory agent, reduces the number of stools in older children with watery diarrhea and improves outcomes when used in combination with antibiotics in traveler's diarrhea. However, loperamide should be used with great caution or not at all in febrile or toxic patients with dysentery and in those with bloody diarrhea.

Antibiotics, with or without loperamide, can also reduce the number of unformed stools. Short-duration (3 days) therapy with fluoroquinolones, trimethoprim-sulfamethoxazole, azithromycin, or rifaximin is effective; the choice of antibiotic depends on the age of the patient, the potential organism, and the organism's local resistance patterns. However, antibiotics often have a negative risk-benefit ratio when weighing potential side effects vs treatment need for a short-lasting and self-limiting disease such as traveler's diarrhea. Azithromycin has several advantages over other antibiotics. It is taken only once (1,000 mg), the rate of antimicrobial resistance is low, and it has a good safety profile. Furthermore, in contrast to rifaximin, it can be used in severe cases of diarrhea with fever or bloody stools and can even be administered in children. Optionally, azithromycin can be combined with antimotility medications such as loperamide. Travelers should be reminded that diarrhea can be a symptom of other severe diseases, such as malaria. Therefore, if diarrhea persists or additional symptoms such as fever occur, travelers should seek medical advice. For up-to-date information on local pathogens and resistant patterns, see www.cdc.gov/travel.

PREVENTION

Travelers should drink bottled or canned beverages or boiled water. They should avoid ice, salads, and fruit they did not peel themselves. Food should be eaten hot, if possible. Raw or poorly cooked seafood is a risk, as is eating in a restaurant rather than a private home. Swimming pools and other recreational water sites can also be contaminated.

Chemoprophylaxis is not routinely recommended for previously healthy children or adults. Nonetheless, travelers should bring azithromycin (younger than 16 yr of age) or ciprofloxacin (older than 16 yr of age) and begin antimicrobial therapy if diarrhea develops.

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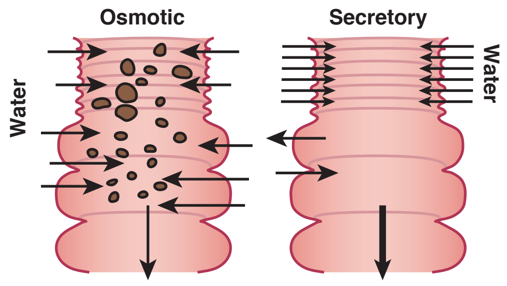

	Osmotic	Secretory
Stool volume:	Moderately increased	Very large
Response to fasting:	Diarrhea stops	Diarrhea continues
Stool osmolality:	Normal to increased	Normal
Ion gap:	$\geq$ 100 mOsm/kg	$<$ 100 mOsm/kg

Figure 341-1 Pathways of osmotic and secretory diarrhea. Osmotic diarrhea is caused by functional or structural damage of intestinal epithelium. Nonabsorbed osmotically active solutes drive water into the lumen. Stool osmolality and ion gap are generally increased. Diarrhea stops in children when not eating. In secretory diarrhea, ions are actively pumped into the intestine by the action of exogenous and endogenous secretagogues. Usually there is no intestinal damage. Osmolality and ion gap are within normal levels. Large volumes of stools are lost independent of food ingestion.

Chapter **341**

Chronic Diarrhea

Alfredo Guarino, David Branski, and Harland S. Winter

DEFINITION AND EPIDEMIOLOGY

Chronic diarrhea is defined as stool volume of more than 10 g/kg/day in toddlers/infants and greater than 200 g/day in older children that lasts for 14 days or more. In practice, this usually means having loose or watery stools more than 3 times a day. *Awakening at night to pass stool is often a sign of an organic cause of diarrhea.* The epidemiology has 2 distinct patterns. In developing countries, chronic diarrhea is, in many cases, the result of an intestinal infection that persists longer than expected. This syndrome is often defined as *protracted diarrhea*, but there is no clear distinction between protracted and chronic diarrhea. In countries with higher socioeconomic conditions, chronic diarrhea is less frequent and the etiology often varies with age. The outcome of diarrhea depends on the cause and ranges from benign, self-limited conditions, such as toddler's diarrhea, to severe congenital diseases, such as microvillus inclusion disease, that may lead to progressive intestinal failure.

PATHOPHYSIOLOGY

The mechanisms of diarrhea are generally divided into secretory and osmotic, but often diarrhea is a combination of both mechanisms. In addition, inflammation and motility disorders may contribute to diarrhea. Secretory diarrhea is usually associated with large volumes of watery stools and persists when oral feeding is withdrawn. Osmotic diarrhea is dependent on oral feeding, and stool volumes are usually not as massive as in secretory diarrhea (Fig. 341-1).

Secretory diarrhea is characterized by active electrolyte and water fluxes toward the intestinal lumen, resulting from either the inhibition of neutral NaCl absorption in villous enterocytes or an increase in electrogenic chloride secretion in secretory crypt cells as a result of the opening of the cystic fibrosis transmembrane regulator (CFTR) chloride channel or both. The result is more secretion from the crypts than absorption in the villous that persists during fasting. The other components of the enterocyte ion secretory machinery are (1) the Na-K 2Cl cotransporter for the electroneutral chloride entrance into the enterocyte; (2) the Na-K pump, which decreases the intracellular Na^+ concentration, determining the driving gradient for further Na^+ influx; and (3) the K^+ selective channel, that enables K^+, once it has entered the cell together with Na^+, to return to the extracellular fluid.

Electrogenic secretion is induced by an increase of intracellular concentration of cyclic adenosine monophosphate, cyclic guanosine monophosphate, or calcium in response to microbial enterotoxins, or to endogenous endocrine or nonendocrine moieties, including inflammatory cytokines. Another mechanism of secretory diarrhea is the inhibition of the electroneutral NaCl-coupled pathway that involves the Na^+/H^+ and the Cl^-/HCO_3^- exchangers. Defects in the genes of the Na^+/H^+ and the Cl^-/HCO_3^- exchangers are responsible for congenital Na^+ and Cl^- diarrhea, respectively.

Osmotic diarrhea is caused by nonabsorbed nutrients in the intestinal lumen as a result of 1 or more of the following mechanisms: (1) intestinal damage (e.g., enteric infection); (2) reduced absorptive surface area (e.g., active celiac disease); (3) defective digestive enzyme or nutrient carrier (e.g., lactase deficiency); (4) decreased intestinal transit time (e.g., functional diarrhea); and (5) nutrient overload, exceeding the digestive capacity (e.g., overfeeding, sorbitol in fruit juice). Whatever the mechanism, the osmotic force generated by nonabsorbed solutes drives water into the intestinal lumen. A very common

example of osmotic diarrhea is lactose intolerance. Lactose, if not absorbed in the small intestine, reaches the colon, where it is fermented to short-chain organic acids, releasing hydrogen that is detected in the lactose breath test, and generating an osmotic overload. In many children chronic diarrhea may be caused by multiple mechanisms.

ETIOLOGY

Enteric infections are by far the most frequent cause of chronic diarrhea, both in developing and industrialized countries but, outcomes are often very different. In the former, comorbid conditions, such as HIV/AIDS, malaria, or tuberculosis, result in malnutrition that impairs the child's immune response, thereby potentiating the likelihood of prolonging diarrhea or acquiring another enteric infection. In children with HIV/AIDS, the viral infection itself impairs immune function and may trigger a vicious circle with malnutrition. Sequential infections with the same or different pathogens may also be responsible for chronic diarrhea.

In developing countries, enteroadherent *Escherichia coli* and *Giardia lamblia* have been implicated in chronic diarrhea, whereas, in developed countries, chronic infectious diarrhea usually runs a more benign course and the etiology is often viral, with a major role of rotavirus and norovirus (Table 341-1). Opportunistic microorganisms induce diarrhea exclusively, more severely or for more prolonged periods, in specific populations, such as immunocompromised children. Specific agents cause chronic diarrhea or exacerbate diarrhea in many chronic diseases. *Clostridium difficile* or cytomegalovirus act as opportunistic agents in oncologic patients as well as in patients with inflammatory bowel diseases. *Cryptosporidium* may induce severe and protracted diarrhea in AIDS patients.

In small intestinal bacterial overgrowth, diarrhea may be the result of either a direct interaction between the microorganism and the enterocyte or the consequence of deconjugation and dehydroxylation of bile salts, and hydroxylation of fatty acids due to an increased proliferation of bacteria in the proximal intestine. Postenteritis diarrhea syndrome is a clinicopathologic condition in which small intestinal mucosal damage persists after acute gastroenteritis. Sensitization to food antigens, secondary disaccharidase deficiency, persistent infections, reinfection with an enteric pathogen, or side effects of medication may be responsible for causing postenteritis diarrhea syndrome, thought to be related to perturbations of the intestinal microbiome. Functional diarrhea which may be related to the pathogenesis of irritable bowel syndrome may be caused by complications of an acute gastroenteritis. Noninfectious chronic diarrhea is the manifestation of a broad number of heterogeneous conditions that vary with the age of the patient (Table 341-2; see also Table 336-5).

Table 341-1 A Comparative List of Prevalent Agents and Conditions in Children with Persistent Infectious Diarrhea in Industrialized and Developing Countries

AGENT/DISEASE	
INDUSTRIALIZED COUNTRIES	**DEVELOPING COUNTRIES**
Clostridium difficile Enteroaggregative *Escherichia coli*	Enteroaggregative *E. coli* Atypical *E. coli* *Shigella* Heat stable/heat labile enterotoxin-producing *E. coli*
Astrovirus Norovirus Rotavirus* Small intestinal bacterial overgrowth (SIBO) Postenteritis diarrhea syndrome	Rotavirus* *Cryptosporidium* *Giardia lamblia* Tropical sprue

*More frequent in industrialized than in developing countries as agent of chronic diarrhea.

A reduction of intestinal absorptive surface is responsible for diarrhea in celiac disease, a genetically determined permanent gluten intolerance that affects as many as 1 in 100 individuals, depending on geographic origin. In the genetically susceptible host, gliadin, the major protein of gluten, reacts with the immune system to cause villous atrophy. The reduction of functional absorptive surface area is reversible upon restriction of gluten from the diet. Celiac disease presents with more severe intestinal symptoms in younger children. **Allergy to cow's milk protein** and other food proteins also may present during infancy with chronic diarrhea. Eosinophilic gastroenteritis is characterized by eosinophilic infiltration of the intestinal wall and is strongly associated with atopy. However, whereas diarrhea in food allergy responds to withdrawal of the responsible food, this does not always occur in eosinophilic gastroenteritis, in which immune suppression may be needed.

Lactose intolerance or carbohydrate malabsorption may be caused by a brush-border enzyme defect in lactase, sucrase-isomaltase, or to a defect in the sodium/glucose cotransporter protein (SGLT1) that is transcribed from the *SLC5A1* gene causing congenital glucose-galactose malabsorption. The result of these genetic mutations is chronic diarrhea. More commonly, lactose intolerance is secondary to lactase deficiency caused by intestinal mucosal damage. Depending on ethnicity, a progressive, age-related, loss of lactase activity may begin around age 7 yr and affects approximately 80% of the nonwhite population, and acquired hypolactasia may be responsible for chronic diarrhea in older children receiving cow's milk (adult-type lactase deficiency).

In older children and adolescents, **inflammatory bowel diseases, including Crohn disease, ulcerative colitis, and inflammatory bowel disease–undetermined,** cause chronic diarrhea that is often associated with abdominal pain, elevated inflammatory markers, and increased concentrations of fecal calprotectin or lactoferrin (see Chapter 336). The age of onset of inflammatory bowel disease is broad, with rare cases described in the 1st few mo of life, but the peak incidence in childhood occurring in adolescence. The severity of the symptoms is highly variable with a pattern characterised by long periods of well-being followed by exacerbations. Growth retardation and delays in sexual maturation may precede the onset of gastrointestinal symptoms by up to 18 mo.

Chronic diarrhea may be the manifestation of maldigestion caused by exocrine **pancreatic disorders**. In most patients with cystic fibrosis, exocrine pancreatic insufficiency results in steatorrhea and protein malabsorption. In Shwachman-Diamond syndrome, exocrine pancreatic hypoplasia may be associated with neutropenia, bone changes, and intestinal protein-losing enteropathy. Specific isolated pancreatic enzyme defects, such as lipase deficiency, result in fat and/or protein malabsorption. Familial pancreatitis, associated with a mutation in the trypsinogen gene, may be associated with exocrine pancreatic insufficiency and chronic diarrhea. Mutations in CFTR, CTRC, PRSS1, SPINK 1, and SPINK 5 are all associated with hereditary pancreatitis.

Liver disorders may lead to a reduction in the bile salts pool resulting in fat malabsorption. Bile acid loss may be associated with diseases affecting the terminal ileum, such as Crohn disease, or following ileal resection. In primary bile acid malabsorption, neonates and young infants present with chronic diarrhea and fat malabsorption caused by mutations of ileal bile transporter.

The most benign etiology of chronic diarrhea is nonspecific diarrhea that encompasses functional diarrhea (or toddler's diarrhea) in children younger than 4 yr of age and irritable bowel syndrome in those 5 yr of age and older. The diseases fall under the umbrella of functional disorders, in that in older children abdominal pain is often associated with diarrhea alternating with constipation and growth and weight gain are normal.

Diarrhea may be the result from an **excessive intake of fluid and carbohydrate**. If the child's fluid intake were >150 mL/kg/24 hr, fluid intake should be reduced not to exceed 90 mL/kg/24 hr. The child is often irritable in the 1st days of the fluid restriction; however, persistence results in a decrease in the stool frequency and volume. If the dietary history suggests that the child is ingesting significant amounts of fruit juice, especially apple juice, then the consumption of juice

Table 341-2 Main Etiologies of Noninfectious Chronic Diarrhea in Children Older and Younger Than 2 Yr of Age

ETIOLOGY	YOUNGER THAN 2 YR	OLDER THAN 2 YR
Abnormal digestive processes	Shwachman-Diamond syndrome, isolated pancreatic enzyme deficiency, chronic pancreatitis, Johanson-Blizzard syndrome, Pearson syndrome. Trypsinogen and enterokinase deficiency: chronic cholestasis; use of bile acids sequestrants; primary bile acid malabsorption	Cystic fibrosis, terminal ileum resection
Nutrient malabsorption	Congenital sucrase-isomaltase deficiency; congenital lactase deficiency; glucose-galactose malabsorption; fructose malabsorption; congenital short bowel	Hypoalactasia; acquired short bowel
Immune/inflammatory	Food allergy; autoimmune enteropathy; primary and secondary immunodeficiencies; IPEX syndrome	Celiac disease; eosinophilic gastroenteritis, inflammatory bowel diseases
Structural defects	Microvillus inclusion disease, tufting enteropathy, phenotypic diarrhea, heparan-sulphate deficiency, $\alpha_2\beta_1$ and $\alpha_6\beta_4$ integrin deficiency, lymphangiectasia, enteric anendocrinosis (neurogenin-3 mutation)	Rare
Defects of electrolyte and metabolite transport	Congenital chloride diarrhea, congenital sodium diarrhea, acrodermatitis enteropathica, selective folate deficiency, abetalipoproteinemia, activating guanylate cyclase mutation	Late onset chloride diarrhea
Motility disorders	Hirschsprung disease, chronic intestinal pseudoobstruction (neurogenic and myopathic)	Thyrotoxicosis
Neoplastic diseases	Neuroendocrine hormone-secreting tumors: Apudomas such as VIPoma, Zollinger- Ellison, and mastocytosis	Neuroendocrine hormone-secreting tumors: Apudomas such as VIPoma, Zollinger-Ellison, and mastocytosis
Diarrhea associated with exogenous substances	Excessive intake of carbonated fluid, foods or drinks containing sorbitol, mannitol, or xylitol; excessive intake of antacids or laxatives containing lactulose or $Mg(OH)_2$; excessive intake of methylxanthines-containing drinks (cola, tea, coffee)	Excessive intake of carbonated fluid, foods or drinks containing sorbitol, mannitol, or xylitol; excessive intake of antacids or laxatives containing lactulose or $Mg(OH)_2$; excessive intake of methylxanthines-containing drinks (cola, tea, coffee)
Chronic nonspecific diarrhea	Functional diarrhea*	Irritable bowel syndrome†

*Until 4 yr of age, according to Rome III criteria.
†Older than 5 yr of age according to Rome III criteria.
IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; VIPoma, vasoactive intestinal polypeptide tumor.

should be decreased. Sorbitol, which is a nonabsorbable sugar, is found in apple, pear, and prune juices, and often causes diarrhea in toddlers. Moreover, apple and pear juices contain higher amounts of fructose than glucose, a feature postulated to cause diarrhea in toddlers. In older children, irritable bowel syndrome is often associated with abdominal pain and may be related to anxiety, depression, and other psychologic disturbances.

The most severe etiology of chronic diarrhea includes a number of heterogeneous congenital conditions leading to syndromes related to **intractable diarrhea**. This is often the result of a permanent defect in the structure or function of the enterocyte, leading to progressive, potentially irreversible intestinal failure. The main etiologies of intractable diarrhea include structural enterocyte defects, disorders of intestinal motility, immune-based disorders, short gut syndrome, and disorders without demonstrable abnormalities.

Structural enterocyte defects are caused by specific molecular defects responsible for early onset, severe diarrhea. In microvillus inclusion disease, microvilli are sequestered in vacuoles as a consequence of autophagocytosis because of a defect in protein trafficking disrupting enterocyte polarity (Fig. 341-2). Intestinal epithelial dysplasia (or tufting enteropathy) is caused by focal crowding of enterocytes that produce epithelial abnormalities resembling tufts (tears). Abnormal deposition of laminin and heparan sulfate proteoglycan on the basement membrane has been detected in intestinal epithelia. An abnormal intestinal distribution of $\alpha_2\beta_1$ and $\alpha_6\beta_4$ integrins is implicated in tufting enteropathy. These ubiquitous proteins are involved in cell–cell and cell–matrix interactions, and play a crucial role in cell development and differentiation.

Electrolyte transport defects are a subgroup of structural enterocyte defects that include congenital chloride diarrhea, in which a mutation in the solute carrier family 26 member 3 gene *(SLC26A3)* leads to severe intestinal Cl^- malabsorption from a defect in or absence of the Cl^-/HCO_3^- exchanger. The consequent defect in bicarbonate secretion leads to metabolic alkalosis and acidification of the intestinal content, with further inhibition of Na^+/H^+ exchanger-dependent Na^+ absorption. Patients with congenital sodium diarrhea show similar clinical features, because of a defective Na^+/H^+ exchanger in the small and large intestine, leading to massive Na^+ fecal loss and severe acidosis. Familial diarrhea syndrome caused by a mutation guanylate cyclase-C is characterized by abdominal pain, dysmotility, and inflammation coupled with mild secretory diarrhea.

Disorders of intestinal motility include abnormal development and function of the enteric nervous system, such as in Hirschsprung disease and chronic idiopathic intestinal pseudoobstruction (which encompass both the neurogenic and the myogenic forms). Other motility disorders may be secondary to extraintestinal disorders, such as in hyperthyroidism and scleroderma. Motility disorders are associated with either constipation or diarrhea or both, with the former usually dominating the clinical picture.

Autoimmune processes may target the intestinal epithelium, alone or in association with extraintestinal symptoms. Autoimmune enteropathy is associated with the production of antienterocyte and antigoblet cell antibodies, primarily immunoglobulin A, but also immunoglobulin G, directed against components of the enterocyte brush-border or cytoplasm and by a cell-mediated autoimmune response with mucosal T-cell activation. An X-linked

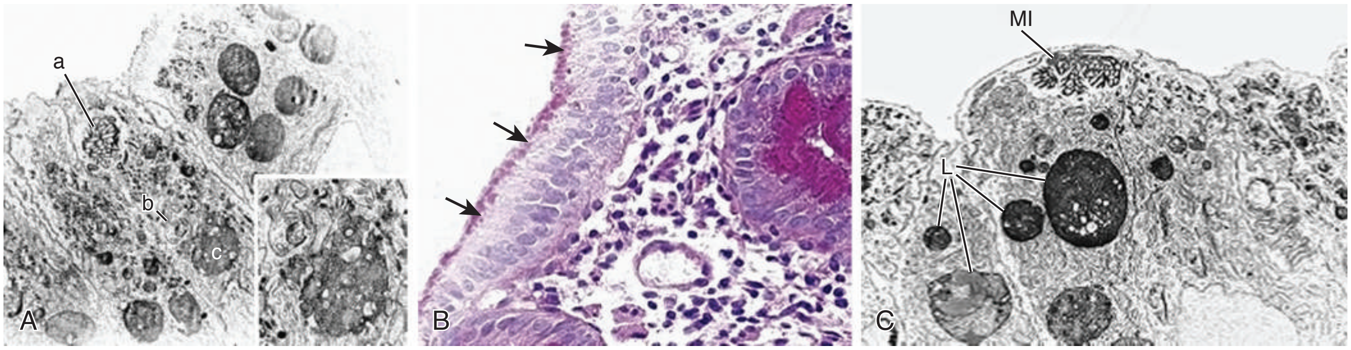

Figure 341-2 Microvillus inclusion disease. **A,** From top to bottom: microvillus inclusion *(a)*, a granule with few microvilli *(b)*, and a lysosome *(c)* detected in the same enterocyte. *Inset:* Higher magnification of *b* and *c* ×11,000, inset ×21,500. **B,** Microvillus inclusion disease. Periodic acid-Schiff (PAS) staining highlights abundant PAS-positive material *(arrows)* in the apical part of the enterocyte cytoplasm. **C,** Microvillus inclusion disease. The villous enterocyte lack brush-border microvilli, whereas their apical cytoplasm contains a microvillus inclusion *(MI)* and numerous lysosomes *(L)* ×5,500. *(**A** from Morroni M, Cangiotti AM, Guarino A, et al. Unusual ultrastructural features in microvillous inclusion disease: a report of two cases.* Virchows Arch *448:805–810, 2006.)*

immune-dysregulation, polyendocrinopathy, and enteropathy (IPEX syndrome) is associated with variable gene mutations and phenotypes of chronic diarrhea. Other immunoregulatory defects, found in patients with agammaglobulinemia, isolated immunoglobulin A deficiency, and combined immunodeficiency disorders, may result in persistent infectious diarrhea.

Phenotypic diarrhea, also defined as syndromic diarrhea or tricho-hepatoenteric syndrome, is a rare disease presenting with facial dysmorphism, woolly hair, severe diarrhea, and malabsorption (Fig. 341-3). Half of the patients have liver disease.

Short bowel syndrome is the single most frequent etiology of chronic diarrhea and intestinal failure (see Chapter 338.7). Many intestinal abnormalities such as stenosis, segmental atresia, and malrotation may require surgical resection, but the most frequent primary cause of short bowel is necrotizing enterocolitis. In these conditions, the residual intestine may be insufficient to carry on its digestive–absorptive functions. Rarely, a child may be born with a congenitally short small bowel resulting in delayed growth. In rare cases of severe chronic diarrhea, the gastrointestinal symptoms may be the initial manifestation of mitochondrial disease, carbohydrate deficient glycoproteins, or a primary immune deficiency. **Multiple food protein hypersensitivity** also is included in the list of causes of protracted diarrhea syndrome. The disease is believed to be the result of a reaction against specific proteins contained in foods. Diarrhea often resolves with fasting or when an amino-acid–based formula is started. Although most children with food intolerance in infancy are eventually able to resume a regular diet, some require restrictions throughout their lives. When the cause of the diarrhea remains undetermined and the clinical course is inconsistent with organic disorders, factitious disorder by proxy should be considered.

Figure 341-3 Phenotypic diarrhea. The child shows facial dysmorphism, hypertelorism, and woolly hair; etiology is unknown, but the presence of affected siblings suggests an autosomal recessive transmission.

GENETIC AND MOLECULAR BASIS OF THE PROTRACTED DIARRHEA SYNDROME

The genetic and molecular basis of many causes of protracted diarrhea have been identified recently and a new classification of congenital diarrheal disorders (CDDs) has been proposed (Table 341-3). CDDs are a group of rare, but severe enteropathies, with a similar clinical presentation despite a different outcome. However, diarrhea is the result of structural and functional abnormalities resulting in either secretory or osmotic diarrhea. Often diarrhea presents at birth or shortly thereafter, but in milder forms diarrhea may go unrecognized for years. CDDs are rare diseases, however in most specific disorders the specific genetic defect and transmission are known. Hereditary fructose intolerance is associated with mutations in the *ASDOB* gene that encodes for the aldolase B enzyme that is found primarily in the liver and is involved in the metabolism of fructose. Individuals with hereditary fructose intolerance may have nausea, abdominal pain/bloating, vomiting, diarrhea, and hypoglycemia. Continued ingestion of fructose results in hepatomegaly and eventually cirrhosis. The incidence of hereditary fructose intolerance is estimated to be 1 in 20,000-30,000. In contrast, fructose malabsorption is common in Western countries with estimates as high as 40% of the population. These individuals cannot absorb fructose and often develop bloating, abdominal pain, diarrhea, and flatulence. They do not have liver disease.

The incidence of other genetic disorders associated with CDD ranges from 1 in 2,500 for cystic fibrosis, 1 in 5,000 for sucrose-isomaltase deficiency, 1 in 60,000 for congenital lactase deficiency, to 1 in 400,000 to trichohepatoenteric syndrome. For most CDDs, such as polyendocrinopathy, X-linked (IPEX) syndrome, or autoimmune polyglandular syndrome type 1, the clinical application of exome

Table 341-3 Classification of Congenital Diarrheal Disorders Based on Their Molecular Defect and Their Inheritance

DEFECTS OF DIGESTION, ABSORPTION, AND TRANSPORT OF NUTRIENTS AND ELECTROLYTES

DISEASE	GENE		TRANSMISSION AND INCIDENCE	MECHANISM
	Name	Location		
Genes Encoding Brush-Border Enzymes				
Congenital lactase deficiency (LD)	*LCT*	2q21.3	AR, 1 in 60,000 in Finland; lower in other ethnic groups	Osmotic
Congenital sucrase-isomaltase deficiency (SID)	*SI*	3q26.1	AR, 1 in 5,000; higher incidence in Greenland, Alaska, and Canada	Osmotic
Congenital maltase-glucoamylase deficiency (MGD)	Not defined	—	Few cases described	Osmotic
Genes Encoding Membrane Carriers				
Glucose-galactose malabsorption (GGM)	*SLC5A1*	22q13.1	AR, few hundred cases described	Osmotic
Fructose malabsorption (FM)	Not defined	—	Up to 40%	Osmotic
Fanconi-Bickel syndrome (FBS)	*SLC2A2*	3q26.2	AR, rare, higher frequency in consanguineous	Osmotic
Acrodermatitis enteropathica (ADE)	*SLC39A4*	8q24.3	AR, 1 in 500,000	Osmotic
Congenital chloride diarrhea (CCD, DIAR 1)	*SLC26A3*	7q31.1	AR, sporadic; frequent in some ethnicities	Osmotic
Lysinuric protein intolerance (LPI)	*SLC7A7*	14q11.2	AR, about 1 in 60,000 in Finland and Japan; rare in other ethnic groups	Osmotic
Primary bile acid malabsorption (PBAM)	*SLC10A2*	13q33.1	AR	Secretory
Cystic fibrosis (CF)	*CFTR*	7q31.2	AR, 1 in 2,500	Osmotic
Genes Encoding Pancreatic Enzymes				
Enterokinase deficiency (EKD)	*PRSS7*	21q21	AR	Osmotic
Hereditary pancreatitis (HP)	*PRSS1* *SPINK1*	7q34 5q32	AR, cases with compound mutations in different genes; *SPINK1* mutations may also cause tropical pancreatitis	Osmotic
Congenital absence of pancreatic lipase (APL)	*PNLIP*	10q25.3	—	Osmotic
Genes Encoding Proteins of Lipoprotein Metabolism				
Abetalipoproteinemia (ALP)	*MTTP*	4q27	AR, about 100 cases described; higher frequency among Ashkenazi Jews	Osmotic
Hypobetalipoproteinemia (HLP)	*Apo B*	2p24.1	Autosomal codominant	Osmotic
Chylomicron retention disease (CRD)	*SAR1B*	5q31.1	AR, about 40 cases described	Osmotic
Genes Encoding Other Types of Proteins				
Congenital sodium diarrhea (CSD, DIAR 3)	*SPINT2* (only syndromic CSD)	19q13.2	AR	Osmotic
Shwachman-Diamond syndrome (SDS)	*SBDS*	7q11	AR	Osmotic
Activating GUCY2C mutation	Guanylate cyclase-C	Unknown	AD	Secretory
Genes Encoding for Other Enzymes				
Defect in triglyceride synthesis	*DGAT1*	Splice variant (chromosome 8, 145541756 A G) in the splice donor site 32 of exon 8, altering the invariant GT to GC	AR	Protein-losing enteropathy

DISEASE	OMIM NUMBER	TRANSMISSION AND INCIDENCE	MECHANISM
DEFECTS OF ENTEROCYTE DIFFERENTIATION AND POLARIZATION			
Microvillous inclusion disease (MVID, DIAR 2)	251850	AR; rare; higher frequency among Navajo	Secretory
Congenital tufting enteropathy (CTE, DIAR 5)	613217	AR; 1 in 50,000-100,000; higher among Arabians	Secretory
Trichohepatoenteric syndrome (THE)	222470	AR; 1 in 400,000	Secretory
DEFECTS OF ENTEROENDOCRINE CELL DIFFERENTIATION			
Congenital malabsorptive diarrhea (CMD, DIAR 4)	610370	AR; few cases described	Osmotic
Proprotein convertase 1/3 deficiency (PCD)	600955	AR	Osmotic
DEFECTS OF MODULATION OF INTESTINAL IMMUNE RESPONSE			
Autoimmune polyglandular syndrome type 1 (APS1)	240300	AR; AD (1 family)	Secretory
Immune dysfunction, polyendocrinopathy, X-linked (IPEX)	601410	X-linked (autosomal cases described), very rare	Secretory
IPEX-like syndrome	—	Not X-linked	Secretory

AD, autosomal dominant; AR, autosomal recessive.

Table 341-4 Degree of Malnutrition as Estimated by Visceral Protein Concentrations in Children with Chronic Diarrhea

VISCERAL PROTEIN	HALF-LIFE	NORMAL VALUES	MILD MALNUTRITION	MODERATE MALNUTRITION	SEVERE MALNUTRITION
Albumin	20 days	30-45 g/L	3.0-2.9 g/L	2.8-2.5 g/L	<2.5 g/L
Prealbumin	2 days	0.2-04 g/L	0.2-0.18 g/L	0.17-0.1 g/L	<0.1 g/L
Retinol binding protein	12 hr	2.6-7.6 g/L	2.5-2.0 g/L	1.9 -1.5 g/L	<1 g/L
Transferrin	8 days	218-411 µg/dL	200-150 µg/dL	149-100 µg/dL	<100 µg/dL
Serum iron	11-19 hr	16-124 µg/dL	15-13 µg/dL	12-10 µg/dL	<10 µg/dL

Consider also the concentrations of the following micronutrients: calcium, zinc, magnesium, iodine, vitamin A, vitamin C, vitamin B_1.

sequencing is likely to increase identification of more patients with these rare causes of chronic diarrhea.

Selected CDDs are more frequent in ethnic groups where consanguineous marriages are common, or in some geographic areas because of founder effects. For example, congenital lactase deficiency is more common in Finland; lysinuric protein intolerance has a higher incidence either in Finland and in Japan because of founder effect, and a specific mutation is typically found in each of the 2 ethnic groups. A defect in the *DGAT1* gene was identified using whole-exome sequencing in an Ashkenazi Jewish family and associated with the early onset of vomiting and nonbloody diarrhea with protein-losing enteropathy.

Most cases of protracted diarrhea syndrome are not easily treated. The natural history of protracted diarrhea is related to the primary intestinal disease and the specific defect in nutrient absorption. Treatment is more favorable for motility disorders and autoimmune enteropathy than for structural enterocyte defects. Children with motility disorders may have persistent symptoms, but they are rarely fatal; whereas children with structural enterocyte defects have a more severe course, poorer prognosis, and are more likely to be candidates for intestinal transplantation (see Chapter 339). Some late-onset CDDs may be relatively mild and are recognized only later in life.

EVALUATION OF PATIENTS

Because of the spectrum of etiologies, the medical approach should be based on diagnostic algorithms that begin with assessment for infectious causes, and then consider the age of the child, growth, and clinical and epidemiologic factors. Early onset may suggest a congenital or severe condition. In later infancy and up to 2 yr of age, infections and allergies are more common; inflammatory diseases are more frequent in older children and adolescents. Celiac disease and chronic nonspecific diarrhea should always be considered independently of age because of their relatively high frequency at all ages.

Specific clues in the family and personal history may provide useful indications, suggesting a congenital, allergic or inflammatory etiology. A history of polyhydramnios is consistent with congenital chloride-sodium diarrhea, or cystic fibrosis. An acute onset of diarrhea that runs a protracted course suggests post-enteritis diarrhea or small intestinal overgrowth or the onset of chronic nonspecific diarrhea (toddler's diarrhea). In children, with chronic nonspecific diarrhea there is often a history of an acute gastroenteritis. The association of diarrhea with specific foods may indicate a nutrient basis, such as intolerance to selected nutrients (fructose). Anthropometric evaluation is essential to understand if diarrhea has affected weight gain and growth. The amount of weight loss over time provides an estimate of the severity of diarrhea. Normal weight and growth strongly support functional diarrhea that may respond to simple dietary management.

Initial clinical examination should include the evaluation of general and nutritional status. Dehydration, marasmus, or kwashiorkor require prompt supportive interventions to stabilize the patient. Nutritional evaluation should start with the evaluation of the weight and height curves, and of the weight-for-height index to determine the impact of diarrhea on growth. Weight is generally impaired before height, but with time, linear growth also becomes affected, and both parameters may be equally abnormal in the long-term. Assessment of nutritional status includes a dietary history and biochemical and nutritional investigations. Caloric intake should be quantitatively determined and the relationship between weight modifications and energy intake should be carefully considered.

Biochemical markers may assist in grading malnutrition (Table 341-4) as the half-life of serum proteins may distinguish between short- and long-term malnutrition. Assessment of body composition may be performed by measuring mid-arm circumference and triceps skinfold thickness or, more accurately, by bioelectrical impedance analysis or dual-emission x-ray absorptiometry scans. Evaluation of micronutrient concentrations should always be considered. Zinc, magnesium, vitamin A, and folate deficiency are associated with chronic diarrhea and should be provided if needed.

Diagnosis of functional diarrhea is based on clinical assessment using established age-related criteria. It should be noted that a child with functional diarrhea may be inappropriately "treated" with a diluted hypocaloric diet in an effort to reduce the diarrhea, resulting in impaired growth.

The search for an etiology may be based on the relevant causes of diarrhea for the age of the child. Continued diarrhea with fasting or fecal electrolyte concentrations discriminate between secretory and osmotic diarrhea. Associated symptoms and selected investigations provide important diagnostic clues. Signs of general inflammation such as fever, mucoid or bloody stools, and abdominal pain may suggest inflammatory bowel disease. The presence of eczema or asthma is associated with an allergic disorder, whereas specific extraintestinal manifestations (arthritis, diabetes, thrombocytopenia, etc.) may suggest an autoimmune disease. Specific skin lesions may be suggestive of acrodermatitis enteropathica that might respond to zinc replacement. Typical facial abnormalities and woolly hair are associated with phenotypic diarrhea (see Fig. 341-3).

INVESTIGATIONS

Microbiologic investigation should include a thorough list of intestinal bacterial, viral, and protozoan pathogens. Proximal intestinal bacterial overgrowth may be determined using the hydrogen breath test, after an oral glucose or lactulose load, but either substrate may give false results.

Initial investigations of a child with chronic diarrhea should always include an assessment of intestinal inflammation using fecal calprotectin or lactoferrin, and serology for celiac disease (see Chapter 338.2). The role of a mucosal biopsy is determined by the noninvasive diagnostic evaluation in consultation with a pediatric gastroenterologist.

Noninvasive assessment of digestive-absorptive function and of intestinal inflammation plays a key role in the diagnostic work-up (Table 341-5). Abnormalities in the digestive–absorptive function tests suggest small bowel involvement, whereas intestinal inflammation, as demonstrated by increased fecal calprotectin or lactoferrin, supports colitis. Histology is important in establishing mucosal involvement, noting changes in the epithelial cells, or in identifying specific

Table 341-5 Noninvasive Tests for Intestinal Digestive–Absorptive Function and Inflammation

TEST	NORMAL VALUES	IMPLICATION
α_1-Antitripsin concentration	<0.9 mg/g	Increased intestinal permeability/protein loss
Steatocrit	<2.5% (older than 2 yr) fold increase over age-related values (younger than 2 yr)	Fat malabsorption
Fecal-reducing substances	Absent	Carbohydrate malabsorption
Elastase concentration	>200 µg/g	Pancreatic function
Chymotrypsin concentration	>7.5 units/g >375 units/24 hr	Pancreatic function
Fecal occult blood	Absent	Blood loss in the stools/inflammation
Fecal calprotectin concentration	<100 µg/g (in children to 4 yr of age) <50 µg/g (older than 4 yr)	Intestinal inflammation
Fecal leukocytes	<5/microscopic field	Colonic inflammation
Nitric oxide in rectal dialysate	<5 µM of NO_2^-/NO_3^-	Rectal inflammation
Dual sugar (cellobiose/mannitol) absorption test	Urine excretion ratio: 0.010 ± 0.018	Increased intestinal permeability
Xylose oral load	25 mg/dL	Reduced intestinal surface

intracellular inclusion bodies caused by pathogens, such as cytomegalovirus, or the presence of parasites. Electron microscopy is essential to detect subcellular structural abnormalities such as microvillous inclusion disease. Immunohistochemistry allows the study of mucosal immunity as well as of other cell types (smooth muscle cells and enteric neuronal cells).

Imaging has a major role in the diagnostic approach. Abdominal ultrasound may help in detecting liver and pancreatic abnormalities or an increase in distal ileal wall thickness that suggests inflammatory bowel disease. A preliminary plain abdominal x-ray is useful for detection of abdominal distention, suggestive of intestinal obstruction, or increased retention of colonic feces. Intramural or portal gas may be seen in necrotizing enterocolitis or intussusception. Structural abnormalities such as diverticula, malrotation, stenosis, blind loop, inflammatory bowel disease, as well as motility disorders, may be investigated through a barium meal and a small bowel follow-through. Capsule endoscopy allows the exploration of the entire intestinal tract searching for structural changes, inflammation or bleeding and the new SmartPill measures pressure, pH, and temperature as it moves through the gastrointestinal tract, assessing motility.

Specific investigations should be carried out for specific diagnostic indications. Prick and patch test may support a diagnosis of food allergy. However, elimination diet with withdrawal of the suspected harmful food from the diet and subsequent challenge is the most reliable strategy by which to establish a diagnosis. Bile malabsorption may be explored by the retention of the bile acid analog ^{75}Se-homocholic acid-taurine (^{75}SeHCAT) in the enterohepatic circulation. A scintigraphic examination, with radio-labeled octreotide is indicated in suspected APUD cell neoplastic proliferation. In other diseases, specific imaging techniques such as computed tomography, or nuclear magnetic resonance endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography may have important diagnostic value.

Once infectious agents have been excluded and nutritional assessment performed, a stepwise approach to the child with chronic diarrhea may be applied. The main causes of chronic diarrhea should be investigated, based on the features of the diarrhea and the specific nutrient(s) that is (are) affected. The use of whole-exome sequencing is of benefit in children suspected of having mendelian-related causes of chronic diarrhea. A step-by-step diagnostic approach is important to minimize the unnecessary use of invasive procedures as well as the cost, while optimizing the yield of the diagnostic work-up (Table 341-6).

TREATMENT

Chronic diarrhea associated with impaired nutritional status should always be considered a serious disease, and therapy should be started promptly. Treatment includes general supportive measures, nutritional rehabilitation, elimination diet, and medications. The latter include therapies for specific etiologies as well as interventions aimed at counteracting fluid secretion and/or promoting restoration of disrupted intestinal epithelium. Because death in most instances is caused by dehydration, replacement of fluid and electrolyte losses is the most important early intervention.

Nutritional rehabilitation is often essential and is based on clinical and biochemical assessment. Potentially harmful nutrients must be identified and avoided. In moderate to severe malnutrition, caloric intake may be progressively increased to 50% or more above the recommended dietary allowances. The intestinal absorptive capacity should be monitored by digestive function tests. In children with steatorrhea, medium-chain triglycerides may be the main source of lipids. A lactose-free diet should be started in all children with chronic diarrhea and is recommended by the World Health Organization. Lactose is generally replaced by maltodextrin or a combination of complex carbohydrates. A sucrose-free formula is indicated in sucrase-isomaltase deficiency. Semielemental or elemental diets have the dual purpose of overcoming food intolerance, which may be the primary cause of chronic diarrhea, particularly in infancy and early childhood, and facilitating nutrient absorption. The sequence of elimination should begin from less to more restricted diets, that is, cow's milk protein hydrolysate to amino-acid–based formulas, depending on the child's situation. In severely compromised infants, it may be prudent to start with amino-acid–based feeding.

When oral nutrition is not feasible or fails, enteral or parenteral nutrition should be considered. Enteral nutrition may be performed via nasogastric or gastrostomy tube and is indicated in a child who is not able to be fed orally, either because of inability to tolerate nutrient requirements or because of extreme weakness. Continuous enteral nutrition is effective in children with a compromised absorptive capacity, such as short bowel syndrome where the remaining mucosal surface is intact. In extreme wasting, enteral nutrition may not be tolerated and parenteral nutrition is required.

Micronutrient and vitamin supplementation are part of nutritional rehabilitation, especially in malnourished children in developing countries. Zinc supplementation is important in both prevention and therapy of chronic diarrhea, since it promotes ion absorption, restores

Table 341-6	Stepwise Diagnostic Approach to Children with Diarrhea
STEP 1 *Intestinal Microbiology* Stool cultures Microscopy for parasites Viruses H_2 breath test *Screening Test for Celiac Disease:* Serology according to age and level of IgA (including AGA IgA/IgG, EMA IgA/IgG, tTG IgA/IgG) *Noninvasive Tests for:* Intestinal function (including double sugar test, xylosemia, iron absorption test) Pancreatic function (amylase, lipase, fecal elastase) Intestinal inflammation (fecal calprotectin, rectal nitric oxide) *Tests for Food Allergy:* Prick/patch tests for foods *Abdominal Ultrasounds (Scan of Last Ileal Loop)*	STEP 2 *Evaluation of Intestinal Morphology:* Endoscopy and standard jejunal/colonic histology* Morphometry PAS staining Electron microscopy Imaging (upper or lower bowel series, capsule endoscopy) STEP 3 *Special Investigations:* Intestinal immunohistochemistry Antienterocyte antibodies Serum chromogranin and catecholamines Autoantibodies ^{75}SeHCAT measurement Brush-border enzymatic activities Motility and electrophysiologic studies

*The decision to perform an upper or a lower endoscopy may be supported by noninvasive tests.
AGA, antigliadin antibody; EMA, endomysial antibody; Ig, immunoglobulin; PAS, periodic acid–Schiff; ^{75}SeHCAT, ^{75}Se-homocholic acid-taurine; tTG, tissue transglutaminase.

Table 341-7 Treatment of Infectious Persistent Diarrhea

	FACTOR	INDICATIONS	DOSAGE	DURATION
Antibiotics	Trimethoprim-sulfamethoxazole	*Salmonella* spp., *Shigella*	10-50 mg/kg/day in 2 divided doses–daily os	7 days
	Azithromycin	*Shigella*	1° day: 12 mg/kg/day once–daily os 2°-5° days: 6 mg/kg/day once–daily os	5 days
	Ciprofloxacin		20-30 mg/kg/day in 2 divided doses–os or iv	7 days
	Ceftriaxone		50-100 mg/kg/day once–im or iv	7 days
	Erythromycin	*Campylobacter*	50 mg/kg/day in 2-3 divided doses–os	7 days
	Metronidazole	*Giardia, Entamoeba*	20-30 mg/kg/day in 2-3 divided doses–os	7 days Small intestinal bacterial overgrowth
Antiparasitic	Nitazoxanide Albendazole	*Amebiasis, Giardiasis, Cryptosporidiosis* and helminth infections	100 mg every 12 hr for children ages 12-47 mo 200 mg every 12 hr for children ages 4-11 yr 500 mg every 12 hr for children older than 11 yr 400 mg once	3 days
Probiotics	*Lactobacillus* GG		1-2 × 10^{11}–1 × 10^{11} CFU/day–os	For a minimum period of 7 days or until diarrhea stopped
	Saccharomyces boulardii		1 × 10^{10} germs live (500 mg)/day–os	For a minimum period of 7 days or till diarrhea stopped
Human serum immunoglobulin		Severe *Rotavirus* diarrhea	300 mg/kg single oral administration	
Antisecretory	Racecadotril	Secretory diarrhea	1.5 mg/kg every 8 hr–os	For a minimum period of 7 days or till diarrhea stopped
Adsorbents	Diosmectite		3-6 g every 12-24 hr–os	5 days

im, Intramuscular; iv, intravenouis; os, by mouth.

epithelial proliferation, and stimulates immune response. Nutritional rehabilitation has a general beneficial effect on the patient's general condition, intestinal function, and immune response.

Functional diarrhea in children may benefit from a diet based on the "4 F" principles (reduce fructose and fluids, increase fat and fiber). Probiotics have been used with some success as adjunctive therapy based on the evidence that changes in intestinal microflora might be beneficial in several other intestinal diseases.

Pharmacologic therapy includes antiinfectious drugs, immune suppression, and drugs that may inhibit fluid loss and promote cell growth. If a bacterial agent is detected, specific antibiotics should be prescribed. Empiric antibiotic therapy may be used in children with either small bowel bacterial overgrowth or with suspected infectious diarrhea. Table 341-7 summarizes the treatment of postinfectious persistent diarrhea. Immune suppression should be considered in selected conditions such as autoimmune enteropathy.

Treatment may be also directed at modifying specific pathophysiologic processes. Secretion of ions may be reduced by proabsorptive agents, such as the enkephalinase inhibitor racecadotril. In diarrhea caused by neuroendocrine tumors, microvillus inclusion disease and enterotoxin-induced severe diarrhea, a trial of somatostatin analog octreotide may be considered. Zinc promotes both enterocyte growth and ion absorption and may be effective when intestinal atrophy and ion secretion are associated. However, when therapeutic attempts have failed, the only option to avoid intestinal failure may be parenteral nutrition or eventually intestinal transplantation.

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341.1 Diarrhea from Neuroendocrine Tumors

Helen Spoudeas and David Branski

Rare tumors of the neuroendocrine cells of the gastroenteropancreatic axis and adrenal and extraadrenal sites derive from the APUD system. They are characterized by an excessive production of 1 or several peptides, which, when released into the circulation, exert their endocrine effects and can be measured by radioimmunologic methods (in the plasma or as their urinary metabolites) and hence act as tumor markers. In clinically functioning tumors, the hypersecretion causes a recognizable syndrome that can include watery diarrhea. Though rare, neuroendocrine tumor (NET) should be considered a potential cause in patients with a particularly severe or chronic course (resulting in electrolyte and fluid depletion), associated flushing, palpitations, or bronchospasm, or a positive family history of multiple endocrine neoplasia 1 or 2 syndromes (Table 341-8).

Depending on the tumor type, the peptide marker(s) in the plasma and/or the 24-hr urinary metabolite(s) measured (on 2 occasions), form the basis of the biochemical diagnosis, the prognosis (tumor load) and treatment monitoring. Baseline tests should include plasma chromogranin A and urinary 5-hydroxyindoloacetic acid, other specific biochemistry being guided by the suspected syndrome (see Table 341-8). Carcinoid tumors are gastroenteropancreatic NETs, typically of the midgut (rather than fore- or hindgut), which may cause flushing and bronchospasm in addition to diarrhea and which, because of their portal drainage, are the most prone to late presentation and malignancy. Localization of any NET is best achieved with a multimodality approach at a center of excellence. Thus whole-body CT, MRI, and somatostatin receptor scintigraphy may be required (because nearly all NETs express membrane receptors for small peptides, e.g., somatostatin), with gallium-68 positron emission tomography/CT recommended for detecting an unknown primary. Long-acting somatostatin analogs might also have a role in palliation.

Tumor resection is the treatment of choice but is potentially hazardous and can precipitate life-threatening adrenergic crises; it should only be undertaken by an endocrine surgeon with experience under carefully controlled medical and anesthetic conditions and in conjunction with an endocrinologist. Tumor histochemistry will confirm the NET type and classification of NETs should be based on the World Health Organization 2010 Union for International Cancer Control TNM criteria (7th edition). This diagnosis in a child should prompt a genetic referral to exclude a tumor predisposition syndrome in which the child is the index case and tumor registration. Management and follow-up is multidisciplinary and should be undertaken in an age-appropriate setting with access to adult specialists with expertise in these rare conditions.

Table 341-8 Diarrhea Caused by Neuroendocrine Tumors

TUMOR AND CELL TYPE	SITE	MARKERS	SIGNS OF HORMONE HYPERSECRETION	THERAPY
Carcinoid	Intestinal argentaffin cells, typically midgut, also foregut and hindgut, ectopic bronchial tree	**Serotonin (5-HT), urine 5-HIAA**[†] (diagnostic) Also produce substance P, neuropeptide K, somatostatin, VIP Chromogranin A	Secretory diarrhea, crampy abdominal pain, flushing, wheezing, (and cardiac valve damage if foregut site)	Resection Somatostatin analog, (palliative) Genetic MEN-1
Gastrinoma, Zollinger-Ellison syndrome	Pancreas, small bowel, liver and spleen	**Gastrin**	Multiple peptic ulcers, secretory diarrhea	H_2-blockers, PPI, tumor resection, (gastrectomy) Genetic MEN-1
Mastocytoma	Cutaneous, intestine, liver, spleen	**Histamine**, **VIP**	Pruritus, flushing, apnea If VIP, diarrhea	H_1- and H_2-blockers, cromolyn, steroids, resection if solitary
Medullary carcinoma	Thyroid C-cells	**Calcitonin**, **VIP**, **prostaglandins**	Secretory diarrhea	Radical thyroidectomy ± lymphadenectomy (genetic MEN-2A/B, familial MTC)
Ganglioneuroma, pheochromocytoma, ganglioneuroblastoma, neuroblastoma	Chromaffin cells; abdominal > other sites; extraadrenal or adrenal	**Metanephrines** and **catecholamines**, **VIP** VMA, HMA in neuroblastoma	Hypertension, tachycardia, paroxysmal palpitations, sweating, anxiety, watery diarrhea*	Perioperative α-adrenergic (BP) and β-adrenergic blockade with volume support tumor resection Genetic MEN-2 (*RET* gene), VHL, NF-1, SDH
Somatostatinoma	Pancreas	**Somatostatin**	Secretory diarrhea, steatorrhea, cholelithiasis, diabetes	Resection Genetic MEN-1
VIPoma	Pancreas	**VIP**, **prostaglandins**	Secretory diarrhea, achlorhydria, hypokalemia	Somatostatin analogs, resection Genetic MEN-1

*Diarrhea has been reported only in adult patients with pheochromocytoma.

[†]Bold indicates major markers.

BP, blood pressure; H_1, histamine receptor type 1; H_2, histamine receptor type 2; HMA, homovanillic acid; MEN-1, multiple endocrine neoplasia type 1; MTC, medullary thyroid carcinoma; NF-1, neurofibromatosis type 1; PPI, proton pump inhibitor; SDH, succinate dehydrogenase; VHL, von Hippel-Lindau disease; VIP, vasoactive intestinal polypeptide; VMA, vanillylmandelic acid.

Adapted from Spoudeas HA, editor: Paediatric endocrine tumours. A multidisciplinary consensus statement of best practice from a working group convened under the auspices of the British Society of Paediatric Endocrinology and Diabetes (BSPED) and the United Kingdom Children's Cancer Study Group (UKCCSG), *Crawley, West Sussex, 2005, Novo Nordisk.*

Chapter 342

Functional Abdominal Pain (Nonorganic Chronic Abdominal Pain)

Raman Sreedharan and Chris A. Liacouras

Recurrent abdominal pain in children was defined as at least 3 episodes of pain over at least 3 mo that interfered with function. In many situations the term *recurrent abdominal pain* was used synonymously with *functional abdominal pain*. Other terms, such as *chronic abdominal pain, nonorganic abdominal pain*, and *psychogenic abdominal pain*, that were also used for describing abdominal pain in children, led to clinical confusion. The American Academy of Pediatrics Subcommittee on Chronic Abdominal Pain and the North American Society for Pediatric Gastroenterology Hepatology and Nutrition Committee on Abdominal Pain suggested that the term recurrent abdominal pain no longer be used. Table 342-1 outlines the recommended clinical definitions for long-lasting intermittent or constant abdominal pain by the same committees.

Chronic abdominal pain can be organic or nonorganic, depending on whether a specific etiology is identified. Nonorganic abdominal pain or functional abdominal pain refers to pain without evidence of anatomic, inflammatory, metabolic, or neoplastic abnormalities. **Functional gastrointestinal disorders (FGIDs)** are a group of gastrointestinal (GI) disorders that include variable combinations of chronic or recurrent GI symptoms not explained by structural or biochemical abnormalities. The Rome Committee updates and modifies the information on FGIDs for clinical and research purposes. The Rome III process had 2 pediatric subcommittees based on age range: Neonate/Toddler (0-4 yr) and Child/Adolescent (4-18 yr). The Child/Adolescent committee categorized abdominal pain–related FGIDs under Category H2 (Table 342-2). Table 342-3 defines the Rome III criteria for the diagnosis of Childhood Functional Abdominal Pain (category H2d) and the Childhood Functional Abdominal Pain Syndrome (category H2d1).

The exact incidence and prevalence of chronic abdominal pain is not known. There are reports of chronic abdominal pain affecting 9-15% of children. There are also reports that 13% of middle school and 17% of high school children have weekly complaints of abdominal pain.

Table 342-1 Recommended Clinical Definitions of Long-Standing Intermittent or Constant Abdominal Pain in Children

DISORDER	DEFINITION
Chronic abdominal pain	Long-lasting intermittent or constant abdominal pain that is functional or organic (disease based)
Functional abdominal pain	Abdominal pain without demonstrable evidence of pathologic condition, such as anatomic metabolic, infectious, inflammatory or neoplastic disorder. Functional abdominal pain can manifest with symptoms typical of functional dyspepsia, irritable bowel syndrome, abdominal migraine or functional abdominal pain syndrome
Functional dyspepsia	Functional abdominal pain or discomfort in the upper abdomen
Irritable bowel syndrome	Functional abdominal pain associated with alteration in bowel movements
Abdominal migraine	Functional abdominal pain with features of migraine (paroxysmal abdominal pain associated with anorexia, nausea, vomiting or pallor as well as maternal history of migraine headaches)
Functional abdominal pain syndrome	Functional abdominal pain without the characteristics of dyspepsia, irritable bowel syndrome, or abdominal migraine

Adapted from Di Lorenzo C, Colletti RB, Lehmann HP, et al; American Academy of Pediatrics Subcommittee on Chronic Abdominal Pain; NASPGHAN Committee on Abdominal Pain: Chronic abdominal pain in children: a clinical report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, J Pediatr Gastroenterol Nutr *40(3):245–248, 2005.*

Table 342-2 Childhood Functional GI Disorders: Child/Adolescent (Category H)

H1. Vomiting and aerophagia
H1a. Adolescent rumination syndrome
H1b. Cyclic vomiting syndrome
H1c. Aerophagia
H2. Abdominal pain—related functional gastrointestinal disorders
H2a. Functional dyspepsia
H2b. Irritable bowel syndrome
H2c. Abdominal migraine
H2d. Childhood functional abdominal pain
H2d1. Childhood functional abdominal pain syndrome
H3. Constipation and incontinence
H3a. Functional constipation
H3b. Nonretentive fecal incontinence

Adapted from Rome Foundation: Rome III disorders and criteria. *www.romecriteria.org/criteria/*.

Table 342-3 Rome III Criteria for Childhood Functional Abdominal Pain H2d and Childhood Functional Abdominal Pain Syndrome H2d1

H2d. CHILDHOOD FUNCTIONAL ABDOMINAL PAIN

Diagnostic criteria* must include **all** of the following:
- Episodic or continuous abdominal pain
- Insufficient criteria for other functional gastrointestinal disorders
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

H2d1. CHILDHOOD FUNCTIONAL ABDOMINAL PAIN SYNDROME

Diagnostic criteria* must satisfy criteria for childhood functional abdominal pain and have at least 25% of the time **one or more** of the following:
- Some loss of daily function
- Additional somatic symptoms such as headache, limb pain, or difficulty sleeping

*Criteria fulfilled at least once per week for ≥2 mo prior to diagnosis.
Adapted from Rome Foundation: Rome III disorders and criteria. *http://www.romecriteria.org/criteria/*.

PATHOPHYSIOLOGY

The symptoms of FGIDs may be the result of dysfunctions of the intestinal sensory and motor systems. The pathophysiology of functional abdominal pain is complex and not fully understood. Visceral hypersensitivity and motility disturbances are thought to be involved in functional abdominal pain. The traditional concept that motility disorders alone have an important role in functional pain has not been confirmed. It is believed that visceral hypersensitivity leading to abnormal bowel sensitivity to stimuli (physiologic, psychologic, noxious) might have a more dominant role in functional abdominal pain. Visceral hypersensitivity could be the result of abnormal interpretation of normal signals by the brain or aberrant signals sent to the brain or a combination. Intestinal pain receptors respond to mechanical and/or chemical stimuli. The visceral receptors can respond to both mechanical and chemical stimuli, but the mucosal receptors are primarily stimulated by chemical stimuli.

The viscera are innervated by dual set of nerves (vagal and splanchnic spinal nerves or pelvic and splanchnic spinal nerves). The spinal afferents carry impulses to the spinal cord. The dorsal horn of the spinal cord regulates conduction of impulses from peripheral nociceptive receptors to the spinal cord and brain, and the pain experience is further influenced by cognitive and emotional centers. Chronic peripheral nervous system pain can produce increased neural activity in higher central nervous system centers, leading to perpetuation of pain. Psychosocial stress can affect pain intensity and quality through these mechanisms. The child's response to pain can be influenced by stress, personality type, and the reinforcement of illness behavior within the family. The autonomic and enteric nervous systems can overlie the initiation, perception, and perpetuation of pain.

A normal functioning enteric nervous system (ENS) is important for coordination of intestinal motility, secretion, and blood flow. Abnormalities of the ENS may be an underlying factor for functional abdominal pain. Inflammation of the intestine and its role in the pathogenesis of functional abdominal pain could be a result of the effects of the inflammatory mediators and cytokines (released by the various inflammatory cells) on the ENS. The dysregulation in the brain–gut interactions can also lead to functional abdominal pain. The role of certain triggers for pain, such as lactose, sorbitol, fructose, bile acids, or fatty acids, could be a result of the altered sensitivity or motor function, because some patients have relief when eliminating these from their diet. Altered intestinal permeability enabling passage of food antigens into the mucosa leading to prolonged stimulation of the intestinal mucosal immune system and the ENS is also a possible cause for functional abdominal pain.

EVALUATION AND DIAGNOSIS

While evaluating a patient with chronic abdominal pain, distinguishing organic pain and functional pain can be challenging. A wide range of potential organic causes of chronic abdominal pain (see Table 306-13) must be considered before establishing a diagnosis of functional pain (nonorganic). Frequently cited causes of chronic abdominal pain include constipation, esophagitis, gastritis, inflammatory bowel disease, and possibly giardiasis. There is little evidence that the frequency, severity, or location of the pain helps to distinguish between organic and nonorganic pain. It is controversial whether nighttime awakening because of pain is concerning for organic disorders or if it can also be seen with functional pain syndromes.

Children with chronic abdominal pain might have associated headaches, anorexia, nausea, vomiting, excessive gas, diarrhea or constipation, and joint pain, but this does not help distinguish between functional and organic disorder. Negative lifestyle events and high life stress levels also do not help to distinguish organic and nonorganic pain, despite several reports of higher levels of life stress in children with chronic abdominal pain. Daily stressors may increase the likelihood for pain episodes, but there is no evidence that psychologic issues distinguishes between organic and nonorganic abdominal pain. Nonetheless, it is important to investigate and manage the psychologic factors because there is evidence suggesting that children with chronic abdominal pain have more anxiety and depression symptoms. Whether this causes pain or is the result of pain is not known.

Children with functional pain do not have higher levels of conduct disorder or oppositional behavior compared to the controls but they can be more prone to emotional symptoms or psychiatric disorders later in life. Parents of patients with functional abdominal pain have more symptoms of somatization, anxiety, and depression. Both the family and the affected child (when the child gets to adult age) have a higher incidence of **irritable bowel syndrome (IBS)**.

A thorough history and physical examination will identify the alarm symptoms and signs (Tables 342-4 and 342-5). The presence of alarm symptoms and signs warrants further investigation. The absence of alarm symptoms and signs, a normal physical examination, and a normal stool Hemoccult test is sufficient for an initial diagnosis of functional abdominal pain. The laboratory, radiologic, or endoscopic approach to children with chronic abdominal pain should be individualized, depending on the findings suggested by a detailed history and physical examination.

Laboratory studies may be unnecessary if the history and physical examination lead to a diagnosis of functional abdominal pain. Nonetheless, medical tests can reassure the patient and family, and at times the physician, if there is significant functional disability and poor quality of life. A complete blood cell count, sedimentation rate, C-reactive protein, basic chemistry panel, celiac panel, stool culture, stool test for ova and parasites, and urinalysis are reasonable screening studies. *The risk of celiac disease may be 4 times higher in these patients compared with the general population.* Elevated stool calprotectin levels usually suggest an inflammatory etiology.

If indicated, an ultrasound examination of the abdomen can give information about kidneys, gallbladder, and pancreas; with lower

Table 342-4	Alarm Symptoms Usually Needing Further Investigations
Pain that wakes up the child from sleep	
Persistent right upper or right lower quadrant pain	
Significant vomiting (bilious vomiting, protracted vomiting, cyclical vomiting, or worrisome pattern to the physician)	
Unexplained fever	
Genitourinary tract symptoms	
Dysphagia	
Chronic severe diarrhea or nocturnal diarrhea	
Gastrointestinal blood loss	
Involuntary weight loss	
Deceleration of linear growth	
Delayed puberty	
Family history of inflammatory bowel disease, celiac disease, and peptic ulcer disease	

Table 342-5	Alarm Signs Usually Needing Further Investigations
Localized tenderness in the right *upper* quadrant	
Localized tenderness in the right *lower* quadrant	
Localized fullness or mass	
Hepatomegaly	
Splenomegaly	
Jaundice	
Costovertebral angle tenderness	
Arthritis	
Spinal tenderness	
Perianal disease	
Abnormal or unexplained physical findings	
Hematochezia	
Anemia	

abdominal pain, a pelvic ultrasonogram may be indicated. An upper GI x-ray series is indicated if one suspects a disorder of the stomach or small intestine.

Helicobacter pylori infection does not seem to be associated with chronic abdominal pain, but in patients with symptoms suggesting gastritis or ulcer, an *H. pylori* test (fecal *H. pylori* antigen) may be performed. Breath hydrogen testing is done for ruling out lactose or sucrose malabsorption. Lactose intolerance is so common that the finding may be coincidental, and the clinician must be cautious in attributing chronic abdominal pain to this condition.

Esophagogastroduodenoscopy is indicated with symptoms that suggest persistent upper GI pathology. In the absence of this suspicion, esophagogastroduodenoscopy is unlikely to identify an abnormality and is usually not necessary.

TREATMENT

Making a positive diagnosis of functional abdominal pain is important and can be done by the primary care pediatrician in most 4-18 yr old children with chronic abdominal pain if there are no alarm symptoms or signs, a normal physical examination, and a negative stool occult blood test. In practice, on many occasions children do not get a conclusive diagnosis of functional abdominal pain. This can lead to unwarranted referrals and increased anxiety to the patient and the family. Even if a diagnostic evaluation is initiated during the initial office visit, a discussion about functional abdominal pain as the most likely diagnosis during that visit will help the patient and family to understand the diagnosis better. Close following and counseling by one consistent healthcare provider is essential.

The most important component of the treatment is reassurance and education of the child and family. The child and family need to be reassured that no evidence of a serious underlying disorder is present. The family and the child with functional pain might worry about the inability to identify an organic cause and may be resistant to a diagnosis of nonorganic disease. Explanation in simple language that although the pain is real, there is no underlying serious disorder usually alleviates the anxiety in the patient and family. Children of families that do not accept a functional cause of the symptoms are more likely to have persistent somatic complaints and school absences. The parents should be instructed to avoid reinforcing the symptoms with secondary gain. If children have missed school or have been removed from routine activities because of the pain, it is important that they return to regular activities.

Treatment goals should be set for return to function and minimizing pain. Complete disappearance of pain would be an unreasonable goal to set. Cognitive-behavioral therapy is helpful in the short term for managing pain and functional disability (Table 342-6). Biofeedback, guided imagery, and relaxation techniques have been useful in some children with functional pain. Even though studies do not show consistent benefits from medications, time-limited use of medications is usually part of the multidisciplinary approach. The commonly used medications include acid suppressants for dyspepsia symptoms, antispasmodics, and low-dose amitriptyline. For chronic abdominal pain with IBS symptoms, antidiarrheals and nonstimulating laxatives are used. Peppermint oil for 2 wk improves IBS symptoms in children. There is no evidence that a lactose-restricted diet or fiber supplements decrease the frequency of attacks in chronic abdominal pain in children. Proton pump inhibitors or visceral muscle relaxants (anticholinergics) are used empirically but are often unhelpful in the absence of specific indication.

Irritable Bowel Syndrome

IBS is characterized as a chronic FGID associated with abdominal pain or discomfort and altered bowel function without evidence of an inflammatory, anatomic, metabolic, or neoplastic process. Table 342-7 presents the Rome III diagnostic criteria for diagnosing IBS in children and adolescents.

Abdominal pain is episodic, cramping, or aching, usually in the lower abdomen, and often relieved by defecation. There may be abdominal discomfort, bloating, and flatulence. Diarrhea and constipation alone or in an alternating pattern must be present. The diarrhea is often watery and frequent and is associated with pain, the passage of mucus per rectum, and a feeling of incomplete emptying. The constipation is associated with a decreased stooling frequency and the passage of hard stools. Symptoms may be traced back to childhood or following an episode of presumed bacterial or viral gastroenteritis. It is important to rule out organic causes of abdominal pain and altered bowel patterns, especially celiac disease, even in the absence of the classic features of this disease.

Many dietary modifications have been suggested for relief of symptoms but not proven. Restriction of dietary fermentable oligosaccharides, disaccharides, monosaccharaides, and polyols in some studies have shown symptom relief.

Table 342-7 Rome III Criteria for Child/Adolescent Irritable Bowel Syndrome H2b

Diagnostic criteria* must include **all** of the following:
1. Abdominal discomfort† or pain associated with 2 or more of the following at least 25% of the time:
   a. Improvement with defecation
   b. Onset associated with a change in frequency of stool
   c. Onset associated with a change in form (appearance) of stool
2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

*Criteria fulfilled at least once per week for at least 6 mo prior to diagnosis.
†"Discomfort" means an uncomfortable sensation not described as pain.
Adapted from Rome Foundation: Rome III disorders and criteria. *http://www.romecriteria.org/criteria/*

Table 342-6 Effectiveness of Treatments for Abdominal Pain in Children

THERAPY	DEFINITION OF DISORDER	EFFECTIVENESS
Cognitive behavioral (family) therapy	Recurrent abdominal pain	Beneficial
Famotidine	Recurrent abdominal pain and dyspeptic symptoms	Inconclusive
Added dietary fiber	Recurrent abdominal pain	Unlikely to be beneficial
Lactose-free diet	Recurrent abdominal pain	Unlikely to be beneficial
Peppermint oil	Irritable bowel syndrome	Likely to be beneficial
Amitriptyline	Functional gastrointestinal disorders, irritable bowel syndrome	Inconsistent results
Lactobacillus GG	Irritable bowel syndrome using Rome III criteria	Unlikely to be beneficial

The effectiveness of analgesics, antispasmodics, sedatives, and antidepressants is currently unknown.
From Berger MY, Gieteling MJ, Benninga MA: Chronic abdominal pain in children, BMJ *334:997–1002, 2007.*

Probiotics are reported to be helpful in diarrhea predominant IBS, but larger trials are necessary to prove probiotics are beneficial. Management focuses on the dominant symptoms. Pain has been managed with cognitive-behavioral therapy, pain clinic referrals, peppermint, antispasmodic agents, and tricyclic antidepressant agents (amitriptyline). Diarrhea has been managed with loperamide, oral nonabsorbable antibiotics, and 5-HT_3 antagonists (alosetron). Constipation is managed with fiber (psyllium), increased fluid intake, lactulose, 5-HT_4 agonists (tegaserod), and selective C2 chloride channel–activating agents. In all medication trials, there is often a high response to placebo.

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Chapter 343
Acute Appendicitis
John J. Aiken and Keith T. Oldham

Acute appendicitis remains the most common acute surgical condition in children and a major cause of childhood morbidity. While prompt appendectomy remains the mainstay of treatment, management has changed substantially in the past several decades with improved antibiotic regimens, advances in imaging techniques, percutaneous drainage procedures by interventional radiologists, initial nonoperative management in select cases, and the use of laparoscopy. Approximately 100,000 children are treated in children's hospitals for appendicitis each year. The incidence of appendicitis increases with age, from a rate of 1-2 per 10,000 children from birth to 4 yr of age, to a rate of 19-28 per 10,000 children younger than age 14 yr annually. Children have a lifetime risk of ≈7% and appendicitis is diagnosed in 1-8% of children presenting to the emergency department for evaluation of abdominal pain. The misdiagnosis of appendicitis is second only to meningitis as a cause of medical malpractice suits in pediatric emergency care. Mortality is low (<1%), but morbidity remains high, mostly in association with complicated (perforated) appendicitis. Advances in surgical (laparoscopy) and imaging technology have significantly escalated treatment-related costs without demonstrable improvement in patient outcomes. In addition, there are marked variations in practice patterns and resource utilization in the evaluation and management of appendicitis. Children have a higher perforation rate than adults and up to 40% of children present with complicated disease.

PATHOLOGY

The clinical entity of acute appendiceal inflammation followed by perforation, abscess formation, and peritonitis is most likely a disease of multiple etiologies, the final common pathway of which involves invasion of the appendiceal wall by bacteria. One pathway to acute appendicitis begins with luminal obstruction; inspissated fecal material, lymphoid hyperplasia, ingested foreign body, parasites, and tumors have been implicated. Obstruction of the appendiceal lumen initiates a progressive cascade including increasing intraluminal pressures from bacterial proliferation and continued secretion of mucus, elevated intraluminal pressure, lymphatic and venous congestion and edema, impaired arterial perfusion, ischemia of the wall of the appendix, bacterial invasion of the appendiceal wall, and necrosis. This progression correlates with the clinical disease progression from simple appendicitis to gangrenous appendicitis and, thereafter, appendiceal perforation. Submucosal lymphoid follicles, which can obstruct the appendiceal lumen, are few at birth but multiply steadily during childhood, reaching a peak in number during the teen years, when acute appendicitis is most common, and declining after age 30 yr. Because of this prominence of lymphoid tissue, some have hypothesized that the appendix may have an immune function similar to that of the thymus or bursa of Fabricius. Fecaliths and appendicitis are more common in developed countries with refined, low-fiber diets than in developing countries with a high-fiber diet; no causal relationship has been established between lack of dietary fiber and appendicitis.

The finding that <50% of specimens from cases of acute appendicitis demonstrate luminal obstruction on radiographic, gross, or pathologic examination has prompted investigations of alternative etiologies. Enteric infection likely plays a role in many cases in association with mucosal ulceration and invasion of the appendiceal wall by bacteria. Bacteria such as *Yersinia*, *Salmonella,* and *Shigella* spp., and viruses such as infectious mononucleosis, mumps, coxsackievirus B, and adenovirus, are implicated. In addition, case reports demonstrate the occurrence of appendicitis from ingested foreign bodies, in association with carcinoid tumors of the appendix or *Ascaris* and following blunt abdominal trauma. Children with cystic fibrosis have an increased incidence of appendicitis; the cause is believed to be the abnormal thickened mucus. Appendicitis in neonates is rare and warrants diagnostic evaluation for cystic fibrosis and Hirschsprung disease.

A primary focus in the management of acute appendicitis is avoidance of sepsis and the infectious complications leading to increased morbidity, mostly seen in association with perforation. Bacteria can be cultured from the serosal surface of the appendix before microscopic or gross perforation and bacterial invasion of the mesenteric veins can result in portal vein or superior mesenteric vein sepsis (pylephlebitis), thrombosis, and liver abscess. Subsequent to perforation, the microbiologic fecal contamination may be localized to the right lower quadrant (RLQ) or pelvis by the omentum and adjacent loops of bowel, resulting in a localized abscess or inflammatory mass (phlegmon), or, alternatively, the fecal contamination can spread throughout the peritoneal cavity, causing diffuse peritonitis. Young children typically have a poorly developed omentum and are often unable to control the local infection. Perforation and abscess formation with appendicitis can lead to fistula formation in adjacent organs, scrotal cellulitis and abscess through a patent processus vaginalis (congenital indirect inguinal hernia), or small bowel obstruction.

CLINICAL FEATURES

Appendicitis is most common in older children, with peak incidence between the ages of 12 and 18 yr; it is rare in children younger than 5 yr of age (<5% of cases) and extremely rare (<1% of cases) in children younger than 3 yr of age. It affects boys slightly more often than girls and whites more often than blacks in the United States. There is a seasonal peak incidence in autumn and spring. There appears to be a familial predisposition in some cases, particularly in children in whom appendicitis develops before age 6 yr. Perforation in appendicitis is more common in children compared to adults, particularly in young children; with perforation rates as high as 82% for children younger than 5 yr and approaching 100% in infants. There is an increased incidence of perforated appendicitis in children of minority race and children with Medicaid health insurance.

Appendicitis in children has an immensely broad spectrum of clinical presentation. The signs and symptoms can be classic or often atypical and quite variable depending on the timing of presentation, the patient's age, the location of the appendix, and individual variability in the evolution of the disease process. Children early in the disease process can appear well and demonstrate minimal symptoms, subtle findings on physical examination, and normal laboratory studies; those with perforation and advanced peritonitis often demonstrate severe illness with bowel obstruction, renal failure, and septic shock.

While the classic presentation of acute appendicitis is well described, this represents <50% of cases; therefore, the majority of cases of appendicitis have an "atypical" presentation. The illness typically begins insidiously with a brief (several hours) period of generalized malaise and anorexia; the child does not appear ill and the family is not likely to seek consultation assuming the child has "stomach flu" or a viral syndrome. Unfortunately, if the diagnosis is appendicitis, the illness escalates rapidly with progressive abdominal pain followed by vomiting, and appendiceal perforation is likely to occur within 48 hr of the

onset of illness. The opportunity for diagnosis before perforation in acute appendicitis in children is generally brief (~36-48 hr).

Abdominal pain is consistently the primary and often the first symptom; beginning shortly (hours) after the onset of illness. As with other visceral organs, there are no somatic pain fibers within the appendix; therefore, early appendiceal inflammation results in pain which is vague, poorly localized, unrelated to activity or position, often colicky, and periumbilical in location as a result of visceral inflammation from a distended appendix. Progression of the inflammatory process in the next 12-24 hr leads to involvement of the adjacent parietal peritoneal surfaces, resulting in somatic pain localized to the RLQ. It is important to note the position of the appendix can vary greatly. In 50% of the population it is located in a retrocecal position; likely resulting in a delayed presentation. In others it is located over the pelvic brim, occasionally descending low down in the pelvis. *The position of the appendix is a critical factor affecting interpretation of presenting signs and symptoms and accurate diagnosis.* The pain becomes steady and more severe and is exacerbated by movement. The child often describes marked discomfort with the "bumpy" car ride to the hospital, moves cautiously, and has difficulty getting onto the examining room stretcher. Nausea and vomiting occur in more than half the patients, and usually *follow* the onset of abdominal pain by several hours. Anorexia is a classic and consistent finding in acute appendicitis, but occasionally, affected patients are hungry. Diarrhea and urinary symptoms are also common, particularly in cases of perforated appendicitis when there is likely inflammation near the rectum and possible abscess in the pelvis. As it progresses, appendicitis is often associated with adynamic ileus; leading to the complaint of constipation and possible misdiagnosis. Because enteric infections can cause appendicitis, diarrhea may be the initial manifestation and gastroenteritis may be the assumed diagnosis. In contrast to gastroenteritis, the abdominal pain in appendicitis is constant (not cramping or relieved by defecation), the emesis may become bile stained and persistent, and the clinical course worsens steadily rather than demonstrating a waxing and waning pattern. Fever is common and typically low-grade unless perforation has occurred. Most patients demonstrate at least mild tachycardia.

The temporal progression of symptoms from vague, mild pain, malaise, and anorexia to severe localized pain, fever, and vomiting typically occurs rapidly, in 24-48 hr in the majority of cases. If the diagnosis is delayed beyond 36-48 hr, the perforation rate exceeds 65%. A period after perforation of lessened abdominal pain and acute symptoms has been described, presumably with the elimination of pressure within the appendix. If the omentum or adjacent intestine is able to wall off the infectious process, the evolution of illness is less predictable and delay in presentation is likely. If perforation leads to diffuse peritonitis, the child generally has escalating diffuse abdominal pain and rapid development of toxicity evidenced by dehydration and signs of sepsis including hypotension, oliguria, acidosis, and high-grade fever. When several days have elapsed in the progression of appendicitis, patients often develop signs and symptoms of developing small bowel obstruction. If the appendix is retrocecal, appendicitis predictably evolves more slowly and patients are likely to relate 4-5 days of illness preceding evaluation. The pain is typically more lateral and posterior and can mimic the symptoms associated with septic arthritis of the hip or a psoas muscle abscess. Occasionally patients will complain of urinary symptoms, presumably related to inflammation adjacent to the ureter and/or bladder. Painful voiding may not be from dysuria but pressure transmitted to an inflamed peritoneum.

PHYSICAL EXAMINATION

Although the hallmark of diagnosing acute appendicitis remains a careful and thorough history and physical examination, all clinicians know the arcane nature of acute appendicitis, the consistent or typical clinical features are not present in all patients, and the diagnosis can be a humbling experience even for the most experienced clinicians. A primary focus of the initial assessment is attention to the temporal evolution of the illness in relation to specific presenting signs and symptoms. In many children, appendicitis can be confidently diagnosed based on history and physical examination alone, and the children can thus be spared the treatment delay, expense, and possible radiation exposure associated with imaging studies.

Physical examination begins with inspection of the child's demeanor as well as the appearance of the abdomen. Because appendicitis most often has an insidious onset, children rarely present <12 hr from the onset of illness, and the children who do present early are likely to have minimal findings. Children with early appendicitis (18-36 hr) typically appear mildly ill and move tentatively, hunched forward and, often, with a slight limp favoring the right side. Supine, they often lie quietly on their right side with their knees pulled up to relax the abdominal muscles, and when asked to lie flat or sit up, they move cautiously and might use a hand to protect the RLQ.

Early in appendicitis, the abdomen is typically flat; abdominal distention suggests more advanced disease characteristic of perforation or developing small bowel obstruction. Auscultation can reveal normal or hyperactive bowel sounds in early appendicitis, which are replaced by hypoactive bowel sounds as the disease progresses to perforation. *The judicious use of morphine analgesia to relieve abdominal pain does not change diagnostic accuracy or interfere with surgical decision making, and patients should receive adequate pain control.*

Localized abdominal tenderness is the single most reliable finding in the diagnosis of acute appendicitis. McBurney described the classic point of localized tenderness in acute appendicitis, which is the junction of the lateral and middle thirds of the line joining the right anterior–superior iliac spine and the umbilicus, but the tenderness can also localize to any of the aberrant locations of the appendix. Localized tenderness is a later and less-consistent finding when the appendix is retrocecal in position (>50% of cases). In cases of an appendix localized entirely in the pelvis, the tenderness on abdominal examination may be minimal and best appreciated on rectal examination.

A gentle touch on the child's arm at the beginning of the examination with the reassurance that the abdominal examination will be similarly gentle can help to establish trust and increase the chance for a reliable and reproducible examination. The examination is best initiated in the left lower abdomen, so that the immediate part of the exam is not uncomfortable, and conducted in a counterclockwise direction moving gently to the left upper abdomen, right upper abdomen, and, lastly, the right lower abdomen. This should alleviate anxiety, allow relaxation of the abdominal musculature, and enhance trust. The examiner makes several "circles" of the abdomen with sequentially more pressure. A soft, compressible, nontender abdominal wall is reassuring. In appendicitis, any abdominal wall movement, including coughing (Dunphy sign), may elicit pain. A consistent finding in acute appendicitis is guarding; rigidity of the overlying rectus muscle. This rigidity may be voluntary, to protect the area of tenderness from the examiner's hand, or involuntary, secondary to peritonitis causing spasm of the overlying muscle.

Examination findings must be interpreted relative to the temporal evolution of the illness. Abdominal tenderness may be vague or even absent early in the course of appendicitis and is often diffuse after rupture. Rebound tenderness and referred tenderness (Rovsing sign) are also consistent findings in acute appendicitis but not always present. Rebound tenderness is elicited by deep palpation of the abdomen followed by the sudden release of the examining hand. This is often very painful to the child and has demonstrated poor correlation with peritonitis, so it should be avoided. Gentle finger percussion is a better test for peritoneal irritation. Similarly, digital rectal examination is uncomfortable and unlikely to contribute to the evaluation of appendicitis in most cases of appendicitis in children. Psoas and obturator internus signs are pain with passive stretch of these muscles. The psoas sign is elicited with active right thigh flexion or passive extension of the hip and typically positive in cases of a retrocecal appendix. The obturator sign is demonstrated by adductor pain after internal rotation of the flexed thigh and typically positive in cases of a pelvic appendix. Physical examination may demonstrate a mass in the RLQ representing an

inflammatory phlegmon around the appendix or a localized abscess (fluid collection).

DIAGNOSTIC STUDIES

Laboratory Findings

A variety of laboratory tests have been used in the evaluation of children with suspected appendicitis. Individually, none are very sensitive or specific for appendicitis, but collectively they can affect the clinician's level of suspicion and decision-making to proceed with pediatric surgery consultation, discharge, or imaging studies. Findings should be interpreted with attention to the temporal evolution of the illness.

A complete blood count with differential and urinalysis are commonly obtained. The leukocyte count in early appendicitis may be normal and typically is only mildly elevated with a left shift (11,000-16,000/mm^3) as the illness progresses in the initial 24-48 hr. Whereas a normal white blood cell (WBC) count never completely eliminates appendicitis, a count <8,000/mm^3 in a patient with a history of illness longer than 48 hr should be viewed as highly suspicious for an alternative diagnosis. The leukocyte count may be markedly elevated (>20,000/mm^3) in perforated appendicitis and rarely in nonperforated cases; a markedly elevated WBC count, other than in cases of advanced, perforated appendicitis, should raise suspicion of an alternative diagnosis.

Urinalysis often demonstrates a few white or red blood cells, as a result of the proximity of the inflamed appendix to the ureter or bladder, but it should be free of bacteria. The urine is often concentrated and contains ketones from diminished oral intake and vomiting. Gross hematuria is uncommon and suggests primary renal pathology such as Henoch-Schönlein purpura.

Electrolytes and liver chemistries are generally normal unless there has been a delay in diagnosis, leading to severe dehydration and/or sepsis. Amylase and liver enzymes are only helpful to exclude alternative diagnoses such as pancreatitis and cholecystitis and are not obtained if appendicitis is the strongly suspected diagnosis. Electrolytes are most helpful to assess level of illness and direct fluid resuscitation, but rarely aid accurate diagnosis.

C-reactive protein increases in proportion to the degree of appendiceal inflammation but is nonspecific and not widely used. Serum amyloid A protein is consistently elevated in patients with acute appendicitis with a sensitivity and specificity of 86% and 83%, respectively.

The Pediatric Appendicitis Score combines history, physical, and laboratory data to assist in the diagnosis (Table 343-1). Scores of ≤2 suggest a very low likelihood of appendicitis, whereas scores ≥8 are highly associated with appendicitis. Scores between 3 and 7 warrant further evaluation or diagnostic studies. Nonetheless, no scoring system is perfectly sensitive or specific and none have demonstrated reliability above history and physical examination by an experienced clinician.

Table 343-1 Pediatric Appendicitis Scores

FEATURE	SCORE
Fever >38°C (100.4°F)	1
Anorexia	1
Nausea/vomiting	1
Cough/percussion/hopping tenderness	2
Right lower quadrant tenderness	2
Migration of pain	1
Leukocytosis >10,000 (10^9/L)	1
Polymorphonuclear-neutrophilia >7,500 (10^9/L)	1
Total	10

From Acheson J, Banerjee J: Management of suspected appendicitis in children, Arch Dis Child Educ Pract Ed *95:9–13, 2010.*

Radiologic Studies

Following a thorough initial evaluation; history, physical examination, and review of vital signs and laboratory studies, if the diagnosis is uncertain, advanced radiographic studies can improve diagnostic accuracy.

Plain Radiographs

Plain abdominal radiographs may be helpful in select cases of abdominal pain/suspected appendicitis. Plain abdominal x-rays can demonstrate several findings in acute appendicitis including sentinel loops of bowel and localized ileus, scoliosis from psoas muscle spasm, a colonic air–fluid level above the right iliac fossa (colon "cutoff" sign), a RLQ soft-tissue mass, or a calcified appendicolith (5-10% of cases), but they are normal in 50% of patients, have a low sensitivity, and are not generally recommended (Fig. 343-1). Plain films are most helpful in evaluating complicated cases in which small bowel obstruction or free air is suspected.

Ultrasound

Ultrasound is usually utilized for diagnostic accuracy in the evaluation of acute appendicitis and has demonstrated >90% sensitivity and specificity in pediatric centers experienced with the technique. Graded abdominal compression is used to displace the cecum and ascending colon and identify the appendix, which has a typical target appearance (Fig. 343-2). The ultrasound criteria for appendicitis include wall thickness ≥6 mm, luminal distention, lack of compressibility, a complex mass in the RLQ, or an appendicolith. The visualized appendix usually

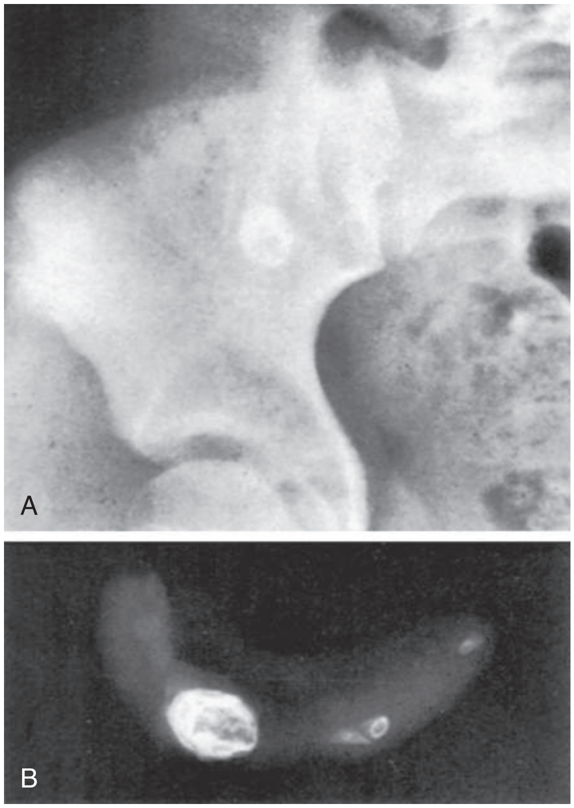

Figure 343-1 Calcified appendicoliths are seen in a coned-down anteroposterior view of the right lower quadrant **(A)** and in the resected appendix of a 10 yr old girl with acute appendicitis **(B).** *(From Kuhn JP, Slovis TL, Haller JO: Caffrey's pediatric diagnostic imaging,* vol 2, *ed 10, Philadelphia, 2004, Mosby, p. 1682.)*

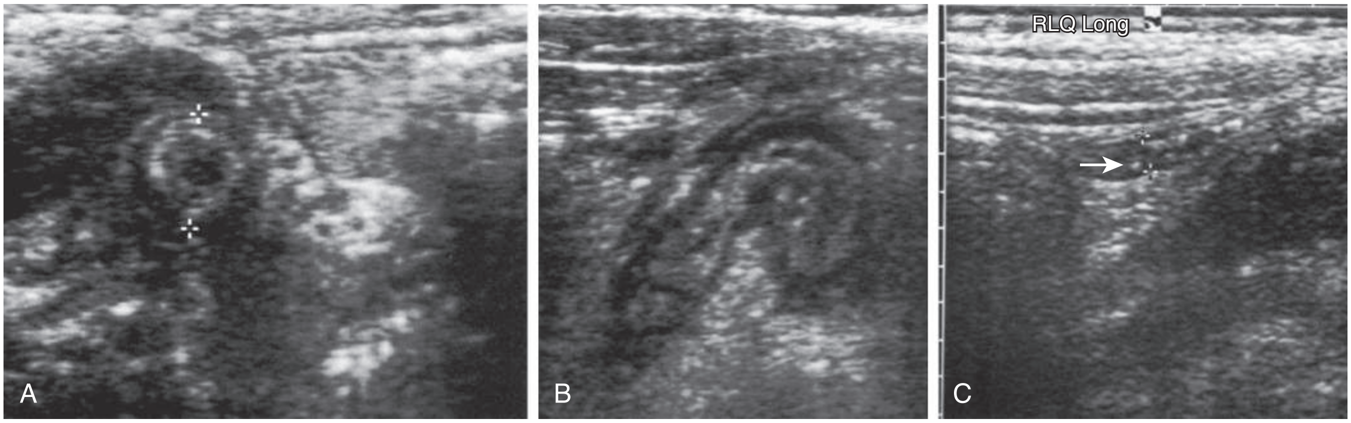

Figure 343-2 Ultrasound examination of patients with appendicitis. **A,** Transverse ultrasound scan of the appendix demonstrates the characteristic "target sign." In this case, the innermost portion is sonolucent, compatible with fluid or pus. **B,** Longitudinal view of another patient demonstrates the alternating hyperechoic and hypoechoic layers with an outermost hypoechoic layer, suggesting periappendiceal fluid. **C,** Longitudinal ultrasound scan of the right lower quadrant demonstrates a dilated, noncompressible appendix. The bright echo within the appendix represents an appendicolith with acoustic shadowing *(arrow). (From Kuhn JP, Slovis TL, Haller JO:* Caffrey's pediatric diagnostic imaging, *vol 2, ed 10, Philadelphia, 2004, Mosby, p. 1684.)*

coincides with the site of localized pain and tenderness. Findings that suggest advanced appendicitis on ultrasound include asymmetric wall thickening, abscess formation, associated free intraperitoneal fluid, surrounding tissue edema, and decreased local tenderness to compression. *The main limitation of ultrasound is an inability to visualize the appendix, which is reported in up to 20% of cases.* **A normal appendix must be visualized to exclude appendicitis by ultrasound.** Certain conditions predictably decrease the sensitivity and reliability of ultrasound for appendicitis, including obesity, bowel distention, and pain, which interferes with the exam. Major advantages of ultrasound include its easy availability, rapid method, low cost, and freedom from need for patient preparation and ionizing radiation. Ultrasound can be particularly helpful in adolescent girls, a group with a high negative appendectomy rate (normal appendix found at surgery), because of its ability to evaluate for ovarian pathology without ionizing radiation. A diagnostic or normal ultrasound exam eliminates the need for CT and should be considered the first exam in a center experienced with the technique.

CT Scan

CT scan had been the gold standard imaging study for evaluating children with suspected appendicitis, but carries the significant negative effects of radiation exposure and increased costs. It should be used only in carefully selected patients and always observing the reduced radiation dosage recommendations for children. CT examination can be performed in many ways, including standard CT scan, helical CT scan, with or without oral and intravenous contrast, examination of both the abdomen and pelvis or pelvis alone, focused appendiceal CT scan, and focused appendiceal CT scan with rectal contrast. All of these techniques have demonstrated >95% sensitivity and specificity for acute appendicitis. Findings on CT scan consistent with appendicitis include a distended (dilated >7 mm) thick-walled appendix, inflammatory streaking of surrounding mesenteric fat, and a pericecal phlegmon or abscess (Figs. 343-3 and 343-4). In addition, appendicoliths are more readily demonstrated on CT scan (40-50%) than on plain radiographs (5-15%). CT scan may be most useful in advanced appendicitis to identify and guide percutaneous drainage of fluid collections and identification of an inflammatory mass, which might prompt a plan for initial nonoperative management. The use of CT scan to "rule out" acute appendicitis and avoid the need (and expenditures) of in-hospital admission is suspect as in early appendicitis CT findings are predictably subtle and in more advanced cases CT scan should be unnecessary as an accurate diagnosis should be able to be made on careful history and physical examination.

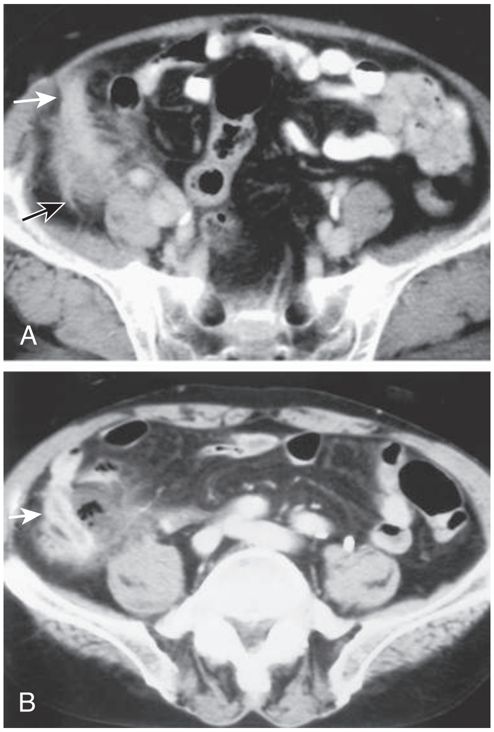

Figure 343-3 **A,** Phlegmon *(open arrow)* is noted around the enlarged appendix *(solid arrow)* in perforated appendicitis. **B,** Extraluminal air is shown adjacent to the wall-enhanced appendix *(arrow)* in perforated appendicitis. *(From Yeung KW, Chang MS, Hsiao CP: Evaluation of perforated and nonperforated appendicitis with CT,* Clin Imaging. *28(6):422–427, 2004.)*

Disadvantages of CT scan include; greater cost; radiation exposure; possible need for intravenous, oral, or rectal contrast; and possible need for sedation. Children have an increased sensitivity to radiation and a longer life ahead to potentially develop a radiation-induced malignancy. A single CT scan has been reported to confirm a 1 in 1,000 lifetime mortality risk, and the risk has been reported as high as 1 in 550 in children younger than age 5 yr. Oral contrast is problematic if

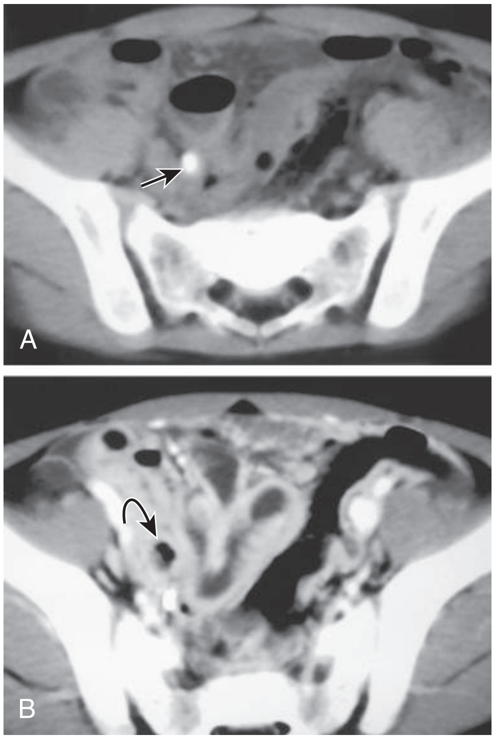

Figure 343-4 **A,** Precontrast-enhanced CT reveals an appendicolith *(arrow)* in perforated appendicitis. **B,** Postcontrast-enhanced CT (1 cm below the level in **A**) reveals intraluminal air in the appendix *(curved arrow)* associated with ileal wall enhancement in perforated appendicitis. *(From Yeung KW, Chang MS, Hsiao CP: Evaluation of perforated and nonperforated appendicitis with CT,* Clin Imaging *28(6):422–427, 2004.)*

appendicitis is confirmed, because of the risk for aspiration at induction of anesthesia. Because the finding of fat stranding in surrounding tissues is a key component of CT evaluation for appendicitis, CT is less reliable in thin children with minimal body fat. For this reason, rectal contrast can increase diagnostic accuracy in this group. CT imaging is also helpful in demonstrating nonappendiceal causes of abdominal pain.

Following initial evaluation, if the diagnosis of acute appendicitis is suspected but uncertain, it is advisable to obtain pediatric surgical consultation before proceeding with a CT scan. An alternative approach to diminish the use of CT scans is the emerging use of observational units for a period up to 23 hr to follow clinical disease progression. Acute appendicitis is most often a rapidly progressive illness and signs and symptoms including fever, tachycardia, nausea and/or vomiting, and focal tenderness, which become more prominent despite intravenous fluids will often lower negative appendectomy rates and enable an accurate diagnosis without the need for advanced imaging.

MRI/White Blood Cell Scan

MRI is at least equivalent to CT in diagnostic accuracy for appendicitis and does not involve ionizing radiation. The use of MRI in the evaluation of appendicitis is limited because it is less available, more costly, often requires sedation, and does not offer equivalent access for drainage of fluid collections. MRI may prove most useful in adolescent girls when advanced imaging is needed. Radionuclide-labeled WBC scans have also been used in some centers in evaluating atypical cases of possible appendicitis in children and demonstrated a high sensitivity (97%) but only modest specificity (80%).

DIFFERENTIAL DIAGNOSIS

The list of illnesses that can mimic acute appendicitis is extensive because many gastrointestinal, gynecologic, and inflammatory disorders can manifest with similar illness history, signs, and symptoms. Differential diagnosis, even limited to common conditions, includes gastroenteritis, mesenteric adenitis, Meckel diverticulitis, inflammatory bowel disease, diabetes mellitus, sickle cell disease, streptococcal pharyngitis, lower lobe pneumonia, cholecystitis, pancreatitis, urinary tract infection, infectious enteritis, and, in girls, ovarian torsion, ectopic pregnancy, ruptured ovarian cysts, and pelvic inflammatory disease (including tuboovarian abscess). Intestinal tract lymphoma, tumors of the appendix (carcinoid in children), and ovarian tumors are rare but can also masquerade as acute appendicitis. In patients with pyelonephritis, the fever and WBC count are likely much higher, symptoms of dysuria will be present, and the tenderness is located more in the flank or costovertebral angle. Rarely, appendicitis may recur in the stump of a previous appendectomy. *Children younger than 3 yr of age and adolescent girls have historically proven to be at particularly high risk for an incorrect diagnosis*.

Most important is differentiation of the patients with gastroenteritis, which is the most common misdiagnosis in the child with appendicitis. The time course of illness (hours, days, weeks) leading to presentation is a critical component of the history. The classic patient with acute appendicitis describes abdominal pain as the preeminent symptom. In general, symptoms of systemic illness such as headache, chills, and myalgias indicate that a patient does not have appendicitis. Acute appendicitis most often begins insidiously as generalized malaise or anorexia, but there is early (within hours) onset of abdominal pain and the illness typically escalates rapidly in the initial 24-48 hr. Most patients with acute appendicitis have 1-3 episodes of vomiting in the initial 24-48 hr of illness; multiple episodes of vomiting are unusual in early appendicitis. In contrast, when gastroenteritis is the diagnosis, diarrhea and vomiting are more likely to be predominant symptoms early in the illness, and abdominal pains may seem associated with the frequent episodes of diarrhea and vomiting. In patients with an acute presentation (<72 hr of illness), vomiting preceding pain, large-volume diarrhea, large amounts of nonbilious vomiting, and high fever suggest gastroenteritis. In addition, patients with appendicitis typically have normal or hypoactive bowel sounds, whereas gastroenteritis typically produces persistently hyperactive bowel sounds. From the onset of illness, the child with appendicitis typically has a steadily deteriorating clinical course, whereas the child with gastroenteritis may have an undulating course, at times feeling better and other times feeling worse.

In the classic child with acute appendicitis who presents within 48 hr of the onset of illness, the WBC count can be low, normal, or elevated but is only rarely elevated >20,000/mm^3. WBC counts in this range should prompt consideration of alternative diagnoses.

A child who presents with a history of illness of longer than 3-4 days is often more challenging. If the diagnosis is appendicitis, perforation has likely occurred and the child's presentation should evidence signs and symptoms of localized abscess/phlegmon in the RLQ or diffuse peritonitis. At this point in the illness, the WBC count should be elevated (>12,000/mm^3) with a left shift; a WBC count <7,000/mm^3 with a lymphocytosis is distinctly unusual in advanced appendicitis and more typical of gastroenteritis. A slightly slower progression of illness is also typical when the appendix is in a retrocecal position and symptoms and anterior abdominal wall tenderness typically are slower to evolve.

An abnormal hemogram combined with purpuric skin lesions, arthritis, and nephritis suggests a diagnosis of Henoch-Schönlein purpura or hemolytic-uremic syndrome. Torsion of an undescended testis and epididymitis are common but should be discovered on physical examination. Meckel diverticulitis is an infrequent condition, but the clinical presentation closely mimics appendicitis and the diagnosis is usually made at surgery. Primary spontaneous peritonitis is classically seen in prepubertal girls is often mistaken for appendicitis.

It should be recognized that "missed" appendicitis is the most common cause of small bowel obstruction in children without history of prior abdominal surgery. Atypical presentations of appendicitis are expected in association with other conditions such as pregnancy, Crohn disease, steroid treatment, and immunosuppressive therapy.

Appendicitis in association with Crohn disease often has a protracted presentation with an atypical pattern of recurring but localized abdominal pain.

The diagnosis of appendicitis in adolescent girls is especially challenging, and some series report negative appendectomy rates as high as 30-40%. Ovarian cysts are often acutely painful as a result of rupture, rapid enlargement, or hemorrhage. Rupture of an ovarian follicle associated with ovulation often causes mid-cycle lateralizing pain (mittelschmerz), but there is no progression of symptoms and systemic illness is absent. Ovarian tumors and torsion can also mimic acute appendicitis, although ovarian torsion is typically characterized by the acute onset of severe pain and is associated with more dramatic nausea and vomiting than is normally seen in early appendicitis. In pelvic inflammatory disease, the pain is typically suprapubic, bilateral, and of longer duration. The need for accurate urgent diagnosis in girls is influenced by concern that perforated appendicitis can predispose the patient to future ectopic pregnancy or tubal infertility, although data have not consistently demonstrated increased incidence of infertility after perforated appendicitis. For these reasons, adjunct diagnostic studies (ultrasound, CT, or diagnostic laparoscopy) should be used more liberally in this group of patients to keep negative appendectomy rates low.

DIAGNOSTIC APPROACH

A diagnosis of acute appendicitis is made in only 50-70% of children at the time of initial assessment; negative appendectomy rates remain high (10-20%) and perforation rates (30-40%) have not changed in the past few decades.

Traditionally, early surgery in equivocal cases was the standard; aimed to minimize perforation rates and complications. Negative laparotomy rates of 10-20% were common and were deemed acceptable to keep perforation rates low. Many authors have criticized these high negative laparotomy rates, citing the risks and expense of unnecessary surgery and anesthesia. In a national database, overall rupture rates for appendicitis varied from 20-76%, with a median of 36%. The median overall negative laparotomy rate (normal appendix at surgery) was 2.6%, significantly lower than traditionally reported rates of 10-20%. The lack of consensus in management approach is reflected by the fact that the use of diagnostic imaging in cases of suspected appendicitis varied from 18-89%.

Some clinicians remain steadfast to the primacy of a careful history and physical examination and rarely order advanced imaging studies. The initial assessment, along with the history and physical examination, may include a complete blood count with differential, urinalysis, and plain films (chest and abdominal series). If the initial assessment leads to a high level of suspicion for appendicitis, pediatric surgical consultation should be the next step, with the likelihood of prompt appendectomy without further studies. If the initial evaluation suggests a nonsurgical diagnosis and a low concern for appendicitis, the child may be discharged with family education regarding the natural history and progression of acute appendicitis and advice to return for repeat evaluation if the child is not improving on liquids and a bland diet in the next 24 hr. This approach has demonstrated high sensitivity and specificity (>90%) at certain institutions, but collective data from many centers have not been able to reproduce this degree of accuracy.

Previous reports recommending CT scans in all equivocal cases to minimize perforation rates and morbidity are not supported in the current climate to reduce the use of CT scan and ionizing radiation. It seems likely that if imaging studies are obtained in all patients with equivocal presentations and a brief duration of illness (<24 hr), the false-negative rate of the imaging studies will increase. Maximum benefit and effectiveness of advanced imaging is obtained when it is used selectively in children for whom the diagnosis is equivocal after careful history and physical examination by an experienced clinician and who are not too early in the temporal evolution of the illness.

In equivocal cases, some centers proceed with a plan of active observation. Many reports substantiate improved diagnostic accuracy by observation and serial examination over a period of 12-24 hr, simplifying the eventual decision to proceed with appendectomy, discharge the patient, or proceed with advanced imaging studies, and report no correlation between surgical morbidity and timing of surgery. The use of observation units, where the child may be observed with intravenous fluids, serial vital signs, and planned repeat physical examination in 6-12 hr. is a strategy gaining increased popularity. At the end of a period of observation, the clinician should decide to discharge the patient based on improved clinical status, proceed to appendectomy, or proceed to further imaging evaluation. Advanced imaging in this equivocal group will be more reliable further into the disease process and hopefully can minimize the negative laparotomy rate without increasing the perforation rate (missed or delayed diagnosis). Less than 2% of children's appendices perforate while under observation.

A thoughtful approach in equivocal cases of appendicitis is to begin with ultrasound if it is available and the hospital has experience with ultrasound for possible appendicitis. In 1 study, ultrasound decreased the need for CT scan in 22% of patients. If ultrasound imaging is inconclusive, the next diagnostic step could be pediatric surgical consultation, a brief period of observation followed by clinical reevaluation and CT scan if the diagnosis remains equivocal. The period of observation (12-24 hr) can occur at home provided the patient is physiologically well; a hospital-based observational unit has the advantage of being able to provide intravenous fluids. CT scan may be used as the first-line test in obese patients, in cases of probable advanced or perforated appendicitis, or when there is gaseous distention of the bowel. Practice guidelines have decreased both length of stay and costs without increasing complications. One such guideline employing clinical judgment and selective imaging attained a positive and negative predictive value for appendicitis of 94% and 99%, respectively.

TREATMENT

Once the diagnosis of appendicitis is confirmed or highly suspected, the standard treatment for acute appendicitis is most often prompt appendectomy. Some reports suggest initial nonoperative management (antibiotics and drainage of fluid collections) as an alternative option in late presentations, depending on the patient's general condition and the state of the appendix. In adults with simple appendicitis, broad-spectrum antibiotics alone have resulted in resolution of symptoms. Nonetheless, there is a 20% chance of recurrence within 1 year of conservative therapy, and of those 20% will present with perforation or a gangrenous appendix. One small nonrandomized trial of nonoperative therapy for uncomplicated appendicitis in children reported a success rate of ~90%. To be considered uncomplicated, patients had pain ≤48 hours, ultrasonographic or CT documentation of a nonruptured appendix, as well as an appendiceal diameter ≤1.1 cm without phlegmon, abscess, or fecalith. Management included a minimum of 24 hr of intravenous antibiotics (piperacillin-tazobactam or ciprofloxacin with metronidazole) followed by amoxicillin-clavulanate or ciprofloxacin with metronidazole to complete a 10-day total antibiotic course.

Emergency (middle of the night) surgery is rarely indicated, and most patients require preoperative supportive measures to stabilize vital signs and to ensure the safety of the procedure, anesthesia, and improve outcomes. In addition, often, unexpected pathology (appendiceal tumors, intestinal lymphoma, congenital renal anomalies, inflammatory bowel disease) is discovered at operation, and intraoperative consultation and frozen section may be needed. There is no correlation between timing of surgery and perforation rates or postoperative morbidity when the operation proceeds within 24-48 hr of diagnosis. In addition, appendectomy can be a challenging operation, with potential for major complications including injury to adjacent intestine, the iliac vessels, or the right ureter. The operation should proceed semielectively within 12-24 hr of diagnosis. Children with appendicitis are typically at least mildly dehydrated and require preoperative fluid resuscitation to correct hypovolemia and electrolyte abnormalities before anesthesia. Fever, if present, should be treated. Pain management begins even before a definitive diagnosis is made, and consultation of a pain service, if available, is appropriate once a decision is made to proceed to surgery. In the majority of cases, preoperative management can be accomplished during the period of diagnostic evaluation and prompt appendectomy can be performed.

In patients in whom perforated appendicitis is identified at the time of diagnosis, the operation is even less urgent and proper preoperative management is more critical. When the illness is protracted owing to a delay in diagnosis or presentation, patients can demonstrate significant physiologic derangements including severe dehydration, hypotension, acidosis, and renal failure. These patients require a longer period of stabilization with fluid resuscitation and antibiotics, including, in occasional cases, admission to an intensive care unit before proceeding with more definitive management. Based on the patient's status, findings on CT scan, and availability of experienced radiologists, the initial plan may be percutaneous drainage of fluid collections by interventional radiology and continued fluid resuscitation and antibiotics. An inflammatory mass (phlegmon) without an identifiable fluid component might initially respond to nonoperative management with fluids and antibiotics. Placement of 1 or more drainage catheters under imaging (CT or ultrasound) guidance has been successful in more than 80% of patients. Most pediatric surgeons recommend delayed appendectomy (during the same hospitalization) or interval appendectomy (4-6 wk after the initial presentation), to prevent recurrent appendicitis (≈20%); this is an area of some controversy.

If diffuse peritonitis exists, most surgeons proceed promptly with appendectomy after a brief period of intravenous fluids and broad spectrum antibiotics. Others continue nonoperative management provided the patient demonstrates clinical improvement by physiologic criteria including hemodynamic stability, urine output, control of fever, and declining leukocyte count. If the patient demonstrates clinical recovery by resolution of fever, sepsis, and return of bowel function, generally a 2 wk course of oral antibiotics is completed and a decision is made regarding interval appendectomy in 6-8 wk. A child who fails to improve within 24-72 hr needs an urgent appendectomy to control sepsis. Emergency appendectomy should only be performed in the occasional circumstance when physiologic resuscitation requires urgent control of advanced peritoneal sepsis not amenable to interventional drainage or this is not available.

Antibiotics

Antibiotics substantially lower the incidence of postoperative wound infections and intraperitoneal abscesses in perforated appendicitis, but their role is less well defined in simple appendicitis. The antibiotic regimen should be directed against the typical bacterial flora found in the appendix, including anaerobic organisms (*Bacteroides, Clostridia,* and *Peptostreptococcus* spp.) and Gram-negative aerobic bacteria (*Escherichia coli, Pseudomonas aeruginosa, Enterobacter,* and *Klebsiella* spp.). Gram-positive organisms are less commonly found in the colon, and the need to provide antibiotic coverage for them (primarily enterococcus) is controversial. Many antibiotic combinations have demonstrated equivalent efficacy in controlled trials in terms of wound infection rate, resolution of fever, length of stay, and incidence of complications.

For simple nonperforated appendicitis, one preoperative dose of a single broad-spectrum agent (cefoxitin) or equivalent is sufficient. The practice in perforated or gangrenous appendicitis, most surgeons prefer combination regimens such as Zosyn (piperacillin/tazobactam), ticarcillin/clavulanate, or ceftriaxone/metronidazole. The traditional "triple" antibiotic regimen (ampicillin, gentamicin, and clindamycin or metronidazole) is still effective, but adds cost and has the concern for ototoxicity. Antibiotic coverage is continued postoperatively for 3-5 days. Oral antibiotics are equally as effective as intravenous, and therefore the patient can be switched to an oral regimen and discharged once bowel function returns. This transition to oral antibiotics has significantly affected length of stay and cost in the management of perforated appendicitis.

Interval Appendectomy

Ruptured appendicitis complicated by a walled-off inflammatory mass or abscess can be treated without immediate appendectomy. This strategy is intended to avoid a predictable higher surgical complication rate and is often useful in children, in whom the overall incidence of perforation approaches 50%. In this group of patients, debate exists over the need for interval appendectomy if the child recovers well without "up front" appendectomy. The risk of developing recurrent appendicitis if the appendix is not removed is unknown, and published reports vary between 10% and 80% (most are closer to 10%). Most cases of recurrent appendicitis develop within 2 yr of the initial illness. Some authors believe interval appendectomy is unnecessary because of the low risk for recurrent appendicitis. Others support interval appendectomy to avoid recurrent appendicitis and to confirm the original diagnosis, citing an incidence of unexpected pathology in 30% of interval appendectomy specimens. The vast majority of pediatric surgeons perform interval appendectomy routinely (4-6 wk interval) after initial nonoperative management of perforated appendicitis.

Surgical Technique

Diagnostic laparoscopy and laparoscopic appendectomy (minimally invasive technique) for both simple and perforated appendicitis are the preferred approaches in most pediatric centers; the open surgery is still performed in selected cases**.** Laparoscopic appendectomy has significant advantages in administrative factors (cost, resource utilization, length of stay), and slight improvement in clinical outcome measures (wound infection rate, intraabdominal abscess, analgesic requirements, return to full activity), but have failed to establish an evidence-based preference between laparoscopic and open appendectomy in children. In nonperforated appendicitis, laparoscopic appendectomy appears to have lower narcotic analgesic requirements, decreased wound morbidity, and improved cosmesis, but operative times seem slightly higher and costs are almost doubled compared to the open procedure. Length of hospitalization is similar for both approaches.

The role of laparoscopy in perforated appendicitis is less-well defined. There are no convincing data to recommend one approach in all patients. Most pediatric surgeons use both approaches selectively. The laparoscopic approach is used most often for obese patients, when alternative diagnoses are suspected, and in adolescent girls to better evaluate for ovarian pathology and pelvic inflammatory disease while avoiding the ionizing radiation associated with CT imaging. Injection of local anesthetic (bupivacaine) into the wound reduces postoperative pain.

Complications

Morbidity rates for appendicitis vary widely in large series from 10-45%. The principal determinant of complications is the severity of the appendicitis. In nonperforated appendicitis, an overall complication rate of 3-7% is expected. With perforation, the complication rate rises to 15-30%. The most common complications are wound infections (3-10%) and intraabdominal abscesses; both are more common after perforation. Perforation and abscess formation can also lead to fistula formation in adjacent organs. Perforation rates are consistently >80% in children younger than 5 yr of age. Delay in return to full activity and function is also predictable in perforated appendicitis. Patients with advanced appendicitis can progress to sepsis and multisystem organ failure, but generally these patients respond promptly to antibiotics, fluids, and other supportive measures preoperatively. Other potential complications include postoperative ileus, diffuse peritonitis, portal vein pylephlebitis (rare), and adhesive small bowel obstruction. Readmission rates are significantly higher in perforated appendicitis (≈20%) and this has become an important marker in recent quality metrics. Mortality with appendicitis is rare (<0.5%) and seen mostly in neonates and immunocompromised patients.

INCIDENTAL APPENDICOLITHS

The question of the "incidental" appendicolith is an intriguing one for pediatric practitioners. These are patients who **do not** have appendicitis but are found to have an appendicolith with imaging. In adults, incidental appendicoliths identified by CT scans vary in incidence from <1% to as high as 10%. An appendicolith is defined as a calcification within the appendiceal lumen. They have a characteristic dense and laminated appearance when compared to other lower abdominal calcifications, including phleboliths (venous calcifications) and, in

girls, ovarian calcifications, most commonly seen in ovarian tumors. They can be appreciated on plain film, ultrasound, and CT scan; CT scan is the most reliable. Occasionally an appendicolith is noted during laparoscopy while visualizing a noninflamed appendix.

When an appendicolith is noted in the evaluation of a child with abdominal pain and suspected appendicitis, the finding of the appendicolith confirms the diagnosis; surgical consultation and prompt appendectomy is indicated. Appendicoliths may be noted in the evaluation of patients who have no signs of appendicitis; such as imaging obtained after trauma or for nonspecific abdominal complaints. The concern in this setting is that the appendicolith may increase the eventual development of acute appendicitis. In addition, there is the concern that appendicitis that develops in association with an appendicolith may have a rapidly escalating course and early perforation. Some physicians believe that an appendicolith may be associated with recurrent RLQ/iliac fossa pain.

Incidental appendicoliths may be transient and in most short-term follow-up studies have a low risk of subsequent acute appendicitis. The risk of subsequent appendicitis may be higher in those presenting with abdominal pain or those younger than 19 yr of age. The lifetime risk for the development of appendicitis in patients with an incidental appendicolith is approximately 5%.

Radiographically detected incidental appendicoliths are usually managed with observation, planned follow up, and patient education for signs of an acute appendicitis, while those detected during laparoscopy to rule out acute appendicitis (when the appendix is normal in appearance) may or may not undergo appendectomy. After discussing the risks and benefits with the family, and persistence of the appendicolith, some conclude that an elective appendectomy may be indicated.

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Chapter 344
Surgical Conditions of the Anus and Rectum

344.1 Anorectal Malformations

Begum Akay and Michael D. Klein

In understanding the spectrum of anorectal anomalies, it is necessary to consider the importance of the sphincter complex, a mass of muscle fibers surrounding the anorectum (Fig. 344-1). This complex is the combination of the puborectalis, levator ani, external and internal sphincters, and the superficial external sphincter muscles, all meeting at the rectum. Anorectal malformations are defined by the relationship of the rectum to this complex and include varying degrees of stenosis to complete atresia. The incidence is 1 per 3,000 live births. Significant long-term concerns focus on bowel control and urinary and sexual functions.

EMBRYOLOGY

The hindgut forms early as the part of the primitive gut tube that extends into the tail fold in the 2nd wk of gestation. At about day 13, it develops a ventral diverticulum, the allantois or primitive bladder. The junction of allantois and hindgut become the cloaca, into which the genital, urinary, and intestinal tubes empty. This is covered by a cloacal membrane. The urorectal septum descends to divide this common channel by forming lateral ridges, which grow in and fuse by the middle of the 7th wk. Opening of the posterior portion of the membrane (the anal membrane) occurs in the 8th wk. Failures in any part of these processes can lead to the clinical spectrum of anogenital anomalies.

Imperforate anus can be divided into low lesions, where the rectum has descended through the sphincter complex, and high lesions, where it has not. Most patients with imperforate anus have a fistula. There is a spectrum of malformation in boys and girls. In boys, low lesions usually manifest with meconium staining somewhere on the perineum along the median raphe (Fig. 344-2*A*). Low lesions in girls also manifest as a spectrum from an anus that is only slightly anterior on the perineal body to a fourchette fistula that opens on the moist mucosa of the introitus distal to the hymen (Fig. 344-3*A*). A high imperforate anus in a boy has no apparent cutaneous opening or fistula, but it usually has a fistula to the urinary tract, either the urethra or the bladder (Fig. 344-2*B*). Although there is occasionally a rectovaginal fistula, in girls, high lesions are usually cloacal anomalies in which the rectum, vagina, and urethra all empty into a common channel or cloacal stem of varying length (Fig. 344-3*B*). The interesting category of boys with imperforate anus and no fistula occurs mainly in children with trisomy 21.

ASSOCIATED ANOMALIES

There are many anomalies associated with anorectal malformations (Table 344-1). The most common are anomalies of the kidneys and urinary tract in conjunction with abnormalities of the sacrum. This complex is often referred to as the **caudal regression syndrome.** Boys with a rectovesical fistula and patients with a persistent cloaca have a 90% risk of urologic defects. Other common associated anomalies are cardiac anomalies and esophageal atresia with or without tracheoesophageal fistula. These can cluster in any combination in a patient. When combined, they are often accompanied by abnormalities of the radial aspect of the upper extremity and are termed the VATERR

Table 344-1 Associated Malformations
GENITOURINARY
Vesicoureteric reflux
Renal agenesis
Renal dysplasia
Ureteral duplication
Cryptorchidism
Hypospadias
Bicornuate uterus
Vaginal septums
VERTEBRAL
Spinal dysraphism
Tethered chord
Presacral masses
Meningocele
Lipoma
Dermoid
Teratoma
CARDIOVASCULAR
Tetralogy of Fallot
Ventricular septal defect
Transposition of the great vessels
Hypoplastic left-heart syndrome
GASTROINTESTINAL
Tracheoesophageal fistula
Duodenal atresia
Malrotation
Hirschsprung disease
CENTRAL NERVOUS SYSTEM
Spina bifida
Tethered cord

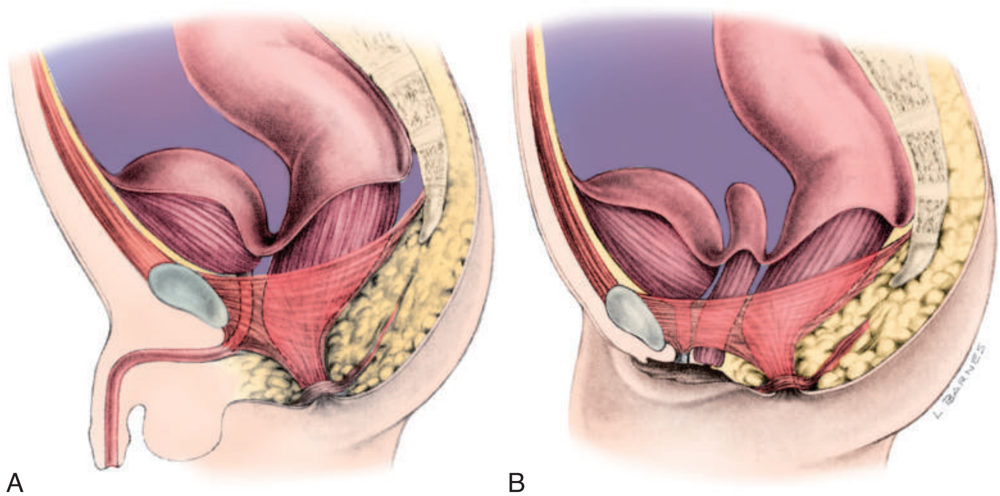

Figure 344-1 Normal anorectal anatomy in relation to pelvic structures. **A,** Male. **B,** Female. *(From Peña A:* Atlas of surgical management of anorectal malformations, *New York, 1989, Springer-Verlag, p. 3.)*

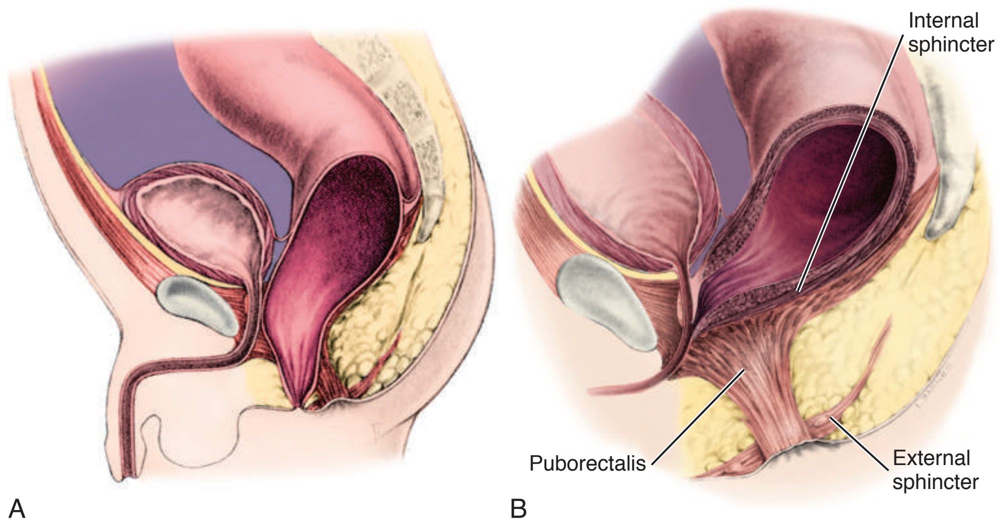

Figure 344-2 Imperforate anus in males. **A,** Low lesions. **B,** High lesions. *(From Peña A:* Atlas of surgical management of anorectal malformations, *New York, 1989, Springer-Verlag, pp. 7, 26.)*

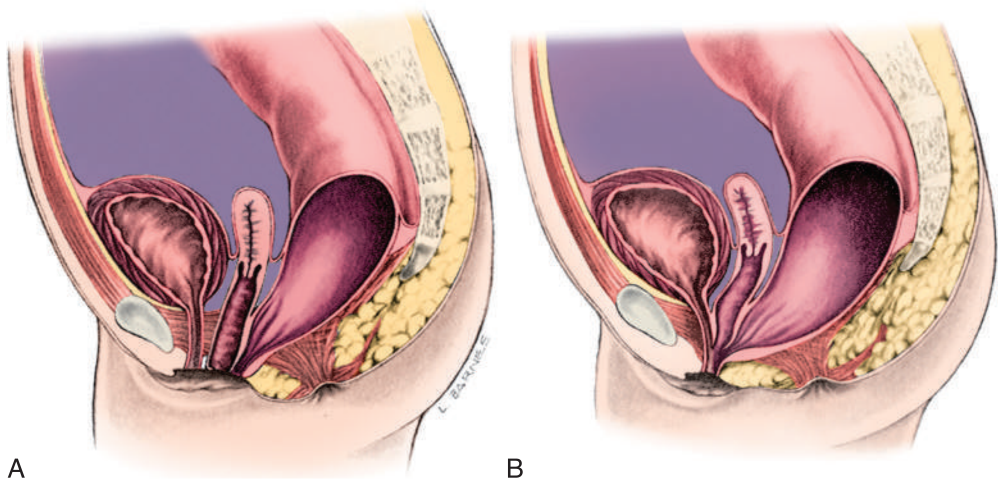

Figure 344-3 Imperforate anus in females. **A,** Vestibular fistula. **B,** Cloaca. *(From Peña A:* Atlas of surgical management of anorectal malformations, *New York, 1989, Springer-Verlag, pp. 50, 60.)*

(*v*ertebral, *a*nal, *t*racheal, *e*sophageal, *r*adial, *r*enal) or VACTERL (*v*ertebral, *a*nal, *c*ardiac, *t*racheal, *e*sophageal, *r*enal, *l*imb) anomalad.

A good correlation exists between the degree of sacral development and future function. Patients with an absent sacrum usually have permanent fecal and urinary incontinence. Spinal abnormalities and different degrees of dysraphism are often associated with these defects. Tethered cord occurs in approximately 25% of patients with anorectal malformations. Untethering of the cord can lead to improved urinary and rectal continence in some patients, although it seldom reverses established neurologic defects. The diagnosis of spinal defects can be established in the 1st 3 mo of life by spinal ultrasound. In older patients, MRI is needed.

MANIFESTATIONS AND DIAGNOSIS

Low Lesions

Examination of a newborn includes the inspection of the perineum. The absence of an anal orifice in the correct position leads to further evaluation. Mild forms of imperforate anus are often called *anal stenosis* or *anterior ectopic anus*. These are probably imperforate anus with a perineal fistula. The normal position of the anus on the perineum is approximately halfway (0.5 ratio) between the coccyx and the scrotum or introitus. Although symptoms, primarily constipation, have been attributed to anterior ectopic anus (ratio: <0.34 in girls, <0.46 in boys), many patients have no symptoms.

If no anus or fistula is visible, there may be a low lesion or “covered anus.” In these cases, there are well-formed buttocks and often a thickened raphe or “bucket handle.” After 24 hr, meconium bulging may be seen, creating a blue or black appearance. In these cases, an immediate perineal procedure can often be performed, followed by a dilation program.

In a boy, the perineal (cutaneous) fistula can track anteriorly along the median raphe across the scrotum and even down the penile shaft. This is usually a thin track, with a normal rectum often just a few millimeters from the skin. Extraintestinal anomalies are seen in <10% of these patients.

In a girl, a low lesion enters the vestibule or fourchette (the moist mucosa outside the hymen but within the introitus). In this case, the rectum has descended through the sphincter complex.

Children with a low lesion can usually be treated initially with perineal manipulation and dilation. Visualizing these low fistulas is so important in the evaluation and treatment that one should avoid passing a nasogastric tube for the 1st 24 hr to allow the abdomen and bowel to distend, pushing meconium down into the distal rectum.

High Lesions

In a boy with a high imperforate anus, the perineum appears flat. There may be air or meconium passed via the penis (urethra) when the fistula is high, entering the bulbar or prostatic urethra, or even the bladder. In **rectobulbar urethral fistulas** (the most common in boys), the sphincter mechanism is satisfactory, the sacrum may be underdeveloped, and an anal dimple is present. In **rectoprostatic urethral fistulas,** the sacrum is poorly developed, the scrotum may be bifid, and the anal dimple is near the scrotum. In **rectovesicular fistulas,** the sphincter mechanism is poorly developed and the sacrum is hypoplastic or absent. In boys with trisomy 21, all the features of a high lesion may be present, but there is no fistula, the sacrum and sphincter mechanisms are usually well developed, and the prognosis is good.

In girls with high imperforate anus, there may be the appearance of a rectovaginal fistula. A true rectovaginal fistula is rare. Most are either the fourchette fistulas described earlier or are forms of a cloacal anomaly.

Persistent Cloaca

In persistent cloaca, the embryologic stage persists in which the rectum, urethra, and vagina communicate in a common orifice, the cloaca. It is important to realize this, because the repair often requires repositioning the urethra and vagina as well as the rectum. Children of both sexes with a high lesion require a colostomy before repair.

Rectal Atresia

Rectal atresia is a rare defect occurring in only 1% of anorectal anomalies. It has the same characteristics in both sexes. The unique feature of this defect is that affected patients have a normal anal canal and a normal anus. The defect is often discovered while rectal temperature is being taken. An obstruction is present approximately 2 cm above the skin level. These patients need a protective colostomy. The functional prognosis is excellent because they have a normal sphincteric mechanism (and normal sensation), which resides in the anal canal.

APPROACH TO THE PATIENT

Evaluation includes identifying associated anomalies (see Table 344-1). Careful inspection of the perineum is important to determine the presence or absence of a fistula. If the fistula can be seen there, it is a low lesion. The invertogram or upside-down x-ray is of little value, but a prone crosstable lateral plain x-ray at 24 hr of life (to allow time for bowel distention from swallowed air) with a radiopaque marker on the perineum can demonstrate a low lesion by showing the renal gas bubble <1 cm from the perineal skin. A plain x-ray of the entire sacrum, including both iliac wings, is important to identify sacral anomalies and the adequacy of the sacrum. An abdominal-pelvic ultrasound and voiding cystourethrogram must be performed. The clinician should also pass a nasogastric tube to identify esophageal atresia and should obtain an echocardiogram. In boys with a high lesion, the voiding cystourethrogram often identifies the rectourinary fistula. In girls with a high lesion, more invasive evaluation, including vaginogram and endoscopy, is often necessary for careful detailing of the cloacal anomaly.

Good clinical evaluation and a urinalysis provide enough data in 80-90% of **male** patients to determine the need for a colostomy. Voluntary sphincteric muscles surround the most distal part of the bowel in cases of perineal and rectourethral fistulas, and the intraluminal bowel pressure must be sufficiently high to overcome the tone of those muscles before meconium can be seen in the urine or on the perineum. The presence of meconium in the urine and a flat bottom are considered indications for the creation of a colostomy. Clinical findings consistent with the diagnosis of a perineal fistula represent an indication for an anoplasty without a protective colostomy. Ultrasound is valuable not only for the evaluation of the urinary tract, but it can also be used to investigate spinal anomalies in the newborn and to determine how close to the perineum the rectum has descended.

More than 90% of the time, the diagnosis in **females** can be established on perineal inspection. The presence of a single perineal orifice is a cloaca. A palpable pelvic mass (hydrocolpos) reinforces this diagnosis. A vestibular fistula is diagnosed by careful separation of the labia, exposing the vestibule. The rectal orifice is located immediately in front of the hymen within the female genitalia and in the vestibule. A perineal fistula is easy to diagnose. The rectal orifice is located somewhere between the female genitalia and the center of the sphincter and is surrounded by skin. Less than 10% of these patients fail to pass meconium through the genitalia or perineum after 24 hr of observation. Those patients can require a prone crosstable lateral film.

OPERATIVE REPAIR

Sometimes a perineal fistula, if it opens in good position, can be treated by simple dilation. Hegar dilators are employed, starting with a No. 5 or 6 and letting the baby go home when the mother can use a No. 8. Twice-daily dilatations are done at home, increasing the size every few weeks until a No. 14 is achieved. By 1 yr of age, the stool is usually well formed and further dilation is not necessary. By the time No. 14 is reached, the examiner can usually insert a little finger. If the anal ring is soft and pliable, dilation can be reduced in frequency or discontinued.

Occasionally, there is no visible fistula, but the rectum can be seen to be filled with meconium bulging on the perineum, or a covered anus is otherwise suspected. If confirmed by plain x-ray or ultrasound of

the perineum that the rectum is <1 cm from the skin, the clinician can do a minor perineal procedure to perforate the skin and then proceed with dilation or do a simple perineal anoplasty.

When the fistula orifice is very close to the introitus or scrotum, it is often appropriate to move it back surgically. This also requires postoperative dilation to prevent stricture formation. This procedure can be done any time from the newborn period to 1 yr. It is preferable to wait until dilatations have been done for several wk and the child is bigger. The anorectum is a little easier to dissect at this time. The posterior sagittal approach of Peña is used, making an incision around the fistula and then in the midline to the site of the posterior wall of the new location. The dissection is continued in the midline, using a muscle stimulator to be sure there is adequate muscle on both sides. The fistula must be dissected cephalad for several centimeters to allow posterior positioning without tension. If appropriate, some of the distal fistula is resected before the anastomosis to the perineal skin.

In children with a high lesion, a double-barrel colostomy is performed. This effectively separates the fecal stream from the urinary tract. It also allows the performance of an augmented pressure colostogram before repair to identify the exact position of the distal rectum and the fistula. The definitive repair or posterior sagittal anorectoplasty (PSARP) is performed at about 1 yr of age. A midline incision is made, often splitting the coccyx and even the sacrum. Using a muscle stimulator, the surgeon stays strictly in the midline and divides the sphincter complex and identifies the rectum. The rectum is then opened in the midline and the fistula is identified from within the rectum. This allows a division of the fistula without injury to the urinary tract. The rectum is then dissected proximally until enough length is gained to suture it to an appropriate perineal position. The muscles of the sphincter complex are then sutured around (and especially behind) the rectum.

Other operative approaches (such as an anterior approach) are used, but the most popular procedure is by laparoscopy. This operation allows division of the fistula under direct visualization and identification of the sphincter complex by transillumination of perineum. Other imaging techniques in the management of anorectal malformations include 3D endorectal ultrasound, intraoperative MRI and colonoscopy-assisted PSARPs, which may help perform a technically "better" operation. None of these other procedures or innovations has demonstrated improved outcomes.

A similar procedure can be done for female high anomalies with variations to deal with separating the vagina and rectum from within the cloacal stem. When the stem is longer than 3 cm, this is an especially difficult and complex procedure.

Usually, the colostomy can be closed 6 wks or more after the PSARP. Two weeks after any anal procedure, twice-daily dilatations are performed by the family. By doing frequent dilatations, each one is not so painful and there is less tissue trauma, inflammation, and scarring.

OUTCOME

The ability to achieve rectal continence depends on both motor and sensory elements. There must be adequate muscle in the sphincter complex and proper positioning of the rectum within the complex. There must also be intact innervation of the complex and of sensory elements as well as the presence of these sensory elements in the anorectum. Patients with low lesions are more likely to achieve true continence. They are also, however, more prone to constipation, which leads to overflow incontinence. It is very important that all these patients are followed closely, and that the constipation and anal dilation are well managed until toilet training is successful. Tables 344-2 and 344-3 outline the results of continence and constipation in relation to the malformation encountered.

Children with high lesions, especially boys with rectoprostatic urethral fistulas and girls with cloacal anomalies, have a poorer chance of being continent, but they can usually achieve a socially acceptable defecation (without a colostomy) pattern with a bowel management program. Often, the bowel management program consists of a daily enema to keep the colon empty and the patient clean until the next enema. If this is successful, an *antegrade continence enema* (ACE) procedure, sometimes called the Malone or MACE procedure, can improve the patient's quality of life. These procedures provide access to the right colon either by bringing the appendix out the umbilicus in a nonrefluxing fashion or by putting a plastic button in the right lower quadrant to access the cecum. The patient can then sit on the toilet and administer the enema through the ACE, thus flushing out the entire colon. Antegrade regimens can produce successful 24 hr cleanliness rates of up to 95%. Of special interest is the clinical finding that most patients improve their control with growth. Patients who wore diapers or pull-ups to primary school are often in regular underwear by high school. Some groups have taken advantage of this evidence of psychologic influences to initiate behavior modification early with good results.

Table 344-2 Results of Surgical Treatment of Anorectal Malformations: Total Continence*

TYPE	PERCENTAGE
LOW	
Perineal fistula	90
Rectal atresia/stenosis	75
Vestibular fistula	71
HIGH	
Imperforate with no fistula	60
Bulbar urethral fistula	50
Short cloaca	50
Prostatic fistula	31
Long cloaca	29
Bladder neck fistula	12

*Voluntary bowel movements, no soiling.
Modified from Levitt MA, Peña A: Outcomes from the correction of anorectal malformations, Curr Opin Pediatr *17:394–401, 2005.*

Table 344-3 Constipation and Type of Anogenital Malformation

TYPE	PERCENTAGE
Vestibular fistula	61
Bulbar urethral fistula	64
Rectal atresia/stenosis	50
Imperforate with no fistula	55
Perineal fistula	57
Long cloaca	35
Prostatic fistula	45
Short cloaca	40
Bladder neck fistula	16

Modified from Levitt MA, Peña A: Outcomes from the correction of anorectal malformations, Curr Opin Pediatr *17:394–401, 2005.*

344.2 Anal Fissure

Begum Akay and Michael D. Klein

Anal fissure is a laceration of the anal mucocutaneous junction. It is an acquired lesion of unknown etiology. While likely secondary to the forceful passage of a hard stool, it is mainly seen in infants younger

than 1 yr of age when the stool is frequently quite soft. Fissures may be the consequence and not the cause of constipation.

CLINICAL MANIFESTATIONS

A history of constipation is often described, with a recent painful bowel movement corresponding to the fissure formation after passing of hard stool. The patient then voluntarily retains stool to avoid another painful bowel movement, exacerbating the constipation, resulting in harder stools. Complaints of pain on defecation and bright red blood on the surface of the stool are often elicited.

The diagnosis is established by inspection of the perineal area. The infant's hips are held in acute flexion, the buttocks are separated to expand the folds of the perianal skin, and the fissure becomes evident as a minor laceration. Often a small skin appendage is noted peripheral to the lesion. This "skin tag" actually represents epithelialized granulomatous tissue, formed in response to chronic inflammation. Findings on rectal examination can include hard stool in the ampulla and rectal spasm.

TREATMENT

The parents must be counseled as to the origin of the laceration and the mechanism of the cycle of constipation. The goal is to ensure that the patient has soft stools to avoid overstretching the anus. The healing process can take several weeks or even several months. A single episode of impaction with passing of hard stool can exacerbate the problem. Treatment requires that the primary cause of the constipation be identified. The use of dietary and behavioral modification and a stool softener is indicated. Parents should titrate the dose of the stool softener based on the patient's response to treatment. Stool softening is best done by increasing water intake or using an oral polyethylene glycolate such as MiraLAX or GlycoLax. Surgical intervention, including stretching of the anus, "internal" anal sphincterotomy, or excision of the fissure, is not indicated or supported by scientific evidence.

Chronic anal fissures in older patients are associated with constipation, prior rectal surgery, Crohn disease, and chronic diarrhea. They are managed initially like fissures in infants, with stool softeners with the addition of sitz baths. Topical 0.2% glyceryl trinitrate reduces anal spasm and heals fissures, but it is often associated with headaches. Calcium channel blockers, such as 2% diltiazem ointment and 0.5% nifedipine cream, are more effective and cause fewer headaches than glyceryl trinitrate. Injection of botulinum toxin from 1.25-25 units is also effective and probably replicates chemically the action of internal sphincterotomy which is the most effective treatment in adults, although seldom used in children.

344.3 Perianal Abscess and Fistula

Begum Akay and Michael D. Klein

Perianal abscess, like all skin and soft-tissue infections, have become much more common since the year 2000 (a 4-fold increase in patients admitted to our hospital, and a 3-fold increase in patients presenting to the emergency room). These usually manifest in infancy and are of unknown etiology. Fistula appears to secondary to abscess rather than a cause. Links to congenitally abnormal crypts of Morgagni have been proposed, suggesting that deeper crypts (3-10 mm rather than the normal 1-2 mm) lead to trapped debris and cryptitis (Fig. 344-4).

Conditions associated with the risk of an anal fistula include Crohn disease, tuberculosis, pilonidal disease, hidradenitis, HIV, trauma, foreign bodies, dermal cysts, sacrococcygeal teratoma, actinomycosis, lymphogranuloma venereum and radiotherapy.

The most common organisms isolated from perianal abscesses are mixed aerobic *(Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus)* and anaerobic (*Bacteroides* spp., *Clostridium, Veillonella*) flora. Ten percent to 15% yield pure growth of *E. coli, S. aureus,* or *Bacteroides fragilis.* There is a strong male predominance in those affected who are younger than 2 yr of age. This imbalance corrects in older patients, where the etiology shifts to associated conditions such as inflammatory bowel disease, leukemia, or immunocompromised states.

CLINICAL MANIFESTATIONS

In younger patients, symptoms are usually mild and can consist of low-grade fever, mild rectal pain, and an area of perianal cellulitis. Often these spontaneously drain and resolve without treatment. In older patients with underlying predisposing conditions, the clinical course may be more serious. A compromised immune system can mask fever and allow rapid progression to toxicity and sepsis. Abscesses in these patients may be deeper in the ischiorectal fossa or even supralevator in contrast to those in younger patients, which are usually adjacent to the involved crypt.

Progression to fistula in patients with perianal abscesses occurs in up to 85% of cases and usually manifests with drainage from the perineal skin or multiple recurrences. Similar to abscess formation, fistulas have a strong male predominance. Histologic evaluation of fistula tracts typically reveals an epithelial lining of stratified squamous cells associated with chronic inflammation. It might also reveal an alternative etiology such as the granulomas of Crohn disease or even evidence of tuberculosis.

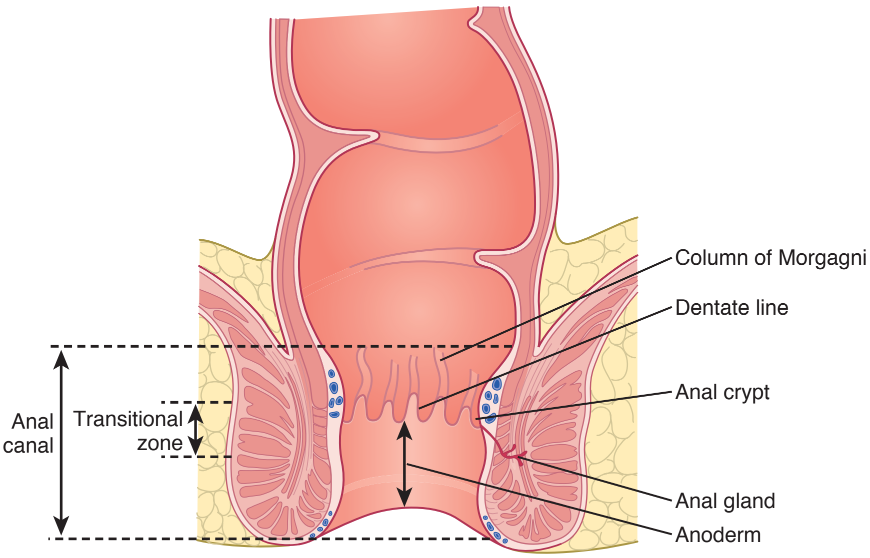

Figure 344-4 Anatomy of the anal canal. *(Adapted from Brunicardi FC, Anderson DK, Billar TR, et al: Schwartz's principles of surgery, ed 8, New York, 2004, McGraw-Hill.)*

TREATMENT

Treatment is rarely indicated in infants with no predisposing disease because the condition is often self-limited. Even in cases of fistulization, conservative management (observation) is advocated because the fistula often disappears spontaneously. Antibiotics are not useful in these patients. When dictated by patient discomfort, abscesses may be drained under local anesthesia. Fistulas requiring surgical intervention may be treated by fistulotomy (unroofing or opening), fistulectomy (excision of the tract leaving it open to heal secondarily), or placement of a seton (heavy suture threaded through the fistula, brought out the anus and tied tightly to itself). In patients with inflammatory bowel disease topical tacrolimus has been effective.

Older children with predisposing diseases might also do well with minimal intervention. If there is little discomfort and no fever or other sign of systemic illness, local hygiene and antibiotics may be best. The danger of surgical intervention in an immunocompromised patient is the creation of an even larger, nonhealing wound. There certainly are such patients with serious systemic symptoms who require more aggressive intervention along with treatment of the predisposing condition. Broad-spectrum antibiotic coverage must be administered and wide excision and drainage are mandatory in cases involving sepsis and expanding cellulitis.

Fistulas in older patients are mainly associated with Crohn disease, a history of pull-through surgery for the treatment of Hirschsprung disease, or, in rare cases, tuberculosis. Those fistulas are often resistant to therapy and require treatment of the predisposing condition.

Complications of treatment include recurrence and, rarely, incontinence.

344.4 Hemorrhoids

Begum Akay and Michael D. Klein

Hemorrhoidal disease does occur in children and adolescents, often related to a diet deficient in fiber and poor hydration. In younger children, the presence of hemorrhoids should also raise the suspicion of portal hypertension. A third of patients with hemorrhoids require treatment.

CLINICAL MANIFESTATIONS

Presentation depends on the location of the hemorrhoids. External hemorrhoids occur below the dentate line (see Figs. 344-4 and 344-5) and are associated with extreme pain and itching, often due to acute thrombosis. Internal hemorrhoids are located above the dentate line and manifest primarily with bleeding, prolapse, and occasional incarceration.

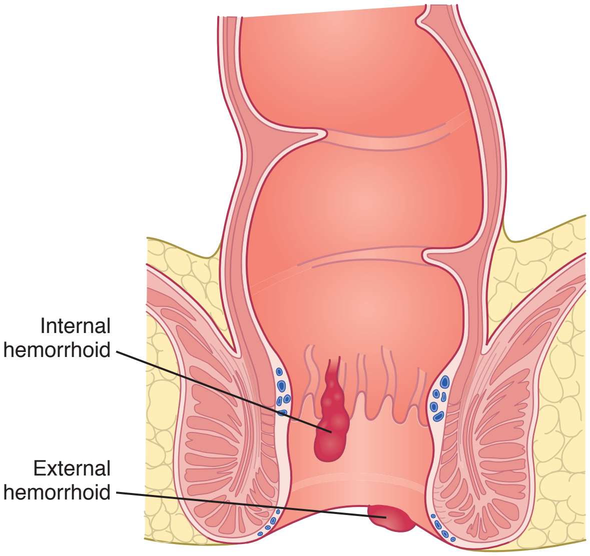

Figure 344-5 Formation of hemorrhoids.

TREATMENT

In most cases, conservative management with dietary modification, decreased straining, and avoidance of prolonged time spent sitting on the toilet results in resolution of the condition. Discomfort may be treated with topical analgesics or anti-inflammatories such as Anusol (pramoxine) and Anusol-HC (hydrocortisone) and sitz baths. The natural course of thrombosed hemorrhoid involves increasing pain, which peaks at 48-72 hr, with gradual remission as the thrombus organizes and involutes over the next 1-2 wk. In cases where the patient with external hemorrhoids presents with excruciating pain soon after the onset of symptoms, thrombectomy may be indicated. This is best accomplished with local infiltration of bupivacaine 0.25% with epinephrine 1 : 200,000, followed by incision of the vein or skin tag and extraction of the clot. This provides immediate relief; recurrence is rare and further follow-up is unnecessary.

Internal hemorrhoids can become painful when prolapse leads to incarceration and necrosis. Pain usually resolves with reduction of hemorrhoidal tissue. Surgical treatment is reserved for patients failing conservative management. Techniques described in adults include excision, rubber banding, stapling, and excision using the LigaSure device. Given the infrequency of hemorrhoidal disease in children, and the need for general anesthesia to treat it, we have been quite satisfied with simple excision ligating the vein proximal and using the Bovie for hemostasis.

Complications are rare (<5%) and include recurrence, bleeding, infection, nonhealing wounds, and fistula formation.

344.5 Rectal Mucosal Prolapse

Begum Akay and Michael D. Klein

Rectal mucosal prolapse is the exteriorization of the rectal mucosa through the anus. In the unusual occurrence when all of the layers of the rectal wall are included, it is called **procidentia or rectocele.** Most cases of rectal tissue protruding through the anus are prolapse and not polyps, hemorrhoids, intussusception, or other tissue.

Most cases of prolapse are idiopathic. The onset is often between 1 and 5 yr of age. It usually occurs when the child begins standing and then resolves by approximately 3-5 yr of age when the sacrum has taken its more adult shape and the anal lumen is oriented posteriorly. Thus, the entire weight of the abdominal viscera is not pushing down on the rectum as it is earlier in development.

Other predisposing factors include intestinal parasites (particularly in endemic areas), malnutrition, diarrhea, ulcerative colitis, pertussis, Ehlers-Danlos syndrome, meningocele (more often associated with procidentia owing to the lack of perineal muscle support), cystic fibrosis, and chronic constipation. Patients treated surgically for imperforate anus can also have varying degrees of rectal mucosal prolapse. This is particularly common in patients with poor sphincteric development.

CLINICAL MANIFESTATIONS

Rectal mucosal prolapse usually occurs during defecation, especially during toilet training. Reduction of the prolapse may be spontaneous or accomplished manually by the patient or parent. In severe cases, the prolapsed mucosa becomes congested and edematous, making it more difficult to reduce. Rectal prolapse is usually painless or produces mild discomfort. If the rectum remains prolapsed after defecation, it can be traumatized by friction with undergarments, with resultant bleeding, wetness, and potentially, ulceration. The appearance of the prolapse varies from bright red to dark red and resembles a beehive. It can be as long as 10-12 cm. See Chapter 345 for a distinction from a prolapsed polyp.

TREATMENT

Initial evaluation should include tests to rule out any predisposing conditions, especially cystic fibrosis and sacral root lesions. Reduction of protrusion is aided by pressure with warm compresses. An easy method of reduction is to cover the finger with a piece of toilet paper, introduce it into the lumen of the mass, and gently push it into the patient's rectum. The finger is then immediately withdrawn. The toilet paper adheres to the mucous membrane, permitting release of the finger. The paper, when softened, is later expelled.

Conservative treatment consists of careful manual reduction of the prolapse after defecation, attempts to avoid excessive pushing during bowel movements (with patient's feet off the floor), use of laxatives and stool softeners to prevent constipation, avoidance of inflammatory conditions of the rectum, and treatment of intestinal parasitosis when present. If all this fails, surgical treatment may be indicated. Existing surgical options are associated with some morbidity, and therefore medical treatment should always be attempted first.

Sclerosing injections have been associated with complications such as neurogenic bladder. We have found linear cauterization effective and with few complications other than recurrence. In the operating room, the prolapse is recreated by traction on the mucosa. Linear burns are made through nearly the full thickness of the mucosa using electrocautery. One can usually make 8 linear burns on the outside and 4 on the inside of the prolapsed mucosa. In the immediate postoperative period, prolapse can still occur, but in the next several weeks, the burned areas contract and keep the mucosa within the anal canal. The Delorme mucosal sleeve resection addresses mucosal prolapse via a transanal approach by incising, prolapsing, and amputating the redundant mucosa. The resulting mucosal defect is then approximated with absorbable suture.

For patients with procidentia or full-thickness prolapse or intussusception of the rectosigmoid (usually from myelodysplasia or other sacral root lesions) other, more invasive options exist. Those most commonly in use by pediatric surgeons today include the following: A modification of the Thiersch procedure involves placing a subcutaneous suture to narrow the anal opening. Complications include obstruction, fecal impaction, and fistula formation. Laparoscopic rectopexy is effective and can be performed as an outpatient. The Altemeier perineal rectosigmoidectomy is a transanal, full-thickness resection of redundant bowel with a primary anastomosis to the anus.

344.6 Pilonidal Sinus and Abscess

Begum Akay and Michael D. Klein

The etiology of pilonidal disease remains unknown; 3 hypotheses explaining its origin have been proposed. The first states that trauma, such as can occur with prolonged sitting, impacts hair into the subcutaneous tissue, which serves as a nidus for infection. The second suggests that in some patients, hair follicles exist in the subcutaneous tissues, perhaps the result of some embryologic abnormality, and that they serve as a focal point for infection, especially with secretion of hair oils. The third speculates that motion of the buttocks disturbs a particularly deep midline crease and works bacteria and hair beneath the skin. This theory arises from the apparent improved short-term and long-term results of operations that close the wound off the midline, obliterating the deep natal cleft.

Pilonidal disease usually manifests in adolescents or young adults with significant hair over the midline sacral and coccygeal areas. It can occur as an acute abscess with a tender, warm, flocculent, erythematous swelling or as draining sinus tracts. This disease does not resolve with nonoperative treatment. An acute abscess should be drained and packed open with appropriate anesthesia. Oral broad-spectrum antibiotics covering the usual isolates (*S. aureus* and *Bacteroides* species) are prescribed, and the patient's family withdraws the packing over the course of a week. When the packing has been totally removed, the area can be kept clean by a bath or shower. The wound usually heals completely in 6 wk. Once the wound is healed, most pediatric surgeons feel that elective excision should be scheduled to avoid recurrence. There are some reports, however, this is only necessary if the disease recurs. Usually, patients who present with sinus tracts are managed with a single elective excision.

Most surgeons carefully identify the extent of each sinus tract and excise all skin and subcutaneous tissue involved to the fascia covering the sacrum and coccyx. Some close the wound in the midline; others leave it open and packed for healing by secondary intention. This method has been modified by the application of a vacuum-assisted (VAC sponge) dressing, This is a system that applies continuous suction to a porous dressing. It is usually changed every 3 days and can be done at home with the assistance of a nurse. Some marsupialize the wound by suturing the skin edges down to the exposed fascia covering the sacrum and coccyx. There appears to be improved success with excision and closure in such a way that the suture line is not in the midline. Currently there appears to be enthusiasm for less radical methods that Bascon has introduced, treating simple sinus tracts with small local procedures and limiting excision to only diseased tissues, while still keeping the incision off the midline. Recurrence or wound-healing problems are relatively common, occurring in 9-27% of cases. The variety of treatments and procedures currently being described indicates that all of them are associated with significant complications and delays in return to normal activity. Still, it is rare for problems to persist beyond 1-2 yr. Recalcitrant cases are treated by a large, full-thickness gluteal flap or skin grafting.

A simple dimple located in the midline intergluteal cleft, at the level of the coccyx, is seen relatively commonly in normal infants. No evidence indicates that this little sinus provokes any problems for the patient. An open dermal sinus is an asymptomatic, benign condition that does not require operative intervention.

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Chapter 345

Tumors of the Digestive Tract

Lydia J. Donoghue

Tumors of the digestive tract in children are mostly polypoid. They are also commonly syndromic tumors and tumors with known genetic identification (Table 345-1). They usually manifest as painless rectal bleeding, but they can serve as lead points for intussusception. Most intestinal tumors can be generally classified into 2 groups: hamartomatous or adenomatous.

HAMARTOMATOUS TUMORS

Hamartomas are benign tumors composed of tissues that are normally found in an organ but that are not organized normally. Juvenile, retention, or inflammatory polyps are hamartomatous polyps, which represent the most common intestinal tumors of childhood, occurring in 1-2% of children. Patients generally present in the 1st decade, most often at ages 2-5 yr, and rarely at younger than 1 year. Polyps may be found anywhere in the gastrointestinal (GI) tract, most commonly in the colon or rectum; they are often solitary but may be multiple.

Histologically, juvenile polyps are composed of hamartomatous collections of mucus-filled glandular and stromal elements with inflammatory infiltrate, covered with a thin layer of epithelium. These polyps are often bulky, vascular, and prone to bleed as their growth exceeds their blood supply with resultant mucosal ulceration, or autoamputation with bleeding from a residual central artery.

Table 345-1 General Features of the Inherited Colorectal Cancer Syndromes

SYNDROME	POLYP DISTRIBUTION	AGE OF ONSET	RISK OF COLON CANCER	GENETIC LESION	CLINICAL MANIFESTATIONS	ASSOCIATED LESIONS
HAMARTOMATOUS POLYPS						
Juvenile polyposis	Large and small intestine, gastric polyps	1st decade	~10-50%	*PTEN, SMAD4, BMPR1A* Autosomal dominant	Possible rectal bleeding, abdominal pain, intussusception	Congenital abnormalities in 20% of the nonfamilial type, clubbing, AV malformations
Peutz-Jeghers syndrome	Small and large intestine	1st decade	Increased	*LKB1/STK11* Autosomal dominant	Possible rectal bleeding, abdominal pain, intussusception	Orocutaneous melanin pigment spots
Cowden syndrome	Colon	2nd decade	Not increased	*PTEN* gene	Macrocephaly, breast/thyroid/endometrial cancers, developmental delay	
Bannayan-Riley-Ruvalcaba syndrome	Colon	2nd decade	Not increased	*PTEN* gene	Macrocephaly, speckled penis, thyroid/breast cancers, hemangiomas, lipomas	
ADENOMATOUS POLYPS						
Familial adenomatous polyposis (FAP)	Large intestine, often >100	16 yr (range: 8-34 yr)	100%	5q (*APC* gene), autosomal dominant	Rectal bleeding, abdominal pain, bowel obstruction	Desmoids, CHRPE, upper GI polyps, osteoma, hepatoblastoma, thyroid cancer
Attenuated familial adenomatous polyposis (AFAP)	Colon (fewer in number)	>18 yr	Increased	*APC* gene	Same as FAP	Fewer associated lesions
MYH-associated polyposis	Colon	>20yr	High risk	*MYH* autosomal recessive	Same as FAP	May be confused with sporadic FAP or AFAP; few extraintestinal findings
Gardner syndrome	Large and small intestine	16 yr (range: 8-34 yr)	100%	5q (*APC* gene)	Rectal bleeding, abdominal pain, bowel obstruction	Desmoid tumors, multiple osteomas, fibromas, epidermoid cysts
Hereditary nonpolyposis colon cancer, (Lynch syndrome)	Large intestine	40 yr	30%	DNA mismatch repair genes *(MMR)* Autosomal dominant	Rectal bleeding, abdominal pain, bowel obstruction	Other tumors (e.g., ovary, ureter, pancreas, stomach)

AV, Arteriovenous; CHRPE, congenital hypertrophy of the retinal pigment epithelium; GI, gastrointestinal.

Patients often present with painless rectal bleeding after defecation. Bleeding is generally scant and intermittent; rarely iron deficiency anemia is the chief presenting symptom. Extensive bleeding can occur but is generally self-limited, requiring supportive care until the bleeding stops spontaneously after autoamputation. Occasionally endoscopic polypectomy is required for control of bleeding. Abdominal pain or cramps are uncommon unless associated with intussusception. Patients can present with prolapse, with a dark, edematous, pedunculated mass protruding from the rectum. Mucus discharge and pruritus are associated with prolapse.

Patients presenting with rectal bleeding require thorough work-up; differential diagnosis includes anal fissure, other intestinal polyposis syndromes, Meckel diverticulum, inflammatory bowel disease, intestinal infections, Henoch-Schönlein purpura, or coagulopathy.

Diagnosis and therapy are best accomplished via endoscopy. Polyps may be visualized via air-contrast barium enema, but this provides no therapeutic advantage and is uncomfortable and usually performed without sedation or anesthesia. Colonoscopy affords opportunity for biopsy, polypectomy by snare cautery, and visualization of synchronous lesions; up to 50% of children have 1 or more additional polyps, and approximately 20% may have more than 5 polyps. Retrieved polyps should be sent for histologic evaluation for definitive diagnosis.

Juvenile Polyposis Syndrome

Patients with juvenile polyposis syndrome (JPS) present with multiple juvenile polyps, ≥5 but typically 50-200. Polyps may be isolated to the colon or distributed throughout the GI tract. There is often a family history (20-50%) with an autosomal dominant pattern of variable penetrance. Alterations in transforming growth factor-β pathways have been identified in some JPS patients and families; mutations in *SMAD4* or *BMPR1A* are found in 50-60% of patients with JPS. Genetic testing is available for both of these mutations. Clinical diagnosis of JPS is established by presence of 1 of the following: 3-10 polyps on colonoscopy; polyps outside the colon; or any number of polyps in a patient with a family history of JPS.

Histologically, these polyps are identical to solitary juvenile polyps; however, the GI malignancy risk is greatly increased (10-50%). Most malignancy is colorectal, although gastric, upper GI, and pancreatic tumors have been described. The risk of malignancy is greater in patients with >3 polyps and a positive family history. These patients

should therefore undergo routine esophagogastroduodenoscopy, colonoscopy, and upper GI contrast studies. Serial polypectomy or polyp biopsy should be undertaken if possible. If dysplasia or malignant degeneration is found, a total colectomy is indicated.

Juvenile polyposis of infancy is characterized by early polyp formation (younger than 2 yr of age) and may be associated with protein-losing enteropathy, hypoproteinemia, anemia, failure to thrive, and intussusception. Early endoscopic or surgical intervention may be needed.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder (incidence: ~1 : 120,000 total population) characterized by mucocutaneous pigmentation and extensive GI hamartomatous polyposis. Macular pigmented lesions may be dark brown to dark blue and are found primarily around the lips and oral mucosa, although these lesions may also be found on the hands, feet, or perineum. Lesions can fade by puberty or adulthood.

Polyps are primarily found in the small intestine (in order of prevalence: jejunum, ileum, duodenum) but may also be colonic or gastric. Histologically, polyps are defined by normal epithelium surrounding bundles of smooth muscle arranged in a branching or frondlike pattern. Symptoms arising from GI polyps in PJS are similar to those of other polyposis syndromes, namely bleeding and abdominal cramping from obstruction or recurrent intussusception. Patients can require repeated laparotomies and intestinal resections.

The diagnosis of PJS is made clinically in patients with histologically proven hamartomatous polyps if 2 of 3 conditions are met: positive family history with an autosomal dominant inheritance pattern, mucocutaneous hyperpigmentation, and small bowel polyposis. Genetic testing can reveal mutations in *LKB1/STK11;* (19p13.3), a serine-threonine kinase that acts as a tumor-suppressor gene. Up to 94% of patients with clinical characteristics of PJS have a mutation at this locus. Only 50% of patients with PJS have an affected family member, suggesting a high rate of spontaneous mutations.

Patients with PJS have increased risk of GI and extraintestinal malignancies. Lifetime cancer risk has been reported from 47-93%. Colorectal, breast, and reproductive tumors are most common. GI surveillance should begin in childhood (by age 8 yr or when symptoms occur) with upper and lower endoscopy. The small bowel may be evaluated radiographically, with enteroscopy, or with wireless capsule endoscopy. Polyps larger than 1.5 cm should be removed. Screening for breast, gynecologic, and testicular cancers should be routine after age 18 yr.

PTEN Hamartoma Tumor Syndromes

Mutations in the tumor-suppressor gene protein tyrosine phosphatase and tensin homolog (*PTEN*) are associated with several rare autosomal dominant syndromes, including Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome. These patients present with multiple hamartomas in skin (99%), brain, breast, thyroid, endometrium, and GI tract (60%). Patients are at increased risk for breast and thyroid malignancies; the risk of GI cancer does not appear to be elevated.

ADENOMATOUS TUMORS

Adenomatous Polyposis Coli-Associated Polyposis Syndromes

Familial adenomatous polyposis (FAP) is the most common genetic polyposis syndrome (incidence 1 : 5,000 to 1 : 17,000 persons) and is characterized by numerous adenomatous polyps throughout the colon, as well as extraintestinal manifestations. FAP and related syndromes (attenuated FAP; Gardner and Turcot syndromes) are linked to mutations in the adenomatous polyposis coli *(APC)* gene, a tumor suppressor mapped to 5q21. *APC* regulates degradation of β-catenin, a protein with roles in regulation of the cytoskeleton, tissue architecture organization, cell migration and adherence, and numerous other functions. Intracellular accumulation of β-catenin may be responsible for colonic epithelial cell proliferation and adenoma formation. More than 400 APC mutations have been described, and up to 30% of patients present with no family history (spontaneous mutations).

Polyps generally develop late in the 1st decade of life or in adolescence (mean age of presentation is 16 yr). At the time of diagnosis, 5 or more adenomatous polyps are present in the colon and rectum. By young adulthood the number typically increases to hundreds or even thousands. Adenomatous polyps (or adenomas) are precancerous lesions within the surface epithelium of the intestine, displaying various degrees of dysplasia. Without intervention, the risk of developing colon cancer is 100% by the 5th decade of life (average age of cancer diagnosis is 40 yr). Other GI adenomas can develop, particularly in the stomach and duodenum (50-90%).The risk of periampullary or duodenal carcinoma is significantly elevated (4-12% lifetime risk). Young patients with FAP are also at increased risk for developing hepatoblastoma (1.6% before age 5 yr).

Extraintestinal manifestations of FAP may be present from birth or develop in early childhood. Lesions include congenital hypertrophy of retinal pigment epithelium, desmoid tumors, epidermoid cysts, osteomas, fibromas, and lipomas. Many of these benign soft-tissue tumors appear before intestinal polyps develop. Expression of extraintestinal findings can depend on location of mutation on the *APC* gene.

Other syndromes associated with *APC* mutations include Gardner syndrome, classically characterized by multiple colorectal polyps, desmoid tumors, and soft-tissue tumors including fibromas, osteomas (typically mandibular), epidermoid cysts, and lipomas. Once thought to be a distinct clinical entity, Gardner syndrome shares many characteristics with FAP. Up to 20% of FAP patients present with the classic extraintestinal manifestations once associated with Gardner syndrome. Some (but not all) cases of Turcot syndrome are also related to *APC*. These patients present with colorectal polyposis and primary brain tumors (medulloblastoma). Attenuated FAP is characterized by a significantly increased risk of colorectal cancer but fewer polyps than classic FAP (average: 30 polyps). The average age of cancer diagnosis in this form of FAP is 50-55 yr. Upper GI tumors and extraintestinal manifestations may be present but are less common.

The clinical presentation of FAP is variable. Polyps are generally asymptomatic initially (and might remain so). If symptoms develop, they can include rectal bleeding (possibly with secondary anemia), cramping, and diarrhea. The presence of symptoms at presentation does not correlate with malignant changes. Diagnosis should be suspected from family history, and ensuing sigmoidoscopy or colonoscopy is confirmatory. Histologic examination of biopsied polyps reveals adenomatous architecture (as opposed to inflammatory or hamartomatous polyps found in other polyposis syndromes) with varying degrees of dysplasia. Genetic testing for *APC* mutations is clinically available, and index patients should be tested. If a mutation is identified, affected family members should be screened and appropriate genetic counseling should be provided. If the index patient does not demonstrate a defined mutation, family members may undergo genetic testing, which might identify novel *APC* mutations. Children with identified *APC* mutations must undergo careful surveillance, with sigmoidoscopy every 1-2 yr. Once polyps are identified, colonoscopy should be performed annually. Patients should also have upper endoscopy after development of colonic polyps to monitor for gastric and especially duodenal lesions.

Treatment of FAP requires prophylactic proctocolectomy to prevent cancer. Ileoanal pull-through procedures restore bowel continuity, with acceptable functional outcomes. Resection should be done once polyposis has become extensive (>20-30) or by the mid-teens. Nonsteroidal antiinflammatory agents, such as sulindac, and cyclooxygenase-2 inhibitors, such as celecoxib, might inhibit polyp progression. No guidelines have been established, however, and their efficacy in preventing malignant transformation of existing polyps is unknown.

Carcinoma

Primary carcinomas of the small bowel or colon are extremely rare in children. Development of adenocarcinoma in adolescence or early

adulthood may be associated with a genetic predisposition or syndrome such as FAP, hereditary nonpolyposis colon carcinoma, PJS, or inflammatory bowel disorders such as Crohn disease or ulcerative colitis.

Colorectal carcinoma, though rare (reported incidence of 1 case per 1,000,000 persons younger than 19 yr of age), is the most common primary GI carcinoma in children. Many cases are spontaneous (i.e., not associated with a genetic predisposition or syndrome). Histologically, tumors tend to be poorly differentiated and pathologically aggressive. Patients may be asymptomatic, or they present with nonspecific signs and symptoms such as abdominal pain, constipation, and vomiting. Delay in diagnosis is common. Many patients present with advanced-stage disease, with microscopic or gross metastases at the time of diagnosis. Surgical resection is the primary treatment modality, although with delayed presentation and advanced-stage disease, complete resection may not be possible. Chemotherapy and radiation have a limited role in patients with metastatic disease.

OTHER GASTROINTESTINAL TUMORS

Lymphoma

Lymphoma is the most common GI malignancy in the pediatric population. Approximately 30% of children with non-Hodgkin lymphoma present with abdominal tumors. Immunocompromised patients have an increased incidence of lymphoma. Predisposing conditions include HIV/AIDS, agammaglobulinemia, long-standing celiac disease, and bone marrow or solid-organ transplantation. Lymphoma can occur anywhere in the GI tract, but it most commonly occurs in distal small bowel and ileocecal region. Presenting symptoms include crampy abdominal pain, vomiting, obstruction, bleeding, or palpable mass. Lymphoma should be considered in patients older than 3 yr of age who present with intussusception.

Nodular Lymphoid Hyperplasia

Lymphoid follicles in the lamina propria and submucosa of the gut normally aggregate in Peyer patches, most prominently in the distal ileum. These follicles can become hyperplastic, forming nodules that protrude into the lumen of the bowel. Some suggested etiologies are infectious (classically *Giardia*), allergic, or immunologic. Nodular lymphoid hyperplasia has been described in infants with enterocolitis secondary to dietary protein sensitivity. This phenomenon has also been described in patients with inflammatory bowel disease and Castleman disease. Patients may be asymptomatic or may present with abdominal pain, rectal bleeding, diarrhea, or intussusception. Nodular lymphoid hyperplasia usually resolves spontaneously and rarely requires therapy; in cases with severe pain or bleeding, corticosteroids may be effective.

Carcinoid Tumor

Carcinoids are neuroendocrine tumors of enterochromaffin cells, which can occur throughout the GI tract, but in children they are typically found in the appendix. This is often an incidental diagnosis at the time of appendectomy. Complete resection of small tumors (<1 cm) with clear surgical margins is curative. Appendiceal tumors >2 cm mandate further bowel resection. Carcinoid tumors outside the appendix (small intestine, rectum, stomach) are more likely to metastasize. Metastatic carcinoid tumor within the liver can give rise to the carcinoid syndrome. Serotonin, 5-hydroxytryptophan, or histamine are elaborated by the tumor, and elevated serum levels cause cramps, diarrhea, vasomotor disturbances (flushing), bronchoconstriction, and right-heart failure. The diagnosis is confirmed by elevated urinary 5-hydroxyindoloacetic acid. Symptomatic relief of carcinoid symptoms may be achieved with administration of somatostatin analogs (octreotide).

Leiomyoma

Leiomyomas are rare benign tumors that can arise anywhere in the GI tract, although most often in the stomach, jejunum, or distal ileum. Age of presentation is variable, from the newborn period through adolescence. Patients may be asymptomatic or can present with an abdominal mass, obstruction, intussusception, volvulus, or pain and bleeding from central necrosis of the tumor. Surgical resection is the treatment of choice. Pathologically, these tumors may be difficult to distinguish from malignant leiomyosarcomas. Smooth muscle tumors occur with increased incidence in children with HIV or those requiring immunosuppression after transplantation.

Gastrointestinal Stromal Cell Tumors

Gastrointestinal stromal cell tumors (GISTs) are intestinal mesenchymal tumors that probably arise from interstitial cells of Cajal or their precursors. Historically, these may have been diagnosed as tumors of smooth muscle or neural cell origin. The World Health Organization recognized GIST in 1990 as a distinct neoplasm. Typically GISTs arise in adults, after the 3rd decade of life. Cases have also been reported in the pediatric population, generally in adolescents. In the pediatric population tumors are most commonly found in the stomach, though they can occur anywhere in the GI tract or even the mesentery or omentum. Patients may be asymptomatic or can present with an abdominal mass, lower GI bleeding, or obstruction. Treatment consists of surgical en bloc resection of local disease. Recurrence rates are high and early postoperative surveillance is recommended. GISTs occurring in adults are typically associated with mutation in the *KIT* oncogene. This mutation is less commonly found in pediatric GISTs (~15%). Adjuvant therapy for *KIT*$^+$ lesions is imatinib or sunitinib, tyrosine kinase inhibitors that are available as oral therapy. Patients with persistent disease or metastases might benefit from treatment.

Vascular Tumors

Vascular malformations and hemangiomas are rare in children. The usual presentation is painless rectal bleeding, which may be chronic or acute, with massive or even fatal hemorrhage. There are usually no associated symptoms, although intussusception has been described. Half of patients have associated cutaneous hemangiomas or telangiectasias. These lesions may be associated with blue rubber bleb nevus syndrome or hereditary hemorrhagic telangiectasia. About half of these lesions are in the colon and can be identified on colonoscopy. During acute bleeding episodes, bleeding can be localized via nuclear medicine bleeding scans, mesenteric angiography, or endoscopy. Colonic bleeding may be controlled by endoscopic means. Surgical intervention is required only occasionally for isolated lesions.

Bibliography is available at Expert Consult.

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Chapter 346

Inguinal Hernias

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Inguinal hernias are one of the most common conditions seen in pediatric practice and the most common surgical procedure performed in pediatric surgical practice. The frequency of this condition in concert with its potential morbidity of ischemic injury to the intestine, testis, or ovary makes proper diagnosis and management an important part of daily practice for pediatric practitioners and pediatric surgeons. The overwhelming majority of inguinal hernias in infants and children are congenital **indirect** hernias (99%) as a consequence of a patent processus vaginalis (PV); a developmental structure important in testicular descent. The incidence of inguinal hernia in children is up to 10 times higher in boys than in girls. Two other types of inguinal hernia are **direct** (acquired) hernia (0.5-1.0%) and **femoral** hernia (<0.5%). Approximately 50% of inguinal hernias manifest clinically in the 1st yr of life, most in the 1st 6 mo. Premature infants have an incidence of

inguinal hernia approaching 30%. The risk of incarceration and possible strangulation of an inguinal hernia is also greatest in the 1st yr of life (30-40%) and mandates prompt identification and operative repair to minimize morbidity and complications.

EMBRYOLOGY AND PATHOGENESIS

Indirect inguinal hernias in infants and children are congenital and result from an arrest of embryologic development; failure of obliteration of the PV rather than a weakness in the inguinal musculature. The pertinent developmental anatomy of indirect inguinal hernia relates to development of the gonads and descent of the testis through the internal ring and into the scrotum late in gestation. The testes descend from the urogenital ridge in the retroperitoneum to the area of the internal ring by about 28 wk of gestation. The final descent of the testes into the scrotum occurs late in gestation between weeks 28 and 36. The testis is preceded in descent to the scrotum by the gubernaculum and the PV. The PV, an outpouring of peritoneum in the lower abdomen, is present in the developing fetus at 12 wk gestation that develops lateral to the deep inferior epigastric vessels and descends anteriorly along the spermatic cord within the cremasteric fascia through the internal inguinal ring. The testis accompanies the PV as it exits the abdomen and descends into the scrotum. The gubernaculum testis forms from the mesonephros (developing kidney), attaches to the lower pole of the testis, and directs the testis through the internal ring, inguinal canal and into the scrotum. The testis passes through the inguinal canal in a few days but takes about 4 wk to migrate from the external ring to the scrotum. The cord-like structures of the gubernaculum occasionally pass to ectopic locations (perineum or femoral region), resulting in ectopic testes.

In the last few weeks of gestation or shortly after birth, the layers of the PV normally fuse together and obliterate the patency from the peritoneal cavity through the inguinal canal to the testis. The PV also obliterates just above the testes, and the portion of the PV that envelops the testis becomes the tunica vaginalis. In girls, the PV obliterates earlier, at approximately 7 mo of gestation, and may explain why girls demonstrate a much lower incidence of inguinal hernia. *Failure of the PV to close permits fluid or abdominal viscera to escape the peritoneal cavity into the extraabdominal inguinal canal and accounts for a variety of inguinal–scrotal abnormalities seen in infancy and childhood.* The ovaries descend into the pelvis from the urogenital ridge but do not exit from the abdominal cavity. The cranial portion of the gubernaculum in girls differentiates into the ovarian ligament, and the inferior aspect of the gubernaculum becomes the round ligament, which passes through the internal ring and attaches to the labia majora. The PV in girls extends into the labia majora through the inguinal canal and is also known as the canal of Nuck. Involution of the left-sided PV precedes that of the right; which is consistent with the increased incidence of indirect inguinal hernias on the right side (60%).

Androgenic hormones, adequate end-organ receptors, and mechanical factors such as increased intra-abdominal pressure influence complete descent of the testis through the inguinal canal. The testes and spermatic cord structures (spermatic vessels and vas deferens) are located in the retroperitoneum but are affected by increases in intraabdominal pressure as a consequence of their intimate attachment to the descending PV. The genitofemoral nerve also has an important role: It innervates the cremaster muscle, which develops within the gubernaculum, and experimental division or injury to both nerves in the fetus prevents testicular descent. Failure of regression of smooth muscle (present to provide the force for testicular descent) might have a role in the development of indirect inguinal hernias. Several studies have investigated genes involved in the control of testicular descent for their role in closure of the patent PV, for example, hepatocyte growth factor and calcitonin gene-related peptide. Unlike in adult hernias, there does not appear to be any change in collagen synthesis associated with inguinal hernias in children (Fig. 346-1).

A **direct inguinal hernia** originates medial to the deep inferior epigastric vessels and is external to the cremasteric fascia; the hernia sac directly through the posterior wall of the inguinal canal. A **femoral hernia** originates medial to the femoral vein and descends inferior to the inguinal ligament along the femoral canal.

GENETICS

There is some genetic risk incurred for siblings of patients with inguinal hernias; the sisters of affected girls are at the highest risk, with a relative risk of 17.8. In general, the risk of brothers of a sibling is approximately 4-5, as is the risk of a sister of an affected brother. Both a multifactorial threshold model and autosomal dominance with incomplete penetrance and sex influence have been suggested as an explanation for this pattern of inheritance.

PATHOLOGY

Failure of closure of the PV leads to a number of common inguinal–scrotal conditions in infants and children including; inguinal hernia, scrotal hydrocele (communicating and noncommunicating), and hydrocele of the spermatic cord. Closure of the PV is often incomplete at birth and continues postnatally; the rate of patency is inversely proportional to the age of the child. It has been estimated that the patency rate of the PV is as high as 80% at birth and decreases to ≈40% during the 1st yr of life, and that ≈20% of boys have a persistent patency of the PV at 2 yr of age. Patency of the PV after birth is an opening from the abdominal cavity to the inguinal region and therefore a potential hernia, but not all patients will develop a clinical hernia. An inguinal hernia occurs clinically when intraabdominal contents escape

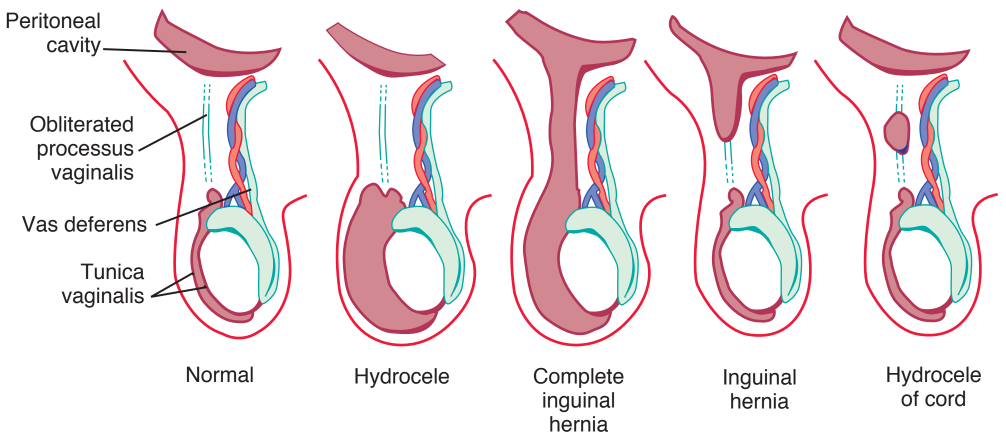

Figure 346-1 Hernia and hydroceles. *(Modified from Scherer LR III, Grosfeld JL: Inguinal and umbilical anomalies,* Pediatr Clin North Am *40:1121–1131, 1993.)*

Table 346-1 Predisposing Factors for Hernias

Prematurity
Urogenital
• Cryptorchidism
• Exstrophy of the bladder or cloaca
• Ambiguous genitalia
• Hypospadias/epispadius
Increased peritoneal fluid
• Ascites
• Ventriculoperitoneal shunt
• Peritoneal dialysis catheter
Increased intraabdominal pressure
• Repair of abdominal wall defects
• Severe ascites (chylous)
• Meconium peritonitis
Chronic respiratory disease
• Cystic fibrosis
Connective tissue disorders
• Ehlers-Danlos syndrome
• Hunter-Hurler syndrome
• Marfan syndrome
• Mucopolysaccharidosis

the abdominal cavity and enter the inguinal region through the patency. Based on their location in the inguinal canal (lateral to the inferior epigastric vessels), these are **indirect** inguinal hernias but are rarely associated with a muscular weakness or defect, as is typical of an adult hernia. Depending on the extent of patency of the PV, the hernia may be confined to the inguinal region or pass down into the scrotum. Complete failure of obliteration of the PV, mostly seen in infants, predisposes to a complete inguinal hernia characterized by a protrusion of abdominal contents into the inguinal canal and possibly extending into the scrotum. Obliteration of the PV distally (around the testis) with patency proximally results in the classic indirect inguinal hernia with the protrusion in the inguinal canal.

A **hydrocele** is when only fluid enters the patent PV; the swelling may exist only in the scrotum (scrotal hydrocele), only along the spermatic cord in the inguinal region (hydrocele of the spermatic cord), or extend from the scrotum through the inguinal canal and even into the abdomen (abdominal–scrotal hydrocele). A hydrocele is termed a *communicating hydrocele* if it demonstrates fluctuation in size, often increasing in size after activity and, at other times, being smaller when the fluid decompresses into the peritoneal cavity. Occasionally, hydroceles develop in older children following trauma, inflammation, or tumors affecting the testis. Although reasons for failure of closure of the PV are unknown, it is more common in cases of testicular nondescent (cryptorchidism) and prematurity. In addition, persistent patency of the PV is twice as common on the right side, presumably related to later descent of the right testis and interference with obliteration of the PV from the developing inferior vena cava and external iliac vein. Table 346-1 lists the risk factors identified as contributing to the development of clinical inguinal hernia and that relate to conditions that predispose to failure of obliteration of the PV. Incidence of inguinal hernia in patients with cystic fibrosis is approximately 15%, believed to be related to an altered embryogenesis of the wolffian duct structures, which leads to an absent vas deferens in males with this condition. There is also an increased incidence of inguinal hernia in patients with **testicular feminization syndrome** and other disorders of sexual development. The rate of recurrence after repair of an inguinal hernia in patients with a connective tissue disorder approaches 50%, and often the diagnosis of connective tissue disorders in children results from investigation after development of a recurrent inguinal hernia.

INCIDENCE

The incidence of congenital indirect inguinal hernia in full-term newborn infants is estimated at 3.5-5.0%. The incidence of hernia in preterm and low birthweight infants is considerably higher, ranging from 9-11%, and approaches 30% in very-low birthweight infants (<1,000 g) and preterm infants (<28 wk of gestation). Inguinal hernia is much more common in boys than girls, with a male : female ratio of approximately 8 : 1. Approximately 60% of inguinal hernias occur on the right side, 30% are on the left side, and 10% are bilateral. The incidence of bilateral hernias is higher in girls and appears to be 20-40%. An increased incidence of congenital inguinal hernia has been documented in twins and in family members of patients with inguinal hernia. There is a history of another inguinal hernia in the family in 11.5% of patients.

CLINICAL PRESENTATION

An inguinal hernia typically appears as a bulge or mass in the inguinal region. In boys, the mass potentially extends through the inguinal area into the scrotum; in girls the mass typically occurs in the upper portion of the labia majora. The bulge or mass is most visible at times of irritability or increased intraabdominal pressure (crying, straining, coughing). It may be present at birth or might not appear until weeks, months, or years later. The bulge is most often first noted by the parents or on routine examination by the primary care physician. The classic history from the parents is of intermittent groin, labial, or scrotal swelling that spontaneously reduces but that is gradually enlarging or is more persistent and is becoming more difficult to reduce. The **hallmark signs** of an inguinal hernia on physical examination are a smooth, firm mass that emerges through the external inguinal ring lateral to the pubic tubercle and enlarges with increased intraabdominal pressure. When the child relaxes, the hernia typically reduces spontaneously or can be reduced by gentle pressure, first posteriorly to free it from the external ring and then upward toward the peritoneal cavity. In boys, the hernia sac contains intestines; female infants often have an ovary and fallopian tube in the hernia sac.

Methods used to demonstrate the hernia on examination vary depending on the age of the child. A quiet infant can be made to strain the abdominal muscles by stretching the infant out supine on the bed with legs extended and arms held straight above the head. Most infants struggle to get free, thus increasing the intraabdominal pressure and pushing out the hernia. Older patients can be asked to perform the Valsalva maneuver by blowing up a balloon or coughing. The older child should be examined while standing and examination after voiding also can be helpful. With increased intraabdominal pressure, the protruding mass is obvious on inspection of the inguinal region or can be palpated by an examining finger invaginating the scrotum to palpate at the external ring. Another test is the **"silk glove sign,"** which describes the feeling of the layers of the hernia sac as they slide over the spermatic cord structures with rolling of the spermatic cord beneath the index finger at the pubic tubercle. A femoral hernia appears as a protrusion on the medial aspect of the thigh, below the inguinal region and does not enter the scrotum or labia. In the absence of a bulge, the finding of increased thickness of the inguinal canal structures on palpation also suggests the diagnosis of an inguinal hernia. It is important on examination to note the position of the testes because retractile testes are common in infants and young boys and can mimic an inguinal hernia with a bulge in the region of the external ring. Because in the female patient approximately 20-25% of inguinal hernias are sliding hernias (the contents of the hernia sac are adherent within the sac and therefore not reducible), a fallopian tube or ovary can be palpated in the inguinal canal as a firm, slightly mobile, nontender mass in the labia or inguinal canal.

As the majority of young child hernias reduce spontaneously, the physical examination in the office can be equivocal. Infants and children with a strong history suggestive of inguinal hernia and an equivocal clinical examination may be offered ultrasound or referral to a pediatric surgeon. In recent years, diagnostic laparoscopy has been increasingly used to evaluate for suspected inguinal hernia; particularly in infants where the risk of incarceration and potential injury to the intestines or testis is high. In an older child with low risk of

incarceration, the parents can be educated and asked to observe for the bulge and take a digital image at home.

EVALUATION OF ACUTE INGUINAL–SCROTAL SWELLING

Commonly in pediatric practice, an inguinal–scrotal mass appears suddenly in an infant or child and is associated with discomfort. The **differential diagnosis** includes incarcerated inguinal hernia, acute hydrocele, torsion of an undescended testis, and suppurative inguinal lymphadenitis. Differentiating between the incarcerated inguinal hernia and the acute hydrocele is probably the most difficult. The infant or child with an incarcerated inguinal hernia is likely to have associated findings suggesting intestinal obstruction, such as colicky abdominal pain, abdominal distention, vomiting, and cessation of stool, and might appear ill. The infant with an acute hydrocele might have discomfort but is consolable and tolerates feedings without signs or symptoms suggesting intestinal obstruction. When the diagnosis is incarcerated inguinal hernia, plain radiographs typically demonstrate distended intestines with multiple air–fluid levels.

On examination of the child with the acute hydrocele, the clinician may note that the mass is somewhat mobile. In addition, in the area between the suspected hydrocele mass and the internal ring, the cord structures can appear only slightly thickened. With the incarcerated hernia, there is a lack of mobility of the groin mass and marked swelling or mass extending from the scrotal mass through the inguinal area and up to and including the internal ring. An experienced clinician can selectively use a bimanual examination to help differentiate groin abnormalities. The examiner palpates the internal ring per rectum, with the other hand placing gentle pressure on the inguinal region over the internal ring. In cases of an indirect inguinal hernia, an intraabdominal organ can be palpated extending through the internal ring.

Another method used in evaluation is **transillumination.** It must be noted that transillumination can be misleading because the thin wall of the infant's intestine can approximate that of the hydrocele wall and both might transilluminate. This is also the reason aspiration to determine the contents of a groin mass is discouraged. **Ultrasonography** can help distinguish between a hernia, a hydrocele, and lymphadenopathy. An expeditious diagnosis is important to avoid the potential complications of an incarcerated hernia, which can develop rapidly. Diagnostic laparoscopy has emerged as an effective and reliable tool in this setting by pediatric surgeons but requires general anesthesia.

The occurrence of suppurative adenopathy in the inguinal region can be confused with an incarcerated inguinal hernia. Examination of the watershed area of the inguinal lymph node might reveal a superficial infected or crusted lesion. In addition, the swelling associated with inguinal lymphadenopathy is typically located more inferior and lateral than the mass of an inguinal hernia, and there may be other associated enlarged nodes in the area. Torsion of an undescended testis can manifest as a painful erythematous mass in the groin. The absence of a gonad in the scrotum in the ipsilateral side should clinch this diagnosis.

Incarcerated Hernia

Incarceration is a common consequence of untreated inguinal hernia in infants and presents as a nonreducible mass in the inguinal canal, scrotum, or labia. Contained structures can include small bowel, appendix, omentum, colon, or, rarely, Meckel diverticulum. In girls, the ovary, fallopian tube, or both are commonly incarcerated. Rarely, the uterus in infants can also be pulled into the hernia sac. A **strangulated hernia** is one that is tightly constricted in its passage through the inguinal canal and, as a result, the hernia contents have become ischemic or gangrenous.

Although incarceration may be tolerated in adults for years, most nonreducible inguinal hernias in children, unless treated, rapidly progress to strangulation with potential infarction of the hernia contents or intestinal obstruction. Initially, pressure on the herniated viscera leads to impaired lymphatic and venous drainage. This leads, in turn, to swelling of the herniated viscera, which further increases the compression in the inguinal canal, ultimately resulting in total occlusion of the arterial supply to the trapped viscera. Progressive ischemic changes take place, culminating in gangrene and/or perforation of the herniated viscera. The testis is at risk of ischemia because of compression of the testicular blood vessels by the strangulated hernia. In girls, herniation of the ovary places it at risk of strangulation and torsion. The incidence of incarceration of an inguinal hernia is between 12% and 17% throughout childhood; two-thirds of incarcerated hernias occur in the 1st yr of life. The greatest risk is in infants younger than 6 mo of age, with reported incidences of incarceration between 25% and 30%. The incidence of incarceration is slightly less in premature infants, although the reasons are unclear.

The symptoms of an incarcerated hernia are irritability, feeding intolerance, and abdominal distention in the infant; pain in the older child. Within a few hours, the infant becomes inconsolable; lack of flatus or stool signals complete intestinal obstruction. A somewhat tense, nonfluctuant mass is present in the inguinal region and can extend down into the scrotum or labia. The mass is well defined, firm, and does not reduce. With the onset of ischemic changes, the pain intensifies, and the vomiting becomes bilious or feculent. Blood may be noted in the stools. The mass is typically tender, and there is often edema and erythema of the overlying skin. The testes may be normal, demonstrate a reactive hydrocele, or may be swollen and hard on the affected side because of venous congestion resulting from compression of the spermatic veins and lymphatic channels at the inguinal ring by the tightly strangulated hernia mass. Abdominal radiographs demonstrate features of partial or complete intestinal obstruction, and gas within the incarcerated bowel segments may be seen below the inguinal ligament or within the scrotum.

Ambiguous Genitalia

Infants with disorders of sexual development commonly present with inguinal hernias, often containing a gonad, and require special consideration. In female infants with inguinal hernias, particularly if the presentation is bilateral inguinal masses, **testicular feminization syndrome** should be suspected (>50% of patients with testicular feminization have an inguinal hernia) (see Chapter 588). Conversely, the true incidence of testicular feminization in all female infants with inguinal hernias is difficult to determine but is approximately 1%. In phenotypic females, if the diagnosis of testicular feminization is suspected preoperatively, the child should be screened with a buccal smear for Barr bodies and appropriate genetic evaluation before proceeding with the hernia repair. The diagnosis of testicular feminization is occasionally made at the time of operation by identifying an abnormal gonad (testis) within the hernia sac or absence of the uterus on laparoscopy or rectal exam. In the normal female infant, the uterus is easily palpated as a distinct midline structure beneath the symphysis pubis on rectal examination. Preoperative diagnosis of testicular feminization syndrome or other disorders of sexual development such as mixed gonadal dysgenesis and selected pseudohermaphrodites enables the family to receive genetic counseling, and gonadectomy can be accomplished at the time of the hernia repair.

MANAGEMENT

The presence of an inguinal hernia in the pediatric age group constitutes the indication for operative repair. An inguinal hernia does not resolve spontaneously, and early repair eliminates the risk of incarceration and the associated potential complications, particularly in the 1st 6-12 mo of life. The timing of operative repair depends on several factors, including age, general condition of the patient, and comorbid conditions. In infants (younger than 1 yr old) with an inguinal hernia, repair should proceed promptly (within 2-3 wk) because as many as 70% of incarcerated inguinal hernias requiring emergency operation occur in infants younger than 11 mo. In addition, the incidence of complications associated with *elective* hernia repair (intestinal injury, testicular atrophy, recurrent hernia, wound infection) are low (≈1%), but rise to as high as 18-20% when repair is performed at the time of

incarceration. The incidence of testicular atrophy after incarceration in infants younger than 3 mo of age has been reported as high as 30%. Therefore, an approach emphasizing prompt elective repair in infants is warranted. In children older than 1 yr, the risk of incarceration is less and the repair can be scheduled with less urgency. For the routine reducible hernia, the operation should be carried out electively shortly after diagnosis. Elective inguinal hernia repair can be safely performed in an outpatient setting with an expectation for full recovery within 48 hr. The operation should be performed at a facility with the ability to admit the patient to an inpatient unit as needed. Certain conditions can dictate postponement of repair, such as marked prematurity, intercurrent pneumonia (especially respiratory syncytial virus), other infections, or severe congenital heart disease. In cases of prematurity (1,800-2,000 g), repair is typically performed before discharge from the neonatal ICU.

The operation is most often performed under general anesthesia, but it can be performed under spinal anesthesia in selected high-risk infants in whom avoidance of intubation is preferable (because of, e.g., chronic lung disease or bronchopulmonary dysplasia). A regional caudal block or local inguinal nerve block using local anesthetic is useful to diminish perioperative pain and increase patient comfort. These techniques, along with the use of rapid-acting general anesthetics, allow the majority of infants to be discharged home within hours of operation. Prophylactic antibiotics are not routinely used except for associated conditions, such as congenital heart disease or the presence of a ventriculoperitoneal shunt. Preterm infants mandate special consideration because of their higher risk for apnea and bradycardia following general anesthesia (see Chapter 61). Infants younger than 44 wk postconceptional age and full-term infants younger than 3 mo of age and with comorbid conditions should be observed overnight with appropriate apnea and cardiorespiratory monitors.

An incarcerated, irreducible hernia without evidence of strangulation in a clinically stable patient should initially be managed nonoperatively. Unless there is clear peritonitis or bowel compromise, incarcerated hernias can usually be reduced manually using a technique called *taxis*. Manual reduction is performed first with traction caudad and posteriorly to free the mass from the external inguinal ring, and then upward to reduce the contents back into the peritoneal cavity. The attempt should not be continued if the infant is crying and resisting the pressure on the hernia. The use of cautious sedation or analgesia with experienced monitoring before attempting reduction can be helpful; this reduces intraabdominal pressure and relieves the pressure on the neck of the hernia sac at the inguinal ring. Care must be taken to avoid respiratory depression, especially common in the premature infant. Other techniques advocated to assist in the nonoperative reduction of an incarcerated inguinal hernia include elevation of the lower torso and legs. Ice packs should be avoided in infants because of the risk of hypothermia but may be used for brief periods in the older child. If reduction is successful but difficult, the patient should be observed (several hours) to ensure that feedings are tolerated and there is no concern that necrotic intestine was reduced; fortunately, this is an uncommon occurrence. Because of the high risk for early recurrent incarceration, surgical repair is performed 24-48 hr later, by which time there is less edema, handling of the sac is easier, and the risk of complications is reduced.

A common presentation in female patients is an irreducible ovary in the inguinal hernia in an otherwise asymptomatic patient. The inguinal mass is soft and nontender to gentle exam, and there is no swelling or edema; thus, there are no findings suggesting strangulation. This represents a **"sliding"** hernia with the fallopian tube and ovary fused to the wall of the hernia sac. Overzealous attempts to reduce the hernia are unwarranted and potentially harmful to the tube and ovary. The risk that incarceration of the ovary in this setting will lead to strangulation is not known. Most pediatric surgeons recommend elective repair of the hernia within 24-48 hr. For any patient who presents with a prolonged history of incarceration, signs of peritoneal irritation, or small bowel obstruction, surgery and operative reduction and repair of the hernia should be urgently performed.

Operative Management

When the hernia cannot be reduced or signs of strangulation are present, immediate operation is indicated to prevent further damage to the contents of the hernia sac or testis. If there are signs of intestinal obstruction or strangulation, urgent, initial management includes nasogastric intubation, intravenous fluids, and administration of broad-spectrum antibiotics. When fluid and electrolyte imbalance has been corrected and the child's condition is satisfactory, exploration is undertaken. The operation consists of opening of the inguinal canal, reduction of the contents of the hernia sac, separation of the hernia sac from the spermatic cord vessels and vas deferens in the inguinal canal, and high ligation of the hernia sac at the internal ring. Resection of nonviable structures within the hernia sac or of an infarcted testis may be indicated based on the experience and judgment of the surgeon. Although often the testis might appear ischemic, most testes recover after the incarceration is relieved and should not be removed.

The elective operative repair of a congenital indirect inguinal hernia is straightforward and consists of high ligation of the hernia sac (PV) at the level of the internal ring, thus preventing protrusion of abdominal contents into the inguinal canal. In boys, this requires careful separation of the sac from the spermatic cord structures and avoidance of injury to these vital structures. An associated hydrocele, present approximately 20% of the time, is released anteriorly to avoid injury to the spermatic cord structures located posteriorly. In girls, surgical repair is simpler because the hernia sac and round ligament can be ligated without concern for injury to the ovary and its blood supply, which generally remain within the abdomen. If the ovary and fallopian tube are within the sac and not reducible, the sac is ligated distal to these structures and the internal ring is closed after reducing the sac and its contents to the abdominal cavity.

Laparoscopic Inguinal Hernia Repair

Although the classic open inguinal hernia repair is most commonly performed, laparoscopic repair is increasingly used by pediatric surgeons experienced in the technique. Like the open technique, the laparoscopic technique is fundamentally a **high ligation** of the indirect inguinal hernia sac. In the open surgical technique, a small inguinal skin crease incision is employed, the inguinal canal is opened and careful identification and separation of the hernia sac from the vas deferens and the testicular blood supply is performed, followed by high ligation of the sac at the level of the internal ring (entrance point to the peritoneal cavity). In female infants, opening of the sac to visualize the ovary and fallopian tube may help avoid injury to these structures during suture ligation of the sac and also rule out testicular feminization syndrome. In laparoscopic inguinal hernia repair, the hernia sac, anterior to the vas deferens and the testicular blood vessels, is suture-ligated at the internal ring without inguinal exploration or handling of the spermatic cord structures. Proponents of the laparoscopic approach cite ease of examining the contralateral internal ring, decreased manipulation of the vas deferens and spermatic vessels, decreased operative time, and an ability to identify unsuspected direct or femoral hernias. In a prospective, randomized study, the laparoscopic approach was associated with decreased pain, parental perception of faster recovery, and parental perception of better wound cosmesis; however, complication and recurrence rates have been slightly higher for the laparoscopic approach and the approach has yet to gain wide acceptance. Laparoscopic procedures in infants should always be performed expeditiously and with low insufflations pressure to avoid the risk of cardiorespiratory compromise. Postoperative pain in both techniques is managed with oral acetaminophen for 24-48 hr; older children may require a brief period of postoperative narcotics.

Contralateral Inguinal Exploration

Controversy exists regarding when to proceed with contralateral groin exploration in infants and children with a unilateral indirect inguinal hernia. The only purpose of contralateral exploration is to avoid the occurrence of a hernia on that side at a later date. The advantages of contralateral exploration include avoidance of parental anxiety and

possibly a second anesthesia, the cost of additional surgery, and the risk of contralateral incarceration. The disadvantages of exploration include potential injury to the spermatic cord vessels, vas deferens, and testis; increased operative and anesthesia time; and the fact that, in many infants, it is an unnecessary procedure. The relevant issues in the debate revolve around the frequency of occurrence of contralateral hernias after one-sided hernia repair and the relation of this to age, gender, and side of the clinically apparent hernia. Most large series noted a chance of developing a contralateral hernia following inguinal hernia repair as 30-40% in children younger than 2 yr of age; leading most pediatric surgeons to recommend routine contralateral exploration in this age group. Unfortunately, infants and young children have delicate spermatic cord structures and when boys were studied 8-20 yr after inguinal hernia repair, 5.8% of them had decreased testicular size on the side of the repair and 1% had testicular atrophy. In girls, because of the higher incidence of bilateral inguinal hernias and elimination of concern for injury to the spermatic cord or testis, routine contralateral exploration is recommended up to age 5 or 6 yr. Laparoscopy enables assessment of the contralateral side without risk of injury to the spermatic cord structures or testis. This procedure can be performed through an umbilical incision or by passing a 30-degree or 70-degree oblique scope through the open hernia sac just before ligation of the hernia sac on the involved side. If patency of the contralateral side is demonstrated, the surgeon can proceed with bilateral hernia repair, and if the contralateral side is properly obliterated, exploration and potential complications are avoided. The downside of this approach include the risks associated with laparoscopy, and that laparoscopy cannot differentiate between a patent PV and a true hernia (Figs. 346-2 and 346-3). Infants and children with risk factors for development of an inguinal hernia or with medical conditions that increase the risk of general anesthesia should be approached with a low threshold for routine contralateral exploration.

DIRECT INGUINAL HERNIA

Direct inguinal hernias are rare in children; approximately 0.5-1%. Direct hernias appear as groin masses that extend toward the femoral vessels with exertion or straining. The etiology is from a muscular defect or weakness in the floor of the inguinal canal *medial* to the epigastric vessels. Thus, direct inguinal hernias in children are generally considered an acquired defect. In one-third of cases, the patient has a history of a prior indirect hernia repair on the side of the direct hernia, which suggests a possible injury to the floor muscles of the inguinal canal at the time of the first herniorrhaphy. Patients with **connective tissue disorders** such as Ehlers-Danlos syndrome or Marfan syndrome and mucopolysaccharidosis such as Hunter-Hurler syndrome are at increased risk for the development of direct inguinal hernias either independently or after indirect inguinal hernia repair.

Operative repair of a direct inguinal hernia involves strengthening of the floor of the inguinal canal, and many standard techniques have been described, similar to repair techniques used in adults. The repair can be performed through a single limited incision and, therefore, laparoscopic repair does not offer significant advantage. Recurrence after repair, in contrast to that in adults, is extraordinarily rare. Because typically the area of muscular weakness is small and pediatric tissues have greater elasticity, primary repair is usually possible. Prosthetic material for direct hernia repair or other approaches, such as preperitoneal repair, are rarely required in the pediatric age group. The older child with a direct inguinal hernia and a connective tissue disorder may be the exception, and a laparoscopic approach and prosthetic material in such a case can be useful for repair.

FEMORAL HERNIA

Femoral hernias are also rare in children (<1% of groin hernias in children). They are more common in girls than boys, with a ratio of 2:1. They are extremely rare in infancy and occur typically in older children. Femoral hernias represent a protrusion through the femoral canal. The bulge of a femoral hernia is located below the inguinal ligament and typically projects toward the medial aspect of the proximal thigh. Femoral hernias are more often missed clinically than direct hernias on physical examination or at the time of indirect hernia repair. Repair of a femoral hernia involves closure of the defect at the femoral canal, generally suturing the inguinal ligament to the pectineal ligament/fascia.

COMPLICATIONS

Complications after elective inguinal hernia repair are uncommon (≈1.5%) but significantly higher in association with incarceration (≈10%). The major risk of elective inguinal hernia repair in infants and children relates to the need for general anesthesia. Surgical complications can be related to technical factors (recurrence, iatrogenic cryptorchidism, inadvertent injury to the vas deferens or spermatic vessels), or to the underlying process, such as bowel ischemia, gonadal infarction, and testicular atrophy following incarceration.

Wound Infection

Wound infection occurs in <1% of elective inguinal hernia repairs in infants and children, but the incidence increases to 5-7% in association with incarceration and emergent repair. The patient typically develops fever and irritability 3-5 days after the surgery, and the wound demonstrates warmth, erythema, and fluctuance. Management consists of opening and draining the wound, a short course of antibiotics, and a

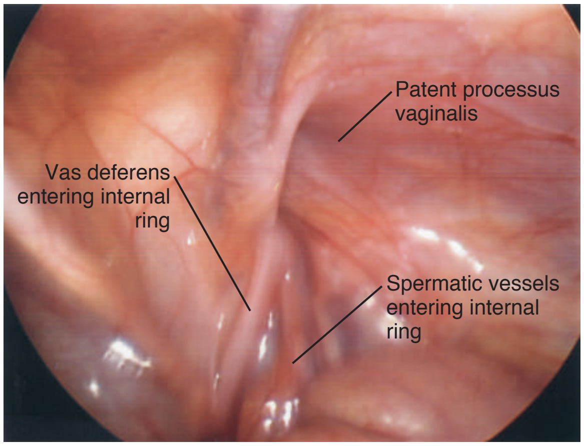

Figure 346-2 Image on laparoscopy of patent processus vaginalis on right side.

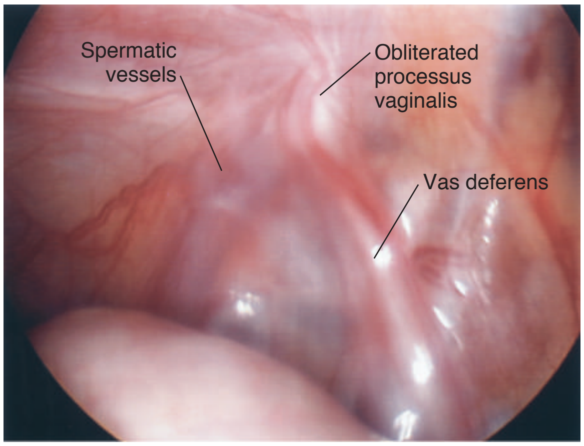

Figure 346-3 Image on diagnostic laparoscopy of obliterated processus vaginalis on left side.

daily wound dressing. Most common organisms are Gram-positive (*Staphylococcus* and *Streptococcus* spp.), and consideration should be given to coverage of methicillin-resistant *Staphylococcus aureus.* The wound generally heals in 1-2 wk with low morbidity and a good cosmetic result.

Recurrent Hernia

The recurrence rate of inguinal hernias after elective inguinal hernia repairs is generally reported as 0.5-1.0%, with rates as high as 2% for premature infants. The rate of recurrence after emergency repair of an incarcerated hernia is much higher; reported as 3-6% in most large series. The true incidence of recurrence is most certainly even higher, given the problem of accurate long-term follow-up. In the group of patients who develop recurrent inguinal hernia, the recurrence occurs in 50% within 1 yr of the initial repair and in 75% by 2 yr. Recurrence of an indirect hernia is most likely the result of a technical problem in the original procedure, such as failure to identify the sac properly, failure to perform high ligation of the sac at the level of the internal ring, or a tear in the sac that leaves a strip of peritoneum along the cord structures. Recurrence as a direct hernia can result from injury to the inguinal floor (transversalis fascia) during the original procedure or failure to identify a direct hernia during the original exploration. Patients with connective tissue disorders (collagen deficiency) or conditions that cause increased intraabdominal pressure (ventriculoperitoneal shunts, ascites, peritoneal catheter for dialysis) are at increased risk for recurrence.

Iatrogenic Cryptorchidism

Iatrogenic cryptorchidism describes malposition of the testis after inguinal hernia repair. This complication is usually related to disruption of the testicular attachment in the scrotum at the time of hernia repair or failure to recognize an undescended testis during the original procedure, allowing the testes to retract, typically to the region of the external ring. At the completion of inguinal hernia repair, the testis should be placed in a dependent intrascrotal position. If the testis will not remain in this position, proper fixation in the scrotum should be performed at the time of the hernia repair.

Incarceration

Incarceration of an inguinal hernia can result in injury to the intestines, the fallopian tube and ovary, or the ipsilateral testis. The incidence of incarceration of a congenital indirect inguinal hernia is reported as 6-18% throughout childhood and as high as 30% for infants younger than 3 mo of age. Intestinal injury requiring bowel resection is uncommon, occurring in only 1-2% of incarcerated hernias. In cases of incarceration in which the hernia is reduced nonoperatively, the likelihood of intestinal injury is low; however, these patients should be observed closely for 6-12 hr following reduction of the hernia persistent for signs and symptoms of intestinal obstruction, such as fever, vomiting, abdominal distention, or bloody stools.

The reported incidence of testicular infarction and subsequent testicular atrophy with incarceration is 4-12%, with higher rates among the irreducible cases requiring emergency operative reduction and repair. The testicular insult can be caused by compression of the gonadal vessels by the incarcerated hernia mass or as a result of damage incurred during operative repair. Young infants are at highest risk, with testicular infarction rates reported as high as 30% in infants younger than 2-3 mo of age. These problems underscore the need for prompt reduction of incarcerated hernias and early repair once the diagnosis is known to avoid repeat episodes of incarceration.

Injury to the Vas Deferens and Male Fertility

Similar to the gonadal vessels, the vas deferens can be injured as a consequence of compression from an incarcerated hernia or during operative repair. This injury is almost certainly underreported because it is unlikely to be recognized until adulthood and, even then, possibly only if the injury is bilateral. Although the vulnerability of the vas deferens has been documented in many studies, no good data exist as to the actual incidence of this problem. One review reported an incidence of injury to the vas deferens of 1.6% based on pathology demonstrating segments of the vas deferens in the hernia sac specimen; this may be overstated, because others have shown that small glandular inclusions found in the hernia sac can represent müllerian duct remnants and are of no clinical importance. The relationship between male fertility and previous inguinal hernia repair is also unknown. There appears to be an association between infertile males with testicular atrophy and abnormal sperm count and a previous hernia repair. A relationship has also been reported between infertile males with spermatic autoagglutinating antibodies and previous inguinal hernia repair. The proposed etiology is that operative injury to the vas deferens during inguinal hernia repair might result in obstruction of the vas with diversion of spermatozoa to the testicular lymphatics, and this breach of the blood–testis barrier produces an antigenic challenge, resulting in formation of spermatic autoagglutinating antibodies.

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Section 5

Exocrine Pancreas

Chapter 347

Embryology, Anatomy, and Physiology

Steven L. Werlin and Michael Wilschanski

The human pancreas develops from the ventral and dorsal domains of the primitive duodenal endoderm beginning at about the 5th wk of gestation (Fig. 347-1). The larger dorsal anlage, which develops into the tail, body, and part of the head of the pancreas, grows directly from the duodenum. The smaller ventral anlage develops as 1 or 2 buds from the primitive liver and eventually forms the major portion of the head of the pancreas. At about the 17th wk of gestation, the dorsal and ventral anlagen fuse as the buds develop and the gut rotates. The ventral duct forms the proximal portion of the major pancreatic duct of Wirsung, which opens into the ampulla of Vater. The dorsal duct forms the distal portion of the duct of Wirsung and the accessory duct of Santorini, which empties independently in approximately 5% of people. Variations in fusion might account for pancreatic developmental anomalies. Pancreatic agenesis has been associated with a base pair deletion in the ipf1 *HOX* gene, *PDX1*, and possibly in the *PTF1A* and *FS123TER* genes. Other genes involved in pancreatic organogenesis include the *IHH*, *SHH* or sonic hedgehog gene, *SMAD2*, and transforming growth factor-1β genes

The pancreas lies transversely in the upper abdomen between the duodenum and the spleen in the retroperitoneum (Fig. 347-2). The head, which rests on the vena cava and renal vein, is adherent to the C loop of the duodenum and surrounds the distal common bile duct. The tail of the pancreas reaches to the left splenic hilum and passes above the left kidney. The lesser sac separates the tail of the pancreas from the stomach.

By the 13th wk of gestation, exocrine and endocrine cells can be identified. Primitive acini containing immature zymogen granules are found by the 16th wk. Mature zymogen granules containing amylase,

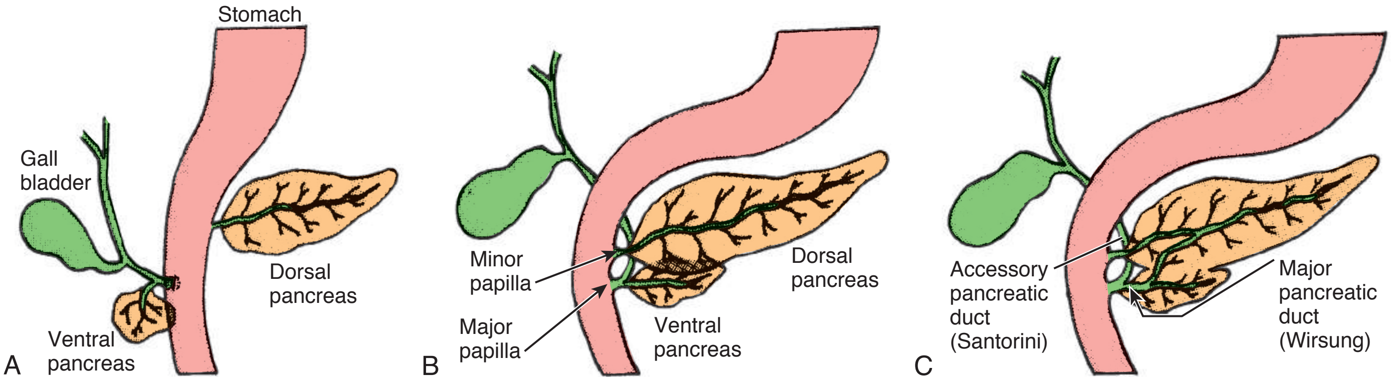

Figure 347-1 Development of the exocrine pancreas. **A,** Gestational age 6 wk. **B,** Gestational age 7-8 wk. The ventral pancreas has rotated but has not yet fused with the dorsal pancreas. **C,** The ventral and dorsal pancreatic ductal systems have fused. *(From Werlin SL: The exocrine pancreas. In Kelly VC, editor:* Practice of pediatrics, *vol 3, Hagerstown, MD, 1980, Harper and Row, Fig. 16-1.)*

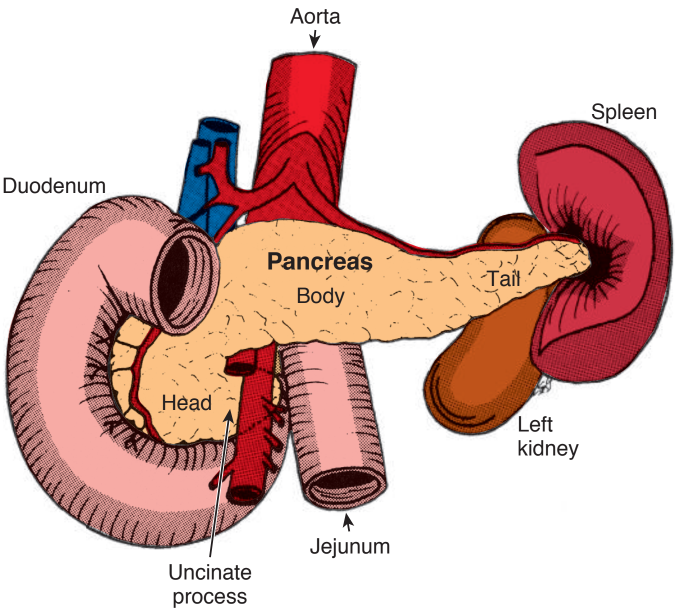

Figure 347-2 Anterior view of the pancreas: relationship to neighboring structures. *(From Werlin SL: The exocrine pancreas. In Kelly VC, editor:* Practice of pediatrics, *vol 3, Hagerstown, MD, 1980, Harper and Row, Fig. 16-2.)*

trypsinogen, chymotrypsinogen, and lipase are present at the 20th wk. Centroacinar and duct cells, which are responsible for water, electrolyte, and bicarbonate secretion, are also found by the 20th wk. The final 3-dimensional structure of the pancreas consists of a complex series of branching ducts surrounded by grape-like clusters of epithelial cells. Cells containing glucagon are present at the 8th wk. Islets of Langerhans appear between the 12th and 16th wk.

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347.1 Anatomic Abnormalities

Steven L. Werlin and Michael Wilschanski

Complete or partial **pancreatic agenesis** is a rare condition. Complete agenesis is associated with severe neonatal diabetes and usually death at an early age (see Chapter 589). Partial or dorsal pancreatic agenesis is often asymptomatic but may be associated with diabetes, congenital heart disease, polysplenia, and recurrent pancreatitis. Pancreatic agenesis is also associated with malabsorption.

An **annular pancreas** results from incomplete rotation of the left (ventral) pancreatic anlage, which may be a result of recessive mutations in the *IHH* or *SHH* genes. Patients usually present in infancy with symptoms of complete or partial bowel obstruction or in the 4th or 5th decade. There is often a history of maternal polyhydramnios. Other congenital anomalies, such as Down syndrome, tracheoesophageal fistula, intestinal atresia, imperforate anus, malrotation and cardiorenal abnormalities, and pancreatitis, may be associated with annular pancreas. Some children present with chronic vomiting, pancreatitis, or biliary colic. The treatment of choice is duodenojejunostomy. Division of the pancreatic ring is not attempted, because a duodenal diaphragm or duodenal stenosis often accompanies annular pancreas.

Ectopic pancreatic rests in the stomach or small intestine occur in approximately 3% of the population. Most cases (70%) are found in the upper intestinal tract. Recognized on barium contrast studies by their typical umbilicated appearance, they are rarely of clinical importance. On endoscopy, they are irregular, yellow nodules 2-4 mm in diameter. A pancreatic rest may rarely be the lead point of an intussusception, produce hemorrhage, or cause bowel obstruction.

Pancreas divisum, which occurs in 5-15% of the population, is the most common pancreatic developmental anomaly. As the result of failure of the dorsal and ventral pancreatic anlagen to fuse, the tail, body, and part of the head of the pancreas drain through the small accessory duct of Santorini rather than the main duct of Wirsung. Some investigators believe that this anomaly may be associated with recurrent pancreatitis when there is relative obstruction of the outflow of the ventral pancreas. Diagnosis is made by endoscopic retrograde cholangiopancreatography or by magnetic resonance cholangiopancreatography. It was recently shown that pancreatitis in patients with pancreas divisum is associated with mutations in the *CFTR* gene. Sphincterotomy is no longer recommended in these patients unless other anomalies are present.

Choledochal cysts are dilations of the biliary tract and usually cause biliary tract symptoms, such as jaundice, pain, and fever. On occasion, the presentation may be pancreatitis. The diagnosis is usually made with ultrasonography, CT or biliary scanning, or magnetic resonance cholangiopancreatography. Similarly, a choledochocele, an intraduodenal choledochal cyst may manifest with pancreatitis. The diagnosis can be difficult and require magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, or endoscopic ultrasound.

A number of rare conditions, such as Ivemark and Johanson-Blizzard syndromes include pancreatic dysgenesis or dysfunction among their features. Many of these syndromes include renal and hepatic dysgenesis along with the pancreatic anomalies.

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347.2 Physiology

Steven L. Werlin and Michael Wilschanski

The acinus is the functional unit of the exocrine pancreas. Acinar cells are arrayed in a semicircle around a lumen. Ducts that drain the acini are lined by centroacinar and ductular cells. This arrangement allows the secretions of the various cell types to mix.

The acinar cell synthesizes, stores, and secretes more than 20 enzymes, which are stored in zymogen granules, some in inactive forms. The relative concentration of the various enzymes in pancreatic juice is affected and perhaps controlled by the diet, probably by regulating the synthesis of specific messenger RNA. The main enzymes involved in digestion include *amylase*, which splits starch into maltose, isomaltose, maltotriose; dextrins; and *trypsin* and *chymotrypsin*, endopeptidases secreted by the pancreas as inactive proenzymes. Trypsinogen is activated in the gut lumen by enterokinase, a brush-border enzyme. Trypsin can then activate trypsinogen, chymotrypsinogen, and procarboxypeptidase into their respective active forms. Pancreatic lipase requires *colipase*, a coenzyme also found in pancreatic fluid, for activity. Lipase liberates fatty acids from the 1 and 3 positions of triglycerides, leaving a monoglyceride.

The stimuli for exocrine pancreatic secretion are neural and hormonal. Acetylcholine mediates the cephalic phase; cholecystokinin (CCK) mediates the intestinal phase. CCK is released from the duodenal mucosa by luminal amino acids and fatty acids. Feedback regulation of pancreatic secretion is mediated by pancreatic proteases in the duodenum. Secretion of CCK is inhibited by the digestion of a trypsin-sensitive, CCK-releasing peptide released in the lumen of the small intestine or by a monitor peptide released in pancreatic fluid.

Centroacinar and duct cells secrete water and bicarbonate. Bicarbonate secretion is under feedback control and is regulated by duodenal intraluminal pH. The stimulus for bicarbonate production is secretin in concert with CCK. Secretin cells are abundant in the duodenum.

Although normal pancreatic function is required for digestion, maldigestion occurs only after considerable reduction in pancreatic function; lipase and colipase secretion must be decreased by 90-98% before fat maldigestion occurs.

Although amylase and lipase are present in the pancreas early in gestation, secretion of both amylase and lipase is low in the infant. Adult levels of these enzymes are not reached in the duodenum until late in the 1st yr of life. Digestion of the starch found in many infant formulas depends in part on the low levels of salivary amylase that reach the duodenum. This explains the diarrhea that may be seen in infants who are fed formulas high in glucose polymers or starch. Neonatal secretion of trypsinogen and chymotrypsinogen is at approximately 70% of the level found in the 1 yr old infant. The low levels of amylase and lipase in duodenal contents of infants may be partially compensated by salivary amylase and lingual lipase. This explains the relative starch and fat intolerance of premature infants.

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Chapter **348**

Pancreatic Function Tests

Steven L. Werlin and Michael Wilschanski

INDIRECT TESTING

Pancreatic function can be measured by direct and indirect methods. An indirect test, the measurement of *fecal elastase*, which has become the standard screening test for pancreatic insufficiency, has a sensitivity and specificity > 90%. A fecal elastase > 100 µg/g of stool has a 99% predictive value in ruling out pancreatic insufficiency based on an abnormal 72 hr fecal fat. Falsely abnormal results can occur in many enteropathies, such as celiac disease, and when the stool is very loose. The activity of other pancreatic enzymes in stool is now rarely measured.

DIRECT TESTING

Classically, a triple-lumen tube was used to isolate the pancreatic secretions in the duodenum. Measurement of bicarbonate concentration and enzyme activity (*trypsin*, *chymotrypsin*, *lipase*, and *amylase*) is performed on the aspirated secretions. Because this test is cumbersome and time consuming it is infrequently used except in the research setting. Although the most commonly used direct test is collection of pancreatic juice at endoscopy after stimulation with secretin and/or cholecystokinin there is controversy over this approach.

A 72 hr stool collection for quantitative analysis of fat content is the gold standard for the diagnosis of malabsorption. The collection is usually performed at home, and the parent is asked to keep a careful dietary record, from which fat intake is calculated. A preweighed, sealable plastic container is used, which the parent keeps in the freezer. Freezing helps to preserve the specimen and reduce odor. Infants are dressed in disposable diapers with the plastic side facing the skin so that the complete sample can be transferred to the container. Normal fat absorption is >93% of intake. The presence of fat malabsorption does not differentiate between pancreatic dysfunction and enteropathies, such as celiac disease. Qualitative examination of the stool for microscopic fat globules can give false-positive and false-negative results.

Pancreatic function can also be measured by a breath test using ^{13}C-triolein as the substrate. This test has not gained widespread acceptance because it is relatively insensitive in detecting mild cases of pancreatic insufficiency, and detection of $^{13}CO_2$ requires a mass spectrophotometer that is not generally available.

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Chapter 349

Disorders of the Exocrine Pancreas

Steven L. Werlin and Michael Wilschanski

DISORDERS ASSOCIATED WITH PANCREATIC INSUFFICIENCY

Other than cystic fibrosis, conditions that cause pancreatic insufficiency are very rare in children. They include Shwachman-Diamond syndrome, Johanson-Blizzard syndrome, isolated enzyme deficiencies, enterokinase deficiency (see Chapter 338), chronic pancreatitis, and protein-calorie malnutrition (see Chapters 46 and 338).

CYSTIC FIBROSIS

(See Chapter 403.)

Cystic fibrosis (CF) is the most common lethal genetic disease in white children. By the end of the 1st yr of life, 85-90% of children with CF have pancreatic insufficiency, which, if untreated, will lead to malnutrition. Treatment of the associated pancreatic insufficiency leads to improvement in absorption, better growth, and more normal stools.

Pancreatic function can be monitored in children with CF with serial measurements of fecal elastase. Ten percent to 15% of CF patients are pancreatic sufficient and their presentation tends to be later in life, including recurrent pancreatitis, male infertility, and chronic bronchiectasis. CF is part of the newborn screen in every state in the United States and in most countries in the Western world.

SHWACHMAN-DIAMOND SYNDROME

(See Chapter 131.)

Shwachman-Diamond syndrome (SDS) is an autosomal recessive syndrome (1 per 20,000 births) caused by a mutation of the Shwachman-Bodian-Diamond *(SBDS)* gene on chromosome 7, which causes ribosomal dysfunction in 90-95% of patients. Signs and symptoms of SDS include pancreatic insufficiency; neutropenia, which may be cyclic, neutrophil chemotaxis defects, metaphyseal dysostosis, failure to thrive, and short stature. Some patients with SDS have liver or kidney involvement, dental disease, or learning difficulty. SDS is a common cause of congenital neutropenia.

Patients typically present in infancy with poor growth and steatorrhea. These children can be readily differentiated from those with CF by their normal sweat chloride levels, lack of mutations in the CF gene, characteristic metaphyseal lesions, and fatty pancreas characterized by a hypodense appearance on CT and MRI scans.

Despite adequate pancreatic replacement therapy and correction of malabsorption, poor growth commonly continues. Pancreatic insufficiency is often transient, and steatorrhea frequently spontaneously improves with age. Recurrent pyogenic infections (otitis media, pneumonia, osteomyelitis, dermatitis, sepsis) are frequent and are a common cause of death. **Thrombocytopenia is found in 70% of patients and anemia in 50%.** Development of a *myelodysplastic syndrome* can occur, with transformation to *acute myeloid leukemia* in 24%. The pancreatic acini are replaced by fat with little fibrosis. Islet cells and ducts are normal. Bone marrow transplant is the treatment of choice in patients who develop acute myeloid leukemia.

PEARSON SYNDROME

Pearson syndrome is caused by a mitochondrial DNA mutation affecting oxidative phosphorylation that manifests in infants with severe **macrocytic anemia** and **variable thrombocytopenia**. The bone marrow demonstrates vacuoles in erythroid and myeloid precursors as well as ringed sideroblasts. In addition to its role in severe bone marrow failure, pancreatic insufficiency contributes to growth failure. Mitochondrial DNA mutations are transmitted through maternal inheritance to both sexes or are sporadic.

JOHANSON-BLIZZARD SYNDROME

The features of the Johanson-Blizzard syndrome include exocrine pancreatic deficiency, aplasia or hypoplasia of the alae nasi, congenital deafness, hypothyroidism, developmental delay, short stature, ectodermal scalp defects, absence of permanent teeth, urogenital malformations, and imperforate anus. This syndrome is caused by a mutation in the *UBR1* gene found on chromosome 15. The UBR1 protein acts as a ubiquitin ligase

ISOLATED ENZYME DEFICIENCIES

Isolated deficiencies of trypsinogen, enterokinase, lipase, and colipase have been reported. Although enterokinase is a brush-border enzyme, deficiency causes pancreatic insufficiency because enterokinase is required to activate trypsinogen to trypsin in the duodenum. Deficiencies of trypsinogen or enterokinase manifest with failure to thrive, hypoproteinemia, and edema. Isolated amylase deficiency is typically developmental and resolves by age 2-3 yr.

OTHER SYNDROMES ASSOCIATED WITH PANCREATIC INSUFFICIENCY

Pancreatic agenesis, congenital pancreatic hypoplasia, and congenital rubella are rare causes of pancreatic insufficiency. Pancreatic insufficiency has also been reported in duodenal atresia and stenosis and may also be seen in an infant with familial or nonfamilial hyperinsulinemic hypoglycemia, who requires 95-100% pancreatectomy to control hypoglycemia. Pancreatic insufficiency, which may be found in children with celiac disease and undernutrition, recovers with nutritional rehabilitation.

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Chapter 350

Treatment of Pancreatic Insufficiency

Steven L. Werlin and Michael Wilschanski

The most important therapy of pancreatic insufficiency is pancreatic enzyme replacement therapy (PERT). The enzymes are enterically coated to protect the enzymes from degradation by gastric acid and from autodigestion in the small intestine. It is common for patients to change from one product to another using a 1 : 1 lipase ratio and then titrating for maximum efficacy.

The North American Cystic Fibrosis Foundation has published dosing guidelines based on age and fat ingestion (Table 350-1). Because these products contain excess protease compared with lipase, the dosage is estimated from the lipase requirement. The final dosage of PERT for children is often established by trial and error. An adequate dose is one that is followed by resumption of normal growth and the return of the stools to normal fat content, which, when desired, can be verified by a 72-hr fecal fat collection and normalization of stool consistency color. Because there is no elastase in enzyme preparations, fecal elastase can not be used to monitor appropriateness of PERT dosage. Enzyme replacement should be divided and given at the beginning of and during the meal. Enzymes should not be chewed, crushed, or dissolved in food, which would allow gastric acid to penetrate the enteric coating and destroy the enzymes. Enzymes must also be given with snacks, which contain fat. Increasing enzyme supplements beyond the recommended dose does not improve absorption, might retard growth, and can cause **fibrosing colonopathy** (see below).

A major issue has been the ingestion of enzymes by infants. The importance of correct enzyme ingestion in infants and children is obvious but there may be difficulty in feeding the infant microspheres, however small they may be. Enterically coated microspheres can be

Table 350-1	Pancreatic Enzyme Replacement Therapy
Infants (up to 12 mo)	2000-4000 units lipase/120 mL breast milk or formula
12 mo-4 yr	1000 units lipase/kg/meal initially, then titrate per response
Children older than 4 yr and adults	500 units lipase/kg/meal initially, up to maximum of 2500 units lipase/kg/meal or 10,000 units lipase/kg/day or 4,000 units lipase/g fat ingested per day
PLUS: one half the standard meal dose to be given with snacks	

Data from Borowitz D, Baker RD, Stallings V: Consensus report in nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 35:246-259, 2002.

mixed with apple sauce for oral use or crushed for use in tube feeding. Patients treated with this approach achieve growth and weight gain, proving their efficacy

Treatment of exocrine pancreatic insufficiency by oral enzyme replacement usually corrects protein malabsorption, but steatorrhea is difficult to completely correct. Factors contributing to fat malabsorption include inadequate dosage, incorrect timing of doses in relation to food consumption or gastric emptying, lipase inactivation by gastric acid, and the observation that *chymotrypsin* in the enzyme preparation digests and thus inactivates *lipase*.

When adequate fat absorption is not achieved, gastric acid neutralization with an H_2-receptor antagonist or, more commonly, a proton pump inhibitor, decreases enzyme inactivation by gastric acid and thus improves delivery of lipase into the intestine. Enteric coating also protects lipase from acid inactivation.

Untoward effects secondary to PERT include allergic reactions, increased uric acid levels, and kidney stones. **Fibrosing colonopathy**, consisting of colonic fibrosis and strictures, can occur 7-12 mo after overdose of PERT.

Fat-soluble vitamin supplements are required by pancreatic insufficiency patients because of the ongoing mild to moderate fat malabsorption that occurs despite PERT.

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Chapter 351
Pancreatitis

351.1 Acute Pancreatitis

Steven L. Werlin and Michael Wilschanski

Acute pancreatitis, the most common pancreatic disorder in children, is increasing in incidence and at least 30-50 cases are now seen in major pediatric centers per year. In children, blunt abdominal injuries, multisystem disease such as the hemolytic uremic syndrome and inflammatory bowel disease, biliary stones or microlithiasis (sludging), and drug toxicity are the most common etiologies. Although many drugs and toxins can induce acute pancreatitis in susceptible persons, in children, valproic acid, L-asparaginase, 6-mercaptopurine, and azathioprine are the most common causes of drug-induced pancreatitis. Other cases follow organ transplantation or are caused by infections, metabolic disorders, or mutations in susceptibility genes (see Chapter 351.2). Fewer than 5% of cases are idiopathic (Table 351-1).

After an initial insult, such as ductal disruption or obstruction, there is premature activation of trypsinogen to trypsin within the acinar cell. Trypsin then activates other pancreatic proenzymes, leading to autodigestion, further enzyme activation, and release of active proteases. Lysosomal hydrolases colocalize with pancreatic proenzymes within the acinar cell. Pancreastasis (similar in concept to cholestasis) with continued synthesis of enzymes occurs. Lecithin is activated by phospholipase A_2 into the toxic lysolecithin. Prophospholipase is unstable and can be activated by minute quantities of trypsin. After the insult, cytokines and other proinflammatory mediators are released.

The healthy pancreas is protected from autodigestion by pancreatic proteases that are synthesized as inactive proenzymes; digestive enzymes that are segregated into secretory granules at pH 6.2 by low calcium concentration, which minimizes trypsin activity; the presence of protease inhibitors both in the cytoplasm and zymogen granules; and enzymes that are secreted directly into the ducts.

Histopathologically, interstitial edema appears early. Later, as the episode of pancreatitis progresses, localized and confluent necrosis, blood vessel disruption leading to hemorrhage, and an inflammatory response in the peritoneum can develop.

Criteria for the diagnosis of pancreatitis in children are defined as 2 of 3 of the following: abdominal pain; serum amylase and/or lipase activity at least 3 times greater than the upper limit of normal; and imaging findings characteristic of, or compatible with, acute pancreatitis.

CLINICAL MANIFESTATIONS

Mild Acute Pancreatitis

The patient with acute pancreatitis has severe abdominal pain, persistent vomiting, and possibly fever. The pain is epigastric or in either upper quadrant, steady, often resulting in the child's assuming an antalgic position with hips and knees flexed, sitting upright, or lying on the side. The child is very uncomfortable and irritable and appears acutely ill. The abdomen may be distended and tender and a mass may be palpable. The pain can increase in intensity for 24-48 hr, during which time vomiting may increase and the patient can require hospitalization for dehydration and might need fluid and electrolyte therapy. The prognosis for complete recovery in the acute uncomplicated case is excellent.

Severe Acute Pancreatitis

Severe acute pancreatitis is rare in children. In this life-threatening condition, the patient is acutely ill with severe nausea, vomiting, and abdominal pain. Shock, high fever, jaundice, ascites, hypocalcemia, and pleural effusions can occur. A bluish discoloration may be seen around the umbilicus (Cullen sign) or in the flanks (Grey Turner sign). The pancreas is necrotic and can be transformed into an inflammatory hemorrhagic mass. The mortality rate, which is approximately 20%, is related to the systemic inflammatory response syndrome with multiple organ dysfunction, shock, renal failure, acute respiratory distress syndrome, disseminated intravascular coagulation, massive gastrointestinal bleeding, and systemic or intraabdominal infection. The percentage of necrosis seen on CT scan and failure of pancreatic tissue to enhance on CT scan (suggesting necrosis) predicts the severity of the disease.

DIAGNOSIS

Acute pancreatitis is usually diagnosed by measurement of serum lipase and amylase activities. Serum lipase is now considered the test of choice for acute pancreatitis as it is more specific than amylase for acute inflammatory pancreatic disease and should be determined when pancreatitis is suspected. The serum lipase rises by 4-8 hr, peaks at 24-48 hr, and remains elevated 8-14 days longer than serum amylase. Serum lipase can be elevated in nonpancreatic diseases. The serum amylase level is typically elevated for up to 4 days. A variety of other conditions can also cause hyperamylasemia without pancreatitis (Table 351-2). Elevation of salivary amylase can mislead the clinician to diagnose pancreatitis in a child with abdominal pain. The laboratory can separate amylase isoenzymes into pancreatic and salivary fractions. Initially, serum amylase levels are normal in 10-15% of patients.

Other laboratory abnormalities that may be present in acute pancreatitis include hemoconcentration, coagulopathy, leukocytosis, hyperglycemia, glucosuria, hypocalcemia, elevated γ-glutamyl transpeptidase, and hyperbilirubinemia.

X-ray of the chest and abdomen might demonstrate nonspecific findings. The chest x-ray might demonstrate atelectasis, basilar infiltrates, elevation of the hemidiaphragm, left- (rarely right-) sided pleural effusions, pericardial effusion, and pulmonary edema. Abdominal x-rays might demonstrate a sentinel loop, dilation of the transverse colon (cutoff sign), ileus, pancreatic calcification (if recurrent), blurring of the left psoas margin, a pseudocyst, diffuse abdominal haziness (ascites), and peripancreatic extraluminal gas bubbles.

Table 351-1 Etiology of Acute and Recurrent Pancreatitis in Children

DRUGS AND TOXINS Acetaminophen overdose Alcohol L-Asparaginase Azathioprine Carbamazepine Cimetidine Corticosteroids Enalapril Erythromycin Estrogen Furosemide Glucagon-like peptide-1 agents Isoniazid Lisinopril 6-Mercaptopurine Methyldopa Metronidazole Octreotide Organophosphate poisoning Pentamidine Retrovirals: DDC (dideoxycytidine), DDI (dideoxyinosine), tenofovir Sulfonamides: mesalamine, 5-aminosalicytates, sulfasalazine, trimethoprim-sulfamethoxazole Sulindac Tetracycline Thiazides Valproic acid Venom (spider, scorpion, Gila monster lizard) Vincristine Volatile hydrocarbons	**OBSTRUCTIVE** Ampullary disease Ascariasis Biliary tract malformations Choledochal cyst Choledochocele Cholelithiasis, microlithiasis, and choledocholithiasis (stones or sludge) Duplication cyst Endoscopic retrograde cholangiopancreatography (ERCP) complication Pancreas divisum Pancreatic ductal abnormalities Postoperative Sphincter of Oddi dysfunction Tumor **SYSTEMIC DISEASE** Autoimmune pancreatitis (IgG_4-related systemic disease) Brain tumor Collagen vascular diseases Crohn disease Diabetes mellitus (ketoacidosis) Head trauma Hemochromatosis Hemolytic uremic syndrome Hyperlipidemia: types I, IV, V Hyperparathyroidism/hypercalcemia Kawasaki disease Malnutrition Organic academia Peptic ulcer Periarteritis nodosa Renal failure Systemic lupus erythematosus Transplantation: bone marrow, heart, liver, kidney, pancreas Vasculitis
GENETIC Cationic trypsinogen gene *(PRSS1)* Chymotrypsin C gene *(CTRC)* Cystic fibrosis gene *(CFTR)* Trypsin inhibitor gene *(SPINK1)*	**TRAUMATIC** Blunt injury Burns Child abuse Hypothermia Surgical trauma Total-body cast
INFECTIOUS Ascariasis Coxsackie B virus Epstein-Barr virus Hepatitides A, B Influenzae A, B Leptospirosis Malaria Measles Mumps Mycoplasma Rubella Rubeola Reye syndrome: varicella, influenza B Septic shock	

CT scanning has a major role in the diagnosis and follow-up of children with pancreatitis. Findings can include pancreatic enlargement, a hypoechoic, sonolucent edematous pancreas, pancreatic masses, fluid collections, and abscesses (Fig. 351-1); 20% or more of children with acute pancreatitis initially have normal imaging studies. In adults, CT findings are the basis of a widely accepted prognostic system. Ultrasonography is more sensitive than CT scanning for the diagnosis of biliary stones. Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography are essential in the investigation of recurrent pancreatitis, nonresolving pancreatitis, and disease associated with gallbladder pathology. Endoscopic ultrasonography also helps visualize the pancreaticobiliary system.

TREATMENT

The aims of medical management are to relieve pain and restore metabolic homeostasis. Analgesia should be given in adequate doses. Fluid, electrolyte, and mineral balance should be restored and maintained. Nasogastric suction is useful in patients who are vomiting. While vomiting, the patient should be maintained with nothing by mouth. Recovery is usually complete within 4-5 days. Refeeding can commence when vomiting has resolved. Early refeeding by nasogastric tube or on demand decreases the complication rate and length of stay.

In severe pancreatitis, antibiotics are used to treat infected necrosis but prophylactic antibiotics are not recommended. Gastric acid is suppressed. Endoscopic therapy can be of benefit when pancreatitis is caused by anatomic abnormalities, such as strictures or stones. Enteral

alimentation by mouth, nasogastric tube, or nasojejunal tube (in severe cases or for those intolerant of oral or nasogastric feedings), within 2-3 days of onset, reduces the length of hospitalization, complication rate and survival in adult patients with severe acute pancreatitis. In children, surgical therapy of nontraumatic, acute pancreatitis is rarely required but may include drainage of necrotic material or abscesses.

Table 351-2	Differential Diagnosis of Hyperamylasemia
PANCREATIC PATHOLOGY	
Acute or chronic pancreatitis	
Complications of pancreatitis (pseudocyst, ascites, abscess)	
Factitious pancreatitis	
SALIVARY GLAND PATHOLOGY	
Parotitis (mumps, *Staphylococcus aureus*, cytomegalovirus, HIV, Epstein-Barr virus)	
Sialadenitis (calculus, radiation)	
Eating disorders (anorexia nervosa, bulimia)	
INTRAABDOMINAL PATHOLOGY	
Biliary tract disease (cholelithiasis)	
Peptic ulcer perforation	
Peritonitis	
Intestinal obstruction	
Appendicitis	
SYSTEMIC DISEASES	
Metabolic acidosis (diabetes mellitus, shock)	
Renal insufficiency, transplantation	
Burns	
Pregnancy	
Drugs (morphine)	
Head injury	
Cardiopulmonary bypass	

PROGNOSIS

Children with uncomplicated acute pancreatitis do well and recover within 4-5 days. When pancreatitis is associated with trauma or systemic disease, the prognosis is typically related to the associated medical conditions.

Bibliography is available at Expert Consult.

351.2 Chronic Pancreatitis

Steven L. Werlin and Michael Wilschanski

Chronic pancreatitis in children is often caused by genetic mutations or by congenital anomalies of the pancreatic or biliary ductal system. Mutations in the *PRSS1* gene (cationic trypsinogen) located on the long arm of chromosome 7, in *SPINK 1* gene (pancreatic trypsin inhibitor) located on chromosome 5, in the cystic fibrosis gene (*CFTR*), and in the chymotrypsin C gene *(CTRC)* may all lead to chronic pancreatitis (see Table 351-1).

Cationic trypsinogen has a trypsin-sensitive cleavage site. Loss of this cleavage site in the abnormal protein permits uncontrolled activation of trypsinogen to trypsin, which leads to autodigestion of the pancreas. Mutations in *PRSS1* act in an autosomal dominant fashion with incomplete penetrance and variable expressivity. Symptoms often begin in the 1st decade but are usually mild at the onset. Although spontaneous recovery from each attack occurs in 4-7 days, episodes become progressively severe. Clinically, hereditary pancreatitis may be diagnosed by the presence of the disease in successive generations of

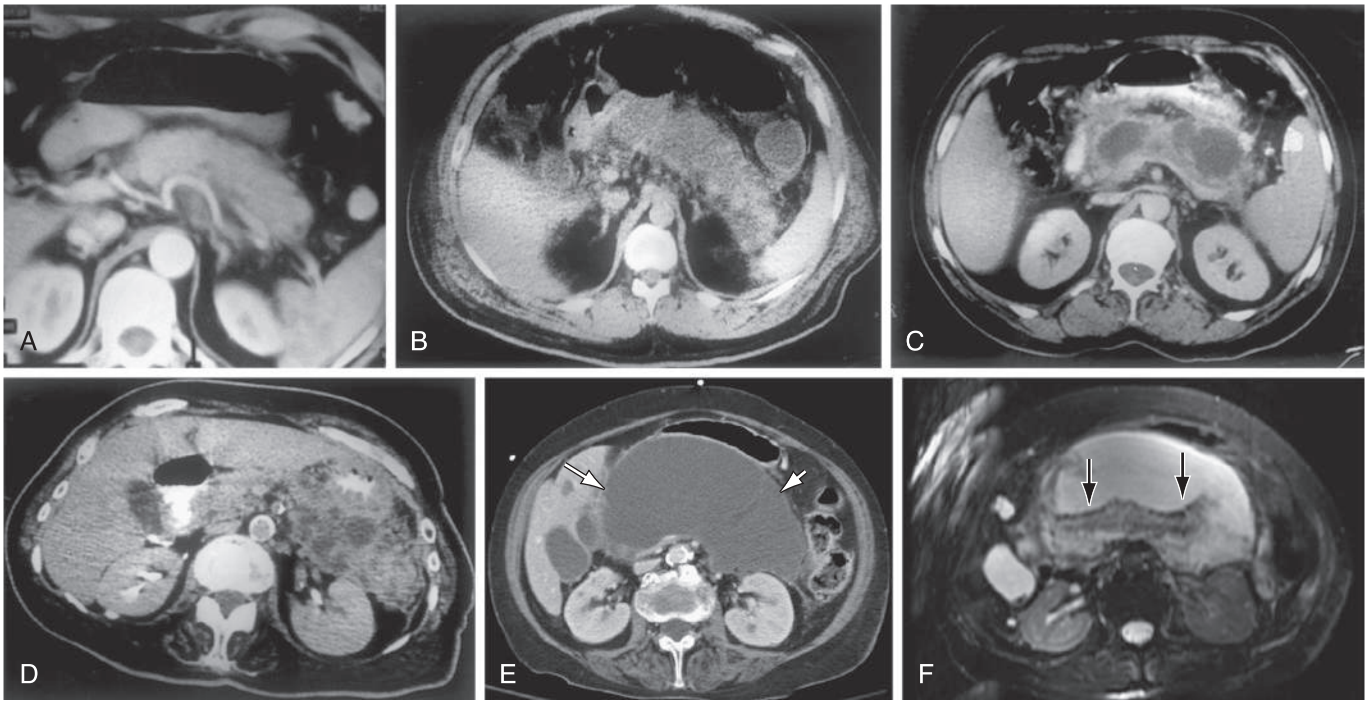

Figure 351-1 CT and MRI appearance of pancreatitis. **A,** Mild acute pancreatitis. Arterial phase spiral CT. Diffuse enlargement of pancreas without fluid accumulation. **B,** Severe acute pancreatitis. Lack of enhancement of the pancreatic parenchyma due to the necrosis of the entire pancreatic gland. **C,** Pancreatic pseudocyst. A round fluid collection with thin capsule is seen within the lesser sac. **D,** Acute severe pancreatitis and peripancreatic abscess formation. Peripancreatic abscess formation is observed within the peripancreatic and the left anterior pararenal space. **E,** Pancreatic necrosis. A well-defined fluid attenuation collection in the pancreatic bed *(white arrows)* seen on contrast-enhanced CT imaging. **F,** The same collection is more complex appearing on the corresponding T2-weighted MR image. The internal debris and necrotic tissue are better appreciated because of the superior soft-tissue contrast of MRI *(black arrows)*. *(**A-D** from Elmas N: The role of diagnostic radiology in pancreatitis,* Eur J Radiol *38[2]:120–132, 2001, Figs. 1, 3b, 4a, and 5.* ***E-F*** *from Soakar A, Rabinowitz CB, Sahani DV: Cross-sectional imaging in acute pancreatitis,* Radiol Clin North Am *45[3]:447–460, 2007, Fig. 14.)*

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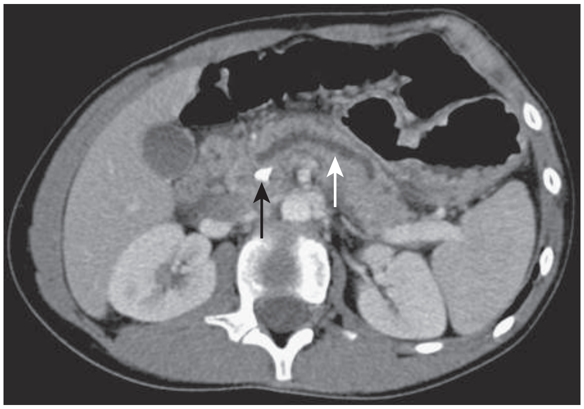

Figure 351-2 Chronic pancreatitis. Computed tomogram showing calcification in the head of the pancreas *(black arrow)* and dilated pancreatic duct *(white arrow)* in a 12 yr old patient. *(Courtesy of Dr. Janet Reid. From Wyllie R, Hyams JS, editors:* Pediatric gastrointestinal and liver disease, *ed 3, Philadelphia, 2006, WB Saunders.)*

a family. An evaluation during symptom-free intervals may be unrewarding until calcifications, pseudocysts, or pancreatic exocrine and endocrine insufficiency develops (Fig. 351-2). Chronic pancreatitis is a risk factor for future development of pancreatic cancer. Multiple mutations of the *PRSS1* gene associated with hereditary pancreatitis have been described.

Trypsin inhibitor acts as a fail-safe mechanism to prevent uncontrolled autoactivation of trypsin. Mutations in the *SPINK1* gene have been associated with recurrent or chronic pancreatitis. In *SPINK1* mutations, this fail-safe mechanism is lost; this gene may be a modifier gene and not the direct etiologic factor.

Mutations of the cystic fibrosis gene *(CFTR)*, associated with pancreatic sufficiency or which do not typically produce pulmonary disease, can cause chronic pancreatitis, possibly from ductal obstruction. Patients with genotypes associated with mild phenotypic effects have a greater risk of developing pancreatitis than patients with genotypes associated with moderate-severe phenotypes.

Mutations in the chymotrypsin C *(CTRC)* gene, which cause a gain of function, may also cause recurrent pancreatitis. Indications for genetic testing include recurrent episodes of acute pancreatitis, chronic pancreatitis, a family history of pancreatitis, or unexplained pancreatitis in children.

Other conditions associated with chronic, relapsing pancreatitis are hyperlipidemia (types I, IV, and V), hyperparathyroidism, and ascariasis. Previously, most cases of recurrent pancreatitis in childhood were considered idiopathic; with the discovery of gene families associated with recurrent pancreatitis, this has changed. Congenital anomalies of the ductal systems, such as pancreas divisum are more common than previously recognized.

Autoimmune pancreatitis typically manifests with jaundice, abdominal pain, and weight loss. The pancreas is typically enlarged and the pancreas is hypodense on CT. The pathogenesis is unknown. Type 1 is a systemic disease and is associated with high serum immunoglobulin (Ig) G_4. In type 2 IgG_4, levels are normal and the disease is limited to the pancreas. Both types respond to steroids. There have been only a few case reports of this condition in children.

Juvenile tropical pancreatitis is the most common form of chronic pancreatitis in developing equatorial countries. The highest prevalence is in the Indian state of Kerala. Tropical pancreatitis occurs during late childhood or early adulthood, manifesting with abdominal pain and irreversible pancreatic insufficiency followed by diabetes mellitus within 10 yr. The pancreatic ducts are obstructed with inspissated secretions, which later calcify. This condition is associated with mutations in the *SPINK* gene in 50% of cases.

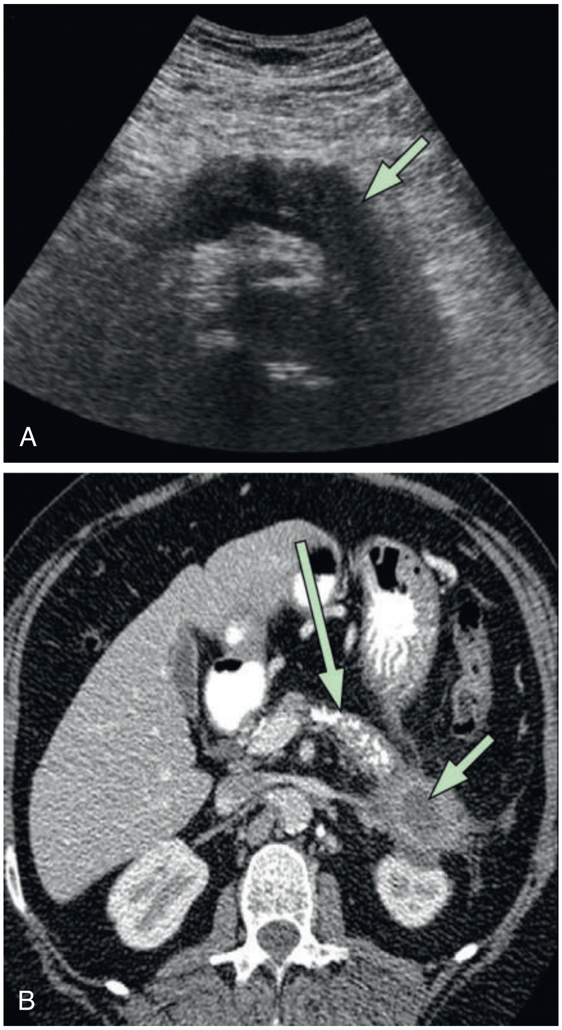

Figure 351-3 Examples of ultrasound and multidetector images in patients with chronic pancreatitis. **A,** Transabdominal ultrasound scan showing a uniformly swollen, hypoechoic pancreas *(arrow)*, typical of autoimmune pancreatitis. **B,** Multidetector CT showing pancreatic calculi in an atrophic pancreas *(long arrow)* and a pseudocyst at the tail of the pancreas *(short arrow)*. *(From Braganza JM, Lee SH, McCloy RF, McMahon MJ: Chronic pancreatitis.* Lancet *377:1184–1197, 2011, Fig. 5, p 1191.)*

A thorough diagnostic evaluation of every child with more than 1 episode of pancreatitis is indicated. Serum lipid, calcium, and phosphorus levels are determined. Stools are evaluated for ascaris, and a sweat test is performed. Plain abdominal films are evaluated for the presence of pancreatic calcifications. Abdominal ultrasound or CT scanning is performed to detect the presence of a pseudocyst (Figs. 351-3 and 351-4). The biliary tract is evaluated for the presence of stones. After genetic counseling, evaluation of *PRSS1*, *SPINK1*, *CFTR*, and *CRTC* genotypes can be measured.

Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography are techniques that can be used to define the anatomy of the gland and are mandatory if surgery is considered. Magnetic resonance cholangiopancreatography is the test of choice when endotherapy is not being considered and should be performed as part of the evaluation of any child with idiopathic, nonresolving, or recurrent pancreatitis and in patients with a pseudocyst before drainage. In these cases a previously undiagnosed anatomic defect that may be amenable to endoscopic or surgical therapy may be detected. Endoscopic treatments include sphincterotomy, stone

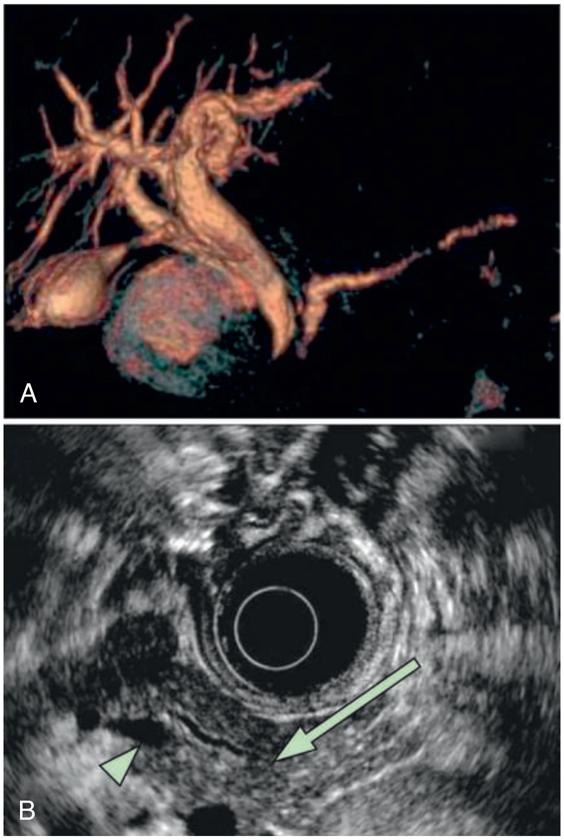

Figure 351-4 **Examples of 3-dimensional magnetic resonance cholangiopancreatogram and endoscopic ultrasound in patients with chronic pancreatitis. A,** Three-dimensional magnetic resonance cholangiopancreatogram shows a minimally dilated biliary tree and moderately dilated irregular main pancreatic duct. **B,** Endoscopic ultrasound scan shows a minimally dilated pancreatic duct in the head of pancreas *(arrow)* consistent with mild chronic pancreatitis: the distal common bile duct appears normal *(arrowhead). (From Braganza JM, Lee SH, McCloy RF, McMahon MJ: Chronic pancreatitis.* Lancet *377:1184–1197, 2011, Fig. 6, p. 1191.)*

extraction, drainage on pseudocysts, and insertion of pancreatic or biliary endoprosthetic stents. These treatments allow successful nonsurgical management of conditions previously requiring surgical intervention. In patients with intractable pain total pancreatectomy and islet cell transfusion is performed in specialized centers.

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Chapter **352**

Pseudocyst of the Pancreas

Steven L. Werlin and Michael Wilschanski

Pancreatic pseudocyst formation is an uncommon sequela to acute or chronic pancreatitis. Pseudocysts are sacs delineated by a fibrous wall in the lesser peritoneal sac. They can enlarge or extend in almost any direction, thus producing a wide variety of symptoms (see Fig. 351-1*C*).

A pancreatic pseudocyst is suggested when an episode of pancreatitis fails to resolve or when a mass develops after an episode of pancreatitis. Clinical features usually include pain, nausea, and vomiting, but many patients are asymptomatic. The most common signs are a palpable mass in 50% of patients and jaundice in 10%. Other findings include ascites and pleural effusions (usually left-sided).

Pancreatic pseudocysts can be detected by transabdominal ultrasonography, CT scanning, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, and endoscopic ultrasound. Because of its ease, availability, and reliability, ultrasonography is the first choice. Sequential ultrasonography studies have demonstrated that most small pseudocysts (<6 cm) resolve spontaneously. It is recommended that the patient with acute pancreatitis undergo an ultrasonographic evaluation 2-4 wk after resolution of the acute episode for an evaluation of possible pseudocyst formation.

Percutaneous and endoscopic drainage of pseudocysts have replaced open surgical drainage, except for complicated or recurrent pseudocysts. Whereas a pseudocyst must be allowed to mature for 4-6 wk before surgical drainage is attempted, percutaneous or endoscopic drainage can be attempted earlier. In some cases, endoscopic creation of a cystgastrostomy is performed. When a surgical treatment is planned an magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography is performed to define anatomic abnormalities and aid the surgeon in planning his approach. Endoscopic ultrasound is helpful when an endoscopic approach is chosen.

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Chapter 353

Pancreatic Tumors

Steven L. Werlin and Michael Wilschanski

Pancreatic tumors can be of either endocrine or nonendocrine origin. Tumors of endocrine origin include insulinomas and gastrinomas. These and other functioning tumors occur in the autosomal dominantly inherited multiple endocrine neoplasia type 1 (MEN-1). Hypoglycemia accompanied by higher-than-expected insulin levels or refractory gastric ulcers (Zollinger-Ellison syndrome) indicate the possibility of a pancreatic tumor (see Chapter 345). Most gastrinomas arise outside of the pancreas. The treatment of choice is surgical removal. If the primary tumor cannot be found, or if it has metastasized, cure might not be possible. Treatment with a high dose of a proton pump inhibitor to inhibit gastric acid secretion is then indicated.

The watery diarrhea–hypokalemia–acidosis syndrome is usually produced by the secretion of vasoactive intestinal peptide by a non–α-cell tumor (VIPoma) (see Table 341-7). Vasoactive intestinal peptide levels are often, but not always, increased in the serum. Treatment is surgical removal of the tumor. When this is not possible, symptoms may be controlled by the use of octreotide acetate (cyclic somatostatin, Sandostatin), a synthetic analog of somatostatin. Pancreatic tumors secreting a variety of hormones, including glucagon, somatostatin, and pancreatic polypeptide have also been described. The treatment is surgical resection when possible.

Pancreatoblastomas, pancreatic adenocarcinomas, cystadenomas, and rhabdomyosarcomas are rarely encountered. Pancreatoblastoma, a malignant embryonal tumor that secretes α-fetoprotein and can contain both endocrine and exocrine elements, is the most common pancreatic neoplasm in young children. Presurgical chemotherapy

should be considered for lesions not primarily resectable. Resection can be curative; adjuvant chemotherapy has been used but its effectiveness is not established.

Carcinoma of the exocrine pancreas is a major problem in adults, accounting for 2% of diagnoses and 5% of deaths from cancer. It is very rare in childhood. No definite causes are known. Several genetic syndromes including mutations in the *PRSS1* and *MEN-1* genes lead to an increased incidence of pancreatic cancer in adult life. The Frantz tumor is a papillary cystic tumor usually found in girls and young women. Typical presenting symptoms are abdominal pain, mass, or jaundice. The treatment of choice is total surgical removal.

Insulinomas and persistent hyperinsulinemic hypoglycemia of infancy produce symptomatic hypoglycemia caused by mutations in a variety of genes, most commonly *GUUD1* and *KATP*. Massive subtotal or total pancreatectomy is the treatment of choice when medical treatment fails (see Chapter 86). These children might then develop pancreatic insufficiency and diabetes as a complication of surgery.

Pancreatic lesions in von Hippel-Lindau disease are usually benign and cystic. Cystadenomas, familial adenocarcinomas, and islet cell tumors are less common. Metastases have been reported, but adjuvant therapy after surgical excision cannot yet be recommended. The diagnosis is suggested by CT scanning.

Prognosis is good for completely resected endocrine tumors but very poor for carcinomas, even with extensive surgery. Children who survive partial or complete pancreatectomy may have decreased pancreatic exocrine and endocrine reserve.

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Table 354-1	Selected Growth Factors, Receptors, Protein Kinases, and Transcription Factors Required for Normal Liver Development in Animal Models
INDUCTION OF HEPATOCYTE FATE THROUGH CARDIAC MESODERM Fibroblast growth factors (FGFs) 1, 2, 8 FGF receptors 1, 4	
INDUCTION OF HEPATOCYTE FATE THROUGH SEPTUM TRANSVERSUM Bone morphogenetic proteins 2, 4, 7	
STIMULATION OF HEPATOBLAST GROWTH AND PROLIFERATION Hepatocyte growth factor (HGF) HGF receptor c-met "Pioneer" transcription factors Foxa1, Foxa2, and Gata4, Gata6 Transcription factors Xbp1, Foxm1b, Hlx, Hex, Prox1 Wnt signalling pathway, β-catenin	
SPECIFICATION OF HEPATOCYTE LINEAGE HGF Transforming growth factor-β and its downstream effectors Smad 2, Smad 3 Hepatocyte nuclear factors (HNFs) 1α, 4α, 6	
SPECIFICATION OF CHOLANGIOCYTE LINEAGE Jagged 1 (Notch ligand) and Notch receptors 1, 2 HNF6, HNF1β Wnt signalling pathway, β-catenin Vacuolar sorting protein Vps33b	

Section 6

The Liver and Biliary System

Chapter 354

Morphogenesis of the Liver and Biliary System

Stacey S. Huppert and William F. Balistreri

During the early embryonic process of gastrulation, the 3 embryonic germ layers (endoderm, mesoderm, ectoderm) are formed. The liver and biliary system arises from cells of the ventral foregut endoderm; their development can be divided into 3 distinct processes (Fig. 354-1). First, through unknown mechanisms, the ventral foregut endoderm acquires *competence* to receive signals arising from the cardiac mesoderm. These mesodermal signals, in the form of various fibroblast growth factors and bone morphogenetic proteins, lead to *specification* of cells that have the potential to form the liver and activate liver-specific genes. During this period of hepatic fate decision, "pioneer" transcription factors, including *Foxa* and *Gata4*, bind to specific binding sites in compacted chromatin, open the local chromatin structure, and mark genes as competent. But these will only be expressed if they are correctly induced by additional transcription factors. Newly specified cells then delaminate from the ventral foregut endoderm and migrate in a cranial ventral direction into the septum transversum in the 4th wk of human gestation to initiate liver *morphogenesis*.

The growth and development of the newly budded liver require interactions with endothelial cells. Certain proteins are important for liver development in animal models (Table 354-1). In addition to these proteins, microRNAs, which consist of small noncoding, single-stranded RNAs, have a functional role in the regulation of gene expression and hepatobiliary development in zebrafish and mouse models.

Within the ventral mesentery, proliferation of migrating cells form anastomosing hepatic cords, with the network of primitive liver cells, sinusoids, and septal mesenchyme establishing the basic architectural pattern of liver lobule (Fig. 354-2). The solid *cranial* portion of the hepatic diverticulum (pars hepatis) eventually forms the hepatic parenchyma and the intrahepatic bile ducts. The hepatic lobules are identifiable in the 6th wk of human gestation. The bile canalicular structures, including microvilli and junctional complexes, are specialized loci of the liver cell membrane; these appear very early in gestation, and large canaliculi bounded by several hepatocytes are seen by 6-7 wk.

Hepatocytes and bile duct cells (cholangiocytes) originate from hepatoblasts as common precursors. Notch signaling, which is impaired in Alagille syndrome, promotes hepatoblast differentiation into biliary epithelium, whereas hepatocyte growth factor antagonizes differentiation. The development of the intrahepatic bile ducts is determined by the development and branching pattern of the portal vein. Around the 8th wk of gestation, starting at the hilum of the liver, primitive hepatoblasts adjacent to the mesenchyme around the portal vein branches form a cylindrical sleeve, termed the *ductal plate*. From 12 wk of gestation onward, a "remodeling" of the ductal plate occurs, with some segments of the ductal plate undergoing tubular dilation and excess ductal plate cells gradually disappearing. The ramification of the biliary tree continues throughout human fetal life and at the time of birth the most peripheral branches of the portal veins are still surrounded by ductal plates; these require 4 more weeks to develop into definitive portal ducts. Lack of remodeling of the ductal plate results in persistence of primitive ductal plate configurations, an abnormality called *ductal plate malformation*. This histopathologic lesion has been

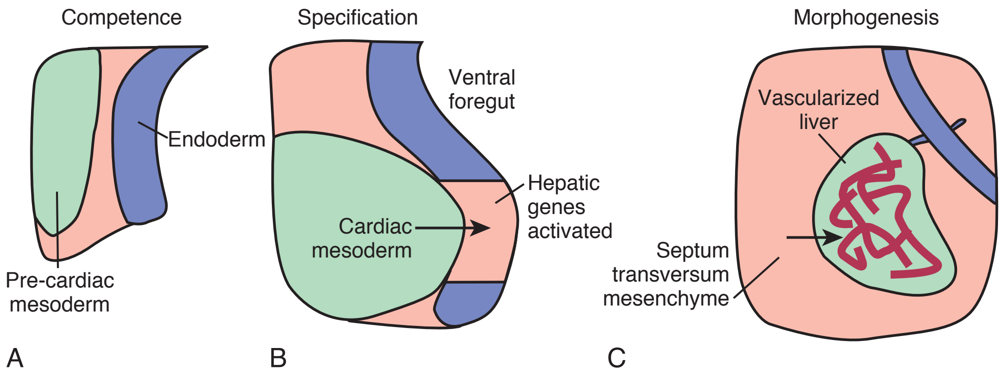

Figure 354-1 **Processes involved in early liver development. A,** The ventral foregut endoderm acquires *competence* to receive signals arising from the cardiac mesoderm. **B,** Specific cells of the ventral foregut endoderm undergo *specification* and activation of liver-specific genes under the influence of mesodermal signals. **C,** Liver *morphogenesis* is initiated as the newly specified cells migrate into the septum transversum under the influence of signaling molecules and extracellular matrix released by septum transversum mesenchymal cells and of primitive endothelial cells. *(Reprinted from Zaret KS: Liver specification and early morphogenesis,* Mech Dev *92:83–88, 2000; copyright 2000, with permission from Elsevier Science.)*

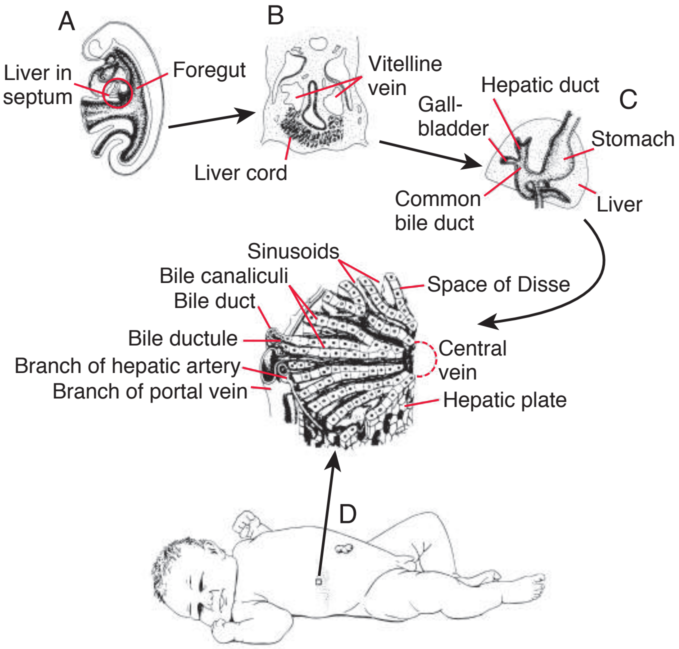

Figure 354-2 **Hepatic morphogenesis. A,** Ventral outgrowth of hepatic diverticulum from foregut endoderm in the 3.5 wk embryo. **B,** Between the 2 vitelline veins, the enlarging hepatic diverticulum buds off epithelial (liver) cords that become the liver parenchyma, around which the endothelium of capillaries (sinusoids) align (4 wk embryo). **C,** Hemisection of embryo at 7.5 wk. **D,** Three-dimensional representation of the hepatic lobule as present in the newborn. *(Reprinted from Andres JM, Mathis RK, Walker WA: Liver disease in infants. Part I: developmental hepatology and mechanisms of liver dysfunction,* J Pediatr *90:686–697, 1977.)*

observed in liver biopsies of a variety of liver conditions, including congenital hepatic fibrosis, Caroli disease, and biliary atresia.

The *caudal* part (pars cystica) of the hepatic diverticulum becomes the gallbladder, cystic duct, and common bile duct. The distal portions of the right and left hepatic ducts develop from the extrahepatic ducts, whereas the proximal portions develop from the first intrahepatic ductal plates. The extrahepatic bile ducts and the developing intrahepatic biliary tree maintain luminal continuity and patency from the beginning of organogenesis (see Fig. 354-2*C*).

Fetal hepatic blood flow is derived from the hepatic artery and from the portal and umbilical veins, which form the portal sinus. The portal venous inflow is directed mainly to the right lobe of the liver and umbilical flow primarily to the left. The ductus venosus shunts blood from the portal and umbilical veins to the hepatic vein, bypassing the sinusoidal network. After birth, the ductus venosus becomes obliterated when oral feedings are initiated. The fetal oxygen saturation is lower in portal than in umbilical venous blood; accordingly, the right hepatic lobe has lower oxygenation and greater hematopoietic activity than the left hepatic lobe.

The transport and metabolic activities of the liver are facilitated by the structural arrangement of liver cell cords, which are formed by rows of hepatocytes, separated by sinusoids that converge toward the tributaries of the hepatic vein (the central vein) located in the center of the lobule (see Fig. 354-2*D*). This establishes the pathways and patterns of flow for substances to and from the liver. In addition to arterial input from the systemic circulation, the liver also receives venous input from the gastrointestinal tract via the portal system. The products of the hepatobiliary system are released by 2 different paths: through the hepatic vein and through the biliary system back into the intestine. Plasma proteins and other plasma components are secreted by the liver. Absorbed and circulating nutrients arrive through the portal vein or the hepatic artery and pass through the sinusoids and past the hepatocytes to the systemic circulation at the central vein. Biliary components are transported via the series of enlarging channels from the bile canaliculi through the bile ductule to the common bile duct.

Bile secretion is first noted at the 12th wk of human gestation. The major components of bile vary with stage of development. Near term, cholesterol and phospholipid content is relatively low. Low concentrations of bile acids, the absence of bacterially derived (secondary) bile acids, and the presence of unusual bile acids reflect low rates of bile flow and immature bile acid synthetic pathways.

The liver reaches a peak relative size of approximately 10% of the fetal weight at the 9th wk. Early in development, the liver is a primary site of hematopoiesis. In the 7th wk, hematopoietic cells outnumber functioning hepatocytes in the hepatic anlage. These early hepatocytes are smaller than at maturity (~20 µm vs 30-35 µm) and contain less glycogen. Near term, the hepatocyte mass expands to dominate the organ, as cell size and glycogen content increase. Hematopoiesis is virtually absent by the 2nd postnatal month in full-term infants. As the density of hepatocytes increases with gestational age, the relative volume of the sinusoidal network decreases. The liver constitutes 5% of body weight at birth but only 2% in an adult.

Several metabolic processes are immature in a healthy newborn infant, owing in part to the fetal patterns of activity of various enzymatic processes. Many fetal hepatic functions are carried out by the maternal liver, which provides nutrients and serves as a route of elimination of metabolic end products and toxins. Fetal liver metabolism is devoted primarily to the production of proteins required for growth.

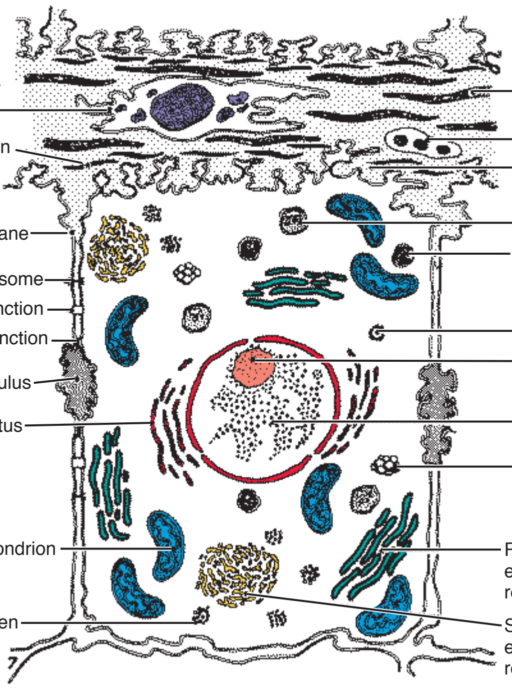

Figure 354-3 Schematic view of the ultrastructure and organelles of hepatocytes. *(Reprinted from Sherlock S: Hepatic cell structure. In Sherlock S, editor:* Diseases of the liver and biliary system, *ed 6, Oxford, 1981, Blackwell Scientific, p. 10, with permission from Blackwell Scientific.)*

Toward term, primary functions become production and storage of essential nutrients, excretion of bile, and establishment of processes of elimination. Extrauterine adaptation requires de novo enzyme synthesis. Modulation of these processes depends on substrate and hormonal input via the placenta and on dietary and hormonal input in the postnatal period.

HEPATIC ULTRASTRUCTURE

Hepatocytes exhibit various ultrastructural features that reflect their biologic functions (Fig. 354-3). Hepatocytes, like other epithelial cells, are polarized, meaning that their structure and function are directionally oriented. One result of this polarity is that various regions of the hepatocyte plasma membrane exhibit specialized functions. Bidirectional transport occurs at the *sinusoidal* surface, where materials reaching the liver via the portal system enter and compounds secreted by the liver leave the hepatocyte. *Canalicular* membranes of adjacent hepatocytes form bile canaliculi, which are bounded by tight junctions, preventing transfer of secreted compounds back into the sinusoid. Within hepatocytes, metabolic and synthetic activities are contained within a number of different cell organelles. The oxidation and metabolism of heterogeneous classes of substrates, fatty acid oxidation, key processes in gluconeogenesis, and the storage and release of energy occur in the abundant mitochondria.

The endoplasmic reticulum, a continuous network of rough- and smooth-surfaced tubules and cisternae, is the site of various processes, including protein and triglyceride synthesis and drug metabolism. Low fetal activity of endoplasmic reticulum–bound enzymes accounts for a relative inefficiency of xenobiotic (drug) metabolism. The Golgi apparatus is active in protein packaging and possibly in bile secretion. Hepatocyte peroxisomes are single-membrane-limited cytoplasmic organelles that contain enzymes such as oxidases and catalase and those that have a role in lipid and bile acid metabolism. Lysosomes contain numerous hydrolases that have a role in intracellular digestion. The hepatocyte cytoskeleton, composed of actin and other filaments, is distributed throughout the cell and concentrated near the plasma membrane. Microfilaments and microtubules have a role in receptor-mediated endocytosis, in bile secretion, and in maintaining hepatocyte architecture and motility.

METABOLIC FUNCTIONS OF THE LIVER

Carbohydrate Metabolism

The liver regulates serum glucose levels closely via several processes, including storage of excess carbohydrate as glycogen, a polymer of glucose readily hydrolyzed to glucose during fasting. To maintain serum glucose levels, hepatocytes produce free glucose by either glycogenolysis or gluconeogenesis. Immediately after birth, an infant is dependent on hepatic glycogenolysis. Gluconeogenic activity is present at a low level in the fetal liver and increases rapidly after birth. Fetal glycogen synthesis begins at about the 9th wk of gestation, with glycogen stores most rapidly accumulated near term, when the liver contains 2-3 times the amount of glycogen of adult liver. Most of this stored glycogen is used in the immediate postnatal period. Reaccumulation is initiated at about the 2nd wk of postnatal life, and glycogen stores reach adult levels at approximately the 3rd wk in healthy full-term infants. In preterm infants, serum glucose levels fluctuate in part because efficient regulation of the synthesis, storage, and degradation of glycogen develops only near the end of full-term gestation. Dietary carbohydrates such as galactose are converted to glucose, but there is a substantial dependence on gluconeogenesis for glucose in early life, especially if glycogen stores are limited.

Protein Metabolism

During the rapid fetal growth phase, specific decarboxylases that are rate limiting in the biosynthesis of physiologically important polyamines have higher activities than in the mature liver. The rate of synthesis of albumin and secretory proteins in the developing liver parallels the quantitative changes in endoplasmic reticulum. Synthesis of albumin appears at approximately the 7th-8th wk in the human fetus and increases in inverse proportion to that of α-fetoprotein, which is the dominant fetal protein. By the 3rd-4th mo of gestation, the fetal liver is able to produce fibrinogen, transferrin, and low-density lipoproteins. From this period on, fetal plasma contains each of the major protein classes at concentrations considerably below those achieved at maturity.

The *postnatal* patterns of protein synthesis vary with the class of protein. Lipoproteins of each class rise abruptly in the 1st wk after birth to reach levels that vary little until puberty. Albumin concentrations are low in a neonate (~2.5 g/dL), reaching adult levels (~3.5 g/dL) after several months. Levels of ceruloplasmin and complement factors increase slowly to adult values in the 1st yr. In contrast, transferrin levels at birth are similar to those of an adult, decline for 3-5 mo, and rise thereafter to achieve their final concentrations. Low levels of activity of specific proteins have implications for the nutrition of an infant. A low level of cystathionine γ-lyase (cystathionase) activity impairs the *trans*-sulfuration pathway by which dietary methionine is converted to cysteine. Consequently, the latter must be supplied in the diet. Similar dietary requirements might exist for other sulfur-containing amino acids, such as taurine.

Lipid Metabolism

Fatty acid oxidation provides a major source of energy in early life, complementing glycogenolysis and gluconeogenesis. Newborn infants are relatively intolerant of prolonged fasting, owing in part to a restricted capacity for hepatic ketogenesis. Rapid maturation of the ability of the liver to oxidize fatty acid occurs in the 1st few days of life. Milk provides the major source of calories in early life; this high-fat, low-carbohydrate diet mandates active gluconeogenesis to maintain blood glucose levels. When the glucose supply is limited, ketone body production from endogenous fatty acids can provide energy for hepatic gluconeogenesis and an alternative fuel for brain metabolism. When carbohydrates are in excess, the liver produces triglycerides. Metabolic processes involving lipids and lipoproteins are

predominantly hepatic; liver immaturity or disease affects lipid concentrations and lipoproteins.

Biotransformation

Newborn infants have a decreased capacity to metabolize and detoxify certain drugs, owing to underdevelopment of the hepatic microsomal component that is the site of the specific oxidative, reductive, hydrolytic, and conjugation reactions required for these biotransformations. The major components of the monooxygenase system, such as cytochrome P450, cytochrome-*c* reductase, and the reduced form of nicotinamide-adenine dinucleotide phosphate, are present in low concentrations in fetal microsomal preparations. In full-term infants, hepatic uridine diphosphate glucuronosyltransferase and enzymes involved in the oxidation of polycyclic aromatic hydrocarbons are expressed at very low levels.

Age-related differences in pharmacokinetics vary from compound to compound. The half-life of acetaminophen in a newborn is similar to that of an adult, whereas theophylline has a half-life of approximately 100 hr in a premature infant, as compared to 5-6 hr in an adult. These differences in metabolism, as well as factors such as binding to plasma proteins and renal clearance, determine appropriate drug dosage to maximize effectiveness and to avoid toxicity. Dramatic examples of the susceptibility of newborn infants to drug toxicity are the responses to chloramphenicol (the "gray baby" syndrome) or to benzoyl alcohol and its metabolic products, which involve ineffective glucuronide and glycine conjugation, respectively. The low concentrations of antioxidants (vitamin E, superoxide dismutase, glutathione peroxidase) in the fetal and early newborn liver lead to increased susceptibility to deleterious effects of oxygen toxicity and oxidant injury through lipid peroxidation.

Conjugation reactions, which convert drugs or metabolites into water-soluble forms that can be eliminated in bile, are also catalyzed by hepatic microsomal enzymes. Newborn infants have decreased activity of hepatic uridine diphosphate glucuronosyltransferase, which converts unconjugated bilirubin to the readily excreted glucuronide conjugate and is the rate-limiting enzyme in the excretion of bilirubin. There is rapid postnatal development of transferase activity irrespective of gestational age, which suggests that birth-related, rather than age-related, factors are of primary importance in the postnatal development of activity of this enzyme. Microsomal activity can be stimulated by administration of phenobarbital, rifampin, or other inducers of cytochrome P450. Alternatively, drugs such as cimetidine can inhibit microsomal P450 activity.

Hepatic Excretory Function

Hepatic excretory function and bile flow are closely related to hepatic *bile acid* excretion and enterohepatic recirculation. Bile acids, the major products of cholesterol degradation, are incorporated into mixed micelles with cholesterol and phospholipid. These micelles act as an efficient vehicle for solubilization and intestinal absorption of lipophilic compounds, such as dietary fats and fat-soluble vitamins. Secretion of bile acids by the liver cells is the major determinant of bile flow in the mature animal. Accordingly, maturity of bile acid metabolic processes affects overall hepatic excretory function, including biliary excretion of endogenous and exogenous compounds.

In humans, the 2 primary bile acids, cholic acid and chenodeoxycholic acid, are synthesized in the liver. Before excretion, they are conjugated with glycine and taurine. In response to a meal, contraction of the gallbladder delivers bile acids to the intestine to assist in fat digestion and absorption. After mediating fat digestion, the bile acids themselves are reabsorbed from the terminal ileum through specific active transport processes. They return to the liver via portal blood, are taken up by liver cells, and are reexcreted in bile. In an adult, this enterohepatic circulation involves 90-95% of the circulating bile acid pool. Bile acids that escape ileal reabsorption reach the colon, where the bacterial flora, through dehydroxylation and deconjugation, produce the secondary bile acids, deoxycholate and lithocholate. In an adult, the composition of bile reflects the excretion of the primary and also the secondary bile acids, which are reabsorbed from the distal intestinal tract.

Table 354-2 Causes of Impaired Bile Acid Metabolism and Enterohepatic Circulation
DEFECTIVE BILE ACID SYNTHESIS OR TRANSPORT
Inborn errors of bile acid synthesis (reductase deficiency, isomerase deficiency)
Progressive familial intrahepatic cholestasis (PFIC1, PFIC2, PFIC3)
Intrahepatic cholestasis (neonatal hepatitis)
Acquired defects in bile acid synthesis secondary to severe liver disease
ABNORMALITIES OF BILE ACID DELIVERY TO THE BOWEL
Celiac disease (sluggish gallbladder contraction)
Extrahepatic bile duct obstruction (e.g., biliary atresia, gallstones)
LOSS OF ENTEROHEPATIC CIRCULATION OF BILE ACIDS
External bile fistula
Cystic fibrosis
Small bowel bacterial overgrowth syndrome (with bile acid precipitation, increased jejunal absorption, and "short-circuiting")
Drug-induced entrapment of bile acids in intestinal lumen (e.g., cholestyramine)
BILE ACID MALABSORPTION
Primary bile acid malabsorption (absent or inefficient ileal active transport)
Secondary bile acid malabsorption
Ileal disease or resection
Cystic fibrosis
DEFECTIVE UPTAKE OR ALTERED INTRACELLULAR METABOLISM
Parenchymal disease (acute hepatitis, cirrhosis)
Regurgitation from cells
Portosystemic shunting
Cholestasis

Intraluminal concentrations of bile acids are low in newborn infants and increase rapidly after birth. The expansion of the bile acid pool is critical because bile acids are required to stimulate bile flow and absorb lipids, a major component of the diet of a newborn. Nuclear receptors, such as farnesoid X receptor, control intrahepatic bile acid homeostasis through several mechanisms, including regulation of expression of the genes encoding 2 key proteins, cholesterol 7α-hydroxylase (CYP7A1) and bile salt export pump (BSEP). These proteins are critical for bile acid synthesis and canalicular secretion, respectively. Neonatal expression of these nuclear receptors varies depending on the studied animal model and is largely unknown for humans.

Because of inefficient ileal reabsorption of bile acids and the low rate of hepatic clearance of bile acids from portal blood, serum concentrations of bile acids are commonly elevated in healthy newborns, often to levels that would suggest liver disease in older persons. Transient phases of "physiologic cholestasis" and "physiologic steatorrhea" can often be observed in low birthweight infants and in full-term infants following perinatal stress, such as hypoxia or infection, but are otherwise uncommon in healthy full-term newborns.

Many of the processes related to immaturity of the newborn in liver morphogenesis and function as discussed earlier are implied in the increased susceptibility of infants to liver disease associated with parenteral nutrition. The reduced bile salt pool, hepatic glutathione depletion, and deficient sulfation contribute to production of toxic lithocholic bile acids and cholestasis, whereas deficiencies of essential amino acids, including taurine and cysteine, and excessive lipid infusion can lead to hepatic steatosis in these infants. Beyond the neonatal period, disturbances in bile acid metabolism may be responsible for diverse effects on hepatobiliary and intestinal function (Table 354-2).

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Chapter 355

Manifestations of Liver Disease

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PATHOLOGIC MANIFESTATIONS

Alterations in hepatic structure and function can be acute or chronic, with varying patterns of reaction of the liver to cell injury. Hepatocyte injury can be caused by viral infection, drugs or toxins, hypoxia, immunologic disorders, or inborn errors of metabolism. The injury results in inflammatory cell infiltration or cell death (necrosis), which may be followed by a healing process of scar formation (fibrosis) and, potentially, nodule formation (regeneration). Cirrhosis is the end result of any progressive liver disease.

Cholestasis is an alternative or concomitant response to injury caused by extrahepatic or intrahepatic obstruction to bile flow. Substances that are normally excreted in bile, such as conjugated bilirubin, cholesterol, bile acids, and trace elements, accumulate in serum. Bile pigment accumulation in liver parenchyma can be seen in liver biopsy specimens. In extrahepatic obstruction, bile pigment may be visible in the intralobular bile ducts or throughout the parenchyma as bile lakes or infarcts. In intrahepatic cholestasis, an injury to hepatocytes or an alteration in hepatic physiology leads to a reduction in the rate of secretion of solute and water. Likely causes include alterations in enzymatic or canalicular transporter activity, permeability of the bile canalicular apparatus, organelles responsible for bile secretion, or ultrastructure of the cytoskeleton of the hepatocyte. The end result can be clinically indistinguishable from obstructive cholestasis.

Cirrhosis, defined histologically by the presence of bands of fibrous tissue that link central and portal areas and form parenchymal nodules, is a potential end stage of any acute or chronic liver disease. Cirrhosis can be macronodular, with nodules of various sizes (up to 5 cm) separated by broad septa, or micronodular, with nodules of uniform size (<1 cm) separated by fine septa; mixed forms occur. The progressive scarring of cirrhosis results in altered hepatic blood flow, with further impairment of liver cell function. Increased intrahepatic resistance to portal blood flow leads to portal hypertension.

The liver can be secondarily involved in neoplastic (metastatic) and nonneoplastic (storage diseases, fat infiltration) processes, as well as a number of systemic conditions and infectious processes. The liver can be affected by chronic passive congestion (congestive heart failure) or acute hypoxia, with hepatocellular damage.

CLINICAL MANIFESTATIONS

Hepatomegaly

Enlargement of the liver can be caused by several mechanisms (Table 355-1). Normal liver size estimations are based on age-related clinical indices, such as the degree of extension of the liver edge below the costal margin, the span of dullness to percussion, or the length of the vertical axis of the liver, as estimated from imaging techniques. In children, the normal liver edge can be felt up to 2 cm below the right costal margin. In a newborn infant, extension of the liver edge more than 3.5 cm below the costal margin in the right midclavicular line suggests hepatic enlargement. Measurement of liver span is carried out by percussing the upper margin of dullness and by palpating the lower edge in the right midclavicular line. This may be more reliable than an extension of the liver edge alone. The 2 measurements may correlate poorly.

The liver span increases linearly with body weight and age in both sexes, ranging from approximately 4.5-5.0 cm at 1 wk of age to approximately 7-8 cm in boys and 6.0-6.5 cm in girls by 12 yr of age. The lower edge of the right lobe of the liver extends downward (Riedel lobe) and can normally be palpated as a broad mass in some people. An

Table 355-1 Mechanisms of Hepatomegaly
INCREASE IN THE NUMBER OR SIZE OF THE CELLS INTRINSIC TO THE LIVER
Storage
Fat: malnutrition, obesity, diabetes mellitus, metabolic liver disease (diseases of fatty acid oxidation and Reye syndrome–like illnesses), lipid infusion (total parenteral nutrition), cystic fibrosis, medication related, pregnancy
Specific lipid storage diseases: Gaucher, Niemann-Pick, Wolman disease
Glycogen: glycogen storage diseases (multiple enzyme defects); total parenteral nutrition; infant of diabetic mother, Beckwith syndrome
Miscellaneous: α_1-antitrypsin deficiency, Wilson disease, hypervitaminosis A, neonatal iron storage disease
Inflammation
Hepatocyte enlargement (hepatitis)
• Viral: acute and chronic
• Bacterial: sepsis, abscess, cholangitis
• Toxic: drugs
• Autoimmune
Kupffer cell enlargement
• Sarcoidosis
• Systemic lupus erythematosus
• Macrophage activating syndrome
INFILTRATION OF CELLS
Primary Liver Tumors: Benign
Hepatocellular
• Focal nodular hyperplasia
• Nodular regenerative hyperplasia
• Hepatocellular adenoma
Mesodermal
• Infantile hemangioendothelioma
• Mesenchymal hamartoma
Cystic masses
• Choledochal cyst
• Hepatic cyst
• Hematoma
• Parasitic cyst
• Pyogenic or amebic abscess
Primary Liver Tumors: Malignant
Hepatocellular
• Hepatoblastoma
• Hepatocellular carcinoma
Mesodermal
• Angiosarcoma
• Undifferentiated embryonal sarcoma
Secondary or metastatic processes
• Lymphoma
• Leukemia
• Histiocytosis
• Neuroblastoma
• Wilms tumor
INCREASED SIZE OF VASCULAR SPACE
Intrahepatic obstruction to hepatic vein outflow
• Venoocclusive disease
• Hepatic vein thrombosis (Budd-Chiari syndrome)
• Hepatic vein web
Suprahepatic
• Congestive heart failure
• Pericardial disease
• Tamponade
Post-Fontan procedure
Constrictive pericarditis
Hematopoietic: sickle cell anemia, thalassemia
INCREASED SIZE OF BILIARY SPACE
Congenital hepatic fibrosis
Caroli disease
Extrahepatic obstruction
IDIOPATHIC
Various
• Riedel lobe
• Normal variant
• Downward displacement of diaphragm

enlarged left lobe of the liver is palpable in the epigastrium of some patients with cirrhosis. Downward displacement of the liver by the diaphragm (hyperinflation) or thoracic organs can create an erroneous impression of hepatomegaly.

Examination of the liver should note the consistency, contour, tenderness, and presence of any masses or bruits, as well as assessment of spleen size. Documentation of the presence of ascites and any stigmata of chronic liver disease is important.

Ultrasound is useful in assessment of liver size and consistency, as well as gallbladder size. Gallbladder length normally varies from 1.5-5.5 cm (average: 3 cm) in infants to 4-8 cm in adolescents; width ranges from 0.5-2.5 cm for all ages. Gallbladder distention may be seen in infants with sepsis. The gallbladder is often absent in infants with biliary atresia.

Jaundice (Icterus)

Yellow discoloration of the sclera, skin, and mucous membranes is a sign of hyperbilirubinemia (see Chapter 102.3). Clinically apparent jaundice in children and adults occurs when the serum concentration of bilirubin reaches 2-3 mg/dL (34-51 µmol/L); the neonate might not appear icteric until the bilirubin level is >5 mg/dL (>85 µmol/L). Jaundice may be the earliest and only sign of hepatic dysfunction. Liver disease must be suspected in the infant who appears only mildly jaundiced but has dark urine or acholic (light-colored) stools. Immediate evaluation to establish the cause is required.

Measurement of the total serum bilirubin concentration allows quantitation of jaundice. Bilirubin occurs in plasma in 4 forms: *unconjugated* bilirubin tightly bound to albumin; *free* or *unbound bilirubin* (the form responsible for kernicterus, because it can cross cell membranes); *conjugated bilirubin* (the only fraction to appear in urine); and *δ fraction* (bilirubin covalently bound to albumin), which appears in serum when hepatic excretion of conjugated bilirubin is impaired in patients with hepatobiliary disease. The δ fraction permits conjugated bilirubin to persist in the circulation and delays resolution of jaundice. Although the terms *direct* and *indirect* bilirubin are used equivalently with *conjugated* and *unconjugated* bilirubin, this is not quantitatively correct, because the direct fraction includes both conjugated bilirubin and δ bilirubin.

Investigation of jaundice in an infant or older child must include determination of the accumulation of both unconjugated and conjugated bilirubin. Unconjugated hyperbilirubinemia might indicate increased production, hemolysis, reduced hepatic removal, or altered metabolism of bilirubin (Table 355-2). Conjugated hyperbilirubinemia reflects decreased excretion by damaged hepatic parenchymal cells or disease of the biliary tract, which may be a result of obstruction, sepsis, toxins, inflammation, and genetic or metabolic disease (Table 355-3).

Pruritus

Intense generalized itching can occur in patients with chronic liver disease often in association with cholestasis (conjugated hyperbilirubinemia). Symptoms can be generalized or localized (commonly to palms and soles), are usually worse at night, are exacerbated with stress and heat, and are relieved by cool temperatures. Pruritus is unrelated to the degree of hyperbilirubinemia; deeply jaundiced patients can be asymptomatic. Although retained components of bile are likely important, the cause is probably multifactorial, as evidenced by the symptomatic relief of pruritus after administration of various therapeutic agents including bile acid-binding agents (cholestyramine), choleretic agents (ursodeoxycholic acid), opiate antagonists, antihistamines, and antibiotics. Plasmapheresis, molecular adsorbent recirculating system therapy, and surgical diversion of bile (partial external biliary diversion) have been used in attempts to provide relief for medically refractory pruritus.

Spider Angiomas

Vascular spiders (telangiectasias), characterized by central pulsating arterioles from which small, wiry venules radiate, may be seen in patients with chronic liver disease; these are usually most prominent

Table 355-2 Differential Diagnosis of Unconjugated Hyperbilirubinemia

INCREASED PRODUCTION OF UNCONJUGATED BILIRUBIN FROM HEME

Hemolytic Disease (Hereditary or Acquired)

Isoimmune hemolysis (neonatal; acute or delayed transfusion reaction; autoimmune)
- Rh incompatibility
- ABO incompatibility
- Other blood group incompatibilities

Congenital spherocytosis
Hereditary elliptocytosis
Infantile pyknocytosis
Erythrocyte enzyme defects
Hemoglobinopathy
- Sickle cell anemia
- Thalassemia
- Others

Sepsis
Microangiopathy
- Hemolytic-uremic syndrome
- Hemangioma
- Mechanical trauma (heart valve)

Ineffective erythropoiesis
Drugs
Infection
Enclosed hematoma
Polycythemia
- Diabetic mother
- Fetal transfusion (recipient)
- Delayed cord clamping

DECREASED DELIVERY OF UNCONJUGATED BILIRUBIN (IN PLASMA) TO HEPATOCYTE

Right-sided congestive heart failure
Portacaval shunt

DECREASED BILIRUBIN UPTAKE ACROSS HEPATOCYTE MEMBRANE

Presumed enzyme transporter deficiency
Competitive inhibition
- Breast milk jaundice
- Lucey-Driscoll syndrome
- Drug inhibition (radiocontrast material)

Miscellaneous
- Hypothyroidism
- Hypoxia
- Acidosis

DECREASED STORAGE OF UNCONJUGATED BILIRUBIN IN CYTOSOL (DECREASED Y AND Z PROTEINS)

Competitive inhibition
Fever

DECREASED BIOTRANSFORMATION (CONJUGATION)

Neonatal jaundice (physiologic)
Inhibition (drugs)
Hereditary (Crigler-Najjar)
- Type I (complete enzyme deficiency)
- Type II (partial deficiency)

Gilbert disease
Hepatocellular dysfunction

ENTEROHEPATIC RECIRCULATION

Breast milk jaundice
Intestinal obstruction
- Ileal atresia
- Hirschsprung disease
- Cystic fibrosis
- Pyloric stenosis

Antibiotic administration

Table 355-3 Differential Diagnosis of Neonatal and Infantile Cholestasis

INFECTIOUS Generalized bacterial sepsis Viral hepatitis • Hepatitides A, B, C, D, E • Cytomegalovirus • Rubella virus • Herpesviruses: herpes simplex, human herpesvirus 6 and 7 • Varicella virus • Coxsackievirus • Echovirus • Reovirus type 3 • Parvovirus B19 • HIV • Adenovirus Others • Toxoplasmosis • Syphilis • Tuberculosis • Listeriosis • Urinary tract infection	• Wilson disease • Neonatal iron storage disease • Indian childhood cirrhosis/infantile copper overload • Congenital disorders of glycosylation • Mitochondrial hepatopathies • Citrin deficiency
TOXIC Sepsis Parenteral nutrition related Drug, dietary supplement, herbal related	GENETIC OR CHROMOSOMAL Trisomies 17, 18, 21
METABOLIC Disorders of amino acid metabolism • Tyrosinemia Disorders of lipid metabolism • Wolman disease • Niemann-Pick disease (type C) • Gaucher disease Cholesterol ester storage disease Disorders of carbohydrate metabolism • Galactosemia • Fructosemia • Glycogenosis IV Disorders of bile acid biosynthesis Other metabolic defects • α_1-Antitrypsin deficiency • Cystic fibrosis • Hypopituitarism • Hypothyroidism • Zellweger (cerebrohepatorenal) syndrome	INTRAHEPATIC CHOLESTASIS SYNDROMES "Idiopathic" neonatal hepatitis Alagille syndrome Intrahepatic cholestasis (progressive familial intrahepatic cholestasis [PFIC]) • FIC-1 deficiency • BSEP (bile salt export pump) deficiency • MDR3 deficiency Familial benign recurrent cholestasis associated with lymphedema (Aagenaes syndrome) ARC (arthrogryposis, renal dysfunction, and cholestasis) syndrome Caroli disease (cystic dilation of intrahepatic ducts) EXTRAHEPATIC DISEASES Biliary atresia Sclerosing cholangitis Bile duct stricture/stenosis Choledochal–pancreaticoductal junction anomaly Spontaneous perforation of the bile duct Choledochal cyst Mass (neoplasia, stone) Bile/mucous plug ("inspissated bile") MISCELLANEOUS Shock and hypoperfusion Associated with enteritis Associated with intestinal obstruction Neonatal lupus erythematosus Myeloproliferative disease (trisomy 21) Hemophagocytic lymphohistiocytosis (HLH) COACH syndrome (coloboma, oligophrenia, ataxia, cerebellar vermis hypoplasia, hepatic fibrosis) Cholangiocyte cilia defects

in the superior vena cava distribution area (on the face and chest). Their size varies between 1 and 10 mm and they exhibit central clearing with pressure. They presumably reflect altered estrogen metabolism in the presence of hepatic dysfunction.

Palmar Erythema

Blotchy erythema, most noticeable over the thenar and hypothenar eminences and on the tips of the fingers, is also noted in patients with chronic liver disease. Abnormal serum estradiol levels and regional alterations in peripheral circulation have been identified as possible causes.

Xanthomas

The marked elevation of serum cholesterol levels (to >500 mg/dL) associated with some forms of chronic cholestasis can cause the deposition of lipid in the dermis and subcutaneous tissue. Brown nodules can develop, first over the extensor surfaces of the extremities; rarely, xanthelasma of the eyelids develops.

Portal Hypertension

Portal hypertension occurs when there is increased portal resistance and/or increased portal flow. The portal system drains the splanchnic area (abdominal portion of the gastrointestinal tract, pancreas, and spleen) into the hepatic sinusoids. Normal portal pressure is between 3 and 6 mm Hg. Portal hypertension is defined as a portal pressure greater than 10 mm Hg. Clinically significant portal hypertension exists when pressure exceeds a threshold of 12 mm Hg or greater. Portal hypertension is the main complication of cirrhosis, directly responsible for 2 of its most common and potentially lethal complications: ascites and variceal hemorrhage.

Ascites

Ascites is a consequence of increased hydrostatic and osmotic pressures within the hepatic and mesenteric capillaries resulting in transfer of fluid from the blood vessels to the lymphatics that overcomes the drainage capacity of the lymphatic system. Ascites can also be associated with nephrotic syndrome and other urinary tract abnormalities, metabolic diseases (such as lysosomal storage diseases), congenital or acquired heart disease, and hydrops fetalis. Factors favoring the intraabdominal accumulation of fluid include decreased plasma colloid osmotic pressure, increased capillary hydrostatic pressure, increased ascitic colloid osmotic fluid pressure, and decreased ascitic fluid hydrostatic pressure. Abnormal renal sodium retention must be considered.

Gastrointestinal Bleeding

Chronic liver disease may manifest as gastrointestinal hemorrhage. Bleeding may result from portal hypertensive gastropathy, gastric antral vascular ectasia, or varix rupture. Variceal hemorrhage is classically from an esophageal origin but may be caused by gastric, duodenal, peristomal, or rectal varices. Variceal hemorrhage results from increased pressure within the varix, which leads to changes in the diameter of the varix and increased wall tension. When the variceal wall strength is exceeded, physical rupture of the varix results. Given the high blood flow and pressure in the portosystemic collateral system, coupled with the lack of a natural mechanism to tamponade variceal bleeding, the rate of hemorrhage can be striking.

Encephalopathy

Hepatic encephalopathy can involve any neurologic function, and it can be prominent or present in subtle forms such as deterioration of school performance, sleep disturbances, depression, or emotional outbursts. It can be recurrent and precipitated by intercurrent illness, drugs, bleeding, or electrolyte and acid-base disturbances. The appearance of hepatic encephalopathy depends on the presence of portosystemic shunting, alterations in the blood–brain barrier, and the interactions of toxic metabolites with the central nervous system. Postulated causes include altered ammonia metabolism, synergistic neurotoxins, decreased cerebral oxygen metabolism and blood flow, or false neurotransmitters with plasma amino acid imbalance.

Endocrine Abnormalities

Endocrine abnormalities are more common in adults with hepatic disease than in children. They reflect alterations in hepatic synthetic, storage, and metabolic functions, including those concerned with hormonal metabolism in the liver. Proteins that bind hormones in plasma are synthesized in the liver, and steroid hormones are conjugated in the liver and excreted in the urine; failure of such functions can have clinical consequences. Endocrine abnormalities can also result from malnutrition or specific deficiencies.

Renal Dysfunction

Systemic disease or toxins can affect the liver and kidneys simultaneously, or parenchymal liver disease can produce secondary impairment of renal function. In hepatobiliary disorders, there may be renal alterations in sodium and water economy, impaired renal concentrating ability, and alterations in potassium metabolism. Ascites in patients with cirrhosis may be related to inappropriate retention of sodium by the kidneys and expansion of plasma volume, or it may be related to sodium retention mediated by diminished effective plasma volume. **Hepatorenal syndrome** is defined as functional renal failure in patients with end-stage liver disease. The pathophysiology of hepatorenal syndrome is related to splanchnic vasodilation, mesenteric angiogenesis, and decreased effective blood volume with resulting decreased renal perfusion. The hallmark is intense renal vasoconstriction (mediated by hemodynamic, humoral, or neurogenic mechanisms) with coexistent systemic vasodilation. The diagnosis is supported by the findings of oliguria (<1 mL/kg/day), a characteristic pattern of urine electrolyte abnormalities (urine sodium < 10 mEq/L, fractional excretion of sodium of <1%, urine : plasma creatinine ratio <10, and normal urinary sediment), absence of hypovolemia, and exclusion of other kidney pathology. The best treatment of hepatorenal syndrome is timely liver transplantation, because complete renal recovery can be expected.

Pulmonary Involvement

Hepatopulmonary syndrome is characterized by the typical triad of hypoxemia, intrapulmonary vascular dilations, and liver disease. There is intrapulmonic right-to-left shunting of blood resulting from enlarged pulmonary vessels that prevents red blood cells traveling through the center of the vessel adequate exposure to oxygen-rich alveoli. Shunting of vasodilatory mediators from the mesentery away from the liver is thought to contribute. It should be suspected and investigated in the child with chronic liver disease with history of shortness of breath or exercise intolerance and clinical examination findings of cyanosis (particularly of the lips and fingers), digital clubbing, and oxygen saturations <96%, particularly in the upright position. Treatment is timely liver transplantation; resolution of pulmonary involvement usually follows.

Portopulmonary hypertension is a condition characterized by an increase in the resistance to pulmonary arterial blood flow in the setting of portal hypertension. It is defined by a pulmonary arterial pressure >25 mm Hg at rest and above 30 mm Hg with exercise, elevated pulmonary vascular resistance with pulmonary arterial occlusion pressure, or a left-ventricular end-diastolic pressure of <15 mm Hg. Although the pathophysiology is unclear, symptoms suggesting a diagnosis include exertional dyspnea, fatigue, syncope, palpitations, and chest pain.

Recurrent Cholangitis

Ascending infection of the biliary system is often seen in pediatric cholestatic disorders, most commonly because of Gram-negative enteric organisms, such as *Escherichia coli, Klebsiella, Pseudomonas,* and *Enterococcus.* Liver transplantation is the definitive treatment for recurrent cholangitis, especially when medical therapy is not effective.

Miscellaneous Manifestations of Liver Dysfunction

Nonspecific signs of acute and chronic liver disease include anorexia, which often affects patients with anicteric hepatitis and with cirrhosis associated with chronic cholestasis; abdominal pain or distention resulting from ascites, spontaneous peritonitis, or visceromegaly; malnutrition and growth failure; and bleeding, which may be a result of altered synthesis of coagulation factors (biliary obstruction with vitamin K deficiency or excessive hepatic damage) or to portal hypertension with hypersplenism. In the presence of hypersplenism, there can be decreased synthesis of specific clotting factors, production of qualitatively abnormal proteins, or alterations in platelet number and function. Altered drug metabolism can prolong the biologic half-life of commonly administered medications.

Bibliography is available at Expert Consult.

355.1 Evaluation of Patients with Possible Liver Dysfunction

James E. Squires and William F. Balistreri

Adequate evaluation of an infant, child, or adolescent with suspected liver disease involves an appropriate and accurate history, a carefully performed physical examination, and skillful interpretation of signs and symptoms. Further evaluation is aided by judicious selection of diagnostic tests, followed by the use of imaging modalities or a liver biopsy. Most of the so-called liver function tests do not measure specific hepatic functions: a rise in serum aminotransferase levels reflects liver cell injury, an increase in immunoglobulin levels reflects an immunologic response to injury, or an elevation in serum bilirubin levels can reflect any of several disturbances of bilirubin metabolism (see Tables 355-2 and 355-3). Any single biochemical assay provides limited information, which must be placed in the context of the entire clinical picture. The most cost-efficient approach is to become familiar with the rationale, implications, and limitations of a selected group of tests so that specific questions can be answered. Young infants with cholestatic jaundice should be evaluated promptly to identify patients needing surgical intervention.

For a patient with suspected liver disease, evaluation addresses the following issues in sequence: Is liver disease present? If so, what is its nature? What is its severity? Is specific treatment available? How can we monitor the response to treatment? What is the prognosis?

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BIOCHEMICAL TESTS

Laboratory tests commonly used to screen for or to confirm a suspicion of liver disease include measurements of serum aminotransferase, bilirubin (total and fractionated), and alkaline phosphatase (AP) levels, as well as determinations of prothrombin time (PT) or international normalized ratio (INR) and albumin level. These tests are complementary, provide an estimation of synthetic and excretory functions, and might suggest the nature of the disturbance (inflammation or cholestasis).

The severity of the liver disease may be reflected in clinical signs or biochemical alterations. Clinical signs include encephalopathy, variceal hemorrhage, worsening jaundice, apparent shrinkage of liver mass owing to massive necrosis, or onset of ascites. Biochemical alterations include hypoglycemia, acidosis, hyperammonemia, electrolyte imbalance, continued hyperbilirubinemia, marked hypoalbuminemia, or a prolonged PT or INR that is unresponsive to parenteral administration of vitamin K.

Acute liver cell injury (parenchymal disease) caused by viral hepatitis, drug- or toxin-induced liver disease, shock, hypoxemia, or metabolic disease is best reflected by a marked increase in serum aminotransferase levels. Cholestasis (obstructive disease) involves regurgitation of bile components into serum; the serum levels of total and conjugated bilirubin and serum bile acids are elevated. Elevations in serum AP, 5′ nucleotidase, and γ-glutamyl transpeptidase levels are also sensitive indicators of obstruction or inflammation of the biliary tract. Fractionation of the total serum bilirubin level into conjugated and unconjugated bilirubin fractions helps to distinguish between elevations caused by processes such as hemolysis and those caused by hepatic dysfunction. A predominant elevation in the conjugated bilirubin level provides a relatively sensitive index of hepatocellular disease or hepatic excretory dysfunction.

Alanine aminotransferase (ALT, serum glutamate pyruvate transaminase) is liver specific, whereas aspartate aminotransferase (AST, serum glutamic-oxaloacetic transaminase) is derived from other organs in addition to the liver. The most marked rises of AST and ALT levels can occur with acute hepatocellular injury; a several thousand–fold elevation can result from acute viral hepatitis, toxic injury, hypoxia, or hypoperfusion. After blunt abdominal trauma, parallel elevations in aminotransferase levels can provide an early clue to hepatic injury. A differential rise or fall in AST and ALT levels sometimes provides useful information. In acute hepatitis, the rise in ALT may be greater than the rise in AST. In alcohol-induced liver injury, fulminant echovirus infection, and various metabolic diseases, more predominant rises in the AST level are reported. In chronic liver disease or in intrahepatic and extrahepatic biliary obstruction, AST and ALT elevations may be less marked. Elevated serum aminotransferase levels are seen in patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH), the notable characteristic is histology similar to alcoholic-induced liver injury in the absence of alcohol abuse.

Hepatic synthetic function is reflected in serum albumin and protein levels and in the PT or INR. Examination of serum globulin concentration and of the relative amounts of the globulin fractions may be helpful. Patients with autoimmune hepatitis often have high γ-globulin levels and increased titers of anti–smooth muscle, antinuclear, and anti–liver-kidney-microsome antibodies. Antimitochondrial antibodies may also be found in patients with autoimmune hepatitis. A resurgence in α-fetoprotein levels can suggest hepatoma, hepatoblastoma, or hereditary tyrosinemia. Hypoalbuminemia caused by depressed synthesis can complicate severe liver disease and serve as a prognostic factor. Deficiencies of factor V and of the vitamin K–dependent factors (II, VII, IX, and X) can occur in patients with severe liver disease or fulminant hepatic failure. If the PT or INR is prolonged as a result of intestinal malabsorption of vitamin K (resulting from cholestasis) or decreased nutritional intake of vitamin K, parenteral administration of vitamin K should correct the coagulopathy, leading to normalization within 12-24 hr. Unresponsiveness to vitamin K suggests severe hepatic disease. Persistently low levels of factor VII are evidence of a poor prognosis in fulminant liver disease.

Interpretation of results of biochemical tests of hepatic structure and function must be made in the context of age-related changes. The activity of AP varies considerably with age. Normal growing children have significant elevations of serum AP activity originating from influx into serum of the isoenzyme that originates in bone, particularly in rapidly growing adolescents. An isolated increase in AP does not indicate hepatic or biliary disease if other liver tests are normal. Other enzymes such as 5′ nucleotidase and γ-glutamyl transpeptidase are increased in cholestatic conditions and may be more specific for hepatobiliary disease. 5′ nucleotidase is not found in bone. γ-Glutamyl transpeptidase exhibits high enzyme activity in early life that declines rapidly with age. Cholesterol concentrations increase throughout life. Cholesterol levels may be markedly elevated in patients with intra- or extrahepatic cholestasis and decreased in severe acute liver disease such as hepatitis.

Interpretation of serum ammonia values must be carried out with caution because of variability in their physiologic determinants and the inherent difficulty in laboratory measurement.

LIVER BIOPSY

Liver biopsy combined with clinical data can suggest a cause for hepatocellular injury or cholestatic disease in most cases. Specimens of liver tissue can be used to determine a precise histologic diagnosis in patients with neonatal cholestasis, chronic hepatitis, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, metabolic liver disease, intrahepatic cholestasis, congenital hepatic fibrosis, or undefined portal hypertension. The sample may be subjected to enzyme analysis to detect inborn errors of metabolism and to analysis of stored material such as iron, copper, or specific metabolites. Liver biopsies can monitor responses to therapy or detect complications of treatment with potentially hepatotoxic agents, such as aspirin, antiinfectives (minocycline, ketoconazole, isoniazid), antimetabolites, antineoplastics, or anticonvulsant agents.

In infants and children, needle biopsy of the liver is easily accomplished percutaneously. The amount of tissue obtained, even in small infants, is usually sufficient for histologic interpretation and for biochemical analyses, if the latter are deemed necessary. Percutaneous liver biopsy can be performed safely in infants as young as 1 wk of age. Contraindications to the percutaneous approach include prolonged PT or INR; thrombocytopenia; suspicion of a vascular, cystic, or infectious lesion in the path of the needle; and severe ascites. If administration of fresh-frozen plasma or of platelet transfusions fails to correct a prolonged PT, INR, or thrombocytopenia, a tissue specimen can be obtained via alternative techniques. Considerations include either the open laparotomy (wedge) approach by a general surgeon or the transjugular approach under ultrasound and fluoroscopic guidance by an experienced pediatric interventional radiologist in an appropriately equipped fluoroscopy suite. The risk of development of a complication such as hemorrhage, hematoma, creation of an arteriovenous fistula, pneumothorax, or bile peritonitis is small.

HEPATIC IMAGING PROCEDURES

Various techniques help define the size, shape, and architecture of the liver and the anatomy of the intrahepatic and extrahepatic biliary trees. Although imaging might not provide a precise histologic and biochemical diagnosis, specific questions can be answered, such as whether hepatomegaly is related to accumulation of fat or glycogen or is caused by a tumor or cyst. These studies can direct further evaluation such as percutaneous biopsy and make possible prompt referral of patients with biliary obstruction to a surgeon. Choice of imaging procedure should be part of a carefully formulated diagnostic approach, with avoidance of redundant demonstrations by several techniques.

A *plain x-ray study* can suggest hepatomegaly, but a carefully performed physical examination gives a more reliable assessment of liver size. The liver might appear less dense than normal in patients with fatty infiltration or denser with deposition of heavy metals such as iron. A hepatic or biliary tract mass can displace an air-filled loop of bowel. Calcifications may be evident in the liver (parasitic or neoplastic disease), in the vasculature (portal vein thrombosis), or in the

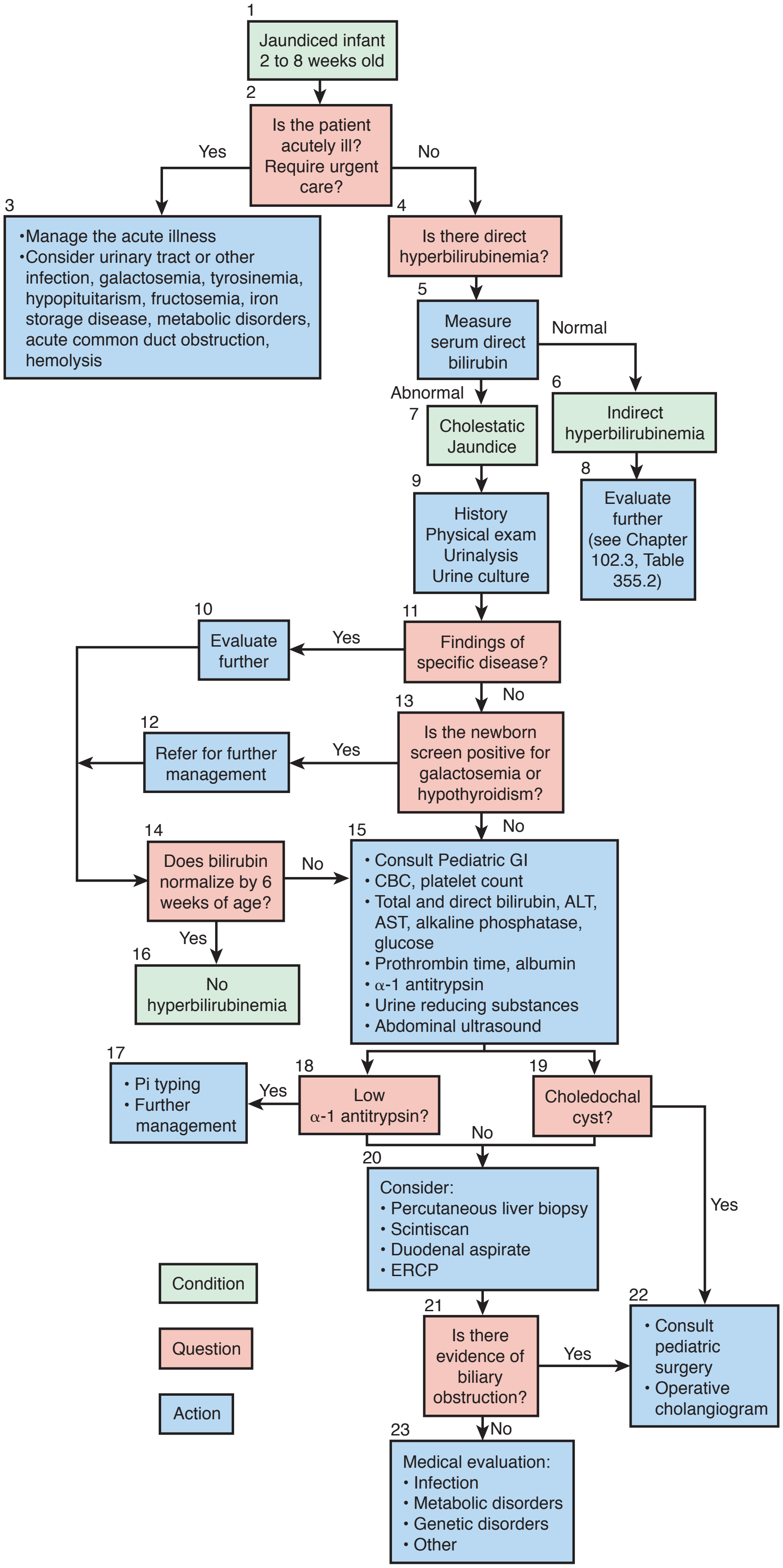

Figure 355-1 Cholestasis clinical practice guideline. Algorithm for a 2-8 wk old. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ERCP, endoscopic retrograde cholangiopancreatography. *(From Moyer V, Freese DK, Whitington PF, et al; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition: Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition,* J Pediatr Gastroenterol Nutr *39:115–128, 2004.)*

gallbladder or biliary tree (gallstones). Collections of gas may be seen within the liver (abscess), biliary tract, or portal circulation (necrotizing enterocolitis).

Ultrasound provides information about the size, composition, and blood flow of the liver. Increased echogenicity is observed with fatty infiltration; mass lesions as small as 1-2 cm may be shown. Ultrasound has replaced cholangiography in detecting stones in the gallbladder or biliary tree. Even in neonates, ultrasound can assess gallbladder size, detect dilation of the biliary tract, and define a choledochal cyst. In infants with biliary atresia, ultrasound findings might include small or absent gallbladder; nonvisualization of the common duct; and presence of the triangular cord sign, a triangular or tubular-shaped echogenic density in the bifurcation of the portal vein, representing fibrous remnants at the porta hepatis. Hyperechogenic hepatic parenchyma can be seen with metabolic disease (glycogen storage disease) or fatty liver (obesity, malnutrition, hyperalimentation, corticosteroids). In patients with portal hypertension, Doppler ultrasound can evaluate patency of the portal vein, demonstrate collateral circulation, and assess size of spleen and amount of ascites. Relatively small amounts of ascitic fluid can also be detected. The use of Doppler ultrasound has been helpful in determining vascular patency after liver transplantation.

CT scanning provides information similar to that obtained by ultrasound but is less suitable for use in patients younger than 2 yr of age because of the small size of structures, the paucity of intraabdominal fat for contrast, and the need for heavy sedation or general anesthesia. CT scan may be more accurate than ultrasound in detecting focal lesions such as tumors, cysts, and abscesses. When enhanced by contrast medium, CT scanning can reveal a neoplastic mass density only slightly different from that of a normal liver. When a hepatic tumor is suspected, CT scanning is the best method to define anatomic extent, solid or cystic nature, and vascularity. CT scanning can also reveal subtle differences in density of liver parenchyma, the average liver attenuation coefficient being reduced with fatty infiltration. MRI is a useful alternative that limits radiation exposure. Magnetic resonance cholangiography can be of value in differentiating biliary tract lesions. MRI with Eovist (gadoxetate disodium) can assist in the detection and characterization of known or suspected focal liver lesions. In differentiating obstructive from nonobstructive cholestasis, CT scanning or MRI identifies the precise level of obstruction more often than ultrasound. Either CT scanning or ultrasound may be used to guide percutaneously placed fine needles for biopsies, aspiration of specific lesions, or cholangiography.

Elastography is a novel noninvasive method to assess for the development of hepatic fibrosis in patients with liver disease. Both ultrasound and MR methods of have been developed. These noninvasive techniques allow for monitoring fibrosis progression and development of cirrhosis, improved characterization of hepatic tumors, and prognostic stratification of diseases such as nonalcoholic fatty liver disease and nonalcoholic steatohepatitis.

Radionuclide scanning relies on selective uptake of a radiopharmaceutical agent. Commonly used agents include technetium-99m–labeled sulfur colloid, which undergoes phagocytosis by Kupffer cells; ^{99m}Tc-iminodiacetic acid agents, which are taken up by hepatocytes and excreted into bile in a fashion similar to bilirubin; and gallium-67, which is concentrated in inflammatory and neoplastic cells. The anatomic resolution possible with hepatic scintiscans is generally less than that obtained with CT scanning, MRI, or ultrasound.

The ^{99m}Tc-sulfur colloid scan can detect focal lesions (tumors, cysts, abscesses) >2-3 cm in diameter. This modality can help to evaluate patients with possible cirrhosis and with patchy hepatic uptake and a shift of colloid uptake from liver to bone marrow.

Cholangiography, direct visualization of the intrahepatic and extrahepatic biliary tree after injection of opaque material, may be required in some patients to evaluate the cause, location, or extent of biliary obstruction. Percutaneous transhepatic cholangiography with a fine needle is the technique of choice in infants and young children. The likelihood of opacifying the biliary tract is excellent in patients in whom CT scanning, MRI, or ultrasound demonstrates dilated ducts. Percutaneous transhepatic cholangiography has been used to outline the biliary ductal system.

Endoscopic retrograde cholangiopancreatography is an alternative method of examining the bile ducts in older children. The papilla of Vater is cannulated under direct vision through a fiberoptic endoscope, and contrast material is injected into the biliary and pancreatic ducts to outline the anatomy. The advantage of endoscopic retrograde cholangiopancreatography is that it allows therapeutic interventions of the extrahepatic biliary tree (stone extraction, stent placement, etc.).

Selective angiography of the celiac, superior mesenteric, or hepatic artery can be used to visualize the hepatic or portal circulation. Both arterial and venous circulatory systems of the liver can be examined. Angiography is often required to define the blood supply of tumors before surgery and is useful in the study of patients with known or presumed portal hypertension. The patency of the portal system, the extent of collateral circulation, and the caliber of vessels under consideration for a shunting procedure can be evaluated. MRI can provide similar information.

DIAGNOSTIC APPROACH TO INFANTS WITH JAUNDICE

Well-appearing infants can have cholestatic jaundice. Biliary atresia and neonatal hepatitis are the most common causes of cholestasis in early infancy. Biliary atresia portends a poor prognosis unless it is identified early. The best outcome for this disorder is with early surgical reconstruction (45-60 days of age). History, physical examination, and the detection of a conjugated hyperbilirubinemia via examination of total and direct bilirubin are the first steps in evaluating the jaundiced infant (Fig. 355-1). Consultation with a pediatric gastroenterologist should be sought early in the course of the evaluation.

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Chapter 356
Cholestasis

356.1 Neonatal Cholestasis

H. Hesham Abdel-Kader Hassan and William F. Balistreri

Neonatal cholestasis is defined biochemically as prolonged elevation of the serum levels of conjugated bilirubin beyond the 1st 14 days of life. Jaundice that appears after 2 wk of age, continues to progress, or does not resolve at this time should be evaluated and a conjugated bilirubin level determined. Cholestasis in a newborn can be caused by infectious, genetic, metabolic, or undefined abnormalities giving rise to *mechanical* obstruction of bile flow or to *functional* impairment of hepatic excretory function and bile secretion (see Table 355-3). Mechanical lesions include stricture or obstruction of the common bile duct; biliary atresia is the prototypic obstructive abnormality. Functional impairment of bile secretion can result from congenital defects or damage to liver cells or to the biliary secretory apparatus.

Neonatal cholestasis can be divided into extrahepatic and intrahepatic disease (Fig. 356-1). The clinical features of any form of cholestasis are similar. In an affected neonate, the diagnosis of certain entities, such as galactosemia, sepsis, or hypothyroidism, is relatively simple and a part of most neonatal screening programs. In most cases, the cause of cholestasis is more obscure. Differentiation among biliary atresia and idiopathic neonatal hepatitis is particularly difficult.

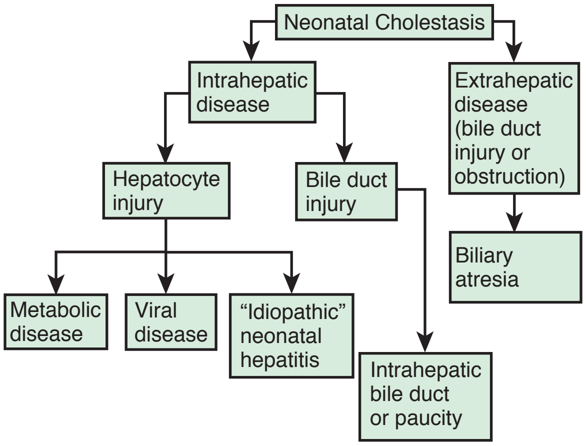

Figure 356-1 **Neonatal cholestasis.** Conceptual approach to the group of diseases presenting as cholestasis in the neonate. There are areas of overlap: patients with biliary atresia might have some degree of intrahepatic injury. Patients with "idiopathic" neonatal hepatitis might, in the future, be determined to have a primary metabolic or viral disease.

MECHANISMS

Metabolic liver disease caused by inborn errors of bile acid metabolism or transport is associated with accumulation of atypical toxic primitive bile acids and failure to produce normal choleretic and trophic bile acids. The clinical and histologic manifestations are nonspecific and are similar to those in other forms of neonatal hepatobiliary injury. Autoimmune mechanisms may also be responsible for some of the enigmatic forms of neonatal liver injury.

Some of the histologic manifestations of hepatic injury in early life are not seen in older patients. Giant cell transformation of hepatocytes occurs commonly in infants with cholestasis and can occur in any form of neonatal liver injury. It is more common and more severe in intrahepatic forms of cholestasis. The clinical and histologic findings that exist in patients with neonatal hepatitis and in those with biliary atresia are quite disparate; the basic process is an undefined initiating insult causing inflammation of the liver cells or of the cells within the biliary tract. If bile duct epithelium is the predominant site of disease, cholangitis can result and lead to progressive sclerosis and narrowing of the biliary tree, the ultimate state being complete obliteration (biliary atresia). Injury to liver cells can present the clinical and histologic picture of "neonatal hepatitis." This concept does not account for the precise mechanism, but it offers an explanation for well-documented cases of unexpected postnatal evolution of these disease processes; infants initially regarded as having neonatal hepatitis, with a patent biliary system shown on cholangiography, can later develop biliary atresia.

Functional abnormalities in the generation of bile flow can also have a role in neonatal cholestasis. Bile flow is directly dependent on effective hepatic bile acid excretion by the hepatocytes. During the phase of relatively inefficient liver cell transport and metabolism of bile acids in early life, minor degrees of hepatic injury can further decrease bile flow and lead to production of atypical and potentially toxic bile acids. Selective impairment of a single step in the series of events involved in hepatic excretion produces the full expression of a cholestatic syndrome. Specific defects in bile acid synthesis are found in infants with various forms of intrahepatic cholestasis (Table 356-1). Severe forms of familial cholestasis are associated with neonatal hemochromatosis and an aberration in the contractile proteins that compose the cytoskeleton of the hepatocyte. **Neonatal hemochromatosis** can also be an alloimmune-mediated gestational (maternal antibodies against fetal hepatocytes) disease responsive to maternal intravenous immunoglobulin. Sepsis is known to cause cholestasis, presumably mediated by an endotoxin produced by *Escherichia coli.*

Table 356-1 Proposed Subtypes of Intrahepatic Cholestasis

A. Disorders of membrane transport and secretion
  1. Disorders of canalicular secretion
    a. Bile acid transport: BSEP deficiency
      i. Persistent, progressive (PFIC type 2)
      ii. Recurrent, benign (BRIC type 2)
    b. Phospholipid transport: MDR3 deficiency (PFIC type 3)
    c. Ion transport: cystic fibrosis *(CFTR)*
  2. Complex or multiorgan disorders
    a. FIC1 deficiency
      i. Persistent, progressive (PFIC type 1, Byler disease)
      ii. Recurrent, benign (BRIC type 1)
    b. Neonatal sclerosing cholangitis *(CLDN1)*
    c. Arthrogryposis-renal dysfunction-cholestasis syndrome *(VPS33B)*
B. Disorders of bile acid biosynthesis and conjugation
  1. 3-oxoΔ-4-steroid 5β-reductase deficiency
  2. 3β-hydroxy-5-C_{27}-steroid dehydrogenase/isomerase deficiency
  3. Oxysterol 7α-hydroxylase deficiency
  4. Bile acid-coenzyme A (CoA) ligase deficiency
  5. BAAT deficiency (familial hypercholanemia)
C. Disorders of embryogenesis
  1. Alagille syndrome (Jagged1 defect, syndromic bile duct paucity)
  2. Ductal plate malformation (ARPKD, ADPLD, Caroli disease)
D. Unclassified (idiopathic "neonatal hepatitis"): mechanism unknown

Note: FIC1 deficiency, BSEP deficiency, and some of the disorders of bile acid biosynthesis are characterized clinically by low levels of serum GGT despite the presence of cholestasis. In all other disorders listed, the serum GGT level is elevated.

ADPLD, autosomal dominant polycystic liver disease (cysts in liver only); ARPKD, autosomal recessive polycystic kidney disease (cysts in liver and kidney); BAAT, bile acid transporter; BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt export pump; CFTR, cystic fibrosis transmembrane regulator; GGT, γ-glutamyl transpeptidase; PFIC, progressive familial intrahepatic cholestasis.

From Balistreri WF, Bezerra JA, Jansen P, et al: Intrahepatic cholestasis: summary of an American Association for the Study of Liver Diseases single-topic conference, Hepatology *42:222–235, 2005.*

EVALUATION

The evaluation of the infant with jaundice should follow a logical, cost-effective sequence in a multistep process (Table 356-2). Although cholestasis in the neonate may be the initial manifestation of numerous and potentially serious disorders, the clinical manifestations are usually similar and provide very few clues about etiology. Affected infants have icterus, dark urine, light or acholic stools, and hepatomegaly, all resulting from decreased bile flow as a result of either hepatocyte injury or bile duct obstruction. Hepatic synthetic dysfunction can lead to hypoprothrombinemia and bleeding. Administration of vitamin K should be included in the initial treatment of cholestatic infants to prevent hemorrhage.

In contrast to unconjugated hyperbilirubinemia, which can be physiologic, cholestasis (conjugated bilirubin elevation of any degree) in the neonate is **always pathologic** and prompt differentiation is imperative. Thus the initial step is to identify the infant who has cholestasis. The next step is to recognize conditions that cause cholestasis and for which specific therapy is available to prevent further damage and avoid long-term complications such as sepsis, an endocrinopathy (hypothyroidism, panhypopituitarism), nutritional hepatotoxicity caused by a specific metabolic illness (galactosemia), or other metabolic diseases (tyrosinemia).

Hepatobiliary disease can be the initial manifestation of homozygous α_1-antitrypsin deficiency or of cystic fibrosis. Neonatal liver disease can also be associated with congenital syphilis and specific viral infections, notably echovirus and herpesviruses including

Table 356-2 Value of Specific Tests in the Evaluation of Patients with Suspected Neonatal Cholestasis

TEST	RATIONALE
Serum bilirubin fractionation (i.e., assessment of the serum level of conjugated bilirubin)	Indicates cholestasis
Assessment of stool color (does the baby have pigmented or acholic stools?)	Indicates bile flow into intestine
Urine and serum bile acids measurement	Confirms cholestasis; might indicate inborn error of bile acid biosynthesis
Hepatic synthetic function (albumin, coagulation profile)	Indicates severity of hepatic dysfunction
α_1-Antitrypsin phenotype	Suggests (or excludes) PiZZ
Thyroxine and TSH	Suggests (or excludes) endocrinopathy
Sweat chloride and mutation analysis	Suggests (or excludes) cystic fibrosis
Urine and serum amino acids and urine reducing substances	Suggests (or excludes) metabolic liver disease
Ultrasonography	Suggests (or excludes) choledochal cyst; might detect the triangular cord sign, suggesting biliary atresia
Hepatobiliary scintigraphy	Documents bile duct patency or obstruction
Liver biopsy	Distinguishes biliary atresia; suggests alternative diagnosis

PiZZ, protease inhibitor ZZ phenotype; TSH, thyroid-stimulating hormone.

cytomegalovirus. These account for a small percentage of cases of neonatal hepatitis syndrome The hepatitis viruses (A, B, C) rarely cause neonatal cholestasis.

The final and critical step in evaluating neonates with cholestasis is to differentiate extrahepatic biliary atresia from neonatal hepatitis.

INTRAHEPATIC CHOLESTASIS

Neonatal Hepatitis

The term *neonatal hepatitis* implies intrahepatic cholestasis (see Fig. 356-1), which has various forms (see Tables 356-1 and 356-3).

Idiopathic neonatal hepatitis, which can occur in either a sporadic or a familial form, is a disease of unknown cause. Patients with the sporadic form presumably have a specific yet undefined metabolic or viral disease. Familial forms, on the other hand, presumably reflect a genetic or metabolic aberration; in the past, patients with α_1-antitrypsin deficiency were included in this category.

Aagenaes syndrome is a form of idiopathic familial intrahepatic cholestasis associated with lymphedema of the lower extremities. The relationship between liver disease and lymphedema is not understood and may be attributable to decreased hepatic lymph flow or hepatic lymphatic hypoplasia. Affected patients usually present with episodic cholestasis with elevation of serum aminotransferases, alkaline phosphatase, and bile acids. Between episodes, the patients are usually asymptomatic and biochemical indices improve. Compared to other types of hereditary neonatal cholestasis, patients with Aagenaes syndrome have a relatively good prognosis because more than 50% can expect a normal life span. The locus for Aagenaes syndrome is mapped to a 6.6 cM interval on chromosome 15q.

Zellweger (cerebrohepatorenal) syndrome is a rare autosomal recessive genetic disorder marked by progressive degeneration of the liver and kidneys (see Chapter 80.2). The incidence is estimated to be 1 in 100,000 births; the disease is usually fatal in 6-12 mo. Affected infants have severe, generalized hypotonia and markedly impaired neurologic function with psychomotor retardation. Patients have an abnormal head shape and unusual facies, hepatomegaly, renal cortical cysts, stippled calcifications of the patellas and greater trochanter, and ocular abnormalities. Hepatic cells on ultrastructural examination show an absence of peroxisomes. MRI performed in the 3rd trimester can allow analysis of cerebral gyration and myelination, facilitating the prenatal diagnosis of Zellweger syndrome.

Neonatal iron storage disease (neonatal hemochromatosis) is a rapidly progressive disease characterized by increased iron deposition in the liver, heart, and endocrine organs without increased iron stores in the reticuloendothelial system. Patients have multiorgan failure and shortened survival. Familial cases are reported, and repeated affected neonates in the same family are common. This is an alloimmune disorder with maternal antibodies directed against the fetal liver. Laboratory findings include hypoglycemia, hyperbilirubinemia, hypoalbuminemia, elevated ferritin and profound hypoprothrombinemia. Serum aminotransferase levels may be high initially but normalize with the progression of the disease. The diagnosis is usually confirmed by buccal mucosal biopsy or MRI demonstrating extrahepatic siderosis. The prognosis is poor; however, liver transplantation can be curative. Despite initially encouraging reports, the use of a combination of antioxidants and prostaglandin infusion with chelation might not uniformly improve outcome in patients with neonatal iron storage disease. Although recovery from neonatal iron storage disease either spontaneously or with medical therapy is unusual, the potential for histologic recovery with regression of fibrosis has been reported. The differential diagnosis includes familial hemophagocytic lymphohistiocytosis, mitochondrial respiratory chain disorders, galactosemia, tyrosinemia, viral hepatitis (HSV, CMV), congenital syphilis, and idiopathic neonatal hepatitis.

Neonatal hemochromatosis seems to be a gestational alloimmune disease, and reoccurrence of severe neonatal hemochromatosis in at-risk pregnancies may be reduced by maternal treatment with weekly (beginning gestational age 18 wk) high-dose intravenous immunoglobulin (1 g/kg) during gestation. After birth, affected neonates are treated with exchange transfusions and intravenous immunoglobulin (1 g/kg), which improves survival and reduces the need for liver transplantation.

Disorders of Transport, Secretion, Conjugation, and Biosynthesis of Bile Acids

Progressive familial intrahepatic cholestasis type 1 (PFIC 1) or FIC1 disease (formerly known as **Byler disease**) is a severe form of intrahepatic cholestasis. The disease was initially described in the Amish kindred of Jacob Byler. Affected patients present with steatorrhea, pruritus, vitamin D–deficient rickets, gradually developing cirrhosis, and **low** γ-glutamyl transpeptidase (GGT) levels. The absence of bile duct paucity and extrahepatic features differentiate this disorder from Alagille syndrome.

PFIC 1 (FIC-1 deficiency) has been mapped to chromosome 18q12 and results from defect in the gene for F1C1 (*ATP8B1*; see Tables 356-3 and 356-4). F1C1 is a P-type adenosine triphosphatase that functions as aminophospholipid flippase, facilitating the transfer of phosphatidyl

Table 356-3 Molecular Defects Causing Liver Disease

GENE	PROTEIN	FUNCTION, SUBSTRATE	DISORDER
ATP8b1	FIC1	P-type ATPase; aminophospholipid translocase that flips phosphatidylserine and phosphatidylethanolamine from the outer to the inner layer of the canalicular membrane	PFIC 1 (Byler disease), BRIC 1, GFC
ABCB11	BSEP	Canalicular protein with ATP-binding cassette (ABC family of proteins); works as a pump transporting bile acids through the canalicular domain	PFIC 2, BRIC 2
ABCB4	MDR3	Canalicular protein with ATP-binding cassette (ABC family of proteins); works as a phospholipid flippase in canalicular membrane	PFIC 3, ICP, cholelithiasis
AKR1D1	5β-reductase	3-oxoΔ-4-steroid 5β-reductase gene; regulates bile acid synthesis	BAS: neonatal cholestasis with giant cell hepatitis
HSD3B7	C27-3β-HSD	3β-hydroxy-5-C_{27}-steroid oxidoreductase (C27-3β-HSD) gene; regulates bile acid synthesis	BAS: chronic intrahepatic cholestasis
CYP7BI	CYP7BI	Oxysterol 7α-hydroxylase; regulates the acidic pathway of bile acid synthesis	BAS: neonatal cholestasis with giant cell hepatitis
JAG1	JAG1	Transmembrane, cell-surface proteins that interact with Notch receptors to regulate cell fate during embryogenesis	Alagille syndrome
TJP2	Tight junction protein	Belongs to the family of membrane-associated guanylate kinase homologs that are involved in the organization of epithelial and endothelial intercellular junction; regulates paracellular permeability	FHC
BAAT	BAAT	Enzyme that transfers the bile acid moiety from the acyl coenzyme A thioester to either glycine or taurine	FHC
EPHX1	Epoxide hydrolase	Microsomal epoxide hydrolase regulates the activation and detoxification of exogenous chemicals	FHC
ABCC2	MRP2	Canalicular protein with ATP-binding cassette (ABC family of proteins); regulates canalicular transport of GSH conjugates and arsenic	Dubin-Johnson syndrome
ATP7B	ATP7B	P-type ATPase; function as copper export pump	Wilson disease
CLDN1	Claudin 1	Tight junction protein	NSC
CIRH1A	Cirhin	Cell signaling?	NAICC
CFTR	CFTR	Chloride channel with ATP-binding cassette (ABC family of proteins); regulates chloride transport	Cystic fibrosis
PKHD1	Fibrocystin	Protein involved in ciliary function and tubulogenesis	ARPKD
PRKCSH	Hepatocystin	Assembles with glucosidase II α subunit in endoplasmic reticulum	ADPLD
VPS33B	Vascular Protein sorting 33	Regulates fusion of proteins to cellular membrane	ARC

ADPLD, autosomal dominant polycystic liver disease; ARC, arthrogryposis–renal dysfunction–cholestasis syndrome*; ARPKD, autosomal recessive polycystic kidney disease; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; BAAT, bile acid transporter; BAS, bile acid synthetic defect; BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt export pump; CFTR, cystic fibrosis transmembrane conductance regulator; FHC, familial hypercholanemia; GFC, Greenland familial cholestasis; GSH, glutathione; ICP, intrahepatic cholestasis of pregnancy; NAICC, North American Indian childhood cirrhosis; NSC, neonatal sclerosing cholangitis with ichthyosis, leukocyte vacuoles, and alopecia; PFIC, progressive familial intrahepatic cholestasis*. (*Low γ-glutamyl transpeptidase [PFIC types 1 and 2, BRIC types 1 and 2, ARC].)

From Balistreri WF, Bezerra JA, Jansen P, et al: Intrahepatic cholestasis: summary of an American Association for the Study of Liver Diseases single-topic conference, Hepatology *42:222–235, 2005.*

serine and phosphatidyl ethanolamine from the outer to inner hemileaflet of the cellular membrane. F1C1 might also play a role in intestinal bile acid absorption, as suggested by the high level of expression in the intestine. Defective F1C1 might also result in another form of intrahepatic cholestasis: **benign recurrent intrahepatic cholestasis (BRIC) type I.** The disease is characterized by recurrent bouts of cholestasis, jaundice, and severe pruritus lasting from 2 wk to 6 mo; it can last up to 5 yr. The episodes vary from few episodes per year to 1 episode per decade and can profoundly affect the quality of life. Nonsense, frame shift, and deletional mutations cause PFIC type 1; missense and split-type mutations result in BRIC type I. Typically, patients with BRIC type I have normal cholesterol and GGT levels.

PFIC type 2 *(BSEP deficiency)* is mapped to chromosome 2q24 and is similar to PFIC 1 but is present in non-Amish families (Middle Eastern and European). The disease results from defects in the canalicular adenosine triphosphate–dependent bile acid transporter BSEP (*ABCB11*). The progressive liver disease results from accumulation of bile acids secondary to reduction in canalicular bile acid secretion. Mutation in *ABC11* is also described in another disorder, BRIC type 2, characterized by recurrent bouts of cholestasis.

In contrast to PFIC 1 and PFIC 2, patients with **PFIC type 3** *(MDR3 disease)* have **high** levels of GGT. The disease results from defects in a canalicular phospholipids flippase, MDR3 (*ABCB4*), which results in deficient translocation of phosphatidylcholine across the canalicular membrane. Mothers who are heterozygous for this gene can develop intrahepatic cholestasis during pregnancy.

Familial hypercholanemia is characterized by elevated serum bile acid concentration, pruritus, failure to thrive, and coagulopathy. Familial hypercholanemia is a complex genetic trait associated with mutation of bile acid coenzyme A (CoA), amino acid *N*-acyltransferase (encoded by *BAAT*), as well as mutations in tight junction protein 2 (encoded by *TJP 2*, also known as *ZO-2*). Mutation of BAAT, which

Table 356-4 Progressive Familial Intrahepatic Cholestasis

	PFIC 1	PFIC 2	PFIC 3
Transmission	Autosomal recessive	Autosomal recessive	Autosomal recessive
Chromosome	18q21-22	2q24	7q21
Gene	*ATP8B1/F1C1*	*ABCB11/BSEP*	*ABCB4/MDR3*
Protein	FIC1	BSEP	MDR3
Location	Hepatocyte, colon, intestine, pancreas; on apical membranes	Hepatocyte canalicular membrane	Hepatocyte canalicular membrane
Function	ATP-dependent aminophospholipid flippase; unknown effects on intracellular signaling	ATP-dependent bile acid transport	ATP-dependent phosphatidylcholine translocation
Phenotype	Progressive cholestasis, diarrhea, steatorrhea, growth failure, severe pruritus	Rapidly progressive cholestatic giant cell hepatitis, growth failure, pruritus	Later-onset cholestasis, portal hypertension, minimal pruritus, intraductal and gallbladder lithiasis
Histology	Initial bland cholestatic; coarse, granular canalicular bile on EM	Neonatal giant cell hepatitis, amorphous canalicular bile on EM	Proliferation of bile ductules, periportal fibrosis, eventually biliary cirrhosis
Biochemical features	Normal serum GGT; high serum, low biliary bile acid concentrations	Normal serum GGT; high serum, low biliary bile acid concentrations	Elevated serum GGT; low to absent biliary PC; absent serum LPX; normal biliary bile acid concentrations
Treatment	Biliary diversion, ileal exclusion, liver transplantation, but post-OLT diarrhea, steatorrhea, fatty liver	Biliary diversion, liver transplantation	UDCA if residual PC secretion; liver transplantation

ATP, adenosine triphosphate; BSEP, bile salt export pump; EM, electron microscopy; GGT, γ-glutamyl transpeptidase; LPX, lipoprotein X; OLT, orthotopic liver transplantation; PC, phosphatidylcholine; PFIC, progressive familial intrahepatic cholestasis; UDCA, ursodeoxycholic acid.

From Suchy FJ, Sokol RJ, Balistreri WF, editors: Liver disease in children, *ed 3, New York, 2007, Cambridge University Press.*

is a bile acid–conjugating enzyme, abrogates the enzyme activity. Patients who are homozygous for this mutation have only unconjugated bile acids in their bile. Mutation of both BAAT and TJP 2 can disrupt bile acid transport and circulation. Patients with familial hypercholanemia usually respond to the administration of ursodeoxycholic acid.

Defective bile acid biosynthesis is postulated to be an initiating or perpetuating factor in neonatal cholestatic disorders; the hypothesis is that inborn errors in bile acid biosynthesis lead to absence of normal trophic or choleretic primary bile acids and accumulation of atypical (hepatotoxic) metabolites. Inborn errors of bile acid biosynthesis cause acute and chronic liver disease; early recognition allows institution of targeted bile acid replacement, which reverses the hepatic injury. Several specific defects have been described:

- **Deficiency of Δ^4-3-oxosteroid-5β reductase,** the 4th step in the pathway of cholesterol degradation to the primary bile acids, manifests with significant cholestasis and liver failure developing shortly after birth, with coagulopathy and metabolic liver injury resembling tyrosinemia. Hepatic histology is characterized by lobular disarray with giant cells, pseudoacinar transformation, and canalicular bile stasis. Mass spectrometry is required to document increased urinary bile acid excretion and the predominance of oxo-hydroxy and oxo-dihydroxy cholenoic acids. **Treatment** with cholic acid and ursodeoxycholic acid is associated with normalization of biochemical, histologic, and clinical features.
- **Deficiency of 3β-hydroxy-Δ^5-C_{27}-steroid oxidoreductase (3β-HSD),** the 2nd step in bile acid biosynthesis, causes progressive familial intrahepatic cholestasis. Affected patients usually have jaundice with increased aminotransferase levels and hepatomegaly; GGT levels and serum cholylglycine levels are **normal.** The histology is variable, ranging from giant cell hepatitis to chronic hepatitis. The diagnosis, suggested by mass spectrometry detection of C^{24} bile acids in urine, which retain the 3β-hydroxy-Δ^5 structure, can be confirmed by determination of 3β-HSD activity in cultured fibroblasts using 7α-hydroxy-Δ^5 cholesterol as a substrate. Primary bile acid therapy, administered orally to down regulate cholesterol 7α-hydroxylase activity, to limit the production of 3β-hydroxy-Δ^5 bile acids, and to facilitate hepatic clearance, has been effective in reversing hepatic injury.

BILE ACID–COENZYME A LIGASE DEFICIENCY

Conjugation with the amino acids glycine and taurine is the final step in bile acid synthesis. Two enzymes catalyze the amidation of bile acids. In the first reaction, a CoA thioester is formed by the rate-limiting bile acid–CoA ligase. The other reaction involves the coupling of glycine or taurine and is catalyzed by a cytosolic bile acid–CoA:amino acid *N*-acyltransferase. Several patients with bile acid–CoA ligase deficiency have been reported. The patients present with conjugated hyperbilirubinemia, growth failure, or fat-soluble vitamin deficiency, and are identified with mutation of the bile acid–CoA ligase gene. Administration of conjugates of the primary bile acid, glycocholic acid may be beneficial and can correct the fat-soluble vitamin malabsorption and improve growth.

DISORDERS OF EMBRYOGENESIS

Alagille syndrome (arteriohepatic dysplasia) is the most common syndrome with intrahepatic bile duct paucity. Bile duct "paucity" (often erroneously called *intrahepatic biliary atresia*) designates an absence or marked reduction in the number of interlobular bile ducts in the portal triads, with normal-size branches of portal vein and hepatic arteriole. Biopsy in early life often reveals an inflammatory process involving the bile ducts; subsequent biopsy specimens then show subsidence of the inflammation, with residual reduction in the number and diameter of bile ducts, analogous to the "disappearing bile duct syndrome" noted in adults with immune-mediated disorders. Serial assessment of hepatic histology often suggests progressive destruction of bile ducts.

Clinical manifestations of Alagille syndrome are expressed in various degrees and can be nonspecific; they include unusual facial characteristics (broad forehead; deep-set, widely spaced eyes; long, straight nose; and an underdeveloped mandible). There may also be

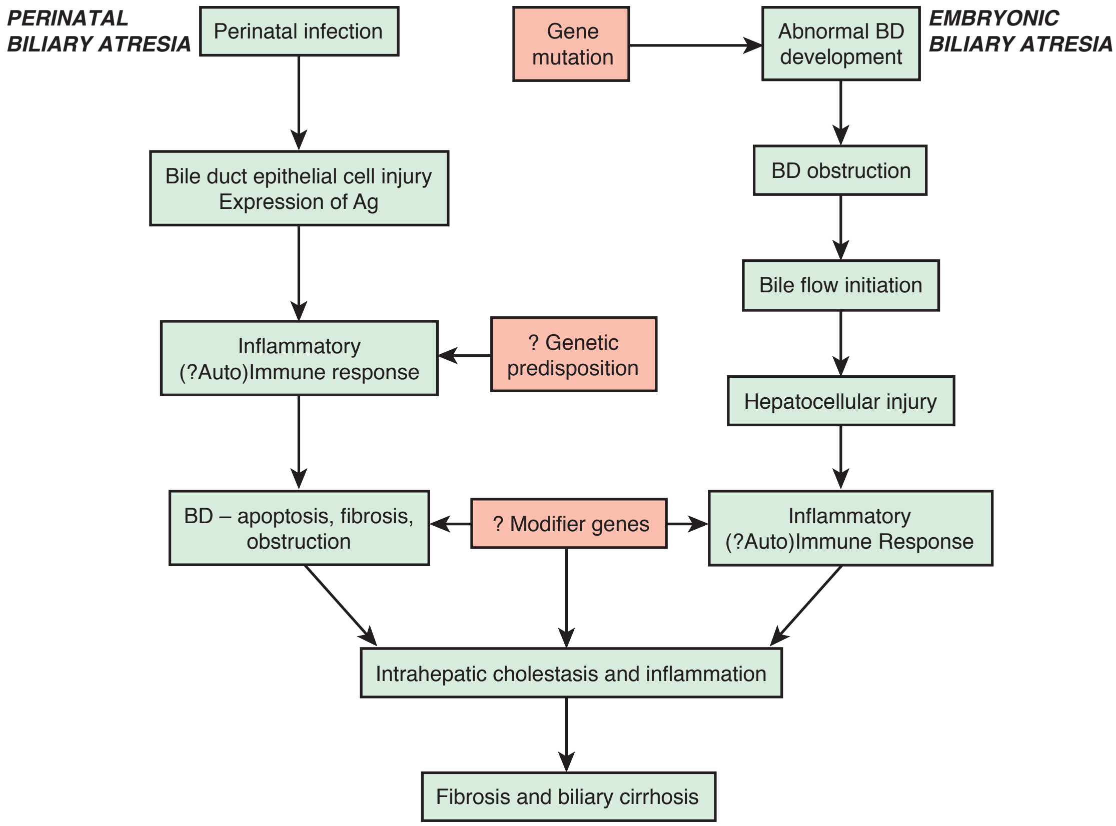

Figure 356-2 Proposed pathways for pathogenesis of 2 forms of biliary atresia (BA). *Perinatal* BA can develop when a perinatal insult, such as a cholangiotropic viral infection, triggers bile duct (BD) epithelial cell injury and exposure of self-antigens or neoantigens that elicit a subsequent immune response. The resulting inflammation induces apoptosis and necrosis of extrahepatic BD epithelium, resulting in fibro-obliteration of the lumen and obstruction of the BD. Intrahepatic bile ducts can also be targets in the ongoing TH1 immune (autoimmune?) attack and the cholestatic injury, resulting in progressive portal fibrosis and culminating in biliary cirrhosis. *Embryonic* BA may be the result of mutations in genes controlling normal bile duct formation or differentiation, which secondarily induces an inflammatory/immune response within the common bile duct and liver after the initiation of bile flow at approximately 11-13 wk of gestation. Secondary hepatocyte and intrahepatic bile duct injury ensue either as a result of cholestatic injury or as targets for the immune (autoimmune?) response that develops. The end result is intrahepatic cholestasis and portal tract fibrosis, culminating in biliary cirrhosis. Other major factors may be the role played by genetic predisposition to autoimmunity and modifier genes that determine the extent and type of cellular and immune response and the generation of fibrosis. *(From Mack CL, Sokol RJ: Unraveling the pathogenesis and etiology of biliary atresia,* Pediatr Res *57:87R–94R, 2005.)*

ocular abnormalities (posterior embryotoxon, microcornea, optic disk drusen, shallow anterior chamber), cardiovascular abnormalities (usually peripheral pulmonic stenosis, sometimes tetralogy of Fallot, pulmonary atresia, ventricular septal defect, atrial septal defect, aortic coarctation), vertebral defects (butterfly vertebrae, fused vertebrae, spina bifida occulta, rib anomalies), and tubulointerstitial nephropathy. Other findings such as short stature, pancreatic insufficiency, and defective spermatogenesis can reflect or produce nutritional deficiency. The prognosis for prolonged survival is good, but patients are likely to have pruritus, xanthomas with markedly elevated serum cholesterol levels, and neurologic complications of vitamin E deficiency if untreated. Mutations in human Jagged1 gene *(JAG1),* which encodes a ligand for the notch receptor, are linked to Alagille syndrome.

BILIARY ATRESIA

The term *biliary atresia* is imprecise because the anatomy of abnormal bile ducts in affected patients varies markedly. A more appropriate terminology would reflect the pathophysiology, namely noncystic obliterative cholangiopathy. The term *obliterative cholangiopathy* may be divided into 2 major types: cystic and noncystic. The cystic disorder will incorporate the different types of choledochal cysts, while the noncystic form will encompass the 2 types of biliary atresia (fetal and perinatal) in addition to neonatal sclerosing cholangitis.

Patients can have distal segmental bile duct obliteration with patent extrahepatic ducts up to the porta hepatis. This is a surgically correctable lesion, but it is uncommon. The most common form of biliary atresia, accounting for approximately 85% of the cases, is obliteration of the entire extrahepatic biliary tree at or above the porta hepatis. This presents a much more difficult problem in surgical management. Most patients with biliary atresia (85-90%) are normal at birth and have a postnatal progressive obliteration of bile ducts; the embryonic or fetal-onset form manifests at birth and is associated with other congenital anomalies (situs inversus, polysplenia, intestinal malrotation, complex congenital heart disease) within the polysplenia spectrum (biliary atresia splenic malformation) (Fig. 356-2; see Chapter 431.11). The postnatal onset may be an immune- or infection-mediated process.

Biliary atresia has been detected in 1 in 10,000-15,000 live births. Biliary atresia is more common in East Asian countries; patients may be born term or preterm. Screening for biliary atresia in infants after birth is not universal, but in high-risk locations, stool color cards that help detect acholic stools have been used with some success. In addition, any infant with new onset or persistent jaundice beyond 8 wk of life should be screened with a total and direct reacting bilirubin level to detect cholestasis.

Differentiation of Idiopathic Neonatal Hepatitis from Biliary Atresia

It may be difficult to clearly differentiate infants with biliary atresia, who require surgical correction, from those with intrahepatic disease

(neonatal hepatitis) and patent bile ducts. No single biochemical test or imaging procedure is entirely satisfactory. Diagnostic schemas incorporate clinical, historical, biochemical, and radiologic features.

Idiopathic neonatal hepatitis has a familial incidence of approximately 20%, whereas biliary atresia is unlikely to recur within the same family. A few infants with fetal onset of biliary atresia have an increased incidence of other abnormalities, such as the polysplenia syndrome with abdominal heterotaxia, malrotation, levocardia, and intraabdominal vascular anomalies. Neonatal hepatitis appears to be more common in infants who are premature or small for gestational age. Persistently acholic stools suggest biliary obstruction (biliary atresia), but patients with severe idiopathic neonatal hepatitis can have a transient severe impairment of bile excretion. Consistently pigmented stools rule against biliary atresia. The finding of bile-stained fluid on duodenal intubation also excludes biliary atresia. Palpation of the liver might find an abnormal size or consistency in patients with biliary atresia; this is less common with idiopathic neonatal hepatitis.

Abdominal ultrasound is a helpful diagnostic tool in evaluating neonatal cholestasis because it identifies choledocholithiasis, perforation of the bile duct, or other structural abnormalities of the biliary tree such as a choledochal cyst. In patients with biliary atresia, ultrasound can detect associated anomalies such as abdominal polysplenia and vascular malformations. The gallbladder either is not visualized or is a microgallbladder in patients with biliary atresia. Children with intrahepatic cholestasis caused by idiopathic neonatal hepatitis, cystic fibrosis, or total parenteral nutrition can have similar ultrasonographic findings. Ultrasonographic triangular cord sign, which represents a cone-shaped fibrotic mass cranial to the bifurcation of the portal vein, may be seen in patients with biliary atresia (Figs. 356-3 and 356-4). The echogenic density, which represents the fibrous remnants at the porta hepatis of biliary atresia cases at surgery, may be a helpful diagnostic tool in evaluating patients with neonatal cholestasis.

Hepatobiliary scintigraphy with technetium-labeled iminodiacetic acid derivatives is a sensitive but not specific test for biliary atresia. It fails to identify other structural abnormalities of the biliary tree or vascular anomalies. The lack of the specificity of the test and the need to wait for 5 days makes this procedure less practical and of limited usefulness in the evaluation of children with suspected biliary atresia.

Percutaneous liver biopsy is the most valuable procedure in the evaluation of neonatal hepatobiliary diseases and provides the most reliable discriminatory evidence. Biliary atresia is characterized by bile ductular proliferation, the presence of bile plugs, and portal or perilobular edema and fibrosis, with the basic hepatic lobular architecture intact. In neonatal hepatitis, there is severe, diffuse hepatocellular disease, with distortion of lobular architecture, marked infiltration with inflammatory cells, and focal hepatocellular necrosis; the bile ductules show little alteration. Giant cell transformation is found in infants with either condition and has no diagnostic specificity.

The histologic changes seen in patients with idiopathic neonatal hepatitis can occur in other diseases, including α_1-antitrypsin deficiency, galactosemia, and various forms of intrahepatic cholestasis. Although paucity of intrahepatic bile ductules may be detected on liver biopsy even in the 1st few wk of life, later biopsies in such patients reveal a more characteristic pattern.

Management of Patients with Suspected Biliary Atresia

All patients with suspected biliary atresia should undergo exploratory laparotomy and direct cholangiography to determine the presence and site of obstruction. Direct drainage can be accomplished in the few patients with a correctable lesion. When no correctable lesion is found, an examination of frozen sections obtained from the transected porta hepatis can detect the presence of biliary epithelium and determine the size and patency of the residual bile ducts. In some cases, the cholangiogram indicates that the biliary tree is patent but of diminished caliber, suggesting that the cholestasis is not due to biliary tract obliteration but to bile duct paucity or markedly diminished flow in the

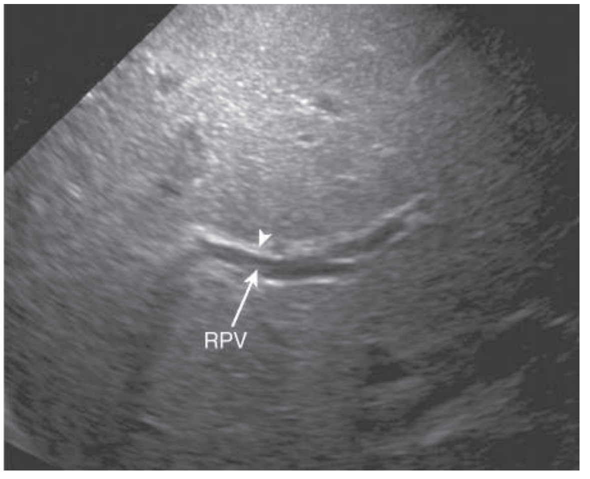

Figure 356-4 **Biliary atresia in an 8 wk old male with elevated direct bilirubin.** Transverse sonogram shows the triangular cord sign seen as a linear cord of echogenicity *(arrowhead)* along the right portal vein *(RPV)*. *(From Lowe LH: Imaging hepatobiliary disease in children,* Semin Roentgenol *43:39–49, 2008, Fig. 1B.)*

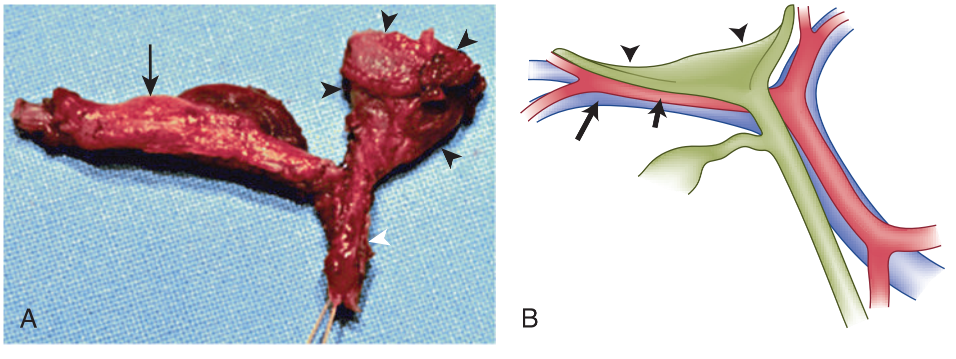

Figure 356-3 **Surgical findings of biliary atresia. A,** Photograph of surgical specimen of obliterated extrahepatic bile ducts shows the fibrous ductal remnant *(black arrowheads)* in the porta hepatis, atretic gallbladder *(arrow)*, and fibrous common bile duct *(white arrowhead)*. The fibrous ductal remnant is a triangular cone-shaped mass. **B,** Schematic represents the anatomic relationship between the fibrous ductal remnant and blood vessels around the porta hepatis. The triangular, cone-shaped, fibrous ductal remnant *(black arrowheads, green)* is positioned anterior and slightly superior to the portal vein *(long arrow, blue)* and the hepatic artery *(short arrow, red)*. *(**A** from Park WH, Choi SO, Lee HJ, et al: A new diagnostic approach to biliary atresia with emphasis on the ultrasonographic triangular cord sign: comparison of ultrasonography, hepatobiliary scintigraphy, and liver needle biopsy in the evaluation of infantile cholestasis,* J Pediatr Surg *32:1555–1559, 1997.)*

presence of intrahepatic disease. In these cases, transection of or further dissection into the porta hepatis should be avoided.

For patients in whom no correctable lesion is found, the **hepatoportoenterostomy (Kasai) procedure** should be performed. The rationale for this operation is that minute bile duct remnants, representing residual channels, may be present in the fibrous tissue of the porta hepatis; such channels may be in direct continuity with the intrahepatic ductule system. In such cases, transection of the porta hepatis with anastomosis of bowel to the proximal surface of the transection might allow bile drainage. If flow is not rapidly established in the 1st mo of life, progressive obliteration and cirrhosis ensue. If microscopic channels of patency > 150 μm in diameter are found, postoperative establishment of bile flow is likely. The success rate for establishing good bile flow after the Kasai operation is much higher (90%) if performed before 8 wk of life. Therefore, early referral and prompt evaluation of infants with suspected biliary atresia is important.

Some patients with biliary atresia, even of the "noncorrectable" type, derive long-term benefits from interventions such as the Kasai procedure. In most, a degree of hepatic dysfunction persists. Patients with biliary atresia usually have persistent inflammation of the intrahepatic biliary tree, which suggests that biliary atresia reflects a dynamic process involving the entire hepatobiliary system. This might account for the ultimate development of complications such as portal hypertension. The short-term benefit of hepatoportoenterostomy is decompression and drainage sufficient to forestall the onset of cirrhosis and sustain growth until a successful liver transplantation can be done.

MANAGEMENT OF CHRONIC CHOLESTASIS

With any form of neonatal cholestasis, whether the primary disease is idiopathic neonatal hepatitis, intrahepatic cholestasis, or biliary atresia, affected patients are at increased risk for progression and complications of chronic cholestasis. These reflect various degrees of residual hepatic functional capacity and are due directly or indirectly to diminished bile flow. Any substance normally excreted into bile is retained in the liver, with subsequent accumulation in tissue and in serum. Involved substances include bile acids, bilirubin, cholesterol, and trace elements. Decreased delivery of bile acids to the proximal intestine leads to inadequate digestion and absorption of dietary long-chain triglycerides and fat-soluble vitamins. Impairment of hepatic metabolic function can alter hormonal balance and utilization of nutrients. Progressive liver damage can lead to biliary cirrhosis, portal hypertension, and liver failure.

Treatment of such patients is empirical, and is guided by careful monitoring (Table 356-5). No therapy is known to be effective in halting the progression of cholestasis or in preventing further hepatocellular damage and cirrhosis.

Growth failure is a major concern and is related in part to malabsorption and malnutrition resulting from ineffective digestion and absorption of dietary fat. Use of a medium-chain triglyceride-containing formula can improve caloric balance.

With chronic cholestasis and prolonged survival, children with hepatobiliary disease can experience deficiencies of the fat-soluble vitamins (A, D, E, K). Inadequate absorption of fat and fat-soluble vitamins may be exacerbated by administration of the bile acid binder cholestyramine. Metabolic bone disease is common.

Serum vitamin A concentration can usually be maintained at normal levels in patients who have chronic cholestasis and who receive oral supplementation of vitamin A esters. It is essential to monitor the vitamin A status in such patients.

A **degenerative neuromuscular syndrome** was found in patients with chronic cholestasis, caused by fat soluble vitamin malabsorption and vitamin E deficiency; affected children experience progressive areflexia, cerebellar ataxia, ophthalmoplegia, and decreased vibratory sensation. Specific morphologic lesions were found in the central nervous system, peripheral nerves, and muscles. These lesions are preventable and are not commonly seen today; they were potentially reversible in children younger than 3-4 yr of age. Affected children have low serum vitamin E concentrations, increased hydrogen peroxide hemolysis, and low ratios of serum vitamin E to total serum lipids (<0.6 mg/g for children younger than 12 yr and <0.8 mg/g for older patients). Vitamin E deficiency may be prevented by oral administration of large doses (up to 1,000 IU/day); patients unable to absorb sufficient quantities may require administration of D-α-tocopheryl polyethylene glycol 1,000 succinate orally. Serum levels may be monitored as a guide to efficacy.

Pruritus is a particularly troublesome complication of chronic cholestasis, often with the appearance of xanthomas. Both features seem to be related to the accumulation of cholesterol and bile acids in serum and in tissues. Elimination of these retained compounds is difficult when bile ducts are obstructed, but if there is any degree of bile duct patency, administration of ursodeoxycholic acid can increase bile flow or interrupt the enterohepatic circulation of bile acids and thus decrease the xanthomas and ameliorate the pruritus (see Table 356-5). Ursodeoxycholic acid therapy can also lower serum cholesterol levels. The recommended initial dose is 15 mg/kg/24 hr.

Table 356-5 Suggested Medical Management of Persistent Cholestasis

CLINICAL IMPAIRMENT	MANAGEMENT
Malnutrition resulting from malabsorption of dietary long-chain triglycerides	Replace with dietary formula or supplements containing medium-chain triglycerides
Fat-soluble vitamin malabsorption:	
Vitamin A deficiency (night blindness, thick skin)	Replace with 10,000-15,000 IU/day as Aquasol A
Vitamin E deficiency (neuromuscular degeneration)	Replace with 50-400 IU/day as oral α-tocopherol or TPGS
Vitamin D deficiency (metabolic bone disease)	Replace with 5,000-8,000 IU/day of D_2 or 3-5 μg/kg/day of 25-hydroxycholecalciferol
Vitamin K deficiency (hypoprothrombinemia)	Replace with 2.5-5.0 mg every other day as water-soluble derivative of menadione
Micronutrient deficiency	Calcium, phosphate, or zinc supplementation
Deficiency of water-soluble vitamins	Supplement with twice the recommended daily allowance
Retention of biliary constituents such as cholesterol (itch or xanthomas)	Administer choleretic bile acids (ursodeoxycholic acid, 15-30 mg/kg/day)
Progressive liver disease; portal hypertension (variceal bleeding, ascites, hypersplenism)	Interim management (control bleeding; salt restriction; spironolactone)
End-stage liver disease (liver failure)	Transplantation

TPGS, D-tocopherol polyethylene glycol 1,000 succinate.

Partial external biliary diversion is efficacious in managing pruritus refractory to medical therapy and provides a favorable outcome in a select group of patients with chronic cholestasis who have not yet developed cirrhosis. The surgical technique involves resecting a segment of intestine to be used as a biliary conduit. One end of the conduit is attached to the gallbladder and the other end is brought out to the skin, forming a stoma. The main drawback of the procedure is the need to use an ostomy bag.

Progressive fibrosis and cirrhosis lead to the development of portal hypertension and consequently to ascites and variceal hemorrhage. The presence of ascites is a risk factor for the development of spontaneous bacterial peritonitis. The 1st step in the management of patients with ascites is to rule out spontaneous bacterial peritonitis and restrict sodium intake to 0.5 g (~1-2 mEq/kg/24 hr). There is no need for fluid restriction in patients with adequate renal output. Should this be ineffective, diuretics may be helpful. The diuretic of choice is spironolactone (3-5 mg/kg/24 hr in 4 doses). If spironolactone alone does not control ascites, the addition of another diuretic such as thiazide or furosemide may be beneficial. Patients with ascites but without peripheral edema are at risk for reduced plasma volume and decreased urine output during diuretic therapy. Tense ascites alters renal blood flow and systemic hemodynamics. Paracentesis and intravenous albumin infusion can improve hemodynamics, renal perfusion, and symptoms. Follow-up includes dietary counseling and monitoring of serum and urinary electrolyte concentrations.

In patients with portal hypertension, variceal hemorrhage and the development of hypersplenism are common. It is important to ascertain the cause of bleeding because episodes of gastrointestinal hemorrhage in patients who have chronic liver disease may be from gastritis or peptic ulcer disease. Because the management of these various complications differs, differentiation, perhaps via endoscopy, is necessary before treatment is initiated. If the patient is volume depleted, blood transfusion should be carefully administered, avoiding overtransfusion, which can precipitate further bleeding. Balloon tamponade is not recommended in children because it can be associated with significant complications. Sclerotherapy or endoscopic variceal ligation may be useful palliative measures in the management of bleeding varices and may be superior to surgical alternatives.

For patients with advanced liver disease, hepatic transplantation has a success rate >85%. If the operation is technically feasible, it will prolong life and might correct the metabolic error in diseases such as α1-antitrypsin deficiency, tyrosinemia, and Wilson disease. Success depends on adequate intraoperative, preoperative, and postoperative care, and on cautious use of immunosuppressive agents. Scarcity of donors of small livers severely limits the application of liver transplantation for infants and children. The use of reduced-size transplants and living donors increases the ability to treat small children successfully.

PROGNOSIS

For patients with idiopathic neonatal hepatitis, the variable prognosis might reflect the heterogeneity of the disease. In sporadic cases, 60-70% recover with no evidence of hepatic structural or functional impairment. Approximately 5-10% have persistent fibrosis or inflammation, and a smaller percentage have more severe liver disease, such as cirrhosis. Infants usually die early in the course of the illness, owing to hemorrhage or sepsis. Of infants with idiopathic neonatal hepatitis of the familial variety, only 20-30% recover; 10-15% acquire chronic liver disease with cirrhosis. Liver transplantation may be required.

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356.2 Cholestasis in the Older Child

H. Hesham Abdel-Kader Hassan and William F. Balistreri

Cholestasis with onset after the neonatal period is most often caused by acute viral hepatitis or exposure to hepatotoxic drugs. However, many of the conditions causing neonatal cholestasis can also cause chronic cholestasis in older patients. Consequently, older children and adolescents with conjugated hyperbilirubinemia should be evaluated for acute and chronic viral hepatitis, α_1-antitrypsin deficiency, Wilson disease, liver disease associated with inflammatory bowel disease, autoimmune hepatitis, drug-induced liver injury, and the syndromes of intrahepatic cholestasis. Other causes include obstruction caused by cholelithiasis, abdominal tumors, enlarged lymph nodes, or hepatic inflammation resulting from drug ingestion. Management of cholestasis in the older child is similar to that proposed for neonatal cholestasis (see Table 356-5).

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Chapter 357

Metabolic Diseases of the Liver

Alexandra N. Menchise and William F. Balistreri

Metabolic liver diseases in children, although individually rare, altogether represent a significant cause of morbidity and mortality. The liver has a central role in synthetic, degradative, and regulatory pathways involving carbohydrate, protein, lipid, trace element, and vitamin metabolism. Inborn errors of metabolism result in metabolic abnormalities, specific enzyme deficiencies or defects, and disorders of protein transport that can have primary or secondary effects on the liver (Table 357-1). Liver disease can arise when absence of an enzyme produces a block in a metabolic pathway, when unmetabolized substrate accumulates proximal to a block, when deficiency of an essential substance produced distal to an aberrant chemical reaction develops, or when synthesis of an abnormal metabolite occurs. The spectrum of pathologic changes includes **hepatocyte injury,** with subsequent failure of other metabolic functions, often eventuating in cirrhosis, liver tumors, or both; **storage** of lipid, glycogen, or other products manifested as hepatomegaly, often with complications specific to deranged metabolism (hypoglycemia with glycogen storage disease); and absence of structural change despite profound **metabolic effects,** as with urea cycle defects. Clinical manifestations of metabolic diseases of the liver mimic infections, intoxications, and hematologic and immunologic diseases (Table 357-2). Many metabolic diseases are detected in expanded newborn metabolic screening programs (see Chapter 84). Clues are provided by family history of a similar illness or by the observation that the onset of symptoms is closely associated with a change in dietary habits; in patients with hereditary fructose intolerance, symptoms follow ingestion of fructose (sucrose). Clinical and laboratory evidence often guides the evaluation. Liver biopsy offers morphologic study and permits enzyme assays, as well as quantitative and qualitative assays of various other constituents (e.g., hepatic copper content in Wilson disease). Genetic/molecular diagnostic approaches are also available. Such studies require cooperation of experienced laboratories and careful attention to collection and handling of specimens. Treatment depends on the specific type of defect and although relatively uncommon, altogether metabolic diseases of the liver account for up to 10% of the indications for liver transplantation in children, a number that may be underestimated given the acute nature of some of these conditions, precluding complete diagnostic investigation prior to transplantation.

Table 357-1	Inborn Errors of Metabolism That Affect the Liver

DISORDERS OF CARBOHYDRATE METABOLISM
Disorders of galactose metabolism
  Galactosemia (galactose-1-phosphate uridyltransferase deficiency)
Disorders of fructose metabolism
  Hereditary fructose intolerance (aldolase deficiency)
  Fructose-1,6 diphosphatase deficiency
Glycogen storage diseases
  Type I
  Von Gierke Ia (glucose-6-phosphatase deficiency)
  Type Ib (glucose-6-phosphatase transport defect)
  Type III Cori/Forbes (glycogen debrancher deficiency)
  Type IV Andersen (glycogen branching enzyme deficiency)
  Type VI Hers (liver phosphorylase deficiency)
Congenital disorders of glycosylation (multiple subtypes)

DISORDERS OF AMINO ACID AND PROTEIN METABOLISM
Disorders of tyrosine metabolism
  Hereditary tyrosinemia type I (fumarylacetoacetate deficiency)
  Tyrosinemia, type II (tyrosine aminotransferase deficiency)
Inherited urea cycle enzyme defects
  CPS deficiency (carbamoyl phosphate synthetase I deficiency)
  OTC deficiency (ornithine transcarbamoylase deficiency)
  Citrullinemia type I (argininosuccinate synthetase deficiency)
  Argininosuccinic aciduria (argininosuccinate deficiency)Argininemia (arginase deficiency)
  N-AGS deficiency (*N*-acetylglutamate synthetase deficiency)
Maple serum urine disease (multiple possible defects*)

DISORDERS OF LIPID METABOLISM
Wolman disease (lysosomal acid lipase deficiency)
Cholesteryl ester storage disease (lysosomal acid lipase deficiency)
Homozygous familial hypercholesterolemia (low-density lipoprotein receptor deficiency)
Gaucher disease type I (β-glucocerebrosidase deficiency)
Niemann-Pick type C (NPC 1 and 2 mutations)

DISORDERS OF BILE ACID METABOLISM
Defects in bile acid synthesis
Zellweger syndrome—cerebrohepatorenal (multiple mutations in peroxisome biogenesis genes)

DISORDERS OF METAL METABOLISM
Wilson disease (ATP7B mutations)
Hepatic copper overload
Indian childhood cirrhosis (ICC)
Neonatal iron storage disease

DISORDERS OF BILIRUBIN METABOLISM
Crigler-Najjar (bilirubin-uridine diphosphoglucuronate glucuronosyltransferase mutations)
  Type I
  Type II
Gilbert disease (bilirubin-uridine diphosphoglucuronate glucuronosyltransferase polymorphism)
Dubin-Johnson syndrome (multiple drug-resistant protein 2 mutation)
Rotor syndrome

MISCELLANEOUS
α_1-Antitrypsin deficiency
Citrullinemia type II (citrin deficiency)
Cystic fibrosis (cystic fibrosis transmembrane conductance regulator mutations)
Erythropoietic protoporphyria (ferrochelatase deficiency)
Polycystic kidney disease

*Maple syrup urine disease can be caused by mutations in branched-chain α-keto dehydrogenase, keto acid decarboxylase, lipoamide dehydrogenase, or dihydrolipoamide dehydrogenase.

Table 357-2	Clinical Manifestations That Suggest the Possibility of Metabolic Disease

Recurrent vomiting, failure to thrive, short stature
Dysmorphic features
Jaundice, hepatomegaly (±splenomegaly), fulminant hepatic failure, edema/anasarca
Hypoglycemia, organic acidemia, lactic acidemia, hyperammonemia, bleeding (coagulopathy)
Developmental delay/psychomotor retardation, hypotonia, progressive neuromuscular deterioration, seizures, myopathy, neuropathy
Cardiac dysfunction/failure
Unusual odors
Rickets
Cataracts

357.1 Inherited Deficient Conjugation of Bilirubin (Familial Nonhemolytic Unconjugated Hyperbilirubinemia)

Alexandra N. Menchise and William F. Balistreri

Bilirubin is the metabolic end product of heme. Before excretion into bile, it is first glucuronidated by the enzyme bilirubin-uridine diphosphoglucuronate glucuronosyltransferase (UDPGT). UDPGT activity is deficient or altered in 3 genetically and functionally distinct disorders (Crigler-Najjar [CN] syndromes type I and II and Gilbert syndrome), producing congenital nonobstructive, nonhemolytic, **unconjugated** hyperbilirubinemia. UGT1A1 is the primary UDPGT isoform needed for bilirubin glucuronidation, and complete absence of UGT1A1 activity causes CN type I. CN type II is caused by decreased UGT1A1 activity.

Gilbert syndrome is caused by a common polymorphism, a TA insertion in the promoter region of UGT1A1 that leads to decreased binding of the TATA binding protein and decreases normal gene activity but only to approximately 30%. Snapback primer genotyping can distinguish all UGT1A1 promoter genotypes. Unlike the CN syndromes, Gilbert syndrome usually occurs after puberty; it is not associated with chronic liver disease and no treatment is required. However, it is more common, affecting up to 5-10% of the white population with total serum bilirubin concentrations that fluctuate from 1-6 mg/dL. Because UGT1A1 is involved in glucuronidation of multiple substrates other than bilirubin (e.g., pharmaceutical drugs, endogenous hormones, environmental toxins, and aromatic hydrocarbons) and glucuronidation leads to inactivation of these substrates, mutations in the UGT1A1 gene are implicated in cancer risk and the predisposition to drug toxicity specifically in cancer chemotherapy and episodes of jaundice when exposed to the agents.

CRIGLER-NAJJAR SYNDROME TYPE I (GLUCURONYL TRANSFERASE DEFICIENCY)

CN type I is rare and inherited as an autosomal recessive trait and is usually secondary to mutations that cause a premature stop codon or frameshift mutation and thereby abolish UGT1A1 activity. As many as 59 mutations have been identified to date. Parents of affected children have partial defects in conjugation as determined by hepatic specific enzyme assay or by measurement of glucuronide formation; their serum unconjugated bilirubin concentrations are normal.

Clinical Manifestations

Severe unconjugated hyperbilirubinemia develops in homozygous affected infants in the 1st 3 days of life, and without treatment, serum unconjugated bilirubin concentrations of 25-35 mg/dL are reached in the 1st mo. Kernicterus, an almost universal complication of this disorder, is usually first noted in the early neonatal period; some treated infants have survived childhood without clinical sequelae. Stools are

pale yellow. Persistence of unconjugated hyperbilirubinemia at levels >20 mg/dL after the 1st wk of life in the absence of hemolysis should suggest the syndrome.

Diagnosis

The diagnosis of CN type I is based on the early age of onset and the extreme level of bilirubin elevation in the absence of hemolysis. In the bile, bilirubin concentration is <10 mg/dL compared with normal concentrations of 50-100 mg/dL; there is no bilirubin glucuronide. Definitive diagnosis is established by measuring hepatic glucuronyl transferase activity in a liver specimen obtained by a closed biopsy; open biopsy should be avoided because surgery and anesthesia can precipitate kernicterus. DNA diagnosis is also available and may be preferable. Identification of the heterozygous state in parents also strongly suggests the diagnosis. The differential diagnosis of unconjugated hyperbilirubinemia is discussed in Chapter 102.3.

Treatment

The serum unconjugated bilirubin concentration should be kept to <20 mg/dL for at least the 1st 2-4 wk of life; in low birthweight infants, the levels should be kept lower. This usually requires repeated exchange transfusions and phototherapy in the immediate neonatal period. Oral calcium phosphate supplementation renders phototherapy more effective as it forms complexes with bilirubin in the gut. Phenobarbital therapy, through CYP450 enzyme induction, should be considered to determine responsiveness and differentiation between types I and II. In patients with CN type I there is no response to phenobarbital treatment.

The risk of kernicterus persists into adult life, although the serum bilirubin levels required to produce brain injury beyond the neonatal period are considerably higher (usually >35 mg/dL). Therefore, phototherapy is generally continued through the early years of life. In older infants and children, phototherapy is used mainly during sleep so as not to interfere with normal activities. Despite the administration of increasing intensities of light for longer periods, the serum bilirubin response to phototherapy decreases with age. Additional adjuvant therapy using agents that bind photobilirubin products such as cholestyramine or agar can also be used to interfere with the enterohepatic recirculation of bilirubin.

Prompt treatment of intercurrent infections, febrile episodes, and other types of illness might help prevent the later development of kernicterus, which can occur at bilirubin levels of 45-55 mg/dL. All patients with CN type I have eventually experienced severe kernicterus by young adulthood.

Orthotopic liver transplantation cures the disease and has been successful in a small number of patients; isolated hepatocyte transplantation has been reported as bridge therapy to liver transplantation, with most, but not all patients eventually requiring orthotopic transplantation. Other therapeutic modalities have included plasmapheresis and limitation of bilirubin production. The latter option, inhibiting bilirubin generation, is possible via inhibition of heme oxygenase using metalloporphyrin therapy.

CRIGLER-NAJJAR SYNDROME TYPE II (PARTIAL GLUCURONYL TRANSFERASE DEFICIENCY)

Like CN type I, CN type II is an autosomal recessive disease; it is caused by homozygous missense mutations in UGT1A1, resulting in reduced (partial) enzymatic activity. More than 45 mutations have been identified to date. Type II disease can be distinguished from type I by the marked decline in serum bilirubin level that occurs in type II disease after treatment with phenobarbital secondary to an inducible phenobarbital response element on the UGT1A1 promoter.

Clinical Manifestations

When this disorder appears in the neonatal period, unconjugated hyperbilirubinemia usually occurs in the 1st 3 days of life; serum bilirubin concentrations can be in a range compatible with physiologic jaundice or can be at pathologic levels. The concentrations characteristically remain elevated into and after the 3rd wk of life, persisting in a range of 1.5-22 mg/dL; concentrations in the lower part of this range can create uncertainty about whether chronic hyperbilirubinemia is present. Development of kernicterus is unusual. Stool color is normal, and the infants are without clinical signs or symptoms of disease. There is no evidence of hemolysis. Liver enzymes and synthetic function tests are typically normal.

Diagnosis

Concentration of bilirubin in bile is nearly normal in patients with CN type II. Jaundiced infants and young children with type II syndrome respond readily to 5 mg/kg/24 hr of oral phenobarbital, with a decrease in serum bilirubin concentration to 2-3 mg/dL in 7-10 days.

Treatment

Long-term reduction in serum bilirubin levels can be achieved with continued administration of phenobarbital at 5 mg/kg/24 hr. The cosmetic and psychosocial benefit should be weighed against the risks of an effective dose of the drug because there is a small long-term risk of kernicterus even in the absence of hemolytic disease. Orlistat, an irreversible inhibitor of intestinal lipase, increases fecal fat excretion and decreases plasma unconjugated bilirubin concentrations (~10%) in patients with CN types I and II.

INHERITED CONJUGATED HYPERBILIRUBINEMIA

Conjugated hyperbilirubinemia can be caused by a small number of rare autosomal recessive conditions characterized by mild jaundice. The transfer of bilirubin and other organic anions from the liver cell to bile is defective. Chronic mild conjugated hyperbilirubinemia is usually detected during adolescence or early adulthood but can occur as early as the second year of life. The results of routine liver function tests are normal. Jaundice can be exacerbated by infection, pregnancy, oral contraceptives, alcohol consumption, and surgery. There is usually no morbidity and life expectancy is normal, but these disorders can initially present difficult problems in the differential diagnosis of more serious diseases.

DUBIN-JOHNSON SYNDROME

Dubin-Johnson syndrome is an autosomal recessive inherited defect with variable penetrance in hepatocyte secretion of bilirubin glucuronide. The defect in hepatic excretory function is not limited to conjugated bilirubin excretion but also involves several organic anions normally excreted from the liver cell into bile. Absent function of multiple drug-resistant protein 2 (MRP2), an adenosine triphosphate–dependent canalicular transporter, is the responsible defect. More than 10 different mutations, including compound heterozygous mutation in the CMOAT gene, have been identified and either affect localization of MRP2 with resultant increased degradation or impair MRP2 transport activity in the canalicular membrane. Bile acid excretion and serum bile acid levels are normal. Total urinary coproporphyrin excretion is normal in quantity but coproporphyrin I excretion increases to approximately 80% with a concomitant decrease in coproporphyrin III excretion. Normally, coproporphyrin III is >75% of the total. Cholangiography fails to visualize the biliary tract and x-ray of the gallbladder is also abnormal. Liver histology demonstrates normal architecture, but hepatocytes contain black pigment similar to melanin. Liver function is normal and prognosis is excellent. The most commonly reported symptoms are abdominal pain and fatigue, jaundice, dark urine, and slight enlargement of the liver. Jaundice fluctuates in intensity and is aggravated by intercurrent disease.

Rotor Syndrome

Patients with Rotor syndrome have an additional deficiency in organic anion uptake. Biallelic inactivating mutations in the linked genes *SLCO1B1* and *SLCO1B3* result in functional deficiencies of both

protein products (OATP1B1 and OATP1B, respectively) and are reported to cause Rotor syndrome. Importantly, these mutations may confer significant drug toxicity risk. Unlike Dubin-Johnson syndrome, total urinary coproporphyrin excretion is elevated, with a relative increase in the amount of the coproporphyrin I isomer. The gallbladder is normal by roentgenography, and liver cells contain no black pigment. In Dubin-Johnson and Rotor syndromes, sulfobromophthalein excretion is often abnormal.

Bibliography is available at Expert Consult.

357.2 Wilson Disease

Alexandra N. Menchise and William F. Balistreri

Wilson disease (hepatolenticular degeneration) is an autosomal recessive disorder that can be associated with degenerative changes in the brain, liver disease, and Kayser-Fleischer rings in the cornea (Fig. 357-1). The incidence is 1 in 55,000 births in the United States and 1 in 30,000 to 1 in 50,000 births worldwide. It is progressive and potentially fatal if untreated; specific effective treatment is available. Rapid diagnostic investigation of the possibility of Wilson disease in a patient presenting with any form of liver disease, particularly if older than 5 yr of age, not only facilitates early institution of management of Wilson disease and related genetic counseling but also allows appropriate treatment of non-Wilsonian liver disease once copper toxicosis is ruled out.

PATHOGENESIS

The abnormal gene for Wilson disease is localized to the long arm of chromosome 13 (13q14.3). The Wilson disease gene encodes a copper transporting P-type adenosine triphosphatase (ATPase), ATP7B, which is mainly but not exclusively expressed in hepatocytes and is critical for biliary copper excretion and for copper incorporation into ceruloplasmin. Absence or malfunction of ATP7B results in decreased biliary copper excretion and diffuse accumulation of copper in the cytosol of hepatocytes. With time, liver cells become overloaded and copper is redistributed to other tissues, including the brain and kidneys, causing toxicity, primarily as a potent inhibitor of enzymatic processes. Ionic copper inhibits pyruvate oxidase in brain and ATPase in membranes, leading to decreased adenosine triphosphate-phosphocreatine and potassium content of tissue.

More than 500 mutations in the gene have been identified from which 380 have a confirmed role in the pathogenesis of the disease, making diagnosis by DNA mutational analysis a difficult task unless a proband mutation is known. Most patients are compound heterozygotes. Mutations that completely knock out gene function are associated with an onset of disease symptoms as early as 2-3 yr of age, when Wilson disease might not typically be considered in the differential diagnosis. Milder mutations can be associated with neurologic symptoms or liver disease as late as 80 yr of age.

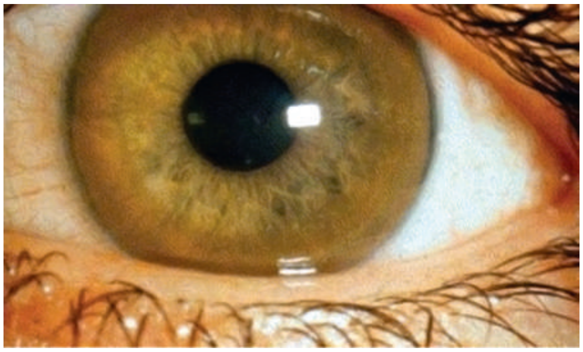

Figure 357-1 Kayser-Fleischer (K-F) ring. There is a brown discoloration at the outer margin of the cornea because of the deposition of copper in Descemet's membrane. Here it is clearly seen against the light green iris. Slit-lamp examination is required for secure detection. *(From Ala A, Walker AP, Ashkan K, et al: Wilson's disease,* Lancet *369:397–408, 2007.)*

CLINICAL MANIFESTATIONS

Forms of Wilsonian hepatic disease include asymptomatic hepatomegaly (with or without splenomegaly), subacute or chronic hepatitis, and acute hepatic failure (with or without hemolytic anemia). Cryptogenic cirrhosis, portal hypertension, ascites, edema, variceal bleeding, or other effects of hepatic dysfunction (delayed puberty, amenorrhea, coagulation defects) can be manifestations of Wilson disease.

Disease presentations are variable, with a tendency to familial patterns. The younger the patient, the more likely hepatic involvement will be the predominant manifestation. Girls are 3 times more likely than boys to present with acute hepatic failure. Clinically evident liver disease may precede neurologic manifestations by as much as 10 yr. After 20 yr of age, neurologic symptoms predominate.

Neurologic disorders can develop insidiously or precipitously, with intention tremor, dysarthria, rigid dystonia, Parkinsonism, choreiform movements, lack of motor coordination, deterioration in school performance, or behavioral changes. Kayser-Fleischer rings are absent in young patients with hepatic Wilson disease up to 50% of the time but are present in 95% of patients with neurologic symptoms and somewhat over half of those without neurologic symptoms. **Psychiatric manifestations** include depression, personality changes, anxiety, or psychosis.

Coombs-negative **hemolytic anemia** may be an initial manifestation, possibly related to the release of large amounts of copper from damaged hepatocytes; this form of Wilson disease is usually fatal without transplantation. During hemolytic episodes, urinary copper excretion and serum copper levels (not ceruloplasmin bound) are markedly elevated. Manifestations of renal Fanconi syndrome and progressive renal failure with alterations in tubular transport of amino acids, glucose, and uric acid may be present. Unusual manifestations include arthritis, pancreatitis, nephrolithiasis, infertility or recurrent miscarriages, cardiomyopathy, and endocrinopathies (hypoparathyroidism).

PATHOLOGY

All grades of hepatic injury occur in patients with Wilson disease with steatosis, hepatocellular ballooning and degeneration, glycogen granules, minimal inflammation, and enlarged Kupffer cells being most common. The earliest histologic feature is often mild steatosis and this may be misdiagnosed as nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. Additionally, the lesion may be indistinguishable from that of autoimmune hepatitis. With progressive parenchymal damage, fibrosis and cirrhosis develop. Ultrastructural changes primarily involve the mitochondria and include increased density of the matrix material, inclusions of lipid and granular material, and increased intracristal space with dilation of the tips of the cristae.

DIAGNOSIS

Wilson disease should be considered in children and teenagers with unexplained acute or chronic liver disease, neurologic symptoms of unknown cause, acute hemolysis, psychiatric illnesses, behavioral changes, Fanconi syndrome, or unexplained bone (osteoporosis, fractures) or muscle disease (myopathy, arthralgia). The clinical suspicion is confirmed by study of indices of copper metabolism.

Most patients with Wilson disease have decreased ceruloplasmin levels (<20 mg/dL). The failure of copper to be incorporated into ceruloplasmin leads to a plasma protein with a shorter half-life and, therefore, a reduced steady-state concentration of ceruloplasmin in the circulation. Caution should be used in interpreting serum ceruloplasmin levels, because they may be elevated in acute inflammation and in states of elevated estrogen such as pregnancy, estrogen supplementation, or oral contraceptive use and may be low in autoimmune hepatitis, celiac disease, familial aceruloplasminemia or in heterozygous carriers of ATP7B mutations who do not show copper overload disease.

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The serum "free" copper level may be elevated in early Wilson disease (>1.6 µmol/L), and urinary copper excretion (usually <40 µg/day) is increased to >100 µg/day and often up to 1,000 µg or more per day (typical findings in Wilson disease: urine copper excretion >1.6 µmol/24 hr, >0.64 µmol/24 hr in children). In equivocal cases, the response of urinary copper output to chelation may be of diagnostic help. During the 24 hr urine collection patients are given two 500 mg oral doses of D-penicillamine 12 hr apart; affected patients excrete >1,600 µg/24 hr.

Demonstration of Kayser-Fleischer rings, which might not be present in younger children, requires a slit-lamp examination by an ophthalmologist. After adequate treatment, Kayser-Fleischer rings resolve.

Liver biopsy is of value for determining the extent and severity of liver disease and for measuring the hepatic copper content (normally <10 µg/g dry weight) but is only required if clinical signs and noninvasive tests do not allow a final diagnosis or if another liver disorder is suspected. Hepatic copper accumulation is the hallmark of Wilson disease and measurement of hepatic parenchymal copper concentration is the method of choice for diagnosis. In Wilson disease, hepatic copper content usually exceeds 250 µg/g dry weight (>4 µmol/g dry weight is the best biochemical evidence for Wilson disease but lowering the threshold to 1.2 µmol/g dry weight improves sensitivity without significantly effecting specificity). In healthy heterozygotes, levels may be intermediate. In later stages of Wilson disease hepatic copper content can be unreliable because cirrhosis leads to variable hepatic copper distribution and sampling error.

Family members of patients with proven cases require screening for presymptomatic Wilson disease. Such screening should include determination of the serum ceruloplasmin level and urinary copper excretion. If these results are abnormal or equivocal, liver biopsy should be carried out to determine morphology and hepatic copper content. Genetic screening by either linkage analysis or direct DNA mutation analysis is possible, especially if the mutation for the proband case is known or the patient is from an area where a specific mutation is known (in central and eastern Europe, the *H1069Q* mutation is present in 50-80% of patients).

TREATMENT

A major attempt should be made to restrict dietary copper intake to <1 mg/day. Foods such as liver, shellfish, nuts, and chocolate should be avoided. If the copper content of the drinking water exceeds 0.1 mg/L, it may be necessary to demineralize the water. Once the diagnosis has been made, treatment needs to be lifelong.

The initial treatment in symptomatic patients is the administration of copper-chelating agents, which leads to rapid excretion of excess deposited copper. Chelation therapy is managed with oral administration of D-penicillamine (β,β-dimethylcysteine) in a dose of 1 g/day in 2 doses before meals for adults and 20 mg/kg/day for pediatric patients or triethylene tetramine dihydrochloride (Trien, TETA, trientine) at a dose of 0.5-2.0 g/day for adults and 20 mg/kg/day for children. In response to chelation, urinary copper excretion markedly increases, and with continued administration, urinary copper levels can become normal, with marked improvement in hepatic and neurologic function and the disappearance of Kayser-Fleischer rings.

Approximately 10-50% of patients initially treated with penicillamine for neurologic symptoms have a worsening of their condition. Toxic effects of penicillamine occur in 10-20% and consist of hypersensitivity reactions (i.e., Goodpasture syndrome, systemic lupus erythematosus, polymyositis), interaction with collagen and elastin, deficiency of other elements such as zinc, and aplastic anemia and nephrosis. Because penicillamine is an antimetabolite of vitamin B_6, additional amounts of this vitamin are necessary. For these reasons, triethylene tetramine dihydrochloride is a preferred alternative, and is considered first-line therapy for some patients. Trientine has few known side effects. Ammonium tetrathiomolybdate is another alternative chelating agent under investigation for patients with neurologic disease; initial results suggest that significantly fewer patients experience neurologic deterioration with this drug compared to penicillamine. The initial dose is 120 mg/day (20 mg between meals tid and 20 mg with meals tid). Side effects include anemia, leukopenia, thrombocytopenia, and mild elevations of transaminases. Because of its extensive decoppering effect, ammonium tetrathiomolybdate also has antiangiogenic effects.

Zinc has also been used as adjuvant therapy, maintenance therapy, or primary therapy in presymptomatic patients, owing to its unique ability to impair the gastrointestinal absorption of copper. Zinc acetate is given in adults at a dose of 25-50 mg of elemental zinc 3 times a day, and 25 mg 3 times a day in children older than 5 yr of age. Side effects are mostly limited to gastric irritation but also include reduced leukocyte chemotaxis and elevations in serum lipase and/or amylase. Current guidelines recommend that all symptomatic patients with Wilson disease receive a chelating agent (penicillamine or trientine). Zinc may have a role as a first-line therapy in patients with neurologic disease but exclusive monotherapy with zinc in symptomatic liver disease is controversial and not recommended.

Antioxidants (vitamin E and curcumin) and pharmacologic chaperones (4-phenylbutyrate and curcumin) may have a role as adjunctive treatment but more research is needed.

PROGNOSIS

Untreated patients with Wilson disease can die of hepatic, neurologic, renal, or hematologic complications. Medical therapy is rarely effective in those presenting with acute liver failure. The prognosis for patients receiving prompt and continuous penicillamine is variable and depends on the time of initiation of and the individual response to chelation. Liver transplantation should be considered for patients with fulminant liver disease, decompensated cirrhosis, or progressive neurologic disease; the last indication remains controversial. Liver transplantation is curative, with a survival rate of approximately 85-90%. In asymptomatic siblings of affected patients, early institution of chelation or zinc therapy can prevent expression of the disease.

Bibliography is available at Expert Consult.

357.3 Indian Childhood Cirrhosis

Alexandra N. Menchise and William F. Balistreri

Indian childhood cirrhosis (ICC) is a chronic liver disease of young children unique to the Indian subcontinent. ICC manifests with jaundice, pruritus, lethargy, and hepatosplenomegaly. Untreated ICC has a mortality of 40-50% within 4 wks. Histologically, it is characterized by hepatocyte necrosis, Mallory bodies, intralobular fibrosis, and inflammation.

The etiology has remained elusive; it was once believed that excess copper ingestion in the setting of a genetic susceptibility to copper toxicosis was the most likely cause. Epidemiologic data demonstrates that the copper toxicity theory is unlikely. The increased hepatic copper content, usually >700 µg/g dry weight, seen in ICC is only seen in the late stages of disease and is accompanied by even higher levels of zinc, a non-hepatotoxic metal. The copper-contaminated utensils used to feed babies and implicated in excess copper ingestion are found in only 10-15% of all cases. The current hypothesis implicates the postnatal use of local hepatotoxic therapeutic remedies, although the exact causative agent is unknown.

Over the last few decades, as the awareness of the disease has increased, the incidence of ICC has decreased and has even been virtually eliminated in some areas of India although established and non-typical cases are probably being missed because of lack of histologic confirmation and unawareness of the protean manifestations and natural history of this disease. Variants of this syndrome have been named according to the population where it has been described, such as Tyrolean childhood cirrhosis or North American ICC. It has also been reported in the Middle East, West Africa, and North and Central America.

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357.4 Neonatal Iron Storage Disease

Alexandra N. Menchise and William F. Balistreri

Neonatal iron storage disease (NISD), also known as **neonatal hemochromatosis,** is a rare form of fulminant liver disease that manifests in the 1st few days of life. It is unrelated to the familial forms of hereditary hemochromatosis that occur later in life. NISD has a high rate of recurrence in families, with approximately 80% probability that subsequent infants will be affected. NISD is postulated to be a gestational alloimmune disease and has also been classified as **congenital alloimmune hepatitis**. Alloimmunity develops in the pregnant mother of the affected infant when she is exposed to an unknown fetal hepatocyte cell surface antigen that she does not recognize as *self.* Maternal immunoglobulin G to this fetal antigen then crosses the placenta and induces hepatic injury via immune system activation. The defining feature of gestational alloimmune liver disease is complement-mediated hepatocyte injury, the evidence for which comes from detection of the C5b-9 complex by immunohistochemistry. Additional evidence of a gestational insult is given by the fact that affected infants may be born prematurely or with intrauterine growth restriction. Several infants with NISD also have renal dysgenesis.

Excess non–transferrin-bound iron in gestational alloimmune liver disease may result from fetal liver injury that causes reduced synthesis of key iron regulatory and transport proteins. The pattern of extrahepatic siderosis appears to be determined by the normal capacity of various tissues to import non–transferrin-bound iron and not export cellular iron. It is now thought that fecal liver injury is the primary event leading to the development of the neonatal hemochromatosis phenotype providing further evidence that this is not a primary iron overload disease.

NISD is a rapidly fatal, progressive illness characterized by hepatomegaly, hypoglycemia, hypoprothrombinemia, hypoalbuminemia, hyperferritinemia, and hyperbilirubinemia. The coagulopathy is refractory to therapy with vitamin K. Liver pathology demonstrates severe liver injury with acute and chronic inflammation, fibrosis, and cirrhosis. The diagnosis can be confirmed in the neonate with severe liver injury and extrahepatic siderosis (biopsy material of buccal mucosal glands is laden with iron) or MRI determination of iron storage in organs such as the pancreas.

The prognosis for affected infants is generally poor, but some patients with NISD have been successfully treated with iron-chelating agents (deferoxamine) combined with aggressive antioxidant therapy. Combining this therapy with double volume exchange transfusion followed by administration of intravenous immunoglobulin (IVIG) has also been shown to remove the injury-causing maternal immunoglobulin G. Liver transplantation should also be an early consideration. Recurrences of NISD may be modified with IVIG administered to the mother once a wk from the 18th wk of gestation until delivery. The largest experience reports 48 women with previous infants with NISD who successfully delivered 52 babies after IVIG treatment. The majority of infants had biochemical evidence of liver disease with elevated serum α-fetoprotein and ferritin. All infants survived with medical therapy or no therapy.

Bibliography is available at Expert Consult.

357.5 Miscellaneous Metabolic Diseases of the Liver

Alexandra N. Menchise and William F. Balistreri

α_1-ANTITRYPSIN DEFICIENCY

A small percentage of patients homozygous for deficiency of the major serum protease inhibitor α_1-antitrypsin manifest neonatal cholestasis or later-onset childhood cirrhosis. α_1-Antitrypsin deficiency is caused by mutation in the SERPINA1 gene and it is an autosomal recessive disorder. α_1-Antitrypsin, a protease inhibitor synthesized by the liver, protects lung alveolar tissues from destruction by neutrophil elastase (see Chapter 393). α_1-Antitrypsin is present in more than 20 different codominant alleles, only a few of which are associated with defective protease inhibitors. The most common allele of the protease inhibitor (Pi) system is M, and the normal phenotype is PiMM. The Z allele predisposes to clinical deficiency; patients with liver disease are usually PiZZ homozygotes and have serum α_1-antitrypsin levels <2 mg/mL (~10-20% of normal). The incidence of the PiZZ genotype in the white population is estimated at 1 in 2,000-4,000 live births. Compound heterozygotes PiZ-, PiSZ, PiZI are not a cause of liver disease alone but can act as modifier genes, increasing the risk of progression in other liver disease such as nonalcoholic fatty liver disease and hepatitis C. The null phenotype because of stop codons in the coding exon of the α_1-antitrypsin gene or complete deletion of α_1-antitrypsin coding exons leads to the complete absence of any protein and causes only lung disease.

Newly formed α_1-antitrypsin peptide normally enters the endoplasmic reticulum, where it undergoes enzymatic modification and folding before transport to the plasma membrane, where it is excreted as a 55 kDa glycoprotein. In affected patients with PiZZ, the rate at which the α_1-antitrypsin peptide folds is decreased, and this delay allows the formation of polymers that are retained in the endoplasmic reticulum. How the polymers cause liver damage is not completely elucidated, but research indicates that accumulation of abnormally folded protein leads to activation of stress and proinflammatory pathways in the endoplasmic reticulum and hepatocyte programmed cell death. In liver biopsies from patients, polymerized α_1-antitrypsin peptides can be seen by electron microscopy and histochemically as periodic acid–Schiff-positive diastase-resistant globules primarily in periportal hepatocytes, but also in Kupffer cells and biliary epithelial cells. The pattern of neonatal liver injury can be highly variable, and liver biopsies might demonstrate hepatocellular necrosis, inflammatory cell infiltration, bile duct proliferation, periportal fibrosis, or cirrhosis.

In affected patients, the course of liver disease is also highly variable. Prospective studies in Sweden have shown that only 10% of patients develop clinically significant liver disease by their 4th decade. Genetic traits or environmental factors must influence the development of disease in α_1-antitrypsin–deficient patients. Infants with liver disease are indistinguishable from other infants with “idiopathic” neonatal hepatitis, of whom they constitute approximately 5-10%. Jaundice, acholic stools, and hepatomegaly are present in the 1st wk of life, but the jaundice usually clears in the 2nd-4th mo. Complete resolution, persistent liver disease, or the development of cirrhosis can follow. Older children can present with asymptomatic hepatomegaly or manifestations of chronic liver disease or cirrhosis, with evidence of portal hypertension. Emphysema is not typically observed in children but an increased risk for developing asthma is reported. Cigarette smoking promotes development of lung disease so children should be counseled on avoidance or smoking cessation as part of their anticipatory guidance. Long-term patients are at risk for hepatocellular carcinoma.

Therapy is supportive; liver transplantation has been curative.

CITRIN DEFICIENCY

Neonatal intrahepatic cholestasis caused by citrin deficiency presents in the 1st few mo of life with manifestations that initially may be indistinguishable from other causes of neonatal cholestasis, especially biliary atresia. Patients may have jaundice, hepatomegaly, liver dysfunction with coagulopathy, fatty liver infiltration, hyperammonemia with or without hypoglycemia. Presymptomatic patients may be identified from the newborn metabolic screen with hypergalactosemia, hypermethionemia, and hyperphenylalanemia, not all patients are identified by newborn screening.

Neonatal intrahepatic cholestasis caused by citrin deficiency is caused by a mutation in the *SLC25A13* gene, which encodes citrin, a mitochondrial carrier protein (calcium binding aspartate-glutamate carrier) and is involved in the urea cycle, gluconeogenesis and glycolysis. The mutation is most common among East Asian populations

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Affected infants have hypergalactosemia, elevated bile acids, vitamin K–dependent coagulopathy, and elevated levels of citrulline and methionine. Treatment includes that for neonatal cholestasis and in many patients but more severely affected patients may develop progressive hepatic failure requiring liver transplantation in the 1st yr of life.

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Chapter 358

Viral Hepatitis

M. Kyle Jensen and William F. Balistreri

Viral hepatitis continues to be a major health problem in both developing and developed countries. This disorder is caused by at least 5 pathogenic hepatotropic viruses recognized to date: hepatitides A (HAV), B (HBV), C (HCV), D (HDV), and E (HEV) viruses (Table 358-1). Many other viruses (and diseases) can cause hepatitis, usually as 1 component of a multisystem disease. These include herpes simplex virus, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, HIV, rubella, adenoviruses, enteroviruses, parvovirus B19, and arboviruses (Table 358-2).

The hepatotropic viruses are a heterogeneous group of infectious agents that cause similar acute clinical illness. In most pediatric patients, the acute phase causes no or mild clinical disease. Morbidity is related to rare cases of **acute liver failure (ALF)** in susceptible patients, and to the chronic disease state and attendant complications that 3 of these viruses (hepatitides B, C, and D) can cause.

ISSUES COMMON TO ALL FORMS OF VIRAL HEPATITIS

Differential Diagnosis

Often what brings the patient with hepatitis to medical attention is clinical icterus, with yellow skin and/or mucous membranes. The liver is usually enlarged and tender to palpation and percussion. Splenomegaly and lymphadenopathy may be present. Extrahepatic symptoms (rashes, arthritis) are more readily seen in HBV and HCV infections. Clinical signs of altered sensorium or hyperreflexia should be carefully sought, because they mark the onset of encephalopathy and ALF.

The differential diagnosis varies with age of presentation.

In the **newborn period,** infection is a common cause of conjugated hyperbilirubinemia; the infectious cause is either a bacterial agent (e.g., *Escherichia coli, Listeria,* syphilis) or a nonhepatotropic virus (e.g., herpes simplex virus, enteroviruses, cytomegalovirus). Metabolic (α_1-antitrypsin deficiency, cystic fibrosis, tyrosinemia), and anatomic causes (biliary atresia, choledochal cysts) and inherited forms of intrahepatic cholestasis should always be excluded.

In later **childhood,** extrahepatic obstruction (gallstones, primary sclerosing cholangitis, pancreatic pathology), inflammatory conditions (autoimmune hepatitis, juvenile rheumatoid arthritis, Kawasaki disease), immune dysregulation (hemophagocytic lymphohistiocytosis), infiltrative disorders (malignancies), toxins and medications, metabolic disorders (Wilson disease, cystic fibrosis), and infection (Epstein-Barr virus, varicella, malaria, leptospirosis, syphilis) should be ruled out.

Pathogenesis

The acute response of the liver to hepatotropic viruses involves a direct cytopathic and an immune-mediated injury. The entire liver is involved. Necrosis is usually most marked in the centrilobular areas. An acute mixed inflammatory infiltrate predominates in the portal areas but also affects the lobules. The lobular architecture remains intact, although balloon degeneration and necrosis of single or groups of parenchymal cells commonly occurs. Fatty change is rare except with HCV infection. Bile duct proliferation but not bile duct damage is common. Diffuse Kupffer cell hyperplasia is noticeable in the sinusoids. Neonates often respond to hepatic injury by forming **giant cells.**

In **fulminant hepatitis,** parenchymal collapse occurs on the just-described background.

With recovery, the liver morphology returns to normal within 3 mo of the acute infection. If chronic hepatitis develops, the inflammatory infiltrate settles in the periportal areas and often leads to progressive scarring. Both of these hallmarks of chronic hepatitis are seen in cases of HBV and HCV.

Common Biochemical Profiles in the Acute Infectious Phase

Acute liver injury caused by the hepatotropic viruses manifests in 3 main functional liver biochemical profiles. These serve as an important guide to supportive care and monitoring in the acute phase of the infection for all viruses.

As a reflection of *cytopathic injury* to the hepatocytes, there is a rise in serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The magnitude of enzyme elevation does not correlate with the extent of hepatocellular necrosis and has little prognostic value. There is usually slow improvement over several weeks, but AST and ALT levels lag behind the serum bilirubin level, which tends to normalize first. Rapidly falling aminotransferase levels can predict a poor outcome, particularly if their decline occurs in conjunction with a rising bilirubin level and a prolonged prothrombin time; this combination of findings usually indicates that massive hepatic injury has occurred.

Cholestasis, defined by elevated serum conjugated bilirubin levels, results from abnormal bile flow at the canalicular and cellular level as a result of hepatocyte damage and inflammatory mediators. Elevation of serum alkaline phosphatase, 5′-nucleotidase, γ-glutamyl transpeptidase, and urobilinogen mark cholestasis. Improvement tends to parallel the acute hepatitis phase. Absence of cholestatic markers

Table 358-1 Features of the Hepatotropic Viruses

VIROLOGY	HAV RNA	HBV DNA	HCV RNA	HDV RNA	HEV RNA
Incubation (days)	15-19	60-180	14-160	21-42	21-63
Transmission					
• Parenteral	Rare	Yes	Yes	Yes	No
• Fecal–oral	Yes	No	No	No	Yes
• Sexual	No	Yes	Yes	Yes	No
• Perinatal	No	Yes	Rare	Yes	No
Chronic infection	No	Yes	Yes	Yes	No
Fulminant disease	Rare	Yes	Rare	Yes	Yes

Table 358-2	Causes and Differential Diagnosis of Hepatitis in Children
INFECTIOUS	
Hepatotropic viruses	
• HAV	
• HBV	
• HCV	
• HDV	
• HEV	
• Hepatitis non–A-E viruses	
Systemic infection that can include hepatitis	
• Adenovirus	
• Arbovirus	
• Coxsackievirus	
• Cytomegalovirus	
• Enterovirus	
• Epstein-Barr virus	
• "Exotic" viruses (e.g., yellow fever)	
• Herpes simplex virus	
• Human immunodeficiency virus	
• Paramyxovirus	
• Rubella	
• Varicella zoster	
Other	
NONVIRAL LIVER INFECTIONS	
Abscess	
Amebiasis	
Bacterial sepsis	
Brucellosis	
Fitz-Hugh-Curtis syndrome	
Histoplasmosis	
Leptospirosis	
Tuberculosis	
Other	
AUTOIMMUNE	
Autoimmune hepatitis	
Sclerosing cholangitis	
Other (e.g., systemic lupus erythematosus, juvenile rheumatoid arthritis)	
METABOLIC	
α_1-Antitrypsin deficiency	
Tyrosinemia	
Wilson disease	
Other	
TOXIC	
Iatrogenic or drug induced (e.g., acetaminophen)	
Environmental (e.g., pesticides)	
ANATOMIC	
Choledochal cyst	
Biliary atresia	
Other	
HEMODYNAMIC	
Shock	
Congestive heart failure	
Budd-Chiari syndrome	
Other	
NONALCOHOLIC FATTY LIVER DISEASE	
Idiopathic	
Reye syndrome	
Other	

From Wyllie R, Hyams JS, editors: Pediatric gastrointestinal and liver disease, *ed 3, Philadelphia, 2006, WB Saunders.*

does not rule out progression to chronicity in HCV or HBV infections.

Altered synthetic function is the most important marker of liver injury. Monitoring of synthetic function should be the main focus in clinical follow-up to define the severity of the disease. In the acute phase, the degree of liver synthetic dysfunction guides treatment and helps to establish intervention criteria. Abnormal liver synthetic function is a marker of liver failure and is an indication for prompt referral to a transplant center. Serial assessment is necessary because liver dysfunction does not progress linearly. Synthetic dysfunction is reflected by a combination of abnormal protein synthesis (prolonged prothrombin time, high international normalized ratio, low serum albumin levels), metabolic disturbances (hypoglycemia, lactic acidosis, hyperammonemia), poor clearance of medications dependent on liver function, and altered sensorium with increased deep tendon reflexes (hepatic encephalopathy).

HEPATITIS A

HAV infection is the most prevalent hepatotropic virus. This virus is also responsible for most forms of acute and benign hepatitis; although fulminant hepatic failure can occur, it is rare (<1% of cases in the United States) and occurs more often in adults than in children.

Etiology

HAV is an RNA virus, a member of the picornavirus family. It is heat stable and has limited host range—namely, the human and other primates.

Epidemiology

HAV infection occurs throughout the world but is most prevalent in developing countries. In the United States, 30-40% of the adult population has evidence of previous HAV infection. Hepatitis A is thought to account for approximately 50% of all clinically apparent acute viral hepatitis in the United States. As a result of aggressive implementation of a childhood vaccination strategy, the prevalence of symptomatic HAV cases in the United States has declined significantly. However, outbreaks in daycare centers (where the spread from young, nonicteric, infected children can occur easily) as well as multiple foodborne and waterborne outbreaks have justified the implementation of a universal vaccination program.

HAV is highly contagious. Transmission is almost always by person-to-person contact through the fecal–oral route. Perinatal transmission occurs rarely. No other form of transmission is recognized. HAV infection during pregnancy or at the time of delivery does not appear to result in increased complications of pregnancy or clinical disease in the newborn. In the United States, increased risk of infection is found in contacts with infected persons, childcare centers, and household contacts. Infection is also associated with contact with contaminated food or water and after travel to endemic areas. Common source foodborne and waterborne outbreaks have occurred, including several caused by contaminated shellfish, frozen berries, and raw vegetables; no known source is found in about half of the cases. The mean incubation period for HAV is approximately 3 wk. Fecal excretion of the virus starts late in the incubation period, reaches its peak just before the onset of symptoms, and resolves by 2 wk after the onset of jaundice in older subjects. The duration of viral excretion is prolonged in infants. The patient is, therefore, contagious before clinical symptoms are apparent and remains so until viral shedding ceases.

Clinical Manifestations

HAV is responsible for acute hepatitis only. Often, this is an anicteric illness, with clinical symptoms indistinguishable from other forms of viral gastroenteritis, particularly in young children.

The illness is much more likely to be symptomatic in older adolescents or adults, in patients with underlying liver disorders, and in those who are immunocompromised. It is characteristically an acute febrile illness with an abrupt onset of anorexia, nausea, malaise, vomiting, and jaundice. The typical duration of illness is 7-14 days (Fig. 358-1).

Other organ systems can be affected during acute HAV infection. Regional lymph nodes and the spleen may be enlarged. The bone marrow may be moderately hypoplastic, and aplastic anemia has been reported. Tissue in the small intestine might show changes in villous structure, and ulceration of the gastrointestinal tract can occur, especially in fatal cases. Acute pancreatitis and myocarditis have been

reported, though rarely, and nephritis, arthritis, vasculitis, and cryoglobulinemia can result from circulating immune complexes.

Diagnosis

Acute HAV infection is diagnosed by detecting antibodies to HAV, specifically, anti-HAV (immunoglobulin [Ig] M) by radioimmunoassay or, rarely, by identifying viral particles in stool. A viral polymerase chain reaction (PCR) assay is available for research use (Table 358-3). Anti-HAV is detectable when the symptoms are clinically apparent, and it remains positive for 4-6 mo after the acute infection. A neutralizing anti-HAV (IgG) is usually detected within 8 wk of symptom onset and is measured as part of a total anti-HAV in the serum. Anti-HAV (IgG) confers long-term protection. Rises in serum levels of ALT, AST, bilirubin, alkaline phosphatase, 5′-nucleotidase, and γ-glutamyl transpeptidase are almost universally found and do not help to differentiate the cause of hepatitis.

Complications

Although most patients achieve full recovery, 2 distinct complications can occur. *ALF* from HAV infection is a rare but not infrequent complication of HAV. Those at risk for this complication are adolescents and adults, but also immunocompromised patients or those with underlying liver disorders. The height of HAV viremia may be linked to the severity of hepatitis. Whereas in the United States, HAV represents < 0.5% of pediatric-age ALF, it is responsible for up to 3% mortality in the adult population with ALF. In endemic areas of the world, HAV constitutes up to 40% of all cases of pediatric ALF. HAV can also progress to a *prolonged cholestatic syndrome* that waxes and wanes over several months. Pruritus and fat malabsorption are problematic and require symptomatic support with antipruritic medications and fat-soluble vitamins. This syndrome occurs in the absence of any liver synthetic dysfunction and resolves without sequelae.

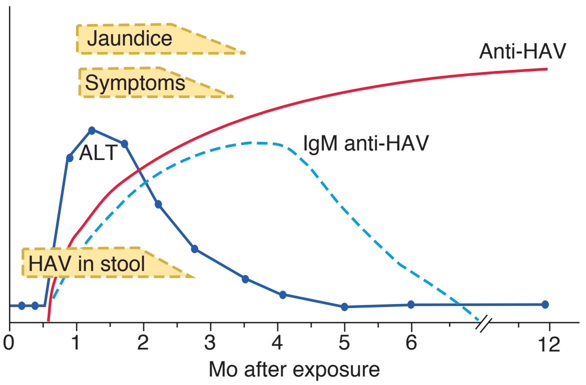

Figure 358-1 The serologic course of acute hepatitis A. *ALT*, alanine aminotransferase; *HAV*, hepatitis A virus. *(From Goldman L, Ausiello D: Cecil textbook of medicine, ed 22, Philadelphia, 2004, WB Saunders, p 913.)*

Treatment

There is no specific treatment for hepatitis A. Supportive treatment consists of intravenous hydration as needed and antipruritic agents and fat-soluble vitamins for the prolonged cholestatic form of disease. Serial monitoring for signs of ALF and, if ALF is diagnosed, a prompt referral to a transplantation center can be lifesaving.

Prevention

Patients infected with HAV are contagious for 2 wk before and approximately 7 days after the onset of jaundice and should be excluded from school, childcare, or work during this period. Careful hand-washing is necessary, particularly after changing diapers and before preparing or serving food. In hospital settings, contact and standard precautions are recommended for 1 wk after onset of symptoms.

Immunoglobulin

Indications for intramuscular administration of Ig (0.02 mL/kg) include preexposure and postexposure prophylaxis (Table 358-4).

Ig is recommended for preexposure prophylaxis for susceptible travelers to countries where HAV is endemic, and it provides effective protection for up to 3 mo. *HAV vaccine given any time before travel is preferred for preexposure prophylaxis in healthy persons, but Ig ensures an appropriate prophylaxis in children younger than 12 mo old, patients allergic to a vaccine component, or those who elect not to receive the vaccine.* If travel is planned in <2 wk, older patients, immunocompromised hosts, and those with chronic liver disease or other medical conditions should receive both Ig and the HAV vaccine.

Ig prophylaxis in postexposure situations should be used as soon as possible (not effective more than 2 wk after exposure). It is exclusively used for children younger than 12 mo old, immunocompromised hosts, those with chronic liver disease or in whom vaccine is contraindicated. Ig is preferred in patients older than 40 yr of age, with HAV

Table 358-3 Diagnostic Blood Tests: Serology and Viral PCR

HAV	HBV	HCV	HDV	HEV
ACUTE/ACTIVE INFECTION				
Anti-HAV IgM(+) Blood PCR positive*	Anti-HBc IgM(+) HBsAg(+) Anti-HBs(–) HBV DNA(+) (PCR)	Anti-HCV(+) HCV RNA(+) (PCR)	Anti-HDV IgM(+) Blood PCR positive HBsAg(+) Anti-HBs(–)	Anti-HEV IgM(+) Blood PCR positive
PAST INFECTION (RECOVERED)				
Anti-HAV IgG(+)	Anti-HBs(+) Anti-HBc IgG(+)	Anti-HCV(–) Blood PCR(–)	Anti-HDV IgG(+) Blood PCR (–)	Anti-HEV IgG(+) Blood PCR(–)
CHRONIC INFECTION				
N/A	Anti-HBc IgG(+) HBsAg(+) Anti-HBs(–) PCR (+)or (–)	Anti-HCV(+) Blood PCR (+)	Anti-HDV IgG(+) Blood PCR (–) HBsAg(+) Anti-HBs(–)	N/A
VACCINE RESPONSE				
Anti-HAV IgG(+)	Anti-HBs(+) Anti-HBc(–)	N/A	N/A	N/A

*Research tool.

HAV, hepatitis A virus; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin; PCR, polymerase chain reaction.

Table 358-4 Hepatitis A Virus Prophylaxis

PREEXPOSURE PROPHYLAXIS (TRAVELERS TO ENDEMIC REGIONS)		
AGE	**EXPECTED EXPOSURE DURATION**	**DOSE**
<1 year of age	<3 months 3-5 months Long term (>5months)	Ig 0.02 mL/kg Ig 0.06 mL/kg Ig 0.06 mL/kg at departure and every 5 mo thereafter
≥1 year of age	Healthy host Immunocompromised host, or one with chronic liver disease or chronic health problems	HAV vaccine HAV vaccine and Ig 0.02 mL/kg

POSTEXPOSURE PROPHYLAXIS*	
EXPOSURE	**RECOMMENDATIONS**
≤2 wk since exposure	<1 year-old: Ig 0.02 mL/kg Immunocompromised host, or host with chronic liver disease or chronic health problems: Ig 0.02 mL/kg and HAV vaccine >1 year and healthy host: HAV vaccine, Ig remains optional Sporadic non–household or close contact exposure: prophylaxis not indicated*
>2 wk since exposure	None

*Decision for prophylaxis in nonhousehold contacts should be tailored to individual exposure and risk. Ig, Immunoglubulin.

vaccine preferred in healthy persons 12 mo-40 yr old. *An alternative approach is to immunize previously unvaccinated patients who are 12 mo old or older with the age-appropriate vaccine dosage as soon as possible.* Ig is not routinely recommended for sporadic nonhousehold exposure (e.g., protection of hospital personnel or schoolmates). The vaccine has several advantages over Ig, including long-term protection, availability and ease of administration, with cost similar to, or less than, that of Ig.

Vaccine

The availability of 2 inactivated, highly immunogenic, and safe HAV vaccines has had a major impact on the prevention of HAV infection. Both vaccines are approved for children older than 12 mo. They are administered intramuscularly in a 2-dose schedule, with the 2nd dose given 6-12 mo after the 1st dose. Seroconversion rates in children exceed 90% after an initial dose and approach 100% after the 2nd dose; protective antibody titer persists for longer than 10 yr in the vast majority of patients. The immune response in immunocompromised persons, older patients, and those with chronic illnesses may be suboptimal; in those patients, combining the vaccine with Ig for pre- and postexposure prophylaxis is indicated. HAV vaccine may be administered simultaneously with other vaccines. A combination HAV and HBV vaccine is approved in adults older than age 18 yr. For healthy persons at least 12 mo old, vaccine is preferable to Ig for preexposure and postexposure prophylaxis (see Table 358-3).

In the United States and some other countries, universal vaccination is now recommended for all children older than 12 mo. Nevertheless, studies show <50% of U.S. adolescents have received 1 dose of the vaccine, and <30% have received the complete vaccine series. The vaccine is effective in curbing outbreaks of HAV because of rapid seroconversion and the long incubation period of the disease.

Prognosis

The prognosis for the patient with HAV is excellent, with no long-term sequelae. The only feared complication is ALF. HAV infection remains a major cause of morbidity; it has a high socioeconomic impact during epidemics and in endemic areas.

HEPATITIS B

Etiology

HBV is a member of the Hepadnaviridae family. HBV has a circular, partially double-stranded DNA genome composed of approximately 3,200 nucleotides. Four genes have been identified: the S (surface), C (core), X, and P (polymer) genes. The surface of the virus includes particles designated *hepatitis B surface antigen (HBsAg),* which is a 22 nm diameter spherical particle and a 22 nm wide tubular particle with a variable length of up to 200 nm. The inner portion of the virion contains hepatitis B core antigen (HBcAg), the nucleocapsid that encodes the viral DNA, and a nonstructural antigen called hepatitis B e antigen (HBeAg), a nonparticulate soluble antigen derived from HBcAg by proteolytic self-cleavage. HBeAg serves as a marker of active viral replication and usually correlates with HBV DNA levels. Replication of HBV occurs predominantly in the liver but also occurs in the lymphocytes, spleen, kidney, and pancreas.

Epidemiology

HBV has been detected worldwide, with an estimated 400 million persons chronically infected. The areas of highest prevalence of HBV infection are sub-Saharan Africa, China, parts of the Middle East, the Amazon basin, and the Pacific Islands. In the United States, the native population in Alaska had the highest prevalence rate before the implementation of universal vaccination programs. An estimated 1.25 million persons in the United States are chronic HBV carriers, with approximately 300,000 new cases of HBV occurring each year, the highest incidence being among adults 20-39 yr of age. One in 4 chronic HBV carriers will develop serious sequelae in their lifetime. The number of new cases in children reported each year is thought to be low but is difficult to estimate because many infections in children are asymptomatic. In the United States, since 1982 when the first vaccine for HBV was introduced, the overall incidence of HBV infection has been reduced by more than half. Since the implementation of universal vaccination programs in Taiwan and the United States, substantial progress has been made toward eliminating HBV infection in children in these countries. In fact, in Alaska, where HBV neared epidemic proportions, universal newborn vaccination with mass screening and immunization of susceptible Alaska Natives virtually eliminated symptomatic HBV and secondary hepatocellular carcinoma.

HBV is present in high concentrations in blood, serum, and serous exudates and in moderate concentrations in saliva, vaginal fluid, and semen. Efficient transmission occurs through blood exposure and sexual contact. Risk factors for HBV infection in children and adolescents include acquisition by intravenous drugs or blood products, contaminated needles used for acupuncture or tattoos, sexual contact, institutional care, and intimate contact with carriers. No risk factors are identified in approximately 40% of cases. HBV is not thought to be transmitted via indirect exposure, such as sharing toys.

In children, the most important risk factor for acquisition of HBV remains perinatal exposure to an HBsAg-positive mother. The risk of transmission is greatest if the mother is also HBeAg-positive; up to 90% of these infants become chronically infected if untreated. Intrauterine infection occurs in 2.5% of these infants. In most cases, serologic markers of infection and antigenemia appear 1-3 mo after birth, suggesting that transmission occurred at the time of delivery. Virus contained in amniotic fluid or in maternal feces or blood may be the source. Immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and the HBV immunization, given within 12 hr of delivery is very effective in preventing infection and protects > 95% of neonates born to HBsAg-positve mothers. Of the 22,000 infants born each year to HBsAg-positive mothers in the United States, >98% receive immunoprophylaxis and are thus protected. Infants who fail to receive the complete vaccination series (e.g., homeless children, international adoptees, and children born outside the United States), however, have the highest incidence of developing chronic HBV. These and all infants born to HBsAg-positive mothers should have follow-up HBsAg and anti-HBs tested to determine appropriate follow-up.

HBsAg is inconsistently recovered in human milk of infected mothers. Breastfeeding of nonimmunized infants by infected mothers does not confer a greater risk of hepatitis than does formula feeding.

The risk of developing **chronic HBV** infection, defined as being positive for HBsAg for longer than 6 mo, is inversely related to age of acquisition. In the United States, although <10% of infections occurs in children, these infections account for 20-30% of all chronic cases. This risk of chronic infection is 90% in children younger than 1 yr; the risk is 30% for those 1-5 yr and 2% for adults. Chronic infection is associated with the development of chronic liver disease and hepatocellular carcinoma. The carcinoma risk is independent of the presence of cirrhosis and was the most prevalent cancer-related death in young adults in Asia where HBV was endemic.

HBV has 8 genotypes (A-H). A is pandemic, B and C are prevalent in Asia, D is seen in Southern Europe, E in Africa, F in the United States, G in the United States and France, and H in Central America. Genetic variants have become resistant to antiviral agents. After infection, the incubation period ranges from 45-160 days, with a mean of approximately 120 days.

Pathogenesis

The acute response of the liver to HBV is the same as for all hepatotropic viruses. Persistence of histologic changes in patients with hepatitis B indicates development of chronic liver disease. HBV, unlike the other hepatotropic viruses, is a predominantly noncytopathogenic virus that causes injury mostly by immune-mediated processes. The severity of hepatocyte injury reflects the degree of the immune response, with the most complete immune response being associated with the greatest likelihood of viral clearance but also the most severe injury to hepatocytes. The 1st step in the process of **acute hepatitis** is infection of hepatocytes by HBV, resulting in expression of viral antigens on the cell surface. The most important of these viral antigens may be the nucleocapsid antigens HBcAg and HBeAg. These antigens, in combination with class I major histocompatibility proteins, make the cell a target for cytotoxic T-cell lysis.

The mechanism for development of **chronic hepatitis** is less well understood. To permit hepatocytes to continue to be infected, the core protein or major histocompatibility class I protein might not be recognized, the cytotoxic lymphocytes might not be activated, or some other, yet unknown mechanism might interfere with destruction of hepatocytes. This **tolerance** phenomenon predominates in the perinatally acquired cases, resulting in a high incidence of persistent infection in children with no or little inflammation in the liver, normal liver enzymes, and markedly elevated HBV viral load. Although end-stage liver disease rarely develops in those patients, the inherent hepatocellular carcinoma risk is very high, possibly related, in part, to uncontrolled viral replication cycles.

ALF has been seen in infants of chronic carrier mothers who have anti-HBe or are infected with a precore-mutant strain. This fact led to the postulate that HBeAg exposure in utero in infants of chronic carriers likely induces tolerance to the virus once infection occurs postnatally. In the absence of this tolerance, the liver is massively attacked by T cells and the patient presents with ALF.

Immune-mediated mechanisms are also involved in the **extrahepatic conditions** that can be associated with HBV infections. **Circulating immune complexes** containing HBsAg can result in polyarteritis nodosa, membranous or membranoproliferative glomerulonephritis, polymyalgia rheumatica, leukocytoclastic vasculitis, and Guillain-Barré syndrome.

Clinical Manifestations

Many acute cases of HBV infection in children are asymptomatic, as evidenced by the high carriage rate of serum markers in persons who have no history of acute hepatitis. The usual acute symptomatic episode is similar to that of HAV and HCV infections but may be more severe and is more likely to include involvement of skin and joints (Fig. 358-2). The first biochemical evidence of HBV infection is elevation of serum ALT levels, which begin to rise just before development of fatigue, anorexia, and malaise, which occurs approximately 6-7 wk after exposure. The illness is preceded in a few children by a serum sickness–like prodrome marked by arthralgia or skin lesions, including urticarial, purpuric, macular, or maculopapular rashes. Papular acrodermatitis, the Gianotti-Crosti syndrome, can also occur. Other extrahepatic conditions associated with HBV infections in children include polyarteritis nodosa, glomerulonephritis, and aplastic anemia. Jaundice is present in approximately 25% of acutely infected patients and usually begins approximately 8 wk after exposure and lasts approximately 4 wk.

In the usual course of resolving HBV infection, symptoms are present for 6-8 wk. The percentage of children in whom clinical evidence of hepatitis develops is higher for HBV than for HAV, and the rate of ALF is also greater. Most patients do recover, but the "chronic carrier state" complicates up to 10% of cases acquired in adulthood. The rate of development of chronic infection depends largely on the mode and age of acquisition and occurs in up to 90% of perinatal cases. Chronic hepatitis, cirrhosis, and hepatocellular carcinoma are only seen with chronic infection. Chronic HBV infection has 3 identified phases: immune tolerant, immune active, and inactive. Most children fall in the immune-tolerant phase, against which no effective therapy has been developed. Most treatments target the immune active phase of the disease, characterized by active inflammation, elevated ALT/AST levels, and progressive fibrosis. Spontaneous HBeAg seroconversion, defined as the development of anti-HBe and becoming HBeAg-negative, occurs in the immune-tolerant phase, albeit at low rates of 4-5% per year. It is more common in childhood-acquired HBV rather than in vertically transmitted infections. Seroconversion can occur over many years, during which time significant damage to

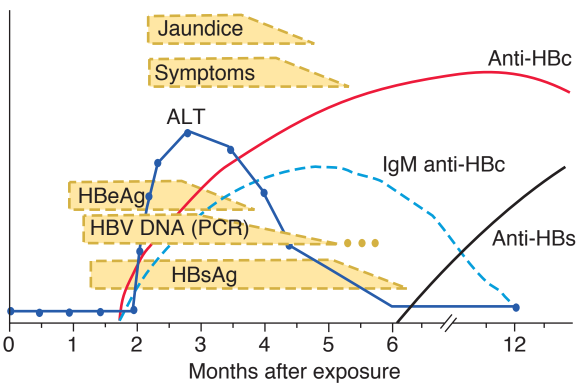

Figure 358-2 The serologic course of acute hepatitis B. *HBc*, hepatitis B core; *HBeAg*, hepatitis B e antigen; *HBs*, hepatitis B surface; *HBsAg*, hepatitis B surface antigen; *HBV*, hepatitis B virus; *PCR*, polymerase chain reaction. *(From Goldman L, Ausiello D:* Cecil textbook of medicine, *ed 22, Philadelphia, 2004, WB Saunders, p 914.)*

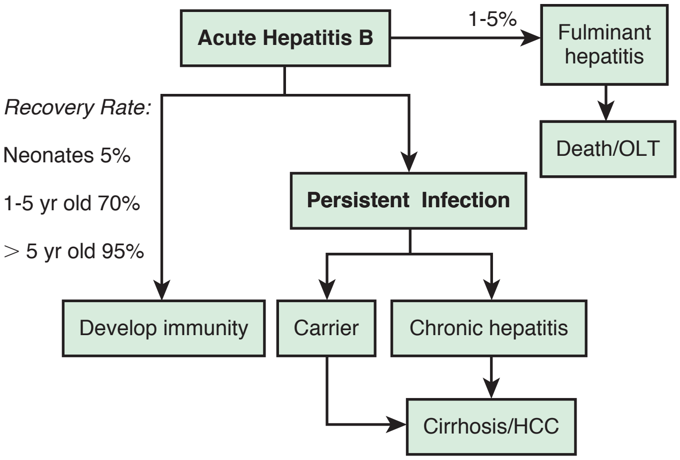

Figure 358-3 Natural history of hepatitis B virus infection. *HCC,* hepatocellular carcinoma; *OLT,* orthotopic liver transplant.

the liver may take place. There are no large studies that help accurately assess the lifetime risks and morbidities of children with chronic HBV infection, making the timing of still less-than-ideal treatments ever so hard to decide. Reactivation of chronic infection has been reported in immunosuppressed children (treated with chemotherapy, biologic immunomodulators such as infliximab, T-cell depleting agents), leading to an increased risk of ALF or to rapidly progressing fibrotic liver disease.

Diagnosis

The serologic profile of HBV infection is more complex than for HAV infection and differs depending on whether the disease is acute or chronic (Fig. 358-3). Several antigens and antibodies are used to confirm the diagnosis of acute HBV infection (see Table 358-3). Routine screening for HBV infection requires assay of multiple serologic markers (HBsAg, anti-HBc, anti-HBs). HBsAg is the first serologic marker of infection to appear and is found in almost all infected persons; its rise closely coincides with the onset of symptoms. Persistence of HBsAg beyond 6 mo defines the chronic infection state. During recovery from acute infection, because HBsAg levels fall before symptoms wane, IgM antibody to HBcAg (anti-HBc IgM) might be the only marker of acute infection. Anti-HBc IgM rises early after the infection and remains positive for many months before being replaced by anti-HBc IgG, which then persists for years. Anti-HBc is therefore a valuable serologic marker of acute HBV infection. Anti-HBs marks serologic recovery and protection. Only anti-HBs is present in persons immunized with hepatitis B vaccine, whereas both anti-HBs and anti-HBc are detected in persons with resolved infection. HBeAg is present in active acute or chronic infection and is a marker of infectivity. The development of anti-HBe, termed seroconversion, marks improvement and is a goal of therapy in chronically infected patients. HBV DNA can be detected in the serum of acutely infected patients and chronic carriers. High DNA titers are seen in patients with HBeAg, and they typically fall once anti-HBe develops.

Complications

Acute liver failure with coagulopathy, encephalopathy, and cerebral edema occurs more commonly with HBV than the other hepatotropic viruses. The risk of ALF is further increased when there is coinfection or superinfection with HDV and in an immunosuppressed host. Mortality from ALF is >30%, and liver transplantation is the only effective intervention. Supportive care aimed at sustaining patients and early referral to a liver transplantation center can be lifesaving. As mentioned, HBV infection can also result in **chronic hepatitis,** which can lead to cirrhosis, end-stage liver disease complications, and primary **hepatocellular carcinoma. Membranous glomerulonephritis** with deposition of complement and HBeAg in glomerular capillaries is a rare complication of HBV infection.

Treatment

Treatment of *acute* HBV infection is largely supportive. Close monitoring for liver failure and extrahepatic morbidities is key.

Treatment of *chronic* HBV infection is in evolution; no one drug currently achieves consistent, complete eradication of the virus. The natural history of HBV chronic infection in children is complex, and there is a lack of reliable long-term outcome data on which to base treatment recommendations. Treatment of chronic HBV infection in children should be individualized and done under the care of a pediatric gastroenterologist experienced in treating liver disease.

The goal of treatment is to reduce viral replication defined by having undetectable HBV DNA in the serum and development of anti-HBe, termed seroconversion. The development of anti-HBe transforms the disease into an inactive form, thereby decreasing infectivity, active liver injury and inflammation, fibrosis progression, and the risk of hepatocellular carcinoma.

Currently, treatment is only indicated for patients in the immune-active form of the disease, as evidenced by elevated ALT and/or AST, who have fibrosis on liver biopsy, putting the child at higher risk for cirrhosis during childhood.

Treatment Strategies

Interferon-α2b (IFN-α2b) has immunomodulatory and antiviral effects. It has been used in children, with long-term viral response rates similar to the 25% rate reported in adults. Interferon (IFN) use is limited by its subcutaneous administration, treatment duration of 24 wk, and possible side effects (flu-like symptoms, marrow suppression, depression, retinal changes, autoimmune disorders). IFN is further contraindicated in decompensated cirrhosis. One advantage of IFN, compared to other treatments, is that viral resistance does not develop with its use.

Lamivudine is an oral synthetic nucleoside analog that inhibits the viral enzyme reverse transcriptase. In children older than age 2 yr, its use for 52 wk resulted in HBeAg clearance in 34% of patients with an ALT > 2 times normal; 88% remained in remission at 1 yr. It has a good safety profile. Lamivudine has to be used for ≥6 mo after viral clearance, and the emergence of a mutant viral strain (YMDD) poses a barrier to its long-term use. Combination therapy in children using IFN and lamivudine did not seem to improve the rates of response in most series.

Adefovir (a purine analog that inhibits viral replication) is approved for use in children older than 12 yr of age, in whom a prospective 1-year study showed 23% seroconversion. No viral resistance was noted in that study but has been reported in adults.

Entecavir (a nucleoside analog that inhibits replication) is currently approved for use in children older than age 16 yr. Prospective data has shown a 21% seroconversion rate in adults with minimal resistance developing. Patients in whom resistance to lamivudine developed, have an increased risk of resistance developing to entecavir.

Tenofovir (a nucleotide analog that inhibits viral replication) is also approved for use in children older than age 16 yr. Data have shown efficacy in children older than age 12 yr. Prospective data have shown a 21% seroconversion rate with a very low rate of resistance developing. Patients with lamivudine-resistant mutations do not appear to have an increased rate of resistance. Concern exists over long-term use and bone mineral density.

Peginterferon-α_2 has the same mechanism of action as IFN, but is given once weekly. This formulation has not been approved in the United States but is recommended for the treatment of chronic HBV in other countries. Patients most likely to respond to currently available drugs have low serum HBV DNA titers, are HBeAg-positive, have active hepatic inflammation (ALT greater than twice the upper limit of normal for at least 6 mo), and recently acquired disease.

Immune tolerant patients—those with normal ALT and AST, who are HBeAg-positive with elevated viral load—are currently not considered for treatment, although the emergence of new treatment

paradigms are promising for this large, yet hard-to-treat, subgroup of patients.

Prevention

The most effective prevention strategies have resulted from the screening of pregnant mothers and the use of HBIG and hepatitis B vaccine in infants as noted earlier. In HBsAg-positive and HBeAg-positive mothers, a 10% risk of chronic HBV infection exists compared to 1% in HBeAg-negative mothers. This knowledge offers screening strategies that may affect both mother and infant through the use of antiviral medications during the 3rd trimester. Recent guidelines suggest that mothers with a HBV DNA viral load >200,000 IU/mL receive an antiviral such as telbivudine, lamivudine, or tenofovir during the 3rd trimester, especially if they had a previous child who developed chronic HBV after receiving HBIG and the hepatitis B vaccine.

Household, sexual, and needle-sharing contacts should be identified and vaccinated if they are susceptible to HBV infection. Patients should be advised about the perinatal and intimate contact risk of transmission of HBV. HBV is not spread by breastfeeding, kissing, hugging, or sharing water or utensils. Children with HBV should not be excluded from school, play, childcare, or work, unless they are prone to biting. A support group might help children to cope better with their disease. Families should not feel obligated to disclose the diagnosis as this information may lead to prejudice or mistreatment of the patient or the patient's family. All patients positive for HBsAg should be reported to the state or local health department, and chronicity is diagnosed if they remain positive past 6 mo.

Hepatitis B Immunoglobulin

HBIG is indicated only for specific postexposure circumstances and provides only temporary protection (3-6 mo; Table 358-5). It plays a pivotal role in preventing perinatal transmission when administered within 12 hr of birth.

Universal Vaccination

In 2005, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices revised its recommendations regarding HBV vaccination. These recommendations have been incorporated into the American Academy of Pediatrics Vaccine schedule. A main focus is **universal infant vaccination,** beginning at birth, to provide a safety net for preventing perinatal infection, prevent early childhood infection, facilitate implementation of universal vaccine recommendations, and prevent infection in adolescents and adults. The ultimate goal is to eliminate HBV transmission in the United States and to integrate HBV vaccination in a harmonized childhood vaccination.

Two single-antigen vaccines (Recombivax HB and Engerix-B) are approved for children and are the only preparations approved for infants younger than age 6 mo. Three combination vaccines can be used for subsequent immunization dosing and enable integration of the HBV vaccine into the regular immunization schedule. The safety profile of HBV vaccine is excellent. The most reported side effects are pain at the injection site (up to 29% of cases) and fever (up to 6% of cases). Seropositivity is >95% with all vaccines, achieved after the 2nd dose in most patients. The 3rd dose serves as a booster and may have an effect on maintaining long-term immunity. In immunosuppressed patients and infants whose birthweight is <2,000 g, a 4th dose is recommended, as is checking for seroconversion. Despite declines in the anti-HBs titer in time, most healthy vaccinated persons remain protected against HBV infection.

Current HBV vaccination recommendations are as follows (see Table 358-5):

- Infants born to HBsAg-negative mothers:
  - For all medically stable infants weighing >2,000 g at birth and born to HBsAg-*negative* mothers, the 1st dose of HBV vaccine should be administered before hospital discharge. Single-dose antigen HBV vaccine should be used for the birth dose. Subsequent doses to complete the series are given at 1-4 mo and at 6-18 mo of age. Routine postvaccination testing of immunized infants born to HBsAg-*negative* women or with anti-HBs is not recommended.
  - In rare circumstances (on a case-by-case basis), the 1st dose may be delayed (up to 2 mo) until after hospital discharge. When a decision to delay is made, however, a physician's order to withhold the birth dose, along with a copy of the original laboratory report indicating that the mother was HBsAg-*negative,* should be placed on the medical record.

Table 358-5 Indications and Dosing Schedule for Hepatitis B Vaccine and Hepatitis B Immunoglobulin

	VACCINE DOSE		
	RECOMBIVAX HB (μg)	**ENGERIX-B (μg)**	**SCHEDULE**
UNIVERSAL PROPHYLAXIS			
Infants of HBsAg(–) women	5	10	Birth, 1-2, 6-18 mo
Children and adolescents (11-19 yr old)	5	10	0, 1, and 6 mo
POSTEXPOSURE PROPHYLAXIS IN SUSCEPTIBLE INDIVIDUALS			
Contact with HBsAg(+) Source			
Infants of HBsAg(+) women	5	10	Birth* (+HBIG†), 1 and 6 mo
Intimate or Identifiable Blood Exposure			
0-19 yr old	5	10	Exposure (+HBIG†), 1 and 6 mo
>19 yr old	10	20	Exposure (+HBIG†), 1 and 6 mo
Household			
0-19 yr old	5	10	Exposure, 1 and 6 mo
>19 yr old	10	20	Exposure, 1 and 6 mo
Casual	None	None	None
Immunocompromised‡	40	40	Exposure (+HBIG†), 1 and 6 mo
Contact with Unknown HBsAg Status; Intimate or Identifiable Blood Exposure			
>19 yr old	10	20	Exposure, 1 and 6 mo
Immunocompromised‡	40	40	Exposure (+HBIG†), 1 and 6 mo

*Both HBIG and vaccine should be administered within 12 hr of the infant's birth and within 24 hr of identifiable blood exposure. HBIG can be given up to 14 days after sexual exposure.

†HBIG dose: 0.5 μL for newborns of HBsAg-positive mothers, and 0.0 6 μL/kg for all others when recommended.

‡Seroconversion status of immunocompromised patients should be checked 1-2 mo after the last dose of vaccine, and yearly thereafter. Booster doses of vaccine should be administered if the anti-HBs titer is <10 mIU/mL. Nonresponsive patients should be considered at high risk for HBV acquisition and counseled about preventive measures.

HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

- Preterm infants weighing <2,000 g at birth and born to HBsAg-*negative* mothers should have their initial dose delayed until 1 mo of age or before hospital discharge.
- To increase coverage of children and adolescents not previously vaccinated, many states have made immunization a requirement for entry into junior high school (middle school).
- Infants born to HBsAg-positive or HBsAg-unknown mothers:
  - To prevent perinatal transmission through improved maternal screening and immunoprophylaxis, infants born to HBsAg-positive women should receive vaccine at birth, 1-2 mo, and 6 mo of age (see Table 358-4). The 1st dose should be accompanied by administration of 0.5 mL of HBIG as soon after delivery as possible (within 12 hr) because the effectiveness decreases rapidly with increased time after birth.
  - If mother's HBsAg status is unknown, the vaccine should be administered within 12 hr of birth regardless of birthweight. For infants weighing <2,000 g, HBIG and the HBV vaccine should be administered within 12 hr of birth. The mother's HBsAg status should be administered as soon as possible and, if she is HBsAg-positive, HBIG should be given for infants weighing ≥2,000 g (no later than age 1 wk).

Postvaccination testing for HBsAg and anti-HBs should be done at 9-18 mo. If the result is positive for anti-HBs, the child is immune to HBV. If the result is positive for HBsAg only, the parent should be counseled and the child evaluated by a pediatric gastroenterologist. If the result is negative for both HBsAg and anti-HBs, a second complete hepatitis B vaccine series should be administered, followed by testing for anti-HBs to determine if subsequent doses are needed.

Administration of 4 doses of vaccine is permissible when combination vaccines are used after the birth dose; this does not increase vaccine response.

Postexposure Prophylaxis

Recommendations for postexposure prophylaxis for prevention of hepatitis B infection depend on the conditions under which the person is exposed to HBV (see Table 358-5). Vaccination should never be postponed if written records of the exposed person's immunization history are not available, but every effort should still be made to obtain those records.

Special Populations

Patients with cirrhosis may not respond as well to the HBV vaccine and repeating anti-HBs titers should be performed. Adult studies suggest higher dosage or shorter interval between dosages may increase the immunization effectiveness. Recent evidence has shown patients with inflammatory bowel disease frequently have not been immunized, or did not develop complete immunity to HBV, as demonstrated by inadequate anti-HBs levels. These patients may be at risk for fulminant HBV when immunosuppression is started as part of their treatment regimen, specifically with biologic agents such as infliximab.

Prognosis

In general, the outcome after acute HBV infection is favorable, despite a risk of ALF. The risk of developing chronic infection brings the risks of liver cirrhosis and hepatocellular carcinoma to the forefront. Perinatal transmission leading to chronicity is responsible for the high incidence of hepatocellular carcinoma in young adults in endemic areas. Importantly, HBV infection and its complications are effectively controlled and prevented with vaccination and multiple clinical trials are ongoing in an effort to improve and guide treatment regimens.

HEPATITIS C

Etiology

HCV is a single-stranded RNA virus, classified as a separate genus within the Flaviviridae family, with marked genetic heterogeneity. It has 6 major genotypes and numerous subtypes and quasi-species, which permit the virus to escape host immune surveillance. Genotype variation might partially explain the differences in clinical course and response to treatment. Genotype 1b is the most common genotype in the United States and is the least responsive to the currently available medications.

Epidemiology

In the United States, HCV infection is the most common cause of chronic liver disease in adults and causes 8,000-10,000 deaths per year. Approximately 4 million people in the United States and 170 million people worldwide are estimated to be infected with HCV. Approximately 85% of infected adults remain chronically infected. In children, seroprevalence of HCV is 0.2% in those younger than age 11 yr and 0.4% in children age 11 yr or older. However, even more children may be infected as only a small percentage of HCV-infected children are identified, and an even smaller number subsequently receive treatment. Appropriate identification, and screening, for infected individuals should be implemented.

Risk factors for HCV transmission in the United States included blood transfusion before 1992 as the most common route of infection, but, with current screening practices, the risk of HCV transmission is approximately 0.001% per unit transfused. Illegal drug use with exposure to blood or blood products from HCV-infected persons accounts for more than half of adult cases in the United States. Sexual transmission, especially through multiple sexual partners, is the second most common cause of infection. Other risk factors include occupational exposure, but approximately 10% of new infections have no known transmission source. In children, perinatal transmission is the most prevalent mode of transmission (see Table 358-1). Perinatal transmission occurs in up to 5% of infants born to viremic mothers. HIV coinfection and high viremia titers (HCV RNA-positive) in the mother can increase the transmission rate to 20%. The incubation period is 7-9 wk (range: 2-24 wk).

Pathogenesis

The pattern of acute hepatic injury is indistinguishable from that of other hepatotropic viruses. In chronic cases, lymphoid aggregates or follicles in portal tracts are found, either alone or as part of a general inflammatory infiltrate of the portal areas. Steatosis is also often seen in these liver specimens. HCV appears to cause injury primarily by cytopathic mechanisms, but immune-mediated injury can also occur. The cytopathic component appears to be mild, because the acute illness is typically the least severe of all hepatotropic virus infections.

Clinical Manifestations

Acute HCV infection tends to be mild and insidious in onset (Fig. 358-4; see also Table 358-1). ALF rarely occurs. HCV is the most likely

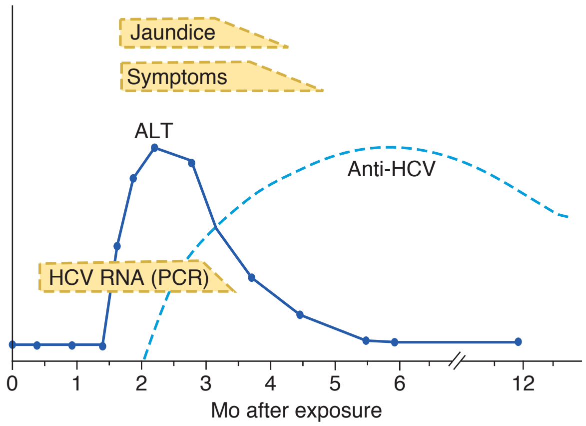

Figure 358-4 The serologic course of acute hepatitis C. *ALT*, alanine aminotransferase; *HCV*, hepatitis C virus; *PCR*, polymerase chain reaction. *(From Goldman L, Ausiello D:* Cecil textbook of medicine, *ed 22, Philadelphia, 2004, WB Saunders, p. 915.)*

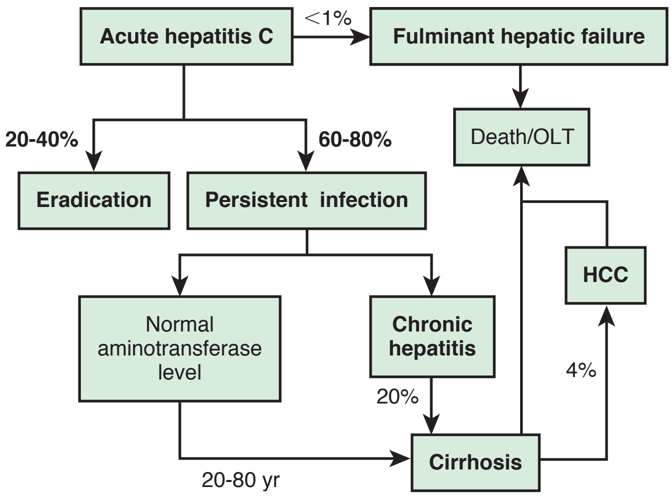

Figure 358-5 Natural history of hepatitis C virus infection. *HCC*, hepatocellular carcinoma; *OLT*, orthotopic liver transplant. *(From Hochman JA, Balistreri WF: Chronic viral hepatitis: always be current!* Pediatr Rev *24:399–410, 2003.)*

hepatotropic virus to cause chronic infection (Fig. 358-5). Of affected adults, <15% clear the virus; the rest develop chronic hepatitis. In pediatric studies, 6-19% of children achieved spontaneous sustained clearance of the virus during a 6 yr follow-up.

Chronic HCV infection is also clinically silent until a complication develops. Serum aminotransferase levels fluctuate and are sometimes normal, but histologic inflammation is universal. Progression of liver fibrosis is slow over several years, unless comorbid factors are present, which can accelerate fibrosis progression. Approximately 25% of infected patients ultimately progress to cirrhosis, liver failure, and, occasionally, primary hepatocellular carcinoma (HCC) within 20-30 yr of the acute infection. Although progression is rare within the pediatric age range, cirrhosis and HCC from HCV have been reported in children. The long-term morbidities constitute the rationale for diagnosis and treatment in children with HCV.

Chronic HCV infection can be associated with **small vessel vasculitis** and is a common cause of essential mixed cryoglobulinemia. Other extrahepatic manifestations, predominantly seen in adults, include cutaneous vasculitis, peripheral neuropathy, cerebritis, membranoproliferative glomerulonephritis, and nephrotic syndrome. Antibodies to smooth muscle, antinuclear antibodies, and low thyroid hormone levels may also be present.

Diagnosis

Clinically available assays for detection of HCV infection are based on detection of antibodies to HCV antigens or detection of viral RNA **(see** Table 358-3**)**; neither can predict the severity of liver disease.

The most widely used **serologic test** is the third-generation enzyme immunoassay to detect anti-HCV. The predictive value of this assay is greatest in high-risk populations, but the false-positive rate can be as high as 50-60% in low-risk populations. False-negative results also occur because antibodies remain negative for as long as 1-3 mo after clinical onset of illness. Anti-HCV is not a protective antibody and does not confer immunity; it is usually present simultaneously with the virus.

The most commonly used **virologic assay** for HCV is a PCR assay, which permits detection of small amounts of **HCV RNA** in serum and tissue samples within days of infection. The *qualitative* PCR detection is especially useful in patients with recent or perinatal infection, hypogammaglobulinemia, or immunosuppression and is very sensitive. The *quantitative* PCR aids in identifying patients who are likely to respond to therapy and in monitoring response to therapy.

Screening for HCV should include all patients with the following risk factors: history of illegal drug use (even if only once), receiving clotting factors made before 1987 (when inactivation procedures were introduced) or blood products before 1992, hemodialysis, idiopathic liver disease, and children born to HCV-infected women (qualitative PCR in infancy and anti-HCV after 12-18 mo of age). In children, it is also important to consider whether the mother has any of the risk factors noted above that would increase her possibility of developing HCV. Routine screening of all *pregnant women* is not recommended. The Centers for Disease Control, did however, recommend in 2012 that all individuals born between 1945 and 1965 be screened.

Determining HCV **genotype** is also important, particularly when therapy is considered, because the response to the current therapeutic agents varies greatly. Genotype 1 is poorly responsive; genotypes 2 and 3 are more reliably responsive to therapy (as discussed later).

Aminotransferase levels typically fluctuate during HCV infection and do not correlate with the degree of liver fibrosis.

A liver biopsy is the only means to assess the presence and extent of hepatic fibrosis, outside of overt signs of chronic liver disease. A liver biopsy is indicated only before starting any treatment and to rule out other causes of overt liver disease.

Complications

The risk of ALF caused by HCV is low, but the risk of **chronic hepatitis** is the highest of all the hepatotropic viruses. In adults, risk factors for progression to hepatic fibrosis include older age, obesity, male sex, and even moderate alcohol ingestion (two 1 oz drinks per day). Progression to cirrhosis or HCC is a major cause of morbidity and the most common indication for liver transplantation in adults in the United States.

Treatment

In adults, *peginterferon* (subcutaneous, weekly) combined with ribavirin (oral, daily) was standard therapy until 2012 for genotype 1. Currently recommended first-line adult therapy for genotype 1 includes these 2 medications with the use of sofosbuvir, an oral, direct-acting antiviral agent, for only 12 wk or an oral regimen of sofosbuvir, simeprevir, and possibly ribavirin. Ongoing studies suggest that future treatments will be even more effective, with fewer side effects.

Traditionally, patients most likely to respond had mild hepatitis, shorter duration of infection, low viral titers and either genotype 2 or 3 virus. Patients with genotype 1 virus responded poorly. Response to peginterferon alfa/ribavirin may be predicted by single-nucleotide polymorphisms near the interleukin 28B gene, but with these newer treatment regimens excellent response rates are being reported with shorter duration, IFN-free regimens. The goal of treatment is to achieve a sustained viral response (SVR), as defined by the absence of viremia 6 mo after stopping the medications; SVR is associated with improved histology and decreased risk of morbidities.

The natural history of HCV infection in children is still being defined. It is believed that children have a higher rate of spontaneous clearance than adults (up to 45% by age 19 yr). A multicenter study followed 359 children infected with HCV over 10 yr. Only 7.5% had cleared the virus, and 1.8% progressed to decompensated cirrhosis. Treatment in adults with **acute** HCV in a pilot study showed an 88% SVR in genotype 1 subjects (treated with IFN and ribavirin for 24 wk). Such data, if confirmed, could actually raise the question whether children, with shorter duration of infection and fewer comorbid conditions than their adult counterparts, could be "ideal" candidates for treatment. Given the adverse effects of currently available therapy, this strategy is not recommended outside of clinical trials.

Peginterferon (Schering), IFN-α2b, and ribavirin are approved by the FDA for use in children older than 3 yr of age with HCV hepatitis. Studies of IFN monotherapy in children demonstrated a higher SVR than in adults, with better compliance and fewer side effects. An SVR up to 49% for genotype 1 was achieved in multiple studies. Factors associated with a higher likelihood of response are age younger than 12 yr, genotypes 2 and 3, and, in patients with genotype 1b, an RNA titer of <2 million copies/mL of blood, and viral response (PCR at weeks 4 and 12 of treatment). Side effects of medications lead to discontinuation of treatment in a high proportion of patients; these include influenza-like symptoms, anemia, and neutropenia. Long-term

effects of these medicines also need to be evaluated as significant differences were noted in children's weight, height, body mass index, and body composition. Most of these delays improved following cessation of treatment, but height z-scores continued to lag behind.

Treatment should be considered for all children infected with genotypes 2 and 3, because they have an 80-90% response rate to therapy with peginterferon and ribavirin. If the child has genotype 1b virus, the treatment choice remains more controversial. Pediatric guidelines recommend treatment to eradicate HCV infection, prevent progression of liver disease and development of HCC, and to remove the stigma associated with HCV. Treatment should be considered for patients with evidence of advanced fibrosis or injury on liver biopsy. The currently approved treatment consists of 48 wk of peginterferon and ribavirin (therapy should be stopped if still detectable on viral PCR at 24 wk of therapy). Treatment of children with normal biochemical profile and mild histologic inflammation should be reserved to a clinical study context.

Newer Treatments

Peginterferon and direct-acting antivirals, including telaprevir and boceprevir (viral protease inhibitors), demonstrated a much improved SVR rate in adults. Telaprevir and boceprevir were the first direct-acting antiviral agents approved to combat hepatitis C. Newer medications, including sofosbuvir and simeprevir, have already replaced telaprevir and boceprevir as the treatment of choice for hepatitis C genotype 1. Studies are pending in pediatrics. Combination therapy schemes and staggered therapy is also being explored in adults. Interleukin 28B, a host marker of immune responsiveness, has also been evaluated to predict host response to treatment with standard peginterferon and ribavirin, but will become even less important as IFN free regimens become standard practice. Varying IFN-free regimens are now available for all HCV genotypes allowing even greater likelihood of achieving viral eradication, with completely oral medication regimens, and without the use of IFN and its attendant side effects. With the rapid development of new medications and regimens, frequent review of up-to-date resources, such as www.hcvguidelines.org, will be vital to provide optimal care.

Prevention

No vaccine is yet available to prevent HCV, although ongoing research suggests this will be possible in the future. Current Ig preparations are not beneficial, likely because Ig preparations produced in the United States do not contain antibodies to HCV because blood and plasma donors are screened for anti-HCV and excluded from the donor pool. Broad neutralizing antibodies to HCV were found to be protective and might pave the road for vaccine development.

Once HCV infection is identified, patients should be screened yearly with a liver ultrasound and serum α-fetoprotein for HCC, as well as for any clinical evidence of liver disease. Vaccinating the affected patient against HAV and HBV will prevent superinfection with these viruses and the increased risk of developing severe liver failure.

Prognosis

Viral titers should be checked yearly to document spontaneous remission. Most patients develop chronic hepatitis. Progressive liver damage is higher in those with additional comorbid factors such as alcohol consumption, viral genotypic variations, obesity, and underlying genetic predispositions. Referral to a pediatric gastroenterologist is strongly advised to take advantage of up-to-date monitoring regimens and to optimize their enrollment in treatment protocols when available.

HEPATITIS D

Etiology

HDV, the smallest known animal virus, is considered defective because it cannot produce infection without concurrent HBV infection. The 36 nm diameter virus is incapable of making its own coat protein; its outer coat is composed of excess HBsAg from HBV. The inner core of the virus is single-stranded circular RNA that expresses the HDV antigen.

Epidemiology

HDV can cause an infection at the same time as the initial HBV infection (coinfection), or HDV can infect a person who is already infected with HBV (superinfection). Transmission usually occurs by intrafamilial or intimate contact in areas of high prevalence, which are primarily developing countries (see Table 358-1). In areas of low prevalence, such as the United States, the parenteral route is far more common. HDV infections are uncommon in children in the United States but must be considered when ALF occurs. The incubation period for HDV superinfection is approximately 2-8 wk; with coinfection, the incubation period is similar to that of HBV infection.

Pathogenesis

Liver pathology in HDV hepatitis has no distinguishing features except that damage is usually quite severe. In contrast to HBV, HDV causes injury directly by cytopathic mechanisms. The most severe cases of HBV infection appear to result from coinfection of HBV and HDV.

Clinical Manifestations

The symptoms of hepatitis D infection are similar to, but usually more severe than those of the other hepatotropic viruses. The clinical outcome for HDV infection depends on the mechanism of infection. In coinfection, acute hepatitis, which is much more severe than for HBV alone, is common, but the risk of developing chronic hepatitis is low. In superinfection, acute illness is rare and chronic hepatitis is common. The risk of ALF is highest in superinfection. Hepatitis D should be considered in any child who experiences ALF.

Diagnosis

HDV has not been isolated and no circulating antigen has been identified. The diagnosis is made by detecting IgM antibody to HDV; the antibodies to HDV develop approximately 2-4 wk after coinfection and approximately 10 wk after a superinfection. A test for anti-HDV antibody is commercially available. PCR assays for viral RNA are available as research tools (see Table 358-2).

Complications

HDV must be considered in all cases of ALF. Coinfection with HBV can also result in a more severe chronic disease.

Treatment

The treatment is based on supportive measures once an infection is identified. There are no specific HDV-targeted treatments to date. The treatment is mostly based on controlling and treating HBV infection, without which HDV cannot induce hepatitis. Small research studies suggest that IFN is the preferred treatment regimen, but ongoing studies still seek the ideal management strategy and the regimen should be personalized for each patient.

Prevention

There is no vaccine for hepatitis D. Because HDV replication cannot occur without hepatitis B coinfection, immunization against HBV also prevents HDV infection. Hepatitis B vaccines and HBIG are used for the same indications as for hepatitis B alone.

HEPATITIS E

Etiology

HEV has been cloned using molecular techniques. This RNA virus has a nonenveloped sphere shape with spikes and is similar in structure to the caliciviruses.

Epidemiology

Hepatitis E is the epidemic form of what was formerly called non-A, non-B hepatitis. Transmission is fecal–oral (often waterborne) and is associated with shedding of 27-34 nm particles in the stool (see Table 358-1). The highest prevalence of HEV infection has been reported in the Indian subcontinent, the Middle East, Southeast Asia, and Mexico, especially in areas with poor sanitation. The prevalence, however, appears to be increasing in the United States and other developed

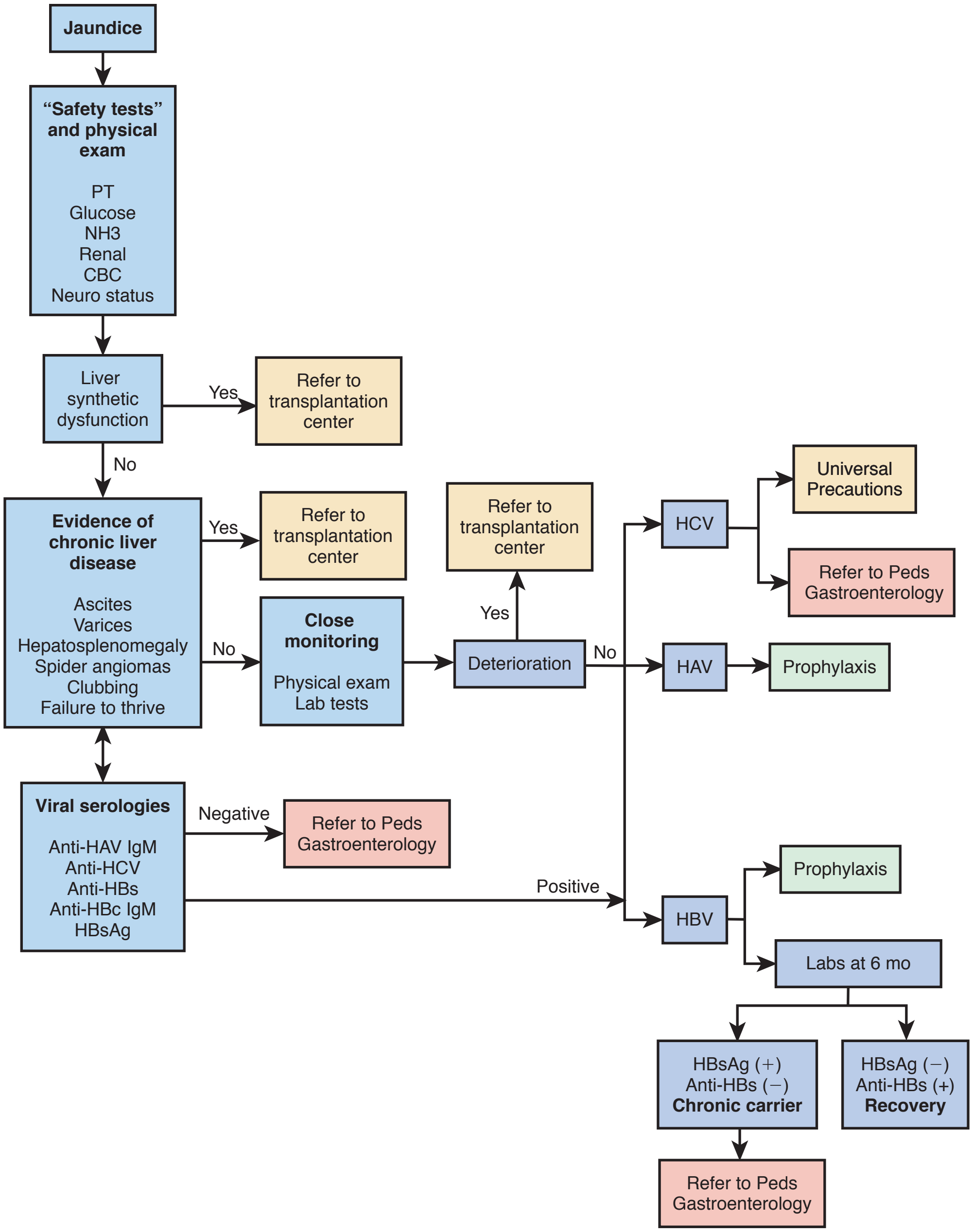

Figure 358-6 Clinical approach to viral hepatitis. *CBC*, complete blood count with differential; *HAV*, hepatitis A virus; *HBs*, hepatitis B surface; *HBsAg*, hepatitis B surface antigen; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *IgM*, immunoglobulin M; *NH_3*, ammonia; *PT*, prothrombin time.

countries and has been postulated to be the most common cause of acute hepatitis and jaundice in the world. The mean incubation period is approximately 40 days (range: 15-60 days).

Pathogenesis

HEV appears to act as a cytopathic virus. The pathologic findings are similar to those of the other hepatitis viruses.

Clinical Manifestations

The clinical illness associated with HEV infection is similar to that of HAV but is often more severe. As with HAV, chronic illness does not occur. In addition to often causing a more severe episode than HAV, HEV tends to affect older patients, with a peak age between 15 and 34 yr. HEV is a major pathogen in pregnant women, in whom it causes ALF with a high fatality incidence. HEV could also lead to decompensation of pre-existing chronic liver disease.

Complications

HEV is associated with a high risk of death in pregnant women. No other complications are recognized in association with this virus.

Diagnosis

Recombinant DNA technology has resulted in development of antibodies to HEV particles, and IgM and IgG assays are available to distinguish between acute and resolved infections (see Table 358-3). IgM antibody to viral antigen becomes positive after approximately 1 wk of illness. Viral RNA can be detected in stool and serum by PCR.

Prevention

A recombinant hepatitis E vaccine is highly effective in adults. No evidence suggests that Ig is effective in preventing HEV infections. Ig pooled from patients in endemic areas might prove to be effective.

APPROACH TO ACUTE OR CHRONIC HEPATITIS

Although new treatment modalities for chronic viral hepatitis are continuously being developed and treatment outcomes have improved, the major medical breakthrough in regard to the pediatric population is prevention, with the availability of effective and safe vaccines for the HAV and HBV infections. The availability of more sensitive and reliable diagnostic tools may lead to improved care for affected patients. The primary care physician is at the forefront of the care and control of patients exposed to these viruses. Aggressive perinatal, childhood, and adolescent immunization strategies have already had a major impact in endemic HAV and HBV areas.

Identifying deterioration of the patient with acute hepatitis and the development of ALF is a major contribution of the primary pediatrician (Fig. 358-6). If ALF is identified, the clinician should immediately refer the patient to a transplantation center; this can be lifesaving.

Once chronic infection is identified, close follow-up and referral to a pediatric gastroenterologist is recommended to enroll the patient in appropriate treatment trials. Treatment of chronic HBV and HCV in children should preferably be delivered within, or using data from pediatric controlled trials as indications, timing, regimen, and outcomes remain to be defined and cannot simply be extrapolated from adult data. All patients with chronic viral hepatitis should avoid, as much as possible, further insult to the liver: HAV vaccine is recommended; patients must avoid alcohol consumption and obesity, and they should exercise care when taking new medications, including nonprescription drugs and herbal medications.

International adoption and ease of travel continue to change the epidemiology of hepatitis viruses. In the United States, chronic HBV and HCV have a high prevalence among international adoptee patients; vigilance is required to establish early diagnosis in order to offer appropriate treatment as well as prophylactic measures to limit viral spread.

Chronic hepatitis can be a stigmatizing disease for children and their families. The pediatrician should offer, with proactive advocacy, appropriate support for them as well as needed education for their social circle. Scientific data and information about support groups are available for families on the websites for the American Liver Foundation (www.liverfoundation.org) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (www.naspghan.org), as well as through pediatric gastroenterology centers.

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Chapter 359

Liver Abscess

Robert M. Kliegman

Pyogenic liver abscesses are rare in children, with an incidence of 10/100,000 hospitalizations. Pyogenic hepatic abscesses can be caused by bacteria entering the liver via the portal circulation in cases of omphalitis, portal vein pylephlebitis, intraabdominal infection, or abscess secondary to appendicitis or inflammatory bowel disease; a primary bacteremia (sepsis, endocarditis); ascending cholangitis associated with biliary tract obstruction caused by gallstones or sclerosing cholangitis, after a Kasai procedure, or secondary to choledochal cysts; contiguous infection (subphrenic abscess) or penetrating trauma; and cryptogenic biliary tract infections. Very rarely, liver abscesses occur after percutaneous liver biopsy. Hepatic abscesses can also occur in neonates in association with sepsis, umbilical vein associated infection, or cannulation; 50% are seen in children younger than 6 yr old. In adults with pyogenic liver abscesses, liver transplantation is a significant risk factor; it is not known if pediatric liver transplant patients are also at increased risk. Children with chronic granulomatous disease, Job syndrome, or cancer are also at increased risk for a hepatic abscess.

In children with pyogenic liver abscesses, the most common pathogenic organisms include *Staphylococcus aureus*, *Streptococcus* spp.; *Escherichia coli, Klebsiella pneumoniae, Salmonella,* and anaerobic organisms; *Entamoeba histolytica* or *Toxocara canis*–associated liver abscesses have also been reported in developing countries or in highly endemic areas.

Amebic disease is rare in the United States and is associated with immigrants from or travel to highly endemic areas. Recovery of *E. histolytica* from the stool is pathogenic and highly suggestive of an amebic abscess, but this must be distinguished from *Entamoeba dispar*, which looks similar but is nonpathogenic; antiamebic antibodies help identify *E. histolytica*. Multiple microabscesses are most commonly secondary to bacteremia, candidemia, or cat scratch disease. Polymicrobial involvement is seen in approximately 50%; cryptogenic abscesses are often monomicrobial with *S. aureus* as the lead single agent in children without underlying liver or intestinal tract disease.

Signs and symptoms are nonspecific and can include fever, chills, night sweats, malaise, fatigue, nausea, abdominal pain with right upper quadrant tenderness, and hepatomegaly; jaundice is uncommon. Diagnosis can be challenging and is often delayed; a high index of suspicion is necessary in children with risk factors. Serum aminotransferase and more often the alkaline phosphatase levels are elevated. The erythrocyte sedimentation rate is high, and leukocytosis is common. The results of blood cultures are positive in 50% of patients. Chest x-rays might show elevation of the right hemidiaphragm with decreased mobility or a right pleural effusion. Ultrasound or CT can confirm diagnosis (Figs. 359-1 to 359-3). Solitary liver abscesses (70% of cases) in the right lobe of the liver (75% of cases) are more common than multiple abscesses or solitary left lobe abscesses. Enzyme-linked immunosorbent assay testing for *E. histolytica* Gal/GalNAc (galactose/*N*-acetyl-D-galactosamine) lectin in serum is usually positive with amebiasis.

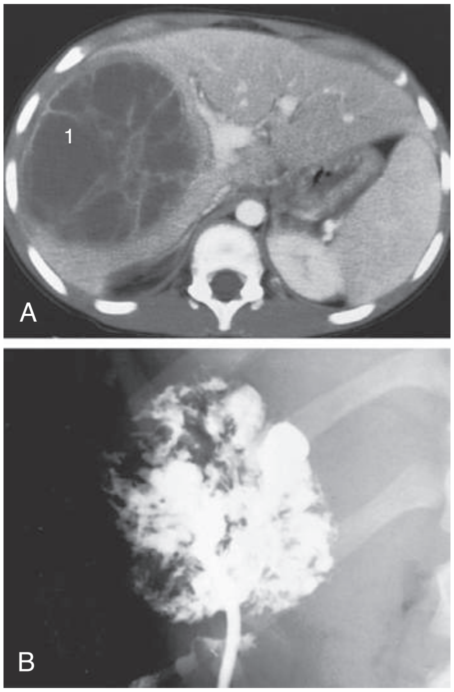

Figure 359-1 Liver abscess. **A,** Contrast-enhanced CT scan demonstrates a multiloculated septated mass of decreased attenuation in the right lobe of the liver. There is increased attenuation of the septa. There is also faintly visible edema between the abscess and the enhanced normal liver. **B,** Injection of contrast material after percutaneous drainage of this documented streptococcal abscess demonstrates the multilocular nature of the lesion and its irregularly marginated wall. *(From Kuhn JP, Slovis TL, Haller JO:* Caffrey's pediatric diagnostic imaging, *vol 2, ed 10, Philadelphia, 2004, Mosby, p. 1470.)*

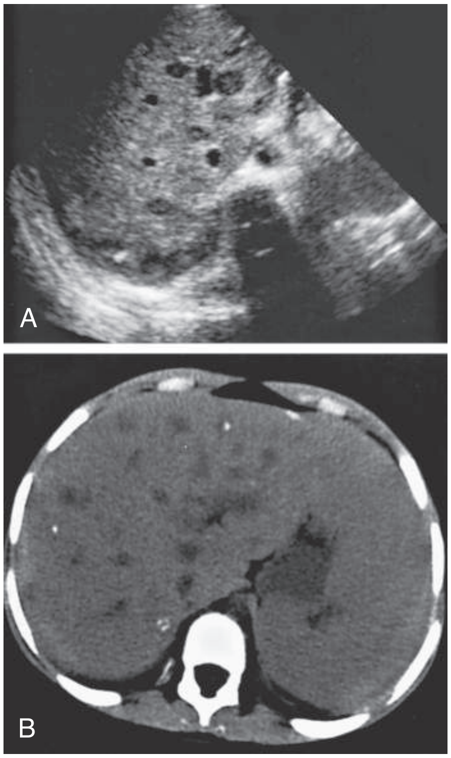

Figure 359-2 Hepatic candidiasis. Transverse sonogram **(A)** and CT scan **(B)** of the upper abdomen demonstrate "bull's-eye" lesions in the right lobe of the liver in an immunocompromised patient. The calcifications seen on the CT scan are presumed to represent sequelae of prior infection. Liver biopsy demonstrated candidiasis. *(From Kuhn JP, Slovis TL, Haller JO:* Caffrey's pediatric diagnostic imaging, *vol 2, ed 10, Philadelphia, 2004, Mosby, p. 1472.)*

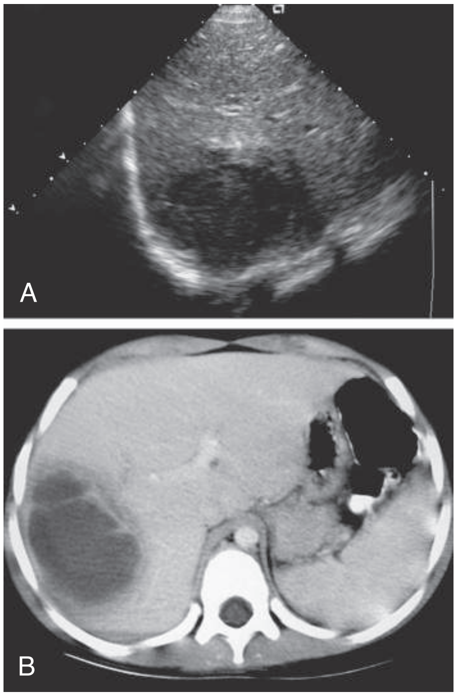

Figure 359-3 Amebic abscess. **A,** Sonogram demonstrates a hypoechogenic mass in the right lobe of the liver with a more hypoechoic surrounding rim. **B,** CT scan demonstrates a low-attenuation mass in the right lobe of the liver with a prominent halo. *(From Kuhn JP, Slovis TL, Haller JO:* Caffrey's pediatric diagnostic imaging, *vol 2, ed 10, Philadelphia, 2004, Mosby, p. 1473.)*

Treatment requires percutaneous ultrasound- or CT-guided needle aspiration and less often open surgical drainage, particularly if multiple or large abscesses are present. Some place a drain and leave it in until the abscess wall collapses, others just do single or repeated aspirations. Aerobic and anaerobic cultures should be obtained. Some treat empirically without aspiration or drainage. If amebic disease is present, most do not attempt aspiration.

Antibiotic therapy should initially be broad spectrum but then narrowed, based on the culture results of the abscess fluid. Empirical initial antibiotic regimens include ampicillin/sulbactam, ticarcillin/clavulanic acid, or piperacillin/tazobactam. Others recommend a combination of a third-generation cephalosporin plus metronidazole. Amebic abscesses are treated with metronidazole or tinidazole plus paromomycin (oral nonabsorbable to treat the associated intestinal amebic infection). Antibiotic therapy for pyogenic abscess is intravenous for 2-3 wk followed by oral therapy to complete a 4-6 wk course. Mortality has decreased significantly since the 1980s with early diagnosis and initiation of appropriate therapy.

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Chapter 360

Liver Disease Associated with Systemic Disorders

Bernadette E. Vitola and William F. Balistreri

Liver disease is found in a wide variety of systemic illnesses, both as a result of the primary pathologic process and as a secondary complication of the disease or associated therapy.

INFLAMMATORY BOWEL DISEASE

Ulcerative colitis and Crohn disease are associated with hepatobiliary disease that includes autoimmune and inflammatory processes related to inflammatory bowel disease (IBD) (sclerosing cholangitis, autoimmune hepatitis), drug toxicity (thiopurines, methotrexate, 5-ASA, biologics), malnutrition and disordered physiology (fatty liver, cholelithiasis), bacterial translocation and systemic infections (hepatic abscess, portal vein thrombosis), hypercoagulability (infarction, Budd-Chiari), and long-term complications of these liver diseases, such as ascending cholangitis, cirrhosis, portal hypertension, and biliary carcinoma. Hepatobiliary manifestations may continue to progress even when intestinal symptoms are well-controlled and are unrelated to either the severity or duration of intestinal disease.

Sclerosing cholangitis is the most common hepatobiliary disease associated with IBD, occurring in 2-8% of adult patients with ulcerative colitis and less often in Crohn disease. Conversely, 70-90% of patients with sclerosing cholangitis have ulcerative colitis. In pediatric patients with IBD, the diagnosis typically occurs in the 2nd decade of life with a median age of 14 yr. Sclerosing cholangitis is characterized by progressive inflammation and fibrosis of segments of the intra- and extrahepatic bile ducts and can progress to complete obliteration. Genetic susceptibility, with associations with the cystic fibrosis transmembrane conductance regulator (CFTR) and several human leukocyte antigens, has been demonstrated. Many patients are asymptomatic and the disease is initially diagnosed by routine liver function testing that reveals elevated serum alkaline phosphatase (AP), 5′-nucleotidase, or

γ-glutamyl transpeptidase activities. Antinuclear or anti–smooth muscle antibodies might also be present in the serum. Ten percent to 15% of adult patients present with symptoms including anorexia, weight loss, pruritus, fatigue, right upper quadrant pain, and jaundice; intermittent acute cholangitis accompanied by fever, jaundice, and right upper quadrant pain can also occur. Portal hypertension can develop with progressive disease. These symptoms are less common in children, in whom hepatobiliary disease is often recognized by routine screening of liver function tests. In children with sclerosing cholangitis, approximately 11% present initially with hepatic manifestations and the associated asymptomatic IBD is discovered only on subsequent endoscopy.

Magnetic resonance cholangiography is an established first-line diagnostic test for sclerosing cholangitis. Characteristic findings include beading and irregularity of the intrahepatic and extrahepatic bile ducts. Liver biopsy typically reveals periductal fibrosis and inflammation, fibroobliterative cholangitis, and portal fibrosis, but it is not required for the diagnosis in patients with radiologic evidence of sclerosing cholangitis.

Sclerosing cholangitis is strongly associated with hepatobiliary malignancies (cholangiocarcinoma, hepatocellular carcinoma, gallbladder carcinoma) with a reported incidence varying between 9% and 14%. In one large series, patients with IBD and sclerosing cholangitis had a 10-fold increased risk of colorectal carcinoma and a 14-fold increased risk of pancreatic cancer compared to the general population. Tumor serology (CA 19-9) and cross-sectional liver imaging may be a useful screening strategy to identify patients with sclerosing cholangitis at increased risk for cholangiocarcinoma.

There is no definitive medical treatment for sclerosing cholangitis; liver transplantation is the only long-term option for progressive cirrhosis, and autoimmune disease can recur in the allograft in 20-25% of patients. Short-term therapy aims at improving biliary drainage and attempting to slow the obliterative process. Ursodeoxycholic acid, at a dose of 15-30 mg/kg/24 hr, improves bile flow and laboratory parameters but has not been shown to improve clinical outcome. Dominant extrahepatic biliary strictures may be dilated or endoscopically stented. Immunosuppressive therapy with corticosteroids and/or azathioprine improves biochemical parameters but has been disappointing in halting long-term histologic progression. Symptomatic therapy should be initiated for pruritus (rifampin, ursodeoxycholic acid, diphenhydramine), malnutrition (enteral supplementation), and ascending cholangitis (antibiotics) as indicated. Total colectomy may not be beneficial in preventing or managing hepatobiliary complications in patients with ulcerative colitis.

IBD-associated **autoimmune hepatitis** (AIH) can closely resemble IBD-associated sclerosing cholangitis, a condition often referred to as **overlap syndrome** or autoimmune sclerosing cholangitis (ASC). These patients typically exhibit hyperglobulinemia (marked increase in serum immunoglobulin G levels). In some children, the disease is initially diagnosed as AIH and later is found to be sclerosing cholangitis after cholangiography; in other cases, AIH manifests years after diagnosis of IBD-associated sclerosing cholangitis. Liver biopsy in patients with ASC shows interface hepatitis, in addition to the bile duct injury associated with sclerosing cholangitis. Immunosuppressive medication (corticosteroids and/or azathioprine) is the mainstay of therapy for ASC; long-term response does not appear to be as favorable as in AIH alone. Long-term survival in children with ASC appears to be similar to those with sclerosing cholangitis, with an overall median (50%) survival free of liver transplantation of 12.7 yr.

Fatty liver disease might also be more prevalent in adult patients with IBD, ranging from 25-40% in 1 large series and often correlates with severity of IBD. Gallstones are more prevalent in those with Crohn disease (11%) than in those with ulcerative colitis (7.5%) and in normal subjects (5%). The true prevalence of these IBD-associated liver diseases in pediatric patients is unknown, however.

BACTERIAL SEPSIS

Sepsis can mimic liver disease and should be excluded in any critically ill patient who develops cholestasis in the absence of markedly elevated serum aminotransferase or AP levels, even when other signs of infection are not evident. Gram-negative organisms are most often isolated from blood cultures, in particular *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa.* Lipopolysaccharides and other bacterial endotoxins are thought to interfere with bile secretion by directly altering the structure or function of bile canalicular membrane transport proteins. The serum bilirubin level, predominantly the conjugated fraction, is elevated. Serum AP and aminotransferase activities may also be elevated. Liver biopsy shows intrahepatic cholestasis with little or no hepatocyte necrosis. Kupffer cell hyperplasia and an increase in inflammatory cells are also common. Similar findings can occur with urosepsis.

CELIAC DISEASE

Celiac disease (see Chapter 338.2) may present with laboratory abnormalities, including aminotransferase elevation and prolonged prothrombin time, as well as histologic changes, such as mild periportal and lobular inflammation. These abnormalities typically all improve on a gluten-free diet. Gastrointestinal symptoms may not be present. Other autoimmune liver diseases (AIH, primary sclerosing cholangitis) are also associated with celiac disease although they do not respond as well to a gluten-free diet.

CARDIAC DISEASE

Hepatic injury can occur as a complication of severe acute or chronic congestive heart failure (see Chapter 442), cyanotic congenital heart disease (see Chapters 430 and 431), and acute ischemic shock. In all conditions, passive congestion and reduced cardiac output can contribute to liver damage. Elevated central venous pressure is transmitted to the hepatic veins, smaller venules, and, ultimately, the surrounding hepatocytes, resulting in hepatocellular atrophy in the centrilobular zone of the liver. Owing to decreased cardiac output, there is decreased hepatic arterial blood flow, and centrilobular hypoxia results. Hepatic necrosis leads to lactic acidosis, elevated aminotransferase levels, cholestasis, prolonged partial thromboplastin time, cirrhosis, and possibly hypoglycemia as a result of impaired hepatocellular metabolism. Jaundice, tender hepatomegaly, and, in some cases, ascites and splenomegaly can occur. However, aminotransferases are often minimally elevated with slowly progressive fibrosis since there is minimal inflammation or cell death.

After acute hypovolemic shock, serum aminotransferase levels can rise dramatically but rapidly return to normal when perfusion and cardiac function improve. Hepatic necrosis or acute liver failure can occur in infants with hypoplastic left heart syndrome and coarctation of the aorta. High systemic venous pressures after Fontan procedures can also lead to hepatic dysfunction, marked by prolonged prothrombin time and cardiac cirrhosis. The aim of therapy in all causes of cardiac-associated liver disease is to improve cardiac output, reduce systemic venous pressures, and monitor for other signs of hypoperfusion. Even mild liver disease can have an impact on mortality after cardiac surgery, with poorer outcomes with progressively worse liver disease. In adults with cirrhosis undergoing cardiac surgery, overall mortality was 17% but varied significantly from 5% with mild disease to 70% with advanced liver disease.

CHOLESTASIS ASSOCIATED WITH TOTAL PARENTERAL NUTRITION

Total parenteral nutrition (TPN) can cause a variety of liver diseases, including hepatic steatosis, gallbladder and bile duct damage, and cholestasis. Cholestasis is the most severe complication and can lead to progressive fibrosis and cirrhosis. It is the major factor limiting effective long-term use of TPN in children and adults. Risk factors for TPN-associated cholestasis include prolonged duration of TPN, prematurity, low birthweight, sepsis, necrotizing enterocolitis, and short bowel syndrome.

The pathogenesis of TPN-associated cholestasis is multifactorial. Sepsis; excess caloric intake; high amounts of protein, fat, or carbohydrate; specific amino acid toxicities; nutrient deficiencies; and toxicities related to components such as manganese, aluminum, and copper can

all contribute to hepatic injury. Recent data implicate both the type and volume of lipid administered. Prolonged enteral fasting compromises mucosal integrity and increases bacterial mucosal translocation. Fasting also decreases release of cholecystokinin, which promotes bile flow. This leads to biliary stasis, cholestasis, and formation of biliary sludge and gallstones, which exacerbates hepatic dysfunction. Sepsis, particularly that caused by Gram-negative bacteria, and associated endotoxins, can also exacerbate liver damage.

Early histologic findings include macrovesicular steatosis, canalicular cholestasis, and periportal inflammation. These changes can regress after cessation of short-term TPN. Prolonged duration of TPN is marked by bile duct proliferation or ductopenia, portal fibrosis, and expansion of portal triads and it can progress to cirrhosis and end-stage liver disease.

Clinical onset is typically marked by gradual onset of cholestasis, developing after more than 2 wk of TPN. In low birthweight infants, the onset of jaundice can overlap the phase of physiologic (unconjugated) hyperbilirubinemia. Any icteric infant who has received TPN for more than 1 wk should have bilirubin fractionated. With prolonged duration, hepatic enlargement or splenomegaly can develop. Serum bile acid concentrations can increase. Rises in serum aminotransferase activities may be a late finding. An elevation in serum AP activity may be caused by rickets, a common complication of TPN in low birthweight infants.

In addition to cholestasis, biliary complications of intravenous nutrition include cholelithiasis and the development of biliary sludge, associated with thick, inspissated gallbladder contents. These may be asymptomatic. Hepatic steatosis or elevated serum aminotransferase levels can also occur in the absence of cholestasis, particularly in older children. This is generally mild and resolves after TPN is discontinued. Serum bilirubin and bile acid levels remain within the normal range. Other causes of liver disease should also be considered, especially if evidence of hepatic dysfunction persists despite weaning from TPN and initiating enteral feeds. If serum AP or aminotransferase levels remain elevated, liver biopsy may be necessary for accurate diagnosis.

Treatment of TPN-associated cholestasis is focused on avoiding progressive liver injury by limiting duration whenever possible. Enteral feeding should be initiated as soon as tolerated and prolonged fasting should be avoided. Even small volumes of nutrients given by intermittent oral feedings or by continuous nasogastric drip promote bile flow, enterohepatic recirculation of bile acids, and intestinal motility, and they enhance mucosal barrier function, reducing the risk of bacterial translocation. Improved TPN solutions that meet the specific needs of neonates can prevent deficiencies and toxicities. The risk of further hepatic injury should always be considered when weighing the option of continuing TPN indefinitely, and all efforts should be made to try to advance enteral feeds whenever possible. There has been concern that the soy-based emulsions provided with TPN may be a significant contributing factor to TPN-associated cholestasis as a result of proinflammatory omega-6 fatty acids. Several strategies have been employed to minimize exposure to these fatty acids by limiting total lipid and/or introducing alternate sources of lipid including fish oil and olive oil to provide more omega-3 fatty acids. The long-term effects of these strategies on essential fatty acid deficiency or growth are unclear although there is some evidence that TPN-associated cholestasis may improve.

Ursodeoxycholic acid therapy may be beneficial in improving jaundice and hepatosplenomegaly. Other therapies, such as administration of antibiotics to reduce intraluminal bacterial overgrowth or oral administration of taurine or cholecystokinin, remain experimental.

CYSTIC FIBROSIS

Cystic fibrosis (CF) (see Chapter 403) is caused by mutations in the *CFTR* gene, which impair chloride transport across the apical membranes of epithelial cells in numerous organs (including cholangiocytes). The majority of patients with CF have some evidence of hepatobiliary disease; however, less than one-third of these patients develop clinically significant liver disease. Hepatobiliary complications account for approximately 2.5% of overall mortality in patients with CF. The onset of liver disease occurs at a median age of 10 yr, and >90% occurs by 20 yr,

Focal biliary cirrhosis is the pathognomonic liver lesion in CF and is postulated to result, in part, from impaired secretory function of the bile duct epithelium. Blockage of biliary ductules secondary to viscid secretions results in periductal inflammation, bile duct proliferation, and increased fibrosis within focal portal tracts. Gradual progression to multilobular cirrhosis can occur and result in portal hypertension and end-stage liver disease in 1-8% of patients. Liver disease tends to occur mainly in males with pancreatic insufficiency and requires 2 CFTR mutations without residual function. One candidate gene modifier for clinical phenotypes of CF-related liver disease that shows a strong association is SERPINA1. However, additional study of mutational analysis is necessary before we are able to predict which patients with CF will develop liver disease. Clinical risk factors that may be associated with liver disease include older age, pancreatic insufficiency, male gender, and possibly a history of meconium ileus.

Treatment with oral ursodeoxycholic acid (10-15 mg/kg/day) may be beneficial in improving liver function, presumably by improving bile flow; further research is necessary to determine whether a true long-term benefit exists. Because it is difficult to predict which patients will develop liver disease, prophylactic therapy is not possible. Progression of liver disease is generally slow. Patients who develop end-stage liver disease might require liver transplantation for survival.

BONE MARROW TRANSPLANTATION

Liver disease is common in patients who have received hematopoietic stem cell transplantation (SCT), whether the cells are harvested from bone marrow or peripheral blood (see Chapters 135-139). The pathogenesis is varied and includes infections (viral, bacterial, or fungal); toxicity from parenteral nutrition, chemotherapy, or radiation; venoocclusive disease (VOD); graft-versus-host disease (GVHD); or hemosiderosis secondary to iron overload from frequent blood transfusions. GVHD, drug toxicity, and sepsis are the most common causes of liver dysfunction after allogeneic SCT.

Diagnosis is often challenging because of the coexistence of multiple risk factors. Clinical course, symptoms and signs, and biochemical liver function and viral serologic tests must be considered in making the correct diagnosis. Percutaneous liver biopsy may be necessary; histology can show extensive bile duct injury in GVHD, viral inclusions in cytomegalovirus disease, or the characteristic endothelial lesion in VOD. It is important to diagnose the cause accurately, because treatment for GVHD differs markedly from that of other conditions (i.e., initiating immunosuppression for GVHD) and can worsen hepatitis secondary to infections.

GVHD of the liver can be acute or chronic but often occurs with the presence of GVHD in other target organs such as the skin and gut (see Chapter 137). Hepatic GVHD is caused by immunologic reaction to bile duct epithelium, leading to a nonsuppurative cholangitis. Histologic features of GVHD include loss of intralobular bile ducts, endothelial injury of hepatic and portal venules, and hepatocellular necrosis.

Onset typically occurs at the time of donor engraftment (days 14-21 after SCT). In acute hepatic GVHD, serum aminotransferase levels can rise markedly in the absence of elevated bilirubin, AP, and γ-glutamyl transpeptidase levels, mimicking viral hepatitis. Acute hepatic GVHD can manifest both early (days 14-21) and late (after day 70) after allogeneic SCT. In chronic hepatic GVHD, serum aminotransferase levels are not as markedly elevated and cholestasis is more prominent, with marked rises in serum conjugated bilirubin, γ-glutamyl transpeptidase, and AP levels. Other signs and symptoms can include hepatic tenderness, dark urine, acholic stools, itching, and anorexia.

VOD of the liver usually develops in the 1st 3 wk after SCT. The incidence ranges from 5-39% in pediatric patients, with reported mortality rates varying from 0-47%. Risk factors include trauma, high-dose

conditioning regimens, coagulopathies, sickle cell anemia, leukemia, polycythemia vera, thalassemia major, hepatic abscesses, irradiation, GVHD, iron overload, preexisting liver disease, and younger age. VOD is caused by fibrous obliteration of the terminal hepatic venules and small lobular veins, with resultant damage to the surrounding hepatocytes and sinusoids. It is not associated with thrombus formation, in contrast with Budd-Chiari syndrome, which involves occlusion of the larger hepatic veins or inferior vena cava by a web, mass, or thrombus.

Pathologic changes in patients with VOD are best demonstrated using special (trichrome) stains to highlight the central veins. The lesions may be patchy. Later in the course, hepatic venules may be completely obliterated.

Symptoms typically include jaundice, painful hepatomegaly, rapid weight gain, and ascites. VOD resolves in the majority of patients but can also lead to multisystem organ failure, hepatic encephalopathy, and fulminant hepatic failure. Less-severe forms may be characterized by jaundice and ascites with a slow resolution; in very mild cases, histologic changes may be the sole manifestation. The diagnosis rests on the exclusion of other diseases, such as GVHD, congestive cardiomyopathy, constrictive pericarditis, and Budd-Chiari syndrome.

Treatment for VOD with defibrotide has been successful in multicenter phase II trials in both adult and pediatric patients; defibrotide, an agent with antithrombotic and thrombolytic properties, is administered at doses of 20-40 mg/kg/day. Complete response rates vary between 36% and 76% and survival of longer than 100 days post-SCT ranges from 32-79%, with better outcomes in pediatric patients. Little toxicity has been noted; however, pediatric patients are at a higher risk of bleeding with treatment compared to adults. Oral ursodeoxycholic acid can decrease the incidence of severe liver disease in patients undergoing SCT and reduces the incidence of VOD and transplant-related mortality in adults. Supportive management includes maintaining intravenous hydration and renal perfusion.

HEMOGLOBINOPATHIES

Patients with sickle cell anemia (see Chapter 462.1) or thalassemia (see Chapter 462.10) can have hepatic dysfunction caused by acute or chronic viral hepatitis, hemosiderosis from frequent transfusion therapy, hepatic crises related to severe intrahepatic cholestasis, sequestration, or ischemic necrosis. Cholelithiasis and hemosiderosis are both common and treatable. Higher volume of transfusions is associated with both higher hepatic iron content and fibrosis. Chelation therapy for iron overload is usually safe and effective.

Hepatic sickle cell crisis or "sickle hepatopathy" occurs in approximately 10% of patients with sickle cell disease. It manifests with intense right upper quadrant pain and tenderness, fever, leukocytosis, and jaundice. Bilirubin levels may be markedly elevated; serum AP levels may be only moderately elevated. It can be difficult to distinguish sickle hepatopathy from viral hepatitis, acute cholecystitis or choledocholithiasis; therefore, these conditions should be excluded. Generally, hepatic sickle cell crisis is self-limited and symptoms resolve within 1-3 wk. **Sickle cell intrahepatic cholestasis** manifests as hepatomegaly, abdominal pain, hyperbilirubinemia, and coagulopathy, and can progress to acute liver failure, leaving transplantation as the only therapeutic option. Transplantation carries a high risk for graft loss from vascular complications.

On occasion, children with sickle cell disease experience a benign elevation of bilirubin levels >20 mg/dL but unaccompanied by severe pain or fever. There is no change in hematocrit or reticulocyte count nor any association with a hemolytic crisis.

HISTIOCYTIC DISORDERS

Langerhans cell histiocytosis (see Chapter 507.1) is the most common of the histiocytoses and typically affects the bone and skin. However, it can cause infiltration of high-risk organs such as the liver resulting in periportal inflammation and sclerosing cholangitis. Liver involvement often results in worse outcomes. Hemophagocytic lymphohistiocytosis (see Chapter 507.2) is a multiorgan, severe, and potentially fatal inflammatory process associated with activation of macrophages that mimics sepsis. The hepatic manifestation of hemophagocytic lymphohistiocytosis is usually acute liver failure with portal inflammatory infiltrates noted on liver biopsy.

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360.1 Nonalcoholic Fatty Liver Disease

Bernadette E. Vitola and William F. Balistreri

Nonalcoholic fatty liver disease (NAFLD) is part of the spectrum of liver disease strongly associated with obesity and is the most common chronic liver disease in children. NAFLD can range from fatty liver alone to a triad of fatty infiltration, inflammation, and fibrosis, termed **nonalcoholic steatohepatitis (NASH),** which resembles alcoholic liver disease but occurs with little or no exposure to ethanol. Unlike adults, NASH in children has 2 distinct histologic types. **Type 1 NASH** resembles adult histologic findings with steatosis and balloon degeneration of hepatocytes and/or periportal fibrosis. **Type 2 NASH** includes steatosis and portal inflammation. Many patients are asymptomatic. Liver histology from autopsy data suggests that 10% of children and 38% of obese children ages 2-19 yr have NAFLD. The risk is lower in African-American children. Elevated serum aminotransferase levels are not sensitive or specific markers for NAFLD. A normal serum alanine aminotransferase level is present in 21-23% of pediatric patients with NAFLD. No biomarkers are currently a reliable alternative to biopsy. Although ultrasonography detects NAFLD, no current imaging modalities distinguish between steatosis and NASH. A liver biopsy may be required for a delimiting diagnosis. The estimated prevalence in adults is thought to be as high as 15-20% for NAFLD overall and 2-4% for NASH. Risk factors in pediatric cohorts include obesity, male gender, white or Hispanic ethnicity, hypertriglyceridemia, and insulin resistance. Hepatic steatosis alone may be benign, but up to a quarter of patients with NASH can develop progressive fibrosis with resultant cirrhosis. The long-term prognosis of NASH that has developed in childhood is unknown. Children diagnosed with NAFLD should be screened for comorbid conditions associated with the metabolic syndrome, including diabetes, hypertension, dyslipidemia, and obstructive sleep apnea. Obese children and overweight children with other risk factors who are older than 3 yr of age should be screened for NAFLD by checking aminotransferase levels and liver ultrasound, even though neither is highly sensitive or specific.

Although there is no definitive treatment for NAFLD, gradual weight loss is effective in normalizing serum alanine aminotransferase and improving NAFLD. Low glycemic index foods, avoiding fructose, and substituting polyunsaturated fatty acids for saturated fats may help. Vitamins E and C provide no additional benefit to the efficacy of lifestyle intervention (diet and exercise) in improving steatosis or biochemical abnormalities in pediatric NAFLD. However, vitamin E does improve balloon degeneration in pediatric NASH. Metformin has produced mixed results in the treatment of NAFLD. Thiazolidinediones (pioglitazone, rosiglitazone) improve liver histology in adults with NASH but have not been well studied in children. Ursodeoxycholic acid has not been efficacious. In view of the potential role of the gut microbiome in contributing to the pathogenesis of NAFLD, the role of probiotics as an adjunct to lifestyle changes is under investigation. A preliminary study using ω-3 docosahexanoic acid in children showed improved insulin sensitivity, alanine aminotransferase, triglycerides, body mass index, and histology in children with NAFLD. Cysteamine bitartrate (slow release), a potential precursor of glutathione, an antioxidant, may reduce liver enzyme levels, as well as serum leptin and adiponectin levels, and is also a potential candidate for the treatment of NAFLD.

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Chapter 361

Mitochondrial Hepatopathies

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Hepatocytes contain a high density of mitochondria, because the liver, with its biosynthetic and detoxifying functions, is highly dependent on adenosine triphosphate. Defects in mitochondrial function can lead to impaired oxidative phosphorylation, increased generation of reactive oxygen species, impairment of other metabolic pathways, and activation of mechanisms of cellular death. Mitochondrial disorders can be divided into primary, in which the mitochondrial defect is the primary cause of the disorder, and secondary, in which mitochondrial function is affected by exogenous injury or a genetic mutation that affects non-mitochondrial proteins (see Chapter 87.4). Primary mitochondrial disorders can be caused by mutations affecting mitochondrial DNA (mtDNA) or by nuclear genes that encode mitochondrial proteins or cofactors (Tables 361-1 and 361-2). Secondary mitochondrial disorders include diseases with an uncertain etiology such as Reye syndrome; disorders caused by endogenous or exogenous toxins, drugs, or metals; and other conditions in which mitochondrial oxidative injury may be involved in the pathogenesis of liver injury.

EPIDEMIOLOGY

Mitochondrial respiratory chain disorders of all types affect 1 in 20,000 children younger than 16 yr of age; liver involvement has been reported in 10-20% of patients with respiratory chain defect.

More than 200 pathogenic point mutations, deletions, insertions, and rearrangements that involve mtDNA and nuclear DNA that encodes mitochondrial proteins are identified. Mitochondrial genetics are unique because mitochondria are able to replicate, transcribe, and translate their mitochondrial-derived DNA independently. A typical hepatocyte contains approximately 1000 copies of mtDNA. Oxidative phosphorylation (the process of adenosine triphosphate production) occurs in the respiratory chain located in the inner mitochondrial membrane and is divided into 5 multienzyme complexes: reduced nicotinamide adenine dinucleotide coenzyme Q reductase (complex I), succinate–coenzyme Q reductase (complex II), reduced coenzyme Q–cytochrome-*c* reductase (complex III), cytochrome-*c* oxidase (complex IV), and adenosine triphosphate synthase (complex V). The respiratory chain peptide components are encoded by both nuclear and mtDNA genes, hence mutations in either genome can result in disorders of oxidative phosphorylation. Thirteen essential polypeptides are synthesized from the small 16.5-kilobase circular double-stranded mtDNA. Mitochondrial DNA also encodes the 24 transfer RNAs required for intramitochondrial protein synthesis, whereas nuclear genes encode more than 70 respiratory chain subunits and an array of enzymes and cofactors required to maintain mtDNA, including DNA polymerase-γ (POLG), thymidine kinase 2, and deoxyguanosine kinase.

Expression of mitochondrial disorders is complex and epidemiologic studies are hampered by technical difficulties collecting and processing tissue specimens needed to make accurate diagnoses, the variability in clinical presentation, and the fact that most disorders display maternal inheritance with variable penetrance (see Chapter 80). mtDNA mutates 10 times more often than nuclear DNA secondary to a lack of introns, protective histones, and an effective repair system in mitochondria. Mitochondrial genetics also display a threshold effect in that the type and severity of mutation required for clinical expression varies among people and organ systems, this is explained by the concept of heteroplasmy, in which cells and tissues harbor both normal and mutant mtDNA in various amounts because of random partitioning during cell division.

Table 361-1	Classification of Primary Mitochondrial Hepatopathies
Respiratory chain (electron transport) defects (oxidative phosphorylation)	
Neonatal liver failure	
Complex I deficiency	
Complex IV deficiency (*SCO1* mutations)	
Complex III deficiency (*BCS1L* mutations)	
Coenzyme Q deficiency	
Multiple complex deficiencies (transfer and elongation factor mutations)	
mtDNA depletion syndrome (*DUGOK*, *MPV17*, *POLG*, *SUCLG1*, *C10orf2/Twinkle* mutations)	
Later-onset liver dysfunction or failure	
Alpers-Huttenlocher disease (*POLG* mutations)	
Pearson marrow-pancreas syndrome (mtDNA deletion)	
Mitochondrial neurogastrointestinal encephalopathy (*TYMP* mutations)	
Navajo neurohepatopathy (*MPV17* mutations)	
Fatty acid oxidation defects	
Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase	
Carnitine palmitoyltransferases I and II deficiencies	
Carnitine–acylcarnitine translocase deficiency	
Urea cycle enzyme deficiencies	
Electron transfer flavoprotein and electron transfer flavoprotein dehydrogenase deficiencies	
Phosphoenolpyruvate carboxykinase (mitochondrial) deficiency; nonketotic hyperglycemia	
Citrin deficiency; neonatal intrahepatic cholestasis caused by citrin deficiency (*SLC25A13* mutations)	

From Lee WS, Sokol RJ: Mitochondrial hepatopathies: advances in genetics, therapeutic approaches and outcomes. J Pediatr 163:942–948, 2013 (Table 1, p. 943).

CLINICAL MANIFESTATIONS

Defects in oxidative phosphorylation can affect any tissue to a variable degree, with the most energy-dependent organs being the most vulnerable. One should consider the diagnosis of a mitochondrial disorder in a patient of any age who presents with progressive, multisystem involvement that cannot be explained by a specific diagnosis. Gastrointestinal complaints include vomiting, diarrhea, constipation, failure to thrive, and abdominal pain; certain mitochondrial disorders have characteristic gastrointestinal presentations. Pearson marrow-pancreas syndrome manifests with sideroblastic anemia and exocrine pancreatic insufficiency, whereas mitochondrial neurogastrointestinal encephalomyopathy manifests with chronic intestinal pseudoobstruction and cachexia. Hepatic presentations range from chronic cholestasis, hepatomegaly, cirrhosis, steatosis to fulminant hepatic failure and death.

PRIMARY MITOCHONDRIAL HEPATOPATHIES

Neonatal Liver Failure

A common presentation of respiratory chain defects is severe liver failure manifested as jaundice, hypoglycemia, coagulopathy, renal dysfunction, and hyperammonemia, with onset within the 1st few wk to mo of life. The key biochemical features include a markedly elevated plasma lactate concentration, an elevated molar ratio of plasma lactate to pyruvate (>25 mol/mol), and a raised ratio of β-hydroxybutyrate to acetoacetate (2.0 mol/mol). Symptoms are nonspecific and include lethargy and vomiting. Most patients additionally have neurologic involvement manifested as a weak suck, recurrent apnea, or myoclonic epilepsy. Liver biopsy shows predominantly microvesicular steatosis, cholestasis, bile duct proliferation, glycogen depletion, and iron overload. With standard therapy, the prognosis is very poor, and most patients die from liver failure or infection in the 1st few mo of life. **Cytochrome-*c* oxidase** (complex IV) is the most common deficiency in these infants, although complexes I and III and mtDNA depletion syndromes also are implicated (see Table 361-1).

Table 361-2 Genotypic Classification of Primary Mitochondrial Hepatopathies and Organ Involvement

GENE	RESPIRATORY CHAIN COMPLEX	HEPATIC HISTOLOGY	OTHER ORGANS INVOLVED	CLINICAL FEATURES
Deletion	Multiple (Pearson)	Steatosis, fibrosis	Kidney, heart, CNS, muscle	Sideroblastic anemia, variable thrombocytopenia and neutropenia, persistent diarrhea
MPV17	I, III, IV	Steatosis	CNS, muscle, gastrointestinal tract	Adult-onset multisystemic involvement: myopathy, ophthalmoplegia, severe constipation, parkinsonism
DGUOK	I, III, IV	Steatosis, fibrosis	Kidneys, CNS, muscle	Nystagmus, hypotonia, renal Fanconi syndrome, acidosis
MPV17	I, III, IV	Steatosis, fibrosis	CNS, PNS	Hypotonia
SUCLG1	I, III, IV	Steatosis	Kidneys, CNS, muscle	Myopathy, sensorineural hearing loss, respiratory failure
POLG1	I, III, IV	Steatosis, fibrosis	CNS, muscle	Liver failure preceded by neurologic symptoms, intractable seizures, ataxia, psychomotor regression
C10orf2/Twinkle	I, III, IV	Steatosis	CNS, muscle	Infantile-onset spinocerebellar ataxia, loss of skills
BCS1L	III (GRACILE)		CNS ±, muscle ±, kidneys	Fanconi-type renal tubulopathy
SCO1	IV	Steatosis, fibrosis	Muscle	
TRMU	I, III, IV	Steatosis, fibrosis		Infantile liver failure with subsequent recovery
EFG1	I, III, IV	Steatosis	CNS	Severe, rapidly progressive encephalopathy
EFTu	I, III, IV	Unknown	CNS	Severe lactic acidosis, rapidly fatal encephalopathy

CNS, central nervous system; *GRACILE*, growth restriction, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death; *PNS*, peripheral nervous system.
From Lee WS, Sokol RJ: Mitochondrial hepatopathies: advances in genetics, therapeutic approaches and outcomes. J Pediatr *163:942–948, 2013 (Table 2, p. 944).*

Alpers Syndrome (Alpers-Huttenlocher Syndrome or Alpers Hepatopathic Poliodystrophy)

Diagnostic criteria include refractory, mixed-type seizures that include a focal component; psychomotor regression that is episodic and triggered by intercurrent infections; and hepatopathy with or without acute liver failure. Alpers syndrome manifests from infancy up to 8 yr of age with seizures, hypotonia, feeding difficulties, psychomotor regression, and ataxia. Patients develop hepatomegaly and jaundice and have a slower progression to liver failure than those with cytochrome-*c* oxidase deficiency. Elevated blood or cerebrospinal fluid lactate and pyruvate levels are supportive for the diagnosis, in addition to characteristic electroencephalogram findings (high-amplitude slow activity with polyspikes), asymmetric abnormal visual evoked responses, and low-density areas or atrophy in the occipital or temporal lobes on computed tomography scanning of the brain. In some patients, complex I deficiency has been found in liver or muscle mitochondria. The disease is inherited in an autosomal recessive fashion; mutations in the catalytic subunit of the nuclear gene mtDNA *POLG* have been identified in multiple families with Alpers syndrome, leading to the advent of molecular diagnosis for Alpers syndrome. *Patients with POLG mutations are susceptible to valproate-induced liver dysfunction.*

Mitochondrial DNA Depletion Syndrome

Mitochondrial DNA depletion syndrome (MDS) is characterized by a tissue-specific reduction in mtDNA copy number, leading to deficiencies in complexes I, III, and IV. MDS manifests with phenotypic heterogeneity, multisystem and localized disease forms include myopathic, hepatocerebral, and liver-restricted presentations. Infants with the hepatocerebral form present in the neonatal period. The first symptoms are metabolic and rapidly progress to hepatic failure with hypoglycemia and vomiting. This stage is followed by neurologic involvement affecting the central and peripheral systems. Laboratory studies are characterized by lactic acidosis, hypoglycemia and markedly elevated α-fetoprotein in plasma. In some patients iron overload has been found with elevated transferrin saturation, high ferritin levels, and iron accumulation in hepatocytes and Kupffer cells. Death usually occurs by 1 yr of age. Spontaneous recovery has been reported in a patient with liver-restricted disease. Inheritance is autosomal recessive and mutations in the nuclear gene deoxyguanosine kinase gene ***(DGUOK)*** have been identified in many patients with hepatocerebral MDS. **Thymidine kinase 2** has been implicated in the myopathic form; no known genetic defect has been identified in liver-restricted MDS. Multiple other nuclear genes including ***POLG, MPV17,*** **Twinkle helicase gene,** and ***SUCLG1,*** have been implicated in hepatocerebral MDS. Liver biopsies of patients with MDS show microvesicular steatosis, cholestasis, focal cytoplasmic biliary necrosis, and cytosiderosis in hepatocytes and sinusoidal cells. Ultrastructural changes are characteristic with oncocytic transformation of mitochondria, which is characterized by mitochondria with sparse cristae, granular matrix, and dense or vesicular inclusions. If the native DNA-encoded complex II is normal and the activities of the other complexes are decreased, one should investigate mtDNA copy numbers for a MDS. **Diagnosis** is established by demonstration of a low ratio of mtDNA (<10%) to nuclear DNA in affected tissues and/or genetic testing. Importantly, the sequence of the mitochondrial genome is normal.

Navajo Neurohepatopathy

Navajo neurohepatopathy (NNH) is an autosomal recessive sensorimotor neuropathy with progressive liver disease found only in Navajo Indians of the southwestern United States. The incidence is 1 in 1,600 live births. Diagnostic criteria include sensory neuropathy; motor neuropathy; corneal anesthesia; liver disease; metabolic or infectious complications including failure to thrive, short stature, delayed puberty, or systemic infection; and evidence of central nervous system demyelination on radiographic imaging and peripheral nerves biopsies. ***MPV17*** gene mutation ***is implicated*** in the pathogenesis of NNH. Interestingly, this is the same gene implicated in MDS (see earlier), demonstrating that NNH may be a specific type of MDS found only in Navajo Indians. NNH is divided into 3 phenotypic variations based on age of presentation and clinical findings.

First, **classic NNH** appears in infancy with severe progressive neurologic deterioration manifesting clinically as weakness, hypotonia, loss of sensation with accompanying acral mutilation, corneal ulcerations, and poor growth. Liver disease, present in the majority of patients, is secondary and variable and includes asymptomatic elevations of liver function tests, Reye syndrome–like episodes,

hepatocellular carcinoma, or cirrhosis. γ-Glutamyl transpeptidase levels tend to be higher than in other forms of NNH. Liver biopsy might show chronic portal tract inflammation and cirrhosis, but it shows less cholestasis, hepatocyte ballooning, and giant cell transformation than other forms of NNH.

Infantile NNH manifests between the ages of 1 and 6 mo with jaundice and failure to thrive, and progresses to liver failure and death by 2 yr of age. Patients have hepatomegaly with moderate elevations in aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase. Liver biopsy demonstrates pseudoacinar formation, multinucleate giant cells, portal and lobular inflammation, canalicular cholestasis, and microvesicular steatosis. Progressive neurologic symptoms are not usually noticed at presentation but do develop later.

Childhood NNH manifests from age 1-5 yr with the acute onset of fulminant hepatic failure that leads to death within months. Most patients also have evidence of neuropathy at presentation. Liver biopsies are similar to those in infantile NNH, except significant hepatocyte ballooning and necrosis, bile duct proliferation, and cirrhosis are also seen.

There is no effective treatment for any of the forms of NNH, and neurologic symptoms often preclude liver transplantation. The identical ***MPV17*** mutation is seen in patients with both the infantile and classic form of NNH highlighting the clinical heterogeneity of NNH.

Pearson Syndrome

Pearson marrow-pancreas syndrome has a neonatal-onset with severe macrocytic anemia, variable neutropenia and thrombocytopenia, and ringed sideroblasts in the bone marrow. Diarrhea and fat malabsorption develop in early childhood secondary to extensive pancreatic fibrosis, acinar atrophy and partial villous atrophy of the small intestine. The liver involvement includes hepatomegaly, steatosis, and cirrhosis. Liver failure and death have been reported before the age of 4 yr. Other features of the syndrome include renal tubular disease, photosensitivity, diabetes mellitus, hydrops fetalis, and the late development of visual impairment, tremor, ataxia, proximal muscle weakness, external ophthalmoplegia, and a pigmentary retinopathy. Methylglutaconic aciduria is a useful diagnostic marker. Large deletions of mtDNA are reported in most patients resulting in complexes I and III deficiency. mtDNA deletions can be detected in patients' cultured fibroblasts as well as in peripheral blood lymphocytes.

Villous Atrophy Syndrome

Children with this disease present with severe anorexia, vomiting, chronic diarrhea, and villous atrophy in the 1st yr of life. Hepatic involvement includes mild elevation of aminotransferase levels, hepatomegaly, and steatosis. Lactic acidosis is worsened with high-dextrose intravenous infusions or enteral nutrition. Diarrhea improved by 5 yr of age in association with the normalization of intestinal biopsies. Subsequently, patients develop retinitis pigmentosa, cerebellar ataxia, sensorineural deafness, and proximal muscle weakness, with eventual death late in the 1st decade of life. The disease is attributed to a mtDNA rearrangement defect. A complex III deficiency was found in the muscle of affected patients.

GRACILE Syndrome

The acronym GRACILE sums the most important clinical features, namely fetal growth restriction (birth weight about −4 SD), aminoaciduria (caused by Fanconi-type tubulopathy), cholestasis (with steatosis and cirrhosis), iron overload, severe lactic acidosis, and early death. The syndrome is associated with mutations of the complex III assembly factor BCS1L. The liver histology shows microvesicular steatosis and cholestasis with abundant iron accumulation in hepatocytes and Kupffer cells. The liver iron content slightly decreases with age, concomitantly with increasing fibrosis and cirrhosis. Abnormal transaminases and coagulation are noted, but the cause of death seems to be related to energy depletion than to liver failure. About half of the cases die within the 1st 2 wk; the oldest infant lived to 4 mo of age.

Mutations in Nuclear Translation and Elongation Factor Genes

Mutations in nuclear translation factor genes *(TRMU)* of the respiratory chain enzyme complexes have been identified as the etiology for acute liver failure manifesting at ages 1 day to 6 mo. The respiratory chain deficit was similar to MDS, where the activity of the native DNA encoded complex II was normal, whereas complexes I, III, and IV were decreased. The elongation factor EFG1 (gene *GFM1*) mutation was associated with fetal growth restriction, lactic acidosis, liver dysfunction that progresses into liver failure and death. The mutation in the elongation factor EFTu manifests as severe lactacidosis and lethal encephalopathy with mild hepatic involvement.

SECONDARY MITOCHONDRIAL HEPATOPATHIES

Secondary mitochondrial hepatopathies are caused by a hepatotoxic metal, drug, toxin, or endogenous metabolite. In the past, the most common secondary mitochondrial hepatopathy was **Reye syndrome,** the prevalence of which peaked in the 1970s and had a mortality rate of >40%. Even though mortality has not changed, the prevalence has decreased from >500 cases in 1980 to approximately 35 cases per year since. As to the decline of Reye syndrome, recent literature data reveal that this is related to more accurate modern diagnosis of infectious, metabolic, or toxic disease, reducing the percentage of idiopathic or true cases of Reye syndrome. Reye syndrome is precipitated in a genetically susceptible person by the interaction of a viral infection (influenza, varicella) and salicylate and or antiemetic use. Clinically, it is characterized by a preceding viral illness that appears to be resolving and the acute onset of vomiting and encephalopathy (Table 361-3). Neurologic symptoms can rapidly progress to seizures, coma, and death. Liver dysfunction is invariably present when vomiting develops, with coagulopathy and elevated serum levels of aspartate aminotransferase, alanine aminotransferase, and ammonia. Importantly, patients remain anicteric and serum bilirubin levels are normal. Liver biopsies show microvesicular steatosis without evidence of liver inflammation or necrosis. Death is usually secondary to increased intracranial pressures and herniation. Patients who survive have full recovery of liver function but should be carefully screened for fatty-acid oxidation and fatty-acid transport defects (Table 361-4).

Acquired abnormalities of mitochondrial function can be caused by several drugs and toxins, including valproic acid, cyanide, amiodarone, chloramphenicol, iron, antimycin A, the emetic toxin of *Bacillus cereus,* and nucleoside analogs. Valproic acid is a branched fatty acid that can be metabolized into the mitochondrial toxin 4-envalproic acid. Children with underlying respiratory chain defects appear more sensitive to the toxic effects of this drug and valproic acid is reported to precipitate liver failure in patients with **Alpers syndrome** and **cytochrome-*c* oxidase deficiency.** Nucleoside analogs directly inhibit mitochondrial respiratory chain complexes. The reverse transcriptase inhibitors zidovudine, didanosine, stavudine, and zalcitabine used to treat HIV-infected patients inhibit DNA polymerase-γ of mitochondria and can block elongation of mtDNA, leading to mtDNA

Table 361-3 Clinical Staging of Reye Syndrome and Reye-Like Diseases

Symptoms at the time of admission:

I. Usually quiet, **lethargic** and sleepy, vomiting, laboratory evidence of liver dysfunction
II. Deep lethargy, **confusion,** delirium, combativeness, hyperventilation, hyperreflexia
III. Obtunded, **light coma** ± seizures, **decorticate** rigidity, intact pupillary light reaction
IV. Seizures, deepening coma, **decerebrate rigidity,** loss of oculocephalic reflexes, fixed pupils
V. Coma, loss of deep tendon reflexes, respiratory arrest, fixed dilated pupils, **flaccidity/decerebration** (intermittent); isoelectric electroencephalogram

Table 361-4 Diseases That Present a Clinical or Pathologic Picture Resembling Reye Syndrome

Metabolic disease
• Organic aciduria
• Disorders of oxidative phosphorylation
• Urea cycle defects (carbamoyl phosphate synthetase, ornithine transcarbamylase)
• Defects in fatty acid oxidation metabolism
• Acyl–coenzyme A dehydrogenase deficiencies
• Systemic carnitine deficiency
• Hepatic carnitine palmitoyltransferase deficiency
• 3-OH, 3-methylglutaryl-coenzyme A lyase deficiency
• Fructosemia
Central nervous system infections or intoxications (meningitis), encephalitis, toxic encephalopathy
Hemorrhagic shock with encephalopathy
Drug or toxin ingestion (salicylate, valproate)

depletion. Other conditions that can lead to mitochondrial oxidative stress include cholestasis, nonalcoholic steatohepatitis, α_1-antitrypsin deficiency, and Wilson disease.

TREATMENT OF MITOCHONDRIAL HEPATOPATHIES

There is no effective therapy for most patients with mitochondrial hepatopathies; neurologic involvement often precludes orthotropic liver transplantation. Several drug mixtures that include antioxidants, vitamins, cofactors, and electron acceptors have been proposed, but no randomized, controlled trials have been completed to evaluate these drug combinations. Current treatment strategies are supportive and include the infusion of sodium bicarbonate for acute metabolic acidosis, low carbohydrate diet may decrease the lactic acidosis, transfusions for anemia and thrombocytopenia, and exogenous pancreatic enzymes for pancreatic insufficiency.

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Table 362-1	Disorders Producing Chronic Hepatitis

Chronic viral hepatitis
- Hepatitis B
- Hepatitis C
- Hepatitis D

Autoimmune hepatitis
- Anti-actin antibody positive
- Anti–liver-kidney microsomal antibody positive
- Anti-soluble liver antigen antibody-positive
- Others (includes antibodies to liver-specific lipoproteins or asialoglycoprotein)
- Overlap syndrome with sclerosing cholangitis and autoantibodies
- Systemic lupus erythematosus
- Celiac disease

Drug-induced hepatitis

Metabolic disorders associated with chronic liver disease
- Wilson disease
- Nonalcoholic steatohepatitis
- α_1-Antitrypsin deficiency
- Tyrosinemia
- Niemann-Pick disease type 2
- Glycogen storage disease type iv
- Cystic fibrosis
- Galactosemia
- Bile acid biosynthetic abnormalities

Chapter 362

Autoimmune Hepatitis

Benjamin L. Shneider and Frederick J. Suchy

Autoimmune hepatitis is a chronic hepatic inflammatory process manifested by elevated serum aminotransaminase concentrations, liver-associated serum autoantibodies, and/or hypergammaglobulinemia. The target of the inflammatory process can include hepatocytes and to a lesser extent bile duct epithelium. Chronicity is determined either by duration of liver disease (typically >3-6 mo) or by evidence of chronic hepatic decompensation (hypoalbuminemia, thrombocytopenia) or physical stigmata of chronic liver disease (clubbing, spider telangiectasia, splenomegaly, ascites). The severity is variable; the affected child might have only biochemical evidence of liver dysfunction, might have stigmata of chronic liver disease, or can present in hepatic failure.

Chronic hepatitis can also be caused by persistent viral infection (see Chapter 358), drugs (see Chapter 363), metabolic diseases (see Chapter 361), or unknown and autoimmune disorders (Table 362-1). Approximately 5% or less of chronic cases in the United States are associated with hepatitis B infection; unusually severe disease may be caused by superimposed infection with hepatitis D (a defective RNA virus that is dependent on replicating hepatitis B virus). More than 90% of hepatitis B infections in the 1st yr of life become chronic, compared with 5-10% among older children and adults. Chronic hepatitis develops in >50% of acute hepatitis C virus infections. Patients receiving blood products or who have had massive transfusions are at increased risk. Hepatitis A does not lead to chronic liver disease. Hepatitis E can become chronic in immunosuppressed patients. **Drugs** commonly used in children that can cause chronic liver injury include isoniazid, methyldopa, pemoline, nitrofurantoin, dantrolene, minocycline, pemoline, and the sulfonamides. **Metabolic diseases** can lead to chronic hepatitis, including α_1-antitrypsin deficiency, inborn errors of bile acid biosynthesis, and Wilson disease. **Nonalcoholic steatohepatitis,** usually associated with obesity and insulin resistance, is another common cause of chronic hepatitis. It can progress to cirrhosis, but responds to weight reduction. In many cases, the cause of chronic hepatitis is unknown; in some, an autoimmune mechanism is suggested by the finding of serum antinuclear and anti–smooth muscle antibodies and by multisystem involvement (arthropathy, thyroiditis, rashes, Coombs-positive hemolytic anemia).

Autoimmune hepatitis is a clinical constellation that suggests an immune-mediated process; it is responsive to immunosuppressive therapy (Table 362-2). Autoimmune hepatitis typically refers to a primarily hepatocyte-specific process, whereas autoimmune cholangiopathy and sclerosing cholangitis are predominated by intra- and extrahepatic bile duct injury. Overlap of the process involving both hepatocyte and bile duct directed injury may be more common in children. De novo hepatitis can be seen in a subset of liver transplant recipients whose initial disease was not autoimmune.

ETIOLOGY

In **autoimmune hepatitis** a dense portal mononuclear cell infiltrate invades the surrounding parenchyma and comprises T and B lymphocytes, macrophages, and plasma cells. The immunopathogenic mechanisms underlying autoimmune hepatitis are unsettled. Triggering factors can include molecular mimicry, infections, drugs, and the environment (toxins) in a genetically susceptible host. Several human leukocyte antigen class II molecules, particularly DR3, DR4, and DR7 isoforms, confer susceptibility to autoimmune hepatitis. Self-antigenic

Table 362-2 Classification of Autoimmune Hepatitis

VARIABLE	TYPE 1 AUTOIMMUNE HEPATITIS	TYPE 2 AUTOIMMUNE HEPATITIS
Characteristic autoantibodies	Antinuclear antibody* Smooth-muscle antibody* Antiactin antibody† Autoantibodies against soluble liver antigen and liver-pancreas antigen‡ Atypical perinuclear antineutrophil cytoplasmic antibody	Antibody against liver-kidney microsome type 1* Antibody against liver cytosol type 1* Antibody against liver-kidney microsomal type 3
Geographic variation	Worldwide	Worldwide; rare in North America
Age at presentation	Any age	Predominantly childhood and young adulthood
Gender of patients	Female in ~75% of cases	Female in ~95% of cases
Association with other autoimmune diseases	Common	Common§
Clinical severity	Broad range, variable	Generally severe
Histopathologic features at presentation	Broad range, mild disease to cirrhosis	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	~100%

*The conventional method of detection is immunofluorescence.
†Tests for this antibody are rarely available in commercial laboratories.
‡This antibody is detected by enzyme-linked immunosorbent assay.
§Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is seen only in patients with type 2 disease.
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peptides are processed by populations of antigen presenting cells and presented to CD4 and CD8 effector T-cells. CD4+ T lymphocytes recognizing a self-antigenic liver peptide orchestrate liver injury. Cell-mediated injury by cytokines released by CD8+ cytotoxic T cells and/or antibody-mediated cytotoxicity can be operative. There is also evidence that regulatory T-cells from autoimmune hepatitis patients are impaired in their ability to control the proliferation of CD4 and CD8 effector cells. Cytochrome P450 2D6 is the main autoantigen in type 2 autoimmune hepatitis.

Antibody-coated hepatocytes may be lysed by complement or Fc-bearing natural killer lymphocytes. Heterozygous mutations in the **autoimmune regulator gene *(AIRE),*** which encodes a transcription factor controlling the negative selection of autoreactive thymocytes, can be found in some children with autoimmune hepatitis types 1 and 2. *AIRE* mutations also cause **autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy** (also called autoimmune polyendocrinopathy syndrome) in which autoimmune hepatitis occurs in approximately 20% of patients.

PATHOLOGY

The histologic features common to untreated cases include inflammatory infiltrates, consisting of lymphocytes and plasma cells that expand portal areas and often penetrate the lobule (interface hepatitis); moderate to severe piecemeal necrosis of hepatocytes extending outward from the limiting plate; variable necrosis, fibrosis, and zones of parenchymal collapse spanning neighboring portal triads or between a portal triad and central vein (bridging necrosis); and variable degrees of bile duct epithelial injury. Distortion of hepatic architecture can be severe; cirrhosis may be present in children at the time of diagnosis. Histologic features in acute liver failure may be obscured by massive necrosis and multilobular collapse. Other histologic features may suggest an alternative diagnosis: characteristic periodic acid–Schiff-positive, diastase-resistant granules are seen in α_1-antitrypsin deficiency, and macrovesicular and microvesicular steatosis is found in Nonalcoholic steatohepatitis and often in Wilson disease. Bile duct injury can suggest an autoimmune cholangiopathy. Ultrastructural analysis might suggest distinct types of storage disorders.

CLINICAL MANIFESTATIONS

The clinical features and course of autoimmune hepatitis are extremely variable. Signs and symptoms at the time of presentation comprise a wide spectrum of disease including a substantial number of asymptomatic patients and some who have an acute, even fulminant, onset. In 25-30% of patients with autoimmune hepatitis, particularly children, the illness mimics acute viral hepatitis. In most, the onset is insidious. Patients can be asymptomatic or have fatigue, malaise, behavioral changes, anorexia, and amenorrhea, sometimes for many months before jaundice or stigmata of chronic liver disease are recognized. Extrahepatic manifestations can include arthritis, vasculitis, nephritis, thyroiditis, Coombs-positive anemia, and rash. Some patients' initial clinical features reflect cirrhosis (ascites, bleeding esophageal varices, or hepatic encephalopathy).

There may be mild to moderate jaundice in severe cases. Spider telangiectasias and palmar erythema may be present. The liver may be tender and slightly enlarged but might not be felt in patients with cirrhosis. The spleen is commonly enlarged. Edema and ascites may be present in advanced cases. Evidence of involvement of other organ systems may be found.

LABORATORY FINDINGS

The findings are related to the severity of presentation. In many asymptomatic cases, serum aminotransferase ranges between 100 and 300 IU/L, whereas levels in excess of 1,000 IU/L can be seen in symptomatic young patients. Serum bilirubin concentrations may be normal in mild cases but are commonly 2-10 mg/dL in more severe cases. Serum alkaline phosphatase and γ-glutamyl transpeptidase activities are normal to slightly increased but may be more significantly elevated in autoimmune cholangiopathy or in the setting of overlap with sclerosing cholangitis. Serum γ-globulin levels can show marked polyclonal elevations. Hypoalbuminemia is common. The prothrombin time is prolonged, most often as a result of vitamin K deficiency but also as a reflection of impaired hepatocellular function. A normochromic normocytic anemia, leukopenia, and thrombocytopenia are present and become more severe with the development of portal hypertension and hypersplenism.

Most patients with autoimmune hepatitis have hypergammaglobulinemia. Serum immunoglobulin G levels usually exceed 16 g/L. Characteristic patterns of serum **autoantibodies** define distinct subgroups of autoimmune hepatitis (see Table 362-2). The most common pattern (type 1) is associated with the formation of non–organ-specific antibodies, such as antiactin (smooth muscle) and antinuclear antibodies. Approximately 50% of these patients are 10-20 yr of age. High titers of a liver-kidney microsomal antibody are detected in another form (type 2) that usually affects children 2-14 yr of age. A subgroup of primarily young women might demonstrate autoantibodies against a soluble liver antigen but not against nuclear or microsomal proteins. Antineutrophil cytoplasmic antibodies may be seen more commonly in autoimmune cholangiopathy. Autoantibodies are rare in healthy children so that titers as low as 1 : 40 may be significant, although nonspecific elevation in autoantibodies can be observed in a variety of liver diseases. Up to 20% of patients with apparent autoimmune hepatitis might not have autoantibodies at presentation. Antibodies to a cytochrome P450 component of liver-kidney microsomal can be found in adult patients with chronic hepatitis C infection. Homologies in antigenic peptide epitopes between the hepatitis C virus and cytochrome P450 might explain this. Other, less-common autoantibodies include rheumatoid factor, antiparietal cell antibodies, and antithyroid antibodies. A Coombs-positive hemolytic anemia may be present.

DIAGNOSIS

Autoimmune hepatitis is a clinical diagnosis based on certain diagnostic criteria; no single test will make this diagnosis. Diagnostic criteria with scoring systems have been developed for adults and modified slightly for children, although these scoring systems were developed as research and not diagnostic tools. Important positive features include female gender, primary elevation in transaminases and not alkaline phosphatase, elevated γ-globulin levels, the presence of autoantibodies (most commonly antinuclear, smooth muscle, or liver-kidney microsome), and characteristic histologic findings (Fig. 362-1). Important negative features include the absence of viral markers (hepatitides B, C, D) of infection, absence of a history of drug or blood product exposure, and negligible alcohol consumption.

Common conditions that might lead to chronic hepatitis should be excluded (see Table 362-1). The differential diagnosis includes α_1-antitrypsin deficiency (see Chapter 357) and Wilson disease (see Chapter 357.2). The former disorder must be excluded by performing α_1-antitrypsin phenotyping and the latter by measuring serum ceruloplasmin and 24 hr urinary copper excretion and/or hepatic copper levels. Chronic hepatitis may occur in patients with inflammatory bowel disease, but liver dysfunction in such patients is more commonly caused by pericholangitis or sclerosing cholangitis. Celiac disease (see Chapter 338.2) is associated with liver disease that is akin to autoimmune hepatitis, and appropriate serologic testing should be performed, including assays for antitissue transglutaminase antibodies or antiendomysial antibodies. An ultrasonogram should be done to identify a choledochal cyst or other structural disorders of the biliary system. MR cholangiography may be very useful for screening for evidence of sclerosing cholangitis. An overlap syndrome with features of primary sclerosing cholangitis and autoimmune hepatitis is being increasingly recognized with wider application of MR cholangiography. Dilated or obliterated veins on ultrasonography suggest the possibility of the Budd-Chiari syndrome.

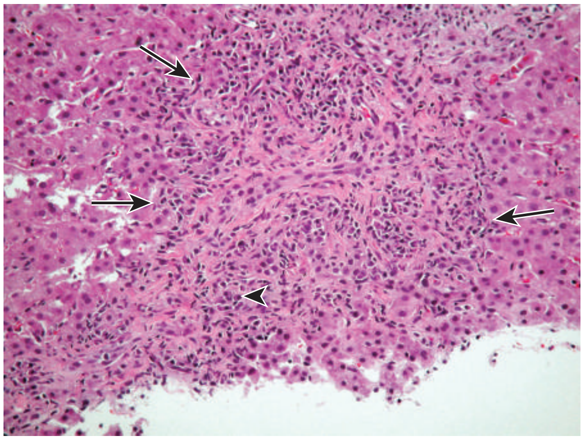

Figure 362-1 Autoimmune hepatitis. Liver biopsy showing fibrous expansion of the portal tracts with moderate portal lymphocytic infiltrates rich in plasma cells *(arrowhead)*. There is extensive interface hepatitis *(arrows)*. Original magnification ×20. *(Courtesy of Margret Magid, Mount Sinai School of Medicine.)*

TREATMENT

Prednisone, with or without azathioprine or 6-mercaptopurine, improves the clinical, biochemical, and histologic features in most patients with autoimmune hepatitis and prolongs survival in most patients with severe disease. The goal is to suppress or eliminate hepatic inflammation with minimal side effects. Prednisone at an initial dose of 1-2 mg/kg/24 hr is continued until aminotransferase values return to less than twice the upper limit of normal. The dose should then be lowered in 5 mg decrements over 2-4 mo until a maintenance dose of 0.1-0.3 mg/kg/24 hr is achieved. In patients who respond poorly, who experience severe side effects, or who cannot be maintained on low-dose steroids, azathioprine (1.5-2.0 mg/kg/24 hr, up to 100 mg/24 hr) can be added, with frequent monitoring for bone marrow suppression. Measurement of thiopurine methyltransferase activity should be done prior to beginning treatment with the thiopurine drugs azathioprine and 6-mercaptopurine. Patients with low activity (10% prevalence) or absent activity (prevalence 0.3%) are at risk for developing severe drug-induced myelotoxicity from accumulation of the unmetabolized drug. Measurement of the drug metabolites, 6-thioguanine nucleotide and 6-methylmercaptopurine, is useful in determining why a patient is not responding to a standard dose of a thiopurine drug and may help in avoiding myelosuppression and hepatotoxicity. Single-agent therapy with alternate-day corticosteroids should be used with great caution, although addition of azathioprine to alternate-day steroids can be an effective approach that minimizes corticosteroid-related toxicity. In patients with a mild and relatively asymptomatic presentation, some favor a lower starting dose of prednisone (10-20 mg) coupled with the simultaneous early administration of either 6-mercaptopurine (1.0-1.5 mg/kg/24 hr) or azathioprine (1.5-2.0 mg/kg/24 hr). Patients with primary sclerosing cholangitis/autoimmune hepatitis overlap syndrome respond similarly to immunosuppressive therapy. Precise diagnostic criteria for autoimmune disease in the setting of sclerosing cholangitis do not exist. Autoimmune markers and immunoglobulin levels are often elevated in children with sclerosing cholangitis and do not necessarily indicate a diagnosis of coincident autoimmune hepatitis. The choleretic agent, ursodeoxycholic acid, is often used in biliary tract disease, but trials in adults with primary sclerosing cholangitis have not shown efficacy, and patients have experienced toxicity at higher doses. There is a potential role for budesonide combined with azathioprine in treatment of noncirrhotic patients. Budesonide is a corticosteroid with high first-pass clearance by the liver and fewer systemic side effects including suppression of hypothalamic–pituitary axis. Cyclosporine, tacrolimus, mycophenolate mofetil, and sirolimus have been used in the management of cases refractory to standard therapy. Use of these agents should be reserved for practitioners with extensive experience in their administration, because the agents have a more restricted therapeutic to toxic ratio.

Histologic progress does not necessarily need to be assessed by sequential liver biopsies, although biochemical remission does not ensure histologic resolution. Follow-up liver biopsy is an important consideration in patients for whom consideration is given to discontinuing corticosteroid therapy. In patients with disappearance of symptoms and biochemical abnormalities and resolution of the necroinflammatory process on biopsy, an attempt at gradual discontinuation of medication is justified. There is a high rate of relapse after discontinuation of therapy. Relapse can require reinstitution of induction dosing of immunosuppression to control disease relapse.

PROGNOSIS

The initial response to therapy in autoimmune hepatitis is generally prompt, with a >75% rate of remission. Transaminases and bilirubin fall to near-normal levels, often in the 1st 1-3 mo. When present, abnormalities in serum albumin and prothrombin time respond over a longer period (3-9 mo). In patients meeting the criteria for tapering and then withdrawal of treatment (25-40% of children), 50% are weaned from all medication; in the other 50%, relapse occurs after a variable period. Relapse usually responds to retreatment. Many children will not meet the criteria for an attempt at discontinuation of immunosuppression and should be maintained on the smallest dose of prednisone that minimizes biochemical activity of the disease. A careful balance of the risks of continued immunosuppression and ongoing hepatitis must be continually evaluated. This requires continual screening for complications of medical therapy (monitoring of linear growth velocity, ophthalmologic examination, bone density measurement, blood pressure monitoring). Intermittent flares of hepatitis can occur and can necessitate recycling of prednisone therapy.

Some children have a relatively steroid-resistant form of hepatitis. More extensive evaluations of the etiology of their hepatitis should be undertaken, directed particularly at reassessing for the presence of either sclerosing cholangitis or Wilson disease. Nonadherence to medical therapy is one of the most common causes of “resistance” to medical therapy. Progression to cirrhosis can occur in autoimmune hepatitis despite a good response to drug therapy and prolongation of life. Corticosteroid therapy in fulminant autoimmune disease may be useful, although it should be administered with caution, given the predisposition of these patients to systemic bacterial and fungal infections.

Liver transplantation has been successful in patients with end-stage or fulminant liver disease associated with autoimmune hepatitis (see Chapter 368). Disease recurs after transplantation in approximately 30% of patients and is associated with increased concentrations of serum autoantibodies and interface hepatitis on liver biopsy.

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Chapter 363

Drug- and Toxin-Induced Liver Injury

Frederick J. Suchy

The liver is the main site of drug metabolism and is particularly susceptible to structural and functional injury after ingestion, parenteral administration, or inhalation of chemical agents, drugs, plant derivatives (home remedies), or environmental toxins. The possibility of drug use or toxin exposure at home or in the parents' workplace should be explored for every child with liver dysfunction. The clinical spectrum of illness can vary from asymptomatic biochemical abnormalities of liver function to fulminant failure. Liver injury may be the only clinical feature of an adverse drug reaction or may be accompanied by systemic manifestations and damage to other organs. In hospitalized patients, clinical and laboratory findings may be confused with the underlying illness. In a recent series after acetaminophen, antimicrobial (50%) and central nervous system agents (40%) were the most commonly implicated drug classes causing liver injury in children.

There is growing concern about environmental hepatotoxins that are insidious in their effects. Many environmental toxins including the plasticizers, biphenyl A and the phthalates, are ligands for nuclear receptors that transcriptionally activate the promoters of many genes involved in xenobiotic and lipid metabolism and may contribute to obesity and nonalcoholic fatty liver disease. Nonalcoholic fatty liver disease now affects 5-10% of all children in the United States and has the potential to evolve to cirrhosis and liver failure.

Hepatic metabolism of drugs and toxins is mediated by a sequence of enzymatic reactions that in large part transform hydrophobic, less-soluble molecules into more nontoxic, hydrophilic compounds that can be readily excreted in urine or bile (see Chapter 59). Relative liver size, liver blood flow, and extent of protein binding also influence drug metabolism. Phase 1 of the process involves enzymatic activation of the substrate to reactive intermediates containing a carboxyl, phenol, epoxide, or hydroxyl group. Mixed-function monooxygenase, cytochrome-*c* reductase, various hydrolases, and the cytochrome P450 (CYP) system are involved in this process. Nonspecific induction of these enzymatic pathways, which can occur during intercurrent viral infection, with starvation, and with administration of certain drugs such as anticonvulsants, can alter drug metabolism and increase the potential for hepatotoxicity. A single agent can be metabolized by >1 biochemical reaction. The reactive intermediates that are potentially damaging to the cell are enzymatically conjugated in phase 2 reactions with glucuronic acid, sulfate, acetate, glycine, or glutathione. Some drugs may be directly metabolized by these conjugating reactions without first undergoing phase 1 activation. Phase 3 is the energy-dependent excretion of drug metabolites and their conjugates by an array of membrane transporters in the liver and kidney such as the multidrug resistant protein 1.

Pathways for biotransformation are expressed early in the fetus and infant, but many phase 1 and phase 2 enzymes are immature, particularly in the 1st yr of life. CYP3A4 is the primary hepatic CYP expressed postnatally and metabolizes more than 75 commonly used therapeutic drugs and several environmental pollutants and procarcinogens. Hepatic CYP3A4 activity is poorly expressed in the fetus but increases after birth to reach 30% of adult values by 1 mo and 50% of adult values between 6 and 12 mo of age. CYP3A4 can be induced by a number of drugs, including phenytoin, phenobarbital, and rifampin. Enhanced production of toxic metabolites can overwhelm the capacity of phase 2 reactions. Conversely, numerous inhibitors of CYP3A4 from several different drug classes, such as erythromycin and cimetidine, can lead to toxic accumulations of CYP3A4 substrates. By contrast, although CYP2D6 is also developmentally regulated (maturation by 10 yr of age), its activity depends more on genetic polymorphisms than on sensitivity to inducers and inhibitors because more than 70 allelic variants of CYP2D6 significantly influence the metabolism of many drugs. Uridine diphosphateglucuronosyltransferase 1A6, a phase 2 enzyme that glucuronidates acetaminophen, is also absent in the human fetus, increases slightly in the neonate, but does not reach adult levels until sometime after 10 yr of age. Mechanisms for the uptake and excretion of organic ions can also be deficient early in life. Impaired drug metabolism via phase 1 and phase 2 reactions present in the 1st few mo of life is followed by a period of enhanced metabolism of many drugs in children through 10 yr of age compared with adults.

Genetic polymorphisms in genes encoding enzymes and transporters mediating phases 1, 2, and 3 reactions can also be associated with impaired drug metabolism and an increased risk of hepatotoxicity. Some cases of idiosyncratic hepatotoxicity can occur as a result of aberrations (polymorphisms) in phase 1 drug metabolism, producing intermediates of unusual hepatotoxic potential combined with developmental, acquired, or relative inefficiency of phase 2 conjugating reactions. Children may be more or less susceptible than adults to hepatotoxic reactions; liver injury after the use of the anesthetic halothane is rare in children, and acetaminophen toxicity is less common in infants than in adolescents, whereas most cases of fatal hepatotoxicity associated with sodium valproate use have been reported in children. Excessive or prolonged therapeutic administration of acetaminophen combined with reductions in caloric or protein intake can produce hepatotoxicity in children. In this setting, acetaminophen metabolism may be impaired by reduced synthesis of sulfated and glucuronated metabolites and reduced stores of glutathione. Immaturity of hepatic drug metabolic pathways can prevent degradation of a

toxic agent; under other circumstances, the same immaturity might limit the formation of toxic metabolites. Severe sodium valproate hepatotoxicity is often associated with an underlying inherited mitochondrial disorder.

Chemical hepatotoxicity can be predictable or idiosyncratic. Predictable hepatotoxicity implies a high incidence of hepatic injury in exposed persons, with dose dependence. It is understandable that only a few drugs in clinical use fall into this category. These agents might damage the hepatocyte directly through alteration of membrane lipids (peroxidation) or through denaturation of proteins; such agents include carbon tetrachloride and trichloroethylene. Indirect injury can occur through interference with metabolic pathways essential for cell integrity or through distortion of cellular constituents by covalent binding of a reactive metabolite; examples include the liver injury produced by acetaminophen or by antimetabolites such as methotrexate or 6-mercaptopurine.

Idiosyncratic hepatotoxicity is uncommon and unpredictable but accounts for the majority of adverse reactions. In contrast to previous dogma that idiosyncratic reactions are independent of dose, there is new information that higher doses of drugs metabolized in the liver have a greater risk for hepatotoxicity.

Idiosyncratic drug reactions in certain patients can reflect aberrant pathways for drug metabolism, possibly related to genetic polymorphisms, with production of toxic intermediates (isoniazid and sodium valproate can cause liver damage through this mechanism). Duration of drug use before liver injury varies (weeks to ≥1 yr) and the response to reexposure may be delayed.

An idiosyncratic reaction can also be immunologically mediated as a result of prior sensitization (hypersensitivity); extrahepatic manifestations of hypersensitivity can include fever, rash, arthralgia, and eosinophilia. Duration of exposure before reaction is generally 1-4 wk, with prompt recurrence of injury on re-exposure. Studies indicate that arene oxides, generated through oxidative (CYP) metabolism of aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine), can initiate the pathogenesis of some hypersensitivity reactions. Arene oxides, formed in vivo, can bind to cellular macromolecules, thus perturbing cell function and possibly initiating immunologic mechanisms of liver injury.

Although the generation of chemically reactive metabolites has received great attention in the pathogenesis of hepatoxicity, increasing evidence now exists for the multifactorial nature of the process, in particular the role played by the host immune system. Activation of liver nonparenchymal Kupffer cells and infiltration by neutrophils perpetuate toxic injury by many drugs by release of reactive oxygen and nitrogen species as well as cytokines. Stellate cells can also be activated, potentially leading to hepatic fibrosis and cirrhosis.

The pathologic spectrum of drug-induced liver disease is extremely wide, is rarely specific, and can mimic other liver diseases (Table 363-1). Predictable hepatotoxins, such as acetaminophen, produce centrilobular necrosis of hepatocytes. Steatosis is an important feature of tetracycline (microvesicular) and ethanol (macrovesicular) toxicities. A cholestatic hepatitis can be observed, with injury caused by erythromycin estolate and chlorpromazine. Cholestasis without inflammation may be a toxic effect of estrogens and anabolic steroids. Use of oral contraceptives and androgens has also been associated with benign and malignant liver tumors. Some idiosyncratic drug reactions can produce mixed patterns of injury, with diffuse cholestasis and cell necrosis. Chronic hepatitis has been associated with the use of methyldopa and nitrofurantoin.

Some herbal supplements are associated with hepatic injury or even liver failure (Table 363-2) related to their intrinsic toxicity or because of contamination with fungal toxins, pesticides, or heavy metals. The mechanism of liver injury due to these agents is unknown in the majority of cases.

Clinical manifestations can be mild and nonspecific, such as fever and malaise. Fever, rash, and arthralgia may be prominent in cases of hypersensitivity. In ill hospitalized patients, the signs and symptoms of hepatic drug toxicity may be difficult to separate from the underlying illness. The differential diagnosis should include acute and chronic viral hepatitis, biliary tract disease, septicemia, ischemic and hypoxic liver injury, malignant infiltration, and inherited metabolic liver disease.

Table 363-1 Patterns of Hepatic Drug Injury

DISEASE	DRUG
Centrilobular necrosis	Acetaminophen Halothane
Microvesicular steatosis	Valproic acid
Acute hepatitis	Isoniazid
General hypersensitivity	Sulfonamides Phenytoin
Fibrosis	Methotrexate
Cholestasis	Chlorpromazine Erythromycin Estrogens
Sinusoidal obstruction syndrome (venoocclusive disease)	Irradiation plus busulfan Cyclophosphamide
Portal and hepatic vein thrombosis	Estrogens Androgens
Biliary sludge	Ceftriaxone
Hepatic adenoma or hepatocellular carcinoma	Oral contraceptives Anabolic steroids

Table 363-2 Potentially Hepatotoxic Herbal or Dietary Supplements

Celandine
Chaparral (creosote bush, greasewood, *Larrea tridentata*)
Chinese herbs
Comfrey leaves (pyrrolizidine alkaloids)
Germander extracts *(Teucrium chamaedrys)*
Kava (*Kava kava*, awa, kew)
LipoKinetix (phenylpropanolamine, sodium usinate, diiodothyronine, yohimbine, caffeine)
Ma huang *(Ephedra)*
Mushroom *(Amanita phalloides, Galerina)*
Senecio
Valerian with skullcap

The laboratory features of drug- or toxin-related liver disease are extremely variable. Hepatocyte damage can lead to elevations of serum aminotransferase activities and serum bilirubin levels and to impaired synthetic function as evidenced by decreased serum coagulation factors and albumin. Hyperammonemia can occur with liver failure or with selective inhibition of the urea cycle (sodium valproate). Toxicologic screening of blood and urine specimens can aid in the detecting drug or toxin exposure. Percutaneous liver biopsy may be necessary to distinguish drug injury from complications of an underlying disorder or from intercurrent infection.

Slight elevation of serum aminotransferase activities (generally <2-3 times normal) can occur during therapy with drugs, particularly anticonvulsants, capable of inducing microsomal pathways for drug metabolism. Liver biopsy reveals proliferation of smooth endoplasmic reticulum but no significant liver injury. Liver test abnormalities often resolve with continued drug therapy.

TREATMENT

Treatment of drug- or toxin-related liver injury is mainly supportive. Contact with the offending agent should be avoided. Corticosteroids might have a role in immune-mediated disease. *N*-Acetylcysteine therapy, by stimulating glutathione synthesis, is effective in preventing or attenuating hepatotoxicity when administered within 16 hr after an acute overdose of acetaminophen and appears to improve survival in

patients with severe liver injury even up to 36 hr after ingestion (see Chapter 63). Intravenous L-carnitine may be of value in treating valproic acid–induced hepatotoxicity. Orthotopic liver transplantation may be required for treatment of drug- or toxin-induced hepatic failure.

PROGNOSIS

The prognosis of drug- or toxin-induced liver injury depends on its type and severity. Injury is usually completely reversible when the hepatotoxic factor is withdrawn. The mortality of submassive hepatic necrosis with fulminant liver failure can, however, exceed 50%. Hyperbilirubinemia, coagulopathy, and elevated serum creatinine are associated with an increased risk of death or need for liver transplantation. With continued use of certain drugs, such as methotrexate, effects of hepatotoxicity can proceed insidiously to cirrhosis, even with normal or near normal liver tests. Neoplasia can follow long-term androgen therapy. Rechallenge with a drug suspected of having caused previous liver injury is rarely justified and can result in fatal hepatic necrosis.

PREVENTION

The prevention of drug-induced liver injury remains a challenge. Monitoring of liver biochemical tests may be useful in some cases, but it can prove difficult to sustain for agents used for many years. Such testing may be particularly important in patients with pre-existing liver disease. For drugs with particular hepatotoxic potential, even if episodes are infrequent in children, such as with the use of isoniazid, patients should be advised to immediately stop the medication with onset of nausea, vomiting, abdominal pain, and fatigue until liver damage is excluded. Obvious symptoms of liver disease such as jaundice and dark urine can lag behind severe hepatocellular injury. Monitoring for toxic metabolites and genotyping can be effective in preventing severe toxicity with the use of azathioprine. Advances in pharmacogenomics, such as the use of gene chips to detect variants in some of the CYP enzymes, hold promise of a personalized approach to prevent hepatotoxicity.

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Chapter 364
Fulminant Hepatic Failure

Frederick J. Suchy

Fulminant hepatic failure (acute liver failure) is a clinical syndrome resulting from massive necrosis of hepatocytes or from severe functional impairment of hepatocytes. Synthetic, excretory, and detoxifying functions of the liver are all severely impaired. In adults, hepatic encephalopathy has been an essential diagnostic feature. This narrow definition may be problematic because early hepatic encephalopathy can be difficult to detect in infants and children. The currently accepted definition in children includes biochemical evidence of acute liver injury (usually <8 wk duration); no evidence of chronic liver disease; and hepatic-based coagulopathy defined as a prothrombin time (PT) >15 sec or international normalized ratio (INR) >1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy, or a PT >20 sec or INR >2 regardless of the presence of clinical hepatic encephalopathy. Liver failure in the perinatal period can be associated with prenatal liver injury and even cirrhosis. Examples include neonatal iron storage (hemochromatosis) disease, tyrosinemia, and some cases of congenital viral infection. Liver disease may be noticed at birth or after several days of apparent well-being. Fulminant Wilson disease also occurs in older children who were previously asymptomatic but, by definition, have preexisting liver disease. In some cases of liver failure, particularly in the idiopathic form of acute hepatic failure, the onset of encephalopathy occurs later, from 8-28 wk after the onset of jaundice.

ETIOLOGY

Fulminant hepatic failure can be a complication of viral hepatitis (A, B, D, E). An unusually high risk of fulminant hepatic failure occurs in young people who have combined infections with the hepatitis B virus (HBV) and hepatitis D. Mutations in the precore and/or promoter region of HBV DNA are associated with fulminant and severe hepatitis. HBV is also responsible for some cases of fulminant liver failure in the absence of serologic markers of HBV infection but with HBV DNA found in the liver. Hepatitides C and E viruses are uncommon causes of fulminant hepatic failure in the United States. Patients with chronic hepatitis C are at risk if they have superinfection with hepatitis A virus. Epstein-Barr virus, herpes simplex virus, adenovirus, enteroviruses, cytomegalovirus, parvovirus B19, human herpesvirus-6, and varicella-zoster infections can also produce fulminant hepatitis in children.

Fulminant hepatic failure can also be caused by autoimmune hepatitis in approximately 5% of cases. Patients have a positive autoimmune marker (e.g., antinuclear antibody, anti–smooth muscle antibody, liver-kidney microsomal antibody, or soluble liver antigen) and possibly an elevated serum immunoglobulin G level. Liver histology, if a biopsy can be safely done, might support the diagnosis.

Acute liver failure is a common feature of hemophagocytic lymphohistiocytosis caused by several gene defects, infections by mostly viruses of the herpes group, and a variety of other conditions including organ transplantation and malignancies. Impaired function of natural killer cells and cytotoxic T-lymphocyte cells with uncontrolled hemophagocytosis and cytokine overproduction is characteristic for genetic and acquired forms of hemophagocytic lymphohistiocytosis. Biochemical markers include elevated ferritin and triglycerides and low fibrinogen.

An idiopathic form of fulminant hepatic failure accounts for 40-50% of cases in children. The disease occurs sporadically and usually without the risk factors for common causes of viral hepatitis. It is likely that the etiology of these cases is heterogeneous, including unidentified or variant viruses, excessive immune activation, and undiagnosed metabolic disorders.

Various hepatotoxic drugs and chemicals can also cause fulminant hepatic failure. Predictable liver injury can occur after exposure to carbon tetrachloride or *Amanita phalloides* mushroom or after acetaminophen overdose. Acetaminophen is the most common etiology of acute hepatic failure in children and adolescents in the United States and England. In addition to the acute intentional ingestion of a massive dose, a therapeutic misadventure leading to severe liver injury can also occur in ill children given doses of acetaminophen exceeding weight-based recommendations for many days. Such patients can have reduced stores of glutathione after a prolonged illness and a period of poor nutrition. Idiosyncratic damage can follow the use of drugs such as halothane, isoniazid, or sodium valproate. Herbal supplements are additional causes of hepatic failure (see Table 363-2).

Ischemia and hypoxia resulting from hepatic vascular occlusion, severe heart failure, cyanotic congenital heart disease, or circulatory shock can produce liver failure. Metabolic disorders associated with hepatic failure include Wilson disease, acute fatty liver of pregnancy, galactosemia, hereditary tyrosinemia, hereditary fructose intolerance, neonatal iron storage disease, defects in β-oxidation of fatty acids, and deficiencies of mitochondrial electron transport particularly mitochondrial DNA depletion disorders.

PATHOLOGY

Liver biopsy usually reveals patchy or confluent massive necrosis of hepatocytes. Multilobular or bridging necrosis can be associated with collapse of the reticulin framework of the liver. There may be little or no regeneration of hepatocytes. A zonal pattern of necrosis may be observed with certain insults. (Centrilobular damage is associated with acetaminophen hepatotoxicity or with circulatory shock.) Evidence of severe hepatocyte dysfunction rather than cell necrosis is occasionally

the predominant histologic finding (microvesicular fatty infiltrate of hepatocytes is observed in Reye syndrome, β-oxidation defects, and tetracycline toxicity).

PATHOGENESIS

The mechanisms that lead to fulminant hepatic failure are poorly understood. It is unknown why only approximately 1-2% of patients with viral hepatitis experience liver failure. Massive destruction of hepatocytes might represent both a direct cytotoxic effect of the virus and an immune response to the viral antigens. One-third to one-half of patients with HBV-induced liver failure become negative for serum hepatitis B surface antigen within a few days of presentation and often have no detectable HBV antigen or HBV DNA in serum. These findings suggest a hyperimmune response to the virus that underlies the massive liver necrosis. Formation of hepatotoxic metabolites that bind covalently to macromolecular cell constituents is involved in the liver injury produced by drugs such as acetaminophen and isoniazid; fulminant hepatic failure can follow depletion of intracellular substrates involved in detoxification, particularly glutathione. Whatever the initial cause of hepatocyte injury, various factors can contribute to the pathogenesis of liver failure, including impaired hepatocyte regeneration, altered parenchymal perfusion, endotoxemia, and decreased hepatic reticuloendothelial function.

The pathogenesis of hepatic encephalopathy can relate to increased serum levels of ammonia, false neurotransmitters, amines, increased γ-aminobutyric acid receptor activity, or increased circulating levels of endogenous benzodiazepine-like compounds. Decreased hepatic clearance of these substances can produce marked central nervous system dysfunction.

CLINICAL MANIFESTATIONS

Fulminant hepatic failure can be the presenting feature of liver disease or it can complicate previously known liver disease (acute-on-chronic liver failure). A history of developmental delay and/or neuromuscular dysfunction can indicate an underlying mitochondrial or β-oxidation defect. A child with fulminant hepatic failure has usually been previously healthy and most often has no risk factors for liver disease such as exposure to toxins or blood products. Progressive jaundice, fetor hepaticus, fever, anorexia, vomiting, and abdominal pain are common. A rapid decrease in liver size without clinical improvement is an ominous sign. A hemorrhagic diathesis and ascites can develop.

Patients should be closely observed for hepatic encephalopathy, which is initially characterized by minor disturbances of consciousness or motor function. Irritability, poor feeding, and a change in sleep rhythm may be the only findings in infants; asterixis may be demonstrable in older children. Patients are often somnolent, confused, or combative on arousal and can eventually become responsive only to painful stimuli. Patients can rapidly progress to deeper stages of coma in which extensor responses and decerebrate and decorticate posturing appear. Respirations are usually increased early, but respiratory failure can occur in stage IV coma (Table 364-1).

LABORATORY FINDINGS

Serum direct and indirect bilirubin levels and serum aminotransferase activities may be markedly elevated. Serum aminotransferase activities do not correlate well with the severity of the illness and can actually decrease as a patient deteriorates. The blood ammonia concentration is usually increased, but hepatic coma can occur in patients with a normal blood ammonia level. PT and the INR are prolonged and often do not improve after parenteral administration of vitamin K. Hypoglycemia can occur, particularly in infants. Hypokalemia, hyponatremia, metabolic acidosis, or respiratory alkalosis can develop.

TREATMENT

Specific therapies for identifiable causes of acute liver failure include *N*-acetylcysteine (acetaminophen), acyclovir (herpes simplex virus), penicillin (*Amanita* mushrooms), nucleos(t)ide analogs such as entecavir or lamivudine (HBV), and prednisone (autoimmune hepatitis). Management of other types of fulminant hepatic failure is supportive. No therapy is known to reverse hepatocyte injury or to promote hepatic regeneration.

An infant or child with acute hepatic failure should be cared for in an institution able to perform a liver transplantation if necessary and managed in an intensive care unit with continuous monitoring of vital functions. Endotracheal intubation may be required to prevent aspiration, to reduce cerebral edema by hyperventilation, and to facilitate pulmonary toilet. Mechanical ventilation and supplemental oxygen are often necessary in advanced coma. Sedatives should be avoided unless needed in the intubated patient because these agents can aggravate or precipitate encephalopathy. Opiates may be better tolerated than benzodiazepines. Prophylactic use of proton pump inhibitors should be considered because of the high risk of gastrointestinal bleeding.

Hypovolemia should be avoided and treated with cautious infusions of isotonic fluids and blood products. Renal dysfunction can result from dehydration, acute tubular necrosis, or functional renal failure (hepatorenal syndrome). Electrolyte and glucose solutions should be administered intravenously to maintain urine output, to correct or prevent hypoglycemia, and to maintain normal serum potassium concentrations. Hyponatremia is common and should be avoided, but it is usually dilutional and not a result of sodium depletion. Parenteral supplementation with calcium, phosphorus, and magnesium may be required. Hypophosphatemia, probably a reflection of liver regeneration, and early phosphorus administration are associated with a better prognosis in acute liver failure, whereas hyperphosphatemia predicts a failure of spontaneous recovery.

Coagulopathy should be treated with parenteral administration of vitamin K and can require infusion of fresh-frozen plasma, cryoprecipitate, and platelets to treat clinically significant bleeding; disseminated intravascular coagulation can also occur. Plasmapheresis can permit temporary correction of the bleeding diathesis without resulting in volume overload. Recombinant factor VIIa has been used for transient correction of coagulopathy refractory to fresh frozen plasma infusions and can facilitate the performance of invasive procedures

Table 364-1 Stages of Hepatic Encephalopathy

	STAGES			
	I	II	III	IV
Symptoms	Periods of lethargy, euphoria; reversal of day–night sleeping; may be alert	Drowsiness, inappropriate behavior, agitation, wide mood swings, disorientation	Stupor but arousable, confused, incoherent speech	Coma IVa responds to noxious stimuli IVb no response
Signs	Trouble drawing figures, performing mental tasks	Asterixis, fetor hepaticus, incontinence	Asterixis, hyperreflexia, extensor reflexes, rigidity	Areflexia, no asterixis, flaccidity
Electroencephalogram	Normal	Generalized slowing, q waves	Markedly abnormal, triphasic waves	Markedly abnormal bilateral slowing, d waves, electric-cortical silence

such as placement of a central line or an intracranial pressure monitor. Continuous hemofiltration is useful for managing fluid overload and acute renal failure.

Patients should be monitored closely for infection, including sepsis, pneumonia, peritonitis, and urinary tract infections. At least 50% of patients experience serious infection. Gram-positive organisms *(Staphylococcus aureus, Staphylococcus epidermidis)* are the most common pathogens, but Gram-negative and fungal infections are also observed.

Gastrointestinal hemorrhage, infection, constipation, sedatives, electrolyte imbalance, and hypovolemia can precipitate encephalopathy and should be identified and corrected. Protein intake should be initially restricted or eliminated, depending on the degree of encephalopathy. The gut should be purged with several enemas. Lactulose should be given every 2-4 hr orally or by nasogastric tube in doses (10-50 mL) sufficient to cause diarrhea. The dose is then adjusted to produce several acidic, loose bowel movements daily. Lactulose syrup diluted with 1-3 volumes of water can also be given as a retention enema every 6 hr. Lactulose, a nonabsorbable disaccharide, is metabolized to organic acids by colonic bacteria; it probably lowers blood ammonia levels through decreasing microbial ammonia production and through trapping of ammonia in acidic intestinal contents. Oral or rectal administration of a nonabsorbable antibiotic such as rifaximin or neomycin can reduce enteric bacteria responsible for ammonia production. Oral antibiotics may be more effective than lactulose in lowering serum ammonia levels. In a recent clinical trial, *N*-acetylcysteine was not effective in improving the outcome of patients with acute liver failure not associated with acetaminophen.

Cerebral edema is an extremely serious complication of hepatic encephalopathy that responds poorly to measures such as corticosteroid administration and osmotic diuresis. Monitoring intracranial pressure can be useful in preventing severe cerebral edema, in maintaining cerebral perfusion pressure, and in establishing the suitability of a patient for liver transplantation. Controlled trials have shown a worsened outcome of fulminant hepatic failure in patients treated with corticosteroids.

Temporary liver support continues to be evaluated as a bridge for the patient with liver failure to liver transplantation or regeneration. Nonbiologic systems, essentially a form of liver dialysis with an albumin-containing dialysate, and biologic liver support devices that involve perfusion of the patient's blood through a cartridge containing liver cell lines or porcine hepatocytes can remove some toxins, improve serum biochemical abnormalities, and, in some cases, improve neurologic function, but there has been little evidence of improved survival, and few children have been treated.

Orthotopic liver transplantation can be lifesaving in patients who reach advanced stages (III, IV) of hepatic coma. Reduced-size allografts and living donor transplantation have been important advances in the treatment of infants with hepatic failure. Partial auxiliary orthotopic or heterotopic liver transplantation is successful in a small number of children, and in some cases it has allowed regeneration of the native liver and eventual withdrawal of immunosuppression. Orthotopic liver transplantation should not be done in patients with liver failure and neuromuscular dysfunction secondary to a mitochondrial disorder because progressive neurologic deterioration is likely to continue after transplantation.

PROGNOSIS

Children with acute hepatic failure fare better than adults. Improved survival can be attributed to careful intensive care and if necessary liver transplantation. In the largest prospective study from the Pediatric Acute Liver Failure Study Group, 709 children were assessed at 21 days: 50.3% of patients survived with supportive care alone, 36.2% survived after liver transplantation, and 13.4% died. A scoring system based on peak values of total serum bilirubin, PT, and plasma ammonia concentration predicted transplant-free survival. Prognosis varies considerably with the cause of liver failure and stage of hepatic encephalopathy. Survival rates with supportive care may be as high as 90% in acetaminophen overdose and with fulminant hepatitis A. By contrast, spontaneous recovery can be expected in only approximately 40% of patients with liver failure caused by the idiopathic form of acute liver failure or an acute onset of Wilson disease. In patients who progress to stage IV coma (see Table 364-1), the prognosis is extremely poor. Brainstem herniation is the most common cause of death. Major complications such as sepsis, severe hemorrhage, or renal failure increase the mortality. The prognosis is particularly poor in patients with liver necrosis and multiorgan failure.

Age <1 yr, stage 4 encephalopathy, an INR >4, and the need for dialysis before transplantation are associated with increased mortality. Pretransplantation serum bilirubin concentration or the height of hepatic enzymes is not predictive of posttransplantation survival. A plasma ammonia concentration >200 μmol/L is associated with a 5-fold increased risk of death.

Children with acute hepatic failure are more likely to die while on the waiting list compared to children with other diagnoses. Owing to the severity of their illness, the 6 mo post–liver transplantation survival of approximately 75% in most studies is significantly lower than the 90% achieved in children with chronic liver disease. Patients who recover from fulminant hepatic failure with only supportive care do not usually develop cirrhosis or chronic liver disease. Aplastic anemia occurs in approximately 10% of children with the idiopathic form of fulminant hepatic failure and is often fatal.

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Chapter 365

Cystic Diseases of the Biliary Tract and Liver

Frederick J. Suchy

Cystic lesions of liver may be initially recognized during infancy and childhood (Table 365-1). Hepatic fibrosis can also occur as part of an associated developmental defect (Table 365-2). Cystic renal disease is usually associated and often determines the clinical presentation and prognosis. Virtually all proteins encoded by genes mutated in combined cystic diseases of the liver and kidney are at least partially localized to primary cilia in renal tubular cells and cholangiocytes.

CHOLEDOCHAL CYSTS

Choledochal cysts are congenital dilatations of the common bile duct that can cause progressive biliary obstruction and biliary cirrhosis. Cylindrical (fusiform) and spherical (saccular) cysts of the extrahepatic ducts are the most common types. Segmental or diffuse dilation can be observed. A diverticulum of the common bile duct or dilation of the intraduodenal portion of the common duct *(choledochocele)* is a variant. Cystic dilation of the intrahepatic bile ducts may be associated with a choledochal cyst or Caroli disease.

The pathogenesis of choledochal cysts remains uncertain. Some reports suggest that junction of the common bile duct and the pancreatic duct before their entry into the sphincter of Oddi might allow reflux of pancreatic enzymes into the common bile duct, causing inflammation, localized weakness, and dilation of the duct. It also has been proposed that a distal congenital stenotic segment of the biliary tree leads to increased intraluminal pressure and proximal biliary dilation. Other possibilities are that choledochal cysts represent malformations of the common duct or that they occur as part of the spectrum of an infectious disease that includes neonatal hepatitis and biliary

Table 365-1 Renal Disorders Associated with Fibropolycystic Liver Diseases

FIBROPOLYCYSTIC LIVER DISEASE	ASSOCIATED RENAL DISORDER
Congenital hepatic fibrosis (CHF)	Autosomal-recessive polycystic kidney disease* Autosomal-dominant polycystic kidney disease Cystic renal dysplasia Nephronophthisis None
Caroli syndrome (CS)	Autosomal-recessive polycystic kidney disease* Autosomal-dominant polycystic kidney disease None
Caroli disease	Autosomal-recessive polycystic kidney disease
von Meyenburg complexes (isolated)	?
von Meyenburg complexes with CHF or CS	Autosomal-recessive polycystic kidney disease
von Meyenburg complexes with polycystic liver disease	Autosomal-dominant polycystic kidney disease
Polycystic liver disease	Autosomal-dominant polycystic kidney disease*
	? None

*Most common associated disorders.

From Suchy FJ, Sokol RJ, Balistreri WF, editors: Liver disease in children, *ed 3, New York, 2007, Cambridge University Press, p. 27.*

Table 365-2 Syndromes Associated with Congenital Hepatic Fibrosis

SYNDROME	FEATURES
Jeune syndrome	Asphyxiating thoracic dystrophy, with cystic renal tubular dysplasia and congenital hepatic fibrosis (15q13)
Joubert syndrome	Oculo-encephalo-hepato-renal *(AH11, HPHP1)*
COACH syndrome	Cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis *(MKS3, CC2D2A, RPGRIP1L)*
Meckel syndrome type 1	Cystic renal dysplasia abnormal bile duct development with fibrosis, posterior encephalocele, and polydactyly (13q13, 17a21, 8q24)
Carbohydrate-deficient glycoprotein syndrome type 1b	Phosphomannose isomerase 1 deficiency (PMI)
Ivemark syndrome type 2	Autosomal-recessive renal-hepatic-pancreatic dysplasia
Miscellaneous syndromes	Intestinal lymphangiectasia, enterocolitis cystic Short rib (Beemer-Langer) syndrome Osteochondrodysplasia

From Suchy FJ, Sokol RJ, Balistreri WF, editors: Liver disease in children, *ed 3, New York, 2007, Cambridge University Press, p. 931.*

atresia. Consistent with this theory, reovirus RNA has been detected in liver and biliary tissues of some infants with choledochal cysts.

Approximately 75% of cases appear during childhood. The infant typically presents with cholestatic jaundice; severe liver dysfunction including ascites and coagulopathy can rapidly evolve if biliary obstruction is not relieved. An abdominal mass is rarely palpable. In an older child, the **classic triad** of abdominal pain, jaundice, and mass occurs in <33% of patients. Features of acute cholangitis (fever, right upper quadrant tenderness, jaundice, leukocytosis) may be present. The diagnosis is made by ultrasonography; choledochal cysts have been identified prenatally using this technique. Magnetic resonance cholangiography is useful in the preoperative assessment of choledochal cyst anatomy.

The **treatment of choice** is primary excision of the cyst and a Roux-en-Y choledochojejunostomy. Simple drainage into the small bowel is less satisfactory owing to a risk of development of carcinoma in the residual cystic tissue. The postoperative course can be complicated by recurrent cholangitis or stricture at the anastomotic site.

Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease (ARPKD) manifests predominantly in childhood (see Chapter 521.2). Bilateral enlargement of the kidneys is caused by a generalized dilation of the collecting tubules. The disorder is invariably associated with congenital hepatic fibrosis and various degrees of biliary ductal ectasia that are discussed in detail later.

The polycystic kidney and hepatic disease 1 *(PKHD1)* gene, mutated in ARPKD, encodes a protein that is called fibrocystin/polyductin, which is localized to cilia on the apical domain of renal collecting cells and cholangiocytes. The primary defect in ARPKD may be ciliary dysfunction related to the abnormality in this protein. Fibrocystin/polyductin appears to have a role in the regulation of cellular adhesion, repulsion, and proliferation and/or the regulation and maintenance of renal collecting tubules and bile ducts, but its exact role in normal and cystic epithelia remains unknown. Kidney and liver disease are independent and variability in severity and not explainable by type of *PKHD1* mutation. Phenotypic variability among affected siblings suggests importance of modifier genes as well as possibly environmental influences.

In ARPKD, the cysts arise as ectatic expansions of the collecting tubules and bile ducts that remain in continuity with their structures of origin. ARPKD normally presents in early life, often shortly after birth, and is generally more severe than autosomal dominant polycystic kidney disease (ADPKD). Fetal ultrasound may visualize large echogenic kidneys, also described as "bright," with low or absent amniotic fluid (oligohydramnios). However, in many instances the features of ARPKD are not visualized on sonogram until the 3rd trimester or after birth.

Patients with ARPKD can die in the perinatal period owing to renal failure or lung dysgenesis. The kidneys in these patients are usually markedly enlarged and dysfunctional. Respiratory failure can result from compression of the chest by grossly enlarged kidneys, from fluid retention, or from concomitant pulmonary hypoplasia (see Chapter 515.2). The clinical pathologic findings within a family tend to breed true, although there has been some variability in the severity of the disease and the time for presentation within the same family. In patients surviving infancy because of a milder renal phenotype, liver disease may be a prominent part of the disorder. The liver disease in ARPKD is related to congenital malformation of the liver with varying degrees of periportal fibrosis, bile ductular hyperplasia, ectasia, and dysgenesis. Initial symptoms are liver related in approximately 26% of patients. This can manifest clinically as variable, cystic dilation of the intrahepatic biliary tree with congenital hepatic fibrosis. Congenital hepatic fibrosis and Caroli disease likely result from an abnormality in remodeling of the embryonic ductal plate of the liver. *Ductal plate malformation* refers to the persistence of excess embryonic bile duct structures in the portal tracts.

Variable abnormalities of bile ducts (irregular dilation, proliferation, cysts) and portal fibrosis can also be associated with Meckel syndrome,

trisomy 17-18, tuberous sclerosis, and asphyxiating thoracic dystrophy (see Table 365-2).

Cystic Dilation of the Intrahepatic Bile Ducts (Caroli Disease)

Congenital saccular dilation can affect several segments of the intrahepatic bile ducts; the dilated ducts are lined by cuboidal epithelium and are in continuity with the main duct system, which is usually normal. Choledochal cysts have also been associated with Caroli disease. Bile duct dilation leads to stagnation of bile and formation of biliary sludge and intraductal lithiasis.

There is a marked predisposition to ascending cholangitis which may be exacerbated by calculus formation within the abnormal bile ducts.

Affected patients usually experience symptoms of acute cholangitis as children or young adults. Fever, abdominal pain, mild jaundice, and pruritus occur, and a slightly enlarged, tender liver is palpable. Elevated alkaline phosphatase activity, direct-reacting bilirubin levels, and leukocytosis may be observed during episodes of acute infection. In patients with Caroli disease, clinical features may be the result of a combination of recurring bouts of cholangitis, reflecting the intrahepatic ductal abnormalities and portal hypertensive bleeding resulting from hepatic fibrosis. Ultrasonography shows the dilated intrahepatic ducts, but definitive diagnosis and extent of disease must be determined by percutaneous transhepatic, endoscopic, or magnetic resonance cholangiography.

Cholangitis and sepsis are treated with appropriate antibiotics. Calculi can require surgery. Partial hepatectomy may be curative in rare cases in which cystic disease is confined to a single lobe. The prognosis is otherwise guarded, largely owing to difficulties in controlling cholangitis and biliary lithiasis and to a significant risk for developing cholangiocarcinoma. ARPKD patients with recurrent cholangitis or complications of portal hypertension may require combined liver-kidney transplant.

Congenital Hepatic Fibrosis

Congenital hepatic fibrosis is usually associated with ARPKD and is characterized pathologically by diffuse periportal and perilobular fibrosis in broad bands that contain distorted bile duct–like structures and that often compresses or incorporate central or sublobular veins (see Table 365-2). Irregularly shaped islands of liver parenchyma contain normal-appearing hepatocytes. Caroli disease and choledochal cysts are associated. Most patients have renal disease, mostly autosomal recessive polycystic renal disease and rarely nephronophthisis. Congenital hepatic fibrosis also occurs as part of the **COACH syndrome** (*c*erebellar vermis hypoplasia, *o*ligophrenia, congenital *a*taxia, *c*oloboma, and *h*epatic fibrosis). Congenital hepatic fibrosis has been described in children with a congenital disorder of glycosylation caused by mutations in the gene encoding phosphomannose isomerase (see Chapter 87.6).

Several different forms of congenital hepatic fibrosis have been defined clinically: portal hypertensive (most common) cholangitic, mixed, and latent. The disorder usually has its onset in childhood, with hepatosplenomegaly or with bleeding secondary to portal hypertension. In a recent study, splenomegaly, as a marker for portal hypertension, developed early in life and was present in 60% of children younger than 5 yr of age.

Cholangitis can occur in patients, as these patients have abnormal biliary tracts even without Caroli disease. Hepatocellular function is usually well preserved. Serum aminotransferase activities and bilirubin levels are usually normal in the absence of cholangitis and choledocholithiasis; serum alkaline phosphatase activity may be slightly elevated. The serum albumin level and prothrombin time are normal. Liver biopsy is rarely required for diagnosis, particularly in patients with obvious real disease.

Treatment of this disorder should focus on control of bleeding from esophageal varices and aggressive antibiotic treatment of cholangitis. Infrequent mild bleeding episodes may be managed by endoscopic sclerotherapy or band ligation of the varices. After more-severe hemorrhage, portacaval anastomosis can relieve portal hypertension. The prognosis may be greatly improved by a shunting procedure, but survival in some patients may be limited by renal failure.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

ADPKD (see Chapter 521.3), a common inherited disease, affects 1 in 1,000 live births. It is characterized by progressive renal cyst development and cyst enlargement and an array of extrarenal manifestations. There is a high degree of intrafamilial and interfamilial variability in the clinical expression of the disease.

ADPKD is caused by mutation in 1 of 2 genes, *PKD1* or *PKD2*, which account for 85-90% and 10-15% of cases, respectively. The proteins encoded by these genes, polycystin-1 and polycystin-2, are expressed in renal tubule cells and in cholangiocytes. Polycystin-1 functions as a mechanosensor in cilia, detecting the movement of fluid through tubules and transmitting the signal through polycystin-2, which acts as a calcium channel.

Dilated, noncommunicating cysts are most commonly observed. Other hepatic lesions are rarely associated with ADPKD, including the ductal plate malformation, congenital hepatic fibrosis, and biliary microhamartomas (the von Meyenburg complexes). Approximately 50% of patients with renal failure have demonstrable hepatic cysts that are derived from, but not in continuity with, the biliary tract. The hepatic cysts increase with age. A recent imaging study showed that prevalence of hepatic cysts was 58% in patients 15-24 yr old. Hepatic cystogenesis appears to be influenced by estrogens. Although the frequency of cysts is similar in boys and girls, the development of large hepatic cysts is mainly a complication in girls. Hepatic cysts are often asymptomatic but can cause pain and are occasionally complicated by hemorrhage, infection, jaundice from bile duct compression, portal hypertension with variceal bleeding, or hepatic venous outflow obstruction from mechanical compression of hepatic veins, resulting in tender hepatomegaly and exudative ascites. Cholangiocarcinoma can occur. Subarachnoid hemorrhage can result from the associated cerebral arterial aneurysms.

Selected patients with severe symptomatic polycystic liver disease and favorable anatomy benefit from liver resection or fenestration. Combined liver-kidney transplantation may be required.

There is considerable evidence for a role of cyclic adenosine monophosphate in epithelial proliferation and fluid secretion in experimental renal and hepatic cystic disease. Several clinical trials in adults have shown that somatostatin analogs can blunt hepatic cyst expansion by blocking secretin-induced cyclic adenosine monophosphate generation and fluid secretion by cholangiocytes.

AUTOSOMAL DOMINANT POLYCYSTIC LIVER DISEASE

Autosomal dominant polycystic liver disease is a distinct clinical and genetic identity in which multiple cysts develop and are unassociated with cystic kidney disease. Liver cysts arise from but are not in continuity with the biliary tract. Girls are more commonly affected than boys, and the cysts often enlarge during pregnancy. Cysts are rarely identified in children. Cyst complications are related to effects of local compression, infection, hemorrhage, or rupture. Genes associated with autosomal dominant polycystic liver disease are *PRKCSH* and *SEC63*, which encode hepatocystin and Sec63, respectively. Hepatocystin is a protein kinase C substrate adK-H that is involved in the proper folding and maturation of glycoproteins. It has been localized to the endoplasmic reticulum. *SEC63* encodes a protein SEC63P, which is a component of the protein translocation machinery in the endoplasmic reticulum.

A solitary liver cyst (nonparasitic) rarely occurs in childhood. Abdominal distention and pain may be present, and a poorly defined right upper quadrant mass may be palpable. These benign lesions are best left undisturbed unless they compress adjacent structures or a complication occurs, such as hemorrhage into the cyst.

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Chapter 366
Diseases of the Gallbladder

Frederick J. Suchy

ANOMALIES

The gallbladder is congenitally absent in approximately 0.1% of the population. Hypoplasia or absence of the gallbladder can be associated with extrahepatic biliary atresia or cystic fibrosis. Duplication of the gallbladder occurs rarely. Gallbladder ectopia may occur with a transverse, intrahepatic, left-sided, or retroplaced location. Multiseptate gallbladder, characterized by the presence of multiple septa dividing the gallbladder lumen, is another rare congenital anomaly of the gallbladder.

ACUTE HYDROPS

Table 366-1 lists the conditions associated with hydrops of the gallbladder.

Acute noncalculous, noninflammatory distention of the gallbladder can occur in infants and children. It is defined by the absence of calculi, bacterial infection, or congenital anomalies of the biliary system. The disorder may complicate acute infections and Kawasaki disease, but the cause is often not identified. Hydrops of the gallbladder may also develop in patients receiving long-term parenteral nutrition, presumably as a result of gallbladder stasis during the period of enteral fasting. Hydrops is distinguished from acalculous cholecystitis by the absence of a significant inflammatory process and a generally benign prognosis.

Affected patients usually have right upper quadrant pain with a palpable mass. Fever, vomiting, and jaundice may be present and are usually associated with a systemic illness such as streptococcal infection. Ultrasonography shows a markedly distended, echo-free gallbladder, without dilation of the biliary tree. Acute hydrops is usually treated conservatively with a focus on supportive care and managing the intercurrent illness; cholecystostomy and drainage are rarely needed. Spontaneous resolution and return of normal gallbladder function usually occur over a period of several wk. If a laparotomy is required, a large, edematous gallbladder is found to contain white, yellow, or green bile. Obstruction of the cystic duct by mesenteric adenopathy is occasionally observed. Cholecystectomy is required if the gallbladder is gangrenous. Pathologic examination of the gallbladder wall shows edema and mild inflammation. Cultures of bile are usually sterile.

Table 366-1	Conditions Associated with Hydrops of the Gallbladder
Kawasaki disease	
Streptococcal pharyngitis	
Staphylococcal infection	
Leptospirosis	
Ascariasis	
Threadworm	
Sickle cell crisis	
Typhoid fever	
Thalassemia	
Total parenteral nutrition	
Prolonged fasting	
Viral hepatitis	
Sepsis	
Henoch-Schönlein purpura	
Mesenteric adenitis	
Necrotizing enterocolitis	

CHOLECYSTITIS AND CHOLELITHIASIS

Acute acalculous cholecystitis is uncommon in children and is usually caused by infection. Pathogens include streptococci (groups A and B), Gram-negative organisms, particularly *Salmonella* and *Leptospira interrogans*. Parasitic infestation with *Ascaris* or *Giardia lamblia* may be found. Calculous cholecystitis may rarely follow abdominal trauma or burn injury or is associated with a systemic vasculitis, such as periarteritis nodosa.

Clinical features include right upper quadrant or epigastric pain, nausea, vomiting, fever, and jaundice. Right upper quadrant guarding and tenderness are present. Ultrasonography discloses an enlarged, thick-walled gallbladder, without calculi. Serum alkaline phosphatase activity and direct-reacting bilirubin levels are elevated. Leukocytosis is usual.

Patients may recover with treatment of systemic and biliary infection. Because the gallbladder can become gangrenous, daily ultrasonography is useful in monitoring gallbladder distention and wall thickness. Cholecystectomy is required in patients who fail to improve with conservative management. Cholecystostomy drainage is an alternative approach in a critically ill patient.

Cholelithiasis is relatively rare in otherwise healthy children, occurring more commonly in patients with various predisposing disorders (Table 366-2). In an ultrasonographic survey of 1570 children (ages 6-19 yr) the overall prevalence of gallstone disease was 0.13% (0.27% in female subjects). In children, >70% of gallstones are the pigment type, 15-20% are cholesterol stones, and the remainder are composed of a mixture of cholesterol, organic matrix, and calcium bilirubinate. Black pigment gallstones, composed mostly of calcium bilirubinate and glycoprotein matrix, are a frequent complication of chronic hemolytic anemias. Brown pigment stones form mostly in infants as a result of biliary tract infection. Unconjugated bilirubin is the predominant component, formed by the high β-glucuronidase activity of infected bile. Cholesterol gallstones are composed purely of cholesterol or contain >50% cholesterol along with a mucin glycoprotein matrix and calcium bilirubinate. Calcium carbonate stones have also been described in children.

Patients with hemolytic disease (including sickle cell anemia, the thalassemias, and red blood cell enzymopathies) and Wilson disease are at increased risk for black pigment cholelithiasis. In sickle cell disease, pigment gallstones can develop before age 4 yr and have been reported in 17-33% of patients 2-18 yr of age. Genetic variation in the promoter of uridine diphosphate-glucuronosyltransferase 1A1 (the [TA]7/[TA]7 and [TA]7/[TA]8 genotypes) underlies **Gilbert syndrome**, a relatively common, chronic form of unconjugated hyperbilirubinemia, and is a risk factor for pigment gallstone formation in sickle cell disease.

Table 366-2	Conditions Associated with Cholelithiasis
Biliary dyskinesia	
Chronic hemolytic disease (sickle cell anemia, spherocytosis, thalassemia, Gilbert disease)	
Ileal resection or disease	
Cystic fibrosis	
Cirrhosis	
Cholestasis	
Crohn disease	
Obesity	
Insulin resistance	
Prolonged parenteral nutrition	
Prematurity with complicated medical or surgical course	
Prolonged fasting or rapid weight reduction	
Treatment of childhood cancer	
Abdominal surgery	
Pregnancy	
Sepsis	
Genetic *(ABCB4, ABCG5/G8)* progressive familial intrahepatic cholestasis	
Cephalosporins	

Cirrhosis and chronic cholestasis also increase the risk for pigment gallstones. Sick premature infants may also have gallstones; their treatment is often complicated by such factors as bowel resection, necrotizing enterocolitis, prolonged parenteral nutrition without enteral feeding, cholestasis, frequent blood transfusions, and use of diuretics. Cholelithiasis in premature infants is often asymptomatic and may resolve spontaneously. Brown pigment stones are found in infants with obstructive jaundice and infected intra- and extrahepatic bile ducts. These stones are usually radiolucent, owing to a lower content of calcium phosphate and carbonate and a higher amount of cholesterol than in black pigment stones. MDR3 deficiency caused by *ABCB4* mutations) is a cholestatic syndrome related to impaired biliary phospholipid excretion. It is associated with symptomatic and recurring cholelithiasis. Patients may show intrahepatic lithiasis, sludge, or microlithiasis along the biliary tree.

Obesity has assumed an increasingly important role as a risk factor for cholesterol cholelithiasis in children, particularly in adolescent girls. Cholesterol gallstones are also found in children with disturbances of the enterohepatic circulation of bile acids, including patients with ileal disease and bile acid malabsorption, such as those with ileal resection, ileal Crohn disease, and cystic fibrosis. Pigment stones can also occur in these patients.

Cholesterol gallstone formation seems to result from an excess of cholesterol in relation to the cholesterol-carrying capacity of micelles in bile. Supersaturation of bile with cholesterol, leading to crystal and stone formation, could result from decreased bile acid or from an increased cholesterol concentration in bile. Other initiating factors that may be important in stone formation include gallbladder stasis or the presence in bile of abnormal mucoproteins or bile pigments that may serve as a nidus for cholesterol crystallization.

Prolonged use of high-dose ceftriaxone, a third-generation cephalosporin, has been associated with the formation of calcium-ceftriaxone salt precipitates *(biliary pseudolithiasis)* in the gallbladder. Biliary sludge or cholelithiasis can be detected in >40% of children who are treated with ceftriaxone for at least 10 days. In rare cases, children become jaundiced and develop abdominal pain; precipitates usually resolve spontaneously within several months after discontinuation of the drug.

Acute or chronic cholecystitis is often associated with gallstones. The acute form may be precipitated by impaction of a stone in the cystic duct. Proliferation of bacteria within the obstructed gallbladder lumen can contribute to the process and lead to biliary sepsis. Chronic calculous cholecystitis is more common. It can develop insidiously or follow several attacks of acute cholecystitis. The gallbladder epithelium commonly becomes ulcerated and scarred.

More than 50% of patients with gallstones have symptoms, and 18% present with a complication as the first indication of cholelithiasis, such as pancreatitis, choledocholithiasis or acute calculous cholecystitis. The most important clinical feature of cholelithiasis is recurrent abdominal pain, which is often colicky and localized to the right upper quadrant. An older child may have intolerance for fatty foods. Acute cholecystitis is characterized by fever, pain in the right upper quadrant, and often a palpable mass. Jaundice occurs more commonly in children than adults. Pain may radiate to an area just below the right scapula. A plain x-ray of the abdomen may reveal opaque calculi, but radiolucent (cholesterol) stones are not visualized. Accordingly, ultrasonography is the method of choice for gallstone detection. Hepatobiliary scintography is a valuable adjunct in that failure to visualize the gallbladder provides evidence of cholecystitis.

Cholecystectomy is curative. Laparoscopic cholecystectomy is routinely performed in symptomatic infants and children with cholelithiasis. Common bile duct stones are unusual in children, occurring in 2-6% of cases with cholelithiasis, often in association with obstructive jaundice and pancreatitis. Operative cholangiography should be done at the time of surgery, however, to detect unsuspected common duct calculi. Endoscopic retrograde cholangiography with extraction of common duct stones is an option before laparoscopic cholecystectomy in older children and adolescents.

Asymptomatic patients with cholelithiasis pose a more difficult management problem. Studies in adults indicate a lag time of more than a decade between initial formation of a gallstone and development of symptoms. Spontaneous resolution of cholelithiasis has been reported in infants and children. If surgery is deferred for any patient, however, parents should be counseled about signs and symptoms consistent with cholecystitis or obstruction of the common bile duct by a gallstone. In patients with chronic hemolysis or ileal disease, cholecystectomy can be carried out at the same time as another surgical procedure. Because laparoscopic surgery can safely be performed in children with sickle cell disease, elective cholecystectomy is being done more frequently at the time of gallstone diagnosis, before symptoms or complications develop. In cases associated with liver disease, severe obesity, or cystic fibrosis, the surgical risk of cholecystectomy may be substantial so that the risks and benefits of the operation need to be carefully considered.

BILIARY DYSKINESIA

Biliary dyskinesia is a motility disorder of the biliary tract that may cause acalculous biliary colic in children, often in association with nausea and fatty food intolerance. There are usually no gallstones on imaging. Sphincter of Oddi dysfunction may be a variant that can present with chronic abdominal pain and recurrent pancreatitis. The diagnosis is based on a cholecystokinin–diisopropyl iminodiacetic acid scan demonstrating a gallbladder ejection fraction of less than 35%. Reproduction of pain on cholecystokinin administration may also be seen, as well as the absence of gallbladder filling on an otherwise normal ultrasound examination. In several recent reports, laparoscopic cholecystectomy was effective in providing both short-term and long-term improvement of symptoms in most children with biliary dyskinesia.

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Chapter 367

Portal Hypertension and Varices

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Portal hypertension, defined as an elevation of portal pressure >10-12 mm Hg, is a major cause of morbidity and mortality in children with liver disease. The normal portal venous pressure is approximately 7 mm Hg. The clinical features of the various forms of portal hypertension may be similar, but the associated complications, management, and prognosis can vary significantly and depend on whether the process is complicated by hepatic insufficiency.

ETIOLOGY

Portal hypertension can result from obstruction to portal blood flow anywhere along the course of the portal venous system. Table 367-1 outlines the various disorders associated with portal hypertension. Portal hypertension can occur as a result of prehepatic, intrahepatic, or posthepatic obstruction to the flow of portal blood.

Extrahepatic portal vein obstruction is an important cause of portal hypertension in childhood. The obstruction can occur at any level of the portal vein. Umbilical infection (**omphalitis**) with or without a history of catheterization of the umbilical vein may be causal in neonates. The infection can potentially spread from the umbilical vein to the left branch of the portal vein and eventually to the main portal venous channel. Intraabdominal infections, including acute

Table 367-1 Causes of Portal Hypertension

EXTRAHEPATIC PORTAL HYPERTENSION
Portal vein agenesis, atresia, stenosis
Portal vein thrombosis or cavernous transformation
Splenic vein thrombosis
Increased portal flow
Arteriovenous fistula
INTRAHEPATIC PORTAL HYPERTENSION
Hepatocellular disease
Acute and chronic viral hepatitis
Cirrhosis
Congenital hepatic fibrosis
Wilson disease
α_1-Antitrypsin deficiency
Glycogen storage disease type IV
Hepatotoxicity
Methotrexate
Parenteral nutrition
Biliary tract disease
Extrahepatic biliary atresia
Cystic fibrosis
Choledochal cyst
Sclerosing cholangitis
Intrahepatic bile duct paucity
Idiopathic portal hypertension
Postsinusoidal obstruction
Budd-Chiari syndrome
Venoocclusive disease

appendicitis and primary peritonitis, can be causal in older children. Portal vein thrombosis is also associated with neonatal dehydration and systemic infection. In older children, inflammatory bowel disease can be associated with a hypercoagulable state and portal venous obstruction. Thrombosis of the portal vein has also occurred in association with biliary tract infections and primary sclerosing cholangitis. **Portal vein thrombosis** is associated with hypercoagulable states, such as deficiencies of factor V Leiden, protein C, or protein S. The portal vein can be replaced by a fibrous remnant or contain an organized thrombus. Rare developmental anomalies producing extrahepatic portal hypertension include agenesis, atresia, or stenosis of the portal vein. Obstruction by a web or diaphragm can also occur. At least half of reported cases have no defined cause.

Uncommonly, presinusoidal hypertension can be caused by increased flow through the portal system as a result of a congenital or acquired arteriovenous fistula.

The intrahepatic causes of portal hypertension are numerous. Obstruction to flow can occur on the basis of a presinusoidal process, including acute and chronic hepatitis, congenital hepatic fibrosis, and schistosomiasis. Portal infiltration with malignant cells or granulomas can also contribute. An idiopathic form of portal hypertension characterized by splenomegaly, hypersplenism, and portal hypertension without occlusion of portal or splenic veins and with no obvious disease in the liver has been described. In some patients, noncirrhotic portal fibrosis has been observed.

Cirrhosis is the predominant cause of portal hypertension and is related to obstruction of blood flow through the portal vein. The numerous causes of cirrhosis include recognized disorders such as biliary atresia, autoimmune hepatitis, chronic viral hepatitis, and metabolic liver disease such as α_1-antitrypsin deficiency, Wilson disease, glycogen storage disease type IV, hereditary fructose intolerance, and cystic fibrosis.

Postsinusoidal causes of portal hypertension are also observed in childhood. The **Budd-Chiari syndrome** occurs with obstruction to hepatic veins anywhere between the efferent hepatic veins and the entry of the inferior vena cava into the right atrium. In most cases, no specific cause can be found, but thrombosis can occur from inherited and acquired hypercoagulable states (antithrombin III deficiency, protein C or S deficiency, factor V Leiden or prothrombin mutations, paroxysmal nocturnal hemoglobinemia, pregnancy, oral contraceptives) and can complicate hepatic or metastatic neoplasms, collagen vascular disease, infection, and trauma. Additional causes of the Budd-Chiari syndrome include Behçet syndrome, inflammatory bowel disease, aspergillosis, dacarbazine therapy, and inferior vena cava webs.

Sinusoidal obstruction syndrome (venoocclusive disease) is the most common cause of hepatic vein obstruction in children. In this disorder, occlusion of the centrilobular venules or sublobular hepatic veins occurs. The disorder occurs after total body irradiation with or without cytotoxic drug therapy that is commonly used before bone marrow transplantation. The disease has also occurred after ingestion of herbal remedies containing the pyrrolizidine alkaloids, which are sometimes taken as medicinal teas.

PATHOPHYSIOLOGY

The primary hemodynamic abnormality in portal hypertension is increased resistance to portal blood flow. This is the case whether the resistance to portal flow has an intrahepatic cause such as cirrhosis or is due to portal vein obstruction. Portosystemic shunting should decompress the portal system and thus significantly lower portal pressures. Despite the development of significant collaterals deviating portal blood into systemic veins, portal hypertension is maintained by an overall increase in portal venous flow and thus maintenance of portal hypertension. A hyperdynamic circulation is achieved by tachycardia, an increase in cardiac output, and decreased systemic vascular resistance. Splanchnic dilation also occurs. Overall, the increase in portal flow likely contributes to an increase in variceal transmural pressure. The increase in portal blood flow is related to the contribution of hepatic and collateral flow; the actual portal blood flow reaching the liver is reduced. It is also likely that hepatocellular dysfunction and portosystemic shunting lead to the generation of various humoral factors that cause vasodilation and an increase in plasma volume.

Many complications of the portal hypertension can be accounted for by the development of a remarkable collateral circulation. Collateral vessels can form prominently in areas in which absorptive epithelium joins stratified epithelium, particularly in the esophagus or anorectal region. The superficial submucosal collaterals, especially those in the esophagus and stomach and, to a lesser extent, those in the duodenum, colon, or rectum, are prone to rupture and bleeding under increased pressure. In portal hypertension, the vascularity of the stomach is also abnormal and demonstrates prominent submucosal arteriovenous communications between the muscularis mucosa and dilated precapillaries and veins. The resulting lesion, a vascular ectasia, has been called **congestive gastropathy** and contributes to a significant risk of bleeding from the stomach.

CLINICAL MANIFESTATIONS

Bleeding from esophageal varices is the most common presentation. Less commonly, patients bleed from varices around a stoma or from anorectal varices. In patients with underlying hepatic disease, physical examination might show jaundice and stigmata of cirrhosis such as palmar erythema and vascular telangiectasias. Growth retardation can occur in patients with cirrhosis and, to a lesser extent, in children with isolated extrahepatic portal vein obstruction. Ascites may be present in patients with intrahepatic causes of portal hypertension and can transiently occur with portal vein obstruction. Dilated cutaneous collateral vessels carrying blood from the portal to systemic circulation may be apparent in the periumbilical region. In the absence of clinical or biochemical features of liver disease and with a liver of normal size, portal vein obstruction is most likely. Well-compensated cirrhosis cannot be completely ruled out under these conditions. Cholestasis and liver dysfunction with elevated serum bilirubin and aminotransferases occur uncommonly in portal vein obstruction as a result of external compression of bile ducts by cavernous transformation of the portal vein. This complication is called **portal hypertensive biliopathy**.

An enlarged, hard liver with minimal disturbance of hepatic function suggests the possibility of congenital hepatic fibrosis.

Hemorrhage, particularly in children with portal vein obstruction, can be precipitated by minor febrile, intercurrent illness. The mechanism is often unclear; aspirin or other nonsteroidal antiinflammatory drugs may be a contributing factor by damaging the integrity of a congested gastric mucosa or interfering with platelet function. Coughing during a respiratory illness can also increase intravariceal pressure. The bleeding may become apparent with hematemesis or with melena. Gastrointestinal hemorrhage can also originate from portal hypertensive gastropathy or from gastric, duodenal, peristomal, or rectal varices.

Splenomegaly, sometimes with hypersplenism, is the next most common presenting feature in portal vein obstruction and may be discovered first on routine physical examination. Because more than half of patients in many series with portal vein obstruction do not experience bleeding until after age 6 yr, the diagnosis should be suggested in a child without hepatocellular disease who had a complicated neonatal course and in whom asymptomatic splenomegaly later developed. Long-term follow-up of patients with portal vein obstruction has revealed a variety of complications including variceal hemorrhage, hypersplenism, biliary obstruction, growth and development retardation, and neuropsychiatric dysfunction.

Children with portal hypertension, regardless of the underlying cause, may have recurrent bouts of life-threatening hemorrhage. In patients with portal vein obstruction and normal hepatic function, the bleeding usually stops spontaneously. In patients with intrahepatic disease, the combination of portal hypertension and poor liver synthetic ability (coagulopathy) can make bleeding much more difficult to control. Moreover, esophageal hemorrhage and cirrhosis can have injurious effects on the liver, further impairing hepatic function and sometimes precipitating jaundice, ascites, and encephalopathy. Blood in the intestinal lumen can promote bacterial translocation, leading to peritonitis. Another serious complication is the hepatopulmonary syndrome, which develops in ≥10% of patients with portal hypertension. It is defined as an arterial oxygenation defect induced by intrapulmonary microvascular dilation, resulting from release of a number of endogenous vasoactive molecules, including endothelin-1 and nitric oxide into the venous circulation.

DIAGNOSIS

In patients with established chronic liver disease or in those in whom portal vein obstruction is suspected, an experienced ultrasonographer should be able to demonstrate the patency of the portal vein, and Doppler flow ultrasonography can demonstrate the direction of flow within the portal system. The pattern of flow correlates with the severity of cirrhosis and encephalopathy. Reversal of portal vein blood flow (hepatofugal flow) is more likely to be associated with variceal bleeding. Ultrasonography is also effective in detecting the presence of esophageal varices. Another important feature of extrahepatic portal vein obstruction is cavernous transformation of the portal vein, in which an extensive complex of small collateral vessels form in the paracholedochal and epicholedochal venous system to bypass the obstruction. Other imaging techniques also contribute to further definition of the portal vein anatomy but are required less often; contrast-enhanced CT and magnetic resonance angiography provide information similar to ultrasonography. Selective arteriography of the celiac axis, superior mesenteric artery, and splenic vein may be useful in precise mapping of the extrahepatic vascular anatomy. This is not required to establish a diagnosis but can prove valuable in planning surgical decompression of portal hypertension. The platelet count, spleen length measured by ultrasonography, and serum albumin are the best noninvasive predictors of portal hypertension in children.

In a patient with hypoxia (**hepatopulmonary syndrome**), intrapulmonary microvascular dilation is demonstrated with contrast-enhanced echocardiography that shows delayed appearance in the left heart of microbubbles from a saline bolus injected into a peripheral vein.

Endoscopy is the most reliable method for detecting esophageal varices and for identifying the source of gastrointestinal bleeding. Although bleeding from esophageal or gastric varices is most common in children with portal hypertension, up to one third of patients, particularly those with cirrhosis, have bleeding from some other source such as portal hypertensive gastropathy or gastric or duodenal ulcerations. There is a strong correlation between variceal size as assessed endoscopically and the probability of hemorrhage. Red spots apparent over varices at the time of endoscopy are a strong predictor of imminent hemorrhage.

TREATMENT

The therapy of portal hypertension can be divided into emergency treatment of potentially life-threatening hemorrhage and prophylaxis directed at prevention of initial or subsequent bleeding. It must be emphasized that the use of many therapies is based on experience in adults with portal hypertension. There is a lack of rigorous studies on the ability of endoscopy screening, endoscopic treatment of varices, and use of nonselective β-blockers to alter the outcome of portal hypertension in children.

Treatment of patients with variceal hemorrhage must focus on fluid resuscitation, initially in the form of crystalloid infusion, followed by the replacement of red blood cells. Correction of coagulopathy by administration of vitamin K and/or infusion of platelets or fresh-frozen plasma may be required. A nasogastric tube should be placed to document the presence of blood within the stomach and to monitor for ongoing bleeding. An H_2-receptor blocker or proton pump inhibitor should be given intravenously to reduce the risk of bleeding from gastric erosions. In most patients, particularly those with extrahepatic portal hypertension and with normal hepatic synthetic function, bleeding usually stops spontaneously. Care should be taken in fluid resuscitation of children after bleeding to avoid producing an excessively high venous pressure and increasing risk for further bleeding.

Pharmacologic therapy to decrease portal pressure may be considered in patients with continued bleeding. Vasopressin or one of its analogs is commonly used and is thought to act by increasing splanchnic vascular tone and thus decreasing portal blood flow. Vasopressin is administered initially with a bolus of 0.33 units/kg over 20 min, followed by a continued infusion of the same dose on an hourly basis or a continuous infusion of 0.2 units/1.73 m^2/min. The drug has a half-life of approximately 30 min. Its use may be limited by the side effects of vasoconstriction, which can impair cardiac function and perfusion to the heart, bowel, and kidneys and can also, as a result, exacerbate fluid retention. Nitroglycerin, usually given as a portion of a skin patch, has also been used to decrease portal pressure and, when used in conjunction with vasopressin, can ameliorate some of its untoward effects. The somatostatin analog octreotide is more commonly used, and it decreases splanchnic blood flow with fewer side effects. It may be administered by continuous intravenous infusion of 1.0-5.0 μg/kg/hr. However, the use of octreotide in adults with variceal hemorrhage has not been associated with a reduction in rates of rebleeding or mortality. Its use and efficacy in children have not been rigorously evaluated.

After an episode of variceal hemorrhage or in patients in whom bleeding cannot be controlled, endoscopic sclerosis or elastic band ligation of esophageal varices are important options. In endoscopic sclerosis, sclerosants are injected either intravariceally or paravariceally until bleeding has stopped. Although bleeding can be controlled acutely in most cases, further sessions of sclerotherapy are required to achieve temporary obliteration of the varices. Treatments may be associated with further bleeding, bacteremia, esophageal ulceration, and stricture formation. Most centers do not perform endoscopic sclerotherapy of varices prophylactically but use the procedure as a bridge to the time of liver transplantation or a surgical shunting procedure. Endoscopic elastic band ligation of varices has been shown in adult and pediatric studies to be more effective and associated with fewer complications than is sclerotherapy.

In patients who continue to bleed despite pharmacologic and endoscopic methods to control hemorrhage, a Sengstaken-Blakemore tube may be placed to stop hemorrhage by mechanically compressing esophageal and gastric varices. The device is rarely used now, but it

may be the only option to control life-threatening hemorrhage. It carries a significant rate of complications and a high rate of bleeding when the device is removed, and it poses a particularly high risk for pulmonary aspiration. The tube is not well tolerated in children without significant sedation.

Various surgical procedures have been devised to divert portal blood flow and to decrease portal pressure. A portacaval shunt diverts nearly all of the portal blood flow into the subhepatic inferior right vena cava. Although portal pressure is significantly reduced, because of the significant diversion of blood from the liver, patients with parenchymal liver disease have a marked risk for hepatic encephalopathy. Even mild hepatic encephalopathy can impair cognitive function, including school performance. More selective shunting procedures, such as mesocaval or distal splenorenal shunt, can effectively decompress the portal system while allowing a greater amount of portal blood flow to the liver. The small size of the vessels makes these operations technically challenging in infants and small children, and there is a significant risk of failure as a result of shunt thrombosis. A shunt may be good option in a child with relatively well-preserved liver function, as sometimes occurs in patients with biliary atresia, congenital hepatic fibrosis, or cystic fibrosis. Portal vein thrombosis has been managed with the Rex shunt (superior mesenteric vein to left portal vein bypass), which restores physiologic portal blood flow and inflow of hepatotrophic factors. Growth and cognitive function improve after this procedure.

A transjugular intrahepatic portosystemic shunt, in which a stent is placed by an interventional radiologist between the right hepatic vein and the right or left branch of the portal vein, can aid in the management of portal hypertension in children, especially in those needing temporary relief before liver transplantation. The transjugular intrahepatic portosystemic shunt procedure can precipitate hepatic encephalopathy and is prone to thrombosis.

Orthotopic liver transplantation represents a much better therapy for portal hypertension resulting from intrahepatic disease and cirrhosis. A prior portosystemic shunting operation does not preclude a successful liver transplantation but makes the operation technically more difficult.

Long-term treatment with nonspecific β-blockers, such as propranolol, has been used extensively in adults with portal hypertension. These agents might act by lowering cardiac output and portal perfusion. Evidence in adult patients shows that β-blockers can reduce the incidence of variceal hemorrhage and improve long-term survival. A therapeutic effect is thought to result when the pulse rate is reduced by ≥25%. There is limited published experience with the use of this therapy in children.

PROGNOSIS

Portal hypertension secondary to intrahepatic disease has a poor prognosis. Portal hypertension is usually progressive in these patients and is often associated with deteriorating liver function. Efforts should be directed toward prompt treatment of acute bleeding and prevention of recurrent hemorrhage with available methods. Patients with progressive liver disease and significant esophageal varices ultimately require orthotopic liver transplantation. Liver transplantation is the only effective therapy for hepatopulmonary syndrome and should also be considered for patients with portal hypertension secondary to hepatic vein obstruction or resulting from severe venoocclusive disease.

In patients with portal vein obstruction, episodes of bleeding can become less frequent and severe with age as a collateral circulation develops, >50% experience bleeding during adolescence. Neurocognitive defects diagnosed by careful psychologic testing indicate portosystemic encephalopathy caused by naturally occurring portosystemic shunts. Progressive liver disease can occur later as a consequence of bile duct compression from dilated collateral venous channels (portal biliopathy). These complications can be treated or prevented by the Rex shunt.

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Chapter 368

Liver Transplantation

Jorge D. Reyes and Evelyn Hsu

Refinements in the management of hepatic failure, organ procurement and implantation techniques, organ preservation, perioperative care, and the development of effective immunosuppressive management (cyclosporine in 1978 and tacrolimus in 1989) survival rates for liver transplantation is now >90%. Complications inherent in the toxicity/infection profile of immunosuppressive drug therapy have occurred and enhancements in our understanding of the relationship between recipient and host immune systems have resulted in the development of tailored immunotherapy. In addition, the search for "tolerance" enhancing protocols, which could lead to transplantation without the need for long-term immunosuppression. The creation of a national system for matching these donor organs with waiting recipients (the Organ Procurement and Transplantation Network and the United Network for Organ Sharing [UNOS]) provides equitable sharing of this scarce organ resource to the neediest patients with the adoption of the Pediatric End-Stage Liver Disease and Medical End-Stage Liver Disease (for adolescents) scoring systems.

INDICATIONS

The diseases for which liver transplantation is indicated can be categorized into the following groups:

- Obstructive biliary tract disease: biliary atresia, sclerosing cholangitis, traumatic or postsurgical injury
- Metabolic disorders: α_1-antitrypsin deficiency, tyrosinemia type I, glycogen storage disease type IV, Wilson disease, neonatal hemochromatosis, Crigler-Najjar type I, familial hypercholesterolemia, primary oxalosis, organic academia, urea cycle defects
- Acute hepatitis: fulminant hepatic failure, viral, toxin, or drug induced
- Chronic hepatitis with cirrhosis: hepatitis B or C, autoimmune
- Intrahepatic cholestasis: idiopathic neonatal hepatitis, Alagille syndrome, progressive familial intrahepatic cholestasis
- Miscellaneous: cryptogenic cirrhosis, congenital hepatic fibrosis, Caroli disease, cystic fibrosis, polycystic kidney and liver disease, cirrhosis induced by total parenteral nutrition
- Primary liver tumors: benign tumors (hamartomas, hemangioendothelioma), unresectable hepatoblastoma, and hepatocellular carcinoma
- Emerging indications: graft-versus-host-disease (a complication of bone marrow transplantation), hemophilia, and portosystemic shunts

Biliary atresia is the most common indication for liver transplantation in children, followed by metabolic and inborn disorders, autoimmune and familial cholestatic disorders, and acute hepatic necrosis.

Biliary atresia may present with 2 clinical patterns: an acquired form for which there may be nonrandom clustering of potential etiologies (80% of cases), and a syndromic/embryonic form that includes other anomalies, such as polysplenia or asplenia, preduodenal portal vein, intestinal malrotation, situs anomalies, and absence of the retrohepatic vena cava. Hepatoportoenterostomy may benefit survival if performed within the 1st 30 days of life, however, some patients with successful drainage later develop cirrhosis with portal hypertension (variceal bleeding and ascites). Children with biliary atresia (or any other obstructive biliary disorder) who do not achieve successful drainage require liver transplantation within the 1st yr of life.

Inborn errors of metabolism result from a single enzyme deficiency that results in alteration of synthesis, breakdown, transport, or function of carbohydrate, fat, or protein. They can be grouped into those diseases which cause structural damage and cirrhosis, and potentially end-stage liver disease, as well as liver cancer (i.e., α_1-antitrypsin deficiency, Wilson disease, cystic fibrosis, progressive familial intrahepatic cholestasis), and those inborn errors that manifest principally by their hepatic enzyme deficiency with no hepatocellular injury; complications occur in "satellite" systems such as the brain (hyperammonemic conditions), the kidney (hyperoxaluria type 1), or heart (familial hypercholesterolemia). Some metabolic disorders place patients at risk for decompensation throughout their entire lives, and others (e.g., Crigler-Najjar) manifest principally after adolescence. Liver transplantation replaces the enzyme deficiency; the value and risk benefit of doing so in the absence of cirrhosis has prompted the pursuit of gene therapy and hepatocyte transplantation as possible alternatives, but their therapeutic benefit is yet to be determined.

Although many patients with **fulminant hepatic failure** will survive without transplant, it accounts for approximately 13% of pediatric liver transplantation and has required the most intense concentration of multimodal management/support, and organ graft options yet devised. It is a diagnosis without clear etiology in more than 50% of cases, and posttransplantation survival varies but is generally poor because of multifactorial issues related to comorbidities and listing/transplantation graft option availability.

Primary hepatic malignancies in children are rare (<2% of all pediatric malignancies), and account for a little less than 10% of transplants. Hepatoblastoma accounts for the majority of cases (75% of primary liver tumors in childhood) and is usually of an advanced stage, yet adjuvant chemotherapy and total hepatectomy with transplantation provide cure and long-term survival for the majority of patients thus treated. Survival of >85% has been reported by the International Society of Pediatric Oncology and several American centers.

Some diseases do not produce life-threatening complications, yet their impact on growth, development, and quality of life can be so devastating that liver transplantation is a valid therapy and cure. The distribution of liver grafts does follow guidelines based on severity of liver disease as reflected in the Pediatric End-Stage Liver Disease scoring system developed by UNOS, which takes into calculation the measurable values of bilirubin, creatinine, and international normalization ratio.

Contraindications to liver transplantation include uncontrolled infection of extrahepatic origin, uncontrolled extrahepatic malignancies, and severely disabling and uncorrectable disease in other organ systems, principally the heart and lungs. Although combined liver and heart or lung transplantation has been performed in adults and children, such cases require special consideration and centers dedicated to the complexities of posttransplantation management. Also, disabling neurologic disease can preclude liver transplantation if the outcome will not allow the child to develop some measure of independence and quality of life.

TECHNICAL INNOVATIONS

There are no limitations on age or weight for liver transplantation, a consequence to improved posttransplantation outcomes as a result of improvements in perioperative management (recipient selection, care, and timing of transplantation as well as intra- and posttransplantation care), and to the development and successful transplantation of segmental liver grafts.

To enhance the availability of liver grafts to children and optimize the timing of transplantation, the use of reduced-size or segmental grafts (a right or left lobe of liver, or the left lateral segment of the left lobe) were developed; this advancement allows the selection of a liver from a larger donor for implantation into a child, thus correcting the size mismatch. Because liver reduction inherently removes a potential graft for an adult recipient, techniques were developed for the use of segments from living donors (using usually the left lateral segment for small pediatric recipients), and then split-liver grafts from deceased donors where the left lateral segment is transplanted into a child and the leftover segment of right lobe and medial segment of left lobe (essentially a right trisegment graft) are transplanted into an adult. Reduction of a liver graft is performed ex vivo; split-liver grafts can be accomplished either ex vivo or in situ (in the hemodynamically stable brain-dead donor). Donors suitable for aforementioned graft variants should ideally be young (younger than 45 yr of age), healthy, and nonobese; however, variations are guided by the severity of illness and urgency for transplantation of the recipient.

The implantation of a liver (either whole organ or segment) involves removal of the native liver and encompasses 4 anastomoses: the suprahepatic vena cava, the portal vein, the hepatic artery, and the bile duct. Modifications of the procedure generally involve retaining (or not) of the retrohepatic vena cava, the performance (or not) of a temporary portocaval shunt to decompress the splanchnic venous system during the anhepatic phase, and the use of vascular homografts of donor iliac vein or artery to replace the native inflow (guided by the presence of recipient anomalies or thrombosis of native vessels). The donor bile duct may be connected to a loop of recipient intestine (Roux-en-Y limb) or the native bile duct.

UNOS reported outcomes analyzing graft types and outcomes have shown improved graft survival in children younger than 3 yr of age for live donor grafts when compared to deceased donor whole, split, and reduced grafts. After the 1st yr, however, patient and allograft survivals were similar regardless of whether the graft was a whole liver, deceased donor segment, or living donor.

IMMUNOSUPPRESSION

The goal of effective clinical immunosuppression after solid-organ transplantation is to inhibit antigen-induced T-lymphocyte activation and cytokine production, interrupt allo–major histocompatibility complex recognition, or block effector responses. To prevent overly weakening the host response to infection, these effects should be accomplished while preserving immunocompetence. A major emphasis is the prevention of acute and chronic rejection and the ability to reverse refractory acute rejection. These efforts have been, for the most part, successful; the current challenge is long-term survival and quality of life, inherently involving strategies to minimize the long-term toxicity of immunosuppressive drug therapy, which can include renal failure, cardiovascular complications, and infections. Studies have led to a better understanding of lymphocyte subsets and function, the discovery that rejection could be reversed with steroids or antilymphocyte globulin, and then the realization that long-lasting donor-specific unresponsiveness could be achieved with less drug therapy, while preserving immunocompetence.

Immediately peri- or posttransplantation therapy may involve antilymphocyte antibody induction with depleting antibodies (monoclonal or polyclonal) such as antithymocyte globulin antibody, or the use of a chimeric mouse–human antibody that blocks the interleukin-2 receptor of the T cell, thus preventing activation and replication of antigen-selected T cells. Corticosteroids act through the suppression of antibody production and cytokine synthesis (interleukin-2, and interferon-γ), decreasing proliferation of T cells (helper, suppressor, and cytotoxic), B cells, and neutrophils. Maintenance immunosuppression is achieved through the use of calcineurin phosphatase inhibitor activity using drugs such as cyclosporine or tacrolimus; these drugs interfere with the production and release of interleukin-2 which plays a critical role in the cytotoxic T-cell response, thus inhibiting T-cell–mediated acute cellular rejection. Tacrolimus has shown to be a more powerful drug, however, the ability to progress or initiate maintenance immunosuppression in the absence of corticosteroids is of particular benefit in the children. Other drugs, such as azathioprine or mycophenolate mofetil, which inhibit the synthesis of purine nucleosides and thus the proliferation of T and B lymphocytes and antibody formation, may be added to enhance the antirejection profile, allow for decrease in the calcineurin dosage, or manage chronic rejection. Rapamycin, a macrolide which binds its' molecular target of mammalian target of rapamycin receptor, decreases

interleukin-2 production, and thus T- and B-cell activation and proliferation.

COMPLICATIONS

Posttransplantation complications can be related to the pretransplantation condition of the recipient and the donor match and type, immunologic responses to the graft and the need for enhanced immunosuppressive drug therapy, and toxicity effects of these drugs or infections from over-immunosuppression. They can occur at varying specific frequencies over a fairly well-defined time course (early, late, remote).

The most predictable complications involve those inherent to the transplantation operation and include primary nonfunction of the graft (rare in pediatric recipients given the selection criteria of potential donors); hepatic artery thrombosis is the most frequent and early vascular complication, occurring in 5-10% of recipients and can have devastating consequences on the graft (acute necrosis and gangrene, and biliary leaks/stricture/bilomas), which may require urgent retransplantation; portal vein or hepatic vein strictures/occlusions are rare and generally occur later posttransplantation. Biliary strictures are the most frequent surgical complication (10-30%) after liver transplantation and should be included in the differential diagnosis of any posttransplantation liver allograft dysfunction. Management of these complication varies and may include interventional radiologic procedures, reoperation, or retransplantation.

Rejection usually occurs after the 1st 2 wk after transplantation, with the highest incidence (30-60%) within the 1st 90 days. Diagnosis is suspected based on abnormal liver function studies, and rarely are there systemic signs such as fever, abdominal pain, new-onset ascites or hydrothorax; the diagnosis requires biopsy confirmation; treatment algorithms include high doses of corticosteroids and antilymphocyte antibodies. Chronic rejection is less frequent (5-10%) and is characterized by progressive damage and loss of bile ductules with consequent cholestasis; treatment involves long-term enhancement of maintenance immunosuppression with corticosteroids and other agents.

The need to treat rejection can place the patient at a higher risk of drug toxicity or infection. The most common transplantation-related infections are cytomegalovirus and Epstein-Barr virus infections, for which there are well-developed algorithms of prophylaxis. Epstein-Barr virus-induced **posttransplant lymphoproliferative disease** represents a unique complication of over-immunosuppression and infection occurring in approximately 10% of patients, and that has been managed by withdrawal of immunosuppression and antiviral therapy; some patients require chemotherapy.

OUTCOMES

The clinical, surgical, and immunosuppressive drug therapy advances since the 1990s have dramatically improved survival of liver transplantation in children. The SPLIT registry data (1092 patients in North America transplanted since 1995) demonstrate 1-yr patient and graft survival of 86.3% and 80.2%, respectively. UNOS data reveal a 1 yr patient and graft survival for biliary atresia of 95% and 87% respectively. Longer-term survival is inherently dependent on adequacy of long term immunosuppression management, adherence to care protocols, and prevention of infection/toxicities/chronic rejection.

With longer survival times, the issues of growth, quality of life, and patient loss with a functioning graft have come to the forefront. The goals have been reset to seek the induction protocols and strategies that can foster minimization of drug therapy and even a drug-free state, the induction of tolerance.

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Section 7

Peritoneum

Chapter 369

Malformations

Melissa Kennedy and Chris A. Liacouras

Congenital peritoneal bands represent anatomically unabsorbed portions of omentum and mesentery and most commonly occur in the regions of the duodenum, duodenojejunal flexure, ileocecal junction, and ascending colon. Although usually benign, they may be responsible for intestinal obstruction or midgut volvulus and resulting intestinal necrosis. Intraabdominal herniations infrequently occur through ring-like formations produced by anomalous peritoneal bands. Numerous other anomalies can occur in the course of the development of the peritoneum but are rarely of clinical importance. Absence of the omentum or its duplication occurs rarely. Omental cysts arise in obstructed lymphatic channels within the omentum. They may be congenital or can result from trauma and are usually asymptomatic. Abdominal pain or partial small bowel obstruction can result from compression or torsion of the small bowel from traction on the omentum.

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Chapter **370**

Ascites

Melissa Kennedy and Chris A. Liacouras

Ascites is the pathologic accumulation of fluid within the peritoneal cavity. Multiple causes of ascites have been described (Table 370-1). In children, hepatic and renal disease are the most common causes, but ascites can also be caused by cardiac disease, trauma, infection, or neoplasia.

The clinical hallmark of ascites is abdominal distention. Early satiety and dyspnea can occur with a moderate amount of ascites. Considerable intraperitoneal fluid can accumulate before ascites is detectable by the classic physical signs: bulging flanks, dullness to percussion, shifting dullness, a fluid wave, and the "puddle sign" (percussion of a supine person's abdomen over the umbilicus becomes dull as the patient is moved to a prone position and ascitic fluid puddles in dependent regions). Umbilical herniation can be associated with tense ascites. Ultrasound examination is useful for detecting small amounts of ascites.

Abdominal paracentesis can provide symptomatic relief and may be diagnostic of the cause of the ascites. Determining the serum-ascites albumin gradient can help to determine the cause of ascites. A gradient greater than 1.1 g/dL (high-gradient ascites) is consistent with ascites caused by portal hypertension, whereas a gradient <1.1 g/dL (low-gradient ascites) indicates ascites of nonportal-hypertensive etiology.

The course, prognosis, and treatment of ascites depend entirely on the cause. For most patients, treatment consists of dietary sodium restriction and diuretic therapy with spironolactone, with the addition of furosemide in more severe cases. Supplemental albumin can also aid in ascitic fluid mobilization. Refractory cases may require large volume paracentesis or transjugular intrahepatic portosystemic shunting.

Table 370-1	Causes of Ascites
HEPATIC Cirrhosis Congenital hepatic fibrosis Portal vein obstruction Fulminant hepatic failure Budd-Chiari syndrome Lysosomal storage disease	
RENAL Nephrotic syndrome Obstructive uropathy Perforation of urinary tract Peritoneal dialysis	
CARDIAC Heart failure Constrictive pericarditis Inferior vena cava web	
INFECTIOUS Abscess Tuberculosis *Chlamydia* Schistosomiasis	
GASTROINTESTINAL Infarcted bowel Perforation Protein-losing enteropathy	
NEOPLASTIC Lymphoma Neuroblastoma	
GYNECOLOGIC Ovarian tumors Ovarian torsion, rupture	
PANCREATIC Pancreatitis Ruptured pancreatic duct	
MISCELLANEOUS Systemic lupus erythematosus Autoinflammatory recurrent fever syndromes Ventriculoperitoneal shunt Eosinophilic ascites Chylous ascites Hypothyroidism	

Patients with any type of ascites are at increased risk for spontaneous bacterial peritonitis.

Bibliography is available at Expert Consult.

370.1 Chylous Ascites

Jessica W. Wen and Chris A. Liacouras

Chylous ascites refers to peritoneal fluid that contains lymphatic drainage with a characteristic milky appearance that is rich in triglycerides. Chylous ascites can result from congenital anomaly, injury, or obstruction of the intra-abdominal portion of the thoracic duct. Although uncommon, it can occur at any age. In the pediatric population, the most common cause is lymphatic malformation. Other causes include surgical injury to the lymphatics, trauma, cirrhosis, peritoneal bands, generalized lymphangiomatosis, chronic inflammatory processes of the bowel, and mycobacterial infection. Malignancy is a fairly common cause in the adult population but uncommon in pediatrics. Congenital anomalies of the lymphatic system can be associated with Turner, Noonan, yellow nail, and Klippel-Trenaunay-Weber syndromes.

The most common presentation is painless abdominal distention, and it may be accompanied by poor weight gain and loose stools. Peripheral edema is common. Massive chylous ascites can result in scrotal edema, inguinal and umbilical herniation, and respiratory difficulties.

Diagnosis of chylous ascites depends on the demonstration of milky ascitic fluid obtained via paracentesis after a fat-containing feeding. Ascites fluid analysis reveals high protein content, elevated triglycerides, and lymphocytosis. If the patient has had nothing by mouth, the fluid may appear serous. Hypoalbuminemia, hypogammaglobulinemia, and lymphopenia are common in these patients.

Treatment includes a high-protein, low-fat diet supplemented with medium-chain triglycerides that are absorbed directly into the portal circulation and decrease lymph production. Parenteral alimentation may be necessary if nutrition remains impaired on oral feedings this may also significantly decrease lymph flow and facilitate sealing at the point of lymph leakage. Octreotide, a somatostatin analog, has been used by subcutaneous route in chylous ascites. The mechanism is not clearly understood; however, it decreases intestinal blood flow leading to decreased portal pressure and it also inhibits lymphatic secretion through somatostatin receptors in the intestinal wall. Paracentesis should be repeated only if abdominal distention causes respiratory distress. Laparotomy may be indicated to search for the site of the leakage if a trial of dietary management has been unsuccessful and a lymphangiogram demonstrates site of leakage.

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Chapter 371

Peritonitis

Jessica W. Wen and Chris A. Liacouras

Inflammation of the peritoneal lining of the abdominal cavity can result from infectious, autoimmune, neoplastic, and chemical processes. Infectious peritonitis is usually defined as primary (spontaneous) or secondary. In primary peritonitis, the source of infection originates outside the abdomen and seeds the peritoneal cavity via hematogenous, lymphatic, or transmural spread. Secondary peritonitis arises from the abdominal cavity itself through extension from or rupture of an intraabdominal viscus or an abscess within an organ. Tertiary peritonitis refers to recurrent diffuse or localized disease and is associated with poorer outcomes than secondary peritonitis.

Clinically, patients have abdominal pain, abdominal tenderness, and rigidity on exam. Peritonitis can result from rupture of a hollow viscus, such as the appendix or a Meckel diverticulum; disruption of the peritoneum from trauma or peritoneal dialysis catheter; chemical peritonitis from other bodily fluid, including bile and urine; and infection. Meconium peritonitis is described in Chapters 102.1 and 330. Peritonitis is considered a surgical emergency and requires exploration and lavage of the abdomen except in spontaneous bacterial peritonitis.

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371.1 Acute Primary Peritonitis

Jessica W. Wen and Chris A. Liacouras

ETIOLOGY AND EPIDEMIOLOGY

Primary peritonitis usually refers to bacterial infection of the peritoneal cavity without a demonstrable intraabdominal source. Most cases occur in children with ascites resulting from cirrhosis and nephrotic syndrome. Infection can result from translocation of gut bacteria as

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well as immune dysfunction. Rarely, primary peritonitis occurs in previously healthy children. Pneumococci (most common), group A streptococci, enterococci, staphylococci, and Gram-negative enteric bacteria, especially *Escherichia coli* and *Klebsiella pneumoniae,* are most commonly found. *Mycobacterium tuberculosis, Neisseria meningitidis,* and *Mycobacterium bovis* are rare causes.

CLINICAL MANIFESTATIONS

Onset may be insidious or rapid and is characterized by fever, abdominal pain and a toxic appearance. Vomiting and diarrhea may be present. Hypotension and tachycardia are common along with shallow, rapid respirations because of discomfort associated with breathing. Abdominal palpation might demonstrate rebound tenderness and rigidity. Bowel sounds are hypoactive or absent. However, signs and symptoms may be subtle at times and increase vigilance is needed in cirrhotic patients who have ascites and present with unexplained leukocytosis, azotemia, or metabolic acidosis.

DIAGNOSIS AND TREATMENT

Peripheral leukocytosis with a marked predominance of polymorphonuclear cells is common, although the white blood cell (WBC) count can be affected by preexisting hypersplenism in patients with cirrhosis. Patients with nephrotic syndrome generally have proteinuria, and low serum albumin in these patients is associated with increased risk of peritonitis. X-ray examination of the abdomen reveals dilation of the large and small intestines, with increased separation of loops secondary to bowel wall thickening. Distinguishing primary peritonitis from appendicitis may be impossible in patients without a history of nephrotic syndrome or cirrhosis; accordingly, the diagnosis of primary peritonitis is made by CT scan, laparoscopy, or laparotomy. In a child with known renal or hepatic disease and ascites, the presence of peritoneal signs should prompt diagnostic paracentesis. Infected fluid usually reveals a WBC count of ≥250 cells/mm^3, with >50% polymorphonuclear cells.

Primary peritonitis is usually monomicrobial. The presence of mixed bacterial flora on ascitic fluid examination or free air on abdominal roentgenogram in children with presumed peritonitis mandates laparotomy to localize a perforation as a likely intraabdominal source of the infection. Inoculation of ascitic fluid obtained at paracentesis directly into blood culture bottles increases the yield of positive cultures. Parenteral antibiotic therapy with broad spectrum coverage, such as cefotaxime, should be started promptly, with subsequent changes dependent on sensitivity testing (vancomycin for resistant pneumococci). Therapy should be continued for 10-14 days.

Culture-negative neutrocytic ascites is a variant of primary peritonitis with a ascetic fluid WBC count of >500 cells/mm^3, a negative culture, no intraabdominal source of infection, and no prior treatment with antibiotics. It should be treated in a similar manner as primary peritonitis.

Bibliography is available at Expert Consult.

371.2 Acute Secondary Peritonitis

Jessica W. Wen and Chris A. Liacouras

Acute secondary peritonitis most often results from entry of enteric bacteria into the peritoneal cavity through a necrotic defect in the wall of the intestines or other viscus as a result of obstruction or infarction or after rupture of an intraabdominal visceral abscess. It most commonly follows perforation of the appendix. Other causes include incarcerated hernias, rupture of a Meckel diverticulum, midgut volvulus, intussusception, hemolytic uremic syndrome, peptic ulceration, inflammatory bowel disease, necrotizing cholecystitis, necrotizing enterocolitis, typhlitis, and traumatic perforation.

Peritonitis in the neonatal period most often occurs as a complication of necrotizing enterocolitis but may be associated with meconium ileus or spontaneous (or indomethacin-induced) rupture of the stomach or intestines. In postpubertal girls, bacteria from the genital tract *(Neisseria gonorrhoeae, Chlamydia trachomatis)* can gain access to the peritoneal cavity via the fallopian tubes, causing secondary peritonitis. The presence of a foreign body, such as a ventriculoperitoneal catheter or peritoneal dialysis catheter, can predispose to peritonitis, with skin microorganisms, such as *Staphylococcus epidermidis, Staphylococcus aureus,* and *Candida albicans,* contaminating the shunt. Secondary peritonitis results from direct toxic effects of bacteria as well as local and systemic release of inflammatory mediators in response to organisms and their products (lipopolysaccharide endotoxin). The development of sepsis depends on various host and disease factors, as well as promptness of antimicrobial and surgical intervention.

CLINICAL MANIFESTATIONS

Similar to primary peritonitis, characteristic symptoms include fever, diffuse abdominal pain, nausea, and vomiting. Physical findings of peritoneal inflammation include rebound tenderness, abdominal wall rigidity, a paucity of body motion (lying still), and decreased or absent bowel sounds from paralytic ileus. Massive exudation of fluid into the peritoneal cavity, along with the systemic release of vasodilative substances, can lead to the rapid development of shock. A toxic appearance, irritability, and restlessness are common. Basilar atelectasis as well as intrapulmonary shunting can develop, with progression to acute respiratory distress syndrome.

Laboratory studies reveal a peripheral WBC count >12,000 cells/mm^3, with a marked predominance of polymorphonuclear forms. X-rays of the abdomen can reveal free air in the peritoneal cavity, evidence of ileus or obstruction, peritoneal fluid, and obliteration of the psoas shadow. Other peritoneal fluid findings suggestive of secondary peritonitis include elevated total protein (>1 g/dL), low glucose (<50 mg/dL).

TREATMENT

Aggressive fluid resuscitation and support of cardiovascular function should begin immediately. Stabilization of the patient before surgical intervention is mandatory. Antibiotic therapy must provide coverage for organisms that predominate at the site of presumed origin of the infection. In contrast to primary peritonitis, secondary peritonitis is typically polymicrobial. For perforation of the lower gastrointestinal tract, a regimen of ampicillin, gentamicin, and clindamycin or metronidazole will adequately address infection by *E. coli, Klebsiella,* and *Bacteroides* spp. and enterococci. Alternative therapy could include ticarcillin-clavulanic acid and an aminoglycoside or piperacillin/tazobactam. Surgery to repair a perforated viscus should proceed after the patient is stabilized and antibiotic therapy is initiated. Intraoperative peritoneal fluid cultures will indicate whether a change in the antibiotic regimen is warranted. Empirical treatment for peritoneal dialysis catheter–related peritonitis may include intraperitoneal cefepime or cefazolin plus ceftazidime. Serious infection from peritoneal dialysis catheters can generally be prevented with good catheter hygiene and prompt removal and replacement with signs of progressive infection.

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371.3 Acute Secondary Localized Peritonitis (Peritoneal Abscess)

Jessica W. Wen and Chris A. Liacouras

ETIOLOGY

Intraabdominal abscesses occur less commonly in children and infants than in adults, but can develop in visceral intraabdominal organs (hepatic, splenic, renal, pancreatic, tuboovarian abscesses) or in the interintestinal, periappendiceal, subdiaphragmatic, subhepatic, pelvic, or retroperitoneal spaces. Most commonly, periappendiceal and pelvic abscesses arise from a perforation of the appendix. Transmural

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inflammation with fistula formation can result in intraabdominal abscess formation in children with inflammatory bowel disease.

CLINICAL MANIFESTATIONS

Prolonged fever, anorexia, vomiting, and lassitude suggest the development of an intraabdominal abscess. The peripheral WBC count is elevated, as is the erythrocyte sedimentation rate. With an appendiceal abscess, there is localized tenderness and a palpable mass in the right lower quadrant. A pelvic abscess is suggested by abdominal distention, rectal tenesmus with or without the passage of small-volume mucous stools, and bladder irritability. Rectal examination might reveal a tender mass anteriorly. Subphrenic gas collection, basal atelectasis, elevated hemidiaphragm, and pleural effusion may be present with a subdiaphragmatic abscess. Psoas abscess can develop from extension of infection from a retroperitoneal appendicitis, Crohn disease, perirenal or intrarenal abscess. Abdominal findings may be minimal, and presentation can include a limp, hip pain, and fever. Ultrasound examination, CT scanning, and MRI may be used to localize intraabdominal abscesses; MRI gives the best resolution of disease involvement.

TREATMENT

An abscess should be drained and appropriate antibiotic therapy provided. Drainage can be performed under radiologic control (ultrasonogram or CT guidance) and an indwelling drainage catheter left in place or surgically depending on location of abscess. Initial broad-spectrum antibiotic coverage such as a combination of ampicillin, gentamicin, and clindamycin or ciprofloxacin and metronidazole should be started and can be modified depending on the results of sensitivity testing. The treatment of appendiceal rupture complicated by abscess formation may be problematic because intestinal phlegmon formation can make surgical resection more difficult. Intensive antibiotic therapy for 4-6 wk followed by an interval appendectomy is often the treatment course followed.

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Chapter **372**

Epigastric Hernia

John J. Aiken and Keith T. Oldham

Epigastric hernias are ventral hernias in the midline of the abdominal wall between the xiphoid and the umbilicus. Epigastric hernias result from defects in the decussating fibers of the linea alba and are more likely congenital than acquired. Because most epigastric hernias are small and asymptomatic, the true incidence is unknown, but the reported incidence in childhood varies from <1% to as high as 5%. Epigastric hernias may be single or multiple and are 2-3 times more common in males than females. The defect typically contains only preperitoneal fat without a peritoneal sac or abdominal viscera. Epigastric (incisional) hernias can occur in a previous incision site or be associated with ventricular-peritoneal shunts.

CLINICAL PRESENTATION

Epigastric hernias typically appear in young children as a visible or palpable mass in the midline, between the umbilicus and the xiphoid, noted by the parents or primary care practitioner. The mass is almost always small (<1 cm) and asymptomatic. The mass is typically present at all times but most apparent at times of irritability or straining. Occasionally, the mass is intermittent and the child relates pain localized to the site of the hernia. Physical examination demonstrates a firm mass, directly in the midline, anywhere between the umbilicus and the xiphoid. Epigastric hernias typically contain only preperitoneal fat and are not reducible because of the small size of the fascial defect. Rarely, a fascial defect is noted without a palpable mass. The mass may be intermittent if the fat reduces with relaxation of the abdominal muscles. Herniation of intestines or abdominal viscera in an epigastric hernia would be exceptionally rare. The mass may be tender to examination, but strangulation of the hernia contents is uncommon. Physical examination is almost always diagnostic and imaging studies are unnecessary.

The natural history of epigastric hernias is for gradual enlargement over time as intermittently more preperitoneal fat is extruded through the defect at times of straining or increased intraabdominal pressure. Left untreated, the defect can enlarge and allow herniation of intraabdominal viscera within a peritoneal sac. Epigastric hernias do not resolve spontaneously, and therefore operative repair is the recommended treatment.

The site should be carefully marked preoperatively because the mass and defect can be difficult to localize after induction of anesthesia. A limited transverse incision is made over the mass and dissection is performed to delineate the edges of the fascial defect. If herniated fat is present, it is dissected free of the subcutaneous tissues and can be reduced or ligated and excised. The defect is closed using absorbable suture. The skin is closed with an absorbable subcuticular suture. Postoperative complications are rare and the recurrence rate is low.

Bibliography is available at Expert Consult.

372.1 Incisional Hernia

John J. Aiken and Keith T. Oldham

Hernia formation at the site of a previous laparotomy is uncommon in childhood. Factors associated with an increased risk of incisional hernia include increased intraabdominal pressure, wound infection, and midline incision. Transverse abdominal incisions are favored because of their increased strength and blood supply, which reduce the likelihood of wound infection and incisional hernia. Although most incisional hernias require repair, operation should be deferred until the child is in optimal medical condition. Some incisional hernias resolve, especially those occurring in infants. Some recommend elastic bandaging to discourage enlargement of the hernia and to promote spontaneous healing. Newborns with abdominal wall defects represent the largest group of children with incisional hernias. Initial management should be conservative, with repair deferred until about 1 yr of age. Incarceration is very uncommon but is an indication for prompt repair.

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Respiratory System

PART XIX

Section 1

Development and Function

Chapter 373 Respiratory Pathophysiology and Regulation

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

The respiratory system serves to supply sufficient oxygen to meet metabolic demands and remove carbon dioxide. Abnormalities in any of the multiple processes (including ventilation, perfusion, and diffusion) that are involved in tissue oxygenation and carbon dioxide removal can lead to respiratory failure. The pathophysiologic manifestations of respiratory disease processes are profoundly influenced by age- and growth-dependent changes in the physiology and anatomy of the respiratory control mechanisms, airway dynamics, and lung parenchymal characteristics. Smaller airways, a more compliant chest wall, and poor hypoxic drive render a younger infant more vulnerable compared to an older child with similar severity of disease.

Respiratory distress may be diagnosed from signs such as cyanosis, nasal flaring, grunting, tachypnea, wheezing, chest wall retractions, and stridor. Respiratory failure can be present without respiratory distress; a patient with abnormalities of central nervous system (CNS) or neuromuscular disease or exhaustion might not be able to mount sufficient effort to appear in respiratory distress. A child who appears in respiratory distress might not have a respiratory illness; a patient with primary metabolic acidosis (diabetic ketoacidosis) or CNS excitatory states (encephalitis) can present in severe respiratory distress without respiratory disease.

Bibliography is available at Expert Consult.

373.1 Lung Volumes and Capacities in Health and Disease

Ashok P. Sarnaik, Jeff A. Clark, and Sabrina M. Heidemann

Traditionally, lung volumes are measured with a spirogram (Fig. 373-1). **Tidal volume (V_T)** is the amount of air moved in and out of the lungs during each breath; at rest, V_T is normally 6-7 mL/kg body weight. **Inspiratory capacity** is the amount of air inspired by maximum inspiratory effort after tidal expiration. **Expiratory reserve volume** is the amount of air exhaled by maximum expiratory effort after tidal expiration. The volume of gas remaining in the lungs after maximum expiration is **residual volume. Vital capacity** is defined as the amount of air moved in and out of the lungs with maximum inspiration and expiration. Vital capacity, inspiratory capacity, and expiratory reserve volume are decreased in lung pathology but are also effort dependent. **Total lung capacity** is the volume of gas occupying the lungs after maximum inhalation.

Flow volume relationship offers a valuable means at the bedside or in an office setting to detect abnormal pulmonary mechanics and response to therapy with relatively inexpensive and easy-to-use devices. After maximum inhalation, the patient forcefully exhales through a mouthpiece into the device until residual volume is reached followed by maximum inhalation (Fig. 373-2). Flow is plotted against volume. **Maximum forced expiratory flow (FEF_{max})** is generated in the early part of exhalation, and it is a commonly used indicator of airway obstruction in asthma and other obstructive lesions. Provided maximum pressure is generated consistently during exhalation, a decrease in flow is a reflection of increased airway resistance. The total volume exhaled during this maneuver is **forced vital capacity (FVC)**. **Volume exhaled in 1 sec** is referred to as **FEV_1**. FEV_1/FVC is expressed as a percentage

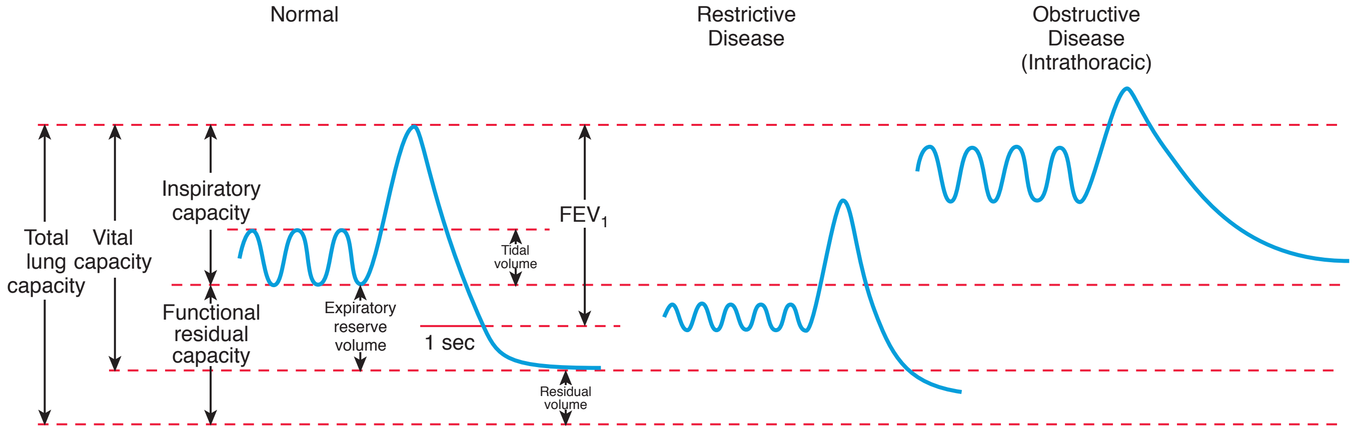

Figure 373-1 Spirogram showing lung volumes and capacities. FEV_1 is the maximum volume exhaled in 1 sec after maximum inspiration. Restrictive diseases are usually associated with decreased lung volumes and capacities. Intrathoracic airway obstruction is associated with air trapping and abnormally high functional residual capacity and residual volume. FEV_1 and vital capacity are decreased in both restrictive and obstructive diseases. The ratio of FEV_1 to vital capacity is normal in restrictive disease but decreased in obstructive disease. FEV, forced expiratory volume.

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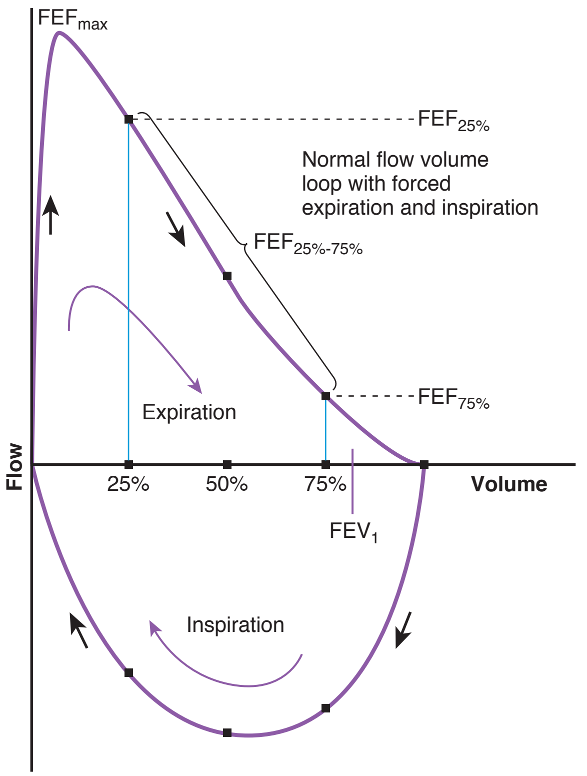

Figure 373-2 **Flow volume loop in a normal person performed after maximal inspiration followed by forced complete expiration and forced complete inhalation.** FEF_{max} represents maximum flow during expiration. This is attained soon after initiation of the expiration. Fall in expiratory flow is gradual until it reaches zero after exhalation is complete. $FEF_{25\%-75\%}$ represents mean flow from 25% ($FEF_{25\%}$) to 75% ($FEF_{75\%}$) of exhaled forced expiratory volume (FEV), also termed *forced vital capacity* (FVC). FEV_1 is amount of volume after 1 sec of forced exhalation. Normally FEV_1 is around 80% of FVC.

of FVC. $FEF_{25\%-75\%}$ is the mean flow between 25% and 75% of FVC and is considered relatively effort independent. Individual values and shapes of flow-volume curves show characteristic changes in obstructive and restrictive respiratory disorders (Fig. 373-3). In intrapulmonary airway obstruction such as asthma or cystic fibrosis, there is a reduction of FEF_{max}, $FEF_{25\%-75\%}$, FVC, and FEV_1/FVC. Also, there is a characteristic concavity in the middle part of the expiratory curve. In restrictive lung disease such as interstitial pneumonia (see Chapter 399.5) and kyphoscoliosis (see Chapter 417.5), FVC is decreased with relative preservation of airflow and FEV_1/FVC. The flow volume curve assumes a vertically oblong shape compared to normal. Changes in shape of the flow volume loop and individual values depend on the type of disease and the extent of severity. Serial determinations provide valuable information regarding disease evolution and response to therapy.

Functional residual capacity (FRC) is the amount of air left in the lungs after tidal expiration. FRC has important pathophysiologic implications. Alveolar gas composition changes during inspiration and expiration. **Alveolar Po_2 (PAo_2)** increases and **alveolar Pco_2 ($PAco_2$)** decreases during inspiration as fresh atmospheric gas enters the lungs. During exhalation, PAo_2 decreases and $PAco_2$ increases as pulmonary capillary blood continues to remove oxygen from and add CO_2 into the alveoli (Fig. 373-4). FRC acts as a buffer, minimizing the changes in PAo_2 and $PAco_2$ during inspiration and expiration. FRC represents the environment available for pulmonary capillary blood for gas exchange at all times.

A decrease in FRC is often encountered in alveolar interstitial diseases and thoracic deformities. The major pathophysiologic consequence of decreased FRC is **hypoxemia**. Reduced FRC results in a sharp decline in PAo_2 during exhalation because a limited volume is available for gas exchange. Po_2 of pulmonary capillary blood therefore falls excessively during exhalation, leading to a decline in **arterial** Po_2 (PAo_2). Any increase in PAo_2 (and therefore Pao_2) during inspiration cannot compensate for the decreased Pao_2 during expiration. The explanation for this lies in the shape of O_2-hemoglobin (Hb) dissociation curve, which is sigmoid shaped (Fig. 373-5). Because most of the oxygen in blood is combined with Hb, it is the percentage of **oxyhemoglobin (So_2)** that gets averaged rather than the Po_2. Although an

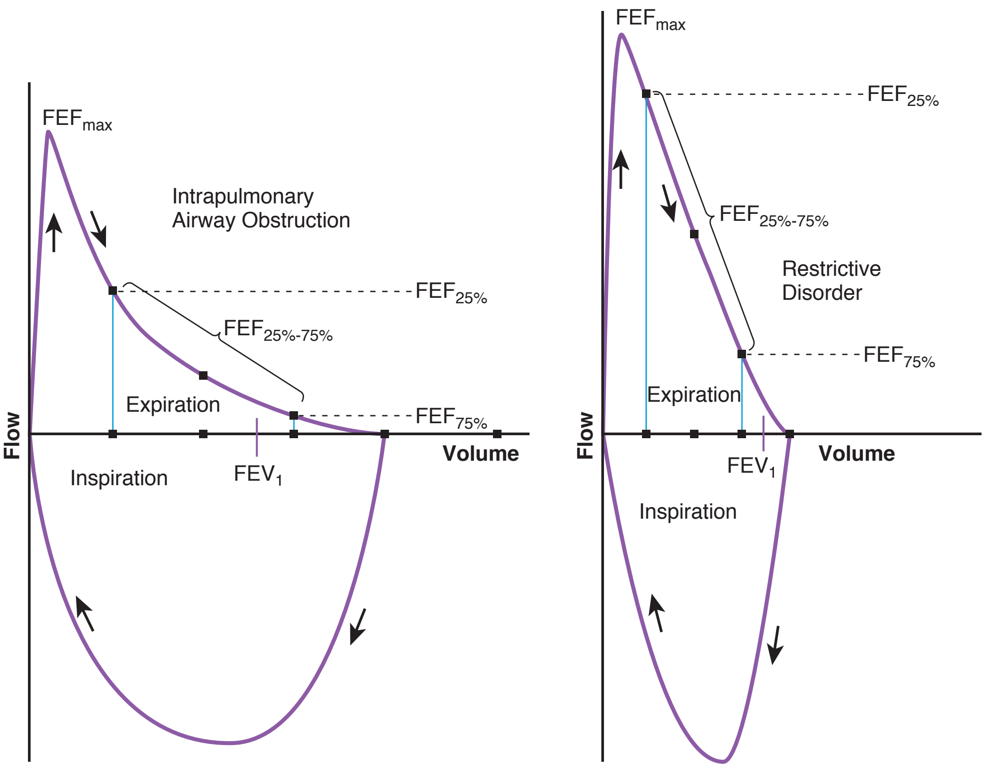

Figure 373-3 **Flow volume loops in intrapulmonary airway obstruction and restrictive disorders.** Note that in intrapulmonary airway obstruction, there is a decrease in FEF_{max}, $FEF_{25\%-75\%}$, and FEV_1/FVC%. The middle part of expiratory loop appears concave. In restrictive disorder, the flow volume loop assumes a more vertically oblong shape with reduction in FVC but not the FEV_1/FVC%. Expiratory and inspiratory flow rates are relatively unaffected. FEF, forced expiratory flow; FEV, forced expiratory volume; FVC, forced vital capacity.

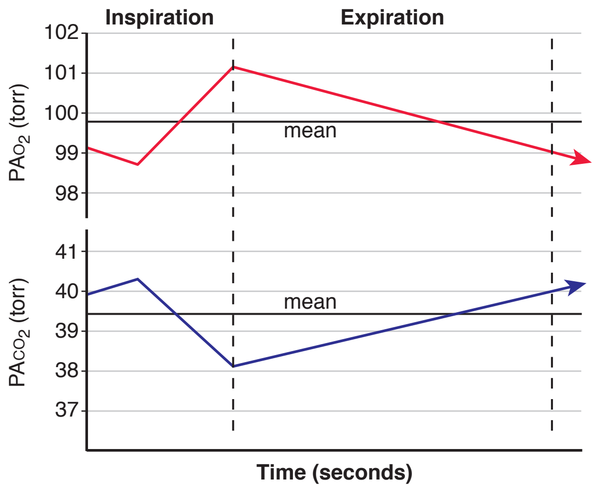

Figure 373-4 **Alveolar P_{O_2} rises and P_{CO_2} falls during inspiration as fresh atmospheric gas is brought into the lungs.** During expiration, the opposite changes occur as pulmonary capillary blood continues to remove O_2 and add CO_2 from the alveoli without atmospheric enrichment. Note that during the early part of inspiration, alveolar P_{O_2} continues to fall and P_{CO_2} continues to rise because of inspiration of the dead space that is occupied by the previously exhaled gas. *(Modified from Comroe JH:* Physiology of respiration, *ed 2, Chicago, 1974, Year Book Medical Publishers, p 12.)*

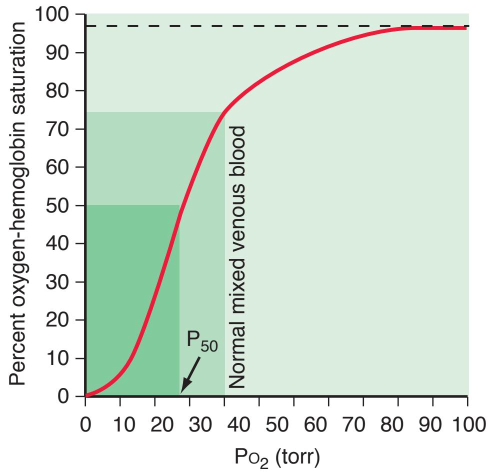

Figure 373-5 **Oxygen-hemoglobin dissociation curve. P_{50} of adult blood is around 27 torr.** Under basal conditions, mixed venous blood has P_{O_2} of 40 torr and oxygen-hemoglobin saturation of 75%. In arterial blood, these values are 100 torr and 97.5%, respectively. Note that there is a steep decline in oxygen-hemoglobin saturation at Pa_{O_2} <50 torr, but relatively little increase in saturation is gained at PO_2 >70 torr.

increase in arterial P_{O_2} cannot increase O_2-Hb saturation >100%, there is a steep desaturation of Hb below a P_{O_2} of 50 torr; thus, decreased S_{O_2} during exhalation as a result of low FRC leads to overall arterial desaturation and hypoxemia. The adverse pathophysiologic consequences of decreased FRC are ameliorated by application of **positive end-expiratory pressure (PEEP)** and increasing the inspiratory time during mechanical ventilation.

The lung pressure–volume relationship is markedly influenced by FRC (Fig. 373-6). Pulmonary compliance is decreased at abnormally low or high FRC.

FRC is abnormally increased in intrathoracic airway obstruction, which results in incomplete exhalation, and abnormally decreased in alveolar-interstitial diseases. At excessively low or high FRC, tidal respiration requires higher inflation pressures compared to normal

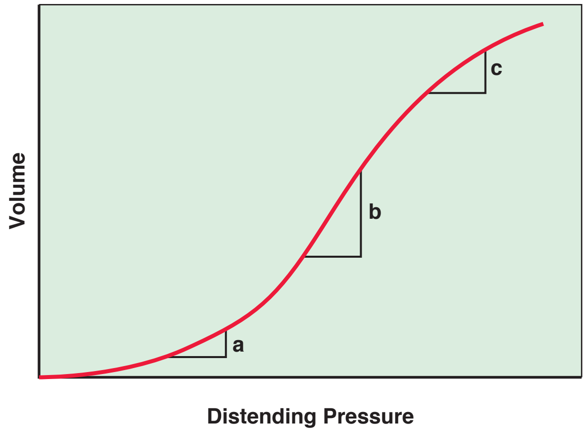

Figure 373-6 **Lung compliance is significantly influenced by the functional residual capacity (FRC).** The same change in pressure is associated with less change in volume when FRC is abnormally decreased *(a)* or abnormally increased *(c)* compared to the normal state *(b)*.

FRC. Abnormalities of FRC result in increased work of breathing with spontaneous respiration and increased barotrauma in mechanical ventilation.

Bibliography is available at Expert Consult.

373.2 Chest Wall

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

The chest wall and diaphragm of an infant are mechanically disadvantaged compared to that of an adult when required to increase thoracic (and therefore the lung) volume. The infant's ribs are oriented much more horizontally and the diaphragm is flatter and less domed. Consequently, the infant is unable to duplicate the efficiency of upward and outward movement of obliquely oriented ribs and downward displacement of the domed diaphragm in an adult to expand the thoracic capacity. Additionally, the infant's rib cage is softer and thus more compliant compared to an adult's rib cage. Although a soft, highly compliant chest wall is beneficial to a baby in its passage through the birth canal and allows future lung growth, it places the young infant in a vulnerable situation under certain pathologic conditions. Chest wall compliance is a major determinant of FRC. Because the chest wall and the lungs recoil in opposite directions at rest, FRC is reached at the point where the outward elastic recoil of the thoracic cage counterbalances the inward lung recoil. This balance is attained at a lower lung volume in a young infant because of the extremely high thoracic compliance compared to older children (Fig. 373-7). The measured FRC in infants is higher than expected because respiratory muscles of infants maintain the thoracic cage in an inspiratory position at all times. Additionally, some amount of air trapping during expiration occurs in young infants.

The increased chest wall compliance is a distinct disadvantage to the young infant under several pathologic conditions. A decrease in muscle tone, as occurs in *rapid eye movement (REM)* sleep or with CNS depression, allows greater chest wall retraction because of less opposition to the lung recoil; the FRC decreases in such states. The respiratory muscles of infants are poorly equipped to sustain large workloads. They are more easily fatigued than those of older children, limiting their ability to maintain adequate ventilation in lung disease. In diseases of poor lung compliance (atelectasis, pulmonary edema), excessive lung recoil results in greater retraction of the soft chest wall and more loss of FRC than occurs in older children and adults with stiffer chest walls. Increased negative intrathoracic pressure required to overcome airway resistance in upper airway obstruction also produces greater chest wall

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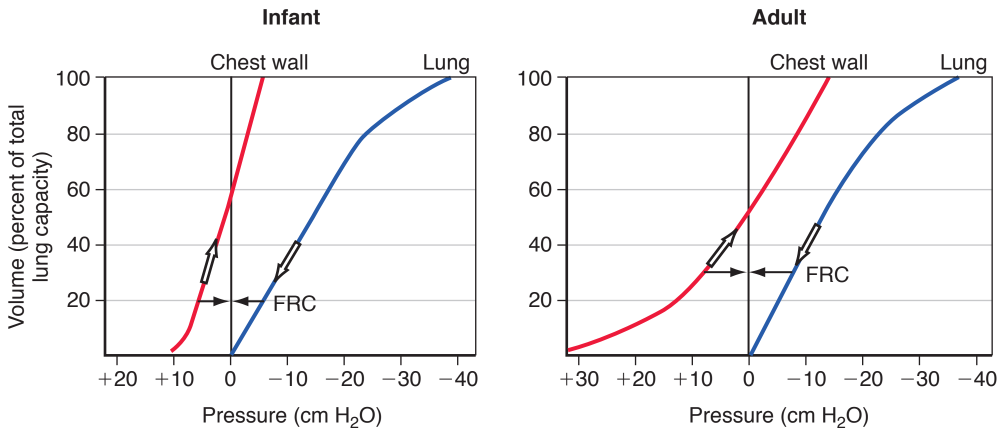

Figure 373-7 Schematic of interaction between chest wall and lung recoil in infants compared to adults. The elastic recoil of a relatively more compliant chest wall is balanced by the lung recoil at a lower volume (FRC) in infants compared to adults. FRC, functional residual capacity.

recoil and reduced FRC in young infants. Application of PEEP is beneficial in such states for stabilizing the chest wall and restoring FRC.

Young infants do not tolerate sustained respiratory loads as well as older children and adults. Respiratory muscle ontogeny is characterized by changes in the composition of muscle fiber types in the diaphragm and intercostals throughout infancy. Type I fibers are slow-twitch and high-oxidative in nature, whereas type II fibers are fast-twitch and low-oxidative. Type I fibers have low contractility but are fatigue resistant. Type II fibers have high contractility but are more prone to fatigue. The proportion of type I fibers in the diaphragm and intercostals of premature infants is only around 10%. This increases to around 25% in full-term newborns and around 50% in children older than age 2 yr. Respiratory muscles of premature babies and young infants are therefore more susceptible to fatigue, resulting in earlier decompensation.

Abnormalities of the chest wall are encountered in certain pathologic conditions. Chest wall instability can result from trauma (fractured ribs, thoracotomy) and neuromuscular diseases that lead to intercostal and diaphragmatic muscle weakness. The increased chest wall compliance makes such children more vulnerable to respiratory decompensation when faced with similar pulmonary pathology compared to older children and adults with stiffer chest walls. Children with rigid, noncompliant chest wall (asphyxiating thoracic dystrophy of Jeune [see Chapters 417.3 and 700], achondroplasia [see Chapter 417.4]) have markedly diminished lung volumes and capacities.

Bibliography is available at Expert Consult.

373.3 Pulmonary Mechanics and Work of Breathing in Health and Disease

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

The movement of air in and out of the lungs requires a sufficient pressure gradient between alveoli and atmosphere during inspiration and expiration. Part of the pressure gradient is required to overcome the lung and chest wall elastance; another part is needed to overcome airway resistance. **Elastance** refers to the property of a substance to oppose deformation or stretching. It is calculated as a change in pressure (ΔP) divided by change in volume (ΔV). Elastic recoil is a property of a substance that enables it to return to its original state after it is no longer subjected to pressure. **Compliance** ($\Delta V \div \Delta P$) is the reciprocal of elastance. In the context of the pulmonary parenchyma, airways, and the chest wall, the compliance refers to their distensibility. **Resistance** is calculated as the amount of pressure required to generate flow of gas across the airways. Resistance to laminar flow is governed by *Poiseuille's law* stated as:

$$R = 8l\eta \div \Pi r^4$$

where R is resistance, l is length, η is viscosity, and r is the radius. The practical implication of pressure-flow relationship is that airway resistance is inversely proportional to its radius raised to the 4th power. If the airway lumen is decreased in half, the resistance increases 16-fold. Newborns and young infants with their inherently smaller airways are especially prone to marked increase in airway resistance from inflamed tissues and secretions. In diseases in which airway resistance is increased, flow often becomes turbulent. **Turbulence** depends to a great extent on the *Reynolds number* (Re), a dimensionless entity, which is calculated as:

$$Re = 2rvd \div \eta$$

where r is radius, v is velocity, d is density, and η is viscosity. Turbulence in gas flow is most likely to occur when Re exceeds 2000. Resistance to turbulent flow is greatly influenced by density. A low-density gas such as helium-oxygen mixture decreases turbulence in obstructive airway diseases such as viral laryngotracheobronchitis and asthma. Neonates and young infants are predominantly nose breathers and therefore even a minimal amount of nasal obstruction is poorly tolerated.

The diaphragm is the major muscle of respiration. When additional **work of breathing (WOB)** is required, intercostal and other accessory muscles of respirations also contribute to the increased work. The V_T and respiratory rate are adjusted, both in health and disease, to maintain the required minute volume with the least amount of energy expenditure. The total WOB (necessary to create pressure gradients to move air) is divided into 2 parts. The first part is to overcome the lung and chest wall elastance and is referred to as **elastic work (W_{elast})**. The second part is to overcome airway and tissue resistance, and is referred to as **resistive work (W_{resist})**. W_{elast} is directly proportional to V_T, whereas W_{resist} is determined by the rate of airflow and, therefore, the respiratory rate. The total WOB is lowest at a rate of 35-40/min for neonates and 14-16/min for older children and adults. W_{elast} is disproportionately increased in diseases with decreased compliance and W_{resist} is increased in airway obstruction. Consequently, respirations are shallow (low V_T) and rapid in diseases of low compliance and deep and relatively slow (low flow rate) in diseases of increased resistance.

Compared to older children, young infants have disproportionately greater W_{elast} because the negative intrapleural pressure during inspiration causes the retractile (more compliant) chest wall to collapse and pose an impediment to air entry. Young infants increase their respiratory rate with any mechanical abnormality. Other examples of compliant chest wall being a disadvantage include flail chest resulting from

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rib fractures, thoracotomy, and neuromuscular weakness. One of the salutary effects of continuous positive airway pressure in such situations is the stabilization of the chest wall. Under normal conditions, the energy cost of WOB contributes to only approximately 2% of total caloric expenditure. In children with chronic lung disease or congestive heart failure the WOB can contribute to as much as 40% of total energy expenditure during physical activity, thus increasing their caloric needs.

Time constant, measured in seconds, is a product of compliance and resistance. It is a reflection of the amount of time required for proximal airway pressure (and therefore volume) to equilibrate with alveolar pressure. It takes 3 time constants for 95%, and 5 time constants for 99% of pressure equilibration to occur. Because intrathoracic airways expand during inspiration and narrow during expiration, expiratory time constant is longer than inspiratory time constant. Diseases characterized by decreased compliance (pneumonia, pulmonary edema, atelectasis) are associated with a shorter time constant and therefore require less time for alveolar inflation and deflation. Diseases associated with increased resistance (asthma, bronchiolitis, aspiration syndromes) have prolonged time constant and therefore require more time for alveolar inflation and deflation. Pathologic alterations in time constants have practical significance during mechanical ventilation. Patients with shorter time constants are best ventilated with relatively smaller tidal volumes and faster rates to minimize peak inflation pressure. In patients with increased airway resistance, a fast respiratory rate (and, therefore, less time) does not allow enough pressure equilibration to occur between the proximal airway and the alveoli. Inadequate inspiratory time results in lower V_T, whereas insufficient exhalation time results in inadvertent PEEP, often referred to as auto-PEEP or intrinsic PEEP. Such patients are best ventilated with relatively slower rates and larger tidal volumes.

Bibliography is available at Expert Consult.

373.4 Airway Dynamics in Health and Disease

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

Because the trachea and airways of an infant are much more compliant than those of older children and adults, changes in intrapleural pressure result in much greater changes in airway diameter. The airway can be divided into 3 anatomic parts: the **extrathoracic airway** extends from the nose to the thoracic inlet, the **intrathoracic–extrapulmonary airway** extends from the thoracic inlet to the main stem bronchi, and the **intrapulmonary airway** is within the lung parenchyma. During normal respirations, intrathoracic airways expand in inspiration as intrapleural pressure becomes more negative and narrow in expiration as they return to their baseline at FRC. The changes in diameter are of little significance in normal respiration. In diseases characterized by airway obstruction, much greater changes in intrapleural pressure are required to generate adequate airflow, resulting in greater changes in airway lumen. The changes in the size of airway during respiration are accentuated in young infants with their softer, more compliant airways.

In extrathoracic airway obstruction (choanal atresia [see Chapter 376], retropharyngeal abscess, laryngotracheobronchitis [see Chapter 385]), the high negative intrapleural pressure during inspiration is transmitted up to the site of obstruction, after which there is a rapid dissipation of pressure. Therefore, the extrathoracic airway below the site of obstruction has markedly increased negative pressure inside, resulting in its collapse, which makes the obstruction worse (Fig. 373-8*A*). This produces inspiratory difficulty, prolongation of inspiration, and inspiratory stridor. Also, the increased negative intrapleural pressure results in chest wall retractions. During expiration, the increased positive intrapleural pressure is again transmitted up the airways to the site of obstruction, leading to a distention of the extrathoracic airway and amelioration of obstruction (Fig. 373-8*B*).

Because of the increased positive intrapleural pressure during exhalation, the chest wall tends to bulge out, which produces the **classic paradoxical respiration,** in which the chest retracts during inspiration and bulges out during expiration. The younger the child, the softer is the chest wall and the more marked is the paradoxical respiration of extrathoracic airway obstruction. A pattern of seesaw respiration may also be evident in newborns and young infants as the compliant chest wall is sucked in and the abdomen bulges out during inspiration, with the converse happening during expiration.

In obstruction of intrathoracic–extrapulmonary airway (vascular ring [see Chapter 386.8], mediastinal tumors) and intrapulmonary airway (asthma, bronchiolitis), the increased negative intrapleural pressure results in a distention of intrathoracic airways during inspiration, thus providing some relief from obstruction (Fig. 373-9*A*).

During expiration, the increased positive intrathoracic pressure is transmitted up to the site of obstruction, after which it dissipates rapidly. The intrathoracic airway above the site of obstruction is

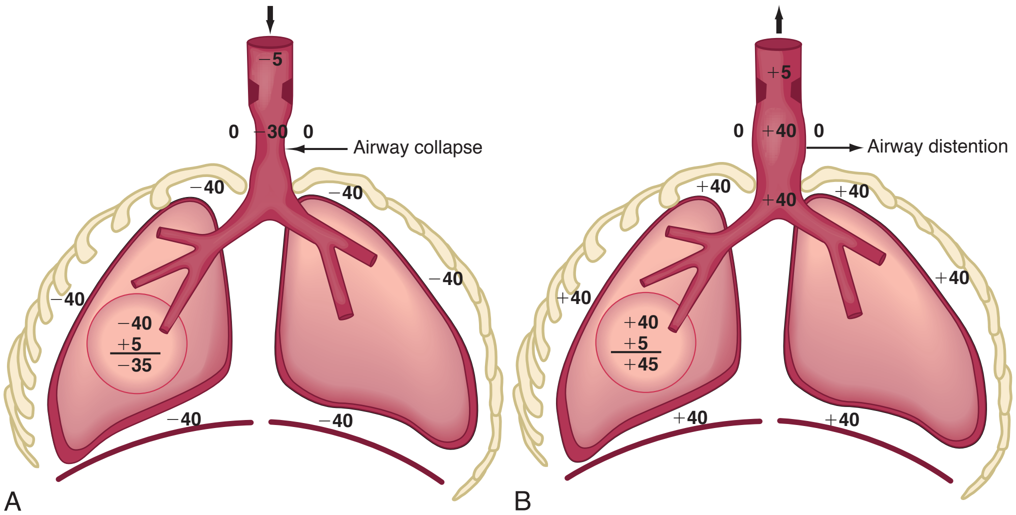

Figure 373-8 A, In extrathoracic airway obstruction, the increased negative pressure during inspiration is transmitted up to the site of obstruction. This results in collapse of the extrathoracic airway below the site of obstruction, making the obstruction worse during inspiration. Note that the pressures are compared to the atmospheric pressure, which is traditionally represented as 0 cm. Terminal airway pressure is calculated as intrapleural pressure plus lung recoil pressure. Lung recoil pressure is arbitrarily chosen as 5 cm for the sake of simplicity. **B,** During expiration, the positive pressure below the site of obstruction results in distention of extrathoracic airway and amelioration of symptoms.

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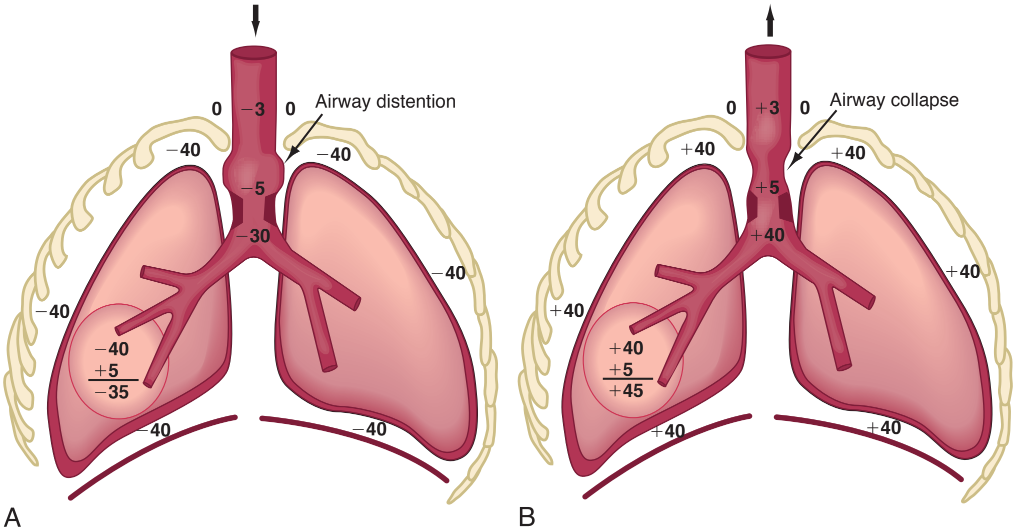

Figure 373-9 **A,** In intrathoracic–extrapulmonary airway obstruction, the increased negative pressure during inspiration is transmitted up to the site of obstruction. This results in the distention of the intrathoracic airway above the lesion because it is surrounded by an even greater negative intrapleural pressure. **B,** During expiration, the increased positive airway pressure rapidly dissipates above the obstruction. Consequently, there is a collapse of the intrathoracic airway above the obstruction as it is subjected to markedly increased positive intrapleural pressure, making the obstruction worse during expiration.

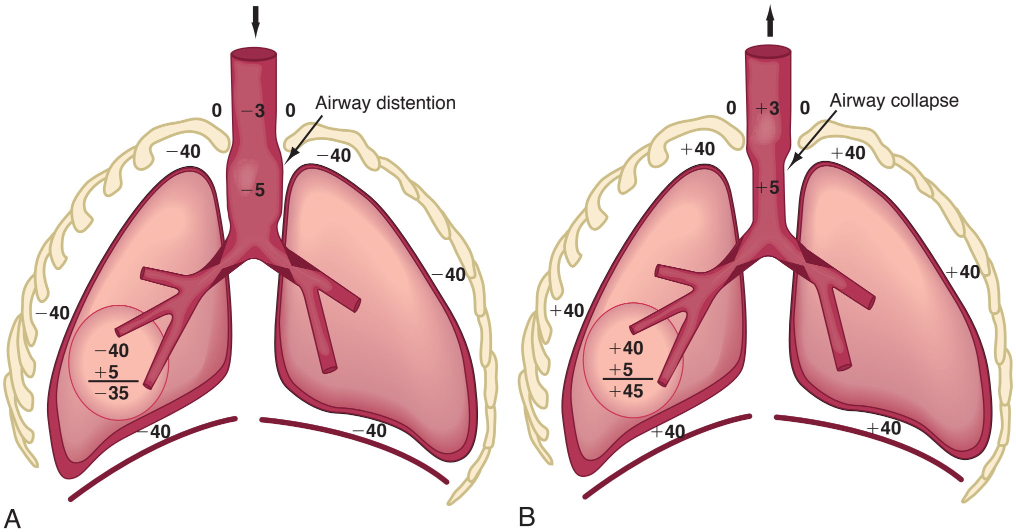

Figure 373-10 **A** and **B,** In intrapulmonary airway obstruction, even a wider segment of intrathoracic airway is subjected to pressure changes compared to those observed in intrathoracic-extrapulmonary airway obstruction. Such lesions are associated with marked increase in airway obstruction during expiration.

therefore subjected to much greater intrapleural pressure from outside, which cannot be adequately balanced by enough positive pressure inside, resulting in collapse above the site of obstruction (see Fig. 373-9*B*).

The site at which pressures inside and outside the airway during exhalation are equal is referred to as the **equal pressure point**. With intrathoracic airway obstruction, the equal pressure point is shifted distally toward the alveolus, causing airway collapse above. Marked inspiratory and expiratory changes in a young infant's airway lumen above the equal pressure point is often termed *collapsible trachea*. **Tracheal collapse** is often a sign of airway obstruction, and it even contributes to its severity, but it is rarely the primary abnormality. With intrapulmonary airway obstruction, an even wider portion of intrathoracic airway is subjected to pressure swings during inspiration and expiration (Fig. 373-10).

Both intrathoracic–extrapulmonary and intrapulmonary airway obstruction result in increasing difficulty during expiration, prolongation of expiration, and expiratory wheezing. Any airway obstruction within the thorax results in expiratory wheezing.

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373.5 Interpretation of Clinical Signs to Localize the Site of Pathology

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

The first step in establishing the diagnosis of respiratory disease is appropriate interpretation of clinical findings. Respiratory distress can occur without respiratory disease, and severe respiratory failure can be present without significant respiratory distress. Diseases characterized by CNS excitation, such as encephalitis, and neuroexcitatory drugs are

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associated with central neurogenic hyperventilation. Similarly, diseases that produce metabolic acidosis, such as diabetic ketoacidosis, salicylism, and shock, result in hyperventilation as a compensatory response. Patients in either group could be considered clinically to have respiratory distress; they are distinguished from patients with respiratory disease by their increased V_T as well as the respiratory rate. Their blood gas values reflect a low $Paco_2$ and a normal Pao_2. Patients with neuromuscular diseases, such as Guillain-Barré syndrome or myasthenia gravis, and those with an abnormal respiratory drive can develop severe respiratory failure but are not able to mount sufficient effort to appear in respiratory distress. In these patients, respirations are ineffective or can even appear normal in the presence of respiratory acidosis and hypoxemia.

The rate and depth of respiration and the presence of retractions, stridor, wheezing, and grunting are valuable signs in localizing the site of respiratory pathology (Table 373-1 and Fig. 373-11). Rapid and shallow respirations (**tachypnea**) are characteristic of parenchymal pathology, in which the elastic WOB is increased disproportionately to the resistive WOB. Chest wall, intercostal, and suprasternal **retractions** are most striking, with increased negative intrathoracic pressure during inspiration. This occurs in extrathoracic airway obstruction as well as diseases of decreased compliance. Inspiratory **stridor** is a hallmark of extrathoracic airway obstruction. Expiratory **wheezing** is characteristic of intrathoracic airway obstruction, either extrapulmonary or intrapulmonary. **Grunting** is produced by expiration against a partially closed glottis and is an attempt to maintain positive airway pressure during expiration for as long as possible. Such prolongation of positive pressure is most beneficial in alveolar diseases that produce widespread loss of FRC, such as in pulmonary edema, hyaline membrane disease, and pneumonia. Grunting is also effective in small airway obstruction (bronchiolitis) to maintain a higher positive pressure in the airway during expiration, decreasing the airway collapse.

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373.6 Ventilation-Perfusion Relationship in Health and Disease

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

Gravitational force pulls the lung away from the nondependent part of the parietal pleura. Therefore, alveoli and airways in the nondependent

Table 373-1 Interpreting the Clinical Signs of Respiratory Disease

SIGN	EXTRATHORACIC AIRWAY OBSTRUCTION	INTRATHORACIC–EXTRAPULMONARY AIRWAY OBSTRUCTION	INTRAPULMONARY AIRWAY OBSTRUCTION	PARENCHYMAL PATHOLOGY
Tachypnea	+	+	++	++++
Retractions	++++	++	++	+++
Stridor	++++	++	–	–
Wheezing	±	+++	++++	±
Grunting	±	±	++	++++

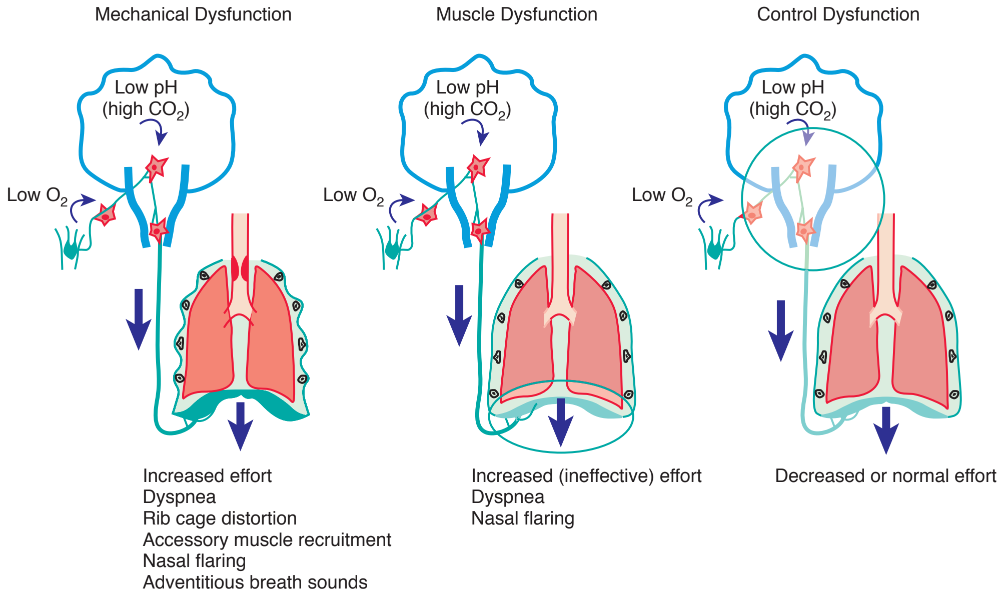

Figure 373-11 Presentation profiles of respiratory failure in childhood. When a mechanical dysfunction is present (by far, the most common circumstance), arterial hypoxemia and hypercapnia (and hence, pH) are sensed by peripheral (carotid bodies) and central (medullary) chemoreceptors. After being integrated with other sensory information from the lungs and chest wall, chemoreceptor activation triggers an increase in the neural output to the respiratory muscles *(vertical arrows)*, which results in the physical signs that characterize respiratory distress. When the problem resides with the respiratory muscles (or their innervation), the same increase in neural output occurs *(arrow)*, but the respiratory muscles cannot increase their effort as demanded; therefore, the physical signs of distress are more subtle. Finally, when the control of breathing is itself affected by disease, the neural response to hypoxemia and hypercapnia is absent or blunted and the gas exchange abnormalities are not accompanied by respiratory distress.

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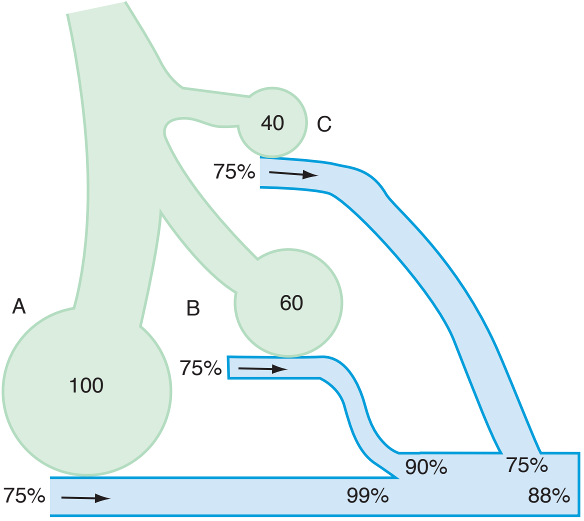

Figure 373-12 **Diagram demonstrating the effects of decreased ventilation–perfusion ratios on arterial oxygenation in the lungs.** Three alveolar–capillary units are illustrated. Unit A has normal ventilation and an alveolar PO_2 of 100 mm Hg (shown by the number in the middle of the space). The blood that circulates through this unit raises its oxygen saturation from 75% (the saturation of mixed venous blood) to 99%. Unit B has a lower ventilation–perfusion ratio and a lower alveolar PO_2 of 60 mm Hg. The blood that circulates through this unit reaches a saturation of only 90%. Finally, unit C is not ventilated at all. Its alveolar PO_2 is equivalent to that of the venous blood, which travels through the unit unaltered. The oxygen saturation of the arterial blood reflects the weighted contributions of these 3 units. If it is assumed that each unit has the same blood flow, the arterial blood would have a saturation of only 88%. Ventilation–perfusion mismatch is the most common mechanism of arterial hypoxemia in lung disease. Supplemental oxygen increases the arterial PO_2 by raising the alveolar PO_2 in lung units that, like B, have a ventilation–perfusion ratio >0.

parts (the upper lobes in upright position) of the lung are subjected to greater negative intrapleural pressure during tidal respiration and are kept relatively more inflated compared to the dependent alveoli and airways (the lower lobes in upright position). The nondependent alveoli are less compliant because they are already more inflated. During tidal inspiration, ventilation therefore occurs preferentially in the dependent portions of the lung that are more amenable to expansion. Although perfusion is also greater in the dependent portions of the lung because of greater pulmonary arterial hydrostatic pressure from gravity, the increase in perfusion is greater than the increase in ventilation in the dependent portions of the lung. Thus, the ratios favor ventilation in the nondependent portions and perfusion in the dependent portions. Because the airways in the dependent portion of the lung are narrower, they close earlier during expiration. The lung volume at which the dependent airways start to close is referred to as the **closing capacity.** In normal children, the FRC is greater than the closing capacity**.** During tidal respiration, airways remain patent both in the dependent and the nondependent portions of the lung. In newborns, the closing capacity is greater than the FRC, resulting in perfusion of poorly ventilated alveoli during tidal respiration; therefore, normal neonates have a lower Pao_2 compared to older children.

The relationship is adversely affected in a variety of pathophysiologic states (Fig. 373-12). Air movement in areas that are poorly perfused is referred to as **dead space ventilation.** Examples of dead space ventilation include pulmonary thromboembolism and hypovolemia. Perfusion of poorly ventilated alveoli is referred to as **intrapulmonary right-to-left shunting** or **venous admixture**. Examples include pneumonia, asthma, and hyaline membrane disease. In intrapulmonary airway obstruction, the closing capacity is abnormally increased and can exceed the FRC. In such situations, perfusion of poorly ventilated alveoli during tidal respiration results in venous admixture.

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373.7 Gas Exchange in Health and Disease

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

The main function of the respiratory system is to remove carbon dioxide from and add oxygen to the systemic venous blood brought to the lung. The composition of the inspired gas, ventilation, perfusion, diffusion, and tissue metabolism have a significant influence on the arterial blood gases.

The total pressure of the atmosphere at sea level is 760 torr. With increasing altitude, the atmospheric pressure decreases. The total atmospheric pressure is equal to the sum of partial pressures exerted by each of its component gases. Alveolar air is 100% humidified and, therefore, for alveolar gas calculations, the inspired gas is also presumed to be 100% humidified. At a temperature of 37°C (98.6°F) and 100% humidity, water vapor exerts pressure of 47 torr, regardless of altitude. In a natural setting, the atmosphere consists of 20.93% oxygen. **Partial pressure of oxygen in inspired gas (Pio_2)** at sea level is therefore (760 − 47) × 20.93% = 149 torr. When breathing 40% oxygen at sea level, Pio_2 is (760 − 47) × 40% = 285 torr. At higher altitudes, breathing different concentrations of oxygen, Pio_2 is less than at sea level, depending on the prevalent atmospheric pressures. In Denver (altitude of 5,000 feet and barometric pressure of 632 torr), Pio_2 in room air is (632 − 47) × 20.93% = 122 torr, and in 40% oxygen, it is (632 − 47) × 40% = 234 torr.

Minute volume is a product of V_T and respiratory rate. Part of the V_T occupies the conducting airways (anatomic dead space), which does not contribute to gas exchange in the alveoli. **Alveolar ventilation** is the volume of atmospheric air entering the alveoli and is calculated as (V_T − dead space) × respiratory rate. Alveolar ventilation is inversely proportional to arterial Pco_2 ($Paco_2$). When alveolar ventilation is halved, $Paco_2$ is doubled. Conversely, doubling of alveolar ventilation decreases $Paco_2$ by 50%. **Alveolar Po_2 (Pao_2)** is calculated by the **alveolar air equation** as follows:

$$PAo_2 = PiO_2 - (PAco_2 \div R)$$

where R is the respiratory quotient. For practical purposes, $PAco_2$ is substituted by **arterial Pco_2** ($Paco_2$) and R is assumed to be 0.8. According to the alveolar air equation, for a given Pio_2, a rise in $Paco_2$ of 10 torr results in a decrease in PAo_2 by 10 ÷ 0.8 or 10 × 1.25 or 12.5 torr. Thus, proportionately inverse changes in PAo_2 occur to the extent of 1.25× the changes in $PAco_2$ (or $Paco_2$).

After the alveolar gas composition is determined by the inspired gas conditions and process of ventilation, gas exchange occurs by the process of diffusion and equilibration of alveolar gas with pulmonary capillary blood. Diffusion depends on the alveolar capillary barrier and amount of available time for equilibration. In health, the equilibration of alveolar gas and pulmonary capillary blood is complete for both oxygen and carbon dioxide. In diseases in which alveolar capillary barrier is abnormally increased (alveolar interstitial diseases) and/or when the time available for equilibration is decreased (increased blood flow velocity), diffusion is incomplete. Because of its greater solubility in liquid medium, carbon dioxide is 20 times more diffusible than oxygen. Therefore, diseases with diffusion defects are characterized by marked **alveolar-arterial oxygen (A-aO_2)** gradients and hypoxemia. Significant elevation of CO_2 does not occur as a result of a diffusion defect unless there is coexistent hypoventilation.

Venous blood brought to the lungs is "arterialized" after diffusion is complete. After complete arterialization, the pulmonary capillary blood should have the same Po_2 and Pco_2 as in the alveoli. The arterial blood gas composition is different from that in the alveoli, even in normal conditions because there is a certain amount of dead space ventilation as well as venous admixture in a normal lung. Dead space ventilation results in a higher $Paco_2$ than $PAco_2$, whereas venous admixture or right-to-left shunting results in a lower Pao_2 compared to the alveolar gas composition (see Fig. 373-12). Pao_2 is a reflection of the amount of oxygen dissolved in blood, which is a relatively minor component of total blood oxygen content. For every 100 torr Po_2, there is 0.3 mL of dissolved O_2 in 100 mL of blood. The total blood oxygen

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content is composed of the dissolved oxygen and the oxygen bound to hemoglobin. Each gram of hemoglobin carries 1.34 mL of O_2 when 100% saturated with oxygen. Thus, 15 g of hemoglobin carries 20.1 mL of oxygen. **Arterial oxygen content (Cao_2)**, expressed as mL O_2/dL blood, can be calculated as ($Pao_2 \times 0.003$) + (Hb × 1.34 × So_2), where Hb is grams of Hb per deciliter of blood and So_2 is percentage of oxyhemoglobin saturation. The relationship of Po_2 and the amount of oxygen carried by the hemoglobin is the basis of the O_2-Hb dissociation curve (see Fig. 373-5). The Po_2 at which hemoglobin is 50% saturated is referred to as P_{50}. At a normal pH, hemoglobin is 94% saturated at Po_2 of 70, and little further gain in saturation is accomplished at a higher Po_2. At Po_2 <50, there is a steep decline in saturation and therefore the oxygen content.

Oxygen delivery to the tissues is a product of oxygen content and cardiac output. When hemoglobin is near 100% saturated, the blood contains approximately 20 mL oxygen per 100 mL or 200 mL/L. In a healthy adult, the cardiac output is approximately 5 L/min, oxygen delivery 1,000 mL/min, and oxygen consumption 250 mL/min. Mixed venous blood returning to the heart has a Po_2 of 40 torr and is 75% saturated with oxygen. Blood oxygen content, cardiac output, and oxygen consumption are important determinants of mixed venous oxygen saturation. Given a steady-state blood oxygen content and oxygen consumption, the mixed venous saturation is an important indicator of cardiac output. A declining mixed venous saturation in such a state indicates decreasing cardiac output.

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373.8 Interpretation of Blood Gases

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

Clinical observations and interpretation of blood gas values are critical in localizing the site of the lesion and estimating its severity (Table 373-2). In airway obstruction above the carina (subglottic stenosis, vascular ring), blood gases reflect overall alveolar hypoventilation. This is manifested by an elevated $PAco_2$ and a proportionate decrease in Pao_2 as determined by the alveolar air equation. A rise in $Paco_2$ of 20 torr decreases Pao_2 by 20 × 1.25 or 25 torr. In the absence of significant parenchymal disease and intrapulmonary shunting, such lesions respond very well to supplemental oxygen in reversing hypoxemia. Similar blood gas values, demonstrating alveolar hypoventilation and response to supplemental oxygen, are observed in patients with a depressed respiratory center and ineffective neuromuscular function, resulting in respiratory insufficiency. Such patients can be easily distinguished from those with airway obstruction by their poor respiratory effort.

In intrapulmonary airway obstruction (asthma, bronchiolitis), blood gases reflect ventilation-perfusion imbalance and venous admixture. In these diseases, the obstruction is not uniform throughout the lungs, resulting in areas that are hyperventilated and others that are hypoventilated. Pulmonary capillary blood coming from hyperventilated areas has a higher Po_2 and lower Pco_2, whereas that coming from hypoventilated regions has a lower Po_2 and higher Pco_2. A lower blood Pco_2 can compensate for the higher Pco_2 because the Hb-CO_2 dissociation curve is relatively linear. In mild disease, the hyperventilated areas predominate, resulting in hypocarbia. An elevated Pao_2 in hyperventilated areas cannot compensate for the decreased Pao_2 in hypoventilated areas because of the shape of the O_2-Hb dissociation curve. This results in venous admixture, arterial desaturation, and decreased Pao_2 (see Fig. 373-12). With increasing disease severity, more areas become hypoventilated, resulting in normalization of $Paco_2$ with a further decrease in Pao_2. A normal or slightly elevated $Paco_2$ in asthma should be viewed with concern as a potential indicator of impending respiratory failure. In severe intrapulmonary airway obstruction, hypoventilated areas predominate, leading to hypercarbia, respiratory acidosis, and hypoxemia. The degree to which supplemental oxygenation raises Pao_2 depends on the severity of the illness and the degree of venous admixture.

In alveolar and interstitial diseases, blood gas values reflect both intrapulmonary right-to-left shunting and a diffusion barrier. Hypoxemia is a hallmark of such conditions occurring early in the disease process. $Paco_2$ is either normal or decreased. An increase in $Paco_2$ is observed only later in the course, as muscle fatigue and exhaustion result in hypoventilation. Response to supplemental oxygen is relatively poor with shunting and diffusion disorders compared to other lesions.

Most clinical entities present with mixed lesions. A child with a vascular ring might also have an area of atelectasis; the arterial blood gas reflects both processes. The blood gas values reflect the more dominant lesion.

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373.9 Pulmonary Vasculature in Health and Disease

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

The tunica media of the pulmonary arteries of the fetus become more muscular in the last trimester of pregnancy (see Chapter 101.1). Up to 90% of the systemic venous return is shunted away from the pulmonary arterial circulation to the systemic arterial circulation through the foramen ovale and the ductus arteriosus. After birth, with functional closure of the foramen ovale and the ductus arteriosus, and dilation of the pulmonary arterial circulation with consequent decrease in **pulmonary vascular resistance** (**PVR**), all of the right ventricular output passes through the lung. The PVR is approximately 50% of the systemic arterial resistance 3 days after birth. In the next several wk after birth as pulmonary arterial musculature in the tunica media involutes, there is a further decline in PVR and therefore in pulmonary artery pressure. Two to 3 mo after birth, the PVR and the pulmonary artery pressure

Table 373-2 Interpretation of Arterial Blood Gas Values

LESION	EFFECT	TYPICAL ABG
Central (above the carina) airway obstruction, or Depressed respiratory center, or Ineffective neuromuscular function	Uniform alveolar hypoventilation	Early increase in Pco_2 Proportionate decrease in Po_2 depending on alveolar air equation Response to supplemental oxygen: Excellent
Intrapulmonary airway obstruction	Venous admixture $\dot{V}/\dot{Q}$ mismatch	Mild: ↓ Pco_2, ↓ Po_2 Moderate: "normal" Pco_2, ↓↓ Po_2 Severe: ↑↑ Pco_2, ↓↓↓ Po_2 Response to supplemental oxygen: good
Alveolar–interstitial pathology	Diffusion defect R → L shunt	Early decrease in Po_2 depending on severity Normal or low Pco_2, ↑ Pco_2 if fatigue develops Response to supplemental oxygen: fair to poor

ABG, arterial blood gas; $\dot{V}/\dot{Q}$, ventilation–perfusion.

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are approximately 15% of the systemic values, a relationship that exists through childhood and adolescence. Pulmonary vasculature constricts in response to hypoxemia, acidosis, and hypercarbia and dilates with increased alveolar and arterial Po_2, alkalosis, and hypocarbia. Younger infants, with their relatively muscular pulmonary arteries, are especially susceptible to pulmonary vasoconstrictive stimuli.

Failure of the pulmonary arterial circulation to dilate after birth results in **persistent pulmonary hypertension of the newborn** (see Chapter 101.7). Because of the persistently high PVR, the systemic venous blood returning to the right side of the heart continues to be shunted across the foramen ovale and the ductus arteriosus to the systemic arterial circulation, leading to a vicious cycle of hypoxemia, acidosis, and further pulmonary vasoconstriction.

The relatively high PVR opposes excessive left-to-right shunting in full-term neonates with ventricular septal defect and patent ductus arteriosus (see Chapter 426). Such infants do not usually manifest heart failure until 2-3 mo after birth, when PVR has sufficiently declined. Premature infants who have lesions capable of left-to-right shunting are susceptible to developing heart failure earlier in life because of less musculature in pulmonary artery tunica media and, therefore, a lower PVR. The gradual physiologic decline in PVR over the 1st 2-3 mo of life also explains how infants with anomalous left coronary artery arising from the pulmonary artery are asymptomatic at birth but present with signs of coronary insufficiency when PVR has fallen sufficiently to critically decrease coronary perfusion. Persistent and long-term left-to-right shunting carries the risk of developing secondary pulmonary vascular disease characterized by the postnatal development of medial muscular hypertrophy followed by intimal proliferation and increased PVR. Early changes in pulmonary vasculature are reversible with correction of the congenital heart defect responsible for left-to-right shunting. Advanced pulmonary vascular disease is characterized by irreversible intimal and medial changes. When PVR is increased to suprasystemic levels, right-to-left shunting occurs and is characterized by a cyanotic state (Eisenmenger syndrome), making the heart defect inoperable in the absence of an accompanying lung transplantation (see Chapter 433.2).

Pulmonary hypertension can develop without a well-defined etiology (primary pulmonary hypertension) or as a consequence of an underlying disease (secondary pulmonary hypertension) (see Chapter 433). Adverse effects of pulmonary hypertension are related to an increased right ventricular afterload, decreased cardiac output, and heart failure characterized by increased systemic venous pressure, hepatomegaly, and edema. In an acute situation, right ventricular failure and decreased cardiac output can worsen oxygen delivery and hypoxemia. Right ventricular failure secondary to pulmonary pathology is referred to as **cor pulmonale.** Secondary pulmonary hypertension is a common occurrence in end-stage chronic obstructive pulmonary disease such as cystic fibrosis (see Chapter 403) and bronchopulmonary dysplasia (see Chapter 416). Pulmonary arterial involvement is sometimes encountered in collagen vascular diseases such as scleroderma (see Chapter 160) and dermatomyositis (see Chapter 159). Functional or structural upper airway obstruction can also produce right ventricular failure. Children with marked obesity are also susceptible to chronic alveolar hypoventilation and right heart failure, termed **Pickwickian syndrome.** Treatment of the underlying cause is the first priority in patients with secondary pulmonary hypertension (see Chapter 433). Pulmonary hypertension is diagnosed by cardiac catheterization in order to rule out other pulmonary vascular diseases and to test for pulmonary reactivity. A diagnosis of pulmonary hypertension is a mean pulmonary artery pressure of ≥25 mm Hg at rest with a normal pulmonary capillary wedge pressure of ≤15 mm Hg and increased PVR index of ≥3 Wood units/m^2. Even though the etiologies are different, most of the drugs used to treat this condition in children are adapted from adult studies. Calcium channel blockers, prostanoids (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (bosentan, ambrisentan) and phosphodiesterase 5-inhibitors (sildenafil, tadalafil) are some of the agents used for treatment.

Bibliography is available at Expert Consult.

373.10 Immune Response of the Lung to Injury

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

Local and systemic diseases can potentially induce an inflammatory response in the lung. Local diseases of the lung capable of inducing the inflammatory response include infectious processes, aspiration, asphyxia, pulmonary contusion, and inhalation of chemical irritants; systemic diseases include sepsis, shock, trauma, and cardiopulmonary bypass. This inflammatory response is mediated through the release of cytokines and other mediators. In the lung, alveolar macrophages are the chief architects of the early cytokine response, producing **tumor necrosis factor-α** and **interleukin-1β.** These cytokines are involved in initiating the inflammatory cascade, resulting in the production of other cytokines, prostaglandins, reactive oxygen species, and upregulating cell adhesion molecules, which, in turn, leads to white cell migration into the lung tissue. The pathophysiologic consequences of the inflammatory response include injury to pulmonary capillary endothelium and the alveolar epithelial cells. Various cytokines and eicosanoids produce pulmonary vasoconstriction, resulting in pulmonary hypertension and increased right ventricular afterload. Injury to the capillary endothelium results in increased permeability and exudation of protein-rich fluid into the pulmonary interstitium and alveoli. Cellular debris and fibrin form the characteristic eosinophilic hyaline membranes along the walls of the alveolar duct. There is sloughing of type 1 pneumocytes. Interstitial and alveolar edema results in decreased FRC, diffusion barrier, intrapulmonary right-to-left shunting across poorly ventilating alveoli, and increase in the A-aO_2 gradient. Clinically, A-aO_2 gradient >200 is characterized as *acute lung injury* and a gradient >300 is termed **acute respiratory distress syndrome (ARDS)** (see Chapter 71). The inflammatory response to lung injury changes from the fetus to the adult. The fetus and neonate are more likely to have less of an inflammatory cytokine response as demonstrated by a decrease in tumor necrosis factor-α production when mononuclear cells are stimulated when compared to the adult.

The pediatrician must consider the potential adverse effects of therapeutic interventions such as oxygen, endotracheal intubation, and mechanical ventilation as part of the pathophysiologic consequences of ARDS. High concentrations of inspired oxygen have a risk of pulmonary capillary and epithelial cell injury; the concentration of oxygen below which it can be considered safe has not been established. In addition to the potential for nosocomial pneumonia, mechanical ventilation carries the risk of ventilator-induced lung injury from physical stress applied to terminal airways, alveolar epithelium, and pulmonary capillaries. Excessive V_T can itself result in mechanical disruption capable of perpetuating the inflammatory response. If alveoli are allowed to deflate excessively during exhalation, they are subjected to greater stress injury from alveolar recruitment and derecruitment. The mechanical ventilation strategy aimed at minimizing ventilator-induced lung injury in ARDS includes alveolar recruitment and maintenance of adequate FRC throughout the respiratory cycle with an optimum PEEP, and ventilation with relatively low (6-8 mL/kg) V_T.

373.11 Regulation of Respiration

Ashok P. Sarnaik, Sabrina M. Heidemann, and Jeff A. Clark

The main function of respiration is to maintain normal blood gas homeostasis to match the metabolic needs of the body with the least amount of energy expenditure. Respiratory rate and V_T are regulated by a complex interaction of **controllers, sensors,** and **effectors.** The central respiratory controller consists of a group of neurons in the CNS that receives and integrates the afferent information from sensors and sends motor impulses to effectors to initiate and maintain respiration. Sensors are a variety of receptors located throughout the body. They

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gather chemical and physical information that is sent to the controller either to stimulate or to inhibit its activity. Effectors are the various muscles of respiration that, under the influence of controllers, coordinate respiration and move air in and out of the lung at a given V_T and rate. The respiratory regulatory mechanism itself undergoes a significant maturation process from the neonatal period throughout infancy and early childhood. **Sleep states** have the potential for profound influences on the control of respiration.

CENTRAL RESPIRATORY CONTROLLER

Although the respiratory cycle is often viewed as having an active phase (inspiration) and a passive phase (expiration), rhythmic breathing is a complex process controlled by interaction of numerous distinct groups of neurons. Neuronal control of respiration occurs in 3 phases—inspiration (I), early expiration (E1), and late expiration (E2)—and each may be dysfunctional in disease states. The respiratory controller mechanism comprises 2 functionally and anatomically distinct groups of neurons located in the CNS: 1 for **voluntary** and the other for **automatic control**. These areas of respiratory control can function independently but are also capable of interacting with each other.

Voluntary control of respiration resides in the cerebral motor cortex and limbic forebrain structure. Information is received from sensory neurons such as pain, touch, temperature, smell, vision, and emotions, and impulses are sent directly to the respiratory muscles through corticobulbar and corticospinal tracts. Voluntary control of respiration is important for protection from aspiration and inhalation of noxious gases. A certain level of consciousness is necessary to exercise voluntary control of respiration. Patients with CNS injury and toxic or metabolic encephalopathies may lose voluntary control of respirations to varying degrees, depending on the extent of CNS dysfunction.

Automatic control of respiration resides in the brainstem. Central pattern generators (CPGs) are neuronal circuits that generate rhythmic motor output, do not require conscious input, and are responsible for numerous coordinated motor functions such as breathing, swallowing, chewing, walking, and vomiting. The primary CPGs responsible for control of breathing are located in the pons and medulla and include the Bötzinger complex (BotC), pre-Bötzinger complex (pre-BotC), rostral ventral respiratory group and the caudal ventral respiratory group in the medulla, and the Kolliker-Fuse and lateral parabrachial areas in the pons. In addition, an area located adjacent to the facial nerve nucleus, the parafacial respiratory group, is an important modulator of respiration and dysfunction here likely plays a key role in congenital central hypoventilation syndrome (CCHS). Pre-BotC and rostral ventral respiratory group are thought to be the primary sites for inspiratory rhythm generation and BotC and caudal ventral respiratory group are thought to be the primary sites of expiratory rhythm generation under normal circumstances. However, each area is under significant influence from other areas including the nucleus tractus solitus, which is the area responsible for receiving visceral sensor afferents (see below). The genetic mutation responsible for Prader-Willi syndrome is similar to a genetic knockout in mice known to be associated with abnormal development of the pre-BotC and is likely responsible for the abnormal O_2 and CO_2 responsiveness associated with this disease.

CPG areas can also be modulated by neurotransmitters, which can stimulate, inhibit, or modify their activity; they possess receptors for substance P (neurokinin), acetylcholine (nicotinic), glutamate, and opioid μ receptors among others. The embryologic development of these areas is regulated by several genes such as Hox paralogs and Hox-regulating genes *kreisler/mafB* and *Krox20*. A group of neurons located in the lower pons is collectively termed the **apneustic center,** which stimulates pre-BotC, resulting in prolonged inspiratory gasps (apneuses) interrupted by transient expiratory efforts. Another group of neurons in the upper pons, called the *pneumotaxic center,* is involved in inhibiting the activity of pre-BotC. The role of apneustic and pneumotaxic centers is to fine-tune the rhythmic respiratory activity generated by pre-BotC neurons.

Abnormalities of respirations are commonly encountered in CNS dysfunction and have given clues to the role each of these areas plays in the regulation of respiration. Global CNS depression can manifest as slow and shallow respirations with resultant hypoventilation and respiratory acidosis. Bihemispheric and diencephalic pathology can lead to **Cheyne-Stokes respirations,** characterized by periods of apnea interspersed with hyperventilation. Injuries within the rostral brainstem or tegmentum can lead to central neurogenic hyperventilation and respiratory alkalosis. Mid to caudal pontine lesion can result in an apneustic breathing pattern characterized by a prolonged inspiratory pause. Medullary lesions result in ataxic, irregular breathing or apnea.

SENSORS

The primary responsibility of the respiratory system is to maintain a steady and adequate supply of oxygen to the blood and help maintain adequate pH by eliminating CO_2. Even short periods of hypoxemia or acidosis are poorly tolerated, and as such, the body has evolved multiple mechanisms to identify hypoxemia and acidosis/increased CO_2. Various receptors throughout the body are responsible for sensing and sending afferent information that modulates the activity of the central respiratory controller. These receptors are sensory nerve endings that respond to changes in their environment. They are termed either **chemoreceptors** or **mechanoreceptors,** depending on the type of stimulus that is sensed. Chemoreceptors are classified as central or peripheral, depending on their location.

Central chemoreceptors are so termed because of their location within the CNS. Chemoreceptors sense a change in the chemical composition of body fluid to which they are exposed. Central chemoreceptors reside over a wide area that includes the posterior hypothalamus, cerebellum, locus ceruleus, raphe, and multiple nuclei within the brainstem. Central chemoreceptors bathe in the extracellular fluid of the brain and respond to the changes in the H^+ concentration. Information sensing an increase in H^+ concentration stimulates ventilatory response of the controller, whereas a decrease inhibits it. The brain's extracellular fluid, represented by the cerebrospinal fluid (CSF), is separated from the blood by the blood-brain barrier, which is relatively impermeable to H^+ and HCO_3^- ions but is readily permeable to CO_2. A rise in $Paco_2$ is quickly reflected in a similar rise in the CSF. The consequent fall in CSF pH is sensed by the central chemoreceptors, causing stimulation of the controller and increase in ventilation. Changes in $Paco_2$ result in stimulation or inhibition of ventilation by changes in CSF pH. CSF pH in normal conditions is approximately 7.32. Compared to blood, CSF has much less CO_2 buffering capacity because of a much lower protein concentration. Consequently, the change in CSF pH is more pronounced than that in the blood for the same change in $Paco_2$. With a persistent elevation in $Paco_2$, the CSF pH eventually tends to normalize as HCO_3^- equilibrates across the blood-brain barrier. Consequently, patients with chronic obstructive pulmonary disease have a relatively normal CSF pH, and they do not show the ventilatory response that is observed with an acute rise in $Paco_2$. Although O_2 chemosensing has traditionally been described as a function of peripheral chemosensors, multiple brainstem areas, including those with CPG function, are oxygen responsive in the range typical to peripheral chemosensor cells.

Peripheral chemoreceptors are located in carotid bodies just above the bifurcation of the common carotid and external carotid arteries, and in the aortic bodies above and below the aortic arch; the carotid bodies are the most important in humans. The most important variable in determining the activity of the carotid bodies is changes in Pao_2 and much of their afferent output result from changes in membrane potential due to oxygen sensitive potassium channels. Although the carotid bodies have a relatively high metabolic rate, they receive a very high flow for their rather small size. In the setting of normal oxygen delivery, the dissolved oxygen reflected by Pao_2 is sufficient for their metabolism. Stimulation of carotid bodies resulting in increased ventilation occurs when their oxygen supply is decreased below their metabolic requirements. This occurs when there is decreased Pao_2, decreased blood flow (low cardiac output), and impaired oxygen use (cyanide poisoning). Anemia and dyshemoglobinemias do not stimulate carotid body activation unless Pao_2 and the cardiac output are compromised. The relationship of Pao_2 and the stimulation of carotid bodies is nonlinear (Fig. 373-13).

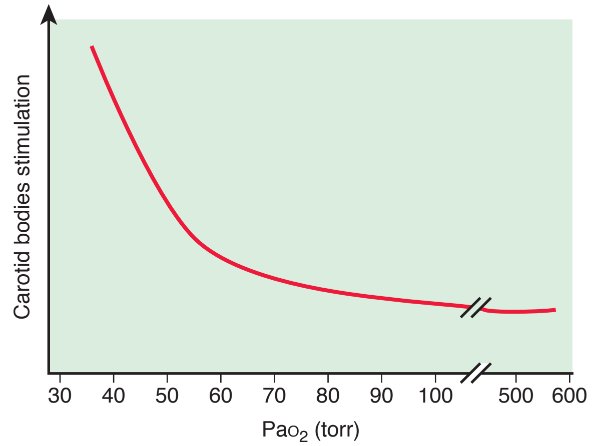

Figure 373-13 Significant stimulation of carotid bodies occurs with PaO_2 level <100 torr. A subjective feeling of dyspnea does not occur, however, until PaO_2 is <50 torr, at which point stimulation of the carotid bodies increases exponentially.

Carotid bodies are activated at a Pao_2 of <500 torr and are responsible for roughly a third of the respiratory drive during normal breathing. Their contribution to respiratory drive increases with decreasing age and may be the major determinant to respiratory drive in premature infants. Periodic breathing and other unstable respiratory patterns seen in newborns may be a result of an increased reliance of peripheral oxygen sensing in maintaining respiratory drive. As Pao_2 decreases, carotid body afferent output increases. A relatively small increase in ventilation occurs until the Pao_2 reaches 100 torr. Where the Pao_2 is <100 torr, the carotid body stimulation increases significantly. The carotid body receptor response rate is fast enough to alter their discharge rate during the respiratory cycle as a result of small cyclic changes in Pao_2 during inspiration and expiration. At Pao_2 levels <50 torr, carotid body stimulation increases exponentially. The most important effect of carotid body stimulation is an increase in respiratory rate and V_T. Additional effects include vasoconstriction, bradycardia, systemic hypertension, release of antidiuretic hormone, and stimulation of the adrenal medulla and adrenal cortex. The bradycardic effect of carotid body stimulation is overshadowed by the pulmonary reflex, which is induced by lung inflation and results in tachycardia. Patients in whom lung inflation is prevented are more likely to develop bradycardia after hypoxic stimulation of carotid bodies. Examples of such situations are fetal hypoxia, CNS depression, neuromuscular blockade, myopathy, neuropathy, and controlled ventilation. The peripheral chemoreceptors are responsible for almost all of the increase in ventilation that occurs in response to hypoxemia.

Peripheral chemoreceptors are also stimulated by an increase in $Paco_2$; this response requires a relatively large change in $Paco_2$ and results in a smaller rise in minute ventilation compared to the effect of CO_2 on central chemoreceptors. The peripheral chemoreceptors respond much more quickly (within 1 sec), however, whereas the central chemoreceptors can take minutes to respond. Thus peripheral chemoreceptors are important in the immediate rise in ventilation in response to a large and abrupt increase in $Paco_2$. Decreased pH also stimulates the peripheral chemoreceptors. The effect of pH is regardless of whether the acidosis is a result of respiratory or metabolic causes. Decreased Pao_2, increased $Paco_2$, and decreased pH act synergistically on carotid bodies. The combined effect is greater than the sum of their individual actions.

In contrast to the central chemoreceptors, the peripheral chemoreceptors are not easily depressed, such as by anesthesia or opiates. They also do not adapt easily to a persistent stimulus such as hypoxia, as do the central chemoreceptors to hypercarbia. The central chemoreceptors in hypoxic patients are relatively unresponsive to CO_2 at a time when respirations are predominantly stimulated by effects of hypoxia on peripheral chemoreceptors.

LUNG RECEPTORS

Stretch receptors are located within the airway smooth muscle. They are stimulated by lung inflation, and the impulse is conducted via the vagus nerve. The main effect of these receptors is to decrease the respiratory rate due to an inhibition of inspiratory muscle activity and an increase in exhalation time. This reflex is termed **Hering-Breuer inflation reflex**. Hering-Breuer deflation reflex stimulates inspiratory muscle activity in response to deflation of the lung. These reflexes are not operative during normal breathing in adults but may be important in newborns. Stretch receptors play an important role in minimizing the energy required for the WOB in respiratory disease. In diseases in which airway resistance is increased (asthma), more energy is needed to overcome airway resistance. Slow and deep breathing is most economical in such a situation because of relatively lower flow rate, and greater alveolar inflation is possible without stretching of the airway smooth muscle earlier during inspiration. In diseases of compliance (pulmonary edema), rapid and shallow breathing is most economical to keep the elastic work at minimum. Because of the stiffer alveoli in such situations, the transpulmonary pressure is transmitted to the airway smooth muscle earlier during inspiration, stimulating the stretch receptors and turning off inspiration.

Irritant receptors are present in between the epithelial cells in the airway mucous membrane. They are stimulated by particulate matter, noxious gases, and chemical fumes in the inspired gas, and also by cold air. The vagus nerve is responsible for conducting the impulse. Stimulation of irritant receptors results in bronchoconstriction and hyperpnea.

J receptors derive their name because of their juxtacapillary location. They lie in the alveolar walls close to the pulmonary capillaries. Pulmonary capillary engorgement and interstitial and alveolar wall edema provide stimuli for activation of the J receptors, resulting in shallow and rapid respirations and dyspnea. This is seen in left heart failure, ARDS, and interstitial diseases.

Muscle receptors important for regulation of respirations are those in the diaphragm and the intercostals. Stretch of the muscle sensed by the muscle spindle is used to control the strength of contraction. Excessive distortion of the diaphragm and the intercostals inhibits inspiratory activity when large negative intrathoracic pressure is required to move air, such as in airway obstruction. The soft chest walls of newborns and young infants are more susceptible to distortion; such children might respond to upper airway obstruction by premature cessation of inspiration and apnea rather than by the prolongation of inspiration required to move sufficient air past the obstruction.

Arterial baroreceptors located in aortic arch and carotid sinuses can influence respiration depending on arterial blood pressure. A decrease in blood pressure results in hyperventilation and an increased blood pressure causes hypoventilation.

Pain and temperature receptors also influence respirations, and they are especially pronounced in the neonates and young infants. A painful stimulus causes breath holding followed by hyperventilation. Increased skin temperature causes hyperventilation, and hypothermia results in hypoventilation. In the context of cold stimulus, the facial area is most important in causing apnea.

EFFECTORS

The most important effectors of respiration are the diaphragm, intercostals, and abdominal muscles. They receive impulses from the controller and effect ventilation. Accessory effectors such as sternocleidomastoids and paraspinal muscles may be called on to make additional contribution to the respiratory efforts in times of need. The effectors can be seriously impaired in malnutrition, spinal injury, and neuromuscular disease.

SLEEP STATES

Respiratory regulation is considerably affected by sleep. Sleep, in general, decreases central chemosensitivity to CO_2. $Paco_2$ is increased by a few torr compared to that in the wakeful state. Two broad categories of sleep states exist: *non–rapid eye movement* (NREM) and **REM**

sleep (see Chapter 19). NREM sleep is characterized by high-voltage, slow waves on electroencephalogram and is associated with fragmented mental activity. Muscle tone and movements are relatively unaffected. NREM sleep is likened to a "relatively inactive brain in a movable body." REM sleep is so termed because of the presence of episodic bursts of REMs.

The most clinically significant aspect of REM sleep is marked suppression of postural muscle tone and lack of spontaneous movements. REM sleep is likened to "a highly activated brain in a paralyzed body." Descending axons from the dorsal pontine tegmentum region are responsible for the REM sleep–specific characteristic atonia and paralysis. The predominant sleep pattern in premature babies is REM sleep. A full-term newborn has 50% REM sleep. Most of the sleep maturation occurs in the 1st 6 mo of life. Older children and adults spend approximately 20% of their sleep in the REM state. Sleep-related respiratory abnormalities are encountered predominantly in REM sleep.

Depression of muscle tone during REM sleep has 2 major effects. The relaxed and therefore increasingly compliant chest wall retracts inward much more during inspiration than a less-compliant chest wall would, resulting in an impediment to air inflow and a paradoxical (seesaw) pattern of breathing in which the abdomen and the chest wall move asynchronously. The second effect is that of relaxation of the genioglossus, palatal, and other upper airway muscles, causing airway obstruction. REM sleep–related respiratory abnormalities are commonly encountered in premature infants and in children with coexistent anatomic upper airway obstruction, obesity, and neuromuscular dysfunction.

REGULATION OF RESPIRATION IN SPECIAL SITUATIONS

Fetus, Newborns, and Young Infants

At various stages of development, the response to chemoreceptor and mechanoreceptor stimulation and the efficiency of effectors are markedly different. Unlike adults, who show an immediate and sustained response to hypoxemia characterized by hyperventilation, the newborn exhibits a biphasic response. After an initial brief period (1-2 min) of hyperventilation, the neonate and young infant develop hypoventilation and apnea when hypoxemia is sustained. This explains why such infants are much more prone to develop respiratory arrest in hypoxic states than are older children and adults. Lower gestational age of the infant is associated with a more pronounced and earlier apneic response to hypoxemia. Fetal respiratory activity, for example, is switched off when faced with oxygen deprivation. Maturation of carotid chemoreceptors may be an explanation for the differences in hypoxic response at various stages of development. Sensitivity of CO_2 sensors also undergoes maturation. Compared to adults and older children, neonates and young infants have decreased CO_2 responsiveness, as measured by an increase in minute alveolar ventilation for a given increase in $Paco_2$. Theophylline and caffeine increase the central chemoreceptor ventilatory response to CO_2 and decrease the number of apneic spells in premature babies.

The neonatal respiratory muscles are poorly equipped to sustain large workloads; they are more easily fatigued than in older children, and this significantly limits their ability to maintain adequate ventilation in lung disease. Also, the excessive inward retraction of the relatively soft infantile chest wall stimulates the intercostal muscles' stretch receptors, sending inhibitory impulses to the respiratory center. Young infants are therefore at greater risk of developing apnea when respiratory muscles are subjected to large elastic loads, such as in upper airway obstruction.

Many neurotransmitters involved in regulation of respiration also undergo developmental maturational changes. Serotoninergic neurons located in the raphe nuclei possess chemosensitive properties and respond to a decrease in pH. An increase in population of these neurons is associated with increasing chemosensitivity in the developing animal. Abnormalities of the arcuate nucleus, the human equivalent of the rat and cat medullary raphe, have been demonstrated at autopsy on infants dying of sudden infant death syndrome (SIDS; Chapter 375). Cohort studies of Japanese, African-American, and white victims of SIDS have implicated a homozygous gene that encodes for the long allele of the serotonin transporter promoter. SIDS victims are more likely to express the long allele of the serotonin transporter promoter and miss the short allele compared to controls. The delay in development of serotoninergic neurons or overexpression of the long allele for serotonin transporter promoter might explain the abnormal respiratory response to adverse conditions, which results in SIDS. Central chemoreception is also severely impaired in congenital central hypoventilation syndrome (**CCHS**), also known as Ondine's curse, which results in sleep-associated respiratory arrests. Mutations of *PHOX2B* gene located on chromosome 4 cause CCHS.

Chronic Hypoxia and Hypercarbia

The respiratory control mechanism is altered when exposed to chronic conditions. In patients with chronic pulmonary insufficiency with elevated $Paco_2$, the CSF pH has been normalized and the central chemoreceptors become unresponsive to CO_2. Renal compensation results in bicarbonate retention and relative normalization of blood pH. Arterial hypoxemia remains the chief stimulus for ventilation, which is predominantly dependent on peripheral chemoreceptor stimulation by a low Pao_2. Administration of a high amount of oxygen in such patients carries a risk of sudden removal of the hypoxic stimulus, cessation of breathing, exacerbation of hypercarbia and CO_2 narcosis, and coma. Patients with chronic obstructive pulmonary disease and neuromuscular disease are especially susceptible to this complication. Children with bronchopulmonary dysplasia or with muscular dystrophy who have had a high $Paco_2$, with or without supplemental oxygen, can develop serious hypoventilation and respiratory acidosis when their Pao_2 is increased more than their baseline with administration of a higher amount of oxygen.

Chronically hypoxic patients, such as those living at high altitude and those with cyanotic heart disease and interstitial lung disease, have a blunted chemoreceptor function and poor response to further hypoxemia. It is of interest to the clinician that children with poorly controlled asthma also show a blunted hypoxic response and can appear to be breathing relatively comfortably in spite of dangerously low Pao_2. Such children and their caretakers are at risk of failing to appreciate the severity of their disease, which can result in delay in instituting appropriate therapy.

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Chapter 374

Diagnostic Approach to Respiratory Disease

Gabriel G. Haddad and Thomas P. Green

A careful history and physical examination are essential to the accurate diagnosis of a child presenting with respiratory signs and/or symptoms. Sometimes, but not always, additional diagnostic tests and modalities are required.

HISTORY

The history begins with a narrative provided by the parent/caretaker with input from the patient. The history should include questions about respiratory symptoms (dyspnea, cough, pain, wheezing, snoring, apnea, cyanosis), chronicity, timing during day or night, and associations with activities including exercise or food intake. The respiratory system interacts with a number of other systems, and questions related

to cardiac, gastrointestinal, central nervous, hematologic, and immune systems may be relevant. Questions related to gastrointestinal reflux, congenital abnormalities (airway anomalies, ciliary dyskinesia), or immune status may be important in a patient with repeated pneumonia. The family history is essential and should include inquiries about siblings and other close relatives with similar symptoms or any chronic disease with respiratory components.

PHYSICAL EXAMINATION

Respiratory dysfunction usually produces detectable alterations in the pattern of breathing. Values for normal respiratory rates are presented in Table 67-1 (in Chapter 67) and depend on many factors, most importantly, age. Repeated respiratory rate measurements are necessary because respiratory rates, especially in the young, are exquisitely sensitive to extraneous stimuli. Sleeping respiratory rates are more reproducible in infants than those obtained during feeding or activity. These rates vary among infants but average 40-50 breaths/min in the 1st few wk of life and usually <60 breaths/min in the 1st few days of life.

Respiratory control abnormalities can cause the child to breathe at a low rate or periodically. Mechanical abnormalities produce compensatory changes that are generally directed at altering minute ventilation to maintain alveolar ventilation. Decreases in lung compliance require increases in muscular force and breathing rate, leading to variable increases in chest wall retractions and nasal flaring. The respiratory excursions of children with restrictive disease are shallow. An expiratory grunt is common as the child attempts to raise the *functional residual capacity* **(FRC)** by closing the glottis at the end of expiration. Children with obstructive disease might take slower, deeper breaths (see Chapter 373). When the obstruction is **extrathoracic** (from the nose to the mid-trachea), inspiration is more prolonged than expiration, and an inspiratory stridor can usually be heard (see Fig. 373-8 in Chapter 373). When the obstruction is **intrathoracic,** expiration is more prolonged than inspiration, and the patient often has to make use of accessory expiratory muscles. Intrathoracic obstruction results in air trapping and, therefore, a larger residual volume and, perhaps, greater FRC (see Fig. 373-10 in Chapter 373).

Lung percussion has limited value in small infants because it cannot discriminate between noises originating from tissues that are close to each other. In adolescents and adults, percussion is usually dull in restrictive lung disease, with a pleural effusion, pneumonia, and atelectasis, but it is tympanitic in obstructive disease (asthma, pneumothorax).

Auscultation confirms the presence of inspiratory or expiratory prolongation and provides information about the symmetry and quality of air movement. In addition, it often detects abnormal or adventitious sounds such as **stridor** (a predominant inspiratory monophonic noise), **crackles** (or **rales**) (high-pitched, interrupted sounds found during inspiration and more rarely during early expiration, which denote opening of previously closed air spaces), or **wheezes** (musical, continuous sounds usually caused by the development of turbulent flow in narrow airways) (Table 374-1). **Digital clubbing** is a sign of chronic hypoxia and chronic lung disease (Fig. 374-1) but may be a result of nonpulmonary etiologies (Table 374-2).

Table 374-1 Lung Sound Nomenclature

TYPE	SOUND
DISCONTINUOUS	
Fine (high pitch, low amplitude, short duration)	Fine crackles/rales
Coarse (low pitch, high amplitude, long duration)	Coarse crackles
CONTINUOUS	
High pitch	Wheezes
Low pitch	Rhonchi

From Cugell DW: Lung sound nomenclature, Am Rev Respir Dis *136:1016, 1987, with permission.*

BLOOD GAS ANALYSIS

See also Chapters 373.7 and 373.8.

An arterial blood gas analysis is probably the single most useful rapid test of pulmonary function. Although this analysis does not specify the cause of the condition or the specific nature of the disease process, it can give an overall assessment of the functional state of the respiratory system and clues about the pathogenesis of the disease. Because the detection of cyanosis is influenced by skin color, perfusion, and blood hemoglobin concentration, the clinical detection by inspection is an unreliable sign of hypoxemia. Arterial hypertension, tachycardia, and diaphoresis are late, and not exclusive, signs of hypoventilation.

Blood gas exchange is evaluated most accurately by the direct measurement of arterial pressure of oxygen (Po_2), pressure of carbon dioxide (Pco_2), and pH. The blood specimen is best collected anaerobically in a heparinized syringe containing only enough heparin solution to displace the air from the syringe. The syringe should be sealed, placed in ice, and analyzed immediately. Although these measurements have no substitute in many conditions, they require arterial puncture and have been replaced to a great extent by noninvasive monitoring, such as capillary samples and/or oxygen saturation.

The age and clinical condition of the patient need to be taken into account when interpreting blood gas tensions. With the exception of neonates, values of arterial Po_2 <85 mm Hg are usually abnormal for a child breathing room air at sea level. Calculation of the alveolar–arterial oxygen gradient is useful in the analysis of arterial oxygenation, particularly when the patient is not breathing room air or in the presence of hypercarbia. Values of arterial Pco_2 >45 mm Hg usually indicate hypoventilation or a severe ventilation–perfusion mismatch, unless they reflect respiratory compensation for metabolic alkalosis (see Chapter 55).

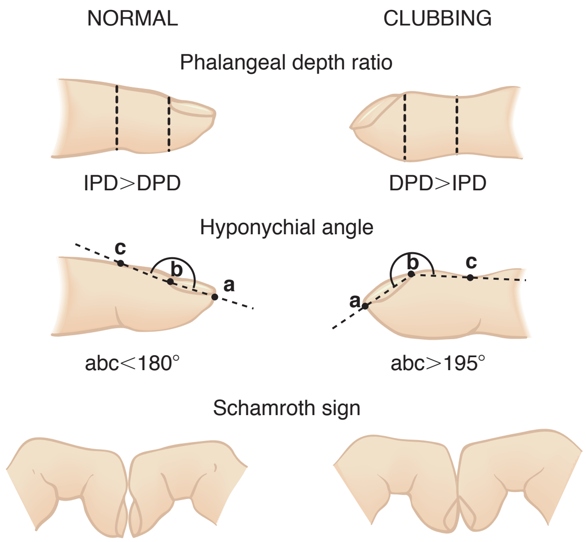

Figure 374-1 Finger clubbing can be measured in different ways. The ratio of the distal phalangeal diameter (DPD) over the interphalangeal diameter (IPD), or the phalangeal depth ratio, is <1 in normal subjects but increases to >1 with finger clubbing. The DPD/IPD can be measured with calipers or, more accurately, with finger casts. The hyponychial angle can be measured from lateral projections of the finger contour on a magnifying screen and is usually <180 degrees in normal subjects but >195 degrees in patients with finger clubbing. For bedside clinical assessment, the Schamroth sign is useful. The dorsal surfaces of the terminal phalanges of similar fingers are placed together. With clubbing, the normal diamond-shaped aperture or "window" at the bases of the nail beds disappears, and a prominent distal angle forms between the ends of the nails. In normal subjects, this angle is minimal or nonexistent. *(From Pasterkamp H: The history and physical examination. In Wilmott RW, Boat TF, Bush A, et al, editors:* Kendig and Chernick's disorders of the respiratory tract in children, *ed 8, Philadelphia, 2012, Elsevier.)*

Table 374-2	Nonpulmonary Diseases Associated with Clubbing
CARDIAC	
Cyanotic congenital heart disease	
Subacute bacterial endocarditis	
Chronic congestive heart failure	
HEMATOLOGIC	
Thalassemia	
Congenital methemoglobinemia (rare)	
GASTROINTESTINAL	
Crohn disease	
Ulcerative colitis	
Celiac disease	
Chronic dysentery, sprue	
Polyposis coli	
Severe gastrointestinal hemorrhage	
Small bowel lymphoma	
Liver cirrhosis (including α_1-antitrypsin deficiency)	
OTHER	
Thyroid deficiency (thyroid acropachy)	
Chronic pyelonephritis (rare)	
Toxic (e.g., arsenic, mercury, beryllium)	
Lymphomatoid granulomatosis	
Fabry disease	
Raynaud disease, scleroderma	
Familial	
UNILATERAL CLUBBING	
Vascular disorders (e.g., subclavian arterial aneurysm, brachial arteriovenous fistula)	
Subluxation of shoulder	
Median nerve injury	
Local trauma	

From Pasterkamp H: The history and physical examination. In Wilmott RW, Boat TF, Bush A, et al, editors: Kendig and Chernick's disorders of the respiratory tract in children, *ed 8, Philadelphia, 2012, Elsevier.*

TRANSILLUMINATION OF THE CHEST

In infants up to at least 6 mo of age, a pneumothorax (see Chapter 101.12) can often be diagnosed by transilluminating the chest wall using a fiberoptic light probe. Free air in the pleural space often results in an unusually large halo of light in the skin surrounding the probe. Comparison with the contralateral chest is often very helpful in interpreting findings. This test is unreliable in older patients and in those with subcutaneous emphysema or atelectasis.

RADIOGRAPHIC TECHNIQUES

Chest X-Rays

A posteroanterior and a lateral view (upright and in full inspiration) should be obtained except in situations in which the child is medically unstable. Portable films, although useful in the latter situation, can give a somewhat distorted image. Expiratory films can be misinterpreted, although a comparison of expiratory and inspiratory films may be useful in evaluating a child with suspected foreign body (localized failure of the lung to empty reflects bronchial obstruction: Chapter 387). If pleural fluid is suspected (see Chapter 410), decubitus films are indicated. Films taken in a recumbent position are difficult to interpret if there is fluid within the pleural space or a cavity.

Upper Airway Film

A lateral view of the neck can yield invaluable information about upper airway obstruction (see Chapter 385) and particularly about the condition of the retropharyngeal, supraglottic, and subglottic spaces (which should also be viewed in an anteroposterior projection). Knowing the phase of respiration during which the film was taken is often essential for accurate interpretation. Magnified airway films are often helpful in delineating the upper airways. Patients with suggested obstruction should not be unattended in the radiology department.

Sinus and Nasal Films

The general utility of roentgenographic examination of the sinuses is uncertain because of the large number of films with positive findings (low sensitivity and specificity). Imaging studies are not necessary to confirm the diagnosis of sinusitis in children younger than age 6 yr. CT scans are indicated if surgery is required, in cases of complications caused by sinus infection, in immunodeficient patients, and for recurrent infections that are not responsive to medical management.

Chest Computed Tomography and Magnetic Resonance Imaging

Chest CT and MRI can potentially provide images of higher quality and sensitivity than is possible with other imaging modalities. For example, chest CT identifies early abnormalities in young children with cystic fibrosis before pathologic changes are detectable by either plain chest radiographs or pulmonary function testing. Several caveats, however, must be noted. Conventional chest CT involves considerably higher radiation doses than plain films (see Chapter 718). The time required to perform chest CT examinations and the complications of respiratory and body motion mandates the use of sedation for this procedure in many infants and young children. However, improvements in imaging hardware and software have drastically reduced required radiation doses as well as imaging time, obviating the need for sedation in many patients. Chest CT is particularly useful in evaluating very small lesions (e.g., early metastases, mediastinal and pleural lesions, solid or cystic parenchymal lesions, pulmonary embolism, and bronchiectasis). The use of intravenous contrast material during CT imaging enhances vascular structures, distinguishing vessels from other soft-tissue densities. MRI does not involve ionizing radiation, but long imaging times are still involved, and sedation will be necessary to limit spontaneous movement. The utility of MRI of the chest is largely limited to the analysis of mediastinal, hilar, and vascular anatomy. Parenchymal structures and lesions are not well evaluated by MRI.

Fluoroscopy

Fluoroscopy is especially useful for evaluating stridor and abnormal movement of the diaphragm or mediastinum. Many procedures, such as needle aspiration or biopsy of a peripheral lesion, are also best accomplished with the aid of fluoroscopy, CT, or ultrasonography. Videotape recording, which does not increase radiation exposure, can allow detailed study through replay capability during a brief exposure to fluoroscopy.

Barium Swallow

A barium swallow study, performed with fluoroscopy and spot films, is indicated in the evaluation of patients with recurrent pneumonia, persistent cough of undetermined cause, stridor, or persistent wheezing. The technique can be modified by using barium of different textures and thicknesses, ranging from thin liquid to solids, to evaluate swallowing mechanics, the presence of vascular rings (see Chapter 386), and tracheoesophageal fistulas (see Chapter 319), especially when aspiration is suspected. A contrast esophagram has been used in evaluating newborns with suggested esophageal atresia, but this procedure entails a high risk of pulmonary aspiration and is not usually recommended. Barium swallows are useful in evaluating suggested gastroesophageal reflux (see Chapter 323), but because of the high incidence of asymptomatic reflux in infants, the applicability of the findings to the clinical problem may be complicated.

Pulmonary Arteriography and Aortograms

Pulmonary arteriography has been used to allow detailed evaluation of the pulmonary vasculature; has been helpful in assessing pulmonary blood flow and in diagnosing congenital anomalies, such as lobar agenesis, unilateral hyperlucent lung, vascular rings, and arteriovenous malformations; and it is sometimes useful in evaluating solid or cystic

lesions. Thoracic aortograms demonstrate the aortic arch, its major vessels, and the systemic (bronchial) pulmonary circulation. They are useful in evaluating vascular rings and suspected pulmonary sequestration. Although most hemoptysis is from the bronchial arteries, bronchial arteriography is seldom helpful in diagnosing or treating intrapulmonary bleeding in children. Real-time and Doppler echocardiography and thoracic CT with contrast are noninvasive methods that often reveal similar information and should be considered before arteriography is performed.

Radionuclide Lung Scans

The usual scan uses intravenous injection of material (macroaggregated human serum albumin labeled with ^{99m}Tc) that will be trapped in the pulmonary capillary bed. The distribution of radioactivity, proportional to pulmonary capillary blood flow, is useful in evaluating pulmonary embolism and congenital cardiovascular and pulmonary defects. Acute changes in the distribution of pulmonary perfusion can reflect alterations of pulmonary ventilation.

The distribution of pulmonary ventilation can also be determined by scanning after the patient inhales a radioactive gas such as xenon-133. After the intravenous injection of xenon-133 dissolved in saline, pulmonary perfusion and ventilation can be evaluated by continuous recording of the rate of appearance and disappearance of the xenon over the lung. Appearance of xenon early after injection is a measure of perfusion, and the rate of washout during breathing is a measure of ventilation in the pediatric population. The most important indication for this test is to demonstrate defects in the pulmonary arterial distribution that can occur with congenital malformations or pulmonary embolism. **Spiral reconstruction CT** with contrast medium enhancement is very helpful in evaluating pulmonary thrombi and emboli. Abnormalities in regional ventilation are also easily demonstrable in congenital lobar emphysema, cystic fibrosis, and asthma.

PULMONARY FUNCTION TESTING

See also Chapters 373.7 and 373.9.

The measurement of respiratory function in infants and young children can be difficult because of the lack of cooperation. Attempts have been made to overcome this limitation by creating standard tests that do not require the patient's active participation. Respiratory function tests still provide only a partial insight into the mechanisms of respiratory disease at early ages.

Whether restrictive or obstructive, most forms of respiratory disease cause alterations in lung volume and its subdivisions. Restrictive diseases typically decrease **total lung capacity (TLC).** TLC includes residual volume, which is not accessible to direct determinations. It must therefore be measured indirectly by gas dilution methods or, preferably, by **plethysmography.** Restrictive disease also decreases **vital capacity (VC).** Obstructive diseases produce gas trapping and thus increase residual volume and FRC, particularly when these measurements are considered with respect to TLC.

Airway obstruction is most commonly evaluated from determinations of gas flow in the course of a forced expiratory maneuver. The **peak expiratory flow** is reduced in advanced obstructive disease. The wide availability of simple devices that perform this measurement at the bedside makes it useful for assessing children who have airway obstruction. Evaluation of peak flows requires a voluntary effort, and peak flows may not be altered when the obstruction is moderate or mild. Other gas flow measurements require that the child inhale to TLC and then exhale as far and as fast as possible for several seconds. Cooperation and good muscle strength are therefore necessary for the measurements to be reproducible. The **forced expiratory volume in 1 sec** (FEV_1) correlates well with the severity of obstructive diseases. The **maximal midexpiratory flow rate,** the average flow during the middle 50% of the forced VC, is a more reliable indicator of mild airway obstruction. Its sensitivity to changes in residual volume and VC, however, limits its use in children with more severe disease. The construction of flow-volume relationships during the forced VC maneuvers overcomes some of these limitations by expressing the expiratory flows as a function of lung volume.

A **spirometer** is used to measure VC and its subdivisions and expiratory (or inspiratory) flow rates (see Fig. 365-1 in Chapter 365). A simple manometer can measure the maximal inspiratory and expiratory force a subject generates, normally at least 30 cm H_2O, which is useful in evaluating the neuromuscular component of ventilation. Expected normal values for VC, FRC, TLC, and residual volume are obtained from prediction equations based on body height.

Flow rates measured by spirometry usually include the FEV_1 and the **maximal midexpiratory flow rate.** More information results from a maximal expiratory flow-volume curve, in which expiratory flow rate is plotted against expired lung volume (expressed in terms of either VC or TLC). Flow rates at lung volumes less than approximately 75% VC are relatively independent of effort. Expiratory flow rates at low lung volumes (<50% VC) are influenced much more by small airways than are flow rates at high lung volumes (FEV_1). The flow rate at 25% VC is a useful index of small airway function. Low flow rates at high lung volumes associated with normal flow at low lung volumes suggest upper airway obstruction.

Airway resistance (R_{AW}) is measured in a plethysmograph, or, alternatively, the reciprocal of R_{AW}, **airway conductance**, may be used. Because R_{AW} measurements vary with the lung volume at which they are taken, it is convenient to use **specific airway resistance,** SR_{AW} ($SR_{AW} = R_{AW}$/lung volume), which is nearly constant in subjects older than age 6 yr (normally <7 sec/cm H_2O).

The **diffusing capacity for carbon monoxide** is related to oxygen diffusion and is measured by rebreathing from a container having a known initial concentration of carbon monoxide or by using a single-breath technique. Decreases in diffusing capacity for carbon monoxide reflect decreases in effective alveolar capillary surface area or decreases in diffusibility of the gas across the alveolar-capillary membrane. Primary diffusion abnormalities are unusual in children; therefore, this test is most commonly employed in children with rheumatologic or autoimmune diseases and in children exposed to toxic drugs to the lungs (e.g., oncology patients) or chest wall radiation. Regional gas exchange can be conveniently estimated with the perfusion-ventilation xenon scan. Determining arterial blood gas levels also discloses the effectiveness of alveolar gas exchange.

Pulmonary function testing, although rarely resulting in a diagnosis, is helpful in defining the type of process (obstruction, restriction) and the degree of functional impairment, in following the course and treatment of disease, and in estimating the prognosis. It is also useful in preoperative evaluation and in confirmation of functional impairment in patients having subjective complaints but a normal physical examination. In most patients with obstructive disease, a repeat test after administering a bronchodilator is warranted.

Most tests require some cooperation and understanding by the patient, and interpretation is greatly facilitated if the test conditions and the patient's behavior during the test are known. Infants and young children who cannot or will not cooperate with test procedures can be studied in a limited number of ways, which often require sedation. Flow rates and pressures during tidal breathing, with or without transient interruption of the flow, may be useful to assess some aspects of R_{AW} or obstruction and to measure compliance of the lungs and thorax. Expiratory flow rates can be studied in sedated infants with passive compression of the chest and abdomen with a rapidly inflatable jacket. Gas dilution or plethysmographic methods can also be used in sedated infants to measure FRC and R_{AW}.

MICROBIOLOGY: EXAMINATION OF LUNG SECRETIONS

The specific diagnosis of infection in the lower respiratory tract depends on the proper handling of an adequate specimen obtained in an appropriate fashion. Nasopharyngeal or throat cultures are often used but might not correlate with cultures obtained by more-direct techniques from the lower airways. Sputum specimens are preferred and are often obtained from patients who do not expectorate by deep throat swab immediately after coughing or by saline nebulization. Specimens can also be obtained directly from the tracheobronchial tree by nasotracheal aspiration (usually heavily contaminated), by

transtracheal aspiration through the cricothyroid membrane (useful in adults and adolescents but hazardous in children), and in infants and children by a sterile catheter inserted into the trachea either during direct laryngoscopy or through a freshly inserted endotracheal tube. A specimen can also be obtained at bronchoscopy. A percutaneous lung tap or an open biopsy is the only way to obtain a specimen absolutely free of oral flora.

A specimen obtained by direct expectoration is usually assumed to be of tracheobronchial origin, but often, especially in children, it is not from this source. The presence of alveolar macrophages (large mononuclear cells) is the hallmark of tracheobronchial secretions. Nasopharyngeal and tracheobronchial secretions can contain ciliated epithelial cells, which are more commonly found in sputum. Nasopharyngeal and oral secretions often contain large numbers of squamous epithelial cells. Sputum can contain both ciliated and squamous epithelial cells.

During sleep, mucociliary transport continually brings tracheobronchial secretions to the pharynx, where they are swallowed. An early-morning fasting gastric aspirate often contains material from the tracheobronchial tract that is suitable for culture for acid-fast bacilli.

The absence of polymorphonuclear leukocytes in a Wright-stained smear of sputum or **bronchoalveolar lavage** (BAL) fluid containing adequate numbers of macrophages may be significant evidence against a bacterial infectious process in the lower respiratory tract, assuming that the patient has normal neutrophil counts and function. Eosinophils suggest allergic disease. Iron stains can reveal hemosiderin granules within macrophages, suggesting pulmonary hemosiderosis. Specimens should also be examined by Gram stain. Bacteria within or near macrophages and neutrophils can be significant. Viral pneumonia may be accompanied by intranuclear or cytoplasmic inclusion bodies visible on Wright-stained smears, and fungal forms may be identifiable on Gram or silver stains.

With advances in the area of genomics and the speed with which it is possible to identify microbes, microbiologic analysis has been expanded. For example, specific bacteria in the lungs of children with cystic fibrosis (see Chapter 403) are linked to morbidity and mortality. There is a correlation between patient age and morbidity and mortality (as expected) but that there are important microbes that are correlated either negatively or positively with early or late pathogenic processes. *Haemophilus influenzae* (see Chapter 194) is negatively correlated and *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* (see Chapter 205) have a strong positive correlation with patient age in cystic fibrosis. The microbiota diversity is much broader in those who are healthier individuals or those that are younger patients with cystic fibrosis than the older and sicker population.

In addition, the microbiomes (see Chapter 171) in the respiratory tract of smokers and nonsmokers differ substantially. In all patients, most of the bacteria found in the lungs are also present in the oral cavity, as expected, although some bacteria, such as *Haemophilus* and enterobacteria are much more represented in the lungs than in the mouth. Principal differences between smokers and nonsmokers are found in the microbiome in the mouth, for example, bacteria like *Neisseria*.

EXERCISE TESTING

Exercise testing (see Chapter 423.5) is a more-direct approach for detecting diffusion impairment as well as other forms of respiratory disease. Exercise is a strong provocateur of bronchospasm in susceptible patients, so exercise testing can be useful in the diagnosis of patients with asthma that is only apparent with activity. Measurements of heart and respiratory rate, minute ventilation, oxygen consumption, carbon dioxide production, and arterial blood gases during incremental exercise loads often provide invaluable information about the functional nature of the disease. Often a simple assessment of the patient's exercise tolerance in conjunction with other, more static forms of respiratory function testing can allow a distinction between respiratory and nonrespiratory disease in children.

SLEEP STUDIES

See Chapter 19.

AIRWAY VISUALIZATION AND LUNG SPECIMEN–BASED DIAGNOSTIC TESTS

Laryngoscopy

The evaluation of stridor, problems with vocalization, and other upper airway abnormalities usually requires direct inspection. Although indirect (mirror) laryngoscopy may be reasonable in older children and adults, it is rarely feasible in infants and small children. Direct laryngoscopy may be performed with either a rigid or a flexible instrument. The safe use of the rigid scope for examining the upper airway requires topical anesthesia and either sedation or general anesthesia, whereas the flexible laryngoscope can often be used in the office setting with or without sedation. Further advantages to the flexible scope include the ability to assess the airway without the distortion that may be introduced by the use of the rigid scope and the ability to assess airway dynamics more accurately. Because there is a relatively high incidence of concomitant lesions in the upper and lower airways, it is often prudent to examine the airways above and below the glottis, even when the primary indication is in the upper airway (stridor).

Bronchoscopy and Bronchoalveolar Lavage

Bronchoscopy is the inspection of the airways. BAL is a method used to obtain a representative specimen of fluid and secretions from the lower respiratory tract, which is useful for the cytologic and microbiologic diagnosis of lung diseases, especially in those who are unable to expectorate sputum. BAL is performed after the general inspection of the airways and before tissue sampling with a brush or biopsy forceps. BAL is accomplished by gently wedging the scope into a lobar, segmental, or subsegmental bronchus and sequentially instilling and withdrawing sterile nonbacteriostatic saline in a volume sufficient to ensure that some of the aspirated fluid contains material that originated from the alveolar space. Nonbronchoscopic BAL can be performed, although with less accuracy and, therefore, less-reliable results, in intubated patients by instilling and withdrawing saline through a catheter passed though the artificial airway and blindly wedged into a distal airway. In either case, the presence of alveolar macrophages documents that an alveolar sample has been obtained. Because the methods used to perform BAL involve passage of the equipment through the upper airway, there is a risk of contamination of the specimen by upper airway secretions. Careful cytologic examination and quantitative microbiologic cultures are important for correct interpretation of the data. BAL can often obviate the need for more-invasive procedures such as open lung biopsy, especially in immunocompromised patients.

Indications for diagnostic bronchoscopy and BAL include recurrent or persistent pneumonia or atelectasis, unexplained or localized and persistent wheeze, the suspected presence of a foreign body, hemoptysis, suspected congenital anomalies, mass lesions, interstitial disease, and pneumonia in the immunocompromised host. Indications for therapeutic bronchoscopy and BAL include bronchial obstruction by mass lesions, foreign bodies or mucus plugs, and general bronchial toilet and bronchopulmonary lavage. The patient undergoing bronchoscopy ventilates around the flexible scope, whereas with the rigid scope, ventilation is accomplished through the scope. Rigid bronchoscopy is preferentially indicated for extracting foreign bodies, for removing tissue masses, and in patients with massive hemoptysis. In other cases, the flexible scope offers the advantages that it can be passed through endotracheal or tracheostomy tubes, can be introduced into bronchi that come off the airway at acute angles, and can be safely and effectively inserted with topical anesthesia and conscious sedation.

Regardless of the instrument used, the procedure performed, or its indications, the most common complications are related to sedation. The relatively more common complications related to the bronchoscopy itself include transient hypoxemia, laryngospasm, bronchospasm, and cardiac arrhythmias. Iatrogenic infection, bleeding, pneumothorax, and pneumomediastinum are rare but reported complications of bronchoscopy or BAL. Bronchoscopy in the setting of possible pulmonary abscess or hemoptysis must be undertaken with advance preparations for definitive airway control, mindful of the possibility that pus or blood might flood the airway. Subglottic edema is a more common complication of rigid bronchoscopy than of flexible procedures, in

which the scopes are smaller and less likely to traumatize the mucosa. Postbronchoscopy croup is treated with oxygen, mist, vasoconstrictor aerosols, and corticosteroids as necessary.

Thoracoscopy

The pleural cavity can be examined through a thoracoscope, which is similar to a rigid bronchoscope. The thoracoscope is inserted through an intercostal space and the lung is partially deflated, thus allowing the operator to view the surface of the lung, the pleural surface of the mediastinum and diaphragm, and the parietal pleura. Multiple thoracoscopic instruments can be inserted, allowing endoscopic biopsy of the lung or pleura, resection of blebs, abrasion of the pleura, and ligation of vascular rings.

Thoracentesis

For diagnostic or therapeutic purposes, fluid can be removed from the pleural space by needle. Generally, as much fluid as possible should be withdrawn, and an upright chest roentgenogram should be obtained after the procedure. Complications of thoracentesis include infection, pneumothorax, and bleeding. Thoracentesis on the right may be complicated by puncture or laceration of the capsule of the liver and, on the left, by puncture or laceration of the capsule of the spleen. Specimens obtained should always be cultured, examined microscopically for evidence of bacterial infection, and evaluated for total protein and total differential cell counts. Lactic acid dehydrogenase, glucose, cholesterol, triglyceride (chylous), and amylase determinations may also be useful. If malignancy is suspected, cytologic examination is imperative.

Transudates result from mechanical factors influencing the rate of formation or reabsorption of pleural fluid and generally require no further diagnostic evaluation. Exudates result from inflammation or other disease of the pleural surface and underlying lung and require a more complete diagnostic evaluation. In general, transudates have a total protein of <3 g/dL or a ratio of pleural protein to serum protein <0.5, a total leukocyte count of fewer than 2,000/mm^3 with a predominance of mononuclear cells, and low lactate dehydrogenase levels. Exudates have high protein levels and a predominance of polymorphonuclear cells (although malignant or tuberculous effusions can have a higher percentage of mononuclear cells). Complicated exudates often require continuous chest tube drainage and have a pH <7.2. Tuberculous effusions can have low glucose and high cholesterol content.

Lung Tap

Using a technique similar to that used for thoracentesis, a percutaneous lung tap is the most direct method of obtaining bacteriologic specimens from the pulmonary parenchyma and is the only technique other than open lung biopsy not associated with at least some risk of contamination by oral flora. After local anesthesia, a needle attached to a syringe containing nonbacteriostatic sterile saline is inserted using aseptic technique through the inferior aspect of an intercostal space in the area of interest. The needle is rapidly advanced into the lung; the saline is injected and reaspirated, and the needle is withdrawn. These actions are performed as quickly as possible. This procedure usually yields a few drops of fluid from the lung, which should be cultured and examined microscopically.

Major indications for a lung tap are infiltrates of undetermined cause, especially those unresponsive to therapy in immunosuppressed patients who are susceptible to unusual organisms. Complications are the same as for thoracentesis, but the incidence of pneumothorax is higher and somewhat dependent on the nature of the underlying disease process. In patients with poor pulmonary compliance, such as children with *Pneumocystis* pneumonia, the rate can approach 30%, with 5% requiring chest tubes. Bronchopulmonary lavage has replaced lung taps for most purposes.

Lung Biopsy

Lung biopsy may be the only way to establish a diagnosis, especially in protracted, noninfectious disease. In infants and small children, thoracoscopic or open surgical biopsies are the procedures of choice, and in expert hands, there is low morbidity. Biopsy through the 3.5 mm diameter pediatric bronchoscopes limits the sample size and diagnostic abilities. As well as ensuring that an adequate specimen is obtained, the surgeon can inspect the lung surface and choose the site of biopsy. In older children, transbronchial biopsies can be performed using flexible forceps through a bronchoscope, an endotracheal tube, a rigid bronchoscope, or an endotracheal tube, usually with fluoroscopic guidance. This technique is most appropriately used when the disease is diffuse, as in the case of *Pneumocystis* pneumonia, or after rejection of a transplanted lung. The diagnostic limitations related to the small size of the biopsy specimens can be mitigated by the ability to obtain several samples. The risk of pneumothorax related to bronchoscopy is increased when transbronchial biopsies are part of the procedure; however, the ability to obtain biopsy specimens in a procedure performed with topical anesthesia and conscious sedation offers advantages to the select population for whom this procedure offers a reasonable diagnostic yield.

Sweat Testing

See Chapter 403.

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Chapter 375

Sudden Infant Death Syndrome

Carl E. Hunt and Fern R. Hauck

Sudden infant death syndrome (SIDS) is defined as the sudden, unexpected death of an infant that is unexplained by a thorough postmortem examination, which includes a complete autopsy, investigation of the scene of death, and review of the medical history. An autopsy is essential to identify possible natural explanations for sudden unexpected death such as congenital anomalies or infection and to diagnose traumatic child abuse (Tables 375-1, 375-2, and 375-3; see Chapter 40). The autopsy typically cannot distinguish between SIDS and intentional suffocation, but the scene investigation and medical history may be of help if inconsistencies are evident. **Sudden unexpected infant death (SUID)** is a term that encompasses all sudden unexpected infant deaths. Unexplained SUID is equivalent to SIDS.

EPIDEMIOLOGY

SIDS is the third leading cause of infant mortality in the United States, accounting for approximately 8% of all infant deaths. It is the most common cause of postneonatal infant mortality, accounting for 40-50% of all deaths between 1 mo and 1 yr of age. The annual rate of SIDS in the United States was stable at 1.3-1.4 per 1,000 live births (approximately 7,000 infants/year) before 1992, when it was recommended that infants sleep nonprone as a way to reduce risk for SIDS. Since then, particularly after initiation of the national Back to Sleep campaign in 1994, the rate of SIDS progressively declined and then leveled off in 2001 at 0.55 per 1,000 live births (2,234 infants). The rates have remained stagnant since that time; in 2009 it was 0.54 per 1,000 live births (2,231 infants). The decline in the number of SIDS deaths in the United States and other countries has been attributed to increasing use of the supine position for sleep. In 1992, 82% of sampled infants in the United States were placed prone for sleep. Several other countries have decreased prone sleeping prevalence to ≤2%, but in the United States in 2009, 11% of infants were still being placed prone for sleep and 13% were being placed in the side position. Among black infants, these rates were even higher: 22% prone and 22% side in 2009.

Table 375-1 Differential Diagnosis of Sudden Unexpected Infant Death

CAUSE OF DEATH	PRIMARY DIAGNOSTIC CRITERIA	CONFOUNDING FACTOR(S)	FREQUENCY DISTRIBUTION (%)
EXPLAINED AT AUTOPSY			
Natural			18-20*
Infections	History, autopsy, and cultures	If minimal findings: SIDS	35-46†
Congenital anomaly	History and autopsy	If minimal findings: SIDS	14-24†
Unintentional injury	History, scene investigation, autopsy	Traumatic child abuse	15*
Traumatic child abuse	Autopsy and scene investigation	Unintentional injury	13-24*
Other natural causes	History and autopsy	If minimal findings: SIDS, or intentional suffocation	12-17*
UNEXPLAINED AT AUTOPSY			
SIDS	History, scene investigation, absence of explainable cause at autopsy	Intentional suffocation	80-82%
Intentional suffocation (filicide)	Perpetrator confession, absence of explainable cause at autopsy	SIDS	Unknown, but <5% of all SUID
Accidental suffocation or strangulation in bed (ASSB)	History and scene investigation, ideally including doll re-enactment	Assigned to ICD-10 code (SIDS) for U.S. vital statistics database Unexplained Undetermined	Varies with individual medical examiners and coroners

*As a percentage of all sudden unexpected infant deaths explained at autopsy.

†As a percentage of all natural causes of sudden unexpected infant deaths explained at autopsy.

ICD-10, International Classification of Diseases, Version 10; SIDS, sudden infant death syndrome; SUDI, sudden unexpected death in infancy.

Adapted from Hunt CE: Sudden infant death syndrome and other causes of infant mortality: diagnosis, mechanisms and risk for recurrence in siblings, Am J Respir Crit Care Med *164:346–357, 2001.*

Table 375-2 Conditions That Can Cause Apparent Life-Threatening Events or Sudden Unexpected Infant Death

CENTRAL NERVOUS SYSTEM
- Arteriovenous malformation
- Subdural hematoma
- Seizures
- Congenital central hypoventilation
- Neuromuscular disorders (Werdnig-Hoffmann disease)
- Chiari crisis
- Leigh syndrome

CARDIAC
- Subendocardial fibroelastosis
- Aortic stenosis
- Anomalous coronary artery
- Myocarditis
- Cardiomyopathy
- Arrhythmias (prolonged Q-T syndrome, Wolff-Parkinson-White syndrome, congenital heart block)

PULMONARY
- Pulmonary hypertension
- Vocal cord paralysis
- Aspiration
- Laryngotracheal disease

GASTROINTESTINAL
- Diarrhea and/or dehydration
- Gastroesophageal reflux
- Volvulus

ENDOCRINE–METABOLIC
- Congenital adrenal hyperplasia
- Malignant hyperpyrexia
- Long- or medium-chain acyl coenzyme A deficiency
- Hyperammonemias (urea cycle enzyme deficiencies)
- Glutaric aciduria
- Carnitine deficiency (systemic or secondary)
- Glycogen storage disease type I
- Maple syrup urine disease
- Congenital lactic acidosis
- Biotinidase deficiency

INFECTION
- Sepsis
- Meningitis
- Encephalitis
- Brain abscess
- Pyelonephritis
- Bronchiolitis (respiratory syncytial virus)
- Infant botulism
- Pertussis

TRAUMA
- Child abuse
- Accidental or intentional suffocation
- Physical trauma
- Factitious syndrome (formerly Munchausen syndrome) by proxy

POISONING (INTENTIONAL OR UNINTENTIONAL)
- Boric acid
- Carbon monoxide
- Salicylates
- Barbiturates
- Ipecac
- Cocaine
- Insulin
- Others

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier Saunders, p. 98.*

Table 375-3	Differential Diagnosis of Recurrent Sudden Infant Death in a Sibship
IDIOPATHIC Recurrent sudden infant death syndrome	
CENTRAL NERVOUS SYSTEM Congenital central hypoventilation Neuromuscular disorders Leigh syndrome	
CARDIAC Endocardial fibroelastosis Wolff-Parkinson-White syndrome Prolonged Q-T syndrome or other cardiac channelopathy Congenital heart block	
PULMONARY Pulmonary hypertension	
ENDOCRINE–METABOLIC See Table 375-2	
INFECTION Disorders of immune host defense	
CHILD ABUSE Filicide or infanticide Factitious syndrome (formerly Munchausen syndrome) by proxy	

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier Saunders, p 101.*

Table 375-4	Identified Genes for Which the Distribution of Polymorphisms Differs in Sudden Infant Death Syndrome Infants Compared to Control Infants
CARDIAC CHANNELOPATHIES (11) Potassium ion channel genes *(KCNE2, KCNH2, KCNQ1, KCNJ8)* Sodium ion channel gene *(SCN5A)* (long QT syndrome 3, Brugada syndrome) *GPD1-L-encoded connexin43* (Brugada syndrome) *SCN3B* (Brugada syndrome) *CAV3* (long QT syndrome 9) *SCN4B* (long QT syndrome 10) *SNTA-1* (long QT syndrome 11) *RyR2* (catecholaminergic polymorphic ventricular tachycardia)	
SEROTONIN (5-HT) (3) 5-HT transporter protein *(5-HTT)* Intron 2 of *SLC6A4* (variable number tandem repeat [VNTR] polymorphism) 5-HT fifth Ewing variant (FEV) gene	
GENES PERTINENT TO DEVELOPMENT OF AUTONOMIC NERVOUS SYSTEM (9) Paired-like homeobox 2a *(PHOX2A)* *PHOX2B* Rearranged during transfection factor *(RET)* Endothelin converting enzyme-1 *(ECE1)* T-cell leukemia homeobox *(TLX3)* Engrailed-1 *(EN1)* Tyrosine hydroxylase *(THO1)* Monamine oxidase A *(MAOA)* Sodium/proton exchanger 3 *(NHE3)* (medullary respiratory control)	
INFECTION AND INFLAMMATION (8) Complement C4A Complement C4B Interleukin-1RN (gene encoding IL-1 receptor antagonist [ra]; proinflammatory) Interleukin-6 (IL-6; proinflammatory) Interleukin-8 (IL-8; proinflammatory; associated with prone sleeping position) Interleukin-10 (IL-10) Vascular endothelial growth factor (VEGF) (proinflammatory) Tumor necrosis factor (TNF)-α (proinflammatory)	
OTHER (3) Mitochondrial DNA (mtDNA) polymorphisms (energy production) Flavin-monooxygenase 3 (*FMO3*) (enzyme metabolizes nicotine; risk factor with smoking mothers) Aquaporin-4 (T allele and CT/TT genotype associated with maternal smoking and with increased brain/body weight ratio in SIDS infants)	

Adapted from Hunt CE, Hauck FR: Sudden infant death syndrome: gene-environment interactions. In Brugada R, Brugada J, Brugada P, editors: Clinical care in inherited cardiac syndromes, *Guildford, UK, 2009, Springer-Verlag London.*

There is increasing evidence that infant deaths previously classified as SIDS are now being classified by medical examiners and coroners as from other causes, notably **accidental suffocation and strangulation in bed**. Between 1994 and 2004, there has been a quadrupling in the rates of accidental suffocation and strangulation in bed, from 2.8-12.5 deaths per 100,000 live births. These sudden and unexpected infant deaths are primarily associated with an unsafe sleeping environment such as prone position or in bed with parents. Based on these trends and the commonality of many of the sleep environment risk factors that are associated with both SIDS and other sleep-related SUID, risk reduction measures will be later described that are applicable to all sleep-related SUID.

PATHOLOGY

There are no autopsy findings pathognomonic for SIDS and no findings required for the diagnosis. There are some common findings. Petechial hemorrhages are found in 68-95% of cases and are more extensive than in explained causes of infant mortality. Pulmonary edema is often present and may be substantial. The reasons for these findings are unknown.

SIDS infants have several identifiable changes in the lungs and other organs and in brainstem structure and function. Nearly 65% of SIDS infants have structural evidence of preexisting, chronic, low-grade asphyxia, and other studies have identified biochemical markers of asphyxia. SIDS victims have higher levels of vascular endothelial growth factor (VEGF) in the cerebrospinal fluid. These increases may be related to VEGF polymorphisms (see "Genetic Risk Factors" below and Table 375-4) or might indicate recent hypoxemic events, because VEGF is upregulated by hypoxia. Brainstem findings include a persistent increase of dendritic spines and delayed maturation of synapses in the medullary respiratory centers, and decreased tyrosine hydroxylase immunoreactivity and catecholaminergic neurons. Cardiac muscle muscarinic receptor overexpression has also been reported in SIDS infants compared to infants who died from noncardiac causes. The regulatory mechanism may be related to increased acetylcholine esterase enzyme activity. The retrotrapezoid nucleus is one of the primary sites of central chemoreception and respiratory drive, and structural and/or PHOX2B-expression abnormalities have been reported in significantly more SIDS and other SUID cases than controls.

The ventral medulla has been a particular focus for studies in SIDS infants. It is an integrative area for vital autonomic functions including breathing, arousal, and chemosensory function. Quantitative 3-dimensional anatomic studies indicate that some SIDS infants have hypoplasia of the arcuate nucleus and up to 60% have histopathologic evidence of less-extensive bilateral or unilateral hypoplasia. Consistent with the apparent overlap between putative mechanisms for SIDS and for unexpected late fetal deaths, approximately 30% of late unexpected and unexplained stillbirths also have hypoplasia of the arcuate nucleus.

Neurotransmitter studies of the arcuate nucleus have also identified receptor abnormalities in some SIDS infants that involve several receptor types relevant to state-dependent autonomic control overall and to ventilatory and arousal responsiveness in particular. These deficits

include significant decreases in binding to kainate, muscarinic cholinergic, and serotonin (5-HT) receptors. Studies of the ventral medulla have identified morphologic and biochemical deficits in 5-HT neurons and decreased γ-aminobutyric acid receptor A receptor binding in the medullary serotonergic system. Immunohistochemical analyses reveal an increased number of 5-HT neurons and an increase in the fraction of 5-HT neurons showing an immature morphology, suggesting a failure or delay in the maturation of these neurons. High neuronal levels of interleukin-1β are present in the arcuate and dorsal vagal nuclei in SIDS victims compared to controls, perhaps contributing to molecular interactions affecting cardiorespiratory and arousal responses.

The neuropathologic data provide compelling evidence for altered 5-HT homeostasis, creating an underlying vulnerability contributing to SIDS. 5-HT is an important neurotransmitter and the 5-HT neurons in the medulla project extensively to neurons in the brainstem and spinal cord that influence respiratory drive and arousal, cardiovascular control including blood pressure, circadian regulation and non–rapid eye movement (REM) sleep, thermoregulation, and upper airway reflexes. Medullary 5-HT neurons may be respiratory chemosensors and may be involved with respiratory responses to intermittent hypoxia and respiratory rhythm generation. Decreases in 5-HT_{1A} and 5-HT_{2A} receptor immunoreactivity have been observed in the dorsal nucleus of the vagus, solitary nucleus, and ventrolateral medulla. There are extensive serotoninergic brainstem abnormalities in SIDS infants, including increased 5-HT neuronal count, a lower density of 5-HT_{1A} receptor-binding sites in regions of the medulla involved in homeostatic function, and a lower ratio of 5-HT transporter (5-HTT) binding density to 5-HT neuronal count in the medulla. Male SIDS infants have lower receptor-binding density than female SIDS infants. These findings suggest that the synthesis and availability of 5-HT is decreased within 5-HT pathways and hence impairs neuronal firing. Medullary tissue levels of 5-HT and its primary biosynthetic enzyme (tryptophan hydroxylase) were observed to be lower in SIDS cases compared to age-matched controls, indicating reduced 5-HT synthesis and hence a deficiency in 5-HT.

Table 375-5 Environmental Factors Associated with Increased Risk for Sudden Infant Death Syndrome

MATERNAL AND ANTENATAL RISK FACTORS
Elevated 2nd trimester serum α-fetoprotein
Smoking
Alcohol use
Drug use (cocaine, heroin)
Nutritional deficiency
Inadequate prenatal care
Low socioeconomic status
Younger age
Lower education
Single marital status
Shorter interpregnancy interval
Intrauterine hypoxia
Fetal growth restriction
INFANT RISK FACTORS
Age (peak 2-4 mo, but may be decreasing)
Male gender
Race and ethnicity (African-American and Native American, other minorities)
Growth failure
No breast-feeding
No pacifier (dummy)
Prematurity
Prone and side sleep position
Recent febrile illness (mild infections)
Inadequate immunizations
Smoking exposure (prenatal and postnatal)
Soft sleeping surface, soft bedding
Bed sharing with parent(s) or other children
Thermal stress, overheating
Colder season, no central heating

ENVIRONMENTAL RISK FACTORS

Declines of 50% or more in rates of SIDS in the United States and around the world have occurred following national education campaigns directed at reducing risk factors associated with SIDS. The reductions in risk appear to be related primarily to decreases in placing infants prone for sleep and increases in placing them supine. A number of other risk factors also have significant associations with SIDS (Table 375-5). Although many are nonmodifiable and most of the modifiable factors have not changed appreciably, self-reported maternal smoking prevalence during pregnancy has decreased by 25% in the past decade in the United States.

Nonmodifiable Environmental Risk Factors

Lower socioeconomic status has consistently been associated with higher risk, although SIDS affects infants from all social strata. In the United States, African-American, Native American, and Alaskan Native infants are 2-3 times more likely than white infants to die of SIDS, whereas Asian, Pacific Islander, and Hispanic infants have the lowest incidence. Some of this disparity may be related to the higher concentration of poverty and other adverse environmental factors found within some, but not all, of the communities with higher incidence.

Infants are at greatest risk of SIDS at 2-4 mo of age, with most deaths having occurred by 6 mo. This characteristic age has decreased in some countries as the SIDS incidence has declined, with deaths occurring at earlier ages and with a flattening of the peak age incidence. Similarly, the commonly observed winter seasonal predominance of SIDS has declined or disappeared in some countries as prone prevalence has decreased, supporting prior findings of an interaction between sleep position and factors more common in colder months (overheating as a consequence of elevated interior temperatures or bundling with blankets and heavy clothing, or infection). Male infants are 30-50% more likely to be affected than female infants.

Modifiable Environmental Risk Factors

Pregnancy-Related Factors

An increased SIDS risk is associated with numerous obstetric factors, suggesting that the in utero environment of future SIDS infants is suboptimal. SIDS infants are more commonly of higher birth order, independent of maternal age, and of gestations after shorter interpregnancy intervals. Mothers of SIDS infants generally receive less prenatal care and initiate care later in pregnancy. Additionally, low birthweight, preterm birth, and slower intrauterine and postnatal growth rates are risk factors.

Cigarette Smoking

There is a major association between intrauterine exposure to cigarette smoking and risk for SIDS. The incidence of SIDS is approximately 3 times greater among infants of mothers who smoke in studies conducted before SIDS risk-reduction campaigns and 5 times higher in studies after implementation of risk-reduction campaigns. The risk of death is progressively greater as daily cigarette use increases. The effects of smoking by the father and other household members are more difficult to interpret because they are highly correlated with maternal smoking. There appears to be a small independent effect of paternal smoking, but data on other household members have been inconsistent.

It is very difficult to assess the independent effect of infant exposure to **environmental tobacco smoke** because parental smoking behaviors during and after pregnancy are also highly correlated. An increased risk of SIDS is also found for infants exposed only to postnatal maternal environmental tobacco smoke. There is a dose–response for the number of household smokers, number of people smoking in the same room as the infant, and the number of cigarettes smoked. These data suggest that keeping the infant free of environmental tobacco smoke can further reduce an infant's risk of SIDS.

Drug and Alcohol Use

Most studies link maternal prenatal drug use, especially opiates, with an increased risk of SIDS, ranging from a 2-15–fold increased risk. Most but not all studies have not found an association between maternal alcohol use prenatally or postnatally and SIDS. In one study of Northern Plains Indians, periconceptional alcohol use and binge drinking in the 1st trimester were associated with a 6-fold and an 8-fold increased risk of SIDS, respectively. A Danish cohort study found that mothers admitted to the hospital for an alcohol- or drug-related disorder at any time before or after the birth of their infants had a 3-times higher risk of their infant dying from SIDS, and a Dutch study reported that maternal alcohol consumption in the 24 hr before the infant died carried a 2-8-fold increased risk of SIDS. Siblings of infants with fetal alcohol syndrome have a 10-fold increased risk of SIDS compared to controls.

Infant Sleep Environment

Sleeping prone has consistently been shown to increase the risk of SIDS. As rates of prone positioning have decreased in the general population, the odds ratios for SIDS in infants still sleeping prone have increased. **The highest risk of SIDS occurs in infants who are usually placed nonprone, but placed prone for last sleep ("unaccustomed prone") or found prone ("secondary prone").** The "unaccustomed prone" position may be more likely to occur in daycare or other settings outside the home and highlights the need for all infant caretakers to be educated about appropriate sleep positioning.

Side-sleeping is also a significant risk factor. The initial SIDS risk-reduction campaign recommendations considered side sleeping to be nearly equivalent to the supine position in reducing the risk of SIDS. Subsequent studies documented that side-sleeping infants were twice as likely to die of SIDS as infants sleeping supine. This increased risk might relate to the relative instability of the position, with some infants placed on the side rolling to the prone position. With the overall decrease in rates of placing infants prone for sleep, a higher proportion of SIDS is now attributed to being placed on the side for sleeping than for being placed prone. Nevertheless, the majority of SIDS occurrences are associated with being found prone. The **current recommendations** call for **supine position for sleeping for all infants except those few with specific medical conditions** for which recommending a different position may be justified, in particular infants with apparent anatomical or functional upper airway compromise.

Many parents and healthcare providers were initially concerned that supine sleeping would be associated with an increase in adverse consequences, such as difficulty sleeping, vomiting, or aspiration. Evidence suggests that the risk of regurgitation and choking is highest for prone-sleeping infants. Some newborn nursery staff still tend to favor side positioning, which models inappropriate infant care practice to parents. Infants sleeping on their backs do not have more episodes of cyanosis or apnea, and reports of apparent life-threatening events actually decreased in Scandinavia after increased use of the supine position. Among infants in the United States who maintained the same sleep position at 1, 3, and 6 mo of age, no clinical symptoms or reasons for outpatient visits (including fever, cough, wheezing, trouble breathing or sleeping, vomiting, diarrhea, or respiratory illness) were more common in infants sleeping supine or on their sides compared with infants sleeping prone. Three symptoms were actually less common in infants sleeping supine or on their sides: fever at 1 mo, stuffy nose at 6 mo, and trouble sleeping at 6 mo. Outpatient visits for ear infection were less common at 3 and 6 mo for infants sleeping supine and also less common at 3 mo for infants sleeping on their side. These results provide reassurance for parents and healthcare providers and should contribute to universal acceptance of supine as the safest and optimal sleep position for infants.

Soft sleep surfaces or bedding, such as comforters, pillows, sheepskins, polystyrene bean pillows, and older or softer mattresses are associated with increased risk of SIDS. **Head and face covering by loose bedding**, particularly heavy comforters, is also associated with increased risk. **Overheating** has been associated with increased risk for SIDS based on indicators such as higher room temperature, a febrile history, sweating, and excessive clothing or bedding. Some studies have identified an interaction between overheating and prone sleeping, with overheating increasing the risk of SIDS only when infants are sleeping prone. Higher external environmental temperatures have not been associated with increased SIDS incidence in the United States.

Several studies have implicated **bed sharing** as a risk factor for SIDS. Bed sharing is particularly hazardous when other children are in the same bed, when the parent is sleeping with an infant on a couch or other soft or confining sleeping surface, and when the mother smokes. Infants younger than 4 mo of age are at increased risk even when mothers are nonsmokers. A meta-analysis of 19 studies found that the low-risk infants (i.e., those who were breastfed and never exposed to cigarette smoke in utero or after birth) still had a 5-fold increased risk of SIDS until the age of 3 mo if bed sharing. Risk is also increased with longer duration of bed sharing during the night, whereas returning the infant to the infant's own crib has not been associated with increased risk. Room sharing without bed sharing is associated with lower SIDS rates, and is therefore recommended.

Infant Feeding Care Practices and Exposures

It is currently believed that there is a **protective effect of breastfeeding on SIDS**, after taking into account confounding factors. A meta-analysis found that there was a 45% reduction in SIDS after adjusting for confounding variables and that this protective effect increased for exclusive breastfeeding compared with partial breastfeeding.

Pacifier (dummy) use is associated with a lower risk of SIDS in the majority of studies when used for last sleep. Although it is not known if this is a direct effect of the pacifier itself or from associated infant or parental behavior, there is increasing evidence that pacifier use even with dislodgment can increase the arousability of infants during sleep. Concerns have been expressed about recommending pacifiers as a means of reducing the risk of SIDS for fear of adverse consequences, particularly interference with breastfeeding. Well-designed studies have found no association between pacifiers and breastfeeding duration.

Upper respiratory tract infections have generally not been found to be an independent risk factor for SIDS, but these and other minor infections may still have a role in the causal pathway of SIDS when other risk factors are present. Risk for SIDS has been found to be increased after illness among prone sleepers, those who were heavily wrapped, and those whose heads were covered during sleep.

No adverse association between immunizations and SIDS has been found. Indeed, SIDS infants are less likely to be immunized than control infants and, in immunized infants, no temporal relationship between vaccine administration and death has been identified. In a meta-analysis of case-control studies that adjusted for potentially confounding factors, the risk of SIDS for infants immunized with diphtheria, tetanus, and pertussis was half that for nonimmunized infants.

SIDS rates remain higher among Native Americans, Alaskan Natives, and African-Americans. This may be due, in part, to group differences in adopting supine sleeping or other risk-reduction practices. Greater efforts are needed to address this persistent disparity and to ensure that SIDS risk-reduction education reaches all parents and all other care providers, including other family members and personnel at daycare centers.

GENETIC RISK FACTORS

As summarized in Table 375-4, there are numerous genetic differences identified in SIDS infants compared to healthy infants and to infants dying from other causes. Polymorphisms occurring at higher incidence in SIDS compared to controls include at least 11 cardiac ion channelopathy genes that are proarrhythmic, 3 5-HT genes, 8 autonomic nervous system development genes, and 8 genes related to infection that are proinflammatory.

Multiple studies confirm the importance of a final common pathway that involves cardiac sodium or potassium channel dysfunction caused by direct or indirect disturbance resulting in **either long QT syndrome (LQTS)** or other arrhythmia associated with current dysfunction. LQTS is a known cause of sudden unexpected death in adults and

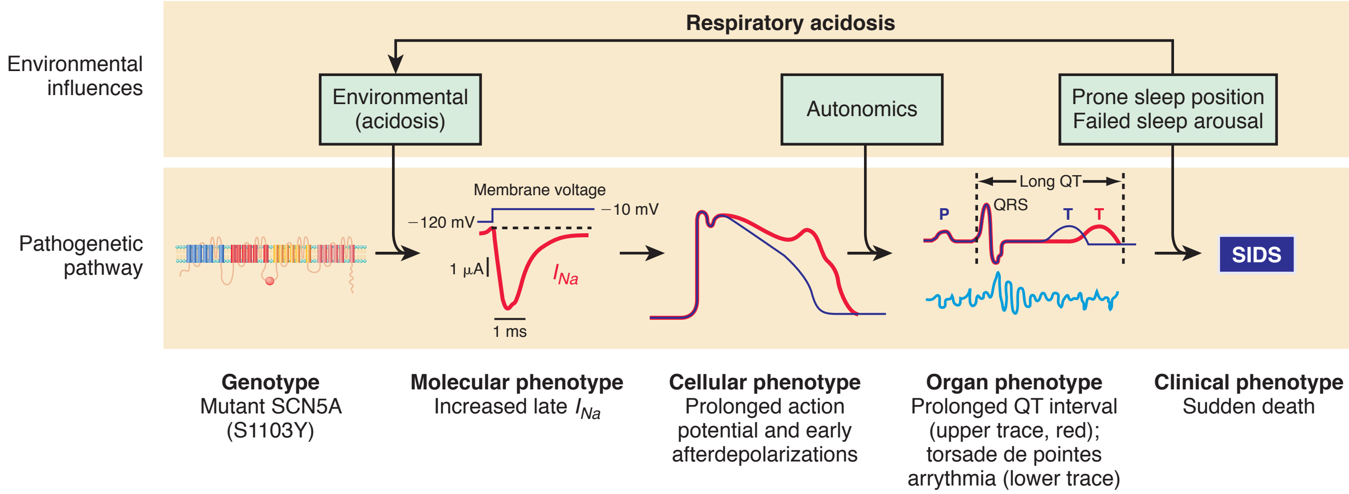

Figure 375-1 **An arrhythmogenic pathogenetic pathway for sudden infant death syndrome (SIDS) from patient genotype to clinical phenotype, with environmental influences noted.** The genetic abnormality—in this instance, a polymorphism in the cardiac Na^+ channel SCN5A—causes a molecular phenotype of increased late Na^+ current (I_{Na}) under the influence of environmental factors such as acidosis. Interacting with other ion currents that may themselves be altered by genetic and environmental factors, the late Na^+ current causes a cellular phenotype of prolonged action potential duration as well as early afterdepolarizations. Prolonged action potential in the cells of the ventricular myocardium and further interaction with environmental factors such as autonomic innervation, which, in turn, may be affected by genetic factors, produce a tissue-organ phenotype of a prolonged Q-T interval on the electrocardiogram (ECG) and torsades de pointes arrhythmia in the whole heart. If this is sustained or degenerates to ventricular fibrillation, the clinical phenotype of SIDS results. Environmental and multiple genetic factors can interact at many different levels to produce the characteristic phenotypes at the molecular, cellular, tissue, organ, and clinical levels. *(From Makielski JC: SIDS: genetic and environmental influences may cause arrhythmia in this silent killer,* J Clin Invest *116:297–299, 2006.)*

children, as the result of a prolonged cardiac action potential by either increasing depolarization or decreasing repolarization current (Fig. 375-1). The first evidence supporting a causal role for LQTS in SIDS was a large Italian study in which a corrected QT interval >440 milliseconds on an electrocardiogram performed on days 3-4 of life was associated with a 41.3 odds ratio for SIDS. Several case reports have subsequently provided proof of concept that cardiac channelopathy polymorphisms are associated with SIDS. LQTS is associated with polymorphisms related mainly to gain-of-function mutations in the **sodium channel gene** *(SCN5A)* that encode critical channel pore-forming α subunits or essential channel-interacting proteins. LQTS also is associated with mainly loss-of-function polymorphisms in potassium channel genes. **Short QTS (SQTS)** is more recently recognized as another cause of life-threatening arrhythmia or sudden death, often during rest or sleep. Gain-of-function mutations in genes including *KCNH2* and *KCNQ1* have been causally linked to SQTS, and some of these deaths have occurred in infants, suggesting that SQTS may also be causally linked to SIDS.

Both LQTS and SQTS are proarrhythmic and associated with cardiac arrest and sudden death. The other cardiac ion-related channelopathy polymorphisms are also proarrhythmic, including Brugada syndrome *(BrS1, BrS2),* and catecholaminergic paroxysmal ventricular tachycardia *(CPVT1).* Collectively, these mutations in cardiac ion channels provide a lethal arrhythmogenic substrate in some infants at risk for SIDS (see Fig. 375-1) and may account for 10% or more of SIDS cases.

Impaired central respiratory regulation is an important biologic abnormality in SIDS and genetic polymorphisms have been identified in SIDS infants that affect both serotonergic and adrenergic neurons. Monamine oxidase A metabolizes both of these neurotransmitters and a recent study has observed a high association between SIDS and low expressing alleles in males, perhaps contributing to the higher incidence of SIDS in males. Many genes are involved in the control of 5-HT synthesis, storage, membrane uptake, and metabolism. Polymorphisms have been identified in the promoter region of the 5-HT transporter (5-HTT) protein gene that occur in greater frequency in SIDS than control infants. The long "L" allele increased effectiveness of the promoter and reduced extracellular 5-HT concentrations at nerve endings compared to the short "S" allele. White, African-American, and Japanese SIDS infants were more likely than ethnicity-matched controls to have the "L" (long) allele, and there was also a negative association between SIDS and the S/S genotype. The L/L genotype was associated with increased 5-HT transporters on neuroimaging and postmortem binding studies. However, in a large San Diego dataset of SIDS infants, no relationship was found between SIDS and the L allele or the LL genotype.

An association has also been observed between SIDS and a 5-HTT intron 2 polymorphism, which differentially regulate *5-HTT* expression. There were positive associations between SIDS and the intron 2 genotype distributions in African-American infants compared to African-American controls. The human *FEV* gene is specifically expressed in central 5-HT neurons in the brain, with a predicted role in specification and maintenance of the serotoninergic neuronal phenotype. An insertion mutation has been identified in intron 2 of the *FEV* gene, and the distribution of this mutation differs significantly in SIDS compared to control infants.

Molecular genetic studies in SIDS victims have also identified mutations pertinent to early embryologic development of the autonomic nervous system (Table 375-4). Eleven protein-changing mutations have been identified in 14 of 92 SIDS cases among the *PHOX2a, RET, ECE1, TLX3,* and *EN1* genes. Only 1 of these mutations *(TLX3)* was found in 2 of 92 controls. African-American infants accounted for 10 of 11 mutations in SIDS infants and in both affected controls with protein-changing mutations. Eight polymorphisms in the *PHOX2B* gene occurred significantly more frequently in SIDS compared to control infants. One study has reported an association between SIDS and a distinct tyrosine hydroxylase gene (*THO1*) allele, which regulates gene expression and catecholamine production.

Genetic differences in SIDS infants compared to control infants have been reported for 2 complement *C4* genes. Some SIDS infants have loss-of-function polymorphisms in the gene promoter region for IL-10, another anti-inflammatory cytokine. Among SIDS infants compared to living controls, sudden infant death was strongly associated with the IL-10 polymorphism. These IL-10 polymorphisms were associated with decreased IL-10 levels and hence could contribute to SIDS by delaying initiation of protective antibody production or reducing capacity to inhibit inflammatory cytokine production. Other studies have not found differences in IL-10 genes in SIDS compared to

control infants, but one study did identify an association with the ATA haplotype in sudden and unexpected infant deaths classified as resulting from infection.

Polymorphisms associated with proinflammatory responses have also been found more frequently in SIDS infants compared to controls. An association was observed between single-nucleotide polymorphisms in the proinflammatory gene encoding interleukin (IL)-8 and SIDS infants sleeping prone compared to SIDS infants found in other sleep positions. IL-1 is another proinflammatory gene, and a higher prevalence has been reported in SIDS infants of the IL-1 receptor antagonist (IL-1RN), which would predispose to higher risk from infection. Significant associations with SIDS are reported for polymorphisms in VEGF, IL-6, and tumor necrosis factor-α. These 3 cytokines are proinflammatory, and these gain-of-function polymorphisms would result in increased inflammatory response to infectious or inflammatory stimuli and hence contribute to an imbalance between proinflammatory and antiinflammatory cytokines. As apparent proof of principle, elevated levels of IL-6 and VEGF have been reported from cerebrospinal fluid in SIDS infants. There were no group differences in the IL6-174G/C polymorphism in a Norwegian SIDS study, but the aggregate evidence nevertheless suggests an activated immune system in SIDS and thus implicates genes involved in the immune system. Almost all SIDS infants in 1 study had positive histories for prone sleeping and fever prior to death and positive HLA-DR expression in laryngeal mucosa, and high HLA-DR expression was associated with high levels of IL-6 in cerebrospinal fluid.

Numerous reports have implicated polymorphisms in genes regulating energy production in SIDS infants, but the importance of these findings requires further study (Table 375-4). Of interest, cardiac arrhythmias, including prolonged QT intervals, have been observed in families with mitochondrial disease. However, the mitochondrial DNA polymorphism T3394C that is associated with cardiac arrhythmia has not been observed to occur with greater frequency in SIDS compared to control infants.

GENE-AND-ENVIRONMENT INTERACTIONS

Interactions between genetic and environmental risk factors determine the actual risk for SIDS in individual infants (Fig. 375-2). There appears to be an interaction between prone sleep position and impaired ventilatory and arousal responsiveness. Facedown or nearly facedown sleeping does occasionally occur in prone-sleeping infants, but normal healthy infants arouse before such episodes become life-threatening. Infants with insufficient arousal responsiveness to asphyxia, however, may be at risk for sudden death from resulting episodes of airway obstruction and asphyxia. There may also be links between modifiable risk factors such as soft bedding, prone sleep position, and thermal stress, and links between genetic risk factors such as ventilatory and arousal abnormalities and temperature or metabolic regulation deficits. Cardiorespiratory control deficits could be related to 5-HTT polymorphisms, for example, or to polymorphisms in genes pertinent to autonomic nervous system development. Affected infants could be at increased risk for sleep-related hypoxemia and hence more susceptible to adverse effects associated with unsafe sleep position or bedding. Infants at increased risk for sleep-related hypoxemia could also be at greater risk for fatal arrhythmias in the presence of a cardiac ion channelopathy polymorphism.

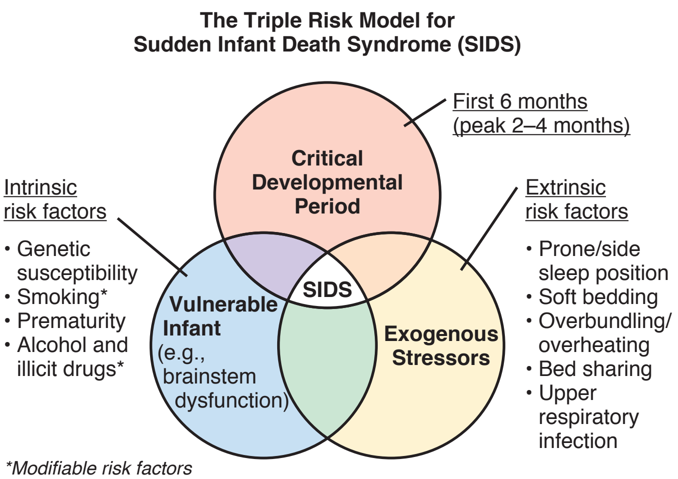

Figure 375-2 Schematic of the triple-risk model for sudden infant death syndrome (SIDS) showing the critical interactions between intrinsic risk factors (including genetic risk factors) resulting in a vulnerable infant, a critical developmental period or age, and exogenous stressors or extrinsic risk factors. *(Adapted from Filiano JJ, Kinney HC: A perspective on the neuropathologic findings in victims of the sudden infant death syndrome: the triple risk model,* Biol Neonate *65:194–197, 1994.)*

In >50% of SIDS victims, recent febrile illnesses, often related to upper respiratory infection, have been documented (see Table 375-5). Otherwise benign infections might increase risk for SIDS if interacting with genetically determined impaired immune responses, including those resulting from partial deletions in the complement C4 gene or to interleukin polymorphisms (see Table 375-4). Deficient inflammatory responsiveness can also occur as a result of mast cell degranulation, which has been reported in SIDS infants; this is consistent with an anaphylactic reaction to a bacterial toxin, and some family members of SIDS infants also have mast cell hyperreleasability and degranulation, suggesting that increased susceptibility to an anaphylactic reaction is another genetic factor influencing fatal outcomes to otherwise minor infections in infants. Interactions between upper respiratory infections or other minor illnesses and other factors such as prone sleeping might also play a role in the pathogenesis of SIDS.

The increased risk for SIDS associated with fetal and postnatal exposure to cigarette smoke may be related at least in part to genetic or epigenetic factors, including those affecting brainstem autonomic control. Human infant studies document decreased ventilatory and arousal responsiveness to hypoxia following fetal nicotine exposure, and impaired autoresuscitation after apnea has been associated with postnatal nicotine exposure. Decreased brainstem immunoreactivity to selected protein kinase C and neuronal nitric oxide synthase isoforms occurs in rats exposed to cigarette smoke prenatally, another potential cause of impaired hypoxic responsiveness. Smoking exposure also increases susceptibility to viral and bacterial infections and increases bacterial binding after passive coating of mucosal surfaces with smoke components, implicating interactions between smoking, cardiorespiratory control, and immune status. Flavin-monooxygenase 3 (*FMO3*) is one of the enzymes that metabolizes nicotine, and a polymorphism has recently been identified that occurs more frequently in SIDS infants compared to controls and more frequently in infants whose mothers reported heavy smoking (Table 375-4). This polymorphism thus provides a potential genetic risk factor for SIDS in infants exposed to cigarette smoke.

In infants with a cardiac ion channelopathy, risk for a fatal arrhythmia during sleep may be substantially enhanced by predisposing perturbations that increase electrical instability. These perturbations could include REM sleep with bursts of vagal and sympathetic activation, minor respiratory infections, or any other cause of sleep-related hypoxemia or hypercarbia, especially those resulting in acidosis. The prone sleeping position is associated with increased sympathetic activity.

INFANT GROUPS AT INCREASED RISK FOR SUDDEN INFANT DEATH SYNDROME

Unexplained Apparent Life-Threatening Events

Infants with an unexplained **apparent life-threatening event (ALTE)** are at increased risk for SIDS. An ALTE is defined as an episode that frightens an observer and manifests with some combination of central, obstructive, or mixed apnea; cyanotic, pallid, plethora, erythematous, color change; hypotonia (rarely hypertonia); and choking or gasping. A history of an unexplained ALTE has been reported in 5-9% of SIDS victims, and the risk of SIDS appears to be higher with 2 or more

unexplained events, but no definitive incidence rates are available. Compared with healthy control infants, the risk for SIDS may be as much as 3-5 times greater in infants having experienced an ALTE. Although most studies of ALTE have not specified gestational age, 30% of ALTE infants in the Collaborative Home Infant Monitoring Evaluation were ≤37 wk gestation at birth.

Subsequent Siblings of a Sudden Infant Death Syndrome Victim

The next-born siblings of first-born infants dying of any noninfectious natural cause are at significantly increased risk for infant death from the same cause, including SIDS. The relative risk is 9.1 for the same cause of recurrent death vs 1.6 for a different cause of death. The relative risk for recurrent SIDS (range: 5.4-5.8) is similar to the relative risk for non-SIDS causes of recurrent death (range: 4.6-12.5). The risk for recurrent infant mortality from the same cause as in the index sibling thus appears to be increased to a similar degree in subsequent siblings for both explained causes and for SIDS. This increased risk for recurrent SIDS in families is consistent with genetic risk factors interacting with environmental risk factors (see Tables 375-4 and 375-5 and Fig. 375-2).

Prematurity

Despite reductions in SIDS and SUID among infants born preterm by more than 50% since initiation of the back-to-sleep campaign in the United States 20 yr ago, the risk for death remains significantly higher than for infants born full term. This increased risk is likely related in part to immaturity of brainstem ventilatory control. Also, although the environmental risk factors for SIDS and SUID are qualitatively similar to those in full-term infants, including nonsupine sleeping position and other unsafe sleep practices, infants born preterm do have more sociodemographic risk factors overall than infants born at term. Among all gestational age groups, the postnatal age of death from SIDS and other SUID progressively decreases as gestational age at birth increases, and the postmenstrual age at death progressively increases as gestational age at birth increases. Compared with infants born at 37-42 wk, the odds ratio for SIDS is greatest for infants born at 24-28 wk gestation (2.57, 95% confidence interval 2.08, 3.17). The odds ratio progressively decreases as gestational age at birth increases, but even at 33-36 wk gestational age at birth remains significantly increased compared to infants born at term.

Physiologic Studies

Physiologic studies have been performed in healthy infants in early infancy, a few of whom later died of SIDS. Physiologic studies have also been performed on infant groups at increased risk for SIDS, especially those with ALTE and subsequent siblings of SIDS. In the aggregate, these studies have indicated brainstem abnormalities in neuroregulation of cardiorespiratory control or other autonomic functions and are consistent with the autopsy findings and genetic studies in SIDS victims (see "Pathology" and "Genetic Risk Factors" above). In addition to chemoreceptor sensitivity, these observed physiologic abnormalities also include respiratory patterns, control of heart and respiratory rate or variability, and asphyxic arousal responsiveness. A deficit in arousal responsiveness may be a necessary prerequisite for SIDS to occur but may be insufficient to cause SIDS in the absence of other genetic or environmental risk factors. **Autoresuscitation (gasping)** is a critical component of the asphyxic arousal response, and a failure of autoresuscitation in SIDS infants may be the final and most devastating physiologic failure. Most normal full-term infants younger than 9 postnatal wk of age in 1 study aroused in response to mild hypoxia, but only 10-15% aroused if older than 9 wk of age. These data thus suggest that ability to arouse to mild to moderate hypoxic stimuli may be at a nadir at the age range of greatest risk for SIDS.

The ability to shorten the QT interval as heart rate increases appears to be impaired in some SIDS victims, suggesting that such infants may be predisposed to ventricular arrhythmia. This is consistent with the observations of cardiac ion channel gene polymorphisms in other SIDS victims (see Table 375-4), but there are no antemortem QT interval data in the SIDS infants having postmortem channelopathy polymorphisms. Infants studied physiologically and dying of SIDS a few weeks later had higher heart rates in all sleep–wake states, diminished heart rate variability during wakefulness, and significantly lower heart rate variability at the respiratory frequency across all sleep–wake cycles. Also, these SIDS infants had longer QT intervals than control infants in both REM and non-REM sleep, especially in the late hours of the night when most SIDS likely occurs. In only 1 of these SIDS infants, however, did the QT interval exceed 440 milliseconds.

Part of the decreased heart rate variability and increased heart rate observed in infants who later died of SIDS may have been related to decreased vagal tone, perhaps at least in part related to vagal neuropathy or to brainstem damage in areas responsible for parasympathetic cardiac control. In a comparison of heart rate power spectra before and after obstructive apneas in clinically asymptomatic infants, infants later dying of SIDS did not have the decreases in low-frequency to high-frequency power ratios observed in infants who survived. Some future SIDS victims thus have different autonomic responsiveness to obstructive apnea, perhaps indicating impaired autonomic nervous system control associated with higher vulnerability to external or endogenous stress factors and hence to reduced electrical stability of the heart.

Home cardiorespiratory monitors with memory capability have recorded the terminal events in some SIDS victims. These recordings did not include pulse oximetry and could not identify obstructed breaths due to reliance on transthoracic impedance for breath detection. In most instances, there has been sudden and rapid progression of severe bradycardia that was either unassociated with central apnea or appeared to occur too soon to be explained by the central apnea. These observations are consistent with an abnormality in autonomic control of heart rate variability, or with obstructed breaths resulting in bradycardia or hypoxemia and associated with impaired autoresuscitation or arousal.

CLINICAL STRATEGIES

Home Monitoring

SIDS cannot be prevented in individual infants because it is not possible to identify prospective SIDS infants, and no effective intervention has been established even if SIDS infants could be prospectively identified. Studies of cardiorespiratory pattern or other autonomic abnormalities do not have sufficient sensitivity and specificity to be clinically useful as screening tests. Home electronic surveillance using existing technology does not reduce the risk of SIDS. Although a prolonged QT interval in an infant may be treated if diagnosed, neither the role of routine postnatal electrocardiographic screening, the cost-effectiveness of diagnosis and treatment, nor the safety of treatment in infants has been established (see Chapter 429). Parental electrocardiographic screening is not helpful because spontaneous mutations are common.

Reducing the Risk of Sudden Infant Death Syndrome

Reducing risk behaviors and increasing protective behaviors among infant caregivers to achieve further reductions and eventual elimination of SIDS is a critical goal. Recent plateaus in placing infants supine for sleep in the United States at approximately 75% for all races and only 56% for African-Americans are cause for concern and require renewed educational efforts. The American Academy of Pediatrics guidelines to reduce the risk of SIDS were updated in 2011 and expanded to include reducing the risk of all sudden and unexpected sleep-related infant deaths. The guidelines are appropriate for most infants, but physicians and other healthcare providers might, on occasion, need to consider alternative approaches. The major components of the American Academy of Pediatrics guidelines are:

- Full-term and premature infants should be placed for sleep in the supine position. There are no adverse health outcomes from supine sleeping. Side sleeping is not recommended.
- It is recommended that infants sleep in the same room as their parents but in their own crib or bassinette that conforms to the

safety standards of the Consumer Product Safety Commission. Placing the crib or bassinette near the mother's bed facilitates nursing and contact.

- Infants should be put to sleep on a firm mattress. Waterbeds, sofas, soft mattresses, or other soft surfaces should not be used. In addition, car seats, strollers, swings and other sitting devices should not be used for sleeping. Sleeping in an upright position can lead to gastroesophageal reflux or upper airway obstruction from head flexion.
- Soft materials in the infant's sleep environment—over, under, or near the infant—should be avoided. These include pillows, comforters, quilts, sheepskins, bumper pads, and stuffed toys. Because loose bedding may be hazardous, blankets, if used, should be tucked in around the crib mattress. Sleeping clothing, such as a sleep sack, can be used in place of blankets.
- Avoid overheating and overbundling. The infant should be lightly clothed for sleep and the thermostat set at a comfortable temperature.
- Infants should be immunized in accordance with recommendations of the American Academy of Pediatrics and the Centers for Disease Control and Prevention. There is no evidence that immunizations increase risk for SIDS. Indeed, recent evidence suggests that immunizations may have a protective effect against SIDS.
- Healthcare professionals, staff in newborn nurseries and neonatal intensive care units, and child care providers should adopt the SIDS reduction recommendations beginning at birth.
- Infants should have some time in the prone position (tummy time) while awake and observed. Alternating the placement of the infant's head as well as his or her orientation in the crib can also minimize the risk of head flattening from supine sleeping (positional plagiocephaly).
- Devices advertised to maintain sleep position, "protect" a bed-sharing infant, or reduce the risk of rebreathing are not recommended.
- Home cardiorespiratory and/or O_2 saturation monitoring may be of value for selected infants who have extreme instability, but there is no evidence that monitoring decreases the incidence of SIDS and it is therefore not recommended for this purpose.
- Breastfeeding is recommended. If possible, mothers should exclusively breastfeed or feed with expressed human milk until the infant is 6 mo of age.
- If a breastfeeding mother brings the infant into the adult bed for nursing, the infant should be returned to a separate sleep surface when the mother is ready for sleep.
- Consider offering a pacifier at bedtime and naptime. The pacifier should be used when placing the infant down for sleep and need not be reinserted once it falls out. For breastfed infants, delay introduction of the pacifier until breastfeeding is well established.
- Mothers should not smoke, drink alcohol, or use illicit drugs during pregnancy or after birth, and infants should not be exposed to secondhand smoke.
- The national Back to Sleep campaign should be expanded to emphasize the multiple characteristics of a safe sleeping environment and to focus on the groups with continuing higher rates of SIDS. Educational strategies must be tailored to each racial or ethnic group to ensure acceptance within that cultural context. Secondary care providers need to be targeted to receive these educational messages, including daycare providers, grandparents, foster parents, and babysitters.
- Research and surveillance should be continued on the risk factors, causes and pathophysiological mechanisms of SIDS and other sleep-related SUID, with the ultimate goal of preventing these deaths entirely. Federal and private funding agencies need to remain committed to this research.

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Section 2

Disorders of the Respiratory Tract

Chapter 376

Congenital Disorders of the Nose

Joseph Haddad Jr. and Sarah Keesecker

NORMAL NEWBORN NOSE

In contrast to children and adults who preferentially breathe through their nose unless nasal obstruction interferes, most newborn infants are obligate nasal breathers and significant nasal obstruction presenting at birth, such as choanal atresia, may be a life-threatening situation for the infant unless an alternative to the nasal airway is established. Nasal congestion with obstruction is common in the 1st yr of life and can affect the quality of breathing during sleep; it may be associated with a narrow nasal airway, viral or bacterial infection, enlarged adenoids, or maternal estrogenic stimuli similar to rhinitis of pregnancy. The internal nasal airway doubles in size in the 1st 6 mo of life, leading to resolution of symptoms in many infants. Supportive care with a bulb syringe and saline nose drops, topical nasal decongestants, and antibiotics, when indicated, improve symptoms in affected infants.

PHYSIOLOGY

The nose is responsible for the initial warming and humidification of inspired air and olfaction. In the anterior nasal cavity, turbulent airflow and coarse hairs enhance the deposition of large particulate matter; the remaining nasal airways filter out particles as small as 6 μm in diameter. In the turbinate region, the airflow becomes laminar and the airstream is narrowed and directed superiorly, enhancing particle deposition, warming, and humidification. Nasal passages contribute as much as 50% of the total resistance of normal breathing. Nasal flaring, a sign of respiratory distress, reduces the resistance to inspiratory airflow through the nose and can improve ventilation (see Chapter 373).

Although the nasal mucosa is more vascular (especially in the turbinate region) than in the lower airways, the surface epithelium is similar, with ciliated cells, goblet cells, submucosal glands, and a covering blanket of mucus. The nasal secretions contain lysozyme and secretory immunoglobulin (Ig) A, both of which have antimicrobial activity, and IgG, IgE, albumin, histamine, bacteria, lactoferrin, and cellular debris, as well as mucous glycoproteins, which provide viscoelastic properties. Aided by the ciliated cells, mucus flows toward the nasopharynx, where the airstream widens, the epithelium becomes squamous, and secretions are wiped away by swallowing. Replacement of the mucous layers occurs about every 10-20 min. Estimates of daily mucus production vary from 0.1-0.3 mg/kg/24 hr, with most of the mucus being produced by the submucosal glands.

CONGENITAL DISORDERS

Congenital *structural nasal malformations* are uncommon compared with acquired abnormalities. The nasal bones can be congenitally absent so that the bridge of the nose fails to develop, resulting in *nasal hypoplasia*. Congenital absence of the nose *(arhinia)*, complete or partial duplication, or a single centrally placed nostril can occur in isolation but is usually part of a malformation syndrome. Rarely,

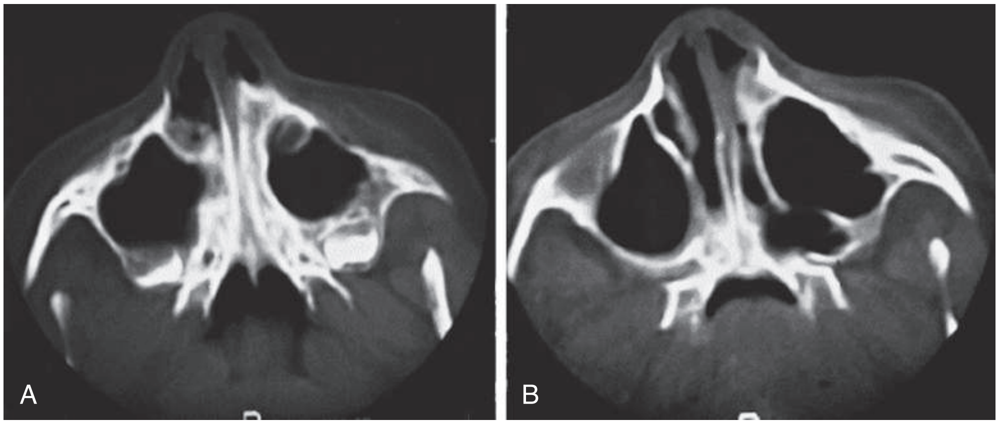

Figure 376-1 CT scan showing **(A)** hypoplastic nasal cavities and **(B)** bony and mucosal choanal atresia. *(From Altuntas A, Yilmaz MD, Kahveci OK, et al: Coexistence of choanal atresia and Tessier's facial cleft number 2,* Int J Pediatr Otorhinolaryngol *68:1081–1085, 2004.)*

supernumerary teeth are found in the nose, or teeth grow into it from the maxilla.

Nasal bones can be sufficiently malformed to produce severe narrowing of the nasal passages. Often, such narrowing is associated with a high and narrow hard palate. Children with these defects can have significant obstruction to airflow during infections of the upper airways and are more susceptible to the development of chronic or recurrent hypoventilation (see Chapter 19). Rarely, the alae nasi are sufficiently thin and poorly supported to result in inspiratory obstruction, or there may be congenital nasolacrimal duct obstruction with cystic extension into the nasopharynx, causing respiratory distress.

CHOANAL ATRESIA

This is the most common congenital anomaly of the nose and has a frequency of approximately 1 in 7,000 live births. It consists of a unilateral or bilateral bony (90%) or membranous (10%) septum between the nose and the pharynx; most cases are a combination of bony and membranous atresia. The pathogenesis is unknown but theories include persistence of the buccopharyngeal membranes or failure of the oronasal membrane to rupture. The unilateral defect is more common and the female : male ratio is approximately 2 : 1. Approximately 50-70% of affected infants have other congenital anomalies (CHARGE syndrome, Treacher-Collins, Kallmann syndrome, VATER [vertebral defects, imperforate anus, tracheoesophageal fistula, and renal defects] association, Pfeiffer syndrome), with the anomalies occurring more often in bilateral cases. The **CHARGE syndrome** (*c*oloboma, *h*eart disease, *a*tresia choanae, *r*etarded growth and development or central nervous system anomalies or both, *g*enital anomalies or hypogonadism or both, and *e*ar anomalies or deafness or both) is one of the more common anomalies associated with choanal atresia—approximately 10-20% of patients with choanal atresia have it. Most patients with CHARGE syndrome have mutations in the *CHD7* gene, which is involved in chromatin organization.

Clinical Manifestations

Newborn infants have a variable ability to breathe through their mouths, so nasal obstruction does not produce the same symptoms in every infant. When the obstruction is unilateral, the infant may be asymptomatic for a prolonged period, often until the first respiratory infection, when unilateral nasal discharge or persistent nasal obstruction can suggest the diagnosis. Infants with bilateral choanal atresia who have difficulty with mouth breathing make vigorous attempts to inspire, often suck in their lips, and develop cyanosis. Distressed children then cry (which relieves the cyanosis) and become calmer, with normal skin color, only to repeat the cycle after closing their mouths. Those who are able to breathe through their mouths at once experience difficulty when sucking and swallowing, becoming cyanotic when they attempt to feed.

Diagnosis

Diagnosis is established by the inability to pass a firm catheter through each nostril 3-4 cm into the nasopharynx. The atretic plate may be seen directly with fiberoptic rhinoscopy. The anatomy is best evaluated by using high-resolution CT (Fig. 376-1).

Treatment

Initial treatment consists of prompt placement of an oral airway, maintaining the mouth in an open position, or intubation. A standard oral airway (such as that used in anesthesia) can be used, or a feeding nipple can be fashioned with large holes at the tip to facilitate air passage. Once an oral airway is established, the infant can be fed by gavage until breathing and eating without the assisted airway is possible. In bilateral cases, intubation or, less often, tracheotomy may be indicated. If the child is free of other serious medical problems, operative intervention is considered in the neonate; transnasal repair is the treatment of choice, with the introduction of small magnifying endoscopes and smaller surgical instruments and drills. Stents are usually left in place for weeks after the repair to prevent closure or stenosis. Tracheotomy should be considered in cases of bilateral atresia in which the child has other potentially life-threatening problems and in whom early surgical repair of the choanal atresia may not be appropriate or feasible. Operative correction of unilateral obstruction may be deferred for several years. In both unilateral and bilateral cases, restenosis necessitating dilation or reoperation, or both, is common. Mitomycin C has been used to help prevent the development of granulation tissue and stenosis.

CONGENITAL DEFECTS OF THE NASAL SEPTUM

Perforation of the septum is most commonly acquired after birth secondary to infection, such as syphilis or tuberculosis, or trauma; rarely, it is developmental. Continuous positive airway pressure cannulas are a cause of iatrogenic perforation. Trauma from delivery is the most common cause of septal deviation noted at birth. When recognized early, it can be corrected with immediate realignment using blunt probes, cotton applicators, and topical anesthesia. Formal surgical correction, when required, is usually postponed to avoid disturbance of midface growth.

Mild septal deviations are common and usually asymptomatic; abnormal formation of the septum is uncommon unless other malformations are present, such as cleft lip or palate.

PYRIFORM APERTURE STENOSIS

Infants with this bony abnormality of the anterior nasal aperture present at birth or shortly thereafter with severe nasal obstruction leading to noisy breathing and respiratory distress that worsen with feeding and improve with crying. It can occur in isolation or in association with other malformations including holoprosencephaly,

Nasal Pyriform Stenosis

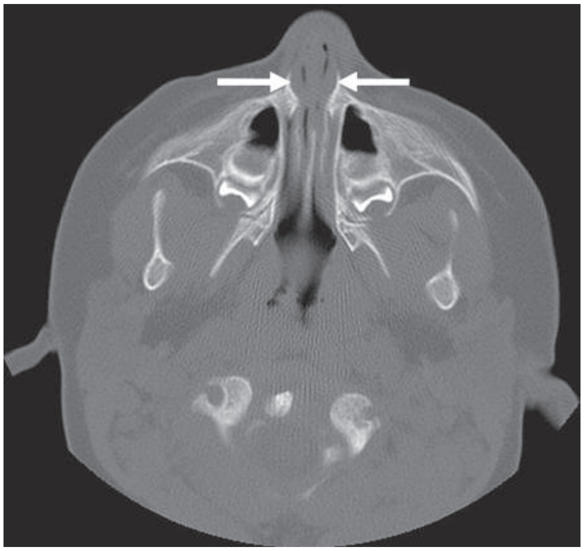

Figure 376-2 CT scan of a child who has congenital nasal pyriform aperture stenosis. Note the inward bowing of the nasal processes of the maxillary bone with the pyriform aperture measuring 7 mm *(arrows). (From Tate JR, Sykes J. Congenital nasal pyriform aperture stenosis.* Otolaryngol Clin North Am *42(3):521–525, 2009, Fig. 2.)*

hypopituitarism, and cardiac and urogenital malformations. Diagnosis is made by CT of the nose (Fig. 376-2). Medical management (nasal decongestants, humidification, nasopharyngeal airway insertion, management of reflux) can be used but surgical repair by means of an anterior, sublabial approach may be needed if the child cannot feed or breathe without difficulty. A drill is used to enlarge the stenotic anterior bone apertures.

CONGENITAL MIDLINE NASAL MASSES

Dermoids, gliomas, and *encephaloceles* (in descending order of frequency) occur intranasally or extranasally and can have intracranial connections or extend intracranially with communication to the subarachnoid space. The theory for the embryologic development of congenital midline nasal masses is faulty retraction of the dural diverticulum. Dermoids and epidermoids are the most common type of congenital midline nasal mass and have been reported to represent up to 61% of lesions. Nasal dermoids often have a dimple or pit on the nasal dorsum, sometimes with hair being present, and can predispose to intracranial infections if an intracranial fistula or sinus is present. Recurrent infection of the dermoid itself is more common. Gliomas or heterotopic brain tissue are firm, whereas encephaloceles are soft and enlarge with crying or the Valsalva maneuver. Diagnosis is based on physical examination findings and results from imaging studies. CT provides the best bony detail, but MRI is helpful also because of its superior ability to define intracranial extension (Fig. 376-3). Surgical excision of these masses is generally required, with the extent and surgical approach based on the type and size of the mass.

Other nasal masses include *hemangiomas, congenital nasolacrimal duct obstruction* (which can occur as an intranasal mass), nasal polyps, and tumors such as rhabdomyosarcoma (see Chapter 500). Nasal polyps are rarely present at birth, but the other masses often present at birth or in early infancy (see Chapter 378).

Poor development of the paranasal sinuses and a narrow nasal airway are associated with recurrent or chronic upper airway infection in Down syndrome (see Chapter 81).

DIAGNOSIS AND TREATMENT

In children with congenital nasal disorders, supportive care of the airway is given until the diagnosis is established. Diagnosis is made through a combination of flexible scoping and imaging studies,

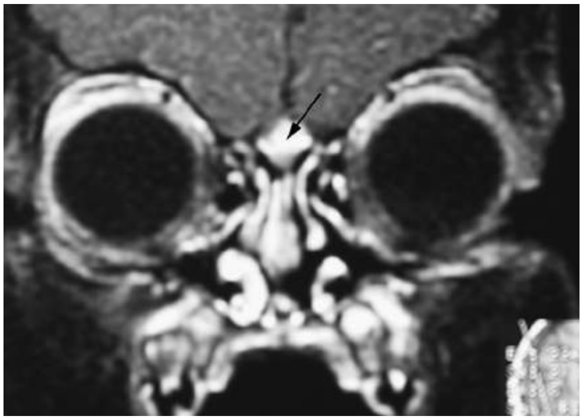

Figure 376-3 Coronal CT scan of nasal dermoid with intracranial extension (arrow). *(From Manning SC, Bloom DC, Perkins JA, et al: Diagnostic and surgical challenges in the pediatric skull base. Otolaryngol Clin North Am 38:773-794, 2005. Fig. 2.)*

primarily CT scan. In the case of surgically correctable congenital problems such as choanal atresia, surgery is performed once the child is deemed healthy and free of life-threatening problems such as congenital heart disease.

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Chapter 377

Acquired Disorders of the Nose

Joseph Haddad Jr. and Sarah Keesecker

Tumors, septal perforations, and other acquired abnormalities of the nose and paranasal sinuses can manifest with epistaxis. Midface trauma with a nasal or facial fracture may be accompanied by epistaxis. Trauma to the nose can cause a *septal hematoma;* if treatment is delayed, this can lead to necrosis of septal cartilage and a resultant *saddle-nose deformity.* Other abnormalities that can cause a change in the shape of the nose and paranasal bones, with obstruction but few other symptoms, include *fibroosseous lesions* (ossifying fibroma, fibrous dysplasia, cementifying fibroma) and *mucoceles of the paranasal sinuses.* These conditions may be suspected on physical examination and confirmed by CT scan and biopsy. Although these are considered benign lesions, they can all greatly change the anatomy of surrounding bony structures and often require surgical intervention for management.

377.1 Foreign Body

Joseph Haddad Jr. and Sarah Keesecker

ETIOLOGY

Foreign bodies (food, beads, crayons, small toys, erasers, paper wads, buttons, batteries, beans, stones, pieces of sponge, and other small objects) are often placed in the nose by small children and developmentally delayed children and constitute ≤1% of pediatric emergency department visits. Nasal foreign bodies can go unrecognized for long periods of time because they initially produce few symptoms and

are difficult to visualize. First symptoms include unilateral obstruction, sneezing, relatively mild discomfort, and, rarely, pain. Presenting clinical symptoms include history of insertion of foreign bodies (86%), mucopurulent nasal discharge (24%), foul nasal odor (9%), epistaxis (6%), nasal obstruction (3%), and mouth breathing (2%). Irritation results in mucosal swelling because some foreign bodies are hygroscopic and increase in size as water is absorbed; signs of local obstruction and discomfort can increase with time. The patient might also present with a generalized body odor known as *bromhidrosis.*

DIAGNOSIS

Unilateral nasal discharge and obstruction should suggest the presence of a foreign body, which can often be seen on examination with a nasal speculum or wide otoscope placed in the nose. Purulent secretions may have to be cleared so that the foreign object can actually be seen; a headlight, suction, and topical decongestants are often needed. The object is usually situated anteriorly, but unskilled attempts at removal can force the object deeper into the nose. A long-standing foreign body can become embedded in granulation tissue or mucosa and appear as a nasal mass. A lateral skull radiograph assists in diagnosis if the foreign body is metallic or radiopaque.

TREATMENT

A quick examination of the nose is made to determine if a foreign body is present, and whether it needs to be removed emergently. Planning is then made for office or operating room extrication of the foreign body. Prompt removal minimizes the danger of aspiration and local tissue necrosis. This can usually be performed with topical anesthesia, using either forceps or nasal suction. Alternatively, a Katz catheter (made specifically for the removal of foreign bodies from the nose and ear) can be inserted above and distal to the object, inflated, and drawn back with gentle traction.

The "mother kiss" approach has been successful in acute situations where a person occludes the unaffected nostril and then, with a complete seal over the child's mouth attempts to dislodge the foreign body by blowing into the mouth. A similar approach uses an Ambu bag over the mouth with the unaffected nostril occluded. If there is marked swelling, bleeding, or tissue overgrowth, general anesthesia may be needed to remove the object. Infection usually clears promptly after the removal of the object and, generally, no further therapy is necessary. Magnets can be used to extract metal foreign bodies, 2% lidocaine can be used to kill live insects before removal, and irrigation should be avoided with vegetable matter or sponges because of the risk of foreign-body swelling.

COMPLICATIONS

Serious complications include posterior dislodgement and aspiration, trauma caused by the object itself or removal attempts, infection, and choanal stenosis. Infection is common and gives rise to a purulent, malodorous, or bloody discharge. Local tissue damage from long-standing foreign body, or alkaline injury from a disk battery, can lead to local tissue loss and cartilage destruction. A synechia or scar band can then form, causing nasal obstruction. Loss of septal mucosa and cartilage can cause a septal perforation. Disk batteries are especially dangerous when placed in the nose; they leach base, which causes pain and local tissue destruction in a matter of hours. Magnets also carry a risk of septal perforation and necrosis.

Tetanus is a rare complication of long-standing nasal foreign bodies in nonimmunized children (see Chapter 211). Toxic shock syndrome is also rare and most commonly occurs from nasal surgical packing (see Chapter 181.2); oral antibiotics should be administered when nasal surgical packing is placed.

PREVENTION

Tempting objects, such as round, shiny beads, should only be used under adult supervision. Disk batteries should be stored away from the reach of small children.

Bibliography is available at Expert Consult.

377.2 Epistaxis

Joseph Haddad Jr. and Sarah Keesecker

Although rare in infancy, nosebleeds are common in children older than 2 yr of age. Their incidence decreases after puberty. Diagnosis and treatment depend on the location and cause of the bleeding.

ANATOMY

The most common site of bleeding is the Kiesselbach plexus, an area in the anterior septum where vessels from both the internal carotid (anterior and posterior ethmoid arteries) and external carotid (sphenopalatine and terminal branches of the internal maxillary arteries) converge. The thin mucosa in this area, as well as the anterior location, make it prone to exposure to dry air and trauma.

ETIOLOGY

Epistaxis can be classified into primary or secondary based on cause and this has implications for diagnosis and management. Common causes of nosebleeds from the anterior septum include digital trauma, foreign bodies, dry air, and inflammation, including upper respiratory tract infections, sinusitis, and allergic rhinitis (Table 377-1). There is often a family history of childhood epistaxis. Nasal steroid sprays are commonly used in children, and their chronic use may be associated with nasal mucosal bleeding. Young infants with significant gastroesophageal reflux into the nose rarely present with epistaxis secondary to mucosal inflammation. Susceptibility is increased during respiratory infections and in the winter when dry air irritates the nasal mucosa, resulting in formation of fissures and crusting. Severe bleeding may be encountered with congenital vascular abnormalities, such as *hereditary hemorrhagic telangiectasia* (see Chapter 432.3), varicosities, hemangiomas, and, in children with thrombocytopenia, deficiency of clotting factors, particularly von Willebrand disease (see Chapter 477), hypertension, renal failure, or venous congestion. Recurrent epistaxis despite cauterization is associated with mild coagulation disorders. The family history may be positive for abnormal bleeding (epistaxis or other sites); specific testing for von Willebrand disease is indicated because the prothrombin time or partial thromboplastin time may be normal despite having a bleeding disorder. Nasal polyps or other intranasal growths may be associated with epistaxis. Recurrent, and often severe, nosebleeds may be the initial presenting symptom in **juvenile nasal angiofibroma,** which occurs in adolescent boys.

Table 377-1	Possible Causes of Epistaxis
Epistaxis digitorum (nose picking)	
Rhinitis (allergic or viral)	
Chronic sinusitis	
Foreign bodies	
Intranasal neoplasm or polyps	
Irritants (e.g., cigarette smoke)	
Septal deviation	
Septal perforation	
Trauma including child abuse	
Vascular malformation or telangiectasia (hereditary hemorrhage telangiectasia)	
Hemophilia	
von Willebrand disease	
Platelet dysfunction	
Thrombocytopenia	
Hypertension	
Leukemia	
Liver disease (e.g., cirrhosis)	
Medications (e.g., aspirin, anticoagulants, nonsteroidal antiinflammatory drugs, topical corticosteroids)	
Cocaine abuse	

From Kucik CJ, Clenney T: Management of epistaxis, Am Fam Physician *71(2):305–311, 2005.*

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CLINICAL MANIFESTATIONS

Epistaxis usually occurs without warning, with blood flowing slowly but freely from 1 nostril or occasionally from both. In children with nasal lesions, bleeding might follow physical exercise. When bleeding occurs at night, the blood may be swallowed and become apparent only when the child vomits or passes blood in the stools. Posterior epistaxis can manifest as anterior nasal bleeding or, if bleeding is copious, the patient might vomit blood as the initial symptom.

TREATMENT

Most nosebleeds stop spontaneously in a few minutes. The nares should be compressed and the child kept as quiet as possible, in an upright position with the head tilted forward to avoid blood trickling back into the throat. Cold compresses applied to the nose can also help. If these measures do not stop the bleeding, local application of a solution of oxymetazoline (Afrin or Neo-Synephrine) (0.25-1%) may be useful. If bleeding persists, an anterior nasal pack may need to be inserted; if bleeding originates in the posterior nasal cavity, combined anterior and posterior packing is necessary. After bleeding is under control, and if a bleeding site is identified, its obliteration by cautery with silver nitrate may prevent further difficulties. Because the septal cartilage derives its nutrition from the overlying mucoperichondrium, only 1 side of the septum should be cauterized at a time to reduce the chance of a septal perforation. During the winter, or in a dry environment, a room humidifier, saline drops, and petrolatum (Vaseline) applied to the septum can help to prevent epistaxis. Antiseptic cream (e.g., mupirocin) significantly increases the proportion of children who have complete resolution of bleeding at 8 wk compared to no treatment. Ointments prevent infection, increase moisture, decrease bleeding, and are commonly used in clinical practice. However, the combination of silver nitrate cautery and antiseptic nasal cream is superior to antiseptic cream alone. Patients with severe epistaxis despite conservative medical measures should be considered for surgical ligation techniques or embolization. In patients with severe or repeated epistaxis, blood transfusions may be necessary. Otolaryngologic evaluation is indicated for these children and for those with bilateral bleeding or with hemorrhage that does not arise from the Kiesselbach plexus. Secondary epistaxis should be managed by identification of the cause, application of appropriate nasal therapy, and correct systemic medical management. Hematologic evaluation (for coagulopathy and anemia), along with nasal endoscopy and diagnostic imaging, may be needed to make a definitive diagnosis in cases of severe recurrent epistaxis. Replacement of deficient clotting factors may be required for patients who have an underlying hematologic disorder (see Chapter 476). Profuse unilateral epistaxis associated with a nasal mass in an adolescent boy near puberty might signal a **juvenile nasopharyngeal angiofibroma.** This unusual tumor has also been reported in a 2 yr old and in 30-40 yr olds, but the incidence peaks in adolescent and preadolescent boys. CT with contrast medium enhancement and MRI are part of the initial evaluation; arteriography, embolization, and extensive surgery may be needed.

Surgical intervention may also be needed for bleeding from the internal maxillary artery or other vessels that can cause bleeding in the posterior nasal cavity.

PREVENTION

The discouragement of nose picking, and attention to proper humidification of the bedroom during dry winter months helps to prevent many nosebleeds. Prompt attention to nasal infections and allergies is beneficial to nasal hygiene. Prompt cessation of nasal steroid sprays prevents ongoing bleeding.

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Chapter 378

Nasal Polyps

Joseph Haddad Jr. and Sarah Keesecker

ETIOLOGY

Nasal polyps are benign pedunculated tumors formed from edematous, usually chronically inflamed nasal mucosa. They commonly arise from the ethmoidal sinus and occur in the middle meatus. Occasionally, they appear within the maxillary antrum and can extend to the nasopharynx (antrochoanal polyp).

It is estimated that between 0.2% and 1% of the population will develop nasal polyps at some time; the incidence of nasal polyps increases with age. Antrochoanal polyps represent only 4-6% of all nasal polyps in the general population but account for approximately one-third of polyps in the pediatric population. Large or multiple polyps can completely obstruct the nasal passage. The polyps originating from the ethmoidal sinus are usually smaller and multiple, as compared with the large and usually single antrochoanal polyp.

Cystic fibrosis (CF; see Chapter 403) is the most common childhood cause of nasal polyposis and up to 50% of CF patients experience obstructing nasal polyposis, which is rare in non-CF children. Therefore, CF should be suspected in any child younger than 12 yr old with nasal polyps, even in the absence of typical respiratory and digestive symptoms. Cystic fibrosis patients with homozygosity for F508del and other severe mutations appear to have an elevated risk of nasal polyps. Nasal polyposis is also associated with chronic sinusitis (see Chapter 380) and allergic rhinitis. In the *Samter triad*, nasal polyps are associated with aspirin sensitivity and asthma; this condition is rare.

CLINICAL MANIFESTATIONS

Obstruction of nasal passages is prominent, with associated hyponasal speech and mouth breathing. Profuse unilateral mucoid or mucopurulent rhinorrhea may also be present. An examination of the nasal passages shows glistening, gray, grape-like masses squeezed between the nasal turbinates and the septum.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Examination of the external nose and rhinoscopy is performed. Ethmoidal polyps can be readily distinguished from the well-vascularized turbinate tissue, which is pink or red; antrochoanal polyps may have a more fleshy appearance (Fig. 378-1). Antrochoanal polyps may prolapse into the nasopharynx; flexible nasopharyngoscopy can assist in

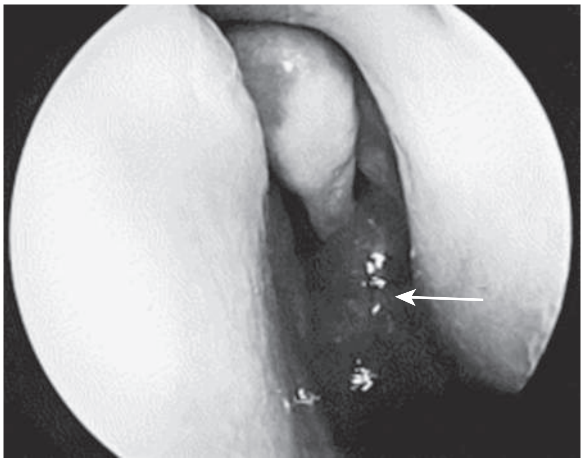

Figure 378-1 Antrochoanal polyp viewed endoscopically *(arrow). (From Basak S, Karaman CZ, Akdilli A, et al: Surgical approaches to antrochoanal polyps in children,* Int J Pediatr Otorhinolaryngol *46:197–205, 1998.)*

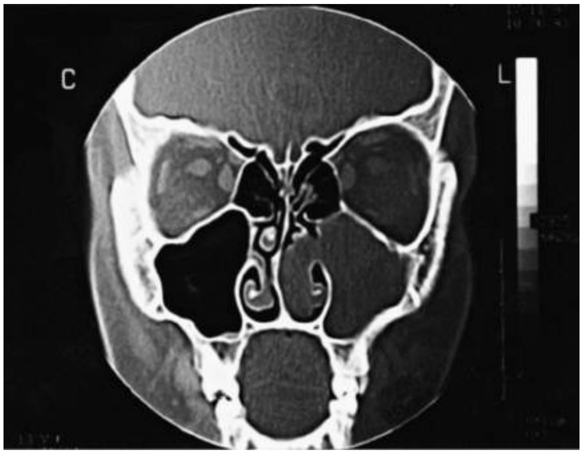

Figure 378-2 A typical CT image of an isolated antrochoanal polyp on the left side. *(From Basak S, Karaman CZ, Akdilli A, et al: Surgical approaches to antrochoanal polyps in children*, Int J Pediatr Otorhinolaryngol *46:197–205, 1998.)*

making this diagnosis. Prolonged presence of ethmoidal polyps in a child can widen the bridge of the nose and erode adjacent osseous structures. Tumors of the nose cause more local destruction and distortion of the anatomy. CT scan of the midface is key to diagnosis and planning for surgical treatment (Fig. 378-2).

TREATMENT

Local or systemic decongestants are not usually effective in shrinking the polyps, although they may provide symptomatic relief from the associated mucosal edema. Intranasal steroid sprays, and sometimes systemic steroids, can provide some shrinkage of nasal polyps with symptomatic relief and have proved useful in children with CF and adults with nasal polyps. Topical nasal steroid therapy, fluticasone, mometasone, and budesonide appears to result in nasal symptom improvement. Doxycycline (200 mg on the 1st day followed by 100 mg daily) has a significant effect on the size of nasal polyps, nasal symptoms, and mucosal and systemic markers of inflammation. Polyps should be removed surgically if complete obstruction, uncontrolled rhinorrhea, or deformity of the nose appears. If the underlying pathogenic mechanism cannot be eliminated (such as CF), the polyps may soon return. Functional endoscopic sinus surgery provides more complete polyp removal and treatment of other associated nasal disease; in some cases, this has reduced the need for frequent surgeries. Nasal steroid sprays should also be started preventively, once postsurgical healing occurs.

Antrochoanal polyps do not respond to medical measures and must be removed surgically. Because these types of polyps are not associated with any underlying disease process, the recurrence rate is much less than for other types of polyps.

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Chapter 379

The Common Cold

E. Kathryn Miller and John V. Williams

The common cold is an acute viral infection of the upper respiratory tract in which the symptoms of rhinorrhea and nasal obstruction are prominent. Systemic symptoms and signs such as headache, myalgia, and fever are absent or mild. The common cold is frequently referred to as *infectious rhinitis* but may also include self-limited involvement of the sinus mucosa and is more correctly termed *rhinosinusitis.*

ETIOLOGY

The most common pathogens associated with the common cold are the more than 200 types of human rhinoviruses (see Chapter 263), but the syndrome can be caused by many different virus families (Table 379-1). Rhinoviruses are associated with more than 50% of colds in adults and children. In young children, other viral etiologies of the common cold include respiratory syncytial virus (RSV; see Chapter 260), human metapneumovirus (see Chapter 261), parainfluenza viruses (see Chapter 259), and adenoviruses (see Chapter 262). Common cold symptoms may also be caused by influenza viruses, nonpolio enteroviruses, and human coronaviruses. Many viruses that cause rhinitis are also associated with other symptoms and signs such as cough, wheezing, and fever.

EPIDEMIOLOGY

Colds occur year-round, but the incidence is greatest from the early fall until the late spring, reflecting the seasonal prevalence of the viral pathogens associated with cold symptoms. In the northern hemisphere, the highest incidence of rhinovirus infection occurs in the early fall (August-October) and in the late spring (April-May). The seasonal incidence for parainfluenza viruses usually peaks in the late fall and late spring and is highest between December and April for RSVs, influenza viruses, human metapneumoviruses, and coronaviruses. Adenoviruses are detected at a low prevalence throughout the cold season, and enteroviruses may also be detected during summer months or throughout the year.

Young children have an average of 6-8 colds per year, but 10-15% of children have at least 12 infections per year. The incidence of illness decreases with age, with 2-3 illnesses per year by adulthood. The incidence of infection is primarily a function of exposure to the virus. Children in out-of-home daycare centers during the 1st yr of life have 50% more colds than children cared for only at home. The difference in the incidence of illness between these groups of children decreases as the length of time spent in daycare increases, although the incidence of illness remains higher in the daycare group through at least the 1st 3 yr of life. When they begin primary school, children who attended daycare have less frequent colds than those who did not. Mannose-binding lectin deficiency with impaired innate immunity may be associated with an increased incidence of colds in children.

PATHOGENESIS

Viruses that cause the common cold are spread by 3 mechanisms: direct hand contact (self-inoculation of one's own nasal mucosa or conjunctivae after touching a contaminated person or object), inhalation of small-particle aerosols that are airborne from coughing, or deposition of large-particle aerosols that are expelled during a sneeze and land on nasal or conjunctival mucosa. Although the different common cold pathogens could be spread by any of these mechanisms, some routes of transmission appear to be more efficient than others for particular viruses. Studies of rhinoviruses and RSV indicate that direct contact is an efficient mechanism of transmission of these viruses, although transmission by large-particle aerosols can also occur. By contrast, influenza viruses and coronaviruses appear to be most efficiently spread by small-particle aerosols.

The respiratory viruses have evolved different mechanisms to avoid host defenses. Infections with rhinoviruses and adenoviruses result in the development of serotype-specific protective immunity. Repeated infections with these pathogens occur because there are a large number of distinct serotypes of each virus. Influenza viruses have the ability to change the antigens presented on the surface of the virus and thus behave as though there were multiple viral serotypes. The interaction of coronaviruses (see Chapter 264) with host immunity is not well defined, but it appears that multiple distinct strains of coronaviruses are capable of inducing at least short-term protective immunity. There are 4 types of parainfluenza viruses and 2 antigenic subgroups of RSV. In addition to antigenic diversity, many of these viruses are able to

Table 379-1 Pathogens Associated with the Common Cold

ASSOCIATION	PATHOGEN	RELATIVE FREQUENCY*	OTHER COMMON SYMPTOMS AND SIGNS
Agents primarily associated with the common cold	Human rhinoviruses	Frequent	Wheezing/bronchiolitis
	Coronaviruses	Occasional	
Agents primarily associated with other clinical syndromes that also cause common cold symptoms	Respiratory syncytial viruses	Occasional	Bronchiolitis in children <2 yr of age
	Human metapneumovirus	Occasional	Pneumonia and bronchiolitis
	Influenza viruses	Uncommon	Influenza, pneumonia, croup
	Parainfluenza viruses	Uncommon	Croup, bronchiolitis
	Adenoviruses	Uncommon	Pharyngoconjunctival fever (palpebral conjunctivitis, watery eye discharge, pharyngeal erythema)
	Enteroviruses	Uncommon	
	Coxsackievirus A		Herpangina (fever and ulcerated papules on posterior oropharynx
	Other nonpolio enteroviruses		Aseptic meningitis

*Relative frequency of colds caused by the agent.

reinfect the upper airway because mucosal immunoglobulin A induced by previous infection is short-lived, and the brief incubation period of these viruses allows the establishment of infection before immune memory responses. Although reinfection is not completely prevented by the adaptive host response to these viruses, the severity of illness is moderated by preexisting immunity.

Viral infection of the nasal epithelium can be associated with destruction of the epithelial lining, as with influenza viruses and adenoviruses, or there can be no apparent histologic damage, as with rhinoviruses and RSV. Regardless of the histopathologic findings, infection of the nasal epithelium is associated with an acute inflammatory response characterized by release of a variety of inflammatory cytokines and infiltration of the mucosa by inflammatory cells. This acute inflammatory response appears to be partially or largely responsible for many of the symptoms associated with the common cold. Viral shedding of most respiratory viruses peaks 3-5 days after inoculation, often coinciding with symptom onset; low levels of viral shedding may persist for up to 2 wk in the otherwise healthy host. Inflammation can obstruct the sinus ostia or eustachian tube, predisposing to bacterial sinusitis or otitis media.

The host immune system is responsible for most cold symptoms, rather than direct damage to the respiratory tract. Infected cells release cytokines, such as interleukin-8, that attract polymorphonuclear cells into the nasal submucosa and epithelium. Rhinoviruses also increase vascular permeability in the nasal submucosa, releasing albumin and bradykinin, which may contribute to symptoms.

Table 379-2 Conditions That Can Mimic the Common Cold

CONDITION	DIFFERENTIATING FEATURES
Allergic rhinitis	Prominent itching and sneezing, nasal eosinophils
Vasomotor rhinitis	May be triggered by irritants, weather changes, spicy foods, etc.
Rhinitis medicamentosa	History of nasal decongestant use
Foreign body	Unilateral, foul-smelling secretions Bloody nasal secretions
Sinusitis	Presence of fever, headache or facial pain, or periorbital edema or persistence of rhinorrhea or cough for longer than 14 days
Streptococcosis	Mucopurulent nasal discharge that excoriates the nares
Pertussis	Onset of persistent or severe paroxysmal cough
Congenital syphilis	Persistent rhinorrhea with onset in the 1st 3 mo of life

CLINICAL MANIFESTATIONS

Symptoms of the common cold vary by age and virus. In infants, fever and nasal discharge may predominate. Fever is uncommon in older children and adults. The onset of common cold symptoms typically occurs 1-3 days after viral infection. The first symptom noted is often sore or scratchy throat, followed closely by nasal obstruction and rhinorrhea. The sore throat usually resolves quickly and, by the 2nd and 3rd day of illness, nasal symptoms predominate. Cough is associated with two-thirds of colds in children and usually begins after the onset of nasal symptoms. Cough may persist for an additional 1-2 wk after resolution of other symptoms. Influenza viruses, RSVs, human metapneumoviruses, and adenoviruses are more likely than rhinoviruses or coronaviruses to be associated with fever and other constitutional symptoms. Other symptoms of a cold may include headache, hoarseness, irritability, difficulty sleeping, or decreased appetite. Vomiting and diarrhea are uncommon. The usual cold persists for approximately 1 wk, although 10% last for 2 wk.

The physical findings of the common cold are limited to the upper respiratory tract. Increased nasal secretion is usually obvious; a change in the color or consistency of the secretions is common during the course of the illness and does not indicate sinusitis or bacterial superinfection but may indicate accumulation of polymorphonuclear cells. Examination of the nasal cavity might reveal swollen, erythematous nasal turbinates, although this finding is nonspecific and of limited diagnostic value. Abnormal middle ear pressure is common during the course of a cold. Anterior cervical lymphadenopathy or conjunctival injection may also be noted on exam.

DIAGNOSIS

The most important task of the physician caring for a patient with a cold is to exclude other conditions that are potentially more serious or treatable. The differential diagnosis of the common cold includes noninfectious disorders as well as other upper respiratory tract infections (Table 379-2).

LABORATORY FINDINGS

Routine laboratory studies are not helpful for the diagnosis and management of the common cold. A nasal smear for eosinophils may be useful if allergic rhinitis is suspected (see Chapter 143). A predominance of polymorphonuclear cells in the nasal secretions is characteristic of uncomplicated colds and does not indicate bacterial superinfection. Self-limited radiographic abnormalities of the paranasal sinuses are common during an uncomplicated cold; imaging is not indicated for most children with simple rhinitis.

The viral pathogens associated with the common cold can be detected by polymerase chain reaction, culture, antigen detection, or

serologic methods. These studies are generally not indicated in patients with colds because a specific etiologic diagnosis is useful only when treatment with an antiviral agent is contemplated, such as for influenza viruses. Bacterial cultures or antigen detection are useful only when group A streptococcus (see Chapter 183) or *Bordetella pertussis* (see Chapter 197) is suspected. The isolation of other bacterial pathogens from nasopharyngeal specimens is not an indication of bacterial nasal infection and is not a specific predictor of the etiologic agent in sinusitis.

TREATMENT

The management of the common cold consists primarily of supportive care and anticipatory guidance as recommended by American Academy of Pediatrics and United Kingdom National Institute for Health and Clinical Excellence guidelines.

Antiviral Treatment

Specific antiviral therapy is not available for rhinovirus infections. Ribavirin, which is approved for treatment of severe RSV infections, has no role in the treatment of the common cold. The neuraminidase inhibitors oseltamivir and zanamivir have a modest effect on the duration of symptoms associated with influenza viral infections in children. Oseltamivir also reduces the frequency of influenza-associated otitis media. The difficulty of distinguishing influenza from other common cold pathogens and the necessity that therapy be started early in the illness (within 48 hr of onset of symptoms) to be beneficial are practical limitations to the use of these agents for mild upper respiratory tract infections. Antibacterial therapy is of no benefit in the treatment of the common cold and should be avoided to minimize possible adverse effects and the development of antibiotic resistance.

Supportive Care and Symptomatic Treatment

Supportive interventions are frequently recommended by providers. Maintaining adequate oral hydration may help to thin secretions and soothe respiratory mucosa. The common home remedy of ingesting warm fluids may soothe mucosa, increase nasal mucous flow, or loosen respiratory secretions. Topical nasal saline may temporarily remove secretions, and saline nasal irrigation may reduce symptoms. Cool, humidified air has not been well studied but may loosen nasal secretions; however, cool-mist humidifiers and vaporizers must be cleaned after each use. The World Health Organization suggests that neither steam nor cool-mist therapy be used in treatment of a cold.

The use of oral **nonprescription** therapies (often containing antihistamines, antitussives, and decongestants) for cold symptoms in children is controversial. Although some of these medications are effective in adults, no study demonstrates a significant effect in children, and there may be serious side effects. Young children cannot participate in the assessment of symptom severity, so studies of these treatments in children have generally been based on observations by parents or other observers, a method that is likely to be insensitive for detection of treatment effects. As a result of the lack of direct evidence for effectiveness and the potential for unwanted side effects, the American Academy of Pediatrics recommends that nonprescription cough and cold products **not** be used for infants and children younger than 6 yr of age. A decision whether to use these medications in older children must consider the likelihood of clinical benefit compared with the potential adverse effects of these drugs. The prominent or most bothersome symptoms of colds vary in the course of the illness. If symptomatic treatments are used, it is reasonable to target therapy to specific bothersome symptoms and care should be taken to ensure that caregivers understand the intended effect and can determine the proper dosage of the medications.

Zinc, given as oral lozenges to previously healthy patients, reduces the duration but not the severity of symptoms of a common cold if begun within 24 hr of symptoms. The function of the rhinovirus 3C protease, an essential enzyme for rhinovirus replication, is inhibited by zinc, but there has been no evidence of an antiviral effect of zinc in vivo. The effect of zinc on symptoms has been inconsistent, with some studies reporting dramatic treatment effects (in adults), whereas other studies find no benefit. Side effects are common and include decreased taste, bad taste, and nausea.

Fever

Fever is not usually associated with an uncomplicated common cold, and antipyretic treatment is generally not indicated.

Nasal Obstruction

Either topical or oral adrenergic agents may be used as nasal decongestants in older children and adults. Effective topical adrenergic agents such as xylometazoline, oxymetazoline, or phenylephrine are available as either intranasal drops or nasal sprays. Reduced-strength formulations of these medications are available for use in younger children, although they are not recommended for use in children younger than 6 yr old. Systemic absorption of the imidazolines (oxymetazoline, xylometazoline) has very rarely been associated with bradycardia, hypotension, and coma. Prolonged use of the topical adrenergic agents should be avoided to prevent the development of **rhinitis medicamentosa,** an apparent rebound effect that causes the sensation of nasal obstruction when the drug is discontinued. The oral adrenergic agents are less effective than the topical preparations and are occasionally associated with systemic effects such as central nervous system stimulation, hypertension, and palpitations. Aromatic vapors (such as menthol) for external rub may improve perception of nasal patency, but do not affect spirometry.

Saline nose drops (wash, irrigation) can improve nasal symptoms and may be used in all age groups.

Rhinorrhea

The first-generation antihistamines may reduce rhinorrhea by 25-30%. The effect of the antihistamines on rhinorrhea appears to be related to the anticholinergic rather than the antihistaminic properties of these drugs, and therefore the second-generation or “nonsedating” antihistamines have no effect on common cold symptoms. The major adverse effects associated with the use of the antihistamines are sedation or paradoxical hyperactivity. Overdose may be associated with respiratory depression or hallucinations. Rhinorrhea may also be treated with ipratropium bromide, a topical anticholinergic agent. This drug produces an effect comparable to the antihistamines but is not associated with sedation. The most common side effects of ipratropium are nasal irritation and bleeding.

Sore Throat

The sore throat associated with colds is generally not severe, but treatment with mild analgesics is occasionally indicated, particularly if there is associated myalgia or headache. The use of acetaminophen during rhinovirus infection is associated with suppression of neutralizing antibody responses, but this observation has no apparent clinical significance. Aspirin should not be given to children with respiratory infections because of the risk of Reye syndrome in children with influenza (see Chapter 361). **Nonsteroidal antiinflammatory drugs** are somewhat effective in relieving discomfort caused by a cold, but there is no clear evidence of their effect on respiratory symptoms. The balance of harm and benefits must be considered when using nonsteroidal antiinflammatory drugs for colds.

Cough

Cough suppression is generally not necessary in patients with colds. Cough in some patients appears to be from upper respiratory tract irritation associated with postnasal drip. Cough in these patients is most prominent during the time of greatest nasal symptoms, and treatment with a first-generation antihistamine may be helpful. Cough lozenges or hard candy may be temporarily effective and are unlikely to be harmful in children for whom they do not pose risk of aspiration (older than age 6 yr). **Honey** (5-10 mL in children ≥1 year old) has a modest effect on relieving nocturnal cough and is unlikely to be harmful in children older than 1 yr of age. Honey should be avoided in children younger than 1 yr of age because of the risk for botulism (see Chapter 210).

In some patients, cough may be a result of **virus-induced reactive airways disease**. These patients can have cough that persists for days to weeks after the acute illness and might benefit from bronchodilator or other therapy. Codeine or dextromethorphan hydrobromide has no effect on cough from colds and has potential enhanced toxicity. Expectorants such as guaifenesin are not effective antitussive agents. The combination of camphor, menthol, and eucalyptus oils may relieve nocturnal cough, but studies of their effectiveness are limited.

Ineffective Treatments

Vitamin C, guaifenesin, and inhalation of warm, humidified air are no more effective than placebo for the treatment of cold symptoms.

Echinacea is a popular herbal treatment for the common cold. Although echinacea extracts have biologic effects, echinacea is not effective as a common cold treatment. The lack of standardization of commercial products containing echinacea also presents a formidable obstacle to the rational evaluation or use of this therapy.

There is no evidence that the common cold or persistent acute purulent rhinitis of less than 10 days in duration benefits from antibiotics. In fact, there is evidence that antibiotics cause significant adverse effects when given for acute purulent rhinitis.

COMPLICATIONS

The most common complication of a cold is **acute otitis media (AOM;** see Chapter 640), which may be indicated by new-onset fever and earache after the 1st few days of cold symptoms. AOM is reported in 5-30% of children who have a cold, with the higher incidence occurring in young infants and in children cared for in a group daycare setting. Symptomatic treatment has no effect on the development of AOM, but treatment with oseltamivir might reduce the incidence of AOM in patients with influenza.

Sinusitis is another complication of the common cold (see Chapter 380). Self-limited sinus inflammation is a part of the pathophysiology of the common cold, but 0.5-2% of viral upper respiratory tract infections in adults, and 5-13% in children, are complicated by acute bacterial sinusitis. The differentiation of common cold symptoms from bacterial sinusitis may be difficult. The diagnosis of bacterial sinusitis should be considered if rhinorrhea or daytime cough persists without improvement for at least 10-14 days, if symptoms worsen over time, or if signs of more severe sinus involvement such as fever, facial pain, or facial swelling develop. There is no evidence that symptomatic treatment of the common cold alters the frequency of development of bacterial sinusitis. Bacterial pneumonia is an uncommon complication of the common cold.

Exacerbation of **asthma** is a relatively uncommon but potentially serious complication of colds. The majority of asthma exacerbations in children are associated with the common cold. There is no evidence that treatment of common cold symptoms prevents this complication; however, studies are underway in patients with underlying asthma to determine effectiveness of preventive or acute treatment at the onset of upper respiratory tract infection symptoms.

Although not a complication, another important consequence of the common cold is the inappropriate use of antibiotics for these illnesses and the associated contribution to the problem of increasing antibiotic resistance of pathogenic respiratory bacteria, as well as adverse effects from antibiotics.

PREVENTION

Chemoprophylaxis or immunoprophylaxis is generally not available for the common cold. Immunization or chemoprophylaxis against influenza can prevent colds caused by this pathogen; influenza is responsible for only a small proportion of all colds. Palivizumab is recommended to prevent RSV lower respiratory infection in high-risk infants but does not prevent upper respiratory infections from this virus. Vitamin C, garlic, or echinacea do not prevent the common cold. Vitamin C prophylaxis may shorten the duration of cold symptoms. Vitamin D deficiency is associated with increased risk of viral respiratory tract infection in some studies, nonetheless, vitamin D prophylaxis does not reduce incidence or severity of the common cold in adults; studies in children are lacking. Zinc sulfate taken for a minimum of 5 mo may reduce the rate of cold development. However, because of duration of use and adverse effects of bad taste and nausea, this is not a recommended prevention modality in children.

Hand-to-hand transmission of rhinoviruses followed by self-inoculation may be prevented by frequent hand washing and avoiding touching one's mouth, nose, and eyes. Some studies report the use of alcohol-based hand sanitizers and virucidal hand treatments were associated with decreased transmission. In the experimental setting, virucidal disinfectants or virucidal-impregnated tissues also reduce transmission of cold viruses; under natural conditions none of these interventions prevents common colds.

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Chapter 380

Sinusitis

Diane E. Pappas and J. Owen Hendley

Sinusitis is a common illness of childhood and adolescence. There are 2 types of acute sinusitis: viral and bacterial, with significant acute and chronic morbidity as well as the potential for serious complications. The common cold produces a viral, self-limited rhinosinusitis (see Chapter 379). Approximately 0.5-2% of viral upper respiratory tract infections in children and adolescents are complicated by acute symptomatic bacterial sinusitis. Some children with underlying predisposing conditions have chronic sinus disease that does not appear to be infectious. The means for appropriate diagnosis and optimal treatment of sinusitis remain controversial.

Typically the **ethmoidal** and **maxillary** sinuses are present at birth, but only the ethmoidal sinuses are pneumatized. The maxillary sinuses are not pneumatized until 4 yr of age. The **sphenoidal** sinuses are present by 5 yr of age, whereas the **frontal sinuses** begin development at age 7-8 yr and are not completely developed until adolescence. The ostia draining the sinuses are narrow (1-3 mm) and drain into the ostiomeatal complex in the middle meatus. The **paranasal sinuses** are normally sterile, maintained by the mucociliary clearance system.

ETIOLOGY

The bacterial pathogens causing acute bacterial sinusitis in children and adolescents include *Streptococcus pneumoniae* (~30%; see Chapter 182), nontypeable *Haemophilus influenzae* (~20%; see Chapter 194), and *Moraxella catarrhalis* (~20%; see Chapter 196). Approximately 50% of *H. influenzae* and 100% of *M. catarrhalis* are β-lactamase positive. Approximately 25% of *S. pneumoniae* may be penicillin resistant. *Staphylococcus aureus,* other streptococci, and anaerobes are uncommon causes of acute bacterial sinusitis in children. Although *S. aureus* (see Chapter 181.1) is an uncommon pathogen for acute sinusitis in children, the increasing prevalence of methicillin-resistant *S. aureus* is a significant concern. *H. influenzae,* α- and β-hemolytic streptococci, *M. catarrhalis, S. pneumoniae,* and coagulase-negative staphylococci are commonly recovered from children with **chronic sinus disease.**

EPIDEMIOLOGY

Acute bacterial sinusitis can occur at any age. Predisposing conditions include viral upper respiratory tract infections (associated with out-of-home daycare or a school-age sibling), allergic rhinitis, and cigarette smoke exposure. Children with immune deficiencies particularly of antibody production (immunoglobulin IgG, IgG subclasses, IgA; see Chapter 124), cystic fibrosis (see Chapter 403), ciliary dysfunction (see Chapter 404), abnormalities of phagocyte function,

gastroesophageal reflux, anatomic defects (cleft palate), nasal polyps, cocaine abuse, and nasal foreign bodies (including nasogastric tubes) can develop chronic or recurrent sinus disease. Immunosuppression for bone marrow transplantation or malignancy with profound neutropenia and lymphopenia predisposes to severe fungal (aspergillus, mucor) sinusitis, often with intracranial extension. Patients with nasotracheal intubation or nasogastric tubes may have obstruction of the sinus ostia and develop sinusitis with the multiple-drug resistant organisms of the intensive care unit.

Acute sinusitis is defined by duration of <30 days; subacute by duration of 1-3 mo; and chronic by duration of longer than 3 mo.

PATHOGENESIS

Acute bacterial sinusitis typically follows a viral upper respiratory tract infection. Initially, the viral infection produces a viral rhinosinusitis; MRI evaluation of the paranasal sinuses demonstrates abnormalities (mucosal thickening, edema, inflammation) of the paranasal sinuses in 68% of healthy children in the normal course of the common cold. Nose blowing has been demonstrated to generate sufficient force to propel nasal secretions into the sinus cavities. Bacteria from the nasopharynx that enter the sinuses are normally cleared readily, but during viral rhinosinusitis, inflammation and edema can block sinus drainage and impair mucociliary clearance of bacteria. The growth conditions are favorable, and high titers of bacteria are produced.

CLINICAL MANIFESTATIONS

Children and adolescents with sinusitis can present with nonspecific complaints, including nasal congestion, purulent nasal discharge (unilateral or bilateral), fever, and cough. Less-common symptoms include bad breath (halitosis), a decreased sense of smell (hyposmia), and periorbital edema. Complaints of headache and facial pain are rare in children. Additional symptoms include maxillary tooth discomfort and pain or pressure exacerbated by bending forward. Physical examination might reveal erythema and swelling of the nasal mucosa with purulent nasal discharge. Sinus tenderness may be detectable in adolescents and adults. Transillumination reveals an opaque sinus that transmits light poorly.

Differentiating bacterial sinusitis from a cold may be difficult, but certain patterns suggestive of sinusitis have been identified. These include **persistence** of nasal congestion, rhinorrhea (of any quality) and daytime cough ≥10 days without improvement; **severe symptoms** of temperature ≥39°C (102°F) with purulent nasal discharge for 3 days or longer; and **worsening symptoms** either by recurrence of symptoms after an initial improvement or new symptoms of fever, nasal discharge and daytime cough.

DIAGNOSIS

The clinical diagnosis of acute bacterial sinusitis is based on history. Persistent symptoms of upper respiratory tract infection, including nasal discharge and cough, for longer than 10 days without improvement, or severe respiratory symptoms, including temperature of at least 39°C (102°F) and purulent nasal discharge for 3-4 consecutive days, suggest a complicating acute bacterial sinusitis. Bacteria are recovered from maxillary sinus aspirates in 70% of children with such persistent or severe symptoms studied. Children with chronic sinusitis have a history of persistent respiratory symptoms, including cough, nasal discharge, or nasal congestion, lasting longer than 90 days.

Sinus aspirate culture is the only accurate method of diagnosis but is not practical for routine use for immunocompetent patients. It may be a necessary procedure for immunosuppressed patients with suspected fungal sinusitis. In adults, *rigid nasal endoscopy* is a less-invasive method for obtaining culture material from the sinus but detects a great excess of positive cultures compared to aspirates. Findings on radiographic studies (sinus plain films, CT scans) including opacification, mucosal thickening, or presence of an air–fluid level are not diagnostic (Fig. 380-1) and are not recommended in otherwise healthy children. Such findings can confirm the presence of sinus inflammation but cannot be used to differentiate among viral, bacterial, or allergic causes of inflammation.

Given the nonspecific clinical picture, differential diagnostic considerations include viral upper respiratory tract infection, allergic rhinitis, nonallergic rhinitis, and nasal foreign body. Viral upper respiratory tract infections are characterized by clear and usually nonpurulent nasal discharge, cough, and initial fever; symptoms do not usually persist beyond 10-14 days, although a few children (10%) have persistent symptoms even at 14 days. Allergic rhinitis can be seasonal; evaluation of nasal secretions should reveal significant eosinophilia.

TREATMENT

It is unclear whether antimicrobial treatment of clinically diagnosed acute bacterial sinusitis offers any substantial benefit. A randomized, placebo-controlled trial comparing 14-day treatment of children with clinically diagnosed sinusitis with amoxicillin, amoxicillin-clavulanate, or placebo found that antimicrobial therapy did not affect resolution of symptoms, duration of symptoms, or days missed from school. A similar study in adults demonstrated improved symptoms at day 7 but not day 10 of treatment. Guidelines from the American Academy of Pediatrics recommend antimicrobial treatment for acute bacterial sinusitis with severe onset or a worsening course to promote resolution of symptoms and prevent suppurative complications, although 50-60% of children with acute bacterial sinusitis recover without antimicrobial therapy.

Initial therapy with amoxicillin (45 mg/kg/day divided bid) is adequate for the majority of children with uncomplicated mild to moderate severity acute bacterial sinusitis. Alternative treatments for the penicillin-allergic patient include cefdinir, cefuroxime axetil, cefpodoxime, or cefixime. In older children, levofloxacin is an alternative antibiotic. Azithromycin and trimethoprim-sulfamethoxazole are no longer indicated because of a high prevalence of antibiotic resistance. For children with risk factors (antibiotic treatment in the preceding 1-3 mo, daycare attendance, or age younger than 2 yr) for the presence of resistant bacterial species, and for children who fail to respond to initial therapy with amoxicillin within 72 hr, or with severe sinusitis, treatment with high-dose amoxicillin-clavulanate (80-90 mg/kg/day of amoxicillin) should be initiated. Ceftriaxone (50 mg/kg, IV or IM) may be given to children who are vomiting or who are at risk for poor compliance; it should be followed by a course of oral antibiotics. Failure to respond to these regimens necessitates referral to an otolaryngologist for further evaluation because maxillary sinus aspiration for culture and susceptibility testing may be necessary. The appropriate duration of therapy for sinusitis has yet to be determined; individualization of therapy is a reasonable approach, with treatment recommended for a minimum of 10 days or 7 days after resolution of symptoms (see Fig. 380-1).

Frontal sinusitis can rapidly progress to serious intracranial complications and necessitates initiation of parenteral ceftriaxone until substantial clinical improvement is achieved (Figs. 380-2 and 380-3). Treatment is then completed with oral antibiotic therapy.

The use of decongestants, antihistamines, mucolytics, and intranasal corticosteroids has not been adequately studied in children and is not recommended for the treatment of acute uncomplicated bacterial sinusitis. Likewise, saline nasal washes or nasal sprays can help to liquefy secretions and act as a mild vasoconstrictor, but the effects have not been systematically evaluated in children.

COMPLICATIONS

Because of the close proximity of the paranasal sinuses to the brain and eyes, serious orbital and/or intracranial complications can result from acute bacterial sinusitis and progress rapidly. Orbital complications, including *periorbital cellulitis* and *orbital cellulitis* (see Chapter 634) are most often secondary to acute bacterial ethmoiditis. Infection can spread directly through the lamina papyracea, the thin bone that forms the lateral wall of the ethmoidal sinus. Periorbital cellulitis produces erythema and swelling of the tissues surrounding the globe, whereas orbital cellulitis involves the intraorbital structures and produces proptosis, chemosis, decreased visual acuity, double vision and impaired extraocular movements, and eye pain (Fig. 380-4). Evaluation should include CT scan of the orbits and sinuses with ophthalmology and otolaryngology consultations. Treatment with intravenous antibiotics

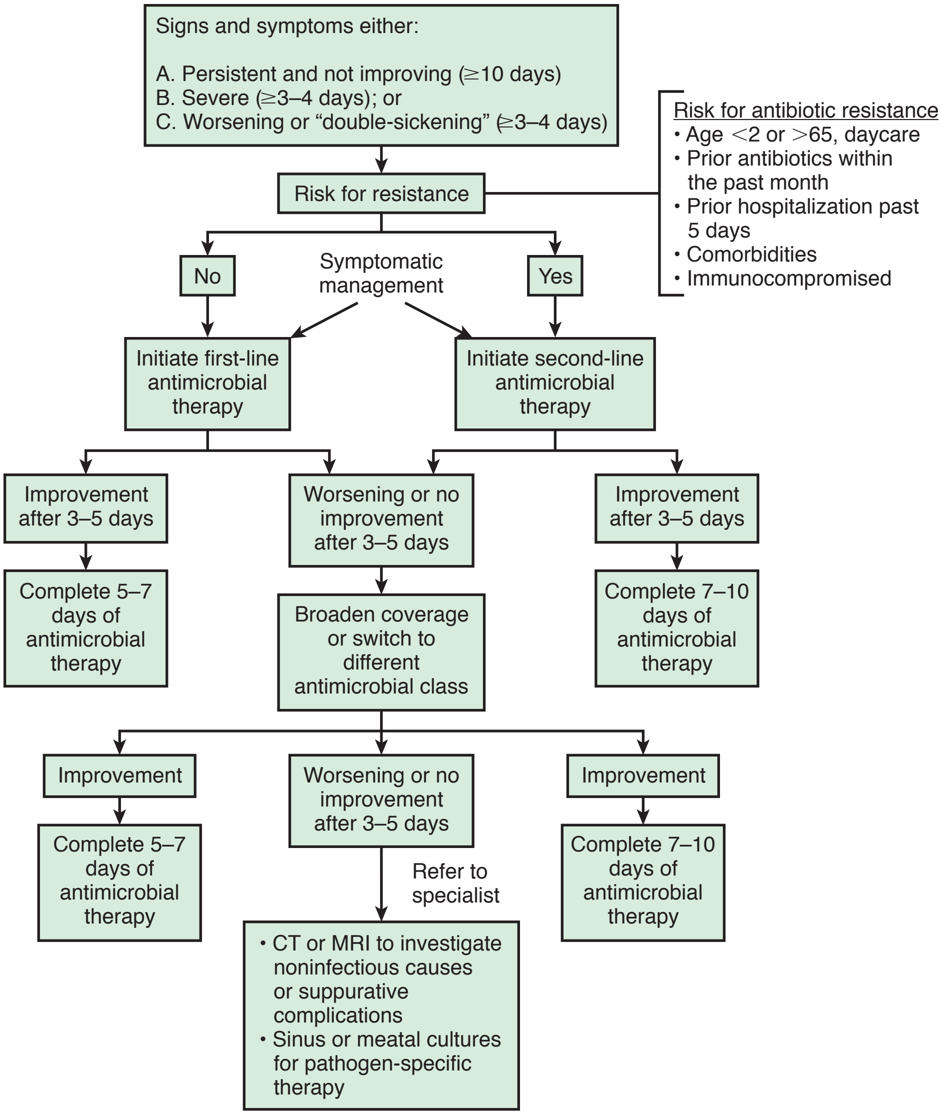

Figure 380-1 Algorithm for the management of acute bacterial rhinosinusitis. *(From Chow AW, Benninger MS, Brook I, et al: Infectious Diseases Society of America. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults.* Clin Infect Dis *54(8):e72–e112, 2012, Fig. 1.)*

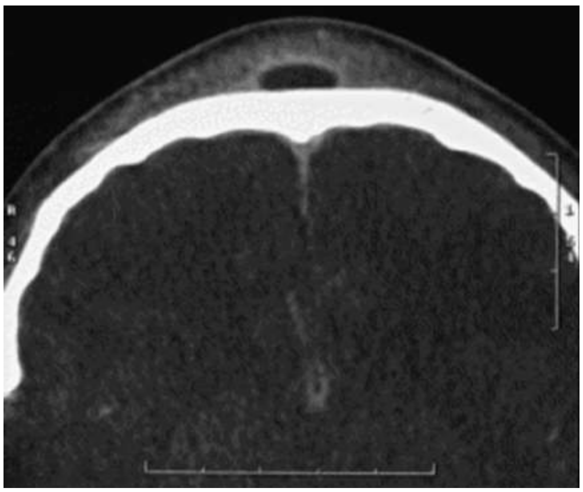

Figure 380-2 Axial plane contrast-enhanced CT scan of an 11 yr old boy with a frontal subperiosteal abscess secondary to acute frontal sinusitis. The CT scan demonstrates a ring-enhancing midline fluid density over the frontal bone. *(From Parikh SR, Brown SM: Image-guided frontal sinus surgery in children,* Operative Tech Otolaryngol Head Neck Surg *15:37–41, 2004.)*

should be initiated. Orbital cellulitis can require surgical drainage of the ethmoidal sinuses.

Intracranial complications can include epidural abscess, meningitis, cavernous sinus thrombosis, subdural empyema, and brain abscess (see Chapter 604). Children with altered mental status, nuchal rigidity, severe headache, focal neurologic findings, or signs of increased intracranial pressure (headache, vomiting) require immediate CT scan of the brain, orbits, and sinuses to evaluate for the presence of intracranial complications of acute bacterial sinusitis. Black children and males are at increased risk, but there is no evidence of increased risk due to socioeconomic status. Treatment with broad-spectrum intravenous antibiotics (usually cefotaxime or ceftriaxone combined with vancomycin) should be initiated immediately, pending culture and susceptibility results. In 50% the abscess is a polymicrobial infection. Abscesses can require surgical drainage. Other complications include osteomyelitis of the frontal bone (**Pott puffy tumor**), which is characterized by edema and swelling of the forehead (see Fig. 380-3), and **mucoceles,** which are chronic inflammatory lesions commonly located in the frontal sinuses that can expand, causing displacement of the eye with resultant diplopia. Surgical drainage is usually required.

PREVENTION

Prevention is best accomplished by frequent handwashing and avoiding persons with colds. Because acute bacterial sinusitis can complicate

influenza infection, prevention of influenza infection by yearly influenza vaccine will prevent some cases of complicating sinusitis. Immunization or chemoprophylaxis against influenza with oseltamivir or zanamivir may be useful for prevention of colds caused by this pathogen and the associated complications; influenza is responsible for only a small proportion of all colds.

Bibliography is available at Expert Consult.

Figure 380-3 **Axial plane contrast-enhanced CT scan of an 11 yr old obtunded girl with a subfrontal lobe abscess secondary to frontal sinusitis.** The CT scan demonstrates an eliptiform ring-enhancing fluid-filled cavity adjacent to the frontal lobe with contralateral shift of the midline. *(From Parikh SR, Brown SM: Image-guided frontal sinus surgery in children*, Operative Tech Otolaryngol Head Neck Surg *15:37–41, 2004.)*

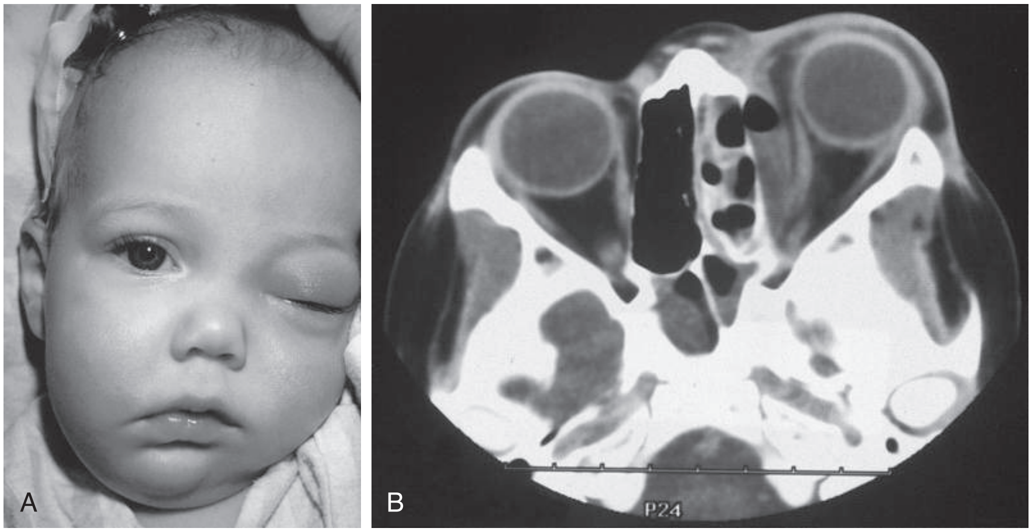

Figure 380-4 **Orbital complications of acute sinusitis. A,** An 11 mo old infant with a swollen left eye and limited ocular movement. **B,** Axial CT shows opacification of sinuses and an inflammatory mass with an air–fluid level displacing the medial rectus laterally. *(From Cooper, ML, Slovis T. The sinuses. In Slovis T, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, Fig. 43-7, p. 573.)*

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Chapter 381

Acute Pharyngitis

Robert R. Tanz

Pharyngitis refers to inflammation of the pharynx, including erythema, edema, exudates, or an enanthem (ulcers, vesicles). Pharyngeal inflammation can be related to environmental exposures, such as tobacco smoke, air pollutants, and allergens; from contact with caustic substances, hot food, and liquids; and from infectious agents. The pharynx and mouth can be involved in various inflammatory conditions such as the periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome, Kawasaki disease, inflammatory bowel disease, Stevens-Johnson syndrome, and systemic lupus erythematous. Noninfectious etiologies are typically evident from history and physical exam, but it can be more challenging to distinguish from among the numerous infectious causes of acute pharyngitis.

Acute infections of the upper respiratory tract account for a substantial number of visits to pediatricians and many feature sore throat as a symptom or evidence of pharyngitis on physical examination. The usual clinical task is to distinguish important, potentially serious, and treatable causes of acute pharyngitis from those that are self-limited and require no specific treatment or follow-up. Specifically, identifying patients who have **group A streptococcus** (GAS; *Streptococcus pyogenes;* see Chapter 183) pharyngitis and treating them with antibiotics forms the core of the management paradigm.

INFECTIOUS ETIOLOGIES

See Table 381-1.

Viruses

In North America and most industrialized countries GAS is the most important bacterial cause of acute pharyngitis, but viruses predominate as acute infectious causes of pharyngitis. Viral upper respiratory tract infections are typically spread by contact with oral or respiratory secretions and occur most commonly in fall, winter, and spring, that is, the "respiratory season." Important viruses that cause pharyngitis include influenza (see Chapter 258), parainfluenza (see Chapter 259), adenoviruses (see Chapter 262), coronaviruses (see Chapter 264), enteroviruses (see Chapter 250), rhinoviruses (see Chapter 263), respiratory

Table 381-1 Infectious Agents That Cause Pharyngitis

VIRUSES	BACTERIA
Adenovirus	*Streptococcus pyogenes* (Group A streptococcus)
Coronavirus	*Arcanobacterium haemolyticum*
Cytomegalovirus	*Fusobacterium necrophorum*
Epstein-Barr virus	*Corynebacterium diphtheriae*
Enteroviruses	*Neisseria gonorrhoeae*
Herpes simplex virus	Group C streptococci
Human immunodeficiency virus	Group G streptococci
Human metapneumovirus	*Francisella tularensis*
Influenza viruses	*Chlamydophila pneumoniae*
Measles virus	*Chlamydia trachomatis*
Parainfluenza viruses	*Mycoplasma pneumoniae*
Respiratory syncytial virus	
Rhinoviruses	

syncytial virus (see Chapter 260), cytomegalovirus (see Chapter 255), Epstein-Barr virus (see Chapter 254), herpes simplex virus (see Chapter 252), and human metapneumovirus (see Chapter 261). Most viral pharyngitis, except mononucleosis, is mild. Common nonspecific symptoms such as rhinorrhea and cough develop gradually before they become prominent. However, specific findings are sometimes helpful in identifying the infectious viral agent.

Gingivostomatitis and ulcerating vesicles throughout the anterior pharynx and on the lips are seen in primary oral herpes simplex virus infection. High fever and difficulty taking oral fluids are common. This infection can last for 14 days.

Discrete **papulovesicular** lesions or **ulcerations** in the posterior oropharynx, severe throat pain, and fever are characteristic of herpangina, caused by various enteroviruses. In hand-foot-mouth disease there are vesicles or ulcers throughout the oropharynx, vesicles on the palms and soles, and sometimes on the trunk and extremities; Coxsackie A16 is the most common agent, but Enterovirus 71 and Coxsackie A6 can also cause this syndrome. Enteroviral infections are most common in the summer.

Various adenoviruses cause pharyngitis. When there is concurrent **conjunctivitis** the syndrome is called *pharyngoconjunctival fever*. The pharyngitis tends to resolve within 7 days but conjunctivitis may persist for up to 14 days. Pharyngoconjunctival fever can be epidemic or sporadic; outbreaks have been associated with exposure in swimming pools.

Intense, diffuse pharyngeal erythema and Koplik spots, the pathognomonic enanthem, occur in advance of the characteristic rash of measles. Splenomegaly or hepatomegaly may be the clue to Epstein-Barr virus infectious mononucleosis in an adolescent with exudative tonsillitis. Primary infection with HIV can manifest as the acute retroviral syndrome, with non-exudative pharyngitis, fever, maculopapular rash, arthralgia, myalgia, adenopathy, and often a maculopapular rash.

Bacteria Other Than Group A Streptococcus

In addition to GAS, bacteria that cause pharyngitis include group C and group G streptococcus (see Chapter 185), *Arcanobacterium haemolyticum, Francisella tularensis* (see Chapter 206), *Neisseria gonorrhoeae* (see Chapter 192), *Mycoplasma pneumoniae* (see Chapter 223), *Chlamydophila* (formerly *Chlamydia*) *pneumoniae* (see Chapter 225), *Chlamydia trachomatis* (see Chapter 226), *Fusobacterium necrophorum*, and *Corynebacterium diphtheriae* (see Chapter 187). *Haemophilus influenzae* and *Streptococcus pneumoniae* may be cultured from the throats of children with pharyngitis, but their role in causing pharyngitis has not been established.

Group C and Group G streptococcus and *A. haemolyticum* pharyngitis have been diagnosed most commonly in adolescents and adults. They resemble group A β-hemolytic streptococcus (GABHS) pharyngitis and a scarlet fever–like rash may be present with *A. haemolyticum* infections.

F. necrophorum has been suggested to be a fairly common cause of pharyngitis in older adolescents and adults (15-30 yr old). Prevalence in studies has varied from 10-48% of patients with non-GABHS pharyngitis, but large surveillance studies have not been performed. *F. necrophorum* pharyngitis is associated with development of **Lemierre syndrome**, internal jugular vein septic thrombophlebitis. Approximately 80% of cases of Lemierre syndrome are caused by this bacterium. Patients present initially with fever, sore throat, exudative pharyngitis, and/or peritonsillar abscess. The symptoms may persist, neck pain and swelling develop, and the patient appears toxic. Septic shock may ensue along with metastatic complications from septic emboli that can involve the lungs, bones and joints, central nervous system, abdominal organs, and soft tissues. The case fatality rate is 4-9%.

Gonococcal pharyngeal infections are usually asymptomatic but can cause acute pharyngitis with fever and cervical lymphadenitis. Young children with proven gonococcal disease should be evaluated for sexual abuse.

Diphtheria is extremely rare in most developed countries thanks to extensive immunization with diphtheria toxoid. However, it remains endemic in many areas of the world, including the former Soviet bloc countries, Africa, Asia, the Middle East, and Latin America. It can be considered in patients with recent travel to or from these areas and in unimmunized patients. Key physical findings are bull neck (extreme neck swelling) and a gray pharyngeal pseudomembrane that can cause respiratory obstruction.

Ingestion of water, milk, or undercooked meat contaminated by *F. tularensis* can lead to oropharyngeal tularemia. Severe throat pain, tonsillitis, cervical adenitis, oral ulcerations, and a pseudomembrane (as in diphtheria) may be present. *M. pneumoniae* and *C. pneumonia*e cause pharyngitis, but other upper and lower respiratory infections are more important and more readily recognized. Development of a severe or persistent cough subsequent to pharyngitis may be the clue to infection with one of these organisms.

Group A Streptococcus

Streptococcal pharyngitis is relatively uncommon before 2-3 yr of age, is quite common among children 5-15 yr old, and declines in frequency in late adolescence and adulthood. Illness occurs throughout the year but is most prevalent in winter and spring. It is readily spread among siblings and schoolmates. GAS causes 15-30% of pharyngitis in school-age children.

Colonization of the pharynx by GAS can result in either asymptomatic carriage or acute infection. After an incubation period of 2-5 days, pharyngeal infection with GAS classically presents as rapid onset of significant sore throat and fever. The pharynx is red, the tonsils are enlarged and often covered with a white, grayish, or yellow exudate that may be blood-tinged. There may be petechiae or "doughnut" lesions on the soft palate and posterior pharynx and the uvula may be red and swollen. The surface of the tongue can resemble a strawberry when the papillae are inflamed and prominent ("strawberry tongue"). Initially, the tongue is often coated white, and with the swollen papillae it is called a "white strawberry tongue." When the white coating is gone after a few days, the tongue is often quite red, and is called a "red strawberry tongue." Enlarged and tender anterior cervical lymph nodes are frequently present. Headache, abdominal pain, and vomiting are frequently associated with the infection, but in the absence of clinical pharyngitis, gastrointestinal signs and symptoms should not be attributed to GAS. Ear pain is a frequent complaint but the tympanic membranes are usually normal. Diarrhea, cough, coryza, ulcerations, croup/laryngitis/hoarseness, and conjunctivitis are not associated with GAS pharyngitis and increase the likelihood of a viral etiology.

Patients infected with GAS that produce streptococcal pyrogenic exotoxin A, B, or C may demonstrate the fine red, papular ("sandpaper") rash of scarlet fever. It begins on the face and then becomes generalized. The cheeks are red and the area around the mouth is more pale, giving the appearance of circumoral pallor. The rash blanches with pressure and it may be more intense in skin creases, especially in the antecubital fossae, axillae, and inguinal creases (Pastia's lines or Pastia's sign). Pastia's lines are sometimes petechial or slightly hemorrhagic.

Capillary fragility can cause petechiae distal to a tourniquet or constriction from clothing, a positive tourniquet test or Rumpel-Leeds phenomenon. Erythema fades in a few days and when the rash resolves it typically peels like a mild sunburn. Sometimes there is sheet-like desquamation around the free margins of the finger nails. Streptococcal pyrogenic exotoxin A, encoded by the gene *spe A*, is the exotoxin most commonly associated with scarlet fever.

The M protein is an important GAS virulence factor that facilitates resistance to phagocytosis. The M protein is encoded by the *emm* gene and determines the M type (or *emm* type). Molecular methods have identified more than 200 *emm* genes (*emm* types). The M protein is immunogenic; an individual can experience multiple episodes of GAS pharyngitis in a lifetime because natural immunity is M type-specific. Numerous GAS M types can circulate in a community simultaneously and they enter and leave communities unpredictably and for unknown reasons.

DIAGNOSIS

The clinical presentations of streptococcal and viral pharyngitis often overlap. In particular, the pharyngitis of mononucleosis can be difficult to distinguish from GAS pharyngitis. Physicians relying solely on clinical judgment often overestimate the likelihood of a streptococcal etiology. Various clinical scoring systems have been described to assist in identifying patients who are likely to have GAS pharyngitis. Criteria developed for adults and modified for children by McIsaac give 1 point for each of the following criteria: history of temperature >38°C (100.4°F); absence of cough; tender anterior cervical adenopathy; tonsillar swelling or exudates; and age 3-14 yr. It subtracts a point for age ≥45 yr. At best, a McIsaac score ≥4 is associated with a positive laboratory test for GAS in less than 70% of children with pharyngitis (Table 381-2), so it, too, overestimates the likelihood of GAS. Consequently, laboratory testing is essential for accurate diagnosis. Clinical findings and/or scoring systems can best be used to assist the clinician in identifying patients in need of testing. Streptococcal antibody tests are not useful in assessing patients with acute pharyngitis.

Throat culture and **rapid antigen-detection tests** (RADTs) are the diagnostic tests for GAS available in routine clinical care. Throat culture remains the “gold standard” for diagnosing streptococcal pharyngitis. There are both false-negative cultures as a consequence of sampling errors or prior antibiotic treatment and false-positive cultures as a consequence of misidentification of other bacteria as GAS. Some laboratories prefer nucleic acid testing that is specific for GAS and no longer use culture to confirm the diagnosis. A child who is chronically colonized with GAS (streptococcal carrier) can have a positive culture if it is obtained when the child is evaluated for pharyngitis that is actually caused by a viral infection.

Streptococcal RADTs detect the group A carbohydrate of GAS. They are used by the vast majority of office-based pediatricians. All RADTs have very high specificity, generally ≥95%, so when a RADT is positive it is assumed to be accurate and throat culture is unnecessary. Because RADTs are generally less sensitive than culture, confirming a negative rapid test with a throat culture is recommended. RADTs and throat culture exhibit spectrum bias: They are more sensitive when the pretest probability of GAS is high (signs and symptoms are typical of GAS infection) and less sensitive when the pretest probability is low. Avoidance of testing when patients have signs and symptoms more suggestive of a viral infection is recommended.

Testing for bacteria other than GAS is performed infrequently, and should be reserved for patients with persistent symptoms and symptoms suggestive of a specific non-GAS bacterial pharyngitis, for example, when there is concern for gonococcal infection or sexual abuse. Special culture media and a prolonged incubation are required to detect *A. haemolyticum*. Viral cultures are often unavailable and are generally too expensive and slow to be clinically useful. Polymerase chain reaction is more rapid and multiplex polymerase chain reaction testing for respiratory pathogens can identify a variety of viral and bacterial agents within a few hours. This may be useful in determining the isolation needs of hospitalized patients, assisting in patient prognosis, and epidemiology, but in the absence of specific treatment for most viral infections such testing is usually not necessary. A complete blood cell count showing many atypical lymphocytes and a positive mononucleosis slide agglutination test can help to confirm a clinical diagnosis of Epstein-Barr virus infectious mononucleosis.

TREATMENT

Specific therapy is unavailable for most viral pharyngitis. However, nonspecific, symptomatic therapy can be an important part of the overall treatment plan. An oral antipyretic/analgesic agent (acetaminophen or ibuprofen) can relieve fever and sore throat pain. Anesthetic sprays and lozenges (often containing benzocaine, phenol, or menthol) can provide local relief in children who are developmentally appropriate to use them. Systemic corticosteroids are sometimes used in children who have evidence of upper airway compromise due to mononucleosis. Although corticosteroids are used fairly commonly in adults with pharyngitis, large scale studies capable of providing safety and efficacy data are lacking in children. *Corticosteroids cannot be recommended for treatment of most pediatric pharyngitis.*

Antibiotic therapy of bacterial pharyngitis depends on the organism identified. On the basis of in vitro susceptibility data, oral penicillin is often suggested for patients with group C streptococcal isolates and oral erythromycin is recommended for patients with *A. haemolyticum*, but the clinical benefit of such treatment is uncertain.

Most untreated episodes of GAS pharyngitis resolve uneventfully within 5 days, but early antibiotic therapy hastens clinical recovery by 12-24 hr. The primary benefit and intent of antibiotic treatment is the prevention of acute rheumatic fever (ARF); it is highly effective when started within 9 days of onset of illness. Antibiotic therapy does not prevent acute poststreptococcal glomerulonephritis (APSGN). Antibiotic therapy should not be delayed for children with symptomatic pharyngitis and a positive GAS RADT or throat culture. Presumptive antibiotic treatment can be started when there is a clinical diagnosis of scarlet fever, a symptomatic child has a household contact with

Table 381-2 Positive Predictive Value of McIsaac Score in Children in Clinical Studies*

SCORE	McISAAC, 2004 (N = 454)	EDMONSON, 2005 (N = 1184)	TANZ, 2009 (N = 1848)	FINE, 2012 (N = 64,789)
0	—	—	7%	17%
1	—	0.5%	19%	23%
2	20.5%	8.9%	20%	34%
3	27.5%	42.4%	29%	50%
≥4	67.8%	48.2%	49%	68%
GAS prevalence	34%	38%	30%	37%

*One point is given for each of the following criteria: history of temperature >38°C (100.4°F); absence of cough; tender anterior cervical adenopathy; tonsillar swelling or exudates; and age 3-14 yr. Note that the Centor score lacks only the age criterion. Positive predictive value refers to the proportion of patients with documented GAS by rapid antigen-detection test and/or throat culture.

Table 381-3 Recommended Treatment for Acute Streptococcal Pharyngitis

MOST PATIENTS				
	WEIGHT <27 kg	**WEIGHT ≥27 kg**	**ROUTE**	**DURATION**
Amoxicillin	50 mg/kg once daily (maximum 1000 mg)		Oral	10 days
Penicillin V	250 mg bid	500 mg bid	Oral	10 days
Benzathine penicillin G	600,000 units	1.2 million units	IM	Once
Benzathine penicillin G + procaine penicillin G	900,000 units + 300,000 units	900,000 units + 300,000 units	IM	Once

PENICILLIN-ALLERGIC PATIENTS			
	ORAL DOSE	**FREQUENCY**	**DURATION**
Cephalosporins*	Varies with agent chosen		10 days
Erythromycin			
Ethylsuccinate	40 mg/kg/day up to 1000 mg/day	bid	10 days
Estolate	20-40 mg/kg/day up to 1000 mg/day	bid	10 days
Clarithromycin	15 mg/kg/day up to 500 mg/day	bid	10 days
Azithromycin†	12 mg/kg day 1; 6 mg/kg days 2-5	qd	5 days
Clindamycin	20 mg/kg/day up to 1.8 g/day	tid	10 days

*First-generation cephalosporins are preferred; dosage and frequency vary among agents. Do not use in patients with history of immediate (anaphylactic) hypersensitivity to penicillin or other β-lactam antibiotics.
†Maximum dose is 500 mg the 1st day, 250 mg subsequent days.

documented streptococcal pharyngitis, or a history of ARF in the patient or a family member, but a diagnostic test should be performed to confirm the presence of GAS.

A variety of antimicrobial agents are effective for GAS pharyngitis (Table 381-3). Group A streptococci are universally susceptible to penicillin and all other β-lactam antibiotics. Penicillin is inexpensive, has a narrow spectrum of activity, and few adverse effects. Amoxicillin is preferred for children because of taste, availability as chewable tablets and liquid, and convenience of once-daily dosing. The duration of oral penicillin and amoxicillin therapy is 10 days. A single intramuscular dose of benzathine penicillin or a benzathine-procaine penicillin G combination is effective and ensures compliance. Follow-up testing for GAS is unnecessary after completion of therapy and is not recommended unless symptoms recur.

Patients allergic to penicillin can be treated with a 10-day course of a narrow-spectrum (first-generation) cephalosporin (cephalexin or cefadroxil) if the previous reaction to penicillin was not an immediate, type I hypersensitivity reaction. Most often, penicillin-allergic patients are treated for 10 days with erythromycin, clarithromycin, or clindamycin, or for 5 days with azithromycin.

The increased use of macrolides and related antibiotics for a variety of infections, especially the azalide, azithromycin, is associated with increased rates of resistance to these drugs among GAS in many countries. Approximately 5% of GAS in the United States and more than 10% in Canada are macrolide-resistant (macrolide resistance includes azalide resistance), but there is considerable local variation in both countries. Some macrolide-resistant GAS isolates are also resistant to clindamycin. Although not a major hindrance for treatment of pharyngitis, clindamycin resistance may be important in management of invasive GAS infections. Use of these antibiotics should be restricted to patients who cannot safely receive a β–lactam drug for GAS pharyngitis. Tetracyclines, fluoroquinolones, or sulfonamides should ***not*** be used to treat GAS pharyngitis.

CHRONIC GROUP A STREPTOCOCCUS CARRIERS

Patients who continue to harbor GAS in the pharynx despite appropriate antibiotic therapy are streptococcal carriers. They have little or no evidence of an immune response to the organism. The pathogenesis of chronic carriage is not known. Carriage generally poses little risk to patients and their contacts, but it can confound testing in subsequent episodes of sore throat. Patients with repeated test-positive pharyngitis create anxiety among their families and physicians. It is usually unnecessary to attempt to eliminate chronic carriage. Instead, evaluation and treatment of pharyngitis should be undertaken without regard for chronic carriage, treating test-positive patients in routine fashion and avoiding antibiotics in patients who have negative tests. Expert opinion suggests that eradication might be attempted in select circumstances: a community outbreak of ARF or APSGN; personal or family history of ARF; an outbreak of GAS pharyngitis in a closed or semiclosed community, nursing home or healthcare facility; repeated episodes of symptomatic GAS pharyngitis in a family with "ping pong" spread among family members despite adequate therapy; when tonsillectomy is being considered because of chronic carriage or recurrent streptococcal pharyngitis; and extreme, unmanageable anxiety related to GAS carriage ("streptophobia") among family members. Clindamycin given by mouth for 10 days is effective therapy (20 mg/kg/day divided in 3 doses; adult dose 150-450 mg tid). Amoxicillin-clavulanate (40 mg amoxicillin/kg/day up to 2000 mg amoxicillin/day divided tid for 10 days) and 4 days of oral rifampin plus either intramuscular benzathine penicillin given once or oral penicillin given for 10 days have also been used.

RECURRENT PHARYNGITIS

True recurrent GAS pharyngitis can occur for several reasons: reinfection with the same M type if type-specific antibody has not developed; poor compliance with oral antibiotic therapy; macrolide resistance if a macrolide was used for treatment; and infection with a new M type. Unfortunately, determining the GAS M type in an acute infection is not available to the clinician. Treatment with intramuscular benzathine penicillin eliminates nonadherence to therapy. Apparent recurrences can represent pharyngitis of another cause in the presence of streptococcal carriage. Chronic GAS carriage is particularly likely if the illnesses are mild and otherwise atypical for GAS pharyngitis. *Undocumented histories of recurrent pharyngitis are an inadequate basis for recommending tonsillectomy.*

Tonsillectomy may lower the incidence of pharyngitis for 1-2 yr among children with frequent episodes of documented pharyngitis (≥7 episodes in the previous year or ≥5 in each of the preceding 2 yr, or ≥3 in each of the previous 3 yr). However, the frequency of pharyngitis (GAS and non-GAS) generally declines over time. By 2 yr posttonsillectomy the incidence of pharyngitis in severely affected children is

similar among those who have tonsillectomy and those who do not. Few children are so severely affected and the limited clinical benefit of tonsillectomy for most must be balanced against the risks of anesthesia and surgery.

Recurrent GAS pharyngitis is rarely, if ever, a sign of an immune disorder. However, recurrent pharyngitis can be part of a recurrent fever or autoinflammatory syndrome such as PFAPA syndrome. Prolonged pharyngitis (>1 wk) can occur in infectious mononucleosis and Lemierre syndrome, but it also suggests the possibility of another disorder such as neutropenia, a recurrent fever syndrome, or an autoimmune disease such as systemic lupus or inflammatory bowel disease. In such instances, pharyngitis would be one of a number of clinical findings that together should suggest the underlying diagnosis.

COMPLICATIONS AND PROGNOSIS

Viral respiratory tract infections can predispose to bacterial middle ear infections and bacterial sinusitis. The complications of GAS pharyngitis include local suppurative complications, such as parapharyngeal abscess, and subsequent nonsuppurative illnesses, such as ARF, APSGN, poststreptococcal reactive arthritis, and possibly PANDAS (pediatric autoimmune neuropsychiatric disorders associated with *S. pyogenes*) or CANS (childhood acute neuropsychiatric symptoms).

PREVENTION

A variety of GAS vaccines are being developed. A recombinant multivalent M-type vaccine uses the terminal portions of various M proteins to take advantage of their immunogenicity. Other vaccines are based on more conserved GAS epitopes in order to avoid the necessity of matching the vaccine with the M types prevalent in a community or target population. None of the investigational GAS vaccines are near licensing for use. Antimicrobial prophylaxis with daily oral penicillin prevents recurrent GAS infections but is recommended only to prevent recurrences of ARF.

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Chapter 382

Retropharyngeal Abscess, Lateral Pharyngeal (Parapharyngeal) Abscess, and Peritonsillar Cellulitis/Abscess

Diane E. Pappas and J. Owen Hendley

The *retropharyngeal* and the *lateral pharyngeal lymph nodes* that drain the mucosal surfaces of the upper airway and digestive tracts are located in the neck within the *retropharyngeal space* (located between the pharynx and the cervical vertebrae and extending down into the superior mediastinum) and the *lateral pharyngeal space* (bounded by the pharynx medially, the carotid sheath posteriorly, and the muscles of the styloid process laterally). The lymph nodes in these deep neck spaces communicate with each other, allowing bacteria from either cellulitis or node abscess to spread to other nodes. Infection of the nodes usually occurs as a result of extension from a localized infection of the oropharynx. A **retropharyngeal abscess** can also result from penetrating trauma to the oropharynx, dental infection, and vertebral osteomyelitis. Once infected, the nodes may progress through 3 stages: *cellulitis, phlegmon,* and *abscess.* Infection in the retropharyngeal and lateral pharyngeal spaces can result in airway compromise or posterior mediastinitis, making timely diagnosis important.

RETROPHARYNGEAL AND LATERAL PHARYNGEAL ABSCESS

Retropharyngeal abscess occurs most commonly in children younger than 3-4 yr of age; as the retropharyngeal nodes involute after 5 yr of age, infection in older children and adults is much less common.

Boys are affected more often than girls and approximately two-thirds of patients have a history of recent ear, nose, or throat infection.

Clinical manifestations of retropharyngeal abscess are nonspecific and include fever, irritability, decreased oral intake, and drooling. Neck stiffness, torticollis, and refusal to move the neck may also be present. The verbal child might complain of sore throat and neck pain. Other signs can include muffled voice, stridor, respiratory distress, or even obstructive sleep apnea. Physical examination can reveal bulging of the posterior pharyngeal wall, although this is present in <50% of infants with retropharyngeal abscess. Cervical lymphadenopathy may also be present. Lateral pharyngeal abscess commonly presents as fever, dysphagia, and a prominent bulge of the lateral pharyngeal wall, sometimes with medial displacement of the tonsil.

The differential diagnosis includes acute epiglottitis and foreign body aspiration. In the young child with limited neck mobility, meningitis must also be considered. Other possibilities include lymphoma, hematoma, and vertebral osteomyelitis.

Incision and drainage and culture of an abscessed node provides the definitive diagnosis, but CT can be useful in identifying the presence of a retropharyngeal, lateral pharyngeal, or parapharyngeal abscess (Figs. 382-1 and 382-2). With CT scans, deep neck infections can be accurately identified and localized, but CT accurately identifies abscess formation in only 63% of patients. Soft-tissue neck films taken during inspiration with the neck extended might show increased width or an air–fluid level in the retropharyngeal space. CT with contrast medium enhancement can reveal central lucency, ring enhancement, or scalloping of the walls of a lymph node. Scalloping of the abscess wall is thought to be a late finding and predicts abscess formation.

Retropharyngeal and lateral pharyngeal infections are most often polymicrobial; the usual pathogens include group A streptococcus (see Chapter 183), oropharyngeal anaerobic bacteria (see Chapter 213), and *Staphylococcus aureus* (see Chapter 181.1). In children younger than age 2 yr, there has been an increase in the incidence of retropharyngeal abscess, particularly with *S. aureus,* including methicillin-resistant strains. Mediastinitis may be identified on CT in some of these patients. Other pathogens can include *Haemophilus influenzae, Klebsiella,* and *Mycobacterium avium-intracellulare.*

Treatment options include intravenous antibiotics with or without surgical drainage. A third-generation cephalosporin combined with ampicillin-sulbactam or clindamycin to provide anaerobic coverage is effective. The increasing prevalence of methicillin-resistant *S. aureus* can influence empiric antibiotic therapy. Studies show that >50% of children with retropharyngeal or lateral pharyngeal abscess as identified by CT can be successfully treated without surgical drainage. Drainage is necessary in the patient with respiratory distress or failure to improve with intravenous antibiotic treatment. The optimal duration of treatment is unknown, but therapy for several days with intravenous antibiotics until the patient has begun to improve followed by a course of oral antibiotic is typically used.

Complications of retropharyngeal or lateral pharyngeal abscess include significant upper airway obstruction, rupture leading to aspiration pneumonia, and extension to the mediastinum. Thrombophlebitis of the internal jugular vein and erosion of the carotid artery sheath can also occur.

An uncommon but characteristic infection of the parapharyngeal space is **Lemierre disease,** in which infection from the oropharynx extends to cause septic thrombophlebitis of the internal jugular vein

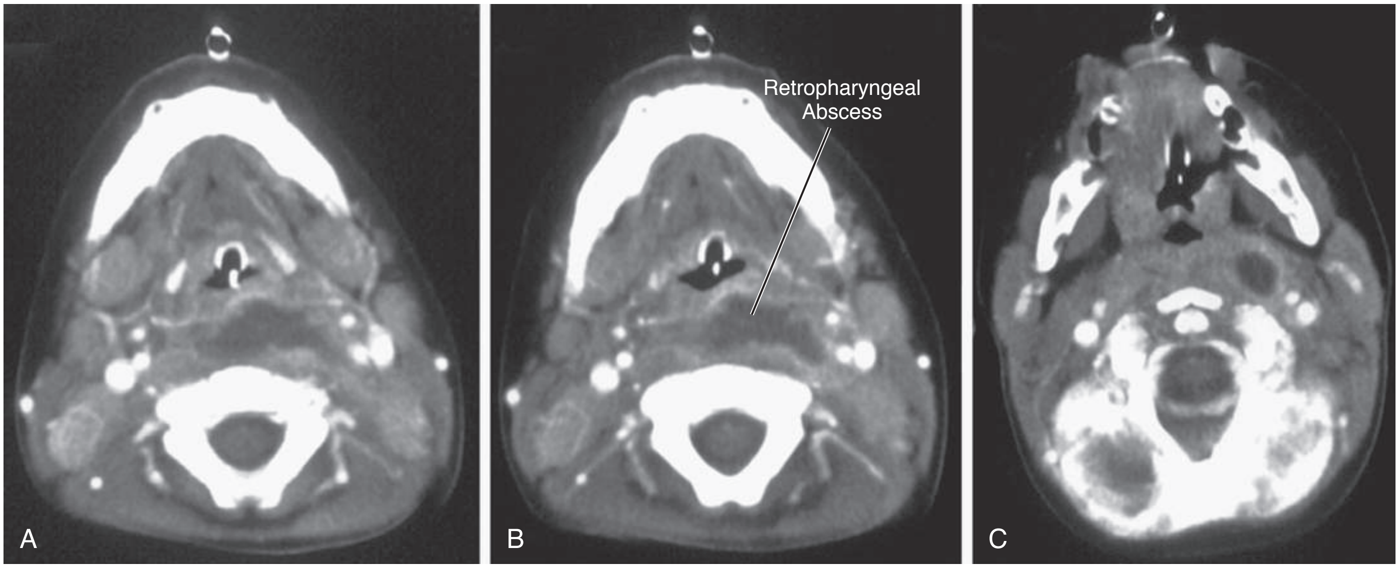

Figure 382-1 CT of retropharyngeal abscess. **A,** CT image at level of epiglottis. **B,** Sequential CT slice exhibiting ring-enhancing lesion. **C,** Further sequential CT slice demonstrating inferior extent of lesion. *(From Philpott CM, Selvadurai D, Banerjee AR: Paediatric retropharyngeal abscess,* J Laryngol Otol *118:925, 2004.)*

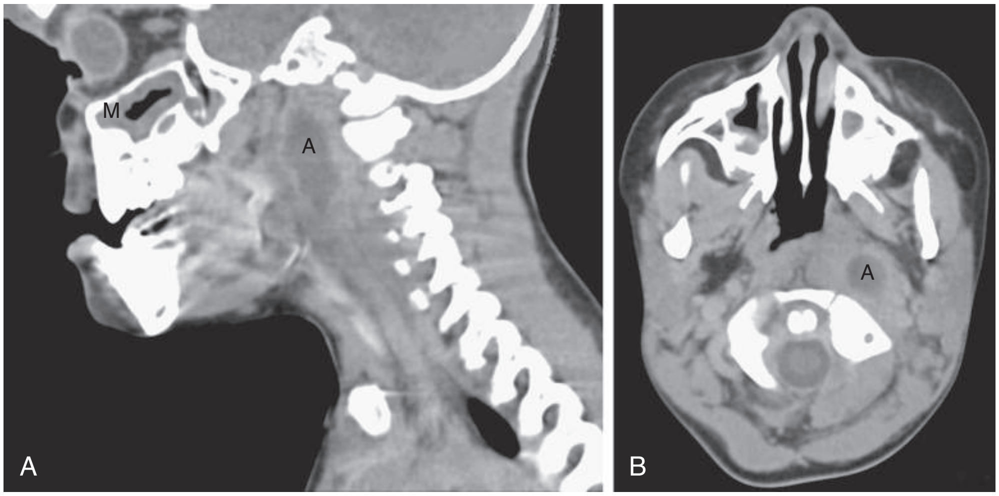

Figure 382-2 CT of parapharyngeal abscess in a 3 yr old child. **A,** Sagittal section demonstrating parapharyngeal abscess *(A)* and mucosal swelling *(M)* in the maxillary sinus. **B,** Coronal section of parapharyngeal abscess *(A).*

and embolic abscesses in the lungs (Fig. 382-3). The causative pathogen is *Fusobacterium necrophorum,* an anaerobic bacterial constituent of the oropharyngeal flora. The typical presentation is that of a previously healthy adolescent or young adult with a history of recent pharyngitis who becomes acutely ill with fever, hypoxia, tachypnea, and respiratory distress. Chest radiography demonstrates multiple cavitary nodules, often bilateral and often accompanied by pleural effusion. Blood culture may be positive. Treatment involves prolonged intravenous antibiotic therapy with penicillin or cefoxitin; surgical drainage of extrapulmonary metastatic abscesses may be necessary (see Chapters 381 and 383).

PERITONSILLAR CELLULITIS AND/OR ABSCESS

Peritonsillar cellulitis and/or abscess, which is relatively common compared to the deep neck infections, is caused by bacterial invasion through the capsule of the tonsil, leading to cellulitis and/or abscess formation in the surrounding tissues. The typical patient with a peritonsillar abscess is an adolescent with a recent history of acute pharyngotonsillitis. Clinical manifestations include sore throat, fever, trismus, and dysphagia. Physical examination reveals an asymmetric tonsillar bulge with displacement of the uvula. An asymmetric tonsillar bulge is diagnostic, but it may be poorly visualized because of trismus. CT is helpful for revealing the abscess. Group A streptococci and mixed oropharyngeal anaerobes are the most common pathogens, with more than 4 bacterial isolates per abscess typically recovered by needle aspiration.

Treatment includes surgical drainage and antibiotic therapy effective against group A streptococci and anaerobes. Surgical drainage may be accomplished through needle aspiration, incision and drainage, or tonsillectomy. Needle aspiration can involve aspiration of the superior, middle, and inferior aspects of the tonsil to locate the abscess. Intraoral ultrasound can be used to diagnose and guide needle aspiration of a peritonsillar abscess. General anesthesia may be required for the uncooperative patient. Approximately 95% of peritonsillar abscesses resolve after needle aspiration and antibiotic therapy. A small percentage of these patients require a repeat needle aspiration. The 5% with infections that fail to resolve after needle aspiration require incision and drainage. Tonsillectomy should be considered if there is failure to improve within 24 hr of antibiotic therapy and needle aspiration,

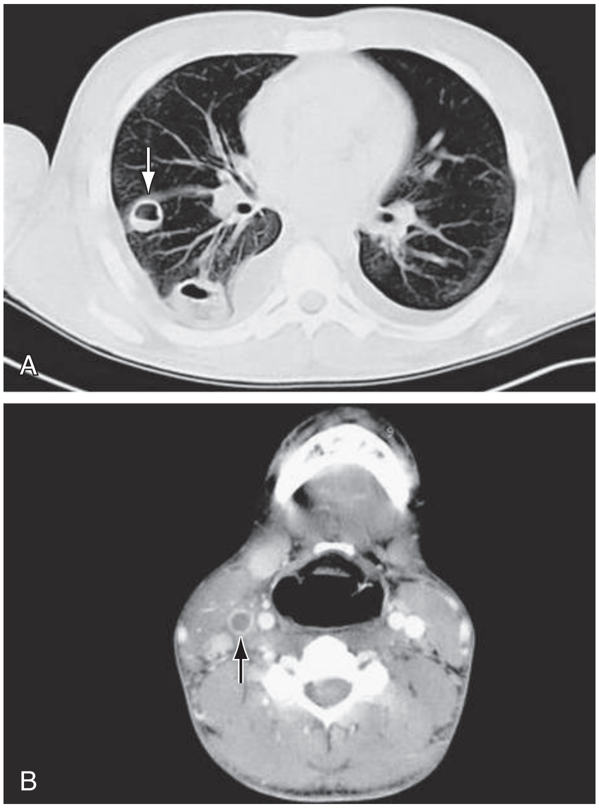

Figure 382-3 CT of Lemierre disease. **A,** CT demonstrating nodular appearance of pulmonary infiltrates *(arrow)*. **B,** CT of neck demonstrating thrombosis of right internal jugular vein *(arrow)*. *(From Plymyer MR, Zoccola DC, Tallarita G: An 18 year old man presenting with sepsis following a recent pharyngeal infection*, Arch Pathol Lab Med *128:813, 2004. Reprinted with permission from Archives of Pathology & Laboratory Medicine. Copyright 2004. College of American Pathologists.)*

history of recurrent peritonsillar abscess or recurrent tonsillitis, or complications from peritonsillar abscess. The feared, albeit rare, complication is rupture of the abscess, with resultant aspiration pneumonitis. There is a 10% recurrence risk for peritonsillar abscess.

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Chapter 383
Tonsils and Adenoids

Ralph F. Wetmore

ANATOMY

The *Waldeyer ring* (the lymphoid tissue surrounding the opening of the oral and nasal cavities into the pharynx) comprises the palatine tonsils, the pharyngeal tonsil or adenoid, lymphoid tissue surrounding the eustachian tube orifice in the lateral walls of the nasopharynx, the lingual tonsil at the base of the tongue, and scattered lymphoid tissue throughout the remainder of the pharynx, particularly behind the posterior pharyngeal pillars and along the posterior pharyngeal wall. The *palatine tonsil* consists of lymphoid tissue located between the palatoglossal fold (anterior tonsillar pillar) and the palatopharyngeal fold (posterior tonsillar pillar) forms. This lymphoid tissue is separated from the surrounding pharyngeal musculature by a thick fibrous capsule. The *adenoid* is a single aggregation of lymphoid tissue that occupies the space between the nasal septum and the posterior pharyngeal wall. A thin fibrous capsule separates it from the underlying structures; the adenoid does not contain the complex crypts that are found in the palatine tonsils but rather more simple crypts. Lymphoid tissue at the base of the tongue forms the *lingual tonsil* that also contains simple tonsillar crypts.

NORMAL FUNCTION

Located at the opening of the pharynx to the external environment, the tonsils and adenoid are well situated to provide primary defense against foreign matter. The immunologic role of the tonsils and adenoids is to induce secretory immunity and to regulate the production of the secretory immunoglobulins. Deep crevices within tonsillar tissue form tonsillar crypts that are lined with squamous epithelium and host a concentration of lymphocytes at their bases. The lymphoid tissue of the Waldeyer ring is most immunologically active between 4 and 10 yr of age, with a decrease after puberty. Adenotonsillar hypertrophy is greatest between ages 3 and 6 yr; in most children tonsils begin to involute after age 8 yr. No major immunologic deficiency has been demonstrated after removal of either or both of the tonsils and adenoid.

PATHOLOGY

Acute Infection

Most episodes of acute pharyngotonsillitis are caused by viruses (see Chapter 381). Group A β-hemolytic streptococcus (GABHS) is the most common cause of bacterial infection in the pharynx (see Chapter 183).

Chronic Infection

The tonsils and adenoids can be chronically infected by multiple microbes, which can include a high incidence of β-lactamase–producing organisms. Both aerobic species, such as streptococci and *Haemophilus influenzae,* and anaerobic species, such as *Peptostreptococcus, Prevotella,* and *Fusobacterium,* contribute. The tonsillar crypts can accumulate desquamated epithelial cells, lymphocytes, bacteria, and other debris, causing cryptic tonsillitis. With time, these cryptic plugs can calcify into tonsillar concretions or tonsillolith. Biofilms appear to play a role in chronic inflammation of the tonsils.

Airway Obstruction

Both the tonsils and adenoids are a major cause of upper airway obstruction in children. Airway obstruction in children is typically manifested in sleep-disordered breathing, including obstructive sleep apnea, obstructive sleep hypopnea, and upper airway resistance syndrome (see Chapter 19). Sleep-disordered breathing secondary to adenotonsillar breathing is a cause of growth failure (see Chapter 41).

Tonsillar Neoplasm

Rapid enlargement of one tonsil is highly suggestive of a tonsillar malignancy, typically lymphoma in children.

CLINICAL MANIFESTATIONS

Acute Infection

Symptoms of GABHS infection include odynophagia, dry throat, malaise, fever and chills, dysphagia, referred otalgia, headache, muscular aches, and enlarged cervical nodes. Signs include dry tongue, erythematous enlarged tonsils, tonsillar or pharyngeal exudate, palatine petechiae, and enlargement and tenderness of the jugulodigastric lymph nodes (Fig. 383-1; see Chapters 183 and 381).

Chronic Infection

Children with chronic or cryptic tonsillitis often present with halitosis, chronic sore throats, foreign-body sensation, or a history of expelling foul-tasting and foul-smelling cheesy lumps. Examination reveals

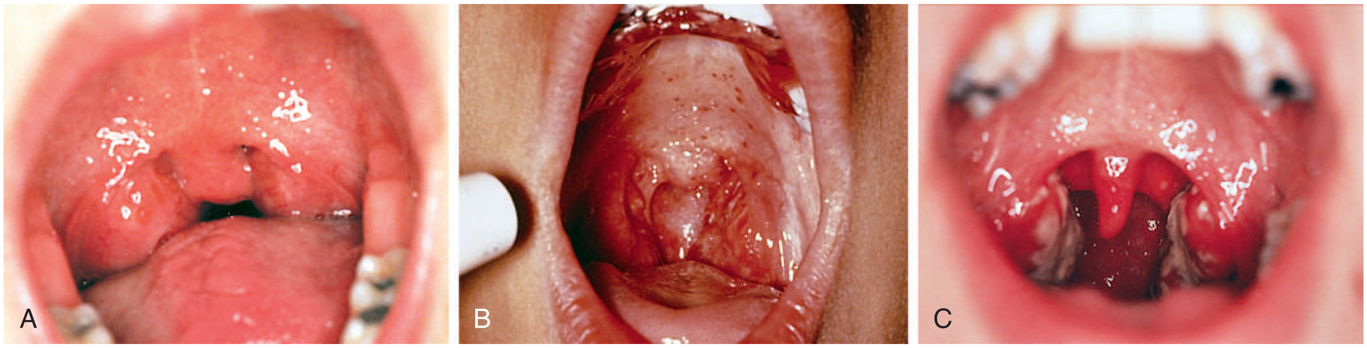

Figure 383-1 Pharyngotonsillitis. This common syndrome has a number of causative pathogens and a wide spectrum of severity. **A,** The diffuse tonsillar and pharyngeal erythema seen here is a nonspecific finding that can be produced by a variety of pathogens. **B,** This intense erythema, seen in association with acute tonsillar enlargement and palatal petechiae, is highly suggestive of group A β-streptococcal infection, though other pathogens can produce these findings. **C,** This picture of exudative tonsillitis is most commonly seen with either group A streptococcal or Epstein-Barr virus infection. *(B courtesy of Michael Sherlock, MD, Lutherville, MD. From Yellon RF, McBride TP, Davis HW: Otolaryngology. In Zitelli BJ, Davis HW, editors:* Atlas of pediatric physical diagnosis, *ed 4, Philadelphia, 2002, Mosby, p. 852.)*

tonsils of a range of sizes which often they contain copious debris within the crypts. The offending organism is not usually GABHS.

Airway Obstruction

The diagnosis of airway obstruction (see Chapter 19) can frequently be made by history and physical examination. Daytime symptoms of airway obstruction, secondary to adenotonsillar hypertrophy, include chronic mouth breathing, nasal obstruction, hyponasal speech, hyposmia, decreased appetite, poor school performance, and, rarely, symptoms of right-sided heart failure. Nighttime symptoms consist of loud snoring, choking, gasping, frank apnea, restless sleep, abnormal sleep positions, somnambulism, night terrors, diaphoresis, enuresis, and sleep talking. Large tonsils are typically seen on examination, although the absolute size might not indicate the degree of obstruction. The size of the adenoid tissue can be demonstrated on a lateral neck radiograph or with flexible endoscopy. Other signs that can contribute to airway obstruction include the presence of a craniofacial syndrome or hypotonia.

Tonsillar Neoplasm

The rapid unilateral enlargement of a tonsil, especially if accompanied by systemic signs of night sweats, fever, weight loss, and lymphadenopathy, is highly suggestive of a tonsillar malignancy. The diagnosis of a tonsillar malignancy should also be entertained if the tonsil appears grossly abnormal. Among 54,901 patients undergoing tonsillectomy, 54 malignancies were identified (0.087% prevalence); all but 6 malignancies had been suspected based on suspicious anatomic features preoperatively.

TREATMENT

Medical Management

The treatment of acute pharyngotonsillitis is discussed in Chapter 381 and antibiotic treatment of GABHS in Chapter 183. Because copathogens such as staphylococci or anaerobes can produce β-lactamase that can inactivate penicillin, the use of cephalosporins or clindamycin may be more efficacious in the treatment of chronic throat infections. Tonsillolith or debris may be expressed manually with either a cotton-tipped applicator or a water jet. Chronically infected tonsillar crypts can be cauterized using silver nitrate.

Tonsillectomy

Tonsillectomy alone is most commonly performed for recurrent or chronic pharyngotonsillitis. Tonsillectomy has been shown to be effective in reducing the number of infections and the symptoms of chronic tonsillitis such as halitosis, persistent or recurrent sore throats, and recurrent cervical adenitis. In resistant cases of cryptic tonsillitis, tonsillectomy may be curative. Rarely in children, tonsillectomy is indicated for biopsy of a unilaterally enlarged tonsil to exclude a neoplasm or to treat recurrent hemorrhage from superficial tonsillar blood vessels. Tonsillectomy has not been shown to offer clinical benefit over conservative treatment in children with mild symptoms.

Table 383-1 Paradise Criteria for Tonsillectomy

CRITERION	DEFINITION
Minimum frequency of sore throat episodes	At least 7 episodes in the previous year, at least 5 episodes in each of the previous 2 yr, or at least 3 episodes in each of the previous 3 yr
Clinical features	Sore throat plus at least 1 of the following features qualifies as a counting episode: Temperature of greater than 38.3°C (100.9°F) Cervical adenopathy (tender lymph nodes or lymph node size >2 cm) Tonsillar exudate Culture positive for group A β-hemolytic streptococcus
Treatment	Antibiotics administered in the conventional dosage for proved or suspected streptococcal episodes
Documentation	Each episode of throat infection and its qualifying features substantiated by contemporaneous notation in a medical record If the episodes are not fully documented, subsequent observance by the physician of 2 episodes of throat infection with patterns of frequency and clinical features consistent with the initial history*

*Allows for tonsillectomy in patients who meet all but the documentation criterion. A 12 mo observation period is usually recommended before consideration of tonsillectomy.

Adapted from Baugh RF, Archer SM, Mitchell RB, et al: American Academy of Otolaryngology–Head and Neck Surgery Foundation. Clinical practice guideline: tonsillectomy in children. Otolaryngol Head Neck Surg *144(1 Suppl):S8, 2011, Table 5.*

There are large variations in surgical rates among children across countries: 144 in 10,000 in Italy; 115 in 10,000 in the Netherlands; 65 in 10,000 in England; and 50 in 10,000 in the United States. Rates are generally higher in boys. With the issuance of practice guidelines, these variations may decrease. The American Academy of Otolaryngology (AAO)–Head and Neck Surgery *Taskforce on Clinical Practice Guidelines: Tonsillectomy in Children* issued evidence-based guidelines in 2011 (Table 383-1). Table 383-2 illustrates the differences and

Table 383-2 Comparison of American, Italian, and Scottish Guidelines for Tonsillectomy in Children and Adolescents

PARAMETER	AAO-HNS GUIDELINES	ITALIAN GUIDELINES	SCOTTISH GUIDELINES
Audience	Multidisciplinary	Multidisciplinary	Multidisciplinary
Target population	Children and adolescents 1-18 yr of age	Children and adults	Children 4-16 yr of age and adults
Scope	Treatment of children who are candidates for tonsillectomy	Appropriateness and safety of tonsillectomy	Management of sore throat and indications for tonsillectomy
Methods	Based on a priori protocol, systematic literature review, American Academy of Pediatrics scale of evidence quality	Systematic literature review, Italian National Program Guidelines scale of evidence quality	Based on a priori protocol, systematic literature review, Scottish Intercollegiate Guidelines Network scale of evidence quality
Recommendations			
Recurrent infection	Tonsillectomy is an option for children with recurrent throat infection that meets the Paradise criteria (see Table 383-1) for frequency, severity, treatment, and documentation of illness	Tonsillectomy is indicated in patients with at least 1 yr of recurrent tonsillitis (5 or more episodes per year) that is disabling and impairs normal activities, but only after an additional 6 mo of watchful waiting to assess the pattern of symptoms using a clinical diary	Tonsillectomy should be considered for recurrent, disabling sore throat caused by acute tonsillitis when the episodes are well documented, are adequately treated, and meet the Paradise criteria (see Table 383-1) for frequency of illness
Pain control	Recommendation to advocate for pain relief (e.g., provide information, prescribe) and educate caregivers about the importance of managing and reassessing pain	Recommendation for acetaminophen before and after surgery	Recommendation for adequate dose of acetaminophen for pain relief in children
Antibiotic use	Recommendation against perioperative antibiotics	Recommendation for short-term perioperative antibiotics*	NA
Steroid use	Recommendation for a single intraoperative dose of dexamethasone	Recommendation for a single intraoperative dose of dexamethasone	Recommendation for a single intraoperative dose of dexamethasone
Sleep-disordered breathing	Recommendation to counsel caregivers about tonsillectomy as a means to improve health in children with sleep-disordered breathing and comorbid conditions	Recommendation for diagnostic testing in children with suspected sleep respiratory disorders	NA
Polysomnography	Recommendation to counsel caregivers about tonsillectomy as a means to improve health in children with abnormal polysomnography	Recommendation for polysomnography when pulse oximetry results are not conclusive in agreement with Brouillette criteria	NA
Surgical technique	NA	Recommendation for "cold" technique	NA
Hemorrhage	Recommendation that the surgeon document primary and secondary hemorrhage after tonsillectomy at least annually	NA	NA
Adjunctive therapy	NA	NA	Recommendation against *Echinacea purpurea* for treatment of sore throat Recommendation for acupuncture in patients at risk of postoperative nausea and vomiting who cannot take antiemetic drugs

*Statement made prior to most recent Cochrane review.

AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery; NA, not applicable.

Adapted with permission from Baugh RF, Archer SM, Mitchell RB, et al: American Academy of Otolaryngology–Head and Neck Surgery Foundation. Clinical practice guideline: tonsillectomy in children. Otolaryngol Head Neck Surg *144(1 Suppl):S23, 2011, Table 9.*

similarities between these guidelines with those of the other major professional groups across the globe.

Adenoidectomy

Adenoidectomy alone may be indicated for the treatment of chronic nasal infection (chronic adenoiditis), chronic sinus infections that have failed medical management, and recurrent bouts of acute otitis media, including those in children with tympanostomy tubes who suffer from recurrent otorrhea. Adenoidectomy may be helpful in children with chronic or recurrent otitis media with effusion. Adenoidectomy alone may be curative in the management of patients with nasal obstruction, chronic mouth breathing, and loud snoring suggesting sleep-disordered breathing. Adenoidectomy may also be indicated for children in whom upper airway obstruction is suspected of causing craniofacial or occlusive developmental abnormalities.

Tonsillectomy and Adenoidectomy

The criteria for both tonsillectomy and adenoidectomy for recurrent infection are the same as those for tonsillectomy alone. The other major indication for performing both procedures together is upper airway obstruction secondary to adenotonsillar hypertrophy that results in sleep-disordered breathing, failure to thrive, craniofacial or occlusive developmental abnormalities, speech abnormalities, or, rarely, cor pulmonale. A high proportion of children with failure to thrive in the context of adenotonsillar hypertrophy resulting in sleep disorder experiences significant growth acceleration after adenotonsillectomy.

COMPLICATIONS

Poststreptococcal Glomerulonephritis and Acute Rheumatic Fever

The 2 major complications of untreated GABHS infection are poststreptococcal glomerulonephritis and acute rheumatic fever (see Chapters 511.1 and 183).

Peritonsillar Infection

Peritonsillar infection can occur as either cellulitis or a frank abscess in the region superior and lateral to the tonsillar capsule (see Chapter 381). These infections usually occur in children with a history of recurrent tonsillar infection and are polymicrobial, including both aerobes and anaerobes. Unilateral throat pain, referred otalgia, drooling, and trismus are presenting symptoms. The affected tonsil is displaced down and medial by swelling of the anterior tonsillar pillar and palate. The diagnosis of an abscess can be confirmed by CT or by needle aspiration, the contents of which should be sent for culture.

Retropharyngeal Space Infection

Infections in the retropharyngeal space develop in the lymph nodes that drain the oropharynx, nose, and nasopharynx (see Chapter 382).

Parapharyngeal Space Infection

Tonsillar infection can extend into the parapharyngeal space, causing symptoms of fever, neck pain and stiffness, and signs of swelling of the lateral pharyngeal wall and neck on the affected side. The diagnosis is confirmed by contrast medium–enhanced CT, and treatment includes intravenous antibiotics and external incision and drainage if an abscess is demonstrated on CT (see Chapter 382). Septic thrombophlebitis of the jugular vein, **Lemierre syndrome,** manifests with fever, toxicity, neck pain and stiffness, and respiratory distress as a result of multiple septic pulmonary emboli and is a complication of a parapharyngeal space or odontogenic infection from *Fusobacterium necrophorum*. Concurrent Epstein-Barr virus mononucleosis (see Chapter 254) can be a predisposing event before the sudden onset of fever, chills, and respiratory distress in an adolescent patient. Treatment includes high-dose intravenous antibiotics (ampicillin-sulbactam, clindamycin, penicillin, or ciprofloxacin) and heparinization.

Recurrent or Chronic Pharyngotonsillitis

See Chapter 381.

CHRONIC AIRWAY OBSTRUCTION

Although rare, children with chronic airway obstruction from enlarged tonsils and adenoids can present with cor pulmonale.

The effects of chronic airway obstruction and mouth breathing on facial growth remain a subject of controversy. Studies of chronic mouth breathing, both in humans and animals, have shown changes in facial development, including prolongation of the total anterior facial height and a tendency toward a retrognathic mandible, the so-called adenoid facies. Adenotonsillectomy can reverse some of these abnormalities. Other studies have disputed these findings.

Tonsillectomy and Adenoidectomy

The risks and potential benefits of surgery must be considered (Table 383-3). Bleeding can occur in the immediate postoperative period or be delayed (consider von Willebrand disease) after separation of the eschar. The Clinical Guidelines for Tonsillectomy include a recommendation for a single intravenous dose of intraoperative dexamethasone (0.5 mg/kg), which decreases postoperative nausea and vomiting and reduces swelling. There is no evidence that use of dexamethasone in postoperative tonsillectomy patients results in an increased risk of postoperative bleeding. Routine use of antibiotics in the postoperative period is ineffective and thus the American Academy of Otolaryngology Clinical Practice Guidelines advise against its use, although this recommendation is not consistent among the major professional organizations who have issued guidelines (see Table 383-2). Codeine is associated with excessive sedation and fatalities and is not recommended.

Swelling of the tongue and soft palate can lead to acute airway obstruction in the 1st few hr after surgery. Children with underlying hypotonia or craniofacial anomalies are at greater risk for suffering this complication. Dehydration from odynophagia is not uncommon in the 1st postoperative week. Rare complications include velopharyngeal insufficiency, nasopharyngeal or oropharyngeal stenosis, and psychologic problems.

Table 383-3 Risks and Potential Benefits of Tonsillectomy or Adenoidectomy or Both

RISKS
Cost*
Risk of anesthetic accidents
Malignant hyperthermia
Cardiac arrhythmia
Vocal cord trauma
Aspiration with resulting bronchopulmonary obstruction or infection
Risk of miscellaneous surgical or postoperative complications
Hemorrhage
Airway obstruction from edema of tongue, palate, or nasopharynx, or retropharyngeal hematoma
Central apnea
Prolonged muscular paralysis
Dehydration
Palatopharyngeal insufficiency
Otitis media
Nasopharyngeal stenosis
Refractory torticollis
Facial edema
Emotional upset
Unknown risks
POTENTIAL BENEFITS
Reduction in frequency of ear, nose, throat illness, and thus in
Discomfort
Inconvenience
School absence
Parental anxiety
Work missed by parents
Costs of physician visits and drugs
Reduction in nasal obstruction with improved
Respiratory function
Comfort
Sleep
Craniofacial growth and development
Appearance
Reduction in hearing impairment
Improved growth and overall well-being
Reduction in long-term parental anxiety

*Cost for tonsillectomy alone and adenoidectomy alone are somewhat lower.
Modified from Bluestone CD, editor: Pediatric otolaryngology, *ed 4, Philadelphia, 2003, WB Saunders, p. 1213.*

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Chapter 384

Chronic or Recurrent Respiratory Symptoms

Anne G. Griffiths and Thomas P. Green

Respiratory tract symptoms, including cough, wheeze, and stridor, occur frequently or persist for long periods in a substantial number of children; other children have persistent or recurring lung infiltrates with or without symptoms. Determining the cause of these chronic findings can be difficult because symptoms can be caused by a close succession of unrelated acute respiratory tract infections or by a single pathophysiologic process. Specific and easily performed diagnostic tests do not exist for many acute and chronic respiratory conditions. Pressure from the affected child's family for a quick remedy because of concern over symptoms related to breathing may complicate diagnostic and therapeutic efforts.

A systematic approach to the diagnosis and treatment of these children consists of assessing whether the symptoms are the manifestation of a minor problem or a life-threatening process; determining the most likely underlying pathogenic mechanism; selecting the simplest effective therapy for the underlying process, which often is only symptomatic therapy; and carefully evaluating the effect of therapy. Failure of this approach to identify the process responsible or to effect improvement signals the need for more extensive and perhaps invasive diagnostic efforts, including bronchoscopy.

JUDGING THE SERIOUSNESS OF CHRONIC RESPIRATORY COMPLAINTS

Clinical manifestations suggesting that a respiratory tract illness may be life-threatening or associated with the potential for chronic disability are listed in Table 384-1. If none of these findings is detected, the chronic respiratory process is more likely to be benign. Active, well-nourished, and appropriately growing infants who present with intermittent noisy breathing but no other physical or laboratory abnormalities require only symptomatic treatment and parental reassurance. Benign-appearing but persistent symptoms are occasionally the harbinger of a serious lower respiratory tract problem. By contrast, occasionally children (e.g., infection-related asthma) have recurrent life-threatening episodes but few or no symptoms in the intervals. Repeated examinations over an extended period, both when the child appears healthy and when the child is symptomatic, may be helpful in sorting out the severity and chronicity of lung disease.

Table 384-1	Indicators of Serious Chronic Lower Respiratory Tract Disease in Children
Persistent fever	
Ongoing limitation of activity	
Failure to grow	
Failure to gain weight appropriately	
Clubbing of the digits	
Persistent tachypnea and labored ventilation	
Shortness of breath and exercise intolerance	
Chronic purulent sputum	
Persistent hyperinflation	
Substantial and sustained hypoxemia	
Refractory infiltrates on chest x-ray	
Persistent pulmonary function abnormalities	
Family history of heritable lung disease	
Cyanosis and hypercarbia	

RECURRENT OR PERSISTENT COUGH

Cough is a reflex response of the lower respiratory tract to stimulation of irritant or cough receptors in the airways' mucosa. The most common cause in children is airway reactivity (asthma). Because cough receptors also reside in the pharynx, paranasal sinuses, stomach, and external auditory canal, the source of a persistent cough may need to be sought beyond the lungs. Specific lower respiratory stimuli include excessive secretions, aspirated foreign material, inhaled dust particles or noxious gases, cold or dry air, and an inflammatory response to infectious agents or allergic processes. Table 384-2 lists some of the conditions responsible for chronic cough.

Table 384-3 presents characteristics of cough that can aid in distinguishing a cough's origin. Additional useful information can include a history of atopic conditions (asthma, eczema, urticaria, allergic rhinitis), a seasonal or environmental variation in frequency or intensity of cough, and a strong family history of atopic conditions, all suggesting an allergic cause; symptoms of malabsorption or family history indicating cystic fibrosis; symptoms related to feeding, suggesting aspiration or gastroesophageal reflux; a choking episode, suggesting foreign-body aspiration; headache or facial edema associated with sinusitis; and a smoking history in older children and adolescents or the presence of a smoker in the house (Table 384-4).

The physical examination can provide much information pertaining to the cause of chronic cough. Posterior pharyngeal drainage combined with a nighttime cough suggests chronic upper airway disease such as sinusitis. An overinflated chest suggests chronic airway obstruction, as

Table 384-2	Differential Diagnosis of Recurrent and Persistent Cough in Children
RECURRENT COUGH	
Reactive airway disease (asthma)	
Drainage from upper airways	
Aspiration	
Frequently recurring respiratory tract infections in immunocompetent or immunodeficient patients	
Symptomatic Chiari malformation	
Idiopathic pulmonary hemosiderosis	
Hypersensitivity (allergic) pneumonitis	
PERSISTENT COUGH	
Hypersensitivity of cough receptors after infection	
Reactive airway disease (asthma)	
Chronic sinusitis	
Chronic rhinitis (allergic or nonallergic)	
Bronchitis or tracheitis caused by infection or smoke exposure	
Bronchiectasis, including cystic fibrosis, primary ciliary dyskinesia, immunodeficiency	
Habit cough	
Foreign-body aspiration	
Recurrent aspiration owing to pharyngeal incompetence, tracheolaryngoesophageal cleft, or tracheoesophageal fistula	
Gastroesophageal reflux, with or without aspiration	
Pertussis	
Extrinsic compression of the tracheobronchial tract (vascular ring, neoplasm, lymph node, lung cyst)	
Tracheomalacia, bronchomalacia	
Endobronchial or endotracheal tumors	
Endobronchial tuberculosis	
Hypersensitivity pneumonitis	
Fungal infections	
Inhaled irritants, including tobacco smoke	
Irritation of external auditory canal	
Angiotensin-converting enzyme inhibitors	

Table 384-3 Characteristics of Cough and Other Clinical Features and Possible Causes

SYMPTOMS AND SIGNS	POSSIBLE UNDERLYING ETIOLOGY*
Auscultatory findings (wheeze, crepitations/crackles, differential breath sounds)	Asthma, bronchitis, congenital lung disease, foreign body aspiration, airway abnormality
Cough characteristics (e.g., cough with choking, cough quality, cough starting from birth)	See text; congenital lung abnormalities
Cardiac abnormalities (including murmurs)	Any cardiac illness
Chest pain	Asthma, functional, pleuritis
Chest wall deformity	Any chronic lung disease
Daily moist or productive cough	Chronic bronchitis, suppurative lung disease
Digital clubbing	Suppurative lung disease, arteriovenous shunt
Dyspnea (exertional or at rest)	Compromised lung function of any chronic lung or cardiac disease
Failure to thrive	Compromised lung function, immunodeficiency, cystic fibrosis
Feeding difficulties (including choking and vomiting)	Compromised lung function, aspiration
Hemoptysis	Bronchitis, foreign body aspiration, suctioning trauma
Immune deficiency	Atypical and typical recurrent respiratory infections
Medications or drugs	Angiotensin-converting enzyme inhibitors, puffers, illicit drug use
Neurodevelopmental abnormality	Aspiration
Recurrent pneumonia	Immunodeficiency, congenital lung problem, airway abnormality
Symptoms of upper respiratory tract infection	Can coexist or be a trigger for an underlying problem

*This is not an exhaustive list; only the more common respiratory diseases are mentioned.

From Chang AB, Landau LI, Van Asperen PP, et al: Cough in children: definitions and clinical evaluation. Thoracic Society of Australia and New Zealand, Med J Aust *184(8):399–403, 2006.*

Table 384-4 Clinical Clues About Cough

CHARACTERISTIC	THINK OF
Staccato, paroxysmal	Pertussis, cystic fibrosis, foreign body, *Chlamydia* spp., *Mycoplasma* spp.
Followed by "whoop"	Pertussis
All day, never during sleep	Habit cough
Barking, brassy	Croup, habit cough, tracheomalacia, tracheitis, epiglottitis
Hoarseness	Laryngeal involvement (croup, recurrent laryngeal nerve involvement)
Abrupt onset	Foreign body, pulmonary embolism
Follows exercise	Reactive airway disease
Accompanies eating, drinking	Aspiration, gastroesophageal reflux, tracheoesophageal fistula
Throat clearing	Postnasal drip, vocal tic
Productive (sputum)	Infection, cystic fibrosis, bronchiectasis
Night cough	Sinusitis, reactive airway disease, gastroesophageal reflux
Seasonal	Allergic rhinitis, reactive airway disease
Immunosuppressed patient	Bacterial pneumonia, *Pneumocystis jiroveci, Mycobacterium tuberculosis, Mycobacterium avium-intracellulare,* cytomegalovirus
Dyspnea	Hypoxia, hypercarbia
Animal exposure	*Chlamydia psittaci* (birds), *Yersinia pestis* (rodents), *Francisella tularensis* (rabbits), Q fever (sheep, cattle), hantavirus (rodents), histoplasmosis (pigeons)
Geographic	Histoplasmosis (Mississippi, Missouri, Ohio River Valley), coccidioidomycosis (Southwest), blastomycosis (North and Midwest)
Workdays with clearing on days off	Occupational exposure

From Kliegman RM, Greenbaum LA, Lyle PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, WB Saunders, p. 19.*

in asthma or cystic fibrosis. An expiratory wheeze, with or without diminished intensity of breath sounds, strongly suggests asthma or asthmatic bronchitis but may also be consistent with a diagnosis of cystic fibrosis, bronchomalacia, vascular ring, aspiration of foreign material, or pulmonary hemosiderosis. Careful auscultation during forced expiration may reveal expiratory wheezes that are otherwise undetectable and that are the only indication of underlying reactive airways. Coarse crackles suggest bronchiectasis, including cystic fibrosis, but can also occur with an acute or subacute exacerbation of asthma. Clubbing of the digits is seen in most patients with bronchiectasis but in only a few other respiratory conditions with chronic cough (see Table 384-2). Tracheal deviation suggests foreign body aspiration or a mediastinal mass.

Allowing sufficient examination time to detect a spontaneous cough is important. If a spontaneous cough does not occur, asking the child to take a maximal breath and forcefully exhale repeatedly usually induces a cough reflex. Most children can cough on request by 4-5 yr of age. Children who cough as often as several times a minute with regularity are likely to have a habit (tic) cough (see Chapter 24). If the cough is loose, every effort should be made to obtain sputum; many older children can comply. It is sometimes possible to pick up small bits of sputum with a throat swab quickly inserted into the lower pharynx while the child coughs with the tongue protruding. Clear mucoid sputum is most often associated with an allergic reaction or asthmatic bronchitis. Cloudy (purulent) sputum suggests a respiratory tract infection but can also reflect increased cellularity (eosinophilia) from an asthmatic process. Very purulent sputum is characteristic of bronchiectasis (see Chapter 401). Malodorous expectorations suggest anaerobic infection of the lungs. In cystic fibrosis (see Chapter 403), the sputum, even when purulent, is rarely foul smelling.

Laboratory tests can help in the evaluation of a chronic cough. Only sputum specimens containing alveolar macrophages should be interpreted as reflecting lower respiratory tract processes. Sputum eosinophilia suggests asthma, asthmatic bronchitis, or hypersensitivity reactions of the lung (see Chapter 391), but a polymorphonuclear cell response suggests infection; if sputum is unavailable, the presence of eosinophilia in nasal secretions also suggests atopic disease. If most of the cells in sputum are macrophages, postinfectious hypersensitivity of cough receptors should be suspected. Sputum macrophages can be stained for hemosiderin content, which is diagnostic of pulmonary hemosiderosis (see Chapter 400), or for lipid content, which in large amounts suggests, but is not specific for, repeated aspiration. Rarely, children may expectorate partial casts of the airway which can be characterized in investigating causes of plastic bronchitis. Children whose coughs persist for more than 6 wk should be tested for cystic fibrosis regardless of their race or ethnicity (see Chapter 403). Sputum culture is helpful in evaluation of cystic fibrosis, but less so for other conditions because throat flora can contaminate the sample.

Hematologic assessment can reveal a microcytic anemia that is the result of pulmonary hemosiderosis (see Chapter 406) or hemoptysis, or eosinophilia that accompanies asthma and other hypersensitivity reactions of the lung. Infiltrates on the chest radiograph suggest cystic fibrosis, bronchiectasis, foreign body, hypersensitivity pneumonitis, or tuberculosis. When asthma-equivalent cough is suggested, a trial of bronchodilator therapy may be diagnostic. If the cough does not respond to initial therapeutic efforts, more-specific diagnostic procedures may be warranted, including an immunologic or allergic evaluation, chest and paranasal sinus imaging, esophagograms, tests for gastroesophageal reflux (see Chapter 323), and special microbiologic studies including rapid viral testing. Evaluation of ciliary morphology, nasal endoscopy, laryngoscopy and bronchoscopy may also be indicated.

Habit cough ("psychogenic cough" or "cough tic") must be considered in any child with a cough that has lasted for weeks or months, that has been refractory to treatment, and that disappears with sleep or with distraction. Typically, the cough is abrupt and loud and has a harsh, honking, or "barking" quality. A disassociation between the intensity of the cough and the child's affect is typically striking. This cough may be absent if the physician listens outside the examination room, but it will reliably appear immediately on direct attention to the child and the symptom. It typically begins with an upper respiratory infection but then lingers. The child misses many days of school because the cough disrupts the classroom. This disorder accounts for many unnecessary medical procedures and courses of medication. It is treatable with assurance that a pathologic lung condition is absent and that the child should resume full activity, including school. This assurance, together with speech therapy techniques that allow the child to reduce musculoskeletal tension in the neck and chest and that increase the child's awareness of the initial sensations that trigger cough, has been very successful. Self-hypnosis is another successful therapy, often effective with 1 session. The designation "habit cough" is preferable to "psychogenic cough" because it carries no stigma and because most of these children do not have significant emotional problems. When the cough disappears, it does not reemerge as another symptom. Nonetheless, other symptoms such as irritable bowel syndrome may be present in the patient or family.

FREQUENTLY RECURRING OR PERSISTENT STRIDOR

Stridor, a harsh, medium-pitched, inspiratory sound associated with obstruction of the laryngeal area or the extrathoracic trachea, is often accompanied by a croupy cough and hoarse voice. Stridor is most commonly observed in children with croup (see Chapter 385); foreign bodies and trauma can also cause acute stridor. A few children, however, acquire recurrent stridor or have persistent stridor from the 1st days or weeks of life (Table 384-5). Most congenital anomalies of large airways that produce stridor become symptomatic soon after birth. Increase of stridor when a child is supine suggests laryngomalacia or tracheomalacia. It is important to note that when evaluating for a specific anatomic cause of abnormal breath sounds, it is not uncommon to identify additional congenital anomalies of the airway. An accompanying history of hoarseness or aphonia suggests involvement of the vocal cords. Associated dysphagia may also suggest a vascular ring. In a child with intermittent stridor that accompanies physical activity and is not responsive to asthma therapies, paradoxical vocal cord dysfunction may be of consideration. Paradoxical vocal cord dysfunction may be highly supported by history and confirmed by laryngoscopy during an exercise challenge test if symptoms are successfully elicited. Speech therapy and behavior modification may be therapeutic.

Table 384-5 Causes of Recurrent or Persistent Stridor in Children
RECURRENT
Allergic (spasmodic) croup
Respiratory infections in a child with otherwise asymptomatic anatomic narrowing of the large airways
Laryngomalacia
PERSISTENT
Laryngeal obstruction
• Laryngomalacia
• Papillomas, other tumors
• Cysts and laryngoceles
• Laryngeal webs
• Bilateral abductor paralysis of the cords
• Foreign body
Tracheobronchial disease
• Tracheomalacia
• Subglottic tracheal webs
• Endobronchial, endotracheal tumors
• Subglottic tracheal stenosis, congenital or acquired
Extrinsic masses
• Mediastinal masses
• Vascular ring
• Lobar emphysema
• Bronchogenic cysts
• Thyroid enlargement
• Esophageal foreign body
Tracheoesophageal fistula
OTHER
Gastroesophageal reflux
Macroglossia, Pierre Robin syndrome
Cri-du-chat syndrome
Paradoxical vocal cord dysfunction
Hypocalcemia
Vocal cord paralysis
Chiari crisis
Severe neonatal episodic laryngospasm caused by *SCN4A* mutation

Physical examination for recurrent or persistent stridor is usually unrewarding, although changes in its severity and intensity due to changes of body position should be assessed. Anteroposterior and lateral radiographs, contrast esophagography, fluoroscopy, CT, and MRI are potentially useful diagnostic tools. In most cases, direct observation by laryngoscopy is necessary for definitive diagnosis. Undistorted views of the larynx are best obtained with fiberoptic laryngoscopy.

RECURRENT OR PERSISTENT WHEEZE

See also Chapter 391.

Parents often complain that their child "wheezes," when, in fact, they are reporting respiratory sounds that are audible without a stethoscope, produce palpable resonance throughout the chest, and occur most

prominently in inspiration. Some of these children have stridor, although many have audible sounds when the supraglottic airway is incompletely cleared of feedings or secretions.

True **wheezing** is a relatively common and particularly troublesome manifestation of obstructive *lower* respiratory tract disease in children. The site of obstruction may be anywhere from the intrathoracic trachea to the small bronchi or large bronchioles, but the sound is generated by turbulence in larger airways that collapse with forced expiration (see Chapter 373). Children younger than 2-3 yr are especially prone to wheezing, because bronchospasm, mucosal edema, and accumulation of excessive secretions have a relatively greater obstructive effect on their smaller airways. In addition, the compliant airways in young children collapse more readily with active expiration. Isolated episodes of acute wheezing, such as can occur with bronchiolitis, are not uncommon, but wheezing that recurs or persists for more than 4 wk suggests other diagnoses (see Table 391-1 in Chapter 391). Most recurrent or persistent wheezing in children is the result of airway reactivity. Nonspecific environmental factors such as cigarette smoke may be important contributors.

Frequently recurring or persistent wheezing starting at or soon after birth suggests a variety of other diagnoses, including congenital structural abnormalities involving the lower respiratory tract or tracheobronchomalacia (see Chapter 386.11). Wheezing that attends cystic fibrosis is most common in the 1st yr of life. Sudden onset of severe wheezing in a previously healthy child should suggest foreign-body aspiration.

Either wheezing or coughing when associated with tachypnea and hypoxemia may be suggestive of **interstitial lung disease** (see Chapter 399.5). However, many patients with interstitial lung disease demonstrate no symptoms other than rapid breathing on initial physical examination. Although chest roentgenograms may be normal in interstitial lung disease, diffuse abnormalities on chest X-ray may support further evaluation in patients suspected to have interstitial lung disease with characteristic findings described on high-resolution CT scan and lung biopsy.

Repeated examination may be required to verify a history of wheezing in a child with episodic symptoms and should be directed toward assessing air movement, ventilatory adequacy, and evidence of chronic lung disease, such as fixed overinflation of the chest, growth failure, and digital clubbing. Patients should be assessed for oropharyngeal dysphagia in cases of suspected recurrent aspiration. Clubbing suggests chronic lung infection and is rarely prominent in uncomplicated asthma. Tracheal deviation from foreign body aspiration should be sought. It is essential to rule out wheezing secondary to congestive heart failure. Allergic rhinitis, urticaria, eczema, or evidence of ichthyosis vulgaris suggests asthma or asthmatic bronchitis. The nose should be examined for polyps, which can exist with allergic conditions or cystic fibrosis.

Sputum eosinophilia and elevated serum immunoglobulin E levels suggest allergic reactions. A forced expiratory volume in 1 sec increase of 15% in response to bronchodilators confirms reactive airways. Specific microbiologic studies, special imaging studies of the airways and cardiovascular structures, diagnostic studies for cystic fibrosis, and bronchoscopy (see Chapter 366) should be considered if the response is unsatisfactory.

RECURRENT AND PERSISTENT LUNG INFILTRATES

Radiographic lung infiltrates resulting from acute pneumonia usually resolve within 1-3 wk, but a substantial number of children, particularly infants, fail to completely clear infiltrates within a 4 wk period. These children may be febrile or afebrile and may display a wide range of respiratory symptoms and signs. Persistent or recurring infiltrates present a diagnostic challenge (Table 384-6).

Symptoms associated with chronic lung infiltrates in the 1st several weeks of life (but not related to neonatal respiratory distress syndrome) suggest infection acquired in utero or during descent through the birth canal. Early appearance of chronic infiltrates can also be associated with cystic fibrosis or congenital anomalies that result in aspiration or

Table 384-6 Diseases Associated with Recurrent, Persistent, or Migrating Lung Infiltrates Beyond the Neonatal Period
Aspiration
Pharyngeal incompetence (e.g., cleft palate)
Laryngotracheoesophageal cleft
Tracheoesophageal fistula
Gastroesophageal reflux
Lipid aspiration
Neurologic dysphagia
Developmental dysphagia
Congenital anomalies
Lung cysts (cystic adenomatoid malformation)
Pulmonary sequestration
Bronchial stenosis or aberrant bronchus
Vascular ring
Congenital heart disease with large left-to-right shunt
Pulmonary lymphangiectasia
Genetic conditions
α_1-Antitrypsin deficiency
Cystic fibrosis
Primary ciliary dyskinesia (Kartagener syndrome)
Sickle cell disease (acute chest syndrome)
Immunodeficiency, phagocytic deficiency
Humoral, cellular, combined immunodeficiency states
Chronic granulomatous disease and related phagocytic defects
Complement deficiency states
Immunologic and autoimmune diseases
Asthma
Allergic bronchopulmonary aspergillosis
Hypersensitivity pneumonitis
Pulmonary hemosiderosis
Collagen-vascular diseases
Infection, congenital
Cytomegalovirus
Rubella
Syphilis
Infection, acquired
Cytomegalovirus
Tuberculosis
HIV
Other viruses
Chlamydia
Mycoplasma, Ureaplasma
Pertussis
Fungal organisms
Pneumocystis jiroveci
Visceral larva migrans
Inadequately treated bacterial infection
Interstitial pneumonitis and fibrosis
Usual interstitial pneumonitis
Lymphoid (AIDS)
Genetic disorders of surfactant synthesis, secretion
Desquamative
Acute (Hamman-Rich)
Alveolar proteinosis
Drug-induced, radiation-induced inflammation and fibrosis
Neoplasms and neoplastic-like conditions
Primary or metastatic pulmonary tumors
Leukemia
Histiocytosis
Eosinophilic pneumonias
Other etiologies
Bronchiectasis
Congenital
Postinfectious
Sarcoidosis

airway obstruction. A history of recurrent infiltrates, wheezing, and cough may reflect asthma, even in the 1st yr of life.

A controversial association has been posed regarding recurrent lung infiltrates in pulmonary hemosiderosis related to cow's milk hypersensitivity or unknown causes appearing in the 1st yr of life. Children with a history of bronchopulmonary dysplasia often have episodes of respiratory distress attended by wheezing and new lung infiltrates. Recurrent pneumonia in a child with frequent otitis media, nasopharyngitis, adenitis, or dermatologic manifestations suggests an immunodeficiency state, complement deficiency, or phagocytic defect (see Chapters 124-127). Primary ciliary dyskinesia is also of consideration in patients with frequent otitis media and suppurative sinopulmonary disease, with or without accompanying heterotaxy or infertility. Pulmonary sequestration may be suspected in patients with recurrent findings on radiograph that occur in the same location, both during illness and when well (see Chapter 395.4). Traction bronchiectasis may also be suggested on radiography with persistent findings in a given region of the film following history of respiratory infection. Particular attention must be directed to the possibility that the infiltrates represent lymphocytic interstitial pneumonitis or opportunistic infection associated with HIV infection (see Chapter 276). A history of paroxysmal coughing in an infant suggests pertussis syndrome or cystic fibrosis. Persistent infiltrates, especially with loss of volume, in a toddler should suggest foreign-body aspiration.

Overinflation and infiltrates suggest cystic fibrosis or chronic asthma. A "silent chest" with infiltrates should arouse suspicion of alveolar proteinosis (see Chapter 405), *Pneumocystis jiroveci* infection (see Chapter 244), genetic disorders of surfactant synthesis and secretion causing interstitial pneumonitis, or tumors. Growth should be carefully assessed to determine whether the lung process has had systemic effects, indicating substantial severity and chronicity as in cystic fibrosis or alveolar proteinosis. Cataracts, retinopathy, or microcephaly suggest in utero infection. Chronic rhinorrhea can be associated with atopic disease, cow's milk intolerance, cystic fibrosis, or congenital syphilis. The absence of tonsils and cervical lymph nodes suggests an immunodeficiency state.

Diagnostic studies should be performed selectively, based on information obtained from history and physical examination and on a thorough understanding of the conditions listed in Table 384-6. Cytologic evaluation of sputum, if available, may be helpful. Chest CT often provides more precise anatomic detail concerning the infiltrate or further characterize a region of anatomic abnormality. Bronchoscopy is indicated for detecting foreign bodies, congenital or acquired anomalies of the tracheobronchial tract, and obstruction by endobronchial or extrinsic masses (see Chapter 394). Bronchoscopy provides access to secretions that can be studied cytologically and microbiologically. Alveolar lavage fluid is diagnostic for alveolar proteinosis and persistent pulmonary hemosiderosis and can suggest aspiration syndromes. If all appropriate studies have been completed and the condition remains undiagnosed, lung biopsy might yield a definitive diagnosis, such as in interstitial lung disease or in fungal disease.

Optimal medical or surgical treatment of chronic lung infiltrates often depends on a specific diagnosis, but chronic conditions may be self-limiting (severe and prolonged viral infections in infants); in these cases, symptomatic therapy can maintain adequate lung function until spontaneous improvement occurs. Helpful measures include inhalation and physical therapy for excessive secretions, antibiotics for bacterial infections, supplementary oxygen for hypoxemia, and maintenance of adequate nutrition. Because the lung of a young child has remarkable recuperative potential, normal lung function may ultimately be achieved with treatment despite the severity of pulmonary insult occurring in infancy or early childhood.

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Chapter 385

Acute Inflammatory Upper Airway Obstruction (Croup, Epiglottitis, Laryngitis, and Bacterial Tracheitis)

Genie E. Roosevelt

Airway resistance is inversely proportional to the 4th power of the radius (see Chapter 373). Because the lumen of an infant's or child's airway is narrow, minor reductions in cross-sectional area as a result of mucosal edema or other inflammatory processes cause an exponential increase in airway resistance and a significant increase in the work of breathing. The larynx is composed of 4 major cartilages (**epiglottic**, **arytenoid**, **thyroid**, and **cricoid cartilages**, ordered from superior to inferior) and the soft tissues that surround them. The cricoid cartilage encircles the airway just below the vocal cords and defines the narrowest portion of the upper airway in children younger than 10 yr of age.

Inflammation involving the vocal cords and structures inferior to the cords is called **laryngitis, laryngotracheitis**, or **laryngotracheobronchitis**, and inflammation of the structures superior to the cords (i.e., arytenoids, aryepiglottic folds ["false cords"], epiglottis) is called **supraglottitis**. The term **croup** refers to a heterogeneous group of mainly acute and infectious processes that are characterized by a bark-like or brassy cough and may be associated with hoarseness, inspiratory stridor, and respiratory distress. **Stridor** is a harsh, high-pitched respiratory sound, which is usually inspiratory but can be biphasic and is produced by turbulent airflow; it is not a diagnosis but a sign of upper airway obstruction (see Chapter 374). Croup typically affects the larynx, trachea, and bronchi. When the involvement of the larynx is sufficient to produce symptoms, they dominate the clinical picture over the tracheal and bronchial signs. A distinction has been made between spasmodic or recurrent croup and laryngotracheobronchitis. Some clinicians believe that spasmodic croup might have an allergic component and improves rapidly without treatment, whereas laryngotracheobronchitis is always associated with a viral infection of the respiratory tract. Others believe that the signs and symptoms are similar enough to consider them within the spectrum of a single disease, in part because studies have documented viral etiologies in both acute and recurrent croup.

385.1 Infectious Upper Airway Obstruction

Genie E. Roosevelt

ETIOLOGY AND EPIDEMIOLOGY

With the exceptions of diphtheria (see Chapter 187), bacterial tracheitis, and epiglottitis, most acute infections of the upper airway are caused by viruses. The parainfluenza viruses (types 1, 2, and 3; see Chapter 259) account for approximately 75% of cases; other viruses

associated with croup include influenza A and B, adenovirus, respiratory syncytial virus, and measles. Influenza A is associated with severe laryngotracheobronchitis. *Mycoplasma pneumoniae* has rarely been isolated from children with croup and causes mild disease (see Chapter 223). Most patients with croup are between the ages of 3 mo and 5 yr, with the peak in the 2nd yr of life. The incidence of croup is higher in boys. It occurs most commonly in the late fall and winter but can occur throughout the year. Recurrences are frequent from 3-6 yr of age and decrease with growth of the airway. Approximately 15% of patients have a strong family history of croup.

In the past, *Haemophilus influenzae* type b was the most commonly identified etiology of acute epiglottitis. Since the widespread use of the *H. influenzae* type b vaccine, invasive disease caused by *H. influenzae* type b in pediatric patients has been reduced by 99% (see Chapter 194). Therefore, other agents, such as *Streptococcus pyogenes, Streptococcus pneumoniae,* nontypeable *H. influenzae*, and *Staphylococcus aureus,* represent a larger portion of pediatric cases of epiglottitis in vaccinated children. In the prevaccine era, the typical patient with epiglottitis caused by *H. influenzae* type b was 2-4 yr of age, although cases were seen in the 1st yr of life and in patients as old as 7 yr of age. Currently, the most common presentation of epiglottitis is an adult with a sore throat, although cases still do occur in underimmunized children; vaccine failures have been reported.

Figure 385-1 Radiograph of an airway of a patient with croup, showing typical subglottic narrowing (steeple sign).

CLINICAL MANIFESTATIONS

Croup (Laryngotracheobronchitis)

Viruses typically cause croup, the most common form of acute upper respiratory obstruction. The term **laryngotracheobronchitis** refers to viral infection of the glottic and subglottic regions. Some clinicians use the term **laryngotracheitis** for the most common and most typical form of croup and reserve the term **laryngotracheobronchitis** for the more severe form that is considered an extension of laryngotracheitis associated with bacterial superinfection that occurs 5-7 days into the clinical course.

Most patients have an upper respiratory tract infection with some combination of rhinorrhea, pharyngitis, mild cough, and low-grade fever for 1-3 days before the signs and symptoms of upper airway obstruction become apparent. The child then develops the characteristic "barking" cough, hoarseness, and inspiratory stridor. The low-grade fever can persist, although temperatures may occasionally reach 39-40°C (102.2-104°F); some children are afebrile. Symptoms are characteristically worse at night and often recur with decreasing intensity for several days and resolve completely within a week. Agitation and crying greatly aggravate the symptoms and signs. The child may prefer to sit up in bed or be held upright. Older children usually are not seriously ill. Other family members might have mild respiratory illnesses with laryngitis. Most young patients with croup progress only as far as stridor and slight dyspnea before they start to recover.

Physical examination can reveal a hoarse voice, coryza, normal to moderately inflamed pharynx, and a slightly increased respiratory rate. Patients vary substantially in their degrees of respiratory distress. Rarely, the upper airway obstruction progresses and is accompanied by an increasing respiratory rate; nasal flaring; suprasternal, infrasternal, and intercostal retractions; and continuous stridor. Croup is a disease of the upper airway, and alveolar gas exchange is usually normal. Hypoxia and low oxygen saturation are seen only when complete airway obstruction is imminent. **The child who is hypoxic, cyanotic, pale, or obtunded needs immediate airway management.** Occasionally, the pattern of severe laryngotracheobronchitis is difficult to differentiate from epiglottitis, despite the usually more acute onset and rapid course of the latter.

Croup is a clinical diagnosis and does not require a radiograph of the neck. Radiographs of the neck can show the typical subglottic narrowing, or steeple sign, of croup on the posteroanterior view (Fig. 385-1). However, the steeple sign may be absent in patients with croup, may be present in patients without croup as a normal variant, and may rarely be present in patients with epiglottitis. The radiographs do not correlate well with disease severity. Radiographs should be considered only after airway stabilization in children who have an atypical presentation or clinical course. Radiographs may be helpful in distinguishing between severe laryngotracheobronchitis and epiglottitis, but airway management should always take priority.

Acute Epiglottitis (Supraglottitis)

This now rare, but still dramatic and potentially lethal condition is characterized by an acute rapidly progressive and potentially fulminating course of high fever, sore throat, dyspnea, and rapidly progressing respiratory obstruction. The degree of respiratory distress at presentation is variable. The initial lack of respiratory distress can deceive the unwary clinician; respiratory distress can also be the first manifestation. Often, the otherwise healthy child suddenly develops a sore throat and fever. Within a matter of hours, the patient appears toxic, swallowing is difficult, and breathing is labored. Drooling is usually present and the neck is hyperextended in an attempt to maintain the airway. The child may assume the tripod position, sitting upright and leaning forward with the chin up and mouth open while bracing on the arms. A brief period of air hunger with restlessness may be followed by rapidly increasing cyanosis and coma. Stridor is a late finding and suggests near-complete airway obstruction. Complete obstruction of the airway and death can ensue unless adequate treatment is provided. The barking cough typical of croup is rare. Usually, no other family members are ill with acute respiratory symptoms.

The diagnosis requires visualization under controlled circumstances of a large, cherry red, swollen epiglottis by laryngoscopy. Occasionally, the other supraglottic structures, especially the aryepiglottic folds, are more involved than the epiglottis itself. In a patient in whom the diagnosis is certain or probable based on clinical grounds, laryngoscopy should be performed expeditiously in a controlled environment such as an operating room or intensive care unit. Anxiety-provoking interventions such as phlebotomy, intravenous line placement, placing the child supine, or direct inspection of the oral cavity should be avoided until the airway is secure. If epiglottitis is thought to be possible but not certain in a patient with acute upper airway obstruction, the patient may undergo lateral radiographs of the upper airway first. Classic radiographs of a child who has epiglottitis show the thumb sign (Fig. 385-2). Proper positioning of the patient for the lateral neck radiograph is crucial in order to avoid some of the pitfalls associated with interpretation of the film. Adequate hyperextension of the head and neck is necessary. In addition, the epiglottis can appear to be round if the lateral neck is taken at an oblique angle. If the concern for epiglottitis still exists after the radiographs, direct visualization should be performed. A physician skilled in airway management and use of

Figure 385-2 Lateral roentgenogram of the upper airway reveals the swollen epiglottis (thumb sign).

intubation equipment should accompany patients with suspected epiglottitis at all times. An older cooperative child might voluntarily open the mouth wide enough for a direct view of the inflamed epiglottis.

Establishing an airway by endotracheal or nasotracheal intubation or, less often, by tracheostomy is indicated in patients with epiglottitis, regardless of the degree of apparent respiratory distress, because as many as 6% of children with epiglottitis without an artificial airway die, compared with <1% of those with an artificial airway. No clinical features have been recognized that predict mortality. Pulmonary edema can be associated with acute airway obstruction. The duration of intubation depends on the clinical course of the patient and the duration of epiglottic swelling, as determined by frequent examination using direct laryngoscopy or flexible fiberoptic laryngoscopy. In general, children with acute epiglottitis are intubated for 2-3 days, because the response to antibiotics is usually rapid. Most patients have concomitant bacteremia; occasionally, other infections are present, such as pneumonia, cervical adenopathy, or otitis media. Meningitis, arthritis, and other invasive infections with *H. influenzae* type b are rarely found in conjunction with epiglottitis.

Acute Infectious Laryngitis

Laryngitis is a common illness. Viruses cause most cases; diphtheria is an exception but is extremely rare in industrialized countries (see Chapter 187). The onset is usually characterized by an upper respiratory tract infection during which sore throat, cough, and hoarseness appear. The illness is generally mild; respiratory distress is unusual except in the young infant. Hoarseness and loss of voice may be out of proportion to systemic signs and symptoms. The physical examination is usually not remarkable except for evidence of pharyngeal inflammation. Inflammatory edema of the vocal cords and subglottic tissue may be demonstrated laryngoscopically. The principal site of obstruction is usually the subglottic area.

Spasmodic Croup

Spasmodic croup occurs most often in children 1-3 yr of age and is clinically similar to acute laryngotracheobronchitis, except that the history of a viral prodrome and fever in the patient and family are often absent. The cause is viral in some cases, but allergic and psychologic factors may be important in others.

Occurring most commonly in the evening or nighttime, spasmodic croup begins with a sudden onset that may be preceded by mild to moderate coryza and hoarseness. The child awakens with a characteristic barking, metallic cough, noisy inspiration, and respiratory distress and appears anxious and frightened. The patient is usually afebrile. The severity of the symptoms generally diminishes within several hr, and the following day, the patient often appears well except for slight hoarseness and cough. Similar, but usually less severe, attacks without extreme respiratory distress can occur for another night or two. Such episodes often recur several times. Spasmodic croup might represent more of an allergic reaction to viral antigens than direct infection, although the pathogenesis is unknown.

DIFFERENTIAL DIAGNOSIS

These 4 syndromes must be differentiated from one another and from a variety of other entities that can present as upper airway obstruction. **Bacterial tracheitis** is the most important differential diagnostic consideration and has a high risk of airway obstruction. Diphtheritic croup is extremely rare in North America, although a major epidemic of diphtheria occurred in countries of the former Soviet Union beginning in 1990 from the lack of routine immunization. Early symptoms of diphtheria include malaise, sore throat, anorexia, and low-grade fever. Within 2-3 days, pharyngeal examination reveals the typical gray-white membrane, which can vary in size from covering a small patch on the tonsils to covering most of the soft palate. The membrane is adherent to the tissue, and forcible attempts to remove it cause bleeding. The course is usually insidious, but respiratory obstruction can occur suddenly. Measles croup almost always coincides with the full manifestations of systemic disease and the course may be fulminant (see Chapter 246).

Sudden onset of respiratory obstruction can be caused by aspiration of a **foreign body** (see Chapter 387). The child is usually 6 mo-3 yr of age. Choking and coughing occur suddenly, usually without prodromal signs of infection, although children with a viral infection can also aspirate a foreign body. A **retropharyngeal** or **peritonsillar abscess** can mimic respiratory obstruction (see Chapter 382). CT scans of the upper airway are helpful in evaluating the possibility of a retropharyngeal abscess. A peritonsillar abscess is a clinical diagnosis. Other possible causes of upper airway obstruction include extrinsic compression of the airway (laryngeal web, vascular ring) and intraluminal obstruction from masses (laryngeal papilloma, subglottic hemangioma); these tend to have chronic or recurrent symptoms.

Upper airway obstruction is occasionally associated with **angioedema** of the subglottic areas as part of anaphylaxis and generalized allergic reactions, edema after endotracheal intubation for general anesthesia or respiratory failure, hypocalcemic tetany, infectious mononucleosis, trauma, and tumors or malformations of the larynx. A croupy cough may be an early sign of asthma. Vocal cord dysfunction can also occur. Epiglottitis, with the characteristic manifestations of drooling or dysphagia and stridor, can also result from the accidental ingestion of very hot liquid.

COMPLICATIONS

Complications occur in approximately 15% of patients with viral croup. The most common is extension of the infectious process to involve other regions of the respiratory tract, such as the middle ear, the terminal bronchioles, or the pulmonary parenchyma. Bacterial tracheitis may be a complication of viral croup rather than a distinct disease. If associated with *S. aureus or S. pyogenes,* toxic shock syndrome can develop. Bacterial tracheitis may have a 2-phased illness, with the 2nd phase after a croup-like illness associated with high fever, toxicity, and airway obstruction. Alternatively, the onset of tracheitis occurs without a 2nd phase and appears as a continuation of the initial croup-like illness but with higher fever and worsening respiratory distress rather than the usual recovery after 2-3 days of viral croup. Pneumonia, cervical lymphadenitis, otitis media, or, rarely, meningitis or septic arthritis can occur in the course of epiglottitis. Pneumomediastinum and pneumothorax are the most common complications of tracheotomy.

TREATMENT

The mainstay of treatment for children with **croup** is airway management and treatment of hypoxia. Treatment of the respiratory distress

should take priority over any testing. Most children with either acute spasmodic croup or infectious croup can be managed safely at home. Despite the observation that cold night air is beneficial, a Cochrane review has found no evidence supporting the use of cool mist in the emergency department for the treatment of croup.

Nebulized racemic epinephrine is an accepted treatment for moderate or severe croup. The mechanism of action is believed to be constriction of the precapillary arterioles through the β-adrenergic receptors, causing fluid resorption from the interstitial space and a decrease in the laryngeal mucosal edema. Traditionally, racemic epinephrine, a 1 : 1 mixture of the D- and L-isomers of epinephrine, has been administered. A dose of 0.25-0.5 mL of 2.25% racemic epinephrine in 3 mL of normal saline can be used as often as every 20 min. Racemic epinephrine was initially chosen over the more active and more readily available L-epinephrine to minimize anticipated cardiovascular side effects such as tachycardia and hypertension. There is evidence that L-epinephrine (5 mL of 1 : 1,000 solution) is equally effective as racemic epinephrine and does not carry the risk of additional adverse effects.

The indications for the administration of nebulized epinephrine include moderate to severe **stridor at rest,** the possible need for intubation, respiratory distress, and hypoxia. The duration of activity of racemic epinephrine is <2 hr. Consequently, observation is mandated. The symptoms of croup might reappear, but racemic epinephrine does not cause rebound worsening of the obstruction. Patients can be safely discharged home after a 2-3 hr period of observation provided they have no stridor at rest; have normal air entry, normal pulse oximetry, and normal level of consciousness; and have received steroids. Nebulized epinephrine should still be used cautiously in patients with tachycardia, heart conditions such as tetralogy of Fallot, or ventricular outlet obstruction because of possible side effects.

The effectiveness of **oral corticosteroids** in viral croup is well established. Corticosteroids decrease the edema in the laryngeal mucosa through their antiinflammatory action. Oral steroids are beneficial, even in mild croup, as measured by reduced hospitalization, shorter duration of hospitalization, and reduced need for subsequent interventions such as epinephrine administration. Most studies that demonstrated the efficacy of oral dexamethasone used a *single dose of 0.6 mg/kg*, a dose as low as 0.15 mg/kg may be just as effective. Intramuscular dexamethasone and nebulized budesonide have an equivalent clinical effect; oral dosing of dexamethasone is as effective as intramuscular administration. A single dose of oral prednisolone is less effective. There are no controlled studies examining the effectiveness of multiple doses of corticosteroids. The only adverse effect in the treatment of croup with corticosteroids is the development of *Candida albicans* laryngotracheitis in a patient who received dexamethasone, 1 mg/kg/24 hr, for 8 days. Corticosteroids should not be administered to children with varicella or tuberculosis (unless the patient is receiving appropriate antituberculosis therapy) because they worsen the clinical course.

Antibiotics are not indicated in croup. Nonprescription cough and cold medications should not be used in children younger than 4 yr of age. A helium-oxygen mixture (heliox) may be considered in the treatment of children with severe croup for whom intubation is being considered although the evidence is inconclusive. Children with croup should be hospitalized for any of the following: progressive stridor, severe stridor at rest, respiratory distress, hypoxia, cyanosis, depressed mental status, poor oral intake, or the need for reliable observation.

Epiglottitis is a medical emergency and warrants immediate treatment with an **artificial airway** placed under controlled conditions, either in an operating room or intensive care unit. All patients should receive oxygen en route unless the mask causes excessive agitation. Racemic epinephrine and corticosteroids are ineffective. Cultures of blood, epiglottic surface, and, in selected cases, cerebrospinal fluid should be collected after the airway is stabilized. *Cefotaxime*, *ceftriaxone,* or *meropenem* should be given parenterally, pending culture and susceptibility reports, because 10-40% of *H. influenzae* type b cases are resistant to ampicillin. After insertion of the artificial airway, the patient should improve immediately, and respiratory distress and cyanosis should disappear. Epiglottitis resolves after a few days of antibiotics, and the patient may be extubated; antibiotics should be continued for at least 10 days. Chemoprophylaxis is not routinely recommended for household, childcare, or nursery contacts of patients with invasive *H. influenzae* type b infections, but careful observation is mandatory, with prompt medical evaluation when exposed children develop a febrile illness. **Indications for rifampin prophylaxis** (20 mg/kg orally once a day for 4 days; maximum dose: 600 mg) for all household members include a child within the home who is younger than 4 yr of age and incompletely immunized, younger than 12 mo of age and has not completed the primary vaccination series, or immunocompromised.

Acute laryngeal swelling on an allergic basis responds to epinephrine (1 : 1,000 dilution in dosage of 0.01 mL/kg to a maximum of 0.5 mL/dose) administered intramuscularly or racemic epinephrine (dose of 0.5 mL of 2.25% racemic epinephrine in 3 mL of normal saline) (see Chapter 149). Corticosteroids are often required (1-2 mg/kg/24 hr of prednisone for 3-5 days). After recovery, the patient and parents should be discharged with a preloaded syringe of epinephrine to be used in emergencies. Reactive mucosal swelling, severe stridor, and respiratory distress unresponsive to mist therapy may follow endotracheal intubation for general anesthesia in children. Racemic epinephrine and corticosteroids are helpful.

Endotracheal/Nasotracheal Intubation and Tracheotomy

With the introduction of routine intubation or, less often, tracheotomy for epiglottitis, the mortality rate for epiglottis has dropped to almost zero. These procedures should always be performed in an operating room or intensive care unit if time permits; prior intubation and general anesthesia greatly facilitate performing a tracheotomy without complications. The use of an endotracheal or nasotracheal tube that is 0.5-1.0 mm smaller than estimated by age or height is recommended to facilitate intubation and reduce long-term sequelae. The choice of procedure should be based on the local expertise and experience with the procedure and postoperative care.

Intubation or tracheotomy is required for most patients with bacterial tracheitis and all young patients with epiglottitis. It is rarely required for patients with laryngotracheobronchitis, spasmodic croup, or laryngitis. Severe forms of laryngotracheobronchitis that require intubation in a high proportion of patients have been reported during severe measles and influenza A virus epidemics. Assessing the need for these procedures requires experience and judgment because they should not be delayed until cyanosis and extreme restlessness have developed (see Chapter 71). As with epiglottitis, an endotracheal or nasotracheal tube that is 0.5-1.0 mm smaller than estimated by age or height is recommended.

The endotracheal tube or tracheostomy must remain in place until edema and spasm have subsided and the patient is able to handle secretions satisfactorily. It should be removed as soon as possible, usually within a few days. Adequate resolution of epiglottic inflammation that has been accurately confirmed by fiberoptic laryngoscopy, permitting much more rapid extubation, often occurs within 24 hr. Racemic epinephrine and dexamethasone (0.5 mg/kg/dose 6-12 hr prior to extubation then every 6 hr for 6 doses with a maximum dose of 10 mg) may be useful in the treatment of upper airway edema seen postintubation.

PROGNOSIS

In general, the length of hospitalization and the mortality rate for cases of acute infectious upper airway obstruction increase as the infection extends to involve a greater portion of the respiratory tract, except in epiglottitis, in which the localized infection itself can prove to be fatal. Most deaths from croup are caused by a laryngeal obstruction or by the complications of tracheotomy. Rarely, fatal out-of-hospital arrests caused by viral laryngotracheobronchitis have been reported, particularly in infants and in patients whose course has been complicated by bacterial tracheitis. Untreated epiglottitis has a mortality rate of 6% in some series, but if the diagnosis is made and appropriate treatment is initiated before the patient is moribund, the prognosis is excellent. The

outcome of acute laryngotracheobronchitis, laryngitis, and spasmodic croup is also excellent.

Bibliography is available at Expert Consult.

385.2 Bacterial Tracheitis

Genie E. Roosevelt

Bacterial tracheitis is an acute bacterial infection of the upper airway that is potentially life threatening. *S. aureus* (see Chapter 181) is the most commonly isolated pathogen with isolated reports of methicillin-resistant *S. aureus*. *S. pneumoniae*, *S. pyogenes*, *Moraxella catarrhalis*, nontypeable *H. influenzae*, and anaerobic organisms have also been implicated. The mean age is between 5 and 7 yr. There is a slight male predominance. Bacterial tracheitis often follows a viral respiratory infection (especially laryngotracheitis), so it may be considered a bacterial complication of a viral disease, rather than a primary bacterial illness. This life-threatening entity is more common than epiglottitis in vaccinated populations.

CLINICAL MANIFESTATIONS

Typically, the child has a brassy cough, apparently as part of a viral laryngotracheobronchitis. High fever and "toxicity" with respiratory distress can occur immediately or after a few days of apparent improvement. The patient can lie flat, does not drool, and does not have the dysphagia associated with epiglottitis. The usual treatment for croup (racemic epinephrine) is ineffective. Intubation or tracheostomy may be necessary, but only 50-60% of patients require intubation for management; younger patients are more likely to need intubation. The major pathologic feature appears to be mucosal swelling at the level of the cricoid cartilage, complicated by copious, thick, purulent secretions, sometimes causing pseudomembranes. Suctioning these secretions, although occasionally affording temporary relief, usually does not sufficiently obviate the need for an artificial airway.

DIAGNOSIS

The diagnosis is based on evidence of bacterial upper airway disease, which includes high fever, purulent airway secretions, and an absence of the classic findings of epiglottitis. X-rays are not needed but can show the classic findings (Fig. 385-3); purulent material is noted below the cords during endotracheal intubation (Fig. 385-4).

TREATMENT

Appropriate antimicrobial therapy, which usually includes antistaphylococcal agents, should be instituted in any patient whose course suggests bacterial tracheitis. Current empiric therapy recommendations for bacterial tracheitis include vancomycin or clindamycin and a third-generation cephalosporin (e.g., cefotaxime or ceftriaxone). When bacterial tracheitis is diagnosed by direct laryngoscopy or is strongly

Figure 385-3 Lateral radiograph of the neck of a patient with bacterial tracheitis, showing pseudomembrane detachment in the trachea. *(From Stroud RH, Friedman NR: An update on inflammatory disorders of the pediatric airway: epiglottitis, croup, and tracheitis, Am J Otolaryngol 22:268–275, 2001. Photo courtesy of the Department of Radiology, University of Texas Medical Branch at Galveston.)*

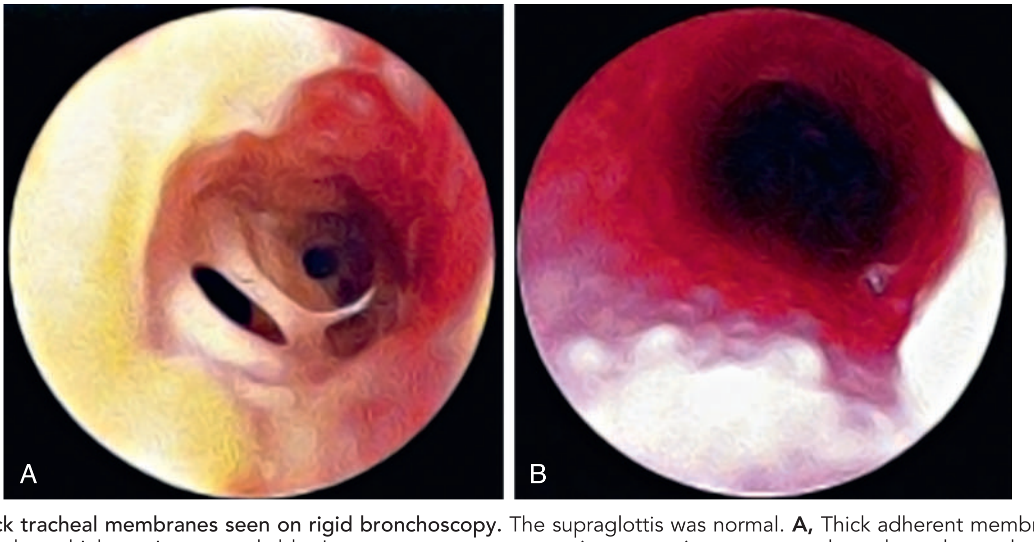

Figure 385-4 Thick tracheal membranes seen on rigid bronchoscopy. The supraglottis was normal. **A,** Thick adherent membranous secretions. **B,** The distal tracheobronchial tree is unremarkable. In contrast to croup, tenacious secretions are seen throughout the trachea, and in contrast to bronchitis, the bronchi are not affected. *(From Salamone FN, Bobbitt DB, Myer CM, et al: Bacterial tracheitis reexamined: is there a less severe manifestation?* Otolaryngol Head Neck Surg *131:871–876, 2004. © 2004 American Academy of Otolaryngology–Head and Neck Surgery Foundation, Inc.)*

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suspected on clinical grounds, an artificial airway should be strongly considered. Supplemental oxygen is usually necessary.

COMPLICATIONS

Chest radiographs often show patchy infiltrates and may show focal densities. Subglottic narrowing and a rough and ragged tracheal air column can often be demonstrated radiographically. If airway management is not optimal, cardiorespiratory arrest can occur. Toxic shock syndrome has been associated with staphylococcal and group A streptococcal tracheitis (see Chapter 181.2).

PROGNOSIS

The prognosis for most patients is excellent. Patients usually become afebrile within 2-3 days of the institution of appropriate antimicrobial therapy, but prolonged hospitalization may be necessary. In recent years, there appears to be a trend toward a less-morbid condition. With a decrease in mucosal edema and purulent secretions, extubation can be accomplished safely, and the patient should be observed carefully while antibiotics and oxygen therapy are continued.

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Chapter 386
Congenital Anomalies of the Larynx, Trachea, and Bronchi

James W. Schroeder Jr. and Lauren D. Holinger

The larynx functions as a breathing passage, a valve to protect the lungs, and the primary organ of communication; symptoms of laryngeal anomalies are those of airway obstruction, difficulty feeding, and abnormalities of phonation (see Chapter 373). Obstructive congenital lesions of the upper airway produce turbulent airflow according to the laws of fluid dynamics. This rapid, turbulent airflow across a narrowed segment of respiratory tract produces distinctive sounds that are diagnostically useful to the clinician. The timing of noisy breathing in relation to the sleep–wake cycle is important. Obstruction of the pharyngeal airway (by enlarged tonsils, adenoids, tongue, or syndromes with midface hypoplasia) typically produces worse obstruction during sleep than during waking. Obstruction that is worse when awake is typically laryngeal, tracheal, or bronchial, and is exacerbated by exertion. The location of the obstruction dictates the respiratory phase, tone and nature of the sound and these qualities direct the differential diagnosis. Intrathoracic lesions typically cause expiratory wheezing and stridor, often masquerading as asthma. The expiratory wheezing contrasts to the inspiratory stridor caused by the extrathoracic lesions of congenital laryngeal anomalies, specifically laryngomalacia and bilateral vocal cord paralysis. Stridor describes the low-pitched inspiratory snoring sound typically produced by nasal or nasopharyngeal obstruction.

With airway obstruction, the severity of the obstructing lesion, the work of breathing, determines the necessity for diagnostic procedures and surgical intervention. Obstructive symptoms vary from mild to severe stridor with episodes of apnea, cyanosis, suprasternal (tracheal tugging) and subcostal retractions, dyspnea, and tachypnea. Congenital anomalies of the trachea and bronchi can create serious respiratory difficulties from the 1st few min of life. Chronic obstruction can cause failure to thrive.

Bibliography is available at Expert Consult.

386.1 Laryngomalacia

James W. Schroeder Jr. and Lauren D. Holinger

CLINICAL MANIFESTATIONS

Laryngomalacia is the most common congenital laryngeal anomaly and the most common cause of stridor in infants and children. Sixty percent of congenital laryngeal anomalies in children with stridor are due to laryngomalacia. Stridor is inspiratory, low-pitched, and exacerbated by any exertion: crying, agitation, or feeding. The stridor is caused, in part, by decreased laryngeal tone leading to supraglottic collapse during inspiration. Symptoms usually appear within the 1st 2 wk of life and increase in severity for up to 6 mo, although gradual improvement can begin at any time. Gastroesophageal reflux disease and neurologic disease influence the severity of the disease and thereby the clinical course.

DIAGNOSIS

The diagnosis is made primarily based on symptoms. The diagnosis is confirmed by outpatient flexible laryngoscopy (Fig. 386-1). When the work of breathing is moderate to severe, airway films and chest radiographs are indicated. Laryngomalacia can contribute to feeding difficulties and dysphagia in some children because of decreased laryngeal sensation and poor suck swallow breath coordination. When the inspiratory stridor sounds wet or is associated with a cough or when there is a history of repeat upper respiratory illness or pneumonia, dysphagia should be considered. When dysphagia is suspected, a contrast swallow study and/or a fiberoptic endoscopic evaluation of swallowing esophagram may be considered. Because 15-60% of infants with laryngomalacia have synchronous airway anomalies, complete bronchoscopy is undertaken for patients with moderate to severe obstruction.

TREATMENT

Expectant observation is suitable for most infants because most symptoms resolve spontaneously as the child and airway grow.

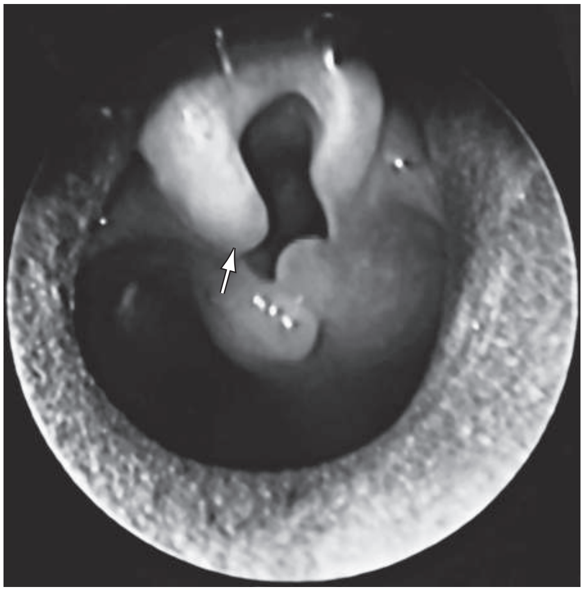

Figure 386-1 Endoscopic example of laryngomalacia. On inspiration, the epiglottic folds collapse into the airway. The lateral tips of the epiglottis are also collapsing inward *(arrow). (From Slovis TL, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby.)*

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Laryngopharyngeal reflux is managed aggressively. In 15-20% of patients symptoms are severe enough to cause progressive respiratory distress, cyanosis, or failure to thrive. In these patients surgical intervention via supraglattoplasty is considered. Supraglattoplasty is 90% successful in relieving upper airway obstruction caused by laryngomalacia.

Bibliography is available at Expert Consult.

386.2 Congenital Subglottic Stenosis

James W. Schroeder Jr. and Lauren D. Holinger

CLINICAL MANIFESTATIONS

Congenital subglottic stenosis is the second most common cause of stridor. The subglottis is the narrowest part of the upper airway in a child. Subglottic stenosis is a narrowing of the subglottic larynx, which is the space extending from the undersurface of the true vocal cords to the inferior margin of the cricoid cartilage. It typically causes respiratory distress and biphasic or primarily inspiratory stridor. It may be congenital or acquired. Symptoms often occur with a respiratory tract infection as the edema and thickened secretions of a common cold narrow an already compromised airway leading to recurrent or persistent croup like symptoms.

Biphasic or primarily inspiratory stridor is the typical presenting symptom for congenital subglottic stenosis. Recurrent or persistent croup usually occurs in these children at 6 mo of age or younger. The edema and thickened secretions of the common cold further narrow an already marginal airway that leads to croup-like symptoms. The stenosis can be caused by an abnormally shaped cricoid cartilage; by a tracheal ring that becomes trapped underneath the cricoid cartilage; or by soft tissue thickening caused by ductal cysts, submucosal gland hyperplasia or fibrosis.

DIAGNOSIS

The diagnosis made by airway radiographs is confirmed by direct laryngoscopy. During diagnostic laryngoscopy the subglottic larynx is visualized directly and sized objectively using endotracheal tubes (Fig. 386-2). The percentage of stenosis is determined by comparing the size of the patients' larynx to a standard of laryngeal dimensions based on age. Stenosis >50% is usually symptomatic and often requires treatment. As with all cases of upper airway obstruction, tracheostomy is avoided when possible. Dilation and endoscopic laser surgery are rarely effective because most congenital stenoses are cartilaginous. Anterior laryngotracheal decompression (cricoid split) or laryngotracheal reconstruction with cartilage grafting is usually effective in avoiding tracheostomy. The differential diagnosis includes other anatomic anomalies as well as a hemangioma or papillomatosis.

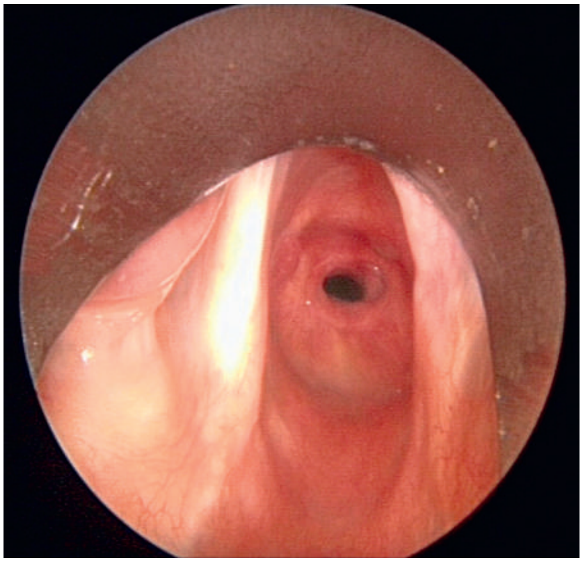

Figure 386-2 Subglottic stenosis. *(Courtesy of Rn Cantab, Wikipedia Commons.)*

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386.3 Vocal Cord Paralysis

James W. Schroeder Jr. and Lauren D. Holinger

CLINICAL MANIFESTATIONS

Vocal cord paralysis is the third most common congenital laryngeal anomaly that produces stridor in infants and children. Congenital central nervous system lesions such as myelomeningocele, Chiari malformation, and hydrocephalus may be associated with bilateral paralysis.

Unilateral vocal cord paralysis is most often iatrogenic as a result of surgical treatment for gastrointestinal (tracheoesophageal fistula) and cardiovascular (patent ductus arteriosis repair) anomalies. Bilateral vocal cord paralysis produces airway obstruction manifested by high-pitched inspiratory stridor: a phonatory sound or inspiratory cry. Unilateral paralysis causes aspiration, coughing, and choking; the cry is weak and breathy, but stridor and other symptoms of airway obstruction are less common.

DIAGNOSIS

The diagnosis of vocal cord paralysis is made by awake flexible laryngoscopy. A thorough investigation for the underlying primary cause is indicated. Because of the association with other congenital lesions, evaluation includes neurology and cardiology consultations as well as diagnostic endoscopy of the larynx, trachea, and bronchi.

TREATMENT

Treatment is based on the severity of the symptoms. Vocal cord paralysis in infants usually resolves spontaneously within 6-12 mo. If it does not resolve within 2-3 yr, it is unlikely to do so. Bilateral paralysis can require temporary tracheotomy. Procedures that widen the posterior glottis to relieve the obstruction include laryngotracheal reconstruction using an endoscopically placed posterior glottis cartilage graft, or arytenoidectomy, or arytenoid lateralization. These procedures are successful in reducing the obstruction. However, they may result in aspiration that may become severe. For unilateral vocal cord paralysis with aspiration, injection laterally to the paralyzed vocal cord moves it medially to reduce aspiration and related complications.

386.4 Congenital Laryngeal Webs and Atresia

James W. Schroeder Jr. and Lauren D. Holinger

Most congenital laryngeal webs are glottic with subglottic extension and associated subglottic stenosis. Chromosomal and cardiovascular anomalies as well as chromosome 22 q 11 deletion are common in patients with congenital laryngeal web. Airway obstruction is not always present and may be related to the subglottic stenosis. Thick webs may be suspected in lateral radiographs of the airway. Diagnosis is made by direct laryngoscopy (Fig. 386-3). Treatment might require only incision or dilation. Webs with associated subglottic stenosis are likely to require cartilage augmentation of the cricoid cartilage (laryngotracheal reconstruction). Laryngeal atresia occurs as a complete glottic web and commonly is associated with tracheal agenesis and tracheoesophageal fistula.

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Figure 386-3 Anterior glottic web. Most of the membranous true vocal cords are involved. *(From Milczuk HA, Smith JD, Evans EC: Congenital laryngeal webs: surgical management and clinical embryology,* Int J Pediatr Otorhinolaryngol *52(1):1–9, 2000.)*

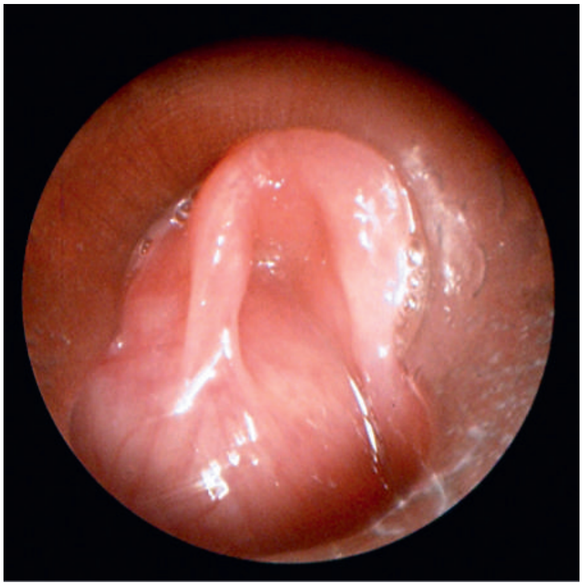

Figure 386-4 Endoscopic photograph of a saccular cyst. *(From Ahmad SM, Soliman AMS: Congenital anomalies of the larynx,* Otolaryngol Clin North Am *40:177–191, 2007, Fig. 3.)*

386.5 Congenital Subglottic Hemangioma

James W. Schroeder Jr. and Lauren D. Holinger

Symptoms of airway obstruction typically occur within the 1st 2 mo. of life. Stridor is biphasic but usually more prominent during inspiration. A barking cough, hoarseness, and symptoms of recurrent or persistent croup are typical. Only 1% of children who have cutaneous hemangiomas will have a subglottic hemangioma. However, 50% of those with a subglottic hemangioma will have a cutaneous hemangioma. A facial hemangioma is not always present, but when it is evident, it is in the beard distribution. Chest and neck radiographs can show the characteristic asymmetric narrowing of the subglottic larynx. Treatment is discussed in Chapter 390.3.

Bibliography is available at Expert Consult.

386.6 Laryngoceles and Saccular Cysts

James W. Schroeder Jr. and Lauren D. Holinger

A laryngocele is an abnormal air-filled dilation of the laryngeal saccule that arises vertically between the false vocal cord, the base of the epiglottic and the inner surface of the thyroid cartilage. It communicates with the laryngeal lumen and, when intermittently filled with air, causes hoarseness and dyspnea. A saccular cyst (congenital cyst of the larynx) is distinguished from the laryngocele in that its lumen is isolated from the interior of the larynx and it contains mucus, not air in infants and children, laryngoceles cause hoarseness and dyspnea that may increase with crying. Saccular cysts may cause respiratory distress and stridor. A saccular cyst may be visible on radiography, but the diagnosis is made by laryngoscopy (Fig. 386-4). Needle aspiration of the cyst confirms the diagnosis but rarely provides a cure. Approaches include endoscopic CO_2 laser excision, endoscopic extended ventriculotomy (marsupialization or unroofing), or, traditionally, external excision.

Bibliography is available at Expert Consult.

386.7 Posterior Laryngeal Cleft and Laryngotracheoesophageal Cleft

James W. Schroeder Jr. and Lauren D. Holinger

The posterior laryngeal cleft is characterized by aspiration and is the result of a deficiency in the midline of the posterior larynx. Posterior laryngeal clefts are categorized into 4 types. Type 1 clefts are mild and the interarytenoid notch only extends down to the level of the true vocal cords; 60% of these will cause no symptoms and will not require surgical repair. In severe cases, the cleft (type 4) extends inferiorly into the cervical or thoracic trachea so there is no separation between the trachea and esophagus, creating a laryngotracheoesophageal cleft. Laryngeal clefts can occur in families and are likely to be associated with tracheal agenesis, tracheoesophageal fistula, and multiple congenital anomalies, as with G syndrome, Opitz-Frias syndrome, and Pallister-Hall syndrome.

Initial symptoms are those of aspiration and recurrent respiratory infections. Esophagogram is undertaken with extreme caution. Confirmation of the diagnosis is made by direct laryngoscopy and bronchoscopy. Treatment is based on the cleft type and the symptoms. Stabilization of the airway is the first priority. Gastroesophageal reflux must be controlled and a careful assessment for other congenital anomalies is undertaken before repair. Several endoscopic and open cervical and transthoracic surgical repairs have been described.

Bibliography is available at Expert Consult.

386.8 Vascular and Cardiac Anomalies

James W. Schroeder Jr. and Lauren D. Holinger

The aberrant innominate artery is the most common cause of secondary tracheomalacia (see Chapter 432). It may be asymptomatic and discovered incidentally or it may cause severe symptoms. Expiratory wheezing and cough occur and, rarely, reflex apnea or "dying spells." Surgical intervention is rarely necessary. Infants are treated expectantly because the problem is self-limited.

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The term *vascular ring* is used to describe vascular anomalies that result from abnormal development of the aortic arch complex. The double aortic arch is the most common complete vascular ring, encircling both the trachea and esophagus, compressing both. With few exceptions, these patients are symptomatic by 3 mo of age. Respiratory symptoms predominate, but dysphagia may be present. The diagnosis is established by barium esophagram that shows a posterior indentation of the esophagus by the vascular ring (see Fig. 432-2 in Chapter 432). CT scan with contrast or MRI with angiography provides the surgeon the information needed.

Other vascular anomalies include the pulmonary artery sling, which also requires surgical correction. The most common open (incomplete) vascular ring is the aberrant right subclavian artery. Although common, it is usually asymptomatic and of academic interest only.

Congenital cardiac defects are likely to compress the left main bronchus or lower trachea. Any condition that produces significant pulmonary hypertension increases the size of the pulmonary arteries, which in turn cause compression of the left main bronchus. Surgical correction of the underlying pathology to relieve pulmonary hypertension relieves the airway compression.

Bibliography is available at Expert Consult.

386.9 Tracheal Stenoses, Webs, and Atresia

James W. Schroeder Jr. and Lauren D. Holinger

Long-segment congenital tracheal stenosis with complete tracheal rings typically occurs within the 1st yr of life, usually after a crisis has been precipitated by an acute respiratory illness. The diagnosis may be suggested by plain radiographs. CT with contrast delineates associated intrathoracic anomalies such as the pulmonary artery sling, which occurs in one third of patients; one fourth have associated cardiac anomalies. Bronchoscopy is the best method to define the degree and extent of the stenosis and the associated abnormal bronchial branching pattern. Treatment of clinically significant stenosis involves tracheal resection of short segment stenosis, slide tracheoplasty for long segment stenosis. Congenital soft-tissue stenoses and thin webs are rare. Dilation may be all that is required.

Bibliography is available at Expert Consult.

386.10 Foregut Cysts

James W. Schroeder Jr. and Lauren D. Holinger

The bronchogenic cyst, intramural esophageal cyst (esophageal duplication), and enteric cyst can all produce symptoms of respiratory obstruction and dysphagia. The diagnosis is suspected when chest radiographs or CT scan delineate the mass, and, in the case of enteric cyst, the associated vertebral anomaly. The treatment of all foregut cysts is surgical excision.

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386.11 Tracheomalacia and Bronchomalacia

See Chapter 389.

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Chapter 387

Foreign Bodies in the Airway

James W. Schroeder Jr. and Lauren D. Holinger

EPIDEMIOLOGY AND ETIOLOGY

Choking is a leading cause of morbidity and mortality among children, especially those younger than age 4 yr, largely because of the developmental vulnerabilities of a young child's airway and the underdeveloped ability to swallow food. Infants and toddlers use their mouths to explore their surroundings. Most victims of foreign-body aspiration are older infants and toddlers (Fig. 387-1). Children, younger than 3 yr of age, account for 73% of cases. Preambulatory toddlers can aspirate objects given to them by older siblings. The most common objects that children choke on are food, coins, balloons, and toys. One-third of aspirated objects are nuts, particularly peanuts. Fragments of raw carrot, apple, dried beans, popcorn, and sunflower or watermelon seeds are also aspirated, as are small toys or toy parts. Hard candy and chewing gum are also commonly involved objects. Adolescents may aspirate objects put in their mouth such as pins, jewelry, or blowgun darts. From 1972-1992, 449 deaths from aspirated nonfood foreign bodies among children were reported by the United States Consumer Product Safety Commission. An infant is developmentally able to suck and swallow and also is equipped with involuntary reflexes (gag, cough, and glottis closure) that help to protect against aspiration during swallowing. Dentition develops at approximately 6 mo with eruption of the incisors. Molars do not erupt until approximately 1.5 yr of age; however, mature mastication takes longer to develop. Despite a strong gag reflex, a young child's airway is more vulnerable to obstruction than an adult's airway in several ways. The smaller diameter is more likely to experience significant blockage by small foreign bodies. Mucous and secretions may form a seal around the foreign body, making it more difficult to dislodge by forced air. In addition, the force of air generated by a cough in an infant or young child is less effective in dislodging an airway obstruction. The American Academy of Pediatrics recommends that children younger than 5 yr old should avoid hard candy, chewing gum and that raw fruits and vegetables be cut into small pieces.

The most serious complication of foreign-body aspiration is complete obstruction of the airway. Globular or round food objects such

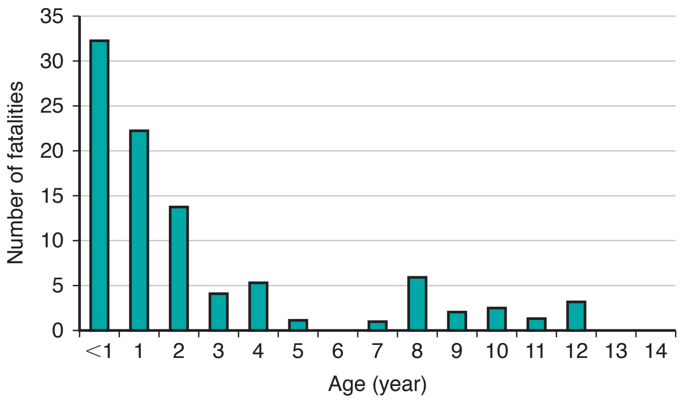

Figure 387-1 Number of fatalities vs victim age, all fatality types. *(From Milkovich SM, Altkorn R, Chen X, et al: Development of the small parts cylinder: lessons learned,* Laryngoscope *118[11]:2082–2086, 2008.)*

as hot dogs, grapes, nuts, and candies are the most frequent offenders. Hot dogs are rarely seen as airway foreign bodies because toddlers who choke on hot dogs asphyxiate at the scene unless treated immediately. Complete airway obstruction is recognized in the conscious child as sudden respiratory distress followed by inability to speak or cough.

CLINICAL MANIFESTATIONS

Three stages of symptoms may result from aspiration of an object into the airway:

1. **Initial event:** Violent paroxysms of coughing, choking, gagging, and possibly airway obstruction occur immediately when the foreign body is aspirated.
2. **Asymptomatic interval:** The foreign body becomes lodged, reflexes fatigue, and the immediate irritating symptoms subside. This stage is most treacherous and accounts for a large percentage of delayed diagnoses and overlooked foreign bodies. It is during this 2nd stage, when the child is first seen, that the possibility of a foreign-body aspiration is minimized, the physician being reassured by the absence of symptoms that no foreign body is present.
3. **Complications:** Obstruction, erosion, or infection develops to direct attention again to the presence of a foreign body. In this 3rd stage, complications include fever, cough, hemoptysis, pneumonia, and atelectasis.

DIAGNOSIS

A positive history must never be ignored. A negative history may be misleading. Choking or coughing episodes accompanied by new onset wheezing are highly suggestive of an airway foreign body. Because nuts are the most common bronchial foreign body, the physician specifically questions the toddler's parents about nuts. If there is any history of eating nuts, bronchoscopy is carried out promptly.

Most airway foreign bodies lodge in a bronchus (right bronchus ~58% of cases); the location is the larynx or trachea in approximately 10% of cases. Occasionally, fragments of a foreign body may produce bilateral involvement or shifting infiltrates if it moves from lobe to lobe. An esophageal foreign body can compress the trachea and be mistaken for an airway foreign body. The patient is asymptomatic and the radiograph is normal in 15-30% of cases. Opaque foreign bodies occur in only 10-25% of cases. CT can help define radiolucent foreign bodies such as fish bones. If there is a high index of suspicion, bronchoscopy should be performed despite negative imaging studies. History is the most important factor in determining the need for bronchoscopy.

TREATMENT

The treatment of choice for airway foreign bodies is prompt endoscopic removal with rigid instruments. Bronchoscopy is deferred only until preoperative studies have been obtained and the patient has been prepared by adequate hydration and emptying of the stomach. Airway foreign bodies are usually removed the same day the diagnosis is first considered.

387.1 Laryngeal Foreign Bodies

James W. Schroeder Jr. and Lauren D. Holinger

Complete obstruction asphyxiates the child unless it is promptly relieved with the Heimlich maneuver (see Chapter 67 and Figs. 67-6 and 67-7). Objects that are partially obstructive are usually flat and thin. They lodge between the vocal cords in the sagittal plane, causing symptoms of croup, hoarseness, cough, stridor, and dyspnea.

387.2 Tracheal Foreign Bodies

James W. Schroeder Jr. and Lauren D. Holinger

Choking and aspiration occurs in 90% of patients with tracheal foreign bodies, stridor in 60%, and wheezing in 50%. Posteroanterior and lateral soft tissue neck radiographs (airway films) are abnormal in 92% of children, whereas chest radiographs are abnormal in only 58%.

387.3 Bronchial Foreign Bodies

James W. Schroeder Jr. and Lauren D. Holinger

Posteroanterior and lateral chest radiographs are standard in the assessment of infants and children suspected of having aspirated a foreign object. The abdomen is included. A good expiratory posteroanterior chest film is most helpful. During expiration the bronchial foreign body obstructs the exit of air from the obstructed lung, producing obstructive emphysema, air trapping, with persistent inflation of the obstructed lung and shift of the mediastinum toward the opposite side (Fig. 387-2). Air trapping is an immediate complication, in contrast to atelectasis, which is a late finding. Lateral decubitus chest films

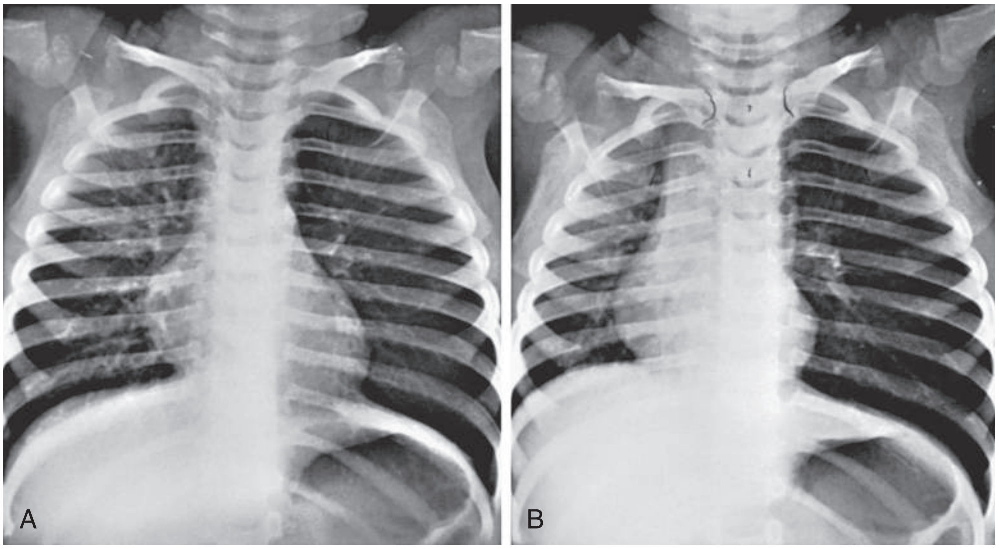

Figure 387-2 **A,** Normal inspiratory chest radiograph in a toddler with a peanut fragment in the left main bronchus. **B,** Expiratory radiograph of the same child showing the classic obstructive emphysema (air trapping) on the involved (left) side. Air leaves the normal right side allowing the lung to deflate. The medium shifts toward the unobstructed side.

or fluoroscopy can provide the same information but are unnecessary. History and physical examination, not radiographs, determine the indication for bronchoscopy.

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Chapter 388

Laryngotracheal Stenosis and Subglottic Stenosis

James W. Schroeder Jr. and Lauren D. Holinger

Laryngotracheal stenosis is the second most common cause of stridor in neonates and is the most common cause of airway obstruction requiring tracheostomy in infants. The glottis (vocal cords) and the upper trachea are also compromised in most laryngeal stenoses, particularly those that develop following endotracheal intubation. Subglottic stenosis is a narrowing of the subglottic larynx, which is the space extending from the undersurface of the true vocal cords to the inferior margin of the cricoid cartilage. Subglottic stenosis is considered to be congenital when there is no other apparent cause such as a history of laryngeal trauma; approximately 90% of cases manifest in the 1st yr of life.

388.1 Congenital Subglottic Stenosis

See Chapter 386.2.

388.2 Acquired Laryngotracheal Stenosis

James W. Schroeder Jr. and Lauren D. Holinger

Ninety percent of acquired stenoses are associated with endotracheal intubation, although with improved ventilatory support, the incidence of this complication is decreasing. Studies published after 1983 reported an incidence of neonatal subglottic stenosis of <4%, and those after 1990 reported an incidence of <0.63%. When the pressure of the endotracheal tube against the mucosa is greater than the capillary pressure, ischemia occurs, followed by necrosis and ulceration. Secondary infection and perichondritis develop with exposure of cartilage. Granulation tissue forms around the ulcerations (Fig. 388-1). These changes and edema throughout the larynx usually resolve spontaneously after extubation. Chronic edema and fibrous stenosis develop in only a small percentage of cases. A number of factors predispose to the development of laryngeal stenosis. Laryngopharyngeal reflux of acid and pepsin from the stomach exacerbates endotracheal tube trauma. More damage is caused in areas left unprotected, owing to loss of mucosa. Congenital subglottic stenosis narrows the larynx which makes the patient more likely to develop acquired subglottic stenosis because significant injury is more likely to occur with use of an endotracheal tube of age-appropriate size. Other risk factors for the development of acquired subglottic stenosis include sepsis and infection, dehydration, malnutrition, chronic inflammatory disorders, and immunosuppression. An oversized endotracheal tube is the most common factor contributing to laryngeal injury. A tube that allows a small air leak at the end of the inspiratory cycle minimizes potential trauma. Other extrinsic factors—traumatic intubation, multiple reintubations, movement of the endotracheal tube, and duration of intubation—can contribute to varying degrees in individual patients.

Figure 388-1 Laryngoscopy in 6 mo old infant 4 hr after extubation showing granulation in subglottic region. *(From Smith MM, Kuhl G, Carvalho PR, Marostica PJ: Flexible fiber-optic laryngoscopy in the first hours after extubation for the evaluation of laryngeal lesions due to intubation in the pediatric intensive care unit.* Int J Pediatr Otorhinolaryngol *71(9):1423–1428, 2007, Fig. 4.)*

CLINICAL MANIFESTATIONS

Symptoms of acquired and congenital stenosis are similar. Spasmodic croup, the sudden onset of severe croup in the early morning hours, is usually caused by laryngopharyngeal reflux with transient laryngospasm and subsequent laryngeal edema. These frightening episodes resolve rapidly, often before the family and child reach the emergency department.

DIAGNOSIS

The diagnosis can be made by posteroanterior and lateral airway radiographs and is confirmed by direct laryngoscopy and bronchoscopy. High-resolution CT imaging is of limited value. This is similar to the work-up associated with congenital subglottic stenosis.

TREATMENT

The severity, location, and type (cartilaginous or soft tissue) of the stenosis determine the treatment. Mild cases can be managed without operative intervention because the airway will improve as the child grows. Moderate soft-tissue stenosis is treated by endoscopy using gentle dilations or CO_2 laser. Severe laryngotracheal stenosis is likely to require laryngotracheal expansion surgery or resection of the narrowed portion of the laryngeal and tracheal airway (partial cricotracheal resection). Every effort is made to avoid tracheotomy using endoscopic techniques or open surgical procedures.

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Chapter 389

Bronchomalacia and Tracheomalacia

Jonathan D. Finder

Tracheomalacia and bronchomalacia refer to chondromalacia of a central airway, leading to insufficient cartilage to maintain airway patency throughout the respiratory cycle. These are common causes of persistent wheezing in infancy. Tracheomalacia and bronchomalacia can be either primary or secondary (Table 389-1). Primary tracheomalacia and bronchomalacia are often seen in premature infants, although most affected patients are born at term. Secondary tracheomalacia and bronchomalacia refers to the situation in which the central airway is compressed by adjacent structure (e.g., vascular ring; see Chapter 432) or deficient in cartilage because of tracheoesophageal fistula (see Chapter 319). Laryngomalacia can accompany primary bronchomalacia or tracheomalacia. Involvement of the entire central airway (laryngotracheobronchomalacia) is also seen.

CLINICAL MANIFESTATIONS

Primary tracheomalacia and bronchomalacia are principally disorders of infants, with a male : female ratio of 2 : 1. The dominant finding, low-pitched monophonic wheezing heard predominantly during expiration, is most prominent over the central airways. Parents often describe persistent respiratory congestion even in the absence of a viral respiratory infection. When the lesion involves only 1 main bronchus (more commonly the left), the wheezing is louder on that side, and there may be unilateral palpable fremitus. In cases of tracheomalacia, the wheeze is loudest over the trachea. Hyperinflation and/or subcostal retractions do not occur unless the patient also has concurrent asthma, viral bronchiolitis, or other causes of peripheral airways obstruction. In the absence of asthma, patients with tracheomalacia and bronchomalacia are not helped by administration of a bronchodilator. Acquired tracheomalacia and bronchomalacia are seen in association with vascular compression (vascular rings, slings, and innominate artery compression). Tracheomalacia is the rule following correction of tracheoesophageal fistula. Other causes of acquired tracheomalacia, which may persist after surgical correction, are cardiomegaly. Bronchomalacia is common following lung transplantation, assumed to be secondary to the loss of bronchial artery supply leading to hypoxia of the cartilage. The importance of the physical exam cannot be understated; 1 study found that pediatric pulmonologists made a correct assessment of malacia based on symptoms, history, and lung function prior to bronchoscopy in 74% of cases.

Table 389-1	Classification of Tracheomalacia
PRIMARY TRACHEOMALACIA Congenital absence of tracheal-supporting cartilages	
SECONDARY TRACHEOMALACIA Esophageal atresia, tracheoesophageal fistula Vascular rings (double aortic arch) Tracheal compression from an aberrant innominate artery Tracheal compression from mediastinal masses Abnormally soft tracheal cartilages associated with connective tissue disorders Prolonged mechanical ventilation, chronic lung disease	

From McNamara VM, Crabbe DC: Tracheomalacia, Paediatr Respir Rev *5:147–154, 2004.*

DIAGNOSIS

Definitive diagnoses of tracheomalacia and bronchomalacia are established by flexible or rigid bronchoscopy (Fig. 389-1). The lesion is difficult to detect on plain radiographs. While fluoroscopy can demonstrate dynamic collapse and avoid the need for invasive diagnostic techniques, it is poorly sensitive. Pulmonary function testing can show a pattern of decreased peak flow and flattening of the flow-volume loop. Other important diagnostic modalities include MRI and CT scanning. MRI with angiography is especially useful when there is a possibility of vascular ring and should be performed when a right aortic arch is seen on plain film radiography.

TREATMENT

Postural drainage can help with clearance of secretions. β-Adrenergic agents should be avoided in the absence of asthma, because they can exacerbate loss of airway patency due to decreased airway tone. Nebulized ipratropium bromide may be useful. Endobronchial stents have been used in severely affected patients but have a high incidence of complications, ranging from airway obstruction due to granulation tissue to erosion into adjacent vascular structures. Continuous positive airway pressure via tracheostomy may be indicated for severe cases. Surgical approach (aortopexy and bronchopexy) is rarely required and only for patients who have life-threatening apnea, cyanosis, and bradycardia (“cyanotic spells”) from airway obstruction, and/or who demonstrated vascular compression.

PROGNOSIS

Primary bronchomalacia and tracheomalacia have excellent prognoses, because airflow improves as the child and the airways grow. Patients with primary airway malacia usually take longer to recover from common respiratory infections. Wheezing at rest usually resolves

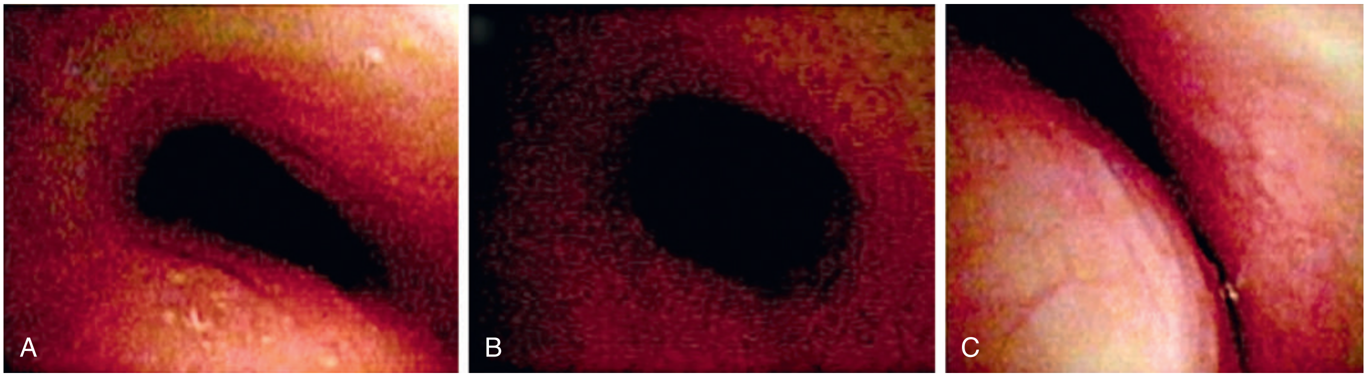

Figure 389-1 Images of tracheomalacia taken 10 mm from site. **A,** Saber-shaped or triangular appearance. **B,** Circumferential appearance. **C,** Crescent (lunate) appearance. *(From Masters IB, Zimmerman PV, Pandeya N, et al: Quantified tracheobronchomalacia disorders and their clinical profiles in children,* Chest *133:461–467, 2008.)*

by age 3 yr. Prolonged bacterial bronchitis has been reported as a complication of bronchomalacia. Prognosis in secondary and acquired forms varies with cause. Patients with concurrent asthma need considerable supportive treatment and careful monitoring of respiratory status.

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Chapter 390
Neoplasms of the Larynx, Trachea, and Bronchi

390.1 Vocal Nodules

James W. Schroeder Jr. and Lauren D. Holinger

Vocal nodules, which are not true neoplasms, are the most common cause of chronic hoarseness in children. Chronic vocal abuse or misuse produces nodules at the junction of the anterior and middle thirds of the phonating edge of the vocal cords. These symmetric, bilateral swellings interfere with voice production and cause children to strain the voice. Vocal nodules can occur in infants.

When vocal abuse is the main factor, the voice is worse in the evenings. Voice therapy may be effective in the cooperative child, but for most toddlers and young children, behavioral therapy is necessary. Nodules usually resolve by early teenage years as the child matures and vocal abuse is moderated. Surgical excision is rarely indicated but may be necessary if the child is unable to communicate adequately, becomes aphonic, or requires tension and straining to make any utterance whatsoever.

When laryngopharyngeal reflux is the main factor, hoarseness is worse in the morning; laryngopharyngeal reflux commonly exacerbates vocal abuse, adding to swelling of the vocal cords. An antireflux regimen is indicated (see Chapter 323.1).

390.2 Recurrent Respiratory Papillomatosis

James W. Schroeder Jr. and Lauren D. Holinger

Papillomas are the most common respiratory tract neoplasms in children, occurring in 4.3 in 100,000. They are simply warts—benign tumors—caused by the human papillomavirus (HPV) (see Chapter 266); the same pathology is found in condylomata acuminata (vaginal warts). HPV types 6 and 11 are most commonly associated with laryngeal disease. Although it is a benign disease that usually involves the larynx, recurrent respiratory papillomatosis (RRP) has a predictable clinical course, tends to recur and spread throughout the aerodigestive tract and can undergo malignant conversion. Fifty percent of recurrent RRP cases occur in children younger than age 5 yr, but the diagnosis may be made at any age; 67% of children with RRP are born to mothers who had condylomata during pregnancy or parturition. The mode of HPV transmission is still not clear. The risk for transmission is approximately 1 in 500 vaginal births in mothers with active condylomata. Neonates have been reported to have RRP, suggesting intrauterine transmission of HPV.

CLINICAL MANIFESTATIONS

These benign squamous lesions can produce chronic hoarseness in the infant. Most occur in the larynx, specifically on the vocal cords, but in 31% these lesions occur in other areas of the respiratory tract: nose, pharynx (especially the uvula and posterior soft palate), trachea, bronchi, and lungs. As growth of the lesions on the vocal cords progresses, hoarseness increases and communication becomes difficult. Respiratory distress develops. Surgical excision is a quality of life issue that warrants removal to improve the voice. Intervention becomes a medical necessity when airway obstruction progresses (Fig. 390-1). Symptoms often occur first during sleep with symptoms typical of obstructive sleep apnea. Progressive respiratory distress during sleep, exertion, daily activities, and finally at rest indicates the need for surgical intervention.

Figure 390-1 Laryngoscopic view of respiratory papillomas causing near complete obstruction at glottic level. *(From Derkay CS, Wiatrak B: Recurrent respiratory papillomatosis: a review,* Laryngoscope *118: 1236–1245, 2008.)*

TREATMENT

The treatment of RRP is endoscopic surgical removal. Most surgeons in North America prefer the microdébrider. Laryngopharyngeal reflux can require treatment when reflux laryngitis is a factor. Although surgical management remains the mainstay therapy, some form of adjunct therapy may be needed in up to 20% of cases. The most widely accepted indications for adjunct therapy are a need for more than 4 surgical procedures per year, rapid regrowth of papillomata with airway compromise, or distal multisite spread of disease. Adjunct therapies include antiviral modalities (interferon, ribavirin, acyclovir, cidofovir), photodynamic therapy, dietary supplement (indole-3-carbinol), nonsteroidal antiinflammatory drug (Celebrex), retinoids, and mumps vaccination.

Bibliography is available at Expert Consult.

390.3 Congenital Subglottic Hemangioma

James W. Schroeder Jr. and Lauren D. Holinger

CLINICAL MANIFESTATIONS

Typically, congenital subglottic hemangiomas are symptomatic within the 1st 2 mo of life, almost all occurring before 6 mo of age. Stridor is biphasic but usually more prominent during inspiration. The infant may be hoarse, have a barking cough, and present with croup. Fifty percent of congenital subglottic hemangiomas are associated with facial lesions. Radiographs classically delineate an asymmetric subglottic narrowing. The diagnosis is made by direct laryngoscopy.

TREATMENT

The treatment of hemangiomas often requires input from a multispecialty vascular anomalies team. Medical management includes systemic steroids. Prednisone 2-4 mg/kg/day is given orally for 4-6 wk, less if the lesions stabilize sooner. The dosage is then tapered. If there is no response, the drug is discontinued. Propranolol 2-3 mg/kg/day is

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emerging as a first-line treatment for hemangiomas with the potential to impair function (airway) or cause disfigurement if there are no cardiac or neurovascular contraindications. Although the exact mechanism of action of propranolol is unknown, it has been shown to stop progression and induce involution of hemangiomas in multiple studies. Because side effects include hypotension, bradycardia, bronchospasm, and hypoglycemia, children treated with propranolol need to be monitored closely.

Although tracheostomy establishes a safe airway, every effort should be made to find an alternative. Corticosteroids can also be injected directly into the lesion. Endoscopic excision with the CO_2 laser is effective. Combining several modalities increases the possibility of avoiding tracheotomy. External surgical excision is suitable for some lesions.

Bibliography is available at Expert Consult.

390.4 Vascular Anomalies

James W. Schroeder Jr. and Lauren D. Holinger

Vascular malformations are not true neoplastic lesions. They have a normal rate of endothelial turnover and various channel abnormalities. They are categorized by their predominant type (capillary, venous, arterial, lymphatic, or a combination thereof). Slow-flow malformations have capillary, lymphatic, or venous components. In the past, these were incorrectly called capillary hemangiomas, cystic hygromas or lymphangiomas, and cavernous hemangiomas, respectively.

Lymphatic malformations (cystic hygromas) rarely occur in the larynx. When they do, they are invariably an extension of disease from elsewhere in the head and neck. Airway obstruction can necessitate tracheostomy. The lesion can be debulked with the CO_2 laser.

Bibliography is available at Expert Consult.

390.5 Other Laryngeal Neoplasms

James W. Schroeder Jr. and Lauren D. Holinger

Neurofibromatosis (see Chapter 596.1) rarely involves the larynx. When children are affected, limited local resection is undertaken to maintain an airway and optimize the voice. Complete surgical extirpation is virtually impossible without debilitating resection of vital laryngeal structures. Most surgeons select the option of less-aggressive symptomatic surgery because of the poorly circumscribed and infiltrative nature of these fibromas. **Rhabdomyosarcoma** (see Chapter 500) and other malignant tumors of the larynx are rare. Symptoms of hoarseness and progressive airway obstruction prompt initial evaluation by flexible laryngoscopy in the office.

390.6 Tracheal Neoplasms

James W. Schroeder Jr. and Lauren D. Holinger

Tracheal tumors include malignant and benign neoplasms. The 2 most common benign tumors are inflammatory pseudotumor and hamartoma. The **inflammatory pseudotumor** is probably a reaction to a previous bronchial infection or traumatic insult. Growth is slow and the tumor may be locally invasive. Hamartomas are tumors of primary tissue elements that are abnormal in proportion and arrangement.

Tracheal neoplasms manifest with stridor, wheezing, cough, or pneumonia and are rarely diagnosed until 75% of the lumen has been obstructed (Fig. 390-2). Symptoms mimic asthma and are often misdiagnosed as such. Chest radiographs or airway films can identify the obstruction. Pulmonary function studies demonstrate an abnormal flow-volume loop. A mild response to bronchodilator therapy may be misleading. Rational treatment is based upon the histopathology.

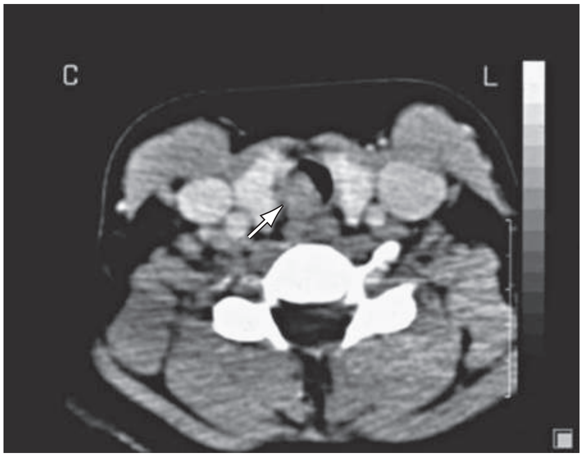

Figure 390-2 A CT scan of the trachea with a circumscribed intraluminal tracheal mass *(arrow)* in the tracheal wall. *(From Venizelos I, Papathomas T, Anagnostou E, et al: Pediatric inflammatory myofibroblastic tumor of the trachea: a case report and review of the literature,* Pediatr Pulmonol *43:831–835, 2008.)*

390.7 Bronchial Tumors

James W. Schroeder Jr. and Lauren D. Holinger

Bronchial tumors are rare. Two-thirds are malignant. Bronchial "adenomas" are the most common, representing 30% of all lung tumors. Bronchogenic carcinoma is the second most common and occurs in approximately 20% of cases. Bronchial carcinoid also occurs. The diagnosis is confirmed at bronchoscopy and biopsy; treatment depends on the histopathology.

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Chapter 391 Wheezing, Bronchiolitis, and Bronchitis

391.1 Wheezing in Infants: Bronchiolitis

Bria M. Coates, Lauren E. Camarda, and Denise M. Goodman

DEFINITIONS AND GENERAL PATHOPHYSIOLOGY

Wheezing, the production of a musical and continuous sound that originates from oscillations in narrowed airways, is heard mostly on expiration as a result of critical airway obstruction. **Monophonic** wheezing refers to a single-pitch sound that is produced in the larger airways during expiration, as in distal tracheomalacia or bronchomalacia. Wheezing is **polyphonic** when there is widespread narrowing of the airways, causing various pitches as air moves through different levels of obstruction to flow, as seen in asthma. When obstruction occurs in the extrathoracic airways during inspiration, the noise is referred to as **stridor.**

Infants are more likely to wheeze than older children and adults as a result of a differing set of lung mechanics. The obstruction to flow is affected by the airway caliber and compliance of the infant lung. Resistance to airflow through a tube is inversely related to the radius of the tube to the 4th power. In children younger than 5 yr old, small-caliber

peripheral airways can contribute up to 50% of the total airway resistance. Marginal additional narrowing can cause further flow limitation and a subsequent wheeze.

With the very compliant newborn chest wall, the inward pressure produced in expiration subjects the intrathoracic airways to collapse. Differences in tracheal cartilage composition and airway smooth muscle tone increase the collapsibility of the infant airways in comparison to older children. These mechanisms combine to make the infant more susceptible to airway obstruction, increased resistance, and subsequent wheezing. Many of these conditions are outgrown in the 1st yr of life.

Immunologic and molecular influences can contribute to the infant's propensity to wheeze. In comparison to older children and adults, infants tend to have higher levels of lymphocytes and neutrophils, rather than mast cells and eosinophils, in bronchoalveolar lavage fluid. The childhood wheezing phenotype has been linked to many early exposures including fetal nutrition, maternal smoking, prenatal and birth maternal complications, prenatal and neonatal exposure to antibiotics, exposure to high levels of environmental allergens, and high infant adiposity. Infections during infancy have been cited as risk factors for later wheezing, including respiratory syncytial virus (RSV; see Chapter 260), rhinovirus (see Chapter 263), cytomegalovirus (see Chapter 255), human metapneumovirus (see Chapter 261), bocavirus, adenovirus, and *Chlamydia pneumoniae*.

A variety of inflammatory mediators have also been implicated in the wheezing infant such as histamine, cytokines, leukotrienes, and interleukins. Taken together, these fetal and/or early postnatal exposures may cause a "programming" of the lung that ultimately affects structure and function.

ETIOLOGY

Although wheezing in infants most frequently results from inflammation (generally bronchiolitis), there are many causes of wheezing (Table 391-1).

Acute Bronchiolitis and Inflammation of the Airway

Infection can cause obstruction to flow by internal narrowing of the airways.

Acute bronchiolitis is predominantly a viral disease. RSV is responsible for more than 50% of cases. Other agents include parainfluenza, adenovirus, rhinovirus, and *Mycoplasma*. Emerging pathogens include human metapneumovirus and human bocavirus, which may be a primary cause of viral respiratory infection or occur as a coinfection with RSV. Although bacterial pneumonia is sometimes confused clinically with bronchiolitis, there is no evidence of a bacterial cause for bronchiolitis and bronchiolitis is rarely followed by bacterial superinfection. Concurrent infection with viral bronchiolitis and pertussis has been described.

Approximately 100,000-126,000 children younger than 1 yr old are hospitalized annually in the United States because of RSV infection. The increasing rates of bronchiolitis that were seen from 1980-1996 (thought to reflect increased attendance of infants in daycare centers, changes in criteria for hospital admission, and/or improved survival of premature infants and others at risk for severe RSV-associated disease), have not continued. In fact, rates have stayed stable in subsequent years despite introduction and routine use of RSV immunoprophylaxis in high-risk populations.

Bronchiolitis is more common in boys, in those who have not been breastfed, and in those who live in crowded conditions. Risk is higher for infants with young mothers or mothers who smoked during pregnancy. Older family members are a common source of infection; they might only experience minor upper respiratory symptoms (colds). The clinical manifestations of lower respiratory tract illness seen in young infants may be minimal in older patients, in whom bronchiolar edema is better tolerated.

Not all infected infants develop lower respiratory tract illness. Host anatomic and immunologic factors play a significant role in the severity of the clinical syndrome, as does the nature of the viral pathogen.

Table 391-1	Differential Diagnosis of Wheezing in Infancy
INFECTION	
Viral	
Respiratory syncytial virus	
Human metapneumovirus	
Parainfluenza	
Adenovirus	
Influenza	
Rhinovirus	
Bocavirus	
Coronavirus	
Enterovirus	
Other	
Chlamydia trachomatis	
Tuberculosis	
Histoplasmosis	
Papillomatosis	
ASTHMA	
Transient wheezer (resolved by 6 yr of age)	
• Initial risk factor is primarily diminished lung size	
Persistent wheezers (persists beyond 6 yr of age)	
• Initial risk factors include parental asthma history, atopic dermatitis, allergen sensitization, peripheral eosinophilia (>4%) and wheezing unrelated to colds in the 1st yr of life	
• At increased risk of developing clinical asthma	
Late-onset wheezer (symptoms begin after age 3 yr and persist)	
ANATOMIC ABNORMALITIES	
Central Airway Abnormalities	
Malacia of the larynx, trachea, and/or bronchi	
Laryngeal or tracheal web	
Tracheoesophageal fistula (specifically H-type fistula)	
Laryngeal cleft (resulting in aspiration)	
Extrinsic Airway Anomalies Resulting in Airway Compression	
Vascular ring or sling	
Mediastinal lymphadenopathy from infection or tumor	
Mediastinal mass or tumor	
Esophageal foreign body	
Intrinsic Airway Anomalies	
Airway hemangioma, other tumor	
Cystic adenomatoid malformation	
Bronchial or lung cyst	
Congenital lobar emphysema	
Aberrant tracheal bronchus	
Sequestration	
Congenital heart disease with left-to-right shunt (increased pulmonary edema)	
Foreign body	
Immunodeficiency States	
Immunoglobulin A deficiency	
B-cell deficiencies	
AIDS	
Bronchiectasis	
MUCOCILIARY CLEARANCE DISORDERS	
Cystic fibrosis	
Primary ciliary dyskinesia	
Bronchiectasis	
ASPIRATION SYNDROMES	
Gastroesophageal reflux disease	
Pharyngeal/swallow dysfunction	
OTHER	
Bronchopulmonary dysplasia	
Interstitial lung disease, including bronchiolitis obliterans	
Heart failure	
Anaphylaxis	
Inhalation injury—burns	

Infants with preexistent smaller airways and diminished lung function have a more severe course. In addition, RSV infection incites a complex immune response. Eosinophils degranulate and release eosinophil cationic protein, which is cytotoxic to airway epithelium. Innate immunity plays a significant role and can depend on polymorphisms in toll-like receptors, interferons, interleukins, and nuclear factor κB. Chemokines and cytokines, such as tumor necrosis factor α, may be differentially expressed, depending on the inciting virus. Coinfection with more than 1 virus can also alter the clinical manifestations and/or severity of presentation.

Acute bronchiolitis is characterized by bronchiolar obstruction with edema, mucus, and cellular debris. Even minor bronchiolar wall thickening significantly affects airflow because resistance is inversely proportional to the 4th power of the radius of the bronchiolar passage. Resistance in the small air passages is increased during both inspiration and exhalation, but because the radius of an airway is smaller during expiration, the resultant respiratory obstruction leads to early air trapping and overinflation. If obstruction becomes complete, trapped distal air will be resorbed and the child will develop atelectasis.

Hypoxemia is a consequence of ventilation–perfusion mismatch early in the course. With severe obstructive disease and tiring of respiratory effort, hypercapnia can develop.

Chronic infectious causes of wheezing should be considered in infants who seem to fall out of the range of a normal clinical course. Cystic fibrosis is one such entity; suspicion increases in a patient with persistent respiratory symptoms, digital clubbing, malabsorption, failure to thrive, electrolyte abnormalities, or a resistance to bronchodilator treatment (see Chapter 403).

Allergy and asthma are important causes of wheezing and probably generate the most questions by the parents of a wheezing infant. Asthma is characterized by airway inflammation, bronchial hyperreactivity, and reversibility of obstruction (see Chapter 144). Three identified patterns of infant wheezing are the transient early wheezer, the persistent wheezer, and the late-onset wheezer. These patterns are seen in 19.9%, 13.7%, and 15% of the general population, respectively, with the remaining 50% of the population never wheezing prior to age 6 yr. Transient early wheezers wheeze at least once with a lower respiratory infection before the age of 3 yr, but never wheeze again. The persistent wheezer has wheezing episodes before age 3 yr and is still wheezing at 6 yr of age. The late-onset wheezer does not wheeze before age 3 yr but is wheezing by 6 yr. Of all the infants who wheezed before 3 yr old, almost 60% stopped wheezing by age 6 yr.

Multiple studies have tried to predict which early wheezers will go on to have asthma in later life. Risk factors for persistent wheezing include parental history of asthma and allergies, maternal smoking, persistent rhinitis (apart from acute upper respiratory tract infections), allergen sensitization, eczema at younger than 1 yr of age, peripheral eosinophilia (>4%), and frequent episodes of wheezing during infancy.

Other Causes

Congenital malformations of the respiratory tract cause wheezing in early infancy. These findings can be diffuse or focal and can be from an external compression or an intrinsic abnormality. *External vascular compression* includes a vascular ring, in which the trachea and esophagus are surrounded completely by vascular structures, or a vascular sling, in which the trachea and esophagus are not completely encircled (see Chapter 432). *Cardiovascular causes* of wheezing include dilated chambers of the heart including massive cardiomegaly, left atrial enlargement, and dilated pulmonary arteries. Pulmonary edema caused by heart failure can also cause wheezing by lymphatic and bronchial vessel engorgement that leads to obstruction and edema of the bronchioles and further obstruction (see Chapter 442).

Foreign-body aspiration (see Chapter 397) can cause acute or chronic wheezing. It is estimated that 78% of those who die from foreign-body aspiration are between 2 mo and 4 yr old. Even in young infants, a foreign body can be ingested if given to the infant by another person, such as an older sibling. Infants who have atypical histories or misleading clinical and radiologic findings can receive a misdiagnosis of asthma or another obstructive disorder as inflammation and granulation develop around the foreign body. An esophageal foreign body can transmit pressure to the membranous trachea, causing compromise of the airway lumen.

Gastroesophageal reflux (see Chapter 323.1) can cause wheezing with or without direct aspiration into the tracheobronchial tree. Without aspiration, the reflux is thought to trigger a vagal or neural reflex, causing increased airway resistance and airway reactivity. Aspiration from gastroesophageal reflux or from the direct aspiration from oral liquids can also cause wheezing.

Trauma and tumors are much rarer causes of wheezing in infants. Trauma of any type to the tracheobronchial tree can cause an obstruction to airflow. Accidental or nonaccidental aspirations, burns, or scalds of the tracheobronchial tree can cause inflammation of the airways and subsequent wheezing. Any space-occupying lesion, either in the lung itself or extrinsic to the lung, can cause tracheobronchial compression and obstruction to airflow.

CLINICAL MANIFESTATIONS

History and Physical Examination

The initial history of a wheezing infant should describe the recent event including onset, duration, and associated factors (Table 391-2). *Birth history* includes weeks of gestation, neonatal intensive care unit admission, history of intubation or oxygen requirement, maternal complications including infection with herpes simplex virus or HIV, and prenatal smoke exposure. Past medical history includes any comorbid conditions including syndromes or associations. *Family history* of cystic fibrosis, immunodeficiencies, asthma in a 1st-degree relative, or any other recurrent respiratory conditions in children should be obtained. *Social history* should include an environmental history including any smokers at home, inside or out, daycare exposure, number of siblings, occupation of inhabitants of the home, pets, tuberculosis exposure, and concerns regarding home environment (e.g., dust mites, construction dust, heating and cooling techniques, mold, cockroaches). The patient's growth chart should be reviewed for signs of failure to thrive.

On **physical examination,** evaluation of the patient's vital signs with special attention to the respiratory rate and the pulse oximetry reading for oxygen saturation is an important initial step. The **exam** is often dominated by wheezing. Auscultation might reveal fine crackles or overt wheezes, with prolongation of the expiratory phase of breathing.

Table 391-2	Pertinent Medical History in the Wheezing Infant
Did the onset of symptoms begin at birth or thereafter? Is the infant a noisy breather and when is it most prominent? Is the noisy breathing present on inspiration, expiration, or both? Is there a history of cough apart from wheezing? Was there an earlier lower respiratory tract infection? Is there a history of recurrent upper or lower respiratory tract infections? Have there been any emergency department visits, hospitalizations, or intensive care unit admissions for respiratory distress? Is there a history of eczema? Does the infant cough after crying or cough at night? How is the infant growing and developing? Is there associated failure to thrive? Is there a history of electrolyte abnormalities? Are there signs of intestinal malabsorption including frequent, greasy, or oily stools? Is there a maternal history of genital herpes simplex virus infection? What was the gestational age at delivery? Was the patient intubated as a neonate? Does the infant bottle-feed in the bed or the crib, especially in a propped position? Are there any feeding difficulties including choking, gagging, arching, or vomiting with feeds? Is there any new food exposure? Is there a toddler in the home or lapse in supervision in which foreign-body aspiration could have occurred? Change in caregivers or chance of nonaccidental trauma?	

Wheezing produces an expiratory whistling sound that can be polyphonic or monophonic. Expiratory time may be prolonged. Biphasic wheezing can occur if there is a central, large airway obstruction. The degree of tachypnea does not always correlate with the degree of hypoxemia or hypercarbia, so pulse oximetry and noninvasive determination of carbon dioxide is essential. Work of breathing may be markedly increased, with nasal flaring and retractions. *Complete obstruction to airflow can eliminate the turbulence that causes wheezing; thus the lack of audible wheezing is not reassuring if the infant shows other signs of respiratory distress.* Barely audible breath sounds suggest very severe disease with nearly complete bronchiolar obstruction.

Aeration should be noted and a trial of a bronchodilator may be warranted to evaluate for any change in wheezing after treatment. Listening to breath sounds over the neck helps differentiate upper airway from lower airway sounds. The absence or presence of stridor should be noted and appreciated on inspiration. Signs of respiratory distress include tachypnea, increased respiratory effort, nasal flaring, tracheal tugging, subcostal and intercostal retractions, and excessive use of accessory muscles. In the upper airway, signs of atopy, including boggy turbinates and posterior oropharynx cobblestoning, can be evaluated in older infants. It is also useful to evaluate the skin of the patient for eczema and any significant hemangiomas; midline lesions may be associated with an intrathoracic lesion. Digital clubbing should be noted (see Chapter 374). Hyperinflation of the lungs can permit palpation of the liver and spleen.

Acute bronchiolitis is usually preceded by exposure to an older contact with a minor respiratory syndrome within the previous week. The infant first develops a mild upper respiratory tract infection with sneezing and clear rhinorrhea. This may be accompanied by diminished appetite and fever of 38.5-39°C (101-102°F), although the temperature can range from subnormal to markedly elevated. Gradually, respiratory distress ensues, with paroxysmal wheezy cough, dyspnea, and irritability. The infant is often tachypneic, which can interfere with feeding. The child does not usually have other systemic complaints, such as diarrhea or vomiting. Apnea may be more prominent than wheezing early in the course of the disease, particularly with very young infants (<2 mo old) or former premature infants.

Diagnostic Evaluation

Initial evaluation depends on likely etiology; a baseline chest radiograph, including posteroanterior and lateral films, is warranted in many cases and for any infant in acute respiratory distress, **but not routinely indicated in children with uncomplicated bronchiolitis.** Infiltrates are most often found in wheezing infants who have a pulse oximetry reading <93%, grunting, decreased breath sounds, prolonged inspiratory to expiratory ratio, and crackles. Pulse oximetry is indicated as hypoxia is common in bronchiolitis and may signify diffuse involvement, air trapping, ventilation–perfusion mismatching, and atelectasis. The chest radiograph may also be useful for evaluating hyperinflation (common in bronchiolitis and viral pneumonia), atelectasis signs of chronic disease such as bronchiectasis, or a space-occupying lesion causing airway compression. A trial of bronchodilator may be diagnostic as well as therapeutic because these medications can reverse conditions such as asthma but will not affect a fixed obstruction. Bronchodilators potentially can worsen a case of wheezing caused by tracheal or bronchial malacia. A sweat test to evaluate for cystic fibrosis and evaluation of baseline immune status are reasonable in infants with recurrent wheezing, failure to thrive, or complicated courses. Further evaluation such as upper gastrointestinal contrast x-rays, chest CT, bronchoscopy, bronchoalveolar lavage, ciliary biopsy, infant pulmonary function testing, video swallow study, and pH probe can be considered 2nd-tier diagnostic procedures in complicated patients.

The diagnosis of **acute bronchiolitis** is clinical, particularly in a previously healthy infant presenting with a 1st-time wheezing episode during a community outbreak. Chest radiography can reveal hyperinflated lungs with patchy atelectasis but is not indicated in all patients with bronchiolitis. The white blood cell and differential counts are usually normal. Viral testing (polymerase chain reaction, rapid immunofluorescence, or viral culture) is helpful if the diagnosis is uncertain or for epidemiologic purposes but is not indicated in uncomplicated bronchiolitis. Because concurrent bacterial infection (sepsis, pneumonia, meningitis) is highly unlikely, confirmation of viral bronchiolitis may obviate the need for a sepsis evaluation in the febrile infant older than 28 days and assist with respiratory precautions and isolation if the patient requires hospitalization.

Treatment

Treatment of an infant with wheezing depends on the underlying etiology. Response to bronchodilators is unpredictable, regardless of cause, but suggests a component of bronchial hyperreactivity. It is appropriate to administer albuterol aerosol and objectively observe the response. For children younger than 3 yr of age, it is acceptable to continue to administer inhaled medications through a metered-dose inhaler with mask and spacer if a therapeutic benefit is demonstrated. Therapy should be continued in all patients with asthma exacerbations from a viral illness.

The use of ipratropium bromide in this population is controversial, but it appears to be somewhat effective as an adjunct therapy. It is also useful in infants with significant tracheal and bronchial malacia who may be made worse by β_2-agonists such as albuterol because of the subsequent decrease in smooth muscle tone.

A trial of inhaled steroids may be warranted in a patient who has responded to multiple courses of oral steroids and who has moderate to severe wheezing or a significant history of atopy including food allergy or eczema. Inhaled corticosteroids are appropriate for maintenance therapy in patients with known reactive airways but are controversial when used for episodic or acute illnesses. Intermittent, high-dose inhaled corticosteroids are not recommended for intermittent wheezing. Early use of inhaled corticosteroids has not been shown to prevent the progression of childhood wheezing or affect the natural history of asthma in children.

Oral steroids are generally reserved for atopic wheezing infants thought to have asthma that is refractory to other medications. Their use in 1st-time wheezing infants or in infants who do not warrant hospitalization is controversial.

Infants with **acute bronchiolitis** who are experiencing respiratory distress (hypoxia, inability to take oral feedings, apnea, extreme tachypnea) should be hospitalized; risk factors for severe disease include age <12 wk, preterm birth, or underlying comorbidity such as cardiovascular, pulmonary, neurologic, or immunologic disease. The mainstay of treatment is supportive. Hypoxemic children should receive cool humidified oxygen. Sedatives are to be avoided because they can depress respiratory drive. The infant is sometimes more comfortable if sitting with head and chest elevated at a 30-degree angle with neck extended. There is a small risk of aspiration of oral feedings in infants with bronchiolitis, owing to tachypnea and the increased work of breathing. If there is any risk for further respiratory decompensation potentially necessitating tracheal intubation, the infant should not be fed orally but be maintained with parenteral fluids. Frequent suctioning of nasal and oral secretions often provides relief of distress or cyanosis. Suctioning of secretions is an essential part of the treatment of bronchiolitis. Oxygen is definitely indicated in all infants with hypoxia. High-flow nasal cannula therapy can reduce the need for intubation in patients with impending respiratory failure.

A number of agents have been proposed as adjunctive therapies for bronchiolitis. Bronchodilators may produce short-term improvement in clinical features. This must be placed in context of potential adverse effects and the lack of any evidence indicating improvement in overall course of the disease. Systematic reviews and meta-analyses of randomized controlled trials have failed to show a benefit from bronchodilators in uncomplicated bronchiolitis. Corticosteroids, whether parenteral, oral, or inhaled, have been used for bronchiolitis despite conflicting and often negative studies. Corticosteroids are not recommended in previously healthy infants with RSV. Ribavirin, an antiviral agent administered by aerosol, has been used for infants with RSV who have congenital heart disease or chronic lung disease. There is no convincing evidence of a positive impact on clinically important

outcomes such as mortality and duration of hospitalization. Antibiotics have no value unless there is coexisting bacterial infection. Likewise, there is no support for RSV immunoglobulin administration during acute episodes of RSV bronchiolitis in previously healthy children. Combined therapy with nebulized epinephrine and dexamethasone has been used with some success, but additional studies are needed to confirm its efficacy and investigate the long-term adverse effects in infants before this combination can be recommended. Nebulized hypertonic saline has been reported to have some benefit, and may shorten hospital length of stay. One study suggested that on demand therapy with inhaled epinephrine or saline was more effective than scheduled fixed dosing. Heliox delivered by tight fitting mask or by continuous positive airway pressure has been of some benefit in moderately to severely affected patients with bronchiolitis.

Certain (10%) low risk patients with bronchiolitis and an oxygen requirement may be discharged from the emergency department to receive **home oxygen therapy**. Criteria for home oxygen therapy includes: typical clinical features (no apnea, wheezing ± crackles); 2 mo-2 yr of age (>44 wk gestational age); first episode of wheezing; illness during RSV season; secretions managed by parents with bulb suctioning; smoke free home; reliable family with good access to healthcare; altitude ≤6,000 feet; absence of toxic appearance or proven bacterial disease; apparent life-threatening event; cardiac, pulmonary, immunodeficiency, or neuromuscular disorders; baseline oxygen requirement prior to current illness; mild illness as evident by feeding well and alert and active; minimal retractions; respiratory rate <50 breaths/min; oxygenation >90% on ≤0.5 L/min of oxygen. All patients must have follow-up within 24 hr of discharge from the emergency room by their primary care provider or by the emergency room staff. Chest physiotherapy does not improve disease course in hospitalized infants with bronchiolitis who are not mechanically ventilated.

PROGNOSIS

Infants with **acute bronchiolitis** are at highest risk for further respiratory compromise in the 1st 48-72 hr after onset of cough and dyspnea; the child may be desperately ill with air hunger, apnea, and respiratory acidosis. The case fatality rate is <1%, with death attributable to apnea, respiratory arrest, or severe dehydration. After this critical period, symptoms can persist. The median duration of symptoms in ambulatory patients is approximately 14 days; 10% may be symptomatic at 3 wk. There is a higher incidence of wheezing and asthma in children with a history of bronchiolitis unexplained by family history or other atopic syndromes. It is unclear whether bronchiolitis incites an immune response that manifests as asthma later or whether those infants have an inherent predilection for asthma that is merely unmasked by their episode of viral bronchiolitis.

PREVENTION

Reduction in the severity and incidence of **acute bronchiolitis** because of RSV is possible through the administration of pooled hyperimmune RSV intravenous immunoglobulin and palivizumab, an intramuscular monoclonal antibody to the RSV F protein, before and during RSV season. Palivizumab should be considered for infants younger than 2 yr of age with chronic lung disease, a history of prematurity, and some forms of congenital heart disease (see Chapter 260). Meticulous hand hygiene is the best measure to prevent nosocomial transmission.

Bibliography is available at Expert Consult.

391.2 Bronchitis

Lauren E. Camarda and Denise M. Goodman

Nonspecific bronchial inflammation is termed **bronchitis** and occurs in multiple childhood conditions. **Acute bronchitis** is a syndrome, usually viral in origin, with cough as a prominent feature.

Acute tracheobronchitis is a term used when the trachea is prominently involved. Nasopharyngitis may also be present, and a variety of viral and bacterial agents, such as those causing influenza, pertussis, and diphtheria, may be responsible. Isolation of common bacteria such as *Staphylococcus aureus* and *Streptococcus pneumoniae* from the sputum might not imply a bacterial cause that requires antibiotic therapy.

ACUTE BRONCHITIS

Clinical Manifestations

Acute bronchitis often follows a viral upper respiratory tract infection. It is more common in the winter when respiratory viral syndromes predominate. The tracheobronchial epithelium is invaded by the infectious agent, leading to activation of inflammatory cells and release of cytokines. Constitutional symptoms including fever and malaise follow. The tracheobronchial epithelium can become significantly damaged or hypersensitized, leading to a protracted cough lasting 1-3 wk.

The child first presents with nonspecific upper respiratory infectious symptoms, such as rhinitis. Three to 4 days later, a frequent, dry, hacking cough develops, which may or may not be productive. After several days, the sputum can become purulent, indicating leukocyte migration but not necessarily bacterial infection. Many children swallow their sputum which can produce emesis. Chest pain may be a prominent complaint in older children and is exacerbated by coughing. The mucus gradually thins, usually within 5-10 days, and then the cough gradually abates. The entire episode usually lasts about 2 wk and seldom longer than 3 wk.

Findings on physical examination vary with the age of the patient and stage of the disease. Early findings are absent or include low-grade fever and upper respiratory signs such as nasopharyngitis, conjunctivitis, and rhinitis. Auscultation of the chest may be unremarkable at this early phase. As the syndrome progresses and cough worsens, breath sounds become coarse, with coarse and fine crackles and scattered high-pitched wheezing. Chest radiographs are normal or can have increased bronchial markings.

The principal objective of the clinician is to exclude pneumonia, which is more likely caused by bacterial agents requiring antibiotic therapy. Absence of abnormality of vital signs (tachycardia, tachypnea, fever) and a normal physical examination of the chest reduce the likelihood of pneumonia.

Differential Diagnosis

Persistent or recurrent symptoms should lead the clinician to consider entities other than acute bronchitis. Many entities manifest with cough as a prominent symptom (Table 391-3).

Treatment

There is no specific therapy for acute bronchitis. The disease is self-limited, and antibiotics, although often prescribed, do not hasten improvement. Frequent shifts in position can facilitate pulmonary drainage in infants. Older children are sometimes more comfortable with humidity, but this does not shorten the disease course. Cough suppressants can relieve symptoms but can also increase the risk of suppuration and inspissated secretions and, therefore, should be used judiciously. Antihistamines dry secretions and are not helpful; expectorants are likewise not indicated. Nonprescription cough and cold medicines should not be used in children younger than 2 yr of age and their use is cautioned in children age 2-11 yr.

CHRONIC BRONCHITIS

Chronic bronchitis is well recognized in adults, formally defined as 3 mo or longer of productive cough each year for 2 or more yr. The disease can develop insidiously, with episodes of acute obstruction alternating with quiescent periods. A number of predisposing conditions can lead to progression of airflow obstruction or chronic obstructive pulmonary disease, with smoking as the major factor (up to 80% of patients have a smoking history). Other conditions include air pollution, occupational exposures, and repeated infections. In children, cystic fibrosis, bronchopulmonary dysplasia, and bronchiectasis must be ruled out.

The applicability of this definition to children is unclear. The existence of chronic bronchitis as a distinct entity in children is

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Table 391-3 Disorders with Cough as a Prominent Finding

CATEGORY	DIAGNOSES
Inflammatory	Asthma
Chronic pulmonary processes	Bronchopulmonary dysplasia Postinfectious bronchiectasis Cystic fibrosis Tracheomalacia or bronchomalacia Ciliary abnormalities Other chronic lung diseases
Other chronic disease or congenital disorders	Laryngeal cleft Swallowing disorders Gastroesophageal reflux Airway compression (such as a vascular ring or hemangioma) Congenital heart disease
Infectious or immune disorders	Immunodeficiency Eosinophilic lung disease Tuberculosis Allergy Sinusitis Tonsillitis or adenoiditis *Chlamydia, Ureaplasma* (infants) *Bordetella pertussis* *Mycoplasma pneumoniae*
Acquired	Foreign-body aspiration, tracheal or esophageal

controversial. Like adults, children with chronic inflammatory diseases or those with toxic exposures can develop damaged pulmonary epithelium. Thus, chronic or recurring cough in children should lead the clinician to search for underlying pulmonary or systemic disorders (see Table 391-3). One proposed entity that shares characteristics with asthma and other forms of suppurative lung disease is persistent or protracted bacterial bronchitis. Protracted bacterial bronchitis is defined as a chronic (>3 wk) wet cough, characterized by bacterial counts of 10^4 colony-forming units/mL or greater from bronchoalveolar lavage and resolution of cough within 2 wk of treatment with antimicrobial therapy.

CIGARETTE SMOKING AND AIR POLLUTION

Exposure to environmental irritants, such as tobacco smoke and air pollution, can incite or aggravate cough. There is a well-established association between tobacco exposure and pulmonary disease, including bronchitis and wheezing. This can occur through cigarette smoking or by exposure to passive smoke. Marijuana smoke and inhalants are other irritants sometimes overlooked when eliciting a history.

A number of pollutants compromise lung development and likely precipitate lung disease, including particulate matter, ozone, acid vapor, and nitrogen dioxide. Proximity to motor vehicle traffic is an important source of these pollutants. Because these substances coexist in the atmosphere, the relative contribution of any 1 to pulmonary symptoms is difficult to discern.

Bibliography is available at Expert Consult.

391.3 Plastic Bronchitis

Brett J. Bordini

Plastic bronchitis is a rare condition characterized by recurrent episodes of airway obstruction secondary to the formation of large proteinaceous branching casts that take on the shape of and obstruct the tracheobronchial tree. It is not a single disease entity, but rather represents an altered state of respiratory epithelial function and is most frequently encountered in the setting of underlying pulmonary or congenital cardiac disease, although there have been reports of plastic bronchitis complicating lymphangitic disorders, pulmonary infections, and the acute chest syndrome of sickle cell disease. In comparison to the smaller bronchial and bronchiolar casts seen with mucus plugging, the lesions of plastic bronchitis are more extensive, with casts that can outline large segments of the airway to the level of the terminal bronchioles (Fig. 391-1). These casts may be spontaneously expectorated or may require bronchoscopic removal for relief of potentially fatal airway obstruction. Cast composition varies, though typically consists of either a fibrin-predominant or mucin-predominant laminated matrix with or without inflammatory cell infiltration. Plastic bronchitis may be classified according to an associated disease, the cast histology, or a combination.

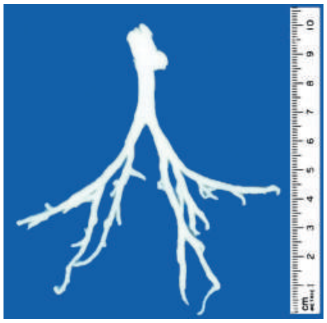

Figure 391-1 Tracheobronchial casts following bronchoscopic extraction. Casts show branched architecture corresponding to the bronchial tree. *(From Hasan RA, Black C, Reddy R: Plastic bronchitis in children.* Fetal Pediatr Pathol *31;87–93, 2012, Fig. 5, p. 91.)*

EPIDEMIOLOGY

Plastic bronchitis is rare, and its true prevalence in the pediatric population is not known but is estimated to be 6.8 cases per 100,000 patients. Prevalence does vary in relation to the underlying associated disease state, with rates as high as 14% estimated in patients who have undergone staged palliation of complex cyanotic congenital heart disease, and much lower rates seen complicating asthma and atopic disease. A slight male predominance exists for cast formation in the setting of structural heart disease, whereas cast formation in the setting of asthma and atopic disease demonstrates a female predominance.

PATHOGENESIS

The mechanism of cast formation is unclear, although it is believed to vary based on the underlying disease association and cast type. One classification system differentiates type 1 inflammatory casts, composed of primarily of fibrin with neutrophilic and more often eosinophilic infiltration, and type 2 casts, composed primarily of mucin with little to no cellular infiltration. Type 1 casts may be associated with inflammatory and infectious disorders of the lung, while type 2 casts may be associated with structural heart disease. However, these distinctions are not absolute; patients with structural heart disease can have mucin-predominant casts and patients with asthma or atopic disease can have fibrin-predominant casts, with both mucin casts and fibrin casts demonstrating various degrees of cellular infiltration.

Cast formation in the setting of structural heart disease may result from alterations in pulmonary blood flow or from alterations in lymphatic drainage, either congenital or secondary to the protein-losing enteropathy associated with Fontan physiology. Mucin-predominant casts are believed to arise secondary to mucus gland hypersecretion as well as decreased mucociliary clearance.

CLINICAL MANIFESTATIONS

Patients with plastic bronchitis may present with cough, dyspnea, wheeze, or pleuritic chest pain. Depending on the degree of airway obstruction, patients may be hypoxemic or in severe respiratory distress. The expectoration of large, branched casts that are often tan in

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color and rubbery in consistency is pathognomonic for plastic bronchitis. Lung examination may reveal diminished breath sounds or wheezing in the affected area. Rarely, auscultation may reveal a sound similar to a flag flapping in the wind *(bruit de drapeau)*, believed to be related to the free end of a cast striking the bronchial wall during inspiration or expiration. Further examination may provide clues to underlying comorbidities.

DIAGNOSIS

The expectoration or endoscopic discovery of large tracheobronchial casts is pathognomonic for plastic bronchitis. History should be directed at assessing for conditions known to be have an associated risk of tracheobronchial cast formation, such as uncorrected or surgically palliated complex congenital heart disease; a history of atopic disease or asthma; lymphangitic disorders such as Noonan syndrome, Turner syndrome, lymphangiectasia, and yellow nail syndrome; sickle cell disease; and infectious exposures, particularly exposure to tuberculosis or atypical mycobacteria. Other predisposing conditions include cystic fibrosis, allergic bronchopulmonary aspergillosis, bronchiectasis, toxic inhalants, and granulomatous lung diseases.

Physical examination may provide indications of an underlying diagnosis. Digital clubbing of the fingers or toes may suggest long-standing hypoxemia associated with cardiac or pulmonary disease. Cardiac examination may provide information suggesting the presence of unrecognized structural heart disease.

Chest radiography may demonstrate collapse of the involved areas of the lung, or areas of bronchiectasis distal to sites of long-standing obstruction.

There should be a high index of suspicion for plastic bronchitis in patients with known comorbidities who present with sudden respiratory decompensation. In the absence of cast expectoration, direct visualization of casts via bronchoscopy is required for diagnosis and is potentially therapeutic in relieving airway obstruction. Cast histology should be defined so as to allow for specific therapies directed at preventing recurrence. In particular, the predominant component of the cast's laminated matrix—either fibrin or mucin—should be defined, and signs of inflammation or infiltration, such as the presence of neutrophils, eosinophils, or Charcot-Leyden crystals, should be documented.

TREATMENT

Treatment is directed at correcting the underlying condition associated with the development of plastic bronchitis, at relieving acute airway obstruction secondary to the presence of casts, and at preventing the development of further casts. Rigid or flexible bronchoscopy is typically required for cast removal. If the predominant content of the cast is known, therapy with either mucolytics or fibrinolytics may be considered as an adjunct to direct removal, and aerosolized fibrinolytics such as tissue plasminogen activator or mucolytics such as *N*-acetylcysteine or deoxyribonuclease may be used for prevention of recurrence. Bronchodilators should be used appropriately in the setting of reactive airway disease, and inhaled or systemic corticosteroids, low-dose azithromycin, and leukotriene inhibitors may be used to minimize airway inflammation. MRI lymphangiography may identify abnormal lymphatic vessels that may benefit from lymphatic embolization procedures.

COMPLICATIONS AND PROGNOSIS

Prognosis is related primarily to the underlying condition associated with the development of plastic bronchitis. Patients whose plastic bronchitis is related to surgically palliated complex congenital heart disease are at high risk for plastic bronchitis-related mortality. Mortality can be high if casts obstruct significant portions of the airway, regardless of underlying etiology. Mortality estimates vary from 6-50% in the setting of asthma or atopic disease, and from 28-60% in the setting of complex congenital heart disease, with central airway obstruction leading to death in the majority of patients.

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Chapter 392

Emphysema and Overinflation

Steven R. Boas and Glenna B. Winnie

Pulmonary emphysema consists of distention of air spaces with irreversible disruption of the alveolar septa. It can involve part or all of a lung. **Overinflation** is distention with or without alveolar rupture and is often reversible. **Compensatory overinflation** can be acute or chronic and occurs in normally functioning pulmonary tissue when, for any reason, a sizable portion of the lung is removed or becomes partially or completely airless, which can occur with pneumonia, atelectasis, empyema, and pneumothorax. **Obstructive overinflation** results from partial obstruction of a bronchus or bronchiole, when it becomes more difficult for air to leave the alveoli than to enter. Air gradually accumulates distal to the obstruction, the so-called bypass, ball-valve, or check-valve type of obstruction.

LOCALIZED OBSTRUCTIVE OVERINFLATION

When a ball-valve type of obstruction partially occludes the main stem bronchus, the entire lung becomes overinflated; individual lobes are affected when the obstruction is in lobar bronchi. Segments or subsegments are affected when their individual bronchi are blocked. When most or all of a lobe is involved, the percussion note is hyperresonant over the area, and the breath sounds are decreased in intensity. The distended lung can extend across the mediastinum into the opposite hemithorax. Under fluoroscopic scrutiny during exhalation, the overinflated area does not decrease, and the heart and the mediastinum shift to the opposite side because the unobstructed lung empties normally.

Unilateral Hyperlucent Lung

The differential diagnosis for of this resultant **unilateral hyperlucent lung** is quite broad and can involve the lung parenchyma, airways, pulmonary vasculature, chest wall (see Chapter 417), and mediastinum. Localized obstructions that can be responsible for overinflation include airway foreign bodies and the inflammatory reaction to them (see Chapter 387), abnormally thick mucus (cystic fibrosis, Chapter 403), endobronchial tuberculosis or tuberculosis of the tracheobronchial lymph nodes (see Chapter 215), and endobronchial or mediastinal tumors.

Patients with unilateral hyperlucent lung can present with **clinical manifestations** of pneumonia, but in some patients the condition is discovered only when a chest radiograph is obtained for an unrelated reason. A few patients have hemoptysis. Physical findings can include hyperresonance and a small lung with the mediastinum shifted toward the more abnormal lung.

Swyer-James or Macleod Syndrome

The condition is thought to result from an insult to the lower respiratory tract following most commonly adenovirus (see Chapter 262), or respiratory syncytial virus (see Chapter 260), *Mycoplasma pneumoniae* (see Chapter 223), or measles (see Chapter 246). Clinically, children with this condition often have chronic cough, recurrent pneumonia, and wheezing, although some are asymptomatic. Some patients show a classic mediastinal shift away from the lesion with exhalation. CT scanning or bronchography can often demonstrate bronchiectasis. Ventilation–perfusion scans can be helpful in the diagnosis. In some patients, previous chest radiographs have been normal or have shown only an acute pneumonia, suggesting that a hyperlucent lung is an acquired lesion. No specific treatment is known; it may become less symptomatic with time. Indications as to which children would benefit from surgery remain controversial.

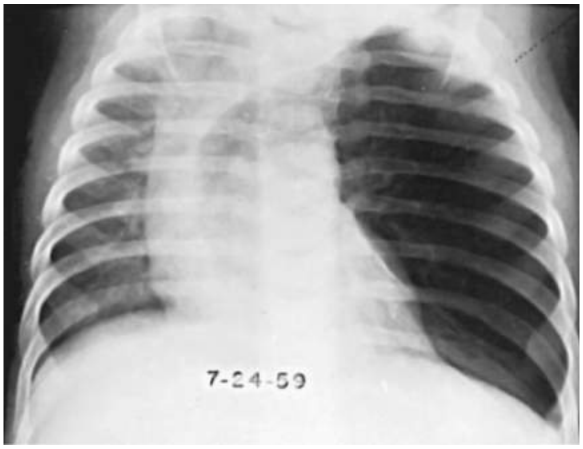

Figure 392-1 Congenital left upper lobe emphysema. Note the extension of the emphysematous lobe into the left lower lobe and its displacement of the mediastinum toward the right.

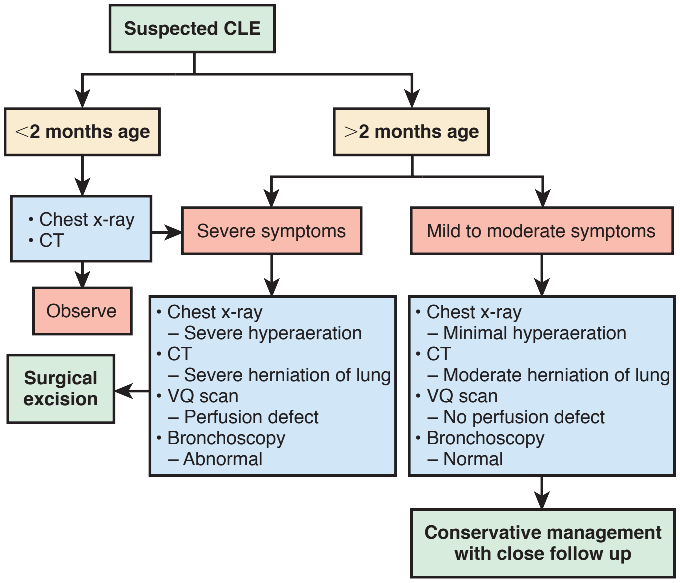

Figure 392-2 Algorithm for evaluation and treatment of congenital lobar emphysema (CLE). *(Adapted from Karnak I, Senocak ME, Ciftci AO, et al: Congenital lobar emphysema: diagnostic and therapeutic considerations,* J Pediatr Surg *34:1347–1351, 1999, Fig. 4.)*

Congenital Lobar Emphysema

Congenital lobar emphysema (CLE) can result in severe respiratory distress in early infancy and can be caused by localized obstruction. Familial occurrence has been reported. In 50% of cases, a cause of CLE can be identified. Congenital deficiency of the bronchial cartilage, external compression by aberrant vessels, bronchial stenosis, redundant bronchial mucosal flaps, and kinking of the bronchus caused by herniation into the mediastinum have been described as leading to bronchial obstruction and subsequent CLE and commonly affects the left upper lobe.

Clinical manifestations usually become apparent in the neonatal period but are delayed for as long as 5-6 mo in 5% of patients. Many cases are diagnosed by antenatal ultrasonography. Babies with prenatally diagnosed cases are not always symptomatic at birth. In some patients, CLE remains undiagnosed until school age or beyond. Clinical signs range from mild tachypnea and wheeze to severe dyspnea with cyanosis. CLE can affect 1 or more lobes; it affects the upper and middle lobes, and the left upper lobe is the most common site. The affected lobe is essentially nonfunctional because of the overdistention, and atelectasis of the ipsilateral normal lung can ensue. With further distention, the mediastinum is shifted to the contralateral side, with impaired function seen as well (Fig. 392-1). A radiolucent lobe and a mediastinal shift are often revealed by radiographic examination. A CT scan can demonstrate the aberrant anatomy of the lesion, and MRI or MR angiography can demonstrate any vascular lesions, which might be causing extraluminal compression. Nuclear imaging studies are useful to demonstrate perfusion defects in the affected lobe. Figure 392-2 outlines evaluation of an infant presenting with suspected CLE. The differential diagnosis includes pneumonia with or without an effusion, pneumothorax, and cystic adenomatoid malformation.

Treatment by immediate surgery and excision of the lobe may be lifesaving when cyanosis and severe respiratory distress are present, but some patients respond to medical treatment. Selective intubation of the unaffected lung may be of value. Some children with apparent CLE have reversible overinflation, without the classic alveolar septal rupture implied in the term *emphysema.* Bronchoscopy can reveal an endobronchial lesion.

Pulmonary Vascular Abnormalities

Unilateral hyperlucency may result from **unilateral pulmonary agenesis** (see Chapter 395) that typically presents in the neonatal period. Volume loss of the affected lung results in a mediastinal shift with hyperinflation of the contralateral lung. An **anomalous origin of the left pulmonary artery** (see Chapter 432), also known as a pulmonary artery sling, can impinge the right mainstem bronchus with resultant right-sided hyperinflation or atelectasis producing hyperlucency on either the ipsilateral or contralateral side. **Pulmonary venolobar syndrome** (see Chapter 426), also known as scimitar syndrome, can also result in a hyperlucent contralateral lung dependent on the extent of hypoplasia of the right lung.

GENERALIZED OBSTRUCTIVE OVERINFLATION

Acute generalized overinflation of the lung results from widespread involvement of the bronchioles and is usually reversible. It occurs more commonly in infants than in children and may be secondary to a number of clinical conditions, including asthma, cystic fibrosis, acute bronchiolitis, interstitial pneumonitis, atypical forms of acute laryngotracheobronchitis, aspiration of zinc stearate powder, chronic passive congestion secondary to a congenital cardiac lesion, and miliary tuberculosis.

Pathology

In chronic overinflation, many of the alveoli are ruptured and communicate with one another, producing distended saccules. Air can also enter the interstitial tissue (i.e., interstitial emphysema), resulting in pneumomediastinum and pneumothorax (see Chapters 412 and 411).

Clinical Manifestations

Generalized obstructive overinflation is characterized by dyspnea, with difficulty in exhaling. The lungs become increasingly overdistended, and the chest remains expanded during exhalation. An increased respiratory rate and decreased respiratory excursion result from the overdistention of the alveoli and their inability to be emptied normally through the narrowed bronchioles. Air hunger is responsible for forced respiratory movements. Overaction of the accessory muscles of respiration results in retractions at the suprasternal notch, the supraclavicular spaces, the lower margin of the thorax, and the intercostal spaces. Unlike the flattened chest during inspiration and exhalation in cases of laryngeal obstruction, minimal reduction in the size of the overdistended chest during exhalation is observed. The percussion note is hyperresonant. On auscultation, the inspiratory phase is usually less prominent than the expiratory phase, which is prolonged and roughened. Fine or medium crackles may be heard. Cyanosis is more common in the severe cases.

Figure 392-3 Increased transradiancy in the right lower zone. A large emphysematous bulla occupies the lower half of the right lung, and the apical changes are in keeping with previous tuberculosis. *(From Padley SPG, Hansell DM: Imaging techniques. In Albert RK, Spiro SG, Jett JR, editors:* Clinical respiratory medicine, *ed 3, Philadelphia, 2008, Mosby, Fig. 1-48.)*

Diagnosis

Radiographic and fluoroscopic examinations of the chest assist in establishing the diagnosis. Both leaves of the diaphragm are low and flattened, the ribs are farther apart than usual, and the lung fields are less dense. The movement of the diaphragm during exhalation is decreased, and the excursion of the low, flattened diaphragm in severe cases is barely discernible. The anteroposterior diameter of the chest is increased, and the sternum may be bowed outward.

Bullous Emphysema

Bullous emphysematous blebs or cysts (pneumatoceles) result from overdistention and rupture of alveoli during birth or shortly thereafter, or they may be sequelae of pneumonia and other infections. They have been observed in tuberculosis lesions during specific antibacterial therapy. These emphysematous areas presumably result from rupture of distended alveoli, forming a single or multiloculated cavity. The cysts can become large and might contain some fluid; an air–fluid level may be demonstrated on the radiograph (Fig. 392-3). The cysts should be differentiated from pulmonary abscesses. In most cases, the cysts disappear spontaneously within a few months, although they can persist for a year or more. Aspiration or surgery is not indicated except in cases of severe respiratory and cardiac compromise.

Subcutaneous Emphysema

Subcutaneous emphysema results from any process that allows free air to enter into the subcutaneous tissue (Fig. 392-4). The most common causes include pneumomediastinum or pneumothorax. Additionally, it can be a complication of fracture of the orbit, which permits free air to escape from the nasal sinuses. In the neck and thorax, subcutaneous emphysema can follow tracheotomy, deep ulceration in the pharyngeal region, esophageal wounds, or any perforating lesion of the larynx or trachea. It is occasionally a complication of thoracentesis, asthma, or abdominal surgery. Rarely, air is formed in the subcutaneous tissues by gas-producing bacteria.

Tenderness over the site of emphysema and a crepitant quality on palpation of the skin are classic manifestations. Subcutaneous emphysema is usually a self-limited process and requires no specific treatment. Minimization of activities that can increase airway pressure (cough, performance of high-pressure pulmonary function testing maneuvers) is recommended. Resolution occurs by resorption of subcutaneous air after elimination of its source. Rarely, dangerous compression of the trachea by air in the surrounding soft tissue requires surgical intervention.

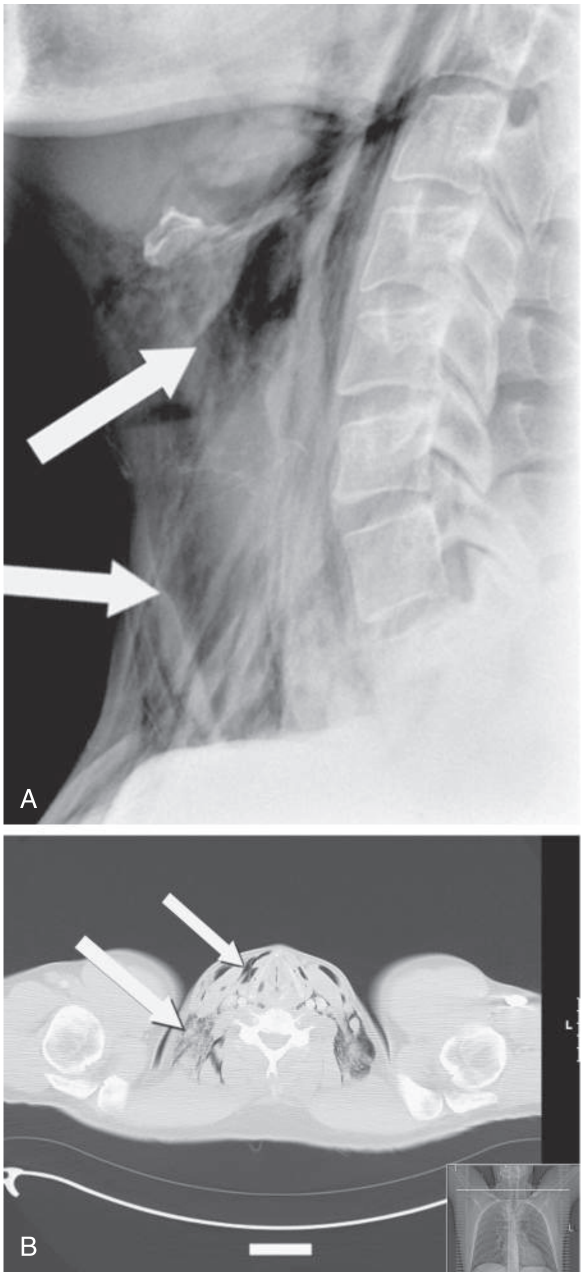

Figure 392-4 **A,** Lateral X-ray of neck showing subcutaneous emphysema. **B,** Axial section CT neck/thorax showing subcutaneous emphysema and pneumomediastinum. *(From Zakaria R, Khwaja H. Subcutaneous emphysema in a case of infective sinusitis: a case report.* J Med Case Rep *4:235, 2010, Figs, 1 and 2.)*

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Chapter 393

α_1-Antitrypsin Deficiency and Emphysema

Glenna B. Winnie and Steven R. Boas

Although it rarely causes lung disease in children, homozygous deficiency of α_1-antitrypsin (α_1-AT) is an important cause of early-onset severe panacinar pulmonary emphysema in adults in the 3rd and 4th decades of life and an important cause of liver disease in children (see Chapter 357.5). It is associated with panniculitis and vasculitis in adults.

PATHOGENESIS

The type and concentration of α_1-AT are inherited as a series of codominant alleles on chromosomal segment 14q31-32.3. (See Chapter 357.5 for a discussion of genotypes and liver disease.) The autosomal recessive deficiency affects 1 in 1,600-2,500 people, or approximately 575,000 (estimated number of deficiency allele combinations) people in the United States, but is underdiagnosed. The highest risk for α_1-AT deficiency is found in whites, followed by Hispanics and Blacks, with the lowest prevalence among Mexican Americans, and little to no risk for Asians. Worldwide there are an estimated 116,000,000 carriers and 1,100,000 subjects with severe α_1-AT deficiency. The normal α_1-AT PiM protein is secreted by the liver into the circulation at a rate of approximately 34 mg/kg/day; it is also produced by lung epithelial cells and monocytes. Mutant protein is not produced (null) or is misfolded (PiZ and others); it can polymerize in the endoplasmic reticulum or be degraded, with subsequent low serum levels. Early adult-onset emphysema associated with α_1-AT deficiency occurs most commonly with PiZZ (mutation in *SERPINA1* gene), although Pi (null) (null) and, to a lesser extent, other mutant Pi types such as SZ have been associated with emphysema.

α_1-AT and other serum antiproteases help inactivate proteolytic enzymes released from dead bacteria or leukocytes in the lung. Deficiency of these antiproteases leads to an accumulation of proteolytic enzymes in the lung, resulting in destruction of pulmonary tissue with subsequent development of emphysema. Furthermore, polymerized mutant protein in the lungs may be proinflammatory. The concentration of proteases (elastase) in the patients' leukocytes may also be an important factor in determining the severity of clinical pulmonary disease with a given level of α_1-AT.

CLINICAL MANIFESTATIONS

Most patients who have the PiZZ defect have little or no detectable pulmonary disease during childhood. A few have early onset of chronic pulmonary symptoms, including dyspnea, wheezing, and cough, and panacinar emphysema has been documented by lung biopsy; it is probable that these findings occur secondarily to infection, causing inflammation with consequent early disease. Smoking greatly increases the risk of emphysema in patients with mutant Pi types. Although newborn screening to identify children with PiZZ phenotype does not affect parental smoking habits, it does decrease smoking rates among affected adolescents.

Physical examination in childhood is usually normal. It very rarely reveals growth failure, an increased anteroposterior diameter of the chest with a hyperresonant percussion note, crackles if there is active infection, and clubbing. Severe emphysema can depress the diaphragm, making the liver and spleen more easily palpable.

LABORATORY FINDINGS

Serum immunoassay measures low levels of α_1-AT; normal serum levels are 150-350 mg/dL. Serum electrophoresis reveals the phenotype, and genotype is determined by polymerase chain reaction. In the rare patient with lung disease in adolescence, chest radiograph reveals overinflation with depressed diaphragms. Chest CT can show more hyperexpansion in the lower lung zones, with occasional bronchiectasis; CT densitometry can be a sensitive method to follow changes in lung disease. Lung function testing is usually normal in children, but it can show airflow obstruction and increased lung volumes, particularly in adolescents who smoke.

TREATMENT

Therapy for α_1-AT deficiency is intravenous replacement with enzyme derived from pooled human plasma. A level of 80 mg/dL is protective for emphysema. This target level for augmentation therapy is usually achieved with doses of 60 mg/kg IV weekly and results in the appearance of the transfused antiprotease in pulmonary lavage fluid. The Food and Drug Administration has approved the use of purified blood-derived human enzyme for ZZ and null-null patients. Replacement therapy appears most beneficial for those with moderately severe obstructive lung disease (forced expiratory volume in 1 sec is 30-65% of predicted) or those with mild lung disease experiencing a rapid decline in lung function. Augmentation therapy is not indicated for persons with the PiMZ type who have pulmonary disease, because their disease is not from enzyme deficiency. Recombinant sources of α_1-AT are under development, but current products are rapidly cleared from the circulation when given intravenously; they may be useful for inhalation therapy. Inhalation of the plasma-derived product is under evaluation. Lung transplantation has been performed for end-stage disease.

SUPPORTIVE THERAPY

Standard supportive therapy for chronic lung disease includes aggressive treatment of pulmonary infection, routine use of pneumococcal and influenza vaccines, bronchodilators, and advice about the serious risks of smoking. Such treatment is also indicated for asymptomatic family members found to have PiZZ or null-null phenotypes, but not those with PiMZ type. The clinical significance of the PiSZ type is unclear, but nonspecific treatment is reasonable. All persons with low levels of serum antiprotease should be warned that the development of emphysema is partially mediated by environmental factors and that cigarette smoking is particularly deleterious. Although identification of affected persons could help prevent development of obstructive lung disease, population screening programs are currently suspended; however, there is increased emphasis on targeted screening programs.

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Chapter 394
Other Distal Airway Diseases

394.1 Bronchiolitis Obliterans

Steven R. Boas

EPIDEMIOLOGY

Bronchiolitis obliterans (BO), a chronic obstructive lung disease of the bronchioles and smaller airways, results from an insult to the lower respiratory tract leading to fibrosis of the small airways. In the nontransplant patient, BO most commonly occurs in the pediatric population after respiratory infections, particularly adenovirus (see Chapter 262), but also *Mycoplasma pneumoniae* (see Chapter 223), measles (see Chapter 246), *Legionella pneumophila* (see Chapter 208), influenza (see Chapter 258), and pertussis (see Chapter 197); other causes

Table 394-1 Etiology of Bronchiolitis Obliterans
POSTINFECTION Adenovirus types 3, 7, and 21 Influenza Parainfluenza Measles Respiratory syncytial virus Varicella *Mycoplasma pneumoniae*
POSTTRANSPLANTATION Chronic rejection of lung or heart/lung transplantation Graft-versus-host disease associated with bone marrow transplantation
CONNECTIVE TISSUE DISEASE Juvenile idiopathic arthritis Sjögren syndrome Systemic lupus erythematosus
TOXIC FUME INHALATION NO_2 NH_3 Diacetyl flavorings (microwave popcorn)
CHRONIC HYPERSENSITIVITY PNEUMONITIS Avian antigens Mold
ASPIRATION Stomach contents: gastroesophageal reflux Foreign bodies
DRUGS Penicillamine Cocaine
STEVENS-JOHNSON SYNDROME Idiopathic Drug induced Infection related

From Moonnumakal SP, Fan LL: Bronchiolitis obliterans in children, Curr Opin Pediatr *20:272–278, 2008.*

include inflammatory diseases (juvenile idiopathic arthritis, systemic lupus erythematosus [see Chapter 158], scleroderma [see Chapter 160], Stevens-Johnson syndrome [see Chapter 152]), and inhalation of toxic fumes or particulate exposure (NO_2, incinerator fly ash, NH_3, diacetyl flavorings from microwave popcorn, papaverine, fiberglass) (Table 394-1).

Bronchiolitis obliterans syndrome (BOS), a clinical entity that relates to graft deterioration after transplantation as a result of progressive airway, is recognized as a long-term complication of lung and bone marrow transplantation; more than one-third of survivors of lung transplantation can develop this disorder. BOS occurs in all age groups, and the prevalence in 1 pediatric autopsy series was 2 per 1,000. The incidence of new cases appears to be decreasing. BOS appears to be more common among older children and adolescents than infants and toddlers. There is some evidence that postinfection obliterans may be more common in the southern hemisphere and among persons of Asian descent.

PATHOGENESIS

After the initial insult, inflammation affecting terminal bronchioles, respiratory bronchioles, and alveolar ducts can result in the obliteration of the airway lumen (Fig. 394-1). Epithelial damage resulting in abnormal repair is characteristic of BO. Complete or partial obstruction of the airway lumen can result in air trapping or atelectasis. **Bronchiolitis obliterans organizing pneumonia (BOOP)** is a fibrosing lung disease that includes the histologic features of BO with extension of the inflammatory process from distal alveolar ducts into alveoli and proliferation of fibroblasts. BOS appears histologically similar to BO.

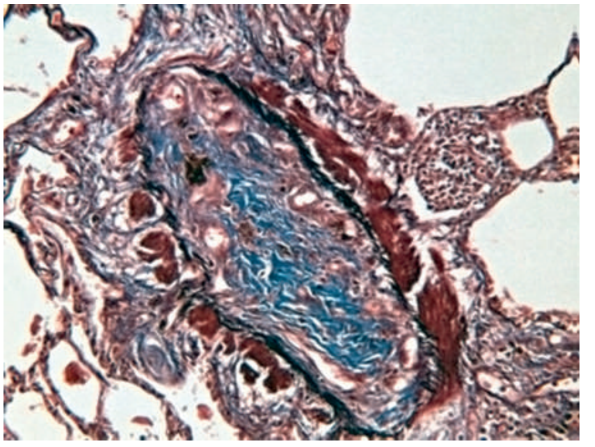

Figure 394-1 Complete obliteration of airway lumen with fibromyxoid tissue in lung transplant recipient with bronchiolitis obliterans. *(From Kurland G, Michelson P: Bronchiolitis obliterans in children,* Pediatr Pulmonol *39:193–208, 2005.)*

The etiology of BOS is unclear, however, and may be unrelated to the mechanisms responsible for BO in nontransplant patients.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Cough, fever, cyanosis, dyspnea, chest pain, and respiratory distress followed by initial improvement may be the initial signs of BO. In this phase, BO is easily confused with pneumonia, bronchitis, or bronchiolitis. Progression of the disease can ensue, with increasing dyspnea, chronic cough, sputum production, and wheezing. Physical examination findings are usually nonspecific and can include wheezing, hypoxemia, and crackles. Chest radiographs may be relatively normal compared with the extent of physical findings but can demonstrate hyperlucency and patchy infiltrates. Occasionally, a Swyer-James syndrome (unilateral hyperlucent lung; see Chapter 392) develops. Pulmonary function tests demonstrate variable findings but typically show signs of airway obstruction with a variable degree of bronchodilator response. Exercise testing shows reduced exercise capacity and impaired oxygen consumption. Ventilation–perfusion scans reveal a typical moth-eaten appearance of multiple matched defects in ventilation and perfusion. High-resolution chest CT often demonstrates patchy areas or a mosaic pattern of hyperlucency, air trapping, and bronchiectasis (Fig. 394-2). (Table 394-2 provides an overview of CT findings of BO and related disorders.) Physical and radiologic signs can wax and wane over weeks or months. Open lung biopsy or transbronchial biopsy remains the best means of establishing the diagnosis of BO or BOOP.

TREATMENT

No definitive therapy exists for BO. Administration of corticosteroids may be beneficial. Immunomodulatory agents, such as sirolimus, tacrolimus, aerosolized cyclosporine, hydroxychloroquine, and macrolide antibiotics, have been used in post–lung transplantation recipients with BO with variable success. Supportive measures with oxygen, antibiotics for secondary infections, and bronchodilators are adjunct therapies. The role of gastroesophageal reflux and its association with BO has been raised, with treatment suggested whenever the diagnosis is made. Azithromycin may be effective in patients with BOS. For BOOP, use of oral corticosteroids for up to 1 yr has been advocated as first-line therapy for symptomatic and progressive disease. Patients with asymptomatic or nonprogressive BOOP can be observed.

PROGNOSIS

Some patients with BO experience rapid deterioration in their condition and die within weeks of the initial symptoms; most nontransplant patients survive with chronic disability. BOS has a higher mortality

Table 394-2 High-Resolution CT Patterns in Child with Interstitial Lung Disease

	STUDIES (N)	GROUND-GLASS OPACITY	THICK SEPTA	NODULES	MOSAIC PATTERN	HONEYCOMBING
Bronchiolitis obliterans	4	—	—	—	X	—
Nonspecific interstitial pneumonitis	6	X	—	—	—	X
Desquamative interstitial pneumonitis	4	X	—	—	—	X
Follicular bronchitis or neuroendocrine cell hyperplasia of infancy	4	X	—	—	X	—
Lymphocytic interstitial pneumonitis	4	—	—	X	—	—
Lymphangiomatosis	2	—	X	—	—	—
Lymphangiectasia	2	—	X	—	—	—
Pulmonary alveolar proteinosis	2	X	X	—	—	—

From Long FR, Interstitial lung disease. In Slovis TL, editor: Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, Table 74-1; original data from Lynch DA, Hay T, Newell JD Jr, et al: Pediatric diffuse lung disease: diagnosis and classification using high-resolution CT.* AJR Am J Roentgenol *173:713–718, 1999, and Copley SJ, Coren M, Nicholson AG, et al: Diagnostic accuracy of thin-section CT and chest radiography of pediatric interstitial lung disease.* AJR Am J Roentgenol *174:549–554, 2000.*

Figure 394-2 **High-resolution CT scan of the chest of a child with bronchiolitis obliterans demonstrating mosaic perfusion and vascular attenuation.** Air-trapping is demonstrated by lack of increase in attenuation or decrease in lung volume in dependent lung. *(Image courtesy of Alan Brody, MD, Cincinnati Children's Hospital Medical Center, Ohio.)*

rate. Unlike in BO, total recovery is seen in 60-80% of patients with BOOP, although this depends on the underlying systemic disease. BOOP can relapse, especially if treatment duration is <1 yr; BOOP is amenable to repeat courses of oral corticosteroids. Unlike the more common idiopathic BOOP, progressive BOOP characterized by acute respiratory distress syndrome is rare but is aggressive in its clinical course, leading to death.

Bibliography is available at Expert Consult.

Figure 394-3 **Follicular bronchiolitis in a 3 yr old girl with mosaic attenuation and cylindrical bronchiectasis.** CT findings suggested BO, but a biopsy documented the presence of follicular bronchiolitis. *(From Long FR, Druhan SM, Kuhn JP. Diseases of the bronchi and pulmonary aeration. In Slovis TL, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, Fig. 73-71.)*

394.2 Follicular Bronchitis

Steven R. Boas

Follicular bronchitis is a lymphoproliferative lung disorder characterized by the presence of lymphoid follicles alongside the airways (bronchi or bronchioles) and infiltration of the walls of bronchi and bronchioles. Although the cause is unknown, an infectious etiology (viral, *L. pneumophila;* see Chapter 208) has been proposed. This disorder has been reported following lung transplant and in an HIV-positive child. It can occur in adults and children; in children, onset of symptoms generally occurs by 6 wk of age and peaks between 6 and 18 mo. Cough, moderate respiratory distress, fever, and fine crackles are common clinical findings. Fine crackles generally persist over time, and recurrence of symptoms is common. Chest radiographs may be relatively benign initially (air trapping, peribronchial thickening) but evolve into the typical interstitial pattern. Chest CT can show a fine reticular pattern as well as bronchiectasis and centrilobular branching but can also appear normal (see Table 394-2). Definitive diagnosis is made by open-lung biopsy (Fig. 394-3). Some patients with follicular bronchitis respond to therapy with corticosteroids. Prognosis is variable, with some patients having significant progression of pulmonary

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disease and others developing only mild obstructive airway disease. In children it is generally associated with immunodeficiency; the differential diagnosis includes the pulmonary complications of HIV infection (see Chapter 276).

Bibliography is available at Expert Consult.

394.3 Pulmonary Alveolar Microlithiasis

Steven R. Boas

Pulmonary alveolar microlithiasis (PAM) is a rare disease characterized by the formation of lamellar concretions of calcium phosphate or "microliths" within the alveoli, creating a classic pattern on the radiograph (Fig. 394-4).

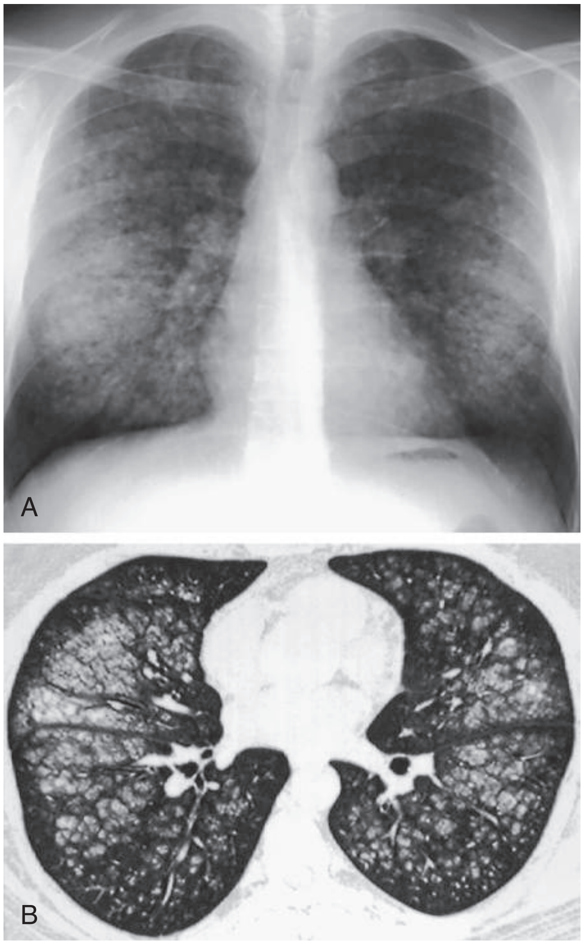

Figure 394-4 Radiographic features of pulmonary alveolar microlithiasis. **A,** Posteroanterior chest radiograph showing the classic "sandstorm" appearance of pulmonary alveolar microlithiasis, including diffuse, patchy, bilateral sharp micronodular disease. **B,** High-resolution CT scan of the chest showing micronodular densities. *(From Brandenburg VM, Schubert H. Images in clinical medicine. Pulmonary alveolar microlithiasis.* N Engl J Med *348:1555, 2003.)*

EPIDEMIOLOGY AND ETIOLOGY

Although the mean age at time of diagnosis is in the mid 30s, the onset of the disease can occur in childhood. PAM is inherited in an autosomal recessive pattern. In 2006, a mutation in the gene that encodes for the type IIb sodium-phosphate cotransporter protein (SCL34A2) was discovered in people with PAM. This gene is expressed in high levels in the lungs predominantly in type 2 epithelial cells. While the precise role of this protein is unknown, it is speculated that it helps remove phosphate from the alveolar space as well as a phosphate regular in other organs.

In some families, progression of disease is rapid. An equal male and female incidence is noted. Although PAM is found throughout the world, there is a high incidence in Turkey and a lesser incidence in Italy, Japan, and India.

CLINICAL MANIFESTATIONS

When symptomatic, patients with PAM usually complain of dyspnea on exertion and nonproductive cough. Physical examination of the lungs can reveal fine inspiratory crackles and diminished breath sounds. Clubbing occurs, although this is usually a more advanced sign. Discordance between the clinical and radiographic manifestations is common. Many children are often asymptomatic on initial presentation and present with symptoms during adulthood. Complications of pneumothorax, pleural adhesions and calcifications, pleural fibrosis, apical bullae, and extrapulmonary sites of microliths have been reported (kidneys, prostate, sympathetic chain, and testes).

DIAGNOSIS

Chest radiography typically reveals bilateral infiltrates with a fine micronodular appearance or **sandstorm** appearance with greater density in the lower and middle lung fields (see Fig. 394-4). CT of the chest shows diffuse micronodular calcified densities, with thickening of the microliths along the septa and around distal bronchioles, especially in the inferior and posterior regions (see Table 394-2). Diffuse uptake of technetium-99 methylene diphosphonate by nuclear scan has been reported. Open lung and transbronchial lung biopsy reveal 0.1-0.3 mm laminated calcific concretions within the alveoli. Although the alveoli are often normal initially, progression to pulmonary fibrosis with advancing disease usually ensues. Sputum expectoration might reveal small microliths, although this finding is not diagnostic for PAM and is not typically seen in children. Detection of calcium deposits in bronchoalveolar lavage fluid on bronchoscopy supports the diagnosis. Pulmonary function testing reveals restrictive lung disease with impaired diffusing capacity as the disease progresses, whereas exercise testing demonstrates arterial oxygen desaturation. Detection of a mutation in the *SCL34A2* gene confirms the diagnosis. The differential diagnosis includes sarcoidosis, miliary tuberculosis, hemosiderosis, healed disseminated histoplasmosis, pulmonary calcinosis, and metastatic pulmonary calcifications.

TREATMENT

No specific treatment is effective, although some clinicians have used glucocorticosteroids, etidronate disodium, and bronchopulmonary lavage with limited success. Lung transplantation has been performed for this condition, although it is unknown whether the disease recurs after transplantation.

PROGNOSIS

Progressive cardiopulmonary disease can ensue, leading to cor pulmonale, superimposed infections, and subsequent death in mid-adulthood. Because of the familial nature of this disease, counseling and chest radiographs of family members are indicated.

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Chapter 395

Congenital Disorders of the Lung

395.1 Pulmonary Agenesis and Aplasia

Joshua A. Blatter and Jonathan D. Finder

ETIOLOGY AND PATHOLOGY

Pulmonary agenesis differs from hypoplasia in that agenesis entails the complete absence of a lung. Agenesis differs from aplasia by the absence of a bronchial stump or carina that is seen in aplasia. Bilateral pulmonary agenesis is incompatible with life, manifesting as severe respiratory distress and failure. Pulmonary agenesis is thought to be an autosomal recessive trait, with an estimated incidence of 1 in 10,000-15,000 births.

CLINICAL MANIFESTATIONS AND PROGNOSIS

Unilateral agenesis or hypoplasia can have few symptoms and nonspecific findings, resulting in only 33% of the cases being diagnosed while the patient is living. Symptoms tend to associated with central airway complications of compression, stenosis, and/or tracheobronchomalacia. In patients in whom the right lung is absent, the aorta can compress the trachea and lead to symptoms of central airway compression. Right lung agenesis has a higher morbidity and mortality than left lung agenesis. Pulmonary agenesis is often seen in association with other congenital anomalies such as the **VACTERL sequence** (*v*ertebral anomalies, *a*nal atresia, *c*ongenital heart disease, *t*racheoesophageal fistula, *r*enal anomalies, and *l*imb anomalies), ipsilateral facial and skeletal malformations, and central nervous system and cardiac malformations. Compensatory growth of the remaining lung allows improved gas exchange, but the mediastinal shift can lead to scoliosis and airway compression. Scoliosis can result from unequal thoracic growth.

DIAGNOSIS AND TREATMENT

Chest radiographic findings of unilateral lung or lobar collapse with a shift of mediastinal structures toward the affected side can prompt referral for suspected foreign-body aspiration, mucous plug occlusion, or other bronchial mass lesions. The diagnosis requires a high index of suspicion to avoid the unnecessary risks of bronchoscopy, including potential perforation of the rudimentary bronchus. CT of the chest is diagnostic, although the diagnosis may be suggested by chronic changes in the contralateral aspect of the chest wall and lung expansion on chest radiographs. Because pulmonary agenesis can be associated with a wide variety of congenital lesions, whole-body MRI can be useful to determine whether other systems (e.g., cardiac, gastrointestinal) are affected. Conservative treatment is usually recommended, although surgery has offered benefit in selected cases.

Bibliography is available at Expert Consult.

395.2 Pulmonary Hypoplasia

Joshua A. Blatter and Jonathan D. Finder

ETIOLOGY AND PATHOLOGY

Pulmonary hypoplasia involves a decrease in both the number of alveoli and the number of airway generations. The hypoplasia may be bilateral in the setting of bilateral lung constraint, as in oligohydramnios or thoracic dystrophy. Pulmonary hypoplasia is usually secondary to other intrauterine disorders that produce an impairment of normal lung development (see Chapter 101). Conditions such as deformities of the thoracic spine and rib cage (thoracic dystrophy), pleural effusions with fetal hydrops, congenital pulmonary airway malformation, and congenital diaphragmatic hernia physically constrain the developing lung. Any condition that produces oligohydramnios (fetal renal insufficiency or prolonged premature rupture of membranes) can also lead to diminished lung growth. In these conditions, airway and arterial branching are inhibited, thereby limiting the capillary surface area. Large unilateral lesions, such as congenital diaphragmatic hernia or pulmonary airway malformation, can displace the mediastinum and thereby produce a contralateral hypoplasia, although usually not as severe as that seen on the ipsilateral side.

CLINICAL MANIFESTATIONS

Pulmonary hypoplasia is usually recognized in the newborn period, owing to either the respiratory insufficiency or the presentation of persistent pulmonary hypertension (see Chapter 101.7). Later presentation (tachypnea) with stress or respiratory viral infection can be seen in infants with mild pulmonary hypoplasia.

DIAGNOSIS AND TREATMENT

A variety of imaging techniques, including MRI and ultrasound, with estimation of oligohydramnios, can be helpful to identify hypoplasia, but not to predict pulmonary function. Mechanical ventilation and oxygen may be required to support gas exchange. Specific therapy to control associated pulmonary hypertension, such as inhaled nitric oxide, may be useful. In cases of severe hypoplasia, the limited capacity of the lung for gas exchange may be inadequate to sustain life. Extracorporeal membrane oxygenation can provide gas exchange for a critical period of time and permit survival. Rib-expanding devices (vertically expansible prosthetic titanium ribs) can improve the survival of patients with thoracic dystrophies (see Chapter 700).

Bibliography is available at Expert Consult.

395.3 Congenital Cystic Malformation

Joshua A. Blatter and Jonathan D. Finder

PATHOLOGY

Congenital pulmonary airway malformation (CPAM), formerly known as cystic adenomatoid malformation, consists of hamartomatous or dysplastic lung tissue mixed with more normal lung, generally confined to 1 lobe. This congenital pulmonary disorder occurs in approximately 1-4 in 100,000 births. Prenatal ultrasonographic findings are classified as **macrocystic** (single or multiple cysts >5 mm) or **microcystic** (echogenic cysts <5 mm). Five histologic patterns have been described. **Type 0** (acinar dysplasia) is least common (<3%) and consists of microcystic disease throughout the lungs. The prognosis is poorest for this type, and infants die at birth. **Type 1** (60%) is macrocystic and consists of a single or several large (>2 cm in diameter) cysts lined with ciliated pseudostratified epithelium; the lesion is localized involving only a part of 1 lobe. One-third of cases have mucus-secreting cells. Presentation is in utero or in the newborn period. Cartilage is rarely seen in the wall of the cyst. This type has a good prognosis for survival. **Type 2** (20%) is microcystic and consists of multiple small cysts with histology similar to that of the type 1 lesion. Type 2 is associated with other serious congenital anomalies (renal, cardiac, diaphragmatic hernia) and carries a poor prognosis. **Type 3** (<10%) is seen mostly in males; the lesion is a mixture of microcysts and solid tissue with bronchiole-like structures lined with cuboidal ciliated epithelium and separated by areas of nonciliated cuboidal epithelium. The prognosis for this type, like type 0, is poor. **Type 4** (10%) is commonly macrocystic and lacks mucus cells. It is associated with malignancy

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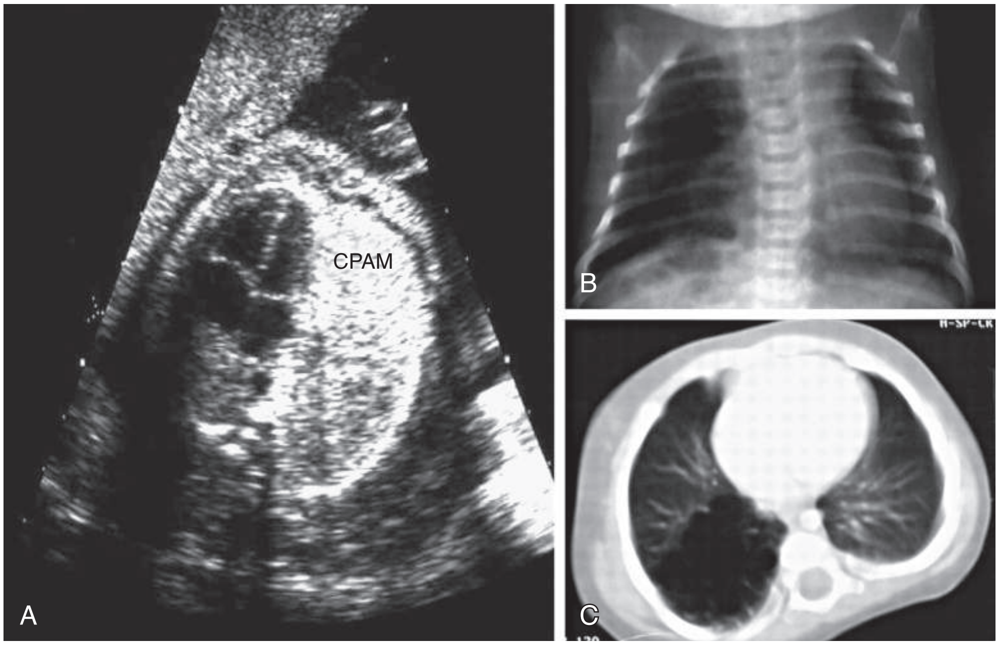

Figure 395-1 Imaging of congenital pulmonary airway malformation of the lung (CPAM) on the same patient with prenatal ultrasound scan **(A),** chest radiograph **(B),** and CT scan **(C).** Note that the lesion is not visible on the chest radiograph. *(From Lakhoo K: Management of congenital cystic adenomatous malformations of the lung,* Arch Dis Child Fetal Neonatal Ed *94:F73–F76, 2009.)*

(pleuropulmonary blastoma) and can present either in childhood or in asymptomatic adults.

ETIOLOGY

The lesion probably results from an embryologic injury before the 35th day of gestation, with maldevelopment of terminal bronchiolar structures. Histologic examination reveals little normal lung and many glandular elements. Cysts are very common; cartilage is rare. The presence of cartilage might indicate a somewhat later embryologic insult, perhaps extending into the 10th-24th wk. Although growth factor interactions and signaling mechanisms have been implicated in altered lung-branching morphogenesis, the exact roles in the maldevelopment seen here remain obscure.

DIAGNOSIS

Cystic airway malformations can be diagnosed in utero by ultrasonography (Fig. 395-1). Fetal cystic lung abnormalities can include CPAM (40%), pulmonary sequestration (14%) (see Chapter 395.4), or both (26%); the median age at diagnosis is usually 21 wk gestation. In 1 series, only 7% had severe signs of fetal distress including hydrops, pleural effusion, polyhydramnios, ascites, or severe facial edema; 96% of the fetuses were born alive, 2 of whom died in the neonatal period. Lesions causing fetal hydrops have a poor prognosis. Large lesions, by compressing adjacent lung, can produce pulmonary hypoplasia in nonaffected lobes (see Chapter 395.2). Even lesions that appear large in early gestation can regress considerably or decrease in relative size and be associated with good pulmonary function in childhood. CT allows accurate diagnosis and sizing of the lesion and is indicated even in asymptomatic neonates.

CLINICAL MANIFESTATIONS

Patients can present in the newborn period or early infancy with respiratory distress, recurrent respiratory infection, and pneumothorax. The lesion may be confused with a diaphragmatic hernia (see Chapter 101.8). Patients with smaller lesions are usually asymptomatic until mid-childhood, when episodes of recurrent or persistent pulmonary infection or chest pain occur. Breath sounds may be diminished, with mediastinal shift away from the lesion on physical examination. Chest radiographs reveal a cystic mass, sometimes with mediastinal shift (Fig. 395-2). Occasionally, an air–fluid level suggests a lung abscess (see Chapter 402).

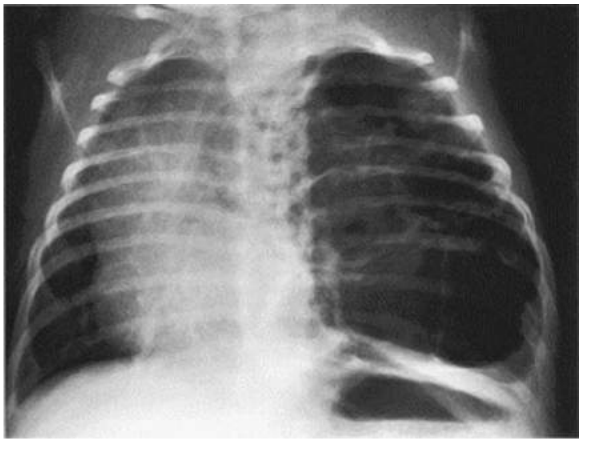

Figure 395-2 Neonatal chest x-ray showing large multicystic mass in the left hemithorax with mediastinal shift as a result of congenital pulmonary airway malformation (CPAM). *(From Williams HJ, Johnson KJ: Imaging of congenital cystic lung lesions,* Paediatr Respir Rev *3:120–127, 2002.)*

TREATMENT

Antenatal intervention in severely affected infants is controversial but can include excision of the affected lobe for microcystic lesions, aspiration of macrocystic lesions, and, rarely, open fetal surgery. In the postnatal period, surgery is indicated for symptomatic patients. Although surgery may be delayed for asymptomatic infants because postnatal resolution has been reported, true resolution appears to be very rare in that abnormalities usually remain detectable on CT or MRI. Sarcomatous and carcinomatous degeneration have been described in patients with CPAM, so surgical resection by 1 year of age is recommended to limit malignant potential. The mortality rate is <10%. Another indication for surgery is to rule out **pleuropulmonary**

blastoma, a malignancy that can appear radiographically similar to type I CPAM.

Bibliography is available at Expert Consult.

395.4 Pulmonary Sequestration

Joshua A. Blatter and Jonathan D. Finder

Pulmonary sequestration is a congenital anomaly of lung development that can be intrapulmonary or extrapulmonary, according to the location within the visceral pleura. The majority of sequestrations are intrapulmonary.

PATHOPHYSIOLOGY

The lung tissue in a sequestration does not connect to a bronchus and receives its arterial supply from the systemic arteries (commonly off the aorta) and returns its venous blood to the right side of the heart through the inferior vena cava (**extralobar**) or pulmonary veins (**intralobar**). The sequestration functions as a space-occupying lesion within the chest; it does not participate in gas exchange and does not lead to a left-to-right shunt or alveolar dead space. Communication with the airway can occur as the result of rupture of infected material into an adjacent airway. Collateral ventilation within intrapulmonary lesions via pores of Kohn can occur. Pulmonary sequestrations can arise through the same pathoembryologic mechanism as a remnant of a diverticular outgrowth of the esophagus. Some propose that intrapulmonary sequestration is an acquired lesion primarily caused by infection and inflammation; inflammation leads to cystic changes and hypertrophy of a feeding systemic artery. This is consistent with the rarity of this lesion in autopsy series of newborns. Gastric or pancreatic tissue may be found within the sequestration. Cysts also may be present. Other associated congenital anomalies, including CPAM (see Chapter 395.3), diaphragmatic hernia (see Chapter 101.8), and esophageal cysts, are not uncommon. Some believe that intrapulmonary sequestration is often a manifestation of CPAM and have questioned the existence of intrapulmonary sequestration as a separate entity.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Physical findings in patients with sequestration include an area of dullness to percussion and decreased breath sounds over the lesion. During infection, crackles may also be present. A continuous or purely systolic murmur may be heard over the back. If findings on routine chest radiographs are consistent with the diagnosis, further delineation is indicated before surgical intervention (Fig. 395-3). CT with contrast can demonstrate both the extent of the lesion and its vascular supply. MR angiography is also useful. Ultrasonography can help rule out a diaphragmatic hernia and demonstrate the systemic artery. Surgical removal is recommended. Identifying the blood supply before surgery avoids inadvertently severing its systemic artery. Coil embolization (transumbilical in neonates; arterial in older patients) has been successful in treating patients with sequestration.

Intrapulmonary sequestration is generally found in a lower lobe and does not have its own pleura. Patients usually present with infection. In older patients, hemoptysis is common. A chest radiograph during a period when there is no active infection reveals a mass lesion; an air–fluid level may be present. During infection, the margins of the lesion may be blurred. There is no difference in the incidence of this lesion in each lung.

Extrapulmonary sequestration is much more common in boys, and almost always involves the left lung. This lesion is enveloped by a pleural covering and is associated with diaphragmatic hernia and other abnormalities such as colonic duplication, vertebral abnormalities, and pulmonary hypoplasia. Many of these patients are asymptomatic when the mass is discovered by routine chest radiography. Other patients present with respiratory symptoms or heart failure. Subdiaphragmatic extrapulmonary sequestration can manifest as an abdominal mass on prenatal ultrasonography. The advent of prenatal ultrasonography has also enabled evidence that fetal pulmonary sequestrations can spontaneously regress.

TREATMENT

Treatment of intrapulmonary sequestration is surgical removal of the lesion, a procedure that usually requires excision of the entire involved lobe. Segmental resection occasionally suffices. Surgical resection of the involved area is recommended for extrapulmonary sequestration. Coil embolization of the feeding artery has also been successful.

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395.5 Bronchogenic Cysts

Joshua A. Blatter and Jonathan D. Finder

ETIOLOGY AND PATHOLOGY

Bronchogenic cysts arise from abnormal budding of the tracheal diverticulum of the foregut before the 16th wk of gestation and are originally lined with ciliated epithelium. They are more commonly found on the right and near a midline structure (trachea, esophagus, carina), but peripheral lower lobe and perihilar intrapulmonary cysts are not

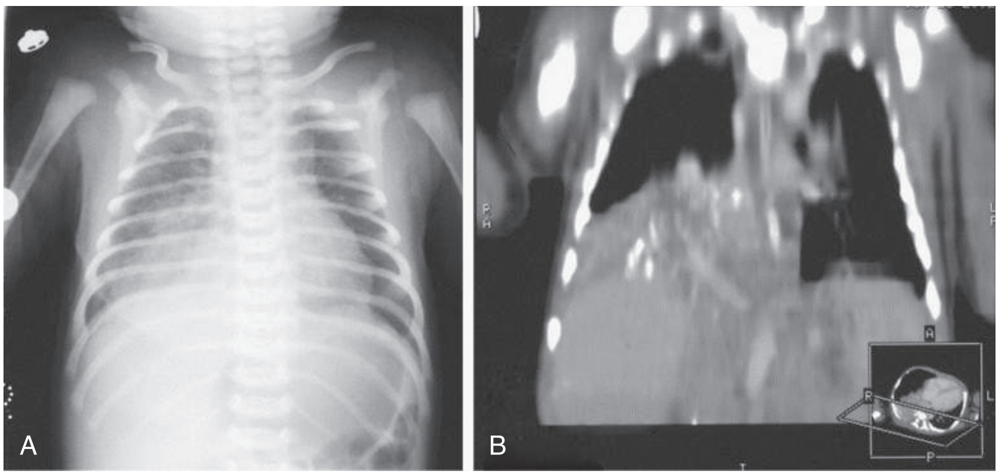

Figure 395-3 A, Plain chest x-ray showing changes in the region of the right lower/middle lobe of the lung. **B,** CT showing parenchymal changes in the right lower lobe of the lung in keeping with a sequestration. *(From Corbett HJ, Humphrey GME: Pulmonary sequestration,* Paediatr Respir Rev *5:59–68, 2004.)*

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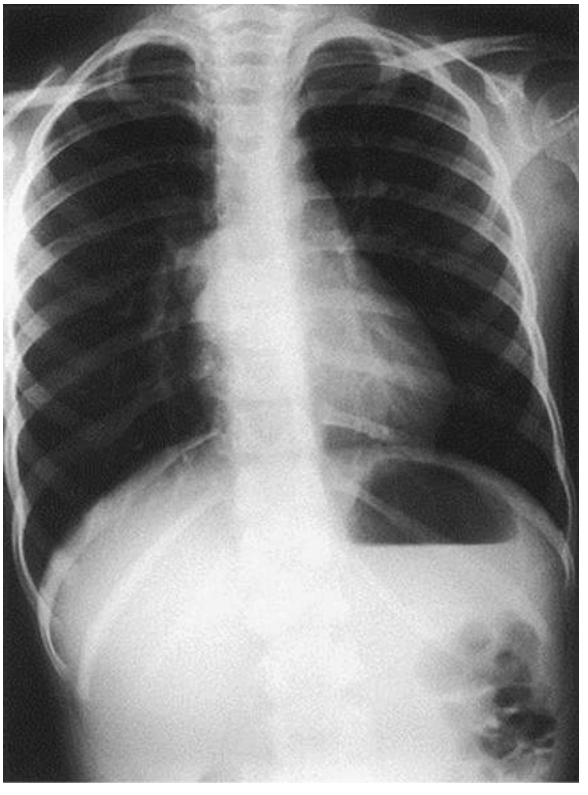

Figure 395-4 Chest x-ray showing an ovoid, well-defined, soft-tissue density causing splaying of the carina due to bronchogenic cyst. *(From Williams HJ, Johnson KJ: Imaging of congenital cystic lung lesions,* Paediatr Respir Rev *3:120–127, 2002.)*

infrequent. Diagnosis may be precipitated by enlargement of the cyst, which causes symptoms by pressure on an adjacent airway. When the diagnosis is delayed until an infection occurs, the ciliated epithelium may be lost, and accurate pathologic diagnosis is then impossible. Cysts are rarely demonstrable at birth. Later, some cysts become symptomatic by becoming infected or by enlarging and compromising the function of an adjacent airway.

CLINICAL MANIFESTATIONS AND TREATMENT

Fever, chest pain, and productive cough are the most common presenting symptoms. Dysphagia may be present; some bronchogenic cysts are asymptomatic. A chest radiograph reveals the cyst, which can contain an air–fluid level (Fig. 395-4). CT scan or MRI is obtained in most cases to better demonstrate anatomy and extent of lesion before surgical resection. Treatment of symptomatic cysts is surgical excision after appropriate antibiotic management. Asymptomatic cysts are generally excised in view of the high rate of infection.

Bibliography is available at Expert Consult.

395.6 Congenital Pulmonary Lymphangiectasia

Joshua A. Blatter and Jonathan D. Finder

ETIOLOGY AND PATHOLOGY

Congenital pulmonary lymphangiectasia is characterized by greatly dilated lymphatic ducts throughout the lung. It can occur in 3 pathologic circumstances: **pulmonary venous obstruction** that produces an elevated transvascular pressure and engorges the pulmonary lymphatics; **generalized lymphangiectasia**, as a generalized disease of several organ systems, including lungs and the intestines (can be associated with Noonan syndrome); and **primary lymphangiectasia** limited to the lung as a manifestation of an abnormality in lymphatic development.

CLINICAL MANIFESTATIONS AND TREATMENT

Children with pulmonary venous obstruction or severe pulmonary lymphangiectasia present with dyspnea and cyanosis in the newborn period. Hydrops fetalis may be diagnosed antenatally. Chest radiographs reveal diffuse, dense, reticular densities with prominence of Kerley B lines. Pleural effusions are common; thoracentesis will reveal chylothorax in this setting. If the lung is not completely involved, the spared areas appear hyperlucent. Respiration is compromised because of impaired diffusion and decreased pulmonary compliance. The diagnosis can be suggested by CT scan and/or cardiac catheterization; definitive diagnosis requires lung biopsy (either thoracoscopic or open).

Treatment is supportive and includes administration of oxygen, mechanical ventilation, nutritional support (including gastrostomy placement and use of feedings containing medium-chain triglycerides), and careful fluid management with diuretics. Primary pulmonary lymphangiectasia can produce severe pulmonary dysfunction that can require long-term mechanical ventilation; long-term survival and resolution of respiratory insufficiency is possible even in severe cases. Occasionally, the pulmonary venous obstruction is secondary to left-sided cardiac lesions; relief of the latter can produce improvement in pulmonary dysfunction. Generalized lymphangiectasia produces milder pulmonary dysfunction, and survival to mid-childhood and beyond is not unusual.

Bibliography is available at Expert Consult.

395.7 Lung Hernia

Joshua A. Blatter and Jonathan D. Finder

ETIOLOGY AND PATHOLOGY

A lung hernia is a protrusion of the lung beyond its normal thoracic boundaries. Approximately 20% are congenital, with the remainder being noted after chest trauma or thoracic surgery or in patients with pulmonary diseases such as cystic fibrosis (see Chapter 403) or asthma (see Chapter 144), which cause frequent cough and generate high intrathoracic pressure. A congenital weakness of the suprapleural membrane (Sibson fascia) or musculature of the neck can play a role in the appearance of a lung hernia. More than half of congenital lung hernias and almost all acquired hernias are **cervical.** Congenital cervical hernias usually occur anteriorly through a gap between the scalenus anterior and sternocleidomastoid muscles. Cervical herniation is usually prevented by the trapezius muscle (posteriorly, at the thoracic inlet) and by the 3 scalene muscles (laterally).

CLINICAL MANIFESTATIONS AND TREATMENT

The presenting sign of a cervical hernia (Sibson hernia) is usually a neck mass noticed while straining or coughing. Some lesions are asymptomatic and detected only when a chest film is taken for another reason. Findings on physical examination are normal except during Valsalva maneuver, when a soft bulge may be noticed in the neck. In most cases, no treatment is necessary, although these hernias can cause problems during attempts to place a central venous catheter through the jugular or subclavian veins. They can resolve spontaneously.

Paravertebral or parasternal hernias are usually associated with rib anomalies. Intercostal hernias usually occur parasternally, where the external intercostal muscle is absent. Posteriorly, despite the seemingly inadequate internal intercostal muscle, the paraspinal muscles usually prevent herniation. Straining, coughing, or playing a musical

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instrument can have a role in causing intercostal hernias, but in most cases, there is probably a preexisting defect in the thoracic wall.

Surgical treatment for lung hernia is occasionally justified for cosmetic reasons. In patients with severe chronic pulmonary disease and chronic cough and for whom cough suppression is contraindicated, permanent correction might not be achieved.

Bibliography is available at Expert Consult.

395.8 Other Congenital Malformations of the Lung

Joshua A. Blatter and Jonathan D. Finder

CONGENITAL LOBAR EMPHYSEMA AND PULMONARY CYSTS

See Chapter 392.

PULMONARY ARTERIOVENOUS MALFORMATION

See Chapters 432 and 444.

BRONCHOBILIARY FISTULA

A bronchobiliary fistula consists of a fistulous connection between the right middle lobe bronchus and the left hepatic ductal system. Although diagnosis can be delayed until adulthood, this rare anomaly typically manifests with life-threatening bronchopulmonary infections in early infancy. Girls are more commonly affected. *Definitive diagnosis* requires endoscopy or exploratory surgery. *Treatment* includes surgical excision of the entire intrathoracic portion of the fistula. If the hepatic portion of the fistula does not communicate with the biliary system or duodenum, the involved segment might also have to be resected. Bronchobiliary communications also occur as acquired lesions resulting from hepatic disease complicated by infection.

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Table 396-1 Etiology of Pulmonary Edema

INCREASED PULMONARY CAPILLARY PRESSURE
Cardiogenic, such as left ventricular failure
Noncardiogenic, as in pulmonary venoocclusive disease, pulmonary venous fibrosis, mediastinal tumors
INCREASED CAPILLARY PERMEABILITY
Bacterial and viral pneumonia
Acute respiratory distress syndrome
Inhaled toxic agents
Circulating toxins
Vasoactive substances such as histamine, leukotrienes, thromboxanes
Diffuse capillary leak syndrome, as in sepsis
Immunologic reactions, such as transfusion reactions
Smoke inhalation
Aspiration pneumonia/pneumonitis
Drowning and near drowning
Radiation pneumonia
Uremia
LYMPHATIC INSUFFICIENCY
Congenital and acquired
DECREASED ONCOTIC PRESSURE
Hypoalbuminemia, as in renal and hepatic diseases, protein-losing states, and malnutrition
INCREASED NEGATIVE INTERSTITIAL PRESSURE
Upper airway obstructive lesions, such as croup and epiglottitis
Reexpansion pulmonary edema
MIXED OR UNKNOWN CAUSES
Neurogenic pulmonary edema
High-altitude pulmonary edema
Eclampsia
Pancreatitis
Pulmonary embolism
Heroin (narcotic) pulmonary edema

Modified from Robin E, Carroll C, Zelis R: Pulmonary edema, N Engl J Med *288:239, 292, 1973; and Desphande J, Wetzel R, Rogers M: In Rogers M, editor:* Textbook of pediatric intensive care, *ed 3, Baltimore, 1996, Williams & Wilkins, pp. 432–442.*

Chapter 396
Pulmonary Edema

Robert L. Mazor and Thomas P. Green

A sequela of several different pathologic processes, pulmonary edema is an excessive accumulation of fluid in the interstitium and air spaces of the lung resulting in oxygen desaturation, decreased lung compliance, and respiratory distress. The condition is common in the acutely ill child.

PATHOPHYSIOLOGY

Although pulmonary edema is traditionally separated into two categories according to cause (*cardiogenic* and *noncardiogenic*), the end result of both processes is a net fluid accumulation within the interstitial and alveolar spaces. Noncardiogenic pulmonary edema, in its most severe state, is also known as **acute respiratory distress syndrome** (see Chapters 71 and 373).

The hydrostatic pressure and colloid osmotic (oncotic) pressure on either side of a pulmonary vascular wall, along with vascular permeability, are the forces and physical factors that determine fluid movement through the vessel wall. Baseline conditions lead to a net filtration of fluid from the intravascular space into the interstitium. This "extra" interstitial fluid is usually rapidly reabsorbed by pulmonary lymphatics. Conditions that lead to altered vascular permeability, increased pulmonary vascular pressure, and decreased intravascular oncotic pressure increase the net flow of fluid out of the vessel (Table 396-1). Once the capacity of the lymphatics for fluid removal is exceeded, water accumulates in the lung.

To understand the sequence of lung water accumulation, it is helpful to consider its distribution among 4 distinct compartments, as follows:

- *Vascular compartment:* This compartment consists of all blood vessels that participate in fluid exchange with the interstitium. The vascular compartment is separated from the interstitium by capillary endothelial cells. Several endogenous inflammatory mediators, as well as exogenous toxins, are implicated in the pathogenesis of pulmonary capillary endothelial damage, leading to the "leakiness" seen in several systemic processes.
- *Interstitial compartment:* The importance of this space lies in its interposition between the alveolar and vascular compartments. As fluid leaves the vascular compartment, it collects in the interstitium before overflowing into the air spaces of the alveolar compartment.
- *Alveolar compartment:* This compartment is lined with type 1 and type 2 epithelial cells. These epithelial cells have a role in active fluid transport from the alveolar space, and they act as a barrier to exclude fluid from the alveolar space. The potential fluid volume of the alveolar compartment is many times greater than that of the interstitial space, perhaps providing another reason that alveolar edema clears more slowly than interstitial edema.

- *Pulmonary lymphatic compartment:* There is an extensive network of pulmonary lymphatics. Excess fluid present in the alveolar and interstitial compartments is drained via the lymphatic system. When the capacity for drainage of the lymphatics is surpassed, fluid accumulation occurs.

ETIOLOGY

The specific clinical findings vary according to the underlying mechanism (see Table 396-1).

Transudation of fluid as a result of increased pulmonary vascular pressure *(capillary hydrostatic pressure)* occurs in several cardiac processes. A significant left-to-right shunting lesion, such as a septal defect, leads to a pressure and volume load on the pulmonary vasculature. The resultant pulmonary edema is one of the hallmarks of congestive heart failure. Left ventricular failure, mitral valve disease, and pulmonary venous obstructive lesions cause increased "backpressure" in the pulmonary vasculature. This results in an increase in pulmonary capillary pressure.

Increased capillary permeability is usually secondary to endothelial damage. Such damage can occur secondary to direct injury to the alveolar epithelium or indirectly through systemic processes that deliver circulating inflammatory mediators or toxins to the lung. Inflammatory mediators (tumor necrosis factor, leukotrienes, thromboxanes) and vasoactive agents (nitric oxide, histamine) formed during pulmonary and systemic processes potentiate the altered capillary permeability that occurs in many disease processes, with sepsis being a common cause.

Fluid homeostasis in the lung largely depends on drainage via the lymphatics. Experimentally, pulmonary edema occurs with obstruction of the lymphatic system. Increased lymph flow and dilation of lymphatic vessels occur in chronic edematous states.

A decrease in intravascular oncotic pressure leads to pulmonary edema by altering the forces promoting fluid reentry into the vascular space. This occurs in dilutional disorders, such as fluid overload with hypotonic solutions, and in protein-losing states, such as nephrotic syndrome and malnutrition.

The excessive negative interstitial pressure seen in upper airway diseases, such as croup and laryngospasm, may promote pulmonary edema. Aside from the physical forces present in these diseases, other mechanisms may also be involved. Theories implicate an increase in CO_2 tension, decreased O_2 tension, and extreme increases in cardiac afterload, leading to transient cardiac insufficiency.

The mechanism causing neurogenic pulmonary edema is not clear. A massive sympathetic discharge secondary to a cerebral injury may produce increased pulmonary and systemic vasoconstriction, resulting in a shift of blood to the pulmonary vasculature, an increase in capillary pressure, and edema formation. Inflammatory mechanisms may also play a role by increasing capillary permeability.

The mechanism responsible for high-altitude pulmonary edema is unclear, but it may also be related to sympathetic outflow, increased pulmonary vascular pressures, and hypoxia-induced increases in capillary permeability (see Chapter 73).

Active ion transport followed by passive, osmotic water movement is important in clearing the alveolar space of fluid. There are some experimental data that β agonists and growth factors increase alveolar fluid removal. Interindividual genetic differences in the rates of these transport processes may be important in determining which individuals are susceptible to altitude-related pulmonary edema. Although the existence of these mechanisms suggests that therapeutic interventions may be developed to promote resolution of pulmonary edema, no such therapies currently exist.

CLINICAL MANIFESTATIONS

The clinical features depend on the mechanism of edema formation. In general, interstitial edema and alveolar edema prevent the inflation of alveoli, leading to atelectasis and decreased surfactant production. This results in diminished pulmonary compliance and tidal volume. The patient must increase respiratory effort and/or the respiratory rate so as to maintain minute ventilation. The earliest clinical signs of pulmonary edema include increased work of breathing, tachypnea, and dyspnea. As fluid accumulates in the alveolar space, auscultation reveals fine crackles and wheezing, especially in dependent lung fields. In cardiogenic pulmonary edema, a gallop may be present as well as peripheral edema and jugular venous distention.

Table 396-2 Radiographic Features That May Help Differentiate Cardiogenic from Noncardiogenic Pulmonary Edema

RADIOGRAPHIC FEATURE	CARDIOGENIC EDEMA	NONCARDIOGENIC EDEMA
Heart size	Normal or greater than normal	Usually normal
Width of the vascular pedicle*	Normal or greater than normal	Usually normal or less than normal
Vascular distribution	Balanced or inverted	Normal or balanced
Distribution of edema	Even or central	Patchy or peripheral
Pleural effusions	Present	Not usually present
Peribronchial cuffing	Present	Not usually present
Septal lines	Present	Not usually present
Air bronchograms	Not usually present	Usually present

*The width of the vascular pedicle in adults is determined by dropping a perpendicular line from the point at which the left subclavian artery exits the aortic arch and measuring across to the point at which the superior vena cava crosses the right mainstem bronchus. A vascular pedicle width >70 mm on a portable digital anteroposterior radiograph of the chest obtained when the patient is supine is optimal for differentiating high from normal-to-low intravascular volume.

From Ware LB, Matthay MA: Acute pulmonary edema, N Engl J Med *353:2788–2796, 2005.*

Chest radiographs can provide useful ancillary data, although findings of initial radiographs may be normal. Early radiographic signs that represent accumulation of interstitial edema include peribronchial and perivascular cuffing. Diffuse streakiness reflects interlobular edema and distended pulmonary lymphatics. Diffuse, patchy densities, the so-called butterfly pattern, represent bilateral interstitial or alveolar infiltrates and are a late sign. Cardiomegaly is often seen with cardiogenic causes of pulmonary edema. Heart size is usually normal in noncardiogenic pulmonary edema (Table 396-2). Chest tomography demonstrates edema accumulation in the dependent areas of the lung. As a result, changing the patient's position can alter regional differences in lung compliance and alveolar ventilation.

Measurement of **brain natriuretic peptide**, often elevated in heart disease, can help differentiate cardiac from pulmonary causes of pulmonary edema. A brain natriuretic peptide level >500 pg/mL suggests heart disease; a level <100 pg/mL suggests lung disease.

TREATMENT

The treatment of a patient with noncardiogenic pulmonary edema is largely supportive, with the primary goal to ensure adequate ventilation and oxygenation. Additional therapy is directed toward the underlying cause. Patients should receive supplemental oxygen to increase alveolar oxygen tension and pulmonary vasodilation. Patients with pulmonary edema of cardiogenic causes should be managed with diuretics, inotropic agents and systemic vasodilators to reduce left ventricular afterload (see Chapter 442). Diuretics are also valuable in the treatment of pulmonary edema associated with total body fluid overload (sepsis, renal insufficiency). Morphine is often helpful as a vasodilator and a mild sedative.

Positive airway pressure improves gas exchange in patients with pulmonary edema. In tracheally intubated patients, positive end-expiratory pressure can be used to optimize pulmonary mechanics. Noninvasive forms of ventilation, such as mask or nasal prong

continuous positive airway pressure, are also effective. The mechanism by which positive airway pressure improves pulmonary edema is not entirely clear but is not associated with decreasing lung water. Rather, continuous positive airway pressure prevents complete closure of alveoli at the low lung volumes present at the end of expiration. It may also recruit already collapsed alveolar units. This leads to increased functional residual capacity and improved pulmonary compliance, improved surfactant function, and decreased pulmonary vascular resistance. The net effect is to decrease the work of breathing, improve oxygenation, and decrease cardiac afterload.

When mechanical ventilation becomes necessary, especially in noncardiogenic pulmonary edema, care must be taken to minimize the risk of development of complications from barotrauma, including pneumothorax, pneumomediastinum, and primary alveolar damage (see Chapter 71.1). Lung protective strategies include setting low tidal volumes, relatively high positive end-expiratory pressure, and allowing for permissive hypercapnia.

High-altitude pulmonary edema should be managed with altitude descent and supplemental oxygen. Portable continuous positive airway pressure or a portable hyperbaric chamber is also helpful. Nifedipine (10 mg initially, and then 20-30 mg by slow release every 12-24 hr) in adults is also helpful. If there is a history of high-altitude pulmonary edema, nifedipine and β-adrenergic agonists (inhaled) may prevent recurrence (see Chapter 73).

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Chapter 397
Aspiration Syndromes
John L. Colombo

Aspiration of material that is foreign to the lower airway produces a varied clinical spectrum ranging from an asymptomatic condition to acute life-threatening events, such as occur with massive aspiration of gastric contents or hydrocarbon products. Other chapters discuss mechanical obstruction of large- or intermediate-size airways as occurs with foreign bodies (see Chapter 387) and infectious complications of aspiration and recurrent microaspiration (see Chapter 398), such as may occur with gastroesophageal reflux (see Chapter 323.1) or dysphagia (see Chapter 306). Occult aspiration of nasopharyngeal secretions into the lower respiratory tract is a normal event in healthy people, usually without apparent clinical significance.

GASTRIC CONTENTS

Aspiration of substantial amounts of gastric contents typically occurs in the context of vomiting. It is an infrequent complication of general anesthesia, gastroenteritis, or altered level of consciousness. Among 63,180 pediatric patients undergoing general anesthesia, 24 cases of aspiration occurred, but symptoms developed in only 9. Pathophysiologic consequences can vary, depending primarily on the pH and volume of the aspirate and the amount of particulate material. Increased clinical severity is noted with volumes greater than approximately 0.8 mL/kg and/or pH <2.5. Hypoxemia, hemorrhagic pneumonitis, atelectasis, intravascular fluid shifts, and pulmonary edema all occur rapidly after massive aspiration. These occur earlier, become more severe, and last longer with acid aspiration. Most clinical changes are present within minutes to 1-2 hr after the aspiration event. In the next 24-48 hr, there is a marked increase in lung parenchymal neutrophil infiltrations, mucosal sloughing, and alveolar consolidation that often correlates with increasing infiltrates on chest radiographs. These changes tend to occur significantly later and are more prolonged after aspiration of particulate material. Although infection usually does not have a role in initial lung injury after aspiration of gastric contents, aspiration may impair pulmonary defenses, predisposing the patient to secondary bacterial pneumonia. In the patient who has shown clinical improvement but then demonstrates clinical worsening, especially with fever and leukocytosis, secondary bacterial pneumonia should be suspected.

Treatment

If large-volume or highly toxic substance aspiration occurs in a patient who already has an artificial airway in place, it is important to perform immediate suctioning of the airway. If immediate suctioning cannot be performed, later suctioning or bronchoscopy is usually of limited therapeutic value except when there is suspicion of significant particulate aspiration. Attempts at acid neutralization are not warranted because acid is rapidly neutralized by the respiratory epithelium. Patients in whom large-volume or toxic aspiration is suspected should be observed, should undergo oxygenation measurement by oximetry or blood gas analysis, and should undergo a chest radiograph, even if they are asymptomatic. If the chest radiograph findings and oxygen saturation are normal, and the patient remains asymptomatic, home observation, after a period of observation in the hospital or office, is adequate. No treatment is indicated at that time, but the caregivers should be instructed to bring the child back in for medical attention should respiratory symptoms or fever develop. For patients who present with abnormal findings or in whom such findings develop during observation, oxygen therapy is given to correct hypoxemia. Endotracheal intubation and mechanical ventilation are often necessary for more severe cases. Bronchodilators may be tried, although they are usually of limited benefit. Animal studies indicate that treatment with corticosteroids does not provide benefit, unless given nearly simultaneously with the aspiration event; use of these agents may increase the risk of secondary infection. Prophylactic antibiotics are not indicated, although in the patient with limited reserve, early antibiotic coverage may be appropriate. If used, antibiotics that cover for anaerobic microbes should be considered. If the aspiration event occurs in a hospitalized or chronically ill patient, coverage of *Pseudomonas*, *Staphylococcus aureus,* and enteric Gram-negative organisms should also be considered. If empiric antibiotics are given, they should be discontinued when cultures and course warrant. A mortality rate of ≤5% is seen if 3 or fewer lobes are involved. Unless complications develop, such as infection or barotrauma, most patients recover in 2-3 wk. Prolonged lung damage may persist, including scarring, bronchiolitis obliterans, and bronchiectasis.

Prevention

Prevention of aspiration should always be the goal when airway manipulation is necessary for intubation or other invasive procedures. Feeding with enteral tubes passed beyond the pylorus, elevating the head of the bed 30-45 degrees in mechanically ventilated patients, and oral decontamination reduce the incidence of aspiration complications in the intensive care unit. Minimizing use of sedation, monitoring for gastric residuals, and gastric acid suppression may all help prevent aspiration. However, the latter is not without some controversy. Any patient with altered consciousness, especially one who is receiving tube feedings, should be considered at high risk for aspiration. Preoperative restriction of oral fluids to otherwise normal children for 6 hr does not appear to provide benefit compared to restriction for only 2 hr in terms of risk for aspiration.

HYDROCARBON ASPIRATION

Aspiration and resulting pneumonitis are typically the most dangerous consequences of acute hydrocarbon ingestion (see Chapter 63). Although significant pneumonitis occurs in <2% of all hydrocarbon ingestions, an estimated 20 deaths occur annually from hydrocarbon aspiration in both children and adults. Some of these deaths represent suicides. Hydrocarbons with lower surface tensions (gasoline,

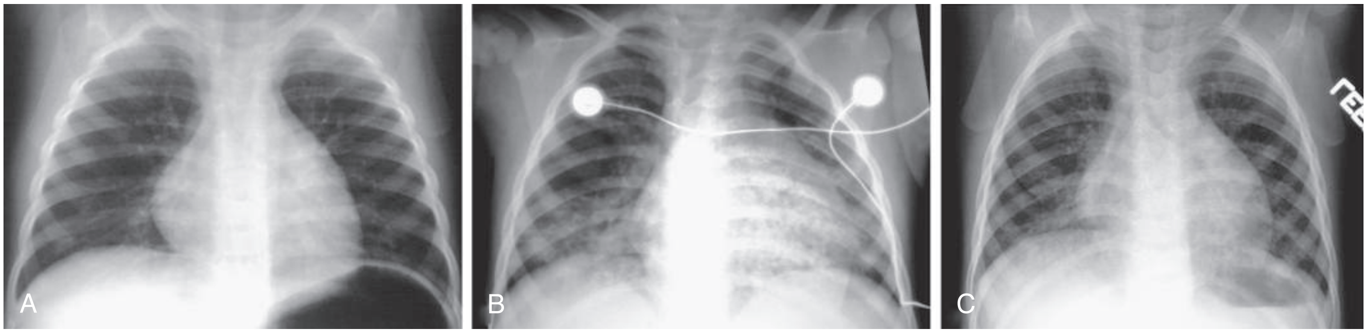

Figure 397-1 Chest radiographs of a 17 mo old who ingested furniture polish. **A,** Three hours after ingestion, the lungs are clear. **B,** At 24 hr, there are bibasilar coalescing nodular opacities. **C,** Three days later there is much clearing. *(From Slovis TL, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, p. 1287.)*

turpentine, naphthalene) have more potential for aspiration toxicity than heavier mineral or fuel oils. Ingestion of >30 mL (approximate volume of an adult swallow) of hydrocarbon is associated with an increased risk of severe pneumonitis. Clinical findings including chest retractions, grunting, cough, and fever may occur as soon as 30 min after aspiration or may be delayed for several hours. Lung radiographic changes usually occur within 2-8 hr, peaking in 48-72 hr (Fig. 397-1). Pneumatoceles and pleural effusions may occur. Patients presenting with cough, shortness of breath, or hypoxemia are at high risk for pneumonitis. Persistent pulmonary function abnormalities can be present many years after hydrocarbon aspiration. Other organ systems, especially the liver, central nervous system, and heart, may suffer serious injury. Cardiac dysrhythmias may occur and may be exacerbated by hypoxia and acid–base or electrolyte disturbances.

Treatment

Gastric emptying is contraindicated in nearly all situations because the risk of aspiration is greater than any systemic toxicity. Treatment is generally supportive, consisting of oxygen, fluids, and ventilatory support, and rarely extracorporeal membrane oxygenation, as necessary. Exogenous surfactant administration has been described as helpful in case reports. The child who has no symptoms and normal chest radiograph findings should be observed for 6-8 hr to ensure safe discharge. Certain hydrocarbons have more inherent systemic toxicity. The pneumonic **CHAMP** refers collectively to the following hydrocarbons: ***c***amphor, ***h***alogenated carbons, ***a***romatic hydrocarbons, and those associated with ***m***etals and ***p***esticides. Patients who ingest these compounds in volumes >30 mL, such as might occur with intentional overdose, may benefit from gastric emptying. This is still a high-risk procedure that can result in further aspiration. If a cuffed endotracheal tube can be placed without inducing vomiting, this procedure should be considered, especially in the presence of altered mental status. Treatment of each case should be considered individually, with guidance from a poison control center.

Other substances that are particularly toxic and cause significant lung injury when aspirated or inhaled include baby powder, chlorine, shellac, beryllium, and mercury vapors. Repeated exposure to low concentrations of these agents can lead to chronic lung disease, such as interstitial pneumonitis and granuloma formation. Corticosteroids may help reduce fibrosis development and improve pulmonary function, although the evidence for this benefit is limited.

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Chapter 398

Chronic Recurrent Aspiration

John L. Colombo

ETIOLOGY

Repeated aspiration of even small quantities of gastric, nasal, or oral contents can lead to recurrent bronchitis or bronchiolitis; recurrent pneumonia; atelectasis; wheezing; cough; apnea; and/or laryngospasm. Pathologic outcomes include granulomatous inflammation, interstitial inflammation, fibrosis, lipoid pneumonia, and bronchiolitis obliterans. Most cases clinically manifest as airway inflammation, and are rarely associated with significant morbidity. Table 398-1 lists underlying disorders that are frequently associated with recurrent aspiration. Oropharyngeal incoordination is reportedly the most common underlying problem associated with recurrent pneumonias in hospitalized children. In 2 reports, from 26-48% of such children were found to have dysphagia with aspiration as the underlying problem. Lipoid pneumonia may occur after the use of home/folk remedies involving oral or nasal administration of animal or vegetable oils to treat various childhood illnesses. Lipoid pneumonia has been reported as a complication of these practices in the Middle East, Asia, India, Brazil, and Mexico. The initial underlying disease, language barriers, and a belief that these are not "medications" may delay the diagnosis (see Chapter 4).

Gastroesophageal reflux disease (GERD; see Chapter 323) is also a common underlying finding that may predispose to recurrent respiratory disease, but it is less frequently associated with recurrent pneumonia than is dysphagia (see Chapter 323). GERD is associated with microaspiration and bronchiolitis obliterans in lung transplant recipients. Aspiration has also been observed in infants with respiratory symptoms but no other apparent abnormalities. Recurrent microaspiration has been reported in otherwise apparently normal newborns, especially premature infants. Aspiration is also a risk in patients suffering from acute respiratory illness from other causes, especially respiratory syncytial virus infection (see Chapter 260). Modified barium swallow and videofluoroscopy reveal silent aspiration in these patients. This finding emphasizes the need for a high degree of clinical suspicion for ongoing aspiration in a child with an acute respiratory illness, being fed enterally, who deteriorates unexpectedly.

DIAGNOSIS

Some underlying predisposing factors (see Table 398-1) are frequently clinically apparent but may require specific further evaluation. Initial

Table 398-1 Conditions Predisposing to Aspiration Lung Injury in Children

ANATOMICAL AND MECHANICAL
Tracheoesophageal fistula
Laryngeal cleft
Vascular ring
Cleft palate
Micrognathia
Macroglossia
Cysts, tumors
Achalasia
Esophageal foreign body
Tracheostomy
Endotracheal tube
Nasal or oral feeding tube
Collagen vascular disease (scleroderma, dermatomyositises)
Gastroesophageal reflux disease
Obesity
NEUROMUSCULAR
Altered consciousness
Immaturity of swallowing/Prematurity
Dysautonomia
Increased intracranial pressure
Hydrocephalus
Vocal cord paralysis
Cerebral palsy
Muscular dystrophy
Hypotonia
Myasthenia gravis
Guillain-Barré syndrome
Spinal muscular atrophy
Ataxia-telangiectasia
Cerebral vascular accident
MISCELLANEOUS
Poor oral hygiene
Gingivitis
Prolonged hospitalization
Gastric outlet or intestinal obstruction
Poor feeding techniques (bottle propping, overfeeding, inappropriate foods for toddlers)
Bronchopulmonary dysplasia
Viral infection/bronchiolitis

Figure 398-1 **Chest radiograph of a developmentally delayed 15 yr old with chronic aspiration of oral formula.** Note posterior (dependent areas) distribution with sparing of heart borders.

Figure 398-2 Chest CT scan of same patient as in Figure 398-1. Note lung consolidation in dependent regions is of similar density to subcutaneous fat.

assessment begins with a detailed history and physical examination. The caregiver should be asked about spitting, vomiting, arching, or epigastric discomfort in an older child; the timing of symptoms in relation to feedings; positional changes; and nocturnal symptoms, such as coughing and wheezing. It is important to remember that coughing or gagging may be minimal or absent in a child with a depressed cough or gag reflex. Observation of a feeding is an essential part of the exam when a diagnosis of recurrent aspiration is being considered. Particular attention should be given to nasopharyngeal reflux, difficulty with sucking or swallowing, and associated coughing and choking. Voice changes (wet voice) and noisy (wet) breathing should be noted. The oral cavity should be inspected for gross abnormalities and stimulated to assess the gag reflex. Drooling or excessive accumulation of secretions in the mouth suggests dysphagia. Lung auscultation may reveal transient crackles or wheezes after feeding, particularly in the dependent lung segments.

The diagnosis of recurrent microaspiration is challenging because of the lack of highly specific and sensitive tests (Table 398-2). A plain chest radiograph is the usual initial study for a child in whom recurrent aspiration is suspected. The classic findings of segmental or lobar infiltrates localized to dependent areas may be found (Fig. 398-1), but there are a wide variety of radiographic findings. These findings include diffuse infiltrates, lobar infiltrates, bronchial wall thickening, hyperinflation, and even no detectable abnormalities. CT scans, though generally not indicated to establish a diagnosis of aspiration, may show infiltrates with decreased attenuation suggestive of lipoid pneumonia (Fig. 398-2). A carefully performed barium esophagram is useful in looking for anatomic abnormalities such as vascular ring, stricture, hiatal hernia, and tracheoesophageal fistula. It also yields qualitative information about esophageal motility and, when extended, of gastric emptying. However, primarily because of the very short viewing time, the esophagram is quite insensitive and nonspecific for aspiration or GERD. A modified barium swallow study with videofluoroscopy (videofluoroscopic swallowing study) is generally considered the gold standard for evaluating the swallowing mechanism. This study is preferably done with the assistance of a pediatric feeding specialist and a caregiver in the attempt to simulate the usual feeding technique of the child. The child is seated in normal eating position, and various consistencies of barium or barium-impregnated foods are offered. This study is more sensitive for demonstrating aspiration than bedside assessment or a traditional barium swallow study. The sensitivity of the modified barium swallow study is such that it occasionally detects aspiration in patients without apparent respiratory abnormalities.

Table 398-2 Summary of Diagnostic Tests of Aspiration

EVALUATION	BENEFITS	LIMITATIONS
Chest radiograph	Inexpensive and widely available Assesses accumulation of injury over time	Insensitive to early subtle changes of lung injury
High-resolution CT	Sensitive in detecting lung injury, such as bronchiectasis, tree-in-bud opacities, and bronchial thickening Less radiation than conventional CT Assesses accumulation of injury over time	More radiation exposure than plain radiograph Expensive
Video swallow study	Evaluates all phases of swallowing Evaluates multiple consistencies Feeding recommendations made at time of study	Information limited if child consumes only small quantities Difficult to perform in child who has not been feeding by mouth Radiation exposure proportional to study duration Cannot be performed at bedside Limited evaluation of anatomy Evaluates 1 moment in time Expensive
FEES/with sensory testing	Ability to thoroughly evaluate functional anatomy Evaluates multiple consistencies Can assess risk of aspiration in non-orally feeding child; airway protective reflexes can be assessed Feeding recommendations made at time of study Visual feedback for caregivers Can be performed at bedside No radiation exposure	Blind to esophageal phase and actual swallow Invasive and may not represent physiological swallowing conditions Evaluates 1 moment in time Not widely available Expensive
BAL	Evaluates anatomy of entire upper and lower airways Samples the end-organ of damage Sample available for multiple cytological and microbiologic tests Widely available	Uncertainty regarding interpretation of lipid-laden macrophage index Index cumbersome to calculate Requires sedation or anesthesia Invasive Expensive
Esophageal pH monitoring	Current gold standard for diagnosis of Acid gastroesophageal reflux Established normative data in children	Blind to majority of reflux (nonacid) events Difficult to establish causal relationship between gastroesophageal reflux and aspiration Somewhat invasive Evaluates short time interval
Esophageal impedance monitoring	Likely gold standard for diagnosis of GERD with supraesophageal manifestations Able to detect acid and nonacid reflux events Detects proximal reflux events Able to evaluate for GERD without stopping medications	Lack of normative data for children Somewhat invasive Expensive and cumbersome to interpret Not widely available Evaluates short time interval
Gastroesophageal scintigraphy	Performed under physiologic conditions Low radiation exposure	Poor sensitivity May not differentiate between aspiration from dysphagia or GERD
Radionuclide salivagram	Child does not have to be challenged with food bolus Low radiation exposure	Unknown sensitivity Unknown relationship to disease outcomes Evaluates 1 moment in time
Dye studies	Can be constructed as screening test or confirmatory test Can evaluate aspiration of secretions or feeds Repeating over time allows for broader evaluation	Uncertainty in interpretation owing to variability of technique Can only be performed in children with tracheostomies
Other biomarkers (pepsin, bile acids) milk protein	Theoretical high specificity and sensitivity	Limited availability and standardization Variable results to date

BAL, bronchoalveolar lavage; FEES, fiberoptic-endoscopic evaluation of swallowing; GERD, gastroesophageal reflux disease.
Modified from Boesch RP, Daines C, Willging JP, et al: Advances in the diagnosis and management of chronic pulmonary aspiration in children, Eur Respir J *28:847–861, 2006; and Tutor JD, Gosa MM: Dysphagia and aspiration in children,* Pediatr Pulmonol *47(4):321–337, 2012.*

A gastroesophageal "milk" scintiscan offers theoretical advantages over a barium swallow in being more physiologic and giving a longer window of viewing than the barium esophagram for detecting aspiration and GERD. However, this study has been found to have a low sensitivity and provides relatively little anatomic detail. Another radionuclide scan termed the "salivagram" may also be useful to assess aspiration of esophageal contents. When this scan is performed by experienced personnel, its sensitivity appears to be comparable to that of the modified barium swallow study. The use of fiberoptic endoscopic evaluation of swallowing has been found useful in adult and some pediatric patients, to observe swallowing directly without radiation exposure. The child's reaction to placement of the endoscope may

alter the assessment of function, depending on level of comfort and cooperation.

Tracheobronchial aspirates can be examined for numerous entities to evaluate for aspiration. For patients with artificial airways, the use of an oral dye and visual examination of tracheal secretions is useful. This test should not be done on a chronic basis, such as in tube feedings, because of possible dye toxicity. In using this test acutely, the best method is to place a few drops of dye on the patient's tongue and perform subsequent suctioning of the airway over the next several minutes. Quantitation of lipid-laden alveolar macrophages from bronchial aspirates has been shown to be a sensitive test for aspiration in children, but false-positive tests occur, especially with endobronchial obstruction, use of intravenous lipids, sepsis, and pulmonary bleeding. Bronchial washings may also be examined for various food substances, including lactose, glucose, food fibers, and milk antigens, as well as pepsin. Specificity and sensitivity of these tests have not been well studied.

TREATMENT

If chronic aspiration is associated with another underlying medical condition, treatment should be directed toward that problem. The level of morbidity from respiratory problems should determine the level of intervention. Often milder dysphagia can be treated with alteration of feeding position, limiting texture of foods to those best tolerated on modified barium esophagram (usually thicker foods), or limiting quantity per feeding. Currently evidence is lacking regarding the advisability of restricting oral intake of water by children whose aspiration is largely of thin fluids. Nasogastric tube feedings can be utilized temporarily during periods of transient vocal cord dysfunction or other dysphagia. Postpyloric feedings may also be helpful, especially if gastroesophageal reflux is present, although this does not eliminate reflux. There are several surgical procedures that may be considered. Tracheostomy (see Chapter 385.1), although sometimes predisposing to aspiration, may provide overall benefit from improved bronchial hygiene and the ability to suction aspirated material. Use of a one-way (Passy-Muir) valve on a tracheostomy tube has been shown to improve swallowing. Fundoplication with gastrostomy or jejunostomy feeding tube will reduce the probability of gastroesophageal reflux-induced aspiration, but recurrent pneumonias often persist because of dysphagia and presumed aspiration of upper airway secretions. Medical treatment with anticholinergics, such as glycopyrrolate or scopolamine, may significantly reduce morbidity from salivary aspiration but often has side effects. Aggressive surgical intervention with salivary gland excision, ductal ligation, laryngotracheal separation, or esophagogastric disconnection can be considered in severe, unresponsive cases. Although usually reserved for the most severe cases, surgical therapy may significantly improve quality of life and ease of care for some patients.

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Chapter 399

Immune and Inflammatory Lung Disease

399.1 Hypersensitivity Pneumonia

Kevin J. Kelly

Hypersensitivity pneumonia (HP), aptly called *extrinsic allergic alveolitis* because the inciting agent is almost uniformly inhaled from the environment, is a complex immunologic-mediated syndrome of the pulmonary alveoli and interstitium. There are numerous specific disease names based on the origin of the offending antigen that is inhaled to describe HP. Prompt recognition of the signs and symptoms allows for complete reversal of the disease without long-term adverse consequences if the source of the exposure is recognized and abated. Failure to recognize the disease early may lead to chronic irreversible lung changes with persistent symptoms in the patient.

ETIOLOGY

The most common sources of offending agents that cause HP include agricultural aerosols, inhaled protein antigens from animals, antigens from microorganisms of bacteria, fungi, or protozoan origin, as well as chemicals of low and high molecular weight (Table 399-1). Although a large number of inciting agents are associated with *occupational diseases* in which children do not regularly work, there are many similar antigen sources in a nonoccupational environment and teenage work exposures that may occur causing the same disease. In addition to HP, the same antigens may lead to allergic asthma or chronic bronchitis as seen with animal proteins, contaminated metal working fluids, and other inhaled antigens.

Primary sources of HP in children have been the result of exposure to **pet birds** (or feathers in bedding) such as parakeets, canaries, cockatiels, or cockatoos or homes contaminated with pigeon antigens from home breeders or contamination. Humidifiers and hot tubs are notorious for contamination with **thermophilic organisms** as well as *Mycobacterium avium* complex. Mold from prior flooding or damp condensation represents an increasing problem experienced by clinicians since the building of homes with inadequate ventilation and insufficient air turnover. Allergic diseases such as asthma, chronic rhinitis, and HP may be seen from the same sources. Other family members may have symptoms of asthma or rhinitis while another may have HP.

CLASSIFICATION AND PATHOGENESIS

HP has been traditionally classified as acute, subacute, or chronic. This classification arose prior to more refined diagnostic modalities such as **high-resolution computerized tomography (HRCT)** scanning of the lungs and more refined immunologic diagnostic tests on **bronchoalveolar lavage (BAL)**. Distinguishing chronic disease from subacute disease is difficult without clear differentiating criteria, but a diagnosis of HP at any stage results in the clinician recommending very specific interventions for improvement. HP is characterized as (1) acute nonprogressive and intermittent, (2) acute progressive and intermittent, (3) chronic nonprogressive, and (4) chronic progressive (Table 399-2).

The sensitivity of the complete criteria is lower than desired as not all patients will have abnormal radiography or the findings of positive precipitins to the offending antigen. The specificity of the criteria may also be problematic. Screening for pigeon breeder's lung disease among a cohort of pigeon breeders will demonstrate that 30% or more of the pigeon breeders have immunoglobulin (Ig) G precipitins to pigeon dropping antigens while only a small number will have disease. Genetic and epigenetic factors yet to be identified are likely involved in determining who develops disease.

A diagnosis of HP is certain when the known exposure with immune response to the offending antigen is identified; the medical history and physical finding are abnormal on examination; BAL and lung biopsy are abnormal. Some clinicians have foregone the lung biopsy when a cluster of cases occurs and 1 patient biopsy is abnormal already.

The immune mechanisms involved include morphologic changes seen with immune complex-mediated disease, especially in the acute phase, accompanied complement activation followed by delayed-type hypersensitivity response. The acute phase of the disease shows alveolitis with a mixed cellular infiltration with lymphocytes, macrophage, plasma cells, and neutrophils. Continued exposure results in the formation of loose, noncaseating granuloma located near the respiratory or terminal bronchioles. It is critical when a biopsy is being performed (transbronchial or surgical) that the pathologist knows that HP is being considered as there are other **interstitial lung diseases** that produce

Table 399-1 Antigen Sources Associated with Specific Causes of Hypersensitivity Pneumonitis

HYPERSENSITIVITY PNEUMONITIS	ANTIGEN SOURCE
Bagassosis (mold on pressed sugar cane)	*Thermoactinomyces sacchari* *Thermoactinomyces vulgaris*
Bat lung (bat droppings)	Bat serum protein
Bible printer's lung	Moldy typesetting water
Bird fancier's lung (parakeets, budgerigars, pigeons)	Droppings, feathers, serum proteins
Byssinosis ("brown lung") (unclear if a true cause of hypersensitivity pneumonitis; asthma is common)	Cotton mill dust (carding and spinning areas of cotton, flax, and soft-hemp)
Canary fancier's lung	Serum proteins
Cheese washer's lung (moldy cheese)	*Penicillium casei* *Aspergillus clavatus*
Chemical hypersensitivity pneumonitis	Diphenylmethane diisocyanate (MDI) Toluene diisocyanate (TDI)
Coffee worker's lung	Coffee-bean dust
Composter's lung	*T. vulgaris* *Aspergillus* species
Contaminated basement (sewage) pneumonitis	*Cephalosporium*
Coptic lung (mummy handler's lung)	Cloth wrappings of mummies
Detergent worker's lung (washing powder lung)	*Bacillus subtilis* enzymes
Dry rot lung	*Merulius lacrymans*
Duck fever	Feathers, serum proteins
Epoxy resin lung	Phthalic anhydride (heated epoxy resin)
Esparto dust (mold in plaster dust)	*Aspergillus fumigatus* Thermophilic actinomycetes
Fish meal worker's lung	Fish meal
Furrier's lung (sewing furs; animal fur dust)	Animal pelts
Grain measurer's lung	Cereal grain (*Sporobolomyces*) Grain dust (mixture of dust, silica, fungi, insects, and mites)
Hot-tub lung (mists; mold on ceiling and around tub)	*Cladosporium* spp. *Mycobacterium avium* complex
Humidifier fever	*Thermoactinomyces (T. vulgaris, T. sacchari, T. candidus)* *Klebsiella oxytoca* *Naegleria gruberi* *Acanthamoeba polyphaga* *Acanthamoeba castellani*
Laboratory worker's lung (rats, gerbils)	Urine, serum, pelts, proteins
Lifeguard lung	Aerosolized endotoxin from pool-water sprays and fountains
Lycoperdonosis (*Lycoperdon* puffballs)	Puffball spores
Machine operator's lung	*Pseudomonas fluorescens* Aerosolized metal working fluid
Malt worker's disease (moldy barley)	*Aspergillus fumigatus, Aspergillus clavatus*
Maple bark disease (moldy maple bark)	*Cryptostroma corticale*
Miller's lung (dust-contaminated grain)	*Sitophilus granarius* (i.e., wheat weevil)
Moldy hay, grain, silage (farmer's lung)	Thermophilic actinomycetes Fungi (e.g., *Aspergillus umbrosus*)
Mollusk shell hypersensitivity pneumonitis	Sea-snail shell
Mushroom worker's lung	Mushroom spores Thermophilic actinomycetes
Paprika slicer's lung (moldy paprika pods)	*Mucor stolonifer*
Pauli's reagent alveolitis	Sodium diazobenzene sulfate
Pearl oyster shell pneumonitis	Oyster shells
Pituitary snuff taker's disease	Dried, powdered cattle or pig pituitary proteins)
Potato riddler's lung (moldy hay around potatoes)	Thermophilic actinomycetes *T. vulgaris* *Faenia rectivirgula* *Aspergillus* spp.
Poultry worker's lung (feather plucker's disease)	Serum proteins (chicken products)
Pyrethrum (pesticide)	Pyrethrum
Sauna taker's lung	*Aureobasidium* spp., other sources
Sequoiosis (moldy wood dust)	*Graphium* *Pullularia* *Trichoderma* spp. *Aureobasidium pullulans*
Suberosis (moldy cork dust)	*Thermoactinomyces viridis* *Penicillium glabrum* Aspergillus conidia
Summer-type pneumonitis	*Trichosporon cutaneum*
Tea grower's lung	Tea plants
Thatched-roof lung (huts in New Guinea)	*Saccharomonospora viridis* (dead grasses and leaves)
Tobacco grower's lung	*Aspergillus* spp. *Scopulariopsis brevicaulis*
Turkey handling disease	Serum proteins (turkey products)
Unventilated shower	*Epicoccum nigrum*
Upholstery fabric (nylon filament, cotton/polyester, and latex adhesive)	Aflatoxin-producing fungus, *Fusarium* spp.
Velvet worker's lung	Unknown (? nylon velvet fiber, tannic acid, potato starch)
Vineyard sprayer's lung	Copper sulfate (bordeaux mixture)
Wine maker's lung (mold on grapes)	*Botrytis cinerea*
Wood dust pneumonitis (oak, cedar, and mahogany dust, pine and spruce pulp)	*Alternaria* spp. *Bacillus subtilis*
Wood pulp worker's disease (oak and maple trees)	*Penicillium* spp.
Wood trimmer's disease (contaminated wood trimmings)	*Rhizopus* spp., *Mucor* spp.

Table 399-2 Criteria Used in the Diagnosis of Hypersensitivity Pneumonitis

1. Identified exposure to offending antigen(s) by:
   - Medical history of exposure to suspected antigen in the patient's living environment
   - Investigations of the environment confirm the presence of an inciting antigen
   - Identification of specific immune responses (immunoglobulin G serum precipitin antibodies against the identified antigen) are suggestive of the potential etiology but are insufficient in isolation to confirm a diagnosis
2. Clinical, radiographic, or physiologic findings compatible with hypersensitivity pneumonitis:
   - Respiratory and often constitutional signs and symptoms
     - Crackles on auscultation of the chest
     - Weight loss
     - Cough
     - Breathlessness
     - Episodic fever
     - Wheezing
     - Fatigue

   NOTE: These findings are especially suggestive of hypersensitivity pneumonitis when they appear or worsen several hours after antigen exposure.
   - A reticular, nodular, or ground glass opacities on chest radiograph or high-resolution CT
   - Abnormalities in the following pulmonary function tests
     - Spirometry (restrictive, obstructive, or mixed patterns)
     - Lung volumes (low or high)
     - Reduced diffusion capacity by carbon monoxide
     - Altered gas exchange either at rest or with exercise (reduced partial pressure of arterial oxygen by blood gas or pulse oximeter testing)
3. Bronchoalveolar lavage with lymphocytosis:
   - Usually with low CD4:CD8 ratio (i.e., CD8 is higher than normal)
   - Lymphocyte stimulation by offending antigen results in proliferation and cytokine production
4. Abnormal response to inhalation challenge testing to the offending antigen:
   - Reexposure to the environment
   - Inhalation challenge to the suspected antigen (rarely done any longer because of the risk of exacerbation of the disease)
5. Histopathology showing compatible changes with hypersensitivity pneumonitis by 1 of these findings:
   - Poorly formed, noncaseating granulomas (most often found closer to the respiratory epithelium where deposition of the offending antigen occurs)
   - Mononuclear cell infiltrate in the pulmonary interstitium

similar granulomas with subtle location differences depending on their origin.

CLINICAL MANIFESTATIONS

Heavy exposure to an offending antigen may lead to **acute HP**. This is the most common form of exposure but is still frequently not recognized. Symptoms are confused with bacterial or viral disease leading to treatment with antibiotics. Four to 6 hr after exposure the abrupt onset of cough, chest tightness, dyspnea, fever, chills, and fatigue are common (Table 399-3) Rarely, findings of wheezing are present on the initial examination. Rather, tachypnea with fine crackles may be heard by auscultation in the lung bases. However, auscultation may be normal at this stage. When **recurrent subacute disease** is present, the symptoms become progressive with weight loss, loss of appetite, and productive cough. When HP becomes **chronic** and progressive, the patient's fingers become clubbed accompanied by persistent symptoms noted above denoting a deteriorating status. If the disease progresses to interstitial fibrosis, the symptoms tend to not respond to therapy and denote a state where mortality risk is increased. Histology is hard to distinguish from **idiopathic pulmonary fibrosis** at this stage.

Table 399-3 Clinical History Clues Leading to a Diagnosis of Hypersensitivity Pneumonitis

Recurrent pneumonia
Pneumonia after repeat exposures (week, season, situation)
Cough, fever, and chest symptoms after making a job change or home change
Cough, fever, wheezing after return to school or only at school
Pet exposure (especially birds that shed dust such as pigeons, canaries, cockatiels, cockatoos)
Bird contaminant exposure (e.g., pigeon infestation)
Farm exposure to birds and hay
History of water damage despite typical cleaning
Use of hot tub, sauna, swimming pool
Other family members or workers with similar recurrent symptoms
Improvement after temporary environment change (e.g., vacation)

LABORATORY

Most of the abnormal laboratory findings in hypersensitivity pneumonitis are not specific and represent evidence of activated inflammatory markers or lung injury. Nonspecific elevation of immune globulins or the erythrocyte sedimentation rate and C-reactive protein may also be found. Circulating immune complexes may be detected. Lactate dehydrogenase may be elevated in the presence of lung inflammation and normalizes with response to therapy.

Serum IgG precipitins to the offending agent are frequently positive given some caveats. Commercial antigen sources from animals and birds may contain insufficient antigen for precipitation. Some laboratories performing these tests on an infrequent basis often have false-negative tests presumed to be a result of commercial antigens lacking the proper epitopes for precipitation. It is critical that laboratories familiar with the performance of these tests be utilized. Those laboratories often recognize the value of processing antigens for precipitation from the environmental source directly as the test substrate with patient serum. Skin testing for IgE-mediated disease is not warranted unless there is evidence of mixed lung pathology such as asthma and interstitial lung opacities.

BAL is one of the most sensitive tests and very helpful to the clinician in supporting the diagnosis of HP. Lymphocytosis frequently exceeding 50% of the recovered cells is seen on the BAL and should alert the clinician to the possibility of HP. Sarcoid, idiopathic pulmonary fibrosis, cryptogenic organizing pneumonia, berylliosis, granite workers lung disease, amiodarone pneumonia, lymphoma, and Langerhans cell histiocytosis may demonstrate lymphocytosis on BAL. All BAL specimens should have flow cytometry measurements of T-cell markers (CD3, CD4, and CD8 at a minimum). The predominant phenotype of the lymphocytosis is CD3+/CD8+/CD56+/CD57+/CD10–. In the normal circulation, lymphocytes with CD4 markers predominate at a ratio of approximately 2 : 1 compared to CD8 lymphocytes. In the lung compartment with HP, this ratio becomes approximately equal to or less than 1 (CD4:CD8 ≤1) with either an increase in CD8 lymphocytes or a decline in CD4 lymphocytes. This ratio assists the clinician in making a diagnosis of HP. This is in sharp contrast to other lymphocytic granulomatous disease, like sarcoidosis, where the CD4:CD8 is ≥2, or pulmonary fibrosis associated with connective tissue disease. Cryptogenic organizing pneumonia, a rare disease in children, also may present with BAL, where the CD4:CD8 is ≤1, and may be confused initially with HP.

Lung Biopsy

Lung biopsy is necessary to confirm a diagnosis of HP when the presence of critical elements, like antigen exposure, typical medical history, characteristic physical exam, and CD8+ cells in the BAL, are not present. Open lung biopsy is often the route of choice in young children because of the difficulty in safely obtaining satisfactory amounts of tissue by transbronchial biopsy. Lack of positive serum precipitins to offending antigen and exposure history are common reasons for obtaining lung biopsies. It is crucial to inform the

pathologist about the suspicion of HP so that the findings can be interpreted appropriately.

Poorly formed, noncaseating granulomas are seen near the respiratory and terminal bronchioles on histology with multinucleated giant cells. This is in sharp contrast to the granuloma of sarcoidosis that are well formed. Lymphocytes and plasma cells infiltrate the alveolar walls predominantly in a bronchocentric pattern. Fibrosis in the peribronchiole region supports a diagnosis of HP. Foamy cytoplasm accompanying large histiocytes in the alveoli and interstitium may be characteristically found.

Radiology

Chest radiograph almost always precedes the use of HRCT of the chest in children because of the need for sedation and concerns regarding risk of irradiation dose from HRCT. The plain radiograph will often demonstrate a ground-glass appearance, interstitial prominence, with a predominant location in the upper and middle lung fields. It is common for a chest radiograph to be considered normal by a radiologist early in the disease progression. Late in the disease, interstitial fibrosis may become prominent in the presence of increasing dyspnea, hypoxemia on room air, and even clubbing of the fingers. Mediastinum widening from lymphadenopathy is not usually present; when present, the lymph nodes are prominent along the airway near the carina, suggesting that the antigen source is inhaled and being responded to by the immune system.

Classical findings of mid zone and upper zone opacities with ground-glass appearance and nodularity on HRCT in the presence of typical clinical exam HP findings (lung crackles, cough, dyspnea) and lymphocytosis on BAL are almost sufficient to make a diagnosis (Fig. 399-1). These finding must prompt the clinician to identify the exposure in order to secure the diagnosis and eliminate the offending antigen. Without therapy, the progressive inflammatory response leads to air trapping, honeycombing, emphysema, and mild fibrosis in the chronic state. It is in this latter stage that idiopathic pulmonary fibrosis and nonspecific interstitial fibrosis are hard to differentiate. Whether true idiopathic pulmonary fibrosis exists in children where fibroblast foci are found on biopsy with usual interstitial fibrosis has been questioned.

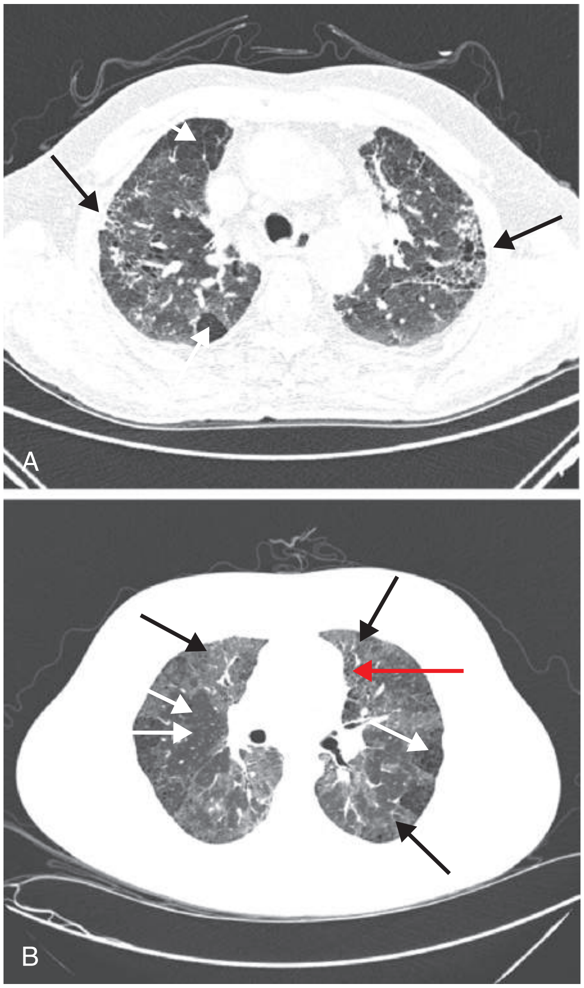

Figure 399-1 Radiologic findings in subacute **(A)** and chronic **(B)** hypersensitivity pneumonitis. **A,** Interstitial fibrosis *(black arrows)* and emphysematous changes *(white arrows)* in chronic HP with superimposed subacute HP. **B,** Ground-glass opacities *(black arrows)*, mosaic perfusion *(white arrows)*, and fibrosis *(red arrow)* in chronic HP caused by pigeon exposure. *(From Douglass JA, Sandrini A, Holgate ST, O'Hehir RE. Allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis. In Adkinson AF, editor:* Middleton's allergy principles and practice*, Philadelphia, 2014, Elsevier, Fig. 61-5.)*

Antigen Challenge By Inhalation

Inhalation challenge can be performed by 2 methods: (1) reexposure of the patient to the environment where the suspected antigen is present and (2) direct inhalation challenge at the hospital to material collected from the suspected source of the antigen. As the second method has resulted in severe exacerbation of disease in some individuals, its use is discouraged (see Chapter 399.2).

Two abnormal responses may be seen. Most commonly, where there is HP without asthma, symptoms occur 6-12 hr after direct challenge in the hospital or reexposure at source of the antigen. The challenges replicate some or all of the symptoms observed in the presenting syndrome with fever, dyspnea, fatigue, and crackles on lung auscultation. Blood drawn prior to challenge and then repeated during these symptoms often demonstrate an increased neutrophil count compared to baseline. Pulmonary function tests demonstrate a fall in **forced vital capacity** and often a concurrent fall in the **forced expiratory volume at 1 sec (FEV_1)** with a stable or increasing ratio of FEV_1:forced vital capacity percentage. Hypoxemia may accompany this decline in pulmonary function as well as a fall in the **diffusion capacity of carbon monoxide (DLCO).** To see the complete effect, exercise during this period may show a considerable fall in oxygenation despite normal arterial blood gas oxygen tension and normal pulse oximetry at rest. This finding denotes the onset of worsening restrictive lung disease. Some patients may also demonstrate an early and late reduction in the FEV_1 as is seen in allergen challenge with asthma. In this dual reaction, the forced vital capacity also declines and is often accompanied by fever and leukocytosis.

TREATMENT

The control of environmental exposure to the offending antigen is a key to curing HP and remains the ideal method of treatment and prevention of recurrence. Counseling about the risk to children of exposure to birds and feathered bedding, or other environmental antigens, biologic aerosols, or agriculture dusts that are known to induce HP are important. Certainly, the source of the antigen and type of antigen appears to affect response to treatment and long-term prognosis. Older individuals who contract farmer's lung are likely to recover with minimal permanent residual effect, whereas individuals with bird fancier's lungs from antigens produced by pigeons have a worse prognosis, especially if fibrosis is detected on lung biopsy. The pediatrician should advise—in the strongest terms—removal of the antigen source from the affected child's environment. This may be an extraordinary challenge given various children's living circumstances and lack of independent control of the environment they live in.

In addition, pediatricians should be familiar with recommendations about the maintenance of heating, ventilation, and air conditioning systems, as well as of humidifiers and vaporizers. Daily drainage, cleansing of residue, and routine cleaning with hydrogen peroxide or bleach help rid humidifiers and vaporizers of harmful pathogens that cause HP.

Glucocorticosteroids at a dose of 0.5-1 mg/kg/day of prednisone or equivalent will reduce the immune inflammatory response in the

lungs. Comparative trials in adults demonstrate that the use of 4 wks of therapy is as effective as 12 wks of therapy. Removal of antigen alone is sufficient to normalize lung function in most patients, but symptoms and pulmonary functions return to normal faster with the use of glucocorticoids. Because of the rapid reversal of symptoms, successful abatement of the environment is sometimes compromised when the family sees improvement prior to the antigen source removal.

Bibliography is available at Expert Consult.

399.2 Occupational and Environmental Lung Disease

Kevin J. Kelly

Occupational and environmental lung diseases constitute a larger part of primary care pediatrics, pediatric emergency medicine, and other pediatric subspecialties than most pediatric practitioners expect or realize. Although occupational and environmental lung diseases includes **occupational asthma**, **reactive airways dysfunction syndrome (RADS)**, HP, hard metal inhalation lung disease, berylliosis, and air pollution, this chapter focuses on occupational asthma and RADS. Berylliosis has a propensity to form granulomas (see Chapter 399.3). Although some diseases will be seen with regularity, the important role that a part-time workplace, school, daycare, neighbors' housing, multiple family housing, and indoor and outdoor environments may have in the causation of signs and symptoms in the patient is not always considered by the clinician.

The vast array of exposures shown to cause disease of the lungs is daunting, such as the inhalation of baking flour or household cleaning fluids causing asthma, microwave popcorn exposure to diacetyl resulting in bronchiolitis obliterans, and exposure to thermophilic organisms or mold resulting in hypersensitivity pneumonitis. The acute eosinophilic pneumonias associated with new onset of smoking and chemical inhalation of 1,1,1-trichloroethane (Scotchgard) require a high index of suspicion and unique lines of questioning. The same antigen encountered in a work, school, home, or outdoor environment may result in different disease presentation because of host factors, dose exposure, and genetic susceptibility. One of the most prominent examples is an investigation of workers who inhaled metal working fluid resulting in the development of asthma, HP, chronic bronchitis, or no symptoms at all from similar exposures. Immunologic evaluation in some exposures has shown similar immune responses in different individuals, but a wide range of disease provocation. When **high molecular weight** proteins cause asthma, symptoms of rhinoconjunctivitis frequently precede the onset of pulmonary symptoms. The medical history in occupational and environmental lung diseases has used an expanded construct with a simple acronym, WHACOS (Table 399-4).

Table 399-4	A Construct (WHACOS) That Has Been Used in Medical Interviewing of Patients, Coworkers, and Family Members When Environmental or Occupational Lung Disease Is Being Considered
W	*What* do you do?
H	*How* do you do what you do?
A	Are symptoms *Acute* or are they *Chronic*?
C	Do any *Coworkers*, family, classmates, or friends have the same symptoms?
O	Do you have any hobbies, travel, or animal/pet exposures *Outside* of school or work?
S	Are you *Satisfied* with work or school?

It is important to remember that in patients with occupational- or environmental-induced disease, the onset of symptoms has a lag time between exposure and symptoms. In occupational asthma, there may be an immediate response within 1-2 hr of exposure, demonstrated as a decline in pulmonary function, specifically the **FEV$_1$**. Usually, lung function returns to normal spontaneously unless persistent exposure occurs. Some patients demonstrate no immediate reduction in lung function, but rather experience a delayed response of 4-6 hr after the exposure. Treating physicians can take advantage of this physiology in occupational and environmental asthma by use of spirometry before and after work or school or peak flow measurements hourly during exposure and after leaving the exposure. Because workers and children in school have prolonged periods of exposure followed by a number of days without exposure, the use of pulmonary function plus bronchial hyperresponsiveness testing is helpful. Pulmonary function tests prior to starting work on a Monday of a typical work week may be normal. By Friday of a typical work or school week, the baseline pulmonary functions may have fallen and bronchial responsiveness may have become more sensitive to a lower concentration of histamine, methacholine, or mannitol. By Monday, the tests may have returned to normal or near normal with no change other than reduced exposure.

In the case of HP, a lag of 4-8 hr between the time of exposure and onset of fever, cough, and dyspnea is common. Unfortunately, the return home from hospitalization for culture-negative pneumonia to a source of antigen causing HP often results in complete reoccurrence of symptoms. Clinicians must have a high index of suspicion for HP with reoccurrence of pulmonary infiltrates shortly after reexposure (see Chapter 399.1).

CLASSIFICATION AND PATHOGENESIS

Occupational and environmental lung diseases include numerous syndromes of human lung disease such as occupational asthma, **RADS**, **reactive upper airway disease syndrome**, hypersensitivity pneumonitis (see Chapter 399.1), air pollution–induced disease, hard metal inhalation lung disease, berylliosis, occupation-induced lung cancer (e.g., mesothelioma from asbestosis), and chronic obstructive pulmonary disease without smoking. Most of these diseases are not problematic for children but adolescents may be exposed through part-time work or by single exposures as seen in RADS.

Occupational and Environmental Asthma

The general principles of diagnosis, clinical signs and symptoms, treatment, and causes of asthma are discussed in Chapter 144. High molecular weight causes of occupational and environmental asthma can be characterized as allergens, which are normally proteins and enzymes, inhaled from multiple sources (Table 399-5). These include various animals, shellfish, fish, enzymes (e.g., *Bacillus subtilis* in laundry detergent), and flour or cereals. Occupational and environmental asthma is also caused by a number of low molecular weight chemicals (Table 399-6). These chemicals are sufficient to induce an immune response but it is often not by an IgE-mediated mechanism. These chemicals appear to act as haptens that bind to human proteins, causing an immune response in the human host.

The pathogenesis of asthma in patients exposed to high molecular weight antigens follows the experience of nonoccupational asthma in patients where atopy, gender, genetics, concentration of antigen, duration of exposure, and other individual factors all contribute to the development of disease. Most individuals require a concentration and duration of exposure sufficient to cause IgE antibody sensitization to the offending allergen with development of bronchial hyperresponsiveness and airway inflammatory disease. If the allergen exposure is sufficient, these proteins can drive the immune response to a T-lymphocyte type 2 phenotype, even in patients without prior atopic disposition, as occurred in the case of latex allergy where many nonatopic individuals and patients exposed to allergen in their personal healthcare developed occupational allergy to multiple proteins from natural rubber latex. Atopic individuals are at the highest risk of developing latex allergy. A longitudinal study demonstrated that powdered latex gloves with high allergen content were the reason for the epidemic of latex allergy and

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Table 399-5 High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma

OCCUPATION OR ENVIRONMENT	SOURCE
ANIMAL-DERIVED ANTIGENS	
Agricultural worker	Cow dander
Bakery	Lactalbumin
Butcher	Cow bone dust, pig, goat dander
Cook	Raw beef
Dairy industry	Lactoserum, lactalbumin
Egg producer	Egg protein
Farmer	Deer dander, mink urine
Frog catcher	Frog
Hairdresser	Sericin
Ivory worker	Ivory dust
Laboratory technician	Bovine serum albumin, laboratory animal, monkey dander
Nacre buttons	Nacre dust
Pharmacist	Endocrine glands
Pork producer	Pig gut (vapor from soaking water)
Poultry worker	Chicken
Tanner	Casein (cow's milk)
Various	Bat guano
Veterinarian	Goat dander
Zookeeper	Birds
CRUSTACEANS, SEAFOOD, FISH	
Canning factory	Octopus
Diet product	Shark cartilage
Fish food factory	Gammarus shrimp
Fish processor	Clam, shrimp, crab, prawn, salmon, trout, lobster, turbot, various fishes
Fisherman	Red soft coral, cuttlefish
Jewelry polisher	Cuttlefish bone
Laboratory grinder	Marine sponge
Oyster farm	Hoya (oyster farm prawn or sea-squirt)
Restaurant seafood handler	Scallop and shrimp
Scallop plant processor	King scallop and queen scallop
Technician	Shrimp meal *(Artemia salina)*
ARTHROPODS	
Agronomist	*Bruchus lentis*
Bottling	Ground bug
Chicken breeder	Herring worm *(Anisakis simplex)*
Engineer at electric power plant	Caddis flies *(Phryganeidae)*
Entomologist	Lesser mealworm (*Alphitobius diaperinus* Panzer), moth, butterfly
Farmer	Grain pests (*Eurygaster* and *Pyrale*)
Fish bait handler	Insect larvae *(Galleria mellonella)*, mealworm larvae *(Tenebrio molitor)*, green bottle fly larvae *(Lucila caesar)*, daphnia, fish-feed Echinodorus larva *(Echinodorus plasmosus)*, Chiromids midge *(Chironomus thummi thummi)*
Fish processing	Herring worm *(Anisakis simplex)*
Flight crew	Screw worm fly *(Cochliomyia hominivorax)*
Honey processors	Honeybee
Laboratory worker	Cricket, fruit fly, grasshopper *(Locusta migratoria)*, locust
Mechanic in a rye plant	Confused flour beetle *(Tribolium confusum)*
Museum curator	Beetles (Coleoptera)
Seed house	Mexican bean weevil *(Zabrotes subfasciatus)*
Sericulture	Silkworm, larva of silkworm
Sewage plant worker	Sewer fly *(Psychoda alternata)*
Technician	Arthropods *(Chrysoperla carnea, Leptinotarsa decemlineata, Ostrinia nubilalis, and Ephestia kuehniella)*, sheep blowfly *(Lucilia cuprina)*
Wool worker	*Dermestidae* spp.
ACARIANS	
Apple grower	Fruit tree red spider mite *(Panonychus ulmi)*
Citrus farmer	Citrus red mite *(Panonychus citri)*
Farmer	Barn mite, two-spotted spider mite *(Tetranychus urticae)*, grain mite
Flour handler	Mites and parasites
Grain-store worker	Grain mite
Horticulturist	*Amblyseius cucumeris*
Poultry worker	Fowl mite
Vine grower	McDaniel spider mite *(Tetranychus mcdanieli)*
MOLDS	
Agriculture	*Plasmopara viticola*
Baker	*Alternaria, Aspergillus* (unspecified)
Beet sugar worker	*Aspergillus* (unspecified)
Coal miner	*Rhizopus nigricans*
Coffee maker	*Chrysonilia sitophila*
Laborer	Sooty molds (*Ascomycetes*, deuteromycetes)
Logging worker	*Chrysonilia sitophila*
Plywood factory worker	*Neurospora*
Sausage processing	*Penicillium nalgiovense*
Sawmill worker	*Trichoderma koningii*
Stucco worker	*Mucor* spp. (contaminating esparto fibers)
Technician	*Dictyostelium discoideum* (mold), *Aspergillus niger*
MUSHROOMS	
Agriculture	*Agaricus bisporus* (white mushroom)
Baker	Baker's yeast *(Saccharomyces cerevisiae), Boletus edulis*
Greenhouse worker	Sweet pea *(Lathyrus odoratus)*
Hotel manager	*Boletus edulis*
Mushroom producer	*Pleurotus cornucopiae*
Mushroom soup processor	Mushroom unspecified
Office worker	*Boletus edulis*
Seller	*Pleurotus ostreatus* (spores of white spongy rot)
ALGAE	
Pharmacist	Chlorella
Thalassotherapist	Algae (species unspecified)
FLOURS	
Animal fodder	Marigold flour *(Tagetes erecta)*
Baker	Wheat, rye, soya, and buckwheat flour; Konjac flour; white pea flour *(Lathyrus sativus)*
Food processing	White Lupin flour *(Lupinus albus)*
POLLENS	
Florist	Cyclamen, rose
Gardener	Canary island date palm *(Phoenix canariensis)*, Bell of Ireland *(Moluccella laevis)*, Bell pepper, chrysanthemum, eggplant *(Solanum melongena)*, *Brassica oleracea* (cauliflower and broccoli)
Laboratory worker	Sunflower (*Helianthus* spp.), thale cress *(Arabidopsis thaliana)*
Olive farmers	White mustard *(Sinapis alba)*
Processing worker	*Helianthus annuus*

Table 399-5 High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma—cont'd

OCCUPATION OR ENVIRONMENT	SOURCE
PLANTS	
Brewery chemist	Hops
Brush-makers	Tampico fiber in agave leaves
Butcher	Aromatic herb
Chemist	Linseed oilcake, *Voacanga africana* seed dust
Cosmetics	Dusts from seeds of Sacha Inchi *(Plukenetia volubilis)*, chamomile (unspecified)
Decorator	Cacoon seed (Entage gigas)
Floral worker	Decorative flower, safflower *(Carthamus tinctorius)* and yarrow *(Achillea millefolium)*, spathe flower, statice *(Limonium tataricum)*, baby's breath *(Gypsophila paniculata)*, ivy *(Hedera helix)*, flower (various), sea lavender *(Limonium sinuatum)*
Food industry	Aniseed, fenugreek, peach, garlic dust, asparagus, coffee bean, sesame seed, grain dust, carrot *(Daucus carota L.)*, green bean *(Phaseolus multiflorus)*, lima bean *(Phaseolus lunatus)*, onion, potato, swiss chard *(Beta vulgaris L.)*, courgette, carob bean, spinach powder, cauliflower, cabbage, chicory, fennel seed, onion seeds (*Allium cepa*, red onion), rice, saffron *(Crocus sativus)*, spices, grain dust
Gardener	Copperleaf *(Acalypha wilkesiana)*, grass juice, weeping fig *(Ficus benjamina)*, umbrella tree (*Schefflera* spp.), amaryllis (*Hippeastrum* spp.), Madagascar jasmine sap *(Stephanotis floribunda)*, vetch *(Vicia sativa)*
Hairdresser	Henna (unspecified)
Herbal tea processor	Herbal tea, sarsaparilla root, sanyak *(Dioscorea batatas)*, Korean ginseng *(Panax ginseng)*, tea plant dust *(Camellia sinensis)*, chamomile (unspecified)
Herbalist	Liquorice roots (*Glycyrrhiza* spp.), wonji *(Polygala tenuifolia)*, herb material
Horticulture	Freesia (Freesia hybrida), paprika *(Capsicum annuum)*, Brazil ginseng *(Pfaffia paniculata)*
Laborer	Citrus food handling (*dl*-limonene, *l*-citronellol, and dichlorophen)
Oil industry	Castor bean, olive oilcake
Pharmaceutical	Rose hip, passion flower *(Passiflora alata)*, cascara sagrada *(Rhamnus purshiana)*
Powder	Lycopodium powder
Sewer	Kapok
Sheller	Almond shell dust
Stucco handler	Esparto (*Stipa tenacissima* and *Lygeum spartum*)
Tobacco manufacturer	Tobacco leaf
PLANT-DERIVED NATURAL PRODUCTS	
Baker	Gluten, soybean lecithin
Candy maker	Pectin
Glove manufacturer	Latex
Health professional	Latex
Rose extraction	Rose oil
BIOLOGIC ENZYMES	
Baker	Fungal amylase, fungal amyloglucosidase and hemicellulase
Cheese producer	Various enzymes in rennet production (proteases, pepsine, chymosins)
Detergent industry	Esterase, *Bacillus subtilis*
Factory worker	*Bacillus subtilis*
Fruit processor	Pectinase and glucanase
Hospital personnel	Empynase (pronase B)
Laboratory worker	Xylanase, phytase from *Aspergillus niger*
Pharmaceutical	Bromelin, flaviastase, lactase, pancreatin, papain, pepsin, serratia peptidase, and lysozyme chloride; egg lysozyme, trypsin
Plastic	Trypsin
VEGETABLE GUMS	
Carpet manufacturing	Guar
Dental hygienist	*Gutta-percha*
Gum importer	Tragacanth
Hairdresser	Karaya
Printer	Acacia

Table 399-6 Low Molecular Weight Chemicals Known to Induce Occupational or Environmental Asthma

CHEMICALS	OCCUPATION OR ENVIRONMENT SOURCE
Diisocyanates	
• Diphenylmethane	Polyurethane
• Hexamethylene	Roofing materials
• Naphthalene	Insulations
• Toluene	Paint
Anhydrides • Trimellitic • Phthalic	Manufacturers or users • Paint • Plastics • Epoxy resins
Dyes • Anthraquinone • Carmine • Henna • Persulfate	Personal or business use of dyes • Hair dye • Fur dye • Fabric dye
Glue or resin • Methacrylate • Acrylates • Epoxy	Plastic • Manufacturers • Healthcare professionals • Orthopedic specialists
Metals • Chromic acid • Potassium dichromate • Nickel sulfate • Vanadium • Platinum salts	Metal work • Plating • Welding
Drugs • β-Lactams • Opioids • Other	Exposure to drugs in environment • Pharmaceutical workers • Farmers • Healthcare workers
Chemicals • Formaldehyde • Glutaraldehyde • Ethylene oxide	Exposure in the healthcare field • Laboratory work • Healthcare professionals
Wood dust • Western red cedar (plicatic acid) • Exotic woods • Maple • Oak	Workers/hobbyists • Sawmill • Carpentry • Woodworking

occupational asthma. Occupational asthma induced from multiple causes persists in individuals affected approximately 50% of the time despite primary removal of the sensitizing allergen.

Reactive Airways Disease Syndrome and Irritant-Induced Asthma

RADS presents with the development of acute respiratory symptoms within minutes or hours following a single inhalation of a *high concentration* of irritant gas, aerosol, or smoke. Table 399-7 lists the criteria for diagnosis of RADS. Asthma-like symptoms and airway hyperresponsiveness then ensue, which often persist for prolonged periods. Unlike typical asthma, RADS is often not reversible by use of a bronchodilator. This is probably a consequence of the direct injury to the epithelium and subsequent submucosal fibrosis. Chlorine gas, acetic acid, dimethylaminoethanol, chlorofluorocarbons, epichlorohydrin, and diisocyanates have been studied by experimental design of comparative groups or epidemiology studies.

Irritant induced asthma is a closely related form of asthma resulting from nonimmunologic provocation of bronchial hyperresponsiveness with airflow obstruction induced by irritant chemicals in *low concentration* after single or multiple exposures. If the resultant pulmonary symptoms occur after multiple exposures at a plant, it is termed *nonimmunologic-induced asthma*.

Predisposing factors for the development of RADS are not well characterized. Atopy and cigarette smoking may increase the risk of developing RADS when exposure through inhalation of irritant chemicals occurs. In addition to host factors, the type of chemical appears to be important. Higher concentrations of chemicals, the type of chemical (vapor or wet aerosols), and bleaching agents are the most offending agents to cause RADS. Dry particle aerosols are less likely to cause RADS. Analysis of the World Trade Center firefighters indicates that the presence of bronchial hyperresponsiveness prior to a chemical exposure does not increase the risk for an individual to develop RADS.

Pathogenesis of RADS follows a typical pattern. Initial histology demonstrates rapid denudation of the mucosa accompanied by submucosal fibrinous, hemorrhagic exudate. Subepithelial edema occurs subsequently with some regeneration of the epithelial layer, proliferation of basal and parabasal cells, and eventually areas of fibrosis. The desquamation, subepithelial fibrosis, thickening of the basement membrane, and regeneration of basal cells are all more prominent in RADS than in occupational asthma. This may explain the limited response to bronchodilator therapy in this syndrome compared to asthma.

The clinical manifestations of RADS and irritant-induced asthma are different from each other mostly in the onset of symptoms. Patients with RADS typically can pinpoint the exact time of onset of symptoms as well as the exact number of hours postexposure. The symptoms are so severe that nearly 80% of subjects in one study presented to an emergency department for care. The lower airway symptoms of cough, dyspnea, chest tightness, and wheezing are prominent features in RADS, with cough being most prevalent. Because of the toxic nature of the inhaled chemical, it is predictable that an upper airway syndrome of throat and nose burning will often accompany the lower airway symptoms. This part of the complex has been referred to as **respiratory upper airway dysfunction syndrome.**

Individuals with irritant-induced asthma present with a more insidious onset of symptoms. Because of the recurrent nature of the low concentration of chemical, patients may not be able to identify the underlying trigger initially. Similar to allergic rhinitis, patients may describe nasal congestion, rhinorrhea, sneezing, postnasal drip, ocular irritation, and conjunctival injection. Pulmonary symptoms include those typically seen with asthma exacerbations.

Initial evaluation of the patient with RADS or irritant-induced asthma usually includes the medical history, physical examination, and pulse oximetry. Because of the acute nature of RADS, a chest radiograph is obtained in order to rule out other acute causes of dyspnea including pneumonia or pulmonary edema. Ideally, if the patient is not in significant distress, complete pulmonary functions with spirometry, lung volumes, and diffusion capacity are very helpful in the initial evaluation. The lack of abnormality on initial chest radiograph reassures the clinician that HRCT is not indicated.

Table 399-7	Criteria for the Diagnosis of Reactive Airways Disease Syndrome
Absence of previous documented respiratory symptom	
Onset of symptoms most often occur after a single specific exposure	
Exposure is most often to a high concentration of gas, smoke, fume, or vapor with irritant qualities	
Symptoms occur within 24 hr of exposure and persist for 3 mo or longer	
Symptoms mimic asthma with cough, wheezing, shortness of breath, and/or dyspnea	
Pulmonary function tests may demonstrate airflow obstruction but not always	
Bronchial hyperresponsiveness is documented by methacholine challenge	
Alternative pulmonary diseases are not able to be found	

TREATMENT

Treatment of RADS and irritant-induced asthma focuses on prevention of exposure. Because the exposure in RADS is often associated with a single known exposure, this task is readily accomplished. The low, persistent exposures are more challenging to identify and remove. Implementing treatment guidelines for asthma from all causes is recommended when intervention is required beyond antigen removal.

Bibliography is available at Expert Consult.

399.3 Granulomatous Lung Disease

Kevin J. Kelly

GRANULOMATOSIS WITH POLYANGIITIS

Granulomatosis with polyangiitis (GPA) is a disease that involves both the lower and upper respiratory tracts with granulomatous inflammation of small vessels; formerly it was known as *Wegener granulomatosis* (see Chapter 167). The pulmonary disease is frequently associated with glomerulonephritis. The simultaneous presence of pulmonary and renal disease should immediately raise the suspicion that either GPA or Goodpasture disease (see Chapter 399.5) may be causing the disease.

Etiology and Epidemiology

The prevalence of GPA disease appears to be increasing by up to 4-fold in the last 2 decades, but without male or female predominance. Diagnostic tests, such as antineutrophil antibodies, may explain some of this increased prevalence.

Pathogenesis

Clinically, the development of both upper and lower airway disease with granulomas in GPA implies that exposure to antigen in the airway of endogenous or exogenous source is involved with aberrant cell-mediated immune response. Cytokine expression by peripheral blood CD4+ lymphocytes and cells collected by BAL indicate there is a predominantly T-lymphocyte type 1 response with overexpression of interferon-γ (IFN-γ) and tumor necrosis factor (TNF). In vitro studies demonstrate a skewed T-lymphocyte type 17 response by blood CD4+ T cells in GPA, suggesting there is an immune regulatory defect that leads to excessive production of T-lymphocyte type 1/T-lymphocyte type 17 cytokines (interleukin [IL]-17, TNF, and IFN-γ) presumed to be from the environment or autoantigens. Such an inflammatory response may be sufficient to induce and sustain granuloma formation.

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Detection of *autoantibodies reactive against proteins in the cytoplasmic granules of neutrophils and monocytes (antineutrophil cytoplasmic antibodies [ANCAs])* are found in 90% of the patients with GPA. The first major type of ANCA is directed against cytoplasmic proteinase-3 and is frequently named c-ANCA. The second major type of ANCA recognizes the enzyme myeloperoxidase. It is found in a small number (<10%) of patients with GPA. Antimyeloperoxidase antibodies fluoresce in a perinuclear pattern and are often referred to as perinuclear ANCA. In contrast, some patients develop the clinical phenotype of GPA in the absence of detectable ANCA.

Clinical Manifestations

Children with GPA present with respiratory complaints accompanied by fever, loss of energy, and vague joint complaints. Some may present with severe nasal disease manifested as ulceration, septal perforation, pain, sinusitis, and or epistaxis. The septal perforation may lead to deformation of the nasal bridge from erosion of the underlying cartilage but is more common in adults. Pulmonary disease occurs in the majority of patients as noted above. Symptoms range from cough, hemoptysis, dyspnea, and chest discomfort to asymptomatic infiltrates on chest radiography. Occasionally, patients with GPA will present with hemoptysis or recurrent fleeting infiltrates from **pulmonary hemorrhage**. The pathology is confusing because granulomatous disease may be difficult to demonstrate and can be confused with microscopic polyangiitis. This is found most frequently in Goodpasture disease, microscopic polyangiitis, and Henoch-Schönlein purpura. Distinguishing GPA from other pulmonary renal syndromes is easiest when there are classical symptoms of upper airway disease (nasal/sinus), lower airway disease with necrosis, granulomas on biopsy of the lung with vasculitis, and renal disease consistent with glomerulonephritis.

As many as 20% of patients with GPA will present with subglottic or endobronchial stenosis from scarring and inflammatory changes. Although it may be the presenting symptom, it often occurs in conjunction with other disease manifestations. Dyspnea and voice changes are common complaints from the patients.

Skin, ocular, and joint symptoms are common in GPA and have been found to accompany the lung and renal disease in most series 50% or more of the time. Biopsy of the skin may show nonspecific leukocytoclastic vasculitis, venulitis, or capillaritis.

Laboratory and Pathology

c-ANCA or anti–proteinase-3 antibodies are found in 90% of patients with GPA. However, they are also found in other types of vasculitis and are not sufficient in themselves to make a diagnosis without a tissue biopsy (see Chapter 167). Because of the necrotizing nature of the vasculitis, lung tissue is required for definitive diagnosis of pulmonary disease. Biopsy of the upper airway may demonstrate evidence of granulomatous disease but it is uncommon to find evidence of vasculitis; lung biopsy is warranted. Usual pathology demonstrates multiple parenchymal nodules that may be located in either the bronchial, vascular, or interstitial tissues (Fig. 399-2). The granulomatous inflammation often is found areas of necrosis and/or vasculitis.

Renal biopsy rarely is able to demonstrate granulomas or vasculitis. Rather, kidney tissues may show focal, segmental, or necrotizing glomerulonephritis without deposits of immune complexes. When the tissues fail to demonstrate classical findings, a variety of diseases (e.g., tuberculosis, sarcoid, microscopic polyangiitis, malignancy, and other autoimmune disorders) must be considered in the evaluation.

Radiology

Chest radiography in GPA will show multiple infiltrates, nodules, cavitary lesions, or interstitial lung disease. Fleeting infiltrates may be seen when recurrent hemorrhage is a part of the clinical manifestation. HRCT often demonstrates more extensive lung disease and the cavitation associated with the necrotizing nature of the disease (Fig. 399-3).

Treatment

Rapidly progressive, debilitating disease may occur when failure to diagnose GPA leads to inadequate treatment. One series of patients showed death occured in 90% of patients within 2 yr of diagnosis. Glucocorticoid therapy alone resulted in relapses and inadequate control of disease in many subjects. Standard initial induction of therapy includes prednisone at 1 mg/kg/day in combination with oral cyclophosphamide at 2 mg/kg/day or intravenous dosing at 15 mg/kg

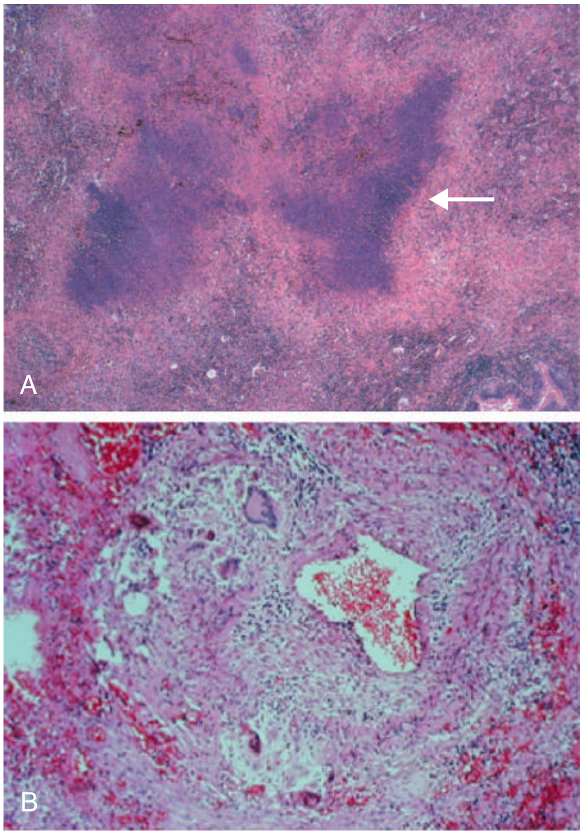

Figure 399-2 A, Low-power view of granulomatous inflammation and geographic necrosis (*arrow*) in a lung biopsy from a patient with GPA. **B,** Granulomatous vasculitis involving a small pulmonary artery in the lung of a patient with GPA. The vessel wall is markedly thickened with an inflammatory infiltrate that includes multinucleated giant cells. *(From Sneller MC, Fontana JR, Shelhamer JH. Immunologic nonasthmatic diseases of the lung. In Adkinson AF, editor:* Middleton's allergy principles and practice, *Philadelphia, 2014, Elsevier, Fig. 61-1B and C.)*

Figure 399-3 Chest CT scan of a patient with granulomatosis with polyangiitis shows typical nodular lung infiltrate with cavitation. *(From Sneller MC, Fontana JR, Shelhamer JH. Immunologic nonasthmatic diseases of the lung. In Adkinson AF, editor:* Middleton's allergy principles and practice, *Philadelphia, 2014, Elsevier, Fig. 61-1A.)*

monthly. This regimen is effective at induction of remission of disease process. The advantage of oral daily dosing is a reduction in relapse of disease once induction has occurred. After induction of remission (usually in 3 mo), prednisone can be tapered to an every-other-day regimen and eventually discontinued in 6-8 mo. After induction of remission, cyclophosphamide should be discontinued because of drug toxicity, serious risk of infections, risk of infertility, or cancer. In those patients with recurring relapse, cyclophosphamide has had limited use.

Once remission was achieved and cyclophosphamide discontinued; both methotrexate and azathioprine demonstrated efficacy with lowered side effects during maintenance of remission therapy for approximately 1 yr.

Adjuvant therapy with plasma exchange may be considered when life-threatening GPA disease presents. This is advocated on the premise that ANCAs are inducing disease and will be removed from the circulation with this intervention; its use has been favorably evaluated in GPA-induced renal disease. Plasmapheresis and exchange is advocated as adjuvant treatment for severe manifestations of GPA and related ANCA-associated disease based on the theoretical benefit of removing potentially pathogenic ANCA. Adjuvant plasma exchange has been studied mainly in patients with severe renal vasculitis, but there are also reports of success in severe pulmonary hemorrhage. The results of a meta-analysis of patients with renal vasculitis in 9 trials, suggest that adjuvant plasma exchange may be associated with improved renal outcome.

The removal of B-cells that produce ANCAs may be effective by reducing the production of pathogenic antibodies. Rituximab, an anti-CD20 chimeric antibody, regimens used in conjunction with glucocorticoids or glucocorticoids with a short course of cyclophosphamide are equally efficacious in inducing remission when compared to more prolonged therapy with steroid plus cyclophosphamide.

Recurrent disease remains a major problem. ANCA levels have not been shown to correlate with activity of disease or severity. Patients with isolated disease of the sinuses and nose may not warrant such toxic therapy. Therapy with topical corticosteroid and antibiotics for infection appear to be warranted. If unsuccessful, steroid with methotrexate appears to be an effective therapy.

The development of subglottic stenosis requires specific treatment. Use of cyclophosphamide with oral corticosteroid may have an incomplete or no response in the airway. Local injection of a prolonged acting corticosteroid locally appears to be indicated to reduce the inflammation and prevent further scarring. If this complication is found at presentation, simultaneous airway intervention with induction of corticosteroid and cyclophosphamide is warranted and encouraged.

SARCOIDOSIS

Sarcoidosis is an idiopathic inflammatory disease involving multiple organ systems, with characteristic histology of noncaseating granulomas (see Chapter 165). It has been postulated that sarcoidosis represents an immune response to a yet-to-be-identified agent from the environment that is likely inhaled in a susceptible host. It remains a diagnosis of exclusion from other diseases with granuloma formation on histology, such as immune deficiency of chronic granulomatous disease, granulomatous lymphocytic interstitial lung disease associated with common variable immune deficiency, HP associated with some drugs and inhalation agents, granuloma with polyangiitis, typical and atypical *Mycobacterium*, *Pneumocystis jiroveci*, and malignancy.

Epidemiology and Pathogenesis

African-American females are disproportionately affected more than any other group. Because an asymptomatic sarcoid-like distribution of noncaseating granulomas may be frequently found at autopsy, the contribution of the granulomas to the disease is not always clear. Some countries do mass chest radiograph screening for multiple diseases. In that setting, up to 50% of diagnosed sarcoidosis is asymptomatic. The severity of the disease appears to be worse in African-Americans who tend to have acute illness, whereas white subjects are more likely to be asymptomatic with a more chronic disease. There have been clusters of disease in families and genetic testing suggests that MHC linkage on the short arm of chromosome 6 is most likely to be observed.

Sarcoidosis is rarely found in children younger than the age of 8 yr; those of African descent are most affected. The disease presentation is similar to adults with multisystem disease being the most common. Skin rash, iridocyclitis, and arthritis are seen most often without pulmonary symptoms. In northern Europe, erythema nodosum with the ocular involvement of iridocyclitis is seen most frequently. Despite the lack of symptoms, chest radiography may be abnormal in approximately 90% of children. The pulmonary disease appears to be less progressive compared to adults and patients recover spontaneously without corticosteroids. Rarely, pulmonary disease may progress to fibrosis. Ocular disease is more likely to be progressive and warrant intervention as the inflammatory response may lead to blindness from complications of iritis.

Unrecognized infection or inhalation of an immune response–inducing antigen continues to be at the forefront of consideration as a cause of the disease. Clusters of sarcoidosis in small populations, variable prevalence by geography and race, transfer of disease by organ transplant, and the reproducible granuloma formation only in patients with sarcoidosis in the skin when homogenized lymph node tissue from patients with sarcoid are injected intradermally (Kveim-Siltzbach test) have supported this hypothesis.

Clinical Manifestations

Patients with lung disease are more likely to be asymptomatic as the presentation often may be an abnormal chest radiograph. When symptomatic, patients demonstrate shortness of breath, cough, and dyspnea. Children are more likely to manifest the disease as iridocyclitis, skin rash, and arthritis. African-American children appear to have more frequent lymph node involvement, nonspecific elevations of gamma globulin, erythema nodosum, and hypercalcemia. Physical exam may reveal only an elevated respiratory rate without crackles or rales by auscultation. Pleural involvement has been seen but is uncommon. When present, a lymphocytic predominant exudate may be observed with laboratory evaluation of the pleural fluid. Unusual but reported findings include cases of pneumothorax, hemothorax, and chylothorax. One specific syndrome, **Lofgren syndrome**, with hilar lymphadenopathy, erythema nodosum, and migratory polyarthralgias, is almost exclusively seen in women. This syndrome has a strong association with HLA-DQB1*0201 and polymorphisms in the C-C chemokine receptor 2 (CCR2); these genetic markers are a predictor of a good outcome.

Although almost 90% of patients with sarcoidosis demonstrate parenchymal or mediastinal disease on chest radiography, there are many who have minimal to no symptoms. Approximately 40% of adults with stage 1 disease have endobronchial involvement found at bronchoscopy. The higher the staging level of disease, the higher the percentage of people with airway involvement.

Diagnostic Laboratory Testing

The most common but nonspecific findings are hypergammaglobulinemia, hypercalciuria, hypercalcemia, elevated alkaline phosphatase when liver disease is present, and, occasionally, anemia of chronic disease. Serum angiotensin-converting enzyme may be elevated in 75% of patients with untreated sarcoid. False-positive tests occur from other diseases so that it is not considered a diagnostic test but rather a test that strongly supports the diagnosis.

Pulmonary function tests are able to be performed accurately in most children older than the age of 4 yr. There are no specific diagnostic findings of spirometry, lung volumes, or diffusion capacity in sarcoidosis. Exercise coupled with pulmonary function tests may demonstrate a decline in diffusion capacity when alveolitis is present in hypersensitivity pneumonitis and could add diagnostic help to the clinician when attempting to differentiate sarcoidosis from HP prior to biopsy.

BAL is of great help when differentiating HP from sarcoid. BAL in sarcoid shows a marked predominance of CD4 cells. A lymphocyte

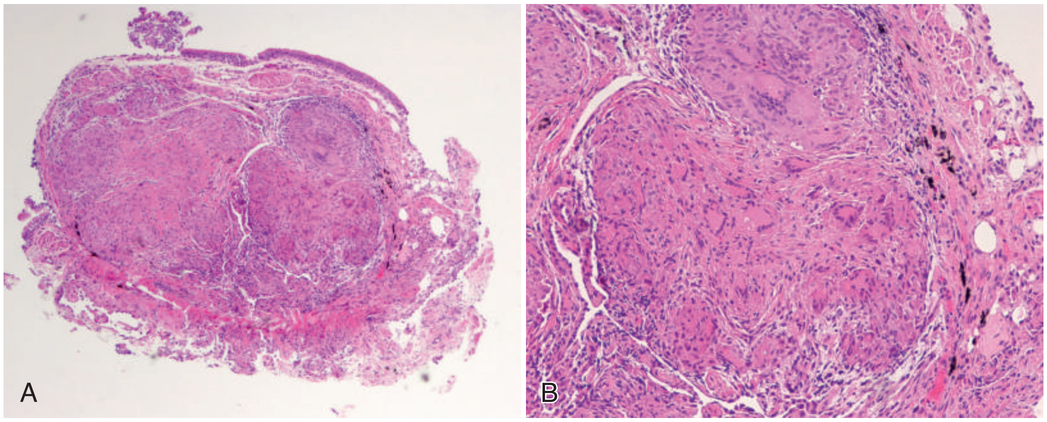

Figure 399-4 Transbronchial biopsy specimen showing a sarcoid granuloma. **A,** The granulomas are located below the bronchiolar epithelial layer that appears at the top of the frame. **B,** A higher-power view of the same biopsy specimen. The epithelioid granuloma is tightly packed and contains multiple multinucleated giant cells. There is no caseous necrosis. Special stains for acid-fast bacilli and fungi were negative. *(From Sneller MC, Fontana JR, Shelhamer JH. Immunologic nonasthmatic diseases of the lung. In Adkinson AF, editor:* Middleton's allergy principles and practice, *Philadelphia, 2014, Elsevier, Fig. 61-6.)*

percentage >16% on BAL, a CD4:CD8 ratio >4, and noncaseating granulomas on bronchial biopsy in the presence of abnormal angiotensin-converting enzyme levels are nearly completely diagnostic for sarcoid. In addition, T cells are activated on BAL. BAL in HP shows a significant change in the balance of CD4 to CD8 cells with the 2 cell types being nearly equal compared to the normal mild predominance of CD4 cells in the circulation. A ratio of CD4:CD8 of <1 predicts 100% of patients with BAL lymphocytosis to *not* have sarcoidosis. Neutrophil counts >2% and/or eosinophil counts >1% exclude the diagnosis of sarcoidosis.

The analysis of D-dimers in BAL fluid from subjects with sarcoidosis demonstrates an elevation in 80% of patients compared to no detectable D-dimers in unaffected control.

Histopathology

The characteristic feature of sarcoidosis is the noncaseating granuloma formation in the lung (Fig. 399-4). These granulomas are found in the bronchial walls, alveolar septa, and vascular walls of pulmonary arteries and veins. The formation of noncaseating granulomas is likely preceded by alveolitis involving the interstitium more than the alveolar spaces. There is accumulation of inflammatory cells, including monocytes, macrophages, and lymphocytes that accompany the granulomas. Multinucleated giant cells are frequently found among the epithelioid cells within the granuloma follicle. These may show cytoplasmic inclusions (e.g., asteroid bodies and Schaumann bodies) as well as some birefringent crystalline particles made of calcium oxalate and other calcium salts. These are most often identified in the upper lobes of the lungs which may lead to confusion with diseases such as hypersensitivity pneumonitis, eosinophilic granuloma, collagen vascular disease, pneumoconiosis, berylliosis, and infectious disease such as tuberculosis or histoplasmosis.

Radiology

Pulmonary imaging in sarcoid has included plain chest radiography, HRCT, **positron emission tomography** using fluorine-18-fluorodeoxyglucose, and radiotracer using gallium-67. The staging of sarcoid is performed using plain radiography and is outlined as follows:

- Stage I—Bilateral hilar lymphadenopathy accompanied by right paratracheal lymphadenopathy
- Stage II—Bilateral hilar lymphadenopathy accompanied by reticular opacities are present. If symptomatic, patients have cough and dyspnea. Occasional fever and fatigue accompany the respiratory symptoms.
- Stage III—Reticular opacities are found predominantly in the upper lobes with regression of hilar lymphadenopathy.
- Stage IV—Reticular opacities start to coalesce and lead to volume loss in the lung fields, traction bronchiectasis from conglomeration of the inflamed tissues. Extensive calcium deposits may be seen at this stage.

HRCT may be helpful in further staging of the disease, as well as in revealing abnormalities not appreciated on chest radiography. Findings in patients with sarcoidosis by HRCT include hilar lymphadenopathy, paratracheal nodules, middle to upper lung parenchymal ground-glass appearance, bronchial wall thickening, bronchiectasis, cystic changes, and fibrosis. The ground-glass appearance suggests that alveolitis, as seen in hypersensitivity pneumonitis, may be present. Biopsy has usually shown granuloma formation as the predominant histologic finding.

Treatment

Because pulmonary sarcoidosis spontaneously resolves without therapy in almost 75% of patients, clear guidelines for treatment focused on minimizing side effects of therapy is required. Glucocorticosteroids (GCSs) have long been the mainstay of therapy in sarcoid and are often used because of extra pulmonary disease. When pulmonary disease is progressive, GCS therapy is aimed at prevention of fibrosis, honeycombing, and irreversible lung disease. Assuring that disseminated infections, heart failure, thromboembolism, or pulmonary hypertension are not present is important. In addition to HRCT of the chest, performance of pulmonary function tests, electrocardiogram and echocardiogram should be considered prior to starting GCS therapy.

GCS therapy is often not started when stage I or II is present without symptoms. This scrutiny of the benefit of therapy was highlighted when prospective evaluation of GCS therapy for pulmonary disease found that nearly 50% of patients receiving GCSs had active or relapsing disease 2 yr later. In contrast, 90% of patients who did not receive GCSs had spontaneous remission of disease with the other 10% needing intervention 2 yr later. Absolute indications include progressive stage III disease with symptoms of shortness of breath, cough, or other chest symptoms such as pain. Progressive restriction shown on pulmonary function testing is an indication for therapy. Specific pulmonary function changes where lung capacity declines total 10% or greater, forced vital capacity declines 15% or more, or diffusion capacity degradation is seen of 20% or more are all indications for GCS intervention.

Dosage with oral prednisone at 0.3-0.5 mg/kg is a reasonable starting point depending on the severity of symptoms. Stability is usually achieved within 6-8 wks, after which slow progressive tapering of GCS may occur every 4-8 wks. Many favor the use of alternate-day steroids to reduce the side effects of GCSs, but little data exist to show efficacy.

Patients who do not tolerate GCSs or develop progressive disease, alternative immunosuppressive agents may add benefit to the regimen. Progressive disease also is a reminder for the clinician to reassess the diagnosis of sarcoid and review the chance that beryllium may have been the underlying reason for the progressive disease.

Inhaled GCSs have been evaluated in patients with stage I disease with variable results. Evaluation of therapy with pulmonary function testing and symptoms are the best methods to judge responsiveness to this therapy. Persistent symptoms after 4-8 wks of therapy suggest that systemic GCSs may be indicated.

BERYLLIOSIS

Chronic beryllium disease or berylliosis is an example of environmental exposure and unique granulomatous response in the lungs. Beryllium is an alkaline metal that is used in a number of industrial settings.

A diagnosis of berylliosis requires 3 criteria: (1) history of beryllium exposure; (2) positive response to lymphocyte proliferation tests to beryllium in lymphocytes obtained by BAL or blood test; and (3) noncaseating granulomas on lung biopsy. Exposure to beryllium may occur in industries such as automotive, ceramic, aerospace, metal extraction, electronics, computer, jewelry making, and dental alloys. Teenagers working summer jobs in machine work, ceramics, or wire production may be exposed. Sensitization is associated with dose and duration of exposure and has been seen to be as high as 20% in certain industries. Secretaries working in buildings where manufacturing with beryllium is active have developed berylliosis.

Pathogenesis

Genetic susceptibility coupled with immunologic response to beryllium are the 2 key contributors to the development of disease. A T-lymphocyte cell–mediated delayed hypersensitivity response to beryllium appears to be the mechanism involved with granuloma formation in the lung. The lymphocyte proliferation by T cells to beryllium is specific and does not occur to other metals. Similar to sarcoidosis, CD4+ T cells predominate on bronchoalveolar response. Beryllium appears to be inhaled and then couple with proteins in the lung or can be ingested by antigen-presenting cells. The cytokines elicited and granuloma formation suggests that sensitization is primarily a T-lymphocyte type 1 response with elevated interferon-γ and IL-2 production.

Clinical Manifestations

The clinical manifestations of berylliosis are not specific. Dry cough, fever, fatigue, weight loss, and shortness of breath all may be present. Although symptoms may occur within 3 mo, new disease has been detected up to 3 decades after exposure. Physical examination is somewhat different than the HPs and sarcoid with bibasilar crackles found on auscultation. The other mentioned diseases are more prominent in the upper lobes. Small nodule on exposed skin may also be present.

Laboratory Testing

Suspicion of berylliosis should prompt the clinician to have blood lymphocyte proliferation studies to beryllium performed as well as complete pulmonary functions. These tests need to be sent to a special center where multiple tests are run with comparison to proper positive and negative controls. When positive, the test has very high specificity for defining the presence of berylliosis at approximately 96%. However, sensitivity of the test hovers at <70%, suggesting that approximately 3 of every 10 patients who have disease may have a negative test.

Similar to other pulmonary granulomatous diseases, increased production of calcitriol is commonly found. The source of this active form of vitamin D is from activated pulmonary macrophages, which may result in hypercalciuria and hypercalcemia.

Radiography

Chest radiographs should be obtained on all patients suspected of having berylliosis. The chest radiograph may be normal, show hilar lymphadenopathy, pulmonary nodules, ground glass, or alveolar opacities. The parenchymal abnormalities may be diffuse or may be more prominent in the upper lobes. These findings are dependent upon the stage of the disease.

HRCT is the most sensitive test in the identification of chronic berylliosis. Almost 25% of the HRCT exams in patients with biopsy proven berylliosis are found to be normal. Similar to other granulomatous and HPs of the lungs, HRCT findings include parenchymal nodules of varying size, thick septal lines, ground-glass opacities, cystic cavitation, and lymphadenopathy in the hilum or mediastinum. Pleural abnormalities are less common, but thickening may be observed in proximity to parenchymal nodules.

Treatment

Managing berylliosis involves avoiding further exposure and therapy with glucocorticoids or other immunosuppressive agents. A decision to intervene depends on the severity of symptoms, physiologic impairment based on pulmonary function tests, and extent of radiographic changes. Treatment is usually started when the patient has dyspnea or cough, >10% decline in lung volumes or gas exchange, or abnormal pulmonary function tests at baseline.

Small case series have demonstrated efficacy of steroids judged by improvement of clinical symptoms, radiographic clearing of disease, and improvement in pulmonary functions, including diffusion capacity. Some patients despite improved symptoms have recurrence which may progress to fibrosis and persistent lung disease.

The differentiation between berylliosis and sarcoidosis appears to be important for long-term outcomes. It appears that the longer the delay in prescribing GCSs to patients with berylliosis may lead to a state where the lung disease is unresponsive to therapy. In contrast, use of steroids may lead to a higher rate of recurrent disease. What makes the 2 responses different is not known.

Dosing of steroids is similar to sarcoid with a starting dose of 0.5 mg/kg/day of prednisone for a duration of 6-12 wks. Once a response is established, conversion to every-other-day corticosteroid use at the same dose followed by tapering should be attempted until the lowest dose is achieved that controls the disease. Patients may require persistent therapy for the rest of their life. Genetic susceptibility to the disease may predict relapse of disease. Mutations in the HLA-DPB1 gene (homozygous for glutamate substitution at the β69 position) appear to predict specific patients who are susceptible to relapse of symptoms.

When patients fail to respond or experience recurrent relapse, methotrexate in low dose has conferred a favorable response in some patients as has been seen with sarcoidosis. Azathioprine may also be considered since sarcoidosis has responded favorably, however there are no published trials using this immunosuppressive agent. A small number of cases have also shown promise with TNF-α inhibitors both in sarcoid and beryllium-induced disease.

GRANULOMATOUS LUNG DISEASE IN PRIMARY IMMUNE DEFICIENCY

Primary immune deficiency (PID) often presents with recurrent or persistent pulmonary symptoms of recurrent infections, pneumonia, bronchiectasis, and interstitial lung disease with or without fibrosis. Immune dysregulation occurs in many of the PID with development of granulomatous lung disease and autoimmune disease. Most effort is focused on discovery of infectious pathogens in the PID causing pulmonary disturbance, but the dysregulation may be the primary problem causing symptoms and disease progression. This requires counterintuitive therapies with suppression of the immune system concurrently with immune deficiency therapy. The 2 most prominent PIDs associated with granulomatous lung disease are **chronic granulomatous disease (CGD)** (see Chapter 130) and **common variable immune deficiency (CVID)** (see Chapter 126).

The prototype organism causing granuloma formation in the lung is *Mycobacterium tuberculosis*. Nontuberculous mycobacterial infections also can cause granulomas in the presence of specific PID. These have been seen in impaired IL-12/IL-23/ IFN-γ signaling, or the presence of autoantibodies to IFN-γ. Patients with defective regulation of nuclear factor-kappa B (nuclear factor-kappa B essential modifier defects) have

also been described as well with nontuberculous mycobacteria. The clinician must be certain that this low-virulence organism is not causing disease before therapy for immune dysregulation is considered.

Pathogenesis

CGD is a PID involving multiple defects in the phagocyte nicotinamide adenine dinucleotide phosphate oxidase system, which impairs the respiratory burst capacity to generate reactive species of oxygen (see Chapter 130).

Up to 25% of patients with CVID develop lung disease (see Chapter 126). These pulmonary changes include organizing pneumonia, ILD, mucosa-associated lymphoid tissue lymphoma, and noncaseating granulomas in **granulomatous and lymphocytic interstitial lung disease (GLILD)**. Elevated levels of TNF from TNF polymorphisms have been implicated as a possible mechanism. GLILD is becoming recognized more frequently in CVID. It is defined by the presence of granulomatous and a lymphocytic proliferative pattern in the lung. Granulomas may be found in other organs including bone marrow, spleen, gastrointestinal tract, skin, and liver.

The etiology of GLILD is unknown. In a case cohort study, a majority of subjects with pathology diagnostic of GLILD were found to have human herpesvirus 8 infection of the lung. These may represent a subgroup of patients with GLILD which may point to a mechanism underlying the development of pulmonary granulomas.

GLILD is sometimes misdiagnosed as sarcoidosis initially because both involve pulmonary granuloma, often accompanied by hilar and/or mediastinal lymphadenopathy. Sarcoidosis has several features that distinguish it from GLILD, such as normal or elevated serum immunoglobulin levels and frequent spontaneous remissions.

Clinical Manifestations of Granulomatous Lung Disease in Primary Immune Deficiency

Chronic respiratory disease as a result of recurrent infections is common in CGD. This is accompanied by clubbing in some patients and the other organ manifestations in the skin, liver, and genitourinary and gastrointestinal tracts. Granulomas are especially problematic in the gastrointestinal and genitourinary tracts. The inhalation of fungal spores and hyphae has led to an acute pneumonia in CGD with rapid progression to respiratory failure with hypoxemia, dyspnea, and fever. This entity, characterized as *mulch pneumonia,* appears to be best treated with antifungal medications and corticosteroids.

Radiography

Hilar and/or mediastinal lymphadenopathy occur with granulomatous lung involvement. These may manifest as parenchymal nodules and/or ground glass abnormalities and can be seen commonly in CVID and CGD. Differentiating infectious causes of pulmonary infiltration in PID is often difficult on chest radiography; HRCT is often mandatory in the initial evaluation of the patients with CVID.

Laboratory and Pulmonary Function Testing

Definitive diagnosis is made by lung biopsy. Transbronchial biopsy in children is often insufficient and lung biopsy by video-assisted thoracoscopy or open biopsy is preferred. Unless the patient's underlying immune deficiency is unknown, other laboratory testing except for infectious organisms does not contribute significantly to the diagnosis. When the child is old enough, complete pulmonary functions with spirometry, flow volume loop, lung volumes, and diffusion capacity should be obtained at baseline and then followed serially for response to therapy or progression of disease.

Therapy

The presence of GLILD in CVID can be associated with significant morbidity and possibly death. Without therapy, progressive pulmonary fibrosis and respiratory failure may occur in GLILD. The parenchymal disease may not always be controlled or relieved by glucocorticoid treatment. Other treatments include TNF antagonists, cyclosporine, or a combination therapy with rituximab and azathioprine. Response to therapy is monitored clinically and by interval HRCT of the chest, and pulmonary function testing, including spirometry, lung volumes, and diffusing capacity.

Bibliography is available at Expert Consult.

399.4 Eosinophilic Lung Disease

Kevin J. Kelly

The eosinophilic lung diseases are a group of heterogeneous pulmonary disorders with a predominant diffuse infiltration of eosinophils in the alveolar spaces or interstitial pulmonary spaces. Lung architecture is well preserved throughout the inflammatory response, often with complete reversal of the inflammation without long-term sequelae in the majority of cases. The peripheral white blood count often (but not always) reveals elevated eosinophils. Prompt recognition of the nature of these diseases allows for lifesaving interventions in the idiopathic **acute eosinophilic pneumonia syndrome (AEP)** or resolution of persistent symptoms in the patients with chronic disease.

ETIOLOGY

Eosinophilic lung diseases are often classified under 2 subheadings: idiopathic disease and known causation (Table 399-8). They are frequently further subdivided as acute and chronic or infectious and noninfectious. The division of acute or chronic is arbitrary based on the length of symptoms present (acute = <1 mo and chronic = >1 mo) but is relevant to the clinician in determining the etiology of the symptoms in the differential diagnosis. **Löffler eosinophilic pneumonia**, induced by *Ascaris lumbricoides* and other ascarids, produces transient symptoms that self-resolve and is classified as neither acute nor chronic. Löffler syndrome has been more correctly termed pulmonary infiltrates with eosinophilia syndrome and is the most common eosinophilic infiltrative disease in children.

PATHOLOGY AND PATHOGENESIS

Eosinophilic lung disease, regardless of the stage of disease or etiology, shows mixed cellular infiltration of the alveoli and interstitial spaces with a predominance of eosinophils when transbronchial biopsy or open lung biopsy is performed. This may be accompanied by a fibrinous exudate with intact lung architecture. Other findings include eosinophilic microabscesses, a nonnecrotizing nongranulomatous vasculitis, and occasional multinucleated giant cells again without granuloma formation. BAL is the diagnostic procedure of choice, especially in the acute situation with the acute eosinophilic pneumonias; the differential cell count on the BAL is ≥25% eosinophils and is often more than 40%. This highly sensitive test and high specificity test has allowed clinicians to forego lung biopsy.

Eosinophils are filled with numerous toxic granules. Evidence of eosinophil degranulation may be found by electron microscopy, biopsy, urine excretion, and BAL fluid. Most commonly, eosinophil-derived neurotoxin, leukotriene E_4, other granule proteins, such as major basic protein, Charcot Leyden crystals, or proinflammatory cytokines, are identified and support the evidence that eosinophils are not only present but contributing to the disease process.

CLINICAL MANIFESTATIONS

Specific eosinophilic lung diseases present with a variable clinical picture; however, there are some common findings across many of the eosinophilic diseases. Dyspnea is the most common and prevalent symptom in patients with acute or chronic eosinophilic pneumonia and is accompanied by cough in the majority of patients (90%). Rhinitis and sinusitis symptoms are of lower prevalence with wide variability in children with eosinophilic pulmonary disease. Only the A specific disorder, **acute eosinophilic pneumonia**, consistently presents with respiratory failure and the requirement for mechanical ventilation at high levels of positive end expiratory pressure and high concentrations of oxygen. Although malignancy (e.g., eosinophilic leukemia) and organizing pneumonia may present with need for mechanical

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Table 399-8 Key Elements in the Medical History and Physical Exam to Raise Clinical Suspicion for Diagnostic Testing to Confirm Eosinophilic Lung Disease

Medical history and examination

- Drug exposure (especially antibiotics, NSAIDs, antiepileptics, antileukotriene modifiers in EGPA)
- Environmental inhalation exposures to dust or inhaled chemicals
- New onset of smoking cigarettes
- Travel or immigration status from areas endemic with various parasites or coccidiomycosis
- Asthma (may be severe or poorly controlled with ABPA, CSS, or is relatively new in onset with IAEP)
- ABPA concurrent in 7-10% of patients with cystic fibrosis
- Extrapulmonary symptoms suggestive of vasculitis, neuropathy, heart failure, or neoplasm)
- Rash (creeping eruption in visceral larval migrans disease or ulceration in EGPA)

Diagnostic imaging and testing

- Radiography helpful in AEP, CEP, and ABPA
- Radiography not diagnostic in EGPA or drug-induced eosinophilic disease of the lung
- Simple chest radiography findings
  - Nonlobar infiltrate
  - Classic description as mirror image of pulmonary edema with peripheral infiltrates
  - Bilateral pleural effusion in AEP
  - Central bronchiectasis in ABPA
- High-resolution computerized tomography of the chest
  - Middle and upper lobe nonlobar infiltrates with areas of ground-glass appearance
  - Mucous plugging in ABPA
  - Central bronchiectasis in ABPA (confused with cystic fibrosis)
- Blood eosinophil count
  - Elevated in many eosinophilic lung diseases
  - Magnitude of eosinophil blood count does not distinguish different pulmonary diseases
  - Usually not elevated in AEP (eosinophilic disease compartmentalized to lungs)
  - May occasionally not be elevated in CEP or after use of corticosteroids
- Total serum IgE elevated in ABPA but not always in patients with cystic fibrosis with ABPA
- Serology for helminthic infections or parasites may be diagnostic but are usually not available acutely
- P-ANCA (MPO ANCA) is positive in 40-70% of EGPA (CSS)
- BAL eosinophil percentage
  - ≥25% eosinophils diagnostic in AEP
  - ≥40% eosinophils diagnostic in CEP or tropical pulmonary eosinophilia
  - Eosinophil percentages below these criteria may require lung biopsy
  - <25% eosinophils seen in connective tissue disease, sarcoid, drug-induced disease, histiocytosis X of pulmonary Langerhans cells, and interstitial pulmonary fibrosis
- Lung biopsy
  - Open lung biopsy or video-assisted thoracoscopic surgery when BAL nondiagnostic
  - Transbronchial biopsy is usually insufficient with peripheral infiltrative disease
  - Histology with alveolar and interstitial infiltrates of eosinophils, non-necrotizing non-granulomatous vasculitis, multinucleated giant cells without granuloma
  - EGPA shows eosinophil rich small to medium vessel, necrotizing, granulomatous vasculitis

ABPA, allergic bronchopulmonary aspergillosis; AEP, acute eosinophilic pneumonia; BAL, bronchoalveolar lavage; CEP, chronic eosinophilic pneumonia; CSS, Churg-Strauss syndrome; EGPA, eosinophilic granulomatosis with polyangiitis; IAEP, idiopathic acute eosinophilic pneumonia; MPO ANCA, myeloperoxidase antineutrophil cytoplasmic antibody; NSAID, nonsteroidal antiinflammatory drug; P-ANCA, perinuclear antineutrophil cytoplasmic antibody.

ventilation, they are less common. A history of asthma is common in the chronic eosinophilic pneumonias and in allergic bronchopulmonary aspergillosis (ABPA) and often precedes the diagnosis of these 2 conditions.

Other symptoms of fever, myalgia, fatigue, weight loss, poor appetite, and night sweats may accompany the acute or chronic eosinophilic pneumonias. When abnormalities of the liver are detected, or if arthralgia, skin changes, pericardial effusion, or peripheral neuropathy accompany the disease presentation, a diagnosis of eosinophilic GPA (formerly known as the Churg-Strauss syndrome) or the hypereosinophilic syndrome should be aggressively investigated.

Chest Imaging

The chest radiograph is one of the most helpful tests in evaluating the child with dyspnea. The characteristic feature of fluffy alveolar infiltrates in the peripheral lung field is classic (Fig. 399-5). The images may be easily recognizable by astute clinicians who have identified the etiology of the disease without eosinophil counts or BAL.

HRCT is the best advanced imaging modality for eosinophilic lung disease. Spontaneous migration of lung opacities is commonly seen in the chronic pneumonias. Most often HRCT shows simultaneous evidence of bilateral alveolar infiltrates with both confluent consolidations and ground glass appearance. The most prominent areas of abnormality are visualized in the upper lobes and subpleural regions. Specific diseases have unique findings, such as proximal bronchiectasis in ABPA and pleural effusion in acute eosinophilic pneumonia. HRCT is most sensitive in identifying the correct etiology of disease when chest radiographic findings are nonspecific.

LÖFFLER SYNDROME

The transient pulmonary infiltrates with eosinophilia syndrome that is most often seen in children (formerly known as Löffler syndrome) is characterized by migrating pulmonary infiltrates with peripheral blood eosinophilia caused by the helminthic infections. *A. lumbricoides* or roundworm is the most common parasite causing this disease in the United States. When a fertilized egg is ingested from contaminated food, it becomes a larval worm that can penetrate the duodenum of the small intestine and migrate in the circulation to the liver, heart, and lungs. In the pulmonary venous circulation, the larvae can break through the interstitial space to the alveoli. The juvenile larva may subsequently migrate to the trachea where they are coughed up and swallowed. The cycle may then recur with subsequent absorption of eggs that are produced in the intestinal track. Other nematodes cannot mature in the intestinal tract so their disease is limited to a single passage into the lungs.

Visceral larva migrans from multiple nematodes may cause this disease. The most common cause of these includes the dog roundworm, *Toxocara canis*, while *Toxocara cati, Strongyloides stercoralis, Baylisascaris procyonis,* and *Lagochilascaris minor* can all produce visceral larva migrans. Outside the United States, the common lung fluke, *Paragonimus westermani*, may cause a similar pulmonary disease in older children and adolescents. Western Africa, Central and South America, and the Far East are regions that paragonimiasis may be found, especially in those who eat raw crabs or crawfish. Many other parasites may have a transient pulmonary syndrome, but their diseases are most commonly manifested in other organs.

The pulmonary syndrome is classic with cough, dyspnea, migratory peripheral pulmonary infiltrates, and blood eosinophilia that is self-limited. Young children most often have a history of pica and eating dirt that is contaminated with the eggs. Because the larva can migrate to other organs as well as multiply in the intestinal and biliary tract, symptoms of abdominal pain, vomiting, rarely obstruction, cholecystitis, and pancreatitis may be found. Diagnosis is frequently made by examination of the stool where the eggs may be detected microscopically. Treatment is aimed at the intestinal disease and not the pulmonary disease per se. It is possible that antihelminthic treatment of other organ disease during the pulmonary phase of the disease will increase the inflammatory response in the lung and may require corticosteroid therapy.

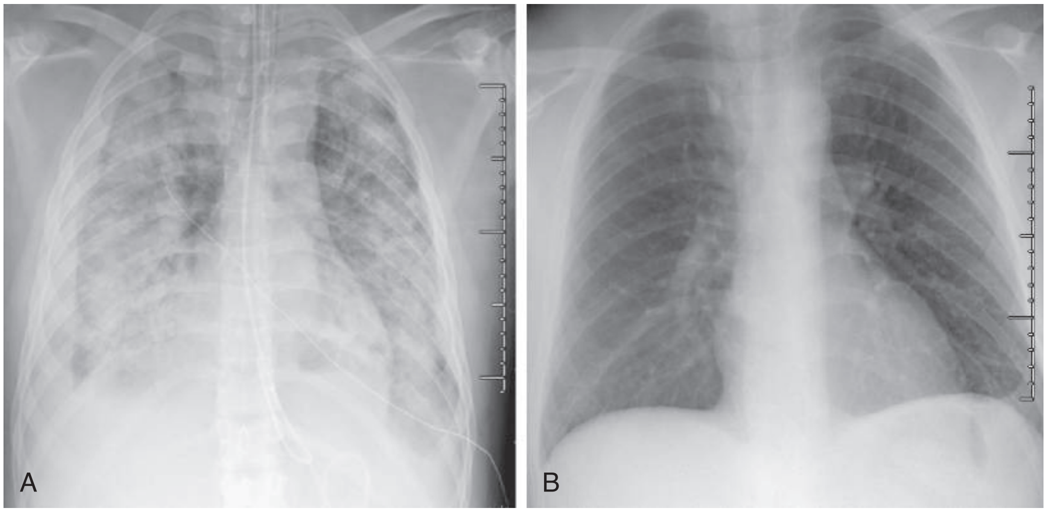

Figure 399-5 Acute eosinophilic pneumonia demonstrating the mirror image **(A)** pulmonary edema with a right pleural effusion on admission and **(B)** complete clearing upon discharge from the hospital after corticosteroid usage.

ACUTE EOSINOPHILIC PNEUMONIA

A unique and dramatic presentation of the eosinophilic pneumonias is AEP. AEP mimics infectious pneumonia or acute respiratory distress syndrome with its rapid onset and marked hypoxemia. In pediatrics, this disease most frequently occurs in the teenage population. Overall, young adults most commonly contract this idiopathic disease. Essentially all patients present within 7 days of symptom onset with dyspnea, fever, and cough, and more than 50% have chest pain. Myalgia and abdominal pain also frequently accompany this disease. Rarely, patients have presented up to 4-5 wks after onset of symptoms. Physical exam demonstrates tachypnea, tachycardia, and crackles in the lung fields on physical exam. Many patients rapidly deteriorate and require mechanical ventilation.

There is an absence of circulating eosinophilia, which contrasts the dramatic number of eosinophils seen in the BAL representing at least 25% of the inflammatory cells (often 40-55%) (Fig. 399-6). This feature helps distinguish it from the chronic pulmonary disease of eosinophilic origin.

Although this disease has been labeled as idiopathic, there have been identifiable exposures (e.g., 1,1,1-trichloroethane or Scotchgard). Numerous reports link onset of smoking tobacco, change in smoking frequency, reinitiation of smoking in young male adolescents or adults, and even massive secondary smoke exposure as critical associations with onset of AEP. World Trade Center dust is associated with development of AEP. A single smoke challenge study is associated with recurrence. Some medications are also linked to the onset of AEP. The most complete and current resource for medications linked to pulmonary disease is "The Drug-Induced Respiratory Disease Website" (http://www.pneumotox.com). When AEP is identified in a patient, the pediatrician's role in educating the patient and family about the link to smoking exposure and risk of AEP upon reexposure is warranted.

In addition to smoke exposure, AEP has been reported after smoking cocaine within hours to days after exposure. Whether this is a unique eosinophilic response to cocaine that represents one manifestation of "crack lung" or is a separate disease is unknown. "Crack lung" refers to diffuse alveolitis with pulmonary hemorrhage from an unknown mechanism that occurs within 48 hr of cocaine smoke inhalation.

Lung function has not been measured frequently in the disease because the patients have proceeded rapidly to the ICU and need for mechanical ventilation. When measured, a restrictive pattern of lung disease and reduced diffusion capacity is the usual finding arterial blood gases will show a significant increase in the alveolar–arterial gradient (see Chapter 373).

The criteria for diagnosis include the acute onset of disease, bilateral pulmonary infiltrates, reduced oxygen saturation or Pa_{O_2} ≤60 mm Hg, BAL of ≥25%, and absence of a determined cause of eosinophilia. The recent onset of tobacco exposure, dust, or chemical inhalation is supporting factors in confirming a diagnosis.

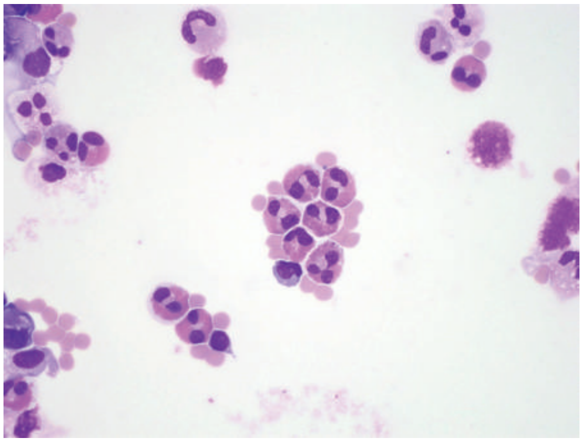

Figure 399-6 Light microscopy of eosinophils in bronchoalveolar lavage fluid.

Treatment has uniformly been the use of a corticosteroid (e.g., methylprednisolone 1-2 mg/kg/day) either intravenously or orally for 2-4 wks. A minimum or maximum treatment time has not been determined, but relapses or persistent symptoms are uncommon. Rare fatalities have been reported. Complete recovery has been seen in days with resolution of pleural effusions within the 4 wk treatment time. Most important, relapse has been rare, which sharply contrasts the idiopathic chronic eosinophilic pneumonias. Follow-up testing of pulmonary functions are usually normal which supports the contention that lung parenchyma heals without evidence of compromise or fibrosis.

CHRONIC EOSINOPHILIC PNEUMONIA

Chronic eosinophilic pneumonia is another idiopathic pulmonary condition without a known exposure to toxin, dust, or chemical inhalation. Eosinophils infiltrate the lung parenchyma resulting in dyspnea, cough, fever, and weight loss. It is primarily a problem for adults, with a female predominance (2:1 female:male ratio) usually in patients who are nonsmokers. Chest examination reveals tachypnea, crackles, and occasional wheezing as preceding asthma is a common finding. The classic finding on chest x-ray of the "radiographic negative of

pulmonary edema" is found in these patients: central clear lung fields but fluffy, patchy peripheral infiltrates of the lung parenchyma.

When compared to AEP, the onset of disease is indolent and subtle but the accompanying fever and weight loss may lead the clinician to a concern for an underlying malignancy prior to chest radiograph and laboratory investigation. Peripheral blood eosinophilia is commonly as high as 5000/mm^3 or greater, accompanied by BAL eosinophilia >40% on the differential count. The peripheral eosinophilia sharply contrasts the lack of eosinophils seen in the blood in AEP. HRCT scan contrasts the AEP with pleural effusion as a rare finding, as well as rare cavitation.

In contrast to AEP, pulmonary function testing shows a mixed obstructive and restrictive pattern as a result of asthma occurring concurrently with pneumonia.

Inflammatory markers associated with migration and activation of eosinophils are predictably found in BAL and the urine. These include the T-lymphocyte type 2 cytokines of IL-4, IL-5, IL-6, IL-10, IL-13, and IL-18. However, T-lymphocyte type 1 cytokines of IL-2 and IL-12 are also present with many of the potent eosinophilic chemoattractants such as CCL5 (RANTES [regulated upon activation, normal T cell expressed and secreted]) and CCL11 (eotaxin-1). Toxic granule proteins of major basic protein, eosinophil-derived neurotoxin, and eosinophil cationic protein are frequently present. Unfortunately, these important molecules help confirm the eosinophilic nature of the disease, but their presence adds no additional sensitivity or specificity over the presence of eosinophils on BAL.

Treatment is similar to most eosinophilic lung syndromes where corticosteroids (oral) are the mainstay of treatment. The minimum dose of steroid needed to induce remission is not known, but most clinicians recommend prednisone (or equivalent) at 0.5 mg/kg/day for 2 wks. The dose is reduced to half (0.025 mg/kg/day) for an additional 2 wks if symptoms have abated. The remaining dose of steroid may need to be weaned over 6 mo. Symptoms and pulmonary infiltrates rapidly disappear after initiation of this treatment but frequently recur with tapering of the steroid. Asthma concurrently in patients with chronic eosinophilic pneumonia identifies a phenotype of the disease that appears to have lower relapse risk yet up to 50% of all identified patients with chronic eosinophilic pneumonia relapse during or after corticosteroid taper.

Many believe that this disease is a precursor to the development of **eosinophilic granulomatosis with polyangiitis (EGPA)** or the Churg-Strauss syndrome. The utility of inhaled corticosteroids in chronic eosinophilic pneumonia is unknown but is warranted for the persistent asthma phenotype of disease. A subset of patients develop permanent lower airway obstruction without reversibility, which requires patients with this disease to have close follow-up and monitoring of pulmonary function tests routinely.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (THE CHURG-STRAUSS SYNDROME)

The EGPA syndrome is a systemic disease involving multiple organs but most prominently the lung. Patients present with difficult to control asthma, allergic rhinitis, and peripheral eosinophilia (>10% or >1,500 cells/μL) in the blood. Evidence of vasculitis on clinical grounds must be present in at least 2 organs. The polyangiitis appears later in the disease process with asthma being the precursor symptom in more than 90% of the cases reported. EGPA affects multiple organs including the skin, heart, gastrointestinal tract, kidneys, and central nervous system. Rhinitis is present in 75% of the patients but is not specific. Symptom complexes of fever, weight loss, fatigue, arthralgia, and myalgia may be seen in approximately two-thirds of patients. Cardiac and renal involvement is insidious in onset and should be screened for. It is the multiple organ involvement that results in the morbidity and mortality of this disease. The typical progression of the disease is in 3 phases: rhinitis and asthma first, tissue eosinophilia second, and, finally, systemic vasculitis.

The pathogenesis of EGPA is still unknown but several factors are suspected to contribute to the development of the disease. The possible link between leukotriene-receptor antagonists (zafirlukast, montelukast, or pranlukast) is controversial but still considered possible. It is suspected that use of this class of adjunctive medications in severe asthma allows for the reduction in use of corticosteroid leading to the full blown (unmasking) manifestation of EGPA. Isolated use of leukotriene-receptor antagonists may induce disease, lead to remission with cessation of leukotriene-receptor antagonists, and cause recurrence of EGPA upon reintroduction of this class of medications. Many refrain from use of leukotriene-receptor antagonists when the EGPA syndrome has been diagnosed.

Clinical and laboratory finding are able to pinpoint the diagnosis with high specificity (99.7%) and sensitivity (85%) when 4 of 6 criteria are met (asthma, eosinophilia >10%, mononeuropathy or polyneuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormalities, and biopsy findings of extravascular eosinophil infiltrates). In contrast to GPA, the rhinitis is not destructive and nasal septal perforation does not occur in EGPA.

Radiography of the chest by plain radiography or HRCT demonstrates the migratory, peripheral predominant opacities with ground-glass appearance to full consolidation. Bronchiectasis and bronchial wall thickening are reported. Pleural effusion should raise suspicion for the presence of heart failure from cardiomyopathy.

Laboratory findings include striking eosinophilia with values generally between 5,000 and 20,000/mm^3 at the time of diagnosis. These counts often parallel the vasculitis activity that is found. The BAL shows striking eosinophilia with differential counts of >60%. Other organ system levels reflect activity of eosinophils and are not specific for the EGPA diagnosis.

ANCAs are present in the EGPA syndrome. The **perinuclear-ANCA targeting myeloperoxidase** are specifically found in EGPA in approximately 40% of the patients; the absence of myeloperoxidase-ANCA does not exclude the diagnosis. Those patients with eosinophilic pneumonia, fever, and cardiac involvement are less likely to have myeloperoxidase-ANCA detected. Those with peripheral neuropathy, renal glomerular disease, and skin purpura usually have detectable myeloperoxidase-ANCAs.

Pulmonary function tests while on bronchodilators and inhaled corticosteroids for asthma show an obstructive pattern. The pulmonary obstruction is responsive to oral corticosteroid use but often has mild persistence of obstruction.

Treatment of EGPA with systemic oral corticosteroid remains the mainstay of therapy at a starting dose of 1 mg/kg/day for 4 wks. This therapy is often required for up to 12 mo or longer with a steady taper in dosage over that time. EGPA resistant to corticosteroid has responded to cyclophosphamide, IFN-α, cyclosporine, intravenous immunoglobulin, and plasmapheresis. The use of anti–IL-5 (mepolizumab) has been encouraging and may be used as a steroid-sparing agent in the future.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

ABPA is a complex mixed immunologic hypersensitivity reaction in the lungs and bronchi in response to exposure and colonization of *Aspergillus* species (usually *Aspergillus fumigatus*; see Chapter 237.1). This disease almost exclusively occurs in patients with preexisting asthma and up to 15% of patients with cystic fibrosis (see Chapter 402). The quantity of *Aspergillus* exposure does not correlate to the severity of disease.

The clinical pattern of disease (Table 399-9) is remarkably similar with a clinical presentation of difficult-to-treat asthma, periods of acute obstructive lung disease with bronchial mucous plugs, elevated total IgE antibody, elevated specific IgE and IgG anti-*Aspergillus* antibodies, skin prick test reactions to *Aspergillus* species, precipitating antibody to *Aspergillus* species, as well as proximal bronchiectasis. Other clinical manifestations include dyspnea, cough, shortness of breath, production of brown mucous plugs frequently characterized as "rubber" plugs, and peripheral eosinophilia, as well as pulmonary eosinophilia with infiltration of the parenchyma. The use of systemic corticosteroid may lower the total IgE antibody levels such that

Table 399-9 The Classification of the Eosinophilic Lung Diseases

IDIOPATHIC	KNOWN ETIOLOGY
Acute eosinophilic pneumonia	Drug-induced eosinophilic pneumonia
Chronic eosinophilic pneumonia	Infectious causes
Eosinophilic granulomatosis with polyangiitis	• Ascariasis (Löffler syndrome)*
Hypereosinophilic syndromes	• *Toxocara* (*canis* or *cati*)
• Myeloproliferative variant	• Filarial (tropical filarial eosinophilic pneumonia)
• Lymphocytic variant	• *Strongyloides stercoralis* Allergic bronchopulmonary aspergillosis Toxic • L-Tryptophan (eosinophilia myalgia syndrome) • Toxic oil syndrome Illicit drug use (cocaine, heroin, cannabis)

*Note: Löffler eosinophilic pneumonia has transient symptoms and is often classified as neither an acute or chronic eosinophilic pneumonia.

a diagnosis may be in question when the first tests are performed at that time.

ABPA should be considered in patients with cystic fibrosis when clinical deterioration occurs without evidence of an identifiable cause. Symptoms heralding such deterioration include increasing cough, wheezing, loss of exercise tolerance, worsening exercise-induced asthma, reduction of pulmonary function, or increased sputum production without another discernible reason. Clinical findings of elevated total IgE antibody, anti-*Aspergillus* IgE, precipitating antibodies to *A. fumigatus*, and/or new abnormalities on chest radiography that fail to clear with antibiotics should alert the clinician to the possibility of ABPA.

When evaluating a child with asthma symptoms, the clinician must distinguish asthma from ABPA. If the diagnosis is suspected, skin prick test for evidence of IgE-specific antibody directed against *A. fumigatus* is essential. Intradermal skin testing when the skin prick test is negative, although not routinely performed because of poor specificity, may be performed. The absence of a positive skin prick test and intradermal test to *A. fumigatus* virtually excludes the diagnosis of ABPA. The prevalence of ABPA in patients with an existing diagnosis of asthma and an abnormal immediate skin prick test response to *A. fumigatus* has been evaluated. Between 2% and 32% of patients with asthma with concurrent skin prick test–positive reactions to *Aspergillus* have evidence of ABPA.

It is uncommon for the patient with cystic fibrosis to develop ABPA before the age of 6 yr. When the total IgE antibody in patients with cystic fibrosis exceed 500 IU/mL (1,200 ng/mL), a strong clinical suspicion of ABPA is necessary.

ABPA pathology has characteristic findings of mucoid bronchi impaction, eosinophilic pneumonia, and bronchocentric granulomas in addition to the typical histologic features of asthma. Septated hyphae are often found in the mucus-filled bronchial tree. However, the fungi do not invade the mucosa in this unique disease. *Aspergillus* may be cultured from sputum in more than 60% of ABPA patients. Interestingly, hyphae may not always be seen on microscopy.

Staging of the disease (Table 399-10) represents distinct phases of the disease but do not necessarily progress in sequence from stage 1 to stage 5. Staging of ABPA is important for treatment considerations. In many hypersensitivity diseases where IgE antibody contributes to the pathogenesis (e.g., asthma), total IgE is often used for screening for an atopic state, but is not a test that helps the clinician with serial

Table 399-10 Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis–central bronchiectasis
- Medical history of asthma*
- Immediate skin prick test reaction to *Aspergillus* antigens*
- Precipitating (IgG) serum antibodies to *Aspergillus fumigatus**
- Total IgE concentration >417 IU/mL (>1000 ng/mL)*
- Central bronchiectasis on chest CT*
- Peripheral blood eosinophilia >500/mm^3
- Lung infiltrates on chest x-ray or chest HRCT
- Elevated specific serum IgE and IgG to *A. fumigatus*

Allergic bronchopulmonary aspergillosis seropositive†
- Medical history of asthma†
- Immediate skin prick test reaction to *A. fumigatus* antigens†
- Precipitating (IgG) serum antibodies to *A. fumigatus*†
- Total IgE concentration >417 IU/mL (>1000 ng/mL)†

Staging of allergic bronchopulmonary aspergillosis

Stage 1	Acute	Upper and middle lob infiltration	High IgE
Stage 2	Remission	No infiltrate off steroids >6 mo	Normal to high IgE
Stage 3	Exacerbation	Upper and middle lobe in filtrations	High IgE
Stage 4	CSD asthma	Minimal infiltrate	Normal to high IgE
Stage 5	End stage	Fibrosis and/or bullae	Normal

*The criteria required for diagnosis of ABPA with central bronchiectasis.
†The first 4 criteria are required for a diagnosis of seropositive ABPA.
CSD, corticosteroid dependent.

measures. In sharp contrast, the measurement of IgE during acute exacerbations, remission, and recurrent ABPA disease is helpful in identifying the activity of disease and may herald the recurrence. During stage 1 disease, the level of IgE antibody is often very high. During stage 2 remission, a fall in the levels may be as much as 35% or more. Recurrence of activity may result in a marked rise of total IgE with a doubling of the baseline level seen during remission. During the use of glucocorticoid therapy, monthly or bimonthly levels of IgE are followed serially to assist the clinician in tapering therapy. Because exacerbations of ABPA are asymptomatic to the patient in approximately 25% of the recurrences, serial IgE accompanied by chest radiography are helpful to the clinician to guide therapy.

Radiography

Plain chest X-ray shows evidence of infiltrates especially in the upper lobes and the classic findings of bronchiectasis (Fig. 399-7). The use of HRCT demonstrates central bronchiectasis in the central regions of the lung (Fig. 399-8). HRCT may add value in the patient with a positive skin prick test and normal chest radiograph in detecting characteristic abnormalities of ABPA.

Treatment

The mainstay of therapy for ABPA has been systemic glucocorticoids with adjunct therapy with antifungal medications and anti-IgE therapy with omalizumab. Exacerbations in stages 1 and 3 are treated for 14 days with 0.5-1 mg/kg of glucocorticoid followed by every-other-day usage and tapering over 3 mo or as long as 6 mo. Stage 2 remission phase and stage 5 where fibrosis has occurred do not require glucocorticoid therapy. Stage 4 denotes a state where glucocorticoid weaning has not been successful and continued long-term therapy is required.

Antifungal therapy with a 16 wk course of itraconazole improves the response rate during exacerbations that allowed reduction of glucocorticoid dosage by 50% accompanied by a reduction of total serum IgE of 25% or more. The proposed mechanisms of action have been to either reduce the antigen load driving the immune response or possibly raising the serum levels of corticosteroid by slowing the metabolism

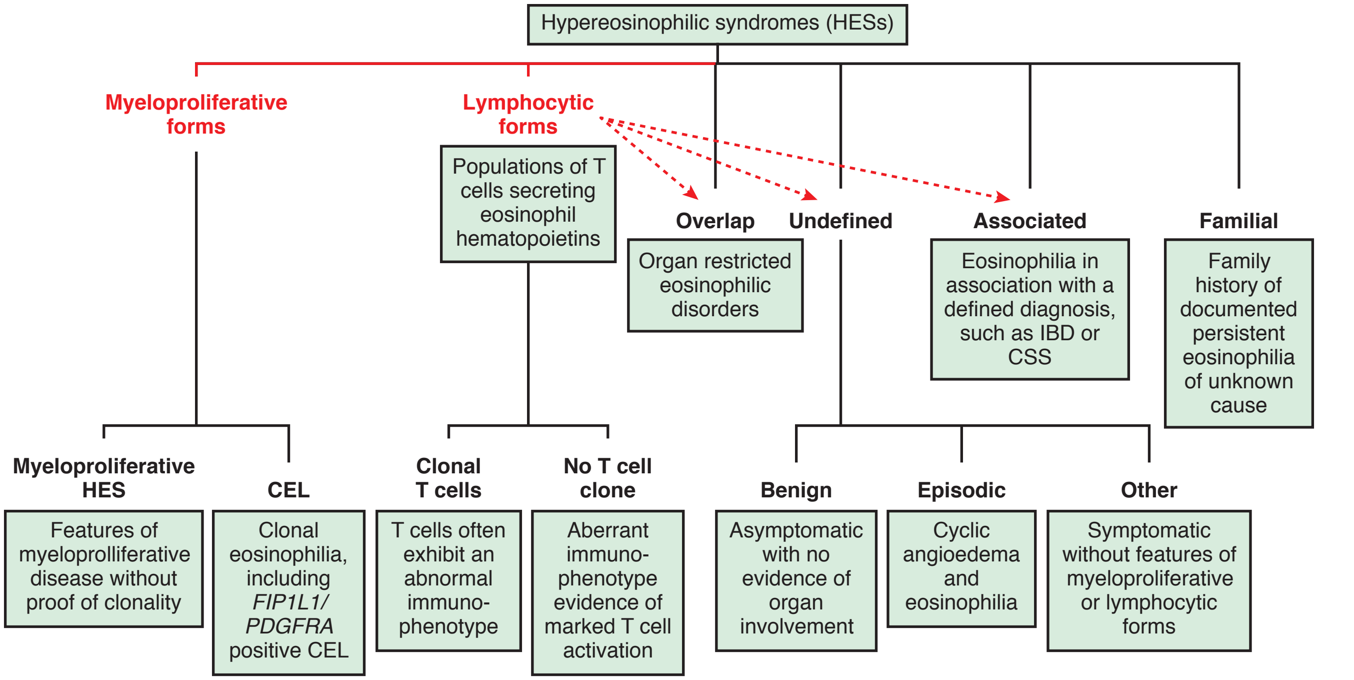

Figure 399-7 A revised classification of hypereosinophilic syndrome (HES). Changes from the previous classification are indicated in red. *Dashed arrows* identify HES forms for which at least some patients have T-cell–driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin-producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES. CSS, Churg-Strauss syndrome; IBD, inflammatory bowel disease. *(From Simon H, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome.* J Allergy Clin Immunol *126:45–49, 2010, Fig. 1.)*

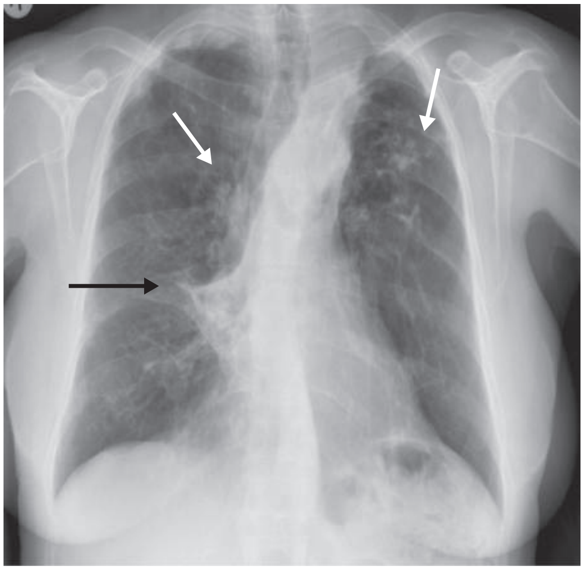

Figure 399-8 Transitory opacities *(white arrows)* and lobar collapse *(black arrow)* in patient with allergic bronchopulmonary aspergillosis. *(From Douglass JA, Sandrini A, Holgate ST, O'Hehir RE: Allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis. In Adkinson AF, editor:* Middleton's allergy principles and practice, *Philadelphia, 2014, Elsevier, Fig. 61-2.)*

of the steroid. This latter mechanism would be true for prednisone, which is methylated in the liver, but not for methylprednisolone, which does not require methylation.

The adult dosage recommendation for itraconazole is 200 mg 3 times per day for 3 days followed by 200 mg twice daily for the remainder of the 16 wks. Children should receive 5 mg/kg/day in a single dose. If the proper calculated dose exceeds 200 mg, then the total dose should be divided equally and given twice daily. Serum levels of itraconazole are necessary to ensure proper absorption of the drug is occurring from the capsule form. The liquid form is more readily absorbed and has achieved levels substantially higher. The use of proton pump inhibitors and histamine 2 antagonists may reduce absorption from blockade of acid production. Voriconazole has been used as a substitute antifungal medication. Proper dosing has been established for invasive *Aspergillus* disease, but not for ABPA. Typical dosage regimen in children of 7 mg/kg/day may cause hepatotoxicity and liver function must be monitored.

Omalizumab, an anti-IgE humanized monoclonal antibody, has been used in case series of patients with cystic fibrosis and ABPA as well as a small cohort of adults without cystic fibrosis but with ABPA. Both case series demonstrated significant reductions in asthma exacerbations, ABPA exacerbations, and glucocorticoid usage. The dose prescribed has been 300-375 mg every 2 wk by subcutaneous injection.

HYPEREOSINOPHILIC SYNDROME

See Chapter 129.

The hypereosinophilic syndrome (HES) is a descriptive name of a group of disorders that are characterized by the persistent overproduction of eosinophils accompanied by eosinophil infiltration in multiple organs with end-organ damage from mediator release. The term HES should only be used when there is eosinophilia with end-organ damage from the eosinophils and not from another cause. The discovery of underlying genetic, biochemical, or neoplastic reasons for HES has led to the classification of primary, secondary, and idiopathic HES (Table 399-11). Specific syndromes such as EGPA (Churg-Strauss) have eosinophilia but the contribution of eosinophils to the organ damage is incompletely understood.

Some variants of HES have genetic mutations in tyrosine kinase receptor platelet-derived growth factor receptor-α (*PDGFRA*); males are almost exclusively affected. Otherwise, HES appears to be distributed equally among females and males.

Hypereosinophilia is defined as an absolute eosinophil number in the blood that exceeds 1.5×10^9 eosinophils on 2 separate occasions

separated by at least 1 mo. Tissues are abnormal when more than 20% of nucleated cells in the bone marrow are of eosinophil origin; a pathologist determines the presence of eosinophilia; or the presence of extensive eosinophilic granule proteins are determined on biopsy to be deposited in large quantities. These disorders can be subclassified into primary (neoplastic), secondary (reactive), and idiopathic (Fig. 399-9).

Clinical manifestations of the HES include organ involvement of the heart (5%), gastrointestinal (14%), skin (37%), and pulmonary (25%-63%). The HES is complicated by thrombosis and/or neurologic disease in many patients, although the exact prevalence of this problem is incompletely categorized. Peripheral neuropathy, encephalopathy, transverse sinus thrombosis, or cerebral emboli are the most common neurologic complications. The exact mechanism of the manifestations is unclear especially in major artery thrombosis such as the femoral artery.

The most frequent pulmonary symptoms include cough and dyspnea. Many patients have obstructive lung disease with clinical wheezing. Evidence of pulmonary fibrosis and pulmonary emboli are seen with regularity. Because biopsy shows eosinophilic infiltrates similar to other pulmonary eosinophilic diseases of the lung, it is the constellation of other organ involvement or thromboembolic phenomena and other organs that must lead the clinician to a high index of suspicion for the HES.

Table 399-11	Hypereosinophilic Syndrome Variants
Myeloproliferative	Nonclonal Clonal–F1P1L1/PDGFRA-positive chronic eosinophilic leukemia
Lymphocytic	Nonclonal T cells Clonal T-cell expansion with T-cell activation
Overlap	Organ restricted
Familial	Family history of eosinophilia without known cause
Associated	Eosinophilia in chronic disease like inflammatory bowel disease or EGPA (Churg-Strauss syndrome)
Undefined	Asymptomatic Cyclic angioedema with eosinophilia (Gleich syndrome) Symptomatic without myeloproliferation or lymphocytic form

EGPA, eosinophilic granulomatosis with polyangiitis; PDGFRA, platelet-derived growth factor receptor-α.

Laboratory evaluation should include evaluation of liver enzymes, kidney function tests, creatine kinase, and troponin. The extent of cardiac involvement should be evaluated by electrocardiogram and echocardiogram. Some unique biomarkers may be tested when evaluating the myeloproliferative and T-lymphocyte HES diagnoses. Vitamin B_{12} and serum tryptase may be elevated, especially the latter, when the myeloproliferative disease is accompanied by mastocytosis. These 2 biomarkers are most frequently elevated when the mutation is present or fusion in the FIP1L1/PDGFRA sites.

Because of the extensive pulmonary disease that is seen in the HES, pulmonary function tests should be performed at diagnosis when possible to include spirometry and lung volumes. Dead space ventilation may be significantly elevated in the patients with pulmonary emboli. Pulse oximeter may be very helpful in the evaluation as well.

Chest radiography and CT are very helpful in the evaluation. Spiral chest CT should also be performed when pulmonary emboli are being considered. In one series of patients, nearly half of the patients with HES had evidence of pulmonary abnormalities including ground-glass appearing infiltrates, pulmonary emboli, mediastinal lymphadenopathy, and/or pleural effusion.

Treatment of HES depends on the type of variant (myeloproliferative, lymphocytic forms, undefined, associated with systemic diseases such as EGPA or familial). Rarely, some patients present with marked eosinophilia where the total count exceeds 100,000 cells/µL and vascular insufficiency symptoms. Prednisone at 15 mg/kg is indicated to acutely reduce the eosinophil count, after diagnostic tests are performed, when safe. If the patient is unstable, the glucocorticoid should be administered to prevent progression of symptoms. Other acute therapies aimed at reduction of eosinophil counts include vincristine, imatinib mesylate, or even leukophoresis.

When eosinophil counts are not as dramatically elevated, therapy begins with glucocorticoids at 1 mg/kg for patients who do not have the FIP1L1/PDGFRA mutation. Patients with this mutation are resistant to glucocorticoids and initial treatment should begin with imatinib, a tyrosine kinase inhibitor. Because this genetic test is often not readily available, surrogate markers for the presence of this mutation are vitamin B_{12} levels >2000 pg/mL or serum tryptase >11.5 ng/mL. It denotes the presence of resistant disease that should initially be treated with imatinib. The goal of therapy is to reduce and maintain eosinophil counts below 1.5×10^9 at the lowest dose of prednisone possible to reduce or avoid corticosteroid side effects. If corticosteroid doses can't be lowered below 10 mg/day, then imatinib can be added as combination therapy in order to spare the dose of steroid. Caution must be used in the presence of cardiac disease as introduction of imatinib has precipitated left ventricular failure.

Additional or alternative adjunct therapies that have shown promise include hydroxyurea, interferon α, anti–IL-5 monoclonal antibody therapy; and a monoclonal antibody directed against CD52. Failure of

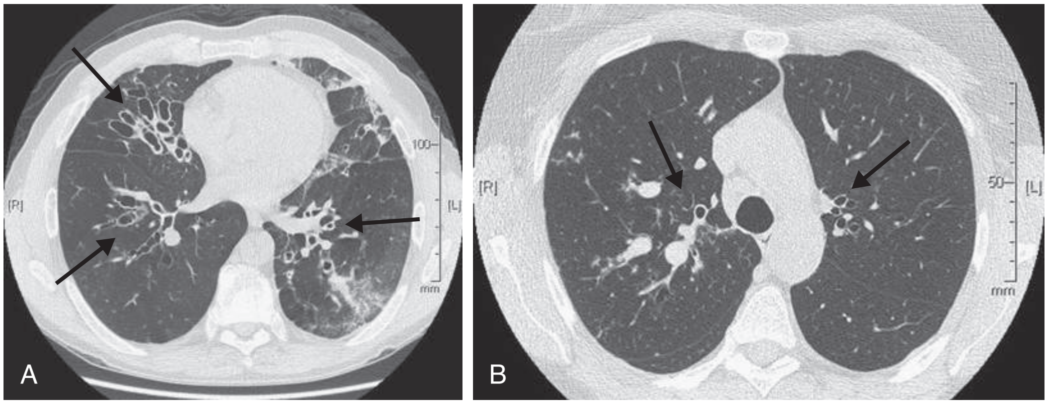

Figure 399-9 **A,** Central bronchiectasis in patient with ABPA *(arrows).* **B,** Central bronchiectasis in the upper lobes *(arrows). (From Douglass JA, Sandrini A, Holgate ST, O'Hehir RE: Allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis. In Adkinson AF, editor:* Middleton's allergy principles and practice, *Philadelphia, 2014, Elsevier, Fig. 61-3.)*

the above modalities may signal a need for hematopoietic stem cell transplantation. This therapy has been successful in some patients.

Bibliography is available at Expert Consult.

399.5 Interstitial Lung Disease

Kevin J. Kelly

ILD in children is caused by a large group of uncommon, heterogeneous, familial, or sporadic diseases that involve the pulmonary parenchyma and cause significant impairment of gas exchange. The ILDs in pediatrics are uncommonly caused by infectious processes and specific immunologic processes when compared to adults. The one exception to this is Goodpasture disease with classic antibasement membrane antibodies. Despite wide variations in cause, these disorders are classified together because of the similar clinical, physiologic, radiographic, and pathologic processes involving disruption of alveolar interstitium and airways. A survey of all German pediatric hospitals found a rate of occurrence of pediatric ILD of 1.3 children/million population. The pathophysiology is believed to be more complex than that of adult disease because pulmonary injury occurs during the process of lung growth and differentiation. In ILD, the initial injury causes damage to the alveolar epithelium and capillary endothelium. Abnormal healing of injured tissue may be more prominent than inflammation in the initial steps of the development of chronic ILD. Some familial cases, especially in the surfactant dysfunction disorders, involve a specific genetic mutation.

CLASSIFICATION AND PATHOLOGY

Classification of ILD in children is not standardized. It is helpful for the clinician to separate diseases into ILD on the basis of age, disorders of known and unknown etiology, and diseases related to systemic disorders (Table 399-12). A diffuse developmental disorder of the lung is likely the result of a primary aberration in lung and/or pulmonary vascular development. Growth abnormalities reflecting deficient development of alveoli are largely secondary to impaired prenatal or postnatal alveolarization from restriction of fetal thoracic space, limitation of pulmonary blood supply, or chronic lung disease of prematurity (e.g., bronchopulmonary dysplasia) (see Chapter 101). Abnormal alveolar growth may also be associated with a variety of chromosomal abnormalities such as trisomy 21. In **neuroendocrine cell hyperplasia of infancy**/persistent tachypnea of infancy, a distinct entity limited to infants and young children, the pathologic findings include hyperplasia of neuroendocrine cells within the bronchioles while the pulmonary histologic background is nearly normal. **Pulmonary interstitial glycogenosis** is characterized by diffuse accumulation of mesenchymal cells in the alveolar interstitium with accumulation of monoparticulate glycogen in the interstitial cell cytoplasm that is confirmed by ultrastructural examination.

Disorders associated with **surfactant metabolism dysfunction** explain many of formerly idiopathic pediatric ILDs. The more-severe surfactant dysfunctions, such as surfactant protein-B mutations, usually manifest as respiratory failure in neonate. **Congenital pulmonary alveolar proteinosis** is more typical of *ABCA3* mutations, and **chronic pneumonitis of infancy** is predominant histologic pattern seen in surfactant protein-C mutations. Age-related but overlapping surfactant disorders in addition to pulmonary alveolar proteinosis and chronic pneumonitis of infancy also include **desquamative interstitial pneumonia** in infants; older children and adolescents more often manifest **nonspecific interstitial pneumonia** or **usual interstitial pneumonia**. *ABCA3* mutations may produce pulmonary alveolar proteinosis, desquamative interstitial pneumonia, or nonspecific interstitial pneumonia; surfactant protein-C deficiency may also produce chronic pneumonitis of infancy in older children.

Diffuse ILD can occur without a known immunodeficiency or systemic disorder, but it can also be seen as a pulmonary manifestation of other systemic disease processes, such as collagen vascular disorders and sarcoidosis.

Table 399-12 The Pediatric Interstitial Lung Diseases

AGE-RELATED ILDS IN INFANCY AND EARLY CHILDHOOD
Diffuse developmental disorders
• Acinar dysplasia
• Congenital alveolar dysplasia
• Alveolar capillary dysplasia with misalignment of pulmonary veins (some due to *FOXF1* mutation)
Growth abnormalities reflecting deficient alveolarization
• Pulmonary hypoplasia
• Chronic neonatal lung disease
• Chromosomal disorders
• Congenital heart disease
Neuroendocrine cell hyperplasia of infancy
Pulmonary interstitial glycogenosis (infantile cellular interstitial pneumonia)
Surfactant dysfunction disorders (pulmonary alveolar proteinosis)
• Surfactant protein–B mutation
• Surfactant protein–C mutation
• *ABCA3* mutation
• Granulocyte-macrophage colony-stimulating factor receptor (*CSF2RA*) mutation
ILD DISORDERS WITH KNOWN ASSOCIATIONS
Infectious/postinfectious processes
• Adenovirus viruses
• Influenza viruses
• *Chlamydia pneumoniae*
• *Mycoplasma pneumoniae*
Environmental agents
• Hypersensitivity pneumonitis
• Toxic inhalation
Aspiration syndromes
PULMONARY DISEASES ASSOCIATED WITH PRIMARY AND SECONDARY IMMUNE DEFICIENCY
Opportunistic infections
Granulomatous lymphocytic ILD associated with common variable immunodeficiency syndrome
Lymphoid intestinal pneumonia (HIV infection)
Therapeutic interventions: chemotherapy, radiation, transplantation, and rejection
Idiopathic ILDs
Usual interstitial pneumonitis
Desquamative interstitial pneumonitis
Lymphocytic interstitial pneumonitis and related disorders
Nonspecific interstitial pneumonitis (cellular/fibrotic)
Eosinophilic pneumonia
Bronchiolitis obliterans syndrome
Pulmonary hemosiderosis and acute idiopathic pulmonary hemorrhage of infancy
Pulmonary alveolar proteinosis
Pulmonary vascular disorders
Pulmonary lymphatic disorders
Pulmonary microlithiasis
Persistent tachypnea of infancy
Brain-thyroid-lung syndrome
SYSTEMIC DISORDERS WITH PULMONARY MANIFESTATIONS
Goodpasture disease
Gaucher disease and other storage diseases
Malignant infiltrates
Hemophagocytic lymphohistiocytosis
Langerhans cell histiocytosis
Sarcoidosis
Systemic sclerosis
Polymyositis/dermatomyositis
Systemic lupus erythematosus
Rheumatoid arthritis
Lymphangioleiomyomatosis
Pulmonary hemangiomatosis
Neurocutaneous syndromes
Hermansky-Pudlak syndrome

Modified from Deutsch GH, Young LR, Deterding RR, et al; ChILD Research Co-operative: Diffuse lung disease in young children: application of a novel classification scheme, Am J Respir Crit Care Med *176:1120–1128, 2007.*

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Persistent pulmonary symptoms can occur after **respiratory infections** caused by adenoviruses, influenza viruses, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*. **Aspiration** is a frequent cause of chronic lung disease in childhood. Children with developmental delay or neuromuscular weakness are at an increased risk for aspiration of food, saliva, or foreign matter secondary to swallowing dysfunction and/or gastroesophageal reflux. An undiagnosed tracheoesophageal fistula can also result in pulmonary complications related to aspiration of gastric contents and interstitial pneumonia.

Children experiencing an exaggerated immunologic response to organic dust, molds, or bird antigens may demonstrate hypersensitivity pneumonitis. Children with malignancies may have ILD related to the primary malignancy or an opportunistic infection or secondary to chemotherapy or radiation treatment.

CLINICAL MANIFESTATIONS

A detailed history is needed to assess the severity of symptoms and the possibility of an underlying systemic disease in a patient with suspected ILD. Identification of precipitating factors, such as exposure to molds or birds and a severe lower respiratory infection, is important in establishing the diagnosis and instituting avoidance measures. A positive family history, especially in an affected infant, is suggestive of a genetic or familial disease, such as a surfactant dysfunction. Tachypnea, dyspnea, cough, and failure to thrive are commonly present. The majority of patients develop hypoxia and hypercarbia, usually a late and ominous complication. Symptoms are usually insidious and occur in a continuous, not episodic, pattern. Tachypnea, crackles on auscultation, and retractions are noted on physical examination in the majority of children with ILD, but chest physical examination findings can be normal. Wheezing and fever are uncommon findings in pediatric ILD. Cyanosis accompanied by a prominent P2 heart sound is indicative of severe disease with the development of secondary pulmonary hypertension. Anemia or hemoptysis suggests a pulmonary vascular disease or pulmonary hemosiderosis. Rashes or joint complaints are consistent with an underlying connective tissue disease.

DIAGNOSIS

Radiography

Chest radiographic abnormalities can be classified as interstitial, reticular, nodular, reticulonodular, or honeycombed. The chest radiographic appearance may also be normal despite significant clinical impairment and may correlate poorly with the extent of disease. HRCT of the chest better defines the extent and distribution of disease and can provide specific information for selection of a biopsy site. Volume-controlled full-inspiratory and end-expiratory protocols used during HRCT can provide more information, possibly showing air trapping, ground-glass patterns, mosaic patterns of attenuation, hyperinflation, bronchiectasis, cysts, and/or nodular opacities. Serial HRCT scans have been beneficial in monitoring disease progression and severity.

Pulmonary Function Tests

Pulmonary function tests are important in defining the degree of pulmonary dysfunction and in following the response to treatment. In ILD, pulmonary function abnormalities demonstrate a restrictive ventilatory deficit with decreased lung volumes and reduced lung compliance. The functional residual capacity is often reduced but is usually less affected than vital capacity and total lung capacity. The residual volume is usually maintained; therefore, ratios of functional residual capacity : total lung capacity and residual volume : total lung capacity are increased. Diffusion capacity of the lung is often reduced. Exercise testing may detect pulmonary dysfunction, even in the early stage of ILD with a decline in oxygen saturation.

Bronchoalveolar Lavage

BAL may provide helpful information regarding secondary infection, bleeding, and aspiration and allows cytology and molecular analyses. Evaluation of cell counts, differential, and lymphocyte markers may be helpful in determining the presence of hypersensitivity pneumonitis or sarcoid. Although BAL does not usually determine the exact diagnosis, it can be diagnostic for disorders such as pulmonary alveolar proteinosis. Lung biopsy for histopathology by conventional thoracotomy or video-assisted thoracoscopy is usually the final step and is often necessary for a diagnosis. Biopsy may have a lower diagnostic yield in young children because of heterogeneous lung changes and often nonspecific histologic findings. Genetic testing for surfactant dysfunction mutational analysis is available. Evaluation for possible systemic disease may also be necessary.

TREATMENT

Supportive care of patients with ILD is essential and includes supplemental oxygen for hypoxia and adequate nutrition for growth failure. Antimicrobial treatment may be necessary for secondary infections. Some children may receive symptomatic relief from the use of bronchodilators. Antiinflammatory treatment with corticosteroids remains the initial treatment of choice. Controlled trials in children are lacking, however, and the clinical responses reported in case studies are variable. The usual dose of prednisone is 1-2 mg/kg/24 hr for 6-8 wks with tapering of dosage dictated by clinical response. Alternative, but not adequately evaluated, agents include hydroxychloroquine, azathioprine, cyclophosphamide, cyclosporine, methotrexate, intravenous immunoglobulin, granulocyte-macrophage colony-stimulating factor, and pulsed high-dose steroids. Investigational approaches involve specific agents directed against the action of cytokines, growth factors, or oxidants. Lung transplantation for progressive or end-stage ILD is successful in some infants and children. Appropriate treatment for underlying systemic disease is indicated. Preventive measures include avoidance of all inhalation irritants, such as tobacco smoke and, when appropriate, molds and bird antigens. Supervised pulmonary rehabilitation programs may be helpful.

Genetic Counseling

A high incidence of ILD in some families suggests a genetic predisposition to either development of the disease or severity of the disorder. Genetic counseling may be beneficial if a positive familial history is obtained.

PROGNOSIS

The overall mortality of ILD is very variable and depends on specific diagnosis. Some children recover spontaneously without treatment, but other children steadily progress to death. Pulmonary hypertension, failure to thrive, and severe fibrosis are considered poor prognostic indicators.

GOODPASTURE DISEASE

Goodpasture disease is the prototypical immunologic mediated interstitial lung disease (see Chapter 517). Because of the concurrent presentation of renal and pulmonary disease, the differential diagnosis focuses on distinguishing Goodpasture disease from GPA, microscopic polyangiitis, Henoch-Schönlein purpura, and idiopathic pulmonary hemorrhage syndromes.

Pathophysiology

Immunology Factors

The development of anti–glomerular basement membrane (anti-GBM) antibodies directly correlates with the development of pulmonary and renal disease. Removal of such antibodies by plasmapheresis results in improvement of the disease process in some patients but not in all. The anti-GBM antibodies are IgG_1 and IgG_4 complement-binding subclasses of IgG which activate complement. Complement fragments signal the recruitment of neutrophils and macrophage in both the lung and kidney basement membranes resulting in damage and capillaritis.

Genetic Factors

Genetics appears to contribute strongly to the development of this disease with the presence of major histocompatibility complex class II alleles DR15, DR4, DRB1*1501, DRB1*04, and DRB1*03 predisposing to disease.

Environmental Factors

Exposure to smoke appears to be a strong factor in the development Goodpasture disease. Whether smoking alters the ultrastructure of the basement membrane or exogenous particles or noxious substances in smoke alter the type IV collagen is unknown. Smokers are more likely to develop pulmonary hemorrhage than non-smokers who have Goodpasture disease. Other injuries to the alveoli from infection, hydrocarbon inhalation, or cocaine inhalation have been reported as associated events prior to development of Goodpasture disease.

Clinical Manifestations

The majority of patients present with many days or weeks of cough, dyspnea, fatigue, and sometimes hemoptysis. Young children tend to swallow small amounts of blood from hemoptysis and may present with vomiting blood. Occasionally, the hemoptysis is large and resultant anemia is a consequence of large quantities of blood loss. Renal compromise is found with abnormal renal function tests. Younger patients tend to present with both the pulmonary and renal syndrome concurrently. Adults are less likely to develop pulmonary disease.

Laboratory

Serologic detection of anti-GBM antibodies are positive in more than 90% of patients with Goodpasture disease. A complete blood count will show anemia that is normocytic and normochromic as seen in chronic inflammatory disease. Urinalysis may reveal hematuria and proteinuria and blood tests demonstrate renal compromise with elevated blood urea nitrogen and creatinine.

Studies for pANCA (antimyeloperoxidase ANCA) should also be performed and are positive in approximately 25-30% of patients concurrently with anti-GBM antibodies. Clinical disease may be more difficult to treat and the presence of these antibodies may herald a more severe form of disease.

Chest Radiography

Chest radiography in Goodpasture disease will often show widely scattered patches of pulmonary infiltrates. If these infiltrates are in the periphery of the lung, they may be difficult to distinguish from the eosinophilic lung diseases. Interstitial patterns of thickening may be found as well. HRCT is usually not performed in this disease as the constellation of pulmonary hemorrhage, renal compromise, and positive serologic tests with anti-GBM antibodies detected often preclude the need for this test.

Pulmonary Function Testing

Pulmonary spirometry often reveals a restrictive defect with reduction in forced vital capacity and forced expiratory volume at 1-second. **DLCO** is a valuable test when pulmonary hemorrhage is a strong consideration. The intent of this test is to measure the ability of the lung to transfer inhaled gas to the red blood cell in the pulmonary capillary bed. This takes advantage of the hemoglobin's high affinity to bind carbon monoxide. It was once thought that reduction of DLCO was a measure of reduced surface area of the alveoli. Current data suggests that it directly correlates with the volume of blood in the pulmonary capillary bed. In pulmonary hemorrhage syndromes, blood in the alveoli plus the blood in the capillary bed increase the DLCO significantly and should alert the clinician to the possibility of pulmonary hemorrhage.

Bronchoscopy and Bronchoalveolar Lavage

Pulmonary abnormalities can often be best assessed by a bronchoscopy with BAL. The visual presence of blood on inspection as well as BAL will be obvious. Infections must be ruled out in many cases, and this technique adds significant value. BAL cell count will show hemosiderin-laden macrophage that have engulfed and broken down the red blood cells, leaving iron in these cells.

Lung Biopsy

Lung biopsy in patients with active disease reveals capillaritis from neutrophils, hemosiderin-laden macrophages, type II pneumocyte hyperplasia, and interstitial thickening at the level of the alveolus. Staining for IgG and complement is found by immunofluorescence in along the basement membrane in a linear pattern. This antibody deposition pattern led to the investigation of endogenous antigens in the basement membrane.

Treatment

More than half of patients with Goodpasture disease who forego treatment die within 2 yr from either respiratory failure, renal failure, or both. After a diagnosis is made, therapy with corticosteroids (e.g., prednisone, 1 mg/kg/day) coupled with oral cyclophosphamide (2.5 mg/kg/day) is begun. The addition of daily plasmapheresis for 2 wks may accelerate improvement. Cyclophosphamide may be discontinued after 2-3 mo. Steroids are often weaned over a 6-9 mo period. Survival is affected by the need for ongoing dialysis. Patients who do not require persistent dialysis have a survival rate at 1 yr of 80% or more.

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Chapter 400

Community-Acquired Pneumonia

Matthew S. Kelly and Thomas J. Sandora

EPIDEMIOLOGY

Pneumonia, defined as inflammation of the lung parenchyma, is the leading cause of death globally among children younger than age 5 yr, accounting for an estimated 1.2 million (18% total) deaths annually (Fig. 400-1). The incidence of pneumonia is more than 10-fold higher (0.29 episodes vs 0.03 episodes), and the number of childhood-related deaths from pneumonia ≈2,000 fold higher, in developing than in developed countries (Table 400-1). Fifteen countries account for more than three-fourths of all pediatric deaths from pneumonia.

In the United States from 1939-1996, pneumonia mortality in children declined by 97%; in 1970, pneumonia accounted for 9% of all deaths of children younger than age 5 yr compared to 2% in 2007. It is probable that this decline results from the introduction of antibiotics, vaccines, and the expansion of medical insurance coverage for children. *Haemophilus influenzae* type b (see Chapter 194) was an important cause of bacterial pneumonia in young children but became uncommon with the routine use of effective vaccines, while measles vaccine greatly reduced the incidence of measles-related pneumonia deaths in developing countries. Improved access to healthcare in rural areas of developing countries and the introduction of pneumococcal conjugate vaccines (see Chapter 182) were also important contributors to the further reductions in pneumonia-related deaths achieved over the past decade.

ETIOLOGY

Although most cases of pneumonia are caused by microorganisms, noninfectious causes include aspiration (of food or gastric acid, foreign bodies, hydrocarbons, and lipoid substances), hypersensitivity reactions, and drug- or radiation-induced pneumonitis. The cause of pneumonia in an individual patient is often difficult to determine because direct culture of lung tissue is invasive and rarely performed. Cultures performed on specimens in children obtained from the upper respiratory tract or sputum typically do not accurately reflect the cause of lower respiratory tract infection. With the use of molecular diagnostic testing, a bacterial or viral cause of pneumonia can be identified in

40-80% of children with community-acquired pneumonia. *Streptococcus pneumoniae* (pneumococcus) is the most common bacterial pathogen in children 3 wk to 4 yr of age, whereas *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are the most frequent bacterial pathogens in children age 5 yr and older. In addition to pneumococcus, other bacterial causes of pneumonia in previously healthy children in the United States include group A streptococcus (*Streptococcus pyogenes*) and *Staphylococcus aureus* (see Chapter 181.1 and Table 400-2). *S. aureus* pneumonia often complicates an illness caused by influenza viruses.

S. pneumoniae, H. influenzae, and *S. aureus* are the major causes of hospitalization and death from bacterial pneumonia among children in developing countries, although in children with HIV infection, *Mycobacterium tuberculosis* (see Chapter 215), atypical mycobacteria,

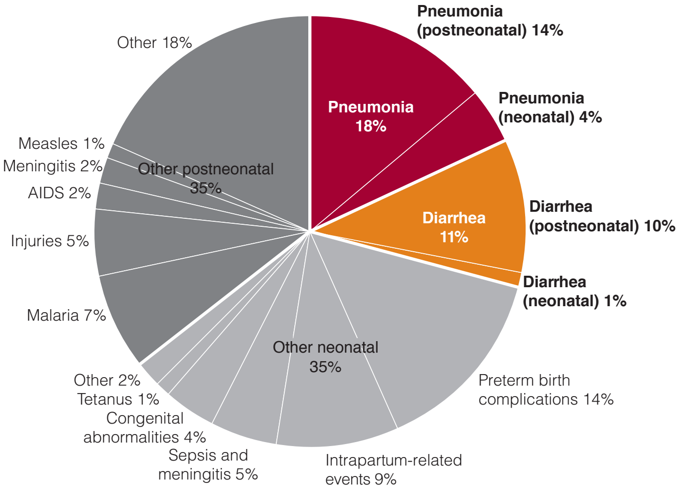

Figure 400-1 Pneumonia is the leading killer of children worldwide, as shown by this illustration of global distribution of cause-specific mortality among children younger than age 5 yr in 2010. Pneumonia causes 18% of all under-5 deaths. Values may not sum to 100% because of rounding. *(From Black RE, Allen LH, Bhutta ZA, et al: Maternal and child undernutrition: global and regional exposures and health consequences.* Lancet *371:243–260, 2008; and Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000.* Lancet *379:2151–2161, 2012, Fig. 2.)*

Salmonella (see Chapter 198), *Escherichia coli* (see Chapter 200), and *Pneumocystis jiroveci* (see Chapter 244) must be considered. The incidence of pneumonia caused by *H. influenzae* or *S. pneumoniae* has been significantly reduced in areas where routine immunization has been implemented.

Viral pathogens are a prominent cause of lower respiratory tract infections in infants and children older than 1 mo but younger than 5 yr of age. Viruses can be detected in 40-80% of children with pneumonia using molecular diagnostic methods. Of the respiratory viruses, respiratory syncytial virus (RSV) (see Chapter 260) and rhinoviruses are the most commonly identified pathogens, especially in children younger than 2 yr of age. However, the role of rhinoviruses in severe lower respiratory tract infection remains poorly defined as these viruses are frequently detected in infections with 2 or more pathogens and among asymptomatic children. Other common viruses causing pneumonia include influenza virus (see Chapter 258), parainfluenza viruses, adenoviruses, enteroviruses, and human metapneumovirus. Infection with more than 1 respiratory virus occurs in up to 20% of cases. The age of the patient may help identify possible pathogens (Table 400-3).

Lower respiratory tract viral infections are much more common in the fall and winter in both the northern and southern hemispheres in relation to the seasonal epidemics of respiratory viral infection that occur each year. The typical pattern of these epidemics usually begins in the fall, when parainfluenza infections appear and most often manifest as croup. Later in winter, RSV, human metapneumovirus, and influenza viruses cause widespread infection, including upper respiratory tract infections, bronchiolitis, and pneumonia. RSV is particularly severe among infants and young children, whereas influenza virus causes disease and excess hospitalization for acute respiratory illness in all age groups. Knowledge of the prevailing viral epidemic may lead to a presumptive initial diagnosis.

Immunization status is relevant because children fully immunized against *H. influenzae* type b and *S. pneumoniae* are less likely to be infected with these pathogens. Children who are immunosuppressed or who have an underlying illness may be at risk for specific pathogens, such as *Pseudomonas* spp. in patients with cystic fibrosis (see Chapter 403).

PATHOGENESIS

The lower respiratory tract is normally kept sterile by physiologic defense mechanisms, including mucociliary clearance, the properties of normal secretions such as secretory immunoglobulin (Ig) A, and

Table 400-1 Incidence of Pneumonia Cases and Pneumonia Deaths Among Children Younger Than Age 5 Yr, by UNICEF Region, 2004*

UNICEF REGIONS	NUMBER OF CHILDREN YOUNGER THAN 5 YR OF AGE (IN THOUSANDS)	NUMBER OF CHILDHOOD PNEUMONIA DEATHS (IN THOUSANDS)	INCIDENCE OF PNEUMONIA CASES (EPISODES PER CHILD PER YEAR)	TOTAL NUMBER OF PNEUMONIA EPISODES (IN THOUSANDS)
South Asia	169,300	702	0.36	61,300
Sub-Saharan Africa	117,300	1,022	0.30	35,200
Middle East and North Africa	43,400	82	0.26	11,300
East Asia and Pacific	146,400	158	0.24	34,500
Latin America and Caribbean	56,500	50	0.22	12,200
Central and Eastern Europe and the Commonwealth of Independent States	26,400	29	0.09	2,400
Developing countries	533,000	2,039	0.29	154,500
Industrialized countries	54,200	1	0.03	1,600
World	**613,600**	**2,044**	**0.26**	**158,500**

*Regional estimates in Columns 2, 3, and 5 do not add up to the world total because of rounding.
From Wardlaw T, Salama P, White Johansson E: Pneumonia: the leading killer of children, Lancet *368:1048–1050, 2006.*

Table 400-2 Causes of Infectious Pneumonia

BACTERIAL	
Common	
Streptococcus pneumoniae	Consolidation, empyema
Group B streptococci	Neonates
Group A streptococci	Empyema
*Mycoplasma pneumoniae**	Adolescents; summer-fall epidemics
*Chlamydophila pneumoniae**	Adolescents
Chlamydia trachomatis	Infants
Mixed anaerobes	Aspiration pneumonia
Gram-negative enterics	Nosocomial pneumonia
Uncommon	
Haemophilus influenzae type b	Unimmunized
Staphylococcus aureus	Pneumatoceles, empyema; infants
Moraxella catarrhalis	
Neisseria meningitidis	
Francisella tularensis	Animal, tick, fly contact; bioterrorism
Nocardia species	Immunosuppressed persons
*Chlamydophila psittaci**	Bird contact (especially parakeets)
Yersinia pestis	Plague; rat contact; bioterrorism
Legionella species*	Exposure to contaminated water; nosocomial
*Coxiella burnetii**	Q fever; animal (goat, sheep, cattle) exposure
VIRAL	
Common	
Respiratory syncytial virus	Bronchiolitis
Parainfluenza types 1-3	Croup
Influenzas A, B	High fever; winter months
Adenovirus	Can be severe; often occurs between January and April
Human metapneumovirus	Similar to respiratory syncytial virus
Uncommon	
Rhinovirus	Rhinorrhea
Enterovirus	Neonates
Herpes simplex	Neonates
Cytomegalovirus	Infants, immunosuppressed persons
Measles	Rash, coryza, conjunctivitis
Varicella	Adolescents or unimmunized
Hantavirus	Southwestern United States, rodents
Coronavirus (severe acute respiratory syndrome, Middle East respiratory syndrome [MERS])	Asia, Arabian peninsula
FUNGAL	
Histoplasma capsulatum	Ohio/Mississippi River valley; bird, bat contact
Blastomyces dermatitidis	Ohio/Mississippi River valley
Coccidioides immitis	Southwest United States
Cryptococcus neoformans	Bird contact
Aspergillus species	Immunosuppressed persons; nodular lung infection
Mucormycosis	Immunosuppressed persons
Pneumocystis jiroveci	Immunosuppressed, steroids
RICKETTSIAL	
Rickettsia rickettsiae	Tick bite
MYCOBACTERIAL	
Mycobacterium tuberculosis	Travel to endemic region; exposure to high-risk persons
Mycobacterium avium complex	Immunosuppressed persons
PARASITIC	
Various parasites (e.g., Ascaris, *Strongyloides* species)	Eosinophilic pneumonia

*Atypical pneumonia syndrome; may have extrapulmonary manifestations, low-grade fever, patchy diffuse infiltrates, poor response to β-lactam antibiotics, and negative sputum Gram stain.

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis & therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 29.*

Table 400-3 Etiologic Agents Grouped by Age of the Patient

AGE GROUP	FREQUENT PATHOGENS (IN ORDER OF FREQUENCY)
Neonates (<3 wk)	Group B streptococcus, *Escherichia coli*, other Gram-negative bacilli, *Streptococcus pneumoniae, Haemophilus influenzae* (type b,* nontypeable)
3 wk-3 mo	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), *S. pneumoniae, H. influenzae* (type b,* nontypeable); if patient is afebrile, consider *Chlamydia trachomatis*
4 mo-4 yr	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), *S. pneumoniae, H. influenzae* (type b,* nontypeable), *Mycoplasma pneumoniae,* group A streptococcus
≥5 yr	*M. pneumoniae, S. pneumoniae, Chlamydophila pneumoniae, H. influenzae* (type b,* nontypeable), influenza viruses, adenovirus, other respiratory viruses, *Legionella pneumophila*

**H. influenzae* type b is uncommon with routine *H. influenzae* type b immunization.

Adapted from Kliegman RM, Marcdante KJ, Jenson HJ, et al: Nelson essentials of pediatrics, *ed 5, Philadelphia, 2006, Elsevier, p. 504.*

clearing of the airway by coughing. Immunologic defense mechanisms of the lung that limit invasion by pathogenic organisms include macrophages that are present in alveoli and bronchioles, secretory IgA, and other immunoglobulins. Trauma, anesthesia, and aspiration increase the risk of pulmonary infection.

Viral pneumonia usually results from spread of infection along the airways, accompanied by direct injury of the respiratory epithelium, which results in airway obstruction from swelling, abnormal secretions, and cellular debris. The small caliber of airways in young infants makes such patients particularly susceptible to severe infection. Atelectasis, interstitial edema, and ventilation–perfusion mismatch causing significant hypoxemia often accompany airway obstruction. Viral infection of the respiratory tract can also predispose to secondary bacterial infection by disturbing normal host defense mechanisms, altering secretions, and modifying the bacterial flora.

Bacterial pneumonia most often occurs when respiratory tract organisms colonize the trachea and subsequently gain access to the lungs, but pneumonia may also result from direct seeding of lung tissue after bacteremia. When bacterial infection is established in the lung parenchyma, the pathologic process varies according to the invading organism. *M. pneumoniae* (see Chapter 223) attaches to the respiratory epithelium, inhibits ciliary action, and leads to cellular destruction and an inflammatory response in the submucosa. As the infection progresses, sloughed cellular debris, inflammatory cells, and mucus cause airway obstruction, with spread of infection occurring along the bronchial tree, as it does in viral pneumonia.

S. pneumoniae produces local edema that aids in the proliferation of organisms and their spread into adjacent portions of lung, often resulting in the characteristic focal lobar involvement.

Group A streptococcus infection of the lower respiratory tract results in more diffuse infection with interstitial pneumonia. The pathology includes necrosis of tracheobronchial mucosa; formation of large amounts of exudate, edema, and local hemorrhage, with extension into the interalveolar septa; and involvement of lymphatic vessels and the increased likelihood of pleural involvement.

S. aureus pneumonia manifests in confluent bronchopneumonia, which is often unilateral and characterized by the presence of extensive areas of hemorrhagic necrosis and irregular areas of cavitation of the lung parenchyma, resulting in pneumatoceles, empyema, or, at times, bronchopulmonary fistulas.

Table 400-4 Differential Diagnosis of Recurrent Pneumonia
HEREDITARY DISORDERS
Cystic fibrosis
Sickle cell disease
DISORDERS OF IMMUNITY
HIV/AIDS
Bruton agammaglobulinemia
Selective immunoglobulin G subclass deficiencies
Common variable immunodeficiency syndrome
Severe combined immunodeficiency syndrome
Chronic granulomatous disease
Hyperimmunoglobulin E syndromes
Leukocyte adhesion defect
DISORDERS OF CILIA
Immotile cilia syndrome
Kartagener syndrome
ANATOMIC DISORDERS
Pulmonary sequestration
Lobar emphysema
Gastroesophageal reflux
Foreign body
Tracheoesophageal fistula (H type)
Bronchiectasis
Aspiration (oropharyngeal incoordination)
Aberrant bronchus

From Kliegman RM, Marcdante KJ, Jenson HJ, et al: Nelson essentials of pediatrics, *ed 5, Philadelphia, 2006, Elsevier, p. 507.*

Recurrent pneumonia is defined **as 2 or more** episodes in a single year **or 3 or more** episodes ever, with radiographic clearing between occurrences. An underlying disorder should be considered if a child experiences recurrent pneumonia (Table 400-4).

CLINICAL MANIFESTATIONS

Pneumonia is frequently preceded by several days of symptoms of an upper respiratory tract infection, typically rhinitis and cough. In viral pneumonia, fever is usually present but temperatures are generally lower than in bacterial pneumonia. Tachypnea is the most consistent clinical manifestation of pneumonia. Increased work of breathing accompanied by intercostal, subcostal, and suprasternal retractions, nasal flaring, and use of accessory muscles is common. Severe infection may be accompanied by cyanosis and lethargy, especially in infants. Auscultation of the chest may reveal crackles and wheezing, but it is often difficult to localize the source of these adventitious sounds in very young children with hyperresonant chests. It is often not possible to distinguish viral pneumonia clinically from disease caused by *Mycoplasma* and other bacterial pathogens.

Bacterial pneumonia in adults and older children typically begins suddenly with high fever, cough, and chest pain. Other symptoms that may be seen include drowsiness with intermittent periods of restlessness; rapid respirations; anxiety; and, occasionally, delirium. In many children, splinting on the affected side to minimize pleuritic pain and improve ventilation is noted; such children may lie on one side with the knees drawn up to the chest.

Physical findings depend on the stage of pneumonia. Early in the course of illness, diminished breath sounds, scattered crackles, and rhonchi are commonly heard over the affected lung field. With the development of increasing consolidation or complications of pneumonia such as pleural effusion or empyema, dullness on percussion is noted and breath sounds may be diminished. A lag in respiratory excursion often occurs on the affected side. Abdominal distention may be prominent because of gastric dilation from swallowed air or ileus. *Abdominal pain is common in lower-lobe pneumonia*. The liver may seem enlarged because of downward displacement of the diaphragm secondary to hyperinflation of the lungs or superimposed congestive heart failure.

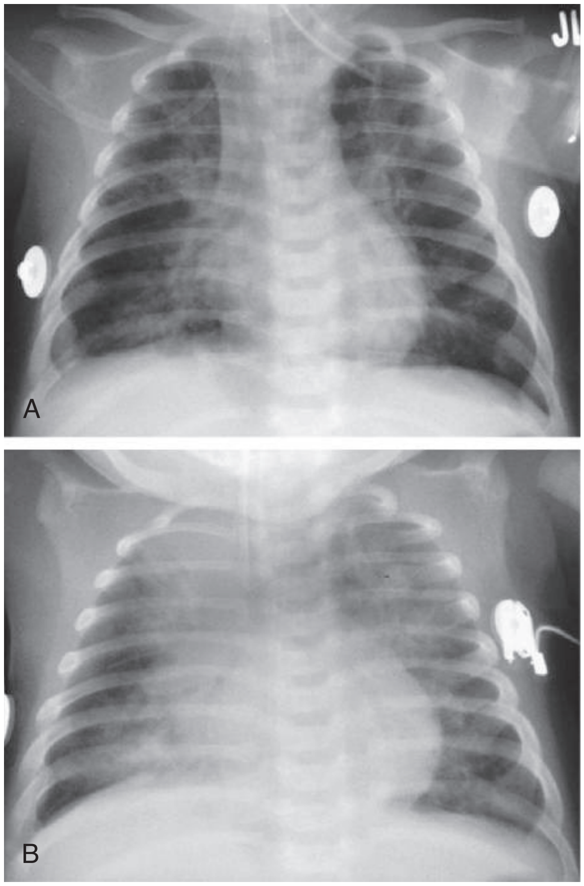

Figure 400-2 A, Radiographic findings characteristic of respiratory syncytial virus pneumonia in a 6 mo old infant with rapid respirations and fever. Anteroposterior radiograph of the chest shows hyperexpansion of the lungs with bilateral fine air space disease and streaks of density, indicating the presence of both pneumonia and atelectasis. An endotracheal tube is in place. **B,** One day later, the anteroposterior radiograph of the chest shows increased bilateral pneumonia.

Symptoms described in adults with pneumococcal pneumonia may be noted in older children but are rarely observed in infants and young children, in whom the clinical pattern is considerably more variable. In infants, there may be a prodrome of upper respiratory tract infection and diminished appetite, leading to the abrupt onset of fever, restlessness, apprehension, and respiratory distress. These infants appear ill, with respiratory distress manifested as grunting; nasal flaring; retractions of the supraclavicular, intercostal, and subcostal areas; tachypnea; tachycardia; air hunger; and often cyanosis. Results of physical examination may be misleading, particularly in young infants, with meager findings disproportionate to the degree of tachypnea. Some infants with bacterial pneumonia may have associated gastrointestinal disturbances characterized by vomiting, anorexia, diarrhea, and abdominal distention secondary to a paralytic ileus. Rapid progression of symptoms is characteristic in the most severe cases of bacterial pneumonia.

DIAGNOSIS

An infiltrate on chest radiograph (posteroanterior **and** lateral views) supports the diagnosis of pneumonia; the film may also indicate a complication such as a pleural effusion or empyema. Viral pneumonia is usually characterized by hyperinflation with bilateral interstitial infiltrates and peribronchial cuffing (Fig. 400-2). Confluent lobar consolidation is typically seen with pneumococcal pneumonia (Fig. 400-3). The radiographic appearance alone is not diagnostic, and other clinical features must be considered. Repeat chest radiographs are not required for proof of cure for patients with uncomplicated pneumonia. Some

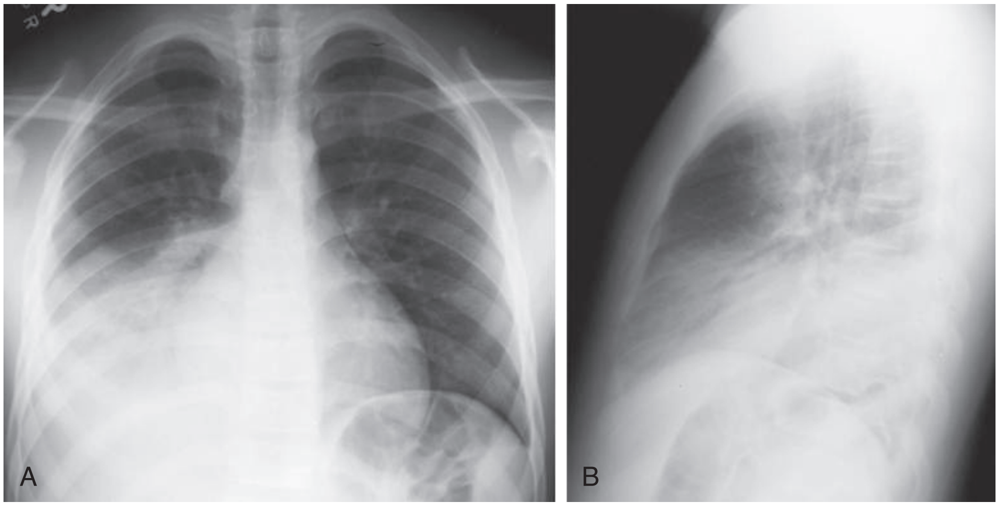

Figure 400-3 Radiographic findings characteristic of pneumococcal pneumonia in a 14 yr old boy with cough and fever. Posteroanterior **(A)** and lateral **(B)** chest radiographs reveal consolidation in the right lower lobe, strongly suggesting bacterial pneumonia.

experts suggest that a chest radiograph may not be necessary for older children with suspected pneumonia (cough, fever, localized crackles, or decreased breath sounds) who are well enough to be managed as outpatients.

Point-of-care use of portable or handheld ultrasonography is highly sensitive and specific in diagnosing pneumonia in children by determining lung consolidations and air bronchograms or effusions.

The peripheral white blood cell (WBC) count can be useful in differentiating viral from bacterial pneumonia. In viral pneumonia, the WBC count can be normal or elevated but is usually not higher than 20,000/mm^3, with a lymphocyte predominance. Bacterial pneumonia is often associated with an elevated WBC count, in the range of 15,000-40,000/mm^3, and a predominance of granulocytes. A large pleural effusion, lobar consolidation, and a high fever at the onset of the illness are also suggestive of a bacterial etiology. **Atypical pneumonia** caused by *C. pneumoniae* or *M. pneumoniae* is difficult to distinguish from pneumococcal pneumonia on the basis of radiographic and laboratory findings, and although pneumococcal pneumonia is associated with a higher WBC count, erythrocyte sedimentation rate, procalcitonin, and C-reactive protein level, there is considerable overlap, particularly with adenoviruses and enteroviruses.

The definitive diagnosis of a viral infection rests on the isolation of a virus or detection of the viral genome or antigen in respiratory tract secretions. Reliable DNA or RNA tests for the rapid detection of many respiratory pathogens, such as mycoplasma, pertussis, and viruses, including RSV, parainfluenza, influenza, and adenoviruses, are available and accurate. Serologic techniques can also be used to diagnose a recent respiratory viral infection but generally require testing of acute and convalescent serum samples for a rise in antibodies to a specific viral agent. This diagnostic technique is laborious, slow, and not generally clinically useful because the infection usually resolves by the time it is confirmed serologically. Serologic testing may be valuable as an epidemiologic tool to define the incidence and prevalence of the various respiratory viral pathogens. Patient peripheral cell gene expression patterns determined by microarray reverse transcription polymerase chain reaction is an emerging technology that may help differentiate viral from bacterial causes of pneumonia.

The definitive diagnosis of a bacterial infection requires isolation of an organism from the blood, pleural fluid, or lung. Culture of sputum is of little value in the diagnosis of pneumonia in young children, while percutaneous lung aspiration is invasive and not routinely performed. Blood culture results are positive in only 10% of children with pneumococcal pneumonia and are not recommended for nontoxic appearing children treated as an outpatient. Blood cultures are recommended for those who fail to improve or have clinical deterioration, in those with complicated pneumonia (Table 400-5) and those requiring hospitalization. Cold agglutinins at titers >1:64 are found in the blood in ≈50% of patients with *M. pneumoniae* infections. Cold agglutinin findings are nonspecific because other pathogens such as influenza viruses may also cause increases. Acute infection caused by *M. pneumoniae* can be diagnosed on the basis of a positive polymerase chain reaction test result or seroconversion in an IgG assay. Serologic evidence, such as the antistreptolysin O titer, may be useful in the diagnosis of group A streptococcal pneumonia.

Table 400-5	Factors Suggesting Need for Hospitalization of Children with Pneumonia
Age <6 mo Sickle cell anemia with acute chest syndrome Multiple lobe involvement Immunocompromised state Toxic appearance Moderate to severe respiratory distress Requirement for supplemental oxygen Complicated pneumonia* Dehydration Vomiting or inability to tolerate oral fluids or medications No response to appropriate oral antibiotic therapy Social factors (e.g., inability of caregivers to administer medications at home or follow-up appropriately)	

*Pleural effusion, empyema, abscess, bronchopleural fistula, necrotizing pneumonia, acute respiratory distress syndrome, extrapulmonary infection (meningitis, arthritis, pericarditis, osteomyelitis, endocarditis), hemolytic uremic syndrome, sepsis.

Adapted from Baltimore RS: Pneumonia. In Jenson HB, Baltimore RS, editors: Pediatric infectious diseases: principles and practice, *Philadelphia, 2002, WB Saunders, p. 801.*

TREATMENT

Treatment of suspected bacterial pneumonia is based on the presumptive cause and the age and clinical appearance of the child. For mildly ill children who do not require hospitalization, amoxicillin is recommended. With the emergence of penicillin-resistant pneumococci, high doses of amoxicillin (80-90 mg/kg/24 hr) should be prescribed unless local data indicate a low prevalence of resistance. Therapeutic alternatives include cefuroxime axetil and amoxicillin/clavulanate. For school-age children and in children in whom infection with *M. pneumoniae* or *C. pneumoniae* is suggested, a macrolide antibiotic such as

azithromycin is an appropriate choice. In adolescents, a respiratory fluoroquinolone (levofloxacin, moxifloxacin) may be considered as an alternative. Despite substantial gains over the past decade, in developing countries only ≈60% of children with symptoms of pneumonia (≈50% in sub-Saharan Africa) are taken to an appropriate caregiver, and less than one-third receive antibiotics. The World Health Organization and other international groups have developed systems to train mothers and local healthcare providers in the recognition and treatment of pneumonia.

The empiric treatment of suspected bacterial pneumonia in a hospitalized child requires an approach based on the clinical manifestations at the time of presentation. In areas without substantial high-level penicillin resistance among *S. pneumoniae*, children who are fully immunized against *H. influenzae* type b and *S. pneumoniae* and are not severely ill should receive ampicillin or penicillin G. For children who do not meet these criteria, ceftriaxone or cefotaxime should be used. If clinical features suggest staphylococcal pneumonia (pneumatoceles, empyema), initial antimicrobial therapy should also include vancomycin or clindamycin.

If viral pneumonia is suspected, it is reasonable to withhold antibiotic therapy, especially for those patients who are mildly ill, have clinical evidence suggesting viral infection, and are in no respiratory distress. However, up to 30% of patients with known viral infection, particularly influenza viruses, may have coexisting bacterial pathogens. Therefore, if the decision is made to withhold antibiotic therapy on the basis of presumptive diagnosis of a viral infection, deterioration in clinical status should signal the possibility of superimposed bacterial infection, and antibiotic therapy should be initiated.

Table 400-5 notes the indications for admission to a hospital. The optimal duration of antibiotic treatment for pneumonia has not been well-established in controlled studies. However, antibiotics should generally be continued until the patient has been afebrile for 72 hr, and the total duration should not be less than 10 days (or 5 days if azithromycin is used). Shorter courses (5-7 days) may also be effective, particularly for children managed on an outpatient basis, but further study is needed. Available data do not support prolonged courses of treatment for uncomplicated pneumonia. In developing countries, oral zinc (10 mg/day for <12 mo, 20 mg/day for ≥12 mo) reduces mortality among children with clinically defined severe pneumonia.

PROGNOSIS

Typically, patients with uncomplicated community-acquired bacterial pneumonia show response to therapy, with improvement in clinical symptoms (fever, cough, tachypnea, chest pain), within 48-96 hr of initiation of antibiotics. Radiographic evidence of improvement lags substantially behind clinical improvement. A number of possibilities must be considered when a patient does not improve with appropriate antibiotic therapy: (1) complications, such as empyema (see Table 400-5); (2) bacterial resistance; (3) nonbacterial etiologies such as viruses or fungi and aspiration of foreign bodies or food; (4) bronchial obstruction from endobronchial lesions, foreign body, or mucous plugs; (5) preexisting diseases such as immunodeficiencies, ciliary dyskinesia, cystic fibrosis, pulmonary sequestration, or congenital pulmonary airway malformation, formerly called cystic adenomatoid malformation; and (6) other noninfectious causes (including bronchiolitis obliterans, hypersensitivity pneumonitis, eosinophilic pneumonia, aspiration, and granulomatosis with polyangiitis, formerly called Wegener granulomatosis). A repeat chest radiograph is the first step in determining the reason for delay in response to treatment. Bronchoalveolar lavage may be indicated in children with respiratory failure; high-resolution CT scans may better identify complications or an anatomic reason for a poor response to therapy.

Mortality from community-acquired pneumonia in developed nations is rare, and most children with pneumonia do not experience long-term pulmonary sequelae. Some data suggest that up to 45% of children have symptoms of asthma 5 yr after hospitalization for pneumonia; this finding may reflect either undiagnosed asthma at the time of presentation or a propensity for development of asthma after pneumonia.

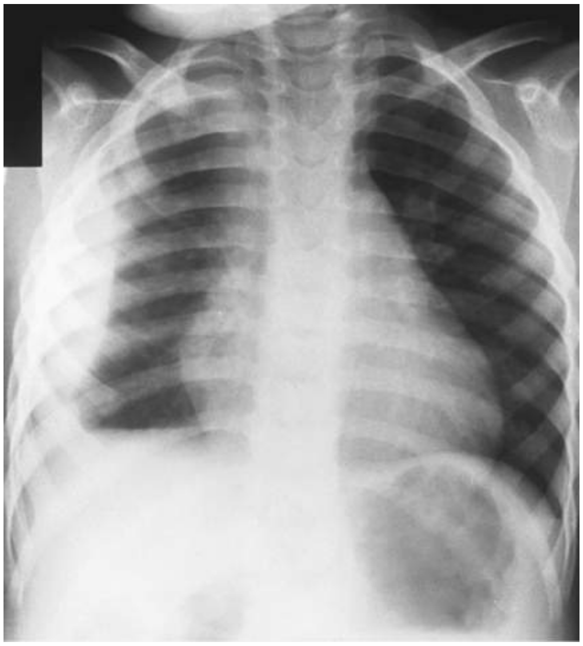

Figure 400-4 **Pneumococcal empyema on the chest radiography of a 3 yr old child who has had upper respiratory symptoms and fever for 3 days.** A pleural fluid collection can be seen on the right side. The patient had a positive pleural tap and blood culture result for pneumococci. The child recovered completely within 3 wk. *(From Kuhn JP, Slovis TL, Haller JO (eds):* Caffrey's pediatric diagnostic imaging, *ed 10, Philadelphia, 2004, Mosby, p. 1002.)*

COMPLICATIONS

Complications of pneumonia (see Table 400-5) are usually the result of direct spread of bacterial infection within the thoracic cavity (pleural effusion, empyema, and pericarditis) or bacteremia and hematologic spread (Fig. 400-4). Meningitis, suppurative arthritis, and osteomyelitis are rare complications of hematologic spread of pneumococcal or *H. influenzae* type b infection.

S. aureus, S. pneumoniae, and *S. pyogenes* are the most common causes of parapneumonic effusions and empyema (Table 400-6). Nonetheless many effusions that complicate bacterial pneumonia are sterile. Universal 16S ribosomal RNA gene polymerase chain reaction identifies the bacterial genome and can determine the bacterial etiology of the effusion if the culture is negative. The treatment of empyema is based on the stage (exudative, fibrinopurulent, organizing). Imaging studies including ultrasonography and CT are helpful in determining the stage of empyema. The mainstays of therapy include antibiotic therapy and drainage with tube thoracostomy. Additional effective approaches include the use of intrapleural fibrinolytic therapy (urokinase, streptokinase, tissue plasminogen activator) and selected video-assisted thoracoscopy to debride or lyse adhesions and drain loculated areas of pus. Early diagnosis and intervention, particularly with fibrinolysis or less often video-assisted thoracoscopy, may obviate the need for thoracotomy and open debridement. Fibrinolysis is more cost-effective than video-assisted thoracoscopy.

PREVENTION

Some evidence exists to suggest that vaccination has reduced the incidence of pneumonia hospitalizations. The annual rate of all-cause pneumonia hospitalization among children younger than 2 yr of age in the United States during the period 1997-1999 was 12.5 per 1,000 children. In February 2000, the 7-valent pneumococcal conjugate vaccine (PCV7) was licensed and recommended. In 2006, the pneumonia hospitalization rate in this age group was 8.1 per 1,000 children, a 35% decrease from the prevaccine rate. Although these data do not establish that PCV7 directly reduced pneumonia hospitalization rates,

Table 400-6 Differentiation of Pleural Fluid		
	TRANSUDATE	**EMPYEMA**
Appearance	Clear	Cloudy or purulent
Cell count (per mm^3)	<1,000	Often >50,000 (cell count has limited predictive value)
Cell type	Lymphocytes, monocytes	Polymorphonuclear leukocytes (neutrophils)
Lactate dehydrogenase	<200 U/L	More than two-thirds upper limit of normal for serum lactate dehydrogenase (LDH)
Pleural fluid : serum LDH ratio	<0.6	>0.6
Protein >3 g	Unusual	Common
Pleural fluid : serum protein ratio	<0.5	>0.5
Glucose*	Normal	Low (<40 mg/dL)
pH*	Normal (7.40-7.60)	<7.10
Gram stain	Negative	Occasionally positive (less than one-third of cases)
Cholesterol		>55 mg/dL
Pleural cholesterol : serum cholesterol ratio	<0.3	>0.3

*Low glucose or pH may be seen in malignant effusion, tuberculosis, esophageal rupture, pancreatitis (positive pleural amylase), and rheumatologic diseases (e.g., systemic lupus erythematosus).

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis & therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 30.*

they do suggest that vaccination has resulted in a sustained benefit in preventing hospitalization for young children with pneumonia.

In 2010, the 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States; it may prevent even more cases of pneumococcal disease not covered by the PCV7 vaccine.

The expansion of influenza vaccine recommendations to include all children >6 mo of age in 2010 might be expected to affect pneumonia hospitalization rates in a similar fashion, and ongoing surveillance is warranted.

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Chapter 401
Bronchiectasis
Oren J. Lakser

Bronchiectasis is characterized by irreversible abnormal dilation and anatomic distortion of the bronchial tree and represents a common end stage of a many nonspecific and unrelated antecedent events. Its incidence has been decreasing overall in industrialized countries, but it persists as a problem in lower and middle income countries and among some ethnic groups in industrialized nations. Females are afflicted more frequently than males.

PATHOPHYSIOLOGY AND PATHOGENESIS

In industrialized nations, cystic fibrosis (see Chapter 403) is the most common cause of clinically significant bronchiectasis. Other conditions associated with bronchiectasis include primary ciliary dyskinesia (see Chapter 404), foreign-body aspiration (see Chapter 387), aspiration of gastric contents, immune deficiency syndromes (especially humoral immunity), and infection, especially pertussis, measles, and tuberculosis (Table 401-1). Bronchiectasis can also be congenital, as in **Williams-Campbell syndrome**, in which there is an absence of annular bronchial cartilage, and **Marnier-Kuhn syndrome** (congenital tracheobronchomegaly), in which there is a connective tissue disorder. Other disease entities associated with bronchiectasis are **right middle lobe syndrome** (chronic extrinsic compression of right middle lobe bronchus by hilar lymph nodes) and **yellow nail syndrome** (pleural effusion, lymphedema, discolored nails).

Three basic mechanisms are involved in the pathogenesis of bronchiectasis. Obstruction can occur because of tumor, foreign body, impacted mucus because of poor mucociliary clearance, external

Table 401-1	Conditions That Predispose to Bronchiectasis in Children
PROXIMAL AIRWAY NARROWING	
Airway wall compression (i.e., vascular ring, adenopathy impinging on airways)	
Airway intraluminal obstruction (e.g., inhaled foreign body, granulation tissue)	
Airway stenosis and malacia	
AIRWAY INJURY	
Bronchiolitis obliterans (e.g., postviral, after lung transplantation)	
Recurrent pneumonitis or pneumonia (e.g., pneumococcal pneumonia, aspiration pneumonia)	
ALTERED PULMONARY HOST DEFENSES	
Cystic fibrosis	
Ciliary dyskinesia	
Impaired cough (e.g., neuromuscular weakness conditions)	
ALTERED IMMUNE STATES	
Primary abnormalities (e.g., hypogammaglobulinemia)	
Secondary abnormalities (e.g., HIV infection, immunosuppressive agents)	
OTHER	
Allergic bronchopulmonary aspergillosis	
Plastic bronchitis	

From Redding GJ: Bronchiectasis in children, Pediatr Clin North Am *56:157–171, 2009, Box 1, p. 158.*

compression, bronchial webs, and atresia. Infections caused by *Bordetella pertussis*, measles, rubella, togavirus, respiratory syncytial virus, adenovirus, and *Mycobacterium tuberculosis* induce chronic inflammation, progressive bronchial wall damage, and dilation. Chronic inflammation similarly contributes to the mechanism by which obstruction leads to bronchiectasis. Activation of toll-like receptors results in the activation of nuclear factor κβ and the release of proinflammatory cytokines interleukin (IL)-1β, IL-8, and tumor necrosis factor-α. IL-8 is a chemoattractant for neutrophils, which are the main inflammatory cell involved in the pathogenesis of bronchiectasis. Once activated neutrophils produce neutrophil elastase and matrix metalloproteinases, MMP-8 and MMP-9. IL-6, IL-8, and tumor necrosis factor-α are elevated in the airways of patients with bronchiectasis. The mechanism by which bronchiectasis occurs in congenital forms is likely related to abnormal cartilage formation. The common thread in the pathogenesis of bronchiectasis consists of difficulty clearing secretions and recurrent infections with a "vicious cycle" of infection and inflammation resulting in airway injury and remodeling.

Bronchiectasis can manifest in any combination of three pathologic forms, best defined by high-resolution CT (HRCT) scan. In cylindrical bronchiectasis, the bronchial outlines are regular, but there is diffuse dilation of the bronchial unit. The bronchial lumen ends abruptly because of mucous plugging. In varicose bronchiectasis, the degree of dilation is greater, and local constrictions cause an irregularity of outline resembling that of varicose veins. There may also be small sacculations. In saccular (cystic) bronchiectasis, bronchial dilation progresses and results in ballooning of bronchi that end in fluid- or mucus-filled sacs. This is the most severe form of bronchiectasis. Bronchiectasis lies within a disease spectrum of chronic pediatric suppurative lung disease. The following definitions have been proposed: **prebronchiectasis** (chronic or recurrent endobronchial infection with nonspecific HRCT changes; may be reversible); **HRCT bronchiectasis** (clinical symptoms with HRCT evidence of bronchial dilation; may persist, progress, or improve and resolve); **established bronchiectasis** (like the previous but with no resolution within 2 yr). Early diagnosis and aggressive therapy are important to prevent the development of established bronchiectasis.

CLINICAL MANIFESTATIONS

The most common complaints in patients with bronchiectasis are cough and production of copious purulent sputum. Younger children may swallow the sputum. Hemoptysis is seen with some frequency. Fever can occur with infectious exacerbations. Anorexia and poor weight gain may occur as time passes. Physical examination typically reveals crackles localized to the affected area, but wheezing as well as digital clubbing may also occur. In severe cases, dyspnea and hypoxemia can occur. Pulmonary function studies may demonstrate an obstructive, restrictive, or mixed pattern. Typically, impaired diffusion capacity is a late finding.

DIAGNOSIS

Conditions that can be associated with bronchiectasis should be ruled out by appropriate investigations (e.g., sweat test, immunologic work-up). Chest radiographs of patients with bronchiectasis tend to be nonspecific. Typical findings can include increase in size and loss of definition of bronchovascular markings, crowding of bronchi, and loss of lung volume. In more severe forms, cystic spaces, occasionally with air–fluid levels and honeycombing, may occur. Compensatory overinflation of unaffected lung may be seen. Thin-section HRCT scanning is the gold standard, because it has excellent sensitivity and specificity. CT provides further information on disease location, presence of mediastinal lesions, and the extent of segmental involvement. The addition of radiolabeled aerosol inhalation to CT scanning can provide even more information. The CT findings in patients with bronchiectasis typically include cylindrical ("tram lines," "signet ring appearance"), varicose (bronchi with "beaded contour"), cystic (cysts in "strings and clusters"), or mixed forms (Fig. 401-1). The lower lobes are most commonly affected.

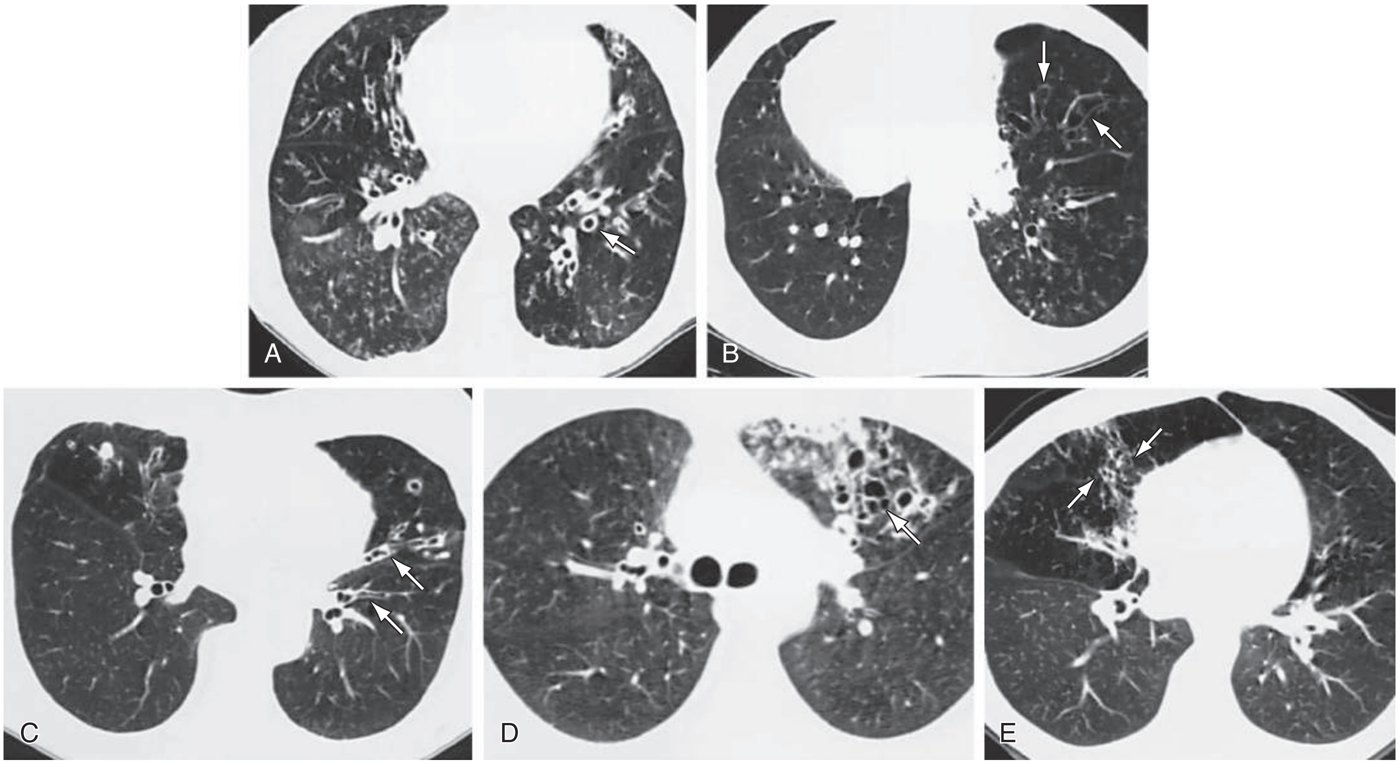

Figure 401-1 High-resolution CT scans of lungs with bronchiectasis. **A,** Dilated and thickened airways *(arrow)*. **B,** Airways do not taper *(arrows)* toward the periphery in a patient with Kartagener syndrome. **C,** Varicose changes (dilated and beaded airways *[arrows]*). **D,** Clustered cysts or saccules *(arrow)* as well as a peripheral infiltrate. **E,** Middle lobe bronchiectasis *(arrows)* in a patient with *Mycobacterium avium* complex infection. *(From Barker AF: Bronchiectasis,* N Engl J Med *346:1383, 2002.)*

TREATMENT

The initial therapy for patients with bronchiectasis is medical and aims at decreasing airway obstruction and controlling infection. Chest physiotherapy (postural drainage), antibiotics, and bronchodilators are essential. Two to 4 wk of parenteral antibiotics is often necessary to manage acute exacerbations adequately. Exacerbations can be defined as the presence of 1 major criteria (wet cough enduring longer than 72 hr, increased cough frequency over 72 hr) *plus* 1 laboratory criteria (C-reactive protein >3 mg/L, serum IL-6 >2 ng/L, serum amyloid A >5 mg/L, elevated neutrophil percentage), 2 major criteria, or 1 major criteria *plus* 2 minor criteria (change in sputum color, breathlessness, chest pain, crackles/crepitations, wheeze). Antibiotic choice is dictated by the identification and sensitivity of organisms found on deep throat, sputum (induced or spontaneous), or bronchoalveolar lavage fluid cultures. The most common organisms found in children with bronchiectasis include *Streptococcus pneumoniae*, *Haemophilus influenzae* non-type b, *Moraxella catarrhalis*, and *Mycoplasma pneumoniae*. Amoxicillin/clavulanic acid (22.5 mg/kg/dose twice daily) has been particularly successful at treating most pulmonary exacerbations. Long-term prophylactic oral (macrolide) or nebulized antibiotics (e.g., tobramycin, colistin, aztreonam) may be beneficial. Airway hydration (inhaled hypertonic saline or mannitol) also improves quality of life in adults with bronchiectasis. Any underlying disorder (immunodeficiency, aspiration) that may be contributing must be addressed. When localized bronchiectasis becomes more severe or resistant to medical management, segmental or lobar resection may be warranted. Lung transplantation can also be performed in patients with bronchiectasis. A review of randomized trials among adult patients with bronchiectasis did not find strong evidence to support the routine use of inhaled corticosteroids, although some studies demonstrate improved quality of life and reduced exacerbations in patients with bronchiectasis treated with inhaled corticosteroids. Although preventative strategies, including immunization against typical respiratory pathogens (influenza, pneumococci), are generally recommended, no studies have been conducted to date to address the efficacy of these recommendations.

PROGNOSIS

Children with bronchiectasis often suffer from recurrent pulmonary illnesses, resulting in missed school days, stunted growth, osteopenia, and osteoporosis. The prognosis for patients with bronchiectasis has improved considerably in the past few decades. Earlier recognition or prevention of predisposing conditions, more powerful and broad-spectrum antibiotics, and improved surgical outcomes are likely reasons.

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Chapter 402
Pulmonary Abscess
Oren J. Lakser

Lung infection that destroys the lung parenchyma, resulting in cavitations and central necrosis, can result in localized areas composed of thick-walled purulent material, called **lung abscesses**. **Primary lung abscesses** occur in previously healthy patients with no underlying medical disorders and are usually solitary. **Secondary lung abscesses** occur in patients with underlying or predisposing conditions and may be multiple. Lung abscesses are much less common in children (estimated at 0.7 per 100,000 admissions per year) than in adults.

PATHOLOGY AND PATHOGENESIS
A number of conditions predispose children to the development of pulmonary abscesses, including aspiration, pneumonia, cystic fibrosis (see Chapter 403), gastroesophageal reflux (see Chapter 323), tracheoesophageal fistula (see Chapter 319), immunodeficiencies, postoperative complications of tonsillectomy and adenoidectomy, seizures, a variety of neurologic diseases, and other conditions associated with impaired mucociliary defense. In children, aspiration of infected materials or a foreign body is the predominant source of the organisms causing abscesses. Initially, pneumonitis impairs drainage of fluid or the aspirated material. Inflammatory vascular obstruction occurs, leading to tissue necrosis, liquefaction, and abscess formation. Abscess can also occur as a result of pneumonia and hematogenous seeding from another site.

If the aspiration event occurred while the child was recumbent, the right and left upper lobes and apical segment of the right lower lobes are the dependent areas most likely to be affected. In a child who was upright, the posterior segments of the upper lobes were dependent and therefore are most likely to be affected. Primary abscesses are found most often on the right side, whereas secondary lung abscesses, particularly in immunocompromised patients, have a predilection for the left side.

Both anaerobic and aerobic organisms can cause lung abscesses. Common anaerobic bacteria that can cause a pulmonary abscess include *Bacteroides* spp., *Fusobacterium* spp., and *Peptostreptococcus* spp. Abscesses can be caused by aerobic organisms such as *Streptococcus* spp., *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and very rarely *Mycoplasma pneumoniae.* Aerobic and anaerobic cultures should be part of the work-up for all patients with lung abscess. Occasionally, concomitant viral–bacterial infection can be detected. Fungi can also cause lung abscesses, particularly in immunocompromised patients.

CLINICAL MANIFESTATIONS
The most common symptoms of pulmonary abscess in the pediatric population are cough, fever, tachypnea, dyspnea, chest pain, vomiting, sputum production, weight loss, and hemoptysis. Physical examination typically reveals tachypnea, dyspnea, retractions with accessory muscle use, decreased breath sounds, and dullness to percussion in the affected area. Crackles and, occasionally, a prolonged expiratory phase may be heard on lung examination.

DIAGNOSIS
Diagnosis is most commonly made on the basis of chest radiography. Classically, the chest radiograph shows a parenchymal inflammation with a cavity containing an air–fluid level (Fig. 402-1). A chest CT scan can provide better anatomic definition of an abscess, including location and size (Fig. 402-2).

An abscess is usually a thick-walled lesion with a low-density center progressing to an air–fluid level. Abscesses should be distinguished from pneumatoceles, which often complicate severe bacterial pneumonias and are characterized by thin- and smooth-walled, localized air collections with or without air–fluid level (Fig. 402-3). Pneumatoceles often resolve spontaneously with the treatment of the specific cause of the pneumonia.

The determination of the etiologic bacteria in a lung abscess can be very helpful in guiding antibiotic choice. Although Gram stain of sputum can provide an early clue as to the class of bacteria involved, sputum cultures typically yield mixed bacteria, and therefore are not always reliable. Attempts to avoid contamination from oral flora include direct lung puncture, percutaneous (aided by CT guidance) or transtracheal aspiration, and bronchoalveolar lavage specimens obtained bronchoscopically. Bronchoscopic aspiration should be avoided as it can be complicated by massive intrabronchial aspiration, and great care should therefore be taken during the procedure. To avoid invasive procedures in previously normal hosts, empiric therapy can be initiated in the absence of culturable material.

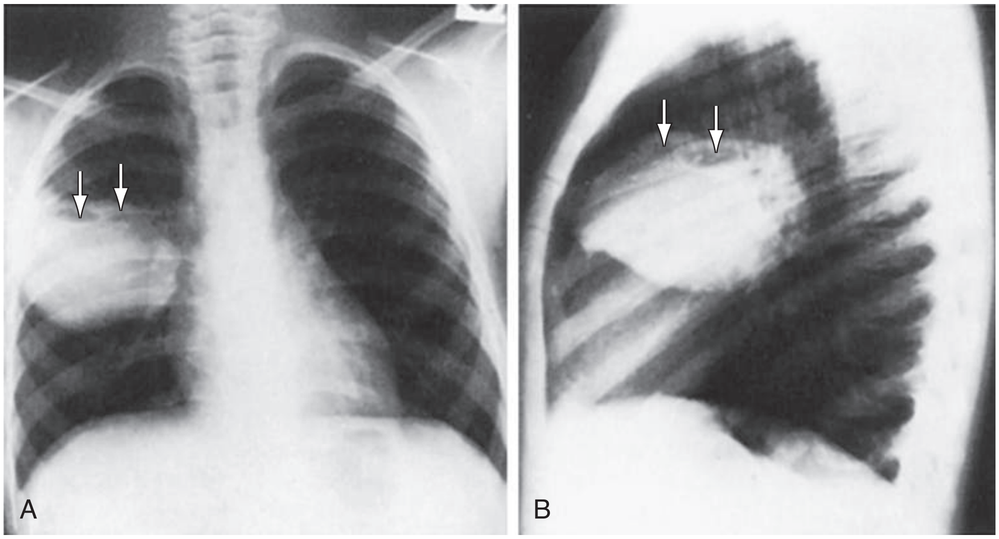

Figure 402-1 **A** and **B,** Multiloculated lung abscess *(arrows). (From Brook I: Lung abscess and pulmonary infections due to anaerobic bacteria. In Chernick V, Boat TF, Wilmott RW, et al, editors:* Kendig's disorders of the respiratory tract in children, *ed 7, Philadelphia, 2006, WB Saunders, p. 482.)*

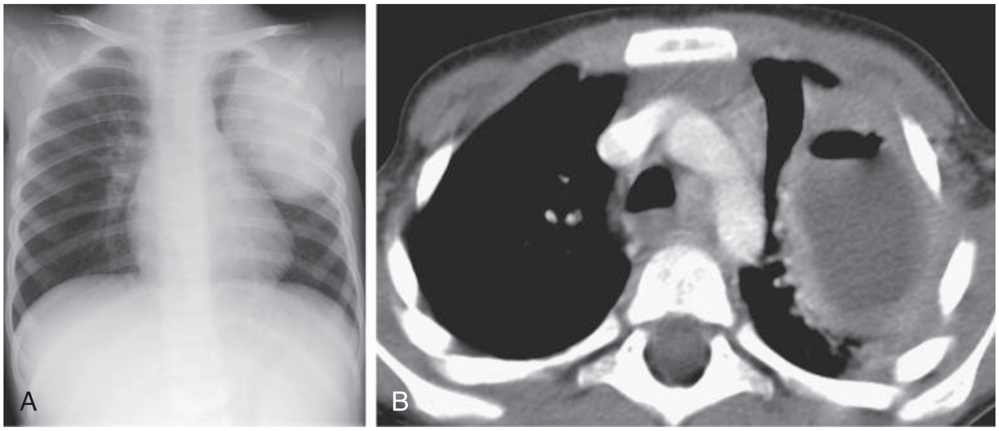

Figure 402-2 Pulmonary abscess in a 2 yr old boy with persistent cough. **A,** Chest radiograph shows large oval mass in the left upper lobe. **B,** CT scan demonstrates an abscess with a thick enhancing wall that contains both air and fluid. *(From Slovis TL, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, Fig. 78-3, p. 1297.)*

TREATMENT

Conservative management is recommended for pulmonary abscess. Most experts advocate a 2-3 wk course of parenteral antibiotics for uncomplicated cases, followed by a course of oral antibiotics to complete a total of 4-6 wk. Antibiotic choice should be guided by results of Gram stain and culture but initially should include agents with aerobic and anaerobic coverage. Treatment regimens should include a penicillinase-resistant agent active against *S. aureus* and anaerobic coverage, typically with clindamycin or ticarcillin/clavulanic acid. If Gram-negative bacteria are suspected or isolated, an aminoglycoside should be added. Early CT-guided percutaneous aspiration or drainage has been advocated as it can hasten the recovery and shorten the course of parenteral antibiotic therapy needed.

For severely ill patients or those whose status fails to improve after 7-10 days of appropriate antimicrobial therapy, surgical intervention should be considered. Minimally invasive percutaneous aspiration techniques, often with CT guidance, are the initial and, often, only intervention required. Thoracoscopic drainage has also been successfully utilized with minimal complications. In rare complicated cases, thoracotomy with surgical drainage or lobectomy and/or decortication may be necessary.

PROGNOSIS

Overall, prognosis for children with primary pulmonary abscesses is excellent. The presence of aerobic organisms may be a negative prognostic indicator, particularly in those with secondary lung abscesses. Most children become asymptomatic within 7-10 days, although the fever can persist for as long as 3 wk. Radiologic abnormalities usually resolve in 1-3 mo but can persist for years.

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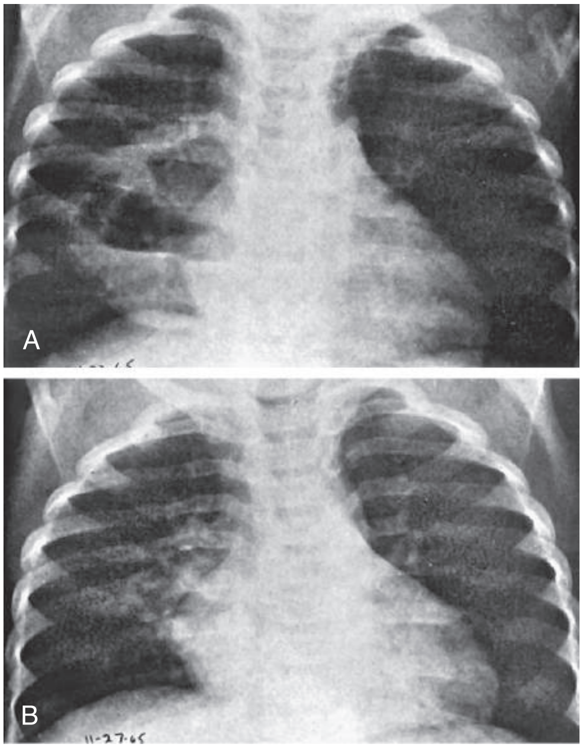

Figure 402-3 Appearance over a period of 5 days of a large multiloculated pneumonocele in a segment of alveolar consolidation. **A,** There is a large cavity with 2 air–fluid levels in a segment of alveolar pneumonia in the right upper lobe. **B,** Five days later, the cavity and most of the pneumonic consolidation have disappeared. *(From Silverman FN, Kuhn JP:* Essentials of Caffey's pediatric x-ray diagnosis, *Chicago, 1990, Year Book, p. 303.)*

Table 403-1	Complications of Cystic Fibrosis
RESPIRATORY	
Bronchiectasis, bronchitis, bronchiolitis, pneumonia	
Atelectasis	
Hemoptysis	
Pneumothorax	
Nasal polyps	
Sinusitis	
Reactive airway disease	
Cor pulmonale	
Respiratory failure	
Mucoid impaction of the bronchi	
Allergic bronchopulmonary aspergillosis	
GASTROINTESTINAL	
Meconium ileus, meconium plug (neonate)	
Meconium peritonitis (neonate)	
Distal intestinal obstruction syndrome (non-neonatal obstruction)	
Rectal prolapse	
Intussusception	
Volvulus	
Fibrosing colonopathy (strictures)	
Appendicitis	
Intestinal atresia	
Pancreatitis	
Biliary cirrhosis (portal hypertension: esophageal varices, hypersplenism)	
Neonatal obstructive jaundice	
Hepatic steatosis	
Gastroesophageal reflux	
Cholelithiasis	
Inguinal hernia	
Growth failure (malabsorption)	
Vitamin deficiency states (vitamins A, K, E, D)	
Insulin deficiency, symptomatic hyperglycemia, diabetes	
Malignancy (rare)	
OTHER	
Infertility	
Delayed puberty	
Edema-hypoproteinemia	
Dehydration–heat exhaustion	
Hypertrophic osteoarthropathy-arthritis	
Clubbing	
Amyloidosis	
Diabetes mellitus	
Aquagenic palmoplantar keratoderma (skin wrinkling)	

Adapted from Silverman FN, Kuhn JP: Essentials of Caffey's pediatric x-ray diagnosis, *Chicago, 1990, Year Book, p. 649.*

Chapter 403

Cystic Fibrosis

Marie E. Egan, Deanna M. Green, and Judith A. Voynow

Cystic fibrosis (CF) is an inherited multisystem disorder of children and adults; it is the most common life-limiting recessive genetic trait among whites. Dysfunction of the *cystic fibrosis transmembrane conductance regulator protein* (CFTR), the primary defect, leads to a wide and variable array of presenting manifestations and complications.

CF is responsible for most cases of exocrine pancreatic insufficiency in early life and is the major cause of severe chronic lung disease in children. It is also responsible for many cases of hyponatremic salt depletion, nasal polyposis, pansinusitis, rectal prolapse, pancreatitis, cholelithiasis, and nonautoimmune insulin-dependent hyperglycemia. Because CF may manifest as failure to thrive and, occasionally, as cirrhosis or other forms of hepatic dysfunction, this disorder enters into the differential diagnosis of many pediatric conditions (Table 403-1).

GENETICS

CF occurs most frequently in white populations of northern Europe, North America, and Australia/New Zealand. The prevalence in these populations varies but approximates 1 in 3,500 live births (1 in 9,200 individuals of Hispanic descent and 1 in 15,000 African-Americans). Although less frequent in African, Hispanic, Middle Eastern, South Asian, and eastern Asian populations, the disorder does exist in these populations as well (Fig. 403-1).

CF is inherited as an autosomal recessive trait. The CF gene codes for the CFTR protein, which is 1,480 amino acids. CFTR is expressed largely in epithelial cells of airways, the gastrointestinal tract (including the pancreas and biliary system), the sweat glands, and the genitourinary system. CFTR is a member of the adenosine triphosphate–binding cassette superfamily of proteins. It functions as a chloride channel and has other regulatory functions that are perturbed variably by the different mutations. More than 1,900 *CFTR* polymorphisms grouped into 5 main classes of mutations that affect protein function are associated with the CF syndrome (Table 403-2). The most prevalent mutation of *CFTR* is the deletion of a single phenylalanine residue at amino acid 508 (F508del). This mutation is responsible for the high incidence of CF in northern European populations and is considerably less frequent in other populations, such as those of southern Europe and Israel. Approximately 50% of individuals with CF who are of northern European ancestry are homozygous for F508del, and more than 80% carry at least 1 F508del gene. Remaining patients have an extensive array of mutations, none of which has a prevalence of more than several percentage points, except in certain populations; for example, the W1282X mutation occurs in 60% of Ashkenazi Jews with CF. The relationship between CFTR genotype and clinical phenotype is

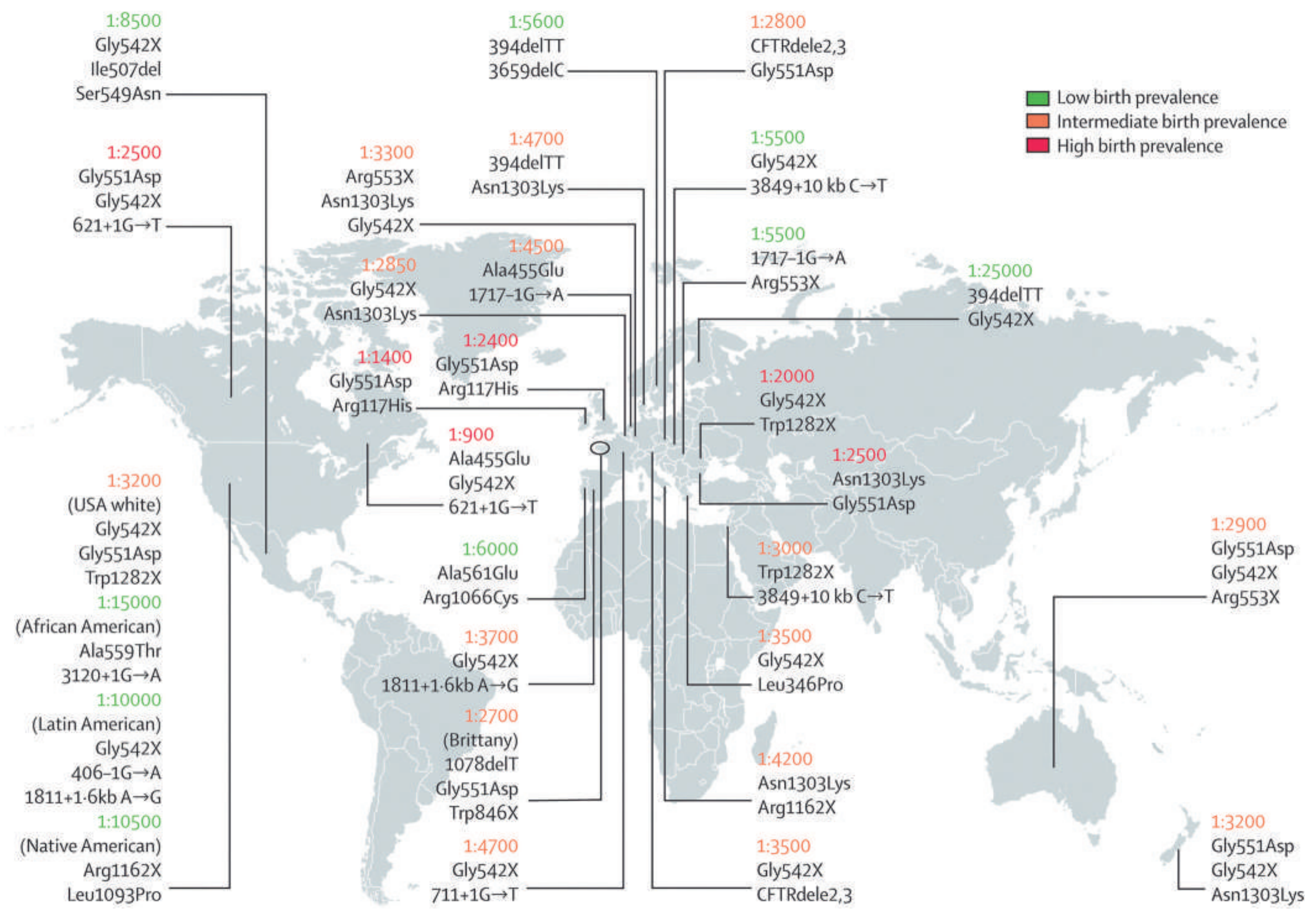

Figure 403-1 **Approximate cystic fibrosis birth prevalence and common mutations for selected countries.** Birth prevalence is reported as number of live births per case of cystic fibrosis. Common/important mutations in each region are listed below the prevalence figures. The birth prevalence can vary greatly among ethnic groups in a country. *(From O'Sullivan BP, Freedman SD: Cystic fibrosis,* Lancet *373:1891–1902, 2009.)*

Table 403-2 One Proposed Classification of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Mutations

CLASS	EFFECT ON CFTR	FUNCTIONAL CFTR PRESENT?	SAMPLE MUTATIONS
I	Lack of protein production	No	Stop codons (designation in X; e.g., Trp1282X, Gly542X); splicing defects with no protein production (e.g., 711+1G→T, 1717-1G→A)
II	Defect in protein trafficking with ubiquitination and degradation in endoplasmic reticulum/Golgi body	No/substantially reduced	Phe508del, Asn1303Lys, Gly85Gly, leu1065Pro, Asp507, Ser549Arg
III	Defective regulation; CFTR not activated by adenosine triphosphate or cyclic adenosine monophosphate	No (nonfunction CFTR present in apical membrane)	Gly551Asp, Ser492Phe, Val520Phe, Arg553Gly, Arg560Thr, Arg560Ser
IV	Reduced chloride transport through CFTR at the apical membrane	Yes	Ala455Glu, Arg117Cys, Asp1152His, Leu227Arg, Arg334Trp, Arg117His*
V	Splicing defect with reduced production of CFTR	Yes	3849+10kbC→T, 1811+16kbA→G, IVS8-5T, 2789+5G→A

*Function of Arg117His depends on the length of the polythymidine track on the same chromosome in intron 8 (IVS8): 5T, 7T, or 9T. There is more normal CFTR function with a longer polythymidine track.

From O'Sullivan BP, Freedman SD: Cystic fibrosis, Lancet *373:1891–1902, 2009.*

highly complex and is not predictable for individual patients. Mutations categorized as "severe" are associated almost uniformly with pancreatic insufficiency but only in general with more rapid progression of lung disease. *A few mutations, such as 3849 + 10kbC→T, are found in patients with normal sweat chloride concentrations.* Some individuals with polymorphisms of both *CFTR* genes have few or no CF manifestations until adolescence or adulthood, when they present with pancreatitis, sinusitis, diffuse bronchiectasis, or male infertility. Whereas *CFTR* mutations are a sine qua non for CF, 2 mutations of *CFTR* can cause disorders that do not meet diagnostic criteria for CF and, occasionally, do not cause discernible clinical problems. Non-CFTR modifier gene polymorphisms appear to be responsible for

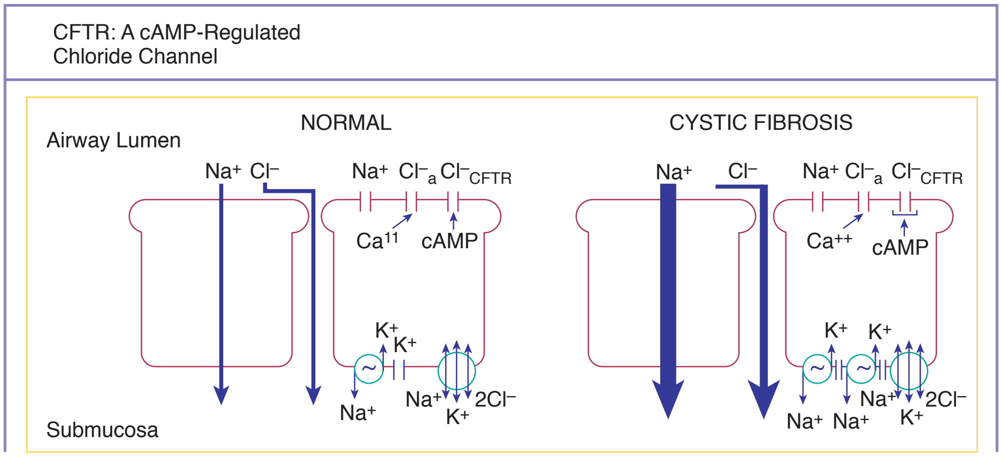

Figure 403-2 The net ion flow across normal and cystic fibrosis (CF) airway epithelia under basal conditions *(large arrows).* Because water follows salt movement, the predicted net flux of water would be from the airway lumen to the submucosa and would be greater across CF epithelia. The increased Na^+ absorption by CF cells is associated with an increased amiloride-sensitive Na^+ conductance across the apical (luminal) membrane and increased Na^+,K^+-adenosine triphosphatase (ATPase) sites at the basolateral membrane. The cyclic adenosine monophosphate (cAMP)–mediated apical membrane conductance of Cl^- associated with the CF transmembrane regulator (CFTR) does not function in CF epithelia, but an alternative, calcium (Ca^{++})–activated Cl^- conductance is present in normal and CF cells. It is postulated that CF cells have a limited ability to secrete Cl^- and absorb Na+ in excessive amounts, limiting the water available to hydrate secretions and allow them to be cleared from the airways lumen. Cl^-a, Ca^{++}–activated Cl^- conductance: Cl^-CTFR, the CFTR Cl^- channel. *(From Knowles MR: Contemporary perspectives on the pathogenesis of cystic fibrosis,* New Insights Cystic Fibrosis *1:1, 1993.)*

much of the variation in the progression of lung disease. Genomewide association studies provide an unbiased approach to test for novel polymorphisms that associate with CF lung disease severity. Genomewide association studies identified a polymorphism on chromosome 11 in the intergenic region between EHF (an epithelial transcription factor) and APIP (an inhibitor of apoptosis) that is associated with lung disease severity, and may influence the expression of *EHF* and *APIP*, as well as other genes in the region, including *PDHX*, *CD44*, and *ELF5*. A region on chromosome 20 was also found to relate to lung disease severity. This region encompasses several genes (*MC3R*, *CASS4*, *AURKA*) that may play a role in lung host-defense involving neutrophil function, apoptosis, and phagocytosis. Genomewide association studies analysis also identified genetic regions that predispose to risk for liver disease, CF-related diabetes, and meconium ileus.

Through the use of probes for 40 of the most common mutations, the genotype of 80-90% of Americans with CF can be ascertained. Genotyping using a discreet panel of mutation probes is quick and less costly than more comprehensive sequencing and is commercially available. In special cases, sequencing the entire *CFTR* gene is necessary to establish the genotype. This procedure is also available commercially and can identify polymorphisms and unique mutations of unknown clinical importance.

The high frequency of *CFTR* mutations has been ascribed to resistance to the morbidity and mortality associated with infectious dysenteries through the ages. In support of this hypothesis, cultured CF intestinal epithelial cells homozygous for the F508del mutation are unresponsive to the secretory effects of cholera toxin. CFTR heterozygous mice experience less mortality when treated with cholera toxin than their unaffected wild type littermates.

PATHOGENESIS

A number of long-standing observations of CF are of fundamental pathophysiologic importance; they include failure to clear mucous secretions, a paucity of water in mucous secretions, an elevated salt content of sweat and other serous secretions, and chronic infection limited to the respiratory tract. Additionally, there is a greater negative potential difference across the respiratory epithelia of patients with CF than across the respiratory epithelia of control subjects. Aberrant electrical properties are also demonstrated for CF sweat gland duct and rectal epithelia. The membranes of CF epithelial cells are unable to secrete chloride ions in response to cyclic adenosine monophosphate–mediated signals, and at least in the respiratory tract, excessive amounts of sodium are absorbed through these membranes (Fig. 403-2). These defects can be traced to a dysfunction of CFTR (Figs. 403-3 and 403-4).

Cyclic adenosine monophosphate–stimulated protein kinase A regulation of chloride conductance is the primary function of CFTR; this function is absent in epithelial cells with many different mutations of the *CFTR* gene. *CFTR* mutations fall into 5 classes in another classification system, albeit with some overlap (see Fig. 403-4). Individuals with classes I, II, and III mutations, on average, have shorter survival than those with "mild" genotypes (class IV or V). The clinical importance of these functional categories is limited because they do not uniformly correlate with specific clinical features or their severity. Rather, clinical features correlate with the residual CFTR activity.

Many hypotheses have been postulated to explain how CFTR dysfunction results in the clinical phenotype. It is likely that no one hypothesis explains the full spectrum of disease. Most believe that the epithelial pathophysiology in airways involves an inability to secrete salt and secondarily to secrete water in the presence of excessive reabsorption of salt and water. The proposed outcome is insufficient water on the airway surface to hydrate secretions. Desiccated secretions become more viscous and elastic (rubbery) and are harder to clear by mucociliary and other mechanisms. In addition it has been suggested that CFTR dysfunction results in an altered microenvironment with low HCO_3^- and a more acidic pH, thus altering mucus rheology and aggravating poor mucociliary clearance. The result is that these secretions are retained and obstruct airways, starting with those of the smallest caliber, the bronchioles. Airflow obstruction at the level of small airways is the earliest observable physiologic abnormality of the respiratory system.

It is plausible that similar pathophysiologic events take place in the pancreatic and biliary ducts (and in the vas deferens), leading to desiccation of proteinaceous secretions and obstruction. Because the function of sweat gland duct cells is to absorb rather than secrete chloride, salt is not retrieved from the isotonic primary sweat as it is transported to the skin surface; chloride and sodium levels are consequently elevated.

Chronic infection in CF is limited to the airways. A likely explanation for infection is a sequence of events starting with failure to clear inhaled bacteria promptly and then proceeding to persistent colonization and an inflammatory response in airway walls. In addition, it has

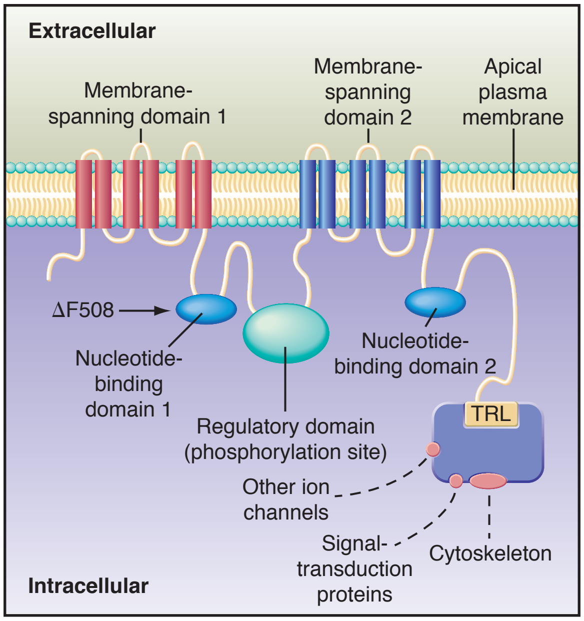

Figure 403-3 **Hypothesized structure of cystic fibrosis transmembrane regulator (CFTR).** The protein contains 1,480 amino acids and a number of discrete globular and transmembrane domains. Activation of CFTR relies on phosphorylation, particularly through protein kinase A but probably involving other kinases as well. Channel activity is governed by the 2 nucleotide-binding domains, which regulate channel gating. The carboxyl terminal (consisting of threonine, arginine, and leucine [TRL]) of CFTR is anchored through a PDZ-type binding interaction with the cytoskeleton and is kept in close approximation *(dashed lines)* to a number of important proteins. These associated proteins influence CFTR functions, including conductance, regulation of other channels, signal transduction, and localization at the apical plasma membrane. Each membrane-spanning domain contains 6 membrane-spanning α helixes, portions of which form a chloride-conductance pore. The regulatory domain is a site of protein kinase A phosphorylation. The common F508del mutation occurs on the surface of nucleotide-binding domain 1. *(From Rowe SM, Miller S, Sorscher EJ: Cystic fibrosis,* N Engl J Med *352:1992–2001, 2005.)*

been proposed that abnormal CFTR creates a proinflammatory state or amplifies the inflammatory response to initial infections (viral or bacterial). Some investigators have identified primary differences in CF-affected immune cells and have suggested that these alterations contribute to this proinflammatory state. It appears that inflammatory events occur first in small airways, perhaps because clearance of altered secretions and microorganisms from these regions is more difficult. Chronic bronchiolitis and bronchitis are the initial lung manifestations (see Chapter 391), but after months to years, structural changes in airway walls produce bronchiolectasis and bronchiectasis. The agents of airway injury include neutrophil products, such as oxidative radicals and proteases, and immune reaction products. With advanced lung disease, infection may extend to peribronchial lung parenchyma.

A finding that is not readily explained by CFTR dysfunction is the high prevalence in patients with CF of airway colonization with *Staphylococcus aureus* (see Chapter 181.1), *Pseudomonas aeruginosa* (see Chapter 205.1), and *Burkholderia cepacia* complex (see Chapter 205.2), organisms that rarely infect the lungs of other individuals. It has been postulated that the CF airway epithelial cells or surface liquids may provide a favorable environment for harboring these organisms. CF airway epithelium may be compromised in its innate defenses against these organisms, through either acquired or genetic alterations. Antimicrobial activity is diminished in CF secretions; this diminution may be related to hyperacidic surface liquids or other effects on innate immunity. Another puzzle is the propensity for *P. aeruginosa* to undergo mucoid transformation in the CF airways. The complex polysaccharide produced by these organisms generates a biofilm that provides a hypoxic environment and thereby protects *Pseudomonas* against antimicrobial agents.

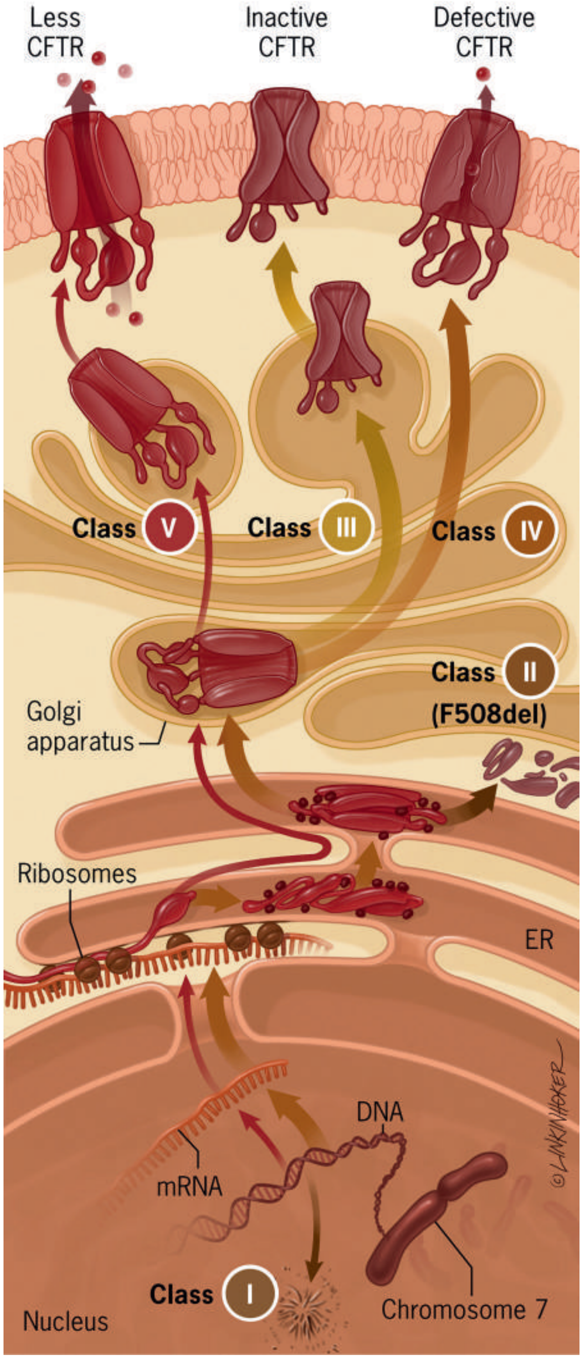

Figure 403-4 **Classes of *CFTR* (cystic fibrosis transmembrane regulator) mutations.** Classes of defects in the *CFTR* gene include the absence of synthesis (class I); defective protein maturation and premature degradation (class II); disordered regulation, such as diminished adenosine triphosphate (ATP) binding and hydrolysis (class III); defective chloride conductance or channel gating (class IV); and a reduced number of CFTR transcripts due to a promoter or splicing abnormality (class V) *(Copyright Michael Linkinhoker, Link Studio.)*

Nutritional deficits, including fatty acid deficiency, have been implicated as predisposing factors for respiratory tract infection. More specifically, concentrations of lipoxins—molecules that suppress neutrophilic inflammation—are suppressed in CF airways. Supporting this idea is the observation that the 10-15% of individuals with CF who retain substantial exocrine pancreatic function have delayed onset of

colonization with *P. aeruginosa* and slower deterioration of lung function. It appears that nutritional factors are only contributory because preservation of pancreatic function does not preclude development of typical lung disease.

PATHOLOGY

The earliest pathologic lesion in the lung is that of **bronchiolitis** (mucous plugging and an inflammatory response in the walls of the small airways); with time, mucus accumulation and inflammation extend to the larger airways (**bronchitis**) (see Chapter 391). Goblet cell hyperplasia and submucosal gland hypertrophy become prominent pathologic findings, which is most likely a response to chronic airway infection. Organisms appear to be confined to the endobronchial space; invasive bacterial infection is not characteristic. With long-standing disease, evidence of airway destruction such as **bronchiolar obliteration, bronchiolectasis,** and **bronchiectasis** (see Chapter 401) becomes prominent. Imaging modalities demonstrate both increased airway wall thickness and luminal cross-sectional area relatively early in lung disease evaluation. Bronchiectatic cysts and emphysematous bullae or subpleural blebs are frequent with advanced lung disease, the upper lobes being most commonly involved. These enlarged air spaces may rupture and cause pneumothorax. Interstitial disease is not a prominent feature, although areas of fibrosis appear eventually. Bronchial arteries are enlarged and tortuous, contributing to a propensity for **hemoptysis** in bronchiectatic airways. Small pulmonary arteries eventually display medial hypertrophy, which would be expected in secondary pulmonary hypertension.

The **paranasal sinuses** are uniformly filled with secretions containing inflammatory products, and the epithelial lining displays hyperplastic and hypertrophied secretory elements (see Chapter 380). Polypoid lesions within the sinuses and erosion of bone have been reported. The nasal mucosa may form large or multiple polyps, usually from a base surrounding the ostia of the maxillary and ethmoidal sinuses.

The **pancreas** is usually small, occasionally cystic, and often difficult to find at postmortem examination. The extent of involvement varies at birth. In infants, the acini and ducts are often distended and filled with eosinophilic material. In 85-90% of patients, the lesion progresses to complete or almost complete disruption of acini and replacement with fibrous tissue and fat. Infrequently, foci of calcification may be seen on radiographs of the abdomen. The islets of Langerhans contain normal-appearing β cells, although they may begin to show architectural disruption by fibrous tissue in the 2nd decade of life.

The **intestinal tract** shows only minimal changes. Esophageal and duodenal glands are often distended with mucous secretions. Concretions may form in the appendiceal lumen or cecum. Crypts of the appendix and rectum may be dilated and filled with secretions.

Focal biliary cirrhosis secondary to blockage of intrahepatic bile ducts is uncommon in early life, although it is responsible for occasional cases of prolonged neonatal jaundice. This lesion becomes much more prevalent and extensive with age and is found in 70% of patients at postmortem examination. This process can proceed to symptomatic multilobular biliary cirrhosis that has a distinctive pattern of large irregular parenchymal nodules and interspersed bands of fibrous tissue. Approximately 30-70% of patients have fatty infiltration of the liver, in some cases despite apparently adequate nutrition. At autopsy, hepatic congestion secondary to cor pulmonale is frequently observed. The gallbladder may be hypoplastic and filled with mucoid material and often contains stones. The epithelial lining often displays extensive mucous metaplasia. Atresia of the cystic duct and stenosis of the distal common bile duct have been observed.

Glands of the **uterine cervix** are distended with mucus, copious amounts of which collect in the cervical canal. In >95% of males, the body and tail of the epididymis, the vas deferens, and the seminal vesicles are obliterated or atretic, resulting in male infertility.

CLINICAL MANIFESTATIONS

Mutational heterogeneity and environmental factors appear responsible for highly variable involvement of the lungs, pancreas, and other organs. A list of presenting manifestations is lengthy, although pulmonary and gastrointestinal presentations predominate (Fig. 403-5). With inclusion of CF newborn screening panels, an increasing proportion of children are diagnosed before symptoms appear.

Respiratory Tract

Cough is the most constant symptom of pulmonary involvement. At first, the cough may be dry and hacking, but eventually it becomes loose and productive. In older patients, the cough is most prominent upon arising in the morning or after activity. Expectorated mucus is usually purulent. Some patients remain asymptomatic for long periods or seem to have prolonged but intermittent acute respiratory infections. Others acquire a chronic cough in the 1st few wk of life, or they

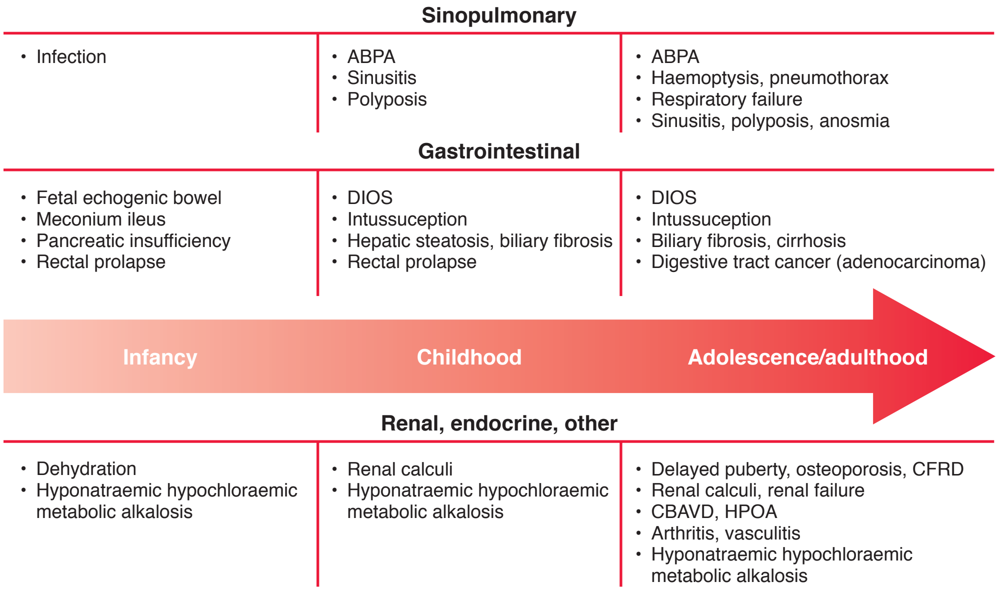

Figure 403-5 Approximate age of onset of clinical manifestations of cystic fibrosis. ABPA, allergic bronchopulmonary aspergillosis; CBAVD, congenital bilateral absence of the vas deferens; CFRD, cystic fibrosis-related diabetes mellitus; DIOS, distal intestinal obstruction syndrome; HPOA, hypertrophic pulmonary osteoarthritis. *(From O'Sullivan BP, Freedman SD: Cystic fibrosis,* Lancet *373:1891–1902, 2009.)*

have pneumonia repeatedly. Extensive bronchiolitis accompanied by wheezing is a frequent symptom during the 1st few yr of life. As lung disease slowly progresses, exercise intolerance, shortness of breath, and failure to gain weight or grow are noted. Exacerbations of lung symptoms, presumably owing to more active airways infection, often require repeated hospitalizations for effective treatment. Cor pulmonale, respiratory failure, and death eventually supervene unless lung transplantation is accomplished. Colonization with *B. cepacia* and other multidrug-resistant organisms may be associated with particularly rapid pulmonary deterioration and death.

The rate of progression of lung disease is the chief determinant of morbidity and mortality. The course of lung disease is largely independent of genotype. Male gender and exocrine pancreatic sufficiency are also associated with a slower rate of pulmonary function decline.

Early **physical findings** include increased anteroposterior diameter of the chest, generalized hyperresonance, scattered or localized coarse crackles, and digital clubbing. Expiratory wheezes may be heard, especially in young children. Cyanosis is a late sign. Common pulmonary complications include atelectasis, hemoptysis, pneumothorax, and cor pulmonale; these usually appear beyond the 1st decade of life.

Even though the paranasal sinuses are virtually always opacified radiographically, acute sinusitis is infrequent. Nasal obstruction and rhinorrhea are common, caused by inflamed, swollen mucous membranes or, in some cases, nasal polyposis. **Nasal polyps** are most troublesome between 5 and 20 yr of age.

Intestinal Tract

In 10-15% of newborn infants with CF, the ileum is completely obstructed by meconium (**meconium ileus**). The frequency is greater (≈30%) among siblings born subsequent to a child with meconium ileus and is particularly striking in monozygotic twins, reflecting a genetic contribution from 1 or more modifying genes. Abdominal distention, emesis, and failure to pass meconium appear in the 1st 24-48 hr of life (see Chapters 102.1 and 330.2). Abdominal radiographs (Fig. 403-6) show dilated loops of bowel with air–fluid levels and, frequently, a collection of granular, "ground-glass" material in the lower central abdomen. Rarely, **meconium peritonitis** results from intrauterine rupture of the bowel wall and can be detected radiographically as the presence of peritoneal or scrotal calcifications. **Meconium plug syndrome** occurs with increased frequency in infants with CF but is less specific than meconium ileus. Ileal obstruction with fecal material *(distal intestinal obstruction syndrome)* occurs in older patients, causing cramping abdominal pain and abdominal distention.

More than 85% of affected children show evidence of protein and fat malabsorption from exocrine pancreatic insufficiency. Symptoms include frequent, bulky, greasy stools and failure to gain weight even when food intake appears to be large. Characteristically, stools contain readily visible droplets of fat. A protuberant abdomen, decreased muscle mass, poor growth, and delayed maturation are typical physical signs. Excessive flatus may be a problem. A number of mutations are associated with preservation of some exocrine pancreatic function, including R117H and 3849 + 10kbC→T. Virtually all individuals homozygous for F508del have pancreatic insufficiency.

Less-common gastrointestinal manifestations include intussusception, fecal impaction of the cecum with an asymptomatic right lower quadrant mass, and epigastric pain owing to duodenal inflammation. Acid or bile reflux with esophagitis symptoms is common in older children and adults. Subacute appendicitis and periappendiceal abscess have been encountered. Historically a relatively common event, rectal prolapse occurs much less frequently as the result of earlier diagnosis and initiation of pancreatic enzyme replacement therapy. Occasionally, hypoproteinemia with anasarca appears in malnourished infants, especially if children are fed soy-based preparations. Neurologic dysfunction (dementia, peripheral neuropathy) and hemolytic anemia may occur because of **vitamin E deficiency.** Deficiency of other fat-soluble vitamins is occasionally symptomatic. **Hypoprothrombinemia** caused by vitamin K deficiency may result in a bleeding diathesis. Clinical manifestations of other fat-soluble vitamin deficiencies, such as decreased bone density and night blindness, have been noted. Rickets is rare.

Biliary Tract

Evidence for liver dysfunction is most often detected in the 1st 15 yr of life and can be found in up to 30% of individuals. Biliary cirrhosis becomes symptomatic in only 5-7% of patients. Manifestations can include icterus, ascites, hematemesis from esophageal varices, and evidence of hypersplenism. A neonatal hepatitis-like picture and massive hepatomegaly owing to steatosis have been reported. Biliary colic secondary to cholelithiasis may occur in the 2nd decade or later. Liver disease occurs independent of genotype but is associated with meconium ileus and pancreatic insufficiency.

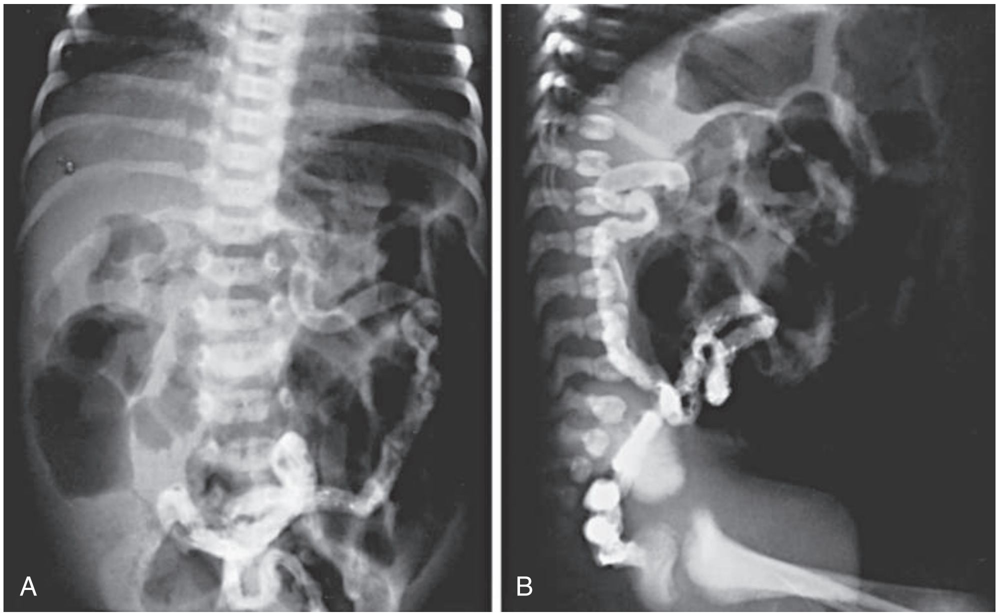

Figure 403-6 **A** and **B,** Contrast enema study in a newborn infant with abdominal distention and failure to pass meconium. Notice the small diameter of the sigmoid and ascending colon and dilated, air-filled loops of small intestine. Several air–fluid levels in the small bowel are visible on the upright lateral view.

Cystic Fibrosis–Related Diabetes and Pancreatitis

In addition to exocrine pancreatic insufficiency, evidence for hyperglycemia and glucosuria, including polyuria and weight loss, may appear, especially in the 2nd decade of life. Ketoacidosis usually does not occur, but eye, kidney, and other vascular complications have been noted in patients living ≥10 yr after the onset of hyperglycemia. Recurrent, acute pancreatitis occurs occasionally in individuals who have residual exocrine pancreatic function and may be the sole manifestation of 2 *CFTR* mutations.

Genitourinary Tract

Sexual development is often delayed but only by an average of 2 yr. More than 95% of males are azoospermic because of failure of development of wolffian duct structures, but sexual function is generally unimpaired. The incidence of inguinal hernia, hydrocele, and undescended testis is higher than expected. Adolescent females may experience secondary amenorrhea, especially with exacerbations of pulmonary disease. The female fertility rate is diminished. Pregnancy is generally tolerated well by women with good pulmonary function but may accelerate pulmonary progression in those with moderate or advanced lung problems. Urinary incontinence associated with cough occurs in 18-47% of female children and adolescents.

Sweat Glands

Excessive loss of salt in the sweat predisposes young children to salt depletion episodes, especially during episodes of gastroenteritis and during warm weather. These children present with **hypochloremic alkalosis.** Hyponatremia is a risk particularly in warm climates. Frequently, parents notice salt "frosting" of the skin or a salty taste when they kiss the child. A few genotypes are associated with normal sweat chloride values.

DIAGNOSIS AND ASSESSMENT

The diagnosis of CF has been based on a positive quantitative sweat test (Cl^- ≥60 mEq/L) in conjunction with 1 or more of the following features: typical chronic obstructive pulmonary disease, documented exocrine pancreatic insufficiency, and a positive family history. With newborn screening, diagnosis is often made prior to obvious clinical manifestations such as failure to thrive and chronic cough. Diagnostic criteria have been recommended to include additional testing procedures (Table 403-3).

Sweat Testing

The sweat test, which involves using pilocarpine iontophoresis to collect sweat and performing chemical analysis of its chloride content, is the standard approach to diagnosis of CF. The procedure requires care and accuracy. An electric current is used to carry pilocarpine into the skin of the forearm and locally stimulate the sweat glands. If an adequate amount of sweat is collected, the specimens are analyzed for chloride concentration. Testing may be difficult in the 1st 2 wk of life because of low sweat rates but is recommended any time after the 1st 48 hr of life. Positive results should be confirmed; for a negative result, the test should be repeated if suspicion of the diagnosis remains.

More than 60 mEq/L of chloride in sweat is diagnostic of CF when 1 or more other criteria are present. Threshold levels of 30-40 mEq/L for infants have been suggested. Borderline (or intermediate) values of 40-60 mEq/L have been reported in patients of all ages who have CF with atypical involvement and require further testing. Chloride concentrations in sweat are somewhat lower in individuals who retain exocrine pancreatic function but usually remain within the diagnostic range. Table 403-4 lists the conditions associated with false-negative and false-positive sweat test results.

Table 403-3	Diagnostic Criteria for Cystic Fibrosis (CF)

Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary)
or
A history of CF in a sibling
or
A positive newborn screening test
plus
Laboratory evidence for CFTR (CF transmembrane regulator) dysfunction:
- Two elevated sweat chloride concentrations obtained on separate days
- *or*
- Identification of two CF mutations
- *or*
- An abnormal nasal potential difference measurement

DNA Testing

Several commercial laboratories test for 30-96 of the most common *CFTR* mutations. This testing identifies ≥90% of individuals who carry 2 CF mutations. Some children with typical CF manifestations are found to have 1 or no detectable mutations by this methodology. Some laboratories perform comprehensive mutation analysis screening for all of the >1,900 identified mutations.

Other Diagnostic Tests

The finding of increased potential differences across nasal epithelium (nasal potential difference) that is the increased voltage response to topical amiloride application, followed by the absence of a voltage response to a β-adrenergic agonist, has been used to confirm the diagnosis of CF in patients with equivocal or frankly normal sweat chloride values.

Pancreatic Function

Exocrine pancreatic dysfunction is clinically apparent in many patients. Documentation is desirable if there are questions about the functional status of the pancreas. The diagnosis of pancreatic malabsorption can be made by the quantification of elastase-1 activity in a fresh stool sample by an enzyme-linked immunosorbent assay specific for human elastase. To determine the degree of fat malabsorption, a 72 hr stool

Table 403-4	Conditions Associated with False-Positive and False-Negative Sweat Test Results

WITH FALSE-POSITIVE RESULTS
Eczema (atopic dermatitis)
Ectodermal dysplasia
Malnutrition/failure to thrive/deprivation
Anorexia nervosa
Congenital adrenal hyperplasia
Adrenal insufficiency
Glucose-6-phosphatase deficiency
Mauriac syndrome
Fucosidosis
Familial hypoparathyroidism
Hypothyroidism
Nephrogenic diabetes insipidus
Pseudohypoaldosteronism
Klinefelter syndrome
Familial cholestasis syndrome
Autonomic dysfunction
Prostaglandin E infusions
Munchausen syndrome by proxy

WITH FALSE-NEGATIVE RESULTS
Dilution
Malnutrition
Edema
Insufficient sweat quantity
Hyponatremia
Cystic fibrosis transmembrane conductance regulator mutations with preserved sweat duct function

collection is performed for total fat quantitation with a simultaneous diet history to determine a coefficient of fat absorption. Normal fat absorption is greater than 93% of fat ingestion. Endocrine pancreatic dysfunction may be more prevalent than previously recognized. Cystic fibrosis–related diabetes affects approximately 19% of adolescents and 40-50% of adults. Many authorities advocate yearly monitoring with a modified 2 hr oral glucose tolerance test after 10 yr of age. This approach is more sensitive than spot checks of blood and urine glucose levels and glycosylated hemoglobin levels.

Radiology

Pulmonary radiologic findings suggest the diagnosis but are not specific. Hyperinflation of lungs occurs early and may be overlooked in the absence of infiltrates or streaky densities. Bronchial thickening and plugging and ring shadows suggesting bronchiectasis usually appear first in the upper lobes. Nodular densities, patchy atelectasis, and confluent infiltrate follow. Hilar lymph nodes may be prominent. With advanced disease, impressive hyperinflation with markedly depressed diaphragms, anterior bowing of the sternum, and a narrow cardiac shadow are noted. Cyst formation, extensive bronchiectasis, dilated pulmonary artery segments, and segmental or lobar atelectasis is often apparent with advanced disease. Figure 403-7 shows typical progression of lung disease. Most CF centers obtain chest radiographs (posteroanterior [PA] and lateral) at least annually. Standardized scoring of roentgenographic changes has been used to follow progression of lung disease. CT of the chest can detect and localize thickening of bronchial airway walls, mucous plugging, focal hyperinflation, and early bronchiectasis (Fig. 403-8); it is generally not used for routine evaluation of chest disease. Many children with normal lung function have bronchiectasis on CT, indicating that this imaging modality is sensitive to early lung changes.

Radiographs of paranasal sinuses reveal panopacification and, often, failure of frontal sinus development. CT provides better resolution of sinus changes if this information is required clinically. Fetal ultrasonography may suggest ileal obstruction with meconium early in the 2nd trimester, but this finding is not predictive of meconium ileus at birth.

Pulmonary Function

Standard pulmonary function studies are not obtained until patients are 4-6 yr of age, by which time many patients show the typical pattern of obstructive pulmonary involvement (see Chapter 384). Decrease in the midmaximal flow rate is an early functional change, reflecting small airway obstruction. This lesion also affects the distribution of

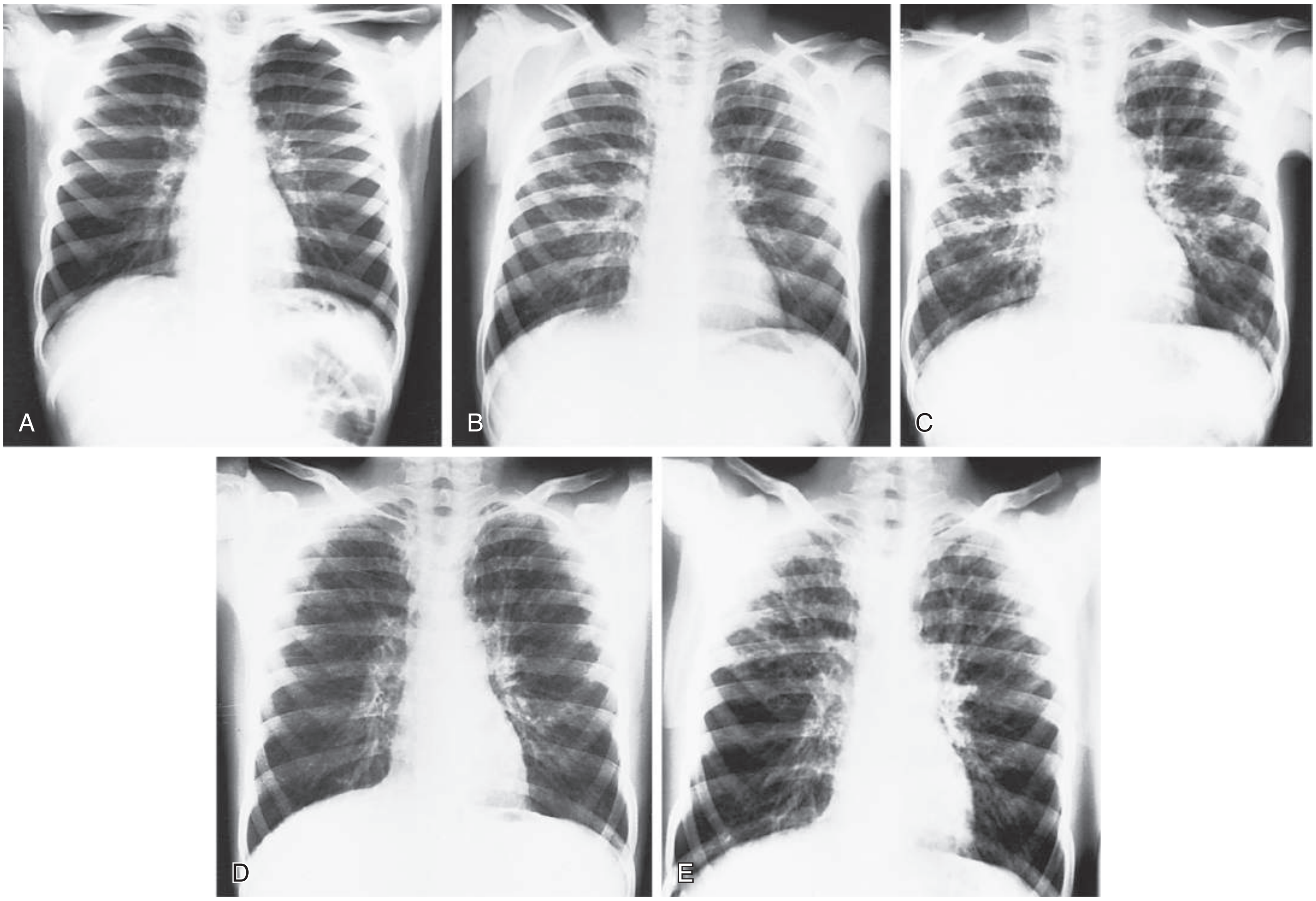

Figure 403-7 Serial radiographs in a boy show the changing appearance of cystic fibrosis over 6 yr. **A,** At 9 yr, frontal radiograph shows minimal peribronchial thickening and hyperaerated lungs indistinguishable from asthma. **B,** Nineteen months later, the radiographic picture has worsened considerably. Extensive peribronchial thickening is now noted. Mucoid impaction of the bronchus is seen in the left upper lobe and hilar shadows have become abnormally prominent. **C,** Ten months later, further deterioration is obvious. Widespread typical changes of CF are noted throughout both lungs. **D,** Follow-up studies show considerable improvement, which suggested that some of the changes evident on **C** were from superimposed infection. **E,** One year later, note the progressive changes of CF—most severe in the upper lobes bilaterally. *(From Long FR, Druhan SM, Kuhn JP. Diseases of the bronchi and pulmonary aeration. In Slovis TL, editor,* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby,* Fig. 73-54.*)*

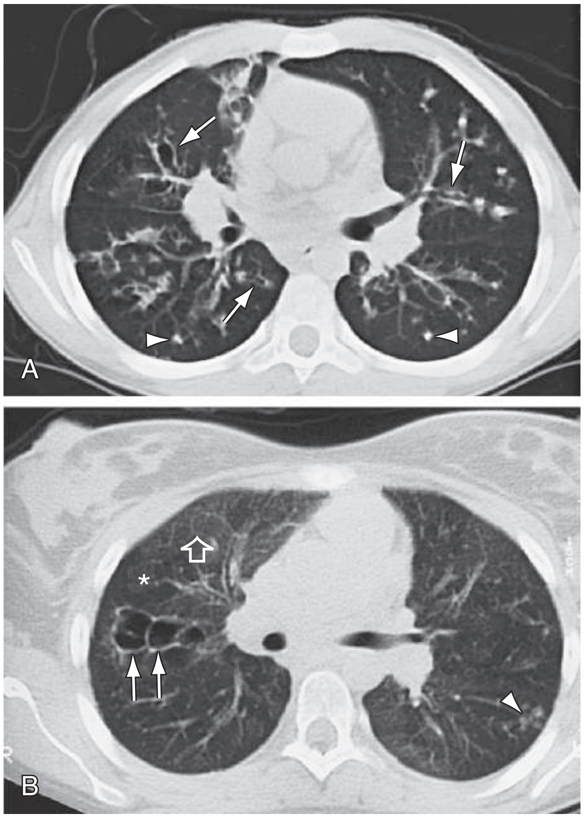

Figure 403-8 CT scans of the chest in cystic fibrosis. **A,** A 12 yr old boy with moderate lung disease. Airway and parenchymal changes are present throughout both lungs. Multiple areas of bronchiectasis *(arrows)* and mucous plugging *(arrowheads)* can be seen. **B,** A 19 yr old girl has mostly normal lung with 1 area of saccular bronchiectasis in the right upper lobe *(arrows)* and a focal area of peripheral mucous plugging in the right lower lobe *(arrowhead).* Lung density is heterogeneous with areas of normal lung *(open arrow)* and areas of low attenuation reflecting segmental and subsegmental air trapping *(asterisk).*

ventilation and increases the alveolar-arterial oxygen difference. The findings of obstructive airway disease and modest responses to a bronchodilator are consistent with the diagnosis of CF at all ages. Residual volume and functional residual capacity are increased early in the course of lung disease. Restrictive changes, characterized by declining total lung capacity and vital capacity, correlate with extensive lung injury and fibrosis and are a late finding. Testing at each clinic visit is recommended to evaluate the course of the pulmonary involvement and allow for early intervention when substantial decrements are documented. Increasing numbers of CF centers are equipped to measure airflow patterns of sedated infants (infant pulmonary function tests). Some patients reach adolescent or adult life with normal pulmonary function and without evidence of overinflation.

Microbiologic Studies

The finding of *S. aureus* or *P. aeruginosa* on culture of the lower airways (sputum) strongly suggests a diagnosis of CF. In particular, mucoid forms of *P. aeruginosa* are often recovered from CF lungs. *B. cepacia complex* recovery also suggests CF. A wide range of other organisms are frequently recovered, particularly in advanced lung disease; they include a variety of Gram-negative rods including *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans*, fungi, and nontuberculous mycobacterial species. Failure of respiratory symptom flares to respond to usual antibiotics triggers testing for *Mycoplasma* and viruses. Fiberoptic bronchoscopy is used to gather lower respiratory tract secretions of infants and young children who do not expectorate.

Heterozygote Detection and Prenatal Diagnosis

Mutation analysis should be fully informative for testing of potential carriers or a fetus, provided that mutations within the family have been previously identified. Testing a spouse of a carrier with a standard panel of probes is ≈90% sensitive, and full CFTR sequence analysis is commercially available if further testing is warranted. Prenatal testing should be offered to all couples planning to have children in addition to individuals with a family history of CF and partners of CF women. The American College of Medical Genetics and the American College of Obstetricians and Gynecologists recommend that CF carrier screening be offered to individuals of Ashkenazi Jewish or white descent and be made available to individuals of other ethnic and racial groups; in one large series, 14% of carrier screening referrals were from Hispanic and African-American individuals, and 12% from individuals with ethnicities other than white or Ashkenazi Jewish. Screening of the siblings of an affected child is also suggested.

Newborn Screening

Newborn screening for CF is mandated in all 50 states. A variety of newborn screening algorithms are in place to identify infants with CF. Most algorithms utilize a combination of immunoreactive trypsinogen results and limited DNA testing on blood spots; all positive screens are followed by a confirmatory sweat analysis. This screening test is ≈95% sensitive. Newborn diagnoses can prevent early nutritional deficiencies and improve long-term growth and may improve cognitive function. Importantly, good nutritional status (50% weight for height or 50% body mass index) is associated with better lung function at 6 yr of age. There is a subset of infants with a positive newborn screen for CF, elevated immunoreactive trypsinogen and 1 or 2 copies of a CFTR mutation, but who have an initial negative sweat test and are asymptomatic. These infants have **CFTR** metabolic syndrome and should be followed in a CF center annually to ensure that they do not develop CF symptoms. Indeed, in some the sweat test becomes abnormal over time; nonetheless if they develop CF the manifestations are mild.

TREATMENT

The treatment plan should be comprehensive and linked to close monitoring and early, aggressive intervention.

General Approach to Care

Initial efforts after diagnosis should be intensive and should include baseline assessment, initiation of treatment, clearing of pulmonary involvement, and education of the patient and parents. Follow-up evaluations are scheduled every 1-3 mo, depending on the age at diagnosis, because many aspects of the condition require careful monitoring. An interval history and physical examination should be obtained at each visit. A sputum sample or, if that is not available, a lower pharyngeal swab taken during or after a forced cough is obtained for culture and antibiotic susceptibility studies. Because irreversible loss of pulmonary function from low-grade infection can occur gradually and without acute symptoms, emphasis is placed on a thorough pulmonary history. Table 403-5 lists symptoms and signs that suggest the need for more intensive antibiotic and physical therapy. Protection against exposure to methicillin-resistant *S. aureus, P. aeruginosa, B. cepacia,* and other resistant Gram-negative organisms is essential, including isolation procedures and careful attention to sterilization of inhalation therapy equipment. A nurse, physical therapist, respiratory therapist, social worker, and dietitian, as members of the multidisciplinary care team, should evaluate children regularly and contribute to the development of a comprehensive daily care plan. Considerable education and programs to empower families and older children to take responsibility for care are likely to result in the best adherence to daily care programs. Standardization of practice, on the part of both caregivers and families, as well as close monitoring and early intervention for new or increasing symptoms appears to result in the best long-term outcomes.

Because secretions of CF patients are not adequately hydrated, attention in early childhood to oral hydration, especially during warm weather or with acute gastroenteritis, may minimize complications

Table 403-5 Symptoms and Signs Associated with Exacerbation of Pulmonary Infection in Patients with Cystic Fibrosis

SYMPTOMS
Increased frequency and duration of cough
Increased sputum production
Change in appearance of sputum
Increased shortness of breath
Decreased exercise tolerance
Decreased appetite
Feeling of increased congestion in the chest
SIGNS
Increased respiratory rate
Use of accessory muscles for breathing
Intercostal retractions
Change in results of auscultatory examination of chest
Decline in measures of pulmonary function consistent with the presence of obstructive airway disease
Fever and leukocytosis
Weight loss
New infiltrate on chest radiograph

From Ramsey B: Management of pulmonary disease in patients with cystic fibrosis, N Engl J Med *335:179, 1996.*

Table 403-6 Complications of Therapy for Cystic Fibrosis*

COMPLICATION	AGENT
Gastrointestinal bleeding	Ibuprofen
Hyperglycemia	Corticosteroids (systemic)
Growth retardation	Corticosteroids (systemic, inhaled)
Renal dysfunction:	
Tubular	Aminoglycosides
Interstitial nephritis	Semisynthetic penicillins, nonsteroidal antiinflammatory drugs
Hearing loss, vestibular dysfunction	Aminoglycosides
Peripheral neuropathy or optic atrophy	Chloramphenicol (prolonged course)
Hypomagnesemia	Aminoglycosides
Hyperuricemia, colonic stricture	Pancreatic extracts (very large doses)
Goiter	Iodine-containing expectorants
Gynecomastia	Spironolactone
Enamel hypoplasia or staining	Tetracyclines (used in 1st 8 yr of life)

*Common hypersensitivity reactions to drugs are not included.

associated with impaired mucus clearance. Intravenous therapy for dehydration should be initiated early.

The goal of therapy is to maintain a stable condition for prolonged periods. This can be accomplished for most patients by interval evaluation and adjustments of the home treatment program. Some children have episodic acute or low-grade chronic lung infection that progresses. For these patients, intensive inhalation and airway clearance and intravenous antibiotics are indicated. Improvement is most reliably accomplished in a hospital setting; selected patients have demonstrated successful outcomes while completing these treatments at home. Intravenous antibiotics may be required infrequently or as often as every 2-3 mo. The goal of treatment is to return patients to their previous pulmonary and functional status.

The basic daily care program varies according to the age of the child, the degree of pulmonary involvement, other system involvement, and the time available for therapy. The major components of this care are pulmonary and nutritional therapies. Because therapy is medication-intensive, iatrogenic problems frequently arise. Monitoring for these complications is also an important part of management (Table 403-6).

Pulmonary Therapy

The object of pulmonary therapy is to clear secretions from airways and to control infection. When a child is not doing well, every potentially useful aspect of therapy should be reconsidered.

Inhalation Therapy

Aerosol therapy is used to deliver medications and hydrate the lower respiratory tract. Metered-dose inhalers can deliver some agents, such as bronchodilators and corticosteroids, with a spacer for younger children. Alternately, these medications can be delivered with a compressor that drives a handheld nebulizer. In some patients β-agonists may decrease $Pa{O_2}$ acutely by increasing ventilation-perfusion mismatch, a concern if the $Pa{O_2}$ is marginal.

Human recombinant DNase (2.5 mg), given as a single daily aerosol dose, improves pulmonary function, decreases the number of pulmonary exacerbations, and promotes a sense of well-being in patients who have moderate disease and purulent secretions. Benefit for those with normal forced expiratory volume in 1 sec (FEV_1) values or advanced lung disease has also been documented. Improvement is sustained for 12 mo or longer with continuous therapy. Another mucolytic agent, *N*-acetylcysteine, nebulized as a 5-10% solution following β_2-agonist nebulization, is useful for airway clearance and may potentially augment airway levels of the antioxidant, glutathione.

Nebulized hypertonic saline, acting as a hyperosmolar agent, is believed to draw water into the airway and rehydrate mucus and the periciliary fluid layer, resulting in improved mucociliary clearance. A number of studies have reported that 7% hypertonic saline nebulized 2-4 times daily results in increased mucus clearance and improved pulmonary function.

Aerosolized antibiotics are often used when the airways are colonized with *Pseudomonas* as part of daily therapy. Aerosolized tobramycin, TOBI, or aerosolized aztreonam, Cayston, used as a suppressive therapy (on 1 mo, off 1 mo) may reduce symptoms, improve pulmonary function, and alleviate the need for hospitalization (see "Aerosolized Antibiotic Therapy" below).

Airway Clearance Therapy

Airway clearance treatment usually consists of chest percussion combined with postural drainage and derives its rationale from the idea that cough clears mucus from large airways but chest vibrations are required to move secretions from small airways, where expiratory flow rates are low. **Chest physical therapy (PT)** can be particularly useful for patients with CF because they accumulate secretions in small airways first, even before the onset of symptoms. Although immediate improvement of pulmonary function generally cannot be demonstrated after PT, cessation of chest PT in children with mild to moderate airflow limitation results in deterioration of lung function within 3 wk, and prompt improvement of function occurs when therapy is resumed. Chest PT is recommended 1-4 times a day, depending on the severity of lung dysfunction. Cough, huffing, or forced expirations are encouraged after each lung segment is "drained." Vest-type mechanical percussors are also useful. Voluntary coughing, repeated forced expiratory maneuvers with and without positive expiratory pressure, patterned breathing, and use of an array of handheld oscillatory devices are additional aids to clearance of mucus. Routine aerobic exercise appears to slow the rate of decline of pulmonary function, and benefit has also been documented with weight training. No one airway clearance technique is superior to any other, so all modes should be considered in the development of an airway clearance prescription.

Adherence to daily therapy is essential; therefore airway clearance technique plans are individualized for each patient.

Antibiotic Therapy

Antibiotics are the mainstay of therapy designed to control progression of lung infection. The goal is to reduce the intensity of endobronchial infection and to delay progressive lung damage. The usual guidelines for acute chest infections, such as fever, tachypnea, or chest pain, are often absent. Consequently, all aspects of the patient's history and examination, including anorexia, weight loss, and diminished activity, must be used to guide the frequency and duration of therapy. Antibiotic treatment varies from intermittent short courses of 1 antibiotic to nearly continuous treatment with 1 or more antibiotics. Dosages for some antibiotics are often 2-3 times the amount recommended for minor infections because patients with CF have proportionately more lean body mass and higher clearance rates for many antibiotics than other individuals. In addition, it is difficult to achieve effective drug levels of many antimicrobials in respiratory tract secretions.

Oral Antibiotic Therapy

Indications for oral antibiotic therapy in a patient with CF include the presence of respiratory tract symptoms and identification of pathogenic organisms in respiratory tract cultures. Whenever possible, the choice of antibiotics should be guided by in vitro sensitivity testing. Common organisms, including *S. aureus,* nontypeable *Haemophilus influenzae, P. aeruginosa; B. cepacia* and other Gram-negative rods, are encountered with increasing frequency. The first 2 can be eradicated from the respiratory tract in CF with use of oral antibiotics, but *Pseudomonas* is more difficult to treat. The usual course of therapy is ≥2 wk, and maximal doses are recommended. Table 403-7 lists useful oral antibiotics. The quinolones are the only broadly effective oral antibiotics for *Pseudomonas* infection, but resistance against these agents emerges rapidly. Infection with mycoplasma or chlamydial organisms has been documented, providing a rationale for the use of macrolides on an empirical basis for flare of symptoms. Macrolides may reduce the virulence properties of *P. aeruginosa,* such as biofilm production, and contribute antiinflammatory effects. Long-term therapy with azithromycin 3 times a week improves lung function in patients with chronic *P. aeruginosa* infection.

Aerosolized Antibiotic Therapy

P. aeruginosa and other Gram-negative organisms are frequently resistant to all oral antibiotics. Aerosol delivery of antibiotics has been used as an option for home delivery of additional agents, such as tobramycin, colistin, and gentamicin. Although these therapies are used, the evidence to support aerosolized antibiotics for an acute pulmonary exacerbation is limited. However, there is good evidence to support the use of inhaled tobramycin as a long-term suppressive therapy in a patient colonized with *P. aeruginosa*. When tobramycin is given at a dose of 300 mg twice daily on alternate months for 6 mo, *Pseudomonas* density in sputum decreases, fewer hospitalizations are required, and pulmonary function can improve by ≥10%. Toxicity is negligible. On the basis of available evidence, this therapy is recommended in patients with chronic colonization with *P. aeruginosa,* to lessen symptoms and/or to improve long-term function in patients with moderate to severe disease. Recently, nebulized aztreonam was also approved for 3 times daily therapy on alternate months for patients with chronic *P. aeruginosa*. Another indication for aerosolized antibiotic therapy is to eradicate *P. aeruginosa* in the airways after initial colonization. Early infection may be cleared for months to several years by several protocols, including oral ciprofloxacin and/or aerosolized colistin or tobramycin. However, once chronically established, *P. aeruginosa* infection is rarely eradicated.

Intravenous Antibiotic Therapy

For the patient who has progressive or unrelenting symptoms and signs despite intensive home measures, intravenous antibiotic therapy is indicated. This therapy is usually initiated in the hospital but may be

Table 403-7 Antimicrobial Agents for Cystic Fibrosis Lung Infection

ROUTE	ORGANISMS	AGENTS	DOSAGE (mg/kg/24 hr)	NO. DOSES/24 hr
Oral	*Staphylococcus aureus*	Dicloxacillin	25-50	4
		Linezolid	20	2
		Cephalexin	50	4
		Clindamycin	10-30	3-4
		Amoxicillin-clavulanate	25-45	2-3
	Haemophilus influenzae	Amoxicillin	50-100	2-3
	Pseudomonas aeruginosa	Ciprofloxacin	20-30	2-3
	Burkholderia cepacia	Trimethoprim-sulfamethoxazole	8-10*	2-4
	Empirical	Azithromycin	10, day 1; 5, days 2-5	1
		Erythromycin	30-50	3-4
Intravenous	*S. aureus*	Nafcillin	100-200	4-6
		Vancomycin	40	3-4
	P. aeruginosa	Tobramycin	8-12	1-3
		Amikacin	15-30	2-3
		Ticarcillin	400	4
		Piperacillin	300-400	4
		Ticarcillin-clavulanate	400†	4
		Piperacillin-tazobactam	240-400‡	3
		Meropenem	60-120	3
		Imipenem-cilastatin	45-100	3-4
		Ceftazidime	150	3
		Aztreonam	150-200	4
	B. cepacia	Chloramphenicol	50-100	4
		Meropenem	60-120	3
Aerosol		Tobramycin (inhaled)	300§	2
		Aztreonam (inhaled)	75	3

*Quantity of trimethoprim.
†Quantity of ticarcillin.
‡Quantity of piperacillin.
§In mg per dose.

completed on an ambulatory basis. Although many patients show improvement within 7 days, it is usually advisable to extend the period of treatment to at least 14 days. Permanent intravenous access can be provided for long-term or frequent courses of therapy in the hospital or at home. Thrombophilia screening should be considered before the use of totally implantable intravenous devices or for recurring problems with venous catheters.

Table 403-7 lists commonly used intravenous antibiotics. In general, treatment of *Pseudomonas* infection requires 2-drug therapy. A third agent may be required for optimal coverage of *S. aureus* or other organisms. The aminoglycosides have a relatively short half-life in many patients with CF. The initial parenteral dose, noted in Table 403-7, is generally given every 8 hr. After blood levels have been determined, the total daily dose should be adjusted. Peak levels of 10-15 mg/L are desirable, and trough levels should be kept at <2 mg/L to minimize the risk of ototoxicity and nephrotoxicity. The regimen of once-daily tobramycin dosing has been demonstrated to have equivalent efficacy and the advantage of decreased toxicity over dosing every 8 hr. For once-daily dosing of tobramycin, peak levels should be between 20 and 30 mg/L and trough levels should be 1 mg/L or less. In toddlers, older children, and adults, once-daily intravenous tobramycin therapy is becoming the standard of care. Changes in therapy should be guided by lack of improvement and by culture results. If patients do not show improvement, complications such as heart failure and reactive airways or infection with viruses, *Aspergillus fumigatus* (see Chapter 237), nontuberculous mycobacteria (see Chapters 217 and 399), or other unusual organisms should be considered. *B. cepacia* complex is the most frequent of a growing list of Gram-negative rods that may be particularly refractory to antimicrobial therapy. Infection control in both the outpatient and inpatient medical setting is critically important to prevent nosocomial spread of resistant bacterial organisms between patients.

Bronchodilator Therapy

Reversible airway obstruction occurs in many children with CF, sometimes in conjunction with frank asthma or acute bronchopulmonary aspergillosis. Reversible obstruction is defined as improvement of ≥12% in flow rates after inhalation of a bronchodilator. In many patients with CF, flow rates may improve by only 5-10%, however. Nevertheless, subjective benefit is claimed by many following use of a β-adrenergic agonist aerosol. Cromolyn sodium and ipratropium hydrochlorides are alternative agents, but there is no evidence to support their use.

Antiinflammatory Agents

Corticosteroids are useful for the treatment of allergic bronchopulmonary aspergillosis and severe reactive airway disease occasionally encountered in children with CF. Prolonged treatment of standard CF lung disease using an alternate-day regimen initially appeared to improve pulmonary function and diminish hospitalization rates. However, a 4-yr double-blind, multicenter study of this regimen for patients with mild to moderate lung disease found only modest efficacy and prohibitive side effects, including growth retardation, cataracts, and abnormalities of glucose tolerance at a dose of 2 mg/kg and growth retardation at 1 mg/kg. Inhaled corticosteroids have theoretical appeal, but there are few data documenting their efficacy and safety; it appears that discontinuing inhaled corticosteroids in patients with CF had no effect on lung function, antibiotic use, or bronchodilator use. Ibuprofen, given long term (dose adjusted to achieve a peak serum concentration of 50-100 μg/mL) for 4 yr, is associated with a slowing of disease progression, particularly in younger patients with mild lung disease. Side effects of nonsteroidal antiinflammatory drugs have been encountered (see Table 403-6); therefore, this therapy has not gained broad acceptance even though ibuprofen is the only antiinflammatory agent with documented efficacy in the patient population.

Endoscopy and Lavage

Treatment of obstructed airways sometimes includes tracheobronchial suctioning or lavage, especially if atelectasis or mucoid impaction is present. Bronchopulmonary lavage can be performed by the instillation of saline or a mucolytic agent through a fiberoptic bronchoscope. Antibiotics (usually gentamicin or tobramycin) can also be instilled directly at lavage in order to transiently achieve a much higher endobronchial concentration than can be obtained by using intravenous therapy. There is no evidence for sustained benefit from repeated endoscopic or lavage procedures.

Other Therapies

Expectorants such as iodides and guaifenesin do not effectively assist with the removal of secretions from the respiratory tract. Inspiratory muscle training can enhance maximum oxygen consumption during exercise as well as FEV_1.

Emerging Therapies

A major breakthrough in CF therapy is ivacaftor, a small molecule potentiator of the CFTR mutation, G551D (present in ~5% of patients). Ivacaftor activates the CFTR-G551D mutant protein, a class III CFTR mutation that results in protein localized to the plasma membrane but loss of chloride channel function. Ivacaftor therapy resulted in improvement in FEV_1 by an average of 10.6%, decreased the frequency of pulmonary exacerbations by 55%, decreased sweat chloride by an average of 48 mEq/L, and increased weight gain by an average of 2.7 kg. Ivacaftor is approved for CFTR-G551D patients ≥6 yr old, as a 150 mg, twice per day, oral therapy. Additional small molecule correctors are being tested for use in combination with Ivacaftor to correct the processing of the most common CFTR mutation, F508del. The goal of this strategy is to correct the localization of the protein to the apical membrane of the cell and then to potentiate its function.

TREATMENT OF PULMONARY COMPLICATIONS

Atelectasis

Lobar atelectasis occurs relatively infrequently; it may be asymptomatic and noted only at the time of a routine chest radiograph. Aggressive intravenous therapy with antibiotics and increased chest PT directed at the affected lobe may be effective. If there is no improvement in 5-7 days, bronchoscopic examination of the airways may be indicated. If the atelectasis does not resolve, continued intensive home therapy is indicated, because atelectasis may resolve during a period of weeks or months. Lobectomy should be considered only if expansion is not achieved and the patient has progressive difficulty from fever, anorexia, and unrelenting cough (see Chapter 408).

Hemoptysis

Endobronchial bleeding usually reflects airway wall erosion secondary to infection. With increasing numbers of older patients, hemoptysis has become a relatively frequent complication. Blood streaking of sputum is particularly common. Small-volume hemoptysis (<20 mL) should not trigger panic and is usually viewed as a need for intensified antimicrobial therapy and chest PT. When the hemoptysis is persistent or increases in severity, hospital admission is indicated. **Massive hemoptysis,** defined as total blood loss of ≥250 mL in a 24-hr period, is rare in the 1st decade and occurs in <1% of adolescents, but it requires close monitoring and the capability to replace blood losses rapidly. Chest PT is often discontinued until 12-24 hr after the last brisk bleeding episode and is then gradually re-instituted. Patients should receive vitamin K for an abnormal prothrombin time. During brisk hemoptysis, the child and parents require a great deal of reassurance that the bleeding will stop. Blood transfusion is not indicated unless there is hypotension or the hematocrit is significantly reduced. Ticarcillin, salicylates, and nonsteroidal antiinflammatory drugs interfere with platelet function and may aggravate hemoptysis. Bronchoscopy rarely reveals the site of bleeding. Lobectomy is to be avoided, if possible, because functioning lung should be preserved. Bronchial artery embolization can be useful to control persistent, significant hemoptysis.

Pneumothorax

Pneumothorax (see Chapter 411) is encountered in <1% of children and teenagers with CF, although it is more frequently encountered in

older patients and may be life-threatening. The episode may be asymptomatic but is often attended by chest and shoulder pain, shortness of breath, or hemoptysis. A small air collection that does not grow can be observed closely. Chest tube placement with or without pleurodesis is often the initial therapy. Intravenous antibiotics are also begun on admission. An open thoracotomy or video-assisted thoracoscopy with plication of blebs, apical pleural stripping, and basal pleural abrasion should be considered if the air leak persists. Surgical intervention is usually well tolerated even in cases of advanced lung disease. The thoracotomy tube is removed as soon as possible, usually on the 2nd or 3rd postoperative day. The patient can then be mobilized, and full postural drainage therapy resumed. Previous pneumothorax with or without pleurodesis is not a contraindication to subsequent lung transplantation.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis occurs in 5-10% of patients with CF and may manifest as wheezing, increased cough, shortness of breath, and marked hyperinflation (see Chapters 237 and 399). In some patients, a chest radiograph shows new, focal infiltrates. The presence of rust-colored sputum, the recovery of *Aspergillus* organisms from the sputum, a positive skin test for *A. fumigatus*, the demonstration of specific immunoglobulin (Ig) E and IgG antibodies against *A. fumigatus,* or the presence of eosinophils in a fresh sputum sample supports the diagnosis. The serum IgE level is usually high. Treatment is directed at controlling the inflammatory reaction with oral corticosteroids. For refractory cases, oral antifungals may be required.

Nontuberculous Mycobacteria Infection

See Chapter 217.

Injured airways with poor clearance may be colonized by *Mycobacterium avium-complex* but also *Mycobacterium abscessus*, *Mycobacterium chelonae*, and *Mycobacterium kansasii.* Distinguishing endobronchial colonization (frequent) from invasive infection (infrequent) is challenging. Persistent fevers and new infiltrates or cystic lesions coupled with the finding of acid-fast organisms on sputum smear suggest infection. Treatment is prolonged and requires multiple antimicrobial agents. Symptoms may improve, but the nontuberculous mycobacteria are not usually cleared from the lungs.

Bone and Joint Complications

Hypertrophic osteoarthropathy causes elevation of the periosteum over the distal portions of long bones and bone pain, overlying edema, and joint effusions. Acetaminophen or ibuprofen may provide relief. Control of lung infection usually reduces symptoms. Intermittent arthropathy unrelated to other rheumatologic disorders occurs occasionally, has no recognized pathogenesis, and usually responds to nonsteroidal antiinflammatory agents. Back pain or rib fractures from vigorous coughing may require pain management to permit adequate airway clearance. These and other fractures may stem from diminished bone mineralization, the result of reduced vitamin D absorption, corticosteroid therapy, diminished weight-bearing exercises, and, perhaps, other factors. There may be a bone phenotype in CF that is unrelated to therapies or nutritional status and may be due to CFTR dysfunction.

Sleep-Disordered Breathing

Particularly with advanced pulmonary disease and during chest exacerbations, individuals with CF may experience more sleep arousals, less time in rapid eye movement sleep, nocturnal hypoxemia, hypercapnia, and associated neurobehavioral impairment. Nocturnal hypoxemia may hasten the onset of pulmonary hypertension and right-sided heart failure. Efficacy of specific interventions for this complication of CF has not been systematically assessed. Prompt treatment of airway symptoms and nocturnal oxygen supplementation or bilevel positive airway pressure support should be considered in selected cases.

Acute Respiratory Failure

Acute respiratory failure (see Chapter 71) rarely occurs in patients with mild to moderate lung disease and is usually the result of a severe viral or other infectious illness. Because patients with this complication can regain their previous status, intensive therapy is indicated. In addition to aerosol, postural drainage, and intravenous antibiotic treatment, oxygen is required to raise the arterial PaO_2. An increasing PCO_2 may require ventilatory assistance. Endotracheal or bronchoscopic suction may be necessary to clear airway inspissated secretions and can be repeated daily. Right-sided heart failure should be treated vigorously. Recovery is often slow. Intensive intravenous antibiotic therapy and postural drainage should be continued for 1-2 wk after the patient has regained baseline status.

Chronic Respiratory Failure

Patients with CF acquire chronic respiratory failure after prolonged deterioration of lung function. Although this complication can occur at any age, it is now seen most frequently in adult patients. Because a long-standing PaO_2 <50 mm Hg promotes the development of right-sided heart failure, patients usually benefit from low-flow oxygen to raise arterial PO_2 to ≥55 mm Hg. Increasing hypercapnia may prevent the use of optimal fraction of inspired oxygen. Most patients improve somewhat with intensive antibiotic and pulmonary therapy measures and can be discharged from the hospital. Low-flow oxygen therapy is needed at home, especially with sleep. Noninvasive ventilatory support can improve gas exchange and has been documented to enhance quality of life. Ventilatory support may be particularly useful for patients awaiting lung transplantation. These patients usually display cor pulmonale and should reduce their salt intake and be given diuretics. Caution should be exercised to avoid ventilation-suppressing metabolic alkalosis that results from CF-related chloride depletion and, in many cases, from diuretic-induced bicarbonate retention. Chronic pain (headache, chest pain, abdominal pain, and limb pain) is frequent at the end of life and responds to judicious use of analgesics, including opioids. Dyspnea has been ameliorated with nebulized fentanyl.

Lung transplantation is an option for end-stage lung disease (see Chapter 443) but a topic of vigorous debate. Criteria for referral continue to be a subject of investigation and ideally include estimates of longevity with and without transplant based on lung function and exercise tolerance data. Because of bronchiolitis obliterans (see Chapter 394.1) and other complications, transplanted lungs cannot be expected to function for the lifetime of a recipient, and repeat transplantation is increasingly common. The demand for donor lungs exceeds the supply, and waiting lists as well as duration of waits continue to grow. The protocol for matching donor organs with lung transplant recipients has been revised to account for the severity of the patients' lung disease. In a review of lung transplantation in children with CF between 1992 and 2002, pretransplantation colonization with *B. cepacia,* diabetes, and older age decreased posttransplantation survival. The review suggests that transplantation is often associated with many complications and may not prolong life nor significantly improve its quality.

Heart Failure

Some patients experience reversible right-sided heart failure (see Chapter 442) as the result of an acute event such as a viral infection or pneumothorax. Individuals with long-standing, advanced pulmonary disease, especially those with severe hypoxemia (PaO_2 <50 mm Hg), often acquire chronic right-sided heart failure. The mechanisms include hypoxemic pulmonary arterial constriction and loss of the pulmonary vascular bed. Pulmonary arterial wall changes contribute to increased vascular resistance with time. Evidence for concomitant left ventricular dysfunction is often found. Cyanosis, increased shortness of breath, increased liver size with a tender margin, ankle edema, jugular venous distention, an unusual weight gain, increased heart size seen on chest radiograph, or evidence for right-sided heart enlargement on electrocardiogram or echocardiogram helps to confirm the diagnosis. Diuresis induced by furosemide (1 mg/kg administered intravenously) confirms the suspicion of fluid retention. Repeated doses are often required at 24-48 hr intervals to reduce fluid accumulation and accompanying symptoms. Concomitant use of spironolactone may protect against potassium depletion and facilitate long-term diuresis. Hypochloremic alkalosis complicates the long-term use of

loop diuretics. Digitalis is not effective in pure right-sided failure but may be useful when there is an associated left-sided dysfunction. The arterial Po_2 should be maintained at >50 mm Hg if possible. Intensive pulmonary therapy, including intravenous antibiotics, is most important. Initially, the salt intake should be limited. Volume overload and antibiotics with high sodium content should be avoided. No clear-cut long-term benefit from pulmonary vasodilators has been demonstrated. The prognosis for heart failure is poor, but a number of patients survive for ≥5 yr after the appearance of heart failure. Heart-lung transplantation may be an option (see preceding section).

Nutritional Therapy

Up to 90% of patients with CF have loss of exocrine pancreatic function as well as inadequate digestion and absorption of fats and proteins. They require dietary adjustment, pancreatic enzyme replacement, and supplementary vitamins. In general, children with CF need to exceed the usual required daily caloric intake to grow. Daily supplements of the fat-soluble vitamins are required.

Diet

Historically, at the time of diagnosis many infants presented with nutritional deficits; this situation is changing because of newborn screening. Sometimes young infants with a history of wheezy breathing were often started on soy-protein formulas prior to their evaluation; they did not use this protein well and often acquired hypoproteinemia with anasarca. Although in the past a low-fat, high-protein, high-calorie diet was generally recommended for older children, it resulted in deficiencies of essential fatty acids and poor growth. With the advent of improved pancreatic enzyme products, increased amounts of fat in the diet are well tolerated and preferred.

Most individuals with CF have a higher-than-normal caloric need because of increased work of breathing and perhaps because of increased metabolic activity related to the basic defect. When anorexia of chronic infection supervenes, weight loss occurs. Encouragement to eat high-calorie foods is important, but weight gain is not generally realized unless lung infection is controlled. Weight stabilization or gain sometimes requires nocturnal feeding via nasogastric tube or percutaneous enterostomy or with short-term intravenous hyperalimentation. Not infrequently, parent–child interactions at feeding time are maladaptive, and behavioral interventions can improve caloric intake. Long-term benefits of these interventions include improved quality of life and psychologic well-being. In addition there is good correlation between improved body mass index and maintenance of FEV_1.

Recombinant growth hormone therapy (3 times per week) has improved nutritional outcomes, including positive effects on nitrogen balance and improved height and weight velocities.

Pancreatic Enzyme Replacement

Pancreatic exocrine replacement therapy given with ingested food reduces but does not fully correct stool fat and nitrogen losses. Enzyme dosage and product should be individualized for each patient. Enteric-coated, pH-sensitive enzyme microspheres are most often prescribed. Several strengths up to 25,000 IU of lipase/capsule are available. Administration of excessive doses has been linked to **colonic strictures** requiring surgery. Consequently, enzyme replacement should not exceed 2,500 lipase units/kg/meal in most circumstances. In general, infants need 2,000-4,000 lipase units per feeding, which is most easily given mixed with applesauce on a spoon. Snacks should also be covered. The dose of enzymes required usually increases with age, but some patients have lower requirements as teenagers and young adults. Some individuals require proton pump inhibitor therapy to correct acid pH in the duodenum which is due to lack of exocrine pancreatic secretions; neutralization of duodenal pH permits activation of enteric coated pancreatic exocrine replacement therapy granules.

Vitamin and Mineral Supplements

Because pancreatic insufficiency results in malabsorption of fat-soluble vitamins (A, D, E, K), vitamin supplementation is recommended. Several vitamin preparations containing all 4 vitamins for patients with CF are available. They should be taken daily. Replacement doses may be required when low serum levels are documented or the patient is symptomatic. Infants with zinc deficiency and an acrodermatitis enteropathica–like rash have been described. In addition, attention should be paid to iron status; in one study, almost 30% of children with CF had low serum ferritin concentrations.

TREATMENT OF INTESTINAL COMPLICATIONS

Meconium Ileus

When meconium ileus (see Chapter 102.1) is suspected, a nasogastric tube is placed for suction and the newborn is hydrated. In many cases, diatrizoate (Gastrografin) enemas with reflux of contrast material into the ileum not only confirm the diagnosis but have also resulted in the passage of a meconium plug and clearing of the obstruction. Use of this hypertonic solution requires careful correction of water losses into the bowel. Children in whom this procedure fails require operative intervention. Children who are successfully treated generally have a prognosis similar to that of other patients with severe CF mutations. Infants with meconium ileus should be treated as if they have CF until adequate diagnostic testing can be carried out.

Distal Intestinal Obstruction Syndrome (Meconium Ileus Equivalent) and Other Causes of Abdominal Symptoms

Despite appropriate pancreatic enzyme replacement, 2-5% of patients accumulate fecal material in the terminal portion of the ileum and in the cecum, which may result in partial or complete obstruction. For intermittent symptoms, pancreatic enzyme replacement should be continued or even increased, and stool softeners (polyethylene glycol [MiraLAX] or docusate sodium [Colace]) given. Increased fluid intake is also recommended. Failure to relieve symptoms signals the need for large-volume bowel lavage with a balanced salt solution containing polyethylene glycol taken by mouth or by nasogastric tube. When there is complete obstruction, a diatrizoate enema, accompanied by large amounts of intravenous fluids, can be therapeutic. Intussusception (see Chapter 333.3) and volvulus (see Chapter 329.4) must also be considered in the differential diagnosis. Intussusception, usually ileocolic, occurs at any age and often follows a 1-2 day history of "constipation." It can often be diagnosed and reduced via a diatrizoate enema. If a nonreducible intussusception or a volvulus is present, laparotomy is required. Repeated episodes of intussusception may be an indication for cecectomy.

Chronic appendicitis with or without periappendiceal abscess may manifest as recurrent or persistent abdominal pain, raising the question of need for a laparotomy. A lack of acid buffering in the duodenum appears to promote duodenitis and ulcer formation in some children. Other reasons for surgical procedures include carcinoma of the colon or biliary tract and sclerosing colonopathy.

Gastroesophageal Reflux

See Chapter 323.

Because several factors raise intraabdominal pressure, including cough and obstructed airways, pathologic gastroesophageal reflux is not uncommon and may exacerbate lung disease secondary to reflex wheezing and repeated aspiration. Dietary, positional, and medication therapies should be considered. Cholinergic agonists are contraindicated because they trigger mucus secretion and progressive respiratory difficulty. Reduction of stomach acid secretion can help, with proton pump inhibitors being the most effective agents. Fundoplication is a procedure of last resort.

Rectal Prolapse

See Chapter 344.5.

Though uncommon, rectal prolapse occurs most often in infants with CF, and less frequently in older children with the disease. It is usually related to steatorrhea, malnutrition, and repetitive cough. The prolapsed rectum can usually be replaced manually by continuous gentle pressure with the patient in the knee-chest position. Sedation

may be helpful. To prevent an immediate recurrence, the buttocks can be taped closed. Adequate pancreatic enzyme replacement, decreased fat and roughage in the diet, stool softener, and control of pulmonary infection result in improvement. Occasionally, a patient may continue to have rectal prolapse and may require sclerotherapy or surgery.

Hepatobiliary Disease

Liver function abnormalities associated with biliary cirrhosis can be improved by treatment with ursodeoxycholic acid. The ability of bile acids to prevent progression of cirrhosis has not been clearly documented. Portal hypertension with esophageal varices, hypersplenism, or ascites occurs in ≤8% of children with CF (see Chapter 367). The acute management of bleeding esophageal varices includes nasogastric suction and cold saline lavage. Sclerotherapy is recommended after an initial hemorrhage. In the past, significant bleeding has also been treated successfully with portosystemic shunting. Splenorenal anastomosis has been the most effective treatment. Pronounced hypersplenism may require splenectomy. Cholelithiasis should prompt surgical consultation. The management of ascites is discussed in Chapter 370.

Obstructive jaundice in newborns with CF needs no specific therapy. Hepatomegaly with steatosis requires careful attention to nutrition and may respond to carnitine repletion. Rarely, biliary cirrhosis proceeds to hepatocellular failure, which should be treated as in patients without CF (see Chapters 364 and 367). End-stage liver disease is an indication for liver transplantation in children with CF, especially if pulmonary function is good (see Chapter 368).

Pancreatitis

Pancreatitis can be precipitated by fatty meals, alcohol ingestion, or tetracycline therapy. Serum amylase and lipase values may remain elevated for long periods. Treatment of this disorder is discussed in Chapter 351.

Hyperglycemia

Onset of hyperglycemia occurs most frequently after the 1st decade. Approximately 20% of young adults are treated for hyperglycemia, although the incidence of CF-related diabetes may be up to 50% in CF adults. Prevalence is greater in females and in F508del homozygotes. Ketoacidosis is rarely encountered. The pathogenesis includes both impaired insulin secretion and insulin resistance. Routine screening consists of an annual modified 2-hr oral glucose tolerance test after the child reaches age 10 yr. Glucose intolerance without urine glucose losses is usually not treated; glycosylated hemoglobin levels should be followed at least annually. With persistent glucosuria and symptoms, insulin treatment should be instituted. Oral hypoglycemic agents, with or without drugs that reduce insulin resistance, may also be effective. Exocrine pancreatic insufficiency and malabsorption make strict dietary control of hyperglycemia difficult. Corticosteroid therapy should be avoided. The development of significant hyperglycemia favors acquisition of *P. aeruginosa* and *B. cepacia* in the airways and may adversely affect pulmonary function. Thus, careful control of blood glucose level is an important goal. Long-term vascular complications of diabetes can occur, providing an additional rationale for good control of blood glucose levels.

OTHER THERAPY

Nasal Polyps

Nasal polyps (see Chapter 378) occur in 15-20% of patients with CF and are most prevalent in the 2nd decade of life. Local corticosteroids and nasal decongestants occasionally provide some relief. When the polyps completely obstruct the nasal airway, rhinorrhea becomes constant, or widening of the nasal bridge is noticed, surgical removal of the polyps is indicated; polyps may recur promptly or after a symptom-free interval of months to years. Polyps inexplicably stop developing in many adults.

Rhinosinusitis

Opacification of paranasal sinuses is not an indication for intervention. Acute or chronic sinus-related symptoms are treated initially with antimicrobials, with or without maxillary sinus aspiration for culture. Functional endoscopic sinus surgery has anecdotally provided benefit.

Salt Depletion

Salt losses from sweat in patients with CF can be high, especially in warm arid climates. Children should have free access to salt, and precautions against overdressing infants should be observed. Salt supplements are often prescribed to newborns identified through newborn screening and to children who live in hot weather climates. Hypochloremic alkalosis should be suspected in any infant who has had symptoms of gastroenteritis, and prompt fluid and electrolyte therapy should be instituted as needed.

Growth and Maturation

Delayed growth should be vigorously addressed by enhancing nutrition, treating lung disease more vigorously, and, in selected instances, endocrine evaluation and, possibly, growth hormone therapy. The risk: benefit ratio for anabolic steroid therapy does not support its use for undersized children with CF. Delayed sexual maturation, often associated with short stature, occurs fairly frequently in children with CF. Although many patients have severe pulmonary infection or poor nutrition, delayed puberty also occurs in those with otherwise mild disease and is not well explained. Adolescents with CF should receive specific counseling throughout their developing years concerning sexual maturation and reproductive potential.

Surgery

Minor surgical procedures, including dental work, should be performed with the use of local anesthesia if possible in children with CF. Patients with good or excellent pulmonary status can tolerate general anesthesia without any intensive pulmonary measures before the procedure. Those with moderate or severe pulmonary infection usually do better with a 1-2 wk course of intensive antibiotic treatment and increased airway clearance before surgery. If this approach is impossible, prompt intravenous antibiotic therapy is indicated once it is recognized that major surgery is required. The total time of anesthesia should be kept to a minimum. After induction, tracheal suctioning is useful and should be repeated. Patients with severe disease require monitoring of blood gas values and may need ventilatory assistance in the immediate postoperative period.

After major surgery, cough should be encouraged and airway clearance treatments should be re-instituted as soon as possible, usually within 24 hr. Adequate analgesia is important if early effective therapy is to be achieved. For those with significant pulmonary involvement, intravenous antibiotics are continued for 7-14 days postoperatively. Early ambulation and intermittent deep breathing are important; an incentive spirometer can also be helpful. After open thoracotomy for treatment of pneumothorax or lobectomy, the chest tube is the greatest single obstacle to effective pulmonary therapy and should be removed as soon as possible so that full postural drainage therapy can resume.

PROGNOSIS

CF remains a life-limiting disorder, although survival has improved dramatically in the past 30-40 yr. Infants with severe lung disease occasionally succumb, but most children survive this difficult period and are relatively healthy into adolescence or adulthood. The slow progression of lung disease eventually reaches disabling proportions. Life table data now indicate a median cumulative survival of 37 yr. Male survival is somewhat better than female survival for reasons that are not readily apparent. Children in socioeconomically disadvantaged families have, on average, a poorer prognosis.

Children with CF usually have good school attendance records and should not be restricted in their activities. A high percentage eventually attend and graduate from college. Most adults with CF find satisfactory employment, and an increasing number marry. Transitioning care from pediatric to adult care centers by 21 yr of age is an important objective and requires a thoughtful, supportive approach involving both the pediatric and internal medicine specialists.

With increasing life span for patients with CF, a new set of psychosocial considerations has emerged, including dependence-independence issues, self-care, peer relationships, sexuality, reproduction, substance abuse, educational and vocational planning, medical care costs and other financial burdens, and anxiety concerning health and prognosis. Many of these issues are best addressed in an anticipatory fashion, before the onset of psychosocial dysfunction. With appropriate medical and psychosocial support, children and adolescents with CF generally cope well. Achievement of an independent and productive adulthood is a realistic goal for many.

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Chapter 404

Primary Ciliary Dyskinesia (Immotile Cilia Syndrome, Kartagener Syndrome)

Thomas W. Ferkol Jr.

Primary ciliary dyskinesia (PCD) is an inherited disorder characterized by impaired ciliary function leading to diverse clinical manifestations, including chronic sinopulmonary disease, persistent middle ear effusions, laterality defects, and infertility. Although the estimated frequency of PCD is 1 in 12,000 to 1 in 20,000 live births, its prevalence in children with repeated respiratory infections has been estimated to be as high as 5%.

NORMAL CILIARY ULTRASTRUCTURE AND FUNCTION

Three types of cilia exist in the humans: motile cilia; primary (sensory) cilia; and nodal cilia.

Motile cilia are hair-like organelles that move fluids, mucous, and inhaled particulates vectorially from conducting airways, paranasal sinuses, and eustachian tubes. The upper and lower respiratory tracts are continuously exposed to inhaled pathogens, and local defenses have evolved to protect the airway. The respiratory epithelium in the nasopharynx, middle ear, paranasal sinuses, and larger airways are lined by a ciliated, pseudostratified columnar epithelium that is essential for mucociliary clearance (Fig. 404-1). A mature ciliated epithelial cell has approximately 200 uniform motile cilia that are anatomically and functionally oriented in the same direction, moving with intracellular and intercellular synchrony. Anchored by a basal body to the apical cytoplasm and extending from the apical cell surface into the airway lumen, each cilium is a complex, specialized structure, composed of hundreds of proteins. It contains a cylinder of microtubule doublets organized around a central pair of microtubules (Fig. 404-2), leading to the characteristic “9+2” arrangement seen on cross-sectional views on transmission electron microscopy. A membrane continuous

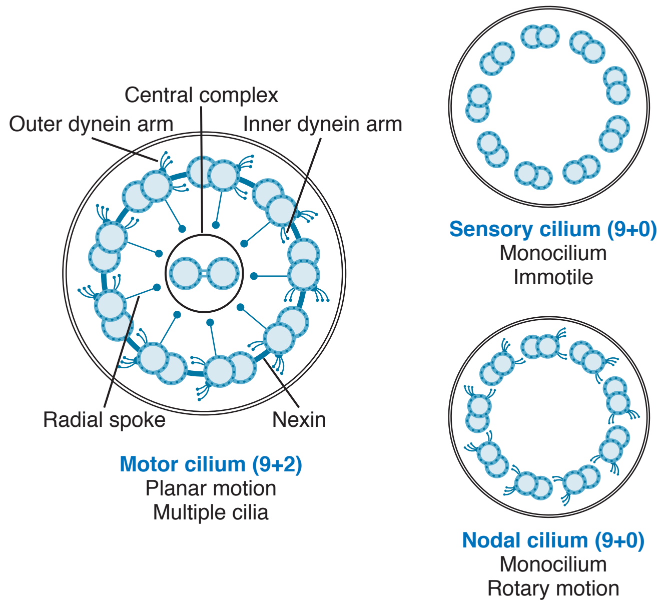

Figure 404-2 Schemata showing the 3 general classes of normal cilia (motile “9+2,” motile “9+0,” and nonmotile “9+0”), which demonstrate the complex structure and arrangement of the ciliary axoneme.

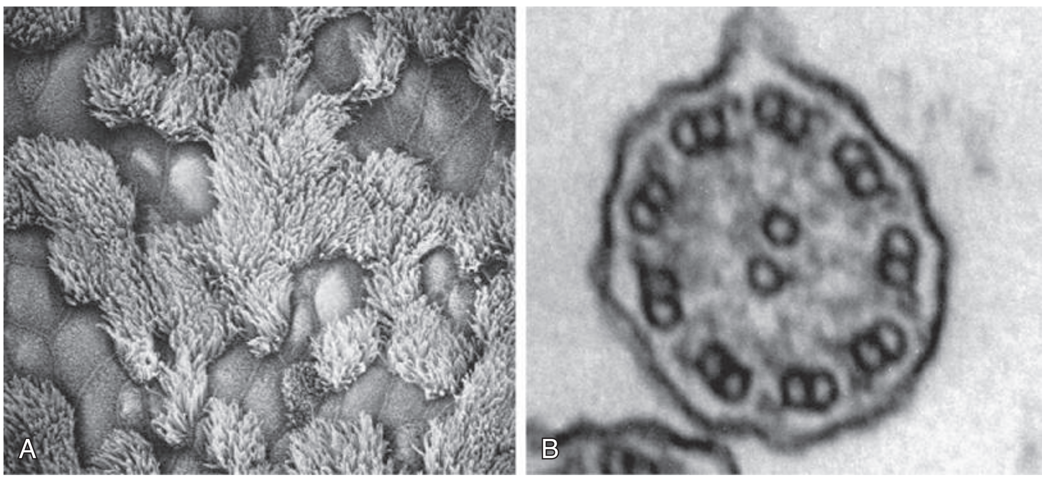

Figure 404-1 Electron photomicrographs showing **(A)** an airway epithelium grown in primary culture, showing ciliated and non-ciliated cells, and **(B)** a normal motor cilium.

with the plasma membrane covers the central fibrillar structure, or axoneme. The ciliary axoneme is highly conserved across species, and the structural elements of simple protozoan flagella and the mammalian cilium are similar. Attached to the A microtubules as distinct inner and outer dynein arms, multiple different adenosine triphosphatases, called **dyneins**, serve as "motors" of the cilium and promote microtubule sliding, which is converted into bending. The inner dynein arm influences the bend shape of the cilium, whereas the outer dynein arm controls beat force and frequency. Nexin links connect adjacent outer microtubular doublets limit the degree of sliding between microtubules, and with the radial spokes are controlled by the dynein regulatory complex. The result is a ciliary stroke and coordinated beating at a frequency constant throughout the airway, 8-20 beats/sec, but can be negatively affected by several factors, such as anesthetics and dehydration. Alternatively, beat frequency may be accelerated by exposure to irritants or bioactive molecules, including β-adrenergic agents, acetylcholine, and serotonin. Cilia beat frequency can be increased through the activity of nitric oxide synthases that are localized in the apical cytoplasm. The coordinated wave-like pattern of ciliary motion has important functions in fluid and cell movement, and any disturbance in the precise, orchestrated movement of the cilia can lead to disease.

Primary (sensory) cilia are present during interphase on most cell types. These cilia lack a central microtubule doublet and dynein arms, thus creating a "9+0" arrangement and leaving them immotile (see Fig. 404-2). For years, these structures were considered nonfunctional vestigial remnants, but primary cilia are important signaling organelles that sense the extracellular environment. They are mechanoreceptors, chemosensors, osmosensors, and, in specialized cases, defect changes in light, temperature, and gravity. Primary cilia are found on the surface of nondividing cells, including the renal nephron, bile ductules, chondrocytes, astrocytes, and cells in sensory organs. Defects are linked to wide-ranging pediatric conditions, such as various polycystic kidney diseases, nephronophthisis, Bardet-Biedl syndrome, Meckel-Gruber syndrome, Joubert syndrome, Alström syndrome, Ellis-van Creveld syndrome, and Jeune thoracic dystrophy.

The third distinct classification of cilia exists only during a brief period of embryonic development. These **nodal cilia** have a "9+0" microtubule arrangement similar to that of primary cilia, but they exhibit a whirling, rotational movement (see Fig. 404-2), resulting in leftward flow of extracellular fluid that establishes body sidedness. Nodal cilia defects result in body orientation abnormalities, such as **situs inversus totalis**, **situs ambiguus**, and **heterotaxy** associated with congenital heart disease, asplenia, and polysplenia (see Chapter 431.11).

GENETICS OF PRIMARY CILIARY DYSKINESIA

PCD is typically has autosomal recessive patterns of inheritance, although rare cases of autosomal dominant and X-linked inheritance have been reported. PCD is a genetically heterogeneous disorder involving multiple genes; mutations in any protein that is involved in ciliary assembly, structure, or function could theoretically cause disease. Early linkage analyses showed substantial locus heterogeneity, which made correlations between ciliary defects and the underlying mutations difficult. Numerous PCD-associated genes have been discovered. The advent of high-throughput sequencing technologies has allowed for even more rapid identification of new mutations in PCD subjects. To date, mutations in 18 different genes have been linked to PCD (Fig. 404-3), including those that encode proteins integral to the outer dynein arm (*DNAH5, DNAI1, DNAL1, DNAI2, TXNDC3,* and *DNAH11*), inner dynein arm and axonemal organization (*CCDC39* and *CCDC40*), and the central apparatus and radial spokes (*RSPH9, RSPH4A,* and *HYDIN*). More recently, mutations in genes that code for cytoplasmic proteins involved in cilia assembly or protein transport (*HEATR2, DNAAF1, DNAAF2, DNAAF3, CCDC103, LRRC6,* and *CCDC114*) have been shown to cause ultrastructural abnormalities. The genetics of PCD has further exposed the gaps in current diagnostic approaches. For instance, *DNAH11* mutations have been shown to cause typical clinical phenotypes without apparent axonemal ultrastructural defects or reduced ciliary beat frequency. Mutations in 2 other genes, *CCDC39* and *CCDC40,* produce inconsistent structural abnormalities characterized by disordered microtubules in some, but not all, cilia, which underscores the observation that current diagnostic testing will miss cases.

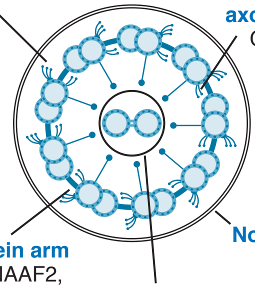

Figure 404-3 Classification of proteins mutated in primary ciliary dyskinesia. *(Adapted from Horani A, Ferkol TW: Molecular genetics of primary ciliary dyskinesia. In* Encyclopedia of Life Sciences *(eLS), 2014. John Wiley & Sons, Chichester, UK. Available at:* http://www.els.net/WileyCDA/ElsArticle/refId-a0024989.html.*)*

Table 404-1 Clinical Manifestations of Primary Ciliary Dyskinesia

RESPIRATORY TRACT	GENITOURINARY TRACT
Lung Neonatal respiratory distress Chronic cough Recurrent pneumonia Bronchiectasis *Middle Ear* Chronic otitis media Conductive hearing loss *Paranasal Sinuses* Neonatal rhinitis Chronic mucopurulent rhinitis Chronic pansinusitis Nasal polyposis	Male and female infertility LEFT-RIGHT ORIENTATION DEFECTS Situs inversus Heterotaxy Congenital heart disease CENTRAL NERVOUS SYSTEM Hydrocephalus Retinitis pigmentosa

CLINICAL MANIFESTATIONS OF PRIMARY CILIARY DYSKINESIA

See Table 404-1.

Most patients with PCD present with **neonatal respiratory distress**, which is manifested as tachypnea, hypoxemia, or even respiratory failure requiring mechanical ventilation. The association of respiratory distress in term neonates with PCD has been underappreciated. The upper respiratory tract is almost universally involved in PCD, and **persistent rhinosinusitis** is common during infancy. Inadequate innate mucus clearance leads to chronic sinusitis (see Chapter 380) and nasal polyposis. Middle ear disease occurs in nearly all children with PCD, with varying degrees of **chronic otitis media** leading to conductive hearing loss and myringotomy tube placement, which is often complicated by intractable otorrhea.

Impaired mucociliary clearance of the lower respiratory tract leads to daily productive cough, often in young children, secondary to chronic bronchitis. Bacterial cultures of sputum or lavage fluid frequently yield nontypeable *Haemophilus influenzae* (see Chapter 194), *Staphylococcus aureus* (see Chapter 181.1), *Streptococcus pneumoniae* (see Chapter 182), and *Pseudomonas aeruginosa* (see Chapter 205.1). Persistent airway infection and inflammation lead to **bronchiectasis**,

even in preschool children. Clubbing is a sign of long-standing pulmonary involvement.

Left-right laterality defects (e.g., *situs inversus totalis*) are found in half of all children with PCD. Without functional nodal cilia in the embryonic period, thoracoabdominal orientation is random. These patients have **Kartagener triad**, defined as *situs inversus totalis*, chronic sinusitis, and bronchiectasis. Approximately 25% of patients with *situs inversus totalis* have PCD, so *situs inversus totalis* alone does not establish the diagnosis of PCD. Other laterality defects, such as heterotaxy, are associated with PCD and may coexist with congenital cardiac defects, asplenia, or polysplenia.

Most men with PCD have dysmotile spermatozoa because flagellar and ciliary ultrastructure is similar. Male infertility is typical, but not always found in this disease. Fertility issues in women have also been reported and are likely a result of ciliary dysfunction in the fallopian tubes.

A few case reports have associated **neonatal hydrocephalus** with PCD. The ependyma of the brain ventricles are lined by ciliated epithelium and are important for cerebrospinal fluid flow through the ventricles and aqueduct of Sylvius. The finding of enlarged brain ventricles on sonograms, when linked with *situs inversus totalis,* has been proposed as a prenatal diagnostic marker for PCD. X-linked retinitis pigmentosa has been associated with recurrent respiratory infections in families with *RPGR* gene mutations. Intraflagellar transport proteins are essential for photoreceptor assembly, and when mutated, lead to apoptosis of the retinal pigment epithelium (see Chapter 630).

Table 404-2 Electron Microscopic Findings in Primary Ciliary Dyskinesia vs Acquired Cilia Abnormality

	PCD	ACQUIRED DEFECTS
EM ultrastructure	Dynein arm deficiency Outer arms Inner arms Both Translocation of central tubules Few or absent cilia (generalized)	Compound cilia Added peripheral tubules Deleted peripheral tubules Added central pairs Translocation of central tubules Few or absent cilia (patchy)
Beat frequency	Hyperkinetic, slow or absent	May be normal or reduced
Wave form	Abnormal	May be normal or abnormal

EM, electron microscopy; PCD, primary ciliary dyskinesia.

From Stillwell PC, Wartchow EP, Sagel SD. Primary ciliary dyskinesia in children: A review for pediatricians, allergists, and pediatric pulmonologists. Pediatr Allergy Immunol Pulmonol *24: 191–196, 2011, Table 1.*

DIAGNOSIS OF PRIMARY CILIARY DYSKINESIA

The diagnosis of PCD should be suspected in children with chronic or recurring upper and lower respiratory tract symptoms that begin in early infancy and is currently based on the presence of characteristic clinical phenotype and ultrastructural defects of cilia, though this approach will miss affected individuals. The diagnosis is often delayed, even in children who have classic clinical features, such as chronic rhinosinusitis in infancy, persistent otitis media, or even *situs inversus totalis*. The average age at PCD diagnosis is approximately 4 yr; a high index of suspicion is necessary.

Imaging studies show extensive involvement of the paranasal sinuses. Chest radiographs frequently demonstrate bilateral lung overinflation, peribronchial infiltrates, and lobar atelectasis. Computerized x-ray tomography of the chest often reveals bronchiectasis, often involving the anatomic right middle lobe or lingual, even in young children. *Situs inversus totalis* in a child who has chronic respiratory tract symptoms is highly suggestive of PCD, but this configuration occurs in only half of patients with PCD. Pulmonary function testing typically shows progressive intrathoracic airway obstruction.

Transmission electron microscopy is the current gold standard to assess structural defects within the cilium. Curettage from the nasal epithelium or endobronchial brushing can provide an adequate specimen for review. Identification of a discrete, consistent defect in any aspect of the ciliary structure with concurrent phenotypic features is sufficient to make the diagnosis. Shortening or absence of dynein arms is the most common abnormality seen in PCD, accounting for 90% of cases with defined ultrastructural defects (see Fig. 404-3). Other axonemal changes consistent with PCD include microtubular transposition, radial spoke and nexin link defects, and ciliary agenesis. Unfortunately, ultrastructural examination of cilia as a diagnostic test for PCD has significant drawbacks. First, the absence of axonemal defects does not exclude PCD; nearly 30% of all affected individuals have normal ciliary ultrastructure. Careful interpretation of the ultrastructural findings is necessary, because nonspecific changes may be seen in relation to exposure to environmental pollutants or infection. Ciliary defects can be acquired (Table 404-2). Acute airway infection or inflammation can result in structural changes (e.g., compound cilia or blebs). Ciliary disorientation has been proposed as a form of PCD, but this phenomenon is the result of airway injury. Frequently, the diagnosis of PCD can be delayed or missed because of inadequate tissue collection or sample processing as well as the lack of an experienced pathologist who can distinguish between primary and acquired ciliary defects. Several reviews have advocated culturing of airway epithelial cells and allowing the secondary changes to resolve.

Qualitative tests to assess ciliary function have been used to screen for PCD. Ciliary beat frequency measurements that use conventional microscopic techniques have been used as a screen, but this method alone will miss cases of PCD. Cilia inspection using standard light microscopy is insufficient to support or exclude the diagnosis. High-resolution, high-speed, digital imaging of ciliary motion in multiple planes has permitted comprehensive analysis of abnormal beat patterns. This approach is available only at a limited number of clinical centers and requires sophisticated software and expertise. Immunofluorescence imaging has been used to show mislocalization of dynein arm proteins. Such techniques are research tools and not widely available.

Another promising approach has exploited the observation that nasal nitric oxide concentrations are reduced in subjects with PCD. Because nasal nitric oxide measurements are relatively easy to perform and noninvasive, this method is a promising screen and potentially a diagnostic test for PCD, provided that cystic fibrosis has been excluded (see Chapter 403). Few studies in younger children have been reported, and the accuracy of nasal nitric oxide measurements in infants has not been established.

PCD is highly heterogenic owing to the large number of proteins involved in cilia assembly and function. Recent advances in gene sequencing techniques have led to the identification of a growing number of PCD-associated genes. The pace of new gene discovery has accelerated during the past 2 yr, and new discoveries are forthcoming. Genetic testing for PCD is available, but commercial laboratories offer testing for only some mutations. It is reasonable to expect that genetic testing will become the preferred diagnostic approach for PCD, but disease-causing mutations have only been linked to approximately 60% of known cases.

TREATMENT

No therapies correct ciliary dysfunction in PCD. Many of the treatments applied to PCD patients are similar to those used in other suppurative lung diseases characterized by impaired airway clearance and bronchiectasis, such as cystic fibrosis, but none have been adequately studied to demonstrate their efficacy in PCD.

Strategies to enhance mucociliary clearance are central to PCD therapy, and routine airway clearance techniques using postural

drainage, percussion vests, positive expiratory pressure devices, or other techniques should be instituted on a daily basis. Because ciliary function is impaired, cough becomes a critical mechanism for mucus clearance and should not be suppressed. Exercise can enhance airway clearance in patients with PCD and should be encouraged. Inhaled mucolytic agents are often used in cystic fibrosis care, and few case reports have shown improvement in lung function in patients with PCD after treatment.

When children with PCD develop increasing respiratory symptoms consistent with infection, antimicrobial therapy should be instituted on the basis of respiratory culture results and bacterial sensitivities. Early eradication strategies to clear bacteria from the PCD lung have not been studied. Maintenance therapy with inhaled or oral antibiotics can be used cautiously in patients with PCD who have bronchiectasis or frequent exacerbations, although current literature lacks evidence supporting long-term antimicrobial therapy. Immunizations against pertussis, influenza, and pneumococci are cornerstones of care. Additional preventive measures include avoidance of cigarette smoke and other airway irritants.

Although β-adrenergic agonists increase ciliary beat frequency in normal epithelial cells, data is lacking that shows these agents improve function of dyskinetic cilia. Moreover, they do not necessarily provide bronchodilation in patients with PCD and obstructive airway disease.

Surgical resection of bronchiectatic lung has been performed on patients with PCD, typically in cases of localized disease with severe hemoptysis or recurrent febrile illnesses. It is unclear whether surgical interventions provide reduction in symptoms or survival benefit.

Progression to end-stage lung disease and respiratory failure has been reported in patients with PCD. Adult patients have undergone successful heart-lung, double lung, or living donor lobar lung transplantation. *Situs inversus totalis* complicates the procedure owing to anatomic considerations. Otherwise, survival is similar to that for other transplant recipients.

Treatment of chronic otitis media and middle ear effusions in patients with PCD is controversial. Myringotomy tubes are frequently placed in affected children, but they are not without complications, because they may lead to chronic mucoid otorrhea, tympanosclerosis, and permanent membrane perforation. Myringotomy tubes have not measurably improved hearing acuity. Although hearing tends to improve with time, it should be routinely screened and hearing aids used when necessary.

Chronic rhinitis and sinusitis are frequent clinical manifestations of PCD. No treatments have been shown to be effective, although patients are often treated with nasal washes, paranasal sinus lavage, and systemic antibiotics when they are symptomatic. As with any overuse of antimicrobial agents, the development of resistant organisms is a concern. When nasal symptoms are severe or refractory to medical management, endoscopic sinus surgery can be used to promote drainage or local delivery of medications, though the benefit may be short-lived.

PROGNOSIS

Although signs and symptoms related to upper respiratory involvement predominate early in PCD, clinical manifestations of lower respiratory tract disease tend to increase with age and become the leading cause of morbidity and mortality in PCD patients. It is believed that progression and extent of lung disease can be slowed with early diagnosis and therapy. Thus, routine surveillance studies recommended for the care of children with PCD include (1) regular spirometry to monitor pulmonary function, (2) chest imaging, and (3) sputum or oropharyngeal cultures to assess lung respiratory flora.

Patients with PCD typically have slower decline in pulmonary function than those with cystic fibrosis. Its prognosis and long-term survival are better. Many patients with PCD have a normal or near-normal life span, although some do experience progressive bronchiectasis and respiratory deterioration earlier in life.

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Chapter 405

Diffuse Lung Diseases in Childhood

See also Chapter 399.

405.1 Inherited Disorders of Surfactant Metabolism

Lawrence M. Nogee, F. Sessions Cole III, and Aaron Hamvas

Pulmonary surfactant is a mixture of phospholipids and proteins synthesized, packaged, and secreted by alveolar type II pneumocytes (AEC2s) that line the distal air spaces. This mixture forms a monolayer at the air–liquid interface that lowers surface tension at end-expiration of the respiratory cycle, preventing atelectasis and ventilation–perfusion mismatch. Four surfactant-associated proteins have been described: surfactant proteins A and D (SP-A, SP-D) participate in host defense in the lung, whereas surfactant proteins B and C (SP-B, SP-C) contribute to the surface tension–lowering activity of the pulmonary surfactant. The adenosine triphosphate–binding cassette protein member A3, ABCA3, is a transporter located on the limiting membrane of lamellar bodies, the storage organelle for surfactant within alveolar type II cells, and has an essential role in surfactant phospholipid metabolism. The proper expression of the surfactant proteins and ABCA3 is dependent on a number of transcription factors, particularly thyroid transcription factor 1 (TTF-1). Two genes for SP-A *(SFTPA1, SFTPA2)* and 1 gene for SP-D *(SFTPD)* are located on human chromosome 10, whereas single genes encode SP-B *(SFTPB),* SP-C *(SFTPC),* TTF-1 *(NKX2-1)* and ABCA3 *(ABCA3),* which are located on human chromosomes 2, 8, 14, and 16, respectively. Inherited disorders of SP-B, SP-C, ABCA3 and TTF-1 have been identified in humans and are collectively termed **surfactant dysfunction disorders** (Table 405-1).

PATHOLOGY

Histopathologically, these disorders share a unique constellation of features, including AEC2 hyperplasia, alveolar macrophage accumulation, interstitial thickening and inflammation, and alveolar proteinosis. A number of different descriptive terms have historically been applied to these disorders, including ones borrowed from adult forms of interstitial lung disease (**desquamative interstitial pneumonia**, nonspecific interstitial pneumonia) as well as a disorder unique to infancy (**chronic pneumonitis of infancy**). These diagnoses in infants and children are strongly indicative of surfactant dysfunction disorders but do not distinguish which gene is responsible. As the prognosis and inheritance patterns differ depending upon the gene involved, genetic testing should be offered when one of these conditions is reported in the lung biopsy or autopsy of a child.

Deficiency of Surfactant Protein B (Surfactant Metabolism Dysfunction, Pulmonary, 1; SMDP1; OMIM #265120)

Clinical Manifestations

Infants with an inherited deficiency of SP-B present in the immediate neonatal period with respiratory failure. This autosomal recessive disorder is clinically and radiographically similar to the respiratory distress syndrome (RDS) of premature infants (see Chapter 101.3) but typically affects full-term infants. The initial degree of respiratory distress is variable, but the disease is progressive and is refractory to mechanical ventilation, surfactant replacement therapy, glucocorticoid

Table 405-1 Comparison of Surfactant Deficiency Syndromes

	SP-B DEFICIENCY	SP-C DISEASE	ABCA3 DEFICIENCY	TTF-1 DEFICIENCY
Gene name	*SFTPB*	*SFTPC*	*ABCA3*	*NKX2-1*
Age of onset	Birth	Birth–adulthood	Birth–childhood	Birth–childhood
Inheritance	Recessive	Dominant/sporadic	Recessive	Sporadic/dominant
Mechanism	Loss of function	Gain of toxic function or dominant negative	Loss of function	Loss of function ?Gain of function
Natural history	Lethal	Variable	Generally lethal, may be chronic	Variable
Diagnosis:				
Biochemical *(tracheal aspirate)*	Absence of SP-B and presence of proSP-C	None	None	None
Genetic *(DNA)*	Sequence *SFTPB*	Sequence *SFTPC*	Sequence *ABCA3*	Sequence *NKX2-1;* deletion analysis
Ultrastructural *(lung biopsy–electron microscopy)*	Disorganized lamellar bodies	Not specific; may have dense aggregates	Small dense lamellar bodies with eccentrically placed dense cores	Variable
Treatment	Lung transplantation or compassionate care	Supportive care, lung transplantation if progressing	Consider lung transplantation	Supportive care; treat coexisting conditions (hypothyroidism)

SP, surfactant protein.

administration, and extracorporeal membrane oxygenation. SP-B deficiency is recognized in diverse racial and ethnic groups. Almost all affected patients have died without lung transplantation, but prolonged survival is possible in cases of partial deficiency of SP-B. Although murine lineages heterozygous for SP-B deficiency are susceptible to oxidant injury and pulmonary infection, humans heterozygous for loss-of-function mutations in *SFTPB* are clinically normal as adults but may be at increased risk for obstructive lung disease if they also have a history of smoking.

Genetics

Multiple loss-of-function mutations in *SFTPB* have been identified. The most common is a net 2 base-pair insertion in codon 121 (originally termed 121ins2) that results in a frameshift, an unstable SP-B transcript, and absence of SP-B protein production. This mutation has accounted for 60-70% of the alleles found to date in patients identified with SP-B deficiency. Most other mutations have been family specific. A large deletion encompassing 2 exons of the SP-B gene has also been reported.

Diagnosis

A rapid, definitive diagnosis can be established with sequence analysis of *SFTPB,* which is available through clinical laboratories (http://www.genetests.org). In families in which a mutation was previously identified, antenatal diagnosis can be established by molecular assays of DNA from chorionic villous biopsy or amniocytes, which permits advanced planning of a therapeutic regimen. Other laboratory tests remain investigational, including analysis of tracheal effluent by for the presence or absence of SP-B protein and for incompletely processed precursor proSP-C peptides that have been found in SP-B–deficient human infants and animals. Immunostaining of lung biopsy tissue for the surfactant proteins can also support the diagnosis, although immunohistochemical assays for SP-B and SP-C are also generally available only on a research basis. Staining for SP-B is usually absent, but robust extracellular staining for proSP-C because of incompletely processed proSP-C peptides is observed and is diagnostic for SP-B deficiency. Such studies require a lung biopsy in a critically ill child but may be performed on lung blocks acquired at the time of autopsy, allowing for retrospective diagnosis. With electron microscopy, a lack of tubular myelin, disorganized lamellar bodies, and an accumulation of abnormal-appearing multivesicular bodies, suggest abnormal lipid packaging and secretion.

Surfactant Protein C Gene Abnormalities (Surfactant Metabolism Dysfunction, Pulmonary, 2; SMDP2; OMIM #610913)

SP-C is a very low-molecular-weight, extremely hydrophobic protein that, along with SP-B, enhances the surface tension–lowering properties of surfactant phospholipids. It is derived from proteolytic processing of a larger precursor protein (proSP-C).

Clinical Manifestations

The clinical presentation of patients with *SFTPC* mutations is quite variable. Some patients present at birth with symptoms, signs, and radiographic findings typical of RDS. Others present later in life, ranging from early infancy until well into adulthood, with gradual onset of respiratory insufficiency, hypoxemia, failure to thrive, and chest radiograph demonstration of interstitial lung disease, or, in the 5th or 6th decade of life, as pulmonary fibrosis. The age and severity of disease vary even within families with the same mutation. The natural history is also quite variable, with some patients improving either spontaneously or as the result of therapy, some with persistent respiratory insufficiency, and some progressing to the point of requiring lung transplantation. This variability in severity and course of the disease does not appear to correlate with the specific mutation and also hinders accurate assessment of prognosis.

Genetics

Multiple mutations in *SFTPC* have been identified in association with acute and chronic lung disease in patients ranging in age from newborn to adult. A mutation on only 1 *SFTPC* allele is sufficient to cause disease. Approximately half of these mutations arise spontaneously, resulting in sporadic disease, but the remainder are inherited as a dominant trait. A threonine substitution for isoleucine in codon 73 (termed p.I73T or p.Ile73Thr) accounts for 25-35% of the cases identified to date. Mutations in *SFTPC* are thought to result in production of misfolded proSP-C that accumulates within the alveolar type II cell and causes cellular injury, or alters the normal intracellular routing of proSP-C. The frequency of mutations or disease caused by mutations in *SFTPC* is unknown but is probably low. Mutations have been identified in diverse racial and ethnic groups.

Diagnosis

Sequencing of *SFTPC,* the only definitive diagnostic test, is available in clinical laboratories. The relatively small size of the gene facilitates such

analyses, which are quite sensitive, but because most *SFTPC* mutations are missense mutations, distinguishing true disease-causing mutations from rare yet benign sequence variants may be difficult. Immunostaining of lung tissue may demonstrate proSP-C aggregates but is available only on a research basis.

Disease Caused by Mutations in ABCA3 (Surfactant Metabolism Dysfunction, Pulmonary, 3; SMDP3; OMIM #610921)

Clinical Manifestations

Lung disease caused by mutations in *ABCA3* generally presents as either a severe, lethal form that manifests in the immediate newborn period clinically similar to SP-B deficiency, or a chronic form that appears most typically in the 1st yr of life with interstitial lung disease similar to SP-C–associated disease. Infants who are homozygous or compound heterozygous for null mutations, that is, the mutation is predicted to result in absence of protein expression, typically present with lethal neonatal disease, whereas infants with other types of mutations have more variable age of onset and outcomes. Heterozygosity for an *ABCA3* mutation may contribute to the severity of RDS in prematurely born infants, who, in contrast to ABCA3-deficient infants with mutations on both alleles, may eventually completely recover from their initial lung disease.

Genetics

Recessive mutations in *ABCA3* were first described in infants who presented with lethal respiratory distress in the newborn period, but now have been identified in older infants and children with interstitial lung disease. There is considerable allelic heterogeneity: More than 200 mutations scattered throughout the gene have been identified, most of which are family specific. A missense mutation that results in a valine substitution for glutamine in codon 292 (p.E292V or p.Glu292Val) in association with a second *ABCA3* mutation has been found in children with severe neonatal respiratory failure and in older children with interstitial lung disease and is present in approximately 0.4% of the general population. *ABCA3* mutations have been identified in diverse racial and ethnic groups. The precise frequency of disease is unknown, but large-scale sequencing projects indicate that the overall carrier rate for *ABCA3* mutations may be as high as 1 in 50 to 1 in 70 individuals. ABCA3 deficiency may thus contribute to a substantial proportion of **unexplained fatal lung disease** in term infants and of **interstitial lung disease** in older children.

Diagnosis

Sequence analysis of *ABCA3* is available in clinical laboratories and is the most definitive approach for diagnosis. Considerable variation in *ABCA3* necessitates careful interpretation regarding the functionality of an individual variant and its contribution to the clinical presentation. Additionally, sequence analysis is not 100% sensitive as functionally significant mutations may exist in untranslated regions that are not generally analyzed. In these situations, lung biopsy with electron microscopy to examine lamellar body morphology may be a useful adjunct to the diagnostic approach. Small lamellar bodies that contain electron-dense inclusions may be observed in association with *ABCA3* mutations. These findings support the hypothesis that ABCA3 function is necessary for lamellar body biogenesis. There are no biochemical markers to establish the diagnosis.

Disease Caused by Mutations in *NKX2-1* (Thyroid Transcription Factor 1, Choreoathetosis, Hypothyroidism, and Neonatal Respiratory Distress, OMIM #600635)

Clinical Manifestations

A large deletion of the region of chromosome 14 (14q13.3) encompassing the *NKX2-1* locus was first recognized in an infant with hypothyroidism and neonatal RDS. Since then, multiple large deletions involving the *NKX2-1* locus and contiguous genes as well as missense, frameshift, nonsense, and small insertion or deletion mutations scattered throughout the gene have been reported in individuals with hypothyroidism, lung disease, and neurologic symptoms, including benign familial chorea. Manifestation of dysfunction in all 3 organ systems has been referred to as **brain-thyroid-lung syndrome**, but disease may manifest in only 1 or 2 organ systems. The lung disease can range from severe and eventually lethal neonatal respiratory distress to chronic lung disease in childhood and adulthood. Recurrent pulmonary infections have been reported, likely caused by reduced expression of the pulmonary collectins, SP-A and SP-D, but could also result from decreased expression of other proteins. No clear genotype–phenotype correlations have emerged, but children harboring complete gene deletions have tended to have more severe and earlier-onset disease. This observation could also be related to the deletion of other adjacent genes. While limited data are available, the pulmonary phenotype may depend upon the expression of which NKX2-1 target genes are most affected. Children with decreased SP-B or ABCA3 expression may present with acute neonatal respiratory failure whereas those with decreased SP-C or pulmonary collection expression are more likely to have chronic lung disease.

Genetics

The gene is small, spanning <3,000 bases, with only 3 exons. TTF-1 is expressed not only in the lung but also in the thyroid gland, as well as in the central nervous system. In the lung it is important for the expression of a wide variety of proteins, including the surfactant proteins, ABCA3, Clara cell secretory protein, and many others. Two transcripts that differ depending upon whether the transcriptional start site is in the 1st or 2nd exon have been recognized, although the shorter transcript is the predominant one in the lung. Most mutations are thought to result in a loss of function, with the mechanism of disease thus being haploinsufficiency, but discordant effects on different target genes have been reported. The incidence of mutations and incidence and prevalence of disease are unknown; mutations in diverse ethnic groups have been recognized. Most reported mutations and deletions have occurred de novo resulting in sporadic disease, but familial disease transmitted in a dominant manner has been recognized.

Diagnosis

Sequence analysis of the *NKX2-1* gene is available through clinical laboratories and is the preferred method for diagnosis. As deletions comprise a significant fraction of reported mutant alleles, specific methods to look for such deletions should also be performed, such as a comparative genomic hybridization assay or multiplex ligation-dependent probe amplification assay. A mutation on 1 allele is sufficient to cause disease. While isolated pulmonary disease has been recognized, the majority of reported affected individuals have had manifestations in 1 or more other organ systems. Thus the presence of hypothyroidism or neurologic abnormality in a proband or a family history of chorea should prompt consideration of the diagnosis. The most specific neurologic finding is chorea, but hypotonia, developmental delay, ataxia, and dysarthria have been reported. In very young, nonambulatory infants the neurologic symptoms may not be evident, or muscle weakness or hypotonia may be attributed to the severity of lung disease or a result of the hypothyroidism. Affected individuals may not be overtly hypothyroid but have compensated hypothyroidism with borderline low T4 (thyroxine) and high thyroid-stimulating hormone levels. The lung pathology associated with *NKX2-1* mutations may be typical of that of other surfactant dysfunction disorders, but because *NKX2-1* is important for lung development, growth abnormalities and arrested pulmonary development also may be seen. Immunostaining studies of surfactant protein expression have yielded variable results, with decreased expression of 1 or more surfactant-related proteins observed in some patients. No characteristic electron microscopy findings have been identified.

TREATMENT OF SURFACTANT DYSFUNCTION DISORDERS

Virtually all patients with SP-B deficiency die within the 1st yr of life. Conventional neonatal intensive care interventions can maintain extrapulmonary organ function for a limited time (weeks to months).

Replacement therapy with commercially available surfactants is ineffective. Lung transplantation has been successful, but the pretransplantation, transplantation, and posttransplantation medical and surgical care is highly specialized and available only at pediatric pulmonary transplantation centers; prompt recognition is critical if patients are to be considered for lung transplantation. Palliative care consultation is helpful.

No specific treatment is available for patients with lung disease caused by mutations in *SFTPC* or *ABCA3*. Therapeutic approaches used for interstitial lung diseases, such as the use of corticosteroids, quinolones, and macrolide antibiotics have been reported but not systematically evaluated. Infants with severe and progressive respiratory failure attributable to ABCA3 deficiency may be candidates for lung transplantation. The variable natural history of patients with *SFTPC* mutations and older children with ABCA3 deficiency makes predictions of prognosis difficult. Lung transplantation is reserved for patients with progressive and refractory respiratory failure who would otherwise qualify for transplantation irrespective of their diagnosis.

Treatment for patients with *NKX2-1* mutations is largely supportive. Hypothyroidism if present should be treated with thyroid replacement. Corticosteroids and other agents used for other types of surfactant dysfunction have not been formally evaluated. Some individuals have progressive lung disease, and lung transplantation has been performed for some subjects with end-stage lung disease. The variable progression of disease and presence of extrapulmonary disease may make evaluation and selection of subjects for transplantation particularly difficult.

Parents of children with surfactant dysfunction disorders should be offered genetic counseling. This allows for defining the recurrence risks for future pregnancies and the availability of antenatal diagnosis and therapeutic options, as well whether testing should be offered to other family members who may not be symptomatic.

Bibliography is available at Expert Consult.

405.2 Pulmonary Alveolar Proteinosis

Lawrence M. Nogee, F. Sessions Cole III, and Aaron Hamvas

Pulmonary alveolar proteinosis (PAP) is a rare type of diffuse lung disease characterized by the intraalveolar accumulation of pulmonary surfactant. Histopathologic examination shows distal air spaces to be filled with a granular, eosinophilic material that stains positively with periodic acid–Schiff reagent and is diastase resistant. This material contains large amounts of surfactant proteins and lipids and the primary mechanism for its accumulation is impaired catabolism by alveolar macrophages. PAP has historically been classified as either primary (idiopathic) or secondary to a number of different conditions, although this terminology is evolving as specific etiologies for PAP are identified. (A fulminant, usually lethal form manifesting shortly after birth has been termed "congenital alveolar proteinosis," but because this condition is caused by disrupted surfactant metabolism or surfactant dysfunction within alveolar type II cells, the disease is included under "Inherited Disorders of Surfactant Metabolism," above (see Chapter 405.1).

ETIOLOGY AND PATHOPHYSIOLOGY

Disordered signaling of granulocyte-macrophage colony-stimulating factor (GM-CSF) leading to impaired alveolar macrophage maturation is the major underlying cause of primary PAP in children and adults. Most cases of primary PAP in older children and adults are mediated by neutralizing autoantibodies directed against GM-CSF, which can be detected in serum and bronchoalveolar lavage (BAL) fluid. These autoantibodies block binding of GM-CSF to its receptor, thereby inhibiting alveolar macrophage maturation and function and surfactant clearance. Mutations in the genes encoding both the α and β subunits of the GM-CSF receptor *(CSF2RA, CSFR2B)* in children with primary alveolar proteinosis account for a genetic basis for some cases of primary PAP in childhood. Alveolar proteinosis has also been reported in children, including young infants, with **lysinuric protein intolerance**, a rare autosomal recessive disorder caused by mutations in the cationic amino acid transporter SLC7A7 (see Chapter 85.14). These children generally present with vomiting, hyperammonemia, and failure to thrive, although their pulmonary disease may prove fatal. Defective macrophage function has been demonstrated in lysinuric protein intolerance and a case of recurrence of the disease after lung transplantation also supports a primary role for alveolar macrophage dysfunction in the pathogenesis of PAP associated with lysinuric protein intolerance. PAP is also associated with some subtypes of **Niemann-Pick disease** (see Chapter 86.4).

Secondary alveolar proteinosis also may occur in association with infection, particularly in immunocompromised individuals. However, because the same pathologic process occurs in severely immunodeficient mice raised in a pathogen-free environment, it is not clear whether this phenotype results from a secondary infection or the underlying immunodeficiency. Environmental exposures to dust, silica, and chemicals and chemotherapeutic agents have also been associated with the development of secondary alveolar proteinosis.

CLINICAL MANIFESTATIONS

Infants and children with PAP present with dyspnea, fatigue, cough, weight loss, chest pain, or hemoptysis. In the later stages, cyanosis and digital clubbing may be seen. Pulmonary function changes include decreased diffusing capacity of carbon monoxide, lung volumes with a restrictive abnormality, and arterial blood gas values indicating marked hypoxemia and/or chronic respiratory acidosis. Alveolar proteinosis in infants and children is rare. Boys are affected 3 times as often as girls. Usually there is no identifiable etiologic factor (primary), although PAP may occur in association with malignancy or infection, particularly in the setting of systemic immunosuppression or congenital immunodeficiency, or following exposure to several inciting agents, such as dust and chemicals (secondary).

DIAGNOSIS

Histopathologic examination of lung biopsy specimens currently remains the gold standard for diagnosis of PAP in children, although this is likely to change as molecular tests become available. Immunohistochemical staining reveals abundant quantities of alveolar and intracellular surfactant proteins A, B, and D. Latex agglutination tests for the presence of anti–GM-CSF antibodies in BAL fluid or blood are highly sensitive and specific for the autoimmune forms of alveolar proteinosis. Elevations of GM-CSF in peripheral blood suggest a GM-CSF receptor defect, and molecular analysis of these genes should be pursued. The examination of sputum or BAL fluid for surfactant components has been used diagnostically in adults, but these methods have not been validated in children. Examination of peripheral blood and/or bone marrow for clonogenic stimulation of monocyte-macrophage precursors, GM-CSF receptor and ligand expression, and GM-CSF binding and signaling studies are available through research protocols.

TREATMENT

The natural history of primary PAP is highly variable, making prognostic and therapeutic decisions difficult. Total lung lavage has been associated with prolonged remissions of PAP in adults and remains a therapeutic option for patients with childhood PAP (Figs. 405-1 and 405-2). Younger infants with PAP may be more likely to have genetic mechanisms underlying their disease, and the role of repeated BAL in children has not been well studied, nor is it likely to be effective. It may provide a temporizing measure in some circumstances and may benefit patients with autoimmune or secondary PAP. Subcutaneous or inhaled administration of recombinant GM-CSF may improve pulmonary function in some adults with later-onset PAP. The role of exogenous GM-CSF treatment in children has not been well studied, although successful treatment has been reported in an adolescent with autoimmune-mediated PAP. Because children with GM-CSF receptor

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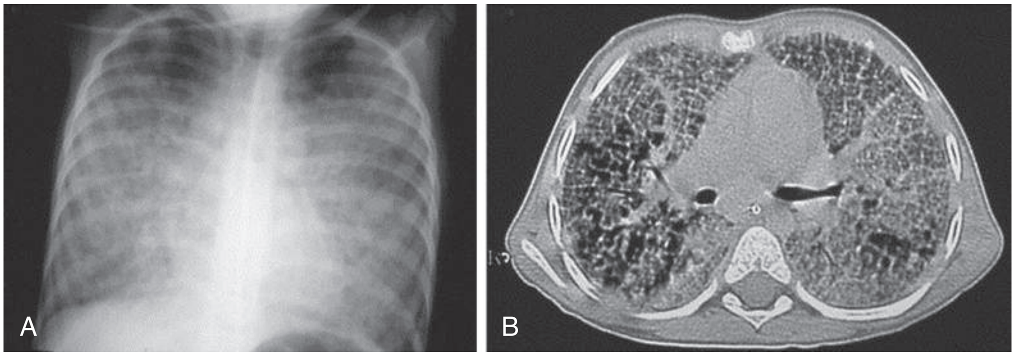

Figure 405-1 **Severe pulmonary alveolar proteinosis in a 5 yr old boy before therapeutic lung lavage. A,** Chest radiograph shows diffuse alveolointerstitial infiltrates. **B,** CT scan demonstrates major air-space opacities and crazy-paving pattern. *(From De Blic J: Pulmonary alveolar proteinosis in children,* Paediatr Respir Rev *5:316–322, 2004.)*

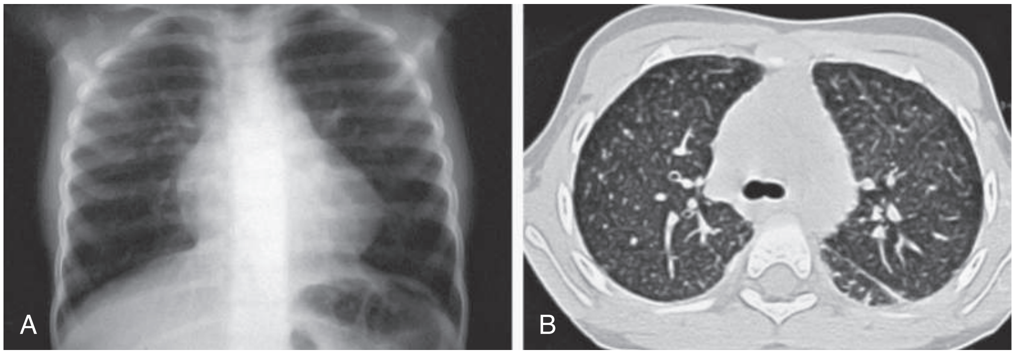

Figure 405-2 **Same patient as in** Figure 405-1 **after 12 therapeutic lung lavages. A,** Chest radiograph demonstrates improvement of alveolointerstitial infiltrates. **B,** CT scan shows regression of the air-space opacities with a residual micronodular pattern. *(From De Blic J: Pulmonary alveolar proteinosis in children,* Paediatr Respir Rev *5:316–322, 2004.)*

defects generally have high serum levels of GM-CSF, exogenous GM-CSF seems unlikely to be effective in most such cases. Depending upon the nature of the mutation(s) responsible for the deficiency, some responsiveness of the receptor may be retained such that a response to exogenous GM-CSF is possible. As the primary defect for PAP resides in the alveolar macrophage, which is a bone marrow–derived cell, lung transplantation would not be expected to correct primary PAP.

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Chapter 406

Pulmonary Hemosiderosis

Mary A. Nevin

Pulmonary hemorrhage may be characterized as focal or diffuse based on the site(s) of bleeding. A detailed review of pulmonary hemorrhage is in Chapter 407.2. The diagnosis of pulmonary hemosiderosis refers to the subset of patients with **diffuse alveolar hemorrhage (DAH)**. Bleeding in DAH occurs as a result of injury to the microvasculature of the lung and may be slow and insidious due to the low pressure pulmonary circulation. Pulmonary hemosiderosis has classically been characterized by the triad of iron-deficiency anemia, hemoptysis, and multiple alveolar infiltrates on chest radiographs. However, many of those affected, particularly young patients are likely to present atypically and a high index of suspicion for this condition must be maintained. Pulmonary hemosiderosis can exist in isolation, but more commonly occurs in association with an underlying condition. A precise etiology for hemorrhage may not always be found. A diagnosis of **idiopathic pulmonary hemosiderosis (IPH)** is made when DAH occurs in isolation and an exhaustive evaluation for an underlying pathologic etiology is found to be unrevealing.

ETIOLOGY

Current classification schemes organize the etiologies of pulmonary hemosiderosis on the basis of the presence of absence of pulmonary capillaritis; a pathologic process that is characterized by inflammation and cellular disruption of the alveolar interstitium and capillary bed. Although the finding of pulmonary capillaritis is nonspecific with regard to underlying diagnosis, its presence appears to be an important negative prognostic factor in DAH and may indicate an underlying systemic vasculitic process or collagen vascular disease.

Disorders associated with pulmonary capillaritis may include systemic lupus erythematosus (SLE; see Chapter 158), drug-induced capillaritis, granulomatosis with polyangiitis (previously Wegener granulomatosis), Goodpasture syndrome, and Henoch-Schönlein purpura (see Chapter 167). The finding of DAH in patients with granulomatosis with polyangiitis and microscopic polyangiitis (MPA) (see Chapter 167) is frequently associated with pathologic evidence of pulmonary capillaritis. In patients with Goodpasture syndrome or SLE, DAH has been reported both with and without the associated finding of capillaritis. A number of systemic autoimmune and inflammatory disorders may predispose a host to DAH with pulmonary capillaritis. Similarly, a variety of drugs are associated with pulmonary capillaritis but the mechanisms here have not been identified.

These disorders are distinguished from those without pulmonary capillaritis. Those disorders in which the pathologic finding of capillary

Table 406-1 Diffuse Alveolar Hemorrhage Syndromes

CLASSIFICATION	SYNDROME
Disorders with pulmonary capillaritis	Idiopathic pulmonary capillaritis
	Granulomatosis with polyangiitis (Wegener granulomatosis)
	Microscopic polyangiitis
	Systemic lupus erythematosus
	Goodpasture syndrome
	Antiphospholipid antibody syndrome
	Henoch-Schönlein purpura
	Immunoglobulin A nephropathy
	Behçet syndrome
	Cryoglobulinemia
	Drug-induced capillaritis (hypersensitivity)
	Idiopathic pulmonary-renal syndrome
	Eosinophilic granulomatosis angiitis (Churg-Strauss syndrome)
Disorders without pulmonary capillaritis:	
Noncardiovascular causes	Idiopathic pulmonary hemosiderosis
	Heiner syndrome
	Acute idiopathic pulmonary hemorrhage of infancy
	Bone marrow transplantation
	Immunodeficiency
	Coagulation disorders
	Hemolytic uremic syndromes
	Celiac disease (Lane-Hamilton syndrome)
	Infanticide (child abuse)
	Infection (HIV, cryptococcosis, Legionnaires disease)
Cardiovascular causes	Mitral stenosis
	Pulmonary venoocclusive disease
	Arteriovenous malformations
	Pulmonary lymphangioleiomyomatosis
	Pulmonary hypertension
	Pulmonary capillary hemangiomatosis
	Chronic heart failure
	Vascular thrombosis with infarction

From Susarla SC, Fan LL: Diffuse alveolar hemorrhage syndromes in children, Curr Opin Pediatr 19:314–320, 2007.

network disruption is absent are further divided into cardiac (pulmonary hypertension, mitral stenosis) and noncardiac (immunodeficiency, Heiner syndrome, coagulopathies, IPH) etiologies. A summary of the diagnoses that may manifest as recurrent or chronic pulmonary bleeding; Table 406-1 lists their classification.

EPIDEMIOLOGY

Disorders that present as DAH are highly variable in their severity, as well as in their associated symptomatology and identifiable abnormalities in laboratory testing; the diagnosis may be significantly delayed, making frequency estimates unreliable. Similarly, the prevalence of IPH is largely unknown. Among many children and young adults who were diagnosed with IPH in the past, the etiology of the hemorrhage might have been discovered if they had been studied with the newer and more advanced diagnostics available today; specific serologic testing has vastly improved our ability to appreciate immune mediated disease. Estimates of prevalence obtained from Swedish and Japanese retrospective case analyses vary from 0.24-1.23 cases per million. In nearly 80% of diagnosed cases the manifestations of IPH are seen before age 10 yr. The remaining 20% of cases are typically diagnosed before age 30 yr. The ratio of affected males : females is 1 : 1 in the childhood diagnosis group, and men are only slightly more affected in the group diagnosed as young adults.

PATHOLOGY

In pulmonary capillaritis, key histologic features include (1) fibrin thrombi, which occlude capillaries, (2) fibrin clots adherent to interalveolar septae, (3) fibrinoid necrosis of capillary walls, and (4) interstitial erythrocytes and **hemosiderin**. Illustrative but nonspecific pathologic findings, such as vascular smooth muscle hypertrophy (pulmonary hypertension), edema (mitral stenosis), or thrombosis (vascular thrombosis with infarction), may be found in those disorders that cause DAH without pulmonary capillaritis. The finding of blood in the airways or alveoli is representative of a recent hemorrhage. With repeated episodes of pulmonary hemorrhage, lung tissue appears brown secondary to this presence of hemosiderin. **Hemosiderin-laden macrophages (HLMs)** are seen with recovering, recurrent, or chronic pulmonary hemorrhage and are identifiable both in bronchoalveolar lavage fluid and in pathologic specimens of lung tissue. It takes 48-72 hr for the alveolar macrophages to convert iron from erythrocytes into hemosiderin. In a murine model, HLMs appear 3 days after a single episode of pulmonary hemorrhage and peak at 7-10 days. HLMs may be detectable for weeks to months after a hemorrhagic event. Other nonspecific pathologic findings include thickening of alveolar septa, goblet cell hyperplasia, and hypertrophy of type II pneumocytes. Fibrosis may be seen with chronic disease.

PATHOPHYSIOLOGY

Diffuse Alveolar Hemorrhage Associated with Pulmonary Capillaritis

Granulomatosis with polyangiitis is a recognized etiology for DAH in children. This disease is classically characterized by necrotizing granuloma formation (with or without cavitation) of the upper and lower respiratory tract and by a necrotizing glomerulonephritis and small vessel vasculitis. In children, presentations attributable to the upper airway, including subglottic stenosis, may suggest the diagnosis. The presence of **antineutrophil cytoplasmic antibodies (ANCAs)** may be helpful in diagnosis and management, but the clinician must be aware that other ANCA-positive vasculitides, such as MPA and Churg-Strauss syndrome, may share this nonspecific laboratory finding. In small-vessel vasculitides, ANCAs cause an inflammatory reaction that results in injury to the microvasculature. **Antiproteinase-3 antibodies** (**cANCA**) are classically associated with granulomatosis with polyangiitis whereas **antimyeloperoxidase antibodies** (**pANCA**) are typically found in patients with MPA.

Patients with **MPA** (previously the microscopic variant of polyarteritis nodosa) demonstrate a systemic necrotizing vasculitis with a predilection for small vessels (venules, arterioles, capillaries) but without necrotizing granuloma formation. This diagnosis is precluded by the finding of immune complex deposition in order to differentiate MPA from other diseases (Henoch-Schönlein purpura, cryoglobulinemic vasculitis) that are associated with immune complex–mediated small-vessel vasculitis.

Goodpasture syndrome is an immune complex–mediated disease in which anti–glomerular basement membrane (GBM) antibody binds to the basement membrane of both the alveolus and the glomerulus. GBM antibodies attach to type IV collagen contained in the vascular endothelium. At the alveolar level, immunoglobulin (Ig) G, IgM, and complement are deposited at alveolar septa. Electron microscopy shows disruption of basement membranes and vascular integrity, which allows blood to escape into alveolar spaces.

Although alveolar hemorrhage is not commonly encountered in association with SLE, its occurrence is often severe and potentially life-threatening; mortality rates exceed 50%. Pathologic vasculitic features may be absent. Some immunofluorescent studies have revealed IgG and C3 deposits at the alveolar septa. However, a clear link between immune complex formation and alveolar hemorrhage has not been established.

In **Henoch-Schönlein purpura,** pulmonary hemorrhage is a rare but recognized complication. Pathologic findings have included transmural neutrophilic infiltration of small vessels, alveolar septal inflammation, and intra-alveolar hemorrhage. Vasculitis is the proposed mechanism for hemorrhage.

Pulmonary renal syndromes are defined as those where pulmonary and renal disease manifestations are predominant. These include the aforementioned granulomatosis with polyangiitis, Goodpasture

syndrome, SLE, and MPA. As Henoch-Schönlein purpura may also have renal involvement, it has been suggested for inclusion as a pulmonary renal syndrome.

Diffuse Alveolar Hemorrhage Not Associated with Pulmonary Capillaritis

A premature infant's neonatal course can be complicated by pulmonary hemorrhage. The alveolar and vascular networks are immature and particularly prone to inflammation and damage by ventilator mechanics, oxidative stress, and infection. Pulmonary hemorrhage may be unrecognized if the volume of blood is insufficient to reach the proximal airways. The chest radiographic findings in pulmonary hemorrhage may be appreciated instead as a worsening picture of respiratory distress syndrome, edema, or infection.

Pulmonary hemosiderosis in association with **cow's milk hypersensitivity** was first reported by Heiner in 1962. This condition is characterized by variable symptoms of milk intolerance. Symptoms can include grossly bloody or occult heme-positive stools, vomiting, failure to thrive, symptoms of gastroesophageal reflux, and/or upper airway congestion. Pathologic findings have included elevations of IgE and peripheral eosinophilia, as well as alveolar deposits of IgG, IgA, and C3. High titers to cow's milk protein are also typically found in cow's milk hypersensitivity. Association with pulmonary hemorrhage has remained controversial but multiple case series have provided support for the anecdotal association. In one series, infants presenting with recurrent respiratory symptoms and iron-deficiency anemia; all infants improved with elimination of cow's milk from their diets and a subset thereafter had a recurrence of pulmonary disease with a cow's milk challenge. However, many patients with milk precipitins did not have symptoms of hemosiderosis and patients with hemosiderosis did not always have milk precipitins; the relationship may be an association rather than causal in nature.

A number of case reports and case series have suggested an association between **celiac disease** (see Chapter 338.2) and DAH. In these reports, a resolution of intestinal and pulmonary symptoms along with resolution of radiographic disease has been seen after the adoption of a gluten-free diet. Consideration of testing for celiac disease in those patients with pulmonary hemorrhage and suggestive gastrointestinal symptomatology is suggested.

A number of additional associated conditions and exposures exist as causes for DAH. These are typically noninflammatory in nature and may be diversely attributable to cardiac, vascular, lymphatic or hematologic etiologies. **Graft-versus-host disease** has been implicated in transplant recipients and DAH may rarely be attributable to nonaccidental trauma. These etiologies for DAH occur relatively infrequently in the pediatric population, and suggested mechanisms for hemorrhage are variable.

The diagnosis of IPH is a diagnosis of exclusion and is only made when there is evidence of chronic or recurrent DAH and when exhaustive evaluations for primary or secondary etiologies have negative results. Renal and systemic involvement should be absent and a biopsy specimen should not reveal any evidence of granulomatous disease, vasculitis, infection, infarction, immune complex deposition or malignancy. Some patients initially diagnosed with IPH will later be found to have Goodpasture syndrome, SLE, or MPA; therefore, some cases of IPH may represent unrecognized immune-mediated disorders.

CLINICAL MANIFESTATIONS

The clinical presentation of pulmonary hemosiderosis is highly variable. In most symptomatic cases, DAH is heralded by symptoms of hemoptysis and dyspnea with associated hypoxemia and the finding of alveolar infiltration on chest radiograph. The diagnosis may be problematic as young children often lack the ability to effectively expectorate and may not present with hemoptysis. As the presence of blood in the lung is a trigger for airway irritation and inflammation, the patient may present after an episode of hemorrhage with wheezing, cough, dyspnea, and alterations in gas exchange, reflecting bronchospasm, edema, mucus plugging, and inflammation; this presentation may result in an incorrect diagnosis of asthma or bronchiolitis. A lack of pulmonary symptoms does not preclude the diagnosis of DAH and children may present only with chronic fatigue or pallor.

Symptoms may reflect an underlying and associated disease process rather than specifically related to pulmonary hemorrhage. Presentations can vary widely from a relative lack of symptoms to shock or sudden death. Bleeding may occasionally be recognized from the presence of alveolar infiltrates on a chest radiograph alone. It should be noted, however, that the absence of an infiltrate does not rule out an ongoing hemorrhagic process.

On physical examination, the patient may be pale with tachycardia and tachypnea. During an acute exacerbation, children are frequently febrile. Examination of the chest may reveal retractions and differential or decreased aeration, with crackles or wheezes. The patient may present in shock with respiratory failure from massive hemoptysis. Children in particular may present with symptoms of chronic anemia, such as failure to thrive.

LABORATORY FINDINGS AND DIAGNOSIS

Pulmonary hemorrhage is classically associated with a microcytic, hypochromic anemia. Reductions of serum iron levels, decreased or normal total iron-binding capacity and normal to increased ferritin levels may be found with chronic disease. An elevated erythrocyte sedimentation rate is a nonspecific finding. The reticulocyte count is frequently elevated. Patients with pulmonary capillaritis have lower hematocrits and higher erythrocyte sedimentation rates. The anemia of IPH can mimic a hemolytic anemia. Elevations of plasma bilirubin are caused by absorption and breakdown of hemoglobin in the alveoli. Any or all of these hematologic manifestations may be absent in the presence of recent hemorrhage.

White blood cell count and differential should be evaluated for evidence of infection and eosinophilia. A peripheral smear and direct Coombs test may suggest a vasculitic process. A stool specimen positive for occult blood may suggest associated gastrointestinal disease but can also reflect swallowed blood. Renal and liver functions should be reviewed. A urinalysis should be obtained to assess for evidence of a pulmonary–renal syndrome. A coagulation profile, quantitative immunoglobulins (including IgE), and complement studies are recommended. Testing for von Willebrand disease is also indicated.

Testing for ANCA (cANCA, pANCA), antinuclear antibody, double-stranded DNA, rheumatoid factor, antiphospholipid antibody, and GBM antibody evaluates for a number of immune-mediated and vasculitic processes that may be associated with pulmonary capillaritis.

Sputum or pulmonary secretions should be analyzed for significant evidence of blood or HLMs and may provide supportive evidence in a patient who is able to adequately expectorate secretions from the lower airway. Gastric secretions may also reveal HLMs. Flexible bronchoscopy provides visualization of any areas of active bleeding. With bronchoalveolar lavage, pulmonary secretions may be sent for pathologic review and culture analysis. The ability to perform flexible bronchoscopy will be limited if there are large amounts of blood or clots in the airway. Active bleeding may be exacerbated by airway occlusion with a bronchoscope and by installation of fluid. A patient with respiratory failure can be ventilated more effectively through a rigid bronchoscope.

Chest x-rays may reveal evidence of acute or chronic disease. Hyperaeration is frequently seen, especially during an acute hemorrhage. Infiltrates are typically symmetric and may spare the apices of the lung. Atelectasis may also be appreciated. With chronic disease, fibrosis, lymphadenopathy and nodularity may be seen. CT findings may demonstrate a subclinical and contributory disease process. The presence of a cardiac murmur, cardiomegaly on X-ray or a clinical suspicion for left-sided heart lesion suggests the need for a complete cardiac evaluation, including electrocardiogram and echocardiogram

Pulmonary function testing will likely reveal primarily obstructive disease in the acute period. With more chronic disease, fibrosis and restrictive disease tend to predominate. Oxygen saturation levels may be decreased. Lung volumes may reveal air trapping acutely and decreases in total lung capacity chronically. The diffusing capacity of carbon monoxide may be low or normal in the chronic phase

but is likely to be elevated in the setting of an acute hemorrhage, because carbon monoxide binds to the hemoglobin in extravasated red blood cells.

Lung biopsy is warranted when DAH occurs without discernible etiology, extrapulmonary disease, or circulating GBM antibodies. When obtained, pulmonary tissue should be evaluated for evidence of vasculitis, immune complex deposition, and granulomatous disease.

Many have supported a diagnosis of IPH without lung biopsy if the patient has a typical presentation with diffuse infiltration on radiography, anemia, HLMs in bronchoalveolar lavage, sputum or gastric aspirate, absence of systemic disease and negative serology for immune-mediated disease. However, a number of patients meeting these criteria have been proven to have pulmonary capillaritis on review of pathologic lung tissue specimens. Therefore, a lung biopsy is recommended in any child presenting with DAH of uncertain etiology.

TREATMENT

Supportive therapy, including volume resuscitation, ventilatory support, supplemental oxygen, and transfusion of blood products, may be warranted in the patient with pulmonary hemosiderosis. Surgical or medical therapy should be directed at any treatable underlying condition. In IPH, systemic corticosteroids are frequently utilized as first-line treatment and are expected to be of particular benefit in the setting of immune-mediated disease. Steroids modulate neutrophil influx and the inflammation associated with hemorrhage; consequently, they may decrease progression toward fibrotic disease.

Treatment may be provided in the form of methylprednisolone 2-4 mg/kg/day divided every 6 hr or in the form of prednisone 0.5-1 mg/kg daily and decreased to every-other-day after resolution of acute symptoms. Successful treatment is also associated with the use of pulse steroid therapy; methylprednisolone may be given at a dose of 10-30 mg/kg (maximum 1 g) infused over 1 hr for 3 consecutive days and repeated monthly. Early treatment with corticosteroids appears to decrease episodes of hemorrhage. Steroid therapy is associated with improved survival and may be tapered as tolerated with disease remission or chronically maintained.

Steroid-sparing agents, including cyclophosphamide, azathioprine, hydroxychloroquine, methotrexate, and intravenous immunoglobulin, have been successfully used as adjunctive therapy in patients with chronic, unremitting or recurrent hemorrhage. Maintenance therapy with 6-mercaptopurine may produce favorable results in achieving long-term remission. The potential adverse effects of these pharmacologic interventions should be recognized and treated patients must be closely monitored for drug-related complications. Cushing syndrome is a well-recognized complication of chronic steroid therapy. Thrombocytopenia in association with low-dose cyclophosphamide has also been reported. Chronically immunosuppressed patients are at risk for opportunistic infection; *Legionella* pneumonia infection has been described in a survivor of IPH.

Plasmapheresis is a recognized therapy for anti-GBM antibody disease. Intravenous immunoglobulin has been used in immune complex–mediated disease.

In chronic disease, progression to debilitating pulmonary fibrosis has been described. Lung transplantation has been performed in patients with IPH refractory to immunosuppressive therapy. In one reported case study, IPH recurred in the transplanted lung.

PROGNOSIS

The outcome of patients suffering from DAH is largely dependent on the underlying disease process. Some conditions respond well to immunosuppressive therapies and remissions of disease are well documented. Other syndromes, especially those associated with pulmonary capillaritis, carry a poorer prognosis. In IPH, mortality is usually attributable to massive hemorrhage or, alternatively, to progressive fibrosis, respiratory insufficiency, and right-sided heart failure.

Long-term prognosis in patients with IPH varies among studies. Initial case study reviews suggested an average survival after symptom onset of only 2.5 yr. In this early review, a minority of patients were treated with steroids. Recent reviews have demonstrated vastly improved 5yr (86%) and 8 yr (93%) survival in association with the use of immunosuppressive therapies. To date, specific immunosuppressive treatment regimens have not been studied in a prospective manner.

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Chapter 407

Pulmonary Embolism, Infarction, and Hemorrhage

407.1 Pulmonary Embolus and Infarction

Mary A. Nevin

Venous thromboembolic disease (VTE) has become an increasingly recognized critical problem in children and adolescents with chronic disease, as well as in those patients without identifiable risk factors (Table 407-1). Improvements in survival with chronic illness have likely contributed to the larger number of children presenting with these thromboembolic events; they are a significant source of morbidity and mortality and may only be recognized on post mortem examination. A high level of clinical suspicion and appropriate identification of at-risk individuals is therefore recommended.

ETIOLOGY

No single classification scheme exists for the etiology of VTE. A number of risk factors may be identified in children and adolescents; the presence of immobility, malignancy, pregnancy, infection, indwelling central venous catheters and a number of inherited and acquired thrombophilic conditions have all been identified as placing an individual at risk. In children, a significantly greater percentage of VTEs are risk associated as compared with their adult counterparts. Children with **deep venous thrombosis (DVT)** and **pulmonary embolism (PE)** are much more likely to have 1 or more identifiable conditions or circumstances placing them at risk. In a retrospective cohort of patients with VTE in U.S. children's hospitals from 2001-2007, the majority (63%) of affected children were found to have 1 or more chronic medical comorbidities. In a large Canadian registry, 96% of pediatric patients were found to have 1 risk factor and 90% had 2 or more risk factors. In contrast, approximately 60% of adults with this disorder have an identifiable risk factor (see Table 407-1).

Embolic disease in children is varied in its origin. An embolus can contain thrombus, air, amniotic fluid, septic material, or metastatic neoplastic tissue. Thromboemboli are the type most commonly encountered. A commonly encountered risk factor for DVT and PE in the pediatric population is the presence of a central venous catheter. More than 50% of DVTs in children and more than 80% in newborns are found in patients with indwelling central venous lines. The presence of a catheter in a vessel lumen, as well as instilled medications, can induce endothelial damage and favor thrombus formation.

Children with malignancies are also at considerable risk. Although PE has been described in children with leukemia, the risk of PE is more significant in children with solid rather than hematologic malignancies. A child with malignancy may have numerous risk factors related to the primary disease process and the therapeutic interventions. Infection from chronic immunosuppression may interact with hypercoagulability of malignancy and chemotherapeutic effects on the endothelium.

Table 407-1	Risk Factors for Pulmonary Embolism
ENVIRONMENTAL	
Long-haul air travel	
Obesity	
Cigarette smoking	
Hypertension	
Immobility	
WOMEN'S HEALTH	
Oral contraceptives, including progesterone-only and, especially, third-generation pills	
Pregnancy	
Hormone replacement therapy	
Septic abortion	
MEDICAL ILLNESS	
Previous pulmonary embolism or deep venous thrombosis	
Cancer	
Heart failure	
Chronic obstructive pulmonary disease	
Diabetes mellitus	
Inflammatory bowel disease	
Antipsychotic drug use	
Long-term indwelling central venous catheter	
Permanent pacemaker	
Internal cardiac defibrillator	
Stroke with limb paresis	
Spinal cord injury	
Nursing home confinement or current or repeated hospital admission	
SURGICAL	
Trauma	
Orthopedic surgery	
General surgery	
Neurosurgery, especially craniotomy for brain tumor	
THROMBOPHILIA	
Factor V Leiden mutation	
Prothrombin gene mutation	
Hyperhomocysteinanemia (including mutation in methylenetetrahydrofolate reductase)	
Antiphospholipid antibody syndrome	
Deficiency of antithrombin III, protein C, or protein S	
High concentrations of factor VIII or XI	
Increased lipoprotein (a)	
NONTHROMBOTIC	
Air	
Foreign particles (e.g., hair, talc, as a consequence of intravenous drug misuse)	
Amniotic fluid	
Bone fragments, bone marrow	
Fat	
Tumors (Wilms tumor)	

Modified from Goldhaber SZ: Pulmonary embolism, Lancet *363:1295–1305, 2004.*

In a retrospective cohort of patients with VTE from 2001-2007, pediatric malignancy was the medical condition most strongly associated with recurrent VTE.

In the neonatal period, thromboembolic disease and PE may be related to indwelling catheters used for parenteral nutrition and medication delivery. **Pulmonary thromboemboli** in neonates generally occurs as a complication of underlying disease; the most common associated diagnosis is congenital heart disease but sepsis and birth asphyxia are also notable associated conditions. Other risk factors include a relative immaturity of newborn infants' coagulation; plasma concentrations of vitamin K–dependent coagulation factors (II, VII, IX, X); factors XII, XI, and prekallikrein and high-molecular-weight kininogen are only approximately half of adult levels (see Chapter 475). PE in neonates may occasionally reflect maternal risk factors, such as diabetes and toxemia of pregnancy. Infants with congenitally acquired homozygous deficiencies of antithrombin, protein C, and protein S are also more likely to present with thromboembolic disease in the neonatal period (see Chapter 478).

Pulmonary air embolism is a defined entity in the newborn or young infant and is attributed to the conventional ventilation of critically ill (and generally premature) infants with severe pulmonary disease. In the majority of instances, the pulmonary air embolism is preceded by an air-leak syndrome. Infants may become symptomatic and critically compromised by as little as 0.4 mL/kg of intravascular air; these physiologic derangements are thought to be secondary to the effects of nitrogen.

Prothrombotic disease can also manifest in older infants and children. Disease can be congenital or acquired. **Inherited thrombophilic** conditions include deficiencies of antithrombin, protein C, and protein S, as well as mutations of *factor V Leiden* (G1691A) (see Chapter 478) and *prothrombin (factor II 20210A mutation)* (see Chapter 478), and elevated values of *lipoprotein A. In addition, multiple acquired thrombophilic conditions exist; these include the presence of lupus anticoagulant (may be present without the diagnosis of systemic lupus erythematosus), anticardiolipin antibody, and anti–β_2-glycoprotein 1 antibody*. Finally, conditions such as hyperhomocysteinemia (see Chapter 86) may have both inheritable and dietary determinants. All have all been linked to thromboembolic disease. DVT/PE may be the initial presentation.

Children with sickle cell disease are also at high risk for pulmonary embolus and infarction. Acquired prothrombotic disease is seen in conditions such as *nephrotic syndrome* (see Chapter 527) and *antiphospholipid antibody syndrome.* From one-quarter to one-half of children with *systemic lupus erythematosus* (see Chapter 158) have thromboembolic disease. There is a significant association with VTE onset in children for each inherited thrombophilic trait evaluated, thereby illuminating the importance of screening for thrombophilic conditions for those at risk for VTE.

Other risk factors include infection, cardiac disease, recent surgery, and trauma. Surgical risk is thought to be more significant when immobility will be a prominent feature of the recovery. Use of oral contraceptives confers additional risk, although the level of risk in patients taking these medications appears to be decreasing, perhaps as a result of the lower amounts of estrogen in current formulations.

Septic emboli are rare in children but may be caused by osteomyelitis, jugular vein or umbilical thrombophlebitis, cellulitis, urinary tract infection, and right-sided endocarditis.

EPIDEMIOLOGY

A retrospective cohort study was performed with patients younger than 18 yr of age, discharged from 35-40 children's hospitals across the United States from 2001-2007. During this time, a dramatic increase was noted in the incidence of VTE; the annual rate of VTE increased by 70% from 34 to 58 cases per 10,000 hospital admissions. Although this increased incidence was noted in all age groups, a bimodal distribution of patient ages was found, consistent with prior studies; infants younger than 1 yr of age and adolescents made up the majority of admissions with VTE, but neonates continue to be at greatest risk. The peak incidence for VTE in childhood appears to occur in the 1st mo of life. It is in this neonatal period that thromboembolic events are more problematic, likely as a result of an imbalance between procoagulant factors and fibrinolysis. According to a 2013 update by Nowak-Göttl et al, the yearly incidence of venous events was estimated at 5.3 per 10,000 hospital admissions in children and 24 per 10,000 in the neonatal intensive care.

Pediatric autopsy reviews have estimated the incidence of thromboembolic disease in children as between 1% and 4%, although not all were clinically significant. Thromboembolic pulmonary disease is often unrecognized, and antemortem studies may underestimate the true incidence. Pediatric deaths from isolated pulmonary emboli are rare. Most thromboemboli are related to central venous catheters. The source of the emboli may be lower or upper extremity veins as well as the pelvis and right heart. In adults, the most common location for DVT

is the lower leg. However, one of the largest pediatric VTE/PE registries found two-thirds of DVTs occurring in the upper extremity.

PATHOPHYSIOLOGY

Favorable conditions for thrombus formation include injury to the vessel endothelium, hemostasis, and hypercoagulability. In the case of PE, a thrombus is dislodged from a vein, travels through the right atrium and lodges within the pulmonary arteries. In children, emboli that obstruct <50% of the pulmonary circulation are generally clinically silent unless there is significant coexistent cardiopulmonary disease. In severe disease, **right ventricular** afterload is increased with resultant right ventricular dilation and increases in right ventricular and pulmonary arterial pressures. In severe cases, a reduction of cardiac output and hypotension may result from concomitant decreases in left ventricular filling. In rare instances of death from massive pulmonary embolus, marked increases in pulmonary vascular resistance and heart failure are usually present.

Arterial hypoxemia results from unequal ventilation and perfusion; the occlusion of the involved vessel prevents perfusion of distal alveolar units, thereby creating an increase in dead space and hypoxia with an elevated alveolar–arterial oxygen tension difference (see Chapter 373). Most patients are hypocarbic secondary to hyperventilation, which often persists even when oxygenation is optimized. Abnormalities of oxygenation and ventilation are likely to be less significant in the pediatric population, possibly owing to less underlying cardiopulmonary disease and greater reserve. The vascular supply to lung tissue is abundant, and pulmonary infarction is unusual with pulmonary embolus but may result from distal arterial occlusion and alveolar hemorrhage.

CLINICAL MANIFESTATIONS

Presentation is variable, and many pulmonary emboli are silent. Rarely, a massive PE may manifest as cardiopulmonary failure. Children are more likely to have underlying disease processes or risk factors but might still present asymptomatically with small emboli. Common symptoms and signs of PE caused by larger emboli include hypoxia (cyanosis), dyspnea, cough, pleuritic chest pain, and hemoptysis. Pleuritic chest pain is the most common presenting symptom in adolescents (84%), whereas unexplained and persistent tachypnea may suggest PE in all pediatric patients. Localized crackles may occasionally be appreciated on examination. A high level of clinical suspicion is required because a variety of diagnoses may cause similar symptoms; nonspecific complaints may frequently be attributed to an underlying disease process or an unrelated/incorrect diagnosis. Confirmatory testing should follow a clinical suspicion for PE. In adults, clinical prediction rules have been published and are based on risk factors, clinical signs, and symptoms. No such clinical prediction rules have been validated in the pediatric population.

LABORATORY FINDINGS AND DIAGNOSIS

The electrocardiogram, arterial blood gas, and chest radiograph may be utilized to rule out contributing or comorbid disease but are not sensitive or specific in the diagnosis of PE. Electrocardiographs may reveal ST-segment changes or evidence of pulmonary hypertension with right ventricular failure (cor pulmonale); such changes are nonspecific and nondiagnostic. Radiographic images of the chest are often normal in a child with PE and any abnormalities are likely to be nonspecific. Patients with septic emboli may have multiple areas of nodularity and cavitation, which are typically located peripherally in both lung fields. Many patients with PE have hypoxemia. The alveolar–arterial oxygen tension difference gradient is more sensitive in detecting gas exchange derangements.

A review of results of a complete blood count, urinalysis, and coagulation profile is warranted. Prothrombotic diseases should be highly suspected on the basis of past medical or family history; additional laboratory evaluations include fibrinogen assays, protein C, protein S, and antithrombin III studies, and analysis for factor V Leiden mutation, as well as evaluation for lupus anticoagulant and anticardiolipin antibodies.

Echocardiograms may be warranted to assess ventricular size and function. An echocardiogram is required if there is any suspicion of intracardiac thrombi or endocarditis.

Noninvasive venous ultrasound testing with Doppler flow can be used to confirm DVT in the lower extremities; ultrasonography may not detect thrombi in the upper extremities or pelvis (Fig. 407-1*A*). In patients with significant venous thrombosis, D dimers are usually elevated. It is a sensitive but nonspecific test for venous thrombosis. The D dimer may not be clinically relevant in the children with PE as this group is more likely to have an underlying comorbid condition that is also associated with an increased level of D dimers. When a high level of suspicion exists, confirmatory testing with venography should be pursued. DVT can be recurrent and multifocal and may lead to repeated episodes of PE.

Although a ventilation–perfusion ($\dot{V}$-$\dot{Q}$) radionuclide scan is a noninvasive and potentially sensitive method of pulmonary embolus detection, the interpretation of $\dot{V}$-$\dot{Q}$ scans can be problematic. Helical or spiral CT with an intravenous contrast agent is valuable and the diagnostic test of choice to detect a PE (see Fig. 407-1*B*). CT studies detect emboli in lobar and segmental vessels with acceptable sensitivities. Poorer sensitivities may be encountered in the evaluation of the subsegmental pulmonary vasculature. Pulmonary angiography is the

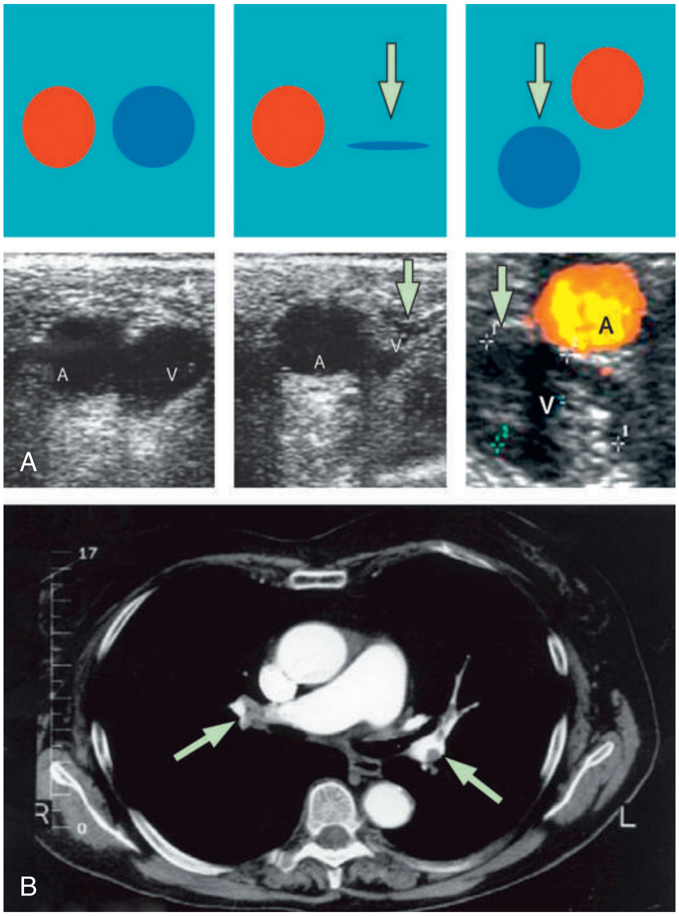

Figure 407-1 A, Compression ultrasound. Upper series, from left to right, representation of vein and artery without and with *(arrow)* gentle compression with the echocardiographic probe; lower series, corresponding echocardiographic findings. The third image from the left show a thrombus in the vein (vein not compressible by the probe). **B,** CT angiography. CT angiography showing several emboli (arrows) in the main right pulmonary artery and in left lobar and segmental arteries. A, artery; V, vein. *(From Goldhaber SZ, Bounameaux H: Pulmonary embolism and deep vein thrombosis.* Lancet *379:1835–1844, 2012, Fig. 2, p. 1838.)*

gold standard for diagnosis of PE, but with current availability of multidetector spiral CT angiography, it is not necessary except in unusual cases.

MRI may be emerging as a diagnostic option for patients with VTE. The accuracy of this method is similar to that of multidetector CT. It may be preferable in patients with allergic reactions to contrast material and in pediatric patients in whom the risk of early exposure to ionizing radiation has been established.

TREATMENT

Initial treatment should always be directed toward stabilization of the patient. Careful approaches to ventilation, fluid resuscitation, and inotropic support are always indicated, because improvement in 1 area of decompensation can often exacerbate coexisting pathology.

After the patient with a PE has been stabilized, the next therapeutic step is anticoagulation. Evaluations for prothrombotic disease must precede anticoagulation. Acute-phase anticoagulation therapy may be provided with **unfractionated heparin (UFH)** or **low-molecular-weight heparin (LMWH)**. Heparins act by enhancing the activity of antithrombin. LMWH is generally preferred in children; this drug can be administered subcutaneously and the need for serum monitoring is decreased. The risk of **heparin-induced thrombocytopenia** is also decreased with LMWH as compared to UFH. Alternatively, UFH is preferred with patients who have an elevated risk of bleeding as UFH has a shorter half-life than LMWH. UFH is also used preferentially in patients with compromised renal function. In monitoring of drug levels, laboratories must be aware of the drug chosen in order to use the appropriate assay. For UFH, the therapeutic range is 0.3-0.7 anti-Xa activity units/mL. In LMWH, the therapeutic range is 0.5-1.0 units/mL. When the anti-Xa assay is not available, the activated **partial thromboplastin time** may be used with a goal of 60-85 sec or approximately 1.5-2 times the upper limit of age appropriate normal values. The recommended duration of heparinization during acute treatment is 5-10 days; this length of therapy has been extrapolated from adult data. Long-term therapy with heparin should be avoided whenever possible. Side effects include the aforementioned heparin-induced thrombocytopenia as well as bleeding and osteoporosis.

Extension of anticoagulation therapy occurs in the subacute phase and may utilize LMWH or warfarin. Warfarin is generally initiated after establishing effective anticoagulation with heparin because severe congenital deficiencies of protein C may be associated with warfarin skin necrosis. The starting dose for warfarin in children is generally 0.1 mg/kg orally administered once daily. Monitoring is via the international normalized ratio (INR) and the therapeutic INR range for warfarin therapy in VTE is 2.0-3.0. The INR is generally monitored 5 days after initiating therapy or a similar period after dose changes and weekly thereafter until stable. The INR should be obtained with any evidence of abnormal bleeding and should be discontinued at least 5 days prior to invasive procedures. The utilization of an anticoagulation team and/or established treatment algorithms is recommended in order to optimize patient safety. With a first occurrence of VTE, anticoagulation is recommended for 3-6 mo in the setting of an identifiable, reversible, and resolved risk factor (e.g., postoperative state). Longer treatment is indicated in patients with idiopathic VTE (6-12 mo) and in those with chronic clinical risk factors (12 mo-lifelong). In the setting of a congenital thrombophilic condition, the duration of therapy is often indefinite.

Inhibitors of factor Xa (rivaroxaban, etc.) may become an alternate therapy for both acute PE and long-term treatment.

Thrombolytic agents such as recombinant tissue plasminogen activator, may be utilized in combination with anticoagulants in the early stages of treatment; their use is most likely to be considered in children with hemodynamically significant PE (echocardiogram evidence of right ventricular dysfunction) or other severe potential clinical sequelae of VTE. Combined therapy may reduce the incidences of progressive thromboembolism, pulmonary embolus, and post-thrombotic syndrome. Mortality rate appears to be unaffected by additional therapies; nonetheless, the additional theoretic risk of hemorrhage limits the use of combination therapy in all but the most compromised patients. The use of thrombolytic agents in patients with active bleeding, recent cerebrovascular accidents, or trauma is contraindicated.

Surgical embolectomy is invasive and is associated with significant mortality. Its application should be limited to those with persistent hemodynamic compromise refractory to standard therapy.

PROGNOSIS

Mortality in pediatric patients with PE is likely to be attributable to an underlying disease process rather than to the embolus itself. Short-term complications include major hemorrhage (either due to the thrombosis or secondary to anticoagulation). Conditions associated with a poorer prognosis include malignancy, infection, and cardiac disease. The mortality rate in children from PE is 2.2%. Recurrent thromboembolic disease may complicate recovery. The practitioner must conduct an extensive evaluation for underlying pathology so as to prevent progressive disease. Postthrombotic syndrome is another recognized complication of pediatric thrombotic disease. Venous valvular damage can be initiated by the presence of DVT, leading to persistent venous hypertension with ambulation and valvular reflux. Symptoms include edema, pain, increases in pigmentation, and ulcerations. Affected pediatric patients may suffer lifelong disability.

Bibliography is available at Expert Consult.

407.2 Pulmonary Hemorrhage and Hemoptysis

Mary A. Nevin

Pulmonary hemorrhage is relatively uncommon but a potentially fatal occurrence in children. The patient with suspected hemoptysis may present acutely or subacutely and to a variety of different practitioners with distinct areas of specialty. Diffuse, slow bleeding in the lower airways may become severe and manifest as anemia, fatigue, or respiratory compromise without the patient ever experiencing episodes of hemoptysis. Hemoptysis must also be separated from episodes of hematemesis or epistaxis, each of which may have indistinguishable presentations in the young patient.

ETIOLOGY

Tables 407-2 and 406-1 (in Chapter 406) present conditions that can manifest as pulmonary hemorrhage or hemoptysis in children. The chronic (opposed to an acute) presence of a foreign body can lead to inflammation and/or infection, thereby inducing hemorrhage. Bleeding is more likely to occur in association with a chronically retained foreign body of vegetable origin.

Hemorrhage most commonly reflects chronic inflammation and infection such as that seen with bronchiectasis due to cystic fibrosis or with cavitary disease in association with infectious tuberculosis. Hemoptysis may occasionally reflect an acute and intense infectious condition such as bronchitis or bronchopneumonia.

Other relatively common etiologies are congenital heart disease and trauma. Pulmonary hypertension secondary to cardiac disease is a prominent etiology for hemoptysis in those patients without cystic fibrosis. Traumatic irritation or damage in the airway may be accidental in nature. Traumatic injury to the airway and pulmonary contusion may result from motor vehicle crashes or other direct force injuries. Bleeding can also be related to instrumentation or iatrogenic irritation of the airway as is commonly seen in a child with a tracheostomy or a child with repeated suction trauma to the upper airway. Children who have been victims of nonaccidental trauma or deliberate suffocation can also be found to have blood in the mouth or airway (see Chapter 40). Fictitious hemoptysis may rarely be encountered in the setting of Factitious Disorder by Proxy (formerly Munchausen's by proxy; see Chapter 40.2).

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Table 407-2 Etiology of Pulmonary Hemorrhage (Hemoptysis)*

FOCAL HEMORRHAGE
Bronchitis and bronchiectasis (especially cystic fibrosis–related)
Infection (acute or chronic), pneumonia, abscess
Tuberculosis
Trauma
Pulmonary arteriovenous malformation
Foreign body (chronic)
Neoplasm including hemangioma
Pulmonary embolus with or without infarction
Bronchogenic cysts
DIFFUSE HEMORRHAGE
Idiopathic of infancy
Congenital heart disease (including pulmonary hypertension, venoocclusive disease, congestive heart failure)
Prematurity
Cow's milk hyperreactivity (Heiner syndrome)
Goodpasture syndrome
Collagen vascular diseases (systemic lupus erythematosus, rheumatoid arthritis)
Henoch-Schönlein purpura and vasculitic disorders
Granulomatous disease (granulomatosis with polyangiitis)
Celiac disease
Coagulopathy (congenital or acquired)
Malignancy
Immunodeficiency
Exogenous toxins
Hyperammonemia
Pulmonary hypertension
Pulmonary alveolar proteinosis
Idiopathic pulmonary hemosiderosis
Tuberous sclerosis
Lymphangiomyomatosis or lymphangioleiomyomatosis
Physical injury or abuse
Catamenial

*See also Table 406-1.

Rare causes for hemoptysis include tumors and vascular anomalies such as arteriovenous malformations (Fig. 407-2). Congenital vascular malformations in the lung may also be associated with **hereditary hemorrhagic telangiectasia**. Tumors must be cautiously investigated when encountered with a flexible fiberoptic bronchoscope as bleeding may be massive and difficult to control.

Syndromes associated with vasculitic, autoimmune, and idiopathic disorders can be associated with diffuse alveolar hemorrhage (see Chapter 406).

Acute idiopathic pulmonary hemorrhage of infancy is a distinct entity and is described as an episode of pulmonary hemorrhage in a previously healthy infant born at greater than 32 wk of gestation and whose age is less than 1 yr with the following: (1) abrupt or sudden onset of overt bleeding or frank evidence of blood in the airway, (2) severe presentation leading to acute respiratory distress or failure and requiring intensive care and invasive ventilatory support, and (3) diffuse bilateral infiltration on chest radiographs or computed tomography. Prior suggestions of an association between acute idiopathic pulmonary hemorrhage of infancy and toxic mold exposure have not been supported on subsequent review.

EPIDEMIOLOGY

The frequency with which pulmonary hemorrhage occurs in the pediatric population is difficult to define. This difficulty is largely related to the variability in disease presentation. Chronic bronchiectasis as seen in cystic fibrosis (see Chapter 403) or ciliary dyskinesia (see Chapter 404) can cause hemoptysis, but usually occurs in children older than 10 yr of age. The incidence of pulmonary hemorrhage may be significantly underestimated because many children and young adults swallow rather than expectorate mucus, a behavior that may prevent recognition of hemoptysis, the primary presenting symptom of the disorder.

PATHOPHYSIOLOGY

Pulmonary hemorrhage can be localized or diffuse. Focal hemorrhage from an isolated bronchial lesion is often secondary to infection or chronic inflammation. Erosion through a chronically inflamed airway into the adjacent bronchial artery is a mechanism for potentially massive hemorrhage. Bleeding from such a lesion is more likely to be bright red, brisk, and secondary to enlarged bronchial arteries and systemic arterial pressures. The severity of more diffuse hemorrhage can be difficult to ascertain. The rate of blood loss may be insufficient to reach the proximal airways. Therefore, the patient may present without hemoptysis. The diagnosis of pulmonary hemorrhage is generally achieved by finding evidence of blood or hemosiderin in the lung. Within 48-72 hr of an episode of bleeding, alveolar macrophages convert the iron from erythrocytes into hemosiderin. It may take weeks to clear these hemosiderin-laden macrophages completely from the alveolar spaces. This fact may allow differentiation between acute and chronic hemorrhage. Hemorrhage is often followed by the influx of neutrophils and other proinflammatory mediators. With repeated or chronic hemorrhage, pulmonary fibrosis can become a prominent pathologic finding.

CLINICAL MANIFESTATIONS

The severity of presentation in patients with hemoptysis and pulmonary hemorrhage is highly variable. Older children and young adults with a focal hemorrhage may complain of warmth or a "bubbling" sensation in the chest wall. This can occasionally aid the clinician in locating the area involved. Rapid and large-volume blood loss manifests as symptoms of cyanosis, respiratory distress, and shock. Chronic, subclinical blood loss may manifest as anemia, fatigue, dyspnea, or altered activity tolerance. Less commonly, patients present with persistent infiltrates on chest radiograph or symptoms of chronic illness such as failure to thrive.

Pulmonary arteriovenous malformations may present with hemoptysis, hemothorax, a round localized mass on x-ray or CT, clubbing, cyanosis, or embolic phenomenon.

LABORATORY FINDINGS AND DIAGNOSIS

A patient with suspected hemorrhage should have a laboratory evaluation with complete blood count and coagulation studies. The complete blood count result may demonstrate a microcytic, hypochromic anemia but may be normal early in an acute bleeding episode. If iron stores are sufficient, a reticulocytosis may be present. Other laboratory findings are highly dependent on the underlying diagnosis. A urinalysis may show evidence of nephritis in patients with a comorbid pulmonary renal syndrome. The classic and definitive finding in pulmonary hemorrhage is that of **hemosiderin-laden macrophages** in pulmonary secretions. Hemosiderin-laden macrophages may be detected by sputum analysis with Prussian blue staining when a patient is able to successfully expectorate sputum from the lower airways. In younger children, or in weak or neurodevelopmentally compromised patients unable to expectorate sputum, induced sputum may provide an acceptable specimen; alternatively, a flexible bronchoscopy with **bronchoalveolar lavage** may be required for specimen retrieval.

Chest radiographs may demonstrate fluffy bilateral densities, as seen in acute idiopathic pulmonary hemorrhage of infancy (Fig. 407-3) or the patchy consolidation seen in idiopathic pulmonary hemosiderosis (Fig. 407-4). Alveolar infiltrates seen on chest radiograph may be regarded as a representation of recent bleeding, but their absence does not rule out the occurrence of pulmonary hemorrhage. Infiltrates, when present, are often symmetric and diffuse and may be preferentially located in the perihilar regions and lower lobes. The costophrenic angles and lung apices are frequently spared. CT may be indicated to assess for underlying disease processes.

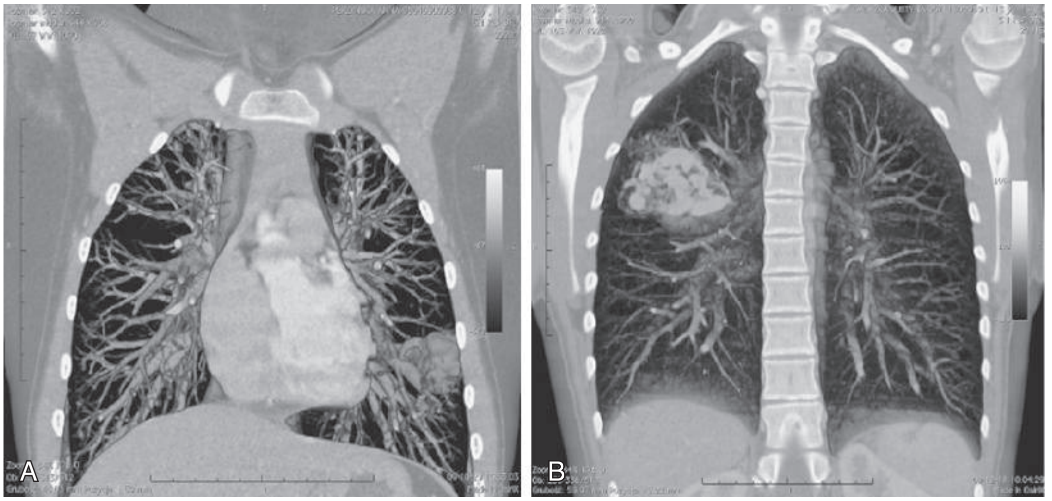

Figure 407-2 **A,** Volume-rendering reconstruction of the contrast-enhanced spiral CT showing a large arteriovenous fistula in the left upper lobe (lingula). **B,** Volume-rendering reconstruction of the contrast-enhanced spiral CT showing an arteriovenous fistula in the right upper lobe. *(From Grzela K, Krenke K, Kulus M: Pulmonary arteriovenous malformations: clinical and radiological presentation.* J Pediatr *158:856, 2011, Figs. 1 and 2, p. 856.)*

Figure 407-3 Radiographic appearance of acute idiopathic pulmonary hemorrhage in infancy. *(From Brown CM, Redd SC, Damon SA; Centers for Disease Control and Prevention [CDC]: Acute idiopathic pulmonary hemorrhage among infants: recommendations from the Working Group for Investigation and Surveillance,* MMWR Recomm Rep *53:1–12, 2004.)*

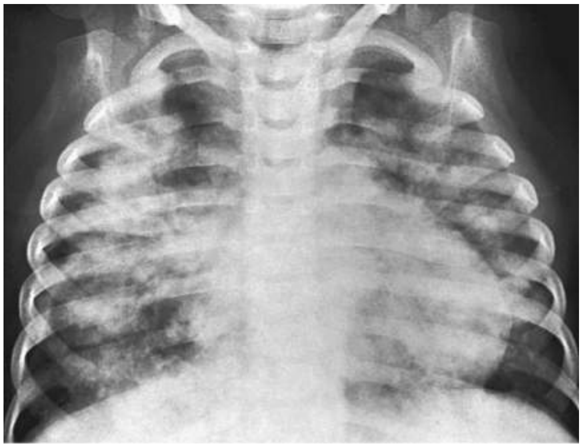

Figure 407-4 Diffuse pulmonary hemorrhage that was thought to be the result of idiopathic pulmonary hemosiderosis in a 3 yr old boy. Frontal radiograph reveals bilateral airspace consolidation that is patchy. Tracheal washing contained large numbers of macrophages filled with hemosiderin. Ten days later, most of the consolidative changes in the lungs had cleared. The patient's anemia was successfully treated with blood transfusion. *(From Slovis T, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby/Elsevier; courtesy of Bertram Girdany, MD, Pittsburgh, PA.)*

Lung biopsy is rarely necessary unless bleeding is chronic or an etiology cannot be determined with other methods. Pulmonary function testing, including a determination of gas exchange, is important to assess the severity of the ventilatory defect. In older children, spirometry may demonstrate evidence of predominantly obstructive disease in the acute period. Restrictive disease secondary to fibrosis is typically seen with more chronic disease. Diffusion capacity of carbon monoxide measurements are typically elevated in the setting of pulmonary hemorrhage because of the strong affinity of the intra-alveolar hemoglobin for carbon monoxide.

TREATMENT

In the setting of massive blood loss, volume resuscitation and transfusion of blood products are necessary. Maintenance of adequate ventilation and circulatory function is crucial. Rigid bronchoscopy may be utilized for localization of bleeding and for removal of debris but active bleeding may be exacerbated by airway manipulation. Flexible bronchoscopy and bronchoalveolar lavage may be required for diagnosis. Ideally, treatment is directed at the specific pathologic process responsible for the hemorrhage. When bronchiectasis is a known entity and a damaged artery can be localized, bronchial artery embolization is often the therapy of choice. If embolization fails, total or partial lobectomy may be required. Embolization is the initial treatment of choice for an arteriovenous malformation. In circumstances of diffuse hemorrhage, corticosteroids and other immunosuppressive agents have been shown to be of benefit. Prognosis depends largely on the underlying disease process and the chronicity of bleeding.

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Chapter 408
Atelectasis

Ranna A. Rozenfeld

Atelectasis is the incomplete expansion or complete collapse of air-bearing tissue, resulting from obstruction of air intake into the alveolar sacs. Segmental, lobar, or whole lung collapse is associated with the absorption of air contained in the alveoli, which are no longer ventilated.

PATHOPHYSIOLOGY

The causes of atelectasis can be divided into 5 groups (Table 408-1). Respiratory syncytial virus (see Chapter 260) and other viral infections, including influenza viruses in young children can cause multiple areas of atelectasis. Mucous plugs are a common predisposing factor to atelectasis. Massive collapse of 1 or both lungs is most often a postoperative complication but occasionally results from other causes, such as trauma, asthma, pneumonia, tension pneumothorax (see Chapter 411), aspiration of foreign material (see Chapters 387 and 397), and paralysis, or after extubation. Massive atelectasis is usually produced by a combination of factors, including immobilization or decreased use of the diaphragm and the respiratory muscles, obstruction of the bronchial tree, and abolition of the cough reflex.

CLINICAL MANIFESTATIONS

Symptoms vary with the cause and extent of the atelectasis. A small area is likely to be asymptomatic. When a large area of previously normal lung becomes atelectatic, especially when it does so suddenly, dyspnea accompanied by rapid shallow respirations, tachycardia, cough, and often cyanosis occurs. If the obstruction is removed, the symptoms disappear rapidly. Although it was once believed that atelectasis alone can cause fever, studies have shown no association between atelectasis and fever. Physical findings include limitation of chest excursion, decreased breath sound intensity, and coarse crackles. Breath sounds are decreased or absent over extensive atelectatic areas.

Table 408-1 Anatomic Causes of Atelectasis

CAUSE	CLINICAL EXAMPLES
External compression on the pulmonary parenchyma	Pleural effusion, pneumothorax, intrathoracic tumors, diaphragmatic hernia
Endobronchial obstruction completely obstructing the ingress of air	Enlarged lymph node, tumor, cardiac enlargement, foreign body, mucoid plug, broncholithiasis
Intraluminal obstruction of a bronchus	Foreign body, asthma, granulomatous tissue, tumor, secretions including mucous plugs, bronchiectasis, pulmonary abscess, chronic bronchitis, acute laryngotracheobronchitis, plastic bronchitis
Intrabronchiolar obstruction	Bronchiolitis, interstitial pneumonitis, asthma
Respiratory compromise or paralysis	Neuromuscular abnormalities, osseous deformities, overly restrictive casts and surgical dressings, defective movement of the diaphragm, or restriction of respiratory effort

Massive pulmonary atelectasis usually presents with dyspnea, cyanosis, and tachycardia. An affected child is extremely anxious and, if old enough, complains of chest pain. The chest appears flat on the affected side, where decreased respiratory excursion, dullness to percussion, and feeble or absent breath sounds are also noted. Postoperative atelectasis usually manifests within 24 hr of operation but may not occur for several days.

Acute lobar collapse is a frequent occurrence in patients receiving intensive care. If undetected, it can lead to impaired gas exchange, secondary infection, and subsequent pulmonary fibrosis. Initially, hypoxemia may result from ventilation-perfusion mismatch. In contrast to atelectasis in adult patients, in whom the lower lobes and, in particular, the left lower lobe are most often involved, 90% of cases in children involve the upper lobes and 63% involve the right upper lobe. There is also a high incidence of upper lobe atelectasis and, especially, right upper lobe collapse in patients with atelectasis being treated in neonatal intensive care units. This high incidence may be a result of movement of the endotracheal tube into the right mainstem bronchus, where it obstructs or causes inflammation of the bronchus to the right upper lobe.

DIAGNOSIS

The diagnosis of atelectasis can usually be established by chest radiographic examination. Typical findings include volume loss and displacement of fissures. Atypical presentations include atelectasis manifesting as a mass like opacity and atelectasis in an unusual location. Lobar atelectasis may be associated with pneumothorax.

In asthmatic children, chest radiography demonstrates an abnormality rate of 44%, compared with a thorax high-resolution CT scan abnormality rate of 75%. Children with asthma and atelectasis have an increased incidence of right middle lobe syndrome, acute asthma exacerbations, pneumonia, and upper airway infections.

In foreign-body aspiration, atelectasis is one of the most common radiographic findings. The site of atelectasis usually indicates the site of the foreign body (see Chapter 377.1). Atelectasis is more common when diagnosis of foreign-body aspiration is delayed for greater than 2 wk.

Bronchoscopic examination reveals a collapsed main bronchus when the obstruction is at the tracheobronchial junction and may also disclose the nature of the obstruction.

Massive pulmonary atelectasis is generally diagnosed on chest radiograph. Typical findings include elevation of the diaphragm, narrowing of the intercostal spaces, and displacement of the mediastinal structures and heart toward the affected side (Fig. 408-1).

TREATMENT

Treatment depends on the cause of the collapse. If effusion or pneumothorax is responsible, the external compression must first be removed. Often vigorous efforts at cough, deep breathing, and percussion will facilitate expansion. Aspiration with sterile tracheal catheters may facilitate removal of mucous plugs. Continuous positive airway pressure may improve atelectasis.

Bronchoscopic examination is immediately indicated if atelectasis is the result of a foreign body or any other bronchial obstruction that can be relieved. For bilateral atelectasis, bronchoscopic aspiration should also be performed immediately. It is also indicated when an isolated area of atelectasis persists for several weeks. If no anatomic basis for atelectasis is found and no material can be obtained by suctioning, the introduction of a small amount of saline followed by suctioning allows recovery of bronchial secretions for culture and, possibly, for cytologic examination. Frequent changes in the child's position, deep breathing, and chest physiotherapy may be beneficial. Intrapulmonary percussive ventilation is a chest physiotherapy technique that is safe and effective. Oxygen therapy is indicated when there is dyspnea or desaturation. Intermittent positive-pressure breathing and incentive spirometry are recommended when atelectasis does not improve after chest physiotherapy.

In some conditions, such as asthma, bronchodilator and corticosteroid treatment may accelerate atelectasis clearance. Recombinant

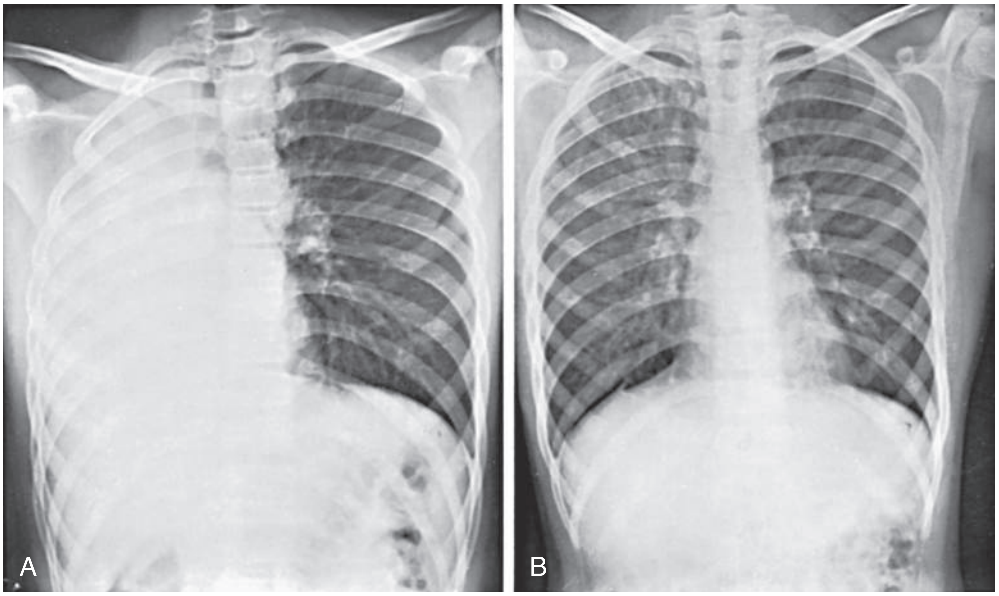

Figure 408-1 **A,** Massive atelectasis of the right lung. The patient has asthma. The heart and other mediastinal structures shift to the right during the atelectatic phase. **B,** Comparison study after reaeration subsequent to bronchoscopic removal of a mucous plug from the right mainstem bronchus.

human deoxyribonuclease, which is approved only for the treatment of cystic fibrosis, has been used off-label for patients without cystic fibrosis who have persistent atelectasis. This product reduces the viscosity of purulent bronchial debris. In patients with acute severe asthma, diffuse airway plugging with thick viscous secretions frequently occurs, with the resulting atelectasis often refractory to conventional therapy. Recombinant human deoxyribonuclease is used in both nebulized form for nonintubated patients with acute asthma as well as intratracheally for atelectasis in intubated asthmatics, with resolution of atelectasis unresponsive to conventional asthma therapies. Recombinant human deoxyribonuclease is also utilized in ventilated infants and children with atelectasis not caused by asthma.

Hypertonic saline solution increases mucociliary clearance in patients with asthma, bronchiectasis, and cystic fibrosis and infants with acute bronchiolitis. It is delivered via nebulization either via face mask or endotracheal tube. It can be delivered alone or in combination with a bronchodilator. This therapy is being utilized in the outpatient and inpatient setting, as well as in both the neonatal intensive care unit and the pediatric intensive care unit, to help facilitate airway clearance.

Lobar atelectasis in cystic fibrosis is discussed in Chapter 403.

Atelectasis can occur in patients with neuromuscular diseases. These patients tend to have ineffective cough and difficulty expelling respiratory tract secretions, which lead to pneumonia and atelectasis. Several devices and treatments are available to assist these patients, including intermittent positive-pressure breathing, a mechanical insufflator–exsufflator, and noninvasive bilevel positive-pressure ventilation via nasal mask or full-face mask. Patients with neuromuscular disease who have undergone surgery are at substantial risk for postoperative atelectasis and subsequent pneumonia. Migrating atelectasis in the newborn infant, a rare and unique presentation, may be secondary to neuromuscular disease.

There is an association between the development of lobar collapse and the requirement for mechanical ventilation. Although lobar collapse is rarely a cause of long-term morbidity, its occurrence may necessitate the prolongation of mechanical ventilation or re-intubation.

Table 408-2	Benefit of Airway Clearance Therapies in Pediatric Conditions
CLEAR AND PROVEN BENEFIT Cystic fibrosis	
PROBABLE BENEFIT Neuromuscular disease Cerebral palsy Atelectasis in children undergoing mechanical ventilation	
POSSIBLE BENEFIT Prevention of postextubation atelectasis in neonates	
MINIMAL TO NO BENEFIT Acute asthma Bronchiolitis Hyaline membrane disease Respiratory failure without atelectasis Prevention of atelectasis immediately following surgery	

From Schechter MS: Airway clearance applications in infants and children, Respir Care *52:1382–1390, 2007.*

In ventilated patients, positive end-expiratory pressure or continuous positive airway pressure is generally indicated.

Airway clearance therapies utilized for adults are often recommended and/or utilized in pediatric populations. However, given the differences in respiratory physiology and anatomy between children and adults, practices applicable to one may or may not apply to the other. Atelectasis caused by cystic fibrosis is the only pediatric entity that clearly benefits from airway clearance therapy, although atelectasis caused by neuromuscular disease, cerebral palsy, or mechanical ventilation probably benefits from such therapy (Table 408-2). Thus far no specific airway clearance therapy has been demonstrated to be superior.

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Chapter **409**

Pulmonary Tumors

Susanna A. McColley

ETIOLOGY

Primary tumors of the lung are rare in children and adolescents. An accurate estimate of frequency is currently not possible because the literature is composed of case reports and case series. A high incidence of "inflammatory pseudotumors" further clouds the statistics. **Bronchial adenomas (including bronchial carcinoid, adenoid cystic carcinoma** and **mucoepidermoid carcinomas)** are the most common primary tumors; bronchial carcinoid tumors represent ≈80%. Carcinoids are low-grade malignancies; carcinoid syndrome is rare in children. Metastatic lesions are the most common forms of pulmonary malignancy in children; primary processes include Wilms tumor, osteogenic sarcoma, and hepatoblastoma (see Part XXII: Cancer and Benign Tumors). Adenocarcinoma and undifferentiated histology are the most common pathologic findings in primary lung cancer; pulmonary blastoma is rarer and frequently occurs in the setting of cystic lung disease. Mediastinal involvement with lymphoma is more common than primary pulmonary malignancies.

CLINICAL MANIFESTATIONS AND EVALUATION

Pulmonary tumors may manifest as fever, hemoptysis, wheezing, cough, pleural effusion, chest pain, dyspnea, or recurrent or persistent pneumonia or atelectasis. Localized wheezing, and wheezing unresponsive to bronchodilators, can occur with bronchial tumors. Tumors may be suspected from plain chest radiographs; CT scanning of the chest is necessary for precise anatomic definition (Fig. 409-1). Depending on the tumor size and location, pulmonary function tests may be normal or show an obstructive, restrictive, or mixed pattern; as with the physical exam, there is no responsiveness to bronchodilators. Bronchial tumors are occasionally diagnosed during fiberoptic bronchoscopy performed for persistent or recurrent pulmonary infiltrates or for hemoptysis.

Patients with symptoms or with radiographic or other laboratory findings suggesting pulmonary malignancy should be evaluated carefully for a tumor at another site before surgical excision is carried out. Isolated primary lesions and isolated metastatic lesions discovered long after the primary tumor has been removed are best treated by excision. The prognosis varies and depends on the type of tumor involved; outcomes for inflammatory pseudotumors and primary pulmonary carcinoid tumors treated with resection are good.

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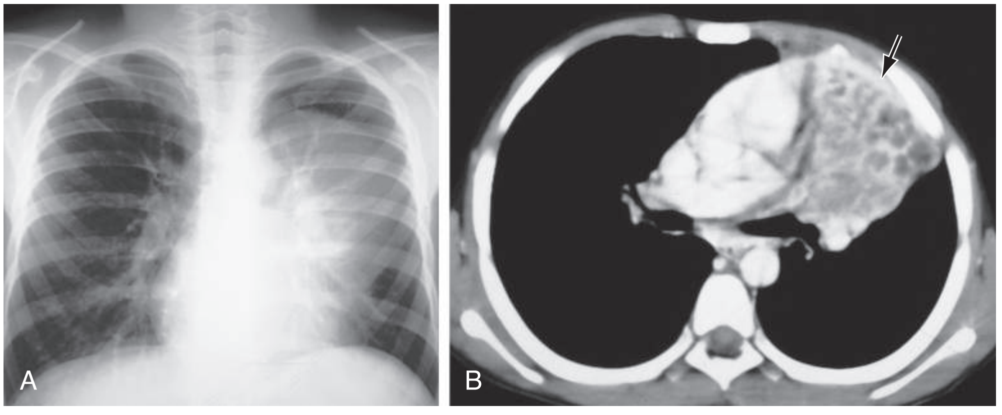

Figure 409-1 Endobronchial mucoepidermoid carcinoma in a 10 yr old boy who presented with cough and fever. **A,** The chest radiograph shows a left upper lobe mass, a hyperinflated left lower lobe, and a prominent left hilum. **B,** The CT scan shows complete obstruction of the left upper lobe bronchus by a low-attenuation mass that extends into the left mainstem bronchus. *(From Slovis TL, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, Fig. 78-20.)*

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Chapter 410

Pleurisy, Pleural Effusions, and Empyema

Glenna B. Winnie and Steven V. Lossef

Pleurisy is the inflammation of the pleura; it may be accompanied by an effusion. The most common cause of pleural effusion in children is bacterial pneumonia (see Chapter 400); heart failure (see Chapter 442), rheumatologic causes, and metastatic intrathoracic malignancy are the next most common causes. A variety of other diseases account for the remaining cases, including tuberculosis (see Chapter 215), lupus erythematosus (see Chapter 158), aspiration pneumonitis (see Chapter 397), uremia, pancreatitis, subdiaphragmatic abscess, and rheumatoid arthritis. Males and females are affected equally.

Inflammatory processes in the pleura are usually divided into 3 types: dry or plastic, serofibrinous or serosanguineous, and purulent pleurisy or empyema.

410.1 Dry or Plastic Pleurisy (Pleural Effusion)

Glenna B. Winnie and Steven V. Lossef

ETIOLOGY

Plastic pleurisy may be associated with acute bacterial or viral pulmonary infections or may develop during the course of an acute upper respiratory tract illness. The condition is also associated with tuberculosis and connective tissue diseases such as rheumatic fever.

PATHOLOGY AND PATHOGENESIS

The process is usually limited to the visceral pleura, with small amounts of yellow serous fluid and adhesions between the pleural surfaces. In tuberculosis, the adhesions develop rapidly and the pleura are often thickened. Occasionally, fibrin deposition and adhesions are severe enough to produce a fibrothorax that markedly inhibits the excursions of the lung.

CLINICAL MANIFESTATIONS

The primary disease often overshadows signs and symptoms. Pain, the principal symptom, is exaggerated by deep breathing, coughing, and straining. Occasionally, pleural pain is described as a dull ache, which is less likely to vary with breathing. The pain is often localized over the chest wall and is referred to the shoulder or the back. Pain with breathing is responsible for grunting and guarding of respirations, and the child often lies on the affected side in an attempt to decrease respiratory excursions. Early in the illness, a leathery, rough, inspiratory and expiratory friction rub may be audible, but it usually disappears rapidly. If the layer of exudate is thick, increased dullness to percussion and decreased breath sounds may be heard. Pleurisy may be asymptomatic. Chronic pleurisy is occasionally encountered with conditions such as atelectasis, pulmonary abscess, connective tissue diseases, and tuberculosis.

LABORATORY FINDINGS

Plastic pleurisy may be detected on radiographs as a diffuse haziness at the pleural surface or a dense, sharply demarcated shadow (Figs. 410-1 and 410-2). The latter finding may be indistinguishable from small amounts of pleural exudate. Chest radiographic findings may be normal, but ultrasonography or CT findings will be positive.

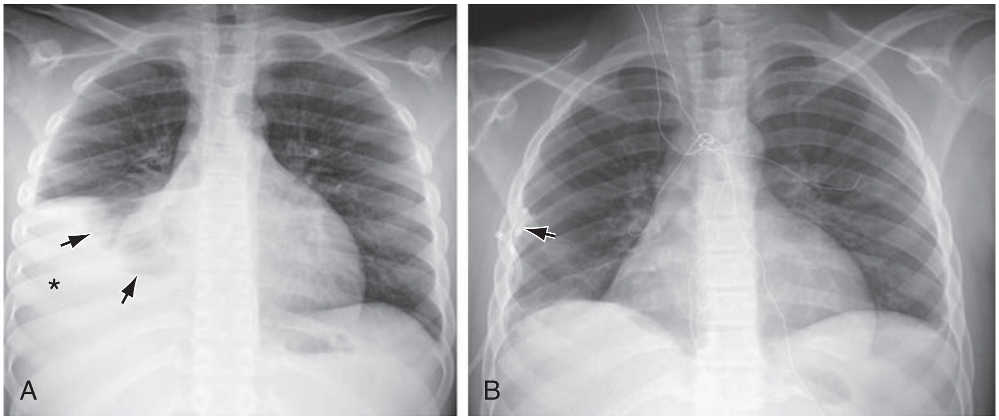

Figure 410-1 **A,** Right pleural effusion *(asterisk)* caused by lupus erythematosus in a 12 yr old child. Note compressed middle and lower lobes of the right lung *(arrows)*. **B,** The effusion was evacuated and the right lung was completely reexpanded after insertion of the pigtail chest tube *(arrow)*.

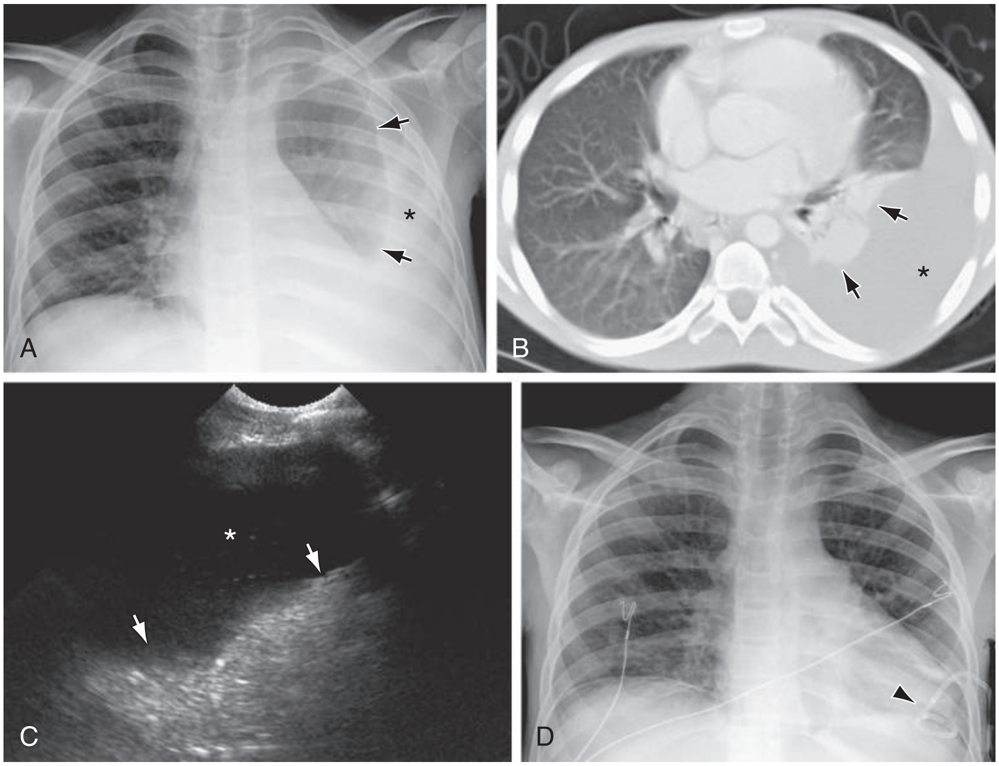

Figure 410-2 **Left pleural effusion in a teenager with AIDS and *Mycobacterium avium-intracellulare* infection.** The pleural effusion *(asterisk)* is clearly seen on the chest radiograph **(A),** CT scan **(B),** and ultrasonogram **(C)** of the left chest. *Arrows* point to the compressed and atelectatic left lung. **D,** A pigtail chest tube (*arrowhead*) was inserted, resulting in reexpansion of the left lung.

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DIFFERENTIAL DIAGNOSIS

Plastic pleurisy must be distinguished from other diseases, such as epidemic pleurodynia, trauma to the rib cage (rib fracture), lesions of the dorsal root ganglia, tumors of the spinal cord, herpes zoster, gallbladder disease, and trichinosis. Even if evidence of pleural fluid is not found on physical or radiographic examination, a CT- or ultrasound-guided pleural tap in suspected cases often results in the recovery of a small amount of exudate, which when cultured may reveal the underlying bacterial cause in patients with an acute pneumonia. Patients with pleurisy and pneumonia should always be screened for tuberculosis.

TREATMENT

Therapy should be aimed at the underlying disease. When pneumonia is present, neither immobilization of the chest with adhesive plaster nor therapy with drugs capable of suppressing the cough reflex is indicated. If pneumonia is not present or is under good therapeutic control, strapping of the chest to restrict expansion may afford relief from pain. Analgesia with nonsteroidal antiinflammatory agents may be helpful.

Bibliography is available at Expert Consult.

410.2 Serofibrinous or Serosanguineous Pleurisy (Pleural Effusion)

Glenna B. Winnie

ETIOLOGY

Serofibrinous pleurisy is defined by a fibrinous exudate on the pleural surface and an exudative effusion of serous fluid into the pleural cavity. Generally it is associated with infections of the lung or with inflammatory conditions of the abdomen or mediastinum; occasionally, it is found with connective tissue diseases such as lupus erythematosus, periarteritis, and rheumatoid, arthritis, and it may be seen with primary or metastatic neoplasms of the lung, pleura, or mediastinum; tumors are commonly associated with a hemorrhagic pleurisy.

PATHOGENESIS

Pleural fluid originates from the capillaries of the parietal pleura and is absorbed from the pleural space via pleural stomas and the lymphatics of the parietal pleura. The rate of fluid formation is dictated by the Starling law, by which fluid movement is determined by the balance of hydrostatic and osmotic pressures in the pleural space and pulmonary capillary bed, and the permeability of the pleural membrane. Normally, only 4-12 mL of fluid is present in the pleural space, but if formation exceeds clearance, fluid accumulates. Pleural inflammation increases the permeability of the plural surface, with increased proteinaceous fluid formation; there may also be some obstruction to lymphatic absorption.

CLINICAL MANIFESTATIONS

Because serofibrinous pleurisy is often preceded by the plastic type, early signs and symptoms may be those of plastic pleurisy. As fluid accumulates, pleuritic pain may disappear. The patient may become asymptomatic if the effusion remains small, or there may be only signs and symptoms of the underlying disease. Large fluid collections can produce cough, dyspnea, retractions, tachypnea, orthopnea, or cyanosis.

Physical findings depend on the amount of effusion. Dullness to flatness may be found on percussion. Breath sounds are decreased or absent, and there are a diminution in tactile fremitus, a shift of the mediastinum away from the affected side, and, occasionally, fullness of the intercostal spaces. If the fluid is not loculated, these signs may shift with changes in position. If extensive pneumonia is present, crackles and rhonchi may also be audible. Friction rubs are usually detected only during the early or late plastic stage. In infants, physical signs are less definite, and bronchial breathing may be heard instead of decreased breath sounds.

LABORATORY FINDINGS

Radiographic examination shows a generally homogeneous density obliterating the normal markings of the underlying lung. Small effusions may cause obliteration of only the costophrenic or cardiophrenic angles or a widening of the interlobar septa. Examinations should be performed with the patient both supine and upright, to demonstrate a shift of the effusion with a change in position; the decubitus position may be helpful. **Ultrasonographic** examinations are useful and may guide thoracentesis if the effusion is loculated. Examination of the fluid is essential to differentiate exudates from transudates and to determine the type of exudate. Depending on the clinical scenario, pleural fluid is sent for culture for bacterial, fungal, and mycobacterial cultures; antigen testing; Gram staining; and chemical evaluation of content, including protein, lactic dehydrogenase and glucose, amylase, specific gravity, total cell count and differential, cytologic examination, and pH. Complete blood count and serum chemistry analysis should be obtained; hypoalbuminemia is often present. **Exudates** usually have at least 1 of the following features: protein level >3.0 g/dL, with pleural fluid : serum protein ratio >0.5; pleural fluid lactic dehydrogenase values >200 IU/L; or fluid : serum lactic dehydrogenase ratio >0.6. Although systemic acidosis reduces the usefulness of pleural fluid pH measurements, pH <7.20 suggests an exudate (see Chapter 400). Glucose is usually <60 mg/dL in malignancy, rheumatoid disease, and tuberculosis; the finding of many small lymphocytes and a pH <7.20 suggest tuberculosis. The fluid of serofibrinous pleurisy is clear or slightly cloudy and contains relatively few leukocytes and, occasionally, some erythrocytes. Gram staining may occasionally show bacteria; however, acid-fast staining rarely demonstrates tubercle bacilli.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Thoracentesis should be performed when pleural fluid is present or is suggested, unless the effusion is small and the patient has a classic-appearing lobar pneumococcal pneumonia. Thoracentesis can differentiate serofibrinous pleurisy, empyema, hydrothorax, hemothorax, and chylothorax. Exudates are usually associated with an infectious process. In hydrothorax, the fluid has a specific gravity <1.015, and evaluation reveals only a few mesothelial cells rather than leukocytes. Chylothorax and hemothorax usually have fluid with a distinctive appearance, but differentiating serofibrinous from purulent pleurisy is impossible without microscopic examination of the fluid. Cytologic examination may reveal malignant cells. Serofibrinous fluid may rapidly become purulent.

COMPLICATIONS

Unless the fluid becomes purulent, it usually disappears relatively rapidly, particularly with appropriate treatment of bacterial pneumonia. It persists somewhat longer if a result of tuberculosis or a connective tissue disease and may recur or remain for a long time if caused by a neoplasm. As the effusion is absorbed, adhesions often develop between the 2 layers of the pleura, but usually little or no functional impairment results. Pleural thickening may develop and is occasionally mistaken for small quantities of fluid or for persistent pulmonary infiltrates. Pleural thickening may persist for months, but the process usually disappears, leaving no residua.

TREATMENT

Therapy should address the underlying disease. With a large effusion, draining the fluid makes the patient more comfortable. When a diagnostic thoracentesis is performed, as much fluid as possible should be removed for therapeutic purposes. Rapid removal of ≥1 L of pleural fluid may be associated with the development of reexpansion pulmonary edema (see Chapter 396). If the underlying disease is adequately treated, further drainage is usually unnecessary, but if sufficient fluid reaccumulates to cause respiratory embarrassment, chest tube drainage should be performed. In older children with suspected parapneumonic effusion, tube thoracostomy is considered necessary if the pleural fluid pH is <7.20 or the pleural fluid glucose level is <50 mg/dL. If the fluid is clearly purulent, tube drainage with **thrombolytic therapy** or less often video-assisted thoracoscopic surgery (VATS) is indicated.

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Patients with pleural effusions may need analgesia, particularly after thoracentesis or insertion of a chest tube. Those with acute pneumonia may need supplemental oxygen in addition to specific antibiotic treatment.

Bibliography is available at Expert Consult.

410.3 Purulent Pleurisy or Empyema

Glenna B. Winnie and Steven V. Lossef

ETIOLOGY

Empyema is an accumulation of pus in the pleural space. It is most often associated with pneumonia (see Chapter 400) caused by *Streptococcus pneumoniae* (see Chapter 182), although *Staphylococcus aureus* (see Chapter 181.1) is most common in developing nations and Asia, as well as in posttraumatic empyema. The relative incidence of *Haemophilus influenzae* (see Chapter 194) empyema has decreased since the introduction of the *H. influenzae* type b vaccination. Group A streptococcus, Gram-negative organisms, tuberculosis, fungi, and malignancy are less common causes. The disease can also be produced by rupture of a lung abscess into the pleural space, by contamination introduced from trauma or thoracic surgery, or, rarely, by mediastinitis or the extension of intraabdominal abscesses.

EPIDEMIOLOGY

Empyema is most frequently encountered in infants and preschool children. It is increasing in frequency. It occurs in 5-10% of children with bacterial pneumonia and in up to 86% of children with necrotizing pneumonia.

PATHOLOGY

Empyema has 3 stages: exudative, fibrinopurulent, and organizational. During the **exudative stage**, fibrinous exudate forms on the pleural surfaces. In the **fibrinopurulent stage**, fibrinous septa form, causing loculation of the fluid and thickening of the parietal pleura. If the pus is not drained, it may dissect through the pleura into lung parenchyma, producing bronchopleural fistulas and pyopneumothorax, or into the abdominal cavity. Rarely, the pus dissects through the chest wall (i.e., empyema necessitatis). During the **organizational stage**, there is fibroblast proliferation; pockets of loculated pus may develop into thick-walled abscess cavities or the lung may collapse and become surrounded by a thick, inelastic envelope (peel).

CLINICAL MANIFESTATIONS

The initial signs and symptoms are primarily those of bacterial pneumonia. Children treated with antibiotic agents may have an interval of a few days between the clinical pneumonia phase and the evidence of empyema. Most patients are febrile, develop increased work of breathing or respiratory distress, and often appear more ill. Physical findings are identical to those described for serofibrinous pleurisy, and the 2 conditions are differentiated only by thoracentesis, which should always be performed when empyema is suspected.

LABORATORY FINDINGS

Radiographically, all pleural effusions appear similar, but the absence of a shift of the fluid with a change of position indicates a loculated empyema (Figs. 410-3 to 410-5). Septa may be confirmed by ultrasonography or CT. The maximal amount of fluid obtainable should be withdrawn by thoracentesis and studied as described in Chapter 410.2. The effusion is empyema if bacteria are present on Gram staining, the pH is <7.20, and there are >100,000 neutrophils/µL (see Chapter 400). The appearance of pus produced by different organisms is not distinctive; cultures of the fluid must always be performed. In pneumococcal empyema, the culture is positive in 58% of cases. In patients with negative culture results for pneumococcus, the pneumococcal polymerase chain reaction analysis is most helpful to making a diagnosis. Blood cultures may be positive and have a higher yield than cultures of the pleural fluid. Leukocytosis and an elevated sedimentation rate may be found.

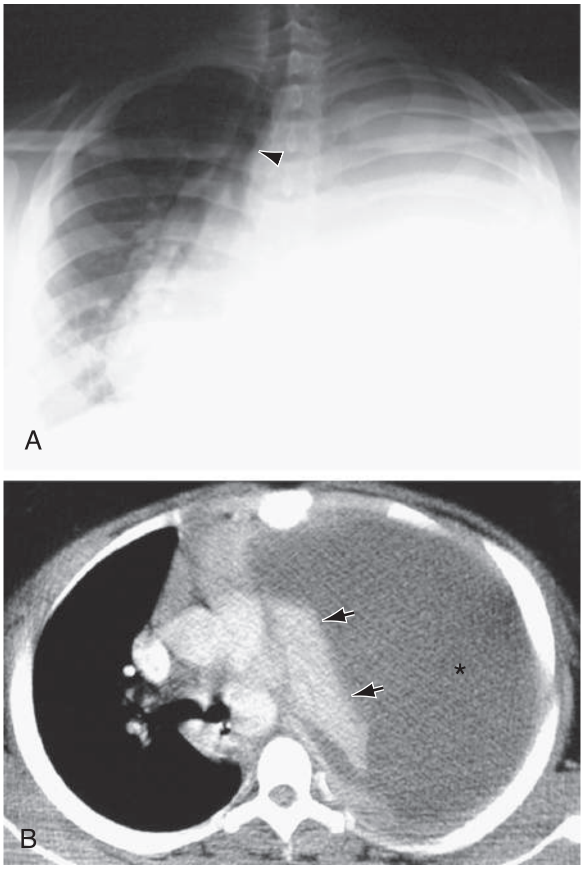

Figure 410-3 Empyema and pneumonia in a teenager. **A,** Chest radiograph shows opacification of the left thorax. Note shift of mediastinum and trachea *(arrowhead)* to right. **B,** Thoracic CT scan shows massive left pleural effusion *(asterisk)*. Note the compression and atelectasis of the left lung *(arrows)* and shift of the mediastinum to the right.

COMPLICATIONS

With staphylococcal infections, bronchopleural fistulas and pyopneumothorax commonly develop. Other local complications include purulent pericarditis, pulmonary abscesses, peritonitis from extension through the diaphragm, and osteomyelitis of the ribs. Septic complications such as meningitis, arthritis, and osteomyelitis may also occur. Septicemia is often encountered in *H. influenzae* and pneumococcal infections. The effusion may organize into a thick "peel," which may restrict lung expansion and may be associated with persistent fever and temporary scoliosis.

TREATMENT

The aim of empyema treatment is to sterilize pleural fluid and restore normal lung function. Treatment includes systemic antibiotics and thoracentesis and chest tube drainage initially with a fibrinolytic agent; if no improvement occurs, VATS is indicated. Open decortication is indicated if fibrinolysis and VATS are ineffective (see Chapter 411). If empyema is diagnosed early, antibiotic treatment plus thoracentesis achieves a complete cure. The selection of antibiotic should be based on the in vitro sensitivities of the responsible organism. See Chapters 181, 182, and 194 for treatment of infections by *Staphylococcus, S. pneumoniae*, and *H. influenzae*, respectively. Clinical response in empyema is slow; even with optimal treatment, there may be little improvement for as long as 2 wk. With staphylococcal infections, resolution is very slow, and systemic antibiotic therapy is required for 3-4 wk. Instillation of antibiotics into the pleural cavity does not improve results.

When pus is obtained by thoracentesis, closed-chest tube drainage with fibrolytics is the initial procedure followed by VATS if there is no improvement. Multiple aspirations of the pleural cavity should not be attempted. If pleural fluid septa are detected on ultrasound, fibrinolysis is attempted followed by VATS if no improvement is noted. Closed-chest tube drainage is controlled by an underwater seal or continuous suction; sometimes more than 1 tube is required to drain loculated areas. Closed drainage is usually continued for 5-7 days. Chest tubes that are no longer draining are removed.

Instillation of fibrinolytic agents into the pleural cavity via the chest tube may promote drainage, decrease fever, lessen need for surgical intervention, and shorten hospitalization; it does not shorten the course of disease when used after VATS. The optimal drug and dosage have not been determined. Streptokinase 15,000 units/kg in 50 mL of 0.9% saline daily for 3-5 days and urokinase 40,000 units in 40 mL saline every 12 hr for 6 doses have been evaluated in randomized trials in children. Alteplase (tissue plasminogen activator) has also been used. There is a risk of anaphylaxis with streptokinase, and all 3 drugs can be associated with hemorrhage and other complications.

Extensive fibrinous changes may take place over the surface of the lungs owing to empyema, but they eventually resolve. In the child who remains febrile and dyspneic for more than 72 hr after initiation of therapy with intravenous antibiotics and thoracostomy tube drainage, surgical decortication via VATS or, less often, open thoracotomy may speed recovery. If pneumatoceles form, no attempt should be made to treat them surgically or by aspiration, unless they reach sufficient size to cause respiratory embarrassment or become secondarily infected. Pneumatoceles usually resolve spontaneously with time. The long-term clinical prognosis for adequately treated empyema is excellent, and follow-up pulmonary function studies suggest that residual restrictive disease is uncommon, with or without surgical intervention.

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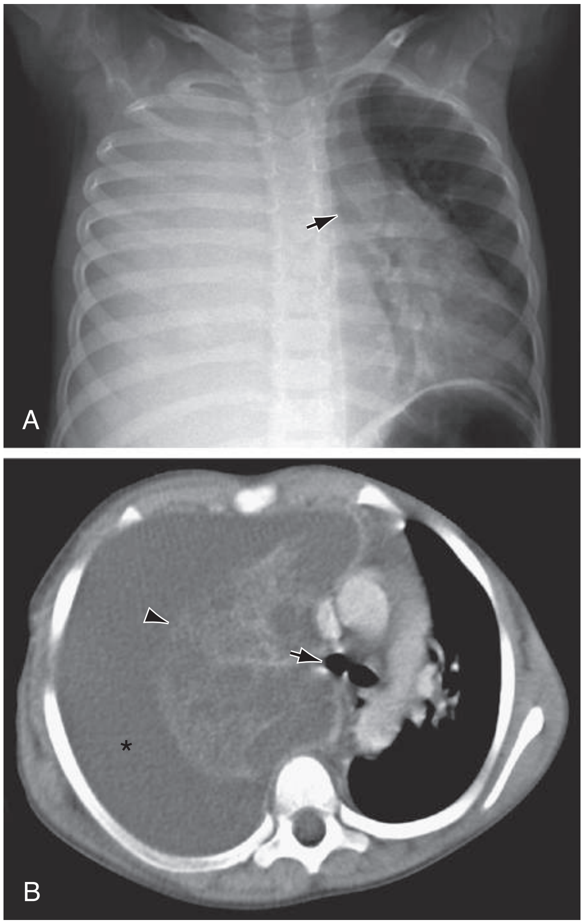

Figure 410-4 Pneumonia and parapneumonic effusion in a 4 yr old child. **A,** Chest radiograph shows complete opacification of the right thorax as a result of a large pleural effusion. Note the shift of the mediastinum and trachea *(arrow)* to the left. **B,** Thoracic CT scan shows a large right pleural effusion (*asterisk*) surrounding and compressing the consolidated right lung *(arrowhead)*. Note the shift of the mediastinum and tracheal carina *(arrow)* to the left.

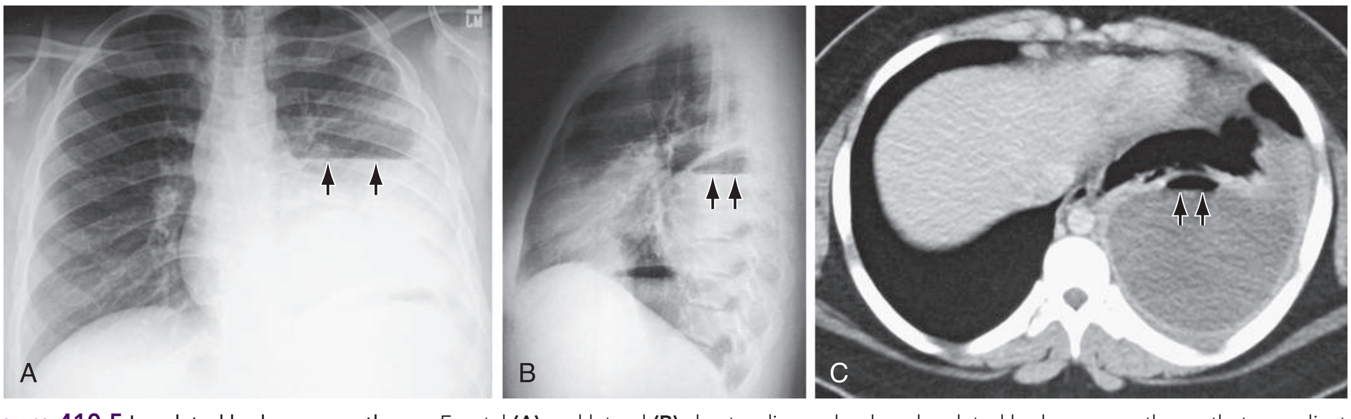

Figure 410-5 Loculated hydropneumothorax. Frontal **(A)** and lateral **(B)** chest radiographs show loculated hydropneumothorax that complicated pneumonia in a 14 yr old child. *Arrows* point to the horizontal air–fluid level at the interface between the intrapleural effusion and air. **C,** Thoracic CT scan helps to localize the loculated hydropneumothorax, with its air–fluid level *(arrows)*.

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Chapter 411

Pneumothorax

Glenna B. Winnie and Steven V. Lossef

Pneumothorax is the accumulation of extrapulmonary air within the chest, most commonly from leakage of air from within the lung. Air leaks can be primary or secondary and can be spontaneous, traumatic, iatrogenic, or catamenial (Table 411-1). Pneumothorax in the neonatal period is also discussed in Chapter 101.12.

ETIOLOGY AND EPIDEMIOLOGY

A **primary spontaneous pneumothorax** occurs without trauma or underlying lung disease. Spontaneous pneumothorax with or without

Table 411-1 Causes of Pneumothorax in Children

SPONTANEOUS
Primary idiopathic—usually resulting from ruptured subpleural blebs
Secondary blebs
Congenital lung disease:
Congenital cystic adenomatoid malformation
Bronchogenic cysts
Pulmonary hypoplasia*
Birt-Hogg-Dube syndrome
Conditions associated with increased intrathoracic pressure:
Asthma
Bronchiolitis
Air-block syndrome in neonates
Cystic fibrosis
Airway foreign body
Smoking (cigarettes, marijuana, crack cocaine)
Infection:
Pneumatocele
Lung abscess
Echinococcosis
Bronchopleural fistula
Diffuse lung disease:
Langerhans cell histiocytosis
Tuberous sclerosis
Marfan syndrome
Ehlers-Danlos syndrome
Metastatic neoplasm—usually osteosarcoma (rare)
Pulmonary blastoma
TRAUMATIC
Noniatrogenic
Penetrating trauma
Blunt trauma
High-flow therapy
Loud music (air pressure)
Iatrogenic
Thoracotomy
Thoracoscopy, thoracentesis
Tracheostomy
Tube or needle puncture
Mechanical ventilation

*Associated with renal agenesis, diaphragmatic hernia, amniotic fluid leaks.
From Kuhn JP, Slovis TL, Haller JO, editors: Caffey's pediatric diagnostic imaging, *ed 10, Philadelphia, 2004, Mosby.*

exertion occurs occasionally in teenagers and young adults, most frequently in males who are tall, thin, and thought to have subpleural blebs. Familial cases of spontaneous pneumothorax occur and have been associated with mutations in the folliculin gene (*FCLN*). *FCLN* mutations may be seen in the Birt-Hogg-Dube syndrome (skin fibrofolliculomas, multiple basal lung cysts, renal malignancies) or in patients with familial or recurrent spontaneous pneumothoraces. Patients with collagen synthesis defects, such as Ehlers-Danlos disease (see Chapter 659) and Marfan syndrome (see Chapter 702) are unusually prone to the development of pneumothorax.

A pneumothorax arising as a complication of an underlying lung disorder but without trauma is a **secondary spontaneous pneumothorax.** Pneumothorax can occur in pneumonia, usually with empyema; it can also be secondary to pulmonary abscess, gangrene, infarct, rupture of a cyst or an emphysematous bleb (in asthma), or foreign bodies in the lung. In infants with staphylococcal pneumonia, the incidence of pneumothorax is relatively high. It is found in ≈5% of hospitalized asthmatic children and usually resolves without treatment. Pneumothorax is a serious complication in cystic fibrosis (see Chapter 403). Pneumothorax also occurs in patients with lymphoma or other malignancies, and in graft-versus-host disease with bronchiolitis obliterans.

External chest or abdominal blunt or penetrating trauma can tear a bronchus or abdominal viscus, with leakage of air into the pleural space. Ecstasy (methylenedioxymethamphetamine), crack cocaine, and marijuana abuse are associated with pneumothorax.

Iatrogenic pneumothorax can complicate transthoracic needle aspiration, tracheotomy, subclavian line placement, thoracentesis, or transbronchial biopsy. It may occur during mechanical or noninvasive ventilation, high-flow nasal cannula therapy, acupuncture, and other diagnostic or therapeutic procedures.

Catamenial pneumothorax, an unusual condition that is related to menses, is associated with diaphragmatic defects and pleural blebs.

Pneumothorax can be associated with a serous effusion (hydropneumothorax), a purulent effusion (pyopneumothorax), or blood (hemopneumothorax). Bilateral pneumothorax is rare after the neonatal period but has been reported after lung transplantation and with *Mycoplasma pneumoniae* infection and tuberculosis.

PATHOGENESIS

The tendency of the lung to collapse, or elastic recoil, is balanced in the normal resting state by the inherent tendency of the chest wall to expand outward, creating negative pressure in the intrapleural space. When air enters the pleural space, the lung collapses. Hypoxemia occurs because of alveolar hypoventilation, ventilation–perfusion mismatch, and intrapulmonary shunt. In simple pneumothorax, intrapleural pressure is atmospheric, and the lung collapses up to 30%. In complicated, or tension, pneumothorax, continuing leak causes increasing positive pressure in the pleural space, with further compression of the lung, shift of mediastinal structures toward the contralateral side, and decreases in venous return and cardiac output.

CLINICAL MANIFESTATIONS

The onset of pneumothorax is usually abrupt, and the severity of symptoms depends on the extent of the lung collapse and on the amount of preexisting lung disease. Pneumothorax may cause dyspnea, pain, and cyanosis. When it occurs in infancy, symptoms and physical signs may be difficult to recognize. Moderate pneumothorax may cause little displacement of the intrathoracic organs and few or no symptoms. The severity of pain usually does not directly reflect the extent of the collapse.

Usually, there is respiratory distress, with retractions, markedly decreased breath sounds, and a tympanitic percussion note over the involved hemithorax. The larynx, trachea, and heart may be shifted toward the unaffected side. When fluid is present, there is usually a sharply limited area of tympany above a level of flatness to percussion. The presence of amphoric breathing or, when fluid is present in the pleural cavity, of gurgling sounds synchronous with respirations suggests an open fistula connecting with air-containing tissues.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of pneumothorax is usually established by radiographic examination (Figs. 411-1 to 411-6). The amount of air outside the lung varies with time. A radiograph that is taken early shows less lung collapse than one taken later if the leak continues. Expiratory views accentuate the contrast between lung markings and the clear area of the pneumothorax (see Fig. 411-1). When the possibility of diaphragmatic hernia is being considered, a small amount of barium may be necessary to demonstrate that it is not free air but is a portion of the gastrointestinal tract that is in the thoracic cavity. Ultrasound can also be used to establish the diagnosis.

It may be difficult to determine whether a pneumothorax is under tension. **Evidence of tension** includes shift of mediastinal structures away from the side of the air leak. A shift may be absent in situations in which the other hemithorax resists the shift, such as in the case of bilateral pneumothorax. When the lungs are both stiff, such as in cystic fibrosis or respiratory distress syndrome, the unaffected lung may not collapse easily and shift may not occur (see Fig. 411-3). On occasion, the diagnosis of tension pneumothorax is made only on the basis of evidence of circulatory compromise or on hearing a "hiss" of rapid exit of air under tension with the insertion of the thoracostomy tube.

Pneumothorax must be differentiated from localized or generalized emphysema, an extensive emphysematous bleb, large pulmonary cavities or other cystic formations, diaphragmatic hernia, compensatory overexpansion with contralateral atelectasis, and gaseous distention of

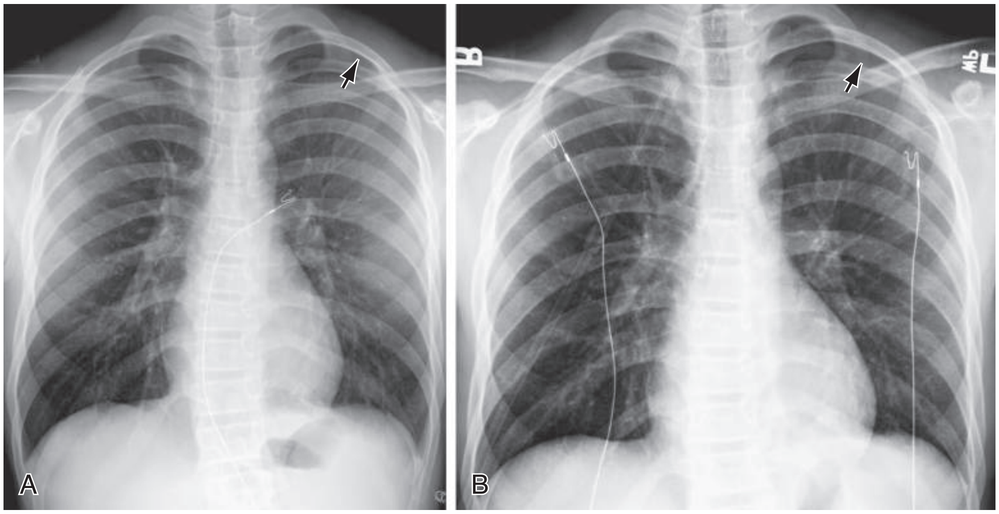

Figure 411-1 Utility of an expiratory film in detection of a small pneumothorax. **A,** Teenage boy with stab wound and subtle radiolucency in the left apical region *(arrow)* on inspiratory chest radiograph. The margin of the visceral pleura is very faintly visible. **B,** On an expiratory film, the pneumothorax *(arrow)* is more obvious as the right lung has deflated and become more opaque, providing better contrast with the air in the pleural space.

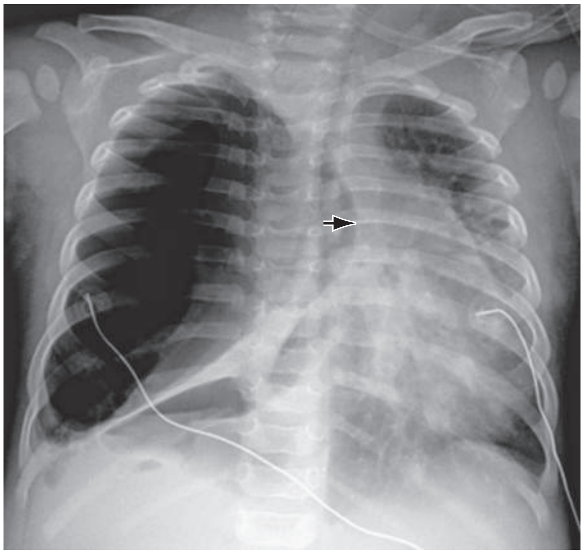

Figure 411-2 Right pneumothorax, with lung collapse of a compliant lung. Shift of the mediastinum to the left *(arrow)* indicates that this is a tension pneumothorax.

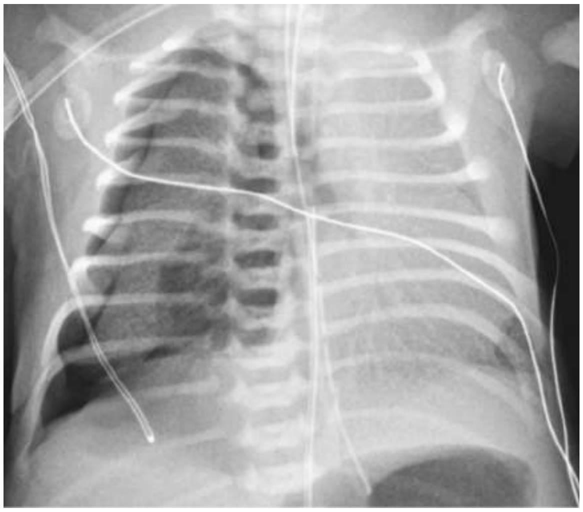

Figure 411-3 Right pneumothorax, with only limited collapse of a poorly compliant lung.

the stomach. In most cases, chest radiography or CT differentiates among these possibilities. In addition, CT may identify underlying pathology such as blebs (Fig. 411-7).

TREATMENT

Therapy varies with the extent of the collapse and the nature and severity of the underlying disease. A small (<5%) or even moderate-sized pneumothorax in an otherwise normal child may resolve without specific treatment, usually within 1 wk. A small pneumothorax complicating asthma may also resolve spontaneously. Administering 100% oxygen may hasten resolution, but patients with chronic hypoxemia should be monitored closely during administration of supplemental oxygen. Pleural pain deserves analgesic treatment. Needle aspiration may be required on an emergency basis for tension pneumothorax and is as effective as tube thoracostomy in the emergency room management of primary spontaneous pneumothorax. If the pneumothorax is recurrent, secondary, or under tension, or there is >5% collapse, chest tube drainage is necessary. Pneumothorax-complicating cystic fibrosis

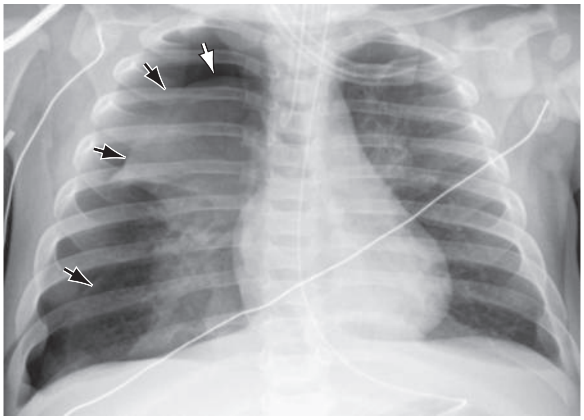

Figure 411-4 Pneumothorax, with collapse of right lung *(arrows)* caused by barotrauma in a 7 mo old child who was intubated for respiratory failure.

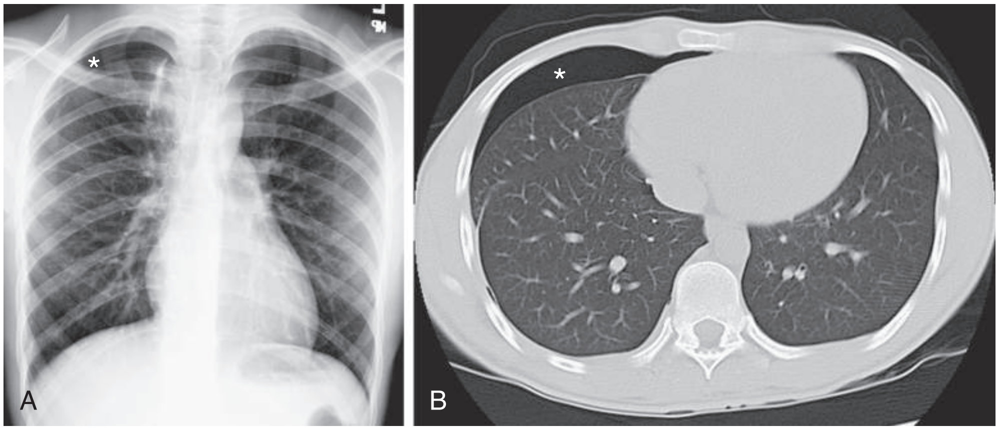

Figure 411-5 **Teenager in whom a spontaneous right pneumothorax developed because of a bleb.** He had a persistent air leak despite recent surgical resection of the causative apical bleb. Chest radiograph **(A)** and CT scan **(B)** clearly show the persistent pneumothorax *(asterisk).*

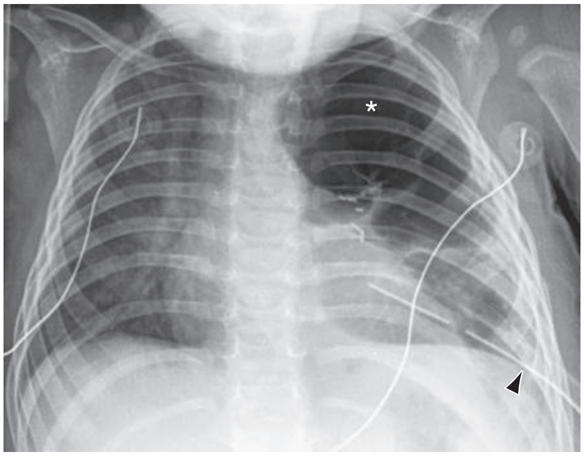

Figure 411-6 **Bronchopleural fistula following surgical resection of the left upper lobe as a result of congenital lobar emphysema.** Chest radiograph shows localized pneumothorax *(asterisk)* that persisted despite prior insertion of a large-bore chest tube *(arrowhead).*

Figure 411-7 **High-resolution CT thorax showing multiple basal cysts.** *(From Hopkins TG, Maher ER, Reid E, Marciniak S: Recurrent pneumothorax.* Lancet *377:1624, 2011, Fig. 1, p. 1624.)*

frequently recurs, and definitive treatment may be justified with the first episode. Similarly, if pneumothorax complicating malignancy does not improve rapidly with observation, chemical pleurodesis or surgical thoracotomy is often necessary. In cases with severe air leak or bronchopleural fistula, occlusion with an endobronchial balloon has been successful.

Closed thoracotomy (simple insertion of a chest tube) and drainage of the trapped air through a catheter, the external opening of which is kept in a dependent position under water, is adequate to reexpand the lung in most patients; pigtail catheters are frequently used. When there have been previous pneumothoraces, it may be indicated to induce the formation of strong adhesions between the lung and chest wall by a sclerosing procedure to prevent recurrence. This can be carried out by the introduction of talc, doxycycline, or iodopovidone into the pleural space (**chemical pleurodesis**). Open thoracotomy through a limited incision, with plication of blebs, closure of fistula, stripping of the pleura (usually in the apical lung, where the surgeon has direct vision), and basilar pleural abrasion is also an effective treatment for recurring pneumothorax. Stripping and abrading the pleura leaves raw, inflamed surfaces that heal with sealing adhesions. Postoperative pain is comparable to that with chemical pleurodesis, but the chest tube can usually be removed in 24-48 hr, compared with the usual 72 hr minimum for closed thoracotomy and pleurodesis. **Video-assisted thoracoscopic surgery** is a preferred therapy for blebectomy, pleural stripping, pleural brushing, and instillation of sclerosing agents, with somewhat less morbidity than occurs with traditional open thoracotomy. There is risk of recurrence after video-assisted thoracoscopic surgery in the pediatric population, although this is often not related to surgical failure, but rather associated with the formation of new bullae.

Pleural adhesions help prevent recurrent pneumothorax, but they also make subsequent thoracic surgery difficult. When lung transplantation may be a future consideration (e.g., in cystic fibrosis), a stepwise approach to treatment of pneumothorax has been proposed. This approach begins with observation and progresses through chest tube drainage and thoracoscopic and then open surgery, and finally to chemical or mechanical pleurodesis. At any step during this approach, the patient and family are given the option of the definitive procedure if they understand that its performance may make lung transplantation difficult or impossible. It should also be kept in mind that the longer a chest tube is in place, the greater the chance of pulmonary deterioration, particularly in a patient with cystic fibrosis, in whom strong coughing, deep breathing, and postural drainage are important. These are all difficult to accomplish with a chest tube in place.

Treatment of the underlying pulmonary disease should begin on admission and should be continued throughout the course of treatment directed at the air leak.

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Chapter **412**

Pneumomediastinum

Glenna B. Winnie

Air or gas in the mediastinum is called **pneumomediastinum.**

ETIOLOGY

Typically, pneumomediastinum is caused by alveolar rupture during acute or chronic pulmonary disease. A diverse group of nonrespiratory entities can also cause it, and the lung is not always the source of the air. Lower respiratory tract infection is a common etiology for pneumomediastinum in children younger than age 7 yr, while acute asthma is the most common cause in older children and teenagers. Simultaneous pneumothorax is unusual in these patients. Pneumomediastinum has been reported after vomiting, dental extractions, adenotonsillectomy, high-flow nasal cannula therapy, normal menses, obstetric delivery, diabetes mellitus with ketoacidosis, acupuncture, anorexia nervosa, and inhalation of helium gas. It can also result from esophageal perforation (Boerhaave syndrome), penetrating chest trauma, or inhaled foreign body. Occasionally, no underlying cause is found.

PATHOGENESIS

After intrapulmonary alveolar rupture, air dissects through the perivascular sheaths and other soft tissue, planes toward the hilum, and enters the mediastinum.

CLINICAL MANIFESTATIONS

Dyspnea and transient stabbing chest pain that may radiate to the neck are the principal features of pneumomediastinum. Isolated abdominal pain, cough, and sore throat also occur. Pneumomediastinum is difficult to detect by physical examination alone. Subcutaneous emphysema, if present, is diagnostic. Cardiac dullness to percussion may be decreased, but the chests of many patients with pneumomediastinum are chronically overinflated, and it is unlikely that the clinician can be sure of this finding. A mediastinal "crunch" (Hamman sign) is occasionally heard but is easily confused with a friction rub.

LABORATORY FINDINGS

Chest radiography reveals mediastinal air, with a more distinct cardiac border than normal (Figs. 412-1 to 412-3). On the lateral projection, the posterior mediastinal structures are clearly defined, there may be a lucent ring around the right pulmonary artery, and retrosternal air can usually be seen (see Fig. 412-2). Vertical streaks of air in the mediastinum and subcutaneous air are often observed (see Fig. 412-1).

COMPLICATIONS

Pneumomediastinum is rarely a major problem in older children because the mediastinum can be depressurized by escape of air into the neck or abdomen. In the newborn, however, the rate at which air can leave the mediastinum is limited, and pneumomediastinum can lead to dangerous cardiovascular compromise or pneumothorax (see Chapters 101.12 and 411).

TREATMENT

Treatment is directed primarily at the underlying obstructive pulmonary disease or other precipitating condition. Analgesics are occasionally needed for chest pain. Rarely, subcutaneous emphysema can cause sufficient tracheal compression to justify tracheotomy; the tracheotomy also decompresses the mediastinum. Collar mediastinotomy and percutaneous drainage catheter placement are other treatment modalities.

Bibliography is available at Expert Consult.

Figure 412-1 Large pneumomediastinum surrounding the heart and dissecting into the neck. *(From Clark DA:* Atlas of neonatology, *ed 7, Philadelphia, 2000, WB Saunders.)*

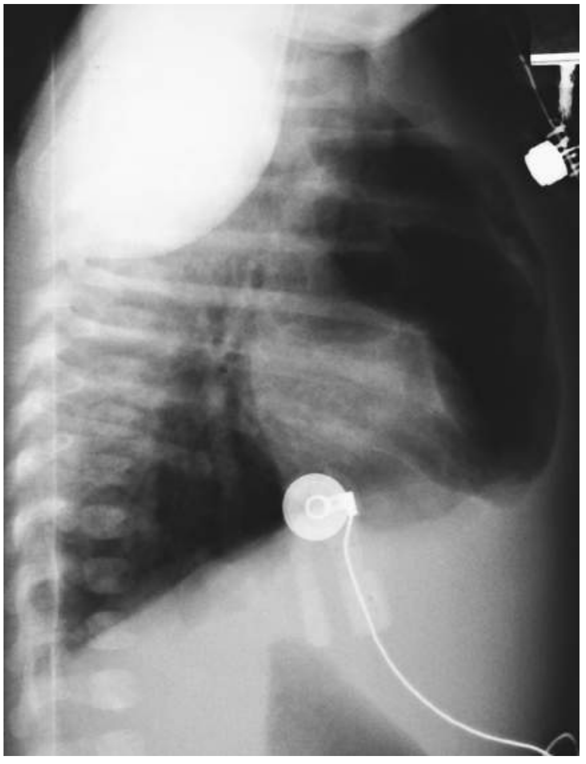

Figure 412-2 Lateral radiograph: upper mediastinal air. *(From Clark DA:* Atlas of neonatology, *ed 7, Philadelphia, 2000, WB Saunders, p. 94.)*

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Figure 412-3 Sail sign—thymic elevation. *(From Clark DA:* Atlas of neonatology, *ed 7, Philadelphia, 2000, WB Saunders, p. 94.)*

LABORATORY FINDINGS

The fluid is noninflammatory, has few cells, and has a lower specific gravity (<1.015) than that of a serofibrinous exudate. The ratio of pleural fluid to serum total protein is <0.5, the ratio of pleural fluid to serum lactic dehydrogenase is <0.6, and the pleural fluid lactic dehydrogenase value is less than 66% of the upper limit of the normal serum lactic dehydrogenase range.

TREATMENT

Therapy is directed at the underlying disorder; aspiration may be necessary when pressure symptoms are notable.

Bibliography is available at Expert Consult.

Chapter **413**

Hydrothorax

Glenna B. Winnie

Hydrothorax is a transudative pleural effusion; typically, it is caused by abnormal pressure gradients in the lung.

ETIOLOGY

Hydrothorax is most often associated with cardiac, renal, or hepatic disease. It can also be a manifestation of severe nutritional edema and hypoalbuminemia. Rarely, it results from vascular obstruction by neoplasms, enlarged lymph nodes, pulmonary embolism, or adhesions. It may occur from a ventriculoperitoneal shunt or peritoneal dialysis and has been reported in congenital parvovirus B19 infection.

CLINICAL MANIFESTATIONS

Hydrothorax is usually bilateral, but in cardiac disease it can be limited to the right side or greater on the right than on the left side. The physical signs are the same as those described for serofibrinous pleurisy (see Chapter 410.2), but in hydrothorax, there is more rapid shifting of the level of dullness with changes of position. It is usually associated with an accumulation of fluid in other parts of the body.

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Chapter 414
Hemothorax
Glenna B. Winnie and Steven V. Lossef

Hemothorax, an accumulation of blood in the pleural cavity, is rare in children.

ETIOLOGY

Bleeding into the chest cavity most commonly occurs after chest trauma, either blunt or penetrating. It can be the result of iatrogenic trauma, including surgical procedures and venous line insertion. Hemothorax can also result from erosion of a blood vessel in association with inflammatory processes such as tuberculosis and empyema. It may complicate a variety of congenital anomalies including sequestration, patent ductus arteriosus, and pulmonary arteriovenous malformation (see Fig. 407-2 in Chapter 407). It is also an occasional manifestation of intrathoracic neoplasms, costal exostoses, blood dyscrasias, bleeding diatheses, or thrombolytic therapy. Rupture of an aneurysm is unlikely during childhood. Hemothorax may occur spontaneously in neonates and older children. A pleural hemorrhage associated with a pneumothorax is a *hemopneumothorax;* it is usually the result of a ruptured bulla with lung volume loss causing a torn pleural adhesion.

CLINICAL MANIFESTATIONS

In addition to the symptoms and signs of pleural effusion (see Chapter 410.2), hemothorax is associated with hemodynamic compromise related to the amount and rapidity of bleeding.

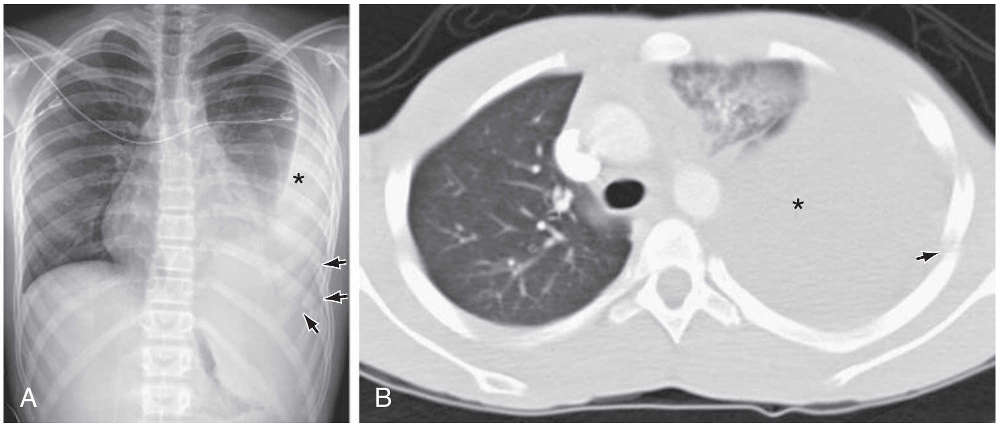

Figure 414-1 Hemothorax *(asterisk)* and associated rib fractures *(arrows)* in a teenager involved in a motor vehicle accident. **A,** Chest radiograph. **B,** CT scan.

DIAGNOSIS

The diagnosis of a hemothorax is initially suspected from radiographs or CT scans but can be made only with thoracentesis (Fig. 414-1). In every case, an effort must be made to determine and treat the cause.

TREATMENT

Initial therapy is tube thoracostomy. Surgical intervention may be required to control active bleeding, and transfusion may be indicated. Inadequate removal of blood in extensive hemothorax may lead to substantial restrictive disease secondary to organization of fibrin; fibrinolytic therapy or a decortication procedure may then be necessary. Embolization is the treatment of choice for an arteriovenous malformation.

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Chapter 415
Chylothorax
Glenna B. Winnie and Steven V. Lossef

Chylothorax is a pleural collection of fluid formed by the escape of chyle from the thoracic duct or lymphatics into the thoracic cavity.

ETIOLOGY
Chylothorax in children occurs most frequently because of thoracic duct injury as a complication of cardiothoracic surgery (Fig. 415-1). Other cases are associated with chest injury (Fig. 415-2), extracorporeal membrane oxygenation, or with primary or metastatic intrathoracic malignancy (Fig. 415-3), particularly lymphoma. In newborns, rapidly increased venous pressure during delivery may lead to thoracic duct rupture. Less common causes include lymphangiomatosis; restrictive pulmonary diseases; thrombosis of the duct, superior vena cava, or subclavian vein; tuberculosis or histoplasmosis; and congenital anomalies of the lymphatic system (Fig. 415-4). Refractory chylothorax in the fetus has been associated with a missense mutation in integrin aα9 gene. Chylothorax can occur in trauma and child abuse (see Chapter 40). It is important to establish the etiology, because treatment varies with the cause. In some patients, no specific cause is identified.

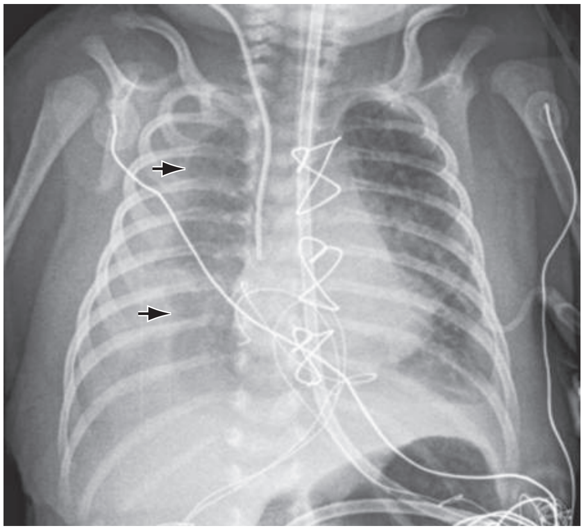

Figure 415-1 Chylothorax *(arrows)* following cardiac surgery in a 2 wk old infant.

CLINICAL MANIFESTATIONS
The signs and symptoms of chylothorax are the same as those from pleural effusion of similar size. Chyle is not irritating, so pleuritic pain is uncommon. Onset is often gradual. However, after trauma to the thoracic duct chyle may accumulate in the posterior mediastinum for days and then rupture into the pleural space with sudden onset of dyspnea, hypotension, and hypoxemia. Approximately 50% of newborns with chylothorax present with respiratory distress in the 1st day of life. Chylothorax is rarely bilateral and usually occurs on the right side.

LABORATORY FINDINGS
Thoracentesis demonstrates a chylous effusion, a milky fluid containing fat, protein, lymphocytes, and other constituents of chyle; fluid may be yellow or bloody. In newborn infants or those who are not ingesting food, the fluid may be clear. A pseudochylous milky fluid may be

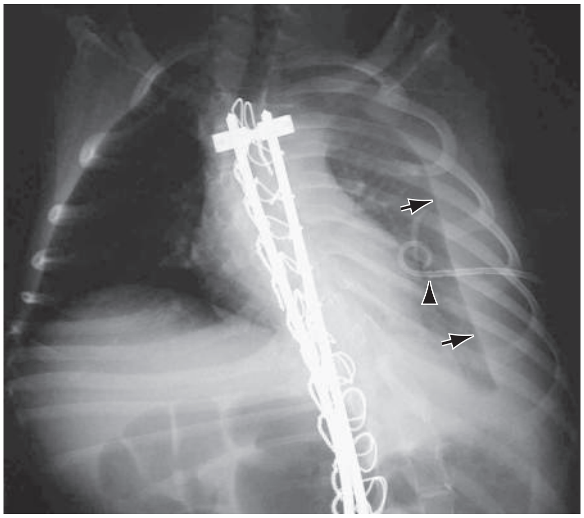

Figure 415-2 Left chylothorax *(arrows)* following spinal fusion with Harrington rods. It is postulated that the thoracic duct was injured during spine surgery. The pigtail chest tube *(arrowhead)* needed to be retracted to better drain the effusion.

Figure 415-3 Large right chylous effusion opacifying much of the right thorax in a teenager with pulmonary lymphangiomatosis and hemangiomatosis. Note the associated interstitial lung disease.

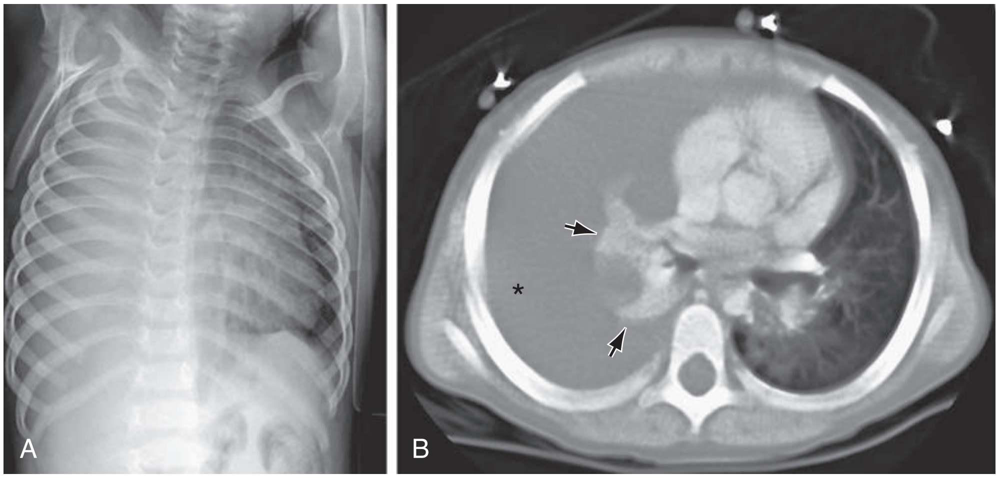

Figure 415-4 Spontaneous chylothorax in a 4 yr old with a duplication of chromosome 6. **A,** Chest radiograph shows opacification of the right thorax. **B,** CT scan shows the chylous pleural effusion *(asterisk)* compressing the atelectatic right lung *(arrows).*

present in chronic serous effusion, in which fatty material arises from degenerative changes in the fluid and not from lymph. In chylothorax, the fluid triglyceride level is >110 mg/dL, the pleural fluid:serum triglyceride ratio is >1.0, and pleural fluid:serum cholesterol ratio is <1.0; lipoprotein analysis reveals chylomicrons. Fluid immunoglobulin levels are elevated. The cells are primarily T lymphocytes. Chest radiographs show an effusion; CT scans show normal pleural thickness and may reveal a lymphoma as the etiology of the chylothorax. A lymphangiogram can localize the site of the leak, and lymphoscintigraphy may demonstrate abnormalities of the lymphatic trunks and peripheral lymphatics.

COMPLICATIONS

Repeated aspirations may be required to relieve the symptoms of pressure. Chyle reaccumulates quickly, and repeated thoracentesis may cause malnutrition with significant loss of calories, protein, and electrolytes. Immunodeficiencies, including hypogammaglobulinemia and abnormal cell-mediated immune responses, have been associated with repeated and chronic thoracenteses for chylothorax. The loss of T lymphocytes is associated with increased risk of infection in neonates; otherwise, infection is uncommon, but patients should not receive live virus vaccines. Lack of resolution of chylothorax can lead to inanition, infection, and death.

TREATMENT

Spontaneous recovery occurs in >50% of cases of neonatal chylothorax. Initial therapy includes enteral feedings with a low-fat or medium-chain triglyceride, high-protein diet or parenteral nutrition. Thoracentesis is repeated as needed to relieve pressure symptoms; tube thoracostomy is often performed. If there is no resolution in 1-2 wk, total parenteral nutrition is instituted; if this measure is unsuccessful, a pleuroperitoneal shunt, thoracic duct ligation, or application of fibrin glue is considered. Surgery should be considered earlier in neonates with massive chylothorax and chyle output of >50 mL/kg/day despite maximum medical therapy for 3 days. Parenteral octreotide at a dose of 0.5-1 μg/kg/hr to a maximum of 10 μg/kg/day intravenously has been used to manage chylothorax, but further study is needed. Other therapeutic approaches include percutaneous thoracic duct embolization, pressure control ventilation with positive end-expiratory pressure, talc or iodopovidone pleurodesis, and inhalation of nitric oxide. Treatment is similar for traumatic chylothorax. Chemical pleurodesis or irradiation is used in malignant chylothorax. OK432 (picibanil) has been used to treat fetal and newborn chylothorax.

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Chapter 416

Bronchopulmonary Dysplasia

Steven O. Lestrud

Bronchopulmonary dysplasia (BPD) is a pathologic process leading to signs and symptoms of chronic lung disease that originates in the neonatal period (see Chapter 101). The pathogenesis of lung disease in the population of neonates weighing <1,000 g includes the contribution of immature development of airway and vascular structures of the lung. The currently accepted definition includes an oxygen requirement for 28 days postnatally, and the disorder is graded as mild, moderate, or severe on the basis of supplemental oxygen requirement and gestational age (Table 416-1).

CLINICAL MANIFESTATIONS

Physical findings of the pulmonary exam vary with the severity of disease. Tachypnea is a common finding. Mouth breathing because of narrowed nasal passages and high arched palate is noted on upper airway exam. The chest demonstrates an increased anteroposterior diameter that suggests air trapping. Intercostal retractions are frequently present. Although breath sounds are frequently clear when the patient is well and abnormal only during an acute exacerbation, many patients have baseline wheeze or coarse crackles. A persistent fixed wheeze or stridor suggests subglottic stenosis (see Chapter 388) or large airway malacia. Fine crackles may be present in patients prone to fluid overload.

The most severely affected patients require prolonged mechanical ventilation to achieve acceptable gas exchange. Supplemental oxygen may be required to maintain acceptable oxygen saturation and often is needed to minimize the work of breathing. Infants with significant lung disease exhibit growth failure from the elevated energy expenditure essential to maintain the increased metabolic demands of respiration. Chronic respiratory insufficiency may be evident as elevation of serum bicarbonate, elevation of pressure of carbon dioxide on blood gas analysis, or polycythemia.

Patients must be monitored for the development of cor pulmonale, especially if they require supplemental oxygen and have chronic respiratory insufficiency.

Table 416-1 Forms of Bronchopulmonary Dysplasia

FEATURES OF ALL BPD	ADDITIONAL FEATURES OF MILD BPD	ADDITIONAL FEATURES OF MODERATE BPD	ADDITIONAL FEATURES OF SEVERE BPD
<32 wk PMA Oxygen requirement 1st 28 days	Breathing room air at 36 wk PMA	<30% Supplemental oxygen at 36 wk PMA	>30% Supplemental oxygen at 36 wk PMA and mechanical support, CPAP, or ventilation
>32 wk PMA Oxygen requirement 1st 28 days of life	Breathing room air at 56 days of life	<30% Supplemental oxygen at 56 days of life	>30% Supplemental oxygen at 56 days of life and mechanical support, CPAP, or ventilation

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; PMA, postmenstrual age.

Gastroesophageal reflux disease (GERD) (see Chapter 323) and pulmonary aspiration complicate pulmonary status, particularly during an exacerbation when the infant is most tachypneic and when pulmonary mechanics increase the risk of GERD. Other conditions resulting from premature birth–complicating BPD include upper airway obstruction leading to hypoxia, neurodevelopmental delay with increased risk of aspiration, systemic hypertension with left ventricular hypertrophy, poor growth, and electrolyte disturbances.

In severely affected patients and patients with disease disproportionate to their risk for development of chronic lung disease, other pulmonary disease must be suspected, such as asthma (see Chapter 144), cystic fibrosis (see Chapter 403), and chronic aspiration pneumonitis (see Chapter 398). Recurrent episodes of respiratory distress are common, but anatomic airway abnormalities, such as subglottic stenosis (see Chapter 388) and airway malacia (see Chapter 386), must also be considered.

A **pulmonary exacerbation** of BPD is typically triggered during viral upper respiratory infections. Other frequent triggers include viral lower respiratory infections, sinusitis, otitis media, weather changes, exposure to cigarette smoke, and exacerbations of gastroesophageal reflux. During an exacerbation, the infant exhibits increased work of breathing, with tachypnea and retractions becoming more prominent. Chest wall configuration may change, with an increased anteroposterior diameter. If wheezing is a prominent baseline finding, poor air entry during an exacerbation may result in less wheezing, signifying a significant deterioration of respiratory status.

TREATMENT

Treatment is directed toward decreasing the work of breathing and normalizing gas exchange, to allow for optimal growth and neurodevelopment. Infants requiring supplemental oxygen past 35 wk postmenstrual age have a higher incidence of lower airway obstruction and bronchodilator responsiveness and are more likely to be hospitalized during the toddler years than their peers. The etiology of wheezing in BPD may be lower airway inflammation, bronchial smooth muscle irritation, bronchial smooth muscle hypertrophy, and airway malacia. The administration of an inhaled bronchodilator is frequently undertaken to evaluate an individual's response. Most commonly, inhaled β-agonists initially increase air movement and improve comfort of breathing, resulting in short-term improvement in pulmonary function values. For patients whose symptoms respond, the medication should be continued, especially during high-risk periods when triggers are present, such as an upper respiratory infection or hot humid days.

β-Agonists may worsen the air exchange, particularly in infants with BPD and concomitant airway malacia. Bronchial smooth muscle may maintain airway caliber in the affected airway; smooth muscle relaxation after administration of a β-agonist results in increased small airway collapse. Patients in whom β-agonists have these effects may benefit from alternative bronchodilators, such as inhaled ipratropium and oral methylxanthines. The administration of preventive anti-inflammatory medications, such as inhaled glucocorticoids and leukotriene-modifying agents, may be considered in patients with frequent inflammatory triggers.

Targeted goals for supplemental oxygen therapy after discharge from the nursery are to improve oxygen saturation values and decrease likelihood of desaturation, reduce the risk of cor pulmonale, diminish the work of breathing, and improve growth. This therapy likely improves neurodevelopmental outcome and may decrease exacerbations caused by hypoxia. Oxygen saturation values should exceed 90%, but the optimal goal above this level is unknown. The addition of diuretic therapy with furosemide or thiazides may improve pulmonary mechanics by decreasing lung water and allow tapering of supplemental oxygen. Therapy beyond several weeks, however, is not known to improve outcome and places the child at risk for electrolyte disorders.

Adequate caloric intake can be difficult for many reasons, including oral aversion, discoordinated suck and swallow, GERD, aspiration, and aspiration with GERD. In addition, tachypnea, episodic respiratory distress, increased work of breathing, and requirement for supplement oxygen place the infant at risk for growth failure. A high caloric intake is necessary, with ranges of 120-160 kcal/kg/day required, frequently in combination with fluid restriction. To provide such high caloric intake in the compromised infant, supplemental feedings through a nasogastric or gastrostomy tube may be considered. Careful attention is necessary to maintain fluid balance.

Gastroesophageal reflux is common and must be suspected in patients not showing response to therapy and in patients with frequent exacerbations, especially exacerbations without clear triggers. Definitive diagnosis is necessary because these patients will be subject to prolonged promotility and antacid medications. Appropriate antireflux therapy in infants with GERD decreases respiratory complications. Gastroesophageal reflux with pulmonary aspiration or aspiration alone may manifest as chronic chest congestion, wheezing, and episodic hypoxic spells. Fundoplication with a gastrostomy tube is performed in patients showing no response to medical therapy. Evaluation and treatment by a speech therapist, pediatric pulmonologist, or otolaryngologist may decrease the risk for development of chronic lung disease associated with aspiration.

Prevention of respiratory viral illness is vitally important; frequent handwashing by caregivers, especially before they handle the baby and avoidance of contact with children and adults with current respiratory symptoms are essential. Respiratory syncytial virus (see Chapter 260) immunoprophylaxis should be considered on the basis of the severity of lung disease, as well as the patient's gestational age and current age.

The prognosis for infants with BPD is generally good. Through school age, the family can expect frequent medical interactions for episodes of respiratory distress, commonly triggered by simple upper respiratory tract infections and weather changes. Pulmonary function in severely affected patients remains decreased, and exercise limitation may be present because of dyspnea. The most severely affected patients benefit from care administered by a multidisciplinary team of caregivers, including the pediatrician, pulmonologist, speech therapist, nutritionist, and developmental specialists.

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Chapter 417

Skeletal Diseases Influencing Pulmonary Function

Steven R. Boas

Pulmonary function is influenced by the structure of the chest wall (see Chapter 373). Chest wall abnormalities can lead to restrictive or obstructive pulmonary disease, impaired respiratory muscle strength, and decreased ventilatory performance in response to physical stress. The congenital chest wall deformities include *pectus excavatum*, *pectus carinatum*, *sternal clefts*, *Poland syndrome*, and skeletal and *cartilage dysplasias*. Vertebral anomalies such as kyphoscoliosis can alter pulmonary function in children and adolescents.

417.1 Pectus Excavatum (Funnel Chest)

Steven R. Boas

ETIOLOGY

Pectus excavatum, midline narrowing of the thoracic cavity is usually an isolated skeletal abnormality. The cause is unknown. Pectus excavatum can occur in isolation or it may be associated with a connective tissue disorder (Marfan [see Chapter 702] or Ehlers-Danlos syndrome [see Chapter 659]). It may be acquired secondarily to chronic lung disease, neuromuscular disease, or trauma.

EPIDEMIOLOGY

Pectus excavatum occurs in 1 in 400 births with a 9 : 1 male preponderance and accounts for >90% of congenital chest wall anomalies. There is a positive family history in one-third of cases.

CLINICAL MANIFESTATIONS

The deformity is present at or shortly after birth in one-third of cases but is usually not associated with any symptoms at that time. In time, fatigue, chest pain, palpitations, recurrent respiratory infections, wheezing, stridor, and cough may be present. Decreased exercise tolerance is one of the most common symptoms. Because of the cosmetic nature of this deformity, children may experience significant psychologic stress. Physical examination may reveal sternal depression, protracted shoulders, kyphoscoliosis, dorsal lordosis, inferior rib flares, rib cage rigidity, forward head tilt, scapular winging, and loss of vertebral contours (Fig. 417-1). Patients exhibit paroxysmal sternal motion and a shift of point of maximal impulse to the left. Innocent systolic murmurs may be heard.

Figure 417-1 **Pectus excavatum in a 15 year old male.** Note the presence of protracted shoulders, inferior rib flares, and sternal depression.

LABORATORY FINDINGS

Lateral chest radiograms demonstrate the sternal depression. Use of the Haller index on chest CT (maximal internal transverse diameter of the chest divided by the minimal anteroposterior diameter at the same level) in comparison with age- and gender-appropriate normative values for determining the extent of depression of the chest wall anomaly has become useful in determining the extent of the anatomic abnormality. An electrocardiogram may show a right-axis deviation or Wolff-Parkinson-White syndrome (see Chapter 436); an echocardiogram may demonstrate mitral valve prolapse (see Chapter 428.3) and ventricular compression. Results of static pulmonary function tests may be normal but commonly show an obstructive defect in the lower airways and, less commonly, a restrictive defect as the result of abnormal chest wall mechanics. Exercise testing may demonstrate either normal tolerance or limitations from underlying cardiopulmonary dysfunction that are associated with the severity of the defect. Ventilatory limitations are commonly seen in younger children and adolescents, whereas cardiac limitations secondary to stroke volume impairments are more commonly seen in older adolescents and young adults.

TREATMENT

Treatment is based on the severity of the deformity and the extent of physiologic compromise as defined by physical examination and physiologic assessment of cardiopulmonary function (lung function and exercise tolerance assessment). Therapeutic options include careful observation, use of physical therapy to address musculoskeletal compromise, and corrective surgery. For patients with significant physiologic compromise, surgical correction may improve the cosmetic deformity and may help minimize or even improve the cardiopulmonary compromise. The 2 main surgical interventions are the Ravitch and Nuss procedures. Although superiority of 1 approach has not been established, there is now more than 20 yr of successful experience with the minimally invasive Nuss procedure. For teenagers with exercise limitations, surgical repair may result in improved exercise tolerance. Normalization of lung perfusion scans and maximal voluntary ventilation have also been observed after surgery. Utilization of a magnetic brace with gradual remodeling of the pectus deformity is under clinical investigation. Ongoing treatment to address the secondary musculoskeletal findings is commonly employed before and after the operation.

Bibliography is available at Expert Consult.

417.2 Pectus Carinatum and Sternal Clefts

Steven R. Boas

PECTUS CARINATUM

Etiology and Epidemiology

Pectus carinatum is a sternal deformity accounting for 5-15% of congenital chest wall anomalies. Anterior displacements of the mid and lower sternum and adjacent costal cartilages are the most common types. They are most commonly associated with protrusion of the upper sternum; depression of the lower sternum occurs in only 15% of patients. Asymmetry of the sternum is common, and localized depression of the lower anterolateral chest is also often observed. Males are affected 4 times more often than females. There is a high familial occurrence and a common association of mild to moderate scoliosis. Mitral valve disease and coarctation of the aorta are associated with this anomaly. Three types of anatomic deformity occur (upper, lower, and lateral pectus carinatum), with corresponding physiologic changes and treatment algorithms.

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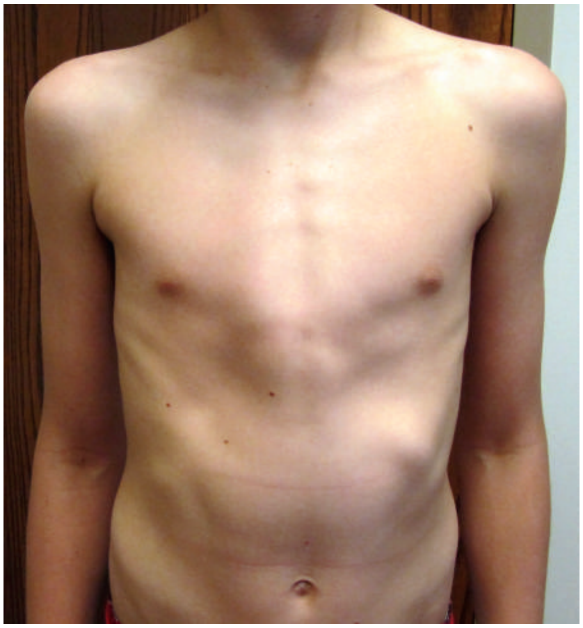

Figure 417-2 Pectus carinatum in a 13 year old male. Note the central sternal prominence.

Clinical Manifestations

In early childhood, symptoms appear minimal. School-age children and adolescents commonly complain of dyspnea with mild exertion, decreased endurance with exercise, and exercise-induced wheezing. The incidence of increased respiratory infections and use of asthma medication is higher than in nonaffected individuals. On physical examination, a marked increase in the anteroposterior chest diameter is seen, with resultant reduction in chest excursion and expansion (Fig. 417-2). Spirometry has demonstrated both restrictive and obstructive patterns, although the majority of individuals have normal values. Increases in residual volume are often present and results in tachypnea and diaphragmatic respirations. Exercise testing shows variable results. Chest radiographs show an increased anteroposterior diameter of the chest wall, emphysematous-appearing lungs, and a narrow cardiac shadow. The pectus severity score (width of chest divided by distance between sternum and spine; analogous to the Haller index) is reduced.

Treatment

For symptomatic patients with pectus carinatum, minimally invasive surgical correction procedures may result in improvement of the clinical symptoms. Many surgeons prefer to utilize bracing techniques as a first-line treatment although prospective outcome data is limited. Although surgery is performed for some individuals who are symptomatic, it is often performed for cosmetic and psychologic reasons.

STERNAL CLEFTS

Sternal clefts are rare congenital malformations that result from the failure of the fusion of the sternum during the 8th wk of gestation. No familial predisposition has been described. Sternal clefts occur in less than 1% of all chest wall deformities. Sternal clefts are classified as partial or complete. Partial sternal clefts are more common and may involve the superior sternum in association with other lesions, such as vascular dysplasias and supraumbilical raphe, or the inferior sternal clefts, which are often associated with other midline defects (pentalogy of Cantrell). Complete sternal clefts with complete failure of sternal fusion are rare. These disorders may also occur in isolation. The paradoxic movement of thoracic organs with respiration may alter pulmonary mechanics. Rarely, respiratory infections and even significant compromise result. Surgery is required early in life, before fixation and immobility occur.

Bibliography is available at Expert Consult.

417.3 Asphyxiating Thoracic Dystrophy (Thoracic-Pelvic-Phalangeal Dystrophy)

Steven R. Boas

ETIOLOGY

A multisystem autosomal recessive disorder, asphyxiating thoracic dystrophy results in a constricted and narrow rib cage. Also known as *Jeune syndrome*, the disorder is associated with a characteristic skeletal abnormalities as well as variable involvement of other systems, including renal, hepatic, neurologic, pancreatic, and retinal abnormalities (see Chapter 700).

CLINICAL MANIFESTATIONS

Most patients with this disorder die shortly after birth from respiratory failure, although less-aggressive forms have been reported in older children. For those who survive the neonatal period, progressive respiratory failure often ensues, owing to impaired lung growth, recurrent pneumonia, and atelectasis originating from the rigid chest wall.

DIAGNOSIS

Physical examination reveals a narrowed thorax that, at birth, is much smaller than the head circumference. The ribs are horizontal, and the child has short extremities. Chest radiographs demonstrate a bell-shaped chest cage with short, horizontal, flaring ribs and high clavicles.

TREATMENT

No specific treatment exists, although thoracoplasty to enlarge the chest wall and long-term mechanical ventilation has been tried. Rib-expanding procedures have resulted in improved survival.

PROGNOSIS

For some children with asphyxiating thoracic dystrophy, improvement in the bony abnormalities occurs with age. However, children younger than age 1 yr often succumb to respiratory infection and failure. Progressive renal disease often occurs with older children. Use of vaccines for influenza and other respiratory pathogens is warranted, as is aggressive use of antibiotics for respiratory infections.

Bibliography is available at Expert Consult.

417.4 Achondroplasia

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ETIOLOGY

Achondroplasia is the most common condition characterized by disproportionate short stature (see Chapter 696). This condition is inherited as an autosomal dominant disorder that results in disordered growth. Much has been learned about this disorder, including its genetic origins (95% of cases caused by mutations in the gene coding for fibroblast growth factor receptor type 3) and how to minimize its serious complications.

CLINICAL MANIFESTATIONS

Restrictive pulmonary disease, affecting <5% of children with achondroplasia who are younger than 3 yr, is more likely at high elevation. Recurrent infections, cor pulmonale, and dyspnea are commonly associated. There is an increased risk of obstructive sleep apnea or hypopneas. Hypoxemia during sleep is a common feature. Onset of restrictive lung disease can begin at a very young age. On examination, the breathing pattern is rapid and shallow, with associated abdominal breathing. The anteroposterior diameter of the thorax is reduced. Special growth curves for chest circumference of patients with achondroplasia from birth to 7 yr are available. Three distinct phenotypes exist: phenotypic group 1 patients possess relative adenotonsillar hypertrophy, group 2 patients have muscular upper airway obstruction and progressive hydrocephalus, and group 3 patients have upper airway obstruction without hydrocephalus. Kyphoscoliosis may develop during infancy.

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DIAGNOSIS

Pulmonary function tests reveal a reduced vital capacity that is more pronounced in males. The lungs are small but functionally normal. Sleep studies are recommended due to the high prevalence of sleep-disordered breathing. Chest radiographs demonstrate the decreased anteroposterior diameter along with anterior cupping of the ribs. The degree of foramen magnum involvement correlates with the extent of respiratory dysfunction.

TREATMENT

Treatment of sleep apnea, if present, is supportive (see Chapter 19). Physiotherapy and bracing may minimize the complications of both kyphosis and severe lordosis. Aggressive treatment of respiratory infections and scoliosis is warranted.

PROGNOSIS

The life span is normal for most children with this condition, except for the phenotypic groups with hydrocephalus or with severe cervical or lumbar spinal compression.

Bibliography is available at Expert Consult.

417.5 Kyphoscoliosis: Adolescent Idiopathic Scoliosis and Congenital Scoliosis

Steven R. Boas

ETIOLOGY

Adolescent idiopathic scoliosis (AIS) is characterized by lateral bending of the spine (see Chapter 679). It commonly affects children during their teen years, as well as during periods of rapid growth. The cause is unknown. Congenital scoliosis is uncommon, affecting girls more than boys, and is apparent in the 1st yr of life (see Chapter 679.2).

CLINICAL MANIFESTATIONS

The pulmonary manifestations of scoliosis may include chest wall restriction, leading to a reduction in total lung capacity, abnormal gas exchange, and airway obstruction. The angle of scoliosis deformity has been correlated with the degree of lung impairment only for patients with thoracic curves. Vital capacity, forced expiratory volume in 1 sec (FEV_1), work capacity, oxygen consumption, diffusion capacity, chest wall compliance, and partial pressure of arterial oxygen decrease as the severity of thoracic curve increases. These findings can be seen in even mild to moderate AIS (Cobb angle <30 degrees) but generally do not occur in other, nonthoracic curves. Respiratory compromise is often more severe in children younger than 5 yr of age with large scoliotic curves. Reduction in peripheral muscle function is associated with AIS through either intrinsic mechanisms or deconditioning. Severe impairment can lead to cor pulmonale or respiratory failure and can occur before age 20 yr. Children with severe scoliosis, especially boys, may have abnormalities of breathing during sleep, and the resultant periods of hypoxemia may contribute to the eventual development of pulmonary hypertension.

DIAGNOSIS

Physical examination and an upright, posteroanterior radiograph with subsequent measurement of the angle of curvature (Cobb technique) remain the gold standard for assessment of scoliosis. Curves >10 degrees define the presence of scoliosis. Lung volume, respiratory muscle strength, and exercise capacity determination are essential in assessing the degree of respiratory compromise associated with scoliosis.

TREATMENT

Depending on the extent of the curve and the degree of skeletal maturation, treatment options include reassurance, observation, bracing, and surgery (spinal fusion). Influenza vaccine should be administered, given the extent of pulmonary compromise that may coexist. Because vital capacity is a strong predictor for the development of respiratory failure in untreated AIS, surgical goals are to diminish the scoliotic curve, maintain the correction, and prevent deterioration in pulmonary function. Abnormalities of vital capacity and total lung capacity, exercise intolerance, and the rate of change of these variables over time should be taken into consideration for the timing of surgical correction. Preoperative assessment of lung function (i.e., lung volumes, oxygen consumption, muscle strength, ventilation/perfusion) may assist in predicting postsurgical pulmonary difficulties. Many patients undergoing surgical correction may be managed postoperatively without mechanical ventilation. Even patients with mild scoliosis may have pulmonary compromise immediately after spinal fusion, secondary to pain and a body cast that may restrict breathing and interfere with coughing. Children with a preoperative FEV_1 <40% predicted are at risk for requiring prolonged postoperative mechanical ventilation. Rib-expanding procedures have been successful in severe cases of congenital scoliosis. Choice of surgical approach may also impact lung function postoperatively.

Bibliography is available at Expert Consult.

417.6 Congenital Rib Anomalies

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CLINICAL MANIFESTATIONS

Isolated defects of the highest and lowest ribs have minimal clinical pulmonary consequences. Missing midthoracic ribs are associated with the absence of the pectoralis muscle (Poland syndrome), and lung function can become compromised. Associated kyphoscoliosis and hemivertebrae may accompany this defect. If the rib defect is small, no significant sequelae ensue. When the 2nd to 5th ribs are absent anteriorly, lung herniation and significant abnormal respiration ensue. The lung is soft and nontender and may be easily reducible on examination. Complicating sequelae include severe lung restriction (secondary to scoliosis), cor pulmonale, and congestive heart failure. Symptoms are often minimal but can cause dyspnea. Respiratory distress is rare in infancy.

DIAGNOSIS

Chest radiographs demonstrate the deformation and absence of ribs with secondary scoliosis. Most rib abnormalities are discovered as incidental findings on a chest film.

TREATMENT

If symptoms are severe enough to cause clinical compromise or significant lung herniation, then homologous rib grafting can be performed. Rib-expanding procedures are also of great value. A modified Nuss procedure has been utilized to correct associated chest wall anomalies with rib abnormalities. Adolescent girls with congenital rib anomalies may require cosmetic breast surgery.

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Chapter 418

Chronic Severe Respiratory Insufficiency

Zehava L. Noah and Cynthia Etzler Budek

The population of pediatric patients receiving long-term mechanical ventilatory support has increased in the United States and many other nations because of improvements in the treatment of acute respiratory failure and advancements in invasive (e.g., tracheostomy with mechanical ventilator) and noninvasive (e.g., mask continuous

positive airway pressure [CPAP] or bilevel positive airway pressure [BiPAP]) ventilation. Despite the growing population, less than 1% of patients admitted to pediatric intensive care units require long-term mechanical ventilation. Infants, children, and adolescents with disorders of central control of breathing, disease of the airways, residual lung disease after severe respiratory illness, persistent pulmonary hypertension, and neuromuscular disorders may experience hypercarbic and/or hypoxemic chronic respiratory failure. Generally, the respiratory failure can be attributed to a primary cause, although many children have multiple causative factors. **Chronic respiratory failure** can be defined as pulmonary insufficiency for a protracted period, usually 28 days or longer.

Patients are maintained on long-term ventilation for varying periods of time depending on the underlying pathology. Patients with reversible neuropathies (Guillain-Barré syndrome, neuropathy of critical illness), bronchopulmonary dysplasia, pulmonary hypertension, airway abnormalities, and congenital heart disease before or after surgical intervention require long-term ventilation as a bridge for full recovery. Patients with conditions such as central hypoventilation, progressive neuromuscular disease, and high quadriplegia may need ventilatory support indefinitely. The goals of long-term mechanical ventilation are to sustain and extend life, enhance the quality of life, reduce morbidity, improve physical and psychologic function, and enhance growth and development. These goals are often optimized in the home setting, which is the preferred site of discharge for children who are ventilator dependent. When social circumstances do not allow for a safe discharge to home, patients may be transferred to a highly skilled nursing facility for long-term care.

In an observational cohort analysis of 228 children enrolled in a home ventilation program 52% had chronic pulmonary disease, many with multiple comorbidities. Eventually 30% of children with chronic pulmonary disease were successfully weaned off ventilation and 19% died. Twenty-seven percent of the total population had neuromuscular disease, of which 6% were weaned off ventilation and 21% died. Twenty percent of the total population had central hypoventilation, of which 4% were weaned from ventilation and 24% died. Causes of death included progression of underlying chronic respiratory failure (34%), cardiac failure (21%), acute respiratory failure, tracheal bleeding and tracheal obstruction (8.5% each), and tracheostomy accident (2%). Regression analysis suggested that children with chronic pulmonary disease were more likely to successfully wean off mechanical ventilation than those children in the other two groups.

418.1 Neuromuscular Diseases

Zehava L. Noah and Cynthia Etzler Budek

Neuromuscular diseases (NMDs) of childhood include muscular dystrophies, metabolic and congenital myopathies, anterior horn cell disorders, peripheral neuropathies, and diseases that affect the neuromuscular junction. Decreased muscle strength and endurance resulting from neuromuscular disorders can affect any skeletal muscle, including muscles involved in respiratory function. Of particular concern are those muscles mediating upper airway patency, generation of cough, and lung inflation. Acute respiratory insufficiency is typically the most prominent clinical manifestation of several acute neuromuscular disorders, including high-level spinal cord injury, poliomyelitis, Guillain-Barré syndrome (see Chapter 616), and botulism (see Chapter 210). Respiratory dysfunction constitutes the leading cause of morbidity and mortality in progressive neuromuscular disorders (e.g., Duchenne muscular dystrophy [see Chapter 609], spinal muscular atrophy, congenital myotonic dystrophy, myasthenia gravis [see Chapter 612], and Charcot-Marie-Tooth disease [see Chapter 613]).

PATHOGENESIS

Early onset of NMD can lead to chest wall deformity and lung disease as a consequence of developmental factors. In infancy, the chest wall is very compliant with relatively stiff lungs and small airways. With progressive weakness of the intercostal muscles, the chest wall becomes even more compliant. Small airways have a tendency to become obstructed, leading to microatelectasis and decreased functional residual capacity. The compliant chest wall with initial sparing of diaphragm function leads to development of a small bell-shaped chest with depressed sternum, protruding abdomen, and paradoxical breathing, typically seen in spinal muscular atrophy (SMA) type 1. As the disease progresses, severe hypotonia develops, chest wall muscles shorten and lose elasticity, costosternal and costovertebral joints contract, and lung volumes decrease. Inspiratory and expiratory pressures subsequently decrease, expiratory pressures more so than inspiratory, causing ineffective cough and poor airway clearance. As the child with NMD ages, kyphoscoliosis commonly develops, increasing the severity of restrictive lung disease. Although central control of breathing remains normal, response to central chemoreceptors may decrease because of chronic hypercapnia.

TREATMENT

Even though gene-targeted therapies are being developed for some NMDs, current interventions are primarily supportive rather than curative. Close surveillance through periodic review of the history and physical examination is critical. The development of personality and behavioral changes, such as irritability, decreased attention span, fatigue, and somnolence, may point to the presence of sleep-associated gas exchange abnormalities and sleep fragmentation. Changes in speech and voice characteristics, nasal flaring, and the use of accessory muscles at rest may indicate progressive muscle dysfunction and respiratory compromise. Although the frequency of periodic reevaluation needs to be tailored to the individual child, guidelines were developed for the Duchenne muscular dystrophy population; an abbreviated summary of such recommendations, applicable to all children with NMDs, is provided in Table 418-1.

Guidelines for evaluation and management of patients with SMA were developed on the basis of expert consensus. Four classifications of SMA, based on age of onset and level of function, are recognized (Table 418-2). Treatment of SMA is focused on level of function (non-sitter, sitter, or walker) rather than SMA type. Unlike patients with Duchenne muscular dystrophy, patients with SMA do not demonstrate correlation between pulmonary function and need for mechanical

Table 418-1 Proposed Guidelines for Initial Evaluation and Follow-Up of Patients with Neuromuscular Disease

INITIAL EVALUATION	BASIC INTERVENTION/ TRAINING
History/physical/anthropometrics	Nutritional consultation and guidance
Lung function and maximal respiratory pressures (PFTs)	Regular chest physiotherapy
Arterial blood gases	Use of percussive devices
Polysomnography*	Respiratory muscle training
Exercise testing (in selected cases)	Annual influenza vaccine
If vital capacity >60% predicted or maximal respiratory pressures >60 cm H_2O	Evaluate PFTs every 6 mo CXR and polysomnography every year
If vital capacity <60% predicted or maximal respiratory pressures <60 cm H_2O	Evaluate PFTs every 3-4 mo CXR, MIP/MEP every 6 mo Polysomnography every 6 mo to year

*Please note that if polysomnography is not readily available, multichannel recordings including oronasal airflow, nocturnal oximetry, and end-tidal carbon dioxide levels may provide an adequate alternative.

CXR, chest x-ray; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; PFT, pulmonary function test.

Table 418-2 Clinical Classification of Spinal Muscular Atrophy

SMA TYPE	AGE OF ONSET	HIGHEST FUNCTION	NATURAL AGE OF DEATH
Type 1 (severe)	0-6 mo	Never sits	<2 yr
Type 2 (intermediate)	7-18 mo	Never stands	<2 yr
Type 3 (mild)	Older than 18 mo	Stands and walks	Adult
Type 4 (adult)	Second or third decade	Walks during adult years	Adult

From Wang CH, Finkel RS, Bertini ES, et al: Consensus statement for standard of care in spinal muscular atrophy, J Child Neurol *22:1027–1049, 2007.*

ventilatory support. Longitudinal monitoring for signs and symptoms of sleep-disordered breathing and ineffective airway clearance should be utilized to direct patient care.

Bibliography is available at Expert Consult.

418.2 Congenital Central Hypoventilation Syndrome

Zehava L. Noah, Cynthia Etzler Budek, and Debra E. Weese-Mayer

Congenital central hypoventilation syndrome (CCHS) is a clinically complex disorder of respiratory and autonomic regulation. In the classic case of CCHS, symptoms of alveolar hypoventilation are manifest in the newborn period and during sleep only—with diminished tidal volume and a typically monotonous respiratory rate with cyanosis and hypercarbia. In more severe cases of CCHS, the hypoventilation is manifest during wakefulness and sleep. And in the cases of later-onset CCHS (LO-CCHS), symptoms are manifest after 1 mo of age (and often into childhood and adulthood) but hypoventilation is typically during sleep only. CCHS and LO-CCHS are further characterized by ventilatory failure to properly respond to hypercarbia and hypoxemia during wakefulness and sleep coupled with physiologic and/or anatomic autonomic nervous system (ANS) dysregulation (ANSD). Physiologic ANSD may include all organ systems affected by the ANS, specifically the respiratory, cardiac (sinus node pauses, asystole), sudomotor, vasomotor, ophthalmologic, neurologic, and enteric systems. The anatomic or structural ANSD includes Hirschsprung disease and tumors of neural crest origin (neuroblastoma, ganglioneuroma, or ganglioneuroblastoma). Diagnosis and management of individuals with CCHS and LO-CCHS have improved considerably, owing to greater knowledge in genetic testing, comprehensive care, and availability of monitoring technology for the home.

GENETICS

Mutations in the paired-like homeobox 2B (*PHOX2B*) gene are the cause of CCHS. *PHOX2B* is essential to the embryologic development of the ANS from the neural crest, and is expressed in key regions that explain much of the CCHS phenotype. Individuals with CCHS are heterozygous for either a polyalanine repeat expansion mutation (PARM) in exon 3 of the *PHOX2B* gene (normal number of alanines is 20 with normal genotype 20/20), such that individuals with CCHS have 24-33 alanines on the affected allele (genotype range is 20/24-20/33), or a non–PARM (NPARM) resulting from a missense, nonsense, frameshift, or stop codon mutation. Roughly 90-92% of the cases of CCHS have PARMs and the remaining 8-10% of cases have NPARMs. LO-CCHS cases have consistently had the 20/24 or 20/25 genotypes, or, occasionally, a very small NPARM. The specific type of *PHOX2B* mutation is clinically significant as it can help with anticipatory guidance in patient management. Less than 1% of CCHS cases will have a deletion of most of exon 3 or the entire *PHOX2B* gene, although the specific phenotype related to these large deletion mutations is not entirely clear. Stepwise clinical *PHOX2B* testing for probands with the CCHS phenotype is advised (step 1: fragment analysis (screening test); then if negative, step 2: sequel sequencing; then if negative, step 3: muliplex ligation-dependent probe amplification) to minimize expense and expedite confirmation of the diagnosis.

The majority of CCHS cases occur because of a de novo *PHOX2B* mutation, but up to 25% of children with CCHS inherit the mutation in an autosomal dominant manner from a seemingly asymptomatic parent who is mosaic for the *PHOX2B* mutation. Therefore, an individual with CCHS has a 50% chance of transmitting the mutation and resulting disease phenotype, to each offspring. Mosaic parents have up to a 50% chance of transmitting the *PHOX2B* mutation to each successive offspring. Genetic counseling is essential for family planning and for delivery room preparedness in anticipation of a CCHS birth. *PHOX2B* testing is advised for both parents of a child with CCHS to anticipate risk of recurrence in subsequent pregnancies and to determine if a parent has yet undiagnosed LO-CCHS. However, only fragment analysis *PHOX2B* testing (also known as the screening test) will identify low level somatic mosaicism (it will be missed by sequencing testing). At present, no clinical testing is available to determine germline mosaicism, but prenatal testing for *PHOX2B* mutation is clinically available (http://www.genetests.org) for families with a known *PHOX2B* mutation.

Ventilator Dependence

A correlation between the *PHOX2B* genotype and ventilator dependence is reported. The greater the number of extra alanines, the more likely the need for continuous ventilatory support, at least among the most common *PHOX2B* PARM genotypes (20/25, 20/26, 20/27). Thus patients with the 20/25 genotype seldom require awake ventilatory support, although they do require support during sleep. Patients with the 20/26 genotype have variable awake support needs, and patients with the 20/27 genotype and those with NPARMs are likely to need continuous ventilatory support.

Hirschsprung Disease

See Chapter 332.3.

Overall, 20% of children with CCHS also have Hirschsprung disease, and any infant or child with CCHS or LO-CCHS who presents with constipation should undergo rectal biopsy to screen for absence of ganglion cells. The type of *PHOX2B* mutation can help the primary physician anticipate which individuals are at higher risk. The frequency of Hirschsprung disease seems to increase with the longer polyalanine tracts (genotypes 20/27-20/33) and in those with NPARMs. Thus far only 1 infant with the 20/25 genotype has been reported to have Hirschsprung disease.

Tumors of Neural Crest Origin

Tumors of neural crest origin are more frequent in patients with NPARMs (50%) than in those with PARMs (1%). These extracranial tumors are more often neuroblastomas in individuals with NPARMs, rather than ganglioneuromas and ganglioneuroblastomas, which have been described in patients with longer PARMs (20/29, 20/30, and 20/33 genotype only). Thus far only 1 infant with a PARM (20/33 genotype) has been reported to have a neuroblastoma.

Cardiac Asystole

Transient, abrupt, and prolonged sinus pauses have been identified in patients with CCHS, necessitating implantation of cardiac pacemakers when the pauses are 3 sec or longer. Among patients with the *PHOX2B*

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genotypes, 19% of those with the 20/26 genotype and 83% of those with the 20/27 genotype have heart beat pauses of 3 sec or longer. Children with the 20/25 genotype are not noted to have prolonged asystole, although 2 adults diagnosed with LO-CCHS demonstrated prolonged asystoles of 4-8 sec duration. Risk for sinus pauses among children with NPARMs is unknown at present.

Autonomic Nervous System Dysregulation

A higher number of polyalanine repeats among the PARMs is associated with an increased number of physiologic symptoms of ANSD. A higher frequency of anatomic ANSD findings is seen in individuals with CCHS who have NPARMs than in those who have PARMs. In addition, there is a spectrum of physiologic ANSD symptoms, including decreased heart rate variability, esophageal/gastric/colonic dysmotility, decreased pupillary response to light, reduced basal body temperature, altered distribution and amount of diaphoresis, and altered perception of anxiety.

Facial Phenotype

Children with CCHS and PARMs have a characteristic facies that is boxy in appearance, flattened on profile, and short relative to its width. The following five variables correctly predict 86% of CCHS cases: upper lip height, binocular width, upper facial height, nasal tip protrusion, and inferior inflection of the lateral one-third of the upper lip vermillion border (lip trait).

Neuropathology

Anatomic findings in the brains of individuals with CCHS from early MRI studies were unremarkable, and those from autopsies were inconsistent before 2003 when *PHOX2B* testing became clinically available. In a small cohort of adolescents with suspected CCHS, although without consistent *PHOX2B* mutation confirmation, neuropathologic brainstem changes were identified by diffusion tensor imaging in structures known to mediate central chemosensitivity and to link a network of cardiovascular, respiratory, and affective responses. The neuroanatomic defects in CCHS are likely the result of focal *PHOX2B* (mis) expression coupled with sequelae of recurrent hypoxemia/hypercarbia in the subset of suboptimally managed patients. On the basis of rodent studies and functional MRI in humans, the following regions pertinent to respiratory control show *PHOX2B* expression in the pons and medulla of the brainstem: locus coeruleus, dorsal respiratory group, nucleus ambiguus, parafacial respiratory group, among other areas. Physiologic evidence suggests that the respiratory failure in these children is mostly based on defects in central mechanisms, but peripheral mechanisms (mainly carotid bodies) may also be important.

Patients with CCHS have deficient carbon dioxide sensitivity during wakefulness and sleep such that they do not respond with a normal increase in ventilation in either state nor do they arouse in response to hypercarbia and/or hypoxemia during sleep. During wakefulness, a subset of patients may respond sufficiently to avoid significant hypercarbia, but most individuals with CCHS have hypoventilation that is severe enough that hypercarbia is apparent in the resting awake state. Children with CCHS also have altered sensitivity to hypoxia while awake and asleep. A key feature of CCHS is the lack of respiratory distress or sense of asphyxia with physiologic compromise (hypercarbia and/or hypoxemia). This lack of responsiveness to hypercarbia and/or hypoxemia with subsequent respiratory failure does not seem to consistently improve with age. A subset of older children with CCHS may show an increase in ventilation (specifically increase in respiratory rate rather than increase in tidal volume) when they are exercised at various work rates, a response that is possibly secondary to neural reflexes from rhythmic limb movements—although the increase in minute ventilation is often insufficient to avoid physiologic compromise.

CLINICAL MANIFESTATIONS

Patients with CCHS usually present in the 1st few hr after birth. Most children are the products of uneventful pregnancies and are term infants with appropriate weight for gestational age; Apgar scores have been variable. The affected infants do not show signs of respiratory distress, but their shallow respirations and respiratory pauses (apnea) evolve to respiratory failure with apparent cyanosis in the 1st day of life. In neonates with CCHS, the $Paco_2$ accumulates during sleep to very high levels, sometimes >90 mm Hg, and may decline to normal levels after the infants awaken. This problem becomes most apparent with failure of multiple attempts at extubation in an intubated neonate (who appears well with ventilatory support but in whom respiratory failure develops after removal of the support). However, the more severely affected infants hypoventilate awake and asleep; thus the previously described difference in $Paco_2$ between states is not apparent. Often, the respiratory rate is higher in rapid eye movement sleep than in nonrapid eye movement sleep in individuals with CCHS.

LO-CCHS should be suspected in infants, children, and adults who have unexplained hypoventilation, especially subsequent to the use of anesthetic agents, sedation, acute respiratory illness, and potentially treated obstructive sleep apnea. These individuals may have other evidence of chronic hypoventilation, including pulmonary hypertension, polycythemia, elevated bicarbonate concentration, difficulty concentrating, and mild unexplained neurocognitive impairment.

Besides treatment for the alveolar hypoventilation, children with CCHS require comprehensive physiologic evaluation and coordinated care to optimally manage associated abnormalities such as Hirschsprung disease, tumors of neural crest origin, symptoms of physiologic ANSD including cardiac asystole, among other findings (details provided in American Thoracic Society 2010 Statement on CCHS).

DIFFERENTIAL DIAGNOSIS

Testing should be performed to rule out primary neuromuscular, lung, and cardiac disease as well as an identifiable brainstem lesion that could account for the full constellation of symptoms characteristic of CCHS. Introduction of clinically available *PHOX2B* genetic testing allows for early and definitive diagnosis of CCHS. Because CCHS mimics many treatable and/or genetic diseases, the following disorders should be considered: X-linked myotubular myopathy, multiminicore disease, congenital myasthenic syndrome, altered airway or intrathoracic anatomy (diagnosis made with bronchoscopy and chest CT), diaphragm dysfunction (diagnosis made with diaphragm fluoroscopy), congenital cardiac disease, a structural hindbrain or brainstem abnormality (diagnosis made with MRI of the brain and brainstem), Möbius syndrome (diagnosis made with MRI of the brain and brainstem and neurologic examination), and specific metabolic diseases, such as Leigh syndrome, pyruvate dehydrogenase deficiency, and discrete carnitine deficiency. However the profound hypercarbia without respiratory distress during sleep will quickly lead the clinician to consider the diagnosis of CCHS or LO-CCHS.

Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation

Previously referred to as LO-CHS with hypothalamic dysfunction, **ROHHAD** (rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation) is a very rare disorder that was renamed to clarify that it is distinct from LO-CCHS (Chapter 47). The acronym describes the general sequence or "unfolding" of presenting symptoms, which can evolve over several years. The most dramatic and sentinel feature of ROHHAD is the rapid-onset weight gain (often >20 lb), which occurs over a 6-12 mo period in a seemingly normal young child. The diagnosis is based on clinical criteria that include onset of obesity and alveolar hypoventilation after the age of 1.5 yr (typically between 2 and 7 yr of age) and evidence of hypothalamic dysfunction as defined by 1 or more of the following findings: rapid-onset obesity, hyperprolactinemia, central hypothyroidism, disordered water balance, failure of response to growth hormone stimulation, corticotropin deficiency, and delayed/precocious puberty. Although it may not be apparent early in the course, all children with ROHHAD will develop hypoventilation. Considering the high prevalence of cardiorespiratory arrest and multisystem involvement, children with this disorder require coordinated comprehensive care with attention to development of hypoventilation (such as with repeated

physiologic recordings awake and asleep), initiation of supported ventilation, bradycardia (via Holter monitor), treatment of hypothalamic dysfunction (with involvement of an pediatric endocrinologist), tumors of neural crest origin (often ganglioneuromas or ganglioneuroblastomas; with involvement of an oncologist), and behavioral/intellectual decline (with annual neurocognitive testing and aggressive educational intervention). With meticulous management of the airway, breathing, and circulation, children with ROHHAD seem to stabilize and begin improvement in awake spontaneous breathing—though longitudinal studies are in a preliminary stage at present. Because of the high incidence of neural crest tumors, ROHHAD may be a paraneoplastic disorder.

Children with ROHHAD may present with **obstructive sleep apnea (OSA)** after development of obesity, but ROHHAD is distinct from **OSA hypoventilation syndrome** and **obesity hypoventilation syndrome**. The child with ROHHAD will go onto to severe hypoventilation despite intervention for the OSA. In children with exogenous obesity, the existence of obesity hypoventilation syndrome is controversial and is often referred to as OSA hypoventilation syndrome because it describes chronic OSA with resulting overnight hypercarbia, hypoxemia, and frequent arousals that lead to an altered set point of the central control of breathing (insensitivity to hypercarbia), awake hypoventilation, and daytime sleepiness. In children with OSA hypoventilation syndrome, treatment of the upper airway obstruction would be expected to result in complete resolution of hypoventilation and daytime sleepiness. In contrast, among children with ROHHAD the relief of upper airway obstruction unveils the central alveolar hypoventilation that requires lifelong ventilatory support. Both are distinguished from LO-CCHS by the absence of a CCHS-related *PHOX2B* mutation and the presence of (often morbid) obesity.

MANAGEMENT

Supported Ventilation—Diaphragm Pacing

Depending on the severity of respiratory control deficit, the individual with CCHS can have various means of artificial ventilation: noninvasive positive pressure ventilation or mechanical ventilation via tracheostomy (see Chapter 418.4). Diaphragm pacing offers another mode of supported ventilation; it involves bilateral surgical implantation of electrodes beneath the phrenic nerves, with connecting wires to subcutaneously implanted receivers. The external transmitter, which is much smaller and lighter in weight than a ventilator, sends a signal to flat donut-shaped antennae that are placed on the skin, over the subcutaneously implanted receivers. A signal travels from the external transmitter, ultimately, to the phrenic nerve to stimulate contraction of the diaphragm. A tracheostomy is typically required, at least initially, because the pacers induce a negative pressure on inspiration as a result of the contraction of the diaphragm being unopposed by pharyngeal dilation. Individuals with CCHS who are ventilator-dependent 24 hr/day are ideal candidates for diaphragm pacing to provide increased ambulatory freedom (without the "ventilator tether") while they are awake; however, they still require mechanical ventilator support while they are asleep. This balance between awake pacing and asleep mechanical ventilation allows for a rest from phrenic nerve stimulation at night. A growing number of children and adults who require artificial ventilatory support during sleep only are now using diaphragm pacing, a more acceptable option since the introduction of thoracoscopic diaphragm pacer implantation and shortened recovery time postoperatively.

Monitoring in the Home

Home monitoring for individuals with CCHS and LO-CCHS is distinctly different from and more conservative than that for other children requiring long-term ventilation because those with CCHS lack innate ventilatory and arousal responses to hypoxemia and hypercarbia. In the event of physiologic compromise, other children are more likely to show clinical signs of respiratory distress. For children and adults with CCHS and LO-CCHS, the only means of determining adequate ventilation and oxygenation is with objective measures from a pulse oximeter, end-tidal carbon dioxide monitor, and close supervision of these values by a trained registered nurse in the home and at school. At a minimum, it is essential that individuals with CCHS have continuous monitoring with pulse oximetry and end-tidal carbon dioxide with registered nurse supervision during all sleep time. Ideally, this such monitoring should be present 24 hr per day because, even while awake, they are not able to sense or adequately respond to a respiratory challenge as may occur with ensuing respiratory illness, increased activity, or even the simple activity of eating. These recommendations apply to all CCHS and LO-CCHS patients regardless of the nature of their artificial ventilatory support—but especially those with diaphragm pacers as they have no intrinsic alarms in the diaphragm pacer device.

Bibliography is available at Expert Consult.

418.3 Other Conditions

Zehava L. Noah and Cynthia Etzler Budek

MYELOMENINGOCELE WITH ARNOLD-CHIARI TYPE II MALFORMATION

Arnold-Chiari type II malformation (see Chapter 591.11) is associated with myelomeningocele, hydrocephalus, and herniation of the cerebellar tonsils, caudal brainstem, and the fourth ventricle through the foramen magnum. Sleep-disordered breathing, including OSA and hypoventilation, has been reported. Direct pressure on the respiratory centers or brainstem nuclei, or increased intracranial pressure because of the hydrocephalus may be responsible. Vocal cord paralysis, apnea, hypoventilation, and bradyarrhythmias have also been reported. Patients with Arnold-Chiari type II malformation have blunted responses to hypercapnia, and to a lesser degree, hypoxia.

Management

An acute change in the ventilatory state of a patient with this malformation requires immediate evaluation. Consideration must be given to posterior fossa decompression and/or treatment of the hydrocephalus. If this treatment is unsuccessful in resolving central hypoventilation or apnea, tracheostomy and long-term mechanical ventilation should be considered.

RAPID-ONSET OBESITY, HYPOTHALAMIC DYSFUNCTION, AND AUTONOMIC DYSREGULATION

See Chapter 418.2.

Obesity Hypoventilation Syndrome

As its name implies, obesity hypoventilation syndrome is a syndrome of central hypoventilation during wakefulness in obese patients with sleep-disordered breathing. Although it was initially described mainly in adult obese patients, obese children have also demonstrated the syndrome. Sleep-disordered breathing is a combination of OSA, hypopnea, and/or sleep hypoventilation syndrome. Patients are hypercapnic with cognitive impairment, morning headache, and hypersomnolence during the day. Chronic hypoxemia may lead to pulmonary hypertension and cor pulmonale.

Obesity is associated with reduced respiratory system compliance, increased airway resistance, reduced functional residual capacity, and increased work of breathing. Affected patients are unable to increase their respiratory drive in response to hypercapnia. Leptin may have a role in this syndrome. The sleep-disordered breathing leads to compensatory metabolic alkalosis. Because of the long half-life of bicarbonate, its elevation causes compensatory respiratory acidosis during wakefulness with elevated $Paco_2$.

Management

The use of **CPAP** during sleep may be sufficient for many patients. Patients with hypoxemia may require **BiPAP** and supplemental oxygen. Tracheostomy may be considered for patients who do not tolerate mask ventilation.

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ACQUIRED ALVEOLAR HYPOVENTILATION

Traumatic, ischemic, and inflammatory injuries to the brainstem, brainstem infarction, brain tumors, bulbar polio, and viral paraneoplastic encephalitis may also result in central hypoventilation.

OBSTRUCTIVE SLEEP APNEA

Epidemiology

Habitual snoring during sleep is extremely common during childhood. As many as 27% of children who snore are affected by **OSA.** The current obesity epidemic has affected the epidemiology of this condition. Peak prevalence is at 2-8 yr of age. The ratio between habitual snoring and OSA is 4 : 1 to 6 : 1.

Pathophysiology

OSA occurs when the luminal cross-sectional area of the upper airway is significantly reduced during inspiration. With increased airway resistance and reduced activation of pharyngeal dilators, negative pressure leads to upper airway collapse. The site of upper airway closure in children with OSA is at the level of tonsils and adenoids. The size of tonsils and adenoids increases throughout childhood up to 12 yr of age. Environmental irritants such as cigarette smoke or allergic rhinitis may accelerate the process. Reports now suggest that early viral infections may affect adenotonsillar proliferation.

Clinical Presentation

Snoring during sleep, behavioral disturbances, learning difficulties, excessive daytime sleepiness, metabolic issues, and cardiovascular morbidity may alert the parent or physician to the presence of OSA. Diagnosis is made with the help of airway radiograms and a polysomnogram.

Treatment

When adenotonsillar hypertrophy is suspected, a consultation with an ear, nose, and throat specialist for adenoidectomy and/or tonsillectomy may be indicated. For patients who are not candidates for surgical intervention or persist with OSA despite adenoidectomy and/or tonsillectomy, CPAP or BiPAP during sleep may alleviate the obstruction (see Chapter 19).

SPINAL CORD INJURY

Epidemiology

There are an estimated 11,000 new spinal cord injuries **(SCIs)** annually in the United States, with more than 50% resulting in quadriplegia. SCI is relatively rare in pediatric patients, with an incidence of 1-13% of all SCI patients. The incidence in infancy and early childhood is similar for boys and girls. The preponderance of SCI in adolescents is in males. Motor vehicle accidents, falls, sports injuries, and assaults are the main causes. SCI usually leads to lifelong disability.

Pathophysiology

Children with SCI have a disproportionately higher involvement of the upper cervical spine, high frequency of spinal cord injury without radiographic abnormality, delayed onset of neurologic deficits, and higher proportion of complete injury. Thus, there is a high likelihood in pediatric SCI of quadriplegia with intercostal muscle and/or diaphragmatic paralysis leading to respiratory failure.

Management

Immobilization and stabilization of the spine must be accomplished simultaneously with initial patient resuscitation. Children with high SCI typically require lifelong ventilation, so the decision to place a tracheostomy for chronic ventilatory support is usually made early in their course of treatment. Depending on the child's age and general condition, diaphragmatic pacing may be considered. Often patients with diaphragmatic pacing need tracheostomy placement if there is dyscoordination between pacing and glottal opening. Muscle spasms occur frequently in the SCI patient and are treated with muscle relaxants. Occasionally the muscle spasms involve the chest and present a serious impediment to ventilation. Continuous intrathecal infusion of muscle relaxant via an implanted subcutaneous pump may be indicated (see Chapter 606.5).

METABOLIC DISEASE

Mucopolysaccharidoses

See Chapter 88.

Mucopolysaccharidoses are a group of progressive hereditary disorders that lack the lysosomal enzymes that degrade glycosaminoglycans. Incompletely catabolized mucopolysaccharides accumulate in connective tissue throughout the body. The inheritance is autosomal recessive except for Hunt syndrome, which is X-linked. The diagnosis is suggested by the presence of glycosaminuria and is confirmed by a lysosomal enzyme assay. I-cell disease mucolipidosis type II is an inherited lysosomal disorder with accumulation of mucolipids. Phenotypically, it is similar to mucopolysaccharidoses, but the age of onset is earlier and there is no mucopolysacchariduria. Mucopolysaccharide deposits are frequently found in the head and neck and cause airway obstruction. Typically, the affected child has a coarse face and large tongue. Significant deposits are found in the adenoids, tonsils, and cartilage. Airway radiograms and a polysomnogram may help define the severity of the upper airway obstruction.

Treatment options have included enzyme replacement therapy and stem cell transplantation with limited success. Adenoidectomy and/or tonsillectomy may be indicated but surgery alone seldom solves the problem of airway obstruction. Noninvasive CPAP or BiPAP, or tracheostomy with ventilatory support may be helpful

Dysplasias

Campomelic dysplasia (see Chapter 698) and thanatophoric dysplasia (see Chapter 696) affect rib cage size, shape, and compliance, leading to respiratory failure. Most patients with these disorders do not survive beyond early infancy. Tracheostomy and ventilation may prolong life.

Glycogenosis Type Ii

See Chapter 87.1.

Glycogenosis type II is an autosomal recessive disorder. Clinical manifestations include cardiomyopathy and generalized muscle weakness. Cardiac issues may include heart failure and arrhythmias. Muscle weakness leads to respiratory insufficiency and sleep-disordered breathing. Treatment includes emerging therapies such as enzyme replacement therapy, chaperone molecules, and gene therapy. Supportive therapy may consist of either noninvasive ventilation, or tracheostomy and mechanical ventilation. Cardiac medications, protein-rich nutrition, and judicious physical therapy are additional measures that can be utilized.

Severe Tracheomalacia and/or Bronchomalacia (Airway Malacia)

Conditions associated with airway malacia include tracheoesophageal fistula, innominate artery compression, and pulmonary artery sling after surgical repair (see Chapter 389). Patients with tracheobronchomalacia present with cough, lower airway obstruction, and wheezing. Diagnosis is made via bronchoscopy, preferably with the patient breathing spontaneously in order to evaluate dynamic airway function. Positive end-expiratory pressure titration during the bronchoscopy helps identify the ideal airway pressure required to maintain airway patency and prevent tracheobronchial collapse.

Neuropathy of Severe Illness

Children recuperating from severe illness in the intensive care unit often have neuromuscular weakness from suboptimal nutrition. This neuromuscular weakness can be devastating when coupled with the catabolic effects of severe illness and the residual effects of sedatives, analgesics, and muscle relaxants, particularly if corticosteroids were administered. Children with neuromuscular compromise have limited ability to increase ventilation and usually do so by increasing respiratory rate. Because of weakness, costal and sternal retractions may not be observed. Children with severe neuromyopathy may respond to increased respiratory load by becoming apneic. A look of panic, a

change in vital signs such as significant tachycardia or bradycardia, and cyanosis may be the only signs of impending respiratory failure.

HEMATOLOGIC STEM-CELL TRANSPLANTATION

Hematologic stem cell transplant (HSCT) is a life-saving therapy for patients with hematologic, oncologic, and immunologic conditions. Historically, outcomes for these patients have been poor. Lung dysfunction after HSCT is a serious and often fatal complication. Common causes of HSCT lung dysfunction include bacterial, viral, and/or fungal infections, posttransplant lymphoproliferative disorder, idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, pulmonary cytolytic thrombi, engraftment syndrome, and bronchiolitis obliterans. Improvements in the management of HSCT have resulted in decreased graft-versus-host disease severity. Improved critical care practices, such as more in-depth diagnostic evaluation and lung-sparing ventilator strategies, have resulted in improved outcomes. Despite improved outcomes, a subset of HSCT patients will require chronic respiratory support for prolonged periods of time. In addition to post HSCT therapy, ongoing care may include noninvasive or invasive home ventilation, tracheostomy placement, diuretics, and supplemental nutrition.

MITOCHONDRIAL DISEASES

See Chapter 86.

Mitochondria are primarily responsible for the production of adenosine triphosphate. Mitochondrial diseases are a heterogeneous group of diseases in which adenosine triphosphate production is disrupted. Mitochondrial diseases are increasingly recognized and diagnosed in the pediatric population. Organs with high-energy requirements such as the neurons, and skeletal and cardiac muscles are particularly vulnerable. Although myopathy is the most frequently recognized presentation of mitochondrial disease, it is often part of a multisystem disease process. Neurologic complications include progressive proximal myopathy, kyphoscoliosis, dyskinesia, dystonia and spasticity, stroke, epilepsy, and visual and hearing impairment. Nonneurologic manifestations include cardiomyopathy, gastrointestinal dysmotility, gastroesophageal reflux, delayed gastric emptying, and pseudoobstruction.

Respiratory complications of mitochondrial disease are multifactorial. Muscle weakness, kyphoscoliosis, muscle spasms, and movement disorders may result in a restrictive pattern, and respiratory compromise. Additionally, dyscoordinated swallow and reflux may result in aspiration. In some mitochondrial diseases such as Leigh syndrome (see Chapter 86), central hypoventilation is an integral part of the disease. Supportive care for these patients may include noninvasive or invasive ventilation, tracheostomy placement, diuretics, appropriate nutrition, and dietary supplements.

Bibliography is available at Expert Consult.

418.4 Long-Term Mechanical Ventilation

Zehava L. Noah and Cynthia Etzler Budek

Many children with chronic severe respiratory insufficiency will benefit from long-term ventilatory support. The goals of chronic ventilation are to maintain normal oxygenation and ventilation, and to minimize the work of breathing. Caring for a child on long-term ventilatory support in the home is a complex, physically demanding, emotionally taxing, and expensive process for the family. It changes the family routines, priorities, and overall lifestyle, and may adversely affect intrafamilial and extrafamilial relationships. The discharge process for a child likely to require long-term ventilatory support should start early in the hospitalization, before the child is medically stable and prior to transition to a portable ventilator that can be maintained in the home.

The child's disease prognosis is a critical factor to consider when deciding to initiate long-term ventilation. Children with degenerative neuromuscular disease, such as SMA type I, suffer from respiratory failure very early in life, often triggered by the first respiratory illness. Although some parents of children with SMA decide to provide only palliative end-of-life care (see Chapter 43), others choose long-term invasive or noninvasive ventilatory support. Young children with chronic lung disease and airway malacia have the potential to improve their pulmonary function and to wean successfully off the ventilator if provided with adequate ventilation, good nutrition, and measures to promote development and prevent further lung injury.

Successful home discharge depends on whether there are adequate resources in the community to support the family. Some hospital programs that transition children home on ventilators utilize professional nurses in the home to assist with round-the-clock care. This level of care depends on adequate funding as well as availability of nursing agencies with skilled nurses. Housing can be a significant barrier to discharge if the home lacks adequate space for the child and caretakers, equipment, and supplies, presents environmental safety issues, including building and electrical code violations, and/or requires extensive home modifications for mobility, including ramping and lifts.

Funding for home care is typically a challenge for this pediatric population. Even if they have private insurance, coverage for home care benefits is often very limited. In the United States, most states have public aid funds available to support the special needs of eligible children who are ventilator dependent, although the extent of coverage varies considerably across the country.

RESPIRATORY EQUIPMENT FOR HOME CARE

Modes of mechanical ventilation support are discussed in Chapter 71.1.

Noninvasive Equipment

Supplemental oxygen and positive pressure support can be administered by nasal cannula. The nasal cannula system has the ability to deliver heated, supersaturated, high-flow gases. There are a number of mechanical devices available for the delivery of CPAP and BiPAP. These devices attach to nasal and full-face masks or nasal pillows and are best suited for the treatment of OSA where ventilatory support is required for only a portion of the day, typically during sleep. Long-term use of mask ventilation in small children may result in mid-face dysplasia or pressure wounds. This type of ventilation has also been used in children with mild forms of respiratory insufficiency due to recurrent atelectasis and/or nocturnal hypoventilation, as well as for palliation in more severely affected patients.

Rocker Bed

A rocker bed moves in a longitudinal seesaw motion at a set cycle rate. The child is secured to the bed with a strap across the body. Movement of the bed and gravitational pull promotes diaphragm movement. The rocker bed may be an option for children with mild neuromuscular weakness such as children recuperating from Guillain-Barré syndrome. For safety reasons this device should not be placed in a home with toddlers or young children, who may get trapped in its rotating mechanism.

Cuirasse

The cuirasse is a negative-pressure device that resembles a hard turtle shell. It is a fiberglass piece that is custom fit over the child's anterior chest and provides a tight seal. A hose attached to the cuirasse applies cycled negative pressure that lifts and releases the anterior chest wall. The cuirasse is suitable only for infants and children with mild neuromuscular weakness and pliable chest walls. A similar negative-pressure device utilizes a plastic bag that fits snugly around the chest and operates under the same principle as the cuirasse to lift and release the chest wall.

Iron Lung

The iron lung is a device that also applies negative pressure to the child's body. The child is placed in the iron lung cylinder with his head

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extending outside of the device. A cuff is placed around the neck to minimize air leaks. Negative pressure is cycled within the iron lung, facilitating chest wall movement. Ventilation is disrupted whenever the device is opened for patient care. The iron lung is suitable for children with muscular weakness who require ventilation for part of the day. Its main advantage is that it does not require a tracheostomy. However, upper airway obstruction may occur, and this risk requires ongoing evaluation. A smaller, lightweight version of this device is available for travel.

Diaphragmatic Pacing

Detailed in the management section of Ch. 418.2, diaphragm pacers may also be considered in children with spinal cord injury above C3, though the immediate advantages are less apparent than in CCHS.

Positive-Pressure Ventilators

Ideally, a ventilator intended for home use is lightweight and small, quiet so it doesn't interfere with activities of daily living or sleep, able to entrain room air, preferably has continuous flow, and has a wide range of settings (particularly for pressure, volume, pressure support, and rate) that allows ventilatory support from infancy to adulthood. Battery power for the ventilator, both internal and external, should be sufficient to permit unrestricted portability in the home and community. The equipment must also be impervious to electromagnetic interference and must be relatively easy to understand and troubleshoot. A variety of ventilators that are approved for home use are available, and familiarity with these devices is necessary to choose the best option for the individual child.

Children who are chronically ventilated via positive-pressure ventilation will require surgical placement of a tracheostomy tube. The tracheostomy tube provides stable access to the airway, a standardized interface for attaching the ventilator circuit to the patient, and the ability to easily remove airway secretions or deliver inhaled medications. Pediatric tracheostomy tubes typically have a single lumen and may have an inflatable cuff. Tracheostomy tubes with/without cuff inflation should be sized to control the air leak around the tube and promote adequate gas exchange, yet allow enough space around the tube to facilitate vocalization and prevent tracheal irritation and erosion from the tube.

When a tracheostomy tube is surgically placed, a slit opening is made in the trachea between the cartilaginous rings. Stay sutures are attached to the margins of the incision to facilitate emergent tube replacement prior to healing of the stoma tract. The tracheostomy tube is often electively changed by an otolaryngologist approximately 1 wk after initial placement, and the child is subsequently cleared for tracheostomy tube changes by the nursing staff. The child's caregivers, usually parents or family members and home nursing staff, are instructed in all aspects of tracheostomy care: stoma care, elective and emergent tracheostomy change, proper securing of the tracheostomy tube, suctioning of secretions, and recognition of tube obstruction or decannulation. The child's caregivers have to demonstrate competency with all the tasks prior to home discharge.

AIRWAY CLEARANCE

Thick, copious secretions may contribute to increased airway resistance and provide substrate for bacterial and fungal growth. Respiratory infections in turn lead to an increase in the amount of secretions and may increase viscosity, contributing to problems in airway clearance. Patients with neuromuscular weakness often have dyscoordination or absence of swallow, putting them at risk for aspiration of oral secretions or food. Reflux resulting in aspiration is also common. Additionally, many patients have poor or nonexistent cough, and some of them may have ciliary dysfunction.

Common modalities that help with clearance of secretions include postural drainage, manual or mechanical percussion or vibration, and vest or wrap percussion therapy. Force of cough may be enhanced with a cough assist device and/or abdominal binder. In addition, oropharyngeal or tracheal suctioning to remove secretions may promote airway clearance. In rare cases where airway clearance is not amenable to these measures, intermittent positive ventilation devices may be a useful adjunct.

Control of oral secretions can be achieved pharmacologically with anticholinergic drugs, localized injection of botulinum toxin (Botox), or surgical ligation of selected salivary ducts. In extreme cases, surgical tracheolaryngeal separation may be indicated. If thick, tenacious secretions are problematic, patient hydration and dosing of anticholinergic medication should be reviewed. Administration of nebulized dornase alfa or *N*-acetylcysteine, hypertonic saline, and/or sodium bicarbonate may be considered to thin secretions. In selected cases, bronchoscopy may be indicated for the removal of inspissated secretions and/or reexpansion of atelectatic pulmonary lobe or segment.

PHYSICAL THERAPY, OCCUPATIONAL THERAPY, AND SPEECH THERAPY

Therapies are very important in management of chronic respiratory failure. Potential goals for physical therapy are mobilization of the patient and strengthening of muscles, particularly truncal and abdominal muscles that are essential to pulmonary rehabilitation. Occupational therapy goals revolve around achieving or maintaining developmental milestones. Child life/developmental therapy focuses on provision of developmentally appropriate environmental stimulation and age-appropriate play. Speech therapy goals deal with oromotor skills for feeding and communication. Evaluation of swallow is a key component of therapy for children with chronic respiratory failure. Sign language is frequently utilized for communication because of delayed speech or hearing loss. Audiology specialists should be involved in the assessment of hearing, as there is a higher incidence of hearing loss in patients undergoing long-term ventilation.

INFECTIONS

Infections—tracheitis (see Chapter 385.2), bronchitis (see Chapter 391.2), and pneumonia (see Chapter 400)—are common in patients with chronic respiratory failure. Infections may be caused by community-acquired viruses (adenovirus, influenza, respiratory syncytial virus, parainfluenza, rhinovirus) or community- or hospital-acquired bacteria. Common pathogens are Gram-negative, highly antimicrobial-resistant pathogens that may cause further deterioration in pulmonary function. Bacterial infection is most likely in the presence of fever, deteriorating lung function (hypoxia, hypercarbia, tachypnea, and retractions), leukocytosis, and mucopurulent sputum. The presence of leukocytes and organisms on Gram stain of tracheal aspirate, as well as the visualization of new infiltrates on radiographs, may be consistent with bacterial infection.

Infection must be distinguished from tracheal colonization of bacteria, which is asymptomatic and associated with normal amounts of clear tracheal secretions. If infection is suspected, it must be treated with antibiotics, based on the culture and sensitivities of organisms recovered from the tracheal aspirate. Starting inhaled tobramycin and polymyxin E early may avert more serious infection. Antibiotics should be used judiciously to prevent further colonization with drug-resistant organisms. However, some patients who have recurrent infections may benefit from prophylaxis with inhaled antibiotics. Preventive measures are essential and include immunizations (influenza, pneumococcus, Haemophilus influenzae type b), passive immunity (respiratory syncytial virus), and good tracheostomy care.

MONITORING

A patient who is ventilated in the home must be electronically and/or physically monitored at all times. Infants and young children, children who are cognitively impaired, and children who are completely tracheostomy dependent for airway patency because of suprastomal obstruction must be under direct observation of the caregivers at all times. Caregivers should also closely monitor children whose pulmonary status is fragile or fluctuant. Continuous monitoring of O_2 saturation and heart rate is recommended during sleep, and either continuous or intermittent monitoring during the daytime, depending on patient stability. Patients with CCHS or pulmonary hypertension are particularly vulnerable to episodes of hypoxemia and/or hypercarbia, and

those with pulmonary hypertension are particularly susceptible to rapid drops in O_2 saturation.

Patients evaluated in pulmonary clinic for follow up should be monitored at each visit for heart rate, O_2 saturation, and transcutaneous and/or end-tidal CO_2 levels. Pulmonary function tests should be considered for those patients who are old enough and able to cooperate, usually after 5 yr of age. Serial echocardiograms should be obtained to monitor progression of pulmonary hypertension. Increased frequency of monitoring and surveillance are recommended for patients whose pulmonary status has improved and are in the process of weaning completely off ventilator support. A polysomnogram performed off the ventilator may be useful when total liberation from mechanical ventilation is being contemplated. In addition to physiologic parameters, patients must be monitored for signs of stress, agitation, and fatigue. Often these signs appear one or more days after the ventilator parameter changes.

WEANING OFF VENTILATOR SUPPORT

Patients recuperating from pulmonary disease, who are on stable ventilator settings with low positive end-expiratory pressure and minimal or no O_2 support, should be evaluated periodically for readiness to begin weaning from mechanical ventilation. Barriers to weaning may include residual lung disease, pulmonary hypertension, impaired central control of breathing, and muscle weakness. Weakness often has a multifactorial etiology. Factors such as underlying neuromuscular disease, use of sedatives, analgesics, steroids and muscle relaxants, and prolonged immobility, as well as utilization of mechanical ventilation, may downregulate mitochondrial activity in the respiratory muscles, and more so the diaphragm, and produce muscular changes resulting in weakness. Consequently, it is important to avoid 24 hr/day patient synchrony with ventilation and titrate the amount of ventilator support to prevent fatigue, yet facilitate spontaneous breathing.

When transitioning from full mechanical ventilatory support to spontaneous breathing, conditioning of the respiratory muscles can be achieved by several methods: gradual decrease of mechanical support by decreasing the ventilator pressures and/or rate, sprints of pressure support ventilation, retraining of the respiratory muscles with breathing exercises against an obstructed airway, and spontaneous breathing sprints off the ventilator. The weaning program may be initiated prior to initial hospital discharge or during follow up clinic visits. An initial weaning schedule may consist of 15 min sprints of free breathing off the ventilator up to 3 times/day while directly observed by caregiver and monitoring of respiratory parameters. The sprints are lengthened gradually with continued monitoring in the home and during frequent clinic visits. Additional factors that reflect tolerance of increased work of breathing, including weight gain, energy levels, general behavior and sleep patterns, are also monitored carefully. When the child has completely weaned off ventilator support while awake and is only on the ventilator approximately 6 hr nightly during sleep, a polysomnogram study performed off the ventilator may be considered prior to complete liberation from the mechanical ventilation device.

DISCHARGE PROCESS

The discharge process for a child going home for the first time on a ventilator is complex. A multidisciplinary, coordinated team approach is needed to develop an individualized, comprehensive plan that addresses medical, psychosocial, developmental, educational, and safety issues. The child should be transitioned to a ventilator suitable for home use that allows portability as well as adequate ventilation. Depending on the type of ventilation employed, a tracheostomy is typically placed to promote comfort and provide a stable airway as soon as the decision for long-term ventilation is made. Medical management should also focus on transitioning oxygen and ventilator parameters to settings appropriate for home care. The ventilated child must demonstrate medical stability at a level that can be safely managed at home; interventions to maintain patient stability should be minimal 1-2 wk before discharge.

Nutrition should be optimized to promote growth yet minimize excessive weight gain and carbon dioxide production. The nutritional requirements of a ventilated child are frequently decreased due to the supported work of breathing. The ventilated child often has problems with uncoordinated swallowing and oral aversion secondary to intubation. Speech therapy should be introduced early to begin oromotor therapy and return of swallow. Many children require gastrostomy tube placement to replace or supplement oral intake. Evaluation and management of reflux and the risk of aspiration should also be considered. Some children with severe reflux may require jejunal feedings. Communication devices to augment speech and introduction of sign language for speech and hearing impaired should be part of the planning.

Training of family caregivers should be initiated early in the discharge process and should be provided by nurses, respiratory care practitioners, and physical, occupational, and speech therapists knowledgeable in the individual child's care. Home caregivers, typically the parents or family members and home nursing staff, are instructed in all aspects of the child's care, including tracheostomy tube changes and care, tube feedings and care, medication administration, ventilator management and troubleshooting, emergency response, and cardiopulmonary resuscitation. Caregiver independence in delivery of care at the bedside and while transporting the child should be emphasized. Special emphasis should be placed on safety and the appropriate response in the event of an emergency. A standardized emergency bag containing critical tracheostomy and ventilator supplies should accompany the child at all times. A minimum of 2 family members should complete instruction and demonstrate their competency by independently providing their child's care for a 24-48 hr period prior to discharge.

Community agencies are identified for provision of home support services, typically including a nursing agency and equipment vendor. The nursing agency may provide private duty nursing services. Home care nurses should have pediatric tracheostomy and ventilator experience and be well versed in the individual child's care before home discharge. An equipment vendor who can provide the ventilator, medical equipment and supplies, and maintenance/repair service should be selected. A care conference involving the hospital team, funding agency, home nursing agency, equipment vendor, and family caregivers should take place before discharge. The conference is critical for coordination of last-minute details and facilitation of a smooth transition to home.

OUTPATIENT FOLLOW UP

Provision of ongoing medical support to the child and family after discharge is essential. The primary care provider in the community has the central role in coordination of care, and provision of well-child, acute, and chronic care, with the exception of ventilatory management. Equally important is the establishment of lines of communication between the primary care provider and the pulmonary/critical care specialists managing ventilator care, and the provision of timely access for advice and troubleshooting during the intervals between respiratory multidisciplinary clinic visits.

The purpose of the respiratory multidisciplinary clinic is to monitor the patient's progress, ensure that the ventilatory support is sufficient to promote growth and development and, when appropriate, to initiate or continue the ventilator weaning process. Physicians and/or advanced practice nurses who are well versed in ventilator care, typically pulmonary or critical care specialists, as well as respiratory care practitioners, evaluate the patient in clinic. Clinical nutrition, social work, and case management services should also be readily available.

The frequency of the clinic visits depends on the stability of the patient and the frequency of medical interventions needed to maintain clinical stability. A patient discharged from the hospital for the first time on a ventilator is typically evaluated in clinic within a month and may require monthly follow-up visits. Once the child is stable, the frequency decreases to every 3-6 mo. Older long-term patients who are no longer having major growth spurts are typically scheduled for annual visits. Patients who are actively weaning from the ventilator are seen more frequently. During the clinic visit respiratory monitoring is obtained while the child is on the ventilator and, if medically indicated,

off the ventilator, and repeated whenever ventilator adjustments are made. Whenever possible, readings obtained from home monitoring devices are compared with clinic monitoring to determine correlation. Recommendations regarding the child's ventilator management are communicated to the primary care provider by letter or phone call after each clinic visit.

TRANSITION OF CARE

The pulmonary team initiates ongoing discussions regarding self-care responsibilities and transitioning of medical care to adult providers with the adolescent and his parents when the patient reaches the early teens. Discussion about self-care should take into consideration realistic expectations about the adolescent's physical and cognitive capabilities. The actual transition of care occurs for most young adults at age 18-21 yr, and includes referral to an internist as well as an adult pulmonologist. Transition of medical care also includes transition from pediatric to adult support services for funding sources and nursing care. Ideally, an outpatient visit that includes current and future adult medical providers together is completed to facilitate communication and formally transition care.

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Chapter 419

Extrapulmonary Diseases with Pulmonary Manifestations

Susanna A. McColley

Respiratory symptoms commonly originate from extrapulmonary processes. The respiratory system adapts to metabolic demands and is exquisitely responsive to cortical input; therefore, **tachypnea** is common in the presence of metabolic stress such as fever, whereas dyspnea may be related to anxiety. **Cough** most commonly arises from upper or lower respiratory tract disorders, but it can originate from the central nervous system, as with cough tic or psychogenic cough, and it can be a prominent symptom in children with gastroesophageal reflux disease. **Chest pain** does not commonly arise from pulmonary processes in otherwise healthy children but more often has a neuromuscular or inflammatory etiology. **Cyanosis** can be caused by cardiac or hematologic disorders, and **dyspnea** and **exercise intolerance** can have a number of extrapulmonary causes. These disorders may be suspected on the basis of the history and physical examination, or they may be considered in children in whom diagnostic studies have atypical findings or who show poor response to usual therapy. Table 419-1 lists more common causes of such symptoms.

EVALUATION

In the evaluation of a child or adolescent with respiratory symptoms, it is important to obtain a detailed past medical history, family history, and review of systems to evaluate the possibility of extrapulmonary origin. A comprehensive physical examination is also essential in obtaining clues to extrapulmonary disease.

Disorders of other organ systems, and many systemic diseases, can have significant respiratory system involvement. Although it is most common to encounter these complications in patients with known diagnoses, respiratory system disease is sometimes the sole or most prominent symptom at the time of presentation. Acute aspiration during feeding can be the presentation of neuromuscular disease in an infant who initially appears to have normal muscle tone and development. Complications can be life-threatening, particularly in immunocompromised patients. The onset of respiratory findings may be insidious; for example, pulmonary vascular involvement in patients with systemic vasculitis may appear as an abnormality in diffusing capacity of the lung for carbon monoxide before the onset of symptoms. Table 419-2 lists disorders that commonly have respiratory complications.

Bibliography is available at Expert Consult.

Table 419-1 Respiratory Signs and Symptoms Originating from Outside the Respiratory Tract

SIGN OR SYMPTOM	NONRESPIRATORY CAUSE(S)	PATHOPHYSIOLOGY	CLUES TO DIAGNOSIS
Chest pain	Cardiac disease	Inflammation (pericarditis), ischemia (anomalous coronary artery, vascular disease)	Precordial pain, friction rub on examination; exertional pain, radiation to arm or neck
Chest pain	Gastroesophageal reflux disease	Esophageal inflammation and/or spasm	Heartburn, abdominal pain
Cyanosis	Congenital heart disease Methemoglobinemia	Right-to-left shunt Increased levels of methemoglobin interfere with delivery of oxygen to tissues	Neonatal onset, lack of response to oxygen Drug or toxin exposure, lack of response to oxygen
Dyspnea	Toxin exposure, drug side effect, or overdose	Variable, but often metabolic acidosis	Drug or toxin exposure confirmed by history or toxicology screen, normal oxygen saturation measured by pulse oximetry
	Anxiety, panic disorder	Increased respiratory drive and increased perception of respiratory efforts	Occurs during stressful situation, other symptoms of anxiety or depression

Continued

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Table 419-1 Respiratory Signs and Symptoms Originating from Outside the Respiratory Tract—cont'd

SIGN OR SYMPTOM	NONRESPIRATORY CAUSE(S)	PATHOPHYSIOLOGY	CLUES TO DIAGNOSIS
Exercise intolerance	Anemia	Inadequate oxygen delivery to tissues	Pallor, tachycardia, history of bleeding, history of inadequate diet
Exercise intolerance	Deconditioning	Self-explanatory	History of inactivity, obesity
Hemoptysis	Nasal bleeding	Posterior flow of bleeding causes appearance of pulmonary origin	History and physical findings suggest nasal source; normal chest examination, and chest radiography
	Upper gastrointestinal tract bleeding	Hematemesis mimics hemoptysis	History and physical examination suggest gastrointestinal source, normal chest examination and chest radiography
Wheezing, cough, dyspnea	Congenital or acquired cardiac disease	Pulmonary overcirculation (atrioseptal defect, ventriculoseptal defect, patent ductus arteriosus), left ventricular dysfunction	Murmur Refractory to bronchodilators Radiographic changes (prominent pulmonary vasculature, pulmonary edema)
Wheezing, cough	Gastroesophageal reflux disease	Laryngeal and bronchial response to stomach contents Vagally mediated bronchoconstriction	Emesis, pain, heartburn Refractory to bronchodilators

Table 419-2 Disorders with Frequent Respiratory Tract Complications

UNDERLYING DISORDER(S)	RESPIRATORY COMPLICATIONS	DIAGNOSTIC TESTS
Autoimmune disorders	Pulmonary vascular disease, restrictive lung disease, pleural effusion (especially systemic lupus erythematosus), upper airway disease (Wegener granulomatosis)	Spirometry, lung volume determination, oximetry, diffusing capacity of the lung for carbon monoxide, chest radiography, upper airway endoscopy, and/or CT
Central nervous system disease (static or progressive)	Aspiration of oral or gastric contents	Chest radiography, videofluoroscopic swallowing study, esophageal pH probe, fiberoptic bronchoscopy
Immunodeficiency	Infection, bronchiectasis	Chest radiography, fiberoptic bronchoscopy, chest CT
Liver disease	Pleural effusion, hepatopulmonary syndrome	Chest radiography, assessment of orthodeoxia
Malignancy and its therapies	Infiltration, metastasis, malignant or infectious effusion, parenchymal infection, graft-versus-host disease (bone marrow transplant)	Chest radiography, chest CT, fiberoptic bronchoscopy, lung biopsy
Neuromuscular disease	Hypoventilation, atelectasis, pneumonia	Spirometry, lung volume determination, respiratory muscle force measurements
Obesity	Restrictive lung disease, obstructive sleep apnea syndrome, asthma	Spirometry, lung volume determination, nocturnal polysomnography

The Cardiovascular System

PART XX

Section 1 Developmental Biology of the Cardiovascular System

Chapter 420 Cardiac Development

Daniel Bernstein

Knowledge of the cellular and molecular mechanisms of cardiac development is necessary for understanding congenital heart defects and will be even more important in developing strategies for prevention, whether cell or molecular therapies or fetal cardiac interventional procedures. Cardiac defects have traditionally been grouped by common morphologic patterns: for example, abnormalities of the outflow tracts (conotruncal lesions such as tetralogy of Fallot and truncus arteriosus) and abnormalities of atrioventricular septation (primum atrial septal defect, complete atrioventricular canal defect). These morphologic categories may be revised or eventually supplanted by new categories as our understanding of the genetic basis of congenital heart disease progresses.

Bibliography is available at Expert Consult.

420.1 Early Cardiac Morphogenesis

Daniel Bernstein

In the early presomite embryo, the first identifiable cardiac progenitor cell clusters are arranged in the anterior lateral plate mesoderm on both sides of the embryo's central axis; these clusters form paired cardiac tubes by 18 days of gestation. The paired tubes fuse in the midline on the ventral surface of the embryo to form the primitive heart tube by 22 days. This straight heart tube is composed of an outer myocardial layer, an inner endocardium, and a middle layer of extracellular matrix known as the cardiac jelly. There are 2 distinct cell lineages: the primary heart field provides precursor cells for the left ventricle, whereas the secondary heart field provides precursors for the atria and right ventricle. Premyocardial cells, including epicardial cells and cells derived from the neural crest, continue their migration into the region of the heart tube. Regulation of this early phase of cardiac morphogenesis is controlled in part by the interaction of specific signaling molecules or ligands, usually expressed by 1 cell type, with specific receptors, usually expressed by another cell type. Positional information is conveyed to the developing cardiac mesoderm by factors such as retinoids (isoforms of vitamin A), which bind to specific nuclear receptors and regulate gene transcription. Migration of epithelial cells into the developing heart tube is directed by extracellular matrix proteins (such as fibronectin) interacting with cell surface receptors (the integrins). Other important regulatory molecules include bone morphogenetic protein 2 (BMP2); fibroblast growth factor 4 (FGF4); the transcription factors Nkx2.5, GATA4, Mesp1, and Mesp2; and members of the Wnt/β-catenin signaling pathway. The clinical importance of these ligands is revealed by the spectrum of **cardiac teratogenic** effects caused by the retinoid-like drug isotretinoin.

As early as 20-22 days, before cardiac looping, the embryonic heart begins to contract and exhibit phases of the cardiac cycle that are surprisingly similar to those in the mature heart. Morphologists initially identified segments of the heart tube that were believed to correspond to structures in the mature heart (Fig. 420-1): the sinus venosus and atrium (right and left atria), the primitive ventricle (left ventricle), the bulbus cordis (right ventricle), and the truncus arteriosus (aorta and pulmonary artery). However, this model is oversimplified. Only the trabecular (most heavily muscularized) portions of the left ventricular myocardium are present in the early cardiac tube; the cells that will become the inlet portion of the left ventricle migrate into the cardiac tube at a later stage (after looping is initiated). Even later to appear are the primordial cells that give rise to the great arteries (truncus arteriosus), including cells derived from the neural crest, which are not present until after cardiac looping is complete. Chamber-specific transcription factors participate in the differentiation of the right and left ventricles. The basic helix-loop-helix (bHLH) transcription factor dHAND is expressed in the developing right ventricle; disruption of this gene or of other transcriptional factors such as myocyte enhancer factors 2C (MEF2C) in mice leads to hypoplasia of the right ventricle. The transcription factor eHAND is expressed in the developing left ventricle and conotruncus and is also critical to their development. How regulation of developmentally coordinated groups of genes is achieved has been the focus of recent research. One mechanism is through the expression of small noncoding RNAs known as microRNAs, each of which regulate the expression of multiple target genes. Another is through modifications in chromatin, the DNA scaffolding which acts as a controller of gene expression. Chromatin remodeling mediated by factors such as Brg1, Chd7, histone demethylases, and methyltransferases is associated with cardiac developmental defects.

420.2 Cardiac Looping

Daniel Bernstein

At approximately 22-24 days, the heart tube begins to bend ventrally and toward the right (see Fig. 420-1). The heart is the first organ to escape from the bilateral symmetry of the early embryo. Looping brings the future left ventricle leftward and in continuity with the sinus venosus (future left and right atria), whereas the future right ventricle is shifted rightward and in continuity with the truncus arteriosus (future aorta and pulmonary artery). This pattern of development explains the relatively common occurrence of the cardiac anomalies double-outlet right ventricle and double-inlet left ventricle and the extreme rarity of double-outlet left ventricle and double-inlet right ventricle (see Chapter 430.5). When cardiac looping is abnormal (situs inversus, heterotaxia), the incidence of serious cardiac malformations is high and there are usually associated abnormalities in the left-right (L-R) patterning of the lungs and abdominal viscera.

Potential mechanisms of cardiac looping include differential growth rates for myocytes on the convex vs the concave surface of the curve, differential rates of programmed cell death (apoptosis), and mechanical forces generated within myocardial cells via their actin cytoskeleton. The signal for this directionality is contained in a concentration gradient between the right and left sides of the embryo in the expression of critical signaling molecules. A number of signaling

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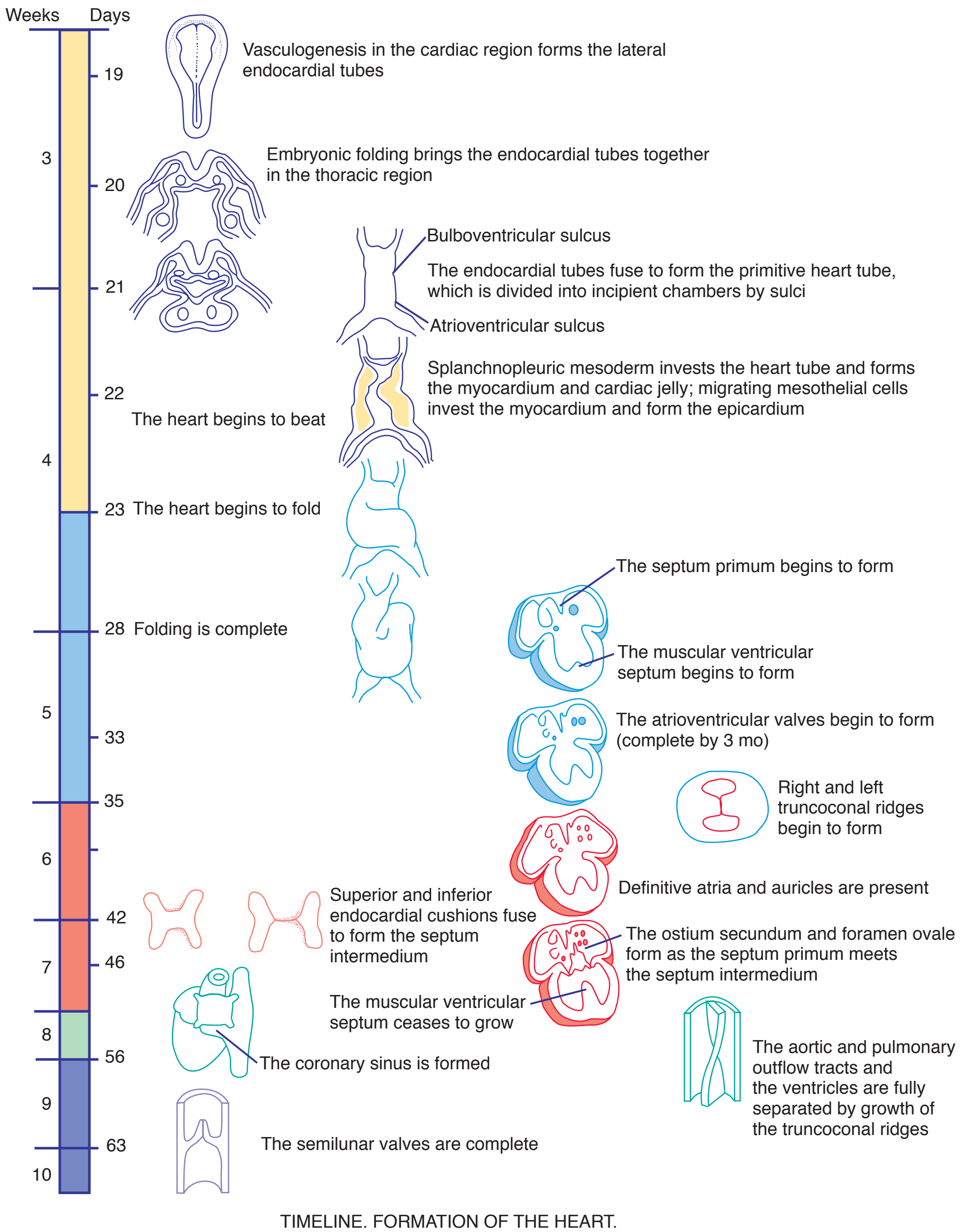

Figure 420-1 Timeline of cardiac morphogenesis. *(From Larsen WJ: Essentials of human embryology, New York, 1998, Churchill Livingstone.)*

pathways have been identified as regulators of this L-R asymmetry, including sonic hedgehog (SHH), transforming growth factor-β, nodal, and LR dynein. Interestingly, mice in which the LR dynein gene has been inactivated display random L-R orientation of the heart and abdominal viscera, with 50% of their hearts looping to the right and 50% looping to the left.

420.3 Cardiac Septation

Daniel Bernstein

When looping is complete, the external appearance of the heart is similar to that of a mature heart; internally, the structure resembles a single tube, although it now has several bulges resulting in the appearance of primitive chambers. The common atrium (comprising both the right and left atria) is connected to the primitive ventricle (future left ventricle) via the atrioventricular canal. The primitive ventricle is connected to the bulbus cordis (future right ventricle) via the bulboventricular foramen. The distal portion of the bulbus cordis is connected to the truncus arteriosus via an outlet segment (the conus).

The heart tube now consists of several layers of myocardium and a single layer of endocardium separated by cardiac jelly, an acellular extracellular matrix secreted by the myocardium. Septation of the heart begins at approximately day 26 with the ingrowth of large tissue masses, the endocardial cushions, at both the atrioventricular and conotruncal junctions (see Fig. 420-1). These cushions consist of protrusions of cardiac jelly, which, in addition to their role in development, also serve a physiologic function as primitive heart valves. Endocardial cells dedifferentiate and migrate into the cardiac jelly in the region of the endocardial cushions, eventually becoming mesenchymal cells that will form part of the atrioventricular valves.

Complete septation of the atrioventricular canal occurs with fusion of the endocardial cushions. Most of the atrioventricular valve tissue

is derived from the ventricular myocardium in a process involving undermining of the ventricular walls. Because this process occurs asymmetrically, the tricuspid valve annulus sits closer to the apex of the heart than the mitral valve annulus does. Physical separation of these 2 valves produces the atrioventricular septum, the absence of which is the primary common defect in patients with **atrioventricular canal defects** (see Chapter 426.5). If the process of undermining is incomplete, the right atrioventricular valve may not separate normally from the ventricular myocardium, a possible cause of **Ebstein anomaly** (see Chapter 430.7).

Septation of the atria begins at ≈30 days with growth of the septum primum downward toward the endocardial cushions (see Fig. 420-1). The orifice that remains is the ostium primum. The endocardial cushions then fuse and, together with the completed septum primum, divide the atrioventricular canal into right and left segments. A 2nd opening appears in the posterior portion of the septum primum, the ostium secundum, and it allows a portion of the fetal venous return to the right atrium to pass across to the left atrium. Finally, the septum secundum grows downward, just to the right of the septum primum. Together with a flap of the septum primum, the ostium secundum forms the foramen ovale, through which fetal blood passes from the inferior vena cava to the left atrium (see Chapter 421).

Septation of the ventricles begins at about embryonic day 25 with protrusions of endocardium in both the inlet (primitive ventricle) and outlet (bulbus cordis) segments of the heart. The inlet protrusions fuse into the bulboventricular septum and extend posteriorly toward the inferior endocardial cushion, where they give rise to the inlet and trabecular portions of the interventricular septum. **Ventricular septal defects** can occur in any portion of the developing interventricular septum (see Chapter 426.6). The outlet or conotruncal septum develops from ridges of cardiac jelly, similar to the atrioventricular cushions. These ridges fuse to form a spiral septum that brings the future pulmonary artery into communication with the anterior and rightward right ventricle and the future aorta into communication with the posterior and leftward left ventricle. Differences in cell growth of the outlet septum lead to lengthening of the segment of smooth muscle beneath the pulmonary valve (conus), a process that separates the tricuspid and pulmonary valves. In contrast, disappearance of the segment beneath the aortic valve leads to fibrous continuity of the mitral and aortic valves. Defects in these processes are responsible for **conotruncal** and **aortic arch defects** (truncus arteriosus, tetralogy of Fallot, pulmonary atresia, double-outlet right ventricle, interrupted aortic arch), a group of cardiac anomalies often associated with deletions of the DiGeorge critical region of chromosome 22q11 (see Chapters 423 and 424). The transcription factor Tbx1 has been implicated as a candidate gene, which may be responsible for DiGeorge syndrome. Several genes have been implicated in valve formation, including *Ptpn11*, which encodes the tyrosine phosphatase Shp-2, and when present in a mutated from is one of the genes responsible for **Noonan syndrome**, associated with pulmonary valve stenosis; and NOTCH1, a regulator of cell differentiation that has been associated with aortic valve disease.

420.4 Aortic Arch Development

Daniel Bernstein

The aortic arch, head and neck vessels, proximal pulmonary arteries, and ductus arteriosus develop from the aortic sac, arterial arches, and dorsal aortae. When the straight heart tube develops, the distal outflow portion bifurcates into the right and left 1st aortic arches, which join the paired dorsal aortae (Fig. 420-2). The dorsal aortae will fuse to form the descending aorta. The proximal aorta from the aortic valve to the left carotid artery arises from the aortic sac. The 1st and 2nd arches largely regress by about 22 days, with the 1st aortic arch giving rise to the maxillary artery and the 2nd to the stapedial and hyoid arteries. The 3rd arches participate in the formation of the innominate artery and the common and internal carotid arteries. The right 4th arch gives rise to the innominate and right subclavian arteries, and the left 4th arch participates in formation of the segment of the aortic arch between

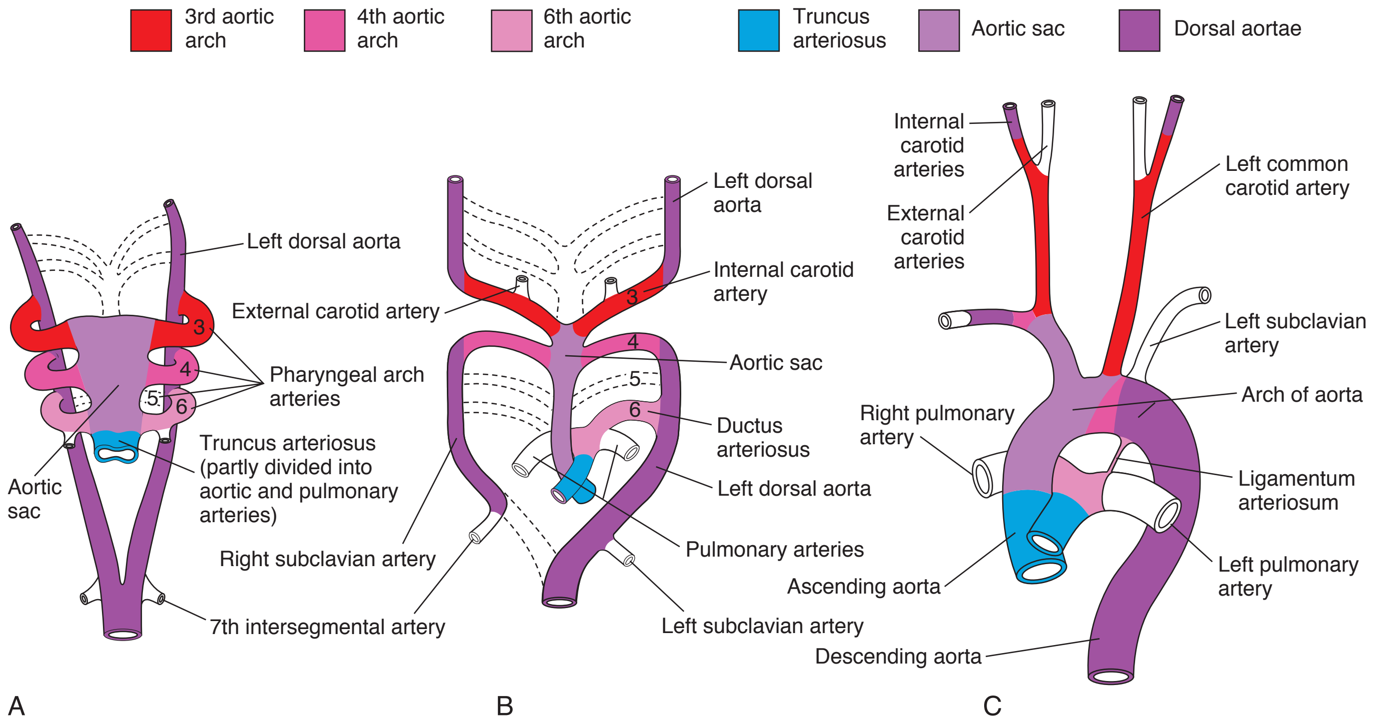

Figure 420-2 Schematic drawings illustrating the changes that result during transformation of the truncus arteriosus, aortic sac, aortic arches, and dorsal aortae into the adult arterial pattern. The vessels that are not shaded or colored are not derived from these structures. **A,** Aortic arches at 6 wk; by this stage the 1st 2 pairs of aortic arches have largely disappeared. **B,** Aortic arches at 7 wk; the parts of the dorsal aortae and aortic arches that normally disappear are indicated by broken lines. **C,** Arterial vessels of a 6 mo old infant. *(From Moore KL, Persaud TVN, Torchia M: The developing human, Philadelphia, 2007, Elsevier.)*

the left carotid artery and the ductus arteriosus. The 5th arch does not persist as a major structure in the mature circulation. The 6th arches join the more distal pulmonary arteries, with the right 6th arch giving rise to a portion of the proximal right pulmonary artery and the left 6th arch giving rise to the ductus arteriosus. The aortic arch between the ductus arteriosus and the left subclavian artery is derived from the left-sided dorsal aorta, whereas the aortic arch distal to the left subclavian artery is derived from the fused right and left dorsal aortae. Abnormalities in development of the paired aortic arches are responsible for **right aortic arch, double aortic arch,** and **vascular rings** (see Chapter 432.1).

420.5 Cardiac Differentiation

Daniel Bernstein

The process by which the totipotential cells of the early embryo become committed to specific cell lineages is differentiation. Precardiac mesodermal cells differentiate into mature cardiac muscle cells with an appropriate complement of cardiac-specific contractile elements, regulatory proteins, receptors, and ion channels. Expression of the contractile protein myosin occurs at an early stage of cardiac development, even before fusion of the bilateral heart primordia. Differentiation in these early mesodermal cells is regulated by signals from the anterior endoderm, a process known as *induction*. Several putative early signaling molecules include fibroblast growth factor, activin, and insulin. Signaling molecules interact with receptors on the cell surface; these receptors activate 2nd messengers, which, in turn, activate specific nuclear transcription factors (GATA-4, MEF2, Nkx, bHLH, and the retinoic acid receptor family) that induce the expression of specific gene products to regulate cardiac differentiation. Some of the primary disorders of cardiac muscle, the **cardiomyopathies,** may be related to defects in some of these signaling molecules (see Chapter 439).

Developmental processes are chamber specific. Early in development, ventricular myocytes express both ventricular and atrial isoforms of several proteins, such as atrial natriuretic peptide (ANP) and myosin light chain (MLC). Mature ventricular myocytes do not express ANP and express only a ventricular-specific MLC 2v isoform, whereas mature atrial myocytes express ANP and an atrial-specific MLC 2a isoform. Heart failure (see Chapter 442), volume overload (see Chapters 426 and 428), and pressure overload hypertrophy (see Chapter 427) are associated with a recapitulation of fetal cell phenotypes in which mature myocytes reexpress fetal proteins. Because different isoforms have different contractile behavior (fast vs. slow activation, high vs. low adenosine triphosphatase activity), expression of different isoforms may have important functional consequences.

The extent to which stem cells can be made to differentiate into cardiac muscle cells is the focus of investigation in the field of regenerative cardiology. The demonstration that fully differentiated adult cells (e.g., skin fibroblasts or peripheral blood mononuclear cells) can be *reprogrammed* into induced pluripotential stem cells and then *differentiated* into beating cardiomyocytes in vitro, has opened up many new avenues to study cardiovascular disease. Some investigators believe that there are precursor cells (cardiac stem cells) resident within the myocardium that can replace damaged myocytes, although at a rate too slow to be clinically useful. Scientists are working on trying to stimulate these cells with the proper regulatory factors, thus inducing them to regenerate damaged cardiac muscle. Others are investigating whether circulating stem cells, bone marrow–derived cells, or the factors they secrete can support cardiac regeneration. Eventually, stem cells grown on biomechanical scaffolds may be used to build a replacement ventricle for patients with hypoplastic left or right heart.

420.6 Developmental Changes in Cardiac Function

Daniel Bernstein

During development, the composition of the myocardium undergoes profound changes that result in an increase in the number and size of myocytes. During prenatal life, this process involves myocyte division (hyperplasia), whereas after the 1st few postnatal weeks, subsequent cardiac growth occurs mostly by an increase in myocyte size (hypertrophy). The myocytes themselves change shape from round to cylindrical, the proportion of myofibrils (which contain the contractile apparatus) increases, and the myofibrils become more regular in their orientation.

The plasma membrane (known as the *sarcolemma* in myocytes) is the location of the ion channels and transmembrane receptors that regulate the exchange of chemical information from the cell surface to the cell interior. Ion fluxes through these channels control the processes of depolarization and repolarization. Developmental changes have been described for the sodium-potassium pump, the sodium-hydrogen exchanger, and voltage-dependent calcium channels. As the myocyte matures, extensions of the sarcolemma develop toward the interior of the cell (the t-tubule system), which dramatically increases its surface area and enhances rapid activation of the myocyte. Regulation of the membrane's α- and β-adrenergic receptors with development enhances the ability of the sympathetic nervous system to control cardiac function as the heart matures.

The sarcoplasmic reticulum (SR), a series of tubules surrounding the myofibrils, controls the intracellular calcium concentration. A series of pumps regulate calcium release to the myofibrils for initiation of contraction (ryanodine-sensitive calcium channel) and calcium uptake for initiation of relaxation (adenosine triphosphate–dependent SR calcium pump). In immature hearts, this SR calcium transport system is less well developed, and such hearts consequently have an increased dependence on transport of calcium from outside the cell for contraction. In a mature heart, the majority of the calcium to activate contraction comes from the SR. This developmental phenomenon may explain the sensitivity of the infant heart to sarcolemmal calcium channel blockers such as verapamil, which can result in a marked depression in contractility (see Chapter 435).

The major contractile proteins (myosin, actin, tropomyosin, and troponin) are organized into the functional unit of cardiac contraction, the sarcomere. Each has several isoforms that are expressed differentially by location (atrium vs. ventricle) and by developmental stage (embryo, fetus, newborn, adult).

Changes in myocardial structure and myocyte biochemistry result in easily quantifiable differences in cardiac function with development. Fetal cardiac function is less responsive to changes in both preload (filling volume) and afterload (systemic resistance). The most effective means of increasing ventricular function in a fetus is through increasing the heart rate. After birth and with further maturation, preload and afterload play an increasing role in regulating cardiac function. The rate of cardiac relaxation is also developmentally regulated. The decreased ability of the immature SR calcium pump to remove calcium from the contractile apparatus is manifested as a decreased ability of the fetal heart to enhance relaxation in response to sympathetic stimulation.

Chapter 421

The Fetal to Neonatal Circulatory Transition

421.1 The Fetal Circulation

Daniel Bernstein

The human fetal circulation and its adjustments after birth are similar to those of other large mammals, although rates of maturation differ. In the fetal circulation, the right and left ventricles exist in a parallel circuit, as opposed to the series circuit of a newborn or adult (Fig. 421-1*A*). In the fetus, the placenta provides for gas and metabolite exchange. Because the lungs do not provide gas exchange, the pulmonary vessels are vasoconstricted, diverting blood away from the pulmonary circulation. Three cardiovascular structures unique to the fetus are important for maintaining this parallel circulation: the ductus venosus, foramen ovale, and ductus arteriosus.

The placenta is not as efficient an oxygen exchange organ as the lungs, so that umbilical venous Po_2 (the highest level of oxygen provided to the fetus) is only about 30-35 mm Hg. Approximately 50% of the umbilical venous blood enters the hepatic circulation, whereas the rest bypasses the liver and joins the inferior vena cava via the ductus venosus, where it partially mixes with poorly oxygenated inferior vena cava blood derived from the lower part of the fetal body. This combined lower body plus umbilical venous blood flow (Po_2 of ≈26-28 mm Hg) enters the right atrium and is preferentially directed by a flap of tissue at the right atrial–inferior vena caval junction, the eustachian valve, across the foramen ovale to the left atrium (see Fig. 421-1*B*). This is the major source of left ventricular blood flow, as pulmonary venous return is minimal. Left ventricular blood is then ejected into the ascending aorta where it supplies predominantly the fetal upper body and brain.

Fetal superior vena cava blood, which is considerably less oxygenated (Po_2 of 12-14 mm Hg), enters the right atrium and preferentially flows across the tricuspid valve, rather than the foramen ovale, into the right ventricle. From the right ventricle, the blood is ejected into the pulmonary artery. Because the pulmonary arterial circulation is vasoconstricted, only approximately 5% of right ventricular outflow enters the lungs. The major portion of this blood bypasses the lungs and flows right-to-left through the ductus arteriosus into the descending aorta to perfuse the lower part of the fetal body, including providing flow to the placenta via the 2 umbilical arteries. Thus, the upper part of the fetal body (including the coronary and cerebral arteries and those to the upper extremities) is perfused exclusively from the left ventricle with blood that has a slightly higher Po_2 than the blood perfusing the lower part of the fetal body, which is derived mostly from the right ventricle. Only a small volume of blood from the ascending aorta (10% of fetal cardiac output) flows all the way around the aortic arch (aortic isthmus) to the descending aorta.

The **total fetal cardiac output**—the combined output of both the left and right ventricles—is ≈450 mL/kg/min. Approximately 65% of descending aortic blood flow returns to the placenta; the remaining 35% perfuses the fetal organs and tissues. In the sheep fetus, where most of these circulatory pathways were studied, right ventricular output is approximately 2 times that of the left ventricle. In the human fetus, which has a larger percentage of blood flow going to the brain, right ventricular output is probably closer to 1.3 times left ventricular flow. Thus, during fetal life the right ventricle is not only pumping against systemic blood pressure but is also performing a greater volume of work than the left ventricle.

It has been postulated that blood flow is an important determinant of growth of fetal cardiac chambers, valves, and blood vessels. Thus, in

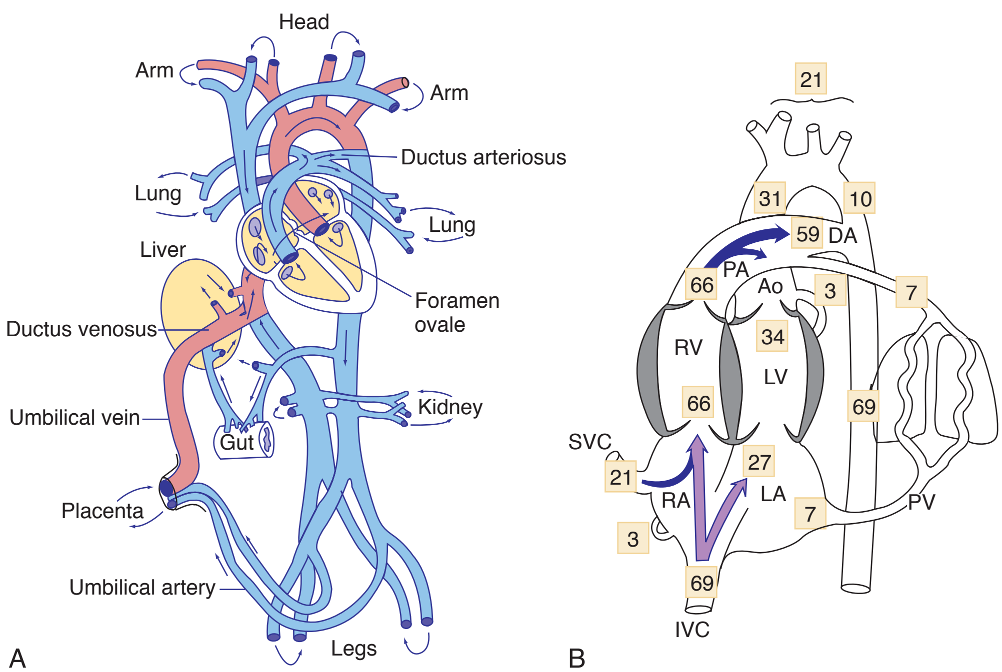

Figure 421-1 **A,** The human circulation before birth (partly after Dawes). Red indicates more highly oxygenated blood, and arrows indicate the direction of flow. More highly oxygenated blood from the placenta passes through the foramen ovale from the right to the left atrium, thus bypassing the lungs. **B,** Percentages of combined ventricular output that return to the fetal heart, that are ejected by each ventricle, and that flow through the main vascular channels. Figures are those obtained from studies of late-gestation fetal lambs. Ao, aorta; DA, ductus arteriosus; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava. *(From Rudolph AM:* Congenital diseases of the heart, *Chicago, 1974, Year Book.)*

the presence of a narrowing (stenosis) of an upstream structure such as the mitral valve, flow downstream into the left ventricle is limited and left ventricular growth may be compromised, leading to hypoplastic left heart syndrome (see Chapter 431.10). Similarly, stenosis of a downstream structure such as the aortic valve can similarly disrupt flow into the left ventricle and lead to hypoplastic left-heart syndrome. Fetal cardiac interventional treatments, currently experimental, are aimed at opening stenotic aortic valves in mid-gestation fetuses, and allowing more normal left ventricular growth.

421.2 The Transitional Circulation

Daniel Bernstein

At birth, mechanical expansion of the lungs and an increase in arterial Po_2 result in a rapid decrease in pulmonary vascular resistance. Concomitantly, removal of the low-resistance placental circulation leads to an increase in systemic vascular resistance. The output from the right ventricle now flows entirely into the pulmonary circulation, and because pulmonary vascular resistance becomes lower than systemic vascular resistance, the shunt through the ductus arteriosus reverses and becomes left to right. In the course of several days, the high arterial Po_2 constricts and eventually closes the ductus arteriosus, which eventually becomes the ligamentum arteriosum. The increased volume of pulmonary blood flow returning to the left atrium from the lungs increases left atrial volume and pressure sufficiently to close the flap of the foramen ovale functionally, although the foramen may remain probe patent for several years.

Removal of the placenta from the circulation also results in closure of the ductus venosus. The left ventricle is now coupled to the high-resistance systemic circulation, and its wall thickness and mass begin to increase. In contrast, the right ventricle is now coupled to the low-resistance pulmonary circulation, and its wall thickness and mass decrease. The left ventricle, which in the fetus pumped blood only to the upper part of the body and brain, must now deliver the entire systemic cardiac output (≈350 mL/kg/min), an almost 200% increase in output. This marked increase in left ventricular performance is achieved through a combination of hormonal and metabolic signals, including an increase in the level of circulating catecholamines and in the density of myocardial β-adrenergic receptors through which catecholamines have their effect.

When congenital structural cardiac defects are superimposed on these dramatic physiologic changes, they often impede this smooth transition and markedly increase the burden on the newborn myocardium. In addition, because the ductus arteriosus and foramen ovale do not close completely at birth, they may remain patent in certain congenital cardiac lesions. Patency of these fetal pathways may either provide a lifesaving pathway for blood to bypass a congenital defect (a patent ductus in pulmonary atresia or coarctation of the aorta or a foramen ovale in transposition of the great vessels) or present an additional stress to the circulation (patent ductus arteriosus in a premature infant, pathway for right-to-left shunting in infants with pulmonary hypertension). Therapeutic agents may either maintain these fetal pathways (prostaglandin E_1) or hasten their closure (indomethacin).

421.3 The Neonatal Circulation

Daniel Bernstein

At birth, the fetal circulation must immediately adapt to extrauterine life as gas exchange is transferred from the placenta to the lungs (see Chapter 101.1). Some of these changes are virtually instantaneous with the first breath, whereas others develop over a period of hours or weeks. With the onset of ventilation, pulmonary vascular resistance is markedly decreased as a consequence of both active (Po_2-related) and passive (mechanical related) pulmonary vasodilation. In a normal neonate, closure of the ductus arteriosus and the fall in pulmonary vascular resistance decreases pulmonary arterial and right ventricular pressures. The largest decline in pulmonary resistance from the high fetal levels to the low "adult" levels in the human infant at sea level usually occurs within the 1st 2-3 days but may be prolonged for 7 days or more. Over the next several weeks of life, pulmonary vascular resistance decreases even further, secondary to a remodeling of the pulmonary vasculature, including thinning of the vascular smooth muscle and recruitment of new vessels. This decrease in pulmonary vascular resistance significantly influences the timing of the clinical appearance of many congenital heart lesions that are dependent on the relative levels of systemic and pulmonary vascular resistances. The left-to-right shunt through an large ventricular septal defect may be minimal in the 1st wk after birth when pulmonary vascular resistance is still high. As pulmonary resistance decreases in the next week or 2, the volume of the left-to-right shunt through the ventricular septal defect increases and eventually leads to symptoms of heart failure within the 1st mo or 2 of life.

Significant differences between the neonatal circulation and that of older infants include: (1) right-to-left or left-to-right shunting may persist across the patent foramen ovale; (2) in the presence of cardiopulmonary disease, continued patency of the ductus arteriosus may allow left-to-right, right-to-left, or bidirectional shunting; (3) the neonatal pulmonary vasculature constricts more vigorously in response to hypoxemia, hypercapnia, and acidosis; (4) the wall thickness and muscle mass of the neonatal left and right ventricles are almost equal; and (5) newborn infants at rest have relatively high oxygen consumption, which is associated with relatively high cardiac output. The newborn cardiac output (approximately 350 mL/kg/min) falls in the 1st 2 mo of life to approximately 150 mL/kg/min and then more gradually to the normal adult cardiac output of approximately 75 mL/kg/min. Although fetal hemoglobin is beneficial to delivery of oxygen in the low Po_2 fetal circulation, the high percentage of fetal hemoglobin present in the newborn may actually interfere with delivery of oxygen to tissues in the high systemic Po_2 neonatal circulation (see Chapter 101.1).

The foramen ovale is usually functionally closed by the 3rd mo of life, although it is possible to pass a probe through the overlapping flaps in a large percentage of children and in 15-25% of adults. Functional closure of the ductus arteriosus is usually complete by 10-15 hr in a normal neonate, although the ductus may remain patent much longer in the presence of congenital heart disease, especially when associated with cyanosis. In premature newborn infants, an evanescent systolic murmur with late accentuation or a continuous murmur may be audible, and in the context of respiratory distress syndrome, the presence of a patent ductus arteriosus should be suspected (see Chapter 101.3).

The normal ductus arteriosus differs morphologically from the adjoining aorta and pulmonary artery in that the ductus has a significant amount of circularly arranged smooth muscle in its medial layer. During fetal life, patency of the ductus arteriosus appears to be maintained by the combined relaxant effects of low oxygen tension and endogenously produced prostaglandins, specifically prostaglandin E_2. In a full-term neonate, oxygen is the most important factor controlling ductal closure. When the Po_2 of the blood passing through the ductus reaches about 50 mm Hg, the ductal wall begins to constrict. The effects of oxygen on ductal smooth muscle may be direct or mediated by its effects on prostaglandin synthesis. Gestational age also appears to play an important role; the ductus of a premature infant is less responsive to oxygen, even though its musculature is developed.

Bibliography is available at Expert Consult.

421.4 Persistent Pulmonary Hypertension of the Neonate (Persistence of Fetal Circulatory Pathways)

See Chapter 101.7.

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Section 2

Evaluation of the Cardiovascular System

Chapter 422

History and Physical Examination

Daniel Bernstein

The importance of the history and physical examination cannot be overemphasized in the evaluation of infants and children with suspected cardiovascular disorders. Patients may require further laboratory evaluation and eventual treatment, or the family may be reassured that no significant problem exists. Although the ready availability of echocardiography may entice the clinician to skip these preliminary steps, an initial evaluation by a skilled cardiologist is preferred for several reasons: (1) a cardiac examination allows the cardiologist to guide the echocardiographic evaluation toward confirming or eliminating specific diagnoses, thereby increasing its accuracy; (2) because most childhood murmurs are innocent, evaluation by a pediatric cardiologist can eliminate unnecessary and expensive laboratory tests; and (3) the cardiologist's knowledge and experience are important in reassuring the patient's family and preventing unnecessary restrictions on healthy physical activity. An experienced pediatric cardiologist can differentiate an innocent murmur from serious congenital heart disease by history and physical alone with a high sensitivity and specificity.

HISTORY

A comprehensive cardiac history starts with details of the perinatal period including the presence of cyanosis, respiratory distress, or prematurity. Maternal complications such as gestational diabetes, teratogenic medications, systemic lupus erythematosus, or substance abuse can be associated with cardiac problems. If cardiac symptoms began during infancy, the timing of the initial symptoms should be noted to provide important clues about the specific cardiac condition.

Many of the symptoms of **heart failure** in infants and children are age specific. In infants, feeding difficulties are common. Inquiry should be made about the frequency of feeding and either the volume of each feeding or the time spent on each breast. An infant with heart failure often takes less volume per feeding and becomes dyspneic or diaphoretic while sucking. After falling asleep exhausted, the baby, inadequately fed, will awaken for the next feeding after a brief time. This cycle continues around the clock and must be carefully differentiated from colic or other feeding disorders. Additional symptoms and signs include those of respiratory distress: rapid breathing, nasal flaring, cyanosis, and chest retractions. In older children, heart failure may be manifested as exercise intolerance, difficulty keeping up with peers during sports or the need for a nap after coming home from school, poor growth, or chronic abdominal complaints. Eliciting a history of fatigue in an older child requires questions about age-specific activities, including stair climbing, walking, bicycle riding, physical education class, and competitive sports; information should be obtained regarding more severe manifestations such as orthopnea and nocturnal dyspnea.

Cyanosis at rest is often overlooked by parents; it may be mistaken for a normal individual variation in color. Cyanosis during crying or exercise, however, is more often noted as abnormal by observant parents. Many infants and toddlers turn "blue around the lips" when crying vigorously or during breath-holding spells; this condition must be carefully differentiated from cyanotic heart disease by inquiring about inciting factors, the length of episodes, and whether the tongue and mucous membranes also appear cyanotic. Newborns often have cyanosis of their extremities (acrocyanosis) when undressed and cold; this response to cold must be carefully differentiated from true cyanosis, where the mucous membranes are also blue.

Chest pain is an unusual manifestation of cardiac disease in pediatric patients, although it is a frequent cause for referral to a pediatric cardiologist, especially in adolescents. Nonetheless, a careful history, physical examination, and, if indicated, laboratory or imaging tests will assist in identifying the cause of chest pain (Table 422-1). For patients with some forms of repaired congenital heart disease or those with a

Table 422-1	Differential Diagnosis of Chest Pain in Pediatric Patients
MUSCULOSKELETAL (COMMON) Trauma (accidental, abuse) Exercise, overuse injury (strain, bursitis) Costochondritis (Tietze syndrome) Herpes zoster (cutaneous) Pleurodynia Fibrositis Slipping rib Precordial catch Sickle cell anemia vasoocclusive crisis Osteomyelitis (rare) Primary or metastatic tumor (rare)	
PULMONARY (COMMON) Pneumonia Pleurisy Asthma Chronic cough Pneumothorax Infarction (sickle cell anemia) Foreign body Embolism (rare) Pulmonary hypertension (rare) Tumor (rare) Bronchiectasis	
GASTROINTESTINAL (LESS COMMON) Esophagitis (gastroesophageal reflux, infectious, pill) Esophageal foreign body Esophageal spasm Cholecystitis Subdiaphragmatic abscess Perihepatitis (Fitz-Hugh-Curtis syndrome) Peptic ulcer disease Pancreatitis	
CARDIAC (LESS COMMON) Pericarditis Postpericardiotomy syndrome Endocarditis Cardiomyopathy Mitral valve prolapse Aortic or subaortic stenosis Arrhythmias Marfan syndrome (dissecting aortic aneurysm) Kawasaki disease Cocaine, sympathomimetic ingestion Angina (familial hypercholesterolemia, anomalous coronary artery)	
IDIOPATHIC (COMMON) Anxiety, hyperventilation Panic disorder	
OTHER (LESS COMMON) Spinal cord or nerve root compression Breast-related pathologic condition (mastalgia) Castleman disease (lymph node neoplasm)	

history of Kawasaki disease (see Chapter 444.1), however, chest pain should be evaluated carefully for a coronary etiology.

Cardiac disease may be a manifestation of a known congenital malformation syndrome with typical physical findings (Table 422-2) or a manifestation of a generalized disorder affecting the heart and other organ systems (Table 422-3). Extracardiac malformations may be noted in 20-45% of infants with congenital heart disease. Between 5% and 10% of patients have a known chromosomal abnormality; the importance of genetic evaluation will increase as our knowledge of specific gene defects linked to congenital heart disease increases.

A careful family history may also reveal early (at age <50 yr) coronary artery disease or stroke (suggestive of familial hypercholesterolemia or thrombophilia), sudden death (suggestive of cardiomyopathy or familial arrhythmic disorder), generalized muscle disease (suggestive of 1 of the muscular dystrophies, dermatomyositis, or familial or metabolic cardiomyopathy), or 1st-degree relatives with congenital heart disease.

GENERAL PHYSICAL EXAMINATION

A general assessment of the patient is always the first part of the examination, with specific attention directed toward the presence of cyanosis, abnormalities in growth, chest wall abnormalities, and any evidence of respiratory distress. Although the murmur may be the most prominent part of the overall examination, any murmur must be placed in context of other physical findings. Frequently, associated findings, such as the quality of the pulses, the presence of a ventricular heave or thrill, or the splitting of the second heart sound, provide important clues to a specific cardiac diagnosis.

Accurate measurement of height and weight and plotting on a standard growth chart are important because both cardiac failure and chronic cyanosis can result in **failure to thrive.** Growth failure is manifested predominantly by poor weight gain; if length or head circumference is also affected, additional congenital malformations or metabolic disorders should be suspected.

Mild cyanosis may be too subtle for early detection, and clubbing of the fingers and toes is not usually manifested until late in the 1st yr of life, even in the presence of severe arterial oxygen desaturation. **Cyanosis** is best observed over the nail beds, lips, tongue, and mucous membranes. Differential cyanosis, manifested as blue lower extremities and pink upper extremities (usually the right arm), is seen with right-to-left shunting across a ductus arteriosus in the presence of coarctation or an interrupted aortic arch. Circumoral cyanosis or blueness around the forehead may be the result of prominent venous plexuses in these areas, rather than decreased arterial oxygen saturation. The extremities of infants often turn blue when the infant is unwrapped and cold (acrocyanosis), and this condition can be distinguished from central cyanosis by examination of the tongue and mucous membranes.

Heart failure in infants and children usually results in some degree of hepatomegaly and occasionally splenomegaly. The sites of **peripheral** edema are age dependent. In infants, edema is usually seen around the eyes and over the flanks, especially on initially waking. Older children and teenagers manifest both periorbital edema and pedal edema. A not uncommon initial complaint in these older patients is that their clothes no longer fit.

The heart rate of newborn infants is rapid and subject to wide fluctuations (Table 422-4). The average rate ranges from 120-140 beats/min and may increase to 170+ beats/min during crying and activity or drop to 70-90 beats/min during sleep. As the child grows older, the average pulse rate decreases and may be as low as 40 beats/min at rest in athletic adolescents. Persistent tachycardia (>200 beats/min in neonates, 150 beats/min in infants, or 120 beats/min in older children), bradycardia, or an irregular heartbeat other than sinus arrhythmia requires investigation to exclude pathologic arrhythmias (see Chapter 435). Sinus arrhythmia can usually be distinguished by the rhythmic nature of the heart rate variations, occurring in concert with the respiratory cycle, and with a P wave before every QRS complex.

Careful evaluation of the character of the **pulses** is an important early step in the physical diagnosis of congenital heart disease. A wide pulse pressure with bounding pulses may suggest an aortic runoff lesion such as patent ductus arteriosus, aortic insufficiency, an arterial-venous communication, or increased cardiac output secondary to anemia, anxiety, or conditions associated with increased catecholamine or thyroid hormone secretion. The presence of diminished pulses in all extremities is associated with pericardial tamponade, left ventricular outflow obstruction, or cardiomyopathy. The radial and femoral pulses should always be palpated simultaneously. Normally, the femoral pulse should be appreciated immediately before the radial pulse. In infants with coarctation of the aorta, the femoral pulses may be decreased. However, in older children with coarctation of the aorta, blood flow to the descending aorta may channel through collateral vessels and results in the femoral pulse being palpable but delayed until after the radial pulse **(radial-femoral delay).**

Blood pressure should be measured in the legs as well as in the arms to be certain that coarctation of the aorta is not overlooked. Palpation of the femoral or dorsalis pedis pulse, or both, is not reliable alone to exclude coarctation. In older children, a mercury sphygmomanometer with a cuff that covers approximately two-thirds of the upper part of the arm or leg may be used for blood pressure measurement. A cuff that is too small results in falsely high readings, whereas a cuff that is too large records slightly decreased pressure. Pediatric clinical facilities should be equipped with 3, 5, 7, 12, and 18 cm cuffs to accommodate the large spectrum of pediatric patient sizes. The 1st Korotkoff sounds indicate systolic pressure. As cuff pressure is slowly decreased, the sounds usually become muffled before they disappear. Diastolic pressure may be recorded when the sounds become muffled (preferred) or when they disappear altogether; the former is usually slightly higher and the latter slightly lower than true diastolic pressure. For lower-extremity blood pressure determination, the stethoscope is placed over the popliteal artery. Ordinarily, the pressure recorded in the legs with the cuff technique is approximately 10 mm Hg higher than that in the arms.

In infants, blood pressure can be determined by auscultation, palpation, or an oscillometric (Dinamap) device that, when properly used, provides accurate measurements in infants as well as older children.

Blood pressure varies with the age of the child and is closely related to height and weight. Significant increases occur during adolescence, and many temporary variations take place before the more stable levels of adult life are attained. Exercise, excitement, coughing, crying, and struggling may raise the systolic pressure of infants and children as much as 40-50 mm Hg greater than their usual levels. Variability in blood pressure in children of approximately the same age and body build should be expected, and serial measurements should always be obtained when evaluating a patient with hypertension (Figs. 422-1 and 422-2).

Although of little use in infants, in cooperative older children, inspection of the **jugular venous pulse** wave provides information about central venous and right atrial pressure. The neck veins should be inspected with the patient sitting at a 90-degree angle. The external jugular vein should not be visible above the clavicles unless central venous pressure is elevated. Increased venous pressure transmitted to the internal jugular vein may appear as venous pulsations without visible distention; such pulsation is not seen in normal children reclining at an angle of 45 degrees. Because the great veins are in direct communication with the right atrium, changes in pressure and the volume of this chamber are also transmitted to the veins. The 1 exception occurs in superior vena cava obstruction, in which venous pulsatility is lost.

CARDIAC EXAMINATION

The heart should be examined in a systematic manner, starting with inspection and palpation. A **precordial bulge** to the left of the sternum with increased precordial activity suggests cardiac enlargement; such bulges can often best be appreciated by having the child lay supine with the examiner looking up from the child's feet. A **substernal thrust** indicates the presence of right ventricular enlargement, whereas an apical heave is noted with left ventricular enlargement. A hyperdynamic precordium suggests a volume load such as that found with a large left-to-right shunt, although it may be normal in a thin patient.

Table 422-2 Congenital Malformation Syndromes Associated with Congenital Heart Disease

SYNDROME	FEATURES
CHROMOSOMAL DISORDERS	
Trisomy 21 (Down syndrome)	Endocardial cushion defect, VSD, ASD
Trisomy 21p (cat eye syndrome)	Miscellaneous, total anomalous pulmonary venous return
Trisomy 18	VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve
Trisomy 13	VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve
Trisomy 9	Miscellaneous
XXXXY	PDA, ASD
Penta X	PDA, VSD
Triploidy	VSD, ASD, PDA
XO (Turner syndrome)	Bicuspid aortic valve, coarctation of aorta
Fragile X	Mitral valve prolapse, aortic root dilatation
Duplication 3q2	Miscellaneous
Deletion 4p	VSD, PDA, aortic stenosis
Deletion 9p	Miscellaneous
Deletion 5p (cri du chat syndrome)	VSD, PDA, ASD
Deletion 10q	VSD, TOF, conotruncal lesions*
Deletion 13q	VSD
Deletion 18q	VSD
SYNDROME COMPLEXES	
CHARGE association (*c*oloboma, *h*eart, *a*tresia choanae, *r*etardation, *g*enital, and *e*ar anomalies)	VSD, ASD, PDA, TOF, endocardial cushion defect
DiGeorge sequence, CATCH 22 (*c*ardiac defects, *a*bnormal facies, *t*hymic aplasia, *c*left palate, and *h*ypocalcemia)	Aortic arch anomalies, conotruncal anomalies
Alagille syndrome (arteriohepatic dysplasia)	Peripheral pulmonic stenosis, PS, TOF
VATER association (*v*ertebral, *a*nal, *t*racheo*e*sophageal, *r*adial, and *r*enal anomalies)	VSD, TOF, ASD, PDA
FAVS (*f*acio*a*uriculo*v*ertebral *s*pectrum)	TOF, VSD
CHILD (congenital hemidysplasia with ichthyosiform erythroderma, limb defects)	Miscellaneous
Mulibrey nanism (muscle, liver, brain, eye)	Pericardial thickening, constrictive pericarditis
Asplenia syndrome	Complex cyanotic heart lesions with decreased pulmonary blood flow, transposition of great arteries, anomalous pulmonary venous return, dextrocardia, single ventricle, single atrioventricular valve
Polysplenia syndrome	Acyanotic lesions with increased pulmonary blood flow, azygos continuation of inferior vena cava, partial anomalous pulmonary venous return, dextrocardia, single ventricle, common atrioventricular valve
PHACE syndrome (*p*osterior brain fossa anomalies, facial *h*emangiomas, *a*rterial anomalies, *c*ardiac anomalies and aortic coarctation, *e*ye anomalies)	VSD, PDA, coarctation of aorta, arterial aneurysms
TERATOGENIC AGENTS	
Congenital rubella	PDA, peripheral pulmonic stenosis
Fetal hydantoin syndrome	VSD, ASD, coarctation of aorta, PDA
Fetal alcohol syndrome	ASD, VSD
Fetal valproate effects	Coarctation of aorta, hypoplastic left side of heart, aortic stenosis, pulmonary atresia, VSD
Maternal phenylketonuria	VSD, ASD, PDA, coarctation of aorta
Retinoic acid embryopathy	Conotruncal anomalies
OTHERS	
Apert syndrome	VSD
Autosomal dominant polycystic kidney disease	Mitral valve prolapse
Carpenter syndrome	PDA
Conradi syndrome	VSD, PDA
Crouzon disease	PDA, coarctation of aorta
Cutis laxa	Pulmonary hypertension, pulmonic stenosis
de Lange syndrome	VSD
Ellis–van Creveld syndrome	Single atrium, VSD
Holt-Oram syndrome	ASD, VSD, 1st-degree heart block
Infant of diabetic mother	Hypertrophic cardiomyopathy, VSD, conotruncal anomalies
Kartagener syndrome	Dextrocardia
Meckel-Gruber syndrome	ASD, VSD
Noonan syndrome	Pulmonic stenosis, ASD, cardiomyopathy
Pallister-Hall syndrome	Endocardial cushion defect
Rubinstein-Taybi syndrome	VSD
Scimitar syndrome	Hypoplasia of right lung, anomalous pulmonary venous return to inferior vena cava
Smith-Lemli-Opitz syndrome	VSD, PDA
TAR syndrome (thrombocytopenia and absent radius)	ASD, TOF
Treacher Collins syndrome	VSD, ASD, PDA
Williams syndrome	Supravalvular aortic stenosis, peripheral pulmonic stenosis

ASD, atrial septal defect; AV, aortic valve; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TOF, tetralogy of Fallot; VSD, ventricular septal defect.
*Conotruncal includes TOF, pulmonary atresia, truncus arteriosus, and transposition of great arteries.

Table 422-3 Cardiac Manifestations of Systemic Diseases

SYSTEMIC DISEASE	CARDIAC COMPLICATIONS
INFLAMMATORY DISORDERS	
Sepsis	Hypotension, myocardial dysfunction, pericardial effusion, pulmonary hypertension
Juvenile idiopathic arthritis	Pericarditis, rarely myocarditis
Systemic lupus erythematosus	Pericarditis, Libman-Sacks endocarditis, coronary arteritis, coronary atherosclerosis (with steroids), congenital heart block
Scleroderma	Pulmonary hypertension, myocardial fibrosis, cardiomyopathy
Dermatomyositis	Cardiomyopathy, arrhythmias, heart block
Kawasaki disease	Coronary artery aneurysm and thrombosis, myocardial infarction, myocarditis, valvular insufficiency
Sarcoidosis	Granuloma, fibrosis, amyloidosis, biventricular hypertrophy, arrhythmias
Lyme disease	Arrhythmias, myocarditis
Löffler hypereosinophilic syndrome	Endomyocardial disease
INBORN ERRORS OF METABOLISM	
Refsum disease	Arrhythmia, sudden death
Hunter or Hurler syndrome	Valvular insufficiency, heart failure, hypertension
Fabry disease	Mitral insufficiency, coronary artery disease with myocardial infarction
Glycogen storage disease IIa (Pompe disease)	Short P-R interval, cardiomegaly, heart failure, arrhythmias
Carnitine deficiency	Heart failure, cardiomyopathy
Gaucher disease	Pericarditis
Homocystinuria	Coronary thrombosis
Alkaptonuria	Atherosclerosis, valvular disease
Morquio-Ullrich syndrome	Aortic incompetence
Scheie syndrome	Aortic incompetence
CONNECTIVE TISSUE DISORDERS	
Arterial calcification of infancy	Calcinosis of coronary arteries, aorta
Marfan syndrome	Aortic and mitral insufficiency, dissecting aortic aneurysm, mitral valve prolapse
Congenital contractural arachnodactyly	Mitral insufficiency or prolapse
Ehlers-Danlos syndrome	Mitral valve prolapse, dilatated aortic root
Osteogenesis imperfecta	Aortic incompetence
Pseudoxanthoma elasticum	Peripheral arterial disease
NEUROMUSCULAR DISORDERS	
Friedreich ataxia	Cardiomyopathy
Duchenne dystrophy	Cardiomyopathy, heart failure
Tuberous sclerosis	Cardiac rhabdomyoma
Familial deafness	Occasionally arrhythmia, sudden death
Neurofibromatosis	Pulmonic stenosis, pheochromocytoma, coarctation of aorta
Riley-Day syndrome	Episodic hypertension, postural hypotension
Von Hippel–Lindau disease	Hemangiomas, pheochromocytomas
ENDOCRINE-METABOLIC DISORDERS	
Graves disease	Tachycardia, arrhythmias, heart failure
Hypothyroidism	Bradycardia, pericardial effusion, cardiomyopathy, low-voltage electrocardiogram
Pheochromocytoma	Hypertension, myocardial ischemia, myocardial fibrosis, cardiomyopathy
Carcinoid	Right-sided endocardial fibrosis
HEMATOLOGIC DISORDERS	
Sickle cell anemia	High-output heart failure, cardiomyopathy, pulmonary hypertension
Thalassemia major	High-output heart failure, hemochromatosis
Hemochromatosis (1° or 2°)	Cardiomyopathy
OTHERS	
Appetite suppressants (fenfluramine and dexfenfluramine)	Cardiac valvulopathy, pulmonary hypertension
Cockayne syndrome	Atherosclerosis
Familial dwarfism and nevi	Cardiomyopathy
Jervell and Lange-Nielsen syndrome	Prolonged QT interval, sudden death
Kearns-Sayre syndrome	Heart block
LEOPARD syndrome (lentiginosis)	Pulmonic stenosis, prolonged Q-T interval
Progeria	Accelerated atherosclerosis
Osler-Weber-Rendu disease	Arteriovenous fistula (lung, liver, mucous membrane)
Romano-Ward syndrome	Prolonged Q-T interval, sudden death
Weill-Marchesani syndrome	Patent ductus arteriosus
Werner syndrome	Vascular sclerosis, cardiomyopathy

LEOPARD, multiple *l*entigines, *e*lectrocardiographic conduction abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals, *r*etardation of growth, sensorineural *d*eafness.

Table 422-4 Pulse Rates at Rest

AGE	LOWER LIMITS OF NORMAL (beats/min)		AVERAGE (beats/min)		UPPER LIMITS OF NORMAL (beats/min)	
Newborn	70		125		190	
1–11 mo	80		120		160	
2 yr	80		110		130	
4 yr	80		100		120	
6 yr	75		100		115	
8 yr	70		90		110	
10 yr	70		90		110	
	GIRLS	BOYS	GIRLS	BOYS	GIRLS	BOYS
12 yr	70	65	90	85	110	105
14 yr	65	60	85	80	105	100
16 yr	60	55	80	75	100	95
18 yr	55	50	75	70	95	90

An overly silent precordium with a barely detectable apical impulse suggests pericardial effusion or severe cardiomyopathy but may be normal in an obese patient.

The relationship of the **apical impulse** to the midclavicular line is also helpful in the estimation of cardiac size: the apical impulse moves laterally and inferiorly with enlargement of the left ventricle. Right-sided apical impulses signify dextrocardia, tension pneumothorax, or left-sided thoracic space-occupying lesions (e.g., diaphragmatic hernia).

Thrills are the palpable equivalent of murmurs and correlate with the area of maximal auscultatory intensity of the murmur. It is important to palpate the suprasternal notch and neck for aortic bruits, which may indicate the presence of aortic stenosis or, when faint, pulmonary stenosis. Right lower sternal border and apical systolic thrills are characteristic of ventricular septal defect and mitral insufficiency, respectively. Diastolic thrills are occasionally palpable in the presence of atrioventricular valve stenosis. The timing and localization of thrills should be carefully noted.

Auscultation is an art that improves with practice. The diaphragm of the stethoscope is placed firmly on the chest for high-pitched sounds; a lightly placed bell is optimal for low-pitched sounds. The physician should initially concentrate on the characteristics of the individual heart sounds and their variation with respirations and later concentrate on murmurs. The patient should be supine, lying quietly, and breathing normally. The **1st heart sound** is best heard at the apex, whereas the **2nd heart sound** should be evaluated at the upper left and right sternal borders. The 1st heart sound is caused by closure of the atrioventricular valves (mitral and tricuspid); the 2nd sound is caused by closure of the semilunar valves (aortic and pulmonary) (Fig. 422-3). During inspiration, the decrease in intrathoracic pressure results in increased filling of the right side of the heart, which leads to an increased right ventricular ejection time and thus delayed closure of the pulmonary valve; consequently, **splitting of the 2nd heart sound** increases during inspiration and decreases during expiration.

Often, the 2nd heart sound seems to be single during expiration. The presence of a normally split 2nd sound is strong evidence against the diagnosis of atrial septal defect, defects associated with pulmonary arterial hypertension, severe pulmonary valve stenosis, aortic and pulmonary atresia, and truncus arteriosus. Wide splitting is noted in atrial septal defect, pulmonary stenosis, Ebstein anomaly, total anomalous pulmonary venous return, and right bundle branch block. An accentuated pulmonic component of the 2nd sound with narrow splitting is a sign of pulmonary hypertension. A single 2nd sound occurs in pulmonary or aortic atresia or severe stenosis, truncus arteriosus, and, often, transposition of the great arteries.

A **3rd heart sound** is best heard with the bell at the apex in mid-diastole. A **4th sound** occurring in conjunction with atrial contraction may be heard just before the 1st heart sound in late diastole. The 3rd sound may be normal in an adolescent with a relatively slow heart rate, but in a patient with the clinical signs of heart failure and tachycardia, it may be heard as a gallop rhythm and may merge with a 4th heart sound, a finding known as a summation gallop. A gallop rhythm is attributed to poor compliance of the ventricle, and exaggeration of the normal 3rd sound is associated with ventricular filling.

Ejection clicks, which are heard in early systole, are usually caused by a mildly to moderately stenotic aortic or pulmonary valve or to a dilated ascending aorta or pulmonary artery. They are heard so close to the 1st heart sound that they may be mistaken for a split 1st sound. Aortic ejection clicks are best heard at the left middle to right upper sternal border and are constant in intensity. They occur in conditions in which the aortic valve is stenotic or the aorta is dilated (tetralogy of Fallot, truncus arteriosus). Pulmonary ejection clicks, which are associated with mild to moderate pulmonary stenosis, are best heard at the left middle to upper sternal border and vary with respirations, often disappearing with inspiration. Split 1st heart sounds are usually heard best at the lower left sternal border. A midsystolic click heard at the apex, often preceding a late systolic murmur, suggests mitral valve prolapse.

Murmurs should be described according to their intensity, pitch, timing (systolic or diastolic), variation in intensity, time to peak intensity, area of maximal intensity, and radiation to other areas. Auscultation for murmurs should be carried out across the upper precordium, down the left or right sternal border, and out to the apex and left axilla. Auscultation should also always be performed in the right axilla and over both sides of the back. Systolic murmurs are classified as ejection, pansystolic, or late systolic according to the timing of the murmur in relation to the 1st and 2nd heart sounds. The intensity of systolic murmurs is graded from I to VI: I, barely audible; II, medium intensity; III, loud but no thrill; IV, loud with a thrill; V, very loud but still requiring positioning of the stethoscope at least partly on the chest; and VI, so loud that the murmur can be heard with the stethoscope off the chest. In patients who have undergone prior heart surgery, a murmur of grade IV or greater may be heard in the absence of a thrill.

Systolic ejection murmurs start a short time after a well-heard 1st heart sound, increase in intensity, peak, and then decrease in intensity; they usually end before the 2nd sound. In patients with severe pulmonary stenosis, however, the murmur may extend beyond the 1st component of the 2nd sound, thus obscuring it. **Pansystolic or holosystolic murmurs** begin almost simultaneously with the 1st heart sound and continue throughout systole, on occasion becoming gradually decrescendo. It is helpful to remember that after closure of the atrioventricular valves (the 1st heart sound), a brief period occurs during which ventricular pressure increases but the semilunar valves remain closed (isovolumic contraction; see Fig. 422-3). Thus, pansystolic murmurs (heard during both isovolumic contraction and the ejection phases of systole) cannot be caused by flow across the semilunar valves because these valves are closed during isovolumic contraction. Pansystolic murmurs must therefore be related to blood exiting the contracting ventricle via either an abnormal opening (a ventricular septal defect) or atrioventricular (mitral or tricuspid) valve insufficiency. Systolic ejection murmurs usually imply increased flow or stenosis across one of the ventricular outflow tracts (aortic or pulmonic). In infants with rapid heart rates, it is often difficult to distinguish between ejection and pansystolic murmurs. If a clear and distinct 1st heart sound can be appreciated, the murmur is most likely ejection in nature.

A **continuous murmur** is a systolic murmur that continues or "spills" into diastole and indicates continuous flow, such as in the presence of a patent ductus arteriosus or other aortopulmonary communication. This murmur should be differentiated from a to-and-fro murmur, where the systolic component of the murmur ends at or before the 2nd sound and the diastolic murmur begins after semilunar valve closure (aortic or pulmonary stenosis combined with insufficiency). A late systolic murmur begins well beyond the 1st heart sound and continues until the end of systole. Such murmurs may be heard

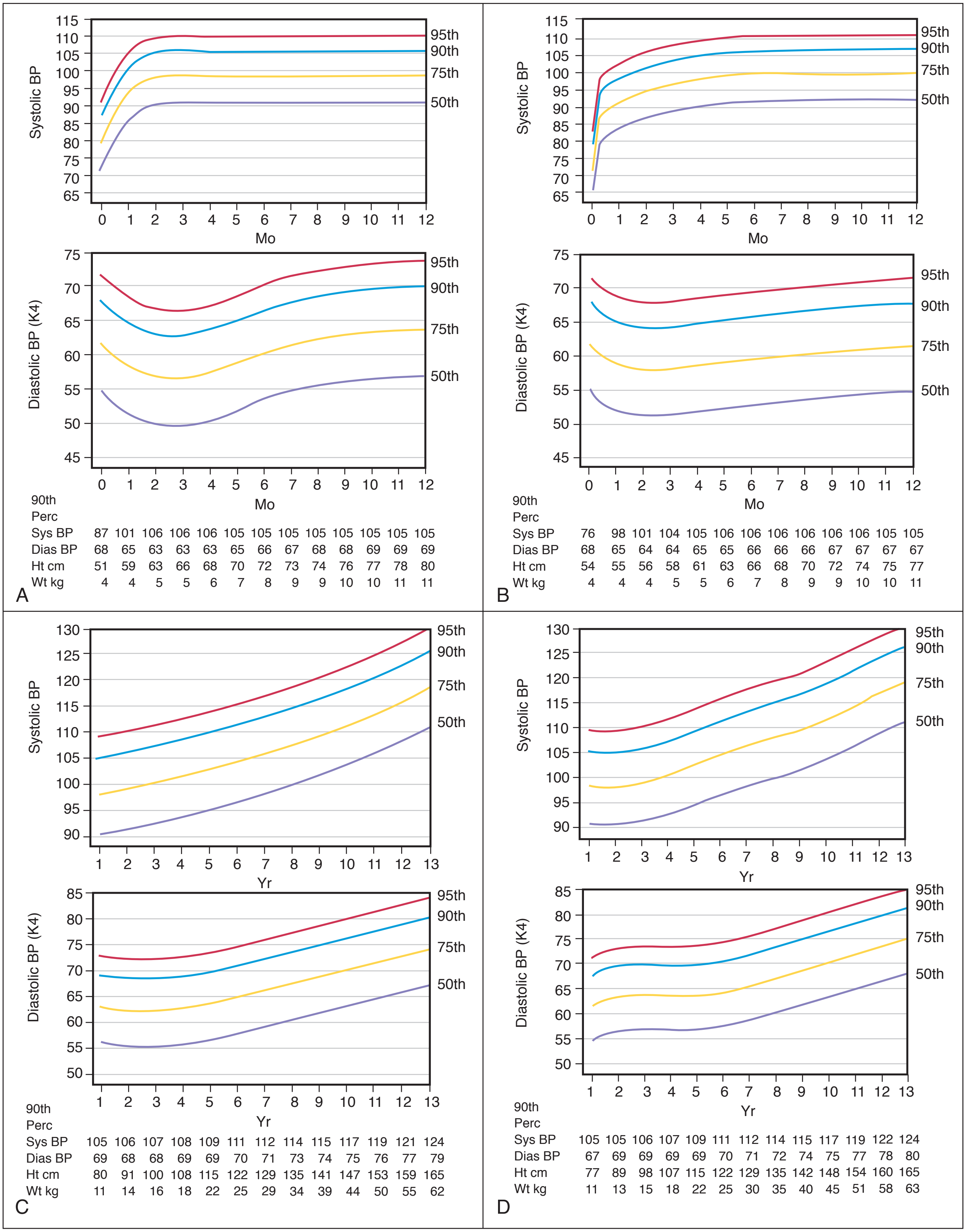

Figure 422-1 **A,** Age-specific percentiles of blood pressure (BP) measurements in boys from birth to 12 mo of age. **B,** Age-specific percentiles of BP measurements in girls from birth to 12 mo of age. **C,** Age-specific percentiles of BP measurements in boys 1-13 yr of age. **D,** Age-specific percentiles of BP measurements in girls 1-13 yr of age; Korotkoff phase IV (K4) used for diastolic BP. Dias, diastolic; Ht, height; Perc, percentile; Sys, systolic; Wt, weight. *(From Report of the Second Task Force on Blood Pressure Control in Children—1987. National Heart, Lung, and Blood Institute, Bethesda, MD, Pediatrics 79:1–25, 1987. Copyright 1987 by the American Academy of Pediatrics.)*

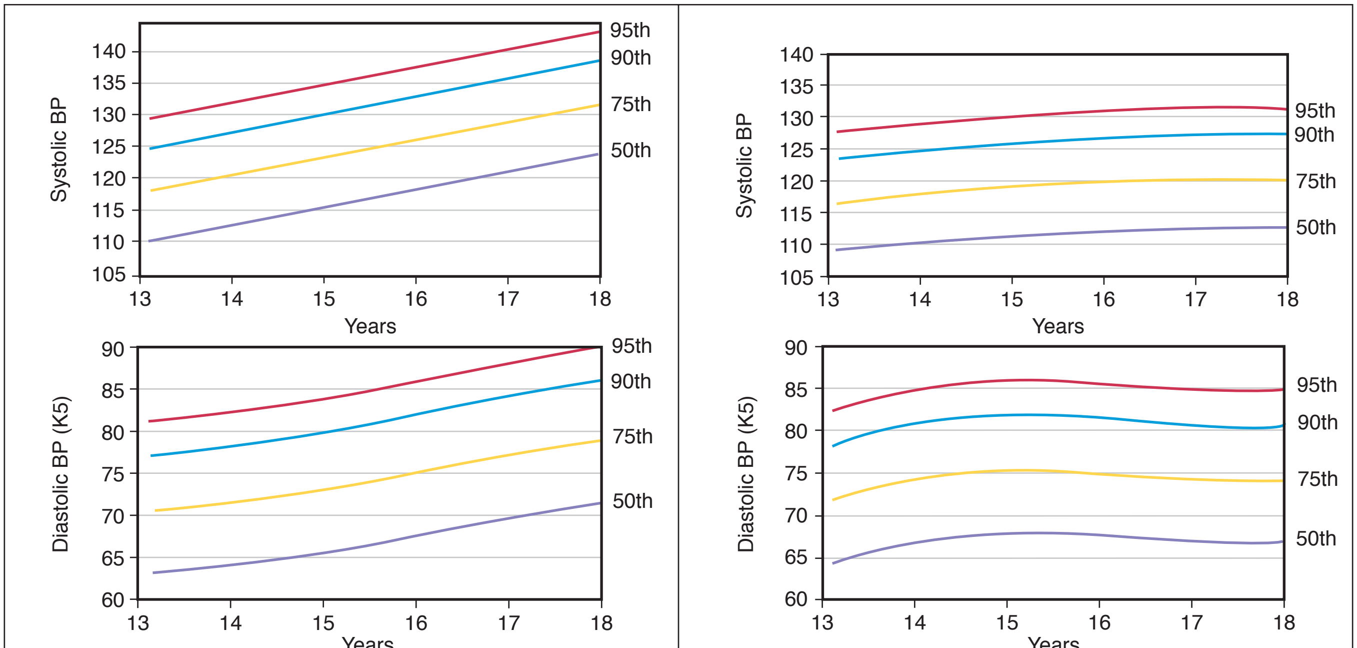

A

90th Perc	13	14	15	16	17	18
Sys BP	124	126	129	131	134	136
Dias BP	77	78	79	81	83	84
Ht cm	165	172	178	182	184	184
Wt kg	62	68	74	80	84	86

B

90th Perc	13	14	15	16	17	18
Sys BP	124	126	126	127	127	127
Dias BP	78	81	82	81	80	80
Ht cm	165	168	169	170	170	170
Wt kg	63	67	70	72	73	74

Figure 422-2 A, Age-specific percentiles of blood pressure (BP) measurements in boys 13-18 yr of age. **B,** Age-specific percentiles of BP measurements in girls 13-18 yr of age; Korotkoff phase V (K5) used for diastolic BP. Dias, diastolic; Ht, height; Perc, percentile; Sys, systolic; Wt, weight. *(From Report of the Second Task Force on Blood Pressure Control in Children—1987, National Heart, Lung, and Blood Institute, Bethesda, MD, Pediatrics 79:1–25, 1987. Copyright 1987 by the American Academy of Pediatrics.)*

after a midsystolic click in patients with mitral valve prolapse and insufficiency.

Several types of **diastolic murmurs** (graded I-IV) can be identified. A decrescendo diastolic murmur is a blowing murmur along the left sternal border that begins with S_2 and diminishes toward mid-diastole. When high-pitched, this murmur is associated with aortic valve insufficiency or pulmonary insufficiency related to pulmonary hypertension. When low-pitched, this murmur is associated with pulmonary valve insufficiency in the absence of pulmonary hypertension. A low-pitched decrescendo diastolic murmur is typically noted after surgical repair of the pulmonary outflow tract in defects such as tetralogy of Fallot or in patients with absent pulmonary valves. A rumbling mid-diastolic murmur at the left middle and lower sternal border may be due to increased blood flow across the tricuspid valve, such as occurs with an atrial septal defect or, less often, because of actual stenosis of this valve. When this murmur is heard at the apex, it is caused by increased flow across the mitral valve, such as occurs with large left-to-right shunts at the ventricular level (ventricular septal defects), at the great vessel level (patent ductus arteriosus, aortopulmonary shunts), or with increased flow because of mitral insufficiency. When an apical diastolic rumbling murmur is longer and is accentuated at the end of diastole (presystolic), it usually indicates anatomic mitral valve stenosis.

The absence of a precordial murmur does not rule out significant congenital or acquired heart disease. Congenital heart defects, some of which are ductal dependent, may not demonstrate a murmur if the ductus arteriosus closes. These lesions include pulmonary or tricuspid valve atresia and transposition of the great arteries. Murmurs may seem insignificant in patients with severe aortic stenosis, atrial septal defects, anomalous pulmonary venous return, atrioventricular septal defects, coarctation of the aorta, or anomalous insertion of a coronary artery. Careful attention to other components of the physical examination (growth failure, cyanosis, peripheral pulses, precordial impulse, heart sounds) increases the index of suspicion of congenital heart defects in these cases. In contrast, loud murmurs may be present in the absence of structural heart disease, for example, in patients with a large noncardiac arteriovenous malformation, myocarditis, severe anemia, or hypertension.

Many murmurs are not associated with significant hemodynamic abnormalities. These murmurs are referred to as functional, normal, insignificant, or innocent (the preferred term). During routine random auscultation, more than 30% of children may have an innocent murmur at one time in their lives; this percentage increases when auscultation is carried out under nonbasal circumstances (high cardiac output because of fever, infection, anxiety). The most **common innocent murmur** is a medium-pitched, vibratory or "musical," relatively short systolic ejection murmur, which is heard best along the left lower and midsternal border and has no significant radiation to the apex, base, or back. It is heard most frequently in children between 3 and 7 yr of age. The intensity of the murmur often changes with respiration and position and may be attenuated in the sitting or prone position. Innocent pulmonic murmurs are also common in children and adolescents and originate from normal turbulence during ejection into the pulmonary artery. They are higher pitched, blowing, brief early systolic murmurs of grades I-II in intensity and are best detected in the 2nd left parasternal space with the patient in the supine position. Features suggestive of heart disease include murmurs that are pansystolic, grade III or higher, harsh, located at the left upper sternal border, and associated with an early or midsystolic click or an abnormal 2nd heart sound.

A **venous hum** is another example of a common innocent murmur heard during childhood. Such hums are produced by turbulence of blood in the jugular venous system; they have no pathologic significance and may be heard in the neck or anterior portion of the upper part of the chest. A venous hum consists of a soft humming sound

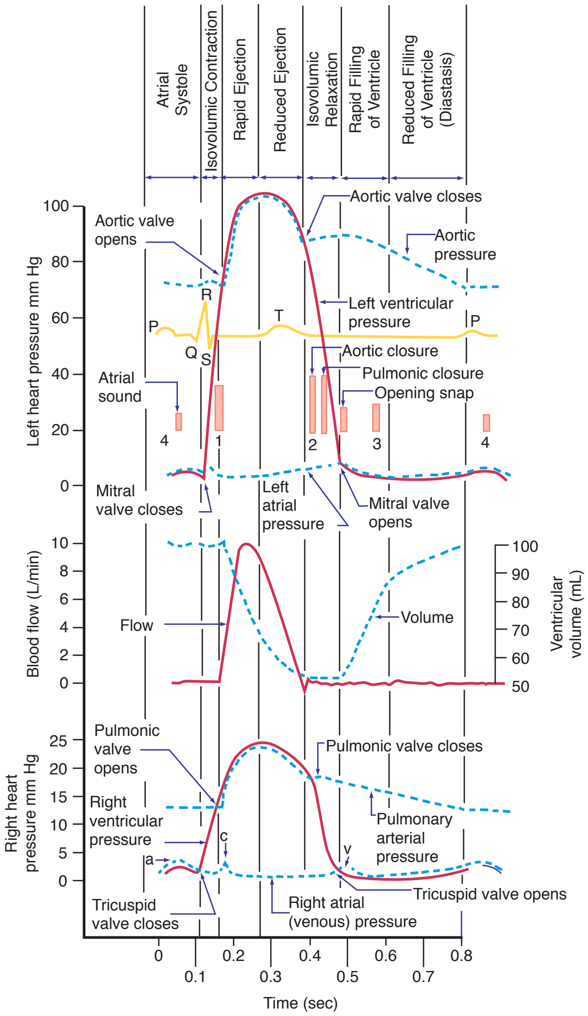

Figure 422-3 Idealized diagram of the temporal events of a cardiac cycle.

heard in both systole and diastole; it can be exaggerated or made to disappear by varying the position of the head, or it can be decreased by lightly compressing the jugular venous system in the neck. These simple maneuvers are sufficient to differentiate a venous hum from the murmurs produced by organic cardiovascular disease, particularly a patent ductus arteriosus.

The lack of significance of an innocent murmur should be discussed with the child's parents. It is important to offer complete reassurance because lingering doubts about the importance of a cardiac murmur may have profound effects on child-rearing practices, most often in the form of overprotectiveness. An underlying fear that a cardiac abnormality is present may negatively affect a child's self-image and subtly influence personality development. The physician should explain that an innocent murmur is simply a "noise" and does not indicate the presence of a significant cardiac defect. When asked, "Will it go away?," the best response is to state that because the murmur has no clinical significance, it does not matter whether it "goes away." Parents should be warned that the intensity of the murmur might increase during febrile illnesses, a time when, typically, another physician examines the child. With growth, however, innocent murmurs are less well heard and often disappear completely. At times, additional studies may be indicated to rule out a congenital heart defect, but "routine" electrocardiographic, chest roentgenographic, and echocardiographic examinations should be avoided in well children with innocent murmurs.

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Chapter 423

Laboratory Evaluation

423.1 Radiologic Assessment

Daniel Bernstein

The chest x-ray remains a highly valuable diagnostic tool and is often the first imaging study performed in a child suspected of having a cardiac defect. It can provide information about cardiac size and shape, pulmonary blood flow (vascularity), pulmonary edema, and associated lung and thoracic anomalies that may be associated with congenital syndromes (skeletal dysplasias, extra or deficient number of ribs, abnormal vertebrae, previous cardiac surgery).

The most frequently used measurement of cardiac size is the maximal width of the cardiac shadow in a posteroanterior chest film taken mid-inspiration. A vertical line is drawn down the middle of the sternal shadow, and perpendicular lines are drawn from the sternal line to the extreme right and left borders of the heart; the sum of the lengths of these lines is the maximal cardiac width. The maximal chest width is obtained by drawing a horizontal line between the right and left inner borders of the rib cage at the level of the top of the right diaphragm. When the maximal cardiac width is more than half the maximal chest width (cardiothoracic ratio >50%), the heart is usually enlarged. Cardiac size should be evaluated only when the film is taken during inspiration with the patient in an upright position. A diagnosis of "cardiac enlargement" on expiratory or prone films is a common cause of unnecessary referrals and laboratory studies.

The cardiothoracic ratio is a less useful index of cardiac enlargement in infants than in older children because the horizontal position of the heart may increase the ratio to >50% in the absence of true enlargement. Furthermore, the thymus may overlap not only the base of the heart but also virtually the entire mediastinum, thus obscuring the true cardiac silhouette.

A lateral chest roentgenogram may be helpful in infants as well as in older children with pectus excavatum or other conditions that result in a narrow anteroposterior chest dimension. In these situations, the heart may appear small in the lateral view and suggest that the apparent enlargement in the posteroanterior projection was due to either the thymic image (anterior mediastinum only) or flattening of the cardiac chambers as a result of a structural chest abnormality.

In the posteroanterior view, the left border of the cardiac shadow consists of 3 convex shadows produced, from above downward, by the aortic knob, the main and left pulmonary arteries, and the left ventricle (Fig. 423-1). In cases of moderate to marked left atrial enlargement, the atrium may project between the pulmonary artery and the left ventricle. The outflow tract of the right ventricle does not contribute to the shadows formed by the left border of the heart. The aortic knob is not as easily seen in infants and children as in adults. The side of the aortic arch (left or right) can often be inferred as being opposite the side of the midline from which the air-filled trachea is visualized. This observation is important because a right-sided aortic arch is often present in cyanotic congenital heart disease, particularly in tetralogy of Fallot. Three structures contribute to the right border of the cardiac silhouette. In the view from above, they are the superior vena cava, the ascending aorta, and the right atrium.

Enlargement of cardiac chambers or major arteries and veins results in prominence of the areas in which these structures are normally outlined on the chest x-ray. In contrast, the electrocardiogram (ECG) is a more sensitive and accurate index of **ventricular hypertrophy.**

The chest roentgenogram is also an important tool for assessing the degree of pulmonary vascularity. Pulmonary overcirculation is usually

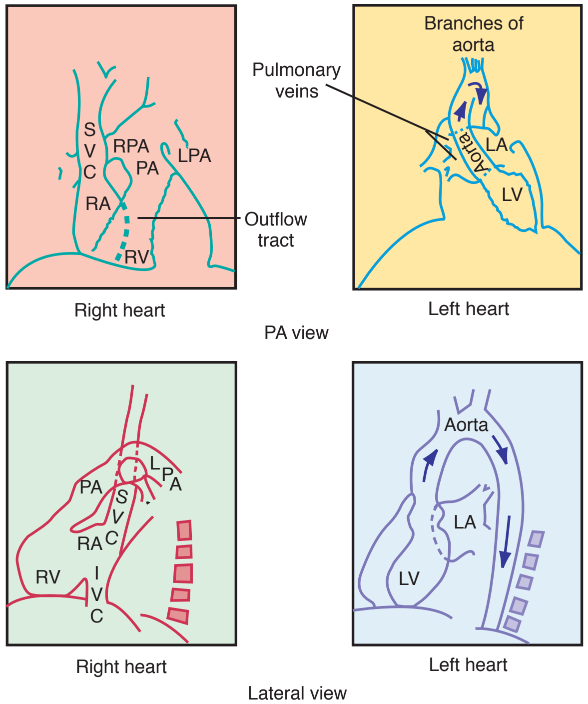

Figure 423-1 **Idealized diagrams showing normal position of the cardiac chambers and great blood vessels.** IVC, inferior vena cava; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; SVC, superior vena cava. *(Adapted and redrawn from Dotter CT, Steinberg I: Angiocardiographic interpretation, Radiology 153:513, 1949.)*

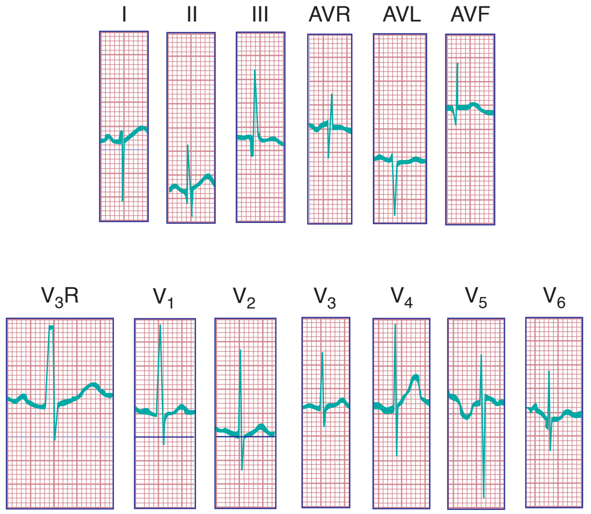

Figure 423-2 Electrocardiogram in a normal neonate <24 hr of age. Note the dominant R wave and upright T waves in leads V_3R and V_1 (V_3R paper speed = 50 mm/sec).

associated with left-to-right shunt lesions, whereas pulmonary undercirculation is associated with obstruction of the outflow tract of the right ventricle. The esophagus is closely related to the great vessels, and a barium esophagogram can help delineate these structures in the initial evaluation of suspected vascular rings, although this has largely been supplanted by CT. Echocardiographic examination best defines the morphologic features of intracardiac chambers, cardiac valves, and intracardiac shunts. CT is used as an adjunct to echo to evaluate extracardiac vascular morphology. MRI is used to quantitate ventricular volumes, cardiac function, and shunt and regurgitant fractions.

423.2 Electrocardiography

Daniel Bernstein

DEVELOPMENTAL CHANGES

The marked changes that occur in cardiac physiology and chamber dominance during the perinatal transition (see Chapter 421) are reflected in the evolution of the ECG during the neonatal period. Because vascular resistance in the pulmonary and systemic circulations is nearly equal in a term fetus, the intrauterine work of the heart results in an equal mass of both the right and left ventricles. After birth, systemic vascular resistance rises when the placental circulation is eliminated, and pulmonary vascular resistance falls when the lungs expand. These changes are reflected in the ECG as the right ventricular wall begins to thin.

The ECG demonstrates these anatomic and hemodynamic features principally by changes in QRS and T-wave morphologic features. Commonly, a 13-lead ECG is performed in pediatric patients, including either lead V_3R or V_4R, which are important in the evaluation of right ventricular hypertrophy. On occasion, lead V_1 is positioned too far leftward to reflect right ventricular forces accurately. This problem is present particularly in premature infants, in whom the electrocardiographic electrode gel may produce contact among all the precordial leads.

During the 1st days of life, right axis deviation, large R waves, and upright T waves in the right precordial leads (V_3R or V_4R and V_1) are the norm (Fig. 423-2). As pulmonary vascular resistance decreases in the 1st few days after birth, the right precordial T waves become negative. In the great majority of instances, this change occurs within the 1st 48 hr of life. Upright T waves that persist in leads V_3R, V_4R, or V_1 beyond 1 wk of life are an abnormal finding indicating right ventricular hypertrophy or strain, even in the absence of QRS voltage criteria. The T wave in V_1 should never be positive before 6 yr of age and may remain negative into adolescence. This finding represents one of the most important, yet subtle differences between pediatric and adult ECGs and is a common source of error when adult cardiologists interpret pediatric ECGs.

In a newborn, the mean **QRS frontal-plane axis** normally lies in the range of +110 to +180 degrees. The right-sided chest leads reveal a larger positive (R) than negative (S) wave and may do so for months because the right ventricle remains relatively thick throughout infancy. Left-sided leads (V_5 and V_6) also reflect right-sided dominance in the early neonatal period, when the R : S ratio in these leads may be <1. A dominant R wave in V_5 and V_6, reflecting left ventricular forces, quickly becomes evident within the 1st few days of life (Fig. 423-3). Over the years, the QRS axis gradually shifts leftward, and the right ventricular forces slowly regress. Leads V_1, V_3R, and V_4R display a prominent R wave until 6 mo to 8 yr of age. Most children have an R : S ratio >1 in lead V_4R until they are 4 yr of age. The T waves are inverted in leads V_4R, V_1, V_2, and V_3 during infancy and may remain so into the middle of the 2nd decade of life and beyond. The processes of right ventricular thinning and left ventricular growth are best reflected in the QRS-T pattern over the right precordial leads. The diagnosis of right or left ventricular hypertrophy in a pediatric patient can be made only with an understanding of the normal developmental physiology of these chambers at various ages until adulthood is reached. As the left ventricle becomes dominant, the ECG evolves to the characteristic pattern of older children (Fig. 423-4) and adults (Fig. 423-5).

Ventricular hypertrophy may result in increased voltage in the R and S waves in the chest leads. The height of these deflections is governed by the proximity of the specific electrode to the surface of the heart; by the sequence of electrical activation through the ventricles, which can result in variable degrees of cancellation of forces; and by hypertrophy of the myocardium. Because the chest wall in infants and children, as

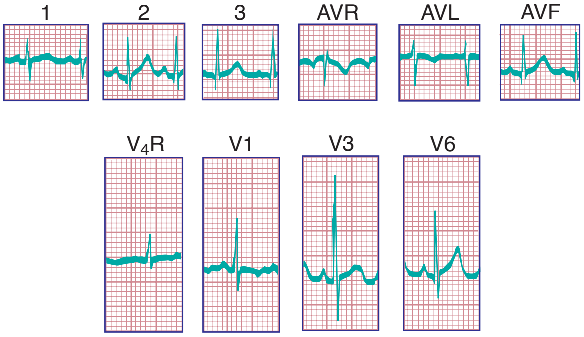

Figure 423-3 **Electrocardiogram of a normal infant.** Note the tall R and small S waves in V_4R and V_1 and the inverted T wave in these leads. A dominant R wave is also present in V_6.

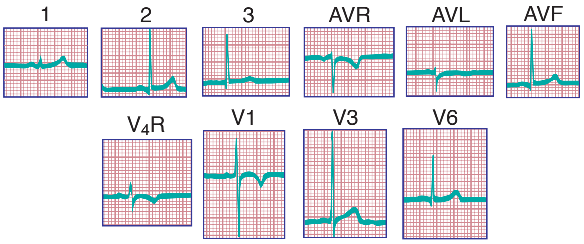

Figure 423-4 **Electrocardiogram of a normal child.** Note the relatively tall R waves and inversion of the T waves in V_4R and V_1.

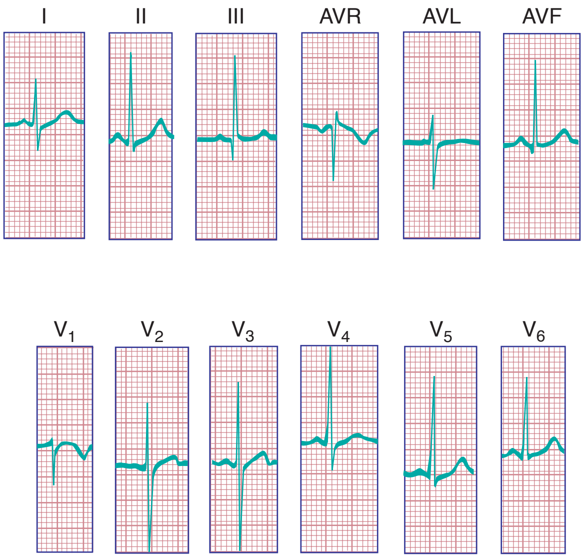

Figure 423-5 **Normal adult electrocardiogram.** Note the dominant S wave in lead V_1. This pattern in an infant would indicate the presence of left ventricular hypertrophy.

well as in adolescents, may be relatively thin, the diagnosis of ventricular hypertrophy should not be based on voltage changes alone.

The diagnosis of pathologic right ventricular hypertrophy is difficult in the 1st wk of life because physiologic right ventricular hypertrophy is a normal finding. Serial tracings are often necessary to determine whether marked right axis deviation and potentially abnormal right precordial forces or T waves, or both, will persist beyond the neonatal period (Fig. 423-6). In contrast, an adult electrocardiographic pattern

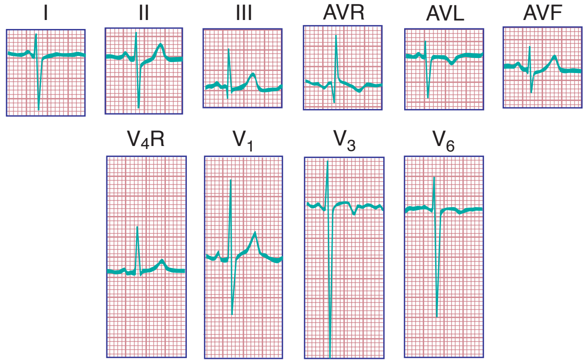

Figure 423-6 **Electrocardiogram of an infant with right ventricular hypertrophy (tetralogy of Fallot).** Note the tall R waves in the right precordium and deep S waves in V_6. The positive T waves in V_4R and V_1 are also characteristic of right ventricular hypertrophy.

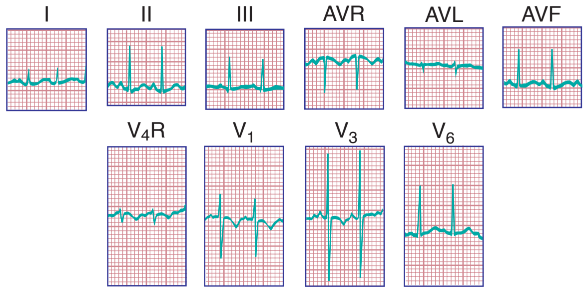

Figure 423-7 **Electrocardiogram of a premature infant (weight 2 kg and age 5 wk at the time of the tracing).** The cardiovascular system was clinically normal. Left ventricular dominance is manifested by R-wave progression across the chest, similar to tracings obtained from older children. Compare with the tracing from a normal full-term infant (see Fig. 423-3).

(see Fig. 423-5) seen in a neonate suggests left ventricular hypertrophy. The exception is a premature infant, who may display a more "mature" ECG than a full-term infant (Fig. 423-7) as a result of lower pulmonary vascular resistance secondary to underdevelopment of the medial muscular layer of the pulmonary arterioles. Some premature infants display a pattern of generalized low voltage across the precordium.

The ECG should always be evaluated systematically to avoid the possibility of overlooking a minor, but important, abnormality. One approach is to begin with an assessment of rate and rhythm, followed by a calculation of the mean frontal-plane QRS axis, measurements of segment intervals, assessment of voltages, and, finally, assessment of ST and T-wave abnormalities.

RATE AND RHYTHM

A brief rhythm strip should be examined to assess whether a P wave always precedes each QRS complex. The P-wave axis should then be estimated as an indication of whether the rhythm is originating from the sinus node. If the atria are situated normally in the chest, the P wave should be upright in leads I and aVF and inverted in lead aVR. With atrial inversion (situs inversus), the P wave may be inverted in lead I. Inverted P waves in leads II and aVF are seen in low atrial, nodal, or junctional rhythms. The absence of P waves indicates a rhythm originating more distally in the conduction system. In this case, the morphologic features of the QRS complexes are important in differentiating a junctional (usually a narrow QRS complex) from a ventricular (usually a wide QRS complex) rhythm.

P WAVES

Tall (>2.5 mm), narrow, and spiked P waves are indicative of **right atrial enlargement** and are seen in congenital pulmonary stenosis,

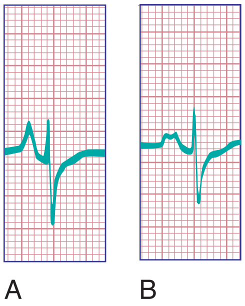

Figure 423-8 **Atrial enlargement. A,** Peaked narrow P waves characteristic of right atrial enlargement. **B,** Wide bifid M-shaped P waves typical of left atrial enlargement.

Ebstein anomaly of the tricuspid valve, tricuspid atresia, and sometimes cor pulmonale. These abnormal waves are most obvious in leads II, V_3R, and V_1 (Fig. 423-8*A*). Similar waves are sometimes seen in thyrotoxicosis. **Broad P waves,** commonly **bifid** and sometimes **biphasic,** are indicative of left atrial enlargement (Fig. 423-8*B*). They are seen in some patients with large left-to-right shunts (ventricular septal defect [VSD], patent ductus arteriosus [PDA]) and with severe mitral stenosis or regurgitation. Flat P waves may be encountered in hyperkalemia.

QRS COMPLEX

Right Ventricular Hypertrophy

For the most accurate assessment of ventricular hypertrophy, pediatric ECGs should include the right precordial lead V_3R or V_4R, or both. The diagnosis of right ventricular hypertrophy depends on demonstration of the following changes (see Fig. 423-6): (1) a qR pattern in the right ventricular surface leads; (2) a positive T wave in leads V_3R-V_4R and V_1-V_3 between the ages of 6 days and 6 yr; (3) a monophasic R wave in V_3R, V_4R, or V_1; (4) an rsR′ pattern in the right precordial leads with the 2nd R wave taller than the initial one; (5) age-corrected increased voltage of the R wave in leads V_3R-V_4R or the S wave in leads V_6-V_7, or both; (6) marked right axis deviation (>120 degrees in patients beyond the newborn period); and (7) complete reversal of the normal adult precordial RS pattern. At least 2 of these changes should be present to support a diagnosis of right ventricular hypertrophy.

Abnormal ventricular loading can be characterized as either systolic (as a result of obstruction of the right ventricular outflow tract, as in pulmonic stenosis) or diastolic (as a result of increased volume load, as in atrial septal defects [ASDs]). These 2 types of abnormal loads result in distinct electrocardiographic patterns. The **systolic overload pattern** is characterized by tall, pure R waves in the right precordial leads. In older children, the T waves in these leads are initially upright and later become inverted. In infants and children <6 yr, the T waves in V_3R-V_4R and V_1 are abnormally upright. The **diastolic overload pattern** (typically seen in patients with ASDs) is characterized by an rsR′ pattern (Fig. 423-9) and a slightly increased QRS duration (minor right ventricular conduction delay). Patients with mild to moderate pulmonary stenosis may also exhibit an rsR′ pattern in the right precordial leads.

Left Ventricular Hypertrophy

The following features indicate the presence of left ventricular hypertrophy (Fig. 423-10): (1) depression of the ST segments and inversion of the T waves in the left precordial leads (V_5, V_6, and V_7), known as a *left ventricular strain* pattern—these findings suggest the presence of a severe lesion; (2) a deep Q wave in the left precordial leads; and (3) increased voltage of the S wave in V_3R and V_1 or the R wave in V_6-V_7, or both. It is important to emphasize that evaluation of left ventricular hypertrophy should not be based on voltage criteria alone. The concepts of systolic and diastolic overload, though not always consistent,

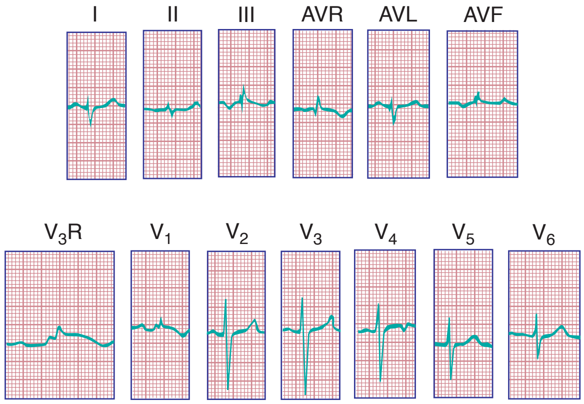

Figure 423-9 Electrocardiogram showing right ventricular conduction delay characterized by an rsR′ pattern in V_1 and a deep S wave in V_6 (V_3R paper speed = 50 mm/sec).

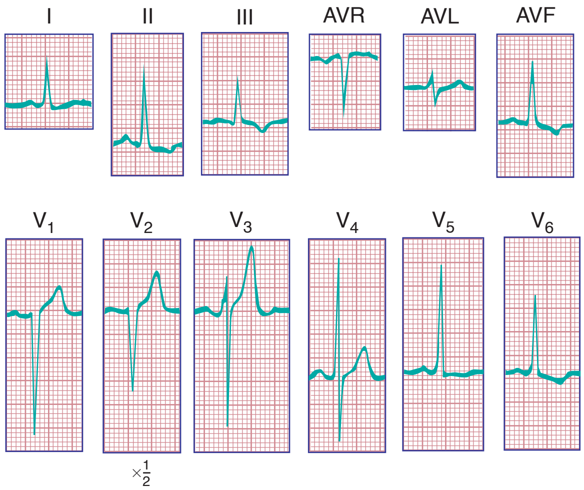

Figure 423-10 **Electrocardiogram showing left ventricular hypertrophy in a 12 yr old child with aortic stenosis.** Note the deep S wave in V_1-V_3 and tall R in V_5. In addition, T-wave inversion is present in leads II, III, aVF, and V_6.

are also useful in evaluating left ventricular enlargement. Severe systolic overload of the left ventricle is suggested by straightening of the ST segments and inverted T waves over the left precordial leads; diastolic overload may result in tall R waves, a large Q wave, and normal T waves over the left precordium. Finally, an infant with an ECG that would be considered "normal" for an older child may, in fact, have left ventricular hypertrophy.

Bundle Branch Block

A complete right bundle-branch block may be congenital or may be acquired after surgery for congenital heart disease, especially when a right ventriculotomy has been performed, as in repair of the tetralogy of Fallot. Congenital left bundle-branch block is rare; this pattern is occasionally seen with cardiomyopathy. A bundle-branch block pattern may be indicative of a bypass tract associated with one of the preexcitation syndromes (see Chapter 435).

P-R AND Q-T INTERVALS

The duration of the P-R interval shortens with increasing heart rate; thus, assessment of this interval should be based on age- and rate-corrected nomograms. A long P-R interval is diagnostic of a **1st-degree heart block,** the cause of which may be congenital, postoperative,

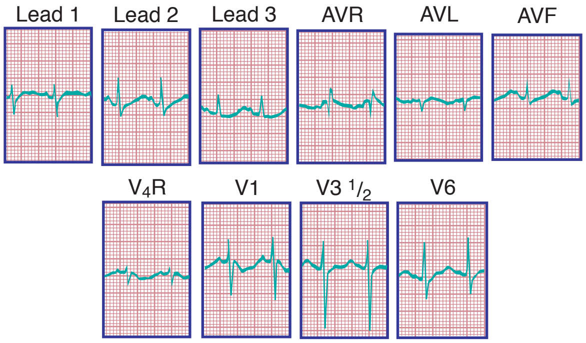

Figure 423-11 Electrocardiogram in hypokalemia (serum potassium, 2.7 mEq/L; serum calcium, 4.8 mEq/L at the time of the tracing). Note the prolongation of electrical systole as evidenced by a widened TU wave, as well as depression of the ST segment in V_4R, V_1, and V_6.

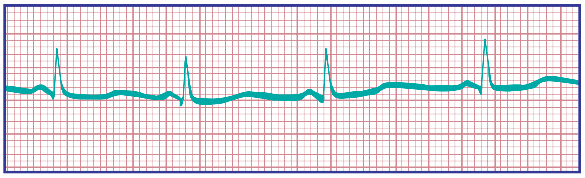

Figure 423-12 Prolonged Q-T interval in a patient with long Q-T syndrome.

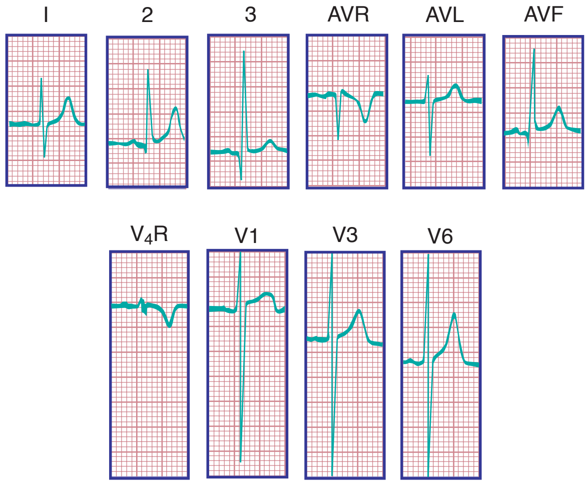

Figure 423-13 Electrocardiogram in hyperkalemia (serum potassium, 6.5 mEq/L; serum calcium, 5.1 mEq/L). Note the tall, tent-shaped T waves, especially in leads I, II, and V_6.

inflammatory (myocarditis, pericarditis, Lyme disease, rheumatic fever), or pharmacologic (digitalis).

The duration of the Q-T interval varies with the cardiac rate; a corrected Q-T interval (Q-Tc) can be calculated by dividing the measured Q-T interval by the square root of the preceding R-R interval. A normal Q-Tc should be <0.45. It is often lengthened with hypokalemia and hypocalcemia; in the former instance, a U wave may be noted at the end of the T wave (Fig. 423-11). There are a number of medications that can also lengthen the Q-T interval. A congenitally prolonged Q-T interval (Fig. 423-12) may also be seen in children with one of the long Q-T syndromes. These patients are at high risk for ventricular arrhythmias, including a form of ventricular tachycardia known as torsades de pointes, and sudden death (see Chapter 435.5).

ST SEGMENT AND T-WAVE ABNORMALITIES

A slight elevation of the ST segment may occur in normal teenagers and is attributed to early repolarization of the heart. In pericarditis, irritation of the epicardium may cause elevation of the ST segment followed by abnormal T-wave inversion as healing progresses. Administration of digitalis is sometimes associated with sagging of the ST segment and abnormal inversion of the T wave.

Depression of the ST segment may also occur in any condition that produces myocardial damage or ischemia, including severe anemia, carbon monoxide poisoning, aberrant origin of the left coronary artery from the pulmonary artery, glycogen storage disease of the heart, myocardial tumors, and mucopolysaccharidoses. An aberrant origin of the left coronary artery from the pulmonary artery may lead to changes indistinguishable from those of acute myocardial infarction in adults. Similar changes may occur in patients with other rare abnormalities of the coronary arteries and in those with cardiomyopathy, even in the presence of normal coronary arteries. These patterns are often misread in young infants because of the unfamiliarity of pediatricians with this "infarct" pattern, and thus a high index of suspicion must be maintained in infants with dilated cardiomyopathy or with symptoms compatible with coronary ischemia (e.g., inconsolable crying).

T-wave inversion may occur in myocarditis and pericarditis, or it may be a sign of either right or left ventricular hypertrophy and strain. Hypothyroidism may produce flat or inverted T waves in association with generalized low voltage. In hyperkalemia, the T waves are commonly of high voltage and are tent-shaped (Fig. 423-13).

Bibliography is available at Expert Consult.

423.3 Hematologic Data

Daniel Bernstein

In acyanotic infants with large left-to-right shunts, the onset of heart failure often coincides with the nadir of the normal physiologic anemia of infancy. Increasing the hematocrit in these patients to >40% may decrease shunt volume and result in an improvement in symptoms; however, this form of treatment is generally reserved for infants who are not otherwise surgical candidates (extremely premature infants or those with exceedingly complex congenital heart disease for whom only palliative surgery is possible). In these select infants, regular evaluation of the hematocrit and booster transfusions when appropriate may be helpful in improving growth.

Polycythemia is frequently noted in cyanotic patients with right-to-left shunts. Patients with severe polycythemia are in a delicate balance between the risks of intravascular thrombosis and a bleeding diathesis. The most frequent abnormalities include accelerated fibrinolysis, thrombocytopenia, abnormal clot retraction, hypofibrinogenemia, prolonged prothrombin time, and prolonged partial thromboplastin time. The preparation of cyanotic, polycythemic patients for elective noncardiac surgery, such as dental extraction, includes evaluation and treatment of abnormal coagulation.

Because of the high viscosity of polycythemic blood (hematocrit >65%), patients with cyanotic congenital heart disease are at risk for the development of vascular thromboses, especially of cerebral veins. Dehydration increases the risk of thrombosis, and thus adequate fluid intake must be maintained during hot weather or intercurrent gastrointestinal illnesses. Diuretics should be used with caution in these patients and may need to be decreased if fluid intake is a concern. Polycythemic infants with concomitant **iron deficiency** are at even greater risk for cerebrovascular accidents, probably because of the decreased deformability of microcytic red blood cells. Iron therapy may reduce this risk somewhat, but surgical treatment of the cardiac anomaly is the best therapy.

Severely cyanotic patients should have periodic determinations of hemoglobin and hematocrit. Increasing polycythemia, often associated with headache, fatigue, dyspnea, or a combination of these conditions, is one indication for palliative or corrective surgical intervention. In cyanotic patients with inoperable conditions, partial exchange

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transfusion may be required to treat symptomatic individuals whose hematocrit has risen to the 65-70% level. This procedure is not without risk, especially in patients with an extreme elevation in pulmonary vascular resistance. Because these patients do not tolerate wide fluctuations in circulating blood volume, blood should be replaced with fresh-frozen plasma or albumin.

423.4 Echocardiography

Daniel Bernstein

Transthoracic echocardiography has replaced invasive studies such as cardiac catheterization for the *initial diagnosis* of most forms of congenital heart disease. The echocardiographic examination can be used to evaluate cardiac structure in congenital heart lesions, estimate intracardiac pressures and gradients across stenotic valves and vessels, quantitate cardiac contractile function (both systolic and diastolic), determine the direction of flow across a defect, examine the integrity of the coronary arteries, and detect the presence of vegetations from endocarditis, as well as the presence of pericardial fluid, cardiac tumors, and chamber thrombi. Echocardiography may also be used to assist in the performance of interventional procedures, including pericardiocentesis, balloon atrial septostomy (see Chapter 431.2), atrial or VSD closure and endocardial biopsy, and in the placement of flow-directed pulmonary artery (Swan-Ganz) monitoring catheters. **Transesophageal echocardiography** is used routinely to monitor ventricular function in patients during surgical procedures and can provide an immediate assessment of the results of surgical repair of congenital heart lesions. A complete transthoracic echocardiographic examination usually entails a combination of M-mode and 2-dimensional (2D) imaging, as well as pulsed, continuous, and color Doppler flow studies. Doppler tissue imaging provides a more quantitative assessments of ventricular function. Three-dimensional (3D) echocardiography provides valuable information regarding cardiac morphology.

M-MODE ECHOCARDIOGRAPHY

M-mode echocardiography displays a 1-dimensional slice of cardiac structure varying over time (Fig. 423-14). It is used mostly for the measurement of cardiac dimensions (wall thickness and chamber size) and cardiac function (fractional shortening, wall thickening). M-mode echocardiography is also useful for assessing the motion of intracardiac structures (opening and closing of valves, movement of free walls and septa) and the anatomy of valves (Fig. 423-15). The most frequently used index of cardiac function in children is percent fractional shortening (%FS), which is calculated as (LVED − LVES)/LVED, where LVED is left ventricular (LV) dimension at end-diastole and LVES is

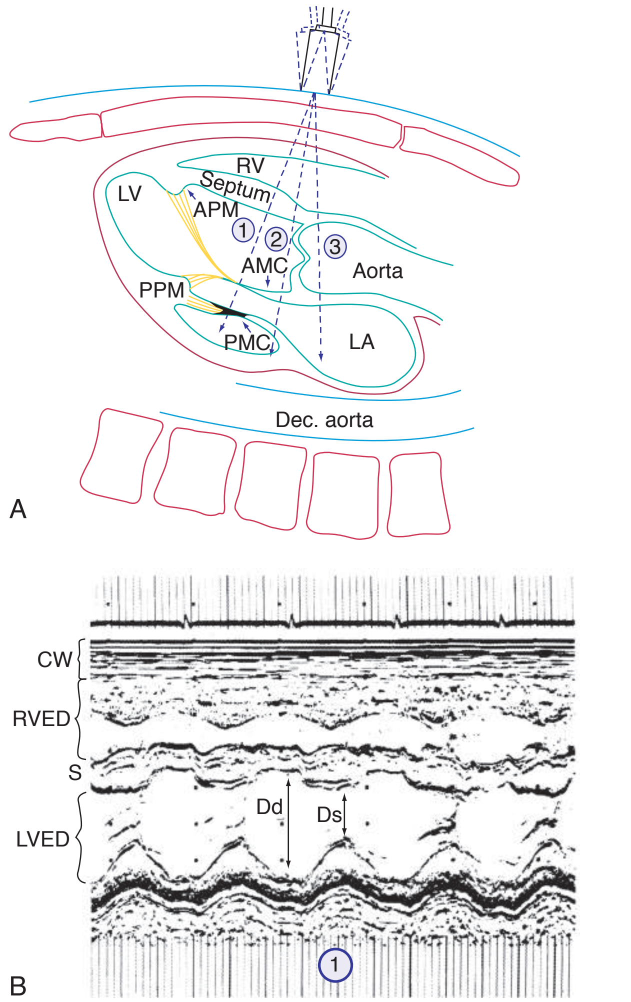

Figure 423-14 M-mode echocardiogram. **A,** Diagram of a sagittal section of a heart showing the structures traversed by the echo beam as it is moved superiorly to positions *(1), (2),* and *(3).* AMC, anterior mitral cusp; APM, anterior papillary muscle; Dec. aorta, descending aorta; LA, left atrium; LV, left ventricle; PMC, posterior mitral cusp; PPM, posterior papillary muscle; RV, right ventricle. **B,** Echocardiogram from transducer position *(1);* this view is the best one for measuring cardiac dimensions and fractional shortening. Fractional shortening is calculated as (LVED − LVES)/LVED. CW, chest wall; Ds, LV dimension in systole; LVED, LV dimension at end-diastole (Dd); RVED, RV dimension at end-diastole.

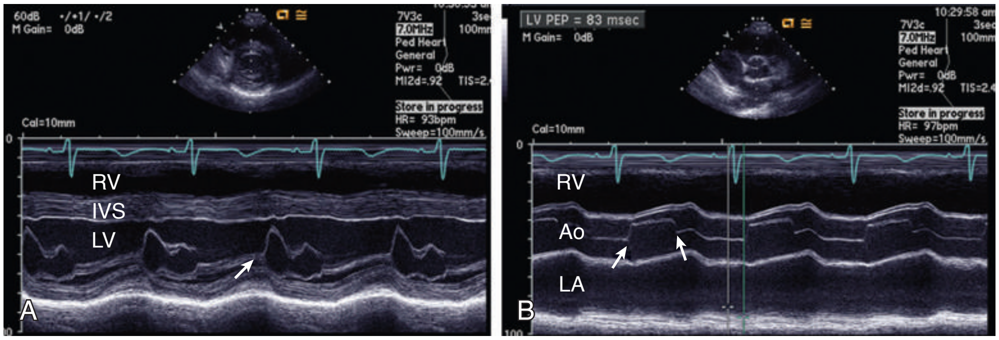

Figure 423-15 M-mode echocardiograms. The small figure at the top of each panel shows the 2D parasternal short axis echo image from which the M-modes are derived. The cursor can be seen midway through the image, indicating the one-dimensional line through which the M-mode is being sampled. **A,** M-mode echocardiogram of a normal mitral valve. *Arrow* shows the opening of the anterior leaflet in early diastole (see ECG tracing above for reference). **B,** M-mode echocardiogram of a normal aortic valve. The opening and closing of the aortic leaflets in systole are outlined by the 2 *arrows.* Ao, aorta; IVS, interventricular septum; LV, left ventricle; RV, right ventricle.

LV dimension at end-systole. Normal fractional shortening is approximately 28-40%. Other M-mode indices of cardiac function include the mean velocity of fiber shortening (mean V_{CF}), systolic time intervals (LVPEP = LV preejection period, LVET = LV ejection time), and isovolemic contraction time. More sophisticated indices of cardiac function can be derived noninvasively with the assistance of echocardiography (pressure–volume relationship, end-systolic wall stress–strain relationship).

TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Two-dimensional echocardiography provides a real-time image of cardiac structures. With 2D echocardiography, the contracting heart is imaged in real time using several standard views, including parasternal long axis (Fig. 423-16), parasternal short axis (Fig. 423-17), apical four chamber (Fig. 423-18), subcostal (Fig. 423-19), and suprasternal (Fig. 423-20) windows, each of which emphasizes specific structures. Two-dimensional echocardiography has replaced cardiac angiography for the preoperative diagnosis of most, but not all congenital heart lesions. When information from the cardiac examination or other studies is not consistent with the echocardiogram (e.g., the size of a left-to-right shunt), cardiac catheterization remains an important tool to confirm the anatomic diagnosis and evaluate the degree of physiologic derangement.

DOPPLER ECHOCARDIOGRAPHY

Doppler echocardiography displays blood flow in cardiac chambers and vascular channels based on the change in frequency imparted to

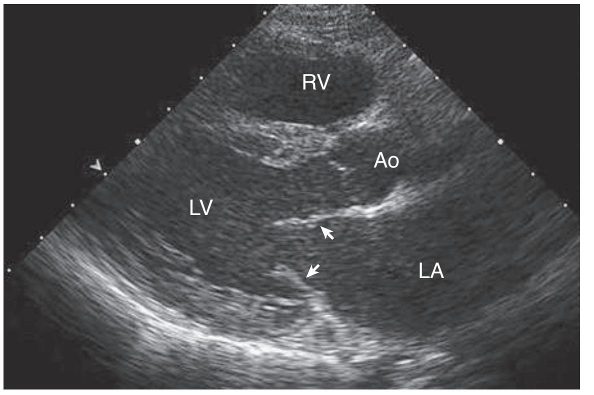

Figure 423-16 Normal parasternal long axis echocardiographic window. The transducer is angulated slightly posteriorly, imaging the left-sided cardiac structures. If the transducer were to be angulated more anteriorly, the right ventricular structures would be imaged. The mitral valve leaflets can be seen in partially open position in early diastole *(arrowheads).* The closed aortic valve leaflets can be seen just below the label Ao. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

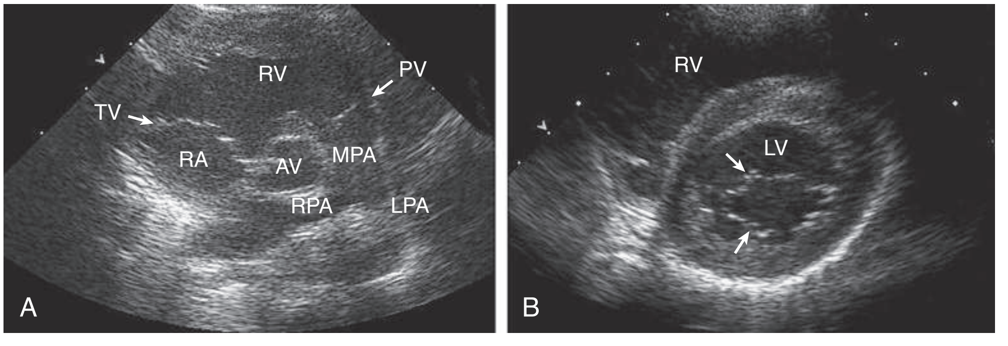

Figure 423-17 Normal parasternal short axis echocardiographic windows. A, With the transducer angled superiorly and rightwards, the aortic valve (AV) is imaged, surrounded by both inflow and outflow portions of the right ventricle (RV). LPA, left pulmonary artery; MPA, main pulmonary artery; PV, pulmonary valve; RA, right atrium; RPA, right pulmonary artery; TV, tricuspid valve. **B,** With the transducer angled inferiorly and leftward, the left ventricular chamber is imaged along with cross-sectional view of the mitral valve *(arrows).* LV, left ventricle; RV, right ventricle.

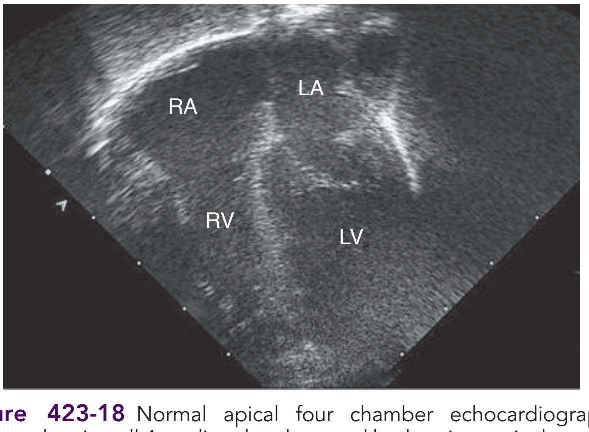

Figure 423-18 Normal apical four chamber echocardiographic window showing all 4 cardiac chambers and both atrioventricular valves opened in diastole. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

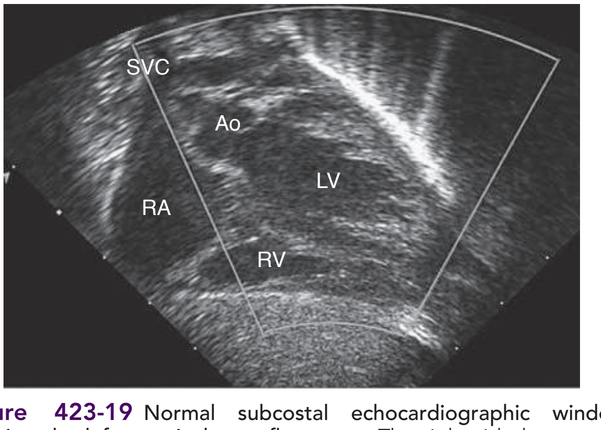

Figure 423-19 Normal subcostal echocardiographic window showing the left ventricular outflow tract. The right-sided structures are not fully imaged in this view. Ao, ascending aorta; LV, left ventricle; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

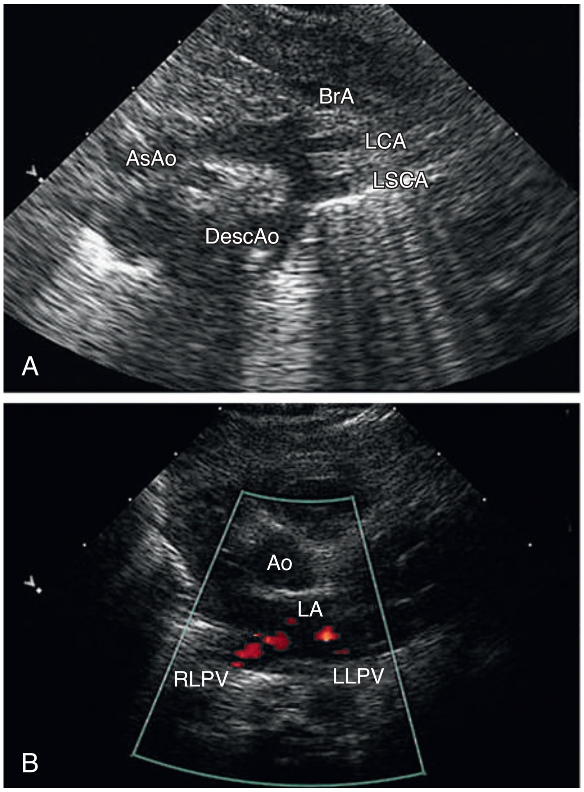

Figure 423-20 **A,** Normal suprasternal echocardiographic window showing the aortic arch and its major branches. AsAo, ascending aorta; BrA, brachiocephalic artery; DescAo, descending aorta; LCA, left carotid artery; LSCA, left subclavian artery. **B,** Normal high parasternal window showing color Doppler imaging of normal pulmonary venous return to the left atrium (LA) of both right (RLPV) and left (LLPV) lower pulmonary veins.

a sound wave by the movement of erythrocytes. In pulsed Doppler and continuous wave Doppler, the speed and direction of blood flow in the line of the echo beam change the transducer's reference frequency. This frequency change can be translated into volumetric flow (L/min) data for estimating systemic or pulmonary blood flow and into pressure (mm Hg) data for estimating gradients across the semilunar or atrioventricular valves or across septal defects or vascular communications such as shunts. Color Doppler permits highly accurate assessment of the presence and direction of intracardiac shunts and allows identification of small or multiple left-to-right or right-to-left shunts (Fig. 423-21). The severity of valvular insufficiency can be evaluated with both pulsed and color Doppler (Fig. 423-22). Alterations in venous Doppler flow patterns can be used to detect abnormalities of systemic and pulmonary veins and alterations of atrioventricular valve Doppler flow patterns can be used to assess ventricular diastolic functional abnormalities.

M-mode, 2D, and Doppler echocardiographic methods of assessing LV systolic and diastolic function (e.g., end-systolic wall stress, dobutamine stress echocardiography, and Doppler tissue imaging) have proved useful in the serial assessment of patients at risk for the development of both systolic and diastolic ventricular dysfunction and ventricular dyssynchrony (where the coordination of left and right ventricular contraction is abnormal). Such patients include those with cardiomyopathies, those receiving anthracycline drugs for cancer chemotherapy, those at risk for iron overload, and those being monitored for rejection or coronary artery disease after heart transplantation.

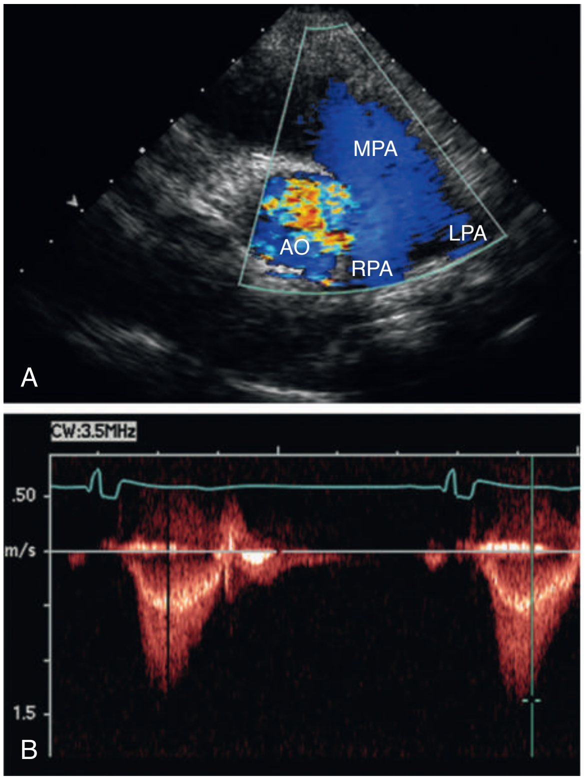

Figure 423-21 **Color and pulsed Doppler evaluation of pulmonary arterial flow. A,** Color Doppler evaluation of a parasternal short axis view showing normal flow through the pulmonary valve to the main and branch pulmonary arteries. The color of the Doppler flow is blue, indicating that the flow is moving away from the transducer (which is located at the top of the figure, at the apex of the triangular ultrasound window). Note that the color assigned to the Doppler signal does not indicate the oxygen saturation of the blood. AO, aorta; LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery. **B,** Pulsed wave Doppler flow pattern through the pulmonary valve showing a low velocity of flow (<1.5 m/sec), indicating the absence of a pressure gradient across the valve. The envelope of the flow signal is below the line, indicating that the flow is moving away from the transducer.

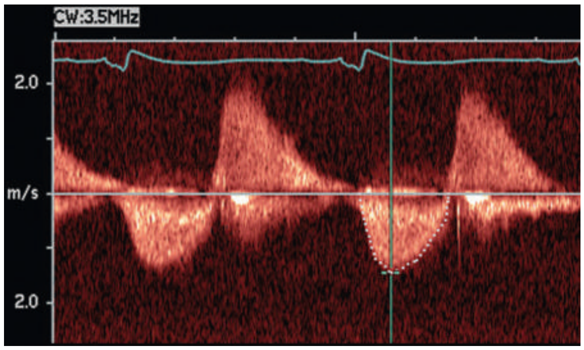

Figure 423-22 Doppler evaluation of a patient who had previously undergone repair of tetralogy of Fallot and who has mild pulmonary stenosis and moderate pulmonary regurgitation. The tracing shows the to-and-fro flow across the pulmonary valve with the signal below the line representing forward flow in systole (see ECG tracing for reference) and the signal above the line representing regurgitation during diastole.

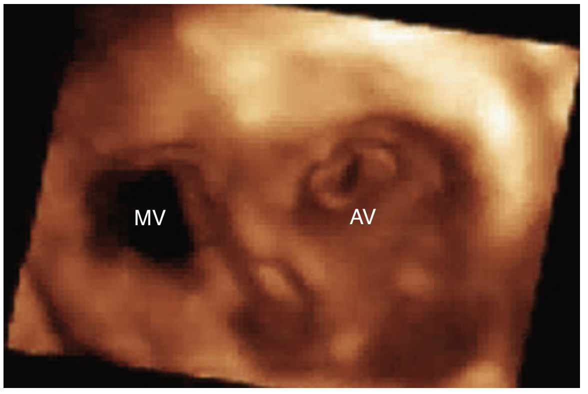

Figure 423-23 **Three-dimensional echocardiogram showing a short axis view of the left ventricle.** AV, aortic valve; MV, mitral valve. *(Courtesy of Dr. Norman Silverman, Stanford University, Stanford, CA.)*

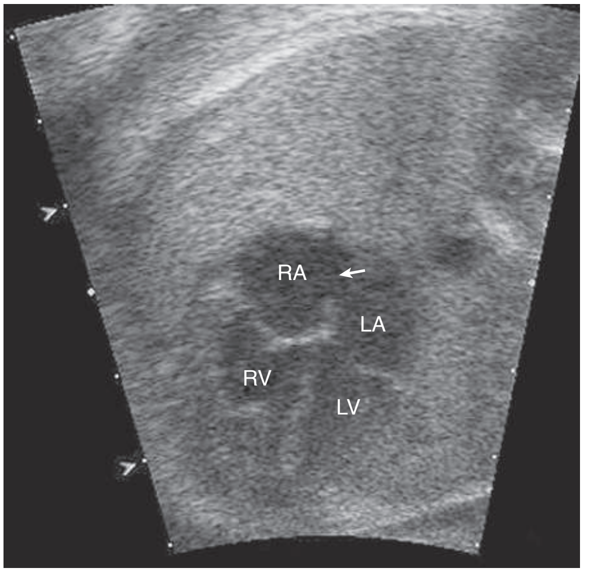

Figure 423-24 **Normal 4-chamber view echocardiogram on a fetus at 20 wk of gestation.** The foramen ovale *(arrow)* can be seen between the right and left atria. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Real-time 3D echocardiographic reconstruction is valuable for the assessment of cardiac morphology (Fig. 423-23). Details of valve structure, the size and location of septal defects, abnormalities of the ventricular myocardium, and details of the great vessels, which may not be as readily apparent using 2D imaging, can often be appreciated on 3D echocardiography. Reconstruction of the view that the surgeon will encounter in the operating room makes this technique a valuable adjunct for preoperative imaging.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Transesophageal echocardiography is an extremely sensitive imaging technique that produces a clearer view of smaller lesions such as vegetations in endocarditis, especially in larger patients. It is useful in visualizing posteriorly located structures such as the atria, aortic root, and atrioventricular valves. Transesophageal echocardiography is extremely useful as an intraoperative technique for monitoring cardiac function during both cardiac and noncardiac surgery and for screening for residual cardiac defects after the patient in initially weaned from cardiopulmonary bypass but before they are disconnected from the bypass circuit. This technique has been especially helpful in evaluating the degree of residual regurgitation or stenosis after valve repairs and in searching for small muscular VSDs that may have been missed during the closure of larger defects.

FETAL ECHOCARDIOGRAPHY

Fetal echocardiography can be used to evaluate cardiac structures or disturbances in cardiac rhythm (Fig. 423-24). Perinatologists often detect gross abnormalities in cardiac structure on routine obstetric ultrasonography or may refer the patient because of unexplained hydrops fetalis, a family history of congenital heart disease, or a maternal condition associated with fetal cardiac pathology such as gestational diabetes. Fetal echocardiography is capable of diagnosing most significant congenital heart lesions as early as 17-19 wk of gestation; accuracy at this early stage is limited and families should understand that these studies cannot totally eliminate the possibility of congenital heart disease. Serial fetal echocardiograms have also demonstrated the importance of flow disturbance in the pathogenesis of congenital heart disease; such studies can show the intrauterine progression of a moderate lesion, such as aortic stenosis, into a more severe lesion, such as hypoplastic left heart syndrome. M-mode echocardiography can diagnose rhythm disturbances in the fetus and can determine the success of antiarrhythmic therapy administered to the mother. A screening fetal echocardiogram is recommended for women with a previous child or 1st-degree relative with congenital heart disease, for those who are at higher risk of having a child with cardiac disease (insulin-dependent diabetics, patients with exposure to teratogenic drugs during early pregnancy), and in any fetus in which a chromosomal abnormality is suspected or confirmed.

Early detection provides the opportunity to counsel and educate the parents about the severity of the cardiac lesion and potential therapeutic or palliative care options. Referral to a high-risk perinatal service is then performed, for further ultrasound screening for associated anomalies of other organs and potential amniocentesis for karyotyping. For those fetuses with ductal dependent lesions, delivery can be planned at a tertiary care center, avoiding the requirement for postnatal transport of an unstable infant. For those fetuses with complex congenital heart disease at high risk for complications immediately at birth (e.g., hypoplastic left heart syndrome with intact atrial septum), delivery can be arranged with an operating room and surgeon standing by.

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423.5 Exercise Testing

Daniel Bernstein

The normal cardiorespiratory system adapts to the extensive demands of exercise with a several-fold increase in oxygen consumption and cardiac output. Because of the large reserve capacity for exercise, significant abnormalities in cardiovascular performance may be present without symptoms at rest or during ordinary activities. When patients are evaluated in a resting state, significant abnormalities in cardiac function may not be appreciated, or if detected, their implications for quality of life may not be recognized. Permission for children with cardiovascular disease to participate in various forms of physical activity is frequently based on totally subjective criteria. As the importance of aerobic exercise is increasingly recognized, even for children with complex congenital heart lesions, exercise testing can provide a quantitative evaluation of the child's ability to safely participate in both competitive and noncompetitive sports. Exercise testing can also play an important role in evaluating symptoms and quantitating the severity of cardiac abnormalities.

In older children, exercise studies are generally performed on a graded treadmill apparatus with timed intervals of increasing grade

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and speed. In younger children, exercise studies are often performed on a bicycle ergometer. Many laboratories have the capacity to measure both cardiac and pulmonary function noninvasively during exercise. This allows measurement of both resting and maximal oxygen consumption (Vo_{2max}) and the point at which anaerobic threshold is reached, important indicators of cardiovascular fitness.

As a child grows, the capacity for work is enhanced with increased body size and skeletal muscle mass. All indices of cardiopulmonary function do not increase in a uniform manner. A major response to exercise is an increase in cardiac output, principally achieved through an increase in heart rate, but stroke volume, systemic venous return, and pulse pressure are also increased. Systemic vascular resistance is greatly decreased as the blood vessels in working muscle dilate in response to increasing metabolic demands. As the child becomes older and larger, the response of the heart rate to exercise remains prominent, but cardiac output increases because of growing cardiac volume capacity and, hence, stroke volume. Responses to dynamic exercise are not dependent solely on age. For any given body surface area, boys have a larger stroke volume than size-matched girls. This increase is also mediated by posture. Augmentation of stroke volume with upright, dynamic exercise is facilitated by the pumping action of working muscles, which overcomes the static effect of gravity and increases systemic venous return.

Dynamic exercise testing defines not only endurance and exercise capacity but also the effect of such exercise on myocardial blood flow and cardiac rhythm. Significant ST segment depression reflects abnormalities in myocardial perfusion, for example, the subendocardial ischemia that commonly occurs during exercise in children with hypertrophied left ventricles. The **exercise ECG** is considered abnormal if the ST segment depression is >2 mm and extends for at least 0.06 sec after the J point (onset of the ST segment) in conjunction with a horizontal-, upward-, or downward-sloping ST segment. Provocation of rhythm disturbances during an exercise study is an important method of evaluating selected patients with known or suspected rhythm disorders. The effect of pharmacologic management can also be tested in this manner.

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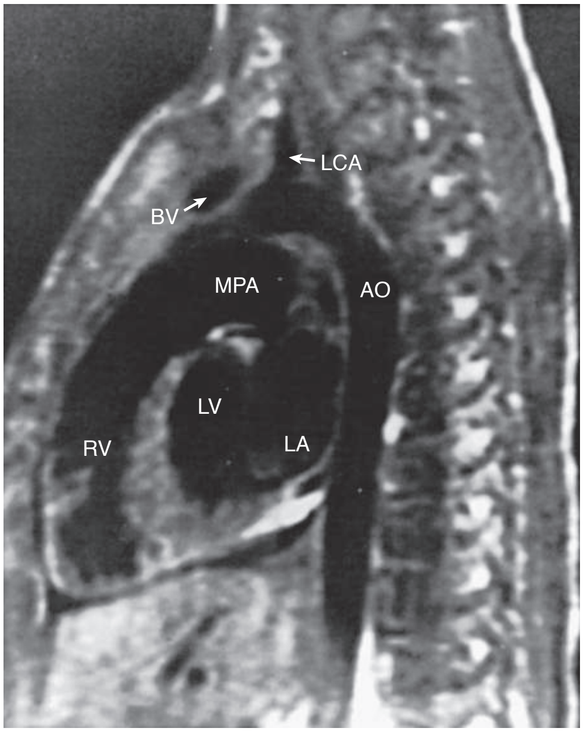

Figure 423-25 Sagittal normal MRI. AO, aorta; BV, brachiocephalic vein; LA, left atrium; LCA, left coronary artery; LV, left ventricle; MPA, main pulmonary artery; RV, right ventricle. *(From Bisset GS III: Cardiac and great vessel anatomy. In El-Khoury GY, Bergman RA, Montgomery WJ, editors: Sectional anatomy by MRI/CT, New York, 1990, Churchill Livingstone.)*

423.6 MRI, MRA, CT, and Radionuclide Studies

Daniel Bernstein

Magnetic resonance imaging (MRI) and **magnetic resonance angiography (MRA)** are extremely helpful in the diagnosis and management of patients with congenital heart disease. These techniques produce tomographic images of the heart in any projection (Fig. 423-25), with excellent contrast resolution of fat, myocardium, and lung, as well as moving blood from blood vessel walls. MRI is useful in evaluating areas that are less well visualized by echocardiography, such as distal branch pulmonary artery anatomy and anomalies in systemic and pulmonary venous return.

MRA allows the acquisition of images in several tomographic planes. Within each plane, images are obtained at different phases of the cardiac cycle. Thus, when displayed in a dynamic "cine" format, changes in wall thickening, chamber volume, and valve function can be displayed and analyzed. Blood flow velocity and blood flow volume can be calculated. MRA is an excellent technique for following patients serially after repair of complex congenital heart disease, such as tetralogy of Fallot. In these patients, MRA can be used to assess right ventricular volume and mass as well as quantify the amount of regurgitation through either the pulmonary or tricuspid valve. Other MRI techniques, such as myocardial delayed enhancement, can be used to quantify areas of myocardial scar in patients with cardiomyopathy or in patients after congenital heart disease repair, especially tetralogy of Fallot. **Magnetic resonance spectroscopy,** predominantly a research tool at present, provides a means of demonstrating relative concentrations of high-energy metabolites (adenosine triphosphate, adenosine diphosphate, inorganic phosphate, and phosphocreatine) within regions of the working myocardium.

Computer processing of MRA images allows the noninvasive visualization of the cardiovascular system from inside of the heart or vessels, a technique known as *fly-through imaging.* These images allow the cardiologist to image the interiors of various cardiovascular structures (Fig. 423-26). These imaging techniques are especially helpful in imaging complex peripheral arterial stenoses, especially after balloon angioplasty.

CT scanning can now be used to perform rapid, respiration-gated cardiac imaging in children with resolutions down to 0.5 mm. Three-dimensional reconstruction of CT images (Fig. 423-27) are especially useful in evaluating branch pulmonary arteries, anomalies in systemic and pulmonary venous return, and great vessel anomalies such as coarctation of the aorta.

Radionuclide angiography may be used to detect and quantify shunts and to analyze the distribution of blood flow to each lung. This technique is particularly useful in quantifying the volume of blood flow distribution between the 2 lungs in patients with abnormalities of the pulmonary vascular tree or after a shunt operation (Blalock-Taussig or Glenn), or to quantify the success of balloon angioplasty and intravascular stenting procedures. Gated blood pool scanning can be used to calculate hemodynamic measurements, quantify valvular regurgitation, and detect regional wall motion abnormalities. Thallium imaging can be performed to evaluate cardiac muscle perfusion. These methods can be used at the bedside of seriously ill children and can be performed serially, with minimal discomfort and low radiation exposure.

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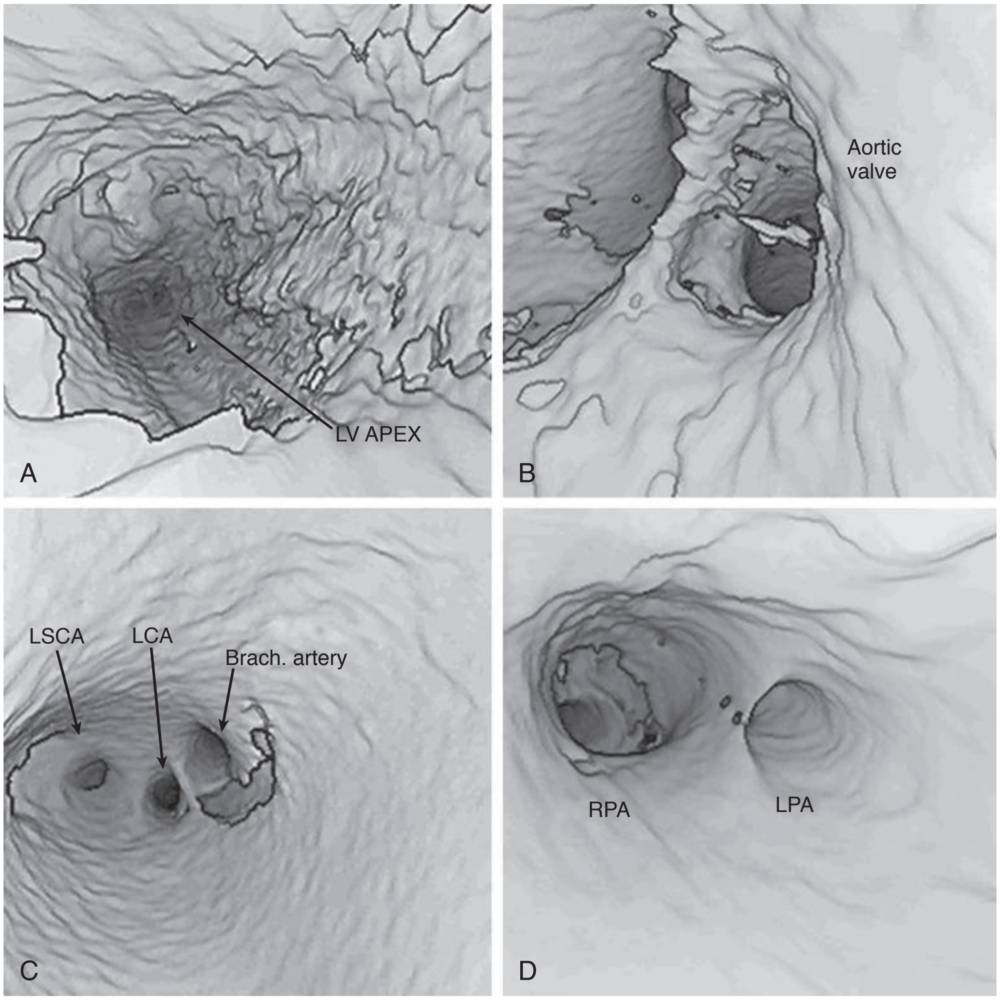

Figure 423-26 **Fly-through imaging in a patient with an aortopulmonary window.** This series of still frames shows the progression from the left ventricular (LV) chamber **(A),** through the aortic valve **(B),** out to the ascending aorta **(C),** and then through the defect to the branch pulmonary arteries **(D).** Brach., brachiocephalic artery; LCA, left carotid artery; LPA, left pulmonary artery; LSCA, left subclavian artery; RPA, right pulmonary artery.

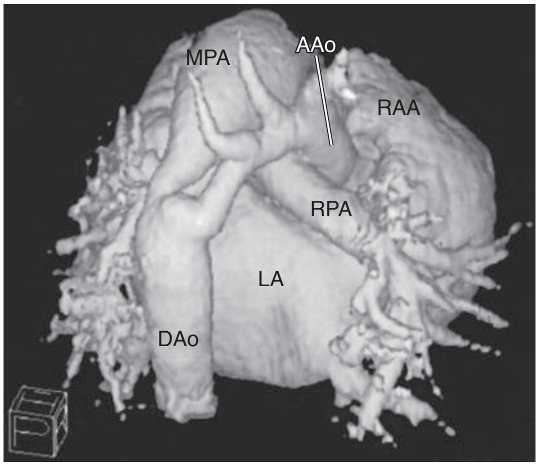

Figure 423-27 **Three-dimensional reconstruction of electron-beam CT images from a neonate with severe coarctation of the aorta.** The patent ductus arteriosus can be seen toward the left leading from the main pulmonary artery to the descending aorta. The tortuous and narrow coarctated segment is just to the right of the ductus. The transverse aorta is hypoplastic as well. AAo, ascending aorta; DAo, descending aorta; LA, left atrium; MPA, main pulmonary artery; RAA, right atrial appendage; RPA, right pulmonary artery. *(Image courtesy of Dr. Paul Pitlick, Stanford University, Stanford, CA.)*

423.7 Diagnostic and Interventional Cardiac Catheterization

Daniel Bernstein

The catheterization laboratory has become the site of high-technology interventional procedures, allowing for the nonsurgical repair or palliation of heart defects that once required open heart surgery. Some centers have developed hybrid catheterization laboratories, combining standard fluoroscopic imaging with an operating suite, allowing combined approaches to treat complex congenital heart lesions.

DIAGNOSTIC CARDIAC CATHETERIZATION

Diagnostic catheterization is still performed: (1) to assist in the initial diagnosis of some complex congenital heart lesions (e.g., tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries, pulmonary atresia with intact ventricular septum and coronary sinusoids, hypoplastic left-heart syndrome with mitral stenosis); (2) in cases in which other imaging studies are equivocal; (3) in patients for whom hemodynamic assessment is critical (to determine the size of a left-to-right shunt in borderline cases, or to determine the presence or absence of pulmonary vascular disease in an older patient with a left-to-right shunt); (4) between stages of repair of complex congenital heart disease (e.g., hypoplastic left- or right-heart syndromes); (5) for myocardial biopsy in the diagnosis of cardiomyopathy or in

screening for cardiac rejection after cardiac transplantation; and (6) for electrophysiologic study in the evaluation of cardiac arrhythmias (see Chapter 435).

Cardiac catheterization should be performed with the patient in as close to a basal state as possible. Conscious sedation is routine; if a deeper level of general anesthesia is required, careful choice of an anesthetic agent is warranted to avoid depression of cardiovascular function and subsequent distortion of the calculations of cardiac output, pulmonary and systemic vascular resistance, and shunt ratios.

Cardiac catheterization in critically ill infants with congenital heart disease should be performed in a center where a pediatric cardiovascular surgical team is available in the event that an operation is required immediately afterward. The complication rate of cardiac catheterization and angiography is greatest in critically ill infants; they must be studied in a thermally neutral environment and treated quickly for hypothermia, hypoglycemia, acidosis, or excessive blood loss.

Catheterization may be limited to the right-sided cardiac structures, the left-sided structures, or both the right and left sides of the heart. The catheter is passed into the heart under fluoroscopic guidance through a percutaneous entry point in a femoral or jugular vein. In infants and in a number of older children, the left side of the heart can be accessed by passing the catheter across a patent foramen ovale to the left atrium and left ventricle. If the foramen is closed, the left side of the heart can be catheterized by passing the catheter retrograde via a percutaneous entry site in the femoral artery, or if necessary, via a transatrial septal puncture. The catheter can be manipulated through abnormal intracardiac defects (ASDs, VSDs). Blood samples are obtained for measuring oxygen saturation and calculating shunt volumes, pressures are measured for calculating gradients and valve areas, and radiopaque contrast is injected to delineate cardiac and vascular structures. A catheter with a thermosensor tip can be used to measure cardiac output by thermodilution. Specialized catheters can be used to measure more sophisticated indices of cardiac function: Those with pressure-transducer tips can be utilized to measure the first derivative of LV pressure (dP/dt); and conductance catheters can be used to generate pressure-volume loops, from which indices of both contractility (end-systolic elastance) and relaxation can be derived. Complete hemodynamics can be calculated, including cardiac output, intracardiac left-to-right and right-to-left shunts, and systemic and pulmonary vascular resistances. Figure 423-28 depicts normal circulatory dynamics.

THERMODILUTION MEASUREMENT OF CARDIAC OUTPUT

The thermodilution method for measuring cardiac output is performed with a flow-directed, thermistor-tipped, pulmonary artery (Swan-Ganz) catheter. A known change in the heat content of the blood is induced at one point in the circulation (usually the right atrium or inferior vena cava) by injecting room temperature saline, and the resultant change in temperature is detected at a point downstream (usually the pulmonary artery). This method is used to measure cardiac output in the catheterization laboratory in patients without shunts. Monitoring cardiac output by the thermodilution method can occasionally be useful in managing critically ill infants and children in an intensive care setting after cardiac surgery or in the presence of shock. In this case, a triple-lumen catheter is used for both cardiac output determination and measurement of pulmonary artery and pulmonary capillary wedge pressure.

ANGIOCARDIOGRAPHY

The major blood vessels and individual cardiac chambers may be visualized by selective angiocardiography, the injection of contrast material into specific chambers or great vessels. This method allows identification of structural abnormalities without interference from the superimposed shadows of normal chambers. Fluoroscopy is used to visualize the catheter as it passes through the various heart chambers. After the cardiac catheter is properly placed in the chamber to be studied, a small amount of contrast medium is injected with a power injector, and cineangiograms are exposed at rates ranging from 15-60 frames/sec.

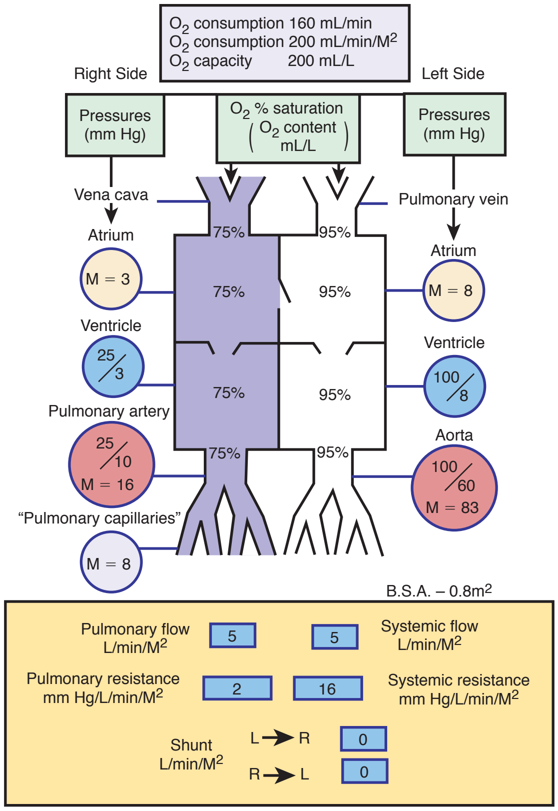

Figure 423-28 Diagram of normal circulatory dynamics with pressure readings, oxygen content, and percent saturation. B.S.A., body surface area. *(Modified from Nadas AS, Fyler DC:* Pediatric cardiology, *ed 3, Philadelphia, 1972, WB Saunders.)*

Modern catheterization labs utilize digital imaging technology, allowing for a significant reduction in radiation exposure. Biplane cineangiocardiography allows detailed evaluation of specific cardiac chambers and blood vessels in 2 planes simultaneously with the injection of a single bolus of contrast material. This technique is standard in pediatric cardiac catheterization laboratories and allows one to minimize the volume of contrast material used, which is safer for the patient. Various angled views (e.g., left anterior oblique, cranial angulation) are used to display specific anatomic features best in individual lesions.

Rapid injection of contrast medium under pressure into the circulation is not without risk, and each injection should be carefully planned. Contrast agents consist of hypertonic solutions, with some containing organic iodides, which can cause complications, including nausea, a generalized burning sensation, central nervous system symptoms, renal insufficiency, and allergic reactions. Intramyocardial injection is generally avoided by careful placement of the catheter before injection. Hypertonicity of the contrast medium may result in transient myocardial depression and a drop in blood pressure, followed soon afterward by tachycardia, an increase in cardiac output, and a shift of interstitial fluid into the circulation. This shift can transiently increase the symptoms of heart failure in critically ill patients.

INTERVENTIONAL CARDIAC CATHETERIZATION

Catheter treatment is the standard of practice for most cases of isolated pulmonary or aortic valve stenosis (see Fig. 421-4) as well as for re-coarctation of the aorta. A special catheter with a sausage-shaped balloon at the distal end is passed through the obstructed valve. Rapid filling of the balloon with a mixture of contrast material and saline solution results in tearing of the stenotic valve tissue, usually at the site of inappropriately fused raphe. Valvular pulmonary stenosis can be treated successfully by balloon angioplasty; in most patients, angioplasty has replaced surgical repair as the initial procedure of choice.

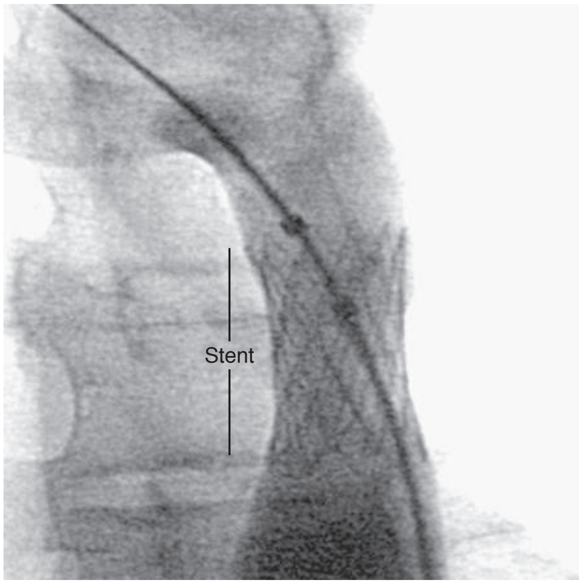

Figure 423-29 Intravascular stent placed in the descending aorta for treatment of recurrent coarctation of the aorta.

The clinical results of this procedure are similar to those obtained by open heart surgery, but without the need for sternotomy or prolonged hospitalization. Balloon valvuloplasty for aortic stenosis has also yielded excellent results, although, as with surgery, aortic stenosis often recurs as the child grows and multiple procedures may thus be required. One complication of both valvuloplasty and surgery is the creation of valvular insufficiency. This complication has more serious implications when it occurs on the aortic vs the pulmonary side of the circulation because regurgitation is less-well tolerated at systemic arterial pressures. Balloon angioplasty is the procedure of choice for patients with restenosis of coarctation of the aorta after earlier surgery. It is controversial whether angioplasty is the best procedure for native (unoperated) coarctation of the aorta because of reports of later aneurysm formation and most centers still refer primary coarctation in infants and young children for surgical repair. However, in older patients with previously undiagnosed coarctation, especially those with decreased LV function, primary angioplasty with possible stent placement may be considered. Other applications of the balloon angioplasty technique include amelioration of mitral stenosis, dilation of surgical conduits (Mustard or Senning atrial baffles), relief of branch pulmonary artery narrowing, dilation of systemic or pulmonary venous obstructions, and the long-used balloon atrial septostomy (Rashkind procedure) for transposition of the great arteries (see Chapter 431.2).

Interventional catheterization techniques are being adapted for use in the **fetus** with lesions such as aortic stenosis in an attempt to prevent their progression to more complex lesions such as hypoplastic left heart syndrome. In these procedures, after administration of appropriate anesthesia, a needle is passed through the maternal abdominal wall, the uterine wall, and the fetal chest wall and directly into the fetal left ventricle (see Fig. 425-13). A coronary angioplasty balloon catheter is passed through the needle and across the stenotic aortic valve, which is then dilated. With the restoration of normal LV blood flow, it is to be hoped that normal LV growth potential is restored. Midterm results with this technique in a growing number of patients show mixed results with good ventricular growth leading to a 2-ventricle circulation in approximately 25% of patients.

In patients with branch pulmonary artery stenoses, the previously mixed results with balloon angioplasty alone have been enhanced with the use of **intravascular stents** (Fig. 423-29) delivered over a balloon catheter and expanded within the vessel lumen. Once placed, they can often be dilated to successively greater sizes as the patient grows, although their use in younger infants and children is limited by the extent to which they can be further expanded. Research into biodissolvable stents may solve this problem in the future. Stents are also being used in adolescents and young adults with coarctation of the aorta.

Closure of a small PDA is routinely achieved with catheter-delivered coils (see Fig. 420-11), whereas a larger PDA can be closed with a variety of sandwich-type devices. Closure of anomalous vascular connections (coronary fistulas, venovenous collaterals in cyanotic heart lesions) can also be achieved using coils. Secundum ASDs are now routinely closed with a double-disc occluder device (see Fig. 420-3). Versions of these devices are currently in clinical trials for closure of surgically hard-to-reach muscular VSDs and even for the more common perimembranous VSD. Catheter-delivered devices may also be used as an adjunct to complex surgical repairs (dilation or stenting of branch pulmonary artery or pulmonary vein stenosis or closure of a difficult to reach muscular VSD). High-risk patients undergoing the Fontan operation (see Chapter 430.4) often have a small fenestration created between the right and left sides of the circulation to serve as a "popoff valve" for high right-sided pressure in the early surgical period. Patients with these "fenestrated Fontans" are usually candidates for subsequent closure of the fenestration with a catheter-delivered device.

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Section 3

Congenital Heart Disease

Chapter 424

Epidemiology and Genetic Basis of Congenital Heart Disease

Daniel Bernstein

PREVALENCE

Congenital heart disease occurs in approximately 0.8% of live births. The incidence is higher in stillborns (3-4%), spontaneous abortuses (10-25%), and premature infants (approximately 2% excluding patent ductus arteriosus [PDA]). This overall incidence does not include mitral valve prolapse, PDA of preterm infants, and bicuspid aortic valves (present in 1-2% of adults). Congenital cardiac defects have a wide spectrum of severity in infants: approximately 2-3 in 1,000 newborn infants will be symptomatic with heart disease in the 1st yr of life. The diagnosis is established by 1 wk of age in 40-50% of patients with congenital heart disease and by 1 mo of age in 50-60% of patients. With advances in both palliative and corrective surgery, the number of children with congenital heart disease surviving to adulthood has increased dramatically. Despite these advances, congenital heart disease remains the leading cause of death in children with congenital malformations. Table 424-1 summarizes the relative frequency of the most common congenital cardiac lesions.

Most congenital defects are well tolerated in the fetus because of the parallel nature of the fetal circulation. Even the most severe cardiac defects (e.g., hypoplastic left-heart syndrome) can usually be well compensated for by the fetal circulation. In this example, the entire fetal

Table 424-1 Relative Frequency of Major Congenital Heart Lesions*

LESION	% OF ALL LESIONS
Ventricular septal defect	35-30
Atrial septal defect (secundum)	6-8
Patent ductus arteriosus	6-8
Coarctation of aorta	5-7
Tetralogy of Fallot	5-7
Pulmonary valve stenosis	5-7
Aortic valve stenosis	4-7
D-Transposition of great arteries	3-5
Hypoplastic left ventricle	1-3
Hypoplastic right ventricle	1-3
Truncus arteriosus	1-2
Total anomalous pulmonary venous return	1-2
Tricuspid atresia	1-2
Single ventricle	1-2
Double-outlet right ventricle	1-2
Others	5-10

*Excluding patent ductus arteriosus in preterm neonates, bicuspid aortic valve, physiologic peripheral pulmonic stenosis, and mitral valve prolapse.

cardiac output would be ejected by the right ventricle via the ductus arteriosus into both the descending and ascending aortae (the latter filling in a retrograde fashion), so that fetal organ blood flow would be minimally perturbed. Because the placenta provides for gas exchange and the normal fetal circulation has mixing between more highly and more poorly oxygenated blood, fetal organ oxygen delivery is also not dramatically affected. It is only after birth when the fetal pathways (ductus arteriosus and foramen ovale) begin to close that the full hemodynamic impact of an anatomic abnormality becomes apparent. One notable exception is the case of severe regurgitant lesions, most commonly of the tricuspid valve. In these lesions (e.g., Ebstein anomaly or severe right ventricular outflow obstruction [see Chapter 430.7]), the parallel fetal circulation cannot compensate for the volume load imposed on the right side of the heart. In utero heart failure, often with fetal pleural and pericardial effusions, and generalized ascites (nonimmune hydrops fetalis) may occur.

Although the most significant transitions in circulation occur in the immediate perinatal period, the circulation continues to undergo changes after birth, and these later changes may also have a hemodynamic impact on cardiac lesions and their apparent incidence. As pulmonary vascular resistance falls in the 1st several weeks of life, left-to-right shunting through intracardiac defects increases and symptoms become more apparent. Thus, in patients with a ventricular septal defect (VSD), heart failure is often first noticed between 1 and 3 mo of age (see Chapter 426.6). The severity of various defects can also change dramatically with growth; some VSDs may become smaller and even close as the child ages. Alternatively, stenosis of the aortic or pulmonary valve, which may be only moderate in the newborn period, may become worse if valve orifice growth does not keep pace with patient growth (see Chapter 427.5). The physician should always be alert for associated congenital malformations, which can adversely affect the patient's prognosis (see Table 422-2 in Chapter 422).

ETIOLOGY

The cause of most congenital heart defects is still unknown. Many cases of congenital heart disease are multifactorial and result from a combination of genetic predisposition and an as-yet-to-be-determined environmental stimulus. A small percentage of congenital heart lesions are related to known chromosomal abnormalities, in particular, trisomy 21, 13, and 18 and Turner syndrome; heart disease is found in more than 90% of patients with trisomy 18, 50% of patients with trisomy 21, and 40% of those with Turner syndrome. Other genetic factors may have a role in congenital heart disease; e.g., certain types of VSDs (supracristal) are more common in Asian children. The risk of occurrence of congenital heart disease increases if a 1st-degree relative (parent or sibling) is affected.

A growing list of congenital heart lesions has been associated with specific chromosomal abnormalities, and several have even been linked to specific gene defects. Fluorescent in situ hybridization analysis allows clinicians rapid screening of suspected cases once a specific chromosomal abnormality has been identified, although clinical laboratory tests for specific gene defects are still uncommon. In addition, microarray genomic hybridization has identified previously unknown copy number variations (microdeletions or microduplications) in many patients with congenital heart disease and suspicion of a congenital anomaly syndrome. These variants are submicroscopic and thus not visible on routine chromosome analysis.

A well-characterized genetic cause of congenital heart disease is the deletion of a large region (1.5-3 Mb) of chromosome 22q11.2, known as the **DiGeorge critical region.** At least 30 genes have been mapped to the deleted region; *Tbx1,* a transcription factor involved in early outflow tract development is one gene that has been implicated as a possible cause of DiGeorge syndrome. The estimated prevalence of 22q11.2 deletions is 1/4,000 live births. Cardiac lesions associated with 22q11.2 deletions are most often seen in association with either the DiGeorge syndrome or the **Shprintzen (velocardiofacial) syndrome.** The acronym *CATCH 22* has been used to summarize the major components of these syndromes (cardiac defects, abnormal facies, thymic aplasia, cleft palate, and hypocalcemia). The specific cardiac anomalies are conotruncal defects (tetralogy of Fallot, truncus arteriosus, double-outlet right ventricle, subarterial VSD) and branchial arch defects (coarctation of the aorta, interrupted aortic arch, right aortic arch). Congenital airway anomalies such as tracheomalacia and bronchomalacia are sometimes present. Although the risk of recurrence is extremely low in the absence of a parental 22q11.2 deletion, it is 50% if 1 parent carries the deletion. More than 90% of patients with the clinical features of DiGeorge syndrome have a deletion at 22q11.2. A second genetic locus on the short arm of chromosome 10 (10p13p14) has also been identified, the deletion of which shares some, but not all, phenotypic characteristics with the 22q11.2 deletion; patients with del(10p) have an increased incidence of sensorineural hearing loss.

Other structural heart lesions that have been associated with specific chromosomal abnormalities include **familial secundum atrial septal defect** associated with **heart block** (the transcription factor Nkx2.5 on chromosome 5q35), familial atrial septal defect without heart block (the transcription factor GATA4), Alagille syndrome (Jagged1 on chromosome 20p12), and Williams syndrome (elastin on chromosome 7q11). Of interest, patients with VSDs and atrioventricular septal defects have been found to have multiple Nkx2.5 mutations in cells isolated from diseased heart tissues, but not from normal heart tissues or from circulating lymphocytes, indicating a potential role for somatic mutations leading to mosaicism in the pathogenesis of congenital heart defects. Tables 424-2 and 424-3 are a compilation of known genetic causes of congenital heart disease.

The most progress in identifying the genetic origin of cardiovascular disease has been made in the genetic cardiomyopathies, and in particular, **hypertrophic cardiomyopathy.** Mutations in several genes have been implicated, most of which encode protein components of the cardiac sarcomere, either components of the thick or thin fibers or associated regulatory subunits, although mutations in mitochondrial genes are increasingly recognized and play a larger role in those presenting with hypertrophic cardiomyopathy as young infants than in older children and adults. Mutations of the cardiac β-myosin heavy-chain gene (chromosome 14q1) and the myosin-binding protein C gene (chromosome 11q11) are the most common (see Table 424-4), with less-common mutations including the cardiac troponin T and I genes, α-tropomyosin, regulatory and essential myosin light chains, titin, and the α-myosin heavy chain. More than 200 mutations have

Table 424-2 Genetics of Congenital Heart Disease: Defects Associated with Syndromes

CARDIOVASCULAR DISEASE	CHROMOSOMAL LOCATION	GENE(S) IMPLICATED*	COMMON CARDIAC DEFECTS
DiGeorge syndrome, velocardiofacial syndrome	22q11.2, 11p13p14	*TBX1*	TOF, IAA, TA, VSD
Familial ASD with heart block	5q35	*NKX2.5*	ASD, heart block
Familial ASD without heart block	8p22-23	*GATA4*	ASD
Alagille syndrome (bile duct hypoplasia, right-sided cardiac lesions)	20p12, 1p12	*JAGGED1, NOTCH2*	Peripheral pulmonary hypoplasia, PS, TOF
Holt-Oram syndrome (limb defects, ASD)	12q24	*TBX5*	ASD, VSD, PDA
Trisomy 21 (Down syndrome)	21q22	Not known	AVSD
Isolated familial AV septal defect (without trisomy 21)	1p31-p21, 3p25	*CRELD1*	AVSD
Familial TAPVR	4p13-q12	Not known	TAPVR
Noonan syndrome (PS, ASD, hypertrophic cardiomyopathy)	12q24, 12p1.21, 2p212, 3p25.2, 7q34, 15q22.31, 11p15.5, 1p13.2, 10q25.2, 11q23.3,17q11.2	*PTPN11, KRAS, SOS1, RAF1, BRAF, MEK1, HRAS, NRAS, SHOC2, CBL, NF1*	PS, ASD, VSD, PDA, cardiomyopathy
Ellis–van Creveld syndrome (polydactyly, ASD)	4p16	*EVC, EVC2*	ASD, common atrium
Char syndrome (craniofacial, limb defects, PDA)	6p12-21.1	*TFAP2B*	PDA
Williams-Beuren syndrome (supravalvular AS, branch PS, hypercalcemia)	7q11.23	*ELN* (Elastin)	Supravalvar AS, peripheral PS
Marfan syndrome (connective tissue weakness, aortic root dilation)	15q21	Fibrillin	Aortic aneurysm, mitral valve disease
Familial laterality abnormalities	Xq24-2q7, 1q42, 9p13-21	*ZIC3, DNAI1*	Situs inversus, complex congenital heart disease
Turner	X	Not known	Coarctation of the aorta, Aortic stenosis
Trisomy 13 (Patau syndrome)	13	Not known	ASD, VSD, PDA, valve abnormalities
Trisomy 18 (Edwards syndrome)	18	Not known	ASD, VSD, PDA, Valve abnormalities
Cri du chat	5p15.2	*CTNND2*	ASD, VSD, PDA, TOF
Cat eye	22q11	Not known	TAPVR, TOF
Jacobsen	11q23	*JAM-3*	HLHS
Costello	11p15.5	*HRAS*	PS, hypertrophic cardiomyopathy, arrhythmias
CHARGE	8p12, 7q21.11	*CHD7, SEMA3E*	ASD, VSD, TOF
Kabuki syndrome	12q13.12	*MLL2*	ASD, VSD, TOF, coarctation, TGA
Carney syndrome	2p16	*PRKAR1A*	Atrial and ventricular myxomas

AS, aortic stenosis; ASD, atrial septal defect; AV, atrioventricular; AVSD, atrioventricular septal defect; HLHS, hypoplastic left-heart syndrome; IAA, interrupted aortic arch; PDA, patent ductus arteriosus; PS, pulmonic stenosis; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.
*In many cases, mutation of a single gene has been closely linked to a specific cardiovascular disease, for example, by finding a high incidence of mutations or deletions of that gene in a large group of patients. These findings are often confirmed by studies in mice in which deletion or alteration of the gene induces a similar cardiac phenotype to the human disease. In others, mutation of a gene may increase the risk of cardiovascular disease, but with decreased penetrance, suggesting that modifier genes or environmental factors play a role. Finally, in some cases, gene mutations have only been identified in a small number of pedigrees, and confirmation awaits screening of larger numbers of patients.

been identified in these genes, and some patients may carry mutations in more than 1 gene. Routine clinical laboratory tests are now available for most of these mutations.

Progress has also been made in identifying the genetic basis of **dilated cardiomyopathy,** which is familial in 20-50% of cases. Autosomal dominant inheritance is most commonly encountered and, similar to hypertrophic cardiomyopathy, multiple genes have been identified (see Table 424-2). X-linked inheritance accounts for 5-10% of cases of familial dilated cardiomyopathy. Mutations in the dystrophin gene (chromosome Xp21) are the most common in this group. Mutations in the gene encoding *tafazzin* are associated with Barth syndrome and some cases of isolated non-compaction of the

Table 424-3 Genetics of Isolated Congenital Heart Disease (Nonsyndromic)

GENE IMPLICATED*	PROTEIN ENCODED	CARDIAC DEFECTS
GENES ENCODING TRANSCRIPTION FACTORS		
ANKRD1	Ankyrin repeat domain	TAPVR
CITED2	cAMP responsive element-binding protein	ASD, VSD
FOG2/ZFPM2	Friend of GATA	TOF
GATA6	GATA6 transcription factor	ASD, VSD, TOF, PS, AVSD, PDA
HAND2	Helix-loop-helix transcription factor	TOF
IRX4	Iroquois homeobox 4	VSD
MED13L	Mediator complex subunit 13-like	TGA
NKX2-5/NKX2.5	Homeobox containing transcription factor	ASD, VSD, TOF, HLHS, CoA, TGA, IAA
TBX20	T-Box 20 transcription factor	ASD, VSD, mitral stenosis
ZIC3	Zinc finger transcription factor	TGA, PS, TAPVR, HLHS, ASD, VSD
GENES ENCODING RECEPTORS AND SIGNALING MOLECULES		
ACVR1/ALK2	BMP receptor	AVSD
ACVR2B	Activin receptor	PS, DORV, TGA
ALDH1A2	Retinaldehyde dehydrogenase	TOF
CFC1/CRYPTIC	Cryptic protein	TOF, TGA, AVSD, ASD, VSD, IAA, DORV
CRELD1	Epidermal growth factor-related proteins	ASD; AVSD
FOXH1	Forkhead activin signal transducer	TOF, TGA
GDF1	Growth differentiation factor-1	TOF, TGA, DORV, heterotaxy
GJA1	Connexin 43	ASD, HLHS, TAPVR
LEFTY2	Left-right determination factor	TGA, AVSD, IAA, CoA
NODAL	Nodal homolog (TGF-β superfamily)	TGA, PA, TOF, DORV, TAPVR, AVSD
NOTCH1	NOTCH1 (Ligand of JAG1)	Bicuspid aortic valve, AS, CoA, HLHS
PDGFRA	Platelet-derived growth factor receptor α	TAPVR
SMAD6	MAD-related protein	Bicuspid aortic valve, CoA, AS
TAB2	TGF-β activated kinase	Outflow tract defects
TDGF1	Teratocarcinoma-derived growth factor 1	TOF, VSD
VEGF	Vascular endothelial growth factor	CoA, outflow tract defects
GENES ENCODING STRUCTURAL PROTEINS		
ACTC	α Cardiac actin	ASD
MYH11	Myosin heavy chain 11	PDA, aortic aneurysm
MYH6	α-Myosin heavy chain	ASD, TA, AS, TGA
MYH7	β-Myosin heavy chain	Ebstein anomaly, ASD

AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; cAMP, cyclic adenosine monophosphate; CoA, coarctation of the aorta; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; PA, pulmonary artery; PDA, patent ductus arteriosus; PS, pulmonic stenosis; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TGF, transforming growth factor; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

*In many cases, mutation of a single gene has been closely linked to a specific cardiovascular disease, for example, by finding a high incidence of mutations or deletions of that gene in a large group of patients. These findings are often confirmed by studies in mice in which deletion or alteration of the gene induces a similar cardiac phenotype to the human disease. In others, mutation of a gene may increase the risk of cardiovascular disease, but with decreased penetrance, suggesting that modifier genes or environmental factors play a role. Finally, in some cases, gene mutations have only been identified in a small number of pedigrees, and confirmation awaits screening of larger numbers of patients.

Partially adapted from Fahed AC, Gelb BD, Seidman JG, Seidman CE: Genetics of congenital heart disease: the glass half empty. Circ Res *112:707–720, 2013.*

left ventricle. Autosomal recessive inheritance is associated with a mutation in cardiac troponin I. Mitochondrial myopathies may be caused by mutations of enzymes of the electron transport chain encoded by nuclear DNA (in which inheritance will follow mendelian genetic patterns) or enzymes of fatty acid oxidation encoded by mitochondrial DNA (which is inherited solely from the mother). Table 424-4 is a compilation of the most common genetic causes of cardiomyopathy.

The genetic basis of **heritable arrhythmias,** most notably the **long Q-T syndromes,** has been linked to mutations of genes coding for subunits of cardiac potassium and sodium channels (see Table 424-2). Other heritable arrhythmias include arrhythmogenic right ventricular dysplasia, familial atrial fibrillation, familial complete heart block, and Brugada syndrome. Table 424-5 is a compilation of the most common genetic causes of arrhythmias.

Of all cases of congenital heart disease, 2-4% are associated with known environmental or adverse maternal conditions and teratogenic influences, including maternal diabetes mellitus, phenylketonuria, or systemic lupus erythematosus; congenital rubella syndrome; and maternal ingestion of drugs (lithium, ethanol, warfarin, thalidomide, antimetabolites, vitamin A derivatives, anticonvulsant agents) (see Table 422-2 in Chapter 422). Associated noncardiac malformations noted in identifiable syndromes may be seen in as many as 25% of patients with congenital heart disease.

Gender differences in the occurrence of specific cardiac lesions have been identified. Transposition of the great arteries and left-sided obstructive lesions are slightly more common in boys (≈65%), whereas atrial septal defect, VSD, PDA, and pulmonic stenosis are more common in girls. No racial differences in the occurrence of congenital heart lesions as a whole have been noted; for specific lesions such as transposition of the great arteries, a higher occurrence is seen in white infants.

GENETIC COUNSELING

Parents who have a child with congenital heart disease require counseling regarding the probability of a cardiac malformation occurring in subsequent children (see Chapter 77). With the exception of syndromes known to be caused by mutation of a single gene, most congenital heart disease is still relegated to a multifactorial inheritance pattern, which should result in a low risk of recurrence. As more genetic etiologies are identified, however, these risks will need constant updating. The incidence of congenital heart disease in the normal population is ≈0.8%, and this incidence increases to 2-6% for a second pregnancy after the birth of a child with congenital heart disease or if a parent is affected. This recurrence risk is highly dependent on the type of lesion in the first child. When two 1st-degree relatives have congenital heart disease, the risk for a subsequent child may reach 20-30%. When a second child is found to have congenital heart disease, it will tend to be of a similar

Table 424-4 Genetics of Cardiomyopathies

Hypertrophic cardiomyopathy	14q1 15q2 1q31 19p13.2-19q13.2 11p13-q13 12q23 13p21 2q31 3p25 Mitochondrial DNA Mitochondrial DNA	β-Myosin heavy chain α-Tropomyosin Troponin T Troponin I Myosin-binding protein C Cardiac slow myosin regulatory light chain Ventricular slow myosin essential light chain Titin Caveolin-3 tRNA-glycine tRNA-isoleucine
Hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome	7q36.1	AMP-activated protein kinase
Other genetic diseases causing cardiac hypertrophy		
Familial amyloid disease	18q12.1	Transthyretin (TTR)
Noonan syndrome	12q24.1, 2p22.1, 3p25,12p12.1	Protein tyrosine phosphatase 11 (PTPN11), son of sevenless homologue 1 (SOS1), RAF1 protooncogene, GTPase KRAS
Fabry disease	Xq22	α-Galactoside A (GLA)
Danon disease	Xq24	Lysosomal-associated membrane protein 2 (LAMP2)
Hereditary hemochromatosis	6p21.3	Hereditary hemochromatosis protein (HFE)
Pompe disease	17q25	Acid α-glucosidase (GAA)
Dilated cardiomyopathy		
X-linked	Xp21 Xp28	Dystrophin Tafazzin
Autosomal recessive	19p13.2-19q13.2	Troponin I

Autosomal dominant: genes encoding multiple proteins have been identified, including cardiac actin; desmin; δ-sarcoglycan; β-myosin heavy chain; cardiac troponin C and T; α-tropomyosin; titin; metavinculin; myosin-binding protein C; muscle LIM protein; α-actinin-2; phospholamban; Cypher/LIM binding domain 3; α-myosin heavy chain; SUR2A (regulatory subunit of K_{ATP} channel); and lamin A/C.
Isolated noncompaction of the left ventricle: autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance patterns have been reported. Genes that have been implicated include: α-dystrobrevin, Cypher/ZASP, lamin A/C, Tafazzin, MIB1, and LIM domain-binding protein 3 (LDB3).

Partially adapted from Dunn KE, Caleshu C, Cirino AL, et al. A clinical approach to inherited hypertrophy: the use of family history in diagnosis, risk assessment, and management. Circ Cardiovasc Genet *6:118-131, 2013.*

Table 424-5 Genetics of Arrhythmias

Complete heart block	19q13	Not known
Long Q-T syndrome		
LQT1 (autosomal dominant)	11p15.5	*KVLQT1* (K^+ channel)
LQT2 (autosomal dominant)	7q35	*HERG* (K^+ channel)
LQT3 (autosomal dominant)	3p21	*SCN5A* (Na^+ channel)
LQT4 (autosomal dominant)	4q25-27	Not known
LQT5 (autosomal dominant)	21q22-q22	*KCNE1* (K^+ channel)
LQT6	21q22.1	*KCNE2* (K^+ channel)
Jervell and Lange-Nielsen syndrome (autosomal recessive, congenital deafness)	11p15.5	*KVLQT1* (K^+ channel)
LQT8-13	Unknown	Private mutations (rare)
Arrhythmogenic RV dysplasia: There are now 11 genes associated with arrhythmogenic right ventricular dysplasia (ARVD1 through 11) usually with autosomal dominant inheritance, but with variable penetrance. These genes are: *TGF-β_3* (transforming growth factor β), *RyR2* (ryanodine receptor), *LAMR1* (laminin receptor-1), *PTPLA* (protein tyrosine phosphatase), *DSP* (desmoplakin), *PKP2* (plakophilin-2), *DSG2* (desmoglein), and *DSC2* (desmocollin).		
Familial atrial fibrillation (autosomal dominant)	10q22-q24, 6q14-16 11p15.5 11p15.5 21q22 17q23.1-q24.2 7q35-q36	Not known *KVLQT1* (K^+ channel) *KCNQ1* (K^+ channel) *KCNE2* (K^+ channel) *KCNJ2* (K^+ channel) *KCNH2* (K^+ channel)
Brugada syndrome (right bundle-branch block, ST segment elevation, unexpected sudden death)	3p21-p24 3p22-p24	*SCN5A* (Na^+ channel) *GPD-1L* (glycerol-3-phosphate dehydrogenase)
Catecholaminergic polymorphic ventricular tachycardia	– –	*RYR2* (autosomal dominant) *CASQ2* (autosomal recessive)

class as the lesion in their 1st-degree relative (conotruncal lesions, left-sided obstructive lesions, right-sided obstructive lesions, atrioventricular septation defects). The degree of severity may be variable, as is the presence of associated defects. Careful echocardiographic screening of 1st-degree relatives will often uncover mild forms of congenital heart disease that were clinically silent. For example, the incidence of bicuspid aortic valve is more than double (5% vs. 2% in the general population) in the relatives of children with left ventricular outflow obstructions (aortic stenosis, coarctation of the aorta, or hypoplastic left heart syndrome). Given the rapid advancements in the field of cardiovascular

genetics, consultation with a knowledgeable genetic counselor is the most reliable way of providing the family with up-to-date information regarding the risk of recurrence.

Fetal echocardiography improves the rate of detection of congenital heart lesions in high-risk patients (see Chapter 423). The resolution and accuracy of fetal echocardiography are excellent, but not perfect; families should be counseled that a normal fetal echocardiogram does not guarantee the absence of congenital heart disease. Congenital heart lesions may evolve in the course of the pregnancy; moderate aortic stenosis with a normal-sized left ventricle at 18 wk of gestation may evolve into aortic atresia with a hypoplastic left ventricle by 34 wk because of decreased flow through the atria, ventricle, and aorta in the latter half of gestation. This progression has prompted initial clinical trials of interventional treatment, such as fetal aortic balloon valvuloplasty, for the prevention of hypoplastic left heart syndrome (see Chapter 423.7).

The major factor in determining whether a **woman with congenital heart disease,** either unoperated or operated, will be able to carry a fetus to term is the mother's cardiovascular status. In the presence of a mild congenital heart defect or after successful repair of a more complex lesion, normal childbearing is likely. In a woman with palliated congenital heart disease or with poor cardiac function, however, the increased hemodynamic burden imposed by pregnancy may result in a significantly increased risk to both the mother and fetus. The incidence of spontaneous abortion in the presence of severe congenital heart disease is high, especially when the mother is cyanotic. The maternal risk in these situations is also high, and these pregnancies should be managed by an experienced perinatologist in conjunction with a cardiologist with expertise in adult congenital heart disease (see Chapter 434.1). It is important to discuss these risks, as well as various methods of birth control, with young women who have repaired or palliated congenital heart lesions. Antibiotic prophylaxis against endocarditis may also be indicated at the time of delivery.

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Chapter 425

Evaluation and Screening of the Infant or Child with Congenital Heart Disease

Daniel Bernstein

The initial evaluation for suspected congenital heart disease involves a systematic approach with 3 major components. First, congenital cardiac defects can be divided into 2 major groups based on the presence or absence of cyanosis, which can be determined by physical examination aided by pulse oximetry. Second, these 2 groups can usually be further subdivided according to whether the chest radiograph shows evidence of increased, normal, or decreased pulmonary vascular markings. Finally, the electrocardiogram can be used to determine whether right, left, or biventricular hypertrophy exists. The character of the heart sounds and the presence and character of any murmurs further narrow the differential diagnosis. The final diagnosis is then confirmed by echocardiography, CT or MRI, or cardiac catheterization.

Multiple studies demonstrate the benefit of routine pulse oximetry screening for all newborns to detect unsuspected critical cyanotic congenital heart disease; lesions include hypoplastic left-heart syndrome, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, truncus arteriosus, as well as neonatal coarctation of the aorta, and aortic arch hypoplasia/atresia. Many of these lesions are ductal dependent, and if the ductus arteriosus closes, severe cardiac decompensation will ensue. Such screening has been endorsed by the American Academy of Pediatrics, the American Heart Association, the American College of Cardiology and the March of Dimes, and recommended, although not mandated, by federal agencies such as Health and Human Services. Screening is performed between 24 and 48 hr of life and before discharge in asymptomatic newborns. A pulse oximetry saturation <90% in the right hand or either foot requires urgent echocardiography. A pulse oximetry saturation <95% in either location or a saturation difference >3% between the right hand and either foot is considered a positive test and should be repeated in an hour; if positive again, it should be repeated in another hour. If it remains positive, echocardiography is indicated. In addition, a careful reexamination of the pulses and blood pressure in the upper and lower extremity as well as a cardiac exam are indicated in children with an initial positive exam.

ACYANOTIC CONGENITAL HEART LESIONS

Acyanotic congenital heart lesions can be classified according to the predominant physiologic load that they place on the heart. Although many congenital heart lesions induce more than one physiologic disturbance, it is helpful to focus on the primary load abnormality for purposes of classification. The most common lesions are those that produce a volume load, and the most common of these are left-to-right shunt lesions. Atrioventricular (AV) valve regurgitation and some of the cardiomyopathies are other causes of increased volume load. The second major class of lesions causes an increase in pressure load, most commonly secondary to ventricular outflow obstruction (pulmonic or aortic valve stenosis) or narrowing of 1 of the great vessels (coarctation of the aorta). The chest radiograph and electrocardiogram are useful tools for differentiating between these major classes of volume and pressure overload lesions.

Lesions Resulting in Increased Volume Load

The most common lesions in this group are those that cause left-to-right shunting (see Chapter 426): atrial septal defect, ventricular septal defect (VSD), AV septal defects (AV canal), and patent ductus arteriosus. The pathophysiologic common denominator in this group is communication between the systemic and pulmonary sides of the circulation, which results in shunting of fully oxygenated blood back into the lungs. This shunt can be quantitated by calculating the ratio of pulmonary to systemic blood flow, or Qp : Qs. Thus, a 3 : 1 shunt implies 3 times the normal pulmonary blood flow.

The direction and magnitude of the shunt across such a communication depend on the size of the defect, the relative pulmonary and systemic pressure and vascular resistances, and the compliances of the 2 chambers connected by the defect. These factors are dynamic and may change dramatically with age: Intracardiac defects may grow smaller with time; pulmonary vascular resistance, which is high in the immediate newborn period, decreases to normal adult levels by several weeks of life; and chronic exposure of the pulmonary circulation to high pressure and blood flow results in a gradual increase in pulmonary vascular resistance (Eisenmenger physiology; see Chapter 433.2). Thus, a lesion such as a large VSD may be associated with little shunting and few symptoms during the initial weeks of life. When pulmonary vascular resistance declines in the next several weeks, the volume of the left-to-right shunt increases, and symptoms begin to appear.

The increased volume of blood in the lungs decreases pulmonary compliance and increases the work of breathing. Fluid leaks into the interstitial space and alveoli and causes pulmonary edema. The infant develops the symptoms we refer to as **heart failure,** such as tachypnea, tachycardia, sweating, chest retractions, nasal flaring, and wheezing. For children with large left-to-right shunts, the term *heart failure* is a misnomer, however; total left ventricular output is not decreased but is actually several times greater than normal, although much of this

output is ineffective because it returns directly to the lungs. To maintain this high level of left ventricular output, heart rate and stroke volume are increased, mediated by an increase in sympathetic nervous system activity. The increase in circulating catecholamines, combined with the increased work of breathing, results in an elevation in total body oxygen consumption, often beyond the oxygen transport ability of the circulation. Sympathetic activation leads to the additional symptoms of sweating and irritability and the imbalance between oxygen supply and demand lead to failure to thrive. Remodeling of the heart occurs, with predominantly chamber dilation and a lesser degree of hypertrophy. If left untreated, pulmonary vascular resistance eventually begins to rise and, by several years of age, the shunt volume will decrease and eventually reverse to right-to-left (Eisenmenger physiology; see Chapter 433.2).

Additional lesions that impose a volume load on the heart include regurgitant lesions (see Chapter 428) and the cardiomyopathies (see Chapter 439). Regurgitation through the AV valves is most commonly encountered in patients with partial or complete AV septal defects (AV canal, endocardial cushion defects). In these lesions, the combination of a left-to-right shunt with AV valve regurgitation increases the volume load on the heart and often leads to more severe symptoms. Isolated regurgitation through the tricuspid valve is seen in mild, moderate and severe forms of Ebstein anomaly (see Chapter 430.7). Regurgitation involving 1 of the semilunar (aortic or pulmonary) valves is usually also associated with some degree of stenosis; however, aortic regurgitation may be encountered in patients with a VSD directly under the aortic valve (supracristal VSD) and in patients with membranous subaortic stenosis.

In contrast to left-to-right shunts, in which intrinsic cardiac muscle function is generally either normal or increased, heart muscle function is decreased in the cardiomyopathies. **Cardiomyopathies** may affect systolic contractility or diastolic relaxation, or both. Decreased cardiac function results in increased atrial and ventricular filling pressure, and pulmonary edema occurs secondary to increased capillary pressure. Poor cardiac output leads to decreased organ blood flow, sympathetic activation, and the symptoms of poor perfusion and decreased urine output. The major causes of cardiomyopathy in infants and children include viral myocarditis, metabolic disorders, and genetic defects (see Chapter 439).

Lesions Resulting in Increased Pressure Load

The pathophysiologic common denominator of these lesions is an obstruction to normal blood flow. The most frequent are obstructions to ventricular outflow: valvular pulmonic stenosis, valvular aortic stenosis, and coarctation of the aorta (see Chapter 427). Less common are obstruction to ventricular inflow: tricuspid or mitral stenosis, cor triatriatum and obstruction of the pulmonary veins. Ventricular outflow obstruction can occur at the valve, below the valve (double-chambered right ventricle, subaortic membrane), or above it (branch pulmonary stenosis or supravalvular aortic stenosis). Unless the obstruction is severe, cardiac output will be maintained and the clinical symptoms of heart failure will be either subtle or absent. This compensation predominantly involves an increase in cardiac wall thickness (hypertrophy), but in later stages the affected chamber will begin to dilate and can progress to ventricular failure.

The clinical picture is different when obstruction to outflow is severe, which is usually encountered in the immediate newborn period. The infant may become critically ill within several hours of birth. Severe pulmonic stenosis in the newborn period (critical pulmonic stenosis) results in signs of right-sided heart failure (hepatomegaly, peripheral edema) as well as cyanosis from right-to-left shunting across the foramen ovale. Severe aortic stenosis in the newborn period (critical aortic stenosis) is characterized by signs of left-sided heart failure (pulmonary edema, poor perfusion) and right-sided failure (hepatomegaly, peripheral edema), and it may progress rapidly to total circulatory collapse. In older children, severe pulmonic stenosis leads to symptoms of right-sided heart failure, but usually not to cyanosis unless a pathway persists for right-to-left shunting (e.g., patency of the foramen ovale).

Coarctation of the aorta in older children and adolescents is usually manifested as upper body hypertension and diminished pulses in the lower extremities. In the immediate newborn period, the presentation of coarctation can range from decreased pulses in the lower extremities to total circulatory collapse, depending on the severity of the narrowing. However, the clinical presentation of coarctation may be delayed because of the presence of a patent ductus arteriosus. In these patients, the open aortic end of the ductus may serve as a conduit for blood flow to partially bypass the obstruction or for blood leaving the right ventricle to directly supply the descending aorta (as it did in the fetus). These infants then become symptomatic, often dramatically, when the ductus finally closes, usually within the 1st few wk of life.

CYANOTIC CONGENITAL HEART LESIONS

This group of congenital heart lesions can also be further divided according to pathophysiology: whether pulmonary blood flow is decreased (tetralogy of Fallot, pulmonary atresia with an intact septum, tricuspid atresia, total anomalous pulmonary venous return with obstruction) or increased (transposition of the great vessels, single ventricle, truncus arteriosus, total anomalous pulmonary venous return without obstruction). The chest radiograph is a valuable tool for initial differentiation between these 2 categories.

Cyanotic Lesions with Decreased Pulmonary Blood Flow

These lesions must include both an obstruction to pulmonary blood flow (at the tricuspid valve or right ventricular or pulmonary valve level) and a pathway by which systemic venous blood can shunt from right to left and enter the systemic circulation (via a patent foramen ovale, atrial septal defect, or VSD). Common lesions in this group include tricuspid atresia, tetralogy of Fallot, and various forms of single ventricle with pulmonary stenosis (see Chapter 430). In these lesions, the degree of cyanosis depends on the degree of obstruction to pulmonary blood flow. If the obstruction is mild, cyanosis may be absent at rest. These patients may have hypercyanotic ("tet") spells during conditions of stress. In contrast, if the obstruction is severe, pulmonary blood flow may be totally dependent on patency of the ductus arteriosus. When the ductus closes in the 1st few days of life, the neonate experiences profound hypoxemia and shock.

Cyanotic Lesions with Increased Pulmonary Blood Flow

This group of lesions is not associated with obstruction to pulmonary blood flow. Cyanosis is caused by either abnormal ventricular–arterial connections or total mixing of systemic venous and pulmonary venous blood within the heart (see Chapter 431). Transposition of the great vessels is the most common of the former group of lesions. In this condition, the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. Systemic venous blood returning to the right atrium is pumped directly back to the body and oxygenated blood returning from the lungs to the left atrium is pumped back into the lungs. The persistence of fetal pathways (foramen ovale and ductus arteriosus) allows for a small degree of mixing in the immediate newborn period; when the ductus begins to close, these infants can become extremely cyanotic.

Total mixing lesions include cardiac defects with a common atrium or ventricle, total anomalous pulmonary venous return, and truncus arteriosus (see Chapter 431). In this group, deoxygenated systemic venous blood and oxygenated pulmonary venous blood mix completely in the heart and, as a result, oxygen saturation is equal in the pulmonary artery and aorta. If pulmonary blood flow is not obstructed, these infants have a combination of cyanosis and pulmonary overcirculation leading to heart failure. In contrast, if pulmonary stenosis is present, these infants may have cyanosis alone, similar to patients with tetralogy of Fallot.

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Chapter **426**

Acyanotic Congenital Heart Disease: Left-to-Right Shunt Lesions

426.1 Atrial Septal Defect

Daniel Bernstein

Atrial septal defects (ASDs) can occur in any portion of the atrial septum (secundum, primum, or sinus venosus), depending on which embryonic septal structure has failed to develop normally (see Chapter 420). Less commonly, the atrial septum may be nearly absent, with the creation of a functional single atrium. Isolated secundum ASDs account for ≈7% of congenital heart defects. The majority of cases of ASD are sporadic; autosomal dominant inheritance does occur as part of the Holt-Oram syndrome (hypoplastic or absent thumbs, radii, triphalangism, phocomelia, 1st-degree heart block, ASD) or in families with secundum ASD and heart block (see Table 424-2 in Chapter 424).

An isolated valve-incompetent patent foramen ovale (PFO) is a common echocardiographic finding during infancy. It is usually of no hemodynamic significance and is not considered an ASD; a PFO may play an important role if other structural heart defects are present. If another cardiac anomaly is causing increased right atrial pressure (pulmonary stenosis or atresia, tricuspid valve abnormalities, right ventricular dysfunction), venous blood may shunt across the PFO into the left atrium with resultant cyanosis. Because of the anatomic structure of the PFO, left-to-right shunting is unusual outside the immediate newborn period. In the presence of a large volume load or a hypertensive left atrium (secondary to mitral stenosis), the foramen ovale may be sufficiently dilated to result in a significant atrial left-to-right shunt. A valve-competent but probe-PFO may be present in 15-30% of adults. An isolated PFO does not require surgical treatment, although it may be a risk for paradoxical (right to left) systemic embolization. Device closure of these defects has been considered in young adults with a history of thromboembolic stroke.

Bibliography is available at Expert Consult.

426.2 Ostium Secundum Defect

Daniel Bernstein

An ostium secundum defect in the region of the fossa ovalis is the most common form of ASD and is associated with structurally normal atrioventricular (AV) valves. Mitral valve prolapse has been described in association with this defect but is rarely an important clinical consideration. Secundum ASDs may be single or multiple (fenestrated atrial septum), and openings ≥2 cm in diameter are common in symptomatic older children. Large defects may extend inferiorly toward the inferior vena cava and ostium of the coronary sinus, superiorly toward the superior vena cava, or posteriorly. Females outnumber males 3:1 in incidence. Partial anomalous pulmonary venous return, most commonly of the right upper pulmonary vein, may be an associated lesion.

PATHOPHYSIOLOGY

The degree of left-to-right shunting is dependent on the size of the defect, the relative compliance of the right and left ventricles, and the relative vascular resistance in the pulmonary and systemic circulations. In large defects, a considerable shunt of oxygenated blood flows from the left to the right atrium (Fig. 426-1). This blood is added to the usual venous return to the right atrium and is pumped by the right ventricle to the lungs. With large defects, the ratio of pulmonary to systemic blood flow (Qp:Qs) is usually between 2:1 and 4:1. The paucity of symptoms in infants with ASDs is related to the structure of the right ventricle in early life when its muscular wall is thick and less compliant, thus limiting the left-to-right shunt. As the infant becomes older and pulmonary vascular resistance drops, the right ventricular wall becomes thinner and the left-to-right shunt across the ASD increases. The increased blood flow through the right side of the heart results in enlargement of the right atrium and ventricle and dilation of the pulmonary artery. The left atrium may also be enlarged, but the left ventricle and aorta are normal in size. Despite the large pulmonary blood flow, pulmonary arterial pressure is usually normal because of the absence of a high-pressure communication between the pulmonary and systemic circulations. Pulmonary vascular resistance remains low throughout childhood, although it may begin to increase in adulthood and may eventually result in reversal of the shunt and clinical cyanosis.

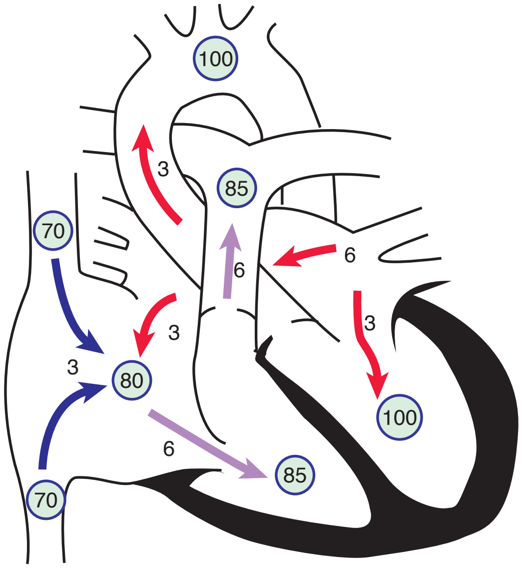

Figure 426-1 Physiology of atrial septal defect. *Circled numbers* represent oxygen saturation values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp:Qs) of 2:1. Desaturated blood enters the right atrium from the vena cavae at a volume of 3 L/min/m^2 and mixes with an additional 3 L of fully saturated blood shunting left to right across the ASD; the result is an increase in oxygen saturation in the right atrium. Six liters of blood flows through the tricuspid valve and causes a mid-diastolic flow rumble. Oxygen saturation may be slightly higher in the right ventricle because of incomplete mixing at the atrial level. The full 6 L flows across the right ventricular outflow tract and causes a systolic ejection flow murmur. Six liters returns to the left atrium, with 3 L shunting left to right across the defect and 3 L crossing the mitral valve to be ejected by the left ventricle into the ascending aorta (normal cardiac output).

CLINICAL MANIFESTATIONS

A child with an ostium secundum ASD is most often asymptomatic; the lesion is often discovered inadvertently during physical examination. Even an extremely large secundum ASD rarely produces clinically evident heart failure in childhood. However, on closer evaluation, in younger children, subtle failure to thrive may be present; in older children varying degrees of exercise intolerance may be noted. Often, the degree of limitation may go unnoticed by the family until after surgical repair, when the child's growth or activity level increases

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markedly. Platypnea (dyspnea on standing, relieved when supine) and orthodeoxia (desaturation on standing, relieved when supine) may occur when right to left shunting occurs through on ASD.

The physical findings of an ASD are usually characteristic but fairly subtle and require careful examination of the heart, with special attention to the heart sounds. Examination of the chest may reveal a mild left precordial bulge. A right ventricular systolic lift may be palpable at the left sternal border. Sometimes a pulmonic ejection click can be heard. In most patients with an ASD, the characteristic finding is that the 2nd heart sound is **widely split and fixed in its splitting** during all phases of respiration. Normally, the duration of right ventricular ejection varies with respiration, with inspiration increasing right ventricular volume and delaying closure of the pulmonary valve. With an ASD, right ventricular diastolic volume is constantly increased and the ejection time is prolonged throughout all phases of respiration. A systolic ejection murmur is heard; it is medium pitched, without harsh qualities, seldom accompanied by a thrill, and best heard at the left middle and upper sternal border. It is produced by the increased flow across the right ventricular outflow tract into the pulmonary artery, not by low-pressure flow across the ASD. A short, rumbling mid-diastolic murmur produced by the increased volume of blood flow across the tricuspid valve is often audible at the lower left sternal border. This finding, which may be subtle and is heard best with the bell of the stethoscope, usually indicates a Qp : Qs ratio of at least 2 : 1.

DIAGNOSIS

The chest roentgenogram shows varying degrees of enlargement of the right ventricle and atrium, depending on the size of the shunt. The pulmonary artery is enlarged, and pulmonary vascularity is increased. These signs vary and may not be conspicuous in mild cases. Cardiac enlargement is often best appreciated on the lateral view because the right ventricle protrudes anteriorly as its volume increases. The electrocardiogram shows volume overload of the right ventricle; the QRS axis may be normal or exhibit right axis deviation, and a minor right ventricular conduction delay (rsR′ pattern in the right precordial leads) may be present.

The echocardiogram shows findings characteristic of right ventricular volume overload, including an increased right ventricular end-diastolic dimension and flattening and abnormal motion of the ventricular septum (Fig. 426-2). A normal septum moves posteriorly during systole and anteriorly during diastole. With right ventricular overload and normal pulmonary vascular resistance, septal motion is either flattened or reversed—that is, anterior movement in systole. The location and size of the atrial defect are readily appreciated by 2-dimensional scanning, with a characteristic brightening of the echo image seen at the edge of the defect (T-artifact). The shunt is confirmed by pulsed and color flow Doppler. The normal entry of all pulmonary veins into the left atrium should be confirmed.

Patients with the classic features of a hemodynamically significant ASD on physical examination and chest radiography, in whom echocardiographic identification of an isolated secundum ASD is made, need not undergo diagnostic catheterization before repair, with the exception of an older patient, in whom pulmonary vascular resistance may be a concern. If pulmonary vascular disease is suspected, cardiac catheterization confirms the presence of the defect and allows measurement of the shunt ratio and pulmonary pressure and resistance.

If catheterization is performed, usually at the time of device closure (see below), the oxygen content of blood from the right atrium will be much higher than that from the superior vena cava. This feature is not specifically diagnostic because it may occur with partial anomalous pulmonary venous return to the right atrium, with a ventricular septal defect (VSD) in the presence of tricuspid insufficiency, with AV septal defects associated with left ventricular to right atrial shunts, and with aorta to right atrial communications (ruptured sinus of Valsalva aneurysm). Pressure in the right side of the heart is usually normal, but small to moderate pressure gradients (<25 mm Hg) may be measured across the right ventricular outflow tract because of functional stenosis related to excessive blood flow. In children and adolescents, the pulmonary vascular resistance is almost always normal. The shunt is

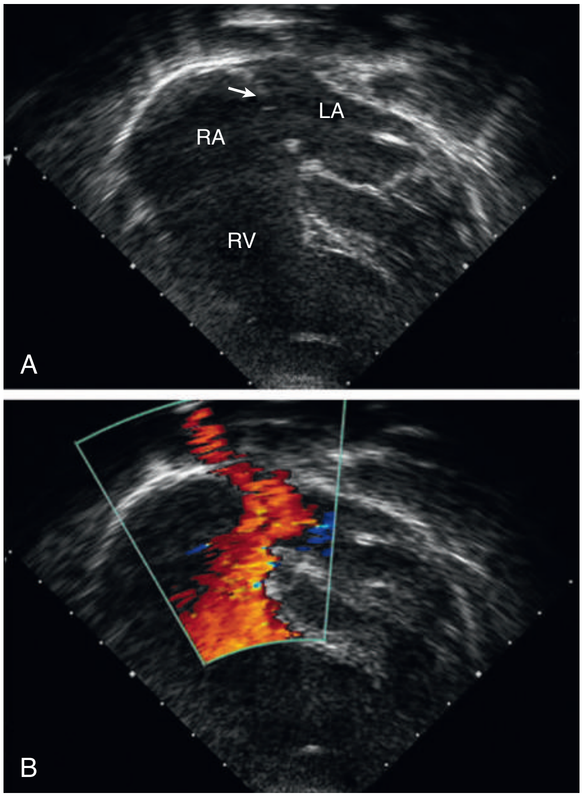

Figure 426-2 Echocardiographic findings in a secundum atrial septal defect. **A,** Two-dimensional echocardiogram (apical 4-chamber view) shows a moderate-sized secundum ASD *(arrow)*. **B,** Color flow Doppler imaging shows left-to-right shunting (the red color represents blood moving toward the ultrasound transducer and does not indicate the level of oxygenation of the blood). LA, left atrium; RA, right atrium; RV, right ventricle.

variable and depends on the size of the defect, but it may be of considerable volume (as high as 20 L/min/m^2). Cineangiography, performed with the catheter through the defect and in the right upper pulmonary vein, demonstrates the defect and the location of the right upper pulmonary venous drainage. Alternatively, pulmonary angiography demonstrates the defect on the levophase (return of contrast to the left side of the heart after passing through the lungs).

COMPLICATIONS

Secundum ASDs are usually isolated, although they may be associated with partial anomalous pulmonary venous return, pulmonary valvular stenosis, VSD, pulmonary artery branch stenosis, and persistent left superior vena cava, as well as mitral valve prolapse and insufficiency. Secundum ASDs are associated with the autosomal dominant Holt-Oram syndrome. The gene responsible for this syndrome, situated in the region 12q21-q22 of chromosome 12, is *TBX5*, a member of the T-box transcriptional family. A familial form of secundum ASD associated with AV conduction delay has been linked to mutations in another transcription factor, Nkx2.5. Patients with familial ASD without heart block may carry a mutation in the transcription factor GATA4, located on chromosome 8p22-23 (see Table 424-2 in Chapter 424).

TREATMENT

Transcatheter or surgical device closure is advised for all symptomatic patients and also for asymptomatic patients with a Qp : Qs ratio of at least 2 : 1 or those with right ventricular enlargement. The timing for elective closure is usually after the 1st yr and before entry into school. Closure carried out at open heart surgery is associated with a mortality rate of <1%. Repair is preferred during early childhood because

surgical mortality and morbidity are significantly greater in adulthood; the long-term risk of arrhythmia is also greater after ASD repair in adults. For most patients, the *procedure of choice* is percutaneous catheter device closure using an atrial septal occlusion device, implanted transvenously in the cardiac catheterization laboratory (Fig. 426-3). The results are excellent and patients are discharged the following day. With the latest generation of devices, the incidence of serious complications such as device erosion is 0.1% and can be decreased by identifying high-risk patients such as those with a deficient rim of septum around the device. Echocardiography can usually determine whether a patient is a good candidate for device closure. In patients with small secundum ASDs and minimal left-to-right shunts without right ventricular enlargement, the consensus is that closure is not required. It is unclear at present whether the persistence of a small ASD into adulthood increases the risk for stroke enough to warrant prophylactic closure of all these defects.

PROGNOSIS

Small- to moderate-sized ASDs detected in term infants may close spontaneously. Secundum ASDs are well tolerated during childhood, and symptoms do not usually appear until the 3rd decade or later. Pulmonary hypertension, atrial dysrhythmias, tricuspid or mitral insufficiency, and heart failure are late manifestations; these symptoms may initially appear during the increased volume load of pregnancy. Infective endocarditis is extremely rare, and antibiotic prophylaxis for isolated secundum ASDs is not recommended.

The results after surgical or device closure in children with moderate to large shunts are excellent. Symptoms disappear rapidly, and growth is frequently enhanced. Heart size decreases to normal, and the electrocardiogram shows decreased right ventricular forces. Late right-heart failure and arrhythmias are less frequent in patients who have had early repair, becoming more common in patients who undergo surgery after 20 yr of age. Although early and midterm results with device closure are excellent, the long-term effects are not yet known. Reports of resolution of migraine headaches in patients after device closure of ASD or PFO are intriguing, suggesting a possible thromboembolic etiology; there are also paradoxical reports of patients whose migraines began or worsened after placement of one of these devices.

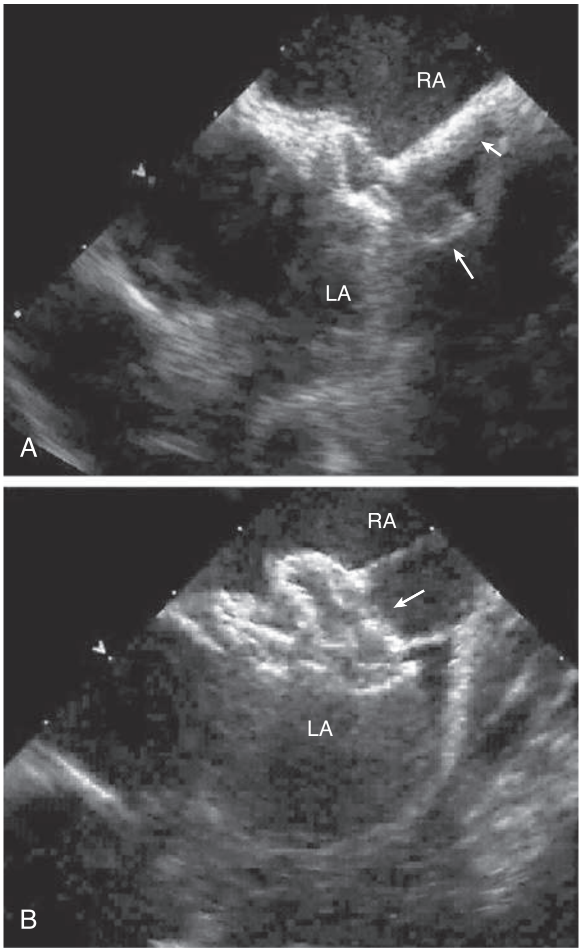

Figure 426-3 Intravascular ultrasound imaging of transcatheter occlusion of an atrial septal defect. **A,** A catheter *(small arrow)* has been advanced across the atrial defect, and the left-sided disk of the device *(large arrow)* has been extruded from the sheath into the left atrium *(LA)*. **B,** The right atrial disk *(arrow)* has now been extruded into the right atrium *(RA)*. The 2 halves of the device are then locked together and the catheter detached from the occluder device and removed.

426.3 Sinus Venosus Atrial Septal Defect

Daniel Bernstein

A sinus venosus ASD is situated in the upper part of the atrial septum in close relation to the entry of the superior vena cava. Often, 1 or more pulmonary veins (usually from the right lung) drain anomalously into the superior vena cava. The superior vena cava sometimes straddles the defect; in this case, some systemic venous blood enters the left atrium, but only rarely does it cause clinically evident cyanosis. The hemodynamic disturbance, clinical picture, electrocardiogram, and roentgenogram are similar to those seen in secundum ASD. The diagnosis can usually be made by 2-dimensional echocardiography. If there are questions regarding pulmonary venous drainage, cardiac CT or MRI is usually diagnostic. Cardiac catheterization is rarely required, with the exception being in adult patients where assessment of pulmonary vascular resistance may be important. Anatomic correction generally requires the insertion of a patch to close the defect while incorporating the entry of anomalous veins into the left atrium. If the anomalous vein drains high in the superior vena cava, the vein can be left intact and the ASD closed to incorporate the mouth of the superior vena cava into the left atrium. The superior vena cava proximal to the venous entrance is then detached and anastomosed directly to the right atrium. This procedure avoids direct suturing of the pulmonary vein with less chance of future stenosis. Surgical results are generally excellent. Rarely, sinus venosus defects involve the inferior vena cava.

426.4 Partial Anomalous Pulmonary Venous Return

Daniel Bernstein

One or several pulmonary veins may return anomalously to the superior or inferior vena cava, the right atrium, or the coronary sinus and produce a left-to-right shunt of oxygenated blood. Partial anomalous pulmonary venous return usually involves some or all of the veins from only 1 lung, more often the right one. When an associated ASD is present, it is generally of the sinus venosus type, although can be of the secundum type (see Chapters 426.2 and 426.3). When an ASD is detected by echocardiography, one must always search for associated partial anomalous pulmonary venous return. The history, physical signs, and electrocardiographic and radiologic findings are indistinguishable from those of an isolated ostium secundum ASD. Occasionally, an anomalous vein draining into the inferior vena cava is visible on chest radiography as a crescentic shadow of vascular density along the right border of the cardiac silhouette **(scimitar syndrome);** in these cases, an ASD is not usually present, but **pulmonary sequestration or ipsilateral lung hypoplasia** and anomalous arterial supply to that lobe are common findings. Total anomalous pulmonary venous return is a cyanotic lesion and is discussed in Chapter 431.7. Echocardiography generally confirms the diagnosis. MRI and CT are also useful if there

is a question regarding pulmonary venous drainage or in cases of scimitar syndrome. If cardiac catheterization is performed, the presence of anomalous pulmonary veins is demonstrated by selective pulmonary arteriography and anomalous pulmonary arterial supply to the right lung is demonstrated by descending aortography.

The prognosis is excellent, similar to that for ostium secundum ASDs. When a large left-to-right shunt is present, surgical repair is performed. The associated ASD should be closed in such a way that pulmonary venous return is directed to the left atrium. A single anomalous pulmonary vein without an atrial communication may be difficult to redirect to the left atrium; if the shunt is small, it may be left unoperated.

426.5 Atrioventricular Septal Defects (Ostium Primum and Atrioventricular Canal or Endocardial Cushion Defects)

Daniel Bernstein

The abnormalities encompassed by AV septal defects are grouped together because they represent a spectrum of a basic embryologic abnormality, a deficiency of the AV septum. An **ostium primum** defect is situated in the lower portion of the atrial septum and overlies the mitral and tricuspid valves. In most instances, a **cleft** in the **anterior leaflet** of the **mitral valve** is also noted. The tricuspid valve is usually functionally normal, although some anatomic abnormality of the septal leaflet is present. The ventricular septum is intact.

An **AV septal defect,** also known as an **AV canal defect** or an **endocardial cushion defect**, consists of contiguous atrial and VSDs with markedly abnormal AV valves. The severity of the valve abnormalities varies considerably; in the complete form of AV septal defect, a single AV valve is common to both ventricles and consists of an anterior and a posterior bridging leaflet related to the ventricular septum, with a lateral leaflet in each ventricle. The lesion is common in children with **Down syndrome**.

Transitional varieties of these defects also occur and include ostium primum defects with clefts in the anterior mitral and septal tricuspid valve leaflets and small VSDs, and, less commonly, ostium primum defects with normal AV valves. In some patients, the atrial septum is intact, but an inlet VSD is similar to that found in the full AV septal defect. Sometimes AV septal defects are associated with varying degrees of hypoplasia of one of the ventricles, known as either *left-* or *right-dominant atrioventricular septal defect*. If the affected ventricular chamber is too small to establish a 2-ventricle circulation, then surgical palliation, aiming for an eventual Fontan procedure, is performed (see Chapters 430.4 and 431.10).

PATHOPHYSIOLOGY

The basic abnormality in patients with ostium primum defects is the combination of a left-to-right shunt across the atrial defect and mitral (or occasionally tricuspid) insufficiency. The shunt is usually moderate to large, the degree of mitral insufficiency is generally mild to moderate, and pulmonary arterial pressure is typically normal or only mildly increased. The physiology of this lesion is, therefore, similar to that of an ostium secundum ASD.

In complete AV septal defects, the left-to-right shunt occurs at both the atrial and ventricular levels (Fig. 426-4). Additional shunting may occur directly from the left ventricle to the right atrium because of absence of the AV septum. Pulmonary hypertension and an early tendency to increase pulmonary vascular resistance are common. AV valvular insufficiency increases the volume load on one or both ventricles. If the defect is large enough, some right-to-left shunting may also occur at both the atrial and ventricular levels and lead to mild arterial desaturation. With time, progressive pulmonary vascular disease increases the right-to-left shunt so that clinical cyanosis develops (Eisenmenger physiology; see Chapter 433.2).

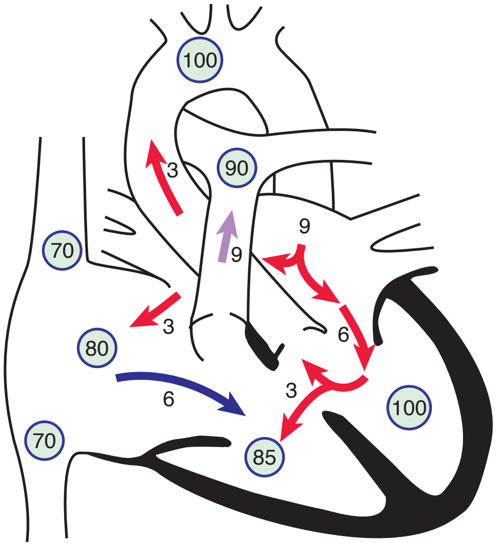

Figure 426-4 Physiology of atrioventricular septal defect. *Circled numbers* represent oxygen saturation values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp : Qs) of 3 : 1. Desaturated blood enters the right atrium from the vena cavae at a volume of 3 L/min/m^2 and mixes with 3 L of fully saturated blood shunting left to right across the atrial septal defect; the result is an increase in oxygen saturation in the right atrium. Six liters of blood flows through the right side of the common AV valve, joined by an additional 3 L of saturated blood shunting left to right at the ventricular level, further increasing oxygen saturation in the right ventricle. The full 9 L flows across the right ventricular outflow tract into the lungs. Nine liters returns to the left atrium, with 3 L shunting left to right across the defect and 6 L crossing the left side of the common AV valve and causing a mid-diastolic flow rumble. Three liters of this volume shunts left to right across the VSD, and 3 L is ejected into the ascending aorta (normal cardiac output).

CLINICAL MANIFESTATIONS

Many children with ostium primum defects are asymptomatic, and the anomaly is discovered during a general physical examination. In patients with moderate shunts and mild mitral insufficiency, the physical signs are similar to those of the secundum ASD, but with an additional apical holosystolic murmur caused by mitral insufficiency.

A history of exercise intolerance, easy fatigability, and recurrent pneumonia may be obtained, especially in infants with large left-to-right shunts and severe mitral insufficiency. In these patients, cardiac enlargement is moderate or marked, and the precordium is hyperdynamic. Auscultatory signs produced by the left-to-right shunt include a normal or accentuated 1st heart sound; wide, fixed splitting of the 2nd sound; a pulmonary systolic ejection murmur sometimes preceded by a click; and a low-pitched, mid-diastolic rumbling murmur at the lower left sternal edge or apex, or both, as a result of increased flow through the AV valves. Mitral insufficiency may be manifested by a harsh (occasionally very high pitched) apical holosystolic murmur that radiates to the left axilla.

With complete AV septal defects, heart failure and intercurrent pulmonary infection usually appear in infancy. The liver is enlarged and the infant shows signs of failure to thrive. Cardiac enlargement is moderate to marked, and a systolic thrill is frequently palpable at the lower left sternal border. A precordial bulge and lift may be present as well. The 1st heart sound is normal or accentuated. The 2nd heart sound is widely split if the pulmonary flow is massive. A low-pitched, mid-diastolic rumbling murmur is audible at the lower left sternal border, and a pulmonary systolic ejection murmur is produced by the large pulmonary flow. The harsh apical holosystolic murmur of mitral insufficiency may also be present.

DIAGNOSIS

Chest radiographs of children with complete AV septal defects often show moderate to severe cardiac enlargement caused by the prominence of both ventricles and atria. The pulmonary artery is large, and pulmonary vascularity is increased.

The electrocardiogram in patients with a complete AV septal defect is distinctive. The principal abnormalities are (1) superior orientation of the mean frontal QRS axis with left axis deviation to the left upper or right upper quadrant, (2) counterclockwise inscription of the superiorly oriented QRS vector loop (often manifest by a Q wave in leads I and aVL), (3) signs of biventricular hypertrophy or isolated right ventricular hypertrophy, (4) right ventricular conduction delay (rSR′ pattern in leads V_3R and V_1), (5) normal or tall P waves, and (6) occasional prolongation of the P-R interval (Fig. 426-5).

The echocardiogram (Fig. 426-6) is diagnostic and shows signs of right ventricular enlargement with encroachment of the mitral valve echo on the left ventricular outflow tract; the abnormally low position of the AV valves results in a "gooseneck" deformity of the left ventricular outflow tract. In normal hearts, the tricuspid valve inserts slightly more toward the apex than the mitral valve does. In AV septal defects, both valves insert at the same level because of absence of the AV septum. In complete AV septal defects, the ventricular septum is also deficient and the common AV valve is readily appreciated. Pulsed and color flow Doppler echocardiography will demonstrate left-to-right shunting at the atrial, ventricular, or left ventricular to right atrial levels and can be used to semiquantitate the degree of AV valve insufficiency. Echocardiography is useful for determining the insertion points of the chordae of the common AV valve and for evaluating the presence of associated lesions such as patent ductus arteriosus (PDA) or coarctation of the aorta.

Cardiac catheterization and angiocardiography is rarely required to confirm the diagnosis unless pulmonary vascular disease is suspected, such as in a patient in whom diagnosis has been delayed beyond early infancy, especially in those with Down syndrome in whom the development of pulmonary vascular disease may be more rapid. Catheterization demonstrates the magnitude of the left-to-right shunt, the degree of elevation of pulmonary vascular resistance, and the severity of insufficiency of the common AV valve. By oximetry, the shunt is usually demonstrable at both the atrial and ventricular levels. Arterial oxygen saturation is normal or only mildly reduced unless severe pulmonary vascular disease is present. Children with ostium primum defects generally have normal or only moderately elevated pulmonary arterial pressure. Conversely, complete AV septal defects are associated with right ventricular and pulmonary hypertension and, in older patients, with increased pulmonary vascular resistance (see Chapter 433.2).

Selective left ventriculography will demonstrate deformity of the mitral or common AV valve and the distortion of the left ventricular outflow tract caused by this valve (gooseneck deformity). The abnormal anterior leaflet of the mitral valve is serrated, and mitral insufficiency is noted, usually with regurgitation of blood into both the left and right atria. Direct shunting of blood from the left ventricle to the right atrium may also be demonstrated.

TREATMENT

Ostium primum defects are approached surgically from an incision in the right atrium. The cleft in the mitral valve is located through the atrial defect and is repaired by direct suture. The defect in the atrial septum is usually closed by insertion of a patch prosthesis. The surgical mortality rate for ostium primum defects is very low.

Surgical treatment of complete AV septal defects is more difficult, although still highly successful. The postoperative course may be prolonged in infants with severe cardiac failure and in those with pulmonary hypertension. Because of the risk of **pulmonary vascular disease** developing as early as 6-12 mo of age, surgical intervention must be performed during infancy. Full correction of these defects can be readily accomplished in infancy; palliation with pulmonary arterial banding, once more common, is reserved for the small subset of patients who have other associated lesions that make early corrective surgery too risky. The atrial and ventricular defects are patched and the AV valves reconstructed. Complications include surgically induced heart block requiring placement of a permanent pacemaker, excessive narrowing of the left ventricular outflow tract requiring surgical revision, and residual tricuspid or mitral regurgitation, which long-term can require replacement with a prosthetic valve.

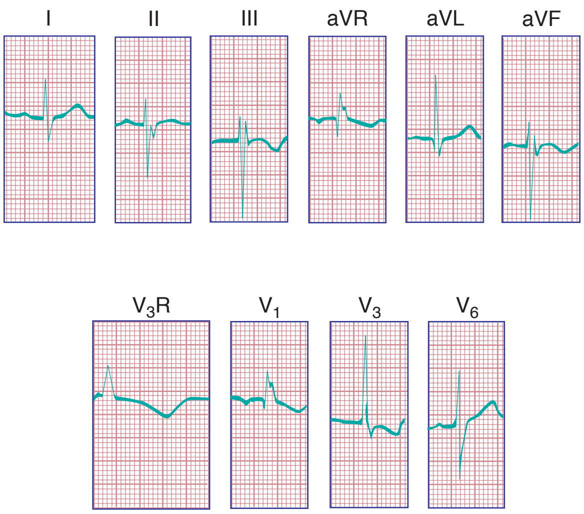

Figure 426-5 **Electrocardiogram from a child with an atrioventricular septal defect.** Note the QRS axis of –60 degrees and the right ventricular conduction delay with an RSR′ pattern in V_1 and V_3R (V_3R paper speed = 50 mm/sec).

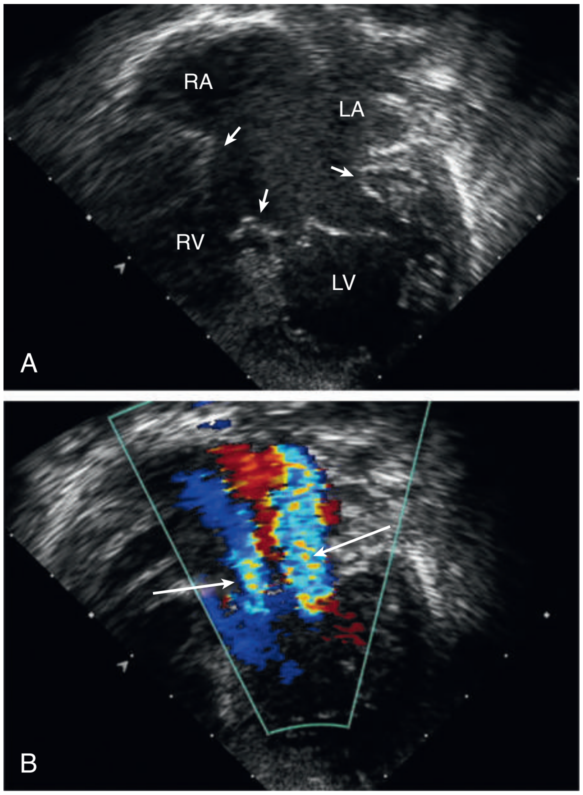

Figure 426-6 Echocardiogram of an atrioventricular septal defect. **A,** Subcostal 4-chamber view demonstrating the common atrioventricular valve *(arrows)* spanning the atrial and ventricular septal defects. **B,** Doppler imaging shows 2 jets of regurgitation through the left side of the common atrioventricular valve *(arrows)*. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

PROGNOSIS

The prognosis for unrepaired complete AV septal defects depends on the magnitude of the left-to-right shunt, the degree of elevation of pulmonary vascular resistance, and the severity of AV valve insufficiency. Death from cardiac failure during infancy used to be frequent before the advent of early corrective surgery. In patients who survived without surgery, pulmonary vascular obstructive disease usually developed. Most patients with ostium primum defects and minimal AV valve involvement are asymptomatic or have only minor, nonprogressive symptoms until they reach the 3rd-4th decade of life, similar to the course of patients with secundum ASDs. Late postoperative complications include atrial arrhythmias and heart block, progressive narrowing of the left ventricular outflow tract requiring surgical revision, and eventual worsening of AV valve regurgitation (usually on the left side) requiring replacement with a prosthetic valve.

Bibliography is available at Expert Consult.

426.6 Ventricular Septal Defect

Daniel Bernstein

VSD is the most common cardiac malformation and accounts for 25% of congenital heart disease. Defects may occur in any portion of the ventricular septum, but most are of the membranous type. These defects are in a posteroinferior position, anterior to the septal leaflet of the tricuspid valve. VSDs between the crista supraventricularis and the papillary muscle of the conus may be associated with pulmonary stenosis and other manifestations of tetralogy of Fallot (see Chapter 430.1). VSDs superior to the crista supraventricularis (supracristal) are less common; they are found just beneath the pulmonary valve and may impinge on an aortic sinus and cause aortic insufficiency. VSDs in the midportion or apical region of the ventricular septum are muscular in type and may be single or multiple (Swiss cheese septum).

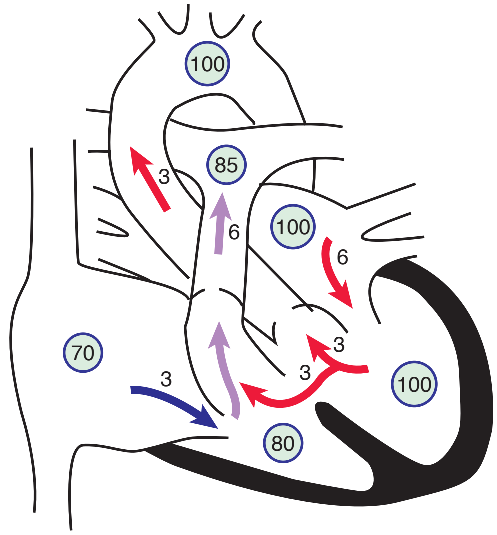

Figure 426-7 Physiology of a large ventricular septal defect. *Circled numbers* represent oxygen saturation values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp:Qs) of 2:1. Desaturated blood enters the right atrium from the vena cava at a volume of 3 L/min/m^2 and flows across the tricuspid valve. An additional 3 L of blood shunts left to right across the VSD, the result being an increase in oxygen saturation in the right ventricle. Six liters of blood is ejected into the lungs. Pulmonary arterial saturation may be further increased because of incomplete mixing at right ventricular level. Six liters returns to the left atrium, crosses the mitral valve, and causes a mid-diastolic flow rumble. Three liters of this volume shunts left to right across the VSD, and 3 L is ejected into the ascending aorta (normal cardiac output).

PATHOPHYSIOLOGY

The physical size of the VSD is a major, but not the only, determinant of the size of the left-to-right shunt. The level of pulmonary vascular resistance in relation to systemic vascular resistance also determines the shunt's magnitude. When a small communication is present (usually <5 mm), the VSD is pressure **restrictive**, meaning that right ventricular pressure is normal. The higher pressure in the left ventricle drives the shunt left to right and the size of the defect limits the magnitude of the shunt. In large **nonrestrictive VSDs** (usually >10 mm), right and left ventricular pressures are equalized. In these defects, the direction of shunting and the shunt magnitude are determined by the ratio of pulmonary to systemic vascular resistance (Fig. 426-7).

After birth in patients with a large VSD, pulmonary vascular resistance may remain elevated, delaying the normal postnatal decrease, and thus the size of the left-to-right shunt may initially be limited. Because of normal involution of the media of small pulmonary arterioles, pulmonary vascular resistance begins to fall in the 1st few wk after birth and the size of the left-to-right shunt increases. Eventually, a large left-to-right shunt develops, and clinical symptoms become apparent. In most cases during early infancy, pulmonary vascular resistance is only slightly elevated, and the major contribution to pulmonary hypertension is the large communication allowing exposure of the pulmonary circulation to systemic pressure and the large pulmonary blood flow. With continued exposure of the pulmonary vascular bed to high systolic pressure and high flow, pulmonary vascular obstructive disease eventually develops. When the ratio of pulmonary to systemic resistance approaches 1:1, the shunt becomes bidirectional, signs of heart failure abate, and the patient begins to show signs of cyanosis (Eisenmenger physiology; see Chapter 433.2). In rare infants with a large VSD, usually those with Down syndrome, pulmonary vascular resistance never decreases, and symptoms may remain minimal until Eisenmenger physiology becomes evident.

The magnitude of intracardiac shunts is usually described by the Qp:Qs ratio. If the left-to-right shunt is small (Qp:Qs < 1.5:1), the cardiac chambers are not appreciably enlarged and the pulmonary vascular bed is probably normal. If the shunt is large (Qp:Qs > 2:1), left atrial and ventricular volume overload occurs, as does right ventricular and pulmonary arterial hypertension. The main pulmonary artery, left atrium, and left ventricle are enlarged.

CLINICAL MANIFESTATIONS

The clinical findings of patients with a VSD vary according to the size of the defect and pulmonary blood flow and pressure. Small VSDs with trivial left-to-right shunts and normal pulmonary arterial pressure are the most common. These patients are asymptomatic, and the cardiac lesion is usually found during routine physical examination. Characteristically, a loud, harsh, or blowing holosystolic murmur is present and heard best over the lower left sternal border, and it is frequently accompanied by a thrill. In a few instances, the murmur ends before the 2nd sound, presumably because of closure of the defect during late systole. A short, harsh systolic murmur localized to the apex in a neonate is often a sign of a tiny VSD in the apical muscular septum. In premature infants, the murmur may be heard early because pulmonary vascular resistance decreases more rapidly.

Large VSDs with excessive pulmonary blood flow and pulmonary hypertension are responsible for dyspnea, feeding difficulties, poor growth, profuse perspiration, recurrent pulmonary infections, and cardiac failure in early infancy. Cyanosis is usually absent, but duskiness is sometimes noted during infections or crying. Prominence of the left precordium is common, as are a palpable parasternal lift, a laterally displaced apical impulse and apical thrust, and a systolic thrill. The holosystolic murmur of a large VSD is generally less harsh than that of a small VSD and more blowing in nature because of the absence of a significant pressure gradient across the defect. It is even less likely to be prominent in the newborn period. The pulmonic component of

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the 2nd heart sound may be increased as a result of pulmonary hypertension. The presence of a mid-diastolic, low-pitched rumble at the apex is caused by increased blood flow across the mitral valve and usually indicates a Qp : Qs ratio of ≥2 : 1. This murmur is best appreciated with the bell of the stethoscope.

DIAGNOSIS

In patients with small VSDs, the chest x-ray is usually normal, although minimal cardiomegaly and a borderline increase in pulmonary vasculature may be observed. The electrocardiogram is generally normal but may suggest left ventricular hypertrophy. The presence of right ventricular hypertrophy is a warning that the defect is not small and that the patient has pulmonary hypertension or an associated lesion such as pulmonic stenosis. In large VSDs, the chest x-ray shows gross cardiomegaly with prominence of both ventricles, the left atrium, and the pulmonary artery (Fig. 426-8). Pulmonary vascular markings are increased, and frank pulmonary edema, including pleural effusions, may be present. The electrocardiogram shows biventricular hypertrophy; P waves may be notched or peaked.

The 2-dimensional echocardiogram (Fig. 426-9) shows the position and size of the VSD. In small defects, especially those of the muscular septum, the defect itself may be difficult to image and is visualized only by color Doppler examination. In defects of the **membranous septum,** a thin membrane (called a **ventricular septal aneurysm** but consisting of tricuspid valve tissue) can partially cover the defect and limit the volume of the left-to-right shunt. Echocardiography is also useful for estimating shunt size by examining the degree of volume overload of the left atrium and left ventricle; in the absence of associated lesions, the extent of their increased dimensions is a good reflection of the size of the left-to-right shunt. Pulsed Doppler examination shows whether the VSD is pressure restrictive by calculating the pressure gradient across the defect. Such calculation allows an estimation of right ventricular pressure and helps determine whether the patient is at risk for the development of early pulmonary vascular disease. The echocardiogram can also be useful to determine the presence of aortic valve insufficiency or aortic leaflet prolapse in the case of supracristal VSDs.

The hemodynamics of a VSD can also be demonstrated by cardiac catheterization, although catheterization is today performed only when laboratory data do not fit well with the clinical findings or when pulmonary vascular disease is suspected. Oximetry demonstrates increased oxygen content in the right ventricle; because some defects eject blood almost directly into the pulmonary artery (streaming), the full magnitude of the oxygen saturation increase is occasionally apparent only when pulmonary arterial blood is sampled. Small, restrictive VSDs are associated with normal right-heart pressures and pulmonary vascular resistance. Large, nonrestrictive VSDs are associated with equal or nearly equal pulmonary and systemic systolic pressure and variable elevations in pulmonary vascular resistance. Pulmonary blood flow may be 2-4 times systemic blood flow. In patients with such **"hyperdynamic pulmonary hypertension,"** pulmonary vascular resistance is only minimally elevated because resistance is equal to pressure divided by flow. However, if left untreated until Eisenmenger syndrome is present, pulmonary artery systolic and diastolic pressure will be elevated but the degree of left-to-right shunting minimal. In these cases, desaturation of blood in the left ventricle is usually encountered.

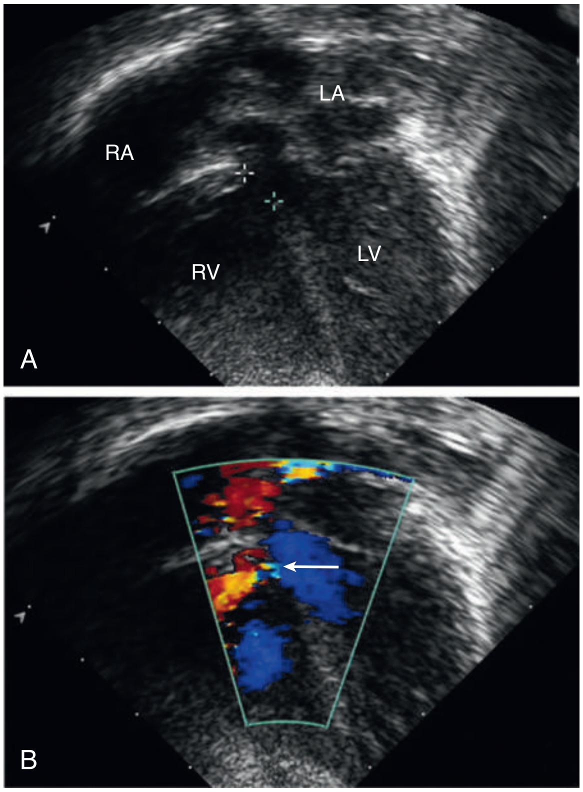

Figure 426-9 Echocardiogram in a patient with a perimembranous ventricular septal defect. **A,** Apical 4-chamber view showing the location of the defect (outlined between 2 *crosshatches*) beneath the aortic valve. **B,** Color Doppler imaging shows the left-to-right shunt *(arrow)* through the defect (the red color represents blood moving toward the ultrasound transducer and does not indicate the level of oxygenation of the blood). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

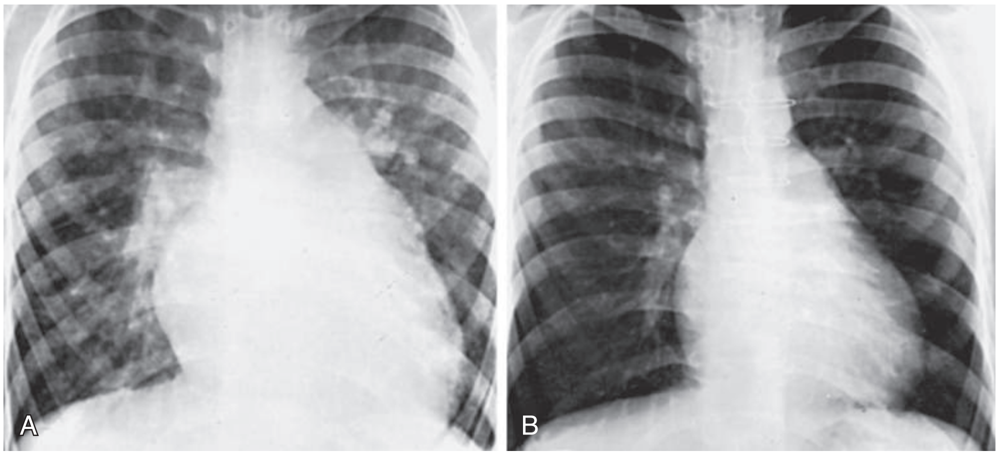

Figure 426-8 **A,** Preoperative radiograph in a patient with a ventricular septal defect with a large left-to-right shunt and pulmonary hypertension. Significant cardiomegaly, prominence of the pulmonary arterial trunk, and pulmonary overcirculation are evident. **B,** Three years after surgical closure of the defect, heart size is markedly decreased, and the pulmonary vasculature is normal.

The size, location, and number of ventricular defects can be demonstrated by left ventriculography. Contrast medium passes across the defect or defects to opacify the right ventricle and pulmonary artery. Administration of 100% oxygen with and without nitric oxide can be used to determine whether the pulmonary vascular resistance, if elevated, is still reactive and therefore more likely to drop after surgical repair.

TREATMENT

The natural course of a VSD depends to a large degree on the size of the defect. A significant number (30-50%) of small defects close spontaneously, most frequently during the 1st 2 yr of life. Small muscular VSDs are more likely to close (up to 80%) than membranous VSDs (up to 35%). The vast majority of defects that close do so before the age of 4 yr, although spontaneous closure has been reported in adults. VSDs that close often have ventricular septal aneurysm (accessory tricuspid valve) tissue that limits the magnitude of the shunt. Most children with small restrictive defects remain asymptomatic, without evidence of an increase in heart size, pulmonary arterial pressure, or resistance; a long-term risk is infective endocarditis. Some long-term studies of adults with unoperated small VSDs show an increased incidence of arrhythmia, subaortic stenosis, and exercise intolerance. Guidelines from the Council on Cardiovascular Disease in the Young of the American Heart Association state that an isolated, small, hemodynamically insignificant VSD is not an indication for surgery. However, the declining risk of open heart surgery has led some to suggest that all VSDs be closed electively by mid-childhood.

It is less common for moderate or large VSDs to close spontaneously, although even defects large enough to result in heart failure may become smaller and up to 8% may close completely. More commonly, infants with large defects have repeated episodes of respiratory infection and heart failure despite optimal medical management. Heart failure may be manifested in many of these infants primarily as failure to thrive. Pulmonary hypertension occurs as a result of high pulmonary blood flow. These patients are at risk for pulmonary vascular disease if the defect is not repaired during early infancy.

Patients with VSD are also at risk for the development of aortic valve regurgitation, the greatest risk occurring in patients with a supracristal VSD (see Chapter 426.7). A small number of patients with VSD develop **acquired infundibular pulmonary stenosis,** which then protects the pulmonary circulation from the short-term effects of pulmonary overcirculation and the long-term effects of pulmonary vascular disease. In these patients, the clinical picture changes from that of a VSD with a large left-to-right shunt to a VSD with pulmonary stenosis. The shunt may diminish in size, become balanced, or even become a net right-to-left shunt. These patients must be carefully distinguished from those in whom an Eisenmenger physiology develops (see Chapter 433.2).

In patients with small VSDs, parents should be reassured of the relatively benign nature of the lesion, and the child should be encouraged to live a normal life, with no restrictions on physical activity. Surgical repair is not recommended. As protection against infective endocarditis, the integrity of primary and permanent teeth should be carefully maintained; with the latest revision of the American Heart Association guidelines, antibiotic prophylaxis is no longer recommended for dental visits or surgical procedures (see Chapter 437). These patients can be monitored by a combination of clinical examination and noninvasive laboratory tests until the VSD has closed spontaneously. Echocardiography is used to estimate pulmonary artery pressure, screen for the development of left ventricular outflow tract pathology (subaortic membrane or aortic regurgitation), and to confirm spontaneous closure.

In infants with a large VSD, management has 2 aims: to get the symptoms of heart failure under control (see Chapter 442) and prevent the development of pulmonary vascular disease. If early treatment is successful, sometimes the shunt may diminish in size with spontaneous improvement, especially during the 1st yr of life. The clinician must be alert not to confuse clinical improvement caused by a decrease in defect size with clinical changes caused by the development of Eisenmenger physiology. Because catheter or surgical closure can be carried out at low risk in most infants, medical management should not be pursued in symptomatic infants after an initial unsuccessful trial. Because pulmonary vascular disease can usually be prevented when surgery is performed within the 1st yr of life, even infants with well-controlled heart failure should not have surgery delayed inordinately unless there is evidence that the defect is becoming pressure restrictive.

Indications for surgical closure of a VSD include patients at any age with large defects in whom clinical symptoms and failure to thrive cannot be controlled medically; infants between 6 and 12 mo of age with large defects associated with pulmonary hypertension, even if the symptoms are controlled by medication; and patients older than 24 mo with a Qp : Qs ratio greater than 2 : 1. Patients with a supracristal VSD of any size are usually referred for surgery because of the high risk for aortic valve regurgitation (see Chapter 426.7). Severe pulmonary vascular disease nonresponsive to pulmonary vasodilators is a contraindication to closure of a VSD.

Transcatheter occlusion closure is most successful in treating muscular VSDs, which may be difficult to access by surgery. Perimembranous VSD catheter closure has a high risk of postprocedure heart block and is not recommended. Hybrid methods employing a sternotomy with device placement through the anterior wall of the right ventricle under transesophageal echo and fluoroscopic visualization has been performed in difficult to approach muscular defects.

PROGNOSIS

The results of primary surgical repair are excellent, and complications leading to long-term problems (residual ventricular shunts requiring reoperation or heart block requiring a pacemaker) are rare. Pulmonary arterial palliative banding with repair in later childhood, once the standard of care, is now reserved for extremely complicated cases or very premature infants. Surgical risks are somewhat higher for defects in the muscular septum, particularly apical defects and multiple (Swiss cheese–type) VSDs. These patients may require pulmonary arterial banding if symptomatic, with subsequent debanding and repair of multiple VSDs at an older age.

After surgical obliteration of the left-to-right shunt, the hyperdynamic heart becomes quiet, cardiac size decreases toward normal (see Fig. 426-8), thrills and murmurs are abolished, and pulmonary artery hypertension regresses. The patient's clinical status improves markedly. Most infants begin to thrive, and cardiac medications are no longer required. Catch-up growth occurs in most patients within the next 1-2 yr. In some instances after successful surgery, systolic ejection murmurs of low intensity persist for months. The long-term prognosis after surgery is excellent. Patients with a small VSD and those who have undergone surgical closure without residua are considered to be at standard risk for health and life insurance.

Bibliography is available at Expert Consult.

426.7 Supracristal Ventricular Septal Defect with Aortic Insufficiency

Daniel Bernstein

A supracristal VSD is complicated by prolapse of the aortic valve into the defect and aortic insufficiency, which may eventually develop in 50-90% of these patients. Although supracristal VSD accounts for ≈5% of all patients with VSD, the incidence is higher in Asian children and in males. The VSD, which may be small or moderate in size, is located anterior to and directly below the pulmonary valve in the outlet septum, superior to the muscular ridge known as the *crista supraventricularis,* which separates the trabecular body of the right ventricle from the smooth outflow portion. The right or, less often, the noncoronary aortic cusp prolapses into the defect and may partially or even completely occlude it. Such occlusion may limit the amount of left-to-right shunting and give the false impression that the defect is not large.

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Aortic insufficiency is most often not recognized until 5-9 yr life or beyond. Of note, aortic insufficiency is occasionally associated with VSDs located in the membranous septum.

Early heart failure secondary to a large left-to-right shunt rarely occurs, but without surgery, severe aortic insufficiency and left ventricular failure may ensue. The murmur of a supracristal VSD is usually heard at the mid to upper left sternal border, as opposed to the lower left sternal border, and it is sometimes confused with that of pulmonic stenosis. A decrescendo diastolic murmur will be appreciated at the upper right or mid left sternal borders if there is aortic insufficiency. More advanced degrees of aortic insufficiency will be associated with a wide pulse pressure and a hyperdynamic precordium. These clinical findings must be distinguished from PDA or other defects associated with aortic runoff.

The clinical manifestations vary widely from trivial aortic regurgitation and small left-to-right shunts in asymptomatic children to florid aortic insufficiency and massive cardiomegaly in symptomatic adolescents. Closure of all supracristal ventricular VSDs at the time of diagnosis is commonly recommended to prevent the development of aortic regurgitation, even in an asymptomatic child. Patients who already have significant aortic insufficiency require surgical intervention to prevent irreversible left ventricular dysfunction. Surgical options depend on the degree of damage to the valve. If the insufficiency is mild, they may include simple closure of the defect to bolster the valve apparatus without touching the valve itself, valvuloplasty for more significant degrees of involvement, and replacement with a prosthesis or homograft or aortopulmonary translocation for severe involvement.

426.8 Patent Ductus Arteriosus

Daniel Bernstein

During fetal life, most of the pulmonary arterial blood is shunted right-to-left through the ductus arteriosus into the aorta (see Chapter 421). Functional closure of the ductus normally occurs soon after birth, but if the ductus remains patent when pulmonary vascular resistance falls, aortic blood then is shunted left-to-right into the pulmonary artery. The aortic end of the ductus is just distal to the origin of the left subclavian artery, and the ductus enters the pulmonary artery at its bifurcation. Female patients with PDA outnumber males 2 : 1. PDA is also associated with maternal rubella infection during early pregnancy, an uncommon occurrence. PDA is a common problem in premature infants, as the smooth muscle in the wall of the preterm ductus is less responsive to high Po_2 and therefore less likely to constrict after birth. In these infants, it can cause severe hemodynamic derangements and several major sequelae (see Chapter 101.3).

When a term infant is found to have a PDA, the wall of the ductus is deficient in both the mucoid endothelial layer and the muscular media, whereas in the premature infant, the PDA usually has a normal structure. Thus, a PDA persisting beyond the 1st few wk of life in a term infant rarely closes spontaneously or with pharmacologic intervention, whereas if early pharmacologic or surgical intervention is not required in a premature infant, spontaneous closure occurs in most instances. A PDA is seen in 10% of patients with other congenital heart lesions and often plays a critical role in providing a source of pulmonary blood flow when the right ventricular outflow tract is stenotic or atretic (see Chapter 430) or in providing systemic blood flow in the presence of aortic coarctation or interruption (see Chapters 426.6 to 427.8).

PATHOPHYSIOLOGY

As a result of the higher aortic pressure postnatally, blood shunts left to right through the ductus, from the aorta to the pulmonary artery. The extent of the shunt depends on the size of the ductus and on the ratio of pulmonary to systemic vascular resistance. If the PDA is small, pressures within the pulmonary artery, the right ventricle, and the right atrium are normal. If the PDA is large, pulmonary artery pressure may be elevated to systemic levels during both systole and diastole. Thus, patients with a large PDA are at high risk for the development of pulmonary vascular disease if left unoperated.

CLINICAL MANIFESTATIONS

A small PDA is usually asymptomatic. A large PDA will result in heart failure similar to that encountered in infants with a large VSD. Retardation of physical growth may be a major manifestation in infants with large shunts. A small PDA is associated with normal peripheral pulses, and a large PDA results in bounding peripheral arterial pulses and a wide pulse pressure, due to runoff of blood into the pulmonary artery during diastole. The heart is normal in size when the ductus is small, but moderately or grossly enlarged in cases with a large communication. In these cases, the apical impulse is prominent and, with cardiac enlargement, is heaving. A thrill, maximal in the 2nd left interspace, is often present and may radiate toward the left clavicle, down the left sternal border, or toward the apex. It is usually systolic but may also be palpated throughout the cardiac cycle. The classic continuous murmur is described as being like machinery in quality. It begins soon after onset of the 1st sound, reaches maximal intensity at the end of systole, and wanes in late diastole. It may be localized to the 2nd left intercostal space or radiate down the left sternal border or to the left clavicle. When pulmonary vascular resistance is increased, the diastolic component of the murmur may be less prominent or absent. In patients with a large left-to-right shunt, a low-pitched mitral mid-diastolic murmur may be audible at the apex as a result of the increased volume of blood flow across the mitral valve.

DIAGNOSIS

If the left-to-right shunt is small, the electrocardiogram is normal; if the ductus is large, left ventricular or biventricular hypertrophy is present. The diagnosis of an isolated, uncomplicated PDA is untenable when right ventricular hypertrophy is present.

Radiographic studies in patients with a large PDA show a prominent pulmonary artery with increased pulmonary vascular markings. Cardiac size depends on the degree of left-to-right shunting; it may be normal or moderately to markedly enlarged. The chambers involved are the left atrium and left ventricle. The aortic knob may be normal or prominent.

On echocardiogram, the cardiac chambers will be normal in size if the ductus is small. With large shunts, left atrial and left ventricular dimensions are increased. The ductus can easily be visualized directly and its size estimated. Color and pulsed Doppler examinations demonstrate systolic or diastolic (or both) retrograde turbulent flow in the pulmonary artery, and aortic retrograde flow in diastole (Fig. 426-10) in the presence of a large shunt.

The clinical signs and echocardiographic findings are sufficiently distinctive to allow an accurate diagnosis by noninvasive methods in most patients. In rare patients with atypical findings, cardiac catheterization may be indicated for confirmation of diagnosis. Cardiac catheterization will demonstrate either normal or increased pressure in the right ventricle and pulmonary artery, depending on the size of the ductus. The presence of oxygenated blood shunting into the pulmonary artery confirms the left-to-right shunt. The catheter may pass from the pulmonary artery through the ductus into the descending aorta. Injection of contrast medium into the ascending aorta shows opacification of the pulmonary artery from the aorta and identifies the ductus.

Other conditions can produce systolic and diastolic murmurs in the pulmonic area in an acyanotic patient and are described in Chapter 422. An **aorticopulmonary window** defect may rarely be clinically indistinguishable from a patent ductus, although, in most cases, the murmur is only systolic and is loudest at the right rather than the left upper sternal border. A sinus of Valsalva aneurysm that has ruptured into the right side of the heart or pulmonary artery, coronary arteriovenous fistulas, and an aberrant left coronary artery with massive collaterals from the right coronary display dynamics similar to that of a PDA with a continuous murmur and a wide pulse pressure. Truncus arteriosus with torrential pulmonary flow also has an aortic runoff physiology. A peripheral arteriovenous fistula also results in a wide pulse pressure, but the distinctive precordial murmur of a PDA is not

present. VSD with aortic insufficiency, repaired tetralogy of Fallot, and combined aortic and mitral insufficiency (usually due to rheumatic fever) may be confused with a PDA, but the murmurs should be differentiated by their to-and-fro rather than continuous nature. The combination of a large VSD and a PDA results in findings more like those of an isolated VSD. Echocardiography should be able to eliminate these other diagnostic possibilities.

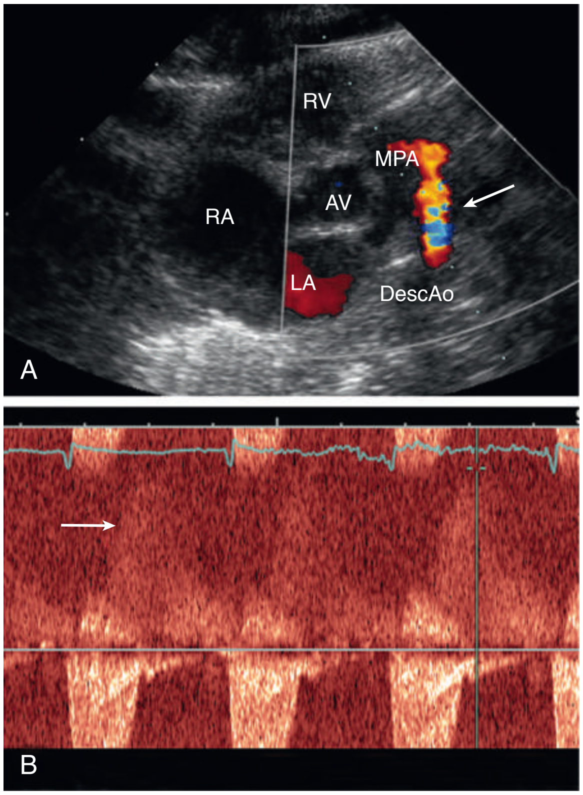

Figure 426-10 **Echocardiogram in a newborn with a small- to moderate-size patent ductus arteriosus. A,** Color Doppler performed in a parasternal short axis view shows flow *(arrow)* from the aorta into the main pulmonary artery. **B,** Doppler evaluation demonstrates retrograde diastolic flow into the pulmonary artery. AV, aortic valve; DescAo, descending aorta; LA, left atrium; MPA, main pulmonary artery; RA, right atrium; RV, right ventricle.

PROGNOSIS AND COMPLICATIONS

Spontaneous closure of the ductus after infancy is extremely rare. Patients with a small PDA may live a normal span with few or no cardiac symptoms, but late manifestations may occur. In patients with a large PDA, cardiac failure most often occurs in early infancy but may occur later in life, even with a moderate-sized communication.

Infective endarteritis may be seen at any age. Pulmonary or systemic emboli may occur. Rare complications include aneurysmal dilation of the pulmonary artery or the ductus, calcification of the ductus, noninfective thrombosis of the ductus with embolization, and paradoxical emboli. Pulmonary hypertension (Eisenmenger syndrome) usually develops in patients with a large PDA who do not undergo ductal closure (see Chapter 433.2).

TREATMENT

Irrespective of age, patients with PDA require catheter or surgical closure. In patients with a small PDA, the rationale for closure is prevention of bacterial endarteritis or other late complications. In patients with a moderate to large PDA, closure is accomplished to treat heart failure or prevent the development of pulmonary vascular disease, or both. Once the diagnosis of a moderate to large PDA is made, treatment should not be unduly postponed after adequate medical therapy for cardiac failure has been instituted.

Transcatheter PDA closure is routinely performed in the cardiac catheterization laboratory (Fig. 426-11). Small PDAs are generally closed with intravascular coils. Moderate to large PDAs may be closed with an umbrella-like device or with a catheter-introduced sac into which several coils are released. Surgical closure of a PDA can be accomplished by a standard left thoracotomy or using thoracoscopic minimally invasive techniques. Because the case fatality rate with interventional or surgical treatment is considerably less than 1% and the risk without it is greater, closure of the ductus is indicated in asymptomatic patients, preferably before 1 yr of age. Pulmonary hypertension is not a contraindication to surgery at any age if it can be demonstrated at cardiac catheterization that the shunt flow is still predominantly left to right and that severe pulmonary vascular disease is not present. After closure, symptoms of cardiac failure rapidly disappear. Infants who had failed to thrive usually have immediate improvement in physical development. The pulse and blood pressure return to normal, and the machinery-like murmur disappears. A functional systolic murmur over the pulmonary area may persist; it may represent turbulence in a persistently dilated pulmonary artery. The radiographic signs of cardiac enlargement and pulmonary overcirculation disappear over a period of several months, and the electrocardiogram becomes normal.

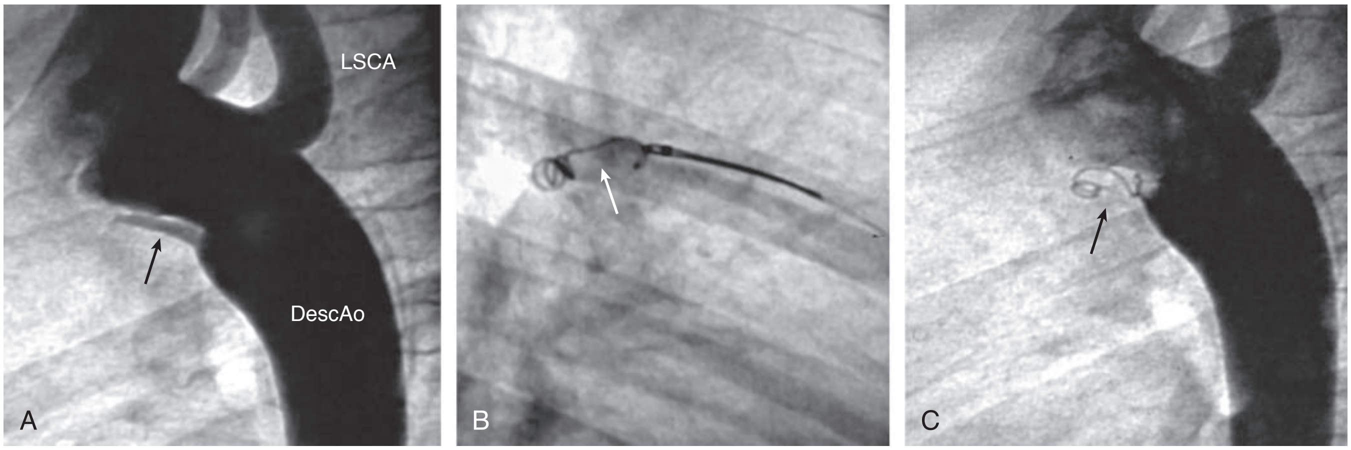

Figure 426-11 **Transcatheter closure of a small patent ductus arteriosus using a coil. A,** Angiogram of transverse and descending aorta shows small PDA *(arrow)*. **B,** Coil *(arrow)* has been extruded from sheath and is being positioned in ductal lumen. **C,** Angiogram demonstrating total occlusion of PDA by coil *(arrow)*. DescAo, descending aorta; LSCA, left subclavian artery.

PATENT DUCTUS ARTERIOSUS IN LOW BIRTHWEIGHT INFANTS

See Chapter 101.

Bibliography is available at Expert Consult.

426.9 Aortopulmonary Window Defect

Daniel Bernstein

An aortopulmonary window defect consists of a communication between the ascending aorta and the main pulmonary artery. The presence of pulmonary and aortic valves and an intact ventricular septum distinguishes this anomaly from truncus arteriosus (see Chapter 431.8). Symptoms of heart failure appear during early infancy; occasionally, minimal cyanosis is present. The defect is usually large, and the cardiac murmur is usually systolic with an apical mid-diastolic rumble as a result of the increased blood flow across the mitral valve. In the rare instance when the communication is smaller and pulmonary hypertension is absent, the findings on examination can mimic those of a PDA (wide pulse pressure and a continuous murmur at the upper sternal borders). The electrocardiogram shows either left ventricular or biventricular hypertrophy. Radiographic studies demonstrate cardiac enlargement and prominence of the pulmonary artery and intrapulmonary vasculature. The echocardiogram shows enlarged left-sided heart chambers; the window defect can best be delineated with color flow Doppler. CT or MRI angiography can also be used to visualize the defect (see Fig. 423-26 in Chapter 423).

Cardiac catheterization, usually performed in older children to evaluate pulmonary vascular resistance, reveals a left-to-right shunt at the level of the pulmonary artery, as well as hyperkinetic pulmonary hypertension, because the defect is almost always large. Selective aortography with injection of contrast medium into the ascending aorta demonstrates the lesion, and manipulation of the catheter from the main pulmonary artery directly to the ascending aorta is also diagnostic.

An aortopulmonary window defect is surgically corrected during infancy. If surgery is not carried out in infancy, survivors carry the risk of progressive pulmonary vascular obstructive disease, similar to that of other patients who have large intracardiac or great vessel communications.

426.10 Coronary Artery Fistula

Daniel Bernstein

A congenital fistula may exist between a coronary artery and an atrium, ventricle (especially the right), or pulmonary artery. Sometimes, multiple fistulas exist. Regardless of the recipient chamber, the clinical signs are similar to those of PDA, although the machinery-like murmur may be more diffuse. If the flow is substantial, the involved coronary artery may be dilated or aneurysmal. The anatomic abnormality is usually demonstrable by color flow Doppler echocardiography and, during catheterization, by injection of contrast medium into the ascending aorta. Small fistulas may be hemodynamically insignificant and may even close spontaneously. If the shunt is large, treatment consists of either transcatheter coil embolization or, for lesions not amenable to catheter intervention, surgical closure of the fistula.

426.11 Ruptured Sinus of Valsalva Aneurysm

Daniel Bernstein

When 1 of the sinuses of Valsalva of the aorta is weakened by congenital or acquired disease, an aneurysm may form and eventually rupture, usually into the right atrium or ventricle. This condition is extremely rare in childhood. The onset is usually sudden. The diagnosis should be suspected in a patient in whom symptoms of acute heart failure develop in association with a new loud to-and-fro murmur. Color Doppler echocardiography and cardiac catheterization demonstrate the left-to-right shunt at the atrial or ventricular level. Urgent surgical repair is generally required. This condition is often associated with infective endocarditis of the aortic valve.

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Chapter **427**

Acyanotic Congenital Heart Disease: Obstructive Lesions

427.1 Pulmonary Valve Stenosis with Intact Ventricular Septum

Daniel Bernstein

Of the various forms of right ventricular outflow obstruction with an intact ventricular septum, the most common is isolated valvular pulmonary stenosis, which accounts for 7-10% of all congenital heart defects. The valve cusps are deformed to various degrees and, as a result, the valve opens incompletely during systole. The valve may be bicuspid or tricuspid and the leaflets partially fused together with an eccentric outlet. This fusion may be so severe that only a pinhole central opening remains. If the valve is not severely thickened, it produces a dome-like obstruction to right ventricular outflow during systole. Isolated infundibular or subvalvular stenosis, supravalvular pulmonary stenosis, and branch pulmonary artery stenosis are also encountered. In cases where pulmonary valve stenosis is associated with a ventricular septal defect (VSD) but without anterior deviation of the infundibular septum and overriding aorta, this condition is better classified as pulmonary stenosis with VSD rather than as tetralogy of Fallot (see Chapter 430.1). Pulmonary stenosis and an atrial septal defect (ASD) are also occasionally seen as associated defects. The clinical and laboratory findings reflect the dominant lesion, but it is important to rule out any associated anomalies. Pulmonary stenosis as a result of valve dysplasia is the most common cardiac abnormality in **Noonan syndrome** (see Chapter 81), and is associated, in approximately 50% of cases, with a mutation in the gene *PTPN11,* encoding the protein tyrosine phosphatase SHP-2 on chromosome 12. The mechanism for pulmonic stenosis is unknown, although maldevelopment of the distal portion of the bulbus cordis and the sequelae of fetal endocarditis have been suggested as etiologies. Pulmonary stenosis can also be a component of **LEOPARD syndrome** (lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, deafness syndrome), often associated with hypertrophic cardiomyopathy. Mutations in the genes PTPN11, RAF1 and BRAF have been implicated in LEOPARD syndrome. Pulmonary stenosis, either of the valve or the branch pulmonary arteries, is a common finding in patients with arteriohepatic dysplasia, also known as **Alagille syndrome** (see Chapter 356). In this syndrome and in some patients with isolated pulmonic stenosis, a mutation is present in the *Jagged1* gene.

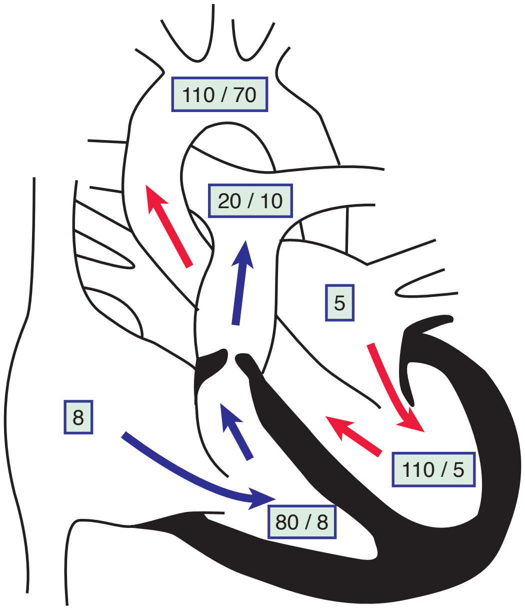

Figure 427-1 Physiology of valvular pulmonary stenosis. Boxed numbers represent pressure in mm Hg. Because of the absence of right-to-left or left-to-right shunting, blood flow through all cardiac chambers is normal at 3 L/min/m^2. The pulmonary-to-systemic blood flow ratio (Qp : Qs) is 1 : 1. Right atrial pressure is increased slightly as a result of decreased right ventricular compliance. The right ventricle is hypertrophied, and systolic and diastolic pressure is increased. The pressure gradient across the thickened pulmonary valve is 60 mm Hg. The main pulmonary artery pressure is slightly low, and poststenotic dilation is present. Left-heart pressure is normal. Unless right-to-left shunting is occurring through a foramen ovale, the patient's systemic oxygen saturation will be normal.

PATHOPHYSIOLOGY

The obstruction to outflow from the right ventricle to the pulmonary artery results in increased right ventricular systolic pressure and wall stress, which leads to hypertrophy of the right ventricle (Fig. 427-1). The severity of these abnormalities depends on the size of the restricted valve opening. In severe cases, right ventricular pressure may be higher than systemic arterial systolic pressure, whereas with milder obstruction, right ventricular pressure is only mildly or moderately elevated. Pulmonary artery pressure (distal to the obstruction) is normal or decreased. Arterial oxygen saturation will be normal even in cases of severe stenosis, unless an intracardiac communication such as a VSD or ASD is allowing blood to shunt from right to left. When severe pulmonic stenosis occurs in a neonate, decreased right ventricular compliance often leads to cyanosis as a result of right-to-left shunting through a patent foramen ovale, a condition termed ***critical pulmonic stenosis***.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Patients with mild or moderate stenosis usually do not have any symptoms. Growth and development are most often normal. If the stenosis is severe, signs of right ventricular failure such as hepatomegaly, peripheral edema, and exercise intolerance may be present. In a neonate or young infant with critical pulmonic stenosis, signs of right ventricular failure may be more prominent, and cyanosis is often present because of right-to-left shunting at the foramen ovale.

With **mild pulmonary stenosis,** venous pressure and pulse are normal. The heart is not enlarged, the apical impulse is normal, and the right ventricular impulse is not palpable. A sharp pulmonic ejection click immediately after the 1st heart sound is heard at the left upper sternal border during expiration. The 2nd heart sound is split, with a pulmonary component of normal intensity that may be slightly delayed. A relatively short, low- or medium-pitched systolic ejection murmur is maximally audible over the pulmonic area and radiates minimally to the lung fields bilaterally. The electrocardiogram is normal or characteristic of mild right ventricular hypertrophy; inversion of the T waves in the right precordial leads may be seen. Remember that the T wave in lead V_1 should normally be inverted until at least 6-8 yr of age. Therefore, a positive T wave in V_1 in a young child is a sign of right ventricular hypertrophy. The only abnormality demonstrable radiographically is usually poststenotic dilation of the pulmonary artery. Two-dimensional echocardiography shows right ventricular hypertrophy and a slightly thickened pulmonic valve, which domes in systole; Doppler studies demonstrate a right ventricle to pulmonary artery gradient of ≤30 mm Hg.

In **moderate pulmonic stenosis,** venous pressure may be slightly elevated; in older children, a prominent *a* wave may be noted in the jugular pulse. A right ventricular lift may be palpable at the lower left sternal border. The 2nd heart sound is split, with a delayed and soft pulmonary component. As valve motion becomes more limited with more severe degrees of stenosis, both the pulmonic ejection click and the pulmonic 2nd sound may become inaudible. With increasing degrees of stenosis, the peak of the systolic ejection murmur is prolonged later into systole, and its quality becomes louder and harsher (higher frequency). The murmur radiates more prominently to both lung fields.

The electrocardiogram reveals right ventricular hypertrophy, sometimes with a prominent spiked P wave. Radiographically, the heart can vary from normal size to mildly enlarged with uptilting of the apex because of the prominence of the right ventricle; pulmonary vascularity may be normal or slightly decreased. The echocardiogram shows a thickened pulmonic valve with restricted systolic motion. Doppler examination demonstrates a right ventricle to pulmonary artery pressure gradient in the 30-60 mm Hg range. Mild tricuspid regurgitation may be present and allows Doppler confirmation of right ventricular systolic pressure.

In **severe stenosis,** mild to moderate cyanosis may be noted in patients with an interatrial communication (ASD or patent foramen ovale). In the absence of any intracardiac shunt, cyanosis is absent. If hepatic enlargement and peripheral edema are present, they are an indication of right ventricular failure. Elevation of venous pressure is common and is caused by a large presystolic jugular *a* wave. The heart is moderately or greatly enlarged, and a conspicuous parasternal right ventricular lift is present and frequently extends to the left midclavicular line. The pulmonary component of the 2nd sound is usually inaudible. A loud, long, and harsh systolic ejection murmur, usually accompanied by a thrill, is maximally audible in the pulmonic area and may radiate over the entire precordium, to both lung fields, into the neck, and to the back. The peak of the murmur occurs later in systole as valve opening becomes more restricted. The murmur frequently encompasses the aortic component of the 2nd sound but is not preceded by an ejection click.

The electrocardiogram shows gross right ventricular hypertrophy, frequently accompanied by a tall, spiked P wave. Radiographic studies confirm the presence of cardiac enlargement with prominence of the right ventricle and right atrium. Prominence of the main pulmonary artery segment may be seen due to poststenotic dilation (Fig. 427-2). Intrapulmonary vascularity is decreased. The 2-dimensional echocardiogram shows severe deformity of the pulmonary valve and right ventricular hypertrophy (Fig. 427-3). In the late stages of the disease, systolic dysfunction of the right ventricle may be seen, and in these cases the ventricle may become dilated, with prominent tricuspid regurgitation. Doppler studies demonstrate a high gradient (>60 mm Hg) across the pulmonary valve. The classic findings of severe pulmonary stenosis in older children are rarely seen because of early intervention. Signs of critical pulmonic stenosis, with all of the features of severe pulmonic stenosis plus cyanosis, are usually encountered in the neonatal period.

Cardiac catheterization is not generally required for diagnostic purposes but is undertaken as part of a **balloon valvuloplasty** procedure. Catheterization demonstrates an abrupt pressure gradient across the

Figure 427-2 **X-ray of a patient with valvular pulmonary stenosis and a normal aortic root.** The heart size is within normal limits, but post-stenotic dilation of the pulmonary artery is present.

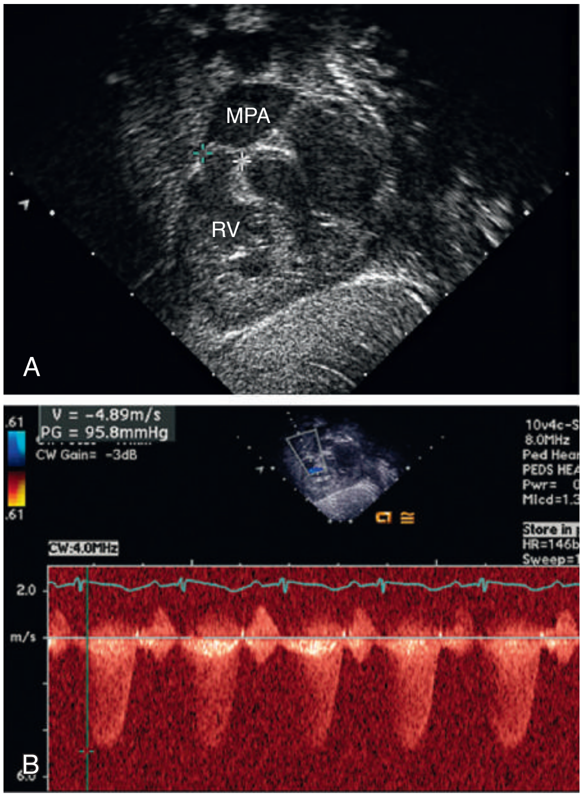

Figure 427-3 **Echocardiogram demonstrating valvar pulmonic stenosis. A,** Subcostal view showing thickened pulmonary valve leaflets (between crosshatches). **B,** Doppler study indicating a 95 mm Hg peak pressure gradient across the stenotic valve. MPA, main pulmonary artery; RV, right ventricle.

pulmonary valve. Pulmonary artery pressure is either normal or low. The severity of the stenosis is graded based on the ratio of right ventricular systolic pressure to systemic systolic pressure or the right ventricle to pulmonary artery pressure gradient: a gradient of 10-30 mm Hg in mild cases, 30-60 mm Hg in moderate cases, and >60 mm Hg or with right ventricular pressure greater than systemic pressure in severe cases. If cardiac output is low or a significant right-to-left shunt exists across the atrial septum, the pressure gradient may underestimate the degree of valve stenosis. Selective right ventriculography demonstrates the thickened, poorly mobile valve. In mild to moderate stenosis, doming of the valve in systole is readily seen. Flow of contrast medium through the stenotic valve in ventricular systole produces a narrow jet of dye that fills the dilated main pulmonary artery. Subvalvular hypertrophy that may intensify the obstruction may be present.

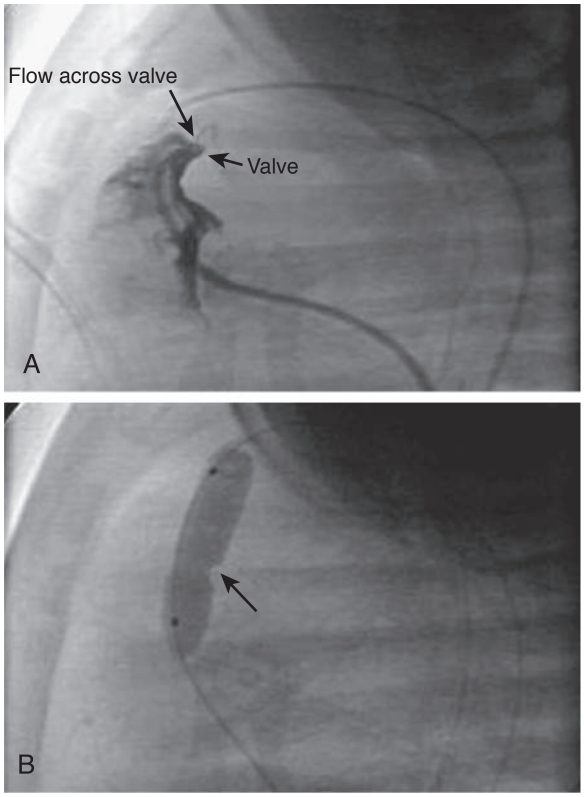

Figure 427-4 **Valvar pulmonary stenosis and balloon valvuloplasty. A,** Right ventricular angiogram showing severely stenotic pulmonary valve with narrow jet of blood flowing across. **B,** Inflation of the balloon catheter showing the indentation *(arrow)* made on the balloon from the stenotic valve. *(Photos courtesy of Dr. Jeffrey Feinstein, Stanford University, Stanford, CA.)*

TREATMENT

Patients with moderate or severe isolated pulmonary stenosis require relief of the obstruction. Balloon valvuloplasty is the initial treatment of choice for the majority of patients (Fig. 427-4). Patients with severely thickened pulmonic valves, especially common in those with Noonan syndrome, may require surgical intervention. In a neonate with critical pulmonic stenosis, urgent treatment by either balloon valvuloplasty or surgical valvotomy is warranted.

Excellent results are obtained in most instances. The gradient across the pulmonary valve is markedly reduced or abolished. In the early period after balloon valvuloplasty, a small to moderate residual gradient may remain because of muscular infundibular narrowing; it usually resolves with time. A short, early decrescendo diastolic murmur may be heard at the mid to upper left sternal border as a result of pulmonary valvular insufficiency. The degree of insufficiency is not usually clinically significant. No difference in patient status after valvuloplasty or surgery is noted at late follow-up; recurrence is unusual after successful treatment except in those patients with extremely dysplastic valves. In the small minority of patients where the degree of pulmonary regurgitation is more severe, right ventricular dilation may ensue, and these patients require careful follow-up and may require surgical intervention.

PROGNOSIS AND COMPLICATIONS

Heart failure occurs only in severe cases and most often during the 1st mo of life. The development of cyanosis from a right-to-left shunt across a foramen ovale is almost exclusively seen in the neonatal period when the stenosis is severe. Infective endocarditis is a risk, but is not common in childhood.

Children with mild stenosis can lead a normal life, but their progress should be evaluated at regular intervals. Patients who have small gradients rarely show progression and do not need intervention, but a significant gradient is more likely to develop in children with moderate stenosis as they grow older. Worsening of obstruction may also be due to the development of secondary subvalvular muscular and fibrous tissue hypertrophy. In untreated severe stenosis, the course may abruptly worsen with the development of right ventricular dysfunction and cardiac failure. Infants with critical pulmonic stenosis require urgent catheter balloon valvuloplasty or surgical valvotomy. Development of right ventricular failure many years after pulmonary balloon valvuloplasty is uncommon. Nonetheless, patients should be followed serially for worsening pulmonary insufficiency and right ventricular dilation.

Bibliography is available at Expert Consult.

427.2 Infundibular Pulmonary Stenosis and Double-Chamber Right Ventricle

Daniel Bernstein

Infundibular pulmonary stenosis is caused by muscular or fibrous obstruction in the outflow tract of the right ventricle. The site of obstruction may be close to the pulmonary valve or well below it; an infundibular chamber may be present between the right ventricular cavity and the pulmonary valve. In many cases, a VSD may have been present initially and later closed spontaneously. When the pulmonary valve is also stenotic, the combined defect is primarily classified as valvular stenosis with secondary infundibular hypertrophy. The hemodynamics and clinical manifestations of patients with isolated infundibular pulmonary stenosis are similar, for the most part, to those described in the discussion of isolated valvular pulmonary stenosis (see Chapter 427.1).

A common variation in right ventricular outflow obstruction below the pulmonary valve is that of a double-chambered right ventricle. In this condition, a muscular band is present in the mid-right ventricular region; the band divides the chamber into 2 parts and creates obstruction between the inlet and outlet portions. An associated VSD that may close spontaneously is often noted. Obstruction is not usually seen early in life but may progress rapidly in a similar manner to the progressive infundibular obstruction observed with tetralogy of Fallot (see Chapter 430.1).

The diagnosis of isolated right ventricular infundibular stenosis or double-chambered right ventricle is usually made by echocardiography. The ventricular septum must be evaluated carefully to determine whether an associated VSD is present. The prognosis for untreated cases of severe right ventricular outflow obstruction is similar to that for valvular pulmonary stenosis. When the obstruction is moderate to severe, surgery is indicated. After surgery, the pressure gradient is abolished or markedly reduced and the long-term outlook is excellent.

427.3 Pulmonary Stenosis in Combination with an Intracardiac Shunt

Daniel Bernstein

Valvular or infundibular pulmonary stenosis, or both, may be associated with either an ASD or a VSD. In these patients, the clinical features depend on the degree of pulmonary stenosis, which determines whether the net shunt is from left to right or from right to left.

The presence of a large left-to-right shunt at the atrial or ventricular level is evidence that the pulmonary stenosis is mild. These patients have symptoms similar to those of patients with an isolated ASD or VSD. With increasing age, worsening of the obstruction may limit the shunt and result in a gradual improvement in symptoms. Eventually, particularly in patients with pulmonary stenosis and VSD, a further increase in obstruction may lead to right-to-left shunting and cyanosis. When a patient with a VSD has evidence of decreasing heart failure and increased right ventricular forces on the electrocardiogram, one must differentiate between the development of increasing pulmonary stenosis versus the onset of pulmonary vascular disease (Eisenmenger syndrome, Chapter 433.2).

These anomalies are readily repaired surgically. Defects in the atrial or ventricular septum are closed, and the pulmonary stenosis is relieved by resection of infundibular muscle or pulmonary valvotomy, or both, as indicated. Patients with a predominant right-to-left shunt have symptoms similar to those of patients with **tetralogy of Fallot** (see Chapter 430.1).

427.4 Peripheral Pulmonary Stenosis

Daniel Bernstein

Single or multiple constrictions may occur anywhere along the major branches of the pulmonary arteries and may range from mild to severe and from localized to extensive. Frequently, these defects are associated with other types of congenital heart disease, including valvular pulmonic stenosis, tetralogy of Fallot, patent ductus arteriosus (PDA), VSD, ASD, and supravalvular aortic stenosis. A familial tendency has been recognized in some patients with peripheral pulmonic stenosis. A high incidence is found in infants with congenital rubella syndrome. The combination of supravalvular aortic stenosis with pulmonary arterial branch stenosis, idiopathic hypercalcemia of infancy, elfin facies, and mental retardation is known as **Williams syndrome,** a condition associated with deletion of the elastin gene in region 7q11.23 on chromosome 7. Peripheral pulmonary stenosis is also associated with the **Alagille syndrome,** which may be associated with a mutation in the *Jagged1* gene.

A mild constriction has little effect on the pulmonary circulation. With multiple severe constrictions, pressure is increased in the right ventricle and in the pulmonary artery proximal to the site of obstruction. When the anomaly is isolated, the diagnosis is suspected by the presence of murmurs in widespread locations over the chest, either anteriorly or posteriorly. These murmurs are usually systolic ejection in quality but may be continuous. Most often, the physical signs are dominated by the associated anomaly, such as tetralogy of Fallot (see Chapter 430.1).

In the immediate newborn period, a mild and transient form of peripheral pulmonic stenosis may be present. Physical findings are generally limited to a soft systolic ejection murmur, which can be heard over either or both lung fields. It is the absence of other physical findings of valvular pulmonic stenosis (right ventricular lift, soft pulmonic 2nd sound, systolic ejection click, murmur loudest at the upper left sternal border) that supports this diagnosis. This murmur usually disappears by 1-2 mo.

If the stenosis is severe, the electrocardiogram shows evidence of right ventricular and right atrial hypertrophy, and the chest radiograph shows cardiomegaly and prominence of the main pulmonary artery. The pulmonary vasculature is usually normal; in some cases, however, small intrapulmonary vascular shadows are seen that represent areas of poststenotic dilation. Echocardiography is limited in its ability to visualize the distal branch pulmonary arteries. Doppler examination demonstrates the acceleration of blood flow through the stenoses and, if tricuspid regurgitation is present, allows an estimation of right ventricular systolic pressure. MRI and CT are extremely helpful in delineating distal obstructions; if moderate to severe disease is suspected, the diagnosis is usually confirmed by cardiac catheterization.

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Severe obstruction of the main pulmonary artery and its primary branches can be relieved during corrective surgery for associated lesions such as the tetralogy of Fallot or valvular pulmonary stenosis. If peripheral pulmonic stenosis is isolated, it may be treated by catheter balloon dilation, sometimes with placement of an intravascular stent (see Fig. 423-29 in Chapter 423).

427.5 Aortic Stenosis

Daniel Bernstein

PATHOPHYSIOLOGY

Congenital aortic stenosis accounts for ≈5% of cardiac malformations recognized in childhood; a bicuspid aortic valve, one of the most common congenital heart lesions overall, is identified in up to 1.5% of adults and may be asymptomatic in childhood. Aortic stenosis is more frequent in males (3:1). There are families with multiple individuals affected with bicuspid aortic valve, and several genes have been implicated, including *NOTCH1* on chromosome 9q34.3.

In the most common form, valvular aortic stenosis, the leaflets are thickened and the commissures are fused to varying degrees. Left ventricular systolic pressure is increased as a result of the obstruction to outflow. The left ventricular wall hypertrophies in compensation; as its compliance decreases, end-diastolic pressure increases as well.

Subvalvular (subaortic) stenosis with a discrete fibromuscular shelf below the aortic valve is also an important form of left ventricular outflow tract obstruction. This lesion is frequently associated with other forms of congenital heart disease such as mitral stenosis and coarctation of the aorta (**Shone syndrome**) and may progress rapidly in severity. It is less commonly diagnosed during early infancy and may develop despite previous documentation of no left ventricular outflow tract obstruction. Subvalvular aortic stenosis may become apparent after successful surgery for other congenital heart defects (coarctation of the aorta, PDA, VSD), may develop in association with mild lesions that have not been surgically repaired, or may occur as an isolated abnormality. Subvalvular aortic stenosis may also be caused by a markedly hypertrophied ventricular septum in association with hypertrophic cardiomyopathy (see Chapter 439.2).

Supravalvular aortic stenosis, the least-common type, may be sporadic, familial, or associated with **Williams syndrome,** which includes mental retardation (IQ range: 41-80), elfin facies (full face, broad forehead, flattened bridge of the nose, long upper lip, and rounded cheeks) (Fig. 427-5), and idiopathic hypercalcemia of infancy. Additional features include loquacious personality, hypersensitivity to sound, spasticity, hypoplastic nails, dental anomalies (partial anodontia, microdontia enamel hypoplasia), joint hypermobility, nephrocalcinosis, hypothyroidism, and poor weight gain. Narrowing of the coronary artery ostia can occur in patients with supravalvar aortic stenosis and should be carefully evaluated. Stenosis of other arteries, in particular, the branch pulmonary arteries, may also be present. Williams syndrome has been shown to be due to a deletion involving the elastin gene on chromosome 7q11.23.

Figure 427-5 Williams syndrome. *(From Jones KL, Smith DW: The Williams elfin facies syndrome: a new perspective,* J Pediatr *86:718, 1975.)*

CLINICAL MANIFESTATIONS

Symptoms in patients with aortic stenosis depend on the severity of the obstruction. Severe aortic stenosis that occurs in early infancy is termed **critical aortic stenosis** and is associated with left ventricular failure and signs of low cardiac output. Heart failure, cardiomegaly, and pulmonary edema are severe, the pulses are weak in all extremities, and the skin may be pale or grayish. Urine output may be diminished. If cardiac output is significantly decreased, the intensity of the murmur at the right upper sternal border may be minimal. Most children with less-severe forms of aortic stenosis remain asymptomatic and display normal growth and development. The murmur is usually discovered during routine physical examination. Rarely, fatigue, angina, dizziness, or syncope may develop in an older child with previously undiagnosed severe obstruction to left ventricular outflow. Sudden death has been reported with aortic stenosis but usually occurs in patients with severe left ventricular outflow obstruction in whom surgical relief has been delayed.

The physical findings are dependent on the degree of obstruction to left ventricular outflow. In mild stenosis, the pulses, heart size, and apical impulse are all normal. With increasing degrees of severity, the pulses become diminished in intensity and the heart may be enlarged, with a left ventricular apical thrust. Mild to moderate valvular aortic stenosis is usually associated with an early systolic ejection click, best heard at the apex and left sternal edge. Unlike the click in pulmonic stenosis, its intensity does not vary with respiration. Clicks are unusual in more-severe aortic stenosis or in discrete subaortic stenosis. If the stenosis is severe, the 1st heart sound may be diminished because of decreased compliance of the thickened left ventricle. Normal splitting of the 2nd heart sound is present in mild to moderate obstruction. In patients with severe obstruction, the intensity of aortic valve closure is diminished, and, rarely in children, the 2nd sound may be split paradoxically (becoming wider in expiration). A 4th heart sound may be audible when the obstruction is severe as a result of decreased left ventricular compliance.

The intensity, pitch, and duration of the systolic ejection murmur are other indications of severity. The louder, harsher (higher pitch), and longer the murmur, the greater the degree of obstruction is. The typical murmur is audible maximally at the right upper sternal border and radiates to the neck and the left midsternal border. It is usually accompanied by a thrill in the suprasternal notch. In patients with subvalvular aortic stenosis, the murmur may be maximal along the left sternal border or even at the apex. A soft decrescendo diastolic murmur indicative of aortic insufficiency is often present when the obstruction is subvalvular or in patients with a bicuspid aortic valve. Occasionally, an apical short mid-diastolic rumbling murmur is audible; this murmur should raise suspicion of associated mitral valve stenosis.

LABORATORY FINDINGS AND DIAGNOSIS

The diagnosis can usually be made on the basis of the physical examination and the severity of obstruction confirmed by laboratory tests. If the pressure gradient across the aortic valve is mild, the electrocardiogram is likely to be normal. The electrocardiogram may occasionally be normal even with more severe obstruction, but evidence of left ventricular hypertrophy and strain (inverted T waves in the left precordial leads) is generally present if severe stenosis is long-standing. The chest radiograph frequently shows a prominent ascending aorta, but the aortic knob is normal. Heart size is typically normal. Valvular calcification has been noted only in older children and adults. Echocardiography identifies both the site and the severity of the obstruction. Two-dimensional imaging shows left ventricular hypertrophy and the thickened and domed aortic valve (Fig. 427-6). The echo will also demonstrate the number of valve leaflets and their morphology, and the presence of a subaortic membrane or supravalvar stenosis. Associated anomalies of the mitral valve or aortic arch or a VSD or PDA are present in up to 20% of cases. In the absence of left ventricular failure, the shortening fraction of the left ventricle may be increased because the ventricle is hypercontractile. In infants with critical aortic stenosis, the left ventricular shortening fraction is usually decreased and may be quite poor. The endocardium may appear bright, indicative of the development of endocardial fibrous scarring, known as **endocardial fibroelastosis.** Doppler studies show the specific site of obstruction and determine the peak and mean systolic left ventricular outflow tract gradients. When severe aortic obstruction is associated with left ventricular dysfunction, the Doppler-derived valve gradient may markedly underestimate the severity of the obstruction because of the low cardiac output across the valve.

Left-heart catheterization, usually performed in conjunction with aortic balloon valvuloplasty, demonstrates the magnitude of the pressure gradient from the left ventricle to the aorta. The aortic pressure curve is abnormal if the obstruction is severe. In patients with severe obstruction and decreased left ventricular compliance, left atrial pressure is increased and pulmonary hypertension may be present. When a critically ill infant with left ventricular outflow tract obstruction undergoes cardiac catheterization, left ventricular function is often markedly decreased. As with the echocardiogram, the gradient measured across the stenotic aortic valve may underestimate the degree of obstruction because of low cardiac output. Actual measurement of cardiac output by thermodilution and calculation of the aortic valve area may be helpful.

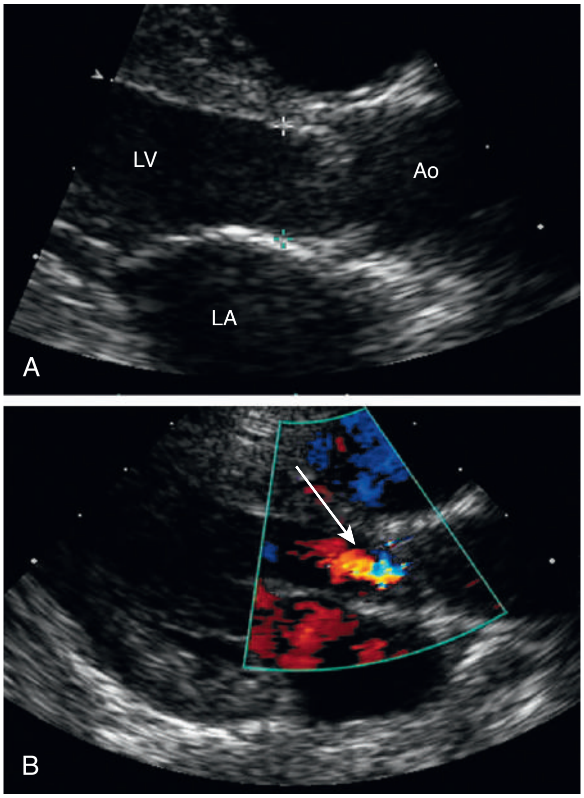

Figure 427-6 Echocardiogram showing valvar aortic stenosis with regurgitation. **A,** In this parasternal long axis view, the stenotic aortic valve can be seen doming in systole. The *crosshatch* marks delineate the aortic annulus. **B,** Doppler study shows the presence of aortic regurgitation *(arrow)*. Ao, aorta; LA, left atrium; LV, left ventricle.

TREATMENT

Balloon valvuloplasty is indicated for children with moderate to severe valvular aortic stenosis to prevent progressive left ventricular dysfunction and the risk of syncope and sudden death. Valvuloplasty should be advised when the peak-to-peak systolic gradient between the left ventricle and aorta exceeds 60-70 mm Hg at rest, assuming normal cardiac output, or for lesser gradients when symptoms or electrocardiographic changes are present. For more rapidly progressive subaortic obstructive lesions, a gradient of 40-50 mm Hg or the presence of aortic insufficiency is considered an indication for surgery. Balloon valvuloplasty is the procedure of choice even in the neonatal period. Surgical treatment is usually reserved for extremely dysplastic aortic valves that are not amenable to balloon therapy or in patients who also have subvalvar or valvar (also known as *supravalvar*) stenosis.

Discrete subaortic stenosis can be resected without damage to the aortic valve, the anterior leaflet of the mitral valve, or the conduction system. This type of obstruction is not usually amenable to catheter treatment. Relief of supravalvular stenosis is also achieved surgically, and the results are excellent if the area of obstruction is discrete and not associated with a hypoplastic aorta. In association with supravalvular aortic stenosis, one or both coronary arteries may be stenotic at their origins because of a thick supra-aortic fibrous ridge. For patients who have aortic stenosis in association with severe tunnel-like subaortic obstruction, the left ventricular outflow tract can be enlarged by “borrowing” space anteriorly from the right ventricular outflow tract (the Konno procedure).

Regardless of whether surgical or catheter treatment has been carried out, aortic insufficiency or calcification with re-stenosis is likely to occur years or even decades later and eventually require reoperation and often aortic valve replacement. When recurrence develops, it may not be associated with early symptoms. Signs of recurrent stenosis include electrocardiographic signs of left ventricular hypertrophy, an increase in the Doppler echocardiographic gradient, deterioration in echocardiographic indices of left ventricular function, and recurrence of signs or symptoms during graded treadmill exercise. Evidence of significant aortic regurgitation includes symptoms of heart failure, cardiac enlargement on roentgenogram, and left ventricular dilation on echocardiogram. The choice of reparative procedure depends on the relative degree of stenosis and regurgitation.

When **aortic valve replacement** is necessary, the choice of procedure often depends on the age of the patient. Homograft valves tend to calcify more rapidly in younger children, but they do not require chronic anticoagulation. Mechanical prosthetic valves are much longer lasting, yet they require anticoagulation, which can be difficult to manage in young children. In adolescent girls who are nearing childbearing age, consideration of the teratogenic effects of warfarin may warrant the use of a homograft valve. None of these options are perfect for a younger child who requires valve replacement because neither homograft nor mechanical valves grow with the patient. An alternative operation is **aortopulmonary translocation (Ross procedure);** it involves removing the patient’s own pulmonary valve and using it to replace the abnormal aortic valve. A homograft is then placed in the pulmonary position. The potential advantage of this procedure is the possibility for growth of the translocated living “neoaortic” valve and the increased longevity of the homograft valve when placed in the lower pressure pulmonary circulation. The long-term success of this operation, especially in young children, is still being investigated. Transcatheter stent valves, which are tissue valves sewn into the inside

of an expandable metal stent, are currently in clinical trials in adults, mainly in those who are not good candidates for standard surgical replacement. These can be implanted in the cardiac catheterization laboratory using a percutaneous approach. Tissue-engineered replacement valves grown in the laboratory from the patient's own arterial endothelial cells are another prospect for long-term palliation and are currently under development in animal models.

PROGNOSIS

Neonates with critical aortic stenosis may have severe heart failure and deteriorate rapidly to a low-output shock state. Emergency surgery or balloon valvuloplasty is lifesaving, but the mortality risk is not trivial. Neonates who die of critical aortic stenosis frequently have significant left ventricular endocardial fibroelastosis. Those who survive may develop signs of left ventricular diastolic muscle dysfunction (restrictive cardiomyopathy) and require cardiac transplantation (see Chapter 443).

In older infants and children with mild to moderate aortic stenosis, the prognosis is reasonably good, although disease progression over a period of 5-10 yr is common. Patients with aortic valve gradients <40-50 mm Hg are considered to have mild disease; those with gradients of 40-70 mm Hg have moderate disease. These patients usually respond well to treatment (either surgery or valvuloplasty), although reoperations on the aortic valve are often required later in childhood or in adult life, and many patients eventually require valve replacement. In unoperated patients with severe obstruction, sudden death is a significant risk and often occurs during or immediately after exercise. Aortic stenosis is one of the causes of sudden cardiac death in the pediatric age group.

Patients with moderate to severe degrees of aortic stenosis should not participate in active competitive sports. In those with milder disease, sports participation is less severely restricted. The status of each patient should be reviewed at least annually and intervention advised if progression of signs or symptoms occurs. Prophylaxis against infective endocarditis is no longer recommended unless a prosthetic valve has been inserted.

Older children and adults with isolated bicuspid aortic valve are at increased risk for developing dilation of their ascending aorta, even in the absence of significant stenosis. This risk increases with age, and the rate of increase is greatest in those with the largest aortic roots. In children, this dilation is usually mild and remains stable over many years of observation, but in older patients the aorta can dilate substantially and progressively. Whether these patients have some undiagnosed form of connective tissue disorder remains to be determined (as this form of dilation is similar to that seen in Marfan syndrome). Patients with Turner syndrome and bicuspid aortic valve do have an increased risk of aortic dilation. Although dissection and rupture are described complications of severe aortic root dilation in adults, there is not yet sufficient data to determine these risks in children. Only isolated cases have been reported.

Bibliography is available at Expert Consult.

427.6 Coarctation of the Aorta

Daniel Bernstein

Constrictions of the aorta of varying degrees may occur at any point from the transverse arch to the iliac bifurcation, but 98% occur just below the origin of the left subclavian artery at the origin of the ductus arteriosus (juxtaductal coarctation). The anomaly occurs twice as often in males as in females. Coarctation of the aorta may be a feature of **Turner syndrome** (see Chapters 81 and 586.1) and is associated with a bicuspid aortic valve in more than 70% of patients. Mitral valve abnormalities (a supravalvular mitral ring or parachute mitral valve) and subaortic stenosis are potential associated lesions. When this group of left-sided obstructive lesions occurs together, they are referred to as the **Shone complex.**

PATHOPHYSIOLOGY

Coarctation of the aorta can occur as a discrete juxtaductal obstruction or as tubular hypoplasia of the transverse aorta starting at one of the head or neck vessels and extending to the ductal area (previously referred to as *preductal* or *infantile-type coarctation*; Fig. 427-7). Often, both components are present. It is postulated that coarctation may be initiated in fetal life by the presence of a cardiac abnormality that results in decreased blood flow anterograde through the aortic valve (e.g., bicuspid aortic valve, VSD). Alternatively, coarctation may be caused by abnormal extension of contractile ductal tissue into the aortic wall.

In patients with discrete juxtaductal coarctation, ascending aortic blood flows through the narrowed segment to reach the descending aorta, although left ventricular hypertension and hypertrophy result. In the 1st few days of life, the PDA may serve to widen the juxtaductal area of the aorta and provide temporary relief from the obstruction. Net left-to-right ductal shunting occurs in these acyanotic infants. With more-severe juxtaductal coarctation or in the presence of transverse arch hypoplasia, right ventricular blood is ejected through the ductus to supply the descending aorta. Perfusion of the lower part of the body is then dependent on right ventricular output (see Fig. 427-7). In this situation, the femoral pulses are palpable, and differential blood pressures may not be helpful in making the diagnosis. The ductal right-to-left shunting is manifested as differential cyanosis, with the upper extremities being pink and the lower extremities blue.

Such infants may have severe pulmonary hypertension and high pulmonary vascular resistance. Signs of heart failure are prominent. Occasionally, severely hypoplastic segments of the aortic isthmus may become completely atretic and result in an interrupted aortic arch, with the left subclavian artery arising either proximal or distal to the interruption. Coarctation associated with arch hypoplasia was once referred to as infantile type because its severity usually led to recognition of the

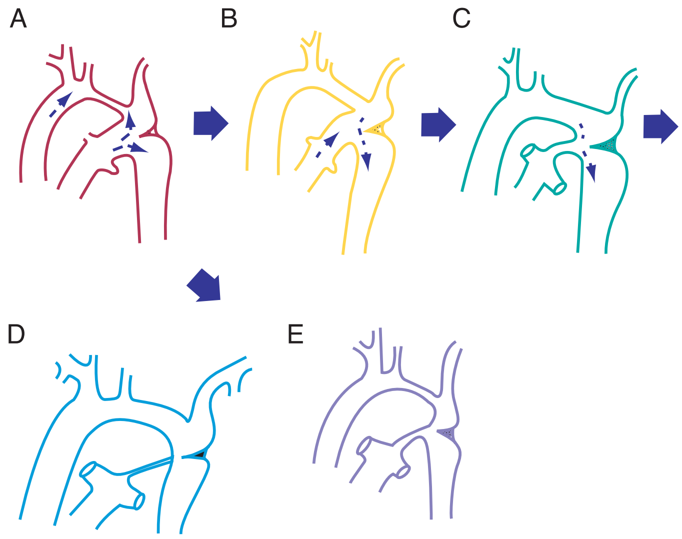

Figure 427-7 Metamorphosis of coarctation. **A,** Fetal prototype with no flow obstruction. **B,** Late gestation. The aortic ventricle increases its output and dilates the hypoplastic segment. Antegrade aortic flow bypasses the shelf via the ductal orifice. **C,** Neonate. Ductal constriction initiates the obstruction by removing the bypass and increasing antegrade arch flow. **D,** Mature juxtaductal stenosis. The bypass is completely obliterated, and intimal hypoplasia on the edge of the shelf is aggravating the stenosis. Collaterals develop. **E,** Persistence of the infantile-type fetal prototype. An intracardiac left-sided heart obstruction precludes an increase in antegrade aortic flow before or after birth. Both isthmus hypoplasia and a contraductal shelf are present. Lower body flow often depends on patency of the ductus. *(From Gersony WM: Coarctation of the aorta. In Adams FH, Emmanouilides GC, Riemenshneider T, editors:* Moss heart disease in infants, children, and adolescents, *ed 4, Baltimore, 1989, Williams & Wilkins.)*

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condition in early infancy. Adult type referred to isolated juxtaductal coarctation, which, if mild, was not usually recognized until later childhood. These terms have been replaced with the more accurate anatomic terms describing the location and severity of the defect.

Blood pressure is elevated in the vessels that arise proximal to the coarctation; blood pressure as well as pulse pressure is lower below the constriction. The hypertension is not caused by the mechanical obstruction alone, but also involves neurohumoral mechanisms. Unless operated on in infancy, coarctation of the aorta usually results in the development of an extensive collateral circulation, chiefly from branches of the subclavian, superior intercostal, and internal mammary arteries, to create channels for arterial blood to bypass the area of coarctation. The vessels contributing to the collateral circulation may become markedly enlarged and tortuous by early adulthood.

CLINICAL MANIFESTATIONS

Coarctation of the aorta recognized after infancy is not usually associated with significant symptoms. Some children or adolescents complain about weakness or pain (or both) in the legs after exercise, but in many instances, even patients with severe coarctation are asymptomatic. Older children are frequently brought to the cardiologist's attention when they are found to be hypertensive on routine physical examination.

The classic sign of coarctation of the aorta is a disparity in pulsation and blood pressure in the arms and legs. The femoral, popliteal, posterior tibial, and dorsalis pedis pulses are weak (or absent in up to 40% of patients), in contrast to the bounding pulses of the arms and carotid vessels. The radial and femoral pulses should always be palpated simultaneously for the presence of a radial-femoral delay. Normally, the femoral pulse occurs slightly before the radial pulse. A radial-femoral delay occurs when blood flow to the descending aorta is dependent on collaterals, in which case the femoral pulse is felt after the radial pulse. In normal persons (except neonates), systolic blood pressure in the legs obtained by the cuff method is 10-20 mm Hg higher than that in the arms. In coarctation of the aorta, blood pressure in the legs is lower than that in the arms; frequently, it is difficult to obtain. This differential in blood pressures is common in patients with coarctation who are older than 1 yr, approximately 90% of whom have systolic hypertension in an upper extremity greater than the 95th percentile for age. It is important to determine the blood pressure in each arm; a pressure higher in the right than the left arm suggests involvement of the left subclavian artery in the area of coarctation. Occasionally, the right subclavian may arise anomalously from below the area of coarctation and result in a left arm pressure that is higher than the right. With exercise, a more prominent rise in systemic blood pressure occurs, and the upper-to-lower extremity pressure gradient will increase.

The precordial impulse and heart sounds are usually normal; the presence of a systolic ejection click or thrill in the suprasternal notch suggests a bicuspid aortic valve (present in 70% of cases). A short systolic murmur is often heard along the left sternal border at the 3rd and 4th intercostal spaces. The murmur is well transmitted to the left infrascapular area and occasionally to the neck. Often, the typical murmur of mild aortic stenosis can be heard in the 3rd right intercostal space. Occasionally, more significant degrees of obstruction are noted across the aortic valve. The presence of a low-pitched mid-diastolic murmur at the apex suggests mitral valve stenosis. In older patients with well-developed collateral blood flow, systolic or continuous murmurs may be heard over the left and right sides of the chest laterally and posteriorly. In these patients, a palpable thrill can occasionally be appreciated in the intercostal spaces on the back.

Neonates or infants with more severe coarctation, usually including some degree of transverse arch hypoplasia, initially have signs of lower body hypoperfusion, acidosis, and severe heart failure. These signs may be delayed days or weeks until after closure of the ductus arteriosus. If detected before ductal closure, patients may exhibit differential cyanosis, best demonstrated by simultaneous oximetry of the upper and lower extremities. On physical examination, the heart is large, and a systolic murmur is heard along the left sternal border with a loud 2nd heart sound.

DIAGNOSIS

Findings on roentgenographic examination depend on the age of the patient and on the effects of hypertension and the collateral circulation. Cardiac enlargement and pulmonary congestion are noted in infants with severe coarctation. During childhood, the findings are not striking until after the 1st decade, when the heart tends to be mildly or moderately enlarged because of left ventricular prominence. The enlarged left subclavian artery commonly produces a prominent shadow in the left superior mediastinum. **Notching** of the **inferior border of the ribs** from pressure erosion by enlarged collateral vessels is common by late childhood. In most instances, the descending aorta has an area of poststenotic dilation.

The electrocardiogram is usually normal in young children but reveals evidence of left ventricular hypertrophy in older patients. Neonates and young infants display right or biventricular hypertrophy. The segment of coarctation can generally be visualized by 2-dimensional echocardiography (Fig. 427-8); associated anomalies of the mitral and aortic valve can also be demonstrated. The descending aorta is hypopulsatile. Color Doppler is useful for demonstrating the specific site of the obstruction. Pulsed and continuous wave Doppler studies determine the pressure gradient directly at the area of coarctation; in the presence of a PDA, however, the severity of the narrowing may be underestimated. CT and MRI are valuable noninvasive tools for evaluation of coarctation when the echocardiogram is equivocal. Cardiac catheterization with selective left ventriculography and aortography is useful in occasional patients with additional anomalies and as a means of visualizing collateral blood flow. In cases that are well defined by echocardiography, CT, or MRI, diagnostic catheterization is not usually required before surgery.

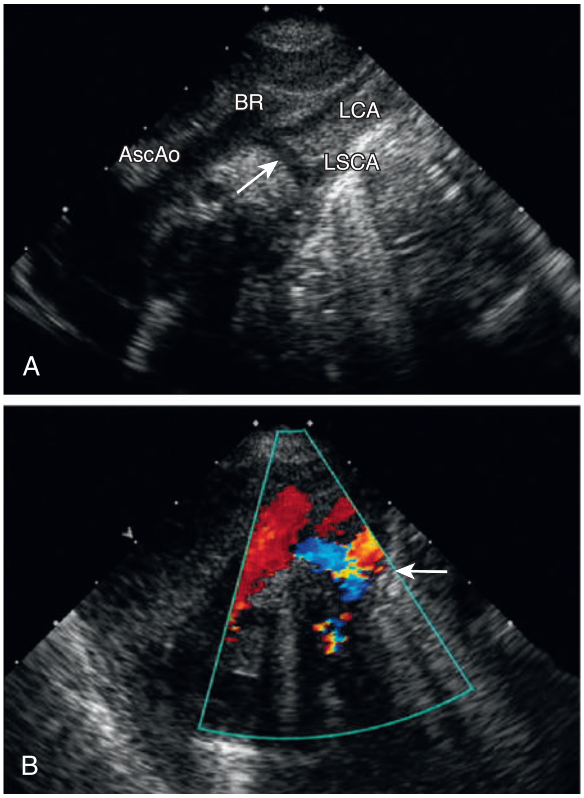

Figure 427-8 Echocardiogram demonstrating coarctation of the aorta with hypoplastic transverse arch. **A,** Suprasternal notch 2-dimensional echocardiogram showing marked narrowing beginning just distal to the brachiocephalic artery. **B,** Color Doppler demonstrates turbulent flow in the juxtaductal area *(arrow)*. AscAo, ascending aorta; BR, brachiocephalic artery; LCA, left carotid artery; LSCA, left subclavian artery.

TREATMENT

In neonates with severe coarctation of the aorta, closure of the ductus often results in hypoperfusion, acidosis, and rapid deterioration. These patients should be given an infusion of **prostaglandin E_1** to reopen the ductus and reestablish adequate lower extremity blood flow. Once a diagnosis has been confirmed and the patient stabilized, surgical repair should be performed. Older infants with heart failure but good perfusion should be managed with anticongestive measures to improve their clinical status before surgical intervention. There is usually no reason to delay surgical repair waiting for patient growth; successful repairs have been performed in small premature infants.

Older children with significant coarctation of the aorta should be treated relatively soon after diagnosis. Delay is unwarranted, especially after the 2nd decade of life, when the operation may be less successful because of decreased left ventricular function and degenerative changes in the aortic wall. Nevertheless, if cardiac reserve is sufficient, satisfactory repair is possible well into mid-adult life.

The procedure of choice for isolated juxtaductal coarctation of the aorta is controversial. Surgery remains the treatment of choice at most centers, and several surgical techniques are used. The area of coarctation can be excised and a primary re-anastomosis performed. Most often, the transverse aorta is splayed open and an "extended end-to-end" anastomosis performed to increase the effective cross-sectional area of the repair. The subclavian flap procedure, which involves division of the left subclavian artery and incorporation of it into the wall of the repaired coarctation has grown out of favor because of a higher degree of residual stenosis. Some centers favor a patch aortoplasty, in which the area of coarctation is enlarged with a roof of prosthetic material. The use of **primary angioplasty** for native coarctation remains controversial due to concern over subsequent recoarctation and aneurysm development. The use of **primary stent placement** is currently under evaluation in clinical trials and is most useful in conditions where surgical intervention may be associated with increased risk in patients with severe left ventricular dysfunction.

After surgery, a striking increase in the amplitude of pulsations in the lower extremities is noted. In the immediate postoperative course, **"rebound" hypertension** is common and requires medical management. This exaggerated acute hypertension gradually subsides and, in most patients, antihypertensive medications can be discontinued. Residual murmurs are common and may be the result of associated cardiac anomalies, of a residual flow disturbance across the repaired area, or of collateral blood flow. Rare operative problems include spinal cord injury from aortic cross-clamping if the collaterals are poorly developed, chylothorax, diaphragm injury, and laryngeal nerve injury. If a left subclavian flap approach is used, the radial pulse and blood pressure in the left arm are diminished or absent.

POSTCOARCTECTOMY SYNDROME

Postoperative **mesenteric arteritis** may be associated with acute hypertension and abdominal pain in the immediate postoperative period. The pain varies in severity and may occur in conjunction with anorexia, nausea, vomiting, leukocytosis, intestinal hemorrhage, bowel necrosis, and small bowel obstruction. Relief is usually obtained with antihypertensive drugs (nitroprusside, esmolol, captopril) and intestinal decompression; surgical exploration is rarely required for bowel obstruction or infarction.

PROGNOSIS

Although restenosis in older patients after coarctectomy is rare, a significant number of infants operated on before 1 yr of age require revision later in childhood. All patients should be monitored carefully for the development of recoarctation and an aortic anastomotic aneurysm. Should recoarctation occur, **balloon angioplasty** is the procedure of choice. In these patients, scar tissue from previous surgery may make reoperation more difficult yet makes balloon angioplasty safer because of the lower incidence of aneurysm formation. Relief of obstruction with this technique is usually excellent. **Intravascular stents** are commonly used, especially in adolescents and young adults, with generally excellent results.

Repair of coarctation in the 2nd decade of life or beyond may be associated with a higher incidence of premature cardiovascular disease, even in the absence of residual cardiac abnormalities. Early onset of adult chronic hypertension may occur, even in patients with adequately resected coarctation.

Abnormalities of the aortic valve are present in most patients. Bicuspid aortic valves are common but do not generally produce clinical signs unless the stenosis is significant. The association of a PDA and coarctation of the aorta is also common. VSDs and ASDs may be suspected by signs of a left-to-right shunt; they are exacerbated by the increased resistance to flow through the left side of the heart. Mitral valve abnormalities are also occasionally seen, as is subvalvular aortic stenosis.

Severe neurologic damage or even death may rarely occur from associated cerebrovascular disease. Subarachnoid or intracerebral hemorrhage may result from rupture of congenital aneurysms in the circle of Willis, rupture of other vessels with defective elastic and medial tissue, or rupture of normal vessels; these accidents are secondary to hypertension. Children with **PHACE syndrome** (posterior brain fossa anomalies, facial hemangiomas, arterial anomalies, cardiac anomalies and aortic coarctation, eye anomalies syndrome) may have strokes (see Table 422-2 in Chapter 422). Abnormalities of the subclavian arteries may include involvement of the left subclavian artery in the area of coarctation, stenosis of the orifice of the left subclavian artery, and anomalous origin of the right subclavian artery.

Untreated, the great majority of older patients with coarctation of the aorta would succumb between the ages of 20 and 40 yr; some live well into middle life without serious disability. The common serious complications are related to systemic hypertension, which may result in premature coronary artery disease, heart failure, hypertensive encephalopathy, or intracranial hemorrhage. Heart failure may be worsened by associated anomalies. Infective endocarditis or endarteritis is a significant complication in adults. Aneurysms of the descending aorta or the enlarged collateral vessels may develop.

Bibliography is available at Expert Consult.

427.7 Coarctation with Ventricular Septal Defect

Daniel Bernstein

Coarctation in the presence of a VSD results in both increased preload and afterload on the left ventricle, and patients with this combination of defects will be recognized either at birth or in the 1st mo of life and often have intractable cardiac failure. The magnitude of the left-to-right shunt through a VSD is dependent on the ratio of pulmonary to systemic vascular resistance. In the presence of coarctation, resistance to systemic outflow is enhanced by the obstruction, and the volume of the shunt is markedly increased. The clinical picture is that of a seriously ill infant with tachypnea, failure to thrive, and typical findings of heart failure. Often, the difference in blood pressure between the upper and lower extremities is not very marked because cardiac output may be low. Medical management should be used to stabilize the patient initially; however, it should not be used to delay corrective surgery inordinately.

In most cases, coarctation is the major anomaly causing the severe symptoms, and resection of the coarcted segment results in striking improvement. Many centers routinely repair both the VSD and coarctation at the same operation through a midline sternotomy using cardiopulmonary bypass. Some centers repair the coarctation through a left lateral thoracotomy and, at the same time, place a pulmonary artery band to decrease the ventricular-level shunt. This may be performed when a complicated VSD is present (multiple VSDs, apical muscular VSD), to avoid open heart surgery during infancy for these complex ventricular septal abnormalities.

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427.8 Coarctation with Other Cardiac Anomalies and Interrupted Aortic Arch

Daniel Bernstein

Coarctation often occurs in infancy in association with other major cardiovascular anomalies, including hypoplastic left heart, severe mitral or aortic valve disease, transposition of the great arteries, and variations of double-outlet or single ventricle. The clinical manifestations depend on the effects of the associated malformations, as well as on the coarctation itself.

Coarctation of the aorta associated with severe mitral and aortic valve disease may have to be treated within the context of the hypoplastic left heart syndrome (see Chapter 431.10), even if the left ventricular chamber is not severely hypoplastic. Such patients usually have a long segment of narrow transverse aortic arch in addition to an isolated coarctation at the site of the ductus arteriosus. Coarctation of the aorta with transposition of the great arteries or single ventricle may be repaired alone or in combination with other corrective or palliative measures.

Complete interruption of the aortic arch is the most severe form of coarctation and is usually associated with other intracardiac pathology. Interruption may occur at any level, although it is most commonly seen between the left subclavian artery and the insertion of the ductus arteriosus (type A), followed in frequency by those between the left subclavian and left carotid arteries (type B), or between the left carotid and brachiocephalic arteries (type C). In newborns with an interrupted aortic arch, the ductus arteriosus provides the sole source of blood flow to the descending aorta, and differential oxygen saturations between the right arm (normal saturation) and the legs (decreased saturation) is noted. When the ductus begins to close, severe congestive heart failure, lower extremity hypoperfusion, anuria, and shock usually develop. Patients with an interrupted aortic arch can be supported with prostaglandin E_1 to keep the ductus patent before surgical repair. As one of the conotruncal malformations, an interrupted aortic arch, especially type B, can be associated with DiGeorge syndrome (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia). Cytogenetic analysis using fluorescence in situ hybridization demonstrates deletion of a segment of chromosome 22q11, known as the DiGeorge critical region.

427.9 Congenital Mitral Stenosis

Daniel Bernstein

Congenital mitral stenosis is a rare anomaly that can be isolated or associated with other defects, the most common being subvalvar and valvar aortic stenosis and coarctation of the aorta **(Shone complex).** The mitral valve may be funnel-shaped, with thickened leaflets and chordae tendineae that are shortened and deformed. Other mitral valve anomalies associated with stenosis include parachute mitral valve, caused by a single papillary muscle, and double-orifice mitral valve.

If the stenosis is moderate to severe, symptoms usually appear within the 1st yr or 2 of life. These infants have failure to thrive and various degrees of dyspnea and pallor. In some patients, wheezing may be a dominant symptom, and a misdiagnosis of bronchiolitis or reactive airway disease may have been made. Heart enlargement as a result of dilation and hypertrophy of the right ventricle and left atrium is common. Most patients have rumbling apical diastolic murmurs, but the auscultatory findings may be relatively obscure. The 2nd heart sound is loud and split. An opening snap of the mitral valve may be present. The electrocardiogram reveals right ventricular hypertrophy and may show bifid or spiked P waves indicative of left atrial enlargement. Roentgenograms usually show left atrial and right ventricular enlargement and pulmonary congestion in a perihilar or venous pattern. The echocardiogram is characteristic and shows thickened mitral valve leaflets a significant reduction of the mitral valve orifice, abnormal papillary muscle structure (or a single papillary muscle), and an enlarged left atrium with a normal or small left ventricle. A double orifice may also be visualized. Doppler studies demonstrate a mean pressure gradient across the mitral orifice. Associated anomalies such as aortic stenosis and coarctation can be evaluated. Cardiac catheterization is usually performed to confirm the transmitral pressure gradient before surgery. An increase in right ventricular, pulmonary arterial, and pulmonary capillary wedge pressure can be noted. Angiocardiography shows delayed emptying of the left atrium and the small mitral orifice.

The results of surgical treatment depend on the anatomy of the valve, but if the mitral orifice is significantly hypoplastic, reduction of the gradient may be difficult. In some patients, a mitral valve prosthesis is required, and if the valve orifice is too small, the prosthesis may be placed in the supramitral position. However, whatever prosthesis is used, it must be replaced serially as the child grows. These patients must be managed by anticoagulation with warfarin, and complications of excessive and insufficient anticoagulation are fairly common in infancy. Transcatheter balloon valvuloplasty has been used as a palliative procedure with disappointing results, except in the situation of rheumatic mitral stenosis.

Bibliography is available at Expert Consult.

427.10 Pulmonary Venous Hypertension

Daniel Bernstein

A variety of lesions may give rise to chronic pulmonary venous hypertension, which when extreme may result in pulmonary arterial hypertension and right-sided heart failure. These lesions include congenital mitral stenosis, mitral insufficiency, total anomalous pulmonary venous return with obstruction, left atrial myxomas, cor triatriatum (stenosis of a common pulmonary vein), individual pulmonary vein stenosis, and supravalvular mitral rings. Early symptoms can be confused with chronic pulmonary disease such as asthma because of a lack of specific cardiac findings on physical examination. Subtle signs of pulmonary hypertension may be present. The electrocardiogram shows right ventricular hypertrophy with spiked P waves. Roentgenographic studies reveal cardiac enlargement and prominence of the pulmonary veins in the hilar region, the right ventricle and atrium, and the main pulmonary artery; the left atrium is normal in size or only slightly enlarged.

The echocardiogram may demonstrate left atrial myxoma, cor triatriatum, stenosis of one or more pulmonary veins, or a mitral valve abnormality, especially supravalvar mitral ring. Cardiac catheterization excludes the presence of a shunt and demonstrates pulmonary hypertension with elevated pulmonary arterial wedge pressure. Left atrial pressure is normal if the lesion is at the level of the pulmonary veins, but it is elevated if the lesion is at the level of the mitral valve. Selective pulmonary arteriography usually delineates the anatomic lesion. Cor triatriatum, left atrial myxoma, and supravalvular mitral rings can all be successfully managed surgically.

The **differential diagnosis** includes pulmonary venoocclusive disease, an idiopathic process that produces obstructive lesions in 1 or more pulmonary veins. The cause is uncertain and disease that begins in 1 vein can spread to others. Although it is usually encountered in patients after repair of obstructed total anomalous pulmonary venous return (see Chapter 431.7), it can occur in the absence of congenital heart disease. The patient initially presents with left-sided heart failure on the basis of congested lungs with apparent pulmonary edema. Dyspnea, fatigue, and pleural effusions are common. Left atrial pressure is normal, but pulmonary arterial wedge pressure is usually elevated. A normal wedge pressure may be encountered if collaterals have formed or the wedge recording is performed in an uninvolved segment. Angiographically, the pulmonary veins return normally to the left atrium, but 1 or more pulmonary veins are narrowed, either focally or diffusely.

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Studies using lung biopsy have demonstrated pulmonary venous and, occasionally, arterial involvement. Pulmonary veins and venules demonstrate fibrous narrowing or occlusion, and pulmonary artery thrombi may be present. Attempts at surgical repair, balloon dilation, and transcatheter stenting have not significantly improved the generally poor prognosis of these patients. Clinical trials of antiproliferative chemotherapy are currently in progress. Combined heart-lung transplantation (see Chapter 443.2) is often the only alternative therapeutic option.

Chapter **428**

Acyanotic Congenital Heart Disease: Regurgitant Lesions

428.1 Pulmonary Valvular Insufficiency and Congenital Absence of the Pulmonary Valve

Daniel Bernstein

Pulmonary valvular insufficiency most often accompanies other cardiovascular diseases or may be secondary to severe pulmonary hypertension. Incompetence of the valve is an expected result after surgery for right ventricular outflow tract obstruction, for example, pulmonary valvotomy in patients with valvular pulmonic stenosis or valvotomy with infundibular resection in patients with tetralogy of Fallot. Isolated congenital insufficiency of the pulmonary valve is rare. These patients are usually asymptomatic because the insufficiency is generally mild.

The prominent physical sign is a decrescendo diastolic murmur at the upper and midleft sternal border, which has a lower pitch than the murmur of aortic insufficiency because of the lower pressure involved. Radiographs of the chest show prominence of the main pulmonary artery and, if the insufficiency is severe, right ventricular enlargement. The electrocardiogram is normal or shows minimal right ventricular hypertrophy. Pulsed and color Doppler studies demonstrate retrograde flow from the pulmonary artery to the right ventricle during diastole. Cardiac magnetic resonance angiography is useful for quantifying both right ventricular volume and the regurgitant fraction. Isolated pulmonary valvular insufficiency is generally well tolerated and does not require surgical treatment. When pulmonary insufficiency is severe, especially if significant tricuspid insufficiency has begun to develop, replacement with a homograft valve may become necessary to preserve right ventricular function.

Congenital absence of the pulmonary valve is usually associated with a ventricular septal defect, often in the context of tetralogy of Fallot (see Chapter 430.1). In many of these neonates, the pulmonary arteries become widely dilated and compress the bronchi, with subsequent recurrent episodes of wheezing, pulmonary collapse, and pneumonitis. The presence and degree of cyanosis are variable. Florid pulmonary valvular incompetence may not be well tolerated, and death may occur from a combination of bronchial compression, hypoxemia, and heart failure. Correction involves plication of the massively dilated pulmonary arteries, closure of the ventricular septal defect, and placement of a homograft across the right ventricular outflow tract.

Bibliography is available at Expert Consult.

428.2 Congenital Mitral Insufficiency

Daniel Bernstein

Congenital mitral insufficiency is rare as an isolated lesion and is more often associated with other anomalies. It is most commonly encountered in combination with an atrioventricular septal defect, either an ostium primum defect, or a complete atrioventricular septal defect (see Chapter 426.5). Mitral insufficiency is also seen in patients with dilated cardiomyopathy (see Chapter 439.1) as their left ventricular function deteriorates, secondary to dilation of the valve ring. Mitral insufficiency may also be encountered in conjunction with coarctation of the aorta, ventricular septal defect, corrected transposition of the great vessels, anomalous origin of the left coronary artery from the pulmonary artery, or Marfan syndrome. In the absence of other congenital heart disease, endocarditis or rheumatic fever should be suspected in a patient with isolated severe mitral insufficiency (Table 428-1).

In isolated mitral insufficiency, the mitral valve annulus is usually dilated, the chordae tendineae are short and may insert anomalously, and the valve leaflets are deformed. When mitral insufficiency is severe enough to cause clinical symptoms, the left atrium enlarges as a result of the regurgitant flow, and the left ventricle becomes hypertrophied and dilated. Pulmonary venous pressure is increased, and the increased pressure ultimately results in pulmonary hypertension and right ventricular hypertrophy and dilation. Mild lesions produce no symptoms;

Table 428-1 Causes and Mechanisms of Mitral Regurgitation

	Organic			Functional
	TYPE I*	TYPE II†	TYPE IIIA‡	TYPE I*/TYPE IIIB‡
Nonischemic	Endocarditis (perforation); degenerative (annular calcification); congenital (cleft leaflet)	Degenerative (billowing/flail leaflets); endocarditis (ruptured chordae); traumatic (ruptured chord/PM); rheumatic (acute RF)	Rheumatic (chronic RF); iatrogenic (radiation/drug); inflammatory (lupus/anticardiolipin), eosinophilic (endocardial disease, endomyocardial fibrosis)	Cardiomyopathy; myocarditis; left-ventricular dysfunction (any cause)

MR, mitral regurgitation; PM, papillary muscle; RF, rheumatic fever.
*Mechanism involves normal leaflet movement.
†Mechanism involves excessive valve movement.
‡Restricted valve movement, IIIa in diastole, IIIb in systole.
Modified from Sarano ME, Akins CW, Vahanian A: Mitral regurgitation, Lancet 373:1382–1394, 2009, p. 1383, Table 1.

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the only abnormal sign is the apical holosystolic murmur of mitral regurgitation. Severe regurgitation results in symptoms that can appear at any age, including poor physical development, frequent respiratory infections, fatigue on exertion, and episodes of pulmonary edema or congestive heart failure. Often, a diagnosis of reactive airway disease will have been made because of the similarity in pulmonary symptoms, including wheezing, which may be a dominant finding in infants and young children.

The typical murmur of mitral insufficiency is a high-pitched, apical holosystolic murmur. If the insufficiency is moderate to severe, it is usually associated with a low-pitched, apical mid-diastolic rumbling murmur indicative of increased diastolic flow across the mitral valve. The pulmonary component of the 2nd heart sound will be accentuated in the presence of pulmonary hypertension. The electrocardiogram usually shows bifid P waves consistent with left atrial enlargement, signs of left ventricular hypertrophy, and sometimes signs of right ventricular hypertrophy. Radiographic examination shows enlargement of the left atrium, which at times is massive. The left ventricle is prominent, and pulmonary vascularity is normal or prominent. The echocardiogram demonstrates the enlarged left atrium and ventricle. Color Doppler demonstrates the extent of the insufficiency, and pulsed Doppler of the pulmonary veins detects retrograde flow when mitral insufficiency is severe. Cardiac catheterization shows elevated left atrial pressure. Pulmonary artery hypertension of varying severity may be present. Selective left ventriculography reveals the severity of mitral regurgitation.

Mitral valvuloplasty can result in striking improvement in symptoms and heart size, but in some patients, installation of a prosthetic mechanical mitral valve may be necessary. Before surgery, associated anomalies must be identified.

428.3 Mitral Valve Prolapse

Daniel Bernstein

Mitral valve prolapse results from an abnormal mitral valve mechanism that causes billowing of one or both mitral leaflets, especially the posterior cusp, into the left atrium toward the end of systole. The abnormality is predominantly congenital but may not be recognized until adolescence or adulthood. Mitral valve prolapse is usually sporadic, is more common in girls, and may be inherited as an autosomal dominant trait with variable expression. It is common in patients with Marfan syndrome, straight back syndrome, pectus excavatum, scoliosis, Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum. The dominant abnormal signs are auscultatory, although occasional patients may have chest pain or palpitations. The apical murmur is late systolic and may be preceded by a click, but these signs may vary in the same patient and, at times, only the click is audible. In the standing or sitting position, the click may occur earlier in systole, and the murmur may be more prominent in late systole. Arrhythmias may occur and are primarily unifocal or multifocal premature ventricular contractions.

The electrocardiogram is usually normal but may show biphasic T waves, especially in leads II, III, aVF, and V_6; the T-wave abnormalities may vary at different times in the same patient. The chest roentgenogram is normal. The echocardiogram shows a characteristic posterior movement of the posterior mitral leaflet during mid- or late systole or demonstrates pansystolic prolapse of both the anterior and posterior mitral leaflets. These echocardiographic findings must be interpreted cautiously because the appearance of minimal mitral prolapse may be a normal variant. Prolapse is more precisely defined by single or bileaflet prolapse of >2 mm beyond the long axis annular plane with or without leaflet thickening. Prolapse with valve thickening >5 mm is "classic"; a lesser degree is "nonclassic." Two-dimensional real-time echocardiography shows that both the free edge and the body of the mitral leaflets move posteriorly in systole toward the left atrium. Doppler can assess the presence and severity of mitral regurgitation.

This lesion is not progressive in childhood, and specific therapy is not indicated. Antibiotic prophylaxis is no longer recommended during surgery and dental procedures (see Chapter 437).

Adults (men more often than women) with mitral valve prolapse are at increased risk for cardiovascular complications (sudden death, arrhythmia, cerebrovascular accidents, progressive valve dilation, heart failure, and endocarditis) in the presence of **thickened** (>5 mm) and **redundant** mitral valve leaflets. Risk factors for morbidity also include poor left ventricular function, moderate to severe mitral regurgitation, and left atrial enlargement.

Often, confusion exists concerning the diagnosis of mitral valve prolapse. The high frequency of mild prolapse on the echocardiogram in the absence of clinical findings suggests that, in these cases, true mitral valve prolapse syndrome is not present. These patients and their parents should be reassured of this fact, and no special recommendations should be made regarding management or frequent laboratory studies.

Bibliography is available at Expert Consult.

428.4 Tricuspid Regurgitation

Daniel Bernstein

Isolated tricuspid regurgitation is generally associated with Ebstein anomaly of the tricuspid valve. Ebstein anomaly may occur either without cyanosis or with varying degrees of cyanosis, depending on the severity of the tricuspid regurgitation and the presence of an atrial-level communication (patent foramen ovale or atrial septal defect). Older children tend to have the acyanotic form, whereas if detected in the newborn period, Ebstein anomaly is usually associated with severe cyanosis (see Chapter 430.7).

Tricuspid regurgitation often accompanies right ventricular dysfunction. When the right ventricle becomes dilated because of volume overload or intrinsic myocardial disease, or both, the tricuspid annulus also enlarges, with resultant valve insufficiency. This form of regurgitation may improve if the cause of the right ventricular dilation is corrected, or it may require surgical plication of the valve annulus. Tricuspid regurgitation is also encountered in newborns with perinatal asphyxia. The cause may be related to an increased susceptibility of the papillary muscles to ischemic damage and subsequent transient papillary muscle dysfunction. Finally, tricuspid regurgitation is seen in up to 30% of children after heart transplantation, which can be a risk factor for graft dysfunction but is also seen as a consequence of valve injury as a result of endomyocardial biopsy.

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Chapter **429**

Cyanotic Congenital Heart Disease: Evaluation of the Critically Ill Neonate with Cyanosis and Respiratory Distress

Daniel Bernstein

See also Chapter 101.

A severely ill neonate with cardiorespiratory distress and cyanosis is a diagnostic challenge. The clinician must perform a rapid evaluation to determine whether congenital heart disease is a cause so that potentially lifesaving measures can be instituted. The differential diagnosis of neonatal cyanosis is presented in Table 101-1 in Chapter 101.

CARDIAC DISEASE LEADING TO CYANOSIS

Congenital heart disease produces cyanosis when obstruction to right ventricular outflow causes intracardiac right-to-left shunting or when complex anatomic defects, many unassociated with pulmonary stenosis, cause an admixture of pulmonary and systemic venous return in the heart. Cyanosis from pulmonary edema may also develop in patients with heart failure caused by left-to-right shunts, although the degree is usually less severe. Cyanosis may be caused by persistence of fetal pathways, for example, right-to-left shunting across the foramen ovale and ductus arteriosus in the presence of pulmonary outflow tract obstruction or persistent pulmonary hypertension of the newborn (PPHN) (see Chapter 101.7).

DIFFERENTIAL DIAGNOSIS

The **hyperoxia test** is 1 method of distinguishing cyanotic congenital heart disease from pulmonary disease. Neonates with cyanotic congenital heart disease are usually not able to significantly raise their arterial Pao_2 during administration of 100% oxygen. If the Pao_2 rises above 150 mm Hg during 100% oxygen administration, an intracardiac right-to-left shunt can usually be excluded, although this is not 100% confirmative, as some patients with cyanotic congenital heart lesions may be able to increase their Pao_2 to >150 mm Hg because of favorable intracardiac streaming patterns. In patients with pulmonary disease, Pao_2 generally increases significantly with 100% oxygen as ventilation-perfusion inequalities are overcome. In infants with cyanosis from a central nervous system disorder, the Pao_2 usually normalizes completely during artificial ventilation. Hypoxia in many heart lesions is profound and constant, whereas in respiratory disorders and in PPHN, arterial oxygen tension often varies with time or changes in ventilator management. Hyperventilation may improve the hypoxia in neonates with PPHN and only occasionally in those with cyanotic congenital heart disease.

Although a significant heart murmur usually suggests a cardiac basis for the cyanosis, several of the more severe cardiac defects (transposition of the great vessels) may not initially be associated with a murmur.

The chest roentgenogram may be helpful in the differentiation of pulmonary and cardiac disease; in the latter, it indicates whether pulmonary blood flow is increased, normal, or decreased.

Two-dimensional echocardiography is the definitive noninvasive test to determine the presence of congenital heart disease. Cardiac catheterization is less often used for diagnostic purposes, and is usually performed to examine structures that are sometime less well visualized by echocardiography, such as distal branch pulmonary arteries or aortopulmonary collateral arteries in patients with tetralogy of Fallot with pulmonary atresia (see Chapter 430.2), coronary arteries and right ventricular sinusoids in patients with pulmonary atresia and intact ventricular septum (see Chapter 430.3). If echocardiography is not immediately available, the clinician caring for a newborn with possible cyanotic heart disease should not hesitate to start a prostaglandin infusion (for a possible ductal-dependent lesion). Because of the risk of hypoventilation associated with prostaglandins, a practitioner skilled in neonatal endotracheal intubation must be available.

Chapter 430

Cyanotic Congenital Heart Lesions: Lesions Associated with Decreased Pulmonary Blood Flow

430.1 Tetralogy of Fallot

Daniel Bernstein

Tetralogy of Fallot is one of the conotruncal family of heart lesions in which the primary defect is an anterior deviation of the infundibular septum (the muscular septum that separates the aortic and pulmonary outflows). The consequences of this deviation are the 4 components: (1) obstruction to right ventricular outflow (pulmonary stenosis), (2) a malalignment type of ventricular septal defect (VSD), (3) dextroposition of the aorta so that it overrides the ventricular septum, and (4) right ventricular hypertrophy (Fig. 430-1). Obstruction to pulmonary arterial blood flow is usually at both the right ventricular infundibulum (subpulmonic area) and the pulmonary valve. The main pulmonary artery may be small, and various degrees of branch pulmonary artery stenosis may be present. Complete obstruction of right ventricular outflow (tetralogy with pulmonary atresia) is classified as an extreme form of tetralogy of Fallot (see Chapter 430.2). The degree of pulmonary outflow obstruction determines the degree of the patient's cyanosis and the age of first presentation.

PATHOPHYSIOLOGY

The pulmonary valve annulus may range from being nearly normal in size to being severely hypoplastic. The valve itself is often bicuspid or unicuspid and, occasionally, is the only site of stenosis. More commonly, the subpulmonic or infundibular muscle, known as the *crista supraventricularis,* is hypertrophic, which contributes to the subvalvar stenosis and results in an infundibular chamber of variable size and contour. When the right ventricular outflow tract is completely

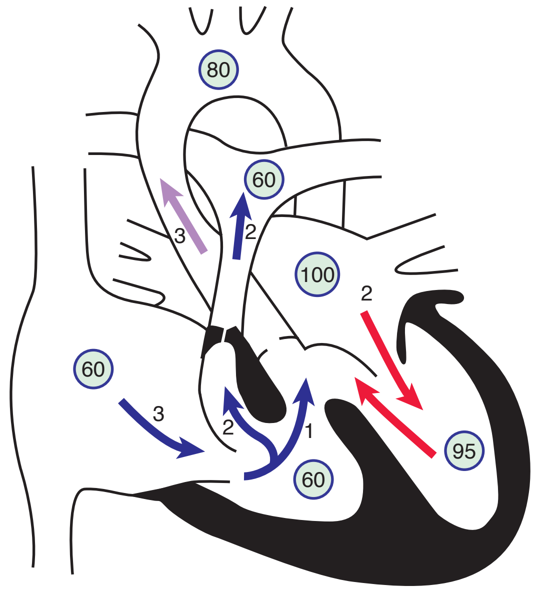

Figure 430-1 Physiology of the tetralogy of Fallot. *Circled numbers* represent oxygen saturation values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). Atrial (mixed venous) oxygen saturation is decreased because of the systemic hypoxemia. A volume of 3 L/min/m^2 of desaturated blood enters the right atrium and traverses the tricuspid valve. Two liters flows through the right ventricular outflow tract into the lungs, whereas 1 L shunts right to left through the ventricular septal defect (VSD) into the ascending aorta. Thus, pulmonary blood flow is two-thirds normal (Qp : Qs [pulmonary-to-systemic blood flow ratio] of 0.7 : 1). Blood returning to the left atrium is fully saturated. Only 2 L of blood flows across the mitral valve. Oxygen saturation in the left ventricle may be slightly decreased because of right-to-left shunting across the VSD. Two liters of saturated left ventricular blood mixing with 1 L of desaturated right ventricular blood is ejected into the ascending aorta. Aortic saturation is decreased, and cardiac output is normal.

obstructed **(pulmonary atresia),** the anatomy of the branch pulmonary arteries is extremely variable. A main pulmonary artery segment may be in continuity with right ventricular outflow, separated by a fibrous but imperforate pulmonary valve; the main pulmonary artery may be moderately or severely hypoplastic but still supply part or all of the pulmonary bed; or the entire main pulmonary artery segment may be absent. Occasionally, the branch pulmonary arteries may be discontinuous. Pulmonary blood flow may be supplied by a patent ductus arteriosus (PDA) or by multiple **major aortopulmonary collateral arteries (MAPCAs)** arising from the ascending and/or descending aorta and supplying various lung segments.

The VSD is usually nonrestrictive and large, is located just below the aortic valve, and is related to the posterior and right aortic cusps. Rarely, the VSD may be in the inlet portion of the ventricular septum (atrioventricular septal defect). The normal fibrous continuity of the mitral and aortic valves is usually maintained, and if not (because of the presence of a subaortic muscular conus) the classification is usually that of double-outlet right ventricle (see Chapter 430.5). The aortic arch is right sided in 20% of cases, and the aortic root is usually large and overrides the VSD to varying degrees. When the aorta overrides the VSD by more than 50% and if there is a subaortic conus, this defect is classified as a form of double-outlet right ventricle; however, the circulatory dynamics are the same as that of tetralogy of Fallot.

Systemic venous return to the right atrium and right ventricle is normal. When the right ventricle contracts in the presence of marked pulmonary stenosis, blood is shunted across the VSD into the aorta. Persistent arterial desaturation and cyanosis result, the degree dependent on the severity of the pulmonary obstruction. Pulmonary blood flow, when severely restricted by the obstruction to right ventricular outflow, may be supplemented by a PDA. Peak systolic and diastolic pressures in each ventricle are similar and at systemic level. A large pressure gradient occurs across the obstructed right ventricular outflow tract, and pulmonary arterial pressure is either normal or lower than normal. The degree of right ventricular outflow obstruction determines the timing of the onset of symptoms, the severity of cyanosis, and the degree of right ventricular hypertrophy. When obstruction to right ventricular outflow is mild to moderate and a balanced shunt is present across the VSD, the patient may not be visibly cyanotic (**acyanotic** or **"pink"** tetralogy of Fallot). When obstruction is severe, cyanosis will be present from birth and worsen when the ductus arteriosus begins to close.

CLINICAL MANIFESTATIONS

Infants with mild degrees of right ventricular outflow obstruction may initially be seen with heart failure caused by a ventricular-level left-to-right shunt. Often, cyanosis is not present at birth; but with increasing hypertrophy of the right ventricular infundibulum as the patient grows, cyanosis occurs later in the 1st yr of life. In infants with severe degrees of right ventricular outflow obstruction, neonatal cyanosis is noted immediately. In these infants, pulmonary blood flow may be partially or nearly totally dependent on flow through the ductus arteriosus. When the ductus begins to close in the 1st few hr or days of life, severe cyanosis and circulatory collapse may occur. Older children with long-standing cyanosis who have not undergone surgery may have dusky blue skin, gray sclerae with engorged blood vessels, and marked clubbing of the fingers and toes. Chapter 434 describes the extracardiac manifestations of long-standing cyanotic congenital heart disease.

In older children with unrepaired tetralogy, dyspnea occurs on exertion. They may play actively for a short time and then sit or lie down. Older children may be able to walk a block or so before stopping to rest. Characteristically, children assume a squatting position for the relief of dyspnea caused by physical effort; the child is usually able to resume physical activity after a few minutes of squatting. These findings occur most often in patients with significant cyanosis at rest.

Paroxysmal hypercyanotic attacks (hypoxic, **"blue,"** or **"tet" spells**) are a particular problem during the 1st 2 yr of life. The infant becomes hyperpneic and restless, cyanosis increases, gasping respirations ensue, and syncope may follow. The spells occur most frequently in the morning on initially awakening or after episodes of vigorous crying. Temporary disappearance or a decrease in intensity of the systolic murmur is usual as flow across the right ventricular outflow tract diminishes. The spells may last from a few minutes to a few hours. Short episodes are followed by generalized weakness and sleep. Severe spells may progress to unconsciousness and, occasionally, to convulsions or hemiparesis. The onset is usually spontaneous and unpredictable. Spells are associated with reduction of an already compromised pulmonary blood flow, which, when prolonged, results in severe systemic hypoxia and metabolic acidosis. Infants who are only mildly cyanotic at rest are often more prone to the development of hypoxic spells because they have not acquired the homeostatic mechanisms to tolerate rapid lowering of arterial oxygen saturation, such as polycythemia.

Depending on the frequency and severity of hypercyanotic attacks, 1 or more of the following procedures should be instituted in sequence: (1) placement of the infant on the abdomen in the knee-chest position while making certain that the infant's clothing is not constrictive, (2) administration of oxygen (although increasing inspired oxygen will not reverse cyanosis caused by intracardiac shunting), and (3) injection of morphine subcutaneously in a dose not in excess of 0.2 mg/kg. Calming and holding the infant in a knee-chest position may abort progression of an early spell. Premature attempts to obtain blood samples may cause further agitation and be counterproductive.

Because metabolic acidosis develops when arterial Po_2 is <40 mm Hg, rapid correction (within several minutes) with intravenous administration of sodium bicarbonate is necessary if the spell is unusually severe and the child shows a lack of response to the foregoing therapy. Recovery from the spell is usually rapid once the pH has returned to normal. Repeated blood pH measurements may be necessary because rapid

recurrence of acidosis may ensue. For spells that are resistant to this therapy, intubation and sedation are often sufficient to break the spell. Drugs that increase systemic vascular resistance, such as intravenous phenylephrine, can improve right ventricular outflow, decrease the right-to-left shunt, and improve the symptoms. β-Adrenergic blockade by the intravenous administration of propranolol (0.1 mg/kg given slowly to a maximum of 0.2 mg/kg) has also been used. Growth and development may be delayed in patients with severe untreated tetralogy of Fallot, particularly when their oxygen saturation is chronically <70%. Puberty may also be delayed in patients who have not undergone surgery.

The pulse is usually normal, as are venous and arterial pressures. In older infants and children, the left anterior hemithorax may bulge anteriorly because of long-standing right ventricular hypertrophy. A substernal right ventricular impulse can usually be detected. A systolic thrill may be felt along the left sternal border in the 3rd and 4th parasternal spaces. The systolic murmur is usually loud and harsh; it may be transmitted widely, especially to the lungs, but is most intense at the left sternal border. The murmur is generally ejection in quality at the upper sternal border, but it may sound more holosystolic toward the lower sternal border. It may be preceded by a click. The murmur is caused by turbulence through the right ventricular outflow tract. It tends to become louder, longer, and harsher as the severity of pulmonary stenosis increases from mild to moderate; however, it can actually become less prominent with severe obstruction, especially during a hypercyanotic spell due to shunting of blood away from the right ventricular outflow through the aortic valve. Either the 2nd heart sound is single, or the pulmonic component is soft. Infrequently, a continuous murmur may be audible, especially if prominent collaterals are present.

DIAGNOSIS

The typical radiologic configuration as seen in the anteroposterior view consists of a narrow base, concavity of the left heart border in the area usually occupied by the pulmonary artery, and normal overall heart size. The hypertrophied right ventricle causes the rounded apical shadow to be uptilted so that it is situated higher above the diaphragm than normal and pointing horizontally to the left chest wall. The cardiac silhouette has been likened to that of a boot ("coeur en sabot") (Fig. 430-2). The hilar areas and lung fields are relatively clear because of diminished pulmonary blood flow or the small size of the pulmonary arteries, or both. The aorta is usually large, and in approximately 20% of patients it arches to the right, which results in an indentation of the leftward-positioned air-filled tracheobronchial shadow in the anteroposterior view.

The electrocardiogram demonstrates right axis deviation and evidence of right ventricular hypertrophy. A dominant R wave appears in the right precordial chest leads (Rs, R, qR, qRs) or an RSR′ pattern. In some cases, the only sign of right ventricular hypertrophy may initially be a positive T wave in leads V_3R and V_1. The P wave is tall and peaked suggesting right atrial enlargement (see Fig. 423-6 in Chapter 423).

Two-dimensional echocardiography establishes the diagnosis (Fig. 430-3) and provides information about the extent of aortic override of the septum, the location and degree of the right ventricular outflow tract obstruction, the size of the pulmonary valve annulus and main and proximal branch pulmonary arteries, and the side of the aortic arch. The echocardiogram is also useful in determining whether a PDA is supplying a portion of the pulmonary blood flow. In a patient without pulmonary atresia, echocardiography usually obviates the need for catheterization before surgical repair. However, in patients with pulmonary atresia, catheterization is necessary to image the source of blood supply to and size of each lung segment.

Cardiac catheterization demonstrates a systolic pressure in the right ventricle equal to the systemic pressure, since the right ventricle is connected directly to the overriding aorta. If the pulmonary artery is entered, the pressure is markedly decreased, although crossing the right ventricular outflow tract, especially in severe cases, may precipitate a tet spell. Pulmonary arterial pressure is usually lower than normal, in the range of 5-10 mm Hg. The level of arterial oxygen saturation depends on the magnitude of the right-to-left shunt; in "pink tets," the systemic oxygen saturation may be normal, whereas in a moderately cyanotic patient at rest, it is usually 75-85%.

Selective right ventriculography will demonstrate all of the anatomical features. Contrast medium outlines the heavily trabeculated right ventricle. The infundibular stenosis varies in length, width, contour, and distensibility (Fig. 430-4). The pulmonary valve is usually thickened, and the annulus may be small. In patients with pulmonary atresia and VSD, echocardiography alone is not adequate to assess the anatomy of the pulmonary arteries and MAPCAs. Cardiac CT is extremely helpful, and cardiac catheterization with injection into each arterial collateral is indicated. Complete and accurate information regarding the size and peripheral distribution of the main pulmonary arteries and any collateral vessels (MAPCAs) is important when evaluating these children as surgical candidates.

Aortography or coronary arteriography outlines the course of the coronary arteries. In 5-10% of patients with the tetralogy of Fallot, coronary artery abnormalities may be present, most commonly an aberrant coronary artery crossing over the right ventricular outflow

Figure 430-2 Chest x-ray of an 8 yr old boy with the tetralogy of Fallot. Note the normal heart size, some elevation of the cardiac apex, concavity in the region of the main pulmonary artery, right-sided aortic arch, and diminished pulmonary vascularity.

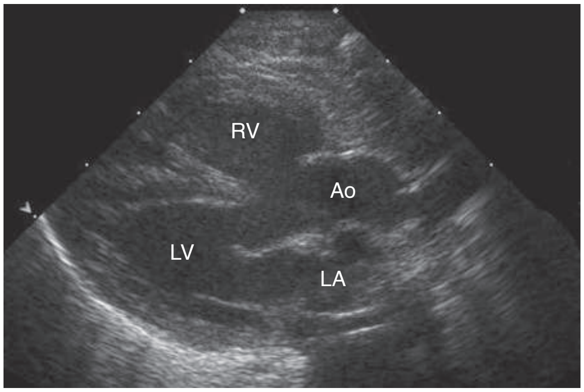

Figure 430-3 Echocardiogram in a patient with the tetralogy of Fallot. This parasternal long-axis 2-dimensional view demonstrates anterior displacement of the outflow ventricular septum that resulted in stenosis of the subpulmonic right ventricular outflow tract, overriding of the aorta, and an associated ventricular septal defect. Ao, overriding aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

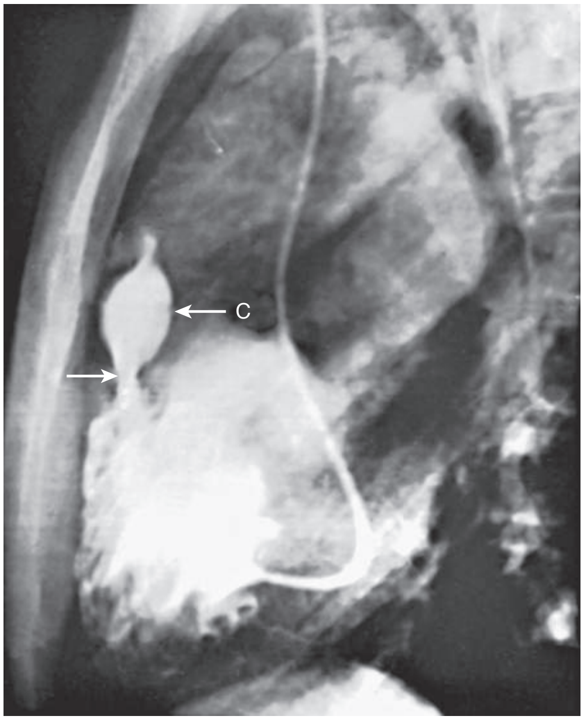

Figure 430-4 Lateral view of a selective right ventriculogram in a patient with the tetralogy of Fallot. The *arrow* points to an infundibular stenosis that is below the infundibular chamber *(C)*. The narrowed pulmonary valve orifice is seen at the distal end of the infundibular chamber.

tract; this artery must not be cut during surgical repair. Verification of normal coronary arteries is important when considering surgery in young infants who may need a patch across the pulmonary valve annulus. Echocardiography can usually delineate the coronary artery anatomy; angiography is reserved for cases in which questions remain.

COMPLICATIONS

Before the age of corrective surgery, patients with tetralogy of Fallot were susceptible to several serious complications. For this reason, most children undergo complete repair (or in some cases palliation) in the 1st few mo of life; consequently, these complications are now rare. **Cerebral thromboses,** usually occurring in the cerebral veins or dural sinuses and occasionally in the cerebral arteries, are a sequelae of extreme polycythemia and dehydration. Thromboses occur most often in patients younger than 2 yr. These patients may have iron-deficiency anemia, frequently with hemoglobin and hematocrit levels in the normal range (but too low for cyanotic heart disease). Therapy consists of adequate hydration and supportive measures. Phlebotomy and volume replacement with albumin or saline are indicated in extremely **polycythemic** patients who are symptomatic.

Brain abscess is less common than cerebral vascular events and extremely rare today. Patients with a brain abscess are usually older than 2 yr. The onset of the illness is often insidious and consists of low-grade fever or a gradual change in behavior, or both. Some patients have an acute onset of symptoms that may develop after a recent history of headache, nausea, and vomiting. Seizures may occur; localized neurologic signs depend on the site and size of the abscess and the presence of increased intracranial pressure. CT or MRI confirms the diagnosis. Antibiotic therapy may help keep the infection localized, but surgical drainage of the abscess is usually necessary (see Chapter 604).

Bacterial endocarditis may occur in the right ventricular infundibulum or on the pulmonic, aortic, or, rarely, tricuspid valves. Endocarditis may complicate palliative shunts or, in patients with corrective surgery, any residual pulmonic stenosis or VSD. Heart failure is not a usual feature in patients with tetralogy of Fallot, with the exception of some young infants with "pink" or acyanotic tetralogy of Fallot. As the degree of pulmonary obstruction worsens with age, the symptoms of heart failure resolve and eventually the patient experiences cyanosis often by 6-12 mo of age. These patients are at increased risk for hypercyanotic spells at this time.

ASSOCIATED ANOMALIES

A PDA may be present, and defects in the atrial septum are occasionally seen. A right aortic arch occurs in ≈20% of patients, and other anomalies of the pulmonary arteries and aortic arch may also be seen. Persistence of a left superior vena cava draining into the coronary sinus is common but not a concern. Multiple VSDs are occasionally present and must be diagnosed before corrective surgery. Coronary artery anomalies are present in 5-10% and can complicate surgical repair. Tetralogy of Fallot may also occur with an atrioventricular septal defect, often associated with Down syndrome.

Congenital absence of the pulmonary valve produces a distinct syndrome that is usually marked by signs of upper airway obstruction (see Chapter 428.1). Cyanosis may be absent, mild, or moderate; the heart is large and hyperdynamic; and a loud to-and-fro murmur is present. Marked aneurysmal dilation of the main and branch pulmonary arteries results in compression of the bronchi and then produces stridulous or wheezing respirations and recurrent pneumonia. If the airway obstruction is severe, reconstruction of the trachea at the time of corrective cardiac surgery may be required to alleviate the symptoms.

Absence of a branch pulmonary artery, most often the left, should be suspected if the roentgenographic appearance of the pulmonary vasculature differs on the 2 sides; absence of a pulmonary artery is often associated with hypoplasia of the affected lung. It is important to recognize the absence of a pulmonary artery because occlusion of the remaining pulmonary artery during surgery seriously compromises the already reduced pulmonary blood flow.

As 1 of the conotruncal malformations, tetralogy of Fallot can be associated with **DiGeorge syndrome** or **Shprintzen velocardiofacial syndrome**, also known by the acronym **CATCH 22** (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia). Cytogenetic analysis using fluorescence in situ hybridization demonstrates deletions of a large segment of chromosome 22q11.2 known as the *DiGeorge critical region.* Deletion or mutation of the gene encoding the transcription factor *Tbx1* has been implicated as a possible cause of DiGeorge syndrome, although several other genes have been identified as possible candidates or modifier genes.

TREATMENT

Treatment of tetralogy of Fallot depends on the severity of the right ventricular outflow tract obstruction. Infants with severe tetralogy require urgent medical treatment and surgical intervention in the neonatal period. Therapy is aimed at providing an immediate increase in pulmonary blood flow to prevent the sequelae of severe hypoxia. The infant should be transported to a medical center adequately equipped to evaluate and treat neonates with congenital heart disease under optimal conditions. Prolonged, severe hypoxia may lead to shock, respiratory failure, and intractable acidosis and will significantly reduce the chance of survival, even when surgically amenable lesions are present. It is critical that normal body temperature be maintained during the transfer because cold increases oxygen consumption, which places additional stress on a cyanotic infant, whose oxygen delivery is already limited. Blood glucose levels should be monitored because hypoglycemia is more likely to develop in infants with cyanotic heart disease.

Neonates with marked right ventricular outflow tract obstruction may deteriorate rapidly because, as the ductus arteriosus begins to close, pulmonary blood flow is further compromised. The intravenous administration of prostaglandin E_1 (0.01-0.20 μg/kg/min), a potent and specific relaxant of ductal smooth muscle, causes dilation of the ductus arteriosus and usually provides adequate pulmonary blood flow

until a surgical procedure can be performed. This agent should be administered intravenously as soon as cyanotic congenital heart disease is clinically suspected and continued through the preoperative period and during cardiac catheterization. Because prostaglandin can cause apnea, an individual skilled in neonatal intubation should be readily available.

Infants with less-severe right ventricular outflow tract obstruction who are stable and awaiting surgical intervention require careful observation. Acyanotic patients can fairly quickly progress to having cyanotic episodes. Prevention or prompt treatment of dehydration is important to avoid hemoconcentration and possible thrombotic episodes. Oral propranolol (0.5-1 mg/kg every 6 hr) had been used in the past to decrease the frequency and severity of hypercyanotic spells, but with the excellent surgical results available today, surgical treatment is now indicated as soon as spells begin.

Infants with symptoms and severe cyanosis in the 1st mo of life usually have marked obstruction of the right ventricular outflow tract. Two options are available in these infants. The first is corrective open heart surgery performed in early infancy and even in the newborn period in critically ill infants. This approach has widespread acceptance today with excellent short- and long-term results and has supplanted palliative shunts (see later) for most cases. Early total repair carries the theoretical advantage that early physiologic correction allows for improved growth of the branch pulmonary arteries. In infants with less-severe cyanosis who can be maintained with good growth and absence of hypercyanotic spells, primary repair is performed electively at between 4 and 6 mo of age.

Corrective surgical therapy consists of relief of the right ventricular outflow tract obstruction by resecting obstructive muscle bundles and by patch closure of the VSD. If the pulmonary valve is stenotic, as it usually is, a valvotomy is performed. If the pulmonary valve annulus is too small or the valve is extremely thickened, a valvectomy may be performed, the pulmonary valve annulus split open, and a transannular patch placed across the pulmonary valve ring. The surgical risk of total correction in major centers is <5%. A right ventriculotomy was once the standard approach; a transatrial–transpulmonary approach is routinely performed to reduce the long-term risks of a large right ventriculotomy. In patients in whom repair has been delayed to childhood, increased bleeding in the immediate postoperative period may be a complicating factor because of their extreme polycythemia.

The second option, more common in previous years, is a palliative systemic-to-pulmonary artery shunt (**Blalock-Taussig shunt**) performed to augment pulmonary artery blood flow. The rationale for this surgery, previously the only option for these patients, is to augment pulmonary blood flow to decrease the amount of hypoxia and improve linear growth, as well as augment growth of the branch pulmonary arteries. The modified Blalock-Taussig shunt is currently the most common aortopulmonary shunt procedure and consists of a Gore-Tex conduit anastomosed side to side from the subclavian artery to the homolateral branch of the pulmonary artery (Fig. 430-5). Sometimes the shunt is brought directly from the ascending aorta to the main pulmonary artery; in this case, it is called a central shunt. Postoperative complications after a Blalock-Taussig shunt include chylothorax, diaphragmatic paralysis, and Horner syndrome. Postoperative pulmonary overcirculation leading to symptoms of cardiac failure may be caused by too large a shunt; Chapter 442 describes its treatment. Vascular problems other than a diminished radial pulse and occasional long-term arm length discrepancy are rarely seen in the upper extremity supplied by the subclavian artery used for the anastomosis.

After a successful shunt procedure, cyanosis diminishes. The development of a continuous murmur over the lung fields after the operation indicates a functioning anastomosis. A good continuous shunt murmur may not be heard until several days after surgery. The duration of symptomatic relief is variable. As the child grows, more pulmonary blood flow is needed and the shunt eventually becomes inadequate. When increasing cyanosis develops rapidly, thrombosis of the shunt should be suspected, often requiring emergent surgery.

Currently, Blalock-Taussig shunts are usually reserved for patients with comorbidities, such as other major congenital anomalies or

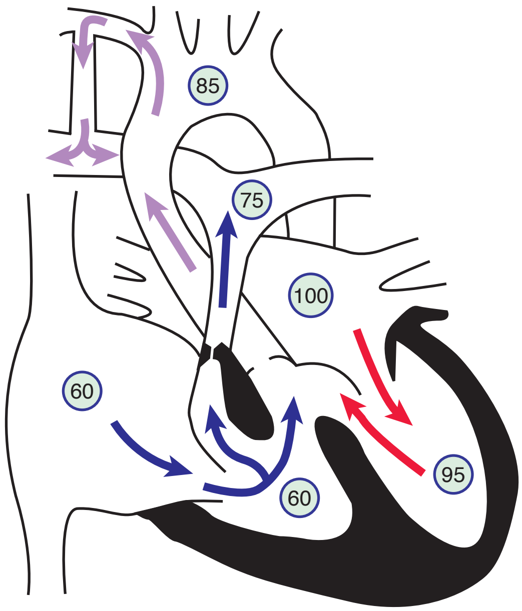

Figure 430-5 Physiology of a Blalock-Taussig shunt in a patient with tetralogy of Fallot. *Circled numbers* represent oxygen saturation values. The intracardiac shunting pattern is as described for Figure 430-1. Blood shunting left to right across the shunt from the right subclavian artery to the right pulmonary artery increases total pulmonary blood flow and results in a higher oxygen saturation than would exist without the shunt (see Fig. 430-1).

prematurity, that would make full repair a higher risk option. However, many surgeons still recommend full repair in these situations, being preferable to the combined risks of a staged procedure, and successful repairs have been done even in small premature infants.

PROGNOSIS

After successful total correction, patients are generally asymptomatic and are able to lead unrestricted lives. Uncommon immediate postoperative problems include right ventricular failure, transient heart block, residual VSD with left-to-right shunting, and myocardial infarction from interruption of an aberrant coronary artery. Postoperative heart failure (particularly in patients with a large transannular outflow patch) may require anticongestive therapy. The long-term effects of isolated, surgically induced pulmonary valvular insufficiency are still being defined as more patients with repaired tetralogy of Fallot reach middle age, but insufficiency is generally well-tolerated through adolescence. Many patients after tetralogy repair and all of those with transannular patch repairs have a to-and-fro murmur at the left sternal border, usually indicative of mild outflow obstruction and mild to moderate pulmonary insufficiency. Patients with more marked pulmonary valve insufficiency may also have moderate to more severe degrees of right ventricular enlargement and may develop tricuspid regurgitation as the tricuspid valve annulus dilates. These patients will develop a holosystolic murmur at the lower left sternal border. Patients with a severe residual gradient across the right ventricular outflow tract may require reoperation, but mild to moderate degrees of residual obstruction usually do not require reintervention.

Follow-up of patients 5-20 yr after surgery indicates that the marked improvement in symptoms is generally maintained. Asymptomatic patients nonetheless have lower than normal exercise capacity, maximal heart rate, and cardiac output. These abnormal findings are more common in patients who underwent placement of a transannular outflow tract patch and may be less frequent when surgery is performed at an early age. As these children move into adolescence and adulthood, some (more commonly those with transannular patches) will develop right ventricular dilation as a result of severe pulmonary

regurgitation. After reaching adulthood, careful lifelong follow-up by a specialist in adult congenital heart disease is important. Serial echocardiography and the more quantitative magnetic resonance angiography are valuable tools for assessing the degree of right ventricular dilation, the presence of right ventricular dysfunction, and for quantifying the regurgitant fraction. Valve replacement is indicated for those patients with increasing right ventricular dilation and tricuspid regurgitation. For patients requiring valve replacement, new nonsurgical options are being developed. Stent valves, which can be delivered in the cardiac catheterization lab, have been used successfully in many patients with repaired tetralogy of Fallot. These are being used predominantly in patients who have previously had a homograft or other artificial conduit placed between the right ventricular and pulmonary arteries.

Conduction disturbances can occur after surgery. The atrioventricular node and the bundle of His and its divisions are in close proximity to the VSD and may be injured during surgery; however, permanent complete heart block after tetralogy repair is rare. When present, it should be treated by placement of a permanently implanted pacemaker. Even transient complete heart block in the immediate postoperative period is rare; it may be associated with an increased incidence of late-onset complete heart block and sudden death. In contrast, right bundle-branch block is quite common on the postoperative electrocardiogram. The duration of the QRS interval has been shown to predict both the presence of residual hemodynamic derangement and the long-term risk of arrhythmia and sudden death. Research is ongoing to determine the effectiveness of biventricular pacing (in which a pacemaker is used to resynchronize the activation of the right and left ventricles) in improving hemodynamics in those patients with long ventricular conduction delays.

A number of children have premature ventricular beats after repair of the tetralogy of Fallot. These beats are of concern in patients with residual hemodynamic abnormalities; 24 hr electrocardiographic (Holter) monitoring studies should be performed to be certain that occult short episodes of ventricular tachycardia are not occurring. Exercise studies may be useful in provoking cardiac arrhythmias that are not apparent at rest. In the presence of complex ventricular arrhythmias or severe residual hemodynamic abnormalities, prophylactic antiarrhythmic therapy, catheter ablation, or implantation of an implantable defibrillator is warranted. Rerepair is indicated if significant residual right ventricular outflow obstruction or severe pulmonary insufficiency is present because arrhythmias may improve after hemodynamics is restored to a more normal level.

Bibliography is available at Expert Consult.

430.2 Tetralogy of Fallot with Pulmonary Atresia

Daniel Bernstein

PATHOPHYSIOLOGY

Tetralogy of a Fallot with pulmonary atresia is the most extreme form of the tetralogy of Fallot. The pulmonary valve is atretic (absent), and the pulmonary trunk may be hypoplastic or atretic as well. The entire right ventricular output is ejected into the aorta. Pulmonary blood flow is then dependent on collateral vessels or MAPCAs, or, rarely, on a PDA. The ultimate prognosis depends on the degree of development of the branch pulmonary arteries, which needs to be assessed by cardiac catheterization. If the pulmonary arteries are severely hypoplastic and fail to grow after palliative shunt procedures, heart-lung transplantation may be the only therapy (see Chapter 443.2). Pulmonary atresia with VSD is also associated with the 22q11.2 deletion and DiGeorge syndrome. The association of severe **tracheomalacia** or **bronchomalacia** with these severe forms of tetralogy/pulmonary atresia may complicate postoperative recovery.

CLINICAL MANIFESTATIONS

Patients with pulmonary atresia and VSD have findings similar to those in patients with severe tetralogy of Fallot. Cyanosis usually appears within the 1st few hr or days after birth; however, the prominent systolic murmur associated with the tetralogy is usually absent. The 1st heart sound may be followed by an ejection click caused by the enlarged aortic root, the 2nd heart sound is single and loud, and continuous murmurs of collateral flow may be heard over the entire precordium, both anteriorly and posteriorly. Most patients are moderately cyanotic and are initially stabilized with a prostaglandin E_1 infusion pending cardiac catheterization or CT scan to further delineate the anatomy. Patients with several large MAPCAs may be less cyanotic and, once the diagnosis is confirmed, can be taken off prostaglandin while awaiting palliative surgical intervention. Some patients may even develop symptoms of heart failure caused by increased pulmonary blood flow via these collateral vessels.

DIAGNOSIS

The chest roentgenogram demonstrates a varying heart size, depending on the amount of pulmonary blood flow, a concavity at the position of the pulmonary arterial segment, and often the reticular pattern of bronchial collateral flow. The electrocardiogram shows right ventricular hypertrophy. The echocardiogram identifies aortic override, a thick right ventricular wall, and atresia of the pulmonary valve. Pulsed and color Doppler echocardiographic studies show an absence of forward flow through the pulmonary valve, with pulmonary blood flow being supplied by MAPCAs, which can usually be seen arising from the descending aorta. At cardiac catheterization, right ventriculography reveals a large aorta, opacified immediately by passage of contrast medium through the VSD, but with no dye entering the lungs through the right ventricular outflow tract. Careful delineation of the native pulmonary arteries, if present, to determine whether they are continuous or discontinuous and whether they arborize to all lung segments is important in planning surgical repair. The location and arborization of all MAPCAs and the presence of any localized stenosis are determined by selective contrast injection. CT angiography has recently been utilized to assist in mapping the extent of MAPCA arborization.

TREATMENT

The surgical procedure of choice depends on whether the main pulmonary artery segment is present and, if so, on the size and branching pattern of the branch pulmonary arteries. If these arteries are well developed, a one-stage surgical repair with a homograft conduit between the right ventricle and pulmonary arteries and closure of the VSD is feasible. If the pulmonary arteries are hypoplastic, extensive reconstruction may be required. This usually involves several staged surgical procedures. If the native pulmonary artery is present but small, a connection made between the aorta and the hypoplastic native pulmonary artery (aortopulmonary window) in the newborn period induces growth. At 3-4 mo of age, the multiple MAPCAs are gathered together (unifocalization procedure) and eventually incorporated into the final repair along with the native pulmonary arteries. This may be accomplished through successive lateral thoracotomies, or through a single midline sternotomy if the anatomy is more favorable.

To be a candidate for full repair, the pulmonary arteries must be of adequate size to accept the full volume of right ventricular output. Complete repair includes closure of the VSD and placement of a homograft conduit from the right ventricle to the pulmonary artery. At the time of reparative surgery, previous shunts are taken down. Because of patient growth as well as homograft narrowing due to proliferation of intimal tissue and calcification, replacement of the homograft conduit replacement is usually required in later life, and multiple replacements may be needed. Many of these patients are candidates for placement of a transcatheter stent valve in the pulmonary position. Patients with obstruction of the very distal branches of the pulmonary arteries may undergo repeat surgical procedures or transcatheter balloon dilation

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of the multiple branch pulmonary arterial stenosis. Careful follow-up is warranted for these patients to ensure maximal chance of growth of all pulmonary artery segments.

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430.3 Pulmonary Atresia with Intact Ventricular Septum

Daniel Bernstein

PATHOPHYSIOLOGY

In pulmonary atresia with an intact ventricular septum, the pulmonary valve leaflets are completely fused to form a membrane and the right ventricular outflow tract is atretic. Because no VSD is present, no egress of blood from the right ventricle can occur. Any blood that enters the right ventricle will regurgitate back across the tricuspid valve into the right atrium. Right atrial pressure increases, and blood shunts via the foramen ovale into the left atrium, where it mixes with pulmonary venous blood and enters the left ventricle (Fig. 430-6). The combined left and right ventricular output is pumped solely by the left ventricle into the aorta. In a newborn with pulmonary atresia, the only source of pulmonary blood flow occurs via a **PDA.** The right ventricle and tricuspid valve are usually hypoplastic, although the degree of hypoplasia varies considerably. Patients who have a small right ventricular cavity also tend to be those with the smallest tricuspid valve annulus, which limits right ventricular inflow. Patients with pulmonary atresia and intact ventricular septum may have **coronary sinusoidal channels** within the right ventricular wall that communicate directly with the coronary arterial circulation. The high right ventricular pressure results in desaturated blood flowing retrograde via these channels into the coronary arteries. Sometimes there are also stenoses of the coronary arteries proximal to where the sinusoids enter, so that distal coronary artery flow is dependent on flow from the right ventricle (known as *right ventricle–dependent coronary circulation*). The prognosis in patients with these sinusoids and proximal stenosis of the coronary arteries is more guarded than in those patients without sinusoids or with sinusoids but no coronary stenoses. Rarely, the proximal coronary artery may be totally absent.

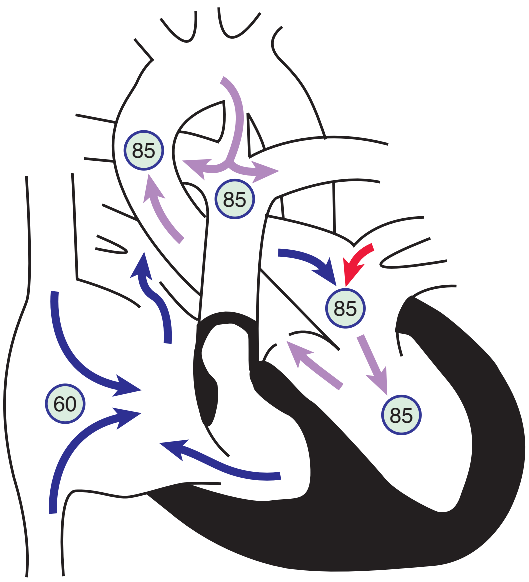

Figure 430-6 Physiology of pulmonary atresia with an intact ventricular septum. *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. A small amount of the blood entering the right atrium may cross the tricuspid valve, which is often stenotic as well. The right ventricular cavity is hypertrophied and may be hypoplastic. No outlet from the right ventricle exists because of the atretic pulmonary valve; thus, any blood entering the right ventricle returns to the right atrium via tricuspid regurgitation. Most of the desaturated blood shunts right to left via the foramen ovale into the left atrium, where it mixes with fully saturated blood returning from the lungs. The only source of pulmonary blood flow is via the patent ductus arteriosus. Aortic and pulmonary arterial oxygen saturation will be identical (definition of a total mixing lesion).

CLINICAL MANIFESTATIONS

As the ductus arteriosus closes in the 1st hr and days of life, infants with pulmonary atresia and an intact ventricular septum become markedly cyanotic because their only source of pulmonary blood flow is removed. Untreated, most patients die within the 1st wk of life. Physical examination reveals severe cyanosis and respiratory distress. The 2nd heart sound, representing only aortic closure, is single and loud. Often, no murmurs are audible; sometimes a systolic or continuous murmur can be heard secondary to ductal blood flow. A harsh holosystolic murmur may be heard at the lower left sternal border if there is significant tricuspid regurgitation.

DIAGNOSIS

The electrocardiogram shows a frontal QRS axis between 0 and +90 degrees, the amount of leftward shift reflecting the degree of hypoplasia of the right ventricle. Tall, spiked P waves indicate right atrial enlargement. QRS voltages are consistent with left ventricular dominance or hypertrophy; right ventricular forces are decreased in proportion to the decreased size of the right ventricular cavity. Most patients with small right ventricles have decreased right ventricular forces, but, occasionally, patients with larger, thickened right ventricular cavities may have evidence of right ventricular hypertrophy. The chest roentgenogram shows decreased pulmonary vascularity, the degree depending on the size of the branch pulmonary arteries and the patency of the ductus. Unlike in patients with pulmonary atresia and tetralogy of Fallot, the presence of major collateral vessels (MAPCAs) is rare.

The 2-dimensional echocardiogram is useful in estimating right ventricular dimensions and the size of the tricuspid valve annulus, which have been shown to be of prognostic value. Echocardiography can often suggest the presence of sinusoidal channels but cannot be used to evaluate coronary stenoses. Thus, cardiac catheterization is necessary for complete evaluation. Pressure measurements reveal right atrial and right ventricular hypertension. Ventriculography demonstrates the size of the right ventricular cavity, the atretic right ventricular outflow tract, the degree of tricuspid regurgitation, and the presence or absence of intramyocardial sinusoids filling the coronary vessels. Aortography shows filling of the pulmonary arteries via the PDA and is helpful in determining the size and branching patterns of the pulmonary arterial bed. An aortogram, or if necessary selective coronary angiography is performed to evaluate for the presence of proximal coronary artery stenosis (right ventricular dependent coronary circulation).

TREATMENT

Infusion of prostaglandin E_1 (0.01-0.20 μg/kg/min) is usually effective in keeping the ductus arteriosus open before intervention, thus reducing hypoxemia and acidemia before surgery. The choice of surgical procedure depends on whether there is an RV dependent coronary circulation and on the size of the right ventricular cavity. In patients with only mild to moderate right ventricular hypoplasia without sinusoids, or in patients with sinusoids but no evidence of coronary stenoses, a surgical pulmonary valvotomy is carried out to relieve outflow obstruction. Often, the right ventricular outflow tract is widened with a patch. To preserve adequate pulmonary blood flow, an aortopulmonary shunt may also be performed during the same procedure. An alternative approach uses interventional catheterization, in which the imperforate pulmonary valve is first punctured either with a wire or a radiofrequency ablation catheter, followed by a balloon valvuloplasty.

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If this course is taken, it may take days to weeks before the right ventricular muscle regresses enough for the patient to be weaned from prostaglandin, and many of these patients will still require surgical intervention. The aim of surgery or interventional catheterization is to encourage growth of the right ventricular chamber by allowing some forward flow through the pulmonary valve while using the shunt to ensure adequate pulmonary blood flow. Later, if the tricuspid valve annulus and right ventricular chamber grow to adequate size, the shunt is taken down and any remaining atrial level shunt can be closed. If the right ventricular chamber remains too small for use as a pulmonary ventricle, then the patient is treated as a single ventricle circulation, with a **Glenn procedure** followed by a modified **Fontan procedure** (see Chapter 430.4), allowing blood to bypass the hypoplastic right ventricle by flowing to the pulmonary arteries directly from the venae cavae. When coronary artery stenoses are present and retrograde coronary perfusion occurs from the right ventricle via myocardial sinusoids, the prognosis is more guarded because of a higher risk of arrhythmias, coronary ischemia, and sudden death. It is important for these patients not to try to open the right ventricular outflow tract, as dropping the right ventricular pressure will reduce coronary perfusion, leading to ischemia. These patients are usually treated with an aortopulmonary shunt, followed by the Glenn and Fontan procedure. Although at higher risk than those without coronary stenoses, recent reports show good success with this approach. A small number of these infants, especially those with total atresia of a proximal coronary artery, are referred instead for heart transplantation.

Bibliography is available at Expert Consult.

430.4 Tricuspid Atresia

Daniel Bernstein

PATHOPHYSIOLOGY

In tricuspid atresia, no outlet from the right atrium to the right ventricle is present; the entire systemic venous return leaves the right atrium and enters the left side of the heart by means of the foramen ovale or, most often, through an atrial septal defect (Fig. 430-7). The physiology of the circulation and the clinical presentation will depend on the presence of other congenital heart defects, most notably on whether the great vessels are normally related or are transposed (aorta arising from the right ventricle, pulmonary artery from the left ventricle). In patients with normally related great vessels, left ventricular blood supplies the systemic circulation via the aorta. Blood also usually flows into the right ventricle via a VSD (if the ventricular septum is intact, the right ventricle will be completely hypoplastic and pulmonary atresia will be present [see Chapter 430.3]). *Pulmonary blood flow (and thus the degree of cyanosis) depends on the size of the VSD and the presence and severity of any associated pulmonic stenosis.* Pulmonary blood flow may be augmented by or be totally dependent on a PDA. The inflow portion of the right ventricle is always missing in these patients, but the outflow portion is of variable size. The clinical presentation of patients with tricuspid atresia and normally related great vessels will depend on the degree of pulmonary obstruction. Patients with at least moderate degrees of pulmonary stenosis are recognized in the early days or weeks of life by decreased pulmonary blood flow and cyanosis. Alternatively, in those with a large VSD and minimal or no right ventricular outflow obstruction, pulmonary blood flow may be high; these patients have only mild cyanosis and present with signs of pulmonary overcirculation and heart failure.

In patients with tricuspid atresia and transposition of the great arteries, left ventricular blood flows directly into the pulmonary artery, whereas systemic blood must traverse the VSD and right ventricle to reach the aorta. In these patients, pulmonary blood flow is usually massively increased and heart failure develops early. If the VSD is restrictive, aortic blood flow may be compromised. Coarctation of the aorta is not uncommon in this setting.

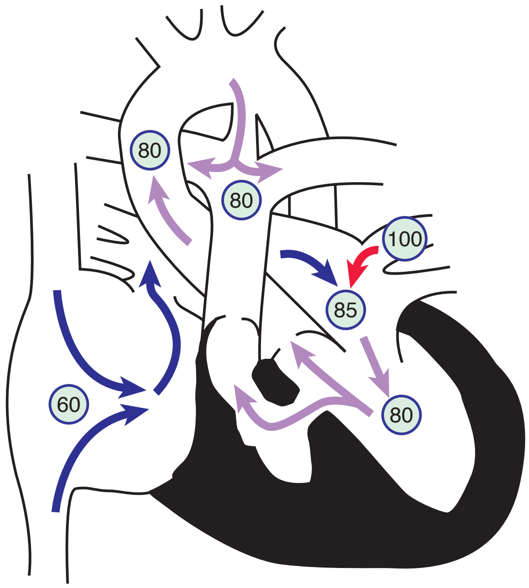

Figure 430-7 **Physiology of tricuspid atresia with normally related great vessels.** *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. The tricuspid valve is nonpatent, and the right ventricle may manifest varying degrees of hypoplasia. The only outlet from the right atrium involves shunting right to left across an atrial septal defect or patent foramen ovale to the left atrium. There, desaturated blood mixes with saturated pulmonary venous return. Blood enters the left ventricle and is ejected either through the aorta or via a ventricular septal defect (VSD) into the right ventricle. In this example, some pulmonary blood flow is derived from the right ventricle, the rest from a patent ductus arteriosus (PDA). In patients with tricuspid atresia, the PDA may close or the VSD may grow smaller and result in a marked decrease in systemic oxygen saturation.

CLINICAL MANIFESTATIONS

Some degree of cyanosis is usually evident at birth, with the extent depending on the degree of limitation to pulmonary blood flow (as noted above). An increased left ventricular impulse may be noted, in contrast to most other causes of cyanotic heart disease, in which an increased right ventricular impulse is usually present. The majority of patients have holosystolic murmurs audible along the left sternal border; the 2nd heart sound is usually single. Pulses in the lower extremities may be weak or absent in the presence of transposition with coarctation of the aorta. Patients with tricuspid atresia are at risk for spontaneous narrowing or even closure of the VSD, which can occasionally occur rapidly and lead to a marked increase in cyanosis.

DIAGNOSIS

Radiologic studies show either pulmonary under circulation (usually in patients with normally related great vessels) or over circulation (usually in patients with transposed great vessels). Left axis deviation and left ventricular hypertrophy are generally noted on the electrocardiogram (except in those patients with transposition of the great arteries), and these features distinguish tricuspid atresia from most other cyanotic heart lesions. Thus the combination of cyanosis and left axis deviation on the electrocardiogram is highly suggestive of tricuspid atresia. In the right precordial leads, the normally prominent R wave is replaced by an rS complex. The left precordial leads show a qR complex, followed by a normal, flat, biphasic, or inverted T wave. RV_6 is normal or tall, and SV_1 is generally deep. The P waves are usually biphasic, with the initial component tall and spiked in lead II. Two-dimensional echocardiography reveals the presence of a fibromuscular membrane in place of a tricuspid valve, a variably small right ventricle, VSD, and the large left ventricle (Fig. 430-8). The relationship of the great vessels (normal or transposed) can be determined. The degree of

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obstruction at the level of the VSD or at the right ventricular outflow tract can be determined by Doppler examination. Blood flow through a patent ductus can be evaluated by color flow and pulsed Doppler.

Cardiac catheterization, indicated usually only if questions remain after echocardiography, shows normal or slightly elevated right atrial pressure with a prominent *a* wave. If the right ventricle is entered through the VSD, the pressure may be lower than on the left if the VSD is restrictive in size. Right atrial angiography shows immediate opacification of the left atrium from the right atrium followed by left ventricular filling and visualization of the aorta. Absence of direct flow to the right ventricle results in an angiographic filling defect between the right atrium and the left ventricle.

TREATMENT

Management of patients with tricuspid atresia depends on the adequacy of pulmonary blood flow. Severely cyanotic neonates should be maintained on an intravenous infusion of prostaglandin E_1 (0.01-0.20 µg/kg/min) until a surgical aortopulmonary shunt procedure can be performed to increase pulmonary blood flow. The Blalock-Taussig procedure (see Chapter 430.1) or a variation is the preferred anastomosis. Rare patients with restrictive atrial-level communications also benefit from a Rashkind balloon atrial septostomy (see Chapter 431.2) or surgical septectomy.

Infants with increased pulmonary blood flow because of an unobstructed pulmonary outflow tract (more often patients with aortopulmonary transposition) may require pulmonary arterial banding to decrease the symptoms of heart failure and protect the pulmonary bed from the development of pulmonary vascular disease. Infants with just adequate pulmonary blood flow who are well balanced between cyanosis and pulmonary overcirculation can be watched closely for the development of increasing cyanosis, which may occur as the VSD begins to get smaller or the pulmonary outflow becomes narrower and is an indication for surgery.

The next stage of palliation for patients with tricuspid atresia involves the creation of an anastomosis between the superior vena cava and the pulmonary arteries (**bidirectional Glenn shunt;** Fig. 430-9*A*). This procedure is performed at usually between 3 and 6 mo of age. The benefit of the Glenn shunt is that it reduces the volume load on the left ventricle and may lessen the chance of left ventricular dysfunction developing later in life.

The **modified Fontan operation** is the preferred approach to later surgical management. It is usually performed between 1.5 and 3 yr of age, usually after the patient is ambulatory. Initially, this procedure was performed by anastomosing the right atrium or atrial appendage directly to the pulmonary artery. The most commonly used procedure today is a modification of the Fontan procedure, known as a *cavopulmonary isolation procedure,* which involves anastomosing the inferior vena cava to the pulmonary arteries, either via a baffle that runs along the lateral wall of the right atrium (lateral tunnel Fontan; see Fig. 430-9*B*) or via a homograft or Gore-Tex tube running outside the heart (external conduit Fontan). The advantage of these later approaches is that blood flows by a more direct route into the pulmonary arteries, thereby decreasing the possibility of right atrial dilation and markedly reducing the incidence of postoperative pleural effusions, which were

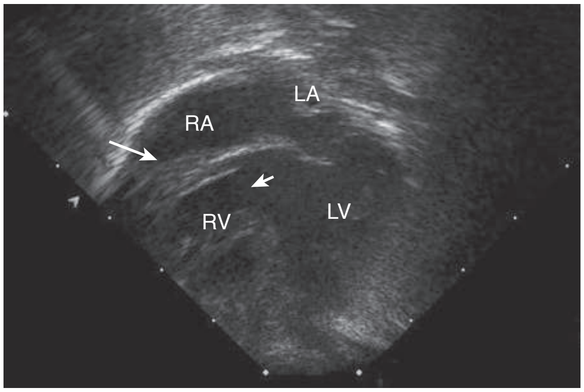

Figure 430-8 Echocardiogram demonstrating tricuspid atresia. The floor of the right atrium consists of a fibromuscular membrane *(large arrow)* instead of the normal tricuspid valve apparatus. The large secundum atrial septal defect can be seen between the right and left atria. The *small arrow* shows the ventricular septal defect. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

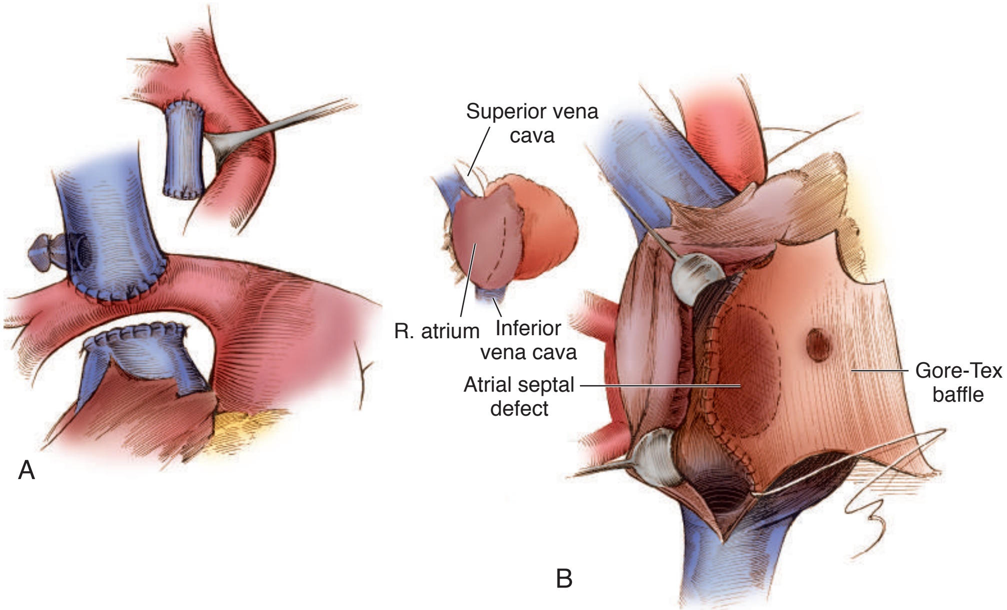

Figure 430-9 A, Bidirectional Glenn shunt showing the superior vena cava–right pulmonary anastomosis. **B,** A modified Fontan procedure (cavopulmonary isolation) is completed with placement of a baffle to convey inferior vena cava blood along the lateral wall of the right atrium to the superior vena cava orifice. A 4-mm fenestration is sometimes made on the medial aspect of the polytetrafluoroethylene baffle. *(From Castañeda AR, Jonas RA, Mayer JE Jr, et al: Single-ventricle tricuspid atresia. In* Cardiac surgery of the neonate and infant, *Philadelphia, 1994, WB Saunders.)*

common with the earlier method. In a completed Fontan repair, desaturated blood flows from both venae cavae directly into the pulmonary arteries. Oxygenated blood returns to the left atrium, enters the left ventricle, and is ejected into the systemic circulation. The volume load is completely removed from the left ventricle, and the right-to-left shunt is abolished. Because of the reliance on passive filling of the pulmonary circulation, the Fontan procedure is contraindicated in patients with elevated pulmonary vascular resistance, in those with pulmonary artery hypoplasia, and in patients with left ventricular dysfunction. The patient must also not have significant mitral insufficiency. Patients who are not in normal sinus rhythm are at increased risk and if a pacemaker is required in these patients, dual chamber pacing is the preferred approach.

Postoperative problems after the Fontan procedure include marked elevation of systemic venous pressure, fluid retention, and pleural or pericardial effusions. In the past, pleural effusions were a problem in 30-40% of patients using the standard Fontan procedure, but the cavopulmonary isolation procedure now in use reduces this risk to approximately 5%. Some centers use a fenestration at the time of the Fontan, consisting of a small communication between the inferior vena cava and the pulmonary artery conduit and the left atrium. This serves as a "pop-off" during early postoperative recovery and may hasten hospital discharge. The fenestration will result in some amount of right-to-left shunting, and is therefore usually closed with a catheter closure device after the immediate postoperative period.

Late complications of the Fontan procedure include baffle obstruction causing superior or inferior vena cava syndrome, vena cava or pulmonary artery thromboembolism, protein-losing enteropathy, plastic bronchitis, supraventricular arrhythmias (atrial flutter, paroxysmal atrial tachycardia), and hepatic cirrhosis (and possibly hepatic carcinoma) as a result of persistently elevated central venous pressures. Oral budesonide or sildenafil has been used with varying success to treat protein losing enteropathy associated with the Fontan procedure. Left ventricular dysfunction may be a late occurrence, usually not until adolescence or young adulthood. Heart transplantation is a successful treatment option for pediatric patients with "failed" Fontan circuits but is a somewhat riskier procedure in adults.

Bibliography is available at Expert Consult.

430.5 Double-Outlet Right Ventricle

Daniel Bernstein

Double-outlet right ventricle (DORV) is characterized when both the aorta and pulmonary artery arise from the right ventricle. The outlet from the left ventricle is through VSD into the right ventricle. Normally, the aortic and mitral valves are in fibrous continuity; in DORV, the aortic and mitral valves are separated by a smooth muscular conus, similar to that seen under the normal pulmonary valve. In DORV, the great arteries may be normally related, with the aorta closer to the VSD, or malposed, with the pulmonary artery closer to the VSD. The great artery closest to the VSD may override the defect by a variable amount but is at least 50% committed to the right ventricle. When the VSD is subaortic, the defect may be viewed as part of a continuum with the tetralogy of Fallot, and the physiology as well as the history, physical examination, electrocardiogram, and roentgenograms are depending on the degree of pulmonary stenosis, similar to the situation in tetralogy of Fallot (see Chapter 430.1). If the VSD is subpulmonic, there may be subvalvar, valvar, or supravalvar aortic stenosis, and coarctation is a possibility as well. This is known as the **Taussig-Bing malformation.** The clinical presentation of these patients will be dependent on the degree of aortic obstruction, but because the pulmonary artery is usually wide open, the presentation will usually include some degree of pulmonary overcirculation and heart failure. If the aortic obstruction is severe or there is a coarctation, poor pulses, hypoperfusion, and cardiovascular collapse are possible presenting signs.

The 2-dimensional echocardiogram demonstrates both great vessels arising from the right ventricle and mitral-aortic valve discontinuity. The relationships between the aorta and pulmonary artery to the VSD can be delineated, and the presence of either pulmonary obstruction or aortic obstruction can be evaluated. Cardiac catheterization is not necessarily required if the echocardiogram is straightforward. Angiography will show that the aortic and pulmonary valves lie in the same horizontal plane and that both arise predominantly or exclusively from the right ventricle.

Surgical correction depends on the relationship of the great vessels to the VSD. If the VSD is subaortic, the repair may be similar to that used for tetralogy of Fallot, or consist of creating an intraventricular tunnel so that the left ventricle ejects blood through the VSD, into the tunnel, and into the aorta. The pulmonary obstruction is relieved either with an outflow patch or with a right ventricular to pulmonary artery homograft conduit **(Rastelli operation).** If the VSD is subpulmonic, the great vessels can be switched (see Chapter 430.6) and the Rastelli operation performed. However, if there is substantial aortic obstruction, or if 1 of the ventricles is hypoplastic, then a Norwood-style single-ventricle repair may be necessary (see Chapter 431.10). In small infants, palliation with an aortopulmonary shunt provides symptomatic improvement and allows for adequate growth before corrective surgery is performed.

430.6 Transposition of the Great Arteries with Ventricular Septal Defect and Pulmonary Stenosis

Daniel Bernstein

This combination of anomalies may mimic tetralogy of Fallot in its clinical features (see Chapter 430.1). However, because of the transposed great vessels, the site of obstruction is in the left as opposed to the right ventricle. The obstruction can be either valvular or subvalvular; the latter type may be dynamic, related to the interventricular septum or atrioventricular valve tissue, or acquired, as in patients with transposition and VSD after pulmonary arterial banding.

The age at which clinical manifestations initially appear varies from soon after birth to later infancy, depending on the degree of pulmonic stenosis. Clinical findings include cyanosis, decreased exercise tolerance, and poor physical development, similar to those described for tetralogy of Fallot; the heart is usually more enlarged. The pulmonary vasculature as seen on the roentgenogram is dependent on the degree of pulmonary obstruction. The electrocardiogram usually shows right axis deviation, right and left ventricular hypertrophy, and sometimes tall, spiked P waves. Echocardiography confirms the diagnosis and is useful in sequential evaluation of the degree and progression of the left ventricular outflow tract obstruction. Cardiac catheterization, if necessary, shows that pulmonary arterial pressure is low and that oxygen saturation in the pulmonary artery exceeds that in the aorta. Selective right and left ventriculography demonstrates the origin of the aorta from the right ventricle, the origin of the pulmonary artery from the left ventricle, the VSD, and the site and severity of the pulmonary stenosis.

An infusion of prostaglandin E_1 (0.01-0.20 μg/kg/min) should be started in neonates who present with cyanosis. When necessary, balloon atrial septostomy is performed to improve atrial-level mixing and to decompress the left atrium (see Chapter 431.2). Cyanotic infants may be palliated with an aortopulmonary shunt (see Chapter 430.1) followed by a Rastelli operation when older as the preferred corrective procedure. The Rastelli procedure achieves physiologic and anatomic correction by (1) closure of the VSD using an interventricular tunnel so that left ventricular blood flow is directed to the aorta, and (2) connection of the right ventricle to the pulmonary artery via an extracardiac homograft conduit between the right ventricle and the distal pulmonary artery (Fig. 430-10). These conduits will eventually become stenotic or functionally restrictive with growth of the patient and require replacement. Patients with milder degrees of pulmonary

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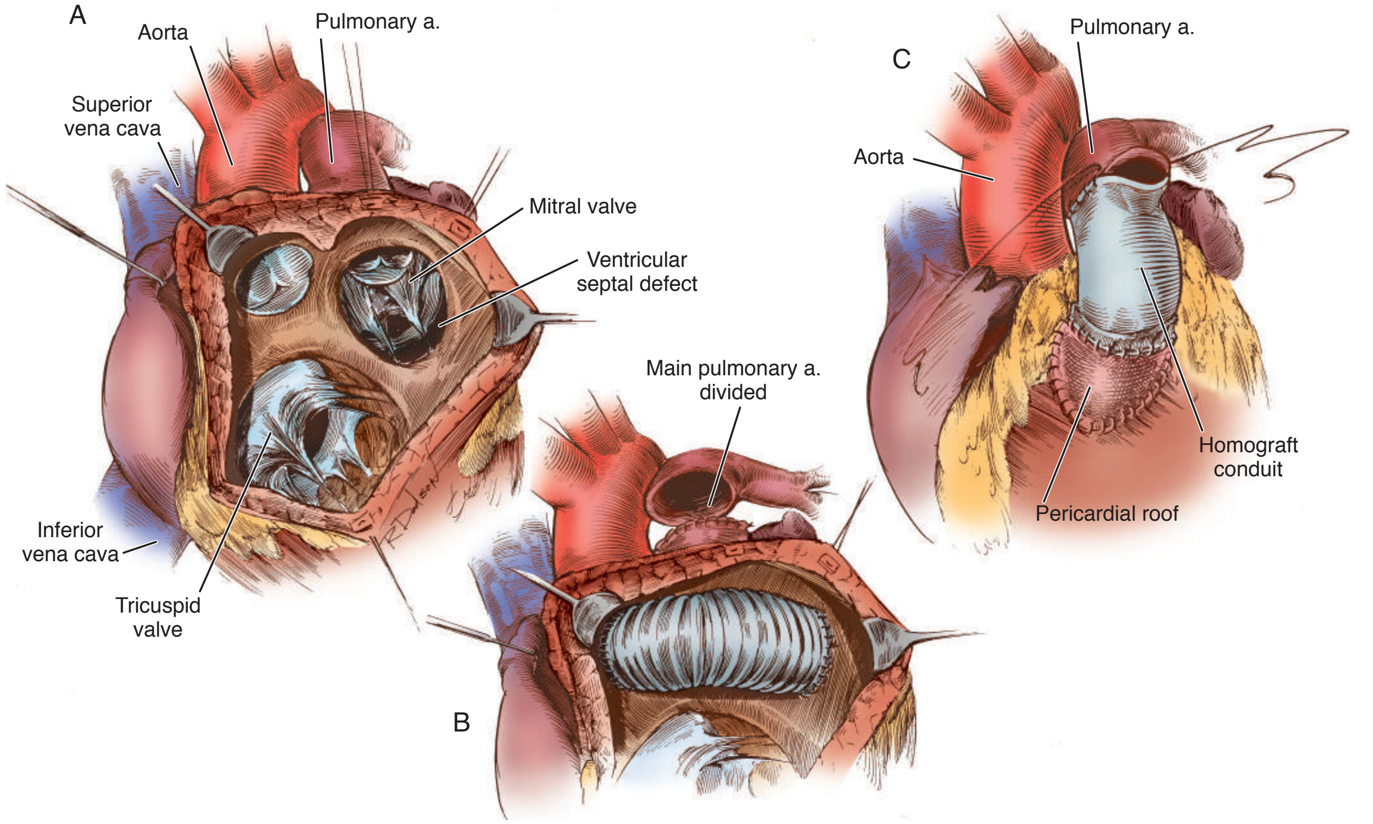

Figure 430-10 **A,** Taussig-Bing type of double-outlet right ventricle with subpulmonary stenosis necessitating repair by the Rastelli technique. **B,** The main pulmonary artery is divided and oversewn proximally. The pulmonary valve lies within the baffle pathway. **C,** Completion of the Rastelli repair with a right ventricle-pulmonary artery allograft conduit. *(From Castañeda AR, Jonas RA, Mayer JE Jr, et al: Single-ventricle tricuspid atresia. In* Cardiac surgery of the neonate and infant, *Philadelphia, 1994, WB Saunders.)*

stenosis amenable to simple valvotomy may be able to undergo complete correction with an arterial switch procedure (see Chapter 431.2) and closure of the VSD. Surgical correction by the Mustard operation (see Chapter 431.2) with simultaneous closure of the VSD and relief of left ventricular outflow obstruction may be an alternative when the position of the VSD is not suitable for a Rastelli operation; however, this procedure leaves the right ventricle as the systemic pumping chamber and has fallen out of favor.

430.7 Ebstein Anomaly of the Tricuspid Valve

Daniel Bernstein

PATHOPHYSIOLOGY

Ebstein anomaly consists of downward displacement of an abnormal tricuspid valve into the right ventricle. The defect arises from failure of the normal process by which the tricuspid valve is separated from the right ventricular myocardium (see Chapter 420). The anterior cusp of the valve retains some attachment to the valve ring, but the other leaflets are adherent to the wall of the right ventricle. The right ventricle is thus divided into 2 parts by the abnormal tricuspid valve: the first, a thin-walled "atrialized" portion, is continuous with the cavity of the right atrium; the second, often smaller portion consists of normal ventricular myocardium. The right atrium is enlarged as a result of tricuspid valve regurgitation, although the degree is extremely variable. In more severe forms of Ebstein anomaly, the effective output from the right side of the heart is decreased because of a combination of the poorly functioning small right ventricle, tricuspid valve regurgitation, and obstruction of the right ventricular outflow tract produced by the large, sail-like, anterior tricuspid valve leaflet. In newborns, right ventricular function may be so compromised that it is unable to generate enough force to open the pulmonary valve in systole, thus producing "functional" pulmonary atresia. Some infants have true anatomic pulmonary atresia. The increased volume of right atrial blood shunts through the foramen ovale (or through an associated atrial septal defect) to the left atrium and produces cyanosis (Fig. 430-11).

CLINICAL MANIFESTATIONS

The severity of symptoms and the degree of cyanosis are highly variable and depend on the extent of displacement of the tricuspid valve and the severity of right ventricular outflow tract obstruction. In many patients, symptoms are mild and may be delayed until the teenage years or young adult life; the patient may initially have fatigue or palpitations as a result of cardiac dysrhythmias. The atrial right-to-left shunt is responsible for cyanosis and polycythemia. Jugular venous pulsations, a index of central venous pressure, may be normal or increased in those with tricuspid insufficiency. On palpation, the precordium is quiet. A holosystolic murmur caused by tricuspid regurgitation is audible over most of the anterior left side of the chest. A gallop rhythm is common and often associated with multiple clicks at the lower left sternal border. A scratchy diastolic murmur may also be heard at the left sternal border. This murmur may mimic a pericardial friction rub.

Newborns with severe forms of Ebstein anomaly have marked cyanosis, massive cardiomegaly, and long holosystolic murmurs. Death may result from cardiac failure, hypoxemia, and pulmonary hypoplasia, the result of severe long-standing intrauterine right atrial enlargement. Spontaneous improvement may occur in some neonates as pulmonary vascular resistance falls and improves the ability of the right ventricle to provide pulmonary blood flow. The majority are

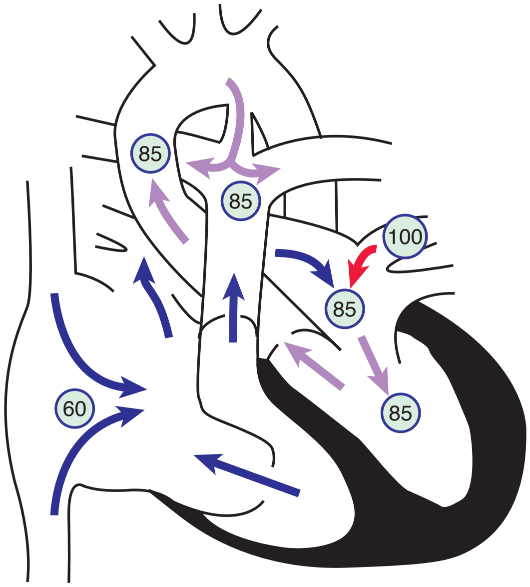

Figure 430-11 Physiology of Ebstein anomaly of the tricuspid valve. *Circled numbers* represent oxygen saturation values. Inferior displacement of the tricuspid valve leaflets into the right ventricle has resulted in a thin-walled, low-pressure "atrialized" segment of right ventricle. The tricuspid valve is grossly insufficient *(clear arrow)*. Right atrial blood flow is shunted right to left across an atrial septal defect or patent foramen ovale into the left atrium. Some blood may cross the right ventricular outflow tract and enter the pulmonary artery; however, in severe cases, the right ventricle may generate insufficient force to open the pulmonary valve, and "functional pulmonary atresia" results. In the left atrium, desaturated blood mixes with saturated pulmonary venous return. Blood enters the left ventricle and is ejected via the aorta. In this example, some pulmonary blood flow is derived from the right ventricle, the rest from a patent ductus arteriosus (PDA). Severe cyanosis will develop in neonates with a severe Ebstein anomaly when the PDA closes.

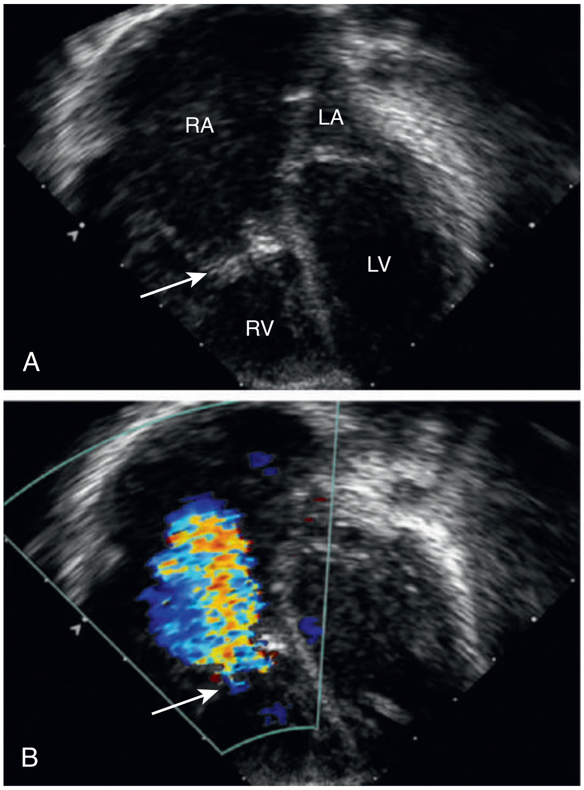

Figure 430-12 Echocardiographic demonstration of Ebstein anomaly of the tricuspid valve. **A,** Subcostal, 4-chamber, 2-dimensional view showing severe displacement of the tricuspid valve leaflets *(large arrow)* inferiorly into the right ventricle. The location of the tricuspid valve annulus is outlined by the 2 *arrowheads.* The portion of the right ventricle between the valve annulus and the valve leaflets is the "atrialized" component. **B,** Color Doppler examination showing severe regurgitation of the dysplastic tricuspid valve. Note that the regurgitant turbulent flow *(arrow)* begins halfway into the right ventricular chamber, at the location of the displaced valve leaflets. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

dependent on a PDA, and thus on a prostaglandin infusion, for pulmonary blood flow.

DIAGNOSIS

The electrocardiogram usually shows a right bundle-branch block without increased right precordial voltage, normal or tall and broad P waves, and a normal or prolonged P-R interval. **Wolff-Parkinson-White syndrome** (see Chapter 435) may be present and these patients may have episodes of supraventricular tachycardia. On radiographic examination, heart size varies from slightly enlarged to massive box-shaped cardiomegaly caused by enlargement of the right atrium. *In newborns with severe Ebstein anomaly, the heart may totally obscure the pulmonary fields.* Echocardiography is diagnostic and shows the degree of displacement of the tricuspid valve leaflets, a dilated right atrium, and any right ventricular outflow tract obstruction (Fig. 430-12). Pulsed and color Doppler examination demonstrates the degree of tricuspid regurgitation. In severe cases, the pulmonary valve may appear immobile and pulmonary blood flow may come solely from the ductus arteriosus. It may be difficult to distinguish true from functional pulmonary valve atresia. Cardiac catheterization, which is not usually necessary, confirms the presence of a large right atrium, an abnormal tricuspid valve, and any right-to-left shunt at the atrial level. The risk of arrhythmia is significant during catheterization and angiographic studies.

PROGNOSIS AND COMPLICATIONS

The prognosis in Ebstein anomaly is extremely variable and depends on the severity of the defect. The prognosis is more guarded for neonates or infants with intractable symptoms and cyanosis. Patients with milder degrees of Ebstein anomaly usually survive well into adult life. There is an association of a form of left ventricular cardiomyopathy, isolated left ventricular noncompaction, in 18% of patients with Ebstein anomaly, and the severity of the left ventricular dysfunction directly impacts the prognosis.

TREATMENT

Neonates with severe hypoxia who are prostaglandin dependent have been treated with an aortopulmonary shunt alone, by repair of the tricuspid valve, or by surgical patch closure of the tricuspid valve, atrial septectomy, and placement of an aortopulmonary shunt (with eventual single ventricle repair using the Fontan procedure [see Chapter 430.4]). Many infants with Ebstein anomaly who have undergone valve repair will still have enough regurgitation that a Glenn shunt is performed to reduce the volume load on the right ventricle (see Chapter 430.4). In older children with mild or moderate disease, control of supraventricular dysrhythmias is of primary importance; surgical treatment may not be necessary until adolescence or young adulthood. In patients with severe tricuspid regurgitation, repair or replacement of the abnormal tricuspid valve along with closure of the atrial septal defect is carried out. In some older patients, a bidirectional Glenn shunt is also performed, with the superior vena cava anastomosed to the pulmonary arteries. This procedure reduces the volume of blood that the dysfunctional right side of the heart has to pump, thus creating a "one-and-one-half ventricle repair."

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Chapter 431

Cyanotic Congenital Heart Disease: Lesions Associated with Increased Pulmonary Blood Flow

431.1 D-Transposition of the Great Arteries

Daniel Bernstein

Transposition of the great vessels, a common cyanotic congenital anomaly, accounts for ≈5% of all congenital heart disease. In this anomaly, the systemic veins return normally to the right atrium and the pulmonary veins return to the left atrium. The connections between the atria and ventricles are also normal (atrioventricular concordance). The aorta arises from the right ventricle and the pulmonary artery from the left ventricle (Fig. 431-1). In normally related great vessels, the aorta is posterior and to the right of the pulmonary artery; in d-transposition of the great arteries (d-TGA), the aorta is anterior and to the right of the pulmonary artery (the *d* indicates a dextropositioned aorta, *transposition* indicates that it arises from the anterior right ventricle). Desaturated blood returning from the body to the right side of the heart goes inappropriately out the aorta and back to the body again, whereas oxygenated pulmonary venous blood returning to the left side of the heart is returned directly to the lungs. Thus, the systemic and pulmonary circulations exist as 2 parallel circuits. Survival in the immediate newborn period is provided by the foramen ovale and the ductus arteriosus, which permit some mixture of oxygenated and deoxygenated blood. Approximately 50% of patients with d-TGA also have a ventricular septal defect (VSD), which usually provides for better mixing. The clinical findings and hemodynamics vary in relation to the presence or absence of associated defects (e.g., VSD or pulmonary stenosis). d-TGA is more common in infants of diabetic mothers and in males (3:1). d-TGA, especially when accompanied by other cardiac defects such as pulmonic stenosis or right aortic arch, can be associated with deletion of chromosome 22q11.2 (DiGeorge syndrome [see Chapter 424]). Before the modern era of corrective or palliative surgery, mortality was >90% in the 1st yr of life.

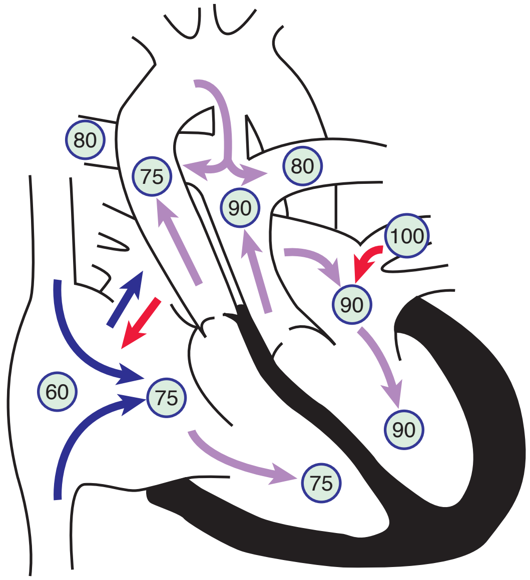

Figure 431-1 Physiology of d-transposition of the great arteries (d-TGA). *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. Desaturated blood enters the right atrium, flows through the tricuspid valve into the right ventricle, and is ejected into the transposed aorta with resultant severe aortic desaturation. Fully saturated pulmonary venous blood flows into the left atrium, across the mitral valve into the left ventricle, and across the transposed pulmonary artery into the lungs. Pulmonary arterial oxygen saturation is thus increased. This lesion would not be compatible with life were it not for the ability of blood to shunt via 2 fetal pathways: the patent foramen ovale (PFO) and patent ductus arteriosus (PDA). Blood may shunt left to right or bidirectionally at the PFO. Because systemic vascular resistance tends to be higher than pulmonary vascular resistance, blood tends to shunt across the PDA mostly from the aorta to the pulmonary artery. As pulmonary resistance drops in the 1st few wk of life, pulmonary blood flow will gradually increase in patients with d-TGA.

431.2 D-Transposition of the Great Arteries with Intact Ventricular Septum

Daniel Bernstein

D-TGA with an intact ventricular septum is also referred to as simple TGA or isolated TGA. Before birth, oxygenation of the fetus is only slightly abnormal, but after birth, once the ductus arteriosus begins to close, the minimal mixing of systemic and pulmonary blood via the patent foramen ovale is usually insufficient and severe hypoxemia ensues, generally within the 1st few days of life.

CLINICAL MANIFESTATIONS

Cyanosis and tachypnea are most often recognized within the 1st hr or days of life. Untreated, the vast majority of these infants would not survive the neonatal period. Hypoxemia is usually moderate to severe, depending on the degree of atrial level shunting and whether the ductus is partially open or totally closed. This condition is a medical emergency, and only early diagnosis and appropriate intervention can avert the development of prolonged severe hypoxemia and acidosis, which lead to death. Physical findings, other than cyanosis, may be remarkably nonspecific. The precordial impulse may be normal, or a parasternal heave may be present. The 2nd heart sound is usually single and loud, although it may be split. Murmurs may be absent, or a soft systolic ejection murmur may be noted at the midleft sternal border.

DIAGNOSIS

The electrocardiogram is usually normal, showing the expected neonatal right-sided dominant pattern. Chest x-rays may show mild cardiomegaly, a narrow mediastinum (the classic "egg-shaped heart"), and normal to increased pulmonary blood flow. In the early newborn period, the chest roentgenogram is generally normal. As pulmonary vascular resistance drops during the 1st several wk of life, evidence of increased pulmonary blood flow becomes apparent. Arterial Po_2 is low and does not rise appreciably after the patient breathes 100% oxygen (hyperoxia test), although this test may not be totally reliable. Echocardiography is diagnostic and confirms the transposed ventricular-arterial connections (Fig. 431-2). The size of the interatrial communication and the ductus arteriosus can be visualized and the degree of mixing assessed by pulsed and color Doppler examination. The presence of any associated lesion, such as left ventricular outflow tract obstruction or a VSD, can also be assessed. The origins of the coronary arteries can be imaged, although echocardiography is generally not as accurate as catheterization for this purpose. Cardiac

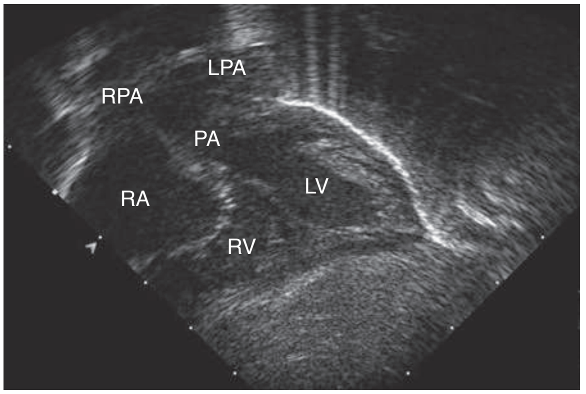

Figure 431-2 **Subcostal 4-chamber 2-dimensional echocardiographic demonstration of d-transposition of the great arteries.** The pulmonary artery (PA) can be seen arising directly from the left ventricle (LV). The immediate bifurcation of this great vessel into the branch pulmonary arteries differentiates it from the aorta, which branches more distally from the heart. LPA, left pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle.

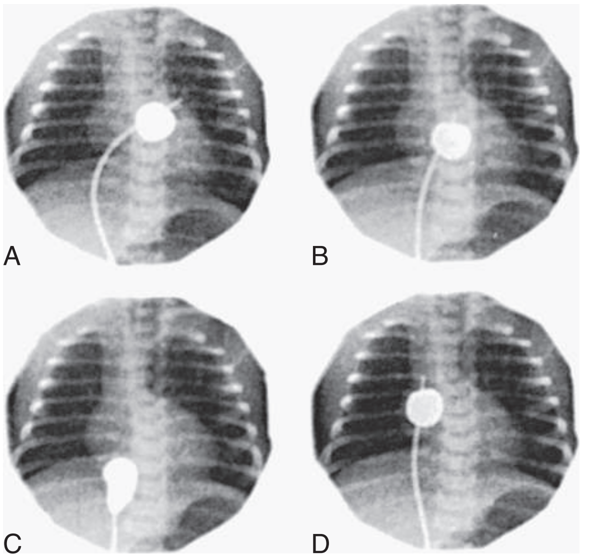

Figure 431-3 **Rashkind balloon atrial septostomy.** Four frames from a continuous cineangiogram show the creation of an atrial septal defect in a hypoxemic newborn infant with transposition of the great arteries and an intact ventricular septum. **A,** Balloon inflated in the left atrium. **B,** The catheter is jerked suddenly so that the balloon ruptures the foramen ovale. **C,** Balloon in the inferior vena cava. **D,** Catheter advanced to the right atrium to deflate the balloon. The time from **A** to **C** is <1 sec.

catheterization may be performed in patients for whom noninvasive imaging is diagnostically inconclusive, where an unusual coronary artery anomaly is suspected, or in patients who require emergency balloon atrial septostomy (Rashkind procedure). Catheterization will show right ventricular pressure to be systemic because this ventricle is supporting the systemic circulation. The blood in the left ventricle and pulmonary artery has a higher oxygen saturation than that in the aorta. Depending on the age at catheterization, left ventricular and pulmonary arterial pressure can vary from systemic level to <50% of systemic-level pressure. Right ventriculography demonstrates the anterior and rightward aorta originating from the right ventricle, as well as the intact ventricular septum. Left ventriculography shows that the pulmonary artery arises exclusively from the left ventricle.

Anomalous coronary arteries are noted in 10-15% of patients and defined by an aortic root injection or by selective coronary arteriography.

TREATMENT

When transposition is suspected, an infusion of prostaglandin E_1 should be initiated immediately to maintain patency of the ductus arteriosus and improve oxygenation (dosage: 0.01-0.20 µg/kg/min). Because of the risk of apnea associated with prostaglandin infusion, an individual skilled in neonatal endotracheal intubation should be available. Hypothermia intensifies the metabolic acidosis resulting from hypoxemia, and thus the patient should be kept warm. Prompt correction of acidosis and hypoglycemia is essential.

Infants who remain severely hypoxic or acidotic despite prostaglandin infusion should undergo **Rashkind balloon atrial septostomy** (Fig. 431-3). A Rashkind atrial septostomy is also usually performed in all patients in whom any significant delay in surgery is necessary. If surgery is planned during the 1st 2 wk of life, and the patient is stable, catheterization and atrial septostomy may be avoided.

A successful Rashkind atrial septostomy should result in a rise in PaO_2 to 35-50 mm Hg and elimination of any pressure gradient across the atrial septum. Some patients with TGA and VSD (see Chapter 431.3) may require balloon atrial septostomy because of poor mixing, even though the VSD is large. Others may benefit from decompression of the left atrium to alleviate the symptoms of increased pulmonary blood flow and left-sided heart failure.

The **arterial switch (Jatene) procedure** is the surgical **treatment of choice** for neonates with d-TGA and an intact ventricular septum and is usually performed within the 1st 2 wk of life. The reason for this time frame is that as pulmonary vascular resistance declines after birth, pressure in the left ventricle (connected to the pulmonary vascular bed) also declines. This drop in pressure results in a decrease in left ventricular mass over the 1st few wk of life. If the arterial switch operation is attempted after left ventricular pressure (and mass) has declined too far, the left ventricle will be unable to generate adequate pressure to pump blood to the high pressure systemic circulation. The arterial switch operation involves dividing the aorta and pulmonary artery just above the sinuses and reanastomosing them in their correct anatomic positions. The coronary arteries are removed from the old aortic root along with a button of aortic wall and reimplanted in the old pulmonary root (the "neoaorta"). By using a button of great vessel tissue, the surgeon avoids having to suture directly onto the coronary artery (Fig. 431-4); this is the major innovation that has allowed the arterial switch to replace previous atrial switch operations for d-TGA. Rarely, a 2-stage arterial switch procedure, with initial placement of a pulmonary artery band, may be used in patients presenting late who already have had a reduction in left ventricular muscle mass and pressure.

The arterial switch procedure has a survival rate of >95% for uncomplicated d-TGA. It restores the normal physiologic relationships of systemic and pulmonary arterial blood flow and eliminates the long-term complications of the previously used atrial switch procedure.

Previous operations for d-TGA consisted of some form of **atrial switch procedure** (**Mustard** or **Senning** operation). These procedures produced excellent early survival (≈85-90%), but had significant long-term morbidities. Atrial switch procedures reverse blood flow at the atrial level by the creation of an interatrial baffle that directs systemic venous blood returning from the vena cavae to the left atrium, where it will enter the left ventricle and then, via the pulmonary artery, the lungs. The same baffle also permits oxygenated pulmonary venous blood to cross over to the right atrium, right ventricle, and aorta. Atrial switch procedures involve significant atrial surgery and have been associated with the late development of atrial conduction disturbances, sick sinus syndrome with bradyarrhythmia and tachyarrhythmia, atrial flutter, sudden death, superior or inferior vena cava syndrome, edema, ascites, and protein-losing enteropathy. The atrial switch procedure also leaves the right ventricle as the systemic pumping chamber and these "systemic" right ventricles often begin to fail in young adulthood. Atrial

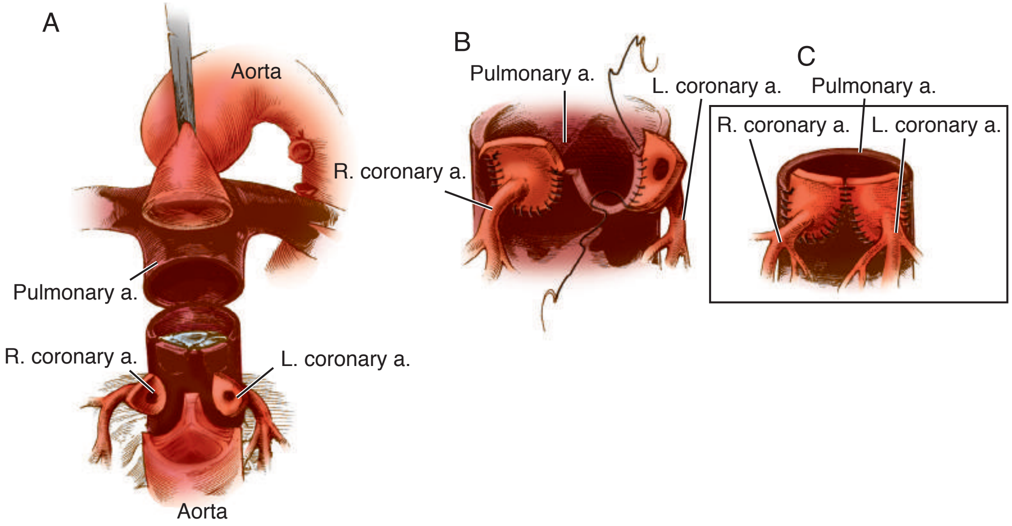

Figure 431-4 **Method for translocating the coronary arteries in the arterial switch (Jatene) procedure. A,** The aorta (anterior) and the pulmonary artery (posterior) have been transected to allow visualization of the left and right coronary arteries. The coronaries have been excised from their respective sinuses, including a large flap (button) of arterial wall. Equivalent segments of the wall of the pulmonary artery (which will become the neoaorta) are also removed. **B,** The aortocoronary buttons are sutured into the proximal portion of the neoaorta. With this technique all sutures are placed in the button of aortic wall rather than directly on the coronary arteries. **C,** Completed anastomosis of the left and right coronary arteries to the neoaorta. *(Adapted from Castañeda AR, Jonas RA, Mayer JE Jr, et al:* Cardiac surgery of the neonate and infant, *Philadelphia, 1994, WB Saunders.)*

switch operations are currently reserved for patients whose anatomy is such that they are not candidates for the arterial switch procedure.

431.3 Transposition of the Great Arteries with Ventricular Septal Defect

Daniel Bernstein

If the VSD associated with d-TGA is small, the clinical manifestations, laboratory findings, and treatment are similar to those described previously for transposition with an intact ventricular septum. A harsh systolic murmur is audible at the lower left sternal border, resulting from flow through the defect. Many of these small defects eventually close spontaneously and may not be addressed at the time of surgery.

When the VSD is large and not restrictive to ventricular ejection, significant mixing of oxygenated and deoxygenated blood usually occurs and clinical manifestations of cardiac failure are seen. The degree of cyanosis may be subtle and sometimes may not be recognized until an oxygen saturation measurement is performed. The murmur is holosystolic and generally indistinguishable from that produced by a large VSD in patients with normally related great arteries. The heart is usually significantly enlarged.

Cardiomegaly, a narrow mediastinal waist, and increased pulmonary vascularity are demonstrated on the chest x-ray. The electrocardiogram shows prominent P waves and isolated right ventricular hypertrophy or biventricular hypertrophy. Occasionally, dominance of the left ventricle is present. Usually, the QRS axis is to the right, but it can be normal or even to the left. The diagnosis is confirmed by echocardiography, and the extent of pulmonary blood flow can also be assessed by the degree of enlargement of the left atrium and ventricle. In equivocal cases, the diagnosis can be confirmed by cardiac catheterization. Right and left ventriculography indicate the presence of arterial transposition and demonstrate the site and size of the VSD. Systolic pressure is equal in the 2 ventricles, the aorta, and the pulmonary artery. Left atrial pressure may be much higher than right atrial pressure, a finding indicative of a restrictive communication at the atrial level. At the time of cardiac catheterization, Rashkind balloon atrial septostomy may be performed to decompress the left atrium, even when adequate mixing is occurring at the ventricular level.

Surgical treatment is advised soon after diagnosis, because heart failure and failure to thrive are difficult to manage and pulmonary vascular disease can develop unusually rapidly in these patients. Preoperative management with diuretics lessens the symptoms of heart failure and stabilizes the patient prior to surgery.

Patients with d-TGA and a VSD without pulmonic stenosis can be treated with an arterial switch procedure combined with VSD closure. In these patients, the arterial switch operation can be safely performed after the 1st 2 wk of life because the VSD results in equal pressure in both ventricles and prevents regression of left ventricular muscle mass. At major centers, however, there is no reason to delay repair, as results are excellent whether the surgery is performed in the neonatal period or later.

431.4 L-Transposition of the Great Arteries (Corrected Transposition)

Daniel Bernstein

In l-transposition (l-TGA), the atrioventricular relationships are discordant: the right atrium is connected to the left ventricle and the left atrium to the right ventricle (also known as *ventricular inversion*). The great arteries are also transposed, with the aorta arising from the right ventricle and the pulmonary artery from the left. In contrast to d-TGA, the aorta arises to the left of the pulmonary artery (hence the designation *l* for levo-transposition). The aorta may be anterior to the pulmonary artery, although often they are nearly side by side.

The physiology of l-TGA is quite different from that of d-TGA. Desaturated systemic venous blood returns via the vena cavae to a normal right atrium, from which it passes through a bicuspid atrioventricular (mitral) valve into a right-sided ventricle that has the architecture and smooth wall morphologic features of the normal left ventricle (Fig. 431-5). Because transposition is also present, however, the desaturated blood ejected from this left ventricle enters the transposed pulmonary artery and flows into the lungs, as it would in the normal circulation. Oxygenated pulmonary venous blood returns to a normal left atrium, passes through a tricuspid atrioventricular valve into a left-sided ventricle, which has the trabeculated morphologic features of a normal right ventricle, and is then ejected into the

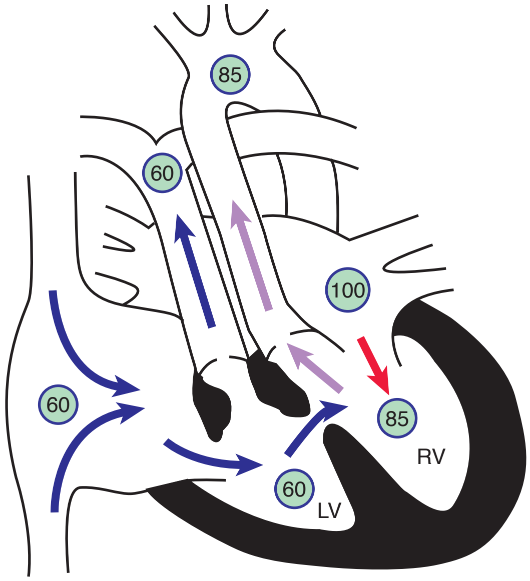

Figure 431-5 Physiology of l- or corrected transposition of the great arteries (l-TGA) with a ventricular septal defect and pulmonic stenosis (VSD + PS). *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. Blood from the right atrium flows through the mitral valve into the "inverted" left ventricle (LV). The left ventricle is, however, attached to the transposed pulmonary artery. Therefore, despite the anomalies, desaturated blood still winds up in the pulmonary circulation. Saturated blood returns to the left atrium, traverses the tricuspid valve into the "inverted" right ventricle (RV), and is pumped into the transposed aorta. This circulation would be totally "corrected" were it not for the frequent association of other congenital anomalies, in this case, VSD + PS. Because of the stenotic pulmonary valve, some left ventricular blood flow crosses the VSD and into the right ventricle and the ascending aorta, and systemic desaturation results.

transposed aorta. The double inversion of the atrioventricular and ventriculoarterial relationships result in desaturated right atrial blood appropriately flowing to the lungs and oxygenated pulmonary venous blood appropriately flowing to the aorta. The circulation is thus physiologically **"corrected."** Without other defects, the hemodynamics would be nearly normal. In most patients, however, associated anomalies coexist: VSD, Ebstein-like abnormalities of the left-sided atrioventricular (tricuspid) valve, pulmonary valvular or subvalvular stenosis (or both), and atrioventricular conduction disturbances (complete heart block, accessory pathways such as Wolff-Parkinson-White syndrome).

CLINICAL MANIFESTATIONS

Symptoms and signs are widely variable and are determined by the associated lesions. If pulmonary outflow is unobstructed, the clinical signs are similar to those of an isolated VSD. If l-TGA is associated with pulmonary stenosis and a VSD, the clinical signs are more similar to those of tetralogy of Fallot.

DIAGNOSIS

The chest x-ray may suggest the abnormal position of the great arteries; the ascending aorta occupies the upper left border of the cardiac silhouette and has a straight profile. The electrocardiogram, in addition to any atrioventricular conduction disturbances, may show abnormal P waves; absent Q waves in V_6; abnormal Q waves in leads III, aVR, aVF, and V_1; and upright T waves across the precordium. The echocardiogram is diagnostic. The characteristic echocardiographic features of the right ventricle (moderator band, coarser trabeculations, tricuspid valve that sits more inferiorly compared to the bicuspid mitral valve, and a smooth muscular conus or infundibulum separating the atrioventricular valve from the semilunar valve) allow the echocardiographer to determine the presence of atrioventricular discordance (right atrium connected to left ventricle; left atrium to right ventricle).

Surgical treatment of the associated anomalies, most often the VSD, is complicated by the position of the bundle of His, which can be injured at the time of surgery and result in heart block. Identification of the usual course of the bundle in corrected transposition (running superior to the defect) has been accomplished by mapping of the conduction system so that the surgeon can avoid the bundle of His during repair. Even without surgical injury, patients with l-TGA are at risk for heart block as they grow older.

Because simple surgical correction leaves the right ventricle as the systemic pumping chamber, and hence vulnerable to late ventricular failure, surgeons have become more aggressive about trying operations that utilize the left ventricle as the systemic pumping chamber. This is accomplished by performing an atrial switch operation, to reroute the systemic and pulmonary venous returns, in combination with an arterial switch operation to reroute the ventricular outflows **(double switch procedure).** The long-term benefit of this approach in preserving systemic ventricular function is still under investigation.

Bibliography is available at Expert Consult.

431.5 Double-Outlet Right Ventricle Without Pulmonary Stenosis

Daniel Bernstein

In double-outlet right ventricle without pulmonary stenosis, both the aorta and the pulmonary artery arise from the right ventricle (see Chapter 430.5). The only outlet from the left ventricle is through a VSD. In the absence of obstruction to pulmonary blood flow, clinical manifestations are similar to those of an uncomplicated VSD with a large left-to-right shunt, although mild systemic desaturation may be present because of mixing of oxygenated and deoxygenated blood in the right ventricle. The electrocardiogram usually shows biventricular hypertrophy. Echocardiography is diagnostic and shows the right ventricular origin of both great arteries, their anteroposterior relationship, as well as the relationship of the VSD to each of the great arteries. Surgical correction is dependent on these relationships. If the VSD is subaortic, it is accomplished by creation of an intracardiac tunnel. Blood is then ejected from the left ventricle via the VSD into the aorta. If the VSD is subpulmonic, an arterial switch may be performed in combination with an intracardiac tunnel. If pulmonary blood flow is excessive enough to cause congestive heart failure, pulmonary arterial banding may be required in infancy, followed by surgical correction when the child is bigger. When associated pulmonary stenosis is present, cyanosis is more marked, pulmonary blood flow is decreased, and clinical presentation may be similar to that of tetralogy of Fallot (see Chapter 430.5).

431.6 Double-Outlet Right Ventricle with Malposition of the Great Arteries (Taussig-Bing Anomaly)

Daniel Bernstein

In double-outlet right ventricle with malposed great arteries, the VSD is usually directly subpulmonary and the aorta distant from the left ventricle. Sometimes both the pulmonary and aortic valves may be located close to the VSD (doubly committed VSD) and sometimes neither is (doubly uncommitted VSD). The term *malposition* is used instead of *transposition* because both great arteries arise from the right ventricle. Aortic obstructive lesions are common, including valvular

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and subvalvular aortic stenosis, coarctation of the aorta, and interruption of the aortic arch. Because pulmonary blood flow is unobstructed, patients experience cardiac failure early in infancy and are at risk for the development of pulmonary vascular disease and cyanosis. If aortic obstructive lesions are a component, patients can present with poor systemic output and cardiovascular collapse, particularly after the ductus begins to close. Cardiomegaly is usual, and a parasternal systolic ejection murmur is audible, sometimes preceded by an ejection click and loud closure of the pulmonary valve. The electrocardiogram shows right axis deviation and right, left, or biventricular hypertrophy. The chest x-ray shows cardiomegaly and prominence of the pulmonary vasculature. The anatomic features of the anomaly and associated abnormalities are usually demonstrated by echocardiography, augmented if necessary by either cardiac catheterization, MRI, or CT. Palliation may be achieved by pulmonary arterial banding in infancy and surgical correction at a later age, which may be accomplished by an arterial switch procedure (see Chapter 431.2) combined with an intracardiac baffle, or some modification of the Rastelli procedure (see Chapter 430.5).

Table 431-1 Total Anomalous Pulmonary Venous Return

SITE OF CONNECTION (% OF CASES)	% WITH SIGNIFICANT OBSTRUCTION
Supracardiac (50)	
Left superior vena cava (40)	40
Right superior vena cava (10)	75
Cardiac (25)	
Coronary sinus (20)	10
Right atrium (5)	5
Infracardiac (20)	95-100
Mixed (5)	

431.7 Total Anomalous Pulmonary Venous Return

Daniel Bernstein

PATHOPHYSIOLOGY

Abnormal development of the pulmonary veins may result in either partial or complete anomalous drainage into the systemic venous circulation. Partial anomalous pulmonary venous return is usually an acyanotic lesion (see Chapter 426.4). Total anomalous pulmonary venous return (TAPVR) is associated with total mixing of systemic venous and pulmonary venous blood flow within the heart and thus produces cyanosis.

In TAPVR, the heart has no direct pulmonary venous connection into the left atrium. The pulmonary veins may drain above the diaphragm into the right atrium directly, into the coronary sinus, or into the superior vena cava via a "vertical vein," or they may drain below the diaphragm and join into a "descending vein" that enters into the inferior vena cava or one of its major tributaries, often via the ductus venosus. This latter form of anomalous venous drainage is most commonly associated with obstruction to venous flow, usually as the ductus venosus closes soon after birth, although supracardiac anomalous veins may also become obstructed. Occasionally, the drainage may be mixed, with some veins draining above and others below the diaphragm.

All forms of TAPVR involve mixing of oxygenated and deoxygenated blood before or at the level of the right atrium (total mixing lesion). This mixed right atrial blood either passes into the right ventricle and pulmonary artery or passes through an atrial septal defect (ASD) or patent foramen ovale into the left atrium, which will be the only source of systemic blood flow. The right atrium and ventricle and the pulmonary artery are generally enlarged, whereas the left atrium and ventricle may be normal or small. The clinical manifestations of TAPVR depend on the presence or absence of obstruction of the venous channels (Table 431-1). If pulmonary venous return is obstructed, severe pulmonary congestion and pulmonary hypertension develop; rapid deterioration occurs without surgical intervention. Obstructed TAPVR is a pediatric cardiac surgical emergency because prostaglandin therapy is usually not effective.

CLINICAL MANIFESTATIONS

Two major clinical patterns of TAPVR are seen, depending on the presence or absence of obstruction. Those neonates with severe obstruction to pulmonary venous return, most prevalent in the infracardiac group (see Table 431-1), present with severe cyanosis and respiratory distress. Murmurs may not be present. These infants are severely ill and fail to respond to mechanical ventilation. Rapid diagnosis and surgical correction are necessary for survival. In contrast, those with mild or no obstruction to pulmonary venous return are usually characterized by the development of heart failure as the pulmonary vascular resistance falls, with mild to moderate degrees of desaturation. Systolic murmurs may be audible along the left sternal border, and a gallop rhythm may be present. Some infants may have mild obstruction in the neonatal period and develop worsening obstruction as time passes.

DIAGNOSIS

The electrocardiogram demonstrates right ventricular hypertrophy (usually a qR pattern in V_3R and V_1, and the P waves are frequently tall and spiked). In neonates with marked pulmonary venous obstruction, the chest x-ray demonstrates a very dramatic perihilar pattern of pulmonary edema and a small heart. This appearance can sometimes be confused with primary pulmonary disease and the differential diagnosis includes persistent pulmonary hypertension of the newborn, respiratory distress syndrome, pneumonia (bacterial, meconium aspiration), pulmonary lymphangiectasia, and other heart defects (hypoplastic left heart syndrome). In older children, if the anomalous pulmonary veins enter the innominate vein and persistent left superior vena cava (Fig. 431-6), a large supracardiac shadow can be seen, which together with the normal cardiac shadow forms a **"snowman"** appearance. In most cases without obstruction, the heart is enlarged, the pulmonary artery and right ventricle are prominent, and pulmonary vascularity is increased.

The echocardiogram demonstrates a large right ventricle and usually identifies the pattern of abnormal pulmonary venous connections (Fig. 431-7). The demonstration of any vein with Doppler flow away from the heart is pathognomonic of TAPVR as normal venous flow is usually toward the heart. Shunting occurs from right to left at the atrial level. The size of the left atrium and left ventricle can be measured and the presence of any associated cardiac defects determined.

Echocardiography should be adequate to demonstrate TAPVR in most cases; however, if there is question about the drainage of 1 or more pulmonary veins, cardiac catheterization, MRI, or CT is performed. Catheterization shows that the oxygen saturation of blood in both atria, both ventricles, and the aorta is similar, indicative of a total mixing lesion. An increase in systemic venous saturation occurs at the site of entry of the abnormal pulmonary venous channel, either above or below the diaphragm. In older patients, pulmonary arterial and right ventricular pressure may be only moderately elevated, but in infants with pulmonary venous obstruction, pulmonary hypertension is usual. Selective pulmonary arteriography shows the anatomy of the pulmonary veins and their point of entry into the systemic venous circulation.

TREATMENT

Surgical correction of TAPVR is indicated during infancy, with emergent repair performed for those patients with venous obstruction. If

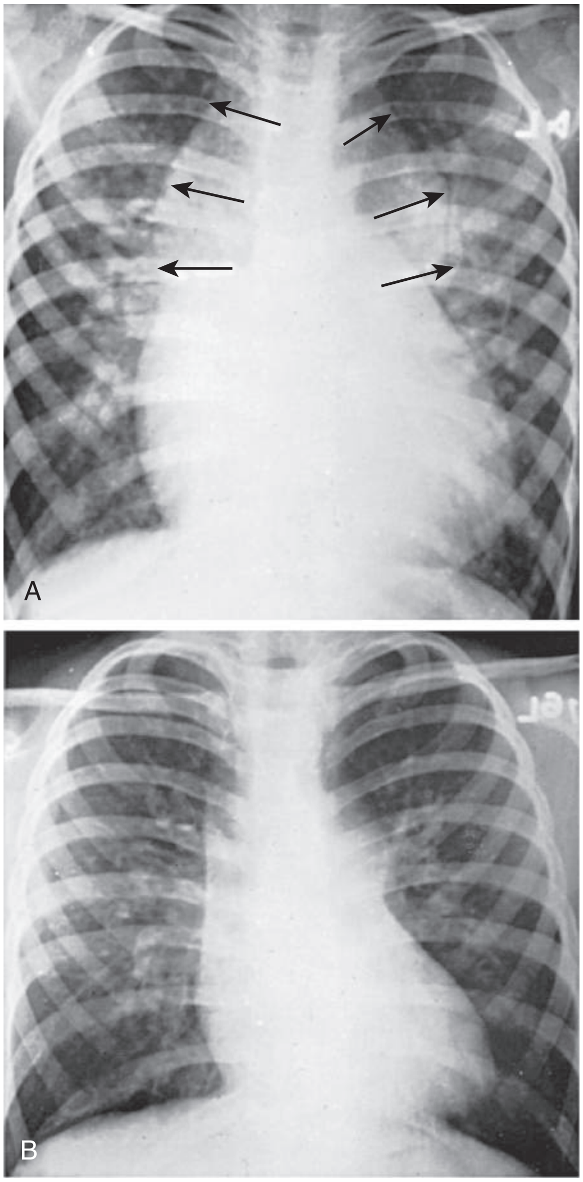

Figure 431-6 Chest x-ray of total anomalous pulmonary venous return to the left superior vena cava. **A,** Preoperative image. *Arrows* point to the supracardiac shadow, which produces the snowman or figure-8 configuration. Cardiomegaly and increased pulmonary vascularity are evident. **B,** Postoperative image showing a decrease in the size of the heart and the supracardiac shadow.

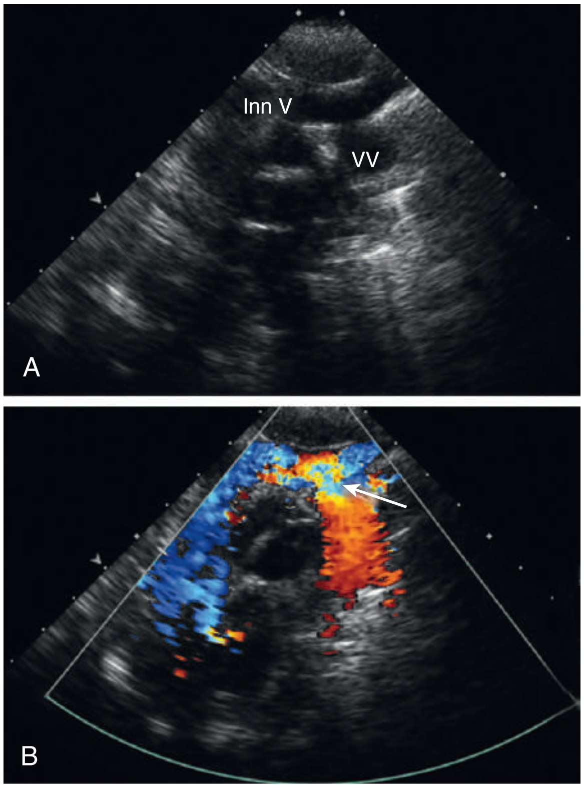

Figure 431-7 Suprasternal 2-dimensional echocardiographic views demonstrating supracardiac total anomalous pulmonary venous return (type I). **A,** The large vertical ascending vein can be seen entering the innominate vein. There is a moderate narrowing where the anomalous vein enters the upper body venous system. **B,** Color Doppler examination shows a venous flow signal *(red color)* indicating that blood is moving away toward the transducer and thus from the heart (all venous flow should normally return toward the heart), diagnostic of anomalous pulmonary venous return. The turbulent acceleration of flow can be seen *(arrow)* where the vertical vein enters the innominate. Inn V, innominate vein; VV, vertical vein.

surgery cannot be performed urgently, extracorporeal membrane oxygenation may be required to maintain oxygenation. Surgically, the pulmonary venous confluence is anastomosed directly to the left atrium, the ASD is closed, and any connection to the systemic venous circuit is interrupted. Early results are generally good, even for critically ill neonates. The postoperative period may be complicated by pulmonary vascular hypertensive crises. In some patients, especially those in whom the diagnosis was delayed or the obstruction was severe, recurrent stenosis and development of pulmonary veno-occlusive disease may occur. Attempts have been made to treat recurrent stenosis with surgery, balloon angioplasty, stents, and antiproliferative chemotherapy. To date, the long-term prognosis in these patients is very guarded and in those with aggressive veno-occlusive disease, **heart-lung transplantation** may be the only option (see Chapter 443.2).

Bibliography is available at Expert Consult.

431.8 Truncus Arteriosus

Daniel Bernstein

PATHOPHYSIOLOGY

In truncus arteriosus, a single arterial trunk (truncus arteriosus) arises from the heart and supplies the systemic, pulmonary, and coronary circulations. A VSD is always present, with the truncus overriding the defect and receiving blood from both the right and left ventricles (Fig. 431-8). The number of truncal valve cusps varies from 2 to as many as 6 and the valve may be stenotic, regurgitant, or both. The pulmonary arteries can arise together from the posterior left side of the persistent truncus arteriosus and then divide into left and right pulmonary arteries **(type I).** In **types II** and **III** truncus arteriosus, no main pulmonary artery is present, and the right and left pulmonary arteries arise from separate orifices on the posterior **(type II)** or lateral **(type III)** aspects of the truncus arteriosus. **Type IV** truncus is a term no longer used because, in this case, there is no identifiable connection between the heart and pulmonary arteries, and pulmonary blood flow is derived from major aortopulmonary collateral arteries arising from the transverse or descending aorta; this is essentially a form of pulmonary atresia (see Chapter 430.2).

Both ventricles are at systemic pressure and both eject blood into the truncus. When pulmonary vascular resistance is relatively high immediately after birth, pulmonary blood flow may be normal; as pulmonary resistance drops in the 1st mo of life, blood flow to the lungs is greatly increased and heart failure ensues. Truncus arteriosus is a total mixing lesion with complete admixture of pulmonary and systemic venous return. Because of the large volume of pulmonary

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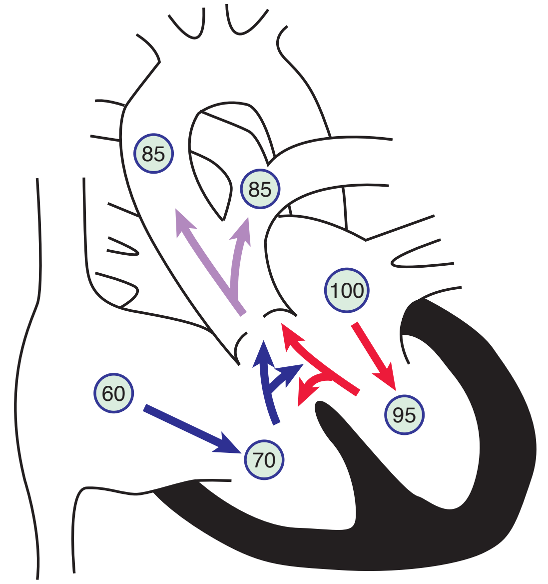

Figure 431-8 **Physiology of truncus arteriosus.** *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. Desaturated blood enters the right atrium, flows through the tricuspid valve into the right ventricle, and is ejected into the truncus. Saturated blood returning from the left atrium enters the left ventricle and is also ejected into the truncus. The common aortopulmonary trunk gives rise to the ascending aorta and to the main or branch pulmonary arteries. Oxygen saturation in the aorta and pulmonary arteries is usually the same (definition of a total mixing lesion). As pulmonary vascular resistance decreases in the 1st few wk of life, pulmonary blood flow increases dramatically and mild cyanosis and congestive heart failure result.

blood flow, clinical cyanosis is usually mild. If the lesion is left untreated, pulmonary resistance eventually increases, pulmonary blood flow decreases, and cyanosis becomes more prominent (Eisenmenger physiology; see Chapter 433.2).

CLINICAL MANIFESTATIONS

The clinical signs of truncus arteriosus vary with age and depend on the level of pulmonary vascular resistance. In the immediate newborn period, signs of heart failure are usually absent; a murmur and minimal cyanosis may be the only initial findings. Over the next 1-2 mo of life, pulmonary blood flow begins to become torrential and the clinical picture is dominated by heart failure, with still mild cyanosis. Runoff of blood from the truncus to the pulmonary circulation may result in a wide pulse pressure and bounding pulses. These findings will be further exaggerated if truncal valve insufficiency is present. The heart is usually enlarged, and the precordium is hyperdynamic. The 2nd heart sound is loud and single. A systolic ejection murmur, sometimes accompanied by a thrill, is generally audible along the left sternal border. The murmur is frequently preceded by an early systolic ejection click due to the abnormal truncal valve. In the presence of truncal valve insufficiency, a high-pitched early diastolic decrescendo murmur is heard at the mid-left sternal border. An apical mid-diastolic rumbling murmur caused by increased flow through the mitral valve is often audible with the bell of the stethoscope, especially as heart failure develops. Truncus arteriosus is a conotruncal malformation and may be associated with **DiGeorge syndrome,** linked to a deletion of a large region of chromosome 22q11 (see Chapter 424).

DIAGNOSIS

The electrocardiogram shows right, left, or combined ventricular hypertrophy. The chest x-ray also shows considerable variation. Cardiac enlargement will develop over the 1st several wk of life, and is a result of the prominence of both ventricles. The truncus may produce a prominent shadow that follows the normal course of the ascending aorta and aortic knob; the aortic arch is right-sided in 50% of patients. Sometimes

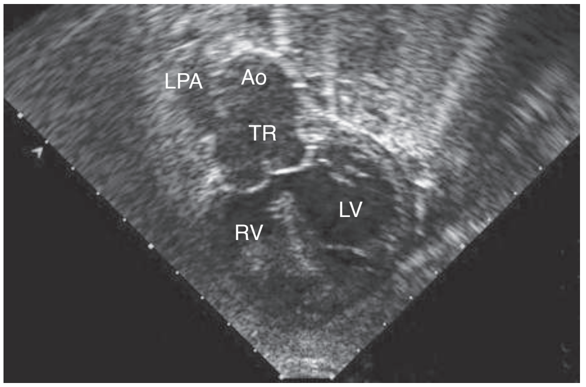

Figure 431-9 **Subcostal 2-dimensional echocardiographic demonstration of truncus arteriosus.** The large truncal valve can be seen overriding the ventricular septal defect. In this case, only the left pulmonary artery (*LPA*) arises from the truncus (*TR*). The pulmonary arteries are discontinuous and the right pulmonary artery arises from the descending aorta via the ductus arteriosus (not shown). Ao, aorta; LV, left ventricle; RV, right ventricle.

a high bulge left of the aortic knob is produced by the main or left pulmonary artery. Pulmonary vascularity is increased after the 1st few wk of life. Echocardiography is diagnostic and demonstrates the large truncal artery overriding the VSD and the pattern of origin of the branch pulmonary arteries (Fig. 431-9). Associated anomalies such as an interrupted aortic arch may be noted. Pulsed and color Doppler studies are used to evaluate truncal valve regurgitation. If required, cardiac catheterization shows a left-to-right shunt at the ventricular level, with right-to-left shunting into the truncus. Systolic pressure in both ventricles and the truncus is similar. Angiography reveals the large truncus arteriosus and more defines the origin of the pulmonary arteries.

PROGNOSIS AND COMPLICATIONS

Surgical results have been excellent, and many patients with repaired truncus are now entering adulthood. The need to replace the right ventricular to pulmonary artery conduit as the child grows means that these patients will need to undergo multiple operations by the time they reach adulthood. When truncus arteriosus is associated with DiGeorge syndrome, the associated endocrine, immunologic, craniofacial, and airway abnormalities may complicate recovery.

TREATMENT

In the 1st few wk of life, many of these infants can be managed with anticongestive medications; as pulmonary vascular resistance falls, heart failure symptoms worsen and surgery is indicated, usually within the 1st few mo. Delay of surgery much beyond this time period may increase the likelihood of pulmonary vascular disease; many centers now perform routine neonatal repair at the time of diagnosis. At surgery, the VSD is closed, the pulmonary arteries are separated from the truncus, and continuity is established between the right ventricle and the pulmonary arteries with a homograft conduit. Immediate surgical results are excellent, but these conduits will develop either regurgitation or stenosis over time, and must be replaced, often several times, as the child grows. If regurgitation is the primary problem, patients can now be treated with a transcatheter stent-valve.

Bibliography is available at Expert Consult.

431.9 Single Ventricle (Double-Inlet Ventricle, Univentricular Heart)

Daniel Bernstein

PATHOPHYSIOLOGY

With a single ventricle, both atria empty through a common atrioventricular valve or via 2 separate valves into a single ventricular chamber, with total mixing of systemic and pulmonary venous return. This

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chamber may have left, right, or indeterminate ventricular anatomic characteristics. The aorta and pulmonary artery both arise from this single chamber, although one of the great vessels may originate from a rudimentary outflow chamber. The aorta may be posterior, anterior (malposition), or side by side with the pulmonary artery and either to the right or to the left. Pulmonary stenosis or atresia is common.

CLINICAL MANIFESTATIONS

The clinical picture is variable and depends on the associated intracardiac anomalies. If pulmonary outflow is obstructed, the findings are usually similar to those of tetralogy of Fallot: marked cyanosis without heart failure. If pulmonary outflow is unobstructed, the findings are similar to those of transposition with VSD: minimal cyanosis with increasing heart failure.

In patients with **pulmonary stenosis**, cyanosis is present in early infancy. Cardiomegaly is mild or moderate, a left parasternal lift is palpable, and a systolic thrill is common. The systolic ejection murmur is usually loud; an ejection click may be audible, and the 2nd heart sound is single and loud. In patients with **unobstructed pulmonary flow**, as pulmonary vascular resistance drops, torrential pulmonary blood flow develops, and these patients present with tachypnea, dyspnea, failure to thrive, and recurrent pulmonary infections. Cyanosis is only mild or moderate. Cardiomegaly is generally marked, and a left parasternal lift is palpable. A systolic ejection murmur is present but is not usually loud or harsh, and the 2nd heart sound is loud and closely split. A 3rd heart sound is common and may be followed by a short mid-diastolic rumbling murmur caused by increased flow through the atrioventricular valves. The eventual development of pulmonary vascular disease reduces pulmonary blood flow so that the cyanosis increases and signs of cardiac failure appear to improve (Eisenmenger physiology; see Chapter 433.2).

DIAGNOSIS

Findings on the electrocardiogram are nonspecific. P waves are normal, spiked, or bifid. The precordial lead pattern suggests right ventricular hypertrophy, combined ventricular hypertrophy, or sometimes left ventricular dominance. The initial QRS forces are usually to the left and anterior. Radiographic examination confirms the degree of cardiomegaly. If present, a rudimentary outflow chamber may produce a bulge on the upper left border of the cardiac silhouette in the posteroanterior projection. In the absence of pulmonary stenosis, pulmonary vasculature is increased, whereas in the presence of pulmonary stenosis, pulmonary vasculature is diminished. Echocardiography will confirm the absence or near absence of the ventricular septum and can usually determine whether the single ventricle has right, left, or mixed morphologic features. The presence of a rudimentary outflow chamber under one of the great vessels can be identified, and pulsed Doppler can be used to determine whether flow through this communication (known as a *bulboventricular foramen*) is obstructed.

If cardiac catheterization is performed, the pressure in the single ventricular chamber is at systemic level; however, a gradient may be demonstrated across the entrance to a rudimentary outflow chamber. Pressure measurements and angiography demonstrate whether pulmonary stenosis is present.

PROGNOSIS AND COMPLICATIONS

Unoperated, some patients succumb during infancy from heart failure. Others may survive to adolescence and early adult life but finally succumb to the effects of chronic hypoxemia or, in the absence of pulmonary stenosis, to the effects of pulmonary vascular disease. Patients with moderate pulmonary stenosis have the best prognosis because pulmonary blood flow, though restricted, is still adequate. Surgical palliation, eventually leading to Fontan-type circulatory physiology (see Chapter 430.4), has very good short- and intermediate-term results.

TREATMENT

If pulmonary stenosis is severe, a **Blalock-Taussig aortopulmonary shunt** is performed to provide a reliable source of pulmonary blood flow (see Chapter 430.1). If pulmonary blood flow is unrestricted, pulmonary arterial banding is used to control heart failure and prevent progressive pulmonary vascular disease. The **bidirectional Glenn shunt** is usually performed at between 2 and 6 mo of age, followed by a **modified Fontan operation** (cavopulmonary isolation procedure; see Chapter 430.4) at 2-3 yr of age. If subaortic stenosis is present because of a restrictive connection to a rudimentary outflow chamber, (restrictive bulboventricular foramen) surgical relief can be provided by anastomosing the proximal pulmonary artery to the side of the ascending aorta **(Damus-Stansel-Kaye operation).**

431.10 Hypoplastic Left-Heart Syndrome

Daniel Bernstein

PATHOPHYSIOLOGY

The term *hypoplastic left heart* is used to describe a related group of anomalies that include various degrees of underdevelopment of the left side of the heart: stenosis or atresia of the aortic and mitral valves and hypoplasia of the left ventricular cavity and ascending aorta. Two broad categories include aortic atresia with hypoplastic but perforate mitral valve or with mitral atresia. The left ventricle may be only moderately hypoplastic, very small and nonfunctional, or totally atretic; in the immediate neonatal period the right ventricle maintains both the pulmonary circulation and the systemic circulation via the ductus arteriosus (Fig. 431-10). Pulmonary venous blood passes through an ASD or dilated foramen ovale from the left to the right side of the heart, where it mixes with systemic venous blood **(total mixing lesion).**

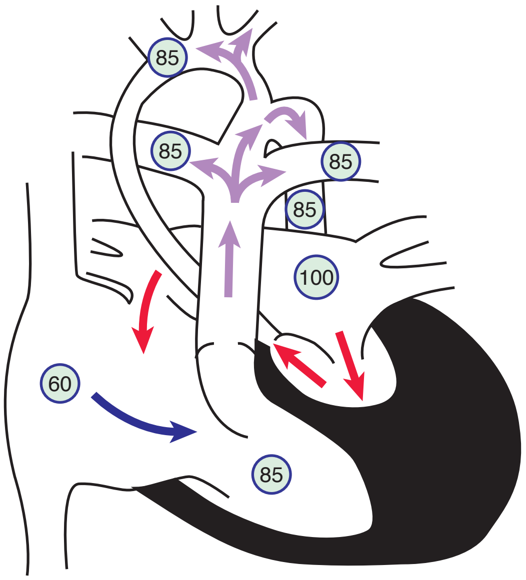

Figure 431-10 Physiology of hypoplastic left-heart syndrome (HLHS). *Circled numbers* represent oxygen saturation values. HLHS is not a single lesion but a constellation of different degrees of hypoplasia of the left-sided heart structures. This drawing shows a patent mitral valve, a small left ventricular cavity, and a diminutive ascending aorta. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. Desaturated blood enters the right atrium, flows through the tricuspid valve into the right ventricle, and is ejected into the pulmonary artery. Because of the markedly decreased left ventricular compliance, most of the pulmonary venous blood returning to the left atrium shunts left to right at the atrial level. A small amount of left atrial blood will cross the mitral valve and be ejected into the tiny ascending aorta. The right ventricular oxygen saturation represents a mixing of desaturated systemic venous blood and saturated pulmonary venous blood. Pulmonary artery blood flows into the pulmonary arteries as well as right to left across the patent ductus arteriosus (PDA) into the aorta. Ductal blood flows prograde to the descending aorta as well as retrograde to the ascending aorta, where it supplies the head and neck vessels in addition to the coronary arteries (which arise off the small ascending aorta). Closure of the PDA results in profound hypoxia and circulatory collapse.

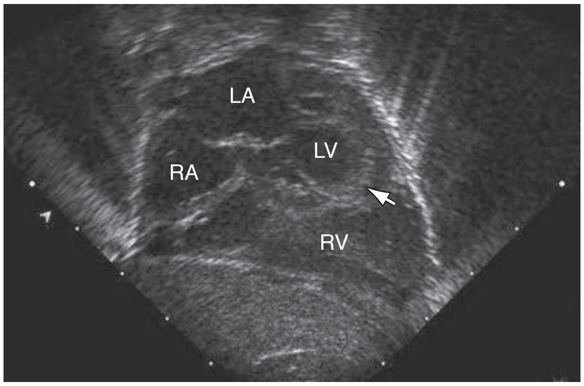

Figure 431-11 Subcostal 2-dimensional echocardiographic diagnosis of hypoplastic left-heart syndrome. The small left ventricular chamber can be seen, the apex of which *(arrowhead)* does not form the apex of the heart. The atrial septum can be seen bowing from the left to the right, indicating that the communication between the 2 atria is pressure restrictive. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

When the ventricular septum is intact, which is usually the case, all the right ventricular blood is ejected into the main pulmonary artery; the descending aorta is supplied via the ductus arteriosus, and flow from the ductus also fills the ascending aorta and coronary arteries in a retrograde fashion. The major hemodynamic abnormalities are inadequate maintenance of the systemic circulation and, depending on the size of the atrial-level communication, either pulmonary venous hypertension (restrictive foramen ovale) or pulmonary overcirculation (moderate or large ASD).

CLINICAL MANIFESTATIONS

Although cyanosis may not always be obvious in the 1st 48 hr of life, a grayish-blue color of the skin is soon apparent and denotes a mix of cyanosis and poor perfusion. The condition is diagnosed in most infants in the 1st few hr or days of life. Once the ductus arteriosus begins to closes, signs of poor systemic perfusion and shock predominate. All of the peripheral pulses may be weak or absent. A palpable right ventricular parasternal lift may be present along with a nondescript systolic murmur.

This lesion may be isolated or associated in 5-15% of patients with known genetic syndromes, such as Turner syndrome, trisomy 13, 18, or 21, Jacobsen syndrome (11q deletion), Holt-Oram syndrome, and Rubinstein-Taybi syndrome. In these circumstances, noncardiac manifestations of the syndrome may be evident and influence the clinical outcomes. Occasionally it is familial and inherited as an autosomal recessive trait.

DIAGNOSIS

On the chest x-ray, the heart is variable in size in the 1st days of life, but cardiomegaly develops rapidly and is associated with increased pulmonary vascularity. The initial electrocardiogram may show only the normal neonatal pattern of right ventricular dominance, but later, P waves become prominent and right ventricular hypertrophy is usual with reduced left ventricular forces. The echocardiogram is diagnostic and demonstrates absence or hypoplasia of the mitral valve and aortic root, a variably small left atrium and left ventricle, and a large right atrium and right ventricle (Fig. 431-11). The size of the atrial communication, by which pulmonary venous blood leaves the left atrium, can be assessed directly and by pulsed and color flow Doppler studies. The small ascending aorta and transverse aortic arch are identified and a discrete coarctation of the aorta in the juxtaductal area may be present, although in the presence of a large ductus, it may be difficult to identify. Doppler echocardiography demonstrates whether the mitral and aortic valves are severely stenotic or totally atretic. The presence of left ventricular coronary sinusoids can be identified. The diagnosis of hypoplastic left-heart syndrome can usually be made without need for cardiac catheterization. If catheterization is necessary, the hypoplastic ascending aorta is demonstrated by angiography.

PROGNOSIS AND COMPLICATIONS

Untreated patients most often succumb during the 1st few mo of life, usually during the 1st or 2nd wk. Occasionally, unoperated patients may live for months or, rarely, years. Up to 30% of infants with hypoplastic left-heart syndrome have evidence of either a major or minor central nervous system abnormality. Other dysmorphic features may be found in up to 40% of patients. Thus, careful preoperative evaluation (genetic, neurologic, ophthalmologic) should be performed in patients being considered for surgical therapy.

Intermediate-term follow up after completion of all 3 stages of the Norwood procedure demonstrates generally good exercise capacity, and complications equivalent to other patients who have had the Fontan palliation (see Chapter 430.4). Some studies show that patients with hypoplastic left-heart syndrome have a higher risk of neurodevelopmental problems than those with other complex congenital heart lesions. Whether the poor neurodevelopmental outcome is due to prenatal associated central nervous system injury or malformation, the alterations of cerebral hemodynamics during bypass surgery, or poor postoperative perfusion is unknown. In addition, poor outcome is associated with prematurity, chromosome syndromes, and poverty.

TREATMENT

Surgical therapy for hypoplastic left-heart syndrome is associated with improving survival rates, reported as high as 90-95% for the 1st-stage palliation in experienced centers. The 1st-stage repair is designed to construct a reliable source of systemic blood flow arising from the single right ventricle using a combination of aortic and pulmonary arterial tissue, and to limit pulmonary blood flow to avoid heart failure and prevent the development of pulmonary vascular disease. The 2 surgical procedures most commonly utilized are the **Norwood procedure** (Fig. 431-12) and the **Sano procedure.** Primary heart transplantation, previously advocated by a few centers, is much less common because of the substantially improved survival rates with standard surgery and the limited supply of donor organs in this age group.

If a Norwood or Sano procedure is to be performed, preoperative medical management includes correction of acidosis and hypoglycemia, maintenance of ductus arteriosus patency with prostaglandin E_1 (0.01-0.20 µg/kg/min) to support systemic blood flow, and prevention of hypothermia. Preoperative management should avoid excessive pulmonary blood flow; either through management of ventilator settings, increasing the concentration of inspired CO_2, or decreasing the concentration of inspired O_2. Balloon dilation of the atrial septum may be indicated.

The Norwood procedure is usually performed in 3 stages. **Stage I** (see Fig. 431-12) includes an atrial septectomy and transection and ligation of the distal main pulmonary artery; the proximal pulmonary artery is then connected to the transversely opened hypoplastic aortic arch to form a neoaorta, extending through the coarcted segment of the juxtaductal aortic arch. A synthetic aortopulmonary (Blalock-Taussig) shunt connects the aorta to the main pulmonary artery to provide controlled pulmonary blood flow. In the Sano modification, a right ventricle to pulmonary artery conduit is used instead of an aortopulmonary shunt to provide pulmonary blood flow, temporarily creating a double-outlet right ventricle. The operative risk for these 1st-stage procedures has improved dramatically in the past 2 decades and the best reported results demonstrate a 90-95% survival rate.

Stage II consists of a Glenn anastomosis to connect the superior vena cava to the pulmonary arteries (see Chapter 431.4), at between 2 and 6 mo of age. **Stage III**, usually performed at 2-3 yr of age, consists of a modified Fontan procedure (cavopulmonary isolation) to connect the inferior vena cava to the pulmonary arteries via either an intraatrial or external baffle. After **stage III,** all systemic venous return enters the pulmonary circulation directly. Pulmonary venous flow enters the left atrium and is directed across the atrial septum to the tricuspid valve and subsequently to the right (now the systemic) ventricle. Blood leaves the right ventricle via the neoaorta, which supplies the systemic

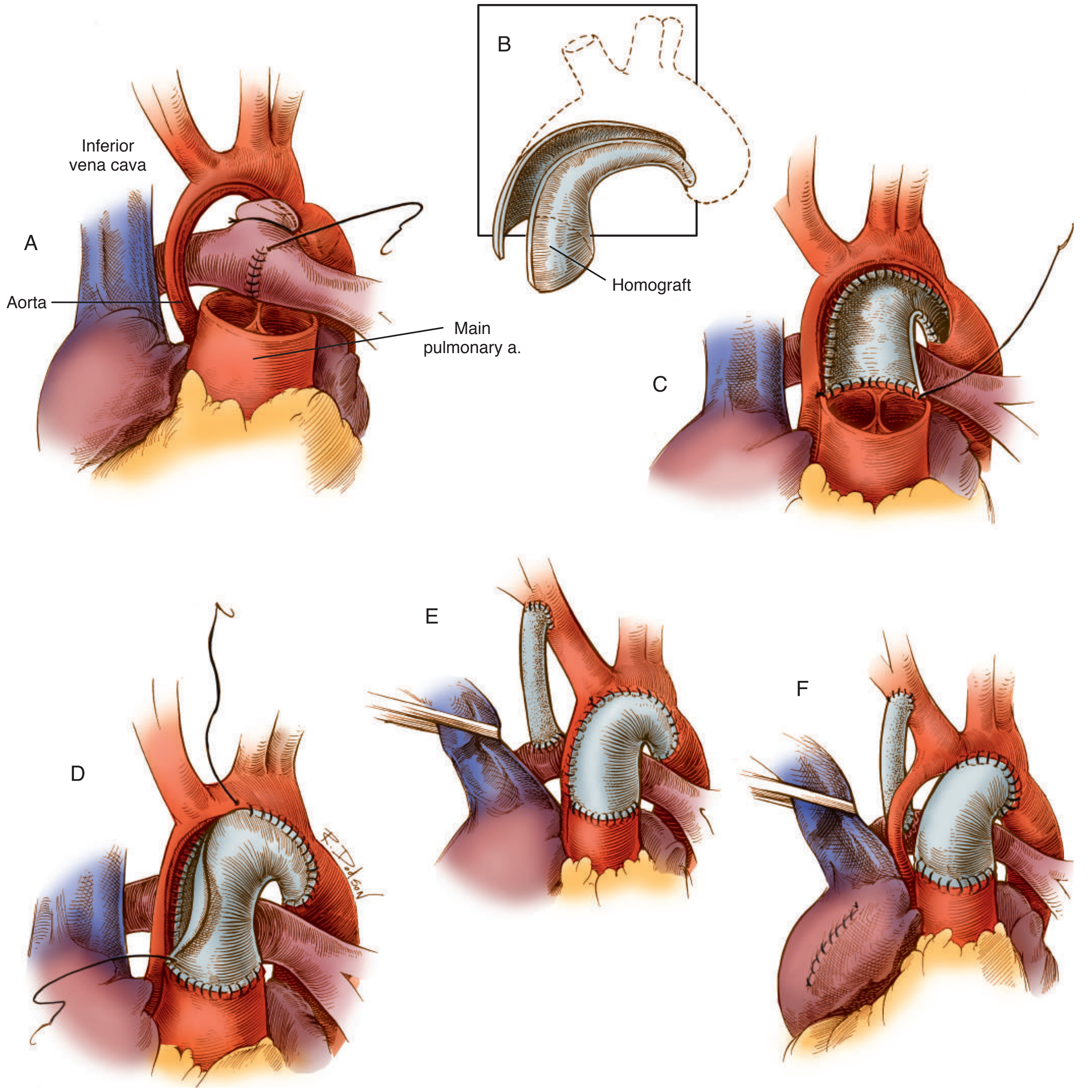

Figure 431-12 The Norwood procedure, 1 of the 2 current techniques for 1st-stage palliation of hypoplastic left-heart syndrome. **A,** Incisions used for the procedure incorporate a cuff of arterial wall allograft. The distal divided main pulmonary artery may be closed by direct suture or with a patch. **B,** Dimensions of the cuff of the arterial wall allograft. **C,** The arterial wall allograft is used to supplement the anastomosis between the proximal divided main pulmonary artery and the ascending aorta, aortic arch, and proximal descending aorta. **D** and **E,** The procedure is completed by an atrial septectomy and a 3.5-mm modified right Blalock shunt. **F,** When the ascending aorta is particularly small, an alternative procedure involves placement of a complete tube of arterial allograft. The tiny ascending aorta may be left in situ, as indicated, or implanted into the side of the neoaorta. *(From Castañeda AR, Jonas RA, Mayer JE Jr, et al: Single-ventricle tricuspid atresia. In* Cardiac surgery of the neonate and infant, *Philadelphia, 1994, WB Saunders.)*

circulation. The old aortic root now attached to the neoaorta provides coronary blood flow. The risks associated with stages II and III are even less than those of stage I; interstage mortality (usually between stages I and II) has been reduced with the use of home monitoring programs. The short- and long-term benefits of using the Norwood versus the Sano procedure remain to be demonstrated.

An alternative therapeutic approach is to perform a **hybrid procedure** for the 1st stage. This involves performing a Rashkind balloon atrial septostomy, catheter placement of a stent in the ductus arteriosus, and surgical placement of bilateral pulmonary artery bands. After the hybrid procedure, patients can be weaned off prostaglandin and discharged from hospital. After the hybrid procedure, patients need to undergo a more extensive 2nd-stage procedure involving construction of a neoaorta and removal of the pulmonary artery bands.

Another alternative therapy is **cardiac transplantation,** either in the immediate neonatal period, thereby obviating stage I of the Norwood procedure, or after a successful stage I Norwood procedure is performed as a bridge to transplantation. After transplantation, patients usually have normal cardiac function and no symptoms of heart failure; however, these patients have the chronic risk of organ rejection and lifelong immunosuppressive therapy (see Chapter 443.1). The combination of donor shortage and improved results with standard surgical and hybrid procedures has caused most centers to stop recommending transplantation except when associated lesions make the Norwood operation an exceptionally high-risk procedure, or for patients who develop poor ventricular function at some time after the standard surgical approach.

There are some subgroups of patients with hypoplastic left-heart syndrome that may be at increased surgical risk, particularly those with mitral stenosis plus aortic atresia. These data need confirmation in larger studies, and alternative approaches to remain to be developed.

PREVENTION

Serial fetal echocardiographic studies demonstrate that in some fetuses, hypoplastic left-heart syndrome may be a progressive lesion, beginning with simple valvar aortic stenosis in midgestation. The decreased flow through the stenotic aortic valve reduces flow through the left ventricle during development, resulting in gradual ventricular chamber hypoplasia. The potential for preventing this hypoplasia has been demonstrated by performing in utero aortic balloon valvuloplasty in midgestation fetuses (Fig. 431-13). Early results are encouraging, although even if the aortic valve is successfully opened, adequate ventricular growth occurs in only about 30% of patients. At present, this procedure is regarded as experimental.

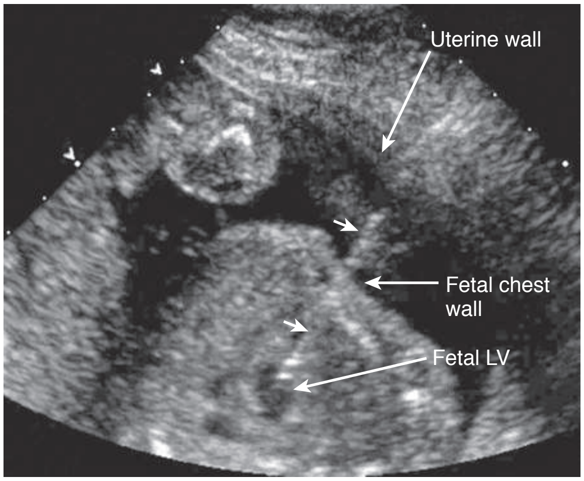

Figure 431-13 **Fetal treatment of critical aortic stenosis to prevent development of hypoplastic left-heart syndrome.** Fetal ultrasound showing insertion of a needle *(arrowheads)* via the maternal abdominal wall, through the uterus and the fetal chest wall, and into the fetal left ventricle (LV). A balloon catheter is next inserted via the needle into the left ventricular chamber and across the stenotic aortic valve. The balloon is inflated to dilate the valve, the catheter and needle are removed. *(Courtesy of Dr. Stanton Perry, Stanford University, Stanford, CA.)*

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431.11 Abnormal Positions of the Heart and the Heterotaxy Syndromes (Asplenia, Polysplenia)

Daniel Bernstein

Classification and diagnosis of abnormal cardiac position are best performed via a segmental approach, with the position of the viscera and atria defined first, and then the ventricles, followed by the great vessels (Fig. 431-14). Determination of **visceroatrial situs** can be made by radiography demonstration of the position of the abdominal organs and the tracheal bifurcation for recognition of the right and left bronchi and by echocardiography. The atrial situs is usually similar to the situs of the viscera and lungs. In **situs solitus**, the viscera are in their normal positions (stomach and spleen on the left, liver on the right), the

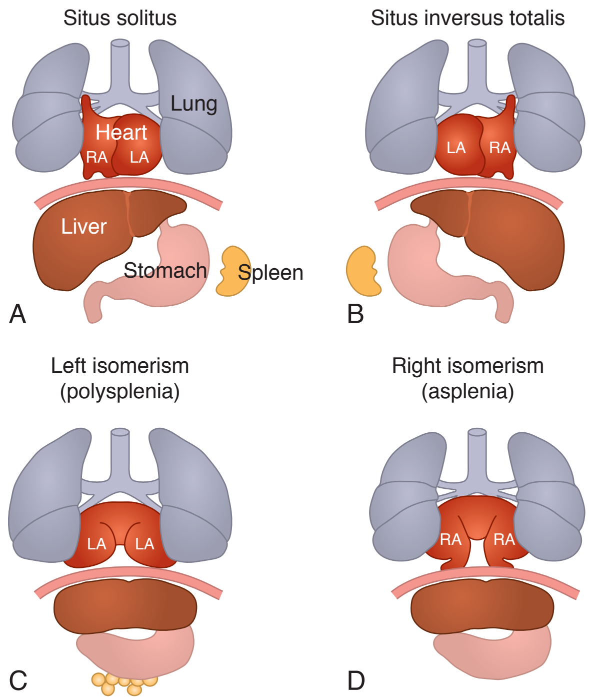

Figure 431-14 Variations in thoracoabdominal situs in congenital heart disease. A, *Situs solitus:* on the right side there is a three-lobed lung, a right atrium (with superior and inferior vena cava entering), and the liver; on the left side there is a two-lobed lung, a left atrium (with pulmonary veins entering), the stomach and the spleen. B, *Situs inversus totalis:* all of the structures are mirror image reversed: on the right side there is a two-lobed lung, a left atrium, the stomach, and the spleen; on the left side there is a three-lobed lung, a right atrium, and the liver. C, *Left isomerism (polysplenia):* there are two left sides: on the right side there is a two-lobed lung and a structure that resembles the left atrium; on the left side there is also a two-lobed lung and a structure that resembles the left atrium; there is usually a midline liver and stomach, and multiple small spleens. D, *Right isomerism (asplenia):* there are two right sides: on the right side there is a three-lobed lung and a structure that resembles the right atrium; on the left side there is also a three-lobed lung and a structure that resembles the right atrium; there is usually a midline liver and stomach, and absent spleen. *(Modified from Fliegauf M, Benzing T, Omran H: When cilia go bad: cilia defects and ciliopathies.* Nat Rev Mol Cell Biol *8:880-893, 2007. Fig 2.)*

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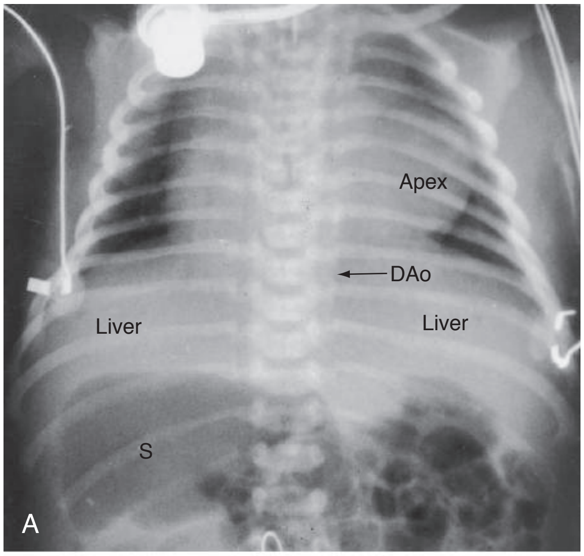

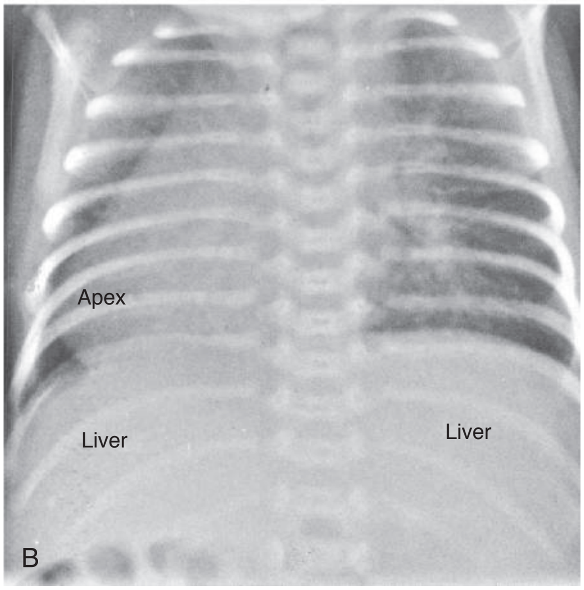

Figure 431-15 **A,** X-ray from an asplenic male neonate with right isomerism. The liver is transverse, the stomach *(S)* is on the right, and the heart is midline, but the base to apex axis points to the left. DAo, descending aorta. **B,** X-ray from an asplenic male neonate with right isomerism. The liver is transverse, the base to apex axis points to the right, and heart is to the right of midline. The ground-glass appearance of the lungs was caused by total anomalous pulmonary venous connection with obstruction. *(From Perloff JK, Marelli AJ:* Perloff's clinical recognition of congenital heart disease, *ed 6, Philadelphia, 2012, Elsevier/Saunders, Fig. 3-31, p 32.)*

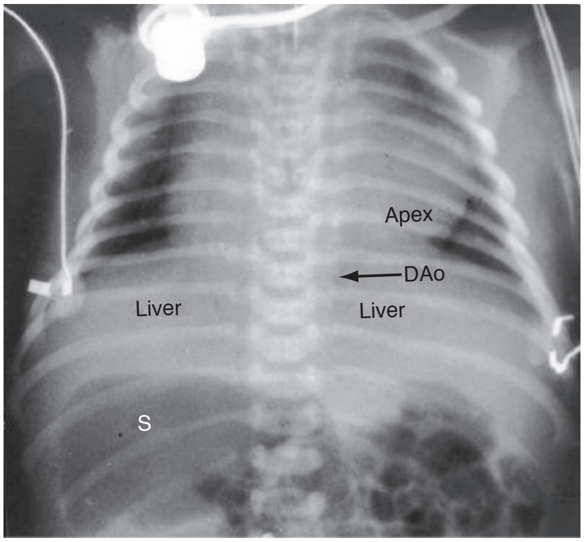

Figure 431-16 X-ray from a polysplenic female neonate with left isomerism. The liver is transverse, the apex is on the left, the stomach *(S)* is on the right, and the descending aorta *(DAo)* is on the left. This opposite-sided arrangement tends to occur in left isomerism. *(From Perloff JK, Marelli AJ:* Perloff's clinical recognition of congenital heart disease, *ed 6, Philadelphia, 2012, Elsevier/Saunders, Fig. 3-40, p 38.)*

3-lobed right lung is on the right, and the 2-lobed left lung on the left; the right atrium is on the right, and the left atrium is on the left. When the abdominal organs and lung lobation are reversed, an arrangement known as **situs inversus** occur, the left atrium is on the right and the right atrium on the left. If the visceroatrial situs cannot be readily determined, a condition known as **situs indeterminus** or **heterotaxia** exists. The 2 major variations are (1) **asplenia syndrome** (right isomerism or bilateral right-sidedness), which is associated with a centrally located liver, absent spleen, and 2 morphologic right lungs (Fig. 431-15); and (2) **polysplenia syndrome** (left isomerism or bilateral left-sidedness), which is associated with multiple small spleens, absence of the intrahepatic portion of the inferior vena cava, and 2 morphologic left lungs (Fig. 431-16). The heterotaxia syndromes are usually associated with severe congenital heart lesions: ASD, VSD, atrioventricular septal defect, hypoplasia of 1 of the ventricles, pulmonary stenosis or atresia, and anomalous systemic venous or pulmonary venous return (Table 431-2).

The next segment is localization of the ventricles, which depends on the direction of development of the embryonic cardiac loop. Initial protrusion of the loop to the right (d-loop) carries the future right ventricle anteriorly and to the right, whereas the left ventricle remains posterior and on the left. With situs solitus, a d-loop yields normal atrioventricular connections (right atrium connecting to the right ventricle, left atrium to the left ventricle). Protrusion of the loop to the left (l-loop) carries the future right ventricle to the left and the left ventricle to the right. In this case, in the presence of situs solitus, the right atrium connects with the left ventricle and the left atrium with the right ventricle **(ventricular inversion).**

The final segment is that of the great vessels. With each type of cardiac loop, the ventricular-arterial relationships may be regarded as either normal (right ventricle to the pulmonary artery, left ventricle to the aorta) or transposed (right ventricle to the aorta, left ventricle to the pulmonary artery). A further classification can be based on the position of the aorta (normally to the right and posterior) relative to the pulmonary artery. In transposition, the aorta is usually anterior and either to the right of the pulmonary artery **(d-transposition)** or to the left **(l-transposition).** These segmental relationships can usually be determined by echocardiographic studies demonstrating both atrioventricular and ventriculoarterial relationships. The clinical manifestations of these syndromes of abnormal cardiac position are determined primarily by their associated cardiovascular anomalies.

Dextrocardia occurs when the heart is in the right side of the chest; **levocardia** (the normal situation) is present when the heart is in the left side of the chest. Dextrocardia without associated situs inversus and levocardia in the presence of situs inversus are most often complicated by other severe cardiac malformations. Surveys of older children and adults indicate that dextrocardia with situs inversus and normally related great arteries ("mirror-image" dextrocardia) is often associated with a functionally normal heart, although congenital heart disease of a less severe nature is common.

Anatomic or functional abnormalities of the lungs, diaphragm, and thoracic cage may result in displacement of the heart to the right **(dextroposition).** In this case, however, the cardiac apex is pointed

Table 431-2	Comparison of Cardiosplenic Heterotaxy Syndromes	
FEATURE	**ASPLENIA (RIGHT ISOMERISM)**	**POLYSPLENIA (LEFT ISOMERISM)**
Spleen	Absent	Multiple
Sidedness (isomerism)	Bilateral right	Bilateral left
Lungs	Bilateral trilobar with eparterial bronchi	Bilateral bilobar with hyparterial bronchi
Sex	Male (65%)	Female ≥ male
Right-sided stomach	Yes	Less common
Symmetric liver	Yes	Yes
Partial intestinal rotation	Yes	Yes
Dextrocardia (%)	30-40	30-40
Pulmonary blood flow	Decreased (usually)	Increased (usually)
Severe cyanosis	Yes	No
Transposition of great arteries (%)	60-75	15
Total anomalous pulmonary venous return (%)	70-80	Rare
Common atrioventricular valve (%)	80-90	20-40
Single ventricle (%)	40-50	10-15
Absent inferior vena cava with azygos continuation	No	Characteristic
Bilateral superior vena cava	Yes	Yes
Other common defects	PA, PS	Partial anomalous pulmonary venous return, ventricular septal defect, double-outlet right ventricle
Risk of pneumococcal sepsis	Yes	Yes
Howell-Jolly and Heinz bodies, pitted erythrocytes	Yes	No
Risk of nosocomial infection	Yes	Yes
Absent gallbladder; biliary atresia	No	Yes

PA, pulmonary atresia; PS, pulmonary stenosis.

normally to the left. This anatomic position is less often associated with congenital heart lesions, although hypoplasia of a lung may be accompanied by anomalous pulmonary venous return from that lung (**scimitar syndrome** [see Chapter 426.4]).

The electrocardiogram is difficult to interpret in the presence of lesions with discordant atrial, ventricular, and great vessel anatomy. Diagnosis usually requires detailed echocardiographic and sometimes MRI, CT, or cardiac catheterization studies. The prognosis and treatment of patients with 1 of the cardiac positional anomalies are determined by the underlying defects and are covered in their respective chapters. Asplenia increases the risk of serious infections such as bacterial sepsis and thus requires daily antibiotic prophylaxis. Patients with polysplenia frequently have poor splenic function and may also require prophylaxis against pneumococcal sepsis. Patients with heterotaxia are also at increased risk of intestinal malrotation and volvulus.

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Chapter 432

Other Congenital Heart and Vascular Malformations

432.1 Anomalies of the Aortic Arch

Daniel Bernstein

RIGHT AORTIC ARCH

In this abnormality, the aorta curves to the right and, if it descends on the right side of the vertebral column, is usually associated with other cardiac malformations. It is found in 20% of cases of tetralogy of Fallot and is also common in truncus arteriosus. A right aortic arch without other cardiac anomalies is not associated with symptoms. It can often be visualized on the chest roentgenogram. The trachea is deviated slightly to the left of the midline rather than to the right, as in the presence of a normal left arch. On a barium esophagogram, the esophagus is indented on its right border at the level of the aortic arch.

VASCULAR RINGS

Congenital abnormalities of the aortic arch and its major branches result in the formation of vascular rings around the trachea and esophagus with varying degrees of compression (Table 432-1). The origin of these lesions can best be appreciated by reviewing the embryology of the aortic arch (see Fig. 420-1 in Chapter 420). The most common anomalies include (1) double aortic arch (Fig. 432-1*A*), (2) right aortic arch with a left ligamentum arteriosum, (3) anomalous innominate artery arising farther to the left on the arch than usual, (4) anomalous left carotid artery arising farther to the right than usual and passing anterior to the trachea, and (5) anomalous left pulmonary artery (vascular sling). In the latter anomaly, the abnormal vessel arises from an elongated main pulmonary artery or from the right pulmonary artery. It courses between and compresses the trachea and the esophagus. Associated congenital heart disease may be present in 5-50% of patients, depending on the vascular anomaly.

Clinical Manifestations

If the vascular ring produces compression of the trachea and esophagus, symptoms are frequently present during infancy. Chronic wheezing is exacerbated by crying, feeding, and flexion of the neck. Extension of the neck tends to relieve the noisy respiration. Vomiting may also be a component. Affected infants may have a brassy cough, pneumonia, or rarely, sudden death from aspiration.

Diagnosis

Standard roentgenographic examination is not usually helpful. In the past, performing a barium esophagogram was the standard method of diagnosis (Fig. 432-2), replaced today by echocardiography in combination with either MRI or CT. Cardiac catheterization is reserved for cases with associated anomalies or in rare cases where these other modalities are not diagnostic. Bronchoscopy may be helpful in more severe cases to determine the extent of airway narrowing.

Treatment

Surgery is advised for symptomatic patients who have evidence of tracheal compression. The anterior vessel is usually divided in patients with a double aortic arch (see Fig. 432-1*B*). Compression produced by a right aortic arch and left ligamentum arteriosum is relieved by division of the latter. Anomalous innominate or carotid arteries cannot be

Table 432-1 Vascular Rings

LESION	SYMPTOMS	PLAIN FILM	BARIUM SWALLOW	BRONCHOSCOPY	MRI ECHOCARDIOGRAPHY	TREATMENT
DOUBLE ARCH 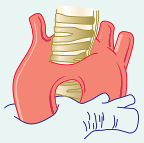	Stridor Respiratory distress Swallowing dysfunction Reflex apnea	AP—wider base of heart Lat.—narrowed trachea displaced forward at C3-C4	Bilateral indentation of esophagus	Bilateral tracheal compression—both pulsatile	Diagnostic	Ligate and divide smaller arch (usually left)
RIGHT ARCH AND LIGAMENTUM/DUCTUS 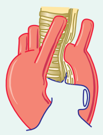	Respiratory distress Swallowing dysfunction	AP—tracheal deviation to left (right arch)	Bilateral indentation of esophagus R > L	Bilateral tracheal compression—r. pulsatile	Diagnostic	Ligate ligamentum or ductus
ANOMALOUS INNOMINATE 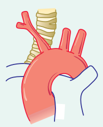	Cough Stridor Reflex apnea	AP—normal Lat.—anterior tracheal compression	Normal	Pulsatile anterior tracheal compression	Unnecessary	Conservative apnea, then suspend
ABERRANT RIGHT SUBCLAVIAN 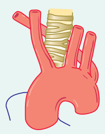	Occasional swallowing dysfunction	Normal	AP—oblique defect upward to right Lat.—small defect on right posterior wall	Usually normal	Diagnostic	Ligate artery
PULMONARY SLING 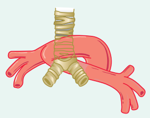	Expiratory stridor Respiratory distress	AP—low L. hilum, r. emphysema/atelectasis Lat.—anterior bowing of right bronchus and trachea	±Anterior indentation above carina between esophagus and trachea	Tracheal displacement to left Compression of right main bronchus	Diagnostic	Detach and reanastomose to main pulmonary artery in front of trachea

AP, anteroposterior; L and l., left; Lat., lateral; MRI, magnetic resonance imaging; R and r., right.
From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 88.*

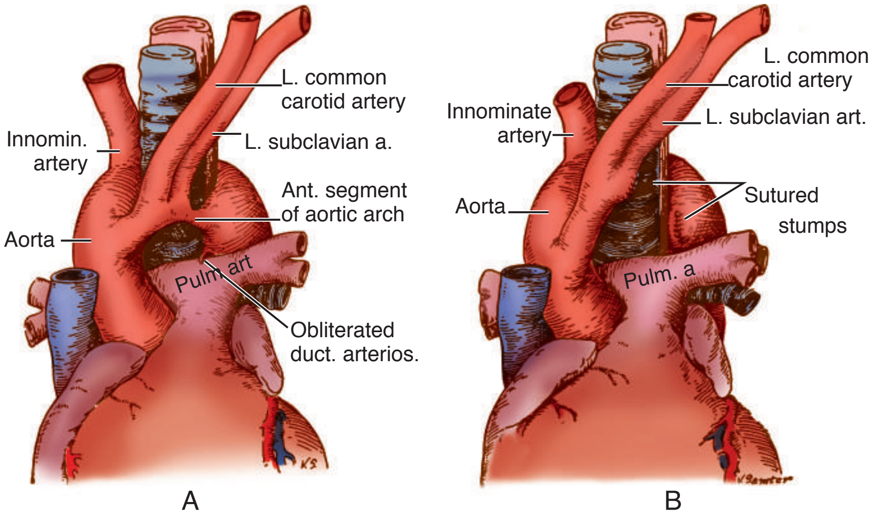

Figure 432-1 Double aortic arch. **A,** Small anterior segment of the double aortic arch (most common type). **B,** Operative procedure for release of the vascular ring.

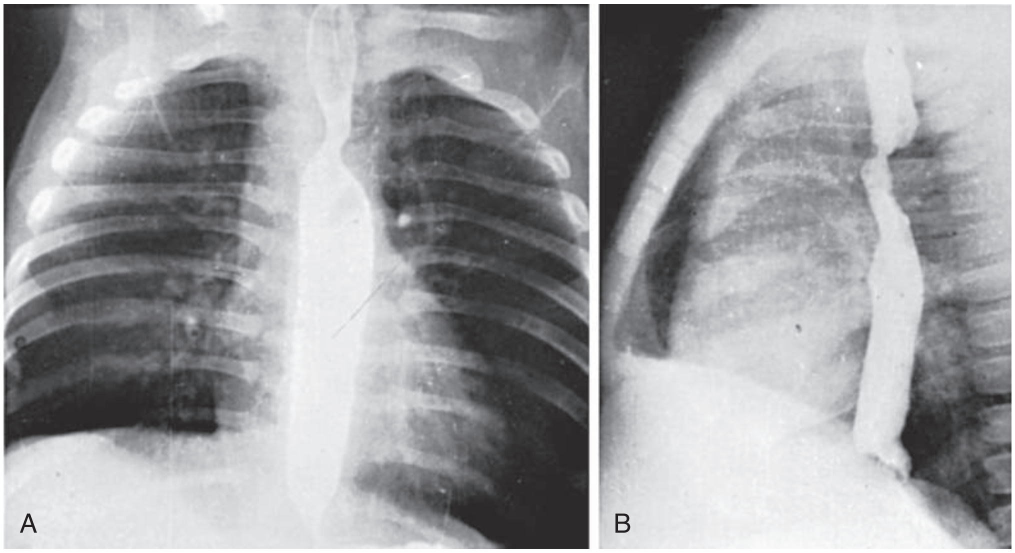

Figure 432-2 Double aortic arch in an infant age 5 mo. **A,** Anteroposterior view. The barium-filled esophagus is constricted on both sides. **B,** Lateral view. The esophagus is displaced forward. The anterior arch was the smaller and was divided at surgery.

divided; attaching the adventitia of these vessels to the sternum usually relieves the tracheal compression. An anomalous left pulmonary artery is corrected by division at its origin and re-anastomosis to the main pulmonary artery after it has been brought in front of the trachea. Severe tracheomalacia, if present, may require reconstruction of the trachea as well.

Bibliography is available at Expert Consult.

432.2 Anomalous Origin of the Coronary Arteries

Daniel Bernstein

Table 432-2 provides a classification system for coronary artery anomalies. Many of these anomalies are isolated. Nonetheless congenital anomalies of the coronary arteries may also be seen in patients with congenital heart disease (tetralogy of Fallot, transposition of the great arteries, congenitally corrected transposition of the great arteries, single ventricle, tricuspid atresia, truncus arteriosus, quadricuspid or bicuspid aortic valves, double-outlet ventricle). In addition, acquired lesions of the coronary arteries caused by existing congenital heart disease may develop as a consequence of hypertension or alterations in blood flow; congenital heart diseases include coarctation of the aorta, supravalvular aortic stenosis, aortic regurgitation, pulmonary atresia with intact ventricular septum, hypoplastic left-heart syndrome, and coronary ectasia secondary to cyanotic heart disease.

ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY

In anomalous origin of the left coronary artery from the pulmonary artery, the blood supply to the left ventricular myocardium is severely compromised. Soon after birth, as pulmonary arterial pressure falls, perfusion pressure to the left coronary artery becomes inadequate; myocardial ischemia, infarction, and fibrosis result. In some cases, interarterial collateral anastomoses develop between the right and left coronary arteries. Blood flow in the left coronary artery is then reversed, and it empties into the pulmonary artery, a condition known as the “myocardial steal” syndrome. The left ventricle becomes dilated, and its performance is decreased. Mitral insufficiency is a frequent complication secondary to a dilated valve ring or infarction of a papillary muscle. Localized aneurysms may also develop in the left ventricular free wall. Occasional patients have adequate myocardial blood flow during childhood and, later in life, a continuous murmur and a small left-to-right shunt via the dilated coronary system (aorta to right coronary to left coronary to pulmonary artery).

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Table 432-2 Congenital Anomalies of Coronary Arteries Unassociated with Congenital Heart Disease

Anomalous Aortic Origin
• Eccentric ostium within an aortic sinus
• Ectopic ostium above an aortic sinus
• Conus artery from the right aortic sinus
• Circumflex coronary artery from the right aortic sinus or from the right coronary artery
• Origin of left anterior descending and circumflex coronary arteries from separate ostia in the left aortic sinus (absence of left main coronary artery)
• Atresia of the left main coronary artery
• Origin of the left anterior descending coronary artery from the right aortic sinus or from the right coronary artery
• Origin of the right coronary artery from the left aortic sinus, from posterior aortic sinus, or from left coronary artery
• Origin of a single coronary artery from the right or left aortic sinus
• Anomalous origin from a noncardiac systemic artery
Anomalous Aortic Origin with Anomalous Proximal Course
• Acute proximal angulation
• Ectopic right coronary artery passing between aorta and pulmonary trunk
• Ectopic left main coronary artery:
• Between aorta and pulmonary trunk
• Anterior to the pulmonary trunk
• Posterior to the aorta
• Within the ventricular septum (intramyocardial)
• Ectopic left anterior descending coronary artery that is anterior, posterior, or between the aorta and pulmonary trunk
Anomalous Origin of a Coronary Artery from the Pulmonary Trunk
• Left main coronary artery
• Left anterior descending coronary artery
• Right coronary artery
• Both right and left coronary arteries
• Circumflex coronary artery
• Accessory coronary artery

From Perloff JK, Marelli J: Perloff's clinical recognition of congenital heart disease, *ed 6, Philadelphia, 2012, Elsevier/Saunders, Table 32-3, p. 532.*

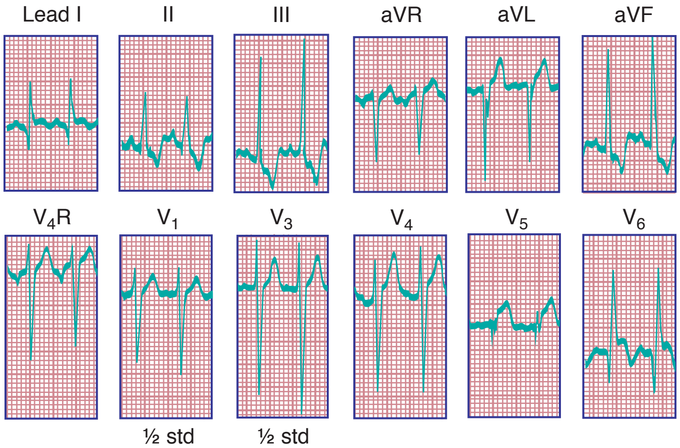

Figure 432-3 **Electrocardiogram of a 3 mo old child with anomalous origin of the left coronary artery from the pulmonary artery.** Lateral myocardial infarction is present as evidenced by abnormally large and wide Q waves in leads I, V_5, and V_6; an elevated ST segment in V_5 and V_6; and inversion of TV_6.

Clinical Manifestations

Evidence of heart failure becomes apparent within the 1st few mo of life, and may be exacerbated by respiratory infection. Recurrent attacks of discomfort, restlessness, irritability, sweating, dyspnea, and pallor occur and probably represent **angina pectoris**. Cardiac enlargement is moderate to massive. A gallop rhythm is common. Murmurs may be of the nonspecific ejection type or may be holosystolic due to mitral insufficiency. Older patients with abundant intercoronary anastomoses may have continuous murmurs and minimal left ventricular dysfunction. During adolescence, they may experience angina during exercise. Rare patients with an anomalous right coronary artery may also have such clinical findings.

Diagnosis

Roentgenographic examination confirms the cardiomegaly. The electrocardiogram resembles the pattern described in lateral wall myocardial infarction in adults. A QR pattern followed by inverted T waves is seen in leads I and aVL. The left ventricular surface leads (V_5 and V_6) may also show deep Q waves and exhibit elevated ST segments and inverted T waves (Fig. 432-3). Two-dimensional echocardiography can usually suggest the diagnosis; however, echocardiography is not always reliable in diagnosing this condition. On 2-dimensional imaging alone, the left coronary artery may appear as though it is arising from the aorta. Color Doppler ultrasound examination has improved the accuracy of diagnosis of this lesion, demonstrating the presence of retrograde flow in the left coronary artery. CT or MRI may be helpful in confirming the origin of the coronary arteries. Cardiac catheterization is diagnostic; aortography shows immediate opacification of the right coronary artery only. This vessel is large and tortuous. After filling of the intercoronary anastomoses, the left coronary artery is opacified, and contrast can be seen to enter the pulmonary artery. Pulmonary arteriography may also opacify the origin of the anomalous left coronary artery. Selective left ventriculography usually demonstrates a dilated left ventricle that empties poorly and mitral regurgitation.

Treatment and Prognosis

Untreated, death often occurs from heart failure within the 1st 6 mo of life. Those who survive generally have abundant intercoronary collateral anastomoses. Medical management includes standard therapy for heart failure (diuretics, angiotensin-converting enzyme inhibitors) and for controlling ischemia (nitrates, β-blocking agents).

Surgical treatment consists of detaching the anomalous coronary artery from the pulmonary artery and anastomosing it to the aorta to establish normal myocardial perfusion. A seriously ill infant with a tiny left coronary artery may present a difficult technical problem. In patients who have already sustained a significant myocardial infarction, cardiac transplantation may be the best option (see Chapter 441.1).

ANOMALOUS ORIGIN OF THE RIGHT CORONARY ARTERY FROM THE PULMONARY ARTERY

Anomalous origin of the right coronary artery from the pulmonary artery is rarely manifested in infancy or early childhood. The left coronary artery is enlarged, whereas the right is thin-walled and mildly enlarged. In early infancy, perfusion of the right coronary artery is from the pulmonary artery, whereas later, perfusion is from collaterals of the left coronary vessels. Angina and sudden death can occur in adolescence or adulthood. When recognized, this anomaly should be repaired by re-anastomosis of the right coronary artery to the aorta.

ECTOPIC ORIGIN OF THE CORONARY ARTERY FROM THE AORTA WITH ABERRANT PROXIMAL COURSE

In ectopic origin of the coronary artery from the aorta with an aberrant proximal course, the aberrant artery may be a left, right, or major branch coronary artery. The site of origin may be the wrong sinus of Valsalva or a proximal coronary artery. The ostium may be hypoplastic, slitlike, or of normal caliber. The aberrant vessel may pass anteriorly, posteriorly, or between the aorta and right ventricular outflow tract; it may tunnel in the conal or interventricular septal tissue. Obstruction

resulting from hypoplasia of the ostia, tunneling between the aorta and right ventricular outflow tract or interventricular septum, and acute angulation produces myocardial infarction. Unobstructed vessels produce no symptoms. Patients with this extremely rare abnormality are often initially seen with severe myocardial infarction, ventricular arrhythmias, angina pectoris, or syncope; sudden death may occur, especially in young athletes.

Diagnostic modalities include an electrocardiogram, stress testing, 2-dimensional echocardiography, CT or MRI, radionuclide perfusion scan, and cardiac catheterization with selective coronary angiography.

Treatment is indicated for obstructed vessels and consists of aortoplasty with reanastomosis of the aberrant vessel or, occasionally, coronary artery bypass grafting. The management of asymptomatic infants with these forms of ectopic coronary origin remains controversial.

Bibliography is available at Expert Consult.

432.3 Pulmonary Arteriovenous Fistula

Daniel Bernstein

Fistulous vascular communications in the lungs may be large and localized or multiple, scattered, and small. The most common form of this unusual condition is the **Osler-Weber-Rendu syndrome** (hereditary hemorrhagic telangiectasia type I), which is also associated with angiomas of the nasal and buccal mucous membranes, gastrointestinal tract, or liver. Mutations in the endoglin gene, a cell surface component of the transforming growth factor-β receptor complex causes this syndrome. The usual communication is between the pulmonary artery and pulmonary vein; direct communication between the pulmonary artery and left atrium is extremely rare. Desaturated blood in the pulmonary artery is shunted through the fistula into the pulmonary vein, thus bypassing the lungs, and then enters the left side of the heart resulting in systemic arterial desaturation and, sometimes, clinically detectable cyanosis. The shunt across the fistula is at low pressure and resistance, so pulmonary arterial pressure is normal; cardiomegaly and heart failure are not present.

The clinical manifestations depend on the magnitude of the shunt. Large fistulas are associated with dyspnea, cyanosis, clubbing, a continuous murmur, and polycythemia. Hemoptysis is rare, but when it occurs, it may be massive. Features of the Osler-Weber-Rendu syndrome are seen in ≈50% of patients (or other family members) and include recurrent epistaxis and gastrointestinal tract bleeding. Transitory dizziness, diplopia, aphasia, motor weakness, or convulsions may result from cerebral thrombosis, abscess, or paradoxical emboli. Soft systolic or continuous murmurs may be audible over the site of the fistula. The electrocardiogram is normal. Roentgenographic examination of the chest may show opacities produced by large fistulas; multiple small fistulas may be visualized by fluoroscopy (as abnormal pulsations), MRI, or CT. Selective pulmonary arteriography demonstrates the site, extent, and distribution of the fistulas.

Treatment consisting of excision of solitary or localized lesions by lobectomy or wedge resection results in complete disappearance of symptoms. In most instances, fistulas are so widespread that surgery is not possible. Any direct communication between the pulmonary artery and the left atrium can be obliterated.

Patients who have undergone a **Glenn cavopulmonary** anastomosis for cyanotic congenital heart disease (see Chapter 430.4) are also at risk for the development of pulmonary arteriovenous malformations. In these patients, the arteriovenous malformations are usually multiple and the risk increases over time after the Glenn procedure. These malformations rarely occur after the heart disease is fully palliated by completion of the Fontan operation. This finding suggests that the pulmonary circulation requires an as yet undetermined hepatic factor to suppress the development of arteriovenous malformations. The hallmark of the development of these malformations is a decrease in the patient's oxygen saturation. The diagnosis can often be made with contrast echocardiography; cardiac catheterization is the definitive test. Completion of the Fontan circuit, so that inferior vena cava blood flow (containing hepatic venous drainage) is routed through the lungs, usually results in improvement or resolution of the malformations.

Bibliography is available at Expert Consult.

432.4 Ectopia Cordis

Daniel Bernstein

In the most common thoracic form of ectopia cordis, the sternum is split and the heart protrudes outside the chest. In other forms, the heart protrudes through the diaphragm into the abdominal cavity or may be situated in the neck. Associated intracardiac anomalies are common. **Pentalogy of Cantrell** consists of ectopia cordis, midline supraumbilical abdominal defect, deficiency of the anterior diaphragm, defect of the lower sternum, and an intracardiac defect (either a ventricular septal defect, tetralogy of Fallot, or diverticulum of the left ventricle). Death may occur early in life, usually from infection, cardiac failure, or hypoxemia. Surgical therapy for neonates without overwhelmingly severe cardiac anomalies consists of covering the heart with skin without compromising venous return or ventricular ejection. Repair or palliation of associated defects is also necessary.

432.5 Diverticulum of the Left Ventricle

Daniel Bernstein

Left ventricular diverticulum is a rare anomaly, where the diverticulum protrudes into the epigastrium. The lesion may be isolated or associated with complex cardiovascular anomalies. A pulsating mass is usually visible and palpable in the epigastrium. Systolic or systolic-diastolic murmurs produced by blood flow into and out of the diverticulum may be audible over the lower part of the sternum and the mass. The electrocardiogram shows a pattern of complete or incomplete left bundle branch block. Roentgenograms of the chest may or may not show the mass. Associated abnormalities include defects of the sternum, abdominal wall, diaphragm, and pericardium (see earlier). Surgical treatment of the diverticulum and associated cardiac defects can be performed in selected cases. Occasionally, a diverticulum may be small and not associated with clinical signs or symptoms. These small diverticula are diagnosed at the time of echocardiographic examination for other indications.

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Chapter 433
Pulmonary Hypertension

433.1 Primary Pulmonary Hypertension

Daniel Bernstein

PATHOPHYSIOLOGY

Primary pulmonary hypertension is characterized by pulmonary vascular obstructive disease and right-sided heart failure. It occurs at any age, although in pediatric patients the mean age at diagnosis is 7-10 yr. In patients with idiopathic or familial disease, females outnumber males 1.7 : 1; in other patients, both genders are represented equally. Some patients have evidence of either an immunologic disorder or a hypercoagulable state. Mutations in the gene for bone morphogenetic protein receptor-2 (*BMPR-2*, a member of the transforming growth factor-β receptor family) on chromosome 2q33 have been identified in 70% of patients with familial primary pulmonary hypertension (known as *PPH1*) and in 10-20% with idiopathic sporadic pulmonary

hypertension. Other potential disease causing genes include *PPH2*, *ALK1*, *ENG*, *SMAD9*, *CAV1*, and *KCNK3*, which causes a channelopathy in familial and sporadic cases of primary pulmonary hypertension. Viral infection, such as with the vasculotropic human herpesvirus 8, has been suggested as a trigger factor in many patients. Diet pills, particularly fenfluramine, have also been implicated. Pulmonary hypertension is a common complication of sickle cell anemia and other hemolytic anemias. Pulmonary hypertension is associated with precapillary obstruction of the pulmonary vascular bed as a result of hyperplasia of the muscular and elastic tissues and a thickened intima of the small pulmonary arteries and arterioles (Fig. 433-1). Secondary atherosclerotic changes may be found in the larger pulmonary arteries as well. In children, **pulmonary venoocclusive disease** may account for some cases of primary pulmonary hypertension. Before a diagnosis of primary pulmonary hypertension can be made, other causes of elevated pulmonary arterial pressure must be eliminated (chronic pulmonary parenchymal disease, persistent obstruction of the upper airway, congenital cardiac malformations, recurrent pulmonary emboli, alveolar capillary dysplasia, liver disease, autoimmune disease,

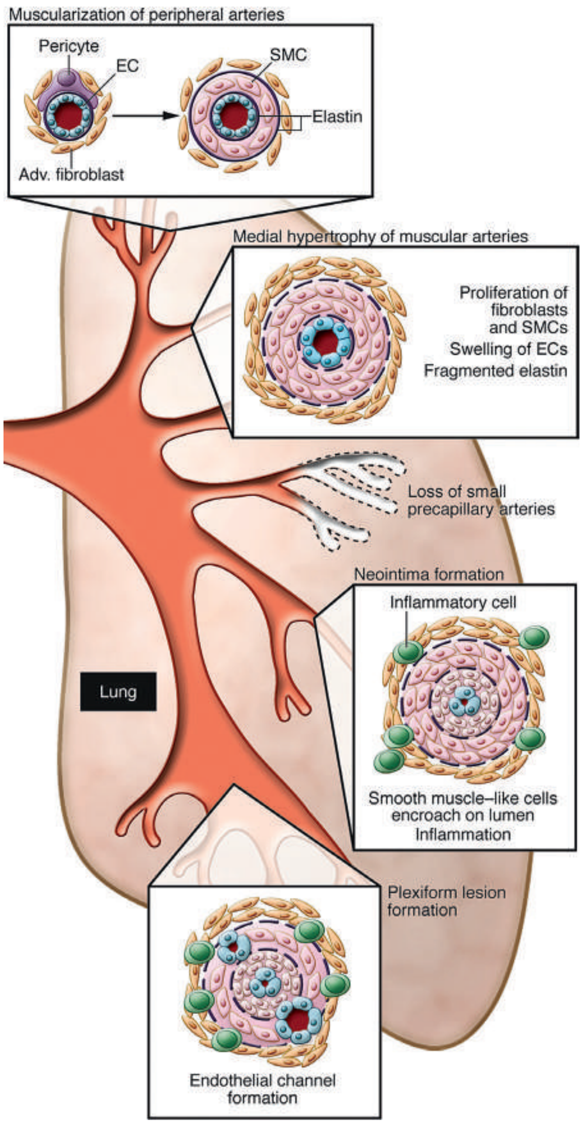

Figure 433-1 Vascular abnormalities associated with pulmonary arterial hypertension: abnormal muscularization of distal and medial precapillary arteries, loss of precapillary arteries, thickening of large pulmonary arterioles, and neointimal formation that is occlusive in vessels <500-100 μM and in plexiform lesions therein. *(From Rabinovitch M: Molecular pathogenesis of pulmonary arterial hypertension.* J Clin Invest *122:4306-4313, 2012, Fig. 1.)*

and moyamoya disease). Table 433-1 provides a classification system. Idiopathic or familial disease is the most common in pediatric patients (~55%), followed by pulmonary hypertension secondary to congenital heart disease (~35%) and chronic respiratory disorders (~15%).

Pulmonary hypertension places an afterload burden on the right ventricle, which results in right ventricular hypertrophy. Dilation of the pulmonary artery is present, and pulmonary valve insufficiency may occur. In the later stages of the disease, the right ventricle dilates, tricuspid insufficiency develops, and cardiac output is decreased. Arrhythmias, syncope, and sudden death are common.

CLINICAL MANIFESTATIONS

The predominant symptoms include exercise intolerance (dyspnea) and fatigability; occasionally, precordial chest pain, dizziness, or headaches are noted. Syncope may be noted in ~30% of pediatric patients. Peripheral cyanosis may be present, especially during exercise or in patients with a patent foramen ovale through which blood can shunt from right to left; in the late stages of disease, patients may have cold extremities and a gray appearance associated with low cardiac output. Arterial oxygen saturation is usually normal unless there is an associated intracardiac shunt. If right-sided heart failure has supervened, jugular venous pressure is elevated, and hepatomegaly and edema are present. Jugular venous *a* waves are present, and in those with functional tricuspid insufficiency, a conspicuous jugular *cv* wave and systolic hepatic pulsations are manifested. The heart is moderately enlarged, and a right ventricular heave can be noted. The 1st heart sound is often followed

Table 433-1	Revised World Health Organization Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension (PAH)
   1.1. Idiopathic (IPAH)
   1.2. Familial (FPAH)
   1.3. Associated with (APAH):
      1.3.1. Connective tissue disorder
      1.3.2. Congenital systemic-to-pulmonary shunts
      1.3.3. Portal hypertension
      1.3.4. HIV infection
      1.3.5. Drugs and toxins
      1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
   1.4. Associated with significant venous or capillary involvement
      1.4.1. Pulmonary venoocclusive disease (PVOD)
      1.4.2. Pulmonary capillary hemangiomatosis (PCH)
   1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left-heart disease
   2.1. Left-sided atrial or ventricular heart disease
   2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Sleep disordered breathing
   3.4. Alveolar hypoventilation disorders
   3.5. Chronic exposure to high altitude
   3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)
   4.1. Thromboembolic obstruction of proximal pulmonary arteries
   4.2. Thromboembolic obstruction of distal pulmonary arteries
   4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous: sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

From ACCF/AHA: 2009 Expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc; and the Pulmonary Hypertension Association, J Am Coll Cardiol *53:1573–1619, 2009.*

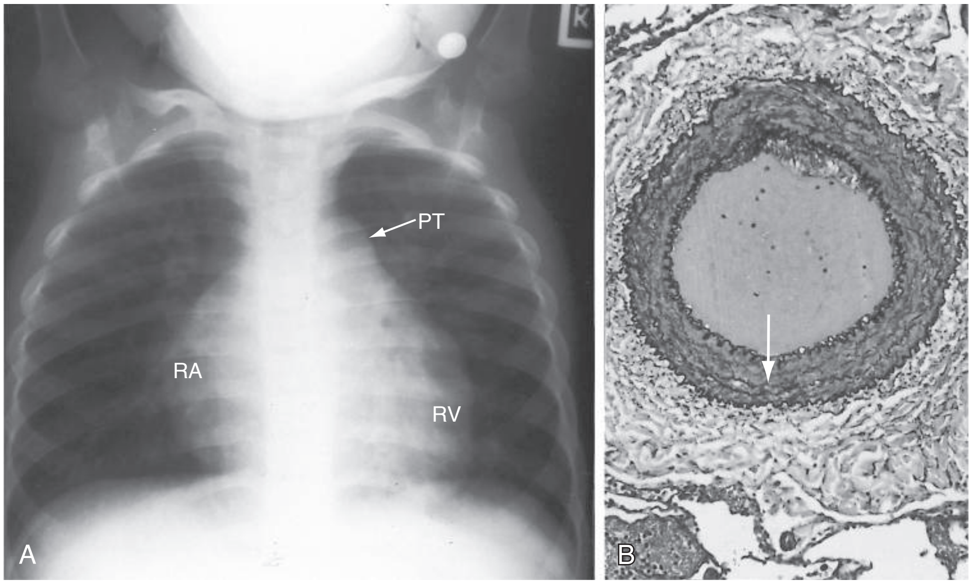

Figure 433-2 **A,** X-ray from a 3 yr old girl with primary pulmonary hypertension. Pulmonary vascularity is reduced. The pulmonary trunk (PT), right atrium (RA), and right ventricle (RV) are considerably enlarged. **B,** Histology of an intrapulmonary artery at necropsy shows medial hypertrophy (arrow). *(From Perloff JK, Marelli AJ:* Perloff's clinical recognition of congenital heart disease, *ed 6, Philadelphia, 2012, Elsevier/Saunders, Fig. 14-17, p. 207.)*

by an ejection click emanating from the dilated pulmonary artery. The 2nd heart sound is narrowly split, loud, and sometimes booming in quality; it is frequently palpable at the upper left sternal border. A presystolic gallop rhythm may be audible at the lower left sternal border. The systolic murmur is soft and short and is sometimes followed by a blowing decrescendo diastolic murmur caused by pulmonary insufficiency. In later stages, a holosystolic murmur of tricuspid insufficiency is appreciated at the lower left sternal border.

DIAGNOSIS

Chest radiographs reveal a prominent pulmonary artery and right ventricle (Fig. 433-2). The pulmonary vascularity in the hilar areas may be prominent, in contrast to the peripheral lung fields in which pulmonary markings are decreased. The electrocardiogram shows right ventricular hypertrophy, often with spiked P waves. Echocardiography is used to screen for any congenital cardiac malformations. Doppler evaluation of the tricuspid valve, if insufficiency is present, will allow estimation of the right ventricular (and hence pulmonary arterial) systolic pressure.

At cardiac catheterization, the presence of left-sided obstructive lesions (pulmonary venous stenosis, mitral stenosis, restrictive cardiomyopathy) that result in pulmonary venous hypertension can be evaluated (see Chapters 427.9, 431.7, and 439.3). The presence of pulmonary arterial hypertension with a normal pulmonary capillary wedge pressure is diagnostic of primary pulmonary hypertension. If the wedge pressure is elevated and left ventricular end-diastolic pressure is normal, obstruction at the level of the pulmonary veins, left atrium, or mitral valve should be suspected. If left ventricular end-diastolic pressure is also elevated, the diagnosis of restrictive cardiomyopathy should be entertained. The risks associated with cardiac catheterization are increased in severely ill patients with primary pulmonary hypertension.

PROGNOSIS AND TREATMENT

Primary pulmonary hypertension is progressive, and no cure is currently available. Some success has been reported with oral calcium channel blocking agents such as nifedipine in children who demonstrate pulmonary vasoreactivity when these agents are administered during catheterization. Continuous intravenous infusion of the arachidonic acid metabolite, prostacyclin (epoprostenol), provides relief as long as the infusion is continued. Despite the success of prostacyclin in reducing symptoms and improving quality of life, it slows but does not stop the progression of the disease. Treprostinil, a prostacyclin analog with a longer half-life has also been shown to be effective. Continuous administration of nitric oxide via nasal cannula, nebulized forms of prostacyclin (iloprost), and orally administered pulmonary vasodilators (bosentan, an antagonist of endothelin receptors; or sildenafil, a phosphodiesterase type 5 inhibitor) have been used with success in adults and in preliminary clinical studies in children (Table 433-2). Anticoagulation may be of value in patients with previous pulmonary thromboemboli; some of these patients may respond to balloon angioplasty of narrowed pulmonary artery segments. Riociguat, a soluble guanylate cyclase stimulator, with vasorelaxation, antiproliferation, and antifibrotic properties, has proven effective in adults with chronic thromboembolic or idiopathic pulmonary hypertension. Despite many advances, definitive therapy is still heart-lung or lung transplantation (see Chapter 443.2). In patients with severe pulmonary hypertension and low cardiac output, the terminal event is often sudden and related to a lethal arrhythmia. Patients with primary pulmonary hypertension diagnosed in infancy often have rapid progression and high mortality.

433.2 Pulmonary Vascular Disease (Eisenmenger Syndrome)

Daniel Bernstein

PATHOPHYSIOLOGY

The term ***Eisenmenger syndrome*** refers to patients with a ventricular septal defect in which blood is shunted partially or totally from right to left as a result of the development of pulmonary vascular disease. This physiologic abnormality can also occur with atrioventricular septal defect, ventricular septal defect, patent ductus arteriosus or any other communication between the aorta and pulmonary artery, and in many forms of complex congenital heart disease with unrestricted pulmonary blood flow. Pulmonary vascular disease with an isolated atrial septal defect can occur, but is less common and does not occur until late in adulthood.

In Eisenmenger syndrome, pulmonary vascular resistance after birth either remains high or, after having decreased during early infancy, rises thereafter because of increased shear stress on pulmonary arterioles. Factors playing a role in the rapidity of development of pulmonary vascular disease include increased pulmonary arterial pressure, increased pulmonary blood flow, and the presence of hypoxia or hypercapnia. Early

Table 433-2 Summary of Drugs Used to Treat Pulmonary Hypertension*

DRUG AND MECHANISM OF ACTION	DOSES USED IN PEDIATRIC STUDIES	COMMON SIDE EFFECTS
Epoprostenol (prostacyclin [PGI_2], a potent vasodilator; also inhibits platelet aggregation)	1 ng/kg/min initially. Increase based on clinical course and tolerance to 5-50 ng/kg/min. Some patients may require even higher doses. Must be given by continuous infusion that is not interrupted	Flushing, headache, nausea, diarrhea, hypotension, chest pain, jaw pain
Iloprost (synthetic analog of PGI_2)	2.5-5.0 µg 6-9 times daily (not more frequently than every 2 hr) via inhalation	Flushing, headache, diarrhea, hypotension, jaw pain, exacerbation of pulmonary symptoms (cough, wheezing)
Treprostinil (synthetic analog of PGI_2)	1 ng/kg/min initially. Target dose ranges from 20-80 ng/kg/min. Given either IV or SC via continuous infusion. Longer half-life than epoprostenol	Flushing, headache, diarrhea, hypotension, jaw pain. Pain at infusion site when given SC
Bosentan, ambrisentan, (endothelin receptor EtA and EtB antagonist)	2 mg/kg/dose bid. Use ½ dose for 1st mo and check for liver function test abnormalities prior to up-titrating	Flushing, headache, diarrhea, hypotension, fluid retention, exacerbation of heart failure, anemia, elevated liver function tests, palpitations
Sildenafil (inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase 5)	1 mg/kg/dose given 3-4 times daily. Initial dosing should be ½ final target dose to evaluate for hypotension	Flushing, headache, diarrhea, myalgia, hypotension, priapism, visual disturbance (blue coloration)
Calcium channel blockers (amlodipine, diltiazem, nifedipine)	Previously widely used. Now indicated only for patients who show a strong response to nitric oxide during cardiac catheterization	Flushing, headache, edema, arrhythmia, headache, hypotension, rash, nausea, constipation, elevated liver function tests

*These medications should only be administered under the direction of a specialist in pulmonary hypertension.

in the course of disease, pulmonary hypertension (elevated pressure in the pulmonary arteries) is the result of markedly increased pulmonary blood flow (hyperkinetic pulmonary hypertension). This form of pulmonary hypertension decreases with the administration of pulmonary vasodilators such as nitric oxide, or oxygen, or both. With the development of Eisenmenger syndrome, pulmonary hypertension is the result of pulmonary vascular disease (obstructive pathologic changes in the pulmonary vessels). This form of pulmonary hypertension is usually only minimally responsive to pulmonary vasodilators or oxygen or not at all.

PATHOLOGY AND PATHOPHYSIOLOGY

The pathologic changes of Eisenmenger syndrome occur in the small pulmonary arterioles and muscular arteries (<300 µm) and are graded on the basis of histologic characteristics (Heath-Edwards classification): **Grade I** changes involve medial hypertrophy alone, **grade II** consists of medial hypertrophy and intimal hyperplasia, **grade III** involves near obliteration of the vessel lumen, **grade IV** includes arterial dilation, and **grades V and VI** include plexiform lesions, angiomatoid formation, and fibrinoid necrosis. Grades IV-VI indicate irreversible pulmonary vascular obstructive disease. Eisenmenger physiology is usually defined by an absolute elevation in pulmonary arterial resistance to greater than 12 Wood units (resistance units indexed to body surface area) or by a ratio of pulmonary to systemic vascular resistance of ≥1.0.

Pulmonary vascular disease occurs more rapidly in patients with trisomy 21 who have left-to-right shunts. It also complicates the natural history of patients with elevated pulmonary venous pressure secondary to mitral stenosis or left ventricular dysfunction, especially in those patients with restrictive cardiomyopathy (see Chapter 445.3). Pulmonary vascular disease can also occur in any patient with transmission of systemic pressure to the pulmonary circulation via a shunt at the interventricular or great vessel level, and in patients chronically exposed to low Po_2 (because of high altitude). Patients with cyanotic congenital heart lesions associated with unrestricted pulmonary blood flow are at particularly high risk.

CLINICAL MANIFESTATIONS

Symptoms do not usually develop until the 2nd or 3rd decade of life, although a more fulminant course may occur. Intracardiac or extracardiac communications that would normally shunt from left to right are converted to right-to-left shunting as pulmonary vascular resistance exceeds systemic vascular resistance. Cyanosis becomes apparent, and dyspnea, fatigue, and a tendency toward dysrhythmias begin to occur. In the late stages of the disease, heart failure, chest pain, headaches, syncope, and hemoptysis may be seen. Physical examination reveals a right ventricular heave and a narrowly split 2nd heart sound with a loud pulmonic component. Palpable pulmonary artery pulsation may be present at the left upper sternal border. A holosystolic murmur of tricuspid regurgitation may be audible along the left sternal border. An early decrescendo diastolic murmur of pulmonary insufficiency may also be heard along the left sternal border. The degree of cyanosis depends on the stage of the disease.

DIAGNOSIS

Roentgenographically, the heart varies in size from normal to greatly enlarged; the latter usually occurs late in the course of the disease. The main pulmonary artery is generally prominent, similar to primary pulmonary hypertension (see Fig. 433-2). The pulmonary vessels are enlarged in the hilar areas and taper rapidly in caliber in the peripheral branches. The right ventricle and atrium are prominent. The electrocardiogram shows marked right ventricular hypertrophy. The P wave may be tall and spiked. Cyanotic patients have various degrees of polycythemia that depend on the severity and duration of hypoxemia.

The echocardiogram shows a thick-walled right ventricle and demonstrates the underlying congenital heart lesion. Two-dimensional echocardiography assists in eliminating from consideration lesions such as obstructed pulmonary veins, supramitral membrane, mitral stenosis, and restrictive cardiomyopathy. Doppler studies demonstrate the direction of the intracardiac shunt and the presence of a typical hypertension waveform in the main pulmonary artery. Tricuspid and pulmonary regurgitation can be used in the Doppler examination to estimate pulmonary arterial systolic and diastolic pressures.

Cardiac catheterization usually shows a bidirectional shunt at the site of the defect. Systolic pressure is generally equal in the systemic and pulmonary circulations. Pulmonary capillary wedge pressure is normal unless a left-sided heart obstructive lesion or left ventricular failure is the cause of the pulmonary arterial hypertension. Arterial oxygen saturation is decreased depending on the magnitude of

the right-to-left shunt. The response to vasodilator therapy (oxygen, prostacyclin, nitric oxide) may identify patients with hyperdynamic pulmonary hypertension. Selective pulmonary artery injections may be necessary if pulmonary venous obstruction is suspected because of high wedge pressure and low left ventricular end-diastolic pressure.

TREATMENT

The best management for patients who are at risk for the development of late pulmonary vascular disease is prevention by early surgical elimination of large intracardiac or great vessel communications during infancy. Some patients may be missed because they have not shown early clinical manifestations. Rarely, pulmonary vascular resistance never decreases at birth in these infants, and therefore they never acquire enough left-to-right shunting to become clinically apparent. Such delayed recognition is a particular risk in patients with congenital heart disease who live at high altitude. It is also a risk in infants with trisomy 21, who have a propensity for earlier development of pulmonary vascular disease. Because of the high incidence of congenital heart disease associated with trisomy 21, routine echocardiography is recommended at the time of initial diagnosis, even in the absence of other clinical findings.

Medical treatment of Eisenmenger syndrome is primarily symptomatic. Many patients benefit substantially from either oral (calcium channel blocker, endothelin antagonist, phosphodiesterase inhibitors) or chronic intravenous (prostacyclin) therapy. Combined heart-lung or bilateral lung transplantation is the only surgical option for many of these patients (see Chapter 443.2).

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Chapter **434**

General Principles of Treatment of Congenital Heart Disease

Daniel Bernstein

Most patients who have mild congenital heart disease require no treatment. The parents and child should be made aware that a normal life is expected and that no restriction of the child's activities is necessary. Overprotective parents may use the presence of a mild congenital heart lesion or even a functional heart murmur as a means to exert excessive control over their child's activities. Although fears may not be expressed overtly, the child may become anxious regarding early death or debilitation, especially when an adult member of the family acquires unrelated symptomatic heart disease. The family may have an unexpressed fear of sudden death, and the rarity of this manifestation should be emphasized in discussions directed at improving their understanding of the child's congenital heart defect. The difference between congenital heart disease and degenerative coronary disease in adults should be emphasized. General health maintenance, including a well-balanced, "heart-healthy" diet; aerobic exercise; and avoidance of smoking, should be encouraged.

Even patients with moderate to severe heart disease need not be restricted from all physical activity, although many will tend to limit their own activities. **Physical education** should be modified appropriately to the child's capacity to participate; the extent of such modification can often be guided by formal exercise testing. Although competitive sports for some patients may need to be discouraged, decisions are made on an individual basis. The influence of coach and peer pressure should be taken into account when recommending competitive versus noncompetitive athletics. Many cardiologists will also prohibit certain high-impact activities ("collision sports") such as tackle football or contact martial arts in patients with some forms of prior open heart surgery.

Routine immunizations should be given, with the inclusion of influenza vaccine during the appropriate season. Prophylaxis against the respiratory syncytial virus is recommended during respiratory syncytial virus season in young infants with unrepaired congenital heart disease and significant hemodynamic abnormalities. However, careful consideration for timing of administration of live-virus vaccination is required in patients who are potential candidates for heart or heart-lung transplantation.

Bacterial infections should be treated vigorously, but the presence of congenital heart disease is not an appropriate reason to use antibiotics indiscriminately. Prophylaxis against bacterial endocarditis should be carried out during dental procedures for appropriate patients. The American Heart Association has recently significantly revised these recommendations, with most patients no longer requiring routine prophylaxis (see Chapter 437). Endocarditis prophylaxis is generally no longer recommended for gastrointestinal or genitourinary procedures.

Cyanotic patients need to be monitored for noncardiac manifestations of oxygen deficiency (Table 434-1). Treatment of iron-deficiency anemia is important in cyanotic patients, who will show improved exercise tolerance and general well-being with adequate hemoglobin levels. These patients should also be carefully observed for excessive polycythemia. Cyanotic patients should avoid situations in which dehydration may occur, which leads to increased viscosity and increases the risk of stroke. Diuretics may need to be decreased or temporarily discontinued during episodes of acute gastroenteritis. High altitudes and sudden changes in the thermal environment should also be avoided. Phlebotomy with partial exchange transfusion is carried out only in symptomatic patients with severe **polycythemia** (usually those whose hematocrit is >65%).

Patients with moderate to severe forms of congenital heart disease or a history of rhythm disturbance should be carefully monitored during anesthesia for even routine surgical procedures. Consultation with an anesthesiologist experienced in the care of children with congenital heart disease is recommended. Women with nonrepaired severe congenital heart disease should be counseled on the risks associated with childbearing and on the use of contraceptives and tubal ligation. Pregnancy may be dangerous to both mother and fetus for patients with chronic cyanosis or pulmonary arterial hypertension. Women with mild to moderate heart disease and many of those who have had corrective surgery can have normal pregnancies, although those with residual hemodynamic derangements or with systemic right ventricles should be followed by a high-risk perinatologist and a cardiologist with expertise in caring for adults with congenital heart disease.

POSTOPERATIVE MANAGEMENT

After successful open heart surgery, the severity of the congenital heart defect, the age and condition (nutritional status) of the patient before surgery, the events in the operating room, and the quality of the postoperative care influence the patient's course. Intraoperative factors that influence survival and that should be noted when a patient returns from the operating room include the duration of cardiopulmonary bypass, the duration of aortic cross-clamping (the time during which the heart is not being perfused), and the duration of profound hypothermia (used in some newborns: the period during which the entire body is not being perfused).

Immediate postoperative care should be provided in an intensive care unit staffed by a team of physicians, nurses, and technicians experienced with the unique problems encountered after open heart surgery in childhood. In most major centers, this occurs in a dedicated pediatric cardiovascular intensive care unit. Preparation for postoperative monitoring begins in the operating room, where the anesthesiologist

Table 434-1 Extracardiac Complications of Cyanotic Congenital Heart Disease and Eisenmenger Physiology

PROBLEM	ETIOLOGY	THERAPY
Polycythemia	Persistent hypoxia	Phlebotomy
Relative anemia	Nutritional deficiency	Iron replacement
CNS abscess	Right-to-left shunting	Antibiotics, drainage
CNS thromboembolic stroke	Right-to-left shunting or polycythemia	Phlebotomy
Low-grade DIC, thrombocytopenia	Polycythemia	None for DIC unless bleeding, then phlebotomy
Hemoptysis	Pulmonary infarct, thrombosis, or rupture of pulmonary artery plexiform lesion	Embolization
Gum disease	Polycythemia, gingivitis, bleeding	Dental hygiene
Gout	Polycythemia, diuretic agent	Allopurinol
Arthritis, clubbing	Hypoxic arthropathy	None
Pregnancy complications: abortion, fetal growth retardation, prematurity increase, maternal illness	Poor placental perfusion, poor ability to increase cardiac output	Bed rest, pregnancy prevention counseling
Infections	Associated asplenia, DiGeorge syndrome, endocarditis	Antibiotics
	Fatal RSV pneumonia with pulmonary hypertension	Ribavirin; RSV immunoglobulin (prevention)
Failure to thrive	Increased oxygen consumption, decreased nutrient intake	Treat heart failure; correct defect early; increase caloric intake
Protein-losing enteropathy	S/P Fontan; high right-sided pressures	Oral budesonide or sildenafil
Chylothorax	Injury to thoracic duct	Medium chain triglyceride diet Octreotide Surgical ligation of thoracic duct
Psychosocial adjustment	Limited activity, cyanotic appearance, chronic disease, multiple hospitalizations	Counseling

CNS, central nervous system; DIC, disseminated intravascular coagulation; RSV, respiratory syncytial virus; S/P, status post (after).

or surgeon places an arterial catheter to allow direct arterial pressure measurements and arterial sampling for blood gas determination. A central venous catheter is also placed for measuring central venous pressure and for infusions of cardioactive medications. In more complex cases, right or left atrial or pulmonary artery catheters may be inserted directly into these cardiac structures and used for pressure monitoring purposes. Temporary pacing wires are placed on the atrium or ventricle, or both, in case temporary postoperative heart block occurs. Transcutaneous oximetry provides for continuous monitoring of arterial oxygen saturation. Near-infrared spectroscopy has been used to monitor cerebral and other end-organ perfusion in the perioperative period.

Functional failure of 1 organ system may cause profound physiologic and biochemical changes in another. Respiratory insufficiency, for example, leads to hypoxia, hypercapnia, and acidosis, which, in turn, compromise cardiac, vascular, and renal function. The latter problems cannot be managed successfully until adequate ventilation is reestablished. Thus, it is essential that the primary source of each postoperative problem be identified and treated.

Respiratory failure is a serious postoperative complication encountered after open heart surgery. Cardiopulmonary bypass carried out in the presence of pulmonary congestion results in decreased lung compliance, copious tracheal and bronchial secretions, atelectasis, and increased breathing effort. Because fatigue and, subsequently, hypoventilation and acidosis may rapidly ensue, mechanical positive pressure endotracheal ventilation is usually continued after open heart surgery for a minimum of several hours in relatively stable patients and for up to 2-3 days or longer in severely ill patients, especially infants. Patients with certain congenital heart lesions, particularly those with DiGeorge syndrome, may also have airway abnormalities (micrognathia, tracheomalacia, bronchomalacia) that can make both ventilation and extubation more difficult.

The electrocardiogram should be monitored continuously during the postoperative period. A change in heart rate, even without arrhythmia, may be the first indication of a serious complication such as hemorrhage, hypothermia, hypoventilation, or heart failure. **Cardiac rhythm disorders** must be diagnosed quickly because a prolonged untreated arrhythmia may add a severe hemodynamic burden to the heart in the critical early postoperative period (see Chapter 435). Injury to the heart's conduction system during surgery can result in postoperative complete heart block. This complication is usually temporary and is treated with surgically placed pacing wires that can later be removed. Occasionally, complete heart block is permanent. If heart block persists beyond 10-14 days postoperatively, insertion of a permanent pacemaker is required. Tachyarrhythmias are a common problem in postoperative patients. Junctional ectopic tachycardia can be a particularly troublesome rhythm to manage (see Chapter 435), although it usually responds to antiarrhythmic medications such as intravenous amiodarone.

Heart failure with poor cardiac output after cardiac surgery may be secondary to respiratory failure, serious arrhythmias, myocardial injury, blood loss, hypovolemia, a significant residual hemodynamic abnormality, or any combination of these factors. Treatment specific to the cause should be instituted. Catecholamines, phosphodiesterase inhibitors, nitroprusside and other afterload-reducing agents, and diuretics are the cardioactive agents most often used in patients with myocardial dysfunction in the early postoperative period (see Chapter 442). Postoperative pulmonary hypertension can be managed with hyperventilation and inhaled nitric oxide. In the rare patients who are unresponsive to standard pharmacologic treatment, various ventricular assist devices are available, depending on the patient's size. If pulmonary function is adequate, a left ventricular assist device may be used. If pulmonary function is inadequate, extracorporeal membrane oxygenation may be used. These extraordinary measures are helpful in maintaining the circulation until cardiac function improves, usually

within 2-5 days. They have also been used as a bridge to transplantation in patients with severe nonremitting postoperative cardiac failure.

Acidosis secondary to low cardiac output, renal failure, or hypovolemia must be prevented, or if present, promptly corrected. Serial monitoring of arterial blood gases and lactate concentrations is performed. A low arterial pH may not only be a sign of decreased perfusion, but also worsen cardiac function and may be the forerunner of arrhythmias or cardiac arrest.

Renal function may be compromised by congestive heart failure and further impaired by prolonged cardiopulmonary bypass. Blood and fluid replacement, cardiac inotropic agents, and vasodilators will usually reestablish normal urine flow in patients with hypovolemia or cardiac failure. Renal failure secondary to tubular injury may require temporary peritoneal or hemodialysis or hemofiltration.

Neurologic abnormalities can develop after cardiopulmonary bypass, especially in the neonatal period. Seizures may occur when the patient awakens from sedation and can usually be controlled with anticonvulsant medications. In the absence of other neurologic signs, self-limited isolated seizures in the immediate postoperative period usually carry a good long-term prognosis. Thromboembolism and stroke are rarer but serious complications of open heart surgery. In the long-term, both subtle and more substantial learning disabilities may develop. Patients who have undergone surgery entailing the use of cardiopulmonary bypass, especially in the newborn period, should be watched carefully during their early school years for signs of mild to moderate learning disabilities or attention deficit disorders, which are often amenable to early remedial intervention. The risk is higher in patients who have undergone repair using hypothermic total circulatory arrest than in those where systemic blood flow is maintained using cardiopulmonary bypass.

The **postpericardiotomy syndrome** may occur toward the end of the 1st postoperative wk or may sometimes be delayed until weeks or months after surgery. This febrile illness is characterized by fever, decreased appetite, listlessness, nausea, and vomiting. Chest pain is not always present, so a high index of suspicion should be maintained in any recently postoperative patient. Echocardiography is diagnostic. In most instances, the postpericardiotomy syndrome is self-limited; however, when pericardial fluid accumulates rapidly, the potential danger of cardiac tamponade should be recognized (see Chapter 440). Rarely, arrhythmias may also occur. Symptomatic patients usually respond to salicylates or indomethacin and bed rest. Occasionally, steroid therapy or pericardiocentesis is required. Late recurrences are rare and can lead to chronic pericarditis.

Hemolysis of mechanical origin is seen, although rarely, after repair of certain cardiac defects, for example, atrioventricular septal defects (AVSDs), or after the insertion of a mechanical prosthetic valve. It is caused by unusual turbulence of blood at increased pressure. Reoperation may be necessary in rare patients with severe and progressive hemolysis who require frequent blood transfusions, but in most instances, the problem slowly regresses.

Infection is another potentially serious postoperative problem. Patients usually receive a broad-spectrum antibiotic for the initial postoperative period. Potential sites of infection include the lungs (generally related to postoperative atelectasis), the subcutaneous tissues at the incision site, the sternum, and the urinary tract (especially after an indwelling catheter has been in place). Sepsis with infective endocarditis is an infrequent complication, and can be difficult to manage, especially if prosthetic material was placed at the time of surgery (see Chapter 437).

LONG-TERM MANAGEMENT

Patients who have undergone surgery for congenital heart disease can be divided into several major categories: (1) lesions for which total repair has been achieved; (2) lesions for which both anatomic and physiologic correction have been achieved; and (3) lesions for which only palliation, albeit potentially long-term, has been achieved. There is some disagreement among cardiologists as to exactly which categories a particular congenital heart lesion might fall, and to some degree every case should be considered individually. Many argue that only for isolated patent ductus arteriosus is total repair really achieved, with no requirement for long-term follow-up. Patients who are able to undergo anatomic and physiologic correction include many of the left-to-right shunt lesions (atrial and ventricular septal defects) and milder forms of obstructive lesions (e.g., valvar pulmonic stenosis, some forms of valvar aortic stenosis, and coarctation of the aorta), and some forms of cyanotic heart disease, for example, uncomplicated tetralogy of Fallot and simple transposition of the great arteries. These patients usually have achieved total or near-total physiologic correction of their lesion; however, they are still at some risk of long-term sequelae, including late heart failure or arrhythmia, or recurrence of a significant physiologic abnormality (e.g., recoarctation of the aorta, worsening mitral regurgitation in patients with AVSDs, or long-standing pulmonary regurgitation in patients with tetralogy of Fallot repaired with a transannular patch). These patients require regular follow-up with a pediatric cardiologist (and when old enough, with an **adult congenital heart disease specialist** [see Chapter 434.1]); however, their long-term prognosis is generally very good, although some will require repeat surgeries. Patients with more complex lesions, such as those with single-ventricle physiology, are at much higher risk of long-term sequelae and require even closer follow-up. These patients, particularly those who have undergone the Fontan procedure, are at risk long-term for arrhythmia, thrombosis, protein losing enteropathy, end-organ (especially hepatic) dysfunction, and heart failure. Some may eventually require cardiac transplantation.

Physical limitations are variable, ranging from minimal to none in patients with physiologic correction, to mild to moderate in patients with palliative procedures. The extent to which a patient should be allowed to participate in athletics, both recreational and competitive, can best be determined by the cardiologist, often with the assistance of the data that can be derived from cardiopulmonary exercise testing (see Chapter 423.5).

Long-term morbidities affecting neurologic function and behavior are influenced by many factors, including the effects of any genetic alterations on the developing central nervous system. Data suggest a greater role for prenatal central nervous system abnormalities (anatomic or secondary to alterations in cerebral blood flow or oxygenation) than previously suspected; these include microcephaly, cerebral atrophy, and altered cerebral biochemistry. Chronic hypoxemia and failure to thrive also may influence the developing brain, and there is evidence that the type of intervention required (cardiopulmonary bypass, hypothermic total circulatory arrest, catheter-based therapy) plays a substantial role. In general, in the absence of a significant genetic syndrome or major perioperative complication, most children function at a fairly high level after repair of congenital heart defects and are able to attend regular school. Group mean scores on standard cognitive tests are not different from the general population; however, some areas appear to be more at risk than others, including certain aspects of motor function, speech, visual-motor tracking, and phonologic awareness. Awareness of these potential issues is critical to obtaining prompt remedial assistance if a child is found to be struggling in school.

Bibliography is available at Expert Consult.

434.1 Congenital Heart Disease in Adults

Salil Ginde and Michael G. Earing

The advent of cardiac surgical procedures such as ligation of patent ductus arteriosus, resection of coarctation of aorta, and the Blalock-Taussig shunt, as well as advances in diagnostic, interventional, and critical care skills have resulted in survival of approximately 90% of children with congenital heart disease to adulthood. More adults than children are living with congenital heart disease in the United States, with a 5% increase every year. In the last decade, 35% of hospitalizations for congenital heart disease were patients over the age of 18 yr (mean age: 55 yr).

LONG-TERM MEDICAL CONSIDERATIONS

Approximately 25% of adults with congenital heart disease have a mild form that has allowed them to survive into adulthood without surgical

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or interventional cardiac catheterization. The most common lesions in this category include mild aortic valve stenosis (usually in setting of bicuspid aortic valve), small restrictive ventricular septal defects, mild pulmonary valve stenosis, and mitral valve prolapse (Table 434-2). These patients need less-frequent follow-up to assess for progression of disease and to identify associated complications. The majority of adults with congenital heart disease living in the United States are patients who have had previous intervention (Table 434-3). Although most children who undergo surgical intervention will survive to adulthood, with few exceptions, total correction is not the rule. The few exceptions include patent ductus arteriosus, ventricular septal defects, and atrial septal defects; this is true only if they are closed early before the development of irreversible pulmonary vascular changes, and no residual lesions exist.

Because adult patients with congenital heart disease (CHD) are surviving longer than ever, it is becoming increasingly apparent that even the simplest lesions can be associated with long-term complications. These long-term complications include both cardiac and noncardiac problems (Tables 434-4 and 434-5, Fig. 434-1). Cardiac complications include arrhythmias and conduction defects, ventricular dysfunction, residual shunts, valvular lesions (regurgitation and stenosis), hypertension, and aneurysms. Noncardiac sequelae (comorbidities) include pulmonary, renal, and hepatic dysfunction that is caused either directly or indirectly by the underlying CHD. Abnormal pulmonary function most commonly presents as restrictive lung physiology, and likely results from prior sternotomy or thoracotomy, scoliosis, diaphragmatic dysfunction, or parenchymal lung disease. Reduced pulmonary function contributes to reduced exercise tolerance and is a risk factor for mortality in adults with CHD. Renal dysfunction may result from chronic cyanosis, multiple surgeries requiring cardiopulmonary bypass, or from other comorbid conditions, such as hypertension and diabetes mellitus. Hepatic injury from chronic liver congestion in patients with elevated central venous pressures, particularly patients palliated with the Fontan procedure, can result in hepatic fibrosis, cirrhosis, hepatic dysfunction and rarely hepatocellular carcinoma. Adults with CHD are at risk for developmental abnormalities such as intellectual impairment, somatic abnormalities such as facial dysmorphism (cleft palate/lip), central nervous abnormalities such as seizure disorders from previous thromboembolic events or cerebrovascular accidents, and impairments of hearing or vision loss. Psychosocial problems involving employment, life and health insurance, participation in sports, sexual activity, and contraception are common. As a result of these long-term complications, the majority of adults with CHD need lifelong follow-up. When adults with CHD are hospitalized, it is usually for heart failure or an arrhythmia; others may require catheterization or another cardiac surgical procedure.

Table 434-2	Congenital Heart Defects Associated with Survival into Adulthood Without Surgery or Interventional Cardiac Catheterization
Mild pulmonary valve stenosis	
Bicuspid aortic valve	
Small to moderate size atrial septal defect	
Small ventricular septal defect	
Small patent ductus arteriosus	
Mitral valve prolapse	
Partial atrioventricular canal (ostium primum atrial septal defect and cleft mitral valve)	
Marfan syndrome	
Ebstein anomaly	
Congenitally corrected transposition (atrioventricular and ventriculoarterial discordance)	

Table 434-3	Most Common Congenital Heart Defects Surviving to Adulthood After Surgery or Interventional Catheterization
Aortic valve disease following balloon valvuloplasty or surgical valvotomy	
Pulmonary valve stenosis following balloon valvuloplasty or surgical valvotomy	
Tetralogy of Fallot	
Ventricular septal defect	
Complete atrioventricular canal defect	
Transposition of the great arteries	
Coarctation of the aorta	
Complex single ventricles after the modified Fontan procedure	

SPECIFIC LESIONS

Left-to-Right Shunts

If the initial lesion has a shunt that is large and nonrestrictive (allowing transmission of near systemic pressure to the pulmonary arteries), irreversible pulmonary vascular changes can occur, resulting in pulmonary hypertension at systemic levels with reversed or bidirectional shunting at the level of the defect (Eisenmenger syndrome) (see Chapter 433.2).

Atrial Septal Defects

See Chapter 426.1.

Although, most individuals with an atrial septal defect are diagnosed during childhood after a murmur is noted, a minority of patients

Table 434-4	Risks in Adults Who Have Congenital Heart Disease
Rhythm disorder	Ventral septal defect
Supraventricular tachycardia	Atrial septal defect
Right bundle branch block	Patent ductus arteriosus
Heart block	**Acquired lesions**
Ventricular tachycardia	Subacute bacterial endocarditis
Sudden death	Subvalvular stenosis
Coarctation of aorta	Supravalvular stenosis
Essential hypertension	Valvular insufficiency
Recoarctation	Valvular restenosis
Aneurysm formation	Eisenmenger complex
Residual lesions (shunts)	**Pregnancy risk (see Table 434-5)**

Table 434-5	Lesion Specific Risks of Maternal and Neonatal Complications of Pregnancy
No additional risk	Small septal defects Surgically closed ASD, VSD, PDA Mild to moderate aortic regurgitation Mild to moderate pulmonary stenosis
Slightly increased risk	Postoperative repair of tetralogy of Fallot Transposition of the great arteries, s/p arterial switch procedure
Moderate risk	Transposition of the great arteries, s/p atrial switch procedure Congenitally corrected transposition of the great arteries Single ventricle physiology, s/p Fontan procedure
Severe risk	Cyanotic congenital heart disease, unoperated or palliated Marfan syndrome Prosthetic valves Obstructive lesions including coarctation
Pregnancy contraindicated	Severe pulmonary hypertension Severe obstructive lesions Marfan syndrome, aortic root >40 mm

ASD, atrial septal defect; PDA, patent ductus arteriosus; s/p, status post (after); VSD, ventricular septal defect.

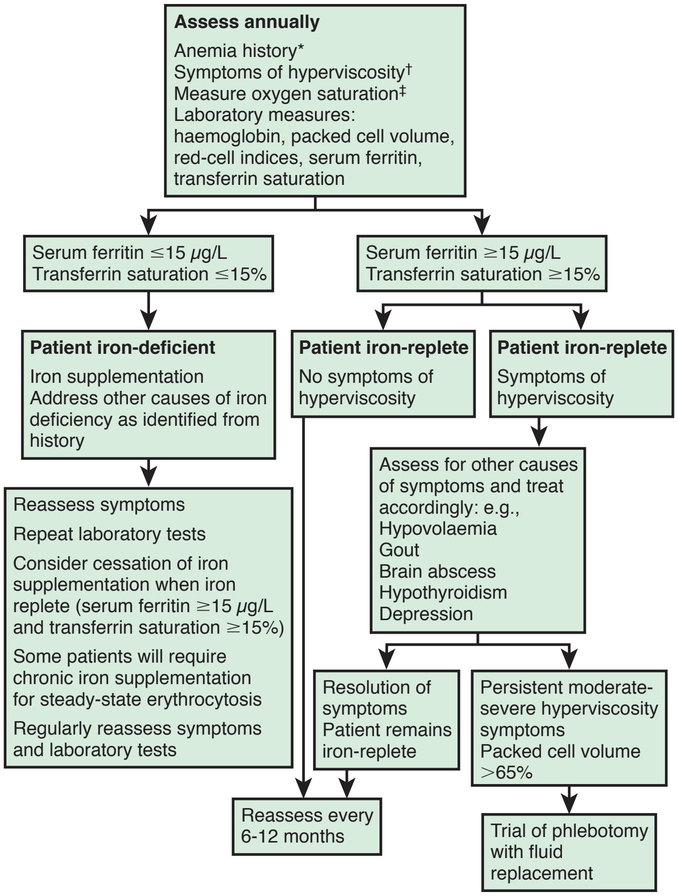

Figure 434-1 Important issues that are crucial to address at time of transition. *(From Spence MS, Balaratnam MS, Gatzoulis MA: Clinical update: cyanotic adult congenital heart disease,* Lancet *370:1530–1532, 2007, p. 1531.)*

present with symptoms for the 1st time as adults. Most patients are asymptomatic during the 1st and 2nd decades of life. In the 3rd decade, an increasing number of patients then develop exercise intolerance, palpitations from atrial arrhythmias, and cardiac enlargement. If untreated, survival into adulthood is the rule; life expectancy, however, is not normal and there is significant long-term morbidity. After the age of 40 yr, the mortality rate increases by 6% per year, and more than 20% of patients will have developed atrial fibrillation. By age 60 yr, the number of patients with atrial fibrillation increases to more than 60%.

Late Outcome Following Closure of Atrial Septal Defect

Most patients who have undergone early closure of a defect will have excellent long-term survival with low morbidity if repair is undertaken before age 25 yr. Older age of repair is associated with decreased late survival with an associated increased risk for the development of atrial arrhythmias, thromboembolic event, and pulmonary hypertension. Long-term late complications and survival following transcatheter device closure remain unknown; early and intermediate results are excellent with a high rate of atrial septal defect closure and few major complications.

Ventricular Septal Defects

See Chapter 426.6.

Although isolated ventricular septal defects (VSDs) are 1 of the most common forms of CHD, the diagnosis of a VSD in an adult is rare. The primary reason for this is that most patients with a hemodynamically significant VSD will have undergone repair in childhood or will have died earlier in life. As result, the spectrum of isolated VSD in adults is limited to (1) those with small restrictive defects, (2) those with Eisenmenger syndrome, and (3) those who had their defects closed in childhood.

For patients with small restrictive VSD, the long-term survival is excellent with estimated 25-yr survival of 96%. In addition, the long-term morbidity for patients with a restrictive VSD also appears to be low. Their clinical course is not completely benign. Reported long-term complications include endocarditis, progressive aortic regurgitation secondary to prolapse of aortic valve into the defect (highest risk is with supracristal type, but also can occur in setting of perimembranous defect), and the development of both right and left outflow tract obstruction from a double-chamber right ventricle or a subaortic membrane. For those patients who develop Eisenmenger syndrome, survival into the 3rd decade is common. With increasing age, the long-term complications of right-heart failure, paradoxical emboli, and polycythemia, usually result in progressive decline in survival, with an average age of death of 37 yr.

Adults with previous VSD closure, without pulmonary hypertension or residual defects, live a normal life expectancy. Because patients with small VSDs are asymptomatic, these patients should be managed conservatively. Given the long-term risks, they do need intermittent follow-up for life to monitor for the development of late complications. The exception to this rule is patients with small supracristal or perimembranous VSD with associated prolapse of the aortic cusp into the defect resulting in progressive aortic regurgitation. These patients should be considered for surgical repair at the time of diagnosis to prevent progressive aortic valve damage.

Complete Atrioventricular Canal

See Chapter 426.5.

The natural history for patients with complete AVSD is characterized by the early development of pulmonary vascular disease, leading to irreversible damage often by age 1 yr (especially in children with Down syndrome). Thus, patients who present in adulthood can be categorized into 2 groups: (1) those with Eisenmenger syndrome and (2) those who had their defects closed in childhood.

Overall, for those patients who underwent early repair before the development of pulmonary vascular disease, the long-term prognosis is good. The most common long-term complication is left atrioventricular valve regurgitation, with approximately 5-10% of patients requiring surgical revision for left atrioventricular valve repair or replacement during follow-up. The second most common long-term complication for this patient group is subaortic stenosis, occurring in up to 5% of patients after repair. Other long-term complications include residual atrial or ventricular level shunts, complete heart block, atrial and ventricular arrhythmias, and endocarditis.

For those patients who have developed Eisenmenger syndrome, all are symptomatic with exertional dyspnea, fatigue, palpitations, edema, and syncope. Survival is similar to other forms of Eisenmenger syndrome, with a mean age of death of 37 yr. Strong predictors for death include syncope, age at presentation of symptoms, poor functional class, low oxygen saturation (<85%), elevated serum creatinine and serum uric acid concentrations, and Down syndrome.

Patients who underwent previous repair and develop significant left atrioventricular valve regurgitation causing symptoms, atrial arrhythmias, or deterioration in ventricular function should undergo elective valve repair or replacement. Those previously repaired patients who develop significant subaortic stenosis (defined as a peak cardiac catheterization or echo gradient of >50 mm Hg) should undergo surgical repair.

Patent Ductus Arteriosus

See Chapter 426.8.

A patent ductus arteriosus (PDA) is usually an isolated lesion in the adult patient. The size of the defect is the primary determinant of clinical course in the adult patient. These clinical courses can be grouped

into 5 main categories: (1) silent PDAs; (2) small, hemodynamically insignificant PDAs; (3) moderate size PDAs; (4) large PDAs; and (5) previously repaired PDAs.

A silent PDA is a tiny defect that cannot be heard by auscultation and is only detected by other nonclinical means such as echocardiography. Life expectancy is always normal in this population and the risk for endocarditis is extremely low.

Patients with a small PDA have an audible long-ejection or continuous murmur heard best at the left upper sternal border that radiates to the back. In addition, they have normal peripheral pulses. Because there is negligible left to right shunting these patients have normal left aorta and left ventricle (LV) size and normal pulmonary artery pressure by echocardiography and chest x-ray. These patients like those with silent PDAs are asymptomatic and live a normal life expectancy. They have a higher risk for endocarditis.

Patients with moderate size PDAs may present during adulthood. These patients often will have wide, bounding peripheral pulses and an audible continuous murmur. These patients all have significant volume overload and develop some degree of left aorta and LV enlargement and some degree of pulmonary hypertension. These patients are symptomatic with dyspnea, palpitations, and heart failure.

Patients with large PDAs typically present with signs of severe pulmonary hypertension and Eisenmenger syndrome. By adulthood, the continuous murmur is typically absent and there is differential cyanosis (lower extremity saturations lower than the right arm saturation). These patients have a similar prognosis as other patients with Eisenmenger syndrome.

Patients who underwent repair of a PDA prior to the development of pulmonary hypertension have a normal life expectancy without restrictions.

All patients with *clinical evidence* of a PDA are at increased risk for endocarditis. As result, all PDAs except for small silent PDAs and those patients with severe irreversible pulmonary hypertension should be considered for closure. Catheter device closure is the preferred method in most centers today. Surgical closure is reserved for patients with PDAs too large for device closure or when the anatomy is distorted, such as in the setting of a large ductal aneurysm.

Cyanotic Heart Disease

See Chapters 429, 430, and 431.

Unlike the acyanotic forms of CHD, the majority of patients with cyanotic CHD will have had at least 1 and often several previous interventions prior to adulthood. The most frequent defects seen in the outpatient adult congenital setting is tetralogy of Fallot, complete transposition of the great arteries (TGA, also known as d-transposition), pulmonary valve stenosis, and various forms of single ventricles. Other defects include total anomalous pulmonary venous return, truncus arteriosus, and double-outlet right ventricle.

Tetralogy of Fallot

See Chapter 430.1.

In the developed world, the unoperated adult patient with tetralogy of Fallot has become a rarity because the majority of patients will have undergone palliation or, more often, repair in childhood. Survival in the unoperated patient to the 7th decade has been described but is rare. In general, only 11% of unoperated patients are alive by age 20 yr and only 3% by age 40 yr.

Late survival following repair of tetralogy of Fallot is excellent. Repair is typically performed at 3-12 mo of age and consists of patch closure of the VSD and relief of the pulmonary outflow tract obstruction by patch augmentation of the right ventricular outflow tract, pulmonary valve annulus, or both. Survival rates at 32 and 35 yr have been reported to be 86% and 85%, respectively, compared to 95% in age- and sex-matched controls. Most patients lived an unrestricted life. Many patients do develop late symptoms that include exertional dyspnea, palpitations, syncope, and sudden cardiac death. Late complications include endocarditis, aortic regurgitation with or without aortic root dilation (typically caused by damage of the aortic valve during VSD closure or secondary to an intrinsic aortic root abnormality), LV dysfunction (secondary to inadequate myocardial protection during previous repair or chronic left ventricular volume overload caused by long-standing palliative arterial shunts), residual pulmonary valve obstruction, residual pulmonary valve regurgitation, right ventricular (RV) dysfunction (as a result of pulmonary regurgitation or pulmonary stenosis), atrial arrhythmias (typically atrial flutter), ventricular arrhythmias, and heart block.

Reintervention is necessary in approximately 10% of patients following reparative surgery at 20-year follow-up. With longer follow-up, the incidence of reintervention continues to increase. The most common indication for reintervention is pulmonary valve replacement for severe pulmonary valve regurgitation.

Transposition of the Great Arteries

See Chapter 431.1.

The natural history of patients with unrepaired TGA is so poor that very few patients survive past childhood without intervention. The first definitive operations for TGA were described by Dr. Senning in 1959 and Dr. Mustard in 1964 (atrial switch procedures). With these procedures, the systemic and pulmonary venous returns are rerouted in the atrium by constructing baffles. The systemic venous return from the superior and inferior vena cavae is directed through the mitral valve and into the LV (connected to the pulmonary artery). The pulmonary venous return is then directed through the tricuspid valve into the right ventricular (connected to the aorta). These procedures can be performed with low mortality but leave the LV as the pulmonary ventricle and the right ventricle as the systemic ventricle. Long-term follow-up studies after the atrial switch procedure show a small but ongoing attrition rate with numerous other intermediate and long-term complications. Two specific problems after the atrial switch procedure are most concerning. These include the loss of sinus rhythm with the development of atrial arrhythmias, occurring at an incidence of 50% by age 25 yr, and the development of systemic ventricular dysfunction, occurring at an incidence of 50% by age 35 yr. Other long-term complications include endocarditis, baffle leaks, baffle obstruction, tricuspid valve regurgitation, and sinus node dysfunction requiring pacemaker placement.

As result of these long-term complications, the arterial switch operation has become the procedure of choice to treat these patients since 1985. During the arterial switch procedure, the great arteries are transected and reanastomosed to the correct ventricle (LV to the aorta and the right ventricle to the pulmonary artery) with coronary artery transfer. Operative survival after the arterial switch procedure in the current surgical era is very good, with a surgical mortality rate of 2-5%. Long-term data on survival and complications does not exist, but intermediate results are promising. Reported intermediate complications include endocarditis, pulmonary outflow tract obstruction (at the supravalvular level or at the takeoff of the peripheral pulmonary arteries), aortic valve regurgitation, and coronary artery compromise (ranging from minor stenosis to complete occlusion).

Because of the high incidence of observed and potential medical problems, all patients who have had both atrial and arterial repair of TGA should have lifelong follow-up by a cardiologist at a center specializing in adult CHD.

Pulmonary Valve Stenosis

See Chapter 427.1.

Most patients with pulmonary valve stenosis are asymptomatic and present with a cardiac murmur. Survival into adult life and the need for intervention however is directly correlated to the degree of obstruction. Patients with trivial stenosis (defined as a peak gradient <25 mm Hg) followed for 25 yr remain asymptomatic and have no significant progression of obstruction over time. For those patients with moderate pulmonary valve stenosis (defined as a peak gradient of 25-49 mm Hg), there is an approximately 20% chance of requiring intervention by age 25 yr. For those patients with severe stenosis (defined as a peak gradient of >50 mm Hg), the majority ultimately require an intervention, either surgery or balloon valvuloplasty by age 25 yr.

Following surgical valvotomy for isolated pulmonary stenosis, long-term survival is excellent. With longer follow-up the incidence of late complications and the need for reintervention do increase. The most common indication for reintervention is pulmonary valve replacement for severe pulmonary regurgitation. Other long-term complications include recurrent atrial arrhythmias, endocarditis, and residual RV outflow tract obstruction.

Patients with moderate to severe pulmonary stenosis (defined as a peak gradient of >50 mm Hg) should be considered for intervention even in the absence of symptoms. Since 1985, percutaneous balloon valvuloplasty has been the accepted treatment for patients of all ages. Prior to 1985, surgical valvotomy had been the gold standard. Surgical valvotomy is reserved for those patients who are unlikely to have successful results from balloon valvuloplasty, such as those with an extremely dysplastic or calcified valve.

Left-Sided Obstructive Lesions

Coarctation of the Aorta

See Chapter 427.6.

The clinical presentation of coarctation of the aorta depends on the severity of obstruction and the associated anomalies. Unrepaired coarctation of the aorta typically presents with symptoms prior to adulthood. These symptoms include headaches related to hypertension, leg fatigue or cramps, exercise intolerance, and systemic hypertension. Those untreated patients surviving to adulthood thus typically have only mild coarctation of the aorta. In the era prior to surgery, without treatment the mean age of death was 32 yr. Causes of death included left ventricular failure, intracranial hemorrhage, endocarditis, aortic rupture/dissection, and premature coronary artery disease.

Following surgical repair, long-term survival is good but is directly correlated with the age at repair, with those repaired after age 14 yr having a lower 20 yr survival than those who were repaired earlier, 91% compared to 79%. With longer follow-up the incidence of long-term complications continues to rise. The most common long-term complication is persistent or new systemic hypertension at rest or during exercise. Other long-term complications include aneurysms of the ascending or descending aorta, recoarctation at the site of previous repair, coronary artery disease, aortic stenosis or regurgitation (in setting of bicuspid aortic valve), rupture of an intracranial aneurysm, and endocarditis.

Patients with significant native or residual coarctation of the aorta (symptomatic patients with a peak gradient across the coarctation of >20 mm Hg) should be considered for intervention, either surgery or catheter intervention with balloon angioplasty with or without stent placement. Surgical repair in the adult patient is technically difficult and is associated with high morbidity. Catheter based intervention has become the preferred method in most experienced adult CHD centers.

Aortic Valve Stenosis

See Chapter 427.5.

The natural history of aortic valve stenosis in adults is quite variable but is characterized by progressive stenosis over time. By age 45 yr, approximately 50% of bicuspid aortic valves will have some degree of stenosis.

Most patients with aortic valve stenosis are asymptomatic and are diagnosed after a murmur is detected. The severity of obstruction at the time of diagnosis correlates with the pattern of progression. Symptoms are rare until patients have severe aortic valve stenosis (mean gradient by echocardiography of >40 mm Hg). Symptoms include chest pain, exertional dyspnea, near syncope, and syncope. When any of these symptoms are present, the risk of sudden cardiac death is very high and as result, surgical intervention is mandated. For patients requiring surgical valvotomy to relieve the stenosis prior to adulthood, the majority of patients do well. However, at 25 yr follow-up, up to 40% of patients will have required a second operation for residual stenosis or regurgitation.

Patients with symptoms and severe aortic valve stenosis should be considered for intervention. Treatment involves manipulating the valve to reduce stenosis. This can be accomplished by transvenous balloon dilation of the valve, open surgical valvotomy, or valve replacement. In absence of significant aortic regurgitation, most centers favor balloon dilation or surgical valvotomy for children and young adults who have pliable valves with fusion of commissures. In older adults, aortic valve replacement is the treatment of choice.

Endocarditis Prophylaxis

See Chapter 437.

The American Heart Association found that very few cases of endocarditis are prevented with antibiotic prophylaxis. Only patients with cardiac conditions associated with the highest risk for adverse outcomes should continue follow antibiotic prophylaxis before surgery: patients with previous endocarditis, unrepaired cyanotic CHD, including palliative shunts and conduits; completely repaired congenital heart defects with prosthetic material or device, whether placed by surgery or by catheter intervention, during the 1st 6 mo after the procedure; and repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization). Except for the conditions just listed, antibiotic prophylaxis is no longer recommended for other forms of CHD.

PREGNANCY AND CONGENITAL HEART DISEASE

CHD is the most common form of heart disease encountered during pregnancy in developed countries. Heart disease does not preclude a successful pregnancy but increases the risk to both the mother and the baby. During pregnancy there are substantial hemodynamic changes that occur. The hemodynamic changes in pregnancy result in a steady increase in cardiac output during pregnancy until the 32nd wk of gestation, at which time, the cardiac output reaches a plateau at 30-50% above the prepregnancy level. At time of delivery, with uterine contractions an additional 300-500 mL of blood enters the circulation. This in conjunction with increased blood pressure and heart rate during labor increases the cardiac output at delivery to 80% the prepregnancy level.

Despite these hemodynamic changes, the outcome of pregnancy is favorable in most women with CHD provided that functional class and systemic ventricular function are good (see Table 434-5). Pulmonary artery hypertension presents a serious risk during pregnancy, particularly when the pulmonary pressure exceeds 70% of systemic pressure, regardless of functional class. Other contraindications to pregnancy include severe obstructive left-sided lesions (coarctation of the aorta, aortic valve stenosis, mitral valve stenosis, hypertrophic cardiomyopathy), Marfan syndrome with coexisting dilated ascending aorta (defined as >4 cm), persistent cyanosis, and systemic ventricular dysfunction (ejection fraction of ≤40%). The need for full anticoagulation during pregnancy, although not a contraindication, poses an increased risk to both mother and fetus. The relative risks and benefits of the different anticoagulant approaches need to be discussed fully with the prospective mother.

Pregnancy counseling should begin early in adolescence and should be part of the routine cardiac follow-up visit. During counseling, a discussion about the risk of CHD in the offspring should take place. In the general population, the incidence of CHD is 1%. In the offspring of a mother with CHD, the risk increases to 5-6%. Often the cardiac lesion in the offspring is not the same as that in the mother, except for in the case of a syndrome with autosomal dominant inheritance (Marfan syndrome, hypertrophic cardiomyopathy). Risk stratification should include the specific CHD lesion but also needs to take in account the maternal functional class. Although the specific CHD lesion is important, multiple studies demonstrate that the maternal functional class prior to pregnancy is highly predictive of both maternal and fetal outcomes, with those having the best functional class having the best outcomes.

CONTRACEPTION

A critical part of caring for adults with CHD is to provide or make available advice on contraception. Unfortunately, there are limited data on the safety of various contraceptive techniques in adult CHD patients. The estrogen-containing oral contraceptive pill can be used in many adult CHD patients but is not recommended in adult CHD patients at risk of thromboembolism, such as those with cyanosis, prior

Table 434-6	Issues That Require Coordination of Care Between the Cardiologist and the Primary Care Physician
Antibiotic prophylaxis for endocarditis Medications and drug interactions Anticoagulation with prosthetic valves Exercise and sports participation Educational and vocational planning Contraception and pregnancy Drug, alcohol, and tobacco use Noncardiac surgical planning Anesthetic issues New symptoms or acute illnesses Coexistent medical conditions Travel	

Fontan procedure, atrial fibrillation, or pulmonary artery hypertension. In addition, this form of contraceptive therapy may upset anticoagulation control. Although slightly less effective than contraceptive pills containing combined estrogen/progesterone, medroxyprogesterone, the progesterone-only pills, and levonorgestrel are good options for most adult CHD patients. Medroxyprogesterone and levonorgestrel, however, can cause fluid retention and thus need to be used with caution in patients with heart failure. These medications are also associated with depression and often breakthrough bleeding. Tubal ligation, although the most secure method of contraception, can be a high-risk procedure in patients with complex CHD or those with pulmonary hypertension. Hysteroscopic sterilization (Essure) may be reasonable for high-risk patients. In the past, intrauterine devices were seldom used in cardiac patients because of the associated risk of bacteremia, pelvic inflammatory disease, and endocarditis. Intrauterine devices such as the Mirena, appear to be safe and effective, and are rapidly becoming one of the most commonly used form of contraception in the adult CHD population.

ADOLESCENT TRANSITION

It is well recognized that, as part of the process of obtaining independence, adolescents or young adults must develop a forward-looking, independent approach to their medical care. For children with heart disease, the transition process must begin during early adolescence and should be encouraged by both the primary care provider and the pediatric cardiologist, who must identify an appropriate adult congenital heart program to which transition and transfer will be made at an appropriate time (Table 434-6).

A successful transition program includes the following elements:

- Development of a written transition plan that should begin by the age of 14 yr
- Because adolescents and young adults are frequently unaware of the details of their cardiac diagnosis and history, a complete, concise, portable medical record, including all pertinent aspects of cardiac care, should be shared with adolescents and their families and prepared for transmittal to the eventual adult care destination.
- The primary care provider and cardiologist must address unique adolescent medical issues as they impact the cardiovascular system. In addition to medical problems, education, vocational planning, psychosocial issues, and access to medical care are all topics that should be discussed with adolescents and their families.

There is a tendency for young adults to avoid medical care because of lack of education, denial, or difficulty with access to the medical care system. Thus, a critical goal of the adolescent transition process is to identify an appropriate site for ongoing medical care and ensure maintenance of the medical record and continuity of care for the young adult. The site of care for a young adult with CHD may be a pediatric program or facility, or may be a specialized center or program for the adult with CHD. The critical issues are the continuity of care, the preparation of the patient, and the patient's participation in the process.

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Section 4

Cardiac Arrhythmias

Chapter 435

Disturbances of Rate and Rhythm of the Heart

George F. Van Hare

The term *arrhythmia* refers to a disturbance in heart rate or rhythm. Such disturbances can lead to heart rates that are abnormally fast, slow, or irregular. They may be transient or incessant, congenital or acquired, or caused by a toxin or by drugs. They may be associated with particular forms of congenital heart disease, may be a complication of surgical repair of congenital heart disease, may be a result of certain genetic causes, or may be a result of fetal inflammation such as in maternal connective tissue disease. Arrhythmias, either slow or fast, may lead to acutely decreased cardiac output, degeneration into a more dangerous arrhythmia such as ventricular fibrillation, or if incessant may lead to cardiomyopathy. Arrhythmias may lead to syncope or to sudden death. When a patient has an arrhythmia, it is important to determine whether the particular rhythm is likely to lead to severe symptoms or to deteriorate into a life-threatening condition. Rhythm abnormalities, such as single premature atrial and ventricular beats, are common and in children without heart disease, in most instances do not pose a risk to the patient.

A number of pharmacologic agents are available for treating arrhythmias; many have not been studied extensively in children. Insufficient data are available regarding pharmacokinetics, pharmacodynamics, and efficacy in the pediatric population, and therefore the selection of an appropriate agent is necessarily empirical. Fortunately, the majority of rhythm disturbances in children can be reliably controlled with a single agent (Table 435-1). Increasingly, transcatheter ablation is acceptable therapy not only for life-threatening or drug-resistant arrhythmias, but also for the cure of arrhythmias. For patients with bradycardia, implantable pacemakers are small enough for use in all ages, and even in premature infants. Implantable cardioverter-defibrillators (ICDs) are available for use in high-risk patients with malignant ventricular arrhythmias and an increased risk of sudden death.

435.1 Principles of Antiarrhythmic Therapy

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When considering drug therapy in the pediatric population, it is important to recognize that there may be marked differences in pharmacokinetics by age and in comparison with adults. Infants may have slower absorption, slow gastric emptying, and differing sizes of drug tissue compartments affecting the volume of distribution. Hepatic metabolism and renal excretion may vary within the pediatric age group as well as in comparison to adults. When considering antiarrhythmic therapy, it is important to recognize that the likely arrhythmia mechanism may be different for the pediatric vs. adult population.

There are many antiarrhythmic agents available for rhythm control. The majority have not been approved by the FDA for use in children; their use is therefore considered "off-label." Pediatric cardiologists have experience with these drugs, and there are well-recognized standards regarding dosing.

With the availability of potentially curative ablation procedures, medical therapy has become less important. Clinicians and patients accept fewer drug side effects. Intolerable side effects, as well as the potential for a proarrhythmia induced by an antiarrhythmic drug, can seriously limit medical therapy and will lead the physician and family toward a potentially curative ablation procedure.

Antiarrhythmic drugs are commonly categorized using the Vaughan Williams classification system. This system comprises 4 classes: Class I includes agents that primarily block the sodium channel, class II includes the β-blockers, class III includes those agents that prolong repolarization, and class IV are the calcium channel blockers. Class I is further divided by the strength of the sodium channel blockade (see Table 435-1).

Table 435-1 Antiarrhythmic Drugs Commonly Used in Pediatric Patients, by Class

DRUG	INDICATIONS	DOSING	SIDE EFFECTS	DRUG INTERACTIONS	DRUG LEVEL
CLASS IA: INHIBITS NA$^+$ FAST CHANNEL, PROLONGS REPOLARIZATION					
Quinidine	SVT, atrial fibrillation, atrial flutter, VT. In atrial flutter, an AV node blocking drug (digoxin, verapamil, propranolol) must be given first to prevent 1:1 conduction	Oral: 30-60 mg/kg/24 hr divided q6h (sulfate) or q8h (gluconate) In adults, 10 mg/kg/day divided q6h Max dose: 2.4g/24 hr	Nausea, vomiting, diarrhea, fever, cinchonism, QRS and QT prolongation, AV nodal block, asystole syncope, thrombocytopenia, hemolytic anemia, SLE, blurred vision, convulsions, allergic reactions, exacerbation of periodic paralysis	Enhances digoxin, may increase PTT when given with warfarin	2-6 µg/mL
Procainamide	SVT, atrial fibrillation, atrial flutter, VT	Oral: 15-50 mg/kg/24 hr divided q4h Max dose: 4 g/24 hr IV: 10-15 mg/kg over 30-45 min load followed by 20-80 µg/kg/min Max dose: 2 g/24 hr	PR, QRS, QT interval prolongation, anorexia, nausea, vomiting, rash, fever, agranulocytosis, thrombocytopenia, Coombs-positive hemolytic anemia, SLE, hypotension, exacerbation of periodic paralysis, proarrhythmia	Toxicity increased by amiodarone and cimetidine	4-8 µg/mL With NAPA <40 µg/mL
Disopyramide	SVT, atrial fibrillation, atrial flutter	Oral: <2 yr: 20-30 mg/kg/24 hr divided q6h or q12h (long-acting form); 2-10 yr: 9-24 mg/kg/24 hr divide q6h or q12h (long-acting form); 11 yr: 5-13 mg/kg/24 hr divided q6h or q12h (long-acting) Max dose: 1.2 g/24 hr	Anticholinergic effects, urinary retention, blurred vision, dry mouth, QT and QRS prolongation, hepatic toxicity, negative inotropic effects, agranulocytosis, psychosis, hypoglycemia, proarrhythmia		2-5 µg/ml
CLASS IB: INHIBITS NA$^+$ FAST CHANNEL, SHORTENS REPOLARIZATION					
Lidocaine	VT, VF	IV: 1 mg/kg repeat q 5 min 2 times followed by 20-50 µg/kg/min (max dose: 3 mg/kg)	CNS effects, confusion, convulsions, high grade AV block, asystole, coma, paresthesias, respiratory failure	Propranolol, cimetidine, increases toxicity	1-5 µg/mL
Mexiletine	VT	Oral: 6-15 mg/kg/24 hr divided q8h	GI upset, skin rash, neurologic	Cimetidine	0.8-2 µg/mL
Phenytoin	Digitalis intoxication	Oral: 3-6 mg/kg/24 hr divided q12h Max dose: 600 mg IV: 10-15 mg/kg over 1 hr load	Rash, gingival hyperplasia, ataxia, lethargy, vertigo, tremor, macrocytic anemia, bradycardia with rapid push	Amiodarone, oral anticoagulants, cimetidine, nifedipine, disopyramide, increase toxicity	10-20 µg/mL
CLASS IC: INHIBITS NA$^+$ CHANNEL					
Flecainide	SVT, atrial tachycardia, VT	Oral: 6.7-9.5 mg/kg/24 hr divided q8h In older children, 50-200 mg/m^2/day divided q12h	Blurred vision, nausea, decrease in contractility, proarrhythmia	Amiodarone increases toxicity	0.2-1 µg/mL
Propafenone	SVT, atrial tachycardia, atrial fibrillation, VT	Oral: 150-300 mg/m^2/24 hr divided q6h	Hypotension, decreased contractility, hepatic toxicity, paresthesia, headache, proarrhythmia	Increases digoxin levels	0.2-1 µg/mL

Continued

Table 435-1 Antiarrhythmic Drugs Commonly Used in Pediatric Patients, by Class—cont'd

DRUG	INDICATIONS	DOSING	SIDE EFFECTS	DRUG INTERACTIONS	DRUG LEVEL
CLASS II: β-BLOCKERS					
Propranolol	SVT, long QT	Oral: 1-4 mg/kg/24 hr divided q6h Max dose 60 mg/24 hr IV: 0.1-0.15 mg/kg over 5 min Max IV dose: 10 mg	Bradycardia, loss of concentration, school performance problems bronchospasm, hypoglycemia, hypotension, heart block, CHF	Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function	
Atenolol	SVT	Oral: 0.5-1 mg/kg/24 hr once daily or divided q12h	Bradycardia, loss of concentration, school performance problems	Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function	
Nadolol	SVT, long QT	Oral: 1-2 mg/kg/24 hr given once daily	Bradycardia, loss of concentration, school performance problems bronchospasm, hypoglycemia, hypotension, heart block, CHF	Coadministration with disopyramide, flecainide or verapamil may decrease ventricular function	
CLASS III: PROLONGS REPOLARIZATION					
Amiodarone	SVT, JET, VT	Oral: 10 mg/kg/24 hr in 1-2 divided doses for 4-14 days; reduce to 5 mg/kg/24 hr for several weeks; if no recurrence, reduce to 2.5 mg/kg/24 hr IV: 2.5-5 mg/kg over 30-60 min, may repeat 3 times, then 2-10 mg/kg/24 hr continuous infusion	Hypothyroidism or hyperthyroidism, elevated triglycerides, hepatic toxicity, pulmonary fibrosis	Digoxin (increases levels), flecainide, procainamide, quinidine, warfarin, phenytoin	0.5-2.5 mg/L
CLASS IV AND MISCELLANEOUS MEDICATIONS					
Digoxin	SVT (not WPW), atrial flutter, atrial fibrillation	Oral/load instructions: Premature: 20 µg/kg Newborn: 30 µg/kg >6 mo: 40 µg/kg Give ½ total dose followed by ¼ q8-12h × 2 doses Maintenance: 10 µg/kg/24 hr divide q12h Max dose: 0.5 mg IV: ¾ PO dose Max dose: 0.5 mg	PAC, PVC, bradycardia, AV block, nausea, vomiting, anorexia, prolongs PR interval	Quinidine Amiodarone, verapamil, increase digoxin levels	1-2 mg/mL
Verapamil	SVT (not WPW)	Oral: 2-7 mg/kg/24 hr divided q8h Max dose: 480 mg IV: 0.1-0.2 mg/kg q 20 min × 2 doses Max dose: 5-10 mg	Bradycardia, asystole, high degree AV block, PR prolongation, hypotension, CHF	Use with β-blocker or disopyramide exacerbates CHF, increases digoxin level and toxicity	
Adenosine	SVT	IV: 50-300 µg/kg by need rapid IV push Begin with 50 µg/kg and increase by 50-100 µg/kg/dose Max dose: 18 mg	Chest pain, flushing, dyspnea, bronchospasm, atrial fibrillation, bradycardia, asystole		

AV, atrioventricular; CHF, congestive heart failure; CNS, central nervous systems; GI, gastrointestinal; IV, intravenous; JET, junctional ectopic tachycardia; NAPA, *N*-acetyl procainamide; PAC, premature atrial contraction; PTT, partial thromboplastin time; PVC, premature ventricular contraction; SLE, systemic lupus erythematosus–like illness; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

435.2 Sinus Arrhythmias and Extrasystoles

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Phasic sinus arrhythmia represents a normal physiologic variation in impulse discharges from the sinus node related to respirations. The heart rate slows during expiration and accelerates during inspiration. Occasionally, if the sinus rate becomes slow enough, an escape beat arises from the atrioventricular (AV) junction region (Fig. 435-1). Normal phasic sinus arrhythmia is caused by the activity of the parasympathetic nervous system and can be quite prominent in healthy children. It may mimic frequent premature contractions, but the relationship to the phases of respiration can be appreciated with careful auscultation. Drugs that increase vagal tone, such as digoxin, may exaggerate sinus arrhythmia; it is usually abolished by exercise. Other irregularities in sinus rhythm, especially bradycardia associated with periodic apnea are commonly seen in premature infants.

Sinus bradycardia is a result of slow discharge of impulses from the sinus node, the heart's natural pacemaker. A sinus rate <90 beats/min in neonates and <60 beats/min in older children is considered to be sinus bradycardia. It is commonly seen in well-trained athletes; in healthy individuals, it is generally without significance. Sinus bradycardia may occur in systemic disease (hypothyroidism or anorexia nervosa), and it resolves when the disorder is under control. It may also be seen in association with conditions in which there is high vagal tone, such as gastrointestinal obstruction or intracranial processes. Low birthweight infants display great variation in sinus rate. Sinus bradycardia is common in these infants in conjunction with apnea, and may be associated with junctional escape beats. Premature atrial contractions are also frequent. These rhythm changes, especially bradycardia, appear more commonly during sleep and are not associated with symptoms. Usually, no therapy is necessary.

Wandering atrial pacemaker (Fig. 435-2) is defined as an intermittent shift in the pacemaker of the heart from the sinus node to another part of the atrium. It is not uncommon in childhood and usually represents a normal variant; it may also be seen in association with sinus bradycardia in which the shift in atrial focus is an escape phenomenon.

Extrasystoles are produced by the premature discharge of an ectopic focus that may be situated in the atrium, the AV junction, or the ventricle. Usually, isolated extrasystoles are of no clinical or prognostic significance. Under certain circumstances, however, premature beats may be caused by organic heart disease (inflammation, ischemia, fibrosis) or drug toxicity.

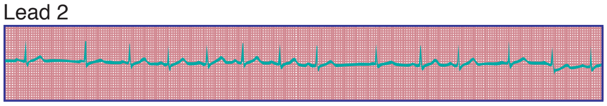

Figure 435-1 Phasic sinus arrhythmia with a junctional escape beat. Note the variation in P-P interval with no significant change in P-wave morphology or PR interval. When the sinus rate is slow enough, the atrioventricular junction takes over and produces escape beats. This rhythm is normal.

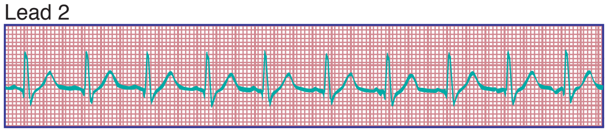

Figure 435-2 Wandering atrial pacemaker. Note the change in P-wave configuration in the 7th, 9th, and 10th beats. The 7th P wave may represent a fusion between the sinus P and the ectopic atrial pacemaker seen in the 10th beat.

Premature atrial contractions are common in childhood, usually in the absence of cardiac disease. Depending on the degree of prematurity of the beat (coupling interval) and the preceding R-R interval (cycle length), premature atrial complexes may result in a normal, a prolonged (aberrancy), or an absent (blocked premature atrial complex) QRS complex. The last occurs when the premature impulse cannot conduct to the ventricle due to refractoriness of the AV node or distal conducting system (Fig. 435-3). Atrial extrasystoles must be distinguished from premature ventricular contractions (PVCs). Careful scrutiny of the electrocardiogram for a premature P wave preceding the QRS will either show a premature P wave superimposed on, and deforming, the preceding T wave, or a P wave that is premature and has a different contour from that of the other sinus P waves. Atrial premature complexes usually reset the sinus node pacemaker, leading to an incomplete compensatory pause, but this feature is not regarded as a reliable means of differentiating atrial from ventricular premature complexes in children.

PVCs may arise in any region of the ventricles. They are characterized by premature, widened, bizarre QRS complexes that are not preceded by a premature P wave (Fig. 435-4). When all premature beats have identical contours, they are classified as uniform, suggesting origin from a common site. When PVCs vary in contour, they are designated as multiform, suggesting origin from more than one ventricular site. Ventricular extrasystoles are often, but not always, followed by a full compensatory pause. The presence of fusion beats, that is, complexes with morphologic features that are intermediate between those of normal sinus beats and those of PVCs, proves the ventricular origin of the premature beat. Extrasystoles produce a smaller stroke and pulse volume than normal and, if quite premature, may not be audible with a stethoscope or palpable at the radial pulse. When frequent, extrasystoles may assume a definite rhythm, for example, alternating with normal beats **(bigeminy)** or occurring after 2 normal beats **(trigeminy).** Most patients are unaware of single PVCs, although some may be aware of a "skipped beat" over the precordium. This sensation is caused by the increased stroke volume of the normal beat after a compensatory pause. Anxiety, a febrile illness, or ingestion of various drugs or stimulants may exacerbate PVCs.

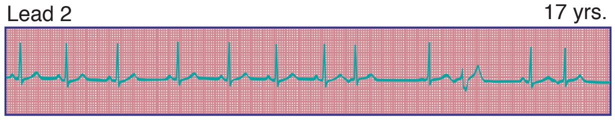

Figure 435-3 Premature atrial contraction (PAC). QRS complexes—the 8th, 10th, and final—in this strip are preceded by a P wave that is inverted, indicative of an ectopic origin of atrial depolarization. Note that the 8th and final QRS complexes resemble those of sinus origin, whereas the 10th is aberrantly conducted. This shift in origin is a function of the preceding cycle length, which influences the refractory period of the bundle branches. The fact that the pause after the PAC is longer than 2 P-P intervals implies that the premature atrial depolarization has invaded and discharged the sinus node and then reset it so that it fires later.

Figure 435-4 Premature ventricular contractions in a bigeminal rhythm, in a patient who is hyperventilating. Note that the premature beat is wide and has a completely different morphology from that of the sinus beat. The premature beat is not preceded by a discernable premature P wave or any appreciable deformation of the preceding T wave.

It is important to distinguish PVCs that are benign from those that are likely to lead to more severe arrhythmias. The former usually disappear during the tachycardia of exercise. If they persist or become more frequent during exercise, the arrhythmia may have greater significance. The following criteria are indications for further investigation of PVCs that could require **suppressive therapy:** (1) 2 or more ventricular premature beats in a row; (2) multiform PVCs; (3) increased ventricular ectopic activity with exercise; (4) R-on-T phenomenon (premature ventricular depolarization occurs on the T wave of the preceding beat); (5) extreme frequency of beats (e.g., >20% of total beats on Holter monitoring); and (6) most importantly, the presence of underlying heart disease, a history of heart surgery, or both. The best therapy for benign PVCs is reassurance that the arrhythmia is not life threatening, although very symptomatic individuals may benefit from suppressive therapy. Malignant PVCs are usually secondary to another medical problem (electrolyte imbalance, hypoxia, drug toxicity, or cardiac injury). Successful treatment includes correction of the underlying abnormality. An intravenous lidocaine bolus and drip is the first line of therapy, with more effective drugs such as amiodarone reserved for refractory cases or for patients underlying ventricular dysfunction or hemodynamic compromise.

435.3 Supraventricular Tachycardia

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Supraventricular tachycardia (SVT) is a general term that includes essentially all forms of paroxysmal or incessant tachycardia except ventricular tachycardia. The category of SVT can be divided into 3 major subcategories: reentrant tachycardias using an accessory pathway, reentrant tachycardias without an accessory pathway, and ectopic or automatic tachycardias. Atrioventricular reciprocating tachycardia (AVRT) involves an accessory pathway and is the most common mechanism of SVT in infants. Atrioventricular node reentry tachycardia (AVNRT) is rare in infancy but there is an increasing incidence of AVNRT in childhood and into adolescence. Atrial flutter is rarely seen in children with normal hearts, whereas intraatrial reentry tachycardia also known as atrial flutter, is common in patients following cardiac surgery. Atrial and junctional ectopic tachycardias are more commonly associated with abnormal hearts (cardiomyopathy) and in the immediate postoperative period following surgery for congenital heart disease.

CLINICAL MANIFESTATIONS

Reentrant SVT is characterized by an abrupt onset and cessation; it may occur when the patient is at rest or exercising, and in infants it may be precipitated by an acute infection. Attacks may last only a few seconds or may persist for hours. The heart rate usually exceeds 180 beats/min and may occasionally be as rapid as 300 beats/min. The only complaint may be awareness of the rapid heart rate. Many children tolerate these episodes extremely well, and it is unlikely that short paroxysms are a danger to life. If the rate is exceptionally rapid or if the attack is prolonged, precordial discomfort and heart failure may occur. In children, SVT may be exacerbated by exposure to nonprescription decongestants or by bronchodilators.

In young infants, the diagnosis may be more obscure because of the inability to communicate their symptoms. The heart rate at this age is normally higher than in older children and it increases greatly with crying. Infants with SVT on occasion initially present with heart failure, because the tachycardia may go unrecognized for a long time. The heart rate during episodes is frequently in the range of 240-300 beats/min. If the attack lasts 6-24 hr or more, heart failure may be recognized, and the infant will have an ashen color, and be restless and irritable, with tachypnea, poor pulses and hepatomegaly. When tachycardia occurs in the fetus, it can cause hydrops fetalis, which is the in utero manifestation of heart failure.

In neonates, SVT is usually manifested as a narrow QRS complex (<0.08 sec). The P wave is visible on a standard electrocardiogram in only 50-60% of neonates with SVT, but it is detectable with a transesophageal lead in most patients. **Differentiation from sinus tachycardia** may be difficult, but is important, as sinus tachycardia requires treatment of the underlying problem (e.g., sepsis, hypovolemia) rather than antiarrhythmic medication. If the rate is >230 beats/min with an abnormal P-wave axis (a normal P wave is positive in leads I and aVF), sinus tachycardia is not likely. The heart rate in SVT also tends to be *relatively unvarying*, whereas in sinus tachycardia the heart rate *varies* with changes in vagal and sympathetic tone. AV reciprocating tachycardia uses a bypass tract that may either be able to conduct bidirectionally **(Wolff-Parkinson-White [WPW] syndrome)** or retrograde only **(concealed accessory pathway)**. Patients with WPW syndrome have a small, but real risk of sudden death. If the accessory pathway rapidly conducts in antegrade fashion, the patient is at risk for atrial fibrillation begetting ventricular fibrillation. Risk stratification, including 24 hr Holter monitoring and exercise study, may help differentiate patients at higher risk for sudden death from WPW. Syncope is an ominous symptom in WPW and any patient with syncope and WPW syndrome should have an electrophysiology study and likely catheter ablation.

The typical electrocardiographic features of the WPW syndrome are seen when the patient is not having tachycardia. These features include a short P-R interval and slow upstroke of the QRS (delta wave) (Fig. 435-5). Although most often present in patients with a normal heart, this syndrome may also be associated with Ebstein anomaly of the tricuspid valve, or hypertrophic cardiomyopathy. The critical anatomic structure is an accessory pathway consisting of a muscular bridge connecting atrium to ventricle on either the right or the left side of the AV ring (Fig. 435-6). During sinus rhythm, the impulse is carried over both the AV node and the accessory pathway; it produces some degree of fusion of the 2 depolarization fronts that results in an abnormal QRS. During AVRT, an impulse is carried in antegrade fashion through the AV node **(orthodromic tachycardia),** which results in a normal QRS complex, and in retrograde fashion

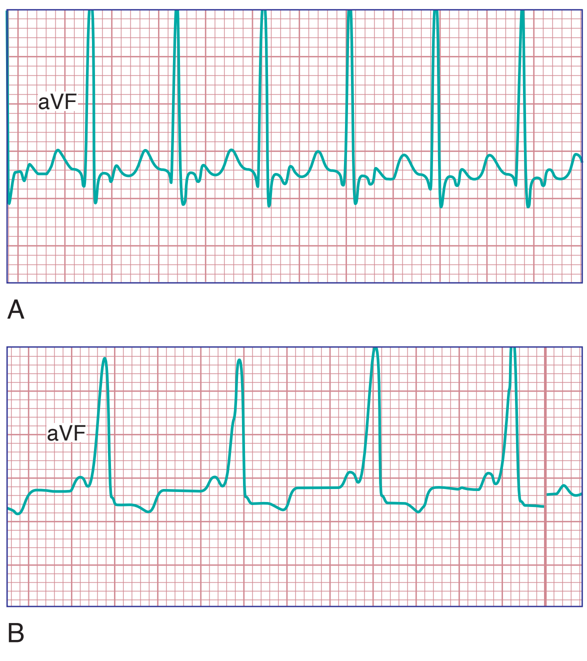

Figure 435-5 **A,** Supraventricular tachycardia in a child with Wolff-Parkinson-White (WPW) syndrome. Note the normal QRS complexes during the tachycardia, as well as clear retrograde P waves seen on the upstroke of the T waves. **B,** Later, the typical features of WPW syndrome are apparent (short P-R interval, delta wave, and wide QRS).

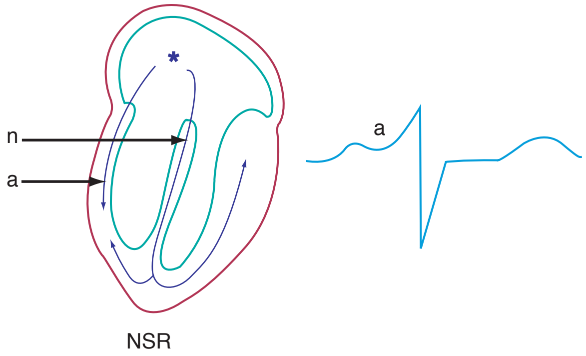

Figure 435-6 Schematic representation of the heart with a right-sided accessory pathway (Wolff-Parkinson-White syndrome). The *asterisk* indicates initiation of the sinus beat. The *arrows* indicate the direction and spread of excitation. The electrocardiographic complex shown represents a fusion beat that combines activation over the normal *(n)* and accessory *(a)* pathways. The latter inscribes the delta wave. NSR, normal sinus rhythm.

through the accessory pathway to the atrium, thereby perpetuating the tachycardia. In these cases, only after cessation of the tachycardia is the typical ECG features of WPW syndrome recognized (see Fig. 435-5). When rapid antegrade conduction occurs through the accessory pathway during tachycardia and the retrograde re-entry pathway to the atrium is via the AV node **(antidromic tachycardia),** the QRS complexes are wide and the potential for more serious arrhythmias (ventricular fibrillation) is greater, especially if atrial fibrillation occurs.

AVNRT involves the use of 2 pathways within the AV node, so-called *slow* and *fast* AV node pathways. This arrhythmia is more commonly seen in adolescence. It is one of the few forms of SVT that is occasionally associated with syncope. This arrhythmia is often seen in association with exercise.

TREATMENT

Vagal stimulation by placing of the face in ice water (in older children) or by placing an ice bag over the face (in infants) may abort the attack. To terminate the attack, older children may be taught vagal maneuvers such as the Valsalva maneuver, straining, breath holding, or standing on their head. Ocular pressure must never be performed, and carotid sinus massage is very rarely effective. When these measures fail, several pharmacologic alternatives are available (see Table 435-1). In stable patients, adenosine by rapid intravenous push is the **treatment of choice** because of its rapid onset of action and minimal effects on cardiac contractility. The dose may need to be increased if no effect on the tachycardia is seen. Because of the potential for adenosine to initiate atrial fibrillation, it should never be administered without a means for direct current (DC) cardioversion near at hand. Calcium channel blockers such as verapamil have also been used in the initial treatment of SVT in older children. Verapamil may reduce cardiac output and produce hypotension and cardiac arrest in infants younger than 1 yr; it is, therefore, contraindicated in this age group. In urgent situations when symptoms of severe heart failure have already occurred, synchronized DC cardioversion (0.5-2 J/kg) is recommended as the initial management (see Chapter 67).

Once the patient has been converted to sinus rhythm, a longer-acting agent may is selected for maintenance therapy. In patients without an antegrade accessory pathway (non-WPW), the β-blockers are the mainstay of drug therapy. Digoxin is also popular and may be effective in infants, but less so in older children. In children with WPW, digoxin or calcium channel blockers may increase the rate of antegrade conduction of impulses through the bypass tract, with the possibility of ventricular fibrillation, and are therefore contraindicated. These patients are usually managed with β-blockers. In patients with resistant tachycardias, flecainide, propafenone, sotalol, and amiodarone have all been used. Most antiarrhythmic agents have the potential of causing new dangerous arrhythmias (**proarrhythmia**) and decreasing heart function. Flecainide and propafenone in particular should be limited to use in patients with otherwise normal hearts.

If cardiac failure occurs because of prolonged tachycardia in an infant with a normal heart, cardiac function usually returns to normal after sinus rhythm is reinstituted, although it may take days to weeks. Infants with SVT diagnosed within the 1st 3-4 mo of life have a lower incidence of recurrence than do those in whom it is initially diagnosed at a later age. These patients have an 80% chance of resolution by the 1st yr of life, although approximately 30% will have recurrences later in childhood; if medical therapy is required, it can be tapered within a year and the patient watched for signs of recurrence. Parents should be taught to measure the heart rate in their infants, so that prolonged unapparent episodes of SVT may be detected before heart failure occurs.

Twenty-four hour electrocardiographic (Holter) recordings are useful in monitoring the course of therapy and in detecting brief runs of asymptomatic tachycardia, particularly in younger children and infants. Some centers use **transesophageal pacing** to evaluate the effects of therapy in infants. More detailed electrophysiologic studies performed in the cardiac catheterization laboratory are often indicated in patients with refractory SVTs who are candidates for **catheter ablation**. During an electrophysiologic study, multiple electrode catheters are placed transvenously in different locations in the heart. Pacing is performed to evaluate the conduction characteristics of the accessory pathway and to initiate the tachyarrhythmia, and mapping is performed to locate the accessory pathway. **Catheter ablation** of an accessory pathway is frequently used in children and teenagers, as well as in patients who require multiple agents or find drug side effects intolerable or for whom arrhythmia control is poor. Ablation may be performed either by radiofrequency ablation, which creates tissue heating, or cryoablation, in which tissue is frozen (Fig. 435-7). The overall initial success rate for catheter ablation ranges from approximately 90-98%, depending on the location of the accessory pathway. Surgical ablation of bypass tracts is only rarely done, and is proposed only in carefully selected patients.

The management of SVT caused by **AVNRT** is nearly identical to that for AVRT. Children with AVNRT are not at increased risk of sudden death, as they do not have a manifest accessory pathway. In practice, their episodes are more likely to be brought on by exercise or other forms of stress, and the heart rates can be quite fast, leading to chest pain, dizziness, and, occasionally, syncope. If chronic antiarrhythmic medication is desired, β-blockers are the drugs of choice; acutely, AVNRT responds to adenosine. Less is known about the natural history, but patients with AVNRT are seen quite commonly in adulthood, so spontaneous resolution seems unlikely. Patients are quite amenable to catheter ablation, either using radiofrequency energy or cryoablation, with high success rates and low complication rates.

Atrial ectopic tachycardia is an uncommon tachycardia in childhood. It is characterized by a variable rate (seldom >200 beats/min), identifiable P waves with an abnormal axis, and either a sustained or incessant nonsustained tachycardia. This form of atrial tachycardia has a single automatic focus. Identification of this mechanism is aided by monitoring the electrocardiogram while initiating vagal or pharmacologic therapy. Reentry tachycardias "break" suddenly, whereas automatic tachycardias gradually slow down and then gradually speed up again. Atrial ectopic tachycardias are usually more difficult to control pharmacologically than are the more common reentrant tachycardias. If pharmacologic therapy with a single agent is unsuccessful, catheter ablation is suggested and has a success rate >90%.

Chaotic or multifocal atrial tachycardia is defined as atrial tachycardia with ≥3 ectopic P waves, frequent blocked P waves, and varying P-R intervals of conducted beats. This arrhythmia occurs most often in infants younger than 1 yr, usually without cardiac disease, although some evidence suggests an association with viral myocarditis or pulmonary disease. The goal of drug treatment is slowing of

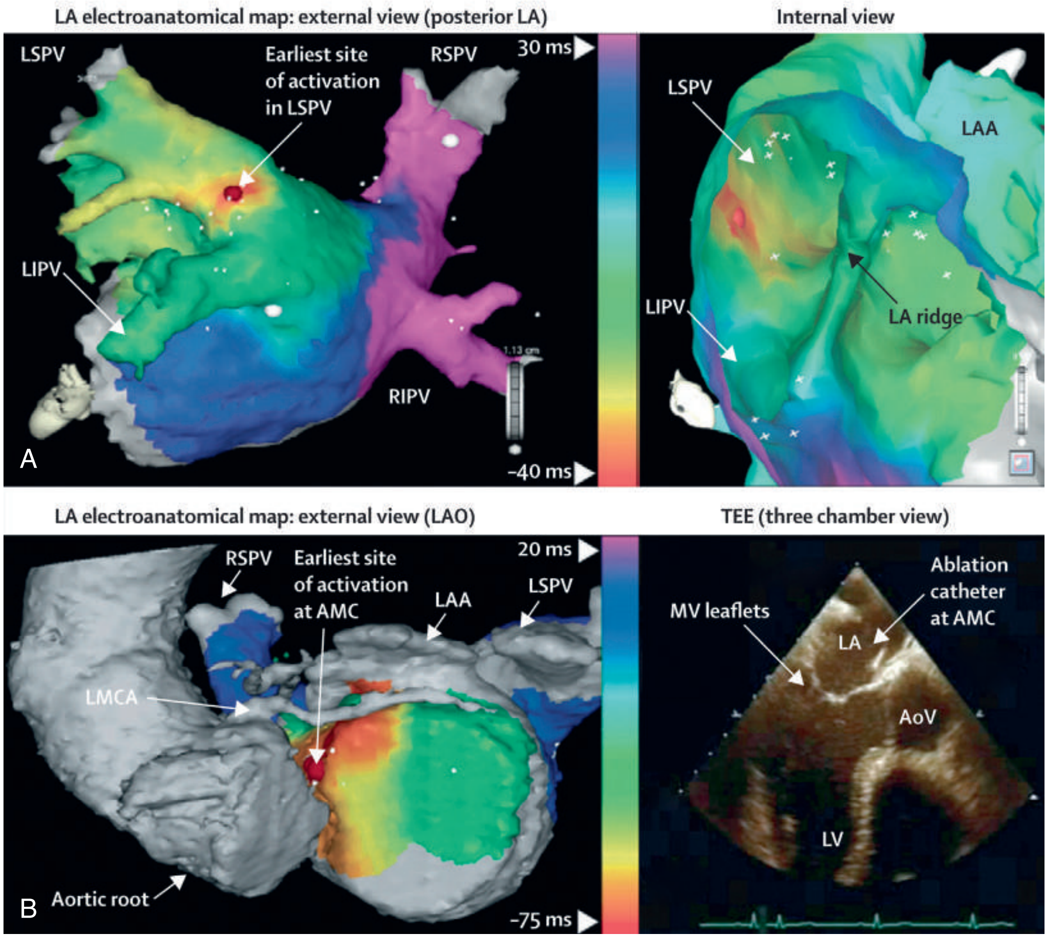

Figure 435-7 Three-dimensional electroanatomical mapping of focal atrial tachycardias. Focal site of early activation *(red)* is shown, with radial propagation away from that central site. The activation map was superimposed onto the patient's cardiac CT scan, taken the day before the procedure and imported into the mapping system. **A,** Earliest site of activation, mapped to the posterior aspect of the LSPV ostium. Posterior external view *(left side)* and endoluminal or internal view looking from within the left atrium into the mouth of the LSPV *(right side)* are shown. **B,** Earliest site mapped to the aortomitral continuity. The anatomic relation between the mitral annulus and the aortic root can be clearly appreciated *(left side)*. The location of the ablation catheter at the site of earliest atrial activation during atrial tachycardia is shown on the TEE image *(right side)*. AMC, aortomitral continuity; AoV, aortic valve; LA, left atrium; LAA, left atrial appendage; LAO, left anterior oblique; LIPV, left inferior pulmonary veins; LMCA, left main coronary artery; LSPV, left superior pulmonary vein; LV, left ventricle; MV, mitral valve; RIPV, right inferior pulmonary veins; RSPV, right superior pulmonary vein; TEE, transesophageal echocardiogram. *(From Lee G, Sanders P, Kalman JM: Catheter ablation of atrial arrhythmias: state of the art.* Lancet *380:1509–1518, 2012, Fig 3.)*

the ventricular rate, as conversion to sinus may not be possible, and multiple agents are often required. When this arrhythmia occurs in infancy, it usually terminates spontaneously by 3 yr of age.

Accelerated junctional ectopic tachycardia (JET) is an automatic (non-reentry) arrhythmia in which the junctional rate exceeds that of the sinus node and AV dissociation results. This arrhythmia is most often recognized in the early postoperative period after cardiac surgery and may be extremely difficult to control. Reduction of the infusion rate of catecholamines and control of fever are important adjuncts to management. Congenital JET may be seen in the absence of surgery. It is incessant, and can lead to dilated cardiomyopathy. Intravenous amiodarone is effective in the treatment of postoperative JET. Patients who require chronic therapy may respond to amiodarone or sotalol. Congenital JET can be cured by catheter ablation, but long-term AV block requiring a pacemaker is a prominent complication.

Atrial flutter, also known as *intraatrial reentrant tachycardia,* is an atrial tachycardia characterized by atrial activity at a rate of 250-300 beats/min in children and adolescents, and 400-600 beats/min in neonates. The mechanism of common atrial flutter consists of a reentrant or rhythm originating in the right atrium circling the tricuspid valve annulus. Because the AV node cannot transmit such rapid impulses, some degree of **AV block** is virtually always present, and the ventricles respond to every 2nd to 4th atrial beat (Fig. 435-8). Occasionally, the response is variable and the rhythm appears irregular.

In older children, atrial flutter usually occurs in the setting of congenital heart disease; neonates with atrial flutter frequently have normal hearts. Atrial flutter may occur during acute infectious illnesses but is most often seen in patients with large stretched atria, such as those associated with long-standing mitral or tricuspid insufficiency, tricuspid atresia, Ebstein anomaly, or rheumatic mitral stenosis. Atrial flutter can also occur after palliative or corrective intra-atrial surgery. Uncontrolled atrial flutter may precipitate heart failure. Vagal maneuvers or adenosine may produce a temporary slowing of the heart rate as a result of increased AV block, allowing a diagnosis to be made. The **diagnosis** is confirmed by electrocardiography, which demonstrates the rapid and regular atrial sawtoothed flutter waves. Atrial flutter usually converts immediately to sinus rhythm by **synchronized DC cardioversion,** which is most often the **treatment of choice.** Patients with chronic atrial flutter in the setting of congenital heart disease may be at increased risk for **thromboembolism** and stroke and should thus undergo anticoagulation before elective cardioversion. β-blockers or calcium channel blockers may be used to slow the ventricular response

in atrial flutter by prolonging the AV node refractory period. Other agents may be used to maintain sinus rhythm, and choices include Class I agents such as procainamide or propafenone, Class III agents such as amiodarone and sotalol. Catheter ablation has been used in patients with normal hearts and those with congenital heart disease with moderate success. Following cardioversion, neonates with normal hearts may be followed or may be treated with digoxin or propranolol for 6-12 mo, after which the medication can usually be discontinued, as neonatal atrial flutter generally does not recur.

Atrial fibrillation is uncommon in children and is rare in infants. The atrial excitation is chaotic and more rapid (400-700 beats/min) and produces an irregularly irregular ventricular response and pulse (Fig. 435-9). This rhythm disorder is often associated with atrial enlargement or disease. Atrial fibrillation may be seen in older children with rheumatic mitral valve stenosis. It is also seen rarely as a complication of atrial surgery, in patients with left atrial enlargement secondary to left AV valve insufficiency, and in patients with WPW syndrome. Thyrotoxicosis, pulmonary embolism, pericarditis, or cardiomyopathy may be suspected in a previously normal older child or adolescent with atrial fibrillation. Very rarely, atrial fibrillation may be familial. The best initial treatment is **rate control,** most effectively with calcium channel blockers, to limit the ventricular rate during atrial fibrillation. Digoxin is not given if WPW syndrome is present. Normal sinus rhythm may be restored with intravenous procainamide, ibutilide or amiodarone, or by DC cardioversion, and DC cardioversion is the first choice in hemodynamically unstable patients. Patients with chronic atrial fibrillation are at risk for the development of thromboembolism and stroke and should undergo anticoagulation with warfarin. Patients being treated by elective cardioversion should also undergo anticoagulation.

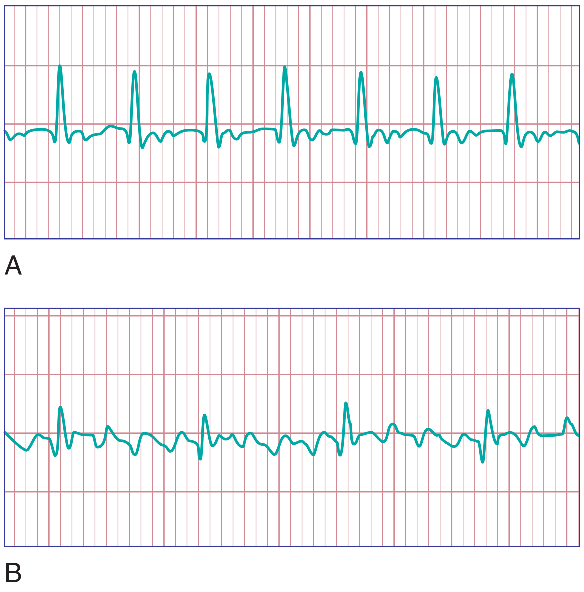

Figure 435-8 Neonatal atrial flutter. Note that the flutter waves are not obvious in the first tracing **(A)** but once a dose of adenosine is given, flutter waves at a rate of about 450 beats/min emerge **(B).**

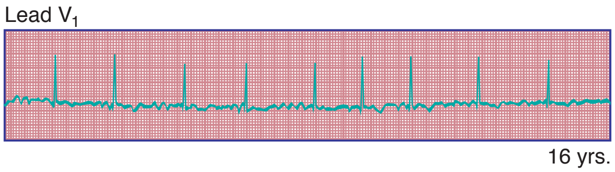

Figure 435-9 **Atrial fibrillation, characterized by the absence of clear P waves and an irregularly irregular ventricular response.** One can appreciate the irregular, rapid undulations (F waves). Fibrillatory waves may not be visible in all leads and should be carefully sought in every tracing with irregular R-R intervals. Note that no 2 R-R intervals are the same.

435.4 Ventricular Tachyarrhythmias

George F. Van Hare

Ventricular tachycardia (VT) is less common than SVT in pediatric patients. VT is defined as at least 3 PVCs at >120 beats/min (Fig. 435-10). It may be paroxysmal or incessant. VT may be associated with myocarditis, anomalous origin of a coronary artery, arrhythmogenic right ventricular dysplasia, mitral valve prolapse, primary cardiac tumors, and dilated or hypertrophic cardiomyopathy. It is seen with prolonged QT interval of either congenital or acquired (proarrhythmic drugs) causation, WPW syndrome, and drug use (cocaine, amphetamines). It may develop years after intraventricular surgery (especially tetralogy of Fallot and related defects) or occur without obvious organic heart disease. VT must be distinguished from SVT with aberrancy or rapid conduction over an accessory pathway (Table 435-2). The presence of clear capture and fusion beats confirms the diagnosis of VT. Although some children tolerate rapid ventricular rates for many hours, this arrhythmia should be promptly treated because hypotension and degeneration into ventricular fibrillation may result. For patients who are hemodynamically stable, intravenous amiodarone, lidocaine, or procainamide are the initial drugs of choice. If treatment is to be successful, it is critical to search for and correct any underlying abnormalities such as electrolyte imbalance, hypoxia, or drug toxicity. Amiodarone is the **treatment of choice** during cardiac arrest (see Chapter 67). Hemodynamically unstable patients with VT should be immediately treated with DC cardioversion. Overdrive ventricular pacing, through temporary pacing wires or a permanent pacemaker, may also be effective, although it may cause the arrhythmia to deteriorate into ventricular fibrillation. In the neonatal period, VT may be associated with an anomalous left coronary artery (see Chapter 432.2) or a myocardial tumor.

Unless a clearly reversible cause is identified, electrophysiologic study is usually indicated for patients in whom VT has developed, and depending on the findings, catheter ablation and/or ICD implantation may be indicated.

A related arrhythmia, **ventricular accelerated rhythm**, is occasionally seen in infants. It is defined the same way as VT, but the rate is only slightly faster than the coexisting sinus rate (within 10%). It is generally benign and resolves spontaneously.

Ventricular fibrillation is a chaotic rhythm that results in death unless an effective ventricular beat is rapidly re-established (see Fig. 435-10). Usually, cardiopulmonary resuscitation and DC defibrillation are necessary. If defibrillation is ineffective or fibrillation recurs, amiodarone or lidocaine may be given intravenously and defibrillation repeated (see Chapter 67). After recovery from ventricular fibrillation, a search should be made for the underlying cause. **Electrophysiologic study** is indicated for patients who have survived

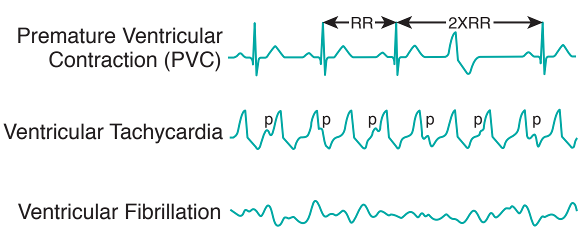

Figure 435-10 **Ventricular arrhythmias.** *(From Park MY:* Pediatric cardiology for practitioners, *ed 5, Philadelphia, 2008, Mosby/Elsevier, p. 429, Fig. 24-6.)*

Table 435-2 Diagnosis of Tachyarrhythmias: Electrocardiographic Findings

	HEART RATE (BEATS/MIN)	P WAVE	QRS DURATION	REGULARITY
Sinus tachycardia	<230	Always present, normal axis	Normal	Rate varies with respiration
Atrial tachycardia	180-320	Present Abnormal P wave morphology and axis	Normal or prolonged (with aberration)	Usually regular but ventricular response may be variable because of Wenckebach conduction
Atrial fibrillation	120-180	Fibrillatory waves	Normal or prolonged (with aberration)	Irregularly irregular (no 2 R-R intervals alike)
Atrial flutter	Atrial: 250-400 Ventricular response variable: 100-320	Sawtoothed flutter waves	Normal or prolonged (with aberration)	Regular ventricular response (e.g., 2:1, 3:1, 3:2, and so on)
Junctional tachycardia	120-280	Atrioventricular dissociation with no fusion, and normal QRS capture beats	Normal or prolonged (with aberration)	Regular (except with capture beats)
Ventricular tachycardia	120-300	Atrioventricular dissociation with capture beats and fusion beats	Prolonged for age	Regular (except with capture beats)

Table 435-3 Inherited Channel Mutations in Long and Short QT Syndromes

	CHROMOSOME	GENE	PROTEIN	ION CURRENT AFFECTED	TRIGGER	SPECIAL FEATURES/ OCCURRENCE
LQTS TYPE						
1	11p15.5	*KCNQ1*	KvLQT1 (Kv7.1)	I_{Ks}	Exercise (swimming), emotion	42-54%
2	7q35-36	*KCNH2*	HERG, (Kv11.1)	I_{Kr}	Rest, emotion, exercise (acoustic, postpartum), surprise (sudden loud noise)	35-45%
3	3p24-21	*SCN5A*	Nav1.5	I_{Na}	Rest, sleep, emotion	1.7-8%; high lethality
4	4q24-27	*ANK2*	Ankyrin-B	$I_{Na\text{-}K}$, $I_{Na\text{-}Ca}$, I_{Na}	Exercise	<1%
5	21q22	*KCNE1*	MinK	I_{Ks}	Exercise, emotion	<1%
6	21q22	*KCNE2*	MiRP1	I_{Kr}	Rest, exercise	<1%
7	17q23	*KCNJ2*	Kir2.1	I_{K1}	Rest, exercise	Periodic paralysis, dysmorphic feature
8	12p13.3	*CACNA1C*	Cav1.2	I_{Ca}	Exercise, emotion	Rare, syndactyly
9	3p25.3	*CAV3*	Caveolin-3	I_{Na}	Nonexertional, sleep	Rare
10	11q23.3	*SCN4B*	NaVβ4	I_{Na}	Exercise, postpartum	<0.1%
11	7q21-22	*AKAP9*	Yotiao	I_{Ks}	Poorly characterized	<1%
12	2q11.2	*SNTA1*	Syntrophin α1	I_{Na}	Poorly characterized	<1%
13	11q24	*KCNJ5*	Kir3.4	K_{Ir}	Poorly characterized	<1%
SHORT QT SYNDROME TYPE						
1	7q35-36	*KCNH2*	HERG (Kv11.1)	I_{Kr}	Exercise, rest (acoustic)	—
2	11p15.5	*KCNQ1*	KvLQT1 (Kv7.1)	I_{Ks}	—	—
3	17q23	*KCNJ2*	Kir2.1	I_{K1}	Sleep	—
4	12p13.3	*CACNA1C*	Cav1.2	I_{Ca}	—	—
5	10p12.33	*CACNB2b*	CaV β2b	I_{Ca}	—	—
JERVELL AND LANGE-NIELSEN SYNDROME TYPE						
1	11p15.5	*KCNQ1*	KvLQT1 (Kv7.1)	I_{Ks}	Exercise (swimming), emotion	1-7%; deafness
2	21q22	*KCNE1*	MinK	I_{Ks}	Exercise (swimming), emotion	<1%; deafness

From Morita H, Wu J, Zipes DP: The QT syndromes: long and short, Lancet 372:750–762, 2008, p. 751, Table 1.

ventricular fibrillation unless a clearly reversible cause is identified. If WPW syndrome is noted, catheter ablation should be performed. For patients in whom no correctable abnormality can be found, an ICD is nearly always indicated, because of the high risk of sudden death.

435.5 Long QT Syndromes

George F. Van Hare

Long QT syndromes (LQTS) are genetic abnormalities of ventricular repolarization, with an estimated incidence of about 1 per 10,000 births (Table 435-3). They present as a long QT interval on the surface electrocardiogram and are associated with malignant ventricular arrhythmias (torsades de pointes and ventricular fibrillation). They are a cause of syncope and sudden death and may be the cause of some cases of sudden infant death syndrome, drowning, and intrauterine fetal demise. In perhaps 80% of cases, there is an identifiable genetic mutation. The old distinction between dominant and recessive forms of the disease (Romano-Ward syndrome vs. Jervell-Lange-Nielsen syndrome) is no longer made, as the latter recessive condition is known to be a result of the homozygous state. Jervell-Lange-Nielsen syndrome is associated with congenital sensorineural deafness. Asymptomatic but at-risk patients carrying the gene mutation may not all have a

Table 435-4 Acquired Causes of QT Prolongation*

DRUGS
Antibiotics—erythromycin, clarithromycin, azithromycin, telithromycin, trimethoprim/sulfamethoxazole, fluoroquinolones†
Antifungal agents†—fluconazole, itraconazole, ketoconazole
Antiprotozoal agents—pentamidine isethionate
Antihistamines—astemizole, terfenadine (Seldane; Seldane has been removed from the market for this reason)
Antidepressants—tricyclics such as imipramine (Tofranil), amitriptyline (Elavil), desipramine (Norpramin), and doxepin (Sinequan)
Antipsychotics—haloperidol, risperidone, phenothiazines such as thioridazine (Mellaril) and chlorpromazine (Thorazine), selective serotonin uptake inhibitors
Antiarrhythmic agents
Class 1A (sodium channel blockers)—quinidine, procainamide, disopyramide
Class III (prolong depolarization)—amiodarone (rare), bretylium, dofetilide, *N*-acetyl-procainamide, sotalol
Lipid-lowering agents—probucol
Antianginals—bepridil
Diuretics (through K^+ loss)—furosemide (Lasix), ethacrynic acid (bumetanide [Bumex])
Opiates—methadone, oxycodone
Oral hypoglycemic agents—glibenclamide, glyburide
Organophosphate insecticides
Motility agents—cisapride, domperidone
Vasodilators—prenylamine
Other drugs—Ondansetron, HIV protease inhibitors, Chinese herbs
ELECTROLYTE DISTURBANCES
Hypokalemia—diuretics, hyperventilation
Hypocalcemia
Hypomagnesemia
UNDERLYING MEDICAL CONDITIONS
Bradycardia—complete atrioventricular block, severe bradycardia, sick sinus syndrome
Myocardial dysfunction—anthracycline cardiotoxicity, congestive heart failure, myocarditis, cardiac tumors
Endocrinopathy—hyperparathyroidism, hypothyroidism, pheochromocytoma
Neurologic—encephalitis, head trauma, stroke, subarachnoid hemorrhage
Nutritional—alcoholism, anorexia nervosa, starvation

*A more exhaustive updated list of medications that can prolong the QTc interval is available at the University of Arizona Center for Education and Research of Therapeutics website (www.azcert.org).
†Combinations of quinolones plus azoles increase the risk of prolonged QT intervals.
From Park MY: Pediatric cardiology for practitioners, *ed 5, Philadelphia, 2008, Mosby/Elsevier, p. 433, Box 24-1.*

prolonged QT duration. QT interval prolongation may become apparent with exercise or during catecholamine infusions.

Genetic studies have identified mutations in cardiac potassium and sodium channels (see Table 435-3). Additional forms (up to 13 variants) of LQTS have been described, but these are much more uncommon. Genotype may predict clinical manifestations; for example, **LQT1 events are usually stress induced,** whereas events in **LQT3 often occur during sleep.** LQT2 events have an intermediate pattern. LQT3 has the highest probability for sudden death, followed by LQT2 and then LQT1. Drugs may prolong the QT interval directly but more often do so when drugs such as erythromycin or ketoconazole inhibit their metabolism (Table 435-4).

The **clinical manifestation** of LQTS in children is most often a syncopal episode brought on by exercise, fright, or a sudden startle; some events occur during sleep (LQT3). Patients can initially be seen with seizures, presyncope, or palpitations; approximately 10% are initially in cardiac arrest. The diagnosis is based on electrocardiographic and clinical criteria. Not all patients with long QT intervals have LQTS, and patients with normal QT intervals on a resting electrocardiogram may have LQTS. A heart rate–corrected QT interval of >0.47 sec is highly indicative, whereas a QT interval of >0.44 sec is suggestive. Other features include notched T waves in 3 leads, T-wave alternans, a low heart rate for age, a history of syncope (especially with stress), and a familial history of either LQTS or unexplained sudden death. Twenty-four hour Holter monitoring and exercise testing are adjuncts to the diagnosis. Genotyping is available and can identify the mutation is approximately 80% of patients known to have LQTS by clinical criteria. Genotyping is not useful in ruling out the diagnosis in individuals suspected of having the disease, but when positive is very useful in identifying asymptomatic affected relatives of the index case.

Short QT syndromes (see Table 435-3) manifest with atrial or ventricular fibrillation and are associated with syncope and sudden death. They are often caused by a gain-of-function mutation in cardiac potassium channels.

Treatment of LQTS includes the use of **β-blocking agents** at doses that blunt the heart rate response to exercise. Propranolol and nadolol may be more effective than atenolol and metoprolol. Some patients require a **pacemaker** because of drug-induced bradycardia. In patients with continued syncope despite treatment, an implantable cardiac defibrillator is indicated for those who do not respond to β-blocking drugs and those who have experienced cardiac arrest. Genotype-phenotype correlative studies have suggested that β-blocking agents are not effective in patients with LQT3, and in those individuals, an ICD is usually indicated.

435.6 Sinus Node Dysfunction

George F. Van Hare

Sinus arrest and **sinoatrial block** may cause a sudden pause in the heartbeat. The former is presumably caused by failure of impulse formation within the sinus node and the latter by a block between the sinus pacemaker complex and the surrounding atrium. These arrhythmias are rare in childhood except in patients who have had extensive atrial surgery.

Sick sinus syndrome is the result of abnormalities in the sinus node or atrial conduction pathways, or both. This syndrome may occur in the absence of congenital heart disease and has been reported in siblings, but it is most commonly seen after surgical correction of congenital heart defects, especially the Fontan procedure and the atrial switch (Mustard or Senning) operation for transposition of the great

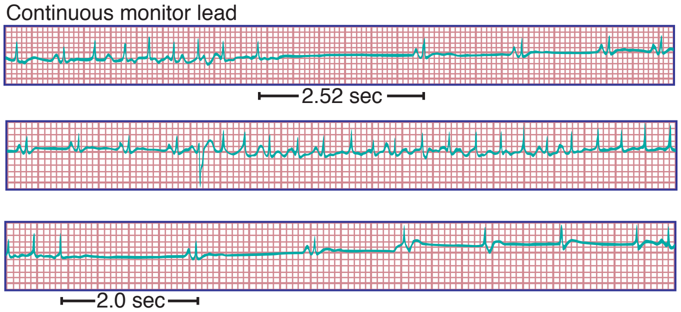

Figure 435-11 The "tachy-brady" syndrome with sinus node dysfunction. Note the bursts of supraventricular tachycardia, probably multifocal atrial in origin, followed by long periods of sinus arrest and by sinus bradycardia. Often, symptoms are caused by the long sinus pauses following termination of tachycardia, rather than by the tachycardia itself.

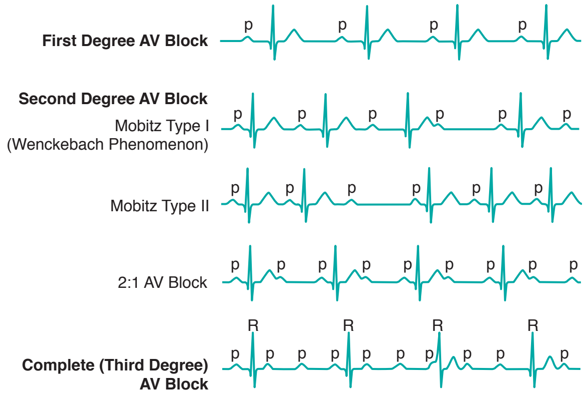

Figure 435-12 Atrioventricular block. *(From Park MY:* Pediatric cardiology for practitioners, *ed 5, Philadelphia, 2008, Mosby/Elsevier, p. 446, Fig. 25-1.)*

arteries. Clinical manifestations depend on the heart rate. Most patients remain asymptomatic without treatment, but dizziness and syncope can occur during periods of marked sinus slowing with failure of junctional escape (Fig. 435-11). Pacemaker therapy is indicated in patients who experience symptoms such as exercise intolerance or syncope.

Patients with sinus node dysfunction may also have episodes of SVT **("tachy-brady syndrome")** with symptoms of palpitations, exercise intolerance, or dizziness. Treatment must be individualized. Drug therapy to control tachyarrhythmias (propranolol, sotalol, amiodarone) may suppress sinus and AV node function to such a degree that further symptomatic bradycardia may be produced. Therefore, insertion of a pacemaker in conjunction with drug therapy is usually necessary for such patients, even in the absence of symptoms ascribable to low heart rate.

435.7 AV Block

George F. Van Hare

AV block may be divided into 3 forms. In **1st-degree AV block,** the PR interval is prolonged, but all the atrial impulses are conducted to the ventricle (Fig. 435-12). In **2nd-degree AV block,** not every atrial impulse is conducted to the ventricle. In the variant of 2nd-degree block known as the **Wenckebach type** (also called **Mobitz type I**), the PR interval increases progressively until a P wave is not conducted. In the cycle following the dropped beat, the PR interval normalizes (see Fig. 435-12). In **Mobitz type II,** there is no progressive conduction delay or subsequent shortening of the PR interval after a blocked beat. This conduction defect is less common but has more potential to cause syncope and may be progressive. A related condition is **high-grade 2nd-degree AV block**, in which 2 or more P waves in a row fail to conduct. This is even more dangerous. In **3rd-degree AV block (complete heart block),** no impulses from the atria reach the ventricles (see Fig. 435-12). An independent escape rhythm is usually present, but may not be reliable, leading to symptoms such as syncope.

Congenital complete AV block in children is presumed to be caused by autoimmune injury of the fetal conduction system by maternally derived immunoglobulin G antibodies (anti-SSA/Ro, anti-SSB/La) in a mother with overt or, more often, asymptomatic systemic lupus erythematosus or Sjögren syndrome. Autoimmune disease accounts for 60-70% of all cases of congenital complete heart block and ≈80% of cases in which the heart is structurally normal (Fig. 435-13). A mutation of the homeobox gene Nkx2-5 is described in which congenital AV block is seen most commonly in association with atrial septal defects. Complete AV block is also seen in patients with complex congenital heart disease and abnormal embryonic development of the

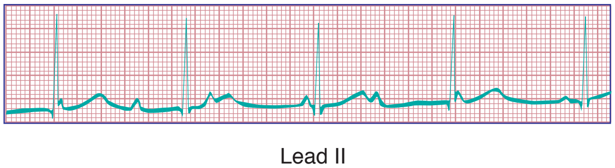

Figure 435-13 Congenital complete atrioventricular (AV) block. The ventricular rate is regular at 53 beats/min. The atrial rate is somewhat variable, from 65-95 beats/min, and completely dissociated from the ventricle. The QRS morphology is normal, which is common in congenital complete AV block.

conduction system. It has been associated with myocardial tumors and myocarditis. It is a known complication of myocardial abscess secondary to endocarditis. It is also seen in genetic abnormalities including LQTS and Kearn-Sayre syndrome. It is also a complication of congenital heart disease repair and, in particular, repairs involving ventricular septal defect closure.

The incidence of congenital complete heart block is 1 per 20,000-25,000 live births; a high fetal loss rate may cause an underestimation of its true incidence. In some infants of mothers with systemic lupus erythematosus, complete heart block is not present at birth but develops within the 1st 3-6 mo after birth. The arrhythmia is often diagnosed in the fetus (secondary to the dissociation between atrial and ventricular contractions seen on fetal echocardiography) and may produce hydrops fetalis. Maternal treatment with steroids to halt progression or reverse AV block is controversial. Infants with associated congenital heart disease and heart failure have a high mortality rate.

In older children with otherwise normal hearts, the condition is often asymptomatic, although syncope and sudden death may occur. Infants and toddlers may have night terrors, tiredness with frequent naps, and irritability. The peripheral pulse is prominent as a result of the compensatory large ventricular stroke volume and peripheral vasodilation; systolic blood pressure is elevated. Jugular venous pulsations occur irregularly and may be large when the atrium contracts against a closed tricuspid valve (cannon wave). Exercise and atropine may produce an acceleration of ≥10-20 beats/min. Systolic murmurs are frequently audible along the left sternal border, and apical mid-diastolic murmurs are not unusual. The 1st heart sound is variable, as a result of variable ventricular filing with AV dissociation. AV block results in enlargement of the heart on the basis of increased diastolic ventricular filling.

The **diagnosis** is confirmed by electrocardiography; the P waves and QRS complexes have no constant relationship (see Fig. 435-13). The

QRS duration may be prolonged, or it may be normal if the heartbeat is initiated high in the AV node or bundle of His.

The **prognosis** for congenital complete heart block is usually favorable; patients who have been observed to the age of 30-40 yr have lived normal, active lives. Some patients have episodes of exercise intolerance, dizziness, and syncope (Stokes-Adams attacks); this symptom requires the implantation of a permanent cardiac pacemaker. Pacemaker implantation should be considered for patients who develop symptoms such as progressive cardiac enlargement, prolonged pauses, or daytime average heart rates of ≤50 beats/min. In addition, prophylactic pacemaker implantation in adolescents is reasonable considering the low risk of the implant procedure and the difficulty in predicting who will develop sudden severe symptoms.

Cardiac pacing is recommended in neonates with low ventricular rates (≤50 beats/min), evidence of heart failure, wide complex rhythms, or congenital heart disease. Isoproterenol, atropine, or epinephrine may be used to try to increase the heart rate temporarily until pacemaker placement can be arranged. Transthoracic epicardial pacemaker implants have traditionally been used in infants; transvenous placement of pacemaker leads is available for young children. Postsurgical complete AV block can occur after any open heart procedure requiring suturing near the AV valves or crest of the ventricular septum. Postoperative heart block is initially managed with temporary pacing wires. The likelihood of a return to sinus rhythm after 10-14 days is low; a permanent pacemaker is recommended after that time.

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Chapter 436
Sudden Death

George F. Van Hare

Sudden death other than sudden infant death syndrome (see Chapter 375) is rare in children younger than 18 yr. Sudden death can be divided into either traumatic or nontraumatic origin. Traumatic causes of sudden death are the most common in children; these include motor vehicle crashes, violent deaths, recreational deaths, and occupational deaths. Nontraumatic sudden deaths are often the result of specific cardiac causes. The incidence of sudden death varies from 0.8-6.2 per 100,000 per year in children and adolescents as opposed to the higher incidence of sudden cardiac death in adults of 1 per 1,000. Approximately 65% of sudden deaths are a result of heart-related problems in patients with either normal or congenitally (corrected, palliated, or unoperated) abnormal hearts. Competitive high-school sports (basketball, football) are high-risk environmental factors. The most common cause of death in competitive athletes is hypertrophic cardiomyopathy, with or without obstruction to left ventricular outflow. Table 436-1 lists other potential causes. These can be classified as structural abnormalities, including aortic stenosis and coronary artery abnormalities; myocardial disease, such as myocarditis; conduction system disease, including long QT syndrome; and miscellaneous causes, including pulmonary hypertension and commotio cordis. Symptoms may be absent before the event but, if present, include syncope, chest pain, dyspnea, and palpitations. Patients may have a family history of heart disease (dilated or hypertrophic cardiomyopathy, long QT interval, arrhythmogenic right ventricular dysplasia, Brugada or Marfan syndromes) or sudden death. Death often follows exertion or exercise.

MECHANISM OF SUDDEN DEATH

There are 3 mechanisms of sudden death: arrhythmic, nonarrhythmic cardiac (circulatory and vascular causes), and noncardiac. Ventricular fibrillation, while the most common final cause of sudden death in adults, is only the final cause in 10-20% of children with sudden cardiac death. More commonly, bradycardia leads either to ventricular fibrillation or asystole (see Chapter 435).

CONGENITAL HEART DISEASE

Valvar aortic stenosis is the congenital defect most commonly associated with sudden death in children. Historically, approximately 5% of children with this disease die, although this has become quite rare in the modern era. A history of syncope, chest pain, and evidence of severe obstruction and left ventricular hypertrophy are risk factors (see Chapter 434.5).

Coronary artery anomalies are also commonly associated with sudden death in children and adolescents. The most common abnormality associated with sudden death is the origin of the left main coronary artery from the right sinus of Valsalva. The coronary artery therefore courses between the aorta and pulmonary artery, and may also be intramural in course. Exercise results in a rise in pulmonary and aortic pressure, and this is thought to compress the left main coronary artery and results in ischemia due to compression or kinking. Anomalous origin of the right coronary artery from the left sinus of Valsalva is much more common, but only rarely is a cause of sudden death.

CARDIOMYOPATHY

All 3 major types of cardiomyopathy (hypertrophic, dilated, and restrictive) are associated with sudden death in the pediatric population; sudden death may be the initial manifestation of the cardiomyopathy (see Chapter 439).

Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden death in the athletic adolescent. The annual risk of sudden death in young patients with HCM is 2% per year. Risk factors for sudden death include a family history of sudden death, symptoms, ventricular arrhythmias, and presentation at an early age. Many patients with HCM have obstruction to the left ventricular outflow tract. The mechanism of sudden death is arrhythmic and may be secondary to development of dynamic obstruction with exercise and resultant loss of cardiac output, or may be related to cardiac ischemia. Thus, patients without left ventricular outflow tract obstruction are also at risk of sudden death. The **dilated cardiomyopathies** are also associated with sudden cardiac death in children, although the risk is clearly lower than in adults.

Arrhythmogenic right ventricular dysplasia is a specific form of cardiomyopathy associated with exercise-induced ventricular arrhythmias and sudden death. The diagnosis can be difficult; MRI, electrophysiology study, or endomyocardial biopsy is used with limited reliability. Pathology includes transmural fatty replacement of right ventricular myocardium, with patchy areas of fibrosis.

Myocarditis has been found commonly on pathology of patients with sudden death of unknown etiology. Symptoms prior to sudden death may be absent, or may include overt heart failure or subtle findings such as a high heart rate. Pediatric patients may have complete heart block or ventricular arrhythmias with this disease.

CARDIAC ARRHYTHMIA

A primary conduction system abnormality may result in sudden death. Causes include Wolff-Parkinson-White (WPW) syndrome, long QT syndrome, and Brugada syndrome. Besides causing supraventricular tachycardia, WPW syndrome can result in atrial fibrillation with rapid conduction across the accessory pathway leading to ventricular fibrillation and sudden death (Fig. 436-1). This is unusual in pediatric patients but has an increasing incidence in adolescence. In adults, there is an incidence of sudden death in asymptomatic patients of 1 per 1,000 patient-years, but this rate may well be higher in children, who by definition have not survived to adulthood. As digoxin and verapamil can augment conduction down accessory pathways, these drugs are contraindicated in WPW syndrome.

Long QT syndrome (see Chapter 435), a group of channelopathies that affect ventricular repolarization, is also associated with sudden

Table 436-1 Potential Causes of Sudden Death in Infants, Children, and Adolescents

Potential Causes
SIDS AND SIDS "MIMICS"
SIDS
Long QT syndromes*
Inborn errors of metabolism
Child abuse
Myocarditis
Ductal-dependent congenital heart disease
CORRECTED OR UNOPERATED CONGENITAL HEART DISEASE
Aortic stenosis
Tetralogy of Fallot
Transposition of great vessels (postoperative atrial switch)
Mitral valve prolapse
Hypoplastic left-heart syndrome
Eisenmenger syndrome
CORONARY ARTERIAL DISEASE
Anomalous origin*
Anomalous tract (tunneled)
Kawasaki disease
Periarteritis
Arterial dissection
Marfan syndrome (rupture of aorta)
Myocardial infarction
MYOCARDIAL DISEASE
Myocarditis
Hypertrophic cardiomyopathy*
Dilated cardiomyopathy
Arrhythmogenic right ventricular dysplasia
Lyme carditis
CONDUCTION SYSTEM ABNORMALITY/ARRHYTHMIA
Long QT syndromes*
Brugada syndrome
Proarrhythmic drugs
Preexcitation syndromes
Heart block
Commotio cordis
Idiopathic ventricular fibrillation
Arrhythmogenic right ventricular dysplasia
Catecholaminergic polymorphic ventricular tachycardia
Heart tumor
MISCELLANEOUS
Pulmonary hypertension
Pulmonary embolism
Heat stroke
Cocaine and other stimulant drugs or medications
Anorexia nervosa
Electrolyte disturbances

SIDS, sudden infant death syndrome.
*Common.

death (Fig. 436-2). The mechanism of sudden death is polymorphic ventricular tachycardia (torsades de pointes) (Fig. 436-3). An initial presentation of sudden cardiac death is found in 9% of patients. Thus, treatment of asymptomatic patients with a long QT interval on electrocardiogram (ECG) and positive family history is advised.

Acquired long QT intervals may be seen in patients with marked electrolyte abnormalities, central nervous system injury, or starvation (including bulimia and anorexia nervosa). Medications can also result in prolongation of the QT interval (see Table 435-4 in Chapter 435). These patients are also at risk of malignant ventricular arrhythmias, and correction of the underlying problem may be necessary to reduce the risk of sudden death.

Brugada syndrome, an autosomal dominant disorder, caused in approximately 30% of patients to a mutation in the *SCN5A* gene, is associated with sudden cardiac death, often associated with fever, drugs, nighttime electrolyte disorders, or after a large meal (see Fig. 436-4). Typical ECG findings include coved ST segment elevations in leads V_1-V_3; death results from either ventricular fibrillation or tachycardia.

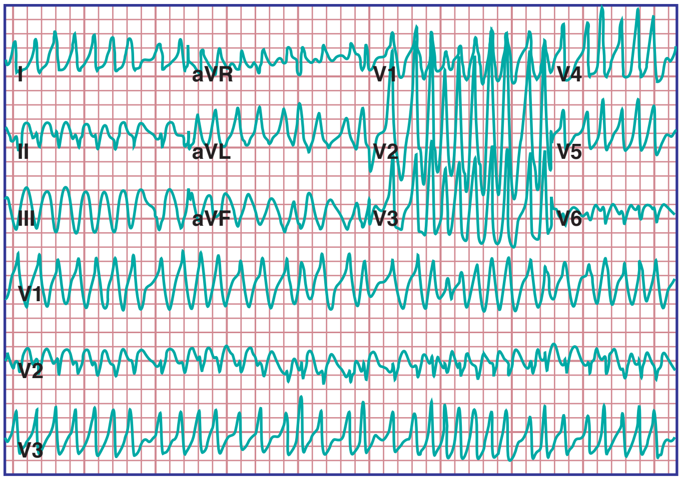

Figure 436-1 **Atrial fibrillation in a patient with Wolff-Parkinson-White syndrome and rapid conduction to the ventricle.** Note the wide QRS complexes, a result of full preexcitation, and the irregularly irregular ventricular response, caused by the atrial fibrillation.

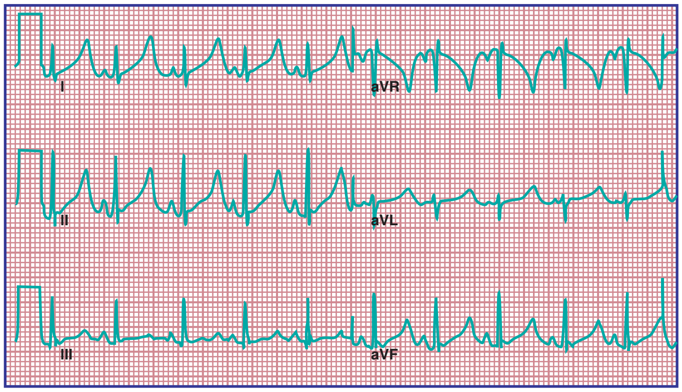

Figure 436-2 **Long QT syndrome in a neonate.** QTc is markedly prolonged. T waves are also peaked and abnormal in appearance.

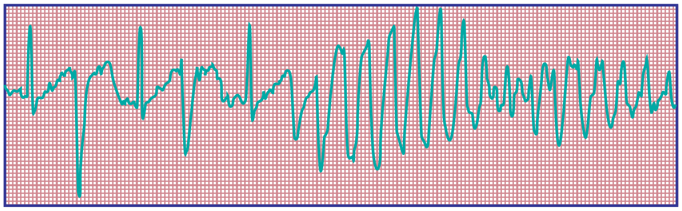

Figure 436-3 **Episode of torsades de pointes in a patient with long QT syndrome.**

MISCELLANEOUS CAUSES

Commotio cordis is a nearly universally fatal condition that follows blunt nonpenetrating trauma to the chest (e.g., from a baseball or hockey puck). Occasionally, innocent-appearing chest blows incurred at home or at a playground may be fatal. Patients experience immediate ventricular fibrillation in the absence of identifiable cardiac trauma (contusion, hematoma, lacerated coronary artery). Historically death results from ventricular fibrillation that is unresponsive to resuscitative efforts in 85-90% of children. Immediate direct current defibrillation may be

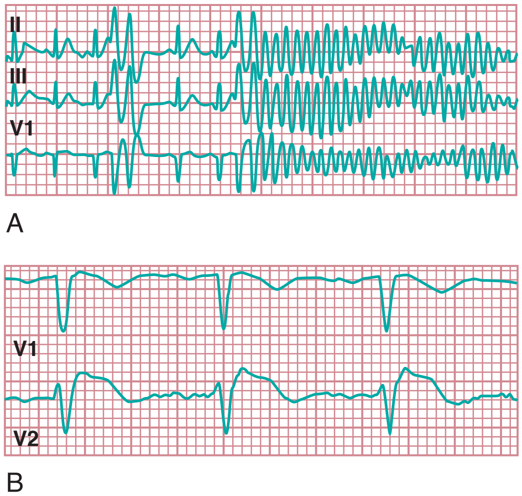

Figure 436-4 Brugada syndrome. **A,** Frequent ventricular ectopy and sustained polymorphic ventricular tachycardia. **B,** Persistent coved type ST segment elevation in lead V_1 and V_2 characteristic for Brugada type I. *From Talib S, van de Poll SE: Brugada syndrome diagnosed after Ramadan.* Lancet *382:100, 2013.*

effective, if available, particularly if employed immediately; however, it is reported to be successful in only approximately 25% of cases.

EVALUATION AND THERAPY FOR RESUSCITATED PATIENTS

It is important to focus therapy on potentially reversible causes of sudden death. These include correction of major hemodynamic defects, pacing therapy for a patient with bradycardia, or supportive therapy for myocarditis. Unfortunately, reversible causes are not always found in young cardiac arrest survivors. Added to this dilemma is the fact that there is a limited ability to predict antiarrhythmic drug response or risk of recurrence. Thus, the implantable cardioverter defibrillator is the **therapy of choice** for survivors of arrhythmic sudden death.

MEDICATION FOR ATTENTION-DEFICIT DISORDER

There has been some concern about the possibility that stimulant medications prescribed for the treatment of children with attention-deficit disorder could potentially increase the risk of sudden death. The concern arises from a limited number of reports to the U.S. Food and Drug Administration of sudden death of unknown etiology in individuals taking stimulant medications, most of whom are adults. In a few cases, left ventricular hypertrophy caused by hypertension, coarctation of the aorta, or HCM has been identified at postmortem examination. There are no prospective studies to support the notion that these medications increase the risk, and little or no evidence that electrocardiographic screening will reliably identify a subgroup at risk. Some suggest ECG screening of children prior to starting these medications, but there is no consensus that such an approach is effective.

PREVENTION OF SUDDEN DEATH

The probability of survival to hospital discharge for a young patient who experiences an out-of-hospital cardiac arrest is <20%. The presence of immediate automatic external defibrillators, when combined with standard cardiopulmonary resuscitation at the site of exercise (gym, track, basketball, or football arena), may improve survival substantially. Thus, identifying patients at risk is extremely important.

Many of the more common causes of sudden death in children and adolescents can be identified from the patient's history (prodromal symptoms), the family history, and physical examination. The American Academy of Pediatrics makes available a downloadable "Preparticipation Physical Evaluation" form that is useful for this purpose (http://www.aap.org). Of paramount importance is the careful evaluation of any child who experiences syncope in association with exercise, as this may be the last opportunity to diagnose a life-threatening condition in such a patient.

Patient avoidance of high-risk behavior (cocaine use, anorexia nervosa) and knowledge of drug side effects or drug interactions and contraindications is critical. Chest-protecting equipment has not been shown to prevent commotio cordis. Prompt bystander cardiopulmonary resuscitation and rapid defibrillation by an automatic external defibrillator has the best chance of leading to survival. Family survivors of victims of sudden death should be evaluated for genetic causes such as long QT syndrome and HCM.

The use of a preparticipation ECG for the detection of those athletes at risk for sudden death is controversial. Because many athletes either have no pre-event symptoms or are unwilling to admit to symptoms for fear of not being able to play, some have proposed that the ECG may identify a small but at-risk group with HCM or the prolonged QT, Brugada, or WPW syndromes. Preparticipation ECG testing is mandatory in several European countries but not in the United States. If the ECG is positive, echocardiography is performed. Cost-effectiveness studies suggest that the cost for implementation of a national program in the United States would be prohibitive because of the low incidence of sudden death in the pediatric population, the high rate of false-positive ECGs, and the difficulty in definitively excluding cardiac disease in patients with borderline ECG findings. Although studies of regional or national screening programs have suggested some benefit (e.g., the Veneto region of Italy) others have failed to demonstrate any effect of screening on the background incidence of sudden death in young individuals.

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Section 5

Acquired Heart Disease

Chapter 437

Infective Endocarditis

Daniel Bernstein

Infective endocarditis includes acute and subacute bacterial endocarditis, as well as nonbacterial endocarditis caused by viruses, fungi, and other microbiologic agents. It is a significant cause of morbidity and mortality in children and adolescents despite advances in the management and prophylaxis of the disease with antimicrobial agents. The inability to eradicate infective endocarditis by prevention or early treatment stems from several factors. The disease represents a complex interplay between a pathogen and host factors such as endothelial disruption and immune function that is still not completely understood; the nature of the infecting organism has changed over time; diagnosis may be difficult during early stages and is thus often delayed until a more serious infection has set in; and special risk groups have emerged, including intravenous drug users; survivors of cardiac surgery, especially those with mechanical prosthesis; patients taking immunosuppressant medications; and patients who require chronic intravascular catheters. Some patients get endocarditis on what was thought to be a previously healthy native valve, although on surgical inspection is found to have mild structural abnormalities.

ETIOLOGY

Viridans-type streptococci (α-hemolytic streptococci) and *Staphylococcus aureus* remain the leading causative agents for endocarditis in pediatric patients. Other organisms cause endocarditis less frequently and, in ≈6% of cases, blood cultures are negative for any organisms (Table 437-1). No relationship exists between the infecting organism and the type of congenital defect, the duration of illness, or the age of the child. Staphylococcal endocarditis is more common in patients with no underlying heart disease; viridans group streptococcal infection is more common after dental procedures; group D enterococci are seen more often after lower bowel or genitourinary manipulation; *Pseudomonas aeruginosa* or *Serratia marcescens* is seen more frequently in intravenous drug users; and fungal organisms are encountered after open heart surgery. Coagulase-negative staphylococci are common in the presence of an indwelling central venous catheter.

EPIDEMIOLOGY

Infective endocarditis is often a complication of congenital or rheumatic heart disease but can also occur in children without any abnormal valves or cardiac malformations. In developed countries, congenital heart disease is the overwhelming predisposing factor. Endocarditis is rare in infancy; in this age group, it usually follows open heart surgery or is associated with a central venous line.

Patients with congenital heart lesions where there is turbulent blood flow because of a hole or stenotic orifice, especially if there is a high-pressure gradient across the defect, are most susceptible to endocarditis. This turbulent flow traumatizes the vascular endothelium, creating a substrate for deposition of fibrin and platelets, leading to the formation of a nonbacterial thrombotic embolus (NBTE) that is thought to be the initiating lesion for infective endocarditis. Biofilms form on the surface of implanted mechanical devices such as valves, catheters, or pacemaker wires that also serve as the adhesive substrate for infection. The development of transient bacteremia then colonizes this NBTE or biofilm, leading to proliferation of bacteria within the lesion. Bacterial surface proteins, such as the FimA antigen in viridans streptococci, act as adhesion factors to the NBTE or biofilm, after which bacteria can rapidly proliferate within the vegetation. Given the heavy colonization of mucosal surfaces (the oropharynx, or gastrointestinal, vaginal, or urinary tracts) by potentially pathogenic bacteria, these surfaces are thought to be the origin of this transient bacteremia. There is controversy over the extent to which daily activities (such as brushing or flossing the teeth) versus invasive procedures (such as dental cleanings or surgery) contribute to this bacteremia. Transient bacteremia is reported to occur in 20-68% of patients after tooth brushing and flossing, and even in 7-51% of patients after chewing food. The magnitude of this bacteremia is also similar to that resulting from dental procedures. Maintenance of good oral hygiene may be a more important factor in decreasing the frequency and magnitude of bacteremia.

Children at **highest risk** of adverse outcome after infective endocarditis include those with prosthetic cardiac valves or other prosthetic material used for cardiac valve repair, unrepaired cyanotic congenital heart disease (including those palliated with shunts and conduits), completely repaired defects with prosthetic material or device during the 1st 6 mo after repair, repaired congenital heart disease with residual defects at or adjacent to the site of a prosthetic patch or device, valve stenosis or insufficiency occurring after heart transplantation, permanent valve disease from rheumatic fever (mitral stenosis, aortic regurgitation), and previous infective endocarditis. Patients with high velocity blood flow lesions such as ventricular septal defects and aortic stenosis are also at high risk. In older patients, congenital bicuspid aortic valves and mitral valve prolapse with regurgitation pose additional risks for endocarditis. Surgical correction of congenital heart disease may reduce but does not eliminate the risk of endocarditis, with the exception of repair of a simple atrial septal defect or patent ductus arteriosus without prosthetic material.

In ≈30% of patients with infective endocarditis, a predisposing factor is presumably recognized. Although a preceding dental procedure may be identified in 10-20% of patients, the time of the procedure may range from 1 to 6 mo prior to the onset of symptoms, hence the continued controversy over the absolute risk of infective endocarditis after dental procedures. Primary bacteremia with *S. aureus* is thought to be another risk for endocarditis. The occurrence of endocarditis directly after most routine heart surgery is relatively low, but it can be an antecedent event, especially if prosthetic material is utilized.

Table 437-1	Bacterial Agents in Pediatric Infective Endocarditis
COMMON: NATIVE VALVE OR OTHER CARDIAC LESIONS	
Viridans group streptococci *(Streptococcus mutans, Streptococcus sanguinis, Streptococcus mitis)*	
Staphylococcus aureus	
Group D streptococcus (enterococcus) *(Streptococcus bovis, Streptococcus faecalis)*	
UNCOMMON: NATIVE VALVE OR OTHER CARDIAC LESIONS	
Streptococcus pneumoniae	
Haemophilus influenzae	
Coagulase-negative staphylococci	
Abiotrophia defectiva (nutritionally variant streptococcus)	
Coxiella burnetii (Q fever)*	
Neisseria gonorrhoeae	
*Brucella**	
*Chlamydia psittaci**	
*Chlamydia trachomatis**	
*Chlamydia pneumoniae**	
*Legionella**	
*Bartonella**	
*Tropheryma whipplei** (Whipple disease)	
HACEK group†	
*Streptobacillus moniliformis**	
*Pasteurella multocida**	
Campylobacter fetus	
Culture negative (6% of cases)	
PROSTHETIC VALVE	
Staphylococcus epidermidis	
Staphylococcus aureus	
Viridans group streptococcus	
Pseudomonas aeruginosa	
Serratia marcescens	
Diphtheroids	
Legionella species*	
HACEK group†	
Fungi‡	

*These fastidious bacteria plus some fungi may produce culture-negative endocarditis. Detection may require special media, incubation for more than 7 days, polymerase chain reaction on blood or valve for 16SrRNA (bacteria) or 18SrRNA (fungi), or serologic tests.

†The HACEK group includes *Haemophilus* species *(H. paraphrophilus, H. parainfluenzae, H. aphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species.

‡*Candida* species, *Aspergillus* species, *Pseudallescheria boydii, Histoplasma capsulatum.*

CLINICAL MANIFESTATIONS

Table 437-2 outlines the manifestations of infective endocarditis.

Early manifestations are usually mild, especially when viridans group streptococci are the infecting organisms. Prolonged fever without other manifestations (except, occasionally, weight loss) that persists for as long as several months may be the only symptom. Alternatively, the onset may be acute and severe, with high, intermittent fever and prostration. Usually, the onset and course vary between these 2 extremes. The symptoms are often nonspecific and consist of low-grade fever with afternoon elevations, fatigue, myalgia, arthralgia, headache, and, at times, chills, nausea, and vomiting. **New or changing heart murmurs** are common, particularly with associated heart failure. Splenomegaly and petechiae are relatively common.

Table 437-2	Manifestations of Infective Endocarditis
HISTORY	
Prior congenital or rheumatic heart disease	
Preceding dental, urinary tract, or intestinal procedure	
Intravenous drug use	
Central venous catheter	
Prosthetic heart valve	
SYMPTOMS	
Fever	
Chills	
Chest and abdominal pain	
Arthralgia, myalgia	
Dyspnea	
Malaise, weakness	
Night sweats	
Weight loss	
CNS manifestations (stroke, seizures, headache)	
SIGNS	
Elevated temperature	
Tachycardia	
Embolic phenomena (Roth spots, petechiae, splinter nail bed hemorrhages, Osler nodes, CNS or ocular lesions)	
Janeway lesions	
New or changing murmur	
Splenomegaly	
Arthritis	
Heart failure	
Arrhythmias	
Metastatic infection (arthritis, meningitis, mycotic arterial aneurysm, pericarditis, abscesses, septic pulmonary emboli)	
Clubbing	
LABORATORY	
Positive blood culture	
Elevated erythrocyte sedimentation rate; may be low with heart or renal failure	
Elevated C-reactive protein	
Anemia	
Leukocytosis	
Immune complexes	
Hypergammaglobulinemia	
Hypocomplementemia	
Cryoglobulinemia	
Rheumatoid factor	
Hematuria	
Renal failure: azotemia, high creatinine (glomerulonephritis)	
Chest radiograph: bilateral infiltrates, nodules, pleural effusions	
Echocardiographic evidence of valve vegetations, prosthetic valve dysfunction or leak, myocardial abscess, new-onset valve insufficiency	

CNS, central nervous system.

Serious neurologic complications such as embolic strokes, cerebral abscesses, mycotic aneurysms, and hemorrhage are most often associated with staphylococcal disease and may be late manifestations. Meningismus, increased intracranial pressure, altered sensorium, and focal neurologic signs are manifestations of these complications. Myocardial abscesses may occur with staphylococcal disease and may damage the cardiac conducting system, causing heart block, or may rupture into the pericardium and produce purulent pericarditis. Pulmonary and other systemic emboli are infrequent, except with fungal disease. Many of the classic skin findings develop late in the course of the disease; they are seldom seen in appropriately treated patients. Such manifestations include **Osler nodes** (tender, pea-size intradermal nodules in the pads of the fingers and toes), **Janeway lesions** (painless small erythematous or hemorrhagic lesions on the palms and soles), and **splinter hemorrhages** (linear lesions beneath the nails). These lesions may represent vasculitis produced by circulating antigen–antibody complexes.

Table 437-3 Diagnostic Approach to Uncommon Pathogens Causing Endocarditis

PATHOGEN	DIAGNOSTIC PROCEDURE
Brucella spp.	Blood cultures; serology; culture, immunohistology, and PCR of surgical material
Coxiella burnetii	Serology (IgG phase I >1 in 800); tissue culture, immunohistology, and PCR of surgical material
Bartonella spp.	Blood cultures; serology; culture, immunohistology, and PCR of surgical material
Chlamydia spp.	Serology; culture, immunohistology, and PCR of surgical material
Mycoplasma spp.	Serology; culture, immunohistology, and PCR of surgical material
Legionella spp.	Blood cultures; serology; culture, immunohistology, and PCR of surgical material
Tropheryma whipplei	Histology and PCR of surgical material

IgG, immunoglobulin G; PCR, polymerase chain reaction.
From Moreillon P, Que YA: Infective endocarditis, Lancet *363:139–148, 2004.*

Identification of infective endocarditis is most often based on a high index of suspicion during evaluation of an infection in a child with an underlying risk factor.

DIAGNOSIS

The critical information for appropriate treatment of infective endocarditis is obtained from blood cultures. All other laboratory data are secondary in importance (see Table 437-2). Blood specimens for culture should be obtained as promptly as possible, even if the child feels well and has no other physical findings. Three to 5 separate blood collections should be obtained after careful preparation of the phlebotomy site. Contamination presents a special problem inasmuch as bacteria found on the skin may themselves cause infective endocarditis. The timing of collections is not important because bacteremia can be expected to be relatively constant. In 90% of cases of endocarditis, the causative agent is recovered from the first 2 blood cultures. Bacteremia is low grade in 80% (<100 colony-forming units [CFU]/mL or blood). The laboratory should be notified that endocarditis is suspected so that, if necessary, the blood can be cultured on enriched media for longer than usual (>7 days) to detect nutritionally deficient and fastidious bacteria or fungi. Although bacteremia may occur in the absence of endocarditis, bacteremia secondary to *Streptococcus mutans*, *Streptococcus bovis I*, *Streptococcus mitior*, *Streptococcus sanguis,* and *S. aureus* (in the absence of focal musculoskeletal infection) is highly concerning for endocarditis. Antimicrobial pretreatment of the patient reduces the yield of blood cultures to 50-60%. The microbiology laboratory should be notified if the patient has received antibiotics so that more sophisticated methods can be used to recover the offending agent. Other specimens that may be cultured include scrapings from cutaneous lesions, urine, synovial fluid, abscesses, and, in the presence of manifestations of meningitis, cerebrospinal fluid. Serologic diagnosis or polymerase chain reaction of resected valve tissues is necessary in patients with unusual or fastidious microorganisms (Table 437-3; Fig. 437-1).

The index of suspicion should be high when evaluating infection in a child with an underlying contributing factor. The combination of transthoracic and transesophageal echocardiography enhances the ability to diagnose endocarditis. Two-dimensional echocardiography can identify the size, shape, location, and mobility of the lesion; when combined with Doppler studies, the presence of valve dysfunction

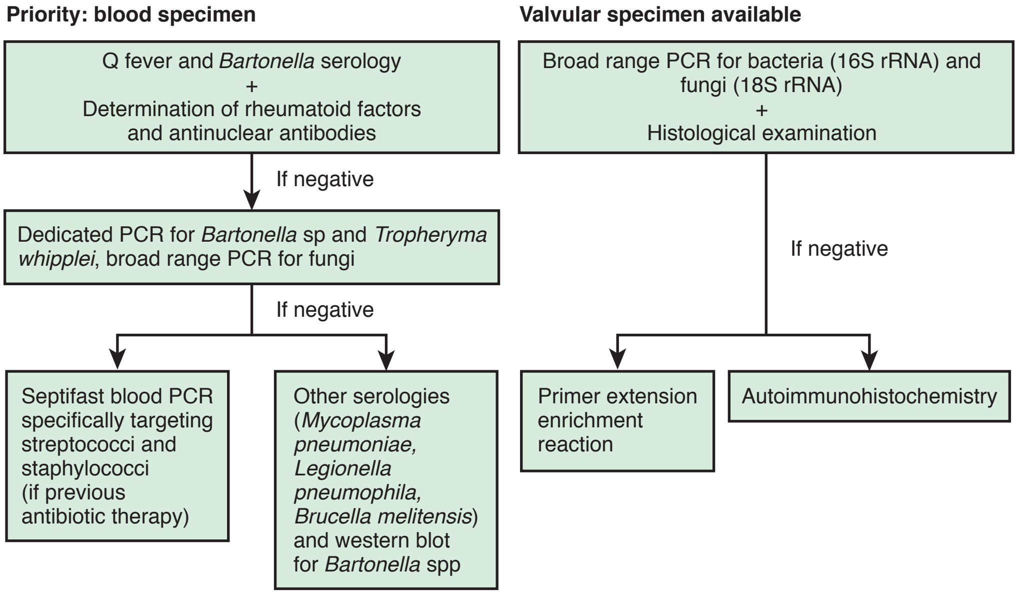

Figure 437-1 Diagnostic tests applied to clinical specimens for the identification of the causative agents of blood culture–negative endocarditis. Septifast, LightCycler SeptiFast (Roche). Serum should be considered a priority specimen, with Q fever and *Bartonella* serologic analysis being routinely done. We also suggest that detection of antinuclear antibodies and rheumatoid factor should be routinely done for diagnosis of noninfective endocarditis. *(From Thuny F, Grisoli D, Collart F, et al. Management of infective endocarditis: challenges and perspectives.* Lancet *379:965–975, 2012, Fig. 2, p. 969.)*

(regurgitation, obstruction) can be determined and its effect on left ventricular performance quantified. Echocardiography may also be helpful in predicting embolic complications, given that lesions >1 cm and fungating masses are at greatest risk for embolization. The absence of vegetations does not exclude endocarditis, and vegetations are often not visualized in the early phases of the disease or in patients with complex congenital heart lesions.

The **Duke criteria** help in the diagnosis of endocarditis. **Major criteria** include (1) positive blood cultures (2 separate cultures for a usual pathogen, 2 or more for less-typical pathogens), and (2) evidence of endocarditis on echocardiography (intracardiac mass on a valve or other site, regurgitant flow near a prosthesis, abscess, partial dehiscence of prosthetic valves, or new valve regurgitant flow). **Minor criteria** include predisposing conditions, fever, embolic-vascular signs, immune complex phenomena (glomerulonephritis, arthritis, rheumatoid factor, Osler nodes, Roth spots), a single, positive blood culture or serologic evidence of infection, and echocardiographic signs not meeting the major criteria. Two major criteria, 1 major and 3 minor, or 5 minor criteria suggest definite endocarditis. A modification of the Duke criteria may increase sensitivity while maintaining specificity. The following minor criteria are added to those already listed: the presence of newly diagnosed clubbing, splenomegaly, splinter hemorrhages, and petechiae; a high erythrocyte sedimentation rate; a high C-reactive protein level; and the presence of central nonfeeding lines, peripheral lines, and microscopic hematuria.

PROGNOSIS AND COMPLICATIONS

Despite the use of antibiotic agents, mortality remains high, in the range of 20-25%. Serious morbidity occurs in 50-60% of children with documented infective endocarditis; the most common is heart failure caused by vegetations involving the aortic or mitral valve. Myocardial abscesses and toxic myocarditis may also lead to heart failure without characteristic changes in auscultatory findings and, occasionally, to life-threatening arrhythmias. Systemic emboli, often with central nervous system manifestations, are a major threat. Pulmonary emboli may occur in children with ventricular septal defect or the tetralogy of Fallot, although massive life-threatening pulmonary embolization is rare. Other complications include mycotic aneurysms, rupture of a sinus of Valsalva, obstruction of a valve secondary to large vegetations, acquired ventricular septal defect, and heart block as a result of involvement (abscess) of the conduction system. Additional complications include meningitis, osteomyelitis, arthritis, renal abscess, purulent pericarditis, and immune complex-mediated glomerulonephritis.

TREATMENT

Antibiotic therapy should be instituted immediately once a definitive diagnosis is made. When virulent organisms are responsible, small delays may result in progressive endocardial damage and are associated with a greater likelihood of severe complications. The choice of antibiotics, method of administration, and length of treatment should be coordinated with consultants from both cardiology and infectious diseases (Tables 437-4 and 437-5). Empirical therapy before the identifiable agent is recovered may be initiated with vancomycin plus gentamicin in patients without a prosthetic valve and when there is a high risk of *S. aureus,* enterococcus, or viridans streptococci (the 3 most common organisms). High serum bactericidal levels must be maintained long enough to eradicate organisms that are growing in relatively inaccessible avascular vegetations. Between 5 and 20 times the minimal in vitro inhibiting concentration must be produced at the site of infection to destroy bacteria growing at the core of these lesions. Several weeks are required for a vegetation to organize completely; therapy must be continued through this period so that recrudescence can be avoided. A total of 4-6 wk of treatment is usually recommended. Depending on the clinical and laboratory responses, antibiotic therapy may require modification and, in some instances, more prolonged treatment is required. With highly sensitive viridans group streptococcal infections, shortened regimens that include oral penicillin for some portion have been recommended. In nonstaphylococcal disease, bacteremia usually resolves in 24-48 hr, whereas fever resolves in 5-6 days with appropriate antibiotic therapy. Resolution with staphylococcal disease takes longer.

If the infection occurs on a valve and induces or increases symptoms and signs of heart failure, appropriate therapy should be instituted, including diuretics, afterload reducing agents, and in some cases, digitalis. Surgical intervention for infective endocarditis is indicated for severe aortic, mitral or prosthetic valve involvement with intractable heart failure. Severe heart failure may be associated with acute valve regurgitation, obstruction, or fistula formation. Rarely, a

Table 437-4 Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus bovis*

REGIMEN	DOSAGE* AND ROUTE	DURATION, WK	COMMENTS
Aqueous crystalline penicillin G sodium	12-18 million U/24 hr IV either continuously or in 4 or 6 equally divided doses	4	Preferred in patients with impairment of 8th cranial nerve function or renal function
or			
Ceftriaxone sodium	2 g/24 hr IV/IM in 1 dose ***Pediatric dose***[†]: penicillin 200,000 U/kg per 24 hr IV in 4-6 equally divided doses; ceftriaxone 100 mg/kg per 24 hr IV/IM in 1 dose	4	
Aqueous crystalline penicillin G sodium	12-18 million U/24 hr IV either continuously or in 6 equally divided doses	2	2 wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired 8th cranial nerve function, or *Abiotrophia*, *Granulicatella*, or *Gemella* spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3-4 μg/mL and trough serum concentration of <1 μg/mL when 3 divided doses are used; nomogram used for single daily dosing
or			
Ceftriaxone sodium	2 g/24 hr IV/IM in 1 dose	2	
plus			
Gentamicin sulfate[‡]	3 mg/kg per 24 hr IV/IM in 1 dose, or 3 equally divided doses ***Pediatric dose:*** penicillin 200,000 U/kg per 24 hr IV in 4-6 equally divided doses; ceftriaxone 100 mg/kg per 24 hr IV/IM in 1 dose; gentamicin 3 mg/kg per 24 hr IV/IM in 1 dose or 3 equally divided doses[§]	2	
Vancomycin hydrochloride[¶]	30 mg/kg per 24 hr IV in 2 equally divided doses not to exceed 2 g/24 hr unless concentrations in serum are inappropriately low ***Pediatric dose:*** 40 mg/kg per 24 hr IV in 2-3 equally divided doses	4	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 hr after infusion completed) serum concentration of 30-45 μg/mL and a trough concentration range of 10-15 μg/mL

Minimum inhibitory concentration ≤0.12 μg/mL.
*Dosages recommended are for patients with normal renal function.
†Pediatric dose should not exceed that of a normal adult.
‡Other potentially nephrotoxic drugs (e.g., nonsteroidal antiinflammatory drugs) should be used with caution in patients receiving gentamicin therapy.
§Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of infective endocarditis exist.
¶Vancomycin dosages should be infused during course of at least 1 hr to reduce risk of histamine-release "red man" syndrome.
From Baddour LM, Wilson WR, Bayer AS, et al: Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications, Circulation *111:e394–e433, 2005; correction:* Circulation *112:2373, 2005.*

mycotic aneurysm, rupture of an aortic sinus, intraseptal abscess causing complete heart block, or dehiscence of an intracardiac patch requires an emergency operation. Other surgical indications include failure to sterilize the blood despite adequate antibiotic levels in 7-10 days in the absence of extracardiac infection, myocardial abscess, recurrent emboli, and increasing size of vegetations while receiving therapy. Vegetations (aortic, mitral, prosthetic valve) >10-15 mm are at high risk of embolism. Although antibiotic therapy should be administered for as long as possible before surgical intervention, active infection is not a contraindication if the patient is critically ill as a result of severe hemodynamic deterioration from infective endocarditis. Removal of vegetations and, in some instances, valve replacement may be lifesaving, and sustained antibiotic administration will most often prevent reinfection. Replacement of infected prosthetic valves carries a higher risk.

Fungal endocarditis is difficult to manage and has a poorer prognosis. It has been encountered after cardiac surgery, in severely debilitated or immunosuppressed patients, and in patients on prolonged courses of antibiotics. The drugs of choice are amphotericin B (liposomal or standard preparation) and 5-fluorocytosine. Surgery to excise infected tissue is occasionally attempted, though often with limited success. Recombinant tissue plasminogen activation may help lyse intracardiac vegetations and avoid surgery in some high-risk patients.

PREVENTION

Recommendations by the American Heart Association for antimicrobial prophylaxis before dental and other surgical procedures received a major revision in 2007. A substantial reduction in the number of patients who require prophylactic treatment and the procedures requiring coverage was recommended. The primary reasons for these revised recommendations were that (1) infective endocarditis is much more likely to result from exposure to the more frequent random bacteremias associated with daily activities than from a dental or surgical procedure; (2) routine prophylaxis may prevent "an exceedingly

Table 437-5 Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

REGIMEN	DOSAGE* AND ROUTE	DURATION	COMMENTS
OXACILLIN-SUSCEPTIBLE STRAINS			
Nafcillin or oxacillin†	12 g/24 hr IV in 4-6 equally divided doses	6 wk	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk
with			
Optional addition of gentamicin sulfate‡	3 mg/kg per 24 hr IV/IM in 2 or 3 equally divided doses	3-5 day	
	Pediatric dose§: Nafcillin or oxacillin 200 mg/kg per 24 hr IV in 4-6 equally divided doses; gentamicin 3 mg/kg per 24 hr IV/IM in 3 equally divided doses		Clinical benefit of aminoglycosides has not been established
For penicillin-allergic (nonanaphylactoid-type) patients:			Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin
Cefazolin	6 g/24 hr IV in 3 equally divided doses	6 wk	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases§
with			
Optional addition of gentamicin sulfate	3 mg/kg per 24 hr IV/IM in 2 or 3 equally divided doses ***Pediatric dose:*** cefazolin 100 mg/kg per 24 hr IV in 3 equally divided doses; gentamicin 3 mg/kg per 24 hr IV/IM in 3 equally divided doses	3-5 day	Clinical benefit of aminoglycosides has not been established
OXACILLIN-RESISTANT STRAINS			
Vancomycin¶	30 mg/kg per 24 hr IV in 2 equally divided doses ***Pediatric dose:*** 40 mg/kg per 24 hr IV in 2 or 3 equally divided doses	6 wk	Adjust vancomycin dosage to achieve 1 hr serum concentration of 30-45 μg/mL and trough concentration of 10-15 μg/mL

IE, infective endocarditis.

*Dosages recommended are for patients with normal renal function.

†Penicillin G 24 million U/24 hr IV in 4-6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration ≤0.1 μg/mL) and does not produce β-lactamase.

‡Gentamicin should be administered in close temporal proximity to vancomycin, nafcillin, or oxacillin dosing.

§Pediatric dose should not exceed that of a normal adult.

¶For specific dosing adjustment and issues concerning vancomycin, see Table 437-4 footnotes.

From Baddour LM, Wilson WR, Bayer AS, et al: Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications, Circulation *111:e394–e433, 2005; corrections* Circulation *112:2373, 2005.*

small" number of cases; and (3) the risk of antibiotic-related adverse events exceeds the benefits of prophylactic therapy. Improving general dental hygiene was felt to be a more important factor in reducing the risk of infective endocarditis resulting from routine daily bacteremias. The current recommendations limit the use of prophylaxis to those patients with cardiac conditions associated with the greatest risk of an adverse outcome from infective endocarditis (Table 437-6). Patients with permanently damaged valves from rheumatic heart disease should also be considered for prophylaxis. Prophylaxis for these patients is recommended for "all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa." Furthermore, "placement of removable prosthodontic or endodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa" are not indications for prophylaxis. Given that many invasive respiratory tract procedures do cause bacteremia, prophylaxis for many of these procedures is considered reasonable. In contrast to prior recommendations, prophylaxis for gastrointestinal or genitourinary procedures is no longer recommended in the majority of cases. Prophylaxis for patients undergoing cardiac surgery with placement of prosthetic material is still recommended. Given the highly individual nature of these recommendations and the continued concern amongst some cardiologists over their adoption, direct consultation with the child's cardiologist is still the best method for determining a specific patient's ongoing need for prophylaxis (Table 437-7).

Continuing education regarding both oral hygiene and, in appropriate cases, the need for prophylaxis is important, especially in teenagers

Table 437-6 2007 Statement of the American Heart Association (AHA): Cardiac Conditions Associated with the Highest Risk of an Adverse Outcome from Infective Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis

CONGENITAL HEART DISEASE (CHD)*
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired CHD with prosthetic material or device, whether placed by surgery or catheter intervention, during the 1st 6 mo after the procedure†
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch, or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

*Except for the conditions listed here, antibiotic prophylaxis is no longer recommended by the AHA for any other form of CHD.

†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 mo after the procedure.

From Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis. Guidelines from the American Heart Association, Circulation *116:1736–1754, 2007.*

Table 437-7 2007 Statement of the American Heart Association (AHA): Prophylactic Antibiotic Regimens for a Dental Procedure

SITUATION	AGENT	ADULTS	CHILDREN
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin *or* cefazolin or ceftriaxone	2 g IM or IV 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin*† *or* Clindamycin *or* Azithromycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone† *or* clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

IM, intramuscular; IV, intravenous.
*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, urticaria with penicillins or ampicillin.
From Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis. Guidelines from the American Heart Association, Circulation *116:1736–1754, 2007.*

and young adults. Vigorous treatment of sepsis and local infections and careful asepsis during heart surgery and catheterization reduce the incidence of infective endocarditis.

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Chapter 438
Rheumatic Heart Disease
Daniel Bernstein

Rheumatic involvement of the valves is the most important sequelae of acute rheumatic fever (see Chapter 183.1). The valvular lesions begin as small verrucae composed of fibrin and blood cells along the borders of one or more of the heart valves. The mitral valve is affected most often, followed in frequency by the aortic valve; right-sided heart manifestations are rare. As the inflammation subsides, the verrucae tend to disappear and leave scar tissue. With repeated attacks of rheumatic fever, new verrucae form near the previous ones, and the mural endocardium and chordae tendineae become involved.

A single episode of acute rheumatic fever usually results in complete healing of valvular lesions while repeated episodes, especially on previously affected valves result in rheumatic heart disease. Diagnosing acute rheumatic fever requires the fulfillment of the Jones criteria (see Chapter 183.1), while the diagnosis of rheumatic heart disease is based on cardiac auscultation signs of mitral or aortic valve involvement, which may not detect early valve injury. Screening large populations at risk for rheumatic heart disease with echocardiography has demonstrated a substantially greater number of patients with rheumatic heart disease than those detected by auscultation (Fig. 438-1). If this is confirmed, it has important public health significance in that many more patients will need to receive prophylaxis to prevent further episodes of acute rheumatic fever and worsening of valve injury.

PATTERNS OF VALVULAR DISEASE
Mitral Insufficiency
Pathophysiology
Mitral insufficiency is the result of structural changes that usually include some loss of valvular substance and shortening and thickening of the chordae tendineae. During acute rheumatic fever with severe cardiac involvement, heart failure is caused by a combination of mitral insufficiency coupled with inflammatory disease of the pericardium, myocardium, endocardium, and epicardium. Because of the high volume load and inflammatory process, the left ventricle becomes enlarged. The left atrium dilates as blood regurgitates into this chamber. Increased left atrial pressure results in pulmonary congestion and symptoms of left-sided heart failure. Spontaneous improvement usually occurs with time, even in patients in whom mitral insufficiency is severe at the onset. The resultant chronic lesion is most often mild or moderate in severity, and the patient is asymptomatic. More than half of patients with acute mitral insufficiency no longer have the mitral murmur 1 yr later. In patients with severe chronic mitral insufficiency, pulmonary arterial pressure becomes elevated, the right ventricle and atrium become enlarged, and right-sided heart failure subsequently develops.

Clinical Manifestations
The physical signs of mitral insufficiency depend on its severity. With mild disease, signs of heart failure are not present, the precordium is quiet, and auscultation reveals a high-pitched holosystolic murmur at the apex that radiates to the axilla. With severe mitral insufficiency, signs of chronic heart failure may be noted. The heart is enlarged, with a heaving apical left ventricular impulse and often an apical systolic thrill. The 2nd heart sound may be accentuated if pulmonary hypertension is present. A 3rd heart sound is generally prominent. A holosystolic murmur is heard at the apex with radiation to the axilla. A short mid-diastolic rumbling murmur is caused by increased blood flow across the mitral valve as a result of the insufficiency. Auscultation of a diastolic murmur does not necessarily mean that mitral stenosis is present. The latter lesion takes many years to develop and is characterized by a diastolic murmur of greater length, usually with presystolic accentuation.

The electrocardiogram and chest x-rays are normal if the lesion is mild. With more severe insufficiency, the electrocardiogram shows prominent bifid P waves, signs of left ventricular hypertrophy, and associated right ventricular hypertrophy if pulmonary hypertension is present. Roentgenographically, prominence of the left atrium and ventricle can be seen. Congestion of perihilar vessels, a sign of pulmonary venous hypertension, may also be evident. Calcification of the mitral valve is rare in children. Echocardiography shows enlargement of the

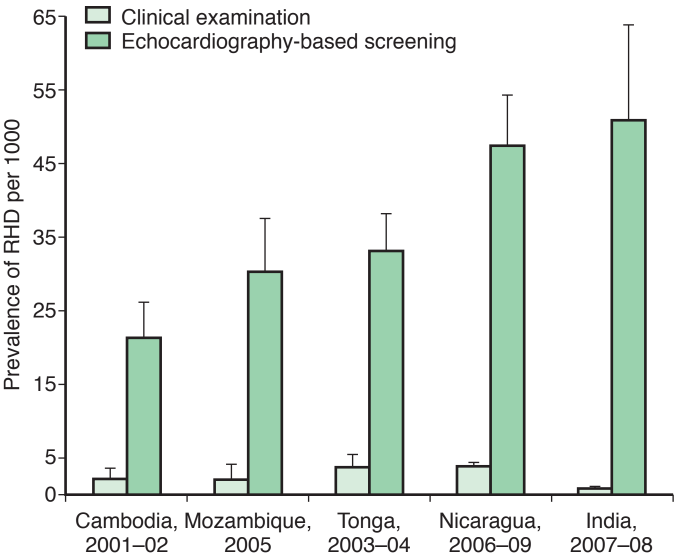

Figure 438-1 Rheumatic heart disease (RHD) prevalence rates in children: echocardiography-based screening versus clinical examination. Results of the first 4 studies to investigate differences in RHD detection methods are shown. In Cambodia and Mozambique, echocardiography-based RHD was defined as regurgitant jet seen in at least 2 planes and morphologic features suggestive of the disease, such as restricted leaflet mobility, focal or generalized valvular thickening, and abnormal subvalvular thickening. In Tonga, echocardiography-based RHD was defined by a combination of World Health Organization criteria (regurgitant jet >1 cm in length in at least 2 planes, mosaic color jet with a peak velocity >2.5 m/sec, persistence of jet throughout systole [mitral valve] and diastole [aortic valve], and morphologic criteria such as valvular thickening and elbow deformity of the anterior mitral valve leaflet). If only mitral regurgitation with no morphologic changes was seen, the case was considered as definite only if mitral regurgitation was graded at least as mild. Mitral or aortic stenoses were a sign of definite RHD, defined by a transmitral mean pressure gradient greater than 4 mm Hg and a transaortic peak velocity greater than 2 m/sec, respectively. If only very mild mitral regurgitation and no morphologic changes were seen, the child was classified as having borderline RHD (not reported here). In Nicaragua, echocardiography-based RHD, including possible cases, was defined by morphologic mitral changes (thickened mitral valve leaflets or dogleg deformity of the anterior mitral valve leaflet or both), and substantial left-side regurgitation (holosystolic mitral regurgitation jet ≥2 cm and ≥1 cm for aortic regurgitation, in 2 planes, of high velocity). In India, echocardiography-based RHD was defined by regurgitant jet greater than 1 cm in length in at least 2 planes, mosaic color jet with a peak velocity greater than 2.5 m/sec, and persistence of jet throughout systole (mitral valve) and diastole (aortic valve). Prevalence would only be 14.1 per 1000 with more stringent criteria combining Doppler echocardiography and pronounced mitral valve thickening (>6 mm). *(From Marijon E, Mirabel M, Celermajer DS, Jouven X: Rheumatic heart disease.* Lancet *379:953-964, 2012, Fig. 5.)*

left atrium and ventricle, an abnormally thickened mitral valve, and Doppler studies demonstrate the severity of the mitral regurgitation. Heart catheterization and left ventriculography are considered only if diagnostic questions are not totally resolved by noninvasive assessment.

Complications

Severe mitral insufficiency may result in cardiac failure that may be precipitated by progression of the rheumatic process, the onset of atrial fibrillation, or infective endocarditis. The effects of chronic mitral insufficiency may become manifest after many years and include right ventricular failure and atrial and ventricular arrhythmias.

Treatment

In patients with mild mitral insufficiency, prophylaxis against recurrences of rheumatic fever is all that is required. Treatment of complicating heart failure (see Chapter 442), arrhythmias (see Chapter 435), and infective endocarditis (see Chapter 437) is described elsewhere. Afterload-reducing agents (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) may reduce the regurgitant volume and preserve left ventricular function. Surgical treatment is indicated for patients who despite adequate medical therapy have persistent heart failure, dyspnea with moderate activity, and progressive cardiomegaly, often with pulmonary hypertension. Although annuloplasty provides good results in some children and adolescents, valve replacement may be required. In patients with a prosthetic mitral valve replacement, prophylaxis against bacterial endocarditis is warranted for dental procedures, as the routine antibiotics taken by these patients for rheumatic fever prophylaxis are insufficient to prevent endocarditis.

Mitral Stenosis

Pathophysiology

Mitral stenosis of rheumatic origin results from fibrosis of the mitral ring, commissural adhesions, and contracture of the valve leaflets, chordae, and papillary muscles over time. It usually takes 10 yr or more for the lesion to become fully established, although the process may occasionally be accelerated. Rheumatic mitral stenosis is seldom encountered before adolescence and is not usually recognized until adult life. Significant mitral stenosis results in increased pressure and enlargement and hypertrophy of the left atrium, pulmonary venous hypertension, increased pulmonary vascular resistance, and pulmonary hypertension. Right ventricular hypertrophy and right atrial dilation ensue and are followed by right ventricular dilation, tricuspid regurgitation, and clinical signs of right-sided heart failure.

Clinical Manifestations

Generally, the correlation between symptoms and the severity of obstruction is good. Patients with mild lesions are asymptomatic. More severe degrees of obstruction are associated with exercise intolerance and dyspnea. Critical lesions can result in orthopnea, paroxysmal nocturnal dyspnea, and overt pulmonary edema, as well as atrial arrhythmias. When pulmonary hypertension has developed, right ventricular dilation may result in functional tricuspid insufficiency, hepatomegaly, ascites, and edema. Hemoptysis caused by rupture of bronchial or pleurohilar veins and, occasionally, by pulmonary infarction may occur.

Jugular venous pressure is increased in severe disease with heart failure, tricuspid valve disease, or severe pulmonary hypertension. In mild disease, heart size is normal; however, moderate cardiomegaly is usual with severe mitral stenosis. Cardiac enlargement can be massive when atrial fibrillation and heart failure supervene. A parasternal right ventricular lift is palpable when pulmonary pressure is high. The principal auscultatory findings are a loud 1st heart sound, an opening snap of the mitral valve, and a long, low-pitched, rumbling mitral diastolic murmur with presystolic accentuation at the apex. The mitral diastolic murmur may be virtually absent in patients who are in significant heart failure. A holosystolic murmur secondary to tricuspid insufficiency may be audible. In the presence of pulmonary hypertension, the pulmonic component of the 2nd heart sound is accentuated. An early diastolic murmur may be caused by associated rheumatic aortic insufficiency or pulmonary valvular insufficiency secondary to pulmonary hypertension.

Electrocardiograms and roentgenograms are normal if the lesion is mild; as the severity increases, prominent and notched P waves and varying degrees of right ventricular hypertrophy become evident. Atrial fibrillation is a common late manifestation. Moderate or severe lesions are associated with roentgenographic signs of left atrial enlargement and prominence of the pulmonary artery and right-sided heart chambers; calcifications may be noted in the region of the mitral valve. Severe obstruction is associated with a redistribution of pulmonary blood flow so that the apices of the lung have greater perfusion (the reverse of normal). Echocardiography shows thickening of the mitral valve, distinct narrowing of the mitral orifice during diastole and left atrial enlargement. Doppler can estimate the transmitral pressure gradient. Cardiac catheterization quantitates the diastolic gradient across

the mitral valve, allows for the calculation of valve area, and assesses the degree of elevation of pulmonary arterial pressure.

Treatment

Intervention is indicated in patients with clinical signs and hemodynamic evidence of severe obstruction but before the severe manifestations outlined earlier. Surgical valvotomy or balloon catheter mitral valvuloplasty generally yields good results; valve replacement is avoided unless absolutely necessary. Balloon valvuloplasty is indicated for symptomatic, stenotic, pliable, noncalcified valves of patients without atrial arrhythmias or thrombi.

Aortic Insufficiency

In chronic rheumatic aortic insufficiency, sclerosis of the aortic valve results in distortion and retraction of the cusps. Regurgitation of blood leads to volume overload with dilation and hypertrophy of the left ventricle. Combined mitral and aortic insufficiency is more common than aortic involvement alone.

Clinical Manifestations

Symptoms are unusual except in severe aortic insufficiency. The large stroke volume and forceful left ventricular contractions may result in palpitations. Sweating and heat intolerance are related to excessive vasodilation. Dyspnea on exertion can progress to orthopnea and pulmonary edema; angina may be precipitated by heavy exercise. Nocturnal attacks with sweating, tachycardia, chest pain, and hypertension may occur.

The pulse pressure is wide with bounding peripheral pulses. Systolic blood pressure is elevated, and diastolic pressure is lowered. In severe aortic insufficiency, the heart is enlarged, with a left ventricular apical heave. A diastolic thrill may be present. The typical murmur begins immediately with the 2nd heart sound and continues until late in diastole. The murmur is heard over the upper and midleft sternal border with radiation to the apex and upper right sternal border. Characteristically, it has a high-pitched blowing quality and is easily audible in full expiration with the diaphragm of the stethoscope placed firmly on the chest and the patient leaning forward. An aortic systolic ejection murmur is frequent because of the increased stroke volume. An apical presystolic murmur **(Austin Flint murmur)** resembling that of mitral stenosis is sometimes heard and is a result of the large regurgitant aortic flow in diastole preventing the mitral valve from opening fully.

Chest x-rays show enlargement of the left ventricle and aorta. The electrocardiogram may be normal, but in advanced cases it reveals signs of left ventricular hypertrophy and strain with prominent P waves. The echocardiogram shows a large left ventricle and diastolic mitral valve flutter or oscillation caused by regurgitant flow hitting the valve leaflets. Doppler studies demonstrate the degree of aortic runoff into the left ventricle. Magnetic resonance angiography (MRA) can be useful in quantitating regurgitant volume. Cardiac catheterization is necessary only when the echocardiographic data are equivocal.

Prognosis and Treatment

Mild and moderate lesions are well tolerated. Unlike mitral insufficiency, aortic insufficiency does not regress. Patients with combined lesions during the episode of acute rheumatic fever may have only aortic involvement 1-2 yr later. Treatment consists of afterload reducers (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) and prophylaxis against recurrence of acute rheumatic fever. Surgical intervention (valve replacement) should be carried out well in advance of the onset of heart failure, pulmonary edema, or angina, when signs of decreasing myocardial performance become evident as manifested by increasing left ventricular dimensions on the echocardiogram. Surgery is considered when early symptoms are present, ST-T wave changes are seen on the electrocardiogram, or evidence of decreasing left ventricular ejection fraction is noted.

Tricuspid Valve Disease

Primary tricuspid involvement is rare after rheumatic fever. Tricuspid insufficiency is more common secondary to right ventricular dilation resulting from unrepaired left-sided lesions. The signs produced by tricuspid insufficiency include prominent pulsations of the jugular veins, systolic pulsations of the liver, and a blowing holosystolic murmur at the lower left sternal border that increases in intensity during inspiration. Concomitant signs of mitral or aortic valve disease, with or without atrial fibrillation, are frequent. In these cases, signs of tricuspid insufficiency decrease or disappear when heart failure produced by the left-sided lesions is successfully treated. Tricuspid valvuloplasty may be required in rare cases.

Pulmonary Valve Disease

Pulmonary insufficiency usually occurs on a functional basis secondary to pulmonary hypertension and is a late finding with severe mitral stenosis. The murmur (**Graham Steell murmur**) is similar to that of aortic insufficiency, but peripheral arterial signs (bounding pulses) are absent. The correct diagnosis is confirmed by two-dimensional echocardiography and Doppler studies.

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Section 6

Diseases of the Myocardium and Pericardium

Chapter 439

Diseases of the Myocardium

Robert L. Spicer and Stephanie M. Ware

The extremely heterogeneous heart muscle diseases associated with structural remodeling and/or abnormalities of cardiac function (cardiomyopathy) are important causes of morbidity and mortality in the pediatric population. Several classification schemes have been formulated in an effort to provide logical, useful, and scientifically based etiologies for the cardiomyopathies. Insight into the molecular genetic basis of cardiomyopathies has increased exponentially and etiologic classification schemes continue to evolve.

Table 439-1 classifies the cardiomyopathies based on their anatomic (ventricular morphology) and functional pathophysiology. Dilated cardiomyopathy, the most common form of cardiomyopathy, is characterized predominantly by left ventricular dilation and decreased left ventricular systolic function (Fig. 439-1). Hypertrophic cardiomyopathy demonstrates increased ventricular myocardial wall thickness, normal or increased systolic function, and often, diastolic (relaxation) abnormalities (Table 439-2; Figs. 439-2 and 439-3). Restrictive cardiomyopathy is characterized by nearly normal ventricular chamber size and wall thickness with preserved systolic function, but dramatically impaired diastolic function leading to elevated filling pressures and atrial enlargement (Fig. 439-4). Arrhythmogenic right ventricular cardiomyopathy and left ventricular noncompaction are characterized by specific morphologic abnormalities and heterogeneous functional disturbances.

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Table 439-1 Etiology of Pediatric Myocardial Disease

CARDIOMYOPATHY	
Dilated Cardiomyopathy (DCM)	
Neuromuscular diseases	Muscular dystrophies (Duchenne, Becker, limb girdle, Emery-Dreifuss, congenital muscular dystrophy, etc.), myotonic dystrophy, myofibrillar myopathy
Inborn errors of metabolism	Fatty acid oxidation disorders (trifunctional protein, VLCAD), carnitine abnormalities (carnitine transport, CPTI, CPTII), mitochondrial disorders (including Kearns-Sayre syndrome), organic acidemias (propionic acidemia)
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic DCM
Genetic syndromes	Alstrom syndrome, Barth syndrome (phospholipid disorders)
Ischemic	Most common in adults
Chronic tachyarrhythmias	
Hypertrophic Cardiomyopathy (HCM)	
Inborn errors of metabolism	Mitochondrial disorders (including Friedreich ataxia, mutations in nuclear or mitochondrial genome), storage disorders (glycogen storage disorders, especially Pompe; mucopolysaccharidoses; Fabry disease; sphingolipidoses; hemochromatosis; Danon disease)
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic HCM
Genetic syndromes	Noonan, Costello, cardiofaciocutaneous, Beckwith-Wiedemann syndrome
Infant of a diabetic mother	Transient hypertrophy
Restrictive Cardiomyopathy (RCM)	
Neuromuscular disease	Myofibrillar myopathies
Metabolic	Storage disorders
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic RCM
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic ARVC
LVNC	X-linked (Barth syndrome), autosomal dominant, autosomal recessive, mitochondrial inheritance, or sporadic LVNC
SECONDARY OR ACQUIRED MYOCARDIAL DISEASE	
Myocarditis (see also Table 439-3)	**Viral:** parvovirus B19, adenovirus, coxsackievirus A and B, echovirus, rubella, varicella, influenza, mumps, Epstein-Barr virus, cytomegalovirus, measles, poliomyelitis, smallpox vaccine, hepatitis C virus, human herpesvirus 6, HIV virus, or opportunistic infections **Rickettsial:** psittacosis, *Coxiella*, Rocky Mountain spotted fever, typhus **Bacterial:** diphtheria, mycoplasma, meningococcus, leptospirosis, Lyme disease, typhoid fever, tuberculosis, streptococcus, listeriosis **Parasitic:** Chagas disease, toxoplasmosis, *Loa loa, Toxocara canis,* schistosomiasis, cysticercosis, echinococcus, trichinosis **Fungal:** histoplasmosis, coccidioidomycosis, actinomycosis
Systemic inflammatory disease	SLE, infant of mother with SLE, scleroderma, Churg-Strauss vasculitis, rheumatoid arthritis, rheumatic fever, sarcoidosis, dermatomyositis, periarteritis nodosa, hypereosinophilic syndrome (Löffler syndrome), acute eosinophilic necrotizing myocarditis, giant cell myocarditis, Kawasaki disease
Nutritional deficiency	Beriberi (thiamine deficiency), kwashiorkor, Keshan disease (selenium deficiency)
Drugs, toxins	Doxorubicin (Adriamycin), cyclophosphamide, chloroquine, ipecac (emetine), sulfonamides, mesalazine, chloramphenicol, alcohol, hypersensitivity reaction, envenomations, irradiation, herbal remedy (blue cohosh)
Coronary artery disease	Kawasaki disease, medial necrosis, anomalous left coronary artery from the pulmonary artery, other congenital coronary anomalies (anomalous right coronary, coronary ostial stenosis), familial hypercholesterolemia
Hematology-oncology	Anemia, sickle cell disease, leukemia
Endocrine-neuroendocrine	Hyperthyroidism, carcinoid tumor, pheochromocytoma

CPTI/CPTII, carnitine palmitoyltransferase 1/2; LVNC, left ventricular noncompaction; SLE, systemic lupus erythematosus; VLCAD, very long chain acyl coenzyme A dehydrogenase.

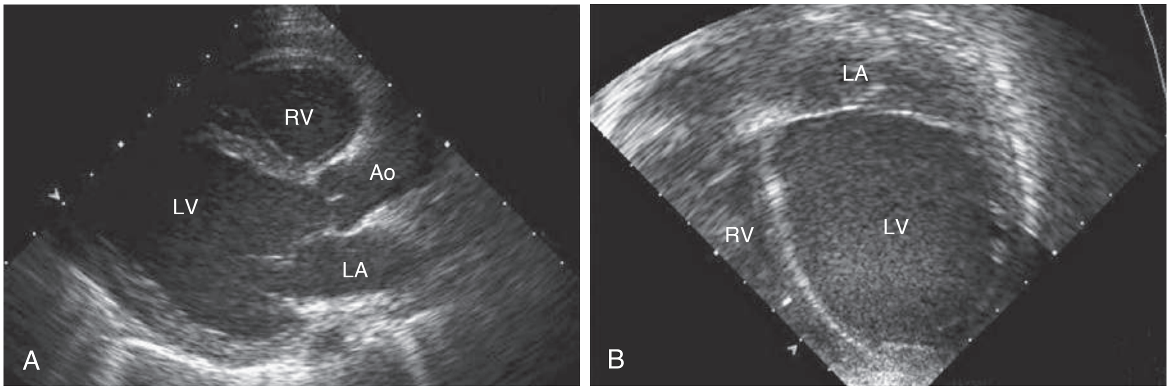

Figure 439-1 Echocardiogram of a patient with dilated cardiomyopathy. **A,** Parasternal long-axis view showing the enlarged left ventricle. **B,** Apical 4-chamber view showing the large left ventricle compressing the right ventricle. Ao, ascending aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

Table 439-2 Cardiomyopathies

	DCM	HCM	RCM	LVNC	ARVC
Prevalence	50/100,000	1/500	Unknown	Unknown	1/2,000
Familial	30-50% AD, AR, X-L, Mt	50% AD, Mt	AD, % unknown	AD, X-L, Mt, % unknown	30-50% AD, rare AR (Naxos disease; Carvajal syndrome)
Genes*	Sarcomere: *MYH7, MYBPC3, TNNI3, TNNT2, TNNC1, MYH6, TPM1, ACTC1* Cytoskeleton or Z-disc: *DMD, TTN, CSRP3, TCAP, VCL, ACTN2, DES, LDB3, SGCD, MYPN, ANKRD1, BAG3, NEBL, NEXN* Nuclear envelope: *LMNA, EMD, TMPO* Cardiolipin metabolism: *TAZ* Mitochondrial function: mt DNA depletion; Mt genome mutations/deletions Other: *CRYAB, SCN5A, EYA4, ABCC9, PLN, PSEN1, PSEN2, FCMD, ALMS1, CAV3, LAMA4, LAMP2, RBM20*	Sarcomere: *MYH7, MYBPC3, MYL2, MYL3, TNNT2, TNNI3, TNNC1, MYH6, TPM1, ACTC1* Cytoskeleton or Z-disc: *TTN, CSRP3, LDB3, TCAP, VCL, ACTN2, MYOZ2, ANKRD1, BAG3* Storage: *PRKAG2, LAMP2, GLA, GAA, AGL* Mitochondrial function: *FRDA, SCO2, SURF1, COX* genes, *ANT1*, Mt genome mutations/deletions Cell signaling: *PTPN11, RAF1, SOS1, KRAS, HRAS, BRAF, MEK1, MEK2, MYLK2* Other: *PLN, JPH2, CALR3*	Sarcomere: *MYH7, TNNT2, TNNI3, ACTC1* Cytoskeleton or Z-disc: *DES*	Cytoskeletal or Z-disc: *DTNA, LDB3* Cardiolipin metabolism: *TAZ* Sarcomere: *MYH7, MYBPC3, ACTC1* Mitochondrial function: see HCM and DCM Other: *CASQ2, DTNA*	Desmosome: *DSP, PKP2, DSG2, DSC2, JUP* Other: *TMEM43, TGFB3, RYR2*
Sudden death	Yes	Yes	Yes	Yes	Yes
Arrhythmias	Atrial, ventricular, and conduction disturbances	Atrial and ventricular	Atrial fibrillation		Ventricular and conduction disturbances
Ventricular function	Systolic and diastolic dysfunction	Diastolic dysfunction Dynamic systolic outflow obstruction	Diastolic dysfunction Normal systolic function	Systolic or diastolic dysfunction	Normal-reduced systolic and diastolic function

ACE, angiotensin-converting enzyme; AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVNC, left ventricular noncompaction; Mt, mitochondrial inheritance; RCM, restrictive cardiomyopathy; X-L, X-linked inheritance.

*Genes are listed using the human gene symbol.

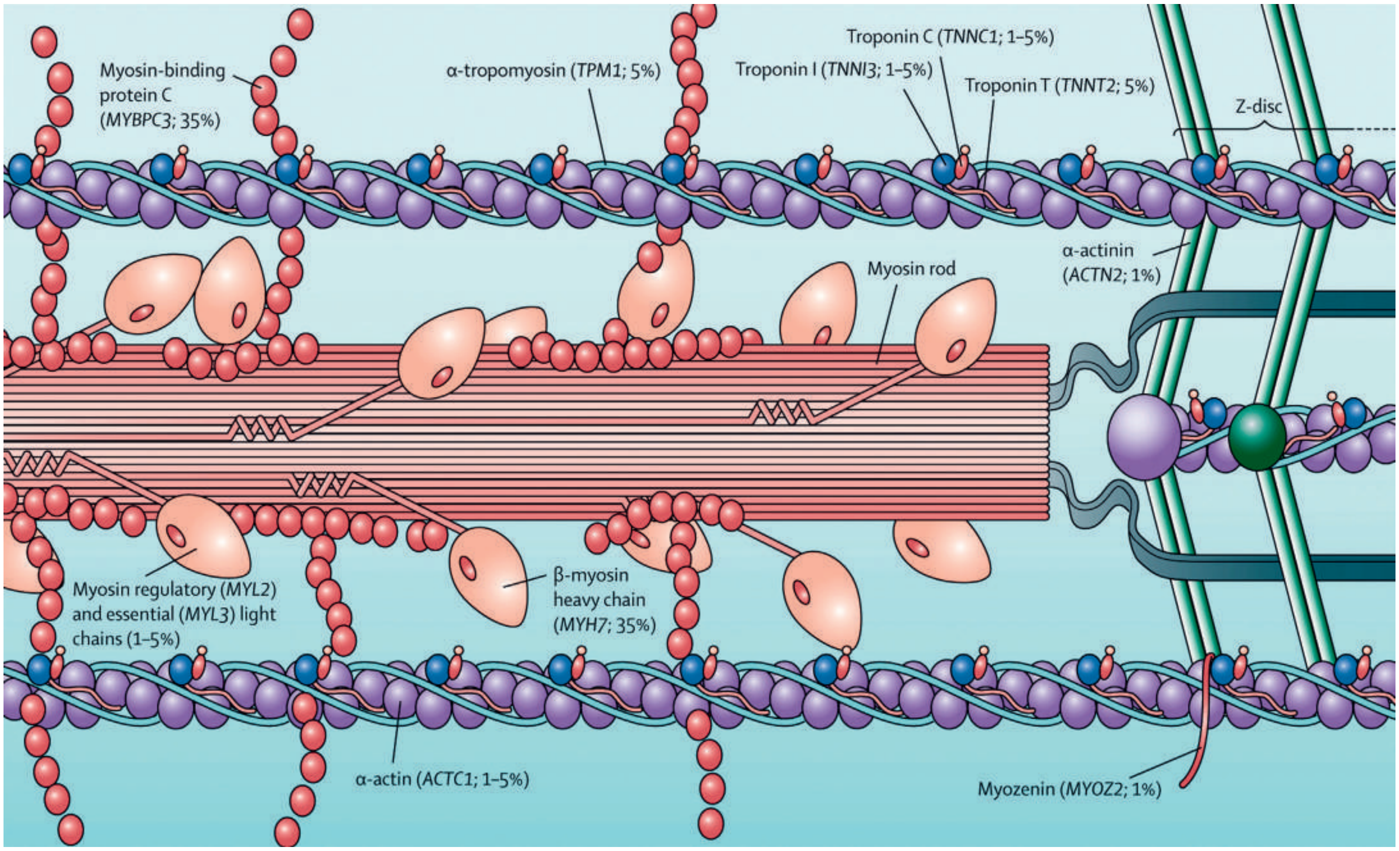

Figure 439-2 **Locations of genes within the cardiac sarcomere known to cause hypertrophic cardiomyopathy.** Prevalence of every gene (derived from data of unrelated hypertrophic cardiomyopathy probands with positive genotyping) is shown in parentheses. *(From Maron BJ, Maron MS: Hypertrophic cardiomyopathy.* Lancet *381:242–252, 2013, Fig. 1, p 243.)*

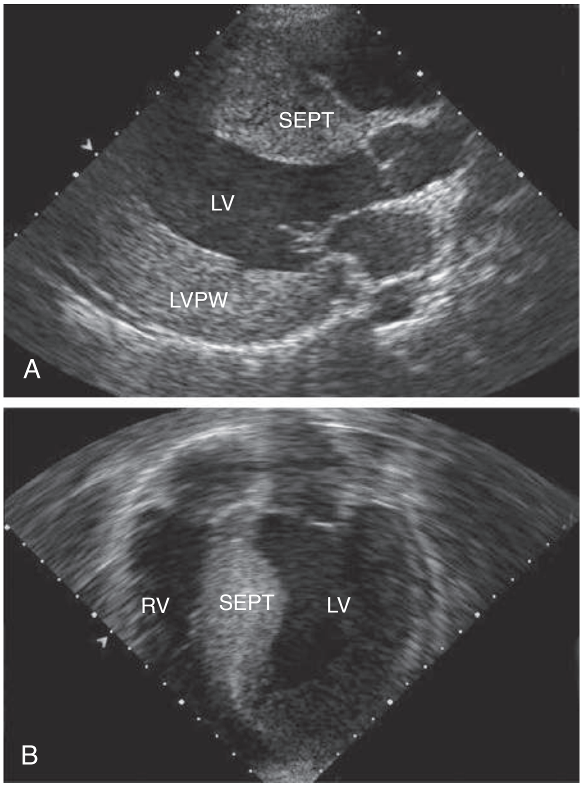

Figure 439-3 **Echocardiograms demonstrating hypertrophic cardiomyopathy. A,** Parasternal long-axis view of a patient with severe concentric left ventricular hypertrophy. **B,** Four-chamber view of a patient with asymmetric septal hypertrophy. LV, left ventricle; LVPW, left ventricular posterior wall; RV, right ventricle; SEPT, septum.

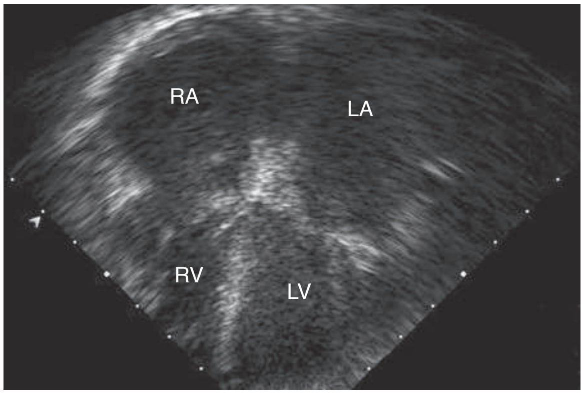

Figure 439-4 **Echocardiogram of a patient with restrictive cardiomyopathy.** The apical 4-chamber view shows the markedly enlarged right and left atria, compared to the normal size left and right ventricular chambers. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

439.1 Dilated Cardiomyopathy

Robert L. Spicer and Stephanie M. Ware

ETIOLOGY AND EPIDEMIOLOGY

Dilated cardiomyopathy (DCM), the most common form of cardiomyopathy in children, is the cause of significant morbidity and mortality as well as a common indication for cardiac transplantation. The etiologies are diverse. Unlike adult patients with DCM, ischemic etiologies are rare in children, although these include anomalous origin of the left coronary artery from the pulmonary artery, premature coronary atherosclerosis (homozygous type II hypercholesterolemia), and coronary inflammatory diseases, such as Kawasaki disease. It is estimated that up to 50% of cases are genetic (usually autosomal dominant; some

are autosomal recessive or X-linked), including some with metabolic causes (see Table 439-1). Although the most common etiology of DCM remains idiopathic, it is likely that undiagnosed familial/genetic conditions and myocarditis predominate. Associate features may include conduction defects or sensorineural hearing loss. The annual incidence of DCM in children younger than 18 yr is 0.57 cases per 100,000 per year. Incidence is higher in males, African-Americans, and in infants less than 1 yr old.

PATHOGENESIS

The pathogenesis of the ventricular dilation and altered contractility seen in DCM varies depending on the underlying etiology; systolic dysfunction and myocyte injury are common. Genetic abnormalities of several components of the cardiac muscle including sarcomere protein, the cytoskeleton, and the proteins that bridge the contractile apparatus to the cytoskeleton, have been identified in autosomal dominant and X-linked inherited disorders. DCM can occur following viral myocarditis and, although the primary pathogenesis varies from direct myocardial injury to viral-induced inflammatory injury, the resulting myocardial damage, ventricular enlargement, and poor function likely occur by a final common pathway similar to that which occurs in genetic disorders.

In 20-50% of cases, the DCM is familial with autosomal dominant inheritance most common (see Table 439-2). **Duchenne and Becker muscular dystrophies** (see Chapter 609.1) are X-linked cardiomyopathies that account for 5-10% of familial DCM cases. These dystrophinopathies result in an abnormal sarcomere–cytoskeleton connection, causing impaired myocardial force generation, myocyte damage/scarring, chamber enlargement, and altered function.

Mitochondrial myopathies, like the muscular dystrophies, may present clinically with a predominance of extracardiac findings and are inherited in a recessive or mitochondrial pattern. Disorders of **fatty acid oxidation** present with systemic derangements of metabolism (hypoketotic hypoglycemia, acidosis, and hepatic dysfunction), some with peripheral myopathy and neuropathy, and others with sudden death or life-threatening cardiac arrhythmias.

Anthracycline cardiotoxicity (doxorubicin [Adriamycin]) on rare occasion causes acute inflammatory myocardial injury, but more classically results in DCM and occurs in up to 30% of patients given a cumulative dose of doxorubicin exceeding 550 mg/m^2. The risk of toxicity appears to be exacerbated by concomitant radiation therapy.

CLINICAL MANIFESTATIONS

Although more prevalent in patients less than 1 yr of age, all age groups may be affected. Clinical manifestations of DCM are most commonly those of heart failure, but can also include palpitations, syncope, and sudden death. Irritability or lethargy can be accompanied by additional nonspecific complaints of failure to thrive, nausea, vomiting, or abdominal pain. Respiratory symptoms (tachypnea, wheezing, cough, or dyspnea on exertion) are often present. Uncommonly, patients may present acutely with pallor, altered mentation, hypotension, and shock. Patients can be tachycardic with narrow pulse pressure and have hepatic enlargement, and rales or wheezing. The precordial cardiac impulse is increased and the heart may be enlarged to palpation or percussion. Auscultation may reveal a gallop rhythm in addition to tachycardia and occasionally murmurs of mitral or, less commonly, tricuspid insufficiency may be present. The presence of hypoglycemia, acidosis, hypotonia, or signs of liver dysfunction suggests an inborn error of metabolism. Neurologic or skeletal muscle deficits are associated with mitochondrial disorders or muscular dystrophies.

LABORATORY FINDINGS

Electrocardiographic screening reveals atrial or ventricular hypertrophy, nonspecific T-wave abnormalities, and, occasionally, atrial or ventricular arrhythmias. The chest x-ray may demonstrate cardiomegaly and pulmonary vascular prominence or pleural effusions. The echocardiogram is often diagnostic, demonstrating the characteristic findings of left ventricular enlargement, decreased ventricular contractility, and occasionally a globular (remodeled) left ventricular contour (see Fig. 439-1). Right ventricular enlargement and depressed function are occasionally noted. Echo Doppler studies can reveal evidence of pulmonary hypertension, mitral regurgitation, or other structural cardiac or coronary abnormalities.

Additional testing should include complete blood count, renal and liver function tests, creatine phosphokinase, cardiac troponin I, lactate, brain natriuretic peptide, plasma amino acids, urine organic acids, and an acylcarnitine profile. Additional genetic and enzymatic testing may be useful (see Table 439-2). Cardiac catheterization and endomyocardial biopsy are not routine but may be useful in patients with acute DCM. Biopsy samples can be examined histologically for the presence of mononuclear cell infiltrates, myocardial damage, storage abnormalities, and for evidence of infection. It is considered standard of care to screen 1st-degree family members utilizing echocardiography and electrocardiogram (ECG) in idiopathic and familial cases of DCM.

PROGNOSIS AND MANAGEMENT

The 1 and 5 yr freedom from death or transplantation in patients diagnosed with DCM is 61% and 47%, respectively. Independent risk factors at DCM diagnosis for subsequent death or transplantation include older age, congestive heart failure, lower left ventricular fractional shortening *z* score, and underlying etiology. DCM is the most common cause for cardiac transplantation in pediatric and adult studies.

The therapeutic approach to patients with DCM includes a careful assessment to uncover possible treatable etiologies, screening of family members, and rigorous pharmacologic therapy. Decongestive therapy may improve symptoms of heart failure, prolong survival, and occasionally results in complete resolution of dysfunction. Patients are often treated with diuretics and angiotensin-converting enzyme inhibitors. The use of digitalis and angiotensin receptor blockers may be of additional benefit. β-Adrenergic blockade with carvedilol or metoprolol is often used in patients with chronic heart failure although pediatric specific outcome data have failed to show effectiveness. In patients presenting with extreme degrees of heart failure or circulatory collapse, intensive care measures are often required, including intravenous inotropes and diuretics, mechanic ventilatory support, and on occasion, mechanical circulatory support, which may include ventricular assist devices, extracorporeal membrane oxygenation, and ultimately cardiac transplantation. In patients with DCM and atrial or ventricular arrhythmias, specific antiarrhythmic therapy should be instituted.

Bibliography is available at Expert Consult.

439.2 Hypertrophic Cardiomyopathy

Robert L. Spicer and Stephanie M. Ware

ETIOLOGY AND EPIDEMIOLOGY

Hypertrophic cardiomyopathy (HCM) is a heterogeneous, relatively common, and potentially life-threatening form of cardiomyopathy. The causes of HCM are heterogeneous and include inborn errors of metabolism, neuromuscular disorders, syndromic conditions, and genetic abnormalities of the structural components of the cardiomyocyte (see Table 439-1). Both the age of onset and associated features are helpful in identifying the underlying etiology.

HCM is a genetic disorder and frequently occurs as a result of mutations in sarcomere or cytoskeletal components of the cardiomyocyte (see Fig. 439-2). Mutations of the genes encoding cardiac β-myosin heavy-chain *(MYH7)* and myosin-binding protein C *(MYBPC3)* are the most common (see Table 439-2). Mutations are inherited in an autosomal dominant pattern with widely variable penetrance; many cases represent de novo mutations. Some patients have mutations in more than 1 sarcomere or cytoskeletal gene and may manifest disease earlier and with more-severe symptoms. Additional genetic causes for HCM include nonsarcomeric protein mutations, such as the γ_2-regulatory subunit of adenosine monophosphate–activated protein kinase *(PRKAG2)* and the lysosome-associated membrane protein 2α-galactosidase (Danon disease, a form of glycogen storage disease). Syndromic conditions, such as Noonan syndrome, may present with

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HCM at birth and recognition of extracardiac manifestations is important in making the diagnosis.

Glycogen storage disorders such as Pompe disease often present in infancy with a heart murmur, abnormal ECG, systemic signs and symptoms, and occasionally heart failure. The characteristic ECG in Pompe disease demonstrates prominent P waves, a short P-R interval, and massive QRS voltages; the echocardiogram confirms severe, often concentric, left ventricular hypertrophy.

PATHOGENESIS

HCM is characterized by the presence of increased left ventricular wall thickness in the absence of structural heart disease or hypertension. Often the interventricular septum is disproportionately involved, leading to the previous designation of idiopathic hypertrophic subaortic stenosis or the current term of asymmetric septal hypertrophy. In the presence of a resting or provokable outflow tract gradient, the term hypertrophic obstructive cardiomyopathy is used. Although the left ventricle is predominantly affected, the right ventricle may be involved, particularly in infancy. The mitral valve can demonstrate systolic anterior motion and mitral insufficiency. Left ventricular outflow tract obstruction occurs in 25% of patients, is dynamic in nature, and may in part be secondary to the abnormal position of the mitral valve as well as the obstructing subaortic hypertrophic cardiac muscle. The cardiac myofibrils and myofilaments demonstrate disarray and myocardial fibrosis.

Typically, systolic pump function is preserved or even hyperdynamic, though systolic dysfunction may occur late. Outflow tract obstruction with or without mitral insufficiency may be provoked by physiologic manipulations such as the Valsalva maneuver, positional changes, and physical activity. Frequently, the hypertrophic and fibrosed cardiac muscle demonstrates relaxation abnormalities (diminished compliance) and left ventricular filling may be impaired (diastolic dysfunction).

CLINICAL MANIFESTATIONS

Many patients are asymptomatic, and 50% of cases present with a heart murmur or during screening when another family member has been diagnosed with HCM. Symptoms of HCM may include palpitations, chest pain, easy fatigability, dyspnea, dizziness, and syncope. Sudden death is a well-recognized but uncommon manifestation that often occurs during physical exertion.

Characteristic physical examination findings include an overactive precordial impulse with a lift or heave, abnormal peripheral pulses (hyperdynamic or diminished), a systolic ejection murmur in the aortic region *not* associated with an ejection click, and an apical blowing murmur of mitral insufficiency.

DIAGNOSIS

The ECG typically demonstrates left ventricular hypertrophy with ST segment and T-wave abnormalities. Intraventricular conduction delays and signs of ventricular preexcitation (Wolff-Parkinson-White syndrome) may be present and should raise the possibility of Danon disease or Pompe disease. Chest radiography demonstrates normal or mildly increased heart size with a prominence of the left ventricle. Echocardiography is diagnostic in identifying, localizing, and quantifying the degree of myocardial hypertrophy (see Fig. 439-3). Doppler interrogation defines, localizes, and quantifies the degree of ventricular outflow tract obstruction and also demonstrates and quantifies the degree of mitral insufficiency. Diastolic dysfunction can be confirmed by M-mode, flow, and tissue Doppler techniques.

Cardiac catheterization may be indicated in some cases of HCM to define the left ventricular outflow gradient with and without pharmacologic provocation, to measure left ventricular diastolic pressures, to perform electrophysiologic testing of assessment of arrhythmia risk, or in rare cases, endomyocardial biopsy.

Additional diagnostic studies include metabolic testing, genetic testing for specific syndromes, or genetic testing for mutations in genes known to cause isolated HCM (see Table 439-2). The clinical availability of these tests is expanding. In adults, where isolated HCM is a common genetic diagnosis, it has been possible to identify a subset of mutations that confer an increased risk for arrhythmia or sudden death. As identification of the molecular basis of disease in children increases, similar correlations are expected to emerge. In addition, genetic diagnosis is useful to identify at-risk family members who require ongoing surveillance.

PROGNOSIS AND MANAGEMENT

Children under 1 yr of age or with inborn errors of metabolism or malformation syndromes or those with a mixed HCM/DCM have a significantly poorer prognosis. The risk of sudden death in older patients is greater in those with a history of cardiac arrest, ventricular tachycardia, exercise hypotension, syncope, excessive (>3 cm) ventricular wall thickness, and a ventricular obstruction gradient greater than 30 mm Hg. Although intrafamilial variability in symptoms occurs, a family history of sudden death is a highly significant predictor of risk.

Competitive sports and strenuous physical activity should be prohibited as most sudden deaths in patients with HCM occur during or immediately after vigorous physical exertion. β-adrenergic blocking agents (propranolol, atenolol) or calcium channel blocking agents (verapamil) may be useful in diminishing ventricular outflow tract obstruction, modifying ventricular hypertrophy, and improving ventricular filling. Although significant symptomatic improvement occurs in some patients, the risk for development of heart failure or sudden death has not been lessened. In patients with atrial or ventricular arrhythmias, specific antiarrhythmic therapy should be used. Patients with documented ventricular arrhythmias, strong family histories of arrhythmias or sudden death, or patients with syncope should be treated with an implantable cardioverter defibrillator.

Innovative interventional procedures to anatomically or physiologically reduce the degree of left ventricular outflow tract obstruction have been used. Dual-chamber pacing, alcohol septal ablation, surgical septal myomectomy, and mitral valve replacement have all met with some success.

First-degree relatives of patients identified as having HCM should be screened with electrocardiography and echocardiography. Genetic testing is available clinically. It is important to first test the affected individual in the family rather than "at-risk" individuals because 20-40% of cases of HCM will not demonstrate mutations in currently available panels of genes. If a causative mutation is identified, "at-risk" members of the family can be effectively tested. In families with HCM without demonstrable gene mutations, repeat noninvasive cardiac screening with ECG and echo should be undertaken in at risk individuals every 3-5 yr for patients younger than 12 yr of age and yearly throughout the teenage years and young adulthood. The clinical course of other affected family members and the results of genetic testing may be of some use in stratifying risk in an affected child.

Bibliography is available at Expert Consult.

439.3 Restrictive Cardiomyopathy

Robert L. Spicer and Stephanie M. Ware

ETIOLOGY AND EPIDEMIOLOGY

Restrictive cardiomyopathy (RCM) accounts for <5% of cardiomyopathy cases. Incidence increases with age, and is more common in females. In equatorial Africa, RCM accounts for a large number of deaths. Infiltrative myocardial causes and storage disorders frequently result in associated left ventricular hypertrophy and may represent HCM with restrictive physiology. Noninfiltrative causes include mutations in genes encoding sarcomeric or cytoskeletal proteins. Although there has been significant success in discovering new gene mutations causing RCM, the majority of are considered idiopathic.

PATHOGENESIS

RCM is characterized by normal ventricular chamber dimensions, normal myocardial wall thickness, and preserved systolic function. Dramatic atrial dilation can occur as a result of the abnormal myocardial compliance and high ventricular diastolic pressure. Autosomal

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dominant inheritance has been demonstrated for families with mutations in sarcomeric and cytoskeletal genes.

CLINICAL MANIFESTATIONS

Abnormal ventricular filling, sometimes referred to as *diastolic heart failure,* is manifest in the systemic venous circulation with edema, hepatomegaly, or ascites. Elevation of left-sided filling pressures result in cough, dyspnea, or pulmonary edema. With activity, patients may experience chest pain, shortness of breath, syncope/near syncope, or even sudden death. Pulmonary hypertension and pulmonary vascular disease develop and may progress rapidly. Heart murmurs are typically absent, but a gallop rhythm may be prominent. In the presence of pulmonary hypertension, an overactive right ventricular impulse and pronounced pulmonary component of the second heart sound are present.

DIAGNOSIS

The characteristic electrocardiographic finding of prominent P waves is usually associated with normal QRS voltages and nonspecific ST and T-wave changes. Right ventricular hypertrophy occurs in patients with pulmonary hypertension. The chest x-ray may be normal or demonstrate a prominent atrial shadow and pulmonary vascular redistribution. The echocardiogram is often diagnostic, demonstrating normal-sized ventricles with preserved systolic function and dramatic enlargement of the atria (see Fig. 439-4). Flow and tissue Doppler interrogation reveal abnormal filling parameters. Differential diagnosis from constrictive pericarditis is critical, as the latter can be treated surgically. Magnetic resonance imaging may be necessary to demonstrate the thickened or calcified pericardium often present in constrictive pericardial disease.

PROGNOSIS AND MANAGEMENT

Pharmacologic treatment modalities are of limited use and the prognosis of patients with RCM is generally poor with often progressive clinical deterioration. Sudden death is a significant risk, with a 2-yr survival of 50%. When signs of heart failure exist, judicious use of diuretics can result in clinical improvement. As a result of the dramatic atrial enlargement, these patients are predisposed to the development of atrial tachyarrhythmias and thromboemboli. Antiarrhythmic agents may be necessary and anticoagulation with platelet inhibitors or Coumadin is indicated.

Cardiac transplantation is the treatment of choice in many centers for patients with RCM, and the results are excellent in patients without pulmonary hypertension, pulmonary vascular disease, or severe congestive heart failure.

Bibliography is available at Expert Consult.

439.4 Left Ventricular Noncompaction, Arrhythmogenic Right Ventricular Cardiomyopathy, and Endocardial Fibroelastosis

Robert L. Spicer and Stephanie M. Ware

Left ventricular noncompaction (LVNC) was initially believed to be a rare disorder found only in children, but is now known to affect individuals of all ages. LVNC is characterized by a distinctive trabeculated or spongy-appearing left ventricle (Fig. 439-5) commonly associated with left ventricular hypertrophy and/or dilation, and at times, systolic or diastolic dysfunction. LVNC may be isolated or associated with structural congenital cardiac defects. Patients may present with signs of heart failure, arrhythmias, syncope, sudden death, or as an asymptomatic finding during screening of family members.

Imaging studies using ultrasound or magnetic resonance can demonstrate the characteristic pattern of deeply trabeculated left ventricle myocardium, most characteristically within the apex of the left ventricle. ECG findings are nonspecific and include chamber hypertrophy, ST and T-wave changes, or arrhythmias. In some patients, preexcitation is

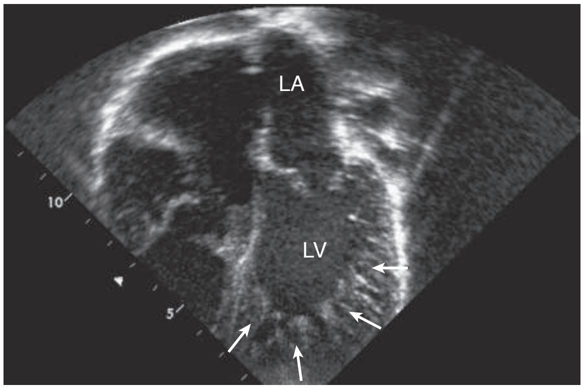

Figure 439-5 Echocardiogram of a patient with left ventricular noncompaction cardiomyopathy. Apical view showing the abnormal trabeculations of the left ventricle at the apex *(arrows).* For comparison, see the smooth walled LV in Figure 439-1. LA, left atrium; LV, left ventricle.

notable and giant QRS voltages occur in approximately 30% of younger children. Metabolic screening should be considered, especially in young children. Elevated serum lactate and urine 3-methylglutaconic acid may be seen in Barth syndrome, an X-linked disorder of phospholipid metabolism caused by a mutation in the tafazzin (*TAZ*) gene. Clinical testing for *TAZ* mutations is available and should be considered, especially in males. Patients with mitochondrial disorders frequently demonstrate signs of LVNC. These children are at risk for atrial or ventricular arrhythmias and thromboembolic complications. Treatment includes anticoagulation, antiarrhythmic therapy if needed, and treatment of heart failure if present. In patients refractory to medical therapy, cardiac transplantation has been used successfully.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is thought to be uncommon in North America but is among the most common forms of cardiomyopathy in Europe, especially Italy. Autosomal dominant inheritance is common. In addition, recessive forms associated with severe ARVC and skin manifestations are known. Comprehensive genetic screening has been reported to identify a cause in up to 50% of cases. ARVC is typically characterized by a dilated right ventricle with fibrofatty infiltration of the right ventricle wall; increasingly, left ventricle involvement is being recognized. Global and regional right and left ventricular dysfunction and ventricular tachyarrhythmias are the major clinical findings. Syncope or aborted sudden death can occur and should be treated with antiarrhythmic medications and placement of a defibrillator. In patients with ventricular dysfunction, heart failure management as indicated for patients with DCM may be of use.

Endocardial fibroelastosis (EFE), at one time an important cause of heart failure in children, is uncommon. The decline in primary EFE is likely related to the abolition of mumps virus infections by immunization practices. Rare familial cases exist, but the causative genes are unknown. Secondary EFE can occur with severe left-sided obstructive lesions such as aortic stenosis or atresia, hypoplastic left heart syndrome, or coarctation of the aorta. EFE is characterized by an opaque, white, fibroelastic thickening on the endocardial surface of the ventricle, which leads to systolic and/or diastolic dysfunction. Surgical removal of the endocardial fibrosis has been successfully utilized to improve cardiac function. Standard heart failure management including transplantation has been utilized in the management of EFE.

Bibliography is available at Expert Consult.

439.5 Myocarditis

Robert L. Spicer and Stephanie M. Ware

Acute or chronic inflammation of the myocardium is characterized by inflammatory cell infiltrates, myocyte necrosis, or myocyte

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Table 439-3 Causes of Myocarditis

INFECTIOUS		IMMUNE-MEDIATED		TOXIC
Viral	Adenovirus	Autoantigens	Churg-Strauss syndrome	Anthracyclines
	Parvovirus		Inflammatory bowel disease	Cocaine
	Coxsackie B virus Epstein-Barr virus		Giant cell myocarditis	Interleukin-2
	Hepatitis C virus		Diabetes mellitus	Ethanol
	Measles virus		Sarcoidosis	Heavy metals
	Human herpes virus		Systemic lupus erythematosus	Spider bite
	Varicella-zoster virus		Thyrotoxicosis	Snake bite
	Human immunodeficiency virus		Takayasu arteritis	Scorpion bite
	Influenza viruses		Kawasaki syndrome	Electric shock
Bacterial	*Mycobacteria*		Celiac disease	
	Streptococcus spp.		Whipple disease	
	Mycoplasma pneumoniae			
	Treponema pallidum			
	Corynebacterium diphtheriae			
	Borrelia burgdorferi			
	Ehrlichia			
Fungal	*Aspergillus*	Hypersensitivity	Granulomatosis with polyangiitis	
	Candida		Sulfonamides	
	Coccidioides		Cephalosporins	
	Cryptococcus		Diuretics	
	Histoplasma		Tricyclic antidepressants	
Protozoal	*Trypanosoma cruzi*		Dobutamine	
	Toxoplasma gondii			
	Babesia			
Parasitic	Schistosomiasis			
	Larva migrans (visceral)			

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degeneration and may be caused by infectious, connective tissue, granulomatous, toxic, or idiopathic processes. There may be associated systemic manifestations of the disease and on occasion the endocardium or pericardium is involved, though coronary pathology is uniformly absent. Patients may be asymptomatic, have nonspecific prodromal symptoms, or present with overt congestive heart failure, compromising arrhythmias, or sudden death. It is thought that viral infections are the most common etiology though myocardial toxins, drug exposures, hypersensitivity reactions, and immune disorders may also lead to myocarditis (Table 439-3).

ETIOLOGY AND EPIDEMIOLOGY

Viral Infections

Coxsackievirus and other enteroviruses, adenovirus, parvovirus, Epstein-Barr virus, parechovirus, influenza virus, and cytomegalovirus are the most common causative agents in children, though most known viral agents have been reported. In Asia, hepatitis C virus appears to be significant as well. The true incidence of viral myocarditis is unknown as mild cases probably go undetected. The disease is typically sporadic but may be epidemic. Manifestations are, to some degree, age dependent: in neonates and young infants, viral myocarditis can be fulminant; in children, it often will occur as an acute, myopericarditis with heart failure; and in older children and adolescents, it may present with signs and symptoms of acute or chronic heart failure or chest pain.

Bacterial Infections

Bacterial myocarditis has become far less common with the advent of advanced public health measures, which have minimized infectious causes such as diphtheria. Diphtheritic myocarditis (see Chapter 187) is unique as bacterial toxin may produce circulatory collapse and toxic myocarditis characterized by atrioventricular block, bundle-branch block, or ventricular ectopy. Any overwhelming systemic bacterial infection can manifest with circulatory collapse and shock with evidence of myocardial dysfunction characterized by tachycardia, gallop rhythm, and low cardiac output. Additional nonviral infectious causes of myocarditis include rickettsia, protozoa, parasitic infections, and fungal disease.

PATHOPHYSIOLOGY

Myocarditis is characterized by myocardial inflammation, injury or necrosis, and ultimately fibrosis. Cardiac enlargement and diminished systolic function occur as a direct result of the myocardial damage. Typical signs of congestive heart failure occur and may progress rapidly to shock, atrial or ventricular arrhythmias, and sudden death. Viral myocarditis may also become a chronic process with persistence of viral nucleic acid in the myocardium, and the perpetuation of chronic inflammation secondary to altered host immune response including activated T lymphocytes (cytotoxic and natural killer cells) and antibody-dependent cell mediated damage. Additionally, persistent viral infection may alter the expression of major histocompatibility complex antigens with resultant exposure of neoantigens to the immune system. Some viral proteins share antigenic epitopes with host cells, resulting in autoimmune damage to the antigenically related myocyte. Cytokines such as tumor necrosis factor-α and interleukin-1 are inhibitors of myocyte response to adrenergic stimuli and result in diminished cardiac function. The final result of viral-associated inflammation can be DCM.

CLINICAL MANIFESTATIONS

Manifestations of myocarditis range from asymptomatic or nonspecific generalized illness to acute cardiogenic shock and sudden death. Infants and young children more often have a fulminant presentation with fever, respiratory distress, tachycardia, hypotension, gallop rhythm, and cardiac murmur. Associated findings may include a rash or evidence of end organ involvement such as hepatitis or aseptic meningitis.

Patients with acute or chronic myocarditis may present with chest discomfort, fever, palpitations, easy fatigability, or syncope/near syncope. Cardiac findings include overactive precordial impulse, gallop rhythm, and an apical systolic murmur of mitral insufficiency.

In patients with associated pericardial disease, a rub may be noted. Hepatic enlargement, peripheral edema, and pulmonary findings such as wheezes or rales may be present in patients with decompensated heart failure.

DIAGNOSIS

Electrocardiographic changes are nonspecific and may include sinus tachycardia, atrial or ventricular arrhythmias, heart block, diminished QRS voltages, and nonspecific ST and T-wave changes, often suggestive of acute ischemia. Chest x-rays in severe, symptomatic cases reveal cardiomegaly, pulmonary vascular prominence, overt pulmonary edema, or pleural effusions. Echocardiography often shows diminished ventricular systolic function, cardiac chamber enlargement, mitral insufficiency, and occasionally, evidence of pericardial infusion.

Cardiac MRI is a standard imaging modality for the diagnosis of myocarditis; information on the presence and extent of edema, gadolinium-enhanced hyperemic capillary leak, myocyte necrosis, left ventricular dysfunction, and evidence of an associated pericardial effusion assist in the cardiac MRI diagnosis of myocarditis.

Endomyocardial biopsy may be useful in identifying inflammatory cell infiltrates or myocyte damage and performing molecular viral analysis using polymerase chain reaction techniques. Catheterization and biopsy, although not without risk (perforation and arrhythmias), should be performed by experienced personnel in patients suspected to have myocarditis or if there is strong suspicion for unusual forms of cardiomyopathy such as storage diseases or mitochondrial defects. Nonspecific tests include sedimentation rate, creatine phosphokinase isoenzymes, cardiac troponin I, and brain natriuretic peptide levels.

DIFFERENTIAL DIAGNOSIS

The predominant diseases mimicking acute myocarditis include carnitine deficiency, other metabolic disorders of energy generation, hereditary mitochondrial defects, idiopathic DCM, pericarditis, EFE, and anomalies of the coronary arteries (see Table 439-1).

TREATMENT

Primary therapy for acute myocarditis is supportive (see Chapter 442). Acutely, the use of inotropic agents, preferably milrinone, should be entertained but used with caution because of their proarrhythmic potential. Diuretics are often required as well. If in extremis, mechanical ventilatory support and mechanical circulatory support with ventricular assist device implantation or extracorporeal membrane oxygenation may be needed to stabilize the patient's hemodynamic status and serve as a bridge to recovery or cardiac transplantation. Diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers are of use in patients with compensated congestive heart failure in the outpatient setting but may be contraindicated in those presenting with fulminant heart failure and cardiovascular collapse. In patients manifesting with significant atrial or ventricular arrhythmias, specific antiarrhythmic agents (for example, amiodarone) should be administered and implantable cardioverter defibrillator placement considered.

Immunomodulation of patients with myocarditis is controversial. **Intravenous immune globulin** may have a role in the treatment of acute or fulminant myocarditis and **corticosteroids** have been reported to improve cardiac function, but the data are not convincing in children. Relapse has been noted in patients receiving immunosuppression who have been weaned from support. There are no studies to recommend specific antiviral therapies for myocarditis.

PROGNOSIS

The prognosis of symptomatic acute myocarditis in newborns is poor, and a 75% mortality has been reported. The prognosis is better for children and adolescents, although patients who have persistent evidence of DCM often progress to need for cardiac transplantation. Recovery of ventricular function has been reported in 10-50% of patients, however.

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Chapter 440

Diseases of the Pericardium

Robert L. Spicer and Stephanie M. Ware

The heart is enveloped in a bilayer membrane, the pericardium, which normally contains a small amount of serous fluid. The pericardium is not vital to normal function of the heart, and primary diseases of the pericardium are uncommon. However, the pericardium may be affected by a variety of conditions (Table 440-1), often as a manifestation of a systemic illness and can result in serious, even life-threatening, cardiac compromise.

440.1 Acute Pericarditis

Robert L. Spicer and Stephanie M. Ware

PATHOGENESIS

Inflammation of the pericardium may have only minor pathophysiologic consequences in the absence of significant fluid accumulation in the pericardial space. When the amount of fluid in the nondistensible pericardial space becomes excessive, pressure within the pericardium increases and is transmitted to the heart resulting in impaired filling. Although small to moderate amounts of pericardial effusion can be well tolerated and clinically silent, once the noncompliant pericardium has been distended maximally, any further fluid accumulation causes abrupt impairment of cardiac filling and is termed cardiac tamponade. When untreated, tamponade can lead to shock and death. Pericardial effusions may be serous/transudative, exudative/purulent, fibrinous, or hemorrhagic.

Table 440-1	Etiology of Pericardial Disease
CONGENITAL Absence (partial, complete) Cysts Mulibrey nanism (*TRIM 37* gene mutation) Camptodactyly-arthropathy-coxa vara-pericarditis syndrome (*PRG4* gene mutation)	
INFECTIOUS Viral (coxsackievirus B, Epstein-Barr virus, influenza, adenovirus, parvovirus, HIV, mumps) Bacterial (*Haemophilus influenzae*, streptococcus, pneumococcus, staphylococcus, meningococcus, mycoplasma, tularemia, listeria, leptospirosis, tuberculosis, Q-fever, salmonella) Immune complex (meningococcus, *H. influenzae*) Fungal (actinomycosis, histoplasmosis) Parasitic (toxoplasmosis, echinococcosis)	
NONINFECTIOUS Idiopathic Systemic inflammatory diseases (acute rheumatic fever, juvenile idiopathic arthritis, systemic lupus erythematosus, mixed connective tissue disorders, systemic sclerosis, Kawasaki disease, Churg-Strauss syndrome, Behçet syndrome, sarcoidosis, familial Mediterranean fever and other recurrent fever syndromes, pancreatitis, granulomatosis with polyangiitis) Metabolic (uremia, hypothyroidism, Gaucher disease, very-long-chain acyl-CoA dehydrogenase deficiency) Traumatic (surgical, catheter, blunt) Lymphomas, leukemia, radiation therapy Primary pericardial tumors	

CLINICAL MANIFESTATIONS

The most common symptom of acute pericarditis is chest pain, typically described as sharp/stabbing, positional, radiating, worse with inspiration, and relieved by sitting upright or prone. Cough, fever, dyspnea, abdominal pain, and vomiting are nonspecific symptoms associated with pericarditis. Additionally, signs and symptoms of organ system involvement may occur in the presence of generalized systemic disease.

Muffled or distant heart sounds, tachycardia, narrow pulse pressure, jugular venous distention, and a pericardial friction rub provide clues to the diagnosis of acute pericarditis. Cardiac tamponade is recognized by the excessive fall of systolic blood pressure (>10 mm Hg) with inspiration. This pulsus paradoxus can be assessed by careful auscultatory blood pressure determination (automated blood pressure cuffs are inadequate), arterial pressure line wave form, or pulse oximeter tracing inspection. Conditions other than cardiac tamponade, which may result in pulsus paradoxus include severe dyspnea, obesity, and positive pressure ventilator support.

DIAGNOSIS

The electrocardiogram is often abnormal in acute pericarditis although the findings are nonspecific. Low voltage QRS amplitude may be seen as a result of pericardial fluid accumulation. Tachycardia and abnormalities of the ST segments, PR segments, and T waves may be present as well.

Although the chest x-ray findings in a patient with pericarditis without effusion are usually normal, in the presence of a significant effusion, cardiac enlargement will be seen and cardiac contour may be unusual (Erlenmeyer flask or water bottle appearance) (Fig. 440-1). Echocardiography is the most sensitive technique for identifying the size and location of a pericardial effusion. Compression and collapse of the right atrium and/or right ventricle are present with cardiac tamponade (Fig. 440-2). Abnormal diastolic filling parameters have also been described in cases of tamponade.

DIFFERENTIAL DIAGNOSIS

Chest pain similar to that present in pericarditis can occur with lung diseases, especially pleuritis, and with gastroesophageal reflux. Pain related to myocardial ischemia is usually more severe, more prolonged, and occurs with exercise, allowing distinction from pericarditis-induced pain. The presence of a pericardial effusion by echocardiography is virtually diagnostic of pericarditis.

Figure 440-1 Water bottle silhouette. This chest radiograph shows marked cardiomegaly, also known as a water bottle silhouette, which is seen in the presence of large pericardial effusions. Also note the associated pulmonary edema from associated high left atrial and left ventricular filling pressures. *(Courtesy of Dr. Steven M. Selbst, Wilmington, DE; from Durani Y, Giordani K, Goudie BW: Myocarditis and pericarditis in children.* Pediatr Clin North Am *57:1281–1303, 2010, Fig 7.)*

Infectious Pericarditis

A number of viral agents are known to cause pericarditis, and the clinical course of the majority of these infections is mild and spontaneously resolving. The term acute benign pericarditis is synonymous for viral pericarditis. Agents identified as causing pericarditis include the enteroviruses, influenza, adenovirus, respiratory syncytial virus, and parvovirus. As the course of this illness is usually benign, symptomatic treatment with nonsteroidal antiinflammatory agents is often sufficient. Patients with large effusions and tamponade may require pericardiocentesis. Presumed viral but often idiopathic pericarditis may have an autoimmune component. In up to 30%, there may be recurrences of pericarditis. Treatment and/or prevention of recurrences with colchicine improve symptoms and avoid recurrences in most of these patients. Patients with idiopathic recurrent pericarditis may also respond to treatment with anakinra. If the condition becomes chronic or relapsing, surgical pericardiectomy or creation of a pericardial window may be necessary.

Echocardiography is useful in differentiating pericarditis from myocarditis, the latter of which will show evidence of diminished myocardial contractility or valvular dysfunction. Pericarditis and myocarditis may occur together in some cases of viral infection.

Purulent pericarditis, often caused by bacterial infections, has become much less common with the advent of new immunizations for haemophilus and pneumococcal disease. Historically, purulent pericarditis was seen in association with severe pneumonias, epiglottitis, meningitis, or osteomyelitis. Patients with purulent pericarditis are acutely ill. Unless the infection is recognized and treated expeditiously, the course can be fulminant, leading to tamponade and death. Tuberculous pericarditis is rare in developed countries, but can be seen as a relatively common complication of HIV infection in regions where tuberculosis is endemic and access to antiretroviral therapy is limited. Immune-complex mediated pericarditis is a rare complication that may result in a nonpurulent (sterile) effusion following systemic bacterial infections such as meningococcus or haemophilus.

Noninfectious Pericarditis

Systemic inflammatory diseases including autoimmune, rheumatologic, and connective tissue disorders may involve the pericardium and result in serous pericardial effusions. Pericardial inflammation may be a component of the type II hypersensitivity reaction seen in patients with acute rheumatic fever. It is often associated with rheumatic valvulitis and responds quickly to antiinflammatory agents including steroids. Tamponade is very uncommon (see Chapters 183.1 and 438).

Juvenile idiopathic arthritis, usually systemic onset disease, can manifest with pericarditis. Differentiating rheumatoid pericardial inflammation from that seen with systemic lupus erythematosus is difficult and requires careful rheumatologic evaluation. Aspirin and/or corticosteroids can result in rapid resolution of a pericardial effusion but may be needed on a chronic basis to prevent relapse. Many of the autoinflammatory recurrent fever syndromes present with pericarditis, usually with other manifestations of those disorders (Chapter 163).

Patients with chronic renal failure or hypothyroidism may have pericardial effusions and should be carefully screened with physical exam, and, if indicated, imaging studies, during the course of their illness should clinical suspicion arise.

Especially common in referral centers with hematology/oncology units is the presence of pericardial effusion related to neoplastic disease. Conditions resulting in effusion include Hodgkin disease, lymphomas, and leukemia. Radiation therapy directed to the mediastinum of patients with malignancy can result in pericarditis and later constrictive pericardial disease.

The postpericardiotomy syndrome occurs in patients having undergone cardiac surgery and is characterized by fever, lethargy, anorexia, irritability, and chest/abdominal discomfort beginning 7-14 days postoperatively. There can be associated pleural effusions and serologic evidence of elevated antiheart antibodies. Postpericardiotomy syndrome is effectively treated with aspirin, nonsteroidal inflammatory

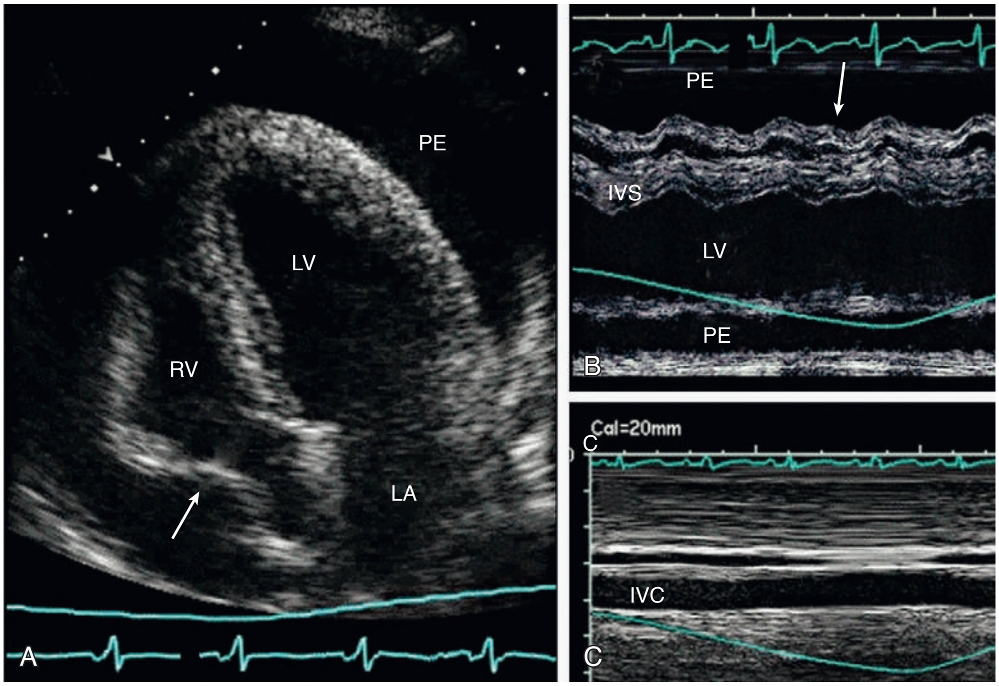

Figure 440-2 **Echocardiographic images of large pericardial effusion with features of tamponade.** **A,** Apical 4-chamber view of LV, LA, and RV that shows large PE with diastolic right-atrial collapse *(arrow).* **B,** M-mode image with cursor placed through RV, IVS, and LV in parasternal long axis. The view shows circumferential PE with diastolic collapse of RV free wall *(arrow)* during expiration. **C,** M-mode image from subcostal window in same patient that shows IVC plethora without inspiratory collapse. IVC, inferior vena cava; IVS, interventricular septum; LA, left atrium; LV, left ventricle; PE, pericardial effusion; RV, right ventricle. *(From Troughton RW, Asher CR, Klein AL: Pericarditis,* Lancet *363:717–727, 2004.)*

agents, and in severe cases, corticosteroids. Pericardial drainage is necessary in those patients with cardiac tamponade.

440.2 Constrictive Pericarditis

Robert L. Spicer and Stephanie M. Ware

Rarely, chronic pericardial inflammation can result in fibrosis, calcification, and thickening of the pericardium. Pericardial scarring may lead to impaired cardiac distensibility and filling and is termed constrictive pericarditis. Constrictive pericarditis can occur following recurrent or chronic pericarditis, cardiac surgery, or radiation to the mediastinum as a treatment for malignancies, most commonly Hodgkin disease or lymphoma.

Clinical manifestations of systemic venous hypertension predominate in cases of restrictive pericarditis. Jugular venous distention, peripheral edema, hepatomegaly, and ascites may precede signs of more significant cardiac compromise such as tachycardia, hypotension, and pulsus paradoxus. A pericardial knock, rub, and distant heart sounds might be present on auscultation. Abnormalities of liver function tests, hypoalbuminemia, hypoproteinemia, and lymphopenia may be present. On occasion, x-rays of the chest demonstrate calcifications of the pericardium.

Constrictive pericarditis may be difficult to distinguish clinically from restrictive cardiomyopathy as both conditions result in impaired myocardial filling (see Chapter 439.3). Echocardiography may be helpful in distinguishing constrictive pericardial disease from restrictive cardiomyopathy, but magnetic resonance imaging and computed tomographic imaging are more sensitive in detecting abnormalities of the pericardium. In rare instances, exploratory thoracotomy with direct examination of the pericardium may be required to confirm the diagnosis.

Although acute pericardial constriction is reported to respond to antiinflammatory agents, the more typical chronic constrictive pericarditis will respond only to surgical pericardiectomy with extensive resection of the pericardium.

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Chapter 441
Tumors of the Heart
Robert L. Spicer and Stephanie M. Ware

Although cardiac tumors occur rarely in pediatric patients, they may result in serious hemodynamic or electrophysiologic abnormalities depending on tumor type and location.

The vast majority of tumors originating from the heart are benign. **Rhabdomyomas** are the most common pediatric cardiac tumors and are associated with tuberous sclerosis in 70-95% of cases (see Chapter 596.2). Rhabdomyomas may occur at any age, from fetal life through late adolescence. They are often multiple, can occur in any cardiac chamber, and originate within the myocardium extending, often, into the atrial or ventricular cavities (Fig. 441-1). Depending on their location and size, they can result in inflow or outflow obstruction leading to cyanosis or cardiac failure; many are asymptomatic. Atrial and ventricular arrhythmias have been reported with rhabdomyomas, and on occasion, ventricular preexcitation (Wolff-Parkinson-White) is present on electrocardiogram.

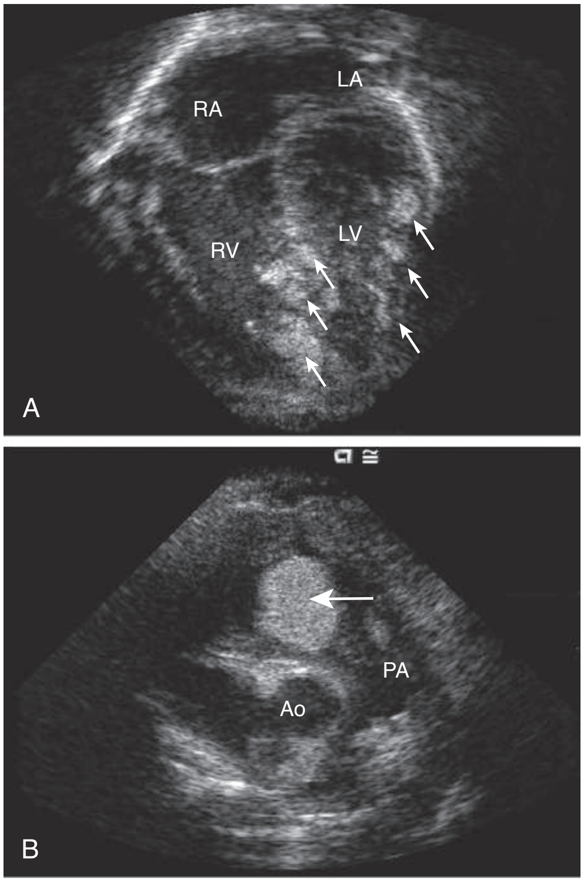

Figure 441-1 Echocardiograms demonstrating rhabdomyomas. **A,** Apical 4-chamber view showing multiple rhabdomyomas *(arrows)* within the septum and left ventricular myocardium. **B,** Short-axis view showing a large rhabdomyoma *(arrow)* extending into the right ventricular outflow tract. Ao, ascending aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

Fibromas are the second most common pediatric cardiac tumor, and in contrast to rhabdomyomas, are usually solitary and intramyocardial. They can, by size and location, lead to heart failure, cyanosis, or rhythm disturbances. Loss of the tumor suppressor *PTCH1* is associated with the development of cardiac fibromas in sporadic cases. There is an increased incidence in patients with **Gorlin syndrome** (3%).

Myxomas, the most common cardiac tumor seen in adults, are infrequent in the pediatric population. Myxomas are predominantly intraatrial, appear pedunculated, and are rather mobile. They may cause obstruction to inflow or outflow and may present with a murmur, heart failure, or syncope. On occasion, atrial myxomas are associated with systemic symptoms of fever, malaise, and arthralgia. **Carney complex** is a familial autosomal dominant multiple neoplasia (often endocrine: pituitary adenoma, thyroid, testis, ovarian) and lentiginosis syndrome in which cardiac myxomas can occur at a young age in any or all cardiac chambers. *PRKAR1A* is the gene mutation in some families.

Other benign tumors include hemangiomas, Purkinje cell tumors, papillomas, lipomas, and mesotheliomas. Depending on their location, these benign tumors can result in valvular function abnormalities, myocardial dysfunction, or heart block and other arrhythmias.

Malignant pediatric cardiac tumors are far less common than benign tumors (75% vs. 25%), and the vast majority of such malignancies are sarcomas including angiosarcomas, rhabdosarcomas, or fibrosarcomas. Lymphomas and pheochromocytomas are reported but rare. Tumors originating from noncardiac sources that invade, extend, or metastasize to the heart are more commonly seen than primary malignant cardiac tumors. In pediatric patients, Wilms tumor and lymphoma/leukemia are the most common causes of such secondary tumors.

Although the manifestations of cardiac tumors in pediatric patients are protean, when a tumor is suspected, noninvasive imaging with echocardiography and/or magnetic resonance imaging may be diagnostic and can determine tumor type, location, extent, and hemodynamic impact. Electrocardiogram and Holter studies are valuable adjuncts when rhythm abnormalities are suspected. Cardiac catheterization is rarely indicated, but may be utilized to confirm tumor location, assess intracardiac hemodynamics, and perform biopsy for histologic assessment. Risks including blood loss, perforation, arrhythmia, and vessel injury should be considered when discussing catheterization and biopsy.

Because the natural history of rhabdomyomas is one of spontaneous diminution or complete resolution, treatment of the majority of cardiac tumors in pediatric patients is usually unnecessary. Everolimus, an inhibitor of the mammalian target of rapamycin, may enhance resolution in symptomatic patients with cardiac rhabdomyomas. Careful clinical follow-up and imaging are important. Antiarrhythmic medications may be prescribed to control rhythm disorders. Surgical removal of a cardiac tumor may be indicated to relieve obstruction, improve myocardial or valve function, or control arrhythmias. Heart transplantation has been performed in cases of unresectable tumors with significant hemodynamic compromise. Wilms tumors extending from the inferior vena cava into the atrium may require cardiopulmonary bypass support during the course of primary resection of the renal tumor. Radiation or chemotherapy can improve cardiac function in rare cases of lymphoma or leukemia compressing the heart with hemodynamic compromise.

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Section 7

Cardiac Therapeutics

Chapter 442

Heart Failure

Daniel Bernstein

Heart failure occurs when the heart cannot deliver adequate cardiac output to meet the metabolic needs of the body. In the early stages of heart failure, various compensatory mechanisms are evoked to maintain normal metabolic function. When these mechanisms become ineffective, increasingly severe clinical manifestations result (see Chapter 70).

PATHOPHYSIOLOGY

The heart can be viewed as a pump with an output proportional to its filling volume and inversely proportional to the resistance against which it pumps. As ventricular end-diastolic volume increases, a healthy heart increases cardiac output until a maximum is reached and cardiac output can no longer be augmented (the Frank-Starling principle; Fig. 442-1). The increased stroke volume obtained in this manner is a result of stretching of myocardial fibers, but it also results in increased wall tension, which elevates myocardial oxygen consumption. Hearts working under various types of stress function along different Frank-Starling curves. Cardiac muscle with compromised intrinsic contractility requires a greater degree of dilation to produce increased stroke volume and does not achieve the same maximal

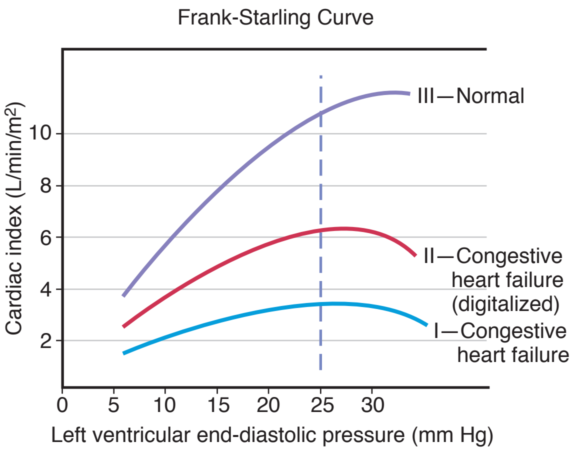

Figure 442-1 **The Frank-Starling relationship.** As left ventricular end-diastolic (LVED) pressure increases, the cardiac index increases, even in the presence of congestive heart failure, until a critical level of LVED pressure is reached. Adding an inotropic agent (digoxin) shifts the curve from I to II. *(From Gersony WM, Steep CN. In Dickerman JD, Lucey JF, editors:* Smith's The critically ill child: diagnosis and medical management, *ed 3, Philadelphia, 1984, WB Saunders.)*

cardiac output as normal myocardium does. If a cardiac chamber is already dilated because of a lesion causing increased preload (e.g., a left-to-right shunt or valvular insufficiency), there is little room for further dilation as a means of augmenting cardiac output. The presence of lesions that result in increased afterload to the ventricle (aortic or pulmonic stenosis, coarctation of the aorta) decreases cardiac performance, thereby resulting in a depressed Frank-Starling relationship.

Systemic oxygen transport is calculated as the product of cardiac output and systemic oxygen content. **Cardiac output** can be calculated as the product of heart rate and stroke volume. The primary determinants of stroke volume are the afterload (pressure work), preload (volume work), and contractility (intrinsic myocardial function). Abnormalities in heart rate can also compromise cardiac output; for example, tachyarrhythmias shorten the diastolic time interval for ventricular filling. Alterations in the oxygen-carrying capacity of blood (e.g., anemia or hypoxemia) also lead to a decrease in systemic oxygen transport and, if compensatory mechanisms are inadequate, can result in decreased delivery of substrate to tissues.

In some cases of heart failure, cardiac output is normal or increased, yet because of decreased systemic oxygen content (secondary to anemia) or increased oxygen demands (secondary to hyperventilation, hyperthyroidism, or hypermetabolism), an inadequate amount of oxygen is delivered to meet the body's needs. This condition, high-output failure, results in the development of signs and symptoms of heart failure when there is no basic abnormality in myocardial function and cardiac output is greater than normal. It is also seen with large systemic arteriovenous fistulas. These conditions reduce peripheral vascular resistance and cardiac afterload and increase myocardial contractility. Heart "failure" results when the demand for cardiac output exceeds the ability of the heart to respond. Chronic severe high-output failure may eventually result in a decrease in myocardial performance as the metabolic requirements of the myocardium are not met.

There are multiple systemic compensatory mechanisms used by the body to adapt to chronic heart failure. Some are mediated at the molecular/cellular level, such as upregulation or downregulation of various metabolic pathway components leading to changes in efficiency of oxygen and other substrate utilization. Others are mediated by neurohormones such as the renin–angiotensin system and the sympathoadrenal axis. One of the principal mechanisms for increasing cardiac output is an increase in sympathetic tone secondary to increased secretion of circulating epinephrine by the adrenals and increased release of norepinephrine at the neuromuscular junction. The initial beneficial effects of sympathetic stimulation include an increase in heart rate and myocardial contractility, mediated by these hormones' action on cardiac β-adrenergic receptors, increasing cardiac output. These hormones also cause vasoconstriction, mediated by their action on peripheral arterial α-adrenergic receptors. Some vascular beds may constrict more readily than others, so that blood flow is redistributed from the cutaneous, visceral, and renal beds to the heart and brain. Whereas these acute effects are beneficial, chronically increased sympathetic stimulation can have deleterious effects, including hypermetabolism, increased afterload, arrhythmogenesis, and increased myocardial oxygen requirements. Peripheral vasoconstriction can result in decreased renal, hepatic, and gastrointestinal tract function. Chronic exposure to circulating catecholamines leads to a decrease in the number of cardiac β-adrenergic receptors (downregulation) and also causes direct myocardial cell damage. Thus, therapeutic agents for heart failure are directed at restoring balance to these neuroendocrine systems.

CLINICAL MANIFESTATIONS

The clinical manifestations of heart failure depend in part on the degree of the child's cardiac reserve. A critically ill infant or child who has exhausted the compensatory mechanisms to the point that cardiac output is no longer sufficient to meet the basal metabolic needs of the body will be symptomatic at rest. Other patients may be comfortable when quiet but are incapable of increasing cardiac output in response to even mild activity without experiencing significant symptoms. Conversely, it may take rather vigorous exercise to compromise cardiac function in children who have less severe heart disease. A thorough history is extremely important in making the diagnosis of heart failure and in evaluating the possible causes. Parents who observe their child on a daily basis may not recognize subtle changes that have occurred over the course of days or weeks. Gradually worsening perfusion or increasing respiratory effort may not be recognized as an abnormal finding. Edema may be passed off as normal weight gain, and exercise intolerance as lack of interest in an activity. The history of a young infant should also focus on feeding (see Chapter 416). An infant with heart failure often takes less volume per feeding, becomes dyspneic while sucking, and may perspire profusely. Eliciting a history of fatigue in an older child requires detailed questions about activity level and its course over several months.

In children, the signs and symptoms of heart failure may be similar to those in adults and include fatigue, effort intolerance, anorexia, dyspnea, and cough. Many children, however, especially adolescents, may have primarily abdominal symptoms (abdominal pain, nausea, anorexia) and a surprising lack of respiratory complaints. Attention to the cardiovascular system may come only after an abdominal roentgenogram unexpectedly catches the lower end of an enlarged heart. The elevation in systemic venous pressure may be gauged by clinical assessment of jugular venous pressure and liver enlargement. Orthopnea and basilar rales are variably present; edema is usually discernible in dependent portions of the body, or anasarca may be present. Cardiomegaly is invariably noted. A gallop rhythm is common; when ventricular dilation is advanced, the holosystolic murmur of mitral or tricuspid valve regurgitation may be heard.

In infants, heart failure may be difficult to distinguish from other causes of respiratory distress. Prominent manifestations include tachypnea, feeding difficulties, poor weight gain, excessive perspiration, irritability, weak cry, and noisy, labored respirations with intercostal and subcostal retractions, as well as flaring of the alae nasi. The signs of cardiac-induced pulmonary congestion may be indistinguishable from those of bronchiolitis; wheezing is often a more prominent finding in young infants with heart failure than rales. Pneumonitis with or without atelectasis is common, especially in the right middle and lower lobes, a result of bronchial compression by the enlarged heart. Hepatomegaly usually occurs, and cardiomegaly is invariably present. In spite of pronounced tachycardia, a gallop rhythm can frequently be recognized. The other auscultatory signs are those produced by the underlying cardiac lesion. Clinical assessment of jugular venous pressure in infants may be difficult because of the shortness of the neck and the difficulty of observing a relaxed state; palpation of an enlarged

Table 442-1	Etiology of Heart Failure
FETAL Severe anemia (hemolysis, fetal-maternal transfusion, parvovirus B19–induced anemia, hypoplastic anemia) Supraventricular tachycardia Ventricular tachycardia Complete heart block Severe Ebstein anomaly or other severe right-sided lesions Myocarditis	
PREMATURE NEONATE Fluid overload Patent ductus arteriosus Ventricular septal defect Cor pulmonale (bronchopulmonary dysplasia) Hypertension Myocarditis Genetic cardiomyopathy	
FULL-TERM NEONATE Asphyxial cardiomyopathy Arteriovenous malformation (vein of Galen, hepatic) Left-sided obstructive lesions (coarctation of aorta, hypoplastic left heart syndrome) Large mixing cardiac defects (single ventricle, truncus arteriosus) Myocarditis Genetic cardiomyopathy	
INFANT-TODDLER Left-to-right cardiac shunts (ventricular septal defect) Hemangioma (arteriovenous malformation) Anomalous left coronary artery Genetic or metabolic cardiomyopathy Acute hypertension (hemolytic-uremic syndrome) Supraventricular tachycardia Kawasaki disease Myocarditis	
CHILD-ADOLESCENT Rheumatic fever Acute hypertension (glomerulonephritis) Myocarditis Thyrotoxicosis Hemochromatosis-hemosiderosis Cancer therapy (radiation, doxorubicin) Sickle cell anemia Endocarditis Cor pulmonale (cystic fibrosis) Genetic or metabolic cardiomyopathy (hypertrophic, dilated)	

liver is a more reliable sign. Edema may be generalized and usually involves the eyelids as well as the sacrum and less often the legs and feet. The differential diagnosis is age dependent (Table 442-1).

DIAGNOSIS

X-rays of the chest show cardiac enlargement. Pulmonary vascularity is variable and depends on the cause of the heart failure. Infants and children with large left-to-right shunts have exaggeration of the pulmonary arterial vessels to the periphery of the lung fields, whereas patients with cardiomyopathy may have a relatively normal pulmonary vascular bed early in the course of disease. Fluffy perihilar pulmonary markings suggestive of venous congestion and acute pulmonary edema are seen only with more severe degrees of heart failure. Cardiac enlargement is often noted as an unexpected finding on a chest roentgenogram performed to evaluate for a possible pulmonary infection, bronchiolitis, or asthma.

Chamber hypertrophy noted by electrocardiography may be helpful in assessing the cause of heart failure but does not establish the diagnosis. In cardiomyopathies, left or right ventricular ischemic changes may correlate with other noninvasive parameters of ventricular function. Low-voltage QRS morphologic characteristics with ST-T–wave abnormalities may also suggest myocardial inflammatory disease, but can be seen with pericarditis as well. The electrocardiogram is the best tool for evaluating rhythm disorders as a potential cause of heart failure, especially tachyarrhythmias.

Echocardiography is the standard technique for assessing ventricular function. The most commonly used parameter in children is fractional shortening (a single dimensional variable), determined as the difference between end-systolic and end-diastolic diameter divided by end-diastolic diameter. Normal fractional shortening is between approximately 28% and 42%. In adults, the most commonly used parameter is ejection fraction (which uses 2-dimensional data to calculate a 3-dimensional volume) and the normal range is 55-65%. In children with right ventricular enlargement or other cardiac pathology resulting in flattening of the interventricular septum, ejection fraction is used because fractional shortening measured in the standard echocardiographic short-axis view will not be accurate. Doppler studies can also be used to estimate cardiac output. Doppler assessment of transmitral flow can also be used as a noninvasive assessment of diastolic function. Doppler tissue imaging can assess not only cardiac function, but wall motion abnormalities that can interfere with normal synchronous cardiac contraction. Magnetic resonance angiography is also very useful in quantifying left and right ventricular function, volume and mass as well as coronary artery anatomy. If valvar regurgitation is present, magnetic resonance angiography can quantify the regurgitant fraction.

Arterial oxygen levels may be decreased when ventilation–perfusion inequalities occurs secondary to pulmonary edema. When heart failure is severe, respiratory or metabolic acidosis, or both, may be present. Infants with heart failure often display hyponatremia as a result of renal water retention. Chronic diuretic treatment can decrease serum sodium levels further. **Serum B-type natriuretic peptide,** a cardiac neurohormone released in response to increased ventricular wall tension, is elevated in adult patients with congestive heart failure. In children, B-type natriuretic peptide may be elevated in patients with heart failure as a result of systolic dysfunction (cardiomyopathy), as well as in children with volume overload (left-to-right shunts such as ventricular septal defect).

TREATMENT

The underlying cause of cardiac failure must be removed or alleviated if possible. If the cause is a congenital cardiac anomaly amenable to surgery, medical treatment of the heart failure is indicated to prepare the patient for surgery. With today's excellent outcomes of primary surgical repair of congenital heart defects, even in the neonatal period, few children require aggressive heart failure management to "grow big enough for surgery." In contrast, if the cause of heart failure is cardiomyopathy, medical management provides temporary relief from symptoms and may allow the patient to recover if the insult is reversible (e.g., myocarditis). If the lesion is not reversible, heart failure management usually allows the child to return to normal activities for some period and delay, sometimes for months or years, the need for heart transplantation.

General Measures

Strict bed rest is rarely necessary except in extreme cases, but it is important that the child be allowed to rest during the day as needed and sleep adequately at night. Some older patients feel better sleeping in a semi-upright position, using several pillows (orthopnea). For infants with heart failure, an infant chair may be advisable. After patients begin to respond to treatment, restrictions on activities can often be modified within the context of the specific diagnosis and the patient's ability. Formal cardiopulmonary exercise testing can be used to assess the patient's ability to perform exercise in a controlled environment and is useful for recommending rational exercise restrictions. For patients with pulmonary edema, positive pressure ventilation may be required along with other drug therapy. For those in low-output heart failure, positive pressure ventilation can significantly reduce total body oxygen consumption by eliminating the work of breathing, and help to reverse metabolic acidosis. β-Adrenergic agonists such as dopamine, dobutamine, and epinephrine are usually used in combination

with phosphodiesterase inhibitors such as milrinone. If the blood pressure will allow, afterload-reducing agents (nitroprusside, angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs]) may be beneficial. These agents are initiated in an intensive care setting with proper invasive monitoring of central venous and arterial blood pressure.

Diet

Infants with heart failure usually fail to thrive because of a combination of increased metabolic demands and decreased caloric intake. Increasing daily calories is an important aspect of their management. Increasing the number of calories per ounce of infant formula (or supplementing breastfeeding) may be beneficial. Many infants do not tolerate an increase beyond 24 calories/oz because of diarrhea or because these formulas provide too large a solute load for compromised kidneys.

Severely ill infants and children may lack sufficient strength for effective sucking because of extreme fatigue, rapid respirations, and generalized weakness. In these circumstances, nasogastric feedings may be helpful. In many patients with cardiac enlargement, gastroesophageal reflux is a major problem. The use of continuous drip nasogastric feedings at night, administered by pump, may improve caloric intake while decreasing problems with reflux. Occasionally, especially in infants with heart failure caused by complex congenital heart disease, medical or surgical intervention to correct reflux is necessary (Nissen fundoplication). Continued malnutrition may be an important factor in the decision to undertake earlier surgical intervention in patients who have an operable congenital heart lesion or for listing for transplantation in patients with cardiomyopathy.

The use of low-sodium formulas in the routine management of infants with heart failure is not recommended because these preparations are often poorly tolerated and may exacerbate diuretic-induced hyponatremia. Human breast milk is the ideal low-sodium nutritional source. The use of more potent diuretic agents allows more palatable standard formulas to be used for nutrition while controlling salt and water balance by chronic diuretic administration. Most older children can be managed with “no added salt” diets and abstinence from foods containing large amounts of sodium. A strict, extremely-low-sodium diet is rarely required, and rarely adhered to.

Diuretics

These agents interfere with reabsorption of water and sodium by the kidneys, which results in a reduction in circulating blood volume and thereby reduces pulmonary fluid overload and ventricular filling pressure. Diuretics are usually the first mode of therapy initiated in patients with congestive heart failure.

Furosemide is the most commonly used diuretic in pediatric patients with heart failure. It inhibits the reabsorption of sodium and chloride in the distal tubules and the loop of Henle. Patients requiring acute diuresis should be given intravenous or intramuscular furosemide at an initial dose of 1-2 mg/kg, which usually results in rapid diuresis and prompt improvement in clinical status, particularly if symptoms of pulmonary congestion are present. Chronic furosemide therapy is then prescribed at a dose of 1-4 mg/kg/24 hr given between 1 and 4 times a day. Careful monitoring of electrolytes is necessary with long-term furosemide therapy because of the potential for significant loss of potassium. Potassium chloride supplementation is usually required unless the potassium-sparing diuretic spironolactone is given concomitantly. Chronic administration of furosemide may cause contraction of the extracellular fluid compartment and result in “contraction alkalosis” (see Chapter 55.7). Diuretic-induced hyponatremia may become difficult to manage in patients with severe heart failure.

Spironolactone is an inhibitor of aldosterone and enhances potassium retention, often eliminating the need for oral potassium supplementation, which is frequently poorly tolerated. This drug is usually given orally in 2 divided doses of 2 mg/kg/24 hr. Combinations of spironolactone and chlorothiazide are sometimes used for convenience. Adults with heart failure have improved survival when an aldosterone inhibitor is included in the diuretic regimen.

Chlorothiazide is also used for diuresis in children with heart failure. It is less immediate in action and less potent than furosemide, and it affects the reabsorption of electrolytes in the renal tubules only. The usual dose is 10-40 mg/kg/24 hr in 2 divided doses. Potassium supplementation is often required if this agent is used alone.

Afterload Reducers, Including Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

These 2 groups of drugs reduce ventricular afterload by decreasing peripheral vascular resistance and thereby improving myocardial performance. Some of these agents also decrease systemic venous tone, which significantly reduces preload. Afterload reducers are especially useful in children with heart failure secondary to cardiomyopathy and in patients with severe mitral or aortic insufficiency. They may also be effective in patients with heart failure caused by left-to-right shunts. They are not generally used in the presence of stenotic lesions of the left ventricular outflow tract because of concern over coronary perfusion. ACEIs and ARBs may have additional beneficial effects on cardiac remodeling independent of their influence on afterload by directly influencing cardiac intracellular signaling pathways. In adult patients with dilated cardiomyopathy, the addition of an ACEI to standard medical therapy reduces both morbidity and mortality. Afterload-reducing agents are most often used in conjunction with other anticongestive drugs such as diuretics and, in some patients, digoxin.

Intravenously administered agents such as nitroprusside should be administered only in an intensive care setting and for as short a time as possible. Nitroprusside’s short intravenous half-life makes it ideal for titrating the dose in critically ill patients. Peripheral arterial vasodilation and afterload reduction are the major effects, but venodilation causing a decrease in venous return to the heart may also be beneficial. Blood pressure must be continuously monitored because sudden hypotension can occur. Consequently, nitroprusside is contraindicated in patients with preexisting hypotension. As the drug is metabolized, small amounts of circulating cyanide are produced and detoxified in the liver to thiocyanate, which is excreted in urine. When high doses of nitroprusside are administered for several days, toxic symptoms related to thiocyanate poisoning may occur (fatigue, nausea, disorientation, acidosis, and muscular spasm). If nitroprusside use is prolonged, blood thiocyanate levels should be monitored. Phosphodiesterase inhibitors (see later) are also excellent, although somewhat less-potent afterload-reducing agents, without the toxicity of nitroprusside.

The orally active ACEIs captopril and enalapril produce arterial dilation by blocking the production of angiotensin II, thereby resulting in significant afterload reduction. Venodilation and consequent preload reduction also have been reported. In addition, these agents interfere with aldosterone production and therefore also help control salt and water retention. ACEIs have additional beneficial effects on cardiac structure and function that may be independent of their effect on afterload. The oral dose for captopril is 0.3-6 mg/kg/24 hr given in 3 divided doses; for enalapril the oral dose is 0.05-0.5 mg/kg/24 hr given in 1 or 2 daily doses. Adverse reactions to ACEIs include hypotension and its sequelae (weakness, dizziness, syncope) and hyperkalemia. A maculopapular pruritic rash is encountered in a small number of patients, but the drug may be continued because the rash often disappears spontaneously with time. Neutropenia, renal toxicity, and chronic cough also occur.

Digitalis Glycosides

Digoxin, once the mainstay of heart failure management in both children and adults, is currently used less frequently, as a result of the introduction of newer therapies and the recognition of its potential toxicities. Many cardiologists will use digitalis as an adjunct to ACEIs and diuretics in patients with symptomatic heart failure, whereas others have moved away from its use altogether. Despite multiple clinical studies, predominantly in adults, the controversy over digitalis remains.

Digoxin is the digitalis glycoside used most often in pediatric patients. It has a half-life of 36 hr and it is absorbed well by the gastrointestinal tract (60-85%), even in infants. An initial effect can be seen as early as 30 min after administration, and the peak effect for oral digoxin occurs at ≈2-6 hr. When the drug is administered intravenously, the initial effect is seen in 15-30 min, and the peak effect occurs at 1-4 hr. The kidney eliminates digoxin, so dosing must be adjusted according to the patient's renal function. The half-life of digoxin may be up to 6 days in patients with anuria because slower hepatic excretion pathways are used in these patients.

Rapid digitalization of infants and children in heart failure may be carried out intravenously. The dose depends on the patient's age (Table 442-2). The recommended digitalization schedule is to give half the total digitalizing dose immediately and the succeeding 2 one-quarter doses at 12-hr intervals later. The electrocardiogram must be closely monitored and rhythm strips obtained before each of the 3 digitalizing doses. Digoxin should be discontinued if a new rhythm disturbance is noted. Prolongation of the P-R interval is not necessarily an indication to withhold digitalis, but a delay in administering the next dose or a reduction in the dosage should be considered, depending on the patient's clinical status. Minor ST segment or T-wave changes are commonly noted with digitalis administration and should not affect the digitalization regimen. Baseline serum electrolyte levels should be measured before and after digitalization. Hypokalemia and hypercalcemia exacerbate digitalis toxicity. Because hypokalemia is relatively common in patients receiving diuretics, potassium levels should be monitored closely in those receiving a potassium-wasting diuretic in combination with digitalis. In patients with active myocarditis, some cardiologists recommend avoiding digitalis altogether and if used, maintenance digitalis should be started at half the normal dose without digitalization due to the increased risk of arrhythmia in these patients.

Patients who are not critically ill may be given digitalis initially by the oral route, and in most instances digitalization is completed within 24 hr. When slow digitalization is desirable, for example, in the

Table 442-2 Dosage of Drugs Commonly Used for the Treatment of Congestive Heart Failure

DRUG	DOSAGE
DIGOXIN	
Digitalization (½ initially, followed by ¼ q12h × 2)	Premature: 20 μg/kg Full-term neonate (up to 1 mo): 20-30 μg/kg Infant or child: 25-40 μg/kg Adolescent or adult: 0.5-1 mg in divided doses NOTE: These doses are PO; IV dose is 75% of PO dose
Maintenance digoxin	5-10 μg/kg/day, divided q12h Trough serum level: 1.5-3.0 ng/mL <6 mo old; 1-2 ng/mL >6 mo old NOTE: These doses are PO; IV dose is 75% of PO dose
DIURETICS	
Furosemide (Lasix)	IV: 0.5-2 mg/kg/dose PO: 1-4 mg/kg/day, divided qd-qid
Bumetanide (Bumex)	IV: 0.01-0.1 mg/kg/dose PO: 0.01-0.1 mg/kg/day q24-48h
Chlorothiazide (Diuril)	PO: 20-40 mg/kg/day, divided bid or tid
Spironolactone (Aldactone)	PO: 1-3 mg/kg/day, divided bid or tid
Nesiritide (B-type natriuretic peptide)	IV: 0.001-0.03 μg/kg/min
ADRENERGIC AGONISTS (ALL IV)	
Dobutamine	2-20 μg/kg/min
Dopamine	2-30 μg/kg/min
Isoproterenol	0.01-0.5 μg/kg/min
Epinephrine	0.1-1.0 μg/kg/min
Norepinephrine	0.1-2.0 μg/kg/min
PHOSPHODIESTERASE INHIBITORS (ALL IV)	
Milrinone	0.25-1.0 μg/kg/min
AFTERLOAD-REDUCING AGENTS	
Captopril (Capoten), all PO	Prematures: start at 0.01 mg/kg/dose; 0.1-0.4 mg/kg/day, divided q6-24h Infants: 1.5-6 mg/kg/day, divided q6-12h Children: 2.5-6 mg/kg/day, divided q6-12h
Enalapril (Vasotec), all PO	0.08-0.5 mg/kg/day, divided q12-24h
Hydralazine (Apresoline)	IV: 0.1-0.5 mg/kg/dose (maximum: 20 mg) PO: 0.75-5 mg/kg/day, divided q6-12h
Nitroglycerin	IV: 0.25-0.5 μg/kg/min start; increase to 20 μg/kg/min maximum
Nitroprusside (Nipride)	IV: 0.5-8 μg/kg/min
β-ADRENERGIC BLOCKERS	
Carvedilol (Coreg)	PO: initial dose 0.1 mg/kg/day (maximum: 6.25 mg) divided bid, increase gradually (usually 2 wk intervals) to maximum of 0.5-1 mg/kg/day over 8-12 wk as tolerated; adult maximal dose: 50-100 mg/day
Metoprolol (Lopressor, Toprol-XL)	PO, nonextended release form: 0.2 mg/kg/day divided bid, increase gradually (usually 2 wk intervals) to maximum dose of 1-2 mg/kg/day PO, extended release form (Toprol-XL) is given once daily; adult initial dose 25 mg/day, maximum dose is 200 mg/day

Note: Pediatric doses based on weight should not exceed adult doses. Because recommendations may change, these doses should always be double-checked. Doses may also need to be modified in any patient with renal or hepatic dysfunction.

Maintenance digitalis therapy is started ≈12 hr after full digitalization. The daily dosage, one quarter of the total digitalizing dose, is divided in 2 and given at 12-hr intervals. The oral maintenance dose is usually 20-25% higher than when digoxin is used parenterally (see Table 442-2). The normal daily dose of digoxin for older children (>5 yr of age) calculated by body weight should not exceed the usual adult dose of 0.125-0.5 mg/24 hr.

immediate postoperative period, initiation of a maintenance digoxin schedule without a previous loading dose achieves full digitalization in 7-10 days.

Measurement of **serum digoxin levels** is useful under several circumstances: (1) when an unknown amount of digoxin has been administered or ingested accidentally, (2) when renal function is impaired or if drug interactions are possible, (3) when questions regarding compliance are raised, and (4) when a toxic response is suspected. Therapeutic trough blood levels are usually 2-4 ng/mL in infants and 1-2 ng/mL in older children. Exceeding these levels does not generally add significantly to the management of heart failure and only increases the risk of toxicity. In suspected toxicity, elevated serum digoxin levels are not in themselves diagnostic of toxicity but must be interpreted as an adjunct to other clinical and electrocardiographic findings (rhythm and conduction disturbances). Hypokalemia, hypomagnesemia, hypercalcemia, cardiac inflammation secondary to myocarditis, and prematurity may all potentiate digitalis toxicity. A cardiac arrhythmia that develops in a child who is taking digitalis may also be related to the primary cardiac disease rather than the drug, however, any arrhythmia occurring after the institution of digitalis therapy must be considered to be drug related until proven otherwise. There are many drugs that interact with digoxin and may increase levels or risk of toxicity, so care should be taken when a patient on digoxin is being considered for additional pharmacologic therapy of any kind.

α- and β-Adrenergic Agonists

These drugs are usually administered in an intensive care setting, where the dose can be carefully titrated to hemodynamic response. Continuous determinations of arterial blood pressure and heart rate are performed; measuring serial mixed venous oxygen saturations or cardiac output directly with a pulmonary thermodilution (Swan-Ganz) catheter may be helpful in assessing drug efficacy, although this technique is much less commonly used in children compared to adults. Though extremely efficacious in the acute intensive care setting, long-term administration of adrenergic agonists has been shown to increase morbidity and mortality in adults with heart failure and is usually avoided unless the patient is totally dependent on these agents.

Dopamine is a predominantly β-adrenergic receptor agonist, but it has α-adrenergic effects at higher doses. Dopamine has less chronotropic and arrhythmogenic effect than the pure β-agonist isoproterenol does. In addition, it results in selective renal vasodilation because of its interaction with renal dopamine receptors, which is particularly useful in patients with the compromised kidney function that is often associated with low cardiac output, although some recent studies in adults question the efficacy of dopamine for this indication. At a dose of 2-10 µg/kg/min, dopamine results in increased contractility with little peripheral vasoconstrictive effect. If the dose is increased beyond 15 µg/kg/min, however, its peripheral α-adrenergic effects may result in vasoconstriction. Fenoldopam is a dopamine DA1 receptor agonist and is used at a low dose (0.03 µg/kg/min) to increase renal blood flow and urine output. It can cause hypotension, so blood pressure should be carefully monitored.

Dobutamine, a derivative of dopamine, is also useful in treating low cardiac output. It has direct inotropic effects and causes a moderate reduction in peripheral vascular resistance. Dobutamine can be used alone or as an adjunct to dopamine therapy to avoid the vasoconstrictive effects of higher-dose dopamine. Dobutamine is also less likely to cause cardiac rhythm disturbances than isoproterenol is. The usual dose is 2-20 µg/kg/min.

Isoproterenol is a pure β-adrenergic agonist that has a marked chronotropic effect; it is most effective in patients with slow heart rates and is less commonly used in patients with heart failure and normal or increased heart rates, because of the increased risk of arrhythmias.

Epinephrine is a mixed α- and β-adrenergic receptor agonist that is usually reserved for patients with cardiogenic shock and low arterial blood pressure. Although epinephrine can raise blood pressure effectively, it also increases systemic vascular resistance, and therefore increases the afterload against which the heart has to work and is associated with an increased risk of arrhythmia.

Phosphodiesterase Inhibitors

Milrinone is useful in treating patients with low cardiac output who are refractory to standard therapy and has been shown to be highly effective in managing the low-output state present in children after open heart surgery. It works by inhibition of phosphodiesterase, which prevents the degradation of intracellular cyclic adenosine monophosphate. Milrinone has both positive inotropic effects on the heart and peripheral vasodilatory effects and has generally been used as an adjunct to dopamine or dobutamine therapy in the intensive care unit. It is given by intravenous infusion at 0.25-1 µg/kg/min, sometimes with an initial loading dose of 50 µg/kg. A major side effect is hypotension secondary to peripheral vasodilation, especially when a loading dose is used. The hypotension can generally be managed by the administration of intravenous fluids to restore adequate intravascular volume.

Chronic Treatment with β-Blockers

Studies in adults with dilated cardiomyopathy show that β-adrenergic blocking agents, introduced gradually as part of a comprehensive heart failure treatment program, improve exercise tolerance, decrease hospitalizations, and reduce overall mortality. The agents most often used are carvedilol, an agent with both α- and β-adrenergic receptor blocking as well as free radical scavenging effects and metoprolol, a β_1-adrenergic receptor selective antagonist. β-Blockers are used for the chronic treatment of patients with heart failure and should not be administered when patients are still in the acute phase of heart failure (i.e., receiving intravenous adrenergic agonist infusions). Although very efficacious in adults, clinical studies in children have shown mixed results, potentially due to the significant heterogeneity of the populations being studied and differences in the types of β-blocking agents.

ELECTROPHYSIOLOGIC APPROACHES TO HEART FAILURE MANAGEMENT

Significant improvements in symptomatology and functional capacity have been achieved in selected adult patients with cardiomyopathy using biventricular resynchronization pacing. This technique improves cardiac output by restoring normal synchrony between right and left ventricular contraction, which is often lost in patients with dilated cardiomyopathy (these patients usually manifest a left bundle branch block on electrocardiogram). There is growing experience with resynchronization pacing in children and reports show early success in patients with left ventricular failure (in the setting of cardiomyopathy), right ventricular failure (in the setting of previously repaired tetralogy of Fallot), and somewhat less so in patients with single ventricular failure (in the setting of complex congenital heart disease).

Arrhythmia is a leading cause of sudden death in patients with severe cardiomyopathy (both dilated and hypertrophic). Although antiarrhythmic medications can sometimes reduce this risk, for patients at particularly high risk (e.g., those with a condition known to be associated with a high risk of ventricular arrhythmia or those who have already experienced a "missed sudden death" episode), use of an implantable cardioverter-defibrillator can be lifesaving (see Chapter 429).

442.1 Cardiogenic Shock

Daniel Bernstein

Cardiogenic shock (see Chapter 70) may occur as a complication of (1) severe cardiac dysfunction before or after cardiac surgery, (2) septicemia, (3) severe burns, (4) anaphylaxis, (5) cardiomyopathy, (6) myocarditis, (7) myocardial infarction or stunning, and (8) acute central nervous system disorders. It is characterized by low cardiac output and hypotension, and therefore results in inadequate tissue perfusion.

Treatment is aimed at reinstitution of adequate cardiac output to prevent the untoward effects of prolonged ischemia on vital organs, as

Table 442-3	Treatment of Cardiogenic Shock*		
	DETERMINANTS OF STROKE VOLUME		
	Preload	**Contractility**	**Afterload**
Parameters measured	CVP, PCWP, LAP, cardiac chamber size on echocardiography	CO, BP, fractional shortening or ejection fraction on echocardiography, MV O_2 saturation	BP, peripheral perfusion, SVR
Treatment to improve cardiac output	Volume expansion (crystalloid, colloid, blood)	β-Adrenergic agonists, phosphodiesterase inhibitors	Afterload-reducing agents: milrinone, nitroprusside, ACE inhibitors

ACE, angiotensin-converting enzyme; BP, blood pressure; CO, cardiac output (measured with a thermodilation catheter); CVP, central venous pressure; LAP, left atrial pressure (measured with an indwelling LA line); MV O_2 saturation, mixed venous oxygen saturation (measured with a central venous catheter); PCWP, pulmonary capillary wedge pressure (measured with a thermodilation catheter); SVR, systemic vascular resistance (calculated from CO and mean BP).

*The goal is to improve peripheral perfusion by increasing cardiac output, where: cardiac output = heart rate × stroke volume.

well as management of the underlying cause. Under normal physiologic conditions, cardiac output is increased as a result of sympathetic stimulation, which increases both contractility and heart rate. If contractility is depressed, cardiac output can be improved by increasing heart rate, increasing ventricular filling pressure (preload) through the Frank-Starling mechanism, or by decreasing systemic vascular resistance (afterload). Optimal filling pressure is variable and depends on a number of extracardiac factors, including ventilatory support and intra-abdominal pressure. The increased pressure necessary to fill a relatively noncompliant ventricle should also be considered, particularly after open heart surgery, or in patients with restrictive or hypertrophic cardiomyopathies. If carefully administered incremental fluid does not result in improved cardiac output, abnormal myocardial contractility or an abnormally high afterload, or both, must be implicated as the cause of the low cardiac output. Although tachycardia is one mechanism to increase cardiac output, an excessive increase in heart rate may reduce cardiac output because of decreased time for diastolic filling.

Myocardial contractility usually improves when treatment of the basic cause of shock is instituted, hypoxia is eliminated, and acidosis is corrected. β-Adrenergic agonists such as dopamine, epinephrine, and dobutamine improve cardiac contractility, increase heart rate, and ultimately increase cardiac output. However, some of these agents also have α-adrenergic effects, which cause peripheral vasoconstriction and increase afterload, so careful consideration of the balance of these effects in an individual patient is important. The use of cardiac glycosides to treat acute low cardiac output states should be avoided.

Patients in cardiogenic shock may have a marked increase in systemic vascular resistance resulting in high afterload and poor peripheral perfusion. If the increased systemic vascular resistance is persistent and the administration of positive inotropic agents alone does not improve tissue perfusion, the use of afterload-reducing agents may be appropriate, for example, nitroprusside or milrinone in combination with a β-adrenergic agonist. Milrinone, which acts through inhibition of phosphodiesterase is also a positive inotropic agent, and combined with a β-adrenergic agonist, works synergistically to increase levels of myocardial cyclic adenosine monophosphate.

Sequential evaluation and management of cardiovascular shock are mandatory (see Chapter 70). Table 442-3 outlines the general treatment principles for acute cardiac circulatory failure under most circumstances. Treatment of infants and children with low cardiac output after cardiac surgery also depends on the nature of the operative procedure, any intraoperative complications, and the physiology of the circulation after repair or palliation (see Chapter 428). If cardiogenic shock does not respond rapidly to medical therapy, consideration of mechanical support is warranted. Modalities available for pediatric patients include extracorporeal membrane oxygenation for short-term support, and left and right ventricular assist devices for longer-term support.

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Chapter 443

Pediatric Heart and Heart-Lung Transplantation

443.1 Pediatric Heart Transplantation

Daniel Bernstein

Pediatric heart transplantation is standard therapy for children with end-stage cardiomyopathy and other lesions not amenable to surgical repair. As of 2010, >7,500 heart transplants had been performed on children in the United States and Europe, with ≈500 transplants annually; a quarter of these being performed on children <1 yr of age. Survival rates among children compare favorably with those of adults. For children transplanted in the 1980s and early 1990s, 1 yr survival has been 75-80%, whereas for those transplanted after 2000, 1 yr survival is now in the range of 90%; during the same time periods, 5 yr survival has improved from 60-65% to 75% (Fig. 443-1). A growing number of children are now reaching their 15, 20, and 30 yr posttransplant anniversaries.

INDICATIONS

Heart transplantation is performed in infants and children with end-stage cardiomyopathy who have become refractory to medical therapy, in patients with previously repaired or palliated congenital heart disease who have developed ventricular dysfunction or other nonoperable late-term complications, and (less frequently) in patients with complex congenital heart disease (pulmonary atresia with intact septum and coronary arterial stenoses, some forms of hypoplastic left-heart syndrome) for whom standard surgical procedures are extremely high risk. Cardiomyopathies account for >50% of heart transplants in pediatric patients older than 1 yr, with the percentage of patients with previously repaired complex congenital heart lesions at ~30%. In infants younger than 1 yr, congenital heart lesions used to represent >80% of transplants; this fraction has dropped to ~60% as standard surgical results for complex congenital heart disease (hypoplastic left heart syndrome) have improved.

RECIPIENT AND DONOR SELECTION

Potential heart transplant recipients must be free of serious noncardiac medical problems such as neurologic disease, active systemic infection, severe hepatic or renal disease, and severe malnutrition. Many children with ventricular dysfunction are at risk for the development of pulmonary vascular disease, which if severe enough would preclude heart transplantation. Therefore, pulmonary vascular resistance is measured

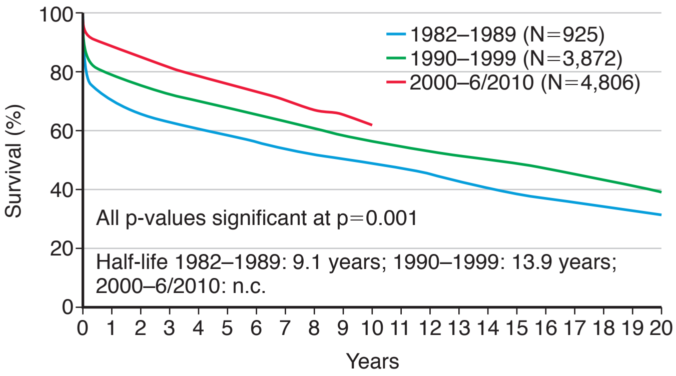

Figure 443-1 Survival after pediatric heart transplantation comparing current and past eras, based on >9,600 patients who received heart transplants in the United States and Europe from 1982 through 2010, as listed with the Registry of the International Society for Heart and Lung Transplantation. Survival has significantly improved over each successive time period. *(From Kirk R, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: thirteenth official pediatric heart transplantation report—2010.* J Heart Lung Transplant *29:1119–1128, 2010, Fig. 7.)*

at cardiac catheterization in heart transplant candidates, both at rest and, if elevated, in response to vasodilators. Patients with fixed elevated pulmonary vascular resistance are at higher risk for heart transplantation and may be considered candidates for either heterotopic heart transplantation (see later) or heart-lung transplantation (see Chapter 443.2). However, with recent advances in postoperative management of pulmonary hypertension (e.g., inhaled nitric oxide), many patients with moderate elevations in pulmonary vascular resistance can undergo heart transplant alone. A comprehensive social services evaluation is an important component of the recipient evaluation. Because of the complex posttransplantation medical regimen, the family must have a history of compliance. Detailed informed consent indicating that the family (and if old enough, the patient) understand the lifelong commitment to immunosuppressive medication and careful monitoring, must be obtained.

Donor shortage is a serious problem for both adults and children. At the national registry of transplant recipients in the United States (the United Network for Organ Sharing [UNOS]), allografts are matched by ABO blood group and body weight. HLA matching is not currently performed unless the recipient has preformed antibodies against a particular HLA antigen, in which case a prospective crossmatch can be obtained. ABO matching may not be required for young infants; the exact age under which ABO tolerance develops has not yet been determined. Contraindications to organ donation include prolonged cardiac arrest with persistent moderate to severe cardiac dysfunction, ongoing systemic illness or infection, and preexisting severe cardiac disease. Physicians caring for a patient who may be a potential donor should always contact the organ donor coordinator at their institution, who can best judge the appropriateness of organ donation and has experience in interacting with potential donor families. A history of resuscitation alone or reparable congenital heart disease is not an automatic exclusion for donation.

The decision of when to place a patient on the transplant waiting list is based on a combination of many factors, including poor ventricular function, markedly decreased exercise tolerance as determined by cardiopulmonary exercise testing (see Chapter 423.5), poor response to medical anticongestive therapy, multiple hospitalizations for heart failure, arrhythmia, progressive deterioration in renal or hepatic function, early stages of pulmonary vascular disease, and poor nutritional status. In patients awaiting transplantation, those with poor left ventricular function are usually started on a regimen of anticoagulation to reduce the risk of mural thrombosis and thromboembolism. Patients with low cardiac output resulting in decreases in end-organ (renal or hepatic) function unresponsive to standard pharmacologic treatment, or those that require chronic assisted ventilation or high-dose inotropic agents are now considered candidates for placement of left ventricular or biventricular assist devices, which can stabilize hemodynamics, improve renal and hepatic function, allow for extubation, and serve as a bridge to transplantation (see Chapter 442). The more recent availability of ventricular assist devices (e.g., the Berlin Heart EXCOR) that are small enough to support young infants has revolutionized the approach to supporting pediatric patients awaiting cardiac transplantation. The role of extracorporeal membrane oxygenation (ECMO) for these patients has been reduced; the need for ECMO support is still a risk factor for poorer outcomes after transplant. There is now limited but growing experience with totally implantable artificial heart devices in older children and adolescents, used either as a bridge to transplant, or in cases (e.g., children with peripheral muscular disorders) where transplantation would be a much higher risk.

PERIOPERATIVE MANAGEMENT

In the classic operation, both donor and recipient hearts were excised so that the posterior portions of the atria containing the venae cavae and pulmonary veins are left intact. The aorta and pulmonary artery are divided above the level of the semilunar valves. The anterior portion of the donor's atria was then connected to the remaining posterior portion of the recipient's atria, thereby avoiding the need for delicate suturing of the venae cavae or pulmonary veins. The donor and recipient great vessels were connected via end-to-end anastomoses. This has largely been supplanted by the bicaval anastomosis, with the donor right atrium (and sinus node) left intact and the suture lines at the superior and inferior vena cavae; the left atrial connection is still performed as in the classic procedure. **Heterotopic heart transplantation** has been used occasionally for patients with left ventricular cardiomyopathy and elevated pulmonary vascular resistance. In this operation, the donor and recipient hearts are connected in parallel so that the recipient right ventricle (which has hypertrophied over time as a result of the elevated pulmonary pressures) pumps mostly to the lungs, and the donor left ventricle pumps mostly to the body. This operation may be preferable to heart-lung transplant for appropriate candidates (patients with pulmonary hypertension but without parenchymal lung disease, without evidence of right ventricular failure, and without serious congenital heart disease), as it is associated with a greater survival at all posttransplant time points.

In the immediate postoperative period, **immunosuppression** is achieved with either a triple- or double-drug regimen, with more centers adopting a minimal steroid or steroid-free regimen. The most common combinations are a calcineurin inhibitor (either cyclosporine or tacrolimus) plus a white blood cell enzyme inhibitor (mycophenolate mofetil or azathioprine), plus or minus prednisone. In many centers, induction therapy (usually an antilymphocyte preparation) is added in the 1st wk, either antithymocyte globulin (ATG) or the humanized anti–interleukin 2 receptor antibodies (basiliximab). In children who do not experience significant graft rejection, steroids can be gradually eliminated after the 1st 6-12 mo. Some centers do not use steroids as part of maintenance immunosuppression, but do use them as bolus treatment for acute rejection episodes.

Most pediatric heart transplant recipients can be extubated within the 1st 48 hr after transplantation and are out of bed within 3-4 days. These patients are often discharged within the 1st 2 wk after transplantation. In patients with preexisting high-risk factors, postoperative recovery may be considerably prolonged. For those with preoperative pulmonary hypertension, the use of nitric oxide in the postoperative period can buy time to allow the donor right ventricle to hypertrophy in response to elevated pulmonary artery pressures. Occasionally, these patients will require right ventricular assist device support.

DIAGNOSIS AND MANAGEMENT OF ACUTE GRAFT REJECTION

Posttransplantation management consists of adjusting medications to maintain a balance between the risk of rejection and the side effects of over-immunosuppression. Along with infection, acute graft rejection is a leading cause of death in pediatric heart transplant

recipients. The incidence of acute rejection is greatest in the 1st 3 mo after transplantation and decreases considerably thereafter. Many pediatric patients experience at least 1 episode of acute rejection in the 1st 2 yr after transplantation, although modern immunosuppressive regimens have decreased the frequency of serious rejection episodes. Because the symptoms of rejection can mimic many routine pediatric illnesses (pneumonia, gastroenteritis), *it is mandatory that the transplant center be notified whenever a heart transplant recipient is seen in the pediatrician's office or emergency room for any acute illness*.

Clinical manifestations of **acute rejection** may include fatigue, fluid retention, fever, diaphoresis, abdominal symptoms, and a gallop rhythm. The electrocardiogram may show reduced voltage, atrial or ventricular arrhythmias, or heart block but is usually nondiagnostic. Roentgenographic examination may show an enlarged heart, effusions, or pulmonary edema, but usually only in the more advanced stages of rejection. Most rejection episodes occur without any detectable clinical symptoms. On echocardiography, indices of systolic left ventricular function may be decreased; however, these usually do not deteriorate until rejection is at least moderately severe. Techniques to evaluate wall thickening and left ventricular diastolic function have not fulfilled their promise as predictors of early rejection. Most transplant centers do not rely on echocardiography alone for rejection surveillance.

Myocardial biopsy is the most reliable method of monitoring patients for rejection. Biopsy specimens are taken from the right ventricular side of the interventricular septum and can be harvested relatively safely, even in small infants. In older children, myocardial biopsies may be performed as often as every 1-4 wk during the 1st 3-6 mo after transplantation. The frequency is then reduced over the next 2 yr to between 2 and 4 biopsies per year unless the patient has an episode of rejection. In infants, surveillance biopsies are usually performed less often and may be as infrequent as once or twice per year. Children may have clinically unsuspected rejection episodes even 5-10 yr after transplantation; most pediatric transplant centers continue routine surveillance biopsies, albeit at less-frequent intervals (every 6-12 mo).

Criteria for **grading cardiac rejection** are based on a system developed by the International Society for Heart and Lung Transplantation (ISHLT); these criteria take into account the degree of cellular infiltration and whether myocyte necrosis is present. ISHLT rejection grade 1R (former grades 1A, 1B, and 2) is usually mild enough that it is often not treated with bolus steroids, and many of these episodes resolve spontaneously. A repeat biopsy specimen is often obtained within a shorter time frame. For patients with ISHLT grade 2R (formerly grade 3A) rejection, treatment is instituted with either intravenous methylprednisolone or a "bump and taper" of oral prednisone. Asymptomatic patients >3 mo posttransplant and with normal echocardiograms are often treated as outpatients. Patients with grade 3R (formerly grades 3B or 4), or anyone with hemodynamic instability, are admitted to the hospital for intravenous steroid and potentially more aggressive antirejection therapy. For rejection episodes resistant to steroid therapy, additional therapeutic regimens include a repeat course of an antilymphocyte preparation (antithymocyte globulin), methotrexate, or total lymphoid irradiation. Patients with repeated episodes of rejection may also benefit from being switched from cyclosporine to tacrolimus (or vice versa). Refractory rejection is not considered a good indication for retransplantation because of the relatively poor outcomes compared with other indications for retransplantation.

Gene expression profiling of peripheral blood mononuclear cells has been validated in adults as a highly sensitive, and moderately selective, method of rejection surveillance. These results have not been confirmed in children. Other current techniques which may hold promise include the profiling of donor cell free DNA released in the serum of patients during episodes of graft injury. Progress has also been made in genetic profiling as a means to determine which patients are most at risk for rejection. Children who have single-nucleotide polymorphisms leading to greater activity of inflammatory cytokines or decreased activity of regulatory cytokines are at increased risk of rejection. This type of profiling may be useful in designing patient-specific immunosuppressive regimens in the future.

Some rejection episodes are not associated with a cellular infiltrate on biopsy. These cases of acellular or humoral rejection are mediated by circulating antibodies and can be detected by immunostaining of the biopsy specimen for the complement component C4d, for macrophages expressing CD68, and for evidence of histologic damage. Humoral rejection is less responsive to standard therapies for acute cellular rejection (e.g., bolus steroids) and has been treated with plasmapheresis, intravenous immunoglobulin, the anti-CD20 monoclonal antibody rituximab, and the proteasome inhibitor bortezomib, all with mixed results.

COMPLICATIONS OF IMMUNOSUPPRESSION

Infection

Infection is 1 of the 2 leading causes of death in pediatric transplant patients (Fig. 443-2). The incidence of infection is greatest in the 1st 3 mo after transplantation when immunosuppressive doses are highest. Viral infections are the most common, which accounts for as many as 25% of infectious episodes. Cytomegalovirus (CMV) infection used to be 1 of the leading causes of morbidity and mortality and may occur as a primary infection in patients without previous exposure to the virus or as a reactivation. Severe CMV infection can be disseminated or associated with pneumonitis or gastroenteritis and may provoke an episode of acute graft rejection or graft coronary disease. Most centers use intravenous ganciclovir or CMV immune globulin (CytoGam), or both, as prophylaxis in any patient receiving a heart from a donor who is positive for CMV or in any recipient who has serologic evidence of previous CMV disease. Oral preparations of ganciclovir with improved absorption profiles are available for chronic therapy and have largely replaced intravenous preparations for prophylaxis. These regimens have significantly reduced the burden of CMV disease in heart transplant patients. Polymerase chain reaction enhances the ability to diagnose CMV infection and to monitor the efficacy of therapy serially.

Most normal childhood viral illnesses are well tolerated and do not usually require special treatment. Otitis media and routine upper respiratory tract infections can be treated in the outpatient setting, although fever or symptoms that last beyond the usual course require further investigation. Gastroenteritis, especially with vomiting, can result in markedly reduced absorption of immunosuppressive medications and provoke a rejection episode. In this setting, drug levels should be closely monitored and the use of intravenous medications considered. Gastroenteritis can also be a sign of rejection, so a high index of suspicion must always be maintained. Varicella is another childhood illness of some concern for immunosuppressed patients. If a heart transplant recipient acquires clinical varicella infection, treatment with intravenous acyclovir usually attenuates the illness.

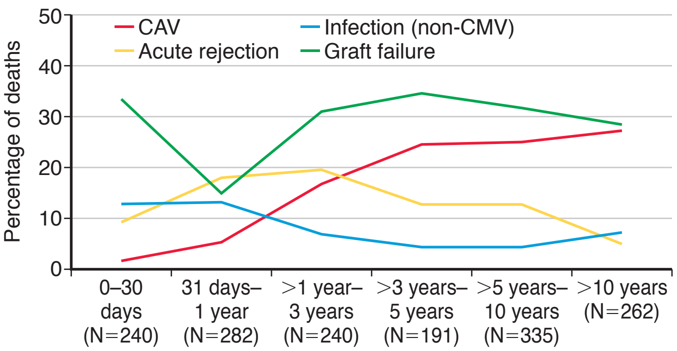

Figure 443-2 **Major causes of death after pediatric heart transplantation by time since transplant.** CAV, coronary artery vasculopathy; CMV, cytomegalovirus. *(From Kirk R, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: thirteenth official pediatric heart transplantation report—2010.* J Heart Lung Transplant *29:1119–1128, 2010, Fig. 9.)*

Bacterial infections are the next most frequent, with the lung being the most common site of infection (35%), followed by the blood, the urinary tract, and, less commonly, the sternotomy site. Other sources of posttransplantation infection include fungi (14%) and protozoa (6%). Many centers use nystatin mouthwash to decrease fungal colonization and trimethoprim/sulfamethoxazole (Bactrim, Septra) during the time a patient is on steroids as prophylaxis to prevent *Pneumocystis carinii* infection.

Growth Retardation

Patients requiring chronic steroid administration usually have decreased linear growth, thus most pediatric transplant programs aim for steroid-free immunosuppression within the 1st yr posttransplant. In those patients who experience rejection when steroids are withdrawn, alternate-day steroid regimens result in improved linear growth. Total lymphoid irradiation has shown promise as a steroid-sparing protocol. Despite these concerns, 75% of long-term survivors of pediatric heart transplantation have normal growth.

Hypertension

Hypertension is common in patients treated with cyclosporine, caused by a combination of plasma volume expansion and defective renal sodium excretion. Corticosteroids usually potentiate cyclosporine-induced hypertension. Patients are typically managed with a combination of a diuretic and a vasodilator. Agents that work via calcium channel blockade have the additional advantage of possibly attenuating graft coronary disease. The incidence of hypertension is slightly lower in patients treated with tacrolimus.

Renal Function

Chronic administration of cyclosporine or tacrolimus can lead to a tubulointerstitial nephropathy in adults, but severe renal dysfunction is less common in children. Most pediatric patients gradually have an increase in serum creatinine in the 1st yr after transplantation; if renal dysfunction occurs, it usually responds to a decrease in calcineurin inhibitor dosage. The addition of sirolimus, a target of rapamycin inhibitor, instead of mycophenolate allows a reduction in the dose of calcineurin inhibitor in patients with renal dysfunction. Infection with BK virus, a growing problem in renal transplant patients, has been described as a source of renal dysfunction in heart transplant patients. Fortunately, pediatric heart transplant patients infrequently require renal transplantation long-term.

Neurologic Complications

Neurologic side effects of cyclosporine and tacrolimus include tremor, myalgias, paresthesias, and, rarely, seizures. These complications can be treated with reduced doses of medication and occasionally with oral magnesium supplementation. Intracranial infections pose a significant risk, especially because some of the more frequent signs (nuchal rigidity) may be absent in immunosuppressed patients. Potential organisms include *Aspergillus, Cryptococcus neoformans,* and *Listeria monocytogenes.* A rare form of encephalopathy, known as PRES (posterior reversible encephalopathy syndrome) can occur in patients on calcineurin inhibitors (either cyclosporine or tacrolimus). PRES presents with hypertension, headaches and seizures, requires MRI for diagnosis, and is usually managed by changing calcineurin inhibitor or in rare cases eliminating calcineurin inhibitors totally in favor of other immunosuppressive agents (e.g., sirolimus/mycophenolate).

Tumors

One of the serious complications limiting long-term survival in pediatric heart transplant patients is the risk of neoplastic disease. The most common is posttransplant lymphoproliferative disease (PTLD), a condition associated with Epstein-Barr virus infection. Patients who are Epstein-Barr virus seronegative at the time of transplant (usually infants and young children) are at increased risk of developing PTLD if they subsequently seroconvert, acquiring the virus either from the donor organ or from primary infection (mononucleosis). Unlike true cancer, many cases of PTLD respond to a reduction in immunosuppression plus antiviral therapy with acyclovir. A monoclonal antibody directed against the CD20 antigen on activated lymphocytes (rituximab) has been effective against some forms of PTLD. However, PTLD can behave more aggressively and many cases eventually require chemotherapy. An increased risk of skin cancer requires that children use appropriate precautions when exposed to sunlight.

Chronic Rejection

Graft coronary artery disease (GCAD) is a manifestation of chronic graft rejection that occurs in ≈20% of children 5 yr after transplant. The cause is still unclear, although it is thought to be a form of immunologically mediated vessel injury (chronic rejection). Hypercholesterolemia and hyperglycemia are thought to increase the risk of this disease. Unlike native coronary atherosclerosis, GCAD is a diffuse process with a high degree of distal vessel involvement. Because the transplanted heart has been denervated, patients may not experience symptoms such as angina pectoris during ischemic episodes, and the initial manifestation may be cardiovascular collapse or sudden death. Most centers perform coronary angiography annually to screen for coronary abnormalities; some also perform coronary intravascular ultrasound on adolescents. Standard coronary artery bypass procedures are usually not helpful because of the diffuse nature of the process, although transcatheter stenting can sometimes be effective for isolated lesions. For severe cases, repeat heart transplantation has been the only effective treatment. Thus, prevention has been the focus of most current research. The cell-cycle inhibitors sirolimus and everolimus have been shown to decrease coronary arterial intimal thickening in adult transplant patients. Other drugs that have been shown to reduce the risk of GCAD include the calcium channel blockers (such as diltiazem) and the cholesterol-lowering HMG-CoA (3-hydroxy-3-methyl-coenzyme A) reductase inhibitors (such as pravastatin or atorvastatin).

Other Complications

Corticosteroids usually result in cushingoid facies, steroid acne, and striae. Cyclosporine can cause a subtle change in facial features such as hypertrichosis and gingival hyperplasia. These cosmetic features can be particularly disturbing to adolescents and may be the motivation for noncompliance, one of the leading risks for late morbidity and mortality. Most of these cosmetic complications are dose related and improve as immunosuppressive medications are weaned. Osteoporosis and aseptic necrosis are additional reasons for reducing the steroid dosage as soon as possible. Diabetes and pancreatitis are rare but serious complications.

Rehabilitation

Despite the potential risks of immunosuppression, the prospect for rehabilitation in pediatric heart transplant recipients is excellent. More than 95% of pediatric heart transplant recipients have no functional limitations in their daily lives. The majority of patients do not require rehospitalization for transplant-related problems.

Pediatric heart transplant recipients can attend daycare or school and participate in non-collision competitive sports (no tackle football or martial arts) and other age-appropriate activities. Standardized measurements of ventricular function are close to normal. Because the transplanted heart is denervated, the increase in heart rate and cardiac output during exercise is slower in transplant recipients, and maximal heart rate and cardiac output responses are mildly attenuated. These subtle abnormalities are rarely noticeable by the patient.

Growth of the transplanted heart is excellent, although a mild degree of ventricular hypertrophy is commonly seen, even years after transplantation. The sites of atrial and great vessel anastomoses usually grow without the development of obstruction. In neonates who undergo transplantation for hypoplastic left heart syndrome, however, juxtaductal aortic coarctation may recur.

As assessed by standardized testing, the psychologic adjustment to heart transplantation in children is usually good. However, a serious problem with noncompliance often occurs once patients reach

adolescence, and life-threatening rejection may result. Early intervention by social workers, counselors, and psychologists may be able to reduce this risk.

Bibliography is available at Expert Consult.

443.2 Heart-Lung and Lung Transplantation

Daniel Bernstein

More than 670 heart-lung and 1,700 lung (single or double) transplants have been performed in children in the United States and Europe, with ≈140 procedures performed annually. Primary indications for heart-lung transplantation include cystic fibrosis, primary pulmonary hypertension, complex congenital heart disease with pulmonary hypoplasia or Eisenmenger syndrome, congenital lung abnormalities, and end-stage parenchymal lung disease (bronchopulmonary dysplasia, chronic lung disease, and interstitial fibrosis). Many of these patients with normal hearts are candidates for single- or double-lung transplantation if right ventricular function is preserved and there has been a trend towards decreasing combined heart-lung transplant for this reason. In some patients with Eisenmenger physiology, double-lung transplantation can be performed in combination with repair of intracardiac defects. Patients with cystic fibrosis are not candidates for single-lung grafts because of the risk of infection from the diseased contralateral lung. Patients are selected according to many of the same criteria as for heart transplant recipients (see Chapter 443.1).

Posttransplant immunosuppression is usually achieved with a triple-drug regimen, combining a calcineurin inhibitor (cyclosporine or tacrolimus) with a white blood cell enzyme inhibitor (mycophenolate or azathioprine) and prednisone. Most patients receive induction therapy with an antithymocyte or anti-T cell preparation. Unlike patients with isolated heart transplants, patients with heart or heart-lung transplants cannot be weaned totally off steroids. Prophylaxis against *P. carinii* infection is achieved with trimethoprim-sulfamethoxazole or aerosolized pentamidine. Ganciclovir and CMV immune globulin prophylaxis are used as in heart transplant recipients (see Chapter 443.1).

Pulmonary rejection is common in lung or heart-lung transplant recipients, whereas heart rejection is encountered much less often than in patients with isolated heart transplants. Symptoms of lung rejection may include fever and fatigue, although many episodes are minimally symptomatic. Surveillance for rejection is performed by monitoring pulmonary function (forced vital capacity; forced expiratory volume in 1 sec [FEV_1]; forced expiratory flow, midexpiratory phase [$FEF_{25-75\%}$]), systemic arterial oxygen tension, and chest roentgenograms and by transbronchial biopsy.

Actuarial survival rates after lung or heart-lung or lung transplantation in children are currently 75% at 1 yr and 50% at 5 yr; improved patient selection and postoperative management are continually improving these survival statistics from prior eras. Graft failure and infection are the leading cause of early death, whereas a form of chronic rejection known as **bronchiolitis obliterans** accounts for nearly 50% of late mortality. Other causes of early morbidity and mortality include tracheal complications, pulmonary venous obstruction, donor lung dysfunction, bleeding, and acute rejection. Additional late complications include the development of airway stenosis, late graft failure, PTLD, and other side effects of chronic immunosuppression.

Postoperative indices of cardiopulmonary function and exercise capacity show significant improvement. Nearly 90% of patients are without activity limitations at 3 yr follow-up and more than 80% at 5 yr follow-up. Problems of donor availability are even more severe with lung transplantation than with isolated heart transplantation. Living related lung transplantation, in which a lobe from a parent is transplanted into a child, has been used to partially alleviate this problem.

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Section 8

Diseases of the Peripheral Vascular System

Chapter 444

Diseases of the Blood Vessels (Aneurysms and Fistulas)

444.1 Kawasaki Disease

Daniel Bernstein

See also Chapter 166.

Aneurysms of the coronary and occasionally the systemic arteries may complicate Kawasaki disease and are the leading cause of morbidity in this disease (Figs. 444-1 and 444-2). Other than in Kawasaki disease, aneurysms are not common in children and occur most frequently in the aorta in association with coarctation of the aorta, patent ductus arteriosus, Ehlers-Danlos type IV (arterial ecchymotic form), hyperimmunoglobulin E syndrome, and Marfan syndrome and in intracranial vessels (see Chapter 601). They may also occur secondary to an infected embolus; infection contiguous to a blood vessel; trauma; congenital abnormalities of vessel structure, especially the medial wall; and arteritis, for example, polyarteritis nodosa, Behçet syndrome, and Takayasu arteritis (see Chapter 167.2).

444.2 Arteriovenous Fistulas

Daniel Bernstein

Arteriovenous fistulas may be limited and small or may be extensive producing systemic complications (see Chapters 505 and 650). The most common sites in infants and children are within the cranium, in the liver, in the lung, in the extremities, and in vessels in or near the thoracic wall. These fistulas, though usually congenital, may follow trauma or be a manifestation of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease). Femoral arteriovenous fistulas are a rare complication of percutaneous femoral catheterization.

CLINICAL MANIFESTATIONS

Clinical symptoms occur only in association with large arteriovenous communications when arterial blood flows into a low-pressure venous system without the resistance of the capillary bed; local venous pressure is increased, and arterial flow distal to the fistula is decreased. Systemic arterial resistance falls because of the runoff of blood through the fistula. Compensatory mechanisms include tachycardia and increased stroke volume so that cardiac output rises. Total blood volume is also increased. In large fistulas, left ventricular dilation, a widened pulse pressure, and high output heart failure occur. CT, MRI, or injection of contrast material into an artery proximal to the fistula confirms the diagnosis.

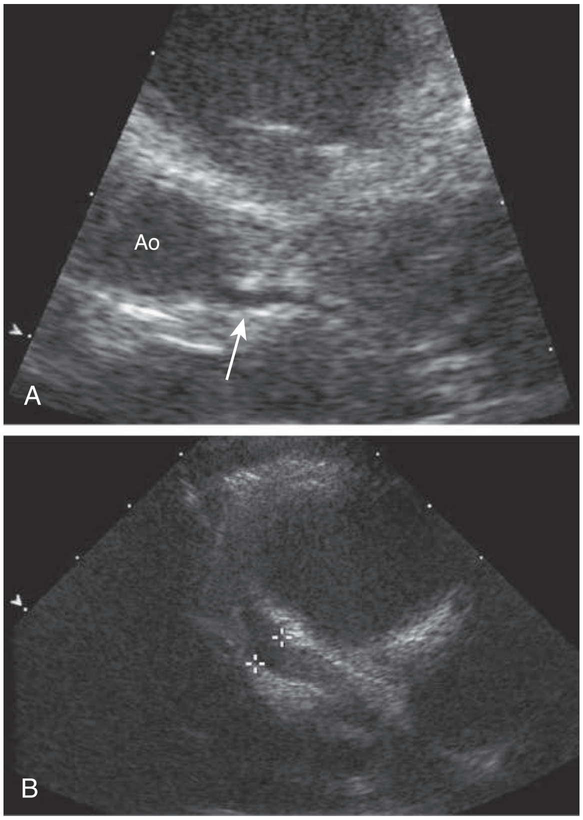

Figure 444-1 Two-dimensional echocardiogram comparing a normal left main coronary artery (*arrow* in **A**) with a giant coronary artery aneurysm (outlined by *cross marks* in **B**) in a patient with Kawasaki disease. Ao, aorta.

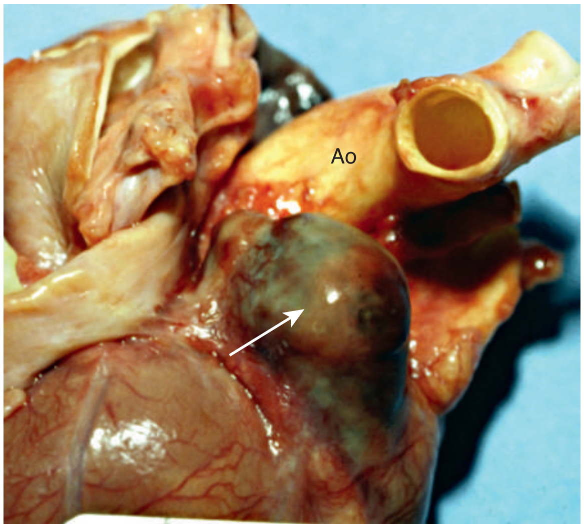

Figure 444-2 Pathologic specimen showing giant aneurysm of left main coronary artery *(arrow).* Ao, ascending aorta.

Large intracranial arteriovenous fistulas most often occur in newborn infants in association with a **vein of Galen malformation.** The large intracranial left-to-right shunt results in heart failure secondary to the demand for high cardiac output. Patients with smaller communications may not have cardiovascular manifestations but may later be disposed to hydrocephalus (see Chapter 591.11) or seizure disorders. The diagnosis can often be made by auscultation of a continuous murmur over the cranium. Older children with more diffuse intracranial arteriovenous malformations may be recognized on the basis of intracranial calcification and high cardiac output without cardiac failure.

Hepatic arteriovenous fistulas may be generalized or localized in the liver and may be hemangioendotheliomas or cavernous hemangiomas. The fistula may be located between the hepatic artery and the ductus venosus or portal vein. Congenital hemorrhagic telangiectasia may also be present. Large arteriovenous fistulas are associated with increased cardiac output and heart failure. Hepatomegaly is usual, and systolic or continuous murmurs may be audible over the liver.

Peripheral arteriovenous fistulas generally involve the extremities and are associated with disfigurement, swelling of the extremity, and visible hemangiomas. Some are located in areas that result in upper airway obstruction. Because only a small minority results in large arterial runoff, cardiac failure is uncommon.

TREATMENT

Medical management of heart failure is initially helpful in neonates with these conditions; with time, the size of the shunt may diminish and symptoms spontaneously regress. Hemangiomas of the liver often eventually disappear completely. Large liver hemangiomas have been treated with steroids, ε-aminocaproic acid, interferon, local compression, embolization, or local irradiation; the beneficial effects of these management options are not firmly established because individual patients display marked variation in clinical course without treatment. Catheter embolization is becoming the treatment of choice for many patients with a symptomatic arteriovenous fistula. Embolic agents that have been used include detachable balloons, steel (Gianturco) coils, and liquid tissue adhesives (cyanoacrylate). Often, multiple procedures are necessary before flow is significantly reduced. Gamma knife radiosurgery has been used successfully in patients with cerebral arteriovenous malformations. Surgical removal of a large fistula may be attempted in patients with severe cardiac failure and lack of improvement with medical treatment. Surgical treatment may be contraindicated or unsuccessful when the lesion is extensive and diffuse or is located in a position where adjoining tissue may be injured during the surgery or related procedures.

444.3 Generalized Arterial Calcification of Infancy/Idiopathic Infantile Arterial Calcification

Robert M. Kliegman

Generalized arterial calcification of infancy (GACI) is a rare and often lethal autosomal recessive disorder characterized by calcification of muscular arteries with fibrotic myointimal proliferation and subsequent vascular stenosis leading to tissue ischemia, poor function or infarction. Diffuse arterial calcification may begin in utero leading to hydrops fetalis; in the neonate diffuse arterial calcification leads to respiratory distress and heart failure or myocardial infarction (coronary, pulmonary arteries), hypertension (renal arteries), and poor femoral pulses (aorta, femoral arteries).

Mutations in the ectonucleotide pyrophosphatase 1gene (*ENPP1*) are noted in 75% of patients. Serum calcium, phosphate and alkaline phosphatase levels are normal and although the vascular calcification may be seen on plain x-rays (Fig. 444-3), ultrasonography (Fig. 444-4), or CT scans may reveal calcifications not visible on plain films.

A subset of patients with GACI have monoallelic or biallelic mutations in the adenosine triphosphate–binding cassette subfamily C number 6 gene (*ABCC6*), which is the gene responsible for pseudoxanthoma elasticum (PXE). PXE, an autosomal recessive disorder, is classically associated with a later onset of ectopic mineralization of elastic fibers in the skin, eyes and arteries. In addition, some surviving infants with *ENPP1* mutation develop PXE symptoms involving skin and retina (angioid streaking).

Infants with GACI have been treated with bisphosphonates with variable success. In addition, some survivors have developed hypophosphatemic rickets.

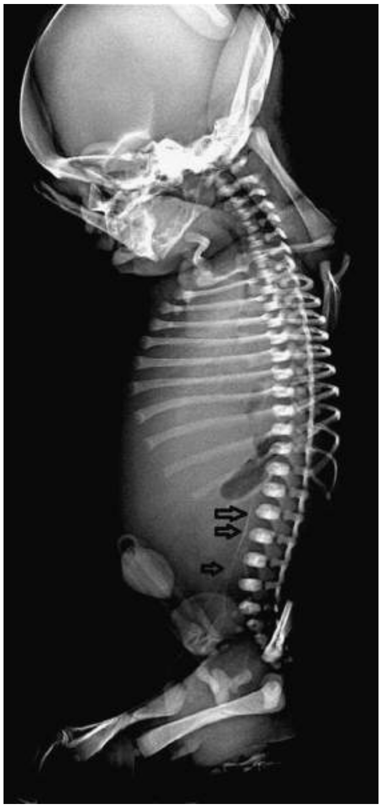

Figure 444-3 Lateral radiograph of the neonate showing calcification of descending aorta and its bifurcation *(arrows). (From Karthikeyan G: Generalized arterial calcification of infancy.* J Pediatr *162:1074, 2013, Fig. 3, p. 1074).*

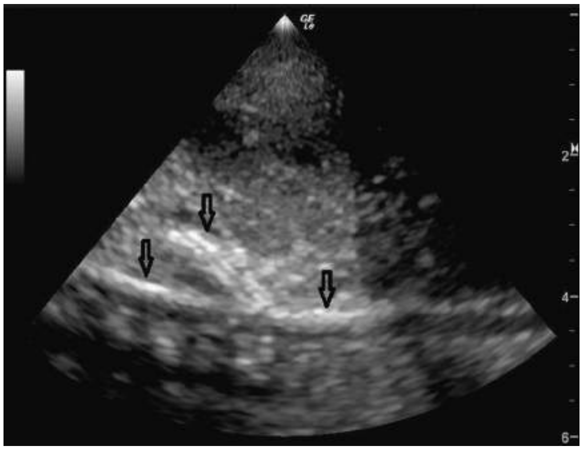

Figure 444-4 Ultrasonography of abdominal aorta showing calcification of descending aorta and its branches *(arrows). (From Karthikeyan G: Generalized arterial calcification of infancy.* J Pediatr *162:1074, 2013, Fig. 1, p. 1074).*

444.4 Arterial Calcifications Caused by Deficiency of CD73

Robert M. Kliegman

This rare autosomal recessive disorder, due to mutations in the 5 exonucleotidase CD73 (*NT5E*) results in joint and arterial (lower extremity) calcification in adults. Patients present with intermittent claudication and joint pain. Onset is probably before adulthood, as patients may be undiagnosed with nonspecific findings during adolescence.

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Chapter 445

Systemic Hypertension

Marc B. Lande

Primary (essential) hypertension occurs commonly in adults and, if untreated, is a major risk factor for myocardial infarction, stroke, and renal failure. In adults with hypertension, a 5 mm Hg increase in diastolic blood pressure (BP) increased the risk of coronary artery disease by 20% and the risk of stroke by 35%. Furthermore, hypertension is implicated in the etiology of nearly 50% of adults with end-stage renal disease. The prevalence of adult hypertension increases with age, ranging from 15% in young adults to 60% in individuals older than 65 yr.

Hypertensive children, although usually asymptomatic, already manifest evidence of target organ damage. Up to 40% of hypertensive children have left ventricular hypertrophy and hypertensive children have increased carotid intima–media thickness, a marker of early atherosclerosis. Primary hypertension during childhood often tracks into adulthood. Children with BP >90th percentile have a 2.4-fold greater risk of having hypertension as adults. Similarly, nearly half of hypertensive adults had a BP >90th percentile as children. There is also an association between childhood hypertension and early atherosclerosis in young adulthood.

PREVALENCE OF HYPERTENSION IN CHILDREN

In infants and young children, systemic hypertension is uncommon, with a prevalence of <1%, but when present, it is often indicative of an underlying disease process **(secondary hypertension)**. *Severe and symptomatic hypertension in children is usually caused by secondary hypertension.* In contrast, the prevalence of primary essential hypertension, mostly in older school-age children and adolescents, has increased in prevalence in parallel with the obesity epidemic. School screening studies show that approximately 10% of U.S. youth overall have prehypertension and 2.5% have hypertension. The influence of obesity on elevated BP is evident in children as young as 2-5 yr old. Approximately 20% of American youth are obese, and up to 10% of obese youth have hypertension.

DEFINITION OF HYPERTENSION

The definition of hypertension in adults is BP ≥140/90 mm Hg, regardless of body size, sex, or age. This is a functional definition that relates level of BP elevation with the likelihood of subsequent cardiovascular events. Because hypertension-associated cardiovascular events, such as myocardial infarction or stroke, usually do not occur in childhood, the definition of hypertension in children is statistical rather than functional. The National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents published the *Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents* (Fourth Report) in 2004. This report established normal values based on the normative distribution of BP in healthy children and included tables with systolic and diastolic values for the 50th, 90th, 95th, and 99th percentile by age, sex, and height percentile. These normative tables can be obtained online at www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm. The Fourth Report defined hypertension as average systolic blood pressure (SBP) and/or diastolic BP that is ≥95th percentile for age, sex, and height on ≥3 occasions. **Prehypertension** was defined as average SBP or diastolic BP that are ≥90th percentile but <95th percentile. In adolescents beginning at age 12 yr, prehypertension is defined as BP between 120/80 mm Hg and the 95th percentile. A child with BP levels

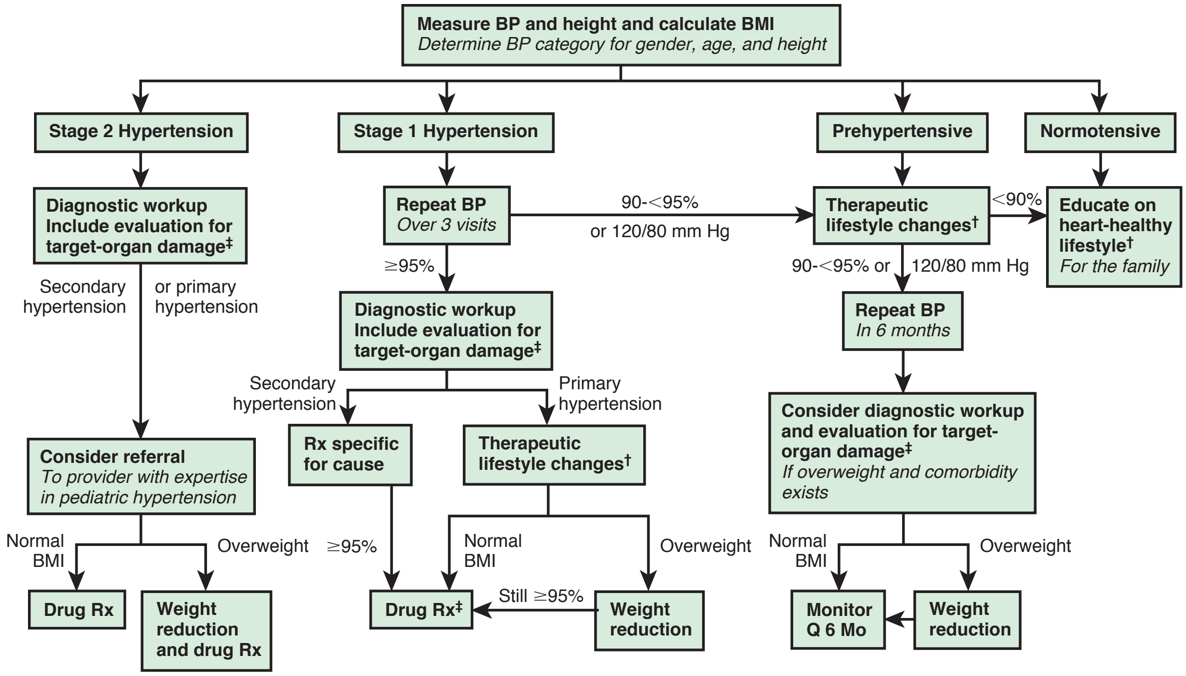

Figure 445-1 Management algorithm. BMI, body mass index; BP, blood pressure; Q, every; Rx, prescription; † diet modification and physical activity; ‡ especially if younger, very high BP, little or no family history, diabetic, or other risk factors. *(From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents,* Pediatrics *114[2 Suppl 4th Report]:571, 2004.)*

≥95th percentile in a medical setting but normal BP outside of the office has **white coat hypertension.**

The Fourth Report further recommended that if BP is ≥95th percentile, then the hypertension should be staged. Children with BP between the 95th and 99th percentile plus 5 mm Hg are categorized as **stage 1 hypertension,** and children with BP above the 99th percentile plus 5 mm Hg have **stage 2 hypertension**. Stage 1 hypertension, if asymptomatic and without target organ damage, allows time for evaluation before starting treatment, whereas stage 2 hypertension calls for more prompt evaluation and pharmacologic therapy (Fig. 445-1).

MEASUREMENT OF BP IN CHILDREN

The Fourth Report and the American Heart Association recommends that children 3 yr or older should have their BP checked during every healthcare episode (the AHA recommends annual BP checks). Selected children <3 yr old should also have their BP checked, including those with a history of prematurity, congenital heart disease, renal disease, solid-organ transplant, cancer, treatment with drugs known to raise BP, other illnesses associated with hypertension (neurofibromatosis, tuberous sclerosis, others), or evidence of increased intracranial pressure. The preferred method is by auscultation and a BP cuff appropriate for the size of the child's arm should be used. Elevated readings should be confirmed on repeat visits before determining that a child is hypertensive. The BP should be measured with the child in the sitting position after a period of quiet for at least 5 min. Careful attention to cuff size is necessary to avoid over diagnosis, as a cuff that is too short or narrow artificially increases BP readings. A wide variety of bladder sizes should be available in any medical office where children are routinely seen. An appropriate sized cuff has an inflatable bladder that is at least 40% of the arm circumference at a point midway along the upper arm. The inflatable bladder should cover at least two thirds of the upper arm length and 80-100% of its circumference.

Systolic pressure is indicated by appearance of the 1st Korotkoff sound. Diastolic pressure has been defined by consensus as the 5th Korotkoff sound. Palpation is useful for rapid assessment of SBP, although the palpated pressure is generally about 10 mm Hg less than that obtained via auscultation. Oscillometric techniques are used frequently in infants and young children, but they are susceptible to artifacts and are best for measuring mean BP.

Ambulatory blood pressure monitoring (ABPM) is a procedure where the child wears a device that records BP frequently, usually every 20-30 min, throughout a 24 hr period while the child goes about usual daily activities, including sleep. This allows calculation of the mean daytime BP, sleep BP, and mean BP over 24 hr. The physician can also determine the proportion of BP measurements that are in the hypertensive range (BP load) and whether there is an appropriate decrease in BP during sleep (nocturnal dip). ABPM is particularly useful in the evaluation for white coat hypertension and may also be useful for determining risk of hypertensive target organ damage, evaluating resistance to pharmacologic therapy, and evaluating patients with hypotensive episodes on antihypertensive medication. ABPM is also useful for certain special populations, such as children with chronic kidney disease, kidney transplant, and diabetes mellitus where it may provide important information on cardiovascular risk that cannot be determined as well by office measurements.

ETIOLOGY AND PATHOPHYSIOLOGY

BP is the product of cardiac output and peripheral vascular resistance. An increase in either cardiac output or peripheral resistance results in an increase in BP; if 1 of these factors increases while the other decreases, BP may not increase. When hypertension is the result of another disease process, it is referred to as secondary hypertension. When no identifiable cause can be found, it is referred to as primary (essential) hypertension. Many factors, including heredity, diet, stress, and obesity, may play a role in the development of primary hypertension. Secondary hypertension is most common in infants and younger children. The younger the child, the higher the BP and the presence of symptoms related to hypertension, the more likely there will be an underlying secondary cause of hypertension. Many childhood diseases can be responsible for chronic hypertension (Table 445-1) or acute/intermittent hypertension (Table 445-2). The most likely cause varies with age. Hypertension in the premature infant is sometimes associated with umbilical artery catheterization and renal artery thrombosis. Hypertension during early childhood may be caused by renal disease,

Table 445-1	Conditions Associated with Chronic Hypertension in Children
RENAL	
Chronic pyelonephritis	
Chronic glomerulonephritis	
Hydronephrosis	
Congenital dysplastic kidney	
Multicystic kidney	
Solitary renal cyst	
Vesicoureteral reflux nephropathy	
Segmental hypoplasia (Ask-Upmark kidney)	
Ureteral obstruction	
Renal tumors	
Renal trauma	
Rejection damage following transplantation	
Postirradiation damage	
Systemic lupus erythematosus (other connective tissue diseases)	
VASCULAR	
Coarctation of thoracic or abdominal aorta	
Renal artery lesions (stenosis, fibromuscular dysplasia, thrombosis, aneurysm)	
Umbilical artery catheterization with thrombus formation	
Neurofibromatosis (intrinsic or extrinsic narrowing for vascular lumen)	
Renal vein thrombosis	
Vasculitis	
Arteriovenous shunt	
Williams-Beuren syndrome	
Moyamoya disease	
Takayasu arteritis	
ENDOCRINE	
Hyperthyroidism	
Hyperparathyroidism	
Congenital adrenal hyperplasia (11β-hydroxylase and 17-hydroxylase defect)	
Cushing syndrome	
Primary aldosteronism	
Apparent mineralcorticoid excess	
Glucocorticoid remedial aldosteronism (familial aldosteronism type 1)	
Glucocorticoid resistance (Chrousos syndrome)	
Pseudohypoaldosteronism type 2 (Gordon syndrome)	
Pheochromocytoma	
Other neural crest tumors (neuroblastoma, ganglioneuroblastoma, ganglioneuroma)	
Liddle syndrome	
Geller syndrome	
CENTRAL NERVOUS SYSTEM	
Intracranial mass	
Hemorrhage	
Residual following brain injury	
Quadriplegia	

Table 445-2	Conditions Associated with Transient or Intermittent Hypertension in Children
RENAL	
Acute postinfectious glomerulonephritis	
Anaphylactoid (Henoch-Schönlein) purpura with nephritis	
Hemolytic-uremic syndrome	
Acute tubular necrosis	
After renal transplantation (immediately and during episodes of rejection)	
After blood transfusion in patients with azotemia	
Hypervolemia	
After surgical procedures on the genitourinary tract	
Pyelonephritis	
Renal trauma	
Leukemic infiltration of the kidney	
Obstructive uropathy associated with Crohn disease	
DRUGS AND POISONS	
Cocaine	
Oral contraceptives	
Sympathomimetic agents	
Amphetamines	
Phencyclidine	
Corticosteroids and adrenocorticotropic hormone	
Cyclosporine or sirolimus treatment posttransplantation	
Licorice (glycyrrhizic acid)	
Lead, mercury, cadmium, thallium	
Antihypertensive withdrawal (clonidine, methyldopa, propranolol)	
Vitamin D intoxication	
CENTRAL AND AUTONOMIC NERVOUS SYSTEM	
Increased intracranial pressure	
Guillain-Barré syndrome	
Burns	
Familial dysautonomia	
Stevens-Johnson syndrome	
Posterior fossa lesions	
Porphyria	
Poliomyelitis	
Encephalitis	
Spinal cord injury (autonomic storm)	
MISCELLANEOUS	
Preeclampsia	
Fractures of long bones	
Hypercalcemia	
After coarctation repair	
White cell transfusion	
Extracorporeal membrane oxygenation	
Chronic upper airway obstruction	

coarctation of the aorta, endocrine disorders, or medications. In older school-age children and adolescents, primary hypertension becomes increasingly common.

Secondary hypertension in children is most commonly caused by renal abnormalities; cardiovascular disease or endocrinopathies are additional etiologies. Renal (chronic glomerulonephritis, reflux or obstructive nephropathy, hemolytic uremic syndrome, polycystic or dysplastic renal diseases), or renovascular hypertension, account for approximately 90% of children with secondary hypertension. Renal parenchymal disease and renal artery stenosis lead to water and sodium retention thought to be, in part, secondary to increased renin secretion. Coarctation of the aorta should always be considered. Several endocrinopathies are associated with hypertension, usually those involving the thyroid, parathyroid, and adrenal glands. Systolic hypertension and tachycardia are common in hyperthyroidism; diastolic pressure is not usually elevated. Hypercalcemia, whether secondary to hyperparathyroidism or other causes, often results in mild elevation in BP because of an increase in vascular tone. Adrenocortical disorders (aldosterone-secreting tumors, sodium retaining congenital adrenal hyperplasia, Cushing syndrome) may produce hypertension in patients with increased mineralocorticoid secretion. It is important to consider conditions associated with real or apparent mineralocorticoid excess (Table 445-3) and thus a suppressed renin level form of secondary hypertension. Pheochromocytomas are catecholamine-secreting tumors that give rise to hypertension because of the cardiac and peripheral vascular effects of epinephrine and norepinephrine. Children with pheochromocytoma usually have sustained rather than intermittent or exercise-induced hypertension. Pheochromocytoma develops in approximately 5% of patients with neurofibromatosis. Rarely, secondary hypertension can be caused by pseudohyperaldosteronism, which leads to elevated BP in the face of a suppressed renin level. Such disorders include Liddle syndrome, apparent mineralocorticoid excess, and dexamethasone suppressible aldosteronism. Altered sympathetic tone can be responsible for acute or intermittent elevation of BP in children with Guillain-Barré syndrome, poliomyelitis, burns, and Stevens-Johnson syndrome. Sympathetic outflow from the central nervous system is also affected by intracranial lesions.

A number of drugs of abuse, therapeutic agents, and toxins may cause hypertension. Cocaine may provoke a rapid increase in BP and can

Table 445-3 Clinical Findings in Patients with Mineralocorticoid Excess

CONDITION	CLINICAL PRESENTATION
CAH: 11β-hydroxylase deficiency	Early growth spurt initially, then short adult stature, advanced bone age, premature adrenarche, acne, precocious puberty in males, amenorrhea/hirsutism/virilism in females
CAH: 17α-hydroxylase deficiency	Pseudohermaphroditism (male), sexual infantilism (female)
Apparent mineralocorticoid excess	Growth retardation/short stature, nephrocalcinosis
Liddle syndrome	Severe hypertension, hypokalemia, and metabolic alkalosis, muscle weakness
Geller syndrome	Early onset of hypertension (before age 20 years), exacerbated in pregnancy
Glucocorticoid remediable aldosteronism (GRA) (familial aldosteronism type 1)	Early onset of hypertension, presence of family history of mortality or morbidity from early hemorrhagic stroke
Pseudohypaldosteronism type 2 (Gordon syndrome)	Short stature, hyperkalemic and hyperchloremic metabolic acidosis, borderline blood pressure
Glucocorticoid resistance (children) (Chrousos syndrome)	Ambiguous genitalia, precocious puberty; women may have acne, excessive hair, oligo/anovulation, infertility

From Melcescu E, Phillips J, Moll G, et al: 11 Beta-hydroxylase deficiency and other syndromes of mineralcorticoid excess as a rare cause of endocrine hypertension. Horm Metab Res 44:867-878, 2012 (Table 1, p. 869).

result in seizures or intracranial hemorrhage. Phencyclidine causes transient hypertension that may become persistent in chronic abusers. Tobacco use may also increase BP. Sympathomimetic agents used as nasal decongestants, appetite suppressants, and stimulants for attention deficit disorder produce peripheral vasoconstriction and varying degrees of cardiac stimulation. Individuals vary in their susceptibility to these effects. Oral contraceptives should be suspected as a cause of hypertension in adolescent girls, although the incidence is lower with the use of low-estrogen preparations. Immunosuppressant agents such as cyclosporine and tacrolimus cause hypertension in organ transplant recipients, and the effect is exacerbated by the co-administration of steroids. BP may be elevated in patients with poisoning by a heavy metal.

Children and adolescents with primary (essential) hypertension are commonly overweight, often have a strong family history of hypertension, and usually have BP values at or only slightly above the 95th percentile for age. Primary hypertension is the most common form of hypertension in adults, and it is recognized more often in adolescents than in young children. The cause of primary hypertension is likely to be multifactorial; obesity, genetic alterations in calcium and sodium transport, vascular smooth muscle reactivity, the renin–angiotensin system, sympathetic nervous system overactivity, and insulin resistance have been implicated in this disorder. Elevated uric acid levels may play a role in the pathophysiology of primary hypertension and proof-of-concept studies have confirmed that lowering of uric acid levels results in lower BP in overweight youth with hypertension or prehypertension. Some children and adolescents demonstrate salt-sensitive hypertension, a factor that is ameliorated with weight loss and sodium restriction.

Normotensive children of hypertensive parents may show abnormal physiologic responses that are similar to those of their parents. When subjected to stress or competitive tasks, the offspring of hypertensive adults, as a group, respond with greater increases in heart rate and BP than do children of normotensive parents. Similarly, some children of hypertensive parents may excrete higher levels of urinary catecholamine metabolites or may respond to sodium loading with greater weight gain and increases in BP than do those without a family history of hypertension. The abnormal responses in children with affected parents tend to be greater in the black population than among white individuals.

CLINICAL MANIFESTATIONS

Children and adolescents with primary hypertension are usually asymptomatic; the BP elevation is usually mild and is detected during a routine examination or evaluation before athletic participation. These children may also be obese. Children with secondary hypertension can have BP elevations ranging from mild to severe. Unless the pressure has been sustained or is rising rapidly, hypertension does not usually produce symptoms. Therefore, clinical manifestations may instead reflect the underlying disease process, such as growth failure in children with chronic kidney disease. With substantial hypertension, headache, dizziness, epistaxis, anorexia, visual changes, and seizures may occur. **Hypertensive encephalopathy** (generalized or posterior reversible encephalopathy syndrome) is suggested by the presence of headache, vomiting, temperature elevation, visual disturbances, ataxia, depressed level of consciousness, CT abnormalities, and seizures (Fig. 445-2). Cardiac failure, pulmonary edema, and renal dysfunction (malignant hypertension) may occur in the face of marked hypertension. Bell palsy may be seen in asymptomatic or symptomatic patients. **Hypertensive crisis** may manifest with decreased vision (retinal hemorrhages of hypertensive retinopathy) and papilledema, encephalopathy (headache, seizures, depressed level of consciousness), heart failure, or accelerated deterioration of renal function.

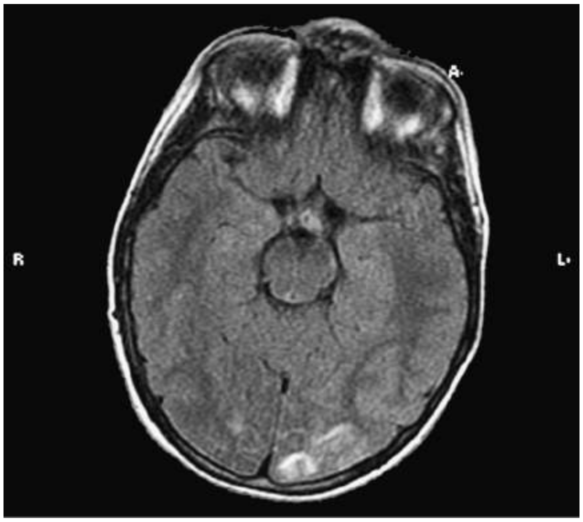

Figure 445-2 Magnetic resonance image of brain of a 6 yr old boy with end-stage renal disease and hypertensive encephalopathy (i.e., posterior reversible leukoencephalopathy syndrome). Bilateral occipital high signal intensity is more pronounced on the left side. *(From Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors,* Bradley's neurology in clinical practice, *ed 6, vol 2, Philadelphia, 2012, Elsevier/Saunders, Fig. 49B.4, p. 924.)*

Subclinical hypertensive target-organ injury is a common clinical manifestation in children with essential hypertension. With the use of

echocardiography using pediatric normative data, left ventricular hypertrophy is detected in up to 40% of hypertensive children. Other markers of target organ damage that have been demonstrated in hypertensive children include increased carotid intima–media thickness, hypertensive retinopathy, and microalbuminuria. Children with prehypertension also have evidence of target organ damage, often at a magnitude intermediate between that of normotensive and hypertensive children.

DIAGNOSIS

The evaluation of the child with chronic hypertension should be directed toward uncovering potential underlying causes of the hypertension, evaluating for comorbidities, and screening for evidence of target organ damage. The extent of the evaluation for underlying causes of hypertension depends on the type of hypertension that is suspected. When secondary hypertension is a strong consideration, as in younger children with severe and symptomatic hypertension, an extensive evaluation may be necessary (Fig. 445-3). Alternatively, overweight adolescents with a family history of hypertension who have mild elevations of BP may need only a limited number of tests.

In all cases, a careful history and physical examination are warranted. A family history for early cardiovascular events should be obtained. Growth parameters should be determined to detect evidence of chronic disease. BP should be obtained in all 4 extremities to detect coarctation (thoracic or abdominal) of the aorta. Table 445-4 identifies other features of the physical examination that may provide evidence of an underlying cause of hypertension. Unless the history and physical examination suggest another cause, children with confirmed hypertension should have an evaluation to detect renal disease, including urinalysis, electrolytes, blood urea nitrogen, creatinine, complete blood count, urine culture, and renal ultrasound. Table 445-5 provides a more complete list of tests to consider in the clinical evaluation of a child with confirmed hypertension. Measuring serum potassium is essential because hypokalemia may be present in Liddle syndrome, glucocorticoid remedial aldosteronism, and apparent mineralcorticoid excess syndrome, while hyperkalemia may be seen in Gordon syndrome.

Renovascular hypertension is often associated with other diseases (Table 445-6) but may be isolated. Magnetic resonance or CT angiography can reveal renal artery stenosis, but fluoroscopic angiography may be needed, especially to detect intrarenal arterial stenosis (Fig. 445-4).

Primary hypertension often clusters with other risk factors. All hypertensive children should be screened for comorbidities that may increase cardiovascular risk, including hyperlipidemia and glucose intolerance. A fasting lipid panel and fasting glucose level should be obtained. In addition, a sleep history should be obtained in children with confirmed hypertension to screen for sleep disordered breathing, an entity that is associated with high BP, particularly in overweight children.

Left ventricular hypertrophy (LVH) is the most common manifestation of target-organ damage in hypertensive children. All children with confirmed hypertension should have echocardiography to evaluate for the presence of LVH. Left ventricular mass measurements should be indexed to height ($m^{2.7}$) to account for the effect of body size. The presence of LVH is an indication to treat the hypertension with pharmacologic therapy.

PREVENTION

Prevention of high BP may be viewed as part of the prevention of cardiovascular disease and stroke, the leading cause of death in adults in the United States. Other risk factors for cardiovascular disease include obesity, elevated serum cholesterol levels, high dietary sodium intake, and a sedentary lifestyle, as well as alcohol and tobacco use. The

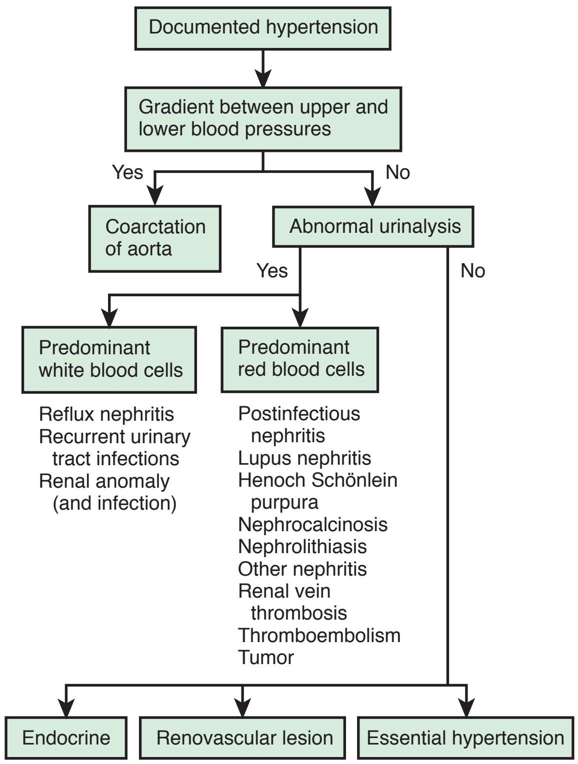

Figure 445-3 Initial diagnostic algorithm in the evaluation of hypertension. *(From Kliegman RM, Greenbaum LA, Lye PS:* Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 222.)*

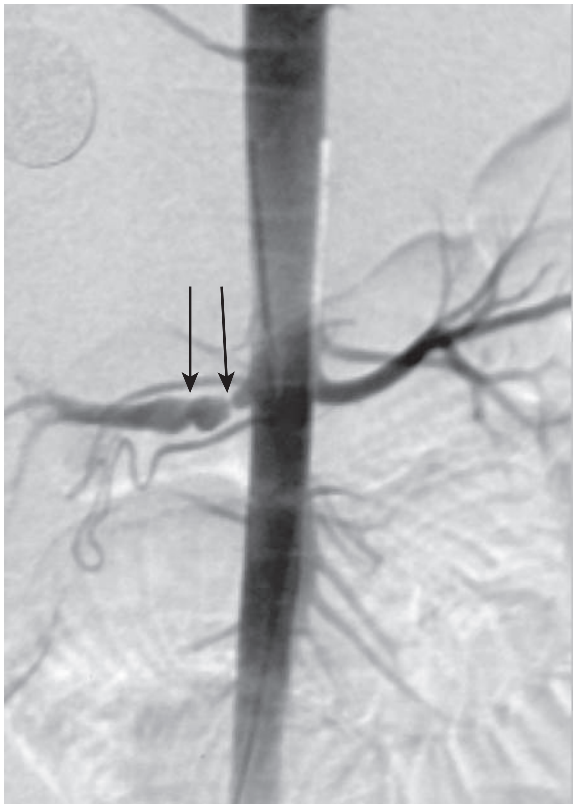

Figure 445-4 Renal angiogram in 7 yr old boy with hypertension. Right renal artery is visible with a string-of-beads appearance characteristic of fibromuscular dysplasia *(arrows)*. The aorta and left renal artery appear normal. *(From Tullus K, Brennan E, Hamilton G, et al: Renovascular hypertension in children,* Lancet *371:1453–1463, 2008, p. 1454, Fig. 1.)*

Table 445-4 Findings to Look for on Physical Examination in Patients with Hypertension

PHYSICAL FINDINGS	POTENTIAL RELEVANCE
GENERAL	
Pale mucous membranes, edema, growth retardation	Chronic renal disease
Elfin facies, poor growth, retardation	Williams syndrome
Webbing of neck, low hairline, widespread nipples, wide carrying angle	Turner syndrome
Moon face, buffalo hump, hirsutism, truncal obesity, striae, acne	Cushing syndrome
HABITUS	
Thinness	Pheochromocytoma, renal disease, hyperthyroidism
Virilization	Congenital adrenal hyperplasia
Rickets	Chronic renal disease
SKIN	
Café-au-lait spots, neurofibromas	Neurofibromatosis, pheochromocytoma
Tubers, "ash-leaf" spots	Tuberous sclerosis
Rashes	Systemic lupus erythematosus, vasculitis (Henoch-Schönlein purpura), impetigo with acute nephritis
Pallor, evanescent flushing, sweating	Pheochromocytoma
Needle tracks	Illicit drug use
Bruises, striae	Cushing syndrome
Acanthosis nigricans	Type 2 diabetes, insulin resistance
EYES	
Extraocular muscle palsy	Nonspecific, chronic, severe
Fundal changes	Nonspecific, chronic, severe
Proptosis	Hyperthyroidism
HEAD AND NECK	
Goiter	Thyroid disease
Adenotonsillar hypertrophy	Sleep disordered breathing
CARDIOVASCULAR SIGNS	
Absent of diminished femoral pulses, low leg pressure relative to arm pressure	Aortic coarctation
Heart size, rate, rhythm; murmurs; respiratory difficulty, hepatomegaly	Aortic coarctation, congestive heart failure
Bruits over great vessels	Arteritis or arteriopathy
Rub	Pericardial effusion secondary to chronic renal disease
PULMONARY SIGNS	
Pulmonary edema	Congestive heart failure, acute nephritis
Picture of bronchopulmonary dysplasia	Bronchopulmonary dysplasia-associated hypertension
ABDOMEN	
Epigastric bruit	Primary renovascular disease or in association with Williams syndrome, neurofibromatosis, fibromuscular dysplasia, or arteritis
Abdominal masses	Wilms tumor, neuroblastoma, pheochromocytoma, polycystic kidneys, hydronephrosis, dysplastic kidneys
NEUROLOGIC SIGNS	
Neurologic deficits	Chronic or severe acute hypertension with stroke
Muscle weakness	Hyperaldosteronism, Liddle syndrome
GENITALIA	
Ambiguous, virilized	Congenital adrenal hyperplasia

increase in arterial wall rigidity and blood viscosity that is associated with exposure to the components of tobacco may exacerbate hypertension. Population approaches to prevention of primary hypertension include a reduction in obesity, reduced sodium intake, and an increase in physical activity through school- and community-based programs.

TREATMENT

The Fourth Report recommended a management algorithm for children with confirmed hypertension according to whether the child has prehypertension, stage 1 hypertension, or stage 2 hypertension (see Figs. 445-1 and 445-5). The mainstay of therapy for children with asymptomatic mild hypertension without evidence of target-organ damage is therapeutic lifestyle modification with dietary changes and regular exercise. Weight loss is the primary therapy in obesity-related hypertension. It is recommended that all hypertensive children have a diet increased in fresh fruits, fresh vegetables, fiber, and nonfat dairy, and reduced in sodium. In addition, regular aerobic physical activity for at least 30-60 min on most days along with a reduction of sedentary activities to less than 2 hr per day is recommended. Indications for pharmacologic therapy include symptomatic hypertension, secondary hypertension, hypertensive target organ damage, diabetes (types 1 and 2), and persistent hypertension despite nonpharmacologic measures (Table 445-7). When indicated, antihypertensive medication should be initiated as a single agent at low dose (see Fig. 445-5). The dose can then be increased until the goal BP is achieved. Once the highest recommended dose is reached or if the child develops side effects, then a second drug from a different class can be added. Acceptable drug classes for use in children include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, and diuretics. Details on recommended doses of different

Table 445-5 Clinical Evaluation of Confirmed Hypertension

STUDY OR PROCEDURE	PURPOSE	TARGET POPULATION
EVALUATION FOR IDENTIFIABLE CAUSES		
History, including sleep history, family history, risk factors, diet, and habits such as smoking and drinking alcohol; physical examination	History and physical examination help focus subsequent evaluation	All children with persistent BP ≥95th percentile
Blood urea nitrogen, creatinine, electrolytes, urinalysis, and urine culture	R/O renal disease and chronic pyelonephritis, mineralocorticoid excess states	All children with persistent BP ≥95th percentile
Complete blood count	R/O anemia, consistent with chronic renal disease	All children with persistent BP ≥95th percentile
Renal ultrasound	R/O renal scar, congenital anomaly, or disparate renal size	All children with persistent BP ≥95th percentile
EVALUATION FOR COMORBIDITY		
Fasting lipid panel, fasting glucose	Identify hyperlipidemia, identify metabolic abnormalities	Overweight patients with BP at 90th-94th percentile; all patients with BP ≥95th percentile; family history of hypertension or cardiovascular disease; child with chronic renal disease
Drug screen	Identify substances that might cause hypertension	History suggestive of possible contribution by substances or drugs.
Polysomnography	Identify sleep disorder in association with hypertension	History of loud, frequent snoring
EVALUATION FOR TARGET-ORGAN DAMAGE		
Echocardiogram	Identify left ventricular hypertrophy and other indications of cardiac involvement	Patients with comorbid risk factors* and BP 90th-94th percentile; all patients with BP ≥95th percentile
Retinal exam	Identify retinal vascular changes	Patients with comorbid risk factors and BP 90th-94th percentile; all patients with BP ≥95th percentile
ADDITIONAL EVALUATION AS INDICATED		
Ambulatory blood pressure monitoring	Identify white coat hypertension, abnormal diurnal BP pattern, BP load	Patients in whom white coat hypertension is suspected, and when other information on BP pattern is needed
Plasma renin determination	Identify low renin, suggesting mineralocorticoid-related disease	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension Positive family history of severe hypertension
Renovascular imaging Isotopic scintigraphy (renal scan) Magnetic resonance angiography Duplex Doppler flow studies 3-Dimensional CT Arteriography: digital subtraction arteriography or classic	Identify renovascular disease	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Plasma and urine steroid levels	Identify steroid-mediated hypertension	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension
Plasma and urine catecholamines	Identify catecholamine-mediated hypertension	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension

R/O, rule out.

*Comorbid risk factors also include diabetes mellitus and kidney disease.

From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics *114(2 Suppl 4th Report):562, 2004.*

Table 445-6 Causes of Renovascular Hypertension in Children

Fibromuscular dysplasia

Syndromic
- Neurofibromatosis type 1
- Tuberous sclerosis
- Williams syndrome
- Marfan syndrome
- Other syndromes

Vasculitis
- Takayasu disease
- Polyarteritis nodosa
- Kawasaki disease
- Other systemic vasculitides

Extrinsic compression
- Neuroblastoma
- Wilms tumor
- Other tumors

Other causes
- Radiation
- Umbilical artery catheterization
- Trauma
- Congenital rubella syndrome
- Transplant renal artery stenosis

From Tullus K, Brennan E, Hamilton G, et al: Renovascular hypertension in children, Lancet *371:1453–1463, 2008, p. 1454, Panel 1.*

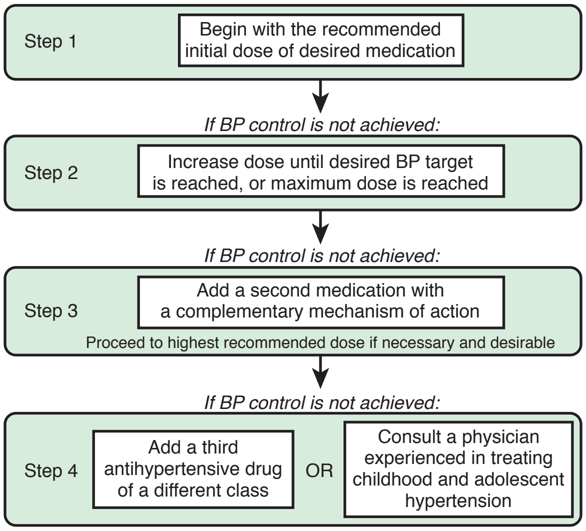

Figure 445-5 **Stepped-care approach to antihypertensive therapy in children and adolescents.** BP, blood pressure. *(From Flynn JT, Daniels SR: Pharmacologic treatment of hypertension in children and adolescents,* J Pediatr *149:746–754, 2006, p. 751, Fig. 2.)*

Table 445-7 Recommended Doses for Selected Antihypertensive Agents for Use in Hypertensive Children and Adolescents

CLASS	DRUG	STARTING DOSE	INTERVAL	MAXIMUM DOSE*
Aldosterone receptor antagonist	Eplerenone	25 mg/day	qd-bid	100 mg/day
	Spironolactone[†]	1 $mg\cdot kg^{-1}\cdot day^{-1}$	qd-bid	3.3 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 100 mg/day
Angiotensin-converting enzyme inhibitors	Benazepril[†]	0.2 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 10 mg/day	qd	0.6 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 40 mg/day
	Captopril[†]	0.3-0.5 mg/kg/dose	bid-tid	6 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 450 mg/day
	Enalapril[†]	0.08 $mg\cdot kg^{-1}\cdot day^{-1}$	qd	0.6 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 40 mg/day
	Fosinopril	0.1 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 10 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Lisinopril[†]	0.07 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 5 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Quinapril	5-10 mg/day	qd	80 mg/day
Angiotensin receptor blockers	Candesartan	1-6 yr, 0.2 $mg\cdot kg^{-1}\cdot day^{-1}$ 6-17 yr, <50 kg 4-8 mg once daily >50 kg 8-16 mg qdqd	qd	1-6 yr, 0.4 mg/kg; 6-17 yr, <50 kg 16 mg qd; >50 kg 32 mg qd
	Losartan[†]	0.75 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 50 mg/day	qd	1.4 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 100 mg/day
	Olmesartan	20 to <35 kg 10 mg qd; ≥35 kg 20 mg qd	qd	20 to <35 kg 20 mg qd ≥35 kg 40 mg qd
	Valsartan[†]	6-17 yr, 1.3 mg/kg/day up to 40 mg/day; <6 yr: 5-10 mg/day	qd	6-17 yr, 2.7 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 160 mg/day; <6 yr: 80 mg/day
α- and β-Adrenergic antagonists	Labetalol[†]	2-3 $mg\cdot kg^{-1}\cdot day^{-1}$	bid	10-12 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 1.2 g/day
	Carvedilol	0.1 mg/kg/dose up to 12.5 mg bid	bid	0.5 mg/kg/dose up to 25 mg bid
β-adrenergic antagonists	Atenolol[†]	0.5-1 $mg\cdot kg^{-1}\cdot day^{-1}$	qd-bid	2 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 100 mg/day
	Bisoprolol/HCTZ	0.04 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 2.5/6.25 mg/day	qd	10/6.25 mg/day
	Metoprolol	1-2 $mg\cdot kg^{-1}\cdot day^{-1}$	bid	6 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 200 mg/day
	Propranolol	1 $mg\cdot kg^{-1}\cdot day^{-1}$	bid-tid	16 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 640 mg/day
Calcium channel blockers	Amlodipine[†]	0.06 $mg\cdot kg^{-1}\cdot day^{-1}$	qd	0.3 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 10 mg/day
	Felodipine	2.5 mg/day	qd	10 mg/day
	Isradipine[†]	0.05-0.15 mg/kg/dose	tid-qid	0.8 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 20 mg/day
	Extended-release nifedipine	0.25-0.5 $mg\cdot kg^{-1}\cdot day^{-1}$	qd-bid	3 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 120 mg/day
Central α-agonist	Clonidine[†]	5-10 µg/kg/day	bid-tid	25 µg/kg/day up to 0.9 mg/day
Diuretics	Amiloride	5-10 mg/day	qd	20 mg/day
	Chlorthalidone	0.3 $mg\cdot kg^{-1}\cdot day^{-1}$	qd	2 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 50 mg/day
	Furosemide	0.5-2.0 mg/kg/dose	qd-bid	6 $mg\cdot kg^{-1}\cdot day^{-1}$
	HCTZ	0.5-1 $mg\cdot kg^{-1}\cdot day^{-1}$	qd	3 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 50 mg/day
Vasodilators	Hydralazine	0.25 mg/kg/dose	tid-qid	7.5 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 200 mg/day
	Minoxidil	0.1-0.2 $mg\cdot kg^{-1}\cdot day^{-1}$	bid-tid	1 $mg\cdot kg^{-1}\cdot day^{-1}$ up to 50 mg/day

bid, Twice-daily; HCTZ, hydrochlorothiazide; qd, once daily; qid, 4 times daily; tid, 3 times daily.

*The maximum recommended adult dose should never be exceeded.

[†]Information on preparation of a stable extemporaneous suspension is available for these agents.

From Flynn JT. Management of hypertension in the young: role of antihypertensive medications. J Cardiovasc Pharmacol *2011:58(2)111–120.*

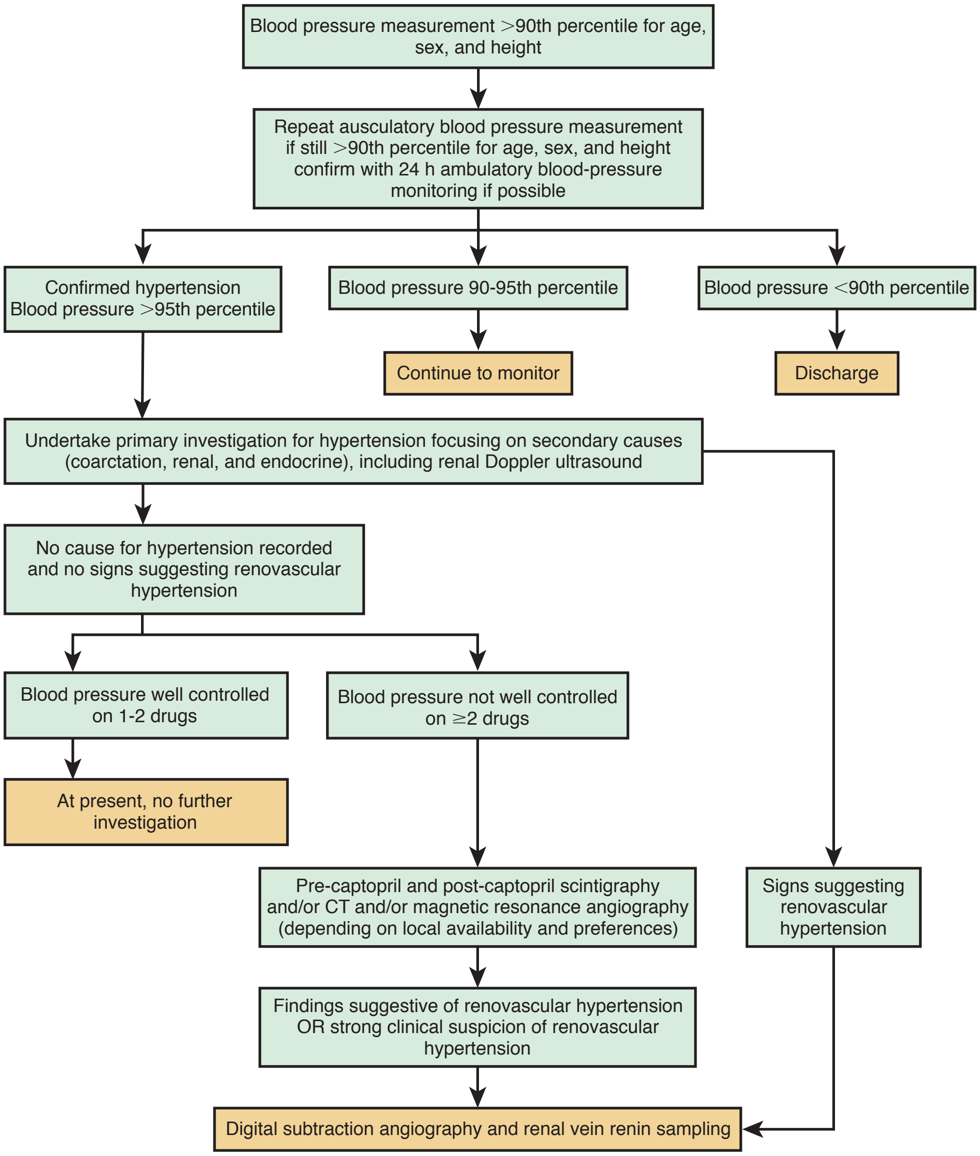

Figure 445-6 Diagnostic pathway for renovascular hypertension. *(From Tullus K, Brennan E, Hamilton G, et al: Renovascular hypertension in children,* Lancet *371:1453–1463, 2008, p. 1458, Fig. 6.)*

Table 445-8 Antihypertensive Drugs for Management of Severe Hypertension in Children 1–17 Yr

DRUG	CLASS	DOSE	ROUTE	COMMENTS
USEFUL FOR SEVERELY HYPERTENSIVE PATIENTS WITH LIFE-THREATENING SYMPTOMS				
Esmolol	β-Adrenergic blocker	100-500 µg/kg/min	IV infusion	Very short acting—constant infusion preferred. May cause profound bradycardia
Hydralazine	Direct vasodilator	0.2-0.6 mg/kg/dose	IV, IM	Should be given q4h when given IV bolus
Labetalol	α- and β-adrenergic blocker	bolus: 0.20-1.0 mg/kg/dose, up to 40 mg/dose infusion: 0.25-3.0 mg/kg/hr	IV bolus or infusion	Asthma and overt heart failure are relative contraindications
Nicardipine	Calcium channel blocker	Bolus: 30 mcg/kg up to 2 mg/dose Infusion: 0.5-4 µg/kg/min	IV bolus or infusion	May cause reflex tachycardia
Sodium nitroprusside	Direct vasodilator	0.5-10 µg/kg/min	IV infusion	Monitor cyanide levels with prolonged (>72 hr) use or in renal failure; or coadminister with sodium thiosulfate
USEFUL FOR SEVERELY HYPERTENSIVE PATIENTS WITH LESS-SIGNIFICANT SYMPTOMS				
Clonidine	Central α-agonist	0.05-0.1 mg/dose, may be repeated up to 0.8 mg total dose	PO	Side effects include dry mouth and drowsiness
Enalaprilat	ACE inhibitor	5-10 µg/kg/dose up to 1.25 mg/dose	IV bolus	May cause prolonged hypotension and acute renal failure, especially in neonates
Fenoldopam	Dopamine receptor agonist	0.2-0.8 µg/kg/min	IV infusion	Produced modest reductions in BP in a pediatric clinical trial in patients up to 12 yr
Hydralazine	Direct vasodilator	0.25 mg/kg/dose up to 25 mg/dose	PO	Extemporaneous suspension stable for only 1 wk
Isradipine	Calcium channel blocker	0.05-0.1 mg/kg/dose up to 5 mg/dose	PO	Stable suspension can be compounded
Minoxidil	Direct vasodilator	0.1-0.2 mg/kg/dose up to 10 mg/dose	PO	Most potent oral vasodilator; long acting

ACE, angiotensin-converting enzyme, IM, intramuscular, IV, intravenous, PO, oral.

From Flynn JT: Correction to severe hypertension in children and adolescents: pathophysiology and treatment, Pediatr Nephrol *27(3):503–504, 2012.*

classes of antihypertensive medications for children can be found in the Fourth Report available free online at www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf.

The goal of therapy for hypertension should be to reduce BP below the 95th percentile, except in the presence of chronic kidney disease, diabetes, or target-organ damage, when the goal should be to reduce BP to less than the 90th percentile. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used for children with diabetes and microalbuminuria or proteinuric renal disease. β-Blockers or calcium channel blockers should be considered for hypertensive children with migraine headaches.

Severe, symptomatic hypertension is a hypertensive emergency that is often accompanied by cardiac failure, retinopathy, renal failure, encephalopathy, and seizures. Intravenous administration is often preferred so that the fall in BP can be carefully titrated (Table 445-8). Drug choices include labetalol, nicardipine, and sodium nitroprusside. Because too rapid a reduction in BP may interfere with adequate organ perfusion, a stepwise reduction in pressure should be planned. In general, the pressure should be reduced by 10% in the 1st hr, and 15% more in the next 3-12 hr, but not to normal during the acute phase of treatment. Hypertensive urgencies, usually accompanied by few serious symptoms such as severe headache or vomiting, can be treated either orally or intravenously. The Fourth Report also includes detailed information on antihypertensive drugs used for the management of severe hypertension in children.

Treatment of secondary hypertension must also focus on the underlying disease such as chronic renal disease, hyperthyroidism, adrenal–genital syndrome, pheochromocytoma, coarctation of the aorta, or renovascular hypertension. The treatment of renovascular stenosis includes antihypertensive medications, angioplasty, or surgery (Fig. 445-6). If bilateral renovascular hypertension or renovascular disease in a solitary kidney is suspected, drugs acting on the renin-angiotensin axis are usually contraindicated because they may reduce glomerular filtration rates and produce renal failure.

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Diseases of the Blood

PART XXI

Section 1 The Hematopoietic System

Chapter 446 Development of the Hematopoietic System

Robert D. Christensen and Robin K. Ohls

HEMATOPOIESIS IN THE HUMAN EMBRYO AND FETUS

Hematopoiesis is the process by which the cellular elements of blood are formed. In the developing human embryo and fetus, hematopoiesis is conceptually divided into 3 anatomic stages: mesoblastic, hepatic, and myeloid. Mesoblastic hematopoiesis occurs in extraembryonic structures, principally in the yolk sac, and begins between the 10th and 14th days of gestation. By 6-8 wk of gestation the liver replaces the yolk sac as the primary site of blood cell production, and during this time the placenta also contributes as a hematopoietic site. By 10-12 wk extraembryonic hematopoiesis has essentially ceased. Hepatic hematopoiesis occurs through the remainder of gestation, although hepatic production diminishes during the second trimester while bone marrow (myeloid) hematopoiesis increases. The liver remains the predominant erythropoietic organ (few if any neutrophils are produced in the human fetal liver) through 20-24 wk of gestation.

Each hematopoietic organ houses distinct populations of cells. At 18-20 wk the fetal liver is predominantly an erythropoietic organ, while the marrow produces both erythrocytes and neutrophils. The types of leukocytes present in the fetal liver and marrow differ with gestation. Macrophages precede neutrophils in the marrow, and the ratio of macrophages to neutrophils decreases as gestation progresses. Regardless of gestational age or anatomic location, production of all hematopoietic tissues begins with pluripotent stem cells capable of both self-renewal and clonal maturation into all blood cell lineages. Progenitor cells differentiate under the influence of hematopoietic growth factors (Table 446-1). Fetal hematopoietic growth factor production is independent of maternal growth factor production (Fig. 446-1).

Erythrocytes in the fetus are larger than in adults, and at 22-23 wk gestation the mean corpuscular volume can be as high as 135 fL (Fig. 446-2, *upper panel*). Similarly, the mean corpuscular hemoglobin is very high at 22-23 wk, and falls relatively linearly with advancing gestation (Fig. 446-2, *lower panel*). In contrast, the mean corpuscular hemoglobin concentration is constant throughout gestation at 34±1 g/dL. While the size and quantity of hemoglobin in erythrocytes diminish during gestation, the hematocrit and blood hemoglobin concentration gradually increase (Fig. 446-3, *upper* and *lower panels*, respectively).

Concentrations of platelets in the blood increase gradually between 22 and 40 wk gestation (Fig. 446-4) but the platelet size, assessed by mean platelet volume, remains constant at 8±1 fL. No differences are observed between males and females in fetal and neonatal reference ranges for erythrocyte indices, hematocrit, hemoglobin, platelet counts, or mean platelet volume measurements.

FETAL GRANULOCYTOPOIESIS

Neutrophils are first observed in the human fetus about 5 wk postconception as small clusters of cells around the aorta. The fetal bone marrow space begins to develop around the 8th wk postconception, and from 8-10 wk the marrow space enlarges, but no neutrophils appear there until 10.5 wk. From 14 wk through term, the most common granulocytic cell type in the fetal bone marrow space is the neutrophil. Neutrophils and macrophages originate from a common progenitor cell but macrophages appear prior to neutrophils in the fetus, first in the yolk sac, liver, lung, and brain, all before the bone marrow cavity is formed.

Granulocyte colony-stimulating factor (G-CSF) and macrophage colony-stimulating factor (M-CSF) are expressed in developing fetal bone as early as 6 wk postconception and both are expressed in the fetal liver as early as 8 wk. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and stem cell factor also are distributed widely in human fetal tissues. However, no changes in expression of any of these factors, or of their specific receptors, appear to be the signal for fetal production of neutrophils or macrophages, as those signals have not yet been identified.

Fetal blood contains few neutrophils until the third trimester. At 20 wk gestation the blood neutrophil count is 0-500/mm^3. Although mature neutrophils are scarce, progenitor cells with the capacity to generate neutrophil clones are abundant in fetal blood. When cultured in vitro in the presence of recombinant G-CSF, they mature into large colonies of neutrophils. The physiologic role of G-CSF includes upregulating neutrophil production, and this appears to be the case for the fetus and neonate, as well as for adults. Thus, the low quantities of circulating neutrophils the mid-trimester human fetus may be partly a result of low production of G-CSF. Monocytes isolated from the blood of adults produce G-CSF when stimulated with a variety of inflammatory mediators such as bacterial lipopolysaccharide (LPS) or interleukin (IL)-1. In contrast, monocytes isolated from the blood or organs of fetuses up to 24 wk gestation generate only small quantities of G-CSF protein and messenger RNA (mRNA) after lipopolysaccharide or IL-1 stimulation. Despite this, G-CSF receptors on the surface of neutrophils of newborn infants are equal in number and affinity to those on adult neutrophils.

In the fetus, actions of the granulocytopoietic factors (G-CSF, M-CSF, GM-CSF, and stem cell factor) are not limited to hematopoiesis. Receptors for each of these are located in areas of the fetal central nervous system and gastrointestinal tract, where their patterns of expression change with development. Important developmental roles exist for these factors beyond hematopoiesis.

FETAL THROMBOPOIESIS

Platelet production occurs from 2 pools of cells: megakaryocyte progenitors and megakaryocytes. Megakaryocyte progenitors are categorized as *burst-forming unit–megakaryocytes* (BFU-MK), which are primitive megakaryocyte progenitors, and *colony-forming unit–megakaryocytes* (CFU-MK), which are more differentiated. BFU-MK produce large multifocal colonies containing ≥50 megakaryocytes, whereas CFU-MK generate smaller (3-50 cells/colony) unifocal colonies. The colonies generated by BFU-MK of fetal origin contain significantly more megakaryocytes than do those of adult origin and on that basis are thought to represent somewhat more primitive cells. Megakaryocytes are identified by their morphologic characteristics, as they undergo endoreduplication, which results in large cells with

Table 446-1 Characteristics of Hematopoietic Growth Factors

GROWTH FACTOR	MOLECULAR MASS (kDa)	CHROMOSOMAL LOCATION	PRINCIPAL TARGET CELL
ERYTHROPOIETIN	30-39	7q11-12	CFU-E, fetal BFU-E, endothelial cells, neurons, astrocytes, oligodendrocytes
COLONY-STIMULATING FACTORS			
G-CSF	18-22	17q11.2-21	CFU-G, CFU-MIX, mature neutrophils
GM-CSF	18-30	5q23-31	CFU-MIX, CFU-GM, BFU-E, monocytes, mature neutrophils
M-CSF	45-70 (Dimer of 2 subunits)	5q33.1	CFU-M, macrophages
SCF	36	12q21.32	CFU-MIX, BFU-E, CFU-GM, mast cells
TGF-β	25 Homodimeric protein	19q13.2	BL-CFC
CSF-1	192 Amino acid protein	1p13.3	Monocytes, macrophages, dendritic cells, Langerhans cells
INTERLEUKINS			
IL-1	17	Alpha 2q13 Beta 2q13-21	Hepatocytes, macrophages, lymphocytes
IL-2	15-20	4q26-27	T cells, cytotoxic lymphocytes
IL-3	14-30	5q23-31	CFU-MIX, CFU-Meg, CFU-GM, BFU-E, macrophage
IL-4	16-20	5q23-31	T cells, B cells, dendritic cells
IL-5	46 (Dimer of 2 subunits)	5q23-31	CFU-Eo, B cells
IL-6	19-26	7p21-24	CFU-MIX, CFU-GM, BFU-E, monocytes, B cells, T cells, cytotoxic lymphocytes
IL-7	35	8q12-13	B cells
IL-8	8-10	4q13.3	Neutrophils, endothelial cells, T cells
IL-9	16	5q31-32	BFU-E, CFU-MIX
IL-10	18.7	1q32.1	Macrophages, lymphocytes
IL-11	23	19q13	CFU-Meg, B cells, keratinocytes
IL-12	70-75 (Dimer of 2 subunits)	p35/p40	3 (p35) and 11 (p40) T cells, NK cells, macrophages
IL-13	9	5q23-31	Pre-B lymphocytes, macrophages
IL-14	53	5q31	B cells
IL-15	14-15	4q25-35	B cells, T cells
IL-16	12-14	15q23-26	T cells
IL-17	20-30	2q31	Marrow stromal cells
IL-18	24	9p13	CD4+ T cells, NK cells
IL-21		4q26-q27	T cells
IL-23	Dimer of subunits	p19/IL-12p40	CD4+ T cells
IL-25		14q11.2	T cells, monocytes, marrow stromal cells
IL-31	4-Helix bundle	12q24.31	T cells, hematopoietic progenitors
IL-34	222 Amino acid protein	16q22.1	Monocytes, macrophages
THROMBOPOIETIN	35-38	3q27–28	Megakaryocyte progenitors, megakaryocytes

BFU-E, burst-forming units–erythroid; BL-CFU, blast colony-forming cell; CFU-E, colony-forming units–erythroid; CFU-Eo, colony-forming units–eosinophil; CFU-G, colony-forming units–granulocyte; CFU-GM, colony-forming units–granulocyte macrophage; CFU-M, colony-forming units–macrophage; CFU-Meg, colony-forming units–megakaryocyte; CFU-MIX, colony-forming units–mixed; CSF-1, colony-stimulating factor-1; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; M-CSF, macrophage colony-stimulating factor; NK, natural killer; SCF, stem cell factor; TGF-β, transforming growth factor-beta.

polyploid nuclei. Megakaryocytes, unlike megakaryocyte progenitors, do not have the capacity to generate clones. Rather, they undergo maturation, progressing from small mononuclear cells to large polyploid cells. The modal megakaryocyte ploidy (the number of sets of complete chromosomes) in normal adult marrow is 16N. In the fetus and neonate, ploidy is lower and megakaryocyte size is smaller. However, umbilical cord blood has a higher concentration of megakaryocytes than adult blood. Large megakaryocytes generate more platelets than do small megakaryocytes; thus, it is assumed that megakaryocytes of neonates produce fewer platelets than do their adult counterparts.

The processes of platelet production and release from megakaryocytes are not well understood. It has been speculated that small buds, proplatelets, are formed on megakaryocytes and that these are released from the marrow as platelets. An alternate possibility is that platelets are principally released from megakaryocytes in the lungs, as a consequence of shear forces.

Thrombopoietin (TPO) is the physiologic regulator of platelet production and acts as a stimulator of all stages of megakaryocyte growth and development (see Table 446-1). The gene encoding TPO is located on the long arm of chromosome 3. TPO-mRNA is expressed primarily in liver and kidney and, to a lesser extent, in marrow stroma. TPO is a primary, but not exclusive, regulator of platelet production and stimulates the proliferation and survival not only of megakaryotic progenitors but also of erythroid, myeloid, and multipotent progenitors. Recombinant TPO supports the growth of megakaryocytic colonies of neonates and children and progenitors of preterm neonates are more sensitive to recombinant TPO than are progenitors of term neonates.

FETAL ERYTHROPOIESIS

Similar to hematopoietic production of other cell lines, fetal erythropoiesis is regulated by growth factors produced by the fetus, not by the mother. Erythropoietin (EPO) does not cross the human placenta. Stimulating maternal EPO production does not stimulate fetal erythropoiesis, and suppressing maternal erythropoiesis by hypertransfusion does not suppress fetal erythropoiesis.

It is unclear to what extent the mechanisms regulating erythropoiesis in adults are operative in the fetus. Of all the factors known to be involved in stimulating erythropoiesis, none plays a more central regulatory role than does EPO, a 30-39 kDa glycoprotein that binds to specific receptors on the surface of erythroid precursors and stimulates their differentiation and clonal maturation into mature

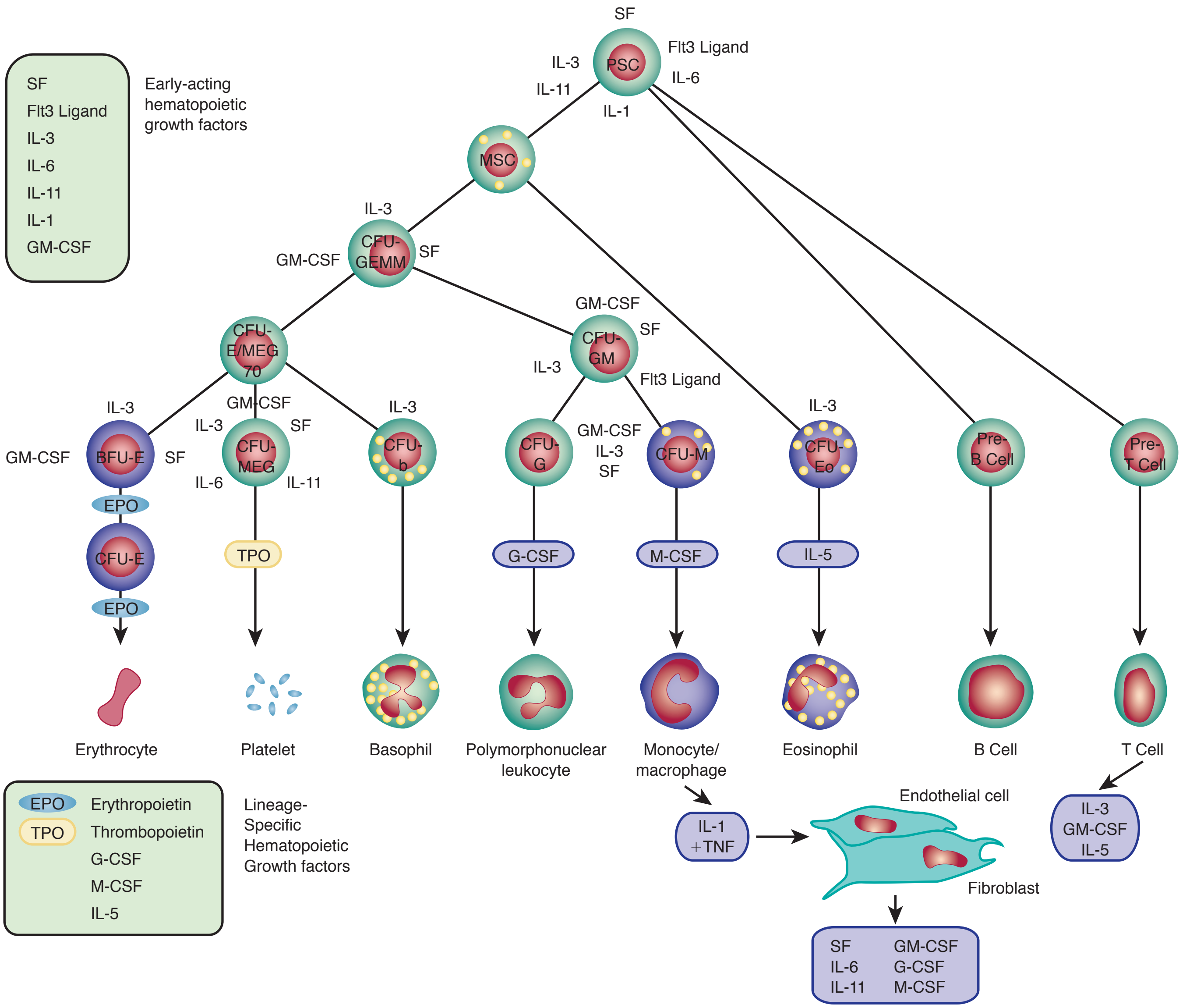

Figure 446-1 **Major cytokine sources and actions to promote hematopoiesis.** Cells of the bone marrow microenvironment, such as macrophages, endothelial cells, and reticular fibroblasts, produce macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF) after stimulation. These cytokines and others listed in the text have overlapping interactions during hematopoietic differentiation, as indicated; for all lineages, optimal development requires a combination of early- and late-acting factors. BFU, burst-forming unit; CFU, colony-forming unit; EPO, erythropoietin; MSC, myeloid stem cells; PSC, pluripotent stem cell. *(From Sieff CA, Nathan DG, Clark SC: The anatomy and physiology of hematopoiesis. In Orkin SH, Nathan DG, editors:* Hematology of infancy and childhood, *ed 5, Philadelphia, 1998, WB Saunders, p. 168.)*

erythrocytes. Regulating EPO gene expression involves an oxygen-sensing mechanism. EPO mRNA production is regulated by *cis*-acting elements in the promoter and 3′ enhancer regions that are responsive to hypoxia. Two factors, hepatic nuclear factor 4 and hypoxia inducible factor (HIF-1), exhibit transcriptional activation for EPO and other hypoxia-inducible genes. Hepatic nuclear factor 4 binds to the EPO promoter and enhancer regions of the gene. HIF-1 is a basic helix-loop-helix transcription factor composed of HIF-1α and HIF-1β subunits that bind to *cis*-acting hypoxia-response elements and induce EPO transcription. HIF-1 is expressed in many cells and is involved in upregulating a variety of oxygen-regulated proteins, including vascular endothelial growth factor. HIF-1α appears to be constitutively expressed and rapidly degraded under normoxic conditions. RNA stability depends on the ubiquitin proteasome degradation system; inhibition of this system leads to increased HIF-1 and increased EPO, even under normoxic conditions.

EPO is produced in fetal liver during the first and second trimesters, principally by cells of monocyte/macrophage origin. After birth, the anatomic site of EPO production shifts to the kidney. The specific stimulus for this shift is unknown but may involve the increase in arterial oxygen tension that occurs at birth. Epigenetic modification of gene expression may also play a role, as it appears that renal and hepatic EPO genes are methylated to different degrees. Although EPO mRNA and protein can be found in the human fetal kidney, it is not known whether this production is biologically relevant. However, it appears that renal production of EPO is not essential for normal fetal erythropoiesis, as evidenced by the normal serum EPO concentrations and normal hematocrits of anephric fetuses.

Hemoglobins in the Fetus and Neonate

The evolutionary development of oxygen-carrying proteins, the **hemoglobins,** increased the ability of blood to transport oxygen. The

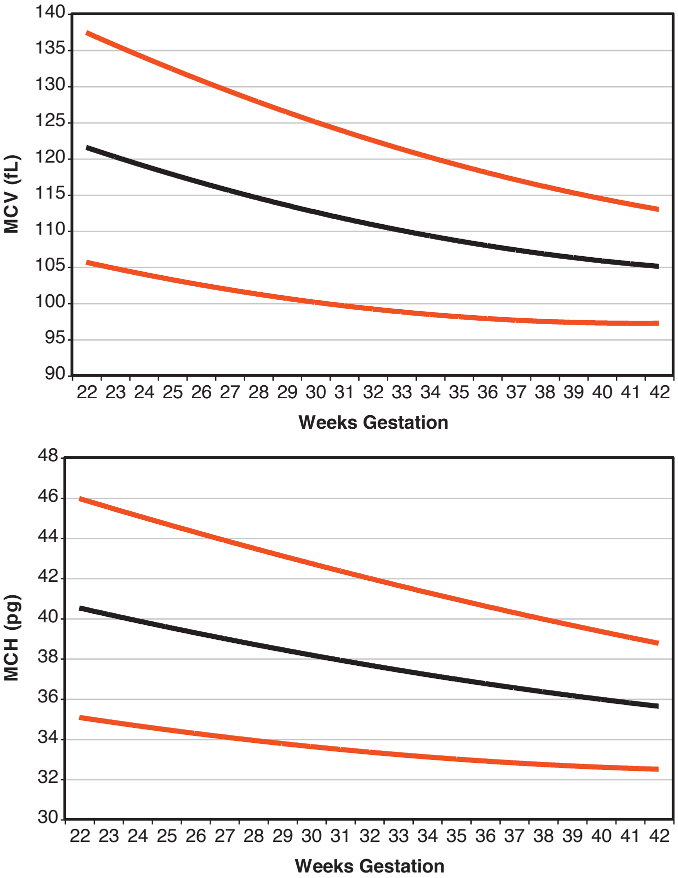

Figure 446-2 Erythrocyte mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) from 22 wk gestation through term. The lines represent the 5th percentile, the mean, and the 95th percentile reference range. *(From Christensen RD, Jopling J, Henry E, et al: The erythrocyte indices of neonates, defined using data from over 12,000 patients in a multihospital healthcare system,* J Perinatol *28:24–28, 2008.)*

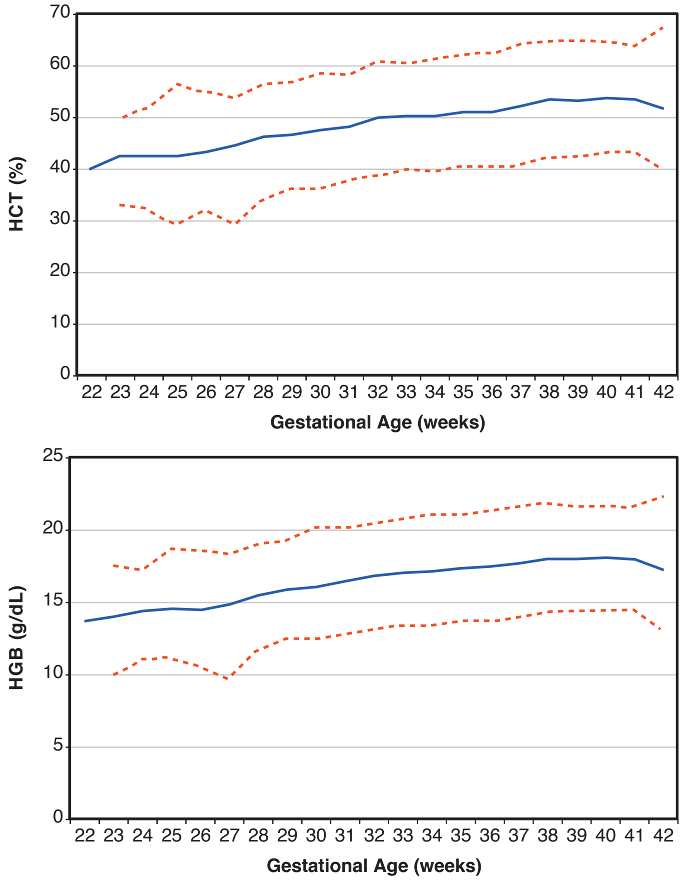

Figure 446-3 Hematocrit (HCT) and blood hemoglobin concentration (HGB) from 22 wk gestation through term. The lines represent the 5th percentile, the mean, and the 95th percentile reference range. *(From Jopling J, Henry E, Wiedmeier SE, et al: Reference ranges for hematocrit and blood hemoglobin concentration during the neonatal period: data from a multihospital healthcare system,* Pediatrics *123:e333–e337, 2009.)*

combination of oxygen with hemoglobin and its dissociation from hemoglobin are accomplished without expenditure of metabolic energy.

Hemoglobin is a complex protein consisting of iron-containing heme groups and the protein moiety globin. A dynamic interaction between heme and globin gives hemoglobin its unique properties in the reversible transport of oxygen. The hemoglobin molecule is a tetramer made up of 2 pairs of polypeptide chains, with each chain having a heme group attached. The polypeptide chains of various hemoglobins are of chemically different types. The major hemoglobin of a normal adult (HbA) is made up of 1 pair of alpha (α) and 1 pair of beta (β) polypeptide chains, represented as $\alpha_2\beta_2$. The major hemoglobin in the fetus (HbF), which is made up of 2 α- and 2 γ-globin chains, is represented by $\alpha_2\gamma_2$.

The various globin chains differ in both the number and sequence of amino acids, and their synthesis is directed by separate genes (Fig. 446-5). Two sets of genes for the α chains are located on human chromosome 16. Two pairs of alleles provide the genetic information for the structure of the α chain. The β, γ, and δ genes are closely linked on chromosome 11.

Within the red blood cell (RBC) mass of an embryo, fetus, child, and adult, 6 different hemoglobins may normally be detected (Fig. 446-6): the **embryonic hemoglobins,** Gower-1, Gower-2, and Portland; **fetal hemoglobin,** HbF; and the **adult hemoglobins,** HbA and HbA_2. The electrophoretic mobilities of hemoglobins vary with their chemical structures. The time of appearance and quantitative relationships among the hemoglobins are determined by complex developmental processes.

Embryonic Hemoglobins

The blood of early human embryos contains 2 slowly migrating hemoglobins, *Gower-1* and *Gower-2,* and *Hb Portland,* which has HbF-like mobility. The zeta (ζ) chains of Hb Portland and Gower-1 are structurally quite similar to α chains. Both Gower hemoglobins contain a unique type of polypeptide chain, the epsilon (ε) chain. Hb Gower-1 has the structure $\zeta_2\varepsilon_2$, while Gower-2 has the structure $\alpha_2\varepsilon_2$. Hb Portland has the structure $\zeta_2\gamma_2$. In embryos of 4-8 wk gestation, the Gower hemoglobins predominate, but by the 3rd mo they have disappeared.

Fetal Hemoglobin

HbF contains γ polypeptide chains in place of the β chains of HbA. Its resistance to denaturation by strong alkali is the basis for determining the presence of fetal RBCs in the maternal circulation (the **Kleihauer-Betke test**). After the 8th wk, HbF is the predominant hemoglobin; at 24 wk gestation it constitutes 90% of the total hemoglobin. During the 3rd trimester, a gradual decline occurs, so that at birth HbF averages 70% of the total hemoglobin. Synthesis of HbF decreases rapidly postnatally (Fig. 446-7), and by 6-12 mo of age only a trace is present. Less than 2.0% can be detected by alkali denaturation in older children and adults.

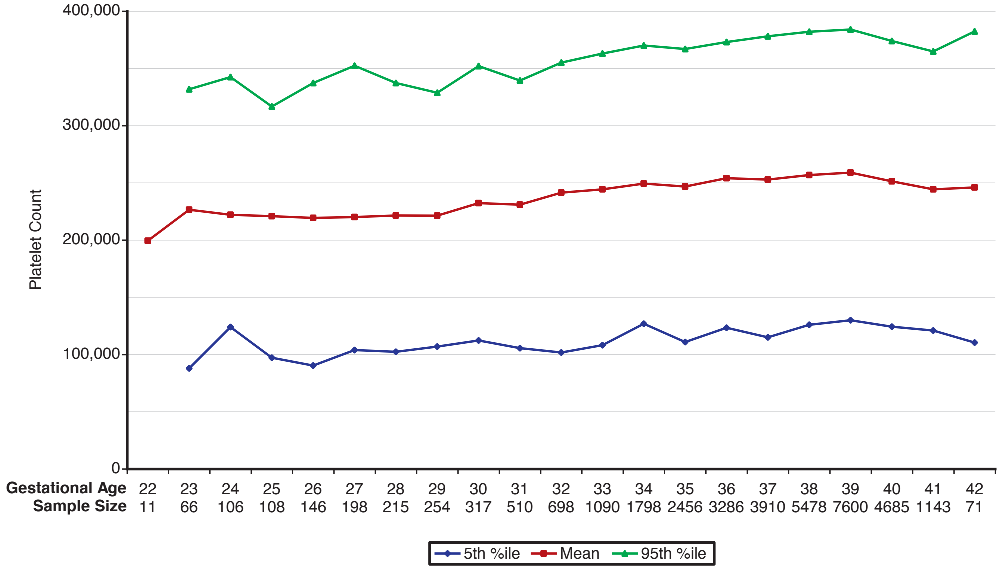

Figure 446-4 **Platelet count from 22 wk gestation through term.** The lines represent the 5th percentile, the mean, and the 95th percentile reference range. *(From Wiedmeier SE, Henry E, Sola-Visner MC, et al: Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system,* J Perinatol *29:130–136, 2009.)*

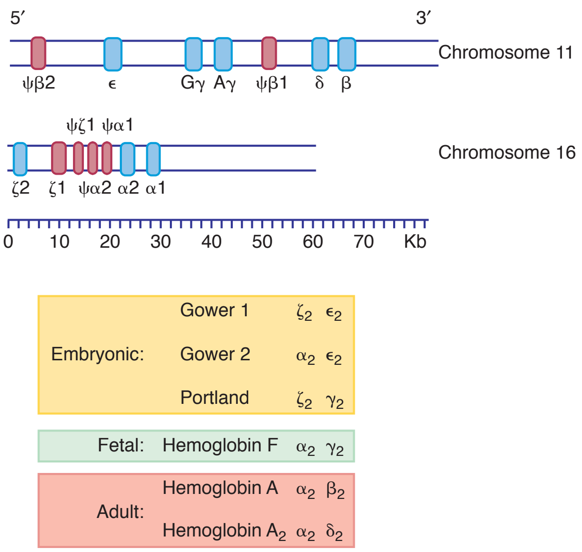

Figure 446-5 **Organization of the globin genes.** The bottom line reflects the scale in kilobases. The upper segment represents the beta-like globin genes on chromosome 11, and the lower segment the alpha-like genes on chromosome 16. Regions of the gene that code for primary globin proteins are shown as blue segments, and regions that code for pseudogenes ("ψ," nonexpressed remnants) are shown as pink segments. The composition of embryonic, fetal, and adult hemoglobins is listed. α, alpha; β, beta; γ, gamma; δ, delta; ε, epsilon; ζ, zeta.

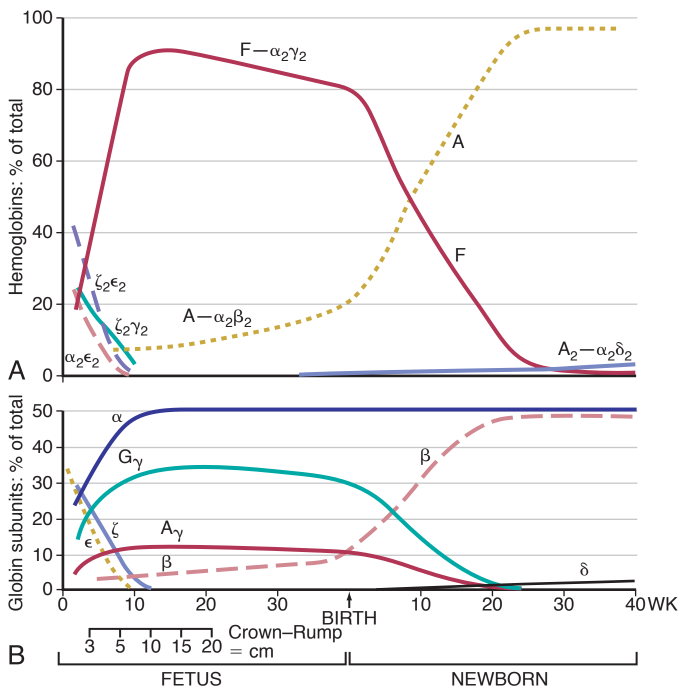

Figure 446-6 **Changes in hemoglobin tetramers (A) and in globin subunits (B) during human development from embryo to early infancy.** *(From Polin RA, Fox WW:* Fetal and neonatal physiology, *ed 2, Philadelphia, 1998, WB Saunders, p. 1769.)*

Adult Hemoglobins

By the 24th wk of gestation, HbA constitutes 5-10% of total hemoglobin. A steady increase follows, so that at term, HbA averages 30%. By 6-12 mo of age, the normal HbA pattern appears. The minor HbA component, HbA_2, contains δ chains and has the structure $\alpha_2\delta_2$. It is seen only when significant amounts of HbA are also present. At birth, <1.0% of HbA_2 is seen, but by 12 mo of age the normal level of 2.0-3.4% is attained. Throughout life, the normal ratio of HbA to HbA_2 is about 30 : 1.

Normal Relationships Among the Hemoglobins

During fetal life and early childhood, the rates of synthesis of γ and β chains and the amounts of HbA and HbF are inversely related. This relationship has been attributed to a "switch mechanism" similar to genetic regulatory mechanisms in bacteria, but the genetic, biologic, and developmental processes that direct a switchover from predominantly γ-chain synthesis in utero to predominantly β-chain synthesis after birth are unclear. It is not certain whether the mechanisms involve selective genetic inhibition or facilitation. The increase in the α_1-globin

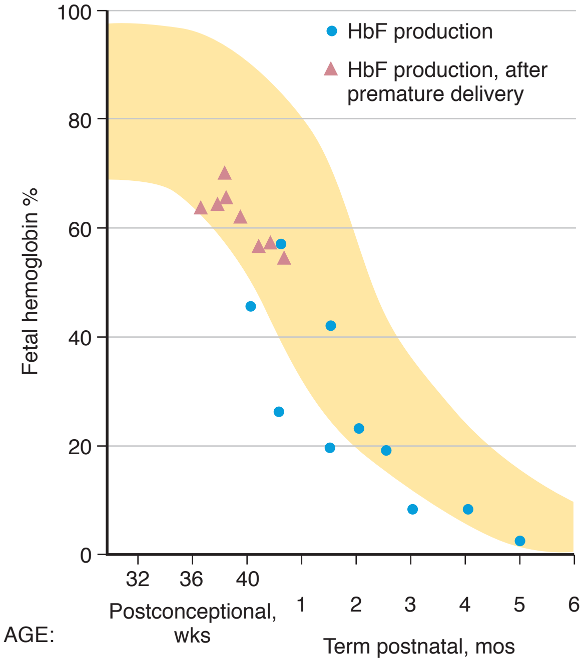

Figure 446-7 **Pre- and postnatal changes in the percentage of total hemoglobin represented by fetal hemoglobin (HbF) (yellow).** The triangles represent postnatal production by reticulocytes in premature infants, and the circles represent cord blood and postnatal reticulocyte production in term infants. *(From Brown MS: Fetal and neonatal erythropoiesis. In Stockman JA, Pochedly C, editors:* Developmental and neonatal hematology, *New York, 1988, Raven Press.)*

to α_2-globin ratio occurring after 36 wk gestation corresponds with a rapid decline in γ-globin synthesis, suggesting that these changes could be regulated by a coordinated molecular mechanism. Differential selection and amplified production of RBC precursors derived from burst-forming unit erythroid cells result in considerable HbF production. This may be the basis for the increased levels of HbF that occur in many hypoproliferative or hemolytic anemias. Alternative explanations involve more basic epigenetic regulation through processes such as methylation and deacetylation in the DNA sequences that flank the hemoglobin gene complexes.

Alterations of the Hemoglobins by Disease

Because hemoglobins containing ε chains normally are present only very early in intrauterine life, in the past they were largely of theoretical interest. Interest has been renewed by the growing method of isolation of free fetal DNA in the maternal circulation, allowing for noninvasive fetal diagnosis of a variety of genetic traits, such as RhD (rhesus antigen D) positivity in the fetus of an RhD negative mother. In addition, small amounts of the Gower hemoglobins have been detectable in a few newborns with trisomy 13. Increased levels of Hb Portland have been found in cord blood of stillborn infants with homozygous α-thalassemia.

HbF levels may be influenced by various factors. Because the HbF level is elevated during the 1st yr of life, knowledge of its normal decline is important (see Figs. 446-6 and 446-7). In persons heterozygous for β-thalassemia (β-thalassemia trait), postpartum decrease of HbF is delayed; approximately 50% of such persons have elevated levels of HbF (>2%) in later life. In homozygous thalassemia (Cooley anemia) and in hereditary persistence of HbF, large amounts of HbF characteristically are found. In patients with major β-chain hemoglobinopathies (HbSS [homozygous hemoglobin S], HbSC [sickle cell hemoglobin C]), HbF usually is increased, particularly during childhood. Preterm infants treated with human recombinant EPO increase HbF production during active erythropoiesis. Moderate elevations of HbF may occur in many diseases accompanied by hematologic stress, such as hemolytic anemias, leukemia, and aplastic anemia, because of a minor population of RBCs that contain increased amounts of HbF. Tetramers of γ chains (γ_4 or Hb Barts) or β chains (β_4, HbH) may be found in α-thalassemia syndromes.

The normal adult level of HbA_2 (2.0-3.4%) is seldom altered. Levels of HbA_2 >3.4% are found in most persons with the β-thalassemia trait and in those with megaloblastic anemias secondary to vitamin B_{12} and folic acid deficiency. Decreased HbA_2 levels are found in those with iron-deficiency anemia (see Chapter 455) and α-thalassemia (see Chapter 462).

RED CELL LIFE SPAN OF THE FETUS AND NEONATE

In general, the highest hematocrit during a person's lifetime occurs at birth, and the lowest occurs about 10 wk later. The reasons for this rapid fall are complex, but a shortened life-span of fetal/neonatal RBC has been suggested as an important component. Specifically, the RBC life span during the fetal and neonatal period is generally thought to be considerably less than the 120 day erythrocyte life span found in normal adults. Estimates of an average 60-90 day life span were derived in the 1960s from studies of chromium (^{51}Cr)-labeled RBC. The "extinction time" is the number of days after transfusing labeled RBC when the label is completely gone from the circulating RBC, thus it estimates the maximal RBC life span. Recent studies indicate that the extinction time of fetal/neonatal RBC is similar to that of adults. For instance, fetal RBC transfused into an ABO-compatible mother, by a fetomaternal transfusion, have an extinction time of 120 days. Moreover, erythrocytes drawn from neonates, labeled with biotin, and transfused back to the neonate, have a half-disappearance time similar to adult donor erythrocytes.

It is possible that some fraction of fetal RBC survive 120 days and are then removed in the spleen by senescence, just as occurs case in healthy adults, while other RBC are removed prematurely by an active process. Neocytolysis is one possibility explaining the active process. Neocytolysis is the active removal of young erythrocytes that were generated in relatively hypoxic conditions, following normoxic or hyperoxic conditions. Neocytolysis is the process whereby the high hematocrit of persons acclimated to high altitude falls rapidly after descent to sea level (a process somewhat analogous to the change from fetal to postbirth oxygen saturations). It will be instructive to determine whether neocytolysis is, indeed, an important regulator of erythrocyte life span and bilirubin production after birth, and whether this process explains the marked fall in hematocrit but a normal RBC "extinction time" in human neonatal physiology.

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Chapter **447**

The Anemias

Norma B. Lerner

Anemia is defined as a reduction of the hemoglobin concentration or red blood cell (RBC) volume below the range of values occurring in healthy persons. "Normal" hemoglobin and hematocrit (packed red cell volume) vary substantially with age and sex (Table 447-1). There are also racial differences, with significantly lower hemoglobin levels in African-American children than in white non-Hispanic children of comparable age (Table 447-2). Anemia is a significant global health problem affecting children and reproductive age women (Figs. 447-1 and 447-2).

Physiologic adjustments to anemia include increased cardiac output, augmented oxygen extraction (increased arteriovenous oxygen difference), and a shunting of blood flow toward vital organs and tissues. In

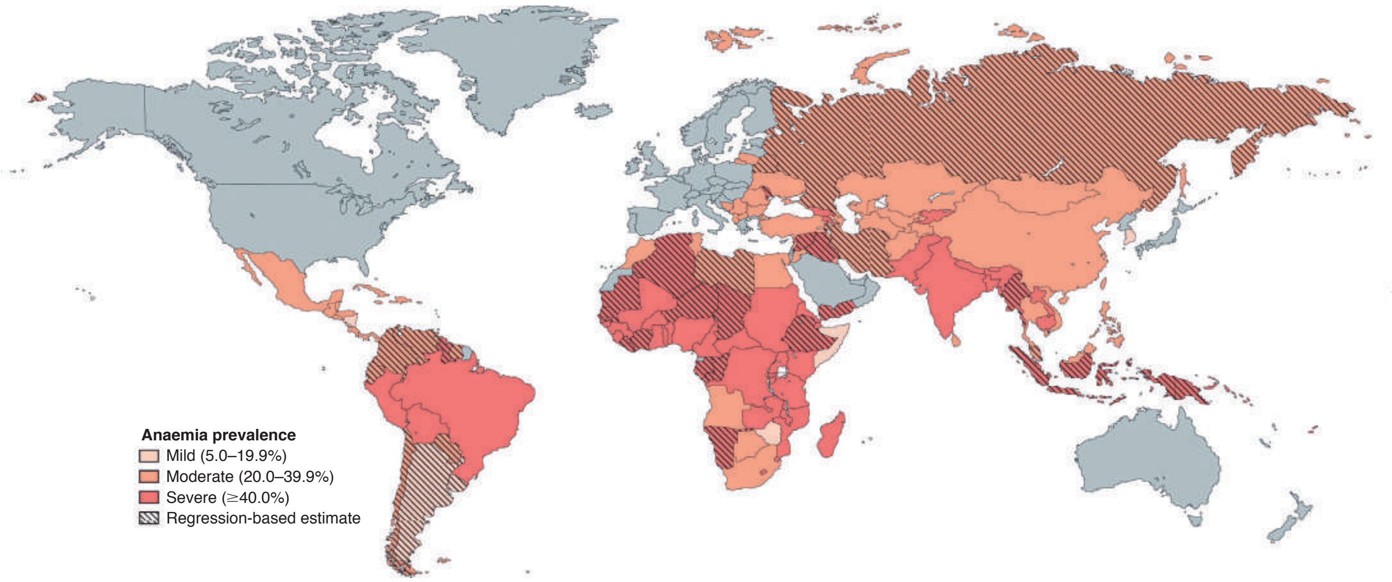

Figure 447-1 Global prevalence of anaemia in children of preschool age (0–5 yr). *(Adapted from* Worldwide prevalence of anaemia 1993–2005: WHO global database on anaemia. *Geneva, Switzerland, 2008, World Health Organization.)*

Table 447-1 Normal Mean and Lower Limits of Normal for Hemoglobin, Hematocrit, and Mean Corpuscular Volume

	HEMOGLOBIN (g/dL)		HEMATOCRIT (%)		MEAN CORPUSCULAR VOLUME (μM³)	
Age (yr)	**Mean**	**Lower Limit**	**Mean**	**Lower Limit**	**Mean**	**Lower Limit**
0.5-1.9	12.5	11.0	37	33	77	70
2-4	12.5	11.0	38	34	79	73
5-7	13.0	11.5	39	35	81	75
8-11	13.5	12.0	40	36	83	76
12-14 female	13.5	12.0	41	36	85	78
12-14 male	14.0	12.5	43	37	84	77
15-17 female	14.0	12.0	41	36	87	79
15-17 male	15.0	13.0	46	38	86	78
18-49 female	14.0	12.0	42	37	90	80
18-49 male	16.0	14.0	47	40	90	80

From Brugnara C, Oski FJ, Nathan DG: Nathan and Oski's hematology of infancy and childhood, *ed 7, Philadelphia, 2009, WB Saunders, p. 456.*

Table 447-2 NHANES III Hemoglobin Values for Non-Hispanic Whites and African-Americans Ages 2-18 Yr

	WHITE NON-HISPANIC		AFRICAN-AMERICAN	
Age (yr)	**Mean**	**–2 SD**	**Mean**	**–2 SD**
2-5	12.21	10.8	11.95	10.37
6-10	12.87	11.31	12.40	10.74
11-15 male	13.76	11.76	13.06	10.88
11-15 female	13.32	11.5	12.61	10.85
16-18 male	15.00	13.24	14.18	12.42
16-18 female	13.39	11.61	12.37	10.37

Sample size is 5,142 (white, 2,264; African-American, 2,878).

Modified from Robbins EB, Blum S: Hematologic reference values for African American children and adolescents, Am J Hematol *82:611–614, 2007.*

addition, the concentration of 2,3-diphosphoglycerate increases within the RBC. The resultant "shift to the right" of the oxygen dissociation curve reduces the affinity of hemoglobin for oxygen and results in more complete transfer of oxygen to the tissues. The same shift in the oxygen dissociation curve can also occur at high altitude. Higher levels of erythropoietin (EPO) and consequent increased red cell production by the bone marrow further assist the body to adapt.

HISTORY AND PHYSICAL EXAMINATION

As with any medical condition, a detailed history and thorough physical exam are essential when evaluating an anemic child. Important historical facts should include age, sex, race and ethnicity, diet, medications, chronic diseases, infections, travel, and exposures. A family history of anemia and/or associated difficulties such as splenomegaly, jaundice, or early age onset of gallstones is also of consequence. There often are few physical symptoms or signs that result solely from a low hemoglobin, particularly when the anemia develops slowly. Clinical findings generally do not become apparent until the hemoglobin level falls to <7-8 g/dL. Clinical features can include pallor, sleepiness,

irritability, and decreased exercise tolerance. Pallor can involve the tongue, nail beds, palms, or palmar creases. A flow murmur is often present. Ultimately, weakness, tachypnea, shortness of breath on exertion, tachycardia, cardiac dilation, and high-output heart failure will result from increasingly severe anemia, regardless of its cause. Unusual physical findings linked to particular underlying disease etiologies are discussed in detail in sections describing the associated disorders.

LABORATORY STUDIES

Initial laboratory testing should include hemoglobin, hematocrit, and red cell indices as well as a white blood cell count and differential, platelet count, reticulocyte count, and examination of the peripheral blood smear. The need for additional laboratory studies is dictated by the history, the physical, and the results of this initial testing.

DIFFERENTIAL DIAGNOSIS

Anemia is not a specific entity but rather can result from any of number of underlying pathologic processes. To narrow the diagnostic possibilities, anemias may be classified on the basis of their morphology and/or physiology (Fig. 447-3).

Anemias may be morphologically categorized on the basis of RBC size (mean corpuscular volume [MCV]), and microscopic appearance. They can be classified as microcytic, normocytic, or macrocytic based on whether the MCV is low, normal, or high, respectively. RBC size also changes with age, and normal developmental changes in MCV should be recognized before a designation is made (see Table 447-1). Examination of a peripheral blood smear often reveals changes in RBC appearance that will help to further narrow the diagnostic categories (Fig. 447-4). Details regarding morphologic changes associated with particular disorders are described in subsequent sections.

Anemias may also be further divided on the basis of underlying physiology. The 2 major categories are decreased production and increased destruction or loss. The 2 groups are not always mutually exclusive. Decreased RBC production may be a consequence of ineffective erythropoiesis or a complete or relative failure of erythropoiesis. Increased destruction or loss may be secondary to hemolysis, sequestration, or bleeding. The peripheral blood reticulocyte percentage or absolute number will help to make a distinction between the 2 physiologic categories. The normal reticulocyte percentage of total RBCs during most of childhood is approximately 1%, with an absolute reticulocyte count of 25,000-75,000/mm^3. In the presence of anemia, EPO production and the absolute number of reticulocytes should rise. Low or normal numbers of reticulocytes generally represent an inadequate response to anemia that is associated with relative bone marrow failure or ineffective erythropoiesis. Increased numbers of reticulocytes represent a normal bone marrow response to ongoing RBC destruction (hemolysis), sequestration, or loss (bleeding).

Figure 447-3 presents a useful approach to assessing the common causes of anemia in the pediatric age group. Children with microcytic anemia and low or normal reticulocyte counts most often have defects in erythroid maturation or ineffective erythropoiesis. *Iron deficiency* (see Chapter 455) is the most common cause. *Thalassemia trait* (see Chapter 462) constitutes the primary differential diagnosis when iron deficiency is suspected. Distinctions between these entities are presented in Table 455-1 (see Chapter 455). *Chronic disease or inflammation (more often normocytic)*, *lead poisoning, and sideroblastic anemias* should also be considered and are discussed in other chapters. Microcytosis and elevated reticulocyte counts are associated with thalassemia syndromes and hemoglobins C and E (see Chapter 462). Notably, thalassemias and hemoglobinopathies are most commonly seen in patients of Mediterranean, Middle Eastern, African, or Asian descent.

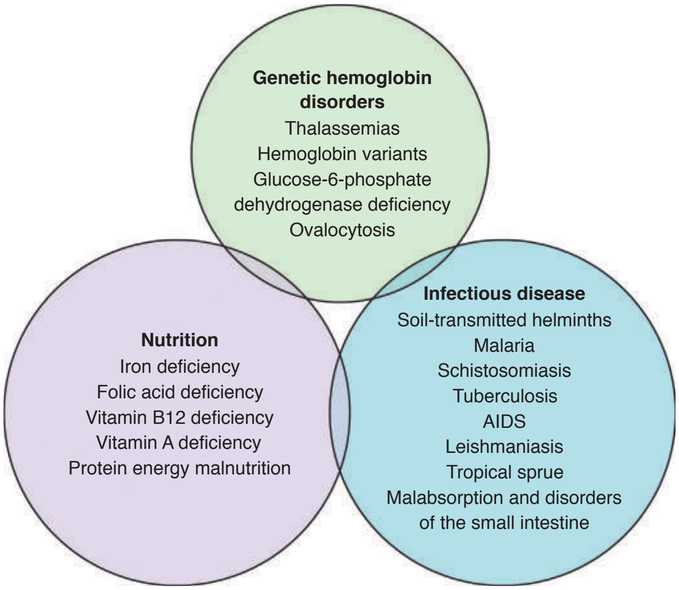

Figure 447-2 Causes of anaemia in countries with low or middle incomes. *(From Balarajan Y, Ramakrishnan U, Özaltin E, et al: Anaemia in low-income and middle-income countries.* Lancet *378:2123–2134, 2011, Fig. 3.)*

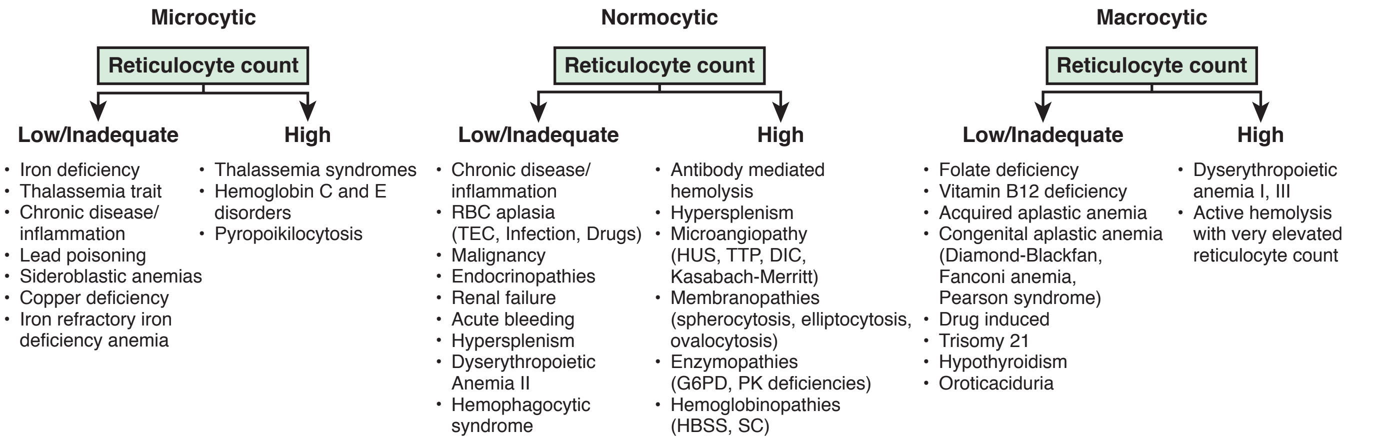

Figure 447-3 Use of the mean corpuscular volume (MCV) and reticulocyte count in the diagnosis of anemia. *(Adapted from Brunetti M, Cohen J:* The Harriet Lane handbook, *ed 17, Philadelphia, 2005, Elsevier Mosby, p 338.)*

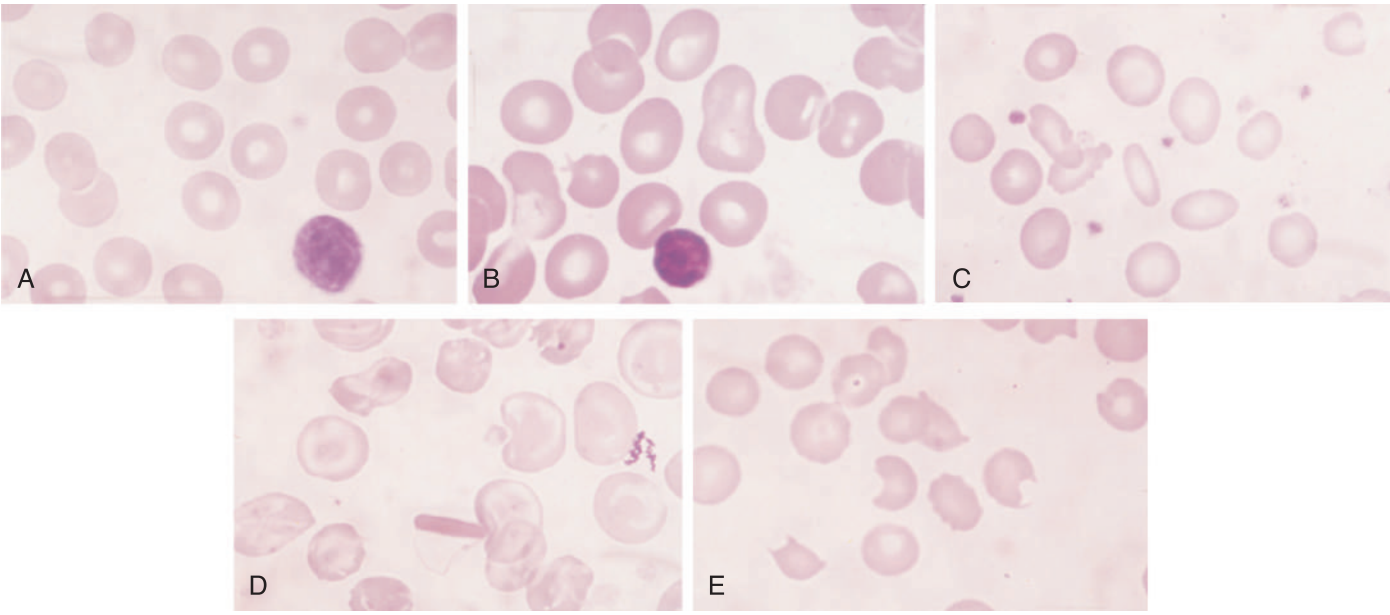

Figure 447-4 **Morphologic abnormalities of the red blood cell. A,** Normal. **B,** Macrocytes (folic acid or vitamin B_{12} deficiency). **C,** Hypochromic microcytes (iron deficiency). **D,** Target cells (HbCC disease). **E,** Schizocytes (hemolytic-uremic syndrome). *(Courtesy of Dr. E. Schwartz.)*

Normocytic anemia and low reticulocyte count characterize a large number of anemias. The *anemia of chronic disease/inflammation* (see Chapter 455) is usually normocytic. The anemia associated with renal failure, primarily a result of reduced EPO production, will invariably be associated with clinical and laboratory evidence of significant kidney disease. Decreased or absent red cell production secondary to transient erythroblastopenia of childhood, infection, drugs, or endocrinopathy usually results in a normocytic anemia, as does bone marrow infiltration by malignancy. In the case of invading leukemia or malignancy, abnormal leukocytes or tumor cells in association with thrombocytopenia or reduced or elevated white cell counts may be seen. Acute bleeding, hypersplenism, and congenital dyserythropoietic anemia type II (see Chapter 452) are also normocytic.

In children with normocytic anemia and an appropriate (high) reticulocyte response, the anemia is usually a consequence of bleeding, hypersplenism, or ongoing hemolysis. In hemolytic conditions, reticulocytosis, indirect hyperbilirubinemia, and increased serum lactate dehydrogenase are indicators of accelerated erythrocyte destruction. There are many causes of hemolysis, resulting from conditions that are extrinsic (usually acquired) or intrinsic (usually congenital) to the red cell. Abnormal RBC morphology (e.g., spherocytes, sickle forms, microangiopathy) identified on the peripheral smear is often helpful in ascertaining the cause.

The anemia seen in children with macrocytic blood cells is sometimes megaloblastic (see Chapter 454), resulting from impaired DNA synthesis and nuclear development. The peripheral blood smear in megaloblastic anemias contains large macroovalocytes, and the neutrophils often show nuclear hypersegmentation. The major causes of megaloblastic anemia include folate deficiency, vitamin B_{12} deficiency, and rare inborn errors of metabolism. Other macrocytic anemias with low or normal reticulocyte counts include acquired and congenital (Diamond-Blackfan and Fanconi) aplastic anemias and hypothyroidism. Patients with trisomy 21 have macrocytic cells, although an accompanying anemia is generally not present. High MCV and reticulocytosis is seen in congenital dyserythropoietic anemias I and III, and in situations wherein hemolysis results in such a large outpouring of young red cells that the mean MCV is abnormally high.

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Section 2

Anemias of Inadequate Production

Chapter 448

Congenital Hypoplastic Anemia (Diamond-Blackfan Anemia)

Norma B. Lerner

Diamond-Blackfan anemia (DBA) is a rare, congenital bone marrow failure syndrome that usually becomes symptomatic in early infancy. More than 90% of cases are recognized in the 1st yr of life. The disorder is characterized by anemia, usually normochromic and macrocytic, reticulocytopenia, and insufficient or absent of red blood cell (RBC) precursors in an otherwise normally cellular bone marrow. Up to 50% of affected individuals have additional, extrahematopoietic anomalies.

ETIOLOGY

DBA associated mutations were initially identified in *RPS19,* a gene that encodes a component protein of the small 40S ribosomal subunit. Such *RPS19* mutations, all dominantly inherited, were found to be present in approximately 25% of patients. Nine other DBA genes were subsequently recognized, each encoding a different small (40S) or large (60S) ribosomal subunit protein. Mutations in 1 of the 10 ribosomal

protein (RP) genes were ultimately identified in 50-70% of cases. Although the disorder is often referred to as a **ribosomopathy**, the mechanism by which RP haploinsufficiency leads to DBA has not been fully elucidated. One hypothesis is that unaffected RPs pile up and then bind and inhibit the p53 regulator, MDM_2. This process allows p53 to accumulate, causing cell-cycle arrest and apoptosis of erythroid precursors.

Two distinct mutations in the hematopoietic transcription factor GATA-1 were identified in 2 siblings and 1 unrelated patient with corticosteroid-dependent DBA. It remains unclear whether two pathways, one related to ribosomal dysfunction and one to impaired GATA-1 production, independently cause the same phenotype, or, alternatively that DBA results from problems in a single pathway involving functional links between ribosomes and GATA-1.

EPIDEMIOLOGY

DBA affects about 7 individuals per 1 million live births. It is primarily an autosomal dominant disease, although other inheritance patterns may yet be demonstrated. Notably, there is substantial phenotypic diversity in DBA, even in families whose members share the same mutation, suggesting that additional genetic modifiers affect phenotypic expression of the disease. International consensus recommendations suggest that a diagnosis of "nonclassical" DBA be applied to family members harboring an established mutation or those without a known mutation but with an associated anomaly or laboratory abnormality.

CLINICAL MANIFESTATIONS

Profound anemia usually becomes evident by 2-6 mo of age, occasionally somewhat later. Approximately 25% of patients are anemic at birth and hydrops fetalis occurs rarely; 92% are diagnosed within the first year of life. Approximately 50% of patients have congenital anomalies and more than 1 anomaly is found in 21% of individuals with DBA (Table 448-1). Craniofacial abnormalities are the most common (50% of patients) and include hypertelorism, snub nose, and high arched palate. Skeletal anomalies, mostly upper limb and hand, affect 30% of patients. Thumb abnormalities, including flattening of the thenar eminence and triphalangeal thumb, may be bilateral or unilateral. The radial pulse may be absent. Genitourinary (38% of patients), cardiac (30% of patients), ophthalmologic, and musculoskeletal anomalies have also been identified. Short stature is common, but it is often unclear whether this characteristic results from the disease itself, related therapies, or both.

Table 448-1 Range of Congenital Anomalies Observed in Diamond-Blackfan Anemia

Craniofacial	Hypertelorism Broad, flat nasal bridge Cleft palate High arched palate Microcephaly Micrognathia Microtia Low-set ears Low hair line Epicanthus Ptosis
Ophthalmologic	Congenital glaucoma Strabismus Congenital cataract
Neck	Short neck Webbed neck Sprengel deformity Klippel-Feil deformity
Thumbs	Triphalangeal Duplex or bifid Hypoplastic Flat thenar eminence Absent radial artery
Urogenital	Absent kidney Horseshoe kidney Hypospadias
Cardiac	Ventricular septal defect Atrial septal defect Coarctation of the aorta Complex cardiac anomalies
Other musculoskeletal	Growth retardation Syndactyly
Neuromotor	Learning difficulties

The list includes the anomalies that are most characteristic of DBA but is not exhaustive. Multiple anomalies, most commonly including craniofacial, are present in up to 25% of affected individuals.

From Vlachos A, Ball S, Dahl N, et al: Diagnosing and treating Diamond Blackfan anaemia: results of an international clinical consensus conference. Br J Haematol *142:859–876, 2008 (Table IV, p. 862).*

LABORATORY FINDINGS

The RBCs are usually macrocytic for age, but no hypersegmented neutrophils or other characteristics of megaloblastic anemia are appreciated on the peripheral blood smear. Red cell enzyme patterns are similar to those of a "fetal" RBC population with increased expression of "i" antigen and elevated fetal hemoglobin. Erythrocyte adenosine deaminase (ADA) activity is increased in most patients with this disorder, a finding that helps distinguish congenital RBC aplasia from acquired *transient erythroblastopenia of childhood* (see Chapter 450). Because elevated ADA activity is not a fetal RBC feature, measurement of this enzyme may be particularly helpful when diagnosing DBA in very young infants. Thrombocytosis or, rarely, thrombocytopenia, and occasionally neutropenia, may also be present. Reticulocyte percentages are characteristically very low despite severe anemia. Bone marrow erythrocyte precursors are markedly reduced in most patients; other marrow elements are usually normal. Serum iron levels are elevated. Unlike Fanconi anemia, there is no increase in chromosomal breaks when lymphocytes are exposed to alkylating agents.

DIFFERENTIAL DIAGNOSIS

DBA must be differentiated from other anemias associated with low reticulocyte counts. The syndrome of **transient erythroblastopenia of childhood (TEC)** is often the primary alternative diagnosis. Table 450-1 in Chapter 450 shows a useful comparison of findings in these two disorders. TEC often is differentiated from DBA by its relatively late onset, although it occasionally develops in infants <6 mo of age (see Chapter 450). Macrocytosis, congenital anomalies, fetal red cell characteristics, and elevated erythrocyte ADA are generally associated with DBA and not with TEC.

Other inherited macrocytic bone marrow failure syndromes, particularly Fanconi anemia and Shwachman-Diamond syndrome, should also be considered in the differential as should myelodysplastic syndrome. Hemolytic disease of the newborn can also mimic features of DBA because it can have a protracted course and can be coupled with markedly reduced erythropoiesis. The anemia in this disorder usually resolves spontaneously at 5-8 wk of age. Several types of chronic hemolytic disease may be complicated by an **aplastic crisis**, characterized by reticulocytopenia and decreased numbers of RBC precursors. This event usually occurs after the first several mo of life and is often caused by parvovirus B19 infection (see Chapter 450). Infection with parvovirus B19 (see Chapter 251) in utero also may be associated with pure RBC aplasia in infancy, and even with hydrops fetalis at birth. When diagnosing DBA in young infants, it is important to rule out parvovirus B19 infection using the polymerase chain reaction. Other infections, including HIV, as well as drugs, immune processes, and Pearson syndrome (see Chapter 449) should also be ruled out.

TREATMENT

Corticosteroids are a mainstay of therapy, and approximately 80% of patients initially respond. Because corticosteroids impair linear growth as well as physical and neurocognitive development, many hematologists maintain infants on chronic transfusion therapy and delay the start of steroids until after age 1 yr. Prednisone or prednisolone in doses totaling 2 mg/kg/day is used as an initial trial. An increase in RBC precursors is usually seen in the bone marrow 1-3 wk after therapy is begun and is followed by peripheral reticulocytosis. The hemoglobin can reach normal levels in 4-6 wk, although the rate of response is quite variable. Once it is established that the hemoglobin concentration is increasing, the dose of corticosteroid may be reduced gradually by tapering and then by eliminating all except a single, lowest effective daily dose. This dose may then be doubled, used on alternate days, and tapered still further while maintaining the hemoglobin level at ≥9 g/dL. The target maintenance dose should not exceed 0.5 mg/kg/day or 1 mg/kg every other day. In some patients, very small amounts of prednisone, as low as 2.5 mg twice a wk, may be sufficient to sustain adequate erythropoiesis. Scheduled surveillance examinations and testing for corticosteroid side effects should be pursued in all patients, regardless of dose. Appropriate *Pneumocystis* prophylaxis should be used after the first month of high-dose steroids and continued until the patient is on low-dose alternate-day therapy. Many children with DBA stop taking corticosteroids, usually because of unacceptable side effects or the evolution of corticosteroid refractoriness. Only 37% of patients in the Diamond-Blackfan Anemia Registry (DBAR) (http://www.dbar.org/) remained on corticosteroids.

Patients who are nonresponders or who fail to tolerate corticosteroid therapy require transfusions at intervals of 3-5 wk to maintain a hemoglobin level greater than 8 g/dL. Some younger children may require hemoglobin levels greater than 9 g/dL in order to sustain normal growth and activities. Appropriate screening and, ultimately, the initiation of chelation therapy will be required as excess iron accumulates secondary to repeated transfusions. In one case report, a patient with DBA who was treated with L-leucine became transfusion independent and remained in remission at >5 mo.

Spontaneous remission of anemia with independence from steroid or red cell transfusion therapy has been reported. The likelihood of remission is 25% by age 25 yr, with the majority of patients experiencing remission during the first decade. Mild macrocytic anemia and increased erythrocyte ADA levels persist in these circumstances.

Hematopoietic stem cell transplantation (HSCT) can be curative. As the best outcomes occur using human leukocyte antigen (HLA)-matched sibling donors in patients 9 yr of age or younger. HLA-matched sibling HSCT is recommended in affected, transfusion dependent children between the ages of 3 and 9 yr. It is important that sibling donors be carefully screened, including genotype if known, to ensure that the donor does not carry the patient's DBA gene. Improvements in alternative donor HSCT suggests that this modality may also provide an important option for select patients.

PROGNOSIS

DBA has been identified as a cancer predisposition syndrome. The risk is increased for myelodysplastic syndrome, acute myeloid leukemia, colon carcinoma, osteogenic sarcoma, and female genital cancers. The overall actuarial survival of all patients with DBA is approximately 75% at age 40 yr, with approximately 87% for those maintained on steroids, and approximately 57% for transfusion-dependent patients. Of reported deaths, 67% were treatment related and 22% were DBA-related (malignancy and severe aplastic anemia).

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Chapter 449

Pearson Syndrome

Norma B. Lerner

Pearson marrow-pancreas syndrome is a rare mitochondrial disorder that presents with a hypoplastic anemia that may be initially confused with Diamond-Blackfan syndrome or transient erythroblastopenia of childhood. The marrow failure usually appears in the neonatal period and is characterized by a macrocytic anemia and, occasionally, neutropenia and thrombocytopenia. There are vacuolated erythroblasts and myeloblasts in the bone marrow. This disorder is considered a unique variant of **congenital sideroblastic anemia** as the marrow also contains ringed sideroblasts. The hemoglobin F level is elevated. There is multiorgan involvement manifested by failure to thrive and symptoms of exocrine pancreas dysfunction, liver and renal tubular defects, malabsorption, and myopathy. Endocrine dysfunction has also been reported. In rare cases, when the disease is not fatal in early childhood, the disorder may evolve to include symptoms consistent with Kearns-Sayre syndrome.

This disorder is caused by a mitochondrial DNA deletion of variable size and location that is similar to the mitochondrial DNA (mtDNA) deletion found in Kearns-Sayre syndrome. There is heterogeneity in different tissues and between patients, accounting for the variable clinical picture. The proportion of deleted mtDNA in the bone marrow correlates with the severity of the hematologic picture, and a change in the percentage of tissue mtDNA types over time may be associated with spontaneous improvement of red blood cell hypoproliferation. Therapy for the hematologic manifestations of the disease is primarily supportive and includes red cell transfusions to correct anemia and granulocyte colony-stimulating factor to reverse episodes of severe neutropenia.

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Chapter 450

Acquired Pure Red Blood Cell Anemia

Norma B. Lerner

TRANSIENT ERYTHROBLASTOPENIA OF CHILDHOOD

Transient erythroblastopenia of childhood (TEC) is the most common *acquired red cell aplasia* occurring in children. It is more prevalent than congenital hypoplastic (Diamond-Blackfan) anemia. This syndrome of severe, transient hypoplastic anemia occurs mainly in previously healthy children between 6 mo and 3 yr of age; most of the children are older than 12 mo at onset. Only 10% of affected patients are >3 yr of age. The annual incidence is estimated to be 4.3 cases per 100,000 children, although it is likely higher, because many cases might go undiagnosed and resolve spontaneously. The suppression of erythropoiesis has been linked to immunoglobulin (Ig) G, IgM, and cell-mediated mechanisms. Familial cases have been reported, suggesting

a hereditary component. TEC often follows a viral illness, although no specific virus has been consistently implicated.

The temporary suppression of erythropoiesis results in reticulocytopenia and moderate to severe normocytic anemia. Some degree of neutropenia occurs in up to 20% of cases. Platelet numbers are normal or elevated. Similar to the situation observed in iron-deficiency anemia and other red blood cell (RBC) hypoplasias, thrombocytosis is presumably caused by increased erythropoietin, which has some homology with thrombopoietin. Mean corpuscular volume (MCV) is characteristically normal for age, and fetal hemoglobin (HbF) levels are normal before the recovery phase. RBC adenosine deaminase levels are normal in this disorder, thus contrasting with the elevation noted in most cases of congenital hypoplastic anemia (Table 450-1). Differentiation from the latter disease is sometimes difficult, but differences in age at onset and in age-related MCV, HbF, and adenosine deaminase are usually helpful. The peak occurrence of TEC coincides with that of iron-deficiency anemia in infants receiving milk as their main caloric source; differences in MCV should help to distinguish between these 2 disorders.

Virtually all children recover within 1-2 mo. RBC transfusions may be necessary for severe anemia in the absence of signs of early recovery. The anemia develops slowly, and significant symptoms usually develop only with severe anemia. Corticosteroid therapy is of no value in this disorder. Any child with presumed TEC who requires >1 transfusion should be reevaluated for another possible diagnosis. In rare instances, a prolonged case of apparent TEC may be caused by parvovirus-induced RBC aplasia, occurring in children with *hemolytic anemia* or *congenital* or *acquired immunodeficiencies*.

Table 450-1 Comparison of Diamond-Blackfan Anemia and Transient Erythroblastopenia of Childhood

FEATURE	DBA	TEC
Male : female	1.1	1.3
AGE AT DIAGNOSIS, MALE (MO)		
Mean	10	26
Median	2	23
Range	0-408	1-120
AGE AT DIAGNOSIS, FEMALE (MO)		
Mean	14	26
Median	3	23
Range	0-768	1-192
Boys >1 yr	9%	82%
Girls >1 yr	12%	80%
Etiology	Genetic	Acquired
Antecedent history	None	Viral illness
Physical examination abnormal (congenital anomalies present)	25%	0%
LABORATORY		
Hemoglobin (g/dL)	1.2-14.8	2.2-12.5
WBCs <5,000/µL	15%	20%
Platelets >400,000/µL	20%	45%
Adenosine deaminase	Increased	Normal
MCV increased at diagnosis	80%	5%
MCV increased during recovery	100%	90%
MCV increased in remission	100%	0%
HbF increased at diagnosis	100%	20%
HbF increased during recovery	100%	100%
HbF increased in remission	85%	0%
i Antigen increased	100%	20%
i Antigen increased during recovery	100%	60%
i Antigen increased in remission	90%	0%

DBA, Diamond-Blackfan anemia; HbF, fetal hemoglobin; MCV, mean cell volume; TEC, transient erythroblastopenia of childhood; WBC, white blood cell.

From Nathan DG, Orkin SH, Ginsburg D, et al, editors: Nathan and Oski's hematology of infancy and childhood, *ed 6, vol 1, Philadelphia, 2003, WB Saunders, p. 329. Adapted from Alter BP: The bone marrow failure syndromes. In Nathan DG, Oski FA, editors:* Hematology of infancy and childhood, *ed 3, Philadelphia, 1987, WB Saunders, p. 159; and Link MP, Alter BP: Fetal erythropoiesis during recovery from transient erythroblastopenia of childhood (TEC),* Pediatr Res *15:1036–1039, 1981.*

RED CELL APLASIA ASSOCIATED WITH PARVOVIRUS B19 INFECTION

Parvovirus B19 is a common infectious agent that causes erythema infectiosum (fifth disease) (see Chapter 251). It is also the best-documented viral cause of RBC aplasia in patients with chronic hemolysis, patients who are immunocompromised, and fetuses in utero. This small, nonenveloped single-stranded virus is particularly infective and cytotoxic to marrow erythroid progenitor cells, interacting specifically via binding to the red cell P antigen. In addition to decreased or absent erythroid precursors, characteristic nuclear inclusions in erythroblasts and giant pronormoblasts may be seen under the light microscope in bone marrow specimens. The virus does not cause significant anemia in immunocompetent individuals with normal red cell life spans.

CHRONIC HEMOLYSIS

Because parvovirus infection is usually transient, with recovery occurring in <2 wk, anemia is either not present or not appreciated in otherwise normal children whose peripheral RBC life span is 100-120 days. The RBC life span is much shorter in patients with hemolysis secondary to conditions such as hereditary spherocytosis, immune hemolytic anemia, or sickle cell disease. In these children, a brief cessation of erythropoiesis can cause severe anemia, a condition known as an **aplastic crisis**. When a definitive diagnosis is required, the work-up should include serum parvovirus IgM and IgG titers and, if needed, viral detection using polymerase chain reaction (PCR) techniques. Recovery from moderate to severe anemia is usually spontaneous, heralded by a wave of nucleated RBCs and subsequent reticulocytosis in the peripheral blood. A RBC transfusion may be necessary if the anemia is associated with significant symptoms. Notably, parvovirus-induced aplastic crisis usually occurs only once in children with chronic hemolysis. In families with >1 child affected with a hemolytic disorder, parents should be warned that a similar aplastic episode can occur in the other children if they have not been previously infected.

IMMUNODEFICIENCY

Persistent parvovirus infection may occur in children with congenital immunodeficiency diseases, lymphoproliferative disorders, those being treated with immunosuppressive agents, and those with HIV/AIDS, because these children may be unable to mount an adequate antibody response. The resultant pure RBC aplasia may be severe, and affected children may be thought to have TEC. This type of RBC aplasia differs from TEC in that there is no spontaneous recovery and >1 transfusion is often needed. The diagnosis of parvovirus infection is made by PCR of peripheral blood or bone marrow DNA because the usual serologic responses, reflected by parvovirus serum IgM or IgG titers, are impaired in immunodeficient children. In chronically infected patients, the disease may be treated with high doses of intravenous immunoglobulin, which contains neutralizing antibody to parvovirus and is effective in the short term.

MISCARRIAGE AND HYDROPS FETALIS

Parvovirus infection and destruction of erythroid precursors can also occur in utero. Such events are associated with increased fetal wastage in the first and second trimesters. Infants may be born with hydrops fetalis (see Chapter 103) and anemia. The presence of persistent congenital parvovirus infection is detected by PCR of peripheral blood and/or bone marrow DNA, because immunologic tolerance to the virus can prevent the usual development of specific antibodies.

OTHER RED CELL APLASIAS IN CHILDREN

Acquired red cell aplasia in adults is usually mediated by a chronic antibody and often associated with disorders such as chronic lymphocytic leukemia, lymphoma, thymoma, lymphoproliferative disorders, and systemic lupus erythematosus. This chronic antibody-mediated type of RBC aplasia, often responsive to immunosuppressive therapy,

is quite rare in childhood. Cases of acquired pure red cell aplasia, attributable to T-cell suppression, have also been described.

Certain drugs, such as chloramphenicol, also can inhibit erythropoiesis in a dose-dependent manner. Reticulocytopenia, erythroid hypoplasia, and vacuolated pronormoblasts in the bone marrow are reversible effects of this drug. These effects are distinct from the idiosyncratic and rare development of severe aplastic anemia in chloramphenicol recipients. Acquired antibody-mediated pure red cell aplasia has also been found to be a rare complication in chronic kidney disease patients treated with erythropoiesis-stimulating agents. In addition to discontinuing erythropoiesis-stimulating agents therapy and addressing anemia with red cell transfusions, further treatment may include immunosuppression and renal transplantation.

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Chapter 451 Anemia of Chronic Disease and Renal Disease

451.1 Anemia of Chronic Disease

Norma B. Lerner

The anemia of chronic disease (ACD), also referred to as **anemia of inflammation**, is found in conditions where there is ongoing immune activation. It occurs in a wide a range of disorders including infections, malignancies, autoimmunity, and graft-versus-host disease. A similar anemia is associated with chronic kidney disease. ACD is typically a mild to moderate normocytic, normochromic, hypoproliferative anemia associated with a decreased serum iron and low transferrin saturation.

ETIOLOGY

Decreased red cell life span, impaired erythropoiesis, and an increased uptake of iron in the reticuloendothelial system are important mechanisms contributing to the anemia. The modest reduction in erythrocyte longevity is perhaps the least well understood part of the pathophysiology of ACD. Elevated levels of cytokines such as interleukin-1 may increase the macrophage's ability to ingest and destroy erythrocytes. Defective erythropoiesis, both proliferation and differentiation of precursors, has been attributed to immune cell/cytokine-driven inhibition of erythropoietin production and suppression of the bone marrow.

ACD associated alterations in iron recycling is characterized by an accumulation of iron in reticuloendothelial macrophages despite low levels of serum iron. The diversion of iron from the circulation into the reticuloendothelial system results in functional iron deficiency, which results in the impaired heme synthesis and iron-restricted erythropoiesis that contribute to anemia. These alterations in iron metabolism have been attributed to inflammation-associated excess synthesis of **hepcidin**, a key regulatory protein that controls intestinal iron absorption and tissue distribution. Hepcidin, although mainly synthesized by hepatocytes, is also expressed in other cells, including monocytes and macrophages. It functions by binding to and initiating the degradation of the iron exporter, ferroportin.

CLINICAL MANIFESTATIONS

Although the important symptoms and signs associated with ACD are those of the underlying disease, the mild to moderate anemia can affect the patient's quality of life.

LABORATORY FINDINGS

Hemoglobin concentrations are generally 6-9 g/dL. The anemia is usually normochromic and normocytic, although some patients have modest hypochromia and microcytosis, particularly if there is concomitant iron deficiency. Absolute reticulocyte counts are normal or low, and leukocytosis is common. The serum iron level is low, without the increase in serum transferrin that occurs in iron deficiency. This pattern of low serum iron and low-to-normal iron-binding protein (serum transferrin) is a regular and valuable diagnostic feature. *The serum ferritin level may be elevated*. The bone marrow has normal cellularity; the red blood cell precursors are decreased or adequate, marrow hemosiderin may be increased, and granulocytic hyperplasia may be present.

TREATMENT

The best approach to ACD is the treatment, when possible, of the underlying disorder. If the associated systemic disease can be controlled, the anemia will improve or resolve. Transfusions raise the hemoglobin concentration temporarily but are rarely indicated. Erythropoietic stimulating agents (ESAs), such as recombinant human erythropoietin (EPO) or related extended half-life formulations, increase the hemoglobin level and improve activity and the sense of well-being. When using ESAs, treatment with iron is usually necessary to produce optimal effect. Response to these agents is highly variable and poorly responsive patients may require high doses to reach target hemoglobin levels. In adults, such high doses are associated with a higher incidence of adverse events, such as stroke, cardiovascular events, cancer progression, and death, leading the FDA to require a black box warning on labels.

ACD does not respond to iron alone unless there is concomitant deficiency. Unfortunately it is a common clinical challenge to identify iron deficiency in patients with an inflammatory disease (see Chapters 447 and 455). In this circumstance, a trial of iron therapy might be helpful, although there may be no response as persistent inflammation impairs iron absorption and utilization; intravenous iron may further increase hepcidin production. Therapeutic agents that target the hepcidin–ferroportin axis are under investigation.

Bibliography is available at Expert Consult.

451.2 Anemia of Renal Disease

Norma B. Lerner

Anemia is common in children with chronic kidney disease (CKD). The anemia is usually normocytic, and the absolute reticulocyte count is normal or low. While most patients with end-stage renal disease (ESRD) are anemic, earlier stages of CKD are associated with a lower prevalence. In adults, lower glomerular filtration rate (GFR) has been correlated with lower hemoglobin concentration, and hemoglobin has been reported to decline below a GFR threshold of 40-60 mL/min/1.73 m^2. In children with CKD, hemoglobin levels decline as the GFR decreases below 43 mL/min/1.73 m^2.

Decreased hemoglobin values are linked to increased incidence of left ventricular hypertrophy, impaired physical activity, and a reduced quality of life in pediatric patients with CKD. In those with ESRD who are on dialysis, anemia is also associated with increased risk of hospitalization and mortality.

ETIOLOGY

Although the anemia of CKD shares many features with the ACD, its predominant cause is decreased EPO production by diseased kidneys. Other important causes include absolute and/or functional iron deficiency as a result of chronic blood loss (from blood sampling, surgeries, and dialysis) and disturbances in the iron metabolic pathway. Higher hepcidin levels have also been implicated in the anemia of CKD. Hepcidin is filtered by the glomerulus and excreted by the kidney; serum concentrations are increased in patients with decreased

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GFR. Inflammation may also be a contributing factor in pediatric dialysis patients who have elevated levels of proinflammatory cytokines. Hyperparathyroidism and deficiencies of vitamin B_{12}, folate, and carnitine may also have a role in anemia of CKD.

LABORATORY FINDINGS

Anemia in children with CKD is defined by age: hemoglobin (Hb) <11.0 g/dL (0.5-5 yr), <11.5 g/dL (5-12 yr), <12 g/dL (12-15 yr), <13.0 g/dL (males older than 15 yr), and <12.0 g/dL (females older than 15 yr). The anemia of CKD is hypoproliferative and usually normocytic and normochromic, unless there is concomitant iron deficiency or vitamin deficiency. The EPO level and absolute reticulocyte count are usually low. White cell and platelet counts are generally normal. Ferritin will be low if there is accompanying iron deficiency, and high if there is associated inflammation.

TREATMENT

Oral iron therapy is recommended for all pediatric CKD patients with anemia. Consideration of IV iron therapy may be given for those receiving maintenance hemodialysis. Oral iron at 3-6 mg of elemental iron/kg of target dry weight once daily for 3 mo and possibly IV iron if transferrin saturation (serum iron × 100/total iron-binding capacity) and/or ferritin fail to improve is recommended.

ESAs are the mainstay of therapy and, particularly for children with ESRD, these medications have greatly reduced the need for frequent transfusions, decreasing the incidence of associated iron overload and alloimmunization. It is suggested to start ESA in all children with CKD when Hb concentrations are at 9-10 g/dL, with a goal of 11-12 g/dL (some recommend 11-13 g/dL) for children on maintenance ESA therapy. Dosing varies with age and dialysis modality. Darbepoetin, a synthetic form of EPO, appears to be equally effective as recombinant human EPO and has the benefit of less-frequent dosing as a consequence of a longer half-life. Iron therapy should be continued when using ESAs as treatment demands additional iron for hemoglobin synthesis.

A subset of patients is hyporesponsive to ESAs. In the past, pediatric nephrologists often responded to EPO resistance by further escalating the dose. The increased incidence of adverse events associated with dose escalation in the adult nondialysis CKD patients has prompted some concern about this approach. Several pediatric studies have demonstrated the value of IV iron supplementation in the setting of ESA hyporesponsiveness. In the rare case in which antibody-mediated (to EPO) pure red cell aplasia develops, ESA therapy should be stopped. A study including pediatric hemodialysis patients showed a nearly 50% decrease in hepcidin levels during treatment, suggesting that for those with ESA hyporesponsiveness and iron-restricted erythropoiesis, more frequent or longer duration sessions might be of benefit.

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Chapter **452**

Congenital Dyserythropoietic Anemias

Norma B. Lerner

The congenital dyserythropoietic anemias (CDAs) are a heterogeneous class of inherited disorders resulting from abnormalities of late erythropoiesis. These rare conditions are characterized by variable degrees of anemia, ineffective erythropoiesis, and secondary hemochromatosis. Dyserythropoiesis is the major cause of anemia but a shortened half-life of circulating red cells may also contribute. The CDAs have historically been classified into 3 major types (I, II, and II) based upon distinctive bone marrow morphology and clinical features, although additional subgroups and variants have also been identified.

TYPE I CONGENITAL DYSERYTHROPOIETIC ANEMIA

Pathogenesis

Type I CDA is an autosomal recessive disorder. The causative gene *(CDAN1)* was mapped to chromosome 15 between q15.1 and q15.3 and then successfully cloned. The gene encodes codanin-1, which is a ubiquitously expressed protein that may expedite histone assembly into chromatin and regulate the cell cycle. Although the majority of patients with bone marrow characteristics indicative of CDA1 have mutations within *CDAN1,* such mutations have not been detected in approximately 20% of families. Two distinctive mutations in the gene *C15ORF4*, predicted to encode an endonuclease, have been identified in 3 different CDA I pedigrees.

Clinical Manifestations

As of 2011, there were 169 cases from 143 families recorded in the literature. Most families were from Europe and the Middle East. Although CDA I may be diagnosed at any age, most cases are recognized during childhood or adolescence. CDA I is rarely diagnosed in utero. In addition to anemia-related symptoms, other findings often include splenomegaly, jaundice, and hepatomegaly. In more severe cases, evidence of extramedullary hematopoiesis in frontal or parietal bones of the skull and in paravertebral tumors may be present. Cholelithiasis and iron overload develop over time. Type I CDA has been associated with dysmorphic features in 4-14% of cases, primarily involving the digits (syndactyly, absence of nails, supernumerary toes). Retinal angioid streaks and macular abnormalities also have been reported.

Laboratory Findings

Hemoglobin concentrations generally range between 7 and 11 g/dL. The anemia is usually macrocytic (mean corpuscular volume 100-120 fL), but normocytic indices may be seen during childhood. Anisopoikilocytosis is appreciated on the peripheral blood smear. In some cases, normoblasts and basophilic stippling of red blood cells (RBCs) may be seen. The reticulocyte count is inadequate for the degree of anemia. Laboratory evidence of iron overload may be present. The bone marrow aspirate shows erythroid hyperplasia, megaloblastosis, and basophilic stippling. Binucleated and, more rarely, multinucleated polychromatophilic erythroblasts are also appreciated. Incompletely divided cells with thin chromatin bridges between nuclei of pairs of erythrocytes are highly specific for type I CDA. Electron microscopy is the gold standard for diagnosis, revealing erythroblasts with a characteristic "Swiss cheese" heterochromatin pattern.

Treatment

Treatment of this disorder is primarily supportive. Approximately 50% of neonates with CDA I will need at least 1 red cell transfusion and some may remain transfusion dependent over subsequent years. Adolescents and adults may only require episodic transfusions during aplastic crises, infection or pregnancy. If anemia is further exacerbated by coinherited disorders, such as thalassemia or RBC enzymopathy, the patient may become transfusion dependent. The most important long-term complication is **hemosiderosis,** which is caused by increased intestinal absorption of iron and ineffective erythropoiesis; consequently, transfusions should be avoided when possible to prevent further iron loading. Regular phlebotomies result in normal ferritin concentrations but if this approach is untenable oral chelation therapy should be employed when repeated ferritin levels exceed 1000 µg/L. In many cases of documented CDA type I, **interferon-α** has effectively raised the hemoglobin concentration, reduced splenomegaly, and reduced iron overload. *Patients do not respond to erythropoietin.* Splenectomy is generally not

recommended. Cholecystectomy is often required. Allogeneic bone marrow transplantation from a human-leukocyte-antigen-identical sibling has been successful in a few severe cases.

TYPE II CONGENITAL DYSERYTHROPOIETIC ANEMIA

Pathogenesis

CDA II is also an autosomal recessive disorder. Genome-wide linkage analysis identified a region of chromosome 20p11.2 as the location of the candidate *CDAN2* gene that was later identified to be the *SEC23B* gene. This gene is known to encode the cytoplasmic coat protein (COP) II component SEC23B that is involved in endoplasmic reticulum vesicle trafficking. *SEC23B* gene mutations have been associated with the majority of CDA II cases.

Clinical Manifestations

As of 2011, there were 454 cases from 356 families with CDA II recorded, making it the most common form of CDA. Families were mostly from Europe and the Middle East. In contrast to CDA I, this diagnosis is usually made later in life, often because symptoms may be milder. Also, CDA II may be initially misdiagnosed as hereditary spherocytosis. Characteristic findings can include anemia, jaundice, splenomegaly, or hepatomegaly. Posterior mediastinal or paravertebral masses of extramedullary hematopoietic tissue may be noted and signs of iron overload may also be present.

Laboratory Findings

The anemia is normocytic and is generally mild. Hemoglobin levels are lower in children than adults and range between 8 and 11 g/dL. The reticulocyte count, although inadequate, may appear to be normal or increased. Anisopoikilocytosis is noted and occasional basophilic stippling, as well as a few, sometimes binucleate, mature erythroblasts may be found on the peripheral smear. The bone marrow aspirate is normoblastic but hypercellular, with erythroid hyperplasia. In contrast to CDA I, there are many binucleate late polychromatic erythroblasts (10-35%) as well as a few that are multinucleate. Pseudo-Gaucher cells may be present. Electron micrographs show vesicles that are laden with endoplasmic reticulum proteins running beneath the plasma membrane. The pathognomonic finding in type II CDA is that the patient's RBCs lyse in acidified serum because of an immunoglobulin M antibody that recognizes an antigen present on CDA II cells but absent on normal cells. Type II CDA is also known by the acronym **HEMPAS** (*h*ereditary *e*rythroblastic *m*ultinuclearity with a *p*ositive *a*cidified *s*erum test) because it features both erythroblast multinuclearity and circulating RBCs that are sensitive to lysis by acidified normal serum. As this test is technically difficult, the diagnosis is usually made by analyzing red cell membrane proteins via sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). In CDAII there is a thinner band size and faster migration of erythrocyte anion transporter (EA1), or band 3, and band 4.5 proteins.

Treatment

Approximately 10% of patients will require red cell transfusions in infancy and childhood but rarely during adulthood. In contrast to type I CDA, splenectomy may provide hematologic improvement. Splenectomy does not prevent further iron overloading, even in those patients whose hemoglobin is normalized, presumably because of persistent ineffective erythropoiesis in the bone marrow. Like CDA I, secondary hemochromatosis is the most prominent long-term complication and should be approached as outlined above. Allogeneic bone marrow transplantation was successful when pursued in an adult with CDA II and β-thalassemia trait. Most patients can lead a normal life and have a normal life expectancy if complications and consequences are managed appropriately.

TYPE III CONGENITAL DYSERYTHROPOIETIC ANEMIA

Type III CDA is an extremely rare, ill-defined entity, manifested by a mild-to-moderate macrocytic anemia. It is inherited in an autosomal dominant fashion, although there have been cases that might represent de novo mutations or other inheritance patterns. The gene for type III CDA is *KIF23*, which encodes a ubiquitous protein that regulates daughter cell separation during mitosis. In contrast to other CDA types, iron overload is not clinically significant (probably because hemolysis is predominantly intravascular) and spleen size is generally normal. Patients can present with angioid streaks with macular degeneration. The blood smear shows macrocytes, anisopoikilocytosis, and occasional basophilic stippling. The bone marrow is notable for giant erythroid precursors that are often multinucleated, containing up to 12 nuclei per cell. Such multinucleated erythroblasts can also be seen in myelodysplasia and erythroleukemia. Transfusions are usually not required.

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Chapter 453

Physiologic Anemia of Infancy

Norma B. Lerner

At birth, normal full-term infants have higher hemoglobin (Hb) levels and larger red blood cells (RBCs) than do older children and adults. However, within the 1st wk of life, a progressive decline in Hb level begins and then persists for 6-8 wk. The resulting anemia is known as the **physiologic anemia of infancy.**

With the onset of respiration at birth, considerably more oxygen becomes available for binding to Hb, and, as a consequence, the Hb–oxygen saturation increases from 50% to 95% or more. There is also a gradual, normal developmental switch from fetal to adult Hb synthesis after birth that results in the replacement of high-oxygen-affinity fetal Hb with lower-affinity adult Hb, capable of delivering more oxygen to tissues. The increase in blood oxygen content and delivery results in the downregulation of erythropoietin (EPO) production, leading to suppression of erythropoiesis. Because there is no erythropoiesis, aged RBCs that are removed from the circulation are not replaced and the Hb level decreases. The Hb concentration continues to decline until tissue oxygen needs become greater than oxygen delivery. Normally, this point is reached between 8 and 12 wk of age, when the Hb concentration is about 11 g/dL. In healthy term infants, the nadir rarely falls below 10 g/dL. At this juncture, EPO production increases and erythropoiesis resumes. The supply of stored reticuloendothelial iron, derived from previously degraded RBCs, remains sufficient for this renewed Hb synthesis, even in the absence of dietary iron intake, until approximately 20 wk of age. In all, this "anemia" should be viewed as a physiologic adaptation to extrauterine life, reflecting the excess oxygen delivery relative to tissue oxygen requirements. There is no hematologic problem, and no therapy is required unless physiologic anemia of infancy is exacerbated by other ongoing processes.

A late **hyporegenerative anemia**, with absence of reticulocytes, can occur in infants with mild hemolytic disease of the newborn. The persistence of maternally derived anti-RBC antibodies in the infant's circulation can lead to an ongoing low-grade hemolytic anemia that can exaggerate the physiologic anemia. Lower-than-expected Hb at the "physiologic" nadir has also been seen in infants after intrauterine or neonatal RBC transfusions. When infants are transfused with adult blood containing HbA, the associated shift of the oxygen dissociation curve facilitates oxygen delivery to the tissues. Accordingly, the definition of anemia and the need for transfusion should be based not only

on the infant's Hb level, but also on oxygen requirements and the ability of circulating RBCs to release oxygen to the tissues.

Premature infants also develop a physiologic anemia, known as *physiologic anemia of prematurity*. The Hb decline is both more extreme and more rapid. Minimal Hb levels of 7-9 g/dL commonly are reached by 3-6 wk of age, and levels may be even lower in very small premature infants (see Chapter 103). The same physiologic factors at play in term infants are operative in preterm infants but are exaggerated. In premature infants, the physiologic Hb decline may be intensified by blood loss from repeated phlebotomies obtained to monitor ill neonates. Demands on erythropoiesis are further heightened by the premature infant's shortened RBC life span (40-60 days) and the accelerated expansion of RBC mass that accompanies the premature baby's rapid rate of growth. Nonetheless, plasma EPO levels are lower than would be expected for the degree of anemia, resulting in a suboptimal erythropoietic response. The reason for diminished EPO levels is not fully understood. During fetal life, EPO synthesis is handled primarily by the liver, whose oxygen sensor is relatively insensitive to hypoxia when compared to the oxygen sensor of the kidney. The developmental switch from liver to kidney EPO production is not accelerated by early birth, and thus the preterm infant must rely on the liver as the primary site for synthesis, leading to diminished responsiveness to anemia. An additional mechanism thought to contribute to diminished EPO levels may be accelerated EPO metabolism. As the pronounced decline in Hb that occurs in many very low birthweight infants is associated with abnormal clinical signs, this "anemia of prematurity" is not considered to be benign and usually requires transfusions.

Some dietary factors, such as folic acid deficiency, can aggravate physiologic anemia. Unless there has been significant blood loss, iron stores should be sufficient to maintain erythropoiesis early on. Vitamin E deficiency does not play a role in anemia of prematurity. Breast milk and infant formulas provide adequate vitamin E.

TREATMENT

In the full-term infant, physiologic anemia requires no therapy beyond ensuring that the infant's diet contains essential nutrients for normal hematopoiesis. In premature infants, an optimal Hb has not been established and is usually dictated by the infant's overall clinical condition. Transfusions may be needed to maintain the Hb at what is considered safe for that child. Premature infants who are feeding well and growing normally rarely need transfusion unless iatrogenic blood loss has been significant. Although factors such as poor weight gain, respiratory difficulties, and abnormal heart rate have prompted transfusion, the beneficial effect has not been documented. Laboratory tests such as blood lactate, EPO, and mixed venous oxygen saturation have poor predictive value. Liberal and restrictive transfusion strategies have been compared in this population. A restrictive strategy does not increase infant morbidity or mortality. In addition, long-term neurodevelopmental outcomes have been found to be poorer in liberally transfused neonates. Late exposure to packed RBC may be related to the development of necrotizing enterocolitis, and early transfusions may be associated with the risk of intraventricular hemorrhage.

When transfusions are necessary, an RBC volume of 10-15 mL/kg is recommended. It is good practice to split units derived from a single donor so that sequential transfusions can be given as required and donor exposure can be minimized. In early preterm infants (weighing <1,250 g), the half-life of transfused RBCs is about 30 days. Delayed cord clamping or umbilical cord milking at birth results in fewer transfusions and a reduction in both intraventricular hemorrhage and necrotizing enterocolitis in preterm infants. Given the impact of phlebotomy losses during monitoring in the neonatal ICU, attention to reducing unnecessary blood draws also has been advocated.

Because premature infants are known to have low plasma EPO levels, recombinant human EPO may be an alternative to transfusion for the treatment of symptomatic preterm infants with anemia of prematurity. In early studies, it was unclear whether EPO reliably reduced donor exposures and reports of adverse effects, such as a possible increase in retinopathy of prematurity, further limited a willingness to use this expensive treatment. One study of preterm infants compared the weekly use of the long-acting agent darbepoetin to triweekly EPO or placebo. Supplemental iron, folate, and vitamin E were provided and the infants were transfused according to an established protocol. Those receiving either EPO or darbepoetin received half the number of transfusions and about half the donors compared with the placebo group. The incidence of mortality, retinopathy, and intracranial hemorrhage was no different between the groups. Nonetheless, this remains an area of controversy.

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Chapter 454

Megaloblastic Anemias

Norma B. Lerner

Megaloblastic anemia describes a group of disorders that are caused by impaired DNA synthesis. Red blood cells (RBCs) are larger than normal at every developmental stage, and there is maturational asynchrony between the nucleus and cytoplasm of erythrocytes. The delayed nuclear development becomes increasingly evident as cell divisions proceed. Myeloid and platelet precursors are also affected, and giant metamyelocytes and neutrophil bands are often present in the bone marrow. *There is often an associated thrombocytopenia and leukopenia*. The peripheral blood smear is notable for large, often oval, RBCs with increased mean corpuscular volume. Neutrophils are characteristically hypersegmented, with many having >5 lobes. Most cases of childhood megaloblastic anemia result from a deficiency of folic acid or vitamin B_{12} (cobalamin), vitamins essential for DNA synthesis. Rarely, these anemias may be caused by inborn errors of metabolism. Megaloblastic anemias resulting from malnutrition are relatively uncommon in the United States, but are important worldwide (see Chapters 46 and 447).

454.1 Folic Acid Deficiency

Norma B. Lerner

Folic acid, or pteroylglutamic acid, consists of pteroic acid conjugated to glutamic acid. Biologically active folates are derived from folic acid and serve as 1-carbon donors and acceptors in many biosynthetic pathways. To form functional compounds, folates must be reduced to tetrahydrofolates in a process catalyzed by the enzyme dihydrofolate reductase. As such, they are essential for DNA replication and cellular proliferation. Like other mammals, humans cannot synthesize folate and depend on dietary sources, including green vegetables, fruits, and animal organs (e.g., liver, kidney). Folates are heat labile and water soluble; consequently, boiling or heating folate sources leads to decreased amounts of vitamin. Naturally occurring folates are in a polyglutamated form that is less efficiently absorbed than the monoglutamate species (i.e., folic acid). Dietary folate polyglutamates are hydrolyzed to simple folates that are absorbed primarily in the proximal small intestine by a specific carrier-mediated system. Folates travel in the bloodstream and are taken up in cells primarily in the form of unconjugated methyltetrahydrofolate, which is subsequently reconjugated (polyglutamated) in the cell. There is an active enterohepatic circulation. Although rare, megaloblastic anemia as a consequence of folate deficiency has its peak incidence at 4-7 mo of age, somewhat earlier than iron-deficiency anemia, although both conditions may be present concomitantly in infants with poor nutrition.

ETIOLOGY

Folic acid deficiency can occur as a consequence of inadequate folate intake, decreased folate absorption, or acquired and congenital disorders of folate metabolism or transport.

Inadequate Folate Intake

In the United States, anemia caused by insufficient folate intake usually occurs in the context of increased vitamin requirements associated with pregnancy, periods of accelerated growth, and/or chronic hemolysis. Folate requirements increase markedly during pregnancy, in part to meet fetal needs, and deficiencies are common in mothers, particularly those who are poor or malnourished. Folate supplementation is recommended from the start of pregnancy to prevent neural tube defects and to meet the needs of the developing fetus. Fortunately, folate-deficient mothers generally do not give birth to infants with clinical folate deficiency because there is selective transfer of folate to the fetus via placental folate receptors. Rapid growth after birth increases demands for folic acid and infants who are premature or ill and those with certain hemolytic disorders will have particularly high folate requirements. Human breast milk, infant formulas, and pasteurized cow's milk provide adequate amounts of folic acid. *Goat's milk is deficient*, and supplementation must be given when it is the child's main food. Unless supplemented, powdered milk may also be a poor source of folic acid.

Malnutrition is the most common cause of folate deficiency in older children, and those with hemoglobinopathies, infections, and/or malabsorption are at increased risk. Because body stores of folate are limited, deficiency can develop quickly in malnourished individuals. On a folate-free diet, megaloblastic anemia will occur after 2-3 mo.

Decreased Folate Absorption

Malabsorption caused by chronic diarrheal states or diffuse inflammatory disease can lead to folate deficiency. In both situations, some of the decreased folate absorption may be caused by impaired folate conjugase activity. Chronic diarrhea also interferes with the enterohepatic circulation of folate, thereby enhancing folate losses because of rapid intestinal passage. Megaloblastic anemia because of folic acid deficiency can occur in celiac disease or chronic infectious enteritis and in association with enteroenteric fistulas. Previous intestinal surgery is another potential cause of decreased folate absorption.

Certain anticonvulsant drugs (e.g., phenytoin, primidone, phenobarbital) can impair folic acid absorption, and many patients treated with these drugs have low serum levels. Frank megaloblastic anemia is rare and readily responds to folic acid therapy, even when administration of the offending drug is continued. Alcohol overuse also is associated with folate malabsorption.

Congenital Abnormalities in Folate Transport and Metabolism

Inborn errors of folate transport or metabolism are rare but can be life-threatening. Those associated with megaloblastic anemia include hereditary folate malabsorption and certain extremely uncommon enzyme deficiencies.

Hereditary folate malabsorption (HFM) is an autosomal recessive disorder that is linked to several loss-of-function mutations in the *SLC46A1* gene encoding the protein-coupled folate transporter. HFM is associated with an inability to absorb folic acid, 5-tetrahydrofolate, 5-methyltetrahydrofolate, or 5-formyltetrahydrofolate (folinic acid). It can become apparent at 2-6 mo of age with megaloblastic anemia and other deficits, including infections and diarrhea. Neurologic abnormalities, attributable to folate deficiency in the central nervous system, include seizures, developmental delay, and mental retardation. Folate transport is impaired in both the intestine and at the brain's choroid plexus. Serum and cerebrospinal fluid (CSF) folate levels are very low, with a loss of the normal 3 : 1 ratio of CSF to serum folate.

Treatment, specifically in the context of HFM, usually involves parenteral folate, although oral administration has been useful in some cases. Reduced folates are more effective than folic acid. Folate sufficiency should be maintained in both the blood and the CSF so as to avoid important complications. The megaloblastic anemia in HFM can be reversed with relatively low levels of serum folate, but adequate CSF levels may be quite difficult to achieve, and very large folate doses may be needed.

Functional methionine synthase deficiency may result from mutations affecting the function of methionine synthase reductase or methionine synthase. These disorders are autosomal recessive and are characterized not only by megaloblastic anemia, but also by cerebral atrophy, nystagmus, blindness, and altered muscle tone. Both respond to hydroxocobalamin plus betaine with variable clinical success. Dihydrofolate reductase deficiency is extremely rare and is associated with homozygous mutations in the DHFR gene. Clinical symptoms include megaloblastic anemia and neurologic manifestations. Although **methylenetetrahydrofolate (MTHFR) deficiency** is the most common inborn error of folate metabolism and severe cases can produce a number of neurologic and vascular complications, there is no associated megaloblastic anemia.

Drug-Induced Abnormalities in Folate Metabolism

A number of drugs have anti–folic acid activity as their primary pharmacologic effect and regularly produce megaloblastic anemia. Methotrexate binds to dihydrofolate reductase and prevents formation of tetrahydrofolate, the active form of folate. Pyrimethamine, used in the therapy of toxoplasmosis, and trimethoprim, used for treatment of various infections, can induce folic acid deficiency and, occasionally, megaloblastic anemia. Therapy with folinic acid (5-formyltetrahydrofolate) is usually beneficial.

CLINICAL MANIFESTATIONS

Besides the clinical features associated with anemia, folate-deficient infants and children may manifest irritability, chronic diarrhea, and/or poor weight gain. Hemorrhages from thrombocytopenia may occur in advanced cases. Congenital folate malabsorption and other rare etiologies of folate deficiency may be further associated with hypogammaglobulinemia, severe infections, failure to thrive, neurologic abnormalities, and cognitive delays.

LABORATORY FINDINGS

The anemia is macrocytic (mean corpuscular volume >100 fL). Variations in RBC shape and size are common (see Fig. 447-4B in Chapter 447). The reticulocyte count is low, and nucleated RBCs with megaloblastic morphology are often seen in the peripheral blood. Neutropenia and thrombocytopenia may be present, particularly in patients with long-standing and severe deficiencies. The neutrophils are large, some with hypersegmented nuclei. The bone marrow is hypercellular because of erythroid hyperplasia, and megaloblastic changes are prominent. Large, abnormal neutrophilic forms (giant metamyelocytes) with cytoplasmic vacuolation are also seen.

Normal serum folic acid levels are 5-20 ng/mL; with deficiency, levels are <3 ng/mL. Levels of RBC folate are a better indicator of chronic deficiency. The normal RBC folate level is 150-600 ng/mL of packed cells. Levels of iron and vitamin B_{12} in serum usually are normal or elevated. Serum activity of lactate dehydrogenase, a marker of ineffective erythropoiesis, is markedly elevated.

TREATMENT

When the diagnosis of folate deficiency is established, folic acid may be administered orally or parenterally at 0.5-1.0 mg/day. If the specific diagnosis is in doubt, smaller doses of folate (0.1 mg/day) may be used for 1 wk as a diagnostic test, because a hematologic response can be expected within 72 hr. Doses of folate >0.1 mg can correct the anemia of vitamin B_{12} deficiency but might aggravate any associated neurologic abnormalities. In most medical settings in developed countries, this therapeutic trial to distinguish the different causes of megaloblastic anemia is rarely necessary because vitamin B_{12} and folate blood levels are usually readily available. Folic acid therapy (0.5-1.0 mg/day) should be continued for 3-4 wk until a definite hematologic response has occurred. Maintenance therapy with a multivitamin (containing 0.2 mg of folate) is adequate. As described above, very high doses of

folate may be required in the setting of HFM. Transfusions are indicated only when the anemia is severe or the child is very ill.

Bibliography is available at Expert Consult.

454.2 Vitamin B_{12} (Cobalamin) Deficiency

Norma B. Lerner

Vitamin B_{12}, a generic term encompassing all biologically active cobalamins, is a water-soluble vitamin with a central, functional cobalt atom and a planar corrin ring. Methylcobalamin and adenosylcobalamin are the metabolically active derivatives, serving as cofactors in 2 essential metabolic reactions, namely methylation of homocysteine to methionine (via methionine synthase) and conversion of methyl-malonyl-coenzyme A (CoA) to succinyl CoA (via L-methyl-malonyl-CoA mutase). The products and by-products of these enzymatic reactions are critical to DNA, RNA, and protein synthesis.

Cobalamin is synthesized exclusively by microorganisms and humans must rely on dietary sources (animal products including meat, eggs, fish, and milk) for their needs. Unlike folate, older children and adults have sufficient vitamin B_{12} stores to last 3-5 yr. In young infants born to mothers with low vitamin B_{12} stores, clinical signs of cobalamin deficiency can become apparent in the first 6-18 mo of life.

METABOLISM

Under normal circumstances, cobalamin is released from food protein in the stomach via peptic digestion. Cobalamin then binds to haptocorrin (HC), a salivary glycoprotein. This complex moves into the duodenum, where HC is digested by pancreatic proteases and cobalamin is liberated. Cobalamin then binds to intrinsic factor (IF), another glycoprotein that is produced by gastric parietal cells. The cobalamin-IF complex subsequently enters mucosal cells of the distal ilium by receptor-mediated endocytosis. The IF-cobalamin receptors are composed of a complex of 2 proteins, cubilin (CUBN) and amnionless (AMN), collectively known as cubam. Following internalization into enterocytes, IF is degraded in the lysosome and cobalamin is released. The transporter ABCC1 (also known as MRP1) exports cobalamin bound to the transport protein transcobalamin (TC), out of the cell. In the bloodstream, cobalamin is associated with either TC (approximately 20%) or HC. TC mediates B_{12}'s transport across cells after complexing with the TC receptor, which is internalized in the lysosome. Lysosomal degradation of TC releases cobalamin which remains in the cell where it is further processed. Two distinct membrane proteins transport cobalamin across the lysosomal membrane into the cytoplasm. There cobalamins are processed to a common intermediate that can be allocated to the methylcobalamin and adenosylcobalamin synthesis pathways to meet cellular needs. It is postulated that the MMACHC protein, a product of the cobalamin (Cbl) C locus, accepts the cobalamins exiting the lysosome. A definitive role for HC is yet to be established, but it has been suggested that it plays a role in B_{12} storage.

ETIOLOGY

Vitamin B_{12} deficiency can result from inadequate dietary intake of Cbl, lack of IF, impaired intestinal absorption of IF-Cbl, or absence of vitamin B_{12} transport protein

Inadequate Vitamin B_{12} Intake

B_{12} deficiency in infants is most often nutritional, resulting from low Cbl levels in the breast milk of B_{12}-deficient mothers. Associated megaloblastic anemia often appears during the 1st yr of life. Maternal deficiency may be caused by pernicious anemia or gastrointestinal disorders such as *Helicobacter pylori* infection, celiac disease, Crohn disease, or pancreatic insufficiency. Previous gastric bypass surgery, treatment with proton pump inhibitors, or inadequate intake from a strict vegetarian diet has also been implicated. Fortunately, as a result of active placental Cbl transport in utero, most children of deficient mothers maintain Cbl levels sufficient to support adequate prenatal development. Such infants are born with low stores, the depletion of which is associated with a gradual onset of clinical manifestations. B_{12} replacement often results in rapid improvement, but the longer the deficient period, the greater the likelihood of permanent disabilities. Neonatal screening programs may detect maternal–neonatal nutritional B_{12} deficiency as a result of an increase in propionyl carnitine, but there is higher sensitivity using a measurement of methylmalonic acid. In high-income countries, dietary deficiency during childhood or adolescence is infrequent but can result, as in adults, from strict vegetarian or vegan diet. Daily requirements range from 0.4-2.4 µg.

Impaired Absorption

Gastric surgery or medications that impair gastric acid secretion may result in IF deficiency, leading to decreased vitamin B_{12} absorption. Pancreatic insufficiency can also lead to Cbl deficiency as a consequence of impaired cleavage and IF complex formation. Patients with neonatal necrotizing enterocolitis, inflammatory bowel disease, celiac disease, or surgical removal of the terminal ileum, may also have impaired absorption of vitamin B_{12}. An overgrowth of intestinal bacteria within diverticula or duplications of the small intestine can cause vitamin B_{12} deficiency by consumption of (or competition for) the vitamin or by splitting of its complex with IF. In these cases, hematologic response can follow appropriate antibiotic therapy. In endemic areas, when the fish tapeworm *Diphyllobothrium latum* infests the upper small intestine, similar mechanisms may be operative. When megaloblastic anemia occurs in such situations, the serum vitamin B_{12} level is low and the gastric fluid contains IF.

Hereditary intrinsic factor deficiency (HIFD) is a rare autosomal recessive disorder caused by a variety of mutations in the IF gene that produce a lack of gastric IF or a functionally abnormal IF. It differs from typical adult pernicious anemia in that gastric acid is secreted normally and the stomach is histologically normal. It is not associated with antibodies or endocrine abnormalities. Unlike Imerslund-Grasbeck syndrome (described below), hereditary IF deficiency is only occasionally associated with proteinuria. Symptoms become prominent at an early age (6-24 mo), consistent with exhaustion of vitamin B_{12} stores acquired in utero. As the anemia becomes severe, weakness, irritability, anorexia, and listlessness occur. The tongue is smooth, red, and painful. Neurologic manifestations include ataxia, paresthesias, hyporeflexia, Babinski responses, and clonus. Oral vitamin B_{12} is usually ineffective and lifelong parenteral (IM) Cbl should be used to bypass the absorption defect. The natural form, hydroxocobalamin (OHCbl) is believed to be more effective than the synthetic form, cyanocobalamin (CNCbl). In one retrospective study involving patients with HIFD and Imerslund-Grasbeck syndrome, patients with acute and severe anemia were initially treated with 1 mg of IM OHCbl daily until reticulocyte recovery after which dosing was spaced to once a week. Those without severe anemia were treated with weekly IM OHCbl or CNCbl. With cautious monitoring, all patients were ultimately safely maintained on a schedule of 1 mg of IM OHCbl or CNCbl every 6 mo.

Imerslund-Grasbeck syndrome is a rare, recessively inherited pediatric disorder resulting in selective vitamin B_{12} malabsorption in the ileum, and consequent vitamin B_{12} deficiency. It usually becomes clinically apparent within the first 6 yr of life. In addition to megaloblastic anemia, the patient may also have neurologic defects (such as hypotonia, developmental delay, brain atrophy, movement disorders, and dementia) and/or proteinuria. Patients carry mutations in either CUBN or AMN, proteins that form the cubam receptor for the ileal IF-Cbl complex. Because CUBN is also a key receptor for protein reabsorption in the kidney, impaired expression at this site results in associated proteinuria. The disease can be fatal if it remains untreated. Early diagnosis and treatment with IM Cbl (see treatment for HIFD above) will reverse the hematologic and neurologic abnormalities. Proteinuria does not respond to therapy.

Classic pernicious anemia (autoimmune gastritis) usually occurs in older adults but can rarely affect children. This disorder (juvenile pernicious anemia) usually presents during adolescence. In such cases,

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the disease is associated with various detectable antibodies, including those against IF and the hydrogen potassium adenosine triphosphatase proton pump in gastric parietal cells. These children can have additional immunologic abnormalities, cutaneous candidiasis, hypoparathyroidism, and other endocrine deficiencies. There may be atrophy of the gastric mucosa and achlorhydria. Parenteral vitamin B_{12} should be administered regularly.

Absence of Vitamin B_{12} Transport Protein

TC deficiency is a rare cause of megaloblastic anemia. A congenital deficiency is inherited as an autosomal recessive condition resulting in a failure to absorb and transport vitamin B_{12}. Most patients lack TC but some have functionally defective forms. This disorder usually manifests in the first weeks of life. Characteristically, there is failure to thrive, diarrhea, vomiting, glossitis, neurologic abnormalities, and megaloblastic anemia. The diagnosis can be difficult given that total serum vitamin B_{12} levels are often normal because approximately 80% of serum Cbl is bound to HC. The diagnosis is suggested by the presence of severe megaloblastic anemia in the face of normal folate levels and no evidence of any other inborn errors of metabolism. Plasma homocysteine and/or methylmalonic acid levels are elevated. A definitive diagnosis is made by measuring plasma TC. The serum vitamin B_{12} levels must be kept high in order to force enough Cbl into cells to allow normal function. Oral Cbl (CNCbl or OHCbl) 500-1,000 µg twice a wk, or IM OHCbl 1,000 µg per wk, may be used for initial therapy. Symptoms and laboratory studies should be monitored and doses adjusted as needed.

Inborn Errors of Cobalamin Metabolism

The conversion of Cbl to methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl) involves a number of steps, abnormalities of which have been tied to several distinct alphabetically labeled disorders. In CblE and CblG, defective N5-methyltetrahydrofolate-homocysteine methyltransferase fails to produce MeCbl. Patients present in infancy with megaloblastic anemia, vomiting, and mental retardation, and are found to have homocystinuria and hyperhomocystinemia. They do not have methylmalonic aciduria or methylmalonic acidemia. They show good response to CNCbl. AdoCbl and MeCbl are both affected by CblC (the most common of the Cbl inborn errors), CblD, and CblF. Patients can present in early infancy through adolescence. Newborns have lethargy, failure to thrive, and neurologic problems. Older patients may present with neurologic difficulties, dementia, and psychological problems. Megaloblastic anemia occurs in about half the cases. Patients have elevations of homocysteine and methylmalonic acid in both urine and blood. Affected individuals respond partially to OHCbl or CNCbl. CblA, CblB, and CblH are associated with methylmalonic aciduria and a variety of serious symptoms, but megaloblastic anemia is absent.

CLINICAL MANIFESTATIONS

Children with Cbl deficiency often present with nonspecific manifestations such as weakness, lethargy, feeding difficulties, failure to thrive, and irritability. Other common findings include pallor, glossitis, vomiting, diarrhea, and icterus. Neurologic symptoms can include paresthesia, sensory deficits, hypotonia, seizures, developmental delay, developmental regression, and neuropsychiatric changes. Neurologic problems from vitamin B_{12} deficiency may occur in the absence of any hematologic abnormalities.

LABORATORY FINDINGS

The hematologic manifestations of folate and Cbl deficiency are identical. The anemia resulting from Cbl deficiency is macrocytic, with prominent macro-ovalocytosis of the RBCs (see Fig. 447-2 in Chapter 447). The neutrophils may be large and hypersegmented. In advanced cases, neutropenia and thrombocytopenia can occur, simulating aplastic anemia or leukemia. Serum vitamin B_{12} levels are low, and the serum concentrations of methylmalonic acid and homocysteine are usually elevated. Concentrations of serum iron and serum folic acid are normal or elevated. Serum lactate dehydrogenase activity is markedly increased, a reflection of ineffective erythropoiesis. Moderate elevations of serum bilirubin levels (2-3 mg/dL) also may be found. Excessive excretion of methylmalonic acid in the urine (normal, 0-3.5 mg/24 hr) is a reliable and sensitive index of vitamin B_{12} deficiency.

DIAGNOSIS

A comprehensive medical history is essential to the clinical recognition of possible Cbl deficiency. Information regarding clinical symptoms, dietary history, diseases, surgeries, or medications are likely to provide important clues. The physical exam may reveal relevant findings such as irritability, pallor, or specific neurologic symptoms. Screening laboratory findings (described above) offer important information but more focused testing will be required to confirm a diagnosis of vitamin B_{12} deficiency and its cause. Cbl deficiency is usually identified by measuring total or TC bound vitamin B_{12} in the blood. Although an extremely low level is generally diagnostic, this may not be the case, and false negatives and positives are reportedly common using currently available assays. As a result, it is wise not to discount vitamin B deficiency, particularly in the face of clinical symptoms, macrocytic anemia, an abnormal blood smear, and a normal folate level. In nontreated patients, methylmalonic acid and total homocystine levels are often helpful as they are markedly elevated in the majority of those with clinical signs of B_{12} deficiency. Excessive excretion of methylmalonic acid in the urine (normal: 0-3.5 mg/24 hr) is also a sensitive index of vitamin B_{12} deficiency. Although modest increases occur with renal failure, elevated methylmalonic acid is otherwise quite specific for vitamin B_{12} deficiency. Notably, however, serum homocystine is also elevated in folate deficiency, homocystinuria, and renal failure.

If B_{12} deficiency has been confirmed and there is no evidence of inadequate dietary intake or, in the case of an infant, inadequate maternal B_{12}, malabsorption should be investigated. In the past, the Schilling test, a measure of Cbl absorption, was the gold standard. The test is no longer available and there is currently no comparable replacement for it. Anti–IF antibodies and anti–parietal cell antibodies are useful for the diagnosis of pernicious anemia. Measurement of IF and help from more specialized laboratories may be required for less common disorders.

TREATMENT

Treatment regimens in children have not been well studied. The cause of vitamin B_{12} deficiency should ultimately dictate treatment dosage as well as the duration of therapy. Dose adjustments should be made in response to clinical status and laboratory values. The physiologic requirement for vitamin B_{12} is about 1-3 µg/day. Hematologic responses have been observed with small doses, indicating that administration of a minidose may be used as a therapeutic test when the diagnosis of vitamin B_{12} deficiency is in doubt or in circumstances where the anemia is severe and higher initial doses might result in severe metabolic disturbances.

Bibliography is available at Expert Consult.

454.3 Other Rare Megaloblastic Anemias

Norma B. Lerner

Orotic aciduria is a rare autosomal recessive disorder that usually appears in the 1st yr of life and is characterized by growth failure, developmental retardation, megaloblastic anemia, and increased urinary excretion of orotic acid (see Chapter 89). This defect is the most common metabolic error in the de novo synthesis of pyrimidines and therefore affects nucleic acid synthesis. The usual form of hereditary orotic aciduria is caused by a deficiency (in all body tissues) of orotic phosphoribosyl transferase and orotidine-5-phosphate decarboxylase, 2 sequential enzymatic steps in pyrimidine nucleotide synthesis. The diagnosis is suggested by the presence of severe megaloblastic anemia with normal serum B_{12} and folate levels and no evidence of TC deficiency. A presumptive diagnosis is made by finding increased urinary orotic acid. However, confirmation of the diagnosis requires assay of the transferase and decarboxylase enzymes in the patient's

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erythrocytes. Physical and mental retardation often accompany this condition. The anemia is refractory to vitamin B_{12} or folic acid, but responds promptly to administration of uridine.

Thiamine-responsive megaloblastic anemia (Rogers syndrome) is a very rare autosomal recessive disorder characterized by megaloblastic anemia, sensorineural deafness, and diabetes mellitus. Congenital heart defects, arrhythmias, visual problems, short stature, tri-lineage myelodysplasia, and strokes are also described. Thiamine-responsive megaloblastic anemia usually presents in infancy but may occasionally develop in childhood and adolescence and occurs in several ethnically distinct populations. The bone marrow is characterized not only by megaloblastic changes but also by ringed sideroblasts. The defect is caused by mutations in the *SCL19A2* gene on chromosome 1, which encodes a high-affinity plasma membrane thiamine transporter. Continuous thiamine supplementation usually reverses the anemia and diabetes but not existing hearing defects.

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Chapter 455

Iron-Deficiency Anemia

Richard Sills

Iron deficiency is the most widespread and common nutritional disorder in the world. It is estimated that 30% of the global population has iron-deficiency anemia, and most of them live in developing countries. In the United States, 9% of children ages 12-36 mo are *iron deficient*, and 30% of this group progresses to iron-deficiency *anemia*.

A full-term newborn infant contains about 0.5 g of iron, compared to 5 g of iron in adults. This change in quantity of iron from birth to adulthood means that an average of 0.8 mg of iron must be absorbed each day during the first 15 yr of life. A small additional amount is necessary to balance normal losses of iron by shedding of cells. It is therefore necessary to absorb approximately 1 mg daily to maintain positive iron balance in childhood. Because <10% of dietary iron usually is absorbed, a dietary intake of 8-10 mg of iron daily is necessary to maintain iron levels. During infancy, when growth is most rapid, the approximately 1 mg/L of iron in cow's and breast milk makes it difficult to maintain body iron. Breastfed infants have an advantage because they absorb iron 2-3 times more efficiently than infants fed cow's milk.

ETIOLOGY

Most iron in neonates is in circulating hemoglobin. As the relatively high hemoglobin concentration of the newborn infant falls during the first 2-3 mo of life, considerable iron is recycled. These iron stores are usually sufficient for blood formation in the first 6-9 mo of life in term infants. Stores are depleted sooner in low-birthweight infants or infants with perinatal blood loss because their iron stores are smaller. Delayed (1-3 min) clamping of the umbilical cord can improve iron status and reduce the risk of iron deficiency, whereas early clamping (<30 sec) puts the infant at risk for iron deficiency. Dietary sources of iron are especially important in these infants. In term infants, anemia caused solely by inadequate dietary iron usually occurs at 9-24 mo of age and is relatively uncommon thereafter. The usual dietary pattern observed in infants and toddlers with nutritional iron-deficiency anemia in developed countries is excessive consumption of cow's milk (low iron content, blood loss from milk protein colitis) in a child who is often overweight. Worldwide, undernutrition is usually responsible for iron deficiency.

Blood loss must be considered as a possible cause in every case of iron-deficiency anemia, particularly in older children and adolescents. Chronic iron-deficiency anemia from occult bleeding may be caused by a lesion of the gastrointestinal (GI) tract, such as peptic ulcer, Meckel diverticulum, polyp, hemangioma, or inflammatory bowel disease. Infants can have chronic intestinal blood loss induced by exposure to whole cow's milk protein. This GI reaction is not related to enzymatic abnormalities in the mucosa, such as lactase deficiency, or to an immunoglobulin E–associated milk allergy. Involved infants characteristically develop anemia that is more severe and occurs earlier than would be expected simply from an inadequate intake of iron. The ongoing loss of blood in the stools can be prevented either by breastfeeding or by delaying the introduction of whole cow's milk in the 1st yr of life and then limiting the quantity to <24 oz/24 hr. Unrecognized blood loss also can be associated with chronic diarrhea and, rarely, with pulmonary hemosiderosis. In developing countries, infections with hookworm, *Trichuris trichiura, Plasmodium,* and *Helicobacter pylori* often contribute to iron deficiency. Celiac disease and giardiasis may interfere with iron absorption.

Approximately 2% of adolescent girls have iron-deficiency anemia, largely as a result of their adolescent growth spurt and menstrual blood loss. The highest risk of iron-deficiency anemia (>30%) is among teenagers who are or have been pregnant.

CLINICAL MANIFESTATIONS

Most children with iron deficiency are asymptomatic and are identified by recommended laboratory screening at 12 mo of age, or sooner if at high risk. Pallor is the most important clinical sign of iron deficiency but is not usually visible until the hemoglobin falls to 7-8 g/dL. It is most readily noted as pallor of the palms, palmar creases, nail beds, or conjunctivae. Parents often fail to note the pallor because of the typical slow decline of hemoglobin over time. Often a visiting friend or relative is the first to notice. In mild to moderate iron deficiency (i.e., hemoglobin levels of 6-10 g/dL), compensatory mechanisms, including increased levels of 2,3-diphosphoglycerate and a shift of the oxygen dissociation curve, may be so effective that few symptoms of anemia aside from mild irritability are noted. When the hemoglobin level falls to <5 g/dL, irritability, anorexia, and lethargy develop, and systolic flow murmurs are often heard. As the hemoglobin continues to fall, tachycardia and high output cardiac failure can occur.

Iron deficiency has nonhematologic systemic effects. Both iron deficiency and iron-deficiency anemia are associated with impaired neurocognitive function in infancy. There is also an association of iron-deficiency anemia and later, possibly irreversible, cognitive defects. Although there is support for iron deficiency with or without anemia causing these defects, it has not been established unequivocally. Some studies suggest an increased risk of seizures, strokes, breathholding spells in children, and exacerbations of restless leg syndrome in adults. Given the frequency of iron deficiency and iron-deficiency anemia and the potential for adverse neurodevelopmental outcomes, minimizing the incidence of iron deficiency is an important goal.

Other nonhematologic consequences of iron deficiency include pica, the desire to ingest nonnutritive substances, and **pagophagia,** the desire to ingest ice. The pica can result in the ingestion of lead-containing substances and result in concomitant **plumbism** (see Chapter 721).

LABORATORY FINDINGS

In progressive iron deficiency, a sequence of biochemical and hematologic events occurs (Tables 455-1 and 455-2). First, tissue iron stores are depleted. This depletion is reflected by reduced serum ferritin, an iron-storage protein, which provides an estimate of body iron stores in the absence of inflammatory disease. Next, serum iron levels decrease, the iron-binding capacity of the serum (serum transferrin) increases, and the transferrin saturation falls below normal. As iron stores decrease, iron becomes unavailable to complex with protoporphyrin to form heme. Free erythrocyte protoporphyrins accumulate, and hemoglobin synthesis is impaired. At this point, iron deficiency progresses to iron-deficiency anemia. With less available hemoglobin in each cell, the red cells become smaller and varied in size. The variation in red cell size is measured by an increasing red cell distribution width. This is followed by a decrease in mean corpuscular volume and mean corpuscular hemoglobin. Developmental changes in mean corpuscular

Table 455-1 Indicators of Iron-Deficiency Anemia

INDICATOR	SELECTED CUTOFF VALUES TO DEFINE IRON DEFICIENCY	COMMENTS
Hemoglobin (g/dL)	<11.0 for non-Hispanic whites ages 0.5-4 yr	When used alone, it has low specificity and sensitivity. Use appropriate age specific normal values found in Table 447-1. Normal values for African-Americans are found in Table 447-2.
Mean corpuscular volume (MCV) (μm^3)	<70 from 6-24 months	A reliable, but late indicator of iron deficiency (ID) Low values can also be a result of thalassemia and other causes of microcytosis. Normal values are found in Table 447-1.
Serum ferritin (SF) (µg/L)	≤5 yr <12 Children >5 yr <15 In all age groups in the presence of infection <30	It is probably the most useful laboratory measure of iron stores and helps identify ID; a low value of SF is diagnostic of iron-deficiency anemia (IDA) in a patient with anemia. SF is an acute phase reactant that increases in many acute or chronic inflammatory conditions independent of iron status. Combining SF with a measurement of C-reactive protein (CRP) helps to identify these false-negative SF results.
Reticulocyte hemoglobin content (CHr) (pg)	In infants and young children <27.5 In adults ≤28.0	A sensitive indicator that falls within days of onset of iron-deficient erythropoiesis and is unaffected by inflammation. It is an excellent tool to recognize ID as well as IDA. False normal values can occur when MCV is increased and in thalassemia. It is not yet widely available on hematology analyzers.
Serum transferrin receptor (sTfR)	Cutoff varies with assay and with patient's age and ethnic origin	This soluble receptor is upregulated in ID and is found in increased amounts in serum. It also increased during enhanced erythropoiesis. sTfR is not substantially affected by the acute-phase response, but it might be affected by malaria, age, and ethnicity. Its application is limited by high cost of commercial assays and lack of an international standard, but it has great promise as an indicator of ID.
Transferrin saturation	<16%	It is inexpensive, but its use is limited by diurnal variation in serum iron and by many clinical disorders that affect transferrin concentrations including in inflammatory conditions.
Erythrocyte zinc protoporphyrin (ZPP) (µmol/mol heme)	≤5 yr >70 Children >5 yr >80 Children >5 yr on washed red cells >40	It can be measured directly on a drop of blood with a portable hematofluorometer. A useful screening test in field surveys, particularly in children, in whom uncomplicated ID is the primary cause of anemia. Lead poisoning can increase values, particularly in urban and industrial settings.
Hepcidin	To be defined; usually ≤10 ng/mL	Extremely elevated in anemia of inflammation and suppressed in iron deficiency anemia

Modified from Zimmermann MB, Hurrell RF: Nutritional iron deficiency, Lancet *370:511–520, 2007.*

Table 455-2 Laboratory Studies Differentiating the Most Common Microcytic Anemias

STUDY	IRON-DEFICIENCY ANEMIA	α- OR β-THALASSEMIA	ANEMIA OF CHRONIC DISEASE
Hemoglobin	Decreased	Decreased	Decreased
MCV	Decreased	Decreased	Normal-decreased
RDW	Increased	Normal or minimally increased	Normal-increased
RBC	Decreased	Normal-increased	Normal-decreased
Serum ferritin	Decreased	Normal	Increased
Total Fe binding capacity	Increased	Normal	Decreased
Transferrin saturation	Decreased	Normal	Decreased
FEP	Increased	Normal	Increased
Transferrin receptor	Increased	Normal	Increased
Reticulocyte hemoglobin concentration	Decreased	Normal	Normal-decreased

FEP, free erythrocyte protoporphyrin; MCV, mean corpuscular volume; RBC, red blood cell count; RDW, red cell distribution width.
Modified from Zimmermann MB, Hurrell RF: Nutritional iron deficiency, Lancet *370:511–520, 2007.*

volume require the use of age-related standards for recognizing microcytosis (see Table 447-1). The red blood cell count also decreases. The reticulocyte percentage may be normal or moderately elevated, but absolute reticulocyte counts indicate an insufficient response to the degree of anemia. The blood smear reveals hypochromic, microcytic red cells with substantial variation in cell size. Elliptocytic or cigar-shaped red cells are often seen (Fig. 455-1). Detection of increased soluble transferrin receptor and decreased reticulocyte hemoglobin concentration provide very useful and early indicators of iron deficiency, but their availability is more limited.

White blood cell count is normal, and thrombocytosis is often present. Thrombocytopenia is occasionally seen with iron deficiency,

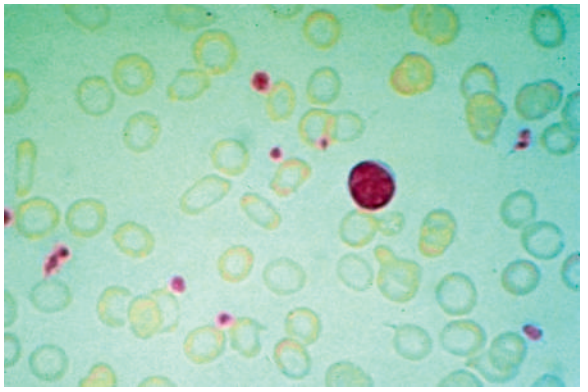

Figure 455-1 Peripheral blood smear from a patient with severe iron-deficiency anemia. The hypochromia is marked. The nucleus of a normal lymphocyte that is comparable in size to a normocytic red cell serves to document many microcytic erythrocytes. The elliptocytic ("cigar-forms") red cells are typical of iron deficiency. Note the variation in red cell size. *(Courtesy of the University of Washington/American Society of Hematology Slide Bank.)*

potentially confusing the diagnosis with bone marrow failure disorders. Stool for occult blood should be checked to exclude blood loss as the cause of iron deficiency.

A presumptive diagnosis of iron-deficiency anemia is most often made by a complete blood count demonstrating a microcytic anemia with a high red cell distribution width, reduced red blood cell count, normal white blood cell count, and normal or elevated platelet count. Other laboratory studies, such as reduced serum ferritin, reduced serum iron, and increased total iron-binding capacity, are not usually necessary unless severe anemia requires a more rapid diagnosis, other complicating clinical factors are present, or the anemia does not respond to iron therapy. An increase in hemoglobin ≥1 g/dL after a month of iron therapy is usually the most practical means to establish the diagnosis.

A diagnosis of iron deficiency in the absence of anemia is more challenging. Serum ferritin is a useful measure whose value is increased by also measuring C-reactive protein to help identify false negative results because of concomitant inflammation. Detection of increased soluble transferrin receptor and decreased reticulocyte hemoglobin concentration may find increasing use as they become more available.

DIFFERENTIAL DIAGNOSIS

The most common alternative causes of microcytic anemia are α- or β-thalassemia and other hemoglobinopathies, including hemoglobins E and C (see Chapter 462.9). The anemia of inflammation is usually normocytic but can be microcytic in a minority of cases (see Chapter 451.1). Lead poisoning can cause microcytic anemia, but more often the microcytic anemia is due to iron deficiency causing pica and secondary lead intoxication (see Chapter 721). Table 455-2 compares the use of laboratory studies in the diagnosis of the most common microcytic anemias. Other etiologies of microcytic anemia are found in Table 455-3. Although the platelet count can be abnormal, the white blood cell count and neutrophil count should be normal.

When anemia is identified solely by hemoglobin or hematocrit, 60% of children in developed countries have anemia not because of iron deficiency. Caution should be used in treating these children with iron without the benefit of a complete blood and differential count to ensure that a more serious diagnosis is not missed.

PREVENTION

Iron deficiency is best prevented to avoid both its systemic manifestations and the anemia. Breastfeeding should be encouraged, with the addition of supplemental iron at 4 mo of age. Infants who are not breastfed should only receive iron-fortified formula (12 mg of iron per liter) for the first year, and thereafter cow's milk should be limited to <20-24 oz daily. This approach encourages the ingestion of foods richer in iron and prevents blood loss as a result of cow's milk–induced enteropathy.

When these preventive measures fail, routine screening helps prevent the development of severe anemia. Routine screening using hemoglobin or hematocrit is done at 12 mo of age, or earlier if at 4 mo of age the child is assessed to be at high risk for iron deficiency. Thereafter screening should continue if risk factors are identified.

Table 455-3 Differential Diagnosis of Microcytic Anemia That Fails to Respond to Oral Iron

- Poor compliance (true intolerance of Fe is uncommon)
- Incorrect dose or medication
- Malabsorption of administered iron
- Ongoing blood loss, including gastrointestinal, menstrual, and pulmonary
- Concurrent infection or inflammatory disorder inhibiting the response to iron
- Concurrent vitamin B_{12} or folate deficiency
- Diagnosis other than iron deficiency
  - Thalassemias
  - Hemoglobins C and E disorders
  - Anemia of chronic disease
  - Lead poisoning
  - Sickle thalassemias, hemoglobin SC disease
  - Iron refractory iron deficiency anemia (IRIDA)
  - Rare microcytic anemias (see Chapter 456)

Table 455-4 Responses to Iron Therapy in Iron-Deficiency Anemia

TIME AFTER IRON ADMINISTRATION	RESPONSE
12-24 hr	Replacement of intracellular iron enzymes; subjective improvement; decreased irritability; increased appetite
36-48 hr	Initial bone marrow response; erythroid hyperplasia
48-72 hr	Reticulocytosis, peaking at 5-7 days
4-30 days	Increase in hemoglobin level
1-3 mo	Repletion of stores

TREATMENT

The regular response of iron-deficiency anemia to adequate amounts of iron is a critical diagnostic and therapeutic feature (Table 455-4). Oral administration of simple ferrous salts (most often ferrous sulfate) provides inexpensive and effective therapy. There is no evidence that the addition of any trace metal, vitamin, or other hematinic substance significantly increases the response to simple ferrous salts. Aside from the unpleasant taste of iron, intolerance to oral iron is uncommon in young children. In contrast, older children and adolescents sometimes have GI complaints.

The therapeutic dose should be calculated in terms of elemental iron. A daily total dose of 3-6 mg/kg of elemental iron in 3 divided doses is adequate, with the higher dose used in more severe cases. The maximum dose would be 150-200 mg of elemental iron daily. Ferrous sulfate is 20% elemental iron by weight and is ideally given between meals with juice, although this timing is usually not critical with a therapeutic dose. Parenteral iron preparations are only used when malabsorption is present or when compliance is poor, because oral therapy is otherwise as fast, as effective, much less expensive and less toxic. When necessary, parenteral iron sucrose, ferric carboxymaltose, and ferric gluconate complex have a lower risk of serious reactions than iron dextran, although only the latter is FDA approved for use in children.

Iron therapy may increase the virulence of malaria and certain Gram-negative bacteria, particularly in developing countries. Iron overdose is associated with *Yersinia* infection.

In addition to iron therapy, dietary counseling is usually necessary. Excessive intake of milk, particularly cow's milk, should be limited. Iron deficiency in adolescent girls secondary to menorrhagia is treated with iron and menstrual control with hormone therapy (see Chapter 116.2).

If the anemia is mild, the only additional study is to repeat the blood count approximately 4 wk after initiating therapy. At this point, the hemoglobin has usually risen by at least 1-2 g/dL and has often normalized. If the anemia is more severe, earlier confirmation of the diagnosis can be made by the appearance of a reticulocytosis usually within 48-96 hr of instituting treatment. The hemoglobin will then begin to increase 0.1-0.4 g/dL per day depending on the severity of the anemia. Iron medication should be continued for 2-3 mo after blood values normalize to reestablish iron stores. Good follow-up is essential to ensure a response to therapy. When the anemia responds poorly or not at all to iron therapy, there are multiple considerations, including diagnoses other than iron deficiency (see Table 455-3).

Because a rapid hematologic response can be confidently predicted in typical iron deficiency, blood transfusion is rarely necessary. It should only be used when heart failure is imminent or if the anemia is severe with evidence of substantial ongoing blood loss. Unless there is active bleeding, transfusions must be given slowly to avoid precipitating or exacerbating congestive heart failure.

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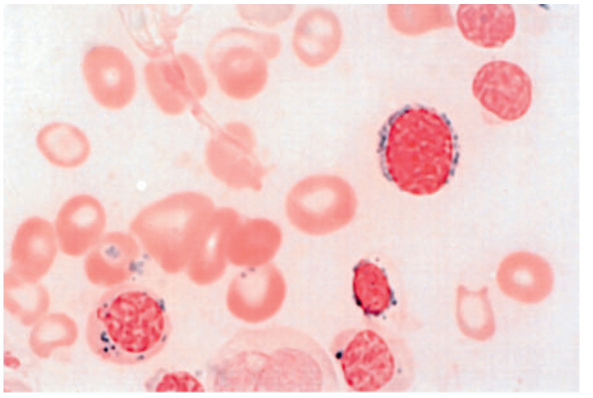

Figure 456-1 Ring sideroblast in myelodysplastic syndrome (refractory anemia with ring sideroblasts)—iron stain. *(From Ryan DH, Cohen HJ: Bone marrow examination. In Hoffman R, Benz EJ Jr, Shattil SJ, et al, editors:* Hematology, *ed 4, Philadelphia, 2005, Churchill Livingstone.)*

Chapter 456

Other Microcytic Anemias

Richard Sills

There are a number of rare microcytic anemias that need to be considered when children with microcytic anemia fail to respond to oral iron and more common diagnoses (see Chapter 462) are eliminated. In addition, although the anemia of chronic inflammation is usually normocytic, it can also be microcytic.

INFANTILE POIKILOCYTOSIS AND HEREDITARY PYROPOIKILOCYTOSIS

Infants with common hereditary elliptocytosis (see Chapter 459) may initially present with hemolytic anemia characterized by marked poikilocytosis with budding and fragmentation of the red blood cells. These small red blood cell fragments reduce the overall mean corpuscular volume, resulting in microcytosis. By 2 yr of age, the findings become typical of hereditary elliptocytosis. Hereditary pyropoikilocytosis is a much less common variant of hereditary elliptocytosis, in which the hemolytic anemia and red cell changes are more severe.

COPPER DEFICIENCY

Copper deficiency is a rare cause of microcytic anemia. It is associated with malabsorption, severe malnutrition often with feeding of milk alone, or parenteral nutrition with inadvertent omission of supplemental copper.

DEFECTS OF IRON METABOLISM

Rare microcytic anemias may be associated with defects in iron trafficking and regulation. Most are inherited and usually identified in childhood. They include defects of iron absorption, transport, utilization, and recycling. A *defect of iron absorption* is **iron refractory iron deficiency anemia**. This defect of transmembrane proteins causes a remarkably severe microcytosis out of proportion to the degree of anemia. This is an autosomal recessive disease due to loss of function mutations in *TMPRSS6*. In most cases, it is unresponsive to oral iron and partially responsive to intravenous iron. *Defects of iron recycling* include **aceruloplasminemia,** in which iron cannot be appropriately transported from macrophages to plasma.

Defects of mitochondrial iron utilization are a diverse group of acquired and inherited defects known as **sideroblastic anemias**. Impaired heme synthesis leads to retention of iron within the mitochondria of marrow red blood cells (RBCs). The perinuclear distribution of mitochondria results in a pattern of iron staining surrounding the nucleus. These are ringed sideroblasts (Fig. 456-1), which are distinct from the more diffuse cytoplasmic distribution of iron in normal RBC precursors. The anemia is characterized by hypochromic microcytic RBCs mixed with normal RBCs, so the complete blood cell count indicates a very high RBC distribution width. The serum iron concentration usually is elevated, and the transferrin saturation of iron is increased.

Congenital sideroblastic anemia is usually an X-linked disorder and is most commonly a result of mutations in erythrocytic isozyme 5-aminolevulinic acid synthetase, the rate-limiting enzyme reaction in heme synthesis. An important cofactor for 5-aminolevulinic acid synthetase is pyridoxal phosphate. Several of these mutations occur near the binding site for pyridoxal phosphate. Severe anemia is recognized in infancy or early childhood, whereas milder cases might not become apparent until early adulthood or later. **Clinical findings** include pallor, icterus, and moderate splenomegaly and/or hepatomegaly. The severity of the anemia varies such that some patients require no therapy and others need regular RBC transfusions. A subset of patients with hereditary sideroblastic anemia manifests a hematologic response to pharmacologic doses of pyridoxine. Iron overload as manifested by elevated serum ferritin, elevated serum iron, and increased transferrin saturation is a major complication of this disorder. Clinical evidence of iron overload (e.g., diabetes mellitus, liver dysfunction) may be found in some patients who have little or no anemia. Stem cell transplantation has been used to treat affected children who are dependent on RBC transfusions.

A unique variant of congenital sideroblastic anemia is **Pearson syndrome** (see Chapter 449), but the anemia is usually macrocytic and not microcytic. Another rare variant of sideroblastic anemia is due to mutations in *TRNT1* and manifests with developmental delay, recurrent fevers, and immunodeficiency in addition to anemia.

Acquired sideroblastic anemias can be triggered by drugs and toxins that disturb mitochondrial iron metabolism, including lead and isoniazid. The acquired neoplastic sideroblastic syndromes seen in adults are very rare in children.

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Section 3

Hemolytic Anemias

Chapter 457

Definitions and Classification of Hemolytic Anemias

George B. Segel

Hemolysis is defined as the premature destruction of red blood cells (RBCs) (a shortened RBC life span). Anemia results when the rate of destruction exceeds the capacity of the marrow to produce RBCs. Normal RBC survival time is 110-120 days (half-life: 55-60 days), and thus, approximately 0.85% of the most senescent RBCs are removed and replaced each day. During hemolysis, RBC survival is shortened, the RBC count falls, erythropoietin is increased, and the stimulation of marrow activity results in heightened RBC production, reflected in an increased percentage of reticulocytes in the blood. Thus, hemolysis should be suspected as a cause of anemia if an elevated reticulocyte count is present. The reticulocyte count may also be elevated as a response to acute blood loss or for a short period after replacement therapy for iron, vitamin B_{12}, or folate deficiency. The marrow can increase its output 2-3–fold acutely, with a maximum of 6-8–fold in long-standing hemolysis. The reticulocyte percentage can be corrected to measure the magnitude of marrow production in response to hemolysis as follows:

$$\text{Reticulocyte index} = \text{reticulocyte\%} \times \frac{\text{Observed hematocrit}}{\text{Normal hematocrit}} \times \frac{1}{\mu}$$

where μ is a maturation factor of 1-3 related to the severity of the anemia (Fig. 457-1). The normal reticulocyte index is 1.0; therefore, the index measures the fold increase in erythropoiesis (e.g., 2-fold, 3-fold).

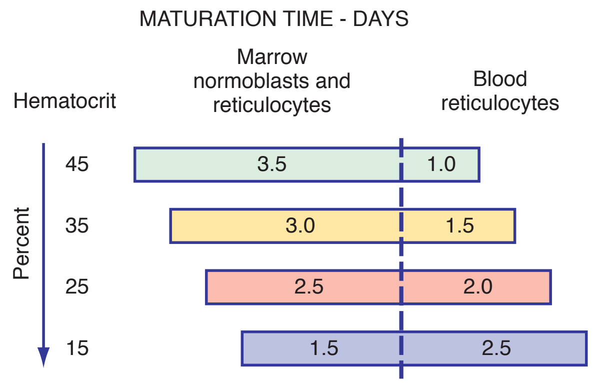

Figure 457-1 **Number of days for maturation of reticulocytes to mature erythrocytes in the marrow and blood.** The duration of maturation as blood reticulocytes is taken as μ, which is used in the correction equation in this chapter. *(Modified from Hillman RS, Finch CA:* Red cell manual, *Philadelphia, 1983, FA Davis.)*

As anemia becomes more severe, the erythropoietin concentration increases and reticulocytes are released from the marrow earlier; they are identifiable as reticulocytes in the blood that last for >1 day. Because the reticulocyte index is essentially a measure of RBC production per day, the maturation factor, μ, provides this correction (see Fig. 457-1).

The erythroid hyperplasia resulting from chronic hemolytic anemia in children, especially thalassemia, may be so extensive that the medullary spaces expand at the expense of the cortical bone. These changes may be evident on physical examination or on radiographs of the skull and long bones (see Fig. 462-7). A propensity to fracture long bones can also occur.

Direct assessment of the severity of hemolysis requires measurement of RBC survival time using RBCs tagged with the radioisotope $Na_2{}^{51}CrO_4$. The normal half-life of chromium 51–labeled RBCs is 25-35 days. This value is less than the expected half-life of 55-60 days because of the elution of chromium 51 from the labeled RBCs at the rate of approximately 1% day. Techniques to measure RBC survival using RBC biotin labeling do not require the use of isotopes.

The exaggerated degradation rate of hemoglobin results in increased biliary excretion of heme pigment derivatives and increased urinary and fecal urobilinogen (Fig. 457-2). Gallstones composed of calcium bilirubinate may be formed in children with chronic hemolysis as young as 4 yr of age. Elevations of serum unconjugated bilirubin and lactate dehydrogenase also can accompany hemolysis.

Three heme-binding proteins in the plasma are altered during hemolysis (see Fig. 457-2). Hemoglobin binds to haptoglobin and hemopexin, both of which are cleared more rapidly as conjugates, resulting in a reduced plasma concentration. Oxidized heme binds to albumin to form methemalbumin, which is increased in the plasma. When the capacity of these binding molecules is exceeded, free hemoglobin appears in the plasma, and the pink color can be seen if the plasma is partitioned after centrifugation in a capillary hematocrit tube. If present, free hemoglobin in the plasma is prima facie evidence of intravascular hemolysis. Free hemoglobin dissociates into dimers and is filtered by the kidneys. When the tubular reabsorptive capacity of the kidneys for hemoglobin is exceeded, free hemoglobin appears in the urine. Even in the absence of hemoglobinuria, iron loss can result from reabsorbed hemoglobin and the shedding of renal epithelial cells in which the iron from hemoglobin is stored as hemosiderin. This iron loss can lead to iron deficiency during chronic intravascular hemolysis. When hemoglobin is degraded, an α-methene bridge is broken in the cyclic tetrapyrrole of the heme moiety, with

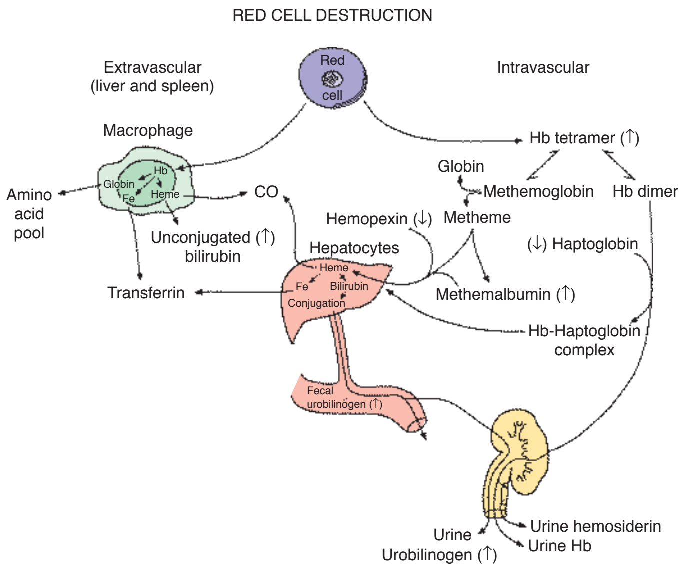

Figure 457-2 **Red cell destruction and catabolism of hemoglobin (Hb) based on the description by Hillman and Finch.** Fe, iron. *(From Hillman RS, Finch CA:* Red cell manual, *Philadelphia, 1983, FA Davis.)*

release of carbon monoxide (CO) (see Fig. 457-2). The amount of CO in the blood or expired air provides a dynamic measure of the hemolytic rate; end-tidal CO is not available in most clinical laboratories to measure hemolysis.

The hematocrit level depends on the severity of hemolysis and on the erythropoietic response. The shortened RBC life span and heightened RBC production result in a marked susceptibility to aplastic or hypoplastic crises, characterized by erythroid marrow failure and reticulocytopenia, accompanied by a rapid reduction in hemoglobin and hematocrit to extremely low levels. The most common cause of aplastic crisis is infection with parvovirus B19, which is erythrocytotropic (see Chapters 251 and 450). An aplastic crisis can produce a precipitous and life-threatening decline in hematocrit that usually lasts 10-14 days. Such transient erythroid marrow failure has only a mild effect in persons with a normal RBC life span, but it has a proportionately greater effect if the RBC life span is shortened by hemolysis. A second infection with parvovirus B19 is uncommon, but other infections can compromise erythroid marrow output, resulting in various degrees of hypoplasia or hypoplastic crises.

Hemolytic anemias may be classified as either cellular, resulting from intrinsic abnormalities of the membrane, enzymes, or hemoglobin; or extracellular, resulting from antibodies, mechanical factors, or plasma factors. Most cellular defects are inherited (paroxysmal nocturnal hemoglobinuria is acquired), and most extracellular defects are acquired (abetalipoproteinemia with acanthocytosis is inherited). Table 457-1 shows the most common hemolytic anemias, their underlying defects, the diagnostic laboratory tests, and recommendations for treatment.

Table 457-1 Hemolytic Anemias and Their Treatment

DIAGNOSIS	DEFECT	LABORATORY TESTS	TREATMENT
CELLULAR DEFECTS			
Membrane Defects			
Hereditary spherocytosis	Cytoskeletal protein defects Often involve vertical interactions of spectrin ankyrin, protein 3	Spherocytes on blood film Negative Coombs test eliminates immune hemolysis Increased incubated osmotic fragility Abnormal cytoskeletal protein analysis	If Hb >10 g/dL and reticulocyte count <10%: none If severe anemia, poor growth, aplastic crises, and age <2 yr: transfusion Folic acid, 1 mg qd Splenectomy (see text)
Hereditary elliptocytosis	Cytoskeletal protein defects Often involve horizontal interactions of spectrin, protein 4.1, and glycophorin c	Elliptocytes on blood film RBCs mildly heat-sensitive Abnormal cytoskeletal protein analysis	Mild types: no treatment Chronic hemolysis: transfusion and splenectomy as recommended for spherocytosis (see above) Folic acid, 1 mg qd
Hereditary pyropoikilocytosis	Cytoskeletal protein defects Homozygous or double heterozygous abnormality in horizontal interactions of α-spectrin	Extreme variation in RBC size and shape on blood film Thermal sensitivity-fragmentation at 45°C (113°F) for 15 min	Transfusion and splenectomy as recommended for spherocytosis (see above) Folic acid, 1 mg qd
Hereditary stomatocytosis	Cytoskeletal protein defects Decreased protein 7.2b (1 subset) Abnormal RBC cation and water content	Stomatocytes on blood film	Splenectomy should be avoided (see text) Folic acid, 1 mg qd
Paroxysmal nocturnal hemoglobinuria	Primary acquired marrow disorder RBCs unusually sensitive to complement-mediated lysis	Decreased WBC CD55 and CD59 or decreased RBC CD59 by flow cytometry Marrow aspirate and biopsy to assess cellularity Decreased decay-accelerating factor	Folic acid, 1 mg qd Mild cytopenias: no treatment Chronic hemolysis and other cytopenias: prednisone, qd initially, and then qod for maintenance therapy Iron for secondary iron deficiency Eculizumab (inhibits C5) Anticoagulation Marrow transplant for pancytopenia
Enzyme Deficiencies			
Pyruvate kinase deficiency	Decreased or abnormal enzyme	Pyruvate kinase assay: decreased V_{max} or, rarely, high K_m variant	In severe anemia with symptoms, poor growth and age <2 yr: transfusion Splenectomy age >6 yr, but earlier if necessary Folic acid, 1 mg qd
G6PD deficiency	A^- type: age-labile enzyme Mediterranean type: no enzyme activity in circulating RBCs	G6PD assay	Avoid oxidant stress to RBCs Transfusion if acute anemia is symptomatic
Hemoglobin Abnormalities			
For discussion of hemoglobinopathies, see sections on these topics.			

Table 457-1 Hemolytic Anemias and Their Treatment—cont'd

DIAGNOSIS	DEFECT	LABORATORY TESTS	TREATMENT
EXTRACELLULAR DEFECTS			
Autoimmune			
"Warm" antibody	Alteration in membrane surface antigen (Rh) or abnormal response of B lymphocytes, causing autoantibody formation "Molecular mimicry" to viral antigen	Spherocytes on blood film Positive direct antiglobulin (Coombs) test to IgG "warm" antibody or anti-C3d directed against RBCs Positive indirect Coombs test and antibody detectable in plasma Thermal amplitude 35-40°C (95-104°F) Some complement (C3b) may be detected on RBCs Tests for underlying disease	If Hb >10 g/dL and reticulocyte count <10%—none Severe anemia may require transfusion; prednisone, 2 mg/kg/24 hr IVIG ***Rituximab*** Splenectomy Immunosuppressives Folic acid, 1 mg/24 hr if chronic
"Cold" antibody	"Cold" or IgM autoantibody directed against I/i antigen system	Agglutination or rouleaux on blood film Positive direct Coombs test to complement (C3b) Tests for underlying disease Serology for infectious mononucleosis; anti-i present Serology for *Mycoplasma pneumoniae;* anti-I present	If Hb >10 g/dL and reticulocyte count <10%: none Severe anemia might require transfusion Avoid exposure to cold If severe: ***Rituximab*** Immunosuppressives and plasmapheresis Prednisone is less effective Splenectomy is not useful Folic acid, 1 mg/24 hr if chronic
Fragmentation Hemolysis			
DIC, TTP, HUS, aHUS, pneumococcal-induced HUS See Table 465-1	Direct damage to RBC membrane	Fragments on blood film	Treat underlying condition Transfusion, but transfused cells also will have shortened life span
Extracorporeal membrane oxygenation	Direct damage to RBC membrane	Fragments on blood film	Supportive Transfusion until ECMO is discontinued
Prosthetic heart valve	Direct damage to RBC membrane	Fragments on blood film	Folic acid, 1 mg/24 hr Iron for secondary iron deficiency
Burns, thermal injury	Direct damage to RBC membrane	Spherocytes on blood film	Supportive Transfusion
Hypersplenism	Effects of sequestration, ↓ pH, lipases and other enzymes, and macrophages on RBCs	Thrombocytopenia and neutropenia	Treat underlying condition: cytopenias all usually mild Splenectomy if complicating other anemia (e.g., thalassemia major) Folic acid, 1 mg/24 hr
Plasma Factors			
Liver disease	Alteration in plasma cholesterol and phospholipids	Target cells or spiculated RBCs on blood film Abnormal liver function tests	Treat underlying condition Transfusion, but transfused cells also will have shortened life span Folic acid, 1 mg/24 hr
Abetalipoproteinemia	Absence of apolipoprotein β Vitamin E deficiency and heightened sensitivity to oxidative damage	Acanthocytes on blood film Absent chylomicrons, VLDL, and LDL	Vitamin E (A, K, and D) Folic acid, 1 mg/24 hr Dietary restriction of triglycerides
Infections	Toxic effects on RBCs	Associated symptoms and signs Cultures	Antibiotics Supportive
Wilson disease	Effect of copper on RBC membrane, usually self-limited	Spherocytes on blood film Copper, ceruloplasmin Kaiser Fleischer rings Penicillamine challenge and urine copper excretion Liver biopsy for Cu content Gene analysis for mutation of ATP7B	Penicillamine Supportive Transfusion if acute anemia is symptomatic

aHUS, atypical hemolytic uremic syndrome; Cu, copper; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; G6PD, glucose-6-phosphate dehydrogenase; Hb, hemoglobin; HUS, hemolytic uremic syndrome; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; LDL, low-density lipoprotein; K_m, Michaelis constant; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura; VLDL, very-low-density lipoprotein; V_{max}, maximal velocity; WBC, white blood cell.

Modified from Asselin BL, Segel GB: In Rakel R, editor: Conn's current therapy, *Philadelphia, 1994, Saunders, pp 338–339.*

Chapter 458

Hereditary Spherocytosis

George B. Segel and Denise Casey

Hereditary spherocytosis (HS) is a common cause of hemolysis and hemolytic anemia, with a prevalence of approximately 1 in 5,000 persons. It is the most common inherited abnormality of the red blood cell (RBC) membrane. Although common among persons of Northern European origin, HS has been described in most ethnic groups. The more rare defects found in the United States and in Europe are the more common mutations described in the Japanese population. The clinical spectrum varies widely. Affected patients may be asymptomatic, without anemia and with minimal hemolysis, or they may have severe hemolytic anemia requiring regular blood transfusions and a splenectomy.

ETIOLOGY

Hereditary spherocytosis usually is transmitted as an autosomal dominant or, less commonly, as an autosomal recessive disorder. As many as 25% of patients have no previous family history. Of these patients, most represent new mutations, and a few cases result from recessive inheritance or represent nonpaternity. The pathophysiology underlying HS involves 5 proteins, which are key components of the cytoskeleton responsible for RBC shape (Table 458-1). Abnormalities of spectrin or ankyrin are the most common molecular defects. Dominant defects have been described in β-spectrin and band 3. Recessive defects have been described in α-spectrin and protein 4.2. Both dominant and recessive defects have been described in ankyrin (Table 458-1). A deficiency in spectrin, band 3, ankyrin, or protein 4.2 results in uncoupling in the "vertical" interactions of the lipid bilayer skeleton and subsequent release of membrane microvesicles. The loss of membrane surface area without a proportional loss of cell volume causes sphering of the RBCs, and an associated increase in cation permeability, cation transport, adenosine triphosphate use, and glycolysis. The decreased deformability of the spherocytic RBCs impairs cell passage from the splenic cords to the splenic sinuses, and the spherocytic RBCs are destroyed prematurely in the spleen (Figs. 458-1 and 458-2). Splenectomy markedly improves RBC life span and may be indicated in some patients with HS.

CLINICAL MANIFESTATIONS

In the neonatal period, HS is a significant cause of hemolytic disease and can be manifest as anemia and hyperbilirubinemia sufficiently severe to require phototherapy or exchange transfusions. Hemolysis may be more prominent in the newborn because hemoglobin F binds 2,3-diphosphoglycerate poorly, and the increased level of free 2,3-diphosphoglycerate destabilizes interactions among spectrin, actin, and protein 4.1 in the RBC membrane (see Fig. 458-1). The need for exchange transfusion at birth or transfusions in infancy is not indicative of more severe disease later in life because infants do not mount an adequate reticulocyte response until several months after birth.

Some patients remain asymptomatic into adulthood, but others have severe anemia with pallor, jaundice, fatigue, and exercise intolerance. Severe cases may be marked by expansion of the diploë of the skull as a result of marrow hyperplasia (frontal bossing), but to a lesser extent than in thalassemia major. Depending on the severity of the anemia and the comorbidities associated with severe anemia, some patients benefit from a splenectomy (Table 458-2).

After infancy, splenomegaly is common; there is no correlation between spleen size and disease severity. Bilirubin gallstone formation is a function of age; they can form as early as age 4-5 yr and are present in the majority of adult patients.

Children with HS are also susceptible to aplastic crises, primarily as a result of parvovirus B19 infection, and to hypoplastic crises associated with various other infections (Fig. 458-3). High RBC turnover in the setting of erythroid marrow failure can result in profound anemia (hematocrit <10%), high-output heart failure, cardiovascular collapse, and death. White blood cell and platelet counts can also fall (Fig. 458-3). Rare complications associated with HS include splenic sequestration crisis, gout, cardiomyopathy, priapism, leg ulcers, and spinocerebellar degeneration.

DIAGNOSIS

Evidence of hemolysis includes reticulocytosis and indirect hyperbilirubinemia. The hemoglobin level usually is 6-10 g/dL, but it can be in the normal range. The reticulocyte percentage often is increased to 6-20%, with a mean of approximately 10%. The mean corpuscular

Table 458-1 Common Gene Mutations in Hereditary Spherocytosis

PROTEIN	GENE	COMMON MUTATIONS*	PREVALENCE	INHERITANCE	DISEASE SEVERITY
Ankyrin-1	*ANK1*	Frameshift Nonsense Splicing Missense Promoter region	50-67% 5-10% in Japan	Dominant and recessive	Mild to moderate
Band 3	*AE1 (SLC4A1)*	Missense Nonsense Polymorphism Mutant protein	15-20%	Mostly dominant	Mild to moderate
β-Spectrin	*SPTB*	Null Nonsense Missense Polymorphism	15-20%	Dominant	Mild to moderate
α-Spectrin	*SPTA1*	Splicing αLEPRA allele	<5%	Recessive	Severe
Protein 4.2	*EPB42*	Missense Nonsense Splicing	<5% 45-50% in Japan	Recessive	Mild to moderate

*Detected mutations in order of frequency

Modified from Bolton-Maggs PHB, Langer JC, Iolascon A, et al: Guidelines for the diagnosis and management of hereditary spherocytosis–2011 update, Br J Haematol *156:37–49, 2011.*

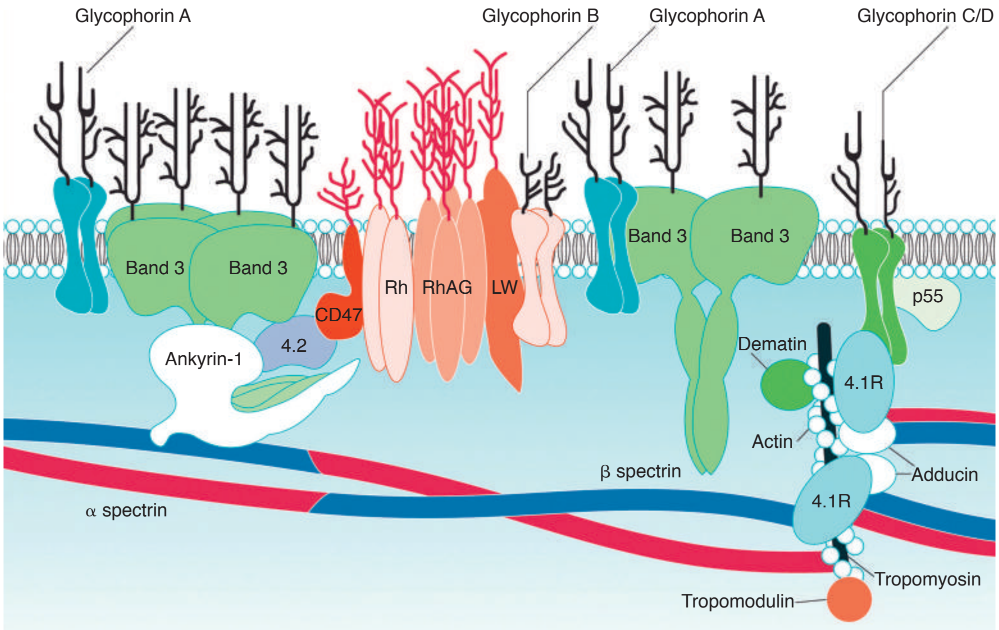

Figure 458-1 **A simplified cross-section of the red blood cell (erythrocyte) membrane.** The lipid bilayer forms the equator of the cross-section with its polar heads (small circles) turned outward. 4.1 R, protein; 4.2, protein 4.2; LW, Landsteiner-Wiener glycoprotein; Rh, Rhesus polypeptide; RhAG, Rh-associated glycoprotein. *(From Perrotta S, Gallagher PG, Mohandas N: Hereditary spherocytosis,* Lancet *372:1411–1426, 2008.)*

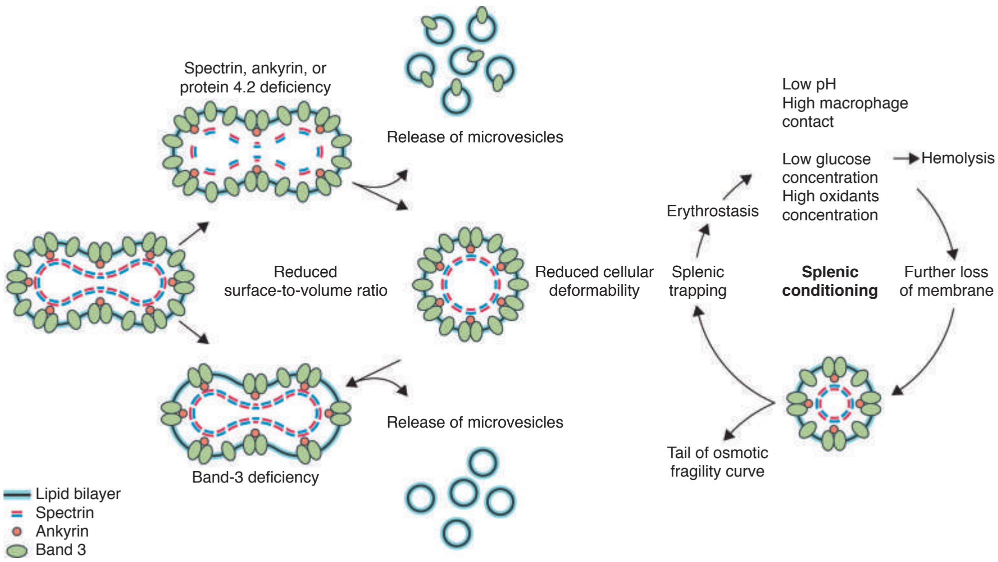

Figure 458-2 **Pathophysiologic effects of hereditary spherocytosis.** *(From Perrotta S, Gallagher PG, Mohandas N: Hereditary spherocytosis,* Lancet *372:1411–1426, 2008.)*

Table 458-2 Hereditary Spherocytosis Disease Classification

	TRAIT	MILD	MODERATE	SEVERE
Hemoglobin (g/dL)	Normal	11-15	8-12	<6-8
Reticulocytes (%)	Normal (<3)	3-6	>6	>10
Bilirubin	<17	17-34	>34	>51
Transfusions	0	0	0-2	Regular
Typical heredity	AD	AD	AD or de novo mutation	AR
Splenectomy	Not indicated	Not indicated	May be indicated*	Indicated

*Splenectomy indicated if patient requires frequent transfusions for hypoplastic crises or shows poor growth or cardiomegaly.

AD, autodominant; AR, autorecessive.

Modified from Bolton-Maggs PHB, Langer JC, Iolascon A, et al: Guidelines for the diagnosis and management of hereditary spherocytosis–2011 update, Br J Haematol *156:37–49, 2011.*

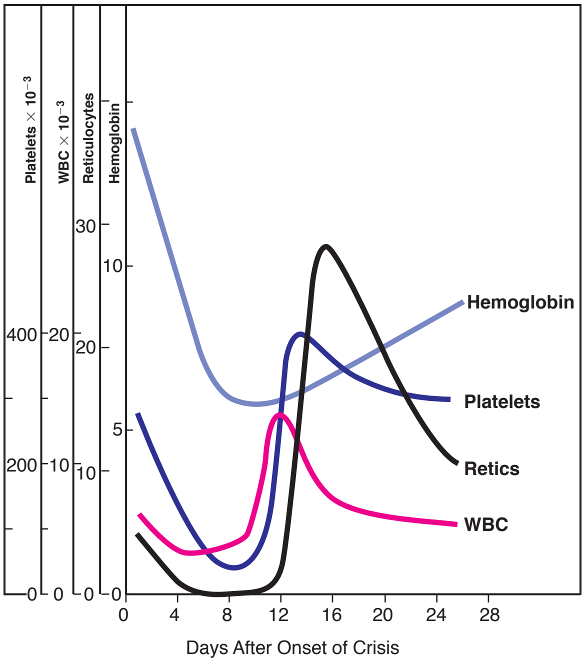

Figure 458-3 **Parvovirus-induced aplastic crisis.** Progression of the changes in blood count is shown for a patient with hereditary spherocytosis and infection with parvovirus. Note that the fall in baseline reticulocytosis is associated with a rapid fall in hemoglobin. White blood cells (WBC) and platelets are also affected. *(Modified from Nathan DG, Orkin SH, Ginsburg D, et al, editors:* Hematology of infancy and childhood, *ed 6, Philadelphia, 2003, WB Saunders.)*

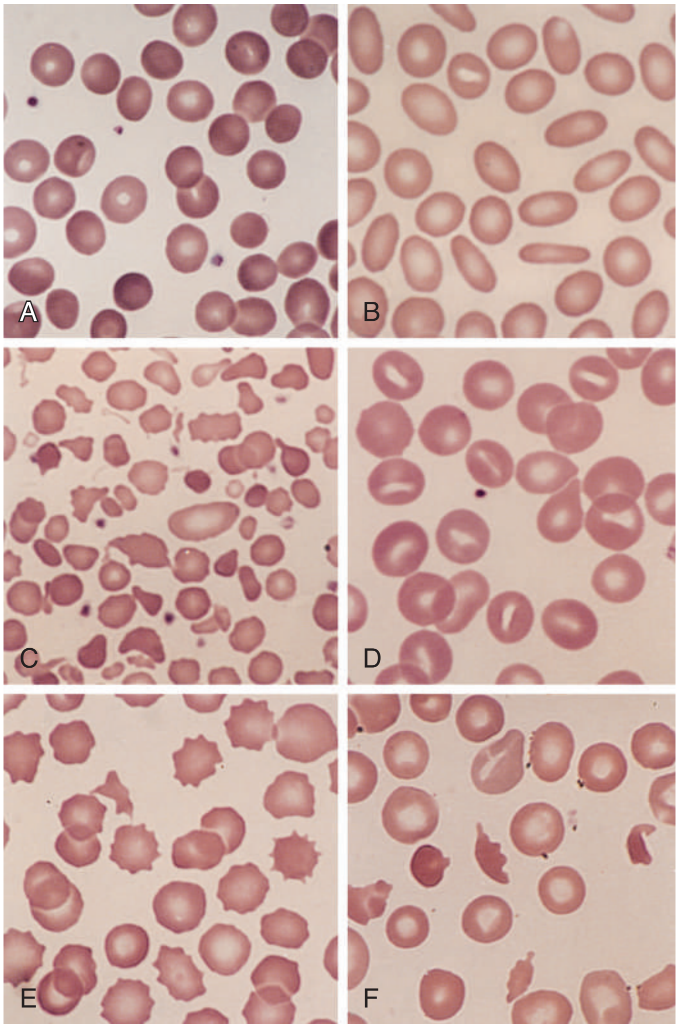

Figure 458-4 Morphology of abnormal red cells. **A,** Hereditary spherocytosis. **B,** Hereditary elliptocytosis. **C,** Hereditary pyropoikilocytosis. **D,** Hereditary stomatocytosis. **E,** Acanthocytosis. **F,** Fragmentation hemolysis.

volume is normal, although the mean corpuscular hemoglobin concentration often is increased (36-38 g/dL RBCs). The RBCs on the blood smear vary in size and include polychromatophilic reticulocytes and spherocytes (Fig. 458-4). The spherocytes are smaller in diameter and appear hyperchromic as a result of the high hemoglobin concentration. The central pallor is less conspicuous than in normal cells. Spherocytes may be the predominant cells or may be relatively sparse, depending on the severity of the disease, but they usually account for >15% of the cells when hemolytic anemia is present. Other evidence of hemolysis includes decreased haptoglobin and the presence of gallstones on ultrasonography.

The diagnosis of HS can be established from a positive family history and the presence of typical clinical and laboratory features of the disease: splenomegaly, spherocytes on the blood smear, reticulocytosis, and an elevated mean corpuscular hemoglobin concentration. If these are present, no additional testing is necessary to confirm the diagnosis. If the diagnosis is less certain, the recommended tests that have a high predictive value for HS are the flow cytometric EMA (eosin-5-maleimide) binding test and the cryohemolysis test. Although no test for HS is 100% reliable, the EMA binding test had a diagnostic sensitivity and specificity of 93% and 98%, respectively, in a recent large study. Other assays, such as the acidified glycerol lysis test and osmotic gradient ektacytometry, also have increased sensitivity for HS. The classic incubated osmotic fragility test can detect the presence of spherocytes in the blood; however, it is not specific to HS and may be abnormal in other hemolytic anemias. The RBCs are incubated in progressive dilutions of sodium chloride causing the RBCs to swell and eventually lyse. Spherocytes lyse at a higher sodium chloride concentration than biconcave cells in hypotonic solutions because they have a lower surface area : volume ratio. Unfortunately, this test has poor sensitivity relative to other screening assays and can miss up to 20% of mild HS cases.

As a research tool and for atypical cases, the specific membrane abnormality can be established by gel electrophoresis analysis of RBC membrane proteins. Molecular diagnosis also is possible because most patients having a family-specific private mutation can be detected by DNA analysis.

DIFFERENTIAL DIAGNOSIS

The major alternative considerations when large numbers of spherocytes are seen on the blood smear are isoimmune and autoimmune hemolysis. Isoimmune hemolytic disease of the newborn, particularly when a result of ABO incompatibility, mimics the cell appearance of HS. The detection of antibody on an infant's RBCs using a direct antiglobulin (Coombs) test should establish the diagnosis of immune hemolysis. Autoimmune hemolytic anemias also are characterized by spherocytes; however, there may be evidence of previously normal values for hemoglobin, hematocrit, and reticulocyte count. Rare causes of spherocytosis include thermal injury, clostridial septicemia, and Wilson disease, each of which can manifest as transient hemolytic anemia (see Table 457-1 in Chapter 457).

TREATMENT

General Supportive Care

Parents should be advised of the risk of newborn jaundice and the potential need for phototherapy and exchange transfusion after birth to decrease bilirubin levels. Infants born to parents with known HS should be monitored carefully as hyperbilirubinemia may peak several days after birth. A minority of infants will be transfusion-dependent

until development of adequate erythropoiesis to compensate for the ongoing hemolysis. Continued transfusion-dependence is not common after 6-12 mo of age.

Once the baseline level of disease severity is reached, an annual visit to the hematologist usually is sufficient. Growth should be monitored, exercise tolerance and spleen size documented, and parents should receive anticipatory guidance regarding the risk of aplastic crisis secondary to parvovirus, and hypoplastic crises with other infections. Parents and patients should be informed of an increased risk for gallstone development. The degree of splenomegaly does not correlate with disease severity. Folic acid supplementation is recommended in moderate and severe HS because of an enhanced requirement with increased erythropoiesis.

Guidelines for Splenectomy

Because the spherocytes are destroyed almost exclusively in the spleen, splenectomy eliminates most of the hemolysis. After splenectomy, the anemia, hyperbilirubinemia, and incidence of gallstones are significantly lessened, if not completely eradicated. However, splenectomy is associated with immediate surgical morbidities in addition to a lifelong increased risk for sepsis, particularly that caused by pneumococcal species. This risk is not completely eliminated with the requisite preoperative and postoperative vaccination against pneumococcus, meningococcus, and *Haemophilus influenzae type b*.

Splenectomy is recommended for patients with severe HS. It should be considered for patients with moderate HS and frequent hypoplastic or aplastic crises, poor growth, or cardiomegaly. It is generally not recommended for patients with mild HS. When splenectomy is indicated, it should be performed after the age of 6 yr, if possible, to avoid the heightened risk of postsplenectomy sepsis in younger children. The laparoscopic approach has less surgical morbidity and is recommended if the surgeon is adequately trained in this approach. Partial splenectomy may be beneficial but needs further study. In children undergoing splenectomy, a concomitant cholecystectomy should be performed if there are gallstones. It is controversial whether to perform a concomitant splenectomy in less-severely ill patients who are undergoing cholecystectomy for gallstone disease. Postsplenectomy thrombocytosis is commonly observed, but requires no treatment and usually resolves spontaneously. Vaccines for encapsulated organisms, such as pneumococcus, meningococcus, and *H. influenzae type b*, should be administered at least 14 days before splenectomy, and prophylactic oral penicillin VK prescribed indefinitely.

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Chapter 459
Hereditary Elliptocytosis

George B. Segel

Hereditary elliptocytosis is a less common disorder than spherocytosis and also varies markedly in severity. Mild hereditary elliptocytosis produces no symptoms; more severe varieties can result in neonatal poikilocytosis (shape variation) and hemolysis, chronic or sporadic hemolytic anemia, or **hereditary pyropoikilocytosis (HPP)**, which is a severe disorder with microspherocytosis and poikilocytosis. Hereditary elliptocytosis is rare in Western populations and is more common among West Africans.

ETIOLOGY

Hereditary elliptocytosis is inherited as a dominant disorder. In the rare instances, when 2 abnormal alleles are inherited (HPP), the patient exhibits particularly severe hemolytic anemia. Various molecular defects have been described in hereditary elliptocytosis; these produce abnormalities of α- and β-spectrin and defective spectrin heterodimer self-association (see Fig. 458-1). The abnormalities (spectrin mutations) can provide resistance to malarial infection. Such defects in horizontal protein interactions result in gross membrane fragmentation, particularly in homozygous HPP. Less commonly, mutations in protein 4.1 and glycophorin C can produce elliptocytosis.

CLINICAL MANIFESTATIONS

Elliptocytosis may be an incidental finding on a blood film examination and might not be associated with clinically significant hemolysis (see Fig. 458-4*B*). The diagnosis of hereditary elliptocytosis is established by the findings on the blood film, the autosomal dominant inheritance pattern, and the absence of other causes of elliptocytosis, such as deficiencies of iron, folic acid, or vitamin B_{12}. Hemolytic elliptocytosis can produce neonatal jaundice, even though characteristic elliptocytosis might not be evident at that time. The blood of the affected newborn can show bizarre poikilocytes and pyknocytes. Transient augmented fragmentation and hemolysis in the newborn can result from the presence of hemoglobin F that binds poorly to the glycolytic intermediate 2,3-diphosphoglycerate. The increased 2,3-diphosphoglycerate tends to destabilize the spectrin–actin–protein 4.1 complex, leading to membrane instability (see Fig. 458-1).

The usual features of a chronic hemolytic process with elliptocytosis are manifested later as anemia, jaundice, splenomegaly, and osseous changes. Cholelithiasis can occur in later childhood; aplastic crises have been reported. The most severe form is HPP, which is characterized by extreme microcytosis (mean corpuscular volume, 50-60 fL/cell), extraordinary variation in cell size and shape, and primarily microspherocytic rather than elliptocytic cells (see Fig. 458-4*C*). The red blood cells (RBCs) have heightened sensitivity to heat, hence the "pyro" designation. These patients usually inherit a mutant spectrin from one parent, who has mild or no elliptocytosis (silent carrier), and a partial spectrin deficiency from the other parent, who is hematologically normal.

Ovalocytes, in contrast to elliptocytes, are less elongated and might reflect a condition known as *Southeast Asian ovalocytosis* (SAO). SAO is associated with an abnormal protein 3, which functions as an anion exchanger. This disorder can produce neonatal hyperbilirubinemia, but it causes little hemolysis later. It might offer protection against *Plasmodium falciparum* malaria because normal protein 3 is one of the malarial receptors. Protein 3 as an anion exchanger is also expressed in renal tubular cells and can cause distal renal tubular acidosis in association with SAO.

LABORATORY FINDINGS

The blood film is the most important test to establish hereditary elliptocytosis (see Fig. 458-4*B*). The RBCs show various degrees of elongation and can actually be rod shaped. In hereditary elliptocytosis, other abnormal RBC shapes may be present, depending on the severity of hemolysis. They include microcytes, spherocytes, and other poikilocytes. The increase in the reticulocyte percentage reflects the severity of hemolysis; erythroid hyperplasia and indirect hyperbilirubinemia may be present. Increased thermal instability is characteristic of HPP. The abnormal spectrin denatures and the cells lyse at 45-46°C (113-114.8°F) instead of the usual 49-50°C (120.2-122°F). The specific protein abnormality can be established by protein separation and analysis techniques. The eosin-5-maleimide binding test, which detects binding to protein band 3 by flow cytometry, may be useful in conjunction with the mean corpuscular volume in diagnosing hereditary elliptocytosis and hereditary spherocytosis. Molecular defects are defined only in research laboratories.

TREATMENT

If hereditary elliptocytosis represents a morphologic abnormality on the blood film without evident hemolysis, no treatment is necessary. Patients with chronic hemolysis should receive folic acid, 1 mg daily, to prevent secondary folic acid deficiency. Splenectomy decreases the

hemolysis and should be considered if the hemoglobin is <10 g/dL and the reticulocyte count is >10%. The RBCs on the blood film may be more abnormal after splenectomy, even though hemoglobin increases and reticulocytes decrease. The hematologic features of SAO do not require treatment beyond the newborn period.

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Chapter 460
Hereditary Stomatocytosis

George B. Segel and Lisa R. Hackney

Hereditary stomatocytosis includes a rare group of dominantly inherited hemolytic anemias in which there are characteristic morphologic changes in the red blood cells (RBCs) and increased red cell cation permeability. The RBCs are cup-shaped, creating a mouth-shaped area (stoma) of central pallor instead of the usual circular area of central pallor. Hereditary stomatocytosis is classified by the RBC hydration status. The 2 major varieties are either overhydrated (hydrocytosis) or dehydrated (xerocytosis).

HYDROCYTOSIS
Pathophysiology
Stomatocytes of the hydrocytic variant have excess intracellular sodium and water content and decreased intracellular potassium content. The principal defect in this variant is an increase in Na^+ and K^+ permeability, caused by mutations in rhesus-associated glycoproteins. However, the amount of Na^+ influx exceeds the K^+ efflux, and the cells subsequently develop increased cation content and water, and thus swell. These hydrocytic cells have increased osmotic fragility. Additionally, the integral membrane protein, stomatin or band 7.2 b, is decreased or absent from the erythrocyte membrane. The function of stomatin is not fully understood, although it might act as a switch that influences the function of GLUT1, the glucose transporter. It has been found that stomatin in the hydrocytic variant is synthesized early in RBC development but is lost as the cell matures. The mechanism for this loss of stomatin is not yet determined. It also is unclear how the loss of stomatin expression contributes to the cation leak, which is characteristic of this variant.

Clinical Features
The hydrocytic variant is the most severe form of hereditary stomatocytosis and is characterized by moderate to severe hemolysis, macrocytosis, and large numbers of stomatocytes on the blood smear. Patients commonly develop jaundice, splenomegaly, and cholelithiasis.

XEROCYTOSIS
Pathophysiology
The xerocytic variant is the more common form of hereditary stomatocytosis and usually results in a milder anemia in affected patients. The underlying cation defect is a net loss of RBC potassium that is not accompanied by an increase in sodium. Subsequently, the erythrocyte develops decreased intracellular water content and becomes dehydrated. It may be associated with a syndrome of perinatal edema and ascites. These findings are transient and remain unexplained.

Clinical Features
Patients affected by the xerocytic variant have a mild compensated macrocytic hemolytic anemia, variable numbers of stomatocytes and/or target cells on peripheral smear, increased mean corpuscular hemoglobin concentration as a result of the cellular dehydration, and, typically, jaundice and splenomegaly.

INTERMEDIATE SYNDROMES
The **Rh deficiency syndrome** is characterized by an absence or profound decrease in the Rh antigen on the RBC membrane. Affected RBCs in this disorder are dehydrated and have decreased cell cation and water content. This decreased cell cation content may be the result of increased potassium leak in spite of increased Na^+-K^+ pump activity. This syndrome is associated with mild to moderate hemolytic anemia, reticulocytosis, and stomatocytes and spherocytes on the blood smear.

Cryohydrocytosis is a mild form of stomatocytosis, typically caused by mutations in *SLC4A1* coding for the band 3 anion exchanger, in which the RBCs lyse on cooling in vitro and may be associated with "pseudohyperkalemia."

Absence of high-density lipoproteins (an **α-lipoproteinemia** or **Tangier disease**) can lead to hematologic manifestations such as a moderate hemolytic anemia, stomatocytosis, and thrombocytopenia. Affected patients can also have large orange tonsils, hepatosplenomegaly, lymphadenopathy, cloudy corneas, and peripheral neuropathy.

One of the most flagrant forms of stomatocytosis is seen in **phytosterolemia**, another metabolic disorder, in which the absorption of sterols, both cholesterol and its plant-derived relatives (e.g., sitosterol), is unlimited and unselective. The cells are not leaky to cations; there is macrothrombocytopenia and a degree of short stature. The plasma cholesterol may or may not be abnormal, but mass spectrography always shows a massive increase in plant sterol levels.

OTHER DISORDERS ASSOCIATED WITH STOMATOCYTOSIS
Acquired stomatocytosis may be seen with liver disease but also in alcoholism, malignancy, and cardiovascular disease. Stomatocytes can be seen on the blood smears of normal patients as a result of drying artifact.

TREATMENT
For severe hemolysis, patients might require RBC transfusion. Splenectomy is not recommended as a treatment for cation-leaky hereditary stomatocytosis. It is not effective and predisposes patients to in situ thrombosis after splenectomy. The thrombosis appears related to abnormal adherence of stomatocytic erythrocytes to the vascular endothelium.

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Chapter 461

Paroxysmal Nocturnal Hemoglobinuria and Acanthocytosis

George B. Segel

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Etiology

Paroxysmal nocturnal hemoglobinuria (PNH) reflects an abnormality of marrow stem cells that affects each blood cell lineage. The disease is

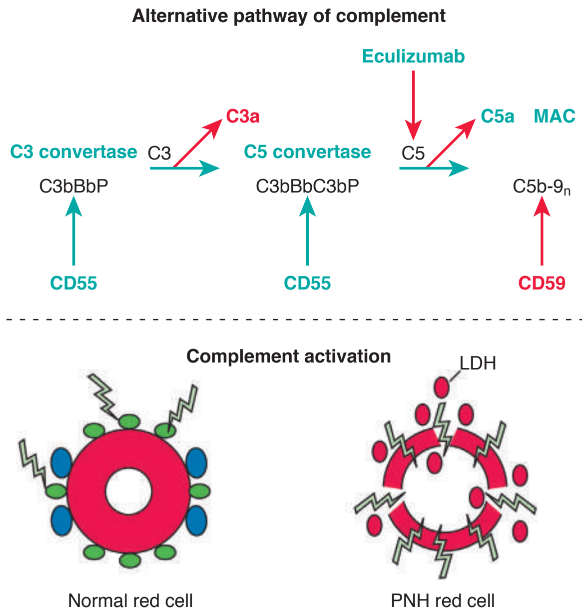

Figure 461-1 Complement-mediated lysis in PNH. Red circles are hemoglobin. Blue circles are decay accelerating factor (CD55). Green circles are membrane inhibitor of reactive lysis (CD59). Bb, activated factor B; C3b, activated C3; C5b, activated C5; GPI, glycosyl phosphatidylinositol; MAC, membrane attack complex (consisting of C5b, C6, C7, C8, and several molecules of C9 [9n]); RBC, red blood cell. *(From Parker C: Eculizumab for paroxysmal nocturnal haemoglobinuria,* Lancet *373:759–767, 2009.)*

an acquired somatic mutation that results in a defect in proteins of the cell membrane that renders the red blood cells (RBCs) and other cells susceptible to damage by normal plasma complement proteins (Fig. 461-1). The deficient membrane-associated proteins include decay-accelerating factor (CD55), the membrane inhibitor of reactive lysis (CD59), the C8 binding protein, and other proteins that normally impede complement lysis at various steps, specifically, the alternative pathway, which is constitutively activated. The underlying defect involves the glycolipid anchor that maintains these protective proteins on the cell surface. Various mutations in the *PIGA* gene that is involved in glycosylphosphatidylinositol anchor protein biosynthesis have been identified in patients with PNH. Glycosylphosphatidylinositol-deficient cells are found at low frequency in normal persons, suggesting that injury to the normal marrow stem cells provides a selective advantage to the progeny of PNH clones in the genesis of this disease.

Clinical Manifestations

PNH is a rare disorder in children. Approximately 60% of pediatric patients have marrow failure, and the remainder have either intermittent or chronic anemia, often with prominent intravascular hemolysis. Nocturnal and morning hemoglobinuria is a classic finding in adults when hemolysis is worse during sleep; chronic hemolysis is more common. In addition to chronic hemolysis, thrombocytopenia and leukopenia are often characteristic. Hemoglobinuria is rarely seen in children compared to adults with PNH. *Thrombosis and thromboembolic phenomena* are serious complications that may be related to altered glycoproteins on the platelet surface and resultant platelet activation and production of procoagulant microparticles. Abdominal venous thrombosis presents as recurrent episodes of abdominal pain, Budd-Chiari syndrome (hepatic veins), or splenomegaly (splenic vein). Furthermore, released free hemoglobin results in depletion of nitric oxide, fostering vasoconstriction, thrombosis, and pain. Back and head pain may also be prominent. Hypoplastic or aplastic pancytopenia can precede or follow the diagnosis of PNH; rarely, PNH may progress to acute myelogenous leukemia. At the time of presentation, more than 90% of patients with PNH have some blood abnormality (including ~35% with anemia alone, ~15% with anemia and thrombocytopenia, ~7% with anemia and neutropenia, and ~30% with pancytopenia), >10% have abdominal pain, and >5% have thrombosis. The mortality in PNH is related primarily to the development of aplastic anemia or thrombotic complications. The predicted survival rate for children before the development of eculizumab (see Treatment below) was 80% at 5 yr, 60% at 10 yr, and 28% at 20 yr.

Laboratory Findings

Hemosiderinuria, an elevated reticulocyte percentage, a low serum haptoglobin, and increased lactic dehydrogenase are common and reflect chronic intravascular hemolysis. Initially, the anemia is normocytic, but if iron deficiency develops, it becomes microcytic. Markedly reduced levels of RBC acetylcholinesterase activity and decay-accelerating factor also are found. Flow cytometry is the diagnostic test of choice for PNH. With the use of anti-CD59 for RBCs and anti-CD55 and anti-CD59 for granulocytes, flow cytometry is more sensitive than the classic RBC lysis (ham or sucrose) tests in detecting these reduced glycolipid-bound membrane proteins. Fluorescent-labeled aerolysin testing can heighten the sensitivity of detection by binding selectively to glycosylphosphatidylinositol anchors.

Treatment

Glucocorticoids such as prednisone (2 mg/kg/24 hr) have been used to treat acute hemolytic episodes; the dosage should be tapered as soon as the hemolysis abates. Prolonged anticoagulation (heparin or low-molecular-weight heparin) therapy may be of benefit when thromboses occur. Because of chronic urinary loss of iron as hemosiderin, iron therapy may be necessary. Androgens (e.g., fluoxymesterone [Halotestin]), antithymocyte globulin, cyclosporine, and growth factors (e.g., erythropoietin and granulocyte colony-stimulating factor) have been used to treat marrow failure. Bone marrow transplantation is successful in treating some cases; nonmyeloablative transplantation can reduce transplant-related mortality and morbidity.

Marrow failure and severe thrombosis are the most serious complications in children. Treatment has included hematopoietic stem cell transplantation if a suitable donor exists. Eculizumab has also resulted in sustained survival in the majority of patients. Eculizumab is an approved and effective treatment for PNH in adults. It is a monoclonal antibody against complement component C5, and it interrupts the excessive complement destruction of RBC and activation of platelets. It decreases the rate of hemolysis, stabilizes hemoglobin levels, reduces the number of transfusions, and reduces the risk of thrombosis. Survival in adults with PNH treated with eculizumab may not be different from sex- and age-matched control patients from the general population. However, the medication does not improve the hematopoietic clonal expansion or prevent marrow failure. Because of the cost and length of treatment required, particularly in children, it may be most useful in preventing thrombosis, anemia, and other symptoms while stem cell transplant is considered. Before beginning eculizumab, it is recommended to immunize patients with the meningococcal vaccine if the patient hasn't already received this vaccine. A poor response to eculizumab may be due to polymorphisms in the C5 gene that produce resistance to eculizumab blockades.

ACANTHOCYTOSIS

Acanthocytosis is characterized by RBCs with irregular circumferential pointed projections (see Fig. 458-4*E*). This morphologic finding is seen with alterations in the cholesterol : phospholipid ratio in some patients with liver disease or vitamin E deficiency, and in congenital abetalipoproteinemia or hypoprebetalipoproteinemia, associated with fat malabsorption, neuromuscular abnormalities, and retinitis pigmentosa (see Chapters 86.3 and 630). Normoproteinemic **neuroacanthocytosis** is also associated with 4 genetically diverse conditions (Table 461-1). These include chorea-acanthocytosis and the rare X-linked McLeod syndrome, which has absence of the KX (Kell) antigen, late-onset myopathy, peripheral neuropathy, chorea, splenomegaly, and hemolysis with acanthocytosis. There is usually >3% acanthocytes on peripheral smear and caudate atrophy noted on MRI. Acanthocytes

Table 461-1 Neuroacanthocytosis		
DISEASE	**INHERITANCE**	**MUTATION**
Chorea acanthocytosis	Autosomal recessive	VPS13A (*CHAC* gene)
McLeod syndrome	X-linked recessive	*XK* gene
Huntington disease–like 2	Autosomal dominant	JPH3
Pantothenate kinase-associated neurodegeneration	Autosomal recessive	PANK2

also are seen in pantothenate kinase-associated neurodegeneration (dystonia, rigidity, chorea, dysarthria, spasticity, retinopathy) and Huntington disease–like 2. The production of acanthocytes in chorea-acanthocytosis appears related to altered Lyn kinase activity with increased tyrosine phosphorylation and altered linkage of band 3 to other RBC membrane proteins.

In contrast, echinocytes or "burr cells" have a more regular distribution of projections or serrations along the surface of the RBCs. They often are seen as artifact, and less often in end-stage renal disease, and in some patients with liver disease.

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Chapter 462 Hemoglobinopathies

Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

HEMOGLOBIN DISORDERS

Hemoglobin is a tetramer consisting of 2 pairs of globin chains. Abnormalities in these proteins are referred to as *hemoglobinopathies.*

More than 800 variant hemoglobins have been described. The most common and useful clinical classification of hemoglobinopathies is based on nomenclature associated with alteration of the involved globin chain. Two hemoglobin gene clusters are involved in the production of hemoglobin and are located at the end of the short arms of chromosomes 16 and 11. Their control is complex, including an upstream locus control region on each respective chromosome and an X-linked control site. On chromosome 16, there are 3 genes within the alpha (α) gene cluster, namely zeta (ζ), alpha 1 (α_1), and alpha 2 (α_2). On chromosome 11, there are 5 genes within the beta (β) gene cluster, namely epsilon (ε), 2 gamma genes (γ), a delta gene (δ), and a beta gene (β).

The order of gene expression within each cluster roughly follows the order of expression during the embryonic period, fetal period, and eventually childhood. After 8 wk of fetal life, the embryonic hemoglobins, Gower-1 ($\zeta_2\varepsilon_2$), Gower-2 ($\alpha_2\varepsilon_2$), and Portland ($\zeta_2\gamma_2$), are formed. At 9 wk of fetal life, the major hemoglobin (Hb) is HbF ($\alpha_2\gamma_2$). HbA ($\alpha_2\beta_2$) first appears at approximately 1 mo of fetal life, but does not become the dominant hemoglobin until after birth, when HbF levels start to decline. HbA_2 ($\alpha_2\delta_2$) is a minor hemoglobin that appears shortly before birth and remains at a low level after birth. The final hemoglobin distribution pattern that occurs in childhood is not achieved until at least 6 mo of age and sometimes later. The normal hemoglobin pattern is ≥95% HbA, ≤3.5 HbA_2, and <2.5% HbF.

462.1 Sickle Cell Disease

Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

Great strides have been made in the management of both acute and chronic complications of sickle cell disease with a significant improvement in the life expectancy of a child born today in the United States. However, the majority of children with sickle cell disease are born outside of the United States with limited access to preventive care and disease-modifying treatments.

Children with sickle cell disease should be followed by experts in the management of this disease, most often by pediatric hematologists. Medical care provided by a pediatric hematologist is also associated with a decreased frequency of emergency department visits and length of hospitalization when compared to patients who were not seen by a hematologist within the last year.

PATHOPHYSIOLOGY

Hemoglobin S (HbS) is the result of a single base-pair change, thymine for adenine, at the sixth codon of the β-globin gene. This change encodes valine instead of glutamine in the 6th position in the β-globin molecule. Sickle cell anemia (HbSS), homozygous HbSS, occurs when both β-globin alleles have the sickle cell mutation (βs). Sickle cell disease refers to not only patients with sickle cell anemia, but also to compound heterozygotes where one β-globin allele includes the sickle cell mutation and the second β-globin allele includes a gene mutation other than the sickle cell mutation, such as HbC, β-thalassemia, HbD, and HbO^{Arab}. In sickle cell anemia, HbS is commonly as high as 90% of the total hemoglobin; whereas as in sickle cell disease, HbS is >50% of all hemoglobin.

In red blood cells, the hemoglobin molecule has a highly-specified conformation allowing for the transport of oxygen in the body. In the absence of globin-chain mutations, hemoglobin molecules do not interact with one another. However, the presence of HbS results in a conformational change in the hemoglobin tetramer and, in the deoxygenated state, HbS molecules can now interact with each other forming rigid polymers that give the red blood cell its characteristic "sickled" shape. The lung is the only organ capable of reversing the polymers, and any disease of the lung can be expected to compromise the degree of reversibility.

Intravascular sickling primarily occurs in the postcapillary venules and is a function of both mechanical obstruction by sickled red blood cells and increased adhesion between red blood cells, leukocytes and the vascular endothelium. Sickle cell disease is also an inflammatory disease based on nonspecific markers of inflammation, including, but not limited to, elevated baseline white blood cell count and cytokines.

DIAGNOSIS AND EPIDEMIOLOGY

Every state in the United States has instituted a mandatory newborn screening program for sickle cell disease. Such programs identify newborns with the disease and provide prompt diagnosis and referral to providers with expertise in sickle cell disease for anticipatory guidance and the initiation of penicillin before 4 mo of age.

The most commonly used procedures for newborn diagnosis include thin layer/isoelectric focusing and high-performance liquid chromatography (HPLC). A confirmatory step is recommended, with all patients who have initial abnormal screens being retested during the first clinical visit and after 6 mo of age to determine the final hemoglobin phenotype. In addition, a complete blood cell count (CBC) and hemoglobin phenotype determination is recommended for both parents to confirm the diagnosis and to provide an opportunity for genetic counseling. Table 462-1 correlates the initial hemoglobin phenotype at birth with the type of hemoglobinopathy, baseline hemoglobin range, and requirement for a hematologist.

In newborn screening programs, the hemoglobin with the greatest quantity is reported first, followed by other hemoglobins in order of decreasing quantity. In newborns with a hemoglobin analysis result

Table 462-1 Various Newborn Sickle Cell Disease Screening Results with Baseline Hemoglobin

NEWBORN SCREENING RESULTS: SICKLE CELL DISEASE*	POSSIBLE HEMOGLOBIN PHENOTYPE†	BASELINE HEMOGLOBIN RANGE	EXPERTISE IN HEMATOLOGY CARE REQUIRED
FS	SCD-SS SCD-S β^0 thal SCD-S β^+ thal SCD-S $\delta\beta^-$ thal S HPFH	6-11 g/dL 6-10 g/dL 9-12 g/dL 10-12 g/dL 12-14 g/dL	Yes Yes Yes Yes Yes
FSC	SCD-SC	10-15 g/dL	Yes
FSA	SCD-S β^+ thal	9-12 g/dL	Yes
FS other	SCD-S β^0 thal SCD-SD, SO^{Arab}, SC^{Harlem}, S^{Lepore}	6-10 g/dL Variable	Yes Yes
AFS	SCD-SS SCD-S β^+ thal SCD-S β^0 thal‡	6-10 g/dL 6-9 g/dL 7-13 g/dL variable	Yes Yes Yes

*Hemoglobins are reported in order of quantity.

†Requires confirmatory hemoglobin analysis after at least 6 mo of age and, if possible, hemoglobin analysis from both parents for accurate diagnosis of hemoglobin phenotype.

‡Impossible to determine the diagnosis because the infant received a blood transfusion before testing.

A, normal hemoglobin; C, hemoglobin C; F, fetal hemoglobin; HPFH, hereditary persistence of fetal hemoglobin; O^{Arab}, hemoglobin O^{Arab}; S, sickle hemoglobin; SC, sickle-hemoglobin C; SCD, sickle cell disease; SS, homozygous sickle cell disease; thal, thalassemia.

of FS, the pattern supports HbSS, HbS hereditary persistent fetal hemoglobin (HPFH), or HbSβ-thalassemia zero. In a newborn with a hemoglobin analysis of FSA, the pattern is supportive of diagnosis HbSβ-thalassemia+. The diagnosis of HbSβ-thalassemia+ is confirmed if at least 50% of the hemoglobin is HbS, HbA is present, and the amount of HbA_2 is elevated (typically >3.5%); although, HbA_2 is not elevated in the newborn period. In newborns with a hemoglobin analysis of FSC, the pattern supports a diagnosis of HbSC. In newborns with a hemoglobin analysis of FAS, the pattern supports a diagnosis of HbAS (sickle cell trait).

A newborn with a hemoglobin analysis of AFS has been transfused with red blood cells prior to collection of the newborn screen because the amount of HbA is greater than the amount of HbF or there has been an error. The patient may have either sickle cell disease or sickle cell trait and should be started on penicillin prophylaxis until the final diagnosis can be determined.

Given the implications of a diagnosis of sickle cell disease versus sickle cell trait in a newborn, repeating the hemoglobin analysis in the patient and obtaining a hemoglobin analysis and CBC to evaluate the smear and red blood cell parameters in the parents for genetic counseling cannot be overemphasized. Unintended mistakes do occur in state newborn screening programs. Newborns who have the initial phenotype of HbFS but whose final true phenotype included HbSβ-thalassemia+ have been described as one of the more common errors identified in newborn screening hemoglobinopathy programs. Determining an accurate phenotype is important for appropriate genetic counseling for the parents.

In the event that the parents are tested for sickle cell trait or hemoglobinopathy trait testing, full disclosure must be provided that in some circumstances, the issue of paternity may be disclosed. For this reason and because of healthcare privacy, we always seek permission for the genetic testing and to ensure confidentiality, we report the hemoglobinopathy trait results back separately to each parent during separate visits.

In the United States, sickle cell disease is the most common genetic disorder identified through the state-mandated newborn screening program, occurring in 1:2,647. In regard to race in the United States, sickle cell disease occurs in African-Americans at a rate of 1:396 births, and in Hispanics at a rate of 1:36,000 births. In the United States, an estimated 90,000 people are affected by sickle cell disease, with an ethnic distribution of 90% African-American and 10% Hispanic. The United States sickle cell disease population represents a fraction of the worldwide burden of the disease, with global estimates of 312,000 neonates born annually with HbSS disease.

CLINICAL MANIFESTATIONS AND TREATMENT OF SICKLE CELL ANEMIA (HB SS)

Fever and Bacteremia

Fever in a child with sickle cell anemia is a medical emergency, requiring prompt medical evaluation and delivery of antibiotics because of the increased risk of bacterial infection and subsequent high mortality rate. Infants with sickle cell anemia, as early as 6 mo of age, develop abnormal immune function due to splenic infarction. By 5 yr of age, most children with sickle cell anemia have complete functional asplenia. Regardless of age, all patients with sickle cell anemia are at increased risk of infection and death from bacterial infection, particularly encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae type b*, and *Neisseria meningitidis*.

The rate of bacteremia in children with sickle cell disease, presenting with fever in busy pediatric emergency department is less than 1%. Several clinical strategies have been developed to manage children with sickle cell anemia who present with fever. These vary from hospital admission for intravenous (IV) antimicrobial therapy to administering a 3rd-generation cephalosporin in an emergency department or outpatient setting to patients without established risk factors for occult bacteremia (Table 462-2). Given the observation that the average time for a positive blood culture is <20 hr in children with sickle cell anemia, admission for 24 hr is probably the most prudent strategy for children and families who live out of town or who are identified as high risk for poor follow-up.

Outpatient management of fever without a source should be considered in children with the lowest risk of bacteremia and after intravenous ceftriaxone or other cephalosporin is given. Observation after antibiotic administration is important as children who have sickle cell anemia treated with ceftriaxone can develop severe, rapid, and life-threatening immune hemolysis. In the event that *Salmonella* spp. or *Staphylococcus aureus* bacteremia occurs, strong consideration should be given to an evaluation for osteomyelitis with a bone scan given the increased risk of osteomyelitis in children with sickle cell anemia when compared to the general population.

Aplastic Crisis

Human parvovirus B19 poses a unique threat for patients with sickle cell anemia because such infections result in temporary **red cell aplasia**, limiting the production of reticulocytes and causing profound anemia. Any child with sickle cell disease, fever, and reticulocytopenia should be considered to have parvovirus B19 until proven otherwise. The acute anemia of an aplastic crisis is treated conservatively using

Table 462-2	Clinical Factors Associated with Increased Risk of Bacteremia Requiring Admission in Febrile Children with Sickle Cell Disease
Seriously ill appearance	
Hypotension: systolic blood pressure <70 mm Hg at 1 yr of age or <70 mm Hg + 2 × the age in yr for older children	
Poor perfusion: capillary-refill time >4 sec	
Temperature >40.0°C (104°F)	
A corrected white-cell count >30,000/mm^3 or <5000/mm^3	
Platelet count <100,000/mm^3	
History of pneumococcal sepsis	
Severe pain	
Dehydration: poor skin turgor, dry mucous membranes, history of poor fluid intake, or decreased output of urine	
Infiltration of a segment or a larger portion of the lung	
Hemoglobin level <5.0 g/dL	

From Wilimas JA, Flynn PM, Harris S et al: A randomized study of outpatient treatment with ceftriaxone for selected febrile children with sickle cell disease, N Engl J Med *329:472–476, 1993.*

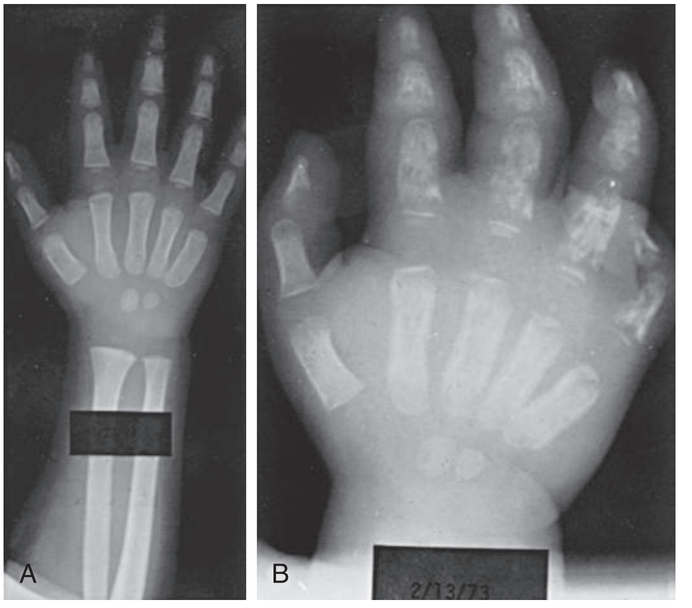

Figure 462-1 Roentgenograms of an infant with sickle cell anemia and acute dactylitis. **A,** The bones appear normal at the onset of the episode. **B,** Destructive changes and periosteal reaction are evident 2 wk later.

red blood cell transfusion when the patient becomes hemodynamically symptomatic or has a concurrent illness, such as acute chest syndrome. In addition, acute infection with parvovirus B19 is associated with pain, splenic sequestration, acute chest syndrome (ACS), glomerulonephritis, and stroke. Patients with parvovirus-associated aplastic crisis are contagious and infection precautions should be taken to avoid nosocomial spread of the infection.

Splenic Sequestration

Acute splenic sequestration is a life-threatening complication occurring primarily in infants and young children with sickle cell anemia. The incidence of splenic sequestration has declined from an estimated 30% to 12.6% with early identification by newborn screening and parental education. Sequestration can occur as early as 5 wk of age, but most often occurs in children between the ages of 6 mo and 2 yr.

Splenic sequestration is associated with rapid spleen enlargement causing left-sided abdominal pain and a decline in hemoglobin of at least 2 g/dL from the patient's baseline. Sequestration may lead to signs of hypovolemia as a result of the trapping of blood in the spleen; profound anemia, with total hemoglobin falling below 3 g/dL, has been reported. Reticulocytosis and a decrease in the platelet count may also be present. Sequestration may be triggered by fever, bacteremia, or viral infections.

Treatment includes early intervention and maintenance of hemodynamic stability using isotonic fluid or blood transfusions. Careful blood transfusions with red blood cells are recommended to treat both the sequestration and the resultant anemia. Blood transfusion aborts the red blood cell sickling in the spleen and allows release of the patient's blood cells that have become sequestered, often raising the hemoglobin above baseline values. We typically recommend only 5 mL/kg of red blood cells because the goal is to prevent hypovolemia. Blood transfusion that results in hemoglobin levels above 10 g/dL may put the patient at risk for hyperviscosity syndrome because of the risk that that patient may release the blood within the spleen.

Repeated episodes of splenic sequestration are common, occurring in two-thirds of patients. Most recurrent episodes develop within 6 mo of the previous episode. Prophylactic splenectomy performed after an acute episode has resolved is the only effective strategy for preventing future life-threatening episodes. Although blood transfusion therapy has been used with the goal of preventing subsequent episodes, evidence strongly suggests this strategy does not reduce the risk of recurrent splenic sequestration when compared to no transfusion therapy. Furthermore, prophylactic blood transfusion therapy may put the patient at risk for autotransfusion (the phenomenon when the blood sequestered in the spleen is released and dramatically increases the hemoglobin concentration, putting the patient at risk for hyperviscosity syndrome).

Hepatic and Gallbladder Involvement

See Chapters 360 and 366.

Sickle Cell Pain

Dactylitis, referred to as **hand-foot syndrome**, is often the first manifestation of pain in infants and young children with sickle cell anemia, occurring in 50% of children by their 2nd yr of life (Fig. 462-1). Dactylitis often manifests with symmetric or unilateral swelling of the hands and/or feet. Unilateral dactylitis can be confused with osteomyelitis, and careful evaluation to distinguish between the two is important because treatment differs significantly. Dactylitis requires palliation with pain medications, such as hydrocodone, whereas osteomyelitis requires at least 4-6 wk of IV antibiotics. Given the recent association between genotype and metabolism of codeine, a subgroup of children may not get pain relief from codeine. Hence, feedback from the parents is needed to determine if therapy was successful in relieving pain.

The cardinal clinical feature of sickle cell anemia is **acute vasoocclusive pain**. No written definition can describe the visual picture of a child with sickle cell anemia experiencing pain. Acute sickle cell pain is characterized as unremitting discomfort that can occur in any part of the body but most often occurs in the chest, abdomen, or extremities. These painful episodes are often abrupt and cause disruption of daily life activities and anguish for children and their caregivers. A patient with sickle cell anemia has approximately 1 painful episode per year that requires medical attention.

The exact etiology of pain is unknown, but the pathogenesis is initiated when blood flow is disrupted in the microvasculature by sickled cells, resulting in tissue ischemia. Acute sickle cell pain may be precipitated by physical stress, infection, dehydration, hypoxia, local or systemic acidosis, exposure to cold, and swimming for prolonged periods. Successful treatment of painful episodes requires education of both the caregivers and patients regarding the recognition of symptoms and the optimal management strategy. Given the absence of any

reliable objective laboratory or clinical parameter associated with pain, trust between the patient and the treating physician is paramount to successful clinical management. Specific therapy for pain varies greatly but generally includes the use of acetaminophen or a nonsteroidal antiinflammatory agent early in the course of pain, followed by escalation to a combination analgesic such as hydrocodone, or to a single-agent short- or long-acting oral opioid.

Some patients require hospitalization for administration of intravenous morphine or derivatives of morphine. The incremental increase and decrease in the use of the medication to relieve pain roughly parallels the 8 phases associated with a chronology of pain and comfort (Table 462-3). The average hospital length of stay for children admitted in pain is 4.4 days. The American Pain Society has published clinical guidelines for treating acute and chronic pain in patients with sickle cell disease of any type. These recommendations are comprehensive and represent a starting point for treating pain (http://www.ampainsoc.org/pub/sc.htm).

The only measure for degree of pain is the patient. Healthcare providers working with children in pain should use a consistent, validated pain scale, such as the Wong-Baker FACES Scale for assessing pain. Although pain scales have proved useful for some children, others require prenegotiated activities to determine when opioid therapy should be initiated and decreased. For instance, sleeping through the night might be an indication for decreasing pain medication by 20% the following morning. The majority of painful episodes in patients with sickle cell anemia are managed at home with comfort measures, such as heating blanket, relaxation techniques, massage, and oral pain medication.

Several myths have been propagated regarding the treatment of pain in sickle cell anemia. The concept that painful episodes in children should be managed without opioids is without foundation and results in unwarranted suffering on the part of the patient. Blood transfusion therapy during an existing painful episode does not decrease the intensity or duration of the painful episode as tissue necrosis occurs well before the ability to administer the transfusion. Intravenous hydration does not relieve or prevent pain and is appropriate when the patient is dehydrated or unable to drink as a result of the severe pain. *Opioid dependency in children with sickle cell anemia is rare and should never be used as a reason to withhold pain medication.* However, patients with multiple painful episodes requiring hospitalization within a year or with pain episodes that require hospitalization for more than 7 days should be evaluated for comorbidities and environmental stressors that are contributing to the frequency or duration of pain. Children with chronic pain should be evaluated for other reasons associated with vasoocclusive pain episodes, including, but not limited to, overexertion with physical activities, such as participating in the school band, sports, or heavy lifting of backpacks to and from school and up and down steps. A careful history is warranted to distinguish chronic pain that often is not relieved by opioids alone versus acute unremitting vasoocclusive pain episodes.

Skeletal pain (bone or bone marrow infarction) with or without fever must be differentiated from osteomyelitis. Both *Salmonella* spp. and *S. aureus* cause osteomyelitis in children with sickle cell anemia, which is often in the diaphysis of long bones (in contrast to children without sickle cell anemia where osteomyelitis is in the metaphyseal region of the bone). Differentiating osteonecrosis from a vasoocclusive

Table 462-3 Summary of the Chronology of Pain in Children with Sickle Cell Disease

PHASE	PAIN CHARACTERISTICS	SUGGESTED COMFORT MEASURES USED
1 (Baseline)	No vasoocclusive pain; pain of complications may be present, such as that connected with avascular necrosis of the hip	No comfort measures used
2 (Prepain)	No vasoocclusive pain; pain of complications may be present; prodromal signs of impending vasoocclusive episode may appear, e.g., "yellow eyes" and/or fatigue	No comfort measures used; caregivers may encourage child to increase fluids to prevent pain event from occurring
3 (Pain start point)	First signs of vasoocclusive pain appear, usually in mild form	Mild oral analgesic often given; fluids increased; child usually maintains normal activities
4 (Pain acceleration)	Intensive of pain increases from mild to moderate Some children skip this level or move quickly from phase 3 to phase 5	Stronger oral analgesic are given; rubbing, heat, or other activities are often used; child usually stays in school until the pain becomes more severe, then stays home and limits activities; is usually in bed; family searches for ways to control the pain
5 (Peak pain experience)	Pain accelerates to high moderate or severe levels and plateaus; pain can remain elevated for extended period Child's appearance, behavior, and mood are significantly different from normal	Oral analgesics are given around the clock at home; combination of comfort measures is used; family might avoid going to the hospital; if pain is very distressing to the child, parent takes the child to the emergency department After child enters the hospital, families often turn over comforting activities to healthcare providers and wait to see if the analgesics work Family caregivers are often exhausted from caring for the child for several days with little or no rest
6 (Pain decrease start point)	Pain finally begins to decrease in intensity from the peak pain level	Family caregivers again become active in comforting the child but not as intensely as during phases 4 and 5
7 (Steady pain decline)	Pain decreases more rapidly, become more tolerable for the child Child and family are more relaxed	Healthcare providers begin to wean the child from the IV analgesic; oral opioids given; discharge planning is started Children may be discharged before they are pain free
8 (Pain resolution)	Pain intensity is at a tolerable level, and discharge is imminent Child looks and acts like "normal" self; mood improves	May receive oral analgesics

Adapted from Beyer JE, Simmons LE, Woods GM, et al: A chronology of pain and comfort in children with sickle cell disease, Arch Pediatr Adolesc Med *153:913–920, 1999.*

crisis and osteomyelitis is often difficult; patients with osteomyelitis often have a longer duration of fever and pain, swelling of the affected area, fewer or only 1 location of pain *and* tenderness, higher white blood cell counts, and an elevated C-reactive protein. Blood cultures, when positive, are helpful.

Imaging studies, which must include MRI with contrast, are helpful in distinguishing osteomyelitis from bone or marrow infarction, although rarely an osteomyelitis may initially appear "cold" (infarctive osteomyelitis), whereas an infarct, over time, may appear hyperemic as it heals. Both lesions may demonstrate marrow signal intensity abnormalities, periosteal elevation, and bone, periosteal, or extraosseous fluid collections. MRI findings suggestive of osteomyelitis include localized medullary fluid, sequestrum, and cortical defects. Ultimately, aspiration with or with or without biopsy and culture will be needed to differentiate the 2 processes (see Chapter 684).

Avascular Necrosis

Avascular necrosis (AVN) occurs at a higher rate among children with sickle cell anemia than in the general population, and is a source of both acute and chronic pain. Most commonly, the femoral head is affected and AVN. Unfortunately, the AVN of the hip may cause limp and leg-length discrepancy. Other sites affected include the humeral head and mandible. Risk factors for AVN include HbSS disease with α-thalassemia trait, frequent vasoocclusive episodes, and elevated hematocrit (for patients with sickle cell anemia). Optimal treatment of AVN has not been determined and individual management requires consultation with the disease-specific specialist, orthopedic surgeon, physical therapist, hematologist and primary care physician. Initial management may include referral to a physical therapist to address strategies to increase strength and decrease weight bearing daily activities that may exacerbate the pain associated with AVN. Opioids are often used, but usually can be tapered after the acute pain has subsided with AVN. Regular blood transfusion therapy has not been demonstrated as an effective therapy to abate the acute and chronic pain associated AVN.

Priapism

Priapism is defined as an unwanted painful erection of the penis and most commonly affects males with sickle cell anemia. The mean age of first episode is 15 yr, although priapism has been reported in children as young as 3 yr. The actuarial probability of a patient experiencing priapism is approximately 90% by 20 yr of age.

Priapism occurs in 2 patterns: prolonged, lasting more than 4 hr, or stuttering, with brief episodes that resolve spontaneously but may occur in clusters and herald a prolonged event. Both types occur from early childhood to adulthood. Most episodes occur between 3 A.M. and 9 A.M. Priapism in sickle cell disease represents a low flow state caused by venous stasis from sickling of red blood cells in the corpora cavernosa. Recurrent prolonged episodes of priapism are associated with impotence.

The optimal treatment for acute priapism is unknown. Acutely, supportive therapy, such as a hot shower, short aerobic exercise, or pain medication, is commonly used by patients at home. A prolonged episode lasting >4 hr should be treated by aspiration of blood from the corpora cavernosa followed by irrigation with dilute epinephrine to produce immediate and sustained detumescence. Urology consultation is required to initiate this procedure, with appropriate input from a hematologist. Simple blood transfusion and exchange transfusion has been proposed for the acute treatment of priapism, but limited evidence supports this strategy as the initial management. We typically refer a patient to the urology service first, and if no benefit is obtained from surgical management, consider transfusion therapy. However, detumescence may not occur for up to 24 hr (far longer than with urologic aspiration) after transfusion and transfusion for priapism has been associated with acute neurologic events.

Neurologic Complications

Neurologic complications associated with sickle cell anemia are varied and complex, ranging from *acute* ischemic stroke with focal neurologic deficit to clinically *silent* abnormalities found on radiologic imaging. Prior to the development of transcranial Doppler to screen for stroke risk among children with sickle cell anemia, approximately 11% experienced an overt stroke and 20% a silent stroke before their 18th birthday. A functional definition of overt stroke is the presence of a focal neurologic deficit lasting for >24 hr and/or abnormal neuroimaging of the brain indicating a cerebral infarct on T2-weighted magnetic resonance imaging (MRI) corresponding to the focal neurologic deficit (Figs. 462-2 and 462-3). A silent cerebral infarct, as its name indicates, lacks focal neurologic findings lasting >24 hr and is diagnosed by abnormal imaging on T2-weighted MRI. Children with other

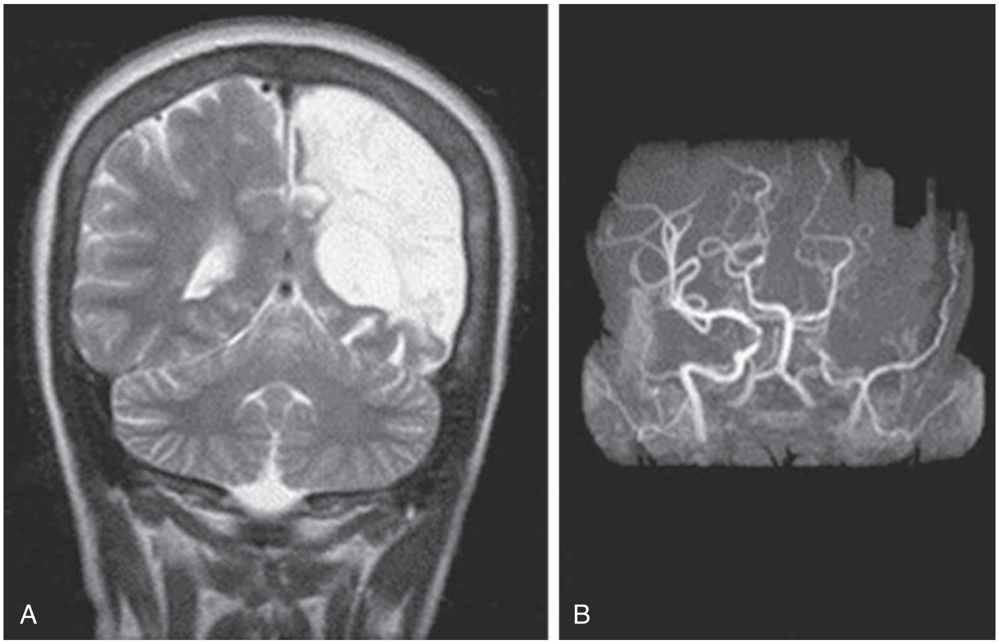

Figure 462-2 T2-weighted MRI and magnetic resonance angiography of the brain. **A,** T2-weighted MRI shows remote infarction of the territories of the left anterior cerebral artery and middle cerebral artery. **B,** Magnetic resonance angiography shows occlusion of the left internal carotid artery siphon distal to the takeoff of the ophthalmic artery.

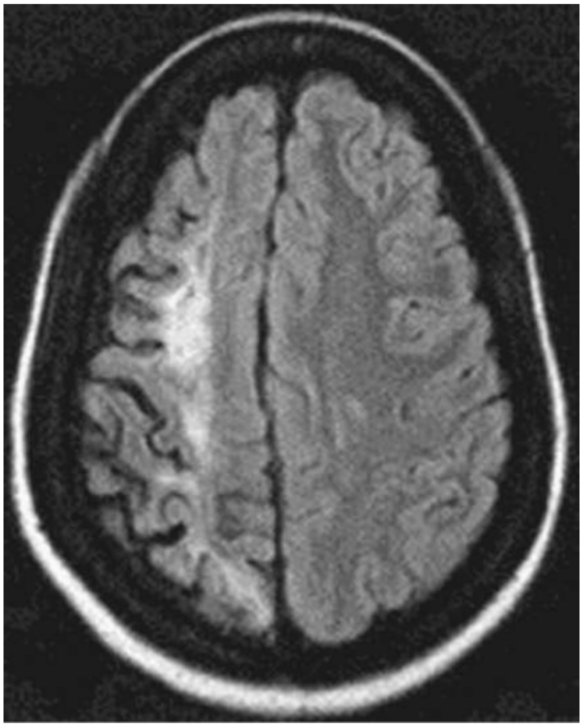

Figure 462-3 Fast fluid-attenuated inversion recovery sequence MRI of the brain showing a right hemisphere border-zone cerebral infarction in a child with sickle cell anemia. *(From Switzer JA, Hess DC, Nichols F, et al: Pathophysiology and treatment of stroke in sickle-cell disease: present and future.* Lancet Neurol *5:501–512, 2006.)*

types of sickle cell disease, such as HbSC or HbSβ-thalassemia+, develop overt or silent cerebral infarcts as well, but at a lower frequency than children with HbSS and HbSβ-thalassemia zero. Other neurologic complications include headaches that may or may not correlate to degree of anemia, seizures, cerebral venous thrombosis and reversible posterior leukoencephalopathy syndrome, also referred to as posterior reversible encephalopathy syndrome (PRES).

For patients presenting with acute focal neurologic deficit, a prompt pediatric neurologic evaluation is recommended, as well as consultation with a pediatric hematologist. In addition, oxygen administration to keep oxygen saturations >96% and simple blood transfusion within 1 hr of presentation with a goal of increasing the hemoglobin to a maximum of 10 g/dL is warranted. A timely simple blood transfusion is important because this is the most efficient strategy to dramatically increase oxygen content of the blood, if the oxygen saturation is above 96%. To exceed this hemoglobin threshold limits oxygen delivery to the brain as a result of hyperviscosity by increasing the hemoglobin significantly over the patient's baseline values. Subsequently, prompt treatment with an exchange transfusion should be considered, either manually or with automated erythrocytapheresis, to reduce the HbS percentage to at least <50%, and ideally to <30%. Exchange transfusion at the time of acute stroke is associated with a decreased risk of second stroke when compared to simple transfusion alone. Computed tomography (CT) of the head to exclude cerebral hemorrhage should be performed as soon as possible, and if available, MRI of the brain with diffusion-weighted imaging to distinguish between ischemic infarcts and PRES. Magnetic resonance (MR) venography is useful to evaluate the possibility of cerebral venous thrombosis, a rare but potential cause of focal neurologic deficit in children with sickle cell disease. MR angiography may identify evidence of cerebral vasculopathy; these images are not critical in the initial time management of a child with sickle cell disease presenting with a focal neurologic deficit.

The clinical presentation of PRES or central venous thrombosis can mimic a stroke but would require a different treatment course. For both PRES and cerebral venous thrombosis, the optimal management has not been defined in patients with sickle cell disease, resulting in the need for consultation with both a pediatric neurologist and a pediatric hematologist.

Transcranial Doppler Ultrasonography

Primary prevention of overt stroke can be accomplished using **transcranial Doppler ultrasonography** (TCD) assessment of the blood velocity in the terminal portion of the internal carotid and the proximal portion of the middle cerebral artery. Children with sickle cell anemia with an elevated time-averaged mean maximum (TAMM) blood-flow velocity >200 cm/sec are at increased risk for a cerebrovascular event. A TAMM measurement of <200 cm/sec but ≥180 cm/sec represents a conditional threshold. A repeat measurement is suggested within a few months because of the high rate of conversion to a TCD velocity >200 cm/sec in this group of patients.

Two distinct methods of measuring TCD velocity exist: a nonimaging and an imaging technique. The nonimaging technique was the method used in the TCD trial sponsored by the National Institutes of Health, whereas most pediatric radiologists in practice use the imaging technique. When compared to each other, the imaging technique produces values that are 10-15% below that of the nonimaging technique. The imaging technique uses the time-averaged mean of the maximum velocity (TAMX), and this measure is believed to be equivalent to the nonimaging calculation of TAMM. A downward adjustment for the transfusion threshold is appropriate for centers using the imaging method to assess TCD velocity. The magnitude of the transfusion threshold in the imaging technique has not been settled, but a transfusion threshold of a TAMX of 185 cm/sec and a conditional threshold of TAMX of 165 cm/sec, seems reasonable.

The primary approach for prevention of recurrent overt stroke is blood transfusion therapy aimed at keeping the maximum HbS concentration <30%. Despite regular blood transfusion therapy, around 20% of patients will have a second stroke and 30% of this group will have a third stroke. Children with TCD values above defined thresholds should begin chronic blood transfusion therapy to maintain HbS levels <30% to decrease the risk of first stroke. This strategy results in an 85% reduction in the rate of overt strokes. Once transfusion therapy is initiated, patients are expected to continue it indefinitely as discontinuation of blood transfusion therapy is associated with an increase in the development of silent infarcts.

Pulmonary Complications

Lung disease in children with sickle cell anemia is the second most common reason for hospital admission and is associated with significant mortality. ACS refers to a life-threatening pulmonary complication of sickle cell disease defined as a new radiodensity on chest radiography plus any 2 of the following: fever, respiratory distress, hypoxia, cough, or chest pain (Fig. 462-4). Even in the absence of respiratory symptoms, all patients with fever should receive a chest radiograph to identify evolving ACS because clinical examination alone is insufficient to identify patients with a new radiographic density and early detection of ACS will alter clinical management. The radiographic findings in ACS are variable but may include single lobe involvement, predominantly left lower lobe; multiple lobes, most often both lower lobes; and pleural effusions, either unilateral or bilateral. ACS may progress rapidly from a simple infiltrate to extensive infiltrates and a pleural effusion. Therefore, continued pulse oximetry and frequent clinical exams are required, and repeat chest x-rays are indicated for progressive hypoxia, dyspnea, tachypnea, and other signs of respiratory distress.

The majority of patients with ACS do not have a single identifiable cause. Infection is the most well-known etiology, yet only 30% of ACS episodes will have positive sputum or bronchoalveolar culture, and the most common pathogens are *S. pneumoniae*, *Mycoplasma pneumoniae,* and *Chlamydia* sp. The most frequent event preceding ACS is a painful episode requiring systemic opioid treatment. Fat emboli has also been implicated as a cause of ACS, arising from infarcted bone marrow, and can be life-threatening if large amounts are released to the lungs. Fat

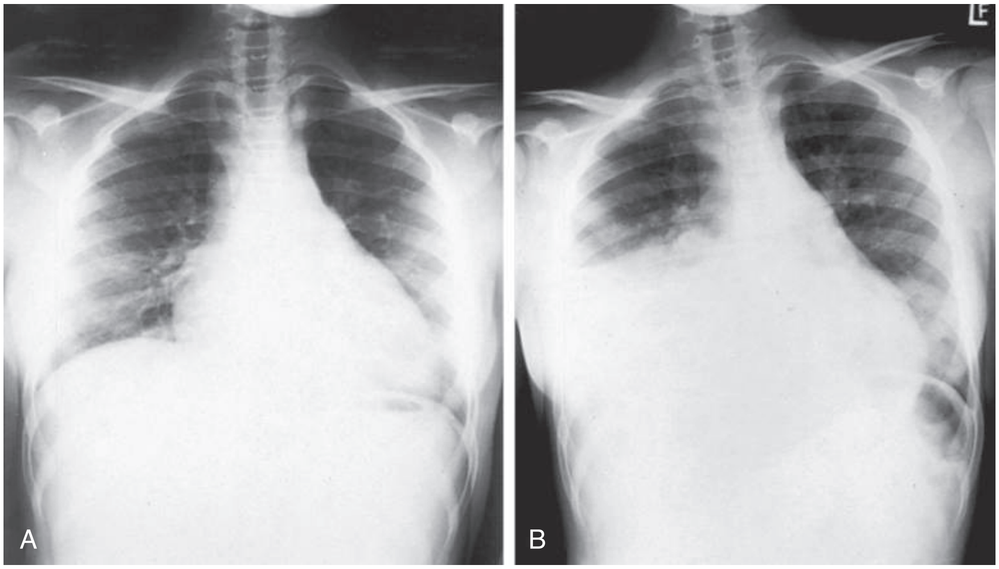

Figure 462-4 **Probable pulmonary infarction in a 15 yr old patient with Hb-SS. A,** Frontal radiograph shows consolidation and a small pleural effusion posteriorly in the right lower lobe. **B,** Radiograph obtained <24 hr later shows massive right middle and lower lobe consolidation and effusion. No organisms could be cultured. The diagnosis of "probably pulmonary infarction" was established clinically. *(Courtesy of Dr. Thomas L. Stovis, Children's Hospital of Michigan, Detroit, MI. From Kuhn JP, Slovis TL, Haller JO:* Caffey's pediatric diagnostic imaging, *vol 1, ed 10, Philadelphia, 2004, Mosby, p. 1087.)*

emboli can be difficult to diagnose but should be considered in any patient with sickle cell disease, presenting with rapid onset of respiratory distress and altered mental status changes. Petechial rash, may also occur, but may be difficult to detect if not looked for carefully.

Given that the causes of ACS are varied, recommended management is also multimodal (Table 462-4). The type of opioid, with morphine being more likely to cause ACS than nalbuphine hydrochloride, is associated with an increase in the risk of ACS in part because of hypoventilation. However, under no circumstance should opioid administration be limited to prevent ACS; rather, care must be taken to prevent ACS from developing. In patients with chest pain, regular use of an incentive spirometer at 10-12 breaths every 2 hr can significantly reduce the frequency of subsequent acute chest pain episodes. As a result of the clinical overlap between pneumonia and ACS, all episodes should be treated promptly with antimicrobial therapy, including at least a macrolide and possibly a third-generation cephalosporin. A previous diagnosis of asthma or airway hyperresponsiveness should prompt treatment following standard of care for an asthma exacerbation with corticosteroids and bronchodilators. The diagnosis of ACS does not negate the recommended management of a patient with asthma exacerbation. Oxygen should be administered for patients who demonstrate hypoxia. Blood transfusion therapy using either simple or exchange (manual or automated) transfusion is the only method to abort a rapidly progressing episode of ACS. The decision when to give blood and whether the transfusion should be a simple or exchange transfusion is less clearly defined. Commonly blood transfusions are given when at least 1 of the following clinical features are present: decreasing oxygen saturation, increasing work of breathing, rapid change in respiratory effort either with or without a worsening chest radiograph, a drop in hemoglobin of 2 g/dL below their baseline, or previous history of severe ACS requiring admission to the intensive care unit.

Pulmonary hypertension has been identified as a major risk factor for death in adults with sickle cell anemia. The natural history of pulmonary hypertension in children with sickle cell anemia is unknown. Optimal strategies for screening at risk patients have not been identified (echocardiogram results are not supported by right heart catheterization results demonstrating elevated pulmonary artery pressures) and the best diagnostic methodology carries significant risk of harm. Attempts to identify targeted therapeutic interventions to alter the natural history of pulmonary hypertension in adults have been unsuccessful.

Table 462-4	Overall Strategies for the Management of Acute Chest Syndrome
PREVENTION	
Incentive spirometry and periodic ambulation in patients admitted for sickle cell pain, surgery, or febrile episodes	
Watchful waiting in any hospitalized child or adult with sickle cell disease (pulse oximetry monitoring and frequent respiratory assessments)	
Cautious use of intravenous fluids	
Intense education and optimum care of patients who have sickle cell anemia and asthma	
DIAGNOSTIC TESTING AND LABORATORY MONITORING	
Blood cultures	
Nasopharyngeal samples for viral culture (respiratory syncytial virus, influenza)	
Blood counts every day and appropriate chemistries	
Continuous pulse oximetry	
Chest radiographs	
TREATMENT	
Blood transfusion (simple or exchange)	
Supplemental O_2 for drop in pulse oximetry by 4% over baseline, or values <90%	
Empirical antibiotics (third-generation cephalosporin and macrolide)	
Continued respiratory therapy (incentive spirometry and chest physiotherapy as necessary)	
Bronchodilators and steroids for patients with asthma	
Optimum pain control and fluid management	

Renal Disease and Enuresis

Renal disease among patients with sickle cell disease is a major comorbid condition that can lead to premature death. Seven sickle cell disease nephropathies have been identified: (1) gross hematuria, (2) papillary necrosis, (3) nephrotic syndrome, (4) renal infarction, (5) hyposthenuria, (6) pyelonephritis, and (7) renal medullary carcinoma. As expected, the presentation of these entities is varied but may include

hematuria, proteinuria, renal insufficiency, concentrating defects, or hypertension.

The common presence of nocturnal enuresis occurring in children with sickle cell anemia is not well defined but is troublesome to affected children and their parents. The overall prevalence of enuresis was 33% in the Cooperative Study of Sickle Cell Disease with the highest prevalence (42%) among children ages 6-8 yr. Furthermore, enuresis may still occur in approximately 9% of the older adolescent group. As would be the case in all children with nocturnal enuresis, we would systematically evaluate the children for recurrent urinary tract infections, kidney function, and possibly obstructive sleep apnea syndrome with a supportive history. Unfortunately, most children with nocturnal enuresis do not have an etiology and targeted therapeutic interventions have been of limited success.

Cognitive and Psychological Complications

As with any child with a chronic illness, good health maintenance must include routine psychological and social assessment. Ongoing evaluation of the family unit and identification of the resources available to cope with a chronic illness are critical for optimal management. Children and adolescents with sickle cell disease also have decreased quality of life, as measured on standardized assessments, compared to their siblings and children with other chronic diseases. Furthermore, children with sickle cell disease are at great risk for academic failure and have a 20% high school graduation rate. One reason behind the low high school graduation rate is that approximately a third of children with sickle cell anemia have had a cerebral infarct—either silent cerebral infarcts or overt strokes. Children with cerebral infarcts require ongoing cognitive and school performance assessment so that education resources can be focused to optimize educational attainment. Relevant support groups and attendance in group activities, such as camps for children with sickle cell disease, may be of direct benefit by improving self-esteem and establishing peer relationships.

Other Complications

In addition to the previously mentioned organ dysfunctions, patients with sickle cell anemia can have other significant complications. These complications include, but are not limited to sickle cell retinopathy, delayed onset of puberty, and leg ulcers. Optimal treatment for each of these entities has not been determined and individual management requires consultation with the disease-specific specialist, a hematologist, and primary care physician.

THERAPEUTIC CONSIDERATIONS

Hydroxyurea

Hydroxyurea, a myelosuppressive agent, is the only drug proven effective in reducing the frequency of painful episodes. In a large clinical trial of adults with sickle cell anemia, hydroxyurea was found to decrease the rate of hospitalization for painful episodes by 50% and the rate of ACS and blood transfusion by almost 50%. Follow-up of the original trial found that adults taking hydroxyurea had shorter hospital stays and required less pain medication during hospitalization. In children with sickle cell anemia, a safety feasibility trial of hydroxyurea demonstrated that hydroxyurea was safe and well tolerated in children >5 yr of age. No clinical adverse events were identified in this study; the primary toxicities were limited to myelosuppression that reversed upon cessation of the drug. Infants treated with hydroxyurea also experienced fewer episodes of pain, dactylitis, and ACS, and were less-often hospitalized or received a blood transfusion. Despite being a myelosuppressive agent, the infants treated with hydroxyurea did not experience increased rates of bacteremia or serious infection.

Hydroxyurea may be indicated for other sickle cell–related complications, especially in patients who are unable to tolerate other treatments. For patients who either will not or cannot continue blood transfusion therapy to prevent recurrent stroke, hydroxyurea therapy may be a reasonable alternative. The trial assessing the efficacy of hydroxyurea as an alternative to transfusions to prevent second stroke was terminated early after the data safety and monitoring found an increased stroke rate in the hydroxyurea arm compared to the transfusion arm (0 vs. 7 [10%]). Hydroxyurea alone is inferior to transfusion therapy for secondary stroke prevention in patients who do not have contraindications to ongoing transfusions. Although not investigated as a primary outcome, hydroxyurea appears to have promise for the prevention of recurrent priapism. One study found hydroxyurea decreased glomerular hyperfiltration in young children with sickle cell anemia.

The long-term toxicity associated with initiating hydroxyurea in very young children has not yet been established. However, all evidence to date suggests that the benefits far outweigh the risks. For these reasons, children >2 yr of age receiving hydroxyurea require well-informed parents and medical care by pediatric hematologists, or at least comanagement by a physician with expertise in immunosuppressive medications. The typical starting dose of hydroxyurea is 15-20 mg/kg given once daily, with an incremental dosage increase every 8 wk of 5 mg/kg, and if no toxicities occur, up to a maximum of 35 mg/kg per dose. The infant hydroxyurea study found young children could safely be started at 20 mg/kg/day without increased toxicity. Achievement of the therapeutic effect of hydroxyurea can require several months, and for this reason, inpatient initiating of hydroxyurea is not optimal. We prefer to introduce the concept to parents within the first year of life, provide literature that describes both the pros and cons of starting hydroxyurea in children with severe symptoms of sickle cell disease, and educate parents on starting hydroxyurea in asymptomatic children as a preventative therapy for repetitive pain and ACS events. Other effects of hydroxyurea that may vary include an increase in the total hemoglobin level and a decrease in the TCD velocity.

Hematopoietic Stem Cell Transplantation

The only cure for sickle cell anemia is transplantation with human leukocyte antigen (HLA)–matched **hematopoietic stem cells** from a sibling or unrelated donor. The most common indications for transplant are recurrent ACS, stroke and abnormal TCD. Sibling-matched stem cell transplantation has a lower risk for graft-versus-host disease than unrelated donors. However, few children have suitable sibling donors. Stem cell transplantation using an unrelated but well-matched donor is the subject of an open clinical trial. The decision to consider unrelated transplantation should involve appropriate consultation and counseling from physicians with expertise in sickle cell transplantation.

Stem cell transplantation for children with sickle cell disease with a genetically matched sibling is not routinely done, in part because of the known risk of transplantation-related mortality and morbidity in a short period of time, commonly less than 2 yr after the transplantation versus the high probability that patients will live to and through adulthood. The use of hydroxyurea has dramatically decreased the disease burden for the patient and family, with associated far fewer hospitalizations for pain or ACS episodes and less use of blood transfusions. Furthermore, the field of stem cell transplantation is progressing so rapidly that in a decade or less haplo-identical transplantation will be considered a viable option for not only individuals with severe disease, but also those with less-severe manifestations. Haplo-identical transplantations in adults with severe manifestations of sickle cell disease resulted in no deaths, and approximately 60% of the participants were cured of the disease. Low intensity, nonmyeloablative HLA-matched sibling allogenic stem cell transplantation has been employed in patients ≥16 years of age.

Red Blood Cell Transfusions

Red blood cell transfusions are frequently used in the management of children with sickle cell anemia, both in the treatment of acute complications such as ACS, aplastic crisis, splenic sequestration, and acute stroke, and to prevent surgery-related ACS and first stroke in patients with abnormal TCD or MRI findings (silent stroke). Patients with sickle cell disease are at increased risk of developing alloantibodies to less-common red cell surface antigens after receiving even a single transfusion. In addition to standard cross-matching for major blood group antigens (A, B, O, RhD), more extended matching should be performed to identify donor units that are C-, E-, and Kell-antigen

negative. Some centers have begun to perform full red blood cell phenotyping for patients receiving chronic blood transfusions.

Three methods of blood transfusion therapy are used in the management of acute and chronic complications associated with sickle cell anemia: automated erythrocytapheresis, manual exchange transfusion (phlebotomy of a set amount of patient's blood followed by rapid administration of donated packed red blood cells), and simple transfusion. Automated erythrocytapheresis is the preferred method for patients requiring chronic blood transfusion therapy because there is a minimum net iron balance after the procedure, followed by manual exchange transfusion. Simple transfusion therapy is the least-preferable method for regular blood transfusion therapy because this strategy results in the highest net-positive iron balance after the procedure. Despite being the preferred method, erythrocytapheresis is less-frequently performed because of the requirement of technical expertise, large venous access, multiple units of matched red blood cells, and an available cytapheresis machine.

Preparation for surgery for children with sickle cell disease requires a coordinated effort between the hematologist, surgeon, and primary care provider. ACS and pain are the 2 most common postoperative complications, with ACS being a significant risk factor for postoperative death. Blood transfusion prior to surgery for children with sickle cell anemia is recommended to raise the hemoglobin level preoperatively to no more than 10 g/dL, although benefit also may be seen at lower hemoglobin values. The rate of serious complications, including a higher rate of ACS in patients who do not receive blood transfusion when compared to those who do. When available, blood transfusion therapy prior to surgery should be the standard approach. When preparing a child with sickle cell anemia for surgery with a simple blood transfusion, caution must be used not to elevate the hemoglobin beyond 10 g/dL because of the risk of hyperviscosity syndrome. For children with sickle cell anemia, exchange transfusion prior to surgery is of no greater benefit than simple blood transfusion and carries significantly higher risk of red blood cell alloimmunization. For children with milder forms of sickle cell disease, such as HbSC or HbSβ-thalassemia, a decision must be made on a case-by-case basis as to whether an exchange transfusion is warranted, because a simple transfusion may raise the hemoglobin to an unacceptable level.

Excessive Iron Stores

The primary toxic effect of blood transfusion therapy relates to **excessive iron stores**, which can result in organ damage and premature death. Excessive iron stores develop after 100 mL/kg of red cell transfusion or about 10 transfusions. The assessment of iron overload in children receiving regular blood transfusions is difficult. The most commonly used and least-invasive method of estimating total-body iron involves serum ferritin levels. Ferritin measurements have significant limitations in their ability to estimate iron stores for several reasons, including, but not limited to, elevation during acute inflammation and poor correlation with excessive iron in specific organs after 2 yr of regular blood transfusion therapy. Advances in technology have improved the assessment of iron stores among children with sickle cell disease receiving regular blood transfusion therapy. MRI of the liver has proven to the most effective and common approach for assessment of iron stores. The imaging strategy is more accurate than serum ferritin in measuring heart and liver iron content. MRI T2* and MRI R2 and R2* sequences are now being used to estimate iron levels in the heart and liver. The standard for iron assessment previously was biopsy of the liver, which is an invasive procedure exposing children to the risk of general anesthesia, bleeding, and pain. Liver biopsy alone does not accurately estimate total-body iron, as iron deposition in the liver is not homogenous and varies among the affected organs; that is, the amount of iron found in the liver is not equivalent to cardiac tissues. The major advantage of a liver biopsy is that histologic assessment of the parenchyma can be ascertained along with appropriate staging of suspected pathology, particularly cirrhosis.

The primary treatment of excessive iron stores resulting from red blood cell transfusion requires iron chelation using medical therapy. In the United States, 3 chelating agents are commercially available and approved for use in transfusional iron overload. Deferoxamine is administered subcutaneously 5 of 7 nights/wk for 10 hr a night. Deferasirox is an effervescent tablet that is dissolved in liquid and taken by mouth daily, and deferiprone is available in tablets taken orally twice a day. The FDA approved deferasirox, the newest orally administered chelator, in 2005 for use in patients age ≥2 yr. Deferiprone is an older oral chelator that has been widely used outside of the United States for many years and was approved by the FDA in 2011, but requires weekly monitoring of complete blood counts because of a risk of neutropenia throughout therapy. Transfusion-related excessive iron stores in children with sickle cell disease should be managed by a physician with expertise in chelation therapy owing to the risk of significant toxicity from available chelation therapies.

OTHER SICKLE CELL SYNDROMES

The most commonly occurring sickle cell syndromes besides HbSS are HbSC, HbSβ-thalassemia zero, and HbSβ-thalassemia+. The other syndromes—HbSD, HbSO^{Arab}, HbS HPFH, and other variants—are much less common. Patients with HbSβ-thalassemia zero have a clinical phenotype similar to those with HbSS. HbSC does not polymerize like HbSS, but crystals of HbC interact with membrane ion transport, dehydrating red cells and inducing sickling. Children who have HbSC disease can experience the same symptoms and complications as those with severe HbSS disease, but the frequency of such experience is less. Children with HbSC also have increased incidence of retinopathy, chronic hypersplenism, splenic sequestration, and renal medullary carcinoma. The natural history of the other sickle cell syndromes is variable and difficult to predict because of the lack of systematic evaluation.

There is no validated model that can predict the clinical course of an individual with sickle cell disease. A patient with HbSC can have a more-severe clinical course than a patient with HbSS. Management of end-organ dysfunction in children with sickle cell syndromes requires the same general principles as managing patients with sickle cell anemia; however, each situation should be managed on a case-by-case basis and requires consultation with a pediatric hematologist.

ANTICIPATORY GUIDANCE

The 2 primary goals of pediatric care are to promote health and prevent disease. Children with sickle cell disease should receive general health maintenance as recommended for all children with special attention to the following disease specific guidance.

Spleen Palpation

Splenomegaly is a common complication of sickle cell anemia and splenic sequestration can be life-threatening. Parents and primary caregivers should be taught how to palpate the spleen to determine if the spleen is enlarging starting at the first visit with reinforcement at subsequent visits. Parents should also demonstrate spleen palpation to the provider.

Prophylactic Penicillin

Children with sickle cell anemia should receive prophylactic oral penicillin VK until at least 5 yr of age (125 mg twice a day up to age 3 yr, and then 250 mg twice a day thereafter). No established guidelines exist for penicillin prophylaxis beyond 5 yr of age, and some clinicians continue penicillin prophylaxis, whereas others recommend discontinuation. Continuation of penicillin prophylaxis should be continued beyond 5 yr of age in children with history of pneumococcal infection because of the increased risk of a recurrent infection. An alternative for children who are allergic to penicillin is erythromycin ethyl succinate 10 mg/kg twice a day.

Immunizations

In addition to penicillin prophylaxis, routine childhood immunizations, as well as the annual administration of influenza vaccine, are highly recommended. Children with sickle cell anemia develop functional asplenia and also require immunizations to protect against encapsulated organisms including additional pneumococcal and meningococcal vaccinations. Vaccination guidelines can be found at

the Centers for Disease Control and Prevention website: http://www.immunize.org/catg.d/p2010.pdf.

Transcranial Doppler Ultrasound

Primary stroke prevention using TCD has resulted in a decrease in the prevalence of overt stroke among children with sickle cell anemia. Children with HbSS or HbSβ-thalassemia zero should be screened annually with TCD starting at age 2 yr. TCD is best performed when the child is quietly awake and in their usual state of health. TCD measurements may be falsely elevated in the setting of acute anemia or falsely low immediately after blood transfusions or if procedural sedation is used. Screening should occur annually from age 2-16 yr. Abnormal values should be repeated within 2-4 wk to identify patients at greatest risk of overt stroke. Conditional values should be repeated within 3 mo, and normal values repeated annually. Routine neuroimaging with MRI in asymptomatic patients is not currently recommended.

Hydroxyurea

Monitoring children on hydroxyurea is labor intensive. Hydroxyurea is a chemotherapeutic agent that requires the same level of nursing and physician oversight as any child with cancer receiving chemotherapy. The parents must be educated about the consequences of therapy, and when ill, children should be promptly evaluated. Complete blood count should be checked at least every 4 wk after initiation of therapy or any dose change to monitor for hematologic toxicity and then every 8 wk.

Hydroxyurea should be temporarily discontinued and dose adjusted if the absolute neutrophil count falls below 2,000/µL or platelets fall below 80,000/µL. Hydroxyurea is a pregnancy class D medication and adolescents should be counseled regarding methods to prevent pregnancy while taking hydroxyurea. Close monitoring of the patient requires a commitment by the parents and patient, as well as diligence by a physician, to identify toxicity early.

Regular Blood Transfusion Therapy

At the initiation of blood transfusion therapy, children with sickle cell anemia should have testing to identify the presence of alloantibodies and red blood cell phenotyping, which is performed to identify the best matched blood. Children meeting criteria for chronic transfusion therapy should receive annual evaluation for transfusion transmitted infections including hepatitis B, hepatitis C, and human immunodeficiency virus (HIV). After receiving 100 mg/kg of red blood cell transfusions, regular assessments of iron overload should begin; usually periodic measurements of serum ferritin. For children requiring chelation therapy, an audiogram should be performed annually, as well as monitoring for organ toxicity, including liver function tests and endocrine evaluation of pituitary dysfunction because of iron deposition.

Pulmonary and Asthma Screening

Pulmonary complications of sickle cell disease are common and life-threatening. Asthma is common particularly in African-American children. As would be the case in all children, good clinical practice necessitates evaluation for asthma symptoms and asthma risk factors in children with sickle cell disease, particularly in light of the insurmountable evidence that asthma is associated with increased rate of sickle cell disease morbidity and mortality. All children should receive annual screening for signs and symptoms of lower airway disease, such as nighttime cough and exercise-induced cough. In children with symptoms consistent with lower airway disease, consider consultation with an asthma specialist. Pulse oximetry readings should be performed during well visits to identify children with abnormally low daytime oxygen saturations. For children with snoring and daytime somnolence, and symptoms associated with obstructive sleep apnea syndrome, referral to a sleep specialist should be considered.

Retinopathy

Effective therapy for retinopathy associated with sickle cell disease exists. Patients at highest risk for the development of retinopathy should receive annual screening by an ophthalmologist to identify vascular changes that would benefit from laser therapy. Although changes may occur earlier, children with sickle cell disease should begin annual screening at age 10 yr.

Renal

Sickle cell–associated renal disease, starts in infancy and may not become clinically manifested until adulthood. Screening for early signs of sickle nephropathy using urinalysis to identify proteinuria is recommended with annual albumin : creatinine ratios. The age to begin screening for proteinuria has not been defined, but some experts recommend screening annually after at least 10 yr of age if not sooner. If the albumin : creatinine ratio is elevated (>30 mg/g), it should be repeated with an early morning urine collection, and if still elevated, the patient should be referred to a pediatric nephrologist. Males with sickle cell disease should also receive counseling regarding the diagnosis and treatment of priapism. Because of the high frequency of enuresis beyond early childhood, approximately 9% of adolescents between 18 and 20 yr of age, parents and caregivers should be educated about the prolonged nature of enuresis in this disease. As is the case in the general population, obstructive sleep apnea syndrome is associated with an increased prevalence of enuresis in sickle cell disease. Unfortunately, no evidence-based therapies have been developed to treat enuresis in children and young adults with sickle cell disease. In children with enuresis who have symptoms and clinical features of obstructive sleep apnea syndrome, referral to sleep specialists for evaluation is recommended.

Echocardiography

Echocardiography has gained popularity as a screening tool to identify individuals with sickle cell disease who have pulmonary artery hypertension. No evidence currently exists that children with sickle cell disease and elevated tricuspid jet velocity above 2.5 cm/sec have an increased rate of mortality. Subsequent studies in adults with sickle cell disease have found the echocardiography to be insensitive at identifying individuals truly at risk for pulmonary hypertension, although an elevated tricuspid velocity measurement may still be a risk factor for premature death in adults with sickle cell disease. The current recommendation is to refer those with severe cardiopulmonary symptoms from associated pulmonary artery hypertension to pediatric cardiologist for a more formal evaluation.

Bibliography is available at Expert Consult.

462.2 Sickle Cell Trait (Hemoglobin AS)

Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

The prevalence of sickle cell trait varies throughout the world; in the United States, the incidence is 7-10% of African-Americans. Because all state newborn screening programs include sickle cell disease, for most children, sickle cell trait is first identified on their newborn screen. Communication of sickle cell trait status from infancy to young adulthood for the affected individual, family, and healthcare providers is often inconsistent and many young adults are unaware of their sickle cell trait status.

The production of HbS is influenced by the number of α-thalassemia genes present, and the amount of HbS. By definition among individuals with sickle cell trait, the HbS level is <50%. The life span of people with sickle cell trait is normal, and serious complications are extremely rare. The CBC is within the normal range (Fig. 462-5*B*). Hemoglobin analysis is diagnostic, revealing a predominance of HbA, typically >50%, and HbS <50%. Rare complications of sickle cell trait are associated with sudden death during rigorous exercise, splenic infarction at high altitude, hematuria, hyposthenuria, deep vein thrombosis, and susceptibility to eye injury with formation of a hyphema (Table 462-5). Renal

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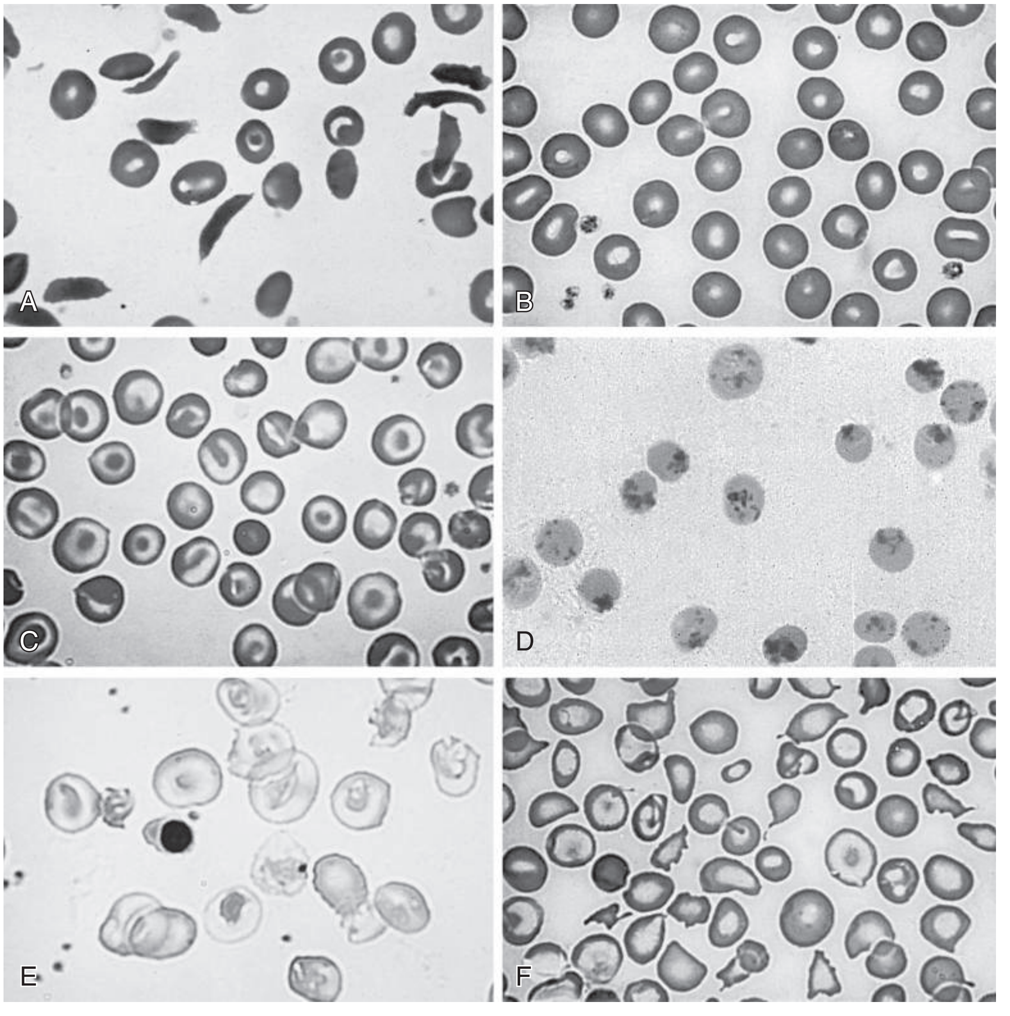

Figure 462-5 **Red blood cell morphology associated with hemoglobin disorders. A,** Sickle cell anemia (HbSS): target cells and fixed (irreversibly sickled) cells. **B,** Sickle cell trait (HbAS): normal red blood cell (RBC) morphology. **C,** Hemoglobin CC: target cells and occasional spherocytes. **D,** Congenital Heinz body anemia (unstable hemoglobin): RBCs stained with supravital stain (brilliant cresyl blue) reveal intracellular inclusions. **E,** Homozygous β0-thalassemia: severe hypochromia with deformed RBCs and normoblasts. **F,** Hemoglobin H disease (α-thalassemia): anisopoikilocytosis with target cells. *(Courtesy of Dr. John Bolles, The ASH Collection, University of Washington, Seattle.)*

Table 462-5	Complications Associated with Sickle Cell Trait
DEFINITE ASSOCIATIONS	
Renal medullary cancer	
Hematuria	
Renal papillary necrosis	
Hyposthenuria	
Splenic infarction	
Exertional rhabdomyolysis	
Exercise-related sudden death	
Protection against severe falciparum malaria	
Microalbuminuria (adults)	

From Tsaras G, Owusu-Ansah A, Boateng O, et al: Complications associated with sickle cell trait: a brief narrative review, Am J Med 122:507–512, 2009.

medullary carcinoma is also associated with sickle cell trait and occurs predominantly in young adults and children.

Children with sickle cell trait do not require limitations on physical activities. Sudden death in persons with sickle cell trait while exercising under extreme conditions is most likely associated with a second genetic factor and/or environmental factors, and not the presence of sickle cell trait itself. No causal pathway has been implicated for the presence of sickle cell trait and sudden death. All patients with sickle cell trait who participate in rigorous athletic activities should receive maximum hydration and appropriate rest during exertion, as would be the precautionary steps for all athletes, particularly when participating in hot humid conditions. The presence of sickle cell trait should never be a reason to exclude a person from athletic participation but rather should serve as an indication that prudent surveillance is necessary to ensure appropriate hydration and prevention of exhaustion from heat or other strenuous exercise. If athletes are to be screened for sickle cell trait, then appropriate genetic counseling should be provided, along with the knowledge that genetic information may provide opportunities to challenge paternity. Such situations are typically handled by a pediatrician or hematologist accustomed to providing both a balanced approach to genetic counseling and addressing the challenges about paternity.

462.3 Other Hemoglobinopathies

Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

HEMOGLOBIN C

The mutation for HbC is at the same site as HbS, with substitution of lysine instead of valine for glutamine. In the United States, hemoglobin C trait (HbAC) occurs in 1:40 and homozygous

hemoglobin C disease (HbCC) occurs in 1 : 5,000 African-Americans. HbAC is asymptomatic. HbCC can result in mild anemia, splenomegaly, and cholelithiasis; rare cases of spontaneous splenic rupture have been reported. Sickling does not occur. This condition is usually diagnosed through newborn screening programs. HbC crystallizes, disrupting the red cell membrane, and HbC crystals may be visible on peripheral smear (see Fig. 462-5*C*).

HEMOGLOBIN E

HbE is an abnormal hemoglobin resulting from a qualitative mutation in the β-globin gene and is the second most common globin mutation worldwide. Patients may have asymptomatic hemoglobin E trait (HbAE) or benign homozygous hemoglobin E disease (HbEE). Compound heterozygous hemoglobin E/β-thalassemia produces clinical phenotypes ranging from moderate to severe anemia depending on the β-thalassemia mutation. In California, HbE/β-thalassemia is found almost exclusively in persons of Southeast Asian descent, with a prevalence of 1 : 2,600 births.

HEMOGLOBIN D

At least 16 variants of HbD exist. HbD-Punjab (Los Angeles) is a rare hemoglobin that is seen in 1-3% of Western Indians and in some Europeans with Asian-Indian ancestry and produces symptoms of sickle cell disease when present in combination with HbS. Heterozygous HbD or hemoglobin D trait (HbAD) is clinically silent. Homozygous HbDD or HbD disease produces a mild to moderate anemia with splenomegaly.

462.4 Unstable Hemoglobin Disorders

Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

At least 200 rare unstable hemoglobins have been identified; the most common is Hb Köln. Most patients seem to have de novo mutations rather than inherited hemoglobin disorders. The best studied unstable hemoglobins are the ones leading to hemoglobin denaturation from mutations affecting heme binding. The denatured hemoglobin can be visualized during severe hemolysis or after splenectomy as Heinz bodies. Unlike the Heinz bodies seen after toxic exposure, in unstable hemoglobins, Heinz bodies are present in reticulocytes and older red cells (see Fig. 462-5*D*). Heterozygotes are asymptomatic.

Children with homozygous gene mutations can present in early childhood with anemia and splenomegaly or with unexplained hemolytic anemia. Hemolysis is increased with febrile illness and with the ingestion of oxidant medications (similar to glucose-6-phosphate dehydrogenase [G6PD] deficiency) with some unstable hemoglobins. If the spleen is functional, the blood smear can appear almost normal or have only hypochromasia and basophilic stippling. A diagnosis may be made by demonstrating Heinz bodies, hemoglobin instability, or an abnormal hemoglobin analysis (although some unstable hemoglobins have normal mobility and are not detected on hemoglobin analysis).

Treatment is supportive. Transfusion may be required during hemolytic episodes in severe cases. Oxidative drugs should be avoided, and folate supplementation may be helpful if dietary deficiency is a concern. Splenectomy may be considered in patients requiring recurrent transfusion or demonstrating poor growth, but the complications of splenectomy, including bacterial sepsis, risk of thrombosis, and the possibility of developing pulmonary hypertension, should be considered before surgery.

462.5 Abnormal Hemoglobins with Increased Oxygen Affinity

Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

More than 110 high-affinity hemoglobins have been characterized. These mutations affect the state of hemoglobin configuration during oxygenation and deoxygenation. Hemoglobin changes structure when in the oxygenated versus the deoxygenated state. The deoxygenated state is termed the T (tense) state and is stabilized by 2,3-diphosphoglycerate. When fully oxygenated, hemoglobin assumes the R (relaxed) state. The exact molecular interactions between these 2 states are unknown. High-affinity hemoglobins contain mutations that either stabilize the R form or destabilize the T form. The interactions between the R and T forms are complex, and the mechanisms of the mutations are not known. In most cases, the high-affinity hemoglobins can be identified by hemoglobin analysis; approximately 20% must be characterized under controlled conditions where measurements are obtained with the P_{50} lowered to 9-21 mm Hg (normal: 23-29 mm Hg). The decreased P_{50} in these hemoglobins leads to an erythrocytosis with hemoglobin levels of 17-20 g/dL. Levels of erythropoietin and 2,3-diphosphoglycerate are normal. Patients are usually asymptomatic and do not need phlebotomy. If phlebotomy is performed, oxygen delivery could be problematic owing to the reduced number of hemoglobin molecules to carry oxygen.

462.6 Abnormal Hemoglobins Causing Cyanosis

Michael R. DeBaun, Allison Grimes, Melissa J. Frei-Jones, and Elliott P. Vichinsky

Abnormal hemoglobins causing cyanosis, also called structural methemoglobinemias, are rare. They are referred to as "M-hemoglobins" and represent a group of hemoglobin variants which result from point mutations in one of the globin chains, α, β, or γ located in the heme pocket. Thirteen known variants exist. These unstable hemoglobins lead to hemolytic anemia, most pronounced when the β-globin gene is affected. Clinically, these children are cyanotic from birth, without other signs or symptoms of disease, if the mutation is in the α-globin gene (HbM Boston, HbM Iwate, Hb Auckland). Infants with β-globin mutations become cyanotic later in infancy after the fetal hemoglobin switch (HbM Saskatoon, HbM Chile, HbM Milwaukee 1 and 2). γ-Chain mutations (HbF-M Fort Ripley, HbF-M Osaka, HbF Cincinnati, HbF Circleville, HbF Toms River, HbF Viseu) are all transient, presenting with cyanosis at birth, which resolves during the neonatal period after HbF production discontinues. The abnormal M hemoglobins exhibit autosomal dominant inheritance and are diagnosed by hemoglobin analysis. HbM variants may be not be isolated reliably using hemoglobin analysis (HPLC or isoelectric focusing [IEF]), consequently diagnostic confirmation may require DNA sequencing or mass spectrometry. There is no specific treatment and affected patients do not respond to treatments used for enzyme-deficient methemoglobinemia. Beyond cyanosis, individuals are otherwise asymptomatic and do not require additional monitoring. Children with the β-globin form should avoid oxidant drugs. Individuals with all forms have a normal life expectancy and pregnancy course.

Low-affinity hemoglobins have less cyanosis than the M hemoglobins. The amino acid substitutions destabilize the oxyhemoglobin and lead to decreased oxygen saturation. The best characterized are Hb Kansas, Hb Beth Israel, and Hb Denver. Hemoglobin analysis (IEF and HPLC techniques) may be normal in affected individuals. When clinically suspected, oxygen affinity studies reveal a right-shifted dissociation curve and heat testing demonstrates unstable hemoglobin. Children present with mild cyanosis only.

462.7 Hereditary Methemoglobinemia

Michael R. DeBaun, Allison Grimes, Melissa J. Frei-Jones, and Elliott P. Vichinsky

Hereditary methemoglobinemia is a clinical syndrome caused by an increase in the serum concentration of methemoglobin either as a result of congenital changes in hemoglobin synthesis or of metabolism

leading to imbalances in reduction and oxidation of hemoglobin. The iron molecule in hemoglobin is normally in the ferrous state (Fe^{2+}), which is essential for oxygen transport. Under physiologic conditions there is a slow, constant loss of electrons to released oxygen, and the ferric (Fe^{3+}) form combines with water, producing methemoglobin (MetHb). The newly formed MetHb has a reduced ability to bind oxygen.

Two pathways for MetHb reduction exist. The physiologic and predominant pathway is a reduced form of nicotinamide adenine dinucleotide (NADH)-dependent reaction catalyzed by cytochrome b5 reductase. This mechanism is >100-fold more efficient than the production of MetHb. The alternate pathway utilizes nicotinamide adenine dinucleotide phosphate generated by G6PD in the hexose monophosphate shunt and requires an extrinsic electron acceptor to be activated (i.e., methylene blue, ascorbic acid, riboflavin). In normal individuals, oxidation of hemoglobin to MetHb occurs at a slow rate, 0.5-3%, which is countered by MetHb reduction to maintain a steady state of 1% MetHb.

MetHb may be increased in the red cell owing to exposure to toxic substances or to absence of reductive pathways, such as NADH-cytochrome b5 reductase deficiency. Toxic methemoglobinemia is much more common than hereditary methemoglobinemia (Table 462-6). Infants are exceptionally vulnerable to hemoglobin oxidation because their erythrocytes have half the amount of cytochrome b5 reductase seen in adults, fetal hemoglobin is more susceptible to oxidation than hemoglobin A, and the more alkaline infant gastrointestinal tract promotes the growth of nitrite-producing Gram-negative bacteria. When MetHb levels are >1.5 g/24 hr, cyanosis is visible (15% MetHb); a level of 70% MetHb is lethal. The MetHb level is usually reported as a percentage of normal hemoglobin, and the toxic level is lower at a lower hemoglobin level. Methemoglobinemia has been described in infants who ingested foods and water high in nitrates, who were exposed to aniline teething gels or other chemicals, and in some infants with severe gastroenteritis and acidosis. Methemoglobin can color the blood brown (Fig. 462-6).

Table 462-6	Known Etiologies of Acquired Methemoglobinemia
MEDICATIONS	
Benzocaine	
Chloroquine	
Dapsone	
EMLA (eutectic mixture of local anesthetics) topical anesthetic (lidocaine 2.5% and prilocaine 2.5%)	
Flutamide	
Lidocaine	
Metoclopramide	
Nitrates	
Nitric oxide	
Nitroglycerin	
Nitroprusside	
Nitrous oxide	
Phenazopyridine	
Prilocaine	
Primaquine	
Riluzole	
Silver nitrate	
Sodium nitrate	
Sulfonamides	
MEDICAL CONDITIONS	
Pediatric gastrointestinal infection, sepsis	
Recreational drug overdose with amyl nitrate ("poppers")	
Sickle cell disease–related painful episode	
MISCELLANEOUS	
Aniline dyes	
Fume inhalation (automobile exhaust, burning of wood and plastics)	
Herbicides	
Industrial chemicals: nitrobenzene, nitroethane (found in nail polish, resins, rubber adhesives)	
Pesticides	
Gasoline octane booster	

From Ash-Bernal R, Wise R, Wright SM: Acquired methemoglobinemia, Medicine (Baltimore) *83:265–273, 2004.*

462.8 Hereditary Methemoglobinemia with Deficiency of NADH Cytochrome b5 Reductase

Michael R. DeBaun, Allison Grimes, Melissa J. Frei-Jones, and Elliott P. Vichinsky

The first reported inherited disorder causing methemoglobinemia resulted from an enzymatic deficiency of NADH cytochrome b5 reductase, which was classified into 2 distinct phenotypes. In type I, the most common form, the deficiency of NADH cytochrome b5 activity is found only in erythrocytes, with other cell types unaffected. In type II, the enzyme deficiency is present in all tissues and results in more significant symptoms beginning in infancy with encephalopathy, mental retardation, spasticity, microcephaly, and growth retardation with death most often by 2 yr of age. Both types exhibit an autosomal recessive inheritance pattern.

Clinically, cyanosis varies in intensity with season and diet. The time of cyanosis onset also varies; in some patients it appears at birth, in others as late as adolescence. Although as much as 50% of the total circulating hemoglobin may be in the form of nonfunctional MetHb, little or no cardiorespiratory distress occurs in these patients, except on exertion.

Daily oral treatment with ascorbic acid (200-500 mg/day in divided doses) gradually reduces the MetHb to approximately 10% of the total

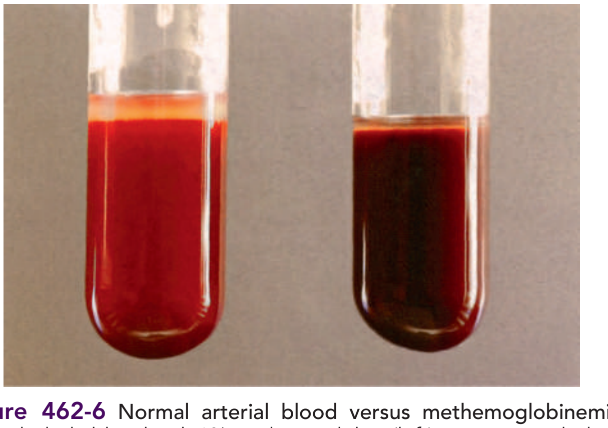

Figure 462-6 Normal arterial blood versus methemoglobinemia. Arterial whole blood with 1% methemoglobin *(left)* versus arterial whole blood with 72% methemoglobin *(right)*. Note the characteristic chocolate-brown color of the sample with an elevated methemoglobin level. Both samples were briefly exposed to 100% oxygen and shaken. This quick analysis is a good bedside test for methemoglobinemia. The sample on the *left* turned bright red, whereas the sample on the *right* remained chocolate-brown. Methods: Whole blood samples were drawn at the same time from the same person. The measured hemoglobin concentration was 11.7 g/dL. Calculated concentration of methemoglobin: 11.7 g/dL × 0.01 = 0.117 g/dL *(left)* and 11.7 g/dL × 0.72 = 8.42 g/dL *(right)*. An elevated methemoglobin level was made in vitro by adding 0.1 mL of a 0.144 molar solution of sodium nitrate *(right)*, and 0.1 mL of normal saline was added as a control *(left)*. Cooximetry measurements were taken on both samples shortly after the blood was drawn and 20 min after the addition of sodium nitrate solution. Both blood samples were exposed to 100% oxygen before the second measurement. *(Protocol based on personal communication with Dr. Ali Mansouri, December 2002.)*

pigment and alleviates the cyanosis as long as therapy is continued. Chronic high doses of ascorbic acid have been associated with hyperoxaluria and renal stone formation. Ascorbic acid should not be used to treat toxic methemoglobinemia. When immediately available, poison control should be contacted to verify the most up-to-date therapeutic strategies. Like ascorbic acid, riboflavin utilizes the alternate pathway of MetHb reduction and is most effective when given in high doses (400 mg once daily). Methylene blue, administered intravenously (1-2 mg/kg initially), is used to treat toxic methemoglobinemia. An oral dose can be administered (100-300 mg PO per day) as maintenance therapy.

Methylene blue should not be used in patients with G6PD deficiency. This treatment is ineffective and can cause severe oxidative hemolysis. In the event that methylene blue is given to a patient with G6PD deficiency, there will be no improvement in symptoms and marked hemolysis has been reported within 24 hr of administration. Because G6PD deficiency status is rarely known at the time of treatment, a careful history should be elicited. When the history is negative for symptoms of G6PD deficiency, treatment with methylene blue should be initiated judiciously, and the patient should be closely monitored for improvement.

462.9 Syndromes of Hereditary Persistence of Fetal Hemoglobin

Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

HPFH syndromes are a form of thalassemia; mutations are associated with a decrease in the production of either or both β- and δ-globins. There is an imbalance in the α:non-α synthetic ratio (see Chapter 462.9) characteristic of thalassemia. More than 20 variants of HPFH have been described. They are deletional, $\delta\beta^0$ (Black, Ghanaian, Italian), nondeletional (Tunisian, Japanese, Australian), linked to the β-globin–gene cluster (British, Italian-Chinese, Black), or unlinked to the β-globin–gene cluster (Atlanta, Czech, Seattle). The $\delta\beta^0$ forms have deletions of the entire δ- and β-globin gene sequences, and the most common form in the United States is the Black (HPFH 1) variant. As a result of the δ and β gene deletions, there is production only of γ-globin and formation of HbF. In the homozygous form, no manifestations of thalassemia are present. There is only HbF with very mild anemia and slight microcytosis. When inherited with other variant hemoglobins, HbF is elevated into the 20-30% range; when inherited with HbS, there is an amelioration of sickle cell disease with fewer complications.

462.10 Thalassemia Syndromes

Michael R. DeBaun, Melissa J. Frei-Jones, and Elliott P. Vichinsky

Thalassemia refers to a group of genetic disorders of globin chain production in which there is an imbalance between the α-globin and β-globin chain production. β-Thalassemia syndromes result from a decrease in β-globin chains, which results in a relative excess of α-globin chains. β^0-Thalassemia refers to the absence of production of the β-globin. When patients are homozygous for the β-thalassemia gene, they cannot make any normal β chains (HbA). β^+-Thalassemia indicates a mutation that makes decreased amounts of normal β-globin, but it is still present (HbA). β^0-Thalassemia syndromes are more severe than β^+-thalassemia syndromes, but there is significant variability between the genotype and phenotype. β-Thalassemia major refers to the severe β-thalassemia patient who requires early transfusion therapy and often is homozygous for β^0 mutations. β-Thalassemia intermedia is a clinical diagnosis of a patient with a less-severe clinical phenotype that usually does not require transfusion therapy in childhood. Many of these patients have at least 1 β^+-thalassemia mutation. β-Thalassemia syndromes usually require a β-thalassemia mutation in both β-globin genes. Carriers with a single β-globin mutation are generally asymptomatic, except for microcytosis and mild anemia. In α-thalassemia, there is an absence or reduction in α-globin production. Normal individuals have 4 α-globin genes. The more genes affected, the more severe the disease. An α^0-mutation indicates no α-chains produced from that gene. An α^+ mutation produces a decreased amount of α-globin chain. The primary pathology in the thalassemia syndromes stems from the quantity of globin produced, whereas the primary pathology in sickle cell disease is related to the quality of β-globin produced.

EPIDEMIOLOGY

There are >200 different mutations resulting in absent or decreased globin production. Although most are rare, the 20 most common abnormal alleles constitute 80% of the known thalassemias worldwide; 3% of the world's population carries alleles for β-thalassemia, and in Southeast Asia 5-10% of the population carry alleles for α-thalassemia. In a particular region, there are fewer common alleles. In the United States, an estimated 2,000 persons have β-thalassemia major.

PATHOPHYSIOLOGY

Two related features contribute to the sequelae of β-thalassemia major: inadequate β-globin gene production leading to decreased levels of normal hemoglobin (HbA) and unbalanced α- and β-globin chain production. In β-thalassemia major, α-globin chains are in excess to non–α-globin chains, and α-globin tetramers (α_4) are formed and appear as red cell inclusions. The free α-globin chains and inclusions are very unstable, precipitate in red cell precursors, damage the red cell membrane, and shorten red cell survival leading to anemia and increased erythroid production. Table 462-7 shows selected features of thalassemia. This results in a marked increase in erythropoiesis with early erythroid precursor death in the bone marrow. Clinically, this is characterized by a lack of maturation of erythrocytes and an inappropriately low reticulocyte count. This ineffective erythropoiesis and the compensatory massive marrow expansion with erythroid hyperactivity characterize β-thalassemia. Because the β^0-thalassemia patient cannot make HbA, the α-chains combine with γ-chains, resulting in HbF ($\alpha_2\gamma_2$) being the dominant hemoglobin. In addition to the natural survival effect, the γ-globin chains may be produced in increased amounts, which is regulated by genetic polymorphisms. δ-Chain synthesis is not usually affected in β-thalassemia or β-thalassemia trait, and, therefore, patients have a relative or absolute increase in HbA_2 production ($\alpha_2\delta_2$).

In the α-thalassemia syndromes, 2 genes with 2 maternal and 2 paternal alleles control α-globin production, which varies from complete absence (hydrops fetalis) to only slightly reduced (α-thalassemia silent carrier). In the α-thalassemia syndromes, an excess of β- and γ-globin chains are produced. These excess chains form Bart hemoglobin (γ_4) in fetal life and HbH (β_4) after birth. These abnormal tetramers are nonfunctional hemoglobins with very high oxygen affinity. They do not transport oxygen and result in extravascular hemolysis. A fetus with the most severe form of α-thalassemia (hydrops fetalis) develops in utero anemia and fetal loss because HbF production requires sufficient amounts of α-globin. In contrast, infants with β-thalassemia major become symptomatic only after birth when HbA predominates and insufficient β-globin production manifests in clinical symptoms.

HOMOZYGOUS β-THALASSEMIA (THALASSEMIA MAJOR, COOLEY ANEMIA)

Clinical Manifestations

If not treated, children with homozygous β^0-thalassemia usually become symptomatic from progressive hemolytic anemia, with profound weakness and cardiac decompensation during the 2nd 6 mo of life. Depending on the mutation and degree of fetal hemoglobin production, transfusions in β-thalassemia major are necessary beginning in the 2nd mo to 2nd yr of life, but rarely later. The decision to transfuse is multifactorial but is not determined solely by the degree of anemia. The developing signs of ineffective erythropoiesis such as growth

Table 462-7 The Thalassemias

THALASSEMIA	GLOBIN GENOTYPE	FEATURES	EXPRESSION	HEMOGLOBIN ANALYSIS
α-THALASSEMIA				
1 Gene allele deletion	$-,\alpha/\alpha,\alpha$	Normal	Normal	Newborn: Bart 1-2%
2 Gene allele deletion trait	$-,\alpha/-,\alpha$ $-$, $-/\alpha,\alpha$	Microcytosis, mild hypochromasia	Normal, mild anemia	Newborn: Bart: 5-10%
3 Gene allele deletion hemoglobin H	$-,-/-,\alpha$	Microcytosis, hypochromic	Mild anemia, transfusions not required	Newborn: Bart: 20-30%
2 Gene allele deletion + Constant Spring	$-,-/\alpha,\alpha^{Constant\ Spring}$	Microcytosis, hypochromic	Moderate to severe anemia, transfusion, splenectomy.	2-3% Constant Spring, 10-15% HbH
4 Gene allele deletion	$-,-/-,-$	Anisocytosis, poikilocytosis	Hydrops fetalis	Newborn: 89-90% Bart with Gower 1 and 2 and Portland
Nondeletional	$\alpha,\alpha/\alpha,\alpha^{variant}$	Microcytosis, mild anemia	Normal	1-2% variant hemoglobin
β-THALASSEMIA				
β^0 or β^+ heterozygote: trait	$\beta^0/A, \beta^+/A$	Variable microcytosis	Normal	Elevated A_2, variable elevation of F
β^0-Thalassemia	β^0/β^0, β^+/β^0, E/β^0	Microcytosis, nucleated RBC	Transfusion dependent	F 98% and A_2 2%, E 30-40%
β^+-Thalassemia severe	β^+/β^+	Microcytosis nucleated RBC	Transfusion dependent/ thalassemia intermedia	F 70-95%, A_2 2%, trace A
Silent	β^+/A	Microcytosis	Normal with only microcytosis	A_2 3.3-3.5%
β^+/β^+	Hypochromic, microcytosis	Mild to moderate anemia	A_2 2-5%, F 10-30%	
Dominant (rare)	B^0/A	Microcytosis, abnormal RBCs	Moderately severe anemia, splenomegaly	Elevated F and A_2
δ-Thalassemia	A/A	Normal	Normal	A_2 absent
$(\delta\beta)^0$-Thalassemia	$(\delta\beta)^0/A$	Hypochromic	Mild anemia	F 5-20%
$(\delta\beta)^+$-Thalassemia Lepore	β^{Lepore}/A	Microcytosis	Mild anemia	Lepore 8-20%
Lepore	$\beta^{Lepore}/\beta^{Lepore}$	Microcytic, hypochromic	Thalassemia intermedia	F 80%, Lepore 20%
γδβ-Thalassemia	$(\gamma^A\delta\beta)^0/A$	Microcytosis, microcytic, hypochromic	Moderate anemia, splenomegaly, homozygote: thalassemia intermedia	Decreased F and A2 compared with δβ-thalassemia
γ-Thalassemia	$(\gamma^A\gamma^G)^0/A$	Microcytosis	Insignificant unless homozygote	Decreased F
HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN				
Deletional	A/A	Microcytic	Mild anemia	F 100% homozygotes
Nondeletional	A/A	Normal	Normal	F 20-40%

failure, bone deformities secondary to marrow expansion, hepatosplenomegaly are important variables in determining transfusion initiation.

The classic presentation of children with severe disease includes thalassemic facies (maxilla hyperplasia, flat nasal bridge, frontal bossing), pathologic bone fractures, marked hepatosplenomegaly, and cachexia and is now primarily seen in countries without access to chronic transfusion therapy. Occasionally, patients with moderate anemia develop these features because of severe compensatory ineffective erythropoiesis.

In nontransfused patients with severe ineffective erythropoiesis, marked splenomegaly can develop with hypersplenism and abdominal symptoms. The features of ineffective erythropoiesis include expanded medullary spaces (with massive expansion of the marrow of the face and skull producing the characteristic thalassemic facies), extramedullary hematopoiesis, and higher metabolic needs (Fig. 462-7). The chronic anemia without transfusion exposure produces an increase in iron absorption from the gastrointestinal tract and secondary hemosiderosis-induced organ injury.

Chronic transfusion therapy dramatically improves the quality of life and reduces the complications of severe thalassemia. Transfusion-induced hemosiderosis becomes the major clinical complication of transfusion-dependent thalassemia. Each mL of packed red cells contains 1 mg of iron. Physiologically, there is no mechanism to eliminate excess body iron. Iron is initially deposited in the liver. Liver hemosiderosis develops after 1 yr of chronic transfusion therapy and is followed by iron deposition in the endocrine system. This leads to a high rate of hypothyroidism, hypogonadotrophic gonadism, growth hormone deficiency, hypoparathyroidism, and diabetes mellitus. After 10 yr of transfusion, cardiac dysfunction secondary to hemosiderosis begins. Eventually, most patients not receiving adequate iron chelation therapy die from cardiac failure and/or cardiac arrhythmias secondary to hemosiderosis. Hemosiderosis induced morbidity can be prevented by adequate iron chelation therapy.

Laboratory Findings

In the United States, some children with β-thalassemia major will be identified on newborn screening as a result of the detection of only HbF on hemoglobin electrophoresis. However, the ethnicity and the mutations associated with transfusion-dependent thalassemia in United States have dramatically changed. Many of the patients have diverse mutations, such as HbE thalassemia, which may not be identified or followed up by a newborn screening program. HbFE in the newborn may be a very common benign mutation caused by homozygous HbEE or an uncommon severe HbE β^0-thalassemia. The lack of standardized neonatal diagnosis of thalassemia disorders requires close follow-up of newborns with unclear thalassemia mutations and/or babies from high-risk ethnic groups.

Infants with serious β-thalassemia disorders have a progressive anemia after the newborn period. Microcytosis (MCV), hypochromia (MCH), and targeting characterize the red cells. Nucleated red cells, marked anisopoikilocytosis, and a relative reticulocytopenia are typically seen (see Fig. 462-5*E*). The hemoglobin level falls progressively to <6 g/dL unless transfusions are given. The reticulocyte count is

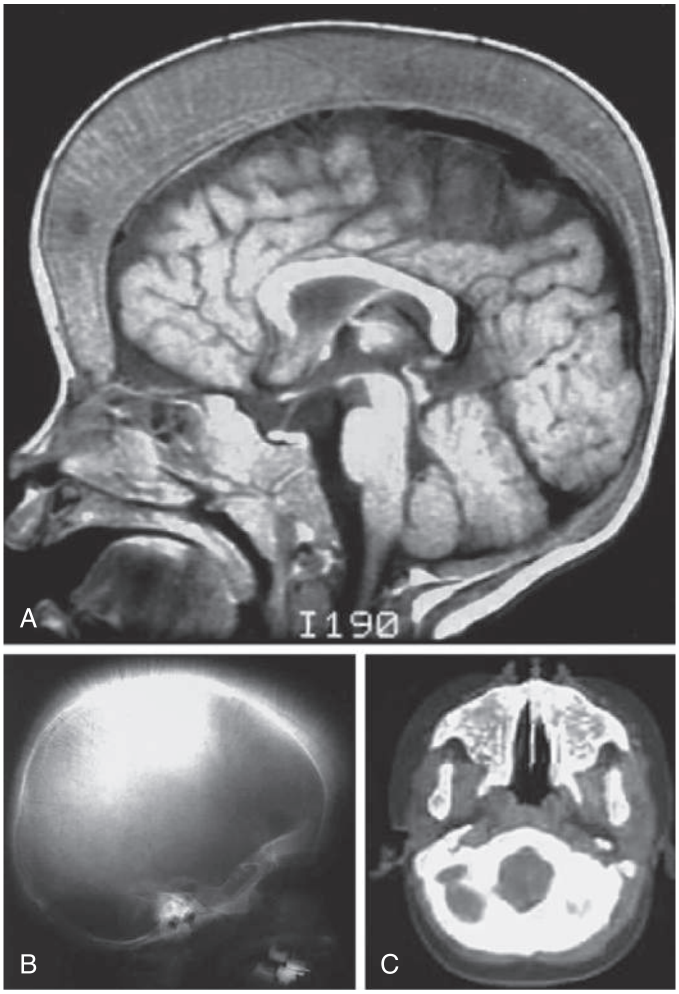

Figure 462-7 Ineffective erythropoiesis in a 3 yr old patient who has β-thalassemia major and has not received a transfusion. **A,** Massive widening of the diploic spaces of the skull as seen on MRI. **B**, Radiographic appearance of the trabeculae as seen on plain radiograph. **C,** Obliteration of the maxillary sinuses with hematopoietic tissue as seen on CT scan.

commonly <8% and is inappropriately low when compared to the degree of anemia as a result of ineffective erythropoiesis. The unconjugated serum bilirubin level is usually elevated, but other chemistries may be normal early on. Even if the child does not receive transfusions, iron eventually accumulates with elevated serum ferritin and transferrin saturation. Bone marrow hyperplasia can be seen on radiographs (see Fig. 462-7).

Early definitive diagnosis is recommended. Newborn screening techniques such as hemoglobin electrophoresis is not definitive. DNA diagnosis of the β-thalassemia mutation, along with testing for common genetic modifiers of the clinical phenotype, is recommended. Coinheritance of an α-thalassemia mutation is common, and it decreases the severity of the β-thalassemia disease. Some patients' mutations cannot be diagnosed by standard electrophoresis or common DNA probes. Referral of the samples to a tertiary laboratory along with parental and family testing are indicated. Following the definitive diagnosis, families should undergo detailed counseling.

Management and Treatment of Thalassemia

Transfusion Therapy

Before initiating chronic transfusions, the diagnosis of transfusion dependent β-thalassemia should be confirmed by both clinical and laboratory parameters. β-Thalassemia major is a clinical diagnosis that requires the integration of laboratory findings and the clinical course. Of patients with homozygous β^0-thalassemia (the most severe mutations), 15-20% may have a clinical course that is phenotypically consistent with thalassemia intermedia. In contrast, 25% of patients with homozygous β^+-thalassemia, typically a more benign genotype, may become transfusion-dependent thalassemia major. Transient clinical events, such as a sudden fall in hemoglobin secondary to an episode of parvovirus requiring transfusion, do not necessarily indicate the patient is a transfusion-dependent patient. The long-term observation of the clinical characteristics, such as growth, bony changes, and hemoglobin, are necessary to determine chronic transfusion therapy.

Guidelines for Transfusion Therapy. Patients at risk for transfusion therapy should have an extended red cell phenotype and/or genotype. Patients should receive red cells depleted of leukocytes and matched for, at least, D, C, c, E, e, and Kell antigens. Cytomegalovirus-negative units are indicated in stem cell transplantation candidates. Transfusions should generally be given at intervals of 3-4 wk, with the goal being to maintain a pretransfusion hemoglobin level of 9.5-10.5 g/dL. Ongoing monitoring for transfusion-associated transmitted infections (hepatitis A, hepatitis B, hepatitis C, HIV), alloimmunization, annual blood transfusion requirements, and transfusion reactions is essential.

Iron Overload Monitoring

Excessive iron stores from transfusion cause many of the complications of β-thalassemia major. Accurate assessment of excessive iron stores is essential to optimal therapy. Serial serum ferritin levels are a useful screening technique in assessing iron balance trends, but results may not accurately predict quantitative iron stores. Undertreatment or overtreatment of presumed excessive iron stores can occur in managing a patient based on serum ferritin alone. Noninvasive measurement of quantitative organ injury is rapidly improving the treatment of iron overload. Quantitative measurement of liver iron and cardiac iron are standard and measurement of pancreatic and gonadal iron may be available soon. This technology, in collaboration with access to multiple chelators, will enable targeted chelation therapy for patients with organ specific hemosiderosis before the onset of overt organ failure. Available data suggests integration of these imaging technologies with chelation therapy may prevent heart failure, diabetes, and other pending organ dysfunction.

Quantitative liver iron by approved MRI technology is the best indicator of total-body iron stores and should be obtained in chronically transfused patients after chronic transfusion therapy has initiated. The liver iron results will help guide the chelation regimen.. Quantitative cardiac iron, determined by T2* MRI cardiac software, should be obtained after 7 yr of transfusion therapy. It is not uncommon to have a discrepancy between the liver iron and the heart iron because of different rates of tissue loading and cardiac chelation efficacy.

Chelation Therapy

Iron-chelation therapy should start as soon as the patient becomes significantly iron overloaded. In general, this occurs after 1 yr of transfusion therapy and correlates with the serum ferritin >1,000 ng/mL and/or a liver iron concentration of >2,500 μg/g dry weight.

There are 3 available iron chelators (deferoxamine, deferasirox, and deferiprone); each varies in its route of administration, pharmacokinetics, adverse events, and efficacy. Many patients require combination chelation therapy at various points in their illness. The overall goal is to prevent hemosiderosis-induced tissue injury and avoid chelation toxicity. This requires close monitoring of the patients. In general, chelation toxicity increases as iron stores decrease.

Deferoxamine (Desferal) is the most studied iron chelator; it has an excellent safety and efficacy profile. It requires subcutaneous, or intravenous, administration because of a half-life of less than 30 min, necessitating administration of at least 8 hr daily, 5-7 days/wk. Deferoxamine is initially started at 20 mg/kg and can be increased to 60 mg/kg in heavily iron-overloaded patients. The major problem with deferoxamine is noncompliance because of the route of administration.

Adverse side effects include ototoxicity, retinal changes, and bone dysplasia with truncal shortening.

The oral iron chelator deferasirox (Exjade) is commercially available in the United States. Of patients on Desferal, 70% have switched to deferasirox because it is orally available. Deferasirox has a half-life of more than 16 hr and requires once-a-day administration of a dispersible tablet in water. Initial dose is 20 mg/kg with gradual escalation to 30 mg/kg. The most common side effects are gastrointestinal symptoms. The most serious side effect of deferasirox is potential kidney damage. Up to 30% of patients have transient increases in creatinine that requires temporary modifications of dosing. All patients require monthly chemistry panels and ongoing monitoring for proteinuria. Long-term studies in thousands of patients have not demonstrated progressive renal dysfunction, but isolated cases of renal failure in patients have occurred.

Deferiprone (Ferriprox), an oral iron chelator previously only available in Europe, is approved in the United States. Deferiprone has a half-life of approximately 3 hr and requires 25 mg/kg 3 times a day. Deferiprone, a small molecule, effectively enters cardiac tissue and may be more effective than other chelators in reducing cardiac hemosiderosis. The most serious side effect of deferiprone is transient agranulocytosis, which occurs in 1% of patients. It is associated with rare deaths where patients were not adequately monitored. The use of deferiprone requires weekly white blood cell counts.

As thalassemia patients are living longer, the iron-chelation goals have changed. Aggressive treatment with combination chelation therapy is often used in heavily iron-overloaded patients to prevent or reverse organ dysfunction. Deferoxamine, in combination with deferiprone, is routinely used in patients with increased cardiac iron. Combination therapy of deferoxamine and deferasirox may also be efficacious in similar patients.

Hydroxyurea

Hydroxyurea, a DNA antimetabolite, increases stress erythropoiesis, which results in increased HbF production. It has been most successfully used in sickle cell disease and in some patients with β-thalassemia intermedia. Studies in β-thalassemia major are limited. In many parts of the world, hydroxyurea therapy is used in thalassemia intermedia patients. Even though increases in HbF levels are observed, they do not predictively correlate with increase in total hemoglobin in these patients. In general, there appears to be a mean increase in hemoglobin of 1 g (range: 0.1-2.5 g). Hydroxyurea therapy in thalassemia intermedia may have other benefits including decreasing the vascular disease associated with thalassemia intermedia. The initial starting dose for thalassemia intermedia is 10 mg/kg and because these patients are more sensitive to toxicity than sickle cell disease, higher doses are used with great caution.

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation has cured >3,000 patients who had β-thalassemia major. In low-risk HLA-matched sibling patients, there is at least a 90% survival and an 80% event-free survival. In general, myeloablative conditioning regimens are required in order to prevent graft rejection and thalassemia recurrence. Most success has been in children younger than 15 yr of age without excessive iron stores and hepatomegaly who undergo sibling HLA-matched allogeneic transplantation. All children who have an HLA-matched sibling should be offered the option of bone marrow transplantation. Alternative transplantation regimens for patients without donors are experimental and have variable success.

Splenectomy

Surgical Asplenia

Splenectomy may be required in thalassemia patients who develop hypersplenism. These patients have a falling steady state hemoglobin and/or a rising transfusion requirement. Overall, splenectomy is less frequently used as a therapeutic option. There is an increased recognition of serious adverse effects of splenectomy beyond infection risk. In thalassemia intermedia, splenectomized patients have a marked increased risk of venous thrombosis, pulmonary hypertension, leg ulcers, and silent cerebral infarction compared to nonsplenectomized patients. All patients should be fully immunized against encapsulated bacteria and should be on long-term penicillin prophylaxis with appropriate instructions regarding fever management. Prophylactic penicillin should be administered postsplenectomy to prevent sepsis, and families need to be educated on the risk of fever and sepsis.

Preventative Monitoring of Thalassemia Patients

Cardiac. Cardiac disease is the major cause of death in thalassemia. Serial echocardiograms should be monitored to evaluate cardiac function and pulmonary artery pressure. Pulmonary hypertension frequently occurs in non-transfused thalassemia patients and may be an indication for transfusion therapy. After 8 yr of chronic transfusion therapy, cardiac hemosiderosis may occur; consequently, cardiac T2* MRI imaging studies are recommended. Patients with cardiac hemosiderosis and decreasing cardiac ejection fraction require intensive combination chelation therapy.

Endocrine. Endocrine function progressively declines with age secondary to hemosiderosis and nutritional deficiencies. Iron deposition in the pituitary and endocrine organs can result in multiple endocrinopathies, including hypothyroidism, growth hormone deficiency, delayed puberty, and hypoparathyroidism, diabetes mellitus, osteoporosis, and adrenal insufficiency. Monitoring for endocrine dysfunction starts early, around 5 yr of age, or after at least 3 yr of chronic transfusions. All children require monitoring of their height, weight, and sitting height semi-annually. Nutritional assessments are required. Most patients need vitamin D, calcium, vitamin B, vitamin C, and zinc replacement. Fertility is a growing concern among patients and should be assessed routinely.

Psychosocial Support. Thalassemia imposes major disruption in the family unit and significant obstacles to normal development. Culturally sensitive anticipatory counseling is necessary, and the early use of child life services decreases psychological trauma of therapy. Early social service consultation to address financial and social issues is mandatory.

OTHER β-THALASSEMIA SYNDROMES

Nontransfusion-Dependent Thalassemia: β-Thalassemia Intermedia

The β-thalassemia syndromes are characterized by decreased production of β-globin chains of HbA. There are 200-300 β-thalassemia alleles that have now been characterized. These mutations can affect any step in the transcription of β-globin genes. As discussed, β^0-thalassemia is absent production of normal β-chains, and production of β^+ is decreased. Some β-thalassemia mutations have structural mutations such as HbE. Others, such as δβ-thalassemia or HPFH, are variants of β-thalassemia that have decreased production of β-globin gene with increased compensation of HbF. Because phenotypic correlation with genotype is variable, β-thalassemia patients are largely classified by their clinical spectrum. Transfusion-dependent thalassemia, or thalassemia major, is the most severe group. Nontransfusion-dependent thalassemia intermedia include a spectrum of patients who initially are not chronically transfused in infancy but may be sporadically transfused throughout their lifetime. The major determining characteristic of these patients is less α–β-globin chain imbalance than observed in thalassemia major. Sometimes, genetic modifiers alter the primary mutation severity and improve the globin chain imbalance. Coinheritance of α-thalassemia trait or polymorphisms of globin promoters such as BCL11 may convert a thalassemia major patient to a nontransfusion-dependent thalassemia intermedia patient. HbEβ-thalassemia is a common cause of both transfusion-dependent and nontransfusion-dependent thalassemia. These secondary genetic modifiers play a role in altering the severity of this disorder. Occasionally, patients with a single β-thalassemia mutation or autosomal dominant β-thalassemia trait have clinical features of thalassemia intermedia, or nontransfusion-dependent thalassemia. Genetic studies of these patients often uncover a coinheritance of genetic modifiers that worsen the condition such as α-gene triplication or an unstable β-globin mutation.

Thalassemia intermedia patients have significant ineffective erythropoiesis that leads to microcytic anemia with hemoglobin of approximately 7 g/dL (range: 6-10 g/dL). These patients have some of the complications characterized in untransfused thalassemia major patients, but the severity varies depending on the degree of ineffective erythropoiesis. They can develop medullary hyperplasia, hepatosplenomegaly, hematopoietic pseudotumors, pulmonary hypertension, thrombotic events, and growth failure. Many patients develop hemosiderosis secondary to increased gastrointestinal absorption of iron requiring chelation. Extramedullary hematopoiesis can occur in the vertebral canal, compressing the spinal cord and causing neurologic symptoms; the latter is a medical emergency requiring immediate local radiation therapy to halt erythropoiesis. Transfusions are indicated in thalassemia intermedia patients with significant clinical morbidity.

Thalassemia trait is often misdiagnosed as iron deficiency in children because the two produce similar hematologic abnormalities on CBC, and iron deficiency is much more prevalent. A short course of iron and reevaluation is all that is required to identify children who will need further evaluation. Children who have β-thalassemia trait have a persistently normal red cell distribution width and low mean corpuscular volume (MCV), whereas patients with iron deficiency develop an elevated red cell distribution width with treatment. On hemoglobin analysis, they have an elevated HbF and usually increased levels of HbA_2. There are "silent" forms of β-thalassemia trait, and if the family history is suggestive, further studies may be indicated.

α-THALASSEMIA SYNDROMES

The same evolutionary pressures that produced β-thalassemia and sickle cell disease produced α-thalassemia. Infants are identified in the newborn period by the increased production of Bart hemoglobin (γ_4) during fetal life and its presence at birth. The α-thalassemia syndromes occur most commonly in Southeast Asia. Deletion mutations are common in α-thalassemia. In addition to deletional mutations, there are nondeletional α-globin gene mutations, the most common being Constant Spring ($\alpha^{CS}\alpha$); these mutations cause a more severe anemia and clinical course than the deletional mutations. There are 4 α-globin gene alleles and 4 deletional α-thalassemia phenotypes. The different phenotypes in α-thalassemia largely result from whether one (α^+-thalassemia) or both (α^o-thalassemia) α-globin genes are deleted in each of the 2 loci.

The deletion of 1 α-globin gene allele (silent trait) is not identifiable hematologically. Specifically, no alterations are noted in the MCV and mean corpuscular hemoglobin. Persons with this deletion are usually diagnosed after the birth of a child with a 2-gene deletion or HbH (β_4), but some newborn screening programs report even low concentrations of Hb Bart. During the newborn period, <3% Hb Bart is observed. The deletion of 1 α-globin gene allele is common in African-Americans.

The deletion of 2 α-globin gene alleles results in α-thalassemia trait. The α-globin alleles can be lost in a *trans*-(−α/−α) or *cis*- ($\alpha,\alpha/^{-SEA}$) configuration. The *trans* or *cis* mutations can combine with other mutations and lead to HbH or α-thalassemia major. In persons from Africa or of African descent, the most common α-globin deletions are in the *trans* configuration; whereas, in persons from or descended from Asia or the Mediterranean region, *cis* deletions are most common.

α-Thalassemia trait manifest as a microcytic anemia that can be mistaken for iron-deficiency anemia (see Fig. 462-5*F*). The hemoglobin analysis is normal, except during the newborn period, when Hb Bart is commonly <8% but >3%. Children with a deletion of 2 α-globin alleles are commonly thought to have iron deficiency, given the presence of both low MCV and mean corpuscular hemoglobin. The simplest approach to distinguish between iron deficiency and α-thalassemia trait is with a good dietary history. Children with iron-deficiency anemia often have a diet that is low in iron and drink significant amount of cow's milk. Alternatively, a brief course of iron supplementation along with monitoring of erythrocyte parameters might confirm the diagnosis of iron deficiency. If both parents of a child diagnosed with α-thalassemia trait are carriers, they are at risk for a future hydrops fetalis pregnancy. Thus, family screening and genetic counseling are indicated.

The deletion of 3 α-globin gene alleles leads to the diagnosis of HbH disease. A more severe form of HbH disease may be caused by a nondeletional α-globin mutation with 2 allele deletions. HbH Constant Spring ($-\alpha/\alpha,\alpha^{CS}$) is the most common type of nondeletional HbH disease.

In California, where a large population of persons of Asian descent resides, approximately 1 : 10,000 of all newborns have HbH disease. The simplest manner of diagnosing HbH disease is during the newborn period, when excess in γ-tetramers are present and Hb Bart is commonly >25%. Obtaining supporting evidence from the parents is also necessary. Later in childhood, there is an excess of β-globin chain tetramers that results in HbH. A definitive diagnosis of HbH disease requires DNA analysis with supporting evidence. Brilliant cresyl blue can stain HbH, but it is rarely used for diagnosis. Patients with HbH disease have a marked microcytosis, anemia, mild splenomegaly, and, occasionally, scleral icterus or cholelithiasis. Chronic transfusion is not commonly required for therapy because the range of hemoglobin is 7-11 g/dL, with MCV 51-73 fL but intermittent transfusions for worsening anemia may be needed.

The deletion of all 4 α-globin gene alleles causes profound anemia during fetal life, resulting in hydrops fetalis; the ζ-globin gene must be present for fetal survival. There are no normal hemoglobins present at birth (primarily Hb Bart, with Hb Gower 1, Gower 2, and Portland). If the fetus survives, immediate exchange transfusion is indicated. These infants with severe α-thalassemia are transfusion dependent, and hematopoietic stem cell transplantation is the only cure.

Treatment of HbH disease requires ongoing monitoring of growth and organ dysfunction. Dietary supplement with folate and multivitamins without iron is indicated. Older patients may develop decreased bone density with calcium and vitamin D deficiency. Iron supplementation should be avoided. Intermittent transfusion requirements during child development and infection may occur, particularly in nondeletional HbH. Splenectomy is occasionally indicated and because of the high risk of postsplenectomy thrombosis, aspirin or other anticoagulant therapy following splenectomy should be considered. Hemosiderosis, secondary to gastrointestinal iron absorption and/or transfusion exposure, may develop in older patients and require therapy. Because HbH is an unstable hemoglobin sensitive to oxidative injury, oxidative medications should be avoided. At-risk couples for hydrops fetalis should be identified and offered molecular diagnosis on fetal tissue obtained early in pregnancy. Later in pregnancy, intrauterine transfusion can improve fetal survival, but chronic transfusion therapy or bone marrow transplantation for survivors will be required.

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Chapter 463
Enzymatic Defects

463.1 Pyruvate Kinase Deficiency

George B. Segel

Congenital hemolytic anemia occurs in persons homozygous or compound heterozygous for autosomal recessive genes that cause either a marked reduction in red blood cell (RBC) pyruvate kinase (PK) or production of an abnormal enzyme with decreased activity resulting in impaired conversion of phosphoenolpyruvate to pyruvate. Generation of adenosine triphosphate (ATP) within RBCs at this step is impaired, and low levels of ATP, pyruvate, and the oxidized form

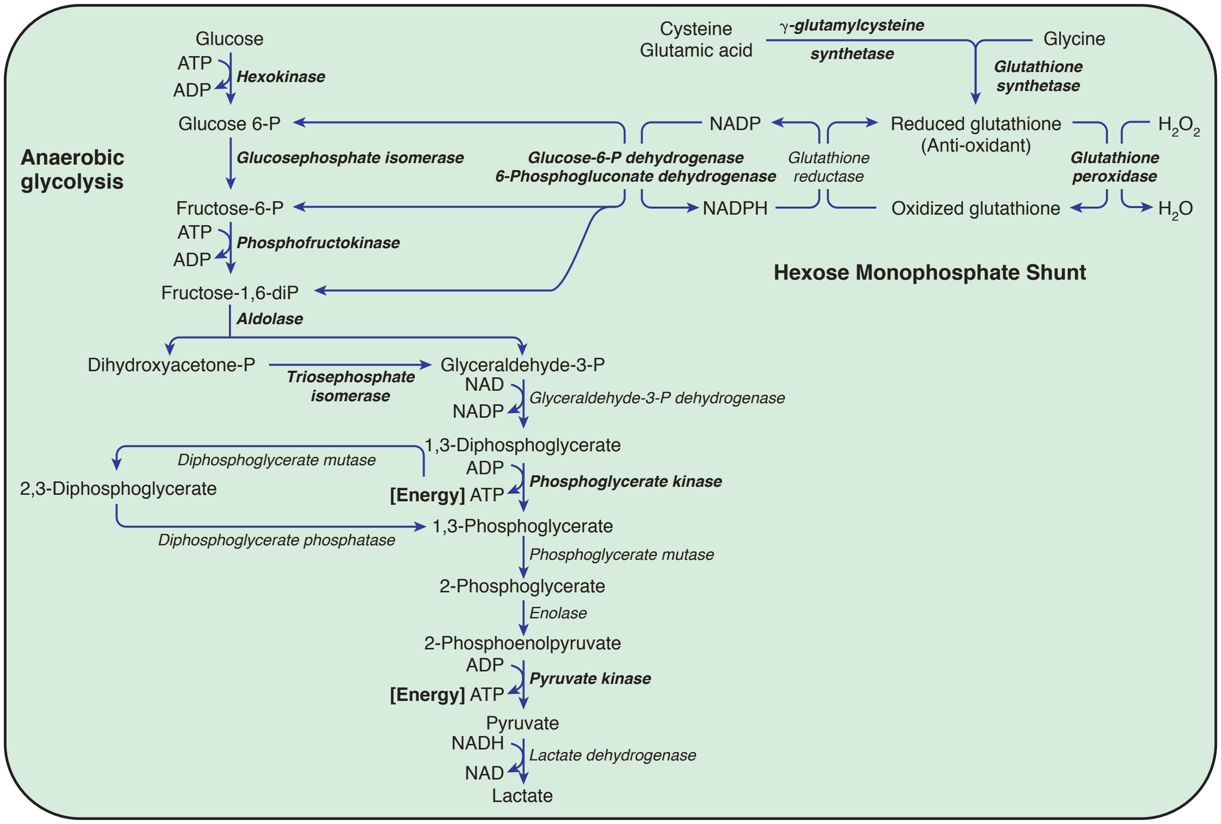

Figure 463-1 Red blood cell metabolism. Glycolysis and the hexose monophosphate pathway. The enzyme deficiencies clearly associated with hemolysis are shown in bold type. ATP, adenosine triphosphate; ADP, adenosine diphosphate; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced form of NADP.

of nicotinamide adenine dinucleotide (NAD^+) are found (Fig. 463-1). The concentration of 2,3-diphosphoglycerate is increased; this isomer is beneficial in facilitating oxygen release from hemoglobin but detrimental in inhibiting hexokinase and enzymes of the hexose monophosphate shunt. In addition, an unexplained decrease occurs in the sum of the adenine (ATP, adenosine diphosphate, and adenosine monophosphate) and pyridine (NAD^+ and the reduced form of NAD) nucleotides, further impairing glycolysis. As a consequence of decreased ATP, RBCs cannot maintain their potassium and water content; the cells become rigid, and their life span is considerably reduced.

ETIOLOGY

There are 2 mammalian PK genes, but only the *PKLR* gene is expressed in red cells. The human *PKLR* gene is located on chromosome 1q21. More than 180 mutations are reported in this structural gene, which codes for a 574–amino-acid protein that forms a functional tetramer. These mutations include missense, splice site, and insertion–deletion alterations, and there is some correlation of the type, location, and amino acid substitution with disease severity. Most affected patients are compound heterozygotes for 2 different PK gene defects. The many possible combinations likely account for the variability in clinical severity. The mutations 1456 C to T and 1529 G to A are the most common mutations in the white population.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

The clinical manifestations of PK deficiency vary from severe neonatal hemolytic anemia to mild, well-compensated hemolysis first noted in adulthood. Severe jaundice and anemia may occur in the neonatal period, and kernicterus has been reported. The hemolysis in older children and adults varies in severity, with hemoglobin values ranging from 8-12 g/dL associated with some pallor, jaundice, and splenomegaly. Patients with these findings usually do not require transfusion. A severe form of the disease has a relatively high incidence among the Amish of the midwestern United States. PK deficiency may possibly provide protection against falciparum malaria.

Polychromatophilia and mild macrocytosis reflect the elevated reticulocyte count. Spherocytes are uncommon, but a few spiculated pyknocytes may be found. Diagnosis relies on demonstration of a marked reduction of RBC PK activity or an increase in the Michaelis-Menten dissociation constant (K_m) for its substrate, phosphoenolpyruvate (high K_m variant). Other RBC enzyme activity is normal or elevated, reflecting the reticulocytosis. No abnormalities of hemoglobin are noted. The white cells have normal PK activity and must be rigorously excluded from the red cell hemolysates used to measure PK activity. Heterozygous carriers usually have moderately reduced levels of PK activity.

TREATMENT

Phototherapy and exchange transfusions may be indicated for hyperbilirubinemia in newborns. Transfusions of packed RBCs are necessary for severe anemia or for aplastic crises. If the anemia is consistently severe and frequent transfusions are required, iron chelation may be necessary, and splenectomy should be performed after the child is 5-6 yr of age. Although it is not curative, splenectomy may be followed by higher hemoglobin levels and by strikingly high (30-60%) reticulocyte counts. Death resulting from overwhelming pneumococcal sepsis has followed splenectomy; thus, immunization with vaccines for encapsulated organisms should be given before splenectomy, and prophylactic penicillin should be administered after the procedure.

463.2 Other Glycolytic Enzyme Deficiencies

George B. Segel

Chronic nonspherocytic hemolytic anemias of varying severity have been associated with deficiencies of other enzymes in the glycolytic pathway, including hexokinase, glucose phosphate isomerase, and aldolase, which are inherited as autosomal recessive disorders. **Phosphofructokinase deficiency,** which occurs primarily in Ashkenazi Jews in the United States, results in hemolysis associated with a myopathy classified as glycogen storage disease type VII (see Chapter 87.1). Clinically, hemolytic anemia is complicated by muscle weakness, exercise intolerance, cramps, and possibly myoglobinuria. Enzyme assays for phosphofructokinase yield low values for RBCs and muscle.

Triose phosphate isomerase deficiency is an autosomal recessive disorder affecting many systems. Affected patients have hemolytic anemia, cardiac abnormalities, and lower motor neuron and pyramidal tract impairment, with or without evidence of cerebral impairment. They usually die in early childhood. The gene for triose phosphate isomerase has been cloned and sequenced and is located on chromosome 12.

Phosphoglycerate kinase (PGK) is the first ATP-generating step in glycolysis. At least 23 kindreds with PGK deficiency have been described. PGK is the only glycolytic enzyme inherited on the X chromosome. Affected males may have progressive extrapyramidal disease, myopathy, seizures, and variable mental retardation in conjunction with hemolytic anemia. Nine Japanese patients had neural or myopathic symptoms with hemolysis; 6 had hemolysis alone; 7 had neural or myopathic symptoms alone; and 1 had no symptoms. The gene for PGK is particularly large, spanning 23 kb, and various genetic abnormalities, including nucleotide substitutions, gene deletions, missense, and splicing mutations, result in PGK deficiency.

DEFICIENCIES OF ENZYMES OF THE HEXOSE MONOPHOSPHATE PATHWAY

The most important function of the hexose monophosphate pathway is to maintain glutathione (GSH) in its reduced state as protection against the oxidation of RBCs (see Fig. 463-1). Approximately 10% of the glucose taken up by RBCs passes through this pathway to provide the reduced form of NAD phosphate (NADPH) necessary for the conversion of oxidized GSH to reduced GSH. Maintenance of reduced GSH is essential for the physiologic inactivation of oxidant compounds, such as hydrogen peroxide, that are generated within RBCs. If glutathione, or any compound or enzyme necessary for maintaining it in the reduced state, is decreased, the SH groups of the RBC membrane are oxidized and the hemoglobin becomes denatured and may precipitate into RBC inclusions called **Heinz bodies**. Once Heinz bodies have formed, an acute hemolytic process results from damage to the RBC membrane by the precipitated hemoglobin, the oxidant agent, and the action of the spleen. The damaged RBCs then are rapidly removed from the circulation.

463.3 Glucose-6-Phosphate Dehydrogenase Deficiency and Related Deficiencies

George B. Segel and Lisa R. Hackney

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, the most frequent disease involving enzymes of the hexose monophosphate pathway, is responsible for 2 clinical syndromes, episodic hemolytic anemia and chronic nonspherocytic hemolytic anemia. The most common manifestations of this disorder are neonatal jaundice and episodic acute hemolytic anemia, which is induced by infections, certain drugs, and, rarely, fava beans. This X-linked deficiency affects more than 400 million people worldwide, representing an overall 4.9% global prevalence. The global distribution of this disorder parallels that of malaria, representing an example of "balanced polymorphism," in which there is an evolutionary advantage of resistance to falciparum malaria in heterozygous females that outweighs the small negative effect of affected hemizygous males.

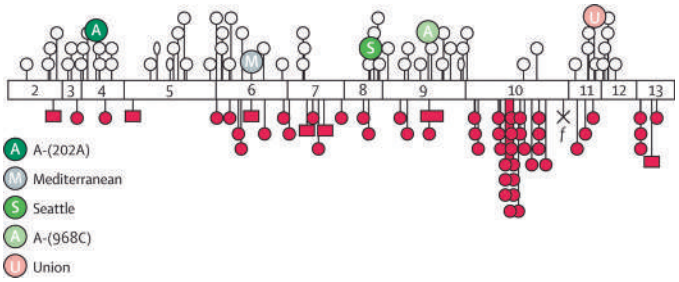

Figure 463-2 Most common mutations along coding sequence of G6PD gene. Exons are shown as *open numbered boxes. Open circles* are mutations causing classes II and III variants. *Filled circles* represent sporadic mutations giving rise to severe variants (class I). *Open ellipses* are mutations causing class IV variants. X a nonsense mutation; *f*, a splice site mutation; *filled square*, small deletion. 202A and 968C are the two sites of base substitution in G6PD-A. *(From Cappellini MD, Fiorelli G: Glucose-6-phosphate dehydrogenase deficiency,* Lancet *371:64–74, 2008.)*

The deficiency is caused by inheritance of any of a large number of abnormal alleles of the gene responsible for the synthesis of the G6PD protein. About 140 mutations have been described in the gene responsible for the synthesis of the G6PD protein. Many of these mutations are single base changes leading to amino acid substitutions and destabilization of the G6PD enzyme. A web-accessible database catalogs G6PD mutations (http://www.bioinf.org.uk/g6pd). Figure 463-2 shows some of the mutations that cause episodic versus chronic hemolysis. Milder disease is associated with mutations near the amino terminus of the G6PD molecule, and chronic nonspherocytic hemolytic anemia is associated with mutations clustered near the carboxyl terminus. The normal enzyme found in most populations is designated G6PD B+. A normal variant, designated G6PD A+, is common in Americans of African descent.

EPISODIC OR INDUCED HEMOLYTIC ANEMIA

Etiology

G6PD catalyzes the conversion of glucose 6-phosphate to 6-phosphogluconic acid. This reaction produces NADPH, which maintains GSH in the reduced, functional state (see Fig. 463-1). Reduced GSH provides protection against oxidant threats from certain drugs and infections that would otherwise cause precipitation of hemoglobin (Heinz bodies) or damage the RBC membrane.

Synthesis of RBC G6PD is determined by a gene on the X chromosome. Thus, heterozygous females have intermediate enzymatic activity and have 2 populations of RBCs: one is normal, and the other is deficient in G6PD activity. Because they have fewer susceptible cells, most heterozygous females do not have evident clinical hemolysis after exposure to oxidant drugs. Rarely, the majority of RBCs is G6PD deficient in heterozygous females because the inactivation of the normal X chromosome is random and sometimes exaggerated (Lyon-Beutler hypothesis).

Disease involving this enzyme therefore occurs more frequently in males than in females. Approximately 13% of male Americans of African descent have a mutant enzyme (**G6PD A–**) that results in a deficiency of RBC G6PD activity (5-15% of normal). Italians, Greeks, and other Mediterranean, Middle Eastern, African, and Asian ethnic groups also have a high incidence, ranging from 5% to 40%, of a variant designated **G6PD B–** (**G6PD Mediterranean**). In these variants, the G6PD activity of homozygous females or hemizygous males is <5% of normal. Therefore, the defect in Americans of African descent is less severe than that in Americans of European descent. A third mutant enzyme with markedly reduced activity (**G6PD Canton**) occurs in approximately 5% of the Chinese population.

Table 463-1 Agents Precipitating Hemolysis in Glucose-6-Phosphate Dehydrogenase Deficiency

MEDICATIONS	Others
Antibacterials	Acetanilide
Sulfonamides	Vitamin K analogs
Dapsone	Methylene blue
Trimethoprim-sulfamethoxazole	Toluidine blue
Nalidixic acid	Probenecid
Chloramphenicol	Dimercaprol
Nitrofurantoin	Acetylsalicylic acid
Antimalarials	Phenazopyridine
Primaquine	Rasburicase
Pamaquine	CHEMICALS
Chloroquine	Phenylhydrazine
Quinacrine	Benzene
Antihelminths	Naphthalene (moth balls)
β-Naphthol	2,4,6-Trinitrotoluene
Stibophen	ILLNESS
Niridazole	Diabetic acidosis
	Hepatitis
	Sepsis

From Asselin BL, Segel GB: In Rakel R, editor: Conn's current therapy, *Philadelphia, 1994, WB Saunders, p. 341.*

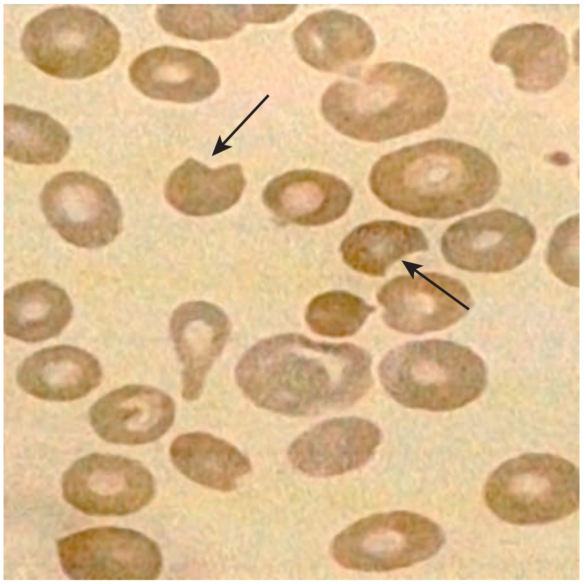

Figure 463-3 **Morphologic erythrocyte changes (anisopoikilocytosis, bite cells) during acute hemolysis in a G6PD-deficient patient.** *Arrows* show bite cells. Anisopoikilocytosis is abnormality in the shape or size of erythrocytes. *(From Cappellini MD, Fiorelli G: Glucose-6-phosphate dehydrogenase deficiency,* Lancet *371:64–74, 2008.)*

Clinical Manifestations

Most individuals with G6PD deficiency are asymptomatic, with no clinical manifestations of illness unless triggered by infection, drugs, or ingestion of fava beans. Typically, hemolysis ensues in about 24-48 hr after a patient has ingested a substance with oxidant properties. In severe cases, hemoglobinuria and jaundice result, and the hemoglobin concentration may fall precipitously. Drugs that elicit hemolysis in these individuals include aspirin, sulfonamides, rasburicase, and antimalarials, such as primaquine (Table 463-1). The degree of hemolysis varies with the inciting agent, amount ingested, and severity of the enzyme deficiency. In some individuals, ingestion of fava beans also produces an acute, severe hemolytic syndrome, known as *favism*. Fava beans contain divicine, isouramil, and convicine, which ultimately lead to production of hydrogen peroxide and other reactive oxygen products. Favism is thought to be more frequently associated with the G6PD B– variant.

In the G6PD A– variant, the stability of the folded protein dimer is impaired, and this defect is accentuated as the RBCs age. Thus, hemolysis decreases as older red cells are destroyed, even if administration of the drug is continued. This recovery results from the age-labile enzyme, which is abundant and more stable in younger RBCs. The associated reticulocytosis produces a compensated hemolytic process in which the blood hemoglobin may be only slightly decreased, despite continued exposure to the offending agent.

G6PD deficiency can produce hemolysis in the neonatal period. In G6PD A–, spontaneous hemolysis and hyperbilirubinemia have been observed in preterm infants. In newborns with the G6PD B– and G6PD Canton varieties, hyperbilirubinemia and even kernicterus may occur. Neonates with coinheritance of G6PD deficiency and a mutation of the promoter of uridine-diphosphate-glucuronyl transferase (UGT1A1), seen in Gilbert syndrome, have more severe neonatal jaundice. When a pregnant woman ingests oxidant drugs, they may be transmitted to her G6PD-deficient fetus, and hemolytic anemia and jaundice may be apparent at birth.

Laboratory Findings

The onset of acute hemolysis usually results in a precipitous fall in hemoglobin and hematocrit. If the episode is severe, the hemoglobin binding proteins, such as haptoglobin, are saturated, and free hemoglobin may appear in the plasma and subsequently in the urine. Unstained or supravital preparations of RBCs reveal precipitated hemoglobin, known as Heinz bodies. The RBC inclusions are not visible on the Wright-stained blood film. Cells that contain these inclusions are seen only within the first 3-4 days of illness because they are rapidly cleared from the blood. Also, the blood film may contain red cells with what appears to be a bite taken from their periphery and polychromasia (evidence of bluish, larger RBCs), representing reticulocytosis (Fig. 463-3).

Diagnosis

The diagnosis depends on direct or indirect demonstration of reduced G6PD activity in RBCs. By direct measurement, enzyme activity in affected persons is ≤10% of normal, and the reduction of enzyme activity is more extreme in Americans of European descent and in Asians than in Americans of African descent. Satisfactory screening tests are based on decoloration of methylene blue, reduction of methemoglobin, or fluorescence of NADPH. Immediately after a hemolytic episode, reticulocytes and young RBCs predominate. These young cells have significantly higher enzyme activity than do older cells in the A– variety (African). Testing may therefore have to be deferred for a few weeks before a diagnostically low level of enzyme can be shown. The diagnosis can be suspected when G6PD activity is within the low-normal range in the presence of a high reticulocyte count. G6PD variants also can be detected by electrophoretic and molecular analysis. G6PD deficiency should be considered in any neonatal patients with hyperbilirubinemia and borderline low G6PD activity.

Prevention and Treatment

Prevention of hemolysis constitutes the most important therapeutic measure. When possible, males belonging to ethnic groups with a significant incidence of G6PD deficiency (e.g., Greeks, southern Italians, Sephardic Jews, Filipinos, southern Chinese, Americans of African descent, and Thais) should be tested for the defect before known oxidant drugs are given. The usual doses of aspirin and trimethoprim-sulfamethoxazole do not cause clinically relevant hemolysis in the A– variety. Aspirin administered in doses used for acute rheumatic fever (60-100 mg/kg/24 hr) may produce a severe hemolytic episode. Infants with severe neonatal jaundice who belong to these ethnic groups also require testing for G6PD deficiency because of their heightened risk for this defect. If severe hemolysis has occurred,

supportive therapy may require blood transfusions, although recovery is the rule when the oxidant agent is discontinued.

CHRONIC HEMOLYTIC ANEMIAS ASSOCIATED WITH DEFICIENCY OF G6PD OR RELATED FACTORS

Chronic nonspherocytic hemolytic anemia has been associated with profound deficiency of G6PD caused by enzyme variants, particularly those defective in quantity, activity, or stability. The gene defects leading to chronic hemolysis are located primarily in the region of the NADP binding site near the carboxyl terminus of the protein (see Fig. 463-2). These include the Loma Linda, Tomah, Iowa, Beverly Hills, Nashville, Riverside, Santiago de Cuba, and Andalus variants. Persons with G6PD B–enzyme deficiency occasionally have chronic hemolysis, and the hemolytic process may worsen after ingestion of oxidant drugs. Splenectomy is of little value in these types of chronic hemolysis.

Other enzyme defects may impair the regeneration of GSH as an oxidant "sump" (see Fig. 463-1). Mild, chronic nonspherocytic anemia has been reported in association with decreased RBC GSH, resulting from γ-glutamylcysteine or GSH synthetase deficiencies. Deficiency of 6-phosphogluconate dehydrogenase has been associated primarily with drug-induced hemolysis, and hemolysis with hyperbilirubinemia has been related to a deficiency of GSH peroxidase in newborn infants.

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Chapter 464

Hemolytic Anemias Resulting from Extracellular Factors—Immune Hemolytic Anemias

Charles H. Packman and George B. Segel

AUTOIMMUNE HEMOLYTIC ANEMIAS

A number of extrinsic agents and disorders may lead to premature destruction of red blood cells (RBCs). Among the most clearly defined are antibodies associated with immune hemolytic anemias. The hallmark of this group of diseases is the positive result of the direct antiglobulin (Coombs) test, which detects a coating of immunoglobulin or components of complement on the RBC surface. The most important immune hemolytic disorder in pediatric practice is hemolytic disease of the newborn (erythroblastosis fetalis), caused by transplacental transfer of maternal antibody active against the RBCs of the fetus, that is, isoimmune hemolytic anemia (see Chapter 103.2). Various other immune hemolytic anemias are autoimmune (Table 464-1) and may be idiopathic or related to various infections (Epstein-Barr virus, and rarely HIV, cytomegalovirus, and mycoplasma), immunologic diseases (systemic lupus erythematosus [SLE], rheumatoid arthritis), immunodeficiency diseases (agammaglobulinemia, autoimmune lymphoproliferative disorder, dysgammaglobulinemias), neoplasms (lymphoma, leukemia, and Hodgkin disease), or drugs (methyldopa, L-dopa). Other drugs (penicillins, cephalosporins) cause hemolysis by means of "drug-dependent antibodies"—that is antibodies directed toward the drug and in some cases toward an RBC membrane antigen as well.

Table 464-1	Diseases Characterized by Immune-Mediated Red Blood Cell Destruction
AUTOIMMUNE HEMOLYTIC ANEMIA CAUSED BY WARM REACTIVE AUTOANTIBODIES	
Primary (idiopathic)	
Secondary	
Lymphoproliferative disorders	
Connective tissue disorders (especially systemic lupus erythematosus)	
Nonlymphoid neoplasms (e.g., ovarian tumors)	
Chronic inflammatory diseases (e.g., ulcerative colitis)	
Immunodeficiency disorders	
AUTOIMMUNE HEMOLYTIC ANEMIA CAUSED BY COLD REACTIVE AUTOANTIBODIES (CRYOPATHIC HEMOLYTIC SYNDROMES)	
Primary (idiopathic) cold agglutinin disease	
Secondary cold agglutinin disease	
Lymphoproliferative disorders	
Infections (*Mycoplasma pneumoniae*, Epstein-Barr virus)	
Paroxysmal cold hemoglobinuria	
Primary (idiopathic)	
Viral syndromes (most common)	
Congenital or tertiary syphilis	
DRUG-INDUCED IMMUNE HEMOLYTIC ANEMIA (see Table 464-2)	
Hapten/drug adsorption (e.g., penicillin)	
Ternary (immune) complex (e.g., quinine or quinidine)	
True autoantibody induction (e.g., methyldopa)	

Modified from Packman CH: Autoimmune hemolytic anemias. In Rakel R, editor: Conn's current therapy, *Philadelphia, 1995, WB Saunders, p. 305.*

AUTOIMMUNE HEMOLYTIC ANEMIAS ASSOCIATED WITH "WARM" ANTIBODIES

Etiology

In the autoimmune hemolytic anemias, autoantibodies are directed against RBC membrane antigens, but the pathogenesis of antibody induction is uncertain. The autoantibody may be produced as an inappropriate immune response to an RBC antigen or to another antigenic epitope similar to an RBC antigen, known as *molecular mimicry.* Alternatively, an infectious agent may alter the RBC membrane so that it becomes "foreign" or antigenic to the host. The antibodies usually react to epitopes (antigens) that are "public" or common to all human RBCs, such as Rh proteins.

In most instances of warm antibody hemolysis, no underlying cause can be found; this is the primary or idiopathic type (see Table 464-1). If the autoimmune hemolysis is associated with an underlying disease, such as a lymphoproliferative disorder, SLE, Evans syndrome, or immunodeficiency, it is secondary. In as many as 20% of cases of immune hemolysis, drugs may be implicated (Table 464-2).

Drugs (penicillin or sometimes cephalosporins) that cause hemolysis via the "hapten" mechanism (immune but not autoimmune) bind tightly to the RBC membrane (see Table 464-1). Antibodies to the drug, either newly or previously formed, bind to the drug molecules on RBCs, mediating their destruction in the spleen. In other cases, certain drugs, such as quinine and quinidine, do not bind to RBCs but, rather, form part of a "ternary complex," consisting of the drug, an RBC membrane antigen, and an antibody that recognizes both (see Table 464-1). Methyldopa and sometimes cephalosporins may, by unknown mechanisms, incite true autoantibodies to RBC membrane antigens, so that the presence of the drug is not required to cause hemolysis. Cephalosporins are the most common cause of drug-immune hemolytic anemia.

Clinical Manifestations

Autoimmune hemolytic anemias may occur in either of 2 general clinical patterns. The first, an acute transient type lasting 3-6 mo and occurring predominantly in children ages 2-12 yr, accounts for 70-80% of patients. It is frequently preceded by an infection, usually respiratory.

Table 464-2 Selected Drugs That Cause Immune-Mediated Hemolysis

MECHANISM	DRUG ADSORPTION (HAPTEN)	TERNARY (IMMUNE) COMPLEX	AUTOANTIBODY INDUCTION
Direct antiglobulin test	Positive (anti-IgG)	Positive (anti-C3)	Positive (anti-IgG)
Site of hemolysis	Extravascular	Intravascular	Extravascular
Medications	Penicillins Cephalosporins 6-mercaptopurine Tetracycline Oxaliplatin Hydrocortisone	Cephalosporins Quinidine Amphotericin B Hydrocortisone Rifampin (Rifadin) Metformin Quinine Probenecid Chlorpromazine Oxaliplatin	α-Methyldopa Cephalosporins Oxaliplatin L-Dopa Procainamide Ibuprofen Diclofenac (Voltaren) Interferon alfa

Ig, immunoglobulin.

Adapted from Packman CH: Hemolytic anemia resulting from immune injury. In Kaushansky K, Lichtman MA, Beutler E, et al, editors: Williams Hematology, *ed 8, New York, 2010, McGraw-Hill, pp. 777–798.*

Onset may be acute, with prostration, pallor, jaundice, fever, and hemoglobinuria, or more gradual, with primarily fatigue and pallor. The spleen is usually enlarged and is the primary site of destruction of immunoglobulin (Ig) G–coated RBCs. Underlying systemic disorders are unusual. A consistent response to glucocorticoid therapy, a low mortality rate, and full recovery are characteristic of the acute form. The other clinical pattern involves a prolonged and chronic course, which is more frequent in infants and in children >12 yr old. Hemolysis may continue for many months or years. Abnormalities involving other blood elements are common, and the response to glucocorticoids is variable and inconsistent. The mortality rate is approximately 10%, and death is often attributable to an underlying systemic disease.

Laboratory Findings

In many cases, anemia is profound, with hemoglobin levels <6 g/dL. Considerable spherocytosis and polychromasia (reflecting the reticulocyte response) are present. More than 50% of the circulating RBCs may be reticulocytes, and nucleated RBCs usually are present. In some cases, a low reticulocyte count may be found, particularly early in the episode. Leukocytosis is common. The platelet count is usually normal, but concomitant immune thrombocytopenic purpura sometimes occurs (**Evans syndrome**). The prognosis for patients with Evans syndrome is guarded, because many have or eventually have a chronic disease, including SLE, an immunodeficiency syndrome, or the autoimmune lymphoproliferative syndrome.

Results of the direct antiglobulin test are strongly positive, and free antibody can sometimes be demonstrated in the serum (indirect Coombs test). These antibodies are active at 35-40°C (95-104°F) ("warm" antibodies) and most often belong to the IgG class. They do not require complement for activity and are usually *incomplete* antibodies that do not produce agglutination in vitro. Antibodies from the serum and those eluted from the RBCs react with the RBCs of many persons in addition to those of the patient. They often have been regarded as nonspecific panagglutinins, but careful studies have revealed specificity for RBC antigens of the Rh system in 70% of patients (≈50% of adult patients). Complement, particularly fragments of C3b, may be detected on the RBCs in conjunction with IgG. The Coombs test result is *rarely* negative *because of* the limited sensitivity of the Coombs reaction. A minimum of 260-400 molecules of IgG per cell is necessary on the RBC membrane to produce a positive reaction. Special tests are required to detect the antibody in cases of "Coombs-negative" autoimmune hemolytic anemia. In warm antibody hemolytic anemia, the direct Coombs test may detect IgG alone, both IgG– and complement fragments, or solely complement fragments if the level of RBC-bound IgG is below the detection limit of the anti-IgG Coombs reagent.

Treatment

Transfusions may provide only transient benefit but may be lifesaving in cases of severe anemia by providing delivery of oxygen until the effect of other treatment is observed. All tested units for transfusion are serologically incompatible. It is important to identify the patient's ABO blood group to avoid a hemolytic transfusion reaction mediated by anti-A or anti-B. The blood bank should also test for the presence of an underlying alloantibody, which could cause rapid hemolysis of transfused red cells. Patients who have neither been previously transfused nor pregnant are unlikely to harbor an alloantibody. Early consultation between the clinician and the blood bank physician is essential. Failure to transfuse a profoundly anemic infant or child may lead to serious morbidity and even death.

Patients with mild disease and compensated hemolysis may not require any treatment. If the hemolysis is severe and results in significant anemia or symptoms, treatment with glucocorticoids is initiated. Glucocorticoids decrease the rate of hemolysis by blocking macrophage function by downregulating Fcγ receptor expression, decreasing the production of the autoantibody, and perhaps enhancing the elution of antibody from the RBCs. Prednisone or its equivalent is administered at a dose of 2 mg/kg/24 hr. In some patients with severe hemolysis, doses of prednisone of up to 6 mg/kg/24 hr may be required to reduce the rate of hemolysis. Treatment should be continued until the rate of hemolysis decreases, and then the dose gradually reduced. If relapse occurs, resumption of the full dosage may be necessary. The disease tends to remit spontaneously within a few weeks or months. The Coombs test result may remain positive even after the hemoglobin level returns to normal. It is usually safe to discontinue prednisone once the direct Coombs test result becomes negative. When hemolytic anemia remains severe despite glucocorticoid therapy, or if very large doses are necessary to maintain a reasonable hemoglobin level, IV immunoglobulin may be tried. Rituximab, a monoclonal antibody that targets B lymphocytes, the source of antibody production, is useful in chronic cases refractory to conventional therapy. Plasmapheresis has been used in refractory cases but generally is not helpful. Splenectomy may be beneficial but is complicated by a heightened risk of infection with encapsulated organisms, particularly in patients <6 yr. Prophylaxis with appropriate vaccines (pneumococcal, meningococcal, and *Haemophilus influenzae* type b) before splenectomy and with oral penicillin after splenectomy are indicated.

Course and Prognosis

Acute idiopathic autoimmune hemolytic disease in childhood varies in severity but is self-limited; death from untreatable anemia is rare. Approximately 30% of patients have chronic hemolysis, often associated with an underlying disease, such as SLE, lymphoma, or leukemia.

The presence of antiphospholipid antibodies in adult patients with immune hemolysis predisposes to thrombosis. Mortality in chronic cases depends on the primary disorder.

AUTOIMMUNE HEMOLYTIC ANEMIAS ASSOCIATED WITH "COLD" ANTIBODIES

"Cold" antibodies agglutinate RBCs at temperatures <37°C (98.6°F). They are primarily of the IgM class and require complement for hemolytic activity. The highest temperature at which RBC agglutination occurs is called the *thermal amplitude.* A higher thermal amplitude antibody—that is, one that can bind to RBCs at temperatures achievable in the body—results in hemolysis with exposure to a cold environment. High antibody titers are associated with a high thermal amplitude.

Cold Agglutinin Disease

Cold antibodies usually have specificity for the oligosaccharide antigens of the I/i system. They may occur in primary or idiopathic cold agglutinin disease, secondary to infections such as those from *Mycoplasma pneumoniae* and Epstein-Barr virus, or secondary to lymphoproliferative disorders. After *M. pneumoniae* infection, the anti-I levels may increase considerably, and occasionally, enormous increases may occur to titers ≥1/30,000. The antibody has specificity for the I antigen and thus reacts poorly with human cord RBCs, which possess the i antigen but exhibit low levels of I. Patients with infectious mononucleosis occasionally have cold agglutinin disease, and the antibodies in these patients often have anti-i specificity. This antibody causes less hemolysis in adults than in children because adults have fewer i molecules on their RBCs. Spontaneous RBC agglutination is observed in the cold and in vitro, and RBC aggregates are seen on the blood film. Mean corpuscular volume may be spuriously elevated because of RBC agglutination. The severity of the hemolysis is related to the thermal amplitude of the antibody, which itself partly depends on the IgM antibody titer.

When very high titers of cold antibodies are present and active near body temperature, severe intravascular hemolysis with hemoglobinemia and hemoglobinuria may occur and may be heightened on a patient's exposure to cold (external temperature or ingested foods). Each IgM molecule has the potential to activate a C1 molecule so that large amounts of complement are found on the RBCs in cold agglutinin disease. These sensitized RBCs may undergo intravascular complement-mediated lysis or may be destroyed in the liver and spleen. Only complement, not IgM, is detected on RBCs because the IgM is removed during the washing steps of the direct antiglobulin test.

Cold agglutinin disease is less common in children than in adults and more frequently results in an acute, self-limited episode of hemolysis. Glucocorticoids are much less effective in cold agglutinin disease than in disease with warm antibodies. Patients should avoid exposure to cold and should be treated for underlying disease. In the uncommon patients with severe hemolytic disease, treatment includes immunosuppression and plasmapheresis. Successful treatment of cold agglutinin disease has been reported with the monoclonal antibody rituximab, which effectively depletes B lymphocytes. Splenectomy is not useful in cold agglutinin disease.

Paroxysmal Cold Hemoglobinuria

Paroxysmal cold hemoglobinuria is mediated by the Donath-Landsteiner (D-L) hemolysin, which is an IgG cold-reactive autoantibody with anti-P specificity. In vitro, the D-L antibody binds to RBCs in the cold and the RBCs are lysed by complement as the temperature is increased to 37 degrees C. A similar sequence is thought to occur in vivo as RBCs move from the cooler extremities to warmer parts of the circulation. Most reported cases are self-limited; many patients experience only one paroxysm of hemolysis. Congenital or acquired syphilis used to be the most common underlying cause of paroxysmal cold hemoglobinuria, but today, most cases are associated with nonspecific viral infections. This disorder accounts for 30% of immune hemolytic episodes among children. Treatment includes transfusion for severe anemia and avoidance of cold ambient temperatures.

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Chapter 465

Hemolytic Anemias Secondary to Other Extracellular Factors

George B. Segel

FRAGMENTATION HEMOLYSIS

(See Table 457-1 in Chapter 457.)

Red blood cell (RBC) destruction may occur in hemolytic anemias because of mechanical injury as the cells traverse a damaged vascular bed. Damage may be microvascular when RBCs are sheared by fibrin in the capillaries during intravascular coagulation or when renovascular disease accompanies the hemolytic-uremic syndrome (HUS) (see Chapter 518) or thrombotic thrombocytopenic purpura (see Chapter 484.5). Larger vessels may be involved in Kasabach-Merritt syndrome (giant hemangioma and thrombocytopenia; see Chapter 505) or when a replacement heart valve is poorly epithelialized. The blood film shows many "schistocytes," or fragmented cells, as well as polychromatophilia, reflecting the reticulocytosis (see Fig. 458-4*F* in Chapter 458). Secondary iron deficiency may complicate the intravascular hemolysis because of urinary hemoglobin and hemosiderin iron loss (see Fig. 457-2 in Chapter 457). Treatment should be directed toward the underlying condition, and the prognosis depends on the effectiveness of this treatment. The benefit of transfusion may be transient because the transfused cells are destroyed as quickly as those produced by the patient.

It is critical to determine the precise etiology of the fragmentation hemolysis because the treatment depends on the underlying problem (Table 465-1). Thrombotic thrombocytopenic purpura results from an antibody to an enzyme (AdamTS13) that regulates the size of von Willebrand multimers. The lack of this enzyme results in a marked increase in multimer size and a resultant thrombotic microangiopathy. The treatment involves plasmapheresis (PLEX) to remove the antibody and replace the AdamTS13. In contrast, HUS results from *Shiga* toxin produced by *Escherichia coli* 0157 and may not be helped by PLEX. Atypical HUS involves activation of the alternative complement pathway and is currently treated with eculizumab (anti C5), an inhibitor of the complement pathway. PLEX may reduce the RBC fragmentation and improve the platelet count but has little effect on the tissue (kidney) vasculopathy and thus is not usually recommended. Pneumococcal-induced HUS results from neuraminidase produced by the bacteria, which damages the membranes of the RBCs and the kidney, exposing the T-antigen. Plasma contains natural antibody to the T-antigen producing hemolysis, renal damage, and a thrombotic microangiopathy.

THERMAL INJURY

Extensive burns may directly damage the RBCs and cause hemolysis that results in the formation of spherocytes. Blood loss and marrow suppression may contribute to anemia and require blood transfusion. Erythropoietin (EPO) has been used as treatment for diminished RBC production.

RENAL DISEASE

The anemia of uremia is multifactorial in origin. EPO production may be decreased and the marrow suppressed by toxic metabolites. Furthermore, the RBC life span often is shortened owing to retention of

Table 465-1 Thrombotic Microangiopathies

DISEASE*	PATHOPHYSIOLOGY	LAB FINDINGS	MANAGEMENT
TTP	Ab to AdamTS13	AdamTS13 <10%[†] Ab to AdamTS13	PLEX with plasma
HUS	*E. coli* 0157, *Shiga* toxin	*E. coli* 0157, *Shiga* toxin	Supportive ? value of PLEX
aHUS	Complement-mediated alternative pathway	AdamTS13 >10% Decreased factors H and I (inhibitors of complement)[‡]	Eculizumab (ab to C5) PLEX not indicated
Pneumococcal-induced HUS	Neuraminidase-induced RBC, platelet, and kidney damage Exposure of T-antigen on RBC and kidney	Pneumococcal infection AdamTS13 >10%	PLEX with albumin for neuraminidase and endogenous T ab removal
DIC	Sepsis, shock, endotoxin	Decreased fibrinogen, increased fibrin split products, decreased clotting factors and platelets	Treat underlying condition; replace factors and platelets if bleeding

*All show fragmentation hemolytic anemia, thrombocytopenia and potential renal and other organ damage. An elevated lactate dehydrogenase and reduced haptoglobin usually are present secondary to hemolysis.
†Rarely a congenital defect in AdamTS13.
‡May be related to inherited defect in factor H or I.
Ab/ab, antibody; aHUS, atypical hemolytic uremic syndrome; DIC, disseminated intravascular coagulation; *E. coli*, *Escherichia coli*; HUS, hemolytic uremic syndrome; PLEX, plasmapheresis; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura.

metabolites and organic acidemia. The use of EPO in chronic renal disease has markedly decreased the need for blood transfusion.

LIVER DISEASE

A change in the ratio of cholesterol to phospholipids in the plasma may result in changes in the composition of the RBC membrane and shortening of the RBC life span. Some patients with liver disease have many target RBCs on the blood film, whereas others have a preponderance of spiculated cells. These morphologic changes reflect the alterations in the plasma lipid composition.

TOXINS AND VENOMS

Bacterial sepsis caused by *Haemophilus influenzae*, staphylococci, or streptococci may be complicated by accompanying hemolysis. Particularly severe hemolytic anemia has been observed in clostridial infections and results from a hemolytic clostridial toxin. Large numbers of spherocytes may be seen on the blood film. Spherocytic hemolysis also may be noted after bites by various snakes, including cobras, vipers, and rattlesnakes, which have phospholipases in their venom. Large numbers of bites by insects, such as bees, wasps, and yellow jackets, also may cause spherocytic hemolysis by a similar mechanism (see Chapter 725).

WILSON DISEASE

(See Chapter 357.2.)

An acute and self-limited episode of hemolytic anemia may precede by years the onset of hepatic or neurologic symptoms in Wilson disease. This event appears to result from the toxic effects of free copper on the RBC membrane. The blood film often (but not always) shows large numbers of spherocytes, and the Coombs test result is negative. Because early diagnosis of Wilson disease permits prophylactic treatment with penicillamine and prevention of hepatic and neurologic disease, correct assessment of this rare type of hemolysis is important.

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Section 4

Polycythemia (Erythrocytosis)

Chapter 466

Polycythemia

Amanda M. Brandow and Bruce M. Camitta

Polycythemia exists when the red blood cell (RBC) count, hemoglobin level, and total RBC volume all exceed the upper limits of normal. In postpubertal individuals, an RBC mass >25% above the mean normal value (based on body surface area) or a hemoglobin >18.5 g/dL (in males) or >16.5 g/dL (in females) indicate absolute erythrocytosis. A decrease in plasma volume, such as occurs in acute dehydration and burns, may result in a high hemoglobin value. These situations are more accurately designated as *hemoconcentration* or *relative polycythemia* because the RBC mass is not increased and normalization of the plasma volume restores hemoglobin to normal levels. Once the diagnosis of true polycythemia is made, sequential studies should be done to determine the underlying etiology (Fig. 466-1).

CLONAL (PRIMARY) POLYCYTHEMIA (POLYCYTHEMIA RUBRA VERA)

Pathogenesis

Polycythemia vera is an acquired clonal myeloproliferative disorder. Although primarily manifesting as erythrocytosis, thrombocytosis and leukocytosis can also be seen. When isolated severe thrombocytosis exists in the absence of erythrocytosis, the myeloproliferative disorder is called *essential thrombocythemia*. Polycythemia vera is rare in children. A gain-of-function mutation of *JAK2,* a cytoplasmic tyrosine kinase, is found in more than 90% of adult patients with polycythemia vera, but in <30% of children with this condition. The erythropoietin

Table 466-1	WHO Diagnostic Criteria for Polycythemia Vera
MAJOR CRITERIA 1. Hb >18.5 g/dL (men) or Hb >16.5 g/dL (women) *or* Hb or Hct >99th percentile of reference range for age, sex, or altitude of residence *or* Hb >17 g/dL (men) or Hb >15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that cannot be attributed to correction of iron deficiency *or* elevated red cell mass >25% above mean normal predicted value 2. Presence of *JAK2* or similar mutation	
MINOR CRITERIA 1. Bone marrow trilineage myeloproliferation 2. Subnormal serum erythropoietin level 3. Endogenous erythroid colony growth	
DIAGNOSIS Both major criteria and one minor criteria *or* first major criteria and 2 minor criteria.	

Hb, hemoglobin; Hct, hematocrit.
From Tefferi A, Vardiman JW: Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia *22:14–22, 2008.*

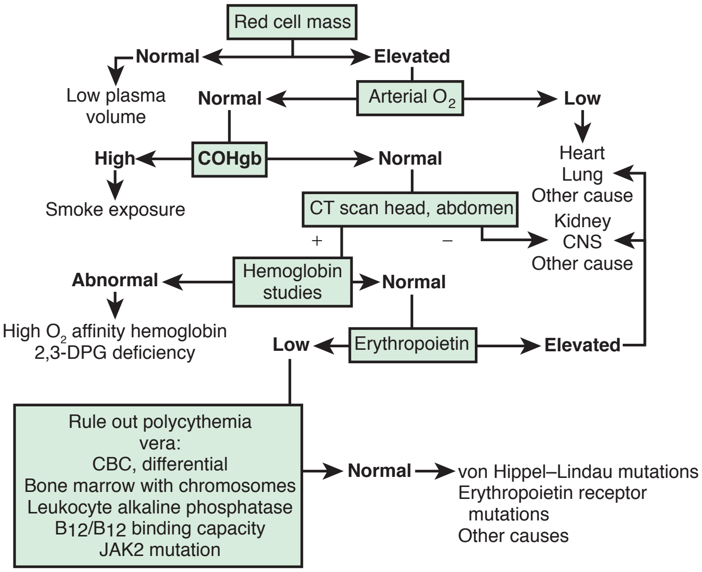

Figure 466-1 **Sequential studies to evaluate polycythemia.** CBC, complete blood count; CNS, central nervous system; COHgb, carboxyhemoglobin; 2,3-DPG, 2,3-diphosphoglycerate.

receptor is normal, and serum erythropoietin levels are normal or low. In vitro cultures do not require added erythropoietin to stimulate growth of erythroid precursors. Risk factors for development of polycythemia vera include a family history of polycythemia vera and presence of an autoimmune disorder such as Crohn disease.

Clinical Manifestations

Patients with polycythemia vera usually have hepatosplenomegaly. Erythrocytosis may cause hypertension, headache, shortness of breath, or neurologic symptoms and increases the risk of thrombosis. Granulocytosis may cause diarrhea or pruritus from histamine release. Thrombocytosis (with or without platelet dysfunction) may cause thrombosis or hemorrhage. Table 466-1 lists the diagnostic criteria for polycythemia vera.

Treatment

Phlebotomy is the initial treatment of choice to alleviate symptoms of hyperviscosity and decrease the risk of thrombosis. Iron supplementation should be given to prevent viscosity problems from iron-deficient microcytosis or thrombocytosis. In patients with marked thrombocytosis, antiplatelet agents (e.g., aspirin) may reduce the risks of thrombosis and bleeding. If these treatments are unsuccessful or the patient has progressive hepatosplenomegaly, antiproliferative treatments (hydroxyurea, anagrelide, interferon-α) may be helpful. The use of JAK2 inhibitors is an active area of investigation. Transformation of the disease into myelofibrosis or acute leukemia is rare in children. Prolonged survival is not unusual.

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Chapter 467

Non-Clonal Polycythemia

Amanda M. Brandow and
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PATHOGENESIS

Nonclonal polycythemia is diagnosed when polycythemia is caused by a physiologic process that is not derived from a single cell (Table 467-1). Nonclonal polycythemia can be congenital or acquired (secondary).

Congenital Polycythemia

Lifelong or familial polycythemia should trigger a search for a congenital problem. These inherited conditions may be transmitted as dominant or recessive disorders. Autosomal dominant causes include hemoglobins that have increased oxygen affinity (P_{50} [partial pressure of oxygen in the blood at which the hemoglobin is 50% saturated] <20 mm Hg), erythropoietin receptor mutations resulting in an enhanced effect of erythropoietin or mutations in the von Hippel–Lindau gene that result in altered intracellular oxygen sensing. Another rare cause is autosomal recessive 2,3-ddiphosphoglyceric acid deficiency, which leads to a left shift of the oxygen dissociation curve, increased oxygen affinity, and consequent polycythemia.

Table 467-1	Differential Diagnosis of Polycythemia

CLONAL (PRIMARY)
Polycythemia vera

NONCLONAL
Congenital
High-oxygen affinity hemoglobinopathy (e.g., hemoglobin Chesapeake, Malmo, San Diego)
Erythropoietin receptor mutations (primary familial and congenital polycythemia [PFCP])
Methemoglobin reductase deficiency
Hemoglobin M disease
2,3-Diphosphoglycerate deficiency
Acquired
Hormonal
- Adrenal disease
  - Virilizing hyperplasia, Cushing syndrome
- Anabolic steroid therapy
- Malignant tumors
  - Adrenal, cerebellar, hepatic, other
- Renal disease
  - Cysts, hydronephrosis, renal artery stenosis

Hypoxia
- Altitude
- Cardiac disease
- Lung disease
- Central hypoventilation
- Chronic carbon monoxide exposure

Neonatal
Delayed cord clamping (placental-fetal transfusion)
- Normal intrauterine environment
- Placental insufficiency (preeclampsia, maternal chronic hypertension, placental abruption)
- Twin–twin or maternal–fetal hemorrhage
- Perinatal asphyxia
- Infants of diabetic mothers
- Intrauterine growth retardation
- Trisomy 13, 18, or 21
- Adrenal hyperplasia
- Thyrotoxicosis

Spurious
Plasma volume decrease

Subtle decreases in oxygen delivery to tissues may cause polycythemia. Congenital methemoglobinemia resulting from an autosomal recessive deficiency of cytochrome b5 reductase may cause cyanosis and polycythemia (see Chapter 462.7). Most affected individuals are asymptomatic. Neurologic abnormalities may be present in patients whose enzyme deficits are not limited to hematopoietic cells. Hemoglobin M disease (autosomal dominant) causes methemoglobinemia and can lead to polycythemia. Cyanosis may occur in the presence of as little as 1.5 g/dL of methemoglobin but is uncommon in other hemoglobin variants unless hyperviscosity results in localized hypoxemia.

Acquired Polycythemia

Polycythemia may be present in clinical situations associated with chronic arterial oxygen desaturation. Cardiovascular defects involving right-to-left shunts and pulmonary diseases interfering with proper oxygenation are the most common causes of hypoxic polycythemia. Clinical findings usually include cyanosis, hyperemia of the sclerae and mucous membranes, and clubbing of the fingers. As the hematocrit rises to >65%, clinical manifestations of hyperviscosity, such as headache and hypertension, may require phlebotomy. Living at high altitudes also causes hypoxic polycythemia; the hemoglobin level increases approximately 4% for each rise of 1,000 m in altitude. Partial obstruction of a renal artery rarely results in polycythemia. Polycythemia has also been associated with benign and malignant tumors that secrete erythropoietin. Exogenous or endogenous excess of anabolic steroids also may cause polycythemia. A common spurious cause is a decrease in plasma volume such as in moderate to severe dehydration.

DIAGNOSIS

Figure 466-1 outlines sequential studies to evaluate polycythemia.

TREATMENT

For mild disease, observation is sufficient. When the hematocrit is >65-70% (hemoglobin >23 g/dL), blood viscosity markedly increases. Periodic phlebotomy may prevent or decrease symptoms such as headache, dizziness, or exertional dyspnea. Apheresed blood should be replaced with plasma or saline to prevent hypovolemia in patients accustomed to a chronically elevated total blood volume. Increased demand for red blood cell production may cause iron deficiency. Iron-deficient microcytic red cells are more rigid, further increasing the risk of intracranial and other thromboses in patients with polycythemia. Periodic assessment of iron status, with treatment of iron deficiency, should be performed.

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Section 5

The Pancytopenias

Chapter 468

The Inherited Pancytopenias

Yigal Dror and Melvin H. Freedman

Pancytopenia refers to a reduction below normal values of all 3 peripheral blood lineages: leukocytes, platelets, and erythrocytes. Pancytopenia requires microscopic examination of a bone marrow biopsy specimen and a marrow aspirate to assess overall cellularity and morphology. There are 3 general categories of pancytopenia depending on the marrow findings.

Hypocellular marrow on biopsy is seen with inherited ("constitutional") marrow failure syndromes, acquired aplastic anemia of varied etiologies (see Chapter 469), the hypoplastic variant of myelodysplastic syndrome (MDS), and some cases of paroxysmal nocturnal hemoglobinuria with pancytopenia.

Cellular marrow is seen (a) with primary bone marrow disease, such as acute leukemia (see Chapter 494), and MDS, and (b) secondary to systemic disease, such as autoimmune disorders (systemic lupus erythematosus; Chapter 158), vitamin B_{12} or folate deficiency (see Chapters 49.6 and 49.7), storage disease (Gaucher and Niemann-Pick diseases; see Chapter 86.4), overwhelming infection, sarcoidosis, and hypersplenism.

Bone marrow infiltration can cause pancytopenia in metastatic solid tumors, myelofibrosis, hemophagocytic lymphohistiocytosis (see Chapter 507) and osteopetrosis (see Chapter 699).

Inherited ("constitutional") pancytopenia is defined as a decrease in marrow production of the 3 major hematopoietic lineages that occurs on an inherited basis, resulting in anemia, neutropenia, and thrombocytopenia. Any of these conditions (Tables 468-1 and 468-2) can be transmitted as a simple mendelian disorder by mutant genes with inherited patterns of autosomal dominant, autosomal recessive, or X-linked types. Modifying genes and acquired factors may also be operative. Inherited pancytopenias account for approximately 30% of cases of pediatric marrow failure. Fanconi anemia is the most common of these disorders.

FANCONI ANEMIA

Etiology and Epidemiology

Fanconi anemia (FA) is primarily inherited in an autosomal recessive manner (one uncommon form is X-linked recessive). It occurs in all racial and ethnic groups. At presentation, patients with FA may have: (1) typical physical anomalies and abnormal hematologic findings (majority of the patients); (2) normal physical features but abnormal hematologic findings (about one-third of patients); or (3) physical anomalies and normal hematologic findings (unknown percentage). There can be sibling discordance in clinical and hematologic findings, even in affected monozygotic twins. Approximately 75% of patients are 3-14 yr of age at the time of diagnosis.

Table 468-1 Inherited Pancytopenia Syndromes

Fanconi anemia
Shwachman-Diamond syndrome
Dyskeratosis congenita
Congenital amegakaryocytic thrombocytopenia
Reticular dysgenesis
Unclassified inherited bone marrow failure syndromes
Other genetic syndromes
Down syndrome
Dubowitz syndrome
Seckel syndrome
Schimke immunoosseous dysplasia
Cartilage-hair hypoplasia
Noonan syndrome

Pathology

Patients have abnormal chromosome fragility, which is seen in metaphase preparations of peripheral blood lymphocytes cultured with phytohemagglutinin and enhanced by adding clastogenic agents such as diepoxybutane (DEB) and mitomycin C. Cell fusion of FA cells with normal cells or with cells from some unrelated patients with FA produces a corrective effect on chromosomal fragility, a process called *complementation.* This phenomenon allows subtyping of cases of FA into discrete complementation groups. Fifteen different complementation groups have been identified with different FA (*FANC*) genes that are mutated in each of them: A, B, C, D1/BRCA2, D2, E, F, G, I, J, L, M, N, O, P). An additional 2 genes, *XRCC2* and *ECCR4,* have been published and need further studies. After their discovery, the genes are prefixed with *FANC* (*FANCA*, *FANCB,* and so on). *FANCD1* is identical to the breast cancer susceptibility gene, *BRCA2.* The protein products of wild-type *FANC* genes are involved in the DNA damage recognition and repair biochemical pathways. Therefore, mutant gene proteins lead to genomic instability and chromosome fragility. An inability of FA cells to remove oxygen-free radicals, resulting in oxidative damage, is an additional mechanism that may contribute to the disease pathogenesis. Leukocyte telomere length is significantly shortened but telomerase activity is increased, suggesting a high proliferative rate of marrow progenitors that ultimately leads to their premature senescence. Increased marrow cell apoptosis occurs and is

Table 468-2 Distinguishing Clinical Features of the Inherited Bone Marrow Failure Syndromes That May Be Initially Diagnosed in Adulthood

Distinguishing Features	DISEASES		
	Fanconi Anemia	**Dyskeratosis Congenita**	**Schwachman-Diamond Anemia**
History	Skeletal and renal malformations, low birthweight, pancytopenia, family member with bone marrow failure, MDS, acute myelogenous leukemia (AML), or squamous cell carcinoma at an early age; family member with Fanconi anemia	Intrauterine growth retardation, developmental delay, and short stature. Family history of MDS, AML, marrow failure, abnormal fingernails or toenails, leukoplakia, head and neck cancer, or pulmonary fibrosis	Pancreatic insufficiency, low birth weight, metaphyseal dysostosis, initial neutropenia, delayed development
Physical findings	Thumb and radial malformations, hyperpigmented skin lesions (café-au-lait spots), short stature, MDS, AML, squamous cell carcinoma at young age, renal and cardiac malformations, microcephaly, hypogonadism	Lacy reticular pigmentation of skin, dystrophic fingernails and toenails, premature graying of hair, hair loss, short stature, oral leukoplakia, squamous cell cancer of head and neck, pulmonary fibrosis, osteopenia, hypogonadism	Short stature, abnormal thorax
Genes inactivated	*FANCA, FANCB, FANCC, FANCD1* (aka *BRCA2*), *FANCD2, FANCE, FANCF, FANCG* (aka *XRCC9*), *FANCI, FANCJ* (aka *BACH1* and *BRIP1*), *FANCL* (aka *PHF9* and *POG*), *FANCM* (aka *Hef*), and *FANCN* (aka *PALB2*) These genes encode proteins known to protect the genome from excessive damage induced by chemical crosslinking agents. These genes account for most cases of Fanconi anemia	*DKC1, TERC, TERT, TINF2, NOLA2,* and *NOLA3* These genes encode proteins known to participate in maintenance of telomeres. They account for only half of dyskeratosis cases, so there are additional genes to be discovered	*SBDS* autosomal recessive marrow clonal expansion in ~15%
Screening and diagnostic tests	1. Chromosomal breakage test (in response to mitomycin C or diepoxybutane) 2. Complementation analysis (flow cytometric analysis of G_2 arrest in melphalan-exposed cells after transduction with retroviral vectors expressing normal Fanconi anemia genes) 3. Gene sequencing	1. Quantitative analysis of telomere length ("flow FISH") 2. Gene sequencing	CT demonstrates fatty infiltration of pancreas Gene testing May evolve to myelodysplasia or leukemia Absence of pancreatic lipomatosis, fecal fat, or dysostosis does not rule out diagnosis

ADA, adenosine deaminase; FISH, fluorescent in situ hybridization.

Modified from Bagby GC: Aplastic anemia and related bone marrow failure states. In Goldman L, Schafer AI, editors, Goldman's Cecil medicine, *ed 24, Philadelphia, 2012, WB Saunders, Table 168-3, p. 1086.*

mediated by Fas, a membrane glycoprotein receptor containing an integral death domain. A consistent finding is diminished cellular interleukin-6 production along with markedly heightened tumor necrosis factor-α generation.

Clinical Manifestations

The most common anomaly in FA is hyperpigmentation of the trunk, neck, and intertriginous areas, as well as café-au-lait spots and vitiligo, alone or in combination (Fig. 468-1 and Table 468-3). Half the patients have short stature. In some patients, growth failure is aggravated by abnormal growth hormone secretion or with hypothyroidism. Absence of radii and thumbs that are hypoplastic, supernumerary, bifid, or absent are common. The "r" radial pulse may be weak or absent. Anomalies of the feet, congenital hip dislocation, and leg abnormalities are seen. A male patient with FA may have an underdeveloped penis; undescended, atrophic, or absence of the testes; and hypospadias or phimosis. Females can have malformations of the vagina, uterus, and ovary. Many patients have a FA "facies," including microcephaly, small eyes, epicanthal folds, and abnormal shape, size, or positioning of the ears (Fig. 468-1). Ectopic, pelvic, or horseshoe kidneys are detected by imaging and may show other organs as duplicated, hypoplastic, dysplastic, or absent kidneys. Cardiovascular and gastrointestinal malformations also occur. Approximately 10% of patients with FA are cognitively delayed.

Table 468-3 Characteristic Physical Anomalies in Fanconi Anemia

ANOMALY	APPROXIMATE FREQUENCY (% OF PATIENTS)
Skin pigment changes ± café-au-lait spots	55
Short stature	51
Upper limb abnormalities (thumbs, hands, radii, ulnas)	43
Hypogonadal and genital changes (mostly male)	35
Other skeletal findings (head/face, neck, spine)	30
Eye/lid/epicanthal fold anomalies	23
Renal malformations	21
Gastrointestinal/cardiopulmonary malformations	11
Hip, leg, foot, toe abnormalities	10
Ear anomalies (external and internal), deafness	9

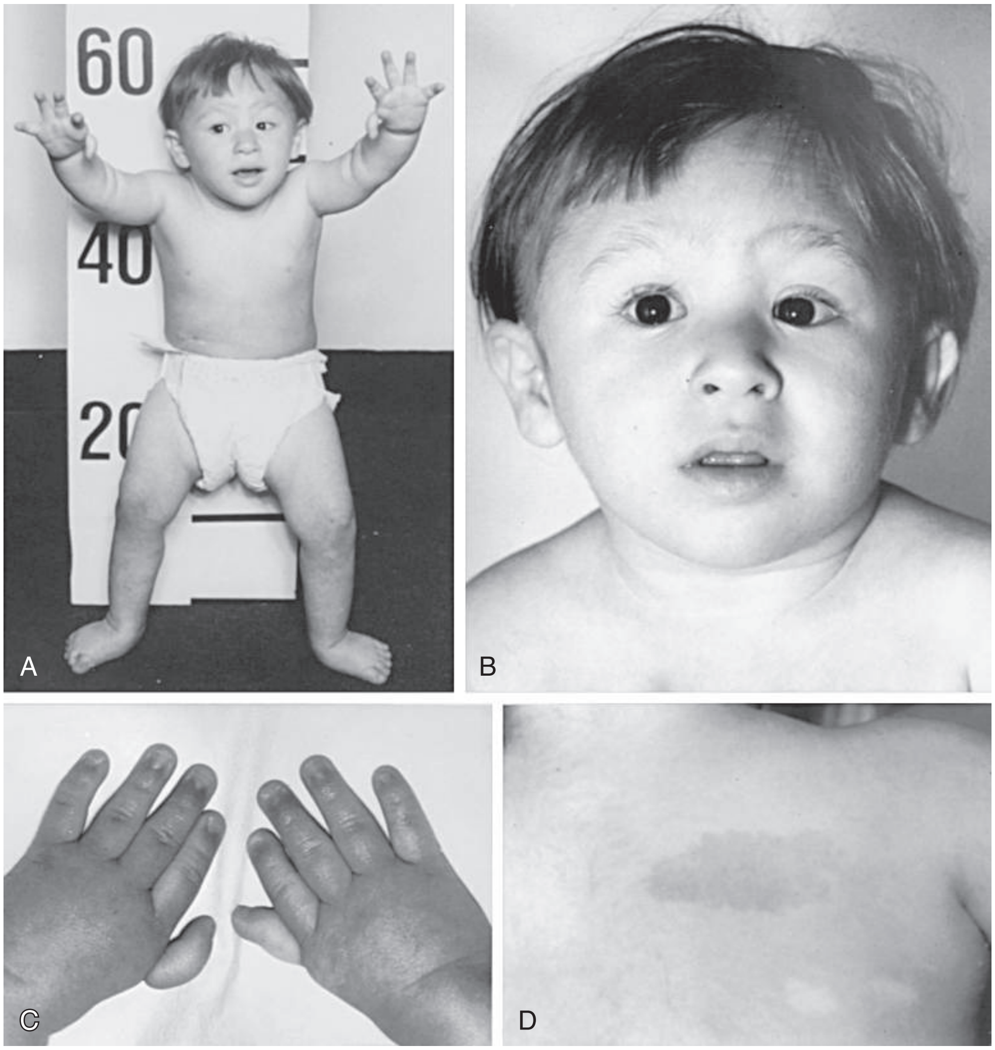

Figure 468-1 A 3 yr old boy with Fanconi anemia who exhibits several classic phenotype features. **A,** Front view. **B,** Face. **C,** Hands. **D,** Back right shoulder. The features to be noted include short stature, dislocated hips, microcephaly, a broad nasal base, epicanthal folds, micrognathia, thumbs attached by a thread, and café-au-lait spots with hypopigmented areas beneath. *(From Nathan DC, Orkin SH, Ginsburg D, et al, editors:* Nathan and Oski's hematology of infancy and childhood, *ed 6, vol I, Philadelphia, 2003, WB Saunders, p. 285.)*

Laboratory Findings

Marrow failure usually ensues in the 1st decade of life. Thrombocytopenia and red blood cell macrocytosis often appears initially, with subsequent onset of granulocytopenia and then anemia. Severe aplasia develops in most cases, but its full expression is variable and evolves over a period of months to years. The marrow becomes progressively hypocellular and fatty, like that in severe acquired aplastic anemia. Chromosome fragility is indicated by spontaneously occurring chromatid breaks, rearrangements, gaps, endoreduplications, and chromatid exchanges in blood lymphocytes cultured with phytohemagglutinin as well as in cultured skin fibroblasts, underscoring the constitutional nature of the disorder. With addition of DEB or mitomycin C, fragility is strikingly enhanced in lymphocyte cultures of patients with FA in comparison with those of controls. For prenatal diagnosis, abnormal chromosome breakage analysis and genetic testing can be performed in amniotic fluid cells or in tissue from a chorionic villus biopsy.

Complications

In addition to the low blood counts and physical anomalies, a major feature of the phenotype of FA is the propensity for cancer. The most frequent solid tumors are squamous cell carcinomas of the head, neck, and upper esophagus, followed by carcinomas of the vulva and/or anus, cervix, and lower esophagus. Human papilloma virus is suspected in the pathogenesis. Some patients experience oral cancer after bone marrow transplantation; it is unclear whether this treatment has an effect on the incidence. Benign and malignant liver tumors occur (adenomas, hepatomas) are usually associated with androgen therapy for aplastic anemia. Androgens are also implicated in the etiology of peliosis hepatis (blood-filled hepatic sinusoids). Peliosis hepatis is reversible when androgen therapy is discontinued, and tumors may regress. Clonal marrow cytogenetic abnormalities are common in FA, and at follow-up can either be stable, intermittently detected, or progressive and develop to advanced MDS and acute myelogenous leukemia. Approximately 15% of patients with FA are at risk for acute leukemia by the age of 35 yr.

Diagnosis

FA should be considered in all children and young adults with unexplained cytopenias. Abnormal hematologic findings and characteristic physical anomalies suggest the diagnosis, which is confirmed with a lymphocyte chromosomal breakage study using DEB. No other inherited pancytopenia is associated with a prominent in vitro hypersensitivity to DEB or mitomycin C by the chromosomal breakage study. Ten percent to 15% of patients with suspected FA have "somatic mosaicism" and their lymphocytes may not show characteristic high level of chromosomal fragility because of mixed populations of somatic cells, some with 2 abnormal alleles and some with 1 (caused by spontaneous somatic gene correction in a portion of the cells). Testing of skin fibroblasts instead of lymphocytes confirms the diagnosis.

Most patients have stable elevations of serum α-fetoprotein expressed constitutively, independent of liver complications or androgen therapy. Because of its low specificity compared to the chromosomal fragility and molecular tests the laboratory measurement of serum α-fetoprotein has not been widely used as a screening test.

As a result of the large number of *FANC* genes, genetic diagnosis has traditionally been commenced with complementation testing. This is done by determining whether cellular hypersensitivity to crosslinking agents (e.g., mitomycin C or radiation) or immunoblotting for *FANCD2* is restored after generating hybridoma of the patient cells with known genetic complementation cells or after transducing the cells with a known *FANC* gene. The mutant gene or the complementation group is deduced when a specific wild-type *FANC* gene corrects the abnormal chromosome fragility.

Treatment

A hematologist and a multidisciplinary team should supervise patients with FA. If the hematologic findings are stable and there are no transfusion requirements, observation is indicated. Subspecialty consultations for anomalies and disabilities can be arranged during this interval. If growth velocity is below expectations, endocrine evaluation is needed to identify growth hormone deficiency or hypothyroidism. Screening for glucose intolerance and hyperinsulinemia should be performed annually or biannually, depending on the degree of hyperglycemia found on initial testing. Blood counts should be performed every 1-3 mo; bone marrow aspiration and biopsy are indicated annually for leukemia and MDS surveillance by means of morphology and cytogenetics. Patients should be assessed for solid tumors at least annually. Beginning at menarche, female patients should be screened annually for gynecologic cancer. Administration of human papilloma virus quadrivalent vaccine to prevent squamous cell carcinoma is currently advised.

Hematopoietic stem cell transplantation (HSCT; see Chapter 135) is the only curative therapy for the hematologic abnormalities. Patients <10 yr old with FA who undergo transplantation using an human leukocyte antigen (HLA)–identical sibling donor have a survival rate >80%. Survival rates are lower for patients >10 yr old who are undergoing the procedure. Preparative regimens are continuously evaluated, refined, and improved worldwide. For patients who do not have an HLA–matched sibling donor, a search for a matched unrelated donor (including a search of umbilical cord blood banks) might be initiated. Because of the need for more intensive preparation regimen and the heightened graft-versus-host response in patients with FA, the survival and cure rates have not been as good as those for matched sibling donor HSCT (≈50% survival). Molecular technology has led to preimplantation genetic diagnosis on parent-derived blastomeres to find an HLA-matched sibling donor without FA.

Androgens produce a response in 50% of patients, heralded by reticulocytosis and a rise in hemoglobin within 1-2 mo. White blood cell counts may increase next, followed by platelet counts, but it may take many months to achieve the maximum response. When the response plateaus, androgen dosage can be slowly tapered but not stopped entirely. Oral oxymetholone is used most frequently once a day. The beneficial effect of adding low-dose prednisone to androgens is controversial, but when administered orally every second day, they may counter androgen-induced growth acceleration and prevent thrombocytopenic bleeding by promoting vascular stability. In many patients who are taking androgens, the disease becomes refractory as marrow failure progresses. Potential side effects include masculinization, elevated hepatic enzymes, cholestasis, peliosis hepatis, and liver tumors. Screening for these changes should be performed serially.

The potential for recombinant growth factor (cytokine) therapy for FA has not been defined. Granulocyte colony-stimulating factor (G-CSF) can usually induce an increase in the absolute neutrophil count and occasionally may boost platelet counts and hemoglobin levels. There may be a heightened risk of expansion of marrow cells with clonal cytogenetic abnormalities such as monosomy 7. Combination therapy consisting of G-CSF given subcutaneously daily or every 2 days along with erythropoietin given subcutaneously or IV 3 times/wk results in improved neutrophil counts in almost all patients and a sustained rise in platelets and hemoglobin levels in approximately one-third of patients, although most patients lose the response after 1 yr owing to progression of marrow failure.

The premise for gene therapy in FA is based on the assumption that corrected hematopoietic cells offer a growth advantage. Attempts at gene therapy have been disappointing, possibly because of the type of vector but also because of the chromosomal fragility and impaired proliferative function of the hematopoietic progenitors. Encouraging preclinical data from studies using lentiviral vectors offer hope that gene therapy will be a safe and effective treatment for FA.

Prognosis

From FA cases reported in the 1990s, the projected median survival was >30 yr of age, an improvement over that in the previous decade. Successes with HSCT have dramatically improved the outlook. Careful surveillance for known complications, especially cancer, and prompt intervention on their detection has also contributed to the improved survival.

SHWACHMAN-DIAMOND SYNDROME

Etiology and Epidemiology

Shwachman-Diamond syndrome (SDS) is inherited in an autosomal recessive manner; it occurs in all racial and ethnic groups. As FA, SDS is also a multisystem disorder. The nonhematologic manifestations are different and usually include exocrine pancreatic insufficiency and skeletal abnormalities such as metaphyseal dysplasia. There is no increased chromosomal breakage after DEB testing of SDS lymphocytes.

Pathology

The mutant gene *SBDS* maps to chromosome 7q11 and in 90% of cases is responsible for the multisystem, pleiotropic phenotype. The wild-type gene protein product is involved in ribosomal biogenesis. Pancreatic insufficiency is a result of failure of pancreatic acinar development. Fatty replacement of pancreatic tissue is prominent. Bone marrow failure is characterized by dysfunctional hematopoietic stem cells, accelerated apoptosis of marrow progenitors and a defective marrow microenvironment that does not support and maintain normal hematopoiesis.

Clinical Manifestations

Most patients with SDS have symptoms of fat malabsorption from birth that are caused by pancreatic insufficiency, but steatorrhea is not always obvious. Approximately 50% of patients appear to exhibit an improvement in pancreatic enzyme secretion as they age. The clinical picture can be dominated by complications from anemia, neutropenia, or thrombocytopenia. Bacterial and fungal infections secondary to neutropenia, neutrophil dysfunction, and immune deficiency can occur. Short stature is a consistent feature of the syndrome; most patients show normal growth velocity yet remain consistently below the 3rd percentile for height and weight. The occasional SDS adult achieves the 25th percentile for height. Although skeletal abnormalities are variable, classic findings are delayed bone maturation, metaphyseal dysplasia, short or flared ribs, and thoracic dystrophy. Some patients have hepatomegaly and elevations of liver enzymes. Most patients have dental abnormalities and poor oral health. Many have neurocognitive problems and poor social skills.

Laboratory Findings

Fatty replacement of pancreatic tissue can be visualized by CT scan or ultrasound. Fat malabsorption is proven by assay on a 72-hr stool collection. Pancreatic function tests show markedly impaired enzyme secretion, but with preservation of ductal function. Age-adjusted serum trypsinogen and isoamylase levels are reduced. Neutropenia is present in 100% of patients with SDS on at least 1 occasion. It can be chronic persistent or intermittent. It has been identified in some neonates during an episode of sepsis. Neutrophils may have a defect in mobility, migration, and chemotaxis owing to alterations in neutrophil cytoskeletal or microtubular function. Anemia, thrombocytopenia, and pancytopenia are seen in 66%, 60%, and up to 44% of cases, respectively. Pancytopenia can be severe as a result of full-blown aplastic anemia. Bone marrow biopsy specimens and aspirates usually show varying degrees of marrow hypoplasia and fat infiltration. Patients may also have B-cell defects with 1 or more of the following: low immunoglobulin G or immunoglobulin G subclasses, low percentage of circulating B lymphocytes, decreased in vitro B-cell proliferation, and lack of specific antibody production. Patients may have a low percentage of circulating T cells, subsets, or natural killer cells, and decreased in vitro T-cell proliferation.

Diagnosis

The clinical diagnosis of SDS relies on having an evidence of bone marrow dysfunction and exocrine pancreatic dysfunction. However, up to 20% of the patients may lack clear evidence of exocrine pancreatic defects at the time of diagnosis. Mutational analysis for *SBDS* is definitive in 90% of cases. Pearson syndrome (see Chapter 450), consisting of refractory sideroblastic anemia, cytoplasmic vacuolization of bone marrow precursors, lactic acidosis, exocrine pancreatic insufficiency, and a diagnostic mitochondrial DNA mutation is similar to SDS, but the clinical course, morphologic features of the bone marrow, and gene mutation are different. Also, severe anemia requiring transfusion, rather than neutropenia, is present from birth to 1 yr of age. SDS shares some manifestations with FA, such as marrow dysfunction and growth failure, but patients with SDS are readily distinguished because of pancreatic insufficiency with fat malabsorption, fatty changes within the pancreatic body that can be visualized by imaging, characteristic skeletal abnormalities not seen in FA, and a normal chromosomal breakage study with DEB.

Complications

Patients with SDS are predisposed to MDS and leukemic transformation. The crude rate of MDS or acute leukemia in patients with SDS is 8-33%. Marrow cell clonal cytogenetic abnormalities are an isolated finding, occurring in up to 41% of patients. Isochromosome 7 [i(7q)] is particularly common, suggesting that it is a fairly specific clonal marker of SDS and probably related to the presence of mutant *SBDS* on 7q11. Other clonal chromosome abnormalities include monosomy 7, i(7q) combined with monosomy 7, deletions or translocations involving part of 7q, and deletions of 20q [Del(20q)]. Although i(7q) and Del(20q) are rarely related to leukemic transformation or MDS, the prognostic significance of all marrow clonal changes requires prospective monitoring.

Treatment

Fat malabsorption responds to oral pancreatic enzyme replacement and supplemental fat-soluble vitamins, administered according to guidelines similar to those for cystic fibrosis (see Chapter 403). A long-term plan should be initiated to monitor changes in peripheral blood counts that require corrective action and to look for early evidence of malignant myeloid transformation. The latter requires serial bone marrow aspirations for smears and cytogenetics and marrow biopsy. One recommendation is to perform marrow testing every 1-2 yr and complete blood counts every 3 mo.

Daily subcutaneous G-CSF for profound neutropenia is effective in inducing a sustained increase in neutrophils. Some patients require transfusion support for management of severe anemia or thrombocytopenia. Experience with erythropoietin is limited. In some patients who received androgens plus steroids, blood counts have improved. The only curative option for severe marrow failure in SDS is allogeneic HSCT, although experience has been limited. Traditional myeloblastic HSCT resulted in treatment-related mortality in 35-50% of the patients. The risk of cardiotoxicity has been noted. Fludarabine-based protocols using reduced-intensity conditioning appear to be safer and effective for SDS HSCT.

Prognosis

The accurate life expectancy of SDS patients is unknown. Analysis of published cases revealed a median survival of 35 yr. Because the number of undiagnosed patients with mild or asymptomatic disease is unknown, the overall prognosis may be better than previously thought. Approximately 50% of patients experience spontaneous conversion from pancreatic insufficiency to pancreatic sufficiency as a result of improvement in pancreatic enzyme secretion. Enzyme replacement therapy is then no longer needed. Although all patients have some degree of hematologic cytopenia, the changes in most patients are mild to moderate and do not require therapeutic intervention. Severe neutropenia responds well to G-CSF, but there is concern that the predisposition to MDS and acute leukemia can be heightened by the agent's powerful growth stimulus on marrow cells. HSCT for severe marrow failure has produced a 50-70% survival rate, but safer protocols are being introduced. Malignant marrow transformation remains ominous.

DYSKERATOSIS CONGENITA

Etiology and Epidemiology

Dyskeratosis congenita (DC) is an inherited multisystem disorder characterized by mucocutaneous abnormalities, bone marrow failure,

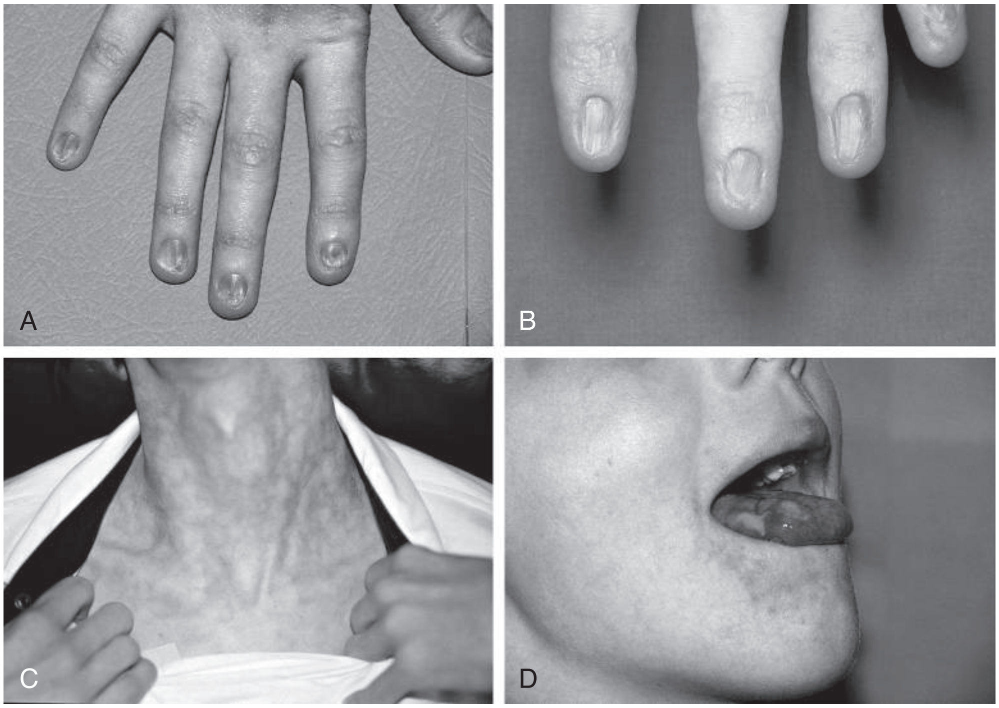

Figure 468-2 Physical findings in patients with dyskeratosis congenita. **A** and **B,** Dystrophic fingernails in 2 different patients. **C,** Lacy reticular pigmentation. **D,** Leukoplakia on the tongue. *(From Nathan DG, Orkin SH, Ginsburg D, et al, editors:* Nathan and Oski's hematology of infancy and childhood, *ed 6, vol I, Philadelphia, 2003, WB Saunders, p. 300.)*

and a predisposition to cancer and MDS. The diagnostic **mucocutaneous (ectodermal) triad** is reticulate skin pigmentation of the upper body, mucosal leukoplakia, and nail dystrophy (Fig. 468-2). Skin and nail findings usually become apparent in the 1st 10 yr of life, whereas oral leukoplakia is seen later. These manifestations tend to progress as patients get older. Varying degrees of bone marrow failure are seen in about 90% of the patients. Severe aplastic anemia occurs in approximately 50% of cases, usually in the 2nd decade of life. Many patients with DC are male, a finding compatible with the high frequency of the X-linked recessive form of the disease. The remainder have either an autosomal dominant or autosomal recessive mode of inheritance.

Pathology

DC is genetically heterogeneous, and patients have mutations in genes that encode components of the telomerase complex (*DKC1*, *TERT*, *TERC*, *NOP10*, and *NHP2*), T-loop disassembly protein (*RTEL1*), telomere capping (*CTC1*), the telomere shelterin complex (*TINF2*), and the telomerase trafficking protein (*TCAB1*), all components critical for telomere maintenance. The **X-linked recessive form** of DC maps to Xq28, and many mutations have been identified in the *DKC1* gene, which codes for the nuclear protein dyskerin. The **autosomal dominant form** is due to mutations in *TINF2,* or in *TERC* or *TERT*, the RNA and enzymatic components of telomerase, respectively. **Autosomal recessive** DC is linked to mutations in *NOP10, NHP2, RTEL1, TCAB1,* and *CTC1*. Because of impaired telomere maintenance in all 3 inherited forms of DC, short telomeres are demonstrated in the peripheral blood cells of all patients and are a cardinal marker for DC and for marrow failure. The failure is likely a result of progressive attrition and depletion of hematopoietic stem cells because of premature senescence, which manifests as pancytopenia.

Clinical Manifestations

Skin pigmentation and nail changes typically appear first, mucosal leukoplakia and excessive ocular tearing appear later, and by the mid-teens, patients with DC have bone marrow failure and malignancy. Many female patients have the same features as male patients. In males, cutaneous findings are the most consistent feature. Lacy reticulated skin pigmentation affecting the face, neck, chest, and arms is a common finding (89%). The degree of pigmentation increases with age and can involve the entire skin surface. There may also be a telangiectatic erythematous component. Nail dystrophy of both hands and feet is the next most common finding (88%). It usually starts with longitudinal ridging, splitting, or pterygium formation and may progress to complete nail loss. Leukoplakia usually involves the oral mucosa (78%), especially the tongue but may also be seen in the conjunctiva and the anal, urethral, or genital mucosa. Hyperhidrosis of the palms and soles is common, and hair loss is sometimes seen. Eye abnormalities are observed in approximately 50% of cases. Excessive tearing (epiphora) secondary to nasolacrimal duct obstruction is common. Other ophthalmologic manifestations include conjunctivitis, blepharitis, loss of eyelashes, strabismus, cataracts, and optic atrophy. An increased rate of dental decay and early loss of teeth are common. Skeletal abnormalities, such as osteoporosis, avascular necrosis, abnormal bone trabeculation, scoliosis, and mandibular hypoplasia, are seen in approximately 20% of cases. Genitourinary abnormalities include hypoplastic testes, hypospadias, phimosis, urethral stenosis, and horseshoe kidney. Gastrointestinal findings, such as esophageal strictures, vascular lesions causing bleeding, hepatomegaly, and fibrosis are seen in 10% of cases. A subset of patients has pulmonary complications, with reduced diffusion capacity and/or a restrictive defect. In fatal cases, lung tissue shows pulmonary fibrosis and abnormalities of the pulmonary vasculature.

Laboratory Findings

The initial hematologic change in DC is usually thrombocytopenia, anemia, or both, followed by full-blown pancytopenia and aplastic anemia. The red cells are often macrocytic, and the fetal hemoglobin value can be elevated initially. Initial bone marrow specimens may be hypercellular, but with time, a symmetric depletion of all hematopoietic lineages ensues. Some patients have immunologic abnormalities, including reduced or elevated immunoglobulin values, decreased B- and/or T-lymphocyte count, and reduction of or absence of lymphocyte proliferative responses to phytohemagglutinin. This is particularly common and severe in the DKC1-associated disease. Primary skin

fibroblasts in culture have abnormal morphologic features and doubling rate and show numerous unbalanced chromosome rearrangements, such as dicentrics, tricentrics, and translocations, in the absence of DEB. These findings provide evidence of a defect that predisposes patient cells to chromosomal rearrangements and possibly to DNA damage.

Diagnosis

The following abnormalities are seen in patients with DC but not in those with FA: nail dystrophy, leukoplakia, and tooth abnormalities, hyperhidrosis of the palms and soles, and hair loss (see Table 468-2). There are overlap syndromes that share some of the features of DC. **Hoyeraal-Hreidarsson syndrome** is a multisystem disorder comprising aplastic anemia, immunodeficiency, microcephaly, growth retardation, and cerebellar hypoplasia. The syndrome is genetically heterogeneous; some cases are X-linked recessive and caused by mutations in *DKC1*, and others are autosomal recessive owing to homozygous *TERT* mutations. **Revesz syndrome** consists of dystrophic nails, leukoplakia, aplastic anemia, cerebellar hypoplasia, growth retardation, microcephaly, and bilateral exudative retinopathy. *TINF2* is mutated in Revesz syndrome, which hence is an autosomal dominant variant of DC. Coats' plus syndrome is caused by mutations in the *CTC1* gene. It is characterized by retinal telangiectasia and exudates, intracranial calcification, leukodystrophy, brain cysts, osteopenia, gastrointestinal bleeding and portal hypertension caused by the development of vasculature ectasias in the stomach, small intestine and liver. Some patients with this disease has the additional manifestations of DC, which include sparse and graying hair, dystrophic nails, and anemia. Telomeres are short.

Complications

Cancer develops in approximately 10-15% of patients with DC, usually in the 3rd and 4th decades of life. Patients with DC are predisposed to MDS as well as to solid tumors. Forty percent of the cancers in such patients are squamous cell carcinomas of the head and neck (tongue, mouth, pharynx). Cancer of the skin and gastrointestinal tract (esophagus, stomach, colon, and especially the anorectal site) is also common. Other life-threatening complications include pulmonary fibrosis and severe gastrointestinal bleeding.

Treatment

Androgens (with or without low-dose prednisone) can induce improvement of marrow function in approximately 50% of patients. When the response is maximal, the androgen dose can be slowly tapered but not stopped. DC can become refractory to androgens as the aplastic anemia progresses. There is no published information on the use of immunosuppressive therapy for this disorder, but the authors are aware of several patients who were misdiagnosed with acquired aplastic anemia and treated with immunosuppressive therapy without response. Although reports are scanty, cytokine therapy with granulocyte-macrophage colony-stimulating factor or with G-CSF alone or combined with erythropoietin appears to offer potential benefit, at least in the short term, especially for improving neutrophil numbers.

Allogeneic HSCT has been used to correct marrow failure in patients with DC, long-term survival is only 50%. Vascular lesions and fibrosis involving various organs are not prevented by HSCT and can occur early and late after transplantation; carrying a high mortality rate. Patients with DC may be more susceptible to endothelial damage that occurs after HSCT as a result of various factors, including the conditioning regimen, infectious disease, and graft-versus-host disease. Up to 40% of patients with DC experience fatal pulmonary complications after transplantation.

Prognosis

Considerable heterogeneity exists in DC. Patients with certain genetic groups (e.g., *TERC* and *TERT*) have milder clinical manifestations. Patients with other genetic groups (e.g., *DKC1*, *TINF2* and *RTEL1*) appear to have more physical anomalies and a higher incidence of aplastic anemia and cancer. The mean age of death for patients with DC who are diagnosed in childhood is approximately 30 yr. The main causes of death are bone marrow failure, complications of HSCT, cancer, fatal pulmonary problems, and gastrointestinal bleeding.

CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIA

Etiology and Epidemiology

Congenital amegakaryocytic thrombocytopenia (CAMT) is the rarest of the 4 major inherited pancytopenias. It is transmitted in an autosomal recessive manner. CAMT manifests in infancy as isolated thrombocytopenia as a result of reduction or absence of marrow megakaryocytes with initial preservation of granulopoietic and erythroid lineages. Pancytopenia caused by aplastic anemia often ensues in the first few years of life. The defect in CAMT is directly related to mutations in *MPL,* the gene for the receptor of thrombopoietin, the growth factor that promotes hematopoietic stem cell survival and stimulates megakaryocyte proliferation and maturation. Carriers of the mutant gene have normal hematology; affected individuals have mutations in both alleles. Genotype–phenotype correlations predict disease course and prognosis. **Nonsense mutations** cause a complete loss of function of the thrombopoietin receptor, causing persistently low platelet counts because of the absence of megakaryocytes and a fast progression to pancytopenia and aplastic anemia (CAMT type I). Because thrombopoietin also has an antiapoptotic and cell survival effect on stem cells, impaired stem cell survival with *MPL* nonsense mutations explains the evolution of CAMT into aplastic anemia. **Missense mutations** of *MPL* are associated with a milder course, a transient increase in platelets during the 1st yr of life, and delayed onset, if any, of pancytopenia, indicating residual receptor function (CAMT type II). Biologically active plasma thrombopoietin is consistently elevated in all patients with CAMT.

Clinical Manifestations

Patients with CAMT have petechial rash, bruising, or bleeding at birth or in the 1st yr of life. Most, but not all, patients with proven *MPL* mutations have normal physical and imaging features. Approximately 20% of published phenotypic CAMT cases involved physical anomalies, but *MPL* mutation analyses were not available in all cases. The most common anomalies in the published cases are neurologic and cardiac. Findings related to cerebellar and cerebral atrophy are frequent, and developmental delay is a prominent feature. Congenital heart disease includes atrial septal defects, ventricular septal defects, patent ductus arteriosus, tetralogy of Fallot, and coarctation of the aorta. Some of these occur in combinations. Other anomalies include abnormal hips or feet, kidney malformations, eye anomalies, and cleft or high-arched palate. Some patients have microcephaly and an abnormal facies.

Laboratory Findings

Thrombocytopenia is the major laboratory finding in CAMT, with normal hemoglobin levels and white blood cell counts initially. Peripheral blood platelets are reduced or totally absent. As in other inherited bone marrow failure syndromes, red blood cells may be macrocytic. Hemoglobin F may be elevated, and there may be increased expression of i antigen. Initial bone marrow aspirates and biopsy specimens show normal cellularity with marked reduction or absence of megakaryocytes. In patients in whom aplastic anemia develops, marrow cellularity is decreased, with fatty replacement; erythropoietic and granulopoietic lineages are also symmetrically reduced.

Diagnosis

If thrombocytopenia persists beyond the neonatal period or is associated with adequate platelet transfusion response and no obvious precipitating cause such as infections or immunologic reactions, a marrow aspirate and biopsy is indicated. Deficient megakaryocytes in such cases suggest the diagnosis, and mutational analysis will confirm it. If CAMT occurs at birth or shortly after, it must be distinguished from other causes of inherited and acquired neonatal thrombocytopenia (see Chapter 484.8). Thrombocytopenia with absent radii (TAR syndrome) is distinguished from CAMT because in TAR syndrome the

radii are absent. The distinction from DC may be evident by mucocutaneous, neurologic, and immunologic findings that are characteristic to the early onset DC. CAMT blood lymphocytes do not show increased chromosomal breakage when exposed to DEB, distinguishing the disease it from FA.

Complications

In some patients, clonal marrow cell cytogenetic abnormalities appear such as monosomy 7 and trisomy 8. CAMT can evolve into MDS and also acute leukemia, but the true risk cannot be defined because of the rarity of the disease and the paucity of published data.

Therapy and Prognosis

The mortality rate in patients with *MPL* **nonsense** mutations from thrombocytopenic bleeding, complications of aplastic anemia, or leukemic transformation has been very close to 100%. Patients with **missense** mutations have a milder course but may still have serious complications. HSCT is the only curative option. The majority of patients with CAMT who undergo HSCT are cured, especially if the procedure is performed with HLA-matched sibling donors. Before transplantation, platelet transfusion should be used discretely. Platelet count should not always be the sole indication; clinical bleeding is an appropriate trigger. Single-donor filtered platelets are preferred to minimize sensitization. Leukodepleted platelet units might be adequate, but further studies are necessary to support such an alternative. In a patient for whom HSCT is a possibility, all blood products should be free of cytomegalovirus. Corticosteroids are not effective for treatment of the thrombocytopenia. For aplastic anemia, androgens may induce a temporary partial improvement. Interleukin-3 may be an important adjunct to the medical management of CAMT, but it was not adopted broadly and is no longer available. The role of thrombomimetic agents has to be studied; however, the induction of fibrosis by these agents and the risk of MDS/leukemia in CAMT render HSCT the preferred treatment for patients with severe cytopenia.

OTHER INHERITED SYNDROMES

Pancytopenia and bone marrow failure can occur in the context of several non-hematologic syndromes and familial settings that do not exactly correspond to the entities already described.

Down Syndrome

Down syndrome (trisomy 21; see Chapter 81.2) has a unique association with aberrant hematologic findings. In addition to the propensity for acute lymphoblastic and myeloblastic leukemias, especially acute megakaryoblastic leukemia, at least 6 patients with Down syndrome have been reported as having pancytopenia caused by aplastic anemia.

Dubowitz Syndrome

Dubowitz syndrome is an autosomal recessive disorder characterized by a peculiar facies, infantile eczema, small stature, and mild microcephaly. The face is small, with a shallow supraorbital ridge, a nasal bridge at the same level as the forehead, short palpebral fissures, variable ptosis, and micrognathia. There is a predilection to cancer as well as to bone marrow dysfunction in these patients. Approximately 10% of patients have hematopoietic disorders including moderate pancytopenia, hypoplastic anemia, bone marrow hypoplasia, and full-blown aplastic anemia. No gene mutation has been identified.

Seckel Syndrome

Seckel (SCKL) syndrome, sometimes called "bird-headed dwarfism," is an autosomal recessive developmental disorder characterized by marked growth failure and mental deficiency, microcephaly, a hypoplastic face with a prominent nose, and low-set and/or malformed ears. Approximately 25% of patients have aplastic anemia or malignancies. There is broad genetic heterogeneity comprising 7 classifiable types: SCKL1, *ATR* mutation; SCKL2, *RBBP8* mutation; SCKL3, maps to 14q21-q22; SCKL4, *CENPJ* mutation; SCKL5, *CEP152* mutation; SCKL6, *CEP63* mutation; and, SCKL7, *NIN* mutation.

Reticular Dysgenesis

Reticular dysgenesis (see Chapter 126) is an immunologic deficiency syndrome coupled with congenital agranulocytosis. The mode of inheritance autosomal recessive in some cases; there is evidence that reticular dysgenesis is caused by homozygous or compound heterozygous mutation in the mitochondrial adenylate kinase-2 gene *AK2* on chromosome 1p35 but an X-linked mode is also possible in some cases. The disorder is a variant of severe combined immune deficiency in which cellular and humoral immunity are absent and severe lymphopenia and neutropenia are also seen. Anemia and thrombocytopenia may also be present. Bone marrow specimens are hypocellular, with markedly reduced myeloid and lymphoid elements. The only curative therapy is HSCT.

Schimke Immunoosseous Dysplasia

Schimke immunoosseous dysplasia is an autosomal recessive disorder caused by mutations in the chromatin remodeling protein *SMARCAL1*. Patients have spondyloepiphyseal dysplasia with exaggerated lumbar lordosis and a protruding abdomen. There are pigmentary skin changes and abnormally discolored and configured teeth. Renal dysfunction can be problematic, with proteinuria and nephrotic syndrome. Approximately 50% of patients have hypothyroidism, 50% have cerebral ischemia, and 10% have bone marrow failure with neutropenia, thrombocytopenia, and anemia, and about 5% are predisposed to non-Hodgkin lymphoma. Lymphopenia and altered cellular immunity are present in almost all patients. In 2 published case reports, 2 patients underwent successful bone marrow transplantation.

Noonan Syndrome

Noonan syndrome is a developmental disorder characterized by the "Noonan facies" (hypertelorism, ptosis, short neck, low-set ears), short stature, congenital heart disease, and multiple skeletal and hematologic abnormalities. It is primarily an autosomal dominant disorder composed of at least 7 genetic types. Heterozygous mutations in *PTPN11* cause approximately 50% of cases of the syndrome; others are caused by mutations in *NF1, KRAS, SOS1*, *RAF1, NRAS,* or *BRAF*. Autosomal recessive forms have also been identified due to a mutation of *SHOC2* or of *CBL*. In addition to an association with juvenile myelomonocytic leukemia, Noonan syndrome patients can develop amegakaryocytic thrombocytopenia as well as pancytopenia with a hypocellular marrow.

Cartilage-Hair Hypoplasia

Cartilage-hair hypoplasia, an autosomal recessive syndrome seen mostly in Finnish or Amish populations, is characterized by metaphyseal dysostosis, short-limbed dwarfism, and fine, sparse hair. Additional skeletal findings are scoliosis, lordosis, chest deformity, and varus lower limbs. Gastrointestinal abnormalities also occur. Mutations in the *RMRP* gene cause cartilage-hair hypoplasia. Macrocytic anemia is seen in most patients and is sometimes severe and persistent. Neutropenia, lymphopenia, and a predisposition to lymphoma and other cancers are also features.

UNCLASSIFIED INHERITED BONE MARROW FAILURE SYNDROMES

Unclassified inherited bone marrow failure syndromes are heterogeneous disorders that may be either atypical presentations of identifiable diseases or new syndromes. Characterized by various cytopenias because of underproductive bone marrow with or without physical manifestations, they do not fit into a classic genetic bone marrow failure disease because all features may not be evident at the time of presentation. Compared with classic disorders (presentation ≈1 mo of age), infants with unclassified disorders present later (≈9 mo) and manifest single or multilineage cytopenia, aplastic anemia, myelodysplasia, or malignancy with variable expression of malformations. Table 468-4 lists the criteria for the diagnosis. With follow-up, some may demonstrate typical physical features of known syndromes, such as SDS, although without obvious mutations in the *SBDS* gene.

Table 468-4	Canadian Inherited Marrow Failure Registry Criteria for Unclassified Inherited Bone Marrow Failure Syndromes

FULFILLS CRITERIA 1 AND 2:
1. Does not fulfill criteria for any categorized inherited bone marrow failure syndrome*
2. Fulfills both of the following

FULFILLS AT LEAST 2 OF THE FOLLOWING:
a. Chronic cytopenia(s) detected on at least 2 occasions over at least 3 mo†
b. Reduced marrow progenitors or reduced clonogenic potential of hematopoietic progenitor cells or evidence of ineffective hematopoiesis‡
c. High fetal hemoglobin for age‡
d. Red blood cell macrocytosis (not caused by hemolysis or a nutritional deficiency)

FULFILLS AT LEAST 1 OF THE FOLLOWING:
a. Family history of bone marrow failure
b. Presentation at age <1 yr
c. Anomalies involving multiple systems to suggest an inherited syndrome

*The Canadian Inherited Marrow Failure Registry diagnostic guidelines for selected syndromes were adapted from the literature and are available at http://www.sickkids.ca/cimfr.

†Cytopenia was defined as follows: neutropenia, neutrophil count of $<1.5 \times 10^9$/L; thrombocytopenia, platelet count of $<150 \times 10^9$/L; anemia, hemoglobin concentration of <2 standard deviations below mean, adjusted for age.

‡Hemoglobinopathies with ineffective erythropoiesis and high hemoglobin F should be excluded by clinical or laboratory testing.

Familial cases with aplastic anemia that cannot be readily classified into discrete diagnostic entities such as FA have been reported. When the patients present not early after birth and without physical malformations an acquired etiology cannot be ruled out. Detailed genetic testing for known inherited bone marrow failure syndrome genes or by whole exome or genome sequencing may identify an inherited etiology.

Bibliography is available at Expert Consult.

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Chapter 469

The Acquired Pancytopenias

Jeffrey D. Hord

ETIOLOGY AND EPIDEMIOLOGY

Drugs, chemicals, toxins, infectious agents, radiation, and immune disorders can result in pancytopenia by direct destruction of hematopoietic progenitors, disruption of the marrow microenvironment, or immune-mediated suppression of marrow elements (Table 469-1). A careful history of exposure to known risk factors should be obtained for every child presenting with pancytopenia. Even in the absence of the classic associated physical findings, the possibility of a genetic predisposition to bone marrow failure should always be considered (see Chapter 468). The majority of cases of acquired marrow failure in childhood are "idiopathic," in that no causative agent is identified. Many are probably immune-mediated through activated T lymphocytes and cytokine destruction of marrow progenitor cells. The overall incidence of acquired aplastic anemia is relatively low, with an approximate incidence in both children and adults in the United States and Europe of 2-6 cases/million population/yr. The incidence is higher in Asia, with as many as 14 cases/million population/yr in Japan.

Table 469-1 Etiology of Acquired Aplastic Anemia
Radiation, drugs, and chemicals:
Predictable: chemotherapy, benzene
Idiosyncratic: chloramphenicol, antiepileptics, gold; 3,4-methylenedioxymethamphetamine
Viruses:
Cytomegalovirus
Epstein-Barr
Hepatitis B
Hepatitis C
Hepatitis non-A, non-B, non-C (seronegative hepatitis)
HIV
Immune diseases:
Eosinophilic fasciitis
Hypoimmunoglobulinemia
Thymoma
Pregnancy
Paroxysmal nocturnal hemoglobinuria
Marrow replacement:
Leukemia
Myelodysplasia
Myelofibrosis
Autoimmune
Other:
Cryptic dyskeratosis congenita (no physical stigmata)
Telomerase reverse transcriptase haploinsufficiency

Severe bone marrow suppression can develop after exposure to many different drugs and chemicals, including certain chemotherapeutic agents, insecticides, antibiotics, anticonvulsants, nonsteroidal antiinflammatory agents, and recreational drugs. Some of the most notable agents are benzene, chloramphenicol, gold, and, 3,4,-methylenedioxymethamphetamine (Ecstasy).

A number of viruses can either directly or indirectly result in bone marrow failure. Parvovirus B19 is classically associated with isolated red blood cell aplasia, but in patients with sickle cell disease or immunodeficiency, it can result in transient pancytopenia (see Chapter 251). Prolonged pancytopenia can occur after infection with many of the hepatitis viruses, herpes viruses, Epstein-Barr virus (see Chapter 254), cytomegalovirus (see Chapter 255), and HIV (see Chapter 276).

Patients with evidence of bone marrow failure should also be evaluated for inherited forms of marrow failure, paroxysmal nocturnal hemoglobinuria (PNH; see Chapter 464), and collagen vascular diseases. Pancytopenia without peripheral blasts may be caused by bone marrow replacement by leukemic blasts or neuroblastoma cells.

PATHOLOGY AND PATHOGENESIS

The hallmark of aplastic anemia is peripheral pancytopenia, coupled with hypoplastic or aplastic bone marrow. The severity of the clinical course is related to the degree of myelosuppression. **Severe aplastic anemia** is defined as a condition in which 2 or more cell components have become seriously compromised (absolute neutrophil count <500/mm^3, platelet count <20,000/mm^3, reticulocyte count <1% after correction for hematocrit) in a patient whose bone marrow biopsy material is moderately or severely hypocellular. Approximately 65% of patients who first present with **moderate aplastic anemia** (absolute neutrophil count 500-1,500/mm^3, platelet count 20,000-100,000/mm^3, reticulocyte count <1%) eventually progress to meet the criteria for severe disease, if they are simply observed. Bone marrow failure may be a consequence of a direct cytotoxic effect on hematopoietic stem cells from a drug or chemical or may result from either cell-mediated or antibody-dependent cytotoxicity. There is strong evidence that many cases of idiopathic aplastic anemia are caused by an immune-mediated process, with increased circulating activated T lymphocytes producing cytokines (interferon-γ) that suppress hematopoiesis. Abnormal telomere

length and telomerase activity in granulocytic precursors and increased expression of cell surface Flt3 ligand (a member of the class III receptor tyrosine kinase family) in the lymphocytes of patients with aplastic anemia suggest that early apoptosis of hematopoietic progenitors may play a role in the pathogenesis of this disease.

CLINICAL MANIFESTATIONS, LABORATORY FINDINGS, AND DIFFERENTIAL DIAGNOSIS

Pancytopenia results in increased risks of cardiac failure, infection, bleeding, and fatigue. Acquired pancytopenia is typically characterized by anemia, leukopenia, and thrombocytopenia in the setting of elevated serum cytokine values. Other treatable disorders, such as cancer, collagen vascular disorders, PNH, and infections that may respond to specific therapies (IV immune globulin for parvovirus), should be considered in the differential diagnosis. Careful examination of the peripheral blood smear for red blood cell, leukocyte, and platelet morphologic features is important. A reticulocyte count should be performed to assess erythropoietic activity. In children, the possibility of congenital pancytopenia must always be considered, and chromosomal breakage analysis should be performed to evaluate for Fanconi anemia (see Chapter 468). The presence of fetal hemoglobin suggests congenital pancytopenia but is not diagnostic. To assess for the possibility of PNH, flow cytometric analysis of erythrocytes for CD55 and CD59 is the most sensitive test. Bone marrow examination should include both aspiration and a biopsy, and the marrow should be carefully evaluated for morphologic features, cellularity, and cytogenetic abnormalities.

TREATMENT

The treatment of children with acquired pancytopenia requires comprehensive supportive care coupled with an attempt to treat the underlying marrow failure. For patients with an human leukocyte antigen–identical family member donor, allogeneic hematopoietic stem cell transplantation (HSCT) offers a 90% chance of long-term survival. The typical preparative regimen today consists of cyclophosphamide, fludarabine, and horse antithymocyte globulin (ATG). The risks associated with this approach include the immediate complications of transplantation, graft failure, and graft versus host disease. Late adverse effects associated with transplantation may include secondary cancers, cataracts, short stature, hypothyroidism, and gonadal dysfunction (see Chapters 136-139). Only 1 in 5 patients has a human leukocyte antigen–matched sibling donor, so matched-related HSCT is not an option for the majority of patients.

For patients without a sibling donor, the major form of therapy is immunosuppression with horse ATG and cyclosporine, with a response rate of 70-80%. The median time to response is 6 mo. As many as 30% of responders experience relapse after discontinuation of immunosuppression, and some patients must continue cyclosporine for several years to maintain a hematologic response. Among those who relapse after immunosuppression, approximately 50% show response to a second course of ATG and cyclosporine. There is an increased risk (<10%) of clonal bone marrow disease, such as leukemia, myelodysplasia (MDS), or PNH after immunosuppression with karyotypic abnormalities most frequently involving chromosomes 6, 7, and 8. To accelerate neutrophil recovery, a hematopoietic colony-stimulating factor (e.g., granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor) is sometimes added to ATG and cyclosporine for treatment of patients with very severe neutropenia (absolute neutrophil count <200/mm^3), but there is no clear evidence that this treatment influences response rate or survival. In a few cases, tacrolimus has been given successfully with ATG for treatment of aplastic anemia in patients unable to tolerate cyclosporine. Higher baseline reticulocyte count correlates with a higher probability of response to immunosuppression and survival. There is an inverse correlation between telomere length and the probability of relapse post-immunosuppression.

For patients who show no response to immunosuppression or who experience relapse after immunosuppression, matched unrelated HSCT and T-cell depleted haploidentical family member donor HSCT are treatment options, with a response rate approaching 90%. Cord blood transplants have been carried out in this refractory group of patients but there is a significant incidence of non-engraftment. High-dose cyclophosphamide has been used successfully in the treatment of patients with newly diagnosed aplastic anemia and in patients without adequate response to immunosuppression. This therapy leads to prolonged severe pancytopenia, increasing the risk of life-threatening infection, especially fungal. Other therapies that have been used in the past with inconsistent results include androgens, corticosteroids, and plasmapheresis. However, preliminary studies with eltrombopag (an oral thrombopoietin mimetic agent) have resulted in a hematologic response with improvements in platelet and neutrophil counts and hemoglobin levels in some patients. In patients who responded, bone marrow biopsies demonstrated trilineage normalization of hematopoiesis; some who were dependent on platelet or erythrocyte transfusions no longer needed transfusions.

COMPLICATIONS

The major complications of severe pancytopenia are predominantly related to the risk of life-threatening bleeding from prolonged thrombocytopenia or to infection secondary to protracted neutropenia. Patients with protracted neutropenia as a result of bone marrow failure are at risk not only for serious bacterial infections but also for invasive mycoses. Patients who have been transfused with red blood cells regularly over a long period are at increased risk of developing alloantibodies to red cell antigens and may require iron chelation therapy for transfusional iron overload. The general principles of supportive care that have evolved from the use of chemotherapy-related myelosuppression to treat patients with cancer should be fully extended to the care of patients with acquired pancytopenia.

PROGNOSIS

Spontaneous recovery from pancytopenia rarely occurs. If left untreated, severe pancytopenia has an overall mortality rate of approximately 50% within 6 mo of diagnosis and of >75% overall, with infection and hemorrhage being the major causes of morbidity and mortality. The majority of children with acquired severe aplastic anemia show response to allogeneic marrow transplantation or immunosuppression, leaving them with normal or near-normal blood cell counts.

PANCYTOPENIA CAUSED BY MARROW REPLACEMENT

Processes that either infiltrate or replace the bone marrow can manifest as acquired pancytopenia. Infiltration can be caused by malignancy (classically, neuroblastoma or leukemia) or occur as a consequence of myelofibrosis, MDS, or osteoporosis. Although uncommon, evidence of hypoplastic anemia can precede the onset of acute leukemia, generally by a few months. This relationship is important to appreciate in evaluating and monitoring children who present with what appears to be acquired aplastic anemia. Morphologic examination of the peripheral blood and bone marrow and marrow cytogenetic studies are critically important in making the diagnoses of leukemia, myelofibrosis, and MDS.

MDS is very rare in children, but when it occurs, its clinical course is more aggressive than the same category of MDS in adults. Pediatric MDS can be subdivided into refractory cytopenia of childhood (peripheral blasts <2% and marrow blasts <5%), refractory anemia with excess blasts (peripheral blasts 2-19% and/or marrow blasts 5-19%), and refractory anemia with excess blasts in transformation (peripheral and/or marrow blasts 20-29%). Disease in children with >30% blasts is usually defined as acute myelocytic leukemia.

A number of inherited conditions are associated with an increased risk for development of MDS, including Down syndrome, severe congenital neutropenia, Noonan syndrome, Fanconi anemia, trisomy 8 mosaicism, neurofibromatosis, and Shwachman syndrome. Significant clonal abnormalities are found within the marrow of approximately 50% of patients with MDS, with monosomy 7 and being most common but prognostically neutral. Those with a structurally complex karyotype have a very poor outcome.

The transition time from pediatric MDS to acute leukemia is relatively short, at 14-26 mo, so aggressive treatment, such as HSCT, must be considered shortly after diagnosis. With allogeneic HSCT, the survival rate is approximately 60%. One exception to such an aggressive therapeutic approach is MDS and acute myelocytic leukemia in children with Down syndrome, because this disease in this specific population is very responsive to conventional chemotherapy, with long-term survival rates >80%.

The decision on how to treat a child with MDS who lacks a suitable hematopoietic stem cell donor should be made with the specific clonal abnormality found within the child's marrow taken into consideration. Lenalidomide produces the best responses among patients who have the chromosomal abnormality, 5q−. Immunosuppressive therapy with ATG and cyclosporine is most effective in patients with trisomy 8, especially in the presence of a PNH clone. Imatinib mesylate targets mutations in the tyrosine kinase receptor family of genes found in patients with t(5;12) and del(4q12). The DNA hypomethylating agents azacitidine and decitabine have also been used in treating MDS without a known molecular target and have some effect.

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Section 6
Blood Component Transfusions

Chapter 470
Red Blood Cell Transfusions and Erythropoietin Therapy
Ronald G. Strauss

Red blood cells (RBCs) are transfused to increase the oxygen-carrying capacity of the blood, with the goal to increase or maintain satisfactory tissue oxygenation; this goal may not be achieved simply by increasing the blood hemoglobin concentration or hematocrit by an RBC transfusion because tissue oxygenation depends on several additional factors including oxygen off-loading from RBCs, microvascular blood flow, and diffusion of oxygen into tissue cells. Although some attempts have been made to accurately relate posttransfusion blood hemoglobin concentration or hematocrit values to changes in posttransfusion tissue oxygenation (e.g., improvements in the ratio of cerebral versus mesenteric oxygenation patterns assessed by serial near-infrared spectroscopy measurements), decisions to transfuse RBCs per physiologic indications, rather than degree of anemia, remain investigational.

Because neonates, especially extremely low birthweight preterms are not "small" children (i.e., RBC physiology and the pathophysiology of the anemia of prematurity are unique), RBC transfusions for neonates and older children will be considered separately. Guidelines for RBC transfusions in children and adolescents are based on maintaining a specified hemoglobin or hematocrit level considered to be optimal (per the best evidence available) for the clinical condition present at the time of the transfusion. The guidelines are similar to those for adults (Table 470-1). Transfusions may be given more stringently to children, because normal hemoglobin levels are lower in healthy children than in adults and, as is often the case, children do not have the underlying multiorgan, cardiorespiratory, and vascular diseases that develop with aging in adults to suggest a need for RBC transfusions Thus, children may compensate better for RBC loss than elderly adults and, as is true for patients of all ages, there is increasing enthusiasm for applying conservative practices (i.e., accept lower pretransfusion hematocrit values to "trigger" a RBC transfusion).

In the perioperative period, it is unnecessary for most children to maintain hemoglobin levels of 8 g/dL or greater, a level frequently desired for adults. The desired preoperative hemoglobin level should take into account the estimated blood loss for the surgical procedure planned and the rate of bleeding. There should be a compelling reason to prescribe any postoperative RBC transfusion, such as continued bleeding with hemodynamic instability, because most children (without continued bleeding) can, in a relatively short time, restore their RBC mass with iron therapy. The most important measures in the treatments of acute hemorrhage are to control the hemorrhage and, if blood loss is modest, to restore the circulating blood volume and tissue perfusion with crystalloid or, less often, colloid solutions. If the estimated blood loss is >25% of the circulating blood volume (>15 mL/kg of an estimated 60 mL/kg total estimated blood volume) *and* the patient's condition is unstable despite intravenous fluids, RBC transfusions may be indicated; given with plasma transfusions at a 1 : 1 ratio of RBC : plasma volumes. Details of combined RBC and plasma transfusions, the volume ratio transfused, and considerations for adding platelet transfusions to treat bleeding patients are controversial. Accordingly, each hospital should develop and follow a "massive transfusion" protocol to ensure consistent practices.

In critically ill children with severe cardiac or pulmonary disease requiring assisted ventilation, it is common practice to maintain the hemoglobin level close to the normal range, although the efficacy of this practice has not been well documented. A similar approach is used for children with acute cardiac, pulmonary, or cardiopulmonary disorders managed with extracorporeal membrane oxygenation.

The pretransfusion blood hemoglobin level or hematocrit that should "trigger" a RBC transfusion is controversial (i.e., restrictive or a low pretransfusion level vs. liberal or a high pretransfusion level)

Table 470-1 Guidelines for Pediatric Red Blood Cell Transfusions*†

CHILDREN AND ADOLESCENTS
1. Maintain stable status with acute loss of >25% of circulating blood volume
2. Maintain hemoglobin >7.0 g/dL† in the perioperative period
3. Maintain hemoglobin >12.0 g/dL with *severe* cardiopulmonary disease
4. Maintain hemoglobin >12.0 g/dL during extracorporeal membrane oxygenation
5. Maintain hemoglobin >7.0 g/dL and *symptomatic* chronic anemia
6. Maintain hemoglobin >7.0 g/dL and *marrow failure*
INFANTS ≤4 MO OLD
1. Maintain hemoglobin >12.0 g/dL and *severe* pulmonary disease
2. Maintain hemoglobin >12.0 g/dL during extracorporeal membrane oxygenation
3. Maintain hemoglobin >10.0 g/dL and *moderate* pulmonary disease
4. Maintain hemoglobin >12.0 g/dL and *severe* cardiac disease
5. Maintain hemoglobin >10.0 g/dL preoperatively and during *major* surgery
6. Maintain hemoglobin >7.0 g/dL postoperatively
7. Maintain hemoglobin >7.0 g/dL and *symptomatic* anemia

*Words in *italics* must be defined for local transfusion guidelines.
†Pretransfusion blood hemoglobin level (convert to hematocrit values if preferred by multiplying hemoglobin values by 3) "triggering" an RBC transfusion. Hemoglobin values to maintain vary among published reports, and the guideline values to maintain should be determined locally to fit the practices judged to be optimal by local MDs.

despite a substantial amount of published information, including randomized clinical trials. The current trend in critical care settings is to transfuse RBCs quite conservatively, following restrictive guidelines, and to permit modest anemia because there appears to be no disadvantage to conservative/restrictive transfusion practices, and some patients with hemoglobin levels maintained close to the normal range by RBC transfusions (i.e., liberal guidelines) have poorer outcomes. Studies in critically ill adults demonstrated better outcomes when the hemoglobin level was maintained at 7-9 g/dL versus 10-12 g/dL. Anemic adults with significant cardiac disease did better with hemoglobin levels maintained at 13 g/dL than at 10 g/dL. Similar studies in children admitted to intensive care units found no inferiority when RBC transfusions were given by restrictive guidelines (transfusion threshold of 7 g/dL). It must be remembered that the children studied were in stable clinical status and needed few transfusions. Therefore, results of the trial cannot be automatically extended to all patients admitted to intensive care units, as unstable critically ill children, who were not studied, may need more liberal RBC transfusions.

With chronic anemia, the decision to transfuse RBCs should not be based solely on blood hemoglobin levels, because children compensate well and may be asymptomatic despite low hemoglobin levels. Patients with iron-deficiency anemia are often treated successfully with oral iron alone, even at hemoglobin levels <5 g/dL. Factors other than hemoglobin concentration to be considered in the decision to transfuse RBCs include: (1) the patient's symptoms, signs, and compensatory capacities; (2) the presence of underlying cardiorespiratory, vascular, and central nervous system disease; (3) the cause and anticipated course of the anemia; and (4) alternative therapies, such as recombinant human erythropoietin (EPO) therapy, which is known to reduce the need for RBC transfusions and to improve the overall condition of children with chronic renal insufficiency (see Chapter 535.2). In anemias that are likely to be permanent, it is also important to balance the detrimental effects of the degree of long-standing anemia on growth and development against the potential toxicity associated with repeated transfusions given to maintain the blood hemoglobin concentration at a specified level. RBC transfusions for disorders such as sickle cell anemia and thalassemia are discussed in Chapters 462.1 and 462.9.

For neonates, nearly all aspects of RBC transfusions remain controversial (i.e., the accepted indications for RBC transfusions; restrictive vs. liberal pretransfusion hemoglobin/hematocrit levels; optimal RBC product to be transfused; fresh vs. stored RBC units), and clinical practices vary greatly. Generally, RBCs are given to maintain a hemoglobin value believed to be the most desirable for each neonate's clinical status (see Table 470-1). Restrictive guidelines (i.e., lower pretransfusion hemoglobin/hematocrit levels) have been compared to more liberal transfusion practices, but both short-term and long-term results/outcomes have been inconsistent and controversial, particularly as to neurodevelopmental status, with poorer outcomes seen in both the restrictive and liberal study arms. Accordingly, conventional guidelines are recommended to avoid problems caused by either undertransfusion or overtransfusion, until more definitive data are published (see Table 470-1).

This clinical approach is imprecise, but more physiologic guidelines/indications such as measurement of RBC mass, calculations of oxygen delivery and tissue extraction, imaging of microcirculatory flow, and comparative measures of tissue perfusion (e.g., ratio of cerebral : mesenteric oxygenation patterns), are too cumbersome for day-to-day clinical practice.

During the first few weeks of life, all neonates experience a decline in circulating RBC mass caused both by physiologic factors and, in sick premature infants, by phlebotomy blood losses. In healthy term infants, the nadir hemoglobin value rarely falls to <11 g/dL at an age of 10-12 wk. This benign *physiologic anemia of infancy* does not require transfusions. In contrast, the decline occurs earlier and is more pronounced in premature infants, in whom the mean hemoglobin concentration falls to approximately 7 g/dL in infants weighing <1 kg at birth, resulting in the *anemia of prematurity*, for which there often is need for RBC transfusions.

A key reason that the nadir hemoglobin values of premature infants are lower than those of term infants is the former group's relatively diminished plasma EPO level in response to anemia (see Chapters 103.1 and 446). Another factor is the rapid disappearance of EPO from infant plasma (i.e., accelerated metabolism).

Low plasma EPO levels provide a rationale for the possible use of recombinant EPO in the treatment of anemia of prematurity; treatment with EPO and iron effectively stimulate neonatal erythropoiesis. Despite its erythropoietic effect, the efficacy of EPO therapy to substantially diminish the need for RBC transfusions has not been convincingly demonstrated, particularly for sick, extremely premature neonates, and recombinant EPO has not been widely accepted as a treatment for anemia of prematurity (see Chapter 103.1).

Because of the controversies over recombinant EPO therapy, many low birthweight preterm infants need RBC transfusions (see Table 470-1). Although the practice to maintain a very high hemoglobin level (hemoglobin >13 g/dL or hematocrit >40%) was once widely recommended, currently more restrictive guidelines have been suggested. Consistent with the rationale for oxygen delivery in neonates with severe respiratory disease, it seems appropriate to keep the hemoglobin value relatively high in neonates with *severe cardiac disease* leading to either cyanosis or congestive heart failure, but convincing and consistent data are lacking.

The optimal hemoglobin level for neonates facing major surgery has not been established. However, it seems reasonable to begin surgery in neonates with the hemoglobin level no lower than 10 g/dL (hematocrit >30%) and to maintain that value during major surgery because even modest blood loss will have a relatively large effect on the small blood volume of the neonate; neonates with underlying pulmonary problems have limited ability to compensate for anemia, and the inferior offloading of oxygen because of the diminished interaction between fetal hemoglobin and 2,3-diphosphoglycerate. Postoperatively, a lower pretransfusion hemoglobin value should be followed to "trigger" a transfusion.

Stable neonates do not require RBC transfusion, regardless of their blood hemoglobin levels, unless they exhibit clinical symptoms attributable to anemia. Proponents of RBC transfusions for symptomatic anemia in preterm neonates believe that the low RBC mass contributes to tachypnea, dyspnea, tachycardia, apnea and bradycardia, feeding difficulties, and lethargy, which can be alleviated by transfusion of RBCs. However, anemia is only one of several possible causes of these problems, and RBC transfusions should only be given when clinical benefit seems likely.

The RBC product of choice to transfuse neonates, infants, children, and adolescents is prestorage leukocyte-reduced RBCs suspended in an anticoagulant/preservative storage solution at a hematocrit value of approximately 60% for storage up to 42 days. The usual dose is 10-15 mL/kg, but transfusion volumes vary greatly, depending on clinical circumstances (continued vs. arrested bleeding, hemolysis). For neonates, some prefer a centrifuged RBC concentrate (hematocrit 70-90%). Unless transfusions are being given to treat rapid bleeding, RBCs are infused slowly (over 2-4 hr) at a dose of approximately 15 mL/kg. In this small-volume setting, because of the small quantity of extracellular fluid transfused and the slow rate of infusion, the type of RBC anticoagulant/preservative solution does not pose any risk for premature infants; there are no data to justify separate inventories of different RBC products for neonates and infants (e.g., citrate-phosphate-dextrose or citrate-phosphate-dextrose-adenine) versus older children (e.g., AS-1, AS-3, or AS-5).

The historical practice of transfusing fresh RBCs (<7 days of storage) for the small-volume (15 mL/kg) transfusions commonly given was supplanted several years ago in most centers by reserving a single unit of RBCs for an infant, from which multiple aliquots were obtained for transfusions as needed throughout the 42 days of storage. Concerns about high concentrations of extracellular potassium, loss of 2,3-diphosphoglycerate, altered RBC shape and deformability, and nitric oxide quenching were found not to pose clinically significant problems. Preterm neonates allocated to "fresh RBC" (<7 day storage) transfusions versus "stored RBC" (up to 42 day storage) transfusions,

have no advantage for fresh RBC transfusions in altering either the composite clinical outcome of mortality plus necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, and intraventricular hemorrhage or of the individual disorders.

For children weighing >30 kg who are to undergo elective surgery for which RBC transfusions are likely to be needed, autologous RBC transfusions offer an alternative to donor allogeneic RBCs. **Preoperative autologous** blood collections from the patient occur up to 6 wk before the surgery and require careful considerations for the volume to be drawn, vascular access, and use of EPO and iron to help restore the donated RBCs. **Acute normovolemic hemodilution** occurs in the preoperative period, in which blood is withdrawn from the patient and replaced with saline, a task often difficult in centers without experience in the process. **Salvaged autologous blood** is collected from blood loss during the operation but is impractical unless the volume of blood salvaged is fairly large to permit washing and transfusion of a significant number of RBCs. Because of all of these difficulties plus the relative safety of the usual allogeneic blood supply, autologous RBC transfusions are not commonly used in the pediatric setting.

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Chapter 471

Platelet Transfusions

Ronald G. Strauss

Guidelines for platelet (PLT) support of children and adolescents with quantitative and qualitative PLT disorders are similar to those for adults (Table 471-1), in whom the risk of life-threatening bleeding after injury or occurring spontaneously can be related somewhat imprecisely, particularly for the occurrence of spontaneous bleeding to the severity of thrombocytopenia.

For children and adolescents with overt bleeding, therapeutic PLT transfusions should be given when the blood PLT count falls below 50 × 10^9/L and repeated as needed to maintain the PLT count >50 × 10^9/L during bleeding and for 48 hr after bleeding ceases to allow the clot to "stabilize." Similarly, for a major invasive procedure (e.g., surgical procedure), the PLT count should be maintained >50 × 10^9/L until any bleeding that occurs ceases and the patient is stable. For minor invasive procedures (e.g., lumbar puncture or placing an intravascular catheter) practices vary, but it is reasonable to maintain the PLT count >25 × 10^9/L.

Table 471-1	Guidelines for Pediatric Platelet Transfusion*
CHILDREN AND ADOLESCENTS	
1. Maintain PLT count >50 × 10^9/L with bleeding	
2. Maintain PLT count >50 × 10^9/L with *major invasive* procedure; >25 × 10^9/L with minor	
3. Maintain PLT count >20 × 10^9/L and *marrow failure* WITH hemorrhagic risk factors	
4. Maintain PLT count >10 × 10^9/L and *marrow failure* WITHOUT hemorrhagic risk factors	
5. Maintain PLT count at any level with PLT dysfunction PLUS bleeding or invasive procedure	
INFANTS ≤4 MO OLD	
1. Maintain PLT count >100 × 10^9/L with bleeding or during extracorporeal membrane oxygenation	
2. Maintain PLT count >50 × 10^9/L and an invasive procedure	
3. Maintain PLT count >20 × 10^9/L and *clinically stable*	
4. Maintain PLT count >50 × 10^9/L and *clinically unstable and/or bleeding or not when on indomethacin, nitric oxide, antibiotics, etc. affecting PLT function*	
5. Maintain PLT count at any level with PLT dysfunction PLUS bleeding invasive procedure	

*Words in *italics* must be defined for local transfusion guidelines.
PLT, platelet.

Historical studies of patients with thrombocytopenia resulting from bone marrow failure suggest that the risk of spontaneous bleeding increases when blood PLT levels fall to <20 × 10^9/L particularly when hemorrhagic risk factors (infection, organ failure, clotting abnormalities, minor skin/mucosal bleeding, mucosal lesions, severe graft-versus-host disease, or anemia) are present. In this high-risk setting, prophylactic PLT transfusions are given to maintain a PLT count >20 × 10^9/L. This threshold has been challenged by several studies of adult patients, who, in many instances, were carefully selected to be in relatively good clinical condition *without* hemorrhagic risk factors. Consequently, a higher PLT transfusion trigger of 50 × 10^9/L is recommended for stable (i.e., low-risk) patients.

In practice, severe thrombocytopenia that is prolonged beyond 1 wk commonly becomes complicated by the development of risk factors including fever, antimicrobial therapy, graft-versus-host disease, active bleeding, need for an invasive procedure, disseminated intravascular coagulation, and liver or kidney dysfunction with clotting abnormalities. In these situations, prophylactic PLT transfusions are given to maintain relatively high PLT counts (e.g., at least >30 × 10^9/L). Despite the desire by some physicians to elevate the blood PLT count to 80 × 10^9/L or 100 × 10^9/L, there are no definitive data to justify a true benefit of PLT transfusions given at a PLT count >50 × 10^9/L, unless bleeding is ongoing with a PLT count between 50 and 100 × 10^9/L *and* thrombocytopenia seems to be the only cause for the bleeding.

Qualitative PLT disorders may be inherited or acquired (in advanced hepatic or renal insufficiency or when blood flows through an extracorporeal circuit, such as during extracorporeal membrane oxygenation or cardiopulmonary bypass). In patients with inherited disorders, PLT transfusions are justified only if the risk of significant bleeding is quite high or if bleeding is overt because inherited PLT dysfunction often is lifelong and repeated transfusions may lead to alloimmunization and refractoriness (i.e., poor response to PLT transfusions). Accordingly, prophylactic PLT transfusions are rarely justified, unless an invasive procedure is planned, and therapeutic PLT transfusions must be given judiciously.

When managing patients with PLT dysfunction, it is important to remember that, an abnormal test result with a modern PLT function device or, historically, a bleeding time more than twice the upper limit of normal provides diagnostic evidence of PLT dysfunction. However, an abnormal bleeding time or any other abnormal laboratory test is poorly predictive of hemorrhagic risk and/or the need to transfuse PLTs. Alternative therapies, particularly desmopressin acetate, should be considered to avoid PLT transfusions. Antiplatelet medications (nonsteroidal antiinflammatory drugs) should also be avoided.

In neonates, thrombopoiesis and the risks of bleeding are substantially different from that in older children; the approach to thrombocytopenia and PLT transfusions likewise differs (see Table 471-1). Thrombopoietin (TPO) levels are higher in healthy neonates than in older individuals. Megakaryocyte progenitors of neonates are more sensitive to TPO, have higher proliferative potential, and give rise to larger megakaryocyte colonies than do adult PLT progenitors. Fetal/neonatal megakaryocytes are smaller in size and have lower ploidy than do their adult counterparts; this is an important factor because small megakaryocytes of low ploidy produce fewer PLTs than larger megakaryocytes of higher ploidy. Presumably, this allows the expanding marrow of the growing fetus and neonate to be supplied with sufficient numbers of megakaryocytes, yet not allowing blood PLT counts to become excessively high during proliferation, because of the lower numbers of PLTs produced by each megakaryocyte.

An important contrasting point is that older children and adults respond to situations of increased demand for PLTs by first increasing megakaryocyte size and ploidy, which is followed in 3-5 days by

increased megakaryocyte number. In thrombocytopenic neonates, megakaryocyte numbers increase, but not their size. Moreover, although cytoplasmic maturation is achieved per TPO stimulation, increases in ploidy are relatively diminished and actually appear to be inhibited by TPO, resulting in large numbers of small megakaryocytes that are cytoplasmically mature, but with low ploidy and, consequently, lower PLT production.

Blood PLT counts $\geq 150 \times 10^9/L$ are present after 17 wk gestational age, and it is accepted that neonates have blood PLT counts in the same range as older children and adults (150,000-450,000/μL). However, recent data suggest a lower limit of 120,000/μL for extremely small preterm infants. Approximately 1% of term infants demonstrate PLT counts $<150 \times 10^9/L$, but bleeding in such infants is rare. In contrast, 25-35% of preterm of neonates treated in intensive care units exhibit blood PLT counts $<150 \times 10^9/L$ at some time during admission, with approximately 4% overall receiving PLT transfusions. Notably, when only extremely low birthweight preterm infants (<1 kg birthweight) were considered in one report, 73% had PLT counts $<150 \times 10^9/L$ and 62% of thrombocytopenic neonates received PLT transfusions. Multiple pathogenetic mechanisms underlie thrombocytopenia in these sick neonates; predominantly accelerated PLT destruction plus diminished PLT production, as evidenced by decreased numbers of megakaryocyte progenitors and relatively low upregulation of TPO levels during thrombocytopenia, compared with thrombocytopenic children and adults.

Blood PLT counts $<100 \times 10^9/L$ pose significant clinical risks for premature neonates. Bleeding time may be prolonged at PLT counts $<100 \times 10^9/L$ in infants with a birthweight <1.5 kg, and PLT dysfunction is suggested by bleeding times (a test no longer performed) that are disproportionately long for the degree of thrombocytopenia. The risk of hemorrhage may be increased in thrombocytopenic infants. However, in a randomized trial, transfusing PLTs prophylactically whenever the PLT count fell to $<150 \times 10^9/L$ (i.e., at the lower limit of the normal range) to maintain the average PLT count at $>200 \times 10^9/L$, compared to not transfusing PLTs until the PLT count fell to $<50 \times 10^9/L$ to maintain the average PLT count at approximately $100 \times 10^9/L$, did not result in a lower incidence of intracranial hemorrhage (28% vs. 26%, respectively). Thus, there is no documented benefit for prophylactic PLT transfusions to maintain PLT counts within the normal range or to correct modest thrombocytopenia (PLT count $>50 \times 10^9/L$). As an exception, infants with inherited PLT dysfunction disorders *and* bleeding, and those at high risk of bleeding owing to acquired PLT dysfunction, such as during extracorporeal membrane oxygenation, commonly receive transfusions to keep their PLT counts $>100 \times 10^9/L$.

Table 471-1 lists guidelines that are acceptable to many neonatologists. One particularly contentious issue is how to manage critically ill neonates receiving drugs/agents known to adversely affect PLT function (e.g., indomethacin, nitric oxide, antibiotics). Some reports suggest increased risk of bleeding for these neonates, but the efficacy of PLT transfusions has not been convincingly proven, particularly when given prophylactically. For optimal PLT transfusion practices, each hospital should modify the guidelines to comply with local practices, and audits/reviews should be performed to avoid violations of the recommended practices. The posttransfusion goal of most PLT transfusions is to raise the PLT count well above $50 \times 10^9/L$, hopefully to $\geq 100 \times 10^9/L$. These increases can be achieved consistently in children weighing up to 30 kg by infusion of 5-10 mL/kg of standard (unmodified) PLT concentrates, obtained either from processing whole blood units or by plateletpheresis. For larger children, the appropriate dose is 3-4 pooled whole blood–derived PLT units or 1 apheresis unit. Because PLT concentration/quantity varies in different PLT products made available for transfusion, each hospital should monitor posttransfusion PLT counts to determine the dose that works best locally. PLT concentrates should be transfused as rapidly as the patient's overall condition permits, certainly within 2 hr. Neonates/infants requiring repeated PLT transfusions should receive leukocyte-reduced blood products, including PLT concentrates, to diminish alloimmunization and PLT refractoriness and to reduce the risk of transfusion-transmitted cytomegalovirus infection.

Routinely reducing the volume of PLT concentrates for infants and small children by additional centrifugation steps is both unnecessary and unwise. Transfusion of 10 mL/kg of an unmodified PLT concentrate is adequate because it adds approximately 10×10^9 PLTs to 70 mL of blood (the estimated intravascular blood volume of a 1 kg neonate), a dose/volume calculated to increase the PLT count by $100 \times 10^9/L$. This calculated increment is consistent with actual posttransfusion increment reported in patients. Moreover, 10 mL/kg is not an excessive transfusion volume, provided that the intake of other IV fluids, medications, and nutrients is monitored and adjusted.

It is important to select PLT units for transfusion with the donor ABO group identical to that of the neonate/infant and to avoid repeated transfusion of group O PLTs to group A or B recipients because passive transfusion anti-A or anti-B in group O plasma, can occasionally lead to hemolysis.

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Chapter **472**

Neutrophil (Granulocyte) Transfusions

Ronald G. Strauss

Table 472-1 lists guidelines for granulocyte transfusion (GTX). GTX has been used sparingly in older infants and children. The current ability to collect markedly higher numbers of neutrophils from donors stimulated with combined recombinant granulocyte colony-stimulating factor (G-CSF) plus dexamethasone has led to renewed interest for patients with neutropenic infections, particularly when severe neutropenia is prolonged (e.g., in the setting of placental/cord blood hematopoietic progenitor cell transplantation). Because of the higher neutrophil yields with this collection approach, adding GTX to antibiotics should be considered at institutions where neutropenic patients continue either to die of progressive bacterial and fungal infections or to suffer substantial morbidity despite optimal antiinfection measures, including antibiotics and recombinant myeloid growth factors.

The use of GTX added to antibiotics for children with severe neutropenia (blood neutrophil count $<0.5 \times 10^9$/L) because of bone marrow failure is similar to that for adults. Unfortunately, two randomized clinical trials comparing antibiotics plus GTX from donors stimulated with G-CSF plus dexamethasone versus antibiotics without GTX

Table 472-1	Guidelines for Pediatric Granulocyte Transfusions*
CHILDREN AND ADOLESCENTS	
1. Severe neutropenia (blood neutrophil count $<0.5 \times 10^9$/L) and infection (bacterial, yeast, or fungal) *unresponsive or progressive* despite appropriate antimicrobial therapy	
2. Qualitative neutrophil defect, neutropenia not required, and infection (bacterial or fungal) *unresponsive or progressive* to appropriate antimicrobial therapy	
INFANTS ≤4 MO OLD†	
Blood neutrophil count $<3.0 \times 10^9$/L in 1st wk of life or $<1.0 \times 10^9$/L thereafter and *fulminant* bacterial infection.	

*Words in italics must be defined for local transfusion guidelines.
†No longer commonly used.

to treat neutropenic infections in children have not provided definitive guidelines. However in practice, neutropenic patients with bacterial infections usually show response to antibiotics alone, provided bone marrow function recovers within the 1st 7-10 days of infection onset so that severe neutropenia is relatively brief. Children with newly diagnosed acute lymphoblastic leukemia show rapid response to induction chemotherapy, and they rarely are candidates for GTX. In contrast, infected children with more sustained bone marrow failure and consequent severe neutropenia (e.g., acute myeloblastic leukemia, malignant neoplasms resistant to treatment, severe aplastic anemia, and placental/cord blood hematopoietic progenitor cell transplant recipients) may benefit when GTX is added to antibiotics.

Currently, the efficacy of GTX obtained from G-CSF plus dexamethasone-stimulated donors for bacterial sepsis unresponsive to antibiotics in patients with severe neutropenia (blood neutrophil count $<0.5 \times 10^9/L$) is not well supported by trials in children. In contrast, GTX efficacy for yeast and fungal infections remains unproven despite transfusing GTX with relatively large numbers of neutrophils.

Children with qualitative neutrophil defects (**neutrophil dysfunction**) usually have adequate or even increased numbers of blood neutrophils but suffer serious infections, because their neutrophils kill pathogenic microorganisms inefficiently. Neutrophil dysfunction syndromes are rare; accordingly, no definitive studies have established GTX efficacy. However, several patients with progressive life-threatening infections have shown striking improvement with the addition of GTX, often given for long periods of time, to antimicrobial therapy. These disorders are chronic, and because of the risk of inducing alloimmunization to leukocyte antigens, and in some patients with chronic granulomatous disease, to antigens of the Kell system of red blood cells, GTX is recommended only when serious infections are clearly unresponsive to antimicrobial drugs.

Neonates are unusually susceptible to severe bacterial infections, and a number of defects of neonatal body defenses contribute, including actual or "relative" neutropenia. Neonates with fulminant sepsis who exhibit relative neutropenia (blood neutrophil count $<3.0 \times 10^9/L$ during the 1st wk of life and $<1.0 \times 10^9/L$ thereafter) and a severely diminished neutrophil marrow storage pool (with <10% of nucleated marrow cells being postmitotic neutrophils) are at risk of dying if treated only with antibiotics. GTX is rarely used because results of clinical trials are mixed and not uniformly convincing, and it is difficult to obtain neutrophil apheresis concentrates in timely fashion.

Current data are insufficient to determine whether recombinant myeloid growth factors have a role in treating septic neonates, despite the fact that both G-CSF and granulocyte-macrophage colony-stimulating factor have been demonstrated to enhance myelopoiesis and raise neutrophil counts in infants. Importantly, G-CSF is efficacious for the long-term treatment of several types of severe congenital neutropenia.

If the decision to provide a GTX has been made, an adequate dose of neutrophils/granulocytes collected by leukapheresis must be transfused as shortly after collection as possible. To facilitate this, experienced donors with required infectious disease (HIV, hepatitis) tests having been done recently (usually within the past 30 days) are selected, and the collected neutrophils are transfused before results of current infectious disease tests are known (i.e., infectious disease test results are "waived").

Neonates and infants weighing <10 kg should receive $1\text{-}2 \times 10^9/kg$ neutrophils per each GTX. Larger infants and small children should receive a minimal total dose of 1×10^{10} neutrophils per each GTX. The preferred dose for adolescents is $5\text{-}8 \times 10^{10}$ neutrophils per each GTX, a dose requiring donors to be stimulated with G-CSF plus dexamethasone. GTX should be given daily until either the infection resolves or the blood neutrophil count is sustained above $1.5 \times 10^9/L$ for a few days. Because neutrophils transfused per the GTX often passively increase the blood neutrophil count, it may be necessary to skip 1-2 days of GTXs to be certain severe neutropenia does not recur, as would be seen if endogenous myelopoiesis had not recovered.

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Chapter 473

Plasma Transfusions

Ronald G. Strauss

Guidelines for plasma transfusion in pediatric patients (Table 473-1) are similar to those for adults but with the understanding that plasma levels of coagulant and anticoagulant proteins can be developmentally quite low in preterm infants so that transfusions of plasma and plasma-derived commercial concentrates should be determined by actual bleeding or a significant risk of bleeding, not simply prolonged clotting time results. Plasma is transfused to replace clinically significant deficiencies of plasma proteins for which more highly purified protein concentrates that have been treated to reduce infectious disease risks are not available nearly always to provide clotting proteins when bleeding is occurring or in settings when prevention of bleeding is deemed critical.

Two interchangeable plasma products are available for transfusion, plasma frozen within 8 hr of collection (**fresh-frozen plasma**) and plasma frozen within 24 hr of collection. Although levels of factors V and VIII are modestly reduced in the latter plasma product (generally, not more than 25% lower), they are equally efficacious for all indications for which plasma is transfused (see Table 473-1). Recommendations for the volume of plasma to be transfused vary with the specific protein being replaced and the severity of the deficiency, but a starting dose of 15 mL/kg is usually sufficient to elevate plasma levels satisfactorily.

Transfusion of plasma is efficacious for the treatment of deficiencies of clotting factors II, V, X, and XI. Deficiencies of factor XIII and fibrinogen are treated either with cryoprecipitate or specific commercial concentrates; although for patients being given large doses of plasma (e.g., in massive transfusion settings or to treat bleeding in liver failure), additional sources of fibrinogen may not be necessary, as plasma contains large amounts of fibrinogen. It is always useful to include a measurement of plasma fibrinogen when performing clotting assays (e.g., prothrombin time [PT]/international normalized ratio [INR] and activated partial thromboplastin time [aPTT]). *Transfusion of plasma is not recommended for the treatment of patients with severe hemophilia A or B, von Willebrand disease, or factor VII deficiency, because safer factors VII, VIII, IX, and von Willebrand factor concentrates are available.* Moreover, mild to moderate hemophilia A and certain types of von Willebrand disease can be treated with intranasal or intravenous desmopressin (see Chapter 477). An important use of plasma is for rapid reversal of the effects of warfarin in patients who are actively bleeding or who require emergency surgery (in whom

Table 473-1	Guidelines for Pediatric Plasma Transfusions*
1. *Severe* clotting factor deficiency AND bleeding	
2. *Severe* clotting factor deficiency AND an invasive procedure	
3. *Emergency reversal* of warfarin effects	
4. Dilutional coagulopathy and bleeding (e.g., massive transfusion)	
5. Anticoagulant protein (antithrombin III, proteins C and S) replacement	
6. Plasma exchange replacement fluid for thrombotic thrombocytopenic purpura or for disorders with overt bleeding or in which there is risk of bleeding because of clotting protein abnormalities (e.g., liver failure)	

*Words in *italics* must be defined for local transfusion guidelines.

functional deficiencies of factors II, VII, IX, and X cannot be rapidly reversed by vitamin K). Prothrombin "complex" concentrates can also be used for this purpose.

Results of screening coagulation tests (PT/INR, aPTT, and thrombin times, and plasma fibrinogen levels) should not be assumed by themselves to reflect the integrity of the coagulation system or be regarded as indications for plasma transfusions. This is particularly true for neonates. To justify plasma transfusions, coagulation test results must be related to the patient's clinical condition pertaining to bleeding and/or the risk of bleeding. Transfusion of plasma in patients with chronic liver disease and prolonged clotting times is not recommended unless bleeding is present or an invasive procedure is planned, because correction of the clotting factor deficiencies is brief and of questionable benefit.

Plasma also contains several anticoagulant proteins (antithrombin III, protein C, and protein S) whose deficiencies have been associated with **thrombosis**. In selected situations, plasma may be appropriate as replacement therapy, along with anticoagulant treatment, in patients with these disorders; when available, purified concentrates are preferred. Other indications for plasma include replacement fluid during plasma exchange in patients with thrombotic thrombocytopenic purpura (i.e., thrombotic microangiopathies) or other disorders for which plasma is likely to be beneficial (plasma exchange in a patient with overt bleeding due to the underlying disorder such as Goodpasture syndrome or vasculitis or disorders with significant severe coagulopathy that would be made substantially more severe by replacement using albumin solutions only). Plasma is not indicated for correction of hypovolemia or as immunoglobulin replacement therapy, because safer alternatives exist (albumin or crystalloid solutions and IV immunoglobulin, respectively).

In neonates, clotting times are "physiologically" prolonged owing to developmental deficiency of clotting proteins; plasma should be transfused only after reference to normal values adjusted for the birthweight and age of the infant (i.e., not to normal ranges for older children and adults). The indications for plasma in neonates include: (1) reconstitution of red blood cell (RBC) concentrates to simulate whole blood for use in massive transfusions (exchange transfusion, cardiac bypass surgery, and extracorporeal membrane oxygenation); (2) hemorrhage secondary to vitamin K deficiency; (3) disseminated intravascular coagulation *with* bleeding; and (4) bleeding in congenital coagulation factor deficiency when more specific treatment is either unavailable or inappropriate. The use of prophylactic plasma transfusion to prevent intraventricular hemorrhage in premature infants is not recommended. Plasma should not be used as a suspending agent to adjust the hematocrit values of RBC concentrates before small-volume RBC transfusions to neonates because it offers no apparent medical benefit over the use of sterile solutions such as crystalloid and albumin. Similarly, the use of plasma in partial exchange transfusion for the treatment of neonatal hyperviscosity syndrome is unnecessary, because safer crystalloid or colloid solutions are available.

In the treatment of bleeding infants, cryoprecipitate is often considered because of its small infusion volume. However, cryoprecipitate contains significant quantities of only fibrinogen, von Willebrand factor, and factors VIII and XIII. Thus, it is not effective for treating the usual clinical situation in bleeding infants in which multiple clotting factor deficiencies exist.

In preliminary studies, infusions of very small volumes of recombinant activated factor VII have been lifesaving in patients with hemorrhage caused by several mechanisms. Because the efficacy and toxicity of factor VIIa have not been fully defined in these "off-label" uses (not approved by the U.S. Food and Drug Administration), it must be considered experimental therapy at this time.

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Chapter 474

Risks of Blood Transfusions

Ronald G. Strauss

The greatest risk of a blood transfusion is receiving a transfusion intended for another patient; misidentification usually as a result of mistakes made labeling the patient's blood sample sent to the blood bank or not accurately matching the unit with the patient at the time the blood is transfused. This risk is particularly high for infants because identification bands may not be attached directly to their bodies, difficulties in drawing blood samples for pretransfusion compatibility testing may lead to deviations from usual policies, and infants cannot speak to identify themselves. Thus, particular care must be taken to ensure accurate patient and blood sample identification.

Although the infectious disease risks of allogeneic blood transfusions are extremely low, transfusions must be given judiciously because "emerging infections" are a constant threat, and testing is not done for every microorganism possibly transmitted by blood transfusions (Table 474-1, Fig. 474-1). Taking nucleic acid amplification testing

Table 474-1 Estimated Risks in Transfusion Per Unit Transfused in the United States

ADVERSE EFFECT	ESTIMATED RISK
Febrile reaction	1/300
Urticaria or other cutaneous reaction	1/50-100
Red blood cell alloimmunization	1/100
Mistranfusion	1/14,000-19,000
Hemolytic reaction	1/6,000
Fatal hemolysis	1/1,000,000
Transfusion-related acute lung injury (TRALI)	1/5,000
HIV1 and HIV2	1/2,000,000-3,000,000
Hepatitis B	1/100,000-200,000
Hepatitis C	1/1,000,000-2,000,000
Human T-cell lymphotrophic virus (HTLV) I and II	1/641,000
Bacterial contamination (usually platelets)	1/5,000,000
Malaria	1/4,000,000
Anaphylaxis	1/20,000-50,000
Graft-versus-host disease	Uncommon
Immunomodulation	Unknown
Hepatitis A	Unknown
Parvovirus	Unknown
Dengue fever	Unknown
Babesiosis	Unknown
West Nile virus	Unknown
Trypanosoma cruzi	Unknown
Leishmania spp.	Unknown
Variant Creutzfeldt-Jakob prion disease	Unknown

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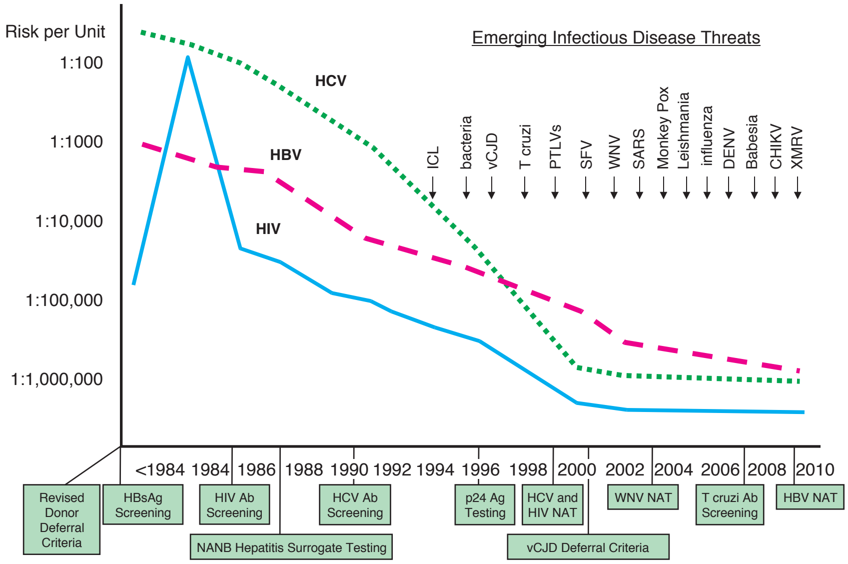

Figure 474-1 **Risks of major transfusion-transmitted viruses related to interventions, and accelerating rate of emerging infectious diseases of concern to blood safety.** Evolution of the risks of transmission by blood transfusion for HIV, hepatitis B virus, and hepatitis C virus. Major interventions to reduce risks are shown below the time line on the x axis. Emerging infectious disease threats in the past 20 yr are shown above in the top right quadrant of the figure. Ab, antibody; Ag, antigen; CHIKV, chikungunya virus; DENV, dengue virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; ICL, idiopathic CD4 T-lymphocytopenia; NANB, non-A, non-B hepatitis; NAT, nucleic acid testing; PTLVs, primate T lymphotropic viruses; SARS, severe acute respiratory syndrome; SFV, simian foamy virus; vCJD, variant Creutzfeldt-Jakob disease; WNV, West Nile virus; XMRV, xenotropic murine leukemia virus-related virus. *(From Busch MP. Transfusion-transmitted viral infections: building bridges to transfusion medicine to reduce risks and understand epidemiology and pathogenesis. 2005 Emily Cooley Award Lecture,* Transfusion *46:1624-1640, 2006.)*

(NAT) and all other donor-screening activities (antibody and epidemiology screening) into account, a current estimate of the risk of transfusion-associated HIV is approximately 1 per every 2,000,000 donor exposures. Similarly, with NAT, the risk of viral hepatitis C is 1 per every 1,500,000-2,000,000 donor exposures (Table 474-1). NAT identifies circulating viral nucleic acids that appear in the window period before antibodies develop, and NAT is used routinely to detect HIV, hepatitis C, and West Nile virus. NAT is also available for hepatitis B, but its use for this purpose is variable and controversial.

Transfusion-associated cytomegalovirus (CMV) has been nearly eliminated by transfusion of leukocyte-reduced cellular blood products or by selection of blood collected from donors who are seronegative for antibody to CMV. Although it is logical to hypothesize that first collecting blood components from CMV-seronegative donors and then removing the white blood cells might further improve safety, no data are available to document the superior efficacy of this combined approach. Importantly, considerable care must be taken not to place children at risk of delayed or missed transfusions while awaiting/searching for blood from CMV-seronegative donors to, then, leukocyte-reduce (i.e., risks must not be taken for practices with no established benefits).

Another consideration is that emerging data suggest that this combined approach using CMV-seronegative blood, surprisingly, may be incorrect. Large quantities of CMV viral material are present “free” in the plasma of healthy-appearing donors during the early phase of primary infection (while CMV antibodies are either absent [“window” phase] or are newly emerging and are at low inconsistently detected levels in plasma), rather than being leukocyte-associated as occurs with CMV as substantial quantities of immunoglobulin G antibodies appear. As a result of this biology of CMV primary infection, plasma “free” virus will not be removed by leukocyte-reduction during early infection, and CMV-seronegative donors who may be asymptomatic or deny symptoms of infection during blood donor screening will be misclassified as being CMV safe. They are not safe because antibody is below the limits of detection, while plasma “free” CMV is plentiful during early infection. Because nearly all plasma “free” CMV disappears and becomes almost exclusively cell-associated, once donors are CMV-seropositive with antibody present for several months, it has been proposed that the best method to reduce CMV risk may be to effectively perform leukocyte reduction of blood from donors known to be CMV-seropositive for at least 1 year. However, data to prove the efficacy of this proposal are lacking, and in practice, several studies have shown that the most efficacious method currently available to prevent transfusion-transmitted CMV is to perform leukocyte-reduction in the blood center/bank without regard for the CMV-antibody status of the donor/unit (i.e., leukocyte-reduction alone performed by the blood center/bank is sufficient).

Additional infectious risks include other types of hepatitis (A, B, E) and retroviruses (human T-cell lymphotropic virus types I and II, and HIV-2), syphilis, parvovirus B19, Epstein-Barr virus, human herpesvirus 8, West Nile virus, yellow fever vaccine virus, malaria, babesiosis, *Anaplasma phagocytophilum*, and Chagas disease. Variant Creutzfeldt-Jacob disease has also been transmitted by blood transfusions in humans. All are reported very uncommonly, but nonetheless, provide the rationale to transfuse only when true benefits are likely.

Transfusion-associated risks of a noninfectious nature that may occur include hemolytic and nonhemolytic transfusion reactions, fluid overload, graft versus host disease, electrolyte and acid-base imbalances, iron overload if repeated transfusions are needed long term, increased susceptibility to oxidant damage, exposure to plasticizers, hemolysis with T-antigen activation of red blood cells, posttransfusion purpura, transfusion-related acute lung injury, post-transfusion immunosuppression and immunomodulation, and alloimmunization (see Table 474-1). The risk of transfusion-related acute lung injury may be reduced by reducing the use of plasma or platelets from female donors who were possibly sensitized during pregnancy or are negative for human leukocyte antigen (HLA) antibodies.

Immunologic adverse effects, including immunosuppression, immunomodulation, and alloimmunization may be reduced by leukocyte-reduction. Transfusion reactions and alloimmunization to red blood cell and leukocyte antigens seem to be uncommon in infants, perhaps because of developmental immaturity of the immune system or deficient cytokine production. When they do occur, adverse effects are seen primarily in massive transfusion settings, such as exchange

transfusions and trauma or surgery, in which relatively large quantities of blood are needed but are rare with the small-volume transfusions usually given.

Premature infants are known to have immune dysfunction, but their relative risk of posttransfusion graft-versus-host disease is controversial. The postnatal age of the infant, the number of immunocompetent lymphocytes in the transfusion product, the degree of HLA compatibility between donor and recipient, and other poorly described phenomena determine which infants are truly at risk for graft-versus-host disease. Regardless, many centers caring for preterm infants transfuse exclusively irradiated cellular products. Directed donations with blood drawn from blood relatives must always be irradiated because of the risk of engraftment with transfused HLA-homozygous, haploidentical lymphocytes. Cellular blood products given as intrauterine and/or exchange transfusions should be irradiated, as are transfusions for patients with severe congenital immunodeficiency disorders (severe combined immunodeficiency syndrome and DiGeorge syndrome requiring heart surgery) and transfusions for recipients of hematopoietic progenitor cell transplants. Other groups who are potentially at risk but for whom no conclusive data are available include patients given T-cell antibody therapy (antithymocyte globulin or OKT3), those with organ allografts, those receiving immunosuppressive drug regimens, and those infected with HIV.

Current practice uses irradiation from a cesium, cobalt, or linear acceleration source at doses ranging from 2,500-5,000 cGy; a minimum dose of 2,500 cGy is required. All cellular blood components should be irradiated, but frozen "acellular" products, such as plasma and cryoprecipitate, do not require it. Leukocyte reduction cannot be substituted for irradiation to prevent graft versus host disease.

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Section 7

Hemorrhagic and Thrombotic Diseases

Chapter 475

Hemostasis

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Hemostasis is the active process that clots blood in areas of blood vessel injury yet simultaneously limits the clot size only to the areas of injury. Over time, the clot is lysed by the fibrinolytic system, and normal blood flow is restored. If clotting is impaired, hemorrhage occurs. If clotting is excessive, thrombotic complications ensue. The hemostatic response needs to be rapid and regulated such that trauma does not trigger a systemic reaction but must initiate a rapid, localized response. Key to the speed and coordination of response is that when a platelet adheres to a site of vascular injury, the platelet surface provides a reaction surface where clotting factors bind. The active enzyme is brought together with its substrate and a catalytic cofactor on a reaction surface, accelerating reaction rates and providing activated products for reaction with clotting factors further down the coagulation cascade. Active clotting is controlled by negative feedback loops that inhibit the clotting process when the procoagulant process comes in contact with intact endothelium. The main components of the hemostatic process are the **vessel wall, platelets, coagulation proteins, anticoagulant proteins,** and **fibrinolytic system.** Most components of hemostasis are multifunctional; fibrinogen serves as the ligand between platelets during platelet aggregation and also serves as the substrate for thrombin that forms the fibrin clot. Platelets provide the reaction surface on which clotting reactions occur, form the plug at the site of vessel injury, and contract to constrict and limit clot size.

THE PROCESS

The intact vascular endothelium is the primary barrier against hemorrhage. The endothelial cells that line the vessel wall normally inhibit coagulation and provide a smooth surface that permits rapid blood flow.

After vascular injury, vasoconstriction occurs and flowing blood comes in contact with the subendothelial matrix (Fig. 475-1). In flowing blood, when exposed to subendothelial matrix proteins, von Willebrand factor (VWF) changes conformation and provides the glue to which the platelet VWF receptor, the glycoprotein Ib complex, binds, tethering platelets to sites of injury. When the VWF receptor binds its ligand, complex signaling occurs from the outside membrane receptor to intracellular pathways, activating the platelets and triggering secretion of storage granules containing adenosine diphosphate (ADP), serotonin, and stored plasma and platelet membrane proteins. Upon activation, the platelet receptor for fibrinogen, $\alpha IIb\beta_3$, is switched on ("inside out" signaling) to bind fibrinogen and triggers the aggregation and recruitment of other platelets to form the platelet plug. Multiple physiologic agonists can trigger platelet activation and aggregation, including ADP, collagen, thrombin, and arachidonic acid. Aggregation involves the interaction of specific receptors on the platelet surface with plasma hemostatic proteins, primarily fibrinogen.

One of the subendothelial matrix proteins that are exposed after vascular injury is tissue factor. Just as exposed subendothelial matrix proteins bind VWF, exposed tissue factor binds to factor VII and

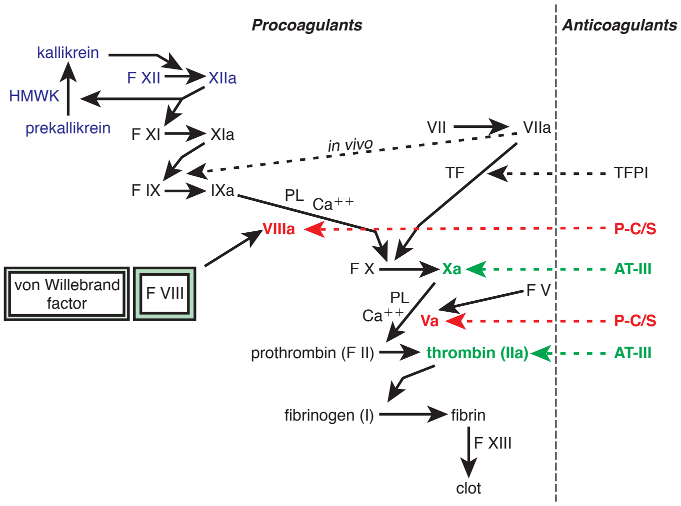

Figure 475-1 The clotting cascade, with sequential activation and amplification of clot formation. Many of the factors (F) are activated by the clotting factors shown above them in the cascade. The activated factors are designated by the addition of an *a*. On the right side, the major anticoagulants and the sites that they regulate are shown: Tissue factor pathway inhibitor (TFPI) regulates tissue factor [TF]); factor VIIa, protein C, and protein S (P-C/S) regulate factors VIII and V; and antithrombin III (AT-III) regulates factor Xa and thrombin (factor IIa). The *dotted line* shows that, in vivo, TF and factor VIIa activate both factors IX and X, but that, in vitro, only the activation of factor X is measured. Unactivated factor VIII, when bound to its carrier protein, von Willebrand factor, is protected from protein C inactivation. When thrombin, or factor Xa activates factor VIII, it becomes unbound from von Willebrand factor, whereupon it can participate with factor IXa in the activation of factor X in the presence of phospholipid (PL) and Ca^{2+} (the "tenase" complex). Factor XIIIa crosslinks the fibrin clot and thereby makes it more stable. Prekallikrein, high-molecular-weight kininogen (HMWK), and factor XII are shown in *blue* because they do not have a physiologic role in coagulation, although they contribute to the clotting time in partial thromboplastin time (PTT).

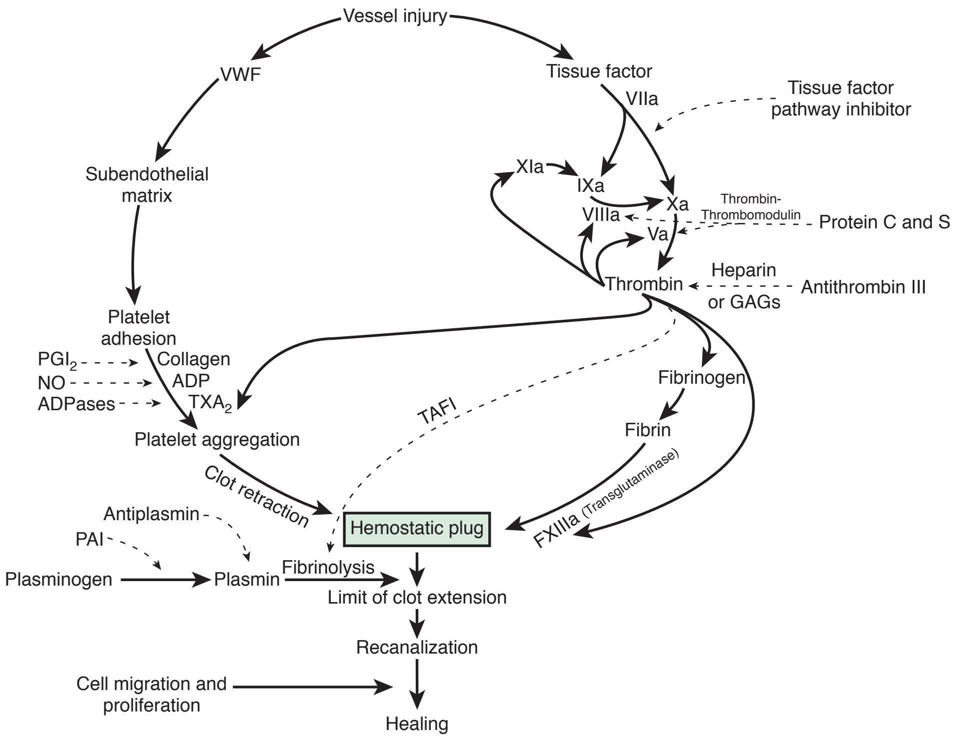

Figure 475-2 The hemostatic mechanism. ADP, adenosine diphosphate; GAGs, glycosaminoglycans; NO, nitric oxide; PGI_2, prostacyclin; PAI, plasminogen activator inhibitor; TAFI, thrombin-activated fibrinolytic inhibitor; TXA_2, thromboxane A_2; VWF, von Willebrand factor.

activates the clotting cascade, as shown in Figure 475-2. The activated clotting factor then initiates the activation of the next sequential clotting factor in a systematic manner. Our understanding of the sequence of steps in the cascade followed assignment of the numerals for the clotting factors for the participant proteins, and thus the sequence seems "out of numerical order." During the process of platelet activation, internalized platelet phospholipids (primarily phosphatidylserine) become externalized and interact at 2 specific, rate-limiting steps in the clotting process—those involving the cofactors factor VIII (X-ase complex) and factor V (prothrombinase complex). Both of these reactions are localized to the platelet surface and bring together the active enzyme, an activated cofactor, and the zymogen that will form the next active enzyme in the cascade. This sequence results in amplification of the process, which supplies a burst of clotting where it is physiologically needed. In vivo, autocatalysis of factor VII generates small amounts of VIIa continuously, so the system is always poised to act. Near the bottom of the cascade, the multipotent enzyme thrombin is formed. Thrombin converts fibrinogen into fibrin, activates factors V, VIII, and XI, and aggregates platelets. Activation of factor XI by thrombin amplifies further thrombin generation and contributes to inhibition of fibrinolysis. Thrombin also activates factor XIII. The stable fibrin-platelet plug is ultimately formed through clot retraction and cross linking of the fibrin clot by factor XIIIa.

Virtually all procoagulant proteins are balanced by an anticoagulant protein that regulates or inhibits procoagulant function. Four clinically important, naturally occurring anticoagulants regulate the extension of the clotting process: antithrombin III (AT-III), protein C, protein S, and tissue factor pathway inhibitor. AT-III is a serine protease inhibitor that regulates factor Xa and thrombin primarily and factors IXa, XIa, and XIIa to a lesser extent. When thrombin in flowing blood encounters intact endothelium, thrombin binds to thrombomodulin, its endothelial receptor. The thrombin–thrombomodulin complex then converts protein C into activated protein C. In the presence of the cofactor protein S, activated protein C proteolyses and inactivates factor Va and factor VIIIa. Inactivated factor Va is, in fact, a functional anticoagulant that inhibits clotting. Tissue factor pathway inhibitor limits activation of factor X by factor VIIa and tissue factor and shifts the activation site of tissue factor and factor VIIa to that of factor IX (see Figs. 475-1 and 475-2).

Once a stable fibrin-platelet plug is formed, the fibrinolytic system limits its extension and also lyses the clot (fibrinolysis) to reestablish vascular integrity. Plasmin, generated from plasminogen by either urokinase-like or tissue-type plasminogen activator, degrades the fibrin clot. In the process of dissolving the fibrin clot, fibrin degradation products are produced. The fibrinolytic pathway is regulated by plasminogen activator inhibitors and α_2-antiplasmin, as well as by the thrombin-activatable fibrinolysis inhibitor. Finally, the flow of blood in and around the clot is crucial, because flowing blood returns to the liver, where activated clotting factor complexes are removed and new procoagulant and anticoagulant proteins are synthesized to maintain homeostasis of the hemostatic system.

PATHOLOGY

Congenital deficiency of an individual procoagulant protein leads to a bleeding disorder, whereas deficiency of an anticoagulant (clotting factor inhibitor) predisposes the patient to thrombosis. In acquired hemostatic disorders, there are frequently multiple problems with homeostasis that perturb and dysregulate hemostasis. A primary illness (sepsis) and its secondary effects (shock and acidosis) activate coagulation and fibrinolysis and impair the host's ability to restore normal hemostatic function. When sepsis triggers **disseminated intravascular coagulation,** platelets, procoagulant clotting factors, and anticoagulant proteins are consumed, leaving the hemostatic system unbalanced and prone to bleeding or clotting. Similarly, newborn infants and patients with severe liver disease have synthetic deficiencies of both procoagulant and anticoagulant proteins. Such dysregulation causes the patient to be predisposed to both hemorrhage and thrombosis with mild or moderate triggers that result in major alterations in the hemostatic process.

In the laboratory evaluation of hemostasis, parameters are manipulated to allow assessment of isolated aspects of hemostasis and limit the multifunctionality of some of its components. The coagulation

process is studied in plasma anticoagulated with citrate to bind calcium, with added phospholipid to mimic the reaction surface normally provided by the platelet membrane and with a stimulus to trigger clotting. Calcium is added to restart the clotting process. This results in anomalies such that the in vivo physiologic pathway of clotting in which factor VIIa activates factor IX is bypassed; instead, in prothrombin time (PT), factor VIIa activates factor X. If this were truly the physiologic situation, then there would be an in vivo bypass mechanism that would ameliorate severe factor VIII and factor IX deficiencies, the 2 most common severe bleeding disorders.

475.1 Clinical and Laboratory Evaluation of Hemostasis

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HISTORY

For most hemostatic disorders, the clinical history provides the most useful information. To evaluate for a bleeding disorder, the history should determine the site or sites of bleeding, the severity and duration of hemorrhage, and the age at onset. Was the bleeding spontaneous, or did it occur after trauma? Was there a previous personal or family history of similar problems? Did the symptoms correlate with the degree of injury or trauma? Does bruising occur spontaneously? Are there lumps with bruises for which there is minimal trauma? If the patient had previous surgery or significant dental procedures, was there any increased bleeding? If a child or adolescent has had surgery that affects the mucosal surfaces, such as a tonsillectomy or major dental extractions, the absence of bleeding usually rules out a hereditary bleeding disorder. Delayed or slow healing of superficial injuries may suggest a hereditary bleeding disorder. In postpubertal females, it is important to take a careful menstrual history. Because some common bleeding disorders, such as von Willebrand disease (VWD), have a fairly high prevalence, mothers and family members may have the same mild bleeding disorder and may not be cognizant that the child's menstrual history is abnormal. Women with mild VWD who have a moderate history of bruising frequently have a reduction of that bruising during pregnancy or after administration of oral contraceptives. Some medications, such as aspirin and other nonsteroidal antiinflammatory drugs, inhibit platelet function and increase bleeding symptoms in patients with a low platelet count or abnormal hemostasis. Standardized bleeding scores have been developed and are undergoing investigation for their sensitivity and specificity in children.

Outside the neonatal period, thrombotic disorders are relatively rare until adulthood. In the neonate, physiologic deficiencies of procoagulants and anticoagulants cause the hemostatic mechanism to be dysregulated, and clinical events can lead to either hemorrhage or thrombosis. If a child or teenager presents with deep venous thrombosis or pulmonary emboli, a detailed family history must be obtained to evaluate for deep venous thrombosis, pulmonary emboli, myocardial infarction, or stroke in other family members. The presence of thrombosis, especially in the absence of a provoking agent in the child or teenager, should induce the clinician to take a careful family history and consideration of evaluation for a hereditary or acquired predisposition to thrombosis.

PHYSICAL EXAMINATION

The physical examination should focus on whether bleeding symptoms are associated primarily with the mucous membranes or skin (mucocutaneous bleeding) or with the muscles and joints (deep bleeding). The examination should determine the presence of petechiae, ecchymoses, hematomas, hemarthroses, or mucous membrane bleeding. Patients with defects in platelet-blood vessel wall interaction (VWD or platelet function defects) usually have mucocutaneous bleeding, which may include epistaxis, menorrhagia, petechiae, ecchymoses, occasional hematomas, and, less commonly, hematuria and gastrointestinal bleeding. Individuals with a clotting factor deficiency of factor VIII or IX (hemophilia A or B) have symptoms of deep bleeding into muscles and joints, with much more extensive ecchymoses and hematoma formation. Patients with mild VWD or other mild bleeding disorders may have no abnormal findings on physical examination. Individuals with disorders of the collagen matrix and vessel wall may have loose joints and lax skin associated with easy bruising (**Ehlers-Danlos syndrome**).

Patients undergoing evaluation for thrombotic disorders should be asked about swollen, warm, tender extremities or internal organs (venous thrombosis), unexplained dyspnea or persistent "pneumonia," especially in the absence of fever (pulmonary emboli), and varicosities and postphlebitic changes. Arterial thrombi usually cause an acute, dramatic impairment of organ function, such as stroke, myocardial infarction, or a painful, white, cold extremity.

LABORATORY TESTS

In patients who have a positive bleeding history or who are actively hemorrhaging, a platelet count, PT, and partial thromboplastin time (PTT) should be performed as screening tests. In individuals with abnormal screening tests, further evaluation should be based upon those results. In a patient with an abnormal bleeding history and a positive family history, normal screening tests should not preclude further laboratory evaluation, which may include a thrombin time, VWF testing, and platelet function studies.

There are no useful routine screening tests for hereditary thrombotic disorders. If the family history is positive or clinical thrombosis is unexplained, specific thrombophilia assays should be performed. Thrombosis is rare in children, and when it is present, the possibility of a hereditary predisposition should be considered (see Chapter 478).

Platelet Count

Platelet count is essential in the evaluation of the child with a positive bleeding history because thrombocytopenia is the most common acquired cause of a bleeding diathesis in children. Patients with a platelet count of >50,000/mm^3 rarely have significant clinical bleeding. Thrombocytosis in children is usually reactive and is not associated with bleeding or thrombotic complications. Persistent, severe thrombocytosis in the absence of an underlying illness may require evaluation for the very rare pediatric presentation of essential thrombocythemia or polycythemia vera.

Prothrombin Time and Activated Partial Thromboplastin Time

Because clotting factors were named in the order of discovery, they do not necessarily reflect the sequential order of activation (Table 475-1). In fact, factors III, IV, and VI were not subsequently found to be independent proteins; thus, these terms are no longer used. Only 2 factors have commonly used names: fibrinogen (factor I) and prothrombin (factor II). The dual mechanisms of activating clotting have been termed the **intrinsic** (surface activation) and **extrinsic** (tissue factor–mediated) pathways. Study of the hemostatic mechanism is further complicated in that the interactions in vivo may use different pathways from those studied in clinical laboratory testing. PT measures the activation of clotting by tissue factor (thromboplastin) in the presence of calcium. Addition of tissue factor causes a burst of factor VIIa generation. The tissue factor–factor VIIa complex activates factor X. Whether factor X is activated by the intrinsic or the extrinsic pathway, factor Xa on the platelet phospholipid surface complexes with factor V and calcium (the "prothrombinase" complex) to activate prothrombin to thrombin (also referred to as *factor IIa*). Once thrombin is generated, fibrinogen is converted to a fibrin clot, the end point of the reaction (see Fig. 475-2). PT is not prolonged with deficiencies of factors VIII, IX, XI, and XII. In most laboratories, the normal PT value is 10-13 sec. PT has been standardized using the **international normalized ratio (INR)** so that values can be compared from one laboratory or instrument to another. This ratio is used to determine similar degrees of anticoagulation with warfarin (Coumadin)–like medications.

Table 475-1 Coagulation Factors

CLOTTING FACTOR	SYNONYM	DISORDER
I	Fibrinogen	Congenital deficiency (afibrinogenemia) or dysfunction (dysfibrinogenemia)
II	Prothrombin	Congenital deficiency or dysfunction
V	Labile factor, proaccelerin	Congenital deficiency (parahemophilia)
VII	Stable factor or proconvertin	Congenital deficiency
VIII	Antihemophilic factor	Congenital deficiency is hemophilia A (classic hemophilia)
IX	Christmas factor	Congenital deficiency is hemophilia B (sometimes referred to as Christmas disease)
X	Stuart-Prower factor	Congenital deficiency
XI	Plasma thromboplastin antecedent	Congenital deficiency (sometimes referred to as hemophilia C)
XII	Hageman factor	Congenital deficiency is not associated with clinical symptoms
XIII	Fibrin-stabilizing factor	Congenital deficiency

Partial Thromboplastin Time

The intrinsic pathway involves the initial activation of factor XII, which is accelerated by 2 other plasma proteins, prekallikrein and high-molecular-weight kininogen. In the clinical laboratory, factor XII is activated using a surface (silica or glass) or a contact activator, such as ellagic acid. Factor XIIa, in turn, activates factor XI to factor XIa, which then catalyzes factor IX to factor IXa. On the platelet phospholipid surface, factor IXa complexes with factor VIII and calcium to activate factor X ("tenase" complex).

This process is accelerated by interaction with phospholipid and calcium at the steps involving factors V and VIII. An isolated deficiency of a single clotting factor may result in isolated prolongation of PT, PTT, or both, depending on the location of the factor in the clotting cascade. This approach is useful in determining hereditary clotting factor deficiencies; however, in acquired hemostatic disorders encountered in clinical practice, >1 clotting factor is frequently deficient, so the relative prolongation of PT and PTT must be assessed.

Measurement of PTT as performed in the clinical laboratory is actually "activated" PTT; however, most refer to it as *PTT.* This test measures the initiation of clotting at the level of factor XII through sequential steps to the final clot end point. It does not measure factor VII, factor XIII, or anticoagulants. PTT uses a contact activator (silica, kaolin, or ellagic acid) in the presence of calcium and phospholipid. Because of differences in reagents and laboratory instruments, the normal range for PTT varies among hospital laboratories. Normal ranges for PTT are much more variable from laboratory to laboratory than those for PT.

Thus, the mechanisms studied by PT and PTT allow the evaluation of clotting factor deficiencies, even though these pathways may not be the same as those occurring physiologically. In vivo, factor VIIa activates factors IX and X, but as routinely studied in the clinical laboratory, the pathway through which factor VIIa activates factor IX is not evaluated. If the tissue factor–factor VIIa complex activated only factor X, it would be difficult to explain why the most severe bleeding disorders are deficiencies of factor VIII (hemophilia A) and factor IX (hemophilia B). In vivo, thrombin is generated and feeds back to activate factor XI and accelerate the clotting process. Clotting in PTT can be prolonged by deficiencies of factor XII, prekallikrein, and high-molecular-weight kininogen, yet these deficiencies are asymptomatic conditions.

Thrombin Time

Thrombin time measures the final step in the clotting cascade, in which fibrinogen is converted to fibrin. The normal thrombin time varies between laboratories but is usually 11-15 sec. Prolongation of thrombin time occurs with reduced fibrinogen levels (*hypofibrinogenemia* or *afibrinogenemia*), with dysfunctional fibrinogen (*dysfibrinogenemia*), or in the presence of substances that interfere with fibrin polymerization, such as heparin and fibrin split products. If heparin contamination is a potential cause of prolonged thrombin time, a reptilase time is usually ordered. Alternatively, heparanase can be added to the sample and the thrombin time repeated.

Reptilase Time

Reptilase time uses snake venom to clot fibrinogen. Unlike thrombin time, reptilase time is not sensitive to heparin and is prolonged only by reduced or dysfunctional fibrinogen and fibrin split products. Therefore, if thrombin time is prolonged but reptilase time is normal, the prolonged thrombin time is due to heparin and does not indicate the presence of fibrin split products or reduced concentration or function of fibrinogen.

Mixing Studies

If there is unexplained prolongation of PT or PTT, a mixing study is usually performed. Normal plasma is added to the patient's plasma, and the PT or PTT is repeated. Correction of PT or PTT by 1 : 1 mixing with normal plasma suggests deficiency of a clotting factor, because a 50% level of individual clotting proteins is sufficient to produce normal PT or PTT. If the clotting time is not corrected or only partially corrected, an inhibitor is usually present. An inhibitor of clotting may be either a chemical similar to heparin that delays coagulation or an antibody directed against a specific clotting factor or the phospholipid used in clotting tests. In the inpatient setting, the most common cause of this finding is heparin contamination of the sample. The presence of heparin in the sample can be ruled in or out either by addition of heparinase to the sample and repeating the thrombin time. If the mixing study is not corrected or if its result becomes more prolonged and the patient has clinical bleeding, an inhibitor of a specific clotting factor (antibody directed against the factor), most commonly factor VIII, factor IX, or factor XI, may be present. If the patient has no bleeding symptoms and both PTT and the mixing study are prolonged, a lupus-like anticoagulant (see Chapter 476) is often present. Patients with these findings usually have a long PTT, do not bleed, and may have a clinical predisposition to excessive clotting.

Bleeding Time

Bleeding time assesses the function of platelets and their interaction with the vascular wall. Disposable standardized devices have been developed that control the length and depth of the skin incision. A blood pressure cuff is applied to the upper arm and inflated to 40 mm Hg for children and adults. In term newborns and younger children, a modified device has been developed that is used with a lower blood pressure cuff pressure. Bleeding time is a difficult laboratory test to standardize, and there is much interlaboratory and interindividual variation. Although platelet counts of <100,000/mm^3 are associated with prolonged bleeding time, disproportionate prolongation of

bleeding time may suggest a qualitative platelet defect or VWD. Use of the bleeding time is declining in many centers.

Platelet Function Analyzer

In an attempt to evaluate the early stages of hemostasis (platelet function and VWF interaction under high shear), several in vitro platelet analyzers have been developed. The greatest experience has been with the platelet function analyzer (PFA-100, Siemens Healthcare Diagnostics, Inc., Deerfield, IL). The PFA-100 measures platelet adhesion-aggregation in whole blood at high shear when exposed to either collagen-epinephrine or collagen-ADP. Results are reported as the closure time measured in sec. The PFA-100 appears to be sensitive to severe forms of VWD and platelet dysfunction. The PFA-100 has variable sensitivity, particularly in the detection of mild VWD and some platelet function defects. Its use as a preoperative screening tool has been disappointing in some studies.

D-Dimer

D-dimer is formed by plasmin degradation of crosslinked fibrin, produced when fibrinogen is clotted by thrombin and cross-linked by factor XIIIa and is more specific for fibrinolysis than fibrin degradation products. D-dimer is elevated in patients with disseminated intravascular coagulation or acute deep vein thrombosis but is relatively nonspecific in that other ill hospitalized patients often have elevated levels of D-dimer. Adult studies show that the D-dimer can be useful to help exclude venous thrombosis and pulmonary embolus because of its high negative predictive value; for example, a patient with a normal D-dimer value is unlikely to have an acute thrombosis.

Clotting Factor Assays

Each of the clotting factors can be measured in the clinical laboratory using individual factor–deficient plasmas. For most clotting factors, activity is measured against pooled normal plasma or against a standard, by which 100% activity is expressed as 100 IU/dL. By definition, 1 IU of each factor is defined as that amount in 1 mL of normal plasma referenced against a standard established by the World Health Organization. For most clotting factors, the normal range is 50-150 IU/dL (50-150%) (Table 475-2).

In patients with hemophilia A or hemophilia B, inhibitors of factor VIII or factor IX may develop after exposure to replacement therapy.

Table 475-2 Reference Values for Coagulation Tests in Healthy Children*

TEST	28-31 Wk GESTATION	30-36 Wk GESTATION	FULL TERM	1-5 Yr	6-10 Yr	11-18 Yr	ADULT
SCREENING TESTS							
Prothrombin time (sec)	15.4 (14.6-16.9)	13.0 (10.6-16.2)	13.0 (10.1-15.9)	11 (10.6-11.4)	11.1 (10.1-12.0)	11.2 (10.2-12.0)	12 (11.0-14.0)
Activated partial thromboplastin time (sec)	108 (80-168)	53.6 (27.5-79.4)[‡§]	42.9 (31.3-54.3)[‡]	30 (24-36)	31 (26-36)	32 (26-37)	33 (27-40)
Bleeding time (min)				6 (2.5-10)[‡]	7 (2.5-13)[‡]	5 (3-8)[‡]	4 (1-7)
PROCOAGULANTS							
Fibrinogen	256 (160-550)	243 (150-373)[‡§]	283 (167-399)	276 (170-405)	279 (157-400)	300 (154-448)	278 (156-40)
Factor II	31 (19-54)	45 (20-77)[‡]	48 (26-70)[‡]	94 (71-116)[‡]	88 (67-107)[‡]	83 (61-104)[‡]	108 (70-146)
Factor V	65 (43-80)	88 (41-144)[§]	72 (34-108)[‡]	103 (79-127)	90 (63-116)[‡]	77 (55-99)[‡]	106 (62-150)
Factor VII	37 (24-76)	67 (21-113)[‡]	66 (28-104)[‡]	82 (55-116)[‡]	86 (52-120)[‡]	83 (58-115)[‡]	105 (67-143)
Factor VIII procoagulant	79 (37-126)	111 (5-213)	100 (50-178)	90 (59-142)	95 (58-132)	92 (53-131)	99 (50-149)
von Willebrand factor	141 (83-223)	136 (78-210)	153 (50-287)	82 (60-120)	95 (44-144)	100 (46-153)	92 (50-158)
Factor IX	18 (17-20)	35 (19-65)[‡§]	53 (15-91)[†‡]	73 (47-104)[‡]	75 (63-89)[‡]	82 (59-122)[‡]	109 (55-163)
Factor X	36 (25-64)	41 (11-71)[‡]	40 (12-68)[‡]	88 (58-116)[‡]	75 (55-101)[‡]	79 (50-117)	106 (70-152)
Factor XI	23 (11-33)	30 (8-52)[‡§]	38 (40-66)[‡]	30 (8-52)[‡]	38 (10-66)	74 (50-97)[‡]	97 (56-150)
Factor XII	25 (5-35)	38 (10-66)[‡§]	53 (13-93)[‡]	93 (64-129)	92 (60-140)	81 (34-137)[‡]	108 (52-164)
Prekallikrein	26 (15-32)	33 (9-89)[‡]	37 (18-69)[‡]	95 (65-130)	99 (66-131)	99 (53-145)	112 (62-162)
High-molecular-weight kininogen	32 (19-52)	49 (9-89)[‡]	54 (6-102)[‡]	98 (64-132)	93 (60-130)	91 (63-119)	92 (50-136)
Factor XIIIa[ǁ]		70 (32-108)[‡]	79 (27-131)[‡]	108 (72-143)	109 (65-151)	99 (57-140)	105 (55-155)
Factor XIIIb[ǁ]		81 (35-127)[‡]	76 (30-122)[‡]	113 (69-156)[‡]	116 (77-154)[‡]	102 (60-143)	98 (57-137)
ANTICOAGULANTS							
Antithrombin-III	28 (20-38)	38 (14-62)[‡§]	63 (39-87)[‡]	111 (82-139)	111 (90-131)	106 (77-132)	100 (74-126)
Protein C		28 (12-44)[‡§]	35 (17-53)[‡]	66 (40-92)[‡]	69 (45-93)[‡]	83 (55-111)[‡]	96 (64-128)
Protein S:							
Total (units/mL)		26 (14-38)[‡§]	36 (12-60)[‡]	86 (54-118)	78 (41-114)	72 (52-92)	81 (61-113)
Free (units/mL)				45 (21-69)	42 (22-62)	38 (26-55)	45 (27-61)
Plasminogen (units/mL)		170 (112-248)	195 (125-265)	98 (78-118)	92 (75-108)	86 (68-103)	99 (77-122)
Tissue-type plasminogen activator (ng/mL)		8.48 (3.00-16.70)	9.6 (5.0-18.9)	2.15 (1.0-4.5)[‡]	2.42 (1.0-5.0)[‡]	2.16 (1.0-4.0)[‡]	1.02 (0.68-1.36)
Antiplasmin (units/mL)		78 (40-116)	85 (55-115)	105 (93-117)	99 (89-110)	98 (78-118)	102 (68-136)
Plasminogen activator inhibitor-I		5.4 (0.0-12.2)[‡]	6.4 (2.0-15.1)	5.42 (1.0-10.0)	6.79 (2.0-12.0)[‡]	6.07 (2.0-10.0)[‡]	3.60 (0.0-11.0)

*All factors except fibrinogen are expressed as units/mL (fibrinogen in mg/mL), in which pooled normal plasma contains 1 unit/mL. All data are expressed as the mean, followed by the upper and lower boundaries encompassing 95% of the normal population (shown in parentheses). Normal ranges above vary based on the reagents and instruments used.

†Levels for 19-27 wk and 28-31 wk gestation are from multiple sources and cannot be analyzed statistically.

‡Values are significantly different from those of adults.

§Values are significantly different from those of full-term infants.

ǁValue given as CTA (Committee on Thrombolytic Agents) units/mL. Normal ranges above vary based on the reagents and instruments used.

Data from Andrew M, Paes B, Johnston M: Development of the hemostatic system in the neonate and young infant, Am J Pediatr Hematol Oncol *12:95, 1990; and Andrew M, Vegh P, Johnston M, et al: Maturation of the hemostatic system during childhood,* Blood *80:1998, 1992.*

To quantitate the amount of inhibitor present, the standardized clinical assay of these clotting inhibitors is the Bethesda assay. One Bethesda unit is defined as the amount that will inhibit 50% of the clotting factor in normal plasma.

Platelet Aggregation

When a qualitative platelet function defect is suspected, platelet aggregation testing is usually ordered. Platelet-rich plasma from the patient is activated with 1 of a series of agonists (ADP, epinephrine, collagen, thrombin or thrombin-receptor peptide, and ristocetin). Some platelet aggregometers measure specific adenosine triphosphate release from the platelets, as reflected in generating luminescence (lumiaggregometer), and are more sensitive in detecting abnormalities of the platelet release reaction from storage granules. Repeat testing or testing of other symptomatic family members can help to determine the hereditary nature of the defect. Many medications, especially aspirin, other nonsteroidal antiinflammatory drugs, and valproic acid, alter platelet function testing. Figure 475-1 provides an approach to the differential diagnosis of many common bleeding disorders based on screening tests.

Testing for Thrombotic Predisposition

Hereditary predisposition to thrombosis is associated with a reduction of anticoagulant function (protein C, protein S, AT-III); the presence of a factor V molecule that is resistant to inactivation by protein C (factor V Leiden); elevated levels of procoagulants (a mutation of the prothrombin gene); or a deficiency of fibrinolysis (plasminogen deficiency); and the rare metabolic disease homocystinuria. When patients are being screened for prothrombotic tendencies, specific tests of the natural anticoagulants and polymerase chain reaction analysis for common prothrombotic mutations are warranted. Although both immunologic and functional tests are usually available, functional assays of protein C, protein S, and AT-III are clinically more useful.

Factor V Leiden is a common mutation in factor V that is associated with an increased risk of thrombosis. A point mutation in the factor V molecule prevents the inactivation of factor Va by activated protein C and, thereby, the persistence of factor Va. This defect, also known as *activated protein C resistance,* is easily diagnosed with DNA testing.

The **prothrombin gene mutation (G20210A)** is a mutation in the noncoding portion of the prothrombin gene, with a glycine (G) at position 20210 being replaced by an alanine (A). This mutation increases the amount of prothrombin messenger RNA, is associated with elevations of prothrombin, and causes a predisposition to thrombosis. This abnormality is easily identified with molecular diagnostic (DNA) testing.

Elevated Homocysteine

Levels of homocysteine may be increased as a result of genetic mutations, causing homocystinuria. Patients with homocysteine elevation are predisposed to arterial and venous thrombosis as well as to an increase in arteriosclerosis.

Tests of the Fibrinolytic System

Euglobulin clot lysis time is a screening test used in some laboratories to assess fibrinolysis. More specific tests are available in most laboratories to determine the levels of plasminogen, plasminogen activator, and inhibitors of fibrinolysis. An increase in fibrinolysis may be associated with hemorrhagic symptoms, and a delay in fibrinolysis is associated with thrombosis.

DEVELOPMENTAL HEMOSTASIS

The normal newborn infant has reduced levels of most procoagulants and anticoagulants (see Table 475-1). In general, there is a more marked abnormality in the preterm infant. Although major differences exist in the normal ranges for newborn and preterm infants, these ranges vary greatly among laboratories based upon the instruments and reagents used. During gestation, there is progressive maturation and increase of the clotting factors synthesized by the liver. The extremely premature infant has prolonged PT and PTT values as well as a marked reduction in anticoagulant protein levels (protein C, protein S, and AT-III). Levels of fibrinogen, factors V and VIII, VWF, and platelets are near-normal throughout the later stages of gestation (see Chapter 103.4). Because protein C and protein S are physiologically reduced, the normal factors V and VIII are not balanced with their regulatory proteins. In contrast, the physiologic deficiency of vitamin K–dependent procoagulant proteins (factors II, VII, IX, and X) is partially balanced by the physiologic reduction of AT-III. The net effect is that newborns (especially premature infants) are at increased risk for complications of bleeding, clotting, or both.

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Chapter 476

Hereditary Clotting Factor Deficiencies (Bleeding Disorders)

J. Paul Scott and Veronica H. Flood

Hemophilia A (factor VIII deficiency) and **hemophilia B** (factor IX deficiency) are the most common and serious congenital coagulation factor deficiencies. The clinical findings in hemophilia A and hemophilia B are virtually identical. **Hemophilia C** is the bleeding disorder associated with reduced levels of factor XI (see Chapter 476.2). Reduced levels of the *contact factors* (factor XII, high-molecular-weight kininogen, and prekallikrein) are associated with significant prolongation of activated partial thromboplastin time (aPTT; also referred to as *PTT*), but are not associated with hemorrhage, as discussed in Chapter 476.3. Other coagulation factor deficiencies that are less common are briefly discussed in subsequent subchapters.

476.1 Factor VIII or Factor IX Deficiency (Hemophilia A or B)

J. Paul Scott

Deficiencies of factors VIII and IX are the most common severe inherited bleeding disorders. Recombinant factor VIII and factor IX concentrates are available to treat patients with hemophilia and thereby avoid the infectious risk of plasma-derived transfusion-transmitted diseases.

PATHOPHYSIOLOGY

Factors VIII and IX participate in a complex required for the activation of factor X. Together with phospholipid and calcium, they form the “tenase,” or factor X–activating, complex. Figure 475-1 in Chapter 475 shows the clotting process as it occurs in the test tube, with factor X being activated by either the complex of factors VIII and IX or the complex of tissue factor and factor VII. In vivo, the complex of factor VIIa and tissue factor activates factor IX to initiate clotting. In the laboratory, prothrombin time (PT) measures the activation of factor X by factor VII and is therefore normal in patients with factor VIII or factor IX deficiency.

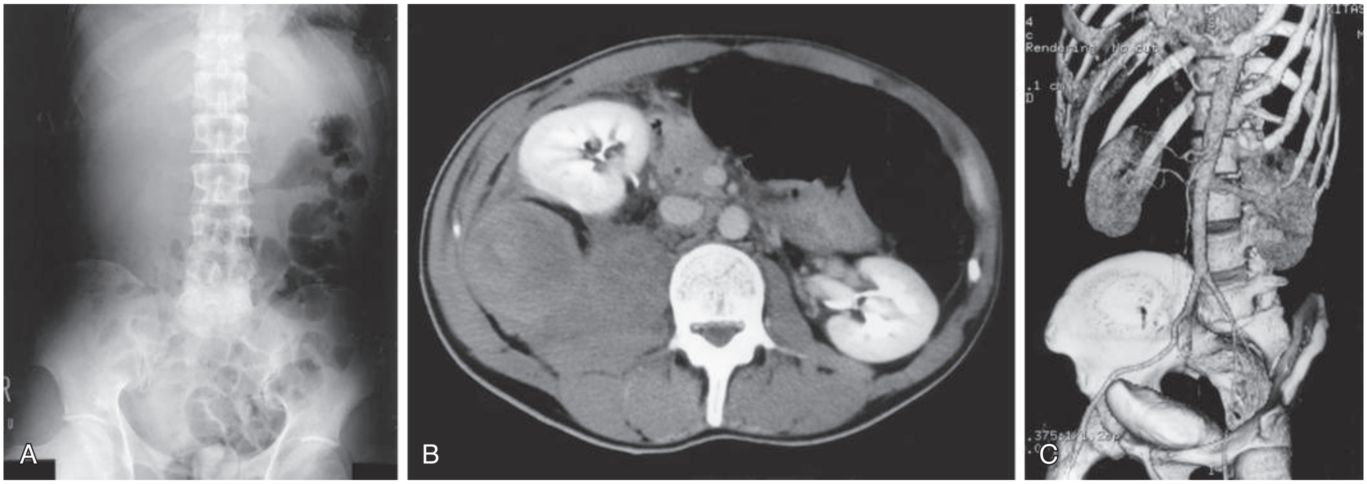

Figure 476-1 Massive hematoma into the iliopsoas muscle in a patient with hemophilia B. A 38 yr old man with severe deficiency of factor IX (hemophilia B) was admitted for right lower abdominal pain of progressively increasing severity and tenderness. He had had a common cold with severe cough and loss of appetite for approximately 1 wk. **A,** Abdominal radiograph shows presence of the psoas sign on the right side and left-shifted colon gas. **B,** CT scan shows massive hematoma in the right iliopsoas muscle, resulting in anterior translocation of the right kidney. **C,** Reconstructed 3-dimensional image shows more clearly the kidney translocation and the extended, but intact, large vessels. These are useful findings for the diagnostic procedures, because progressive right lower abdominal pain may closely simulate acute appendicitis. The hemorrhage was successfully managed by replacement of factor IX for 1 wk without any recurrence. The patient did not have any inhibitors to factor IX. *(From Miyazaki K, Higashihara M: Massive hemorrhage into the iliopsoas muscle,* Intern Med *44:158, 2005.)*

After injury, the initial hemostatic event is formation of the platelet plug, together with the generation of the fibrin clot that prevents further hemorrhage. In hemophilia A or B, clot formation is delayed and is not robust. Inadequate thrombin generation leads to failure to form a tightly crosslinked fibrin clot to support the platelet plug. Patients with hemophilia slowly form a soft, friable clot. When untreated bleeding occurs in a closed space, such as a joint, cessation of bleeding may be the result of tamponade. With open wounds, in which tamponade cannot occur, profuse bleeding may result in significant blood loss. The clot that is formed may be friable, and rebleeding occurs during the physiologic lysis of clots or with minimal new trauma.

CLINICAL MANIFESTATIONS

Neither factor VIII nor factor IX crosses the placenta; bleeding symptoms may be present from birth or may occur in the fetus. Only 2% of neonates with hemophilia sustain intracranial hemorrhages, and 30% of male infants with hemophilia bleed with circumcision. Thus, in the absence of a positive family history (hemophilia has a high rate of spontaneous mutation), hemophilia may go undiagnosed in the newborn. Obvious symptoms such as easy bruising, intramuscular hematomas, and hemarthroses begin when the child begins to cruise. Bleeding from minor traumatic lacerations of the mouth (a torn frenulum) may persist for hours or days and may cause the parents to seek medical evaluation. Even in patients with severe hemophilia, only 90% have evidence of increased bleeding by 1 yr of age. Although bleeding may occur in any area of the body, the hallmark of hemophilic bleeding is **hemarthrosis.** Bleeding into the joints may be induced by minor trauma; many hemarthroses are spontaneous. The earliest joint hemorrhages appear most commonly in the ankle. In the older child and adolescent, hemarthroses of the knees and elbows are also common. Whereas the child's early joint hemorrhages are recognized only after major swelling and fluid accumulation in the joint space, older children are frequently able to recognize bleeding before the physician does. They complain of a warm, tingling sensation in the joint as the first sign of an early joint hemorrhage. Repeated bleeding episodes into the same joint in a patient with severe hemophilia may become a "target" joint. Recurrent bleeding may then become spontaneous because of the underlying pathologic changes in the joint.

Although most muscular hemorrhages are clinically evident owing to localized pain or swelling, bleeding into the iliopsoas muscle requires specific mention. A patient may lose large volumes of blood into the **iliopsoas muscle,** verging on hypovolemic shock, with only a vague area of referred pain in the groin. The hip is held in a flexed, internally rotated position owing to irritation of the iliopsoas. The diagnosis is made clinically from the inability to extend the hip but must be confirmed with ultrasonography or CT (Fig. 476-1). Life-threatening bleeding in the patient with hemophilia is caused by bleeding into vital structures (central nervous system, upper airway) or by exsanguination (external trauma, gastrointestinal or iliopsoas hemorrhage). Prompt treatment with clotting factor concentrate for these life-threatening hemorrhages is imperative. If head trauma is of sufficient concern to suggest radiologic evaluation, factor replacement should precede radiologic evaluation. Simply put: "Treat first, image second!" Life-threatening hemorrhages require replacement therapy to achieve a level equal to that of normal plasma (100 IU/dL, or 100%).

Patients with mild hemophilia who have factor VIII or factor IX levels >5 IU/dL usually do not have spontaneous hemorrhages. These individuals may experience prolonged bleeding after dental work, surgery, or injuries from moderate trauma and may not be diagnosed until they are older.

LABORATORY FINDINGS AND DIAGNOSIS

The laboratory screening test that is affected by a reduced level of factor VIII or factor IX is PTT. In severe hemophilia, the PTT value is usually 2-3 times the upper limit of normal. Results of the other screening tests of the hemostatic mechanism (platelet count, bleeding time, prothrombin time, and thrombin time) are normal. Unless the patient has an inhibitor to factor VIII or IX, the mixing of normal plasma with patient plasma results in correction of PTT value. The specific assay for factors VIII and IX will confirm the diagnosis of hemophilia. If correction does not occur on mixing, an inhibitor may be present. In 25-35% of patients with hemophilia who receive infusions of factor VIII or factor IX, a factor-specific antibody may develop. These antibodies are directed against the active clotting site and are termed *inhibitors.* In such patients, the quantitative Bethesda assay for inhibitors should be performed to measure the antibody titer.

DIFFERENTIAL DIAGNOSIS

In young infants with severe bleeding manifestations, the differential diagnosis includes severe thrombocytopenia; severe platelet function

disorders, such as Bernard-Soulier syndrome and Glanzmann thrombasthenia; type 3 (severe) von Willebrand disease; and vitamin K deficiency. Hemostatic screening tests should differentiate these entities from hemophilia.

GENETICS AND CLASSIFICATION

Hemophilia occurs in approximately 1 : 5,000 males, with 85% having factor VIII deficiency and 10-15% having factor IX deficiency. Hemophilia shows no apparent racial predilection, appearing in all ethnic groups. The severity of hemophilia is classified on the basis of the patient's baseline level of factor VIII or factor IX, because factor levels usually correlate with the severity of bleeding symptoms. By definition, 1 IU of each factor is defined as that amount in 1 mL of normal plasma referenced against a standard established by the World Health Organization (WHO); thus, 100 mL of normal plasma has 100 IU/dL (100% activity) of each factor. For ease of discussion, henceforth in this chapter, we use the term *% activity* to refer to the percentage found in normal plasma (100% activity). Factor concentrates are also referenced against an international WHO standard, so treatment doses are usually referred to in IU. **Severe hemophilia** is characterized as having <1% activity of the specific clotting factor, and bleeding is often spontaneous. Patients with **moderate hemophilia** have factor levels of 1-5% and usually require mild trauma to induce bleeding. Individuals with **mild hemophilia** have levels >5%, may go many years before the condition is diagnosed, and frequently require significant trauma to cause bleeding. The hemostatic level for factor VIII is >30-40%, and for factor IX, it is >25-30%. The lower limit of levels for factors VIII and IX in normal individuals is approximately 50%.

The genes for factors VIII and IX are carried near the terminus of the long arm of the X chromosome and are therefore X-linked traits. The majority of patients with hemophilia have reduced clotting factor protein; 5-10% of those with hemophilia A and 40-50% of those with hemophilia B make a dysfunctional protein. Approximately 45-50% of patients with severe hemophilia A have the same mutation, in which there is an internal inversion within the factor VIII gene that results in production of no protein. This mutation can be detected in the blood of patients or carriers and in the amniotic fluid by molecular techniques. African-Americans often have a different factor VIII haplotype, and this difference may be the reason that African-Americans have higher inhibitor formation (see later). Because of the multiple genetic causes of either factor VIII or factor IX deficiency, most cases of hemophilia are classified according to the amount of factor VIII or factor IX clotting activity. In the newborn, factor VIII values may be artificially elevated because of the acute-phase response elicited by the birth process. This artificial elevation may cause a mildly affected patient to have normal or near-normal levels of factor VIII. Patients with severe hemophilia do not have detectable levels of factor VIII. In contrast, factor IX levels are physiologically low in the newborn. If severe hemophilia is present in the family, an undetectable level of factor IX is diagnostic of severe hemophilia B. In some patients with mild factor IX deficiency, the presence of hemophilia can be confirmed only after several weeks of life.

Through lyonization of the X chromosome, some **female carriers** of hemophilia A or B have sufficient reduction of factor VIII or factor IX to produce mild bleeding disorders. Levels of these factors should be determined in all known or potential carriers to assess the need for treatment in the event of surgery or clinical bleeding.

Because factor VIII is carried in plasma by von Willebrand factor, the ratio of factor VIII to von Willebrand factor is sometimes used to diagnose carriers of hemophilia. When possible, specific genetic mutations should be identified in the propositus and used to test other family members who are at risk of either having hemophilia or being carriers.

TREATMENT

Early, appropriate therapy is the hallmark of excellent hemophilia care. When mild to moderate bleeding occurs, values of factor VIII or factor IX must be raised to hemostatic levels, in the 35-50% range. For life-threatening or major hemorrhages, the dose should aim to achieve levels of 100% activity.

Calculation of the dose of recombinant factor VIII (FVIII) or recombinant factor IX (FIX) is as follows:

$$\text{Dose of rFVIII (IU)} = \%\ \text{desired (rise in rFVIII)} \times \text{Body weight (kg)} \times 0.5$$

$$\text{Dose of rFIX (IU)} = \%\ \text{desired (rise in plasma FIX)} \times \text{Body weight (kg)} \times 1.4$$

For factor VIII, the correction factor is based on the volume of distribution of factor VIII. For factor IX, the correction factor is based on the volume of distribution and the observed rise in plasma level after infusion of recombinant factor IX.

Table 476-1 summarizes the treatment of some common types of hemorrhage in a patient with hemophilia.

With the availability of recombinant replacement products, **prophylaxis is the standard of care** for most children with severe hemophilia, to prevent spontaneous bleeding and early joint deformities. In addition to currently available recombinant factors, products are being developed to increase the plasma half-life and reduce the immunogenicity of hemostatic factors. A study comparing prophylaxis with aggressive episodic treatment provides evidence for the superiority of prophylaxis in preventing debilitating joint disease. If target joints develop, "secondary" prophylaxis is often initiated.

With mild factor VIII hemophilia, the patient's endogenously produced factor VIII can be released by the administration of desmopressin acetate. In patients with moderate or severe factor VIII deficiency, the stored levels of factor VIII in the body are inadequate, and desmopressin treatment is ineffective. The risk of exposing the patient with mild hemophilia to transfusion-transmitted diseases and the cost of recombinant products warrant the use of desmopressin, if it is effective. A concentrated intranasal form of **desmopressin acetate**, not the enuresis or pituitary replacement dose, can also be used to treat patients with mild hemophilia A. The dose is 150 μg (1 puff) for children weighing <50 kg and 300 μg (2 puffs) for children and young adults weighing >50 kg. Most centers administer a trial of desmopressin to determine the level of factor VIII achieved after its infusion. Desmopressin is not effective in the treatment of factor IX–deficient hemophilia.

Preliminary trials of an adeno-associated virus vector containing the factor IX gene are underway with some encouraging initial results.

PROPHYLAXIS

Many patients are now given lifelong prophylaxis to prevent spontaneous joint bleeding. The National Hemophilia Foundation recommends that prophylaxis be considered optimal therapy for children with severe hemophilia. Usually, such programs are initiated with the first joint hemorrhage. Young children often require the insertion of a central catheter to ensure venous access. Such programs are expensive but are highly effective in preventing or greatly limiting the degree of joint pathology; however, complications include central line infection and thrombosis. Treatment is usually provided every 2-3 days to maintain a measurable plasma level of clotting factor (1-2%) when assayed just before the next infusion (trough level). Whether prophylaxis should be continued into adulthood has not yet been adequately studied. If moderate arthropathy develops, prevention of future bleeding will require higher plasma levels of clotting factors. In the older child who is not given primary prophylaxis, secondary prophylaxis is frequently initiated if a target joint develops.

SUPPORTIVE CARE

Although it is easy to tell parents that their child should avoid trauma, this advice is not practical in active children and adolescents. Toddlers are active, are curious about everything, and injure themselves easily. Effective measures include anticipatory guidance, including the use of car seats, seatbelts, and bike helmets, and the importance of avoiding high-risk behaviors. Older boys should be counseled to avoid violent contact sports, but this issue is a challenge. Boys with severe hemophilia often sustain hemorrhages in the absence of known trauma. Early psychosocial intervention helps the family achieve a balance

Table 476-1 Treatment of Hemophilia

TYPE OF HEMORRHAGE	HEMOPHILIA A	HEMOPHILIA B
Hemarthrosis*	50-60 IU/kg factor VIII concentrate† on day 1; then 20-30 IU/kg on days 2, 3, 5 until joint function is normal or back to baseline. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.	80-100 IU/kg on day 1; then 40 IU/kg on days 2, 4. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.
Muscle or significant subcutaneous hematoma	50 IU/kg factor VIII concentrate; 20 IU/kg every-other-day treatment may be needed until resolved	80 IU/kg factor IX concentrate‡; treatment every 2-3 days may be needed until resolved
Mouth, deciduous tooth, or tooth extraction	20 IU/kg factor VIII concentrate; antifibrinolytic therapy; remove loose deciduous tooth	40 IU/kg factor IX concentrate‡; antifibrinolytic therapy§; remove loose deciduous tooth
Epistaxis	Apply pressure for 15-20 min; pack with petrolatum gauze; give antifibrinolytic therapy; 20 IU/kg factor VIII concentrate if this treatment fails‖	Apply pressure for 15-20 min; pack with petrolatum gauze; antifibrinolytic therapy; 30 IU/kg factor IX concentrate‡ if this treatment fails
Major surgery, life-threatening hemorrhage	50-75 IU/kg factor VIII concentrate, then initiate 25 IU/kg q8-12h to maintain trough level >50 IU/dL for 5-7 days, then 50 IU/kg q24h to maintain trough >25 IU/dL for 7 days	120 IU/kg factor IX concentrate‡, then 50-60 IU/kg every 12-24 hr to maintain factor IX at >40 IU/dL for 5-7 days, and then at >30 IU/dL for 7 days
Iliopsoas hemorrhage	50 IU/kg factor VIII concentrate, then 25 IU/kg every 12 hr until asymptomatic, then 20 IU/kg every other day for a total of 10-14 days**	120 IU/kg factor IX concentrate‡; then 50-60 IU/kg every 12-24 hr to maintain factor IX at >40 IU/dL until patient is asymptomatic; then 40-50 IU every other day for a total of 10-14 days**††
Hematuria	Bed rest; 1.5× maintenance fluids; if not controlled in 1-2 days, 20 IU/kg factor VIII concentrate; if not controlled, give prednisone (unless patient is HIV-infected)	Bed rest; 1.5× maintenance fluids; if not controlled in 1-2 days, 40 IU/kg factor IX concentrate‡; if not controlled, give prednisone (unless patient is HIV-infected)
Prophylaxis	20-40 IU/kg factor VIII concentrate every other day to achieve a trough level ≥1%	30-50 IU/kg factor IX concentrate‡ every 2-3 days to achieve a trough level ≥1%

*For hip hemarthrosis, orthopedic evaluation for possible aspiration is advisable to prevent avascular necrosis of the femoral head.
†For mild or moderate hemophilia, desmopressin, 0.3 μg/kg, should be used instead of factor VIII concentrate, if the patient is known to respond with a hemostatic level of factor VIII; if repeated doses are given, monitor factor VIII levels for tachyphylaxis.
‡Stated doses apply for recombinant factor IX concentrate; for plasma-derived factor IX concentrate, use 70% of the stated dose.
§Do not give antifibrinolytic therapy until 4-6 hr after a dose of prothrombin complex concentrate.
‖Nonprescription coagulation-promoting products may be helpful.
**Repeat radiologic assessment should be performed before discontinuation of therapy.
††If repeated doses of factor IX concentrate are required, use highly purified, specific factor IX concentrate.
Adapted from Montgomery RR, Gill JC, Scott JP: Hemophilia and von Willebrand disease. In Nathan DG, Orkin SH, editors: Nathan and Oski's hematology of infancy and childhood, *ed 5, Philadelphia, 1998, WB Saunders.*

between overprotection and permissiveness. Patients with hemophilia should avoid aspirin and other nonsteroidal antiinflammatory drugs that affect platelet function. The child with a bleeding disorder should receive the appropriate vaccinations against hepatitis B, even though recombinant products may avoid exposure to transfusion-transmitted diseases. Patients exposed to plasma-derived products should be screened periodically for hepatitis B and C, HIV, and abnormalities in liver function.

CHRONIC COMPLICATIONS

Long-term complications of hemophilia A and B include chronic arthropathy, the development of an inhibitor to either factor VIII or factor IX, and the risk of transfusion-transmitted infectious diseases. Although an aggressive, or prophylactic, approach to treatment has reduced the problems of chronic arthropathy, these problems have not been eliminated.

Historically, chronic arthropathy has been the major long-term disability associated with hemophilia. The natural history of untreated hemophilia is one of cyclic recurrent hemorrhages into specific joints, including hemorrhages into the same (target) joint. In young children, the joint distends easily and a large volume of blood may fill the joint until tamponade ensues or therapy intervenes. After joint hemorrhage, proteolytic enzymes are released by white blood cells into the joint space, and heme iron induces macrophage proliferation, leading to inflammation of the synovium. The synovium thickens and develops frondlike projections into the joint that are susceptible to being pinched and may induce further hemorrhage. The cartilaginous surface becomes eroded and ultimately may even expose raw bone, leaving the joint susceptible to articular fusion. In the older patient with advanced arthropathy, bleeding into the target joint, with its thickened synovium, causes severe pain, because the joint may have little space to accommodate blood. Once a target joint is seen to be developing, the patient is usually given short- or long-term prophylaxis to prevent progression of the arthropathy and reduce inflammation.

Inhibitor Formation

Infusion of the deficient clotting factor may initiate an immune response in patients with either factor VIII or factor IX deficiency. Inhibitors are antibodies directed against factor VIII or factor IX that block the clotting activity. Failure of a bleeding episode to respond to appropriate replacement therapy is usually the first sign of an inhibitor. Less often, inhibitors are identified during routine follow-up screening for inhibitors. Inhibitors develop in approximately 25-35% of patients with hemophilia A; the percentage is somewhat lower in patients with hemophilia B, many of whom make an inactive dysfunctional protein that renders them less susceptible to an immune response. Highly purified factor IX or recombinant factor IX seems to increase the frequency of inhibitor development, and some anti–factor IX inhibitors induce anaphylaxis. Many patients who have an inhibitor lose it with continued regular infusions. Others have a higher titer of antibody with subsequent infusions and may need to go through **desensitization** (immune tolerance induction) programs, in which high doses of factor VIII for hemophilia A or factor IX for hemophilia B are infused in an attempt to saturate the antibody and permit the body to develop tolerance. Factor IX immune tolerance programs have resulted in nephrotic syndrome in some patients. Rituximab has been used,

off-label (i.e., in a use not approved by the FDA), as an alternate therapy for patients with high inhibitor titers in whom immune tolerance programs have failed. Some centers first begin with prednisone with or without cyclophosphamide; others add cyclosporine if there is a poor response. If desensitization fails, bleeding episodes are treated with either recombinant factor VIIa or activated prothrombin complex concentrates (factor VIII inhibitor bypassing activity). The use of these products bypasses the inhibitor in many instances but may increase the risk of thrombosis. Some patients with low titers of inhibitor can be treated with high-dose factor VIII during a bleeding episode. Patients with inhibitors require referral to a center that cares for many such patients and has a comprehensive hemophilia program.

In the past, plasma-derived treatment products transmitted hepatitis B and C as well as HIV to large numbers of patients with hemophilia. In the era of recombinant products, the risk of acquiring such infections should be minimal, but patients should receive appropriate immunizations against hepatitis B. Those who are exposed to blood products should be monitored for transfusion-related infections. Reports have also identified the transmission of variant Creutzfeldt-Jakob disease to patients receiving therapeutic plasma and may warrant study of patients with hemophilia for prion transmission from plasma-derived factor concentrates.

COMPREHENSIVE CARE

Patients with hemophilia are best managed through comprehensive hemophilia care centers. Such centers are dedicated to patient and family education as well as to the prevention and/or treatment of the complications of hemophilia, including chronic joint disease and inhibitor development as well as infection, such as hepatitis B and C or HIV. Such centers involve a team of physicians, nurses, orthopedists, physical therapists, and psychosocial workers, among others. Education remains crucial in hemophilia care, because patients who are receiving prophylaxis may be less "experienced" in recognizing bleeding episodes than affected children from previous eras.

Bibliography is available at Expert Consult.

476.2 Factor XI Deficiency (Hemophilia C)

J. Paul Scott

Factor XI deficiency is an autosomal deficiency associated with mild to moderate bleeding symptoms. It is frequently encountered in Ashkenazi Jews but has been found in many other ethnic groups. In Israel, 1-3/1,000 individuals are homozygous for this deficiency.

The bleeding tendency is not as severe as in factor VIII or factor IX deficiency. The bleeding associated with factor XI deficiency is not correlated with the amount of factor XI. Some patients with severe deficiency may have minimal or no symptoms at the time of major surgery. Because factor XI augments thrombin generation and leads to activation of the fibrinolytic inhibitor thrombin-activatable fibrinolysis inhibitor, surgical bleeding is more prominent in sites of high fibrinolytic activity like the oral cavity. Unless the patient previously had surgery without bleeding, replacement therapy should be considered and given preoperatively, depending on the nature of the surgical procedure. No approved concentrate of factor XI is available in the United States; therefore, the physician must use fresh-frozen plasma (FFP).

Bleeding during minor surgery can be controlled with local pressure. Patients undergoing dental extractions can be monitored closely and may benefit from treatment with fibrinolytic inhibitors like aminocaproic acid, with plasma replacement therapy used only if hemorrhage occurs. In a patient with homozygous deficiency of factor XI, PTT is often longer than it is in patients with either severe factor VIII or factor IX deficiency. The paradox of fewer clinical symptoms in combination with longer PTT is surprising, but it occurs because factor VIIa can activate factor IX in vivo. The deficiency of factor XI can be confirmed by specific factor XI assays. Plasma infusions of 1 IU/kg usually increase the plasma concentration by 2%. Thus, infusion of plasma at 10-15 mL/kg will result in a plasma level of 20-30%, which is usually sufficient to control moderate hemorrhage. Frequent infusions of plasma would be necessary to achieve higher levels of factor XI. Because the half-life of factor XI is usually ≥48 hr, maintaining adequate levels of factor XI commonly is not difficult.

Chronic joint bleeding is rarely a problem in factor XI deficiency, and for most patients, the deficiency is a concern only at the time of major surgery unless there is a second underlying hemostatic defect (e.g., von Willebrand disease).

Bibliography is available at Expert Consult.

476.3 Deficiencies of the Contact Factors (Nonbleeding Disorders)

J. Paul Scott

Deficiency of the "contact factors" (factor XII, prekallikrein, and high-molecular-weight kininogen) causes prolonged PTT but no bleeding symptoms. Because these contact factors function at the step of initiation of the intrinsic clotting system by the reagent used to determine PTT, the PTT is markedly prolonged when these factors are absent. Thus, there is the paradoxical situation in which PTT is extremely prolonged with no evidence of clinical bleeding. It is important that individuals with these findings be well informed about the meaning of their clotting factor deficiency because they do not need treatment, even for major surgery.

476.4 Factor VII Deficiency

J. Paul Scott

Factor VII deficiency is a rare autosomal bleeding disorder that is usually detected only in the homozygous state. Severity of bleeding varies from mild to severe with hemarthroses, spontaneous intracranial hemorrhage, and mucocutaneous bleeding, especially nosebleeds and menorrhagia. Patients with this deficiency have markedly prolonged PT but normal PTT. Factor VII assays show a marked reduction in factor VII. Because the plasma half-life of factor VII is 2-4 hr, therapy with FFP is difficult and is often complicated by fluid overload. A commercial concentrate of recombinant factor VIIa is effective in treating patients with factor VII deficiency.

Bibliography is available at Expert Consult.

476.5 Factor X Deficiency

J. Paul Scott

Factor X deficiency is a rare (estimated 1/1,000,000) autosomal disorder with variable severity. Mild deficiency results in mucocutaneous and posttraumatic bleeding, whereas severe deficiency results in spontaneous hemarthroses and intracranial hemorrhages. Factor X deficiency is the result of either a quantitative deficiency or a dysfunctional molecule. A reduced factor X level is associated with prolongation of both PT and PTT. In patients with hereditary factor X deficiency, factor X levels can be increased with use of either FFP or prothrombin complex concentrate. The half-life of factor X is approximately 30 hr, and its volume of distribution is similar to that of factor IX. Thus, 1 unit/kg will increase the plasma level of factor X by 1%.

Although it is rarely a problem in pediatric patients, **systemic amyloidosis** may be associated with factor X deficiency, owing to the adsorption of factor X on the amyloid protein. In the setting of amyloidosis, transfusion therapy often is not successful because of the rapid clearance of factor X.

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476.6 Prothrombin (Factor II) Deficiency

J. Paul Scott

Prothrombin deficiency is caused either by a markedly reduced prothrombin level (hypoprothrombinemia) or by functionally abnormal prothrombin (dysprothrombinemia). Laboratory testing in homozygous patients shows prolonged PT and PTT. Factor II, or prothrombin, assays show a markedly reduced prothrombin level. Mucocutaneous bleeding in infancy and posttraumatic bleeding later are common. Patients are treated with either FFP or, rarely, prothrombin complex concentrates. In prothrombin deficiency, FFP is useful, because the half-life of prothrombin is 3.5 days. Administration of 1 IU/kg of prothrombin will increase the plasma activity by 1%.

Bibliography is available at Expert Consult.

476.7 Factor V Deficiency

J. Paul Scott

Deficiency of factor V is an autosomal recessive, mild to moderate bleeding disorder that has also been termed **parahemophilia.** Hemarthroses occur rarely; mucocutaneous bleeding and hematomas are the most common symptoms. Severe menorrhagia is a frequent symptom in women. Laboratory evaluation shows prolonged PTT and PT. Specific assays for factor V show a reduction in factor V levels. FFP is the only currently available therapeutic product that contains factor V. Factor V is lost rapidly from stored FFP. Patients with severe factor V deficiency are treated with infusions of FFP at 10 mL/kg every 12 hr. Rarely, a patient with a negative family history of bleeding has an acquired antibody to factor V. Often, such a patient does not bleed because the factor V in platelets prevents excessive bleeding.

Bibliography is available at Expert Consult.

476.8 Combined Deficiency of Factors V and VIII

J. Paul Scott

Combined deficiency of factors V and VIII occurs secondary to the absence of an intracellular transport protein that is responsible for transporting factors V and VIII from the endoplasmic reticulum to the Golgi compartments. This explains the paradoxical deficiency of 2 factors, one encoded on chromosome 1 and the other on the X chromosome. Bleeding symptoms are often milder than for hemophilia A and are treated with FFP to replace both factors V and VIII.

476.9 Fibrinogen (Factor I) Deficiency

J. Paul Scott

Congenital afibrinogenemia is a rare autosomal recessive disorder in which there is an absence of fibrinogen. Patients with this disorder do not bleed as frequently as patients with hemophilia and rarely have hemarthroses. Affected patients may present in the neonatal period with gastrointestinal hemorrhage or hematomas after vaginal delivery. In addition to marked prolongation of PT and PTT, thrombin time is prolonged. In the absence of consumptive coagulopathy, an unmeasurable fibrinogen level is diagnostic. In addition to the quantitative deficiency of fibrinogen, a number of dysfunctional fibrinogens have been reported (**dysfibrinogenemia**). Rarely patients with dysfibrinogenemia present with thrombosis. A human fibrinogen concentrate is commercially available for therapy of bleeding episodes in afibrinogenemic patients. Because the plasma half-life of fibrinogen is 2-4 days, treatment with either FFP or cryoprecipitate is also effective. The hemostatic level of fibrinogen is >60 mg/dL. Each bag of cryoprecipitate contains 100-150 mg of fibrinogen. Some clinical assays for fibrinogen are inhibited by high doses of heparin. Thus, a markedly prolonged thrombin time associated with a low fibrinogen level should be evaluated with determination of reptilase time. Prolonged reptilase time confirms that functional levels of fibrinogen are low and that heparin is not present.

476.10 Factor XIII Deficiency (Fibrin-Stabilizing Factor or Transglutaminase Deficiency)

J. Paul Scott

Because factor XIII is responsible for the crosslinking of fibrin to stabilize the fibrin clot, symptoms of delayed hemorrhage are secondary to instability of the clot. Typically, patients have trauma 1 day and then have a bruise or hematoma the next day. Clinical symptoms include mild bruising, delayed separation of the umbilical stump beyond 4 wk in neonates, poor wound healing, and recurrent spontaneous abortions in women. Rare kindreds with XIII deficiency with hemarthroses and intracranial hemorrhage have been described. Results of the usual screening tests for hemostasis are normal in patients with factor XIII deficiency. Screening tests for factor XIII deficiency are based on the observation that there is increased solubility of the clot because of the failure of crosslinking. The normal clot remains insoluble in the presence of 5M urea, whereas in a patient with XIII deficiency, the clot dissolves. More specific assays for factor XIII are immunologic. The half-life of factor XIII is 5-7 days and the hemostatic level is 2-3% activity. There is a heat-treated, lyophilized concentrate of coagulation factor XIII available to treat bleeding episodes or for prophylaxis.

Bibliography is available at Expert Consult.

476.11 Antiplasmin or Plasminogen Activator Inhibitor Deficiency

J. Paul Scott

Deficiency of either antiplasmin or plasminogen activator inhibitor, both of which are antifibrinolytic proteins, results in increased plasmin generation and premature lysis of fibrin clots. Affected patients have a mild bleeding disorder characterized by mucocutaneous bleeding but rarely have joint hemorrhages. Because results of the usual hemostatic tests are normal, further work-up of a patient with a positive bleeding history should include euglobulin clot lysis time (if available), which measures fibrinolytic activity and yields a shortened result in the presence of these deficiencies. Specific assays for α_2-antiplasmin and plasminogen activator inhibitor are available. Bleeding episodes are treated with FFP; bleeding in the oral cavity may respond to aminocaproic acid.

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Chapter 477

Von Willebrand Disease

Veronica H. Flood and J. Paul Scott

von Willebrand disease (VWD) is the most common inherited bleeding disorder, with an estimated prevalence cited at 1 : 100 to 1 : 10,000 depending on the criteria used for diagnosis. Patients with VWD typically present with mucosal bleeding. A family history of either VWD or bleeding symptoms and confirmatory laboratory testing are also required for the diagnosis of VWD.

PATHOPHYSIOLOGY

VWD is caused by a defect in von Willebrand factor (VWF). VWF has several functions in coagulation. First, VWF serves to tether platelets to injured subendothelium via binding sites for platelets and for collagen. Second, VWF serves as a carrier protein for factor VIII (FVIII), protecting FVIII from degradation in plasma. VWF is stored in endothelial cells and in platelet Weibel-Palade bodies and circulates as a large multimeric glycoprotein. Shear stress induces a conformational change in VWF that facilitates its ability to bind platelets through a binding site on platelet glycoprotein Ib (GPIb). This enables VWF to recruit platelets to the site of clot formation, a function that is dependent on the high-molecular-weight multimer forms of VWF.

VWD typically presents with mucosal bleeding, similar to that seen with other platelet defects. Epistaxis, easy bruising, and menorrhagia in women are common complaints. Symptoms, however, are variable, and do not necessarily correlate well with VWF levels. Surgical bleeding, particularly with dental extractions or adenotonsillectomy, is another common presentation. Severe type 3 VWD may present with joint bleeds. Most patients will have a family history of bleeding. Women are more likely to be diagnosed with VWD because of the potential for symptoms with menorrhagia, but men and women are equally likely to have VWD. Diagnosis based on symptoms may be difficult, however, as minor bruising and epistaxis are not uncommon in childhood. Significant unexplained bruising is more often from nonaccidental trauma than from an underlying bleeding disorder.

CLASSIFICATION

VWD may be caused by quantitative or qualitative defects in VWF. Mild to moderate quantitative defects are classified as type 1 VWD, while severe quantitative defects, in which there is no detectable VWF protein, are classified as type 3 VWD. The qualitative defects are grouped together as type 2 VWD.

Type 1 VWD is by far the most common type, accounting for 60-80% of all VWD patients. Typical symptoms include mucosal bleeding, such as epistaxis and menorrhagia as well as easy bruising and potentially surgical bleeding. Guidelines from the National Heart, Lung, and Blood Institute of the National Institutes of Health use a VWF level, as measured by the VWF antigen assay (VWF : Ag), of <30 IU/dL for diagnosis of VWD. Patients with VWF : Ag <20-30 IU/dL are most likely to have a genetic defect in VWF. Patients with VWF : Ag between 30 and 50 IU/dL are said to have "low VWF." Whether or not this category truly represents VWD is a subject of some debate. Because some patients with VWF levels in this range do experience bleeding, many physicians elect to treat them, especially for surgeries such as tonsillectomy.

Patients with low VWF may have VWD as a result of increased clearance of their VWF, or type 1C VWD. Diagnosis of this subtype is important because treatment of these patients with desmopressin is likely to be ineffective, necessitating administration of VWF-containing products.

VWF levels can be influenced by external factors. Blood type has long been known to affect VWF, with lower VWF levels seen in people with blood group O. Stress, exercise, and pregnancy all increase VWF levels; therefore, a single normal VWF level does not necessarily rule out the presence of VWD. Certain diseases, such as *hypothyroidism*, and medications, such as *valproic acid*, can lower VWF levels in affected patients. Repeat testing may be required to rule out or confirm a diagnosis of VWD.

Type 3 VWD is the most severe form and presents with symptoms similar to those seen in mild hemophilia. In type 3 VWD, the VWF protein is completely absent. Type 3 VWD is seen at a frequency of approximately 1 in 1,000,000. In addition to mucosal bleeding, patients may experience joint bleeds or central nervous system hemorrhage. Some physicians elect to treat patients with prophylaxis, or modified prophylaxis following injury, given that these patients typically have very low FVIII (<10 IU/dL). Because type 3 VWD is caused by a lack of VWF, treatment with VWF-containing concentrates is required.

Type 2A VWD is characterized by a defect in VWF multimerization and decreased VWF activity in terms of platelet binding. It is the most common of the type 2 variants, accounting for approximately 10% of VWD cases. Type 2A VWD can result from mutations that affect multimer assembly and processing, or mutations that result in increased proteolysis of secreted VWF. Some mutations affect both secretion and clearance of the VWF. Regardless of the mechanism, all type 2A VWD patients lack the high-molecular-weight multimers, and therefore have reduced VWF activity which results in bleeding. Symptoms are typically more severe than those seen in type 1 VWD. Desmopressin may have clinical efficacy for treatment of minor bleeding, but significant surgical challenges or major bleeding symptoms generally require a VWF-containing concentrate for treatment.

Type 2B VWD results from gain-of-function mutations that increase the ability of VWF to bind platelets. This leads to increased clearance of both VWF and platelets from circulation and results in the loss of high-molecular-weight multimers and decreased VWF activity, similar to that seen in type 2A VWD. Special testing is, therefore, required to diagnose type 2B VWD, either by direct measurement of the increased platelet binding or by an increased response to low-dose ristocetin on platelet aggregation testing. Thrombocytopenia is not always present and may be more prominent during times of stress such as surgery or pregnancy. Desmopressin is relatively contraindicated in type 2B VWD as it may accelerate VWF-platelet binding and clearance.

Platelet-type, pseudo-VWD occurs when a mutation in platelet GPIb causes spontaneous binding to VWF and also presents with decreased VWF activity, loss of high-molecular-weight multimers, and thrombocytopenia similar to type 2B VWD. Specific testing is required to distinguish the 2 conditions. Because the defect involves platelets, treatment generally requires platelet transfusion.

Type 2M VWD includes those patients with decreased VWF activity but normal (or near-normal) multimer distribution. This is generally caused by a defect in the ability of VWF to bind platelet GPIb, but this category also includes patients with defects in VWF-collagen interactions. Some minor bleeding in type 2M VWD may respond to desmopressin, but because type 2M VWD is a functional defect, treatment with VWF-containing concentrates is usually required.

Type 2N VWD is characterized by a defect in the ability of VWF to bind FVIII. Some patients with type 2N VWD may be misdiagnosed as mild hemophilia, therefore a high index of suspicion for this diagnosis is required in patients with low FVIII and an absent family history of FVIII deficiency.

LABORATORY DIAGNOSIS

There are no reliable screening tests for VWD. Patients with significant bleeding may present with anemia, and some patients with type 2B VWD or platelet-type, pseudo-VWD may have thrombocytopenia. The partial thromboplastin time may be prolonged if FVIII is low, but especially in mild type 1 VWD it is often normal, precluding use of the partial thromboplastin time as a screening test. Platelet function analysis has been considered as a screening test for VWD, but suboptimal

	Normal	Type 1	Type 1C (Vicenza)	Type 3	Type 2A	Type 2B	Type 2N	Type 2M	PT-VWD
VWF:Ag	N	↓	↓↓	absent	↓	↓	N or ↓	↓ or N	↓
VWF:RCo	N	↓	↓↓	absent	↓↓↓	↓↓	N or ↓	↓↓	↓↓
FVIII:C	N	N or ↓	↓	2-10 IU/dL	N or ↓	N or ↓	↓↓	N	N or ↓
VWFpp/VWF:Ag ratio	N	N	↑↑	absent	N or ↑	↑	N	N	↑
RIPA	N	often N	↓	absent	↓	often N	N	N or ↓	often N
LD-RIPA	absent	absent	absent	absent	absent	↑↑↑	absent	absent	↑↑↑
PFA'	N	N or ↑	↑	↑↑↑	↑	↑	N	↑	↑
BT'	N	N or ↑	↑	↑↑↑	↑	↑	N	↑	↑
Platelet count	N	N	N	N	N	↓ or N	N	N	↓
VWF multimers	N	N but ↓	N but ↓	absent	abnormal	abnormal	N but ↓	N but ↓	abnormal

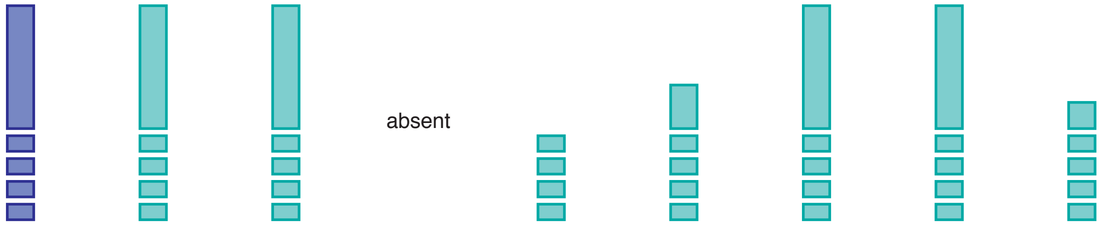

Figure 477-1 Specialized laboratory testing for VWD. ↓,↓↓,↓↓↓, Relative decrease; ↑,↑↑,↑↑↑, relative increase; BT, bleeding time; FVIII:C, factor VIII coagulant activity; LD-RIPA, low-dose ristocetin-induced platelet aggregation; N, normal; N but ↓, normal but decreased in intensity; PT-VWD, platelet-type VWD; RIPA, ristocetin-induced platelet aggregation; VWF:Ag, VWF antigen; VWF:RCo, VWF activity by ristocetin cofactor; VWFpp, VWF propeptide. *(Courtesy of Dr. Robert R. Montgomery.)*

Table 477-1 Laboratory Testing for VWD

TEST	ABBREVIATION	PURPOSE
VWF antigen	VWF:Ag	Measures total amount of VWF protein present
VWF activity	VWF:RCo	Assess interaction of VWF and platelets as mediated by ristocetin
VWF activity/antigen ratio	VWF:RCo/VWF:Ag	A decreased ratio (<0.7) is found in type 2A, type 2B, and type 2M VWD
Factor VIII activity	FVIII	Measures circulating FVIII, which will be very low in type 2N and type 3 VWD
Multimer distribution	VWF multimers	Allows visualization of VWF multimers, used to identify high-molecular-weight multimers, which will be absent in types 2A and 2B VWD

sensitivity and specificity render results difficult to interpret. Bleeding times are similarly unreliable in diagnosis of VWD.

Unfortunately there is no single test that can reliably diagnose VWD. Therefore a panel of tests is usually required. Table 477-1 lists the laboratory tests commonly used in diagnosis of VWD. These include VWF antigen (VWF:Ag), which measures the total amount of VWF protein present, and VWF activity, which is typically performed using the ristocetin cofactor activity assay (VWF:RCo) and provides a measure of the amount of functional VWF. FVIII activity is also usually included in the workup. Another important test is the VWF multimer distribution, although this is not routinely performed by all laboratories. Table 477-2 summarizes the expected laboratory findings for each type of VWD. Figure 477-1 provides more detailed analysis.

Additional specialized testing may be employed to help ascertain the correct diagnosis. Specific testing for type 1C (clearance defects), type 2B, and type 2N VWD can confirm these diagnoses. Genetic diagnosis is not typically performed, partly as a result of the large size of the VWF gene and the large number of benign sequence variations. Large gene deletions are responsible for some cases of VWD and will not be picked up on routine DNA sequencing. Use of genetic diagnosis is increasing, however, particularly for types 2A, 2B, 2M, and 2N VWD.

TREATMENT

Treatment of VWD depends on the type of VWD present and on the reason for treatment. Table 477-3 outlines the options for treatment. In general, type 1 VWD patients may be treated with desmopressin, which increases the amount of circulating VWF by release from storage. The exceptions are the rare type 1 patient who lacks a response to desmopressin, and patients with type 1C VWD who do respond with an increase in VWF levels, but whose rapid clearance of circulating endogenous VWF results in a rapid return to baseline levels. Treatment of types 2 and 3 VWD requires VWF-containing concentrates similar to the treatment of hemophilia. Dosing depends on the type of VWD, and reason for treatment. Careful monitoring of VWF and FVIII levels is recommended to tailor treatment for surgeries and major trauma. For all types of VWD, adjunct therapy should be

Table 477-2 VWD Classification

	TYPE 1	TYPE 3	TYPE 2A	TYPE 2B*	TYPE 2M	TYPE 2N
VWF:Ag	↓	Absent	↓	↓	↓	Normal or ↓
VWF:RCo	↓	Absent	↓↓	↓↓	↓↓	Normal or ↓
FVIII	Normal	↓↓	Normal or ↓	Normal or ↓	Normal or ↓	↓↓
Multimer distribution	Normal	Absent	Loss of HMWM	Loss of HMWM	Normal	Normal

*Platelet count is also usually decreased in type 2B VWD.
FVIII, factor VIII; HMWM, high-molecular-weight multimers; VWF:Ag, VWF antigen; VWF:RCo, VWF ristocetin cofactor activity.

Table 477-3 VWD Treatment

TREATMENT	VWD TYPES	ADMINISTRATION	DOSING
Desmopressin*	Type 1 VWD Some type 2 VWD (use with caution)	IV or IN	0.3 μg/kg IV[†] 1 spray IN (<50 kg) 2 sprays IN (>50 kg)
von Willebrand factor concentrates[‡]	Type 3 VWD Type 2 VWD Severe type 1 VWD (or type 1 clearance defects)	IV	40-60 ristocetin cofactor activity units/kg (adjust dose depending on baseline VWF level and desired peak VWF level)
Antifibrinolytics	Mucosal bleeding, all types of VWD	PO or IV	Aminocaproic acid: 100 mg/kg PO loading dose followed by 50 mg/kg q 6 hours[§] Tranexamic acid: 1300 mg PO tid × 5 days

*Recommended treatment with Stimate brand nasal spray, as this form is concentrated to give 150 μg/spray. Other forms are much more dilute and will not result in desired increase in VWF.
[†]Maximum recommended dose is 20-30 μg/day.
[‡]Currently both Humate-P and Wilate are approved for treatment of VWD. A recombinant VWF preparation is currently undergoing clinical trials.
[§]Maximum recommended dose is 24 g/day.
IN, intranasal; IV, intravenous; PO, oral administration.

considered when possible, such as the use of antifibrinolytics for oral surgery or hormonal treatment for menorrhagia.

Alternate treatment strategies should also be considered, particularly for difficult symptoms or severe VWD. Hormonal therapy for women with menorrhagia, although not specific to VWD, can be very helpful in managing symptoms and improving quality of life. Local treatment of epistaxis, such as nasal cautery or packing, may be helpful in some circumstances. Iron therapy for patients with iron-deficiency anemia may also be required.

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Chapter 478

Hereditary Predisposition to Thrombosis

Leslie J. Raffini and J. Paul Scott

Pediatricians are frequently asked to evaluate children for inherited risk factors for thrombosis with symptomatic thrombosis or asymptomatic children who have relatives affected with either thrombosis or thrombophilia. The clinical utility of thrombophilia testing is debated, both in adults and children.

Thrombophilia testing rarely influences the acute management of a child with a thrombotic event. The association between inherited thrombophilia and pediatric thrombosis varies based on the clinical scenario: children with unprovoked thrombotic events have a high prevalence of inherited defects, while the role of thrombophilic defects in children with catheter-related thrombotic events is questionable. Although some thrombophilic defects are associated with a higher risk of recurrent venous thromboembolism in children, how to use these results to guide the duration of therapy has not been determined. Prospective longitudinal analyses of such patients to determine outcome and response to treatment as well as the impact of known thrombophilic states on these outcomes are clearly needed.

The decision to perform thrombophilia testing in an otherwise healthy child with a family history of thrombosis or thrombophilia should be carefully considered, weighing the potential advantages and limitations of such an approach. Given that the absolute risk of thrombosis in children is extremely low (0.07/100,000), it is unlikely that an inherited thrombophilia will have any impact on clinical decision-making for a young child. The risk of thrombosis increases with age, so identification of a thrombophilic defect in an adolescent may guide thromboprophylaxis in high-risk situations (lower extremity casting or prolonged immobility), inform the discussion about estrogen-based contraceptives, and promote lifestyle modification to avoid behavioral prothrombotic risk factors (sedentary lifestyle, dehydration, obesity, and smoking). Limitations of such testing include the cost as well as the potential for causing unnecessary anxiety or false reassurance.

Table 478-1 lists the most common inherited thrombophilias and their prevalence in the general population. The inherited defects in which the pathogenic link is best understood include the factor V Leiden mutation, the prothrombin gene mutation, and deficiencies of

Table 478-1 Common Inherited Thrombophilias and Accompanying Diagnostic Laboratory Studies

THROMBOPHILIA	PREVALENCE IN WHITE POPULATION %	ODDS RATIO FOR FIRST EPISODE VTE IN CHILDHOOD*	LABORATORY STUDIES
Factor V Leiden mutation			DNA-based PCR assay (or screen with activated protein C resistance)
Heterozygote	3-7	3.8	
Homozygote	0.06-0.25	80-100	
Prothrombin 20210 mutation			DNA-based PCR assay
Heterozygote	1-3	2.6	
Homozygote	–	–	
Antithrombin deficiency	0.02-0.04	9.4	Antithrombin activity via chromogenic or clotting assay
Protein S deficiency	0.03-0.13	5.8	Protein S activity via assay or immunologic assay of free and total protein S antigen
Protein C deficiency	0.2	7.7	Protein C activity via chromogenic or clotting assay
Hyperhomocystinemia	–	–	Fasting homocysteine
Elevated VIII	–	–	Factor VIII activity via one-stage clotting or chromogenic assay

*Data from Young G, Albisetti M, Bonduel M, et al: Impact of inherited thrombophilia on venous thromboembolism in children. *Circulation* 118:1373–1382, 2008.
PCR, polymerase chain reaction; VTE, venous thromboembolism.

protein C, protein S, and antithrombin (AT). Elevated levels of factor VIII and homocysteine are associated with thrombosis, though these are less-well characterized and not necessarily genetically determined. Although there are additional alterations in coagulation that have been associated with thrombotic risk, including elevated concentrations of factors IX and XI, heparin cofactor II deficiency, elevated lipoprotein (a), and dysfibrinogenemia, none has gained widespread acceptance in routine testing of children for inherited thrombophilia.

The **factor V Leiden mutation** is the result of a single nucleotide change at nucleotide 1765 within the factor V gene. This mutation causes factor Va to become resistant to inactivation by activated protein C and is the most common inherited risk factor for thrombosis. This defect is also known as *activated protein C resistance*. Approximately 5% of the U.S. white population is heterozygous for this mutation, and it is less prevalent in other ethnic groups. Individuals who are heterozygous have a 5-7–fold increase in risk of venous thrombosis, while homozygotes have a relative risk of 80-100. The baseline annual risk of thrombosis for young women of reproductive age is 1 per 12,500 and increases to 1 per 3,500 for those on oral contraceptives. For young women who are heterozygous for the factor V Leiden mutation and are taking oral contraceptives, this baseline annual risk is increased 20-30–fold (relative risk) to approximately to 1 per 500 women.

The **prothrombin 20210 gene mutation** is a G-to-A transition in the 3′ untranslated region of the gene that results in increased levels of prothrombin messenger RNA. This variant is present in approximately 2% of U.S. whites. It is a weaker risk factor for venous thrombosis than factor V Leiden, with a relative risk of 2-3.

Deficiencies of protein C, protein S, and AT, the natural anticoagulant proteins, are more rare than the common genetic mutations described previously but are associated with a stronger risk of thrombosis. Although heterozygous deficiencies do not often present during childhood, homozygous defects may result in significant symptoms in infancy. Neonates with homozygous deficiencies of AT, protein C, or protein S may present with purpura fulminans. This condition is characterized by rapidly spreading purpuric skin lesions resulting from thromboses of the small dermal vessels followed by bleeding into the skin. In addition, these infants may also develop cerebral thrombosis, ophthalmic thrombosis, disseminated intravascular coagulation, and large vessel thrombosis. An infant with purpuric skin lesions of unknown cause should receive initial replacement with fresh-frozen plasma. Definitive diagnosis can be difficult in the sick premature neonate who may have undetectable levels of these factors but not have a true genetic deficiency. Protein C and AT concentrates are also available and have been demonstrated to be effective.

Both venous and arterial thromboses are common in young patients with **homocystinuria,** an inborn error of metabolism caused by deficiency of cystathione β-synthase. In this very rare condition, plasma levels of homocysteine exceed 100 μmol/L. Much more common are mild to moderate elevations of homocysteine, which may be acquired or associated with a polymorphism in the methylenetetrahydrofolate reductase (*MTHFR*) gene. Although moderate elevations of homocysteine have been associated with both venous and arterial thrombotic events, testing for polymorphisms in the *MTHFR* gene are not indicated, because these polymorphisms are not associated with venous thromboembolism. The pathogenic mechanisms for thrombosis in homocystinemia are not well understood.

Increased plasma concentrations of **factor VIII** (>150 IU/dL) appear to be regulated by both genetic and environmental factors and are associated with an increased risk of thrombosis. Although there is a strong component of heritability contributing to factor VIII levels, the molecular mechanisms responsible for elevated factor VIII are not well understood. Factor VIII is also considered to be an acute-phase reactant, and may increase transiently during periods of inflammation.

Although interpretation of genetic studies (Factor V Leiden and Prothrombin gene mutations) are fairly straightforward, there are several **challenges in interpretation of thrombophilia studies** that are unique to pediatric patients. Neonates have decreased concentrations of protein C, protein S, and AT that increase rapidly over the first 6 mo of life; protein C concentrations remain below adult levels throughout much of childhood. It is important to use pediatric normal ranges when evaluating these values, and recognize that often the normal range overlaps with heterozygous defects and retesting may be required, particularly in young children. There are several nongenetic factors that many also influence the results of inherited thrombophilia testing, including acute thrombosis, infection, inflammation, hepatic dysfunction, nephrotic syndrome, medication and vitamin K deficiency. In some cases, the hereditary nature may be confirmed by testing the parents.

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Chapter 479

Thrombotic Disorders in Children

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Compared to adults, children are generally protected from venous and arterial thromboses. Advancements in the treatment and supportive care of critically ill children, coupled with a heightened awareness of genetic risk factors for thrombosis, have led to an increase in the diagnosis of thromboembolic events (TEs) in children. As a result, TEs are not infrequent in pediatric tertiary care centers and may result in significant acute and chronic morbidity. Despite the fact that TEs in children are increasing in relative terms, they are still rare. This rarity has been the major impediment to prospective clinical trials, resulting in a deficit of evidence-based medicine. Diagnosis and treatment is often extrapolated from adult data.

EPIDEMIOLOGY

Studies have confirmed a significant increase in the diagnosis of venous thromboembolism (VTE) in pediatric tertiary hospitals across the United States. Although the overall incidence of thrombosis in the general pediatric population is quite low (0.07/100,000), the rate of VTE in hospitalized children is 60/10,000 admissions. Infants <1 yr old account for the largest proportion of pediatric VTEs, with a second peak during adolescence.

The majority of children who develop a TE have multiple risk factors that may be acquired, inherited, and/or anatomic (Table 479-1). The presence of a central venous catheter (CVC and peripherally inserted central venous catheter) is the single most important risk factor for VTE in pediatric patients, associated with approximately 90% of neonatal VTE and 60% of childhood VTE. These catheters are often necessary for the care of premature neonates and children with acute and chronic diseases and are used for intravenous hyperalimentation, chemotherapy, dialysis, antibiotics, or supportive therapy. CVCs may damage the endothelial lining and/or cause blood flow disruption, increasing the risk of thrombosis. There are multiple other acquired risk factors that are associated with thrombosis, including trauma, infection, chronic medical illnesses, and medications. Cancer, congenital heart disease, and prematurity are the most common medical conditions associated with TEs.

Antiphospholipid antibody syndrome (APS) is a well-described syndrome in adults characterized by recurrent fetal loss and/or thrombosis. Antiphospholipid antibodies are associated with both venous and arterial thrombosis. The mechanism by which these antibodies cause thrombosis is not well understood. A diagnosis of APS requires the presence of both clinical and laboratory abnormalities (see "Laboratory Testing" below). The laboratory abnormalities must be persistent for 12 wk. Because of the high risk of recurrence, patients with APS often require long-term anticoagulation. It is important to note that healthy children may have a transient lupus anticoagulant, often diagnosed because of a prolonged partial thromboplastin time on routine preoperative testing. These antibodies may be associated with a recent viral infection and are not a risk factor for thrombosis.

Anatomic abnormalities that impede blood flow also predispose patients to thrombosis at an earlier age. Atresia of the inferior vena cava has been described in association with acute and chronic lower extremity deep venous thrombosis (DVT). **May-Thurner syndrome** (compression of the left iliac vein by the overlying right iliac artery) should be considered in patients who present spontaneously with left iliofemoral thrombosis, and **thoracic outlet obstruction** (**Paget-Schroetter syndrome**) frequently presents with effort-related axillary-subclavian vein thrombosis.

Table 479-1	Risk Factors for Thrombosis
General	Indwelling catheter including PICC (peripherally inserted central venous catheter) lines Infection Trauma Surgery Cancer Immobility Cardiac disease/prosthetic valve Systemic lupus Rheumatoid arthritis Inflammatory bowel disease Polycythemia/dehydration Nephrotic syndrome Diabetes Pregnancy Obesity Prematurity Paroxysmal nocturnal hemoglobinuria Antiphospholipid antibody syndrome Thrombotic thrombocytopenic purpura
Inherited thrombophilia	Factor V Leiden mutation Prothrombin mutation Antithrombin deficiency Protein C deficiency Protein S deficiency Homocystinuria Elevated factor VIII Dysfibrinogenemia
Anatomic	Thoracic outlet obstruction (Paget-Schroetter syndrome) May-Thurner syndrome Absence of the inferior vena cava
Medications	Estrogen-containing contraceptives Asparaginase Heparin (heparin-induced thrombocytopenia) Corticosteroids

CLINICAL MANIFESTATIONS

Extremity Deep Vein Thrombosis

Children with acute DVT often present with extremity pain, swelling, and discoloration. A history of a current or recent CVC in that extremity should be very suggestive. Many times, symptoms of CVC-associated thrombosis are more subtle and chronic, including repeated CVC occlusion or sepsis, or prominent venous collaterals on the chest, face, and neck.

Pulmonary Embolism

Symptoms of pulmonary embolism (PE) include shortness of breath, pleuritic chest pain, cough, hemoptysis, fever, and, in the case of massive PE, hypotension and right-heart failure. Based on autopsy studies, PE is often not diagnosed, perhaps because young children are unable to accurately describe their symptoms and their respiratory deterioration may be masked by other conditions (see Chapter 407.1).

Cerebral Sinovenous Thrombosis

Symptoms may be subtle and may develop over many hours or days. Neonates often present with seizures, whereas older children often complain of headache, vomiting, seizures, and focal signs. They may also have papilledema and abducens palsy. Some patients may have a concurrent sinusitis or mastoiditis that has contributed to the thrombosis.

Renal Vein Thrombosis

Renal vein thrombosis is the most common spontaneous TE in neonates. Affected infants may present with hematuria, an abdominal mass, and/or thrombocytopenia. Infants of diabetic mothers are at increased risk, although the mechanism for this increased risk is unknown. Approximately 25% of cases are bilateral.

Peripheral Arterial Thrombosis

With the exception of stroke, the majority of arterial TEs in children are secondary to catheters, often in neonates related to umbilical artery lines or in patients with cardiac defects undergoing cardiac catheterization. Patients with an arterial thrombosis affecting blood flow to an extremity will present with a cold, pale, blue extremity with poor or absent pulses.

Stroke

Ischemic stroke commonly presents with hemiparesis, loss of consciousness, or seizures. This condition may occur secondary to pathology that affects the intracranial arteries (e.g., sickle cell disease, vasculopathy, or traumatic arterial dissection) or may be a result of venous thrombi that embolize to the arterial circulation (placental thrombi, children with congenital heart disease or patent foramen ovale).

Rapidly Progressive Thrombosis/Thrombotic Storm

Rapid progression or multifocal thrombosis is a rare complication of the APS, heparin-induced thrombocytopenia with thrombosis or thrombotic thrombocytopenia purpura while on appropriate antithrombotic therapy. Multiple organ dysfunctions develop in the presence of small vessel occlusion and elevated D-dimer levels. Recurrences may occur as well as postthrombotic syndrome (PTS). Treatment includes aggressive anticoagulation, often with direct thrombin inhibitors or fondaparinux followed by prolonged warfarin therapy.

DIAGNOSIS

Ultrasound with Doppler flow is the most commonly employed imaging study for the diagnosis of upper, or more often lower, extremity VTE. Spiral CT is used most frequently for the diagnosis of PE (Fig. 479-1). Other diagnostic imaging options include CT and MR venography, which are noninvasive, although the sensitivity and specificity of these studies is not known. They may be particularly helpful in evaluating proximal thrombosis. For the diagnosis of cerebral sinovenous thrombosis and acute ischemic stroke, the most sensitive imaging study is brain magnetic resonance imaging with venography or diffusion weighted imaging.

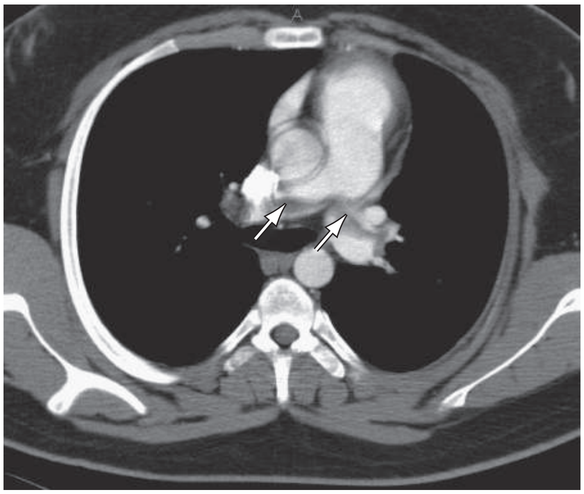

Figure 479-1 Chest CT from a 15 yr old male with a large pulmonary embolism. There are large filling defects in both the right and left main pulmonary arteries.

LABORATORY TESTING

All children with a TE should have a complete blood count and a baseline prothrombin time (PT) and activated partial thromboplastin time (aPTT) to assess their coagulation status. In adults suspected to have a DVT, the D-dimer level has a high negative predictive value. The D-dimer is a fragment produced when fibrin is degraded by plasmin and is a measure of fibrinolysis. Based on the clinical scenario, other laboratory studies, such as renal and hepatic function, may be indicated. Testing for APS includes evaluation for the lupus anticoagulant as well as anticardiolipin and anti–β_2-glycoprotein antibodies.

There is some debate regarding which patients should have testing for inherited risk factors. Thrombophilia testing rarely influences the acute management of a child with a thrombotic event. Identification of an inherited thrombophilia may influence the duration of treatment, particularly for those with combined defects, and may aid in counseling the patient about their risk of recurrence.

The evaluation of coagulation studies in pediatric patients is often complicated the developing hemostatic system and the differences in normal ranges between infants and adults In addition, there is often significant variation in the laboratory assays used to test anticoagulant levels. It is important to refer to the age-related normal ranges when interpreting pediatric coagulation studies. One limitation of these normal ranges is that they were performed many years ago, using assays that may not be equivalent to those used today. Molecular assays are not age dependent.

TREATMENT

Therapeutic options for children with thrombosis include anticoagulation, thrombolysis, surgery, and observation. The goal of **anticoagulation** is to reduce the risk of embolism, halt clot extension, and prevent recurrence. In premature neonates and critically ill children who may have an increased risk of bleeding, the potential benefits must be weighed against the risks. Anticoagulants and thrombolysis are discussed in greater detail in Chapter 479.1. Surgery may be necessary for life- or limb-threatening thrombosis when there is a contraindication to thrombolysis. The optimal treatment for a child with acute ischemic stroke depends on the likely etiology and the size of the infarct. Children with sickle cell disease who develop stroke are treated with chronic red blood cell transfusions to reduce recurrence.

COMPLICATIONS

Complications of VTE include recurrent thrombosis (either local or distant), and development of PTS. A thrombosed blood vessel may partially or fully recanalize or may remain occluded. Over time, an occluded deep vein may cause venous hypertension, resulting in blood flow being directed from the deep system into the superficial veins and potentially producing pain, swelling, edema, discoloration, and ulceration. This clinical picture is known as PTS and may be chronically disabling. Several prospective studies in adults have shown PTS to be present in 17-50% of patients with a history of thrombosis. The likelihood of developing PTS is highest in the first 2 yr but continues to increase over time.

479.1 Anticoagulant and Thrombolytic Therapy

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Initial options for anticoagulation in children include unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) (Table 479-2). Although there are additional agents, including target specific oral anticoagulants, none have been carefully investigated in children. Both UFH and LMWH act by catalyzing the action of antithrombin (AT)- III. UFH consists of large-molecular-weight polysaccharide chains that interact with AT, catalyzing the inhibition of factor Xa and thrombin, as well as other serine proteases. In contrast, LMWH contains smaller-molecular-weight polysaccharide chains. The interaction of the smaller chains with AT-III results primarily in the inhibition of

Table 479-2 Comparison of Antithrombotic Agents

	rTPA	UNFRACTIONATED HEPARIN*	WARFARIN	LMW HEPARIN (ENOXAPARIN)
Indication	Recent onset of life- or limb-threatening thrombus	Acute or chronic thrombus, prophylaxis	Subacute or chronic thrombosis, thromboprophylaxis for cardiac valves	Acute or chronic thrombus, prophylaxis
Administration	IV, Continuous infusion	IV, Continuous infusion	PO, once daily	SC injection, twice daily
Monitoring	"Lytic state": FDP or D-dimer	PTT	INR	Anti-Xa activity
Other	Higher risk of bleeding	Difficult to titrate, requires frequent dose adjustments	Heavily influenced by drug and diet	More stable and easy to titrate; concern of osteopenia with long-term use

FDP, fibrin degradation product; INR, international normalized ratio; LMW, low-molecular-weight; PTT, partial thromboplastin time; rTPA, recombinant tissue-type plasminogen activator.
*Higher dose is required in newborns.

Xa, with less of an effect on thrombin. There are several LMWHs available, and they have variable inhibitory effects on thrombin. For this reason, the PTT is not a reliable measure of the anticoagulant effect of LMWH, and the anti–factor Xa activity is used instead.

The optimal **duration of anticoagulation** for children with TEs is not well established. Current guidelines recommend that neonates receive 6 wk-3mo of therapy for VTE, and older children receive 3-6 mo of therapy. Patients with strong inherited thrombophilia, recurrent thrombosis, and APS may require indefinite anticoagulation.

UNFRACTIONATED HEPARIN

Heparin Dosing

Based on adult data, a therapeutic heparin dose achieves a prolongation of the aPTT of 1.5-2.5 the upper limit of normal. A bolus dose of 75-100 units/kg results in a therapeutic PTT in the majority of children. This bolus should be followed by a continuous infusion. Initial dosing is based on age, with infants having the highest requirements. It is important to continue to monitor the PTT closely. In some situations, such as patients with a lupus anticoagulant, elevated factor VIII, or neonates, the partial thromboplastin time may not accurately reflect the degree of anticoagulation, and heparin can be monitored using a heparin anti-Xa level of 0.35-0.7 units/mL.

Heparin Complications

Maintaining the aPTT in the therapeutic range can be difficult in young children for several reasons. The bioavailability of heparin is difficult to predict and may be influenced by plasma proteins. In many patients, this results in multiple dose adjustments requiring close monitoring with frequent venipuncture. UFH also requires continuous intravenous access, which may be difficult to maintain in young children.

The most common adverse effect related to heparin therapy is bleeding. This is well documented in the adult medical literature, and there are case reports of serious life-threatening bleeding in children treated with heparin. The true frequency of bleeding in pediatric patients on heparin has not been well established and is reported as 1-24%. If the anticoagulant effect of heparin must be reversed immediately, protamine sulfate may be administered to neutralize the heparin.

Other adverse effects include osteoporosis and heparin-induced thrombocytopenia (HIT). Although rare in pediatric populations, HIT is a prothrombotic, immune-mediated complication in which antibodies develop to a complex of heparin and platelet factor 4. These antibodies result in platelet activation, stimulation of coagulation, thrombocytopenia, and in some cases, life-threatening thrombosis. If HIT is strongly suspected, heparin must be discontinued immediately. There are several alternative parenteral anticoagulants (argatroban, lepirudin, or bivalirudin) that may be used in this situation.

LOW-MOLECULAR-WEIGHT HEPARIN

Because of the ease of dosing and need for less monitoring, **LMWH** is being used more frequently in pediatric patients. Unlike UFH, which is monitored using the aPTT, LMWH is monitored via the anti-Xa activity. The LMWH formulation that has been used most often in pediatric patients is enoxaparin

Enoxaparin Dosing

The recommended standard starting dose of enoxaparin for infants <2 mo is 1.5 mg/kg/dose SQ every 12 hr; for patients >2 mo it is 1 mg/kg SQ every 12 hr. In general, peak levels are achieved 2-6 hr following an injection. A therapeutic anti–factor Xa level, drawn 4 hr after the 2nd or 3rd dose, should be between 0.5 and 1.0 IU/mL. The dose can be titrated to achieve this range. The elimination half-life of enoxaparin is 4-6 hr. Enoxaparin is cleared by the kidney and should be used with caution in patients with renal insufficiency. It should be avoided in patients with renal failure.

After an initial period of anticoagulation with heparin or LMWH, patients may continue to receive LMWH as an outpatient for the duration of therapy, or may be transitioned to an oral anticoagulant, such as warfarin.

WARFARIN

Warfarin is an oral anticoagulant that competitively interferes with vitamin K metabolism, exerting its action by decreasing concentrations of the vitamin K–dependent coagulation factors II, VII, IX, and X, as well as protein C and protein S. Therapy should be started while a patient is anticoagulated with heparin or LMWH because of the risk of warfarin-induced skin necrosis. This transient hypercoagulable condition may occur when levels of protein C drop more rapidly than the procoagulant factors.

Warfarin Dosing

Warfarin therapy is often initiated with a loading dose, with subsequent dose adjustments made according to a nomogram. When initiating a patient on warfarin, UFH or LMWH should be continued until the international normalized ratio (INR) is therapeutic for 2 days. In most cases, this takes 5-7 days. The PT is used to monitor the anticoagulant effect of warfarin. Because the thromboplastin reagents used in PT assays have widely varying sensitivities, it is not possible to compare the PT performed in one laboratory to that performed in another laboratory. As a result, the INR was developed as a mechanism to standardize the variation in the thromboplastin reagent. The target INR range depends on the clinical situation. In general, a range of 2.0-3.0 is the target for the treatment of VTE. High-risk patients, such as those with mechanical heart valves, APS, and recurrent thrombosis, may require a higher target range.

Warfarin Complications

As with the other anticoagulants, bleeding is the most common adverse effect. The risk of serious bleeding in children receiving warfarin for the treatment of VTE has been reported at 1.7%. Children who have supratherapeutic INRs are at higher risk. There is considerable interpatient variation in dose. Diet, medications, and illness may influence the metabolism of warfarin, requiring frequent dose adjustments and laboratory studies. Numerous medications can affect the pharmacokinetics of warfarin by altering its clearance or rate of absorption. This can have a profound effect on the INR, and must be considered when monitoring a patient on warfarin.

The strategies used to reverse warfarin therapy depend on the clinical situation and whether or not there is bleeding. Vitamin K can be administered to reverse the effect of warfarin but takes some time to have effect. If the patient is having significant bleeding, fresh-frozen plasma (15 mL/kg) should be given along with the vitamin K.

Nonhemorrhagic complications are uncommon in children. Warfarin is a teratogen, particularly in the first trimester. Warfarin embryopathy is characterized by bone and cartilage abnormalities known as chondrodysplasia punctata. Affected infants may have nasal hypoplasia and excessive calcifications in the epiphyses and vertebrae.

DIRECT THROMBIN OR FACTOR XA INHIBITORS

Direct thrombin inhibitors (dabigatran) or inhibitors of factor Xa (apixaban, rivaroxaban) have been tested as agents to prevent or treat venous thrombosis in adult populations with increased risk of thrombosis (surgery, immobilization, atrial fibrillation). Fixed dosing, oral administration, no dietary interference with vitamin K, and no need to monitor laboratory tests, as well as initial results suggesting noninferiority to warfarin and fewer bleeding episodes, have favored the use of these agents. Currently there is a paucity of evidence of their utility in children.

THROMBOLYTIC THERAPY

Although anticoagulation alone is often effective at managing thrombosis, there are times when more rapid clot resolution is necessary or desirable. In these situations, thrombolytic agents that activate the fibrinolytic system are of potential benefit. The pharmacologic activity of thrombolytic agents is dependent on the conversion of endogenous plasminogen to plasmin. Plasmin is then able to degrade several plasma proteins including fibrin and fibrinogen. Because of the high risk of bleeding, thrombolytic therapy is generally reserved for patients with life or limb-threatening thrombosis.

Tissue plasminogen activator (TPA) is available as a recombinant product and has become the primary agent used for thrombolysis in children, although proper dose finding studies have not been performed in a pediatric population.

Dosing

There is an extremely wide range of doses of TPA that have been used for systemic therapy, and there is no consensus as to the optimal dose. Previously recommended doses of systemic TPA were 0.1-0.6 mg/kg/hr; however there are recent reports of successful therapy with fewer bleeding complications using prolonged infusions with very low doses—0.01-0.06 mg/kg/hr.

Monitoring

There is no specific laboratory test to document a “therapeutic range” for thrombolytic therapy. It is important to maintain the fibrinogen >100 mg/dL and the platelet count >75,000/mm^3 during treatment. Supplementation of plasminogen using fresh-frozen plasma is generally recommended in neonates prior to initiating thrombolysis because of their low baseline levels.

The clinical and radiologic response to thrombolysis should be closely monitored. The duration of therapy depends on the clinical response. Invasive procedures including urinary catheterization, arterial puncture and rectal temperatures should be avoided.

The role of adjuvant UFH during thrombolytic therapy is controversial. Animal models have demonstrated that thrombolytic therapy can induce a procoagulant state with activation of the coagulation system, generation of thrombin, and extension or reocclusion of the thrombosis. In pediatric patients thought to be at low risk for bleeding, adjuvant UFH should be considered using doses of 10-20 units/kg/hr.

Complications

The most serious complication from thrombolysis is bleeding, which has been reported in 0-40% of patients. Absolute contraindications to thrombolysis include major surgery within 7 days, history of significant bleeding (intracranial, pulmonary or gastrointestinal), peripartum asphyxia with brain damage, uncontrolled hypertension and severe thrombocytopenia. In the event of serious bleeding, thrombolysis should be stopped and cryoprecipitate may be given to replace fibrinogen.

THROMBOPROPHYLAXIS

There have been no formal trials of prevention of venous thromboembolic disease in children. Hospitalized adolescents with multiple risk factors for thrombosis who are immobilized for a protracted time may benefit from prophylactic treatment with enoxaparin 0.5 mg/kg q12hr (maximum: 30 mg).

ANTIPLATELET THERAPY

Inhibition of platelet function using agents such as **aspirin** is more likely to be protective against arterial TEs than VTEs. Aspirin, also known as acetylsalicylic acid, exerts its antiplatelet effect by irreversibly inhibiting cyclooxygenase, preventing platelet thromboxane A_2 production. Aspirin is used routinely in children with Kawasaki disease and may also be useful in children with stroke, ventricular assist devices, and those with single-ventricle cardiac defects. The recommended dose of aspirin to achieve an antiplatelet effect in children is 1-5 mg/kg/day.

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Chapter 480

Postneonatal Vitamin K Deficiency

J. Paul Scott

Although "late" hemorrhagic disease has been reported in breastfed children, vitamin K deficiency occurring after the neonatal period is usually secondary to a lack of oral intake of vitamin K, alterations in the gut flora as a consequence of the long-term use of broad-spectrum antibiotics, liver disease, or malabsorption of vitamin K. Intestinal malabsorption of fats may accompany cystic fibrosis or biliary atresia and result in a deficiency of fat-soluble dietary vitamins, with reduced synthesis of vitamin K–dependent clotting factors (factors II, VII, IX, and X, and proteins C and S). Prophylactic administration of water-soluble vitamin K orally is indicated in these cases (2-3 mg/24 hr for children and 5-10 mg/24 hr for adolescents and adults), or vitamin K may be administered at 1-2 mg IV. In patients with advanced cirrhosis, synthesis of many of the clotting factors may be reduced because of hepatocellular damage. In these patients, vitamin K may be ineffective. The anticoagulant properties of warfarin (Coumadin) and related anticoagulants depend on interference with vitamin K, with a concomitant reduction of factors II, VII, IX, and X. Rat poison (superwarfarin) produces a similar deficiency; vitamin K is a specific antidote.

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Chapter **481**

Liver Disease

J. Paul Scott

Because all of the clotting factors, except factor VIII, are produced exclusively in the liver, coagulation abnormalities are very common in patients with severe liver disease. Only 15% of such patients have significant clinical bleeding states. The severity of the coagulation abnormality appears to be directly proportional to the extent of hepatocellular damage. The most common mechanism causing the defect is decreased synthesis of coagulation factors. Patients with severe liver disease characteristically have normal to increased (not reduced) levels of factor VIII activity in plasma. In some instances, disseminated intravascular coagulation (see Chapter 483) or hyperfibrinolysis may complicate liver disease, making laboratory differentiation of severe liver disease from disseminated intravascular coagulation difficult.

Treatment of the coagulopathy of liver disease should be reserved for patients with clinical bleeding. Because a reduction in vitamin K–dependent coagulation factors is common in those with acute or chronic liver disease, vitamin K therapy can be given as a trial. Vitamin K can be given orally, subcutaneously, or intravenously (not intramuscularly) at a dose of 1 mg/24 hr for infants, 2-3 mg/24 hr for children, and 5-10 mg/24 hr for adolescents and adults. Inability to correct coagulopathy with vitamin K indicates that the coagulopathy may be caused by reduced levels of clotting factors that are not vitamin K–dependent and/or by inadequate production of precursor vitamin K proteins. Treatment for bleeding consists of factor replacement with fresh-frozen plasma (FFP) or cryoprecipitate. FFP (10-15 mL/kg) contains all clotting factors, but replacement of fibrinogen for severe hypofibrinogenemia may require cryoprecipitate at a dose of 1 bag/5 kg body weight. In severe liver disease, it is often difficult to attain correction of abnormal clotting studies despite vigorous therapy with FFP and cryoprecipitate. Some patients with bleeding as a result of liver disease have responded to therapy with desmopressin, and others have responded to treatment with recombinant factor VIIa.

Frequently, severe liver disease is associated with moderate prolongation of bleeding time that is not corrected by either vitamin K or plasma replacement. Desmopressin (0.3 µg/kg IV) is effective in shortening bleeding time and is used effectively to augment hemostasis before liver biopsy. In clinical trials of adults, recombinant factor VIIa has not been shown to be effective for the treatment of bleeding caused by severe liver disease.

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Chapter **482**

Acquired Inhibitors of Coagulation

J. Paul Scott

Acquired circulating anticoagulants (inhibitors) are antibodies that react or crossreact with clotting factors or components used in coagulation screening tests (phospholipids), thereby prolonging screening tests, such as prothrombin time and partial thromboplastin time. Some of these anticoagulants are autoantibodies that react with phospholipid and thereby interfere with clotting in vitro but not in vivo. The most common form of these antiphospholipid antibodies has been referred to as the *lupus anticoagulant* (see Chapter 476.1). This anticoagulant is found in patients with systemic lupus erythematosus (see Chapter 158), in those with other collagen-vascular diseases, and in association with HIV. In otherwise healthy children, spontaneous lupus-like inhibitors have developed transiently after incidental viral infection. These transient inhibitors are usually not associated with either bleeding or thrombosis.

Although the classic lupus anticoagulant is more often associated with a predisposition to thrombosis than with bleeding symptoms, bleeding symptoms in a patient with the lupus anticoagulant may be caused by thrombocytopenia, as a manifestation of the antiphospholipid syndrome or of lupus itself, or, rarely, by a coexistent specific autoantibody against prothrombin (factor II). This antiprothrombin antibody does not inactivate prothrombin, but causes accelerated clearance of the protein, resulting in low levels of prothrombin.

Rarely, antibodies may arise spontaneously against a specific clotting factor, such as factor VIII or von Willebrand factor, similar to those seen more frequently in elderly patients. These patients are prone to excessive hemorrhage and may require specific treatment. In patients with a hereditary deficiency of a clotting factor (factor VIII or factor IX), antibodies may develop after exposure to transfused factor concentrates. These hemophilic inhibitory antibodies are discussed in Chapter 479.1.

LABORATORY FINDINGS

Inhibitors against specific coagulation factors usually affect factors VIII, IX, and XI, or, rarely, prothrombin. Depending on the target of the antibody, prothrombin time, partial thromboplastin time, or both may be prolonged. The mechanism by which the inhibitory antibody functions determines whether mixing patient plasma with normal plasma will normalize (correct) the clotting time. Patient plasma containing antibodies directed against the active site of the clotting factor (factor VIII or factor IX) will not correct on 1 : 1 mixing with normal plasma, whereas antibodies that lead to increased clearance of the factor (prothrombin) will correct on 1 : 1 mixing. Specific factor assays are used to determine which factor is involved.

TREATMENT

Management of the bleeding patient with an inhibitor against factor VIII or IX is the same as for the patient with hemophilia who has an alloantibody against factor VIII or factor IX. Infusions of recombinant factor VIIa or activated prothrombin complex concentrate may be needed to control significant bleeding. Immunosuppressive agents have used off-label to treat the inhibitor or reduce titers. Acute bleeding caused by an antiprothrombin antibody can often be treated with a plasma infusion and may benefit from a short course of corticosteroid therapy.

Asymptomatic spontaneous inhibitors that arise after a viral infection tend to disappear within a few weeks to months. Inhibitors seen with an underlying disease, such as systemic lupus erythematosus, often disappear when the primary disease is effectively treated.

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Chapter **483**

Disseminated Intravascular Coagulation

J. Paul Scott and Leslie J. Raffini

Thrombotic microangiopathy refers to a heterogeneous group of conditions, including disseminated intravascular coagulation (DIC), that result in consumption of clotting factors, platelets, and anticoagulant proteins. Consequences of this process include widespread intravascular deposition of fibrin, leading to tissue ischemia and necrosis, a generalized hemorrhagic state, and hemolytic anemia.

ETIOLOGY

Any life-threatening severe systemic disease (Table 483-1) associated with hypoxia, acidosis, tissue necrosis, shock, and/or endothelial damage may trigger DIC. Better understanding of the pathophysiology of hemostasis has lead to an appreciation of the critical interaction of the coagulation pathways with the innate immune system and inflammatory response that likely contributes to the widespread dysregulation present in DIC. Activation and release of cytokines and chemokines alter endothelial function to a more prothrombotic state, enhancing the formation of microvascular thromboses, with resultant consumption of pro- and anticoagulant proteins. Excessive activation of clotting consumes both the physiologic anticoagulants (protein C, protein S, and antithrombin III) and procoagulants, resulting in a deficiency of factor V, factor VIII, prothrombin, fibrinogen, and platelets. Commonly, the clinical result of this sequence of events is hemorrhage. The hemostatic dysregulation may also result in thromboses in the skin, kidneys, and other organs.

CLINICAL MANIFESTATIONS

DIC accompanies a severe systemic disease process, usually with shock. Bleeding frequently first occurs from sites of venipuncture or surgical incision. The skin may show petechiae and ecchymoses. Tissue necrosis may involve many organs and can be most spectacularly seen as infarction of large areas of skin, subcutaneous tissue, or kidneys. Anemia caused by hemolysis may develop rapidly, owing to microangiopathic hemolytic anemia.

LABORATORY FINDINGS

There is no well-defined sequence of events. Certain coagulation factors (factors II, V, and VIII, and fibrinogen) and platelets may be consumed by the ongoing intravascular clotting process, with resultant prolongation of the prothrombin, partial thromboplastin, and thrombin times. Platelet counts may be profoundly depressed. The blood smear may contain fragmented, burr- and helmet-shaped red blood cells (schistocytes). In addition, because the fibrinolytic mechanism is activated, fibrinogen degradation products (D-dimers) appear in the blood. The D-dimer is formed by fibrinolysis of a crosslinked fibrin clot. The D-dimer assay is as sensitive as the fibrinogen degradation product test and more specific for activation of coagulation and fibrinolysis.

TREATMENT

The first 2 steps in the treatment of DIC are the most critical: (a) treat the trigger that caused DIC and (b) restore normal homeostasis by correcting the shock, acidosis, and hypoxia that usually complicate DIC. If the underlying problem can be controlled and the patient stabilized, bleeding quickly ceases, and there is improvement of the abnormal laboratory findings. Blood components are used for replacement therapy in patients with hemorrhage and may consist of platelet infusions (for thrombocytopenia), cryoprecipitate (for hypofibrinogenemia), and/or fresh-frozen plasma (for replacement of other coagulation factors and natural inhibitors).

The role of heparin in DIC is limited to patients who have vascular thrombosis in association with DIC or who require prophylaxis because they are at high risk for venous thromboembolism. Such individuals should be treated as outlined in Chapter 479, with careful attention to replacement therapy to maintain an adequate platelet count and thus limit bleeding complications.

Table 483-1 Causes of Disseminated Intravascular Coagulation

INFECTIOUS
Meningococcemia (purpura fulminans)
Bacterial sepsis (staphylococcal, streptococcal, *Escherichia coli*, *Salmonella*)
Rickettsia (Rocky Mountain spotted fever)
Virus (cytomegalovirus, herpes simplex, hemorrhagic fevers)
Malaria
Fungus
TISSUE INJURY
Central nervous system trauma (massive head injury)
Multiple fractures with fat emboli
Crush injury
Profound shock or asphyxia
Hypothermia or hyperthermia
Massive burns
MALIGNANCY
Acute promyelocytic leukemia
Acute monoblastic or promyelocytic leukemia
Widespread malignancies (neuroblastoma)
VENOM OR TOXIN
Snake bites
Insect bites
MICROANGIOPATHIC DISORDERS
"Severe" thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome
Giant hemangioma (Kasabach-Merritt syndrome)
GASTROINTESTINAL DISORDERS
Fulminant hepatitis
Ischemic bowel
Pancreatitis
HEREDITARY THROMBOTIC DISORDERS
Antithrombin III deficiency
Homozygous protein C deficiency
NEWBORN
Maternal toxemia
Bacterial or viral sepsis (group B streptococcus, herpes simplex)
Abruptio placenta
Severe respiratory distress syndrome
Necrotizing enterocolitis
Erythroblastosis fetalis
Fetal demise of a twin
MISCELLLANEOUS
Severe acute graft rejection
Acute hemolytic transfusion reaction
Severe collagen-vascular disease
Kawasaki disease
Heparin-induced thrombosis
Infusion of "activated" prothrombin complex concentrates
Hyperpyrexia/encephalopathy, hemorrhagic shock syndrome

Modified from Montgomery RR, Scott IP: Hemostasis: diseases of the fluid phase. In Nathan DG, Oski FA, editors: Hematology of infancy and childhood, *vol 2, ed 4, Philadelphia, 1993, WB Saunders.*

The prognosis of patients with DIC is primarily dependent on the outcome of the treatment of the primary disease and prevention of end-organ damage.

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Chapter 484

Platelet and Blood Vessel Disorders

J. Paul Scott

MEGAKARYOPOIESIS

Platelets are nonnucleated cellular fragments produced by megakaryocytes within the bone marrow and other tissues. Megakaryocytes are large polyploid cells. When the megakaryocyte approaches maturity, budding of the cytoplasm occurs and large numbers of platelets are liberated. Platelets circulate with a life span of 10-14 days. **Thrombopoietin** (TPO) is the primary growth factor that controls platelet production (Fig. 484-1). Levels of TPO appear to correlate inversely with platelet number and megakaryocyte mass. Levels of TPO are highest in the thrombocytopenic states associated with decreased marrow megakaryopoiesis and may be variable in states of increased platelet production.

The platelet plays multiple hemostatic roles. The platelet surface possesses a number of important receptors for adhesive proteins, including von Willebrand factor (VWF) and fibrinogen, as well as receptors for agonists that trigger platelet aggregation, such as thrombin, collagen, and adenosine diphosphate (ADP). After injury to the blood vessel wall, the extracellular matrix containing adhesive and procoagulant proteins is exposed. Subendothelial collagen binds VWF. VWF undergoes a conformational change that induces binding of the platelet glycoprotein Ib (GPIb) complex, the VWF receptor. This process is called *platelet adhesion*. Platelets then undergo activation. During the process of activation, the platelets generate thromboxane A_2 from arachidonic acid via the enzyme cyclooxygenase. After activation, platelets release agonists, such as ADP, adenosine triphosphate (ATP), Ca^{2+}, serotonin, and coagulation factors, into the surrounding milieu. Binding of VWF to the GPIb complex triggers a complex signaling cascade that results in activation of the fibrinogen receptor, the major platelet integrin glycoprotein αIIb-β_3 (GPIIb-IIIa). Circulating fibrinogen binds to its receptor on the activated platelets, complex linking platelets together in a process called *aggregation*. This series of events forms a hemostatic plug at the site of vascular injury. The serotonin and histamine that are liberated during activation increase local vasoconstriction. In addition to acting in concert with the vessel wall to form the platelet plug, the platelet provides the catalytic surface on which coagulation factors assemble and eventually generate thrombin through a sequential series of enzymatic cleavages. Last, the platelet contractile proteins and cytoskeleton mediate clot retraction.

THROMBOCYTOPENIA

The normal platelet count is 150-450 × 109/L. *Thrombocytopenia* refers to a reduction in platelet count to <150 × 10^9/L. Causes of thrombocytopenia include decreased production on either a congenital or an acquired basis, sequestration of the platelets within an enlarged spleen or other organ, and increased destruction of normally synthesized platelets on either an immune or a nonimmune basis (see Chapter 475; Tables 484-1 and 484-2 and Fig. 484-2).

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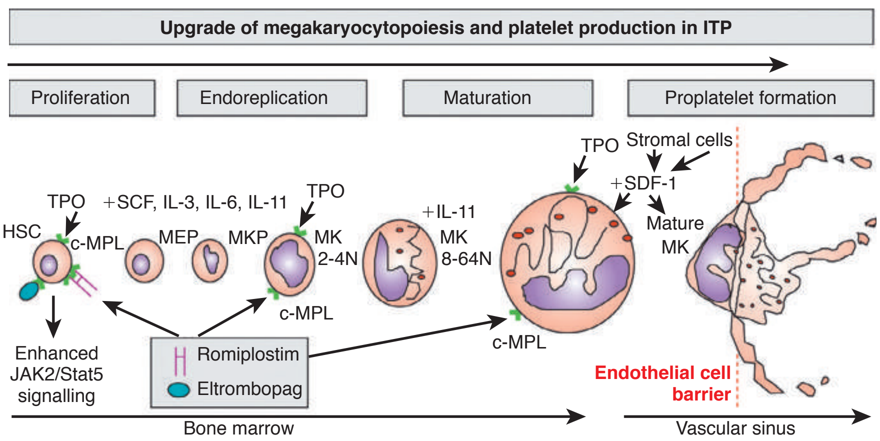

Figure 484-1 **Scheme of megakaryocytopoiesis and platelet production in idiopathic thrombocytopenic purpura.** Hematopoietic stem cells (HSC) are mobilized and megakaryocyte (MK) and erythroid progenitors (MEP) accumulate with MK-committed progenitors (MKP) giving rise to mature MKs under control of thrombopoietin (TPO) working with chemokines, cytokines, and growth factors, including stem cell factor (SCF) and interleukin (IL)-3, IL-6, and IL-11. Endoreplication results in ploidy changes in MKs and increased chromosome number (up to 64N). Mature MKs migrate to the endothelial cell barrier delimiting the vascular sinus and, under the influence of stromal-derived factor-1 (SDF-1), give rise to proplatelets that protrude into the circulation and produce large numbers of platelets under hemodynamic determinants. Therapeutically given romiplostim and eltrombopag enter the marrow and join with TPO to stimulate megakaryocytopoiesis and platelet production. *(From Nurden AT, Viallard JF, Nurden P: New-generation drugs that stimulate platelet production in chronic immune thrombocytopenic purpura*, Lancet *373:1562–1568, 2009, p. 1563.)*

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Table 484-1 Differential Diagnosis of Thrombocytopenia in Children and Adolescents

DESTRUCTIVE THROMBOCYTOPENIAS

Primary Platelet Consumption Syndromes

Immune thrombocytopenias
- Acute and chronic ITP
- Autoimmune diseases with chronic ITP as a manifestation
  - Cyclic thrombocytopenia
  - Autoimmune lymphoproliferative syndrome and its variants
  - Systemic lupus erythematosus
  - Evans syndrome
  - Antiphospholipid antibody syndrome
  - Neoplasia-associated immune thrombocytopenia
- Thrombocytopenia associated with HIV
- Neonatal immune thrombocytopenia
  - Alloimmune
  - Autoimmune (e.g., maternal ITP)
- Drug-induced immune thrombocytopenia (including heparin-induced thrombocytopenia)
- Posttransfusion purpura
- Allergy and anaphylaxis
- Posttransplant thrombocytopenia

Nonimmune thrombocytopenias
- Thrombocytopenia of infection
  - Bacteremia or fungemia
  - Viral infection
  - Protozoan
- Thrombotic microangiopathic disorders
  - Hemolytic-uremic syndrome
  - Eclampsia, HELLP syndrome
  - Thrombotic thrombocytopenic purpura
  - Bone marrow transplantation-associated microangiopathy
  - Drug-induced
- Platelets in contact with foreign material
- Congenital heart disease
- Drug-induced via direct platelet effects (ristocetin, protamine)
- Type 2B VWD or platelet-type VWD

Combined Platelet and Fibrinogen Consumption Syndromes
- Disseminated intravascular coagulation
- Kasabach-Merritt syndrome
- Virus-associated hemophagocytic syndrome

IMPAIRED PLATELET PRODUCTION
- Hereditary disorders
- Acquired disorders
  - Aplastic anemia
  - Myelodysplastic syndrome
  - Marrow infiltrative process—neoplasia
  - Osteopetrosis
  - Nutritional deficiency states (iron, folate, vitamin B_{12}, anorexia nervosa)
  - Drug- or radiation-induced thrombocytopenia
  - Neonatal hypoxia or placental insufficiency

SEQUESTRATION
- Hypersplenism
- Hypothermia
- Burns

HELLP, hemolysis, elevated liver enzymes, and low platelets; HIV, human immunodeficiency virus; ITP, immune thrombocytopenic purpura; VWD, von Willebrand disease.

From Wilson DB: Acquired platelet defects. In Orkin SH, Nathan DG, Ginsburg D, et al, editors: Nathan and Oski's hematology of infancy and childhood, *ed 7, Philadelphia, 2009, WB Saunders, p. 1555, Box 33-1.*

Table 484-2 Classification of Fetal and Neonatal Thrombocytopenias*

	CONDITION
Fetal	**Alloimmune thrombocytopenia** **Congenital infection** (e.g., CMV, toxoplasma, rubella, HIV) **Aneuploidy** (e.g., trisomy 18, 13, or 21, or triploidy) **Autoimmune condition** (e.g., ITP, SLE) Severe Rh hemolytic disease Congenital/inherited (e.g., Wiskott-Aldrich syndrome)
Early-onset neonatal (<72 hr)	**Placental insufficiency** (e.g., PET, IUGR, diabetes) **Perinatal asphyxia** **Perinatal infection** (e.g., *Escherichia coli*, GBS, herpes simplex) **DIC** **Alloimmune thrombocytopenia** **Autoimmune condition** (e.g., ITP, SLE) Congenital infection (e.g., CMV, toxoplasma, rubella, HIV) Thrombosis (e.g., aortic, renal vein) Bone marrow replacement (e.g., congenital leukemia) Kasabach-Merritt syndrome Metabolic disease (e.g., proprionic and methylmalonic acidemia) Congenital/inherited (e.g., TAR, CAMT)
Late-onset neonatal (>72 hr)	**Late-onset sepsis** **NEC** Congenital infection (e.g., CMV, toxoplasma, rubella, HIV) Autoimmune Kasabach-Merritt syndrome Metabolic disease (e.g., proprionic and methylmalonic acidemia) Congenital/inherited (e.g., TAR, CAMT)

*The most common conditions are shown in bold.

CAMT, congenital amegakaryocytic thrombocytopenia; CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; GBS, group B streptococcus; ITP, idiopathic thrombocytopenic purpura; IUGR, intrauterine growth restriction; NEC, necrotizing enterocolitis; PET, preeclampsia; SLE, systemic lupus erythematosus; TAR, thrombocytopenia with absent radii.

From Roberts I, Murray NA: Neonatal thrombocytopenia: causes and management, Arch Dis Child Fetal Neonatal Ed *88:F359–F364, 2003.*

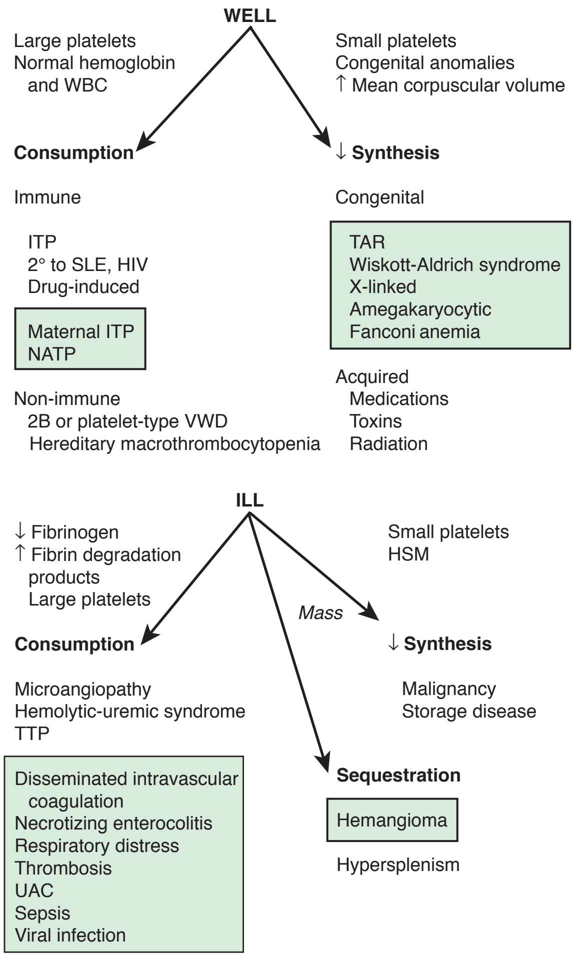

Figure 484-2 **Differential diagnosis of childhood thrombocytopenic syndromes.** The syndromes initially are separated by their clinical appearance. Clues leading to the diagnosis are shown in *italics*. The mechanisms and common disorders leading to these findings are shown in the *lower part* of the figure. Disorders that commonly affect neonates are listed in the *shaded boxes*. HSM, hepatosplenomegaly; ITP, idiopathic immune thrombocytopenic purpura; NATP, neonatal alloimmune thrombocytopenic purpura; SLE, systemic lupus erythematosus; TAR, thrombocytopenia-absent radius; TTP, thrombotic thrombocytopenic purpura; UAC, umbilical artery catheter; VWD, von Willebrand disease; WBC, white blood cell. *(From Scott JP: Bleeding and thrombosis. In Kliegman RM, editor:* Practical strategies in pediatric diagnosis and therapy, *Philadelphia, 1996, WB Saunders, p. 849; Kliegman RM, Marcdante KJ, Jenson HB, et al, editors:* Nelson essentials of pediatrics, *ed 5, Philadelphia, 2006, Elsevier/Saunders, p. 716.)*

484.1 Idiopathic (Autoimmune) Thrombocytopenic Purpura

J. Paul Scott

The most common cause of acute onset of thrombocytopenia in an otherwise well child is (autoimmune) idiopathic thrombocytopenic purpura (ITP).

EPIDEMIOLOGY

In a small number of children, estimated at 1 in 20,000, 1-4 wk after exposure to a common viral infection, an autoantibody directed against the platelet surface develops with resultant sudden onset of thrombocytopenia. A recent history of viral illness is described in 50-65% of cases of childhood ITP. The peak age is 1-4 yr, although the age ranges from early in infancy to the elderly. In childhood, males and females are equally affected. ITP seems to occur more often in late winter and spring after the peak season of viral respiratory illness.

PATHOGENESIS

Why some children develop the acute presentation of an autoimmune disease is unknown. The exact antigenic target for most such antibodies in most cases of childhood acute ITP remains undetermined. Although in chronic ITP, many patients demonstrate antibodies against the platelet glycoprotein complexes, αIIb-β_3 and GPIb. After binding of the antibody to the platelet surface, circulating antibody-coated platelets are recognized by the Fc receptor on splenic macrophages, ingested, and destroyed. Most common viruses have been described in association with ITP, including Epstein-Barr virus (see Chapter 254) and HIV (see Chapter 276). Epstein-Barr virus-related ITP is usually of short duration and follows the course of infectious mononucleosis. HIV-associated ITP is usually chronic. In some patients ITP appears to arise in children infected with *Helicobacter pylori* or rarely following vaccines.

CLINICAL MANIFESTATIONS

The classic presentation of ITP is a previously healthy 1-4 yr old child who has sudden onset of generalized petechiae and purpura. The parents often state that the child was fine yesterday and now is covered with bruises and purple dots. There may be bleeding from the gums and mucous membranes, particularly with profound thrombocytopenia (platelet count $<10 \times 10^9$/L). There is a history of a preceding viral infection 1-4 wk before the onset of thrombocytopenia. Findings on physical examination are normal, other than the finding of petechiae and purpura. Splenomegaly, lymphadenopathy, bone pain, and pallor are rare. An easy to use classification system has been proposed from the United Kingdom to characterize the severity of bleeding in ITP on the basis of symptoms and signs, but not platelet count:

1. No symptoms
2. Mild symptoms: bruising and petechiae, occasional minor epistaxis, very little interference with daily living
3. Moderate: more severe skin and mucosal lesions, more troublesome epistaxis and menorrhagia
4. Severe: bleeding episodes—menorrhagia, epistaxis, melena—requiring transfusion or hospitalization, symptoms interfering seriously with the quality of life

The presence of abnormal findings such as hepatosplenomegaly, bone or joint pain, remarkable lymphadenopathy other cytopenias, or congenital anomalies suggests other diagnoses (leukemia, syndromes). When the onset is insidious, especially in an adolescent, chronic ITP or the possibility of a systemic illness, such as systemic lupus erythematosus (SLE), is more likely.

OUTCOME

Severe bleeding is rare (<3% of cases in 1 large international study). In 70-80% of children who present with acute ITP, spontaneous resolution occurs within 6 mo. Therapy does not appear to affect the natural history of the illness. Fewer than 1% of patients develop an intracranial hemorrhage. Those who favor interventional therapy argue that the objective of early therapy is to raise the platelet count to $>20 \times 10^9$/L and prevent the rare development of intracranial hemorrhage. There is no evidence that therapy prevents serious bleeding. Approximately 20% of children who present with acute ITP go on to have chronic ITP. The outcome/prognosis may be related more to age, as ITP in younger children is more likely to resolve whereas the development of chronic ITP in adolescents approaches 50%.

LABORATORY FINDINGS

Severe thrombocytopenia (platelet count $<20 \times 10^9$/L) is common, and platelet size is normal or increased, reflective of increased platelet turnover (Fig. 484-3). In acute ITP, the hemoglobin value, white blood cell (WBC) count, and differential count should be normal. Hemoglobin may be decreased if there have been profuse nosebleeds or menorrhagia. Bone marrow examination shows normal granulocytic and erythrocytic series, with characteristically normal or increased

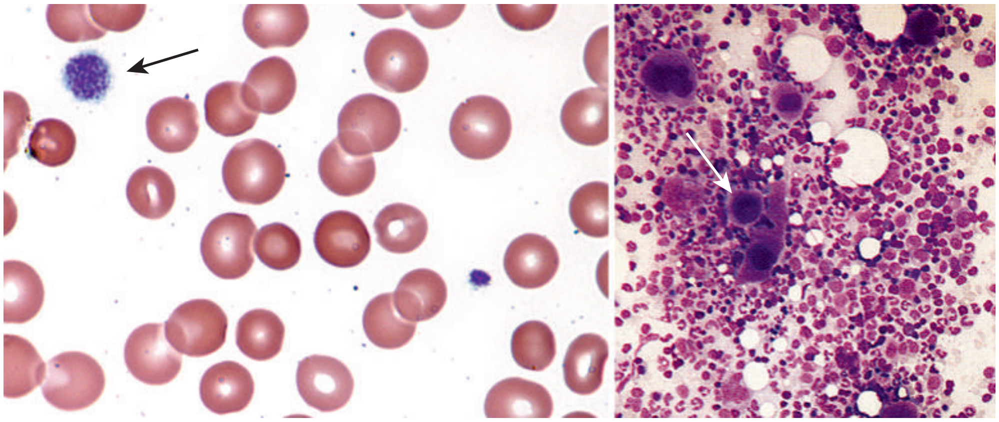

Figure 484-3 Blood smear and bone marrow aspirate from a child who had ITP showing large platelets (blood smear *[left]*) and increased numbers of megakaryocytes, many of which appear immature (bone marrow aspirate *[right]*). *(From Blanchette V, Bolton-Maggs P: Childhood immune thrombocytopenic purpura: diagnosis and management,* Pediatr Clin North Am *55:393–420, 2008, p. 400, Fig. 4.)*

numbers of megakaryocytes. Some of the megakaryocytes may appear to be immature and are reflective of increased platelet turnover. **Indications for bone marrow** aspiration/biopsy include an abnormal WBC count or differential or unexplained anemia as well as findings on history and physical examination suggestive of a bone marrow failure syndrome or malignancy. Other laboratory tests should be performed as indicated by the history and physical examination. HIV studies should be done in at-risk populations, especially sexually active teens. Platelet antibody testing is seldom useful in acute ITP. A direct antiglobulin test (Coombs) should be done if there is unexplained anemia to rule out Evans syndrome (autoimmune hemolytic anemia and thrombocytopenia) (see Chapter 458) or before instituting therapy with IV anti-D.

DIAGNOSIS/DIFFERENTIAL DIAGNOSIS

The well-appearing child with moderate to severe thrombocytopenia, an otherwise normal complete blood cell count (CBC), and normal findings on physical examination has a limited differential diagnosis that includes exposure to medication that induces drug-dependent antibodies, splenic sequestration because of previously unappreciated portal hypertension, and, rarely, early aplastic processes, such as Fanconi anemia (see Chapter 468). Other than congenital thrombocytopenia syndromes (see Chapter 484.8), such as thrombocytopenia-absent radius (TAR) syndrome and MYH9-related thrombocytopenia, most marrow processes that interfere with platelet production eventually cause abnormal synthesis of red blood cells (RBCs) and WBCs, and therefore manifest diverse abnormalities on the CBC. Disorders that cause increased platelet destruction on a nonimmune basis are usually serious systemic illnesses with obvious clinical findings (e.g., hemolytic-uremic syndrome [HUS], disseminated intravascular coagulation [DIC]) (see Table 483-1 in Chapter 483, and Fig. 484-2). Patients on heparin may develop heparin-induced thrombocytopenia. Isolated enlargement of the spleen suggests the potential for hypersplenism owing to either liver disease or portal vein thrombosis. Autoimmune thrombocytopenia may be an initial manifestation of SLE, HIV infection, common variable immunodeficiency, and, rarely, lymphoma or autoimmune lymphoproliferative syndrome. Wiskott-Aldrich syndrome (WAS; Chapter 126.2) must be considered in young males found to have thrombocytopenia with small platelets, particularly if there is a history of eczema and recurrent infection.

TREATMENT

There are no data showing that treatment affects either short- or long-term clinical outcome of ITP. Many patients with new-onset ITP have mild symptoms, with findings limited to petechiae and purpura on the skin, despite severe thrombocytopenia. Compared with untreated control subjects, treatment appears to be capable of inducing a more rapid rise in platelet count to the theoretically safe level of $>20 \times 10^9$/L, although there are no data indicating that early therapy prevents intracranial hemorrhage. Antiplatelet antibodies bind to transfused platelets as well as they do to autologous platelets. Thus, platelet transfusion in ITP is usually contraindicated unless life-threatening bleeding is present. Initial approaches to the management of ITP include the following:

1. No therapy other than education and counseling of the family and patient for patients with minimal, mild, and moderate symptoms, as defined earlier. This approach emphasizes the usually benign nature of ITP and avoids the therapeutic roller coaster that ensues once interventional therapy is begun. This approach is far less costly, and side effects are minimal.
2. Per the American Society of Hematology Guidelines: "A single dose of IVIG [intravenous immunoglobulin] (0.8-1.0 g/kg) or a short course of corticosteroids should be used as first-line treatment." IVIG at a dose of 0.8-1.0 g/kg/day for 1-2 days induces a rapid rise in platelet count (usually $>20 \times 10^9$/L) in 95% of patients within 48 hr. IVIG appears to induce a response by downregulating Fc-mediated phagocytosis of antibody-coated platelets. IVIG therapy is both expensive and time-consuming to administer. Additionally, after infusion, there is a high frequency of headaches and vomiting, suggestive of IVIG-induced aseptic meningitis.
3. Prednisone. Corticosteroid therapy has been used for many years to treat acute and chronic ITP in adults and children. Doses of prednisone of 1-4 mg/kg/24 hr appear to induce a more rapid rise in platelet count than in untreated patients with ITP. Corticosteroid therapy is usually continued for short course until a rise in platelet count to $>20 \times 10^9$/L has been achieved to avoid the long-term side effects of corticosteroid therapy, especially growth failure, diabetes mellitus, and osteoporosis.
4. Intravenous anti-D therapy. For Rh-positive patients, IV anti-D at a dose of 50-75 μg/kg causes a rise in platelet count to $>20 \times 10^9$/L in 80-90% of patients within 48-72 hr. When given to Rh-positive individuals, IV anti-D induces mild hemolytic anemia. RBC-antibody complexes bind to macrophage Fc receptors and interfere with platelet destruction, thereby causing a rise in platelet count. IV anti-D is ineffective in Rh-negative patients. Rare life-threatening episodes of intravascular hemolysis have occurred in children and adults following infusion of IV anti-D.

Each of these medications may be used to treat ITP exacerbations, which commonly occur several weeks after an initial course of therapy. In the special case of intracranial hemorrhage, multiple modalities should be used, including platelet transfusion, IVIG, high-dose corticosteroids, and prompt consultation by neurosurgery and surgery.

There is no consensus regarding the management of acute childhood ITP, except that patients who are bleeding significantly (less than 5% of children with ITP) should be treated. Intracranial hemorrhage

remains rare, and there are no data showing that treatment actually reduces its incidence.

The role of splenectomy in ITP should be reserved for 1 of 2 circumstances. The older child (≥4 yr) with severe ITP that has lasted >1 yr (chronic ITP) and whose symptoms are not easily controlled with therapy is a candidate for splenectomy. Splenectomy must also be considered when life-threatening hemorrhage (intracranial hemorrhage) complicates acute ITP, if the platelet count cannot be corrected rapidly with transfusion of platelets and administration of IVIG and corticosteroids. Splenectomy is associated with a lifelong risk of overwhelming postsplenectomy infection caused by encapsulated organisms, increased risk of thrombosis, and the potential development of pulmonary hypertension in adulthood. As an alternative to splenectomy, rituximab has been used off-label in children to treat chronic ITP. In 30-40% of children, rituximab has induced a partial or complete remission.

CHRONIC AUTOIMMUNE THROMBOCYTOPENIC PURPURA

Approximately 20% of patients who present with acute ITP have persistent thrombocytopenia for **>12 mo** and are said to have chronic ITP. At that time, a careful reevaluation for associated disorders should be performed, especially for autoimmune disease, such as SLE; chronic infectious disorders, such as HIV; and nonimmune causes of chronic thrombocytopenia, such as type 2B and platelet-type von Willebrand disease, X-linked thrombocytopenia, autoimmune lymphoproliferative syndrome, common variable immunodeficiency syndrome, autosomal macrothrombocytopenia, and WAS (also X-linked). The presence of coexisting *H. pylori* infection should be considered and, if found, treated. Therapy should be aimed at controlling symptoms and preventing serious bleeding. In ITP, the spleen is the primary site of both antiplatelet antibody synthesis and platelet destruction. Splenectomy is successful in inducing complete remission in 64-88% of children with chronic ITP. This effect must be balanced against the lifelong risk of overwhelming postsplenectomy infection. This decision is often affected by quality of life issues, as well as the ease with which the child can be managed using medical therapy, such as IVIG, corticosteroids, IV anti-D, or rituximab. Two effective agents that act to stimulate thrombopoiesis, romiplastin and eltrombopag (see Fig. 484-1), are approved by the FDA to treat adults with chronic ITP. Preliminary data using thrombopoietic agents in children are encouraging.

Bibliography is available at Expert Consult.

484.2 Drug-Induced Thrombocytopenia

J. Paul Scott

A number of drugs are associated with immune thrombocytopenia as the result of either an immune process or megakaryocyte injury. Some common drugs used in pediatrics that cause thrombocytopenia include valproic acid, phenytoin, carbamazepine, sulfonamides, vancomycin, and trimethoprim-sulfamethoxazole. Heparin-induced thrombocytopenia (and, rarely, an associated thrombosis) is seldom seen in pediatrics, but it occurs when, after exposure to heparin, the patient has an antibody directed against the heparin–platelet factor 4 complex. Recommended treatment for heparin-induced thrombocytopenia in adults includes argatroban, lepirudin, or danaparoid.

Bibliography is available at Expert Consult.

484.3 Nonimmune Platelet Destruction

J. Paul Scott

The syndromes of DIC (see Chapter 483), HUS (see Chapters 484.4 and 518), and thrombotic thrombocytopenic purpura (TTP) (see Chapter 484.5) share the hematologic picture of a thrombotic microangiopathy in which there is RBC destruction and consumptive thrombocytopenia caused by platelet and fibrin deposition in the microvasculature. The microangiopathic hemolytic anemia is characterized by the presence of RBC fragments, including helmet cells, schistocytes, spherocytes, and burr cells.

484.4 Hemolytic-Uremic Syndrome

See Chapter 518.

484.5 Thrombotic Thrombocytopenic Purpura

J. Paul Scott

TTP is a rare pentad of **fever, microangiopathic hemolytic anemia, thrombocytopenia, abnormal renal function,** and **central nervous system changes** that is clinically similar to HUS, although TTP can be congenital, it usually presents in adults and occasionally in adolescents. Microvascular thrombi within the central nervous system cause subtle, shifting neurologic signs that vary from changes in affect and orientation to aphasia, blindness, and seizures. Initial manifestations are often nonspecific (weakness, pain, emesis); prompt recognition of this disorder is critical. Laboratory findings provide important clues to the diagnosis and show microangiopathic hemolytic anemia characterized by morphologically abnormal RBCs, with schistocytes, spherocytes, helmet cells, and an elevated reticulocyte count in association with thrombocytopenia. Coagulation studies are usually nondiagnostic. Blood urea nitrogen and creatinine are sometimes elevated. The treatment of TTP is plasmapheresis (plasma exchange), which is effective in 80-95% of cases. Treatment with plasmapheresis should be instituted on the basis of thrombocytopenia and microangiopathic hemolytic anemia even if other symptoms are not yet present. Rituximab, corticosteroids, and splenectomy are reserved for refractory cases.

The majority of cases of TTP are caused by an autoantibody–mediated deficiency of a metalloproteinase (ADAMTS-13) that is responsible for cleaving the high-molecular-weight multimers of VWF and appears to play a pivotal role in the evolution of the thrombotic microangiopathy. In contrast, levels of the metalloproteinase in HUS are usually normal. **Congenital deficiency** of the metalloproteinase causes rare familial cases of TTP/HUS, usually manifested as recurrent episodes of thrombocytopenia, hemolytic anemia, and renal involvement, with or without neurologic changes, that often present in infancy after an intercurrent illness. Abnormalities of the complement system have now also been implicated in rare cases of familial TTP. ADAMTS-13 deficiency can be treated by repeated infusions of fresh-frozen plasma.

Bibliography is available at Expert Consult.

484.6 Kasabach-Merritt Syndrome

J. Paul Scott

See also Chapter 650.

The association of a giant hemangioma with localized intravascular coagulation causing thrombocytopenia and hypofibrinogenemia is called *Kasabach-Merritt syndrome.* In most patients, the site of the hemangioma is obvious, but retroperitoneal and intraabdominal hemangiomas may require body imaging for detection. Inside the hemangioma there is platelet trapping and activation of coagulation, with fibrinogen consumption and generation of fibrin(ogen) degradation products. Arteriovenous malformation within the lesions can cause heart failure. Pathologically, Kasabach-Merritt syndrome appears to develop more often as a result of a kaposiform hemangioendothelioma

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or tufted hemangioma rather than a simple hemangioma. The peripheral blood smear shows microangiopathic changes. Multiple modalities have been used to treat Kasabach-Merritt syndrome, including propranolol, surgical excision (if possible), laser photocoagulation, high-dose corticosteroids, local radiation therapy, antiangiogenic agents, such as interferon-α_2, and vincristine. Over time, most patients who present in infancy have regression of the hemangioma. Treatment of the associated coagulopathy may benefit from a trial of antifibrinolytic therapy with ε-aminocaproic acid (Amicar).

484.7 Sequestration

J. Paul Scott

Thrombocytopenia develops in individuals with massive splenomegaly because the spleen acts as a sponge for platelets and sequesters large numbers. Most such patients also have mild leukopenia and anemia on CBC. Individuals who have thrombocytopenia caused by splenic sequestration should undergo a work-up to diagnose the etiology of splenomegaly, including infectious, inflammatory, infiltrative, neoplastic, obstructive, and hemolytic causes.

484.8 Congenital Thrombocytopenic Syndromes

J. Paul Scott

See Table 484-2.

Congenital amegakaryocytic thrombocytopenia (CAMT) usually manifests within the 1st few days to week of life, when the child presents with petechiae and purpura caused by profound thrombocytopenia. CAMT is caused by a rare defect in hematopoiesis as a result of a mutation in the stem cell TPO receptor (MPL). Other than skin and mucous membrane abnormalities, findings on physical examination are normal. Examination of the bone marrow shows an absence of megakaryocytes. These patients often progress to marrow failure (aplasia) over time. Hematopoietic stem cell transplantation is curative.

TAR syndrome consists of thrombocytopenia (absence or hypoplasia of megakaryocytes) that presents in early infancy with bilateral radial anomalies of variable severity, ranging from mild changes to marked limb shortening (Fig. 484-4). Many such individuals also have other skeletal abnormalities of the ulna, radius, and lower extremities. Thumbs are present. Intolerance to cow's milk formula (present in 50%) may complicate management by triggering gastrointestinal bleeding, increased thrombocytopenia, eosinophilia, and a leukemoid reaction. The thrombocytopenia of TAR syndrome frequently remits over the 1st few yrs of life. The molecular basis of TAR syndrome remains to be defined. A few patients have been reported to have a syndrome of **amegakaryocytic thrombocytopenia with radioulnar synostosis** caused by a mutation in the *HOXA11* gene. Different from TAR syndrome, this mutation causes marrow aplasia.

WAS is characterized by thrombocytopenia, with tiny platelets, eczema, and recurrent infection as a consequence of immune deficiency (see Chapter 126.2). WAS is inherited as an X-linked disorder, and the gene for WAS has been sequenced. The WAS protein appears to play an integral role in regulating the cytoskeletal architecture of both platelets and T lymphocytes in response to receptor-mediated cell signaling. The WAS protein is common to all cells of hematopoietic lineage. Molecular analysis of families with X-linked thrombocytopenia has shown that many affected members have a point mutation within the WAS gene, whereas individuals with the full manifestation of WAS have large gene deletions. Examination of the bone marrow in WAS shows the normal number of megakaryocytes, although they may have bizarre morphologic features. Transfused platelets have a normal life span. Splenectomy often corrects the thrombocytopenia, suggesting that the platelets formed in WAS have accelerated destruction. After splenectomy, these patients are at increased risk for overwhelming infection and require lifelong antibiotic prophylaxis against encapsulated organisms. Approximately 5-15% of patients with WAS develop lymphoreticular malignancies. Successful hematopoietic stem cell transplantation cures WAS. **X-linked macrothrombocytopenia** and **dyserythropoiesis** have been linked to mutations in the *GATA-1* gene, an erythroid and megakaryocytic transcription factor.

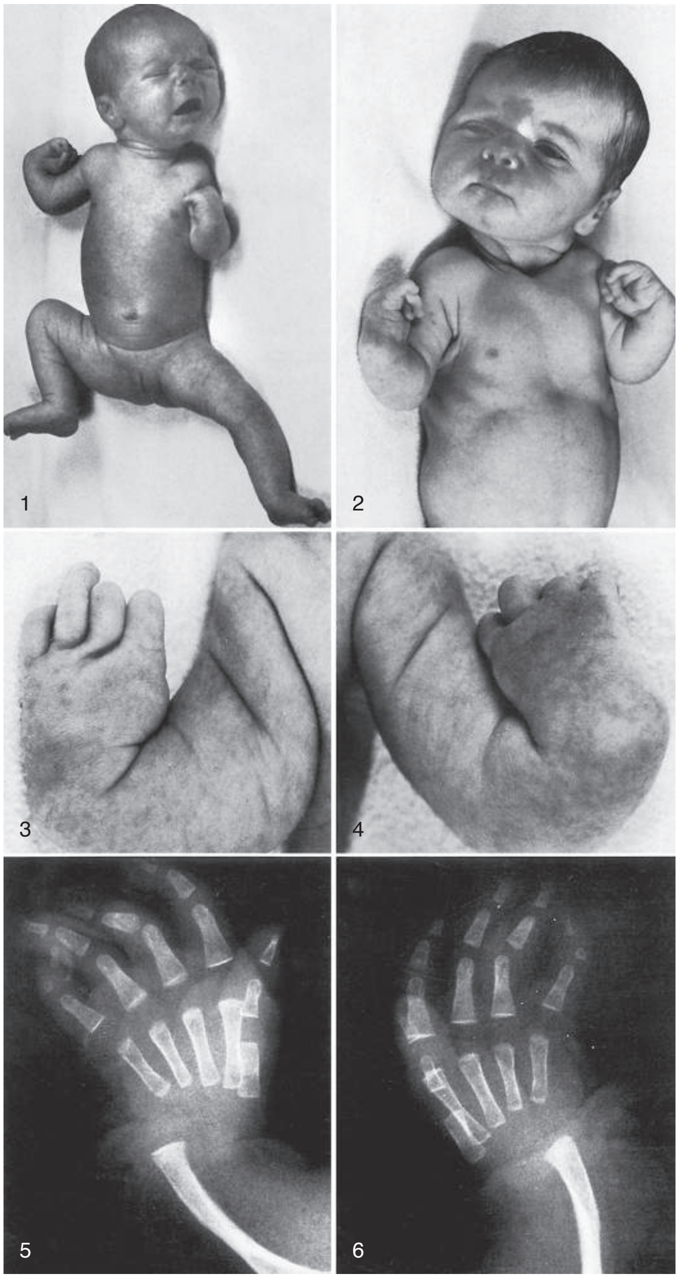

Figure 484-4 A newborn, the first child of young, healthy parents, with fully expressed TAR syndrome, including thrombocytopenia, hypereosinophilia, and anemia. Hypoplasia of the distal humeri and the shoulder girdles, bilateral hip dysplasia, mild talipes calcaneus, and clinodactyly of both little fingers are seen. This patient had a pronounced allergy to cow's milk, with exposure followed by diarrhea, vomiting, and decreased weight and platelet count, making a cow's milk–free diet mandatory. A persistent depressed nasal bridge and development of pronounced bowed legs are seen. *(From Wiedemann H-R, Kunze J, Grosse F-R, editors:* Clinical syndromes, *ed 3, [English translation], London, 1997, Mosby-Wolfe, p. 430.)*

MYH9-related thrombocytopenia: A diverse number of hereditary thrombocytopenia syndromes, given names such as Sebastian, Epstein,

May-Hegglin, and Fechtner syndromes, are characterized by autosomal dominant macrothrombocytopenia, neutrophil inclusion bodies, and a variety of physical anomalies, including sensorineural deafness, renal disease, and/or eye disease. These have all been shown to be caused by different mutations in the *MYH9* gene (nonmuscle myosin-IIa heavy chain). The thrombocytopenia is usually mild and not progressive. Some other individuals with recessively inherited macrothrombocytopenia have abnormalities in chromosome 22q11. Mutations in the gene for glycoprotein Ibβ, an essential component of the platelet VWF receptor, can result in Bernard-Soulier syndrome (see Chapter 484.13).

Bibliography is available at Expert Consult.

484.9 Neonatal Thrombocytopenia

J. Paul Scott

See also Chapter 103.4.

Thrombocytopenia in the newborn rarely is indicative of a primary disorder of megakaryopoiesis but more often is the result of either systemic illness or transfer of maternal antibodies directed against fetal platelets (see Table 484-2). Neonatal thrombocytopenia often occurs in association with congenital viral infection, especially rubella; cytomegalovirus; protozoal infection, such as toxoplasmosis; syphilis; and perinatal bacterial infection, especially those caused by Gram-negative bacilli. Thrombocytopenia associated with DIC may be responsible for severe spontaneous bleeding. The constellation of marked thrombocytopenia and abnormal abdominal findings is common in necrotizing enterocolitis and other causes of necrotic bowel. Thrombocytopenia in an ill child requires a prompt search for viral and bacterial pathogens.

Antibody-mediated thrombocytopenia in the newborn occurs because of transplacental transfer of maternal antibodies directed against fetal platelets. Neonatal alloimmune thrombocytopenic purpura (NATP) is caused by the development of maternal antibodies against antigens present on fetal platelets that are shared with the father and recognized as foreign by the maternal immune system. This is the platelet equivalent of Rh disease of the newborn. The incidence of NATP is 1/4,000-5,000 live births. The clinical manifestations of NATP are those of an apparently well child who, within the 1st few days after delivery, has generalized petechiae and purpura. Laboratory studies show a normal maternal platelet count, yet moderate to severe thrombocytopenia in the newborn. Detailed review of the history should show no evidence of maternal thrombocytopenia. Up to 30% of infants with severe NATP may have intracranial hemorrhage, either prenatally or in the perinatal period. Unlike Rh disease, first pregnancies may be severely affected. Subsequent pregnancies are often more severely affected than the first.

The **diagnosis** of NATP is made by checking for the presence of maternal alloantibodies directed against the father's platelets. Specific studies can be done to identify the target alloantigen. The most common cause is incompatibility for the platelet alloantigen HPA-1a. Specific DNA sequence polymorphisms have been identified that permit informative prenatal testing to identify at-risk pregnancies. The differential diagnosis of NATP includes transplacental transfer of maternal antiplatelet autoantibodies (maternal ITP), and, more commonly, viral or bacterial infection.

Treatment of NATP requires the administration of IVIG prenatally to the mother. Therapy usually begins in the 2nd trimester and is continued throughout the pregnancy. Fetal platelet count can be monitored by percutaneous umbilical blood sampling. Delivery should be performed by cesarean section. After delivery, if severe thrombocytopenia persists, transfusion of 1 unit of platelets that share the maternal alloantigens (e.g., washed maternal platelets) will cause a rise in platelet counts to provide effective hemostasis. After there has been 1 affected child, genetic counseling is critical to inform the parents of the high risk of thrombocytopenia in subsequent pregnancies.

Children born to mothers with ITP **(maternal ITP)** appear to have a lower risk of serious hemorrhage than infants born with NATP, although severe thrombocytopenia may occur. The mother's preexisting platelet count may have some predictive value in that severe maternal thrombocytopenia before delivery appears to predict a higher risk of fetal thrombocytopenia. In mothers who have had splenectomy for ITP, the maternal platelet count may be normal and is not predictive of fetal thrombocytopenia.

Treatment includes prenatal administration of corticosteroids to the mother and administration of IVIG and sometimes corticosteroids to the infant after delivery. Thrombocytopenia in an infant, whether a result of NATP or maternal ITP, usually resolves within 2-4 mo after delivery. The period of highest risk is the immediate perinatal period.

Two syndromes of congenital failure of platelet production often present in the newborn period. In **CAMT,** the newborn manifests petechiae and purpura shortly after birth. Findings on physical examination are otherwise normal. Megakaryocytes are absent from the bone marrow. This syndrome is caused by a mutation in the megakaryocyte TPO receptor that is essential for development of all hematopoietic cell lines. Pancytopenia eventually develops, and hematopoietic stem cell transplantation is curative. **TAR syndrome** consists of thrombocytopenia that presents in early infancy, with bilateral radial anomalies of variable severity, ranging from mild changes to marked limb shortening. Thumbs are present. In many such individuals, there are also other skeletal abnormalities of the lower extremities. Intolerance to cow's milk formula is present in 50% of patients. TAR syndrome frequently remits over the 1st few yr of life (see Chapter 484.8) (see Fig. 484-4).

Bibliography is available at Expert Consult.

484.10 Thrombocytopenia from Acquired Disorders Causing Decreased Production

J. Paul Scott and Veronica Flood

Disorders of the bone marrow that inhibit megakaryopoiesis usually affect RBC and WBC production. Infiltrative disorders, including malignancies, such as acute lymphocytic leukemia, histiocytosis, lymphomas, and storage disease, usually cause either abnormalities on physical examination (lymphadenopathy, hepatosplenomegaly, or masses) or abnormalities of the WBC count, or anemia. Aplastic processes may present as isolated thrombocytopenia, although there are usually clues on the CBC (leukopenia, neutropenia, anemia, or macrocytosis). Children with constitutional aplastic anemia (Fanconi anemia) often have abnormalities on examination, including radial anomalies, other skeletal anomalies, short stature, microcephaly, and hyperpigmentation. Bone marrow examination should be performed when thrombocytopenia is associated with abnormalities found on physical examination or on examination of the other blood cell lines.

484.11 Platelet Function Disorders

J. Paul Scott

Bleeding time and the platelet function analyzer (PFA-100) are the only commonly available tests to screen for abnormal platelet function. Bleeding time measures the interaction of platelets with the blood vessel wall and thus is affected by both platelet count and platelet function. The predictive value of bleeding time is problematic because bleeding time is dependent on a number of other factors, including the skill of the technician and the cooperation of the patient, often a challenge in the infant or young child. A normal bleeding time does not rule out a mild platelet function defect in a clinically symptomatic individual. The PFA-100 measures platelet adhesion and aggregation in whole blood at high shear when the blood is exposed to either

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collagen-epinephrine or collagen-ADP. Results are reported as the closure time measured in sec. Many clinical laboratories have replaced bleeding time with the use of the PFA-100. Both the PFA-100 and bleeding time are sensitive to moderate/severe von Willebrand disease and platelet dysfunction. Both are variably insensitive to mild platelet function abnormalities and mild von Willebrand disease. The use of the PFA-100 as a screening test remains controversial and, like the bleeding time, lacks specificity. Bleeding time is the only commonly available test to assess platelet–vessel wall interaction. For patients with a positive history of bleeding suggestive of von Willebrand disease or platelet dysfunction, specific VWF testing and platelet function studies should be done, irrespective of the results of the bleeding time or PFA-100.

Platelet function in the clinical laboratory is currently measured using platelet aggregometry. In the aggregometer, agonists, such as collagen, ADP, ristocetin, epinephrine, arachidonic acid, and thrombin (or the thrombin receptor peptide), are added to platelet-rich plasma, and the clumping of platelets over time is measured by an automated machine. At the same time, other instruments measure the release of granular contents, such as ATP, from the platelets after activation. The ability of platelets to aggregate and their metabolic activity can be assessed simultaneously. When a patient is being evaluated for possible platelet dysfunction, it is critically important to exclude the presence of other exogenous agents and to study the patient, if possible, off all medications for 2 wk. Further evaluation using flow cytometric analysis or molecular testing are often necessary to make a more definitive diagnosis.

484.12 Acquired Disorders of Platelet Function

J. Paul Scott

A number of systemic illnesses are associated with platelet dysfunction, most commonly, liver disease, kidney disease (uremia), and disorders that trigger increased amounts of fibrin degradation products. These disorders frequently cause prolonged bleeding time and are often associated with other abnormalities of the coagulation mechanism. The most important element of management is to treat the primary illness. If treatment of the primary process is not feasible, infusions of desmopressin have been helpful in augmenting hemostasis and correcting bleeding time. In some patients, transfusions of platelets and/or cryoprecipitate have also been helpful in improving hemostasis.

Many drugs alter platelet function. The most commonly used drug in adults that alters platelet function is acetylsalicylic acid (aspirin). Aspirin irreversibly acetylates the enzyme cyclo-oxygenase, which is critical in the formation of thromboxane A_2. Aspirin usually causes moderate platelet dysfunction that becomes more prominent if there is another abnormality of the hemostatic mechanism. In children, commonly used drugs that affect platelet function include other nonsteroidal antiinflammatory drugs, valproic acid, and high-dose penicillin. Specific agents to inhibit platelet function therapeutically include those that block the platelet ADP receptor (clopidogrel) and αIIb-β_3 receptor antagonists, as well as aspirin.

484.13 Congenital Abnormalities of Platelet Function

J. Paul Scott

Severe platelet function defects usually present with petechiae and purpura shortly after birth, especially after vaginal delivery. Defects in the platelet GPIb complex (the VWF receptor) or the αIIb-β_3 complex (the fibrinogen receptor) cause severe congenital platelet dysfunction.

Bernard-Soulier syndrome, a severe congenital platelet function disorder, is caused by absence or severe deficiency of the VWF receptor (GPIb complex) on the platelet membrane. This syndrome is characterized by thrombocytopenia, with giant platelets and markedly prolonged bleeding time (>20 min) or PFA-100 closure time. Platelet aggregation tests show absent ristocetin-induced platelet aggregation, but normal aggregation to all other agonists. Ristocetin induces the binding of VWF to platelets and agglutinates platelets. Results of studies of VWF are normal. The GPIb complex interacts with the platelet cytoskeleton; a defect in this interaction is believed to be the cause of the large platelet size. Bernard-Soulier syndrome is inherited as an autosomal recessive disorder. Genetic mutations causing Bernard-Soulier syndrome are usually identified in the genes forming the GPIb complex of glycoproteins Ibα, Ibβ, V, and IX.

Glanzmann thrombasthenia is a congenital disorder associated with severe platelet dysfunction that yields prolonged bleeding time and a normal platelet count. Platelets have normal size and morphologic features on the peripheral blood smear, and closure times for PFA-100 or bleeding time are markedly abnormal. Aggregation studies show abnormal or absent aggregation with all agonists used except ristocetin, because ristocetin agglutinates platelets and does not require a metabolically active platelet. This disorder is caused by deficiency of the platelet fibrinogen receptor αIIb-β_3, the major integrin complex on the platelet surface that undergoes conformational changes by inside out signaling when platelets are activated. Fibrinogen binds to this complex when the platelet is activated and causes platelets to aggregate. Caused by identifiable mutations in the genes for αIIb or β_3, this disorder is inherited in an autosomal recessive manner. For both Bernard-Soulier syndrome and Glanzmann thrombasthenia, the diagnosis is confirmed by flow cytometric analysis of the patient's platelet glycoproteins.

Hereditary deficiency of platelet storage granules occurs in 2 well-characterized but rare syndromes that involve deficiency of intracytoplasmic granules. **Dense body deficiency** is characterized by absence of the granules that contain ADP, ATP, Ca^{2+}, and serotonin. This disorder is diagnosed by the finding that ATP is not released on platelet aggregation studies and ideally is characterized by electron microscopic studies. **Gray platelet syndrome** is caused by the absence of platelet α granules, resulting in large platelets that are large and appear gray on Wright stain of peripheral blood. In this rare syndrome, aggregation and release are absent with most agonists other than thrombin and ristocetin. Electron microscopic studies are diagnostic.

OTHER HEREDITARY DISORDERS OF PLATELET FUNCTION

Abnormalities in the pathways of platelet signaling/activation and release of granular contents cause a heterogeneous group of platelet function defects that are usually manifested as increased bruising, epistaxis, and/or menorrhagia. Symptoms may be subtle and are often made more obvious by high-risk surgery, such as tonsillectomy or adenoidectomy, or by administration of nonsteroidal antiinflammatory drugs. In the laboratory, bleeding time is variable and closure time as measured by the PFA-100 is frequently, but not always, prolonged. Platelet aggregation studies show deficient aggregation with 1 or 2 agonists and/or abnormal release of granular contents.

The formation of thromboxane from arachidonic acid after the activation of phospholipase is critical to normal platelet function. Deficiency or dysfunction of enzymes, such as cyclo-oxygenase and thromboxane synthase, which metabolize arachidonic acid, causes abnormal platelet function. In the aggregometer, platelets from such patients do not aggregate in response to arachidonic acid.

The most common platelet function defects are those characterized by variable bleeding time/PFA closure times and abnormal aggregation with 1 or 2 agonists, usually ADP and/or collagen. These patients have normal aggregation with thrombin receptor peptide. Some of these individuals have only decreased release of ATP from intracytoplasmic granules; the significance of this finding is debated.

TREATMENT OF PATIENTS WITH PLATELET DYSFUNCTION

Successful treatment depends on the severity of both the diagnosis and the hemorrhagic event. In all but severe platelet function defects, desmopressin 0.3 μg/kg IV may be used for mild to moderate bleeding

episodes. In addition to its effect on stimulating levels of VWF and factor VIII, desmopressin corrects bleeding time and augments hemostasis in many individuals with mild to moderate platelet function defects. For individuals with Bernard-Soulier syndrome or Glanzmann thrombasthenia, platelet transfusions of 1 unit/5-10 kg corrects the defect in hemostasis and may be lifesaving. Rarely, antibodies develop to the deficient platelet protein, rendering the patient refractory to the transfused platelets. In such patients, the off-label use of recombinant factor VIIa has been effective, and this treatment is undergoing clinical trials. In both conditions, hematopoietic stem cell transplantation has been curative.

Bibliography is available at Expert Consult.

484.14 Disorders of the Blood Vessels

J. Paul Scott

Disorders of the vessel walls or supporting structures mimic the findings of a bleeding disorder although coagulation studies are usually normal. The findings of petechiae and purpuric lesions in such patients are often attributable to an underlying vasculitis/vasculopathy. Skin biopsy can be particularly helpful in elucidating the type of vascular pathology.

HENOCH-SCHÖNLEIN PURPURA

See Chapter 167.1.

EHLERS-DANLOS SYNDROME

See Chapter 659.

OTHER ACQUIRED DISORDERS

Scurvy, chronic corticosteroid therapy, and severe malnutrition are associated with "weakening" of the collagen matrix that supports the blood vessels. Therefore, these factors are associated with easy bruising, and particularly in the case of scurvy, bleeding gums and loosening of the teeth. Lesions of the skin that initially appear to be petechiae and purpura may be seen in vasculitic syndromes, such as SLE.

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Section 8

The Spleen

Chapter 485

Anatomy and Function of the Spleen

Amanda M. Brandow and Bruce M. Camitta

ANATOMY

The splenic precursor is recognizable by 5 wk of gestation. At birth, the spleen weighs approximately 11 g. Thereafter, it enlarges until puberty, reaching an average weight of 135 g, and then diminishes in size during adulthood. Approximately 15% of patients will have an accessory spleen. The major splenic components are a lymphoid compartment *(white pulp)* and a filtering system *(red pulp)*. The white pulp consists of periarterial lymphatic sheaths of T lymphocytes with embedded germinal centers containing B lymphocytes. The red pulp has a skeleton of fixed reticular cells, mobile macrophages, partially collapsed endothelial passages (cords of Billroth), and splenic sinuses. A *marginal zone* rich in dendritic (antigen-presenting) cells separates the red pulp from the white pulp. The splenic capsule contains smooth muscle and contracts in response to epinephrine. Approximately 10% of the blood delivered to the spleen flows rapidly through a closed vascular network. The other 90% flows more slowly through an open system (the *splenic cords*), where it is filtered through 1-5 µm slits before entering the splenic sinuses.

FUNCTION

The unique anatomy and blood flow of the spleen enable it to perform reservoir, filtering, and immunologic functions. The spleen receives 5-6% of the cardiac output, but normally contains only 25 mL of blood. It can retain much more when it enlarges leading to cytopenias. Hematopoiesis is a major splenic function at 3-6 mo of fetal life but then disappears. Splenic hematopoiesis can be resumed in patients with myelofibrosis or severe hemolytic anemia. Factor VIII and one-third of the circulating platelet mass are sequestered in the spleen and can be released by stress or epinephrine injection. Thrombocytosis and leukocytosis occur with loss of the splenic reservoir function. A high platelet count after the loss of splenic function or splenectomy is not associated with an increased risk of thrombosis in children.

Slow blood flow past macrophages and through small openings in the sinus walls facilitates the filtering functions of the spleen. Excess membrane is removed from young red blood cells (RBCs); loss of this function is characterized by target cells, poikilocytosis, and decreased osmotic fragility. The spleen is the primary site for destruction of old RBCs; this function is assumed by other reticuloendothelial cells after splenectomy. The spleen also removes damaged/abnormal red cells (such as spherocytes and antibody-coated RBCs) and damaged/senescent platelets. Intracytoplasmic inclusions may be removed from RBCs without cell lysis. Functional or anatomic hyposplenia is characterized by continued circulation of cells containing nuclear remnants **(Howell-Jolly bodies)**, denatured hemoglobin **(Heinz bodies)**, and other debris in RBCs. This debris may appear as "**pits**" on indirect microscopy.

The spleen plays a large role in host defense against infection. The spleen is the largest lymphoid organ in the body and contains nearly half of the body's total immunoglobulin-producing B lymphocytes. The spleen processes foreign material to stimulate production of opsonizing antibody. Properdin and tuftsin are also produced in the spleen. Thus, young (nonimmune) or hyposplenic individuals are at increased risk for **sepsis** caused by pneumococci and other encapsulated bacteria. The spleen can also use phagocytosis to trap and destroy intracellular parasites. The spleen has a minor role in antibody response to intramuscularly or subcutaneously injected antigens but is required for early antibody production after exposure to intravenous antigens. The spleen may be an important site of antibody production in immune thrombocytopenia purpura.

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Chapter 486

Splenomegaly

Amanda M. Brandow and Bruce M. Camitta

CLINICAL MANIFESTATIONS

A soft, thin spleen is palpable in 15% of neonates, 10% of normal children, and 5% of adolescents. In most individuals, the spleen must be 2-3 times its normal size before it is palpable. The spleen is best examined when standing on the right side of a supine patient by

Table 486-1 Differential Diagnosis of Splenomegaly by Pathophysiology

ANATOMIC LESIONS Cysts, pseudocysts Hamartomas Polysplenia syndrome Hemangiomas and lymphangiomas Hematoma or rupture (traumatic) Peliosis	**Parasitic** Malaria Toxoplasmosis, especially congenital *Toxocara canis, Toxocara cati* (visceral larva migrans) Leishmaniasis (kala-azar) Schistosomiasis (hepatic-portal involvement) Trypanosomiasis Fascioliasis Babesiosis
HYPERPLASIA CAUSED BY HEMATOLOGIC DISORDERS **Acute and Chronic Hemolysis*** Hemoglobinopathies (sickle cell disease in infancy with or without sequestration crisis and sickle variants, thalassemia major, unstable hemoglobins) Erythrocyte membrane disorders (hereditary spherocytosis, elliptocytosis, pyropoikilocytosis) Erythrocyte enzyme deficiencies (severe G6PD deficiency, pyruvate kinase deficiency) Immune hemolysis (autoimmune and isoimmune hemolysis) Paroxysmal nocturnal hemoglobinuria **Chronic Iron Deficiency** **Extramedullary Hematopoiesis** Myeloproliferative diseases: CML, juvenile CML, myelofibrosis with myeloid metaplasia, polycythemia vera Osteopetrosis Patients receiving granulocyte and granulocyte-macrophage colony-stimulating factors	IMMUNOLOGIC AND INFLAMMATORY PROCESSES* Systemic lupus erythematosus Rheumatoid arthritis Mixed connective tissue disease Systemic vasculitis Serum sickness Drug hypersensitivity, especially to phenytoin Graft-versus-host disease Sjögren syndrome Cryoglobulinemia Amyloidosis Sarcoidosis Autoimmune lymphoproliferative syndrome Posttransplant lymphoproliferative disease Large granular lymphocytosis and neutropenia Histiocytosis syndromes Hemophagocytic syndromes (nonviral, familial)
INFECTIONS† **Bacterial** Acute sepsis: *Salmonella typhi, Streptococcus pneumoniae, Haemophilus influenzae* type b, *Staphylococcus aureus* Chronic infections: infective endocarditis, chronic meningococcemia, brucellosis, tularemia, cat-scratch disease Local infections: splenic abscess (*S. aureus*, streptococci, less often *Salmonella* species, polymicrobial infection), pyogenic liver abscess (anaerobic bacteria, Gram-negative enteric bacteria), cholangitis **Viral*** Acute viral infections, especially in children Congenital CMV, herpes simplex, rubella Hepatitides A, B, and C; CMV EBV Viral hemophagocytic syndromes: CMV, EBV, HHV-6 HIV **Spirochetal** Syphilis, especially congenital syphilis Leptospirosis **Rickettsial** Rocky Mountain spotted fever Q fever Typhus **Fungal/Mycobacterial** Miliary tuberculosis Disseminated histoplasmosis South American blastomycosis Systemic candidiasis (in immunosuppressed patients)	MALIGNANCIES Primary: leukemia (acute, chronic), lymphoma, angiosarcoma, Hodgkin disease, mastocytosis Metastatic STORAGE DISEASES Lipidosis (Gaucher disease, Niemann-Pick disease, infantile GM1 gangliosidosis) Mucopolysaccharidoses (Hurler, Hunter-type) Mucolipidosis (I-cell disease, sialidosis, multiple sulfatase deficiency, fucosidosis) Defects in carbohydrate metabolism: galactosemia, fructose intolerance, glycogen storage disease IV Sea-blue histiocyte syndrome Tangier disease Wolman disease Hyperchylomicronemia type I, IV CONGESTIVE* Heart failure Intrahepatic cirrhosis or fibrosis Extrahepatic portal (thrombosis), splenic, and hepatic vein obstruction (thrombosis, Budd-Chiari syndrome)

*Common.
†Chronic or recurrent infection suggests underlying immunodeficiency.
CML, chronic myelogenous leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; G6PD, glucose-6-phosphate dehydrogenase; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus.

palpating across the abdomen as the patient inspires deeply or with the patient in the right lateral decubitus position. A splenic edge felt more than 2 cm below the left costal margin is abnormal. An enlarged spleen might descend into the pelvis; when splenomegaly is suspected, the abdominal examination should begin at a lower starting point. Superficial abdominal venous distention may be present when splenomegaly is a result of portal hypertension. Patients may also complain of left upper quadrant pain as the spleen enlarges. Radiologic detection or confirmation of splenic enlargement is done with ultrasonography, CT, or technetium-99 sulfur colloid scan. The latter also assesses splenic function.

DIFFERENTIAL DIAGNOSIS

Table 486-1 lists specific causes of splenomegaly. A thorough history with a focus on systemic complaints (fever, night sweats, malaise, weight loss) and a complete physical exam (with special attention to adenopathy), in combination with a complete blood count and careful review of the peripheral smear can help guide diagnosis.

Pseudosplenomegaly

Abnormally long mesenteric connections may produce a wandering or ptotic spleen. An enlarged left lobe of the liver, a left upper quadrant mass, or a splenic hematoma may be mistaken for splenomegaly.

Splenic cysts may contribute to splenomegaly or mimic it; these may be congenital (epidermoid) or acquired (pseudocyst) after trauma or infarction. Cysts are usually asymptomatic and are found on radiologic evaluation. Splenosis after splenic rupture or an accessory spleen (present in 15% of normal individuals) may also mimic splenomegaly; most are not palpable. The syndrome of congenital polysplenism includes cardiac defects, left-sided organ anomalies, bilobed lungs, biliary atresia, and pseudosplenomegaly (see Chapter 431.11).

Hypersplenism

Increased splenic function (sequestration or destruction of circulating cells) can result in peripheral blood cytopenias (thrombocytopenia, neutropenia, anemia), increased bone marrow activity, and splenomegaly. It is usually secondary to another disease and may be cured by treatment of the underlying condition or, if absolutely necessary, moderated by splenectomy.

Congestive Splenomegaly (Banti Syndrome)

Splenomegaly may result from obstruction in the hepatic, portal, or splenic veins leading to hypersplenism. Wilson disease (see Chapter 357.2), galactosemia (see Chapter 87.2), biliary atresia (see Chapter 356.1), and α_1-antitrypsin deficiency (see Chapter 357) may result in hepatic inflammation, fibrosis, and vascular obstruction. Congenital abnormalities (absence or hypoplasia) of the portal or splenic veins may cause vascular obstruction. Septic omphalitis or thrombophlebitis (spontaneous or as a result of umbilical venous catheterization in neonates) may result in secondary obliteration of these vessels. Splenic venous flow may be obstructed by masses of sickled erythrocytes leading to infarction. When the spleen is the site of vascular obstruction, splenectomy cures hypersplenism. However, since obstruction usually is in the hepatic or portal systems, portacaval shunting may be more helpful, because both portal hypertension and thrombocytopenia contribute to variceal bleeding.

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Chapter 487

Hyposplenism, Splenic Trauma, and Splenectomy

Amanda M. Brandow and Bruce M. Camitta

HYPOSPLENISM

Congenital absence of the spleen is associated with complex cyanotic heart defects, dextrocardia, bilateral trilobed lungs, and heterotopic abdominal organs (Ivemark syndrome; see Chapter 431.11). Splenic function is usually normal in children with **congenital polysplenia. Functional hyposplenism** may occur in normal neonates, especially premature infants. Children with sickle cell hemoglobinopathies (see Chapter 462.1) may have splenic hypofunction as early as 6 mo of age. Initially, this is caused by vascular obstruction, which can be reversed with red blood cell (RBC) transfusion or hydroxyurea. The spleen eventually autoinfarcts and becomes fibrotic and permanently nonfunctional. Functional hyposplenism may also occur in malaria (see Chapter 288), after irradiation to the left upper quadrant, and when the reticuloendothelial function of the spleen is overwhelmed (as in severe hemolytic anemia or metabolic storage disease). Splenic hypofunction has been reported occasionally in patients with autoimmune diseases (i.e., rheumatoid arthritis, lupus, sarcoidosis), nephritis, inflammatory bowel disease, celiac disease, chronic hepatitis, Pearson syndrome, Fanconi anemia, and graft-versus-host disease) (Table 487-1).

Table 487-1 Diseases Associated with Hyposplenism or Splenic Atropy

CONGENITAL FORMS Normal and premature neonates Isolated congenital hypoplasia Ivemark syndrome Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome Hypoparathyroidism syndrome Stormorken syndrome Heterotaxia syndromes	**AUTOIMMUNE DISORDERS** Systematic lupus erythematosus Rheumatoid arthritis Glomerulonephritis Wegener granulomatosis Goodpasture syndrome Sjögren syndrome Nodous polyarteritis Thyroiditis Sarcoidosis
GASTROINTESTINAL DISORDERS Coeliac disease Inflammatory bowel disease Whipple disease Dermatitis herpetiformis Intestinal lymphangiectasia Idiopathic chronic ulcerative enteritis	**INFECTIOUS DISEASES** HIV/AIDS Pneumococcal meningitis Malaria
HEPATIC DISORDERS Active chronic hepatitis Primary biliary cirrhosis Hepatic cirrhosis and portal hypertension Alcoholism and alcoholic hepatopathy	**IATROGENIC FORMS** Exposure to methyldopa High-dose steroids Total parenteral nutrition Splenic irradiation
ONCOHEMATOLOGIC DISORDERS Hemoglobin S diseases Bone marrow transplantation Chronic graft-versus-host disease Acute leukemia Chronic myeloproliferative disorders Fanconi syndrome Splenic tumors Mastocytosis	**ALTERATION IN SPLENIC CIRCULATION** Thrombosis of splenic artery Thrombosis of splenic vein Thrombosis of coeliac artery **MISCELLANEOUS** Amyloidosis

From Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states, Lancet 378(9785):86-97, 2011.

Splenic hypofunction is characterized by RBC inclusions in peripheral blood smears (Howell-Jolly bodies or Heinz bodies), **"pits"** on interference microscopy, and poor uptake of technetium or other spleen scans (Table 487-2, Fig. 487-1). Reduced immunoglobulin M memory B cells may also be detected and is a risk factor for overwhelming sepsis. Patients with functional hyposplenism or asplenia are at increased risk for sepsis from encapsulated bacteria and benefit from antibiotic prophylaxis.

SPLENIC TRAUMA

Injury to the spleen may occur with abdominal trauma. Small splenic capsular tears may cause abdominal or referred left shoulder pain as a result of diaphragmatic irritation by blood. Larger tears result in more severe blood loss, with similar pain and signs of hypovolemic shock. Previously enlarged spleens (as in patients with infectious mononucleosis) are more likely to rupture with minor trauma. Patients with splenomegaly should avoid contact sports and other activities that increase the risk of splenic trauma. CT scan with IV contrast is the best imaging modality to assess splenic trauma.

Treatment of a small capsular injury should include careful observation with attention to changes in vital signs or abdominal findings, serial hemoglobin determinations, and the availability of prompt surgical intervention if a patient's condition deteriorates (see Chapter 72).

Table 487-2 Diagnostic Techniques for and Features of Spleen Dysfunction

	DESCRIPTION	COMMENTS
Immunoglobulin M memory B cells	Cells dependent on spleen for survival. Produced in marginal zone	Special tests required
Technetium-99m–labeled sulphur colloidal scintiscan	Quantitation of splenic uptake of colloidal sulphur particles enables a fairly accurate static assessment of spleen function	Hypertrophy of the left hepatic lobe might be a limiting factor (this technique does not clearly show whether the mass originated in the liver or the spleen in the presence of an overlapping hypertropic left hepatic lobe)
Technetium-99m–labeled or rubidium-81–labeled heat-damaged autologous erythrocyte clearance	Measurement of clearance time allows a dynamic evaluation of spleen function	Preexisting erythrocyte defects, difficult erythrocyte incorporation of the radioisotope, false-positive or false-negative results in relation to excessive or insufficient heat damage make the test not suitable for clinical practice
Detection of Howell-Jolly bodies by staining	Erythrocytes with nuclear remnants Flow cytometry	No need for special equipment; inaccurate in the quantitation of splenic hypofunction
Detection of pitted erythrocytes by phase-interference microscopy	Erythrocytes with membrane indentations (4% upper limit of the normal range)	Need for phase-interference microscopy; counts enable a wide range of measurements and correlate with radioisotopic methods

From Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states, Lancet *378(9785):86-97, 2011, Table 1.*

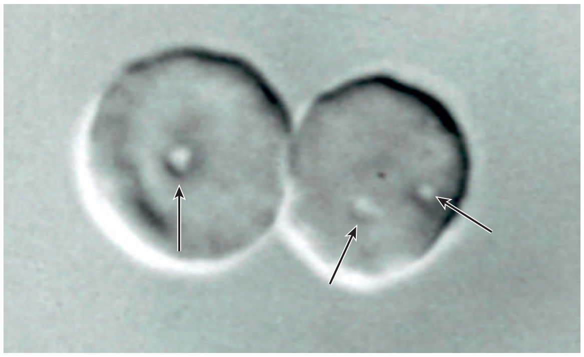

Figure 487-1 **Characteristic pitted erythrocytes.** A pitted erythrocyte is recognizable on phase-interference microscopy by the characteristic "pit" on the cell membrane *(arrows). (From Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states,* Lancet *378[9785]:86-97, 2011, Fig. 2.)*

RBC transfusion requirements should be minimal (<25 mL/kg/48 hr). These patients are usually hospitalized for 10-14 days and have their activities restricted for months. Laparotomy, with or without splenectomy, is indicated for more marked abdominal bleeding, in patients who have clinical instability or deterioration, or when other organ damage is suspected. Partial splenectomy and splenic repair should be substituted for total splenectomy when feasible to maintain some splenic immune function.

SPLENECTOMY

Splenectomy should be limited to specific indications where medical therapy is (or has been) ineffective. These include traumatic splenic rupture, anatomic defects, severe transfusion dependent hemolytic anemia, immune cytopenias, metabolic storage diseases, and secondary hypersplenism. The major long-term risk of splenectomy is sudden, overwhelming postsplenectomy infections (sepsis or meningitis). This risk is especially high in children younger than 5 yr at the time of surgery. The risk of sepsis is less when splenectomy is performed for trauma, RBC membrane defects, and immune thrombocytopenia (2-4%) than when there is sickle cell anemia, thalassemia, or a preexisting immune deficiency (Wiskott-Aldrich syndrome, Hodgkin disease) or reticuloendothelial blockade (storage disease, severe hemolytic anemia) (8-30%). The overall risk is 2-5 per 1,000 asplenic patient years, with a lifelong risk of overwhelming postsplenectomy infections of 5%; more than half occur within 2 yr after splenectomy, although the risk remains lifelong. The use of laparoscopic splenectomy has decreased surgical morbidity and hospitalization time.

Encapsulated bacteria, such as *Streptococcus pneumoniae* (>60% of cases), *Haemophilus influenzae,* and *Neisseria meningitidis,* account for >80% of cases of postsplenectomy sepsis. Because the spleen is responsible for filtering the blood and for early antibody responses, sepsis (with or without meningitis) can progress rapidly, leading to death within 12-24 hr of onset. Febrile splenectomized patients should be evaluated and treated promptly with antibiotics to cover the organisms previously mentioned. This treatment should be initiated at home if access to definitive medical care will be delayed. A broad-spectrum cephalosporin (cefotaxime or ceftriaxone) is recommended until specific antibiotic susceptibility and presence or absence of meningitis is known. Vancomycin (to cover penicillin-resistant pneumococci) should be initiated, depending on the illness severity and susceptibilities of pneumococci at the institution. Splenectomized patients are also at increased risk for contracting protozoal infections, such as malaria and babesiosis. Serious infection may occur after an animal bite (particularly dogs) and is due to *Capnocytophaga canimorsus* or *C. cynodegmi*. Prophylactic antibiotics should be given after a bite to potentially prevent sepsis caused by these organisms (see Chapter 724).

Preoperative, intraoperative, and **postoperative** management may decrease the risk of postsplenectomy infection. It is important to be certain of the need for splenectomy and, if possible, to postpone the operation until the patient is 5 yr of age or older. Pneumococcal, meningococcal, and *H. influenzae* conjugate vaccines given at least 14 days before splenectomy may reduce postsplenectomy sepsis. The 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7) was replaced with the 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13). Thus, depending on what primary pneumococcal vaccine was given, a single dose of PCV13 may be recommended. In addition, the 23-valent pneumococcal polysaccharide vaccine (Pneumovax) should be given at age ≥2 yr and a second dose 5 yr later. Yearly influenza vaccine should also be given as influenza infection is a risk factor for secondary pneumococcal infections. Prophylaxis with oral penicillin VK (125 mg twice daily for children younger than 5 yr; 250 mg twice daily for children 5 yr or older) should be given until at least 5 yr of age and for at least 2 yr after splenectomy. Although the greatest risk is in the immediate postoperative period, reports of deaths occurring years after splenectomy suggest that the risk (and the need for prophylaxis) may be lifelong. Lifelong prophylaxis should be strongly considered in patients who have had an invasive pneumococcal infection or who have an underlying immune deficiency. In children with sickle cell disease, penicillin prophylaxis should be started as soon as the diagnosis is made.

Prophylaxis may be continued into adulthood for higher-risk patients, including those with a history of pneumococcal sepsis, but effectiveness in this older group has not been well documented.

In patients with traumatic injury, splenic repair or partial splenectomy should be considered in an attempt to preserve splenic function. Partial splenectomy or partial splenic embolization may be sufficient to ameliorate some forms of hemolytic anemia. Up to 50% of children whose spleen is removed because of trauma have spontaneous **splenosis**; surgical splenosis (distributing small pieces of spleen throughout the abdomen) may decrease the risk of sepsis in patients whose splenectomy is necessitated by trauma. However, in both of these settings, the splenic tissue that regrows frequently has poor function.

In addition to postsplenectomy sepsis, splenectomized patients may be at risk for **thromboembolic** complications, including arterial and venous thrombosis and **pulmonary hypertension**. These findings have been reported regardless of the underlying reason for splenectomy and the postsplenectomy platelet count. Proposed mechanisms include loss of filtering function of the spleen, allowing abnormal RBCs to remain in the circulation and activate the coagulation cascade. Portal vein thrombosis has been reported as a complication of laparoscopic splenectomy.

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Section 9

The Lymphatic System

Chapter 488

Anatomy and Function of the Lymphatic System

Richard L. Tower and Bruce M. Camitta

The lymphatic system participates in many biologic processes, including fluid homeostasis, absorption of dietary fat, and initiation of specific immune responses. This system includes circulating lymphocytes, lymphatic vessels, lymph nodes, spleen, tonsils, adenoids, Peyer patches, and thymus. Lymph, an ultrafiltrate of blood, is collected by lymphatic capillaries that are present in all organs except the brain, bone marrow, retina, cartilage, epidermis, hair, and nails. These join to form progressively larger vessels that drain regions of the body. The lymphatic vessels carry lymph to the lymph nodes, where it is filtered through sinuses, particulate matter and infectious organisms are phagocytosed, and antigens are presented to surrounding lymphocytes. These actions stimulate antibody production, T-cell responses, and cytokine secretion (see Chapter 123). Lymph is ultimately returned to the intravascular circulation.

The composition of lymph can vary with the site of lymph drainage. It is usually clear, but lymph drained from the intestinal tract may be milky (chylous) because of the presence of fats. The protein content is intermediate between that of an exudate and a transudate. The protein level may be increased with inflammation and in lymph drained from the liver or intestines. Lymph also contains variable numbers of lymphocytes and antigen-presenting cells.

Embryonic lymphatic development (primary lymphangiogenesis) proceeds from the stage of lymphatic competence, through lymphatic commitment, specification, coalescence, and maturation. Secondary lymphangiogenesis occurs in the settings of wound healing and inflammation. Many genes are crucial to normal lymphatic development and function, including *Prox1*, vascular endothelial growth factor–C (*VEGF-C*), and vascular endothelial growth factor receptor–3 (*VEGFR-3*).

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Chapter 489

Abnormalities of Lymphatic Vessels

Richard L. Tower and Bruce M. Camitta

Abnormalities of the lymph vessels may be congenital or acquired. Signs and symptoms result from increased lymphatic tissue mass or from leakage of lymph. **Lymphangiectasia** is dilation of the lymphatics. Pulmonary lymphangiectasia causes respiratory distress (see Chapter 395.6). Involvement of the intestinal lymphatics causes hypoproteinemia and lymphocytopenia secondary to loss of lymph into the intestines (see Chapter 338). Therapy includes minimizing the hydrostatic pressure in the lymphatic system. Reducing dietary intake of long-chain fatty acids and substituting medium-chain triglycerides may accomplish this goal. If unsuccessful, octreotide or propanolol may be tried. **Lymphangioma** is a congenital lymphatic malformation, usually detected by age 2 yr. **Lymphangioma circumscriptum** is defined as the presence of many small, superficial lymphangiomas. Deeper lymphangiomas are classified as either **cavernous lymphangiomas** or **cystic hygromas**.

Lymphangiomatosis is the presence of multiple or disseminated malformations. Some of these lesions also have a hemangiomatous component (see Chapter 505). Thoracic lymphangiomatosis presents with chylothorax, a mass, or with pulmonary infiltrates. Associated features include bone, skin, and splenic lesions. The disorder is either diffuse or multifocal and is differentiated from lymphangiectasia by the presence of complex anastomosis of vessels with dilation rather than simple dilation of preexisting lymphatic capillaries. Emergent surgical treatment is infrequently necessary due to mass effects. Most lesions may be observed for 18-24 mo to assess for involution. Surgery is effective for superficial lesions, but there is a high incidence of recurrence when used for deeper lesions. Intralesional sclerosing with OK-432, a streptococcal derivative, has been used successfully in selected patients. Other sclerotherapy agents include pure ethanol and bleomycin. Macrocystic lesions appear to respond better than microcystic lymphangiomas to sclerotherapy. Radiofrequency ablation has been used for lymphatic lesions of the tongue. **Lymphatic dysplasia** may cause multisystem problems. These include lymphedema, chylous ascites, chylothorax, and lymphangiomas of the bone, lung, or other sites.

Lymphangioleiomyomatosis is characterized by proliferation of lymphatic endothelial cells and smooth muscle cells in the lungs, leading to airway and lymphatic obstruction, cyst formation, pneumothorax, and respiratory failure. It may initially be mistaken for asthma. Lymphangioleiomyomatosis occurs in young women and is also associated with mutations in the tuberous sclerosis tumor-suppressor gene *TSC2* in one-third of cases. Sirolimus (rapamycin) stabilizes lung function, reduces symptoms, and improves life quality; lung transplantation may be required.

Lymphedema, a localized swelling caused by impaired lymphatic flow, can be congenital or acquired. Congenital lymphedema may be found in Turner syndrome, Noonan syndrome, and the autosomal dominantly inherited Milroy disease, among other chromosomal abnormalities. Several families with Milroy disease have mutations in the vascular endothelial growth factor receptor–3 gene (*VEGFR-3*).

Autosomal recessive and X-linked inheritance has also been reported. Mutations in *GJC2* are associated with hereditary lymphedema. **Lymphedema praecox** (Meige disease) causes progressive lower extremity edema, usually in females during the peripubertal period or pregnancy. **Hypotrichosis-lymphedema-telangiectasia syndrome**, which has dominant and recessive inheritance patterns, has been linked to mutations in *SOX18*. Lymphedema has also been found in association with intestinal lymphangiectasia, cerebrovascular malformation, ptosis, yellow dystrophic nails, distichiasis, and cholestasis. Mutations in *FOXC2* are associated with lymphedema-distichiasis syndrome, which has a pubertal onset of lymphedema. Mutations in *CCBE1*, *PTPN14*, and *GATA2* are associated with Hennekam lymphangiectasia-lymphedema syndrome (lymphedema of the extremities, intestinal lymphangiectasia, mental retardation), lymphedema-choanal atresia syndrome, and Emberger syndrome (lymphedema of the lower extremities and genitalia, deafness, immune dysfunction, and warts), respectively.

Acquired obstruction of the lymphatics can result from tumor, postirradiation fibrosis, and postinflammatory scarring. **Filariasis** is an important cause of lymphedema in Africa, Asia, and Latin America; of the estimated 120 million infected persons, approximately 40 million (primarily older adolescents and adults) are believed to have lymphedema or hydrocele. Injury to the major lymphatic vessels can cause collection of lymph fluid in the abdomen (chylous ascites) or chest (chylothorax). Untreated lymphedema can be disabling and is associated with immune dysfunction, inflammation, fibrosis, adipose tissue overgrowth, and **lymphangiosarcoma**. Current treatment modalities attempt to reduce localized swelling through massage, exercise, and compression. No drugs have been proven efficacious. Diuretic use should be avoided. The recently discovered gene mutations provide potential for targeted therapy, including gene therapy. Autologous lymph node transplantation and use of growth factors to stimulate lymphangiogenesis may also be on the horizon for treatment of lymphedema.

Lymphangitis is an inflammation of the lymphatics that drain an area of infection. Tender, erythematous streaks extend proximally from the infected area. Regional nodes may also be tender. Group A streptococci and *Staphylococcus aureus* are the most frequent pathogens and therapy should include antibiotics that treat these organisms.

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Table 490-1	Differential Diagnosis of Systemic Generalized Lymphadenopathy	
INFANT	**CHILD**	**ADOLESCENT**
COMMON CAUSES		
Syphilis Toxoplasmosis CMV HIV	Viral infection EBV CMV HIV Toxoplasmosis	Viral infection EBV CMV HIV Toxoplasmosis Syphilis
RARE CAUSES		
Chagas disease (congenital) Leukemia Tuberculosis Reticuloendotheliosis Lymphoproliferative disease Metabolic storage disease Histiocytic disorders	Serum sickness SLE, JIA Leukemia/ lymphoma Tuberculosis Measles Sarcoidosis Fungal infection Plague Langerhans cell histiocytosis Chronic granulomatous disease Sinus histiocytosis Drug reaction	Serum sickness SLE, JIA Leukemia/lymphoma/ Hodgkin disease Lymphoproliferative disease Tuberculosis Histoplasmosis Sarcoidosis Fungal infection Plague Drug reaction Castleman disease

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; JIA, juvenile idiopathic arthritis (as Still disease); SLE, systemic lupus erythematosus.

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 863.*

Chapter **490**

Lymphadenopathy

Richard L. Tower and Bruce M. Camitta

Palpable lymph nodes are common in pediatrics. Lymph node enlargement is caused by proliferation of normal lymphoid elements or by infiltration with malignant or phagocytic cells. In most patients, a careful history and a complete physical examination suggest the proper diagnosis.

DIAGNOSIS

Is the mass a lymph node? Nonlymphoid masses (cervical rib, thyroglossal cyst, branchial cleft cyst or infected sinus, cystic hygroma, goiter, sternomastoid muscle tumor, thyroiditis, thyroid abscess, neurofibroma) occur frequently in the neck and less often in other areas. **Is the node enlarged?** Lymph nodes are not usually palpable in the newborn. With antigenic exposure, lymphoid tissue increases in volume. They are not considered enlarged until their diameter exceeds 1 cm for cervical and axillary nodes and 1.5 cm for inguinal nodes. Other lymph nodes usually are not palpable or visualized with plain radiographs. **What are the characteristics of the node?** Acutely infected nodes are usually tender. There may also be erythema and warmth of the overlying skin. Fluctuance suggests abscess formation. Tuberculous nodes may be matted. With chronic infection, many of these signs are not present. Tumor-bearing nodes are usually firm and nontender and may be matted or fixed to the skin or underlying structures.

Is the lymphadenopathy localized or generalized? Generalized adenopathy (enlargement of >2 noncontiguous node regions) is caused by systemic disease (Table 490-1) and is often accompanied by abnormal physical findings in other systems. In contrast, regional adenopathy is most frequently the result of infection in the involved node and/or its drainage area (Table 490-2). When caused by infectious agents other than bacteria, adenopathy may be characterized by atypical anatomic areas, a prolonged course, a draining sinus, lack of prior pyogenic infection, and unusual clues in the history (cat scratches, tuberculosis exposure, venereal disease). A firm, fixed node should always raise the question of malignancy, regardless of the presence or absence of systemic symptoms or other abnormal physical findings.

TREATMENT

Evaluation and treatment of lymphadenopathy is guided by the probable etiologic factor, as determined from the history and physical examination. Many patients with cervical adenopathy have a history compatible with viral infection and need no intervention. If bacterial infection is suspected, antibiotic treatment covering at least streptococci and staphylococci is indicated. Those who do not respond to oral antibiotics, as demonstrated by persistent swelling and fever, require IV antistaphylococcal antibiotics. If there is no response in 1-2 days, or if there are signs of airway obstruction or significant toxicity, ultrasound, CT, or MRI of the neck should be obtained. If pus is present, it may be aspirated, with CT or ultrasound guidance, or if it is extensive, may require incision and drainage. Gram stain and culture of the pus should be obtained. The sizes of involved nodes should be documented before treatment. Failure to decrease in size within 10-14 days also suggests the need for further evaluation. This may include a complete blood cell

Table 490-2 Sites of Local Lymphadenopathy and Associated Diseases

CERVICAL
Oropharyngeal infection (viral or group A streptococcal, staphylococcal)
Scalp infection/infestation (head lice)
Mycobacterial lymphadenitis (tuberculosis and nontuberculous mycobacteria)
Viral infection (EBV, CMV, HHV-6)
Cat-scratch disease
Toxoplasmosis
Kawasaki disease
Thyroid disease
Kikuchi disease
Sinus histiocytosis (Rosai-Dorfman disease)
Autoimmune lymphoproliferative disease
Periodic fever, aphthous stomatitis, pharyngitis, cervical adenopathy (PFAPA) syndrome
ANTERIOR AURICULAR
Conjunctivitis
Other eye infection
Oculoglandular tularemia
Facial cellulitis
Otitis media
Viral infection (especially rubella, parvovirus)
SUPRACLAVICULAR
Malignancy or infection in the mediastinum (right)
Metastatic malignancy from the abdomen (left)
Lymphoma
Tuberculosis
EPITROCHLEAR
Hand infection, arm infection*
Lymphoma†
Sarcoid
Syphilis
INGUINAL
Urinary tract infection
Venereal disease (especially syphilis or lymphogranuloma venereum)
Other perineal infections
Lower extremity suppurative infection
Plague
HILAR (NOT PALPABLE, FOUND ON CHEST RADIOGRAPH OR CT)
Tuberculosis†
Histoplasmosis†
Blastomycosis†
Coccidioidomycosis†
Leukemia/lymphoma†
Hodgkin disease†
Metastatic malignancy*
Sarcoidosis†
Castleman disease
AXILLARY
Cat-scratch disease
Arm or chest wall infection
Malignancy of chest wall
Leukemia/lymphoma
Brucellosis
ABDOMINAL
Malignancies
Mesenteric adenitis (measles, tuberculosis, *Yersinia*, group A streptococcus)

*Unilateral.
†Bilateral.
CMV, cytomegalovirus; CT, computed tomography; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6.
From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 864.*

count with differential; Epstein-Barr virus, cytomegalovirus, *Toxoplasma,* and cat-scratch disease titers; antistreptolysin O or anti-DNAse serologic tests; tuberculin skin test; and chest radiograph. If these are not diagnostic, consultation with an infectious disease or oncology specialist may be helpful. Biopsy should be considered if there is persistent or unexplained fever, weight loss, night sweats, supraclavicular location, mediastinal mass, hard nodes, or fixation of the nodes to surrounding tissues. Biopsy may also be indicated if there is an increase in size over baseline in 2 wk, no decrease in size in 4-6 wk, no regression to "normal" in 8-12 wk, or if new signs and symptoms develop.

Differentiating benign disorders from a malignancy may initially be difficult. Hard, nontender, nonerythematous nodes involving multiple regions (including mediastinum and abdomen), hepatic or splenic enlargement, fever, night sweats, and weight loss suggest malignancy or a granulomatous process. Persistence of symptoms and lymphadenopathy greater than 2 wk and certain locations (supraclavicular, mediastinal, abdomen) also suggest malignancy. Cytopenias and elevated blood lactate dehydrogenase are associated with malignancy and certain inflammatory disorders. CT imaging is helpful in identifying other affected nodes and organs; CT or ultrasonographic guided biopsy is helpful in determining the etiology. Fine needle aspiration or excisional biopsy may be needed for superficial nodes to determine a diagnosis.

Bibliography is available at Expert Consult.

490.1 Kikuchi-Fujimoto Disease (Histiocytic Necrotizing Lymphadenitis)

Richard L. Tower and Bruce M. Camitta

Kikuchi-Fujimoto disease is a rare, usually self-limiting disease that was originally reported in patients of Asian heritage. Cases are now described in all ethnic groups. Familial cases have been reported. Presentation is varied and may include fever of unknown origin, but more often, it occurs in children 8-16 yr of age as firm unilateral posterior cervical adenitis, fever, malaise, elevated erythrocyte sedimentation rate, atypical lymphocytosis, and leukopenia. Nodes range in size from only 0.5-6.0 cm, are painful or tender in only 50% of cases, may be multiple, and must be differentiated from lymphoma. Node involvement may occasionally be bilateral or present in axillary or supraclavicular nodes.

The etiology is unknown, although viral and bacterial causes have been suggested. Growing evidence supports an abnormal immune response; the diagnosis is made by lymph node biopsy. Histologic features include necrosis with karyorrhexis, a histiocytic infiltrate, crescentic plasmacytoid monocytes and an absence of neutrophils. The disease is self-limiting and usually spontaneously resolves within 6 mo, although relapses have occurred up to 16 yr later. Therapy with systemic steroids is reserved for cases with severe symptoms. Rarely, the disease has been fatal. Many autoimmune diseases have been associated with Kikuchi-Fujimoto disease, most commonly systemic lupus erythematosus. The differential diagnosis includes lymphoma, tuberculosis, and systemic lupus erythematosus.

Bibliography is available at Expert Consult.

490.2 Sinus Histiocytosis with Massive Lymphadenopathy (Rosai-Dorfman Disease)

Richard L. Tower and Bruce M. Camitta

This uncommon, benign, and usually self-limited disease has a worldwide distribution but is more common in Africa and the Caribbean. The etiology is unknown, but immune dysfunction is suspected. Patients present with massive bilateral, painless, mobile cervical adenopathy, along with fever, leukocytosis, high erythrocyte sedimentation

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rate, and polyclonal elevation of immunoglobulin G (hypergammaglobulinemia). Night sweats and weight loss are common. Autoimmune hemolytic anemia is an uncommon associated finding. It rarely occurs at birth or in siblings, and males are affected more often than females.

Other nodal chains may be involved. Extranodal involvement occurs in 40% of cases. Soft-tissue involvement of all organ systems has been reported. The most common sites are the skin, followed by the nasal cavity and sinuses, palate, orbit, bone, and central nervous system. Occasionally autoantibodies to erythrocytes or synovium may be present. A biopsy that demonstrates pale histiocytes containing engulfed lymphocytes (**emperipolesis**), and immunoreactivity to S100 protein in large histiocytes, in conjunction with expected clinical features, is diagnostic. The differential diagnosis includes Langerhans cell histiocytosis, myeloproliferative disorders, and lymphoma.

Therapy is usually not needed for this self-limited disease. However, the disease may recur frequently for many years. Life- or organ-threatening disease or exacerbations may respond to prednisone. Refractory cases have been treated with surgical excision or radiation. Rare patients have been treated with immune-modulating therapy, including interferon-α, 2-chlorodeoxyadenosine, imatinib, and rituximab. Therapy with antibiotics and chemotherapy has been unsuccessful.

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490.3 Castleman Disease

Richard L. Tower and Bruce M. Camitta

Castleman disease is an uncommon lymphoproliferative disease and is also called *angiofollicular lymph node hyperplasia*. The underlying etiology is unknown, although an association with human herpesvirus 8 has been identified. Human herpesvirus 8 may stimulate excessive production of interleukin 6 (IL-6). The disease usually presents in adolescents or young adults. Enlargement of a single node, most often in the mediastinum or abdomen, is the most common localized presentation. Some patients may have fever, night sweats, weight loss, and fatigue. Management includes surgery and/or radiation therapy.

Multicentric Castleman disease is a systemic lymphoproliferative disorder that causes lymphadenopathy, hepatosplenomegaly, fever, anemia, overexpression of IL-6, and polyclonal hypergammaglobulinemia. Multicentric Castleman disease may be associated with HIV infection, autoimmune disease–associated lymphadenopathy, and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-proteins, and skin lesions). Non-Hodgkin lymphoma may be concurrent or may develop as a result of disease progression. There is no standard treatment for multicentric Castleman disease. Therapeutic options include chemotherapy, steroids, monoclonal antibodies to CD20 (rituximab), monoclonal antibodies (siltuximab) to IL-6, anti-IL-6–receptor antibodies (tocilizumab), antiviral agents, and interferon-α. Chemotherapy regimens used for diffuse large B-cell lymphoma and/or rituximab is currently the most common frontline therapies and has achieved durable remissions. Ganciclovir is the most active antiviral agent. Steroids and anti-IL-6 therapies provide symptomatic relief, but symptoms return after stopping therapy.

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Cancer and Benign Tumors

PART XXII

Chapter 491

Epidemiology of Childhood and Adolescent Cancer

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Cancer in patients younger than 20 yr of age is uncommon, with an age-adjusted annual incidence of 18.7 per 100,000 children ages 0-19 yr, representing only approximately 1% of all new cancer cases in a year in the United States or an estimated 16,600 new cases/yr in 2014. This translates to nearly a 1 in 300 chance of developing cancer by age 20 yr. Although the relative 5 yr survival rates have improved from 61% in 1977 to 83.6% in 2010 in all age groups 0-19 yr (Fig. 491-1), malignant neoplasms remain the leading cause of disease-related (noninjury) mortality (12%) among persons 1-19 yr of age with 1,800-1,900 cancer-related deaths annually in the United States among children and adolescents 0-19 yr of age. The relative contribution of cancer to the overall mortality in infants 0-1 yr old and adolescents 15-19 yr old is lower than for children ages 1-14 yr. The impressive improvements in survival over the past 3.5 decades are attributed primarily to advances in treatment and enrollment in clinical trials for the majority of patients. Multiinstitutional cooperative clinical trials investigating novel therapies and investigating ways to improve survival rates even further and to decrease treatment-related long-term complications are ongoing. Because increasingly more patients survive their disease, clinical investigations also are focusing on the quality of life among survivors and the late outcomes of therapy for pediatric and adult survivors of childhood cancer. The National Cancer Institute estimates that in 2010 there were 380,000 persons alive (in all age groups) who had survived childhood cancer, corresponding to 1 in 810 of persons younger than 20 yr of age and 1 in 1,000 persons 20-39 yr of age in the U.S. population.

Pediatric malignancies differ markedly from adult malignancies in both prognosis and distribution by histology and tumor site. Lymphohematopoietic cancers (i.e., acute lymphoblastic leukemia, myeloid leukemia, Hodgkin and non-Hodgkin lymphomas) account for approximately 40%, central nervous system cancers for approximately 30%, and embryonal tumors and sarcomas for approximately 10% among the broad categories of childhood cancers (Table 491-1). In contrast, epithelial tumors of organs such as lung, colon, breast, and prostate, which are commonly seen among adults, are rare malignancies in children. Incidence patterns in the pediatric age group show 2 peaks: the first in early childhood and the second in adolescence (Fig. 491-2). During the 1st yr of life, *embryonal tumors* such as neuroblastoma, nephroblastoma (Wilms tumor), retinoblastoma, rhabdomyosarcoma, hepatoblastoma, and medulloblastoma are most common (Figs. 491-3 and 491-4). These tumors are much less common in older children and adults after cell differentiation processes have slowed considerably. Embryonal tumors, acute leukemias, non-Hodgkin lymphomas, and gliomas peak in incidence from 2-5 yr of age. As children age, bone malignancies, Hodgkin disease, gonadal germ cell malignancies (testicular and ovarian carcinomas), and other carcinomas increase in incidence. Adolescence is a transitional period between the common early childhood malignancies and characteristic carcinomas of adulthood (Fig. 491-4). Incidence rates also vary by gender (generally higher in boys vs girls), race/ethnicity (more common in whites), and between countries (data assembled by the International Agency for Research in Cancer in Lyon, France, http://www.iarc.fr/). Over the past 35 yr, 1975-2010, there has been some increase in the incidence of children and adolescents diagnosed with cancer particularly in occurrence of leukemia and among adolescents. These variations are not fully understood but likely reflect differences in genetic susceptibility and environmental exposures related to both known and unknown causes and risk factors for cancer (Table 491-2).

Childhood cancer includes a diverse array of malignant tumors, termed "cancers," and nonmalignant tumors arising from disorders of genetic processes involved in control of cellular growth and development. Although many genetic conditions are associated with increased risks for childhood cancer, such conditions are believed to account for <5% of all occurrences (see Chapter 492). The most notable genetic conditions that impart susceptibility to childhood cancer are neurofibromatosis types 1 and 2, Down syndrome, Beckwith-Wiedemann syndrome, tuberous sclerosis, von Hippel-Lindau disease, xeroderma pigmentosum, ataxia-telangiectasia, nevus basal cell carcinoma syndrome, and Li-Fraumeni (*P53*) syndrome. The varying incidence patterns of individual childhood cancers around the world imply additional genetic and epidemiologic risk factors that remain uncharacterized.

Compared with adult epithelial tumors, an extremely small fraction of pediatric cancers appear to be explained by known environmental exposures (see Table 491-2). Ionizing radiation exposure and several chemotherapeutic agents explain only a small number of pediatric cases (see Chapter 718). The association between fetal exposures and pediatric cancer is largely not established, with the exception of maternal diethylstilbestrol intake during pregnancy and subsequent vaginal adenocarcinoma in adolescent daughters. Environmental exposures that have been studied without convincing evidence for a causal role include nonionizing power frequency electromagnetic fields, pesticides, parental occupational chemical exposures, dietary factors, in vitro fertilization, and environmental cigarette smoke. Viruses have been associated with certain pediatric cancers, such as polyomaviruses (BK, JC, SV40) associated with brain cancer and Epstein-Barr virus with non-Hodgkin lymphoma, but the etiologic importance remains unclear. The etiology of cancer in children still is poorly understood, and epidemiology studies demonstrate that the likely mechanisms are multifactorial, possibly resulting from potential interactions between genetic susceptibility traits and environmental exposures. Ongoing studies are investigating the role of polymorphisms of genes encoding enzymes, which function in the activation or metabolism of xenobiotics, protection of cells against oxidative stress, DNA repair, and/or immune modulation.

Curative therapy with chemotherapy, radiation, and/or surgery can adversely affect a child's development and result in serious long-term medical and psychosocial effects in childhood and adulthood. Potential adverse late effects include subsequent second malignancy, early mortality, infertility, reduced stature, cardiomyopathy, pulmonary fibrosis, osteoporosis, neurocognitive impairment, affective disorders, and altered social functioning. Much has been learned about the incidence of late effects from large multisite cohort studies such as the Childhood Cancer Survivor Study, an ongoing study of medical and psychosocial outcomes in survivors, which has provided data for the development of clinical care guidelines for survivors (http://www.survivorshipguidelines.org).

Given the relative rarity of specific types of childhood cancer and the sophisticated technology and expertise required for diagnosis, treatment, and monitoring of late effects, all children with cancer

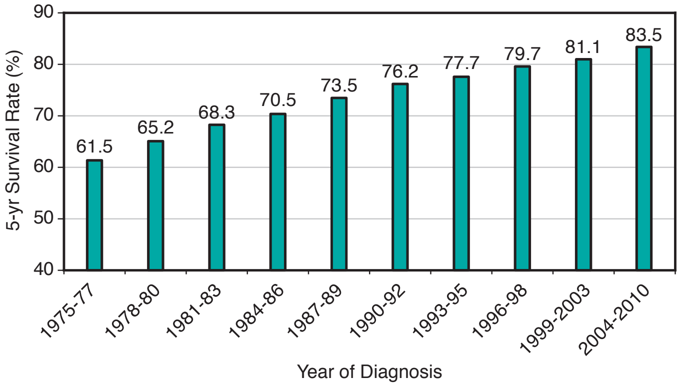

Figure 491-1 **Five yr relative survival rates (%) by year of diagnosis of all cancers in children 19 yr of age or younger.** The difference between the periods 1975-1977 and 2004-2010 is statistically significant ($p < 0.05$). Rates based on follow-up of patients into 2011 from Surveillance, Epidemiology, and End Results (SEER) database. *(Data compiled from Howlader N, Noone AM, Krapcho M, et al, editors: SEER Cancer Statistics Review, 1975-2011, Section 28. Bethesda, MD, National Cancer Institute. Available at http://seer.cancer.gov/csr/1975_2011/, posted to the SEER website, April 2014.)*

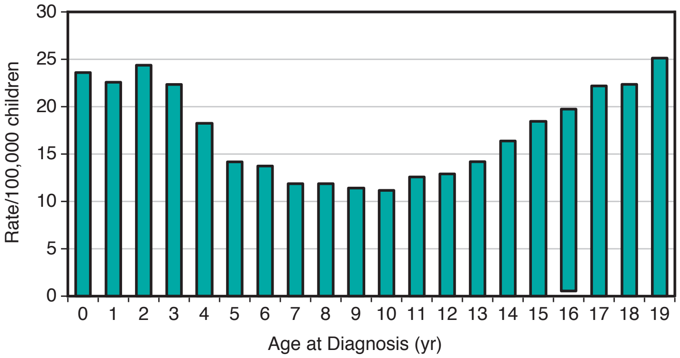

Figure 491-2 **Age-specific cancer incidence rates per 100,000 children within the United States.** Rates based on data from 2007-2011 from Surveillance, Epidemiology, and End Results (SEER) database. *(Data compiled from Howlader N, Noone AM, Krapcho M, et al, editors: SEER Cancer Statistics Review, 1975-2011, Section 28. Bethesda, MD, National Cancer Institute. Available at http://seer.cancer.gov/csr/1975_2011/, posted to the SEER website, April 2014.)*

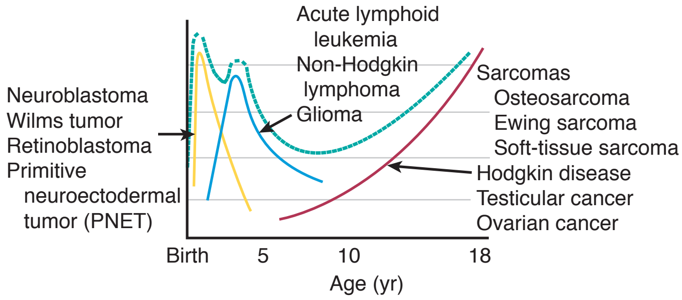

Figure 491-3 **Generalized incidence of the most common types of cancer in children by age.** The cumulative incidence of all cancers is shown as a dashed line. *(Courtesy of Archie Bleyer, MD.)*

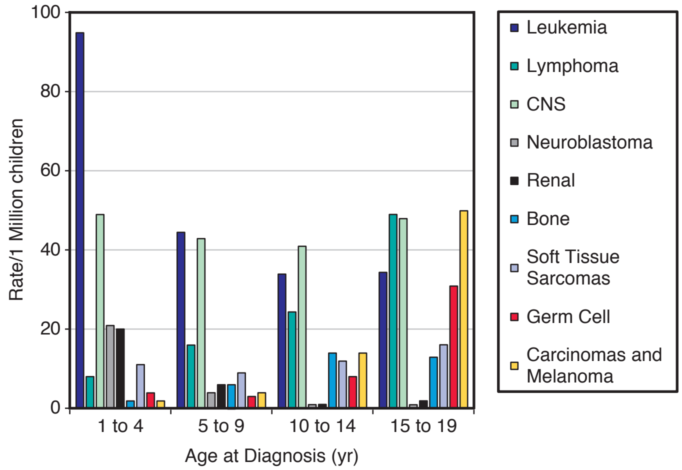

Figure 491-4 Surveillance, Epidemiology, and End Results (SEER) incidence rates by International Classification of Childhood Cancer (ICCC) and age group <20 yr. CNS, central nervous system. *(Data compiled from Howlader N, Noone AM, Krapcho M, et al, editors: SEER Cancer Statistics Review, 1975-2011, Section 29. Bethesda, MD, National Cancer Institute. Available at http://seer.cancer.gov/csr/1975_2011/, posted to the SEER website, April 2014.)*

Table 491-1 Age-Adjusted Incidence and Survival Rates of Malignant Neoplasms By Tumor Type Among U.S. Children

	ANNUAL INCIDENCE RATES PER 1 MILLION CHILDREN, 2007-2011					5-YR SURVIVAL (%) AGE ≤19 YR AT DIAGNOSIS, 2004-2011
	Age <1 Yr	Age 1-4 Yr	Age 5-9 Yr	Age 10-14 Yr	Age 15-19 Yr	
All malignancies combined	242	221	128	136	219	82.5
Leukemia (ALL/AML)	52 (20/19)	95 (80/11)	44 (37/4.5)	34 (22/7)	34 (18/10)	82 (87/62)
Lymphoma (Hodgkin)	5.5 (—)	8 (1)	16 (5.4)	24.5 (12)	49 (32)	92 (96)
CNS tumors	49	49	43	41	48	73
Neuroblastoma	51	21	4	1	0.9	78
Nephroblastoma/Wilms (renal cell carcinoma)	15 (—)	20 (—)	5 (—)	0.7 (—)	— (1.5)	90
Bone	—	2	6	14	13	69.5
Soft tissue sarcomas	20	11	9	12	16	71
Retinoblastoma	28	9	—	—	—	97
Hepatoblastoma (hepatic carcinoma)	10 (—)	6 (—)	— (—)	— (0.8)	— (1.4)	80 (70)
Germ cell tumors	19	4	3	8	31	92
Malignant epithelial cancer	—	1.8	4	14	50	92 (99.5*/95†)

Based on the International Classification of Childhood Cancer (ICCC). Rates are per 1,000,000 children and are age-adjusted to the 2000 U.S. standard population.

*Thyroid carcinoma.

†Malignant melanoma.

—, Indicates that the rate could not be calculated with <16 cases for the time interval; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CNS, central nervous system.

Data compiled From Howlader N, Noone AM, Krapcho M, et al, editors: SEER Cancer Statistics Review, 1975-2011, Section 29. Bethesda, MD, National Cancer Institute. Available at http://seer.cancer.gov/csr/1975_2011/, posted to the SEER website, April 2014.

Table 491-2 Known Risk Factors for Selected Childhood Cancers

CANCER TYPE	RISK FACTOR	COMMENTS
Acute lymphoid leukemia	Ionizing radiation	Although primarily of historical significance, prenatal diagnostic x-ray exposure increases risk. Therapeutic irradiation for cancer treatment also increases risk.
	Race	White children have a 2-fold higher rate than black children in the United States.
	Genetic factors*	Down syndrome is associated with an estimated 10-20–fold increased risk. NF1, Bloom syndrome, ataxia-telangiectasia, and Langerhans cell histiocytosis, among others, are associated with an elevated risk.
Acute myeloid leukemias	Chemotherapeutic agents	Alkylating agents and epipodophyllotoxins increase risk.
	Genetic factors*	Down syndrome and NF1 are strongly associated. Familial monosomy 7 and several other genetic syndromes are also associated with increased risk.
Brain cancers	Therapeutic ionizing radiation to the head	With the exception of cancer radiation therapy, higher risk from radiation treatment is essentially of historical importance.
	Genetic factors*	NF1 is strongly associated with optic gliomas, and, to a lesser extent, with other central nervous system tumors. Tuberous sclerosis and several other genetic syndromes are associated with increased risk.
Hodgkin disease	Family history	Monozygotic twins and siblings are at increased risk.
	Infections	EBV is associated with increased risk.
Non-Hodgkin lymphoma	Immunodeficiency	Acquired and congenital immunodeficiency disorders and immunosuppressive therapy increase risk.
	Infections	EBV is associated with Burkitt lymphoma in Africa.
Osteosarcoma	Ionizing radiation	Cancer radiation therapy and high radium exposure increase risk.
	Chemotherapy	Alkylating agents increase risk.
	Genetic factors*	Increased risk is apparent with Li-Fraumeni syndrome and hereditary retinoblastoma.
Ewing sarcoma	Race	White children have about a 9-fold higher incidence rate than black children in the United States.
Neuroblastoma		Neurocristopathies.
Retinoblastoma	Genetic factors*	No established other risk factors.
Wilms tumor	Congenital anomalies	Aniridia, Beckwith-Wiedemann syndrome, and other congenital and genetic conditions are associated with increased risk.
	Race	Asian children reportedly have about half the rates of white and black children.
Renal medullary carcinoma	Sickle cell trait	Etiology unknown.
Rhabdomyosarcoma	Congenital anomalies and genetic conditions	Li-Fraumeni syndrome and NF1 are believed to be associated with increased risk. There is some concordance with major birth defects.
Hepatoblastoma	Genetic factors*	Beckwith-Wiedemann syndrome, hemihypertrophy, Gardner syndrome, and family history of adenomatous polyposis are associated with increased risk.
Leiomyosarcoma	Immunosuppression and EBV infection	EBV is associated with leiomyosarcoma for all forms of congenital and acquired immunosuppression but not leiomyosarcoma among immunocompetent persons.
Malignant germ cell tumors	Cryptorchidism	Cryptorchidism is a risk factor for testicular germ cell tumors.

*See Chapter 492, Table 492-2.

EBV, Epstein-Barr virus; NF1, neurofibromatosis type 1.

Scheurer ME, Bondy ML, Gurney JG: Epidemiology of childhood cancer. In Pizzo PA, Poplack DG, editors: Principles and practice of pediatric oncology, *ed 6, Philadelphia, 2011, Lippincott Williams & Wilkins, p. 15.*

should be treated with standardized clinical protocols in pediatric clinical research settings whenever possible. Promoting such treatment, the Children's Oncology Group is a multiinstitutional research consortium that facilitates cooperative clinical, biologic, and epidemiologic research in more than 200 affiliated institutions in the United States, Canada, and other countries (http://childrensoncologygroup.org/). Coordinated participation in such research trials has been a major factor in the increased survival for many children with cancer. Such ongoing efforts are critical to better understand the etiology of childhood cancers, improve survival for malignancies with a poor prognosis, and maximize the quality of life for survivors.

INFLUENCING THE INCIDENCE OF CANCER

Pediatricians have a unique opportunity to educate children and adolescents, and their parents, regarding means of preventing cancer. There are only a few recognized environmental causes of childhood cancer that can be avoided or counteracted. One example is immunization against hepatitis B, which does decrease the risk of hepatocellular carcinoma in adolescence and adulthood; another is human papillomavirus vaccination, which prevents cervical cancer. Associations between cumulative radiation exposure from common diagnostic radiologic tests such as CT scans and an increased risk of malignancy later in life are of great concern for pediatricians. Guidelines to ensure the safe clinical use of diagnostic imaging are being evaluated (http://www.imagegently.org/). An objective of pediatric medicine is to teach children how to adopt healthy lifestyles to reduce their risk of cancer during adulthood, such as avoiding tobacco, alcohol, high-fat diets, and obesity. The earlier these habits are instilled, the greater the lifelong benefit and the more likely it is to be present and sustained during adulthood.

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Chapter **492**

Molecular and Cellular Biology of Cancer

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Cancer is a complex of diseases arising from alterations that can occur in a wide variety of genes. Alterations in normal cellular processes such as signal transduction, cell-cycle control, DNA repair, cellular growth and differentiation, translational regulation, senescence, and apoptosis (programmed cell death) can result in a malignant phenotype.

GENES INVOLVED IN ONCOGENESIS

Two major classes of genes are implicated in the development of cancer: oncogenes and tumor-suppressor genes. **Protooncogenes** are cellular genes that are important for normal cellular function and code for various proteins, including transcriptional factors, growth factors, and growth factor receptors. These proteins are vital components in the network of signal transduction that regulate cell growth, division, and differentiation. Protooncogenes can be altered to form **oncogenes**—genes that, when translated, can result in the malignant transformation of a cell.

Oncogenes can be divided into 5 different classes based on their mechanisms of action. Changes in any of these normal cellular components can result in unchecked cell growth. Some oncogenes code for **growth factors** that bind to a receptor and stimulate the production of a protein. Other oncogenes code for **growth factor receptors.** These are proteins on the cell surface. When growth factors bind to a growth factor receptor, they can turn the receptor on or off. Mutational or posttranslational modifications of the receptor can result in a receptor being permanently turned on with consequent unregulated growth. **Signal transducers** or effectors make up another class. Signal transducers are responsible for taking the signal from the cell surface receptor to the cell nucleus. *NRAS*, as described below, is an example of this class of protein. **Transcription factors** are molecules that bind to specific areas of the DNA and control transcription. *MYC,* described below, is an example of a transcription factor that results in overstimulation of cell division. The final class of oncogenes interferes with apoptosis. Cells that no longer respond to the signal to die can continue to proliferate.

The 3 main mechanisms by which protooncogenes can be activated include amplification, point mutations, and translocation (Table 492-1). *MYC,* which codes for a protein that regulates transcription, is an example of a protooncogene that is activated by amplification. Patients with neuroblastoma in which the *MYC* gene is amplified 10-300–fold have a poorer outcome. Point mutations can also activate protooncogenes. The *NRAS* protooncogene codes for a guanine nucleotide–binding protein with guanosine triphosphatase activity that is important in signal transduction and is mutated in 25-30% of acute nonmyelogenous leukemias, resulting in a constitutively active protein. The RET protein is a transmembrane tyrosine kinase receptor that is important in signal transduction. A point mutation in the *RET* gene results in the constitutive activation of a tyrosine kinase, as found in multiple neoplasia syndromes and familial thyroid carcinoma.

The third mechanism by which protooncogenes become activated is by chromosomal translocation. In some leukemias and lymphomas, transcription factor controlling sequences are relocated in front of T-cell receptors or immunoglobulin genes, resulting in unregulated transcription of the genes and leukemogenesis. Chromosomal translocations can also result in **fusion genes**; transcription of the fusion gene can result in the production of a chimeric protein with new and potentially oncogenic activity. Examples of cancers associated with fusion genes include the childhood solid tumors like Ewing sarcoma [t(11;22)] and alveolar rhabdomyosarcoma [t(2;13) or t(1;13)]. The translocations result in novel proteins that are useful as diagnostic markers. The best-described translocation in leukemia is the **Philadelphia chromosome's t(9;22)**, which results in the BCR/ABL protein found in chronic myelogenous leukemia. This translocation results in a tyrosine kinase protein that is constitutively activated. In addition, the protein is localized to the cytoplasm instead of the nucleus, exposing the kinase to a new spectrum of substrates.

Alteration in the regulation of tumor-suppressor genes is another mechanism involved in oncogenesis. Tumor-suppressor genes are important regulators of cellular growth and apoptosis. They have been called recessive oncogenes because the inactivation of both alleles of a tumor-suppressor gene is required for expression of a malignant phenotype.

Knudson's **"2-hit" model of cancer development** was based on the observation of the behavior of the *RB* tumor-suppressor gene. In sporadic cases of retinoblastoma, both alleles of the *RB* gene must be inactivated. However, in familial cases, children inherit an inactivated allele from 1 parent and consequently require the inactivation of the only remaining normal allele. This helps explain why familial cases of retinoblastoma occur earlier in childhood than sporadic cases, because only 1 "hit" is required.

Another major tumor-suppressor protein is P53, which is known as the "guardian of the genome" because it detects the presence of

Table 492-1 Oncogene Activators of Pediatric Tumors

MECHANISM	CHROMOSOME	GENES	PROTEIN FUNCTION	TUMOR
Chromosomal translocation	t(9;22)	*BCR-ABL*	Chimeric tyrosine kinase	CML, ALL
	t(1:19)	*E2A-PBX1*	Chimeric transcription factor	Pre-B ALL
	t(14:18)	*CMYC*	Transcription factor	Burkitt lymphoma
	t(15;17)	*APL-RARα*	Chimeric transcription factor	APL
	11:q23 and others	*MLL*	Methyl transferase activity	ALL AML Biphenotypic
	t(12;q21)	*TEL-AML 1*	Chimeric protein	ALL
	t(2;13)(q35;q14) or t(1,13)(p36q14)	*FKHF-PAX3*	Transcription factor	Rhabdomyosarcoma
	t(11;q22) or t(7;q22)	*EWS-FLI1*	Transcription factor	Wilms
Gene amplification	Amplicon	*NMYC*	Transcription factor	Neuroblastoma
	Amplicon	*EGFR*	Growth factor kinase, tyrosine kinase	Glioblastoma
	Amplicon	*Flt3*	Tyrosine kinase receptor	AML
Point mutation	1p	*NRAS*	Guanosine triphosphatase	AML
	10q	*RET*	Tyrosine kinase	MEN2

ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; APL, acute promyelocytic leukemia; CML, chronic myelogenous leukemia; MEN2, multiple endocrine neoplasia, type 2.

chromosomal damage and prevents the cell from dividing until repairs have been made. In the presence of damage beyond repair, P53 initiates apoptosis and the cell dies. More than 50% of all tumors have abnormal P53 proteins. Mutations in the *P53* gene are important in many cancers, including breast, colorectal, lung, esophageal, stomach, ovarian, and prostatic carcinomas as well as gliomas, sarcomas, and some leukemias.

PTEN (phosphatase and tensin homolog) is one of the most commonly lost tumor suppressors in human cancer. PTEN is a phosphatase that regulates cell-cycle progression. The dephosphorylation of proteins disrupts the Akt/PKB signaling pathway that moderates cell-cycle progression. Loss of PTEN enzyme activity is seen in Proteus, Cowden, and Bannayan-Riley-Ruvalcaba syndromes and in glioblastoma, endometrial carcinoma, and prostate cancer. Decreased phosphatase activity is found in lung and breast cancer. More than 170 putative tumor-suppressor genes are identified.

SYNDROMES PREDISPOSING TO CANCER

Several syndromes are associated with an increased risk of developing malignancies, which can be characterized by different mechanisms (Table 492-2). One mechanism involves the inactivation of tumor-suppressor genes such as *RB* in **familial retinoblastoma**. Interestingly, patients with retinoblastoma in which 1 of the alleles is inactivated throughout all of the patient's cells are also at a very high risk for developing osteosarcoma. A familial syndrome, **Li-Fraumeni syndrome**, in which 1 mutant *P53* allele is inherited, also has been described in patients who develop sarcomas, leukemias, and cancers of the breast, bone, lung, and brain. **Neurofibromatosis** is a condition characterized by the proliferation of cells of neural crest origin, leading to neurofibromas. These patients are at a higher risk of developing malignant schwannomas and pheochromocytomas. Neurofibromatosis is often inherited in an autosomal dominant fashion, although 50% of the cases present without a family history and occur secondary to the high rate of spontaneous mutations of the *NF1* gene.

A second mechanism responsible for an inherited predisposition to develop cancer involves defects in DNA repair. Syndromes associated with an excessive number of broken chromosomes due to repair defects include **Bloom syndrome** (short stature, photosensitive telangiectatic erythema), ataxia-telangiectasia (childhood ataxia with progressive neuromotor degeneration), and **Fanconi anemia** (short stature, skeletal and renal anomalies, pancytopenia). As a result of the decreased ability to repair chromosomal defects, cells accumulate abnormal DNA that results in significantly increased rates of cancer, especially leukemia. **Xeroderma pigmentosum** likewise increases the risk of skin cancer, owing to defects in repair to DNA damaged by ultraviolet light. These disorders display an autosomal recessive pattern.

Table 492-2 Familial or Genetic Susceptibility to Malignancy

DISORDER	TUMOR/CANCER	COMMENT
CHROMOSOMAL SYNDROMES		
Chromosome 11p deletion syndrome with sporadic aniridia	Wilms tumor	Associated with genitourinary anomalies, mental retardation, *WT1* gene
Chromosome 13q deletion syndrome	Retinoblastoma, sarcoma	Associated with intellectual disability, skeletal malformations; autosomal dominant (bilateral) or sporadic new mutations, *RB1* gene
Trisomy 21	Lymphocytic or nonlymphocytic leukemia, especially megakaryocytic leukemia; transient leukemoid reaction	Risk of ALL is increased 20%; risk of AML is increased 400%; patients have an increased sensitivity to chemotherapy
Klinefelter syndrome (47,XXY)	Breast cancer, extragonadal germ cell tumors	
Trisomy 8	Preleukemia	
Noonan syndrome	JMML	Autosomal dominant; mutations in *PTPN11* gene
Monosomy 5 or 7	Myelodysplastic syndrome	Recurrent infections may precede neoplasia
CHROMOSOMAL INSTABILITY		
Xeroderma pigmentosum	Basal cell and squamous cell carcinomas; melanoma	Autosomal recessive; failure to repair UV-damaged DNA. Mutations in *XP* gene on chromosome 3p25
Fanconi anemia	Leukemia, myelodysplastic syndrome, liver neoplasias, rare head and neck tumors, GI and GU cancers	Autosomal recessive; chromosome fragility; positive diepoxybutane test result. Mutations in *FANCX* gene family
Bloom syndrome	Leukemia, lymphoma, and solid tumors	Autosomal recessive; increase sister chromatid exchange; mutations in *BLM* gene; member of the RecQ helicase gene
Ataxia-telangiectasia	Lymphoma, leukemia, less commonly central nervous system and nonneural solid tumors	Autosomal recessive; sensitive to X-irradiation, radiomimetic drugs; mutation in *ATM* tumor-suppressor gene
Dysplastic nevus syndrome	Melanoma	Autosomal dominant; some cases associated with mutations in *CDKN2A* gene
Rothmund-Thompson syndrome	Osteosarcoma; skin cancers	Autosomal recessive; mutation in RecQ helicase gene family
Werner syndrome (premature aging)	Soft tissue sarcomas	Autosomal recessive; mutation in the *WRN* gene; member of the RecQ helicase gene family
IMMUNODEFICIENCY SYNDROMES		
Wiskott-Aldrich syndrome	Lymphoma, leukemia	X-linked recessive; *WAS* gene mutation (Xp11.22-23); WASP protein functions in signal transduction associated with cytoskeletal actin filament rearrangement
X-linked immunodeficiency (Duncan syndrome)	Lymphoproliferative disorder	X-linked; Epstein-Barr viral infection can result in fatal outcome; mutation in *SH2D1A* gene locus
X-linked agammaglobulinemia (Bruton disease)	Lymphoma, leukemia	X-linked; mutation in *BKT* gene resulting in absence of mature B cells
Severe combined immunodeficiency	Leukemia, lymphoma	X-linked; mutations in *ADA* gene

Table 492-2 Familial or Genetic Susceptibility to Malignancy—cont'd

DISORDER	TUMOR/CANCER	COMMENT
OTHERS		
Neurofibromatosis 1	Neurofibroma, optic glioma, acoustic neuroma, astrocytoma, meningioma, pheochromocytoma, sarcoma	Autosomal dominant; mutation in tumor-suppressor gene, *NF1*
Neurofibromatosis 2	Bilateral acoustic neuromas, meningiomas	Autosomal dominant; mutation in tumor-suppressor gene, *NF2*
Tuberous sclerosis	Fibroangiomatous nevi, myocardial rhabdomyoma	Autosomal dominant
Gorlin-Goltz syndrome (nevus basal cell carcinoma syndrome)	Multiple basal cell carcinomas; medulloblastoma	Autosomal dominant; mutation in *PTCH* gene
Li-Fraumeni syndrome	Bone, soft tissue sarcoma, breast	Mutation of *P53* tumor-suppressor gene, autosomal dominant
Retinoblastoma	Sarcoma	Autosomal recessive; increased risk of secondary malignancy 10-20 yr later; mutation in *RB* tumor-suppressor gene
Hemihypertrophy ± Beckwith syndrome	Wilms tumor, hepatoblastoma, adrenal carcinoma	*WT1* gene; 25% develop tumor, most in 1st 5 yr of life
von Hippel-Landau disease	Hemangioblastoma of the cerebellum and retina, pheochromocytoma, renal cancer	Autosomal dominant; mutation of tumor-suppressor gene, *VHL* gene
Multiple endocrine neoplasia syndrome, type 1 (Wermer syndrome)	Parathyroid, pancreatic islet, and pituitary tumors	Autosomal dominant; mutation in *PYGM* tumor-suppressor gene
Multiple endocrine neoplasia syndrome, type 2A (Sipple syndrome)	Medullary carcinoma of the thyroid, hyperparathyroidism, pheochromocytoma	Autosomal dominant; mutations in CYS-rich regions of the *RET* gene activate this protooncogene; *RET* codes for a tyrosine kinase; monitor calcitonin and calcium levels
Multiple endocrine neoplasia type 2B (multiple mucosal neuroma syndrome)	Mucosal neuroma, pheochromocytoma, medullary thyroid carcinoma, Marfan habitus; neuropathy	Autosomal dominant; mutation in catalytic site (codon 883 or 914) activates protooncogene; *RET* codes for a tyrosine kinase
Familial adenomatous polyposis	Colorectal, thyroid carcinoma, duodenal and periampullar carcinomas; pediatric hepatoblastoma	Autosomal dominant; mutation in *APC* gene
Familial juvenile polyposis	Colorectal carcinoma	Autosomal dominant; mutation in *SMAD4* gene
Hereditary nonpolyposis colon cancer (Lynch syndrome, NHPCC)	Colon cancer	Autosomal dominant; mutation in mismatch repair genes; *hMSH2, hMLH1, PMS1, PMS2, hMSH6, hMSG3*
Turcot syndrome	Pediatric brain tumors and increased risk of colon carcinoma and polyps	Mutation in *APC* gene
Familial adenomatous polyposis coli	Adenocarcinoma of colon	Autosomal dominant, *APC* gene
Gardner syndrome	Adenocarcinoma of colon, skull and soft tissue tumors	Autosomal dominant, *APC* gene
Peutz-Jeghers syndrome	Gastrointestinal carcinoma, ovarian neoplasia	Autosomal dominant, *LKB1* gene codes for a Ser/Thr kinase that regulates cell cycle, metabolism, cell polarity
Hemochromatosis	Hepatocellular carcinoma	Autosomal dominant; malignancy associated with cirrhotic liver
Glycogen storage disease 1 (von Gierke disease)	Hepatocellular carcinoma	Autosomal recessive; malignancy associated with cirrhotic liver Mutation in glucose-6-phosphatase or glucose-6-phosphatase translocase genes
Tyrosinemia, galactosemia	Hepatocellular carcinoma	Autosomal recessive; tumor associated with cirrhotic liver
BRCA1 and *BRCA2*	Breast, ovarian	DNA repair defect
Diamond-Blackfan anemia	AML, myelodysplastic syndrome, osteogenic sarcoma	Autosomal dominant; family 9 genes encoding ribosomal proteins
Shwachman-Diamond syndrome	AML, myelodysplasia	Autosomal recessive; *SBDS* gene; chromosome 7q11.21
Hereditary diffuse gastric cancer	Gastric cancer	Autosomal dominant; *CDH1* gene
Pleuropulmonary blastoma family tumor and dysplasia syndrome (DICER1)	Pulmonary blastoma	Encoded protein is a ribonuclease required for microRNA processing
Hereditary neuroblastoma	Neuroblastoma	Two genes have been identified: • Anaplastic lymphoma kinase *(ALK)* at chromosome 2p23 • Paired-like homeobox 2b *(PHOX2B)* at chromosome 4q12
Hereditary paraganglioma–pheochromocytoma syndrome	Paraganglioma Pheochromocytomas	Mutation in the mitochondrial enzyme succinate dehydrogenase protein (SDH)
Congenital or cyclic neutropenia	Myelodysplastic syndrome AML	*ELANE* mutation at 19p13.3; elastase; neutrophil expressed

ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; GI, gastrointestinal; GU, genitourinary; JMML, juvenile myelomonocytic leukemia; NHPCC, nonhereditary polyposis colon cancer.

The third category of inherited cancer predisposition is characterized by **defects in immune surveillance**. This group includes patients with Wiskott-Aldrich syndrome, severe combined immunodeficiency, common variable immunodeficiency, and the X-linked lymphoproliferative syndrome. The most common types of malignancy in these patients are lymphoma and leukemia. Cure rates for immunodeficient children with cancer are much poorer than for nonimmunodeficient children with similar malignancies, suggesting a role for the immune system in cancer treatment as well as in cancer prevention.

OTHER FACTORS ASSOCIATED WITH ONCOGENESIS

Viruses

Several viruses have been implicated in the pathogenesis of malignancy. The association of the Epstein-Barr virus (EBV) with Burkitt lymphoma and nasopharyngeal carcinoma was identified more than 30 yr ago, but EBV infection alone is not sufficient for malignant transformation. EBV is also associated with mixed cellularity and lymphocyte-depleted Hodgkin disease, as well as some T-cell lymphomas, which is particularly intriguing because EBV normally does not infect T lymphocytes. The most conclusive evidence for a role of EBV in lymphogenesis is the direct causal role of EBV for B-cell lymphoproliferative disease in immunocompromised persons, especially those with AIDS.

Children who are chronically infected with hepatitis B (hepatitis B surface antigen–positive) have a >200-fold increased risk of developing hepatocellular carcinoma. In adults, the latency period between viral infection and the development of hepatocellular carcinoma approaches 20 yr. However, in children who acquire the viral infection through perinatal transmission, the latency period can be as short as 6-7 yr. The additional factors that are required for the malignant transformation of the virally infected hepatocytes are not clear. Hepatitis C virus infection is another risk factor for hepatocellular carcinoma and is also associated with splenic lymphoma.

Nearly all cervical carcinomas contain human papillomavirus (HPV). High-risk HPVs include types 16 and 18 but also types 31, 33, 35, 45, and 56, which are also commonly found in women without lesions. The low-risk HPVs, including 6 and 11 that are commonly found in genital warts, are almost never associated with malignancies. Like other virus-associated cancers, the presence of HPV alone is not sufficient to cause malignant transformation. The mechanism by which HPV 19 induces malignant transformation is thought to involve *P53* and *RB* tumor-suppressor genes, which regulate the cell cycle by acting as gatekeepers of the G1/S and G2/M checkpoints. By interfering with these proteins, HPV alters the regulation of cell growth.

Human herpesvirus 8 is associated with Kaposi sarcoma, primary effusion B-cell lymphoma, and the plasma cell variant of Castleman disease, all of which occur primarily in persons with AIDS. Human T-cell leukemia virus 1 is associated with adult T-cell leukemia and lymphoma.

Genomic Imprinting

The development of cancer has also been linked to genomic imprinting, which is the selective inactivation of 1 of 2 alleles of a certain gene. The inactivated gene is determined by whether the gene is inherited from the mother or father. For example, normally the maternal *IGF2* (insulin-like growth factor receptor 2) gene is inactivated. The inactivation is thought to be secondary to methylation of specific CpG sequences upstream of the *IGF2* promoter, which interferes with the transcription of the *IGF2* gene. In some Wilms tumors, there is loss of methylation in the upstream area of the maternal gene, which, in turn, allows transcript expression of the maternal *IGF2* gene. At the same time the *H19* gene (whose function is not yet clear), a previously actively transcribed maternal gene, is silenced by methylation. Beckwith-Wiedemann syndrome, an overgrowth syndrome characterized by macrosomia, macroglossia, hemihypertrophy, omphalocele, and renal anomalies, is associated with an increased risk of Wilms tumor, hepatoblastoma, rhabdomyosarcoma, neuroblastoma, and adrenal cortical carcinoma. The increased risk in developing cancer is associated with changes in the methylation pattern of genes on the 11p15 chromosome. Studies indicate that methylation patterns in a given individual change over time and that specific groups of methylation changes tend to cluster within families, suggesting heritability of the pattern of changes.

Telomerase

Telomeres are a series of tens to thousands of TTAGGG repeats at the ends of chromosomes that are important for stabilizing the chromosomal ends and limiting breakage, translocation, and loss of DNA material. With DNA replication there is a progressive shortening of telomere length, which is a hallmark of cellular aging and may be a senescence signal. In some instances telomerase, an enzyme that adds telomeres to the ends of chromosomes, becomes active. The addition of telomeres can be found in immortalized cell lines and most tumor types, and as a consequence, these cells might have a survival advantage, allowing them to undergo additional cell divisions. Therapy aimed at inhibiting telomerase activity can result in cell death.

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Chapter 493

Principles of Diagnosis

A. Kim Ritchey and Erika Friehling

Childhood cancer is uncommon and can manifest with symptoms seen with benign illnesses. The challenge for the pediatrician is to be alert to the clues suggesting a diagnosis of cancer. In addition to the classic manifestations, any persistent, unexplained symptom or sign should be evaluated as potentially emanating from a cancerous or precancerous condition. As part of the diagnostic evaluation, the pediatrician and pediatric oncologist must convey the possible diagnosis to the patient and family in a sensitive and informative manner.

SIGNS AND SYMPTOMS

The symptoms and signs of cancer are variable and nonspecific in pediatric patients. The types of cancer that occur during the 1st 20 yr of life vary dramatically as a function of age—more so than at any other comparable age range (see Chapter 491). Unlike cancers in adults, childhood cancers usually originate from the deeper, visceral structures and from the parenchyma of organs rather than from the epithelial layers that line the ducts and glands of organs and compose the skin. In children, dissemination of disease at diagnosis is common, and presenting symptoms or signs are often caused by systemic involvement. Pain was one of the initial presenting symptoms in more than 50% of children with cancer in one study. Infants and young children cannot express or localize their symptoms well. Another factor is the variability in the physiology and biology of the host that are related to growth and development during infancy, childhood, and adolescence.

The signs of cancer in children are often attributed to other causes before the malignancy is recognized. Delays in diagnosis are particularly problematic during late adolescence and are the result of a variety of factors prominent in this age group, including loss of health insurance coverage.

Although there is no clearly established set of warning signs of cancer in young people, the most common cancers in children suggest some guidelines that may be helpful in early recognition of signs and symptoms of cancer (Table 493-1). Most of the symptoms and signs are not specific and might represent other possibilities in a differential diagnosis. Nonetheless, these hints encompass the common cancers of childhood and have been very useful in early detection.

Table 493-1 Common Manifestations of Childhood Malignancies

	SIGNS AND SYMPTOMS	POTENTIAL ETIOLOGY	POSSIBLE ONCOLOGIC DIAGNOSIS
Constitutional/Systemic	Fever, persistent or recurrent infection, neutropenia	Bone marrow infiltration	Leukemia, neuroblastoma
	Fever of unknown origin, weight loss, night sweats	Lymphoma	Hodgkin and non-Hodgkin lymphoma
	Painless lymphadenopathy	Lymphoma, metastatic solid tumor	Leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, thyroid carcinoma
	Hypertension	Renal or adrenal tumor	Neuroblastoma, pheochromocytoma, Wilms tumor
	Soft tissue mass	Local or metastatic tumor	Ewing sarcoma, osteosarcoma, neuroblastoma, thyroid carcinoma, rhabdomyosarcoma, Langerhans cell histiocytosis
Neurologic/Ophthalmologic	Headache with emesis, visual disturbances, ataxia, papilledema, cranial nerve palsies	Increased intracranial pressure	Primary brain tumor; metastasis
	Leukokoria (white pupil)	Retinal mass	Retinoblastoma
	Periorbital ecchymosis	Metastasis	Neuroblastoma
	Miosis, ptosis, heterochromia	Horner syndrome: compression of cervical sympathetic nerves	Neuroblastoma
	Opsoclonus myoclonus, ataxia	Neurotransmitters? Autoimmunity?	Neuroblastoma
	Exophthalmos, proptosis	Orbital tumor	Rhabdomyosarcoma, lymphoma, Langerhans cell histiocytosis
Respiratory/Thoracic	Cough, stridor, pneumonia, tracheal-bronchial compression; superior vena cava syndrome	Anterior mediastinal mass	Germ cell tumor, non-Hodgkin lymphoma, Hodgkin lymphoma
	Vertebral or nerve root compression; dysphagia	Posterior mediastinal mass	Neuroblastoma, neuroenteric cyst
Gastrointestinal	Abdominal mass	Adrenal, renal, or lymphoid tumor	Neuroblastoma, Wilms tumor, lymphoma
	Diarrhea	Vasoactive intestinal polypeptide	Neuroblastoma, ganglioneuroma
Hematologic	Pallor, anemia	Bone marrow infiltration	Leukemia, neuroblastoma
	Petechiae, thrombocytopenia	Bone marrow infiltration	Leukemia, neuroblastoma
Musculoskeletal	Bone pain, limp, arthralgia	Primary bone tumor, metastasis to bone	Osteosarcoma, Ewing sarcoma, leukemia, neuroblastoma
Endocrine	Diabetes insipidus, galactorrhea, poor growth	Neuroendocrine involvement of hypothalamus or pituitary gland	Adenoma, craniopharyngioma, prolactinoma, Langerhans cell histiocytosis

Modified from Marcdante KJ, Kliegman RM, Jenson HB, et al, editors: Nelson essentials of pediatrics, *ed 6, Philadelphia, 2011, WB Saunders, p. 588.*

PHYSICAL EXAMINATION

Physical examination findings in a child with malignancy are dependent on whether the cancer is systemic (see Table 493-1) or localized. The cancers most common in children involve the lymphohematopoietic system. When the bone marrow is compromised by malignancy (e.g., leukemia, disseminated neuroblastoma), typical findings include pallor from anemia; bleeding, petechiae, or purpura from thrombocytopenia or coagulopathy; cellulitis or other localized infection from leukopenia; skin nodules (especially in infants) and hepatosplenomegaly from malignant leukocytosis. Abnormalities found in lymphatic malignancies include peripheral adenopathy (Fig. 493-1) and signs of superior vena cava syndrome from an anterior mediastinal mass (Fig. 493-2), including respiratory distress, and facial and neck plethora and edema. Enlargement of cervical lymph nodes is common in children, but when persistent, progressive, and painless it often suggests lymphoma. In particular, supraclavicular adenopathy suggests underlying malignancy.

Abnormalities of the central nervous system that can indicate cancer include decreased level of consciousness, cranial nerve palsies, ataxia, afebrile seizures, ptosis, decreased visual activity, neuroendocrine deficits, and increased intracranial pressure, which may be diagnosed by the presence of papilledema (Fig. 493-3). Any focal neurologic deficit in the motor or sensory system, especially a decrease in cranial nerve function, should prompt further investigation for malignancy.

Abdominal masses can be divided into upper, middle, and lower locations. Malignancies in the upper abdomen include Wilms tumor, neuroblastoma, hepatoblastoma, germ cell tumors, and sarcomas. Enlargement of the liver or spleen from leukemia can be mistaken for an upper abdominal mass. Midabdominal masses include non-Hodgkin lymphoma, neuroblastoma, germ cell tumors, and sarcomas. Lower abdominal masses include ovarian tumors, germ cell tumors, and sarcomas.

Rhabdomyosarcoma commonly appears as an extremity mass, particularly in adolescents. These tumors can be deceptively benign in appearance, but as with all unexplained masses they require immediate attention. Sacrococcygeal masses in neonates are usually teratomas, which are usually benign but can undergo malignant transformation if not removed promptly. Neuroblastoma can present as "blueberry muffin" spots on the skin of neonates or as periorbital ecchymosis in older children.

Ophthalmologic presentation of malignancy includes a white pupillary reflex (Fig. 493-4) rather than the usual red reflection from

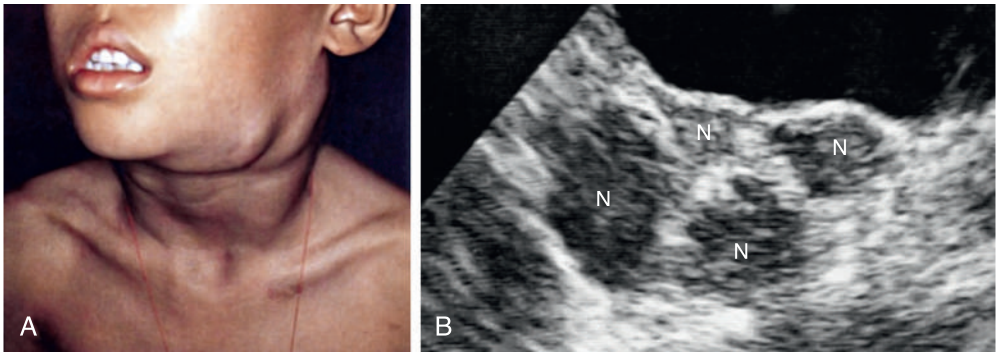

Figure 493-1 **Cervical lymphadenopathy.** Manifestations on physical examination **(A)** and on ultrasound examination **(B).** *N,* Abnormally enlarged lymph nodes. *(From Sinniah D, D'Angio GJ, Chatten J, et al:* Atlas of pediatric oncology, *London, 1996, Arnold.)*

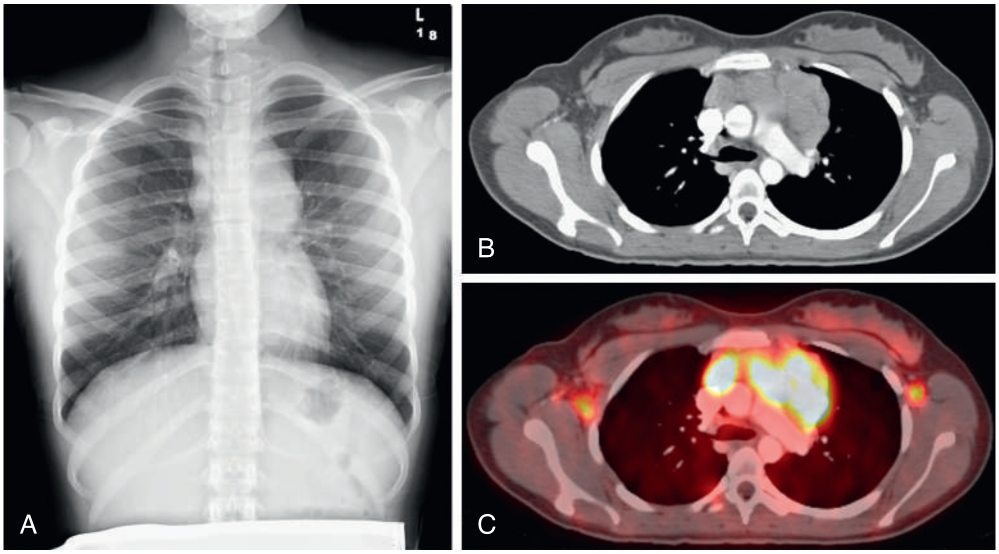

Figure 493-2 **Anterior upper mediastinal mass from non-Hodgkin lymphoma. A,** Plain chest X-ray. **B,** CT scan. **C,** Positron emission tomography (PET) scan.

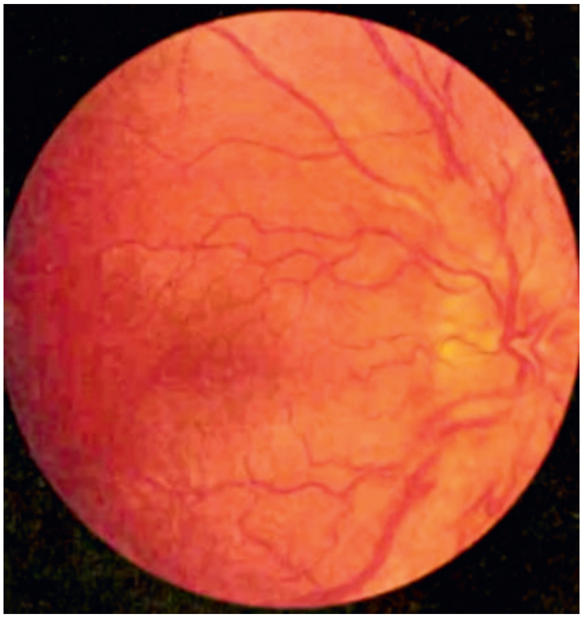

Figure 493-3 **Papilledema on funduscopic examination.** *(From Sinniah D, D'Angio GJ, Chatten J, et al:* Atlas of pediatric oncology, *London, 1996, Arnold.)*

Figure 493-4 **White pupillary reflex in the left eye.** *(From Sinniah D, D'Angio GJ, Chatten J, et al:* Atlas of pediatric oncology, *London, 1996, Arnold.)*

incident light. A white pupillary reflex is essentially pathognomonic for retinoblastoma, although some benign conditions can mimic this finding. Proptosis can be produced by rhabdomyosarcoma, neuroblastoma, lymphoma, and Langerhans cell histiocytosis. Horner syndrome, iris heterochromia, and opsoclonus-myoclonus all suggest a diagnosis of neuroblastoma.

AGE-RELATED MANIFESTATIONS

Because various types of cancer in children occur at specific ages, the physician should tailor the history and physical examination based on the age of the child. The embryonal tumors, including neuroblastoma, Wilms tumor, retinoblastoma, hepatoblastoma, and rhabdomyosarcoma, usually occur during the 1st 2 yr of life (see Fig. 491-4). From 1-4 yr of age, acute lymphoblastic leukemia peaks in incidence. Brain tumors have a peak incidence in the 1st decade of life. Non-Hodgkin lymphomas are uncommon earlier than 5 yr of age but steadily increase thereafter. During adolescence, bone tumors, Hodgkin disease, and the gonadal and soft tissue sarcomas predominate. Hence, for infants and toddlers, special attention should be paid to the possibility of embryonal and intraabdominal tumors. Preschool-age and early school-age children showing compatible signs and symptoms should be specifically evaluated for leukemia. School-age children might present with lymphoma or with brain tumors. Adolescents require assessment for bone and soft tissue sarcomas and gonadal malignancies, as well as for Hodgkin lymphoma.

EARLY DETECTION

The prognosis of malignancy in children depends primarily on tumor type, extent of disease at diagnosis, and rapidity of response to treatment. Early diagnosis helps to ensure that appropriate therapy is given in a timely fashion and hence optimizes the chances of cure. Because most physicians in general practice rarely encounter children with undiagnosed cancer, they should remember to investigate the possibility of malignancy, especially when they encounter an atypical course of a common childhood condition, unusual manifestations that do not fit common conditions, and any persistent symptom that defies diagnosis.

Delays in diagnosis are particularly likely in certain clinical situations. The cardinal symptom of both osteosarcoma and Ewing sarcoma is localized and usually persistent pain. Because these tumors occur during the 2nd decade of life, a time of increased physical activity, patients often assume the pain results from trauma. Prompt radiologic evaluation can help confirm the diagnosis. Lymphoma, especially during adolescence, often manifests as an anterior mediastinal mass. Symptoms such as chronic cough, unexplained shortness of breath, or "new-onset asthma" are typical with this presentation and are often overlooked. Tumors of the nasopharynx or middle ear can mimic infection. Prolonged, unexplained ear pain, nasal discharge, retropharyngeal swelling, and trismus should be investigated as possible signs of malignancy.

Early symptoms of leukemia may be limited to prolonged or unexplained low-grade fever or bone and joint pain. Blood counts with abnormalities in two or more cell lines might indicate the need for bone marrow examination, even when leukemic blast cells are not seen in the blood smear (see Table 493-1).

Mass screening for children with malignancy is not feasible. A screening program to detect early-stage neuroblastoma was successful in documenting more cases of the disease, but it had no impact on overall outcome. However, certain children are at increased risk for cancer and require an individualized plan to ensure early detection of malignancy. Selected examples include children with certain chromosome abnormalities, such as Down syndrome, Klinefelter syndrome, WAGR syndrome (Wilms tumor, aniridia, genital abnormalities, and mental retardation); children with overgrowth syndromes, such as Beckwith-Wiedemann syndrome, and hemihypertrophy; children with certain inherited single-gene disorders, including retinoblastoma, *P53* mutations (Li-Fraumeni syndrome), familial adenomatous polyposis, and neurofibromatosis (see Table 492-2).

ENSURING THE DIAGNOSIS

When a malignant neoplasm is suspected, the immediate goal is to confirm the diagnosis. A tentative diagnosis can often be established on the basis of the patient's age, symptoms, and location of masses. Selected imaging techniques and tumor markers can facilitate the diagnostic approach (Table 493-2). Especially when a solid tumor is present,

Table 493-2 Work-up of Common Pediatric Malignancies to Assess Primary Tumor and Potential Metastases

MALIGNANCY	BONE MARROW ASPIRATE OR BIOPSY	CHEST X-RAY	CT SCAN	MRI	PET SCAN	BONE SCAN	CSF ANALYSIS	SPECIFIC MARKERS	OTHER TESTS
Leukemia	Yes (includes flow cytometry, cytogenetics, molecular studies)	Yes	—	—	—	—	Yes	—	—
Non-Hodgkin lymphoma	Yes (includes flow cytometry, cytogenetics, molecular studies)	Yes	Yes	—	Yes	Yes (selected cases)	Yes	—	—
Hodgkin lymphoma	Yes (in advanced stage)	Yes	Yes	—	Yes	Yes (selected cases)	—	—	—
CNS tumors	—	—	—	Yes	—	—	Yes (selected tumors)	—	—
Neuroblastoma	Yes (includes cytogenetics, molecular studies)	—	Yes	—	—	Yes	—	VMA, HVA	MIBG scan; bone x-rays
Wilms tumor	—	Yes	Yes	—	—	—	—	—	—

Continued

Table 493-2 Work-up of Common Pediatric Malignancies to Assess Primary Tumor and Potential Metastases—cont'd									
MALIGNANCY	**BONE MARROW ASPIRATE OR BIOPSY**	**CHEST X-RAY**	**CT SCAN**	**MRI**	**PET SCAN**	**BONE SCAN**	**CSF ANALYSIS**	**SPECIFIC MARKERS**	**OTHER TESTS**
Rhabdomyosarcoma	Yes	Yes	Yes	Yes (selected sites)	—	Yes	Yes (for parameningeal tumors only)	—	—
Osteosarcoma	—	Yes	Yes (of chest)	Yes (for primary tumors)	—	Yes	—	—	—
Ewing sarcoma	Yes	Yes	Yes (of chest)	Yes (for primary tumors)	—	Yes	—	—	—
Germ cell tumors	—	Yes	Yes	Consider MRI of brain	—	—	—	AFP, HCG	—
Liver tumors	—	Yes	Yes	—	—	—	—	AFP	—
Retinoblastoma	Selected cases	—	Yes	Yes (includes brain)	—	Selected cases	Selected cases	—	—

AFP, α-Fetoprotein; CNS, central nervous system; CSF, cerebrospinal fluid; HCG, human chorionic gonadotropin; HVA, homovanillic acid; MIBG, metaiodobenzylguanidine; PET, positron emission tomography; VMA, vanillylmandelic acid.

Modified from Marcdante KJ, Kliegman RM, Jenson HB, et al, editors: Nelson essentials of pediatrics, *ed 6, Philadelphia, 2011, WB Saunders, p. 589.*

the pediatric oncologist, surgeon, and pathologist should work as a team to determine the site of biopsy, amount of tissue required, and whether fine-needle aspiration, percutaneous image-guided biopsy, incisional biopsy, or excisional biopsy and tumor resection are indicated. For selected situations, at the time of the initial diagnostic procedure, plans for bone marrow aspiration and biopsy and placement of central venous access may be appropriate.

Pathologic evaluation of pediatric malignancies requires appropriate handling of tissue so that multiple different techniques can be used. It is important that fresh tissue not be placed in formalin. Besides routine light microscopy, pathologic evaluation may include immunochemistry, flow cytometry, cytogenetics, and molecular genetic studies (fluorescence in situ hybridization, reverse-transcriptase polymerase chain reaction). Emerging technologies include DNA microarray analysis and cancer genome sequencing that can identify specific gene expression patterns and sequences in tumors. In time, these technologies might ensure more accurate classification and treatment.

STAGING

Once a specific diagnosis is confirmed, studies to define the extent of the malignancy are necessary to determine prognosis and treatment. Table 493-2 outlines the minimum evaluation required for common pediatric malignancies. In addition, for many tumors (e.g., Wilms tumor, neuroblastoma, rhabdomyosarcoma) a surgical staging system is used. Surgical stage can be determined at the time of the initial diagnostic procedure or subsequently. For example, a patient who has abdominal surgery for possible Wilms tumor or neuroblastoma should have careful evaluation and biopsy of all adjacent lymph nodes. A child with rhabdomyosarcoma can require a subsequent biopsy of sentinel lymph nodes as determined by scintigraphy or dye injection adjacent to the primary tumor. The pathologist facilitates staging by examining margins of the specimen to determine residual tumor.

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Chapter 494

Principles of Treatment

Archie Bleyer, A. Kim Ritchey, and Erika Friehling

Treatment of children with cancer begins with an absolute requirement for the correct diagnosis (including subtype), proceeds through accurate and thorough staging of the extent of disease and determination of prognostic subgroup, provides appropriate multidisciplinary and usually multimodal therapy, and requires assiduous evaluation of the possibilities of recurrent disease and of adverse late effects of the disease and the therapies rendered. Throughout treatment, every child with cancer should have the benefit of the expertise of specialized teams of providers of pediatric cancer care, including pediatric oncologists, pathologists, radiologists, surgeons, radiotherapists, nurses, and support staff, including nutritionists, social workers, psychologists, pharmacists, other medical specialists, and teachers trained to work with seriously ill children.

The best chance for cure of cancer is during the initial course of treatment; the cure rates for patients with recurrent disease are much lower than those for patients with primary disease. All patients with cancer should be referred to an appropriate specialized center as soon as possible when the diagnosis of cancer is suspected. All such centers in North America are identified on the Children's Oncology Group website (http://www.childrensoncologygroup.org) and on the National Cancer Institute cancer trials website (http://www.clinicaltrials.gov). The remarkable increases in cure rates for childhood malignancies since the 1970s would not have occurred without the collective participation of patients and their physicians in clinical research programs at these centers. In the United States, the National Cancer Institute's Clinical Trials Cooperative Groups Program is associated with a >80% reduction in the incidence of mortality from childhood cancer despite an overall increase in cancer incidence during this interval (Fig. 494-1). After what appeared to be a plateau in the rate of decline in mortality in the early 2000s, there is now evidence that the mortality rate

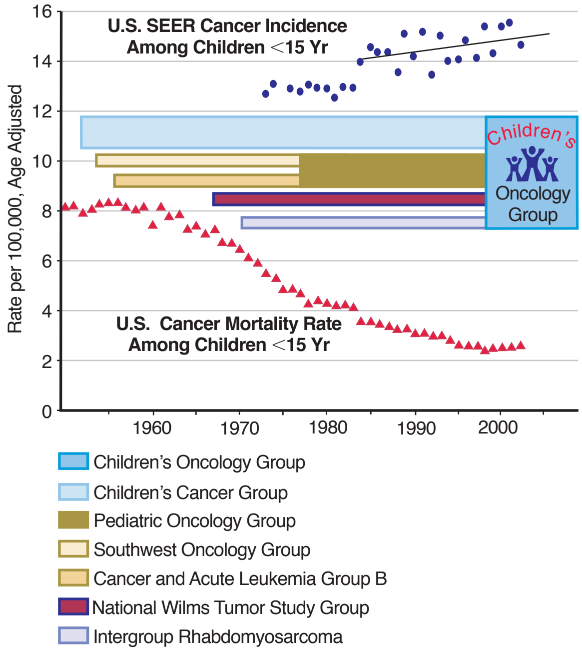

Figure 494-1 Reduction in the national cancer mortality rate among children younger than 15 yr of age *(triangles)* in the United States as a direct consequence of the National Cooperative Group Program sponsored by the National Cancer Institute, and in comparison to the rising incidence of cancer before age 15 yr *(circles)*. The *horizontal bars* indicate the duration of the existence of the national pediatric cancer cooperative groups, beginning with the Children's Cancer Group in 1955. Other groups are the Pediatric Oncology Group, which was derived from the Pediatrics Divisions of the Southwest Oncology Group and the Cancer and Acute Leukemia Group B, the National Wilms Tumor Study Group, and the Intergroup Rhabdomyosarcoma Study Group. In 2000, the 4 pediatric cooperative groups merged into the Children's Oncology Group. *(Incidence and mortality rate data from Ries LAG, Eisner MP, Kosary CL, et al, editors: SEER Cancer Statistics Review, 1975-2002, Bethesda, MD, National Cancer Institute;* http://seer.cancer.gov/csr/1975_2002/, *based on November 2004 SEER [Surveillance Epidemiology and End Results] data submission. The mortality rate data are national rates, and the incidence data are derived from the SEER program, representing approximately 15% of the United States. The most current information on treatment of all types of childhood cancer is available in the PDQ [Physician Data Query] on the National Cancer Institute website [http://www.cancer.gov/cancertopics/pdq/pediatrictreatment].)*

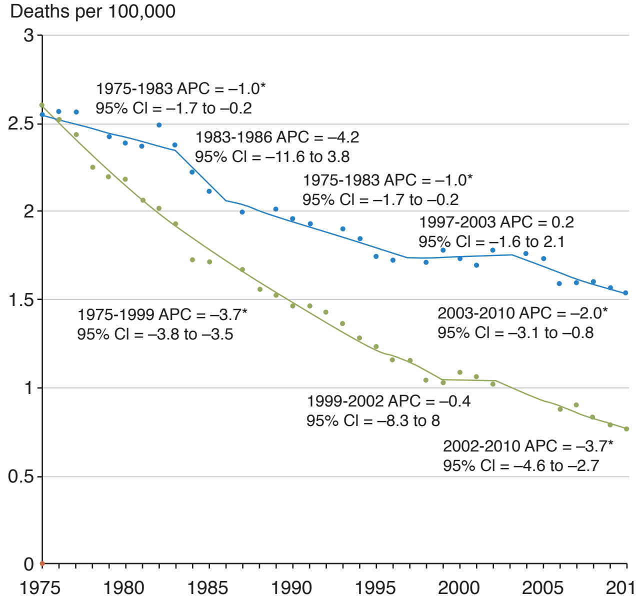

Figure 494-2 Age-adjusted mortality trends for all malignant cancers among children age <20 years in the United States from 1975 through 2010 along with annual percentage changes (APCs) for joinpoint segments. Asterisk indicates that the slope of the joinpoint segment is statistically different from zero ($P<.05$). The green line indicates leukemias and lymphomas, and the blue line indicates all other cancer sites. CI indicates confidence interval. *(From Smith MA, Altekruse SF, Adamson PC, et al: Declining childhood and adolescent cancer mortality,* Cancer *120:2497-2506, 2014.)*

continues to decline. Notably, a greater decline in mortality has been seen in the adolescent and young adult population when compared to children <15 yr old, reversing prior trends (Fig. 494-2). The most current information on treatment of all types of childhood cancer is available in the PDQ (Physician Data Query) on the National Cancer Institute website (http://www.cancer.gov/cancertopics/pdq/pediatrictreatment).

DIAGNOSIS AND STAGING

Accurate diagnosis and staging of the extent of disease are imperative, especially for childhood cancers that have high cure rates, because the nature of therapy depends strongly on the type of cancer. In addition, **prognostic subgroups** based on the stage of disease have been established for most cancers that occur in children. Accordingly, children with a better prognosis are treated with less-intensive therapy, including lower doses of chemotherapy or radiation therapy, a shorter duration of treatment, or elimination of at least one treatment modality (radiation therapy, chemotherapy, surgery). Accurate staging thus reduces the risk of excessive acute adverse effects and long-term complications of therapy in patients whose prognosis indicates that less therapy is required for cure. Overtreatment of patients with a more favorable prognosis is a definite risk if the patient is not referred to a cancer treatment center for management of adverse effects of such treatment. Conversely, undertreatment also is a clear risk if the diagnosis and stage are not correct, resulting in a compromise of an otherwise high potential for cure.

Diagnostic imaging is a critical phase of evaluation in most children with solid tumors (i.e., cancers other than leukemia). MRI, CT, ultrasonography, scintigraphy (nuclear medicine scans), positron emission tomography, and spectroscopy, as appropriate, all serve a clear purpose in the evaluation of children with cancer, not only before treatment to determine the extent of disease and the appropriate therapy but also during follow-up to determine whether the therapy was effective. In addition, response to treatment as determined by imaging techniques is being increasingly used to guide changes in the therapy.

Expertise in pathology and laboratory medicine provides critical diagnostic support and guides therapy in most children with cancer. Relatively noninvasive methods of obtaining tumor tissue (such as fine-needle aspiration and percutaneous image-guided biopsies) can be performed in pediatric centers with appropriate expertise in diagnostic imaging, interventional radiology, cytology, and anesthesia support. Sentinel node mapping is increasingly being applied in the staging of children's cancers. Determining the adequacy of surgery by evaluating frozen sections of the surgical margins for tumor cells is essential in many tumor operations.

A MULTIMODAL, MULTIDISCIPLINARY APPROACH

Many pediatric subspecialties are involved in the evaluation, treatment, and management of children with cancer, including provision of primary therapy and supportive care services (Fig. 494-3). More than two of the primary modalities are often used together, with chemotherapy being the most widely used, followed, in order of use, by surgery, radiation therapy, and biologic agent therapy (Fig. 494-4).

The leukemias that occur in childhood usually are managed with chemotherapy alone, with a small proportion of patients receiving cranial or craniospinal radiation therapy to prevent or treat overt central nervous system (CNS) leukemia. Children with non-Hodgkin

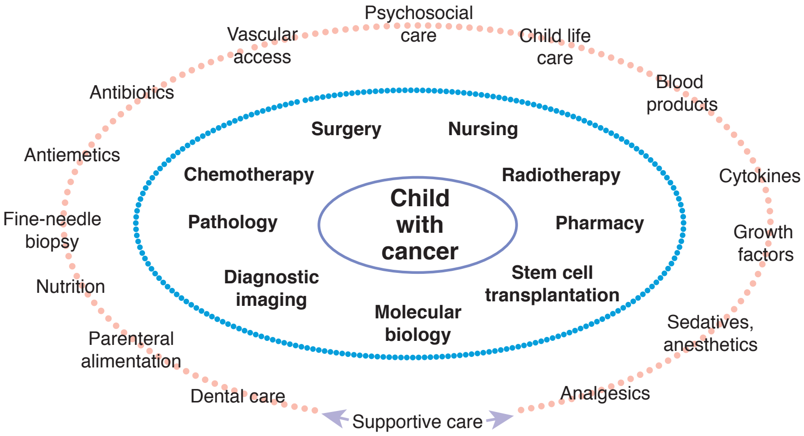

Figure 494-3 Multidisciplinary care of children with cancer. The *inner circle* designates primary modalities, and the *outer ring* identifies supportive care elements to which all children with cancer have access.

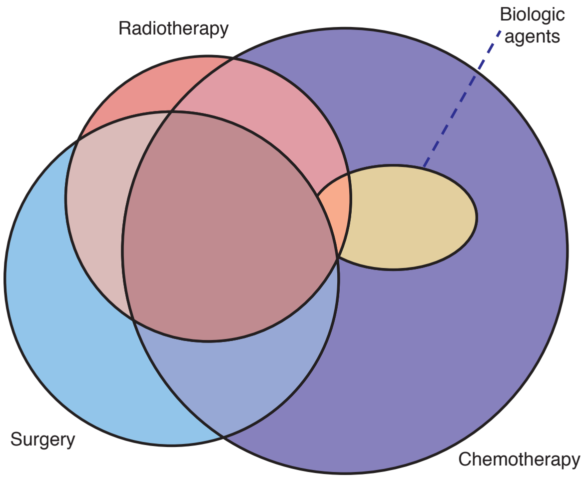

Figure 494-4 The primary modalities of therapy used in the treatment of children with cancer. The relative sizes of the circles designate the approximate proportion of overall role in the management of pediatric cancers.

lymphoma also are treated with chemotherapy alone, with the exception of radiation therapy for CNS involvement. Localized therapy with surgery or irradiation, or both, is an important component of treatment of most solid tumors, including Hodgkin lymphoma, but systemic multiagent chemotherapy usually is necessary because tumor dissemination generally is present even if it is undetectable. Chemotherapy alone usually is not adequate to eradicate gross residual tumors. Hence, it is not unusual for children with malignant tumors to require treatment with all 3 modalities (see Fig. 494-3). Unfortunately, most treatments that are effective in children with cancer have a narrow therapeutic index (a low ratio of efficacy to toxicity). The acute and chronic adverse effects of these treatments can be minimized but not entirely avoided.

Biologic agent therapy has become an important modality in a few childhood cancers (see Fig. 494-4). This type of treatment generally refers to immunotherapy, biologic response modifiers, or endogenously occurring molecules that have therapeutic effects in supraphysiologic doses. Examples are retinoic acid therapy in acute promyelocytic leukemia, monoclonal antibody therapy for neuroblastoma and certain non-Hodgkin lymphomas, tyrosine kinase inhibitors such as imatinib mesylate for chronic myelogenous and Philadelphia chromosome–positive leukemias, and radioactive metaiodobenzylguanidine therapy for neuroblastoma.

Chemotherapy is used more widely in children than in adults because children better tolerate the acute adverse effects and the malignant diseases that occur in childhood are more responsive to chemotherapy than are malignant diseases of adults. Radiation therapy is used sparingly in children because they are more vulnerable than adults to its late adverse effects.

Whenever possible, treatment is given on an outpatient basis. Children should remain living at home and in school as much as possible throughout treatment. Increasingly, pediatric cancer therapies are being administered to ambulatory patients, with the advent of such innovations as programmable infusion pumps, oral chemotherapeutic regimens, early discharge from hospital with intensive outpatient supportive care, and home healthcare services. Some patients miss a considerable amount of school in the 1st yr after diagnosis because of the intensity of therapy or its adverse effects and of the ensuing complications of the disease or therapy. Tutoring should be encouraged so that children do not fall behind in their schooling; counseling should be provided as appropriate. In-hospital school services should be provided for patients who must spend much of their time as inpatients receiving therapy for disease or for managing adverse effects.

Development of selective, highly effective therapy for cancer in both children and adults had been hindered by a lack of understanding of the molecular mechanisms that underlie malignant transformation. De novo or acquired resistance to chemotherapy and radiation therapy remains an obstacle to cure. Ongoing discoveries of molecular and cellular mechanisms that explain the cancer process have led to increasingly specific antineoplastic therapies, generally referred to as **molecularly targeted therapies.** Their most prominent feature is a relative lack of normal tissue toxicity, such that the additional therapeutic benefit occurs with minimum additional toxicity. Many of the new biologic agent therapies, such as imatinib and rituximab, fall into this category (Table 494-1). **Complementary** and **alternative remedies** are increasingly being provided by parents to their children with cancer, with or without knowledge of the medical professionals entrusted with the child's care (see Chapter 64). Many of these have not been evaluated by rigorous testing and most are ineffective; some are toxic or interfere with the metabolism of other drugs.

DISCUSSING THE TREATMENT PLAN WITH THE PATIENT AND FAMILY

The diagnostic and treatment plan must be carefully explained to parents and, if the child is old enough to understand, to the patient. An honest discussion of the facts is the best policy. Children should be given as much information as they can understand and would find useful or that information they express a desire or wish to know. Effects of treatment, such as the possible need to amputate a limb, loss of hair during chemotherapy, and possible temporary or permanent functional impairment must be anticipated and fully discussed. The possibility and probability of death from cancer should be covered in an age-appropriate manner. It usually is necessary to repeat explanations several times before distraught family members fully understand. Throughout treatment, parents, patients, siblings, and medical staff will need help in expressing feelings of anxiety, depression, guilt, and anger. The pediatrician, pediatric oncologist, and nurses should call on experienced professionals, including pediatric social workers, child

Table 494-1 Protein Tyrosine Kinase Inhibitors and Monoclonal Antibodies		
AGENT	**TARGET**	**MALIGNANCY**
Imatinib	BCR-ABL PDGFRα PDGFRβ cKIT	CML Philadelphia chromosome–positive ALL Hypereosinophilic syndrome Systemic mastocytosis CMML Systemic mastocytosis Gastrointestinal stromal tumor
Dasatinib, Nilotinib	BCR-ABL	CML Philadelphia chromosome–positive ALL
Gefitinib, Erlotinib, Cetuximab	EGFR	Non–small cell lung cancer
Rituximab	CD20	Non-Hodgkin lymphoma
Trastuzumab	ERBB2/HER-2	Breast cancer
Bevacizumab	VEGFR-1, -2	Non–small cell lung cancer Breast cancer Renal cell carcinoma Colorectal cancer Glioblastoma

ALL, Acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia.

psychologists and psychiatrists, child-life specialists, and schoolteachers with special expertise in managing students with cancer to assist when needed.

TREATMENTS

Chemotherapy

The most widely used modality in pediatric cancer therapy is chemotherapy (see Fig. 494-3). Therapy nearly always involves combinations of drugs, such as VAC (vincristine, dactinomycin [Actinomycin D], and cyclophosphamide) and CHOP (cyclophosphamide, doxorubicin [hydroxydaunorubicin/Adriamycin], vincristine [Oncovin], and prednisone). Sequential single-drug therapy rarely results in complete responses, and partial responses usually are infrequent and transient and grow progressively shorter in duration with each drug used. Combination chemotherapy is the standard when combinations of drugs with different mechanisms of action and non-overlapping toxicities were first demonstrated to be effective in childhood leukemia. Most of the cytotoxic drugs for childhood cancer are selected from several classes of agents, including alkylating agents, antimetabolites, antibiotics, hormones, plant alkaloids, and topoisomerase inhibitors (Table 494-2). The increased metabolic and cell-cycle activity of malignant cells makes them more susceptible to the cytotoxic effects of these types of agents (Fig. 494-5).

Because most antineoplastic agents are cell-cycle dependent, their adverse effects usually are related to the proliferation kinetics of individual cell populations. Most susceptible are tissues or organs with high rates of cell turnover: bone marrow, oral and intestinal mucosa, epidermis, liver, and spermatogonia. The most common acute adverse

Table 494-2 Common Chemotherapeutic Agents Used in Children

DRUG	MECHANISM OF ACTION OR CLASSIFICATION	INDICATION(S)	ADVERSE REACTIONS (PARTIAL LIST)	COMMENTS
Methotrexate	Folic acid antagonist; inhibits dihydrofolate reductase	ALL, non-Hodgkin lymphoma, osteosarcoma, Hodgkin lymphoma, medulloblastoma	Myelosuppression, mucositis, stomatitis, dermatitis, hepatitis With long-term administration; osteopenia and bone fractures With high-dose administration; renal and CNS toxicity With intrathecal administration; arachnoiditis, leukoencephalopathy, leukomyelopathy	Systemic administration may be PO, IM, or IV; also may be administered intrathecally Plasma methotrexate levels must be monitored with high-dose therapy and when low doses are administered to patients with renal dysfunction, and leucovorin rescue applied accordingly
6-Mercaptopurine (Purinethol)	Purine analog; inhibits purine synthesis	ALL	Myelosuppression, hepatic necrosis, mucositis; allopurinol increases toxicity	Allopurinol inhibits metabolism
Cytarabine (cytosine arabinoside; Ara-C)	Pyrimidine analog; inhibits DNA polymerase	ALL, AML, non-Hodgkin lymphoma, Hodgkin lymphoma	Nausea, vomiting, myelosuppression, conjunctivitis, mucositis, CNS dysfunction With intrathecal administration; arachnoiditis, leukoencephalopathy, leukomyelopathy	Systemic administration may be PO, IM, or IV; may also be administered intrathecally
Cyclophosphamide (Cytoxan)	Alkylates guanine; inhibits DNA synthesis	ALL, non-Hodgkin lymphoma, Hodgkin lymphoma, soft tissue sarcoma, Ewing sarcoma, Wilms tumor, neuroblastoma	Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, bladder cancer, anaphylaxis	Requires hepatic activation and thus is less effective in presence of liver dysfunction. Mesna prevents hemorrhagic cystitis
Ifosfamide (Ifex)	Alkylates guanine; inhibits DNA synthesis	Non-Hodgkin lymphoma, Wilms tumor, soft tissue sarcoma	Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, CNS dysfunction, cardiac toxicity, anaphylaxis	Mesna prevents hemorrhagic cystitis

Continued

Table 494-2 Common Chemotherapeutic Agents Used in Children—cont'd

DRUG	MECHANISM OF ACTION OR CLASSIFICATION	INDICATION(S)	ADVERSE REACTIONS (PARTIAL LIST)	COMMENTS
Doxorubicin (Adriamycin), daunorubicin (Cerubidine), and idarubicin (Idamycin)	Binds to DNA, intercalation	ALL, AML, osteosarcoma, Ewing sarcoma, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma	Nausea, vomiting, cardiomyopathy, red urine, tissue necrosis on extravasation, myelosuppression, conjunctivitis, radiation dermatitis, arrhythmia	Dexrazoxane reduces risk of cardiotoxicity
Dactinomycin	Binds to DNA, inhibits transcription	Wilms tumor, rhabdomyosarcoma, Ewing sarcoma	Nausea, vomiting tissue necrosis on extravasation, myelosuppression, radiosensitizer, mucosal ulceration	
Bleomycin (Blenoxane)	Binds to DNA, cleaves DNA strands	Hodgkin disease, non-Hodgkin lymphoma, germ cell tumors	Nausea, vomiting, pneumonitis, stomatitis, Raynaud phenomenon, pulmonary fibrosis, dermatitis	
Vincristine (Oncovin)	Inhibits microtubule formation	ALL, non-Hodgkin lymphoma, Hodgkin disease, Wilms tumor, Ewing sarcoma, neuroblastoma, rhabdomyosarcoma	Local cellulitis, peripheral neuropathy, constipation, ileus, jaw pain, inappropriate ADH secretion, seizures, ptosis, minimal myelosuppression	IV administration only; must not be allowed to extravasate
Vinblastine (Velban)	Inhibits microtubule formation	Hodgkin lymphoma, non-Hodgkin lymphoma, Langerhans cell histiocytosis, CNS tumors	Local cellulitis, leukopenia	IV administration only; must not be allowed to extravasate
L-Asparaginase	Depletion of L-asparagine	ALL; AML, when used in combination with cytarabine	Allergic reaction pancreatitis, hyperglycemia, platelet dysfunction and coagulopathy, encephalopathy	PEG-asparaginase now preferred to L-asparaginase
Pegaspargase (Oncaspar)	Polyethylene glycol conjugate of L-asparagine	ALL	Indicated for prolonged asparagine depletion and for patients with allergy to L-asparaginase	
Prednisone and dexamethasone (Decadron)	Lymphatic cell lysis	ALL; Hodgkin lymphoma, non-Hodgkin lymphoma	Cushing syndrome, cataracts, diabetes, hypertension, myopathy, osteoporosis, avascular necrosis, infection, peptic ulceration, psychosis	
Carmustine (BiCNU)	Carbamylation of DNA; inhibits DNA synthesis	CNS tumors, non-Hodgkin lymphoma, Hodgkin lymphoma	Nausea, vomiting, delayed myelosuppression (4-6 wk); pulmonary fibrosis, carcinogenic stomatitis	Phenobarbital increases metabolism, decreases activity
Carboplatin and cisplatin (Platinol)	Inhibits DNA synthesis	Osteosarcoma, neuroblastoma, CNS tumors, germ cell tumors	Nausea, vomiting, renal dysfunction, myelosuppression, ototoxicity, tetany, neurotoxicity, hemolytic-uremic syndrome, anaphylaxis	Aminoglycosides may increase nephrotoxicity
Etoposide (VePesid)	Topoisomerase inhibitor	ALL, non-Hodgkin lymphoma, germ cell tumor, Ewing sarcoma	Nausea, vomiting, myelosuppression, secondary leukemia	
Tretinoin (all *trans*-retinoic acid); and isotretinoin (cis-retinoic acid; Accutane)	Enhances normal differentiation	Acute promyelocytic leukemia; neuroblastoma	Dry mouth, hair loss, pseudotumor cerebri, premature epiphyseal closure, birth defects	

ADH, antidiuretic hormone; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CNS, central nervous system; PEG, polyethylene glycol.

effects are myelosuppression (with neutropenia and thrombocytopenia being the most problematic), immunosuppression, nausea and vomiting, hepatic dysfunction, upper and lower gastrointestinal mucositis, dermatitis, and alopecia. Fortunately, the tissues affected also recover relatively quickly, so that the acute adverse effects are nearly always reversible. Life-threatening effects of many chemotherapy agents include severe neutropenia with infection, fungemia or fungal pneumonia as a result of immunosuppression, and septicemia, not infrequently linked to indwelling intravascular devices (Table 494-3; see Chapters 178 and 179). Cardiomyopathy caused by anthracyclines (e.g., doxorubicin and daunorubicin) and renal failure from platinum-containing agents also may be life-threatening or disabling.

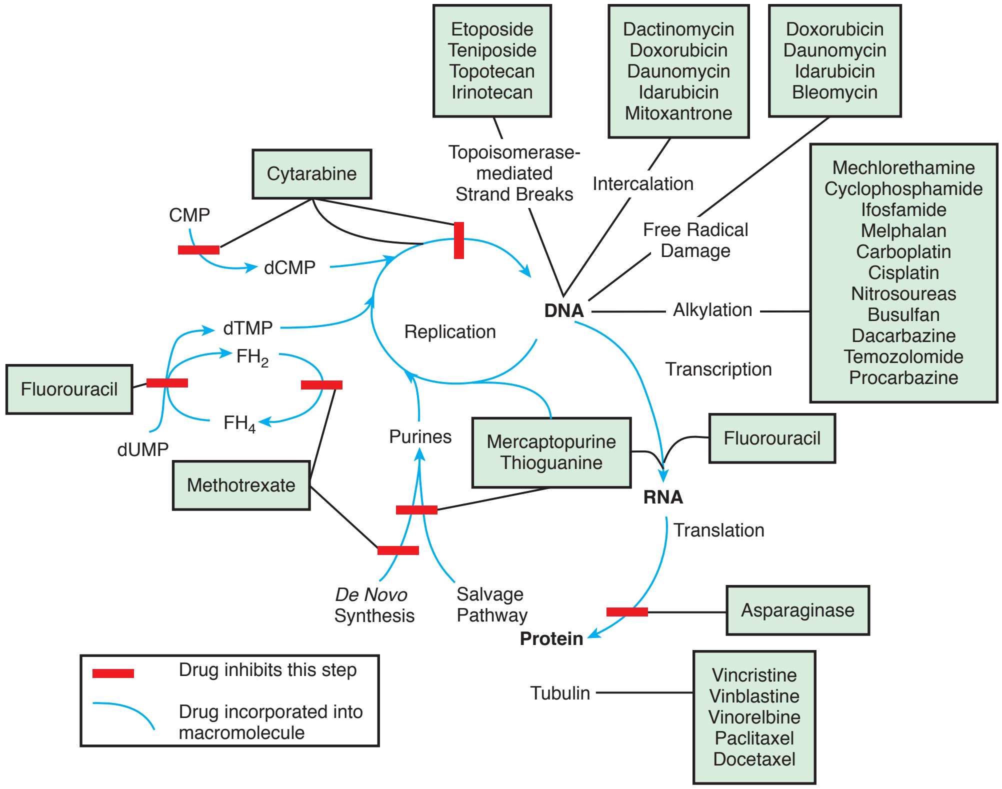

Figure 494-5 Site of action of the commonly used anticancer drugs. *CMP*, Cytidine monophosphate; *dCMP*, deoxycytidine monophosphate; *dTMP*, deoxythymidine monophosphate; *dUMP*, deoxyuridine monophosphate; *FH2*, dihydrofolate; *FH4*, tetrahydrofolate. *(Redrawn from Adamson PC, Balis FM, Blaney SM: General principles of chemotherapy. In Pizzo PA, Poplack DG, editors:* Principles and practice of pediatric oncology, *ed 6, Philadelphia, 2011, Lippincott Williams & Wilkins, p. 283.)*

Table 494-3 Infectious Complications of Malignancy

PREDISPOSING FACTOR	ETIOLOGY	SITE OF INFECTION	INFECTIOUS AGENTS
Neutropenia	Chemotherapy, bone marrow infiltration	Sepsis, shock, pneumonia, soft tissue, proctitis, mucositis	*Streptococcus viridans, Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa, Candida, Aspergillus,* anaerobic oral and rectal bacteria
Immunosuppression, lymphopenia, lymphocyte-monocyte dysfunction	Chemotherapy, corticosteroid	Pneumonia, meningitis, disseminated viral infection	*Pneumocystis jiroveci, Cryptococcus neoformans, Mycobacterium, Nocardia, Listeria monocytogenes, Candida, Aspergillus, Strongyloides, Toxoplasma,* varicella-zoster virus, cytomegalovirus, herpes simplex
Indwelling central venous catheter	Nutrition, administration of chemotherapy	Line sepsis, tract of tunnel, exit site	*S. epidermidis, S. aureus, Candida albicans, P. aeruginosa, Aspergillus, Corynebacterium, Streptococcus faecalis, Mycobacterium fortuitum, Propionibacterium acnes*

Modified from Kliegman RM, Marcdante KJ, Jenson HB, et al, editors: Nelson essentials of pediatrics, *ed 6, Philadelphia, 2011, WB Saunders, Chapter 121.*

Least susceptible to chemotherapy and radiation therapy are cells that do not replicate or that replicate slowly, such as neurons, muscle cells, connective tissue, and bone. However, children are not exempt from toxicities of these tissues, probably because they are still undergoing proliferation, albeit at a slower pace than other tissues, during growth and growth spurts.

Physically, children can endure the acute adverse effects of chemotherapy better than adults can in many ways. The maximum tolerated dosage in children, when expressed on the basis of body surface area or body weight, commonly is greater than that in adults. A comparison of anticancer drugs tested in phase I trials in both adult and pediatric patients showed that the maximum tolerated dosage in children was greater than that in adults for 70% of the agents, equal to that in adults for 15% of the agents, and less than the adult dose for only 15% of the agents. For all the drugs that were compared, the mean pediatric maximum tolerated dosage was greater than the adult mean.

Tumor-directed therapies are evolving in the field of pediatric oncology. Tumor antigen–specific monoclonal antibodies have been incorporated into the standard therapy of neuroblastoma (anti–ganglioside GD_2). The antiangiogenic agent bevacizumab (monoclonal antibody against vascular endothelial growth factor A) shows promise in the treatment of CNS tumors, especially low-grade gliomas.

Surgery

Superb pediatric surgical and anesthesia services are indispensable for children with cancer. The pediatric surgeon's role varies, depending on the type of tumor. For solid tumors, complete resection with

documented evidence of negative margins often is required for cure or long-term control. Considerable prolongation of life nearly always depends on whether the tumor is resectable and on the actual extent of resection.

With the exception of brainstem tumors and retinoblastoma, all solid tumors in children require a tissue diagnosis; therefore, biopsy of the suspected neoplasm is paramount. Staging with sentinel node biopsies has become the standard of care for several pediatric malignancies. Surgical expertise is essential for implantation of vascular access devices and removal and replacement of such devices when infection or thrombosis supervenes (see Chapter 179).

Increasingly, minimally invasive endoscopic surgical techniques are being used when indicated and, if the patient's condition permits, for biopsy and resection of tumor, direct ascertainment of residual disease and assessment of response, lysis of adhesions, and splenectomy.

Radiation Therapy

Radiation therapy is used sparingly in children, who are more susceptible than are adults to the adverse delayed effects of ionizing radiation. A major advance in pediatric radiation therapy is the application of **conformal irradiation** to children with cancer. This technique, most commonly applied as **intensity-modulated radiation therapy,** spares normal tissue by conforming the radiation volume to the shape of the tumor, thereby enabling delivery of higher doses to the tumor with lower exposure of normal tissue adjacent to the tumor or in the path of the radiation beam. Another example is proton-beam radiotherapy, which has just begun to be more widely available for children with cancer. With more focused beams and better sedation and immobilization techniques, radiation therapy is becoming more commonly used in children. Acute adverse effects from radiation therapy are less severe than those from chemotherapy and depend on which part of the body is irradiated and the means of administration. Dermatitis is the most common general adverse effect, because skin is always in the treatment field. Nausea and diarrhea are common subacute adverse effects with abdominal radiation therapy. Mucositis nearly always occurs to some extent whenever oral or intestinal mucosa is in the treatment volume. Somnolence is common with cranial irradiation. Alopecia occurs where hair is in the radiation field.

Most radiation therapy schedules require treatment 5 days per week for 4-7 wk, depending on the dose needed to control the tumor and on the amount and nature of normal tissue in the field. Most adverse effects are not noted until the second half of the course of irradiation. Late effects can occur months to years after radiation therapy and usually are dose-limiting manifestations. The type of delayed toxicity also depends on the site of irradiation. Examples are impaired growth resulting from cranial or vertebral irradiation, endocrine dysfunction from midbrain irradiation, pulmonary or cardiac insufficiency from chest irradiation, strictures and adhesions from abdominal irradiation, and infertility from pelvic irradiation. Second malignancy can also develop in the radiation field, for example, breast cancer from chest irradiation and brain tumors from CNS irradiation.

ACUTE TOXIC EFFECTS AND SUPPORTIVE CARE

Adverse treatment effects that occur early in therapy can result in oncologic emergencies. These include metabolic disorders, bone marrow suppression, and compression by tumors on vital structures (Table 494-4). In tumor lysis syndrome (TLS), uric acid, phosphates, and potassium are released in the circulation in large quantities from death of tumor cells. Hyperuricemia can lead to impairment of renal function, which further exacerbates the metabolic abnormalities. TLS can occur before therapy in patients with a large tumor burden (e.g., Burkitt lymphoma, lymphoblastic lymphoma, and high white blood cell count leukemia), but it is usually seen within 12-48 hr of initiating chemotherapy. TLS is infrequently reported in other tumors (Hodgkin lymphoma, neuroblastoma, hepatoblastoma). Before therapy is initiated, the serum levels of uric acid, electrolytes, calcium, phosphorus, and creatinine should be measured and adequate hydration ensured. Allopurinol (a xanthine oxidase inhibitor) should be started to prevent further accumulation of uric acid. In patients with established TLS with high uric acid levels or those at high risk for TLS, rasburicase (an enzyme that degrades uric acid) should be given instead of allopurinol. Symptomatic hyperkalemia and hyperphosphatemia with subsequent hypocalcemia can develop in the setting of inadequate renal function.

Virtually all chemotherapy regimens can produce **myelosuppression,** as can malignancies that invade and replace bone marrow. Anemia can be corrected by transfusions of packed erythrocytes, and thrombocytopenia can be corrected by platelet infusions. Patients receiving immunosuppressive therapy should receive irradiated blood products to prevent graft-versus-host disease and leukoreduced blood products to prevent transfusion-associated reactions and infections. Neutropenia (neutrophil counts <500/µL) poses a risk of life-threatening infection. Febrile neutropenic patients should be hospitalized and treated with empiric broad-spectrum intravenous antimicrobial therapy pending the results of appropriate cultures of blood, urine, or any obvious sites of infection (see Chapter 178). Treatment is continued until fever resolves and the neutrophil count rises. If fever persists for more than 3-5 days while the patient is receiving broad-spectrum antibiotics, the possibility of fungal infection must be considered. Fungal infections caused by *Candida* and *Aspergillus* are common in immunosuppressed patients. Opportunistic organisms such as *Pneumocystis jiroveci* can produce fatal pneumonia. Prophylactic treatment with trimethoprim-sulfamethoxazole is given when severe or prolonged immunosuppression is anticipated.

Viruses of low pathogenicity can produce serious disease in the setting of immunosuppression caused by malignancy or its treatment. Patients should not be given live virus vaccines. Children who are receiving chemotherapy and who are exposed to chickenpox should receive varicella-zoster immunoglobulin, or, if varicella-zoster immunoglobulin is not available, oral acyclovir should be considered. If clinical disease develops, the child should be hospitalized and treated with intravenous acyclovir.

Adequate **pain management** is critical. The World Health Organization (WHO) guidelines are particularly useful in the management of pain associated with cancer and cancer therapy (see Chapter 62).

Depending on the type of cancer therapy, patients can lose more than 10% of body weight. Patients sometimes reduce their food intake because of temporary, treatment-associated nausea, stomatitis, and vomiting. Appetite loss is not a cause for alarm. Malnutrition is a particular risk in patients receiving radiation therapy involving the abdomen or the head and neck, intensive chemotherapy, or total-body irradiation and high-dose chemotherapy before marrow transplantation. If oral supplementation proves inadequate, such patients can require enteral tube feedings or parenteral hyperalimentation.

LATE ADVERSE EFFECTS

Injury to tissues with low repair potential often results in long-lasting or permanent deficit. These effects can be either from the tumor or its treatment. For example, a brain or spinal tumor can leave the child with a permanent paresis or autonomic dysfunction, anthracycline-induced cardiomyopathy usually produces refractory cardiac dysfunction, and the leukoencephalopathy caused by intrathecal methotrexate and by CNS radiation therapy often is only partially reversible. The potential types of late adverse effects depend on the child's age at the time of treatment, the location(s) of the cancer, and the therapy administered. A good resource for the pediatrician, patient, and family who have to anticipate the possibilities is available at http://www.survivorshipguidelines.org.

Late adverse effects of therapy can cause substantial morbidity (Table 494-5). Successful surgical resection can result in loss of important functional structures. Irradiation can produce irreversible organ damage, with symptoms and functional limitations depending on the organ involved and the severity of the damage. Many problems related to radiation therapy do not become obvious until the patient is fully grown, such as asymmetry between irradiated and nonirradiated areas or extremities. Irradiation of fields that include endocrine organs can cause hypothyroidism, pituitary dysfunction, or infertility. In sufficient

Table 494-4 Oncologic Emergencies

CONDITION	MANIFESTATIONS	ETIOLOGY	MALIGNANCY	TREATMENT
METABOLIC				
Hyperuricemia	Uric acid nephropathy	Tumor lysis syndrome	Lymphoma, leukemia	Allopurinol, alkalinize urine; hydration and diuresis, rasburicase
Hyperkalemia	Arrhythmias, cardiac arrest	Tumor lysis syndrome	Lymphoma, leukemia	Kayexalate, sodium bicarbonate, glucose, and insulin; check for pseudohyperkalemia from leukemic cell lysis in test tube
Hyperphosphatemia	Hypocalcemic tetany; metastatic calcification, photophobia, pruritus	Tumor lysis syndrome	Lymphoma, leukemia	Hydration, forced diuresis; stop alkalinization; oral aluminum hydroxide to bind phosphate
Hyponatremia	Seizure, lethargy (may also be asymptomatic)	SIADH; fluid, sodium losses in vomiting	Leukemia, CNS tumor	Restrict free water for SIADH; replace sodium if depleted
Hypercalcemia	Anorexia, nausea, polyuria, pancreatitis, gastric ulcers; prolonged PR, shortened QT interval	Bone resorption; ectopic parathormone, vitamin D, or prostaglandins	Metastasis to bone, rhabdomyosarcoma, leukemia	Hydration and furosemide diuresis; corticosteroids; calcitonin, bisphosphonates
HEMATOLOGIC				
Anemia	Pallor, weakness, heart failure	Bone marrow suppression or infiltration; blood loss	Any with chemotherapy	Packed red blood cell transfusion
Thrombocytopenia	Petechiae, hemorrhage	Bone marrow suppression or infiltration	Any with chemotherapy	Platelet transfusion
Disseminated intravascular coagulation	Shock, hemorrhage	Sepsis, hypotension, tumor factors	Promyelocytic leukemia, others	Fresh-frozen plasma; platelets, cryoprecipitate, treat underlying disorder
Neutropenia	Infection	Bone marrow suppression or infiltration	Any with chemotherapy	If febrile, administer broad-spectrum antibiotics, and filgrastim (G-CSF) if appropriate
Hyperleukocytosis (>100,000/mm^3)	Hemorrhage, thrombosis; pulmonary infiltrates, hypoxia; tumor lysis syndrome	Leukostasis; vascular occlusion	Leukemia	Leukapheresis; chemotherapy; hydroxyurea
Graft-versus-host disease	Dermatitis, diarrhea, hepatitis	Immunosuppression and nonirradiated blood products; bone marrow transplantation	Any with immunosuppression	Corticosteroids; cyclosporine; tacrolimus; antithymocyte globulin
SPACE-OCCUPYING LESIONS				
Spinal cord compression	Back pain ± radicular *Cord above T10:* symmetric weakness, increased deep tendon reflex; sensory level present; toes up *Conus medullaris (T10-L2):* symmetric weakness, increased knee reflexes; decreased ankle reflexes; saddle sensory loss; toes up or down *Cauda equina (below L2):* asymmetric weakness; loss of deep tendon reflex and sensory deficit; toes down	Metastasis to vertebra and extramedullary space	Neuroblastoma; medulloblastoma	MRI or myelography for diagnosis; corticosteroids; radiotherapy; laminectomy; chemotherapy
Increased intracranial pressure	Confusion, coma, emesis, headache, hypertension, bradycardia, seizures, papilledema, hydrocephalus; cranial nerves III and VI palsies	Primary or metastatic brain tumor	Neuroblastoma, astrocytoma; glioma	CT or MRI for diagnosis; corticosteroids; phenytoin; ventriculostomy tube; radiotherapy; chemotherapy
Superior vena cava syndrome	Distended neck veins plethora, edema of head and neck, cyanosis, proptosis, Horner syndrome	Superior mediastinal mass	Lymphoma	Chemotherapy; radiotherapy
Tracheal compression	Respiratory distress	Mediastinal mass compressing trachea	Lymphoma	Radiation, corticosteroids

CNS, Central nervous system; G-CSF, granulocyte colony-stimulating factor; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
Modified from Kliegman RM, Marcdante KJ, Jenson HB, et al, editors: Nelson essentials of pediatrics, *ed 6, Philadelphia, 2011, WB Saunders, p. 590.*

Table 494-5 Late Effects and High-Risk Features of Childhood Cancer and Its Treatment

LATE EFFECTS	EXPOSURE	SELECTED HIGH-RISK FACTORS	AT-RISK DIAGNOSTIC GROUPS
NEUROCOGNITIVE			
Neurocognitive deficits Functional deficits in: • Executive function • Sustained attention • Memory • Processing speed • Visual-motor integration Learning deficits Diminished IQ Behavioral change	Chemotherapy: • Methotrexate Radiation affecting brain: • Cranial • Ear/infratemporal • Total-body irradiation (TBI)	Age <3 yr at time of treatment Female sex Supratentorial tumor Premorbid or family history of learning or attention problems Radiation doses >24 Gy Whole-brain irradiation	Acute lymphoblastic leukemia Brain tumor Sarcoma (head and neck or osteosarcoma)
NEUROSENSORY			
Hearing loss, sensorineural	Chemotherapy: • Cisplatin • Carboplatin Radiation affecting hearing: • Cranial • Infratemporal • Nasopharyngeal	Higher cisplatin dose (360 mg/m^2) Higher radiation dose impacting ear (>30 Gy) Concurrent radiation and cisplatin	Brain tumor Germ cell tumor Sarcoma (head and neck) Neuroblastoma Hepatoblastoma
Hearing loss, conductive Tympanosclerosis Otosclerosis Eustachian tube dysfunction	Radiation affecting hearing: • Cranial • Infratemporal • Nasopharyngeal	Higher radiation dose affecting ear (>30 Gy)	Brain tumor Sarcoma (head and neck)
Visual impairment Cataracts Lacrimal duct atrophy Xerophthalmia Retinopathy Glaucoma	Chemotherapy: • Busulfan • Glucocorticoids Radiation affecting eye: • Cranial • Orbital/eye • TBI	Higher radiation dose impacting eye (≥15 Gy for cataracts; >45 Gy for retinopathy and visual impairment)	Brain tumor Acute lymphoblastic leukemia Retinoblastoma Rhabdomyosarcoma (orbital) Allogeneic HSCT
Peripheral neuropathy, sensory	Chemotherapy: • Vincristine • Vinblastine • Cisplatin • Carboplatin	Higher cisplatin dose (≥300 mg/m^2)	Acute lymphoblastic leukemia Brain tumor Hodgkin lymphoma Germ cell tumor Non-Hodgkin lymphoma Sarcoma Neuroblastoma Wilms tumor Carcinoma
NEUROMOTOR			
Peripheral neuropathy, motor	Chemotherapy: • Vincristine • Vinblastine		Acute lymphoblastic leukemia Hodgkin lymphoma Non-Hodgkin lymphoma Sarcoma Brain tumor Neuroblastoma Wilms tumor
ENDOCRINE			
GH deficiency Precocious puberty	Radiation affecting HPA: • Cranial • Orbital/eye	Female sex Radiation dose to HPA >18 Gy	Acute lymphoblastic leukemia Sarcoma (facial) Carcinoma (nasopharyngeal)
Obesity	Ear/infratemporal Nasopharyngeal	Female sex Younger age (<4 yr)	Acute lymphoblastic leukemia
Hypothyroidism, central Gonadotropin deficiency Adrenal insufficiency, central	TBI	Radiation dose to HPA >18 Gy	Brain tumor Sarcoma (facial) Carcinoma (nasopharyngeal)
Hypothyroidism, primary	Neck, mantle irradiation	Radiation dose to thyroid >20 Gy	Hodgkin lymphoma

Table 494-5 Late Effects and High-Risk Features of Childhood Cancer and Its Treatment—cont'd

LATE EFFECTS	EXPOSURE	SELECTED HIGH-RISK FACTORS	AT-RISK DIAGNOSTIC GROUPS
REPRODUCTIVE			
Gonadal dysfunction Delayed or arrested puberty Premature menopause Germ cell dysfunction or failure Infertility	Chemotherapy, alkylating: • Busulfan • Carmustine (BCNU) • Chlorambucil • Cyclophosphamide • Ifosfamide • Lomustine (CCNU) • Mechlorethamine • Melphalan • Procarbazine Radiation affecting reproductive system: • Whole abdomen (girls) • Pelvic • Lumbar/sacral spine (girls) • Testicular (boys) • TBI	Higher alkylating agent dose Alkylating agent conditioning for HSCT Radiation dose ≥15 Gy in prepubertal girls Radiation dose ≥10 Gy in pubertal girls For germ cell failure in boys, any pelvic irradiation For androgen insufficiency, gonadal irradiation, ≥20-30 Gy in boys	Acute lymphoblastic leukemia, high risk Brain tumor Hodgkin lymphoma, advanced or unfavorable Non-Hodgkin lymphoma, advanced or unfavorable Sarcoma Neuroblastoma Wilms tumor, advanced Autologous or allogeneic HSCT
CARDIAC			
Cardiomyopathy Arrhythmias	Chemotherapy: • Daunorubicin • Doxorubicin • Idarubicin	Female sex Age <5 yr at time of treatment Higher doses of chemotherapy (≥300 mg/m^2) Higher doses of cardiac radiation (≥30 Gy) Combined-modality therapy with cardiotoxic chemotherapy and irradiation	Hodgkin lymphoma Leukemia Non-Hodgkin lymphoma Sarcoma Wilms tumor Neuroblastoma
Cardiomyopathy Arrhythmias Pericardial fibrosis Valvular disease Myocardial infarction Atherosclerotic heart disease	Radiation affecting heart: • Chest • Mantle • Mediastinum • Axilla • Spine • Upper abdomen		
PULMONARY			
Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease Obstructive lung disease	Chemotherapy: • Bleomycin • Busulfan • Carmustine (BCNU) • Lomustine (CCNU) Radiation impacting lungs: • Mantle • Mediastinum • Whole lung • TBI	Higher doses of chemotherapy Combined modality therapy with pulmonary toxic chemotherapy and irradiation	Brain tumor Germ cell tumor Hodgkin lymphoma Sarcoma (chest wall or intrathoracic) Autologous or allogeneic HCST
GASTROINTESTINAL			
Chronic enterocolitis Strictures Bowel obstruction	Radiation affecting gastrointestinal tract (≥30 Gy) Abdominal surgery	Higher radiation dose to bowel (≥45 Gy) Combined modality therapy with abdominal irradiation and radiomimetic chemotherapy (dactinomycin or anthracyclines) Combined modality therapy with abdominal surgery and irradiation	Sarcoma (retroperitoneal or pelvic primary)
HEPATIC			
Hepatic fibrosis Cirrhosis	Radiation affecting liver	Higher radiation dose or treatment volume (20-30 Gy to entire liver or ≥40 Gy to at least one third of liver)	Sarcoma Neuroblastoma
RENAL			
Renal insufficiency Hypertension Glomerular injury Tubular injury	Chemotherapy: • Ifosfamide • Cisplatin • Carboplatin Radiation affecting kidneys: • Whole abdomen • Upper abdominal fields • TBI		

GH, Growth hormone; HPA, hypothalamic–pituitary–adrenal axis; HSCT, hematopoietic stem cell transplantation; TBI, total-body irradiation.

From Kurt BA, Arnstrong GT, Cash DK, et al: Primary care management of the childhood cancer survivor, J Pediatr 152:458–466, 2008.

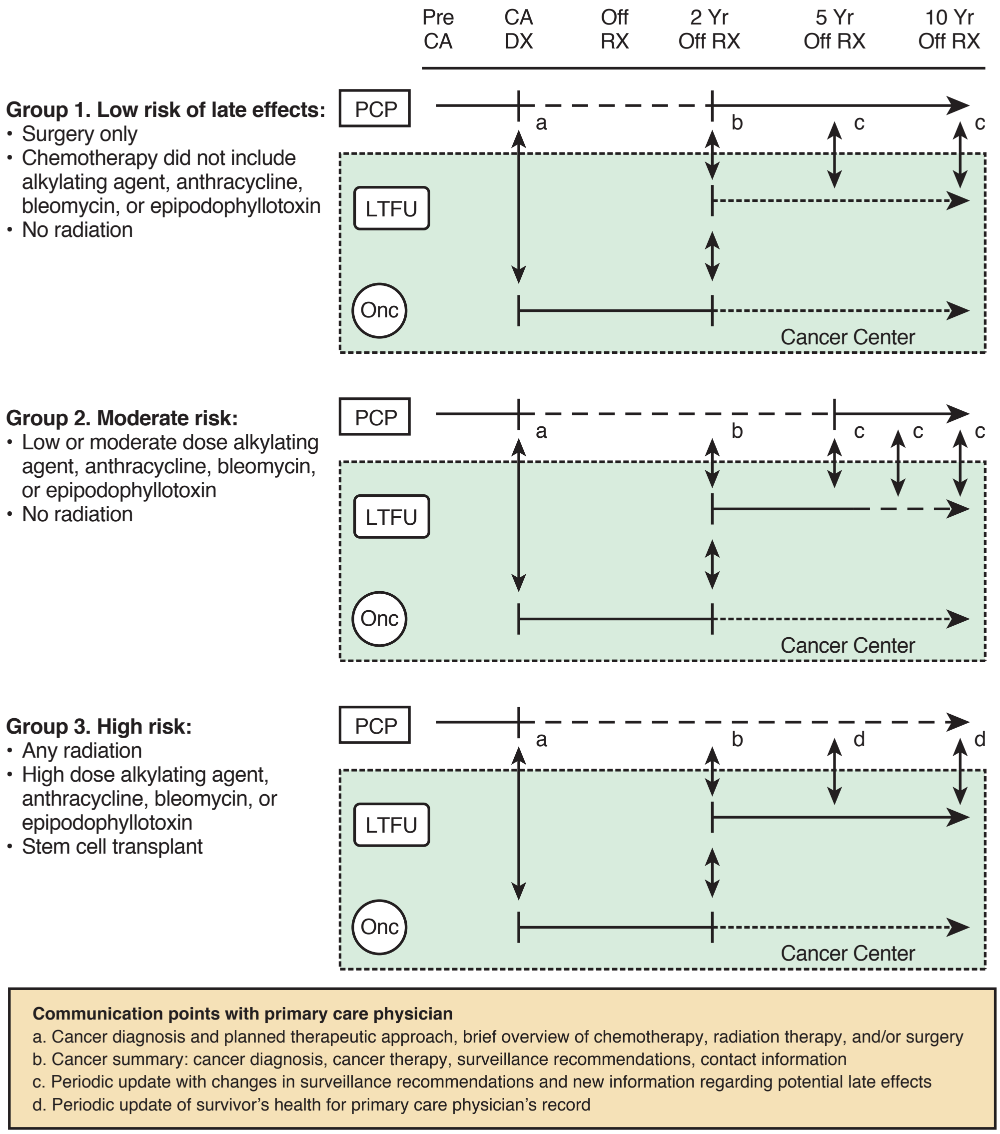

Figure 494-6 Proposed risk-stratified shared care model for childhood cancer survivors. *Solid line* denotes primary responsibility for risk-based care; risk stratification based upon determination of the long-term follow-up staff. *CA*, Cancer; *DX*, diagnosis; *Onc*, oncologist; *PCP*, primary care provider; *RX*, therapy. *(Adapted from Oeffinger KC, McCabe MS. Models for delivering survivorship care,* J Clin Oncol *24(32):5119, 2006; with permission from the American Society of Clinical Oncology. From Oeffinger KC, Nathan PC, Kremer LCM: Challenges after curative treatment for childhood cancer and long-term follow up of survivors,* Pediatr Clin North Am *55:251–273, 2008.)*

doses, cranial irradiation can produce neurologic dysfunction and spinal irradiation can produce growth retardation.

Chemotherapy also carries the risk of long-lasting organ damage. Of particular concern are leukoencephalopathy after high-dose methotrexate therapy; infertility in male patients treated with alkylating agents (e.g., cyclophosphamide); myocardial damage caused by anthracyclines; pulmonary fibrosis caused by bleomycin; renal dysfunction caused by ifosfamide, nitrosourea, or platinum agents; and hearing loss from cisplatin. Development of these sequelae may be dose-related and usually is irreversible. Appropriate baseline and intermittent testing should be performed before these drugs are administered to ensure that there is no preexisting damage to the organs likely to be affected and to permit monitoring of the adverse effects of treatment-induced changes.

Perhaps the most serious late adverse effect is the occurrence of **second cancers** in patients successfully cured of a first malignancy. The risk appears to be cumulative, increasing by approximately 0.5% per year, resulting in approximately a 12% incidence at 25 yr after treatment. Patients who have been treated for childhood cancer should be examined annually, with particular attention to possible late adverse effects of therapy, including second malignancies (Fig. 494-6).

PALLIATIVE CARE

At all stages of caring for children with cancer, principles of palliative care should be applied to relieve pain and suffering and to provide comfort (see Chapter 43). Pain is a serious cause of suffering among patients with cancer. It may be the result of organ obstruction or compression or bone metastasis, or it may be neuropathic. Pain should be managed in a stepwise manner, as recommended by the WHO, in accordance with the principles of selecting the appropriate analgesic, prescribing the appropriate dosage, administering the drug by the appropriate route, and choosing an appropriate dosing schedule to prevent persistent pain and to relieve breakthrough pain (see Chapter 62). In addition, the dosage should be titrated aggressively while attempts are made to prevent, anticipate, and manage side effects. Adjuvant drugs and sequential trials of analgesic drugs should be considered.

The goals in the care of dying patients are to avoid distress for the patient, family, and caregivers; to provide care consistent with the patient's and family's wishes; and to comply with and advocate for clinical, cultural, and ethical standards.

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Chapter 495

The Leukemias

David G. Tubergen, Archie Bleyer, A. Kim Ritchey, and Erika Friehling

The leukemias are the most common malignant neoplasms in childhood, accounting for approximately 31% of all malignancies that occur in children younger than 15 yr of age. Each year leukemia is diagnosed in approximately 3,250 children younger than 15 yr of age in the United States, an annual incidence of 4.5 cases per 100,000 children. Acute lymphoblastic leukemia (ALL) accounts for approximately 77% of cases of childhood leukemia, acute myelogenous leukemia (AML) for approximately 11%, chronic myelogenous leukemia (CML) for 2-3%, and juvenile myelomonocytic leukemia (JMML) for 1-2%. The remaining cases consist of a variety of acute and chronic leukemias that do not fit classic definitions for ALL, AML, CML, or JMML.

The leukemias may be defined as a group of malignant diseases in which genetic abnormalities in a hematopoietic cell give rise to an unregulated clonal proliferation of cells. The progeny of these cells have a growth advantage over normal cellular elements, because of their increased rate of proliferation and a decreased rate of spontaneous apoptosis. The result is a disruption of normal marrow function and, ultimately, marrow failure. The clinical features, laboratory findings, and responses to therapy vary depending on the type of leukemia.

495.1 Acute Lymphoblastic Leukemia

Erika Friehling, A. Kim Ritchey, David G. Tubergen, and Archie Bleyer

Childhood ALL was the first disseminated cancer shown to be curable. It actually is a heterogeneous group of malignancies with a number of distinctive genetic abnormalities that result in varying clinical behaviors and responses to therapy.

EPIDEMIOLOGY

ALL is diagnosed in approximately 2,400 children younger than 15 yr of age in the United States each year. ALL has a striking peak incidence at 2-3 yr of age and occurs more in boys than in girls at all ages. This peak age incidence was apparent decades ago in white populations in advanced socioeconomic countries, but it has since been confirmed in the black population of the United States as well. The disease is more common in children with certain chromosomal abnormalities, such as Down syndrome, Bloom syndrome, ataxia-telangiectasia, and Fanconi anemia. Among identical twins, the risk to the second twin if 1 twin develops leukemia is greater than that in the general population. The risk is >70% if ALL is diagnosed in the first twin during the 1st yr of life and the twins shared the same (monochorionic) placenta. If the first twin develops ALL by 5-7 yr of age, the risk to the second twin is at least twice that of the general population, regardless of zygosity.

ETIOLOGY

In virtually all cases, the etiology of ALL is unknown, although several genetic and environmental factors are associated with childhood leukemia (Table 495-1). Most cases of ALL are thought to be caused by postconception somatic mutations in lymphoid cells. However, the identification of the leukemia-specific fusion-gene sequences in archived neonatal blood spots of some children who develop ALL at a later date indicates the importance of in utero events in the initiation of the malignant process in some cases. The long lag period before the onset of the disease in some children, reported to be as long as 14 yr, supports the concept that additional genetic modifications are required for disease expression. Moreover, those same mutations have been found in neonatal blood spots of children who never go on to develop leukemia.

Table 495-1	Factors Predisposing to Childhood Leukemia
GENETIC CONDITIONS	
Down syndrome	
Fanconi anemia	
Bloom syndrome	
Diamond-Blackfan anemia	
Shwachman-Diamond syndrome	
Kostmann syndrome	
Neurofibromatosis type 1	
Ataxia-telangiectasia	
Severe combined immune deficiency	
Paroxysmal nocturnal hemoglobinuria	
Li-Fraumeni syndrome	
ENVIRONMENTAL FACTORS	
Ionizing radiation	
Drugs	
Alkylating agents	
Epipodophyllotoxin	
Benzene exposure	

Exposure to medical diagnostic radiation both in utero and in childhood is associated with an increased incidence of ALL. In addition, published descriptions and investigations of geographic clusters of cases have raised concern that environmental factors can increase the incidence of ALL. Thus far, no such factors other than radiation have been identified in the United States. In certain developing countries, there is an association between B-cell ALL (B-ALL) and Epstein-Barr viral infections.

CELLULAR CLASSIFICATION

The classification of ALL depends on characterizing the malignant cells in the bone marrow to determine the morphology, phenotype as measured by cell membrane markers, and cytogenetic and molecular genetic features. **Morphology** is usually adequate alone to establish a diagnosis, but the other studies are essential for disease classification, which can have a major influence on the prognosis and the choice of appropriate therapy. The current system used is the World Health Organization (WHO) classification of leukemias. Phenotypically, surface markers show that approximately 85% of cases of ALL are classified as B lymphoblastic leukemia (previously termed precursor B-ALL or pre–B-ALL), approximately 15% are T-lymphoblastic leukemia, and approximately 1% are derived from mature B cells. The rare leukemia of mature B cells is termed *Burkitt leukemia* and is one of the most rapidly growing cancers in humans, requiring a different therapeutic approach than other subtypes of ALL. A small percentage of children with leukemia have a disease characterized by surface markers of both lymphoid and myeloid derivation.

Chromosomal abnormalities are used to subclassify ALL into prognostic groups (Table 495-2). Many genetic alterations, including inactivation of tumor-suppressor genes and mutations that activate the *NOTCH1* or *RAS* pathways, have been discovered and might one day be incorporated into clinical practice (Fig. 495-1).

The polymerase chain reaction and fluorescence in situ hybridization techniques offer the ability to pinpoint molecular genetic abnormalities and can be used to detect small numbers of malignant cells at diagnosis as well as during follow-up (**minimal residual disease [MRD]**, see below) and are of proven clinical utility. The development of DNA microanalysis makes it possible to analyze the expression of thousands of genes in the leukemic cell. This technique promises to further enhance the understanding of the fundamental biology and to provide clues to the therapeutic approach of ALL.

CLINICAL MANIFESTATIONS

The initial presentation of ALL usually is nonspecific and relatively brief. Anorexia, fatigue, malaise, and irritability often are present, as is

Table 495-2	Common Chromosomal Abnormalities in Acute Lymphoblastic Leukemia of Childhood			
SUBTYPE	**CHROMOSOMAL ABNORMALITY**	**GENETIC ALTERATION**	**PROGNOSIS**	**INCIDENCE**
B-ALL	Trisomies 4, 10, and 17	—	Favorable	25%
B-ALL	t(12;21)	*ETV6-RUNX1*	Favorable	20-25%
B-ALL	t(1;19)	*E2A-PBX*	None	5-6%
B-ALL	t(4;11)	*MLL-AF4*	Unfavorable	2%
B-ALL	t(9;22)	*BCR-ABL*	Unfavorable	3%
Mature B-cell leukemia (Burkitt)	t(8;14)	*IGH-MYC*	None	1-2%
B-ALL	Hyperdiploidy	—	Favorable	20-25%
B-ALL	Hypodiploidy	—	Unfavorable	1%
T-ALL	t(10;14)	*TLX1/HOX11*	Favorable	5-10%
Infant	11q23	*MLL* rearrangements	Unfavorable	2-10%

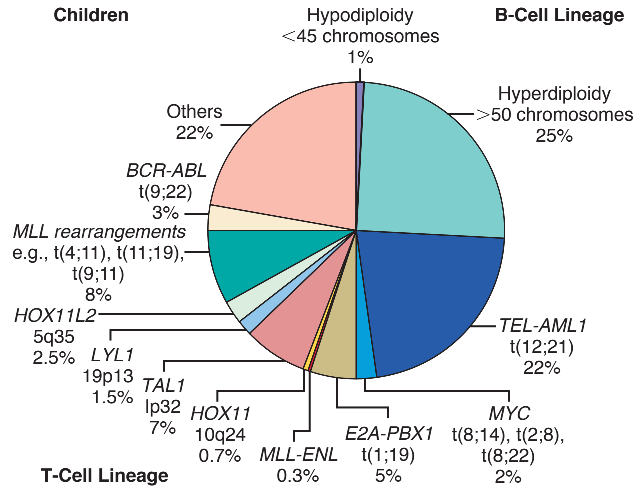

Figure 495-1 Estimated frequency of specific genotypes in childhood ALL. The genetic lesions that are exclusively seen in cases of T-cell ALL are indicated in *gold* and those commonly associated with B-cell ALL in *blue*. The *darker gold* or *blue* color indicates those subtypes generally associated with poor prognosis. *(From Pui CH, Mulligan CG, Evans WE: Pediatric acute lymphoblastic leukemia: where are we going and how do we get there?* Blood *120:1165–1174, 2012.)*

an intermittent, low-grade fever. Bone or joint pain, particularly in the lower extremities, may be present. Less commonly, symptoms may be of several months' duration, may be localized predominantly to the bones or joints, and can include joint swelling. Bone pain is severe and can wake the patient at night. As the disease progresses, signs and symptoms of bone marrow failure become more obvious with the occurrence of pallor, fatigue, exercise intolerance, bruising, or epistaxis, as well as fever, which may be caused by infection or the disease. Organ infiltration can cause lymphadenopathy, hepatosplenomegaly, testicular enlargement, or central nervous system (CNS) involvement (cranial neuropathies, headache, seizures). Respiratory distress may be due to severe anemia or mediastinal node compression of the airways.

On **physical examination,** findings of pallor, listlessness, purpuric and petechial skin lesions, or mucous membrane hemorrhage can reflect bone marrow failure (see Chapter 493). The proliferative nature of the disease may be manifested as lymphadenopathy, splenomegaly, or, less commonly, hepatomegaly. In patients with bone or joint pain, there may be exquisite tenderness over the bone or objective evidence of joint swelling and effusion. Nonetheless, with marrow involvement, deep bone pain may be present but tenderness will not be elicited. Rarely, patients show signs of increased intracranial pressure that indicate leukemic involvement of the CNS. These include papilledema (see Fig. 493-3), retinal hemorrhages, and cranial nerve palsies. Respiratory distress usually is related to anemia but can occur in patients with an obstructive airway problem (wheezing) as the result of a large anterior mediastinal mass (e.g., in the thymus or nodes). This problem is most typically seen in adolescent boys with T-cell ALL (T-ALL). T-ALL also usually has a higher leukocyte count.

B-lymphoblastic leukemia is the most common immunophenotype, with onset at 1-10 yr of age. The median leukocyte count at presentation is 33,000/µL, although 75% of patients have counts <20,000/µL; thrombocytopenia is seen in 75% of patients, and hepatosplenomegaly is seen in 30-40% of patients. In all types of leukemia, CNS symptoms are seen at presentation in 5% of patients (5-10% have blasts in the cerebrospinal fluid [CSF]). Testicular involvement is rarely evident at diagnosis, but prior studies indicate occult involvement in 25% of boys. There is no indication for testicular biopsy.

DIAGNOSIS

The diagnosis of ALL is strongly suggested by peripheral blood findings that indicate bone marrow failure. Anemia and thrombocytopenia are seen in most patients. Leukemic cells might not be reported in the peripheral blood in routine laboratory examinations. Many patients with ALL present with total leukocyte counts of <10,000/µL. In such cases, the leukemic cells often are reported initially to be atypical lymphocytes, and it is only on further evaluation that the cells are found to be part of a malignant clone. When the results of an analysis of peripheral blood suggest the possibility of leukemia, the bone marrow should be examined promptly to establish the diagnosis. It is important that all studies necessary to confirm a diagnosis and adequately classify the type of leukemia be performed, including bone marrow aspiration and biopsy, flow cytometry, cytogenetics, and molecular studies.

ALL is diagnosed by a bone marrow evaluation that demonstrates >25% of the bone marrow cells as a homogeneous population of lymphoblasts. Initial evaluation also includes CSF examination. If lymphoblasts are found and the CSF leukocyte count is elevated, overt CNS or meningeal leukemia is present. This finding reflects a worse stage and indicates the need for additional CNS and systemic therapies. The staging lumbar puncture may be performed in conjunction with the first dose of intrathecal chemotherapy, if the diagnosis of leukemia was previously established from bone marrow evaluation. An experienced proceduralist should perform the initial lumbar puncture, because a traumatic lumbar puncture is associated with an increased risk of CNS relapse.

DIFFERENTIAL DIAGNOSIS

The diagnosis of leukemia is readily made in the patient with typical signs and symptoms, anemia, thrombocytopenia, and elevated white blood count with blasts present on smear. Elevation of the lactate dehydrogenase is often a clue to the diagnosis of ALL. When only pancytopenia is present, aplastic anemia (congenital or acquired) and myelofibrosis should be considered. Failure of a single cell line, as seen in transient erythroblastopenia of childhood, immune thrombocytopenia, and congenital or acquired neutropenia, is rarely the presenting feature of ALL. A high index of suspicion is required to differentiate ALL from infectious mononucleosis in patients with acute onset of fever and lymphadenopathy and from juvenile idiopathic arthritis in patients with fever, bone pain but often no tenderness, and joint swelling. These presentations also can require bone marrow examination.

ALL must be differentiated from AML and other malignant diseases that invade the bone marrow and can have clinical and laboratory findings similar to ALL, including neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and retinoblastoma.

TREATMENT

The single most important prognostic factor in ALL is the treatment: without effective therapy, the disease is fatal. Considerable progress has been made in event-free survival for children with ALL since the 1970s through use of multiagent chemotherapeutic regimens, intensification of therapy, and selection of treatment based upon relapse risk (Fig. 495-2). Survival is also related to age (Fig. 495-3) and subtype (Fig. 495-4).

Risk-directed therapy has become the standard of current ALL treatment and takes into account age at diagnosis, initial white blood cell count, immunophenotypic and cytogenetic characteristics of blast populations, rapidity of early treatment response (i.e., how quickly the leukemic cells can be cleared from the marrow or peripheral blood),

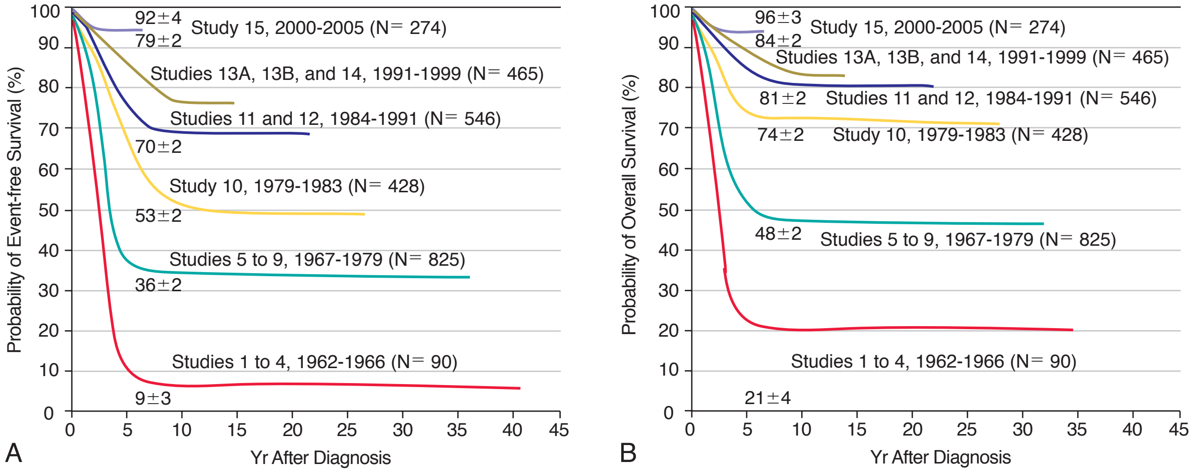

Figure 495-2 **Kaplan-Meier analyses of event-free survival (A) and overall survival (B) in 2,628 children with newly diagnosed ALL.** The patients participated in 15 consecutive studies conducted at St. Jude Children's Research Hospital from 1962-2005. The 5 yr event-free and overall survival estimates (±SE) are shown, except for Study 15, for which preliminary results at 4 yr are provided. The results demonstrate steady improvement in clinical outcome over the past 4 decades. The difference in event-free and overall survival rates has narrowed in the more recent periods, suggesting that relapses or second cancers that occur after contemporary therapy are more refractory to treatment. *(From Pui CH, Evans WE: Treatment of acute lymphoblastic leukemia*, N Engl J Med *354:166–178, 2006.)*

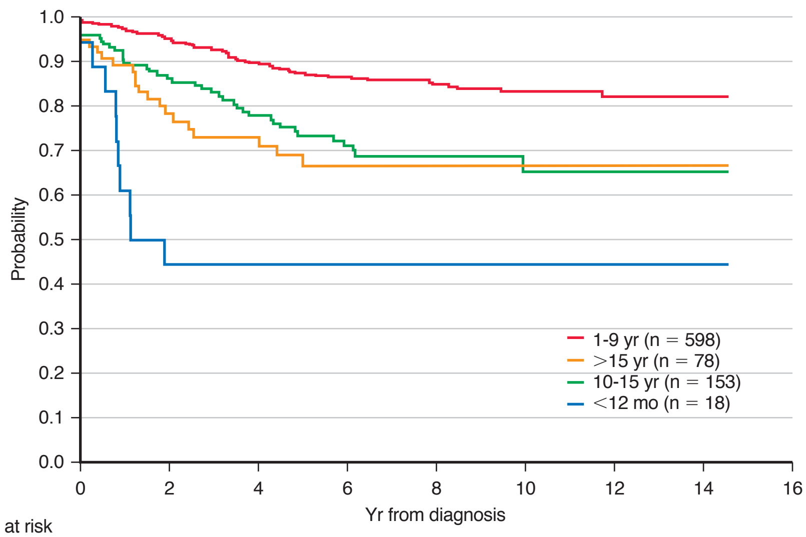

Number at risk

	0	2	4	6	8	10	12	14	16
<12 mo	18	11	8	8	6	1	1	0	0
1-9 yr	598	528	378	295	213	149	85	31	4
10-15 yr	153	130	100	77	50	26	11	6	1
>15 yr	78	60	40	29	20	7	1	0	0

Figure 495-3 **Kaplan-Meier estimates of event-free survival according to age at diagnosis of acute lymphoblastic leukemia.** *(From Pui CH, Robinson LL, Look AT: Acute lymphoblastic leukaemia*, Lancet *371:1030–1042, 2008.)*

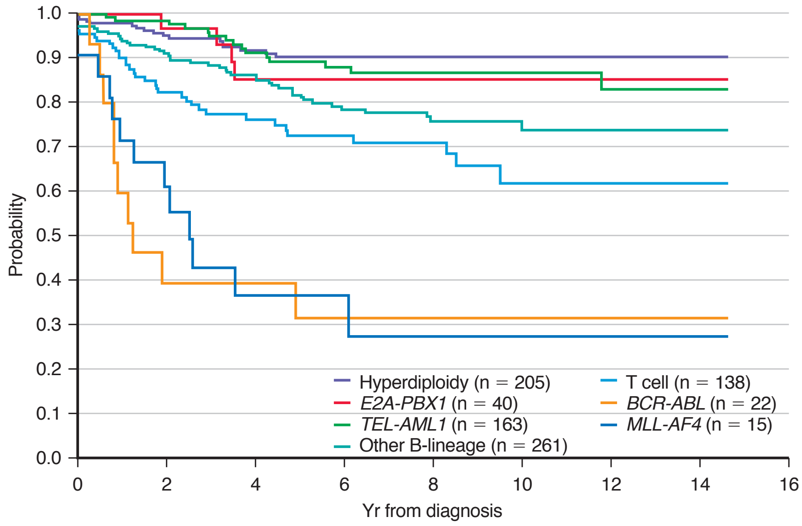

Number at risk

	0	2	4	6	8	10	12	14	16
Hyperdiploidy	205	190	144	108	80	52	25	10	1
E2A-PBX1	40	36	27	19	14	9	6	0	0
TEL-AML1	163	144	105	83	60	46	30	10	0
Other B-lineage	261	221	161	130	92	50	28	13	3
T cell	138	112	75	60	36	22	8	3	1
BCR-ABL	22	15	7	5	3	2	0	0	0
MLL-AF4	15	9	6	4	4	2	1	1	0

Figure 495-4 Kaplan-Meier analysis of event-free survival according to biologic subtype of leukemia. *(From Pui CH, Robinson LL, Look AT: Acute lymphoblastic leukaemia,* Lancet *371:1030–1042, 2008.)*

and assessment of MRD at the end of induction therapy. Different study groups use various factors to define risk, but age between 1 and 10 yr old and a leukocyte count of <50,000/µL are used by the National Cancer Institute to define standard risk. Children who are younger than 1 or older than 10 yr of age or who have an initial leukocyte count of >50,000/µL are considered to be high risk. Additional characteristics that adversely affect outcome include T-cell immunophenotype or a slow response to initial therapy. Chromosomal abnormalities, including hypodiploidy, the Philadelphia chromosome, and *MLL* gene rearrangements, portend a poorer outcome. Other mutations, such as in the *IKZF1* gene, have been shown to be associated with a poor prognosis and may become important in treatment algorithms in the future. More favorable characteristics include a rapid response to therapy, hyperdiploidy, trisomy of specific chromosomes (4, 10, and 17), and rearrangements of the *ETV6-RUNX1* (formerly *TEL-AML1*) genes.

The outcome for patients at higher risk can be improved by administration of more intensive therapy despite the greater toxicity of such therapy. Infants with ALL, along with patients who present with specific chromosomal abnormalities, such as t(4;11), have an even higher risk of relapse despite intensive therapy. However, the poor outcome of Philadelphia chromosome positive ALL with t(9;22) has dramatically changed by the addition of imatinib to an intensive chemotherapy backbone. Imatinib is an agent specifically designed to inhibit the BCR-ABL kinase resulting from the translocation. With this new approach, the event-free survival has improved from 30% to 70%. Clinical trials demonstrate that the prognosis for patients with a slower response to initial therapy may be improved by therapy that is more intensive than the therapy considered necessary for patients who respond more rapidly.

Most children with ALL are treated in clinical trials conducted by national or international cooperative groups. Standard treatment involves chemotherapy for 2-3 yr and most achieve remission at the end of the induction phase. Patients in clinical remission can have **MRD** that can only be detected with specific molecular probes to translocations and other DNA markers contained in leukemic cells or specialized flow cytometry. MRD can be quantitative and can provide an estimate of the burden of leukemic cells present in the marrow. Higher levels of MRD present at the end of induction suggest a poorer prognosis and higher risk of subsequent relapse. MRD of >0.01% on the marrow on day 29 of induction is a significant risk factor for shorter event-free survival for all risk categories, when compared with patients with negative MRD. Therapy for ALL intensifies treatment in patients with evidence of MRD at the end of induction.

Initial therapy, termed **remission induction**, is designed to eradicate the leukemic cells from the bone marrow. During this phase, therapy is given for 4 wk and consists of vincristine weekly, a corticosteroid such as dexamethasone or prednisone, and usually a single dose of a long-acting, pegylated asparaginase preparation. Patients at higher risk also receive daunomycin at weekly intervals. With this approach, 98% of patients are in **remission,** as defined by <5% blasts in the marrow and a return of neutrophil and platelet counts to near-normal levels after 4-5 wk of treatment. Intrathecal chemotherapy is always given at the start of treatment and at least once more during induction.

The second phase of treatment, **consolidation**, focuses on intensive **CNS therapy** in combination with continued intensive systemic therapy in an effort to prevent later CNS relapses. Intrathecal chemotherapy is given repeatedly by lumbar puncture. The likelihood of later CNS relapse is thereby reduced to <5%, from historical incidence as high as 60%. A small percentage of patients with features that predict a high risk of CNS relapse may receive irradiation to the brain in later phases of therapy. This includes patients who, at the time of diagnosis, have lymphoblasts in the CSF and either an elevated CSF leukocyte count or physical signs of CNS leukemia, such as cranial nerve palsy.

Subsequently, many regimens provide 14-28 wk of therapy, with the drugs and schedules used varying depending on the risk group of the patient. This period of treatment is often termed **intensification** and includes phases of aggressive treatment **(delayed intensification)** as well as relatively nontoxic phases of treatment (**interim maintenance**). Multiagent chemotherapy, including such medications as cytarabine, methotrexate, asparaginase, and vincristine, is used during these phases to eradicate residual disease.

Finally, patients enter the **maintenance** phase of therapy, which lasts for 2-3 yr, depending on the protocol used. Patients are given daily mercaptopurine and weekly oral methotrexate, usually with intermittent doses of vincristine and a corticosteroid.

A small number of patients with particularly poor prognostic features, such as those with induction failure or extreme hypodiploidy, may undergo bone marrow transplantation during the first remission.

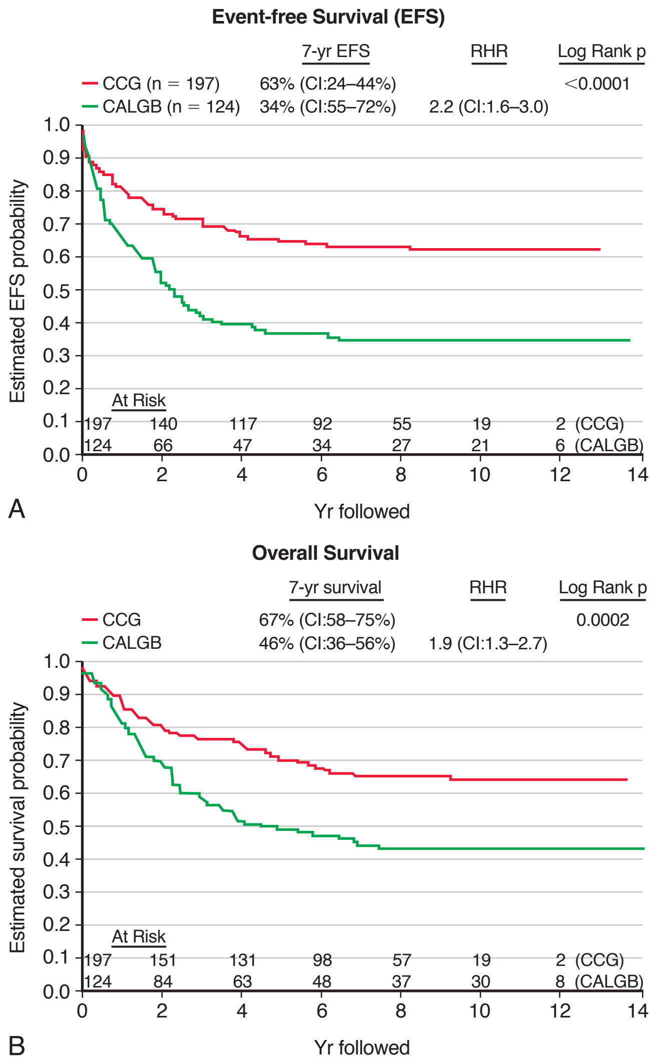

Figure 495-5 Comparison of event-free survival among Cancer and Leukemia Group B (CALGB) (adult protocol, *green line*) and Children's Cancer Group (CCG) (pediatric protocol, *red line*) patients. *(From Stock W, La M, Sanford B, et al: What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies,* Blood *112: 1646–1654, 2008.)*

Adolescents and young adults with ALL have an inferior prognosis compared to children younger than 15 yr old. They often have adverse prognostic factors and require more intensive therapy. Patients in this age group have a superior outcome when treated with pediatric as opposed to adult treatment protocols (Fig. 495-5). Although the explanation for these findings may be multifactorial, it is important that these patients be treated with pediatric treatment protocols, ideally in a pediatric cancer center.

There are genetic polymorphisms of enzymes important in drug metabolism, which may impact both the efficacy and toxicity of chemotherapeutic medications. **Pharmacogenetic testing** of the thiopurine *S*-methyltransferase *(TPMT)* gene, which encodes one of the metabolizing enzymes of mercaptopurine, can identify patients who are wild type (normal TPMT enzyme activity), heterozygous (slightly decreased TPMT enzyme activity), or homozygous (low or absent enzyme activity). Decreased TPMT enzyme activity results in an accumulation of a toxic metabolite of mercaptopurine and results in severe myelosuppression, requiring dose reductions of the chemotherapy (see Chapter 59). In the future, treatment also may be stratified by gene expression profiles of leukemic cells. In particular, gene expression arrays induced by exposure to a chemotherapeutic agent can predict which patients have drug-resistant ALL.

Treatment of Relapse

The major impediment to a successful outcome is relapse of the disease. Outcomes remain poor among those that relapse, with the most important prognostic indicators being time from diagnosis and the site of relapsed disease. In addition, other factors, such as immunophenotype (T-ALL worse than B-ALL) and age at initial diagnosis, have prognostic significance.

Relapse occurs in the bone marrow in 15-20% of patients with ALL and carries the most serious implications, especially if it occurs during or shortly after completion of therapy. Intensive chemotherapy with agents not previously used in the patient followed by allogeneic stem cell transplantation can result in long-term survival for some patients with bone marrow relapse (see Chapter 135).

The incidence of CNS relapse has decreased to <5% since introduction of preventive CNS therapy. CNS relapse may be discovered at the time of a routine lumbar puncture in the asymptomatic patient. Symptomatic patients with relapse in the CNS usually present with signs and symptoms of increased intracranial pressure and can present with isolated cranial nerve palsies. The diagnosis is confirmed by demonstrating the presence of leukemic cells in the CSF. The treatment includes intrathecal medication and cranial or craniospinal irradiation. Systemic chemotherapy also must be used, because these patients are at high risk for subsequent bone marrow relapse. Most patients with leukemic relapse confined to the CNS do well, especially those in whom the CNS relapse occurs longer than 18 mo after initiation of chemotherapy.

Testicular relapse occurs in less than 2% of boys with ALL, usually after completion of therapy. Such relapse occurs as painless swelling of 1 or both testes. The diagnosis is confirmed by biopsy of the affected testis. Treatment includes systemic chemotherapy and possibly local irradiation. A high proportion of boys with a testicular relapse can be successfully retreated, and the survival rate of these patients is good.

The most current information on treatment of childhood ALL is available in the PDQ (Physician Data Query) on the National Cancer Institute website (http://www.cancer.gov/cancertopics/pdq/treatment/childALL/healthprofessional/).

SUPPORTIVE CARE

Close attention to the medical supportive care needs of the patients is essential in successfully administering aggressive chemotherapeutic programs. Patients with high white blood counts are especially prone to tumor lysis syndrome as therapy is initiated. The kidney failure associated with very high levels of serum uric acid can be prevented or treated with allopurinol or urate oxidase. Chemotherapy often produces severe myelosuppression, which can require erythrocyte and platelet transfusion and which always requires a high index of suspicion and aggressive empiric antimicrobial therapy for sepsis in febrile children with neutropenia. Patients must receive prophylactic treatment for *Pneumocystis jiroveci* pneumonia during chemotherapy and for several months after completing treatment.

The successful therapy of ALL is a direct result of intensive and often toxic treatment. However, such intensive therapy can incur substantial academic, developmental, and psychosocial costs for children with ALL and considerable financial costs and stress for their families. Both long-term and acute toxicity effects can occur. An array of cancer care professionals with training and experience in addressing the myriad of problems that can arise is essential to minimize the complications and achieve an optimal outcome.

PROGNOSIS

Improvements in therapy and risk stratification have resulted in significant increases in survival rates, with current data showing overall 5 yr survival around 90% (Fig. 495-6). However, survivors are more likely to experience significant chronic medical conditions compared to siblings, including musculoskeletal, cardiac, and neurologic conditions. Overall, long-term management following ALL should be

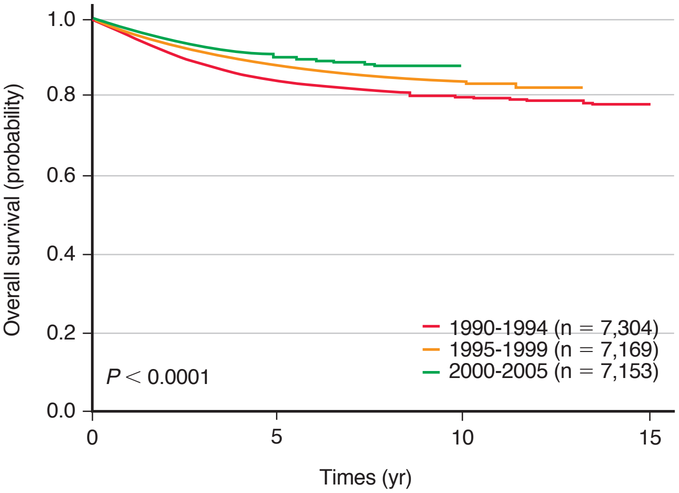

Figure 495-6 Overall survival probabilities by treatment era for patients with ALL enrolled in Children's Oncology Group trials in 1990-1994, 1995-1999, and 2000-2005. *(From Hunger SP, Lu X, Devidas M, et al: Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: A report from the Children's Oncology Group,* J Clin Oncol *30:1663–1669, 2012.)*

conducted in a clinic where children and adolescents can be followed by a variety of specialists to address the challenges of these unique patients.

Bibliography is available at Expert Consult.

495.2 Acute Myelogenous Leukemia

David G. Tubergen, Archie Bleyer, Erika Friehling, and A. Kim Ritchey

EPIDEMIOLOGY

AML accounts for 11% of the cases of childhood leukemia in the United States; it is diagnosed in approximately 370 children annually. The relative frequency of AML increases in adolescence, representing 36% of cases of leukemia in 15-19 yr olds. One subtype, acute promyelocytic leukemia (APL), is more common in certain regions of the world, but the incidence of the other types is generally uniform. Several chromosomal abnormalities associated with AML have been identified, but no predisposing genetic or environmental factors can be identified in most patients (see Table 495-1). Nonetheless, a number of risk factors have been identified, including ionizing radiation, chemotherapeutic agents (e.g., alkylating agents, epipodophyllotoxin), organic solvents, paroxysmal nocturnal hemoglobinuria, and certain syndromes: Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome, Shwachman-Diamond syndrome, Diamond-Blackfan syndrome, Li-Fraumeni syndrome, and neurofibromatosis type 1.

CELLULAR CLASSIFICATION

The characteristic feature of AML is that >20% of bone marrow cells on bone marrow aspiration or biopsy touch preparations constitute a fairly homogeneous population of blast cells, with features similar to those that characterize early differentiation states of the myeloid-monocyte-megakaryocyte series of blood cells. Current practice requires the use of flow cytometry to identify cell surface antigens and use of chromosomal and molecular genetic techniques for additional diagnostic precision and to aid the choice of therapy. The WHO has proposed a new classification system that incorporates morphology, chromosome abnormalities, and specific gene mutations. This system provides significant biologic and prognostic information (Table 495-3).

Table 495-3	WHO Classification of Acute Myeloid Neoplasms

Acute myeloid leukemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- APL with t(15;17)(q22;q12); *PML-RARA*
- AML with t(9;11)(p22;q23); *MLLT3-MLL*
- AML with t(6;9)(p23;q34); *DEK-NUP214*
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
- AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
- *Provisional entity: AML with mutated NPM1*
- *Provisional entity: AML with mutated CEBPA*

Acute myeloid leukemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise specified
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Acute erythroid leukemia
  - Pure erythroid leukemia
  - Erythroleukemia, erythroid/myeloid
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

Myeloid sarcoma
Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis
- Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

AML, acute myelogenous leukemia; APL, acute promyelocytic leukemia.

CLINICAL MANIFESTATIONS

The production of symptoms and signs of AML is a result of replacement of bone marrow by malignant cells and caused by secondary bone marrow failure. Patients with AML can present with any or all of the findings associated with **marrow failure** in ALL. In addition, patients with AML present with signs and symptoms that are uncommon in ALL, including **subcutaneous nodules** or "blueberry muffin" lesions (especially in infants), infiltration of the gingiva (especially in monocytic subtypes), signs and laboratory findings of **disseminated intravascular coagulation** (especially indicative of APL), and discrete masses, known as **chloromas** or **granulocytic sarcomas.** These masses can occur in the absence of apparent bone marrow involvement and typically are associated with a t(8;21) translocation. Chloromas also may be seen in the orbit and epidural space.

DIAGNOSIS

Analysis of bone marrow aspiration and biopsy specimens of patients with AML typically reveals the features of a hypercellular marrow consisting of a monotonous pattern of cells. Flow cytometry and special stains assist in identifying myeloperoxidase-containing cells, thus confirming both the myelogenous origin of the leukemia and the diagnosis. Some chromosomal abnormalities and molecular genetic markers are characteristic of specific subtypes of disease (Table 495-4).

PROGNOSIS AND TREATMENT

Aggressive multiagent chemotherapy is successful in inducing remission in approximately 85-90% of patients. Survival has increased dramatically since the 1970s, when only 15% of newly diagnosed patients survived, compared to a current survival rate of 60-70% with modern therapy (Fig. 495-7). Targeting therapy to genetic markers may be beneficial (see Table 495-4). Up to 5% of patients die of either infection or bleeding before a remission can be achieved. Matched-sibling bone marrow or stem cell transplantation after remission achieves long-term disease-free survival in about two thirds of patients. Continued chemotherapy for patients who do not have a matched sibling donor is

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Table 495-4 Prognostic Implications of Common Chromosomal Abnormalities in Pediatric Acute Myelogenous Leukemia

CHROMOSOMAL ABNORMALITY	GENETIC ALTERATION	USUAL MORPHOLOGY	PROGNOSIS
t(8;21)	*AML1-ETO*	Myeloblasts with differentiation	Favorable
inv(16)	*CBFB-MYHII*	Myeloblasts plus abnormal eosinophils with dysplastic basophilic granules	Favorable
t(15;17)	*PML-RARA*	Promyelocytic	Favorable
11q23 abnormalities	*MLL* rearrangements	Monocytic	Unfavorable
FLT3 mutation	*FLT3*-ITD	Any	Unfavorable
del(7q), –7	Unknown	Myeloblasts without differentiation	Unfavorable

Modified from Nathan DG, Orkin SH, Ginsburg D, et al, editors: Nathan and Oski's hematology of infancy and childhood, *ed 6, Philadelphia, 2003, WB Saunders, p. 1177.*

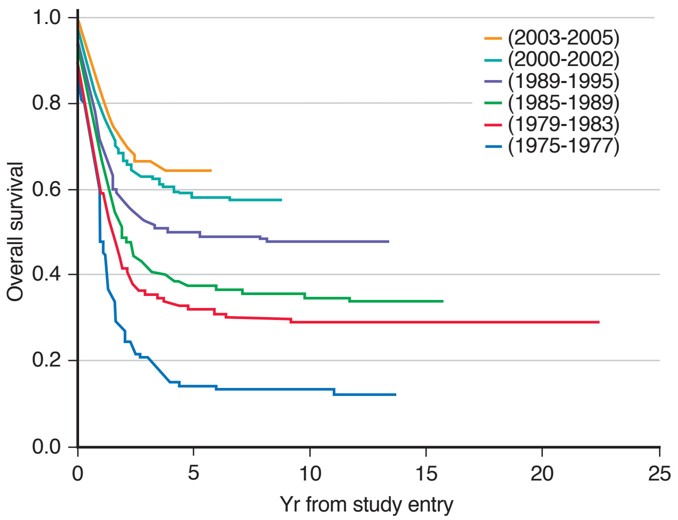

Figure 495-7 Overall survival showing incremental improvements over the last 40 yr in Children's Oncology Group and legacy trials in childhood AML. *(From Gamis AS, Alonzo TA, Perentesis JP, Meshinchi S, on behalf of the COG Acute Myeloid Leukemia Committee: Children's Oncology Group's 2013 blueprint for research: acute myeloid leukemia,* Pediatr Blood Cancer *60:964–971, 2013.)*

generally less effective than marrow transplantation, but nevertheless is curative in about half of patients. However, for selected patients with favorable prognostic features [t(8;21); t(15;17); inv(16); APL] and improved outcome with chemotherapy, matched sibling stem cell transplantation is recommended only after a relapse. Matched unrelated donor stem cell transplants may be effective therapy, but they carry the risk of significant graft-vs-host disease as well as the complications associated with intensive myeloablative therapy. Matched unrelated donor transplants are usually reserved for patients who have a relapse. However, patients with unfavorable prognostic features (e.g., monosomies 7 and 5, 5q–, and 11q23 abnormalities) who have inferior outcome with chemotherapy might benefit from matched unrelated donor stem cell transplant in first remission.

APL, characterized by a gene rearrangement involving the retinoic acid receptor [t(15;17); PML-RARA], is very responsive to **all-*trans*-retinoic acid (ATRA, tretinoin)** combined with anthracyclines and cytarabine. The success of this therapy makes marrow transplantation in first remission unnecessary for patients with this disease. Arsenic trioxide is an effective noncytotoxic therapy for APL. Data from trials in adults show promising results with the use of combined ATRA/arsenic without cytotoxic drugs as initial therapy for APL and would support a new trial of this regimen in children.

Increased supportive care is needed in patients with AML because the intensive therapy they receive produces prolonged bone marrow suppression with a very high incidence of serious infections, especially *Streptococcal viridans* sepsis and fungal infection. These patients may require prolonged hospitalization, filgrastim (granulocyte colony-stimulating factor), and prophylactic antimicrobials.

The most current information on treatment of AML is available in the PDQ (Physician Data Query) on the National Cancer Institute website (http://www.cancer.gov/cancertopics/pdq/treatment/childAML/healthprofessional/).

Bibliography is available at Expert Consult.

495.3 Down Syndrome and Acute Leukemia and Transient Myeloproliferative Disorder

David G. Tubergen, Archie Bleyer, Erika Friehling, and A. Kim Ritchey

Acute leukemia occurs about 15-20 times more frequently in children with Down syndrome than in the general population (see Chapters 81 and 492). The ratio of ALL to AML in patients with Down syndrome is the same as that in the general population. The exception is during the 1st 3 yr of life, when AML is more common. In children with Down syndrome who have ALL, the expected outcome of treatment is slightly inferior to that for other children, which can be partially explained by a lack of good prognostic characteristics, such as *ETV6-RUNX1* and trisomies, as well as genetic abnormalities that are associated with an inferior prognosis, such as *IKZF1*. Patients with Down syndrome demonstrate a remarkable sensitivity to methotrexate and other antimetabolites, which can result in substantial toxicity if standard doses are administered. In AML, however, patients with Down syndrome have much better outcomes than non–Down syndrome children, with a >80% long-term survival rate. After induction therapy, these patients receive therapy that is less intensive to achieve better results.

Approximately 10% of neonates with Down syndrome develop a transient leukemia or **myeloproliferative disorder** characterized by high leukocyte counts, blast cells in the peripheral blood, and associated anemia, thrombocytopenia, and hepatosplenomegaly. These features usually resolve within the 1st 3 mo of life. Although these neonates can require temporary transfusion support, they do not require chemotherapy unless there is evidence of life-threatening complications. However, patients who have Down syndrome and who develop this transient leukemia or myeloproliferative disorder require close follow-up, because 20-30% will develop typical leukemia (often acute megakaryocytic leukemia) by 3 yr of life (mean onset, 16 mo). *GATA1* mutations (a transcription factor that controls megakaryopoiesis) are present in blasts from patients with Down syndrome who have

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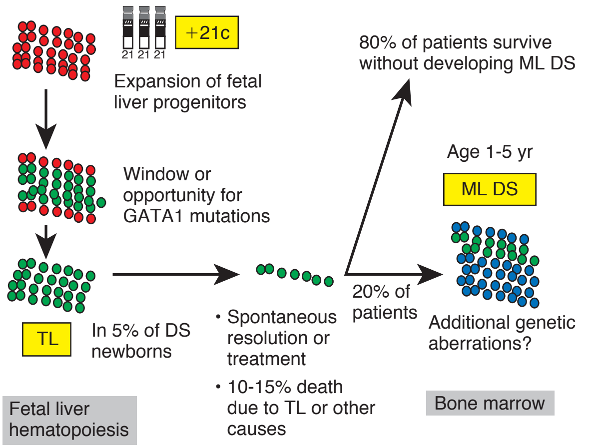

Figure 495-8 Stepwise development of myeloid leukemia in Down syndrome (ML DS) following transient leukemia (TL). TL arises from expanded fetal liver progenitors as a result of constitutional trisomy 21, providing a window of opportunity for the occurrence of acquired mutations in the hematopoietic transcription factor GATA1. In most cases TL spontaneously disappears, but some children need treatment because of severe TL-related symptoms. Approximately 20% of children with TL subsequently develop ML DS, which requires additional hits. *(From Zwaan MC, Reinhardt D, Hitzler J, Vyas P: Acute leukemias in children with Down syndrome,* Pediatr Clin North Am *55:53–70, 2008.)*

transient myeloproliferative disease and also in those with leukemia (Fig. 495-8). Transient myeloproliferative disease also can occur in patients who do not have phenotypic features of Down syndrome. Blasts from these patients might have trisomy 21, suggesting a mosaic state.

Bibliography is available at Expert Consult.

495.4 Chronic Myelogenous Leukemia

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CML is a clonal disorder of the hematopoietic tissue that accounts for 2-3% of all cases of childhood leukemia. Approximately 99% of the cases are characterized by a specific translocation, t(9;22)(q34;q11), known as the **Philadelphia chromosome,** resulting in a *BCR-ABL* fusion protein.

The presenting symptoms of CML are nonspecific and can include fever, fatigue, weight loss, and anorexia. Splenomegaly also may be present, resulting in pain in the left upper quadrant of the abdomen. The diagnosis is suggested by a high white blood cell count with myeloid cells at all stages of differentiation in the peripheral blood and bone marrow and is confirmed by cytogenetic and molecular studies that demonstrate the presence of the characteristic Philadelphia chromosome and the *BCR-ABL* gene rearrangement. This translocation, although characteristic of CML, is also found in a small percentage of patients with ALL.

The disease is characterized by an initial chronic phase in which the malignant clone produces an elevated leukocyte count with a predominance of mature forms but with increased numbers of immature granulocytes. In addition to leukocytosis, blood counts can reveal mild anemia and thrombocytosis. Typically, the chronic phase terminates 3-4 yr after onset, when the CML moves into the accelerated or "blast crisis" phase. At this point, the blood counts rise dramatically and the clinical picture is indistinguishable from acute leukemia. Additional manifestations can occur, including neurologic symptoms from hyperleukocytosis, which causes increased blood viscosity with decreased CNS perfusion.

Imatinib (Gleevec), an agent designed specifically to inhibit the *BCR-ABL* tyrosine kinase, has been used in adults and children and has shown an ability to produce major cytogenetic responses in >70% of patients (see Table 494-1). Experience in children suggests it can be used safely with results comparable to those seen in adults. Second-generation tyrosine kinase inhibitors, such as **dasatinib**, have improved remission rates in adults and are now included in the first-line therapy in that population while they are being studied in children. While waiting for a response to the tyrosine kinase inhibitor, disabling or threatening signs and symptoms of CML can be controlled during the chronic phase with hydroxyurea, which gradually returns the leukocyte count to normal. Prolonged morphologic and cytogenetic responses are expected, but the opportunity for cure is enhanced by human leukocyte antigen–matched family donor allogeneic stem cell transplant, with up to 80% of children achieving a cure.

Bibliography is available at Expert Consult.

495.5 Juvenile Myelomonocytic Leukemia

David G. Tubergen, Archie Bleyer, Erika Friehling, and A. Kim Ritchey

JMML, formerly termed **juvenile CML,** is a clonal proliferation of hematopoietic stem cells that typically affects children younger than 2 yr of age. JMML is rare, constituting <1% of all cases of childhood leukemia. Patients with this disease do not have the Philadelphia chromosome that is characteristic of CML. Patients with JMML present with rashes, lymphadenopathy, splenomegaly, and hemorrhagic manifestations. Analysis of the peripheral blood often shows an elevated leukocyte count with increased monocytes, thrombocytopenia, and anemia with the presence of erythroblasts. The bone marrow shows a myelodysplastic pattern, with blasts accounting for <20% of cells. Most patients with JMML have been found to have mutations that lead to activation of the *RAS* oncogene pathway including *NF1* and *PTPN11*. Patients with neurofibromatosis type 1 and Noonan syndrome have a predilection for this type of leukemia, since they have germline mutations involved in *RAS* signaling. Therapeutic reports are largely anecdotal. Stem cell transplantation offers the best opportunity for cure but much less so than for classic CML.

Bibliography is available at Expert Consult.

495.6 Infant Leukemia

David G. Tubergen, Archie Bleyer, Erika Friehling, and A. Kim Ritchey

Approximately 2% of cases of leukemia during childhood occur before the age of 1 year. In contrast to older children, the ratio of ALL to AML is 2 : 1. Leukemic clones have been noted in cord blood at birth before symptoms appear, and in 1 case the same clone was noted in maternal cells (maternal to fetal transmission). Chromosome translocations can also occur in utero during fetal hematopoiesis, thus leading to malignant clone formation.

Several unique biologic features and a particularly poor prognosis are characteristic of ALL during infancy. More than 80% of the cases demonstrate rearrangements of the *MLL* gene, found at the site of the 11q23 band translocation, the majority of which are the t(4;11). This subset of patients largely accounts for the very high relapse rate. These patients often present with hyperleukocytosis and extensive tissue infiltration producing organomegaly, including CNS disease. Subcutaneous nodules, known as **leukemia cutis,** and tachypnea caused by diffuse pulmonary infiltration by leukemic cells are observed more often in infants than in older children. The leukemic cell morphology is usually that of large irregular lymphoblasts, with a phenotype

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negative for the CD10 (common ALL antigen) marker (pro-B) unlike most older children with B-ALL who are CD10+.

Very intensive chemotherapy programs, including stem cell transplantation, are being explored in infants with *MLL* gene rearrangements, but none has yet proved satisfactory. Infants with leukemia who lack the 11q23 rearrangements have a prognosis similar to that of older children with ALL.

Infants with AML often present with CNS or skin involvement and have a subtype known as **acute myelomonocytic leukemia.** The treatment may be the same as that for older children with AML, with similar outcome. Meticulous supportive care is necessary because of the young age and aggressive therapy needed in these patients.

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Chapter 496
Lymphoma

Jessica Hochberg, Lisa Giulino-Roth, and Mitchell S. Cairo

Lymphoma is the third most common cancer among U.S. children (age 14 yr or younger), with an annual incidence of 15 cases per 1 million children. It is the most common cancer in adolescents, accounting for >25% of newly diagnosed cancers in persons 15-19 yr old. The 2 broad categories of lymphoma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), have different clinical manifestations and treatments.*

496.1 Hodgkin Lymphoma

Jessica Hochberg, Lisa Giulino-Roth, and Mitchell S. Cairo

Hodgkin lymphoma (HL) is a malignant process involving the lymphoreticular system that accounts for 6% of childhood cancers. In the United States, HL accounts for approximately 5% of cancers in persons 14 yr of age or younger; it accounts for approximately 15% of cancers in adolescents (15-19 yr of age), making HL the most common malignancy in this age group.

EPIDEMIOLOGY

The worldwide incidence of HL is approximately 2-4 new cases/100,000 population/yr; there is a bimodal age distribution, with peaks at 15-35 yr of age and again after 50 yr. It is the most common cancer seen in adolescents and young adults, and the third most common in children younger than the age of 15 yr. In developing countries, the early peak tends to occur prior to adolescence. A male : female predominance is found among young children, but lessens with age. Infectious agents may be involved, such as human herpesvirus 6, cytomegalovirus, and **Epstein-Barr virus (EBV)**. The role of EBV is supported by prospective serologic studies. Infection with EBV confers a 4-fold higher risk of developing HL and may precede the diagnosis by years. EBV antigens have been demonstrated in HL tissues, particularly type II latent membrane proteins 1 and 2, although EBV status is not thought to be prognostic of outcome.

PATHOGENESIS

The **Reed-Sternberg (RS) cell,** a pathognomonic feature of HL, is a large cell (15-45 µm in diameter) with multiple or multilobulated nuclei. This cell type is considered the hallmark of HL, although similar cells are seen in infectious mononucleosis, NHL, and other conditions. The RS cell is clonal in origin and arises from the germinal center B cells but typically has lost most B-cell gene expression and function. There is no single simple genetic aberration that leads to malignant transformation of the RS cell, but rather a combination of somatic mutations, chromosomal instability, and complex chromosomal rearrangements have been reported with no particular pattern or frequency. This typically leads to cell regulation defects such as constitutive activation of the nuclear factor-κB pathway or abnormal regulation of the Bcl-2 family of proteins. HL is characterized by a variable number of RS cells surrounded by an inflammatory infiltrate of lymphocytes, plasma cells, and eosinophils in different proportions, depending on the HL histologic subtype. The interaction between the RS cell and these background inflammatory cells with their associated cytokine release is important in the development and progression of HL. Reactive infiltration of eosinophils and CD68+ macrophages, and increased concentrations of cytokines, such as interleukins 1 and 6 and tumor necrosis factor, are all associated with an unfavorable prognosis, including advanced stage, the presence of "B" symptoms, decreased response to therapy, and reduced survival. In addition, evidence of CD8+ T cells surrounding the RS cell offers evidence of an important role in T-cell promotion of malignant cell survival, perhaps through the CD30 and CD40 ligands found on RS cells. Other features that distinguish the histologic subtypes include various degrees of fibrosis and the presence of collagen bands, necrosis, or malignant reticular cells (Fig. 496-1). The distribution of subtypes varies with age.

The **Revised World Health Organization Classification of Lymphoid Neoplasms** (Table 496-1) includes 2 modifications of the older Rye system. HL appears to arise in lymphoid tissue and spread to adjacent lymph node areas in a relatively orderly fashion. Hematogenous spread also occurs, leading to involvement of the liver, spleen, bone, bone marrow, or brain, and is usually associated with systemic symptoms.

CLINICAL MANIFESTATIONS

Patients commonly present with painless, nontender, firm, rubbery, cervical or supraclavicular lymphadenopathy and usually some degree of mediastinal involvement. Clinically detectable hepatosplenomegaly is rarely encountered. Depending on the extent and location of nodal and extranodal disease, patients may present with symptoms and signs of airway obstruction (dyspnea, hypoxia, cough), pleural or pericardial effusion, hepatocellular dysfunction, or bone marrow infiltration (anemia, neutropenia, or thrombocytopenia). Disease manifesting below the diaphragm is rare and occurs in approximately 3% of all cases. Systemic symptoms**,** classified as **B symptoms** that are considered important in staging, are unexplained fever >38°C (100.4°F), weight loss >10% total body weight over 6 mo, and drenching night sweats. Less common and not considered of prognostic significance are symptoms of pruritus, lethargy, anorexia, or pain that worsens after ingestion of alcohol. Patients also exhibit immune system abnormalities that often persist during and after therapy.

DIAGNOSIS

Any patient with persistent, unexplained lymphadenopathy unassociated with an obvious underlying inflammatory or infectious process should undergo chest radiography to identify the presence of a large mediastinal mass before undergoing lymph node biopsy. Formal excisional biopsy is preferred over needle biopsy to ensure that adequate tissue is obtained, both for light microscopy and for appropriate immunohistochemical and molecular studies. Once the diagnosis of HL is established, extent of disease (stage) should be determined to allow selection of appropriate therapy (Table 496-2). Evaluation includes history, physical examination, and imaging studies, including chest radiograph; CT scans of the neck, chest, abdomen, and pelvis; and positron emission tomography (PET) scan. Laboratory studies should include a complete blood cell count to identify abnormalities that might suggest marrow involvement; erythrocyte sedimentation rate; and measurement of serum ferritin, which is of some prognostic

*The views expressed are the result of independent work and do not necessarily represent the views or findings of the U.S. Food and Drug Administration or the United States.

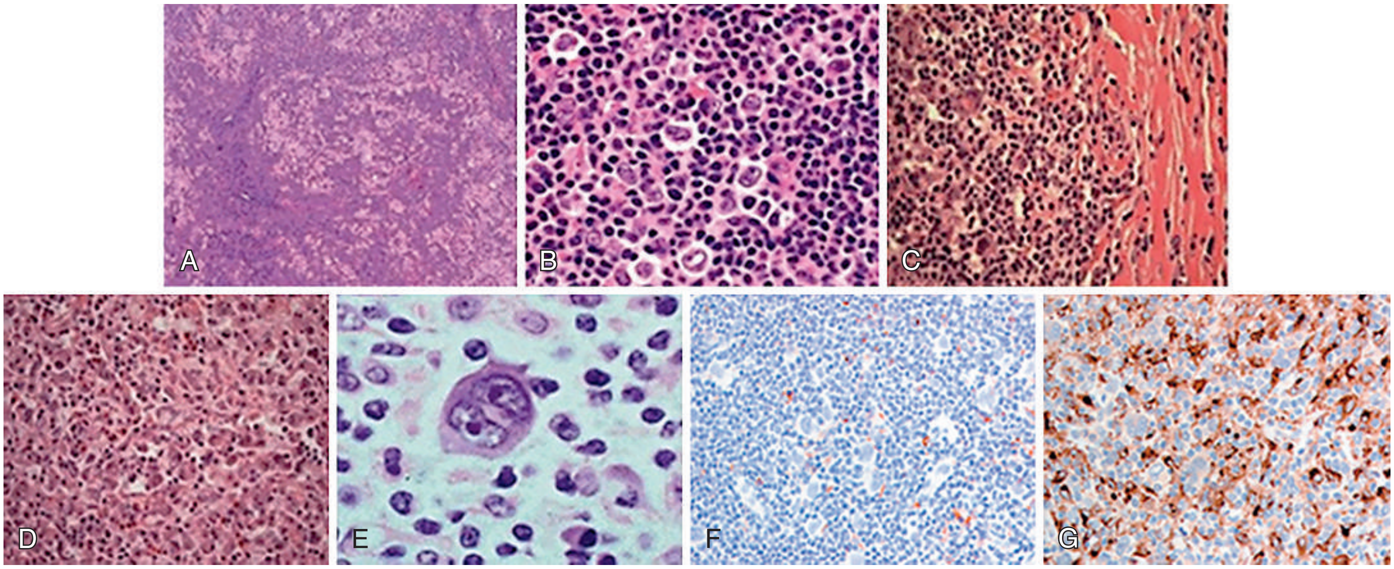

Figure 496-1 **Histologic subtypes of Hodgkin lymphoma.** **A,** Hematoxylin & eosin stains of nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) demonstrating a nodular proliferation with a moth-eaten appearance. **B,** High-power view demonstrating the neoplastic L and H cells found in NLPHL. **C,** Classic Hodgkin lymphoma, nodular sclerosis subtype. Large mononuclear and binucleate Reed-Sternberg cells are seen admixed in the inflammatory cell background. **D,** Classic Hodgkin lymphoma, mixed cellularity subtype, demonstrating increased numbers of Reed-Sternberg cells in a mixed inflammatory background without sclerotic changes. **E,** High-power view of a classic Reed-Sternberg cell showing binucleate cells with prominent eosinophilic nucleoli and relatively abundant cytoplasm. **F,** Few CD68+ macrophages in a treatment success patient. **G,** Many CD68+ macrophages in a treatment failure patient.

Table 496-1 New World Health Organization/Revised European–American Classification of Lymphoid Neoplasms Classification System for Hodgkin Lymphoma

Nodular lymphocyte predominance
Classical Hodgkin lymphoma
Lymphocyte rich
Mixed cellularity
Nodular sclerosis
Lymphocyte depletion

From Harris NL, Jaffe ES, Diebold J, et al: The World Health Organization classification of neoplastic diseases of the haematopoietic and lymphoid tissues: report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November 1997, Histopathology *36:69–87, 2000.*

significance and, if abnormal at diagnosis, serves as a baseline to evaluate the effects of treatment. A chest radiograph is particularly important for measuring the size of the mediastinal mass in relation to the maximal diameter of the thorax (Fig. 496-2). This determines "bulk" disease and becomes prognostically significant. Chest CT more clearly defines the extent of a mediastinal mass if present and identifies hilar nodes and pulmonary parenchymal involvement, which may not be evident on chest radiographs. Bone marrow aspiration and biopsy should be performed to rule out advanced disease. Bone scans are performed in patients with bone pain and/or elevation of alkaline phosphatase. Gallium scan can be particularly helpful in identifying areas of increased uptake, which can then be reevaluated at the end of treatment. Fluorodeoxyglucose PET imaging has advantages over gallium scanning, as it is a 1-day procedure with higher resolution, better dosimetry, less intestinal activity, and the potential to quantify disease. PET scans are being evaluated as a prognostic tool in HL, enabling therapy to be reduced in those predicted to have a good outcome.

The staging classification currently used for HL was adopted at the **Ann Arbor Conference** in 1971 and was revised in 1989 (see Table 496-2). HL can be subclassified into A or B categories: *A* is used to

Table 496-2 Ann Arbor Staging Classification for Hodgkin Lymphoma*

STAGE	DEFINITION
I	Involvement of a single lymph node (I) or of a single extralymphatic organ or site (IE)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and 1 or more lymph node regions on the same side of the diaphragm (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by involvement of the spleen (IIIS) or by localized involvement of an extralymphatic organ or site (IIIE) or both (IIISE)
IV	Diffuse or disseminated involvement of 1 or more extralymphatic organs or tissues with or without associated lymph node involvement

*The absence or presence of fever >38°C (100.4°F) for 3 consecutive days, drenching night sweats, or unexplained loss of >10% of body weight in the 6 mo preceding admission are to be denoted in all cases by the suffix letter A or B, respectively.

From Lister TA, Crowther D, Sutcliffe SB, et al: Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting, J Clin Oncol *7:1630–1636, 1989.*

identify asymptomatic patients and *B* is for patients who exhibit any B symptoms. Extralymphatic disease resulting from direct extension of an involved lymph node region is designated by category E. A complete response in HL is defined as the complete resolution of disease on clinical examination and imaging studies or at least 70-80% reduction of disease and a change from initial positivity to negativity on either gallium or PET scanning because residual fibrosis is common.

TREATMENT

Multiple agents allow different mechanisms of action to have nonoverlapping toxicities so that full doses can be given to each patient.

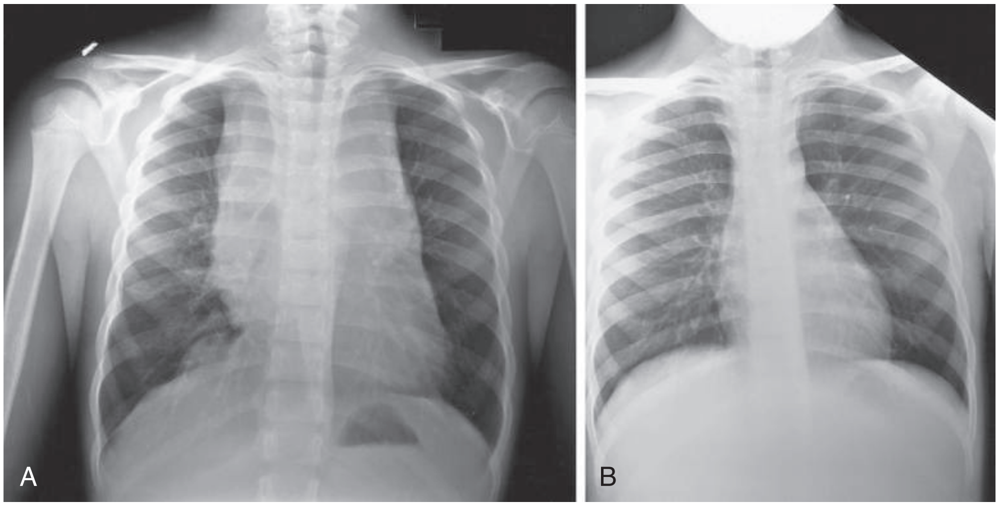

Figure 496-2 **A,** Anterior mediastinal mass in a patient with Hodgkin disease before therapy. **B,** After 2 mo of chemotherapy, the mediastinal mass has disappeared.

Chemotherapy and radiation therapy are both effective in the treatment of HL. Treatment of HL in pediatric patients is risk adapted and involves the use of combined chemotherapy with or without low-dose involved-field radiation therapy based on response. Treatment is determined largely by disease stage, presence or absence of B symptoms, and the presence of bulky nodal disease. Radiation therapy alone, once given at higher doses, initially resulted in prolonged remission and cure rates in patients with low-stage HL. However, this treatment also caused significant long-term morbidity in pediatric patients, including growth retardation, thyroid dysfunction, and cardiac and pulmonary toxicity. The development of effective multiagent combination chemotherapy was a major milestone in the treatment of HL resulting in a complete response rate of 70-80% and cure rate of 40-50% in patients with advanced-stage disease. However, this regimen also led to significant acute and long-term toxicity. The desire to reduce side effects and morbidity has stimulated attempts to reduce the intensity of chemotherapy as well as radiation dose and volume. Newer combinations of chemotherapy have reduced the risk of secondary cancers. Also, current radiation therapy utilizes lower amounts of overall radiation in addition to narrowing the radiation treatment field to either involved-field or even involved-node irradiation. The current Children's Oncology Group trials are investigating whether radiation therapy can be eliminated altogether in patients who have a very good rapid early response to pre-radiation induction chemotherapy.

Chemotherapy agents commonly used to treat children and adolescents with HL include cyclophosphamide, procarbazine, vincristine or vinblastine, prednisone or dexamethasone, doxorubicin, bleomycin, dacarbazine, etoposide, methotrexate, and cytosine arabinoside. The combination chemotherapy regimens in current use are based on **COPP** (cyclophosphamide, vincristine [Oncovin], procarbazine, and prednisone) or **ABVD** (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine), with the addition of prednisone, cyclophosphamide, and etoposide (**ABVE-PC** and **BEACOPP**) or **BAVD** (brentuximab vedotin, doxorubicin [Adriamycin], vincristine, dacarbazine) in various combinations for intermediate- and high-risk groups (Table 496-3). "Risk-adapted" protocols are based on both staging criteria and rapidity of response to initial chemotherapy. The aim is to reduce total drug doses and treatment duration and to eliminate radiation therapy if possible.

Agents such as those that disrupt the nuclear factor-κB pathway or monoclonal antibodies that target RS tumor cells as well as the benign reactive cells that surround them are currently being investigated. Ongoing clinical trials report encouraging results with the use of anti-CD20 antibody (rituximab), particularly in nodular lymphocyte-predominant Hodgkin lymphoma where trials in relapsed disease have shown an overall response rate of 94%. In addition, anti-CD30 agents

Table 496-3 Chemotherapy Regimens Commonly Used for Children, Adolescents, and Young Adults with Hodgkin Lymphoma

CHEMOTHERAPY REGIMEN	CORRESPONDING AGENTS
ABVD	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine
ABVD-Rituxan	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine, rituximab
ABVD	Doxorubicin (Adriamycin), brentuximab, vinblastine, dacarbazine
ABVE (DBVE)	Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide
VAMP	Vincristine, doxorubicin (Adriamycin), methotrexate, prednisone
OPPA ± COPP (females)	Vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
OEPA ± COPP (males)	Vincristine (Oncovin), etoposide, prednisone, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
COPP/ABV	Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), bleomycin, vinblastine
BEACOPP (advanced stage)	Bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
COPP	Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
CHOP	Cyclophosphamide, doxorubicin (Adriamycin), vincristine (Oncovin), prednisone
ABVE-PC (DBVE-PC)	Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide, prednisone, cyclophosphamide
ICE ± (Brentuximab)	Ifosfamide, carboplatin, etoposide ± brentuximab
Ifos/Vino ± (Brentuximab)	Ifosfamide, vinorelbine ± brentuximab

are being used that are targeted to the RS cells themselves, where CD30 is abundantly expressed. Brentuximab vedotin is an antibody–drug conjugate that is now FDA approved to treat Hodgkin lymphoma. It combines the chimeric anti-CD30 antibody brentuximab linked to the antimitotic agent monomethyl auristatin E. This agent shows impressive efficacy as single-agent therapy in refractory HL and is currently being tested as part of upfront therapy combined with chemotherapy in patients with newly diagnosed disease. EBV-specific cytotoxic T lymphocytes (CTLs) can also be generated from allogeneic donors for patients with advanced HL (Fig. 496-3). In clinical trials, these show promising results, with enhanced antiviral activity and stabilization of disease even though all patients continue to have persistent disease. EBV-CTLs have been developed and are currently being investigated. These enhanced EBV-CTLs are designed to be latent membrane protein 1/2 specific and can be generated from second (in the case of bone marrow transplant recipients) or even third-party donors for patients with refractory disease. These newer approaches represent an exciting new direction in adoptive cellular tumor immunology, and it remains to be determined whether CTLs will have improved cytotoxicity that can overcome inhibitory signals.

RELAPSE

Most relapses occur within the 1st 3 yr after diagnosis, but relapses as late as 10 yr have been reported. Relapse cannot be predicted accurately with this disease. Poor prognostic features include tumor bulk, stage at diagnosis, extralymphatic disease, and presence of B symptoms. Patients who achieve an initial chemosensitive response but relapse or progress less than 12 mo from diagnosis are candidates for myeloablative chemotherapy and autologous stem cell transplantation with or without the addition of radiation therapy. Retrospective studies show a significant decrease in relapse in patients with HL following allogeneic vs autologous stem cell transplant (18% vs 41%). Although in earlier studies there was no improvement in overall survival owing to a high transplantation-related mortality, reduced-intensity conditioning or nonmyeloablative regimens are successful at reducing regimen-related morbidity and mortality associated with myeloablative allogeneic stem cell transplantation while still achieving a strong graft-versus-HL effect. For more difficult-to-treat refractory cases, agents such as Zevalin or Bexxar are being trialed, often in combination with stem cell transplantation strategies. Both are monoclonal anti-CD20 antibodies to which a radioactive isotope is directly linked. Clinical trials show each to be more effective than rituximab in NHL patients, and there is some interest in studying their use in the CD20 subpopulation of HL patients.

PROGNOSIS

With the use of current therapeutic regimens, patients with favorable prognostic factors and early-stage disease have an event-free survival (EFS) of 85-90% and an overall survival (OS) at 5 yr of >95%. Patients with advanced-stage disease have slightly lower EFS (80-85%) and OS (90%), respectively, although OS has approached 100% with dose-intense chemotherapy (Table 496-4). Prognosis after relapse depends

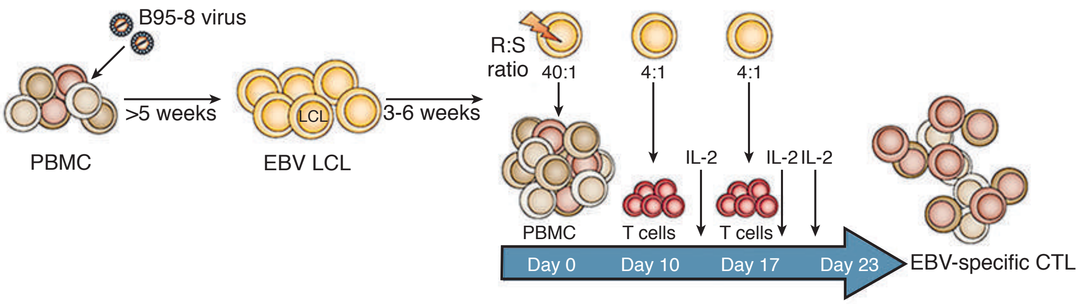

Figure 496-3 **Epstein-Barr virus (EBV)–specific cytotoxic T lymphocyte (CTL) production.** EBV-transformed B-cell lymphoblastoid cell line (LCLs) are prepared from the CTL donor by infection of peripheral blood mononuclear cells (PBMCs) with a clinical-grade laboratory strain of EBV (B95-8) in the presence of cyclosporine. Once the LCL is established (about 6 wk), it is irradiated and used to stimulate PBMCs from the same donor at a 40:1 ratio of PBMC:LCL. From 9-12 days later and weekly thereafter, the T cells are restimulated with the LCL at a 4:1 ratio. Interleukin 2 is added 3 days after the second stimulation and twice weekly thereafter. The CTLs should kill autologous LCLs but not autologous phytohemagglutinin blasts. Their specificity is donor dependent and they may have specificity for any of the 10 latency-associated antigens and/or for early lytic cycle proteins that are expressed by a small fraction of the LCLs, which are grown in acyclovir to prevent the production of infectious virus by blocking the viral thymidine kinase. *(Adapted from Bollard CM, Rooney CM, Heslop HE. T-cell therapy in the treatment of post-transplant lymphoproliferative disease. Nat Rev Clin Oncol 9:510–519, 2012, Fig. 2.)*

Table 496-4 Treatment Regimens and Outcome by Disease Staging

		LOCALIZED/LOW STAGE	INTERMEDIATE	ADVANCED
Hodgkin lymphoma	Treatment	*POG study 9426/GPOH-HD 95:* ABVD-type therapy ± IFRT (risk adapted based on early response to chemotherapy)	*Stanford/DAL-HD-90:* COPP-based or dose-intense multiagent chemotherapy + low-dose RT *POG 9426/CCG 5942:* ABVD-type therapy ± IFRT (risk adapted)	*POG 8725/DAL-HD-90:* Dose-intense multiagent chemotherapy + low-dose RT *HD9/HD12/CCG 59704:* Dose-intense BEACOPP ± IFRT
	Prognosis	5 yr EFS: 85-90% 5 yr OS: 95%	*Stanford/DAL-HD-90:* 5 yr EFS: 89-92% *POG 9426/CCG 5942:* 5 yr EFS: 84% 5 yr OS: 91%	*POG 8725:* 5-yr EFS: 72-89% (age based) *DAL-HD-90:* 5 yr EFS: 86% 5 yr OS: 85-90% *HD9/HD12/CCG 59704:* 5 yr EFS/OS: 88-93/~100%

Table 496-4 Treatment Regimens and Outcome by Disease Staging—cont'd

		LOCALIZED/LOW STAGE	INTERMEDIATE	ADVANCED
Burkitt lymphoma and diffuse large B-cell lymphoma	Treatment	*FAB/LMB 96 Group A therapy:* Complete surgical resection followed by 2 cycles of chemotherapy	*FAB/LMB 96 Group B* therapy with reduced cyclophosphamide and no maintenance therapy; *COG ANHL01P1*: FAB/LMB Group B therapy + rituximab	*FAB/LMB 96:* standard-intensity Group C therapy: Reduction, induction, intensification, and maintenance therapy *COG ANHL01P1*: FAB/LMB Group C therapy + rituximab
	Prognosis	4 yr EFS: 98% (CI_{95} 94-99.5%) 4 yr OS: 99% (CI_{95} 96-99.9%)	*FAB/LMB96:* 4 yr EFS: 92% (CI_{95} 90-94%) 4 yr OS: 95% (CI_{95} 93-96%) *PMB DLBCL has worse prognosis (EFS/OS: 66/73%) *COG ANHL01P1:* 3 yr EFS 93% (CI_{95} 79-98%) 3 yr OS 95% (CI_{95} 83-99%)	*FAB/LMB96:* 4 yr EFS: BM+/CNS–: 91% ± 3% BM–/CNS+: 85% ± 6% BM+/CNS+: 66% ± 7% *COG ANHL01P1:* 3 yr EFS/OS: BM+ or CNS+: 90% (CI_{95} 75-96%) CNS+: 93% (CI_{95} 61-99%)
Lymphoblastic lymphoma	Treatment	*NHL-BFM86/90/95:* *COG A5971:* ALL-type therapy × 2 yr without prophylactic cranial RT	No intermediate group; disease classified as localized (stages I/II) or advanced (stages III/IV)	*NHL-BFM86/90/95:* ALL-type therapy × 2 yr ± px CRT *CCG 5941:* Intensive chemotherapy × 1 yr + cranial RT if CNS + at diagnosis
	Prognosis	*COG A5971:* 5 yr EFS: 90 (CI_{95} 78-96%) 5 yr OS: 96 (CI_{95} 84-99%)	No intermediate group; see above	*NHL-BFM95:* 5 yr EFS: 90% ± 3% (III), 95 ± 5% (IV) *CCG 5941:* 5 yr EFS/OS: 78% ± 5%/85% ± 4%
Anaplastic large cell lymphoma	Treatment	*EICHNL ALCL 99:* Short intensive chemotherapy + HD MTX Completely resected stage I disease may be treated with surgery alone	No intermediate group; disease classified as standard risk (no skin, visceral, or mediastinal involvement) or high risk (presence of skin, mediastinal, or visceral involvement)	*ALCL 99, CCG 5941:* Short intensive chemotherapy + HD MTX *COG ANHL0131*: APO (doxorubicin, prednisone, vincristine) ± vinblastine
	Prognosis	*EICHNL database:* 5 yr PFS: 89% (CI_{95} 82-96%) 5 yr OS: 94% (CI_{95} 89-99%)	No intermediate group; see above	*ALCL99:* 2 yr EFS: 71% (CI_{95} 75-77%) 2 yr OS: 94% (CI_{95} 89-95%) *COG5941:* 5 yr EFS 68% (CI_{95} 57-78%) 5 yr OS: 80% (CI_{95} 69-87%) *COH ANHL0131:* 2 yr EFS 79% (CI_{95} 71-88%) 2 yr OS 89% (CI_{95} 83-95%)

ABVD, doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; BEACOPP, bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; BM, bone marrow (involvement); CCG, Children's Cancer Group; CI_{95}, 95% confidence interval; CNS, central nervous system (involvement); COG, Children's Oncology Group; COPP, cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; CRT, chemoradiotherapy; EFS, event-free survival; EICHNL, European Intergroup for Childhood Non-Hodgkin Lymphoma; FAB, French-American-British; HD MTX, high-dose methotrexate; IFRT, involved field radiation therapy; LMB, Lymphome Malins de Burkit; MTX, methotrexate; NHL-BFM, non-Hodgkin lymphoma Berlin-Frankfurt-Munster; OS, overall survival; PFS, progression-free survival; PMB DLBCL, primary mediastinal B-cell diffuse large B-cell lymphoma; POG, Pediatric Oncology Group; px, prophylactic; RT, radiation therapy.

on the time from completion of treatment to recurrence, site of relapse (nodal vs extranodal), and presence of B symptoms at relapse. Patients whose disease relapses >12 mo after chemotherapy alone or combined-modality therapy have the best prognosis, and their relapses usually respond to additional standard therapy, resulting in a long-term survival of 60-70%. A myeloablative autologous stem cell transplantation in patients with refractory disease or relapse within 12 mo of therapy results in a long-term survival rate of only 40-50%. Allogeneic stem cell transplantation has shown promise in patients with poor risk features at relapse/progression.

Bibliography is available at Expert Consult.

496.2 Non-Hodgkin Lymphoma

Jessica Hochberg, Lisa Giulino-Roth, and Mitchell S. Cairo

Non-Hodgkin lymphoma (NHL) accounts for approximately 60% of lymphomas in children and is the second most common malignancy in patients age 15-35 yr. The annual incidence of pediatric NHL in the United States is 750-800 cases/yr. In contrast to adult NHL, which is typically indolent, pediatric NHL is usually high grade and aggressive. Although more than 70% of patients present with advanced disease, the prognosis has improved dramatically, with survival rates of 90-95% for localized disease and 70-95% with advanced disease.

EPIDEMIOLOGY

Although most children and adolescents with NHL present with de novo disease, a small number of patients have NHL secondary to specific etiologies, including inherited or acquired immune deficiencies (e.g., severe combined immunodeficiency syndrome, Wiskott-Aldrich syndrome), viruses (e.g., HIV, EBV), and as part of genetic syndromes (e.g., ataxia-telangiectasia, Bloom syndrome). However most children in North America and Europe in whom NHL develops have no obvious genetic or environmental etiology.

PATHOGENESIS

The 4 major pathologic subtypes of childhood and adolescent NHL are **lymphoblastic lymphoma (LBL), Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL),** and **anaplastic large cell**

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lymphoma (**ALCL**; Figs. 496-4 and 496-5). LBL arises from immature B or T lymphocytes whereas BL, DLBCL, and ALCL are mature B- or T-cell neoplasms. DLBCL is further divided into several subtypes: the germinal center B-cell–like, which carries a favorable prognosis and accounts for the vast majority of pediatric cases of DLBCL, and the subtypes with poorer prognosis, activated B-cell–like and primary mediastinal B-cell subtypes. The cell of origin varies among NHL histologic subtypes. Almost all BLs and DLBCLs are of B-cell origin; 90% cases of LBL are of T-cell origin and 10% of B-cell origin; and 70% of cases of ALCL are of T-cell origin, 20% are of null-cell origin, and 10% are of B-cell origin. Cellular surface markers can aid in differentiating NHL subtypes and also present opportunities for targeted treatments. BL and DLBCL frequently express the B-cell antigens CD19, CD20, and CD22. ALCL, in contrast, expresses the CD30 antigen. Some pathologic subtypes have specific cytogenetic aberrations. Children with BL commonly have a t(8;14) translocation (90%) or, less commonly, a t(2;8) or t(8;22) translocation (10%). Children with BL who have a 13q deletion or complex karyotype have a poor prognosis. Those with DLBCL may have a t(8;14) translocation (30%) and often have a complex (80%) and aneuploid (80%) karyotype. Patients with ALCL commonly have a t(2;5) translocation (90%), which results in the formation of a fusion gene encoding the constitutively active nucleophosmin-anaplastic lymphoma kinase tyrosine kinase. Variant anaplastic lymphoma kinase (ALK) translocations, all with a breakpoint at 2p23, have also been reported. T-cell LBL harbors many of the same cytogenetic abnormalities as T-cell acute lymphoblastic leukemia (T-ALL), including rearrangements with breakpoints at 14q11.2 involving the T-cell receptor, and t(5;14) translocation (20%), which does not involve the 14q11.2 breakpoint.

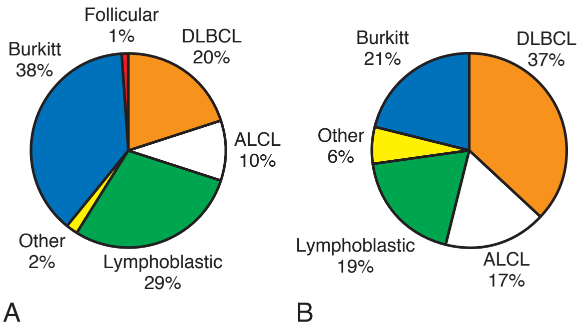

Figure 496-4 Incidence of non-Hodgkin lymphoma subtypes in **(A)** 0-14 yr age group and **(B)** 15-19 yr age group. *ALCL*, anaplastic large cell lymphoma; *DLBCL*, diffuse large B-cell lymphoma. *(Adapted from Hochberg J, Waxman IM, Kelly KM, et al: Adolescent non-Hodgkin lymphoma and Hodgkin lymphoma: state of the science*, Br J Haematol *144:24–40, 2008.)*

Genomic studies have offered insights into NHL pathogenesis as well as elucidated potential targets for novel therapies. Gene expression profiling of T-LBL and T-ALL has implicated the activation of oncogenic transcription factors as a result of aberrant T-cell receptor gene rearrangement. One of the most frequently activated signaling pathways is NOTCH1, which may be amenable to therapeutic targeting with γ-secretase inhibitors. In BL and DLBCL, extensive genomic work has identified unique gene expression signatures that differentiate these 2 mature B-cell neoplasms. In addition, next-generation sequencing of BL has identified genetic lesions in *TCF3* and *ID3*, which lead to activation of the AKT/PI3 kinase pathway. Other genetic lesions that have been described in BL include loss of function of the chromatin remodeling genes ARID1A and SMARCA4. Importantly, many of these alterations are potentially targetable by agents that are currently in development.

CLINICAL MANIFESTATIONS

The clinical manifestations of childhood and adolescent NHL depend primarily on pathologic subtype and sites of involvement. The staging system used for NHL is the St. Jude/Murphy classification (Table 496-5), although this classification schema is currently under an

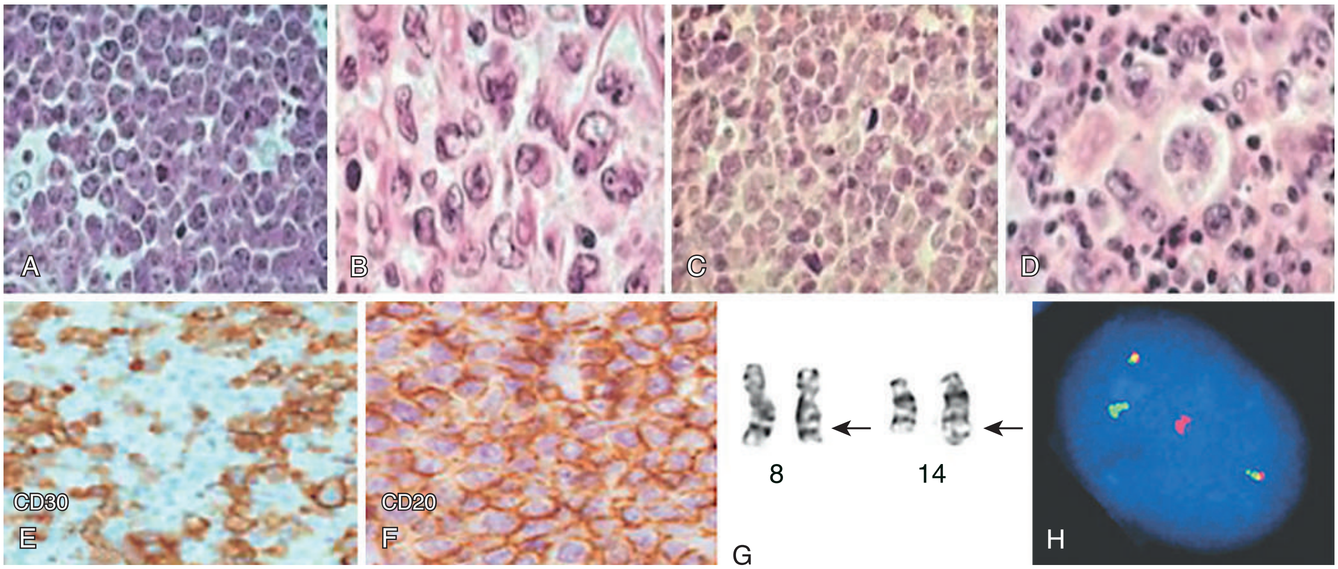

Figure 496-5 Histologic subtypes of childhood and adolescent non-Hodgkin lymphoma. **A-D:** Hematoxylin & eosin stains showing morphology of Burkitt lymphoma (**A,** high power), diffuse large B-cell lymphoma (**B,** high power), precursor T-lymphoblastic lymphoma (**C,** high power), and anaplastic large cell lymphoma (**D,** high power). **E-F:** Characteristic surface markers for ALCL (CD30; **E**) and BL (CD20; **F**). **G-H:** Cytogenetic analysis of BL demonstrating t(8;14). **G:** Karyotype showing the conventional t(8;14)(q24;q32). **H:** Interphase fluorescence in situ hybridization showing a balanced translocation involving MYC and immunoglobulin (Ig) H loci. The chromosome 8 centromere is labeled with spectrum aqua, MYC probe is labeled with spectrum orange, and IgH is labeled with spectrum green. Two fusion signals are seen as well as one red and one green representing the normal chromosomes. *(**A-D** from Cairo MS, Raetz E, Lim MS, et al: Childhood and adolescent non-Hodgkin lymphoma: new insights in biology and critical challenges for the future*, Pediatr Blood Cancer *45:753–769, 2005.* ***E-H*** *from Giulino-Roth, Cesarman E: Molecular biology of Burkitt lymphoma. In Robertson ES, editor,* Burkitt's lymphoma. *New York, 2012, Springer.)*

Table 496-5 St. Jude Staging System for Childhood Non-Hodgkin Lymphoma

STAGE	DESCRIPTION
I	A single tumor (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen
II	A single tumor (extranodal) with regional node involvement Two or more nodal areas on the same side of the diaphragm Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only, which must be grossly (>90%) resected
III	Two single tumors (extranodal) on opposite sides of the diaphragm Two or more nodal areas above and below the diaphragm Any primary intrathoracic tumor (mediastinal, pleural, or thymic) Any extensive primary intraabdominal disease
IV	Any of the above, with initial involvement of central nervous system or bone marrow at time of diagnosis

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Table 496-6 Risk Stratification Groups for Pediatric B-Cell NHL

Risk	Berlin-Frankfurt-Munster (BFM)	French-American-British (FAB)
Low Risk ↓	**R1** Stage I or II, completely resected	**Group A** Resected stage I and abdominal completely resected stage II
	R2 Stage I or II, not resected Stage III with LDH <500 U/L	**Group B** All patients not in Group A or C
	R3 Stage III with LDH ≥500 to <1000 U/L or Stage IV with LDH <1000 U/L and CNS-negative	
High Risk	**R4** Stage III or IV with LDH ≥1000 U/L and/or CNS-positive	**Group C** Bone marrow disease (≥25% L3 blasts) and/or CNS-positive

CNS, central nervous system; LDH, lactate dehydrogenase.

international revision. Patients are further classified based on risk categories according to pediatric international cooperative group trials (Table 496-6). Approximately 70% of patients with NHL present with advanced disease (stage III or IV), including extranodal disease with bone marrow and central nervous system (CNS) involvement. B symptoms of fever, weight loss, and night sweats can be seen, particularly in ALCL, but are not prognostic. Capillary leak syndrome may be seen in ALK+ ALCLs.

The primary site of tumor involvement and metastasis pattern varies by pathologic subtype. LBL commonly manifests as an intrathoracic or mediastinal supradiaphragmatic mass and also has a predilection for spreading to the bone marrow and CNS. BL commonly manifests as abdominal (sporadic type) or head and neck (endemic type) tumor and can metastasize to the bone marrow or CNS. DLBCL commonly manifests as either an abdominal or mediastinal primary and, rarely, disseminates to the bone marrow or CNS. ALCL manifests either as a primary cutaneous manifestation (10%) or as systemic disease (90%) with dissemination to liver, spleen, lung, or mediastinum. Bone marrow or CNS disease is rare in ALCL. Site-specific manifestations of NHL include painless, rapid lymph node enlargement; cough or dyspnea with thoracic involvement; superior mediastinal syndrome; ascites, increased abdominal girth or intestinal obstruction with an abdominal mass; nasal congestion, earache, hearing loss, or tonsil enlargement with Waldeyer ring involvement; and localized bone pain.

NHL can present as a life-threatening oncologic emergency. These manifestations are important to recognize as they require intensive supportive care and, in some cases, alterative treatment. Superior mediastinal syndrome can occur as a consequence of a large mediastinal mass causing obstruction of blood flow or respiratory airways. Spinal cord tumors can cause cord compression and acute paraplegias requiring emergent radiation therapy. Lastly, tumor lysis syndrome (TLS) can occur from rapid cell turnover, which is especially common in BL. TLS can result in severe metabolic abnormalities including hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. This can rapidly lead to renal insufficiency/failure as well as cardiac abnormalities if not aggressively treated.

LABORATORY FINDINGS

Recommended laboratory and radiologic testing includes complete blood cell count; measurements of electrolytes, lactate dehydrogenase, uric acid, calcium, phosphorus, blood urea nitrogen, creatinine, bilirubin, alanine aminotransferase, and aspartate aminotransferase; bone marrow aspiration and biopsy; lumbar puncture with cerebrospinal fluid cytology, cell count and protein; chest radiographs; and neck, chest, abdominal, and pelvic CT scans (head CT for suspicion of CNS disease), and PET scan. Tumor tissue (i.e., biopsy, bone marrow, cerebrospinal fluid, or pleurocentesis/paracentesis fluid) should be tested by flow cytometry for immunophenotypic origin (T, B, or null) and cytogenetics (karyotype). Additional tests might include fluorescent in situ hybridization or quantitative reverse transcription polymerase chain reaction for specific genetic translocations, T- and B-cell gene rearrangement studies, and molecular profiling by oligonucleotide microarray.

TREATMENT

The primary modality of treatment for childhood and adolescent NHL is **multiagent systemic chemotherapy with intrathecal chemotherapy** (see Table 496-4). Surgery is used mainly for diagnosis. Radiation therapy is used only in special circumstances, such as CNS involvement in LBL or, in the presence of acute superior mediastinal syndrome or paraplegias. Newly diagnosed patients, especially those with BL and LBL, are at high risk for TLS. These patients require vigorous hydration, frequent electrolyte monitoring, and either a xanthine oxidase inhibitor (allopurinol, 10 mg/kg/day PO divided into 3 doses daily) or recombinant urate oxidase (rasburicase, 0.2 mg/kg/day IV once daily for up to 5 days). Recombinant urate oxidase is preferred in patients with a high risk of tumor lysis. Frequently, only a single dose is needed; however, repeat doses can be given if a subsequent rise in uric acid is seen.

Burkitt Lymphoma and Diffuse Large B-cell Lymphoma

Pediatric BL and DLBCL are treated with similar chemotherapy regimens, which are designed for mature B-NHL. Regimens vary based on stage and risk stratification. For patients with localized disease, multiagent chemotherapy is given over a 6 wk to 6 mo period and the prognosis is excellent. In the international FAB/LMB 96 (French-American-British Lymphoma, mature B cell) trial, patients with

localized, completely resected disease received 2 cycles of COPAD (cyclophosphamide, vincristine, prednisone, and doxorubicin) resulting in a 4 yr OS of 99%. Advanced disease is usually treated with a 4-6 mo regimen of multiagent chemotherapy, such as FAB/LMB 96 protocol therapy or NHL-BFM (Berlin-Frankfurt-Munich) 95 protocol therapy with an OS of 79-90%. A subset of patients that likely require a different treatment approach are those with primary mediastinal B-cell lymphoma (PMBCL). PMBCL is a histologic subtype that represents 2% of mature B-NHLs. Pediatric patients with PMBCL have an inferior outcome when treated with standard mature B-NHL protocols (EFS of only 66%). Alternative treatment strategies, including rituximab and other novel agents, may be of benefit to this group.

Rituximab is a monoclonal antibody directed at CD20 that improves outcomes in adult patients with B-NHL. As nearly all pediatric BLs and DLBCLs express CD20, rituximab has been examined in pediatric B-NHL; however, the efficacy in this setting is not yet known. A window study of rituximab given to pediatric patients with newly diagnosed BL and DLBCL demonstrated its activity as a single agent with a response rate of 41%. Additionally, a Children's Oncology Group study examined the safety and pharmacokinetics of rituximab when added to standard chemotherapy for intermediate-risk patients. Rituximab was found to be safe, and survival in this cohort was the best reported to date (3 yr OS of 95%). In a similar cohort of CNS-positive patients, the addition of rituximab to the chemotherapy backbone resulted in a 93% EFS.

Lymphoblastic Lymphoma

Localized or advanced LBL requires 12-24 mo of therapy including chemotherapy, intrathecal therapy, and cranial radiation in some cases. The best results in advanced LBL have been obtained using the NHL-BFM 90 protocol, which uses therapeutic approaches similar to those for childhood acute leukemia, including induction, consolidation, interim maintenance, and reinduction (advanced disease only) phases as well as a year-long maintenance phase with 6-mercaptopurine and methotrexate. Studies have attempted to determine whether cranial radiation can be omitted, with promising results; however, the sample size in these studies is small. For patients with relapsed disease, the outcome is poor (OS of 10%) and novel treatments are needed. Nelarabine is a purine analog with significant T-lymphocyte toxicity; nelarabine has been investigated in T-LBL. Nelarabine is currently undergoing investigation in high-risk patients with T-ALL and T-LBL.

Anaplastic Large Cell Lymphoma

For patients who present with localized disease, surgical resection alone is sufficient. The majority of patients, however, have advanced disease, which requires multiagent chemotherapy. Various chemotherapy regimens have been studied with similar outcomes and survival ranging from 70-79%. CNS prophylaxis consists of intrathecal chemotherapy; however, it may be possible to omit this with the substitution of high-dose methotrexate. CNS disease, although rare, can be seen and is treated with intrathecal chemotherapy and cranial radiation.

Two novel targeted agents have shown substantial promise in early-phase trials in ALCL. The CD30 antibody–drug conjugate brentuximab and the ALK inhibitor crizotinib both have impressive activity and minimal toxicity in patients with relapsed ALCL. Given the high efficacy and low toxicity profile, it may be possible to use these agents in newly diagnosed patients to eliminate the reliance on and toxicity of conventional chemotherapy.

Relapsed Non-Hodgkin Lymphoma

Patients with NHL in whom progressive or relapsed disease develops require reinduction chemotherapy and either allogeneic or autologous stem cell transplantation (SCT). The specific reinduction regimen or transplantation type depends on the pathologic subtype, previous therapy, site of reoccurrence, and stem cell donor availability. Although there are no randomized trials examining autologous vs allogeneic SCT for relapsed NHL, data from retrospective studies suggest that outcomes are similar with the exception of LBL and ALCL where allogeneic SCT is superior, perhaps because of a graft-vs-lymphoma effect.

As relapsed NHL can be difficult to treat, efforts have been made to identify those patients at higher risk of relapse to tailor the initial therapy. The measurement of minimal residual disease may serve as a prognostic marker and aid in risk stratification. Minimal residual disease is prognostic in ALCL and LBL. In ALCL, there is also evidence that a humoral response to the ALK kinase can be used to predict outcome with a superior outcome in patients who mount an antibody titer to ALK. Minimal residual disease measurement in intermediate-risk B-NHL is feasible and is currently being evaluated in an international trial.

COMPLICATIONS

Patients receiving multiagent chemotherapy for advanced disease are at acute risk for serious mucositis, infections, cytopenias that require red blood cell and platelet blood product transfusions, electrolyte imbalances, and poor nutrition. Long-term complications include the risk of growth retardation, cardiac toxicity, gonadal toxicity with infertility, and secondary malignancies.

PROGNOSIS

The prognosis is excellent for most forms of childhood and adolescent NHL (see Table 496-4). Patients with localized disease have a 90-100% chance of survival, and those with advanced disease have a 70-95% chance of survival. As outcomes for pediatric patients with NHL have improved substantially, the focus has now shifted to minimizing the long-term toxicity of therapy. Novel targeted agents are desirable as they have the potential to improve outcomes and decrease the reliance on toxic conventional chemotherapy.

Bibliography is available at Expert Consult.

496.3 Late Effects in Children and Adolescents with Lymphoma

Jessica Hochberg, Lisa Giulino-Roth, and Mitchell S. Cairo

The majority of patients with newly diagnosed HL and NHL have OS rates above 90%. There are approximately 270,000 survivors of childhood cancer in the United States, which equates to about 1 of every 640 adults between the ages of 20 and 40 yr. However, this survival has often been achieved at the expense of an increased relative risk of long-term complications, including solid tumors, leukemia, cardiac disease, pulmonary complications, thyroid disease, and infertility. An analysis of more than 1,000 long-term childhood NHL survivors found increased rates of death >20 yr after treatment. A review of Surveillance, Epidemiology and End Results data over a 25 yr follow-up period demonstrates that the relative survival curves do not plateau after 10 yr following diagnosis of HL but, rather, accelerate. This finding highlights the importance of late morbidity and mortality among survivors of lymphoma. The first Childhood Cancer Survivor Study, a retrospective cohort study of 10,397 cancer survivors, shows that 62.3% of survivors report at least 1 chronic condition, with 27.5% reporting severe or life-threatening conditions. The survivor's adjusted relative risk of a severe or life-threatening chronic condition, compared with that of a sibling, was 8.2 (95% confidence interval, 6.9-9.7). When disease-specific health outcomes were looked at, both HL and NHL were found to be associated with a cumulative incidence of chronic health conditions approaching 70-80%, with severe conditions being reported in close to 50% of HL survivors (Fig. 496-6).

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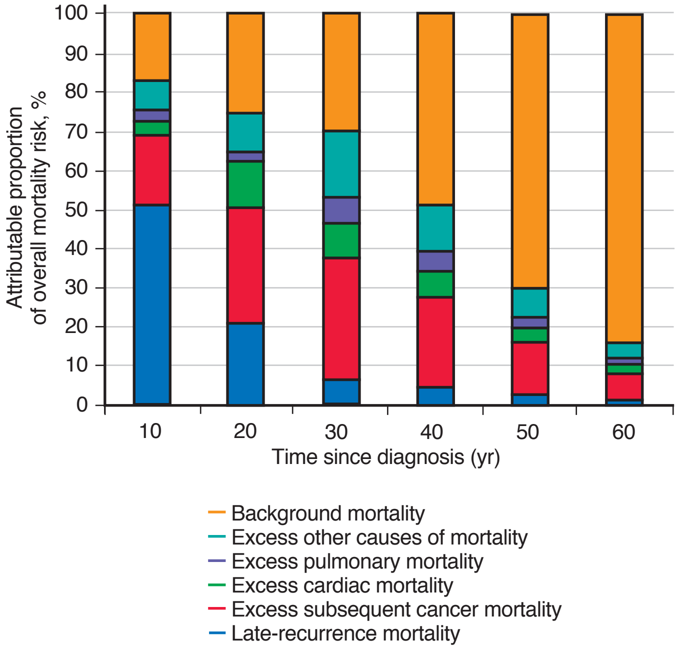

Figure 496-6 Percentage of attributable proportions of overall mortality risk in survivors of childhood cancer. *(Adapted from Yeh JM, Nekhlyudov L, Goldie SJ, et al: A model-based estimate of cumulative excess mortality in survivors of childhood cancer,* Ann Intern Med *152[7]:409–417, 2010.)*

Chapter **497**

Brain Tumors in Childhood

Joann L. Ater and John F. Kuttesch Jr.

Primary central nervous system (CNS) tumors are a heterogeneous group of diseases that are, collectively, the second most common malignancy in childhood and adolescence. The overall mortality among this group approaches 30%. Patients with CNS tumors have the highest morbidity—primarily neurologic—of all children with malignancies. Outcomes have improved over time with innovations in neurosurgery and radiation therapy as well as the introduction of chemotherapy as a therapeutic modality. The treatment approach for these tumors is multimodal. Surgery with complete resection, if feasible, is the foundation, with radiation therapy and chemotherapy utilized according to the diagnosis, patient age, and other factors.

ETIOLOGY

The etiology of pediatric brain tumors is not well defined. A male predominance is noted in the incidence of medulloblastoma and ependymoma. Familial and hereditary syndromes associated with an increased incidence of brain tumors account for approximately 5% of cases (Table 497-1). Cranial exposure to ionizing radiation also is associated with a higher incidence of brain tumors. There are sporadic reports of brain tumors within families without evidence of a heritable syndrome. The molecular events associated with tumorigenesis of pediatric brain tumors are not known.

EPIDEMIOLOGY

Approximately 4,600 primary brain tumors are diagnosed each year in children and adolescents in the United States, with an overall annual incidence of approximately 47 cases/1 million children younger than 20 yr of age. The incidence of CNS tumors is highest in infants and children 5 yr of age or younger (approximately 52 cases/1 million children).

PATHOGENESIS

More than 100 histologic categories and subtypes of primary brain tumors are described in the World Health Organization (WHO) classification of tumors of the CNS. In children 0-14 yr of age, the most common tumors are pilocytic astrocytomas (PAs) and medulloblastoma/primitive neuroectodermal tumors (PNETs). In adolescents (15-19 yr), the most common tumors are pituitary tumors and PAs (Fig. 497-1).

The Surveillance, Epidemiology, and End Results program reported a slight predominance of infratentorial tumor location (43.2%), followed by the supratentorial region (40.9%), spinal cord (4.9%), and multiple sites (11%) (Fig. 497-2, Table 497-2). There are age-related differences in primary location of tumor. During the 1st yr of life, supratentorial tumors predominate and include, most commonly, choroid plexus complex tumors and teratomas. In children 1-10 yr of age, infratentorial tumors predominate, owing to the high incidence of juvenile PA and medulloblastoma. After 10 yr of age, supratentorial tumors again predominate, with diffuse astrocytomas most common. Tumors of the optic pathway and hypothalamus region, the brainstem, and the pineal–midbrain region are more common in children and adolescents than in adults.

CLINICAL MANIFESTATIONS

The clinical presentation of the patient with a brain tumor depends on the tumor location, the tumor type, and the age of the child. Signs and symptoms are related to obstruction of cerebrospinal fluid (CSF) drainage paths by the tumor, leading to **increased intracranial pressure (ICP)** or causing focal brain dysfunction. Subtle changes in personality, mentation, and speech may precede these classic signs and symptoms; such changes often occur with supratentorial (cortical) lesions. In young children, the diagnosis of a brain tumor may be delayed because the symptoms are similar to those of more common illnesses, such as gastrointestinal disorders, with associated vomiting. Infants with open cranial sutures may present with signs of increased ICP, such as vomiting, lethargy, and irritability, as well as the later finding of macrocephaly. The **classic triad** of headache, nausea, and vomiting as well as papilledema is associated with midline or infratentorial tumors. Disorders of equilibrium, gait, and coordination occur with infratentorial tumors. **Torticollis** may occur in cases of cerebellar tonsil herniation. Blurred vision, diplopia, and nystagmus also are associated with infratentorial tumors. Tumors of the brainstem region may be associated with gaze palsy, multiple cranial nerve palsies, and upper motor neuron deficits (e.g., hemiparesis, hyperreflexia, clonus). **Supratentorial tumors** are more commonly associated with lateralized deficits, such as focal motor weakness, focal sensory changes, language disorders, focal seizures, and reflex asymmetry. Infants with supratentorial tumors may present with premature hand preference. Optic pathway tumors manifest as visual and/or afferent oculomotor disturbances, such as decreased visual acuity, Marcus Gunn pupil (afferent pupillary defect), nystagmus, and/or visual field defects. Suprasellar region tumors and third ventricular region tumors may manifest initially as **neuroendocrine deficits,** such as subacute development of obesity, abnormal linear growth velocity, diabetes insipidus, galactorrhea, precocious puberty, delayed puberty, and hypothyroidism. In fact, signs of endocrine dysfunction preceded symptoms of neuroophthalmologic dysfunction by an average of 1.9 yr, and their recognition as a possible sign of hypothalamic or pituitary neoplasm can hasten diagnosis and improve outcome. The **diencephalic syndrome,** which manifests as failure to thrive, emaciation despite normal caloric intake, and inappropriately normal or happy affect, occurs in infants and young children with tumors in these regions. **Parinaud syndrome** is seen with pineal region tumors and is manifested by paresis of upward gaze, pupillary caliber reactive to accommodation but not to light (pseudo-Argyll Robertson pupil), nystagmus to convergence or retraction, and eyelid retraction. Spinal cord tumors and spinal cord dissemination of brain tumors may manifest as long nerve tract motor and/or sensory

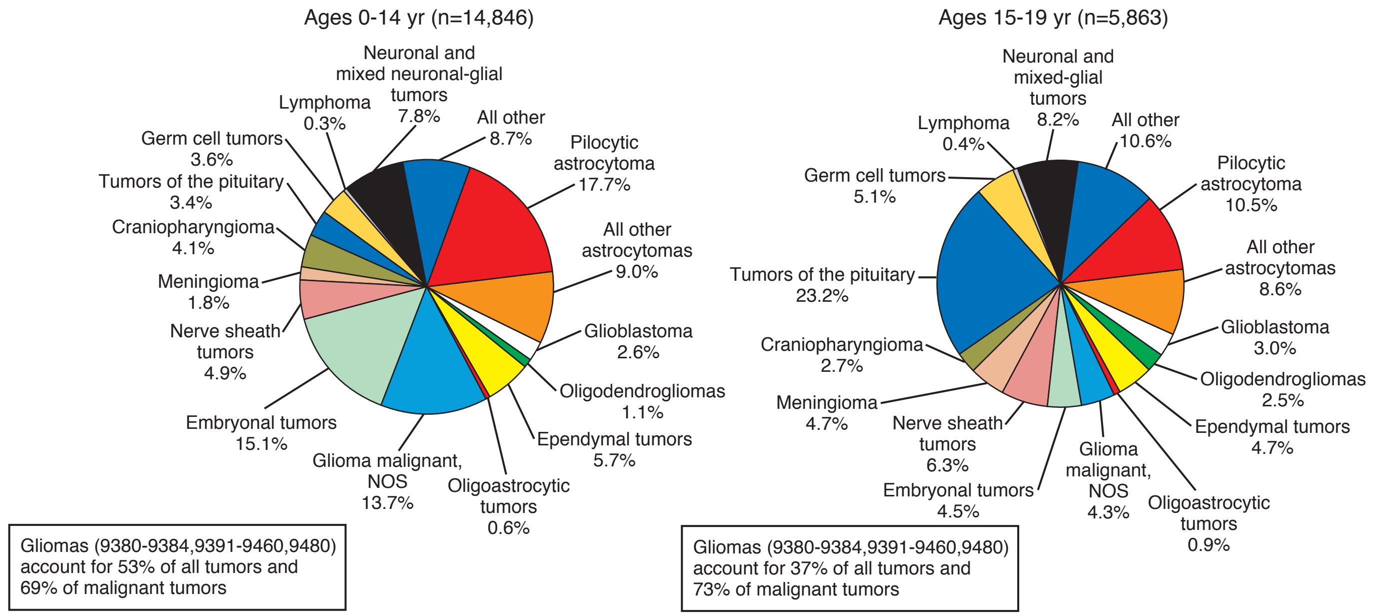

Figure 497-1 Distribution of childhood primary brain and CNS tumors by histology. *(From Dolecek TA, Propp JM, Stroup NE, Kruchko C: CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009,* Neuro Oncol 14:v1-v49, *2012.)*

Table 497-1 Familial Syndromes Associated with Pediatric Brain Tumors

SYNDROME	CENTRAL NERVOUS SYSTEM MANIFESTATIONS	CHROMOSOME	GENE
Neurofibromatosis type 1 (autosomal dominant)	Optic pathway gliomas, astrocytoma, malignant peripheral nerve sheath tumors, neurofibromas	17q11	*NF1*
Neurofibromatosis type 2 (autosomal dominant)	Vestibular schwannomas, meningiomas, spinal cord ependymoma, spinal cord astrocytoma, hamartomas	22q12	*NF2*
von Hippel–Lindau (autosomal dominant)	Hemangioblastoma	3p25-26	*VHL*
Tuberous sclerosis (autosomal dominant)	Subependymal giant cell astrocytoma, cortical tubers	9q34 16q13	*TSC1* *TSC2*
Li-Fraumeni (autosomal dominant)	Astrocytoma, primitive neuroectodermal tumor	17q13	*TP53*
Cowden (autosomal dominant)	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease)	10q23	*PTEN*
Turcot (autosomal dominant)	Medulloblastoma Glioblastoma	5q21 3p21 7p22	*APC* *hMLH1* *hPSM2*
Nevoid basal cell carcinoma Gorlin (autosomal dominant)	Medulloblastoma	9q31	*PTCH1*

Modified from Kleihues P, Cavenee WK: World Health Organization classification of tumors: pathology and genetics of tumors of the nervous system, *Lyon, 2000, IARC Press.*

deficits often localized to below a specific spinal level, bowel and bladder deficits, and back or radicular pain. The signs and symptoms of meningeal metastatic disease from brain tumors or leukemia include head or back pain and symptoms referable to compression of cranial nerves or spinal nerve roots.

DIAGNOSIS

The evaluation of a patient in whom a brain tumor is suspected is an emergency. Initial evaluation should include a complete history, physical (including ophthalmic) examination, and neurologic assessment with neuroimaging. For primary brain tumors, **MRI** with and without gadolinium is the neuroimaging standard. Tumors in the pituitary/suprasellar region, optic path, and infratentorium are better delineated with MRI than with CT. Patients with tumors of the midline and the pituitary/suprasellar/optic chiasmal region should undergo evaluation for **neuroendocrine dysfunction.** Formal ophthalmologic examination is beneficial in patients with optic path region tumors to document the impact of the disease on oculomotor function, visual acuity, and fields of vision. The suprasellar and pineal regions are preferential sites for germ cell tumors (Fig. 497-3). Both serum and CSF measurements of **β-human chorionic gonadotropin** and **α-fetoprotein** can assist in the diagnosis of germ cell tumors. In tumors with a propensity for spreading to the leptomeninges, such as medulloblastoma/PNET, ependymoma, and germ cell tumors, lumbar puncture with cytologic analysis of the CSF is indicated; lumbar puncture is contraindicated in individuals with newly diagnosed hydrocephalus secondary to CSF flow obstruction, in tumors that cause supratentorial midline shift, and in individuals with infratentorial tumors. Lumbar puncture in

these individuals may lead to brain herniation, resulting in neurologic compromise and death. Therefore, in children with newly diagnosed intracranial tumors and signs of increased ICP, the lumbar puncture usually is delayed until surgery or shunt placement.

SPECIFIC TUMORS

Astrocytomas

Astrocytomas are a heterogeneous group of tumors that account for approximately 40% of pediatric CNS malignancies. These tumors occur throughout the CNS.

Low-grade astrocytomas (LGAs), the predominant group of astrocytomas in childhood, are characterized by an indolent clinical course. **PA** is the most common astrocytoma in children, accounting for approximately 20% of all brain tumors. On the basis of clinicopathologic features using the WHO Classification System, PA is classified as a WHO grade I tumor. Although PA can occur anywhere in the CNS, the classic site is the **cerebellum** (Fig. 497-4*A*). Other common sites include the hypothalamic/third ventricular region and the optic nerve and chiasmal region (Fig. 497-4*B*). The classic but not exclusive neuroradiologic finding in PA is the presence of a contrast medium–enhancing nodule within the wall of a cystic mass (Fig. 497-4*A*). The microscopic findings include the biphasic appearance of bundles of compact fibrillary tissue interspersed with loose microcystic, spongy areas. The presence of **Rosenthal fibers,** which are condensed masses of glial filaments occurring in the compact areas, helps establish the diagnosis. PA has a low metastatic potential and is rarely invasive. A

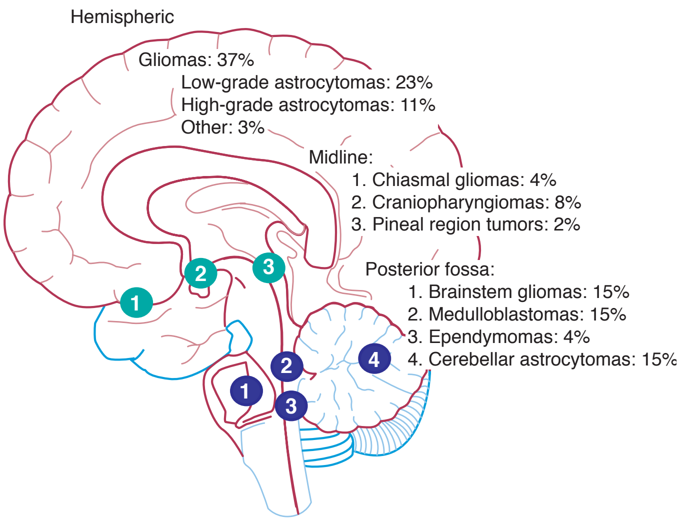

Figure 497-2 **Childhood brain tumors occur at any location within the central nervous system.** The relative frequency of brain tumor histologic types and the anatomic distribution are shown. *(Redrawn from Albright AL: Pediatric brain tumors,* CA Cancer J Clin *43:272–288, 1993.)*

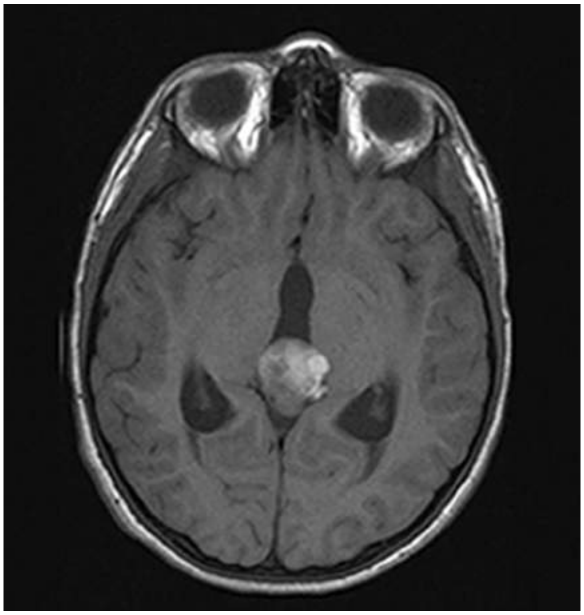

Figure 497-3 Axillary T1-weighted MR image with gadolinium of a 10 yr old boy presenting with mixed germ cell tumor of the pineal region, with early onset of puberty, headaches, and elevated α-fetoprotein and β–human chorionic gonadotropin in the spinal fluid and serum.

Table 497-2 Posterior Fossa Tumors of Childhood

TUMOR	RELATIVE INCIDENCE (%)	PRESENTATION	DIAGNOSIS	PROGNOSIS
Medulloblastoma	35-40	2-3 mo of headaches, vomiting, truncal ataxia	Heterogeneously or homogeneously enhancing fourth ventricular mass; may be disseminated	65-85% survival; dependent on stage/type; poorer (20-70%) in infants
Cerebellar astrocytoma	35-40	3-6 mo of limb ataxia; secondary headaches, vomiting	Cerebellar hemisphere mass, usually with cystic and solid (mural nodule) components	90-100% survival in totally resected pilocytic type
Brainstem glioma	10-15	1-4 mo of double vision, unsteadiness, weakness, and cranial nerve dysfunction, including facial weakness, swallowing dysfunction, and oculomotor abnormalities	Diffusely expanded, minimally or partially enhancing mass in 80%; 20% more focal tectal or cervicomedullary lesion	>90% mortality in diffuse tumors; better in localized
Ependymoma	10-15	2-5 mo of unsteadiness, headaches, double vision, and facial asymmetry	Usually enhancing, fourth ventricular mass with cerebellopontine predilection	>75% survival in totally resected lesions
Atypical teratoid/rhabdoid	>5 (10-15% of infantile malignant tumors)	As in medulloblastoma, but primarily in infants; often associated facial weakness and strabismus	As in medulloblastoma, but often more laterally extended	≤20% survival in infants

Modified from Packer RJ, MacDonald T, Vezina G: Central nervous system tumors, Pediatr Clin North Am *55:121–145, 2008.*

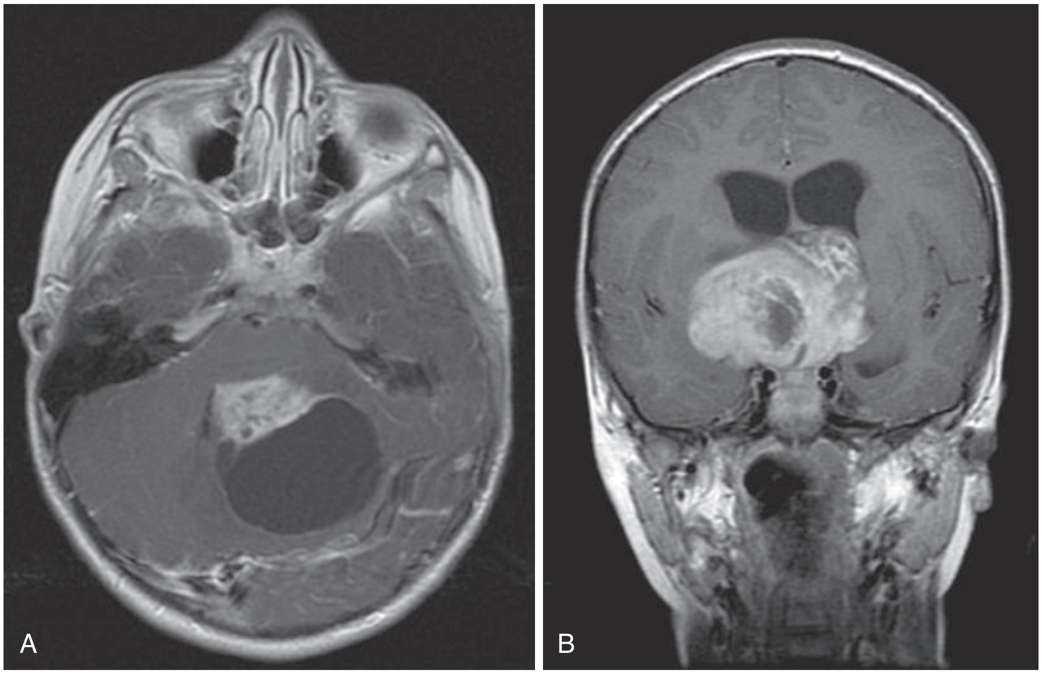

Figure 497-4 **A,** Gadolinium-enhanced axial T1-weighted MR image in a 4 yr old child with cerebellar pilocytic astrocytoma presenting with headaches, emesis, and ataxia demonstrates a predominantly cystic mass with enhancement of the solid component and enhancement of the capsule. **B,** Gadolinium-enhanced coronal view of a cystic juvenile pilocytic astrocytoma of the suprasellar region from a 4 yr old child presenting with visual loss and headaches.

small proportion of these tumors can progress and develop leptomeningeal spread, particularly when they occur in the optic path region. A PA very rarely undergoes malignant transformation to a more aggressive tumor. A PA of the optic nerve and chiasmal region is a relatively common finding in patients with neurofibromatosis type 1 (15% incidence). Unlike in diffuse fibrillary astrocytomas, there are no characteristic cytogenetic abnormalities in PA. Other tumors occurring in the pediatric age group with clinicopathologic characteristics similar to those of PA include pleomorphic xanthoastrocytoma, desmoplastic cerebral astrocytoma of infancy, and subependymal giant cell astrocytoma.

The second most common astrocytoma is **fibrillary infiltrating astrocytoma,** which consists of a group of tumors characterized by a pattern of diffuse infiltration of tumor cells amidst normal neural tissue and potential for anaplastic progression. On the basis of their clinicopathologic characteristics, they are grouped as LGAs (WHO grade II), malignant astrocytomas (anaplastic astrocytoma; WHO grade III), and glioblastoma multiforme (WHO grade IV). Fibrillary LGA accounts for 15% of brain tumors. Histologically, these low-grade tumors demonstrate greater cellularity than normal brain parenchyma, with few mitotic figures, nuclear pleomorphism, and microcysts. The characteristic MRI finding is a lack of enhancement after contrast agent infusion. Molecular genetic abnormalities found among low-grade diffuse infiltrating astrocytomas include mutations of *P53* and overexpression of platelet-derived growth factor α-chain and platelet-derived growth factor receptor-α. **Evolution of fibrillary infiltrating astrocytoma** into malignant astrocytoma is associated with cumulative acquisition of multiple molecular abnormalities.

Pilomyxoid astrocytoma occurs most commonly in the hypothalamic/optic chiasmic region and carries a high risk of local as well as cerebrospinal spread. This astrocytoma affects young children and infants. It is classified as a WHO grade II tumor.

The **clinical management** of LGAs focuses on a multimodal approach incorporating surgery as the primary treatment as well as radiation therapy and chemotherapy. With complete surgical resection the overall survival approaches 80-100%. In patients with partial resection (<80% resection), overall survival varies from 50-95%, depending on the anatomic location of the tumor. In the patient who has undergone partial tumor resection and has stable neurologic status, the current approach is to follow the patient closely by examination and imaging. With evidence of progression, a second surgical resection should be considered. In patients in whom a second procedure was less than complete or is not feasible, radiation therapy is beneficial. Radiation therapy is delivered to the tumor bed at a total cumulative dose ranging from 50-55 Gy given on a daily schedule over 6 wk. Historically, patients with deep midline tumors have been treated empirically with radiation therapy and without surgery or biopsy, with variable survival rates from 33-75%. Modern surgical techniques and innovative radiation therapy methodology, including proton-beam radiation, may have a positive impact on the survival and clinical outcome of these patients. The role of chemotherapy in the management of LGAs is evolving. Because of concerns regarding morbidity from radiation therapy in young children, several chemotherapy approaches have been evaluated, especially in children younger than 10 yr of age. Complete response to chemotherapy is uncommon; however, these approaches have yielded durable control of disease in 70-100% of patients. Patients with midline tumors in the hypothalamic/optic chiasmatic region (see Fig. 497-4*B*) have tended to do less well. Taken together, the chemotherapy approaches have permitted delay and, potentially, avoidance of radiation therapy. Chemotherapy agents given singly or in combination for LGA include carboplatin, vincristine, lomustine, procarbazine, temozolomide, and vinblastine. Observation is the primary approach in clinical management of selected patients with LGAs that are biologically indolent. One such group includes patients with neurofibromatosis type 1, in whom an LGA of the optic chiasm/optic pathway or brainstem may be found incidentally. Another group includes patients with midbrain astrocytoma who have resolution of clinical symptoms after ventricular shunting and do not require further intervention. Astrocytomas associated with tuberous sclerosis have responded to everolimus, a mammalian target of rapamycin inhibitor.

Malignant astrocytomas are much less common in children and adolescents than in adults, accounting for 7-10% of all childhood tumors. Among this group, **anaplastic astrocytoma** (WHO grade III,

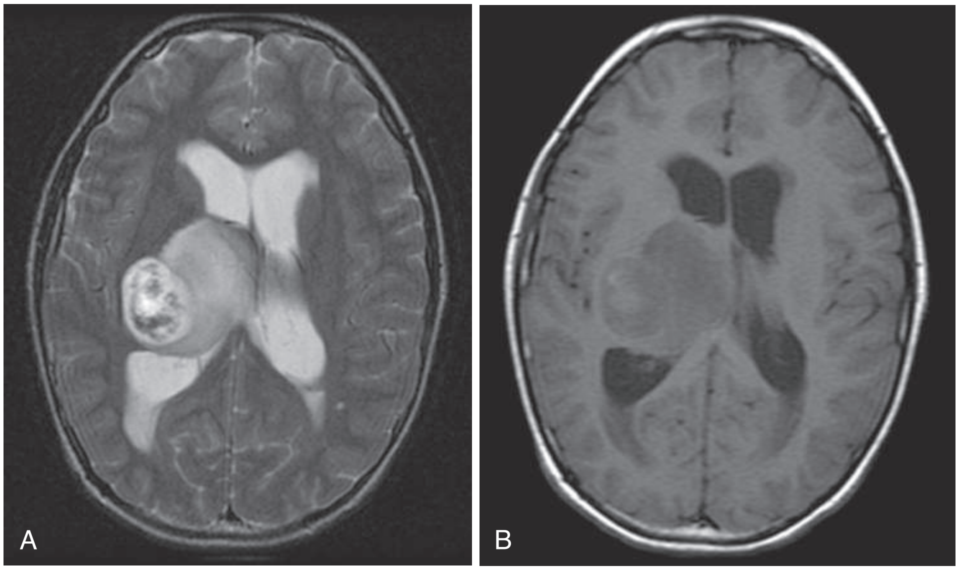

Figure 497-5 **A,** Nonenhanced axial T2-weighted MR image of grade III astrocytoma of the right thalamus demonstrating diffuse hyperintensity and area of necrotic cyst formation. **B,** Gadolinium-enhanced sagittal T1-weighted MR image showing slight enhancement and hypodensity of grade III astrocytoma of the thalamus. This 14 yr old child presented with left arm and leg numbness and weakness and right-sided headaches.

Fig. 497-5) is more common than **glioblastoma multiforme** (WHO grade IV). The histopathology of anaplastic astrocytomas demonstrates greater cellularity than that of low-grade diffuse astrocytomas, with cellular and nuclear atypia, presence of mitoses, and, variably, microvascular proliferation. Characteristic histopathologic findings in glioblastoma multiforme include dense cellularity, high mitotic index, microvascular proliferation, and foci of tumor necrosis. Limited information is available regarding the molecular abnormalities in malignant astrocytomas in children. Overexpression of *P53* in malignant astrocytoma in a child is an adverse prognostic factor. The frequency of mutations in *P53* and of the loss of heterozygosity at 19q and 22q in childhood malignant astrocytomas are similar to that noted in adults, although the frequency of such mutations in malignant astrocytomas of children younger than 3 yr of age is lower. This finding suggests differing mechanisms of oncogenesis in younger and older children, respectively. Optimal therapeutic approaches for malignant astrocytomas have yet to be defined. Standard therapy continues to be surgical resection followed by involved-field radiation therapy. A study of adult glioblastoma showed significantly better survival with temozolomide during and after irradiation than with irradiation alone. Current therapeutic approaches incorporate novel chemotherapeutic agents with radiation therapy. Enrollment in a clinical trial may be the best therapeutic option in these tumors where standard therapy is suboptimal.

Oligodendrogliomas are uncommon tumors of childhood. These infiltrating tumors occur predominantly in the cerebral cortex and originate in the white matter. Histologically, oligodendrogliomas consist of rounded cells with little cytoplasm and microcalcifications. Observation of a **calcified cortical mass** on CT in a patient presenting with a seizure is suggestive of oligodendroglioma. Treatment approaches are similar to those for infiltrating astrocytomas.

Ependymal Tumors

Ependymal tumors are derived from the ependymal lining of the ventricular system. Ependymoma (WHO grade II) is the most common of these neoplasms, occurring predominantly in childhood and accounting for 10% of childhood tumors. Approximately 70% of ependymomas in childhood occur in the posterior fossa. The mean age of patients is 6 yr, with approximately 40% of cases occurring in children younger than 4 yr of age. The incidence of leptomeningeal spread approaches 10% overall. Clinical presentation can be insidious and often depends on the anatomic location of the tumor. MRI demonstrates a well-circumscribed tumor with variable and complex patterns of gadolinium enhancement, with or without cystic structures (Fig. 497-6). These tumors usually are noninvasive, extending into the ventricular lumen and/or displacing normal structures, sometimes leading to significant obstructive hydrocephalus. Histologic characteristics include perivascular pseudorosettes, ependymal rosettes, monomorphic nuclear morphology, and occasional nonpalisading foci of necrosis. Other histologic subtypes include anaplastic ependymoma (WHO grade III), which is much less common in childhood and is characterized by a high mitotic index and histologic features of microvascular proliferation and pseudopalisading necrosis. Myxopapillary ependymoma (WHO grade I) is a slow-growing tumor arising from the filum terminale and conus medullaris and appears to be a biologically different subtype. There are no well-defined characteristic cytogenetic or molecular genetic alterations in ependymoma, largely owing to their heterogeneous nature, although association of various genotypes with susceptibility to ependymoma have been implicated. Preliminary studies suggest that there are genetically distinct subtypes of ependymoma, exemplified by an association between alterations in the *NF2* gene and spinal ependymoma. Surgery is the primary treatment modality, with extent of surgical resection a major prognostic factor. Two other major prognostic factors are age, with younger children having poorer outcomes, and tumor location, with localization in the posterior fossa, which often is seen in young children, associated with poorer outcomes. Surgery alone is rarely curative. Multimodal therapy incorporating irradiation with surgery has resulted in long-term survival in approximately 40% of patients with ependymoma undergoing gross total resection. Recurrence is predominantly local. Ependymoma is sensitive to a spectrum of chemotherapeutic agents; the role of chemotherapy in multimodal therapy of ependymoma is still unclear. Current investigations are directed toward identification of optimal radiation dose, surgical questions addressing the use of second-look procedures after chemotherapy, and further evaluation of classic as well as novel chemotherapeutic agents.

Choroid Plexus Tumors

Choroid plexus tumors account for 2-4% of childhood CNS tumors. They are the most common CNS tumor in children younger than 1 yr of age and account for 10-20% of CNS tumors in infants. These tumors are intraventricular epithelial neoplasms arising from the choroid plexus. Children present with signs and symptoms of increased ICP.

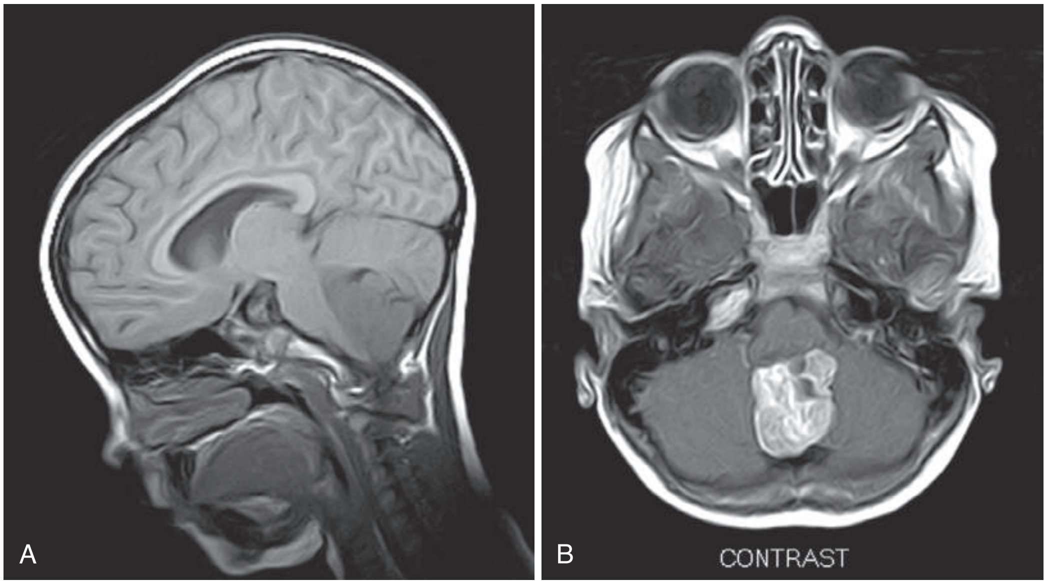

Figure 497-6 **A,** Sagittal T1-weighted MR image of a 6 yr old patient with ependymoma, demonstrating a hypointense mass within the fourth ventricle compressing the brainstem. **B,** Gadolinium-enhanced axial T1-weighted image of an ependymoma showing an enhancing mass within the fourth ventricle.

Infants may present with macrocephaly and focal neurologic deficits. In children, these tumors predominantly occur supratentorially in the lateral ventricles. **Choroid plexus papilloma** (WHO grade I), the most common of this group, is a well-circumscribed lesion on neuroimaging and closely resembles normal choroid plexus histologically. **Choroid plexus carcinoma** (WHO grade III) is a malignant tumor with metastatic potential to seed into the CSF pathways. This malignancy has the following histologic characteristics: nuclear pleomorphism, high mitotic index, and increased cell density. Immunopositivity for transthyretin (prealbumin) is useful in confirming the diagnosis of choroid plexus tumors. These tumors are associated with the **Li-Fraumeni syndrome. Simian virus 40** may also play an etiologic role in choroid plexus tumors. After complete surgical resection, the frequency of cure for choroid plexus papilloma approaches 100%, whereas the frequency of cure for choroid plexus carcinoma approaches 20-40%. Reports suggest that radiation therapy and/or chemotherapy may lead to better disease control for choroid plexus carcinoma.

Embryonal Tumors

Embryonal tumors or **PNETs** are the most common group of *malignant* CNS tumors of childhood, accounting for approximately 20% of pediatric CNS tumors. They have the potential to metastasize to the neuraxis and beyond. The group includes medulloblastoma, supratentorial PNET, ependymoblastoma, medulloepithelioblastoma, and atypical teratoid/rhabdoid tumor, all of which are histologically classified as WHO grade IV tumors.

Medulloblastoma, which accounts for 90% of embryonal CNS tumors, is a cerebellar tumor occurring predominantly in males and at a median age of 5-7 yr. Most of these tumors occur in the midline cerebellar vermis; however, older patients may present with tumors in the cerebellar hemisphere. CT and MRI demonstrate a solid, homogeneous, contrast medium–enhancing mass in the posterior fossa causing fourth ventricular obstruction and hydrocephalus (Fig. 497-7). Up to 30% of patients with medulloblastoma present with neuroimaging evidence of leptomeningeal spread. Among a variety of diverse histologic patterns of this tumor, the most common is a monomorphic sheet of undifferentiated cells classically noted as small, blue, round cells. Neuronal differentiation is more common among these tumors and is characterized histologically by the presence of Homer Wright rosettes and by immunopositivity for synaptophysin. An anaplastic variant is often more aggressive and may be associated with worse prognosis. Patients present with signs and symptoms of increased ICP (i.e., headache, nausea, vomiting, mental status changes, and hypertension) and cerebellar dysfunction (i.e., ataxia, poor balance, dysmetria). Standard clinical staging evaluation includes MRI of the brain and spine, both preoperatively and postoperatively, as well as lumbar puncture after the increased ICP has resolved. The Chang staging system, originally based on surgical information, has been modified to incorporate information from neuroimaging to identify risk categories. Clinical features that have consistently demonstrated prognostic significance include age at diagnosis, extent of disease, and extent of surgical resection. Patients younger than 4 yr of age have a poor outcome, partly as the result of a higher incidence of disseminated disease on presentation and past therapeutic approaches that have used less intense therapies. Patients with disseminated disease at diagnosis (M >0), including positive CSF cytologic result alone (M1), have a markedly worse outcome than those patients with no dissemination (M0). Similarly, patients with gross residual disease after surgery have worse outcomes than those in whom surgery achieved gross total resection of disease.

Cytogenetic and molecular genetic studies have demonstrated multiple abnormalities in medulloblastoma. The most common abnormality involves chromosome 17p deletions, which occur in 30-40% of all cases. These deletions are not associated with *P53* mutations. Several signaling pathways have been shown to be active in medulloblastomas, including the sonic hedgehog (SHH) pathway, predominately associated with the desmoplastic variants, and the WNT pathway, which can occur in up to 15% of cases and has been associated with improved survival. Integrative genomic studies have recently identified at least 4 distinct molecular subgroups of medulloblastoma—WNT, SHH, group 3, and group 4—which exhibit highly discriminate transcriptional, cytogenetic, and mutational spectra, in addition to divergent patient demographics and clinical behavior. These prognostic groups still must be validated in larger prospective studies. With the evolution of gene array technology, preliminary studies have identified clusters of genes/gene expression that appear to be associated with metastatic medulloblastoma and outcome.

A multimodal treatment approach is pursued in medulloblastoma, with surgery as the starting point of treatment. Medulloblastoma is sensitive to both chemotherapy and radiation therapy. With technologic advances in neurosurgery, neuroradiology, and radiation therapy, as well as identification of chemotherapy as an effective modality, the overall outcome among all patients approaches 60-70%. Standard

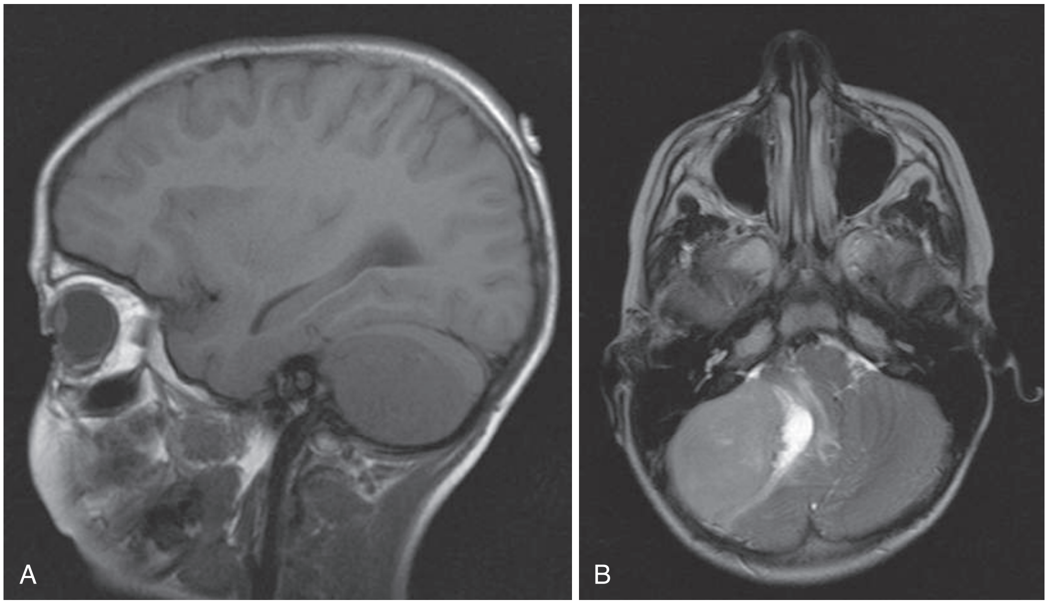

Figure 497-7 **A,** Sagittal T1-weighted MR image shows hypointense mass involving the cerebellar hemisphere in a 6 yr old child with desmoplastic variant of medulloblastoma. **B,** Axial T2-weighted image of the same child shows hyperintense mass involving the cerebellar hemisphere.

radiation treatment in standard risk medulloblastoma incorporates craniospinal radiation at a total cumulative dose of 24 Gy, with a cumulative dose of 50-55 Gy to the tumor bed. Craniospinal radiation at this dose in children younger than 3 yr of age results in severe late neurologic sequelae, including microcephaly, learning disabilities, cognitive impairment, neuroendocrine dysfunction (growth failure, hypothyroidism, hypogonadism, and absence/delay of puberty), and/or second malignancies. Similarly, in older children, late sequelae, such as learning disabilities, neuroendocrine dysfunction, and/or second malignancies, can occur. These observations have resulted in stratification of treatment approaches into the following 3 strata: (1) patients younger than 3 yr of age; (2) standard-risk patients older than 3 yr of age with surgical total resection and no disease dissemination (M0); and (3) high-risk patients older than 3 yr of age with disease dissemination (M >0) and/or bulky residual disease after surgery. With the risk-based approach to treatment, children with high-risk medulloblastoma receive high-dose cranial–spinal radiation (36 Gy) with chemotherapy during and after radiation therapy, and those with standard-risk (nonmetastatic) disease receive lower-dose craniospinal radiation (24 Gy) with chemotherapy during and after radiation therapy. Because the dose of radiation depends on the risk stratification, complete staging with MRI of the spine before starting treatment is essential for the best chance of survival. Approaches in young children (younger than 4 yr of age) incorporate high-dose chemotherapy with peripheral stem cell reinfusion and exclude radiation therapy. Overall survival in children with nonmetastatic medulloblastoma and gross total tumor resection approaches 85%. The presence of bulky residual tumor (56% survival) or metastases (38% survival) confers a poor prognosis.

Supratentorial primitive neuroectodermal tumors (SPNETs) account for 2-3% of childhood brain tumors, primarily in children within the 1st decade of life. These tumors are similar histologically to medulloblastoma and are composed of undifferentiated or poorly differentiated neuroepithelial cells. Historically, patients with SPNETs have had poorer outcomes than those with medulloblastoma after combined-modality therapy. In current clinical trials, children with SPNETs are considered among the high-risk group and receive dose-intense chemotherapy with craniospinal radiation therapy.

Atypical teratoid/rhabdoid tumor is a very aggressive embryonal malignancy that occurs predominantly in children younger than 5 yr of age and can occur at any location in the neuraxis. The histology demonstrates a heterogeneous pattern of cells, including rhabdoid cells that express epithelial membrane antigen and neurofilament antigen. The characteristic cytogenetic pattern is partial or complete deletion of chromosome 22q11.2 that is associated with mutation in the *INI1* gene. The relation between this mutation and tumorigenesis is unclear. Outcome after combined-modality therapy with intensive chemotherapy is very poor and there is no standard chemotherapy. However, long-term survival is reported for some children, primarily with complete resection and focal radiotherapy.

Pineal Parenchymal Tumors

The pineal parenchymal tumors are the most common malignancies after germ cell tumors that occur in the pineal region. These include pineoblastoma, occurring predominantly in childhood, pineocytoma, and the mixed pineal parenchymal tumors. The therapeutic approach in this group of diseases is multimodal. There was significant concern regarding the location of these masses and the potential complications of surgical intervention. With developments in neurosurgical technique and surgical technology, the morbidity and mortality associated with these approaches have markedly decreased. Stereotactic biopsy of these tumors may be adequate to establish diagnosis; however, consideration should be given to total resection of the lesion before institution of additional therapy. Pineoblastoma, the more malignant variant, is considered a subgroup of childhood PNETs. Chemotherapy regimens incorporate cisplatin, cyclophosphamide (Cytoxan), etoposide (VP-16), and vincristine and/or lomustine. Data have shown that survival outcome of combined chemotherapy and radiation therapy in pineal-region PNETs approaches 70% at 5 yr, similar to that noted for medulloblastoma. Pineocytoma usually is approached with surgical resection.

Craniopharyngioma

Craniopharyngioma (WHO grade I) is a common tumor of childhood, accounting for 7-10% of all childhood tumors. The adamantinomatous variant of craniopharyngioma predominates in childhood. Children with craniopharyngioma often present with endocrinologic abnormalities such as growth failure and delayed sexual maturation. Visual changes can occur and may include decreased acuity or visual field abnormalities. These tumors are often quite large and heterogeneous, displaying both solid and cystic components, and occur within the suprasellar region. They are minimally invasive, adhere to

adjacent brain parenchyma, and engulf normal brain structures. MRI demonstrates the solid tumor with cystic structures containing fluid of intermediate density. CT may show calcifications associated with the solid and cystic wall components. Surgery is the primary treatment modality, with gross total resection curative in small lesions. Controversy exists regarding the relative roles of surgery and radiation therapy in large, complex tumors. Significant morbidity (panhypopituitarism, growth failure, visual loss) is associated with these tumors and their therapy, owing to the anatomic location. There is no role for chemotherapy in craniopharyngioma.

Germ Cell Tumors

Germ cell tumors of the CNS are a heterogeneous group of tumors that are primarily tumors of childhood, arising predominantly in midline structures of the pineal and suprasellar regions (see Fig. 497-3). They account for 3-5% of pediatric brain tumors. The peak incidence of these tumors is in children 10-12 yr of age. Overall, there is a male preponderance, although there is a female preponderance for suprasellar tumors. Germ cell tumors occur multifocally in 5-10% of cases. This group of tumors is much more prevalent in Asian populations than European populations. Delays in diagnosis can occur because these tumors have a particularly insidious course; the initial presenting symptoms may be subtle, including poor school performance and behavior problems. As in peripheral germ cell tumors, the analysis of protein markers, **α-fetoprotein,** and **β-human chorionic gonadotropin** may be useful in establishing the diagnosis and monitoring treatment response. Surgical biopsy is recommended to establish the diagnosis; however, nongerminomatous germ cell tumors may be diagnosed on the basis of protein marker elevations. Therapeutic approaches to germinomas and mixed germ cell tumors are different. The survival proportion among patients with pure germinoma exceeds 90%. The postsurgical treatment of pure germinomas is somewhat controversial in defining the relative roles of chemotherapy and radiation therapy. Clinical trials have investigated the use of chemotherapy and reduced-dose radiation after surgery in pure germinomas. The therapeutic approach to nongerminomatous germ cell tumors is more aggressive, combining more intense chemotherapy regimens with craniospinal radiation therapy. Survival rates among patients with these tumors are markedly lower than those noted in patients with germinoma, ranging from 40-70% at 5 yr. Trials have shown the benefit of the use of high doses of chemotherapy with peripheral blood stem cell rescue.

Tumors of the Brainstem

Tumors of the brainstem are a heterogeneous group of tumors that account for 10-15% of childhood primary CNS tumors. Outcome depends on tumor location, imaging characteristics, and the patient's clinical status. Patients with these tumors may present with motor weakness, cranial nerve dysfunction, cerebellar dysfunction, and/or signs of increased ICP. On the basis of MRI evaluation and clinical findings, tumors of the brainstem can be classified into 4 types: focal (5-10% of patients); dorsally exophytic (5-10%); cervicomedullary (5-10%); and diffuse intrinsic (70-85%) (Fig. 497-8). Surgical resection is the primary treatment approach for focal and dorsally exophytic tumors and leads to a favorable outcome. Histologically, these 2 groups usually are low-grade gliomas. Cervicomedullary tumors, owing to their location, may not be amenable to surgical resection but are sensitive to radiation therapy. Diffuse intrinsic tumors, characterized by the diffuse infiltrating pontine glioma, are associated with a very poor outcome independent of histologic diagnosis. These tumors are not amenable to surgical resection. Biopsy in children in whom MRI shows a diffuse intrinsic tumor is controversial and is not recommended unless there is suspicion of another diagnosis, such as infection, vascular malformation, multiple sclerosis or other disorder of myelination, or metastatic tumor. These diagnoses are much more common in adults. The standard approach for treatment of diffuse infiltrating pontine gliomas has been radiation therapy, and median survival with this treatment is 12 mo, at best. Use of chemotherapy, including high-dose chemotherapy with peripheral blood stem cell rescue, has not yet been of survival benefit in this group of patients. Current approaches include evaluation of investigational agents alone or in combination with radiation therapy, similar to approaches being pursued in patients with malignant gliomas.

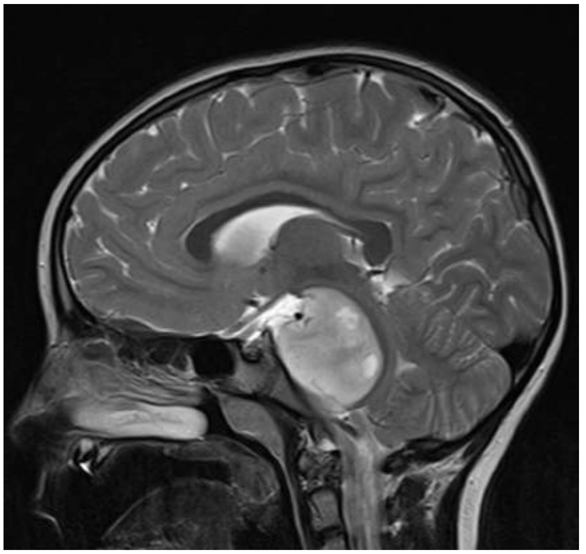

Figure 497-8 T2-weighted sagittal MR image of a diffuse infiltrating pontine glioma in a 5 yr old girl presenting with headaches, left facial droop, and lethargy.

Metastatic Tumors

Metastatic spread of other childhood malignancies to the brain is uncommon. Childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma can spread to the leptomeninges, causing symptoms of communicating hydrocephalus. **Chloromas,** which are collections of myeloid leukemia cells, can occur throughout the neuraxis. Rarely, brain parenchymal metastases occur from lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, and clear cell sarcoma of the kidney. Therapeutic approaches are based on the specific histologic diagnosis and may incorporate radiation therapy, intrathecal administration of chemotherapy, and/or systemic administration of chemotherapy. Medulloblastoma is the childhood brain tumor that most commonly metastasizes extraneurally. Less commonly, extraneural metastases from malignant glioma, PNET, and ependymoma can occur. Ventriculoperitoneal shunts have been known to allow extraneural metastases, primarily within the peritoneal cavity but also systemically.

COMPLICATIONS AND LONG-TERM MANAGEMENT

Data from the National Cancer Institute Surveillance, Epidemiology and End Results Program indicate that more than 70% of patients with childhood brain tumors will be long-term survivors. At least 50% of these survivors will experience chronic problems as a direct result of their tumors and treatment. These problems include chronic neurologic deficits such as focal motor and sensory abnormalities, seizure disorders, neurocognitive deficits (e.g., developmental delays, learning disabilities), and neuroendocrine deficiencies (e.g., hypothyroidism, growth failure, delay or absence of puberty). These patients are also at significant risk for secondary malignancies. Supportive multidisciplinary interventions for children with brain tumors both during and after therapy may help improve the ultimate outcome. Optimal seizure management, physical therapy, endocrine management with timely growth hormone and thyroid replacement therapy, tailored educational programs, and vocational interventions may enhance the childhood brain tumor survivor's quality of life.

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Chapter 498

Neuroblastoma

Peter E. Zage and Joann L. Ater

Neuroblastomas are embryonal cancers of the peripheral sympathetic nervous system with heterogeneous clinical presentation and course, ranging from tumors that undergo spontaneous regression to very aggressive tumors unresponsive to very intensive multimodal therapy. The causes of most cases remain unknown, and although significant advances have been made in the treatment of children with these tumors, the outcomes for aggressive forms of neuroblastoma remain poor.

EPIDEMIOLOGY

Neuroblastoma is the most common extracranial solid tumor in children and the most commonly diagnosed malignancy in infants. Approximately 600 new cases are diagnosed each year in the United States, accounting for 8-10% of childhood malignancies and one third of cancers in infants. Neuroblastoma accounts for >15% of the mortality from cancer in children. The median age of children at diagnosis of neuroblastoma is 22 mo, and 90% of cases are diagnosed by 5 yr of age. The incidence is slightly higher in boys and in whites.

PATHOLOGY

Neuroblastoma tumors, which are derived from primordial neural crest cells, form a spectrum with variable degrees of neural differentiation, ranging from tumors with primarily undifferentiated small round cells (neuroblastoma) to tumors consisting of mature and maturing Schwannian stroma with ganglion cells (ganglioneuroblastoma or ganglioneuroma). The tumors may resemble other **small round blue cell tumors,** such as rhabdomyosarcoma, Ewing sarcoma, and non-Hodgkin lymphoma. The prognosis of children with neuroblastoma varies with the histologic features of the tumor, and prognostic factors include the presence and amount of Schwannian stroma, the degree of tumor cell differentiation, and the mitosis-karyorrhexis index.

PATHOGENESIS

The etiology of neuroblastoma in most cases remains unknown. Familial neuroblastoma accounts for 1-2% of all cases, is associated with a younger age at diagnosis, and is linked to mutations in the *PHOX2B* and *ALK* genes. The *BARD1* gene has also been identified as a major genetic contributor to neuroblastoma risk. Neuroblastoma is associated with other neural crest disorders, including Hirschsprung disease, central hypoventilation syndrome, and neurofibromatosis type I, and potentially congenital cardiovascular malformations (Table 498-1). Children with Beckwith-Wiedemann syndrome and hemihypertrophy also have a higher incidence of neuroblastoma. Increased incidence of neuroblastoma is associated with some maternal and paternal occupational chemical exposures, farming, and work related to electronics, although no single environmental exposure has been shown to directly cause neuroblastoma.

Genetic characteristics of neuroblastoma tumors that are of prognostic importance include amplification of the *MYCN* (*N-myc*) proto-oncogene and tumor cell DNA content, or ploidy (Tables 498-2 to 498-4). Amplification of *MYCN* is strongly associated with advanced tumor stage and poor outcomes. Hyperdiploidy confers better prognosis if the child is younger than 1 yr of age at diagnosis. Other chromosomal abnormalities, including loss of heterozygosity of 1p, 11q, and 14q, and gain of 17q, are commonly found in neuroblastoma tumors and are also associated with worse outcomes. In addition, many other biologic factors are associated with neuroblastoma outcomes, including tumor vascularity and the expression levels of nerve growth factor receptors (TrkA, TrkB), ferritin, lactate dehydrogenase, ganglioside GD2, neuropeptide Y, chromogranin A, CD44, multidrug resistance–associated protein, and telomerase. These factors and many others are under investigation in clinical trials to determine whether they can be used to reduce therapy for children predicted to fare well with minimal therapy and to intensify therapy for those predicted to be at high risk for relapse.

CLINICAL MANIFESTATIONS

Neuroblastoma may develop at any site of sympathetic nervous system tissue. Approximately half of neuroblastoma tumors arise in the adrenal glands, and most of the remainder originate in the paraspinal sympathetic ganglia. Metastatic spread, which is more common in children older than 1 yr of age at diagnosis, occurs via local invasion or distant hematogenous or lymphatic routes. The most common sites of metastasis are the regional or distant lymph nodes, long bones and skull, bone marrow, liver, and skin. Lung and brain metastases are rare, occurring in >3% of cases.

The signs and symptoms of neuroblastoma reflect the tumor site and extent of disease, and the symptoms of neuroblastoma can mimic many other disorders, a fact that can result in a delayed diagnosis. Metastatic disease can cause a variety of signs and symptoms, including fever, irritability, failure to thrive, bone pain, cytopenias, bluish subcutaneous nodules, orbital proptosis, and periorbital ecchymoses (Fig. 498-1). Localized disease can manifest as an asymptomatic mass or can cause

Table 498-1 Syndromes Associated with Neuroblastoma

EPONYM	FEATURES
Pepper syndrome	Massive involvement of the liver with metastatic disease with or without respiratory distress.
Horner syndrome	Unilateral ptosis, myosis, and anhidrosis associated with a thoracic or cervical primary tumor. Symptoms do not resolve with tumor resection.
Hutchinson syndrome	Limping and irritability in young child associated with bone and bone marrow metastases.
Opsoclonus-myoclonus-ataxia syndrome	Myoclonic jerking and random conjugate eye movements with or without cerebellar ataxia. Often associated with a biologically favorable and differentiated tumor. The condition is likely immune mediated, may not resolve with tumor removal, and often exhibits progressive neuropsychologic sequelae.
Kerner-Morrison syndrome	Intractable secretory diarrhea due to tumor secretion of vasointestinal peptides. Tumors are generally biologically favorable.
Neurocristopathy syndrome	Neuroblastoma associated with other neural crest disorders, including congenital hypoventilation syndrome or Hirschsprung disease. Germline mutations in the paired homeobox gene *PHOX2B* have been identified in a subset of patients with this disease.
ROHHAD	Approximately 40% may have neural crest-derived tumors. Obesity and neurologic issues may be part of a paraneoplastic syndrome.

ROHHAD, rapid-onset obesity, hypothalamic dysfunction, hypoventilation, autonomic dysregulation.
From Park JR, Eggert A, Caron H: Neuroblastoma: biology, prognosis, and treatment, Pediatr Clin North Am *55:97–120, 2008.*

Table 498-2 Children's Oncology Group Neuroblastoma Risk Stratification

RISK GROUP	STAGE	AGE	*MYCN* AMPLIFICATION STATUS	PLOIDY	SHIMADA
Low risk	1	Any	Any	Any	Any
Low risk	2A/2B	Any	Not amplified	Any	Any
High risk	2A/2B	Any	Amplified	Any	Any
Intermediate risk	3	<547 days	Not amplified	Any	Any
Intermediate risk	3	≥547 days	Not amplified	Any	FH
High risk	3	Any	Amplified	Any	Any
High risk	3	≥547 days	Not amplified	Any	UH
High risk	4	<365 days	Amplified	Any	Any
Intermediate risk	4	<365 days	Not amplified	Any	Any
High risk	4	365 to <547 days	Amplified	Any	Any
High risk	4	365 to <547 days	Any	DNA index = 1	Any
High risk	4	365 to <547 days	Any	Any	UH
Intermediate risk	4	365 to <547 days	Not amplified	DNA index > 1	FH
High risk	4	≥547 days	Any	Any	Any
Low risk	4S	<365 days	Not amplified	DNA index > 1	FH
Intermediate risk	4S	<365 days	Not amplified	DNA index = 1	Any
Intermediate risk	4S	<365 days	Not amplified	Any	UH
High risk	4S	<365 days	Amplified	Any	Any

FH, Favorable histology; UH, unfavorable histology.
Courtesy of Children's Oncology Group; from Park JR, Eggert A, Caron H: Neuroblastoma: biology, prognosis, and treatment, Pediatr Clin North Am *55:97–120, 2008.*

Table 498-3 International Neuroblastoma Staging System

STAGE	DEFINITION	INCIDENCE (%)	SURVIVAL AT 5 YR* (%)
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive)	5	≥90
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically	10	70-80
2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically	10	70-80
3	Unresectable unilateral tumor infiltrating across the midline,† with or without regional lymph node involvement; *or* localized unilateral tumor with contralateral regional lymph node involvement; *or* midline tumor with bilateral extension by infiltration (resectable) or by lymph node involvement	25	40-70
4	Any primary tumor with dissemination to distant lymph nodes; bone, bone marrow, liver, skin, and other organs (except as defined for stage 4S)	60	85-90 if age at diagnosis is <18 mo 30-40 if age at diagnosis is >18 mo
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and bone marrow‡ (limited to infants <1 yr of age)	5	>80

*Survival is influenced by other characteristics, such as *MYCN* amplification. Percentages are approximate.
†The *midline* is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the other side of the vertebral column.
‡Marrow involvement in stage 4S should be minimal (i.e., <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate). More extensive marrow involvement would be considered stage 4. Results of the metaiodobenzylguanidine (MIBG) scan (if performed) should be negative in the marrow.
Modified from Kliegman RM, Marcdante KJ, Jenson HB, et al, editors: Nelson essentials of pediatrics, *ed 5, Philadelphia, 2006, WB Saunders, p. 746; and Brodeur GM, Pritchard J, Berthold F, et al: Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment,* J Clin Oncol *11:1466–1477, 1993.*

symptoms because of the mass itself, including spinal cord compression, bowel obstruction, and superior vena cava syndrome.

Children with neuroblastoma can also present with neurologic signs and symptoms. Neuroblastoma originating in the superior cervical ganglion can result in **Horner syndrome.** Paraspinal neuroblastoma tumors can invade the neural foramina, causing spinal cord and nerve root compression. Neuroblastoma can also be associated with a paraneoplastic syndrome of autoimmune origin, termed *opsoclonus–myoclonus–ataxia syndrome,* in which patients experience rapid, uncontrollable jerking eye and body movements, poor coordination,

Table 498-4 Phenotypic and Genetic Features of Neuroblastoma, Treatment, and Survival According to Prognostic Category

VARIABLE	PROGNOSTIC CATEGORY*			
	Low Risk	**Intermediate Risk**	**High Risk**	**Tumor Stage 4S**
Pattern of disease	Localized tumor	Localized tumor with locoregional lymph node extension; metastases to bone marrow and bone in infants	Metastases to bone marrow and bone (except in infants)	Metastases to liver and skin (with minimal bone marrow involvement) in infants
Tumor genomics	Whole-chromosome gains	Whole-chromosome gains	Segmental chromosomal aberrations	Whole-chromosome gains
Treatment	Surgery†	Moderate-intensity chemotherapy; surgery†	Dose-intensive chemotherapy, surgery, and external-beam radiotherapy to primary tumor and resistant metastatic sites; myeloablative chemotherapy with autologous hematopoietic stem cell rescue; isotretinoin with anti–ganglioside GD2 immunotherapy	Supportive care‡
Survival rate	>98%	90-95%	40-50%	>90%

*Patients are assigned to prognostic groups according to risk, as described by the Children's Oncology Group, with the level of risk defining the likelihood of death from disease. Stage 4S disease is considered separately here because of the unique phenotype of favorable biologic features and relentless early progression but ultimately full and complete regression of the disease.

†The goal of surgery is to safely debulk the tumor mass and avoid damage to surrounding normal structures while also obtaining sufficient material for molecular diagnostic studies. Some localized tumors may spontaneously regress without surgery.

‡Low-dose chemotherapy or radiation therapy, or both, is used in patients with life-threatening hepatic involvement, especially in infants <2 mo of age, who are at much higher risk for life-threatening complications from massive hepatomegaly.

From Maris JM: Recent advances in neuroblastoma, N Engl J Med *362:2202–2210, 2010.*

Figure 498-1 Periorbital metastases of neuroblastoma with ecchymoses and proptosis.

and cognitive dysfunction. Some tumors produce catecholamines that can cause increased sweating and hypertension, and some release vasoactive intestinal peptide, causing a profound secretory diarrhea. Children with extensive tumors can also experience tumor lysis syndrome and disseminated intravascular coagulation. Infants younger than 1 yr of age also can present in unique fashion, termed *stage 4S,* with widespread subcutaneous tumor nodules, massive liver involvement, limited bone marrow disease, and a small primary tumor without bone involvement or other metastases.

DIAGNOSIS

Neuroblastoma is usually discovered as a mass or multiple masses on plain radiography, CT, or MRI (Fig. 498-2*A*). The mass often contains calcification and hemorrhage that can be appreciated on plain radiography or CT. Prenatal diagnosis of neuroblastoma on maternal ultrasound scans is sometimes possible. Tumor markers, including catecholamine metabolites homovanillic acid and vanillylmandelic acid, are elevated in the urine of approximately 95% of cases and help to confirm the diagnosis. A pathologic diagnosis is established from tumor tissue obtained by biopsy. Neuroblastoma can be diagnosed without a primary tumor biopsy if small round blue tumor cells are observed in bone marrow samples (Fig. 498-3) and the levels of vanillylmandelic acid or homovanillic acid are elevated in the urine.

Evaluations for metastatic disease should include CT or MRI of the chest and abdomen, bone scans to detect cortical bone involvement, and at least 2 independent bone marrow aspirations and biopsies to evaluate for marrow disease. **Iodine-123 metaiodobenzylguanidine (^{123}I-MIBG)** studies should be used when available to better define the extent of disease (see Fig. 498-2*B* and *C*). MRI of the spine should be performed in cases with suspected or potential spinal cord compression, but imaging of the brain with either CT or MRI is not routinely performed unless dictated by the clinical presentation.

The **International Neuroblastoma Staging System (INSS)** is currently used to stage patients with neuroblastoma after initial surgical resection (see Table 498-3). INSS stage 1 tumors are confined to the organ or structure of origin and are completely resected. INSS stage 2 tumors extend beyond the structure of origin but not across the midline, either with (stage 2B) or without (stage 2A) ipsilateral lymph node involvement. INSS stage 3 tumors extend beyond the midline, with or without bilateral lymph node involvement, whereas INSS stage 4 tumors are disseminated, with metastases to bones, bone marrow, liver, distant lymph nodes, and other organs. INSS stage 4S refers to neuroblastoma in children younger than 1 yr of age with dissemination to liver, skin, and/or bone marrow without bone involvement and with a primary tumor that would otherwise be staged as INSS stage 1 or 2. A new International Neuroblastoma Risk Group Staging System was recently developed to allow for more effective comparisons of treatments and outcomes worldwide.

TREATMENT

Treatment strategies for neuroblastoma have changed dramatically over the past 20 yr, with significant reduction in treatment intensity for children who have localized low-risk tumors and with continued increased treatment intensity and addition of new agents for treatment of children who have high-risk neuroblastoma. The patient's age and tumor stage are combined with cytogenetic and molecular features of the tumor to determine the treatment risk group and estimated prognosis for each patient (see Tables 498-2 to 498-4). The usual treatment for children with low-risk neuroblastoma is surgery for stages 1 and 2 and observation for stage 4S with cure rates generally >90% without further therapy. Treatment with chemotherapy or radiation for the rare child with local recurrence can still be curative. Children with spinal cord compression at diagnosis also may require urgent treatment with chemotherapy, surgery, or radiation to avoid neurologic

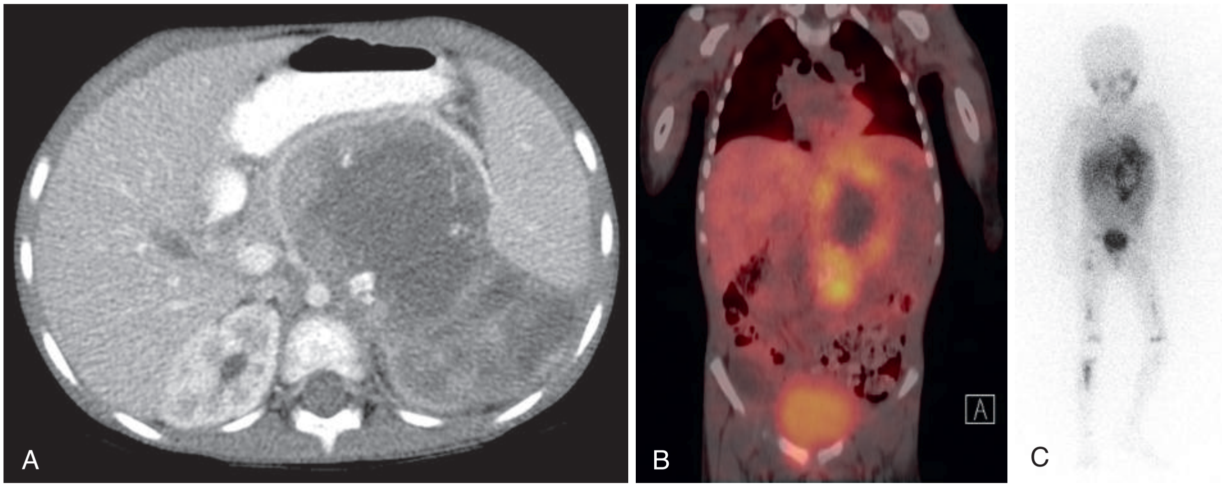

Figure 498-2 **A,** CT scan of an abdominal neuroblastoma with central necrosis at diagnosis. **B,** Coronal fused CT and metaiodobenzylguanidine (MIBG) image of same child with extensive retroperitoneal mass and central necrosis, probably an adrenal primary with extensive lymph node involvement. **C,** MIBG avid neuroblastoma with increased uptake of radiolabeled tracer can be detected in multiple sites of disease, including bone and soft tissue.

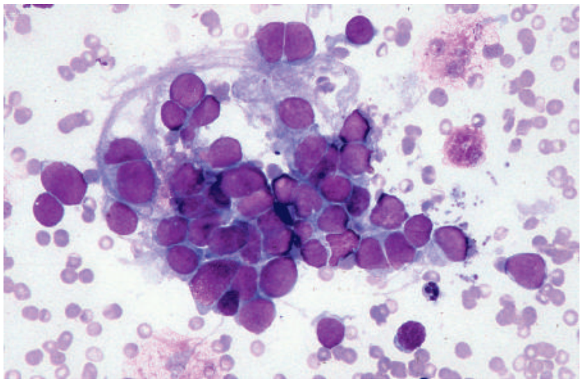

Figure 498-3 Neuroblastoma cells aspirated from the bone marrow. Clumps of cells often contain ≥3 cells with or without evidence of rosette formation. Rosettes of cells surrounding an inner mass of fibrillary material are characteristic of neuroblastoma.

damage. Stage 4S neuroblastomas have a very favorable prognosis, and many regress spontaneously without therapy. Chemotherapy or resection of the primary tumor does not improve survival rates, but for infants with massive liver involvement and respiratory compromise, small doses of cyclophosphamide or low-dose hepatic irradiation may alleviate symptoms. For children with stage 4S neuroblastoma who require treatment for symptoms, the survival rate is 81%.

Treatment of intermediate-risk neuroblastoma includes surgery, chemotherapy, and, in some cases, radiation therapy. The chemotherapy usually includes moderate doses of cisplatin or carboplatin, cyclophosphamide, etoposide, and doxorubicin given for several months. Radiation therapy is used for tumors with incomplete response to chemotherapy. Children with intermediate-risk neuroblastoma, including children with stage 3 disease and infants with stage 4 disease and favorable characteristics, have an excellent prognosis and >90% survival with this moderate treatment. In this intermediate-risk group, obtaining adequate diagnostic material for determination of the underlying biologic features of the tumor, such as the Shimada pathologic classification and *MYCN* gene amplification, is critical, so that children with unfavorable characteristics can receive more-aggressive treatment and those with favorable features can be spared excessive toxic therapy.

Children with high-risk neuroblastoma have long-term survival rates between 25% and 35% with current treatment that consists of intensive chemotherapy, high-dose chemotherapy with autologous stem cell rescue, surgery, radiation, and 13-*cis*-retinoic acid (isotretinoin, Accutane). Induction chemotherapy for children with high-risk neuroblastoma includes combinations of cyclophosphamide, topotecan, doxorubicin, vincristine, cisplatin, and etoposide. After completion of induction chemotherapy, resection of the residual primary tumor is followed by high-dose chemotherapy with autologous stem cell rescue and focal radiation therapy to tumor sites. A national cooperative group trial demonstrated significantly better survival with chemotherapy plus autologous stem cell rescue than with chemotherapy alone. The further addition of 13-*cis*-retinoic acid after autologous stem cell transplantation resulted in further improvements in survival rates. In addition, a national clinical trial has demonstrated an increase in short-term survival rates with the addition of the monoclonal antibody ch14.18, interleukin 2, and granulocyte-macrophage colony-stimulating factor to 13-*cis*-retinoic acid therapy.

Cases of high-risk neuroblastoma are associated with frequent relapses, and children with recurrent neuroblastoma have a <50% response rate to alternative chemotherapy regimens. New treatment strategies and agents are needed for children with both high-risk and recurrent neuroblastoma. Therapies currently under investigation include new chemotherapeutic agents and other novel therapies directed against critical intracellular signaling pathways, radiolabeled targeted agents (such as ^{131}I-MIBG), immunotherapy, and antitumor vaccines. Ongoing biologic studies of neuroblastoma will also hopefully lead to the identification of new molecular and genetic targets for therapy.

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Chapter 499

Neoplasms of the Kidney

499.1 Wilms Tumor

Najat C. Daw, Vicki Huff, and Peter M. Anderson

Wilms tumor (WT), also known as nephroblastoma, is the most common primary malignant renal tumor of childhood; other renal tumors are very rare. It is the second most common malignant

abdominal tumor in childhood. The most common sites of metastases are the lungs, regional lymph nodes, and liver. Histologically, the classic WT is made up of varying proportions of blastemal, stromal, and epithelial cells, recapitulating stages of normal renal development. The treatment includes surgery and chemotherapy with or without radiotherapy. The use of multimodality treatment and multiinstitutional cooperative group trials has dramatically improved the cure rate of WT from <30% to approximately 90% (Table 499-1).

EPIDEMIOLOGY

WT accounts for 6% of pediatric malignancies and more than 95% of kidney tumors in children. In the United States, the incidence of WT is approximately 8 cases per 1 million children younger than 15 yr of age per year, and about 650 new cases are diagnosed each year. Approximately 75% of the cases occur in children younger than 5 yr with a peak incidence at 2-3 yr of age. It can arise in 1 or both kidneys; the incidence of bilateral WTs is 7%. Most cases are sporadic, but approximately 2% of patients have a family history. In 8-10% of patients, WT is observed in the context of hemihypertrophy, aniridia, genitourinary anomalies, and a variety of rare syndromes, including **Beckwith-Wiedemann syndrome** and **Denys-Drash syndrome** (Table 499-2). An earlier age of diagnosis and an increased incidence of bilateral disease are generally observed in syndromic and familial cases.

Table 499-1 Ten Yr Outcomes for Patients with Wilms Tumor Treated in the National Wilms Tumor Study IV

HISTOLOGY	STAGE	RECURRENCE-FREE SURVIVAL (%)	OVERALL SURVIVAL (%)
Favorable	I	91	96
Favorable	II	85	93
Favorable	III	84	89
Favorable	IV	75	81
Favorable	V	65	78
Anaplastic	I	69	82
Anaplastic	II-III	43	49
Anaplastic	IV	18	18

Table 499-2 Syndromes Associated with Wilms Tumor

SYNDROME	CLINICAL CHARACTERISTICS	GENETIC ANOMALIES
Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation (WAGR)	Aniridia, genitourinary abnormalities, mental retardation	Del 11p13 (*WT1* and *PAX6*)
Denys-Drash	Early-onset renal failure with renal mesangial sclerosis, male pseudohermaphroditism	*WT1* missense mutation
Beckwith-Wiedemann	Organomegaly (liver, kidney, adrenal, pancreas) macroglossia, omphalocele, hemihypertrophy	Unilateral paternal disomy, duplication of 11p15.5, loss of imprinting, mutation of *p57KIP57* Del 11p15.5 *IGF2* and *H19* imprinting control region

ETIOLOGY: GENETICS AND MOLECULAR BIOLOGY

WT is thought to be derived from incompletely differentiated renal mesenchyme, and tumors are typically composed of cells reminiscent of the undifferentiated and partially differentiated cells that normally arise from renal mesenchyme. Foci of benign, undifferentiated mesenchyme (nephrogenic rests) that persist abnormally in the kidney into postnatal life are observed in approximately 1% of children in the general population, but are present in up to 90% of children who have a family history of WT, develop bilateral tumors, or display features of WT-related syndromes. Nephrogenic rests usually regress or differentiate, but those that persist can become malignant.

To date genetic mutations have been detected, either individually or in combination, in a third of WTs. Mutations in *WT1*, a gene located at 11p13 and encoding a zinc finger transcription factor, are observed in 15-20% of tumors. These are homozygous and result in loss of *WT1* function. The majority of *WT1* mutations are somatic, result in loss of *WT1* function, and are present homozygously. However, germline *WT1* mutations are also observed, primarily in patients with WT-associated syndromes, or sometimes in patients with bilateral disease. In these instances, the wild-type allele present in the germline is mutated or lost in the tumor, resulting in loss of *WT1* function. Interestingly, nephrogenic rests assessed from patients heterozygous for a germline *WT1* mutation are homozygous for the *WT1* mutation, with additional somatic mutations being observed in the autologous tumors. The vast majority of *WT1* mutations are deletion/truncating mutations or missense mutations that affect amino acid residues critical for *WT1* function. Germline truncating mutations are usually associated with WT in the context of genitourinary anomalies or the WAGR (Wilms, aniridia, genitourinary anomalies, mental retardation) syndrome. Missense germline mutations are usually observed in children with Denys-Drash syndrome in which early-onset renal failure is observed.

Mutations in *CTNNB1*, encoding β-catenin, which acts as a major regulatory point in the wnt signaling pathway and also acts at the cytoplasmic membrane, are observed in approximately 15% of WTs, very often those that have sustained *WT1* mutations. *WTX*, a gene located on the X chromosome that encodes a protein that also plays a role in wnt pathway regulation, is mutated in approximately 20% of tumors. *CTNNB1* and *WTX* mutations are somatic. Somatic mutation of the p53 gene, *TP53*, is observed in approximately 5% of tumors and is associated with anaplastic tumor histology, a poor prognostic feature of WT.

In approximately 70% of tumors, loss of heterozygosity (usually copy number neutral) or loss of imprinting at imprinted loci at 11p15 is observed. This epigenetic alteration (the observation of which led to the designation of a "*WT2*" gene) occurs in tumors both with and without *WT1, CTNNB1*, or *WTX* mutations, and often results in biallelic expression of *IGF2*, a normally imprinted gene that encodes insulin-like growth factor 2, in addition to the loss of imprinting of other 11p15 genes. Families with Beckwith-Wiedemann syndrome, a somatic overgrowth syndrome in which predisposition to embryonal tumors (including WT) is observed, have been genetically linked to 11p15, and microdeletions within the *IGF2* imprinting control region are present in Beckwith-Wiedemann syndrome families in which WT is observed.

WT is occasionally observed in families with a predisposition to **pleuropulmonary blastoma**, and mutations in the *DICER1* gene, located at 14q31 and encoding a key protein in the generation of microRNAs, are observed in these families. However, outside the context of these families, *DICER1* mutations are rare in WTs.

A family history of WT is noted in approximately 2% of WT patients, and predisposition is inherited as an autosomal dominant trait with incomplete penetrance. Predisposition to other tumor types or other phenotypes are not observed in the vast majority of these families. *WT1* mutations are detected in <5% of families, and these *WT1*-related families are small, with only 2 affected individuals. Genetic linkage analyses of large WT families have localized predisposition genes to 19q and 17q, but neither gene has been identified yet. However, some

Table 499-3 Differential Diagnosis of Abdominal and Pelvic Tumors in Children

TUMOR	PATIENT AGE	CLINICAL SIGNS	LABORATORY FINDINGS
Wilms	Preschool	Unilateral flank mass, aniridia, hemihypertrophy	Hematuria, polycythemia, thrombocytosis, elevated partial thromboplastin time value
Neuroblastoma	Preschool	Gastrointestinal/genitourinary obstruction, raccoon eyes, myoclonus opsoclonus, diarrhea, skin nodules	Increased urinary vanillylmandelic acid, or homovanillic acid, or ferritin, stippled calcification in the mass
Non-Hodgkin lymphoma	>1 yr	Intussusception in patients >2 yr old	Increased lactic dehydrogenase, blood cytopenia from bone marrow involvement
Rhabdomyosarcoma	All	Gastrointestinal/genitourinary obstruction, abdominal pain, vaginal bleeding, paratesticular mass	Hypercalcemia, blood cytopenia from bone marrow involvement
Germ cell tumor/teratoma	Preschool, teenage	Girls: abdominal pain, vaginal bleeding Boys: testicular mass, new-onset hydrocele, sacrococcygeal mass/dimple	Increased human chorionic gonadotropin, increased α-fetoprotein
Hepatoblastoma	Birth-3 yr	Large firm liver	Increased α-fetoprotein
Hepatoma	School age, teenage	Large firm nodule, hepatitis B, cirrhosis	Increased α-fetoprotein

families carry neither of these mutations, suggesting that additional WT loci exist. Some families are not linked to either of these genomic regions, indicating that additional WT predisposition genes exist. Similarly, somatic alterations at 1q, 7p, 16q, chromosome 12, and other genomic regions are observed in some WTs and are thought to harbor genes important in WT development.

CLINICAL PRESENTATION

The most common initial clinical presentation for WT is the incidental discovery of an asymptomatic **abdominal mass** by parents while bathing or clothing an affected child or by a physician during a routine physical examination (Table 499-3). At presentation the mass can be quite large because retroperitoneal masses can grow unhampered by strict anatomic boundaries. Functional defects in paired organs like the kidney, with good functional reserve, are also unlikely to be detected early. **Hypertension** is present in approximately 25% of tumors at presentation and has been attributed to increased renin activity. **Abdominal pain, gross painless hematuria, and fever** are other frequent findings at diagnosis. Occasionally, rapid **abdominal enlargement and anemia** occur as a result of bleeding into the renal parenchyma or pelvis. WT thrombus extends into the inferior vena cava in 4-10% of patients, and rarely into the right atrium. Patients might also have microcytic anemia from iron deficiency or anemia of chronic disease, polycythemia, elevated platelet count, and acquired deficiency of von Willebrand factor or factor VII deficiency.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

An abdominal mass in a child should be considered malignant until diagnostic imaging, laboratory findings, and pathology can define its true nature (see Table 499-3). Imaging studies include plain abdominal radiography, abdominal ultrasonography, and CT of the abdomen to define the intrarenal origin of the mass and differentiate it from adrenal masses (e.g., neuroblastoma) and other masses in the abdomen. Abdominal ultrasonography helps differentiate solid from cystic masses. WT might show focal areas of necrosis or hemorrhage and hydronephrosis caused by obstruction of the renal pelvis by the tumor. Ultrasonography with Doppler imaging of renal veins and the inferior vena cava is a useful first study that not only can look for WT but also can evaluate the collecting system and demonstrate tumor thrombi in the renal veins and inferior vena cava.

CT (Fig. 499-1) is useful to define the extent of the disease, integrity of the contralateral kidney, and metastasis. MRI requires sedation in young children and is not routinely used; it may be helpful in defining an extensive tumor thrombus that extends up to the level of the hepatic veins or even into the right atrium, and to distinguish WT from nephrogenic rests. Chest CT is more sensitive than chest radiography to screen for pulmonary metastasis, and is preferably performed before surgery because effusions and atelectasis can confound the interpretation of postoperative imaging studies. A bone scan is performed if the histologic diagnosis confirms clear cell sarcoma of the kidney to look for bone metastasis. Brain imaging with CT or MRI is obtained in cases of clear cell sarcoma of the kidney or rhabdoid tumor of the kidney as these tumors can spread to the brain.

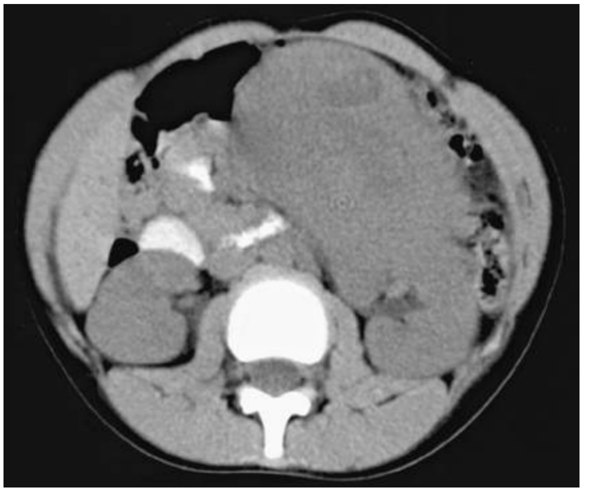

Figure 499-1 Abdominal CT scan showing a Wilms tumor arising from the left kidney. Because of their retroperitoneal location, such tumors can become very large (>10 cm) before clinical symptoms occur.

WT lesions are metabolically active and concentrate fluorodeoxyglucose. Regional spread and metastatic lesions can be visualized on positron emission tomography/CT scanning. The diagnosis is usually made by imaging studies and confirmed by histology at the time of nephrectomy. Although biopsy is a reliable diagnostic tool, it is discouraged as it results in disease upstaging. A core needle biopsy obtained via a posterior approach should be performed in cases of unusual presentation (older age, signs of infection, inflammation) or unusual imaging findings (significant adenopathy, no renal parenchyma seen, intratumoral calcification).

TREATMENT

There are 2 major schools of thought in the management of WT. The Children's Oncology Group, formerly National Wilms Tumor Study Group, advocates upfront surgery prior to initiating treatment. On the

Table 499-4	Staging of Wilms Tumor
Stage I	Tumor *confined to the kidney* and completely resected. Renal capsule or sinus vessels not involved. Tumor not ruptured or biopsied. Regional lymph nodes examined and negative.
Stage II	Tumor extends *beyond the kidney* but is completely resected with negative margins and lymph nodes. At least 1 of the following has occurred: (a) penetration of renal capsule, (b) invasion of renal sinus vessels.
Stage III	*Residual tumor* present following surgery confined to the abdomen, including gross or microscopic tumor; spillage of tumor preoperatively or intraoperatively; biopsy prior to nephrectomy, regional lymph node metastases; tumor implants on the peritoneal surface; extension of tumor thrombus into the inferior vena cava including thoracic vena cava and heart.
Stage IV	*Hematogenous metastases* (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region.
Stage V	*Bilateral* renal involvement by tumor.

other hand, the International Society of Pediatric Oncology recommends preoperative chemotherapy. Each approach has advantages and limitations but they have similar outcomes. Early surgery provides accurate diagnosis and staging, and can facilitate risk-adapted therapy. Preoperative chemotherapy can make surgery easier and reduces the risk of intraoperative tumor rupture and hemorrhage. Surgery entails a radical nephrectomy with meticulous dissection to avoid rupture of the tumor capsule and lymph node sampling despite the absence of abnormal nodes on preoperative imaging studies or intraoperative assessment. Partial nephrectomy is performed in patients with bilateral disease or with unilateral WT and a predisposing syndrome such as Denys-Drash and WAGR, so as to minimize the risk of future renal failure.

Prognostic factors for risk-adapted therapy include age, stage, tumor weight, and loss of heterozygosity at chromosomes 1p and 16q (Table 499-4). Histology plays a major role in risk stratification of WT. Absence of anaplasia is considered a favorable histologic finding. Presence of anaplasia is further classified as focal or diffuse, both of which are unfavorable histologic findings.

The Children's Oncology Group has specific drug dose and schedule recommendations for risk-adapted treatment of WT. Patients with favorable histologic findings of WT have a good outcome and are generally treated in the outpatient setting. Nephrectomy alone may be sufficient for patients younger than 2 yr of age with stage I disease and a tumor weighing <550 g. Patients with stages I and II disease receive chemotherapy with 2 drugs, vincristine and actinomycin D (also called dactinomycin), every 1-3 wk for a total of 18 wk (regimen EE4A). Patients with stage III or IV disease receive chemotherapy with 3 drugs (vincristine, doxorubicin, and actinomycin D) every 1-3 wk for a total of 24 wk (regimen DD4A) and radiation therapy. Patients with regional lymph node metastases, residual disease after surgery, or tumor rupture receive radiation therapy to the flank or abdomen, and those with lung metastases receive radiation therapy to the lungs. The presence of loss of heterozygosity at 1p and 16q confers an adverse prognosis, and deserves treatment intensification.

Anaplastic histology (focal and diffuse) accounts for approximately 11% of WT cases. Patients with diffuse anaplasia, in particular, have a poor outcome. They are treated with intensive chemotherapy regimens that include vincristine, cyclophosphamide, doxorubicin, etoposide, carboplatin, and ifosfamide, in addition to radiation therapy.

RECURRENT DISEASE

Approximately 15% of WT patients with favorable histology and 50% of those with anaplastic histology suffer relapse; most relapses occur early (within 2 yr of diagnosis). Factors associated with a favorable outcome after relapse include low stage (I/II) at diagnosis, treatment with vincristine and actinomycin D only, no prior radiotherapy, favorable histology, relapse to lung only, and interval from nephrectomy to relapse 12 mo or longer. Patients with recurrent WT who previously received only vincristine and actinomycin D had a 4 yr survival of approximately 80%, whereas those who previously received the 3 drug regimen of vincristine, actinomycin D, and doxorubicin had a 4 yr survival of only 50%. Other agents used to treat recurrent WT include doxorubicin, carboplatin, cyclophosphamide, ifosfamide, etoposide, and topotecan. Metachronous WT may not represent tumor relapse but instead may indicate development of a new tumor in the opposite kidney.

PROGNOSIS

Despite some adverse risk factors that decrease prognosis (metastases, unfavorable histology, recurrent disease, and loss of heterozygosity of both 1p and 16q), most children with WT have a very favorable prognosis. Overall, the survival of children with WT approaches 90%, with some prognostic factors (low stage, favorable histology, young age, low tumor weight) conferring even better outcomes.

LATE EFFECTS

Current strategies are successful with relatively few long-term effects of therapy. Late complications are a consequence of treatment type and intensity; the use of radiotherapy and anthracyclines increases the risk of these complications. Clinically significant late sequelae include musculoskeletal effects, cardiac toxicity, pulmonary disease, reproductive problems, renal dysfunction, and the development of second malignant neoplasms.

499.2 Other Pediatric Renal Tumors

Najat C. Daw, Vicki Huff, and Peter M. Anderson

MESOBLASTIC NEPHROMA

Mesoblastic nephroma is the most common solid renal tumor identified in the **neonatal period** and the most frequent benign renal tumor in childhood. It represents 3-10% of all pediatric renal tumors. Many cases are diagnosed with prenatal ultrasound and can manifest as polyhydramnios, hydrops, and premature delivery. Most of the patients are diagnosed before 3 mo of age, whereas WT is rarely diagnosed before 6 mo of age. Radical nephrectomy is the treatment of choice and may be sufficient by itself. Local recurrence is uncommon. Although rare, malignant variants do occur, marked by metastases to the lung, liver, heart, and brain.

CLEAR CELL SARCOMA OF THE KIDNEY

Clear cell sarcoma of the kidney is an uncommon renal neoplasm of childhood with approximately 20 new cases diagnosed each year in North America. Peak incidence is between 1 and 4 yr of age, usually presenting as an abdominal mass. Gene expression profiles of clear cell sarcoma of the kidney suggest the cell of origin to be a renal mesenchymal cell with neural markers. Bone is the most common site of distant metastasis followed by lung, abdomen, retroperitoneum, brain, and liver. Therefore, the staging work-up should include a bone scan. Early-stage disease has an excellent prognosis, especially with the addition of doxorubicin.

RHABDOID TUMOR OF THE KIDNEY

Malignant rhabdoid tumor of the kidney has rhabdomyoblast-like morphology. It is a rare but aggressive cancer. Hematuria is a common presenting feature. Both rhabdoid tumor of the kidney and central nervous system atypical teratoid rhabdoid tumors have deletions and mutations of the *hSNF5/INI1* gene and are considered to be related. Prognosis is poor with current therapeutic protocols. The 5 yr overall survival rate is <30%.

RENAL CELL CARCINOMA

Renal cell carcinoma (RCC) is rare in children, accounting for <5% of all renal tumors of childhood. Patients may present with frank hematuria, flank pain, and/or a palpable mass, although RCC can be asymptomatic and detected incidentally. It has a propensity to metastasize to the lungs, bone, liver, and brain. RCC can be associated with von Hippel–Lindau disease. Unlike the case for adult RCC, local lymph node involvement is not a poor prognostic indicator in pediatric RCC. Nephrectomy alone may be adequate for early-stage RCC.

Bibliography is available at Expert Consult.

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Chapter 500
Soft Tissue Sarcomas
Carola A.S. Arndt

The annual incidence of soft tissue sarcomas is 8.4 cases per 1 million white children younger than 14 yr of age. Rhabdomyosarcoma accounts for more than 50% of soft tissue sarcomas. The prognosis most strongly correlates with age and extent of disease at diagnosis, primary tumor site and histology, and expression of the fusion protein, PAX-FOXO1.

RHABDOMYOSARCOMA
Epidemiology
The most common pediatric soft tissue sarcoma, rhabdomyosarcoma, accounts for approximately 3.5% of childhood cancers. These tumors may occur at virtually any anatomic site but are usually found in the head and neck (25%), orbit (9%), genitourinary tract (24%), and extremities (19%); retroperitoneal and other sites account for the remainder of primary sites. The incidence at each anatomic site is related to both patient age and tumor type. Extremity lesions are more likely to occur in older children and to have alveolar histology. Rhabdomyosarcoma occurs with increased frequency in patients with neurofibromatosis and other family cancer predisposition syndromes such as Li-Fraumeni syndrome.

Pathogenesis
Rhabdomyosarcoma is thought to arise from the same embryonic mesenchyme as striated skeletal muscle although a large percentage of these tumors arise in areas lacking skeletal muscle (e.g., bladder, prostate, vagina). On the basis of light microscopic appearance, it belongs to the general category of small round cell tumors that includes Ewing sarcoma, neuroblastoma, and non-Hodgkin lymphoma. Definitive diagnosis of a pathologic specimen requires immunohistochemical studies using antibodies to skeletal muscle (desmin, muscle-specific actin, myogenin) and reverse transcription polymerase chain reaction or, in the case of alveolar tumors, fluorescent in situ hybridization for PAX-FOX01 transcript.

Determination of the specific histologic subtype is important in treatment planning and assessment of prognosis. There are 3 recognized histologic subtypes. The **embryonal type** accounts for approximately 60% of all cases and has an intermediate prognosis. The **botryoid type,** a variant of the embryonal form in which tumor cells and an edematous stroma project into a body cavity like a bunch of grapes, is found most often in the vagina, uterus, bladder, nasopharynx, and middle ear. The **alveolar type** accounts for approximately 25-40% of cases and often is characterized by the presence of PAX-FOXO1 fusion transcript. The tumor cells tend to grow in nests that often have cleft-like spaces resembling alveoli. Alveolar tumors occur most often in the trunk and extremities and carry the poorest prognosis. The **pleomorphic type** (adult form) is rare in childhood, accounting for <1% of cases.

Clinical Manifestations
The most common presenting feature of rhabdomyosarcoma is a mass that may or may not be painful. Symptoms are caused by displacement or obstruction of normal structures (Table 500-1). Origin in the nasopharynx may be associated with nasal congestion, mouth breathing, epistaxis, and difficulty with swallowing and chewing. Regional extension into the cranium can produce cranial nerve paralysis, blindness, and signs of increased intracranial pressure with headache and vomiting. When the tumor develops in the face or cheek, there may be swelling, pain, trismus, and, as extension occurs, paralysis of cranial nerves. Tumors in the neck can produce progressive swelling with neurologic symptoms after regional extension. Orbital primary tumors are usually diagnosed early in their course because of associated proptosis, periorbital edema, ptosis, change in visual acuity, and local pain. When the tumor arises in the middle ear, the most common early signs are pain, hearing loss, chronic otorrhea, or a mass in the ear canal; extensions of tumor produce cranial nerve paralysis and signs of an intracranial mass on the involved side. An unremitting croupy cough and progressive stridor can accompany rhabdomyosarcoma of the larynx. Because most of these signs and symptoms also are associated with common childhood conditions, clinicians must be alert to the possibility of tumor.

Rhabdomyosarcoma of the trunk or extremities often is first noticed after trauma and initially may be regarded as a hematoma. If the swelling does not resolve or increases, malignancy should be suspected. Involvement of the genitourinary tract can produce hematuria, obstruction of the lower urinary tract, recurrent urinary tract infections, incontinence, or a mass detectable on abdominal or rectal examination. Paratesticular tumor usually manifests as a painless, rapidly growing mass in the scrotum. Vaginal rhabdomyosarcoma may manifest as a grape-like mass of tumor tissue bulging through the vaginal orifice, known as **sarcoma botryoides**, and can cause urinary tract or large bowel symptoms. Vaginal bleeding or obstruction of the urethra or rectum may occur. Similar findings can be noted with uterine primaries.

Table 500-1 Staging System for Rhabdomyosarcoma

STAGE	SITE	T STAGE	SIZE	NODE STATUS	METASTASIS
1	Favorable	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Unfavorable	T1 or T2	a	N0 or Nx	M0
3	Unfavorable	T1 or T2	a b	N1 N0 or N1 or Nx	M0
4	Any	T1 or T2	a or b	N0 or N1 or Nx	M1

T1, confined to anatomic site of origin; T2, extension and/or fixative to surrounding tissue.
Size: a, <5 cm in diameter; b, ≥5 cm in diameter.
Nodes: N0, regional nodes not involved; N1, regional nodes involved; Nx, regional node status unknown.
Metastases: M0, no distant metastases; M1, metastases present (includes positive cytology in CSF, pleural, or peritoneal fluid).

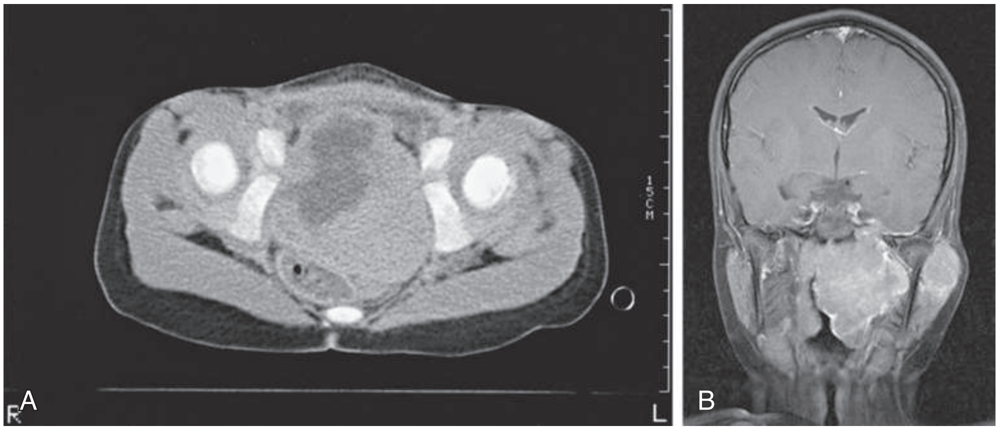

Figure 500-1 **A,** Pelvic CT scan of a child with a bladder rhabdomyosarcoma. **B,** MR image of a child with a parameningeal rhabdomyosarcoma.

Table 500-2 Risk Groups and Outcome for Rhabdomyosarcoma, Children's Oncology Group

RISK GROUP	STAGE/GROUP	HISTOLOGY	LONG-TERM EFS
Low, subset 1	Stage 1, Groups I-II Stage 1, Group III (orbit) Stage 2, Groups I-II	Embryonal	85-95%
Low, subset 2	Stage 1, Group III (nonorbit) Stage 3, Groups I-II	Embryonal	70-85%
Intermediate	Stage 2-3, Group III Stage 1-3, Groups I-III	Embryonal Alveolar	73% 65%
High	Stage 4, Group IV Stage 4, Group IV	Embryonal Alveolar	35% 15%

From Hawkins DS, Spunt SL, Skapek SX: Children's Oncology Group's 2013 blueprint for research: soft tissue sarcomas. Pediatr Blood Cancer *60:1001–1008, 2013, Table I, p. 1002.*

Tumors in any location may disseminate early and cause symptoms of pain or respiratory distress associated with pulmonary metastases. Extensive bone involvement can produce symptomatic hypercalcemia. In such cases, it may be difficult to identify the primary lesion.

Diagnosis

Early diagnosis of rhabdomyosarcoma requires a high index of suspicion. The microscopic appearance is that of a small, round, blue cell tumor. Neuroblastoma, lymphoma, and Ewing sarcoma also are **small, round, blue cell tumors** from which suspected rhabdomyosarcomas must be differentiated. The differential diagnosis depends on the site of presentation. Definitive diagnosis is established by biopsy, microscopic appearance, and results of immunohistochemical stains and analysis of PAX/FOXO1 expression. A lesion in an extremity may be thought to be a hematoma or hemangioma; an orbital lesion resulting in proptosis may be treated as an orbital cellulitis; or bladder-obstructive symptoms may be missed. Adolescents may ignore or be embarrassed to mention paratesticular lesions for a long time. Unfortunately, several months often elapse between the initial symptoms and biopsy. Diagnostic procedures are determined mainly by the area of involvement. CT or MRI is necessary for evaluation of the primary tumor site. With signs and symptoms in the head and neck area, radiographs should be examined for evidence of a tumor mass and for indications of bony erosion. MRI should be performed to identify intracranial extension or meningeal involvement and also to reveal bony involvement or erosion at the base of the skull. For abdominal and pelvic tumors, CT with a contrast agent or MRI can help delineate the tumor (Fig. 500-1). A radionuclide bone scan, chest CT, and bilateral bone marrow aspiration and biopsy should be performed to evaluate the patient for the presence of metastatic disease and to plan treatment. Fluorodeoxyglucose positron emission tomography is being used more frequently to enhance staging. The most critical element of the diagnostic work-up is examination of tumor tissue, which includes the use of special histochemical stains and immunostains. Molecular genetics is important to detect fusion transcripts present in alveolar rhabdomyosarcoma (PAX-FOX1). Lymph nodes also should be sampled for the presence of disease spread, especially in tumors of the extremities and in boys older than 10 yr of age with paratesticular tumors.

Treatment

Treatment is multidisciplinary and includes the pediatric oncologist, pediatric surgeon or other surgical subspecialist, and most often radiation oncologist. Only if the tumor is able to be completely resected, with negative margins, without loss of function or major cosmetic deformity should this be attempted initially. Unfortunately, most rhabdomyosarcomas are not completely resectable at initial diagnosis. Treatment is based on risk classification of the tumor, which is determined by the stage of tumor, the tumor histology, and the amount of tumor that was surgically resected prior to chemotherapy ("surgical group"). Stage is dependent on primary site (favorable vs unfavorable), tumor invasiveness (T1 or T2), lymph node status, tumor size, and presence of metastasis. Favorable sites include female genital, paratesticular, and head and neck (nonparameningeal) regions; all other sites are considered unfavorable. Table 500-1 shows the Children's Oncology Group staging system for rhabdomyosarcoma.

Patients should be offered enrollment in clinical trials. Table 500-2 shows current risk stratification and outcome based on results of recent studies. Patients with low-risk disease can be cured with minimal therapy consisting of vincristine and of actinomycin with or without lower doses of cyclophosphamide; radiation therapy can be used in the case of residual disease after initial surgery. Treatment for patients with intermediate-risk disease consists of vincristine, actinomycin, and cyclophosphamide along with radiation. Clinical trials in North

Table 500-3 Features of Most Common Types of Nonrhabdomyosarcoma Soft Tissue Sarcomas

TISSUE TYPE	TUMOR	NATURAL HISTORY AND BIOLOGY
Adipose	Liposarcoma	A very rare tumor. Usually arises in the extremities or retroperitoneum; associated with a nonrandom translocation, t(12;16)(q13;p11). Tends to be locally invasive and rarely metastasizes; wide local excision is the treatment of choice. The role of radiation therapy and chemotherapy in treating gross residual or metastatic disease is not established.
Fibrous	Fibrosarcoma	Most common soft tissue sarcoma in children younger than 1 yr. Congenital fibrosarcoma is a low-grade malignancy that commonly arises in the extremities or trunk and rarely metastasizes. Surgical excision is treatment of choice; dramatic responses to preoperative chemotherapy may occur. In children older than 4 yr, the natural history is similar to that in adults (a 5 yr survival rate of 60%); wide surgical excision and preoperative chemotherapy are commonly used. Associated with t(12;15)(p13;q25) or trisomy 11, also +8, +17, +20.
	Malignant fibrous histiocytoma	Most commonly arises in the trunk and extremities, deep in the subcutaneous layer. Histologically subdivided into storiform, giant cell, myxoid, and angiomatoid variants. The angiomatoid type tends to affect younger patients and is curable with surgical resection alone. Wide surgical excision is the treatment of choice. Chemotherapy has produced objective tumor regressions.
Vascular	Hemangiopericytoma	Often arises in the lower extremities or retroperitoneum; may manifest as hypoglycemia and hypophosphatemic rickets. Both benign and malignant histology. Nonrandom translocations t(12;19)(q13;q13) and t(13;22)(q22;q13.3) have been described. Complete surgical excision is the treatment of choice. Chemotherapy and radiation therapy may produce responses.
	Angiosarcoma	Rare in children; 33% arise in skin, 25% in soft tissue, and 25% in liver, breast, or bone. Associated with chronic lymphedema and exposure to vinyl chloride in adults. Survival rate is poor (12% at 5 yr) despite some responses to chemotherapy/radiation therapy.
	Hemangioendothelioma	Can occur in soft tissue, liver, and lung. Localized lesions have a favorable outcome; lesions in lung and liver often are multifocal and have a poor prognosis.
Peripheral nerves	Neurofibrosarcoma	Also known as the malignant peripheral nerve sheath tumor. Develops in up to 16% of patients with neurofibromatosis type 1 (NF1); almost 50% occur in patients with NF1. Deletions of chromosome 22q11-q13 or 17q11 and p53 mutations have been reported. Commonly arises in trunk and extremities and is usually locally invasive. Complete surgical excision is necessary for survival; response to chemotherapy is suboptimal.
Synovium	Synovial sarcoma	The most common nonrhabdomyosarcoma soft tissue sarcoma in some series. Often manifesting in the 3rd decade, but 33% of patients are younger than age 20 yr. Typically arises around the knee or thigh and is characterized by a nonrandom translocation t(X;18)(p11;q11). Wide surgical excision is necessary. Radiation therapy is effective in microscopic residual disease, and ifosfamide-based therapy is active in advanced disease.
Unknown	Alveolar soft part sarcoma	Slow-growing tumor; tends to recur or to metastasize to lung and brain years after diagnosis. Often arises in the extremities and head and neck.
Smooth muscle	Leiomyosarcoma	Often arises in the gastrointestinal tract and may be associated with a t(12;14)(q14;q23) translocation. Associated with Epstein-Barr virus in immunodeficiency syndromes (including AIDS). Complete surgical excision is the treatment of choice.

America are investigating the role of topoisomerase inhibitors in this group of patients. For patients with high-risk disease, newer approaches using intensive multiagent chemotherapy along with biologic agents are being investigated.

Prognosis

Prognostic factors include age, stage, histology, and primary site. Among patients with resectable tumor and favorable histology, 80-90% have prolonged disease-free survival. Unresectable tumor localized to certain favorable sites, such as the orbit, also has a high likelihood of cure. Approximately 65-70% of patients with incompletely resected tumor also achieve long-term disease-free survival. Patients with disseminated disease have a poor prognosis; only approximately 50% achieve remission, and fewer than 50% of these are cured. Older children have a poorer prognosis than younger children. For all patients, surveillance for late effects of cancer treatment is extremely important. Some examples of late effects include infertility from cyclophosphamide, late effects in the radiation field such as bladder dysfunction, infertility, cataracts, impaired bone growth, and secondary malignancies.

OTHER SOFT TISSUE SARCOMAS

The nonrhabdomyosarcoma soft tissue sarcomas constitute a heterogeneous group of tumors that account for 3% of all childhood malignancies (Table 500-3). Because they are relatively rare in children, much of the information about their natural history and treatment has been derived from studies in adult patients. In children, the median age at diagnosis is 12 yr, with a male : female ratio of 2.3 : 1. These tumors commonly arise in the trunk or lower extremities. The most common histologic types are synovial sarcoma (42%), fibrosarcoma (13%), malignant fibrous histiocytoma (12%), and neurogenic tumors (10%). Molecular genetic studies often prove useful in diagnosis, because several of these tumors have characteristic chromosomal translocations. Tumor size, stage (clinical group), invasiveness, and histologic grade correlate with survival.

Surgery remains the mainstay of therapy, but a careful search for lung and bone metastases should be undertaken before surgical excision. Chemotherapy and radiation therapy should be considered for large, high-grade, and unresectable tumors. The role of chemotherapy for nonrhabdomyosarcoma soft tissue sarcomas is not as well defined as for rhabdomyosarcoma. Patients with unresectable or metastatic disease are treated with multiagent chemotherapy in addition to irradiation and/or surgery. Patients with completely resected small (<5 cm) tumors are generally treated with surgery alone and can be expected to have an excellent outcome regardless of whether the tumor is high or low grade.

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Chapter 501
Neoplasms of Bone

501.1 Malignant Tumors of Bone

Carola A.S. Arndt

The annual incidence of malignant bone tumors in the United States is approximately 7 cases per 1 million white children younger than 14 yr of age, with a slightly lower incidence in African-American children. Osteosarcoma is the most common primary malignant bone tumor in children and adolescents, followed by Ewing sarcoma (Table 501-1; Fig. 501-1). In children younger than 10 yr of age, Ewing sarcoma is more common than osteosarcoma. Both tumor types are most likely to occur in the second decade of life.

OSTEOSARCOMA

Epidemiology

The annual incidence of osteosarcoma in the United States is 5.6 cases per 1 million children younger than 15 yr of age. The highest risk period for development of osteosarcoma is during the adolescent growth spurt, suggesting an association between rapid bone growth and malignant transformation. Patients with osteosarcoma are taller than their peers of similar age.

Pathogenesis

Although the cause of osteosarcoma is unknown, certain genetic or acquired conditions predispose patients to development of osteosarcoma. Patients with **hereditary retinoblastoma** have a significantly increased risk for development of osteosarcoma. The sites of osteosarcoma in these patients were initially thought to be only in previously irradiated areas, but later studies show them to arise in sites far from the original retinoblastoma radiation field. Predisposition to development of osteosarcoma in these patients may be related to loss of heterozygosity of the *RB* gene. Osteosarcoma also occurs in the **Li-Fraumeni syndrome**, which is a familial cancer syndrome associated with germline mutations of the *P53* gene. Kindreds with

Table 501-1 Comparison of Features of Osteosarcoma and the Ewing Family of Tumors

FEATURE	OSTEOSARCOMA	EWING FAMILY OF TUMORS
Age	Second decade	Second decade
Race	All races	Primarily whites
Sex (M:F)	1.5:1	1.5:1
Cell	Spindle cell–producing osteoid	Undifferentiated small round cell, probably of neural origin
Predisposition	Retinoblastoma, Li-Fraumeni syndrome, Paget disease, radiotherapy	None known
Site	Metaphyses of long bones	Diaphyses of long bones, flat bones
Presentation	Local pain and swelling; often, history of injury	Local pain and swelling; fever
Radiographic findings	Sclerotic destruction (less commonly lytic); sunburst pattern	Primarily lytic, multilaminar periosteal reaction ("onion-skinning")
Differential diagnosis	Ewing sarcoma, osteomyelitis	Osteomyelitis, eosinophilic granuloma, lymphoma, neuroblastoma, rhabdomyosarcoma
Metastasis	Lungs, bones	Lungs, bones
Treatment	Chemotherapy Ablative surgery of primary tumor	Chemotherapy Radiotherapy and/or surgery of primary tumor
Outcome	Without metastases, 70% cured; with metastases at diagnosis, ≤20% survival	Without metastases, 60% cured; with metastases at diagnosis, 20-30% survival

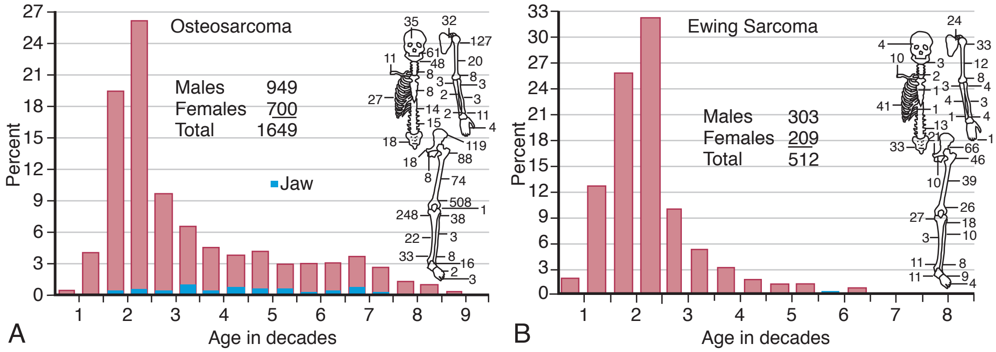

Figure 501-1 **A,** Age and skeletal distribution of 1,649 cases of osteosarcoma in the Mayo Clinic files. **B,** Age and skeletal distribution of 512 cases of Ewing sarcoma in the Mayo Clinic files. *(From Unni KK, editor:* Dahlin's bone tumors: general aspects and data on 11,087 cases, *ed 5, Philadelphia, 1996, Lippincott-Raven. Reprinted by permission of the Mayo Foundation.)*

Li-Fraumeni syndrome have a spectrum of malignancies in 1st-degree relatives, including carcinoma of the breast, soft tissue sarcomas, brain tumors, leukemia, adrenal cortical carcinoma, and other malignancies. **Rothmund-Thomson syndrome** is a rare syndrome associated with short stature, skin telangiectasia, small hands and feet, hypoplasticity or absence of the thumbs, and a high risk of osteosarcoma. Osteosarcoma also can be induced by irradiation for Ewing sarcoma, craniospinal irradiation for brain tumors, or high-dose irradiation for other malignancies. Other benign conditions that can be associated with malignant transformation to osteosarcoma include Paget disease, enchondromatosis, multiple hereditary exostoses, and fibrous dysplasia.

The pathologic diagnosis of osteosarcoma is made by demonstration of a highly malignant, pleomorphic, spindle cell neoplasm associated with the formation of malignant osteoid and bone. There are 4 pathologic subtypes of conventional high-grade osteosarcoma: osteoblastic, fibroblastic, chondroblastic, and telangiectatic. No significant differences in outcome are associated with the various subtypes, although the chondroblastic component of that subtype may not respond as well to chemotherapy. The role in prognosis of various genes such as drug resistance–related genes, tumor-suppressor genes, and genes related to apoptosis is being evaluated.

Telangiectatic osteosarcoma may be confused with aneurysmal bone cyst because of its lytic appearance on radiography. High-grade osteosarcoma typically arises in the diaphyseal region of long bones and invades the medullary cavity. It also may be associated with a soft tissue mass. Two variants of osteosarcoma, parosteal and periosteal osteosarcoma, should be distinguished from conventional osteosarcoma because of their characteristic clinical features. **Parosteal osteosarcoma** is a low-grade, well-differentiated tumor that does not invade the medullary cavity and most commonly is found in the posterior aspect of the distal femur. Surgical resection alone often is curative in this lesion, which has a low propensity for metastatic spread. **Periosteal osteosarcoma** is a rare variant that arises on the surface of the bone but has a higher rate of metastatic spread than the parosteal type and an intermediate prognosis.

Clinical Manifestations

Pain, limp, and swelling are the most common presenting manifestations of osteosarcoma. Because these tumors occur most often in active adolescents, initial complaints may be attributed to a sports injury or sprain; any bone or joint pain not responding to conservative therapy within a reasonable time should be investigated thoroughly. Additional clinical findings may include limitation of motion, joint effusion, tenderness, and warmth. Results of routine laboratory tests, such as a complete blood cell count and chemistry panel, are usually normal, although alkaline phosphatase or lactate dehydrogenase values may be elevated.

Diagnosis

Bone tumor should be suspected in a patient who presents with deep bone pain, often causing nighttime awakening, in whom there is a palpable mass and radiographs that demonstrate a lesion. The lesion may be mixed lytic and blastic in appearance, but new bone formation is usually visible. The classic radiographic appearance of osteosarcoma is the **sunburst pattern** (Fig. 501-2). When osteosarcoma is suspected, the patient should be referred to a center with experience in managing bone tumors. The biopsy and the surgery should be performed by the same surgeon so that the incisional biopsy site can be placed in a manner that will not compromise the ultimate limb salvage procedure. Tissue usually is obtained for molecular and biologic studies at the time of the initial biopsy. Before biopsy, MRI of the primary lesion and the entire bone should be performed to evaluate the tumor for its proximity to nerves and blood vessels, soft tissue and joint extension, and skip lesions. The metastatic work-up, which should be performed before biopsy, includes CT of the chest and radionuclide bone scanning to evaluate for lung and bone metastases, respectively. The **differential diagnosis** of a lytic bone lesion includes histiocytosis, Ewing sarcoma, lymphoma, and bone cyst.

Figure 501-2 Radiograph of an osteosarcoma of the femur with typical "sunburst" appearance of bone formation.

Treatment

With chemotherapy and surgery, the 5-yr disease-free survival rate of patients with nonmetastatic extremity osteosarcoma is 65-75%. Complete surgical resection of the tumor is important for cure. The current approach is to treat patients with preoperative chemotherapy in an attempt to facilitate limb salvage operations and to treat micrometastatic disease immediately. Up to 80% of patients are able to undergo limb salvage operations after initial chemotherapy. It is important to resume chemotherapy as soon as possible after surgery. Lung metastases present at diagnosis should be resected by thoracotomies at some time during the course of treatment. Active agents currently in use in multidrug chemotherapy regimens for conventional osteosarcoma include doxorubicin, cisplatin, methotrexate, and ifosfamide.

One of the most important prognostic factors in osteosarcoma is the histologic response to chemotherapy. An international cooperative group is performing a randomized trial of the postoperative addition of high-dose ifosfamide with etoposide to standard 3 drug therapy with cisplatin, doxorubicin, and methotrexate to improve the outcome of patients with a poor histologic response. Patients with a good histologic response were randomized to the addition of pegylated interferon-α2b. Results are anticipated in the near future. For patients with metastatic disease, a new approach is the addition of zoledronic acid, a bisphosphonate, to intensive chemotherapy, with results pending. After limb salvage surgery, intensive rehabilitation and physical therapy are necessary to ensure maximal functional outcome.

For patients who require amputation, early prosthetic fitting and gait training are essential to enable patients to resume normal activities as soon as possible. Before definitive surgery, patients with tumors on weight-bearing bones should be instructed to use crutches to avoid stressing the weakened bones and causing pathologic fracture. The role of chemotherapy in parosteal and periosteal osteosarcomas is not well defined, and chemotherapy is generally reserved for use in patients with tumors which have a high-grade microscopic appearance.

Prognosis

Surgical resection alone is curative only for patients with parosteal osteosarcoma. Conventional osteosarcoma requires multiagent chemotherapy. Up to 75% of patients with nonmetastatic extremity osteosarcoma are cured with current multiagent treatment protocols. The prognosis is not as favorable for patients with pelvic tumors as for those with primary tumors in the extremities. Twenty percent to 30% of patients who have limited numbers of pulmonary metastases also can be cured with aggressive chemotherapy and resection of lung nodules. Patients with bone metastases and those with widespread lung metastases have an extremely poor prognosis. Long-term follow-up of patients with osteosarcoma is important to monitor for late effects of chemotherapy, such as cardiotoxicity from anthracycline and hearing loss from cisplatin. Patients in whom late, isolated lung metastases develop may be cured with surgical resection of the metastatic lesions alone.

EWING SARCOMA

Epidemiology

The incidence of Ewing sarcoma in the United States is 2.1 cases per 1 million children. It is rare among African-American children. Ewing sarcoma, an undifferentiated sarcoma of bone, also may arise from soft tissue. The term **Ewing sarcoma family of tumors** refers to a group of small, round cell, undifferentiated tumors thought to be of neural crest origin that generally carry the same chromosomal translocation. This family of tumors includes Ewing sarcoma of bone and soft tissue and peripheral **primitive neuroectodermal tumor**. Treatment protocols for these tumors are the same whether the tumors arise in bone or soft tissue. Anatomic sites of primary tumors arising in bone are distributed evenly between the extremities and the central axis (pelvis, spine, and chest wall). Primary tumors arising in the chest wall are often referred to as **Askin tumors**.

Figure 501-3 Radiograph of tibial Ewing sarcoma showing periosteal elevation or "onion-skinning."

Pathogenesis

Immunohistochemical staining assists in the diagnosis of Ewing sarcoma to differentiate it from **small, round, blue cell tumors** such as lymphoma, rhabdomyosarcoma, and neuroblastoma. Histochemical stains may react positively with certain neural markers on tumor cells (neuron-specific enolase and S-100), especially in peripheral primitive neuroectodermal tumors. Reactivity with muscle markers (e.g., desmin, actin) is absent. Additionally, MIC-2 (CD99) staining is usually positive. A specific chromosomal translocation, t(11;22), or a variant thereof is found in most of the Ewing sarcoma family of tumors. Analysis for the translocation by FISH (fluorescent in situ hybridization) or polymerase chain reaction analysis for the chimeric fusion gene products EWS/FLI1 or EWS/ERG is utilized routinely in diagnosis.

Clinical Manifestations

Symptoms of Ewing sarcoma are similar to those of osteosarcoma. Pain, swelling, limitation of motion, and tenderness over the involved bone or soft tissue are common presenting symptoms. Patients with huge chest wall primary tumors may present with respiratory distress. Patients with paraspinal or vertebral primary tumors may present with symptoms of cord compression. Ewing sarcoma often is associated with **systemic manifestations**, such as fever and weight loss; patients may have undergone treatment for a presumptive diagnosis of osteomyelitis or a fever of unknown origin. Patients also may have a delay in diagnosis when their pain or swelling is attributed to a sports injury.

Diagnosis

The diagnosis of Ewing sarcoma should be suspected in a patient who presents with pain and swelling, with or without systemic symptoms, and with a radiographic appearance of a primarily lytic bone lesion with periosteal reaction, the characteristic **onion-skinning** (Fig. 501-3). A large, associated, soft tissue mass often is visualized on MRI or CT (Fig. 501-4). The **differential diagnosis** includes osteosarcoma, osteomyelitis, Langerhans cell histiocytosis, primary lymphoma of bone, metastatic neuroblastoma, or rhabdomyosarcoma in the case of a pure soft tissue lesion. Patients should be referred to a center with

Figure 501-4 MR image of tibial Ewing sarcoma showing a large associated soft tissue mass.

experience in managing bone tumors for evaluation and biopsy. Thorough evaluation for metastatic disease includes CT of the chest, radionuclide bone scan, and bone marrow aspiration and biopsy specimens from at least 2 sites. MRI of the tumor and the entire length of involved bone should be performed to determine the exact extension of the soft tissue and bony mass and the proximity of tumor to neurovascular structures. Fluorodeoxyglucose positron emission tomography scanning is being incorporated to enhance staging. Studies are also using fluorodeoxyglucose positron emission tomography to evaluate response to therapy.

To avoid compromising an ultimate potential for limb salvage by a poorly planned biopsy incision, the same surgeon should perform the biopsy and the surgical procedure. CT-guided biopsy of the lesion often provides diagnostic tissue. It is important to obtain adequate tissue for special stains and molecular studies.

Treatment

Tumors of the Ewing sarcoma family are best managed with a comprehensive multidisciplinary approach in which the surgeon, chemotherapist, and radiation oncologist plan therapy. Multiagent chemotherapy is important because it can shrink the tumor rapidly and is usually given before local control is attempted. In North America, standard chemotherapy for nonmetastatic Ewing sarcoma includes vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide. Chemotherapy usually causes dramatic shrinkage of the soft tissue mass and rapid, significant pain relief. The most recent published randomized study for patients with nonmetastatic Ewing sarcoma showed a statistically significantly better outcome when patients were treated on a 14 day schedule than on a 21 day schedule. Current studies are evaluating the addition of topoisomerase inhibitors to standard chemotherapy, and plans are under way to investigate the role of insulin-like growth factor receptor inhibitors for certain groups of patients. An international cooperative group trial is evaluating whether myeloablative chemotherapy and stem cell rescue is superior to chemotherapy with lung irradiation for patients with pulmonary metastases. Ewing sarcoma is considered a radiosensitive tumor, and local control may be achieved with irradiation or surgery. Radiation therapy is associated with a risk of radiation-induced second malignancies, especially osteosarcoma, as well as failure of bone growth in skeletally immature patients. Many centers prefer surgical resection, if possible, to achieve local control. It is important to provide the patient with crutches if the tumor is in a weight-bearing bone, to avoid a pathologic fracture before definitive local control. Chemotherapy should be resumed as soon as possible after surgery.

Prognosis

Patients with small, nonmetastatic, distally located extremity tumors have the best prognosis, with a cure rate of up to 75%. Patients with pelvic tumors have, until recently, had a much worse outcome. Patients with metastatic disease at diagnosis, especially bone or bone marrow metastases, have a poor prognosis, with <30% surviving long term. New approaches, such as very intensive chemotherapy with peripheral blood stem cell rescue, are being investigated in these patients.

Long-term follow-up of patients with Ewing sarcoma is important because of the potential for late effects of treatment, such as anthracycline cardiotoxicity; second malignancies, especially in the radiation field; and late relapses, even as long as 10 yr after initial diagnosis.

501.2 Benign Tumors and Tumor-Like Processes of Bone

Carola A.S. Arndt

Benign bone lesions in children are common in comparison with the relatively rare malignant neoplasms of bone. They present diagnostic challenges. Some, although histologically benign, can be life-threatening. No single element in the history or diagnostic test is sufficient to rule out malignancies or suggest the existence of non-neoplastic conditions. A broad range of diagnostic possibilities must be considered when the physician is confronted with an undiagnosed bone lesion. Benign lesions may be painless or painful, especially if a pathologic fracture is impending. Night pain that awakens a child suggests malignancy, but relief of such pain with aspirin is common with benign lesions such as osteoid osteomas. Rapidly enlarging lesions usually are associated with malignancy, but several benign lesions, such as aneurysmal bone cysts, can enlarge faster than most malignancies. Several conditions, such as osteomyelitis, can simulate the appearance of benign bone tumors.

Many benign bone tumors are diagnosed incidentally or after pathologic fracture. Management of these fractures is similar to that of nonpathologic fractures in the same location. It is unusual for benign bone tumors to interfere with fracture healing. Likewise, the fractures rarely result in changes or healing of these tumors, which usually are treated after the fracture has healed.

Radiographs of any suspected bone lesion should always be obtained in 2 planes. Additional studies may be necessary to help arrive at the correct diagnosis and to guide treatment. Although these lesions are benign, many do require intervention.

Osteochondroma (exostosis) is one of the most common benign bone tumors in children. Because many are completely asymptomatic and unrecognized, the true incidence of this lesion is unknown. Most osteochondromas develop in childhood, arising from the metaphysis of a long bone, particularly the distal femur, proximal humerus, and proximal tibia. The lesion enlarges with the child until skeletal maturity. Most are discovered at 5-15 yr of age, when the child or parent notices a bony, nonpainful mass. Some are discovered because they are irritated by pressure during athletic or other activities. Osteochondromas appear radiographically as stalks or broad-based projections from the surface of the bone, usually in a direction away from the adjacent joint. Invariably, the lesion is radiographically smaller than suggested by palpation because the cartilage cap covering the lesion is not seen. This cartilage cap may be up to 1 cm thick. Both the cortex of the bone and the marrow space of the involved bone are continuous with the lesion. Malignant degeneration of a chondrosarcoma is rare in children but occurs in as many as 1% of adults. Routine removal is not performed unless the lesion is large enough to cause symptoms or grows rapidly.

Multiple hereditary exostoses is a related but rare condition characterized by the presence of multiple osteochondromas. Severely involved children can have short stature, limb-length inequality, premature partial physeal arrests, and deformity of both the upper and lower extremities. These children must be monitored carefully during growth.

Enchondroma is a benign lesion of hyaline cartilage that occurs centrally in the bone. Most of these lesions are asymptomatic and occur in the hands. Most are discovered incidentally, although pathologic fractures often lead to the diagnosis. Radiographically, the lesions occupy the medullary canal, are radiolucent, and are sharply marginated. Punctate or stippled calcification may be present within the lesion, but this is much more common in adults than in children. Almost all enchondromas are solitary. Most can simply be observed, with curettage and bone grafting reserved for lesions that are symptomatic or large enough to weaken the bone structurally. Multifocal involvement is referred to as **Ollier disease** and can result in bone dysplasia, short stature, limb-length inequality, and joint deformity. Surgery may be necessary to correct or prevent such deformities. When multiple enchondromas are associated with angiomas of the soft tissue, the condition is referred to as **Maffucci syndrome**. A high rate of malignant transformation has been reported in both of these multifocal conditions.

Chondroblastoma is a rare lesion usually found in the epiphysis of long bones. Most patients present in the 2nd decade with complaints of mild to moderate pain in the adjacent joint. Common sites include the hip, shoulder, and knee. Muscle atrophy and local tenderness may be the only clinical findings. The lesion appears radiographically as a sharply marginated radiolucency within the epiphysis or apophysis, occasionally with metaphyseal extension across the physis. Proximity to the joint can cause deformity of the subchondral bone, an effusion, or erosion into the joint. Recognition is important because most lesions

can be cured with curettage and bone grafting before joint destruction occurs.

Chondromyxoid fibroma is an uncommon benign bone tumor in children. This metaphyseal lesion usually causes pain and local tenderness. The lesion occasionally is asymptomatic. Chondromyxoid fibroma appears radiographically as eccentric, lobular, metaphyseal radiolucency with sharp, sclerotic, and scalloped margins. The lower extremity is involved most often. Treatment usually consists of curettage and bone grafting or en bloc resection.

Osteoid osteoma is a small benign bone tumor. Most of these tumors are diagnosed between 5 and 20 yr of age. The clinical pattern is characteristic, consisting of unremitting and gradually increasing pain that often is worst at night and is relieved by aspirin. Boys are affected more often than girls. Any bone can be involved, but the most common sites are the proximal femur and tibia. Vertebral lesions can cause scoliosis or symptoms that mimic a neurologic disorder. Examination can reveal a limp, atrophy, and weakness when the lower extremity is involved. Palpation and range of motion do not alter the discomfort. Radiographs are distinctive, showing a round or oval metaphyseal or diaphyseal lucency (0.5-1.0 cm in diameter) surrounded by sclerotic bone. The central lucency, or nidus, shows intense uptake on bone scan. Approximately 25% of osteoid osteomas are not visualized on plain radiographs but can be identified with CT. Because of the small size of the lesion and its location adjacent to thick cortical bone, MRI is poor at detecting osteoid osteomas. Treatment is directed at removing the lesion. This can involve en bloc excision, curettage, or percutaneous CT-guided ablation of the nidus. Patients with mild pain may be treated with salicylates. Some lesions resolve spontaneously after skeletal maturity.

Osteoblastoma is a locally destructive, progressively growing lesion of bone with a predilection for the vertebrae, although almost any bone may be involved. Most patients note the insidious onset of dull aching pain, which may be present for months before patients seek medical attention. Spinal lesions can cause neurologic symptoms or deficits. The radiographic appearance is variable and less distinctive than that of other benign bone tumors. Approximately 25% show features suggesting a malignant neoplasm, making biopsy necessary in many cases. Expansile spinal lesions often involve the posterior elements. Treatment involves curettage and bone grafting or en bloc excision; care must be taken to preserve nerve roots when treating spinal lesions. Surgical stabilization of the spine may be necessary.

Fibromas (nonossifying fibroma, fibrous cortical defect, metaphyseal fibrous defect) are fibrous lesions of bone that occur in 40% of children older than 2 yr of age. They most likely represent a defect in ossification rather than a neoplasm and usually are asymptomatic. Most are discovered incidentally when radiographs are taken for other reasons, usually to rule out a fracture after trauma. Occasional pathologic fractures can occur through rare large lesions. Physical examination usually is unrevealing. Radiographs show a sharply marginated eccentric lucency in the metaphyseal cortex. Lesions may be multilocular and expansile, with extension from the cortex into the medullary bone. The long axis of the lesion runs parallel to that of the bone. Approximately 50% are bilateral or multiple. Because of the characteristic radiographic appearance, most lesions do not require biopsy or treatment. Spontaneous regression can be expected after skeletal maturity. Curettage and bone grafting may be recommended for lesions occupying >50% of the bone diameter because of the risk of a pathologic fracture.

Unicameral bone cysts can occur at any age in childhood but are rare in children younger than 3 yr of age and after skeletal maturity. The cause of these fluid-filled lesions is unknown. Some resolve spontaneously after skeletal maturity is reached. Most are asymptomatic until diagnosis, which usually follows a pathologic fracture. Such fractures can occur with relatively minor trauma, such as with throwing or catching a ball. Unicameral bone cysts appear radiographically as solitary, centrally located lesions within the medullary portion of the bone. These cysts are most common in the proximal humerus or femur. They often extend to (but not through) the physis and are sharply marginated. The cortex expands, but that does not exceed the width of the adjacent physis. Treatment involves allowing the pathologic fracture to heal, followed by aspiration and injection with methylprednisolone or bone marrow. Repeat injections, curettage, and bone grafting occasionally are necessary to treat recurrent lesions.

Aneurysmal bone cyst is a reactive lesion of bone seen in persons younger than 20 yr of age. The lesion is characterized by cavernous spaces filled with blood and solid aggregates of tissue. Although the femur, tibia, and spine are most commonly involved, this progressively growing, expansile lesion develops in any bone. Pain and swelling are common. Spinal involvement can lead to cord or nerve root compression and associated neurologic symptoms, including paralysis. Radiographs show eccentric lytic destruction and expansion of the metaphysis surrounded by a thin sclerotic rim of bone. Posterior elements of the spine are involved more commonly than the vertebral body. Unlike most other benign bone tumors, which usually are confined to a single bone, aneurysmal bone cysts can involve adjacent vertebrae. Rapid growth is characteristic and can lead to confusion with malignant neoplasms. Treatment consists of curettage and bone grafting or excision. Spinal lesions can require stabilization after excision. As with other benign tumors, attempts are made to preserve nerve roots and other vital structures. Recurrence after surgical treatment occurs in 20-30% of patients, is more common in younger than older children, and usually occurs in the 1st 1-2 yr after treatment.

Fibrous dysplasia is a developmental abnormality characterized by fibrous replacement of cancellous bone. Lesions may be solitary or multifocal (polyostotic), relatively stable, or progressively more severe. Most children are asymptomatic, although those with skull involvement might have swelling or exophthalmos. Pain and limp are characteristic of proximal femoral involvement. Limb-length discrepancy, bowing of the tibia or femur, and pathologic fractures may be presenting complaints. The triad of polyostotic disease, precocious puberty, and cutaneous pigmentation is known as Albright syndrome. Radiographic features of fibrous dysplasia include a lytic or ground-glass expansile lesion of the metaphysis or diaphysis. The lesion is sharply marginated and often is surrounded by a thick rim of sclerotic bone. Bowing, especially of the proximal femur, may be present. Treatment usually involves observation. Surgery is indicated for patients with progressive deformity, pain, or impending pathologic fractures. Bone grafting is not as successful in the treatment of fibrous dysplasia as with other benign tumors, because the lesion often recurs within the grafted bone. Reconstructive surgical techniques often are necessary to provide stability.

Osteofibrous dysplasia affects children 1-10 yr of age. This lesion usually involves the tibia. It is clinically, radiographically, and histologically distinct from fibrous dysplasia. Most children present with anterior swelling or enlargement of the leg. Progression is unlikely after 10 yr of age. Radiographs show solitary or multiple lucent cortical diaphyseal lesions surrounded by sclerosis. Anterior bowing of the tibia often is present. The radiographic appearance closely resembles that of adamantinoma, a malignant neoplasm, making biopsy more common than with other benign bone tumors. Treatment involves observation. Some lesions heal spontaneously. Excision and bone grafting should be delayed until the child is older than 10 yr of age because of a high recurrence rate before this age. Pathologic fractures heal with immobilization.

Langerhans cell histiocytosis is a monostotic or polyostotic disease that can also involve the skin, liver, or other organs. Single-site disease should be distinguished from the other forms of Langerhans cell histiocytosis (Hand-Schüller-Christian or Letterer-Siwe variants), which can have a less favorable prognosis (see Chapter 507). Langerhans cell histiocytosis usually occurs during the 1st 3 decades of life and is most common in boys 5-10 yr of age. The skull is most commonly affected, but any bone may be involved. Patients usually present with local pain and swelling. Marked tenderness and warmth often are present in the area of the involved bone. Spinal lesions can cause pain, stiffness, and occasional neurologic symptoms. The radiographic appearance of the skeletal lesions is similar in all forms of Langerhans cell histiocytosis but is variable enough to mimic many other benign and malignant lesions of bone. The radiolucent lesions have well-defined or irregular margins with expansion of the involved bone and periosteal new bone formation. Spine involvement can cause uniform compression or flattening of the vertebral body. A skeletal survey is warranted because

polyostotic involvement and the typical skull lesions strongly suggest the diagnosis of eosinophilic granuloma. Biopsy often is necessary to confirm the diagnosis because of the broad radiographic differential diagnosis. Treatment includes curettage and bone grafting, low-dose radiation therapy, or corticosteroid injection. Observation for symptomatic lesions is reasonable because most osseous lesions heal spontaneously and do not recur. Children with bone lesions should be evaluated for visceral involvement because treatment of Hand-Schüller-Christian disease and Letterer-Siwe disease is more complex and often systemic.

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Chapter 502

Retinoblastoma

Nidale Tarek and Cynthia E. Herzog

Retinoblastoma is an embryonal malignancy of the retina and the most common intraocular tumor in children. Although the survival rate of children in the United States and developed countries with retinoblastoma is extremely high, retinoblastoma progresses to metastatic disease and death in over 50% of children worldwide. Furthermore, the associated loss of vision and side effects of therapy are significant problems that remain to be addressed.

EPIDEMIOLOGY

Approximately 250-350 new cases of retinoblastoma are diagnosed each year in the United States, with no known racial or gender predilection. The cumulative lifetime incidence of retinoblastoma is approximately 1 : 20,000 live births, and retinoblastoma accounts for 4% of all pediatric malignancies. The median age at diagnosis is approximately 2 yr, and more than 90% of cases are diagnosed in children younger than 5 yr of age. Overall, about 66-75% of children with retinoblastoma have unilateral tumors, with the remainder having bilateral retinoblastoma. Bilateral involvement is more common in younger children, particularly in those diagnosed younger than the age of 1 yr, and is always heritable. There is a possible increased risk of retinoblastoma in children conceived by in vitro fertilization.

Retinoblastoma can be either hereditary or sporadic. Hereditary cases usually are diagnosed at a younger age and are multifocal and bilateral, whereas sporadic cases are usually diagnosed in older children who tend to have unilateral, unifocal involvement. The hereditary form is associated with loss of function of the **retinoblastoma gene *(RB1)*** via gene mutation or deletion. The *RB1* gene is located on chromosome 13q14 and encodes the **retinoblastoma protein,** a tumor-suppressor protein that controls cell-cycle phase transition and has roles in apoptosis and cell differentiation. Many different causative mutations have been identified, including translocations, deletions, insertions, point mutations, and epigenetic modifications such as gene methylation. The nature of the predisposing mutation can affect the penetrance and expressivity of retinoblastoma development.

According to Knudson's "two-hit" model of oncogenesis, 2 mutational events are required for retinoblastoma tumor development (see Chapter 492). In the hereditary form of retinoblastoma, the first mutation in the *RB1* gene is inherited through germinal cells and a second mutation occurs subsequently in somatic retinal cells. Second mutations that lead to retinoblastoma often result in the loss of the normal allele and concomitant loss of heterozygosity. Parents and siblings of a child with a germline mutation should be referred to a genetic specialist for testing; most children with hereditary retinoblastoma have spontaneous new germinal mutations, and both parents have wild-type retinoblastoma genes. All 1st-degree relatives of children with known or suspected hereditary retinoblastoma should have retinal examinations to identify retinomas or retinal scars, which may suggest hereditary retinoblastoma even though malignant retinoblastoma did not develop. In the sporadic form of retinoblastoma, the 2 mutations occur in somatic retinal cells. Heterozygous carriers of oncogenic *RB1* mutations demonstrate variable phenotypic expression.

PATHOGENESIS

Histologically, retinoblastoma appears as a small round blue cell tumor with rosette formation (Flexner-Wintersteiner rosettes). It may arise in any of the nucleated layers of the retina and exhibit various degrees of differentiation. Retinoblastoma tumors tend to outgrow their blood supply, resulting in necrosis and calcification.

Endophytic tumors arise from the inner surface of the retina and grow into the vitreous, and can also grow as tumors suspended within the vitreous itself, known as **vitreous seeding.** Exophytic tumors grow from the outer retinal layer and can cause retinal detachment. Diffuse infiltrating tumors grow intraretinally and remain flat; these are less common and can cause iris neovascularization. Tumors can also be both endophytic and exophytic. These tumors can also spread by direct extension to the choroid or along the optic nerve beyond the lamina cribrosa to the central nervous system, or by hematogenous or lymphatic spread to distant sites, including bones, bone marrow, and lungs.

CLINICAL MANIFESTATIONS

Retinoblastoma classically presents with **leukocoria,** a white pupillary reflex (Fig. 502-1), which often is first noticed when a red reflex is not present at a routine newborn or well-child examination or in a flash photograph of the child. Strabismus often is an initial presenting complaint. Decreased vision, orbital inflammation, hyphema, and pupil irregularity can occur with advancing disease. Pain can occur if secondary glaucoma is present. Only approximately 10% of retinoblastoma cases are detected by routine ophthalmologic screening in the context of a positive family history.

DIAGNOSIS

The diagnosis is established by the characteristic ophthalmologic findings of a chalky, white-gray retinal mass with a soft, friable consistency.

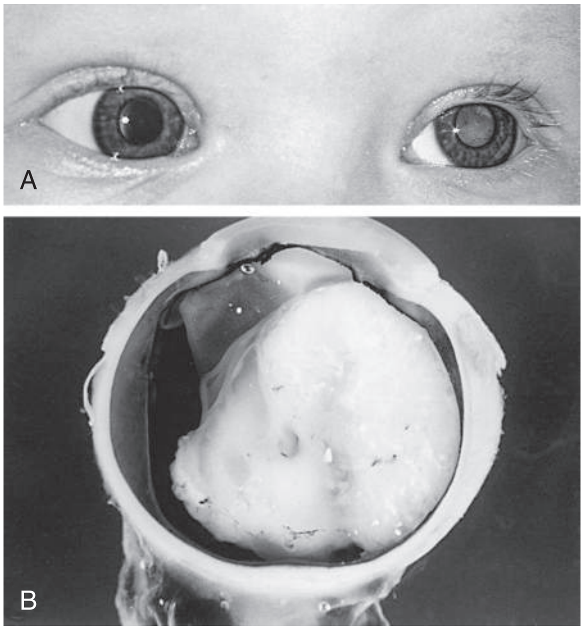

Figure 502-1 A, Leukocoria noted in the left eye of a child presenting with retinoblastoma. **B,** A large white tumor mass noted within the posterior chamber of the enucleated eye. *(From Shields JA, Shields CL: Current management of retinoblastoma,* Mayo Clin Proc *69:50–56, 1994.)*

Imaging studies are not diagnostic, and biopsies are contraindicated. Indirect ophthalmoscopy with slit-lamp evaluation can detect retinoblastoma tumors, but a complete evaluation requires an examination under general anesthesia by an experienced ophthalmologist to obtain complete visualization of both eyes, which also facilitates photographing and mapping of the tumors. Retinal detachment or vitreous hemorrhage can complicate the evaluation.

Orbital ultrasonography, CT, or MRI is used to evaluate the extent of intraocular disease and extraocular spread. Occasionally (~60%), a pineal area (primitive neuroectodermal) tumor is detected in a child with hereditary and bilateral retinoblastoma, a phenomenon known as **trilateral retinoblastoma.** MRI allows for better evaluation of optic nerve involvement. Metastatic disease is rarely present at diagnosis; evaluation of the cerebrospinal fluid and bone marrow for tumor metastasis and radionuclide bone scan are required only if indicated by other clinical, laboratory, or imaging findings.

The **differential diagnosis** of retinoblastoma includes other causes of leukocoria, including persistent hyperplastic primary vitreous, Coats disease, vitreous hemorrhage, cataract, endophthalmitis from *Toxocara canis*, choroidal coloboma, retinopathy of prematurity, and familial exudative vitreoretinopathy.

TREATMENT

Treatment is determined by the size and location of the tumors, if the disease is localized to the eye or has spread either to the brain or to the rest of the body, and whether the child has hereditary or sporadic disease. The primary goal of treatment is always cure; the secondary goals include preserving vision and the eye itself and decreasing the risk of late side effects, mainly secondary malignancies. As newer modalities for local control of intraocular tumors and more effective systemic chemotherapy have emerged, primary enucleation is being performed less often.

Most unilateral disease presents with a solitary, large tumor. Enucleation is performed if there is no potential for the salvage of useful vision. With bilateral disease, chemoreduction in combination with **focal therapy** (laser photocoagulation or cryotherapy) has replaced the traditional approach of enucleation of the more severely affected eye and irradiation of the remaining eye. If feasible, small tumors can be treated with focal therapy with careful follow-up for recurrence or new tumor growth. Larger tumors often respond to multiagent chemotherapy, including carboplatin, vincristine, and etoposide. If this approach fails, external-beam irradiation should be considered, although this approach may result in significant orbital deformity and increased incidence of second malignancies in patients with germline *RB1* mutations. Brachytherapy, or episcleral plaque radiotherapy, is an alternative with less morbidity. Enucleation may be required for unresponsive or recurrent tumors. Alternative treatment options currently under investigation include other systemic chemotherapy agents such as topotecan, other methods of chemotherapy administration, including periocular, intravitreal, and ophthalmic artery infusions, and intense multiagent chemotherapy with autologous stem cell rescue for patients with metastatic disease.

PROGNOSIS

Approximately 95% of children in the United States with retinoblastoma are cured with modern treatment. Current efforts using chemotherapy in combination with focal therapy are intended to preserve useful vision and avoid external-beam radiation or enucleation. Routine ophthalmologic examinations should continue until children are older than age 7 yr. Unfortunately, the diagnosis of retinoblastoma in many children from 3rd-world countries is delayed, resulting in spread of the tumor outside of the orbit. The prognosis for children with retinoblastoma that has spread outside of the eye is poor. Trilateral retinoblastoma, disease involving both eyes and the pineal region, is almost universally fatal.

Children with germline *RB1* mutations are at significant risk for development of second malignancies, especially osteosarcoma and also soft tissue sarcomas and malignant melanoma. The risk of second malignancies is further increased by the use of radiation therapy. Other radiation-related late adverse effects include cataracts, orbital growth deformities, lacrimal dysfunction, and late retinal vascular injury.

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Chapter 503

Gonadal and Germ Cell Neoplasms

Cynthia E. Herzog and Winston W. Huh

EPIDEMIOLOGY

Malignant germ cell tumors (GCTs) and gonadal tumors are rare, with an incidence of 12 cases per 1 million persons younger than 20 yr of age. Most malignant tumors of the gonads in children are GCTs. The incidence varies according to age and sex, although the incidence of GCTs in adolescent males has increased over time. Sacrococcygeal tumors occur predominantly in infant girls. Testicular GCTs occur predominantly before age 4 yr and after puberty. Klinefelter syndrome is associated with an increased risk of mediastinal GCTs; Down syndrome, undescended testes, infertility, testicular atrophy, testicular microlithiasis, testicular dysgenesis syndrome, and inguinal hernias are associated with an increased risk of testicular cancer. The risk of testicular cancer in patients with cryptorchidism is reduced but not eliminated if orchiopexy is performed before 13 yr of age. The risk of testicular GCT is increased in 1st-degree relatives and is highest among monozygotic twins.

PATHOGENESIS

The GCTs and non-GCTs arise from primordial germ cells and coelomic epithelium, respectively. Testicular and sacrococcygeal GCTs arising during early childhood characteristically have deletions at chromosome arms 1p and 6q and gains at 1q, and lack the isochromosome 12p that is highly characteristic of malignant GCTs of adults. Testicular GCT also may demonstrate loss of imprinting. Ovarian GCTs from older girls characteristically have deletions at 1p and gains at 1q and 21. Because GCTs may contain benign and mixed malignant elements in different areas of the tumor, extensive sectioning is essential to confirm the correct diagnosis. The many histologically distinct subtypes of GCTs include teratoma (mature and immature), endodermal sinus tumor, and embryonal carcinoma (Fig. 503-1). Non-GCTs of the ovary include epithelial (serous and mucinous) and sex cord–stromal tumors; non-GCTs of the testicle include sex cord/stromal (e.g., Leydig cell, Sertoli cell) tumors. *DICER1* mutations have been observed in nonepithelial ovarian cancers, especially in Sertoli-Leydig tumors.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical presentation of germ cell neoplasms depends on location. Ovarian tumors often are quite large by the time they are diagnosed (Fig. 503-2). Extragonadal GCTs occur in the midline, including the suprasellar region, pineal region, neck, mediastinum, and retroperitoneal and sacrococcygeal areas (Fig. 503-3). Symptoms relate to mass effect, but the intracranial GCTs often present with anterior and posterior pituitary deficits (see Chapter 497).

The **serum α-fetoprotein (AFP)** level is elevated with endodermal sinus tumors and may be minimally elevated with teratomas. Infants normally have higher levels of AFP, which fall to normal adult levels by about age 8 mo; consequently, high AFP levels must be interpreted with caution in this age group. Elevation of the β subunit of **human chorionic gonadotropin,** which is secreted by syncytiotrophoblasts, is seen with choriocarcinoma and germinomas. Lactate dehydrogenase,

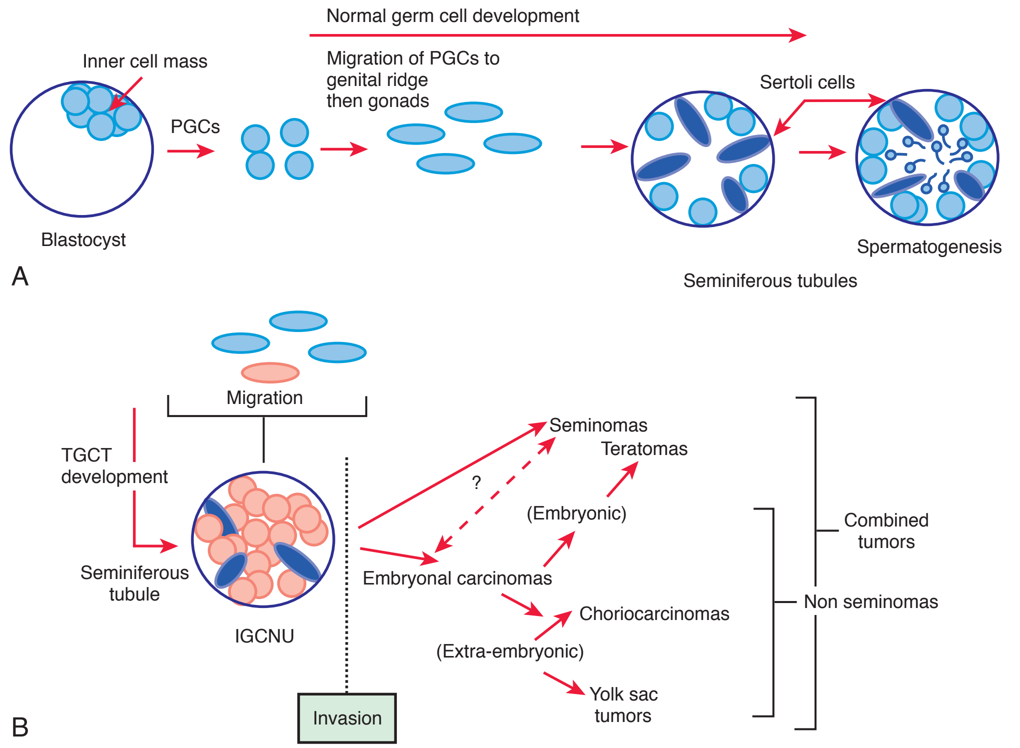

Figure 503-1 **A,** Normal germ cell development. **B,** Model for the origin and histogenesis of different subtypes of testicular germ cell tumors. *IGCNU*, intratubular germ cell neoplasia unclassified; *PGC*, primary germ cell; *TGCT*, testicular germ cell tumor(s).

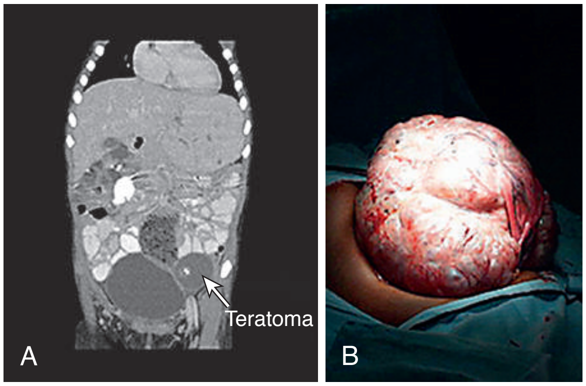

Figure 503-2 **A,** Postnatal MRI showing a left ovarian teratoma with bony calcification. **B,** Massive ovarian teratoma. *(From Lakhoo K. Neonatal teratomas.* Early Hum Dev *86(10):643–647, 2010.)*

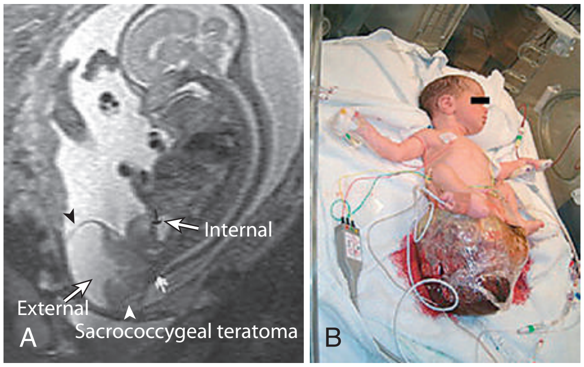

Figure 503-3 **A,** Prenatal MRI showing sacrococcygeal teratoma with a small internal and large external component. **B,** Postnatal large bleeding sacrococcygeal teratoma. *(From Lakhoo K. Neonatal teratomas.* Early Hum Dev *86(10):643–647, 2010.)*

although nonspecific, may be a useful marker. If elevated, these markers provide important confirmation of the diagnosis and provide a means to monitor the patient for tumor response and recurrence. Both serum and cerebrospinal fluid should be assayed for these markers in patients with intracranial lesions.

Diagnosis begins with physical examination and imaging studies, including plain radiographs of the chest and ultrasonography of the abdomen. CT or MRI can further delineate the primary tumor. If germ cell malignancy is strongly suggested, preoperative staging with CT of the chest and bone scan is appropriate. Primary surgical resection is indicated for tumors deemed resectable. For older patients with testicular tumors, ipsilateral retroperitoneal lymph node sampling may be required to determine extent of disease and aid in treatment planning. Ovarian tumors also require detailed surgical evaluation including lymph node removal and pelvic washings for cytologic analysis for peritoneal spread. Diagnosis of intracranial lesions can be established with imaging and AFP or β-human chorionic gonadotropin determinations of serum and cerebrospinal fluid.

Gonadoblastomas often occur in patients with gonadal dysgenesis and all or parts of a Y chromosome. Gonadal dysgenesis is characterized by failure to fully masculinize the external genitalia. If this syndrome is diagnosed, imaging of the gonad with ultrasonography or CT is performed, and surgical resection of the tumor usually is curative. Prophylactic resection of dysgenetic gonads at the time of diagnosis is recommended, because gonadoblastomas, some of which contain malignant GCT elements, often develop. Gonadoblastomas may produce abnormal amounts of estrogen.

Teratomas occur in many locations, presenting as masses. They are not associated with elevated markers unless malignancy is present. The sacrococcygeal region is the most common site for teratomas. Sacrococcygeal teratomas occur most commonly in infants and may be diagnosed in utero or at birth, with most found in girls. The rate of malignancy in this location varies, ranging from <10% in children younger than 2 mo of age to >50% in children older than 4 mo of age.

Germinomas occur intracranially, in the mediastinum, and in the gonads. In the ovary, they are called **dysgerminomas;** in the testis,

seminomas. They usually are tumor-marker–negative masses despite being malignant. Endodermal sinus or yolk sac tumor and choriocarcinoma appear highly malignant by histologic criteria. Both occur at gonadal and extragonadal sites. Embryonal carcinoma most often occurs in the testes. Choriocarcinoma and embryonal carcinoma rarely occur in the pure form and are usually found as part of a mixed malignant GCT.

Non–germ cell gonadal tumors are very uncommon in pediatrics and occur predominantly in the ovary. Epithelial carcinomas (usually an adult tumor), Sertoli-Leydig cell tumors, and granulosa cell tumors may occur in children. Carcinomas account for about one third of ovarian tumors in females younger than 20 yr of age; most of these occur in older teens and are of the serous or mucinous subtype. Sertoli-Leydig cell tumors and granulosa cell tumors produce hormones that can cause virilization, feminization, or precocious puberty, depending on pubertal stage and the balance between Sertoli cells (estrogen production) and Leydig cells (androgen production). Diagnostic evaluation usually focuses on the chief complaint of inappropriate sex steroid effect and includes hormone measurements, which reflect gonadotropin-independent sex steroid production. Appropriate imaging also is performed to rule out a functioning gonadal tumor. Surgery usually is curative. No effective therapy for nonresectable disease has been found.

TREATMENT

Complete surgical excision of the tumor usually is indicated, except for patients with intracranial tumors, where the primary therapy consists of radiation therapy and chemotherapy. For testicular tumors, an inguinal approach is indicated, and complete resection should include the entire spermatic cord. When complete excision cannot be accomplished, preoperative chemotherapy is indicated, with second-look surgery. For completely resected nonseminomatous testicular tumors, there is debate on whether patients can be clinically observed following surgery. For teratomas, both mature and immature, and completely resected malignant tumors of the testes, surgery alone is the treatment. For ovarian tumors, unless the contralateral ovary is obviously also involved by tumor, a fertility-sparing surgery should be performed. Cisplatin-based chemotherapy regimens usually are curative in GCTs that cannot be completely resected, even if metastases are present. However, sex cord–stromal tumors tend to be refractory to chemotherapy. Except for GCTs of the central nervous system, radiation therapy is limited to those tumors that are not amenable to complete excision and are refractory to chemotherapy.

PROGNOSIS

The overall cure rate for children with GCTs is >80%. Age is the most predictive factor of survival for extragonadal GCTs. Children older than 12 yr of age have a 4-fold higher risk of death, and a 6-fold higher risk if the tumor is thoracic. Histology has little effect on prognosis. Nonresected extragonadal GCTs have a slightly worse prognosis.

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Chapter 504
Neoplasms of the Liver
Nidale Tarek and Cynthia E. Herzog

Hepatic tumors are rare in children. Primary tumors of the liver account for approximately 1% of malignancies in children younger than 15 yr of age, with an annual incidence of 1.6 cases per 1 million children in the United States. Between 50% and 60% of hepatic tumors in children are malignant, with >65% of these malignancies being hepatoblastomas and most of the remainder being hepatocellular carcinomas. Rare hepatic malignancies include embryonal sarcoma, angiosarcoma, malignant germ cell tumor, rhabdomyosarcoma of the liver, and undifferentiated sarcoma. More common childhood malignancies, such as neuroblastoma, Wilms tumor, and lymphoma, can metastasize to the liver. Benign liver tumors, which usually present in the 1st 6 mo of life, include hemangiomas, hamartomas, and hemangioendotheliomas.

HEPATOBLASTOMA
Epidemiology
Approximately 100 new cases of hepatoblastoma are diagnosed each yr in the United States. Hepatoblastoma occurs predominantly in children younger than 3 yr of age and the median age of diagnosis is 1 yr. The etiology is unknown. Hepatoblastomas are associated with familial adenomatous polyposis. Alterations in the antigen-presenting cell/β-catenin pathway have been found in most of the tumors evaluated. Hepatoblastomas are also associated with Beckwith-Wiedemann syndrome, hemihyperplasia, and other somatic overgrowth syndromes. Increased expression of insulin-like growth factor 2 secondary to genetic mutations or epigenetic changes is implicated in hepatoblastoma development in patients with Beckwith-Wiedemann syndrome. All children with Beckwith-Wiedemann syndrome or hemihyperplasia should be routinely screened with α-fetoprotein (AFP) levels and abdominal ultrasounds. Prematurity and low birthweight is associated with increased incidence of hepatoblastoma, with the risk increasing as birthweight decreases.

Pathogenesis
Hepatoblastoma arises from precursors of hepatocytes and is histologically classified as whole epithelial type, containing fetal or embryonal malignant cells (either as a mixture or as pure elements), and mixed type, containing both epithelial and mesenchymal elements. Histologic classification has a direct correlation with clinical outcome. The pure fetal histology subtype predicts a more favorable outcome and the small cell undifferentiated subtype is associated with normal AFP levels and predicts a worse outcome.

Clinical Manifestations
Hepatoblastoma usually presents as a large, asymptomatic abdominal mass. It arises from the right lobe 3 times more often than the left and usually is unifocal. As the disease progresses, fatigue, fever, weight loss, anorexia, vomiting, and abdominal pain may ensue. Rarely, hepatoblastoma presents with hemorrhage secondary to trauma or spontaneous rupture. Metastatic spread of hepatoblastoma most commonly involves regional lymph nodes and the lungs.

Diagnosis
A biopsy of liver tumors is necessary to establish the diagnosis. A valuable serum tumor marker, **AFP,** is used in the diagnosis and monitoring of hepatic tumors. The AFP levels are elevated in almost all hepatoblastomas. Bilirubin and liver enzymes usually are normal. Anemia is common, and thrombocytosis occurs in approximately 30% of patients. Serologic testing for hepatitides B and C should be performed, but the results usually are negative in hepatoblastoma.

Diagnostic imaging should include plain radiographs and ultrasonography of the abdomen to characterize the hepatic mass. Ultrasonography can differentiate malignant hepatic masses from benign vascular lesions. Either CT or MRI is an accurate method of defining the extent of intrahepatic tumor involvement and the potential for surgical resection. Evaluation for metastatic disease should include CT of the chest.

Treatment
In general, the cure of malignant hepatic tumors in children depends on complete resection of the primary tumor (Fig. 504-1); as much as 85% of the liver can be resected, with hepatic regeneration noted within 3-4 mo after surgery. Treatment of hepatoblastoma is based on surgery and systemic chemotherapy using cisplatin in combination with vincristine and 5-fluorouracil or doxorubicin. In 30% of cases,

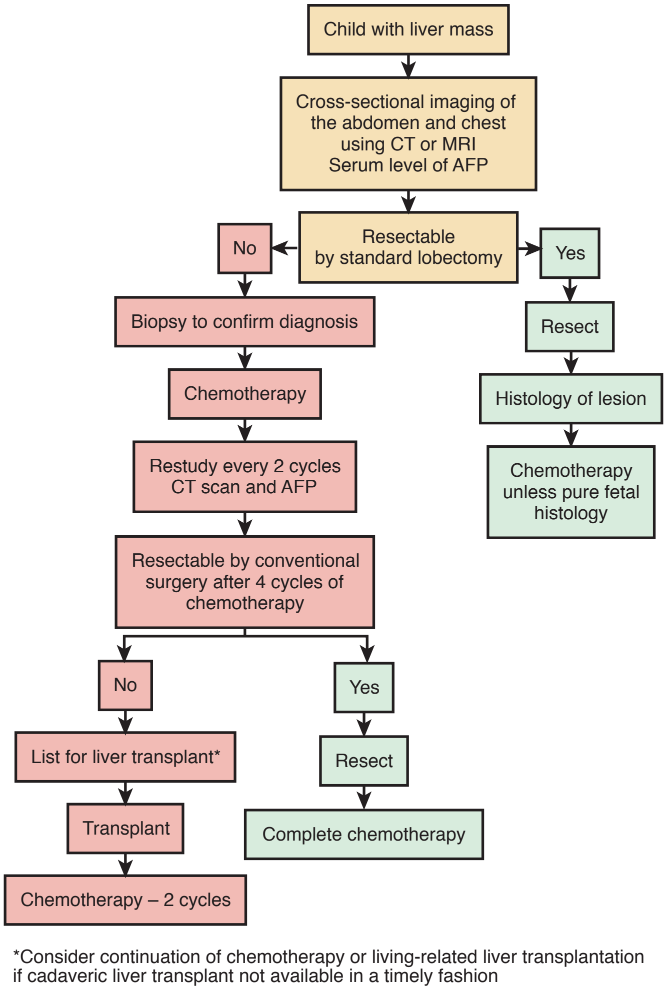

Figure 504-1 Algorithm for the management of a child who presents with a hepatoblastoma. *AFP*, α-fetoprotein. *(From Tiao GM, Bobey N, Allen S, et al: The current management of hepatoblastoma: a combination of chemotherapy, conventional resection, and liver transplantation,* J Pediatr *146:204–211, 2005.)*

tumors are resectable at diagnosis; a safe attempt for initial gross total resection should be made followed by adjuvant chemotherapy. Unresectable tumors with or without metastatic disease, at presentation, usually respond to chemotherapy; preresection chemotherapy is indicated, and excision of the primary tumor and extrahepatic disease should be attempted as soon as it becomes feasible, followed by additional chemotherapy. Liver transplant is a viable option for unresectable primary hepatic malignancies and results in good long-term survival. The pretransplant medical condition is an important predictor of outcome, and thus transplant is much more effective as the primary surgery than as salvage therapy. Alternative treatment options currently under investigation include other systemic chemotherapy agents such as carboplatin, ifosfamide, etoposide, and irinotecan. Other treatment approaches include transarterial chemoembolization, cryoablation, and radiofrequency ablation.

Prognosis

In low-stage tumors, survival rates >90% can be achieved with multimodal treatment, including surgery and adjuvant chemotherapy. With tumors unresectable at diagnosis, survival rates of approximately 60% can be obtained. Metastatic disease further reduces survival, but complete regression of disease often can be obtained with chemotherapy and surgical resection of the primary tumor and isolated pulmonary metastatic disease, resulting in survival rates of approximately 25%. Treatment-related long-term adverse effects include cardiac toxicity with doxorubicin and renal and ototoxicity with cisplatin.

HEPATOCELLULAR CARCINOMA

Epidemiology

Hepatocellular carcinoma occurs mostly in adolescents and often is associated with hepatitis B or C infection. It is more common in East Asia and other areas where hepatitis B is endemic; the incidence has decreased following the introduction of hepatitis B vaccination. In these areas it also tends to occur in a bimodal pattern, with the younger age peak overlapping the age of hepatoblastoma presentation. It also occurs in the chronic form of hereditary tyrosinemia, galactosemia, glycogen storage disease, α_1-antitrypsin deficiency, and biliary cirrhosis. Aflatoxin B contamination of food is another risk factor.

Pathogenesis

Hepatocellular carcinoma usually arises in an abnormal or cirrhotic liver and presents as a multicentric, invasive tumor consisting of large pleomorphic cells of epithelial origin. Compared to adults, cirrhosis in children is less common and congenital liver disorders are more common. Hepatocellular carcinomas are classified as classical or fibrolamellar. The fibrolamellar variant occurs more often in adolescent and young adult patients and is not associated with cirrhosis. Although previous reports have suggested that the fibrolamellar type has a better prognosis, more recent data analysis refutes this.

Clinical Manifestations

Hepatocellular carcinoma usually presents as a hepatic mass with abdominal distention and symptoms of anorexia, weight loss, and abdominal pain. Hepatocellular carcinoma can present as an acute abdominal crisis with rupture of the tumor and hemoperitoneum. Metastatic spread usually involves regional lymph nodes and the lungs. The AFP level is elevated in approximately 60% of children. Evidence of hepatitides B and C infection usually is found in endemic areas but not in Western countries or with the fibrolamellar type. Bilirubin usually is normal, but liver enzymes may be abnormal.

Diagnostic imaging should include plain radiographs and ultrasonography of the abdomen to characterize the hepatic mass. Ultrasonography can differentiate malignant hepatic masses from benign vascular lesions. Either CT or MRI is an accurate method of defining the extent of intrahepatic tumor involvement and the potential for surgical resection. Evaluation for metastatic disease should include CT of the chest.

Treatment

Complete tumor resection is crucial for curative treatment. Because of the multicentric origin of hepatocellular carcinoma and underlying liver disease, complete resection is accomplished in only 30-40% of cases. A gross total resection should be attempted at diagnosis when possible; combination chemotherapy following surgery is necessary. For unresectable tumors, chemotherapy followed by surgical assessment is essential; liver transplant is an option for unresectable tumors. Even with complete surgical resection, only 30% of children are long-term survivors. Chemotherapy, including cisplatin, doxorubicin, etoposide, and 5-fluorouracil, has shown some activity against this tumor, but improved long-term outcome has been difficult to achieve. Other techniques, such as cryosurgery, radiofrequency ablation, transarterial chemoembolization, and ethanol injection, are under study as therapy for hepatocellular carcinomas.

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Chapter 505
Benign Vascular Tumors

505.1 Hemangiomas

Cynthia E. Herzog

Hemangiomas, the most common benign tumors of infancy, occur in approximately 5-10% of term infants (see Chapter 650). The risk of hemangioma is 3-5 times higher in girls than boys. The risk is doubled in premature infants and 10 times higher in offspring of women who had chorionic villus sampling. Hemangiomas can be present at birth but usually arise shortly after birth and grow rapidly during the 1st yr of life, with slowing of growth in the next 5 yr and involution by 10-15 yr of age.

CLINICAL MANIFESTATIONS

More than 50% of all hemangiomas are located in the head and neck region. Most are solitary lesions, but the presence of more than 1 cutaneous lesion increases the likelihood of visceral hemangiomas. The liver is the primary site of visceral involvement; other involved organs include the brain, intestines, and lung. Infantile hemangiomas can be differentiated from other lesions with which they may be confused by the expression of GLUT1. Most hemangiomas require no therapy, but approximately 10% of hemangiomas cause significant impairment and 1% are life-threatening because of their location. Hemangiomas around the airway can cause airway obstruction, and those around the eyes can result in loss of vision. Ulceration is a common complication and can lead to secondary infection. With or without treatment, after involution of a hemangioma, residual skin abnormalities remain. Large hepatic hemangiomas or hemangioendotheliomas may result in hepatomegaly, anemia, thrombocytopenia, and high-output heart failure.

Kasabach-Merritt syndrome (see Chapter 650) is characterized by a rapidly enlarging lesion, thrombocytopenia, microangiopathic hemolytic anemia, and coagulopathy as a result of platelet and red blood cell trapping and activation of the clotting system within the vasculature of the hemangioma. This syndrome is associated with kaposiform hemangioendotheliomas or tufted angiomas but not with infantile hemangiomas.

Cutaneous lesions usually can be diagnosed by typical appearance and rapid proliferation. Segmental hemangiomas, or those with geographic localization and some plaque-like features, recently have been shown to have a higher risk of complications and association with developmental abnormalities. A deep lesion may require imaging studies to help differentiate it from a lymphangioma. The presence of a midline hemangioma in the lumbosacral area indicates the need for an MRI to search for underlying asymptomatic neurologic abnormalities. Location also may dictate the need for an ophthalmologic or surgical consultation. An ultrasonographic scan or MRI of the liver should be performed if multiple cutaneous lesions are present.

TREATMENT

See Chapter 650.

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505.2 Lymphangiomas and Cystic Hygromas

Cynthia E. Herzog

Lymphatic malformations, including lymphangiomas and cystic hygromas, which arise in the embryonic lymph sac, are the second most common benign vascular tumors in children. About half are located in the head and neck area. Approximately 50% are present at birth, with most presenting by 2 yr of age. There is no gender predisposition. Spontaneous regression has been reported but is not typical.

Lymphatic malformations present as soft, painless masses that transilluminate if superficial. Intrathoracic lymphatic malformation can present as symptoms related to a mediastinal mass or pericardial or pleural effusion. Rapid enlargement can occur with infection or hemorrhage. Localized lesions may be surgically resected, but this can be difficult, owing to their infiltrative nature. Recurrence is common with incompletely resected lesions. Aspiration can provide temporary relief in an emergency, such as in the presence of dyspnea, but reaccumulation will occur. Treatment by injection of sclerosing agents, laser therapy, and systemic interferon therapy also has been used. The streptococcal immunotherapeutic agent OK-432 (Picibanil) is the sclerosing agent of choice; its use will prevent the need for surgery in most cases. Bleomycin is also an effective sclerosing agent but has a risk of pulmonary toxicity. It appears to be especially effective for the treatment of macrocystic lymphangiomas of the head and neck.

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Chapter 506
Rare Tumors

506.1 Thyroid Tumors

Steven G. Waguespack

See Chapter 569.

BENIGN THYROID TUMORS

Benign thyroid tumors represent approximately 75% of all thyroid nodules presenting in the pediatric population. The work-up of a suspected thyroid nodule includes the laboratory assessment of thyroid function, ultrasound to assess the nodule and regional lymph node characteristics, and fine-needle aspiration biopsy under ultrasound guidance for definitive pathologic diagnosis. Nuclear scintigraphy using radioactive iodine (^{123}I) or ^{99m}Tc-pertechnetate is not recommended in the initial diagnostic evaluation, except in the event of a suppressed thyroid-stimulating hormone (TSH) level.

MALIGNANT THYROID TUMORS

Pediatric thyroid malignancies are rare tumors that include medullary thyroid carcinoma (MTC) and the differentiated thyroid carcinomas (DTCs): papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma. PTC represents the vast majority of thyroid cancers in children, who have an excellent overall prognosis with anticipated survival over decades, even in the presence of metastatic disease at diagnosis. The major established environmental risk factor for the development of PTC is exposure to ionizing radiation.

MTC is a very uncommon disease in childhood that almost always occurs in the context of an autosomal dominant, hereditary endocrine tumor syndrome that arises secondary to activating mutations in the *RET* (*RE*arranged during *T*ransfection) protooncogene: multiple endocrine neoplasia type 2a (MEN2A) or type 2b (MEN2B). In addition to the almost complete penetrance of MTC in the most common *RET* mutations, patients with MEN2A and MEN2B have up to a 50% lifetime risk of developing pheochromocytomas. Up to 20% of MEN2A patients will develop primary hyperparathyroidism. Patients with MEN2B do not develop hyperparathyroidism but have a distinct phenotype with a characteristic facial appearance, marfanoid body habitus, and a generalized ganglioneuromatosis, manifested most obviously by the presence of oral mucosal neuromas (Fig. 506-1). The

Figure 506-1 Classic appearance of oral mucosal neuromas on the tongue in a boy with MEN2B secondary to the typical M918T mutation in the *RET* protooncogene.

pathognomonic phenotype of MEN2B is not apparent in very early childhood, although an inability to cry tears and constipation represent early clues to diagnosis in these patients.

Children with thyroid cancer usually present with an asymptomatic thyroid mass and/or cervical lymphadenopathy, although children with MEN2 are often diagnosed only after a positive genetic test result or, in the case of MEN2B, after the clinical phenotype is recognized. Lymph node metastases are present in the majority of PTC cases and lung metastases are identified in up to 20% of patients, primarily in those children with a high burden of neck disease.

The primary therapy for thyroid cancer is a total thyroidectomy and a compartment-oriented lymph node dissection, as indicated, performed by a highly experienced thyroid cancer surgeon. In DTC, ^{131}I is used postoperatively to treat distant metastasis and unresectable residual neck disease. In PTC, the routine use of ^{131}I is limited to those children who are most likely to benefit from treatment. Children with MTC do not require ^{131}I therapy. The TSH level is initially suppressed by giving supraphysiologic levothyroxine in the case of DTC, as TSH stimulates DTC tumor growth; the TSH is kept normal in the case of MTC. Long-term follow-up involves monitoring of tumor markers (thyroglobulin in DTC and calcitonin/carcinogenic embryonic antigen in MTC), as well as routine imaging, primarily neck ultrasound.

In MEN2, there are well-documented genotype-phenotype correlations, and the biologic aggressiveness of MTC depends on the hereditary setting in which it develops. With the advent of genetic testing for *RET* mutations, MTC has become one of the few malignancies that can be cured via early thyroidectomy before the cancer becomes metastatic. Recommendations regarding the age at surgery of children who are carriers of a *RET* mutation are evolving and incorporate clinical testing (ultrasound and calcitonin levels) in addition to knowledge regarding the genotype. Novel oral tyrosine kinase inhibitors are approved by the FDA for the treatment of advanced MTC and DTC in adults.

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506.2 Melanoma

Dennis P.M. Hughes and Cynthia E. Herzog

See Chapter 651.

The incidence of melanoma in persons younger than 20 yr of age in the United States is 4.2 cases per 1 million, with 73% occurring in 15-19 year olds, 17% in 10-14 year olds, and 10% occurring in children younger than 10 yr of age (see Chapter 651). Melanoma is more common among adolescent females than males. In the United States, incident rates of melanoma in younger age groups are increasing, although at a slower rate than in adults. UV light, especially sun exposure, is a well-known risk factor for melanoma in adults, and also contributes to teenage melanoma, as shown by the tendency of lesions to develop on sun-exposed areas in this age group. In younger patients, melanoma does not appear to be associated with sun exposure and often occurs in skin that is not frequently exposed to the sun. Pediatricians should counsel patients regarding avoidance of sun exposure and the use of tanning beds to decrease the risk of later development of melanoma. Patients with fair skin and a family history of melanoma are at particularly high risk. Known risk factors for children are a giant hairy nevus (>10 cm), dysplastic nevus syndrome, and xeroderma pigmentosum. These conditions merit total skin examination at least annually.

Findings of a rapidly enlarging nevus that is dark, has changed colors, has irregular borders, or bleeds easily should raise a concern of melanoma. However, more than half of pediatric melanomas are nonpigmented, and can easily be confused with a wart or other benign finding. Diagnosis is based on pathology, and a punch biopsy is preferred. However, extra care must be taken in the diagnosis of melanoma in children because making the distinction from other lesions, particularly Spitz nevus, can be difficult. Management in a center with expertise in pediatric melanoma may be advisable, especially for anything other than thin melanomas (Breslow thickness of 1 mm or greater).

Prognosis and treatment recommendations have previously been extrapolated from adult data; however, specific prognostic factors for pediatric melanoma are starting to accrue. The initial diagnosis is best made with a punch biopsy. Shave biopsy is specifically discouraged, as this method tends to leave the base of the lesion behind, and specific information about the depth of invasion is lost. Biopsy sites that test positive for melanoma should be reexcised with appropriate margins based on thickness. Lymph node mapping and sentinel node biopsy should also be performed for all melanomas with a Breslow thickness >0.5-1 mm, or any lesions in which the tumor base was not resected. If the sentinel node is positive, a formal lymph node dissection is essential for ensuring the best probability of survival. To date, the treatment of childhood melanoma still mirrors treatment of adult melanoma. High-dose adjuvant interferon shows some efficacy in the treatment of adult melanoma, whereas chemotherapy in combination with biologic agents and vaccine therapy has been used for treatment of distant metastases. Although novel therapies such as targeted B-Raf inhibitors and immune-modulating agents have received regulatory approval for treatment of adult melanoma, their use in children is still investigational.

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506.3 Nasopharyngeal Carcinoma

Cynthia E. Herzog

Nasopharyngeal carcinoma is rare in the pediatric population but is one of the most common nasopharyngeal tumors in pediatric patients. In adults, the incidence is highest in South China, but it is also high among the Inuit people and in North Africa and Northeast India. In China, it is rare in the pediatric population, but in other populations a substantial proportion of cases occur in the pediatric age group, primarily in adolescents. It occurs in males twice as often as in females and is more common in blacks. In the pediatric population the tumors are more commonly of undifferentiated histology and associated with Epstein-Barr virus. Nasopharyngeal carcinoma is associated with specific human leukocyte antigen types, and other genetic factors may play a role, especially in low-incidence populations.

Most pediatric patients present with advanced locoregional disease manifesting as cervical lymphadenopathy. Epistaxis, trismus, and cranial nerve deficits also may be present. The diagnosis is established from biopsy of the nasopharynx or cervical lymph nodes. In most cases the lactate dehydrogenase level is elevated, but this finding is nonspecific. CT or MRI evaluation of the head and neck is performed to

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determine the extent of locoregional disease. Chest radiography, CT, bone scan, and liver scan are used to evaluate for metastatic disease. Positron emission tomography scans appear to be useful for monitoring both primary disease and looking for metastases. Epstein-Barr virus DNA levels correlate with disease stage, have prognostic value, and can be used to monitor for recurrence.

Treatment is a combination of chemotherapy and irradiation. Cisplatin given concurrently with radiation, with or without neoadjuvant cisplatin-based chemotherapy, is the standard treatment. The outcome depends on the extent of disease; patients with distant metastases have a very poor prognosis. Using intensity-modulated radiation therapy improves local control and reduces the late adverse effects associated with radiation therapy, including hormonal dysfunction, dental caries, fibrosis, and second malignancies. Use of proton therapy may result in further reduction of adverse effects.

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506.4 Adenocarcinoma of the Colon and Rectum

Cynthia E. Herzog and Winston W. Huh

Colorectal carcinoma (CRC) is rare in the pediatric population with an estimated incidence rate of approximately 1 case per 1 million. Even in patients with predisposing conditions, CRC usually does not present until late adolescence or adulthood. Hereditary nonpolyposis colon cancer (HNPCC) is an autosomal dominant disorder, with germline mutations in DNA mismatch repair genes *(MMR)* causing DNA repair errors and microsatellite instability. Familial adenomatous polyposis (FAP) and attenuated FAP are autosomal disorders, with germline mutations in the *APC* gene. In addition to CRC, patients with HNPCC, FAP, and attenuated FAP are predisposed to a number of extracolonic cancers. Desmoid tumors can occur in patients with FAP, whereas patients with HNPCC have an increased risk for tumors involving the genitourinary tract, stomach, and small intestine. *MYH*-associated polyposis, Peutz-Jeghers syndrome, and juvenile polyposis also predispose to CRC.

Genetic testing is available, and screening for cancer in HNPCC and FAP should begin during childhood or adolescence. Likewise, genetic evaluation for these conditions should be pursued in young patients presenting with colon cancer, even when there is no history of predisposing genetic conditions.

Presenting symptoms include bloody stools or melena, abdominal pain, weight loss, and changes in bowel patterns. In many cases, signs are vague, often resulting in a delay in diagnosis, sometimes not until the disease has reached an advanced stage. The histologic subtype differs from that seen in adults, with the majority of pediatric tumors being either mucinous adenocarcinoma or signet ring cell carcinoma. Treatment consists of surgical resection when possible, with chemotherapy for unresectable tumors. Adequate lymph node removal should be performed at the time of surgical resection of primary tumor. Radiation therapy is useful in the treatment of rectal carcinomas.

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506.5 Adrenal Tumors

Steven G. Waguespack

See Chapters 579 to 581.

Adrenocortical tumors (ACTs) arise from the outer adrenal cortex, whereas pheochromocytomas (PHEOs) derive from the catecholamine-producing chromaffin cells of the adrenal medulla. When catecholamine-producing tumors arise outside of the adrenal medulla, they are called paragangliomas (PGLs). The pathologic categorization of these tumors as benign or malignant does not always correlate well with the clinical behavior, making it difficult to differentiate malignant from benign disease based upon pathology alone. Hence, long-term follow-up is warranted. Because of the greater association with genetic disease, genetic counseling is also advised for all children diagnosed with an ACT or PHEO/PGL.

ACTs are very rare and tend to present before age 5 yr. They have a female predominance and are functional tumors in >90% of cases, primarily producing androgens and causing clinically apparent virilization. ACT may also present as an abdominal mass or pain. In children, ACTs are associated with Li-Fraumeni syndrome (germline inactivating mutations in the *TP53* tumor-suppressor gene), Beckwith-Wiedemann syndrome, hemihyperplasia other than that seen as part of Beckwith-Wiedemann syndrome, and, very rarely, congenital adrenal hyperplasia. Other unusual causes of nodular adrenocortical disease, which usually present with Cushing syndrome, include the Carney complex and macronodular adrenal hyperplasia.

PHEOs/PGLs are rare tumors that are more likely to be bilateral, malignant, and secondary to a heritable tumor syndrome when diagnosed in children. von Hippel–Lindau disease is the most common genetic cause of PHEOs/PGLs in the pediatric population, followed by the familial PGL syndromes caused by mutations in the succinate dehydrogenase gene. MEN2 (types 2A and 2B) and neurofibromatosis type 1 are also in the differential diagnosis, but are mostly associated with a PHEO diagnosis during adulthood. Although hypertension is usually paroxysmal in adults with PHEO, hypertension is usually sustained in children, who may also lack the typical triad of headache, palpitations, and diaphoresis seen commonly in adults. The best screening test for PHEO/PGL is measurement of plasma and/or urine metanephrine levels.

The initial treatment of ACT and PHEO/PGL is surgery. Children with PHEO/PGL require **preoperative medical management**, typically with α and β blockade. First-line medical therapy for metastatic ACT includes mitotane and chemotherapy with cisplatin, etoposide, and doxorubicin. Metastatic PHEO/PGL has historically been treated with cyclophosphamide, vincristine, and dacarbazine. In cases of both ACT and PHEO/PGL, novel targeted agents are being studied for the treatment of advanced metastatic disease, which is typically nonresponsive to standard chemotherapeutic approaches. Endocrine therapy targeting hormonal overproduction may also be needed to palliate symptoms and improve quality of life.

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506.6 Desmoplastic Small Round Cell Tumor

Nidale Tarek and Cynthia E. Herzog

Desmoplastic small round cell tumor is a very rare and aggressive mesenchymal tumor that occurs predominantly in adolescent and young adult males. It is associated with a diagnostic chromosomal translocation between the Ewing tumor gene and the Wilms tumor gene, t(11;22)(p13;q12). Patients typically present with a bulky abdominal mass, multiple peritoneal and omental implants, and symptoms of abdominal sarcomatosis, including pain, ascites, intestinal obstruction, hydronephrosis, and weight loss. Desmoplastic small round cell tumor mainly involves the abdominal cavity but can spread to the lymph nodes, liver, lungs, and bones. Aggressive treatment with combination chemotherapy, debulking surgery, and whole abdominopelvic irradiation results almost universally in a poor outcome. Median survival ranges between 17 and 25 mo, and the 5 yr overall survival remains less than 20%. Alternative treatment options currently under investigation include hyperthermic intraperitoneal chemotherapy and radioimmunotherapy with monoclonal antibodies targeting different surface antigens on tumor cells.

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Chapter 507

Histiocytosis Syndromes of Childhood

Stephan Ladisch

The childhood histiocytoses constitute a diverse group of disorders, which, although individually rare, are frequently severe in their clinical expression. These disorders are grouped together because they have in common a prominent proliferation or accumulation of cells of the monocyte–macrophage system of bone marrow origin. Although these disorders sometimes are difficult to distinguish clinically, accurate diagnosis is essential nevertheless for facilitating progress in treatment. A systematic classification of the childhood histiocytoses is based on histopathologic findings (Table 507-1). A thorough, comprehensive evaluation of a biopsy specimen obtained at the time of diagnosis is essential. This evaluation includes studies such as electron microscopy and immunostaining that may require special sample processing.

CLASSIFICATION AND PATHOLOGY

Three classes of childhood histiocytosis are defined, based on histopathologic findings. The most well-known childhood histiocytosis, **Langerhans cell histiocytosis (LCH)**, previously known as **histiocytosis X,** includes the clinical entities of eosinophilic granuloma, **Hand-Schüller-Christian disease,** and **Letterer-Siwe disease.** The normal Langerhans cell is an antigen-presenting cell of the skin. The hallmark of LCH in all forms is the presence of a clonal proliferation of cells of the monocyte lineage containing the characteristic electron microscopic findings of a Langerhans cell. This is the **Birbeck granule,** a tennis racket–shaped bilamellar granule that, when seen in the cytoplasm of lesional cells in LCH, is diagnostic of the disease. The Birbeck granule expresses a newly characterized antigen, langerin (CD207), which is involved in antigen presentation to T lymphocytes. CD207 expression has been established to be uniformly present in LCH lesions and thus becomes an additional reliable diagnostic marker. It appears more likely that the LCH cell is not actually a (differentiated) Langerhans cell but rather an immature cell of myeloid origin, possibly in an arrested state of development. Nevertheless, the definitive diagnosis of LCH is established by demonstrating CD1a-positivity of lesional cells, which is done using fixed tissue (Fig. 507-1). Lesional cells must be distinguished from normal Langerhans cells of the skin, which are also CD1a-positive but are not diagnostic of LCH. The lesions may contain various proportions of these Langerhans granule-containing CD1a-positive cells, lymphocytes, granulocytes, monocytes, and eosinophils.

In contrast to the prominence of an antigen-presenting cell in LCH, the other common group of histiocytoses are nonmalignant proliferative disorders that are characterized by accumulation of activated antigen-processing cells (macrophages and lymphocytes). These are known as the **hemophagocytic lymphohistiocytoses (HLHs).** They are the result of uncontrolled hemophagocytosis and uncontrolled activation (upregulation) of inflammatory cytokines with some similarities to the macrophage activation syndrome (see Table 155-5). Tissue infiltration by activated CD8 T lymphocytes, activated macrophages, and hypercytokinemia are classic features (Fig. 507-2). With the characteristic morphology of normal macrophages by light microscopy, these phagocytic cells (Fig. 507-1) are negative for the markers (Birbeck granules, CD1a-positivity, CD207-positivity) characteristic of LCH cells but are CD163-positive.

The 2 major forms of hemophagocytic lymphohistiocytosis have indistinguishable pathologic findings but are very important to distinguish from one another because of implications for both treatment and for prognosis. One is **familial hemophagocytic lymphohistiocytosis (FHLH),** originally named **familial erythrophagocytic lymphohistiocytosis,** which is an autosomal recessive disorder and represents approximately 25% of patients with HLH. Genes are known for 4 of the 5 FHLH syndromes; these mutations affect the ability of T lymphocytes and natural killer cells to synthesize and release perforin and granzymes, thus reducing cytotoxic granule formation. The other is the **infection-associated hemophagocytic syndrome,** also called secondary hemophagocytic lymphohistiocytosis (Table 507-2). Both

Table 507-1 Classification of the Childhood Histiocytoses

	DISEASE	CELLULAR CHARACTERISTICS OF LESIONS	TREATMENT
LCH	Langerhans cell histiocytosis	Langerhans-like cells (CD1a-positive, CD207-positive) with Birbeck granules (LCH cells)	Local therapy for isolated lesions; chemotherapy for disseminated disease
HLH	Familial hemophagocytic lymphohistiocytosis Infection-associated hemophagocytic syndrome† Associated with albinism syndromes* Associated with immunocompromised states Associated with autoimmune/autoinflammatory states	Morphologically normal reactive macrophages with prominent erythrophagocytosis, and CD8-positive T cells	Chemotherapy; allogeneic bone marrow transplantation
Other	Juvenile xanthogranuloma	Characteristic vacuolated lesional histiocytes with foamy cytoplasm	None or excisional biopsy for localized disease; chemotherapy, radiotherapy for disseminated disease
	Rosai-Dorfman disease	Hemophagocytic histiocytes	None if localized; surgery for bulk reduction; chemotherapy if organ systems involvement
	Malignant histiocytosis	Neoplastic proliferation of cells with characteristics of monocytes/macrophages or their precursors	Antineoplastic chemotherapy, including anthracyclines
Other	Acute monocytic leukemia‡	M5 by FAB classification	Antineoplastic chemotherapy

*Chediak-Higashi and Hermansky-Pudlak syndromes.
†Also called secondary hemophagocytic lymphohistiocytosis.
‡See Chapter 495.2.
FAB, French-American-British; LCH, Langerhans cell histiocytosis; HLH, hemophagocytic lymphohistiocytosis.

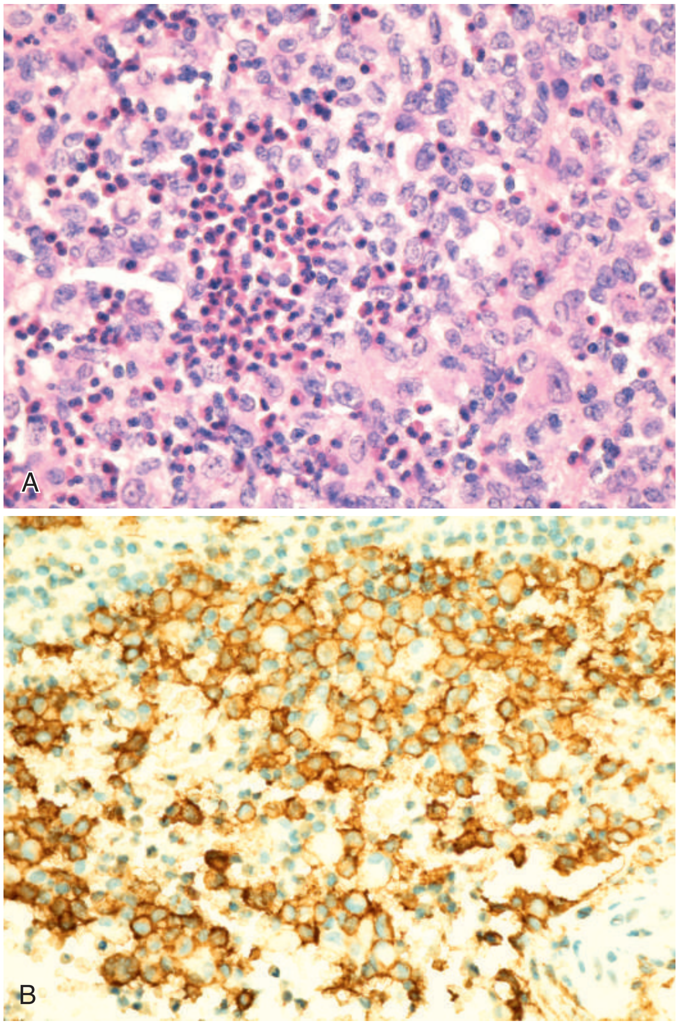

Figure 507-1 **A,** Histopathology of Langerhans cell histiocytosis (LCH). Shown is the eosinophilic granuloma of a lytic bone lesion of the femoral head. Multiple LCH cells with characteristic grooved nuclei, as well as numerous eosinophils, are visible in this mixed infiltrate. **B,** CD1a staining, characteristic and diagnostic of lesions with LCH cells.

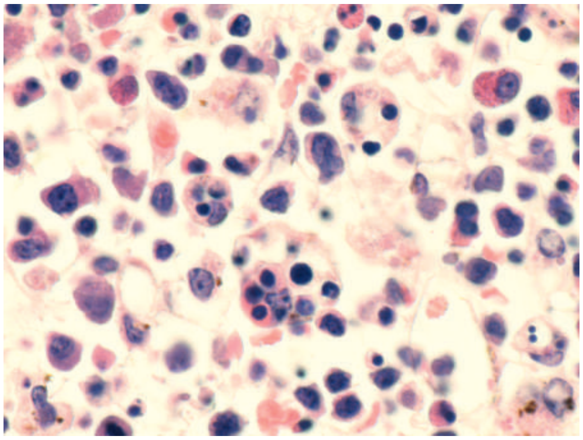

Figure 507-2 Bone marrow aspirate of a child with familial (genetically confirmed) hemophagocytic lymphohistiocytosis. Numerous characteristic hemophagocytic cells (which are CD163-positive macrophages) ingesting various blood elements are visualized.

Table 507-2	Infections Associated with Hemophagocytic Syndrome
VIRAL Adenovirus Cytomegalovirus Dengue virus Epstein-Barr virus Enteroviruses Herpes simplex viruses (HSV1, HSV2) Human herpesviruses (HHV6, HHV8) Human immunodeficiency virus Influenza viruses Parvovirus B19 Varicella-zoster virus Hepatitis viruses Measles Parechovirus	
BACTERIAL *Babesia microti* *Brucella abortus* Enteric Gram-negative rods *Haemophilus influenzae* *Mycoplasma pneumoniae* *Staphylococcus aureus* *Streptococcus pneumoniae*	
FUNGAL *Candida albicans* *Cryptococcus neoformans* *Histoplasma capsulatum* *Fusarium*	
MYCOBACTERIAL *Mycobacterium tuberculosis*	
RICKETTSIAL *Coxiella burnetii* Other rickettsial diseases	
PARASITIC *Leishmania donovani* *Plasmodium*	

From Nathan DG, Orkin SH, Ginsburg D, et al, editors: Nathan and Oski's hematology of infancy and childhood, *ed 6, Philadelphia, 2003, WB Saunders, p. 1381.*

diseases are characterized by disseminated lesions that involve many organ systems. The lesions are characterized by infiltration of the involved organ with activated phagocytic macrophages and lymphocytes, in which the lymphocyte defects (cytolytic pathway) are considered to be the primary abnormality.

Noninfectious causes that may trigger secondary HLH include drugs (phenytoin, highly active antiretroviral therapy), bone marrow transplantation, chemotherapy, autoimmune diseases, inflammatory bowel disease, and immunodeficiency states (DiGeorge syndrome, Bruton agammaglobulinemia, severe combined immunodeficiency syndrome, chronic granulomatous disease, cancer).

These diseases together comprise **HLH** (Table 507-3 and Fig. 507-3). Multiple different steps in granule formation and release by cytotoxic T cells, when inhibited by genetic mutation, can result in primary HLH (Fig. 507-3, bottom). In an analogous way, a trigger (e.g., infection) can result in secondary HLH (Fig. 507-3, top).

The mixed cellular lesions of both LCH and HLH are increasingly believed to point to these being disorders of immune regulation resulting from either an unusual and unidentified antigenic stimulation and/or an abnormal and defective cellular immune response. Mutations in the perforin (*PRF1*) gene or the *MUNC13-4* gene are the most common causes of defective function of the cytotoxic lymphocytes whose activity is inhibited in FHLH. Some cases of LCH demonstrate clonality of individual lesions. In LCH, a mutated form of the *BRAF* gene has been identified in many patients; its pathophysiologic significance is being

Table 507-3	Classification of Primary HLH, Notable Clinical Findings, and Rapid Diagnostic Results			
	DEFECTIVE GENE	**FUNCTION**	**NOTABLE CLINICAL FINDINGS**	**RAPID DIAGNOSIS BY FLOW CYTOMETRY**
HLH TYPE				
FHLH-1	*Unknown*	Unknown		
FHLH-2	*PRF1*	Pore formation		Decreased/absent perforin expression
FHLH-3	*Munc 13.4*	Vesicle priming	Increased incidence of CNS HLH	Decreased CD107a expression
FHLH-4	*STX11*	Vesicle fusion	Mild, recurrent HLH, colitis	Decreased CD107a expression
FHLH-5	*STXBP2*	Vesicle fusion	Colitis, bleeding, hypogammaglobulinemia	Decreased CD107a expression
SYNDROMES				
Griscelli syndrome type II	*RAB27A*	Vesicle docking	Partial albinism and silvery-gray hair	Decreased CD107a expression, abnormal hair shaft examination*
Chediak-Higashi syndrome	*LYST*	Vesicle trafficking	Partial albinism, bleeding tendency, and recurrent pyogenic infection	Decreased CD107a expression, abnormal neutrophil granules†
Hermansky-Pudlak syndrome type II	*AP3B1*	Vesicle trafficking	Partial albinism, bleeding tendency, and immunodeficiency	Decreased CD107a expression
EPSTEIN-BARR VIRUS–DRIVEN				
XLP-1	*SAP/SH2D1A*	Signaling in T, NK, and NK T cells	Hypogammaglobulinemia and lymphoma	Decreased/absent SAP expression
XLP-2/XIAP‡	*BIRC4*	Signaling pathways involving NF-κB	Mild, recurrent HLH and colitis	Decreased/absent XIAP expression
IL-2–inducible T-cell kinase deficiency	*ITK*	Signaling in T cell	AR, Hodgkin lymphoma	NA (gene sequencing required)
CD27 deficiency	*CD27*	Lymphocyte costimulatory molecule	AR, combined immunodeficiency	Absent CD27 expression on B cells
XMEN	*MAGT1*	T-cell activation via T-cell receptor	Combined immunodeficiency, chronic viral infections, and lymphoma	Decreased CD4 cells and defects in T-cell receptor signaling

*Light microscopy examination of a hair shaft shows a characteristic abnormal clumping of pigment.

†Light microscopy examination of peripheral blood smear shows giant granules in neutrophils and other leukocytes.

‡Defect is present in all tissues.

AR, autosomal recessive; CNS, central nervous system; FHLH, familial hemophagocytic lymphohistiocytosis; HLH, hemophagocytic lymphohistiocytosis; IL, interleukin; NA, not available; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; NK, natural killer; SAP, signaling lymphocyte-activating molecule–associated protein; XIAP, X-linked inhibitor of apoptosis protein; XLP, X-linked lymphoproliferative; XMEN, X-linked immunodeficiency with Mg^{2+} defect, Epstein-Barr virus infection, and neoplasia.

(From Chandrakasan S, Filipovich AH. Hemophagocytic lymphohistiocytosis: advances in pathophysiology, diagnosis, and treatment. J Pediatr *163(5):1253-1259, 2013.)*

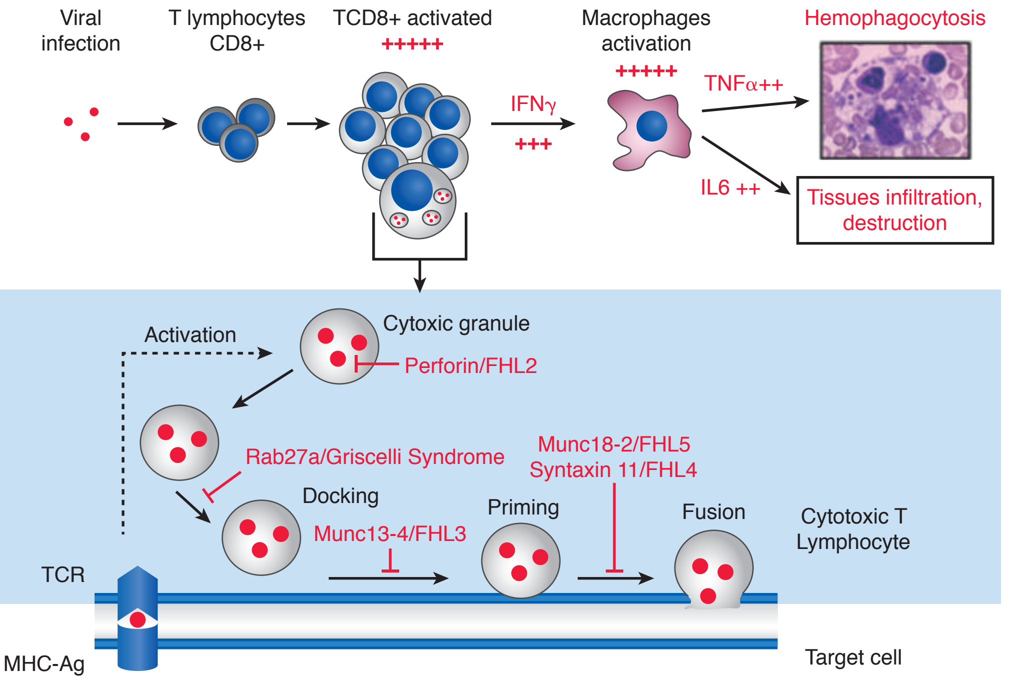

Figure 507-3 **Inborn errors in the cytotoxic activity of lymphocytes.** *Top:* Schematic diagram of the immune mechanisms leading to the occurrence of a hemophagocytic syndrome. Following a viral infection, antigen-specific $CD8^+$ T lymphocytes undergo massive expansion and activation and secrete high levels of interferon (IFN)-γ. The overwhelming activated effector cells induce excessive macrophage activation and pro-inflammatory cytokine production including tumor necrosis factor (TNF)-α and interleukin-6 (IL-6). Macrophages spontaneously phagocytose blood elements (here shown: platelets, red blood cells, and a polymorphonuclear cell). Activated lymphocytes and macrophages infiltrate various organs, resulting in massive tissue necrosis and organ failure. *Bottom:* The genetic defects causing hemophagocytic lymphohistiocytic syndrome (HLH) affect a precise step of the cytotoxic machinery, i.e. granule content, docking, priming, or fusion. Only the defects causing Griscelli syndrome (GS) and familial hemophagocytic lymphohistiocytosis (FHL) are shown. *(From Pachlopnik Schmid J, Cote M, Menager MM, et al: Inherited defects in cytotoxic lymphocyte activity.* Immunol Rev *235:10–23, 2010.)*

assessed. The *BRAF* mutation suggests both that there is an autonomous proliferative element to the disease and that there may potentially be a new avenue for therapeutic approaches.

In addition to these two most common forms of childhood histiocytosis, LCH and HLH, a number of rarer diseases are also included under this rubric, because they have in common various abnormalities of these cell populations of myeloid origin. These other diseases include **juvenile xanthogranuloma**, in which the lesional histiocytes are vacuolated, with foamy cytoplasm, and the lesions evolve into mixed granulomas also containing eosinophils, lymphocytes, and other cells. Another rare histiocytosis is **Rosai-Dorfman disease**, also known as **sinus histiocytosis** with massive lymphadenopathy. Packing of sinusoids of the lymph nodes with histiocytes that are hemophagocytic characterizes Rosai-Dorfman disease, although extranodal involvement is not uncommon. The etiology of these 2 diseases is unknown. Finally, there is also a group of unequivocal malignancies of cells of monocyte–macrophage lineage. By this definition, acute monocytic leukemia and true malignant histiocytosis are included among the class III histiocytoses (see Chapter 495). True neoplasms of Langerhans cells, while extremely rare, have been reported.

507.1 Langerhans Cell Histiocytosis

Stephan Ladisch

CLINICAL MANIFESTATIONS

LCH has an extremely variable presentation. The skeleton is involved in 80% of patients and may be the only affected site, especially in children older than 5 yr of age. Bone lesions may be single or multiple and are seen most commonly in the skull (Fig. 507-4). Other sites include the pelvis, femur, vertebra, maxilla, and mandible. They may be asymptomatic or associated with pain and local swelling. Involvement of the spine may result in collapse of the vertebral body, which can be seen radiographically, and may cause secondary compression of the spinal cord. In flat and long bones, osteolytic lesions with sharp borders occur and no evidence exists of reactive new bone formation until the lesions begin to heal. Lesions that involve weight-bearing long bones may result in pathologic fractures. Chronically draining, infected ears are commonly associated with destruction in the mastoid area. Bone destruction in the mandible and maxilla may result in teeth that, on radiographs, appear to be free floating. With response to therapy, healing may be complete.

Approximately 50% of patients experience skin involvement at some time during the course of disease, usually as a hard-to-treat scaly, papular, seborrheic dermatitis of the scalp, diaper, axillary, or posterior

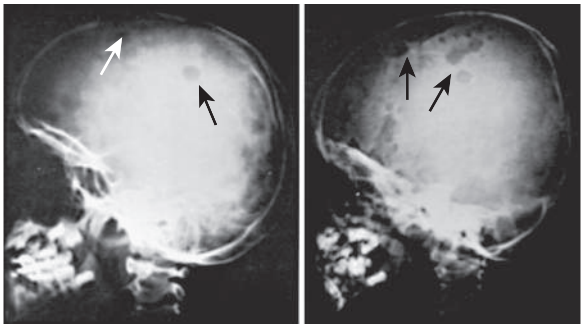

Figure 507-4 Two skull radiographs from patients with Langerhans cell histiocytosis (LCH). *Left,* The patient was older than 2 yr of age and had involvement limited to isolated bone lesions *(arrows).* She had a good recovery. *Right,* The patient was younger than 2 yr of age and had extensive bone disease *(arrows),* a febrile course, anemia, severe skin eruption, generalized lymphadenopathy, hepatosplenomegaly, pulmonary infiltrates, and a fatal outcome despite antitumor chemotherapy. These patients represent opposite ends of the clinical spectrum of LCH.

auricular regions. The lesions may spread to involve the back, palms, and soles. The exanthem may be petechial or hemorrhagic, even in the absence of thrombocytopenia. Localized or disseminated lymphadenopathy is present in approximately 33% of patients. Hepatosplenomegaly occurs in approximately 20% of patients. Various degrees of hepatic malfunction may occur, including jaundice and ascites.

Exophthalmos, when present, often is bilateral and is caused by retroorbital accumulation of granulomatous tissue. Gingival mucous membranes may be involved with infiltrative lesions that appear superficially like candidiasis. Otitis media is present in 30-40% of patients; deafness may follow destructive lesions of the middle ear. In 10-15% of patients, pulmonary infiltrates are found on radiography. The lesions may range from diffuse fibrosis and disseminated nodular infiltrates to diffuse cystic changes. Rarely, pneumothorax may be a complication. If the lungs are severely involved, tachypnea and progressive respiratory failure may result.

Pituitary dysfunction or hypothalamic involvement may result in growth retardation. In addition, patients may have diabetes insipidus; patients suspected of having LCH should demonstrate the ability to concentrate their urine before going to the operating room for a biopsy. Rarely, panhypopituitarism may occur. Primary hypothyroidism as a result of thyroid gland infiltration also may occur.

Patients with multisystem disease who are affected more severely are those who have systemic manifestations, including fever, weight loss, malaise, irritability, and failure to thrive. These systemic manifestations will distinguish between patients who are at high risk of mortality (i.e., "risk organ"-positive patients), and those without, who are at low risk (i.e., "risk organ"-negative patients). The risk organs are liver, spleen hematopoietic system, and lung. The distinction is important for deciding the intensity of the treatment approach and has been incorporated into standard treatment approaches for LCH, as delineated in the Histiocyte Society protocols. Bone marrow involvement may cause anemia and thrombocytopenia. Two uncommon but serious manifestations of LCH are hepatic involvement (leading to fibrosis and cirrhosis) and a peculiar central nervous system (CNS) involvement characterized by ataxia, dysarthria, and other neurologic symptoms. Hepatic involvement is associated with multisystem disease that is often already present at the time of diagnosis. In contrast, the CNS involvement, which is progressive and histopathologically characterized by gliosis, and for which no treatment is known, may be observed only many years after the initial diagnosis of LCH, which itself may have consisted only of mild bone disease. Neither of these manifestations evidences Langerhans cells or Birbeck granules, and both are suspected to be driven initially by cytokine abnormalities.

After tissue biopsy, which is diagnostic and is easiest to perform on skin or bone lesions, a thorough clinical and laboratory evaluation should be undertaken. This should include a series of studies in all patients (complete blood cell count, liver function tests, coagulation studies, skeletal survey, chest radiograph, and measurement of urine osmolality). In addition, detailed evaluation of any organ system that has been shown to be involved by physical examination or by these studies should be performed to establish the extent of disease before initiation of treatment.

TREATMENT AND PROGNOSIS

The clinical course of single-system disease (usually bone, lymph node, or skin) generally is benign, with a high chance of spontaneous remission. Therefore, treatment should be minimal and should be directed at arresting the progression of a bone lesion that could result in permanent damage before it resolves spontaneously. Curettage or, less often, steroid injection or low-dose local radiation therapy (5-6 Gy) may accomplish this goal. Multisystem disease, in contrast, should be treated with systemic multiagent chemotherapy. Several different regimens have been proposed, but central elements are the inclusion of vinblastine and steroids, both of which have been found to be very effective in treating LCH. Etoposide has more recently been excluded from standard treatment of multisystem LCH, while treatment of multisystem LCH includes therapy with multiple agents, designed to reduce mortality, reactivation of disease, and long-term consequences.

The response rate to therapy is now quite high, and mortality in severe LCH has been substantially reduced by multiagent chemotherapy, especially if the diagnosis is made accurately and expeditiously. The most recent treatment results, employing lengthened continuation therapy, show a greater than 85% survival rate in severe multisystem disease and a reduced rate of reactivation. Experimental therapies, suggested only for unresponsive disease (often in very young children with multisystem disease and organ dysfunction who have not responded to multiagent initial treatment), include immunosuppressive therapy with cyclosporine/antithymocyte globulin and possibly imatinib, 2-chlorodeoxyadenosine, and stem cell transplantation. Late (fibrotic) complications, whether hepatic or pulmonary, are irreversible and require organ transplantation to be definitively treated. Current treatment approaches and experimental protocols for both LCH and HLH can be obtained at the website for the Histiocyte Society (http://www.histiocytesociety.org). An unresolved problem is treatment of the (usually late-onset) severe, progressive, and intractable LCH-associated neurodegenerative syndrome.

Bibliography is available at Expert Consult.

507.2 Hemophagocytic Lymphohistiocytosis

Stephan Ladisch

(See "Classification and Pathology" above.)

CLINICAL MANIFESTATIONS

The major forms of HLH, FHLF and secondary HLH, have a remarkably similar presentation consisting of a generalized disease process, most often with fever (90-100%), maculopapular and/or petechial rash (10-60%), weight loss, and irritability (see Tables 507-4 and 507-5). FHLH also is characterized by severe immunodeficiency. Children with FHLH generally are younger than 4 yr of age, and children with secondary HLH may present at an older age, but both forms are recognized as presenting at any age. **Physical examination** often reveals hepatosplenomegaly (70-100%), lymphadenopathy (20-50%), respiratory distress (40-90%), jaundice, and symptoms of CNS involvement (~50%) that are not unlike those of aseptic meningitis or acute demyelinating encephalomyelitis (see Chapter 600.3). MRI may demonstrate systemic T2-weighted/FLAIR hyperintensities in gray and white matter and in supratentorial and infratentorial regions. The cerebrospinal fluid pleocytosis (50-90%) in CNS involvement of FHLH is characterized by cells that are the same phagocytic macrophages found in the peripheral blood or bone marrow. The **diagnosis** can be made either on the basis of a molecular (genetic) defect (see "Treatment and Prognosis" below) or on the pathologic findings of hemophagocytosis in bone marrow biopsy, and is suggested by clinical findings of fever, splenomegaly, and associated laboratory findings (in both forms of HLH), including hypertriglyceridemia (80-100%), hypofibrinogenemia (65-85%), elevated levels of hepatic enzymes (30-90%), extremely elevated levels of circulating soluble interleukin-2 receptors released by the activated lymphocytes, very high levels of serum ferritin (often >10,000), and cytopenias (in ~90-100%; especially pancytopenia from hemophagocytosis in the marrow). Hemophagocytosis is not specific for HLH without other features. In addition, in some subgroups of HLH perforin assays may be normal. In the absence of genetic mutations, the diagnosis of HLH is based on a set of specific criteria formulated by the Histiocyte Society, the presence of 5 of 8 of which is considered diagnostic of HLH (see Table 507-4): fever, splenomegaly, cytopenia of 2 cell lines, hypertriglyceridemia or hypofibrinogenemia, hyperferritinemia, elevated soluble CD25 (interleukin-2 receptor), reduced or absent natural killer cells, and bone marrow, cerebrospinal fluid, or lymph node evidence of hemophagocytosis. There are patients with FHLH who have no known identifiable gene mutation. No absolute clinical or laboratory distinction can be made between FHLH and secondary HLH, although genetic markers for FHLH can complement a positive family history for other affected children.

In the absence of either (1) documented genetic defect coupled with defective NK cell cytotoxicity or (2) frank hemophagocytosis, great care should be taken in making the diagnosis of (secondary) HLH, with its implication of the use of cytotoxic chemotherapy. This is because the otherwise nonspecific criteria (indicative of inflammation) used to diagnose HLH can also be seen in diseases that are not always associated with hemophagocytosis (such as an overwhelming acute viral infection without T cell overactivation) in which the cytotoxic and immunosuppressive therapy used in treating HLH might be contraindicated.

TREATMENT AND PROGNOSIS

The diagnostic distinction between FHLH and secondary HLH sometimes can be based on the acute onset of secondary HLH in the presence of a documented infection. In this case, treatment of the underlying infection, coupled with supportive care, is critical. If the diagnosis is made in a setting of iatrogenic immunodeficiency, immunosuppressive treatment should be withdrawn and supportive care should be instituted along with specific therapy for underlying infection. When FHLH (gene mutations in perforin or Munc13-4 proteins) is diagnosed or is suspected together with no documentation of an infection, therapy currently includes etoposide, corticosteroids, and intrathecal methotrexate. It should be stressed that pancytopenia is not a

Table 507-4	Diagnostic Guidelines for Hemophagocytic Lymphohistiocytosis

The diagnosis of HLH is established by fulfilling one of the following two criteria:

1. A molecular diagnosis consistent with HLH (e.g., PRF mutations, SAP mutations)

or

2. Having 5 of the following 8 signs or symptoms:
   a. Fever
   b. Splenomegaly
   c. Cytopenia (affecting ≥2 cell lineages; hemoglobin ≤9 g/dL [or ≤10 g/dL for infants <4 wk of age], platelets <100,000/µL, neutrophils <1,000/µL)
   d. Hypertriglyceridemia (≥265 mg/dL) and/or hypofibrinogenemia (≤150 mg/dL)
   e. Hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy
   f. Low or absent natural killer cell cytotoxicity
   g. Hyperferritinemia (≥500 ng/mL)
   h. Elevated soluble CD25 (interleukin-2Rα chain; ≥2,400 U/mL)

Adapted from Verbsky JW, Grossman WJ: Hemophagocytic lymphohistiocytosis: diagnosis, pathophysiology, treatment, and future perspectives, Ann Med *38:20–31, 2006, p. 21, Table 1.*

Table 507-5	Spectrum of Diseases Characterized By Hemophagocytosis
PRIMARY HLH (see Table 507-3)	
HLH WITH IMMUNODEFICIENCY, AUTOINFLAMMATORY STATES (see Table 507-3)	
INFECTION-ASSOCIATED HLH (see Table 507-2)	
MALIGNANCY-ASSOCIATED HLH Lymphoma Leukemia	
MACROPHAGE ACTIVATION SYNDROME (MAS) ASSOCIATED WITH AUTOIMMUNE DISEASE	
Systemic-onset juvenile idiopathic arthritis Systemic lupus erythematosus Enthesitis-related arthritis Inflammatory bowel disease	

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contraindication to cytotoxic therapy in FHLH. Some recommend antithymocyte globulin and cyclosporine for maintenance therapy. Nevertheless, even with chemotherapy, FHLH remains ultimately fatal, often after a relapse of the disease. Allogeneic **stem cell transplantation** is effective in curing approximately 60% of patients with FHLH.

In contrast, in secondary HLH, it is critical that the underlying disease (e.g., infection, malignancy, or other) be identified and successfully treated. In many cases, such as when an infection can be documented and effectively treated, the prognosis may be excellent without any other specific treatment. However, when a treatable infection or other cause cannot be documented, which is the case in many patients presumed to have secondary HLH, the prognosis may be as poor as that of FHLH, and an identical chemotherapeutic approach, including etoposide, is recommended, even in the face of cytopenias. It is theorized that in both cases, by its cytotoxic effect on macrophages, etoposide interrupts cytokine production, the hemophagocytic process, and the accumulation of macrophages, all of which may contribute to the pathogenesis of infection-associated hemophagocytic syndrome. A broad spectrum of infectious agents, including viruses (e.g., cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), fungi, protozoa, and bacteria, may trigger secondary HLH, often in the setting of immunodeficiency (see Table 507-2). A thorough evaluation for infection should be undertaken in immunodeficient patients with hemophagocytosis. The same syndrome may be identified in conjunction with a rheumatologic disorder (e.g., systemic lupus erythematosus, Kawasaki disease) or a neoplasm (leukemia); in these cases, effective treatment of the underlying disease may cause resolution of the hemophagocytosis. In some patients, interferon and intravenous immunoglobulin have been effective.

Bibliography is available at Expert Consult.

507.3 Other Histiocytoses

Stephan Ladisch

Other rare histiocytoses are appropriately named for their clinical presentation. Examples include xanthogranuloma in juvenile xanthogranuloma and striking lymphadenopathy in Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy). Juvenile xanthogranuloma may require systemic treatment with cytotoxic chemotherapy if the disease is disseminated. Rosai-Dorfman disease is usually not treated, although the massive lymphadenopathy may require treatment because of its tendency to cause physical obstruction. Acute monocytic leukemia and true malignant histiocytosis are included because they are unequivocal malignancies of the monocyte-macrophage lineage; they are discussed in Chapter 490.

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Nephrology

PART XXIII

Section 1
Glomerular Disease

Chapter 508
Introduction to Glomerular Diseases

508.1 Anatomy of the Glomerulus

Cynthia G. Pan and Ellis D. Avner

The kidneys lie in the retroperitoneal space slightly above the level of the umbilicus. They range in length and weight, respectively, from approximately 6 cm and 24 g in a full-term newborn to ≥12 cm and 150 g in an adult. The kidney (Fig. 508-1) has an outer layer, **the cortex**, which contains the glomeruli, proximal and distal convoluted tubules, and collecting ducts; and an inner layer, **the medulla**, that contains the straight portions of the tubules, the loops of Henle, the vasa recta, and the terminal collecting ducts (Fig. 508-2).

The blood supply to each kidney usually consists of a main renal artery that arises from the aorta; multiple renal arteries can occur. The main artery divides into segmental branches within the medulla, becoming the interlobar arteries that pass through the medulla to the corticomedullary junction. At this point, the interlobar arteries branch to form the arcuate arteries, which run parallel to the surface of the kidney. Interlobular arteries originate from the arcuate arteries and give rise to the afferent arterioles of the glomeruli. Specialized muscle cells in the wall of the afferent arteriole and specialized distal tubular cells adjacent to the glomerulus (macula densa) form the juxtaglomerular apparatus that controls the secretion of renin. The afferent arteriole divides into the glomerular capillary network, which then recombines into the efferent arteriole (see Fig. 508-2). The juxtamedullary efferent arterioles are larger than those in the outer cortex and provide the blood supply, as the vasa recta, to the tubules and medulla.

Each kidney contains approximately 1 million nephrons (each consisting of a glomerulus and associated tubules). There is a large distribution of "normal nephron number" in humans, with the mean ±2 SD ranging from 200,000 to 2 million nephrons/kidney. This variation can have major pathophysiologic significance as a risk factor for the later development of hypertension and progressive renal dysfunction. In humans, formation of nephrons is complete at 36-40 wk of gestation, but functional maturation with tubular growth and elongation continues during the 1st decade of life. Because new nephrons cannot be formed after birth, any disease that results in progressive loss of nephrons can lead to renal insufficiency. A decreased number of nephrons secondary to low birthweight, prematurity, and/or unknown genetic or environmental factors has been implicated as a significant risk factor for the development of primary hypertension and progressive renal dysfunction in adulthood. Low nephron number presumably results in hyperfiltration and eventual sclerosis of "overworked" nephron units.

The glomerular network of specialized capillaries serves as the filtering mechanism of the kidney. The glomerular capillaries are lined by endothelial cells (Fig. 508-3) and have very thin cytoplasm that contains many holes (fenestrations). The glomerular basement membrane (GBM) forms a continuous layer between the endothelial and mesangial cells on one side and the epithelial cells on the other. The membrane has 3 layers: a central electron-dense lamina densa; the lamina rara interna, which lies between the lamina densa and the endothelial cells; and the lamina rara externa, which lies between the lamina densa and the epithelial cells. The visceral epithelial cells cover the capillary and project cytoplasmic foot processes, which attach to the lamina rara externa. Between the foot processes are spaces or filtration slits. The

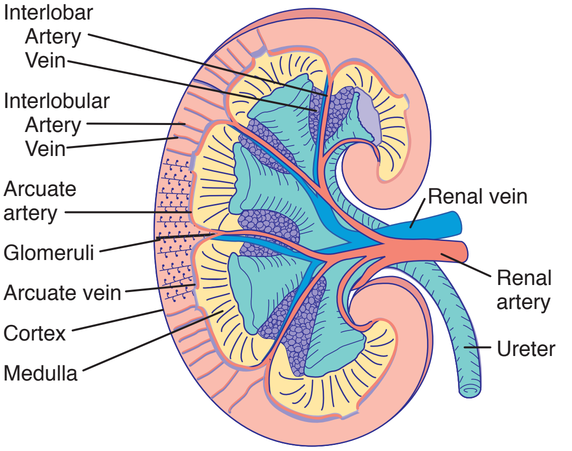

Figure 508-1 Gross morphology of the renal circulation. *(From Pitts RF:* Physiology of the kidney and body fluids, *ed 3, Chicago, 1974, Year Book Medical Publishers.)*

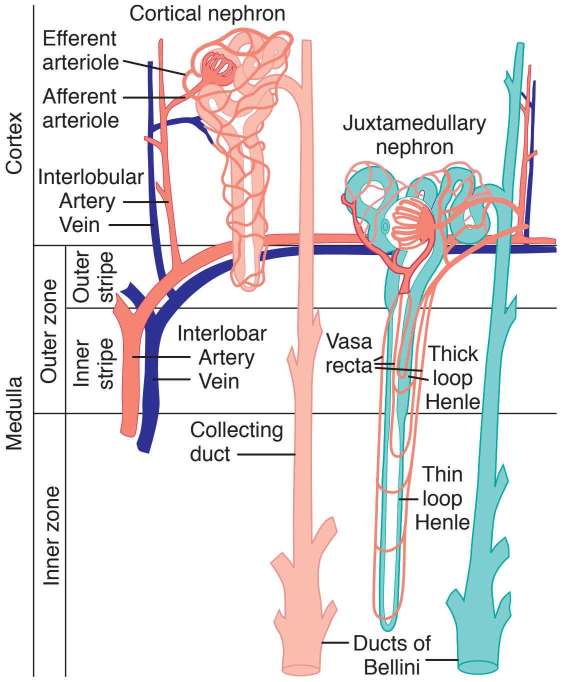

Figure 508-2 Comparison of the blood supplies of cortical and juxtamedullary nephrons. *(From Pitts RF:* Physiology of the kidney and body fluids, *ed 3, Chicago, 1974, Year Book Medical Publishers.)*

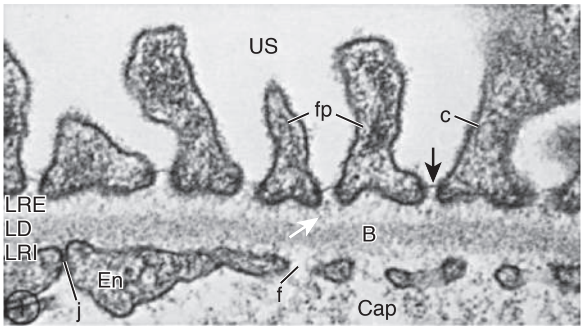

Figure 508-3 Electron micrograph of the normal glomerular capillary (Cap) wall demonstrating the endothelium (En) with its fenestrations (f), the glomerular basement membrane (B) with its central dense layer, the lamina densa (LD), and adjoining lamina rara interna (LRI) and externa (LRE) (*white arrow*), and the epithelial cell foot processes (fp) with their thick cell coat (c). The glomerular filtrate passes through the endothelial fenestrae, crosses the basement membrane, and passes through the filtration slits (*black arrow*) between the epithelial cell foot processes to reach the urinary space (US) (×60,000). J is the junction between 2 endothelial cells. *(From Farquhar MG, Kanwar YS: Functional organization of the glomerulus: state of the science in 1979. In Cummings NB, Michael AF, Wilson CB, editors:* Immune mechanisms in renal disease, *New York, 1982, Plenum.)*

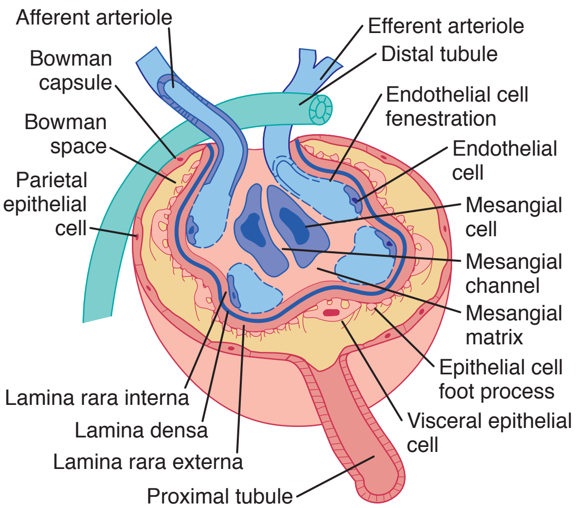

Figure 508-4 Schematic depiction of the glomerulus and surrounding structures.

mesangium (mesangial cells and matrix) lies between the glomerular capillaries on the endothelial cell side of the GBM and forms the medial part of the capillary wall. The mesangium may serve as a supporting, stalk-like structure for the glomerular capillaries and probably has a role in the regulation of glomerular blood flow, filtration, and the removal of macromolecules (such as immune complexes) from the glomerulus. Bowman's capsule, which surrounds the glomerulus, is composed of a basement membrane, which is continuous with the basement membranes of the glomerular capillaries and the proximal tubules, and the parietal epithelial cells, which are adjacent to the visceral epithelium (Fig. 508-4).

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508.2 Glomerular Filtration

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Kidney function is best measured as glomerular filtration rate (GFR). As the blood passes through the glomerular capillaries, the plasma is filtered through the glomerular capillary walls. The ultrafiltrate, which is cell free, contains all of the substances in plasma (electrolytes, glucose, phosphate, urea, creatinine, peptides, low-molecular-weight proteins) except proteins having a molecular weight of ≥68 kDa (such as albumin and globulins). The filtrate is collected in Bowman's space and enters the tubules. There its composition is modified by tightly regulated secretion and absorption of solute and fluid by the multiple tubular segments of the nephron and the ductal system, until it exits the kidney, via the ureter, as urine.

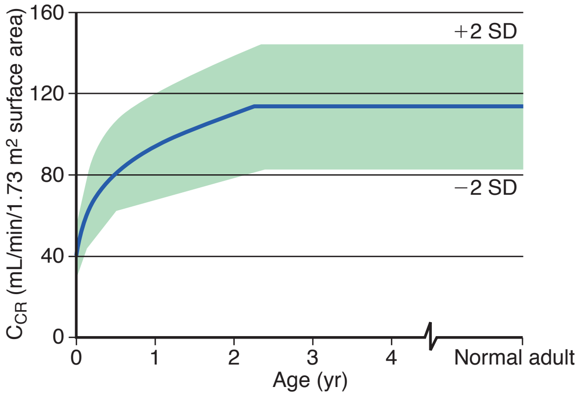

Figure 508-5 Changes in the normal value of the glomerular filtration rate, as measured by the creatinine clearance (Ccr), when standardized to mL/min/1.73 m^2 of body surface area. The *solid line* depicts the mean, and the *shaded area* includes 2 SD. *(From McCrory W: Developmental nephrology, Cambridge, MA, 1972, Harvard University Press.)*

Glomerular filtration is the net result of opposing forces applied across the capillary wall. The force for ultrafiltration (glomerular capillary hydrostatic pressure) is a result of systemic arterial pressure, modified by the tone of the afferent and efferent arterioles. The major force opposing ultrafiltration is glomerular capillary oncotic pressure, created by the gradient between the high concentration of plasma proteins within the capillary and the almost protein-free ultrafiltrate in Bowman's space. Filtration may be modified by the rate of glomerular plasma flow, the hydrostatic pressure within Bowman's space, and/or the permeability of the glomerular capillary wall.

Although glomerular filtration begins at approximately the 6th wk of fetal life, kidney function is not necessary for normal intrauterine homeostasis because the placenta serves as the major fetal excretory organ. After birth, the GFR increases until renal growth ceases (by age ~18-20 yr in most people). To compare GFRs of children and adults, the GFR is standardized to the body surface area (1.73 m^2) of an "ideal" 70-kg adult. Even after correction for surface area, the GFR of a child does not approximate adult values until the 3rd yr of life (Fig. 508-5). The GFR may be estimated by measurement of the serum creatinine level. Creatinine is derived from muscle metabolism. Its production is relatively constant, and its excretion is primarily through glomerular filtration, although tubular secretion can become important as serum creatinine rises in renal insufficiency. In contrast to the concentration of blood urea nitrogen, which is affected by state of hydration and nitrogen balance, the serum creatinine level is primarily influenced by muscle mass and the level of glomerular function. The serum creatinine is of value only in estimating the GFR under steady-state conditions. A patient can have a normal serum creatinine level without effective renal function very shortly after the onset of acute renal failure with anuria. In this clinical setting, serum creatinine is an insensitive measure of decreased renal function because its level does not rise above normal until GFR falls by 30-40%.

The precise measurement of the GFR is accomplished by quantitating the clearance of a substance that is freely filtered across the capillary wall and is neither reabsorbed nor secreted by the tubules. The clearance (C_s) of such a substance is the volume of plasma that, when completely cleared of the contained substance, would yield an equal

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quantity of that substance excreted in the urine over a specified time. Renal clearance is calculated by the following formula:

$$C_s\,(\text{mL/min}) = U_s(\text{mg/mL}) \times V\,(\text{mL/min})/P_s(\text{mg/mL})$$

where C_s equals the clearance of substance s, U_s reflects the urinary concentration of s, V represents the urinary flow rate, and P_s equals the plasma concentration of s. To correct the clearance for individual body surface area, the formula is:

$$\text{Corrected clearance}\,(\text{mL/min/1.73 m}^2) = C_s(\text{mL/min}) \times \frac{1.73}{\text{Surface area}\,(\text{m}^2)}$$

The GFR is optimally measured by the clearance of inulin, a fructose polymer having a molecular weight of approximately 5 kDa. Because the inulin clearance technique is cumbersome for use in clinical practice, the GFR is commonly estimated by the clearance of endogenous creatinine. Formulas that estimate creatinine clearance accurately in clinical settings have been useful tools in patient care. The "bedside" Schwartz formula is the most widely used pediatric formula and is based on the serum creatinine, patient height, and an empirical constant. The accuracy of this equation is further improved utilizing an additional endogenous marker, cystatin C, in addition to serum creatinine. Cystatin C is a 13.6 kDa protease inhibitor produced by nucleated cells. It continues to be tested as a clinical tool to completely replace creatinine-based formulas, as it has distinct advantages in estimating GFR. Unlike creatinine, cystatin C is unaffected by sex, height, muscle mass, bilirubin, or red blood cell hemolysis, and is not secreted by the renal tubules under any conditions.

The absence of plasma proteins larger than the size of albumin from the glomerular filtrate confirms the effectiveness of the glomerular capillary wall as a filtration barrier. Major factors restricting the filtration of these and other macromolecules include their size and their ionic charge. Morphologic studies suggest that the size-selective filtration barrier resides within the GBM. The endothelial cell, basement membrane, and epithelial cell of the glomerular capillary wall all possess strong negative ionic charges (heparan sulfate and glycoproteins containing sialic acid). Proteins in the blood have a relatively low isoelectric point, carry a net negative charge, and are repelled by the negatively charged sites of the glomerular capillary wall, thus restricting filtration.

Bibliography is available at Expert Consult.

508.3 Glomerular Diseases

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PATHOGENESIS

Glomerular injury may be a result of genetic, immunologic, perfusion, or coagulation disorders. Genetic disorders of the glomerulus may result from mutations in DNA exons encoding proteins located within the glomerulus, interstitium, or tubular epithelium; mutations in regulatory genes controlling DNA transcription; abnormal posttranscriptional modification of RNA transcripts; or abnormal posttranslational modification of proteins. Immunologic injury to the glomerulus results in **glomerulonephritis,** which is a generic term for several diseases, but more precisely a histopathologic term defining inflammation of the glomerular capillaries. Evidence that glomerulonephritis is caused by immunologic injury includes morphologic and immunopathologic similarities to experimental immune-mediated glomerulonephritis; the demonstration of immune reactants (immunoglobulin, complement) in glomeruli; abnormalities in serum complement; and the finding of autoantibodies (anti-GBM) in some of these diseases (Fig. 508-6). There appear to be 2 major mechanisms of immunologic injury: glomerular deposition of circulating antigen–antibody immune complexes and interaction of antibody with glomerular antigens in situ. In the latter circumstance, the antigen may be a normal component of the glomerulus (the noncollagenous domain [NC-1] of type IV

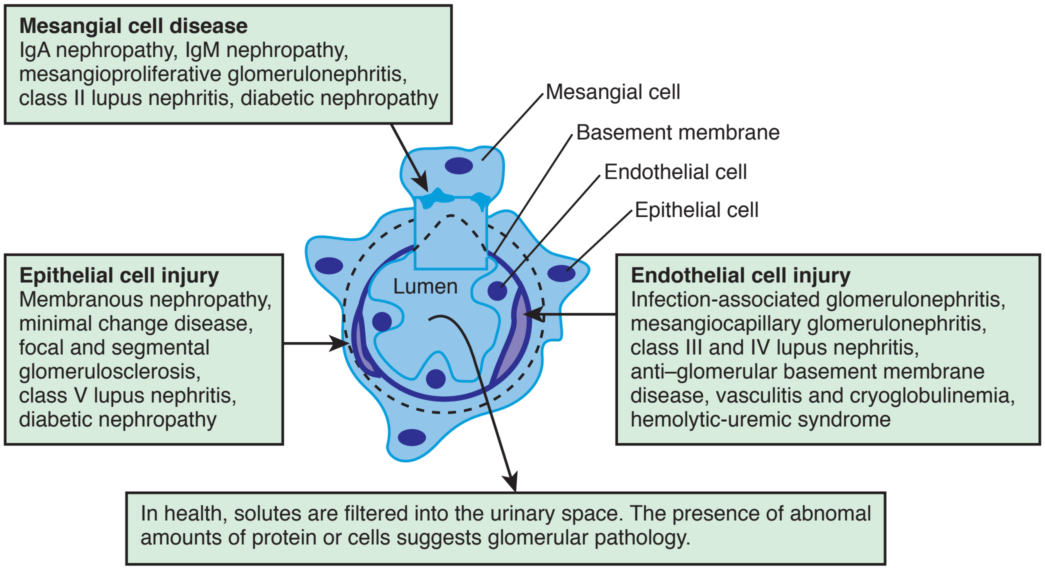

Figure 508-6 Cellular location of injury during glomerulonephritis. Mesangial cells are directly exposed to the circulation. Deposition of immune complexes within these cells is typically seen in disorders such as immunoglobulin A (IgA) nephropathy; it results in proliferation and expansion of the cells, leading to hematuria, proteinuria, and renal impairment. Epithelial cells, in conjunction with basement membrane, allow filtration of plasma solutes but retard passage of cells and plasma proteins. Disease related to these cells is typified by the presence of subepithelial deposits and flattening of the foot processes that engage the basement membrane, resulting in disruption of the filtration barrier and proteinuria. Endothelial cell disease can result from deposition of immune complex (as occurs in mesangiocapillary glomerulonephritis), attachment of antibody to the basement membrane (Goodpasture disease), or trauma and activation of coagulation (hemolytic-uremic syndrome). Endothelial cell proliferation and necrosis are accompanied by leukocyte accumulation, and rupture of the basement membrane, crescent formation, and disruption of glomerular architecture can develop. A nephritic or rapidly progressive presentation ensues. *(From Chadban SJ, Atkins RC: Glomerulonephritis,* Lancet *365:1797–1806, 2005.)*

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collagen, a putative antigen in human anti-GBM nephritis) or an antigen that has been deposited in the glomerulus.

In **immune complex–mediated** diseases, antibody is produced against, and combines with, a circulating antigen that is usually unrelated to the kidney (see Fig. 508-6). The immune complexes accumulate in GBMs and activate the complement system, leading to immune injury. Acute serum sickness in rabbits is produced by a single intravenous injection of bovine albumin. Within 1 wk after injection, a rabbit produces antibody against bovine albumin, and the antigen remains in the blood in high concentration. As antibody enters the circulation, it forms immune complexes with antigen. Although the amount of antigen in the circulation exceeds that of antibody (antigen excess), the complexes formed are small, remain soluble in the circulation, and are deposited in glomeruli. The processes involved in glomerular localization are not well understood but include characteristics of the complex (concentration, charge, size) and/or the glomerulus (mesangial trapping, negatively charged capillary wall); hydrodynamic forces; and the influence of various chemical mediators (angiotensin II, prostaglandins).

With deposition of immune complexes in glomeruli, rabbits develop an acute proliferative glomerulonephritis. Immunofluorescence microscopy demonstrates granular **("lumpy-bumpy")** deposits containing immunoglobulin and complement in the glomerular capillary wall. Electron microscopic studies show these deposits to be on the epithelial side of the GBM and in the mesangium. For the next few days, as additional antibody enters the circulation, the antigen is ultimately removed from the circulation and the glomerulonephritis subsides.

An example of in situ antigen–antibody interaction is **anti–GBM antibody disease,** in which antibody reacts with antigen(s) of the GBM. Immunopathologic studies reveal linear deposition of immunoglobulin and complement along the GBM in Goodpasture syndrome (see Chapter 517) and certain types of rapidly progressive glomerulonephritis (see Chapter 516).

The inflammatory reaction that follows immunologic injury results from activation of 1 or more mediator pathways. The most important of these is the complement system, which has 2 initiating sequences: the classic pathway, which is activated by antigen–antibody immune complexes, and the alternative or properdin pathway, which is activated by polysaccharides and endotoxin. These pathways converge at C3; from that point on, the same sequence leads to lysis of cell membranes (see Chapter 133). The major noxious products of complement activation are produced after activation of C3 and include anaphylatoxin (which stimulates contractile proteins within vascular walls and increases vascular permeability) and chemotactic factors (C5a) that recruit neutrophils and perhaps macrophages to the site of complement activation, leading to consequent damage to vascular cells and basement membranes. Therapeutic agents to block the antibody production and components of the complement cascade are available and may provide additional tools to treat immune-mediated kidney injury (see Chapters 514 and 518).

The coagulation system may be activated **directly**, after endothelial cell injury that exposes the thrombogenic subendothelial layer (thereby initiating the coagulation cascade), or it may be activated **indirectly**, after complement activation. Consequently, fibrin is deposited within glomerular capillaries or within Bowman's space as crescents. Activation of the coagulation cascade can also activate the kinin system, which produces additional chemotactic and anaphylatoxin-like factors.

PATHOLOGY

The glomerulus may be injured by several mechanisms, but it has only a limited number of histopathologic responses; different disease states can produce similar microscopic changes.

Proliferation of glomerular cells occurs in most forms of glomerulonephritis and may be generalized (involving all glomeruli) or focal (involving only some glomeruli and sparing others). Within a single glomerulus, proliferation may be diffuse (involving all parts of the glomerulus) or segmental (involving only 1 or more tufts, but not others). Proliferation commonly involves the endothelial and mesangial cells and is often associated with an increase in the mesangial matrix (see Fig. 508-6). Mesangial proliferation can result from deposition of immune complex within the mesangium. The resultant increase in cell size and number, and production of mesangial matrix, can increase glomerular size and narrow the lumens of glomerular capillaries, leading to renal insufficiency.

Crescent formation in Bowman's space (capsule) is a result of proliferation of parietal epithelial cells and is often associated with clinical signs of renal dysfunction. Crescents develop in several forms of glomerulonephritis (termed **rapidly progressive** or **crescentic**; see Chapter 516) and are a characteristic response to deposition of fibrin in Bowman's space. Newly formed crescents contain fibrin, the proliferating epithelial cells of Bowman's space, basement membrane–like material produced by these cells, and macrophages that might have a role in the genesis of glomerular injury. Over the subsequent days to weeks, the crescent is invaded by connective tissue and becomes a fibroepithelial crescent. This process generally results in glomerular obsolescence and the clinical development of chronic renal failure. Crescent formation is often associated with glomerular cell death. The necrotic glomerulus has a characteristic eosinophilic appearance and usually contains nuclear remnants. Crescent formation is usually associated with generalized proliferation of the mesangial cells and with either immune complex or anti-GBM antibody deposition in the glomerular capillary wall.

Certain forms of acute glomerulonephritis show glomerular exudation of blood cells, including neutrophils, eosinophils, basophils, and mononuclear cells. The thickened appearance of GBM can result from a true increase in the width of the membrane (as seen in membranous glomerulopathy; see Chapter 512), from massive deposition of immune complexes that have staining characteristics similar to the membrane (as seen in systemic lupus erythematosus; see Chapter 514), or from the interposition of mesangial cells and matrix into the subendothelial space between the endothelial cells and the GBM. The last can give the basement membrane a split appearance, as seen in type I membranoproliferative glomerulonephritis (see Chapter 513) and other diseases.

Sclerosis refers to the presence of scar tissue within the glomerulus. Occasionally, pathologists use this term to refer to an increase in mesangial matrix.

Tubulointerstitial fibrosis is present in all patients who have glomerular disease and who develop progressive renal injury. This fibrosis is initiated by injury to either the glomeruli, which, if severe, may secondarily involve the tubules, or direct injury to the tubules themselves. Tubular injury recruits mononuclear cell infiltrate, which releases a variety of soluble factors that have fibrosis-promoting effects. Matrix proteins of the renal interstitium begin to accumulate, leading to eventual destruction of renal tubules and peritubular capillaries. The actual transformation of tubular epithelium to mesenchymal tissue can contribute to progressive tubulointerstitial fibrosis, a process termed *epithelial-mesenchymal transformation.*

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Section 2
Conditions Particularly Associated with Hematuria

Chapter 509
Clinical Evaluation of the Child with Hematuria

Cynthia G. Pan and Ellis D. Avner

Hematuria is defined as the presence of at least 5 red blood cells (RBCs) per microliter of urine and occurs with a prevalence of 0.5-2.0% among school-age children. Quantitative studies demonstrate that normal children can excrete more than 500,000 RBCs per 12 hr period; this increases with fever and/or exercise. In the clinical setting, qualitative estimates are provided by a urinary dipstick that uses a very sensitive peroxidase chemical reaction between hemoglobin (or myoglobin) and a colorimetric chemical indicator impregnated on the dipstick. Chemstrip (Boehringer Mannheim), a common commercially available dipstick, is capable of detecting 3-5 RBCs/µL of unspun urine. The presence of 10-50 RBCs/µL may suggest underlying pathology, but significant hematuria is generally considered as >50 RBCs/µL. False-negative results can occur in the presence of formalin (used as a urine preservative) or high urinary concentrations of ascorbic acid (i.e., in patients with vitamin C intake >2000 mg/day). False-positive results may be seen in a child with an alkaline urine (pH > 8), or more commonly following contamination with oxidizing agents such as hydrogen peroxide used to clean the perineum before obtaining a specimen. Microscopic analysis of 10-15 mL of freshly voided and centrifuged urine is essential in confirming the presence of RBCs suggested by >10 RBCs/µL, or a 1+ positive urinary dipstick reading.

Red urine **without** RBCs is seen in a number of conditions (Table 509-1). Clinically significant heme-positive urine without RBCs may be caused by the presence of either hemoglobin or myoglobin. Hemoglobinuria without hematuria can occur in the presence of acute or chronic hemolysis. Myoglobinuria without hematuria occurs in the presence of rhabdomyolysis resulting from skeletal muscle injury and is generally associated with a 5-fold increase in the plasma concentration of creatinine kinase. **Rhabdomyolysis** is always clinically significant as it may lead to acute renal injury. It can occur secondary to viral myositis, crush injury, severe electrolyte abnormalities (hypernatremia, hypophosphatemia), hypotension, disseminated intravascular coagulation, toxins (drugs, venom), metabolic disorders of muscles, and prolonged seizures. Clinically innocuous heme-negative urine can appear red, cola colored, or burgundy, owing to ingestion of various drugs, foods (blackberries, beets), or dyes used in food and candy, whereas dark brown (or black) urine can result from various urinary metabolites.

Table 509-1 Other Causes of Red Urine	
HEME POSITIVE Hemoglobin Myoglobin	**Dyes (Vegetable/Fruit)** Beets Blackberries Food and candy coloring Rhubarb
HEME NEGATIVE **Drugs** Chloroquine Deferoxamine Ibuprofen Iron sorbitol Metronidazole Nitrofurantoin Phenazopyridine (Pyridium) Phenolphthalein Phenothiazines Rifampin Salicylates Sulfasalazine	**Metabolites** Homogentisic acid Melanin Methemoglobin Porphyrin Tyrosinosis Urates

Evaluation of the child with hematuria begins with a careful history, physical examination, and urinalysis. This information is used to determine the level of hematuria (upper vs lower urinary tract) and to determine the urgency of the evaluation based on symptomatology. Special consideration needs to be given to family history, identification of anatomic abnormalities and malformation syndromes, presence of gross hematuria, and manifestations of hypertension, edema, or heart failure.

Table 509-2 lists causes of hematuria. Upper urinary tract sources of hematuria originate within the nephron (glomerulus, tubular system, or interstitium). Lower urinary tract sources of hematuria originate from the pelvocaliceal system, ureter, bladder, or urethra. Hematuria from within the glomerulus is often associated with brown, cola- or tea-colored, or burgundy urine, proteinuria >100 mg/dL via dipstick, urinary microscopic findings of RBC casts, and deformed urinary RBCs (particularly acanthocytes). Hematuria originating within the tubular system may be associated with the presence of leukocytes or renal tubular casts. Lower urinary tract sources of hematuria may be associated with gross hematuria that is bright red or pink, terminal hematuria (gross hematuria occurring at the end of the urine stream), blood clots, normal urinary RBC morphology, and minimal proteinuria on dipstick (<100 mg/dL).

Patients with hematuria can present with a number of symptoms suggesting specific disorders. Tea- or cola-colored urine, facial or body edema, hypertension, and oliguria are classic symptoms of **glomerulonephritis.** Diseases commonly manifesting as glomerulonephritis include postinfectious glomerulonephritis, immunoglobulin A (IgA) nephropathy, membranoproliferative glomerulonephritis, Henoch-Schönlein purpura (HSP) nephritis, systemic lupus erythematosus (SLE) nephritis, granulomatosis with polyangiitis (formerly Wegener granulomatosis), microscopic polyarteritis nodosa, Goodpasture syndrome, and hemolytic-uremic syndrome. A history of recent upper respiratory, skin, or gastrointestinal infection suggests postinfectious glomerulonephritis, hemolytic-uremic syndrome, or HSP nephritis. Rash and joint complaints suggest HSP or SLE nephritis.

Hematuria associated with glomerulonephritis is typically painless, but can be associated with flank pain when acute or unusually severe. Frequency, dysuria, and unexplained fevers suggest a urinary tract infection, whereas renal colic suggests nephrolithiasis. A flank mass can suggest hydronephrosis, renal cystic diseases, renal vein thrombosis, or tumor. Hematuria associated with headache, mental status changes, visual changes (diplopia), epistaxis, or heart failure suggests significant hypertension. Patients with hematuria and a history of trauma require immediate evaluation (see Chapter 72). Child abuse must always be suspected in the child presenting with unexplained perineal bruising and hematuria.

A careful family history is critical in the initial assessment of the child with hematuria given the numerous genetic causes of renal disorders. Hereditary glomerular diseases include hereditary nephritis (Alport syndrome), thin glomerular basement membrane disease, SLE nephritis, and IgA nephropathy (Berger disease). Other hematuric renal disorders with a hereditary component include both autosomal recessive and autosomal dominant polycystic kidney

diseases, atypical hemolytic-uremic syndrome, urolithiasis, and sickle cell disease/trait.

A complete physical examination is critical to assess the cause of hematuria. Hypertension, edema, or signs of heart failure suggest acute glomerulonephritis. Several malformation syndromes are associated with renal disease including VATER (*v*ertebral body anomalies, *a*nal atresia, *t*racheo*e*sophageal fistula, and *r*enal dysplasia) syndrome. Abdominal masses may be caused by bladder distention in posterior urethral valves, hydronephrosis in ureteropelvic junction obstruction, polycystic kidney disease, or Wilms tumor. Hematuria seen in patients with neurologic or cutaneous abnormalities may be the result of a number of syndromic renal disorders including tuberous sclerosis, von Hippel-Lindau syndrome, and Zellweger (cerebrohepatorenal) syndrome. Anatomic abnormalities of the external genitalia may be associated with hematuria and/or renal disease.

Patients with gross hematuria present additional challenges because of the associated parental anxiety. The most common cause of gross hematuria is bacterial urinary tract infection. **Urethrorrhagia**, which is urethral bleeding in the absence of urine, is associated with dysuria and blood spots on underwear after voiding. This condition, which often occurs in prepubertal boys at intervals several months apart, has a benign self-limited course. Less than 10% of patients have evidence of glomerulonephritis. Recurrent episodes of gross hematuria suggest IgA nephropathy, Alport syndrome, or thin glomerular basement membrane disease. Dysuria and abdominal or flank pain are symptoms of idiopathic hypercalciuria, or urolithiasis. Table 509-3 lists common causes of gross hematuria; Figure 509-1 outlines a general approach to the laboratory and radiologic evaluation of the patient with glomerular or extraglomerular hematuria. Asymptomatic patients with isolated microscopic hematuria should not undergo extensive diagnostic evaluation, because such hematuria is often transient and benign.

Table 509-2 Causes of Hematuria in Children
UPPER URINARY TRACT DISEASE
Isolated renal disease
Immunoglobulin (Ig) A nephropathy (Berger disease)
Alport syndrome (hereditary nephritis)
Thin glomerular basement membrane nephropathy
Postinfectious GN (poststreptococcal GN)*
Membranous nephropathy
Membranoproliferative GN*
Rapidly progressive GN
Focal segmental glomerulosclerosis
Anti–glomerular basement membrane disease
Multisystem disease
Systemic lupus erythematosus nephritis*
Henoch-Schönlein purpura nephritis
Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
Polyarteritis nodosa
Goodpasture syndrome
Hemolytic-uremic syndrome
Sickle cell glomerulopathy
HIV nephropathy
Tubulointerstitial disease
Pyelonephritis
Interstitial nephritis
Papillary necrosis
Acute tubular necrosis
Vascular
Arterial or venous thrombosis
Malformations (aneurysms, hemangiomas)
Nutcracker syndrome
Hemoglobinopathy (sickle cell trait/disease)
Crystalluria
Anatomic
Hydronephrosis
Cystic-syndromic kidney disease
Polycystic kidney disease
Multicystic dysplasia
Tumor (Wilms tumor, rhabdomyosarcoma, angiomyolipoma, medullary carcinoma)
Trauma
LOWER URINARY TRACT DISEASE
Inflammation (infectious and noninfectious)
Cystitis
Urethritis
Urolithiasis
Trauma
Coagulopathy
Heavy exercise
Bladder tumor
Factitious syndrome, factitious syndrome by proxy[†]

*Denotes glomerulonephritides presenting with hypocomplementemia.
[†]Formerly Munchausen syndrome and Munchausen syndrome by proxy.
GN, glomerulonephritis.

Table 509-3 Common Causes of Gross Hematuria
Urinary tract infection
Meatal stenosis
Perineal irritation
Trauma
Urolithiasis
Hypercalciuria
Coagulopathy
Tumor
Glomerular
Postinfectious glomerulonephritis
Henoch-Schönlein purpura nephritis
IgA nephropathy
Alport syndrome (hereditary nephritis)
Thin glomerular basement membrane disease
Systemic lupus erythematosus nephritis

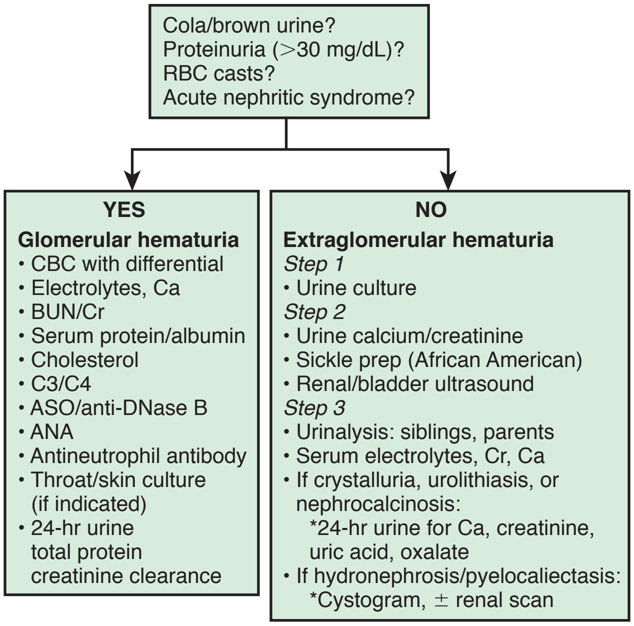

Figure 509-1 Algorithm of the general approach to the laboratory and radiologic evaluation of the patient with glomerular or extraglomerular hematuria. ANA, antinuclear antibody; ASO, antistreptolysin O; BUN, blood urea nitrogen; C3/C4, complement; CBC, complete blood cell count; Cr, creatinine; RBC, red blood cell.

The child with completely asymptomatic isolated microscopic hematuria that persists on at least 3 urinalyses observed over a minimum of a 2 wk period poses a dilemma in regard to the degree of further diagnostic testing that should be performed. Significant disease of the urinary tract is uncommon with this clinical presentation. The initial evaluation of these children should include a urine culture followed by a spot urine for hypercalciuria with a calcium : creatinine ratio in culture-negative patients. In African-American patients, a sickle cell screen should be included. If these studies are normal, urinalysis of all first-degree relatives is indicated. Renal and bladder ultrasonography should be considered to rule out structural lesions such as tumor, cystic disease, hydronephrosis, or urolithiasis. Ultrasonography of the urinary tract is most informative in patients presenting with gross hematuria, abdominal pain, flank pain, or trauma. If these initial studies are normal, assessment of serum creatinine and electrolytes is recommended.

The finding of certain hematologic abnormalities can narrow the differential diagnosis. Anemia in this setting may be caused by hypervolemia with dilution associated with acute renal failure; decreased RBC production in chronic renal failure; hemolysis from hemolytic-uremic syndrome, a chronic hemolytic anemia, or SLE; blood loss from pulmonary hemorrhage, as seen in Goodpasture syndrome; or melena in patients with HSP or hemolytic-uremic syndrome. Inspection of the peripheral blood smear might reveal a microangiopathic process consistent with the hemolytic-uremic syndrome. The presence of autoantibodies in SLE can result in a positive Coombs test, the presence of antinuclear antibody, leukopenia, and multisystem disease. Thrombocytopenia can result from decreased platelet production (malignancies) or increased platelet consumption (SLE, idiopathic thrombocytopenic purpura, hemolytic-uremic syndrome, renal vein thrombosis, or congenital hepatic fibrosis with portal hypertension secondary to autosomal recessive polycystic kidney disease). Although urinary RBC morphology may be normal with lower tract bleeding and dysmorphic from glomerular bleeding, it is not sensitive enough to unequivocally delineate the site of hematuria. A bleeding diathesis is an unusual cause of hematuria. Coagulation studies are not routinely obtained unless personal or family history suggests a bleeding tendency.

A voiding cystourethrogram is only required in patients with a urinary tract infection, renal scarring, hydroureter, or pyelocaliectasis. Cystoscopy is an unnecessary and costly procedure in most pediatric patients with hematuria, and carries the associated risks of anesthesia. The diagnosis of "possible urethral stenosis" as an indication for cystoscopy should be viewed with a high degree of suspicion, because true urethral stenosis is quite rare. This procedure should be reserved for evaluating the rare child with a bladder mass noted on ultrasound, urethral abnormalities caused by trauma, posterior urethral valves, or tumor. The finding of unilateral gross hematuria localized by cystoscopy is rare, but it can indicate a vascular malformation or another anatomic abnormality.

Children with persistent asymptomatic isolated hematuria and a completely normal evaluation should have their blood pressure and urine checked every 3 mo until the hematuria resolves. Referral to a pediatric nephrologist should be considered for patients with persistent asymptomatic hematuria greater than 1 yr duration and is recommended for patients with nephritis (glomerulonephritis, tubulointerstitial nephritis), hypertension, renal insufficiency, urolithiasis or nephrocalcinosis, or a family history of renal disease such as polycystic kidney disease or hereditary nephritis. Renal biopsy is indicated for some children with persistent microscopic hematuria, and most children with recurrent gross hematuria associated with decreased renal function, proteinuria, or hypertension.

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Chapter 510

Isolated Glomerular Diseases with Recurrent Gross Hematuria

Cynthia G. Pan and Ellis D. Avner

Approximately 10% of children with gross hematuria have an acute or a chronic form of glomerulonephritis that may be associated with a systemic illness. The gross hematuria, which is usually characterized by brown or cola-colored urine, may be painless or associated with vague flank or abdominal pain. Presentation with gross hematuria is common within 1-2 days after the onset of an apparent viral upper respiratory tract infection in immunoglobulin (Ig) A nephropathy, and typically resolves within 5 days. This relatively short period contrasts to a latency period of 7-21 days occurring between the onset of a streptococcal pharyngitis or impetiginous skin infection and the development of poststreptococcal acute glomerulonephritis. Gross hematuria in these circumstances can last as long as 4-6 wk. Gross hematuria can also be seen in children with glomerular basement membrane (GBM) disorders such as hereditary nephritis (Alport syndrome [AS]) and thin GBM disease. These glomerular diseases can also manifest as microscopic hematuria and/or proteinuria without gross hematuria.

510.1 Immunoglobulin A Nephropathy (Berger Nephropathy)

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IgA nephropathy is the most common chronic glomerular disease in children. It is characterized by a predominance of IgA within mesangial glomerular deposits in the absence of systemic disease. Diagnosis requires renal biopsy, which is performed when clinical features warrant confirmation of the diagnosis or characterization of the histologic severity, which might affect therapeutic decisions.

PATHOLOGY AND PATHOLOGIC DIAGNOSIS

Focal and segmental mesangial proliferation and increased mesangial matrix are seen in the glomerulus (Fig. 510-1). Renal histology

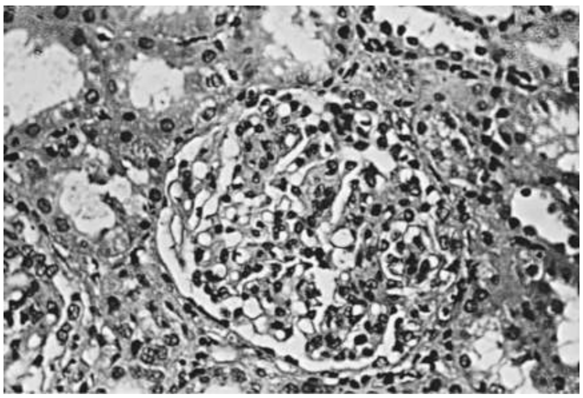

Figure 510-1 Light microscopy of IgA nephropathy demonstrating segmental mesangial proliferation and increased matrix (×180).

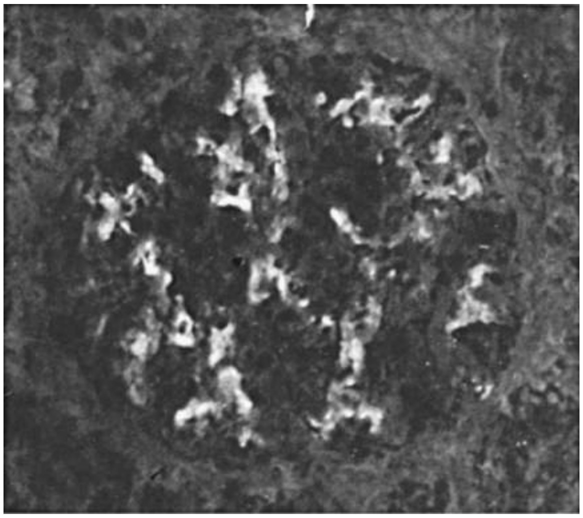

Figure 510-2 Immunofluorescence microscopy of the biopsy specimen from a child with episodes of gross hematuria demonstrating mesangial deposition of IgA (×150).

demonstrates mesangial proliferation that may be associated with epithelial cell crescent formation and sclerosis. IgA deposits in the mesangium are often accompanied by C3 complement (Fig. 510-2).

IgA nephropathy is an immune complex disease initiated by excessive amounts of poorly galactosylated IgA_1 in the serum causing the production of IgG and IgA autoantibodies. The abnormalities identified in the IgA system have also been observed in patients with Henoch-Schönlein purpura, and this finding lends support to the hypothesis that these 2 diseases are part of the same disease spectrum. Familial clustering of IgA nephropathy cases suggests the importance of genetic factors. Genome-wide linkage analysis suggests the linkage of IgA nephropathy to 6q22-23 in multiplex IgA nephropathy kindreds.

CLINICAL AND LABORATORY MANIFESTATIONS

IgA nephropathy is seen more often in male than in female patients. Although there are rare cases of rapidly progressive forms of the disease, the clinical presentation of childhood IgA nephropathy is often benign in comparison to that of adults. IgA nephropathy is an uncommon cause of end-stage renal failure during childhood. A majority of children with IgA nephropathy in the United States and Europe present with gross hematuria, whereas microscopic hematuria and/or proteinuria is a more common presentation in Japan. Other presentations include acute nephritic syndrome, nephrotic syndrome, or a combined nephritic-nephrotic picture. Gross hematuria often occurs within 1-2 days of onset of an upper respiratory or gastrointestinal infection, in contrast to the longer latency period observed in acute postinfectious glomerulonephritis, and may be associated with loin pain. Proteinuria is often <1000 mg/24 hr in patients with asymptomatic microscopic hematuria. Mild to moderate hypertension is most often seen in patients with nephritic or nephrotic syndrome, but is rarely severe enough to result in hypertensive emergencies. Normal serum levels of C3 in IgA nephropathy help to distinguish this disorder from post-streptococcal glomerulonephritis. Serum IgA levels have no diagnostic value because they are elevated in only 15% of pediatric patients.

PROGNOSIS AND TREATMENT

Although IgA nephropathy does not lead to significant kidney damage in most children, progressive disease develops in 20-30% of patients 15-20 yr after disease onset. Therefore, most children with IgA nephropathy do not display progressive renal dysfunction until adulthood, prompting the need for careful long-term follow-up. Poor prognostic indicators at presentation or follow-up include persistent hypertension, diminished renal function, and significant, increasing, or prolonged proteinuria. A more severe prognosis is correlated with histologic evidence of diffuse mesangial proliferation, extensive glomerular crescents, glomerulosclerosis, and diffuse tubulointerstitial changes, including inflammation and fibrosis.

The primary treatment of IgA nephropathy is appropriate blood pressure control and management of significant proteinuria. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists are effective in reducing proteinuria and retarding the rate of disease progression when used individually or in combination. Fish oil, which contains antiinflammatory omega-3 polyunsaturated fatty acids, may decrease the rate of disease progression in adults. If renin-angiotensin blockade proves ineffective and significant proteinuria persists, then addition of immunosuppressive therapy with corticosteroids is recommended. Corticosteroids reduce proteinuria and improve renal function in those patients with a glomerular filtration rate >60 mL/min/m^2. It remains unclear if the effects of glucocorticoids deter progression to end-stage renal failure to a degree to offset their significant side effects. To date, additional immunosuppression with cyclophosphamide or azathioprine has not appeared to be effective, but further randomized clinical trials are in progress. Tonsillectomy has been used as treatment for IgA nephropathy in many countries including Japan. Performing a tonsillectomy in the absence of significant tonsillitis in association with IgA nephropathy is currently not recommended until appropriate prospective, controlled trials have been performed and demonstrate efficacy. Patients with IgA nephropathy may undergo successful kidney transplantation. Although recurrent disease is frequent, allograft loss caused by IgA nephropathy occurs in only 15-30% of patients.

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510.2 Alport Syndrome

Cynthia G. Pan and Ellis D. Avner

AS, or hereditary nephritis, is a genetically heterogeneous disease caused by mutations in the genes coding for type IV collagen, a major component of basement membranes. These genetic alterations are associated with marked variability in clinical presentation, natural history, and histologic abnormalities.

GENETICS

Approximately 85% of patients have X-linked inheritance caused by a mutation in the *COL4A5* gene encoding the α5 chain of type IV collagen. Patients with a subtype of X-linked AS and diffuse leiomyomatosis demonstrate a contiguous mutation within the *COL4A5* and *COL4A6* genes that encodes the α5 and α6 chains, respectively, of type IV collagen. Autosomal recessive forms of AS are caused by mutations in the *COL4A3* and *COL4A4* genes on chromosome 2 encoding the α3 and α4 chains, respectively, of type IV collagen. An autosomal dominant form of AS linked to the *COL4A3-COL4A4* gene locus occurs in 5% of cases.

PATHOLOGY

Kidney biopsy specimens during the 1st decade of life show few changes on light microscopy. Later, the glomeruli may develop mesangial proliferation and capillary wall thickening, leading to progressive glomerular sclerosis. Tubular atrophy, interstitial inflammation and fibrosis, and lipid-containing tubular or interstitial cells, called *foam cells,* develop as the disease progresses. Immunopathologic studies are usually nondiagnostic.

In most patients, electron microscopy reveals diffuse thickening, thinning, splitting, and layering of the glomerular and tubular basement membranes (Fig. 510-3). To confound diagnosis, ultrastructural analysis of the GBM in all genetic forms of AS may be completely normal, display nonspecific alterations, or demonstrate only uniform thinning.

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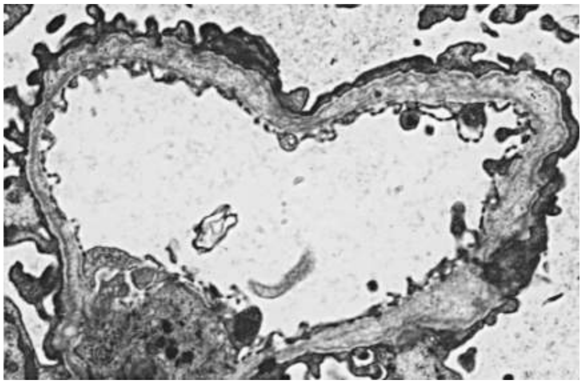

Figure 510-3 Electron micrograph of a biopsy specimen from a child with AS depicting thickening, thinning, splitting, and layering of the GBM (×1,650). *(From Yum M, Bergstein JM: Basement membrane nephropathy,* Hum Pathol *14:996–1003, 1983.)*

CLINICAL MANIFESTATIONS

All patients with AS have asymptomatic microscopic hematuria, which may be intermittent in girls and younger boys. Single or recurrent episodes of gross hematuria commonly occurring 1-2 days after an upper respiratory infection are seen in approximately 50% of patients. Proteinuria is often seen in boys but may be absent, mild, or intermittent in girls. Progressive proteinuria, often exceeding 1 g/24 hr, is common by the 2nd decade of life and can be severe enough to cause nephrotic syndrome.

Bilateral sensorineural hearing loss, which is never congenital, develops in 90% of hemizygous males with X-linked AS, 10% of heterozygous females with X-linked AS, and 67% of patients with autosomal recessive AS. This deficit begins in the high-frequency range, but progresses to involve hearing associated with normal speech, prompting the need for hearing aids. Ocular abnormalities, which occur in 30-40% of patients with X-linked AS, include anterior lenticonus (extrusion of the central portion of the lens into the anterior chamber), macular flecks, and corneal erosions. Leiomyomatosis of the esophagus, tracheobronchial tree, and female genitals in association with platelet abnormalities has been reported, but is rare.

DIAGNOSIS

A combination of careful family history, a screening urinalysis of 1st-degree relatives, an audiogram, and an ophthalmologic examination are critical in making the diagnosis of AS. The presence of anterior lenticonus is pathognomonic. AS is highly likely in the patient who has hematuria and at least 2 of the following characteristic clinical features: macular flecks, recurrent corneal erosions, GBM thickening and thinning, or sensorineural deafness. Absence of epidermal basement membrane staining for the α5 chain of type IV collagen in male hemizygotes and discontinuous epidermal basement membrane staining in female heterozygotes on skin biopsy is pathognomonic for X-linked AS and can preclude diagnostic renal biopsy. Genetic testing is clinically available for X-linked AS and *COL4A5* mutations. Prenatal diagnosis is available for families with members who have X-linked AS and who carry an identified mutation.

PROGNOSIS AND TREATMENT

The risk of progressive renal dysfunction leading to end-stage renal disease (ESRD) is highest among hemizygotes and autosomal recessive homozygotes. ESRD occurs before age 30 yr in approximately 75% of hemizygotes with X-linked AS. The risk of ESRD in X-linked heterozygotes is 12% by age 40 yr and 30% by age 60 yr. Risk factors for progression are gross hematuria during childhood, nephrotic syndrome, and prominent GBM thickening. Intrafamilial variation in phenotypic expression results in significant differences in the age of ESRD among family members. No specific therapy is available to treat AS, although angiotensin-converting enzyme inhibitors (and possibly angiotensin-2 receptor inhibitors) can slow the rate of progression. Careful management of renal failure complications such as hypertension, anemia, and electrolyte imbalance is critical. Patients with ESRD are treated with dialysis and kidney transplantation (see Chapter 535). Approximately 5% of kidney transplantation recipients develop anti-GBM nephritis, which occurs primarily in males with X-linked AS who develop ESRD before age 30 yr.

Pharmacologic treatment of proteinuria with angiotensin-converting enzyme inhibition or angiotensin II receptor blockade has proven effective in other glomerular diseases and has also shown promise in AS. Screening of heterozygote carriers for significant renal disease in later adulthood and possible treatment of significant proteinuria is also recommended.

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510.3 Thin Basement Membrane Disease

Cynthia G. Pan and Ellis D. Avner

Thin basement membrane disease (TBMD) is defined by the presence of persistent microscopic hematuria and isolated thinning of the GBM (and, occasionally, tubular basement membranes) on electron microscopy. Microscopic hematuria is often initially observed during childhood and may be intermittent. Episodic gross hematuria can also be present, particularly after a respiratory illness. Isolated hematuria in multiple family members without renal dysfunction is referred to as **benign familial hematuria**. Although most of these patients will not undergo renal biopsy, it is often presumed that the underlying pathology is TBMD. TBMD may be sporadic or transmitted as an autosomal dominant trait. Heterozygous mutations in the *COL4A3* and *COL4A4* genes, which encode the α3 and α4 chains of type IV collagen present in the GBM, result in TBMD. Rare cases of TBMD progress, and such patients develop significant proteinuria, hypertension, or renal insufficiency. Homozygous mutations in these same genes result in autosomal recessive AS. Therefore, in these rare cases, the absence of a positive family history for renal insufficiency or deafness would not necessarily predict a benign outcome. Consequently, monitoring patients with benign familial hematuria for progressive proteinuria, hypertension, or renal insufficiency is important through childhood and young adulthood.

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Chapter 511

Glomerulonephritis Associated with Infections

511.1 Acute Poststreptococcal Glomerulonephritis

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Group A β-hemolytic streptococcal infections are common in children and can lead to the postinfectious complication of acute glomerulonephritis (GN). Acute poststreptococcal glomerulonephritis (APSGN) is a classic example of the **acute nephritic syndrome** characterized by the sudden onset of gross hematuria, edema, hypertension, and renal insufficiency. It is one of the most common glomerular causes of gross

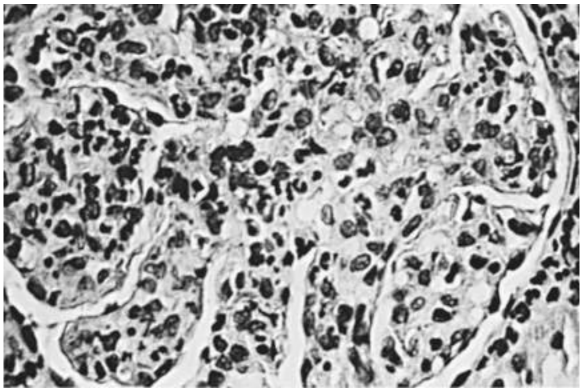

Figure 511-1 Glomerulus from a patient with poststreptococcal glomerulonephritis appears enlarged and relatively bloodless and shows mesangial proliferation and exudation of neutrophils (×400).

hematuria in children and is a major cause of morbidity in group A β-hemolytic streptococcal infections.

ETIOLOGY AND EPIDEMIOLOGY

APSGN follows infection of the throat or skin by certain "nephritogenic" strains of group A β-hemolytic streptococci. Epidemics and clusters of household (camps, military) cases occur throughout the world, and 97% of cases occur in less-developed countries. The overall incidence has decreased in industrialized nations, presumably as a result of improved hygienic conditions and the near eradication of streptococcal pyoderma. Poststreptococcal GN commonly follows streptococcal pharyngitis during cold-weather months and streptococcal skin infections or pyoderma during warm-weather months. Although epidemics of nephritis have been described in association with throat (serotypes M1, M4, M25, and some strains of M12) and skin (serotype M49) infections, this disease is most commonly sporadic.

PATHOLOGY

Glomeruli appear enlarged and relatively bloodless and show diffuse mesangial cell proliferation, with an increase in mesangial matrix (Fig. 511-1). Polymorphonuclear leukocyte infiltration is common in glomeruli during the early stage of the disease. Crescents and interstitial inflammation may be seen in severe cases, but these changes are not specific for poststreptococcal GN. Immunofluorescence microscopy reveals a pattern of "lumpy-bumpy" deposits of immunoglobulin and complement on the glomerular basement membrane and in the mesangium. On electron microscopy, electron-dense deposits, or "humps," are observed on the epithelial side of the glomerular basement membrane (Fig. 511-2).

PATHOGENESIS

Morphologic studies and a depression in the serum complement (C3) level provide strong evidence that ASPGN is mediated by immune complexes. Circulating immune complex formation with streptococcal antigens and subsequent glomerular deposition is thought less likely to be a pathogenic mechanism. Molecular mimicry whereby circulating antibodies elicited by streptococcal antigens react with normal glomerular antigens, in situ immune complex formation of antistreptococcal antibodies with glomerular deposited antigen, and complement activation by directly deposited streptococcal antigens continue to be considered as probable mechanisms of immunologic injury.

Group A streptococci possess M proteins, and nephritogenic strains are related to the M protein serotype. The search for the precise nephritogenic antigen(s) that cause disease suggests that streptococcal pyogenic exotoxin (SPE) B and nephritis-associated streptococcal plasmin receptor are promising candidates. Both have been identified in glomeruli of affected patients, and in 1 study, circulating antibodies to SPE B were found in all patients. Cross-reactivity of SPE B and other M proteins with various components of the glomerular basement membrane also give evidence for molecular mimicry.

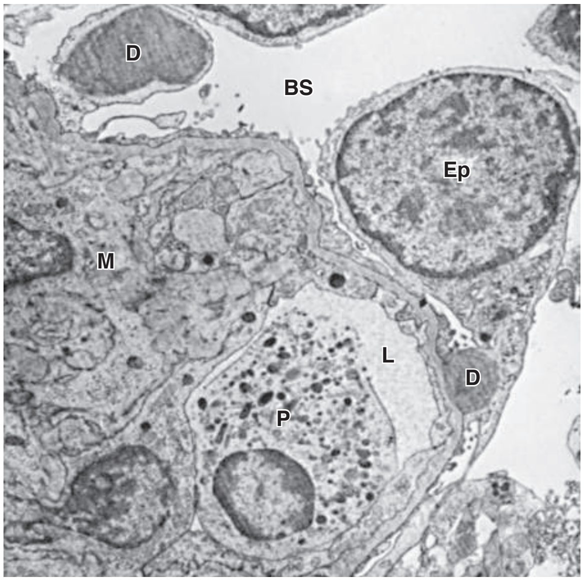

Figure 511-2 **Electron micrograph in poststreptococcal glomerulonephritis demonstrating electron-dense deposits (D) on the epithelial cell (Ep) side of the glomerular basement membrane.** A polymorphonuclear leukocyte (P) is present within the lumen (L) of the capillary. BS, Bowman space; M, mesangium.

CLINICAL MANIFESTATIONS

Poststreptococcal GN is most common in children ages 5-12 yr and uncommon before the age of 3 yr. The typical patient develops an acute nephritic syndrome 1-2 wk after an antecedent streptococcal pharyngitis or 3-6 wk after a streptococcal pyoderma. The history of a specific infection may be absent, because symptoms may have been mild or have resolved without patients receiving specific treatment or seeking the care of a medical provider.

The severity of kidney involvement varies from asymptomatic microscopic hematuria with normal renal function to gross hematuria with acute renal failure. Depending on the severity of renal involvement, patients can develop various degrees of edema, hypertension, and oliguria. Patients are at risk for developing encephalopathy and/or heart failure secondary to hypertension or hypervolemia. Hypertensive encephalopathy must be considered in patients with blurred vision, severe headaches, altered mental status, or new seizures. The effects of acute hypertension not only depend on the severity of hypertension but also the absolute change in comparison to the patient's baseline blood pressure and the rate at which it has risen. Respiratory distress, orthopnea, and cough may be symptoms of pulmonary edema and heart failure. Peripheral edema typically results from salt and water retention and is common; nephrotic syndrome develops in a minority (<5%) of childhood cases. Nonspecific symptoms such as malaise, lethargy, abdominal pain, or flank pain are common. Atypical presentations of APSGN include those with subclinical disease and those with severe symptoms but an absence of initial urinary abnormalities; in individuals who present with a purpuric rash, it is difficult to distinguish APSGN from Henoch-Schönlein purpura without a renal biopsy.

The acute phase generally resolves within 6-8 wk. Although urinary protein excretion and hypertension usually normalize by 4-6 wk after onset, persistent microscopic hematuria can persist for 1-2 yr after the initial presentation.

DIAGNOSIS

Urinalysis demonstrates red blood cells, often in association with red blood cell casts, proteinuria, and polymorphonuclear leukocytes. A

mild normochromic anemia may be present from hemodilution and low-grade hemolysis. The serum C3 level is significantly reduced in >90% of patients in the acute phase, and returns to normal 6-8 wk after onset. Although serum CH_{50} is commonly depressed, C4 is most often normal in APSGN, or only mildly depressed.

Confirmation of the diagnosis requires clear evidence of a prior streptococcal infection. A positive throat culture report might support the diagnosis or might represent the carrier state. A rising antibody titer to streptococcal antigen(s) confirms a recent streptococcal infection. The antistreptolysin O titer is commonly elevated after a pharyngeal infection but rarely increases after streptococcal skin infections. The best single antibody titer to document cutaneous streptococcal infection is the antideoxyribonuclease B level. If available, a positive streptozyme screen (which measures multiple antibodies to different streptococcal antigens) is a valuable diagnostic tool. Serologic evidence for streptococcal infections is more sensitive than the history of recent infections and far more sensitive than positive bacterial cultures obtained at the time of onset of acute nephritis.

Magnetic resonance imaging of the brain is indicated in patients with severe neurologic symptoms and can demonstrate **posterior reversible encephalopathy syndrome** in the parietooccipital areas on T2-weighted images. Chest x-ray is indicated in those with signs of heart failure or respiratory distress, or physical exam findings of a heart gallop, decreased breath sounds, rales, or hypoxemia.

The clinical diagnosis of poststreptococcal GN is quite likely in a child presenting with acute nephritic syndrome, evidence of recent streptococcal infection, and a low C3 level. However, it is important to consider other diagnoses such as systemic lupus erythematosus, endocarditis, membranoproliferative GN, and an acute exacerbation of chronic GN. Renal biopsy should be considered only in the presence of acute renal failure, nephrotic syndrome, absence of evidence of streptococcal infection, or normal complement levels. In addition, renal biopsy is considered when hematuria and proteinuria, diminished renal function, and/or a low C3 level persist more than 2 mo after onset. Persistent hypocomplementemia can indicate a chronic form of postinfectious GN or another disease such as membranoproliferative GN.

The differential diagnosis of poststreptococcal GN includes many of the causes of hematuria listed in Tables 509-2 and 511-1, and an algorithm to help with diagnosis is presented in Figure 511-3. Acute postinfectious GN can also follow other infections with coagulase-positive and coagulase-negative staphylococci, *Streptococcus pneumoniae,* and Gram-negative bacteria. The clinical course, histopathology, and laboratory features are similar to those described for APSGN. For some, the terms APSGN and acute postinfectious GN are used synonymously. Acute GN can occur after certain fungal, rickettsial, protozoan, parasitic, or viral diseases. Among the latter, influenza and parvovirus infections are particularly notable.

COMPLICATIONS

Acute complications result from hypertension and acute renal dysfunction. Hypertension is seen in 60% of patients and is associated

Table 511-1 Summary of Primary Renal Diseases That Manifest as Acute Glomerulonephritis

DISEASES	POSTSTREPTOCOCCAL GLOMERULONEPHRITIS	IgA NEPHROPATHY	GOODPASTURE SYNDROME	IDIOPATHIC RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS
CLINICAL MANIFESTATIONS				
Age and sex	All ages, mean 7 yr, 2:1 male	10-35 yr, 2:1 male	15-30 yr, 6:1 male	Adults, 2:1 male
Acute nephritic syndrome	90%	50%	90%	90%
Asymptomatic hematuria	Occasionally	50%	Rare	Rare
Nephrotic syndrome	10-20%	Rare	Rare	10-20%
Hypertension	70%	30-50%	Rare	25%
Acute renal failure	50% (transient)	Very rare	50%	60%
Other	Latent period of 1-3 wk	Follows viral syndromes	Pulmonary hemorrhage; iron deficiency anemia	None
Laboratory findings	↑ ASO titers (70%) Positive streptozyme (95%) ↓C3-C9; normal C1, C4	↑ Serum IgA (50%) IgA in dermal capillaries	Positive anti-GBM antibody	Positive ANCA in some
Immunogenetics	HLA-B12, D "EN" (9)*	HLA-Bw 35, DR4 (4)*	HLA-DR2 (16)*	None established
RENAL PATHOLOGY				
Light microscopy	Diffuse proliferation	Focal proliferation	Focal → diffuse proliferation with crescents	Crescentic GN
Immunofluorescence	Granular IgG, C3	Diffuse mesangial IgA	Linear IgG, C3	No immune deposits
Electron microscopy	Subepithelial humps	Mesangial deposits	No deposits	No deposits
Prognosis	95% resolve spontaneously 5% RPGN or slowly progressive	Slow progression in 25-50%	75% stabilize or improve if treated early	75% stabilize or improve if treated early
Treatment	Supportive	Uncertain (options include steroids, fish oil, and ACE inhibitors)	Plasma exchange, steroids, cyclophosphamide	Steroid pulse therapy

*Relative risk.

ACE, angiotensin-converting enzyme; ANCA, antineutrophil cytoplasmic antibody; ASO, anti-streptolysin O; GBM, glomerular basement membrane; GN, glomerulonephritis; HLA, human leukocyte antigen; Ig, immunoglobulin; RPGN, idiopathic rapidly progressive glomerulonephritis.

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier, p. 427.*

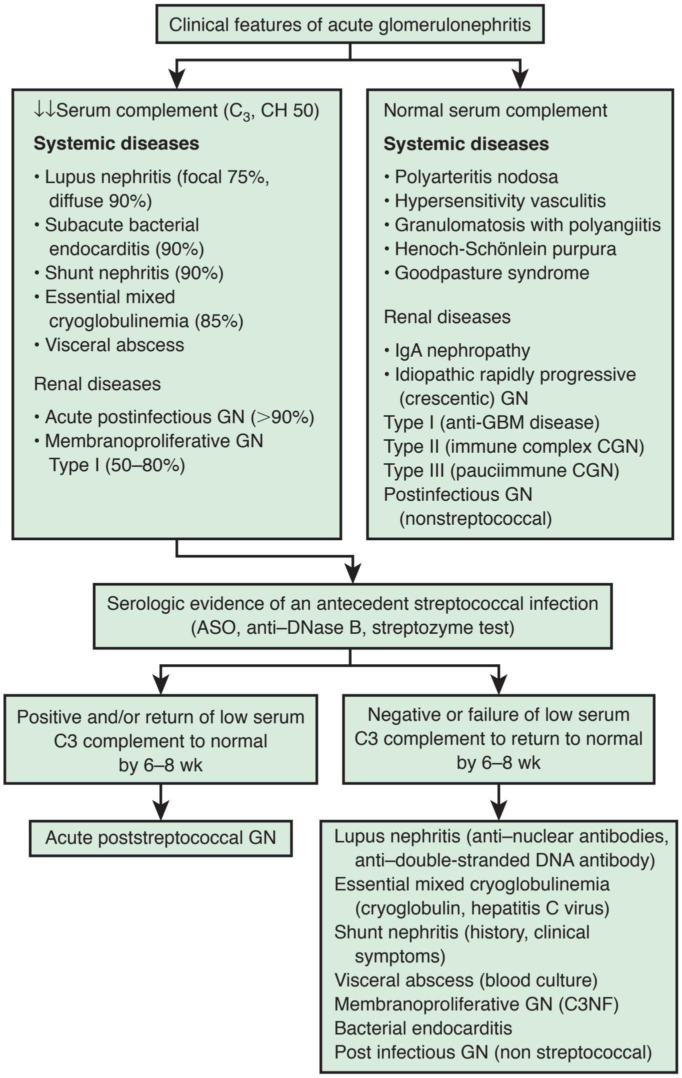

Figure 511-3 Differential diagnosis of acute glomerulonephritis (GN). ASO, anti–streptolysin O; GBM, glomerular basement membrane; NF, nuclear factor. *(Adapted from Sulyok E: Acute proliferative glomerulonephritis. In Avner ED, Harmon WE, Niaudet P, editors:* Pediatric nephrology, *ed 5, Philadelphia, 2004, Lippincott Williams & Wilkins, Fig. 30-4.)*

with hypertensive encephalopathy in 10% of cases. Although the neurologic sequelae are often reversible with appropriate management, severe prolonged hypertension can lead to intracranial bleeding. Other potential complications include heart failure, hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, seizures, and uremia. Acute renal failure can require treatment with dialysis.

PREVENTION

Early systemic antibiotic therapy for streptococcal throat and skin infections does not eliminate the risk of GN. Family members of patients with acute GN, especially young children, should be considered at risk and be cultured for group A β-hemolytic streptococci and treated if positive. Family pets, particularly dogs, have also been reported as carriers.

TREATMENT

Management is directed at treating the acute effects of renal insufficiency and hypertension (see Chapter 535.1). Although a 10 day course of systemic antibiotic therapy with penicillin is recommended to limit the spread of the nephritogenic organisms, antibiotic therapy does not affect the natural history of APSGN. This is unlike the GN seen in the context of ongoing or chronic infections, as noted in Chapter 511.2. Sodium restriction, diuresis (usually with intravenous furosemide), and pharmacotherapy with calcium channel antagonists, vasodilators, or angiotensin-converting enzyme inhibitors, are standard therapies used to treat hypertension.

PROGNOSIS

Complete recovery occurs in >95% of children with APSGN. Recurrences are extremely rare. Mortality in the acute stage can be avoided by appropriate management of acute renal failure, cardiac failure, and hypertension. Infrequently, the acute phase is severe and leads to glomerulosclerosis and chronic renal disease in <2% of affected children.

Bibliography is available at Expert Consult.

511.2 Other Chronic Infections

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GN is a recognized complication of various chronic infections. Classic examples include bacterial endocarditis caused by viridans streptococcus and other organisms, and ventriculoatrial shunts infected with *Staphylococcus epidermidis.* Other infections, observed less commonly in children than in adults, include hepatitis B virus, hepatitis C virus, syphilis, and candidiasis. Parasitic infections associated with glomerular disease include malaria, schistosomiasis, leishmaniasis, filariasis, hydatid disease, trypanosomiasis, and toxoplasmosis. In each condition, the infecting organism has low virulence and the host is chronically infected with foreign antigen. In the presence of high levels of circulating antigen, the host's antibody response leads to formation of immune complexes that deposit in the kidneys and initiate glomerular inflammation. Foreign antigens can also stimulate an autoimmune response through the production of antibodies that cross-react with such antigens incorrectly "recognized" as glomerular structural components.

The renal histopathology can resemble poststreptococcal GN, membranous GN, or membranoproliferative GN. The clinical manifestations are generally those of an acute nephritic or nephrotic syndrome. The serum C3 and CH_{50} complement levels are often decreased.

In HIV-associated nephropathy, direct viral infection of nephrons occurs because renal cells express a variety of lymphocyte chemokine receptors that are essential for and facilitate viral invasion. The renal expression of HIV infection is quite variable and includes an immune complex injury and a direct cytopathic effect. The classic histopathologic lesion of HIV-associated nephropathy is focal segmental glomerulosclerosis, but systemic lupus erythematosus–like glomerulonephritis, immunoglobulin A nephropathy, and membranous nephropathy have been reported. In the era of antiretroviral therapy, the decline in mortality has led to the increased recognition of renal disorders as an important complication to perinatally HIV-infected children.

Prompt eradication of any infection before severe glomerular injury occurs usually results in resolution of the GN. Progression to end-stage renal failure has been described but is uncommon. Spontaneous resolution of hepatitis B infection is common in children (30-50%) and results in remission of the glomerulopathy. Specific antivirals, interferon therapy, plasmapheresis, and immunosuppressive treatment have all been used successfully in adults with hepatitis C disease, but no controlled trials with any of these agents have been performed in pediatric patients.

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Chapter 512
Membranous Nephropathy

Scott K. Van Why and Ellis D. Avner

Membranous nephropathy (MN), amongst the most common causes of nephrotic syndrome in adults, is a rare cause of nephrotic syndrome in children. MN is classified as the primary, idiopathic form, where there is isolated renal disease, or secondary MN, where nephropathy is associated with other identifiable systemic diseases or medications. In children, secondary MN is far more common than primary, idiopathic MN. The most common etiologies of secondary MN are systemic lupus erythematosus or chronic infections. Among the latter, chronic hepatitis B infection and congenital syphilis are the best characterized and recognized causes of MN. Other chronic infections have also been associated with MN, including malaria, which is likely the most common cause of nephrotic syndrome worldwide. Certain medications, such as penicillamine and gold, or chronic factor replacement in patients with hemophilia can also cause MN. Rare causes associated with MN include tumors, such as neuroblastoma, or other idiopathic systemic diseases. Identification of secondary causes of MN is critical, because removal of the offending agent or treatment of the causative disease often leads to resolution of the associated nephropathy and improves patient outcome.

PATHOLOGY

Glomeruli have diffuse thickening of the glomerular basement membrane (GBM), without significant cell proliferative changes. Immunofluorescence and electron microscopy typically demonstrate granular deposits of immunoglobulin G and C3 located on the epithelial side of the GBM. The GBM thickening presumably results from the production of membrane-like material in response to deposition of immune complexes.

PATHOGENESIS

MN is believed to be caused by in situ immune complex formation. Therefore, antigens from the infectious agents or medications associated with secondary MN directly contribute to the pathogenesis of the renal disease. The causative antigen in idiopathic MN is not established, but the M-type phospholipase A_2 receptor, present on normal podocytes, may be a target antigen in idiopathic MN. Antigen from this receptor is found in immune deposits extracted from glomeruli in patients with idiopathic MN. The majority of idiopathic MN patients have circulating antibody against this podocyte membrane antigen, as well as against several podocyte cytoplasmic antigens. Childhood MN may be associated with anticationic bovine serum albumin antibodies. In addition, neutral endopeptidase antigen may be the antigen in neonatal onset MN.

CLINICAL MANIFESTATIONS

In children, MN is most common in the 2nd decade of life, but it can occur at any age, including infancy. The disease usually manifests as nephrotic syndrome and accounts for 2-6% of all cases of childhood nephrotic syndrome. Most patients also have microscopic hematuria and only rarely present with gross hematuria. Approximately 20% of children have hypertension at presentation. A subset of patients with MN present with a major venous thrombosis, commonly renal vein thrombosis. This well-known complication of nephrotic syndrome (see Chapter 527) is particularly common in patients with MN. Serum C3 and CH_{50} levels are normal, except in cases of systemic lupus erythematosus, where levels may be depressed (see Fig. 511-3 in Chapter 511).

DIAGNOSIS

MN might be suspected on clinical grounds, particularly in the setting of known risk factors for secondary forms of the disease. The diagnosis can only be established by renal biopsy. No serologic test is specific for MN, but finding an active carrier state for hepatitis B or congenital syphilis would make the diagnosis probable in the appropriate clinical setting. Common indications for renal biopsy leading to the diagnosis of MN include presentation with nephrotic syndrome in a child >10 yr or unexplained persistent hematuria with significant proteinuria.

PROGNOSIS AND TREATMENT

The clinical course of idiopathic membranous glomerulopathy is variable. Children presenting with asymptomatic, low-grade proteinuria can enter remission spontaneously. Retrospective reports of children 1-15 yr after diagnosis, treated with a variety of regimens, indicate that 20% progress to chronic renal failure, 40% continue with active disease, and 40% achieve complete remission. Although no controlled trials have been performed in children, immunosuppressive therapy with an extended course of prednisone can be effective in promoting complete resolution of symptoms. The addition of chlorambucil or cyclophosphamide appears to provide further benefit to those not responding to steroids alone. Rituximab has shown significant promise in adults and has been proposed by some as first line treatment but has yet to be studied in a randomized controlled trial in any age group. For those unresponsive to immunosuppression, or with mild clinical features, proteinuria can be reduced with angiotensin-converting enzyme inhibitors, and by analogy, probably angiotensin-II–receptor blockers.

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Chapter 513

Membranoproliferative Glomerulonephritis

Scott K. Van Why and Ellis D. Avner

Membranoproliferative glomerulonephritis (MPGN), also known as mesangiocapillary glomerulonephritis, most commonly occurs in children or young adults. MPGN can be classified into primary (idiopathic) and secondary forms of glomerular disease. Secondary forms of MPGN are most commonly associated with subacute and chronic infection, including hepatitides B and C, syphilis, subacute bacterial endocarditis, and infected shunts, especially ventriculoatrial shunts (shunt nephritis). MPGN can also be one of the glomerular lesions seen in lupus nephritis (see Chapter 514).

PATHOLOGY

Primary MPGN is defined by the histologic pattern of glomeruli as seen by light, immunofluorescence, and electron microscopy. Two subtypes have been defined on histologic criteria and are associated with different clinical phenotypes. **Type I MPGN** is most common. Glomeruli have an accentuated lobular pattern from diffuse mesangial expansion, endocapillary proliferation, and an increase in mesangial cells and matrix. The glomerular capillary walls are thickened, often with splitting from interposition of the mesangium. Crescents, if present, indicate a poor prognosis. Immunofluorescence microscopy reveals C3 and lesser amounts of immunoglobulin in the mesangium and along the peripheral capillary walls in a lobular pattern. Electron

microscopy confirms numerous deposits in the mesangial and subendothelial regions.

Far less common is **type II MPGN,** also called dense deposit disease, which has similar light microscopic findings as type I MPGN. Differentiation from type I disease is by immunofluorescence and electron microscopy. In type II disease, C3 immunofluorescence typically is prominent, without concomitant immunoglobulin. By electron microscopy, the lamina densa in the glomerular basement membrane undergoes a very dense transformation, without evident immune complex–type deposits.

C3 glomerulonephritis (C3GN) is a related but separate diagnostic category. By light and electron microscopy C3GN usually has features indistinguishable from classical MPGN. Immunofluorescence studies distinguish between the two, with C3GN having only C3 deposition and MPGN having both C3 and immunoglobulin fluorescence.

PATHOGENESIS

Although the histology of **type I MPGN** produced by primary and secondary forms is indistinguishable, it appears that **type I** disease occurs when circulating immune complexes become trapped in the glomerular subendothelial space, which then causes injury, resulting in the characteristic proliferative response and mesangial expansion. Further evidence confirming this pathway to glomerular injury is the finding of complement activation through the classical pathway in as many as 50% of affected patients.

Type II MPGN appears **not** to be mediated by immune complexes. The pathogenesis of the disease is not known, but the characteristic finding of severely depressed serum complement levels suggests that deranged complement regulation might play a major role in the disease. A typical finding is markedly depressed serum C3 complement levels, with normal levels of other complement components. In many patients with type II MPGN, **C3 nephritic factor** (anti–C3 convertase antibody) is present. This factor activates the alternative complement pathway. In unusual cases, patients with type II MPGN demonstrate an associated systemic disease called **partial lipodystrophy**, where there is diffuse loss of adipose tissue and decreased complement in the presence of C3 nephritic factor. Correlation between the presence of C3 nephritic factor, complement levels, and disease presence or severity is not strong, indicating that the complement abnormalities alone are not sufficient to cause the disease.

Type II MPGN (dense deposit disease) is considered part of the broader spectrum of C3GN. The latter, as defined above pathologically, appears to be caused by primary dysregulation of the alternative or terminal cascade complement pathways.

CLINICAL MANIFESTATIONS

MPGN is most common in the 2nd decade of life. Systemic features may provide clues to which type of MPGN may be present, but the two histologic types of idiopathic MPGN are indistinguishable in terms of their renal manifestations. Patients present in equal proportions with nephrotic syndrome, acute nephritic syndrome (hematuria, hypertension, and some level of renal insufficiency), or persistent asymptomatic microscopic hematuria and proteinuria. Serum C3 complement levels are low in the majority of cases (see Fig. 511-3 in Chapter 511).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes all forms of acute and chronic glomerulonephritis, including idiopathic and secondary forms, along with postinfectious glomerulonephritis. Postinfectious glomerulonephritis, far more common than MPGN, usually does not have nephrotic features but typically has hematuria, hypertension, renal insufficiency, and transiently low C3 complement, all features that may be seen with MPGN or C3GN. In contrast to MPGN and C3GN, where C3 levels usually remain persistently low, C3 returns to normal within 2 mo after onset of postinfectious glomerulonephritis (see Chapter 511.3). The diagnosis of MPGN is made by renal biopsy. Indications for biopsy include nephrotic syndrome in an older child, significant proteinuria with microscopic hematuria, and hypocomplementemia lasting >2 mo in a child with acute nephritis. If C3 but no immunoglobulin deposition is found in glomeruli with MPGN, genetic testing and functional assays to define defects of complement cascade regulation should be pursued.

PROGNOSIS AND TREATMENT

It is important to determine whether MPGN is idiopathic or secondary to a systemic disease, particularly lupus or chronic infection, because treatment of the causative disease can result in resolution of MPGN. Untreated, idiopathic MPGN, regardless of type, has a poor prognosis. By 10 yr following onset, 50% of patients with MPGN have progressed to end-stage renal disease. By 20 yr following onset, up to 90% have lost renal function. Those with nephrotic syndrome at the time of presentation progress to renal failure more rapidly. No definitive therapy exists, but several reports, including a randomized controlled trial, indicate that extended courses of alternate-day prednisone (for years) provide benefit. Some patients treated with steroids enter a complete clinical remission of their disease, but many have ongoing disease activity. Nevertheless, an extended course of prednisone is associated with significant preservation of renal function when compared with patients receiving no such treatment.

The prognosis of C3GN, separate from dense deposit disease (considered a part of C3GN by some) and other forms of classically defined MPGN is as yet hard to define, since reports of outcome of such patients previously had been grouped in studies of all forms of MPGN (types I and II, and even a poorly characterized type III form not considered above). The apparent pathophysiology of C3GN promises that treatments targeting the interruption of complement activation pathways, such as complement factor H replacement or shutting down the terminal complement cascade by blocking C5 activation with eculizumab (anti–C5 antibody), could be beneficial in preventing progression of renal disease.

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Chapter 514

Glomerulonephritis Associated with Systemic Lupus Erythematosus

Cynthia G. Pan and Ellis D. Avner

Systemic lupus erythematosus (SLE) is characterized by fever, weight loss, dermatitis, hematologic abnormalities, arthritis, and involvement of the heart, lungs, central nervous system, and kidneys (see Chapter 158). Glomerulonephritis is the most important cause of morbidity and mortality in SLE. Renal disease in childhood SLE is present in up to 80% of patients and is more active than that seen in adults. Occasionally, renal disease is the only presenting clinical manifestation.

PATHOGENESIS AND PATHOLOGY

The clinical manifestations of SLE are mediated by immune complexes. Autoantibodies are directed predominantly at nuclear antigens which act as immunogens. Binding of autoantibodies to glomerular components rather than the passive "trapping" of circulating immune complexes is central to the development of glomerulonephritis. Other pathogenic mechanisms include alterations in innate immunity that

result in amplification of inflammation. Deficiency of the complement component C1q is rare but is the strongest single genetic risk for SLE.

Kidney biopsy and evaluation of renal histopathology remain the gold standard for establishing the diagnosis of SLE nephritis and determining specific therapeutic regimens. The World Health Organization (WHO) classification of lupus nephritis is based on a combination of features including light microscopy, immunofluorescence, and electron microscopy. In patients with **WHO class I nephritis** (minimal mesangial lupus nephritis), no histologic abnormalities are detected on light microscopy but mesangial immune deposits are present on immunofluorescence or electron microscopy. In **WHO class II nephritis** (mesangial proliferative nephritis), light microscopy shows both mesangial hypercellularity and increased matrix along with mesangial deposits containing immunoglobulin and complement.

WHO class III nephritis and **WHO class IV nephritis** are interrelated lesions characterized by both mesangial and endocapillary lesions. Class III nephritis is defined by <50% glomeruli with involvement and class IV has ≥50% glomerular involvement. Immune deposits are present in both the mesangium and subendothelial areas. A subclassification scheme helps grade severity of the proliferative lesion based on whether the glomerular lesions are segmental (<50% glomerular tuft involved) or global (≥50% glomerular tuft involved). The WHO classification scheme also delineates whether there is a predominance of chronic disease versus active disease. Chronic injury results in glomerular sclerosis and is felt to be the consequence of significant proliferative disease seen in classes III and IV. Other signs of active disease include capillary walls that are thickened secondary to subendothelial deposits (creating the wire-loop lesion), necrosis, and crescent formation. WHO class IV nephritis is associated with poorer outcomes but can be successfully treated with aggressive immunosuppressive therapy.

WHO class V nephritis (membranous lupus nephritis) is less commonly seen as an isolated lesion and resembles idiopathic membranous nephropathy with subepithelial immune deposits. This lesion is often seen in combination with class III or IV proliferative nephritis, and if the membranous lesion is present in >50% glomeruli, both classes are noted in designation. This classification scheme also identifies cases with combinations of mixed classes III, IV, and V lesions, directing appropriate treatment for such patients. Another classification scheme by both the International Society of Nephrology and the Renal Pathology Society differs mainly in its subclassification of class IV into diffuse global and diffuse segmental lesions (Table 514-1). The value of utilizing this classification scheme, and more importantly, its impact on therapy and the results of clinical trials is unknown at this time.

Transformation of the histologic lesions of lupus nephritis from one class to another is common. This is more likely to occur among inadequately treated patients and usually results in progression to a more severe histologic lesion.

Table 514-1 Classification of Lupus Nephritis

CLASS	CLINICAL FEATURES
I. Minimal mesangial LN	No renal findings
II. Mesangial proliferative LN	Mild clinical renal disease; minimally active urinary sediment; mild to moderate proteinuria (never nephrotic) but may have active serology
III. Focal proliferative LN <50% glomeruli involved A. Active A/C. Active and chronic C. Chronic	More active sediment changes; often active serology; increased proteinuria (approximately 25% nephrotic); hypertension may be present; some evolve into class IV pattern; active lesions require treatment, chronic do not
IV. Diffuse proliferative LN (>50% glomeruli involved); all may be with segmental or global involvement (S or G) A. Active A/C. Active and chronic C. Chronic	Most severe renal involvement with active sediment, hypertension, heavy proteinuria (frequent nephrotic syndrome), often reduced glomerular filtration rate; serology very active. Active lesions require treatment
V. Membranous LN glomerulonephritis	Significant proteinuria (often nephrotic) with less active lupus serology
VI. Advanced sclerosing LN	More than 90% glomerulosclerosis; no treatment prevents renal failure

LN, lupus nephritis.

From Appel GB, Radhakrishnan J: Glomerular disorders and nephrotic syndromes. In Goldman L, Schafer AI, editors, Goldman's Cecil medicine, *ed 24, St. Louis, 2012, Elsevier Saunders, Table 123-7, p. 769.*

CLINICAL MANIFESTATIONS

The majority of children with SLE are adolescent females. Lupus nephritis affects most pediatric patients, and although commonly presenting within the first year of diagnosis, may occur at any time during the course of the disease. Ethnicity and socioeconomic factors strongly predict the development of lupus nephritis in adults with SLE but not in children. The clinical findings in patients having milder forms of lupus nephritis (all classes I-II, some class III) include hematuria, normal renal function, and proteinuria <1 g/24 hr. Some patients with class III and all patients with class IV nephritis have hematuria and proteinuria, hypertension, reduced renal function, nephrotic syndrome, or acute renal failure. The urinalysis may be normal on rare occasions in patients with proliferative lupus nephritis. Patients with class V nephritis commonly present with nephrotic syndrome.

DIAGNOSIS

The diagnosis of SLE is confirmed by the detection of circulating antinuclear antibodies and by demonstrating antibodies that react with native double-stranded DNA. In most patients with active disease, C3 and C4 levels are depressed. In view of the lack of a clear correlation between the clinical manifestations and the severity of the renal involvement, renal biopsy should be performed in all patients with SLE. Histopathologic findings are used to determine the selection of specific immunosuppressive therapies.

TREATMENT

Children with SLE should be treated by pediatric specialists in medical centers where medical and psychologic support can be provided for patients and their families. The goal of immunosuppressive therapy in lupus nephritis is to produce both a clinical remission, defined as normalization of renal function and proteinuria, and a serologic remission, defined as normalization of anti-DNA antibody, C3, and C4 levels. Therapy is initiated in all patients with prednisone at a dose of 1-2 mg/kg/day in divided doses followed by a slow steroid taper over 4-6 mo beginning 4-6 wk after achieving a serologic remission. For patients with severe forms of nephritis (WHO classes III and IV), induction therapy consists of 6 consecutive monthly intravenous infusions of cyclophosphamide at a dose of 500-1,000 mg/m^2. Pulse intravenous methylprednisolone (1000 mg/m^2) is also used in addition to oral corticosteroids. In adult clinical trials, mycophenolate mofetil was shown to be equally efficacious for induction therapy and may be considered for use in children using 600 mg/m^2 per dose twice daily. Maintenance therapy previously consisted of additional Cytoxan infusions every 3 mo for 18 mo, which reduced the risk of progressive renal dysfunction. Maintenance therapy using mycophenolate mofetil or azathioprine may be as efficacious as intravenous cyclophosphamide and result in less-serious side effects, such as infections, hair loss, hemorrhagic cystitis, and gonadal failure. Mycophenolate mofetil is particularly more efficacious than cyclophosphamide in African-Americans. Azathioprine, at a single daily dose of 1.5-2.0 mg/kg, may be used as a steroid-sparing agent in patients with WHO class I or II

lupus nephritis. Rituximab, a chimeric monoclonal antibody specific for human CD20, is ineffective for induction therapy for diffuse proliferative disease but may be considered in cases where resistance to conventional treatment is demonstrated. Plasmapheresis is ineffective in lupus nephritis unless there is accompanying thrombotic thrombocytopenic purpura or antineutrophilic cytoplasmic antibody–associated disease. New therapies include belimumab, a fully humanized monoclonal antibody against a type II transmembrane protein that functions in the normal survival and differentiation of B cells, which is FDA-approved for use in SLE. Its role in lupus nephritis, either in combination with current therapies or to replace them, requires extensive further study.

Hydrochloroquine is prescribed in most patients with SLE for extrarenal manifestations, but is thought to have a beneficial effect in maintaining remission in lupus nephritis. It is a rational choice given its low side effect profile. Use of antihypertensive drugs to aggressively treat hypertension as well as the specific use of drugs that block the renin–angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers) to reduce proteinuria are also important therapies that appear to decrease long-term progression of renal disease.

PROGNOSIS

Overall, renal survival (defined as chronic kidney disease without the need for end-stage renal disease therapy) is seen in 80% of patients 10 yr after the diagnosis of SLE nephritis. Patients with diffuse proliferative WHO class IV lupus nephritis exhibit the highest risk for progression to end-stage renal disease. Concerns regarding the side effects of chronic immunosuppressive therapy and the risk of recurrent disease are lifelong. Close monitoring for relapse of disease is critical to ensure maximally successful renal outcomes. Special care must be taken to minimize the risks of infection, osteoporosis, obesity, poor growth, hypertension, and diabetes mellitus associated with chronic corticosteroid therapy. Patients require counseling regarding the risk of malignancy or infertility, which may be increased in those receiving a cumulative dose of >20 g of cyclophosphamide or other immunosuppressant therapies.

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Chapter 515

Henoch-Schönlein Purpura Nephritis

Scott K. Van Why and Ellis D. Avner

Henoch-Schönlein purpura (HSP) is the most common small vessel vasculitis in childhood. It is characterized by a purpuric rash and commonly accompanied by arthritis and abdominal pain (see Chapter 167.1). Approximately 50% of patients with HSP develop renal manifestations, which vary from asymptomatic microscopic hematuria to severe, progressive glomerulonephritis.

PATHOGENESIS AND PATHOLOGY

The pathogenesis of HSP nephritis appears to be mediated by the deposition of polymeric immunoglobulin A (IgA) in glomeruli. This is analogous to the same type of IgA deposits seen in systemic small vessels, primarily those of the skin and intestine. The glomerular findings can be indistinguishable from those of IgA nephropathy (see Chapter 510.1). IgA deposits are present by immunofluorescence, and a broad spectrum of glomerular lesions that can range from mild proliferation to necrotic and crescentic changes can be seen.

CLINICAL AND LABORATORY MANIFESTATIONS

The nephritis associated with HSP usually follows onset of the rash, often presenting weeks or even months after the initial presentation of the disease. Nephritis can be manifest at initial presentation, but only rarely before onset of the rash. Patients at presentation rarely display a severe combined acute nephritic and nephrotic picture (hematuria, hypertension, renal insufficiency, significant proteinuria, and nephrotic syndrome). Most patients have only mild renal manifestations, principally isolated microscopic hematuria without significant proteinuria. Initial mild renal involvement can occasionally progress to more severe nephritis despite resolution of all other features of HSP. The severity of the systemic manifestations does not correlate with the severity of the nephritis. Most patients who develop nephritis have urinary abnormalities by 1 mo, and nearly all have abnormalities by 3 mo after onset of HSP. Therefore, a urinalysis should be performed weekly in patients with HSP during the period of active clinical disease. Thereafter, a urinalysis should be performed once a month for up to 6 mo. If all urinalyses are normal during this follow-up interval, nephritis is unlikely to develop. If proteinuria, renal insufficiency, or hypertension develops along with hematuria, consultation with a pediatric nephrologist is indicated.

PROGNOSIS AND TREATMENT

The prognosis of HSP nephritis for most patients is excellent. Spontaneous and complete resolution of the nephritis typically occurs in the majority of patients with mild initial manifestations (isolated hematuria with insignificant proteinuria). However, such patients uncommonly can progress to severe renal involvement, including development of chronic renal failure. Patients with acute nephritic or nephrotic syndrome at presentation have a guarded renal prognosis, particularly if they are found to have concomitant necrosis or substantial crescentic changes on renal biopsy. Untreated, the risk of developing chronic kidney disease, including renal failure, is 2-5% in all patients with HSP, but almost 50% in those with the most severe early renal clinical and histologic features.

No studies have demonstrated any efficacy of short courses (weeks) of oral corticosteroids administered promptly after onset of HSP on either preventing the development of nephritis or decreasing the severity of subsequent HSP nephritis. Tonsillectomy has been proposed as an intervention for HSP nephritis, but it also does not appear to have any measurable effect on renal outcome. Mild HSP nephritis does not require treatment, because it usually resolves spontaneously.

Efficacy of treatment for moderate or severe HSP nephritis, which is far more likely to progress to chronic renal failure, is more difficult to assess. Limited prospective controlled trials for severe HSP nephritis have not shown benefit from any therapy studied. Several uncontrolled studies have reported significant benefit from aggressive immunosuppression (high-dose and extended courses of corticosteroids with cyclophosphamide or azathioprine) in patients with poor prognostic features on renal biopsy; such patients are at high risk of progressing to chronic renal failure based on historic controls. Anecdotal reports of treatment of high-risk patients with either plasmapheresis or rituximab have indicated a potential benefit. Balancing the absence of controlled data with the severe side effects of aggressive therapies in patients with poor renal prognostic factors is difficult. Aggressive therapy with careful monitoring may be reasonable in those with the most severe HSP nephritis (>50% crescents on biopsy).

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Chapter 516

Rapidly Progressive (Crescentic) Glomerulonephritis

Scott K. Van Why and Ellis D. Avner

"Rapidly progressive" describes the clinical course of several forms of glomerulonephritis whose unifying feature is the histopathologic finding of crescents in the majority of glomeruli (Fig. 516-1). The terms *rapidly progressive glomerulonephritis* (RPGN) and *crescentic glomerulonephritis* (CGN) are synonymous. The natural history of most forms of CGN is rapid and relentless progression to end-stage renal failure.

CLASSIFICATION

CGN can be a severe manifestation of essentially every defined primary and secondary glomerulonephritis (GN), but particular forms of GN are more likely to present as, or evolve into, RPGN (Table 516-1). If no underlying cause is identified by systemic features, serologic testing, or histologic examination, the disease is classified as idiopathic CGN. The incidence of specific etiologies of CGN in children varies widely; certain common themes are shared in all such reports. Patients with systemic vasculitis appear to be particularly prone to develop CGN. Patients with Henoch-Schönlein purpura (HSP), antineutrophil cytoplasmic antibody (ANCA)–mediated GN (microscopic polyangiitis and granulomatosis with polyangiitis), and systemic lupus erythematosus account for the majority of patients with CGN. Postinfectious GN or endocarditis rarely progresses to CGN, but because it is the most common form of GN in childhood it accounts for a significant percentage of patients with CGN in most reports. Membranoproliferative GN and idiopathic disease make up most of the remaining cases of CGN. Immunoglobulin (Ig) A nephropathy, a common GN, only rarely is rapidly progressive. Goodpasture disease often has rapidly progressive GN as a component of the syndrome, but its rarity in childhood results in its making up only a small percentage of children with CGN.

Table 516-1 Classification of Rapidly Progressive ("Crescentic") Glomerulonephritis
PRIMARY
Type I: Anti–glomerular basement membrane antibody disease, Goodpasture syndrome (with pulmonary disease)
Type II: Immune complex mediated
Type III: Pauciimmune (usually antineutrophil cytoplasmic antibody-positive)
SECONDARY
Membranoproliferative glomerulonephritis
Immunoglobulin A nephropathy, Henoch-Schönlein purpura
Poststreptococcal glomerulonephritis
Systemic lupus erythematosus
Polyarteritis nodosa, hypersensitivity angiitis

From Appel GB, Radhakrishnan J: Glomerular disorders and nephrotic syndromes. In Goldman L, Schafer AI, editors: Goldman's Cecil medicine, *ed 24, St. Louis, 2012, Elsevier Saunders, Table 122-3, p. 758.*

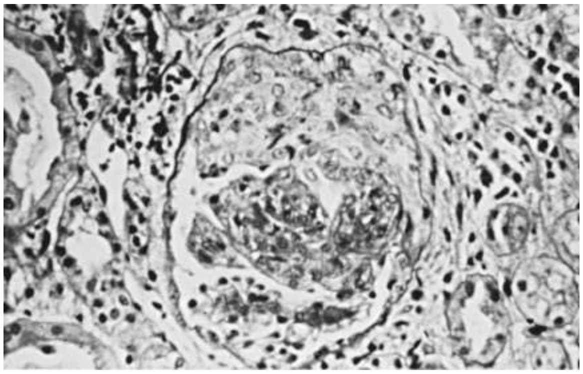

Figure 516-1 Light micrograph of a biopsy specimen from a child with Henoch-Schönlein purpura glomerulonephritis demonstrating a crescent overlying the glomerulus (×180).

PATHOLOGY AND PATHOGENESIS

The hallmark of CGN is the histopathologic finding of crescents in glomeruli (see Fig. 516-1). Crescent formation, through proliferation of parietal epithelial cells in Bowman's space, may be the final pathway of any severe inflammatory glomerular injury. Podocytes and renal progenitor cells are involved in the pathogenesis of CGN. Fibrous crescents, in which proliferative cellular crescents are replaced by collagen, are a late finding. The immunofluorescence findings, as well as the pattern of any deposits by electron microscopy can delineate the underlying glomerulopathy in CGN secondary to lupus, HSP nephritis, membranoproliferative glomerulonephritis, postinfectious GN, IgA nephropathy, or Goodpasture disease. Rare or absent findings by immunofluorescence and electron microscopy typify pauciimmune GN (Wegener disease and microscopic polyangiitis) and idiopathic crescentic GN.

CLINICAL MANIFESTATIONS

Most children present with acute nephritis (hematuria, some degree of renal insufficiency, and hypertension) and usually have concomitant proteinuria, often with nephrotic syndrome. Occasional patients present late in the course of disease with oliguric renal failure. Extrarenal manifestations, such as pulmonary involvement, joint symptoms, or skin lesions, can help lead to the diagnosis of the underlying systemic disease causing the CGN.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of CGN is made by biopsy. Delineation of the underlying etiology is reached by a combination of additional biopsy findings (described earlier), extrarenal symptoms and signs, and serologic testing, including evaluation of antinuclear and anti-DNA antibodies, serum complement levels, and ANCA. If the patient has no extrarenal manifestations and a negative serologic evaluation, and if the biopsy has no immune or electron microscopy deposits, the diagnosis is idiopathic, rapidly progressive CGN.

PROGNOSIS AND TREATMENT

Although the outcome is not uniformly positive, children with crescentic postinfectious GN can spontaneously recover. The natural course of CGN is far more severe in the setting of other etiologies, including the idiopathic category, and progression to end-stage renal failure within weeks to months from onset is common. Having a majority of fibrous crescents on a renal biopsy portends a poor prognosis, because the disease usually has progressed to irreversible injury. Although there are few controlled data, the consensus of most nephrologists is that the combination of high-dose corticosteroids and cyclophosphamide may be effective in preventing progressive renal failure in patients with systemic lupus erythematosus, HSP nephritis, Wegener granulomatosis, and IgA nephropathy if given early in the course when acute cellular crescents predominate. Although such therapy can also be effective in the other diseases causing RPGN, renal outcomes in those settings are less favorable. Progression to end-stage renal disease often occurs despite aggressive immunosuppressive therapy. In combination with immunosuppression, plasmapheresis has been reported to

benefit patients with Goodpasture disease. Plasmapheresis may also benefit patients with ANCA-associated CGN, in particular those with the most severe renal dysfunction at presentation. The possible benefits of plasmapheresis in other forms of RPGN are unclear.

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Chapter 517

Goodpasture Disease

Scott K. Van Why and Ellis D. Avner

Goodpasture disease is characterized by pulmonary hemorrhage and glomerulonephritis. The disease results from attack on these organs by antibodies directed against certain epitopes of type IV collagen, located within the alveolar basement membrane in the lung and glomerular basement membrane (GBM) in the kidney. The production of pathologic autoantibody against specific domains in type IV collagen is triggered by an acquired conformational change in α345NC1 hexamers, central structural elements in type IV collagen. The resulting structural alteration reveals neoepitopes that become the target of the pathogenic Goodpasture autoantibody.

PATHOLOGY

Kidney biopsy shows crescentic glomerulonephritis in most patients. Immunofluorescence microscopy demonstrates continuous linear deposition of immunoglobulin G along the GBM (Fig. 517-1).

CLINICAL MANIFESTATIONS

Goodpasture disease is rare in childhood. Patients usually present with hemoptysis from pulmonary hemorrhage that can be life-threatening. Concomitant renal manifestations include acute glomerulonephritis with hematuria, proteinuria, and hypertension, which usually follows a rapidly progressive course. Renal failure commonly develops within days to weeks of clinical presentation. Uncommonly, patients can have anti-GBM nephritis manifesting as isolated, rapidly progressive glomerulonephritis without pulmonary hemorrhage. In essentially all cases, serum anti-GBM antibody is present and complement C3 level is normal. Antineutrophilic cytoplasmic antibody levels can be found to be elevated along with the anti-GBM antibody; such patients doubly positive for these autoantibodies, who have severe disease at presentation, appear to have a more severe prognosis.

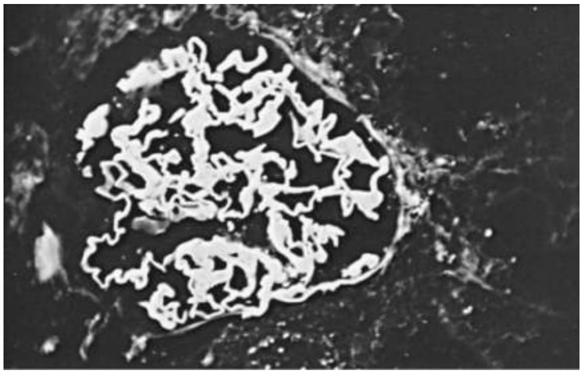

Figure 517-1 Immunofluorescence micrograph demonstrating the continuous linear staining of immunoglobulin G along the glomerular basement membrane in Goodpasture disease (×250).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is made by a combination of the clinical presentation of pulmonary hemorrhage with acute glomerulonephritis, the presence of serum antibodies directed against GBM (anti–type IV collagen in GBM), and characteristic renal biopsy findings. Other diseases that can cause a pulmonary-renal syndrome need to be considered and include systemic lupus erythematosus, Henoch-Schönlein purpura, granulomatosis with polyangiitis, nephrotic syndrome–associated pulmonary embolism, and microscopic polyangiitis. These diseases are ruled out by the absence of other characteristic clinical features, kidney biopsy findings, and negative serologic studies for antibodies against nuclear (antinuclear antibody), DNA (anti-dsDNA), and neutrophil cytoplasmic components (antineutrophilic cytoplasmic antibody).

PROGNOSIS AND TREATMENT

Untreated, the prognosis of Goodpasture disease is poor. The combination of high-dose intravenous methylprednisolone, cyclophosphamide, and plasmapheresis appears to improve survival. Nevertheless, patients who survive the pulmonary hemorrhage often progress to end-stage renal failure despite ongoing immunosuppressive therapy.

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Chapter 518

Hemolytic-Uremic Syndrome

Scott K. Van Why and Ellis D. Avner

Hemolytic-uremic syndrome (HUS) is a common cause of community-acquired acute kidney injury in young children. It is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency. HUS has clinical features in common with thrombotic thrombocytopenic purpura (TTP) (see Chapter 484.5). The etiology and pathophysiology of the more common forms of HUS clearly delineate childhood HUS as separate from idiopathic TTP.

ETIOLOGY

The various etiologies of HUS and other related thrombotic microangiopathies allow classification into infection-induced, genetic, medication- induced, and HUS associated with systemic diseases characterized by microvascular injury (Tables 518-1 and 518-2). The most common form of HUS is caused by toxin-producing *Escherichia coli* that causes prodromal acute enteritis and is commonly termed *diarrhea-associated HUS*. In the subcontinent of Asia and in southern Africa, the toxin of *Shigella dysenteriae* type 1 is causative, whereas in Western countries, verotoxin or Shiga-like toxin producing *E. coli* (STEC) is the usual cause.

Several serotypes of *E. coli* can produce the toxin; O157:H7 is most common in Europe and the Americas. A large epidemic of HUS in Europe was caused by Shiga toxin–producing *E. coli* O104:H4. The reservoir of STEC is the intestinal tract of domestic animals, usually cows. Disease commonly is transmitted by undercooked meat or unpasteurized (raw) milk and apple cider. Local outbreaks have followed ingestion of undercooked, contaminated hamburger or other foods cross-contaminated on unwashed cutting boards at fast food restaurants; contaminated municipal water supplies; petting farms; and swimming in contaminated ponds, lakes, or pools. With broad food distribution, wider epidemics have been traced to lettuce, raw spinach, and bean sprouts contaminated with STEC. Less often, STEC has been spread by person-to-person contact within families or child care centers. A rare but distinct entity of infection-triggered HUS is related

Table 518-1 Thrombotic Microangiopathies Overview and Classification

TMA associated with genetic or immune-mediated abnormalities of the complement system
Genetically determined factor H deficiency
Genetic membrane cofactor protein (CD46) abnormalities
Complement factor 1 deficiency
Gain-of-function mutations of complement factor B
Complement C3 mutations
Acquired anti-C3 autoantibodies
Immune-mediated factor H deficiency
TTP associated with genetic or immune-mediated ADAMTS13 abnormalities
Infectious disease–associated TMA
STEC-HUS
Neuraminidase (pneumococcal)–associated TMA
HIV infection
Systemic disease–associated TMA
Antiphospholipid syndrome
Systemic lupus erythematosus
Scleroderma
Malignant hypertension
Malignancy
Pregnancy-associated TMA
TTP
Hemolysis, elevated liver enzymes, and low platelet count syndrome
Postpartum HUS
Drug-associated TMA (>50 substances reported)
Mitomycin
Quinidine
Ticlopidine
Clopidogrel
Calcineurin inhibitors
Oral contraception
Gemcitabine
Anti-VEGF
Metabolic disease–associated TMA
Deficiency in cobalamin C metabolism HUS
Transplant-associated TMA
De novo HUS
Recurrent posttransplantation HUS

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; HIV, human immunodeficiency virus; HUS, hemolytic-uremic syndrome; STEC-HUS, Shiga toxin–producing *Escherichia coli* hemolytic-uremic syndrome; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; VEGF, vascular endothelial growth factor.

From Ruggenenti P, Cravedi P, Remuzzi G: Thrombotic microangiopathies including hemolytic uremic syndrome. In Floege J, Johnson R, Feehally J, editors: Comprehensive Clinical Nephrology, vol 1, St. Louis, 2010, Elsevier Saunders, pp. 344–355.

to **neuraminidase-producing** *Streptococcus pneumoniae*. HUS develops during acute infection with this organism, typically manifesting as pneumonia with empyema. A thrombotic microangiopathy, similar to HUS or TTP, also can occur in patients with untreated HIV infection.

Genetic forms of HUS (atypical, nondiarrheal) compose the second major category of the disease (see Tables 518-1 and 518-2). Inherited deficiencies of either von Willebrand factor–cleaving protease (ADAMTS13) or complement factor H, I, or B, and defects in vitamin B_{12} metabolism can cause HUS. A specific genetic defect has not been identified in approximately 50% of familial cases transmitted in classic mendelian autosomal dominant or recessive patterns. A major feature characteristic of genetic forms of HUS is the absence of a preceding diarrhea prodrome. Genetic forms of HUS can be indolent and unremitting once they become manifest, or they can have a relapsing pattern precipitated by an infectious illness. The latter feature likely explains the association of many infectious agents with HUS, particularly in reports published before the recognition of the unique pathophysiology of STEC and neuraminidase-producing pneumococci in causing HUS.

HUS can be superimposed on any disease associated with microvascular injury, including malignant hypertension, systemic lupus erythematosus, and antiphospholipid syndrome (see Chapter 484.4). It can also occur following bone marrow or solid organ transplantation, and may be triggered by the use of the calcineurin inhibitors cyclosporine and tacrolimus in that setting. Several other medications also can induce HUS (see Table 518-1).

PATHOLOGY

Kidney biopsies are only rarely performed in HUS because the diagnosis is usually established by clinical criteria and the risks of biopsy are significant during the active phase of the disease. Early glomerular changes include thickening of the capillary walls caused by swelling of endothelial cells and accumulation of fibrillar material between endothelial cells and the underlying basement membrane, causing narrowing of the capillary lumens. Platelet–fibrin thrombi are often seen in glomerular capillaries. Thrombi are also seen in afferent arterioles and small arteries with fibrinoid necrosis of the arterial wall, leading to renal cortical necrosis from vascular occlusion. Late findings include glomerular sclerosis and obsolescence secondary to either severe direct glomerular involvement or glomerular ischemia from arteriolar involvement.

PATHOGENESIS

Microvascular injury with endothelial cell damage is characteristic of all forms of HUS. In the diarrhea-associated form of HUS, enteropathic organisms produce either Shiga toxin or the highly homologous Shiga-like verotoxin both of which directly cause endothelial cell damage. Shiga toxin can directly activate platelets to promote their aggregation. In pneumococcal-associated HUS, neuraminidase cleaves sialic acid on membranes of endothelial cells, red cells, and platelets to reveal the underlying cryptic Thomsen-Friedenreich (T) antigen. Endogenous immunoglobulin M (IgM) recognizes the T antigen and triggers the microvascular angiopathy.

The familial recessive and dominant forms of HUS, including the inherited deficiencies of ADAMTS13 and regulators of the complement cascade, probably predispose patients to developing HUS but do not cause the disease per se, because these patients might not develop HUS until later childhood or even adulthood. In such cases, HUS is often triggered by an inciting event such as an infectious disease. The absence of ADAMTS13 impairs cleavage of von Willebrand factor multimers, which enhances platelet aggregation. Factor H plays a central role in complement regulation, primarily arresting amplification and propagation of complement activation. It is possible that mild endothelial injury that would normally resolve instead evolves to an aggressive microangiopathy because of the inherited deficiencies of these factors.

In each form of HUS, capillary and arteriolar endothelial injury in the kidney leads to localized thrombosis, particularly in glomeruli, causing a direct decrease in glomerular filtration. Progressive platelet aggregation in the areas of microvascular injury results in consumptive thrombocytopenia. Microangiopathic hemolytic anemia results from mechanical damage to red blood cells as they pass through the damaged and thrombotic microvasculature.

CLINICAL MANIFESTATIONS

HUS is most common in preschool and school-age children, but it can occur in adolescents and adults. In HUS caused by toxigenic *E. coli*, onset of HUS occurs a few days after onset of gastroenteritis with fever, vomiting, abdominal pain, and diarrhea. The prodromal intestinal symptoms may be severe and require hospitalization, but they can also be relatively mild and considered trivial. The diarrhea is often bloody, but not necessarily so. Following the prodromal illness, the sudden onset of pallor, irritability, weakness, and lethargy heralds the onset of HUS. Oliguria can be present in early stages but may be masked by ongoing diarrhea, because the prodromal enteritis often overlaps the onset of HUS, particularly with ingestion of large doses of toxin. Thus, patients with HUS can present with either significant dehydration or volume overload, depending on whether the enteritis or renal

Table 518-2 Genetic Abnormalities and Clinical Outcome in Patients with Atypical Hemolytic-Uremic Syndrome

GENE	PROTEIN AFFECTED	MAIN EFFECT	FREQUENCY (%)	RESPONSE TO SHORT-TERM PLASMA THERAPY*	LONG-TERM OUTCOME†	OUTCOME OF KIDNEY TRANSPLANTATION
CFH	Factor H	No binding to endothelium	20-30	Rate of remission: 60% (dose and timing dependent)	Rate of death or ESRD: 70-80%	Rate of recurrence: 80-90%‡
CFHR1/3	Factor HR1, R3	Anti–factor H antibodies	6	Rate of remission 70-80% (plasma exchange combined with immunosuppression)	Rate of ESRD: 30-40%	Rate of recurrence: 20%§
MCP	Membrane cofactor protein	No surface expression	10-15	No definitive indication for therapy	Rate of death or ESRD: <20%	Rate of recurrence: 15-20%§
CFI	Factor I	Low level or low cofactor activity	4-10	Rate of remission: 30-40%	Rate of death or ESRD: 60-70%	Rate of recurrence: 70-80%‡
CFB	Factor B	C3 convertase stabilization	1-2	Rate of remission: 30%	Rate of death or ESRD: 70%	Recurrence in one case
C3	Complement C3	Resistance to C3b inactivation	5-10	Rate of remission: 40-50%	Rate of death or ESRD: 60%	Rate of recurrence: 40-50%
THBD	Thrombomodulin	Reduced C3b inactivation	5	Rate of remission: 60%	Rate of death or ESRD: 60%	Recurrence in 1 patient

*Remission was defined as either complete remission or partial remission (i.e., hematologic remission with renal sequelae).
†The long-term outcome was defined as the outcome 5-10 yr after onset.
‡Patients in this category were eligible for combined liver and kidney transplantation.
§Patients in this category were eligible for single kidney transplantation.
ESRD, end-stage renal disease.
From Norris M, Remuzzi G: Atypical hemolytic-uremic syndrome, N Engl J Med *361:1676–1687, 2009.*

insufficiency from HUS predominates, and the amount of fluid that has been administered.

Patients with pneumococci-associated HUS usually are ill with pneumonia, empyema, and bacteremia when they develop HUS. Onset can be insidious in patients with the genetic forms of HUS, with HUS triggered by a variety of illnesses, including mild, nonspecific gastroenteritis or respiratory tract infections.

HUS can be relatively mild, or can progress to a severe and fatal multisystem disease. Leukocytosis, severe prodromal enteritis, hyponatremia, and antibiotic use portend a severe course, but no presenting features reliably predict the severity of HUS in any given patient. Patients with HUS who appear mildly affected at presentation can rapidly develop severe, multisystem, life-threatening complications. Renal insufficiency can be mild but also can rapidly evolve into severe oliguric or anuric renal failure. The combination of rapidly developing renal failure and severe hemolysis can result in life-threatening hyperkalemia. Volume overload, hypertension, and severe anemia can all develop soon after onset of HUS, and together can precipitate heart failure. Direct cardiac involvement is rare, but pericarditis, myocardial dysfunction, or arrhythmias can occur without predisposing features of hypertension, volume overload, or electrolyte abnormalities.

The majority of patients with HUS have some central nervous system (CNS) involvement. Most have mild manifestations, with significant irritability, lethargy, or nonspecific encephalopathic features. Severe CNS involvement occurs in ≤20% of cases. Seizures and significant encephalopathy are the most common manifestations in those with severe CNS involvement, resulting from focal ischemia secondary to microvascular CNS thrombosis. Small infarctions in the basal ganglion and cerebral cortex have also been reported, but large strokes and intracranial hemorrhage are rare. Hypertension may produce an encephalopathy and seizures. Intestinal complications can be protean and include severe inflammatory colitis, ischemic enteritis, bowel perforation, intussusception, and pancreatitis. Patients can develop petechiae, but significant or severe bleeding is rare despite very low platelet counts.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is made by the combination of microangiopathic hemolytic anemia with schistocytes, thrombocytopenia, and some degree of kidney involvement. The anemia can be mild at presentation, but rapidly progresses. Thrombocytopenia is an invariable finding in the acute phase, with platelet counts usually 20,000-100,000/mm^3. Partial thromboplastin and prothrombin times are usually normal. The Coombs test is negative, with the exception of pneumococci-induced HUS, where the Coombs test is usually positive. Leukocytosis is often present and significant. Urinalysis typically shows microscopic hematuria and low-grade proteinuria. The renal insufficiency can vary from mild elevations in serum blood urea nitrogen and creatinine to acute, anuric kidney failure.

The etiology of HUS is often clear with the presence of a diarrheal prodrome or pneumococcal infection. The presence or absence of toxigenic organisms on stool culture has little role in making the diagnosis of diarrhea-associated, enteropathic HUS. Only a minority of patients infected with those organisms develops HUS, and the organisms that cause HUS may be rapidly cleared. Therefore, the stool culture is often negative in patients who have diarrhea-associated HUS. If no history of diarrheal prodrome or pneumococcal infection is obtained, then evaluation for genetic forms of HUS should be considered, because those patients are at risk for recurrence, have a severe prognosis, and can benefit from different therapy. Other causes of acute kidney injury associated with a microangiopathic hemolytic anemia and thrombocytopenia should be considered and excluded, such as systemic lupus erythematosus, malignant hypertension, and bilateral renal vein thrombosis (see Table 518-1). A kidney biopsy is rarely indicated to diagnose HUS.

PROGNOSIS AND TREATMENT

With early recognition and intensive supportive care, the mortality for diarrhea-associated HUS is <5% in most major medical centers. Up to half of patients may require dialysis support during the acute phase of the disease. Most recover renal function completely, but of surviving patients, 5% remain dependent on dialysis, and up to 30% are left with some degree of chronic renal insufficiency. The prognosis for HUS not associated with diarrhea is more severe. Pneumococci-associated HUS causes increased patient morbidity, with mortality reported as 20%. The familial, genetic forms of HUS can be insidiously progressive or relapsing diseases and have a poor prognosis (see Table

518-2). Identification of specific factor deficiencies in some of these genetic forms provides opportunity for directed therapy to improve outcome.

The primary approach that has substantially improved acute outcome in HUS is early recognition of the disease, monitoring for potential complications, and meticulous supportive care. Supportive care includes careful management of fluid and electrolytes, including prompt correction of volume deficit, control of hypertension, and early institution of dialysis if the patient becomes significantly oliguric or anuric, particularly with hyperkalemia. Early intravenous volume expansion before the onset of oligo anuria may be nephroprotective in diarrhea-associated HUS. Red cell transfusions are usually required as hemolysis can be brisk and recurrent until the active phase of the disease has resolved. In pneumococci-associated HUS, it is critical that **any administered red cells be washed** before transfusion to remove residual plasma, because endogenous IgM directed against the revealed T antigen can play a role in accelerating the pathogenesis of the disease. Platelets should generally not be administered, regardless of platelet count, to patients with HUS because they are rapidly consumed by the active coagulation and theoretically can worsen the clinical course. Despite low platelet counts, serious bleeding is very rare in patients with HUS.

There is no evidence that any therapy directed at arresting the disease process of the most common, diarrhea-associated form of HUS provides benefit, and some can cause harm. Attempts have been made using anticoagulants, antiplatelet agents, fibrinolytic therapy, plasma therapy, immune globulin, and antibiotics. Anticoagulation, antiplatelet, and fibrinolytic therapies are specifically contraindicated because they increase the risk of serious hemorrhage. Antibiotic therapy to clear enteric toxigenic organisms (STEC) can result in increased toxin release, potentially exacerbating the disease, and therefore is not recommended. However, prompt treatment of causative pneumococcal infection is important. The European experience with *E. coli* O104:H4 in adults who were treated with azithromycin demonstrated more rapid elimination of the organism. Furthermore, in vitro evidence suggests that meropenem, rifaximin, and azithromycin downregulate the release and expression of Shiga toxin. Nonetheless in children with *E. coli* O157:H7–associated HUS, antibiotics are considered contraindicated.

Plasma infusion or plasmapheresis has been proposed for patients suffering severe manifestations of HUS with serious CNS involvement. There are no controlled data demonstrating the effectiveness of this approach, and it is specifically contraindicated in those with pneumococcal-associated HUS as it could exacerbate the disease. The use of plasma therapy in STEC-HUS was one of many treatment strategies during one of the largest reported outbreaks of STEC-HUS, which occurred in Europe in 2011. This outbreak was caused by an uncommon serotype (O104:H4) that had unique virulence factors. Thought initially to cause more severe disease, it differed epidemiologically from other STEC-HUS serotypes by affecting primarily healthy adults, rather than the usual pattern of affecting children and the elderly. Treatment in this epidemic included plasma exchange in most of the adult patients, as well as the use of eculizumab.

Eculizumab is an anti-C5 antibody that inhibits complement activation, a pathway that contributes to active disease in some forms of atypical familial HUS; this pathway may contribute to the process in STEC-HUS. Eculizumab is FDA approved for the treatment of atypical HUS. Because of the risk of meningococcal disease in patients with congenital defects in terminal complement components, it is recommended to give the meningococcal vaccine prior to giving eculizumab (if the patient has not been primarily immunized). While initial reports suggested that eculizumab provided benefit in patients with diarrhea-associated HUS, subsequent systematic analysis showed no benefit from either plasma exchange or eculizumab.

Plasma therapy can be of substantial benefit to patients with identified deficits of ADAMTS13 or factor H. It may also be considered in patients with other genetic forms of HUS, such as the undefined familial (recessive or dominant) form or sporadic but recurrent HUS. In contrast to its use in STEC-HUS, eculizumab shows great promise in treatment of atypical HUS, including HUS occurring following renal transplantation. Whether it should be combined with plasma therapy, or used as a primary treatment of atypical HUS, is still undetermined.

Most patients with diarrhea-associated HUS recover completely with little risk of long-term sequelae. Patients with hypertension, any level of renal insufficiency, or residual urinary abnormalities persisting a year after an episode of diarrhea-positive HUS (particularly significant proteinuria) require careful follow-up. Patients who have recovered completely with no residual urinary abnormalities after a yr are unlikely to manifest long-term sequelae. Because of some reports of late sequelae in such patients, annual examinations with a primary physician are still warranted.

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Chapter 519

Upper Urinary Tract Causes of Hematuria

519.1 Interstitial Nephritis

See Chapter 523.

519.2 Toxic Nephropathy

See Chapter 533.

519.3 Cortical Necrosis

See Chapter 534.

519.4 Pyelonephritis

See Chapter 538.

519.5 Nephrocalcinosis

See Chapter 547.

519.6 Vascular Abnormalities

Craig C. Porter and Ellis D. Avner

Hemangiomas, hemangiolymphangiomas, angiomyomas, and arteriovenous malformations of the kidneys and lower urinary tract are rare causes of hematuria. They can present clinically with microscopic hematuria or gross hematuria with clots. When associated cutaneous vascular malformations are present, they can offer a clue to these underlying causes of hematuria. Renal colic can develop with any upper tract vascular abnormality that obstructs urinary drainage, induces an inflammatory response, or distends the renal capsule. The diagnosis may be confirmed by angiography or endoscopy.

Unilateral bleeding of varicose veins of the left ureter, resulting from compression of the left renal vein between the aorta and superior mesenteric artery (mesoaortic compression), is referred to as the **nutcracker syndrome.** Patients with this syndrome typically present with

persistent microscopic hematuria (and occasionally, recurrent gross hematuria) that may be accompanied by proteinuria, left lower abdominal pain, left flank pain, or orthostatic hypotension. Diagnosis requires a high degree of suspicion and is confirmed by Doppler ultrasonography, CT, phlebography of the left renal vein, or magnetic resonance angiography.

Bibliography is available at Expert Consult.

519.7 Renal Vein Thrombosis

Craig C. Porter and Ellis D. Avner

EPIDEMIOLOGY

Renal vein thrombosis (RVT) occurs in 2 distinct clinical settings: (1) In newborns and infants, RVT is commonly associated with asphyxia, dehydration, shock, sepsis, congenital hypercoagulable states, and maternal diabetes; and (2) in older children, RVT is seen in patients with nephrotic syndrome, cyanotic heart disease, inherited hypercoagulable states, sepsis, following kidney transplantation, and following exposure to angiographic contrast agents.

PATHOGENESIS

RVT begins in the intrarenal venous circulation and can then extend to the main renal vein and even the inferior vena cava. Thrombus formation is mediated by endothelial cell injury resulting from hypoxia, endotoxin, or contrast media. Other contributing factors include hypercoagulability from either nephrotic syndrome or mutations in genes that encode clotting factors (i.e., factor V Leiden deficiency); hypovolemia and decreased venous blood flow associated with septic shock, dehydration, or nephrotic syndrome; and intravascular sludging caused by polycythemia.

CLINICAL MANIFESTATIONS

The development of RVT is classically heralded by the sudden onset of gross hematuria and unilateral or bilateral flank masses. However, patients can also present with any combination of microscopic hematuria, flank pain, hypertension, or a microangiopathic hemolytic anemia with thrombocytopenia or oliguria. RVT is usually unilateral. Bilateral RVT results in acute kidney failure.

DIAGNOSIS

The diagnosis of RVT is suggested by the development of hematuria and flank masses in patients seen in the high-risk clinical settings or with the predisposing clinical features noted above. Ultrasonography shows marked renal enlargement, and radionuclide studies reveal little or no renal function in the affected kidney(s). Doppler flow studies of the inferior vena cava and renal vein confirm the diagnosis. Contrast studies should be avoided to minimize the risk of further vascular damage.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of RVT includes other causes of hematuria that are associated with rapid development of microangiopathic hemolytic anemia or enlargement of the kidney(s). These include hemolytic-uremic syndrome, hydronephrosis, polycystic kidney disease, Wilms tumor, and intrarenal abscess or hematoma. All patients should be evaluated for congenital and acquired hypercoagulable states.

TREATMENT

The primary treatment of RVT starts with aggressive supportive intensive care, including correction of fluid and electrolyte imbalance and treatment of renal insufficiency. The American College of Chest Physicians recommends that the additional initial treatment of bilateral RVT should include tissue plasminogen activator and unfractionated heparin followed by continued anticoagulation with unfractionated or low-molecular-weight heparin. Treatment recommendations for unilateral RVT with inferior vena cava extension include either unfractionated or low-molecular-weight heparin. There is no consensus as to whether unilateral RVT without extension should be managed with heparin or with supportive therapy alone. Aggressive treatment with thrombolytic agents in all of these clinical settings, as well as antithrombotic prevention of patients with documented thrombotic risk, remains controversial despite such recommendations given the significant risks of bleeding. Evidence-based data, particularly in children, do not exist despite such “best-practice” recommendations. Children with severe hypertension secondary to RVT who are refractory to antihypertensive medications may require nephrectomy.

PROGNOSIS

Perinatal mortality from RVT has decreased significantly over the past 20 yr. Partial or complete renal atrophy is a common sequela of RVT in the neonate, leading to an increased risk of renal insufficiency, renal tubular dysfunction, and systemic hypertension. These complications are also seen in older children. However, recovery of renal function is not uncommon in older children with RVT resulting from nephrotic syndrome or cyanotic heart disease with correction of the underlying etiology.

Bibliography is available at Expert Consult.

519.8 Idiopathic Hypercalciuria

Craig C. Porter and Ellis D. Avner

Idiopathic hypercalciuria, which may be inherited as an autosomal dominant disorder, can clinically present as recurrent gross hematuria, persistent microscopic hematuria, dysuria, or abdominal pain in the absence of stone formation. Hypercalciuria can also accompany conditions resulting in hypercalcemia, such as hyperparathyroidism, vitamin D intoxication, immobilization, and sarcoidosis. Hypercalciuria may be associated with Cushing syndrome, corticosteroid therapy, tubular dysfunction secondary to Fanconi syndrome (Wilson disease, oculocerebrorenal syndrome), Williams syndrome, distal renal tubular acidosis, or Bartter syndrome (see Chapter 531). Hypercalciuria may also be seen in patients with **Dent disease,** which is an X-linked form of nephrolithiasis associated with hypophosphatemic rickets. Although microcrystal formation with consequent tissue irritation is believed to mediate symptoms, the precise mechanism by which hypercalciuria causes hematuria or dysuria is unknown.

DIAGNOSIS

Hypercalciuria is diagnosed by a 24 hr urinary calcium excretion >4 mg/kg. A screening test for hypercalciuria may be performed on a random urine specimen by measuring the calcium and creatinine concentrations. A spot urine calcium : creatinine ratio (mg/dL : mg/dL) >0.2 suggests hypercalciuria in an older child. Normal ratios may be as high as 0.8 in infants <7 mo of age.

TREATMENT

Left untreated, hypercalciuria leads to nephrolithiasis in approximately 15% of cases. Hypercalciuria has also been associated with an increased risk for development of low bone mineral density as well as an increased incidence of urinary tract infections. Idiopathic hypercalciuria has been identified as a risk factor in 40% of children with kidney stones, and a low urinary citrate level has been associated as a risk factor in approximately 38% of this group. Oral thiazide diuretics can normalize urinary calcium excretion by stimulating calcium reabsorption in the proximal and distal tubules. Such therapy can lead to resolution of gross hematuria or dysuria and can prevent nephrolithiasis. The precise indications for thiazide treatment (including its duration if initiated) remain controversial.

In patients with persistent gross hematuria or dysuria, therapy is initiated with hydrochlorothiazide at a dose of 1-2 mg/kg/24 hr as a single morning dose. The dose is titrated upward until the 24 hr urinary calcium excretion is <4 mg/kg and clinical manifestations

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resolve. After 1 yr of treatment, hydrochlorothiazide is usually discontinued, but may be resumed if gross hematuria, nephrolithiasis, or dysuria recurs. During hydrochlorothiazide therapy, the serum potassium level should be monitored periodically to avoid hypokalemia. **Potassium citrate** at a dose of 1 mEq/kg/24 hr may also be beneficial, particularly in patients with low urinary citrate excretion and symptomatic dysuria.

Sodium restriction is important because urinary calcium excretion parallels sodium excretion. Importantly, *dietary calcium restriction is not recommended* (except in children with massive calcium intake >250% of recommended dietary allowance by dietary history) because calcium is a critical requirement for growth, and no evidence supports a relationship between decreased calcium intake and decreased urinary calcium levels. This is particularly important given the association of hypercalciuria in some patients with reduced bone mineral density. A number of uncontrolled, small-scale studies support a role for bisphosphonate therapy, which leads to a reduction in urinary calcium excretion and improvement in bone mineral density. Controlled studies are necessary to establish a clear role for such therapy in children with hypercalciuria.

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Chapter 520
Hematologic Diseases Causing Hematuria

520.1 Sickle Cell Nephropathy

Craig C. Porter and Ellis D. Avner

Gross or microscopic hematuria may be seen in children with sickle cell disease or sickle trait. Hematuria tends to resolve spontaneously in the majority of children (see Chapters 462.1 and 462.2). With the exception of an association with renal cell carcinoma, clinically apparent renal involvement occurs more commonly in patients with sickle cell disease than in those with sickle cell trait.

ETIOLOGY

The renal manifestations of sickle cell nephropathy (SSN) are generally related to microthrombosis secondary to sickling in the relatively hypoxic, acidic, hypertonic renal medulla where vascular stasis is present. Analgesic use, volume depletion with consequent prerenal failure, infection, and iron-related hepatic disease are independent contributing factors. Glomerular hyperfiltration, mediated by the intrarenal production of prostaglandins and synthesis of nitric oxide, is involved in the pathogenesis of proteinuria and kidney failure in SSN.

PATHOLOGY

Ischemia, papillary necrosis, and interstitial fibrosis are common pathologic findings in SSN. The specific sickle cell glomerular lesion consists of glomerular hypertrophy, with glomerulomegaly and distended capillaries. In addition, a variety of glomerular lesions are also found in SSN; most commonly these include focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and thrombotic microangiopathy. The pathophysiology of these specific glomerulonephritic lesions in SSN is poorly understood but is probably associated with the same factors that produce idiopathic or secondary disease as previously described (see Chapters 511-513).

CLINICAL MANIFESTATIONS

Clinical manifestations of SSN include polyuria caused by a urinary concentrating defect, renal tubular acidosis, and proteinuria associated with the glomerular lesions noted above.

Approximately 20-30% of patients with sickle cell disease develop proteinuria. Nephrotic-range proteinuria with or without clinically apparent nephrotic syndrome occurs in up to 30% of patients with SSN, and when present generally heralds progressive renal failure.

TREATMENT

Tubular manifestations have no specific treatment other than those recommended generally for patients with sickle cell disease. However, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor inhibitors can be used to effect a significant reduction in urine protein excretion in patients with daily urine protein excretion exceeding 500 mg, and may slow progression of renal failure. Gross hematuria secondary to papillary necrosis may respond to treatment with ε-aminocaproic acid or desmopressin acetate. Hydroxyurea and newer treatments for sickle cell disease (see Chapter 462.1) have decreased the manifestations of SSN in proportion to the other complications of the primary hemoglobinopathy.

PROGNOSIS

SSN can eventually lead to hypertension, renal insufficiency, and progressive kidney failure. Dialysis and eventual kidney transplantation are successful treatment modalities when kidney failure is irreversible.

Bibliography is available at Expert Consult.

520.2 Coagulopathies and Thrombocytopenia

Craig C. Porter and Ellis D. Avner

Gross or microscopic hematuria may be associated with inherited or acquired disorders of coagulation (hemophilia, disseminated intravascular coagulation, thrombocytopenia). In these cases, however, hematuria is not usually the presenting complaint or a major factor affecting clinical management of outcome (see Chapters 475-484).

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Chapter 521

Anatomic Abnormalities Associated with Hematuria

521.1 Congenital Anomalies

Craig C. Porter and Ellis D. Avner

Gross or microscopic hematuria may be associated with many different types of malformations of the urinary tract. The sudden onset of gross hematuria after minor trauma to the flank is often associated with ureteropelvic junction obstruction, cystic kidneys, or enlarged kidneys from any cause (see Chapter 537).

521.2 Autosomal Recessive Polycystic Kidney Disease

Craig C. Porter and Ellis D. Avner

Also previously referred to as **infantile polycystic disease,** autosomal recessive polycystic kidney disease (ARPKD) is an autosomal recessive disorder occurring with an incidence of 1 : 10,000 to 1 : 40,000, and a gene carrier rate in the general population of 1/70. The gene for ARPKD *(PKHD1 [polycystic kidney and hepatic disease])* encodes fibrocystin, a large protein (>4,000 amino acids) with multiple isoforms.

PATHOLOGY

Both kidneys are markedly enlarged and grossly show innumerable cysts throughout the cortex and medulla. Microscopic studies demonstrate dilated, ectatic collecting ducts radiating from the medulla to the cortex, although transient proximal tubule cysts have been reported in the fetus. Development of progressive interstitial fibrosis and tubular atrophy during advanced stages of disease eventually leads to renal failure. ARPKD causes dual-organ disease and should be considered as *ARPKD/congenital hepatic fibrosis*. Liver involvement is characterized by a basic ductal plate abnormality that leads to bile duct proliferation and ectasia, as well as progressive hepatic fibrosis.

PATHOGENESIS

Fibrocystin may form a multimeric complex with proteins of other primary genetic cystic diseases. It appears that altered intracellular signaling from these complexes, located at epithelial apical cell surfaces, intercellular junctions, and basolateral cell surfaces in association with the focal adhesion complex, is a critical feature of disease pathophysiology.

A large number of mutations in *PKHD1* (without identified specific "hot spots") cause disease, and the same mutation can give variable degrees of disease severity in the same family. This clinical observation is consistent with preclinical data demonstrating many environmental and unknown genetic factors affecting disease expression. The false-negative rate for genetic diagnosis is approximately 10%. Limited available information suggests only gross genotype-phenotype correlation: mutations that modify fibrocystin appear to cause less-severe disease than those that truncate fibrocystin.

CLINICAL MANIFESTATIONS

The typical child presents with bilateral flank masses during the neonatal period or in early infancy. ARPKD may be associated with oligohydramnios, pulmonary hypoplasia, respiratory distress, and spontaneous pneumothorax in the neonatal period. Perinatal demise (approximately 25-30%) appears to be associated with truncating mutations. Components of the oligohydramnios complex (Potter syndrome), including low-set ears, micrognathia, flattened nose, limb-positioning defects, and intrauterine growth restriction, may be present at death from pulmonary hypoplasia. Hypertension is usually noted within the first few weeks of life, is often severe, and requires aggressive multidrug therapy for control. Oliguria and acute renal failure are uncommon, but transient hyponatremia, often in the presence of acute renal failure, often responds to diuresis. Renal function is usually impaired but may be initially normal in 20-30% of patients. Approximately 50% of patients with a neonatal-perinatal presentation develop end-stage renal disease (ESRD) by age 10 yr.

ARPKD is increasingly recognized in infants (and, rarely, in adolescents and young adults) with a mixed renal-hepatic clinical picture. Such children and young adults often present with predominantly hepatic manifestations in combination with variable degrees of renal disease. Hepatic disease manifests as portal hypertension, hepatosplenomegaly, gastroesophageal varices, episodes of ascending cholangitis, prominent cutaneous periumbilical veins, reversal of portal vein flow, and thrombocytopenia. Renal findings in patients with a hepatic presentation may range from asymptomatic abnormal renal ultrasonography to systemic hypertension and renal insufficiency. In the newborn, clinical evidence of liver disease by radiologic or clinical laboratory assessment is present in approximately 45% of children and believed to be universal by microscopic evaluation. Natural history studies of ARPKD patients presenting as infants and young children have classified this group in terms of the severity of their dual-organ phenotype: 40% severe renal/severe kidney and 20% of each of the following—severe kidney/mild liver, severe liver/mild kidney, and mild kidney/mild liver.

DIAGNOSIS

The diagnosis of ARPKD is strongly suggested by bilateral palpable flank masses in an infant with pulmonary hypoplasia, oligohydramnios, and hypertension and the absence of renal cysts by sonography of the parents (Fig. 521-1). Markedly enlarged and uniformly hyperechogenic kidneys with poor corticomedullary differentiation are commonly seen on ultrasonography (Fig. 521-2). The diagnosis is supported by clinical and laboratory signs of hepatic fibrosis, pathologic findings of ductal plate abnormalities seen on liver biopsy, anatomic and pathologic proof of ARPKD in a sibling, or parental consanguinity. The diagnosis can be confirmed by genetic testing. The differential diagnosis includes other causes of bilateral renal enlargement and/or cysts, such as multicystic dysplasia, hydronephrosis, Wilms tumor, and bilateral renal vein thrombosis (Tables 521-1 and 521-2).

Nephronophthisis, an autosomal recessive disorder with renal fibrosis, tubular atrophy, and cyst formation is a common cause of ESRD in children and adolescents (Tables 521-1 and 521-2). Associated external findings include retinal degeneration (Senior-Loken syndrome), cerebellar ataxia (Joubert syndrome), and hepatic fibrosis (Boichis disease). Symptoms include polyuria (salt wasting, poor concentrating ability), failure to thrive, and anemia. Hypertension and edema are seen later when ESRD develops. Prenatal diagnostic testing using genetic linkage analysis or direct mutation analysis is available in families with a previously affected child.

Preimplantation genetic diagnosis with in vitro fertilization may avoid the birth of another affected child with ARPKD.

TREATMENT

The current treatment of ARPKD is supportive. Aggressive ventilatory support is often necessary in the neonatal period secondary to pulmonary hypoplasia, hypoventilation, and the respiratory illnesses of prematurity. Careful management of hypertension (angiotensin-converting enzyme inhibitors), fluid and electrolyte abnormalities, osteopenia, and clinical manifestations of renal insufficiency is essential. Children with severe respiratory failure or feeding intolerance from enlarged kidneys can require unilateral or, more commonly, bilateral nephrectomies, prompting the need for renal replacement therapy. For many children approaching ESRD therapy, significant portal hypertension is present. This in combination with the dramatic improvement in liver transplantation survival has led to consideration of dual renal and hepatic transplantation in a carefully selected group of patients. Dual transplantation thus avoids the later development of end-stage liver disease despite successful renal transplantation.

PROGNOSIS

Mortality has improved dramatically, although approximately 30% of patients die in the neonatal period from complications of pulmonary hypoplasia. Neonatal respiratory support and renal replacement therapies have increased the 10 yr survival of children surviving beyond the 1st yr of life to >80%. Fifteen-year survival is currently estimated at 70-80%. Consideration of dual renal and hepatic transplantation and the development of disease-specific therapies for pediatric clinical trials will further positively impact the natural history of ARPKD. An important resource for families of patients is the ARPKD/CHF Alliance (**www.arpkdchf.org**).

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Table 521-1 Comparison of Clinical Features of Cystic Kidney Diseases

DISEASE	INHERITANCE	FREQUENCY	GENE PRODUCT	AGE OF ONSET	CYST ORIGIN	RENOMEGALY	CAUSE OF ESRD	OTHER MANIFESTATIONS
ADPKD	AD	400-1,000	Polycystin 1 Polycystin 2	20s and 30s; <2% before age 15 Occasional perinatal onset	Anywhere (including the Bowman capsule)	Yes	Yes	Liver cysts Cerebral aneurysms Hypertension Mitral valve prolapse Kidney stones UTIs
ARPKD	AR	6,000-10,000	Fibrocystin/ polyductin	First yr of life; perinatal onset	Distal nephron, CD	Yes	Yes	Hepatic fibrosis Pulmonary hypoplasia Hypertension
ACKD	No	90% of ESRD patients at 8 yr	None	Years after onset of ESRD	Proximal and distal tubules	Rarely	No	None
Simple cysts	No	50% in those older than 40 yr	None	Adulthood	Anywhere (usually cortical)	No	No	None
Nephronophthisis	AR	80,000	Nephrocystins (NPHP1-9)	Childhood or adolescence	Medullary DCT	No	Yes	Retinal degeneration; neurologic, skeletal, hepatic, cardiac malformations
MCKD	AD	Rare	Uromodulin, others	Adulthood	Medullary DCT	No	Yes	Hyperuricemia, gout
MSK	No	5,000-20,000	None	30s	Medullary CD	No	No	Kidney stones Hypercalciuria
Tuberous sclerosis	AD	10,000	Hamartin (TSC1) Tuberin (TSC2)	Childhood	Loop of Henle, DCT	Rarely	Rarely	Renal cell carcinoma Tubers, seizures Angiomyolipoma Hypertension
VHL syndrome	AD	40,000	VHL protein	20s	Cortical nephrons	Rarely	Rarely	Retinal angioma, CNS hemangioblastoma, renal cell carcinoma, pheochromocytoma
Oral-facial-digital syndrome	XD	250,000	OFD1 protein	Childhood or adulthood	Renal glomeruli	Rarely	Yes	Malformation of the face, oral cavity, and digits; liver cysts; mental retardation
Bardet-Biedl syndrome	AR	65,000-160,000	BBS 14	Adulthood	Renal calyces	Rarely	Yes	Syndactyly and polydactyly, obesity, retinal dystrophy, male hypogenitalism, hypertension, mental retardation

ACKD, acquired cystic kidney disease; AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; AR, autosomal recessive; ARPKD, autosomal recessive polycystic kidney disease; CD, collecting duct; CNS, central nervous system; DCT, distal convoluted tubule; ESRD, end-stage renal disease; MCKD, medullary cystic kidney disease; MSK, medullary sponge kidney; UTI, urinary tract infection; VHL, von Hippel-Lindau; XD, X-linked dominant.

From Arnaout MA: Cystic kidney disease. In Goldman L, Schafer AI, editors: Goldman's Cecil medicine, *ed 24, Philadelphia, 2012, Elsevier Saunders, Table 129-1, p. 796.*

Table 521-2 Autosomal Recessive Polycystic Kidney Disease and Hepatorenal Fibrocystic Disease Phenocopies

DISEASE	GENE(S)	RENAL DISEASE	HEPATIC DISEASE	SYSTEMIC FEATURES
ARPKD	*PKHD1*	Collecting duct dilation	CHF; Caroli disease	No
ADPKD	*PKD1; PKD2*	Cysts along entire nephron	Biliary cysts; CHF (rare)	Yes: adults
NPHP	*NPHP1-NPHP16*	Cysts at the corticomedullary junction	CHF	+/–
Joubert syndrome and related disorders	*JBTS1-JBTS20*	Cystic dysplasia; NPHP	CHF; Caroli disease	Yes
Bardet-Biedel syndrome	*BBS1-BBS18*	Cystic dysplasia; NPHP	CHF	Yes
Meckel-Gruber syndrome	*MKS1-MKS10*	Cystic dysplasia	CHF	Yes
Oral-facial-digital syndrome, type I	*OFD1*	Glomerular cysts	CHF (rare)	Yes
Glomerulocystic disease	*PKD1; HNF1B; UMOD*	Enlarged; normal or hypoplastic kidneys	CHF (with PKD1 mutations)	+/–
Jeune syndrome (asphyxiating thoracic dystrophy)	*IFT80 (ATD2) DYNC2H1 (ADT3) ADT1, ADT4, ADT5*	Cystic dysplasia	CHF; Caroli disease	Yes
Renal-hepatic-pancreatic dysplasia (Ivemark II)	*NPHP3, NEK8*	Cystic dysplasia	Intrahepatic biliary dysgenesis	Yes
Zellweger syndrome	*PEX1-3;5-6;10-11;13;14;16;19;26*	Renal cortical microcysts	Intrahepatic biliary dysgenesis	Yes

NPHP, Nephronophthisis. CHF, congenital hepatic fibrosis.

Modified from Guay-Woodford LM, Bissler JJ, Braun MC, et al: Consensus expert recommendations for the diagnosis and management of autosomal recessive polycystic kidney disease: Report of an international conference. J Pediatr *165:611-617, 2014.*

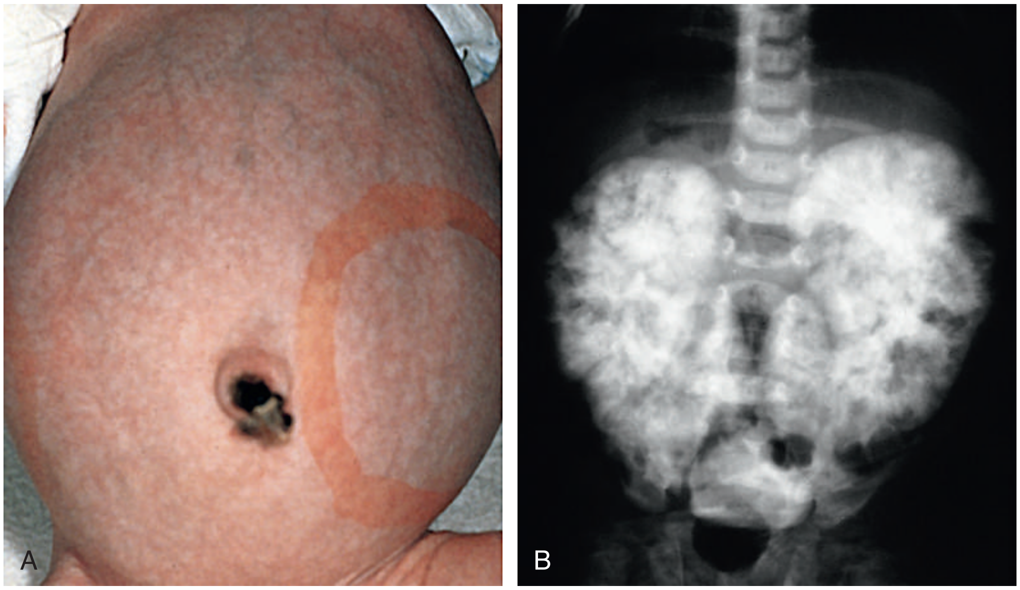

Figure 521-1 **Infant with infantile polycystic kidney disease. A,** This infant shows marked abdominal distention and bilaterally enlarged kidneys, as indicated by the *outlined area.* **B,** Intravenous pyelogram of the same patient shows the characteristic mottled nephrogram with brush-like medullary opacification secondary to retention of contrast material in dilated cortical and medullary collecting ducts. *(From Zitelli BJ, Davis HW, editors:* Atlas of pediatric physical diagnosis, *ed 4, St. Louis, 2002, Mosby, p. 470.)*

521.3 Autosomal Dominant Polycystic Kidney Disease

Craig C. Porter and Ellis D. Avner

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary human kidney disease, with an incidence of 1/400 to 1/1,000. It is a systemic disorder with possible cyst formation in multiple organs (liver, pancreas, spleen, brain) and the development of saccular cerebral aneurysms.

PATHOLOGY

Both kidneys are enlarged and show cortical and medullary cysts originating from all regions of the nephron.

PATHOGENESIS

Approximately 85% of patients with ADPKD have mutations that map to the *PKD1* gene on the short arm of chromosome 16, which encodes polycystin, a transmembrane glycoprotein. Another 10-15% of ADPKD mutations map to the *PKD2* gene on the long arm of chromosome 4, which encodes polycystin 2, a proposed nonselective cation channel.

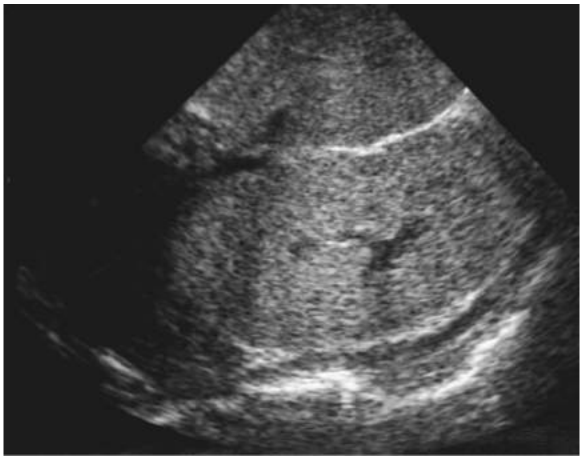

Figure 521-2 Ultrasound examination of a neonate with autosomal recessive polycystic kidney disease demonstrating renal enlargement (9 cm) and increased diffuse echogenicity with complete loss of corticomedullary differentiation resulting from multiple small cystic interfaces.

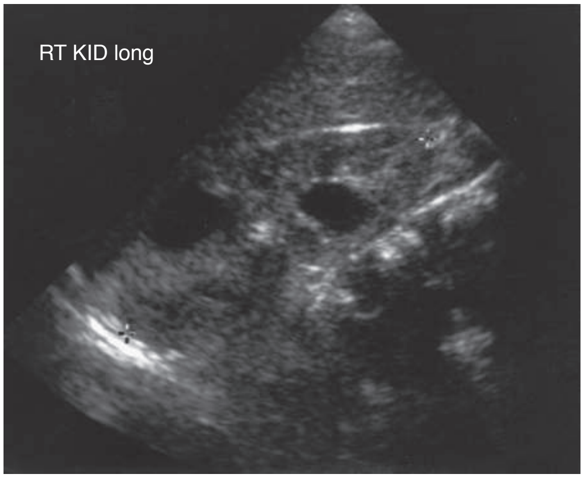

Figure 521-3 Ultrasound examination of an 18 mo old boy with autosomal dominant polycystic kidney disease demonstrating renal enlargement (10 cm) and 2 large cysts.

The majority of mutations appear to be unique to a given family. At present, a mutation can be found in 85% of patients with well-characterized disease. Approximately 8-10% of patients will have de novo, disease-causing mutations. Mutations of *PKD1* are associated with more severe renal disease than mutations of *PKD2*. The pathophysiology of the disease appears to be related to disruption of normal multimeric cystoprotein complexes, with consequent abnormal intracellular signaling resulting in abnormal proliferation, tubular secretion, and cyst formation. Abnormal growth factor expression, coupled with low intracellular calcium and elevated cyclic adenosine monophosphate, appear to be important features leading to formation of cysts and progressive enlargement.

CLINICAL PRESENTATION

The severity of renal disease and the clinical manifestations of ADPKD are highly variable. Although symptomatic ADPKD commonly occurs in the 4th or 5th decade of life, symptoms, including gross or microscopic hematuria, bilateral flank pain, abdominal masses, hypertension, and urinary tract infection, may be seen in neonates, children, and adolescents. With the increased utilization of abdominal sonography in the pediatric population, as well as ADPKD families now requesting possible screening in their asymptomatic, at-risk offspring (with the passage of the Genetic Information Nondiscrimination Act in the United States), most children with ADPKD are diagnosed by abnormal renal sonography in the absence of symptoms. Renal ultrasonography usually demonstrates multiple bilateral macrocysts in enlarged kidneys (Fig. 521-3), although normal kidney size and unilateral disease may be seen in the early phase of the disease in children.

ADPKD is a multiorgan disorder affecting many tissue types. Cysts may be asymptomatic but present within the liver, pancreas, spleen, and ovaries and when present help confirm the diagnosis in childhood. **Intracranial aneurysms,** which appear to segregate within certain families, have an overall prevalence of 15% and are an important cause of mortality in adults, but occasionally occur in children. Mitral valve prolapse is seen in approximately 12% of children; aortic and coronary artery aneurysms and aortic valve insufficiency are noted in affected adults. Hernias, bronchiectasis, and intestinal diverticula can also occur in these children.

DIAGNOSIS

ADPKD is confirmed by the presence of enlarged kidneys with bilateral macrocysts in a patient with an affected 1st-degree relative. De novo mutations occur in 8-10% of patients with newly diagnosed disease. The diagnosis might be made in children before their affected parent, making parental renal sonography an important diagnostic test to be performed in families with no apparent family history. Among patients with genetically defined ADPKD, screening renal ultrasonography results may be normal in ≤20% by 20 yr of age and <5% by 30 yr of age.

Prenatal diagnosis is suggested from the presence of enlarged kidneys with or without cysts on ultrasonography in families with known ADPKD. Prenatal DNA testing is available in families with affected members whose disease is caused by identified mutations in the *PKD1* or *PKD2* genes.

The differential diagnosis includes renal cysts associated with glomerulocystic kidney disease, tuberous sclerosis, and von Hippel-Lindau disease, which may be inherited in an autosomal dominant pattern (see Table 521-1). The neonatal manifestations of ADPKD and ARPKD may rarely be indistinguishable.

TREATMENT AND PROGNOSIS

Treatment of ADPKD is primarily supportive. Control of blood pressure is critical because the rate of disease progression in ADPKD correlates with the presence of hypertension. Angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists are agents of choice. Obesity, caffeine ingestion, smoking, multiple pregnancies, male gender, and possibly the use of calcium channel blockers appear to accelerate disease progression. Older patients with a *family history* of intracranial aneurysm rupture should be screened for cerebral aneurysms.

Although neonatal ADPKD may be fatal, long-term survival of the patient and the kidneys is possible for children surviving the neonatal period. ADPKD that occurs initially in older children has a favorable prognosis, with normal renal function during childhood seen in >80% of children.

Although disease-specific therapy is not yet available, a number of clinical trials are in progress based on promising preclinical laboratory investigation (www.clinicaltrials.gov). A valuable resource for patients and their families is the Polycystic Kidney Disease Foundation (www.pkdcure.org).

Bibliography is available at Expert Consult.

521.4 Trauma

Craig C. Porter and Ellis D. Avner

Infants and children are more susceptible to renal injury following blunt or penetrating injury to the back or abdomen because of their

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decreased muscle mass "protecting" the kidney. Gross or microscopic hematuria, flank pain, and abdominal rigidity can occur; associated injuries may be present (see Chapter 72). In the absence of hemodynamic instability, most renal trauma can be managed nonoperatively. Urethral trauma can result from crush injury, often associated with a fractured pelvis or from direct injury. Such injury is suspected in the appropriate clinical setting when gross blood appears at the external urethral meatus. Rhabdomyolysis and consequent renal failure is another complication of crush injury that can be ameliorated by vigorous fluid resuscitation. There may be a relationship between microscopic hematuria and recreational accidents in individuals >16 yr of age, none of whom exhibited hypotension or required surgical intervention.

Bibliography is available at Expert Consult.

521.5 Renal Tumors

See Chapters 498 and 499.

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Chapter 522
Lower Urinary Tract Causes of Hematuria

522.1 Infectious Causes of Cystitis and Urethritis

Priya Pais and Ellis D. Avner

Gross or microscopic hematuria may be associated with bacterial, mycobacterial, or viral infections of the bladder (see Chapter 538).

522.2 Hemorrhagic Cystitis

Priya Pais and Ellis D. Avner

Hemorrhagic cystitis is defined as the presence of sustained hematuria and lower urinary tract symptoms (e.g., dysuria, frequency, urgency) in the absence of other bleeding conditions such as vaginal bleeding, a generalized bleeding condition, or a bacterial urinary tract infection. Depending on the severity, patients can present with microscopic or gross hematuria, often with clots. In severe forms, bleeding can lead to a significant decrease in blood hemoglobin levels.

Hemorrhagic cystitis can occur in response to chemical toxins (cyclophosphamide, penicillins, busulfan, thiotepa, dyes, insecticides), viruses (adenovirus types 11 and 21 [see Chapter 262] and influenza A), radiation, and amyloidosis. The polyoma BK virus, present latently in immunocompetent hosts, is associated with the development of drug-induced cystitis in immunosuppressed patients. The pediatric bone marrow transplantation population is particularly susceptible to hemorrhagic cystitis.

For chemical irritation related to use of cyclophosphamide, hydration and the use of mesna disulfide, which inactivates urinary cyclophosphamide metabolites, help to protect the bladder. Administration of oral cyclophosphamide in the morning followed by aggressive oral hydration throughout the remainder of the day is very effective in minimizing the risk of hemorrhagic cystitis. Treatment of hemorrhagic cystitis consists of a combination of intensive intravenous hydration, forced diuresis, analgesia, and spasmolytic drugs. Consultation with a urologist is recommended for more invasive measures if the cystitis does not respond to conservative measures. Gross hematuria associated with viral hemorrhagic cystitis usually resolves within 1 wk.

Bibliography is available at Expert Consult.

522.3 Vigorous Exercise

Priya Pais and Ellis D. Avner

Gross or microscopic hematuria can follow vigorous exercise. Exercise hematuria is less common in females and can be associated with dysuria. Approximately 30-60% of runners completing marathons have dipstick-positive urine for blood. In limited follow-up, none appeared to have any significant urinary tract abnormalities. The color of the urine following vigorous exercise can vary from red to black. Blood clots may be rarely present in the urine. Findings on urine culture, intravenous pyelography, voiding cystourethrography, and cystoscopy are normal in most patients. This seems to be a benign condition, and the hematuria generally resolves within 48 hr after cessation of exercise. The absence of red blood cell casts or evidence of renal disease and the presence of dysuria and blood clots in some patients suggest that the source of bleeding lies in the lower urinary tract. **Rhabdomyolysis** with myoglobinuria or hemoglobinuria must be considered in the differential diagnosis when associated with symptoms in the appropriate clinical context. Hydronephrosis or anatomic abnormalities must be considered in any child who presents with hematuria (particularly gross) after mild exercise or following mild trauma. Appropriate imaging studies are indicated in this setting.

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Section 3

Conditions Particularly Associated with Proteinuria

Chapter 523

Introduction to the Child with Proteinuria

Priya Pais and Ellis D. Avner

NORMAL PHYSIOLOGY

The charge and size selective properties of the glomerular capillary wall prevent significant amounts of albumin, globulin, and other large plasma proteins from entering the urinary space (see Chapter 508). Smaller proteins (low-molecular-weight proteins) do cross the capillary wall but are reabsorbed by the proximal tubule. A very small amount of protein that normally appears in the urine is the result of normal tubular secretion. The normally excreted protein mostly consists of Tamm-Horsfall protein (uromodulin), a protective glycoprotein secreted by the tubules that inactivates cytokines.

PATHOPHYSIOLOGY OF PROTEINURIA

Abnormal amounts of protein may appear in the urine from 3 possible mechanisms: **glomerular proteinuria**, which occurs as a result of

Table 523-1 Methods Available to Test for Proteinuria

METHOD	INDICATIONS	NORMAL RANGE	COMMENTS
Dipstick testing	Routine screening for proteinuria performed in the office	Negative or trace in a concentrated urine specimen (specific gravity: ≥1.020)	False-positive test can occur if urine is very alkaline (pH > 8.0) or very concentrated (specific gravity: >1.025)
24 hr urine for protein and creatinine* excretion	Quantitation of proteinuria (as well as creatinine clearances)	<100 mg/m^2/24 hr or <150 mg/24 hr in a documented 24 hr collection	More accurate than spot urine analysis; inconvenient for patient; limited use in pediatric practice
Spot urine for protein/creatinine ratio—preferably on first morning urine specimen	Semiquantitative assessment of proteinuria	<0.2 mg protein/mg creatinine in children >2 yr old <0.5 mg protein/mg creatinine in those 6–24 mo old	Simplest method to quantitate proteinuria; less accurate than measuring 24 hr proteinuria
Microalbuminuria	Assess risk of progressive glomerulopathy in patients with diabetes mellitus	<30 mg urine albumin per gram of creatinine on first morning urine	Therapy should be intensified in diabetics with microalbuminuria

*Note that in a 24 hr urine specimen, the creatinine content should be measured to determine whether the specimen is truly a 24 hr collection. The amount of creatinine in a 24 hr specimen can be estimated as follows: females, 15-20 mg/kg; males, 20-25 mg/kg.

Adapted from Hogg RJ, Portman RJ, Milliner D, et al, Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a Pediatric Nephrology Panel Established at the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk Assessment, Detection, and Elimination (PARADE), Pediatrics *105(6):1242–1249, 2000.*

disruption of the glomerular capillary wall; **tubular proteinuria,** a tubular injury or dysfunction that leads to ineffective reabsorption of mostly low-molecular-weight proteins; and **increased production of plasma proteins**—in multiple myeloma, rhabdomyolysis, or hemolysis—which may cause the production or release of very large amounts of protein that are filtered at the glomerulus and overwhelm the absorptive capacity of the proximal tubule.

MEASUREMENT OF URINE PROTEIN

Urine protein can be measured in random collected samples or in timed (e.g., 24 hr or overnight) samples. Tests to accurately quantify urine protein concentration rely on precipitation with sulfosalicylic acid and measurement of turbidity (Table 523-1).

Urine Dipstick Measurement of Protein

Total protein concentration in urine can be estimated with chemically impregnated plastic strips that contain a pH-sensitive colorimetric indicator that changes color when negatively charged proteins, such as albumin, bind to it. Dipsticks primarily detect albuminuria and are less sensitive for other forms of proteins (low-molecular-weight proteins, Bence Jones protein, gamma globulins). Visual changes in the color of the dipstick are a semiquantitative measure of urinary protein concentration. The dipstick is reported as negative, trace (10-29 mg/dL), 1+ (30-100 mg/dL), 2+ (100-300 mg/dL), 3+ (300-1000 mg/dL), and 4+ (>1000 mg/dL). **False-positive** results can occur with a very high urine pH (>7.0), a highly concentrated urine specimen, or contamination of the urine with blood. **False-negative** test results can occur in patients with dilute urine or a large volume of urine output or in disease states in which the predominant urinary protein is not albumin.

Positive urine dipstick test for protein is considered to be present if there is more than a trace (10-29 mg/dL) in a urine sample in which the specific gravity is <1.010. If the specific gravity is >1.015, the dipstick must read ≥1+ (>30 mg/dL) to be considered clinically significant.

Because the dipstick reaction offers only a qualitative measurement of urinary protein excretion, children with persistent proteinuria should have proteinuria quantitated more precisely. **Timed (24 hr) urine collections** offer more precise information regarding urine protein excretion than a randomly performed dipstick test. Urinary protein excretion in the normal child is less than 100 mg/m^2/day or a total of 150 mg/day. In neonates, normal urinary protein excretion is higher, up to 300 mg/m^2, because of reduced reabsorption of filtered proteins. A reasonable upper limit of normal protein excretion in healthy children is 150 mg/24 hr. More specifically, normal protein excretion in children is defined as ≤4 mg/m^2/hr; abnormal proteinuria is defined as excretion of 4-40 mg/m^2/hr; and nephrotic-range proteinuria is defined as >40 mg/m^2/hr.

Timed urine collections are cumbersome to obtain, and the sensitivity and specificity of the test can be influenced by fluid intake, the volume of urine output, and the importance of including a complete collection without missed voids.

Urine Protein-to-Creatinine Ratio Measurement

Urine protein-to-creatinine ratio measurement of an untimed (spot) urine specimen has largely replaced timed urine collection. In children, urine protein-to-creatinine ratios have been shown to significantly correlate with measurements of 24 hr urine protein and are useful to screen for proteinuria and to longitudinally monitor urine protein levels.

This ratio is calculated by dividing the urine protein concentration (mg/dL) by the urine creatinine concentration (mg/dL) to provide a simple measure. It should be ideally performed on a first morning voided urine specimen to eliminate the possibility of orthostatic (postural) proteinuria (see Chapter 525). A ratio of <0.5 in children <2 yr of age and <0.2 in children >2 yr of age suggests normal urinary protein excretion. A ratio greater than 2 suggests nephrotic-range proteinuria.

CLINICAL CONSIDERATIONS

The finding of proteinuria in children and adolescents in a single, non–first morning urine specimen is common, varying between 5% and 15%. The prevalence of persistent proteinuria on repeated testing is much less common. The challenge is to differentiate the child with proteinuria related to renal disease from the otherwise healthy child with transient or other benign forms of proteinuria. When proteinuria is detected it is important to determine if it is transient, orthostatic, or fixed in nature.

Microalbuminuria is defined as the presence of albumin in the urine above the normal level but below the detectable range of conventional urine dipstick methods. In adults, persistent microalbuminuria (defined as a urinary albumin excretion of 30-300 mg/g creatinine on at least 2-3 samples) is accepted as evidence of diabetic nephropathy and also a predictor of cardiovascular and renal disease. The mean level of urinary albumin excretion falls between 8 and 10 mg/g of creatinine in children >6 yr of age. Similar to adults, microalbuminuria in children has been found to be associated with obesity and to predict, with reasonable specificity, the development of diabetic nephropathy in type 1 diabetes mellitus.

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Chapter 524

Transient Proteinuria

Craig C. Porter and Ellis D. Avner

The majority of children found to have positive tests for protein on urinary dipsticks will have negative evaluations on repeated dipsticks and normal urinary protein if formally quantitated. Approximately 10% of children who undergo random urinalysis have proteinuria by a single dipstick measurement. Across the school-age spectrum, this finding occurs more commonly in adolescents than in younger children. In most cases, serial testing of the patient's urine demonstrates resolution of the abnormality. This phenomenon defines **transient proteinuria,** and its cause remains elusive. Defined contributing factors include a temperature >38.3°C (101°F), exercise, dehydration, cold exposure, heart failure, seizures, or stress. Transient proteinuria usually does not exceed 1-2+ on the dipstick. No evaluation or therapy is needed for children with this benign condition. Persistence of proteinuria, even if low grade, is not consistent with the diagnosis and suggests the need for additional evaluation.

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Increased body mass index is recognized as a strong correlate of orthostatic proteinuria. Long-term follow-up studies in young adults suggest that orthostatic proteinuria is a benign process, but similar data are not available for children. Therefore, long-term follow-up of children is prudent. Patients should be monitored for the development of nonorthostatic proteinuria, particularly in the presence of hematuria, hypertension, or edema. Such findings may herald underlying kidney disease.

Bibliography is available at Expert Consult.

Chapter **525**

Orthostatic (Postural) Proteinuria

Craig C. Porter and Ellis D. Avner

Orthostatic proteinuria is the most common cause of persistent proteinuria in school-age children and adolescents, occurring in up to 60% of children with persistent proteinuria. Children with this condition are usually asymptomatic, and the condition is discovered by routine urinalysis. Patients with orthostatic proteinuria excrete normal or minimally increased amounts of protein in the supine position. In the upright position, urinary protein excretion may be increased 10-fold, up to 1,000 mg/24 hr (1 g/24 hr). *Hematuria, hypertension, hypoalbuminemia, edema, and renal dysfunction are absent.*

In a child with persistent asymptomatic proteinuria, the initial evaluation should include an assessment for orthostatic proteinuria. It begins with the collection of a first morning urine sample, with subsequent testing of any urinary abnormalities by a complete urinalysis and determination of a spot protein : creatinine (Pr : Cr) ratio. The correct collection of the first morning urine sample is critical. The child must fully empty the bladder before going to bed and then collect the first voided urine sample immediately upon arising in the morning. The absence of proteinuria (dipstick negative or trace for protein; and a normal ratio of urinary protein [mg/dL] to urinary creatinine [mg/dL] = [uPr/uCr] <0.2) on the first morning urine sample for 3 consecutive days confirms the diagnosis of orthostatic proteinuria. No further evaluation is necessary, and the patient and family should be reassured of the benign nature of this condition. However, if there are other abnormalities of the urinalysis (e.g., hematuria), or if the urine uPr : uCr ratio is >0.2, the patient should be referred to a pediatric nephrologist for a complete evaluation.

The cause of orthostatic proteinuria is unknown, although altered renal hemodynamics and partial left renal vein obstruction in the upright, lordotic position have been proposed as possible causes.

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Chapter 526

Fixed Proteinuria

Priya Pais and Ellis D. Avner

Children found to have fixed proteinuria on a first morning urine sample on 3 separate occasions should be further investigated. Fixed proteinuria is defined as a first morning urine sample that is ≥1+ on dipstick testing with a urine specific gravity >1.015 or with a protein-to-creatinine ratio of ≥0.2. Fixed proteinuria indicates a potential kidney disease caused by either glomerular or tubular disorders.

526.1 Glomerular Proteinuria

Priya Pais and Ellis D. Avner

The glomerular capillary wall consists of 3 layers: the fenestrated capillary endothelium, the glomerular basement membrane, and the podocytes (with foot processes and intercalated slit diaphragms) (Fig. 526-1). Glomerular proteinuria results from alterations in the permeability of any of the layers of the glomerular capillary wall to normally filtered proteins and occurs in a variety of renal diseases (Table 526-1). Glomerular proteinuria can range widely from <1 g to >30 g of protein in a 24 hr period. The podocyte is the predominant cell of injury in most glomerular diseases characterized by heavy proteinuria.

Glomerular proteinuria should be suspected in any patient with a first morning urine protein : creatinine ratio >1.0, or significant proteinuria of any degree, accompanied by hypertension, hematuria, edema, or renal dysfunction (elevated blood urea nitrogen, creatinine). Disorders characterized primarily by proteinuria include idiopathic (minimal change) nephrotic syndrome, focal segmental glomerulosclerosis, mesangial proliferative glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, diabetic nephropathy, and obesity-related glomerulopathy. Other renal disorders that can include proteinuria as a prominent feature include acute postinfectious glomerulonephritis, immunoglobulin A nephropathy, lupus nephritis, Henoch-Schönlein purpura nephritis, and Alport syndrome.

Initial evaluation of a child with fixed proteinuria should include measurement of serum creatinine and electrolyte panel, first morning urine protein : creatinine ratio, serum albumin level, and complement levels. The child should be referred to a pediatric nephrologist for further evaluation and management. Renal biopsy is often necessary to establish a diagnosis and guide therapy.

In asymptomatic patients with low-grade proteinuria (protein : creatinine ratio between 0.2 and 1.0) in whom all other findings are normal, renal biopsy might not be indicated because the underlying process may be transient or resolving or because specific pathologic features of a chronic kidney disease might not yet be apparent. Such patients should have periodic reevaluation (ideally every 4-6 mo unless the patient is symptomatic). The evaluation should consist of a physical examination with accurate blood pressure measurement, urinalysis, measurement of serum creatinine and a repeat first morning urine

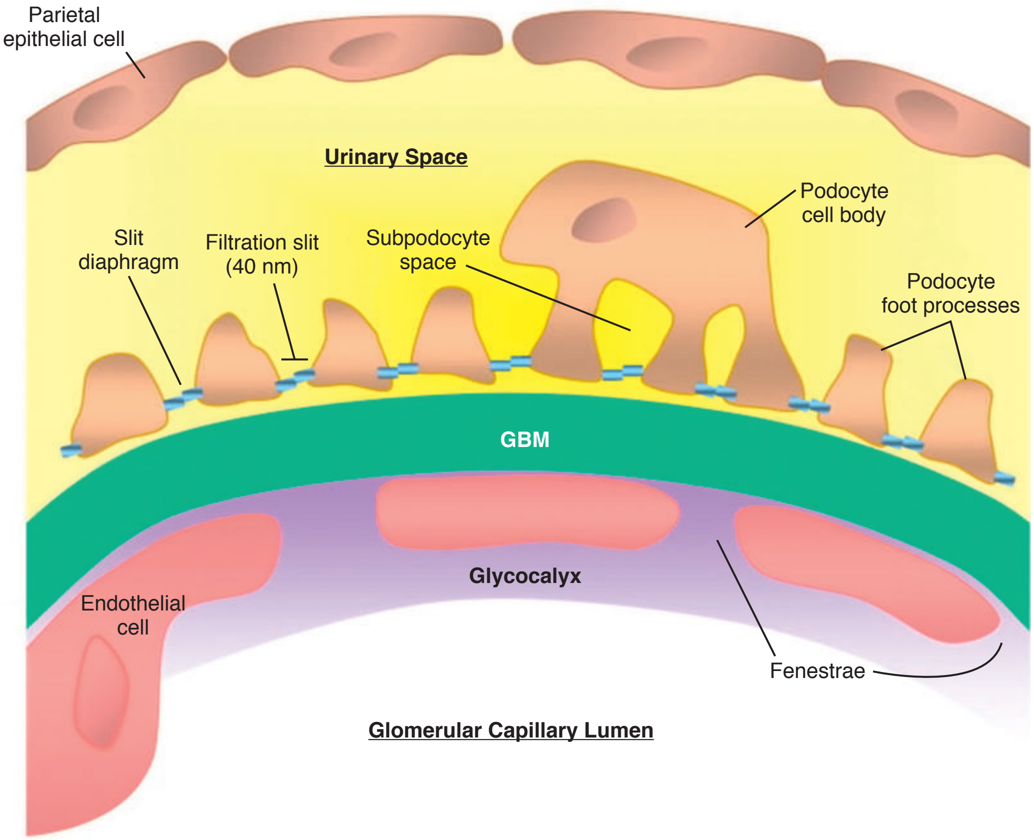

Figure 526-1 **Glomerular capillary wall.** The 3 layers of the capillary wall (glomerular endothelial cell, glomerular basement membrane [GBM], and podocyte) act as the glomerular filtration barrier (GFB), preventing proteins and large molecules from passing from the capillary lumen into the urinary space. The podocyte cell body lies with in the urinary space, and the cell is attached to the GBM through foot processes. Adjacent foot processes are separated by the filtration slit, bridged by the slit diaphragm. Disruption of the GFB leads the passage of protein across the capillary wall, leading to proteinuria. *(From Jefferson JA, Nelson PJ, Najafian B, Shankland SJ. Podocyte disorders: core curriculum 2011.* Am J Kidney Dis *58:666–677, 2011, Fig 1.)*

Table 526-1 Causes of Proteinuria

TRANSIENT PROTEINURIA Fever Exercise Dehydration Cold exposure Congestive heart failure Seizure Stress	GLOMERULAR DISEASES WITH PROTEINURIA AS A PROMINENT FEATURE Acute postinfectious glomerulonephritis (streptococcal, endocarditis, hepatitis B or C virus, HIV) Immunoglobulin A nephropathy Henoch-Schönlein purpura nephritis Lupus nephritis Serum sickness Alport syndrome Vasculitic disorders Reflux nephropathy
ORTHOSTATIC (POSTURAL) PROTEINURIA	
GLOMERULAR DISEASES CHARACTERIZED BY ISOLATED PROTEINURIA Idiopathic (minimal change) nephrotic syndrome Focal segmental glomerulosclerosis Mesangial proliferative glomerulonephritis Membranous nephropathy Membranoproliferative glomerulonephritis Amyloidosis Diabetic nephropathy Sickle cell nephropathy	TUBULAR DISEASES Cystinosis Wilson disease Lowe syndrome Dent disease (X-linked recessive nephrolithiasis) Galactosemia Tubulointerstitial nephritis Acute tubular necrosis Renal dysplasia Polycystic kidney disease Reflux nephropathy Drugs (penicillamine, lithium, NSAID) Heavy metals (lead, gold, mercury)

NSAID, nonsteroidal antiinflammatory drug.

protein : creatinine ratio. Indications for renal biopsy include increasing proteinuria (protein : creatinine >1.0) or the development of hematuria, hypertension, or diminished renal function.

Bibliography is available at Expert Consult.

526.2 Tubular Proteinuria

Priya Pais and Ellis D. Avner

A variety of renal disorders that primarily involve the tubulointerstitial compartment of the kidney can cause low-grade fixed proteinuria (protein : creatinine ratio 0.2 : 1.0). In the healthy state, large amounts of proteins of lower molecular weight than albumin are filtered by the glomerulus and reabsorbed in the proximal tubule. Injury to the proximal tubules can result in diminished reabsorptive capacity and the loss of these low-molecular-weight proteins in the urine.

Tubular proteinuria (see Table 526-1) may be seen in acquired and inherited disorders and may be associated with other defects of proximal tubular function, such as the Fanconi syndrome (glycosuria, phosphaturia, bicarbonate wasting, and aminoaciduria). Tubular proteinuria is a consistent finding among patients with the X-linked tubular syndrome, Dent disease, caused by mutations of the renal chloride channel.

Asymptomatic patients having persistent proteinuria generally have glomerular rather than tubular proteinuria. In occult cases, glomerular and tubular proteinuria can be distinguished by electrophoresis of the urine. In tubular proteinuria, little or no albumin is detected, whereas in glomerular proteinuria, the major protein is albumin.

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Chapter 527
Nephrotic Syndrome

Priya Pais and Ellis D. Avner

Nephrotic syndrome is the clinical manifestation of glomerular diseases associated with heavy (nephrotic-range) proteinuria. Nephrotic-range proteinuria is defined as proteinuria >3.5 g/24 hr or a urine protein : creatinine ratio >2. The **triad of clinical findings associated with nephrotic syndrome** arising from the large urinary losses of protein are hypoalbuminemia (≤2.5 g/dL), edema, and hyperlipidemia (cholesterol >200 mg/dL).

Nephrotic syndrome affects 1-3 per 100,000 children <16 yr of age. Without treatment, nephrotic syndrome in children is associated with a high risk of death, most commonly from infections. Fortunately, 80% of children with nephrotic syndrome respond to corticosteroid therapy. Although glucocorticoid therapy is standard therapy for nephrotic syndrome, neither the target cell nor the mechanism of action of steroids has been determined. Early referral to a pediatric nephrologist is recommended for initial management of nephrotic syndrome. However, continued care of these children is always a collaborative effort between the nephrologist and the primary care physician.

ETIOLOGY

Most children with nephrotic syndrome have a form of **primary** or idiopathic nephrotic syndrome (Table 527-1). Glomerular lesions associated with idiopathic nephrotic syndrome include minimal change disease (the most common), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, C3 glomerulopathy, and membranous nephropathy (Table 527-2). These etiologies have different age distributions (Fig. 527-1). Nephrotic syndrome may also be **secondary** to systemic diseases such as systemic lupus erythematosus, Henoch-Schönlein purpura, malignancy (lymphoma and leukemia), and infections (hepatitis, HIV, and malaria) (see Table 527-1). A number of **hereditary** proteinuria syndromes are caused by mutations in genes that encode critical protein components of the glomerular filtration apparatus (Table 527-3).

PATHOGENESIS

Role of the Podocyte

The underlying abnormality in nephrotic syndrome is an increased permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia. The podocyte plays a crucial role in the development of proteinuria and progression of glomerulosclerosis. The podocyte is a highly differentiated epithelial cell located on the outside of the glomerular capillary loop (see Chapter 508.1). Foot processes are extensions of the podocyte that terminate on the glomerular basement membrane. The foot processes of a podocyte interdigitate with those from adjacent podocytes and are connected by a slit called the slit diaphragm. The podocyte functions as structural support of the capillary loop, is a major component of the glomerular filtration barrier to proteins, and is involved in synthesis and repair of the glomerular basement membrane. The slit diaphragm is one of the major impediments to protein permeability across the glomerular capillary wall. Slit diaphragms are not simple passive filters—they consist of numerous proteins that contribute to complex signaling pathways and play an important role in podocyte function. Important component proteins of the slit diaphragm include nephrin, podocin, CD2AP, and α-actinin 4. Podocyte injury or genetic mutations of genes producing podocyte proteins may cause nephrotic-range proteinuria (see Table 527-3).

In idiopathic, hereditary, and secondary forms of nephrotic syndrome, there are immune and nonimmune insults to the podocyte that lead to foot process effacement of the podocyte, a decrease in number of functional podocytes, and altered slit diaphragm integrity. The end result is increased protein "leakiness" across the glomerular capillary wall into the urinary space.

Role of the Immune System

Minimal change nephrotic syndrome (MCNS) may occur after viral infections and allergen challenges. MCNS has also been found to occur in children with Hodgkin lymphoma and T-cell lymphoma. That immunosuppression occurs with drugs such as corticosteroids and cyclosporine provides indirect additional evidence that the immune system contributes to the overall pathogenesis of the nephrotic syndrome.

CLINICAL CONSEQUENCES OF NEPHROTIC SYNDROME

Edema

Edema is the most common presenting symptom of children with nephrotic syndrome. Despite its almost universal presence, there is uncertainty as to the exact mechanism of edema formation. There are 2 opposing theories, the *underfill hypothesis* and the *overfill hypothesis*, that have been proposed as mechanisms causing nephrotic edema.

The *underfill hypothesis* is based on the fact that nephrotic-range proteinuria leads to a fall in the plasma protein level with a corresponding decrease in intravascular oncotic pressure. This leads to leakage of plasma water into the interstitium, generating edema. As a result of reduced intravascular volume, there is increased secretion of vasopressin and atrial natriuretic factor, which, along with aldosterone, result in increased sodium and water retention by the tubules. Sodium and water retention therefore occur as a consequence of intravascular volume depletion.

This hypothesis does not fit the clinical picture of some patients with edema caused by nephrotic syndrome who have clinical signs of intravascular volume overload, not volume depletion. Treating these patients with albumin alone may not be sufficient to induce a diuresis

Table 527-1 Causes of Childhood Nephrotic Syndrome

IDIOPATHIC NEPHROTIC SYNDROME	SECONDARY CAUSES OF NEPHROTIC SYNDROME
Minimal change disease	Infections
Focal segmental glomerulosclerosis	Endocarditis
Membranous nephropathy	Hepatitides B, C
Glomerulonephritis associated with nephrotic syndrome–membranoproliferative glomerulonephritis, crescentic glomerulonephritis, immunoglobulin A nephropathy	HIV-1
	Infectious mononucleosis
GENETIC DISORDERS ASSOCIATED WITH PROTEINURIA OR NEPHROTIC SYNDROME	Malaria
Nephrotic Syndrome (Typical)	Syphilis (congenital and secondary)
Finnish-type congenital nephrotic syndrome (absence of nephrin)	Toxoplasmosis
Focal segmental glomerulosclerosis (mutations in nephrin, podocin, *MYO1E*, α-actinin 4, TRPC6)	Schistosomiasis
Diffuse mesangial sclerosis (mutations in laminin β_2 chain)	Filariasis
Denys-Drash syndrome (mutations in WT1 transcription factor)	Drugs
Congenital nephrotic syndrome with lung and skin involvement (integrin α-3 mutation)	Captopril
Mitochondrial disorders)	Penicillamine
Proteinuria With or Without Nephrotic Syndrome	Gold
Nail-patella syndrome (mutation in LMX1B transcription factor)	Nonsteroidal antiinflammatory drugs
Alport syndrome (mutation in collagen biosynthesis genes)	Pamidronate
Multisystem Syndromes With or Without Nephrotic Syndrome	Interferon
Galloway-Mowat syndrome	Mercury
Charcot-Marie-Tooth disease	Heroin
Jeune syndrome	Lithium
Cockayne syndrome	Immunologic or Allergic Disorders
Laurence-Moon-Biedl-Bardet syndrome	Vasculitis syndromes
Metabolic Disorders With or Without Nephrotic Syndrome	Castleman disease
Alagille syndrome	Kimura disease
α_1-Antitrypsin deficiency	Beesting
Fabry disease	Food allergens
Glutaric acidemia	Serum sickness
Glycogen storage disease	Associated With Malignant Disease
Hurler syndrome	Lymphoma
Partial lipodystrophy	Leukemia
Mitochondrial cytopathies	Solid tumors
Sickle cell disease	Glomerular Hyperfiltration
	Oligomeganephronia
	Morbid obesity
	Adaptation to nephron reduction

Adapted from Eddy AA, Symons JM: Nephrotic syndrome in childhood, Lancet *362:629–638, 2003.*

without the concomitant use of diuretics. Also, reducing the renin–aldosterone axis with mineralocorticoid receptor antagonists does not result in a marked increase in sodium excretion. With the onset of remission of MCNS, many children will have increased urine output before their urinary protein excretion is measurably reduced.

The *overfill hypothesis* postulates that nephrotic syndrome is associated with primary sodium retention, with subsequent volume expansion and leakage of excess fluid into the interstitium. There is accumulating evidence that the epithelial sodium channel in the distal tubule may play a key role in sodium reabsorption in nephrotic syndrome. The clinical weaknesses of this hypothesis are evidenced by the numerous nephrotic patients who present with an obvious clinical picture of intravascular volume depletion: low blood pressure, tachycardia, and elevated hemoconcentration. Furthermore, amiloride, an epithelial sodium channel blocker, used alone is not sufficient to induce adequate diuresis.

The goal of therapy should be a gradual reduction of edema with judicious use of diuretics, sodium restriction, and cautious use of intravenous albumin infusions, if indicated.

Hyperlipidemia

There are several alterations in the lipid profile in children with nephrotic syndrome, including an increase in cholesterol, triglycerides, low-density lipoprotein, and very-low-density lipoproteins. The high-density lipoprotein level remains unchanged or is low. In adults, this results in an increase in the adverse cardiovascular risk ratio, although the implications for children are not as serious, especially those with steroid-responsive nephrotic syndrome. Hyperlipidemia is thought to be the result of increased synthesis as well as decreased catabolism of lipids. Although commonplace in adults, the use of lipid-lowering agents in children is uncommon.

Increased Susceptibility to Infections

Children with nephrotic syndrome are especially susceptible to infections such as cellulitis, spontaneous bacterial peritonitis, and bacteremia. This occurs as a result of many factors, particularly hypoglobulinemia as a result of the urinary losses of immunoglobulin (Ig) G. In addition, defects in the complement cascade from urinary loss of complement factors (predominantly C3 and C5), as well as alternative pathway factors B and D, lead to impaired opsonization of microorganisms. Children with nephrotic syndrome are at significantly increased risk for infection with encapsulated bacteria and, in particular, pneumococcal disease. **Spontaneous bacterial peritonitis** presents with fever, abdominal pain, and peritoneal signs. Although *Pneumococcus* is the most frequent cause of peritonitis, Gram-negative bacteria also are associated with a significant number of cases. Children with nephrotic syndrome and fever or other signs of infection must be evaluated aggressively, with appropriate cultures drawn, and should be treated promptly and empirically with antibiotics. Peritoneal leukocyte counts >250 are highly suggestive of spontaneous bacterial peritonitis.

Hypercoagulability

Nephrotic syndrome is a hypercoagulable state resulting from multiple factors: vascular stasis from hemoconcentration and intravascular volume depletion, increased platelet number and aggregability, and changes in coagulation factor levels. There is an increase in hepatic production of fibrinogen along with urinary losses of antithrombotic

Table 527-2 Summary of Primary Renal Diseases That Manifest as Idiopathic Nephrotic Syndrome

FEATURES	MINIMAL CHANGE NEPHROTIC SYNDROME	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	MEMBRANOUS NEPHROPATHY	MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	
				Type I	Type II
DEMOGRAPHICS					
Age (yr)	2-6, some adults	2-10, some adults	40-50	5-15	5-15
Sex	2:1 male	1.3:1 male	2:1 male	Male-female	Male-female
CLINICAL MANIFESTATIONS					
Nephrotic syndrome	100%	90%	80%	60%*	60%*
Asymptomatic proteinuria	0	10%	20%	40%	40%
Hematuria (microscopic or gross)	10-20%	60-80%	60%	80%	80%
Hypertension	10%	20% early	Infrequent	35%	35%
Rate of progression to renal failure	Does not progress	10 yr	50% in 10-20 yr	10-20 yr	5-15 yr
Associated conditions	Usually none	HIV, heroin use, sickle cell disease, reflux nephropathy	Renal vein thrombosis; medications; SLE; hepatitides B, C; lymphoma; tumors	None	Partial lipodystrophy
GENETICS	None except in congenital nephrotic syndrome (see Table 527-3)	Podocin, α-actinin 4, TRPC6 channel, INF-2, MYH-9	None	None	None
LABORATORY FINDINGS	Manifestations of nephrotic syndrome ↑ BUN in 15-30% Normal complement levels	Manifestations of nephrotic syndrome ↑ BUN in 20-40% Normal complement levels	Manifestations of nephrotic syndrome Normal complement levels	Low complement levels—C1, C4, C3-C9	Normal complement levels—C1, C4, low C3-C9
RENAL PATHOLOGY					
Light microscopy	Normal	Focal sclerotic lesions	Thickened GBM, spikes	Thickened GBM, proliferation	Lobulation
Immunofluorescence	Negative	IgM, C3 in lesions	Fine granular IgG, C3	Granular IgG, C3	C3 only
Electron microscopy	Foot process fusion	Foot process fusion	Subepithelial deposits	Mesangial and subendothelial deposits	Dense deposits
REMISSION ACHIEVED AFTER 8 WK OF ORAL CORTICOSTEROID THERAPY	90%	15-20%	Resistant	Not established/ resistant	Not established/ resistant

*Approximate frequency as a cause of idiopathic nephrotic syndrome. Approximately 10% of cases of adult nephrotic syndrome are a result of various diseases that usually manifest as acute glomerulonephritis.
↑, Elevated; BUN, blood urea nitrogen; C, complement; GBM, glomerular basement membrane; Ig, immunoglobulin; SLE, systemic lupus erythematosus.
Modified from Couser WG: Glomerular disorders. In Wyngaarden JB, Smith LH, Bennett JC, editors: Cecil textbook of medicine, *ed 19, Philadelphia, 1992, WB Saunders, p. 560.*

factors such as antithrombin III and protein S. Deep venous thrombosis may occur in any venous bed, including the cerebral venous sinus, renal vein, and pulmonary veins. The clinical risk is low in children (2-5%) compared to adults, but has the potential for serious consequences.

Bibliography is available at Expert Consult.

527.1 Idiopathic Nephrotic Syndrome

Priya Pais and Ellis D. Avner

Approximately 90% of children with nephrotic syndrome have idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome is associated with primary glomerular disease without an identifiable causative disease or drug. Idiopathic nephrotic syndrome includes multiple histologic types: minimal change disease, mesangial proliferation, focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis.

PATHOLOGY

In minimal change nephrotic syndrome (**MCNS**) (approximately 85% of total cases of nephrotic syndrome in children), the glomeruli appear normal or show a minimal increase in mesangial cells and matrix. Findings on immunofluorescence microscopy are typically negative, and electron microscopy simply reveals effacement of the epithelial cell foot processes. More than 95% of children with minimal change disease respond to corticosteroid therapy.

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Table 527-3 Nephrotic Syndrome in Children Caused by Genetic Disorders of the Podocyte

GENE	NAME	LOCATION	INHERITANCE	RENAL DISEASE
STEROID-RESISTANT NEPHROTIC SYNDROME				
NPHS1	Nephrin	19q13.1	Recessive	Finnish-type congenital nephrotic syndrome
NPHS2	Podocin	1q25	Recessive	FSGS
WT1	Wilms tumor-suppressor gene	11p13	Dominant	Denys-Drash syndrome with diffuse mesangial sclerosis Frasier syndrome with FSGS
LMX1B	LIM-homeodomain protein	9q34	Dominant	Nail-patella syndrome
SMARCAL1	SW1/SNF2-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1	2q35	Recessive	Schimke immunoosseous dysplasia with FSGS*

*Podocyte expression of *SMARCAL1* is presumptive but not yet established. Mutations in another protein, CD2-AP or NEPH1 (a novel protein structurally related to nephrin), cause congenital nephrotic syndrome in mice. A mutational variant in the *CD2AP* gene has been identified in a few patients with steroid-resistant nephrotic syndrome.

FSGS, focal segmental glomerulosclerosis.

Modified from Eddy AA, Symons JM: Nephrotic syndrome in childhood, Lancet *362:629–638, 2003.*

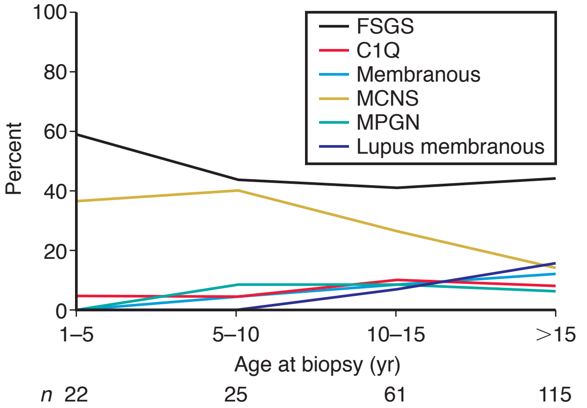

Figure 527-1 Kidney biopsy results from 223 children with proteinuria referred for diagnostic kidney biopsy (Glomerular Disease Collaborative Network, J. Charles Jennette, MD, Hyunsook Chin, MS, and D.S. Gipson, 2007). C1Q, nephropathy; FSGS, focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome; MPGN, membranoproliferative glomerulonephritis; n, number of patients. *(From Gipson DS, Massengill SF, Yao L, et al: Management of childhood onset nephrotic syndrome,* Pediatrics *124:747–757, 2009.)*

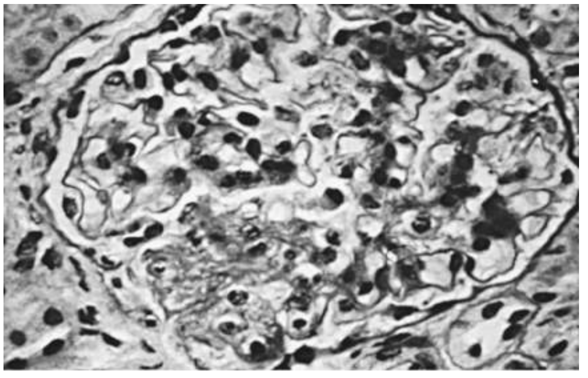

Figure 527-2 Glomerulus from a patient with steroid-resistant nephrotic syndrome showing mesangial hypercellularity and an area of sclerosis in the lower portion (×250).

Mesangial proliferation is characterized by a diffuse increase in mesangial cells and matrix on light microscopy. Immunofluorescence microscopy might reveal trace to 1+ mesangial IgM and/or IgA staining. Electron microscopy reveals increased numbers of mesangial cells and matrix as well as effacement of the epithelial cell foot processes. Approximately 50% of patients with this histologic lesion respond to corticosteroid therapy.

In **focal segmental glomerulosclerosis (FSGS)**, glomeruli show lesions that are both focal (present only in a proportion of glomeruli) and segmental (localized to ≥1 intraglomerular tufts). The lesions consist of mesangial cell proliferation and segmental scarring on light microscopy (Fig. 527-2 and see Table 527-2). Immunofluorescence microscopy is positive for IgM and C3 staining in the areas of segmental sclerosis. Electron microscopy demonstrates segmental scarring of the glomerular tuft with obliteration of the glomerular capillary lumen. Similar lesions may be seen secondary to HIV infection, vesicoureteral reflux, and intravenous use of heroin and other drugs of abuse. Only 20% of patients with FSGS respond to prednisone. The disease is often progressive, ultimately involving all glomeruli, and ultimately leads to end-stage renal disease in most patients.

MINIMAL CHANGE NEPHROTIC SYNDROME

Clinical Manifestations

The idiopathic nephrotic syndrome is more common in boys than in girls (2 : 1) and most commonly appears between the ages of 2 and 6 yr (see Fig. 527-1). However, it has been reported as early as 6 mo of age and throughout adulthood. MCNS is present in 85-90% of patients <6 yr of age. In contrast, only 20-30% of adolescents who present for the first time with nephrotic syndrome have MCNS. The more common cause of idiopathic nephrotic syndrome in this older age group is FSGS. The incidence of FSGS may be increasing; it may be more common in African-American, Hispanic, and Asian patients.

The initial episode of idiopathic nephrotic syndrome, as well as subsequent relapses, usually follows minor infections and, uncommonly, reactions to insect bites, beestings, or poison ivy.

Children usually present with mild edema, which is initially noted around the eyes and in the lower extremities. Nephrotic syndrome can initially be misdiagnosed as an allergic disorder because of the periorbital swelling that decreases throughout the day. With time, the edema becomes generalized, with the development of ascites, pleural effusions, and genital edema. Anorexia, irritability, abdominal pain, and diarrhea are common. Important features of minimal change idiopathic nephrotic syndrome are the absence of hypertension and gross hematuria (the so-called nephritic features).

The differential diagnosis of the child with marked edema includes protein-losing enteropathy, hepatic failure, heart failure, acute or chronic glomerulonephritis, and protein malnutrition. A diagnosis other than MCNS should be considered in children <1 yr of age, with a positive

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family history of nephrotic syndrome, and/or the presence of extrarenal findings (e.g., arthritis, rash, anemia), hypertension or pulmonary edema, acute or chronic renal insufficiency, and gross hematuria.

Diagnosis

Recommendations for the Initial Evaluation of Children with Nephrotic Syndrome

Confirming the Diagnosis of Nephrotic Syndrome. The diagnosis of nephrotic syndrome is confirmed by urinalysis with first morning urine protein : creatinine ratio and serum electrolytes, blood urea nitrogen, creatinine, albumin, and cholesterol levels; evaluation to rule out secondary forms of nephrotic syndrome (children ≥10 yr): complement C3 level, antinuclear antibody, double-stranded DNA and hepatitides B and C, and HIV in high-risk populations; and kidney biopsy (for children ≥12 yr, who are less likely to have MCNS).

The urinalysis reveals 3+ or 4+ proteinuria, and microscopic hematuria is present in 20% of children. A spot urine protein : creatinine ratio should be >2.0. The serum creatinine value is usually normal, but it may be abnormally elevated if there is diminished renal perfusion from contraction of the intravascular volume. The serum albumin level is <2.5 g/dL, and serum cholesterol and triglyceride levels are elevated. Serum complement levels are normal. A renal biopsy is not routinely performed if the patient fits the standard clinical picture of MCNS.

Treatment

Children with their first episode of nephrotic syndrome and mild to moderate edema may be managed as outpatients. Such outpatient management is not practiced in all major centers, because the time required for successful education of the family regarding all aspects of the condition can require a short period of hospitalization. The child's parents must be able to recognize the signs and symptoms of the complications of the disease and may be taught how to use a dipstick and interpret the results to monitor for the degree of proteinuria. Tuberculosis must be ruled out prior to starting immunosuppressive therapy with corticosteroids by placing a purified protein derivative or obtaining an interferon release assay, and confirming a negative result.

Children with onset of uncomplicated nephrotic syndrome between 1 and 8 yr of age are likely to have steroid-responsive MCNS, and steroid therapy may be initiated without a diagnostic renal biopsy. Children with features that make MCNS less likely (gross hematuria, hypertension, renal insufficiency, hypocomplementemia, or age <1 yr or >12 yr) should be considered for renal biopsy before treatment.

Use of Corticosteroids to Treat Minimal Change Nephrotic Syndrome

Corticosteroids are the mainstay of therapy for MCNS. The treatment guidelines for corticosteroid use presented below are adapted from and based on the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines on glomerulonephritis.

Treatment of Initial Episode of Nephrotic Syndrome

In children with presumed MCNS, prednisone or prednisolone should be administered as a single daily dose of 60 mg/m^2/day or 2 mg/kg/day to a maximum of 60 mg daily for 4-6 wk followed by alternate-day prednisone (starting at 40 mg/m^2 qod or 1.5 mg/kg qod) for a period ranging from 8 wk to 5 mo, with tapering of the dose. When planning the duration of steroid therapy, the side effects of prolonged corticosteroid administration must be kept in mind.

Approximately 80-90% of children respond to steroid therapy. **Response** is defined as the attainment of remission within the initial 4 wk of corticosteroid therapy. **Remission** consists of a urine protein : creatinine ratio of <0.2 or <1+ protein on urine dipstick for 3 consecutive days. The vast majority of children who respond to prednisone therapy do so within the first 5 wk of treatment.

Managing the Clinical Sequelae of Nephrotic Syndrome

Edema. Children with severe symptomatic edema, including large pleural effusions, ascites, or severe genital edema, should be hospitalized. In addition to sodium restriction (<1500 mg daily), water/fluid restriction may be necessary if the child is hyponatremic. A swollen scrotum may be elevated with pillows to enhance fluid removal by gravity. Diuresis may be augmented by the administration of loop diuretics (furosemide), orally or intravenously**, although extreme caution should be exercised**. Aggressive diuresis can lead to intravascular volume depletion and an increased risk for acute renal failure and intravascular thrombosis.

When a patient has severe generalized edema with evidence of intravascular volume depletion (e.g., hemoconcentration, hypotension, tachycardia), IV administration of 25% albumin (0.5-1.0 g albumin/kg) as a slow infusion followed by furosemide (1-2 mg/kg/dose IV) is sometimes necessary. Such therapy should be used only in collaboration with a pediatric nephrologist and mandates close monitoring of volume status, blood pressure, serum electrolyte balance, and renal function. Symptomatic volume overload, with hypertension, heart failure, and pulmonary edema, is a potential complication of parenteral albumin therapy, particularly when administered as rapid infusions.

Dyslipidemia. Dyslipidemia should be managed with a low-fat diet. Dietary fat intake should be limited to <30% of calories with saturated fat intake <10% calories. Dietary cholesterol intake should be <300 mg/day. There are insufficient data to recommend the use of 3-hydroxy-3-methylgluataryl coenzyme A (HMG-CoA) reductase inhibitors routinely in children with dyslipidemia.

Infections. Families of children with nephrotic syndrome should be counseled regarding the signs and symptoms of infections such as cellulitis, peritonitis, and bacteremia. If there is suspicion of infection, a blood culture should be drawn prior to starting empiric antibiotic therapy. In the case of spontaneous bacterial peritonitis, peritoneal fluid should be collected if there is sufficient fluid to perform a paracentesis and sent for cell count, Gram stain, and culture. The antibiotic provided must be of broad enough coverage to include *Pneumococcus* and Gram-negative bacteria. A 3rd-generation cephalosporin is a common choice of IV antibiotic.

Thromboembolism. Children who present with the clinical signs of thromboembolism should be evaluated by appropriate imaging studies to confirm the presence of a clot. Studies to delineate a specific underlying hypercoagulable state are recommended. Anticoagulation therapy in children with thrombotic events appears to be effective—heparin, low-molecular-weight heparin, and warfarin are therapeutic options.

Obesity and Growth. Glucocorticoids may increase the body mass index in children who are overweight when steroid therapy is initiated, and these children are more likely to remain overweight. Anticipatory dietary counseling is recommended. Growth may be affected in children who require long-term corticosteroid therapy. Steroid-sparing strategies may improve linear growth in children who require prolonged courses of steroids.

Relapse of Nephrotic Syndrome. Relapse of nephrotic syndrome is defined as a urine protein : creatinine ratio of >2 or ≥3+ protein on urine dipstick testing for 3 consecutive days. Relapses are common, especially in younger children, and are often triggered by upper respiratory or gastrointestinal infections. Relapses are usually treated in a manner similar to the initial episode, except that daily prednisone courses are shortened. Daily high-dose prednisone is given until the child has achieved remission, and the regimen is then switched to alternate-day therapy. The duration of alternate day therapy varies depending on the frequency of relapses of the individual child. Children are classified as infrequent relapsers or frequent relapsers, and as being steroid dependent based on the number of relapses in a 12 mo period or their inability to remain in remission following discontinuation of steroid therapy.

Steroid Resistance. Steroid resistance is defined as the failure to achieve remission after 8 wk of corticosteroid therapy. Children with steroid-resistant nephrotic syndrome require further evaluation, including a diagnostic kidney biopsy, evaluation of kidney function, and quantitation of urine protein excretion (in addition to urine dipstick testing). Steroid-resistant nephrotic syndrome is

usually caused by FSGS (80%), MCNS, or membranoproliferative glomerulonephritis.

Implications of Steroid-Resistant Nephrotic Syndrome. Steroid-resistant nephrotic syndrome, and specifically FSGS, is associated with a 50% risk for end-stage kidney disease within 5 yr of diagnosis if patients do not achieve a partial or complete remission. Persistent nephrotic syndrome is associated with poor patient-reported quality of life, hypertension, serious infections, and thromboembolic events. Children reaching end-stage kidney disease have a greatly reduced life expectancy compared to their peers.

Alternative Therapies to Corticosteroids in the Treatment of Nephrotic Syndrome. Steroid-dependent patients, frequent relapsers, and steroid-resistant patients are candidates for alternative therapies, particularly if they have severe corticosteroid toxicity (cushingoid appearance, hypertension, cataracts, and/or growth failure). **Cyclophosphamide** prolongs the duration of remission and reduces the number of relapses in children with **frequently relapsing** and **steroid-dependent** nephrotic syndrome. The potential side effects of the drug (neutropenia, disseminated varicella, hemorrhagic cystitis, alopecia, sterility, increased risk of future malignancy) should be carefully reviewed with the family before initiating treatment. Cyclophosphamide (2 mg/kg) is given as a single oral dose for a total duration of 8-12 wk. Alternate-day prednisone therapy is often continued during the course of cyclophosphamide administration. During cyclophosphamide therapy, the white blood cell count must be monitored weekly and the drug should be withheld if the count falls below 5,000/mm^3. The cumulative threshold dose above which oligospermia or azoospermia occurs in boys is >250 mg/kg.

Calcineurin inhibitors (cyclosporine or tacrolimus) are recommended as initial therapy for children with steroid-resistant nephrotic syndrome. Children must be monitored for side effects, including hypertension, nephrotoxicity, hirsutism, and gingival hyperplasia. **Mycophenolate** can maintain remission in children with steroid-dependent or frequently relapsing nephrotic syndrome. **Levamisole,** an antihelmintic agent with immunomodulating effects that has been shown to reduce the risk of relapse in comparison to prednisone, is not available in the United States. There are also uncontrolled preliminary data regarding prolonged remissions achieved with **rituximab**, the chimeric monoclonal antibody against CD20, in children with steroid-dependent and/or steroid-resistant nephrotic syndrome. There are no data from randomized clinical trials directly comparing the various corticosteroid-sparing agents. Most children who respond to cyclosporine, tacrolimus, or mycophenolate therapy tend to relapse when the medication is discontinued. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may be helpful as adjunct therapy to reduce proteinuria in steroid-resistant patients.

Immunizations in Children with Nephrotic Syndrome. To reduce the risk of serious infections in children with nephrotic syndrome, give full pneumococcal vaccination (with the 13-valent conjugant vaccine and 23-valent polysaccharide vaccine) and influenza vaccination annually to the child and their household contacts; defer vaccination with live vaccines until the prednisone dose is below either 1 mg/kg daily or 2 mg/kg on alternate days. Live virus vaccines are contraindicated in children receiving corticosteroid-sparing agents such as cyclophosphamide or cyclosporine. Following close contact with varicella infection, give immunocompromised children on immunosuppressive agents varicella-zoster immune globulin if available; immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child, but avoid direct exposure of the child to gastrointestinal or respiratory secretions of vaccinated contacts for 3-6 wk after vaccination.

Table 527-4 provides monitoring recommendations for children with nephrotic syndrome.

Prognosis

Most children with steroid-responsive nephrotic syndrome have repeated relapses, which generally decrease in frequency as the child grows older. Although there is no proven way to predict an individual child's course, children who respond rapidly to steroids and those who have no relapses during the first 6 mo after diagnosis are likely to follow an infrequently relapsing course. It is important to indicate to the family that the child with steroid-responsive nephrotic syndrome is unlikely to develop chronic kidney disease, that the disease is rarely hereditary, and that the child (in the absence of prolonged cyclophosphamide therapy) will remain fertile. To minimize the psychologic

Table 527-4 Monitoring Recommendations for Children with Nephrotic Syndrome

DISEASE AND TREATMENT	HOME URINE PROTEIN	WEIGHT, GROWTH, BMI	BLOOD PRESSURE	CREATININE	ELECTROLYTES	SERUM GLUCOSE	CBC	LIPID PROFILE	DRUG LEVELS	LIVER FUNCTION	URINALYSIS	CPK
DISEASE TYPE												
Mild (steroid responsive)	•	•	•								•	
Moderate (frequent relapsing, steroid dependent)	•	•	•	•				•			•	
Severe (steroid resistant)	•	•	•	•				•			•	
THERAPY												
Corticosteroids		•	•			•		•				
Cyclophosphamide				•			•				•	
Mycophenolate mofetil							•			•		
Calcineurin inhibitors			•	•	•	•		•	•			
ACEIs/ARBs			•	•	•		•					
HMG-CoA reductase inhibitors								•		•		•

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CBC, complete blood count; CPK, creatine phospho kinase; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

From Gipson DS, Massengill SF, Yao L, et al: Management of childhood onset nephrotic syndrome, Pediatrics *124:747–757, 2009.*

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effects of the condition and its therapy, children with idiopathic nephrotic syndrome should not be considered chronically ill and should participate in all age-appropriate childhood activities and maintain an unrestricted diet when in remission.

Children with steroid-resistant nephrotic syndrome, most often caused by FSGS, generally have a much poorer prognosis. These children develop progressive renal insufficiency, ultimately leading to end-stage renal disease requiring dialysis or kidney transplantation. Recurrent nephrotic syndrome develops in 30-50% of transplant recipients with FSGS.

Bibliography is available at Expert Consult.

527.2 Secondary Nephrotic Syndrome

Priya Pais and Ellis D. Avner

Nephrotic syndrome can occur as a secondary feature of many forms of glomerular disease. Membranous nephropathy, membranoproliferative glomerulonephritis, postinfectious glomerulonephritis, lupus nephritis, and Henoch-Schönlein purpura nephritis can all have a nephrotic component (see Tables 527-1 and 527-2). Secondary nephrotic syndrome should be suspected in patients >8 yr and those with hypertension, hematuria, renal dysfunction, extrarenal symptoms (rash, arthralgias, fever), or depressed serum complement levels. In certain areas of the world, malaria and schistosomiasis are the leading causes of nephrotic syndrome. Other infectious agents associated with nephrotic syndrome include hepatitis B virus, hepatitis C virus, filaria, leprosy, and HIV.

Nephrotic syndrome has been associated with malignancy, particularly in the adult population. In patients with solid tumors, such as carcinomas of the lung and gastrointestinal tract, the renal pathology often resembles membranous glomerulopathy. Immune complexes composed of tumor antigens and tumor-specific antibodies presumably mediate the renal involvement. In patients with lymphomas, particularly Hodgkin lymphoma, the renal pathology most often resembles MCNS. The proposed mechanism of the nephrotic syndrome is that the lymphoma produces a lymphokine that increases permeability of the glomerular capillary wall. Nephrotic syndrome can develop before or after the malignancy is detected, resolve as the tumor regresses, and return if the tumor recurs.

Nephrotic syndrome has also developed during therapy with numerous drugs and chemicals. The histologic picture can resemble membranous glomerulopathy (penicillamine, captopril, gold, nonsteroidal antiinflammatory drugs, mercury compounds), MCNS (probenecid, ethosuximide, methimazole, lithium), or proliferative glomerulonephritis (procainamide, chlorpropamide, phenytoin, trimethadione, paramethadione).

Bibliography is available at Expert Consult.

527.3 Congenital Nephrotic Syndrome

Priya Pais and Ellis D. Avner

Nephrotic syndrome (massive proteinuria, hypoalbuminemia, edema, and hypercholesterolemia) has a poorer prognosis when it occurs in the 1st yr of life, when compared to nephrotic syndrome manifesting in childhood. Congenital nephrotic syndrome is defined as nephrotic syndrome manifesting at birth or within the *1st 3 mo of life*. Congenital nephrotic syndrome may be classified as primary or as secondary to a number of etiologies such as in utero infections (cytomegalovirus, toxoplasmosis, syphilis, hepatitides B and C, HIV), infantile systemic lupus erythematosus, or mercury exposure.

Primary congenital nephrotic syndrome is due to a variety of syndromes inherited as autosomal recessive disorders (see Table 527-3). A number of structural and functional abnormalities of the glomerular filtration barrier causing congenital nephrotic syndrome have been elucidated. In a large European cohort of children with congenital nephrotic syndrome, 85% carried disease-causing mutations in 4 genes (*NPHS1, NPHS2, WT1,* and *LAMB2*), the first 3 of which encode components of the glomerular filtration barrier. The Finnish type of congenital nephrotic syndrome is caused by mutations in the *NPHS1* or *NPHS2* gene, which encodes nephrin and podocin, critical components of the slit diaphragm. Affected infants most commonly present at birth with edema caused by massive proteinuria, and they are typically delivered with an enlarged placenta (>25% of the infant's weight). Severe hypoalbuminemia, hyperlipidemia, and hypogammaglobulinemia result from loss of filtering selectivity at the glomerular filtration barrier. Prenatal diagnosis can be made by the presence of elevated maternal and amniotic α-fetoprotein levels.

Denys-Drash syndrome is caused by mutations in the *WT1* gene, which results in abnormal podocyte function. Patients present with early-onset nephrotic syndrome, progressive renal insufficiency, ambiguous genitalia, and Wilms tumors.

Mutations in the *LAMB2* gene, seen in **Pierson syndrome,** lead to abnormalities of β_2-laminin, a critical component of glomerular and ocular basement membranes. In addition to congenital nephrotic syndrome, affected infants display bilateral microcoria (fixed narrowing of the pupil).

Regardless of the etiology of congenital nephrotic syndrome, diagnosis is made clinically in newborns or infants who demonstrate severe generalized edema, poor growth and nutrition with hypoalbuminemia, increased susceptibility to infections, hypothyroidism (from urinary loss of thyroxin-binding globulin), and increased risk of thrombotic events. Most infants have progressive renal insufficiency.

Secondary congenital nephrotic syndrome can resolve with treatment of the underlying cause, such as syphilis (Table 527-5). The management of primary congenital nephrotic syndrome includes intensive supportive care with intravenous albumin and diuretics, regular administration of intravenous γ-globulin, and aggressive nutritional support (often parenteral), while attempting to pharmacologically decrease urinary protein loss with angiotensin-converting enzyme

Table 527-5 Causes of Nephrotic Syndrome in Infants Younger Than 1 Year

SECONDARY CAUSES
Infections
Syphilis
Cytomegalovirus
Toxoplasmosis
Rubella
Hepatitis B
HIV
Malaria
Drug reactions
Toxins
Mercury
Systemic lupus erythematosus
Syndromes with associated renal disease
Syndromes with associated renal disease
Nail-patella syndrome
Lowe syndrome
Nephropathy associated with congenital brain malformation
Denys-Drash syndrome: Wilms tumor
Hemolytic-uremic syndrome
PRIMARY CAUSES
Congenital nephrotic syndrome
Diffuse mesangial sclerosis
Minimal change disease
Focal segmental sclerosis
Membranous nephropathy

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Saunders, p. 418.*

inhibitors, angiotensin II receptor inhibitors, and prostaglandin synthesis inhibitors, or even unilateral nephrectomy. If conservative management fails and patients suffer from persistent anasarca or repeated severe infections, bilateral nephrectomies are performed and chronic dialysis is initiated. Renal transplantation is the definitive treatment of congenital nephrotic syndrome, though recurrence of the nephrotic syndrome has been reported to occur after transplantation.

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Section 4
Tubular Disorders

Chapter 528
Tubular Function

Rajasree Sreedharan and Ellis D. Avner

Water and electrolytes are freely filtered at the level of the glomerulus. Thus, the electrolyte content of ultrafiltrate at the beginning of the proximal tubule is similar to that of plasma. Carefully regulated processes of tubular reabsorption and/or tubular secretion determine the final water content and electrolyte composition of urine. Bulk movement of solute tends to occur in the proximal portions of the nephron, and fine adjustments tend to occur distally (see Chapter 55).

SODIUM

Sodium is essential in maintaining extracellular fluid balance and, thus, volume status. The kidney is capable of effecting large changes in sodium excretion in a variety of normal and pathologic states.

There are 4 main sites of sodium transport. Approximately 60% of sodium is absorbed in the proximal tubule by coupled transport with glucose or amino acids, 25% in the ascending loop of Henle (mediated by NKCC2, the bumetanide-sensitive sodium-potassium 2 chloride transporter), and 15% in the distal tubule (mediated by NCCT, the thiazide-sensitive sodium chloride cotransporter) and collecting tubule (mediated by ENaC, the epithelial sodium channel).

The urinary excretion of sodium normally approximates the sodium intake of 2-6 mEq/kg/24 hr for a child consuming a typical American diet, minus 1-2 mEq/kg/24 hr required for normal metabolic processes. However, in states of volume depletion (dehydration, blood loss) or decreased effective circulating blood volume (septic shock, hypoalbuminemic states, heart failure), there may be a dramatic decrease in urinary sodium excretion to as low as 1 mEq/L. Changes in systemic volume status are detected by (1) baroreceptors in the atria, afferent arteriole, and carotid sinus and (2) by the macula densa, which detects changes in chloride delivery.

The major hormonal mechanisms mediating sodium balance include the renin–angiotensin–aldosterone axis, atrial natriuretic factor, and norepinephrine. Angiotensin II and aldosterone increase sodium reabsorption in the proximal tubule and distal tubule, respectively. Norepinephrine, released in response to volume depletion, does not directly act on tubular transport mechanisms but affects sodium balance by decreasing renal blood flow, thus decreasing the filtered load of sodium as well as stimulating renin release. With more severe volume depletion, antidiuretic hormone is also released (see Chapter 530). Sodium excretion is promoted by atrial natriuretic factor and suppression of renin.

POTASSIUM

Extracellular potassium homeostasis is regulated because small changes in plasma potassium concentrations have dramatic effects on cardiac, neural, and neuromuscular function (see Chapter 55.4). Essentially, all filtered potassium is fully reabsorbed in the proximal tubule. Therefore, urinary excretion of potassium is completely dependent on tubular secretion by potassium channels present in the principal cells of the collecting tubule. Factors that promote potassium secretion include aldosterone, increased sodium delivery to the distal nephron, and increased urine flow rate.

CALCIUM

A significant portion of filtered calcium (70%) is reabsorbed in the proximal tubule. Additional calcium is reabsorbed in the ascending loop of Henle (20%) and the distal tubule and collecting duct (5-10%). Calcium is reabsorbed by passive movement between cells (paracellular absorption) in a process driven by sodium chloride reabsorption and potassium recycling into the lumen. In addition, calcium uptake is actively regulated by calcium receptors, specific transporters, and calcium channels. Factors that promote calcium reabsorption include parathyroid hormone (released in response to hypocalcemia), calcitonin, vitamin D, thiazide diuretics, and volume depletion (see Chapter 570). Factors that promote calcium excretion include volume expansion, increased sodium intake, and diuretics such as mannitol and furosemide.

PHOSPHATE

The majority of filtered phosphate is reabsorbed in the proximal tubule by active transport. Reabsorption is increased by dietary phosphorus restriction, volume contraction, and growth hormone. Parathyroid hormone and volume expansion increase phosphate excretion.

MAGNESIUM

Approximately 25% of filtered magnesium is reabsorbed in the proximal tubule. Modulation of renal magnesium excretion occurs primarily in the ascending loop of Henle, with some contribution of the distal convoluted tubule. Although specific magnesium transporters have been identified, the precise mechanisms by which they are regulated remain unclear.

ACIDIFICATION AND CONCENTRATING MECHANISMS

Acidification and concentration are addressed in the sections on renal tubular acidosis and nephrogenic diabetes insipidus, respectively (see Chapters 529 and 530).

DEVELOPMENTAL CONSIDERATIONS

Tubular transport capabilities of neonates (especially premature infants) and young infants are less than those of adults. Although nephrogenesis (the formation of new glomerular/tubular units) is complete by about 36 wk of gestation, significant tubular maturation occurs during infancy. Renal tubular immaturity, reduced glomerular filtration rate, decreased concentrating gradient, and diminished responsiveness to antidiuretic hormone are characteristic of young infants. These factors can contribute to impaired regulation of water, solute, and electrolyte and acid–base homeostasis, particularly during times of acute illness.

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Chapter 529

Renal Tubular Acidosis

Rajasree Sreedharan and Ellis D. Avner

Renal tubular acidosis (RTA) is a disease state characterized by a normal anion gap (hyperchloremic) metabolic acidosis in the setting of normal or near-normal glomerular filtration rate. There are 4 main types: proximal (type II) RTA, classic distal (type I) RTA, hyperkalemic (type IV) RTA, and combined proximal and distal (type III). Proximal RTA results from impaired bicarbonate reabsorption and distal RTA from failure to secrete acid. Either of these defects may be inherited and persistent from birth or acquired, as is seen more commonly in clinical practice.

NORMAL URINARY ACIDIFICATION

Kidneys contribute to acid–base balance by reabsorption of filtered bicarbonate (HCO_3^-) and excretion of hydrogen ion (H^+) produced every day. Hydrogen ion secretion from tubule cells into the lumen is key in the reabsorption of HCO_3^-, and the formation of titratable acid (H^+ bound to buffers such as HPO_4^{2-}), and ammonium ions (NH_4^+). Because loss of filtered HCO_3^- is equivalent to addition of H^+ to the body, all filtered bicarbonate should be absorbed before dietary H^+ can be excreted. Approximately 90% of filtered bicarbonate is absorbed in the proximal tubule, and the remaining 10% in the distal segments, mostly the thick ascending limb and outer medullary collecting tubule (Fig. 529-1). In the proximal tubule and thick ascending limb of the loop of Henle, H^+ from water is secreted by the Na^+-H^+ exchanger on the luminal membrane. H^+ combines with filtered bicarbonate resulting in the formation of H_2CO_3, which splits into water and CO_2 in the presence of carbonic anhydrase IV. CO_2 diffuses freely back into the cell, combines with OH^- (from H_2O) to form HCO_3^- in the presence of carbonic anhydrase II, and returns to the systemic circulation via a Na^+-HCO_3^- cotransporter situated at the basolateral membrane of the cell. In the collecting tubule, H^+ is secreted into lumen by H^+ATPase (adenosine triphosphatase) and HCO_3^- is returned to the systemic circulation by the HCO_3^--Cl^- exchanger located on the basolateral membrane. The H^+ secreted proximally and distally in excess of the filtered HCO_3^- is excreted in the urine either as titratable acid or as NH_4^+.

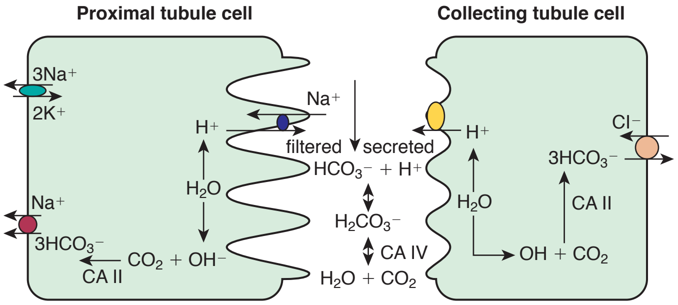

Figure 529-1 **Major cellular luminal events in acid–base regulation in the proximal and the collecting tubule cells.** In the proximal tubule, H^+, split from H_2O, is secreted into the lumen via Na^+/H^+ exchanger, and HCO_3^-, formed by combination of OH^- (split from H_2O) with CO_2 in the presence of carbonic anhydrase (CA) II, is returned to the systemic circulation by an Na^+-$3HCO_3^-$ cotransporter. Similarly, in the collecting tubule, H^+ is secreted into the lumen by an active H^+-ATPase (adenosine triphosphatase), and HCO_3^- is returned to the systemic circulation via an HCO_3^--Cl^- exchanger. H^+ secreted into the lumen combines with filtered HCO_3^- to form carbonic acid (H_2CO_3) and then CO_2 and H_2O in the presence of CA IV, which can be passively reabsorbed. *(Modified from Rose BD, Post TW:* Clinical physiology of acid-base and electrolyte disorders, *ed 5, New York, 2001, McGraw-Hill.)*

529.1 Proximal (Type II) Renal Tubular Acidosis

Rajasree Sreedharan and Ellis D. Avner

PATHOGENESIS

Proximal RTA can be inherited and persistent from birth or occur as a transient phenomenon during infancy. Although rare, it may be primary and isolated. Proximal RTA usually occurs as a component of global proximal tubular dysfunction or **Fanconi syndrome,** which is characterized by low-molecular-weight proteinuria, glycosuria, phosphaturia, aminoaciduria, and proximal RTA. Table 529-1 outlines the causes of proximal RTA (pRTA) and Fanconi syndrome. Many of these causes are inherited disorders. In addition to **cystinosis** and **Lowe syndrome,** autosomal recessive and dominant pRTA are addressed further in this section. Other inherited forms of Fanconi syndrome include **galactosemia** (see Chapter 87.2), **hereditary fructose intolerance** (see Chapter 87.3), **tyrosinemia** (see Chapter 85.2), and **Wilson disease** (see Chapter 357.2). **Dent disease** or X-linked nephrolithiasis, is discussed in Chapter 531.3. In children, an important form of secondary Fanconi syndrome is exposure to ifosfamide, a component of many treatment regimens for Wilms tumor and other solid tumors.

Autosomal Recessive Disease

Isolated **autosomal recessive pRTA** is caused by mutations in the gene encoding the sodium bicarbonate cotransporter NBC1. It manifests with ocular abnormalities (band keratopathy, cataracts, and glaucoma, often leading to blindness), short stature, enamel defects of the teeth, intellectual impairment, and occasionally basal ganglia calcification along with pRTA. Autosomal dominant pattern of inheritance has been identified in a single pedigree with 9 members presenting with hyperchloremic metabolic acidosis, normal ability to acidify urine, normal renal function, and growth retardation.

Cystinosis

Cystinosis is a systemic disease caused by a defect in the metabolism of cysteine that results in accumulation of cystine crystals in most of the major organs of the body, notably the kidney, liver, eye, and brain. It occurs at an incidence of 1 : 100,000 to 1 : 200,000. In certain populations, such as French Canadians, the incidence is much higher. At least 3 clinical patterns have been described. Young children with the most severe form of the disease (*infantile* or *nephropathic cystinosis*) present in the 1st 2 yr of life with severe tubular dysfunction and growth failure. If the disease is not treated, the children develop end-stage renal disease by the end of their 1st decade. A milder form of the disease manifests in adolescents and is characterized by less-severe tubular abnormalities and a slower progression to renal failure. A benign adult form with no renal involvement also exists.

Cystinosis is caused by mutations in the *CTNS* gene, which encodes a novel protein, cystinosin. Cystinosin is thought to be an H^+-driven lysosomal cystine transporter. Genotype–phenotype studies demonstrate that patients with severe nephropathic cystinosis carry mutations that lead to complete loss of cystinosin function. Patients with milder clinical disease have mutations that lead to expression of partially functional protein. Patients with nephropathic cystinosis present with **clinical manifestations** reflecting their pronounced tubular dysfunction and Fanconi syndrome, including polyuria and polydipsia, growth failure, and rickets. Fever, caused by dehydration or diminished sweat production, is common. Patients are typically fair skinned and blond because of diminished pigmentation. Ocular presentations include photophobia, retinopathy, and impaired visual acuity. Patients also can develop hypothyroidism, hepatosplenomegaly, and delayed sexual

Table 529-1 Common Causes of Renal Tubular Acidosis

PROXIMAL RENAL TUBULAR ACIDOSIS
Primary
Sporadic
Inherited
• Inherited renal disease (idiopathic Fanconi)
  • Sporadic (most common)
  • Autosomal dominant
  • Autosomal recessive
  • X-linked (Dent disease)
• Inherited syndromes
  • Cystinosis
  • Tyrosinemia type 1
  • Galactosemia
  • Oculocerebral dystrophy (Lowe syndrome)
  • Wilson disease
• Hereditary fructose intolerance
Secondary
Intrinsic renal disease
• Autoimmune diseases (Sjögren syndrome)
• Hypokalemic nephropathy
• Renal transplant rejection
Hematologic disease
• Myeloma
Drugs
• Gentamicin
• Cisplatin
• Ifosfamide
• Sodium valproate
Heavy metals
• Lead
• Cadmium
• Mercury
Organic compounds
• Toluene
Nutritional
• Kwashiorkor
Hormonal
• Primary hyperparathyroidism
	Secondary
	Intrinsic renal
	• Interstitial nephritis
	• Pyelonephritis
	• Transplant rejection
	• Sickle cell nephropathy
	• Lupus nephritis
	• Nephrocalcinosis
	• Medullary sponge kidney
	Urologic
	• Obstructive uropathy
	• Vesicoureteral reflux
	• Hepatic
	• Cirrhosis
	Toxins or medications
	• Amphotericin B
	• Lithium
	• Toluene
	• Cisplatin

DISTAL RENAL TUBULAR ACIDOSIS
Primary
Sporadic
Inherited
• Inherited renal diseases
  • Autosomal dominant
  • Autosomal recessive
  • Autosomal recessive with early-onset hearing loss
  • Autosomal recessive with later-onset hearing loss
• Inherited syndromes associated with type I renal tubular acidosis
  • Marfan syndrome
  • Wilson syndrome
  • Ehlers-Danlos syndrome
• Familial hypercalciuria
	HYPERKALEMIC RENAL TUBULAR ACIDOSIS
	Primary
	Sporadic
	Genetic
	• Hypoaldosteronism
	• Addison disease
	• Congenital adrenal hyperplasia
	• Pseudohypoaldosteronism (type I or II)
	Secondary
	Urologic
	• Obstructive uropathy
	Intrinsic renal
	• Pyelonephritis
	• Interstitial nephritis
	Systemic
	• Diabetes mellitus
	• Sickle cell nephropathy
	Drugs
	• Trimethoprim/sulfamethoxazole
	• Angiotensin-converting enzyme inhibitors
	• Cyclosporine
	• Prolonged heparinization
	Addison disease

maturation. With progressive tubulointerstitial fibrosis, renal insufficiency is invariant.

The **diagnosis** of cystinosis is suggested by the detection of cystine crystals in the cornea and confirmed by measurement of increased leukocyte cystine content. Prenatal testing is available for at-risk families.

Treatment of cystinosis is directed at correcting the metabolic abnormalities associated with Fanconi syndrome or chronic renal failure. In addition, specific therapy is available with **cysteamine,** which binds to cystine and converts it to cysteine. This facilitates lysosomal transport and decreases tissue cystine. Oral cysteamine does not achieve adequate levels in ocular tissues, so additional therapy with cysteamine eyedrops is required. Early initiation of the drug can prevent or delay deterioration of renal function. Patients with growth failure that does not improve with cysteamine might benefit from treatment with growth hormone. Kidney transplantation is a viable option in patients with renal failure. With prolonged survival, additional complications may become evident, including central nervous system abnormalities, muscle weakness, swallowing dysfunction, and pancreatic insufficiency. It is unclear whether long-term cysteamine therapy will decrease these complications.

Lowe Syndrome

Lowe syndrome *(oculocerebrorenal syndrome of Lowe)* is a rare X-linked disorder characterized by congenital cataracts, mental retardation, and Fanconi syndrome. The disease is caused by mutations in the *OCRL1* gene, which encodes the phosphatidylinositol polyphosphate 5-phosphatase protein. The abnormalities seen in Lowe syndrome are thought to be caused by abnormal transport of vesicles within the Golgi apparatus. Kidneys show nonspecific tubulointerstitial changes. Thickening of glomerular basement membrane and changes in proximal tubule mitochondria are also seen.

Patients with Lowe syndrome typically present in infancy with cataracts, progressive growth failure, hypotonia, and Fanconi syndrome. Significant proteinuria is common. Blindness and renal insufficiency often develop. Characteristic behavioral abnormalities are also seen, including tantrums, stubbornness, stereotypy (repetitive behaviors), and obsessions. There is no specific therapy for the renal disease or neurologic deficits. Cataract removal is generally required.

CLINICAL MANIFESTATIONS OF PROXIMAL RENAL TUBULAR ACIDOSIS AND FANCONI SYNDROME

Patients with isolated, sporadic, or inherited pRTA present with growth failure in the 1st yr of life. Additional symptoms can include polyuria, dehydration (from sodium loss), anorexia, vomiting, constipation, and hypotonia. Patients with primary Fanconi syndrome have additional symptoms, secondary to phosphate wasting, such as rickets. Those with systemic diseases present with additional signs and symptoms specific to their underlying disease. *A non–anion gap metabolic acidosis is present*. Urinalysis in patients with isolated pRTA is generally unremarkable. The urine pH is acidic (<5.5) because distal acidification mechanisms are intact in these patients. Urinary indices in patients with Fanconi syndrome demonstrate varying degrees of phosphaturia, aminoaciduria, glycosuria, uricosuria, and elevated urinary sodium or potassium. Depending on the nature of the underlying disorder, laboratory evidence of chronic renal insufficiency, including elevated serum creatinine, may be present.

529.2 Distal (Type I) Renal Tubular Acidosis

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PATHOGENESIS

Distal RTA can be sporadic or inherited. It can also occur as a complication of inherited or acquired diseases of the distal tubules. Primary or secondary causes of distal RTA can result in damaged or impaired functioning of one or more transporters or proteins involved in the acidification process, including the H^+/ATPase, the HCO_3^-/Cl^- anion exchangers, or the components of the aldosterone pathway. Because of impaired hydrogen ion excretion, urine pH cannot be reduced to <5.5, despite the presence of severe metabolic acidosis. Loss of sodium bicarbonate distally, owing to lack of H^+ to bind to in the tubular lumen (see Fig. 529-1), results in increased chloride absorption and hyperchloremia. Inability to secrete H^+ is compensated by increased K^+ secretion distally, leading to hypokalemia. **Hypercalciuria** is usually present and can lead to nephrocalcinosis or nephrolithiasis. Chronic metabolic acidosis also impairs urinary citrate excretion. **Hypocitraturia** further increases the risk of calcium deposition in the tubules. Bone disease is common, resulting from mobilization of organic components from bone to serve as buffers to chronic acidosis.

CLINICAL MANIFESTATIONS

Distal RTA shares features with those of pRTA, including non–anion gap metabolic acidosis and growth failure; distinguishing features of distal RTA include nephrocalcinosis and hypercalciuria. The phosphate and massive bicarbonate wasting characteristic of pRTA is generally absent. Table 529-1 lists the causes of primary and secondary distal RTA. Although inherited forms are rare, 3 specific inherited forms of distal RTA have been identified, including an autosomal recessive form associated with sensorineural deafness.

Medullary sponge kidney is a relatively rare sporadic disorder in children, although not uncommon in adults. It is characterized by cystic dilation of the terminal portions of the collecting ducts as they enter the renal pyramids. Ultrasonographically, patients often have medullary nephrocalcinosis. Although patients with this condition typically maintain normal renal function through adulthood, complications include nephrolithiasis, pyelonephritis, hyposthenuria (inability to concentrate urine), and distal RTA. Associations of medullary sponge kidney with Beckwith-Wiedemann syndrome or hemihypertrophy have been reported.

529.3 Hyperkalemic (Type IV) Renal Tubular Acidosis

Rajasree Sreedharan and Ellis D. Avner

PATHOGENESIS

Type IV RTA occurs as the result of impaired aldosterone production *(hypoaldosteronism)* or impaired renal responsiveness to aldosterone *(pseudohypoaldosteronism)*. Acidosis results because aldosterone has a direct effect on the H^+/ATPase responsible for hydrogen secretion. In addition, aldosterone is a potent stimulant for potassium secretion in the collecting tubule; consequently, lack of aldosterone results in hyperkalemia. This further affects acid–base status by inhibiting ammoniagenesis and, thus, H^+ excretion. Aldosterone deficiency typically occurs as a result of adrenal gland disorders such as Addison disease or some forms of congenital adrenal hyperplasia. In children, aldosterone unresponsiveness is a more common cause of type IV RTA. This can occur transiently, during an episode of acute pyelonephritis or acute urinary obstruction, or chronically, particularly in infants and children with a history of obstructive uropathy. The latter patients can have significant hyperkalemia, even in instances when renal function is normal or only mildly impaired. Rare examples of inherited forms of type IV RTA have been identified.

CLINICAL MANIFESTATIONS

Patients with type IV RTA can present with growth failure in the first few years of life. Polyuria and dehydration (from salt wasting) are common. Rarely, patients (especially those with pseudohypoaldosteronism type 1) present with life-threatening hyperkalemia. Patients with obstructive uropathies can present acutely with signs and symptoms of pyelonephritis, such as fever, vomiting, and foul-smelling urine. Laboratory tests reveal a hyperkalemic non–anion gap metabolic acidosis. Urine may be alkaline or acidic. Elevated urinary sodium levels with inappropriately low urinary potassium levels reflect the absence of aldosterone effect.

DIAGNOSTIC APPROACH TO RENAL TUBULAR ACIDOSIS

The first step in the evaluation of a patient with suspected RTA is to confirm the presence of a normal anion gap metabolic acidosis, identify electrolyte abnormalities, assess renal function, and rule out other causes of bicarbonate loss such as diarrhea (see Chapter 55). Metabolic acidosis associated with diarrheal dehydration is extremely common, and acidosis generally improves with correction of volume depletion. Patients with protracted diarrhea can deplete their total-body bicarbonate stores and can have persistent acidosis despite apparent restoration of volume status. In instances where a patient has a recent history of severe diarrhea, full evaluation for RTA should be delayed for several days to permit adequate time for reconstitution of total-body bicarbonate stores. If acidosis persists beyond a few days in this setting, additional studies are indicated.

Serum electrolytes, blood urea nitrogen, calcium, phosphorus, creatinine, and pH should be obtained by venous puncture. Traumatic blood draws (such as heel-stick specimens), small volumes of blood in "adult-size" specimen collection tubes, or prolonged specimen transport time at room temperature can lead to falsely low bicarbonate levels, often in association with an elevated serum potassium value. True hyperkalemic acidosis is consistent with type IV RTA, whereas the finding of normal or low potassium suggests type I or II. The **blood anion gap** should be calculated using the formula $[Na^+] - [Cl^- + HCO_3^-]$. Values of <12 demonstrate the absence of an anion gap. Values of >20 indicate the presence of an anion gap. If such an anion gap is found, then other diagnoses (lactic acidosis, inborn errors of

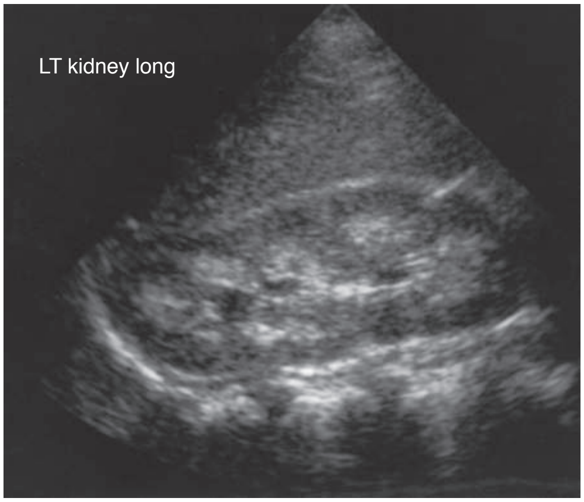

Figure 529-2 Ultrasound examination of a child with distal RTA demonstrating medullary nephrocalcinosis.

metabolism, ingested toxins) should be investigated. If tachypnea is noted, evaluation of an arterial blood gas might help to rule out the possibility of a mixed acid-base disorder primarily involving respiratory and metabolic components. A detailed history, with particular attention to growth and development, recent or recurrent diarrheal illnesses, and a family history of mental retardation, failure to thrive, end-stage renal disease, infant deaths, or miscarriages is essential. Physical examination should determine growth parameters and volume status as well as the presence of any dysmorphic features suggesting an underlying syndrome.

Once the presence of a non–anion gap metabolic acidosis is confirmed, urine pH can help distinguish distal from proximal causes. A urine pH <5.5 in the presence of acidosis suggests pRTA, whereas patients with distal RTA typically have a urine pH >6.0. The **urine anion gap** ([urine Na^+ + urine K^+] – urine Cl^-) is sometimes calculated to confirm the diagnosis of distal RTA. A positive gap suggests a deficiency of ammoniagenesis and, thus, the possibility of a distal RTA. A negative gap is consistent with proximal tubule bicarbonate wasting (gastrointestinal bicarbonate wasting). A urinalysis should also be obtained to determine the presence of glycosuria, proteinuria, or hematuria, suggesting more global tubular damage or dysfunction. Random or 24 hr urine calcium and creatinine measurements will identify hypercalciuria. Renal ultrasonography should be performed to identify underlying structural abnormalities such as obstructive uropathies as well as to determine the presence of nephrocalcinosis (Fig. 529-2).

TREATMENT AND PROGNOSIS

The mainstay of therapy in all forms of RTA is bicarbonate replacement. Patients with pRTA often require large quantities of bicarbonate, up to 20 mEq/kg/24 hr, in the form of sodium bicarbonate or sodium citrate solution (Bicitra or Shohl solution). The base requirement for distal RTAs is generally in the range of 2-4 mEq/kg/24 hr, although patients' requirements can vary. Patients with Fanconi syndrome usually require phosphate supplementation. Patients with distal RTA should be monitored for the development of hypercalciuria. Those with symptomatic hypercalciuria (recurrent episodes of gross hematuria), nephrocalcinosis, or nephrolithiasis can require thiazide diuretics to decrease urine calcium excretion. Patients with type IV RTA can require chronic treatment for hyperkalemia with sodium-potassium exchange resin (Kayexalate).

Prognosis of RTA depends to a large part on the nature of any existing underlying disease. Patients with treated isolated proximal or distal RTA generally demonstrate improvement in growth, provided serum bicarbonate levels can be maintained in the normal range. Patients with systemic illness and Fanconi syndrome can have ongoing morbidity with growth failure, rickets, and signs and symptoms related to their underlying disease.

Bibliography is available at Expert Consult.

529.4 Rickets Associated with Renal Tubular Acidosis

Russell W. Chesney

Rickets may be present in primary RTA, particularly in type II or pRTA. Hypophosphatemia and phosphaturia are common in the renal tubular acidoses, which are also characterized by hyperchloremic metabolic acidosis, various degrees of bicarbonaturia, and, often, hypercalciuria and hyperkaluria. Bone demineralization without overt rickets usually is detected in type I and distal RTA. This metabolic bone disease may be characterized by bone pain, growth retardation, osteopenia, and, occasionally, pathologic fractures. Although acute metabolic acidosis in vitamin D–deficient animals can impair the conversion of 25-hydroxyvitamin D (25[OH]D) to 1,25-dihydroxyvitamin D (1,25[OH]$_2$D), resulting in reduced levels of this active metabolite, the circulating levels of 1,25(OH)$_2$D in patients with either type of RTA are generally normal. If patients with RTA have chronic renal insufficiency, serum 1,25(OH)$_2$D levels are reduced in relation to the degree of renal impairment.

Bone demineralization in distal RTA probably relates to dissolution of bone because the calcium carbonate in bone serves as a buffer against the metabolic acidosis due to the hydrogen ions retained by patients with RTA.

Administration of sufficient bicarbonate to reverse acidosis reverses bone dissolution and the hypercalciuria that is common in distal RTA. Proximal RTA is treated with both bicarbonate and oral phosphate supplements to heal rickets. Doses of phosphate similar to those used in familial hypophosphatemia or Fanconi syndrome may be indicated. Vitamin D is required to offset the secondary hyperparathyroidism that complicates oral phosphate therapy. Following therapy, growth in patients with type II (proximal) RTA is greater than in patients with primary Fanconi syndrome. In addition, "double osteomalacia" may be evident when patients with either type of RTA also have vitamin D deficiency.

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Chapter 530

Nephrogenic Diabetes Insipidus

Rajasree Sreedharan and Ellis D. Avner

Nephrogenic diabetes insipidus (NDI) is a rare congenital or, more commonly, acquired, disorder of water metabolism characterized by an inability to concentrate urine, even in the presence of antidiuretic hormone (ADH). The most common pattern of inheritance in congenital NDI is as an X-linked recessive disorder. Rarely, affected females are seen, presumably secondary to partial X-chromosome inactivation. Approximately 10% of cases of congenital NDI are inherited as autosomal dominant or recessive disorders, with males and females affected equally. The clinical phenotype of autosomal recessive forms is similar to that of the X-linked form. Secondary (acquired), either partial or complete, forms of NDI are not uncommon. They may be seen in many disorders affecting renal tubular

function including obstructive uropathies, acute or chronic renal failure, renal cystic diseases, interstitial nephritis, nephrocalcinosis, or toxic nephropathy caused by hypokalemia, hypercalcemia, lithium, or amphotericin B.

PATHOGENESIS

The ability to concentrate urine (and thus absorb water) requires the delivery of urine to the collecting tubule; an intact concentrating gradient in the renal medulla; and the ability to modulate water permeability in the collecting tubule by ADH. ADH (also called arginine vasopressin [AVP]), is synthesized in the hypothalamus and stored in the posterior pituitary. Under basal situations, the collecting tubule is impermeable to water. However, in response to increased serum osmolarity (as detected by osmoreceptors in the hypothalamus) and/or severe volume depletion, ADH is released into the systemic circulation. It then binds to its receptor, vasopressin V_2 (AVPR2), on the basolateral membrane of the collecting tubule cell. Binding of the hormone to its receptor activates a cyclic adenosine monophosphate–dependent cascade that results in movement of preformed water channels (aquaporin 2 [AQP2]) to the luminal membrane of the collecting duct, rendering it permeable to water.

Defects in the *AVPR2* gene cause the more common X-linked form of NDI. Mutations in the *AQP2* gene have been identified in patients with the rarer autosomal dominant and recessive forms. Prenatal testing is available for families at risk for X-linked NDI. Patients with secondary forms of NDI can have ADH resistance owing to defective aquaporin expression (lithium intoxication). Secondary ADH resistance usually occurs as the result of loss of the hypertonic medullary gradient as a result of solute diuresis or tubular damage, resulting in the inability to absorb sodium or urea.

CLINICAL MANIFESTATIONS

Patients with congenital NDI typically present in the newborn period with massive polyuria, volume depletion, hypernatremia, and hyperthermia. Irritability and crying are common features. Constipation and poor weight gain are also seen. After multiple episodes of hypernatremic dehydration, patients can have developmental delay and mental retardation. Enuresis, caused by large urine volumes, is common. Because of the need to consume large volumes of water during the day, patients often have diminished appetite and poor food intake. However, even with adequate caloric supplementation, patients still exhibit growth abnormalities. Patients with congenital NDI also exhibit behavioral problems, including hyperactivity and short-term memory problems. Patients with the secondary form generally present later in life, primarily with hypernatremia and polyuria. Associated symptoms such as developmental delay and behavioral abnormalities are less common in this latter group.

DIAGNOSIS

The diagnosis is suggested in a male infant with polyuria, hypernatremia, and diluted urine. Simultaneous serum and urine osmolality measurements should be obtained. **If the serum osmolality value is 290 mOsm/kg or higher with a simultaneous urine osmolality value of <290 mOsm/kg, a formal water deprivation test is not necessary.** Because the differential diagnosis includes causes of **central diabetes insipidus,** the inability to respond to ADH (and thus the presence of NDI) should then be confirmed by the administration of vasopressin (10-20 μg intranasally) followed by serial urine and serum osmolality measurements hourly for 4 hr. In patients with possible "partial" or secondary diabetes insipidus, in whom the initial serum osmolality value may be <290 mOsm/kg, a water-deprivation test should be considered. Fluids should be withheld and urine and serum osmolalities measured periodically until the serum osmolality value is >290 mOsm/kg; vasopressin is then given as before. Criteria for premature termination of a water-deprivation test include a decrease in body weight of >3%. If NDI is confirmed or suspected, additional evaluation should include a detailed history to assess possible toxic exposures, determination of renal function by serum creatinine and blood urea nitrogen levels, and renal ultrasonography to identify obstructive uropathies or cystic disease. Because of massive urine output, patients with congenital NDI can have *nonobstructive hydronephrosis* of varying severity.

TREATMENT AND PROGNOSIS

Treatment of NDI includes maintenance of adequate fluid intake and access to free water, minimizing urine output by limiting solute load with a low-osmolar, low-sodium diet, and administering medications directed at decreasing urine output. For infants, human milk or a low-solute formula, such as Similac PM 60/40, is preferred. Most infants with congenital NDI require gastrostomy or nasogastric feedings to ensure adequate fluid administration throughout the day and night. Sodium intake in older patients should be <0.7 mEq/kg/24 hr. Thiazide diuretics (2-3 mg/kg/24 hr of hydrochlorothiazide) effectively induce sodium loss and stimulate proximal tubule reabsorption of water. Potassium-sparing diuretics, in particular, amiloride (0.3 mg/kg/24 hr in 3 divided doses), are often indicated. Patients who have an inadequate response to diuretics alone might benefit from the addition of indomethacin (2 mg/kg/24 hr), which has an additive effect in reducing water excretion in some patients. Renal function must be monitored closely in such patients because indomethacin can cause deterioration in renal function over time. Patients with secondary NDI might not require medications but should have access to free water. Such patients should have serum electrolytes and volume status monitored closely, particularly during periods of superimposed acute illnesses.

Prevention of recurrent dehydration and hypernatremia in patients with congenital NDI has significantly improved the neurodevelopmental outcome of these patients. However, behavioral issues remain a significant problem. In addition, chronic use of nonsteroidal antiinflammatory drugs can predispose patients to renal insufficiency. Prognosis of patients with secondary NDI generally depends on the nature of the underlying disease.

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Chapter 531

Bartter and Gitelman Syndromes and Other Inherited Tubular Transport Abnormalities

531.1 Bartter Syndrome

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Bartter syndrome is a group of disorders characterized by hypokalemic metabolic alkalosis with hypercalciuria and salt wasting (see Chapter 55) (Table 531-1). **Antenatal** Bartter syndrome (types I, II, and IV; also called **hyperprostaglandin E syndrome**) typically manifests in infancy and has a more-severe phenotype than **classic** Bartter syndrome (type III); perinatal onset includes maternal polyhydramnios, neonatal salt wasting, and severe episodes of recurrent dehydration. The milder

Table 531-1 Bartter and Gitelman Syndromes

	TYPE I BARTTER SYNDROME	TYPE II BARTTER SYNDROME	TYPE III BARTTER SYNDROME	TYPE IV BARTTER SYNDROME	TYPE V BARTTER SYNDROME	GITELMAN SYNDROME
Inheritance	AR	AR	AR	AR	AD	AR
Affected tubular region	TAL	TAL + CCD	TAL + DCT	TAL + DCT	TAL	DCT
Gene	*SLC12A2*	*KCNJ1*	*CLCBRK*	*BSND*	*CASR*	*SLC12A3* Few have *CLCNKB*
Onset	Prenatal, postnatal	Prenatal, postnatal	Variable	Prenatal, postnatal	Variable	Adolescent, adult
Urine PGE2	Very high	Very high	Slightly elevated	Elevated	Elevated	Normal
Hypokalemic metabolic alkalosis	Present	Present	Present	Present	Present	Present
Features	Polyhydramnios, prematurity, nephrocalcinosis, dehydration, hyposthenuria, polyuria, failure to thrive	Same as type I	Failure to thrive, dehydration, salt craving, low serum magnesium in 20%, mildest form	Same as type I, with sensorineural hearing loss and no nephrocalcinosis	Hypocalcemia, low parathyroid hormone levels, hypercalciuria, uncommon cause of Bartter syndrome	Hypomagnesemia in 100%, mild dehydration, occasional growth retardation, tetany

AD, autosomal dominant; AR, autosomal recessive; CCD, cortisol collecting duct; DCT, descending convoluted tubule; PGE_2, prostaglandin E_2; TAL, thick ascending loop of Henle.

phenotype, **classic** Bartter syndrome, manifests in childhood with failure to thrive and a history of recurrent episodes of dehydration. A phenotypically related disease, Gitelman syndrome, has a distinct genetic defect and is discussed in Chapter 531.2 (Table 531-1). One distinct variant of antenatal Bartter syndrome is associated with sensorineural deafness (type IV).

PATHOGENESIS

The biochemical features of Bartter syndrome, including hypokalemic metabolic alkalosis with hypercalciuria, resemble those seen with chronic use of loop diuretics and reflect a defect in sodium, chloride, and potassium transport in the ascending loop of Henle. The loss of sodium and chloride, with resultant volume contraction, stimulates the renin–angiotensin II–aldosterone axis. Aldosterone promotes sodium uptake and potassium secretion, exacerbating the hypokalemia. It also stimulates hydrogen ion secretion distally, worsening the metabolic alkalosis. Hypokalemia stimulates prostaglandin synthesis, which further activates the renin–angiotensin II–aldosterone axis. Bartter syndrome has been associated with 5 distinct genetic defects in loop of Henle transporters (see Table 531-1). Each contributes, in some manner, to sodium and chloride transport. Mutations in the genes that encode the $Na^+/K^+/2Cl^-$ transporter (NKCC2, the site of action of furosemide), the luminal potassium channel (ROMK), combined chloride channel (CLC-Ka, CLC-Kb), or subunit of chloride channels (barttin) cause neonatal Bartter syndrome. Isolated defects in the genes that produce a specific basolateral chloride channel (ClC-Kb) cause classic Bartter syndrome.

CLINICAL MANIFESTATIONS

A history of maternal polyhydramnios with or without prematurity may be elicited. Dysmorphic features, including triangular facies, protruding ears, large eyes with strabismus, and drooping mouth may be present on physical examination. Consanguinity suggests the presence of an autosomal recessive disorder. Older children can have a history of recurrent episodes of polyuria with dehydration, failure to thrive, nonspecific fatigue, dizziness and chronic constipation. Older children may also present with muscle cramps and weakness secondary to chronic hypokalemia. Blood pressure is usually normal, although patients with the antenatal form can have severe salt wasting, resulting in dehydration and hypotension. Serum chemistry reveals the classic biochemical abnormalities of a hypokalemic metabolic alkalosis. Renal function is typically normal. Urinary calcium levels are typically elevated, as are urinary potassium and sodium levels. Serum renin, aldosterone, and prostaglandin E levels are often markedly elevated, particularly in the more-severe antenatal form. Nephrocalcinosis, resulting from hypercalciuria, may be seen on ultrasound examination (types I and II).

DIAGNOSIS

The diagnosis is usually made based on clinical presentation and laboratory findings. The diagnosis in the neonate or infant is suggested by severe hypokalemia, usually <2.5 mmol/L, with metabolic alkalosis. Hypercalciuria is typical; hypomagnesemia is seen in a minority of patients but is more common in Gitelman syndrome. Because features of Bartter syndrome resemble chronic use of loop diuretics, diuretic abuse should be considered in the differential diagnosis, even in young children. Chronic vomiting can also give a similar clinical picture but can be distinguished by **measurement** of **urinary chloride,** which is elevated in Bartter syndrome and low in patients with chronic vomiting. Kidneys demonstrate hyperplasia of the juxtaglomerular apparatus. Renal biopsy is rarely performed to diagnose this condition.

TREATMENT AND PROGNOSIS

Treatment of Bartter syndrome is directed at preventing dehydration, maintaining nutritional status, and correcting hypokalemia. Potassium supplementation, often at very high doses, is required; potassium-sparing (aldosterone antagonist) diuretics may be of value. Even with appropriate therapy, serum potassium values might not normalize, particularly in patients with the neonatal form. Infants and young children require a high-sodium diet and at times sodium supplementation. Indomethacin, a prostaglandin inhibitor, can also be effective. If hypomagnesemia is present, magnesium supplementation is required. With close attention to electrolyte balance, volume status, and growth, the long-term prognosis is generally good. In a minority of patients, chronic hypokalemia, nephrocalcinosis, and chronic indomethacin therapy can lead to chronic interstitial nephritis and chronic renal failure.

531.2 Gitelman Syndrome

Rajasree Sreedharan and Ellis D. Avner

Gitelman syndrome (often called a "Bartter syndrome variant") is a rare autosomal recessive cause of hypokalemic metabolic alkalosis, with distinct features of **hypocalciuria** and **hypomagnesemia.** Patients with Gitelman syndrome typically present in late childhood or early adulthood (see Table 531-1).

PATHOGENESIS

The biochemical features of Gitelman syndrome resemble those of chronic use of thiazide diuretics. Thiazides act on the sodium chloride cotransporter NCCT, present in the distal convoluted tubule. Through linkage analysis and mutational studies, defects in the gene encoding NCCT have been demonstrated in patients with Gitelman syndrome.

CLINICAL MANIFESTATIONS

Patients with Gitelman syndrome typically present at a later age than those with Bartter syndrome and may have symptoms similar to older children with Bartter syndrome (see Chapter 531.1). Patients often have a history of recurrent muscle cramps and spasms, presumably caused by low serum magnesium levels, nocturia, polyuria, and occasional hypotension. They usually do not have a history of recurrent episodes of dehydration. Biochemical abnormalities include hypokalemia, metabolic alkalosis, and hypomagnesemia. The urinary calcium level is usually very low (in contrast to the elevated urinary calcium level often seen in Bartter syndrome), and the urinary magnesium level is elevated. Renin and aldosterone levels are usually normal, and prostaglandin E secretion is not elevated. Growth failure is less prominent in Gitelman syndrome than in Bartter syndrome.

DIAGNOSIS

The diagnosis of Gitelman syndrome is suggested in an adolescent or adult presenting with hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria.

TREATMENT

Therapy is directed at correcting hypokalemia and hypomagnesemia with supplemental potassium and magnesium. Sodium supplementation or treatment with prostaglandin inhibitors is generally not necessary because patients typically do not have episodes of volume depletion or elevated prostaglandin E excretion.

531.3 Other Inherited Tubular Transport Abnormalities

Rajasree Sreedharan and Ellis D. Avner

Inherited abnormalities in distinct transporters in each segment of the nephron have now been identified and the molecular defects have been characterized. Renal tubular acidosis and nephrogenic diabetes insipidus are discussed in detail in Chapters 529 and 530, respectively. **Cystinuria** is an autosomal recessive disorder seen primarily in patients of Middle Eastern descent and is characterized by recurrent stone formation. The disease is caused by a defective high-affinity transporter for L-cystine and dibasic amino acids present in the proximal tubule.

Dent disease is an X-linked proximal tubulopathy with characteristic abnormalities that include low-molecular-weight proteinuria, hypercalciuria, and other features of Fanconi syndrome, such as glycosuria, aminoaciduria, and phosphaturia. Although some patients develop nephrocalcinosis, nephrolithiasis, progressive renal failure, and hypophosphatemic rickets, patients with Dent disease typically do not have proximal renal tubular acidosis or extrarenal manifestations. Loss-of-function mutations of the *CLCN5* gene, which is located in Xp11.22 and encodes a renal Cl^-/H^+ antiporter (ClC-5), are reported in patients with Dent disease. Genetic heterogeneity of Dent disease in some patients who exhibit mutations in the gene for OCRL1 (responsible for Lowe syndrome) also meets Dent disease criteria: Dent-2 disease. Dent disease includes X-linked recessive nephrolithiasis with renal failure, X-linked recessive hypophosphatemic rickets, and idiopathic low-molecular-weight proteinuria seen in Japanese children.

Mutations in an extracellular basolateral calcium-sensing receptor, normally present in the loop of Henle, can cause a **dominant Bartter syndrome–like picture**. These patients' predominant symptoms are hypocalcemic and suppressed parathyroid hormone function, which differentiates them from patients with Bartter syndrome.

In the distal convoluted tubule, gain-of-function mutations in *WNK1* and loss-of-function mutations in *WNK4*, both serine threonine kinases, lead to excessive NCCT-mediated salt reabsorption with the clinical picture of pseudohypoaldosteronism type 2 (familial hyperkalemic hypertension, or **Gordon syndrome**).

In the collecting duct, gain-of-function mutations of the gene that encodes the epithelial sodium channel cause an inherited form of hypertension, **Liddle syndrome.** Patients with this disorder have constitutive sodium uptake in the collecting duct, with hypokalemia and suppressed aldosterone. Conversely, loss-of-function mutations cause pseudohypoaldosteronism, characterized by severe sodium wasting and hyperkalemia. A variant of the latter disorder is associated with systemic abnormalities, including defects in sweat chloride, and can resemble cystic fibrosis.

Renal hypouricemia, a defect in the *SLC22A12* gene, presents with low serum uric acid levels and is complicated by exercise-induced acute renal failure. Patients have elevated urine uric acid levels and present with loin pain, nausea, and vomiting after exercise. Treatment is for acute renal failure and reducing the intensity of exercise.

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Chapter 532

Tubulointerstitial Nephritis

Craig C. Porter and Ellis D. Avner

Tubulointerstitial nephritis (TIN, also called interstitial nephritis) is the term applied to conditions characterized by tubulointerstitial inflammation and damage with relative sparing of glomeruli and vessels. Both acute and chronic primary forms exist. Interstitial nephritis can also be present with primary glomerular diseases as well as systemic diseases affecting the kidney.

ACUTE TUBULOINTERSTITIAL NEPHRITIS

Pathogenesis and Pathology

The hallmarks of acute TIN are lymphocytic infiltration of the tubulointerstitium, tubular edema, and varying degrees of tubular damage. Eosinophils may be present, particularly in drug-induced TIN; occasionally, granulomas occur. The pathogenesis is not fully understood, but a T-cell–mediated immune mechanism has been postulated. A large number of medications, especially antimicrobials, anticonvulsants, and analgesics, have been implicated as etiologic agents (Table 532-1). Other causes include infections, primary glomerular diseases, and systemic diseases such as systemic lupus erythematosus.

Table 532-1 Etiology of Interstitial Nephritis

ACUTE	CHRONIC

Drugs
• Antimicrobials
  • Penicillin derivatives
  • Cephalosporins
  • Sulfonamides
  • Trimethoprim-sulfamethoxazole
  • Ciprofloxacin
  • Tetracyclines
  • Vancomycin
  • Erythromycin derivatives
  • Rifampin
  • Amphotericin B
  • Acyclovir
• Anticonvulsants
  • Carbamazepine
  • Phenobarbital
  • Phenytoin
  • Sodium valproate
• Other drugs
  • Allopurinol
  • All-*trans*-retinoic acid
  • 5-Aminosalicylic acid
  • Cimetidine
  • Cyclosporine
  • Diuretics
  • Escitalopram
  • Interferon
  • Mesalazine
  • Quetiapine
  • Olanzapine
  • Nonsteroidal antiinflammatory drugs
  • Protease inhibitors
  • Proton pump inhibitors
  • Aristolochic acid (traditional Chinese herb)
Infections
• Adenovirus
• Bacteria associated with acute pyelonephritis
• BK virus
• *Brucella*
• Streptococcal species
• Cytomegalovirus
• Epstein-Barr virus
• Hepatitis B virus
• Histoplasmosis
• Human immunodeficiency virus
• Hantavirus
• Leptospirosis
• *Toxoplasma gondii*
Disease-associated
• Glomerulonephritis (e.g., systemic lupus erythematosus)
• Acute allograft rejection
• Tubulointerstitial nephritis and uveitis (TINU) syndrome
Idiopathic
	Drugs and toxins
	• Analgesics
	• Cyclosporine
	• Lithium
	• Heavy metals
	Infections (see Acute)
	Disease-associated
	• Metabolic and hereditary
	• Cystinosis
	• Oxalosis
	• Fabry disease
	• Wilson disease
	• Sickle cell nephropathy
	• Alport syndrome
	• Juvenile nephronophthisis, medullary cystic disease
	Immunologic
	• Systemic lupus erythematosus
	• Crohn disease
	• Chronic allograft rejection
	• Tubulointerstitial nephritis and uveitis (TINU) syndrome
	• Antitubular basement disease
	Urologic
	• Posterior urethral valves
	• Eagle-Barrett syndrome
	• Ureteropelvic junction obstruction
	• Vesicoureteral reflux
	Miscellaneous
	• Balkan nephropathy
	• Radiation
	• Sarcoidosis
	• Neoplasm
	Idiopathic

Clinical Manifestations

The classic presentation of acute TIN is fever, rash, and arthralgia in the setting of a rising serum creatinine. Although the full triad may be noted in drug-induced TIN, many patients with acute TIN do not demonstrate all of the typical features. The rash can vary from maculopapular to urticarial and is often transient. Patients often have nonspecific constitutional symptoms of nausea, vomiting, fatigue, and weight loss. Flank pain may be present, presumably secondary to stretching of the renal capsule from acute inflammatory enlargement of the kidney. If acute TIN is caused by a systemic disease such as systemic lupus erythematosus, the clinical presentation will be consistent with specific signs and symptoms of the underlying disease. Unlike the typical presentation of oliguric acute renal failure seen with glomerular diseases, 30-40% of patients with acute TIN are nonoliguric, and hypertension is less common. Peripheral eosinophilia can occur, especially with drug-induced TIN. Some degree of microscopic hematuria is invariably present, but significant hematuria or proteinuria >1.5 g/day is uncommon. One exception is patients whose TIN is caused by nonsteroidal antiinflammatory drugs (NSAIDs), who can present with the nephrotic syndrome. Urinalysis can reveal white blood cell, granular, or hyaline casts, but red blood cell casts (a characteristic of glomerular disease) are absent. The presence of urine eosinophils is neither sensitive nor specific. *Because of pyuria, the initial diagnosis may be a urinary tract infection.*

Diagnosis

The diagnosis is usually based on clinical presentation and laboratory findings. A renal biopsy will establish the correct diagnosis in cases where the etiology or clinical course confounds the diagnosis. A careful history of the timing of disease onset in relation to drug exposure is essential in suspected drug-induced TIN. Because of the immune-mediated nature of TIN, signs or symptoms generally appear

within 1-2 wk following exposure. In children, antimicrobials are a common inciting agent. NSAIDs are an important cause of acute TIN in children, and volume depletion or underlying chronic renal disease can increase the risk of occurrence. Urinalysis and serial measurements of serum creatinine and electrolytes should be monitored. Renal ultrasonography is not diagnostic but can demonstrate enlarged, echogenic kidneys. Removal of a suspected offending agent followed by spontaneous improvement in renal function is highly suggestive of the diagnosis, and additional testing is generally not performed in this setting. In more severe cases, in which the cause is unclear or the patient's renal function deteriorates rapidly, a renal biopsy is indicated.

Treatment and Prognosis

Treatment includes supportive care directed at addressing complications of acute renal failure such as hyperkalemia or volume overload (see Chapter 535.1). Corticosteroid administration within 2 wk of the discontinuation of certain offending agents (e.g., NSAIDs or antibiotics) can hasten recovery and improve the long-term prognosis in drug-induced TIN. Whether such therapy is indicated in other causes on TIN is not clear. For patients with prolonged renal insufficiency, the prognosis remains guarded, and severe acute TIN from any cause can progress to chronic TIN.

CHRONIC TUBULOINTERSTITIAL NEPHRITIS

In children, chronic TIN most commonly occurs in the context of (1) an underlying congenital urologic renal disease, such as obstructive uropathy or vesicoureteral reflux, or (2) an underlying metabolic disorder affecting the kidneys (see Table 532-1) Chronic TIN can occur as an idiopathic disease, although this is more common in adults.

The juvenile nephronophthisis (JN)–medullary cystic kidney disease complex (MCKD) is a group of inherited, genetically determined cystic renal diseases that share the common histologic finding of chronic TIN. At least 15 different genes are associated with JN, usually inherited as an autosomal recessive disease. These genes only define 30% of cases, and new genes are being identified at a rapid pace. Although uncommon in the United States, JN causes 10-20% of pediatric end-stage renal disease (ESRD) in Europe. Patients with JN typically present with polyuria, growth failure, unexplained anemia, and chronic renal failure in late childhood or adolescence. As a ciliopathy, JN is often associated with extrarenal features such as retinal degeneration, hepatobiliary disease, cerebellar vermis hypoplasia, laterality defects, intellectual disability, and shortening of bones. These features are represented in a number of syndromes, such as **Senior-Løken syndrome (retinitis pigmentosa), Joubert syndrome (cerebellar vermis hypoplasia), Bardet-Biedel syndrome (intellectual disability, obesity),** and **Jeune asphyxiating thoracic dystrophy** (**shortening of the long bones, narrow rib cage),** and many others. **MCKD** is an autosomal dominant disease that typically manifests in adulthood. **TIN with uveitis** is a rare autoimmune syndrome of chronic TIN with anterior uveitis and bone marrow granulomas that occurs primarily in adolescent girls. Chronic TIN is seen in all forms of progressive renal disease, regardless of the underlying cause, and the severity of interstitial disease is the single most important factor predicting progression to ESRD.

Pathogenesis and Pathology

The pathophysiology of chronic TIN is undefined, but data suggest that, in addition to abnormal cilia structure and function in JN and MCKD, it is immune mediated. Cells making up the interstitial infiltrate appear to be a combination of native interstitial cells, inflammatory cells recruited from the circulation, and resident tubular cells that undergo epithelial-mesenchymal transformation. Grossly, kidneys can appear pale and small for age. Microscopically, tubular atrophy and "dropout" with interstitial fibrosis and a patchy lymphocytic interstitial inflammation are seen. Patients with JN often have characteristic small cysts in the corticomedullary region. In primary chronic TIN, glomeruli are relatively spared until late in the disease course. Patients with chronic TIN secondary to a primary glomerular disease have histologic evidence of the primary disease.

Clinical Manifestations

The clinical features of chronic TIN are often nonspecific and can reflect signs and symptoms of chronic renal insufficiency (see Chapter 535). Fatigue, growth failure, polyuria, polydipsia, and enuresis are often present. Anemia that is seemingly disproportionate to the degree of renal insufficiency is common and is a particularly prominent feature in JN. Because tubular damage often leads to renal salt wasting, significant hypertension is unusual. Fanconi syndrome, proximal renal tubular acidosis, distal renal tubular acidosis, and hyperkalemic distal renal tubular acidosis can occur.

Diagnosis

The diagnosis is suggested by signs or symptoms of renal tubular damage such as polyuria and an elevated serum creatinine value, coupled with a history suggestive of a chronic disease, such as long-standing enuresis or the presence of anemia resistant to iron therapy. Radiographic studies, in particular ultrasonography, can give additional evidence of chronicity, such as small, echogenic kidneys, corticomedullary microcysts suggesting JN, or findings of obstructive uropathy. A vesicocystourethrogram can demonstrate the presence of vesicoureteral reflux or bladder abnormalities. If JN is suspected, molecular diagnosis is available. In instances in which the cause is unclear, a renal biopsy may be performed. In cases of advanced disease, a renal biopsy might not be diagnostic. Many end-stage kidney diseases display a common histologic appearance of tubular fibrosis and inflammation.

Treatment and Prognosis

Therapy is directed at maintaining fluid and electrolyte balance and avoiding further exposure to nephrotoxic agents. Patients with obstructive uropathies can require salt supplementation and treatment with potassium-binding resin (Kayexalate). Prevention of infection by antibiotic prophylaxis can slow progression of renal damage in appropriate patients. Prognosis in patients with chronic TIN depends in large part on the nature of the underlying disease. Patients with obstructive uropathy or vesicoureteral reflux can have a variable degree of renal damage and thus a variable course. ESRD can develop over mo to years. Patients with JN uniformly progress to ESRD by adolescence. Patients with metabolic disorders can benefit from treatment when available.

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Section 5

Acute Kidney Injury and Chronic Kidney Disease

Chapter 533

Toxic Nephropathy

Craig C. Porter and Ellis D. Avner

Aberrant renal function often results from purposeful or accidental exposure to any number of agents that are potential or actual nephrotoxins. Iodinated radiocontrast agents are generally well tolerated by most patients without significant adverse consequences. In volume-depleted patients or patients with underlying chronic kidney

Table 533-1 Renal Syndromes Produced by Nephrotoxins

NEPHROTIC SYNDROME Angiotensin-converting enzyme inhibitors Gold salts Interferon Mercury compounds Nonsteroidal antiinflammatory drugs Penicillamine	FANCONI SYNDROME Aminoglycosides Chinese herbs (aristolochic) Cisplatin Heavy metals (cadmium, lead, mercury, and uranium) Ifosfamide Lysol Outdated tetracycline
NEPHROGENIC DIABETES INSIPIDUS Amphotericin B Cisplatin Colchicine Demeclocycline Lithium Methoxyflurane Propoxyphene Vinblastine	RENAL TUBULAR ACIDOSIS Amphotericin B Lead Lithium Toluene
RENAL VASCULITIS Hydralazine Isoniazid Penicillins Propylthiouracil Sulfonamides Numerous other drugs that can cause a hypersensitivity reaction	INTERSTITIAL NEPHRITIS Amidopyrine *p*-Aminosalicylate Carbon tetrachloride Cephalosporins Cimetidine Cisplatin Colistin Copper Cyclosporine Ethylene glycol Foscarnet Gentamicin Gold salts Indomethacin Interferon-α Iron Kanamycin Lithium Mannitol Mercury salts Mitomycin C Neomycin Nonsteroidal antiinflammatory drugs Penicillins (especially methicillin) Pentamidine Phenacetin Phenylbutazone Poisonous mushrooms Polymyxin B Radiocontrast agents Rifampin Salicylate Streptomycin Sulfonamides Tacrolimus Tetrachloroethylene Trimethoprim-sulfamethoxazole
THROMBOTIC MICROANGIOPATHY Cyclosporine A Oral contraceptive agents Mitomycin C	
NEPHROCALCINOSIS OR NEPHROLITHIASIS Allopurinol Bumetanide Ethylene glycol Furosemide Melamine Methoxyflurane Topiramate Vitamin D	
ACUTE RENAL FAILURE Acetaminophen Acyclovir Aminoglycosides Amphotericin B Angiotensin-converting enzyme inhibitors Biologic toxins (snake, spider, bee, wasp) Cisplatin Cyclosporine Ethylene glycol Halothane Heavy metals Ifosfamide Lithium Methoxyflurane Nonsteroidal antiinflammatory drugs Radiocontrast agents Tacrolimus Vancomycin	
OBSTRUCTIVE UROPATHY Sulfonamides Acyclovir Methotrexate Protease inhibitors Ethylene glycol Methoxyflurane	

disease, their use poses a serious risk for the development of acute kidney injury with significant attendant morbidity and mortality. Biologic nephrotoxins include venomous exposures from insects, reptiles, amphibians, and a wide variety of sea-dwelling animals. The most common forms of toxic nephropathy unfortunately relate to the exposure of children to pharmacologic agents, accounting for close to 20% of episodes of acute kidney injury occurring in children and adolescents. Age, underlying medical condition, including surgical exposure, genetics, exposure dose, and the concomitant use of other drugs all influence the likelihood of developing acute kidney injury.

Table 533-1 summarizes the agents that commonly cause acute kidney injury and some of their clinical manifestations. Mechanisms

of injury often help to explain the presentation; multiple toxic exposures in patients with complicated clinical histories often limit the ability to clearly establish clinical cause and effect. For example, diminished urine output may be the clinical hallmark of tubular obstruction caused by agents such as methotrexate or agents that cause acute tubular necrosis, such as amphotericin B or pentamidine. Alternatively, nephrogenic diabetes insipidus may be the critical clinical manifestation of agents that cause interstitial nephritis, such as lithium or cisplatin. Nephrotoxicity is often reversible if the noxious agent is promptly removed.

Clinical use of potential nephrotoxins should be used judiciously. Necessity of exposure, dosing parameters, and the use of drug levels or pharmacogenomic data, when available, should always be considered. Caution is particularly mandated for patients with complex medical conditions that include preexisting renal disease, cardiac disease, diabetes, and/or complicated surgeries. Alternative approaches to imaging, or use of different pharmacologic options should be considered when possible. Imaging modalities such as ultrasonography, radionuclide scanning, or magnetic resonance imaging may be preferable to contrast studies in some patients. Alternatively, judicious volume expansion with or without the administration of *N*-acetylcysteine might offer renoprotection when radioiodinated contrast studies are critical. Pharmacologic agents with no known renal effects can often be substituted for known nephrotoxins with equal clinical efficacy. In all cases, simultaneous use of known nephrotoxins should be avoided whenever necessary.

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Chapter **534**

Cortical Necrosis

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Renal cortical necrosis is a rare cause of acute renal failure occurring secondary to extensive ischemic damage of the renal cortex. It occurs most commonly in neonates and in adolescents of childbearing age (see Chapter 535).

ETIOLOGY

In newborns, cortical necrosis is most commonly associated with hypoxic or ischemic insults caused by perinatal asphyxia, placental abruption, and twin–twin or fetal-maternal transfusion. Other causes include renal vascular thrombosis and severe congenital heart disease. After the neonatal period, cortical necrosis is most commonly seen in children with septic shock or severe hemolytic-uremic syndrome. In adolescents and women, cortical necrosis occurs in association with obstetric complications including prolonged intrauterine fetal death, placental abruption, or amniotic fluid embolism.

Less-common causes of cortical necrosis include malaria, extensive burns, snakebites, infectious endocarditis, and medications (e.g., nonsteroidal antiinflammatory agents). Acute renal cortical necrosis has also been reported to occur in systemic lupus erythematosus–associated antiphospholipid antibody syndrome.

CLINICAL MANIFESTATIONS

Cortical necrosis clinically presents as acute renal failure in patients with predisposing causes. Urine output is diminished and gross and/or microscopic hematuria may be present. Hypertension is common, and thrombocytopenia may be present as a result of renal microvascular injury.

LABORATORY AND RADIOLOGIC FINDINGS

Laboratory results are consistent with acute renal failure: an elevated blood urea nitrogen and creatinine, hyperkalemia, and metabolic acidosis. Anemia and thrombocytopenia are common. Urinalysis reveals hematuria and proteinuria.

Ultrasound examination with Doppler flow studies or CT scan demonstrates decreased perfusion to both kidneys. A radionuclide renal scan shows decreased uptake with significantly delayed or absent function.

TREATMENT

It is important to prevent or treat the underlying cause of acute cortical necrosis, when possible. Therapy involves medical management of acute renal failure, often with the initiation of dialysis as indicated. Management is otherwise supportive and involves volume repletion, correction of asphyxia, and treatment of sepsis.

PROGNOSIS

Untreated, renal cortical necrosis has a high mortality rate. Twenty to 40% of patients have partial recovery of renal function, the extent of which depends on the amount of preserved cortical tissue. All patients require long-term follow-up for chronic kidney disease.

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Chapter 535
Renal Failure

535.1 Acute Kidney Injury

Rajasree Sreedharan and Ellis D. Avner

Acute kidney injury (AKI), formerly called acute renal failure, is a clinical syndrome in which a sudden deterioration in renal function results in the inability of the kidneys to maintain fluid and electrolyte homeostasis. AKI occurs in 2-3% of children admitted to pediatric tertiary care centers and in as many as 8% of infants in neonatal intensive care units. A classification system has been proposed to standardize the definition of AKI in adults. These criteria of **risk**, **injury**, **failure**, **loss**, and **end-stage renal disease** were given the acronym of RIFLE. A modified RIFLE criteria (pRIFLE) was developed to characterize the pattern of AKI in critically ill children (Table 535-1). Because RIFLE focuses on the glomerular filtration rate (GFR), a modification (Acute Kidney Injury Network) categorizes severity by rise in serum creatinine: stage 1 >150%, stage II >200%, stage III >300%.

PATHOGENESIS

AKI has been conventionally classified into 3 categories: prerenal, intrinsic renal, and postrenal (Table 535-2 and Fig. 535-1).

Table 535-1 Pediatric-Modified Rifle (pRIFLE) Criteria

CRITERIA	ESTIMATED CCL	URINE OUTPUT
Risk	eCCl decrease by 25%	<0.5 mL/kg/hr for 8 hr
Injury	eCCl decrease by 50%	<0.5 mL/kg/hr for 16 hr
Failure	eCCl decrease by 75% or eCCl <35 mL/min/1.73 m^2	<0.3 mL/kg/hr for 24 hr or anuric for 12 hr
Loss	Persistent failure >4 wk	
End-stage	End-stage renal disease (persistent failure >3 mo)	

CCl, creatinine clearance; eCCl, estimated creatinine clearance; pRIFLE, pediatric risk, injury, failure, loss, and end-stage renal disease.

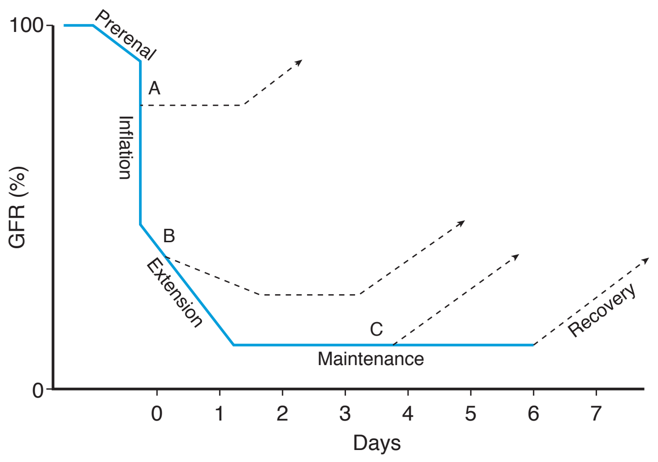

Figure 535-1 Phases of acute kidney injury. GFR, glomerular filtration rate. *(From Sutton TA, Fisher CJ, Molitoris BA. Microvascular endothelial injury and dysfunction during ischemic acute renal failure,* Kidney Int *62:1539–1549, 2002.)*

Table 535-2 Common Causes of Acute Kidney Injury

PRERENAL
Dehydration
Hemorrhage
Sepsis
Hypoalbuminemia
Cardiac failure
INTRINSIC RENAL
Glomerulonephritis
• Postinfectious/poststreptococcal
• Lupus erythematosus
• Henoch-Schönlein purpura
• Membranoproliferative
• Anti–glomerular basement membrane
Hemolytic-uremic syndrome
Acute tubular necrosis
Cortical necrosis
Renal vein thrombosis
Rhabdomyolysis
Acute interstitial nephritis
Tumor infiltration
Tumor lysis syndrome
POSTRENAL
Posterior urethral valves
Ureteropelvic junction obstruction
Ureterovesicular junction obstruction
Ureterocele
Tumor
Urolithiasis
Hemorrhagic cystitis
Neurogenic bladder

Prerenal AKI, also called *prerenal azotemia,* is characterized by diminished effective circulating arterial volume, which leads to inadequate renal perfusion and a decreased GFR. Evidence of kidney damage is absent. Common causes of prerenal AKI include dehydration, sepsis, hemorrhage, severe hypoalbuminemia, and cardiac failure. If the underlying cause of the renal hypoperfusion is reversed promptly, renal function returns to normal. If hypoperfusion is sustained, intrinsic renal parenchymal damage can develop.

Intrinsic renal AKI includes a variety of disorders characterized by renal parenchymal damage, including sustained hypoperfusion and ischemia. Many forms of **glomerulonephritis,** including postinfectious glomerulonephritis, lupus nephritis, Henoch-Schönlein purpura nephritis, membranoproliferative glomerulonephritis, and anti–glomerular basement membrane nephritis, can cause AKI. Ischemic/hypoxic injury and nephrotoxic insults are the most common causes of intrinsic AKI in the United States, and are more common with an underlying comorbid condition; most are associated with cardiac, oncologic, urologic, renal, and genetic disorders or prematurity. Severe and prolonged ischemic/hypoxic injury and nephrotoxic insult lead to **acute tubular necrosis (ATN),** seen most often in critically ill infants and children. Mechanisms leading to ischemic AKI include hypotension/intravascular volume depletion (hemorrhage, third-space fluid losses, diarrhea), decreased effective intravascular volume (heart failure, cirrhosis, hepatorenal syndrome, peritonitis, abdominal compartment syndrome), vasodilation/vasoconstriction (sepsis, hepatorenal syndrome), renal artery obstruction (thrombosis, embolization, stenosis), intrarenal artery disease (vasculitis, hemolytic-uremic syndrome, sickle cell anemia, transplant rejection), and impaired renal blood flow (cyclosporine, tacrolimus, angiotensin-converting enzyme [ACE] inhibitors, angiotensin-receptor blocking agents, radiocontrast agents).

The typical pathologic feature of ATN is tubular cell necrosis, although significant histologic changes are not consistently seen in patients with clinical ATN. The mechanisms of injury in ATN can include alterations in intrarenal hemodynamics, tubular obstruction, and passive backleak of the glomerular filtrate across injured tubular cells into the peritubular capillaries.

Tumor lysis syndrome is a specific form of AKI related to spontaneous or chemotherapy-induced cell lysis in patients with lymphoproliferative malignancies. This disorder is primarily caused by obstruction of the tubules by uric acid crystals (see Chapters 495 and 496). **Acute interstitial nephritis** is another common cause of AKI and is usually a result of a hypersensitivity reaction to a therapeutic agent or various infectious agents (see Chapter 532).

Postrenal AKI includes a variety of disorders characterized by obstruction of the urinary tract. In neonates and infants, congenital conditions, such as posterior urethral valves and bilateral ureteropelvic junction obstruction, account for the majority of cases of AKI. Other conditions, such as urolithiasis, tumor (intraabdominal lesion or within the urinary tract), hemorrhagic cystitis, and neurogenic bladder, can cause AKI in older children and adolescents. In a patient with 2 functioning kidneys, obstruction must be bilateral to result in AKI. Relief of the obstruction usually results in recovery of renal function, except in patients with associated renal dysplasia or prolonged urinary tract obstruction.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A carefully taken history is critical in defining the cause of AKI. An infant with a 3 day history of vomiting and diarrhea most likely has prerenal AKI caused by volume depletion, but hemolytic-uremic syndrome (HUS) must be a consideration. A 6 yr old child with a recent pharyngitis who presents with periorbital edema, hypertension, and gross hematuria most likely has intrinsic AKI related to acute postinfectious glomerulonephritis. A critically ill child with a history of protracted hypotension or with exposure to nephrotoxic medications most likely has ATN. A neonate with a history of hydronephrosis on prenatal ultrasound and a palpable bladder most likely has congenital urinary tract obstruction, probably related to posterior urethral valves.

The physical examination must be thorough, with careful attention to volume status. Tachycardia, dry mucous membranes, and poor peripheral perfusion suggest an inadequate circulating volume and the possibility of prerenal AKI (see Chapter 57). Hypertension, peripheral edema, rales, and a cardiac gallop suggest volume overload and the possibility of intrinsic AKI from glomerulonephritis or ATN. The presence of a rash and arthritis might indicate systemic lupus erythematosus (SLE) or Henoch-Schönlein purpura nephritis. Palpable flank masses may be seen with renal vein thrombosis, tumors, cystic disease, or urinary tract obstruction.

LABORATORY FINDINGS

Laboratory abnormalities can include anemia (the anemia is usually dilutional or hemolytic, as in SLE, renal vein thrombosis,

Table 535-3 Urinalysis, Urine Chemistries, and Osmolality in Acute Kidney Injury

	HYPOVOLEMIA	ACUTE TUBULAR NECROSIS	ACUTE INTERSTITIAL NEPHRITIS	GLOMERULONEPHRITIS	OBSTRUCTION
Sediment	Bland	Broad, brownish granular casts	White blood cells, eosinophils, cellular casts	Red blood cells, red blood cell casts	Bland or bloody
Protein	None or low	None or low	Minimal but may be increased with NSAIDs	Increased, >100 mg/dL	Low
Urine sodium, mEq/L*	<20	>30	>30	<20	<20 (acute) >40 (few days)
Urine osmolality, mOsm/kg	>400	<350	<350	>400	<350
Fractional excretion of sodium %†	<1	>1	Varies	<1	<1 (acute) >1 (few days)

*The sensitivity and specificity of urine sodium of <20 mEq/L in differentiating prerenal azotemia from acute tubular necrosis are 90% and 82%, respectively.
†Fractional excretion of sodium is the urine:plasma (U:P) ratio of sodium divided by U:P of creatinine ×100. The sensitivity and specificity of fractional excretion of sodium of <1% in differentiating prerenal azotemia from acute tubular necrosis are 96% and 95%, respectively.
NSAIDs, nonsteroidal antiinflammatory drugs.
From Singri N, Ahya SN, Levin ML: Acute renal failure, JAMA *289:747–751, 2003.*

HUS); leukopenia (SLE, sepsis); thrombocytopenia (SLE, renal vein thrombosis, sepsis, HUS); hyponatremia (dilutional); metabolic acidosis; elevated serum concentrations of blood urea nitrogen, creatinine, uric acid, potassium, and phosphate (diminished renal function); and hypocalcemia (hyperphosphatemia).

The serum C3 level may be depressed (postinfectious glomerulonephritis, SLE, or membranoproliferative glomerulonephritis), and antibodies may be detected in the serum to streptococcal (poststreptococcal glomerulonephritis), nuclear (SLE), neutrophil cytoplasmic (granulomatosis with polyangiitis, microscopic polyarteritis), or glomerular basement membrane (Goodpasture disease) antigens.

The presence of hematuria, proteinuria, and red blood cell or granular urinary casts suggests intrinsic AKI, in particular glomerular disease and ATN. The presence of white blood cells and white blood cell casts with low-grade hematuria and proteinuria suggests tubulointerstitial disease. Urinary eosinophils may be present in children with drug-induced tubulointerstitial nephritis.

Urinary indices may be useful in differentiating prerenal AKI from intrinsic AKI (Table 535-3). Patients whose urine shows an elevated specific gravity (>1.020), elevated urine osmolality (UOsm > 500 mOsm/kg), low urine sodium (UNa < 20 mEq/L), and fractional excretion of sodium <1% (<2.5% in neonates) most likely have prerenal AKI. Those with a specific gravity of <1.010, low urine osmolality (UOsm < 350 mOsm/kg), high urine sodium (UNa > 40 mEq/L), and fractional excretion of sodium >2% (>10% in neonates) most likely have intrinsic AKI.

Chest radiography may reveal cardiomegaly, pulmonary congestion (fluid overload), or pleural effusions. Renal ultrasonography can reveal hydronephrosis and/or hydroureter, which suggest urinary tract obstruction, or nephromegaly, consistent with intrinsic renal disease. Renal biopsy can ultimately be required to determine the precise cause of AKI in patients who do not have clearly defined prerenal or postrenal AKI.

Although serum creatinine is used to measure kidney function, it is an insensitive and delayed measure of decreased kidney function following AKI. Other biomarkers under investigation include changes in plasma neutrophil gelatinase–associated lipocalin and cystatin C levels and urinary changes in neutrophil gelatinase-associated lipocalin, interleukin 18, and kidney injury molecule-1.

TREATMENT

Medical Management

In infants and children with urinary tract obstruction, such as in a newborn with suspected posterior ureteral valves, a bladder catheter should be placed immediately to ensure adequate drainage of the urinary tract. The placement of a bladder catheter may also be considered in nonambulatory older children and adolescents to accurately monitor urine output during AKI; however, precautions to prevent iatrogenic infection should be taken.

Determination of the volume status is of critical importance when initially evaluating a patient with AKI. If there is no evidence of volume overload or cardiac failure, intravascular volume should be expanded by intravenous administration of isotonic saline, 20 mL/kg over 30 min. In the absence of blood loss or hypoproteinemia, colloid-containing solutions are not required for volume expansion. Severe hypovolemia may require additional fluid boluses (see Chapters 56, 57, and 70). Determination of the central venous pressure may be helpful if adequacy of the blood volume is difficult to determine. After volume resuscitation, hypovolemic patients generally void within 2 hr; failure to do so suggests intrinsic or postrenal AKI. Hypotension caused by sepsis requires vigorous fluid resuscitation followed by a continuous infusion of norepinephrine.

Diuretic therapy should be considered only after the adequacy of the circulating blood volume has been established. Furosemide (2-4 mg/kg) and mannitol (0.5 g/kg) may be administered as a single IV dose. Bumetanide (0.1 mg/kg) may be given as an alternative to furosemide. If urine output is not improved, then a continuous diuretic infusion may be considered. To increase renal cortical blood flow, many clinicians administer dopamine (2-3 µg/kg/min) in conjunction with diuretic therapy, although no controlled data support this practice. There is little evidence that diuretics or dopamine can prevent AKI or hasten recovery. Mannitol may be effective in prevention of pigment (myoglobin, hemoglobin)-induced renal failure. Atrial natriuretic peptide may be of value in preventing or treating AKI, although there is little pediatric evidence to support its use.

If there is no response to a diuretic challenge, diuretics should be discontinued and fluid restriction is essential. Patients with a relatively normal intravascular volume should initially be limited to 400 mL/m^2/24 hr (insensible losses) plus an amount of fluid equal to the urine output for that day. Extrarenal (blood, gastrointestinal tract) fluid losses should be replaced, milliliter for milliliter, with appropriate fluids. Markedly hypervolemic patients can require further fluid restriction, omitting the replacement of insensible fluid losses, urine output, and extrarenal losses to diminish the expanded intravascular volume. Fluid intake, urine and stool output, body weight, and serum chemistries should be monitored on a daily basis.

In AKI, rapid development of **hyperkalemia** (serum potassium level > 6 mEq/L) can lead to cardiac arrhythmia, cardiac arrest, and death. The earliest electrocardiographic change seen in patients with developing hyperkalemia is the appearance of peaked T waves. This may be followed by widening of the QRS intervals, ST segment depression, ventricular arrhythmias, and cardiac arrest (see Chapter 55.4).

Procedures to deplete body potassium stores should be initiated when the serum potassium value rises to >6.0 mEq/L. Exogenous sources of potassium (dietary, intravenous fluids, total parenteral nutrition) should be eliminated. Sodium polystyrene sulfonate resin (Kayexalate), 1 g/kg, should be given orally or by retention enema. This resin exchanges sodium for potassium and can take several hr to take effect. A single dose of 1 g/kg can be expected to lower the serum potassium level by about 1 mEq/L. Resin therapy may be repeated every 2 hr, the frequency being limited primarily by the risk of sodium overload.

More severe elevations in serum potassium (>7 mEq/L), especially if accompanied by electrocardiographic changes, require emergency measures in addition to Kayexalate. The following agents should be administered:

- Calcium gluconate 10% solution, 1.0 mL/kg IV, over 3-5 min
- Sodium bicarbonate, 1-2 mEq/kg IV, over 5-10 min
- Regular insulin, 0.1 units/kg, with glucose 50% solution, 1 mL/kg, over 1 hr

Calcium gluconate counteracts the potassium-induced increase in myocardial irritability but does not lower the serum potassium level. Administration of sodium bicarbonate, insulin, or glucose lowers the serum potassium level by shifting potassium from the extracellular to the intracellular compartment. A similar effect has been reported with the acute administration of β-adrenergic agonists in adults, but there are no controlled data in pediatric patients. Because the duration of action of these emergency measures is just a few hours, persistent hyperkalemia should be managed by dialysis.

Mild **metabolic acidosis** is common in AKI because of retention of hydrogen ions, phosphate, and sulfate, but it rarely requires treatment. If acidosis is severe (arterial pH < 7.15; serum bicarbonate < 8 mEq/L) or contributes to significant hyperkalemia, treatment is indicated. The acidosis should be corrected partially by the intravenous route, generally giving enough bicarbonate to raise the arterial pH to 7.20 (which approximates a serum bicarbonate level of 12 mEq/L). The remainder of the correction may be accomplished by oral administration of sodium bicarbonate after normalization of the serum calcium and phosphorus levels. Correction of metabolic acidosis with intravenous bicarbonate can precipitate tetany in patients with renal failure as rapid correction of acidosis reduces the ionized calcium concentration (see Chapter 55).

Hypocalcemia is primarily treated by lowering the serum phosphorus level. Calcium should not be given intravenously, except in cases of tetany, to avoid deposition of calcium salts into tissues. Patients should be instructed to follow a low-phosphorus diet, and phosphate binders should be orally administered to bind any ingested phosphate and increase GI phosphate excretion. Common agents include sevelamer (Renagel), calcium carbonate (Tums tablets or Titralac suspension), and calcium acetate (PhosLo). Aluminum-based binders, commonly employed in the past, should be avoided because of the risk of aluminum toxicity.

Hyponatremia is most commonly a dilutional disturbance that must be corrected by fluid restriction rather than sodium chloride administration. Administration of hypertonic (3%) saline should be limited to patients with symptomatic hyponatremia (seizures, lethargy) or those with a serum sodium level <120 mEq/L. Acute correction of the serum sodium to 125 mEq/L (mmol/L) should be accomplished using the following formula:

$$\text{mEq sodium required} = 0.6 \times \text{weight in kg} \times (125 - \text{serum sodium in mEq/L}).$$

AKI patients are predisposed to **GI bleeding** because of uremic platelet dysfunction, increased stress, and heparin exposure if treated with hemodialysis or continuous renal replacement therapy. Oral or intravenous H_2 blockers such as ranitidine are commonly administered to prevent this complication.

Hypertension can result from hyperreninemia associated with the primary disease process and/or expansion of the extracellular fluid volume and is most common in AKI patients with acute glomerulonephritis or HUS. Salt and water restriction is critical, and diuretic administration may be useful (see Chapter 445). Isradipine (0.05-0.15 mg/kg/dose, maximum dose 5 mg qid) may be administered for relatively rapid reduction in blood pressure. Longer-acting agents such as calcium channel blockers (amlodipine, 0.1-0.6 mg/kg/24 hr qd or divided bid) or β blockers (propranolol, 0.5-8.0 mg/kg/24 hr divided bid or tid; labetalol, 4-40 mg/kg/24 hr divided bid or tid) may be helpful in maintaining control of blood pressure. Children with severe symptomatic hypertension (hypertensive urgency or emergency) should be treated with continuous infusions of nicardipine (0.5-5.0 µg/kg/min), sodium nitroprusside (0.5-10.0 µg/kg/min), labetalol (0.25-3.0 mg/kg/hr), or esmolol (150-300 µg/kg/min) and converted to intermittently dosed antihypertensives when more stable.

Neurologic symptoms in AKI can include headache, seizures, lethargy, and confusion (encephalopathy). Potential etiologic factors include hypertensive encephalopathy, hyponatremia, hypocalcemia, cerebral hemorrhage, cerebral vasculitis, and the uremic state. Benzodiazepams are the most effective agents in acutely controlling seizures, and subsequent therapy should be directed toward the precipitating cause.

The **anemia** of AKI is generally mild (hemoglobin 9-10 g/dL) and primarily results from volume expansion (hemodilution). Children with HUS, SLE, active bleeding, or prolonged AKI can require transfusion of packed red blood cells if their hemoglobin level falls below 7 g/dL. In hypervolemic patients, blood transfusion carries the risk of further volume expansion, which can precipitate hypertension, heart failure, and pulmonary edema. Slow (4-6 hr) transfusion with packed red blood cells (10 mL/kg) diminishes the risk of hypervolemia. The use of fresh, washed red blood cells minimizes the acute risk of hyperkalemia, and the chronic risk of sensitization if the patient becomes a future candidate for renal replacement therapy. In the presence of severe hypervolemia or hyperkalemia, blood transfusions are most safely administered during dialysis or ultrafiltration.

Nutrition is of critical importance in children who develop AKI. In most cases, sodium, potassium, and phosphorus should be restricted. Protein intake should be moderately restricted while maximizing caloric intake to minimize the accumulation of nitrogenous wastes. In critically ill patients with AKI, parenteral hyperalimentation with essential amino acids should be considered.

Dialysis

Indications for dialysis in AKI include the following:

- Anuria/oliguria
- Volume overload with evidence of hypertension and/or pulmonary edema refractory to diuretic therapy
- Persistent hyperkalemia
- Severe metabolic acidosis unresponsive to medical management
- Uremia (encephalopathy, pericarditis, neuropathy)
- Blood urea nitrogen >100-150 mg/dL (or lower if rapidly rising)
- Calcium:phosphorus imbalance, with hypocalcemic tetany that cannot be controlled by other measures

An additional indication for dialysis is the inability to provide adequate nutritional intake because of the need for severe fluid restriction. In patients with AKI, dialysis support may be necessary for days or for up to 12 wk. Many patients with AKI require dialysis support for 1-3 wk. Table 535-4 lists the advantages and disadvantages of the 3 types of dialysis.

Intermittent hemodialysis is useful in patients with relatively stable hemodynamic status. This highly efficient process accomplishes both fluid and electrolyte removal in 3-4 hr sessions using a pump-driven extracorporeal circuit and large central venous catheter. Intermittent hemodialysis may be performed 3-7 times per week based on the patient's fluid and electrolyte balance.

Peritoneal dialysis is most commonly employed in neonates and infants with AKI, although this modality may be used in children and adolescents of all ages. Hyperosmolar dialysate is infused into the peritoneal cavity via a surgically or percutaneously placed peritoneal dialysis catheter. The fluid is allowed to dwell for 45-60 min and is then drained from the patient by gravity (manually or with the use of machine-driven cycling), accomplishing fluid and electrolyte removal. Cycles are repeated for 8-24 hr/day based on the patient's

fluid and electrolyte balance. Anticoagulation is not necessary. Peritoneal dialysis is contraindicated in patients with significant abdominal pathology.

Continuous renal replacement therapy (CRRT) is useful in patients with unstable hemodynamic status, concomitant sepsis, or multiorgan failure in the intensive care setting. CRRT is an extracorporeal therapy in which fluid, electrolytes, and small- and medium-size solutes are continuously removed from the blood (24 hr/day) using a specialized pump-driven machine. Usually, a double-lumen catheter is placed into the subclavian, internal jugular, or femoral vein. The patient is then connected to the pump-driven CRRT circuit, which continuously passes the patient's blood across a highly permeable filter.

CRRT may be performed in 3 basic fashions. In continuous venovenous hemofiltration, a large volume of fluid is driven by systemic or pump-assisted pressure across the filter, bringing with it by convection other molecules such as urea, creatinine, phosphorus, and uric acid. The blood volume is reconstituted by IV infusion of a replacement fluid having a desirable electrolyte composition similar to that of blood. Continuous venovenous hemofiltration dialysis uses the principle of diffusion by circulating dialysate in a countercurrent direction on the ultrafiltrate side of the membrane. No replacement fluid is used. Continuous hemodiafiltration employs both replacement fluid and dialysate, offering the most effective solute removal of all forms of CRRT.

Table 535-4 compares the relative risks and benefits of the various renal replacement therapies.

PROGNOSIS

The mortality rate in children with AKI is variable and depends entirely on the nature of the underlying disease process rather than on the renal failure itself. Children with AKI caused by a renal-limited condition such as postinfectious glomerulonephritis have a very low mortality rate (<1%); those with AKI related to multiorgan failure have a very high mortality rate (>90%).

The prognosis for recovery of renal function depends on the disorder that precipitated AKI. Recovery of renal function is likely after AKI resulting from prerenal causes ATN, acute interstitial nephritis, or tumor lysis syndrome. Recovery of renal function is unusual when AKI results from most types of rapidly progressive glomerulonephritis, bilateral renal vein thrombosis, or bilateral cortical necrosis. Medical management may be necessary for a prolonged period to treat the sequelae of AKI, including chronic renal insufficiency, hypertension, renal tubular acidosis, and urinary concentrating defect.

Bibliography is available at Expert Consult.

Table 535-4 Comparison of Peritoneal Dialysis, Intermittent Hemodialysis, and Continual Renal Replacement Therapy

	PD	IHD	CRRT
BENEFITS			
Fluid removal	+	++	++
Urea and creatinine clearance	+	++	+
Potassium clearance	++	++	+
Toxin clearance	+	++	+
COMPLICATIONS			
Abdominal pain	+	–	–
Bleeding	–	+	+
Dysequilibrium	–	+	–
Electrolyte imbalance	+	+	+
Need for heparinization	–	+	+/–
Hyperglycemia	+	–	–
Hypotension	+	++	+
Hypothermia	–	–	+
Central line infection	–	+	+
Inguinal or abdominal hernia	+	–	–
Peritonitis	+	–	–
Protein loss	+	–	–
Respiratory compromise	+	–	–
Vessel thrombosis	–	+	+

PD, peritoneal dialysis; IHD, intermittent hemodialysis; CRRT, continual renal replacement therapy.

Adapted from Rogers MC: Textbook of pediatric intensive care, *Baltimore, 1992, Williams & Wilkins.*

535.2 Chronic Kidney Disease

Rajasree Sreedharan and Ellis D. Avner

Chronic kidney disease (CKD) is determined by the presence of kidney damage and level of kidney function (GFR), irrespective of diagnosis. The stage of the CKD is assigned based on the level of kidney function (Tables 535-5 and 535-6). The prevalence of CKD in the pediatric population is approximately 18 per 1 million. The prognosis for the infant, child, or adolescent with CKD has improved dramatically since the 1970s because of improvements in medical management (aggressive nutritional support, recombinant erythropoietin, recombinant growth hormone), dialysis techniques, and kidney transplantation.

ETIOLOGY

In children, CKD may be the result of congenital, acquired, inherited, or metabolic renal disease, and the underlying cause correlates closely with the age of the patient at the time when CKD is first detected. CKD in children <5 yr old is most commonly a result of congenital abnormalities such as renal hypoplasia, dysplasia, or obstructive uropathy. Additional causes include congenital nephrotic syndrome, prune belly syndrome, cortical necrosis, focal segmental glomerulosclerosis, autosomal recessive polycystic kidney disease, renal vein thrombosis, and HUS.

After 5 yr of age, acquired diseases (various forms of glomerulonephritis including lupus nephritis) and inherited disorders (familial

Table 535-5 Criteria for Definition of Chronic Kidney Disease (NKF KDOQI Guidelines)

Patient has CKD if either of the following criteria are present:
1. Kidney damage for ≥3 mo, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by 1 or more of the following features:
   - Abnormalities in the composition of the blood or urine
   - Abnormalities in imaging tests
   - Abnormalities on kidney biopsy
2. GFR <60 mL/min/1.73 m^2 for ≥3 mo, with or without the other signs of kidney damage described above

NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Table 535-6 Standardized Terminology for Stages of Chronic Kidney Disease (NKF KDOQI Guidelines)

STAGE	DESCRIPTION	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	5-29
5	Kidney failure	<15 or on dialysis

GFR, glomerular filtration rate; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

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juvenile nephronophthisis, Alport syndrome) predominate. CKD related to metabolic disorders (cystinosis, hyperoxaluria) and certain inherited disorders (both autosomal dominant and recessive polycystic kidney disease) can occur throughout the childhood years.

PATHOGENESIS

In addition to progressive injury with ongoing structural or metabolic genetic diseases, renal injury can progress despite removal of the original insult.

Hyperfiltration injury may be an important final common pathway of glomerular destruction, independent of the underlying cause of renal injury. As nephrons are lost, the remaining nephrons undergo structural and functional hypertrophy characterized by an increase in glomerular blood flow. The driving force for glomerular filtration is thereby increased in the surviving nephrons. Although this compensatory hyperfiltration temporarily preserves total renal function, it can cause progressive damage to the surviving glomeruli, possibly by a direct effect of the elevated hydrostatic pressure on the integrity of the capillary wall and/or the toxic effect of increased protein traffic across the capillary wall. Over time, as the population of sclerosed nephrons increases, the surviving nephrons suffer an increased excretory burden, resulting in a vicious cycle of increasing glomerular blood flow and hyperfiltration injury.

Proteinuria itself can contribute to renal functional decline. Proteins that traverse the glomerular capillary wall can exert a direct toxic effect on tubular cells and recruit monocytes and macrophages, enhancing the process of glomerular sclerosis and tubulointerstitial fibrosis. Uncontrolled **hypertension** can exacerbate disease progression by causing arteriolar nephrosclerosis and by increasing the hyperfiltration injury.

Hyperphosphatemia can increase progression of disease by leading to calcium phosphate deposition in the renal interstitium and blood vessels. Hyperlipidemia, a common condition in CKD patients, can adversely affect glomerular function through oxidant-mediated injury.

CKD may be viewed as a continuum of disease, with increasing biochemical and clinical manifestations as renal function deteriorates. Regardless of etiology, the progression of tubulointerstitial fibrosis is the primary determinant of progression of CKD. Table 535-7 outlines the pathophysiologic manifestations of CKD. End-stage renal disease (ESRD) is an administrative term in the United States; it is used to define all patients who are treated with dialysis or kidney transplantation. Patients with ESRD are a subset of the patients with stage 5 CKD.

Table 535-7 Pathophysiology of Chronic Kidney Disease

MANIFESTATION	MECHANISMS
Accumulation of nitrogenous waste products	Decrease in glomerular filtration rate
Acidosis	Decreased ammonia synthesis Impaired bicarbonate reabsorption Decreased net acid excretion
Sodium retention	Excessive renin production Oliguria
Sodium wasting	Solute diuresis Tubular damage
Urinary concentrating defect	Solute diuresis Tubular damage
Hyperkalemia	Decrease in glomerular filtration rate Metabolic acidosis Excessive potassium intake Hyporeninemic hypoaldosteronism
Renal osteodystrophy	Impaired renal production of 1,25-dihydroxycholecalciferol Hyperphosphatemia Hypocalcemia Secondary hyperparathyroidism
Growth retardation	Inadequate caloric intake Renal osteodystrophy Metabolic acidosis Anemia Growth hormone resistance
Anemia	Decreased erythropoietin production Iron deficiency Folate deficiency Vitamin B_{12} deficiency Decreased erythrocyte survival
Bleeding tendency	Defective platelet function
Infection	Defective granulocyte function Impaired cellular immune functions Indwelling dialysis catheters
Neurologic symptoms (fatigue, poor concentration, headache, drowsiness, memory loss, seizures, peripheral neuropathy)	Uremic factor(s) Aluminum toxicity Hypertension
Gastrointestinal symptoms (feeding intolerance, abdominal pain)	Gastroesophageal reflux Decreased gastrointestinal motility Serositis (uremia)
Hypertension	Volume overload Excessive renin production
Hyperlipidemia	Decreased plasma lipoprotein lipase activity
Pericarditis, cardiomyopathy	Uremic factor(s) Hypertension Fluid overload
Glucose intolerance	Tissue insulin resistance

CLINICAL MANIFESTATIONS

The clinical presentation of CKD is varied and depends on the underlying renal disease. Children and adolescents with CKD from chronic glomerulonephritis can present with edema, hypertension, hematuria, and proteinuria. Infants and children with congenital disorders such as renal dysplasia and obstructive uropathy can present in the neonatal period with failure to thrive, polyuria, dehydration, urinary tract infection, or overt renal insufficiency. Congenital kidney disease is diagnosed with prenatal ultrasonography in many infants, allowing early diagnostic and possible therapeutic intervention. Children with familial juvenile nephronophthisis can have a very subtle presentation with nonspecific complaints such as headache, fatigue, lethargy, anorexia, vomiting, polydipsia, polyuria, and growth failure over a number of years.

The physical examination in patients with CKD can reveal pallor and a sallow appearance. Patients with long-standing untreated CKD can have short stature and the bony abnormalities of renal osteodystrophy (see Chapter 529.4). Children with CKD caused by chronic glomerulonephritis (or children with advanced renal failure from any cause) can have edema, hypertension, and other signs of extracellular fluid volume overload.

LABORATORY FINDINGS

Laboratory findings can include elevations in blood urea nitrogen and serum creatinine and can reveal hyperkalemia, hyponatremia (if volume overloaded), hypernatremia (loss of free water), acidosis, hypocalcemia, hyperphosphatemia, and an elevation in uric acid. Patients with heavy proteinuria can have hypoalbuminemia. A complete blood cell count may show a normochromic, normocytic anemia. Serum cholesterol and triglyceride levels are often elevated. In children with CKD caused by glomerulonephritis, the urinalysis shows hematuria and proteinuria. In children with CKD from congenital lesions

such as renal dysplasia, the urinalysis usually has a low specific gravity and minimal abnormalities by dipstick or microscopy.

Inulin clearance is the gold standard to determine GFR, but it is not easy to measure. Endogenous creatinine clearance is the most widely used marker of GFR, but creatinine secretion falsely elevates the calculated GFR. Several other markers are under investigation to accurately determine GFR in children, such as cystatin C and iohexol. In children age 1-16 yr, the degree of renal dysfunction may be determined by applying a new bedside formula that estimates GFR between 15 and 75 mL/min/1.73 m^2: estimated GFR = 0.43 × height in cm/serum creatinine in mg/dL

TREATMENT

The treatment of CKD is aimed at replacing absent or diminished renal functions, which progressively deteriorate in parallel with the progressive loss of GFR, and slowing the progression of renal dysfunction. Children with CKD should be treated at a pediatric center capable of supplying multidisciplinary services, including medical, nursing, social service, nutritional, and psychological support.

The management of CKD requires close monitoring of a patient's clinical and laboratory status. Blood studies to be followed routinely include serum electrolytes, blood urea nitrogen, creatinine, calcium, phosphorus, albumin, alkaline phosphatase, and hemoglobin levels. Periodic measurement of intact parathyroid hormone (PTH) levels and roentgenographic studies of bone may be of value in detecting early evidence of renal osteodystrophy. Echocardiography should be performed periodically to identify left ventricular hypertrophy and cardiac dysfunction that can occur as a consequence of the complications of CKD.

Nutrition

Nutritional management by a dietician experienced in pediatric renal patients is recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI). Counseling based on individualized assessment should be considered for all children and their families with CKD stages 2 to 5 and 5D. Patients should receive 100% of estimated energy requirement for age, individually adjusted for physical activity level, body mass index, and response in rate of weight gain or loss. When oral supplemental nutrition with increased calories or fluid volume is insufficient, tube feeding should be considered. Calories should be balanced between carbohydrate, unsaturated fat in physiological ranges (per dietary reference intake [DRI]), and protein. Protein intake recommendation is 100-140% of the DRI for ideal weight for children with stage 3 CKD, 100-120% of the DRI in stages 4 and 5 CKD, and 100% with allowance for dialysis loss in CKD stage 5D, with use of commercial supplements as needed. Children with CKD stages 2-5 should receive 100% of DRI of vitamins and trace elements; water-soluble vitamin supplements are often required in CKD stage 5D.

Renal Osteodystrophy

The term *renal osteodystrophy* is used to indicate a spectrum of bone disorders seen in patients with CKD. The most common condition seen in children is high-turnover bone disease caused by secondary hyperparathyroidism. The skeletal pathologic finding in this condition is osteitis fibrosa cystica.

The **pathophysiology** of renal osteodystrophy is complex. Early in the course of CKD, when the GFR declines to approximately 50% of normal, the decrease in functional kidney mass leads to a decline in renal 1α-hydroxylase activity, with decreased production of activated vitamin D (1,25-dihydroxycholecalciferol). This deficiency in activated vitamin D results in decreased intestinal calcium absorption, hypocalcemia, and increased parathyroid gland activity. Excessive PTH secretion attempts to correct the hypocalcemia by increasing bone resorption. Later in the course of CKD, when the GFR declines to 20-25% of normal, compensatory mechanisms that have been operative to enhance renal phosphate excretion become inadequate, resulting in hyperphosphatemia, which further promotes hypocalcemia and increased PTH secretion.

Clinical manifestations of renal osteodystrophy include muscle weakness, bone pain, and fractures with minor trauma. In growing children, rachitic changes, varus and valgus deformities of the long bones, and slipped capital femoral epiphyses may be seen. Laboratory studies can demonstrate a decreased serum calcium level and increased serum phosphorus, alkaline phosphatase, and PTH levels. Radiographs of the hands, wrists, and knees show subperiosteal resorption of bone with widening of the metaphyses.

The goals of **treatment** are to prevent bone deformity and normalize growth velocity using both dietary and pharmacologic interventions. The target phosphorus level for adolescents is between 3.5 and 5.5 mg/dL, and for children 1-12 yr of age it is 4-6 mg/dL. Children and adolescents should follow a low-phosphorus diet, and infants should be provided with a low-phosphorus formula such as Similac PM 60/40. It is impossible to fully restrict phosphorus intake, and so phosphate binders are used to enhance GI phosphate excretion. Although calcium-based binders have historically been the most commonly used, non–calcium-based binders such as sevelamer (Renagel) are increasing in use, particularly in older children and adolescent patients who are prone to hypercalcemia. Because aluminum may be absorbed from the GI tract and can lead to aluminum toxicity, aluminum-based binders should be avoided.

The cornerstone of therapy for renal osteodystrophy is vitamin D administration. **Vitamin D therapy** is indicated in patients with 1,25-dihydroxy-vitamin D levels below the established goal range for the child's particular stage of CKD or in patients with PTH levels above the established goal range for CKD stage. Patients with low 1,25-dihydroxy-vitamin D and elevated PTH levels should be treated with 0.01-0.05 µg/kg/24 hr of calcitriol (Rocaltrol, 0.25-µg capsules or 1 µg/mL suspension). Newer activated vitamin D analogs such as paricalcitol and doxercalciferol are increasingly used, especially in patients who are predisposed to hypercalcemia. Phosphate binders and vitamin D should be adjusted to maintain the PTH level within the designated goal range and the serum calcium and phosphorus levels within the normal range for age. Many nephrologists also attempt to maintain the calcium/phosphorus product ($Ca \times PO_4$) at <55 mg^2/dL^2 in adolescents and <65 mg^2/dL^2 in younger children to minimize the possibility of tissue deposition of calcium phosphorus salts with consequent damage.

Adynamic Bone Disease

Adynamic bone disease (low-turnover bone disease) has been recognized in children and adults with CKD. The pathologic finding is osteomalacia and is associated with oversuppression of PTH, perhaps related to the widespread use of calcium-containing phosphate binders and vitamin D analogs.

Fluid and Electrolyte Management

Most children with CKD maintain normal sodium and water balance, with the sodium intake derived from an appropriate diet. Infants and children whose CKD is a consequence of renal dysplasia may be polyuric, with significant urinary sodium or free water losses. These children may benefit from high-volume, low-caloric-density feedings with sodium supplementation. Children with high blood pressure, edema, or heart failure may require sodium restriction and diuretic therapy. Fluid restriction is rarely necessary in children with CKD until the development of ESRD requires the initiation of dialysis.

In most children with CKD, potassium balance is maintained until renal function deteriorates to the level at which dialysis is initiated. Hyperkalemia can develop, however, in patients with moderate renal insufficiency who have excessive dietary potassium intake, severe acidosis, or hyporeninemic hypoaldosteronism (related to destruction of the renin-secreting juxtaglomerular apparatus). Hyperkalemia may be treated by restriction of dietary potassium intake, administration of oral alkalinizing agents, and/or treatment with Kayexalate.

Acidosis

Metabolic acidosis develops in almost all children with CKD as a result of decreased net acid excretion by the failing kidneys. Either Bicitra

(1 mEq sodium citrate/mL) or sodium bicarbonate tablets (650 mg = 8 mEq of base) may be used to maintain the serum bicarbonate level >22 mEq/L.

Growth

Short stature is a significant long-term sequela of childhood CKD. Children with CKD have an apparent growth hormone–resistant state, with elevated growth hormone levels but decreased insulin-like growth factor 1 levels and major abnormalities of insulin-like growth factor–binding proteins.

Children with CKD who remain less than −2 SD for height despite optimal medical support (adequate caloric intake and effective treatment of renal osteodystrophy, anemia, and metabolic acidosis) might benefit from treatment with pharmacologic doses of recombinant human growth hormone (rHuGH). Treatment may be initiated with rHuGH (0.05 mg/kg/24 hr) subcutaneously, with periodic adjustment in the dose to achieve a goal of normal height velocity for age.

Treatment with rHuGH continues until the patient reaches the 50th percentile for midparental height, achieves a final adult height, or undergoes kidney transplantation. Long-term rHuGH treatment significantly improves final adult height and induces persistent catch-up growth; some patients achieve normal adult height.

Anemia

Anemia in patients with CKD is primarily the result of inadequate erythropoietin production by the failing kidneys and usually becomes manifest in patients with stages 3-4 CKD.

Other possible contributory factors include iron deficiency, folic acid or vitamin B_{12} deficiency, and decreased erythrocyte survival. Recombinant human erythropoietin (rHuEPO) therapy has decreased the need for transfusion in patients with CKD. Erythropoietin is usually initiated when the patient's hemoglobin concentration falls below 10 g/dL, at a dose of 50-150 mg/kg/dose subcutaneously 1-3 times weekly. The dose is adjusted to maintain the hemoglobin concentration between 11 and 12 g/dL. All patients receiving rHuEPO therapy should be provided with either oral or intravenous iron supplementation. Patients who appear to be resistant to rHuEPO should be evaluated for iron deficiency, occult blood loss, a chronic infection or inflammatory state, vitamin B_{12} or folate deficiency, or bone marrow fibrosis related to secondary hyperparathyroidism. An alternative option to rHuEPO is darbepoetin alfa (Aranesp), a longer-acting agent administered at a dose of 0.45 µg/kg/wk. The chief advantage of this agent is that it may be dosed once weekly to once monthly because of its extended duration of action.

Hypertension

Children with CKD can have sustained hypertension related to volume overload and/or excessive renin production related to glomerular disease. Hypertensive children with suspected volume overload should follow a salt-restricted diet (<2 g/24 hr) and may benefit from diuretic therapy. Thiazide diuretics (hydrochlorothiazide 2 mg/kg/24 hr divided bid) are the initial diuretic class of choice for children with mild renal dysfunction (CKD stages 1-3). However, when a patient's estimated GFR falls below this range, thiazides are ineffective and loop diuretics (furosemide 1-2 mg/kg/dose bid or tid) become the diuretic class of choice. **ACE inhibitors** (enalapril, lisinopril) and **angiotensin II receptor blockers** (losartan) are the antihypertensive medications of choice in all children with proteinuric renal disease because of their potential ability to decrease proteinuria and slow the progression to ESRD (by mechanisms still not completely delineated). Extreme care must be used with these agents, however, to monitor renal function and electrolyte balance, particularly in children with advanced CKD. Calcium channel blockers (amlodipine), β-blockers (propranolol, atenolol), and centrally acting agents (clonidine) may be useful as adjunctive agents in children with CKD whose blood pressure cannot be controlled using dietary sodium restriction, diuretics, and ACE inhibitors.

Immunizations

Children with CKD should receive all standard immunizations according to the schedule used for healthy children. An exception must be made in withholding live virus vaccines from children with CKD related to glomerulonephritis, or any disease, during treatment with immunosuppressive medications. It is critical, however, to make every attempt to administer live virus vaccines for measles, mumps, rubella, and varicella before kidney transplantation. These vaccines are not advised for use in immunosuppressed patients. All children with CKD should receive a yearly influenza vaccine. Data from a number of studies suggest that children with CKD might respond suboptimally to immunizations.

Adjustment In Drug Dose

Because many drugs are excreted by the kidneys, their dosing might need to be adjusted in patients with CKD to maximize effectiveness and minimize the risk of toxicity. Strategies in dosage adjustment include lengthening of the interval between doses or decreasing the absolute dose, or both. Such adjustments become even more important as pharmacogenomic profiling of drug metabolism becomes routine.

Progression of Disease

Although there are no definitive treatments to improve renal function in children or adults with CKD other than treatment of a specific underlying disorder when possible, there are several general strategies that may be effective in slowing the rate of progression of renal dysfunction. Optimal control of hypertension (maintaining the blood pressure at lower than the 75th percentile and perhaps even lower) is critical in all patients with CKD. ACE inhibitors or angiotensin II receptor blockers should be the antihypertensive drugs of choice in hypertensive children with chronic proteinuric renal disease as previously noted. Such agents should also be strongly considered in children with CKD who have significant proteinuria, even in the absence of hypertension, although there are no controlled studies to support this approach. Serum phosphorus should be maintained within the normal range for age and the calcium–phosphorus product <55 to minimize renal calcium–phosphorus deposition. Prompt treatment of infectious complications and episodes of dehydration can minimize additional loss of renal parenchyma.

Other potentially beneficial recommendations include correction of anemia with erythropoietin or darbepoetin alfa therapy, control of hyperlipidemia, avoidance of cigarette smoking, prevention of obesity, and avoidance of nonsteroidal antiinflammatory and other potential nephrotoxic medications. This includes a variety of illegal street drugs as well as herbal and/or homeopathic medications or "supplements." Although dietary protein restriction may be useful in adults, this recommendation is generally not suggested for children with CKD because of the concern about adverse effects on growth and development.

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535.3 End-Stage Renal Disease

Rajasree Sreedharan and Ellis D. Avner

ESRD represents the state in which a patient's renal dysfunction has progressed to the point at which homeostasis and survival can no longer be sustained with native kidney function and maximal medical management. At this point, renal replacement therapy (dialysis or renal transplantation) becomes necessary. The ultimate goal for children with ESRD is successful kidney transplantation (see Chapter 536)

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because it provides the most normal lifestyle and possibility for rehabilitation for the child and family.

In the United States, 75% of children with ESRD require a period of dialysis before transplantation can be performed. It is recommended that plans for renal replacement therapy be initiated when a child reaches stage 4 CKD. The optimal time to actually initiate dialysis, however, is based on a combination of the biochemical and clinical characteristics of the patient including refractory fluid overload, electrolyte imbalance, acidosis, growth failure, or uremic symptoms, including fatigue, nausea, and impaired school performance. In general, most nephrologists attempt to initiate dialysis early enough to prevent the development of severe fluid and electrolyte abnormalities, malnutrition, and uremic symptoms. Preemptive transplantation before initiation of dialysis is increasingly being utilized.

The selection of dialysis modality must be individualized to fit the needs of each child. In the United States, two thirds of children with ESRD are treated with peritoneal dialysis, whereas one third are treated with hemodialysis. Age is a defining factor in dialysis modality selection: 88% of infants and children from birth to 5 yr of age are treated with peritoneal dialysis, and 54% of children >12 yr of age are treated with hemodialysis.

Peritoneal dialysis is a technique that employs the patient's peritoneal membrane as a dialyzer. Excess body water is removed by an osmotic gradient created by the high dextrose concentration in the dialysate; wastes are removed by diffusion from the peritoneal capillaries into the dialysate. Access to the peritoneal cavity is achieved by a surgically inserted, tunneled catheter.

Peritoneal dialysis may be provided either as continuous ambulatory peritoneal dialysis or as an automated therapy using a cycler (continuous cyclic peritoneal dialysis, intermittent peritoneal dialysis, or nocturnal intermittent peritoneal dialysis). The majority of U.S. children treated with peritoneal dialysis use cycler-driven therapy, which allows the child and family to be free of dialysis demands during the waking hours. The exchanges are performed automatically during sleep by machine. This permits an uninterrupted day of activities, a reduction in the number of dialysis catheter connections and disconnections (which decreases the risk of peritonitis), and a reduction in the time required by patients and parents to perform dialysis, reducing the risk of fatigue and burnout. Because peritoneal dialysis is not as efficient as hemodialysis, it must be performed daily rather than 3 times weekly. Table 535-8 outlines the benefits of peritoneal dialysis.

Hemodialysis, unlike peritoneal dialysis, is usually performed in a hospital setting. Children and adolescents typically have 3 treatments (3-4 hr each) per wk during which fluid and solute wastes are removed. Access to the child's circulation is achieved by a surgically created arteriovenous fistula, graft, or indwelling subclavian or internal jugular catheter.

Bibliography is available at Expert Consult.

Table 535-8	Merits of Peritoneal Dialysis in Pediatric Patients with End-Stage Renal Disease
ADVANTAGES	
Ability to perform dialysis treatment at home	
Technically easier than hemodialysis, especially in infants	
Ability to live a greater distance from medical center	
Freedom to attend school and after-school activities	
Less-restrictive diet	
Less expensive than hemodialysis	
Independence (adolescents)	
DISADVANTAGES	
Catheter malfunction	
Catheter-related infections (peritonitis, exit site)	
Impaired appetite (due to full peritoneal cavity)	
Negative body image	
Caregiver burnout	

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Chapter 536
Renal Transplantation
Minnie M. Sarwal

Kidney transplantation is the optimal therapy for children with end-stage renal disease (ESRD). Five yr survival rates in children who receive a kidney transplant are greater than survival rates of those who remain on hemodialysis or peritoneal dialysis. Children and adolescents with ESRD have special needs that differ from adults, including the need to achieve normal growth and cognitive development. Successful transplantation leads to improvement in their linear growth and allows them to attend school and be free of dietary restrictions. Immunosuppression protocols that employ steroid minimization or avoidance after transplantation demonstrate dramatic improvements in growth patterns for young children after transplantation. Improvements in surgical techniques and a reduction in the early complications of thrombosis have given young children the best long-term outcomes of all age groups among transplant recipients.

INCIDENCE AND ETIOLOGY
The incidence of ESRD in pediatric patients in the United States varies by age group (Table 536-1). There is an adjusted incident rate of 14.4 per million population for ages 0-19 yr.

The etiology of ESRD in children varies significantly by age (Table 536-2). Congenital, hereditary, and cystic diseases cause ESRD in more than 52% of children 0-4 yr of age, whereas glomerulonephritis and focal segmental glomerulosclerosis (FSGS) account for 38% of cases of ESRD in patients 10-19 yr of age. The most common diagnosis in children with *transplanted kidneys* is structural disease (49%), followed by various forms of glomerulonephritis (14%) and FSGS (12%).

INDICATIONS
Almost all children with ESRD are considered to be candidates for renal transplantation. There are very few absolute contraindications for pediatric kidney transplantation. Relative contraindications include children with preexisting metastatic malignancy or HIV. Patients with remission of malignancy off maintenance treatment for a minimum of 2 yr may be reconsidered on an individual basis for transplantation, with close posttransplantation surveillance. Similarly, patients with autoimmune diseases resulting in ESRD are candidates for transplantation after a period of immunologic quiescence of the primary disease for a period of at least 1 yr before transplantation. Another relative contraindication includes severe neurologic dysfunction, but the wishes of the parents and the potential for rehabilitation must be considered.

Table 536-1 Incident Rates of Reported ESRD in the United States

AGE RANGE (YR)	ADJUSTED INCIDENT RATES* PER MILLION POPULATION
0-4	9.5
5-9	6.1
10-14	13
15-19	29

*Rates are adjusted for sex and race.
ESRD, end-stage renal disease.
From U.S. Renal Data System, USRDS 2009 Annual data report: atlas of end-stage renal disease in the United States, *National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2009,* www.usrds.org.

Table 536-2 Common Causes of ESRD in Pediatric Transplant Recipients (N = 9854)

CAUSES	% OF RECIPIENTS
Aplasia, hypoplasia, dysplasia	15.9
Obstructive uropathy	15.6
Focal segmental glomerulosclerosis	11.7
Reflux nephropathy	5.2
Chronic glomerulonephritis	3.3
Polycystic disease	2.9
Medullary cystic disease	2.8
Hemolytic-uremic syndrome	2.6
Prune belly syndrome	2.6
Congenital nephrotic syndrome	2.6
Familial nephritis	2.3
Cystinosis	2.0
Idiopathic crescentic glomerulonephritis	1.7
MPGN type I	1.7
Berger (IgA) nephritis	1.3
Henoch-Schönlein nephritis	1.1
MPGN type II	0.8

ESRD, end-stage renal disease; MPGN, membranoproliferative glomerulonephritis.
Data from the North American Pediatric Renal Trials and Collaborative Studies, https://web.emmes.com/study/ped/.

Renal transplantation is considered for any child when renal replacement therapy is indicated. In children, dialysis may be required for a period before transplantation to optimize nutritional and metabolic conditions, to achieve an appropriate size in small children, or to keep a patient stable until a suitable donor is available. For young infants, a recipient may need to weigh at least 8-10 kg to minimize the risk for vascular thrombosis and to accommodate an adult-size kidney. This can require a period of dialysis support until the child is at least 12-18 mo of age. Transplantation with an adult-size kidney has been successful in children who weighed <10 kg or were <6 mo of age.

Preemptive transplantation (i.e., transplantation without prior dialysis) continues to account for approximately 25% of all pediatric renal transplants, based mostly on a desire by the child and the family to avoid dialysis. There may be a small benefit in allograft outcome if transplantation occurs without prior dialysis, which might relate to a lower incidence of infections and cardiovascular risk factors. Preemptive renal transplant should be considered when the glomerular filtration rate (GFR) is <10-15 mL/min/1.73 m^2 and with symptomatic ESRD or rapidly declining GFR and need for dialysis within 6-12 mo. The rates of preemptive transplantation differ moderately for different age groups, being 20% for recipients age ≤2 yr, 24% for age 2-5 yr, 28% for age 6-12 yr, and 22% for age 13-17 yr.

CHARACTERISTICS OF DONORS AND RECIPIENTS

Almost half of all pediatric kidney transplants come from living donors. The highest rates of transplantation are in the 5-9 yr old group, with 40 live donor transplants and 46 cadaver donor transplants performed per 100 dialysis patient-years. The Organ Procurement and Transplantation Network (OPTN) provides preference for children waiting for a deceased-donor renal transplant. Owing to improved outcomes in deceased-donor pediatric transplantation using donors 5-35 yr of age, OPTN in 2005 implemented a pediatric kidney allocation policy that gave priority for kidneys from deceased donors <35 yr of age. These kidneys were assigned to recipients <18 yr, after 0 mismatch transplants, recipients with a panel reactive antibody >80, or candidates receiving a kidney with a nonrenal origin. This policy shortened the wait time for children versus adults and is associated with improved outcomes.

Living-donor kidney transplantation graft survival has improved over the years, and from 2003-2007 the graft survival rate in living-donor renal transplants was 96.1%, unchanged from the 1999-2002 rate of 95.9%. Graft survival rates for deceased donors from 2003-2007 are 94.4%, also improved from 92.7% in 1999-2002. For children awaiting deceased-donor renal transplants the goals are to minimize waiting times, transplanting kidneys into children 0-6 yr of age within 6 mo, children 7-12 yr within 12 mo, and children 12-18 yr within 18 mo.

EVALUATION AND PREPARING FOR TRANSPLANTATION

The team approach includes evaluations by a transplantation surgeon, nephrologist, nutritionist, social worker, psychologist, financial counselor, pretransplantation nurse, and dialysis nurse (if the patient is undergoing dialysis).

Primary renal disease can recur in a number of renal diseases, but it is not a contraindication to transplantation. Recurrent disease in the renal graft accounts for graft loss in almost 7% of primary transplantations and 10% in repeat transplantations.

With FSGS and primary oxalosis, patients are at risk for major renal function impairment with recurrence of disease. Grafts in approximately 20-30% of patients with the diagnosis of FSGS fail because the disease recurs. In patients with the original disease of FSGS whose grafts fail, the mean time to failure is 17 mo. Alport syndrome can recur as an anti–glomerular basement membrane (anti-GBM) glomerulonephritis in approximately 3-4% of patients after transplantation and lead to graft loss. Histologic evidence of recurrence of membranoproliferative glomerulonephritis type I varies widely, from 20% to 70%, and graft loss can occur in ≤30% of cases. Histologic recurrence of membranoproliferative glomerulonephritis type II disease occurs in virtually all cases, with graft loss in ≤50% cases. Histologic recurrence with mesangial immunoglobulin (Ig) A deposits is common and occurs in about half of the patients with IgA nephropathy and in approximately 30% of patients with Henoch-Schönlein purpura. Congenital nephrotic syndrome rarely recurs after transplantation, although patients can develop antinephrin antibodies and present with nephrotic syndrome. Some cases (~25%) of nephrotic syndrome after transplantation are likely de novo. Membranous nephropathy occurs very rarely in children. The recurrence rate after kidney transplantation for patients who have been treated for Wilms tumor is approximately 13%.

Owing to the high risk of developing Wilms tumor, patients with Denys-Drash syndrome should undergo bilateral nephrectomy before transplantation. Other *indications for bilateral native nephrectomies* include hyposthenuria with polyuria, significant proteinuria, and severe hypertension resistant to medical management. Nephrectomies are also indicated in cases such as polycystic kidney disease, where more room may be needed to place the transplanted kidney and to create space in the abdominal cavity to improve feeding tolerability and the infant's ability to thrive.

Failure to maintain adequate perfusion of the adult-size kidney, secondary to a "perfusion steal" by the native kidneys results in a histologic picture of "chronic" acute tubular necrosis and a negative impact on graft function.

Urologic problems, such as vesicoureteral reflux, posterior urethral valves, abnormal urinary bladders, and/or neurogenic bladders, should be addressed before surgery. Malformations and voiding abnormalities (e.g., neurogenic bladder, bladder dyssynergia, remnant posterior urethral valves, and urethral strictures) should be identified and repaired if possible. Children with urologic disease and renal dysplasia often require multiple operations to optimize urinary tract anatomy and function. Such procedures include ureteric reimplantation to correct vesicoureteral reflux, bladder augmentation or reconstruction, creation of a vesicocutaneous fistula by using the appendix to provide a simple, continent, and cosmetically acceptable way for intermittent

catheterization (Mitrofanoff procedure), and excision of duplicated systems or ectopic ureteroceles that could cause recurrent infections. There are reports of excellent outcomes often being achieved in posterior urethral valve bladders by following a staged procedure of initial valve resection to limit any injury to the posterior urethra, and bladder rehabilitation, without the requirement of augmentation, by a process of regimented double voiding.

A comprehensive **nutritional assessment** needs to be done to ensure that optimal nutritional status is achieved before transplant. Many children with ESRD and especially those on dialysis require nutritional supplements to provide them with sufficient protein and calories. Infants and young children on dialysis often require nasogastric or gastric tube feedings to overcome decreased oral intake from nausea and anorexia due to uremia. Optimal outcomes result from transplanting adult-size kidneys from living donors when the child weighs ≥10 kg.

Bone disease needs to be evaluated for and treated before transplantation. Secondary hyperparathyroidism needs to be treated before transplant to avoid posttransplant urinary phosphate wasting and hypercalcemia. High calcium phosphorus product before transplantation leads to vascular stiffness and calcifications, increasing the patient's risk for cardiovascular disease.

In the United States, >25% of the mortality in children on maintenance dialysis is a result of **cardiovascular disease**. Cardiac death is the leading cause of death in young patients after transplant in childhood. Therefore, evaluation of cardiac function is required before a kidney transplant in a pediatric patient to be sure that patient has sufficient cardiac function to tolerate the large fluid load that accompanies kidney transplantation. All patients being evaluated for kidney transplant have at least an echocardiogram and electrocardiogram. Hypertension is common and can result from fluid overload and/or intrinsic native renal disease. Blood pressure needs to be under optimal control before transplant. If blood pressure cannot be controlled with medical management, bilateral nephrectomy may need to be performed before transplant to control the hyperreninemic response from the failing kidneys.

Anemia needs to be treated before transplantation. Most patients are taking erythropoietin, folate, and iron to maintain goals for hemoglobin levels between 11 and 12 g/dL. Blood transfusions should be avoided owing to concerns for sensitizing the patient to human leukocyte antigens before transplant. If a blood transfusion is required, patients should receive cytomegalovirus negative, leukoreduced red blood cells. Blood should not be irradiated owing to concerns for trauma to the cells and potential for increased antigen exposure.

Evaluation for **venous thrombosis** and **hypercoagulable states** is important before renal transplantation. The third leading cause of graft failure is vascular thrombosis; the leading causes are chronic (34.9%) and acute (13.1%) rejection. Risk factors for graft thrombosis include surgical technique, perfusion and reperfusion injury of graft, young donor age (<2 yr), young recipient (<5 yr), cold ischemia time >24 hr, arterial hypotension, prior history of peritoneal dialysis, and/or hypoperfusion of adult kidney transplant in a small child. Particularly in the young recipient, before transplantation, there needs to be evaluation for thrombosis of iliac vessels or inferior vena cava if the patient has had previous surgery or central line placement. Femoral line catheterizations greatly increase the risk for inferior vena cava thrombosis. Children who have large protein losses, such as from nephrotic syndrome and/or peritoneal dialysis, can be at increased risk for thrombosis because of protein loss, such as protein S, protein C, and antithrombin III. Doppler ultrasound, computed tomographic angiography, and magnetic resonance angiography have all been used to evaluate vessels. Magnetic resonance angiography has been used less owing to the concern about exposure to gadolinium and nephrogenic systemic fibrosis. In patients with renal compromise receiving contrast media, intravenous hydration is needed before and after the study for patients with residual renal function, acidosis should be corrected before giving contrast, and *N*-acetyl cysteine should be administered before and after the CT angiogram to reduce the risk of contrast nephropathy. If the patient is on dialysis, dialysis clearance can be done after contrast administration; hemodialysis is the optimal method for clearance.

Infections need to be identified and treated before transplantation. Infectious disease screening includes a complete history of household contacts with treatment for active or latent tuberculosis, vaccine history for varicella and pertussis, travel history within the past 2 yr and/or if there was significant time spent in another country, history of bacille Calmette-Guérin, animal and/or insect exposure, sexual activity, and consumption of high-risk foods such as unpasteurized products. Screening includes tuberculosis skin test (purified protein derivative), cytomegalovirus IgG, Epstein-Barr virus (EBV) antibody panel, varicella titer, measles antibody, hepatitis B serologies, hepatitis C antibody, HIV, and toxoplasmosis. Additional testing for patients who lived in or visited the central valleys of California, Utah, Nevada, Arizona, and/or New Mexico includes *Coccidioides* immunodiffusion. Patients from the Ohio River valley should also have *Histoplasma* antibody checked. Patients from Mexico should have *Coccidioides* immunodiffusion, *Histoplasma* antibody, and ova and parasite screen to evaluate for *Strongyloides.* Those from South America should have *Coccidioides* immunodiffusion, *Histoplasma* antibody, and *Toxoplasma* antibody. Sexually active patients should also be screened for syphilis, gonorrhea, HIV, and *Chlamydia.*

Immunizations need to be up to date before transplantation. All live vaccines need to be given before transplantation because these vaccines should not be given to immunosuppressed patients. Therefore, measles-mumps-rubella and varicella should be given before transplant and antibody titers should be checked to monitor for response. Measles-mumps-rubella may be given as early as 6 mo of age. Inhaled influenza vaccine should not be given to transplant patients, family members, or healthcare providers.

Psychiatric evaluation should be performed before transplantation to evaluate patients' and their families' ability to cope with the stressors that accompany caring for a child with a kidney transplant. A psychologist should also evaluate the patient and their caregivers for depression, substance abuse, and/or noncompliance so that problems can be identified and managed before kidney transplantation. If noncompliance is identified or anticipated, interventions should be in place before transplantation. These should include social and psychiatric interventions, where possible.

Children need 2 ABO blood types checked before being listed for a kidney transplantation and a donor should be sought who shares HLA-A, HLA-B, and/or HLA-DR antigens. The 2008 North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) data have shown increased risk for rejection and graft failure with 2-DR mismatch compared to a 0-DR mismatch. The recipient's blood is also checked to see if the patient is sensitized. Patients can become sensitized by prior transplant, blood transfusions, sepsis, and/or pregnancy.

IMMUNOSUPPRESSION

Most pediatric kidney transplant centers employ a combination of drug therapy consisting of a calcineurin inhibitor and corticosteroids with or without an antiproliferative agent. Approximately 80% of transplantation patients receive a 3-drug regimen at 6 mo after transplantation. The rationale for this combination therapy in children is to provide effective immunosuppression and at the same time minimize the toxicity of any single drug.

Induction Therapy

Induction therapy is commonly used in pediatric renal transplant recipients to prevent acute rejection. Graft survival rates are higher in patients treated with antilymphocyte induction therapy. Acute rejection episodes are approximately 30% less frequent and tend to occur later. Induction therapy may consist of T-cell antibodies, interleukin-2 receptor antibodies, and/or therapies that target B cells.

T-Cell Antibodies

Antithymocyte globulin (ATGAM) and Thymoglobulin are polyclonal antibodies that should be given intravenously through a central line to avoid sclerosis and injury to smaller vessels. These medications are

used to prevent the development of the first rejection. Thymoglobulin is polyclonal antibodies against human T-lymphocyte antigens resulting in a rapid depletion of T lymphocytes. Some limit the use of Thymoglobulin induction to sensitized high-risk patients or patients who have concerns for delayed graft function and want to avoid high calcineurin inhibitor levels in the early postoperative period. Dosage is 1.5-2.0 mg/kg/dose, with daily monitoring of $CD3^+$ subsets; the dose should not be given if the $CD3^+$ count exceeds 20 cells/mm^3.

OKT3 is a monoclonal antibody that is also given daily for 10-14 days. Studies have not shown a clear advantage using OKT3.

Interleukin-2 Receptor Antibodies

Monoclonal antibodies, such as basiliximab and daclizumab, chimeric or humanized monoclonal anti-CD25 antibodies, prevent T-cell proliferation but do not cause T-cell depletion. Basiliximab is given on day 0 and day 4 of the transplant as 12 mg/m^2/dose in children. Daclizumab is given on day 0 and then every 2 wk for a total of 5 doses at 1 mg/kg/dose in patients with steroid-based immunosuppression. Patients who are steroid free receive a 2 mg/kg dose on day 0 and the remaining doses at 1 mg/kg at wk 2, 4, 6, 8, 11, 15, 19, and 23. This provides the patient with extra immunosuppression for 3 mo for steroid-based patients and 6 mo for steroid-free patients. Patients tend to tolerate IL-2 receptor antagonists well. With the withdrawal of daclizumab from the market because of manufacturing deficits, many pediatric transplantation programs are using basiliximab or a short course (3 days) of Thymoglobulin at 1.5 mg/kg/day for children at low risk of sensitization and the recommended dosing of Thymoglobulin (5-7 days) or alemtuzumab for children at high risk of sensitization (see below).

Alemtuzumab (Campath-1H) is a monoclonal antibody against CD52 antigen present on T and B cells, monocytes, and natural killer cells. The pediatric data on the use of alemtuzumab show promising results.

Other Induction Therapies

Other induction therapies for highly sensitized patients include targeting B cells and/or removing neutralizing antibodies by using rituximab against the CD20 epitope on early-and intermediate-lineage B cells, the proteosome inhibitor bortezomib, and plasmapheresis and/or high-dose intravenous immunoglobulin for removing donor-specific antibodies.

Belatacept is a fusion protein composed of the Fc fragment of a human IgG_1 linked to the extracellular domain of CTLA-4, which is a molecule crucial for T-cell costimulation, selectively blocking the process of T-cell activation. Belatacept usage extends from induction to limited maintenance therapy, and is intended to provide optimal immunosuppression and limiting of the toxicity generated by standard immune-suppressing regimens, such as calcineurin inhibitors, thus limiting fibrosing graft injury and improving renal function. Complications include a higher incidence and grade of acute rejection episodes and a higher incidence of posttransplant lymphoproliferative disorders, with greatest risk in EBV seronegative recipients.

Maintenance Immunosuppression

For maintenance immunosuppression, calcineurin inhibitors, mycophenolate mofetil (MMF), steroids, azathioprine, and/or rapamycin may be used. Most pediatric kidney transplant recipients are maintained with a triple-immunosuppressant regimen. Central to many current pediatric immunosuppressive regimens is a calcineurin inhibitor (cyclosporine or tacrolimus) in combination with steroids and an adjunctive antiproliferative agent (azathioprine, sirolimus, or MMF). MMF is used as the adjunctive agent in more than two thirds of the pediatric kidney transplants performed. Sirolimus is used in 10-15%, and azathioprine is used in only approximately 2%. Corticosteroids continue to be used in approximately 80-85% of transplant recipients.

Calcineurin Inhibitors

The side-effect profile of **cyclosporine** in children is similar to that seen in adults, but the impact on children is more pronounced. Hypertrichosis, gingival hyperplasia, and coarsening facial features may be particularly troublesome in children. Hispanic and African-American children appear to be at higher risk for significant hypertrichosis. In the adolescent population, especially girls, these side effects can cause severe emotional distress, possibly leading to noncompliance. Seizures, although uncommon, are observed more commonly in children treated with cyclosporine than in adults. Children are likely to develop hypercholesterolemia and hypertriglyceridemia and may be candidates for lipid-lowering agents. Hyperglycemia occurs in <5% of children treated with cyclosporine.

The hyperlipidemia associated with cyclosporine and other immunosuppressive agents is also absent with **tacrolimus**. On the other hand, posttransplantation glucose intolerance, tremor, alopecia, and mild sleep disturbances are more common with tacrolimus. Historically, **posttransplant lymphoproliferative disease** has been significantly more common in children receiving tacrolimus. The lack of cosmetic side effects makes tacrolimus a very attractive alternative for children. This is especially true for young adolescents and female patients, in whom the cosmetic side effects can lead to noncompliance.

Direct comparative data in pediatrics between cyclosporine and tacrolimus are limited. The published results comparing these 2 agents show that overall acute rejection rates at 6 mo were 59.1% versus 36.9% for cyclosporine and tacrolimus, respectively. In the tacrolimus group, graft function was better at 1 yr after transplantation. The mean total steroid dose from time of transplant to 6 mo posttransplantation was significantly lower in the tacrolimus group. The overall safety profiles of the 2 calcineurin inhibitors were equivalent, with essentially no difference in posttransplant lymphoproliferative disorder or in diabetes requiring insulin treatment. The combination of drugs (tacrolimus and sirolimus) may be the biggest risk factor for PTLD.

Mycophenolate Mofetil

MMF is the morpholinoethylester prodrug of mycophenolic acid, an inhibitor of de novo purine synthesis. MMF is part of the initial maintenance immunosuppression regimen in approximately 66% of U.S. pediatric renal transplant recipients. It has largely replaced azathioprine. Acute rejection rates with MMF are approximately 20-30% when used with cyclosporine and corticosteroids. When MMF is used with tacrolimus and/or humanized monoclonal antibodies to the IL-2 receptor, lower rejection rates are usually seen.

The use of MMF has often facilitated the use of a lower dose of corticosteroids after transplantation. It has also proved useful in calcineurin inhibitor–sparing protocols, in which MMF is combined with sirolimus and corticosteroids. In steroid-avoidance regimens in kidney transplantation, the bioavailability of mycophenolic acid has been found to be greater than when the drug is used with steroids. This has allowed reduced dosing of MMF when combined with steroid avoidance in children. The absence of nephrotoxicity, hyperlipidemia, and hepatotoxicity has also contributed to the usefulness of MMF.

Gastrointestinal and hematologic side effects can be troublesome. Most of these instances can be treated with a dosage reduction and/or brief discontinuation of the drug, with resumption after 7-14 days at a lower dose. Enteric-coated mycophenolic acid has been shown to decrease the upper gastrointestinal side effects of MMF in adult transplant recipients.

Sirolimus

Sirolimus, an inhibitor of the mammalian target of rapamycin, is used primarily as an adjunctive immunosuppressive agent in combination with a calcineurin inhibitor. It is used in approximately 10-15% of pediatric renal transplant recipients. Limited anecdotal experience with sirolimus as a rescue agent in cases of refractory acute rejection, chronic allograft nephropathy, calcineurin inhibitor nephrotoxicity, and PTLD has been promising.

Most early reports in pediatric kidney transplantation appear to describe combinations of sirolimus with either tacrolimus or MMF; usually these are combined with prednisone, although efficacy has also been demonstrated with dual therapy (MMF and sirolimus) with complete steroid avoidance.

Corticosteroids

Corticosteroids remain an integral part of many immunosuppressive protocols despite their multifaceted toxicities. In children, retarded skeletal growth is the most noteworthy side effect of corticosteroids. Concerns remain about side effects, such as hypertension, obesity, diabetes mellitus, hyperlipidemia, osteopenia, and aseptic necrosis of bone (particularly the femoral heads). Cosmetic side effects, such as cushingoid faces and acne, are significant additional problems of chronic steroid use. Such side effects often tempt children and adolescent to stop taking their immunosuppressive drugs.

Steroid withdrawal attempts have led to improvements in blood pressure, lipid profiles, and growth. The benefits of steroid withdrawal have been overshadowed by high rates of acute rejection that occur in 25-70% of children. Studies using tacrolimus maintenance have shown safety in late steroid withdrawal, with low rates of acute rejection and no rebound early rejections. A steroid withdrawal trial using sirolimus had low rates of acute rejection but a high incidence of PTLD, which resulted in premature discontinuation of the study.

Complete steroid avoidance has emerged as an alternative strategy to prevent steroid-associated morbidities in children. The immunologic outcomes of these studies are the lower rates of acute rejection seen in these studies compared with standard of care protocols using steroids, suggesting that steroid avoidance might also have immunologic benefits. Building on such observations, investigators at a single center (Stanford University, Stanford, CA) initiated a steroid-avoidance protocol and demonstrated that complete steroid avoidance can be successfully achieved with excellent long-term outcomes at 8 yr, using tacrolimus in combination with MMF, and an extended 6 mo course of daclizumab. Other centers have had similar experience with complete steroid avoidance, using a similar protocol with tacrolimus and MMF and induction with either extended daclizumab or Thymoglobulin. The Stanford steroid-avoidance protocol has been replicated in a randomized multicenter U.S. trial (NIH/NIAID/CCTPT UO1 AI-55795) across 12 different pediatric kidney transplant programs in the United States, and this seminal trial confirms the safety of steroid avoidance in low-risk pediatric kidney transplant recipients with lower acute rejection rates, and significant benefits for growth, hypertension, and hyperlipidemia. Importantly, this study also confirmed the overall safety of steroid avoidance, with no adverse effects on generation of donor-specific antibody posttransplantation or histologic injury.

FLUID MANAGEMENT IN INFANTS AND SMALL CHILDREN

Maintenance of adequate blood flow to an adult-sized kidney in an infant or small child is crucial to avoid acute tubular necrosis (ATN) and graft loss from vascular thrombosis and primary nonfunction. The recipient aortic blood flow early after transplantation of an adult-size kidney more than doubles from pretransplantation aortic blood flow. The maximum blood flow that can be obtained in an adult-size kidney transplanted into a small child is approximately 65% of what was in the donor. Low blood flow states such as with hypovolemia or hypotension increase the risk for ATN, graft thrombosis, and graft nonfunction. In the postoperative period, patients are maintained on high fluid volumes.

Close attention is paid to blood pressure and hydration status in the operating room in an attempt to reduce the incidence of delayed graft function. Typically, a central venous catheter is inserted to monitor the central venous pressure throughout the operation. To achieve adequate renal perfusion, a central venous pressure of 12-15 cm H_2O should be achieved before removing the vascular clamps; a higher central venous pressure may be desirable in the case of a small infant receiving an adult-size kidney. Dopamine is usually started in the operating room at 2 to 3 μg/kg/min, increased if required, and continued for 24-48 hr postoperatively. It is used to facilitate diuresis and perhaps to affect renal vasodilation. The mean arterial blood pressure is kept >65-70 mm Hg by adequate hydration with a crystalloid solution and 5% albumin, and, if necessary, by using dopamine at higher doses. A blood transfusion with packed red blood cells may be required in very small recipients because the hemoglobin can drop as a result of sequestration of approximately 150-250 mL of blood in the transplanted kidney. Mannitol and/or furosemide may be given before removing the vascular clamps to increase the effective circulatory volume and facilitate diuresis. Mannitol can also act as a free-radical scavenger, and together with renal dose dopamine it is a critical factor for minimizing the ischemia–reperfusion injury in steroid-avoidance regimens. After the transplanted kidney starts to produce urine, volume replacement should be immediately started with normal saline.

Infants continue to receive aggressive fluid management by nasogastric or gastrostomy tube feedings of at least 2500 mL/m^2/day for ≥6 mo after transplant if the child is unable to take in sufficient volume. This aggressive fluid management showed 30 mL/min greater GFR in infants who received adult-size kidneys and who were maintained on this higher fluid requirement than infants who were not.

RENAL BIOPSY

Renal biopsy is the gold standard for diagnosis of acute allograft dysfunction. Protocol biopsies may improve graft outcome by detecting early pathology and help monitor drug nephrotoxicity. The largest serial analysis of protocol biopsies at implantation, 3, 6, 12, and 24 mo posttransplantation (the NIH SNSO1 trial, 2004-9) established that the prime risk factor for chronic histologic injury was discrepancy between recipient size and donor mass and time posttransplantation.

REJECTION

Hyperacute rejection occurs immediately when the kidney is transplanted and is caused by preformed antibodies against the donor HLA, ABO, or other antigens. Hyperacute rejection is rare. The only treatment is removal of the graft.

Acute cellular rejection needs to be identified and treated early. Diagnosis of acute rejection in the very young transplant recipient is often not straightforward. Because most small children receive adult-size kidneys, an elevation in serum creatinine may be a late sign of rejection as a result of the large renal reserve compared with the body mass. Thus, significant allograft dysfunction may be present with little or no increase in the serum creatinine level. One of the earliest and most sensitive signs of rejection is the development of hypertension along with low-grade fever. In children, any increase in serum creatinine, especially if it is accompanied by hypertension, should be considered a symptom of acute rejection until proved otherwise. Late diagnosis and treatment of rejection are associated with a higher incidence of resistant rejections and graft loss. Genomic studies in pediatric kidney transplantation have demonstrated molecular heterogeneity for different acute rejection episodes, not distinguishable by pathologic grading, but with a key established role for B cells as antigen-presenting cells for aggressive T-cell–mediated recalcitrant rejection.

Chronic rejection is the leading cause of graft loss and primarily results from immune and nonimmune injuries such as hypertension, diabetes, and hyperlipidemia. Children often have a gradual decline in their renal function and often have fixed proteinuria and hypertension. Despite initial excitement about the potential of MMF and sirolimus mitigating chronic graft injury, this has not translated readily into observable clinical benefits. Humoral immunity, relating the generation of posttransplant donor-specific anti-HLA antibodies, has been implicated in this injury; attention has also shifted to evaluating the impact of non-HLA antibodies after organ transplantation, as direct mediators of organ injury.

GRAFT SURVIVAL

Five yr graft survival is higher in living-donor recipients compared to grafts from deceased donors. The OPTN/SRTR 2007 annual report gives graft survival at 5 yr (2000-2005) for living-donor kidney transplant as 88.0% for recipients 1-5 yr of age, 84.6% for those 6-10 yr of age, and 74.4% for those 11-17 yr of age. Survival in deceased-donor recipients was 74.4% for those 1-5 yr of age, 72.1% for those 6-10 yr of age, and 63% for those 11-17 yr of age.

From the NAPRTCS data, graft survival rates of pediatric kidney transplants have improved since 1987 with 1 yr survival rates during 2003-2006 of 95.7% for living-donor transplants and 95%

for deceased-donor transplants. Children <10 yr of age have the best long-term graft and patient survival rates of all transplant recipients. Graft survival in adolescent patients is the lowest of all the age groups. It is well known that noncompliance is a difficult problem in this age group. Other risk factors for graft failure are race, previous transplant history, history of multiple blood transfusions, HLA-B matches, sex, and transplant year. Approximately 25% of pediatric kidney transplants are preemptive. Graft survival for living and deceased-donor kidneys is significantly better in the preemptive group compared to patients who are on dialysis first. The 3 most common causes of graft failure are chronic rejection of graft (34.9%), acute rejection of graft (13%), and vascular thrombosis (10.1%). Approximately 6.4% of patients had graft failure as a result of recurrence of primary disease (NAPRTCS 2007). The NAPRTCS 2003-2007 data showed the probability of the first rejection at 12 mo being 8.7% for the living donor and 17.7% for the deceased donor.

Graft survival is significantly worse in the presence of ATN in either donor group. ATN is defined by NAPRTCS as requiring the use of dialysis within the first transplant week. NAPRTCS 2008 data report a 5.1% delay in graft function in living-donor renal transplants compared to the ATN rate of 16.4% in children who received deceased-donor transplants.

COMPLICATIONS WITH IMMUNOSUPPRESSION INFECTIONS

Since the mid-1990s, the incidence of acute rejection has decreased but the incidence of infections after transplantation has been increasing.

Pneumonia and urinary tract infection are the most common post-transplant bacterial infections. Urinary tract infections can progress rapidly to urosepsis and may be confused with episodes of acute rejection. Trimethoprim-sulfamethoxazole is used for urinary tract infection antibiotic prophylaxis as well as *Pneumocystis carinii* pneumonia prophylaxis for at least the first 6 mo after transplant. Opportunistic infections associated with unusual organisms usually do not occur until after the first month after transplantation.

The **herpesviruses** (cytomegalovirus, herpesvirus, varicella-zoster virus, and EBV) pose a special problem in view of their common occurrence in children. Many young children have not yet been exposed to these viruses, and because they lack protective immunity, their predisposition to serious primary infection is high. The incidence of cytomegalovirus seropositivity is approximately 30% in children >5 yr of age and rises to approximately 60% in teenagers. Thus, the younger child is at a greater potential risk for serious infection when a cytomegalovirus-positive donor kidney is transplanted. About half the children are seronegative for EBV, and infection occurs in approximately 75% of these patients. Most EBV infections are clinically silent. PTLD in children may be related to EBV infection in the presence of vigorous immunosuppression. The incidence of these infections is higher in children who receive antibody induction therapy and after treatment of acute rejection. It has also been shown in children that subclinical replication of these viruses is much higher in regimens with maintenance steroids, versus protocols with complete steroid avoidance, and that even subclinical viral replication can have a detrimental effect on the incidence of acute rejection and graft function. Antiviral prophylaxis with ganciclovir and valganciclovir for 3-12 mo after transplantation, especially in the higher-risk groups (recipient-negative, donor-positive), have been effective in reducing the incidence of clinical cytomegalovirus disease. Serial surveillance for these viruses by quantitative polymerase chain reaction for viral load in the peripheral blood has also allowed educated minimization of immunosuppression with resultant reduction in viral burden.

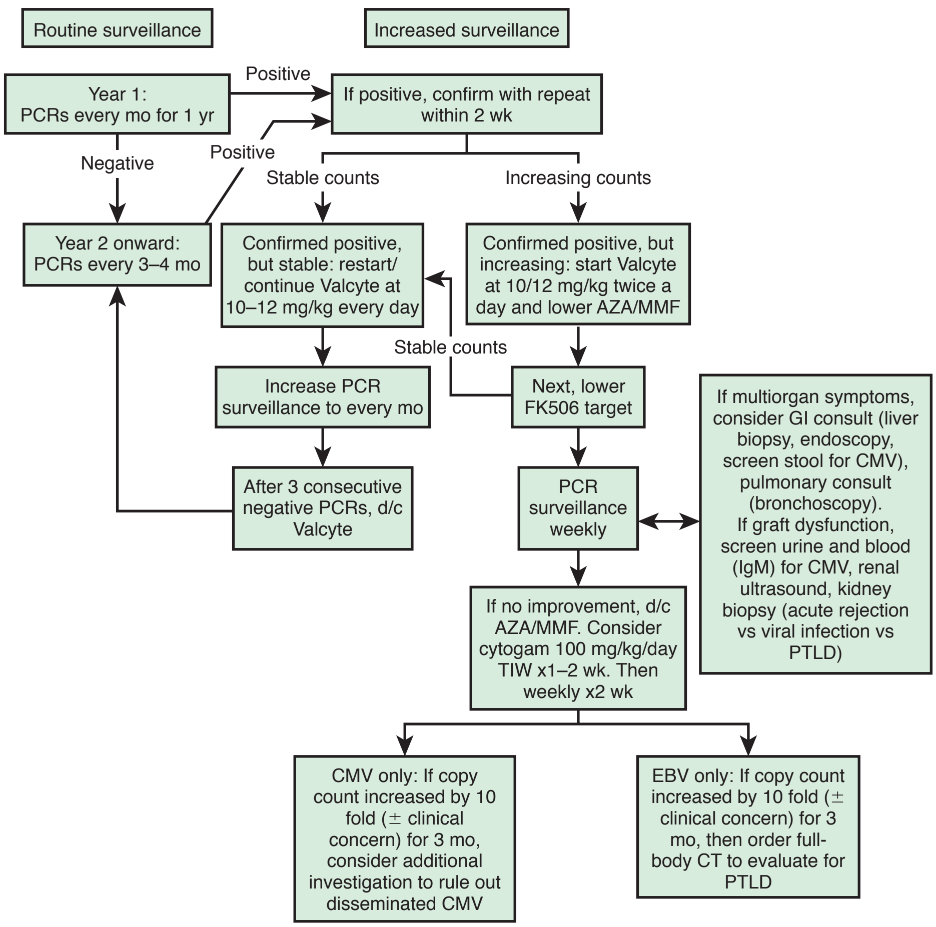

Figure 536-1 Surveillance for cytomegalovirus and Epstein-Barr virus infections after pediatric kidney transplantation.

Polyomavirus nephropathy is an important cause of allograft dysfunction; almost 30% of children have BK viruria, although allograft dysfunction is observed in lower numbers (~5%). The increased incidence of polyomavirus nephropathy is thought to be the result of more-potent immunosuppressive regimens. A renal biopsy, with identification of polyoma by immunoperoxidase staining, may be required to make the diagnosis with certainty. Reducing immunosuppression is the main form of therapy, and cidofovir and leflunomide are used as adjunctive therapies.

It is important to monitor for **PTLD** with routine examinations for lymphadenopathy, hepatosplenomegaly, and EBV screen. Figure 536-1 provides a schematic plan to monitor for EBV, cytomegalovirus, and PTLD.

Hypertension, hyperlipidemia, and posttransplant diabetes mellitus are other potential complications of immunosuppressant medications that need to be monitored for and treated when necessary.

Nonadherence with immunosuppressive medications is one of the most important and most elusive problems facing the medical team. At least half of the pediatric deceased-donor transplant recipients demonstrated significant medication nonadherence in the posttransplantation period by using as an assessment direct reporting to the medical team. This figure exceeded 60% in adolescents. Because direct reporting of nonadherence can significantly underestimate its true incidence, this analysis points out the potential magnitude of the problem. Nonadherence appears to be the principal cause of graft loss in 10-15% of all pediatric kidney transplant recipients; for patients with retransplants, this figure might exceed 25%. Risk factors that suggest an increased propensity toward medication nonadherence include female sex, adolescent age, family instability, insufficient emotional support, lower social economic class, and maladaptive behavior.

Although **growth** improves after transplantation, chronic steroid use does not allow a child to reach full potential height. The precise mechanism by which steroids impair skeletal growth is unknown. Steroids could reduce the release of growth hormone, reduce insulin growth factor activity, impair growth cartilage directly, decrease calcium absorption, or increase renal phosphate wasting. The use of recombinant human growth hormone in pediatric renal transplant recipients significantly improves growth velocity and standard deviation score (SDS). An allograft GFR of <60 mL/min/1.73 m^2 is associated with poor growth and low insulin growth factor levels; optimal growth occurs with a GFR >90 mL/min/1.73 m^2. Graft function is the most important factor after a high corticosteroid dosage in the genesis of posttransplantation growth failure. Steroid minimization and withdrawal protocols have demonstrated growth benefits, and the steroid-avoidance data in children show significant catch-up growth at 5 yr after transplantation. These factors have even greater weight than for age-matched, and gender-matched peers. It is thus likely that with a well-functioning kidney and no maintenance steroids, children might now be able to realize their full height potential.

LONG-TERM OUTCOME

With advances in transplant care and treatment modalities and with diligent attention to the pediatric patient's psychosocial, educational, vocational, and developmental rehabilitation, the social and emotional functioning of the child and the child's family appears to return to preillness levels within 1 yr of successful transplantation. Renal transplantation leads to improvement in linear growth in children. School function tests improve after renal transplantation. Most patients can reenter school and social activities after a short recovery time of 4-6 wk after surgery. A 3 yr follow-up shows that nearly 90% of children are in their appropriate school or job placement positions. Surveys of 10 year survivors of pediatric kidney transplants report that most patients consider their health to be good, and they engage in appropriate social, educational, and sexual activities while experiencing a very good to excellent quality of life.

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Urologic Disorders in Infants and Children

PART XXIV

Chapter 537

Congenital Anomalies and Dysgenesis of the Kidneys

Jack S. Elder

EMBRYONIC DEVELOPMENT

The kidney is derived from interaction between the ureteral bud and the metanephric blastema. During the 5th wk of gestation, the ureteral bud arises from the mesonephric (wolffian) duct and penetrates the metanephric blastema, which is an area of undifferentiated mesenchyme on the nephrogenic ridge. The ureteral bud undergoes a series of approximately 15 generations of divisions and by the 20th wk of gestation forms the entire collecting system: the ureter, renal pelvis, calyces, papillary ducts, and collecting tubules. Signals from the mesenchymal cells induce ureteric bud formation from the wolffian duct as well as ureteric bud branching. Reciprocal signals from the ureteric bud and, later, from its branching tips induce mesenchymal cells to condense, proliferate, and convert into epithelial cells. Under the inductive influence of the ureteral bud, nephron differentiation begins during the 7th wk of gestation. By the 20th wk of gestation, when the collecting system is developed, approximately 30% of the nephrons are present. Nephrogenesis continues at a nearly exponential rate and is complete by the 36th wk of gestation. During nephrogenesis, the kidneys ascend to a lumbar site just below the adrenal glands. At least 16 signaling agents have been identified that regulate renal development. Defects in any of the signaling activities could cause a kidney not to form **(renal agenesis),** or to differentiate abnormally **(renal dysgenesis).** Dysgenesis of the kidney includes **aplasia**, **dysplasia**, **hypoplasia,** and certain forms of **renal cystic disease**.

The fetal kidneys play a minor role in the maintenance of fetal salt and water homeostasis. The rate of urine production increases throughout gestation; at term, volumes have been reported to be 50 mL/hr. The glomerular filtration rate is 25 mL/min/1.73 m^2 at term and triples by 3 mo postterm. The increase in glomerular filtration rate is caused by a reduction in intrarenal vascular resistance and redistribution of intrarenal blood flow to the cortex, where more nephrons are located.

RENAL AGENESIS

Renal agenesis, or absent kidney development, can occur secondary to a defect of the wolffian duct, ureteric bud, or metanephric blastema. Unilateral renal agenesis has an incidence of 1 in 450-1,000 births. Unilateral renal agenesis often is discovered during the course of an evaluation for other congenital anomalies (VACTERL [vertebral defects, imperforate anus, congenital heart disease, tracheoesophageal fistula, renal and limb defects] syndrome; e.g., see Chapter 344). Its incidence is increased in newborns with a single umbilical artery. In true agenesis, the ureter and the ipsilateral bladder hemitrigone are absent. The contralateral kidney undergoes compensatory hypertrophy, to some degree prenatally but primarily after birth. Approximately 15% of these children have contralateral vesicoureteral reflux, and most males have an ipsilateral absent vas deferens because the wolffian duct is absent. Because the wolffian and müllerian ducts are contiguous, müllerian abnormalities in girls also are common. The **Mayer-Rokitansky-Küster-Hauser** syndrome (1 in 4,000-1 in 10,000 female births) is a group of associated findings that may include vaginal aplasia, uterine maldevelopment, and normal ovaries. Two types are described—type I and type II. In type II, renal anomalies, for example, unilateral renal agenesis or a horseshoe kidney, are common, and skeletal anomalies are present in 10% (see Chapter 554).

Renal agenesis is distinguished from aplasia, in which a nubbin of nonfunctioning tissue is seen capping a normal or abnormal ureter. This distinction may be difficult but usually is clinically insignificant. Unilateral renal agenesis is diagnosed in some patients based on the finding of an absent kidney on ultrasonography or renal scintigraphy (renal scan). Some of these patients were born with a hypoplastic kidney or a multicystic dysplastic kidney that underwent complete cyst regression. Although the specific diagnosis is not critical, if the finding of an absent kidney is based on an ultrasonogram, a functional imaging study such as an MR urogram or renal scan should be performed because some of these patients have an ectopic kidney in the pelvis. If there is a normal contralateral kidney, long-term renal function usually remains normal.

Bilateral renal agenesis is incompatible with extrauterine life and produces the **Potter syndrome.** Death occurs shortly after birth from pulmonary hypoplasia. The newborn has a characteristic facial appearance, termed *Potter facies* (Fig. 537-1). The eyes are widely separated with epicanthic folds, the ears are low set, the nose is broad and compressed flat, the chin is receding, and there are limb anomalies. Bilateral renal agenesis should be suspected when maternal ultrasonography demonstrates **oligohydramnios,** nonvisualization of the bladder, and absent kidneys. The incidence of this disorder is 1 in 3,000 births, with a male predominance, and represents 20% of newborns with the Potter phenotype. Other common causes of neonatal renal failure associated with the Potter phenotype include cystic renal dysplasia and obstructive uropathy. Less-common causes are autosomal recessive polycystic kidney disease (infantile), renal hypoplasia, and medullary dysplasia. Neonates with bilateral renal agenesis die of pulmonary insufficiency from pulmonary hypoplasia rather than renal failure (see Chapter 101).

The term **familial renal adysplasia** describes families in which renal agenesis, renal dysplasia, multicystic kidney (dysplasia), or a combination, occurs in a single family. This disorder has an autosomal dominant inheritance pattern with a penetrance of 50-90% and variable expression. Because of this association, some clinicians advise screening 1st-degree relatives of persons who have renal agenesis or dysplasia, but this is not standard practice.

Whether persons with a solitary kidney should avoid contact sports such as football and karate is unresolved. The arguments favoring participation are that there are other solitary organs (spleen, liver, and brain) that do not preclude participation in contact sports, and there have been only a few reports of persons losing a kidney from sports injuries. The arguments against such participation are that the contralateral normal kidney is hypertrophic and not as well protected by the ribs, and a serious renal injury could have serious lifelong consequences. The American Academy of Pediatrics recommends an "individual assessment for contact, collision, and limited-contact sports."

RENAL DYSGENESIS: DYSPLASIA, HYPOPLASIA, AND CYSTIC ANOMALIES

Renal dysgenesis refers to maldevelopment of the kidney that affects its size, shape, or structure. The 3 principal types of dysgenesis are dysplastic, hypoplastic, and cystic. Although dysplasia always is accompanied by a decreased number of nephrons (hypoplasia), the converse is not true: Hypoplasia can occur in isolation. When both conditions are

Figure 537-1 Stillborn infant with renal agenesis exhibiting characteristic Potter facies.

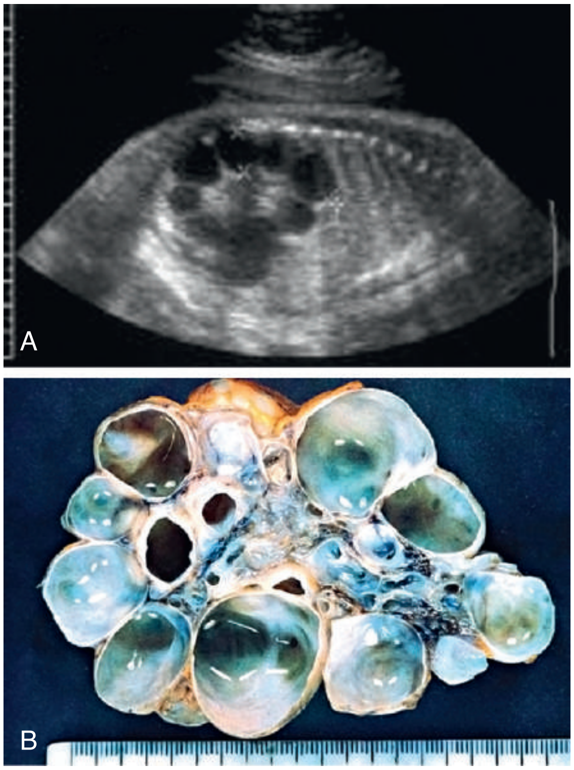

Figure 537-2 **A,** Prenatal sonogram demonstrating multicystic dysplastic kidney. **B,** Surgical specimen.

present, the term **hypodysplasia** is preferred. The term **dysplasia** is technically a histologic diagnosis and refers to focal, diffuse, or segmentally arranged primitive structures, specifically primitive ductal structures, resulting from abnormal metanephric differentiation. Nonrenal elements, such as cartilage, also may be present. The condition can affect all or only part of the kidney. If cysts are present, the condition is termed **cystic dysplasia.** If the entire kidney is dysplastic with a preponderance of cysts, the kidney is referred to as a **multicystic dysplastic kidney** (MCDK) (Fig. 537-2).

The pathogenesis of dysplasia is multifactorial. The "bud" theory proposes that if the ureteral bud arises in an abnormal location, such as an ectopic ureter, there is abnormal penetration and induction of the metanephric blastema, which causes abnormal kidney differentiation, resulting in dysplasia. Renal dysplasia also can occur with severe obstructive uropathy early in gestation, as with the most severe cases of posterior urethral valves or in an MCDK, in which a portion of the ureter is absent or atretic.

MCDK is a congenital condition in which the kidney is replaced by cysts and does not function; it can result from ureteral atresia. Kidney size is highly variable. The incidence is approximately 1 in 2,000. Some clinicians incorrectly use the terms *multicystic kidney* and *polycystic kidney* interchangeably. However, polycystic kidney disease is an inherited disorder that may be autosomal recessive or autosomal dominant and affects both kidneys (see Chapter 521). MCDK usually is unilateral and generally is not inherited. Bilateral MCDKs are incompatible with life.

MCDK is the most common cause of an abdominal mass in the newborn, but the vast majority are nonpalpable at birth. In most cases, it is discovered incidentally during prenatal sonography. In some patients, the cysts are identified prenatally, but the cysts regress in utero and no kidney is identified on imaging at birth. Contralateral hydronephrosis is present in 5-10% of patients. Sonography shows the characteristic appearance of a kidney replaced by multiple cysts of varying sizes that do not communicate, and no identifiable parenchyma is present. In the past, most cases were confirmed with a renal scan, which should demonstrate nonfunction. However, presently the diagnosis of MCDK is usually straightforward based on the renal ultrasound, and a scan generally is unnecessary. In some patients, usually boys, a small nonobstructing ureterocele is present in the bladder (see Chapter 540). Although 15% have contralateral vesicoureteral reflux, it is usually low grade, and obtaining a voiding cystourethrogram also is unnecessary, unless there is significant contralateral hydronephrosis or the child develops an upper urinary tract infection. Management is controversial. Complete cyst regression occurs in nearly half of MCDKs by age 7 yr. The risk of associated hypertension is 0.2-1.2%, and the risk of Wilms tumor arising from an MCDK is approximately 1 in 1,200. Because neoplasms arise from the stromal rather than the cystic component, even if the cysts regress completely, the likelihood that the kidney could develop a neoplasm is not altered.

Because of the occult nature of these potential problems, many clinicians advise annual follow-up with sonography and blood pressure measurement. The most important aspect of follow-up is being certain that the solitary kidney is functioning normally. If there is an abdominal mass, the cysts enlarge, the stromal core increases in size, or hypertension develops, nephrectomy is recommended. In lieu of follow-up screening, laparoscopic nephrectomy may be performed.

Renal hypoplasia refers to a small nondysplastic kidney that has fewer than the normal number of calyces and nephrons. The term encompasses a group of conditions with an abnormally small kidney and should be distinguished from aplasia, in which the kidney is rudimentary. If the condition is unilateral, the diagnosis usually is made incidentally during evaluation for another urinary tract problem or hypertension. Bilateral hypoplasia usually manifests with signs and symptoms of chronic renal failure and is a leading cause of end-stage renal disease during the 1st decade of life. A history of polyuria and polydipsia is common. Urinalysis results may be normal. In a rare form of bilateral hypoplasia called **oligomeganephronia,** the number of nephrons is markedly reduced and those present are markedly hypertrophied.

The **Ask-Upmark kidney,** also termed **segmental hypoplasia,** refers to small kidneys, usually weighing not more than 35 g, with 1 or more

Figure 537-3 **Crossed renal ectopia. Intravenous urography shows both renal collecting systems to the left of the spine.** Segmentation anomalies of the sacrum, which are subtle in this child, are one of the skeletal anomalies associated with renal ectopia. *(From Slovis T, editor:* Caffey's pediatric diagnostic imaging, *ed 11, vol 2, Philadelphia, 2008, Mosby, Fig. 145-23A, p. 2244.)*

deep grooves on the lateral convexity, underneath which the parenchyma consists of tubules resembling those in the thyroid gland. It is unclear whether the lesion is congenital or acquired. Most patients are 10 yr or older at diagnosis and have severe hypertension. Nephrectomy usually controls the hypertension.

ANOMALIES IN SHAPE AND POSITION

During renal development the kidneys normally ascend from the pelvis into their normal position behind the ribs. The normal process of ascent and rotation of the kidney may be incomplete, resulting in renal ectopia or nonrotation. The ectopic kidney may be in a pelvic, iliac, thoracic, or contralateral position. If the ectopia is bilateral, in 90% of persons the 2 kidneys fuse. The incidence of renal ectopia is approximately 1 in 900 (Fig. 537-3).

Renal fusion anomalies are more common. The lower poles of the kidneys can fuse in the midline, resulting in a horseshoe kidney (Fig. 537-4); the fused portion is termed the *isthmus* and may be thick functioning parenchyma or a thin fibrous strand. Horseshoe kidneys occur in 1 in 400-500 births but are seen in 7% of patients with Turner syndrome. Horseshoe kidney is one of the many renal anomalies that occur in 30% of patients with Turner syndrome (see Chapter 586). Wilms tumors are 4 times more common in children with horseshoe kidneys than in the general population. Stone disease and hydronephrosis secondary to ureteropelvic junction obstruction are other potential late complications. The incidence of MCDK affecting 1 of the 2 sides of a horseshoe kidney also appears to be increased. With crossed fused ectopia, 1 kidney crosses over to the other side and the parenchyma of the 2 kidneys is fused. Renal function usually is normal. In the most common finding, the left kidney may cross over and fuse with the lower pole of the right kidney. The insertion of the ureter to the bladder does not change, and the adrenal glands remain in their normal positions. The clinical significance of this anomaly is that if renal surgery is necessary, the blood supply is variable and can make partial nephrectomy more difficult.

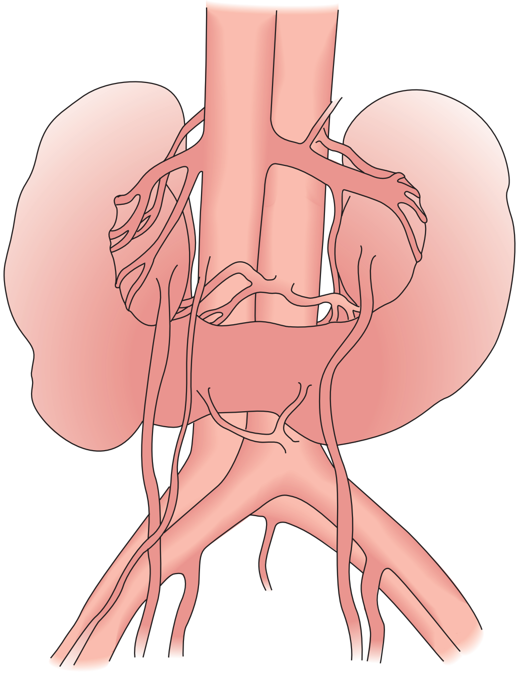

Figure 537-4 Horseshoe kidney.

ASSOCIATED PHYSICAL FINDINGS

Upper urinary tract anomalies are more common in children with certain physical findings. The incidence of renal anomalies is increased if there is a single umbilical artery and an abnormality of another organ system (congenital heart disease). External ear anomalies (particularly if the child has multiple congenital anomalies), imperforate anus, and scoliosis are associated with renal anomalies. Infants with these physical findings should undergo a renal sonogram.

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Chapter 538

Urinary Tract Infections

Jack S. Elder

PREVALENCE AND ETIOLOGY

Urinary tract infections (UTIs) occur in 1% of boys and 1-3% of girls. The prevalence of UTIs varies with age. During the 1st yr of life, the male : female ratio is 2.8-5.4 : 1. Beyond 1-2 yr, there is a female preponderance, with a male : female ratio of 1 : 10. In boys, most UTIs occur during the 1st yr of life; UTIs are much more common in uncircumcised boys, especially in the 1st yr of life. In girls, the first UTI usually occurs by the age of 5 yr, with peaks during infancy and toilet training.

UTIs are caused primarily by colonic bacteria. In girls, 75-90% of all infections are caused by *Escherichia coli* (see Chapter 200), followed by *Klebsiella* spp. and *Proteus* spp. (see Chapter 109). Although *E. coli* is also the most common organism in males, some series report that in boys older than 1 yr of age, *Proteus* is as common a cause as *E. coli;* others report a preponderance of Gram-positive organisms in boys. *Staphylococcus saprophyticus* and enterococcus are pathogens in both

sexes. Adenovirus and other viral infections also can occur, especially as a cause of cystitis with gross hematuria.

UTIs have been considered a risk factor for the development of renal insufficiency or end-stage renal disease in children, although some have questioned the importance of UTI as an isolated risk factor, because only 2% of children with renal insufficiency report a history of UTI. This paradox may be secondary to better recognition of the risks of UTI and prompt diagnosis and therapy. Furthermore, many children receive antibiotics for fever without a specific diagnosis (e.g., treating a questionable otitis media) resulting in a partially treated UTI.

CLINICAL MANIFESTATIONS AND CLASSIFICATION

The 3 basic forms of UTI are **pyelonephritis**, **cystitis**, and **asymptomatic bacteriuria**. Focal pyelonephritis ("nephronia") and renal abscesses are less common.

Clinical Pyelonephritis

Clinical pyelonephritis is characterized by any or all of the following: abdominal, back, or flank pain; fever; malaise; nausea; vomiting; and, occasionally, diarrhea. *Fever may be the only manifestation*. Newborns can show nonspecific symptoms such as poor feeding, irritability, jaundice, and weight loss. Pyelonephritis is the most common serious bacterial infection in infants younger than 24 mo of age who have fever without an obvious focus (see Chapter 177). These symptoms are an indication that there is bacterial involvement of the upper urinary tract. Involvement of the renal parenchyma is termed *acute pyelonephritis,* whereas if there is no parenchymal involvement, the condition may be termed *pyelitis.* Acute pyelonephritis can result in renal injury, termed *pyelonephritic scarring.*

Acute lobar nephronia (acute lobar nephritis) is a renal mass caused by acute focal infection without liquefaction. It may be an early stage in the development of a renal abscess. Manifestations are identical to pyelonephritis; renal imaging demonstrates the abnormality (Fig. 538-1). *Renal abscess* can occur following a pyelonephritic infection caused by the usual uropathogens or may be secondary to hematogenous infection *(Staphylococcus aureus). Perinephric abscess* (Fig. 538-2) can occur secondary to contiguous infection in the perirenal area (e.g., vertebral osteomyelitis, psoas abscess) or pyelonephritis that dissects to the renal capsule.

Xanthogranulomatous pyelonephritis is a rare type of renal infection characterized by granulomatous inflammation with giant cells and foamy histiocytes. It can manifest clinically as a renal mass or an acute or chronic infection. Renal calculi, obstruction, and infection with *Proteus* spp. or *E. coli* contribute to the development of this lesion, which usually requires total or partial nephrectomy.

Cystitis

Cystitis indicates that there is bladder involvement; symptoms include dysuria, urgency, frequency, suprapubic pain, incontinence, and malodorous urine. Cystitis does not cause fever and does not result in renal injury. Malodorous urine is not specific for a UTI.

Acute hemorrhagic cystitis often is caused by *E. coli;* it also has been attributed to adenovirus types 11 and 21. Adenovirus cystitis is more common in boys; it is self-limiting, with hematuria lasting approximately 4 days.

Eosinophilic cystitis is a rare form of cystitis of obscure origin that occasionally is found in children. The usual symptoms are those of

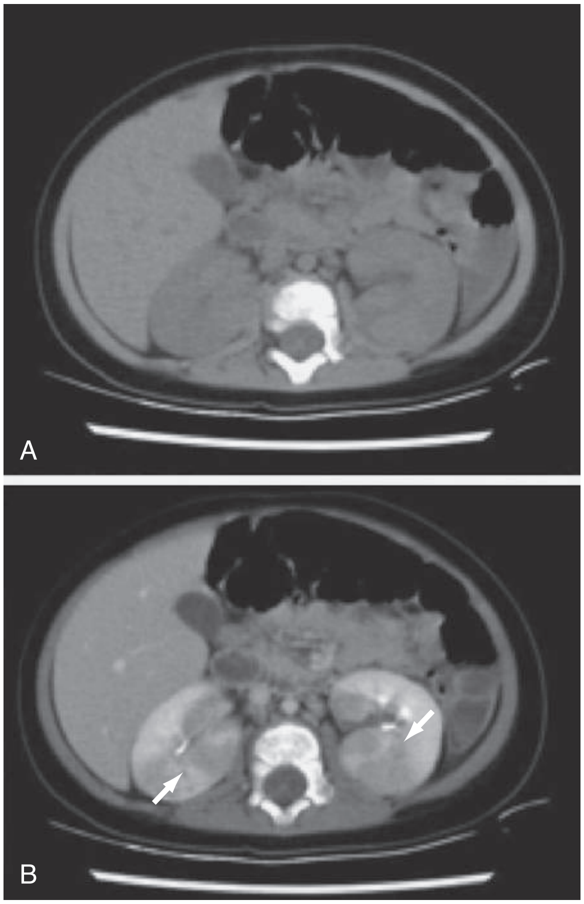

Figure 538-1 Characteristic precontrast **(A)** and contrast-enhanced **(B)** CT scans for an 8 mo old patient who had acute lobar nephronia and presented with severe bilateral nephromegaly but without a focal mass sonographically. No attenuation area is seen in the kidney before enhancement. *(From Cheng CH, Tsau YK, Lin TY: Effective duration of antimicrobial therapy for the treatment of acute lobar nephronia,* Pediatrics *117:e84–e89, 2006.)*

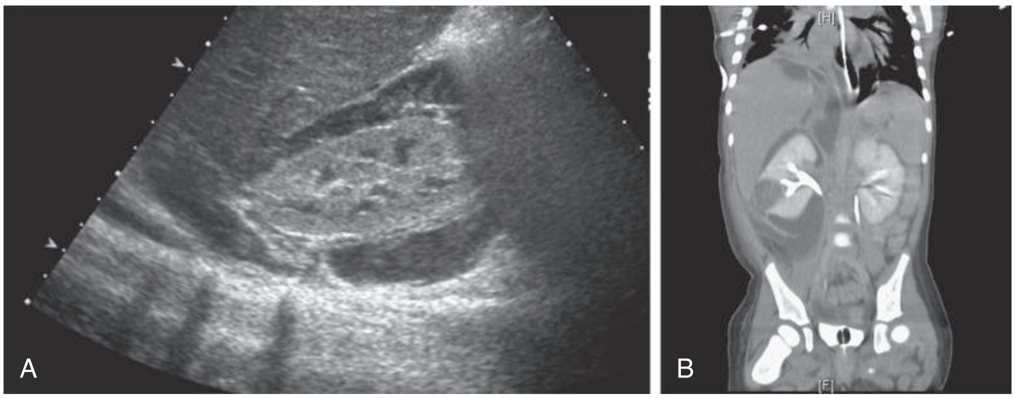

Figure 538-2 **A,** Renal sonogram, 19 mo old girl with perirenal abscess secondary to methicillin-resistant *Staphylococcus aureus.* **B,** CT scan demonstrates extensive perinephric and focal intrarenal abscess. Patient underwent incision and drainage.

cystitis with hematuria. On imaging, typically there are multiple solid bladder masses that consist histologically of inflammatory infiltrates with eosinophils. Ureteral dilation with hydronephrosis also is common. Children with eosinophilic cystitis may have been exposed to an allergen. Bladder biopsy often is necessary to exclude a neoplastic process. Treatment usually includes antihistamines and nonsteroidal antiinflammatory agents.

Interstitial cystitis is characterized by irritative voiding symptoms such as urgency, frequency, and dysuria, and bladder and pelvic pain relieved by voiding with a negative urine culture. The disorder is most likely to affect adolescent girls and is idiopathic. Diagnosis is made by cystoscopic observation of mucosal ulcers with bladder distention. Treatments have included bladder hydrodistention and laser ablation of ulcerated areas, but no treatment provides sustained relief.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria refers to a condition in which there is a positive urine culture without any manifestations of infection. It is most common in girls. The incidence is <1% in preschool and school-age girls and is rare in boys. This condition is benign and does not cause renal injury, except in pregnant women, in whom asymptomatic bacteriuria, if left untreated, can result in a symptomatic UTI. Some girls are mistakenly identified as having asymptomatic bacteriuria, whereas they actually are experiencing day or night incontinence or perineal discomfort secondary to UTI; these patients should undergo antibiotic therapy.

PATHOGENESIS AND PATHOLOGY

Nearly all UTIs are ascending infections. The bacteria arise from the fecal flora, colonize the perineum, and enter the bladder via the urethra. In uncircumcised boys, the bacterial pathogens arise from the flora beneath the prepuce. In some cases, the bacteria causing cystitis ascend to the kidney to cause pyelonephritis. Rarely, renal infection occurs by hematogenous spread, as in endocarditis or in some neonates.

If bacteria ascend from the bladder to the kidney, acute pyelonephritis can occur. Normally the simple and compound papillae in the kidney have an antireflux mechanism that prevents urine in the renal pelvis from entering the collecting tubules. However, some compound papillae, typically in the upper and lower poles of the kidney, allow intrarenal reflux. Infected urine then stimulates an immunologic and inflammatory response. The result can cause renal injury and scarring (Figs. 538-3 and 538-4). Children of any age with a febrile UTI can have acute pyelonephritis and subsequent renal scarring, but the risk is highest in those younger than 2 yr of age.

Table 538-1 lists the host risk factors for UTI. Vesicoureteral reflux is discussed in Chapter 539. If there is grade III, IV, or V vesicoureteral reflux and a febrile UTI, 90% have evidence of acute pyelonephritis on renal scintigraphy or other imaging studies. In girls, UTIs often occur at the onset of toilet training because of bladder/bowel dysfunction that occurs at that age. The child is trying to retain urine to stay dry, yet the bladder may have uninhibited contractions forcing urine out. The result may be high-pressure, turbulent urine flow or incomplete bladder emptying, both of which increase the likelihood of bacteriuria. Bladder/bowel dysfunction can occur in the toilet-trained child who voids infrequently. Similar problems can arise in school-age children who refuse to use the school bathroom. Obstructive uropathy resulting in hydronephrosis increases the risk of UTI because of urinary stasis. Urethral catheterization for urine output monitoring or during a voiding cystourethrogram or nonsterile catheterization can infect the bladder with a pathogen. Constipation with fecal impaction can increase the risk of UTI because it can cause bladder dysfunction.

The pathogenesis of UTI is based in part on the presence of bacterial pili or fimbriae on the bacterial surface. There are 2 types of fimbriae, type I and type II. Type I fimbriae are found on most strains of *E. coli.* Because attachment to target cells can be blocked by D-mannose, these fimbriae are referred to as *mannose sensitive.* They have no role in pyelonephritis. The attachment of type II fimbriae is not inhibited by mannose, and these are known as *mannose resistant.* These fimbriae

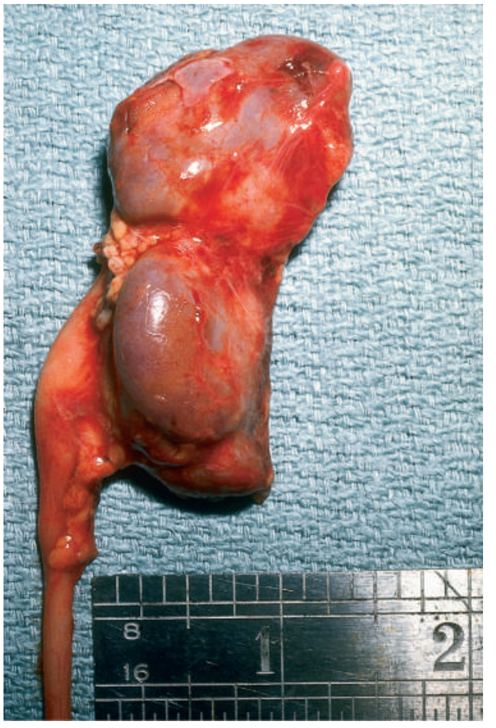

Figure 538-3 Scarred kidney from recurrent pyelonephritis.

Figure 538-4 CT scan showing an area of parenchymal thinning corresponding to an underlying calyx, characteristic of pyelonephritic scarring or reflux nephropathy.

Table 538-1 Risk Factors for Urinary Tract Infection

Female gender	Tight clothing (underwear)
Uncircumcised male	Pinworm infestation
Vesicoureteral reflux*	Constipation
Toilet training	Bacteria with P fimbriae
Voiding dysfunction	Anatomic abnormality (labial adhesion)
Obstructive uropathy	Neuropathic bladder
Urethral instrumentation	Sexual activity
Wiping from back to front in girls	Pregnancy
Bubble bath?	

*Risk increased for clinical pyelonephritis, not cystitis.

are expressed by only certain strains of *E. coli*. The receptor for type II fimbriae is a glycosphingolipid that is present on both the uroepithelial cell membrane and red blood cells. The Gal 1-4 Gal oligosaccharide fraction is the specific receptor. Because these fimbriae can agglutinate by P blood group erythrocytes, they are known as P fimbriae. Bacteria with P fimbriae are more likely to cause pyelonephritis. Between 76% and 94% of pyelonephritogenic strains of *E. coli* have P fimbriae, compared with 19-23% of cystitis strains.

Other host factors for UTI include anatomic abnormalities precluding normal micturition, such as a labial adhesion. This lesion acts as a barrier and causes vaginal voiding. A neuropathic bladder can predispose to UTIs if there is incomplete bladder emptying and/or detrusor–sphincter dyssynergia. Sexual activity is associated with UTIs in girls, in part because of incomplete bladder emptying. From 4-7% of pregnant women have asymptomatic bacteriuria, which can develop into a symptomatic UTI. The incidence of UTI in infants who are breastfed is lower than in those fed with formula.

DIAGNOSIS

UTI may be suspected based on symptoms or findings on urinalysis, or both; *a urine culture is necessary for confirmation and appropriate therapy*. There are several ways to obtain a urine sample; some are more accurate than others. In toilet-trained children, a midstream urine sample usually is satisfactory; the introitus should be cleaned before obtaining the specimen. In uncircumcised boys, the prepuce must be retracted; if the prepuce is not retractable, a voided sample may be unreliable and contaminated with skin flora. According to the 2011 American Academy of Pediatrics (AAP) Clinical Guideline for children 2-24 mo, in children who are not toilet trained, a catheterized or suprapubic aspirate urine sample should be obtained. Alternatively, the application of an adhesive, sealed, sterile collection bag after disinfection of the skin of the genitals can be useful only if the culture is negative or if a single uropathogen is identified. However, a positive culture can result from skin contamination, particularly in girls and uncircumcised boys. If treatment is planned immediately after obtaining the urine culture, a bagged specimen should not be the method because of a high rate of contamination, often with mixed organisms. A suprapubic aspirate generally is unnecessary.

Nitrites and leukocyte esterase usually are positive in infected urine. Microscopic hematuria is common in acute cystitis, but microhematuria alone does not suggest UTI. White blood cell casts in the urinary sediment suggest renal involvement, but in practice these are rarely seen. If the child is asymptomatic and the urinalysis result is normal, it is unlikely that there is a UTI. However, if the child is symptomatic, a UTI is possible, even if the urinalysis result is negative (Table 538-2).

Pyuria (leukocytes on urine microscopy) suggests infection, but infection can occur in the absence of pyuria; this finding is more confirmatory than diagnostic. Conversely, pyuria can be present without UTI. Figure 538-3 shows the predictive value of leukocyte esterase, nitrites, and leukocytes.

Sterile pyuria (positive leukocytes, negative culture) may occur in partially treated bacterial UTIs, viral infections, renal tuberculosis, renal abscess, UTI in the presence of urinary obstruction, urethritis as a consequence of a sexually transmitted infection (see Chapter 120), inflammation near the ureter or bladder (appendicitis, Crohn disease), or interstitial nephritis (eosinophils). Prompt plating of the urine sample for culture is important, because if the urine sits at room temperature for more than 60 min, overgrowth of a minor contaminant can suggest a UTI when the urine might not be infected. Refrigeration is a reliable method of storing the urine until it can be cultured.

If the culture shows >50,000 colonies of a single pathogen (suprapubic or catheter sample), or if there are 10,000 colonies and the child is symptomatic, the child is considered to have a UTI. In a bag sample, if the urinalysis result is positive, the patient is symptomatic, and there is a single organism cultured with a colony count >100,000, there is a presumed UTI. If any of these criteria are not met, confirmation of infection with a catheterized sample is recommended.

With acute renal infection, leukocytosis, neutrophilia, and elevated serum erythrocyte sedimentation rate, procalcitonin, and C-reactive protein are common. However these are all nonspecific markers of inflammation, and their elevation does not prove that the child has acute pyelonephritis. With a renal abscess, the white blood cell count is markedly elevated to >20,000-25,000/mm^3. An elevated serum procalcitonin level is associated with pyelonephritis and a high risk of renal scarring. Because sepsis is common in pyelonephritis, particularly in infants and in any child with obstructive uropathy, blood cultures should be drawn before starting antibiotics if possible.

According to the 2011 AAP Guidelines for children 2-24 mo, risk factors for girls include white race, age younger than 12 mo, temperature >39°C (102.2°F), fever for longer than 2 days, and absence of another source of infection. Risk factors for boys include nonblack race, temperature >39°C (102.2°F), fever for longer than 24 hr, and absence of another source of infection. Atypical features include failure to respond within 48 hr of appropriate antibiotics, poor urine flow, an abdominal flank or suprapubic mass, non–*E. coli* pathogen, urosepsis, and an elevated creatinine level.

TREATMENT

Acute cystitis should be treated promptly to prevent possible progression to pyelonephritis. If the symptoms are severe, presumptive treatment is started pending results of the culture. If the symptoms are mild or the diagnosis is doubtful, treatment can be delayed until the results of culture are known, and the culture can be repeated if the results are uncertain. If treatment is initiated before the results of a culture and sensitivities are available, a 3- to 5-day course of therapy with trimethoprim-sulfamethoxazole (TMP-SMX) or trimethoprim is effective against many strains of *E. coli*. Nitrofurantoin (5-7 mg/kg/24 hr in 3-4 divided doses) also is effective and has the advantage of being active against *Klebsiella* and *Enterobacter* organisms. Amoxicillin (50 mg/kg/24 hr) also is effective as initial treatment but has a high rate of bacterial resistance.

In acute febrile infections suggesting **clinical pyelonephritis,** a 7-14 day course of broad-spectrum antibiotics capable of reaching significant tissue levels is preferable. Children who are dehydrated, are vomiting, are unable to drink fluids, are 1 mo of age or younger, have complicated infection, or in whom urosepsis is a possibility should be admitted to the hospital for IV rehydration and IV antibiotic therapy. Parenteral treatment with ceftriaxone (50-75 mg/kg/24 hr, not to

Table 538-2 Sensitivity and Specificity of Components of Urinalysis, Alone and in Combination

TEST	SENSITIVITY (RANGE) %	SPECIFICITY (RANGE) %
Leukocyte esterase test	83 (67-94)	78 (64-92)
Nitrite test	53 (15-82)	98 (90-100)
Leukocyte esterase or nitrite test positive	93 (90-100)	72 (58-91)
Microscopy (white blood cells)	73 (32-100)	81 (45-98)
Microscopy (bacteria)	81 (16-99)	83 (11-100)
Leukocyte esterase test, nitrite test, or microscopy positive	99.8 (99-100)	70 (60-92)

From Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management: Clinical practice guideline. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in Febrile infants and children 2 to 24 months. Pediatrics *128:595–610, 2011.*

exceed 2 g) or cefotaxime (100 mg/kg/24 hr), or ampicillin (100 mg/kg/24 hr) with an aminoglycoside such as gentamicin (3-5 mg/kg/24 hr in 1-3 divided doses) is preferable. The potential ototoxicity and nephrotoxicity of aminoglycosides should be considered; serum creatinine should be obtained before initiating treatment, and daily trough gentamicin levels should be obtained during therapy. Treatment with aminoglycosides is particularly effective against *Pseudomonas* spp., and alkalinization of urine with sodium bicarbonate increases its effectiveness in the urinary tract.

Oral third-generation cephalosporins such as cefixime are as effective as parenteral ceftriaxone against a variety of Gram-negative organisms other than *Pseudomonas,* and these medications are considered by some authorities to be the treatment of choice for oral outpatient therapy. Nitrofurantoin should not be used routinely in children with a febrile UTI because it does not achieve significant renal tissue levels. The oral fluoroquinolone ciprofloxacin is an alternative agent for resistant microorganisms, particularly *Pseudomonas,* in patients older than age 17 yr. It also has been used on occasion for short-course therapy in younger children with *Pseudomonas* UTI. Levofloxacin is an alternative quinolone with a good safety profile in children. However, the clinical use of fluoroquinolones in children should be used with caution because of potential cartilage damage. In some children with a febrile UTI, intramuscular injection of a loading dose of ceftriaxone followed by oral therapy with a third-generation cephalosporin is effective. A urine culture 1 wk after the termination of treatment of a UTI ensures that the urine is sterile but is not routinely needed. A urine culture during treatment almost invariably is negative.

Children with a renal or perirenal abscess or with infection in obstructed urinary tracts can require surgical or percutaneous drainage in addition to antibiotic therapy and other supportive measures (see Fig. 538-2). Small abscesses may initially be treated without drainage.

In a child with recurrent UTIs, identification of predisposing factors is beneficial. Many school-age girls have **bladder–bowel dysfunction** (see Chapter 543); treatment of this condition often reduces the likelihood of recurrent UTI. Some children with UTIs void infrequently, and many also have severe constipation (see Chapters 306 and 332). Behavioral modification, with treatment of constipation as described in Chapter 543, often is effective. Antimicrobial prophylaxis using trimethoprim or nitrofurantoin at 30% of the normal therapeutic dose once a day is another approach to this problem but is unnecessary in most children with recurrent UTIs in the absence of severe reflux. Prophylaxis with TMP-SMZ, amoxicillin, or cephalexin can also be effective, but the risk of breakthrough UTI may be higher because bacterial resistance may be induced. Urologic conditions for recurrent UTIs that might benefit from long-term prophylaxis include neuropathic bladder, urinary tract stasis and obstruction, severe vesicoureteral reflux (see Chapter 539), and urinary calculi. There is interest in probiotic therapy, which replaces pathologic urogenital flora, and cranberry juice, which prevents bacterial adhesion and biofilm formation, but these agents have not proved beneficial in preventing UTI in children.

The main consequences of chronic renal damage caused by pyelonephritis are arterial hypertension and end-stage renal insufficiency; when they are found they should be treated appropriately (see Chapters 445 and 535).

IMAGING STUDIES IN CHILDREN WITH A FEBRILE UTI

The goal of imaging studies in children with a UTI is to identify anatomic abnormalities that predispose to infection, determine whether there is active renal involvement, and to assess whether renal function is normal or at risk.

There are 2 *historical* approaches to imaging, the traditional "bottom-up" and the "top-down" approaches.

1. The "bottom-up" method was a renal sonogram plus voiding cystourethrogram; this approach will identify upper and lower urinary tract abnormalities, including vesicoureteral reflux, bladder–bowel dysfunction, and bladder abnormalities, such as a paraureteral diverticulum. It is unlikely to detect renal scarring unless it is significant (renal cortical irregularity, small kidney on renal ultrasound). A dimercaptosuccinic acid (DMSA) scan is necessary to provide the best assessment of renal scarring.
   In some centers, the voiding cystourethrogram (VCUG) is delayed for 2-6 wk to allow inflammation in the bladder to resolve; however, the incidence of reflux is identical, regardless of whether the VCUG is obtained acutely at the time of treatment of the UTI or after 6 wk. Obtaining the VCUG before the child is discharged from the hospital is appropriate and ensures that the evaluation is complete. If available, a radionuclide VCUG rather than a contrast VCUG can be used in girls; this technique causes less radiation exposure to the gonads than does the contrast study. However, the radioisotope VCUG does not provide anatomic definition of the bladder, allow precise grading of reflux, demonstrate a paraureteral diverticulum, or show whether reflux is occurring into a duplicated collecting system or an ectopic ureter. In boys, VCUG definition of the urethra is important to detect posterior urethral valves (see Chapter 504).
2. The "top-down" approach was intended to reduce the number of VCUG examinations. It begins with a DMSA renal scan, to identify areas of acute pyelonephritic involvement, termed **acute pyelonephritis** (Fig. 538-5). The DMSA scan in younger children generally requires sedation. This condition is characterized by fever, malaise, abdominal or flank pain, and occasionally nausea and vomiting, and is a significant risk factor for renal injury and scarring. On DMSA, involved areas of the kidney are photopenic and the kidney is enlarged. Of children with a febrile UTI, approximately 50% have a positive DMSA scan. Of those with a positive scan, approximately 50% develop renal scarring in the areas of acute pyelonephritis, and in the remainder with acutely positive scans, the renal appearance will normalize. In children with dilating grades of reflux (III, IV, V), 80-90% with a febrile UTI have a DMSA scan consistent with acute pyelonephritis. Children with grades I and II reflux and those without reflux can also develop acute pyelonephritis. In longitudinal studies of children with grades I and II reflux and acute pyelonephritis, the reflux usually resolves. If the DMSA scan is normal during a febrile UTI, no scarring will result from that particular infection. CT is another diagnostic tool that can image acute pyelonephritis, but clinical experience with DMSA is much greater, and CT scans have significant radiation. If the DMSA scan is positive, then a VCUG is performed (Fig. 538-6), because 90% of children with dilating reflux have a positive DMSA scan. If reflux is identified, treatment is based on the perceived long-term risk of the reflux to the child (see Chapter 539). One limitation to this approach is that many hospitals caring for children with a febrile UTI might not have facilities for performing a DMSA scan in children. In these cases, a renal sonogram should be performed, after which the clinician decides whether to send the child to a facility with

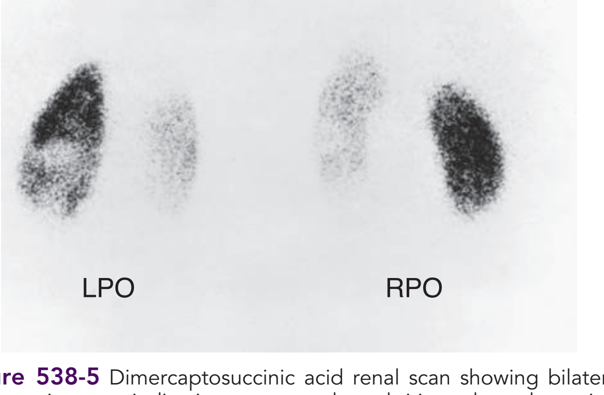

Figure 538-5 Dimercaptosuccinic acid renal scan showing bilateral photopenic areas indicating acute pyelonephritis and renal scarring. *LPO*, left posterior oblique; *RPO*, right posterior oblique.

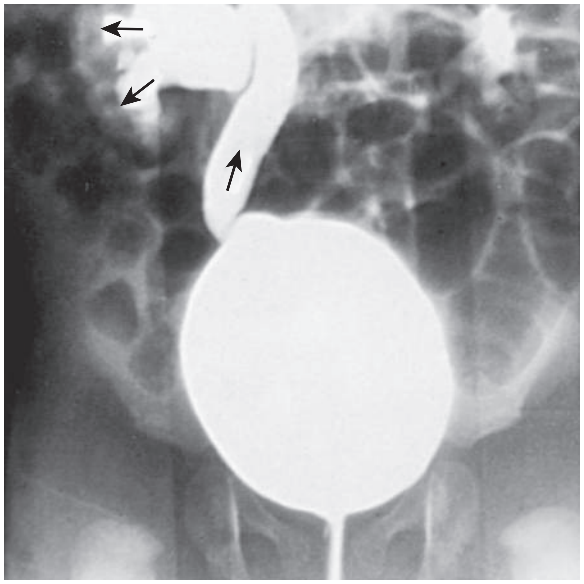

Figure 538-6 **Intrarenal reflux.** Voiding cystourethrogram in an infant boy with a past history of a urinary tract infection. Note the right vesicoureteral reflux with ureteral dilation, with opacification of the renal parenchyma representing intrarenal reflux.

DMSA capability or instead do a VCUG. In addition, if the DMSA scan is positive, then a follow-up scan is indicated 4-6 mo later to determine whether renal scarring occurred.

The AAP recommends that in a typical first-episode of UTI, initial imaging should be ultrasonography of the kidneys, ureters, and bladder. VCUG is indicated if the ultrasound study is abnormal, the patient has atypical features, or after a recurrent febrile UTI (Table 538-3).

In children with a history of cystitis, (dysuria, urgency, frequency, suprapubic pain), imaging is usually unnecessary. Instead, assessment and treatment of bladder and bowel dysfunction is important. If there are numerous lower UTIs, then a renal sonogram is appropriate, but a VCUG rarely adds useful information.

The AAP recommendation has resulted in a significant decrease in the number of VCUGs ordered. However, the pediatric urologic community has raised numerous concerns regarding the recommendations, and prospective studies will be necessary before determining whether they should be adopted. One consequence is that many primary care physicians have generalized these recommendations, which were intended for children *2-24 mo*, to *all* children.

Similarly, in 2007, the NICE (National Institute for Health and Clinical Excellence, UK) guidelines for diagnosis, management, and imaging after UTI were released (Table 538-4). These recommendations divided children into those younger than 6 mo, 6 mo-3 yr, and older than 3 yr of age. An initial VCUG is recommended only in children younger than age 6 mo. These recommendations are highly controversial

Table 538-3 Guideline Recommendations for Diagnostic Evaluation Following a Febrile Urinary Tract Infection in Infants

GUIDELINE	ULTRASONOGRAPHY	VCUG	LATE DMSA SCAN
National Institute for Health And Care Excellence (NICE)*	(see Table 538-4)		
American Academy of Pediatrics	Yes	If abnormal ultrasonogram	No
Italian Society for Paediatric Nephrology (ISPN)	Yes	If abnormal ultrasonogram or if risk factors are present†	If abnormal ultrasonogram or VUR

*Upper urinary tract dilation on ultrasonography, poor urinary flow, infection with organism other than *E. coli*, or family history of vesicoureteral reflux.
†Abnormal antenatal ultrasonogram of fetal urinary tract, family history of reflux, septicemia, renal failure, age younger than 6 mo in a male infant, likely family noncompliance, incomplete bladder emptying, no clinical response to appropriate antibiotic therapy within 72 hr, or infection with organism other than *E. coli*.
DMSA, dimercaptosuccinic acid; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

Table 538-4 Recommended Imaging Schedule for Children with Urinary Tract Infection

	Type of Infection		
CHILD AGE AND TESTS	RESPONDS WELL TO TREATMENT WITHIN 48 HR	ATYPICAL INFECTION	RECURRENT INFECTION
CHILDREN YOUNGER THAN 6 MO OLD			
Ultrasound scan during acute infection	No	Yes	Yes
Ultrasound scan within 6 wk of infection	Yes	No	No
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
Micturating cystograms	Consider if ultrasound scan abnormal	Yes	Yes
CHILDREN 6 MO-3 YR OLD			
Ultrasound scan during acute infection	No	Yes	No
Ultrasound scan within 6 wk of infection	No	No	Yes
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
Micturating cystograms	No	Not routine, consider if dilation on ultrasound, poor urine flow, non–*E. coli* infection, or family history of vesicoureteric reflux	
CHILDREN OLDER THAN AGE 3 YR			
Ultrasound scan during acute infection	No	Yes	No
Ultrasound scan within 6 wk of infection	No	No	Yes
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
Micturating cystograms	No	No	No

DMSA, dimercaptosuccinic acid.
Adapted from National Institute for Health and Clinical Excellence. Urinary tract infection in children: diagnosis, treatment, and long-term management. *NICE clinical guidelines, no. 54. London, 2007, RCOG Press, Tables 6-13, 6-14, and 6-15.*

because the methodology was not based on evidence but on expert opinion. In addition, there was no retrospective or prospective assessment of the potential of this approach to identify significant uropathology. There is evidence that a significant number of children with uropathology would not have been identified under these guidelines.

PROPHYLAXIS OF RECURRENT URINARY TRACT INFECTION

See Chapter 539.

In children with a first episode of pyelonephritis in an otherwise anatomically normal urinary tract and no evidence of reflux, no antimicrobial prophylaxis is required in an attempt to prevent a recurrence or renal scarring.

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Chapter 539

Vesicoureteral Reflux

Jack S. Elder

Vesicoureteral reflux (**VUR**) describes the retrograde flow of urine from the bladder to the ureter and kidney. The ureteral attachment to the bladder normally is oblique, between the bladder mucosa and detrusor muscle, creating a flap-valve mechanism that prevents VUR (Fig. 539-1). VUR occurs when the submucosal tunnel between the mucosa and detrusor muscle is short or absent. Affecting 1-2% of children, VUR usually is congenital and often is familial. VUR is present in approximately 30% of females who had a urinary tract infection and in 5-15% of infants with antenatal hydronephrosis.

VUR predisposes to kidney infection (pyelonephritis) by facilitating the transport of bacteria from the bladder to the upper urinary tract (see Chapter 538). The inflammatory reaction caused by pyelonephritis can result in renal injury or scarring, also termed **reflux-related renal injury** or **reflux nephropathy.** In children with a febrile ***urinary tract infection*** **(UTI)**, those with VUR are 3 times more likely to develop renal injury compared to those without VUR. Extensive renal scarring impairs renal function and can result in renin-mediated hypertension (see Chapter 445), renal insufficiency or end-stage renal disease (see Chapter 535), impaired somatic growth, and morbidity during pregnancy. Scarring associated with reflux may be present at birth or develop in the absence of infection.

In the past, reflux nephropathy accounted for as much as 15-20% of end-stage renal disease in children and young adults. With greater attention to the management of UTIs and a better understanding of VUR, end-stage renal disease secondary to reflux nephropathy is uncommon. Reflux nephropathy remains a common cause of hypertension in children. VUR in the absence of infection or elevated bladder pressure (e.g., neuropathic bladder, posterior urethral valves) rarely causes renal injury.

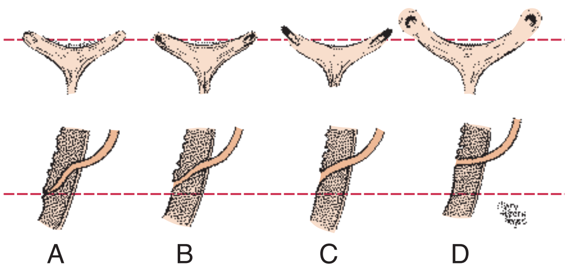

Figure 539-1 **Normal and abnormal configuration of the ureteral orifices.** Shown from *left* to *right*, progressive lateral displacement of the ureteral orifices and shortening of the intramural tunnels. *Top*, Endoscopic appearance. *Bottom*, Sagittal view through the intramural ureter.

CLASSIFICATION

VUR severity is graded using the International Reflux Study Classification of I-V and is based on the appearance of the urinary tract on a contrast ***voiding cystourethrogram*** **(VCUG)** (Figs. 539-2 and 539-3). The higher the VUR grade the greater the likelihood of renal injury. VUR severity is an indirect indication of the degree of abnormality of the ureterovesical junction.

VUR may be primary or secondary (Table 539-1). Bladder–bowel dysfunction can worsen preexisting VUR if there is a marginally competent ureterovesical junction. In the most severe cases, there is such massive VUR into the upper tracts that the bladder becomes

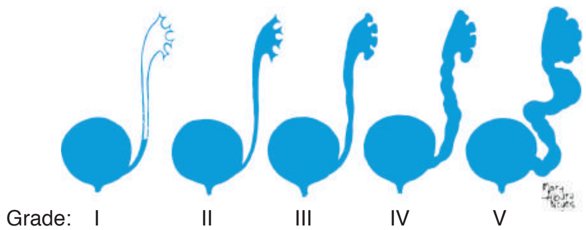

Figure 539-2 **Grading of vesicoureteral reflux.** Grade I: VUR into a nondilated ureter. Grade II: VUR into the upper collecting system without dilation. Grade III: VUR into dilated ureter and/or blunting of calyceal fornices. Grade IV: VUR into a grossly dilated ureter. Grade V: massive VUR, with significant ureteral dilation and tortuosity and loss of the papillary impression.

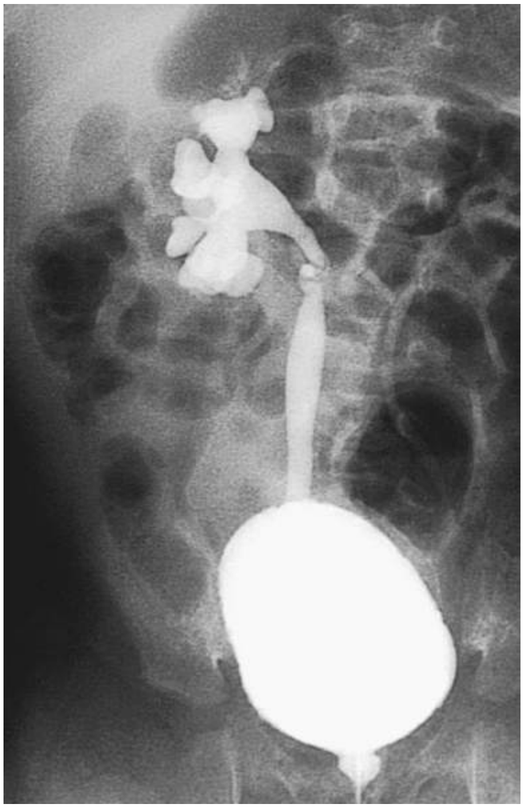

Figure 539-3 **Voiding cystourethrogram showing grade IV right vesicoureteral reflux.**

overdistended. This condition, the **megacystis-megaureter syndrome,** occurs primarily in boys and may be unilateral or bilateral (Fig. 539-4). Reimplantation of the ureters into the bladder to correct VUR corrects the condition.

Approximately 1 in 125 children have a **duplication** of the upper urinary tract, in which 2 ureters rather than 1 drain the kidney. Duplication may be partial or complete. In partial duplication, the ureters join above the bladder and there is 1 ureteral orifice. In complete duplication, the attachment of the lower pole ureter to the bladder is superior and lateral to the upper pole ureter. The valve-like mechanism for the lower pole ureter often is marginal, and VUR into the lower ureter occurs in as many as 50% of cases. VUR occurs into both the lower and upper systems in some persons (Fig. 539-5). With a duplication anomaly, some patients have an ectopic ureter, in which the upper pole ureter drains outside the bladder (see Chapters 540 and 543 and Figs. 543-6 and 543-7). If the ectopic ureter drains into the bladder neck, typically it is obstructed and refluxes. Duplication anomalies also are common in children with a ureterocele, which is a cystic swelling of the intramural portion of the distal ureter. These patients often have VUR into the associated lower pole ureter or the contralateral ureter. In addition, generally VUR is present when the ureter enters a bladder diverticulum (Fig. 539-6).

VUR is present at birth in 25% of children with **neuropathic bladder,** as occurs in myelomeningocele (see Chapter 591.4), sacral agenesis, and many cases of high imperforate anus. VUR is seen in 50% of boys with posterior urethral valves. VUR with increased intravesical pressure (as in detrusor–sphincter dyssynergia or bladder outlet obstruction) can result in renal injury because of increased intravesical pressure transmitted to the upper urinary tract, even in the absence of infection.

Primary VUR occurs in association with several congenital urinary tract abnormalities. Of children with a multicystic dysplastic kidney or renal agenesis (see Chapter 537), 15% have VUR into the contralateral kidney, and 10-15% of children with a ureteropelvic junction obstruction have VUR into either the hydronephrotic kidney or the contralateral kidney.

Table 539-1 Classification of Vesicoureteral Reflux

TYPE	CAUSE
Primary	Congenital incompetence of the valvular mechanism of the vesicoureteral junction
Primary associated with other malformations of the ureterovesical junction	Ureteral duplication Ureterocele with duplication Ureteral ectopia Paraureteral diverticula
Secondary to increased intravesical pressure	Neuropathic bladder Nonneuropathic bladder dysfunction Bladder outlet obstruction
Secondary to inflammatory processes	Severe bacterial cystitis Foreign bodies Vesical calculi Clinical cystitis
Secondary to surgical procedures involving the ureterovesical junction	Surgery

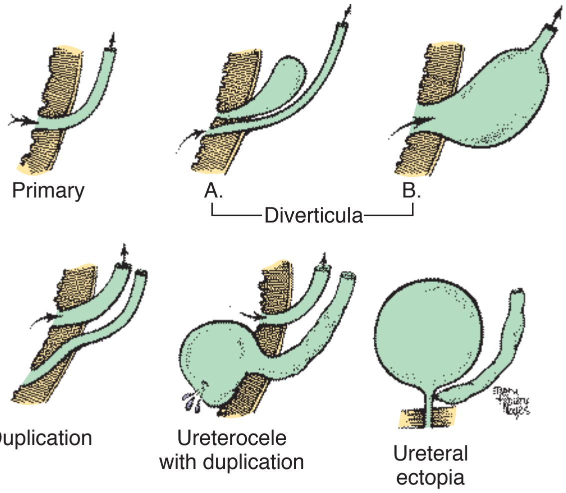

Figure 539-5 Various anatomic defects of the ureterovesical junction associated with vesicoureteral reflux.

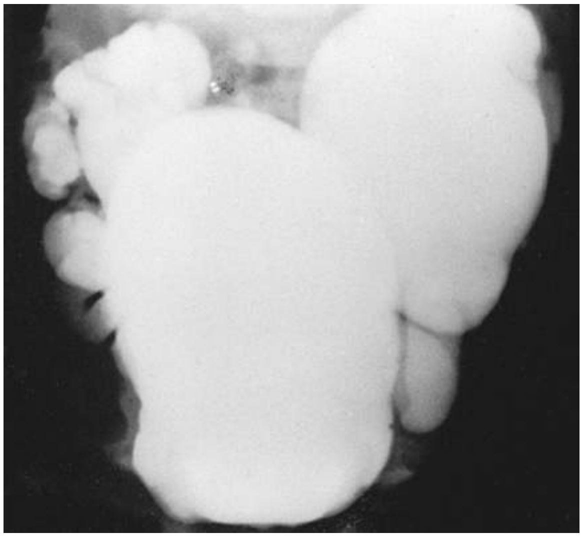

Figure 539-4 Voiding cystourethrogram in newborn boy with megacystis-megaureter syndrome. Note the massive ureteral dilation caused by high-grade vesicoureteral reflux. The bladder is very distended. There was no urethral obstruction or neuropathic dysfunction.

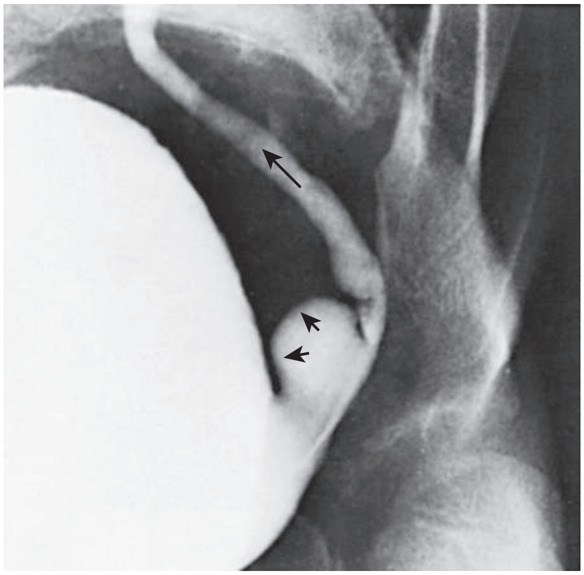

Figure 539-6 VUR and bladder diverticulum. The voiding cystourethrogram demonstrates left vesicoureteral reflux and a paraureteral diverticulum.

VUR (idiopathic) appears to be an autosomal dominant inherited trait with variable penetrance. Approximately 35% of siblings of children with VUR also have VUR, and VUR is found in nearly half of newborn siblings. The likelihood of a sibling having VUR is independent of the grade of VUR or sex of the index child. Approximately 12% of asymptomatic siblings with VUR have evidence of renal scarring. In addition, 50% of children born to women with a history of VUR also have VUR. In 2010 the American Urological Association Vesicoureteral Reflux Guidelines Panel stated that, in siblings of individuals with VUR, a VCUG or radionuclide cystogram is recommended if there is evidence of renal cortical abnormalities or renal size asymmetry on sonography, or if the sibling has a history of UTI. Otherwise, screening is optional. VUR may be suggested on a prenatal ultrasound, which demonstrates dilated renal calyces. Primary VUR is uncommon in African-Americans.

CLINICAL MANIFESTATIONS

VUR usually is discovered during evaluation for a UTI (see Chapter 538). Among these children, 80% are female, and the average age at diagnosis is 2-3 yr. In other children, a VCUG is performed during evaluation of bladder–bowel dysfunction, renal insufficiency, hypertension, or other suspected pathologic process of the urinary tract. Primary VUR also may be discovered during evaluation for antenatal hydronephrosis. In this select population, 80% of affected children are male, and the VUR grade usually is higher than in girls whose VUR is diagnosed following a UTI. The UTI may be symptomatic, an isolated febrile event, or more often both febrile and symptomatic (abdominal pain, dysuria, etc.). Bladder and bowel dysfunction (constipation) may be present in 50% of children with reflux and a UTI.

DIAGNOSIS

Diagnosis of VUR requires catheterization of the bladder, instillation of a solution containing iodinated contrast or a radiopharmaceutical, and radiologic imaging of the lower and upper urinary tract: a contrast VCUG or ***radionuclide cystogram***, respectively. The bladder and upper urinary tracts are imaged during bladder filling and voiding. VUR occurring during bladder filling is termed *low-pressure* VUR; VUR during voiding is termed *high-pressure* VUR. VUR in children with low-pressure VUR is significantly less likely to resolve spontaneously than in children who exhibit only high-pressure VUR. Radiation exposure during a radionuclide cystogram is significantly less than that from a contrast VCUG. However, the contrast VCUG provides more anatomic information, such as demonstration of a duplex collecting system, ectopic ureter, paraureteral (bladder) diverticulum, bladder outlet obstruction in boys, upper urinary tract stasis, and signs of voiding dysfunction, such as a "spinning top" urethra in girls. The VUR grading system is based on the appearance on contrast VCUG, and the grade reported is the maximum grade observed during the study. For follow-up evaluation, some prefer the radionuclide cystogram because of the lower radiation exposure (Fig. 539-7), although it is difficult to determine whether the VUR severity has changed.

Children undergoing cystography may be psychologically traumatized by the catheterization. Careful preparation by caregivers, use of Child Life individuals, or administration of oral or nasal midazolam (for sedation and amnesia) or propofol before the study can result in a less-distressing experience.

Indirect cystography is a technique of detecting VUR without catheterization that involves injecting an intravenous radiopharmaceutical that is excreted by the kidneys, waiting for it to be excreted into the bladder, and imaging the lower urinary tract while the patient voids. This technique detects only 75% of VUR cases. Another technique, which avoids radiation exposure, involves instilling sonographic contrast medium through a urethral catheter. The kidneys are imaged sonographically to determine whether any of the material refluxes. This technique is investigational.

After VUR is diagnosed, assessment of the upper urinary tract is important. The goal of upper tract imaging is to assess whether renal scarring and associated urinary tract anomalies are present. Renal imaging typically is performed with a renal sonogram or renal scintigraphy (Fig. 539-8; see Chapter 538).

The child should be evaluated for bladder–bowel dysfunction, including urgency, frequency, diurnal incontinence, infrequent voiding,

Figure 539-7 Radionuclide cystogram shows bilateral VUR.

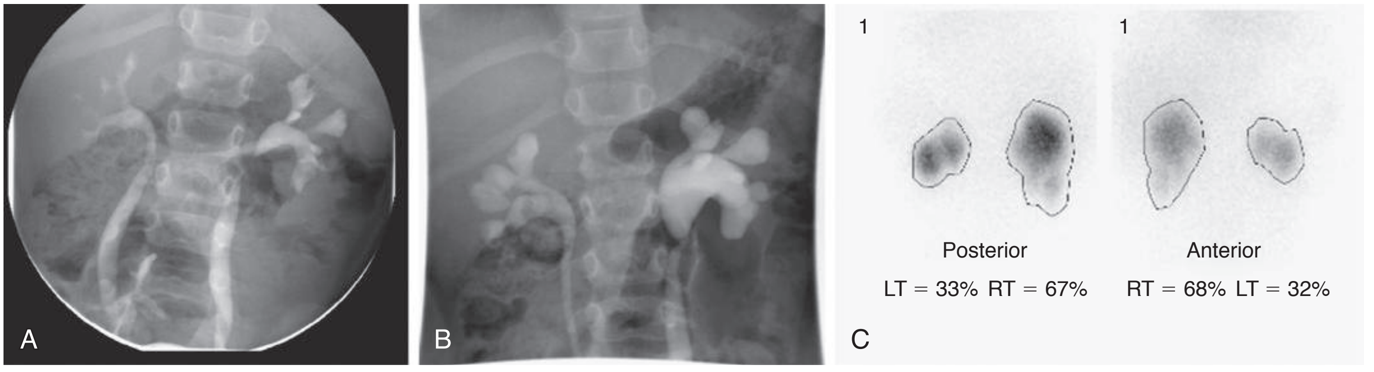

Figure 539-8 **A,** Voiding cystourethrogram (VCUG) in a 3 yr old girl with 2 febrile urinary tract infections shows bilateral grade III VUR. **B,** At 5 yr, repeat VCUG shows worsening VUR and calyceal clubbing, indicating renal scarring. **C,** At 11 yr, she has developed renin-mediated hypertension. Dimercaptosuccinic acid (DMSA) renal scan shows significant VUR-related renal scarring.

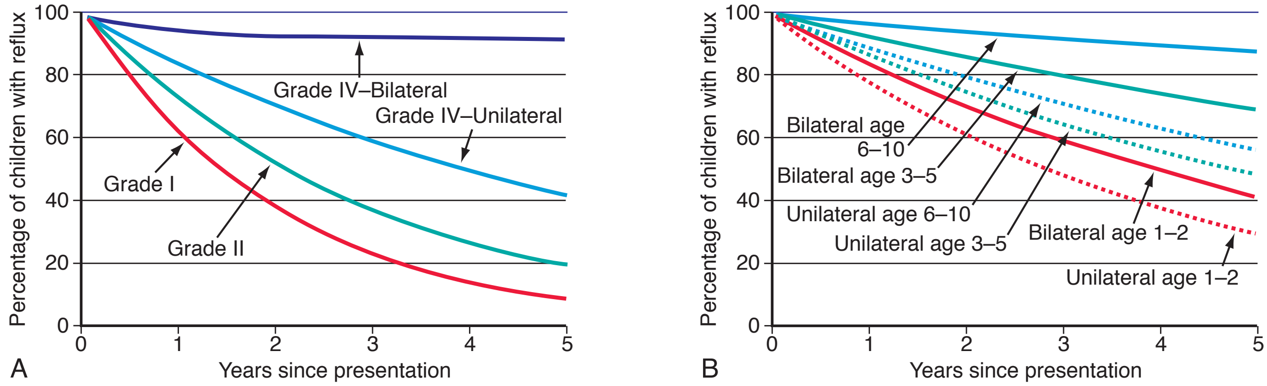

Figure 539-9 **A,** Percentage chance of VUR persistence, grades I, II, and IV, for 1-5 yr after presentation. **B,** Percentage chance of VUR persistence by age at presentation, grade III, for 1-5 yr after presentation. *(From Elder JS, Peters CA, Arant BS Jr, et al: Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral vesicoureteral reflux in children,* J Urol *157:1846–1851, 1997.)*

or a combination of these (see Chapter 543). Children with an overactive bladder often undergo a regimen of behavioral modification with timed voiding, and, on occasion, anticholinergic therapy.

After diagnosis, the child's height, weight, and blood pressure should be measured and monitored. If upper tract imaging shows renal scarring, a serum creatinine measurement should be obtained. The urine should be assessed for infection and proteinuria.

NATURAL HISTORY

The incidence of reflux-related renal scarring increases with VUR grade. With bladder growth and maturation, the VUR grade often resolves or improves. Lower grades of VUR are much more likely to resolve than are higher grades. For grades I and II VUR, the likelihood of resolution is similar regardless of age at diagnosis and whether it is unilateral or bilateral. For grade III, a younger age at diagnosis and unilateral VUR usually are associated with a higher rate of spontaneous resolution (Fig. 539-9). Bilateral grade IV VUR is much less likely to resolve than is unilateral grade IV VUR. Grade V VUR rarely resolves. The mean age at VUR resolution is 6 yr.

VUR does not usually cause renal injury in the absence of infection, but in situations with high-pressure VUR, as in children with posterior urethral valves, neuropathic bladder, and nonneurogenic neurogenic bladder (i.e., Hinman syndrome), sterile VUR can cause significant renal damage. Children with high-grade VUR who acquire a UTI are at significant risk for acute and recurrent pyelonephritis and new renal scarring (see Fig. 539-8).

TREATMENT

The goals of treatment are to prevent pyelonephritis, VUR-related renal injury, and other complications of VUR. Medical therapy is based on the principle that VUR often resolves over time and that if UTIs can be prevented, the morbidity or complications of VUR may be avoided without surgery. Medical therapy includes observation with behavioral modification or behavioral modification with antimicrobial prophylaxis in some patients. The basis for surgical therapy is that in selected children, ongoing VUR has caused or has significant potential for causing renal injury or other VUR-related complications, and that elimination of VUR minimizes the risk of these problems. Therapy for VUR should be individualized based on a particular patient's risk factors.

Observation

In children undergoing observation, therapeutic emphasis is directed to minimizing the risk of UTI by behavioral modification. These methods include timed voiding during the day, ensuring regular fecal elimination, increased fluid intake, periodic assessment of satisfactory bladder emptying, and prompt assessment and treatment of UTIs, particularly febrile UTIs. This approach is most appropriate for children with grades I and II VUR, and perhaps older children with persistent VUR and normal kidneys who have not experienced clinical pyelonephritis.

Antimicrobial Prophylaxis

In the past, based on clinical series demonstrating the effectiveness of antibiotic prophylaxis and the 1997 ***American Urological Association*** (**AUA**) Reflux Guidelines, daily prophylaxis was recommended as initial therapy for most children with VUR. Currently, many families express concern regarding the safety and benefit of prophylaxis. In addition, as a result of several prospective clinical trials, the benefit of prophylaxis has been questioned in children with VUR. The risk of recurrent UTI is highest in patients with grade III or IV reflux, those with bowel and bladder dysfunction, and those whose first reflux associated UTI was febrile rather than just symptomatic without fever. Antibiotic prophylaxis after a reflux associated UTI decreases the risk of recurrent UTI but increases the risk of developing resistant bacteria. In one study, antibiotic prophylaxis reduced the risk of new renal scars in children with grade III or IV reflux; while in another larger study antibiotic prophylaxis did not have an effect on the incidence of new renal scars in those with severe reflux (approximately 10% developed new scars regardless of prophylaxis).

Surgery

The purpose of surgical therapy is to minimize the risks of ongoing VUR and nonsurgical therapy (prophylaxis and follow-up testing). VUR can be corrected through a lower abdominal or inguinal incision (open), laparoscopically (with or without robotic assistance), or endoscopically with subureteral injection.

Open surgical management involves modifying the abnormal ureterovesical attachment to create a 4 : 1 to 5 : 1 ratio of intramural ureter length : ureteral diameter. The operation can be performed from either outside or inside the bladder. When VUR is associated with severe ureteral dilation (i.e., megaureter), the ureter must be tailored or narrowed to a more normal size to allow a smaller length : width ratio for the intramural tunnel, and a corner of the bladder is attached to the psoas tendon, forming a *psoas hitch*. Most children can be discharged 1-2 days following the surgical procedure. If the refluxing kidney is poorly functioning, nephrectomy or nephroureterectomy is indicated. Laparoscopic VUR correction and robotic-assisted laparoscopic ureteral reimplantation have being investigated and have been shown to have similar results to conventional open surgery in older children.

The success rate of conventional open ureteral reimplantation in children with primary VUR is >95-98% for grades I-IV, with 2% experiencing persistent VUR and 1% having ureteral obstruction that requires correction. The success rate is so high that many pediatric urologists do not perform a postoperative VCUG unless the child develops clinical pyelonephritis. For grade V VUR, the success rate is

approximately 80%. In lower grades of VUR, a failed reimplantation is most likely to occur in children with undiagnosed bladder-bowel dysfunction. In children with secondary VUR (posterior urethral valves, neuropathic bladder), the success rate is slightly lower than with primary VUR. The risk of pyelonephritis in children with grades III and IV VUR is significantly lower following open surgical correction compared with medical management. Surgical repair will not reverse renal scarring or cause improvement in renal function.

Endoscopic repair of VUR involves injection of a bulking agent through a cystoscope just beneath the ureteral orifice, creating an artificial flap-valve (Figs. 539-10 and 539-11). In 2001, the FDA approved the use of a biodegradable material, dextranomer microspheres suspended in hyaluronic acid (Deflux), for subureteral injection. The advantage of subureteral injection is that it is a noninvasive outpatient procedure (performed under general anesthesia) with no recovery time. The success rate is 70-80% and is highest for lower grades of VUR. If the first injection is unsuccessful, 1 or 2 repeat injections can be performed. The VUR recurrence rate is approximately 10%.

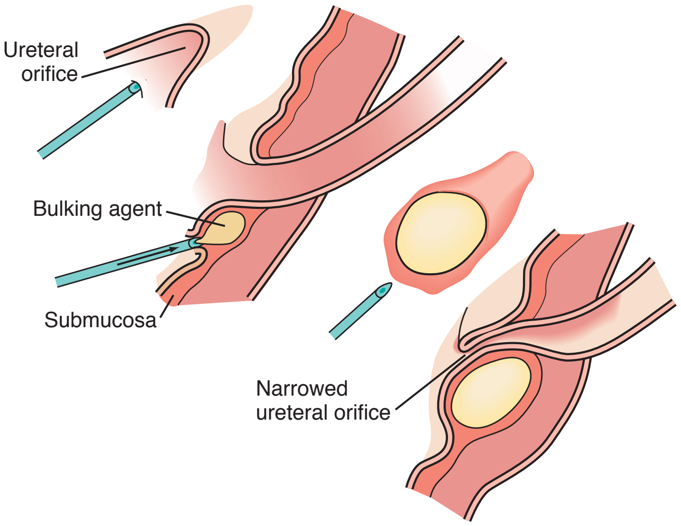

Figure 539-10 Endoscopic correction of VUR. Through a cystoscope, a needle is inserted into the submucosal plane deep to the ureteral orifice and bulking agent is injected, creating a flap-valve to prevent VUR. *(Adapted from Ortenberg J: Endoscopic treatment of vesicoureteral reflux in children,* Urol Clin North Am *25:151–156, 1998.)*

Current Vesicoureteral Reflux Guidelines

In 2010 the AUA provided updated evidence-based guidelines regarding VUR management, and in 2012 the European Association of Urology published expert opinion based guidelines. Both society recommendations were based on risk assessment of children with VUR.

The long-standing belief regarding the benefit of antibiotic prophylaxis in children with VUR has been questioned. Multiple randomized controlled prospective trials suggested that the risk of UTI in children with VUR is not reduced by prophylaxis. Most of the children in these trials had grades I-III VUR, and few younger than 1 yr old were studied. In contrast, the PRIVENT (Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts) trial from Australia showed significant benefit to prophylaxis in children with VUR. The Swedish VUR Trial in Children studied children younger than 2 yr of age with grades III and IV VUR; they compared antibiotic prophylaxis to observation and endoscopic injection therapy. Girls in the surveillance group had a significantly higher incidence of febrile UTI and new renal scarring compared to the other treatment groups. The largest randomized trial (RIVUR [Randomized Intervention for Children with Vesicoureteral Reflux]) enrolled more than 600 children and demonstrated a reduction in the recurrence rate of UTIs but no reduction of the occurrence of renal scarring with antibiotic prophylaxis.

Prophylaxis is recommended by the AUA in children at greatest risk for VUR-related renal injury (i.e., those younger than 1 yr of age). In addition, evaluation for ***bladder and bowel dysfunction*** is considered a standard part of initial and ongoing patient evaluation in children with VUR. Because children with bladder and bowel dysfunction and VUR are much more likely to have recurrent UTIs and renal scarring, prophylaxis is recommended for these children. In children with VUR who are being managed by surveillance, if a febrile UTI occurs, prophylaxis is recommended. The decision whether to recommend observation, medical therapy, or surgery is based on the risk of VUR to the patient, the likelihood of spontaneous resolution, and the parents' and patient's preferences, and the family should understand the risks and benefits of each treatment approach.

Another aspect of VUR management pertains to screening. VUR is known to be a familial disorder with autosomal dominant transmission with variable penetrance. The advantage of early VUR detection is to implement treatment before a potentially damaging episode of clinical pyelonephritis. In siblings of an index patient with VUR, optional management includes screening of asymptomatic siblings or offspring with a renal ultrasound or VCUG. The AUA recommends that a VCUG should be obtained if a screening ultrasound demonstrated a renal abnormality or if the sibling had a UTI.

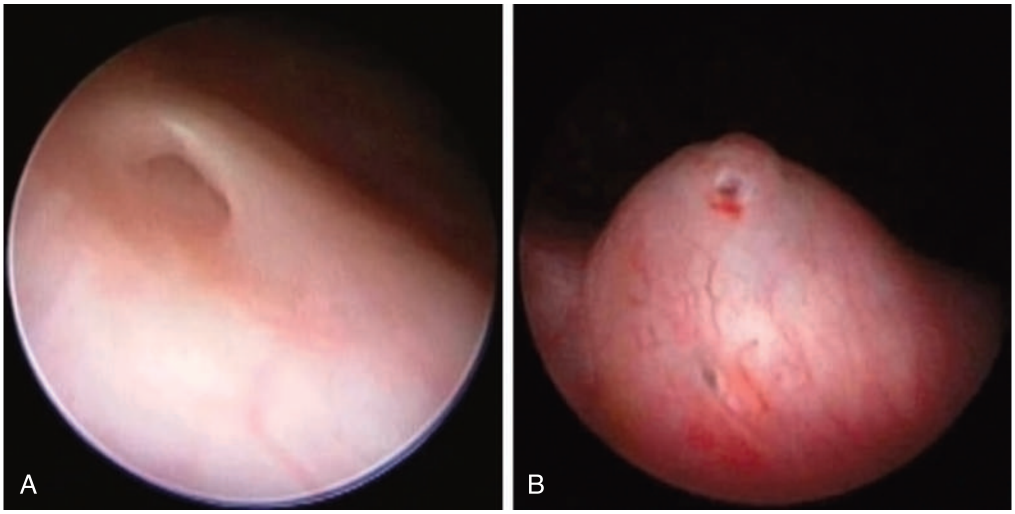

Figure 539-11 **A,** Endoscopic view of right vesicoureteral refluxing ureter. **B,** The same ureter after subureteral injection of dextranomer microspheres.

The AUA also determined that female newborns with renal pelvic dilation were significantly more likely than male newborns to have VUR. The AUA recommended that a VCUG should be performed in neonates with grade 3-4 antenatal hydronephrosis (moderate to severe pelvocaliceal dilation), hydroureter, or an abnormal bladder. In children with less-severe renal pelvic dilation, an observational approach without screening for VUR, with prompt treatment of any UTI, is appropriate. However, they also indicated that obtaining a VCUG is considered an appropriate option for neonates with lesser grades of hydronephrosis.

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Chapter 540

Obstruction of the Urinary Tract

Jack S. Elder

Most childhood obstructive lesions are congenital, although urinary tract obstruction can be caused by trauma, neoplasia, calculi, inflammatory processes, or surgical procedures. Obstructive lesions occur at any level from the urethral meatus to the calyceal infundibula (Table 540-1). The pathophysiologic effects of obstruction depend on its level, the extent of involvement, the child's age at onset, and whether it is acute or chronic.

ETIOLOGY

Ureteral obstruction occurring early in fetal life results in renal dysplasia, ranging from multicystic kidney, which is associated with ureteral or pelvic atresia (see Fig. 537-2 in Chapter 537), to various degrees of histologic renal cortical dysplasia that are seen with less-severe obstruction. Chronic ureteral obstruction in late fetal life or after birth results in dilation of the ureter, renal pelvis, and calyces, with alterations of renal parenchyma ranging from minimal tubular changes to dilation of Bowman's space, glomerular fibrosis, and interstitial fibrosis. After birth, infections often complicate obstruction and can increase renal damage.

Prenatal screening with ultrasonography may detect antenatal hydronephrosis, which is graded by the trimester and the anterior-posterior diameter of the renal pelvis (Table 540-2); most are mild. Table 540-3 notes the eventual etiology.

CLINICAL MANIFESTATIONS

Obstruction of the urinary tract generally causes **hydronephrosis,** which typically is asymptomatic in its early phases. An obstructed kidney secondary to a **ureteropelvic junction (UPJ)** or **ureterovesical junction** obstruction can manifest as a unilateral mass or cause upper abdominal or flank pain on the affected side. Pyelonephritis can occur because of urinary stasis. An upper urinary tract stone can occur, causing abdominal and flank pain and hematuria. With bladder outlet obstruction, the urinary stream may be weak; urinary tract infection (UTI; see Chapter 538) is common. Many of these lesions are identified by antenatal ultrasonography; an abnormality involving the genitourinary tract is suspected in as many as 1 in 100 fetuses.

Obstructive renal insufficiency can manifest itself by failure to thrive, vomiting, diarrhea, or other nonspecific signs and symptoms. In older children, *infravesical obstruction* can be associated with overflow urinary incontinence or a poor urine stream. *Acute ureteral obstruction* causes flank or abdominal pain; there may be nausea and vomiting. *Chronic ureteral obstruction* can be silent or can cause vague abdominal or typical flank pain with increased fluid intake.

Table 540-1 Types and Causes of Urinary Tract Obstruction

LOCATION	CAUSE
Infundibula	Congenital Calculi Inflammatory (tuberculosis) Traumatic Postsurgical Neoplastic
Renal pelvis	Congenital (infundibulopelvic stenosis) Inflammatory (tuberculosis) Calculi Neoplasia (Wilms tumor, neuroblastoma)
Ureteropelvic junction	Congenital stenosis Calculi Neoplasia Inflammatory Postsurgical Traumatic
Ureter	Congenital obstructive megaureter Midureteral structure Ureteral ectopia Ureterocele Retrocaval ureter Ureteral fibroepithelial polyps Ureteral valves Calculi Postsurgical Extrinsic compression Neoplasia (neuroblastoma, lymphoma, and other retroperitoneal or pelvic tumors) Inflammatory (Crohn disease, chronic granulomatous disease) Hematoma, urinoma Lymphocele Retroperitoneal fibrosis
Bladder outlet and urethra	Neurogenic bladder dysfunction (functional obstruction) Posterior urethral valves Anterior urethral valves Diverticula Urethral strictures (congenital, traumatic, or iatrogenic) Urethral atresia Ectopic ureterocele Meatal stenosis (males) Calculi Foreign bodies Phimosis Extrinsic compression by tumors Urogenital sinus anomalies

Table 540-2 Definition of Antenatal Hydronephrosis by Anterior-Posterior Diameter

DEGREE OF ANTENATAL HYDRONEPHROSIS	SECOND TRIMESTER	THIRD TRIMESTER
Mild	4 to <7 mm	7 to <9 mm
Moderate	7 to ≤10 mm	9 to ≤15 mm
Severe	>10 mm	>15 mm

From Nguyen HT, Herndon CDA, Cooper C, et al: The society for fetal urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol *6:212–231, 2010, Table 2, p. 215.*

DIAGNOSIS

Urinary tract obstruction may be diagnosed prenatally by ultrasonography, which typically shows hydronephrosis and occasionally a distended bladder. More complete evaluation, including imaging studies, should be undertaken in these children in the neonatal period.

Urinary tract obstruction is often silent. In the newborn infant, a palpable abdominal mass most commonly is a hydronephrotic or multicystic dysplastic kidney. With posterior urethral valves, which is an infravesical obstructive lesion in boys, a walnut-sized mass representing the bladder is palpable just above the pubic symphysis. A **patent draining urachus** also can suggest urethral obstruction. **Urinary ascites** in the newborn usually is caused by renal or bladder urinary extravasation secondary to posterior urethral valves. Infection and sepsis may be the first indications of an obstructive lesion of the urinary tract. The combination of infection and obstruction poses a serious threat to infants and children and generally requires parenteral administration of antibiotics and drainage of the obstructed kidney. Renal ultrasonography should be performed in all children during the acute stage of an initial febrile UTI.

Imaging Studies

Renal Ultrasonography

Hydronephrosis is the most common characteristic of obstruction (Fig. 540-1). Upper urinary tract dilation is not diagnostic of obstruction and often persists after surgical correction of a significant obstructive lesion. Dilation can result from vesicoureteral reflux, or it may be a manifestation of abnormal development of the urinary tract, even when there is no obstruction. Renal length, degree of caliectasis and parenchymal thickness, and presence or absence of ureteral dilation should be assessed. Most pediatric urologists grade the severity of hydronephrosis from 1-4 using the Society for Fetal Urology grading scale (Table 540-4), whereas pediatric radiologists generally utilize the adjectives mild, moderate, and severe. The clinician should ascertain that the contralateral kidney is normal, and the bladder should be imaged to see whether the bladder wall is thickened, the lower ureter is dilated, and bladder emptying is complete. In acute or intermittent obstruction, the dilation of the collecting system may be minimal and ultrasonography may be misleading.

Table 540-3 The Etiology of Antenatal Hydronephrosis

ETIOLOGY	INCIDENCE
Transient hydronephrosis	41-88%
Ureteropelvic junction obstruction	10-30%
Vesicoureteral reflux	10-20%
Ureterovesical junction obstruction/megaureters	5-10%
Multicystic dysplastic kidney	4-6%
Posterior urethral valve/urethral atresia	1-2%
Ureterocele/ectopic ureter/duplex system	5-7%
Others: prune belly syndrome, cystic kidney disease, congenital ureteric strictures, and megalourethra	Uncommon

From Nguyen HT, Herndon CDA, Cooper C, et al: The society for fetal urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol *6:212–231, 2010, Table 5, p. 217.*

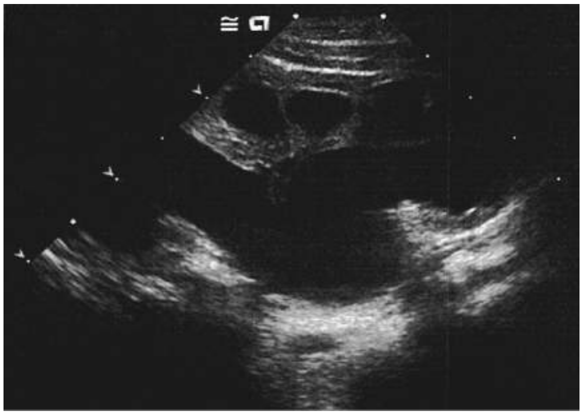

Figure 540-1 Ultrasonographic image of the kidney with marked pelvic and calyceal dilation (grade 4 hydronephrosis) in a newborn with ureteropelvic junction obstruction.

Voiding Cystourethrogram

In neonates and infants with congenital grade 3 or 4 hydronephrosis and in any child with ureteral dilation, a **contrast voiding cystourethrogram (VCUG)** should be obtained, because the dilation is secondary to vesicoureteral reflux in 15% of cases. In boys, the VCUG also is performed to rule out urethral obstruction, particularly in cases of suspected posterior urethral valves. In older children, the urinary flow rate can be measured noninvasively with a urinary flowmeter; decreased flow with a normal bladder contraction suggests infravesical obstruction (e.g., posterior urethral valves, urethral stricture). When the urethra cannot be catheterized to obtain a VCUG, the clinician should suspect a urethral stricture or an obstructive urethral lesion. Retrograde urethrography with contrast medium injected into the urethral meatus helps delineate the anatomy of the urethral obstruction.

Radioisotope Studies

Renal scintigraphy is used to assess renal anatomy and function. The 2 most commonly used radiopharmaceuticals are mercaptoacetyl triglycine (MAG-3) and technetium-99m-labeled dimercaptosuccinic acid. MAG-3, which is excreted by renal tubular secretion, is used to assess differential renal function, and when furosemide is administered, drainage also can be measured. An alternative to MAG-3 is diethylene tetrapentaacetic acid, which is cleared by glomerular filtration. The background activity of diethylene tetrapentaacetic acid is much higher than that of MAG-3. Dimercaptosuccinic acid is a renal cortical imaging agent and is used to assess differential renal function and to demonstrate whether renal scarring is present. It is used infrequently in children with obstructive uropathy.

In a MAG-3 diuretic renogram, a small dose of technetium-labeled MAG-3 is injected intravenously (Figs. 540-2 and 540-3). During the 1st 2-3 min, renal parenchymal uptake is analyzed and compared, allowing computation of differential renal function. Subsequently,

Table 540-4 Society for Fetal Urology Grading System for Hydronephrosis

GRADE OF HYDRONEPHROSIS	Renal Image: CENTRAL RENAL COMPLEX	Renal Image: RENAL PARENCHYMAL THICKNESS
0	Intact	Normal
1	Slight splitting	Normal
2	Evident splitting, complex confined within renal border	Normal
3	Wide splitting pelvis dilated outside renal border, calyces uniformly dilated	Normal
4	Further dilation of pelvis and calyces (calyces may appear convex)	Thin

After Maizels M, Mitchell B, Kass E, et al: Outcome of nonspecific hydronephrosis in the infant: a report from the registry of the Society for Fetal Urology, J Urol *152:2324–2327, 1994.*

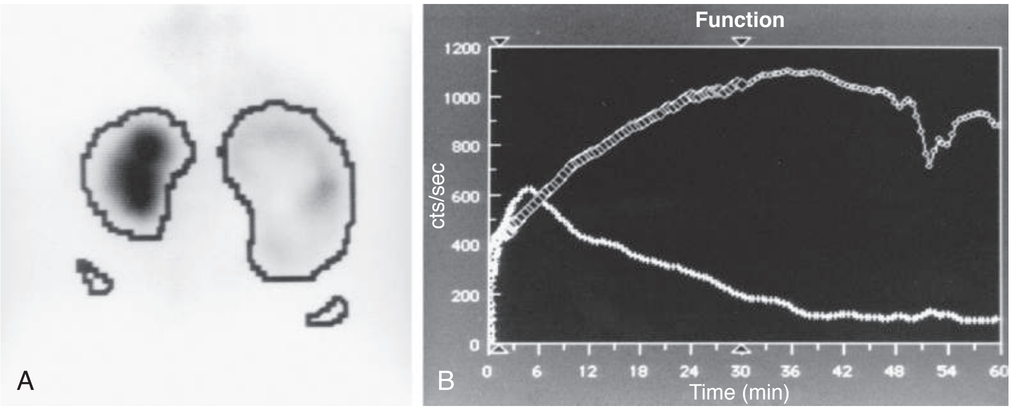

Figure 540-2 Same patient as in Figure 540-1. MAG-3 diuretic renogram of a 6 wk old patient. The right kidney is on the *right* side of the image. **A,** Differential renal function: left kidney 70%, right kidney 30%. **B,** After administration of furosemide, drainage from the left kidney was normal and drainage from the right kidney was slow, consistent with right ureteropelvic junction obstruction. Pyeloplasty was performed on the right kidney.

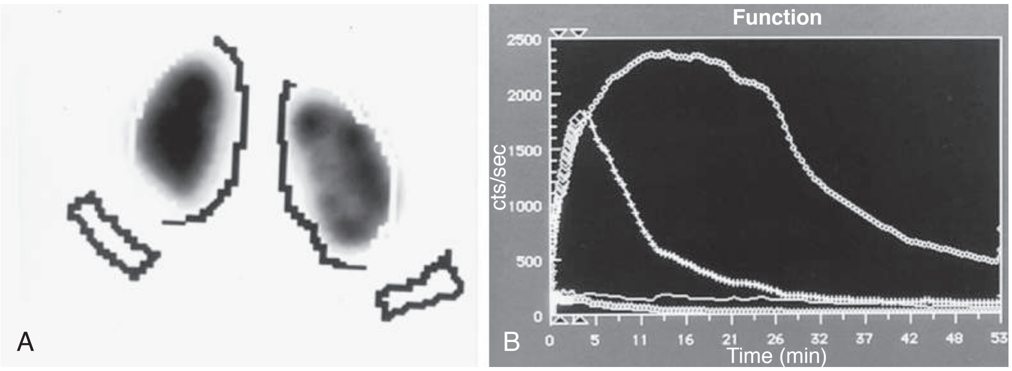

Figure 540-3 Same patient as in Figure 540-1. **A,** MAG-3 diuretic renogram at 14 mo of age shows equal function in the 2 kidneys. **B,** Prompt drainage after the administration of furosemide.

excretion is evaluated. After 20 min, furosemide 1 mg/kg is injected intravenously, and the rapidity and pattern of drainage from the kidneys to the bladder are analyzed. If no obstruction is present, half of the radionuclide should be cleared from the renal pelvis within 10-15 min, termed the half-time ($t_{1/2}$). If there is significant upper tract obstruction, the $t_{1/2}$ usually is longer than 20 min. A $t_{1/2}$ of 15-20 min is indeterminate. An elevated $t_{1/2}$ is suggestive but not diagnostic of obstruction. The images generated usually provide an accurate assessment of the site of obstruction. Numerous variables affect the outcome of the diuretic renogram. For example, newborn kidneys are functionally immature, and, in the 1st mo of life, normal kidneys might not demonstrate normal drainage after diuretic administration. Patient dehydration prolongs parenchymal transit and can blunt the diuretic response. Giving an insufficient dose of furosemide can result in slow drainage. If vesicoureteral reflux is present, continuous bladder drainage is mandatory to prevent the radionuclide from refluxing from the bladder into the dilated upper tract, which would prolong the washout phase..

The MAG-3 diuretic renogram is considered superior to the excretory urogram in infants and children with hydronephrosis, because bowel gas and immaturity of renal function often cause the intravenous pyelogram (IVP) images to be suboptimal. The diuretic renogram provides an objective assessment of the relative function of each kidney.

Excretory Urogram

Excretory urogram is rarely used in assessing the pediatric urinary tract, although it may be useful in selected cases with indeterminate upper urinary tract obstruction or a suspected duplication anomaly.

Magnetic Resonance Urography

MR urography is also used to evaluate suspected upper urinary tract pathology. The child is hydrated and given intravenous furosemide. Gadolinium-diethylene tetrapentaacetic acid is injected and routine T1-weighted and fat-suppressed fast spin-echo T2-weighted imaging is performed through the kidneys, ureters, and bladder. This study provides superb images of the pathology, and methodology permits assessment of differential renal function and drainage (Fig. 540-4). There is no radiation exposure; however, young children need sedation or anesthesia. It is used primarily when renal sonography and nuclear imaging fail to delineate complex pathology.

Computed Tomography

In children with a suspected ureteral calculus, noncontrast spiral CT of the abdomen and pelvis is a standard method of demonstrating whether a calculus is present, its location, and whether there is significant proximal hydronephrosis. This study is the initial study of choice in many of these patients. The disadvantage of CT is the significant radiation exposure, and it should be used only when the results will direct management decisions (see Chapter 718).

Ancillary Studies

In unusual cases, an **antegrade pyelogram** (insertion of a percutaneous nephrostomy tube and injection of contrast agent), can be performed to assess the anatomy of the upper urinary tract. This procedure usually requires general anesthesia. In addition, an **antegrade pressure-perfusion flow study** (Whitaker test) may be performed, in which fluid is infused at a measured rate, usually 10 mL/min. The pressures

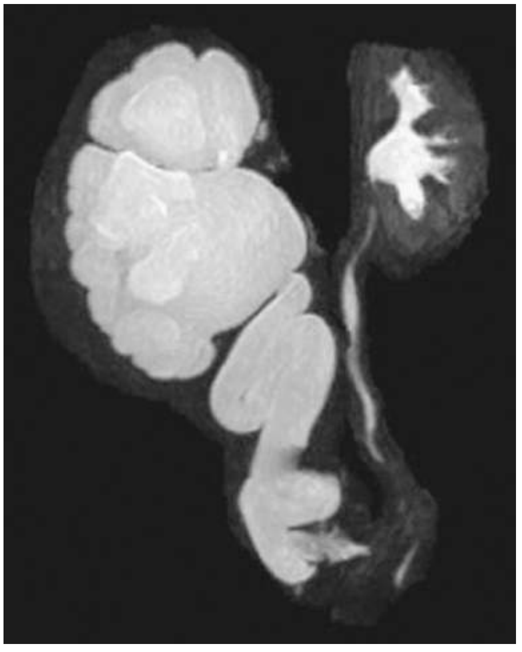

Figure 540-4 MR urogram in boy with distal ureterovesical obstruction.

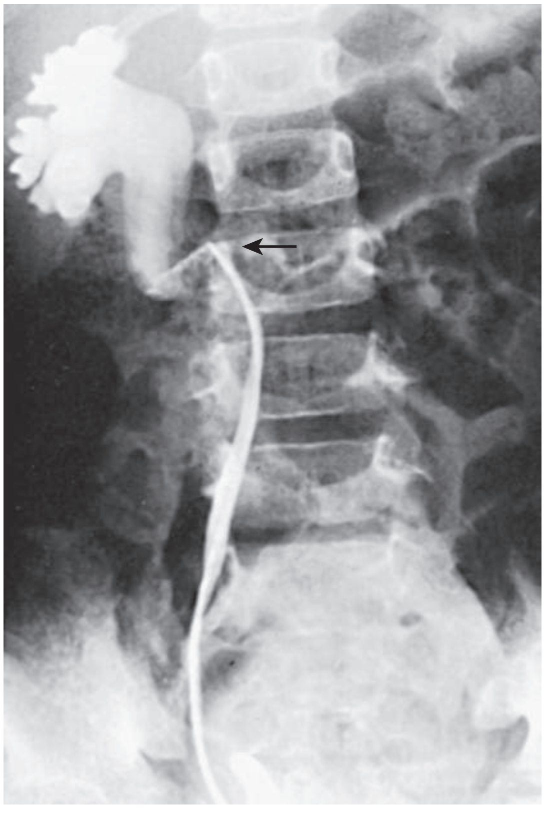

Figure 540-5 Retrograde pyelogram showing medial deviation of a dilated upper ureter to the level of the 3rd lumbar vertebra, characteristic of a retrocaval ureter.

in the renal pelvis and the bladder are monitored during this infusion, and pressure differences exceeding 20 cm H_2O suggest obstruction. In other cases, cystoscopy with retrograde pyelography provides excellent images of the upper urinary tract (Fig. 540-5).

SPECIFIC TYPES OF URINARY TRACT OBSTRUCTION AND THEIR TREATMENT

Hydrocalycosis

The term *hydrocalycosis* refers to a localized dilation of the calyx caused by obstruction of its infundibulum, termed *infundibular stenosis.* This condition can be developmental in origin or secondary to inflammatory processes, such as UTI. It usually is discovered during evaluation for pain or UTI. The diagnosis of infundibular stenosis is usually established by sonograph and CT scan or MR urography.

Ureteropelvic Junction Obstruction

UPJ obstruction is the most common obstructive lesion in childhood and usually is caused by intrinsic stenosis (see Figs. 540-1 to 540-3). An accessory artery to the lower pole of the kidney also can cause extrinsic obstruction. The typical appearance on ultrasonography is grade 3 or 4 hydronephrosis without a dilated ureter. UPJ obstruction most commonly manifests on antenatal sonography revealing fetal hydronephrosis; as a palpable renal mass in a newborn or infant; as abdominal, flank, or back pain; as a febrile UTI; or as hematuria after minimal trauma. Approximately 60% of cases occur on the left side, and the male : female ratio is 2 : 1. *UPJ obstruction is bilateral in only 10% of cases*. In kidneys with UPJ obstruction, renal function may be significantly impaired from pressure atrophy, but approximately half of affected kidneys have relatively normal glomerular function. The anomaly is corrected by performing a pyeloplasty, in which the stenotic segment is excised and the normal ureter and renal pelvis are reattached. Success rates are 91-98%. Pyeloplasty can be performed using laparoscopic techniques, often robotic-assisted using the da Vinci robot.

Lesser degrees of UPJ narrowing might cause mild hydronephrosis, which usually is nonobstructive, and typically these kidneys function normally. The spectrum of UPJ abnormalities has been referred to as *anomalous UPJ.* Another cause of mild hydronephrosis is fetal folds of the upper ureter, which also are nonobstructive.

The diagnosis can be difficult to establish in an asymptomatic infant in whom dilation of the renal pelvis is found incidentally in a prenatal ultrasonogram. After birth, the sonographic study is repeated to confirm the prenatal finding. A VCUG is necessary because 10-15% of patients have ipsilateral vesicoureteral reflux. Because neonatal oliguria can cause temporary decompression of a dilated renal pelvis, it is ideal to perform the first postnatal sonogram after the 3rd day of life. Delaying the sonogram may be impractical. If no dilation is found on the initial sonogram, a repeat study should be performed at 1 mo of age. If the kidney shows grade 1 or 2 hydronephrosis and the renal parenchyma appears normal, a period of observation usually is appropriate, with sequential renal ultrasonograms to monitor the severity of hydronephrosis, and the hydronephrosis usually disappears. **Antibiotic prophylaxis** is not indicated for children with mild hydronephrosis. If the hydronephrosis is grade 3 or 4, spontaneous resolution is less likely and obstruction is more likely to be present, particularly if the renal pelvic diameter is 3 cm. A diuretic renogram with MAG-3 is performed at 4-6 wk of age. If there is poor upper tract drainage or the differential renal function is poor, pyeloplasty is recommended. After pyeloplasty the differential renal function often improves, and improved drainage with furosemide stimulation is expected.

If the differential function on renography is normal, and drainage is satisfactory, the infant can be followed with serial ultrasonograms, even with grade 4 hydronephrosis. If the hydronephrosis remains severe with no improvement, a repeat diuretic renogram after 6-12 mo can help in the decision between continued observation and surgical repair. Prompt surgical repair is indicated in infants with an abdominal mass, bilateral severe hydronephrosis, a solitary kidney, or diminished function in the involved kidney. In unusual cases in which the differential renal function is <10% but the kidney definitely has some function, insertion of a percutaneous nephrostomy tube allows drainage of the hydronephrotic kidney for a few weeks to allow reassessment of renal function. In older children who present with symptoms, the diagnosis of UPJ obstruction usually is established by ultrasonography and diuretic renography.

The following entities should be considered in the **differential diagnosis:** megalycosis, a congenital nonobstructive dilation of the calyces without pelvic or ureteric dilation; vesicoureteral reflux with marked dilation and kinking of the ureter; midureteral or distal ureteral obstruction when the ureter is not well visualized on the urogram; and retrocaval ureter.

Midureteral Obstruction

Congenital ureteral stenosis or a ureteral valve in the midureter is rare. It is corrected by excision of the strictured segment and reanastomosis of the normal upper and lower ureteral segments. A **retrocaval ureter** is an anomaly in which the upper right ureter travels posterior to the inferior vena cava. In this anomaly, the vena cava can cause extrinsic compression and obstruction. An IVP or MR urogram shows the right ureter to be medially deviated at the level of the 3rd lumbar vertebra. The diagnosis may be confirmed by retrograde pyelography (see Fig. 540-5). Surgical treatment consists of transection of the upper ureter, moving it anterior to the vena cava, and reanastomosing the upper and lower segments. Repair is necessary only when obstruction is present. Retroperitoneal tumors, fibrosis caused by surgical procedures, inflammatory processes (as in chronic granulomatous disease), and radiation therapy can cause acquired midureteral obstruction.

Ectopic Ureter

A ureter that drains outside the bladder is referred to as an **ectopic ureter.** This anomaly is 3 times as common in girls as in boys and usually is detected prenatally. The ectopic ureter typically drains the upper pole of a duplex collecting system (2 ureters).

In girls, approximately 35% of these ureters enter the urethra at the bladder neck, 35% enter the urethrovaginal septum, 25% enter the vagina, and a few drain into the cervix, uterus, Gartner duct, or a urethral diverticulum. Often the terminal aspect of the ureter is narrowed, causing hydroureteronephrosis. With the exception of the ectopic ureter entering the bladder neck, in girls an ectopic ureter causes continuous urinary incontinence from the affected renal moiety. UTI is common because of urinary stasis.

In boys, ectopic ureters enter the posterior urethra (above the external sphincter) in 47%, the prostatic utricle in 10%, the seminal vesicle in 33%, the ejaculatory duct in 5%, and the vas deferens in 5%. Consequently, in boys, an ectopic ureter does not cause incontinence, and most patients present with a UTI or epididymitis.

Evaluation includes a renal sonogram, VCUG, and renal scan, which demonstrates whether the affected segment has significant function. The sonogram shows the affected hydronephrotic kidney or dilated upper pole and ureter down to the bladder (Fig. 540-6). If the ectopic ureter drains into the bladder neck (female), a VCUG usually shows reflux into the ureter. Otherwise, there is no reflux into the ectopic ureter, but there may be reflux into the ipsilateral lower pole ureter or contralateral collecting system.

Treatment depends on the status of the renal unit drained by the ectopic ureter. If there is satisfactory function, ureteral reimplantation into the bladder or ureteroureterostomy (anastomosing the ectopic upper pole ureter into the normally inserting lower pole ureter) is indicated. If function is poor, partial or total nephrectomy is indicated. In many centers this procedure is done laparoscopically and often with robotic assistance using the da Vinci robot.

Ureterocele

A ureterocele is a cystic dilation of the terminal ureter and is obstructive because of a pinpoint ureteral orifice. Ureteroceles are much more common in girls than in boys. Affected children usually are discovered by prenatal ultrasonography, but some present with a febrile UTI. Ureteroceles may be ectopic, in which case the cystic swelling extends through the bladder neck into the urethra, or orthotopic, in which case the ureterocele is entirely within the bladder. Both orthotopic and ectopic ureteroceles can be bilateral.

In girls, ureteroceles nearly always are associated with ureteral duplication (Fig. 540-7), whereas in 50% of affected boys there is only 1

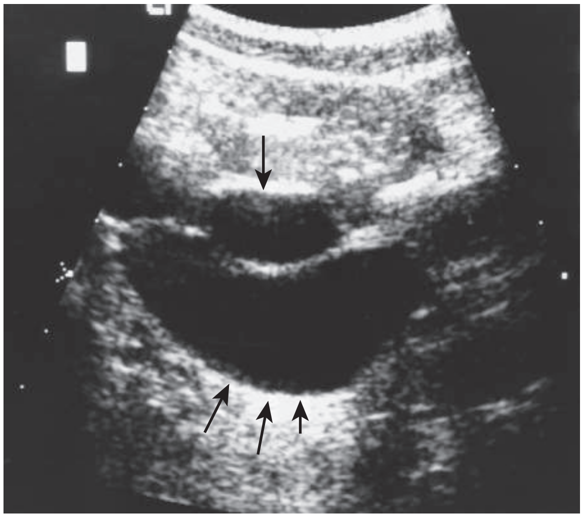

Figure 540-6 Ultrasonographic image of the right dilated ureter *(bottom arrows)* extending behind and caudal to a nearly empty bladder *(top arrow)* in a girl with urinary incontinence and ectopic ureter draining into the vagina.

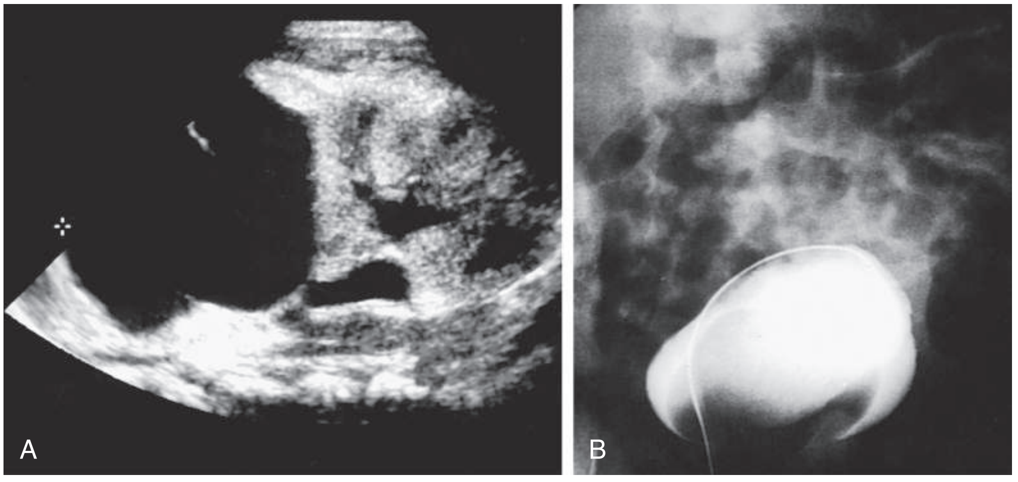

Figure 540-7 **A,** Infant with ectopic ureterocele. Sonogram of the left kidney shows massive dilation of the upper pole and a normal lower pole. **B,** Voiding cystourethrogram shows large ureterocele, draining the left upper pole, in the bladder. No reflux is present.

ureter. When associated with a duplication anomaly, the ureterocele drains the upper renal moiety, which commonly functions poorly or is dysplastic because of congenital obstruction. The lower pole ureter drains into the bladder superior and lateral to the upper pole ureter and may reflux.

An **ectopic ureterocele** extends submucosally into the urethra. Rarely, large ectopic ureteroceles can cause bladder outlet obstruction and retention of urine with bilateral hydronephrosis. In girls, the ureterocele can prolapse from the urethral meatus. Ultrasonography is effective in demonstrating the ureterocele and whether the associated obstructed system is duplicated or single. VCUG usually shows a filling defect in the bladder, sometimes large, corresponding to the ureterocele, and it often shows reflux into the adjacent lower pole collecting system with typical findings of a "drooping lily" appearance to the kidney. Nuclear renal scintigraphy is most accurate in demonstrating whether the affected renal moiety has significant function.

Treatment of ectopic ureteroceles varies among different medical centers and depends on whether the upper pole functions on renal scan and whether there is reflux into the lower pole ureter. If there is nonfunction of the upper pole of the kidney and there is no reflux, treatment usually involves laparoscopic, robotic, or open excision of the obstructed upper pole and most of the associated ureter. If there is function in the upper pole or significant reflux into the lower pole ureter, or if the patient is septic from infection of the hydronephrotic kidney, then transurethral incision with cautery is appropriate initial therapy to decompress the ureterocele. Reflux into the incised ureterocele is common, and subsequent excision of the ureterocele and ureteral reimplantation usually is necessary. An alternative method is to perform a upper-to-lower ureteroureterostomy, allowing the obstructed upper pole ureter to drain through the normal lower ureter; this procedure often is performed with minimally invasive laparoscopic (robotic) technique or through a small incision.

Orthotopic ureteroceles are associated with duplicated or single collecting systems, and the orifice is in the expected location in the bladder (Fig. 540-8). These anomalies usually are discovered during an investigation for prenatal hydronephrosis or a UTI. Ultrasonography is sensitive for detecting the ureterocele in the bladder and hydroureteronephrosis. IVP reveals varying degrees of ureteral and calyceal dilation, and there is a round filling defect in the bladder. In delayed films, cystic dilation of the ureter may be clearly visible and full of contrast material. Transurethral incision of the ureterocele effectively relieves the obstruction, but it can result in vesicoureteral reflux, necessitating ureteral reimplantation later. Some prefer open excision of the ureterocele and reimplantation as the initial form of treatment. Small, simple ureteroceles discovered incidentally without upper tract dilation generally do not require treatment.

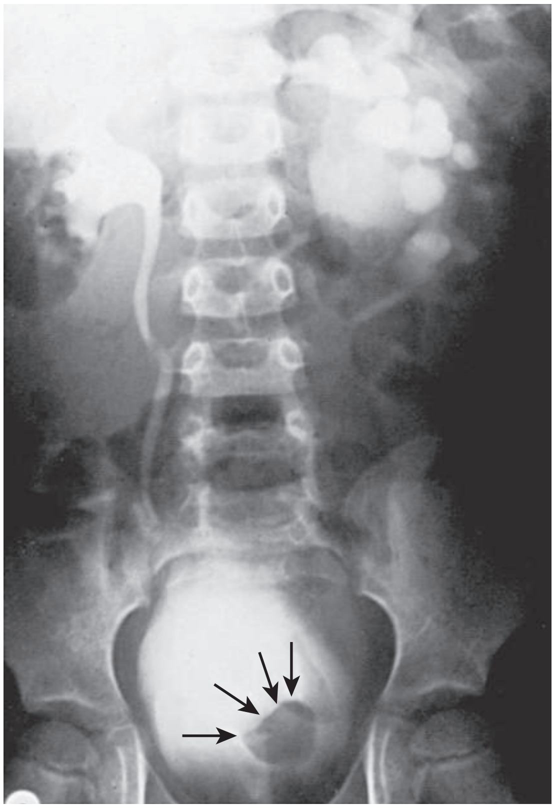

Figure 540-8 Simple intravesical ureterocele. The excretory urogram shows left hydronephrosis and a round filling defect on the left side of the bladder corresponding to a simple ureterocele causing left ureteral obstruction. This lesion was treated by transurethral incision and drainage of the ureterocele.

Megaureter

Table 540-5 presents a classification of megaureters (dilated ureter). Numerous disorders can cause ureteral dilation, and many are nonobstructive.

Megaureters usually are discovered during antenatal sonography, postnatal UTI, hematuria, or abdominal pain. A careful history, physical examination, and VCUG identify causes of secondary megaureters and refluxing megaureters as well as the prune-belly syndrome. Primary obstructed megaureters and nonobstructed megaureters probably represent varying degrees of severity of the same anomaly.

The primary obstructed nonrefluxing megaureter results from abnormal development of the distal ureter, with collagenous tissue replacing the muscle layer. Normal ureteral peristalsis is disrupted, and the proximal ureter widens. In most cases there is not a true stricture. On IVP or an MR urogram, the distal ureter is more dilated in its distal segment and tapers abruptly at or above the junction of the bladder (Fig. 540-9). The lesion may be unilateral or bilateral. Significant hydroureteronephrosis suggests obstruction. Megaureter predisposes to UTI, urinary stones, hematuria, and flank pain because of urinary stasis. In most cases, diuretic renography and sequential sonographic studies can reliably differentiate obstructed from nonobstructed megaureters. In most nonobstructed megaureters, the hydroureteronephrosis diminishes gradually (Fig. 540-10). Truly obstructed megaureters require surgical treatment, with excision of the narrowed segment, ureteral tapering, and reimplantation of the ureter. The results of surgical reconstruction usually are good, but the prognosis depends on preexisting renal function and whether complications develop.

If differential renal function is normal (>45%) and the child is asymptomatic, it is safe to manage the patient with observation with serial ultrasonography and periodic diuretic renography to monitor renal function and drainage. In children with grade 4 hydroureteronephrosis, prophylactic antimicrobial therapy should be prescribed, as these children are prone to upper UTI. If renal function deteriorates, upper urinary tract drainage slows, or UTI occurs, ureteral reimplantation is recommended. Approximately 15% of children with a nonrefluxing megaureter undergo ureteral reimplantation.

Prune-Belly Syndrome

Prune-belly syndrome, also called **triad syndrome** or **Eagle-Barrett syndrome,** occurs in approximately 1 in 40,000 births; 95% of affected children are male. The characteristic association of deficient abdominal muscles, undescended testes, and urinary tract abnormalities probably results from severe urethral obstruction in fetal life (Fig. 540-11). Oligohydramnios and pulmonary hypoplasia are common complications in the perinatal period. Many affected infants are stillborn. Urinary tract abnormalities include massive dilation of the ureters and upper tracts and a very large bladder, with a patent urachus or a urachal diverticulum. Most patients have vesicoureteral reflux. The prostatic urethra usually is dilated, and the prostate is hypoplastic. The anterior urethra may be dilated, resulting in a megalourethra. Rarely, there is urethral stenosis or atresia. The kidneys usually show various degrees of dysplasia, and the testes usually are intraabdominal. Malrotation of the bowel often is present. Cardiac abnormalities occur in 10% of cases; >50% have abnormalities of the musculoskeletal system, including

Table 540-5 Classification of Megaureter

Refluxing		Obstructed		Nonrefluxing and Nonobstructed	
PRIMARY	**SECONDARY**	**PRIMARY**	**SECONDARY**	**PRIMARY**	**SECONDARY**
Primary reflux	Neuropathic bladder	Intrinsic (primary obstructed megaureter)	Neuropathic bladder	Nonrefluxing, nonobstructive	Diabetes insipidus
Megacystic-megaureter syndrome	Hinman syndrome	Ureteral valve	Hinman syndrome		Infection
Ectopic ureter	Posterior urethral valves	Ectopic ureter	Posterior urethral valves		Persistent after relief of obstruction
Prune-belly syndrome	Bladder diverticulum Postoperative	Ectopic uterocele	Ureteral calculus Extrinsic Postoperative		

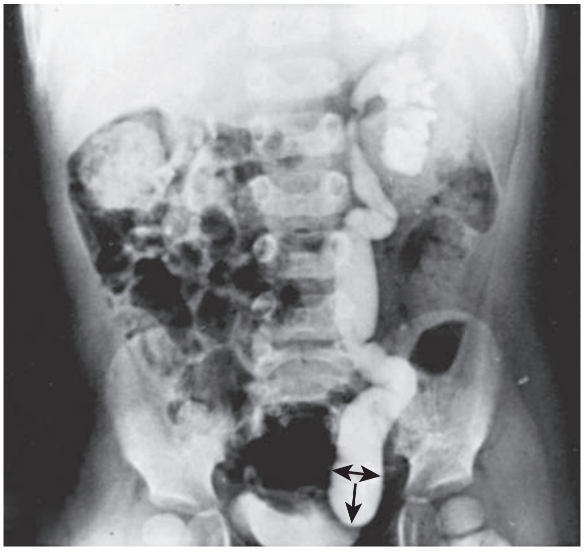

Figure 540-9 Obstructed nonrefluxing megaureter. Excretory urogram in a girl with a history of a febrile urinary tract infection. The right side is normal. The left side reveals hydroureteronephrosis with predominant dilation of the distal ureter. Note the characteristic appearance of the distal ureter. There was no vesicoureteral reflux. The diagnosis of obstruction was confirmed by diuretic renography.

limb abnormalities and scoliosis. In girls, anomalies of the urethra, uterus, and vagina usually are present.

Many neonates with prune-belly syndrome have difficulty with effective bladder emptying because the bladder musculature is poorly developed, and the urethra may be narrowed. When no obstruction is present, the goal of treatment is the prevention of UTI with antibiotic prophylaxis. When obstruction of the ureters or urethra is demonstrated, temporary drainage procedures, such as a vesicostomy, can help to preserve renal function until the child is old enough for surgery. Some children with prune-belly syndrome have been found to have classic or atypical posterior urethral valves. UTIs occur often and should be treated promptly. Correction of the undescended testes by orchidopexy can be difficult in these children because the testes are located high in the abdomen and surgery is best accomplished in the 1st 6 mo of life. Reconstruction of the abdominal wall offers cosmetic and functional benefits.

The prognosis ultimately depends on the degree of pulmonary hypoplasia and renal dysplasia. One third of children with prune-belly syndrome are stillborn or die in the 1st few mo of life because of pulmonary hypoplasia. As many as 30% of the long-term survivors develop end-stage renal disease from dysplasia or complications of infection or reflux and eventually require renal transplantation. Renal transplantation in these children offers good results.

Bladder Neck Obstruction

Bladder neck obstruction usually is secondary to ectopic ureterocele, bladder calculi, or a tumor of the prostate (rhabdomyosarcoma). The manifestations include difficulty voiding, urinary retention, UTI, and bladder distention with overflow incontinence. Apparent bladder neck obstruction is common in cases of posterior urethral valves, but it seldom has any functional significance. Primary bladder neck obstruction is extremely rare.

Posterior Urethral Valves

The most common cause of severe obstructive uropathy in children is posterior urethral valves, affecting 1 in 8,000 boys. The urethral valves are tissue leaflets fanning distally from the prostatic urethra to the external urinary sphincter. A slit-like opening usually separates the leaflets. Valves are of unclear embryologic origin and cause varying degrees of obstruction. Approximately 30% of patients experience end-stage renal disease or chronic renal insufficiency. The prostatic urethra dilates, and the bladder muscle undergoes hypertrophy. Vesicoureteral reflux occurs in 50% of patients, and distal ureteral obstruction can result from a chronically distended bladder or bladder muscle hypertrophy. The renal changes range from mild hydronephrosis to severe renal dysplasia; their severity probably depends on the severity of the obstruction and its time of onset during fetal development. As in other cases of obstruction or renal dysplasia, there may be oligohydramnios and pulmonary hypoplasia.

Affected boys with posterior urethral valves often are discovered prenatally when maternal ultrasonography reveals bilateral hydronephrosis, a distended bladder, and, if the obstruction is severe, oligohydramnios. Prenatal bladder decompression by percutaneous vesicoamniotic shunt or open fetal surgery has been reported. Experimental and clinical evidence of the possible benefits of fetal intervention is lacking, and few affected fetuses are candidates. Prenatally diagnosed posterior urethral valves, particularly when discovered in the 2nd trimester, carry a poorer prognosis than those detected in the 3rd trimester following a normal second fetal ultrasound. In the male neonate, posterior urethral valves are suspected when there is a palpably **distended bladder** and the **urinary stream is weak.** If the obstruction is severe and goes unrecognized during the neonatal period, infants can present later in life with failure to thrive because of uremia or sepsis caused by infection in the obstructed urinary tract. With lesser degrees of obstruction, children present later in life with difficulty in achieving diurnal urinary continence or with UTI. The diagnosis is established with a VCUG (Fig. 540-12) or by perineal ultrasonography.

After the diagnosis is established, renal function and the anatomy of the upper urinary tract should be carefully evaluated. In the healthy neonate, a small polyethylene feeding tube (No. 5 or No. 8 French) is inserted in the bladder and left for several days. Passing the feeding

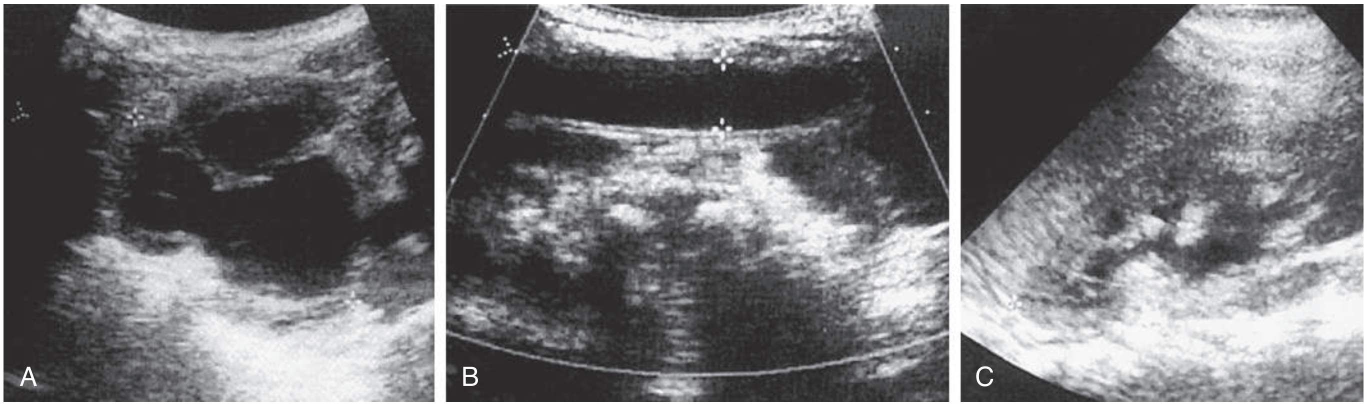

Figure 540-10 Neonate with primary nonrefluxing megaureter. **A,** Renal sonogram shows grade 4 hydronephrosis. **B,** Dilated ureter. Renal scan showed equal function with the contralateral kidney and satisfactory drainage with diuresis stimulation. **C,** Follow-up sonogram at 10 mo shows complete resolution of hydronephrosis.

Figure 540-11 Photograph of a 1,600-g newborn with the prune-belly syndrome. Note the lack of tonicity of the abdominal wall and the wrinkled appearance of the skin.

tube may be difficult, because the tip of the tube can coil in the prostatic urethra. A sign of this problem is that urine drains around the catheter rather than through it. A Foley (balloon) catheter **should not be used**, because the balloon can cause severe bladder spasm, which can produce severe ureteral obstruction.

If the serum creatinine level remains normal or returns to normal, treatment consists of transurethral ablation of the valve leaflets, which is performed endoscopically under general anesthesia. If the urethra is too small for transurethral ablation, temporary vesicostomy is preferred, in which the dome of the bladder is exteriorized on the lower abdominal wall. When the child is older, the valves may be ablated and the vesicostomy closed.

If the serum creatinine level remains high or increases despite bladder drainage by a small catheter, secondary ureteral obstruction, irreversible renal damage, or renal dysplasia should be suspected. In such cases, a vesicostomy should be considered. Cutaneous pyelostomy rarely affords better drainage when compared with cutaneous vesicostomy, and the latter also allows continued bladder growth and gradual improvement in bladder wall compliance.

In the septic and uremic infant, lifesaving measures must include prompt correction of the electrolyte imbalance and control of the infection by appropriate antibiotics. Drainage of the upper tracts by percutaneous nephrostomy and hemodialysis may be necessary. After the patient's condition becomes stable, evaluation and treatment may be undertaken. Posterior valves are diagnosed in some older boys because of a poor stream, diurnal incontinence, or a UTI; these boys generally are treated by primary valve ablation.

Figure 540-12 Voiding cystourethrogram in an infant with posterior urethral valves. Note the dilation of the prostatic urethra and the transverse linear filling defect corresponding to the valves.

Favorable prognostic factors include a normal prenatal ultrasonogram between 18 and 24 wk of gestation, a serum creatinine level <0.8-1.0 mg/dL after bladder decompression, and visualization of the corticomedullary junction on renal sonography. In several situations, a "popoff valve" can occur during urinary tract development, which preserves the integrity of 1 or both kidneys. For example, 15% of boys with posterior urethral valves have unilateral reflux into a nonfunctioning dysplastic kidney, termed the **VURD syndrome** (*v*alves, *u*nilateral *r*eflux, *d*ysplasia). In these boys, the high bladder pressure is dissipated into the nonfunctioning kidney, allowing normal development of the contralateral kidney. In newborn boys with urinary ascites, the urine generally leaks out from the obstructed collecting system through the renal fornices, allowing normal development of the kidneys. Unfavorable prognostic factors include the presence of oligohydramnios in utero, identification of hydronephrosis before 24 wk of gestation, a serum creatinine level >1.0 mg/dL after bladder decompression, identification of cortical cysts in both kidneys, and persistence of diurnal incontinence beyond 5 yr of age.

The prognosis in the newborn is related to the child's degree of pulmonary hypoplasia and potential for recovery of renal function. Severely affected infants often are stillborn. Of those who survive the neonatal period, approximately 30% eventually require kidney transplantation and 15% have renal insufficiency. In some series, kidney transplantation in children with posterior urethral valves has a lower success rate than does transplantation in children with normal bladders, presumably because of the adverse influence of altered bladder function on graft function and survival.

After valve ablation, antimicrobial prophylaxis is beneficial in preventing UTI, because hydronephrosis to some degree often persists for many years. These boys should be evaluated annually with a renal ultrasonogram, physical examination including assessment of somatic growth and blood pressure, urinalysis, and determination of serum levels of electrolytes. Many boys have significant polyuria resulting from a concentrating defect secondary to prolonged obstructive uropathy. If these children acquire a systemic illness with vomiting and/or diarrhea, urine output cannot be used to assess their hydration status. They can become dehydrated quickly, and there should be a low threshold for hospital admission for intravenous rehydration. Some of these patients have renal tubular acidosis, requiring oral bicarbonate therapy. If there is any significant degree of renal dysfunction, growth impairment, or hypertension, the child should be followed closely by a pediatric nephrologist. When vesicoureteral reflux is present, expectant treatment and prophylactic doses of antibacterial drugs are advisable. If breakthrough UTI occurs, surgical correction should be undertaken.

After treatment, boys with urethral valves often do not achieve diurnal urinary continence as early as other boys. Incontinence can result from a combination of factors, including uninhibited bladder contractions, poor bladder compliance, bladder atonia, bladder neck dyssynergia, or polyuria. Often these boys require urodynamic evaluation with urodynamics or videourodynamics to plan therapy. Boys with noncompliance are at significant risk for ongoing renal damage, even in the absence of infection. Overnight catheter drainage has been shown to be beneficial in boys with polyuria and can help preserve renal function. Urinary incontinence usually improves with age, particularly after puberty. Meticulous attention to bladder compliance, emptying, and infection can improve results in the future.

Urethral Atresia

The most severe form of obstructive uropathy in boys is urethral atresia, a rare condition. In utero there is a distended bladder, bilateral hydroureteronephrosis, and oligohydramnios. In most cases, these infants are stillborn or succumb to pulmonary hypoplasia. Some boys with prune-belly syndrome also have urethral atresia. If the urachus is patent, oligohydramnios is unlikely and the infant usually survives. Urethral reconstruction is difficult, and most patients are managed with continent urinary diversion.

Urethral Hypoplasia

Urethral hypoplasia is a rare form of obstructive uropathy in boys that is less severe than urethral atresia. In urethral hypoplasia, the urethral lumen is extremely small. Neonates with urethral hypoplasia typically have bilateral hydronephrosis and a distended bladder. Passage of a small pediatric feeding tube through the urethra is difficult or impossible. Usually a cutaneous vesicostomy must be performed to relieve upper urinary tract obstruction, and the severity of renal insufficiency is variable. The most severely affected boys have end-stage renal disease. Treatment includes urethral reconstruction, gradual urethral dilation, or continent urinary diversion.

Urethral Strictures

Urethral strictures in boys usually result from urethral trauma, either iatrogenic (catheterization, endoscopic procedures, previous urethral reconstruction) or accidental (straddle injuries, pelvic fractures). Because these lesions can develop gradually, the decrease in force of the urinary stream is seldom noticed by the child or the parents. More commonly, the obstruction causes symptoms of bladder instability, hematuria, or dysuria. Catheterization of the bladder usually is impossible. The diagnosis is made by a retrograde urethrogram, in which contrast is injected toward the bladder through a catheter inserted into the distal urethra. Ultrasonography also has been used to diagnose urethral strictures. Endoscopy is confirmatory. Endoscopic treatment of short strictures by direct vision urethrotomy is often successful initially and results in a profoundly improved urinary stream, but often the stricture recurs and is found at long-term follow-up. Longer strictures surrounded by periurethral fibrosis often require urethroplasty. Repeated endoscopic procedures generally should be avoided, because they can cause additional urethral damage. Noninvasive measurement of the urinary flow rate and pattern is useful for diagnosis and follow-up.

In girls, true urethral strictures are rare because the female urethra is protected from trauma, particularly in childhood. In the past it was thought that a distal urethral ring commonly caused obstruction of the female urethra and UTI and that affected girls benefited from urethral dilation. The diagnosis was suspected when a "spinning top" deformity of the urethra was found in the VCUG (see Fig. 543-3 in Chapter 543) and was confirmed by urethral calibration. There is no correlation between the radiologic appearance of the urethra in the VCUG and the urethral caliber and no significant difference in urethral caliber between girls with recurrent cystitis and normal age-matched controls. The finding usually is secondary to detrusor–sphincter dyssynergia. Consequently, urethral dilation in girls rarely is indicated.

Anterior Urethral Valves and Urethral Diverticula in the Male

Anterior urethral valves are rare. The obstruction is not obstructing valve leaflets, as occurs in the posterior urethra. Rather, it is a urethral diverticulum in the penile urethra that expands during voiding. Distal extension of the diverticulum causes extrinsic compression of the distal penile urethra, causing urethral obstruction. Typically there is a soft mass on the ventral surface of the penis at the penoscrotal junction. In addition, the urinary stream often is weak, and the physical findings associated with posterior urethral valves often are present. The diverticulum may be small and minimally obstructive, or, in other cases, may be severely obstructive and cause renal insufficiency. The diagnosis is suspected on physical examination and is confirmed by the VCUG. Treatment involves open excision of the diverticulum or transurethral excision of the distal urethral cusp. Urethral diverticula occasionally occur after extensive hypospadias repair.

Fusiform dilation of the urethra or **megalourethra** can result from underdevelopment of the corpus spongiosum and support structures of the urethra. This condition is commonly associated with the prune-belly syndrome.

Male Urethral Meatal Stenosis

See Chapter 544 for information on urethral meatal stenosis in males.

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Chapter 541

Anomalies of the Bladder

Jack S. Elder

BLADDER EXSTROPHY

Exstrophy of the urinary bladder occurs in approximately 1 in 35,000-40,000 births. The male : female ratio is 2 : 1. The severity ranges from simple **epispadias** (in boys) to complete exstrophy of the cloaca involving exposure of the entire hindgut and the bladder (termed **cloacal exstrophy**).

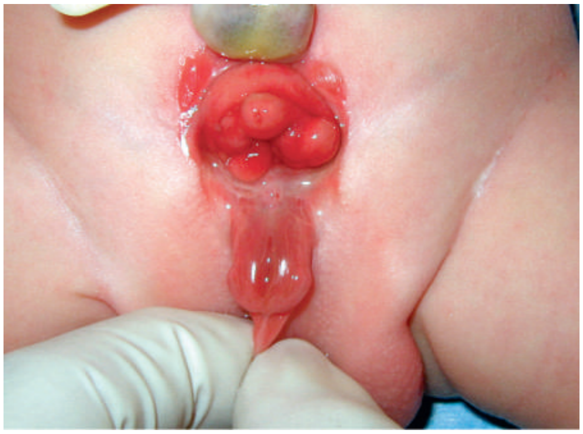

Figure 541-1 Classic bladder exstrophy in a newborn boy. The bladder is exposed in the midline, the umbilical cord is displaced caudad, the penis is epispadiac, and the scrotum is broad.

Clinical Manifestations

Anomalies of the bladder are hypothesized to result when the mesoderm fails to invade the cephalad extension of the cloacal membrane; the extent of this failure determines the degree of the anomaly. In classic bladder exstrophy (Fig. 541-1), the bladder protrudes from the abdominal wall and its mucosa is exposed. The umbilicus is displaced downward, the pubic rami are widely separated in the midline, and the rectus muscles are separated. In boys, there is complete epispadias with dorsal chordee, and the overall penile length is approximately half that of unaffected boys. The scrotum typically is separated slightly from the penis and is wide and shallow. Undescended testes and inguinal hernias are common. Girls also have epispadias, with separation of the 2 halves of the clitoris and wide separation of the labia. The anus is displaced anteriorly in both sexes, and there may be rectal prolapse. The pubic rami are widely separated. Persons with exstrophy tend to be shorter than normal.

The consequences of untreated bladder exstrophy are total urinary incontinence and an increased incidence of bladder cancer, usually adenocarcinoma. The genital deformities can produce sexual disability in both sexes, particularly in males. The wide separation of the pubic rami causes a characteristic broad-based gait but no significant disability. In classic bladder exstrophy, the upper urinary tracts usually are normal.

Treatment

Management of bladder exstrophy should start at birth. The bladder should be covered with plastic wrap to keep the bladder mucosa moist. **Application of gauze or petroleum-gauze to the bladder mucosa should be avoided, because significant inflammation will result.** The infant should be transferred promptly to a center with pediatric urologic and anesthetic support for the treatment of such anomalies. These children are prone to **latex allergy,** so latex precautions should be practiced in their care.

There are 2 surgical approaches: staged reconstruction and total single-stage reconstruction. Most babies also undergo bilateral iliac osteotomy, which allows the pubic symphysis to be approximated, which supports the bladder closure. In a staged reconstruction, the initial stage is bladder closure, the 2nd stage (in boys) is epispadias repair, and the final stage is bladder neck reconstruction. The single-stage reconstruction attempts to reconstruct the entire malformation in a single procedure. When this operation is performed in the newborn, there is an increased risk of intraoperative penile injury and postoperative hydronephrosis, compared with the staged reconstruction. The complication rate is high with both approaches and there is no consensus on which is better.

Although bladder closure within 48 hr has been the standard in the past, more recently, many centers of excellence defer the procedure for 1-2 wk to be certain that the appropriate experienced surgical and anesthetic team is available. During bladder exstrophy closure, the abdominal wall is mobilized and the pubic rami are brought together in the midline following pelvic osteotomy. Early bladder closure can be performed in almost all neonates with classic bladder exstrophy. Treatment should be deferred in selected situations when surgical therapy would be excessively risky or complex, such as in a premature baby or when it would have to be performed by inexperienced surgeons. In the staged approach, in boys, epispadias repair usually is performed at 1-2 yr of age. At this point the child has total urinary incontinence because there is no functional external urinary sphincter. At 3-6 yr, if the bladder is sufficiently large, bladder neck reconstruction is performed to try to create a functional sphincter.

Total single-stage reconstruction includes closure of the bladder, closure of the abdominal wall, and, in boys, correction of epispadias using a technique of penile disassembly, in which the 2 corpora cavernosa and the midline urethra are mobilized separately into 3 parts. Postoperatively, the infant's upper urinary tract is monitored closely for the possible development of hydronephrosis and infection. Most infants with bladder exstrophy have vesicoureteral reflux and should receive antibiotic prophylaxis. The final stage of reconstruction involves creation of a sphincter muscle for bladder control and correction of the vesicoureteral reflux. At this point the child is 3-6 yr old, the bladder capacity should be at least 80-90 mL, and the child must have gained rectal control. Typically, bladder capacity is monitored every 12-24 mo using cystoscopy under anesthesia.

At puberty, often the pubic hair is distributed to the sides of the external genitals. A monsplasty can performed to provide a normal escutcheon.

Long-Term Prognosis

This plan of treatment has yielded a continence rate of 60-70% in a few centers, with <15% deterioration of the upper urinary tract. This continence rate reflects not only the successful reconstruction but also the quality and size of the bladder. The reconstructed bladder neck does not relax during voiding as in a normal child; instead the patient must void by Valsalva. Children who undergo reconstructive surgery as newborns have a greater chance of obtaining a normally functioning bladder.

Children who remain incontinent for more than 1 yr after bladder neck reconstruction or those who are not eligible for bladder neck reconstruction because of a small bladder capacity are candidates for an alternative reconstructive procedure to achieve dryness. In selected cases, cystoscopic injection of dextranomer or polydimethylsiloxane microspheres into the bladder neck can provide sufficient bladder neck coaptation to establish continence. Alternatively, if the child is not a candidate for endoscopic therapy, options include:

- Augmentation cystoplasty, in which the bladder is enlarged with a patch of small or large bowel to increase its capacity.
- Creation of a neobladder out of small and large bowel with placement of a continent abdominal stoma through which clean intermittent catheterization can be performed.
- Placement of an artificial urinary sphincter, with possible augmentation cystoplasty.
- Ureterosigmoidostomy, in which the ureters are detached from the bladder and sutured to the sigmoid colon; individuals void urine and stool from the rectum and rely on their anal sphincter for continence.
- Mainz II procedure, in which the sigmoid colon is reconfigured into a "bladder" into which the ureters are connected, and the patient voids 3-6 times daily through the rectum, and the stool tends to be more solid.

Ureterosigmoidostomy carries a significant risk of chronic pyelonephritis (see Chapter 538), upper urinary tract damage, metabolic acidosis resulting from absorption of hydrogen ion and chloride in the intestine, and at least a 15% long-term risk of colon carcinoma. Patients from less-developed countries often undergo the Mainz II procedure because the continence rate is high and pyelonephritis and upper tract changes are uncommon.

Figure 541-2 Girl with complete epispadias. *(From Gearhart JP, Rink RC, Mouriquand PDE, editors:* Pediatric urology, *ed 2, Philadelphia, 2010, WB Saunders.)*

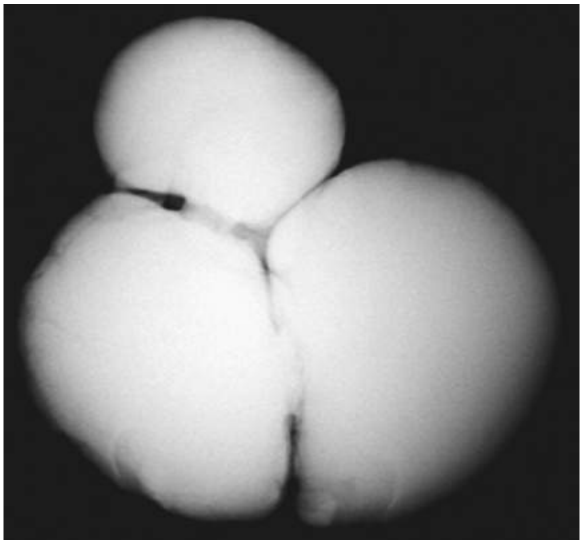

Figure 541-3 Girl with Menkes syndrome with multiple large bladder diverticula causing inability to void and recurrent urinary tract infections. The condition was managed by bladder diverticulectomy.

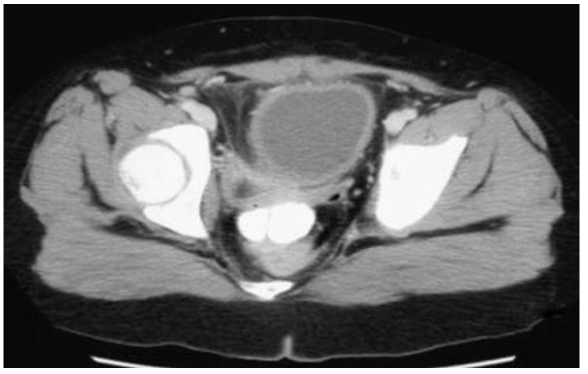

Figure 541-4 CT scan demonstrating infected urachal abscess in an 8 yr old girl. The condition was managed by drainage and excision.

Late follow-up has shown that although men with exstrophy have a penis that is half normal length, they usually experience satisfactory sexual function. Fertility has been low, possibly because of iatrogenic injury to the secondary sexual organs during reconstruction. With artificial reproductive technology, nearly all men can be fertile. In women, fertility is not affected, but uterine prolapse during pregnancy is a problem. In women who have undergone a continent urinary diversion, delivery by cesarean section may be necessary.

OTHER EXSTROPHY ANOMALIES

Children with more complex cases of **cloacal exstrophy,** which has an incidence of 1 in 400,000, have an omphalocele and severe abnormalities of the colon and the rectum and often have short bowel syndrome (see Chapter 338.7), the most devastating anomaly managed by pediatric urologists. Approximately 50% of patients have an upper urinary tract anomaly, and 50% have spina bifida (see Chapter 591). Children with cloacal exstrophy do not achieve normal urine or stool continence. Reconstructive techniques result in a satisfactory outcome in most patients with permanent urinary diversion (either ileal conduit or continent urinary diversion) and a colostomy. Because the penis in boys with cloacal exstrophy usually is diminutive, genital reconstruction in boys with cloacal exstrophy has been unsatisfactory. Until recently, most specialists recommended assigning a female gender to such infants, but currently there is debate whether these children, who have a 46,XY karyotype and androgen imprinting in utero, can have a satisfactory female gender identity (see Chapter 110.2). Many assume male gender characteristics by adolescence. Decisions regarding gender assignment should be made jointly by the physicians caring for the infant (surgical team, pediatric endocrinologist, child psychiatrist, and ethicist) and family.

Epispadias is in the spectrum of exstrophy anomalies, affecting approximately 1 in 117,000 boys and 1 in 480,000 girls. In boys, the diagnosis is obvious because the prepuce is distributed primarily on the ventral aspect of the penile shaft and the urethral meatus is on the dorsum of the penis. Distal epispadias in boys usually is associated with normal urinary control and normal upper urinary tracts and should be repaired by 6-12 mo of age. In girls, the clitoris is bifid and the urethra is split dorsally (Fig. 541-2). In more severely affected boys and in all girls with epispadias, there is total urinary incontinence because the sphincter is incompletely formed, and there is wide separation of the pubic rami. These children require surgical reconstruction of the bladder neck, similar to the final management stage in children with classic bladder exstrophy.

BLADDER DIVERTICULA

Bladder diverticula develop as herniations of bladder mucosa between defects of bladder smooth muscle fibers. Primary bladder diverticula usually develop at the ureterovesical junction and may be associated with vesicoureteral reflux, because the diverticulum interferes with the normal flap-valve attachment between the ureter and bladder. In rare circumstances the diverticulum is so large that it interferes with normal micturition by obstructing the bladder neck. Bladder diverticula also commonly are associated with distal urethral obstruction such as posterior urethral valves or neurogenic bladder dysfunction. They occur commonly in children with connective tissue disorders including Williams syndrome, Ehlers-Danlos syndrome, and Menkes syndrome (Fig. 541-3). Small diverticula require no treatment other than that of the primary disease, whereas large diverticula can contribute to inefficient voiding, residual urine, urinary stasis, and urinary tract infections and should be excised.

URACHAL ANOMALIES

The urachus is an embryologic canal connecting the dome of the fetal bladder with the allantois, a structure that contributes to the formation of the umbilical cord. The lumen of the urachus is normally obliterated during embryonic development, transforming the urachus into a solid cord. Urachal abnormalities are more common in boys than in girls. A **patent urachus** can occur as an isolated anomaly; it may be associated with prune-belly syndrome or posterior urethral valves (see Chapter 540). In this condition there is continuous urinary drainage from the umbilicus. The tract should be excised. Another urachal anomaly is the **urachal cyst**, which can become infected. Typical symptoms and physical findings include suprapubic pain, fever, irritative voiding symptoms, and an infraumbilical mass, which can be erythematous. Diagnosis is made by ultrasonography or CT (Fig. 541-4).

Treatment is intravenous antibiotic therapy and drainage and excision. Other urachal anomalies include the **vesicourachal diverticulum**, which is a diverticulum of the bladder dome, and **umbilical–urachal sinus**, which is a blind external sinus that opens at the umbilicus. These lesions should be excised.

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Chapter 542

Neuropathic Bladder

Jack S. Elder

Neuropathic bladder dysfunction in children usually is congenital, generally resulting from neural tube defects or other spinal abnormalities. Acquired diseases and traumatic lesions of the spinal cord are less common. Central nervous system tumors, sacrococcygeal teratoma, spinal abnormalities associated with imperforate anus (see Chapter 344), and spinal cord trauma also can result in abnormal innervation of the bladder and/or sphincter.

NEURAL TUBE DEFECTS

Neural tube defects, resulting from failure of the neural tube to close spontaneously between the 3rd and 4th wk in utero, result in abnormalities of the vertebral column that affect spinal cord function, including myelomeningocele and meningocele (see Chapter 591). A few medical centers in the United States have been performing antenatal myelomeningocele closure. Long-term results from one large trial (the “MOMS trial”), have not shown a definite improvement in lower urinary tract function, although some children have demonstrated nearly normal bladder function, and overall there has been a significant reduction in the need for ventriculoperitoneal shunting.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The most important urologic consequences of neuropathic bladder dysfunction associated with neural tube defects are urinary incontinence (see Chapter 543), urinary tract infections (UTIs; see Chapter 538), and hydronephrosis from vesicoureteral reflux (see Chapter 539), or detrusor–sphincter dyssynergia (see Chapter 540). Pyelonephritis and renal functional deterioration (see Chapter 535) are common causes of premature death of affected patients.

In the neonate, renal ultrasonography, assessment of postvoid residual urine volumes, and a voiding cystourethrogram are performed after closure of the myelomeningocele. Approximately 10-15% of newborns with myelomeningocele have hydronephrosis, and renal malformations are common; 25% have vesicoureteral reflux. A urodynamic study also should be performed. This study involves filling the bladder with saline, measuring the bladder volume and pressure, and assessing sphincter tone. During bladder filling, the bladder might show (1) uninhibited (premature) contractions (termed hyperreflexia) at low volumes, (2) normal bladder volume with contraction at an appropriate volume, or (3) atonia (lack of bladder contraction). Bladder compliance or elasticity also may be reduced. The sphincter can show (1) normal tonicity with relaxation during bladder contraction, (2) reduced or absent tonicity, or (3) normal or increased tonicity that increases during a bladder contraction (termed detrusor-sphincter dyssynergia) (Fig. 542-1).

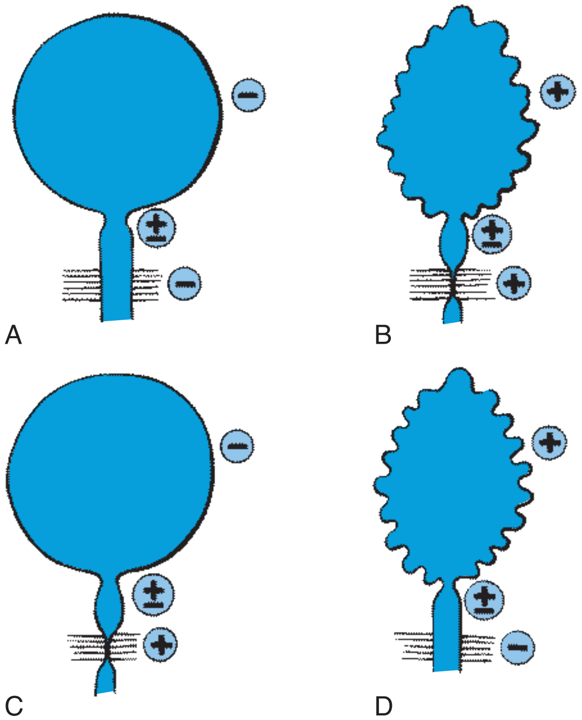

Figure 542-1 **Grouping of neurogenic bladder dysfunction according to the innervation, tonicity, and coordination of the detrusor and sphincters described by Guzman.** This grouping is based on data from imaging studies, cystometrography, and electromyography of the sphincters. Patients in group B are at risk of developing reflux and hydronephrosis. For guidance in the treatment of incontinence, group A benefits from procedures that increase outlet resistance, group B from anticholinergics or bladder augmentation surgery, and group C from intermittent catheterization. Group D requires both increased outlet resistance and pharmacologic or surgical bladder enlargement. Most patients require intermittent catheterization to empty. *(Modified from Gonzalez R: Urinary incontinence. In Kelalis PK, King LR, Belman AB, editors:* Clinical pediatric urology, *Philadelphia, 1992, WB Saunders, p. 387.)*

RENAL DAMAGE

Renal damage usually results from detrusor–sphincter dyssynergia. This dyssynergia causes functional obstruction of the bladder outlet, leading to bladder muscle hypertrophy and trabeculation, high intravesical pressure, and transmission of this high pressure into the upper urinary tracts, causing hydronephrosis (Fig. 542-2). Vesicoureteral reflux and UTI compound the problem. Treatment includes reduction of bladder pressure with anticholinergic drugs (e.g., oxybutynin, 0.2 mg/kg/24 hr in 2 or 3 divided doses) and clean intermittent catheterization every 3-4 hr. If the child has vesicoureteral reflux or UTI, antimicrobial prophylaxis also is prescribed.

Temporary urinary diversion by cutaneous vesicostomy is an alternative in the newborn or infant with severe reflux, if intermittent catheterization is difficult or anticholinergic medications are not well tolerated. Another option to treat the severely trabeculated bladder is transurethral injection of botulinum toxin (Botox) into the detrusor muscle, which reduces bladder hypertonicity for approximately 6 mo. A different approach in these children is to temporarily inactivate the tight sphincter by urethral overdilation or transurethral injection of botulinum toxin into the sphincter. In children with upper tract changes, continuous overnight bladder drainage allows significant bladder relaxation and can reduce bladder wall thickening and lessen hydronephrosis.

Clean intermittent catheterization and anticholinergic therapy cure reflux in up to 80% of children with grade I or II reflux. Children with more severe reflux often require subureteral endoscopic injection therapy (see Chapter 539) or open antireflux surgery followed by intermittent catheterization and anticholinergic drugs. In older children with myelomeningocele with high-grade reflux, UTI, and hydronephrosis, augmentation enterocystoplasty (enlarging the bladder with a

Figure 542-2 Voiding cystourethrogram in an infant with myelodysplasia shows a severely trabeculated bladder with multiple diverticula and grade V (out of V) right vesicoureteral reflux. Evaluation showed severe detrusor–sphincter dyssynergia.

patch of intestine) with intermittent catheterization may be necessary. This intervention allows a normal capacity bladder with low bladder pressure and effective drainage of the bladder.

URINARY INCONTINENCE

Incontinence in the child with neuropathic bladder can result from total or partial denervation of the sphincter, bladder hyperreflexia, poor bladder compliance, chronic urinary retention, or a combination of these factors.

Incontinence often is addressed around 4 yr of age and is tailored to the individual child. Nearly all children require clean intermittent catheterization to stay dry. This technique allows efficient bladder emptying with minimal risk of symptomatic UTI. The urinary tract should be reevaluated with renal ultrasonography, a voiding cystourethrogram, and a urodynamic study, including bladder capacity. If the external sphincter tone is sufficient and the bladder has adequate compliance, intermittent catheterization every 3-4 hr usually is successful in keeping the child dry. If there are unstable bladder contractions, an anticholinergic medication such as oxybutynin chloride, hyoscyamine, or tolterodine is prescribed to increase bladder capacity. If there is sphincter incompetence, α-adrenergic medications are prescribed to enhance outlet resistance. Bacteriuria is seen in up to 50% of children using intermittent self-catheterization, but it seldom causes symptoms. In the absence of reflux, there seems to be little cause for concern. Performing intermittent catheterization with a new catheter (hydrophilic or standard silicone) each time also is quite effective in preventing bacteriuria and avoids the need for antibiotic prophylaxis. With this treatment plan, 40-85% of patients are dry, depending on the definition of continence; some children wear a pad in their underwear or a diaper but feel that they are dry.

If there is persistent incontinence despite medical therapy, reconstructive urinary tract surgery nearly always can provide complete or satisfactory continence. If urethral resistance is low, bladder neck reconstructive procedures such as a periurethral sling often are successful. Alternatively, implantation of an artificial sphincter usually is successful. This sphincter consists of an inflatable cuff that is placed around the bladder neck, a pressure-regulating balloon implanted in the extraperitoneal space, and a pumping mechanism that is implanted in the scrotum of boys and in the labia majora of girls. If the bladder capacity or bladder compliance is low, or if there are persistent uninhibited contractions despite anticholinergic therapy, enlargement of the bladder with a patch of small or large intestine, termed **augmentation cystoplasty** or **enterocystoplasty,** is effective.

These patients still need to perform clean intermittent catheterization. If urethral catheterization is difficult, a continent urinary stoma may be incorporated into the urinary tract reconstruction. A common method is the **Mitrofanoff procedure,** in which the appendix is isolated from the cecum on its vascular pedicle and is interposed between the bladder and abdominal wall to allow intermittent catheterization through a dry stoma. An ileal conduit with a bag on the abdominal wall is rarely used.

Complications of Augmentation Cystoplasty

Urinary Tract Infection

The urine may be colonized with Gram-negative bacteria, and attempts to sterilize the urine for prolonged periods usually fail. There is no evidence that chronic bacteriuria in patients who have had enterocystoplasty is associated with renal damage; therefore, only symptomatic UTIs should be treated.

Metabolic Acidosis

The enteric mucosal surface in contact with the urine absorbs ammonium, chloride, and hydrogen ions and loses potassium. Hyperchloremic metabolic acidosis can result, possibly requiring medical treatment (see Chapter 55). Chronic acidosis can compromise skeletal growth. This condition is common with colocystoplasty but is rare with ileocystoplasty. Metabolic acidosis also is common in patients with compromised renal function. To overcome this limitation of enterocystoplasty in patients with chronic renal insufficiency, a composite augmentation using stomach and small or large bowel gastric segment can be used. The stomach secretes chloride and hydrogen ions; thus, preexisting metabolic acidosis remains stable or improves.

Spontaneous Perforation

Perforation of the augmented bladder is a life-threatening complication that results most often from acute or chronic overdistention of the augmented bladder. Patients with this complication typically present with severe abdominal pain and signs of peritonitis. Prompt diagnosis and treatment with exploratory laparotomy and bladder closure are necessary. Meticulous adherence to the prescribed program of intermittent catheterization to avoid bladder overdistention is important.

Bladder Calculi

Bladder calculi have developed in as many as 70% of children followed for 10 yr after enterocystoplasty. The calculi develop in response to mucus that accumulates in the bladder and act as a nidus for stone formation. This complication can be prevented by daily irrigation of the bladder with sterile saline.

Malignant Neoplasm

Invasive transitional cell carcinoma has been reported in nearly 2% of patients undergoing enterocystoplasty (compared with a 1% risk in spina bifida patients without enterocystoplasty). The pathogenesis is uncertain but is speculated that it is related to bacteriuria and the bowel-bladder contact. The risk seems to be highest following gastrocystoplasty. The risk seems to increase 10 yr following enterocystoplasty. Although these patients probably should undergo screening, there are no guidelines or recommendations regarding this practice. It seems appropriate to advise yearly endoscopic examinations or urine cytologic studies beginning in the 10th postoperative year.

Future Management

The development of a tissue-engineered bladder using a composite scaffold, which could be attached to the dome of the bladder to increase capacity and compliance, might help patients achieve continence

(Fig. 542-3). In addition, there is a nerve-rerouting procedure in which the dorsal nerve root from the lumbar nerve is sutured to the ventral sacral nerve root, allowing the child to scratch the thigh to stimulate a bladder contraction. This procedure is controversial.

ASSOCIATED DISORDERS

Constipation

Many patients with spina bifida also have bowel problems with constipation, and a vigorous bowel regimen is important. Some benefit from the **Malone antegrade continence enema procedure,** in which the appendix is brought out to the skin to allow a catheter to be inserted into the cecum for antegrade enema. The stoma is continent, and an antegrade enema can be performed with tap water each day. This form of management allows the patient to be continent of stool and be more self-sufficient.

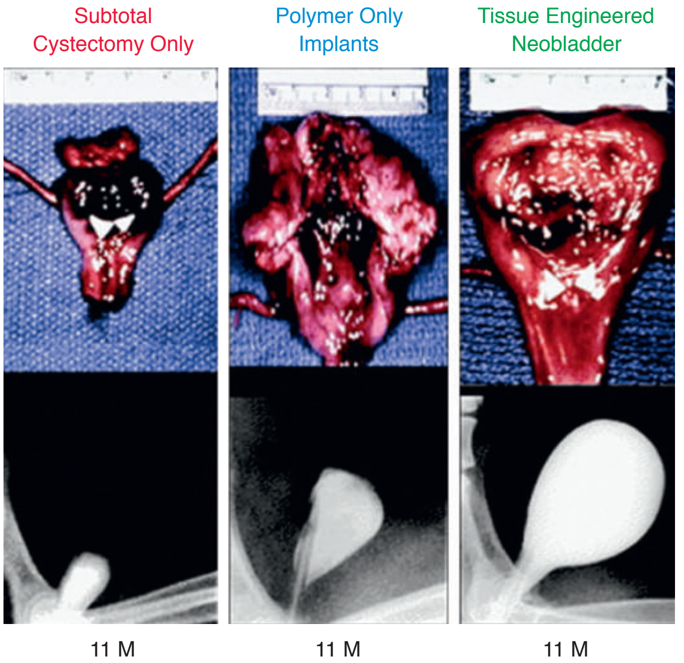

Figure 542-3 Gross specimens and cystograms at 11 mo of the cystectomy-only, nonseeded controls, and cell-seeded tissue engineered bladder replacements in dogs. The cystectomy-only bladder had a capacity of 22% of the preoperative value and a decrease in bladder compliance to 10% of the preoperative value. The nonseeded controls showed significant scarring and had a capacity of 46% of the preoperative value and a decrease in bladder compliance to 42% of the preoperative value. An average bladder capacity of 95% of the original precystectomy volume was achieved in the cell-seeded tissue engineered bladder replacements, and the compliance showed almost no difference from preoperative values that were measured when the native bladder was present (106%). *(From Atala A: Bioengineered tissues for urogenital repair in children,* Pediatr Res *63:569–575, 2008.)*

Latex Allergy

Latex allergy is a very serious problem encountered by as many as half of patients with spina bifida and other urologic conditions who require clean intermittent catheterization and urinary tract reconstructive procedures. This immunoglobulin E–mediated allergy is acquired and is secondary to repeated exposure to the latex allergen. Latex allergy can manifest as watery eyes, sneezing, itching, hives, or anaphylaxis when blowing up a balloon or if an examiner is using latex gloves. Intraoperatively, a sensitized patient can experience anaphylactic shock. A latex-free environment should be provided for all children with spina bifida in the office, during hospitalization, and during operative procedures. Affected children also should wear a medical alert bracelet.

Occult Spinal Dysraphism

Approximately 1 in 4,000 patients have occult spinal dysraphism, a category that includes lipomeningocele, intradural lipoma, diastematomyelia, tight filum terminale, dermoid cyst-sinus, aberrant nerve roots, anterior sacral meningocele, and cauda equina tumor. More than 90% of patients have a cutaneous abnormality overlying the lower spine, including a small dimple, tuft of hair, dermal vascular malformation, or subcutaneous lipoma (Fig. 542-4). Often these children have high-arched feet, discrepancy in muscle size and strength between the legs, and a gait abnormality. Newborns and young infants often have a normal neurologic examination. Older children often have absent perineal sensation and back pain. Lower urinary tract function is abnormal in 40% of patients, including incontinence, recurrent UTI, and fecal soiling. The likelihood of a normal examination is inversely related to the child's age at surgical correction of the spinal lesion. In infants with abnormal urodynamics, 60% revert to normal; in older children, only 27% become normal. Management of the urinary tract in other children is similar to that described earlier for neural tube defects.

Sacral Agenesis

Sacral agenesis is defined as the absence of part or all of ≥2 lower vertebral bodies. This condition is more common in the offspring of women with diabetes. These children have a flattened buttock and a low, short gluteal cleft but usually have no orthopedic deformity, although some have high-arched feet. Palpation of the coccygeal area detects the absent vertebrae. Approximately 20% of cases are undetected until the age of 3-4 yr; many are diagnosed after unsuccessful

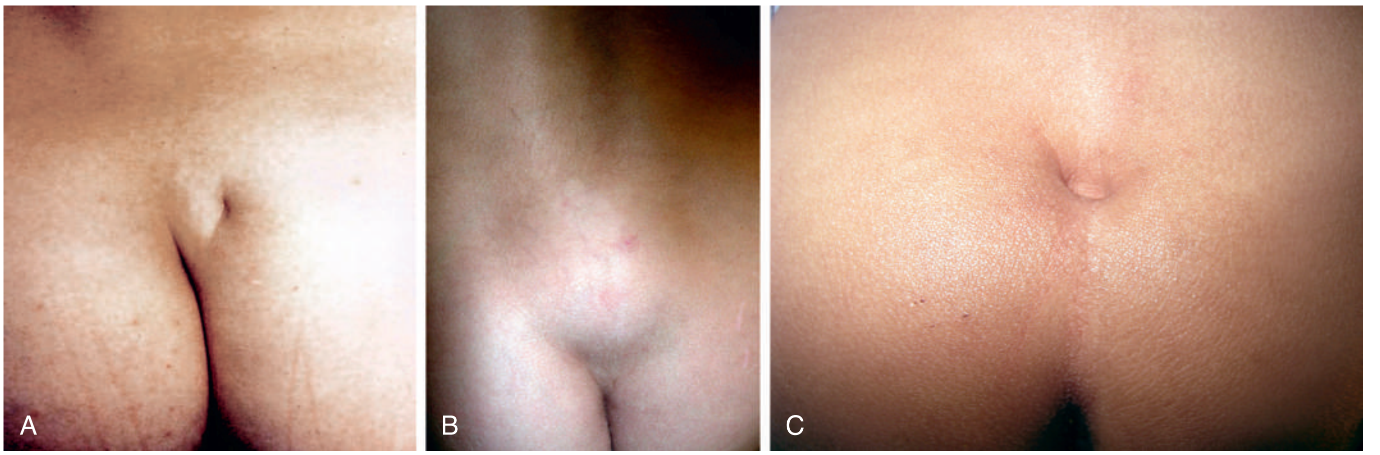

Figure 542-4 A, Buttocks of teenage boy with tethered cord secondary to lipomeningocele. Note sacral dimple and deviation of gluteal fold to the left. **B,** Fat deposit over sacrum in girl with tethered cord secondary to lipomeningocele. **C,** Deep sacral pit in child with neuropathic bladder.

toilet training. Urodynamic studies in these children show a variety of patterns, and most need clean intermittent catheterization and pharmacotherapy to stay dry.

Imperforate Anus

Approximately 30-45% of children with a high imperforate anus have a neuropathic bladder, often because of sacral agenesis. Newborns with imperforate anus should undergo a spinal ultrasound during their initial evaluation, and if these children have difficulty with toilet training, complete urologic evaluation with upper and lower urinary tract imaging and urodynamics should be performed. See Chapter 344 for further details.

Cerebral Palsy

Children with cerebral palsy (see Chapter 598.1) often have reasonable bladder control. However, they achieve continence at a later age than unaffected children. Overall, 25-50% are incontinent, and the risk is directly related to the severity of physical impairment. Their upper urinary tracts usually are normal. Urodynamic studies have shown that most have uninhibited bladder contractions. Timed voiding and anticholinergic therapy are usually effective. Clean intermittent catheterization rarely is necessary.

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Table 543-1	Causes of Urinary Incontinence in Childhood
Overactive bladder (urge incontinence or diurnal urge syndrome) Infrequent voiding (underactive bladder) Voiding postponement Detrusor–sphincter dyssynergia Nonneurogenic neurogenic bladder (Hinman syndrome) Vaginal voiding Giggle incontinence Cystitis Bladder outlet obstruction (posterior urethral valves) Ectopic ureter and fistula Sphincter abnormality (epispadias, exstrophy; urogenital sinus abnormality) Neuropathic Overflow incontinence Traumatic Iatrogenic Behavioral Combinations	

Chapter 543

Enuresis and Voiding Dysfunction

Jack S. Elder

NORMAL VOIDING AND TOILET TRAINING

Fetal voiding occurs by reflex bladder contraction in concert with simultaneous contraction of the bladder and relaxation of the sphincter. Urine storage results from sympathetic and pudendal nerve-mediated inhibition of detrusor contractile activity accompanied by closure of the bladder neck and proximal urethra with increased activity of the external sphincter. The infant has coordinated reflex voiding as often as 15-20 times/day. Over time, bladder capacity increases. In children up to the age of 14 yr, the mean bladder capacity in ounces is equal to the age (in years) plus 2.

At 2-4 yr, the child is developmentally ready to begin toilet training. To achieve conscious bladder control, several conditions must be present: awareness of bladder filling; cortical inhibition (suprapontine modulation) of reflex (unstable) bladder contractions; ability to consciously tighten the external sphincter to prevent incontinence; normal bladder growth; and motivation by the child to stay dry. The transitional phase of voiding refers to the period when children are acquiring bladder control. Girls typically acquire bladder control before boys, and bowel control typically is achieved before bladder control.

A common condition in children is **bladder–bowel dysfunction**. This term was coined by the American Urological Association Vesicoureteral Reflux Guidelines Committee and refers to disorders of bladder and/or bowel function. The previous term for this condition was dysfunctional elimination syndrome.

DIURNAL INCONTINENCE

Daytime incontinence not secondary to neurologic abnormalities is common in children. The most common cause of daytime incontinence is an **overactive bladder (urge incontinence)**. At age 5 yr, 95% have been dry during the day at some time and 92% are dry. At 7 yr, 96% are dry, although 15% have significant urgency at times. At 12 yr, 99% are dry during the day. Table 543-1 lists the causes of diurnal incontinence in children.

The history should assess the pattern of incontinence, including the frequency, the volume of urine lost during incontinent episodes, whether the incontinence is associated with urgency or giggling, whether it occurs after voiding, and whether the incontinence is continuous. The frequency of voiding and whether there is nocturnal enuresis, a strong, continuous urinary stream, or sensation of incomplete bladder emptying should be assessed. A diary of when the child voids and whether the child was wet or dry is helpful. Other urologic problems such as urinary tract infections (UTIs), vesicoureteral reflux, neurologic disorders, or a family history of duplication anomalies should be assessed. Bowel habits also should be evaluated, because incontinence is common in children with constipation and/or encopresis. Diurnal incontinence can occur in girls with a history of sexual abuse. Physical examination is directed at identifying signs of organic causes of incontinence: short stature, hypertension, enlarged kidneys and/or bladder, constipation, labial adhesion, ureteral ectopy, back or sacral anomalies (see Fig. 542-4 in Chapter 542), and neurologic abnormalities.

Assessment tools include urinalysis, with culture if indicated; bladder diary (recorded times and volumes voided, whether wet or dry); postvoid residual urine volume (generally obtained by bladder scan); and **Dysfunctional Voiding Symptom Score** (Fig. 543-1). An alternative to the Dysfunctional Voiding Symptom Score is the **Vancouver Nonneurogenic Lower Urinary Tract Dysfunction/Dysfunctional Elimination Syndrome** questionnaire. This questionnaire is a validated tool that consists of 14 questions scored on a 5-point Likert scale to assess lower urinary tract and bowel dysfunction. In most cases, a uroflow with or without electromyography (noninvasive assessment of urinary flow pattern and measurement of external sphincter activity) is indicated. Another item that may be useful in children older than age 5 yr is the **Pediatric Symptom Checklist (PSC)**. The Pediatric Symptom Checklist is a brief screening questionnaire consisting of 35 questions that is used by pediatricians and other health professionals to improve the recognition and treatment of psychosocial problems in children.

Bowel function should be assessed also. The Bristol Stool Form Score (Fig. 543-2) also should be recorded. In addition, the clinician should utilize the Rome III diagnostic criteria, which classify functional gastrointestinal disorders that do not have underlying structural or tissue-based causes. Children 4 yr of age or older are diagnosed as being

Patient name:
Hospital number:
Reason for referral:
Date:

Over the last month	Almost never	Less than half the time	About half the time	Almost every time	Not available
1. I have had wet clothes or wet underwear during the day.	0	1	2	3	NA
2. When I wet myself, my underwear is soaked.	0	1	2	3	NA
3. I miss having a bowel movement every day.	0	1	2	3	NA
4. I have to push for my bowel movements to come out.	0	1	2	3	NA
5. I only go to the bathroom one or two times each day.	0	1	2	3	NA
6. I can hold onto my pee by crossing my legs, squatting or doing the "pee dance."	0	1	2	3	NA
7. When I have to pee, I cannot wait.	0	1	2	3	NA
8. I have to push to pee.	0	1	2	3	NA
9. When I pee it hurts.	0	1	2	3	NA
10. Parents to answer. Has your child experienced something stressful like the example below?	No (0)			Yes (3)	
Total*					

- New baby.
- New home.
- New school.
- School problems.
- Abuse (sexual/physical).
- Home problems (divorce/death).
- Special events (birthday).
- Accident/injury.
- Others.

*Females with a score ≥6 and males with a score ≥9 are most likely to have dysfunctional voiding.

Figure 543-1 Dysfunctional Voiding Symptom Score questionnaire. *(From Farhat W, Bagli DJ, Capolicchio G, et al: The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children,* J Urol *164:1011–1015, 2000.)*

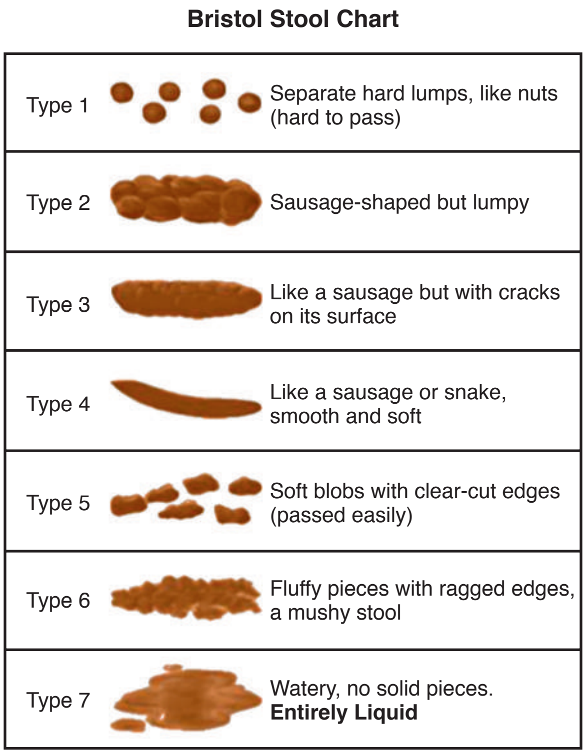

Figure 543-2 Bristol Stool Chart for evaluating bowel function.

constipated if they fulfill 2 or more of the following criteria over a period of 2 mo: 2 or fewer defecations in the toilet per week, at least 1 episode of fecal incontinence per week, a history of retentive posturing or excessive volitional stool retention, history of painful or hard bowel movements, presence of a large fecal mass in the rectum, and history of large-diameter stools that obstruct the toilet.

Imaging is performed in children who have significant physical findings, a family history of urinary tract anomalies or UTIs, and those who do not respond to therapy appropriately. A renal ultrasonogram with or without a **voiding cystourethrogram** is indicated. Urodynamics should be performed if there is evidence of neurologic disease and may be helpful if empirical therapy is ineffective. If there is any evidence of a neurologic disorder, an MRI of the lower spine should be obtained.

OVERACTIVE BLADDER (DIURNAL URGE SYNDROME)

Children with an overactive bladder typically exhibit urinary frequency, urgency, and urge incontinence. Often a girl will squat down on her foot to try to prevent incontinence (termed *Vincent's curtsy*). The bladder in these children is functionally, but not anatomically, smaller than normal and exhibits strong uninhibited contractions. Approximately 25% of children with nocturnal enuresis also have symptoms of an overactive bladder. Many children indicate they do not feel the need to urinate, even just before they are incontinent. In girls, a history of recurrent UTI is common, but incontinence can persist long after infections are brought under control. It is not clear if the voiding dysfunction is a sequela of the UTIs or if the voiding dysfunction predisposes to recurrent UTIs. In girls, voiding cystourethrography often shows a dilated urethra ("spinning-top deformity," Fig. 543-3) and narrowed bladder neck with bladder wall hypertrophy. The urethral finding results from inadequate relaxation of the external

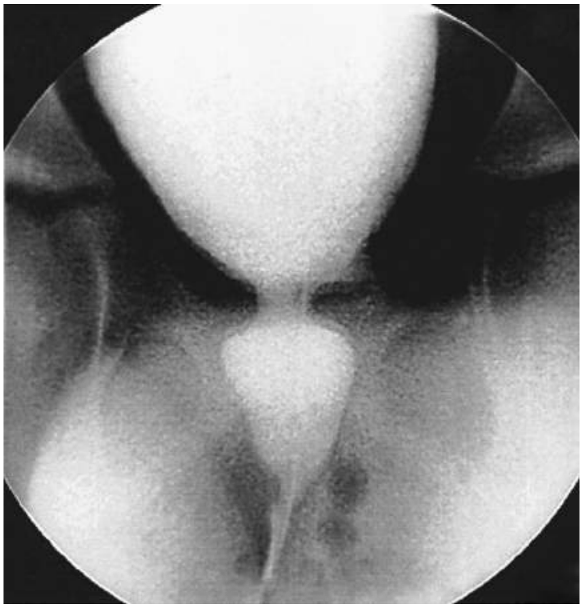

Figure 543-3 **Spinning-top deformity.** Voiding cystourethrogram demonstrating dilation of the urethra with distal urethral narrowing and contraction of the bladder neck.

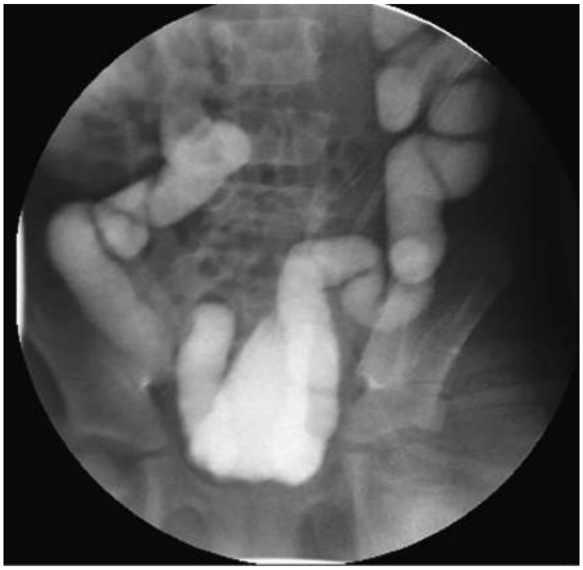

Figure 543-4 Voiding cystourethrogram demonstrating severe bladder trabeculation and vesicoureteral reflux in a 12 yr old boy with Hinman syndrome. The patient presented with day and night incontinence, had chronic renal failure, and underwent kidney transplantation.

urinary sphincter. Constipation is common and should be treated, particularly with any child with Bristol Stool Score 1 or 2.

The overactive bladder nearly always resolves, but the time to resolution is highly variable, sometimes not until the teenage years. Initial therapy is timed voiding, every 1.5-2.0 hr. Treatment of constipation and UTIs is important. Another treatment is biofeedback, in which children are taught pelvic floor exercises **(Kegel exercises)**, because there is evidence that daily performance of these exercises can reduce or eliminate unstable bladder contractions. Biofeedback often includes participation with animated computer games. Biofeedback also may include periodic uroflow studies with sphincter electromyography to be certain that the pelvic floor relaxes during voiding, and assessment of postvoid residual urine volume by sonography. Anticholinergic therapy with oxybutynin chloride, hyoscyamine, or tolterodine reduces bladder overactivity and may help the child achieve dryness. Treatment with an α-adrenergic blocker such as terazosin or doxazosin can aid in bladder emptying by promoting bladder neck relaxation; α-adrenergic blockers also have mild anticholinergic properties. If pharmacologic therapy is successful, the dosage should be tapered periodically to determine its continued need. Children who do not respond to therapy should be evaluated urodynamically to rule out other possible forms of bladder or sphincter dysfunction. In refractory cases, sacral nerve stimulation (InterStim) is a surgical procedure that has shown promise.

If the child has constipation based on the criteria described above, treatment generally is initiated with polyethylene glycol powder, which has been shown to be safe in children and generally more effective than other laxative preparations.

NONNEUROGENIC NEUROGENIC BLADDER (HINMAN SYNDROME)

Hinman syndrome is a very serious but uncommon disorder involving failure of the external sphincter to relax during voiding in children without neurologic abnormalities. Children with this syndrome, also called **nonneurogenic neurogenic bladder**, typically exhibit a staccato stream, day and night wetting, recurrent UTIs, constipation, and encopresis. Evaluation of affected children often reveals vesicoureteral reflux, a trabeculated bladder, and a decreased urinary flow rate with an intermittent pattern (Fig. 543-4). In severe cases, hydronephrosis, renal insufficiency, and end-stage renal disease can occur. The pathogenesis of this syndrome is thought to involve learning abnormal voiding habits during toilet training; the syndrome is rarely seen in infants. Urodynamic studies and magnetic resonance imaging of the spine are indicated to rule out a neurologic cause for the bladder dysfunction.

The treatment usually is complex and can include anticholinergic and α-adrenergic blocker therapy, timed voiding, treatment of constipation, behavioral modification, and encouragement of relaxation during voiding. Biofeedback has been used successfully in older children to teach relaxation of the external sphincter. In some cases botulinum toxin (Botox) injection into the external sphincter can provide temporary sphincteric paralysis and thereby reduce outlet resistance. In severe cases, intermittent catheterization is necessary to ensure bladder emptying. In selected patients, external urinary diversion is necessary to protect the upper urinary tract. These children require long-term treatment and careful follow-up.

INFREQUENT VOIDING (UNDERACTIVE BLADDER)

Infrequent voiding is a common disorder of micturition, usually associated with UTIs. Affected children, usually girls, void only twice a day rather than the normal 4-7 times. With bladder overdistention and prolonged retention of urine, bacterial growth can lead to recurrent UTIs. Some of these children are constipated. Some also have occasional episodes of incontinence from overflow or urgency. The disorder is behavioral. If the child has UTIs, treatment includes antibacterial prophylaxis and encouragement of frequent voiding and complete emptying of the bladder by double voiding until a normal pattern of micturition is re-established.

VAGINAL VOIDING

In girls with vaginal voiding, incontinence typically occurs after urination after the girl stands up. Usually the volume of urine is 5-10 mL. One of the most common causes is labial adhesion (Fig. 543-5). This lesion, typically seen in young girls, can be managed either by topical application of estrogen cream to the adhesion or lysis in the office. Some girls experience vaginal voiding because they do not separate their legs widely during urination. These girls either are overweight

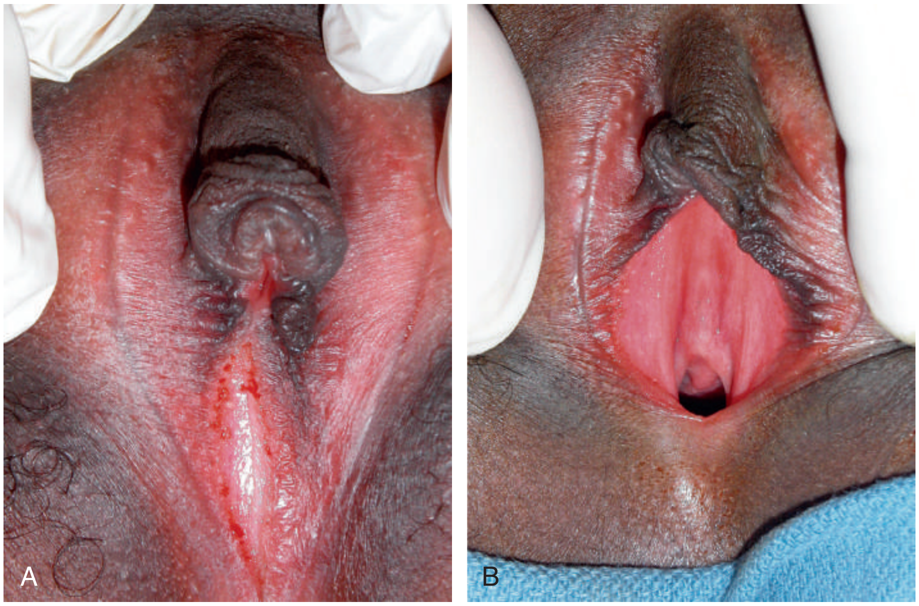

Figure 543-5 **A,** Labial adhesion. Note the inability to visualize the urethral meatus and vagina. **B,** Normal female external genitalia following lysis of labial adhesion.

or do not pull their underwear down to their ankles when they urinate. Management involves encouraging the girl to separate the legs as widely as possible during urination. The most effective way to do this is to have the child sit backward on the toilet seat during micturition.

OTHER CAUSES OF INCONTINENCE IN GIRLS

Ureteral ectopia, usually associated with a duplicated collecting system in girls, refers to a ureter that drains outside the bladder, often into the vagina or distal urethra. It can produce urinary incontinence characterized by constant urinary dripping all day, even though the child voids regularly. Sometimes the urine production from the renal segment drained by the ectopic ureter is small, and urinary drainage is confused with watery vaginal discharge. Children with a history of vaginal discharge or incontinence and an abnormal voiding pattern require careful study. The ectopic orifice usually is difficult to find. On ultrasonography or intravenous urography, one may suspect duplication of the collecting system (Fig. 543-6), but the upper collecting system drained by the ectopic ureter usually has poor or delayed function. CT scanning of the kidneys or an MR urogram should demonstrate subtle duplication anomalies. Examination under anesthesia for an ectopic ureteral orifice in the vestibule or the vagina may be necessary (Fig. 543-7). The treatment in these cases is either partial nephrectomy, with removal of the upper pole segment of the duplicated kidney and its ureter down to the pelvic brim, or ipsilateral ureteroureterostomy, in which the upper pole ectopic ureter is anastomosed to the normally positioned lower pole ureter. These procedures often are performed by minimally invasive laparoscopy with or without robotic assistance.

Giggle incontinence typically affects girls 7-15 yr of age. The incontinence occurs suddenly during giggling, and the entire bladder volume is lost. The pathogenesis is thought to be sudden relaxation of the urinary sphincter. Anticholinergic medication and timed voiding occasionally are effective. The most effective treatment is low-dose methylphenidate.

Total incontinence in girls may be secondary to **epispadias** (see Fig. 541-2 in Chapter 541). This condition, which affects only 1 in 480,000 females, is characterized by separation of the pubic symphysis, separation of the right and left sides of the clitoris, and a patulous urethra. Treatment is bladder neck reconstruction or placement of an artificial urinary sphincter to repair the incompetent urethra.

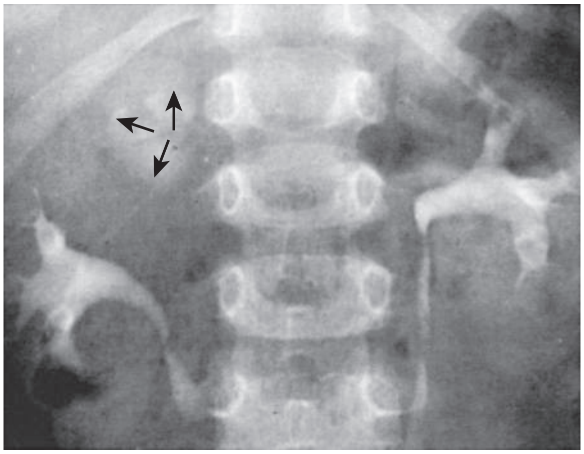

Figure 543-6 **Duplication of the right collecting system with ectopic ureter.** Excretory urogram in a girl presenting with a normal voiding pattern and constant urinary dribbling. The left kidney is normal, and the right side, well visualized, is the lower collecting system of a duplicated kidney. On the upper pole opposite the 1st and 2nd vertebral bodies, note the accumulation of contrast material corresponding with a poorly functioning upper pole drained by a ureter opening in the vestibule.

A short, incompetent urethra may be associated with certain urogenital sinus malformations. The diagnosis of these malformations requires a high index of suspicion and a careful physical examination of all incontinent girls. In these cases, urethral and vaginal reconstruction often restores continence.

VOIDING DISORDERS WITHOUT INCONTINENCE

Some children have abrupt onset of severe urinary frequency, voiding as often as every 10-15 min during the day, without dysuria, UTI, daytime incontinence, or nocturia. The most common age for these symptoms to occur is 4-6 yr, after the child is toilet trained, and the vast majority are boys. This condition is termed the **daytime frequency syndrome of childhood** or **pollakiuria**. The condition is functional;

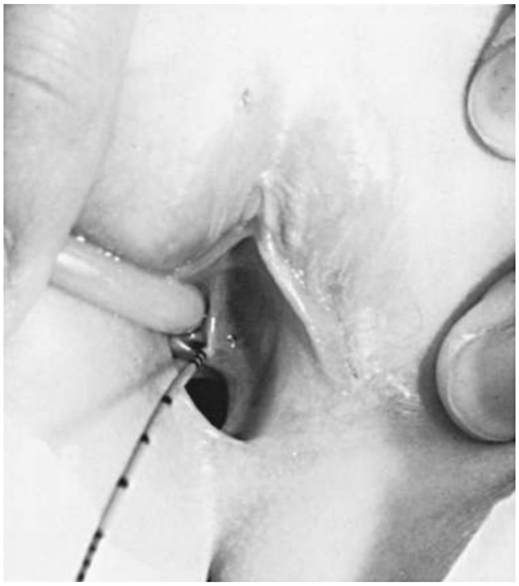

Figure 543-7 This photograph shows an ectopic ureter entering the vestibule next to the urethral meatus. The thin ureteral catheter with transverse marks has been introduced into this ectopic ureter. This girl had a normal voiding pattern and constant urinary dribbling.

Table 543-2	Nocturnal Enuresis
CAUSES	
Delayed maturation of the cortical mechanisms that allow voluntary control of the micturition reflex	
Defective sleep arousal	
Reduced antidiuretic hormone production at night, resulting in an increased urine output (nocturnal polyuria)	
Genetic factors, with chromosomes 12 and 13q the likely sites of the gene for enuresis	
Bladder factors (lack of inhibition, reduced capacity, overactive)	
Constipation	
Organic factors, such as urinary tract infection or obstructive uropathy	
Sleep disorders	
Sleep disordered breathing secondary to enlarged adenoids	
Psychologic factors more often implicated in secondary enuresis	
OTHER FEATURES	
Enuresis can occur in any stage of sleep (but usually non–rapid eye movement sleep)	
All children are most difficult to arouse in the first third of the night and easiest to awaken in the last third, but enuretic children are more difficult to arouse than those with normal bladder control	
Enuretic children often are described as "soaking the bed"	
Family history in enuretic children often positive for enuresis	
Risk increased with developmental delay, attention-deficit/hyperactivity disorder, autism spectrum disorders	

no anatomic problem is detected. Often the symptoms occur just before a child starts kindergarten or if the child is having emotional family stress-related problems. These children should be checked for UTIs, and the clinician should ascertain that the child is emptying the bladder satisfactorily. Occasionally, pinworms cause these symptoms. The condition is self-limited, and symptoms generally resolve within 2-3 mo. Anticholinergic therapy rarely is effective.

Some children have the **dysuria-hematuria syndrome**, in which the child has dysuria without UTI but with microscopic or gross hematuria. This condition affects children who are toilet-trained and is often secondary to hypercalciuria. A 24-hr urine sample should be obtained and calcium and creatinine excretion assessed. A 24-hr calcium excretion of >4 mg/kg is abnormal and deserves treatment with thiazides, because some of these children are at risk for urolithiasis.

NOCTURNAL ENURESIS

By 5 yr of age, 90-95% of children are nearly completely continent during the day, and 80-85% are continent at night. Nocturnal enuresis refers to the occurrence of involuntary voiding at night after 5 yr, the age when volitional control of micturition is expected. Enuresis may be primary (estimated 75-90% of children with enuresis; nocturnal urinary control never achieved) or secondary (10-25%; the child was dry at night for at least a few months and then enuresis developed). In addition, 75% of children with enuresis are wet only at night, and 25% are incontinent day and night. This distinction is important, because children with both forms are more likely to have an abnormality of the urinary tract. **Monosymptomatic enuresis** is more common than non-monosymptomatic enuresis (associated urgency, hesitancy, frequency, day time incontinence).

Epidemiology

Approximately 60% of children with nocturnal enuresis are boys. Family history is positive in 50% of cases. Although primary nocturnal enuresis may be polygenetic, candidate genes have been localized to chromosomes 12 and 13. If one parent was enuretic, each child has a 44% risk of enuresis; if both parents were enuretic, each child has a 77% likelihood of enuresis. Nocturnal enuresis without overt daytime voiding symptoms affects up to 20% of children at the age of 5 yr; it ceases spontaneously in approximately 15% of involved children every year thereafter. Its frequency among adults is <1%.

Pathogenesis

The pathogenesis of nocturnal enuresis (normal daytime voiding habits) is multifactorial (Table 543-2).

Clinical Manifestations and Diagnosis

A careful history should be obtained, especially with respect to fluid intake at night and pattern of nocturnal enuresis. Children with diabetes insipidus (see Chapter 558), diabetes mellitus (see Chapter 589), and chronic renal disease (see Chapter 535) can have a high obligatory urinary output and a compensatory polydipsia. The family should be asked whether the child snores loudly at night. A complete physical examination should include palpation of the abdomen and rectal examination after voiding to assess the possibility of a chronically distended bladder. The child with nocturnal enuresis should be examined carefully for neurologic and spinal abnormalities. There is an increased incidence of bacteriuria in enuretic girls, and, if found, it should be investigated and treated (see Chapter 538), although this does not always lead to resolution of bedwetting. A urine sample should be obtained after an overnight fast and evaluated for specific gravity or osmolality to exclude polyuria as a cause of frequency and incontinence and to ascertain that the concentrating ability is normal. The absence of glycosuria should be confirmed. If there are no daytime symptoms, the physical examination and urinalysis are normal, and the urine culture is negative, further evaluation for urinary tract pathology generally is not warranted. A renal ultrasonogram is reasonable in an older child with enuresis or in children who do not respond appropriately to therapy.

Treatment

The best approach to treatment is to reassure the child and parents that the condition is self-limited and to avoid punitive measures that can affect the child's psychologic development adversely. Fluid intake should be restricted to 2 oz after 6 or 7 PM. The parents should be certain that the child voids at bedtime. Avoiding extraneous sugar and caffeine after 4 PM also is beneficial. If the child snores and the adenoids are enlarged, referral to an otolaryngologist should be considered, because adenoidectomy can cure the enuresis.

Active treatment should be avoided in children younger than 6 yr of age, because enuresis is extremely common in younger children. Treatment is more likely to be successful in children approaching puberty compared with younger children. In addition, treatment is most likely to be effective in children who are motivated to stay dry. Treatment should be viewed as a facilitator that requires active participation by the child (e.g., a coach and an athlete).

The simplest initial measure is **motivational therapy** and includes a star chart for dry nights. Waking children a few hours after they go to sleep to have them void often allows them to awaken dry, although this measure is not curative. Some have recommended that children try holding their urine for longer periods during the day, but there is no evidence that this approach is beneficial. **Conditioning therapy** involves use of a loud auditory or vibratory alarm attached to a moisture sensor in the underwear. The alarm sounds when voiding occurs and is intended to awaken children and alert them to void. This form of therapy has a reported success of 30-60%, although the relapse rate is significant. Often the auditory alarm wakes up other family members and not the enuretic child; persistent use of the alarm for several months often is necessary to determine whether this treatment is effective. Conditioning therapy tends to be most effective in older children. Another form of therapy to which some children respond is self-hypnosis. The primary role of psychologic therapy is to help the child deal with enuresis psychologically and help motivate the child to void at night if he or she awakens with a full bladder.

Pharmacologic therapy is intended to treat the symptom of enuresis and thus is regarded as second line and is not curative. Direct comparisons of the bell and bed with pharmacologic therapy favor the former because of lower relapse rates, although initial response rates are equivalent.

One form of treatment is **desmopressin acetate**, a synthetic analog of antidiuretic hormone that reduces urine production overnight. This medication is FDA-approved and is available as a tablet, with a dosage of 0.2-0.6 mg at bedtime. In the past a nasal spray was used, but some children experienced hyponatremia and convulsions with this formulation and the nasal spray is no longer recommended for nocturnal enuresis. Hyponatremia has not been reported in children using the oral tablets. Fluid restriction at night is important, and the drug should not be used if the child has a systemic illness with vomiting or diarrhea or if the child has polydipsia. Desmopressin acetate is effective in as many as 40% of children. If effective, it should be used for 3-6 mo, and then an attempt should be made to taper the dosage. If tapering results in recurrent enuresis, the child should return to the higher dosage. Few adverse events have been reported with the long-term use of desmopressin acetate.

For therapy-resistant enuresis or children with symptoms of an overactive bladder, **anticholinergic therapy** is indicated. Oxybutynin 5 mg or tolterodine 2 mg at bedtime often are prescribed. If the medication is ineffective, the dosage may be doubled. The clinician should monitor for constipation as a potential side effect.

A third-line treatment is **imipramine**, which is a tricyclic antidepressant. This medication has mild anticholinergic and α-adrenergic effects, reduces urine output slightly, and also might alter the sleep pattern. The dosage of imipramine is 25 mg in children age 6-8 yr, 50 mg in children age 9-12 yr, and 75 mg in teenagers. Reported success rates are 30-60%. Side effects include anxiety, insomnia, and dry mouth, and heart rhythm may be affected. If there is any history of palpitations or syncope in the child, or sudden cardiac death or unstable arrhythmia in the family, long QT syndrome in the patient needs to be excluded. The drug is one of the most common causes of poisoning by prescription medication in younger siblings.

In unsuccessful cases, combining therapies often is effective. Alarm therapy plus desmopressin is more successful than either alone. The combination of oxybutynin chloride and desmopressin is more successful than either alone. Desmopressin and imipramine also may be combined.

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Chapter 544

Anomalies of the Penis and Urethra

Jack S. Elder

HYPOSPADIAS

Hypospadias is a urethral opening on the ventral surface of the penile shaft affecting 1 in 250 male newborns. Typically an isolated defect, but its incidence is increased in disorders of sex differentiation, anorectal malformation, and congenital heart disease. Usually there is incomplete development of the prepuce, called a **dorsal hood**, in which the foreskin is on the sides and dorsal aspect of the penile shaft and deficient or absent ventrally. Some boys with hypospadias, particularly those with proximal hypospadias, have **chordee**, in which there is ventral penile curvature during erection. The incidence of hypospadias appears to be increasing, possibly because of in utero exposure to estrogenic or antiandrogenic endocrine-disrupting chemicals (e.g., polychlorobiphenyls, phytoestrogens).

Clinical Manifestations

Hypospadias is classified according to the position of the urethral meatus after taking into account whether chordee is present (Fig. 544-1). The deformity is described as glanular (on the glans penis), coronal, subcoronal, midpenile, penoscrotal, scrotal, or perineal. Approximately 65% of cases are distal, 25% are subcoronal or midpenile, and 10% are proximal. In the most severe cases, the scrotum is bifid and sometimes there is moderate penoscrotal transposition. As many as 10% of affected boys have a **megameatal variant**, in which the foreskin is developed normally (megameatus intact prepuce variant), and there is either glanular or subcoronal hypospadias with a “fish mouth” meatus. These cases might not be diagnosed until after a circumcision is performed.

Approximately 10% of boys with hypospadias have an undescended testis; inguinal hernias also are common. In the newborn, the differential diagnosis of midpenile or proximal hypospadias associated with an undescended testis should include forms of a disorder of sex development, particularly mixed gonadal dysgenesis, partial androgen insensitivity, true hermaphroditism, and congenital adrenal hyperplasia in a female (see Chapter 576). In the latter situation, neither gonad would be palpable. A karyotype should be obtained in patients with midpenile or proximal hypospadias and cryptorchidism (see Chapter 588). In boys with penoscrotal hypospadias, a voiding cystourethrogram should be considered because 5-10% of these children have a dilated prostatic utricle, which is a remnant of the müllerian system (see Chapter 554). The incidence of upper urinary tract abnormalities is low unless there are abnormalities of other organ systems.

Complications of untreated hypospadias include deformity of the urinary stream, typically ventral deflection or severe splaying; sexual dysfunction secondary to penile curvature; infertility if the urethral meatus is proximal; meatal stenosis (congenital), which is uncommon; and cosmetic appearance. The goal of hypospadias surgery is to correct the functional and cosmetic deformities. Whereas hypospadias repair is recommended for all boys with midpenile and proximal hypospadias, some boys with distal hypospadias have no functional abnormality and do not need any surgical correction.

Treatment

Management begins in the newborn period. Circumcision should be avoided, because the foreskin often is used in the repair in most cases. The ideal age for repair in a healthy infant is 6-12 mo, because the risk of general anesthesia at this age is similar to older children; penile growth over the next several years is slow; the child does not remember the surgical procedure; and postoperative analgesic needs are less than

Figure 544-1 Varying forms of hypospadias. **A,** Glanular hypospadias. **B,** Subcoronal hypospadias. Note the dorsal hood of foreskin. **C,** Penoscrotal hypospadias with chordee. **D,** Perineal hypospadias with chordee and partial penoscrotal transposition. **E,** Megameatal variant of hypospadias diagnosed following circumcision; note absence of hooded foreskin. **F,** Complete penoscrotal transposition with scrotal hypospadias.

in older children. With the exception of proximal hypospadias, virtually all cases are repaired in a single operation on an ambulatory basis. The most common repair involves tubularization of the urethral plate distal to the urethral meatus, with coverage by a vascularized flap from the foreskin, termed a *tubularized incised plate* repair. Proximal cases might require a 2-stage repair. The complication rate is low: 5% for distal hypospadias, 10% for midpenile hypospadias, and 20% for proximal hypospadias. The most common complications include urethrocutaneous fistula and meatal stenosis. Other complications include a deformed urinary stream, persistent penile curvature, and dehiscence of the hypospadias repair. Treatment of these complications generally is straightforward. In complex cases, a buccal mucosa graft is used to create urethral mucosa. Repair of hypospadias is a technically demanding operation and should be performed by a surgeon with specialty training in pediatric urology and extensive experience.

CHORDEE WITHOUT HYPOSPADIAS

In some boys there is mild or moderate ventral penile curvature **(chordee)** and incomplete development of the foreskin **(dorsal hood)**, but the urethral meatus is at the tip of the glans (Fig. 544-2). In most of these boys, the urethra is normal but there is insufficient ventral penile skin or prominent, inelastic ventral bands of dartos fascia that prevent a straight erection. In some cases, the urethra is hypoplastic, and a formal urethroplasty is necessary for repair. The only sign of this anomaly in the neonate may be the hooded foreskin, and delayed repair under general anesthesia at 6 mo of age is recommended.

PHIMOSIS AND PARAPHIMOSIS

Phimosis refers to the inability to retract the prepuce. At birth, phimosis is physiologic. Over time, the adhesions between the prepuce and glans lyse and the distal phimotic ring loosens. In 80% of uncircumcised boys the prepuce becomes retractable by 3 yr of age. Accumulation of epithelial debris under the infant's prepuce is physiologic and does not mandate circumcision. In older boys, phimosis may be physiologic, may be pathologic from inflammation and scarring at the tip of the foreskin (Fig. 544-3), or occurs after circumcision. The prepuce might have been retracted forcefully on 1 or 2 occasions in the past, which can result in a cicatricial scar that prevents subsequent retraction of the foreskin. In boys with persistent physiologic or pathologic phimosis, application of corticosteroid cream to the foreskin 3 times daily for 1 mo loosens the phimotic ring in two-thirds of cases. If there is ballooning of the foreskin during voiding or phimosis beyond 10 yr of age and topical corticosteroid therapy is ineffective, circumcision is recommended.

Paraphimosis occurs when the foreskin is retracted proximal to the coronal sulcus and the prepuce cannot be pulled back over the glans

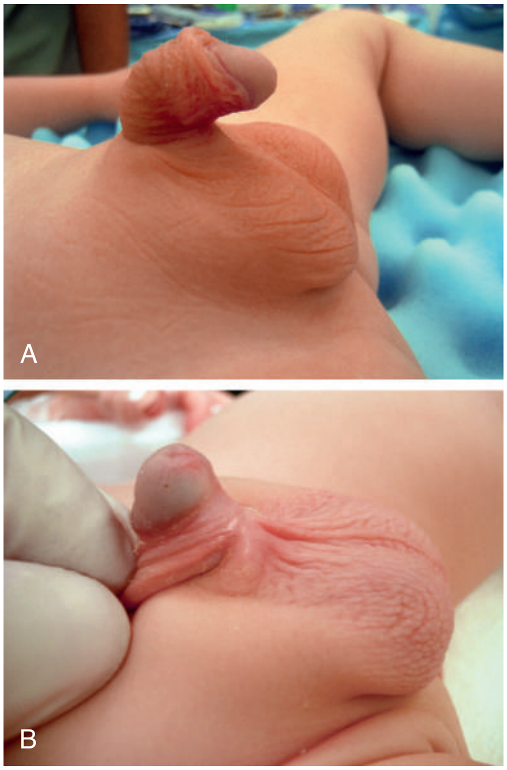

Figure 544-2 **A** and **B,** Two examples of chordee without hypospadias. Note hooded foreskin and normal location of urethral meatus.

Figure 544-3 **Balanitis xerotica obliterans.** Note whitish cicatricial plaque.

(Fig. 544-4). Painful venous stasis in the retracted foreskin results, with edema leading to severe pain and inability to reduce the foreskin (pull it back over the glans). Treatment includes lubricating the foreskin and glans and then simultaneously compressing the glans and placing distal traction on the foreskin to try to push the phimotic ring past the coronal sulcus. Topical application of granulated sugar has been reported to aid in reduction of edema by creation of an osmotic gradient, facilitating reduction of paraphimosis. In addition, injection of

Figure 544-4 **Paraphimosis.** The foreskin has been retracted proximal to the glans penis and has become markedly swollen secondary to venous congestion.

hyaluronidase into the edematous skin has been reported to result in immediate reduction in swelling. In rare cases, emergency circumcision under general anesthesia is necessary.

CIRCUMCISION

In the United States, circumcision usually is performed for cultural reasons. In 2012, a multidisciplinary task force of the American Academy of Pediatrics stated that evidence indicates that the health benefits of newborn male circumcision outweigh the risks and that the procedure's benefits justify access to this procedure for families who choose it. Specific benefits identified included prevention of urinary tract infections (UTIs), penile cancer, reducing the risk and transmission of some sexually transmitted infections, including HIV. The American College of Obstetricians and Gynecologists endorsed this policy statement. By contrast, European medical professional groups have been less likely to endorse this practice.

When performing a neonatal circumcision, local analgesia, such as a dorsal nerve block or application of EMLA (eutectic mixture of local anesthetics) cream (lidocaine 2.5% and prilocaine 2.5%) is recommended.

UTIs are 10-15 times more common in uncircumcised infant boys than in circumcised infants, with the urinary pathogens arising from bacteria that colonize the space between the prepuce and glans. The risk of febrile UTI (see Chapter 538) is highest between birth and 6 mo, but there is an increased risk of UTI until at least 5 yr of age. Many recommend circumcision in infants who are predisposed to UTI, such as those with congenital hydronephrosis and vesicoureteral reflux. Circumcision reduces the risk of sexually transmitted infections in adults (see Chapter 120), in particular HIV (see Chapter 276). There have been only a handful of reports of men who were circumcised at birth and subsequently acquired penile carcinoma, but in Scandinavian countries, where few men are circumcised and hygiene is good, the incidence of penile cancer is low.

Complications after neonatal circumcision include bleeding, wound infection, meatal stenosis, secondary phimosis, removal of insufficient foreskin, and fibrous penile adhesions (skin bridge; Fig. 544-5); 0.2-3.0% of patients undergo a subsequent operative procedure. Boys with a large hydrocele or hernia are at particular risk for secondary phimosis because the scrotal swelling tends to displace the penile shaft skin over the glans. Potentially serious complications include sepsis, amputation of the distal part of the glans, removal of an excessive amount of foreskin, and urethrocutaneous fistula. Circumcision should not be performed in neonates with hypospadias, chordee without hypospadias, or a dorsal hood deformity (relative contraindication) or in those with

Figure 544-5 Complications of circumcision. **A,** Denuded penile shaft. With local care, the penis healed and appeared normal. **B,** Midline epithelial inclusion cyst. **C,** Fibrous penile skin bridges.

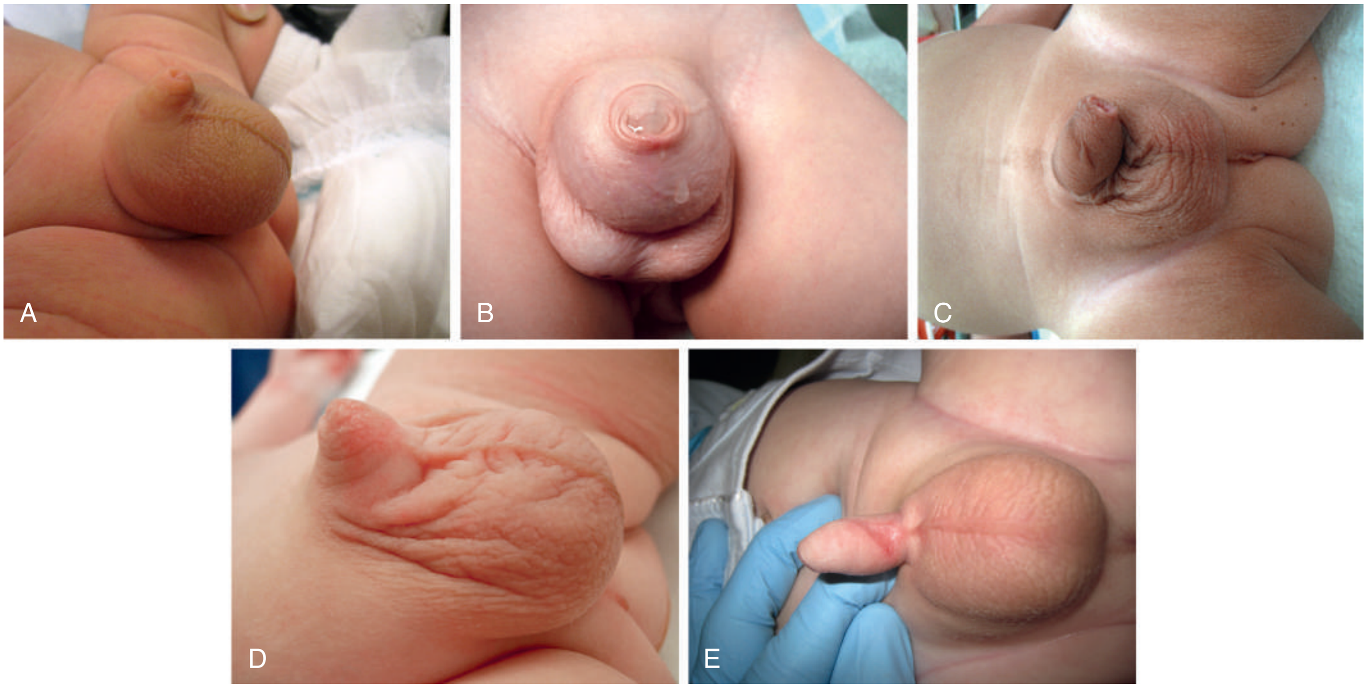

Figure 544-6 Examples of congenital deformities in which neonatal circumcision may be contraindicated. **A,** Hidden penis. **B,** Megaprepuce. **C,** Penile torsion to left side. **D,** Webbed penis; note scrotal attachment to penile shaft. **E,** Example of wandering raphe, with deviation of the median raphe to the left side. This finding may be an indication of penile torsion or hypospadias.

a small penis (Fig. 544-6). In boys with a **wandering raphe** (Fig. 544-6), in which the median raphe deviates to 1 side, there may be underlying penile torsion or hypospadias, and evaluation by a pediatric urologist is suggested before performing a circumcision.

PENILE TORSION

Penile torsion, a rotational defect of the penile shaft, usually occurs in a counterclockwise direction (to the left side: see Fig. 544-6). In most cases, penile development is normal, and the condition is unrecognized until circumcision is performed or the foreskin is retractable. In many cases the midline raphe of the penile shaft is deviated. Penile torsion also occurs in some boys with hypospadias. The defect has primarily cosmetic significance and correction is unnecessary if the rotation is <60 degrees from the midline.

INCONSPICUOUS PENIS

The term *inconspicuous penis* refers to a penis that appears to be small. A **webbed penis** is a condition in which the scrotal skin extends onto the ventral penile shaft. This deformity represents an abnormality of the attachment between the penis and scrotum. Although the deformity might appear mild, if a routine circumcision is performed, the penis can retract into the scrotum, resulting in secondary phimosis **(trapped penis)**. The concealed **(hidden or buried)** penis is a normally developed penis that is camouflaged by the suprapubic fat pad (Fig. 544-7). This anomaly may be congenital, iatrogenic after circumcision, or a result of obesity. Surgical correction is indicated for cosmetic reasons or if there is a functional abnormality with a splayed stream.

A **trapped penis** is an acquired form of inconspicuous penis and refers to a phallus that becomes embedded in the suprapubic fat pad after circumcision (Fig. 544-8). This deformity can occur after neonatal circumcision in an infant who has significant scrotal swelling from a large hydrocele or inguinal hernia or after routine circumcision in an infant with a webbed penis. This complication can predispose to UTIs and can cause urinary retention. Initial treatment of a trapped penis should include topical corticosteroid cream, which often loosens the phimotic ring. In some cases secondary repair is necessary at 6-9 mo.

MICROPENIS

Micropenis is defined as a normally formed penis that is at least 2.5 SD below the mean in size (Fig. 544-9). Typically, the ratio of the length

of the penile shaft to its circumference is normal. The pertinent measurement is the **stretched penile length**, which is measured by stretching the penis and measuring the distance from the penile base under the pubic symphysis to the tip of the glans. The mean length of the term newborn penis is 3.5 ± 0.7 cm and the diameter is 1.1 ± 0.2 cm. The diagnosis of micropenis is made if the stretched length is <1.9 cm.

Micropenis usually results from a hormonal abnormality that occurs after 14 wk of gestation. Common causes include hypogonadotropic hypogonadism, hypergonadotropic hypogonadism (primary testicular failure), and idiopathic micropenis. If growth hormone deficiency also is present, neonatal hypoglycemia can occur. The most common cause of micropenis is failure of the hypothalamus to produce an adequate amount of gonadotropin-releasing hormone, as typically occurs in Kallmann syndrome (see Chapter 583), Prader-Willi syndrome (see Chapter 108), and Lawrence-Moon-Bardet-Biedl syndrome. In some cases, there is growth hormone deficiency. Primary testicular failure can result from gonadal dysgenesis or rudimentary testes syndrome and also occurs in **Robinow syndrome** (characterized by hypoplastic genitalia, shortening of the forearms, frontal bossing, hypertelorism, wide palpebral fissures, short broad nose, long philtrum, small chin, brachydactyly, and a normal karyotype).

A pediatric endocrinologist, geneticist, and pediatric urologist should examine all children with these syndromes. **Evaluation** includes a karyotype, assessment of anterior pituitary function and testicular function, and MRI to determine the anatomic integrity of the hypothalamus and the anterior pituitary gland as well as the midline structure of the brain. One of the difficult questions is whether androgen therapy is essential during childhood, because androgenic stimulation of penile growth in a prepubertal boy can limit the growth potential of the penis in puberty. Studies of small groups of men with micropenis suggest that many, although not all, have satisfactory sexual function. Consequently, a decision for gender reassignment is made infrequently.

PRIAPISM

Priapism is a persistent penile erection at least 4 hr in duration that continues beyond, or is unrelated to, sexual stimulation. Typically, only the corpora cavernosa are affected. There are 3 subtypes:

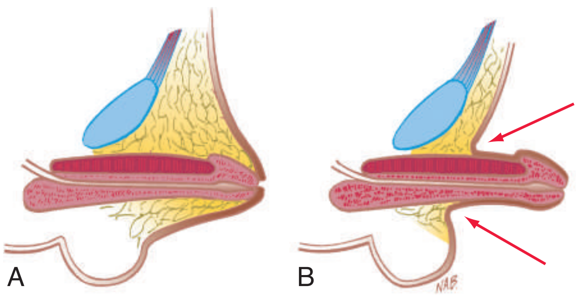

Figure 544-7 Concealed penis **(A),** which may be visualized by retracting skin lateral to penile shaft **(B).** *(From Wein AJ, Kavoussi LR, Novick AC, et al, editors:* Campbell-Walsh urology, *ed 9, Philadelphia, 2007, WB Saunders, Fig. 126-4, p. 2339.)*

Figure 544-9 Micropenis secondary to hypopituitarism in an 8-year-old boy. *(From Wein AJ, Kavoussi LR, Novick AC, et al, editors:* Campbell-Walsh urology, *ed 9, Philadelphia, 2007, WB Saunders, Fig. 126-5a, p. 2341.)*

Figure 544-8 **A,** Trapped (concealed) penis resulting from circumcision. **B,** Same patient after revision of circumcision. *(From Wein AJ, Kavoussi LR, Novick AC, et al, editors:* Campbell-Walsh urology, *ed 9, Philadelphia, 2007, WB Saunders, Fig. 126-2, p. 2340.)*

- Ischemic (venoocclusive, low-flow) priapism is characterized by little or no cavernous blood flow, and cavernous blood gases are hypoxic, hypercapnic, and acidotic. The corpora are rigid and tender to palpation.
- Nonischemic (arterial, high-flow) priapism is caused by unregulated cavernous arterial inflow. Typically, the penis is neither fully rigid nor painful. There is often a history of antecedent trauma resulting in a cavernous artery–corpora cavernosa fistula.
- Stuttering (intermittent) priapism is a recurrent form of ischemic priapism with painful erections with intervening periods of detumescence.

The most common cause of priapism in children is sickle cell disease, which is characterized by predominance of sickle cell hemoglobin (see Chapter 462.1). As many as 27.5% of children with sickle cell disease develop priapism. The priapism is generally related to a low-flow state, secondary to sickling of red blood cells within the sinusoids of the corpora cavernosa during normal erection, resulting in venous stasis. This situation results in decreased local oxygen tension and pH, which potentiates further stasis and sickling. Priapism typically occurs during sleep, when mild hypoventilatory acidosis depresses oxygen tension and pH in the corpora. There is typically significant corporal engorgement with sparing of the glans penis. If the spongiosum is involved, voiding may be impaired. Evaluation includes complete blood count and serum chemistry. If sickle cell status is unknown, hemoglobin electrophoresis should be performed. In some cases, corporal aspiration is performed to distinguish between a high-flow and low-flow state. Other causes of low-flow priapism include sildenafil ingestion and leukemia.

In priapism secondary to sickle cell disease, medical therapy includes exchange transfusion, intravenous hydration, alkalinization, pain management with morphine, and oxygen. The American Urological Association guideline on priapism also recommends concurrent intracavernous treatment beginning with corporal aspiration and irrigation with a sympathomimetic agent, such as phenylephrine. If priapism has been present >48 hr, ischemia and acidosis impair the intracavernous smooth muscle response to sympathomimetics. If irrigation and medical therapy are unsuccessful, a corporoglanular shunt should be considered. For stuttering priapism, administration of an oral α-adrenergic agent (pseudoephedrine) once or twice daily is first-line therapy. If this treatment is unsuccessful, an oral β-agonist (terbutaline) is recommended; a gonadotropin-releasing hormone analog plus flutamide is recommended as third-line therapy. Long-term follow-up of adults treated for sickle cell disease as children shows that satisfactory erectile function is inversely related to the patient's age at onset of priapism and duration of priapism.

Nonischemic (high-flow) priapism most commonly follows perineal trauma, such as a straddle injury, that results in laceration of the cavernous artery. Typically, the aspirated blood is bright red, and the aspirate is similar to arterial blood. Color Doppler ultrasonography often demonstrates the fistula. The priapism can spontaneously resolve. If it does not, angiographic embolization is indicated.

OTHER PENILE ANOMALIES

Agenesis of the penis affects approximately 1 in 10 million boys. The karyotype is almost always 46,XY, and the usual appearance is that of a well-developed scrotum with descended testes and an absent penile shaft. Upper urinary tract abnormalities are common. In most cases, gender reassignment is recommended in the newborn period. **Diphallia** ranges from a small accessory penis to complete duplication. **Lateral penile curvature** usually is caused by overgrowth or hypoplasia of a corporal (erectile) body and usually is congenital. Surgical repair is recommended at age 6-12 mo.

MEATAL STENOSIS

Meatal stenosis is a condition that almost always is acquired and occurs after neonatal circumcision. It probably results from severe inflammation of the denuded glans, and is difficult to prevent. If the meatus is pinpoint, boys void with a forceful, fine stream that goes a great distance. These boys can experience dysuria, frequency, hematuria, or a combination of these conditions, typically at age 3-8 yr. UTI is uncommon. Other boys have dorsal deflection of the urinary stream. Although the meatus may be small, hydronephrosis or voiding difficulty is extremely rare unless there is associated **balanitis xerotica obliterans** (see Fig. 544-3; chronic dermatitis of unknown etiology, generally involving the glans and prepuce, occasionally extending into the urethra). **Treatment** is meatoplasty, in which the urethral meatus is opened surgically; this procedure can be performed either under anesthesia as an outpatient or in the office using local anesthesia (EMLA cream) with or without sedation. Routine cystoscopy is unnecessary.

OTHER MALE URETHRAL ANOMALIES

Parameatal urethral cyst manifests as an asymptomatic small cyst on one side of the urethral meatus. Treatment is excision under anesthesia. **Congenital urethral fistula** is a rare deformity in which a fistula is present from the penile urethra. It usually is an isolated abnormality. Treatment is fistula closure. **Megalourethra** is a large urethra that usually is associated with abnormal development of the corpus spongiosum. This condition is most commonly associated with prune-belly syndrome (see Chapter 540). **Urethral duplication** is a rare condition in which the 2 urethral channels lie in the same sagittal plane. There are many variations with complete and incomplete urethral duplication. These boys often have a double stream. Most commonly the dorsal urethra is small and the ventral urethra is normal caliber. Treatment involves excision of the small urethra. **Urethral hypoplasia** is a rare condition in which the urethra is extremely small but patent. In some cases, a temporary cutaneous vesicostomy is necessary for satisfactory urinary drainage. Either gradual enlargement of the urethra or major urethroplasty is necessary. **Urethral atresia** refers to maldevelopment of the urethra and nearly always is fatal unless the urachus remains patent throughout gestation.

URETHRAL PROLAPSE (FEMALE)

Urethral prolapse is encountered predominantly in black girls 1-9 yr of age. The most common signs are bloody spotting on the underwear or diaper, although dysuria or perineal discomfort also can occur (Fig. 544-10). An inexperienced examiner can mistake the finding for sexual

Figure 544-10 Urethral prolapse in a 4 yr old African-American girl who had bloody spotting on her underwear.

Figure 544-11 Paraurethral cyst in a newborn girl.

Figure 544-12 Prolapsed ectopic ureterocele in a female infant. She had a nonfunctioning upper pole collecting system connected to the ureterocele.

abuse. The usual therapy consists of application of estrogen cream 2-3 times daily for 3-4 wk and sitz baths. Surgical excision and reapproximation of the mucosal edges is recommended for girls that fail medical therapy and is curative.

OTHER FEMALE URETHRAL LESIONS

Paraurethral cyst results from retained secretions in the Skene glands secondary to ductal obstruction (Fig. 544-11). These lesions are present at birth, and most regress in size during the 1st 4-8 wk, although occasionally incision and drainage is necessary. A **prolapsed ectopic ureterocele** appears as a cystic mass protruding from the urethra and is a presenting symptom in 10% of girls with a ureterocele, which is a cystic swelling of the terminal ureter (Fig. 544-12). Ultrasonography should be performed to visualize the upper urinary tracts to confirm the diagnosis. Usually, either the ureterocele is incised or an upper urinary tract reconstructive procedure is necessary.

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Chapter 545

Disorders and Anomalies of the Scrotal Contents

Jack S. Elder

UNDESCENDED TESTIS (CRYPTORCHIDISM)

The absence of a palpable testis in the scrotum indicates that the testis is undescended, absent, or retractile.

Epidemiology

An undescended **(cryptorchid)** testis is the most common disorder of sexual differentiation in boys. At birth, approximately 4.5% of boys have an undescended testis. Because testicular descent occurs at 7-8 mo of gestation, 30% of premature male infants have an undescended testis; the incidence is 3.4% at term. The majority of congenital undescended testes descend spontaneously during the 1st 3 mo of life, and by 6 mo the incidence decreases to 0.8%. Spontaneous descent occurs secondary to a temporary testosterone surge during the 1st 2 mo, which also results in significant penile growth. If the testis has not descended by 4 mo, it will remain undescended. Cryptorchidism is bilateral in 10% of cases. There is some evidence that the incidence of cryptorchidism is increasing. Although cryptorchidism usually is considered to be congenital, some boys have a scrotal testis that "ascends" to a low inguinal position, and therefore requires an orchiopexy. In addition, 1-2% of neonatal and young boys undergoing hernia repair have secondary cryptorchidism.

Pathogenesis

The process of testicular descent is regulated by an interaction between hormonal and mechanical factors, including testosterone, dihydrotestosterone, müllerian-inhibiting factor, the gubernaculum, intraabdominal pressure, and the genitofemoral nerve. The testis develops at 7-8 wk of gestation. At 10-11 wk, the Leydig cells produce testosterone, which stimulates differentiation of the wolffian (mesonephric) duct into the epididymis, vas deferens, seminal vesicle, and ejaculatory duct. At 32-36 wk, the testis, which is anchored at the internal inguinal ring by the gubernaculum, begins its process of descent. The gubernaculum distends the inguinal canal and guides the testis into the scrotum. Following testicular descent, the patent processus vaginalis (hernia sac) normally involutes. A small percentage have Klinefelter syndrome or mutations in the insulin-like factor 3 receptor.

Clinical Manifestations

Undescended testes are classified as **abdominal** (nonpalpable), **peeping** (abdominal but can be pushed into the upper part of the inguinal canal), **inguinal, gliding** (can be pushed into the scrotum but retracts immediately to the pubic tubercle), and **ectopic** (superficial inguinal pouch or, rarely, perineal). Most undescended testes are palpable just distal to the inguinal canal over the pubic tubercle.

A **disorder of sex development** should be suspected in a newborn phenotypic male with bilateral nonpalpable testes, as the child could be a virilized girl with congenital adrenal hyperplasia (see Chapter 576). In a boy with midpenile or proximal hypospadias and a palpable undescended testis, disorder of sexual development is present in 15%, and the risk is 50% if the testis is nonpalpable.

The **consequences of cryptorchidism** include poor testicular growth, infertility, testicular malignancy, associated hernia, torsion of the cryptorchid testis, and the possible psychologic effects of an empty scrotum.

The undescended testis is normal at birth histologically, but pathologic changes can be demonstrated by 6-12 mo. Delayed germ cell maturation, reduction in germ cell number, hyalinization of the

seminiferous tubules, and reduced Leydig cell number are typical; these changes are progressive over time if the testis remains undescended. Similar, although less severe, changes are found in the contralateral descended testis after 4-7 yr. After treatment for a unilateral undescended testis, 85% of patients are fertile, which is slightly less than the 90% rate of fertility in an unselected population of men. In contrast, following bilateral orchiopexy, only 50-65% of patients are fertile.

The risk of a **germ cell malignancy** (see Chapter 503) developing in an undescended testis is 4 times higher than in the general population and is approximately 1 in 80 with a unilateral undescended testis and 1 in 40-50 for bilateral undescended testes. Testicular tumors are less common if the orchiopexy is performed before 10 yr of age, but they still occur, and adolescents should be instructed in testicular self-examination. The peak age for developing a testis tumor is 15-45 yr. The most common tumor developing in an undescended testis in an adolescent or adult is a **seminoma** (65%); after orchiopexy, nonseminomatous tumors represent only 65% of testis tumors. Orchiopexy seems to reduce the risk of seminoma. Whether early orchiopexy reduces the risk of developing cancer of the testis is controversial, but it is uncommon for testis tumors to occur if the orchiopexy performed before the age of 2 yr. The contralateral scrotal testis is not at increased risk for malignancy.

An indirect inguinal hernia usually accompanies a congenital undescended testis but rarely is symptomatic. Torsion and infarction of the cryptorchid testis also are uncommon but can occur because of excessive mobility of undescended testes. Consequently, inguinal pain and/or swelling in a boy with an undescended testis should raise the suspicion of an incarcerated hernia or testicular torsion of the undescended testis.

"Acquired" or **ascending undescended testes** occurs when a boy has a descended testis at birth, but during childhood, usually between 4-10 yr of age, the testis does not remain in the scrotum. Such boys often have a history of a retractile testis. With testicular ascent, on physical examination the testis often can be manipulated into the scrotum, but there is obvious tension on the spermatic cord. This condition is speculated to result from incomplete involution of the processus vaginalis, restricting spermatic cord growth, resulting in the testis gradually moving out of its scrotal position during a boy's somatic growth.

Retractile testes may be misdiagnosed as undescended testes. Boys older than age 1 yr often have a brisk cremasteric reflex, and if the child is anxious or ticklish during scrotal examination, the testis may be difficult to manipulate into the scrotum. Boys should be examined with their legs in a relaxed frogleg position, and if the testis can be manipulated into the scrotum comfortably, it is probably retractile. It should be monitored every 6-12 mo with follow-up physical examinations, because it can become an acquired undescended testis. Overall, as many as one-third of boys with a retractile testis develop an acquired undescended testis, and boys younger than 7 yr of age at diagnosis of a retractile testis are at greatest risk. Although definitive data are not available, it is generally thought that boys with a retractile testis are not at increased risk for infertility or malignancy.

Approximately 10% of undescended testes are **nonpalpable testis**. Of these, 50% are viable testes in the abdomen or high in the inguinal canal, and 50% are atrophic or absent, almost always in the scrotum, secondary to spermatic cord torsion in utero **(vanishing testis).** If the nonpalpable testis is abdominal, it will not descend after 3 mo of age. Although sonography often is performed to try to identify whether the testis is present, it rarely changes clinical management, because the abdominal testis and atrophic testis are not identified on sonography. As part of the ABIM Choosing Wisely campaign, in 2012 the American Urological Association recommended that inguinal/scrotal sonography not be performed routinely in boys with a nonpalpable testis, because it rarely alters the surgical management. However, inguinal/scrotal sonography might be beneficial in obese boys with a nonpalpable testis; in this clinical setting, the undescended testis often is nonpalpable, and an inguinal/scrotal sonogram can be beneficial in surgical planning. CT scanning is relatively accurate in demonstrating the presence of the testis, but the radiation exposure is significant. MRI is even more accurate, but the disadvantage is that general anesthesia is necessary in most young children. None of these imaging studies are 100% accurate and in general do not add significantly to clinical decision making by the pediatric urologist or pediatric surgeon. Consequently, its routine use is discouraged.

On **physical examination** of the scrotum, the child should be entirely undressed, to help him relax. The examiner should examine the patient's scrotum and inguinal canal using their dominant hand. The nondominant hand is positioned over the pubic tubercle and is pushed inferiorly toward the scrotum. The examiner's dominant hand is used to try to palpate the testis. If the testis is nonpalpable, the "soap test" often is useful; soap is applied to the inguinal canal and the examiner's hand, significantly reducing friction and facilitating identification of an inguinal testis. In addition, pulling on the scrotum can pull a high inguinal testis into a palpable position. One soft sign that a testis is absent is contralateral testicular hypertrophy, but this finding is not 100% diagnostic.

Treatment

The congenital undescended testis should be treated surgically by 9-15 mo of age. With anesthesia by a pediatric anesthesiologist, surgical correction at 6 mo is appropriate, because spontaneous descent of the testis will not occur after 4 mo of age. Most testes can be brought down to the scrotum with an orchiopexy, which involves an inguinal incision, mobilization of the testis and spermatic cord, and correction of an indirect inguinal hernia. The procedure is typically performed on an outpatient basis and has a success rate of 98%. In some boys with a testis that is close to the scrotum, a prescrotal orchiopexy can be performed. In this procedure, the entire operation is performed through an incision along the edge of the scrotum. Often the associated inguinal hernia also can be corrected with this incision. Advantages of this approach over the inguinal approach include shorter operative time and less postoperative discomfort.

In boys with a nonpalpable testis, diagnostic laparoscopy is performed in most centers. This procedure allows safe and rapid assessment of whether the testis is intraabdominal. In most cases, orchiopexy of the intraabdominal testis located immediately inside the internal inguinal ring is successful, but orchiectomy should be considered in more difficult cases or when the testis appears to be atrophic. A 2-stage orchiopexy sometimes is needed in boys with a high abdominal testis. Boys with abdominal testes are managed with laparoscopic techniques at many institutions. Testicular prostheses are available for older children and adolescents when the absence of the gonad in the scrotum might have an undesirable psychologic effect. The FDA has approved a saline testicular implant. Solid silicone "carving block" implants also are used (Fig. 545-1). Placement of testicular prostheses early in childhood is recommended for boys with anorchia (absence of both testes).

The American Urological Association released guidelines for the evaluation and treatment of boys with an undescended testis in 2014. Table 545-1 summarizes the primary statements.

SCROTAL SWELLING

Scrotal swelling may be acute or chronic and painful or painless. Abrupt onset of painful scrotal swelling necessitates prompt evaluation because some conditions, such as testicular torsion and incarcerated inguinal hernia, require emergency surgical management. Tables 545-2 and 545-3 show the differential diagnosis.

Clinical Manifestations

A detailed history is helpful in determining the cause of the swelling and includes onset of pain—with testicular torsion, the pain often is sudden in onset and may be associated with exercise or minor genital trauma; duration of pain; radiation of pain—inguinal discomfort is common with testicular torsion, inguinal hernia, or epididymitis, and associated flank pain can occur with passage of a ureteral calculus; previous episodes of similar pain, which are common in boys with intermittent testicular torsion or inguinal hernia; nausea and vomiting, which are associated with testicular torsion and inguinal hernia; and irritative urinary symptoms, such as dysuria, urgency, and frequency,

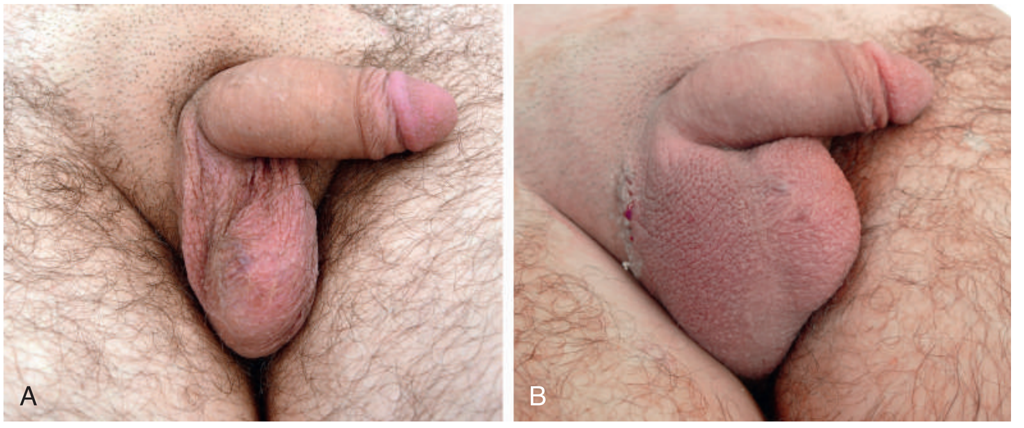

Figure 545-1 **A,** Adolescent with solitary left testis. **B,** Appearance following implantation of right testicular prosthesis.

Table 545-1 American Urological Association Guidelines for Evaluation and Treatment of Boys with an Undescended Testis

DIAGNOSIS

Primary care providers should palpate testes for quality and position at each recommended well-child visit. (Standard)

Providers should refer infants with a history of cryptorchidism (detected at birth) who do not have spontaneous testicular descent by 6 mo (corrected for gestational age) to an appropriate surgical specialist for timely evaluation. (Standard)

Providers should refer boys with the possibility of newly diagnosed (acquired) cryptorchidism after 6 mo. (Standard)

Providers must immediately consult an appropriate specialist for all phenotypic male newborns with bilateral, nonpalpable testes for evaluation of a possible disorder of sex development (DSD). (Standard)

Providers should not perform ultrasound (US) or other imaging modalities in the evaluation of boys with cryptorchidism before referral because these studies rarely assist in decision making. (Standard)

Providers should assess the possibility of a disorder of sex development (DSD) when there is increasing severity of hypospadias with cryptorchidism. (Recommendation)

In boys with retractile testes, providers should monitor the position of the testes at least annually to monitor for secondary ascent. (Standard)

TREATMENT

Providers should not use hormonal therapy to induce testicular descent, since evidence shows low response rates and lack of evidence for long-term efficacy. (Standard)

In the absence of spontaneous testicular descent by 6 mo (corrected for gestational age), specialists should perform surgery within the next year. (Standard)

In prepubertal boys with nonpalpable testes, surgical specialists should perform examination under anesthesia to reassess for palpability of testes. If nonpalpable, surgical exploration and, if indicated, abdominal orchidopexy should be performed. (Standard)

In boys with a normal contralateral testis, surgical specialists may perform an orchiectomy (removal of the undescended testis) if a boy has a normal contralateral testis and either very short testicular vessels and vas deferens, dysmorphic or very hypoplastic testis, or postpubertal age. (Clinical Principle)

Providers should counsel boys with a history of cryptorchidism and/or monorchidism and their parents regarding potential long-term risks and provide education on infertility and cancer risk. (Clinical Principle)

Adapted from Kolon TF, Herndon CDA, Baker LA, et al: Evaluation and treatment of cryptorchidism: AUA Guideline. http://www.auanet.org/common/pdf/education/clinical-guidance/Cryptorchidism.pdf

Table 545-2 Differential Diagnosis of Scrotal Masses in Boys and Adolescents

PAINFUL	PAINLESS
Testicular torsion	Hydrocele
Torsion of appendix testis	Inguinal hernia*
Epididymitis	Varicocele*
Trauma: ruptured testis, hematocele	Spermatocele*
Inguinal hernia (incarcerated)	Testicular tumor*
Mumps orchitis	Henoch-Schönlein purpura*
Testicular vasculitis	Idiopathic scrotal edema

*May be associated with discomfort.

Table 545-3 Differential Diagnosis of Scrotal Swelling in Newborn Boys

Hydrocele	Scrotal hematoma
Inguinal hernia (reducible)	Testicular tumor
Inguinal hernia (incarcerated)*	Meconium peritonitis
Testicular torsion*	Epididymitis*

*May be associated with discomfort.

which indicate a urinary tract infection that can cause epididymitis. Some boys report a recent history of scrotal trauma. There are multiple reports of familial testicular torsion. Boys with lower urinary tract pathology such as urethral stricture or neuropathic bladder may be prone to epididymitis.

Physical examination may be difficult in boys with a painful scrotum. Some have advocated performing a spermatic cord block or administering intravenous analgesia to facilitate the examination, but such measures usually are unnecessary. Scrotal wall erythema is common in testicular torsion, epididymitis, torsion of the appendix testis, and an incarcerated hernia. In boys with a normal cremasteric reflex, testicular torsion is unlikely. Absence of a cremasteric reflex is nondiagnostic.

Laboratory Findings and Diagnosis

Pertinent laboratory studies include a urinalysis and culture. A positive urinalysis suggests bacterial epididymitis. Serum studies are not helpful in establishing a diagnosis, unless a testicular malignancy is suspected. After initial evaluation, in boys with testicular pain color Doppler ultrasonography often is helpful in establishing the diagnosis, because it assesses whether testicular blood flow is normal, reduced, or increased (Fig. 545-2). If a hydrocele is present and the testis is nonpalpable, or if an abnormality of the testis is found, sonography also is indicated. Imaging studies are not 100% accurate; they should not be used to decide whether a boy with testicular pain should be referred for urologic evaluation.

Color Doppler ultrasonography allows assessment of testicular blood flow and testicular morphologic features. Accuracy is >95% if

the ultrasonographer is experienced and the patient is older than 2 yr old. A false-negative study (demonstrates normal testicular blood flow) can occur in a boy with testicular torsion if the degree of torsion is <360 degrees and the duration of torsion is short, because there may be continued testicular perfusion. In young boys, including neonates, blood flow may be difficult to demonstrate in 15% of normal testes.

TESTICULAR (SPERMATIC CORD) TORSION

Etiology

Testicular torsion requires prompt diagnosis and treatment to salvage the testis. Torsion is the most common cause of testicular pain in boys age 12 yr and older, and is uncommon before age 10 yr. It is caused by inadequate fixation of the testis within the scrotum, resulting from a redundant tunica vaginalis, allowing excessive mobility of the testis. The abnormal attachment is termed a *bell clapper deformity* and often is bilateral. Shortly after torsion occurs, venous congestion begins and subsequently arterial flow is interrupted. The likelihood of testis survival depends on the duration and severity of torsion. Following 4-6 hr of absent blood flow to the testis, irreversible loss of spermatogenesis can occur. Torsion may be familial in approximately 10% of males.

Diagnosis

Testicular torsion produces acute pain and swelling of the scrotum. On examination, the scrotum is swollen, and the testis is exquisitely tender and often difficult to examine. The cremasteric reflex nearly always is absent. The position (lie) of the testis is abnormal and there is often associated nausea and vomiting. The condition can be differentiated from an incarcerated hernia because swelling in the inguinal area typically is absent with torsion. If the pain duration is <4-6 hr, manual detorsion may be attempted. In 65% of cases the torsed testis rotates inward, so detorsion should be attempted in the opposite direction (e.g., the left testis is rotated clockwise). Successful manual detorsion results in dramatic pain relief.

Some adolescents experience *intermittent testicular torsion*. These boys report episodes of severe unilateral testicular pain that resolves spontaneously after 30-60 min. Treatment is elective bilateral scrotal orchiopexy (see Treatment).

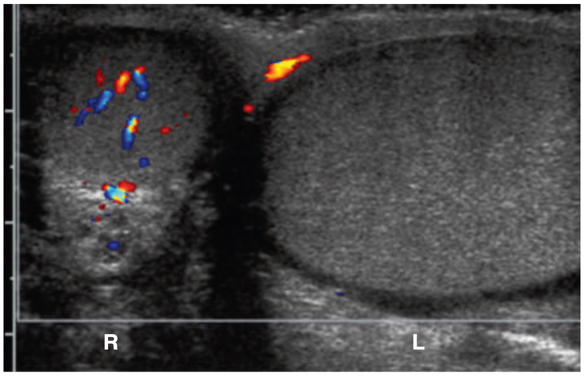

Figure 545-2 **Testicular torsion and axis change.** A color Doppler ultrasound in the transverse plane shows color flow in the right testicle. The right testicle is oval to circular, because it has been evaluated in the transverse plane. The left testicle is elongated as if it is in longitudinal plane. This axis change is the ultrasound equivalent of the worrisome clinical finding suggestive of torsion when accompanied by a history of sudden pain. Lack of color Doppler flow in the left testicle confirms a left testicular torsion. *(From Coley BD, editor:* Caffey's pediatric imaging, *ed 12, Philadelphia, Elsevier, 2013, Fig. 126-13, p. 1300).*

Treatment

Treatment is prompt surgical exploration and detorsion. If the testis is explored within 6 hr of torsion, up to 90% of the gonads survive. Testicular salvage decreases rapidly with a delay of >6 hr. If the degree of torsion is 360 degrees or less, the testis might have sufficient arterial flow to allow the gonad to survive, even after 24-48 hr. Following detorsion the testis is fixed in the scrotum with nonabsorbable sutures, termed *scrotal orchiopexy,* to prevent torsion in the future. The contralateral testis also should be fixed in the scrotum because the predisposing anatomic condition often is bilateral. If the testis appears nonviable, orchiectomy is performed (Fig. 545-3*A*). Some adolescents do not undergo prompt evaluation and treatment and present with "late phase testicular torsion," in which the spermatic cord contracts and the testis is high in the scrotum and nontender (Fig. 545-3*B*). Fertility is reduced in men who experience spermatic cord torsion in adolescence, irrespective of whether detorsion or orchiectomy is performed.

Spermatic cord torsion also can occur in the fetus or neonate. This condition results from incomplete attachment of the tunica vaginalis to the scrotal wall and is "extravaginal." When torsion occurs in utero, the baby usually is born with a large, firm, nontender testis. Usually the ipsilateral hemiscrotum is ecchymotic (Fig. 545-4). In these cases, the testis rarely is viable because torsion was a remote event. However, the contralateral testis is at increased risk for torsion until 1-2 mo beyond term. The pediatric urology community is divided regarding whether immediate exploration is necessary in a male newborn who has suspected testicular torsion at birth, but if observation is recommended, the family needs to be counseled regarding the risk of contralateral spermatic cord torsion. On the other hand, if the initial exam is normal, and the newborn subsequently develops scrotal swelling and erythema, and imaging is consistent with spermatic cord torsion, emergency scrotal exploration is indicated.

TORSION OF THE APPENDIX TESTIS

Torsion of the appendix testis is the most common cause of testicular pain in boys 2-10 yr but is rare in adolescents. The appendix testis is a stalk-like structure that is a vestigial embryonic remnant of the müllerian (paramesonephric) ductal system that is attached to the upper

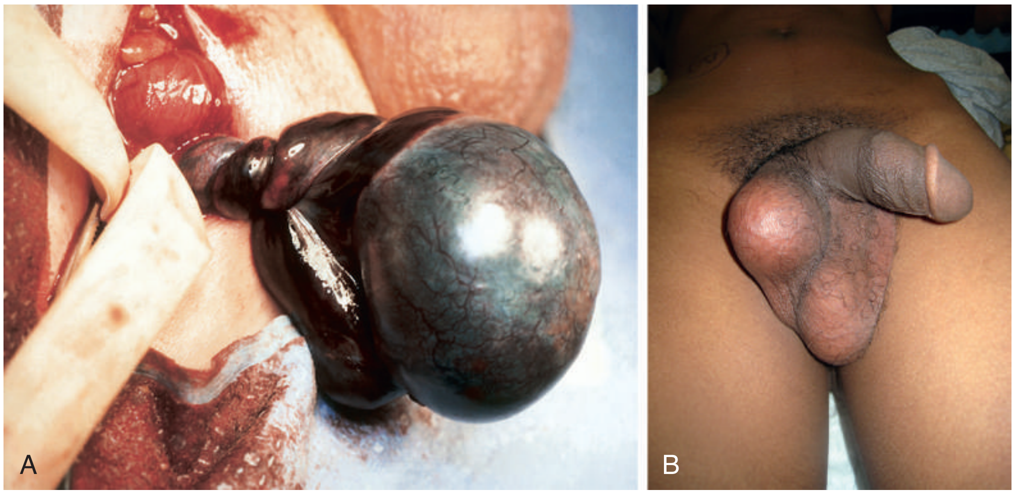

Figure 545-3 **A,** Left testicular torsion in adolescent with acute scrotum; the testis is necrotic. **B,** "Late-phase torsion" in an adolescent with severe testicular pain 1 mo previously. Note absence of inflammation and high position of testis in scrotum.

Figure 545-4 **A** and **B,** Right testicular torsion in a newborn. The right hemiscrotum is darker, and the testis was indurated and enlarged.

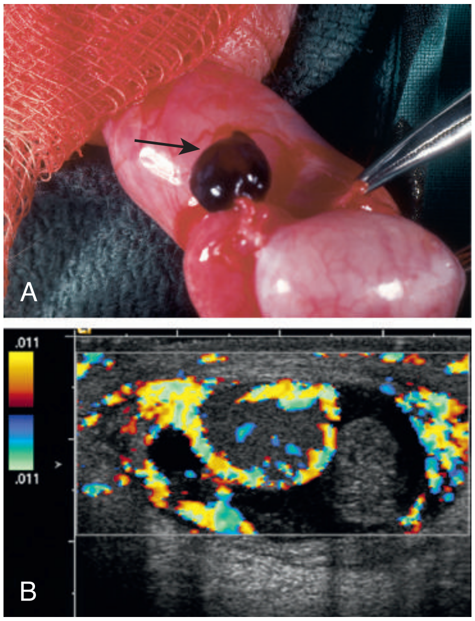

Figure 545-5 **A,** Torsion of the appendix testis; the appendix testis is necrotic *(arrow)*. **B,** Color Doppler scrotal sonogram showing hyperemia to the testis and absent flow to the appendix testis *(right side)*. Symptoms resolved with medical therapy.

pole of the testis. When it undergoes torsion, progressive inflammation and swelling of the testis and epididymis occurs, resulting in testicular pain and scrotal erythema. The onset of pain usually is gradual. Palpation of the testis usually reveals a 3-5 mm tender indurated mass on the upper pole (Fig. 545-5*A*). In some cases, the appendage that has undergone torsion may be visible through the scrotal skin, in the "blue dot" sign. In some boys, distinguishing torsion of the appendix from testicular torsion is difficult. In such cases, a testicular flow scan or color Doppler ultrasonography is useful because testicular blood flow should be normal or increased. In such cases, the radiologist often recognizes epididymal enlargement and makes the diagnosis of epididymitis, reflecting the inflammatory reaction (Fig. 545-5*B*).

The natural history of torsion of the appendix testis is for the inflammation to resolve in 3-10 days. Nonoperative treatment is recommended, including bed rest for 24 hr and analgesia with nonsteroidal antiinflammatory medication for 5 days. If the diagnosis is uncertain, scrotal exploration is recommended.

EPIDIDYMITIS

Acute inflammation of the epididymis is an ascending retrograde infection from the urethra, through the vas into the epididymis. This condition causes acute scrotal pain, erythema, and swelling. It is rare before puberty and should raise the question of a congenital abnormality of the wolffian duct, such as an ectopic ureter entering the vas. In younger boys, the responsible organism is often *Escherichia coli* (see Chapter 200). After puberty, bacterial epididymitis becomes progressively more common and is the principal cause of acute painful scrotal swelling in young sexually active men. Urinalysis usually reveals pyuria. Epididymitis can be infectious (usually gonococcus or *Chlamydia*; see Chapters 192 and 226), but often the organism remains undetermined. Additional etiologies include familial Mediterranean fever, enterovirus, and adenoviruses. Treatment consists of bed rest and antibiotics as indicated. Differentiation from torsion can be difficult, and surgical exploration may be required in children.

Henoch-Schönlein purpura (see Chapter 484) is a systemic vasculitis that involves multiple organ systems and that can involve the kidney and spermatic cord. When the spermatic cord is involved, typically there is bilateral painful scrotal swelling with purpuric lesions involving the scrotum. Scrotal sonography should show normal testicular blood flow. Treatment is directed toward systemic treatment of the Henoch-Schönlein purpura. Isolated testicular vasculitis is less common than that in Henoch-Schönlein purpura; polyarteritis nodosa should be suspected.

VARICOCELE

A varicocele is a congenital condition in which there is abnormal dilation of the pampiniform plexus in the scrotum, often described as a "bag of worms" (Fig. 545-6). Dilation of the pampiniform venous plexus results from valvular incompetence of the internal spermatic vein. Approximately 15% of adult men have a varicocele; of these, approximately 10-15% are subfertile. Varicocele is the most common (and virtually the only) surgically correctable cause of subfertility in men. A varicocele is found in 5-15% of adolescent boys, but it rarely is diagnosed in boys younger than 10 yr old, because the varicocele becomes distended only after the increased blood flow associated with puberty occurs. Varicoceles occur predominantly on the left side, are bilateral in 2% of cases, and rarely involve the right side only. A varicocele in a boy younger than age 10 yr or on the right side might indicate an abdominal or retroperitoneal mass; an abdominal sonogram or CT scan should be performed in such cases.

A varicocele typically is a painless paratesticular mass. Occasionally patients describe a dull ache in the affected testis. Usually the varicocele is not apparent when the patient is supine because it is decompressed; in contrast, the varicocele becomes prominent when the patient is

Figure 545-6 Left varicocele in an adolescent boy.

Figure 545-7 Newborn with large right hydrocele.

standing and enlarges with a Valsalva maneuver. Many pediatricians do not routinely screen adolescents for a varicocele. Varicoceles typically are graded from 1-3 with the boy standing: **grade 1** is palpable only with Valsalva; **grade 2** is palpable without Valsalva but is not visible on inspection; and **grade 3** is visible with inspection. Boys with a grade 3 varicocele are at greatest risk for testicular growth arrest. Testicular size should be documented with calipers, an orchidometer, or scrotal sonography, because if the affected left testis is significantly smaller than the right testis, spermatogenesis probably has been adversely affected. A semen analysis should be considered in sexually mature adolescents who are Tanner stage V.

The goal of varicocelectomy is to maximize chances for fertility. Surgical treatment of varicoceles is indicated in boys with a significant disparity in testicular size or pain in the affected testis or if the contralateral testis is diseased or absent. Typically the involved testis enlarges and catches up with the normal testis over the following 1-2 yr. Varicocelectomy should also be considered in boys with a large grade 3 varicocele, even if there is not a disparity in testicular size. Surgical repair is accomplished with a variety of techniques by ligation of the veins of the pampiniform plexus laparoscopically or through an inguinal or subinguinal incision (with or without an operating microscope) or by ligating the internal spermatic vein in the retroperitoneum. The operation is performed on an ambulatory basis.

SPERMATOCELE

A spermatocele is a cystic lesion that contains sperm and is attached to the upper pole of the sexually mature testis. Spermatoceles usually are painless and are incidental findings on physical examination. Enlargement of the spermatocele or significant pain is an indication for removal.

HYDROCELE

Etiology

A hydrocele is an accumulation of fluid in the tunica vaginalis (Fig. 545-7). Between 1% and 2% of neonates have a hydrocele. In most cases, the hydrocele is noncommunicating (the processus vaginalis was obliterated during development). In such cases, the hydrocele fluid disappears by 1 yr of age. If there is a persistently patent processus, the hydrocele persists and becomes progressively larger during the day and is small in the morning. A rare variant of a hydrocele is the abdominoscrotal hydrocele, in which there is a large, tense hydrocele that extends into the lower abdominal cavity. In some older boys, a noncommunicating hydrocele can result from an inflammatory condition within the scrotum, such as testicular torsion, torsion of the appendix testis, epididymitis, or testicular tumor. The long-term risk of a communicating hydrocele is the development of an inguinal hernia. Some older boys and adolescents also develop a hydrocele. In some cases hydrocele develop acutely after an episode of scrotal trauma or epididymoorchitis, whereas others develop more insidiously.

Diagnosis

On examination, hydroceles are smooth and nontender. Transillumination of the scrotum confirms the fluid-filled nature of the mass. It is important to palpate the testis, because some young men develop a hydrocele in association with a testis tumor. If compression of the fluid-filled mass completely reduces the hydrocele, an inguinal hernia/hydrocele is the likely diagnosis.

Treatment

Most congenital hydroceles resolve by 12 mo of age following reabsorption of the hydrocele fluid. If the hydrocele is large and tense, however, early surgical correction should be considered, because it is difficult to verify that the child does not have a hernia, and large hydroceles rarely disappear spontaneously. Hydroceles persisting beyond 12-18 mo usually are communicating and should be repaired. Surgical correction is similar to a herniorrhaphy (see Chapter 346). Through an inguinal incision, the spermatic cord is identified, the hydrocele fluid is drained, and a high ligation of the processus vaginalis is performed. If an older boy has a large hydrocele, often diagnostic laparoscopy can be performed to determine whether there is a patent processus vaginalis, and if the internal ring is closed, then the hydrocele may be corrected with a scrotal incision.

INGUINAL HERNIA

Inguinal hernia is discussed in Chapter 346.

TESTICULAR TUMOR

Testicular and paratesticular tumors can occur at any age, even in the newborn. Approximately 35% of prepubertal testis tumors are malignant; most commonly they are yolk sac tumors, although rhabdomyosarcoma and leukemia also can occur in this age group. In adolescents, 98% of painless solid testicular masses are malignant (see Chapter 503). Most manifest as a painless, hard testicular mass that does not transilluminate. Scrotal ultrasonography should be performed to confirm the finding of a testicular mass and it can help to delineate the type of testis tumor. Serum tumor markers, including **α-fetoprotein** and **β-human**

chorionic gonadotropin, should be drawn. Definitive therapy includes surgical exploration through an inguinal incision. In most cases, a radical orchiectomy, consisting of removal of the entire testis and spermatic cord, is performed. In a prepubertal boy, if the ultrasonographic study or surgical exploration suggests that the tumor is localized and benign, such as a teratoma or epidermoid cyst, testis-sparing surgery with removal only of the mass may be appropriate.

Testicular microlithiasis identified incidentally with ultrasonography may be a risk factor for future neoplasia.

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Chapter 546

Trauma to the Genitourinary Tract

Jack S. Elder

ETIOLOGY

Most injuries to the genitourinary tract in children result from blunt trauma during falls, athletic activities, or motor vehicle crashes (see Chapter 72). Children are at greater risk of blunt renal injury than are adults, because they have less body fat and because the kidneys are not located directly behind the ribs. Children with a preexisting renal anomaly, such as hydronephrosis secondary to a ureteropelvic junction obstruction, horseshoe kidney, or renal ectopia, also are at increased risk for renal injury. Blunt abdominal or flank trauma often causes a renal injury. Falling can cause a deceleration injury that results in an injury to the renal pedicle, interrupting blood flow to the kidney. If the bladder is full, blunt lower abdominal trauma can cause a bladder rupture. Rupture of the membranous urethra occurs in 5% of pelvic fractures. Straddle injuries usually are associated with trauma to the bulbous urethra.

Symptoms and signs of urinary tract injury include gross or microscopic hematuria, bleeding from the urethral meatus, abdominal or flank pain, a flank mass, fractured lower ribs or lumbar transverse processes, and a perineal or scrotal hematoma.

In more than 50% of cases there also are major injuries to the brain, spinal cord, skeleton, lungs, or abdominal organs.

DIAGNOSIS

Evaluation of the patient begins after an adequate airway has been established and the patient is hemodynamically stable (see Chapter 67). With significant abdominal injury, gross hematuria or >50 red blood cells per high-power field, or suspicion of renal injury (deceleration injury, flank pain or bruise), renal imaging is indicated. The bladder should be catheterized unless blood is dripping from the urethral meatus, which is an indication of potential urethral injury. Passing the catheter in the presence of a urethral injury can increase the extent of the damage and convert a partial membranous urethral tear into a total disruption. In these patients, a retrograde urethrogram should be performed by injecting radiopaque contrast medium into the urethral meatus under fluoroscopy. Oblique radiographs demonstrate the extent of the injury and whether urethral continuity is preserved or has been disrupted.

A **3-phase spiral CT scan** should be performed to evaluate the kidneys, ureters, and bladder. The delayed images are important to detect renal extravasation of blood or urine. Prompt function of both kidneys without extravasation usually excludes significant renal injury. Renal injuries are classified according to the grading scale presented in Table 546-1. Minor renal injuries are most common; these include contusion of the renal parenchyma and shallow cortical lacerations not involving the collecting system. Major renal injuries include deep lacerations involving the collecting system, the shattered kidney, and renal pedicle injuries (Fig. 546-1). Complete absence of function of 1 kidney without contralateral compensatory hypertrophy (indicating congenital absence) should be regarded as an indication of major injury to the renal pedicle. Renal angiography, once used for further evaluation of renal injuries, particularly if a renal pedicle injury is suspected, now is rarely used because such patients are often hemodynamically unstable, and management is not significantly affected by the findings. In some cases, a preexisting renal anomaly is demonstrated on the study. A ruptured ureteropelvic junction obstruction may be apparent if the kidney is intact but the distal ureter is not visualized.

If there is a pelvic fracture, a urethral transection injury should be suspected. The risk is directly related to the number of broken pubic

Table 546-1 Grading of Renal Injuries

GRADE	DESCRIPTION
1	Renal contusion or subcapsular hematoma
2	Nonexpanding perirenal hematoma, <1 cm parenchymal laceration, no urinary extravasation; all renal fragments viable; confined to renal retroperitoneum
3	Nonexpanding perirenal hematoma, >1 cm parenchymal laceration, no urinary extravasation; renal fragments may be viable or devitalized
4	Laceration extending into the collecting system with urinary extravasation; renal fragments may be vital or devitalized *or* Injury to the main renal vasculature with contained hemorrhage
5	Completely shattered kidney; by definition multiple major lacerations >1 cm associated with multiple devitalized fragments *or* Injury to the main renal vasculature with uncontrolled hemorrhage, renal hilar avulsion

Figure 546-1 CT scan of a girl who sustained major renal injury when she fell off a bicycle. The scan demonstrates a ruptured right kidney with urinary extravasation.

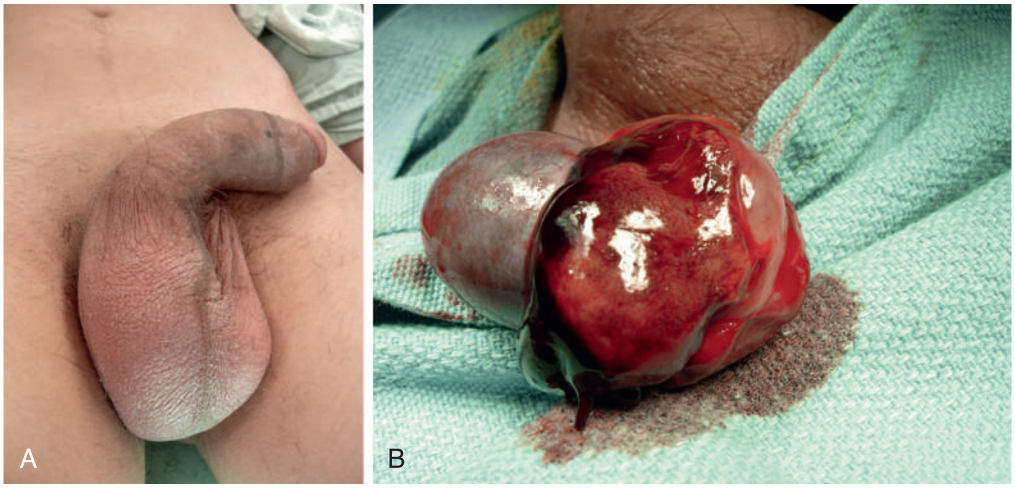

Figure 546-2 **A,** Adolescent boy with blunt right testicular injury. **B,** Tunica albuginea of testis is ruptured; the patient underwent debridement and closure of testicular capsule.

rami and whether there is separation of the pubic symphysis or displacement of the posterior pubic arch. Radiographic evaluation with retrograde urethrography should be performed if there is blood at the urethral or vaginal meatus, inability to void, and a perineal or penile hematoma.

TREATMENT

Minor renal injuries such as contusions are managed by bed rest and monitoring of vital signs until abdominal or flank discomfort and gross hematuria have resolved. Children with a major renal injury usually are admitted to an intensive care unit for continuous monitoring of vital signs and urine output. Intravenous antibiotics are also administered. These injuries also are managed nonoperatively, because Gerota's fascia often causes tamponade of bleeding from the kidney, and dramatic healing of the injured parenchyma can occur even with significant urinary extravasation.

Approximately 10% of children with a major renal injury undergo surgical exploration because of hemodynamic instability, persistent extravasation, or persistent hematuria or to correct a congenital renal deformity. It can be difficult to identify normal and devitalized parenchyma, and the likelihood of having to remove the kidney is significant. If the child is undergoing exploration for other abdominal injuries, the injured kidney is examined. If there is persistent extravasation because of intermittent ureteral obstruction from a blood clot, passage of a temporary double-J stent endoscopically between the bladder and kidney might allow resolution. If the renal pedicle is injured, nephrectomy is necessary. The kidney can be salvaged by emergency renal revascularization only if the kidney is explored within 2-3 hr of the injury. Virtually all penetrating injuries of the kidneys should be explored.

In addition to loss of renal function, the main long-term complication of renal injury is renin-mediated hypertension. Children who sustain significant renal injuries should have periodic measurement of blood pressure if they have any residual renal abnormality.

Ureteral injuries usually are iatrogenic. Injuries of the ureter by blunt or penetrating trauma require immediate surgical attention.

When the bladder can be catheterized, a static cystogram is obtained, infusing a contrast solution through the catheter by gravity, ideally using fluoroscopy. Flat and oblique views are often obtained; a postvoid film also should be obtained because, in some cases, extravasation may be hidden by the full bladder.

Bladder ruptures can be intraperitoneal or extraperitoneal. All intraperitoneal ruptures require surgical repair. Minor extraperitoneal near-ruptures might be treated by catheter drainage but generally require surgical treatment.

Treatment of a membranous urethral injury is controversial. Erectile dysfunction, urethral stricture, and urinary incontinence are the major late complications of rupture of the membranous urethra, and therapy is directed at minimizing the risk of these problems. A large pelvic hematoma with tamponade often is present, and an immediate attempt to repair the injury can be technically difficult and result in significant hemorrhage. Many such injuries are managed initially by temporary suprapubic cystostomy, with continuous bladder drainage for 3-6 mo. Subsequently, open or endoscopic urethroplasty can be performed. Alternatively, some try to achieve urethral continuity under anesthesia and leave a urethral catheter for several months. These patients typically require subsequent open urethroplasty.

Penile injury is uncommon. A risk of newborn circumcision with a Mogen clamp is partial or complete glans amputation. With immediate surgical repair, often the excised glans tissue can be replaced as a free graft. Some boys who are in the process of toilet training sustain an injury to the glans penis if the lid of the toilet falls while they are urinating. These boys often have a hematoma covering the distal half of the glans. Typically, they have no difficulty urinating and do not need extensive evaluation. Some male infants develop an inadvertent hair coil tourniquet or strangulation injury. Typically a very narrow constriction is noted with severe distal penile swelling and pain. Identification and incision of the hair allows prompt resolution of the edema. The urethra and penile vascularity should be assessed after release of the hair coil. Adolescent boys who indulge in extremely vigorous sexual intercourse may sustain rupture of one of the corporal bodies. These boys have severe swelling of the penile shaft and require emergency exploration and repair. Boys with penetrating injuries of the penis also require emergency debridement and repair.

Testicular injuries are relatively uncommon in children because of the small size of the testes and their mobility within the scrotum. Such injuries usually result from blunt trauma during athletic activity. Typically, these boys have significant scrotal swelling, testicular pain, and tenderness (Fig. 546-2*A*). Ultrasonography demonstrates rupture of the tunica albuginea, which is the capsule of the testis, and surrounding hemorrhage. Prompt surgical treatment of testicular injuries increases the salvage rate (Fig. 546-2*B*). An uncommon injury is the zipper injury, which can affect either the scrotum or foreskin. This problem generally occurs in boys who do not wear underwear. The zipper can be cut with bone cutters or metal cutters. Sedation generally is unnecessary.

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Chapter 547

Urinary Lithiasis

Jack S. Elder

Urinary lithiasis in children is related to genetic, climatic, dietary, and socioeconomic factors. The incidence is increasing: in 1996 the rate of symptomatic nephrolithiasis was 7.9 in 10,000, whereas in 2007 it was 18.5 in 10,000. Adolescents are 10 times more likely to have a symptomatic calculus compared to children 0-3 yr. The increase in stone disease in the United States is attributed to obesity and changes in dietary habits, such as increased sodium and fructose intake, and decreased calcium and water intake.

Urolithiasis is less common in the United States than in other parts of the world. Approximately 7% of urinary calculi occur in children younger than 16 yr of age. In the United States, many children with stone disease have a metabolic abnormality. The exceptions are patients with a neuropathic bladder (see Chapter 542), who are prone to infection-initiated renal stones, and those who have urinary tract reconstruction with small or large intestine, which predisposes to bladder calculi. The incidence of metabolic stones is similar in boys and girls; they are most common in southeastern United States and are uncommon in African-Americans. In Southeast Asia, urinary calculi are endemic and are related to dietary factors. Contamination of infant formula with the organic base and illegally added nitrogen-containing food additive melamine was reported in China in 2008 and is the source of much study in that country.

STONE FORMATION

Nearly 90% of urinary stones contain calcium as a major constituent, and 60% are composed of calcium oxalate. Most "spontaneous" stones are composed of calcium, oxalate, or phosphate crystals; others are caused by uric acid, cystine, ammonium crystals, or phosphate crystals, or a combination of these substances (Table 547-1). The risk of stone formation increases in the presence of increasing concentrations of these crystals and is reduced with increasing concentrations of urinary inhibitors. Renal calculi develop from crystals that form on the calyx and aggregate to form a calculus. Bladder calculi may be stones that formed in the kidney and traveled down the ureter, or they can form primarily in the bladder.

Low urine volume, low urine pH, calcium, sodium, oxalate, and urate are known to promote stone formation. Many inorganic (e.g., citrate, magnesium) and organic (e.g., glycosaminoglycans, osteopontin) substances are known to inhibit stone formation. Organic inhibitory compounds adsorb to the surface of the crystal, thereby inhibiting crystal growth and nucleation.

Stone formation depends on 4 factors: matrix, precipitation–crystallization, epitaxy, and the absence of inhibitors of stone formation in the urine. **Matrix** is a mixture of protein, nonamino sugars, glucosamine, water, and organic ash that makes up 2-9% of the dry weight of urinary stones and is arranged within the stones in organized concentric laminations. **Precipitation–crystallization** refers to supersaturation of the urine with specific ions composing the crystal. Crystals aggregate by chemical and electrical forces. Increasing the saturation of urine with respect to the ions increases the rate of nucleation, crystal growth, and aggregation and increases the likelihood of stone formation and growth. **Epitaxy** refers to the aggregation of crystals of different composition but similar lattice structure, thus forming stones of a heterogeneous nature. The lattice structures of calcium oxalate and monosodium urate have similar structures, and calcium oxalate crystals can aggregate on a nucleus of monosodium urate crystals. Urine also contains **inhibitors of stone formation,** including citrate, diphosphonate, and magnesium ion.

Table 547-1 Classification of Urolithiasis
CALCIUM STONES (CALCIUM OXALATE AND CALCIUM PHOSPHATE)*
Hypercalciuria
Absorptive: increased Ca absorption from gut; types I and II
Renal leak: decreased tubular reabsorption of Ca
Resorptive
Primary hyperparathyroidism (rare in children)
Iatrogenic
Loop diuretics
Ketogenic diet
Corticosteroids
Adrenocorticotropic hormone administration
Methylxanthines (theophylline, aminophylline)
Distal renal tubular acidosis, type 1 (calcium phosphate)
Hypocitraturia—citrate most important inhibitor of Ca crystallization
Vitamin D excess
Immobilization
Sarcoidosis
Cushing disease
Hyperuricosuria
Heterozygous cystinuria
Hyperoxaluria (calcium oxalate)
Primary hyperoxaluria, types 1 and 2
Secondary hyperoxaluria
Enteric hyperoxaluria
CYSTINE STONES
Cystinuria
STRUVITE STONES (MAGNESIUM AMMONIUM PHOSPHATE)
Urinary tract infection (urea-splitting organism)
Foreign body
Urinary stasis
URIC ACID STONES
Hyperuricosuria
Lesch-Nyhan syndrome
Myeloproliferative disorders
After chemotherapy
Inflammatory bowel disease
INDINAVIR STONES
MELAMINE
NEPHROCALCINOSIS

*Most common.

CLINICAL MANIFESTATIONS

Children with urolithiasis usually have gross or microscopic hematuria. If the calculus causes obstruction, then severe flank pain (renal colic) or abdominal pain occurs. The calculus typically causes obstruction at areas of narrowing of the urinary tract—the ureteropelvic junction, where the ureter crosses the iliac vessels, and the ureterovesical junction. The ureter progressively narrows distally, and its most narrow segment is the ureterovesical junction. Typically the pain radiates anteriorly to the scrotum or labia. Often the pain is intermittent, corresponding to periods of obstruction of urine flow, which increases the pressure in the collecting system. If the calculus is in the distal ureter, the child can have irritative symptoms of dysuria, urgency, and frequency. If the stone passes into the bladder, the child usually is asymptomatic. If the stone is in the urethra, dysuria and difficulty voiding can result, particularly in boys. Some children pass small amounts of gravel-like material. Stones can also be asymptomatic, although it is uncommon to pass a ureteral calculus without symptoms.

DIAGNOSIS

Approximately 90% of urinary calculi are calcified to some degree and consequently are radiopaque on a plain abdominal film. However, many calculi are only a few millimeters in diameter and are difficult to

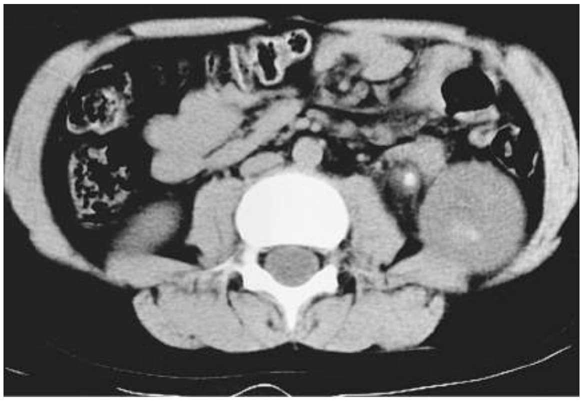

Figure 547-1 Noncontrast CT scan of the midabdomen in a male infant with cystinuria shows a left-sided calculus at the ureteropelvic junction with proximal hydronephrosis.

see, particularly if they are in the ureter. Struvite (magnesium ammonium phosphate) stones are radiopaque. Cystine, xanthine, and uric acid calculi may be radiolucent but often are slightly opacified. Some children have **nephrocalcinosis,** which is calcification of the renal tissue itself. Nephrocalcinosis is seen most commonly in premature neonates receiving furosemide, which causes hypercalciuria, and in children with medullary sponge kidney.

In a child with suspected renal colic, there are multiple imaging options. The most accurate study is an **unenhanced spiral CT scan** of the abdomen and pelvis (Fig. 547-1). This study takes only a few minutes to perform, has 96% sensitivity and specificity in delineating the number and location of calculi, and demonstrates whether the involved kidney is hydronephrotic. However, the radiation exposure is high. An alternative is to obtain a plain radiograph of the abdomen and pelvis plus a renal ultrasonogram. These studies can demonstrate hydronephrosis and possibly the calculus on the radiograph; however, the calculus is not visualized on sonography unless it is adjacent to the bladder. In addition, renal calculi <3 mm typically are not seen. Consequently, the clinician needs to carefully balance the risks of CT imaging against the lower sensitivity of the plain abdominal film plus sonography.

In 2008 the Society for Pediatric Radiology initiated the Image Gently initiative to educate providers on the risks of radiologic imaging in children and to encourage the use of limited imaging in children, particularly those with suspected urolithiasis (http://www.pedrad.org/associations/5364/ig/). In a child with an already-diagnosed calculus, serial plain x-rays or renal ultrasonography can be used to follow the status of the calculus, such as whether it has grown or diminished in size or has moved. If a child has a renal pelvic calculus, a ureteropelvic junction obstruction should be suspected. In some cases, it can be difficult to determine whether hydronephrosis in such a child is secondary to an obstructing stone, ureteropelvic junction obstruction, or both.

Any material that resembles a calculus should be sent for analysis by a laboratory that specializes in identifying the components of urinary calculi.

METABOLIC EVALUATION

A metabolic evaluation for the most common predisposing factors should be undertaken in all children with urolithiasis, bearing in mind that structural, infectious, and metabolic factors often coexist. This evaluation should not be undertaken in a child who is in the process of passing a stone, because the altered diet and hydration status, as well as the effect of obstruction on the kidney, can alter the results of the study. Table 547-2 lists the basic laboratory studies required, and Table 547-3 shows the normal values for 24-hr urine collections. In children with hypercalciuria, further studies of calcium excretion with dietary calcium restriction and calcium loading are necessary.

Table 547-2 Laboratory Tests Suggested for Evaluation of Urolithiasis

SERUM	URINE
Calcium	Urinalysis
Phosphorus	Urine culture
Uric acid	Calcium : creatinine ratio
Electrolytes and anion gap	Spot test for cystinuria
Creatinine	24 hr collection for:
Alkaline phosphatase	Creatinine clearance
	Calcium
	Phosphate
	Oxalate
	Uric acid
	Dibasic amino acids (if cystine spot test result is positive)

PATHOGENESIS OF SPECIFIC RENAL CALCULI

Calcium Oxalate and Calcium Phosphate Calculi

Most urinary calculi in children in the United States are composed of calcium oxalate and/or calcium phosphate. The most common metabolic abnormality in these patients is normocalcemic **hypercalciuria.** Between 30% and 60% of children with calcium stones have hypercalciuria without hypercalcemia. Other metabolic aberrations that predispose to stone disease include hyperoxaluria, hyperuricosuria, hypocitruria, heterozygous cystinuria, hypomagnesuria, hyperparathyroidism, and renal tubular acidosis (see Chapter 529).

Hypercalciuria may be absorptive, renal, or resorptive. The primary disturbance in absorptive hypercalciuria is intestinal hyperabsorption of calcium. In some children, an increase in 1,25-dihydroxyvitamin D is associated with the increased calcium absorption, whereas in others the process is independent of vitamin D. **Renal hypercalciuria** refers to impaired renal tubular reabsorption of calcium (see Chapter 519.8). Renal leak of calcium causes mild hypocalcemia, which triggers an increased production of parathyroid hormone, with increased intestinal absorption of calcium and increased mobilization of calcium stores. Resorptive hypercalciuria is uncommon and is found in patients with primary hyperparathyroidism. Excess parathyroid hormone secretion stimulates intestinal absorption of calcium and mobilization of calcium stores. Table 547-4 summarizes the metabolic evaluation of children with hypercalciuria.

Hyperoxaluria is another potentially important cause of calcium stones. Oxalate increases the solubility product of calcium oxalate crystallization 7-10 times more than calcium. Consequently, hyperoxaluria significantly increases the likelihood of calcium oxalate precipitation. Oxalate is found in high concentration in tea, coffee, spinach, and rhubarb. Primary hyperoxaluria is a rare autosomal recessive disorder that can be subclassified into glycolic aciduria and L-glyceric aciduria. Most patients with primary hyperoxaluria have glycolic aciduria; oxalic and glycolic acids are increased in the urine of affected persons. Both defects cause increased endogenous production of oxalate, with hyperoxaluria, urolithiasis, nephrocalcinosis, and injury to the kidneys. Death from renal failure occurs by age 20 yr in untreated patients. **Oxalosis,** defined as extrarenal deposition of calcium oxalate, occurs when renal insufficiency is present with elevated plasma oxalate. Calcium oxalate deposits appear first in blood vessels and bone marrow, and with time they appear throughout the body. Secondary hyperoxaluria is more common and can occur in patients with increased intake of oxalate and oxalate precursors such as vitamin C, in those with pyridoxine deficiency, and in children with intestinal malabsorption.

Enteric hyperoxaluria refers to disorders such as inflammatory bowel disease (see Chapter 336), pancreatic insufficiency (see Chapter 350), and biliary disease (see Chapter 356), in which there is gastrointestinal malabsorption of fatty acids, which bind intraluminal calcium and form salts that are excreted in the feces. Normally, calcium forms a complex with oxalate to reduce oxalate absorption, but if calcium is unavailable, there is increased absorption of unbound oxalate.

Table 547-3 Urine Chemistry: Normal Values

URINE CONSTITUENT	AGE	RANDOM	TIMED	COMMENTS
Calcium	0-6 mo 7-12 mo ≥2 yr	<0.8 mg/mg creat <0.6 mg/mg creat <0.21 mg/mg creat	<4 mg/kg/24 hr	Prandial variation Sodium-dependent
Oxalate*	<1 yr 1-<5 yr 5-12 yr >12 yr	0.15-0.26 mmol/mmol creat 0.11-0.12 mmol/mmol creat 0.006-0.15 mmol/mmol creat 0.002-0.083 mmol/mmol creat	≥2 yr: <0.5 mmol/1.73 m^2/24 hr	Random urine mmol/mmol highly age-dependent Excretion rate/1.73 m^2 constant through childhood and adulthood
Uric acid	Term infant >3 yr	3.3 mg/dL GFR† <0.53 mg/dL GFR	<815 mg/1.73 m^2/24 hr	Excretion rate/1.73 m^2 from >1 yr age; constant through childhood
Magnesium	>2 yr	<0.12 mg/mg creat	<88 mg/1.73 m^2/24 hr	Excretion rate/1.73 m^2 constant through childhood
Citrate		>400 mg/g creat		Limited data available for children
Cystine		<75 mg/g creat	<60 mg/1.73 m2/24 hr	Cystine >250 mg/g creat suggests homozygous cystinuria

*Oxalate oxidase assay.
†(mg/dL uric acid) (serum creatinine concentration/urine creatinine concentration).
creat, Creatinine; GFR, glomerular filtration rate.
From Milliner DS: Urolithiasis. In Avner ED, Harmon WE, Naiudet P, editors: Pediatric nephrology, *ed 5, Philadelphia, 2004, Lippincott Williams & Wilkins, p. 1103, with permission.*

Table 547-4 Metabolic Evaluation of Children with Hypercalciuria

TYPE	SERUM CALCIUM	RESTRICTED CALCIUM (URINE)	FASTING CALCIUM (URINE)	CALCIUM LOAD (URINE)	PARATHYROID HORMONE (SERUM)
Absorptive	N	N or I	N	I	I
Renal	N	I	I	I	N
Resorptive	I	I	I	I	I

I, increased; N, normal.

Hypocitraturia refers to a low excretion of citrate, which is an important inhibitor of calcium stone formation. Citrate acts as an inhibitor of calcium urolithiasis by forming complexes with calcium, increasing the solubility of calcium in the urine, and inhibiting the aggregation of calcium phosphate and calcium oxalate crystals. Disorders such as chronic diarrhea, intestinal malabsorption, and renal tubular acidosis (see below) can cause hypocitraturia. It may also be idiopathic.

Renal tubular acidosis (RTA) is a syndrome involving a disturbance of acid–base balance within the kidney that can be classified into 3 types, one of which predisposes to renal calculi that typically are calcium phosphate (see Chapter 529). In type 1 RTA, the distal nephron does not secrete hydrogen ion into the distal tubule. The urine pH is never <5.8, and hyperchloremic hypokalemic acidosis results. Patients acquire nephrolithiasis, nephrocalcinosis, muscle weakness, and osteomalacia. Type 1 RTA can be an autosomal dominant disorder, but more often it is acquired and associated with systemic diseases such as Sjögren syndrome, Wilson disease, primary biliary cirrhosis, and lymphocytic thyroiditis, or it results from amphotericin B, lithium, or toluene (an organic solvent associated with glue sniffing).

From 5-8% of patients with **cystic fibrosis** (see Chapter 403) have urolithiasis. Typically the stones are calcium, and they often become manifest in adolescence or young adulthood. Microscopic nephrocalcinosis also occurs in younger children with the disease. These patients do not have hypercalciuria, and the propensity for urolithiasis has been speculated to result from an inability to excrete a sodium chloride load or from intestinal malabsorption.

Other disorders can play a role in causing calcium stones. **Hyperuricosuria** may be related to the epitactic growth of calcium oxalate crystals around a nucleus of uric acid crystals or to the action of uric acid as a counter inhibitor of urinary mucopolysaccharides, which inhibit calcium oxalate crystallization. **Heterozygous cystinuria** is found in some patients with calcium stones. The mechanism is unknown but may be similar to that of uric acid. Sarcoidosis (see Chapter 165) causes an increased sensitivity to vitamin D_3 and thus an increased absorption of calcium from the gastrointestinal tract. In Lesch-Nyhan syndrome (see Chapter 89), there is excessive uric acid synthesis. These patients are more likely to form uric acid stones, but some of these stones may be calcified. **Immobility** can cause hypercalciuria by mobilization of calcium stores. High-dose corticosteroids can cause hypercalciuria and calcium oxalate precipitation. Furosemide, which is administered in the neonatal intensive care unit, also can cause severe hypercalciuria, urolithiasis, and nephrocalcinosis.

In some children, calcium calculi are idiopathic. A complete metabolic evaluation must be performed before this diagnosis is made.

Cystine Calculi

Cystinuria accounts for 1% of renal calculi in children. The condition is a rare autosomal recessive disorder of the epithelial cells of the renal tubule that prevents absorption of the 4 dibasic amino acids (cystine, ornithine, arginine, lysine) and results in excessive urinary excretion of these products. The only known complication of this familial disease is the formation of calculi, because of the low solubility of cystine. The patients usually have acidic urine, which leads to a higher rate of

precipitation. In the homozygous patient, the daily excretion of cystine usually exceeds 500 mg, and stone formation occurs at an early age. Heterozygotes excrete 100-300 mg/day and typically do not have clinical urolithiasis. The sulfur content of cystine gives these stones their faint radiopaque appearance.

Struvite Calculi

Urinary tract infections (see Chapter 538) caused by urea-splitting organisms (most often *Proteus* spp., and occasionally *Klebsiella* spp., *Escherichia coli, Pseudomonas* spp., and others) result in urinary alkalinization and excessive production of ammonia, which can lead to the precipitation of magnesium ammonium phosphate (struvite) and calcium phosphate. In the kidney, the calculi often have a staghorn configuration, filling the calyces. The calculi act as foreign bodies, causing obstruction, perpetuating infection, and causing gradual kidney damage. Patients with struvite stones also can have metabolic abnormalities that predispose to stone formation. These stones often are seen in children with neuropathic bladder, particularly those who have undergone a urinary tract reconstructive procedure (see Chapter 542). Struvite stones also can form in the reconstructed bladder of children who have undergone augmentation cystoplasty or continent urinary diversion.

Uric Acid Calculi

Calculi containing uric acid represent <5% of all cases of lithiasis in children in the United States but are more common in less-developed areas of the world. Hyperuricosuria with or without hyperuricemia is the common underlying factor in most cases. The stones are radiolucent on x-ray. The diagnosis should be suspected in a patient with persistently acid urine and urate crystalluria.

Hyperuricosuria can result from various inborn errors of purine metabolism that lead to overproduction of uric acid, the end product of purine metabolism in humans. Children with the Lesch-Nyhan syndrome and patients with glucose-6-phosphatase deficiency (see Chapter 87) form urate calculi as well. In children with short-bowel syndrome (see Chapter 338.7), and particularly those with ileostomies, chronic dehydration and acidosis sometimes are complicated by uric acid lithiasis.

One of the most common causes of uric acid lithiasis is the rapid turnover of purine with some tumors and myeloproliferative diseases. The risk of uric acid lithiasis is especially great when treatment of these diseases causes rapid breakdown of nucleoproteins. Uric acid calculi or “sludge” can fill the entire upper collecting system and cause renal failure and even anuria. Urates also are present within calcium-containing stones. In these cases, >1 predisposing factor for stone formation can exist.

Indinavir Calculi

Indinavir sulfate is a protease inhibitor approved for treating HIV infection (see Chapter 276). Up to 4% of patients acquire symptomatic nephrolithiasis. Most of the calculi are radiolucent and are composed of indinavir-based monohydrate, although calcium oxalate and/or phosphate have been present in some. After each dose, 12% of the drug is excreted unchanged in the urine. The urine in these patients often contains crystals of characteristic rectangles and fan-shaped or starburst crystals. Indinavir is soluble at a pH of <5.5. Consequently, dissolution therapy by urinary acidification with ammonium chloride or ascorbic acid should be considered.

Nephrocalcinosis

Nephrocalcinosis refers to calcium deposition within the renal tissue. Often nephrocalcinosis is associated with urolithiasis. The most common causes are furosemide (administered to premature neonates), distal RTA, hyperparathyroidism, medullary sponge kidney, hypophosphatemic rickets, sarcoidosis, cortical necrosis, hyperoxaluria, prolonged immobilization, Cushing syndrome, hyperuricosuria, monogenetic causes of hypertension, and renal candidiasis.

TREATMENT

In a child with a renal or ureteral calculus, the decision whether to remove the stone depends on its location, size, and composition (if known) and whether obstruction and/or infection is present. Pain is managed with nonsteroidal antiinflammatory drugs or opiates. Small ureteral calculi often pass spontaneously, although the child might experience severe renal colic. The narrowest segment of the ureter is the ureterovesical junction. **α-Adrenergic blockers,** such as tamsulosin, terazosin, and doxazosin, facilitate stone passage in children and adults by decreasing ureteral pressure below the stone and decreasing the frequency of the peristaltic contractions of the obstructed ureter. In many cases, passage of a **ureteral stent** past the stone endoscopically relieves pain and dilates the ureter sufficiently to allow the calculus to pass. In cases such as children with a uric acid calculus or an infant with a furosemide-associated calculus, dissolution alkaline therapy may be effective.

If the calculus does not pass or seems unlikely to pass or if there is associated urinary tract infection, removal is necessary (Table 547-5). **Lithotripsy** of bladder, ureteral, and small renal pelvic calculi using the holmium laser through a flexible or rigid ureteroscope is quite effective. Extracorporeal shock wave lithotripsy has been successfully applied to children with renal and ureteral stones, with a success rate of >75%. Another alternative is percutaneous nephrostolithotomy, in which access to the renal collecting system is obtained percutaneously, and the calculi are broken down by ultrasonic lithotripsy. In cases in which these modalities are unsuccessful, an alternative is laparoscopic removal; this procedure can be performed using the da Vinci robot.

In children with urolithiasis, the underlying metabolic disorder should be addressed (Table 547-6). Because lithiasis results from elevated concentrations of specific substances in the urine, maintaining a continuous high urine output by maintaining a high fluid intake often is an effective method of preventing further stones. The high fluid intake should be continued at night, and usually it is necessary for the child to get up at least once at night to urinate and drink more water.

Table 547-5 Primary Surgical Treatment Options vs Stone Size and Location

STONES	SHOCK WAVE LITHOTRIPSY	URETEROSCOPY	PERCUTANEOUS NEPHROLITHOTOMY
RENAL			
<1 cm	Most common	Optional	Optional
1-2 cm	Most common	Optional	Optional
>2 cm	Optional	Rare	Most common
LOWER POLE			
<1 cm	Most common	Optional	Optional
>1 cm	Optional	Optional	Most common
URETERAL			
Proximal	Most common	Optional	Occasional
Distal	Optional	Most common	Rare

After Durkee CT, Balcom A: Surgical management of urolithiasis, Pediatr Clin North Am *53:465–477, 2006, with permission.*

Table 547-6 Suggested Therapy for Urolithiasis Caused by Metabolic Abnormalities		
METABOLIC ABNORMALITY	**INITIAL TREATMENT**	**SECOND-LINE TREATMENT**
Hypercalciuria	Reduction of dietary Na+ Dietary calcium at RDA Thiazides	Potassium citrate Neutral phosphate
Hyperoxaluria	Adjustment of dietary oxalate Potassium citrate	Neutral phosphate* Magnesium Pyridoxine*
Hypocitric aciduria	Potassium citrate Bicarbonate	
Hyperuricosuria	Alkalinization	Allopurinol
Cystinuria	Alkalinization Reduction of dietary Na+	Tiopronin (Thiola) D-Penicillamine Captopril

*Initial therapy in primary hyperoxaluria.
RDA, recommended dietary allowance.
From Milliner DS: Urolithiasis. In Avner ED, Harmon WE, Niaudet P, editors: Pediatric nephrology, *ed 5, Philadelphia, 2004, Lippincott Williams & Wilkins, p. 1104, with permission.*

A daily fluid intake of 2-2.5 L in adolescent stone formers is recommended, with greater intake during summer months.

Dietary sodium intake in children has increased significantly, up to 6.8 g/day as a consequence of increased consumption of salty, processed foods. High sodium intake increases urinary excretion of calcium and may result in hypocitraturia. In addition, increased salt intake induces metabolic acidosis. To compensate for the acid load, the kidneys conserve anions, including urinary citrate, which contributes to hypocitraturia. Reduction in dietary intake of sodium and increased potassium intake is indicated.

Although counterintuitive, low-calcium diets are less effective in the treatment of calcium stones than diets containing normal amounts of calcium and limited amounts of sodium and animal protein. Low-sodium, low-protein diets reduce urinary calcium and oxalate excretion. Children with stone disease should avoid excess calcium intake. However, children require calcium for bone development and recommendations for daily calcium intake vary by age. Consequently, calcium restriction in children should be avoided. Thiazide diuretics also reduce renal calcium excretion. Addition of potassium citrate, an inhibitor of calcium stones, with a dosage of 1-2 mEq/kg/24 hr is beneficial. An excellent source of citrate is lemonade, because 4 oz of lemon juice contains 84 mEq of citric acid. A daily mixture of 4 oz of reconstituted lemon juice in 2 L of water and sweetened to taste should significantly increase the urinary citrate level. In difficult cases, neutral orthophosphate should be given also, although it is poorly tolerated.

In patients with uric acid stones, allopurinol is effective. Allopurinol is an inhibitor of xanthine oxidase and is effective in reducing the production of both uric acid and 2,8-dihydroxyadenine and can help control recurrence of both types of stones. In addition, urinary alkalinization with sodium bicarbonate or sodium citrate is beneficial. The urine pH should be ≥6.5 and can be monitored at home by the family.

Maintaining a high urine pH can also prevent recurrence of cystine calculi. Cystine is much more soluble when the urinary pH is >7.5, and alkalinization of urine with sodium bicarbonate or sodium citrate is effective. Another important medication is D-penicillamine, which is a chelating agent that binds to cysteine or homocysteine, increasing the solubility of the product. Although poorly tolerated by many patients, it has been reported to be effective in dissolving cystine stones and in preventing recurrences when hydration and urinary alkalinization fail. *N*-Acetylcysteine appears to have low toxicity and may be effective in controlling cystinuria, but long-term experience with it is lacking.

Treatment of type 1 RTA involves correcting the metabolic acidosis and replacing lost potassium and sodium. Sodium or potassium citrate therapy, or both, is necessary. When the metabolic acidosis is corrected, the urinary citrate excretion returns to normal.

Treatment of primary hyperoxaluria involves liver transplantation because the defective enzymes are hepatic. Ideally, this procedure is performed before renal failure occurs. In the most severe cases, kidney transplantation is also necessary.

Bibliography is available at Expert Consult.

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Gynecologic Problems of Childhood

PART XXV

Chapter 548

History and Physical Examination

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HISTORY

The approach to both the history and physical examination of a child is often a collaborative effort that involves the child, her caregiver, and the provider. With a preverbal or very young patient, clinicians obtain the majority of the history from a parent or caregiver. Even for the very young patient, developmentally appropriate social questions directed to the patient can put her at ease and help to develop cooperation and rapport that will facilitate a subsequent examination. Specific patient, caregiver, or provider concerns about vaginal discharge or bleeding, pruritus, external genital lesions or abnormalities should direct a problem-focused history. In a patient presenting with vaginal bleeding, questions should focus on recent growth and development, signs of pubertal progression, trauma, vaginal discharge, medication exposure, and any history of foreign objects in the vagina. For complaints of vulvovaginal irritation, pruritus, or discharge, questions should concentrate on perineal hygiene, the onset and duration of symptoms, the presence and quality of discharge, exposure to skin irritants, recent antibiotic use, travel, presence of medical comorbidities or infections in the patient and her family members, and other systemic symptoms of illness or skin conditions. Throughout the history, the patient should be encouraged to ask her own questions. Occasionally, the child is brought to the clinician because she or her parents have concerns about anatomic findings, developmental changes, or congenital anomalies. It helps to understand the family's concerns and if a specific reason, event, or family history raised the need for a gynecologic consultation.

GYNECOLOGIC EXAMINATION

The physical examination of the patient should be tailored to the child's age, complaint, and any other concerns elicited in the history. The menstrual period should be included with an assessment of other vital signs as age appropriate.

Neonates

The delivering obstetrician should briefly examine the external genitals of female infants to confirm the patency of the vagina and assess the presence of any obvious genital anomalies. The pediatrician's newborn examination should note any abnormal findings such as ambiguous genitalia, imperforate hymen, urogenital abnormalities, abdominal mass, or inguinal hernia that might herald a gynecologic problem.

Placing the infant in the supine position with thighs flexed against the abdomen allows visualization of the neonate's external genitals. Estrogenic effects commonly notable in neonates include prominence of the labia majora and a white vaginal discharge. The labia minora and hymen may protrude slightly from the vestibule. A small amount of neonatal vaginal bleeding from endometrial sloughing following maternal hormone withdrawal might occur. Bleeding that is excessive or persistent beyond 1 mo of life requires further evaluation. Breast buds may be palpable at the time of the neonatal examination but should regress in the 1st mo of life; occasionally, nipple discharge occurs.

The vaginal orifice may be difficult to see. Gentle lateral traction on the labia majora usually allows complete visualization of the hymen and vaginal orifice. The hymen should be evaluated for patency. Most hymenal variations—imperforate, microperforate, septate—do not require treatment during the neonatal period. Variations should be noted and readdressed in subsequent visits. The hymen originates from the urogenital sinus. The uterus and vagina originate from the müllerian ducts. The concomitant renal malformations seen with müllerian anomalies are not associated with hymenal anomalies. Hymenal polyps seen in newborns typically regress in size as the maternal estrogen effects subside. Cervicovaginal mucus secretions can accumulate behind the blocked outflow tract of an imperforate hymen and manifest as a mucocolpos. *In this instance, correction of the imperforate hymen in the neonatal period is indicated if urinary obstruction occurs.*

The clitoris may appear large in proportion to the other genital structures, especially in premature infants. If the clitoris appears enlarged, the clitoral width should be measured; values >6 mm in a newborn indicate a need for further evaluation. *If clitoromegaly and ambiguous genitals are present, the obstetrician and pediatrician should immediately obtain expert consultation for evaluation of the infant and to counsel the parents.* Congenital adrenal hyperplasia is the most common cause of ambiguous genitals (accounting for more than 90% of cases), and the salt-wasting forms can lead to rapid dehydration with subsequent fluid and electrolyte imbalance (see Chapter 576). Delay in the diagnosis and treatment of congenital adrenal hyperplasia may be life-threatening.

In the neonate, the ovaries are <1 cm in diameter and average 1 cm^3 in volume. Antenatal or postnatal abdominopelvic ultrasound might reveal small simple ovarian cysts, which represent normal follicles. Because of the abdominal location of ovaries in the neonate, ovarian enlargement can manifest as a palpable abdominal mass. Large cysts (>4-5 cm) or those of a complex nature pose the risk of ovarian torsion, hemorrhage into the cyst, or, uncommonly, an ovarian tumor. A nonresolving or enlarging neonatal ovarian cyst warrants expert consultation. If the mass causes respiratory compromise or gastrointestinal obstruction, decompression is usually performed. Cyst aspiration can give temporary relief, but it is not recommended as the fluid aspirated is not reliable for diagnosis and fluid may reaccumulate. If a cystectomy is done for appropriate clinical indications the cyst wall should be surgically excised to prevent reaccumulation of fluid and to provide a pathologic diagnosis, the remaining ovarian tissue should be left in situ, and the contralateral ovary should be inspected. Preservation of normal ovarian tissue is recommended for all benign lesions, and salpingo-oophorectomy should not be performed unless clinically indicated.

Infants and Prepubertal Girls

As the maternal estrogen effect subsides, the genitals of the female infant change in appearance. The labia begin to flatten. The hymenal membrane loses its redundancy and becomes translucent. The hypoestrogenic prepubertal vaginal epithelium appears thin, red, and sensitive to the touch. The vaginal mucosa of young children can have longitudinal ridges running along the axis of the vagina at 3 o'clock, 6 o'clock, and 9 o'clock, which can cause small protrusions on the hymen at these locations. The cervix usually appears flat and flush with the vaginal vault. During infancy, the uterus regresses in size and does not return to its birth size until the 5th or 6th year. The prepubertal cervix : fundus ratio is 2 : 1.

As puberty approaches, the child experiences increasing endocrine activity of the hypothalamus, pituitary gland, adrenal gland, and ovaries (see Chapter 561). The labia majora begin to fill out, and the labia minora thicken and elongate as a result of increased estrogen levels. The hymen thickens and becomes more redundant. Clear or white physiologic secretions may be present. Breast buds begin to appear, either bilateral or initially unilateral with subsequent development of the contralateral breast.

Indications for Genital Examination

Genitourinary complaints or suspected genitourinary pathology warrant assessment of the external and internal genitals of pediatric patients, specifically in cases of vaginal bleeding, vaginal discharge, vulvar trauma, presence of a foreign body, perineal or pelvic masses, vulvovaginal ulcerative or inflammatory lesions, congenital anomalies, or suspected sexual abuse.

Preparation

The genital examination in prepubertal girls requires a gentle, patient approach to maximize cooperation and minimize fear and embarrassment. A clear, simple explanation of what the exam involves can facilitate the child's comfort and cooperation. The presence of a parent or caregiver during the entire examination provides reassurance for most children. For the older prepubertal patient, the physician may discuss whether the patient wishes to have a family member present during the examination. Even in the presence of the caregiver, the examiner should speak directly to the child. Prior to initiating any part of the examination, the provider should explicitly verify with both the patient and her caregiver that the caregiver has given permission for the examination. This provides an opportunity to explain to the child the privacy of body parts and who may examine or touch those areas. It is useful to educate the patient and caregiver about the basic anatomy and hygiene of the external genital area. Before each step of the examination, the physician should explain what will occur. Allowing an older child the option of watching her examination with a handheld mirror may contribute to her comfort and understanding. Forcible restraint is never indicated; if optimal evaluation is not possible, the clinician must assess the acuity of the complaint and pathology and determine the potential need for a multi-visit examination or an examination under anesthesia.

Positioning

A variety of techniques and positions can facilitate the genital examination in prepubertal patients. Children younger than 4 yr of age can be placed on the parent or caregiver's lap with the child's legs straddling the parent's thighs. If the child permits, she may be positioned on the table in the supine position with the hips fully abducted and the feet together in the frogleg (diamond or butterfly) position. Older children may prefer to use the stirrups. The head of the examination table should be raised so that eye contact can be maintained with the patient throughout the examination. When the child is supine, grasping the labia majora along the inferior portion between the thumb and index finger and gently pulling outward and posteriorly (labial traction) allows visualization of the vaginal introitus. Alternatively, the child may be placed in the knee–chest position with elevation of the buttocks and hips. This position provides exposure of the inferior portion of the hymen, the lower vagina, and possibly the upper vagina and cervix but has the disadvantage of having the child face away from the examiner.

Some extremely cooperative children tolerate a vaginoscopic examination in an outpatient office setting for better intravaginal assessment. The endoscope (either a cystoscope or a hysteroscope) is placed in the vagina and the labia are gently opposed, allowing the vagina to distend with water. This technique permits visualization of the vagina and cervix, allowing for the evaluation of an injury, lesion, and anatomic variant or for the presence of a foreign body. Application of 2% lidocaine gel at the introitus makes the insertion easier and less irritating for the patient. If a more complete examination is indicated or if the child is too young, frightened or unable to cooperate, an examination under anesthesia is recommended.

Documentation

Clinicians should thoroughly and accurately document genital exam findings in the medical record, reserving conclusions and diagnostic terms for the impression and plan portion of the documentation rather than in the description of exam findings. Each structure visualized should be noted (e.g., clitoris, labia majora, labia minora, urethra, vestibule, and rectum) with attention to describing normal appearance and any anatomic variations (e.g., the configuration of the hymen as annular, crescentic, etc.). Describing any findings or lesions using a clock-face method provides a consistent reference point; a sketch or magnified photograph may also be helpful. Future examiners will rely on this documentation as a record with which they compare their findings and note any variances. Changes should be noted in any follow-up examinations.

Adolescents

Some teens prefer to initially meet and discuss the reason for their visit with the provider without their parent or guardian present, and this request should be honored (see Chapter 112). A majority of the time, obtaining a history from an adolescent begins with meeting the patient and her parent or caregiver together to review her history and the reason for the visit and to explain the concepts of confidentiality and privacy. Familiarity with local laws governing limitations to confidential services should guide the protection of the adolescent and her parents' rights to information access and privacy. The Guttmacher Institute provides an up-to-date listing of state and federal laws in the United States affecting access to medical care (http://www.guttmacher.org/statecenter/spibs/index.html). Brief discussions of normal pubertal development and menstruation can reassure both patients and their parents or guardians and provide valuable education on appropriate menstrual flow, menstrual hygiene and the duration and frequency of bleeding. Introducing the menstrual diary as an invaluable tool for the teen can help patients, parents, and clinicians identify abnormal bleeding patterns that might require further evaluation. Many apps are available for tracking menstrual periods on a smart phone or computer.

After the initial interview with the teen and her parent or caregiver, the confidential and sensitive portion of the history, particularly sexual history and alcohol, tobacco, and drug use, is taken with the teen alone. Such a request could be phrased as follows: "I would like to give your daughter an opportunity to ask any questions she might have privately, so would you mind stepping out of the room for a moment?" Concerns for the presence of vaginal discharge, the potential for sexually transmitted infections, pregnancy, or menstrual aberration should be explored. Teens and their parents should be informed of the proper use and accessibility of condoms, all contraceptive methods, and emergency contraception.

A number of resources for educating adolescents regarding their first pelvic examination and in-depth sexual history and psychosocial screening tools are available. These include the North American Society for Pediatric and Adolescent Gynecology (http://www.naspag.org), the American Academy of Pediatrics (http://www.aap.org), the Society for Adolescent Health and Medicine (http://www.adolescenthealth.org), and the American College of Obstetricians and Gynecologists (http://acog.org/Patients).

Pelvic Examination

Table 548-1 presents the indications for the first pelvic examination in adolescents: age older than 21 yr, abnormal uterine bleeding, vulvovaginitis, severe dysmenorrhea, unexplained dysuria or abdominal pain, evaluation and removal of a foreign body, and placement of an intrauterine device. If an adolescent does not meet 1 of the criteria

Table 548-1	Suggested Indications for Pelvic Examination in Adolescents

Age 21 yr for initial Pap test
Unexplained menstrual irregularities, including pubertal aberrations
Severe dysmenorrhea
Unexplained abdominal pain
Unexplained dysuria
Abnormal vaginal discharge
Placement of intrauterine device
Removal of foreign body

Modified from The initial reproductive visit. Committee Opinion No. 460. American College of Obstetricians and Gynecologists. Obstet Gynecol *116:240–243, 2010.*

Table 548-2	Recommendations for First Gynecologic Evaluation

Between 13 and 15 yr of age
First gynecologic encounter focuses on patient education; pelvic examination is generally not indicated
First pelvic examination with Pap test at 21 yr of age, unless otherwise indicated by Table 548-1

Modified from Well-woman visit. Committee Opinion No. 534. American College of Obstetricians and Gynecologists. Obstet Gynecol *120:421–424, 2012.*

listed in Table 548-1, the American College of Obstetricians and Gynecologists recommends that the first gynecologic encounter occur between the ages of 13 and 15 yr (Table 548-2) with attention toward anticipatory guidance focusing on normal pubertal development and menstruation. Patients should undergo screening for sexually transmitted infection with each new sexual partner. With the availability of urine and vaginal swab nucleic acid amplification testing for chlamydia and gonorrhea, sexually transmitted infection screening does not necessitate a speculum exam.

Prior to the initiation of a physical examination, all young women should be offered the choice of having a medical attendant, family member, or friend present during her examination. At the initial gynecologic exam, the physician should explain the process in understandable terms. A thorough evaluation begins with an assessment of body mass index, blood pressure, menstruation status, thyroid, lymph nodes, breast development, abdominal exam, and skin. The external genitals should be examined with the patient in the dorsal lithotomy position while communication is maintained between the physician and patient. Elevating the head of the examination table allows the teen and her examiner to maintain eye contact. The teen can hold a mirror to follow along with the examination, and she should be encouraged to ask questions. Inspection of the vulva is followed by inspection of the Bartholin, urethral, and Skene glands. The clitoris, normally 2-4 mm in width, is then assessed; a clitoris wider than 10 mm, especially in the presence of other signs of virilization, suggests a need for further evaluation. The hymenal anatomy should also be evaluated. Throughout the examination, the proper nomenclature for genital anatomy should be emphasized with the teen to empower her to use proper wordage with the avoidance of slang when referring to her body.

Because the initial Papanicolaou test is deferred until 21 yr of age and cultures for sexually transmitted infections can be obtained from urine or vaginal swabs, the need for a speculum exam is decreasing in this age group. If a speculum exam is indicated, use an appropriate sized speculum, such as the Huffman (½ in wide × 4 in long) or Pedersen (⅞ in wide × 4 in long). Shorter speculums will not allow visualization of the entire vaginal canal. The adolescent patient should be reassured that the exam may be uncomfortable but should not be painful and that her request to stop or wait will be honored. Encouraging the patient to watch with a hand-held mirror facilitates patient education and can be empowering. She may be told before the insertion of the speculum that she will experience a pressure sensation. Before touching the introitus, it may be useful to touch the inner thigh with the speculum. Compression of the urethra anteriorly should be avoided. Gentle pressure with a finger for displacement of the fourchette posteriorly further facilitates proper speculum placement. After visualization of the vagina and cervix, specimens should be obtained as indicated. A bimanual examination, sometimes with a single digit, allows palpation of the vaginal walls and cervix and bimanual assessment of the uterus and adnexa. Reassurance of normal findings throughout the examination should be provided, and normal variants to anatomy should be pointed out to the teen as they are encountered (e.g., asymmetric labia minora).

Following the examination, it is appropriate to review the exam findings with the teen (and her parent) and initiate a collaborative discussion of the management plan. Encouraging the adolescent to participate in decision making empowers her to undertake responsibility for her health, may strengthen compliance with the medical plan, and acknowledge her as a unique individual.

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Chapter 549
Vulvovaginitis

Holly R. Hoefgen and Diane F. Merritt

Vulvovaginitis, the most common gynecologic-based problem for prepubertal children, is typically caused by either inadequate or excessive hygiene or chemical irritants. The condition is usually improved by hygiene measures and education of the caregivers and child.

ETIOLOGY

Vulvitis refers to external genital pruritus, burning, redness, or rash. **Vaginitis** implies inflammation of the vagina, which can manifest as a discharge with or without an odor or bleeding. These may occur simultaneously as vulvovaginitis. When a child presents with vulvovaginitis, the history should include questions on hygiene (wiping from front to back) and information about possible chemical irritants (bath soaps, laundry detergents, swimming pools, or hot tubs). The caregiver can be asked about a history of diarrhea, perianal itching, or nighttime itching. The possibility of foreign objects being placed into the vagina should also be asked, although the young child is unlikely to remember or recall. Children are especially prone to nonspecific vulvovaginitis for a variety of reasons, including their nonestrogenized state, poor perianal hygiene, and the proximity of the anus to the vagina, which is without geographic barriers given the flattened labia and lack of pubic hair (Fig. 549-1 and Table 549-1).

EPIDEMIOLOGY

Infectious vulvovaginitis, where a specific pathogen is isolated as the cause of symptoms, may be caused by fecal or respiratory pathogens and cultures might reveal *Escherichia coli* (see Chapter 200), *Streptococcus pyogenes, Staphylococcus aureus* (see Chapter 181), *Haemophilus influenzae* (see Chapter 194), *Enterobius vermicularis,* and, rarely, *Candida* spp. (see Chapter 234). These organisms may be transmitted by the child using improper toilet hygiene and manually from the nasopharynx to the vagina. The children present with perianal redness, an inflamed introitus, and often a yellow-green or mildly bloody discharge. They may be observed to be grabbing their genital area or "digging" in their underwear, which is usually stained with yellow-brown discharge. Attempts to treat these bacterial etiologies with antifungal medication will fail and often the antifungal product will lead to more irritation. Table 549-2 gives specific treatment recommendations based on the bacteria localized.

Neisseria gonorrhoeae or *Chlamydia trachomatis* also are causes of specific infectious vulvovaginitis (see Chapter 120). Management of children who have sexually transmitted infections requires close cooperation between clinicians and child-protection authorities. Official investigations for sexual abuse, when indicated, should be initiated promptly (see Chapter 40). If acquired after the neonatal period, some diseases (e.g., gonorrhea, syphilis, and chlamydia) are virtually 100% indicative of sexual contact. For other diseases (e.g., human papillomavirus infection and herpes simplex virus), the association with sexual contact is not as clear. Presumptive treatment for children who have been sexually assaulted or abused is not recommended because (1) the incidence of most sexually transmitted infections in children is low after abuse/assault, (2) prepubertal girls appear to be at lower risk for ascending infection than adolescent or adult women, and (3) regular follow-up of children usually can be ensured. Although *Trichomonas vaginalis* can be transmitted vertically and can be seen in children up to 1 yr of age, it is an uncommon cause of specific infectious vulvovaginitis in the unestrogenized prepubertal girl.

Figure 549-1 Labial adhesions. *(Photo courtesy of Diane F. Merritt, MD.)*

Other causes of specific infectious vulvovaginitis include *Shigella* (see Chapter 199), which often manifests with a blood-tinged purulent discharge, and *Yersinia enterocolitica* (see Chapter 203). *Candida* infections (yeast) commonly cause diaper rash, but they are unlikely to cause vaginitis in children because the alkaline pH of the prepubertal vagina does not support fungal infections. Exceptions can occur in diabetic or immunocompromised children or children on prolonged antibiotics. Pinworms are the most common helminthic infestation in the United States, with the highest rates in school-age and preschool children. Perianal itching can lead to excoriation and, rarely, bleeding.

CLINICAL MANIFESTATIONS

Diaper Dermatitis

Diaper dermatitis is the most common dermatologic problem in infancy and occurs in half of all diaper-wearing infants and children. The moisture and contact with urine and feces irritates the skin, and colonization with *Candida* spp. increases the severity of the dermatitis. First-line treatment includes hygiene measures such as increasing the frequency of diaper changes, allowing the infant to be diaper free,

Table 549-1 Specific Vulvar Disorders in Children

ORGANISM	PRESENTATION	DIAGNOSIS	TREATMENT
Molluscum contagiosum (Fig. 549-7)	1-5 mm discrete, skin-colored, dome-shaped, umbilicated lesions with a central cheesy plug	Diagnosis usually is made by visual inspection	The disease generally is self-limited and the lesions can resolve spontaneously Treatment choices in children may include cryosurgery, laser, application of topical anesthetic and curettage, podophyllotoxin, and topical silver nitrate Use of topical 5% imiquimod cream and 10% potassium hydroxide has been reported with similar effects
Condyloma acuminata	Skin-colored papules, some with a shaggy, cauliflower-like appearance	Diagnosis usually is made by visual inspection. Biopsy should be reserved for when the diagnosis is in question. Human papillomavirus DNA testing is not helpful	Many lesions in children resolve spontaneously, “wait and see” often utilized in children (60 days). Topical treatment with imiquimod cream and podophyllotoxin is the most studied (daily qhs 3 times/wk × 16 wk, wash 6-10 hr after application). General anesthesia is usually required for surgical/ablative procedures (cryotherapy, laser therapy, electrocautery)–reserve for symptomatic or large lesions. Other treatments have been utilized in adults, including trichloroacetic acid, 5-fluorouracil, sinecatechins, topical cidofovir, and cimetidine. The efficacy and safety of these treatments in children has not been established
Herpes simplex	Blisters that break, leaving tender ulcers	Visual inspection confirmed by culture from lesion	*Infants:* Acyclovir 20 mg/kg body weight IV q8 hr × 21 days for disseminated and central nervous system disease or × 14 days for disease limited to the skin and mucous membranes *Genital/mucocutaneous disease:* Age 3 mo–2 yr: 15 mg/kg/day IV divided in q8h × 5-7 days Age 2-12 yr (1st episode): Same as above or 1,200 mg/day divided in q8h dosing × 7-10 days Age 2-12 yr (Reoccurrence): 1,200 mg/day in q8h dosing or 1,600 mg/day in bid dosing × 5 days (give 3-5 days for children older than 12 yr)

Table 549-1 Specific Vulvar Disorders in Children—cont'd

ORGANISM	PRESENTATION	DIAGNOSIS	TREATMENT
Labial agglutination (see Fig. 549-1)	May be asymptomatic or can cause vulvitis, urinary dribbling, urinary tract infection, or urethritis	Diagnosis is made by visual inspection of the adherent labia, often with a central semitranslucent line	Does not require treatment if the patient is asymptomatic *Symptomatic patients:* Topical estrogen cream or betamethasone ointment applied alone or in combination daily for 6 wk directly to the line of adhesion, using a cotton swab while applying gentle labial traction Estrogen should be interrupted if breast budding occurs Mechanical or surgical separation of the adhesions is rarely indicated The adhesions usually resolve in 6-12 wk; unless good hygiene measures are followed, reoccurrence is common To decrease the risk of recurrence, an emollient (petroleum jelly, A and D ointment) should be applied to the inner labia for 1 mo or longer at bedtime
Lichen sclerosus (Fig. 549-4)	A sclerotic, atrophic, parchment-like plaque with an hourglass or keyhole appearance of vulvar, perianal, or perineal skin, subepithelial hemorrhages may be misinterpreted as sexual abuse or trauma The patient can experience perineal itching, soreness, or dysuria	Diagnosis usually is made by visual inspection Biopsy should be reserved for when the diagnosis is in question	Ultrapotent topical corticosteroids are the first-line therapy (clobetasol propionate ointment 0.05%) once or twice a day for 4-8 wk Once symptoms are under control, the patient should be tapered off the drug unless therapy is required for a flare-up In many girls, the condition resolves with puberty; however, this is not always the case and patients may require long-term follow-up
Psoriasis	Children are more likely than adults to have vulvar psoriasis noted as pruritic, well-demarcated, nonscaly, brightly erythematous, symmetrical plaques. The classic extragenital lesion are similar but with a silver scaly appearance	Diagnosis may be confirmed by locating other affected areas on the scalp or in nasolabial folds or behind the ears	Vulvar lesions may be treated with low to medium potency topical corticosteroids, increasing strength as necessary
Atopic dermatitis	Chronic cases can result in crusty, weepy lesions that are accompanied by intense pruritus and erythema Scratching often results in excoriation of the lesions and secondary bacterial or candidal infection	It may be seen in the vulvar area but characteristically affects the face, neck, chest, and extremities	Children with this condition should avoid common irritants and use topical corticosteroids (such as 1% hydrocortisone) for flare-ups If dry skin is present, lotion or bath oil can be used to seal in moisture after bathing
Contact dermatitis	Erythematous, edematous, or weepy vulvar vesicles or pustules can result, but more often the skin appears inflamed	Associated with exposure to an irritant, such as perfumed soaps, bubble bath, talcum powder, lotions, elastic bands of undergarments, or disposable diaper components	Avoidance of irritant Topical corticosteroids for flare-ups
Seborrheic dermatitis	Erythematous and greasy, yellowish scaling on vulva and labial crural folds associated with greasy dandruff-type rash of scalp, behind ears and face	Diagnosis usually is made by visual inspection	Gentle cleaning, topical clotrimazole with 1% hydrocortisone added
Vitiligo (Fig. 549-5)	Sharply demarcated hypopigmented patches, often symmetric in vaginal and anal regions. May be present in periphery at body orifices and extensor surfaces	Clinical. Test for associated illness if clinically warranted (thyroid disease, Addison disease, pernicious anemia, diabetes mellitus)	If desired, treat limited lesions with low-potency corticosteroids or tacrolimus. See dermatologist for extensive lesions.

Table 549-2 Antibiotic Recommendations for Specific Vulvovaginal Infections

ETIOLOGY	TREATMENT
Streptococcus pyogenes *Streptococcus pneumoniae*	Penicillin V, 250 mg PO bid-tid ×10 days Amoxicillin 50 mg/kg/day (max: 500 mg/dose) divided into 3 doses daily × 10 days Erythromycin ethyl succinate, 30-50 mg/kg/day (max: 400 mg/dose) divided into 4 doses daily TMP-SMX 6-10 mg/kg/day (TMP component) divided into 2 doses daily × 10 days Clarithromycin 7.5 mg/kg bid (max: 1 g/day) × 5-10 days Reoccurrence most likely from asymptomatic pharyngeal carriage in child or family member. However, failure of penicillin regimens can occur For penicillin resistance: Rifampin 10 mg/kg every 12 hr × 2 days
Staphylococcus aureus	Topical mupirocin 2% 3 times daily to the affected skin area If systemic therapy required: Amoxicillin-clavulanate, 45 mg/kg/day (amoxicillin) PO divided into 2 or 3 doses daily × 7 days (first-line treatment because of high penicillin resistance) Extensive resistance to common antibiotics noted, recommend susceptibility testing for further antibiotic use MRSA: TMP-SMX double-strength 8-10 mg/kg/day; culture abscesses, incision and drainage
Haemophilus influenzae	Amoxicillin, 40 mg/kg/day divided into 3 doses daily × 7 days Cases of treatment failure or non-encapsulated *H. influenzae*, amoxicillin–clavulanate is recommended
Yersinia	TMP-SMX 6 mg/kg (TMP component) daily for 3 days
Shigella	TMP-SMX 10/50 mg/kg/day (max: 160/600) divided into 2 doses daily × 5 days Ampicillin 50-100 mg/kg/day divided into 4 doses daily (adult max: 4 g/day) × 5 days Azithromycin 12 mg/kg (max: 500) × 1 day, then 6 mg/kg/day (max: 250 mg) × 4 days (in areas of high resistance to above regimens or when sensitivities are unknown) For resistant organisms: Ceftriaxone 50-75 mg/kg/day IV or IM divided into 1 or 2 doses (max: 2 g/day) × 2-5 days
Chlamydia trachomatis	*Children weighing <45 kg:* Erythromycin base or ethylsuccinate 50 mg/kg/day PO divided into 4 daily doses × 14 days *Children weighing >45 kg but age younger than 8 yr:* azithromycin 1 g PO in a single dose *Children age older than 8 yr (treat per adult regimens):* *Preferred regimens:* Azithromycin 1 g PO in a single dose *or* Doxycycline 100 mg PO twice daily × 7 days *Alternative regimens:* Erythromycin base 500 mg PO 4 times daily × 7 days Erythromycin ethylsuccinate 800 mg PO 4 times daily × 7 days Levofloxacin 500 mg PO daily × 7 days Ofloxacin 300 mg PO twice daily for 7 days
Neisseria gonorrhoeae	*Children weighing <45 kg:* Ceftriaxone, 125 mg IM in a single dose *Children weighing ≥45 kg:* Treat with adult regimen of 250 mg IM in a single dose *Children with bacteremia or arthritis:* Ceftriaxone, 50 mg/kg (max dose for children weighing <45 kg: 1 g) IM or IV in a single dose daily × 7 days *Dual treatment:* Addition of either azithromycin 1 g PO in a single dose or doxycycline 100 mg PO twice daily × 7 days to the above regimens may assist in hindering the development of antibiotic resistance. *Note:* The CDC removed cefixime 400 mg PO in a single dose from recommended medications because of increasing resistance; however, can be used as part of a dual therapy if ceftriaxone is unavailable
Trichomonas	Metronidazole, 15-30 mg/kg/day tid (max: 250 mg tid) × 5-7 days *or* Tinidazole 50 mg/kg (≤2 g) as a single dose for children older than 3 yr
Pinworms *(Enterobius vermicularis)*	Mebendazole (Vermox), 1 chewable 100 mg tablet, repeated in 2 wk *or* Albendazole, 100 mg for child younger than age 2 yr or 400 mg for older child, repeated in 2 wk Pyrantel pamoate 10 mg/kg in a single administration

MRSA, methicillin-resistant *Staphylococcus aureus;* TMP-SMX, trimethoprim-sulfamethoxazole.

frequent bathing, and application of water-repellant barriers such as zinc oxide. If diaper dermatitis persists after these conservative measures, or if the classic satellite lesions of *Candida* are present, treatment with an antifungal can decrease the inflammation.

Physiologic Leukorrhea

Neonates and peripubertal girls can present with a white or clear or mucus discharge, which is a physiologic effect of estrogen. Some girls complain of the moisture and mucus, but an explanation should reassure the patient and her mother.

Genital Ulcers

Acute genital ulceration of the vulva (Fig. 549-2) is described in young adolescents who are not sexually active and can occur in association with oral aphthous ulcers. Although linked to infectious causes such as Epstein-Barr, cytomegalovirus, mycoplasma, and influenza A, recent data suggest these ulcers may be idiopathic vulvar aphthoses.

Other potential etiologies include inflammatory bowel disease, Behçet disease, pemphigoid, Stevens-Johnson syndrome, drug eruption, or mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome.

These lesions usually appear on the mucosal surfaces of the introitus as painful red or white lesions that evolve into sharply demarcated red-rimmed ulcers with a necrotic or eschar-like base. The time course is generally 10-14 days until remission occurs. The lesions are quite painful and pain management and urinary diversion with a Foley catheter may be necessary. Patients with acute genital ulcers show a fairly consistent picture of flu-like prodromal symptoms, dysuria, and

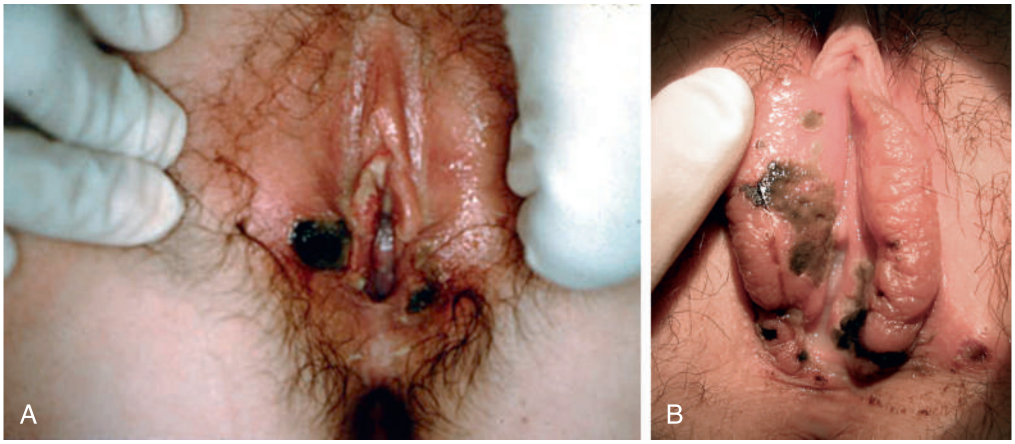

Figure 549-2 Aphthous ulcers. *(Photo courtesy of Diane F. Merritt, MD.)*

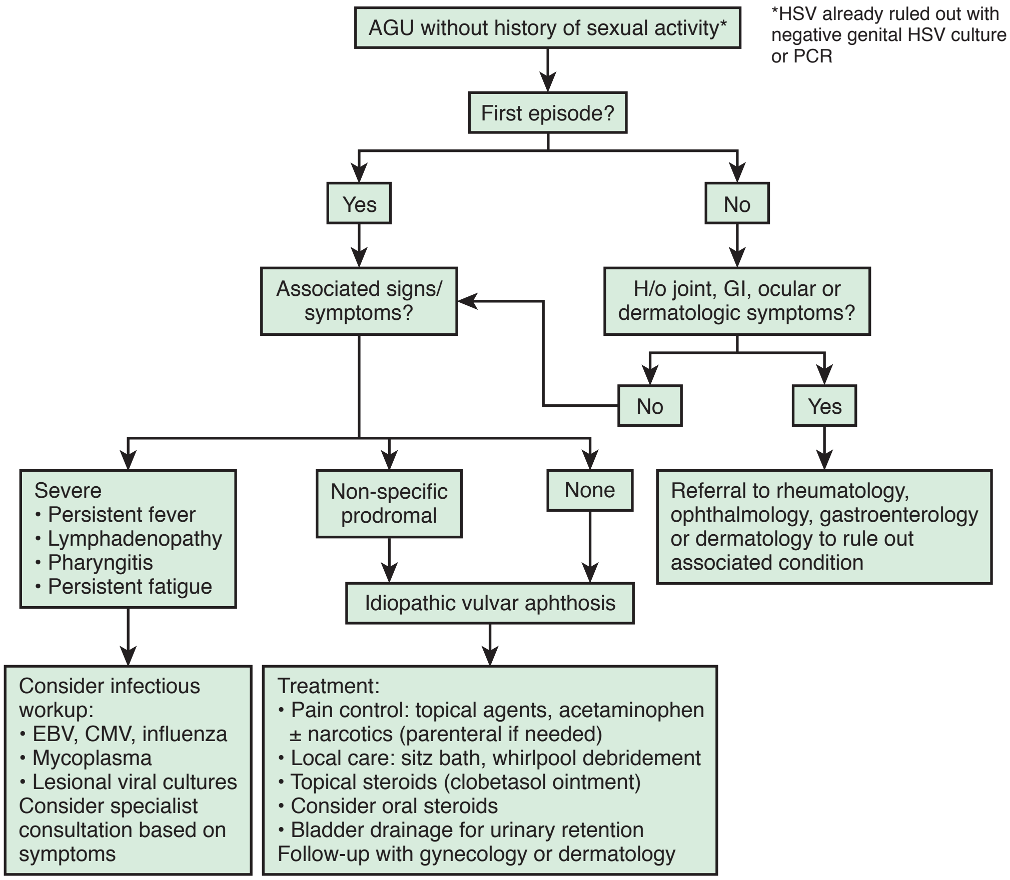

Figure 549-3 Algorithm for evaluation and management of acute genital ulcers in nonsexually active young girls. *(From Rosman IS, Berk DR, Bayliss SJ, et al: Acute genital ulcers in nonsexually active young girls: case series, review of the literature, and evaluation and management recommendations.* Pediatr Dermatol *29(2);147–153, 2012.)*

vulvar pain. One-third of patients present with a history of or develop oral ulcerations. Evaluation includes culture for herpes simplex virus to exclude this etiology. Special testing for systemic disease depends on history. Biopsies are usually nondiagnostic as they yield acute and chronic inflammatory changes. Figure 549-3 outlines suggested evaluation and management for initial and recurrent disease. Evaluation for Behçet disease (see Chapter 161) using the International Study Group diagnostic guidelines should be considered with recurrent or severe cases. (See Table 549-1 for other common etiologies.) Treatment of acute genital ulcers should include topical Xylocaine 2% jelly, sitz baths, good hygiene, and acetaminophen. Nonsteroidal antiinflammatory drug avoidance is suggested because of a possible causative link. Hospitalization may be required for pain management not controlled with oral narcotics, urinary retention requiring Foley catheterization or for whirlpool debridement should hygiene become difficult. Antibiotic treatment is not required unless evidence of bacterial superinfection exists or the patient is immunocompromised. Insufficient evidence exists to recommend whether oral steroid treatment is effective but may be helpful in the setting of recurrent outbreaks. Ultrapotent topical steroids (clobetasol 0.05% ointment), however, are beneficial in oral aphthous ulcers and may prove helpful in acute genital ulcers as well.

Figure 549-4 Lichen sclerosus. *(Photo courtesy of Diane F. Merritt, MD.)*

Dermatoses

Dermatologic conditions often affect the vulvar area in children; it is important to determine if the girl presenting with vulvar irritation has a skin condition elsewhere on the body. Lichen sclerosus is commonly seen in the anogenital region and has a characteristic appearance of white skin changes associated with areas of erosion, ulceration, and petechia. This disease can cause severe discomfort and most commonly presents with vulvar or perianal pruritus, dysuria, and constipation. Patients may also present without any symptoms, which may lead to underrecognition and under treatment. If untreated, lichen sclerosus can lead to destruction and scarring of normal genital architecture, including labial resorption, obliteration of the clitoris, narrowing of the introitus, and painful fissures that may become secondarily infected. Once thought to resolve with puberty, this theory is now controversial and many postmenarchal adolescents still suffer from disease (Fig. 549-4). Lichen sclerosis may be treated with potent topical steroids, clobetasol propionate 0.05% applied once or twice daily until the symptoms resolve.

Vitiligo is an acquired skin depigmentation resulting from an autoimmune process directed at epidermal melanocytes. Lesions appear as sharply demarcated patches of pigment loss, often symmetrically located around vagina and anal area. Similar lesions of hypopigmentation can be found surrounding body orifices and extensor surfaces (Fig. 549-5). Although diagnosis is clinical, there is an association with other autoimmune or endocrine disorders (hypothyroidism, Graves disease, Addison disease, pernicious anemia, insulin-dependent diabetes mellitus) and workup should include evaluation for at least thyroid dysfunction. Mild topical corticosteroid cream or ointment may be prescribed for children. Dermatologists may offer immunomodulators (tacrolimus), and phototherapy.

Vulvar psoriasis presents as pruritic, well-demarcated nonscaly, erythematous, symmetrical plaques that involve the vulva, perineum and/or gluteal folds. Lesions on the mons pubis may have the more characteristic scaly appearance. The classic signs of psoriasis may also be appreciated with pitting nail beds, posterior auricular erythema or a silvery scaling rash found elsewhere on the body. Many of the treatments used in adults may not be appropriate in children. Psoriasis may be treated with moisturizers, topical steroids, and light therapy. Teens may be treated with coal tar, retinoids, tacrolimus, and calcipotriene, which is a derivative of vitamin D_3.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Children with symptoms of vulvovaginitis often have had a previous evaluations and treatment failures. Cultures with sensitivities to test for specific pathogens may be obtained with cotton swabs or urethral (Calgiswab) swabs moistened with nonbacteriostatic saline. Use of a swab can cause discomfort or, rarely, minimal bleeding. The premoistened swab can be placed vertically between the labia minora to collect secretions, as it is not necessary to place the swab into the vagina.

Figure 549-5 Vitiligo. *(Photo courtesy of Diane F. Merritt, MD.)*

Testing for gonorrhea and chlamydia may be done by culture or by nucleic acid amplification testing, depending on institutional or state and Centers for Disease Control guidelines. Tests for *Shigella* and *H. influenzae* might require special media and collection procedures.

If pinworms (see Chapter 294) are suspected, transparent adhesive tape or an anal swab should be applied to the anal region in the morning before defecation or bathing and then placed on a slide. Eggs seen on microscopic examination confirm the diagnosis, and sometimes the pinworms can be seen at the anal verge. Clinical history is often more indicative of disease than physical exam, and a negative tape test does not rule out this pathogen as a cause.

If the vaginal discharge is serosanguineous, if a foul odor is present, or if the discharge fails to respond to hygiene measures, consider presence of a vaginal foreign body (Fig. 549-6). If inspection suggests presence of a foreign body, the vagina can be irrigated, or an examination under anesthesia may reveal the foreign body. Vaginoscopy is an excellent diagnostic tool and can be performed in an unsedated cooperative patient in an outpatient setting, or under general anesthesia if necessary. Using a cystoscope with saline or water irrigation to gravity, insert the endoscopic device into the vagina, gently oppose the labia, the vagina will distend and the entire vaginal cavity and cervix may be easily assessed.

TREATMENT AND PREVENTION

The treatment of specific vulvovaginitis should be directed at the organism causing the symptoms (see Table 549-1). Treatment of nonspecific vulvovaginitis includes sitz baths and avoidance of irritating or harsh soaps and chemicals and tight clothing that abrades the perineum. External application of bland emollient barriers such as nonprescription diaper rash medications and petroleum jelly may be helpful. Proper perineal hygiene is critical for long-term improvement. Younger children need supervised perineal hygiene, and caregivers should be advised to wipe the genital area from front to back. Use of a warm moistened washcloth or diaper wipe is helpful after initially wiping with toilet tissue. Girls should wear cotton underwear and limit time spent in tights, leotards, jeggings, tight jeans, and wet swimsuits. Soaking in warm clean bathwater for 15 min intervals (no shampoo or

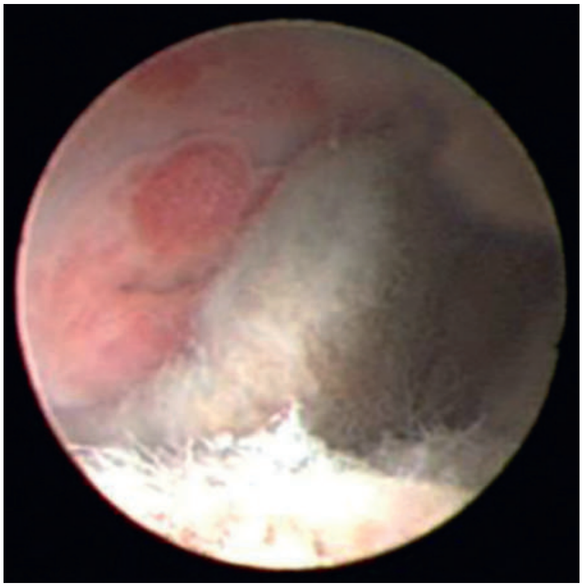

Figure 549-6 Vaginal foreign body as seen through vaginoscope. *(Photo courtesy of Diane F. Merritt, MD.)*

Figure 549-7 Molluscum contagiosum. *(Photo courtesy of Diane F. Merritt, MD.)*

bubble bath) is soothing and helps with cleaning the area. Parents should be counseled to avoid all scented, antiseptic, and deodorant-based soaps, and to eliminate the use of fabric softeners or dryer sheets when laundering undergarments.

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Chapter 550
Bleeding
Diane F. Merritt

Vaginal bleeding in infants and prepubescent children should always be evaluated. Bleeding can be seen as early as the 1st wk of life, resulting from endometrial sloughing associated with maternal estrogen withdrawal. A thorough history and physical must be obtained as the 1st step in evaluating the problem. Common causes for vaginal bleeding in children are vulvovaginitis, vaginal foreign bodies, dermatologic conditions, and urethral prolapse; less common causes are endogenous or exogenous estrogenic effects; and the most worrisome causes include neoplasms and trauma.

Vulvovaginitis (see Chapter 549) may be caused by respiratory, oral and fecal pathogens, some of which produce serosanguineous drainage (e.g., *Streptococcus, Shigella*) or cause vulvar bleeding resulting from irritation and excoriation of the skin. Prepubertal girls are at a higher risk for developing these irritations because the protective labia of pubertal girls are not fully developed and thus, the vaginal opening and vagina are easily more exposed to irritants. Further, the hypoestrogenic vaginal mucosa is thin and lacks the protective effects of an acidic pH from lactobacilli. The alkaline vaginal pH noted in prepubertal girls results in an environment more prone to infection. Handwashing, improved perineal hygiene (wiping front to back, use of wet wipes after bowel movement), and avoidance of topical irritants, chemicals, and perfumed or deodorant soaps and bubble baths will reduce nonspecific vulvovaginitis. External application of bland emollient barriers such as over the counter diaper rash ointments or petroleum jelly may helpful (see Table 549-2 in Chapter 549). Antibiotics will help with recurrent or persistent infections if a specific pathogen is identified by culture.

Hematuria is suspected when the urine is red or brown. Gross hematuria may be confused with vaginal bleeding. A positive urinary dipstick can confirm blood, but pigments and metabolites may also cause red or brown urine (see Chapter 509). The cause of gross hematuria in symptomatic children is usually elicited by a complete history, physical examination and urinalysis. Additional diagnostic studies may include ultrasound of the kidneys and bladder, urine culture, measurements of urine calcium/creatinine, and serum C3 and creatinine. Treatment depends on the diagnosis.

Dermatoses may present with bleeding. Lichen sclerosus (see Fig. 549-4 and Table 549-1 in Chapter 549). is characterized by chronic inflammation, intense pruritus, loss of normal architecture, thinning and whitening of the vulvar and perianal skin often in a butterfly or keyhole distribution. Petechiae or blood blisters can arise and be mistaken as a sign of sexual abuse. Diagnosis is based on these classic clinical characteristics, but may be confirmed by a tissue biopsy if necessary. As a first-line treatment, potent topical steroids, such as clobetasol propionate ointment 0.05%,may be applied sparingly to the affected tissue 1-2 times a day under physician supervision; they usually result in improvements in appearance and pruritus. The steroid should be used for the shortest duration necessary then be stopped or tapered. Flare-ups can occur and require retreatment.

Foreign bodies are a common cause of vaginal bleeding, and children present with blood-stained and foul-smelling discharge. The most common object found in prepubertal girls is toilet paper. A physical exam in knee–chest or frogleg position can sometimes reveal the object. Vaginal irrigation may be done in the office setting using a small feeding tube, a syringe, and warm water. If the object is not visible on examination, irrigation is unlikely to remove it and examination under anesthesia and vaginoscopy are often required. Vaginoscopy not only allows removal of a foreign object but also can facilitate diagnosis of other causes of the bleeding.

Trauma to the vulva or vagina is especially concerning. Most of these injuries are accidental, but physical and sexual abuse must be ruled out (see Chapter 40). Straddle injuries such as falling on the cross bar of a bicycle or slipping in the bathtub may result in bruising, hematomas, and lacerations. In general, if the trauma is accidental, the hymen and vagina are spared as most accidental injuries involve the mons and labia. *If there are no eyewitnesses to the injury, if there is no history to explain the clinical findings, and especially if there is a laceration of the hymen, abuse must be considered in the differential diagnosis, and a forensic interview of the patient and family should take place.* If the injury is penetrating, further examination and imaging are necessary to evaluate the urethra, bladder, anus, and intraabdominal structures. General anesthesia may be needed to fully assess injuries and allow adequate repair; while minor lacerations may be repaired in a cooperative child under sedation or local anesthesia. If the patient is able to

void spontaneously, nonexpanding hematomas can be observed and treated with ice, pressure, and pain medications. Large expanding hematomas should be carefully evaluated and may require drainage, ligation of the bleeding vessels, and/or placement of a closed suction drain, especially if the overlying skin is showing signs of necrosis. A Foley catheter should be placed for children who are having difficulty with voiding.

Urethral prolapse (see Chapter 544) is another potential cause of bleeding in the prepubertal girl. The patient may present with a circular protrusion of the urethral mucosa through the external meatus forming a friable vulvar mass. Downward traction at the introitus enables visualization of the vaginal orifice separate from the urethral mass and assists with confirming the correct diagnosis. Patients may be asymptomatic or present with bleeding, dysuria, or difficulty with urination. Low estrogen state, trauma, chronic cough, and constipation are believed to be predisposing factors. Treatment is conservative, with application of estrogen cream at the area of prolapse twice daily for 1-2 wk and then, if prolapse is still present, continued use until the prolapse resolves. Surgical excision is very rarely necessary to remove necrotic tissue.

Neoplasms of the vulva and vagina are rare (see Chapter 553). Infantile hemangiomas are the most common benign vascular neoplasm of infancy, affecting 5% of all infants. Most lesions proliferate then involute, and only a few require intervention. Hemangiomas of the perineum may be associated with spinal dysraphism, so a neurologic assessment should be performed. Intralesion and systemic steroids have been used to treat infantile hemangiomas. Propranolol therapy results in a good response rate. Laser therapy and surgical excision are sometimes used.

Like hemangiomas, hymenal polyps are usually benign. If these polyps are noted at birth, they generally regress after maternal levels of estrogen decrease in the infant. If hymenal polyps persist, grow, or cause discomfort they may be removed. Vaginal polyps, especially if they cause bleeding, should be removed (not followed) and sent for pathologic evaluation. Yolk sac (endodermal sinus) tumors of the vagina are rare but may cause vaginal bleeding. Serum α-fetoprotein is a reliable marker. Rhabdomyosarcoma is the most common soft-tissue sarcoma of childhood. In children, the most common sites are the head and neck (35%) and genitourinary region (25%) (see Chapter 500). Rhabdomyosarcoma arising in the genitourinary tract are commonly the sarcoma botryoides variant and are typically seen in the 1st decade, often before age 3 yr, and present with vaginal discharge and bleeding. Treatment consists of a multimodal approach, including surgery, radiation therapy, and chemotherapy. The survival rate is >90% when an early diagnosis is made.

Vaginal bleeding can be a presenting sign of precocious puberty, which is defined as pubertal development that is 2.5-3.0 SD earlier than the average age. Guidelines for the evaluation of premature development state that pubic hair or breast development requires evaluation generally when it occurs before age 7 yr in non–African-American girls and before age 6 yr in African-American girls (see Chapters 561 and 562). Rapidity of pubertal progression, such as Tanner stage 3 breast development before 8 yr of age, may also require evaluation. The most common etiology is gonadotropin-dependent or central precocious puberty (see Chapter 562.1) where there is premature enhancement of pulsatile gonadotropin-releasing hormone release resulting in ovarian follicle growth and estrogen production. Gonadotropin-independent precocious puberty, where estrogen production is not under hypothalamic control and is produced peripherally, such as from an ovarian/adrenal tumor or McCune Albright syndrome, is less common.

A thorough physical exam must be done, looking for secondary sex characteristics and documenting breast and pubic hair development using the Sexual Maturation Index (Tanner Staging; see Chapter 110.1). Documenting height and weight on a growth chart will assist in identifying accelerated growth velocity. Diagnostic tests include a left wrist x-ray to look for advanced bone age. Elevated serum luteinizing hormone levels are highly suggestive of central precocity, but the gold standard is measurement of gonadotropins after gonadotropin-releasing hormone or gonadotropin-releasing hormone–agonist stimulation. In all cases of central precocious puberty, MRI imaging of the brain is needed to determine if a tumor is present. Pelvic ultrasound might show presence of ovarian or adrenal pathology or uterine maturation in response to estrogen. Benign premature ovarian follicles or malignant ovarian germ cell tumors can produce elevated serum estradiol levels >100 pg/mL. If the estradiol is elevated, pelvic imaging by transabdominal ultrasound is mandated. Usually benign ovarian follicles produce short periods of estrogen elevation which is enough to stimulate the endometrial lining and result in endometrial shedding. Usually by the time the pelvic ultrasound is obtained the follicular structure has collapsed and resolved and the estrogen level has dropped to prepubertal range. If indicated central precocious puberty can be suppressed with leuprolide injections or histrelin implants. Germ cell tumors are treated by excision, staging and chemo or radiation therapy by protocols provided by oncologists.

Juvenile hypothyroidism commonly causes pubertal delay. Patients with severe, long-standing and untreated hypothyroidism may present with premature breast development, vaginal bleeding and abdominal distention resulting from ovarian enlargement and possibly ascites associated with deceleration of linear growth. A proposed mechanism is thyroid-releasing hormone–associated elevations of thyroid-stimulating hormone crossreacting with follicle-stimulating hormone resulting in follicle maturation and estradiol production. Treatment of the hypothyroidism results in improvement and reversal of symptoms.

Another etiology for childhood vaginal bleeding is exogenous exposures to estrogens. These exposures can occur from ingestion of birth control pills, foods, beauty products, and plastics that contain estrogen or estrogen-like components. Several other studies have assessed the risk of bisphenol A leaching from plastic cups and bottles. The importance of this is still being studied, but bisphenol A is known to have an estrogenic effect and thus could potentially be a cause for vaginal bleeding if ingested in high levels.

Vaginal bleeding in the prepubertal girl or infant can have many causes, which range from benign to malignant. A thoughtful history and physical examination must be done to identify the source of bleeding so that treatment can occur. The risk benefit of any therapy should be reviewed carefully with the family.

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Chapter 551

Breast Concerns

Kora N. Felsch and Diane F. Merritt

Presenting concerns of girls with breast disorders typically including the development or appearance of their breasts, breast pain, nipple discharge, or concerns about the presence of a mass. Although children and adolescents are very unlikely to have malignant or life-threatening breast problems, this population of patients should be referred to practitioners who have experience and familiarity with the immature and developing breast to avoid overtreatment with unnecessary diagnostic or surgical procedures.

BREAST DEVELOPMENT

Development of the breast begins around wk 5 of gestation, when the ectoderm on the anterior body wall thickens into 2 ridges known as the *mammary ridges*. They extend from the area of the developing axilla to the area of the developing inguinal canal. The ridge above and below the area of the pectoralis muscle recedes in utero, leaving the mammary primordium, which is the origin of the lactiferous ducts.

The initial lactiferous ducts form between wk 10 and 20 and become interspersed through the developing mesenchyme, which becomes the fibrous and fatty portions of the breast. The breast bud, under the stimulation of maternal estrogen, becomes palpable at wk 34 of gestation. This breast bud regresses within the 1st mo of life, because the estrogen stimulation is no longer present. The areola appears at 5 mo of gestation, and the nipple is seen shortly after birth. It is initially depressed and later becomes elevated.

Thelarche, or the onset of pubertal breast development, is hormonally mediated and normally occurs between the ages of 8 and 13 yr, with an average age of 10.3 yr. The initiation of thelarche and progression in females is affected by race, with normal thelarche occurring earlier in African-American girls than in white or Asian girls. This occurs when the hypothalamus releases gonadotropin-releasing hormone, which stimulates the pituitary gland to produce follicle-stimulating hormone and luteinizing hormone, which then stimulates the ovaries to produce estrogen. The estrogen leads to breast development.

Once thelarche is initiated, normal development of the breast occurs over 2-4 yr and is classified by the **sexual maturity rating** system (also known as Tanner Staging) into 5 stages (Chapter 110.1). Maturation can sometimes occur asymmetrically owing to fluctuation of the hormonal environments and various end organ sensitivities. Lack of development by age 13 yr is considered delayed and warrants endocrinology evaluation. Menarche usually occurs approximately 2 yr after initiation of breast development.

BREAST EXAMINATION

A breast examination should be included in the annual examination of all children and adolescents. Examination of the *newborn* includes assessment of breast size, nipple position, presence of accessory nipples, and nipple discharge. Examination of the *prepubertal girl* includes inspection and palpation of the chest wall for masses, pain, nipple discharge, and signs of premature thelarche. Examination of the *adolescent* is performed with the patient in the supine position; the arm ipsilateral to the breast that is being examined should be placed next to the patient's head. The breast tissue is examined with the flat pads of the middle fingers and the examiner can feel for abnormalities on the breast with a pattern similar to spokes on a wheel, in a circular clockwise pattern with concentric circles or by moving in a rotary fashion around the breast. Whatever the method used, the goal is to palpate all the breast tissue in a uniform fashion. The sexual maturity rating should be noted and axillary, supraclavicular, and infraclavicular nodes evaluated for lymphadenopathy. The areola should be compressed to assess for nipple discharge.

BREAST SELF-EXAMINATION

Controversy exists as to the utility of breast self-examination in the adolescent population. Experts believe that it might be ill advised to encourage breast self-examination in the adolescent because of a potential for unnecessary anxiety and possible unwarranted treatment in a population that is at low risk for malignant disease. The American College of Obstetricians and Gynecologists states that despite a lack of definitive data for or against breast self-examination, breast self-examination may be recommended beginning at age 19 yr. Women with previous exposure to *therapeutic chest radiation* therapy are advised to begin breast self-examination 8 yr after radiation therapy.

ABNORMAL DEVELOPMENT

Neonatal Breast Abnormalities

The condition in which breasts enlarge in the newborn period is *neonatal breast hypertrophy*. This is quite common in term infants of either sex and can occur as a result of elevated circulating maternal endogenous steroid hormones in late gestation. As maternal estrogen levels fall, prolactin levels can increase and the breasts can produce a clear or cloudy (milk-like) nipple discharge ("witch's milk") in male and female infants. Repeated manipulation of the breast can exacerbate the condition. On occasion, the hypertrophy is associated with mastitis caused by a staphylococcal or streptococcal infection; antibiotics should be administered.

Precocious Puberty

Premature thelarche is usually an isolated condition and is more common than previously thought. In one study, patients with a sexual maturity rating 2 or greater at 7 yr of age were 10.4% of white, 23.4% of black non-Hispanic, and 14.9% of Hispanic girls. However, it may also be the first symptom of precocious puberty. Precocious puberty occurs in 14-18% of girls with premature thelarche (see Chapter 562). Serial examinations, with particular emphasis on growth velocity, secondary sex characters such as pubic hair, pigmentation of the labia or areola, or vaginal bleeding are imperative to identify precocious puberty. Unless there are associated signs of precocious puberty, the parents should be reassured and the child should be followed.

Amastia

Complete absence of the breast, or amastia, is rare and is thought to occur from lack of formation or obliteration of the mammary ridge. Amastia is usually unilateral and can be congenital or associated with systemic disorders (e.g., ectodermal dysplasia, Crohn disease) or endocrine disorders (e.g., congenital adrenal hyperplasia, gonadal dysgenesis, hypogonadotropic hypogonadism). Novel gene mutations have been discovered that may be linked to syndromic amastia, including *PTPRF*, a protein tyrosine receptor type F gene, and ectodysplasin A receptor *(EDAR)*. It can be associated with anomalies of the underlying mesoderm, such as abnormal pectoralis muscles seen in Poland syndrome (aplasia of the pectoralis muscles, rib deformities, webbed fingers, and radial nerve aplasia) (Fig. 551-1). Amastia or hypomastia can also be iatrogenic, resulting from injuries sustained during thoracotomy, chest tube placement, radiotherapy, severe burns, and inappropriate biopsy of the breast bud. Treatment is surgical correction.

Polymastia and Polythelia

Supernumerary breast tissue (polymastia) and accessory nipples (polythelia) occur in approximately 1-6% of the population (Fig. 551-2). The abnormally placed tissue can be seen anywhere along the mammary ridges as a result of incomplete involution but is usually noted on the chest, upper abdomen, or just inferior to the normally positioned breast. There is an association between polythelia and anomalies of the urinary and cardiovascular system. Surgical excision of the accessory breasts or nipple is not usually needed. Resection of accessory tissue may be warranted if the patient has pain or for cosmetic reasons.

Breast Asymmetry and Hypomastia

Some degree of asymmetry is normal in women, and it may be more pronounced during puberty while the breasts are developing.

Figure 551-1 Preoperative frontal view of a patient with left breast hypoplasia secondary to Poland syndrome. *(From Sadove AM, van Aalst JA: Congenital and acquired pediatric breast anomalies: a review of 20 years' experience,* Plast Reconstr Surg *115:1039–1050, 2005, Fig. 13A.)*

Figure 551-2 Accessory nipple located inferior to the left breast. *(From Sadove AM, van Aalst JA: Congenital and acquired pediatric breast anomalies: a review of 20 years' experience,* Plast Reconstr Surg *115:1039–1050, 2005, Fig. 3.)*

Figure 551-3 Virginal mammary hypertrophy in a 12 yr old female. *(From Al-Saif AA, Al-Yahya GM, Al-Qattan MM: Juvenile mammary hypertrophy: Is reduction mammoplasty always feasible?* J Plast Reconstr Aesthet Surg *62:1470–1472, 2009, Fig. 1.)*

Table 551-1 Differential Diagnosis of Macromastia

Juvenile hypertrophy	Adrenal cortical tumors
Tumors of the breast	Exogenous hormones
Giant fibroadenoma	Estrogen
Hamartoma	Testosterone
Cystosarcoma phyllodes	Gonadotropins
Carcinoma	Corticosterone
Hormonally active tumors	Medications
Ovarian granulosa cell tumor	Cannabis
Ovarian follicular cysts	

From Desilva N, Brandt M: Breast disorders in children and adolescents. In Sanfilippo J, Lara-Torre E, editors: Clinical pediatric and adolescent gynecology, *London, 2008, Taylor & Francis.*

Hypoplasia of the breasts varies in degree from a nearly total absence of breast tissue to well-formed breasts that are considered by the patient to be too small. There are several causes for poor or absent breast development. The onset of breast development may be delayed with normal secondary sex characters; the breasts develop slowly but are normal in all other respects; a patient's family history might include late breast development. Other causes include ovarian dysfunction, hypothyroidism, and chest wall irradiation or surgery. Hypoplastic breast tissue can also be associated with a tuberous breast anomaly. Treatment depends on the underlying cause. Patients with mild asymmetry and with no other associated pathology should be reassured. Surgical correction is an option for women with marked asymmetry but should be delayed until after puberty.

Juvenile or Virginal Hypertrophy

Spontaneous massive growth of the breasts during puberty and adolescence is thought to be the result of excessive end-organ sensitivity to gonadal hormones, although both the hormone receptors and serum estradiol levels are normal. The underlying cause, if any, should be determined and removed (Table 551-1). When growth is extreme it is termed *macromastia* or *gigantomastia.* It is more commonly bilateral, often occurs over a brief period, and most commonly affects adolescent girls (Fig. 551-3). Physical and psychologic problems can affect posture and quality of life. Strong emotional support should be provided as this can affect an adolescent's self-esteem at a vulnerable time in her psychologic development. Management should be individualized and may range from reassurance or the use of supportive brassieres to reduction mammoplasty or even mastectomy. Medical therapy, such as tamoxifen, is available to slow breast growth in extreme cases until surgery can be performed. Surgical intervention often necessitates relocation of the nipple, which can result in decreased sensation and altered lactation, and it is not uncommon for the lesion to recur.

INFECTIONS

Mastitis is the most common infection of the breast. Although it is most common in lactating mothers, it can occur in young infants and adolescents. Neonatal mastitis is an infection that usually occurs in term or near-term infants. It should be treated aggressively to reduce the risk of forming abscesses. Adolescents can develop nonlactational mastitis or a breast abscess for unknown reasons, as a result of irritation of the skin (through shaving or nipple stimulation), trauma, a foreign body (e.g., piercing), ductal abnormality (such as ductal ectasia), or infection of an epidermal cyst. The initial therapy of all breast infections is antibiotics and analgesics. *Staphylococcus aureus* (see Chapter 181.1) or anaerobic bacilli (*bacteroides*) are the offending organism is almost all cases, and methicillin-resistant *S. aureus* coverage should be considered in communities where prevalence is high. Owing to the potential for breast abscess, the neonatal population should be treated with parenteral antibiotics for methicillin-resistant *S. aureus* or guided by gram stain, when available. Adolescents may be initially treated with warm compresses and oral antibiotics. Abscesses should be surgically evaluated (with ultrasound guidance if necessary) and drained as necessary. If incision and drainage is performed, a small, periareolar incision is indicated.

TRAUMA AND INFLAMMATION

Breast trauma is common in adolescent girls participating in contact sports. The trauma usually takes the form of contusion or hematoma and can resolve spontaneously or may be associated with late cystic changes in the breast or fibrosis with retraction of the skin or the nipple over the injured area.

NIPPLE DISCHARGE

Nipple discharge must be carefully evaluated and a distinction made among galactorrhea (milky white discharge), blood, or other discharge (Table 551-2). A careful history and physical examination directed at the possible etiologies of galactorrhea will help the practitioner determine the etiology. Examination of the discharge assists in diagnosis. Benign conditions are usually associated with a milky, sticky, thick discharge; infection is associated with a purulent discharge; intraductal papilloma and cancer are associated with a serous, serosanguineous, or bloody discharge. Preoperative evaluations by mammography, hemoccult, ductography, and cytology are poor predictors of histologic diagnosis. Therefore, patients with pathologic nipple discharge should undergo biopsy for accurate diagnosis.

Galactorrhea

Cytologic evaluation of nipple discharge is not recommended. Serum pregnancy testing and prolactin and thyroid levels are obtained to rule out the presence of a thyroid abnormality, a pituitary prolactinoma, and pregnancy (in the postpubertal adolescent). If the prolactin level

Table 551-2 Common Causes of Nipple Discharge
Pregnancy
Medicines
Hormones (oral contraceptives, estrogen, progesterone)
Blood pressure drugs (methyldopa, verapamil)
Tricyclic antidepressants
Tranquilizers (antipsychotics)
Antinausea drugs (metoclopramide)
Herbs (nettle, fennel, blessed thistle, anise, fenugreek seed)
Illicit drugs (marijuana, opiates)
Stimulation of the breast (sexual or from exercise)
Thyroid abnormalities
Chronic emotional stress
Hypothalamic tumors
Chest wall conditions
Herpes zoster
Trauma
Burns
Tumors
Breast conditions
Mammary duct ectasia
Chronic cystic mastitis
Intraductal cysts
Intraductal papillomas

is elevated, visual field studies and a head MRI might reveal presence of a pituitary adenoma (see Chapter 560). Treatment is directed by results of history, physical exam, and lab studies. Patients should be instructed to avoid nipple stimulation and stop any offending drugs. Hypothyroidism should be treated and prolactin tumors managed with appropriate medical or surgical care. Treatment of galactorrhea (not thyroid related) consists primarily of dopamine agonists such as bromocriptine or cabergoline. Surgical intervention, usually transsphenoidal hypophysectomy, is rarely required.

Bloody Discharge

In adolescent athletes, bloody discharge may be due to chronic nipple irritation (jogger's nipple), discharge from the ducts of Montgomery (on the edge of the areola, not through the nipple) or duct ectasia. Cytologic assessment should be performed. Surgical consultation for a mass is indicated because intraductal breast papillomas have occurred in adolescents. However, there have been no reported cases of breast cancer in infants. Bloody nipple discharge in infants is most likely from mammary duct ectasia, and if the following studies are normal (prolactin, estradiol, thyrotropin, and ultrasound) then watchful waiting may be appropriate.

MASTALGIA

The most common causes of breast pain in adolescents are exercise and benign breast changes. Physiologic swelling and tenderness occur on a cyclic basis, most commonly during the premenstrual phase, and are secondary to hormonal stimulation and resulting proliferative changes. Hormonal imbalance can cause exaggerated responses in the breast tissue, especially in the upper and outer quadrants. Nodularity, poorly localized tenderness, and a soreness radiating to the axilla and arm are usual accompanying findings. The preferable term for these changes is *benign breast changes* rather than fibrocystic disease. Treatments recommended for this condition and exercise-induced pain include a firm supportive sports-type bra, heat, and analgesics. Oral contraceptives often improve the breast pain. A course of nonsteroidal antiinflammatory drugs is also effective. Methylxanthines (caffeine in coffee, tea, carbonated drinks) and smoking should be eliminated. Evening primrose oil and vitamin E are popular but unproven treatments.

BREAST MASSES

Peripubertal Masses

A mass in the developing breast can be of concern to the adolescent and her family. Initial breast development at the onset of thelarche can be asymmetric and thus mistaken for a "mass." The breast bud is palpable in these cases and should be distinguishable. Such asynchronous thelarche should be recognized to avoid biopsy and potential injury to the maturing breast. If there is any question, ultrasound can be used to evaluate for a mass. Unilateral thelarche has also been reported as a side effect of cimetidine and is reversible when the medication is stopped.

Table 551-3 Breast Masses in the Adolescent Girl
BENIGN
Fibroadenoma
Fibrocystic changes or cysts
Unilateral thelarche
Hemangioma
Intramammary lymph node
Fat necrosis
Abscess
Mastitis
Lipoma
Hematoma
Hamartoma
Macromastia (juvenile hypertrophy)
Galactocele
Intraductal papilloma
Juvenile papillomatosis
Lymphangioma
MALIGNANT
Malignant cystosarcoma phyllodes
Breast carcinoma
Metastatic disease
Lymphoma, neuroblastoma, sarcoma, rhabdomyosarcoma, acute leukemia

Data from Dehner LP, Hill DA, Deschryver K: Pathology of the breast in children, adolescents, and young adults, Semin Diagn Pathol *16:235–247, 1999; Simmons PS: Diagnostic considerations in breast disorders of children and adolescents,* Obstet Gynecol Clin North Am *19:91–102, 1992; and Divasta AD, Weldon C, Labow BI: The breast examination and lesions. In Emans SJ, Laufer MR, Goldstein DP, editors:* Pediatric and adolescent gynecology, *ed 6, Philadelphia, 2012, Lippincott Williams & Wilkins, pp. 405–420.*

Common Adolescent Breast Masses

Table 551-3 shows the differential diagnosis for breast masses in the adolescent patient. The patient should be questioned about the variation in symptoms with the menstrual cycle, associated symptoms such as nipple discharge, recent trauma to the breast, family history of breast masses or cancer, and history of chest radiation or malignancy. Because breast cancer in the adolescent is extremely rare, masses can be expectantly managed for extended periods with little concern for malignancy in this population.

The most common solid mass seen in adolescent girls is the **fibroadenoma**. Fibroadenomas are most often located in the upper outer quadrant of the breast. The average size is 2-3 cm, and 10-25% of patients have multiple lesions. The physical examination is usually diagnostic because these lesions are well circumscribed, rubbery, mobile, and not tender. In equivocal cases, an ultrasound may be helpful in making the diagnosis. Mammography is not indicated in the adolescent patient.

Fibroadenomas can develop because of a local exaggerated response to estrogen stimulation, and they can enlarge during the menstrual cycle. These lesions may be safely watched for at least 2 menstrual cycles, and some investigators suggest observation until adulthood. Approximately 10% of fibroadenomas regress spontaneously. The option of expectantly managing the patient until adulthood should be considered because the risk of primary cancer is very low in this population. If expectant management is chosen, serial ultrasounds every 6-12 mo may be done to ensure that the mass does not have malignant characteristics on imaging and that it is not enlarging or changing in contour until it starts regressing at which time the ultrasounds can be done on longer intervals. Approximately 4% of fibroadenomas grow, and so fine-needle aspiration or excision is recommended when a mass is enlarging, grows >5 cm (because of the risk of giant fibroadenoma or **cystosarcoma phyllodes**), or the mass is causing anxiety to the

patient or her family. Combined estrogen-progesterone birth control pills have been found to be protective of fibroadenomas.

Cysts are very common masses seen in the pediatric breast. Cysts vary in size over the course of a menstrual cycle, so a patient with a possible cyst should be reexamined a few weeks after the initial evaluation to see if the mass is still present. If a mass persists, then it may be imaged by sonography or aspirated with a needle to evaluate if it truly is a cyst. Aspirated fluid that is clear may be discarded. Bloody fluid and other aspirated material should be sent for cytology. Cystic lesions that resolve with aspiration should be reevaluated in 3 mo. If they recur they should be evaluated with sonography.

Malignant Masses

Primary breast cancer is extremely rare in adolescents. Surveillance Epidemiology and End Results data from 1975-2009 establishes an incidence of invasive breast cancer of 0.2/100,000 for females ages 15-19 yr and 1.6/100,000 for females ages 20-24 yr. Although malignancy is rare, lesions with suspicious imaging findings or progressive growth should undergo cytologic or histologic examination. A small study in Austria noted a 4.7% malignancy rate among palpable masses in teens.

Cystosarcoma phyllodes can occur in adolescents and has been reported in a child as young as 10 yr old. It is characterized by asymmetric breast enlargement in association with a firm, mobile, circumscribed mass. It can mimic a giant fibroadenoma. The tumor often grows rapidly and can become quite large. The majority of these tumors have a favorable prognosis, but malignant cystosarcoma phyllodes has been reported to recur both locally and with metastases. Fatal metastatic cystosarcoma phyllodes in an adolescent has occurred. Excision with 1 cm margins is the preferred initial therapy in adolescent patients, regardless of the histologic classification of the lesion.

Juvenile papillomatosis is a marker for increased breast cancer risk in family members, and in patients with these, up to 15% may have a juvenile secretory carcinoma. Treatment of juvenile papillomatosis is total resection of the lesion with preservation of the breast.

Secondary cancers in adolescents with previous therapeutic radiation to the chest or with malignancies with the potential to metastasize to the breast should be monitored more closely for breast masses. Rhabdomyosarcoma is the most common to metastasize to the breast. Breast tumors also may be the first manifestation of relapse (extramedullary) in acute lymphoblastic leukemia.

Imaging of Breast Masses

Because the dense breast tissue of the adolescent obstructs the visualization of a palpable mass, mammography is not advised for this age group. Ultrasonography is the imaging modality of choice for breast abnormalities in the pediatric population. Color Doppler ultrasound can be useful in evaluating breast abnormalities such as fibroadenomas or abscesses.

Recommendations for Daughters of Women with Breast Cancer

Risk Reduction

There are a limited number of things that young women can do to lower their risk of breast cancer. The American Cancer Society recommends regular physical activity, limiting alcohol, and maintaining a healthy weight. Breastfeeding has a slight effect on breast cancer risk and that effect is only among women who have breastfed for a long time. Breastfeeding seems to be more protective against the most aggressive types of breast cancer, including tumors in women with mutations in the *BRCA-1* gene, hormone-receptor negative, and possibly triple-negative tumors.

Screening Procedures

Breast self-examination is an option for women starting in their 20s. Women should be told about the benefits and limitations of breast self-examination. Women should report any breast changes to their health professional. Women in their 20s and 30s should have a clinical breast exam as part of a periodic (regular) health exam by a health professional, at least every 3 yr. After age 40 yr, women should have a breast exam by a health professional every year and a screening mammogram every year and should continue to do so for as long as they are in good health.

Genetic Testing in Children

Genetic testing for mutations in cancer susceptibility genes in children is particularly complex. Both parents and providers may request or recommend testing for minor children; however, many experts (including the American Society of Clinical Oncology) recommend that unless there is evidence that the test result will influence the medical management of the child or adolescent, genetic testing should be deferred until legal adulthood (18 yr or older) because of concerns about autonomy, potential discrimination, and possible psychosocial effects.

COSMETIC SURGERY

A dramatic increase in adolescents desiring breast augmentation has occurred since the turn of the century. Breast augmentation in adolescents is discouraged owing to associated psychologic and physical immaturity. The American Society of Plastic Surgeons discourages breast augmentation in girls younger than age 18 yr for purely cosmetic reasons. The FDA also considers breast implants in adolescents younger than age 18 yr for solely cosmetic reasons to be an off-label use.

Breast reduction surgery might be considered when an adolescent is bothered by extremely large breasts that result in neck and back pain and prevent participation in sports. Breast reduction allows these girls to feel less self-conscious, have less pain, and be more active. Also girls with marked asymmetry in breasts from the pathologies noted earlier can feel self-conscious and request breast surgery. Before performing breast-altering surgery, practitioners must ensure proper selection of teens and families who have an appropriate understanding of the risks and benefits of surgery and realistic expectations of the procedure.

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Chapter 552

Polycystic Ovary Syndrome and Hirsutism

Mark Gibson and Heather G. Huddleston

POLYCYSTIC OVARY SYNDROME

Etiology and Definition

Polycystic ovary syndrome (PCOS) is a common disorder of reproductive hormone function that is characterized by the triad of oligoovulation or anovulation, clinical or biochemical hyperandrogenism, and ovaries with a polycystic morphology on ultrasound examination (≥12 follicles in 1 ovary and/or ovarian volume >10 mm^3). Various expert bodies prioritize these elements differently for establishing the diagnosis, and few require the presence of all 3 (Table 552-1). Hyperandrogenism with ovulatory dysfunction (with exclusion of other causes) is most often considered sufficient for diagnosis in the United States. Abnormalities commonly associated with PCOS include obesity, insulin resistance, and the metabolic syndrome, but the phenotype is variable and affected individuals may display none of these. The disorder, affecting 5-8% of women of reproductive age, typically emerges in adolescence when a normal menstrual pattern is not established and there is clinical evidence of androgen excess.

Pathology Pathogenesis and Genetics

PCOS has a high concordance rate in twins, and in some studies either epigenetic or dominant inheritance patterns are observed. Nonetheless, a consistent hereditary pattern has not been identified.

Gonadotropic dysregulation with increased luteinizing hormone (LH) pulsatility and abnormally high ratios of circulating LH to follicle-stimulating hormone (FSH) are found in many patients with PCOS. Increased *ovarian* production of androgen in response to LH and impaired folliculogenesis owing to lower FSH are attributed to this gonadotropic pattern. Abnormal regulation of gonadotropin-releasing hormone agonist and abnormal gonadotropin secretion more likely reflect the abnormal hormonal milieu of the syndrome than explain its origin (Fig. 552-1). An increased ratio of circulating levels of LH : FSH is *not* a diagnostic criterion for PCOS.

Alterations in activities of steroidogenic enzymes that would explain *ovarian androgenic* hyperfunction are seen in PCOS subjects, but they are not consistently present in all patients and it is unclear whether these alterations are a cause of PCOS or are a consequence of ovarian dysregulation. The mass of ovarian stromal cells responsible for androgen production is increased, and surgery that reduces this ovarian component (ovarian wedge resection, or laparoscopic ablative procedures) reduces circulating androgen levels and often restores ovarian cyclicity. Patients with hyperandrogenic congenital or adult-onset adrenal hyperplasia exhibit PCOS-like ovarian dysfunction that can be reversed by reducing the *adrenal-derived* androgens with glucocorticoid therapy. A primary role for androgen excess in the pathophysiology of all instances of PCOS seems unlikely; many patients have minimal hyperandrogenism, and elimination of androgen excess (with gonadotropin-releasing hormone agonists) does not affect associated insulin resistance.

Measures of insulin resistance are greater and more prevalent among women with PCOS than controls even when accounting for body mass index (BMI). Insulin enhances ovarian androgen production directly and contributes to elevations of free testosterone levels through its suppression of hepatic production of sex steroid–binding globulin. Treatment with insulin sensitivity–enhancing agents that can reduce insulin levels is associated with modest reductions in measures of androgen excess and, in some patients, restoration of regular ovulation. The association of insulin resistance with weight might explain the appearance of features of PCOS among some women who gain weight as well as the resolution of PCOS among affected women who lose weight.

Clinical Manifestations

PCOS, a lifelong disorder, commonly becomes manifest as puberty progresses, but its onset can occur later during young adulthood.

Table 552-1 Diagnostic Criteria for Polycystic Ovary Syndrome

NATIONAL INSTITUTES OF HEALTH CRITERIA	ROTTERDAM CRITERIA	ANDROGEN EXCESS SOCIETY
Oligo or anovulation *and* Clinical or biochemical hyperandrogenism	Two of 3 of the following: Oligo or anovulation Polycystic ovaries on ultrasonography (12 or more follicles in a single ovary or ovarian volume of >10 mm^3 in 1 ovary) Clinical and/or biochemical hyperandrogenism	Clinical or biochemical hyperandrogenism and at least 1 of the following: Polycystic ovaries *or* Oligo or anovulation

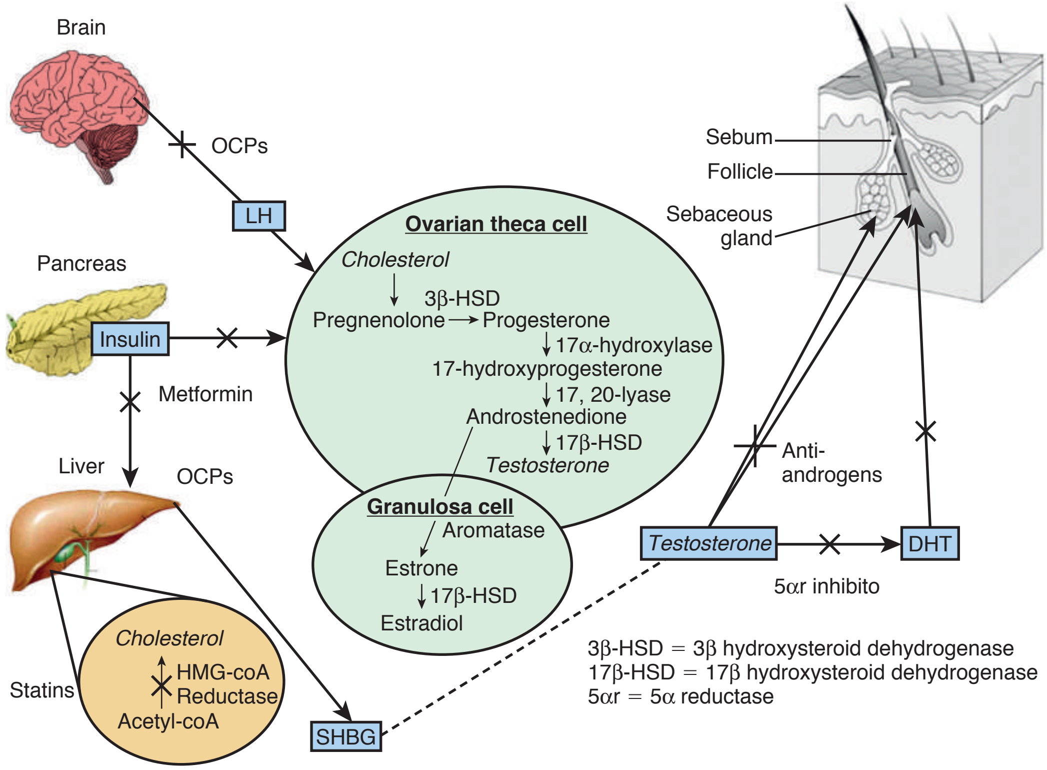

Figure 552-1 Schematic of pathophysiology of polycystic ovary syndrome and mechanism of therapeutic drugs. DHT, dihydrotestosterone; LH, luteinizing hormone; OCPs, oral contraceptive pills; SHBG, sex hormone-binding globulin. *(Adapted from Hassan A, Gordon CM: Polycystic ovary syndrome in adolescence,* Curr Opin Pediatr *19[4]:389–397, 2007.)*

Table 552-2 Phenotypes for Polycystic Ovary Syndrome Based on 2003 Rotterdam Criteria

SIGNS, RISKS, AND PREVALENCE	SEVERE PCOS	HYPERANDROGENISM AND CHRONIC ANOVULATION	OVULATORY PCOS	MILD PCOS
Periods	Irregular	Irregular	Normal	Irregular
Ovaries on ultrasonography	Polycystic	Normal	Polycystic	Polycystic
Androgen concentrations	High	High	High	Mildly raised
Insulin concentrations	Increased	Increased	Increased	Normal
Risks	Potential long-term	Potential long-term	Unknown	Unknown
Prevalence in affected women	61%	7%	16%	16%

PCOS, polycystic ovary syndrome.
From Norman RJ, Dewailly D, Legro RS, et al: Polycystic ovary syndrome, Lancet *370:685–696, 2007.*

Clinical hallmarks are menstrual abnormalities and manifestations of *hyperandrogenism* but the severity of the disorder is variable (Table 552-2). Ovulation is typically irregular or absent, and menses are consequently irregular or absent. When menstrual bleeding does occur, it may be anovulatory bleeding, which is often heavy and/or protracted as a result of an extended period of unopposed endometrial growth. Alternatively, bleeding can be relatively normal in character as a consequence of a preceding ovulation. Protracted spells of anovulation, with accompanying unopposed estrogen is a risk factor for endometrial hyperplasia, and more severe premalignant and frankly malignant changes may eventuate.

The diagnosis of PCOS in adolescents may be made on the basis of a lack of resolution of the normal pattern of anovulatory menstrual cycles present in the 1st 2 postmenarchal years. Less commonly, the diagnosis is made in the setting of primary amenorrhea. Serum androgen levels may be elevated and clinical findings of androgen excess are common, although distinction of normal androgenic expressions of puberty (acne, mild hirsutism) from early manifestations of PCOS may be difficult and serum hormonal testing may be helpful.

Obesity is common among affected women, and in some patients expression of PCOS features is conditional on elevation of BMI and reversible with weight loss. However, there is a subset of patients present with a "lean" PCOS phenotype and thus absence of excess weight should not preclude consideration of the PCOS diagnosis. PCOS is associated with an increased prevalence of insulin resistance and type 2 diabetes independent of the tendency for many affected patients to have an elevated BMI. Additionally, PCOS confers a substantial and specific increase in risk for metabolic syndrome (hyperlipidemia, insulin resistance, type 2 diabetes) in adolescent girls after accounting for BMI.

Laboratory Findings, Diagnosis, and Differential Diagnosis

The diagnosis of PCOS requires exclusion of disorders that would otherwise account for hyperandrogenism and anovulation. Serum 17-hydroxyprogesterone should be measured when there is clear androgen excess to screen for adult-onset 21-hydroxylase deficiency (see Chapter 576). In the adolescent with amenorrhea but minimal hyperandrogenic findings, consideration should be given to functional hypothalamic suppression as a result of excessive exercise and/or dieting, and a careful history taken to rule out such behavioral patterns. All patients should be clinically evaluated for Cushing syndrome, and biochemical evaluation is indicated when findings, including hypertension and/or characteristic body habitus features, are suggestive (see Chapter 577). The 2 disorders have in common a tendency for overweight and varying degrees of insulin resistance and androgen excess, but they differ in that Cushing syndrome demonstrates muscle wasting as a result of catabolism.

Evidence for androgen excess that is rapid in onset and/or severe especially if masculinizing, warrants measurement of androgens (total testosterone, dehydroepiandrosterone [DHEAS]) to exclude the possibility of an androgen-secreting adrenal or ovarian tumor. The laboratory evaluation is completed with the exclusion of hyperprolactinemia, premature ovarian failure, and thyroid disease as causes of anovulation: determinations of functional hyperprolactinemia, FSH, and thyroid-stimulating hormone, respectively.

The diagnosis of PCOS is confirmed from the constellation of oligoovulation or anovulation, androgen excess (clinically or with biochemical confirmation), and typical ovarian morphology on ultrasound. Various experts weigh these 3 features differently and do not, as a rule, require the presence of all (see Table 552-1). Young women often exhibit the ovarian appearance of PCOS without any other evidence, and not all patients with PCOS by the criteria of hyperandrogenism and ovulatory disruption exhibit ovarian changes typical of PCOS. Ultrasound study to diagnose PCOS is not always required if oligoovulation and features of androgen excess are present. Clinical androgen excess (particularly acne) often appears in late puberty and does not necessarily signal PCOS. Nevertheless, young women with persistent oligoovulation or anovulation, accompanied by androgen excess, will likely have persistence of these symptoms and should be considered to have PCOS.

Insulin resistance is common among women with PCOS, and although not requisite for diagnosis, should be considered when PCOS is likely. Adolescents with hyperandrogenemia and anovulation should be evaluated for diabetes or impaired glucose tolerance with a 2 hr (75 g glucose load) glucose tolerance test.

Complications and Long-Term Outlook

Fertility management, prevention of endometrial cancer, and reduction in the likelihood and severity of the common accompanying metabolic disorders are long-term tasks for the PCOS patient and her healthcare providers (Table 552-3). Notwithstanding its reversibility with weight loss in some patients and a tendency to ameliorate in some women later in reproductive life, PCOS usually requires management throughout the reproductive years. Young patients should be counseled that modern fertility management allows most affected women to have children without great difficulty, and they should also know that the disorder does not confer reliable protection from unintended pregnancy. Endometrial cancer can develop as early as the 3rd decade in women with PCOS who are not managed with progestins or ovulation induction; patients should understand the importance of long-term strategies for endometrial protection. Impaired glucose tolerance, type 2 diabetes, and metabolic syndrome are more common among obese adolescents with PCOS; their prevalence increases over time. Weight control through diet and lifestyle measures, detection and management of impaired glucose tolerance and diabetes, and management of abnormal lipids are targets for long-term management.

Treatment

Management focuses on the menstrual abnormalities, symptoms of androgen excess, and associated metabolic changes. Weight loss through lifestyle change, use of hormonal contraceptive agents for menstrual regulation as well as androgen suppression, antiandrogens as adjuncts for hirsutism treatment, and insulin-sensitizing agents are common components of treatment.

Table 552-3 Lifelong Health Complications

PRENATAL OR CHILDHOOD	ADOLESCENCE, REPRODUCTIVE YEARS	POSTMENOPAUSAL
REPRODUCTIVE		
Premature adrenarche Early menarche	Menstrual irregularity Hirsutism Acne Infertility Endometrial cancer Miscarriage Pregnancy complications	Delayed menopause?
METABOLIC		
Abnormal fetal growth	Obesity Impaired glucose tolerance Insulin resistance Dyslipidemia Type 2 diabetes	Obesity Impaired glucose tolerance Insulin resistance Dyslipidemia Type 2 diabetes
OTHER		
	Sleep apnea Fatty liver Depression	Cardiovascular disease?

From Norman RJ, Dewailly D, Legro RS, et al: Polycystic ovary syndrome, Lancet *370:685–696, 2007.*

Lifestyle Changes

Several studies have shown that comprehensive lifestyle programs for overweight and obese *women* with PCOS aimed at fitness and weight loss can yield high rates of restoration of normal menstrual function, reduction of free androgen index, reduction in measures of insulin resistance, and improvements in serum lipids. Limited data show similar benefits from such interventions for obese *adolescents* with PCOS. Successful weight loss programs for adolescents with PCOS using both psychologic and nutritional counseling do result in improved menstrual function.

Hormonal Contraceptives

Combined (estrogen and progestin) hormonal contraceptive medications are considered first-line therapy for adults not desiring fertility and for adolescents (see Chapter 117). Adolescents with PCOS are at risk for unintended pregnancy; their fertility would be expected to be reduced relative to that of their peers, but they are still at risk for pregnancy.

Avoidance of hyperplastic endometrial states resulting from unopposed estrogen and management of abnormal uterine bleeding in anovulatory episodes can be accomplished with the use of combined hormonal contraceptives. The progestational component inhibits endometrial proliferation and the schedule of pill administration predictably regulates menstrual bleeding. The estrogenic component of combined oral contraceptive elevates circulating sex hormone-binding globulin, which reduces free and bioavailable testosterone levels. Both of the hormonal elements in oral contraceptives combine to suppress gonadotropic (particularly LH) stimulation of ovarian androgen production. DHEAS levels, often contributory to hyperandrogenemia in PCOS, are usually decreased by combined contraceptive use. Products with less-androgenic progestational components (drospirenone, desogestrel) may provide better relief from androgenic symptoms.

Using a product that is well tolerated in long-term use is more important than using a product with particular progestational component. Products with reduced frequency and duration of pill-free intervals can provide superior androgen suppression and a welcome decrease in frequency of bleeding episodes. Depot medroxyprogesterone acetate for contraception, endometrial protection, and androgen suppression may be a suitable alternative to combined hormonal contraceptives; it provides even more profound suppression of ovarian androgen production, but it does not elevate sex hormone-binding globulin. Low-dose progestin-only regimens (oral minipills, implantable progestational contraceptives, and progestin-releasing intrauterine devices) also provide effective endometrial protection but would be expected to provide only partial and/or inconsistent androgen suppression, would not elevate sex hormone-binding globulin, and have not been shown to be consistently helpful in regard to abnormal bleeding patterns.

Patients without the need for management of hyperandrogenic symptoms or contraception are often treated with periodic use of oral progestins to induce predictable menstrual bleeding and prevent endometrial hyperplasia and malignancy. Twelve-day courses of medroxyprogesterone acetate 10 mg daily or norethindrone acetate 5 mg daily are effective and safe for this purpose when taken every 1-2 mo.

Metformin

Metformin is a biguanide medication used to treat type 2 diabetes, its only FDA-approved indication. It has been used in a variety of settings and with differing objectives for patients with PCOS. Metformin exerts its principal effect by reducing hepatic production of glucose and limiting intestinal absorption of glucose. Studies show that a subset of women with PCOS resume regular ovulation and menses when treated with metformin, obviating the need for progestational therapy or ovulation-induction medications to protect endometrial health. For some patients the resulting normal reproductive function is appealing regardless of interest in fertility.

Metformin reduces insulin resistance and the levels of androgens. Its extended use can reduce the likelihood of development of impaired glucose tolerance or the progression of impaired glucose tolerance to type 2 diabetes; these effects are not yet proved for patients with PCOS. It should not be used in the presence of renal or hepatic impairment. Typical dosing is 1,500-2,000 mg/day, achieved through gradual increments because gastrointestinal intolerance is common. Long-acting preparations are helpful when gastrointestinal intolerance is a problem.

The use of metformin in the treatment of PCOS depends on the patient's goals and preference. For the treatment of hyperandrogenic symptoms, metformin effects may be modest compared to other available agents. There are no empiric data supporting the theoretical benefits of long-term use of metformin in adolescents with PCOS and obesity compared to the outcomes achieved with weight loss and oral contraceptive medications. Use of metformin as a first-line agent is favored by some experts, in part for improvement in serum measures of intermediate outcomes, and in part because of evidence in other populations of reduced progression of insulin resistance. There is no evidence for long-term benefit to clinical outcomes of adding metformin to treatment for women managed primarily with oral contraceptives. For adolescents receiving metformin as a first-line medication, progestational management (combined contraceptives or periodic progestins) will still be necessary for those not resuming ovulatory function and oral contraceptives may still be an important adjunct for management of clinical hyperandrogenism and/or contraception.

Antiandrogens

Antiandrogenic medications may be added to other therapies or used alone for the treatment of hirsutism. These agents are usually used integrally or adjunctively with ovarian hormonal suppression, in part because of better reduction in hirsutism when antiandrogens are combined with ovarian suppression but also to reduce the risk of unintended embryonic or fetal exposure. The highly active androgen antagonist and progestin, cyproterone, is available in Europe and in Canada as a single agent for treatment of hirsutism or in combination with ethinyl estradiol as an oral contraceptive with enhanced antiandrogenic profile. In the United States, spironolactone is the most commonly used antiandrogen. Spironolactone antagonizes androgens at their receptor and also impairs androgen synthesis. Doses of 100-200 mg daily are commonly used. Other agents that have been studied are finasteride, a 5α-reductase inhibitor, and flutamide, a nonsteroidal and highly specific androgen receptor antagonist. These are

rarely used because of lack of evidence of superior effectiveness, cost, and, in the case of flutamide, the potential for hepatotoxicity.

HIRSUTISM

Hirsutism is defined as abnormally increased terminal (mature, heavy, dark) hair growth in areas of the body where hair growth is normally androgen dependent (see Chapter 662). Its presence is a result of the combination of extent of androgenic stimulation and familial regional follicle sensitivity to androgens, which varies considerably among ethnic groups. Patients' cosmetic concerns generally determine whether findings of hirsutism are a matter for clinical investigation and treatment. Hirsutism as an isolated finding is to be distinguished from masculinization. The latter includes alteration in muscle mass, clitoral enlargement, and voice change, generally manifesting as a rapid evolution (over months). Masculinization mandates a search for neoplastic source of androgen. Elevations of testosterone or DHEAS commonly indicate an ovarian or adrenal androgen source, respectively; specific imaging and occasionally selective catheterization studies are indicated.

Hirsutism without masculinization is common. The potential causes to consider are PCOS (when there is hyperandrogenism and anovulation), benign functional androgen excess (measurable hyperandrogenism without anovulation), idiopathic hirsutism (increased hair in androgen-dependent areas without measurable androgen excess), and adult-onset adrenal hyperplasia (Table 552-4). Patients can be primarily distinguished by evidence of ovulatory disorder by menstrual history, and for those with absent or irregular menses, a diagnosis of PCOS can be made. The remainder, for whom adult-onset adrenal hyperplasia and PCOS have been excluded, either have normal androgen levels with enhanced end-organ sensitivity owing to familial or ethnic predisposition or have a functional and benign overproduction of ovarian androgens. Measures of androgens (testosterone, DHEAS) may be normal or mildly elevated in the latter group. Testosterone suppresses circulating sex-steroid binding globulin, so states of testosterone overproduction might not be accompanied by elevated measures of total testosterone, although estimates of "free" or "bioavailable" testosterone reveal hyperandrogenism. Measures of unbound testosterone distinguish idiopathic hirsutism from mild benign hyperandrogenic states; making this distinction contributes little to patient management and adds cost. Idiopathic hirsutism (without evidence of androgen excess) usually responds to antiandrogen or androgen suppression therapy similarly to hirsutism associated with elevated androgens and anovulation (PCOS), and benign hyperandrogenism not associated with PCOS.

If hirsutism is present, and clinical evaluation excludes neoplasm, adult-onset adrenal hyperplasia, and Cushing syndrome, then management for symptoms for hyperandrogenism (regardless of whether measures of circulating androgens are elevated or not) can proceed as for patients with PCOS. Estrogen and progestin suppression of ovarian function, with or without added antiandrogen treatment, is the mainstay of therapy for these patients. Androgen suppression and/or antagonism results in gradual regression of the size and productivity of follicles in androgen-sensitive areas of the face and body, and these changes will evolve over successive and months-long generations of hair growth and shedding. Patients should therefore be advised that the effects of medical therapy accrue slowly, over many months.

Bibliography is available at Expert Consult.

Table 552-4 Causes of Hirsutism
PERIPHERAL
Idiopathic
Partial androgen insensitivity (5α-reductase deficiency)
HAIR-AN syndrome (*h*irsutism, *a*ndrogenization, *i*nsulin *r*esistance, and *a*canthosis *n*igricans)
Hyperprolactinemia
GONADAL
Polycystic ovary syndrome (polycystic ovaries, chronic anovulation)
Ovarian neoplasm (Sertoli-Leydig cell, granulosa cell, thecoma, gynandroblastoma, lipoid cell, luteoma, hypernephroma, Brenner tumor)
Gonadal dysgenesis (Turner mosaic with XY or H-Y antigen–positive)
ADRENAL
Cushing syndrome
Adrenal hyperresponsiveness
Congenital adrenal hyperplasia (classic, cryptic, adult onset)
21-Hydroxylase deficiency
11-Hydroxylase deficiency
3β-Hydroxysteroid deficiency
17β-Hydroxylase deficiency
Adrenal neoplasm (adenoma, cortical carcinoma)
EXOGENOUS
Minoxidil
Dilantin
Cyclosporine
Anabolic steroids
Acetazolamide (Diamox)
Penicillamine
Oral contraceptives with androgenic progestins
Danazol
Androgenic steroids
Psoralens
Hydrochlorothiazide
Phenothiazines
CONGENITAL ANOMALIES
Trisomy 18 (Edwards syndrome)
Cornelia de Lange syndrome
Hurler syndrome
Juvenile hypothyroidism

Adapted from Bailey-Pridham DD, Sanfilippo JS: Hirsutism in the adolescent female, Pediatr Clin North Am *36:581–599, 1989.*

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Chapter 553

Neoplasms and Adolescent Screening for Human Papillomavirus

Nora T. MacZura and Diane F. Merritt

GYNECOLOGIC MALIGNANCIES

After injuries, cancer is the second most common cause of death in adolescents. Although rare, gynecologic malignancies can be followed by infertility, depression, and poor self-image, which may be lifelong.

The most common type of gynecologic malignancy found in children and adolescents is of ovarian origin and usually manifests as an abdominal mass, which must be distinguished from other organ-based tumors and ovarian functional, physiologic, inflammatory/infectious, or pregnancy-related processes. Ovarian neoplasms constitute 1% of all childhood malignancies, but account for 60-70% of all gynecologic malignancies in this age group. Approximately 10-30% of all childhood or adolescent ovarian neoplasms are malignant. Less often, the vagina or cervix is a site of malignant lesions in children, with a few specific tumors having their greatest incidence within this population. Cervical dysplasia can occur in adolescents, and healthcare providers need to be aware of current screening guidelines as well as updates on preventive measures. Vulvar malignancies in children and adolescents are exceedingly rare.

IMPACT OF CANCER THERAPY ON FERTILITY

Chemotherapy and radiation therapy are associated with acute ovarian failure and premature menopause (Table 553-1). Risk factors include

older age, abdominal or spinal radiation, and certain chemotherapeutic drugs, such as alkylating agents (cyclophosphamide, busulfan). Uterine irradiation is associated with infertility, spontaneous pregnancy loss, and intrauterine growth restriction. Decreased uterine volume has been noted in girls who received abdominal radiation. The vagina, bladder, ureters, urethra, and rectum can also be injured by radiation. Vaginal shortening, vaginal stenosis, urinary tract fistulas, and diarrhea are important side effects of pelvic irradiation for pelvic cancers. Pregnancy outcomes appear to be influenced by prior chemotherapy and radiation treatment; 15% of childhood cancer survivors have infertility. Cancer survivors have an increased rate of spontaneous abortions, premature deliveries, and low birthweight infants compared to their normal healthy siblings. No data support an increased incidence of congenital malformations in offspring.

Childhood cancer survivors require extensive counseling about these specific future health implications. As part of informed consent

Table 553-1 Effect of Cancer Treatment on Development of Amenorrhea

	CANCER TREATMENT PROTOCOL	PATIENT AND DOSE FACTORS	COMMON USAGE	FERTILITY PLANNING CONSIDERATIONS
High Risk	Any alkylating agent (e.g., busulfan, carmustine, cyclophosphamide, ifosfamide, lomustine, melphalan, procarbazine) + total body irradiation		Conditioning for HSCT for leukemias, lymphomas, myelomas, Ewing's sarcoma, neuroblastoma, choriocarcinoma	>70% of women develop amenorrhea after treatment. Any treatments containing high doses of alkylating agents and/or radiation to the abdomen, pelvis, or hypothalamic axis present the highest level of risk for gonadal impact and immediate amenorrhea. Patients should be counseled about fertility preservation before treatment.
	Any alkylating agent + pelvic radiation		Sarcomas, ovarian	
	Total cyclophosphamide	5 g/m^2 in women age >40 7.5 g/m^2 in women and girls age <20	Multiple cancers: breast cancer, NHL, conditioning for HSCT	
	Protocols containing procarbazine: MOPP BEACOPP	>3 cycles >6 cycles	Hodgkin lymphoma	
Intermediate Risk	Protocols containing temozolomide or BCNU + cranial radiation		Brain tumor	~30-70% of women develop amenorrhea post-treatment. Lower levels of alkylating agents and/or radiation to the abdomen, pelvis or hypothalamic axis reduce risk of immediate amenorrhea but do not eliminate risk of gonadal damage. Patients should be counseled about fertility preservation prior to treatment. For Bevacizumab, risk of amenorrhea is intermediate, yet the outcome of fertility is unknown.
	Whole abdominal or pelvic radiation doses	>6 Gy in adult women >10 Gy in postpubertal girls >15 Gy in prepubertal girls	Wilms' tumor, neuroblastoma, sarcomas, Hodgkin lymphoma, ovarian	
	Total body irradiation (TBI) doses		HSCT	
	Cranial radiation	>40 Gy	Brain tumor	
	Total cyclophosphamide	5 g/m^2 in women age 30-40	Multiple cancers, breast	
	AC for breast cancer	×4 + paclitaxel or Docetaxel in women age <40	Breast	
	Monoclonal antibodies, e.g., bevacizumab (Avastin)		Colon, non-small cell lung, head and neck, breast	
	FOLFOX$_4$		Colon	
	Protocols containing cisplatin		Cervical	
	Abdominal/pelvic radiation	10-15 Gy in prepubertal girls 5-10 Gy in postpubertal girls	Wilms' tumor, neuroblastoma, spinal tumors, brain tumor, relapsed ALL or NHL	
Lower Risk	Protocols containing nonalkylating agents or lower levels of alkylating agents (e.g., ABVD, CHOP, COP; multi-agent therapies for leukemia)		Hodgkin lymphoma, NHL, leukemia	<30% of women develop amenorrhea after treatment. These treatments are unlikely to cause immediate amenorrhea at standard dosage; however, patients should be counseled that they may be at risk for early menopause. Patients may want to consider fertility preservation before or after treatment.
	Protocols for breast cancer containing cyclophosphamide (e.g., CMF, CEF, or CAF)	Women < 30	Breast	
	Anthracycline + cytarabine		AML	
Very Low / No Risk	Multi-agent therapies using vincristine		Leukemia, lymphoma, breast and lung cancer	
	Radioactive iodine		Thyroid	
Unknown	Monoclonal antibodies, e.g., cetuximab (Erbitux), trastuzumab (Herceptin)		Colon, non-small cell lung, head and neck, breast	Negligible to no effects on menses. Patients should be counseled regarding the lack of conclusive data about the reproductive effects of these drugs; fertility preservation options should be discussed.
	Tyrosine kinase inhibitors, e.g., erlotinib (Tarceva), imatinib (Gleevec)		Non-small cell lung, pancreatic, CML, GIST	

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for cancer therapy, the possibility of infertility should be discussed with young patients and their families. Counseling and embryo or mature oocyte cryopreservation for postpubertal females before gonadotoxic therapy should be offered as standard of care. Cryopreservation of ovarian tissue for prepubertal children remains experimental and may be offered as part of a research protocol. Premature ovarian insufficiency is associated with an increased risk for cardiovascular complications, osteoporosis, and difficulties with sexual function. Risks and benefits of hormonal therapy need to be addressed.

OVARIES

Neonatal and Pediatric Ovarian Cysts

Normal follicles or physiologic ovarian cysts are seen by ultrasound examination of the ovaries in all healthy prepubertal girls. Most of these are <1 cm in diameter and not pathologic. In the neonatal period, physiologic follicular cysts as a result of maternal estrogen stimulation usually resolve spontaneously and may be followed with serial ultrasounds in the asymptomatic child. Children with an ovarian mass might have no symptoms and the mass may be detected incidentally or during a routine examination. Other children present with abdominal pain that may be accompanied by nausea, vomiting, or urinary frequency or retention. The cyst's most common complication, **ovarian torsion**, can result in loss of the ovary (autoamputation of the ovary has been documented to occur antenatally). Successful reports of antenatal aspiration and postnatal laparoscopic treatment exist. Large cysts (>4-5 cm), those with complex characteristics, or any ovarian cyst in premenarchal girls with associated signs or symptoms of hormonal stimulation deserve prompt evaluation. The incidence of ovarian cysts increases again with puberty.

Functional Cysts

Hemorrhagic cysts are an expected part of follicular development during the menstrual cycle. Normally, a dominant follicle forms and increases in size. Following ovulation, the dominant follicle becomes a corpus luteum that, if it bleeds, is termed a *hemorrhagic corpus luteum.* These can become symptomatic owing to size or peritoneal irritation from blood, and they have a characteristic complex appearance on ultrasound. Expectant management for a presumed functional or hemorrhagic cyst is appropriate. Physiologic cysts are usually ≤5 cm and resolve over the course of 6-8 wk during subsequent ultrasound imaging. Monophasic oral contraceptives can be used to suppress follicular development to prevent formation of additional cysts.

Teratomas

The most common neoplasm in adolescents is the *mature cystic teratoma (dermoid cyst*). Most are benign and contain mature tissue of ectodermal (skin, hair, sebaceous glands), mesodermal, or endodermal origin. Occasionally, well-formed teeth, cartilage, and bone are found. Calcification on an abdominal radiograph is often a hallmark of a benign teratoma. These tumors may be asymptomatic and found incidentally, or they can manifest as a mass or with abdominal pain (associated with torsion or rupture). If the major component of the dermoid is thyroid tissue (struma ovarii), hyperthyroidism can be the clinical presentation. Benign teratomas should be carefully resected, preserving as much normal ovarian tissue as possible. Oophorectomy (and salpingo-oophorectomy) for this benign lesion is excessive treatment. During surgery, both ovaries should be evaluated, and if there is any question about the nature of the lesion, the specimen should be evaluated by a pathologist. An association of dermoid tumors with neural elements and *anti*–N-*methyl*-D-*aspartase receptor encephalitis* has been reported. Excision of the ovarian tumor has led to improvement in neurologic symptoms in some patients.

Immature teratoma of the ovary is an uncommon tumor, accounting for <1% of ovarian teratomas. In contrast to the mature cystic teratoma, which is encountered most often during the reproductive years but occurs at all ages, the immature teratoma has a specific age incidence, occurring most commonly in the 1st 2 decades of life. By definition, an immature teratoma contains immature neural elements. Because the lesion is rarely bilateral in its ovarian involvement, the present method of therapy consists of unilateral salpingo-oophorectomy with wide sampling of peritoneal implants.

Cystadenomas

Serous and mucinous cystadenomas are the second most common benign ovarian tumor. These cystic lesions can become very large, yet with care, the tumor can be resected, preserving normal ovarian tissue for future reproductive potential.

Endometriomas

Endometriosis is a syndrome defined by the presence of ectopic endometrial tissue usually located within the pelvis and abdomen. The principal clinical symptoms in adolescents consist of severe menstrual pain and pelvic pain. Endometriomas (chocolate cysts) form when the ovaries are involved and are collections of old blood and hemosiderin within an endometrium-lined cyst. They have a typical homogeneous echogenic appearance on ultrasound and are more common in adults than in adolescents. Conservative management (suppressive therapy with ovulation suppression, and nonsteroidal antiinflammatory drugs) and ovarian cystectomy with preservation of as much functioning ovary as possible is recommended for adolescents.

Pelvic Inflammatory Disease and Tuboovarian Abscess

Pelvic inflammatory disease complicated by a tuboovarian abscess should be considered in a sexually active adolescent with an adnexal mass and pain on examination (see Chapter 120). These patients also typically exhibit fever with leukocytosis and cervical motion tenderness. Treatment consists of administration of intravenous antibiotics. If the lesion persists or is refractory to antibiotics, drainage of the pelvic abscess by interventional radiology should be considered.

Adnexal Torsion

Adnexal torsion of the ovary and/or fallopian tube can occur in children or adolescents with normal adnexa or more often those enlarged by cystic (follicular, tubal) changes or ovarian (teratoma, cystadenoma) neoplasms. When torsion occurs, the venous outflow is obstructed first, and the ovary swells and becomes hemorrhagic. Once the arterial flow is interrupted, necrosis begins. It is not known how long torsed adnexa will remain viable. When a female patient presents with acute lower abdominal pain, either episodic or constant, and if imaging studies shows unilateral enlargement of an adnexa, the diagnosis of adnexal torsion must be considered and acted upon. The sonographic presence of Doppler flow does not exclude the diagnosis of torsion. Prompt surgical intervention (laparoscopic detorsion) is warranted if clinical suspicion is high. Detorsion of the adnexa and observation for viability is recommended, with excision only for obviously nonviable necrotic tissues. Recovery of ovarian function after detorsion has been reported with identification of normal follicle development. Oophoropexy (plication) of the affected and the contralateral adnexa remains controversial.

Ovarian Carcinoma

Ovarian cancer is very uncommon in children; only 2% of all ovarian cancers are diagnosed in patients younger than 25 yr old. The Surveillance, Epidemiology, and End Results (SEER) incidence rates are ≤0.8/100,000 at age 0-14 yr and 1.5/100,000 at ages 15-19 yr. Germ cell tumors are the most common and originate from primordial germ cells that then develop into a number of heterogeneous tumor types including dysgerminomas, malignant teratomas, endodermal sinus tumors, embryonal carcinomas, mixed cell neoplasms, and gonadoblastomas. Immature teratomas and endodermal sinus tumors are more aggressive malignancies than dysgerminomas and occur in a significantly higher proportion of younger girls (younger than 10 yr of age). Sex-cord stromal tumors are more common among adolescents (Table 553-2). Tumor markers such as α-fetoprotein, carcinoembryonic antigen, and the antigen CA-125 are also used for diagnosis and treatment surveillance (Table 553-3).

Table 553-2 Malignant Ovarian Tumors in Children and Adolescents

TUMOR	OVERALL 5-YR SURVIVAL	CLINICAL FEATURES
GERM CELL TUMORS		
Dysgerminoma	85%	10-20% bilateral Most common ovarian malignancy Gonadal dysgenesis/androgen insensitivity Sensitive to chemotherapy/radiation
Immature teratoma	97-100%	All 3 germ layers present
Endodermal sinus tumor	80%	Almost always large (>15 cm) Schiller-Duval bodies
Choriocarcinoma	30%	Rare Can mimic ectopic pregnancy
Embryonal carcinoma	25%	Endocrinologic symptoms (precocious puberty) Highly malignant
Gonadoblastoma	100%	Primary amenorrhea Virilization 45,X or 45,X/46,XY mosaicism
SEX CORD STROMAL TUMORS		
Juvenile granulosa stroma cell tumor	92%	Produce estrogen Menstrual irregularities Isosexual precious pseudopuberty Call-Exner bodies rare
Sertoli-Leydig cell tumor	70-90%	Virilization in 40% Produce testosterone
Lipoid cell tumors	~80%	Rare heterogenous group with lipid-filled parenchyma
Gynandroblastoma	90% or greater	Rare low-grade mixed tumors that produce either estrogen or androgen

Table 553-3 Serum Tumor Markers

TUMOR	CA-125	AFP	hCG	LDH	E2	T	INHIBIN	MIS	VEGF	DHEA
Epithelial tumor	+									
Immature teratoma	+	+			+					+
Dysgerminoma			+	+	+					
Endodermal sinus tumor		+								
Embryonal carcinoma		+	+		+					
Choriocarcinoma			+							
Mixed germ cell		+	+	+						
Granulosa cell tumor	+				+		+	+		
Sertoli-Leydig						+	+			
Gonadoblastoma					+	+	+			+
Theca-fibroma									+	

AFP, α-fetoprotein; CA-125, cancer antigen 125; DHEA, dehydroepiandrostenedione; E2, estradiol; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; T, testosterone, MIS, müllerian inhibiting substance; VEGF, vascular endothelial growth factor.

Treatment is surgical excision followed by postoperative chemotherapy that usually consists of bleomycin, etoposide, and cisplatin. Radiotherapy is sometimes administered for disease recurrence in dysgerminomas, but it is otherwise not included in routine treatment. Staging at the beginning of therapy is of the utmost importance. In rare cases, a second-look laparotomy may be indicated for neoplasms with teratomatous elements or for those incompletely resected.

Epithelial ovarian cancers account for 19% of ovarian masses in the pediatric population, with a total of 16% being malignant. These tumors manifest almost exclusively after puberty. Common presenting symptoms include dysmenorrhea, abdominal pain, abdominal distention, nausea and vomiting, and vaginal discharge. Tumors of low malignant potential are common in adolescents and account for 30% of epithelial ovarian cancers in this age group. Given the young age of this population, although not the standard of care for adult patients, consideration may be given to conserving the contralateral ovary and uterus if they appear normal. Data suggest that in patients with early-stage disease, such an approach with appropriate surgical staging results in optimal outcomes. Overall 5 yr survival rates are approximately 73%. The number of term pregnancies and use of oral contraceptives decrease the risk of invasive epithelial ovarian cancer. Young women with a family history of ovarian cancer should seriously consider using long-term oral contraceptives for the preventive benefits when pregnancy is not being sought.

UTERUS

Rhabdomyosarcomas are the most common type of soft-tissue sarcoma occurring in patients younger than 20 yr of age (see Chapter 500). They can develop in any organ or tissue within the body except bone, and roughly 3% originate from the uterus or vagina. Of the various histologic subtypes, embryonal rhabdomyosarcomas in the female patient most often occur in the genital tract of infants or young children. They are rapidly growing entities that can cause the tumor to be expelled through the cervix, with subsequent complications such as uterine inversion or large cervical polyps. Irregular vaginal bleeding may be another presenting clinical symptom. They are defined histologically by the presence of mesenchymal cells of skeletal muscle in various stages of differentiation intermixed with myxoid stroma.

Treatment recommendations are based on protocols coordinated by the Intergroup Rhabdomyosarcoma Study Group and consist of a multimodal approach including radiation therapy and chemotherapy. Vincristine, Adriamycin, and cyclophosphamide with or without radiation therapy are the first line of treatment. Resection rates are now very low; chemotherapy with restrictive surgery has enabled many patients to retain their uterus while achieving excellent long-term survival rates.

Leiomyosarcomas and **leiomyomas** are extremely rare, occurring in <2 in 10 million individuals within the pediatric/adolescent age group, although their numbers are increasing among pediatric patients with AIDS. They usually involve the spleen, lung, or gastrointestinal tract, but they could also originate from uterine smooth muscle. Pathogenesis is thought to correlate with the Epstein-Barr virus (see Chapter 254). Despite treatment that demands complete surgical resection (and chemotherapy for the sarcomas), they tend to recur frequently.

Endometrial stromal sarcoma and endometrial adenocarcinoma of the uterine corpus are extremely rare in children and adolescents, with only case reports noted in the literature. Vaginal bleeding not associated with sexual precocity is a common presenting sign. Treatment consists of hysterectomy, with removal of the ovaries, followed by adjunctive radiotherapy and/or chemotherapy, depending on the operative findings.

VAGINA

Sarcoma botryoides is a variant of embryonal rhabdomyosarcoma that occurs most commonly in the vagina of pediatric patients. Sarcoma botryoides tends to arise in the anterior wall of the vagina and manifests as a submucosal lesion that is grape-like in appearance; if located at the cervix it could resemble a cervical polyp or polypoid mass. These lesions were formerly treated with exenterative procedures; equal success has occurred with less-radical surgery (polypectomy, conization, and local excision) and adjuvant chemotherapy with or without radiotherapy. A combination of vincristine, dactinomycin, and cyclophosphamide appears to be effective. Outcomes depend on tumor size, extent of disease at time of diagnosis, and histologic subtype. The 5-year survival rates for patients with clinical stages I-IV were 83%, 70%, 52%, and 25%, respectively.

Vaginal adenosis can lead to the development of clear cell adenocarcinoma of the vagina in females exposed to diethylstilbestrol in utero. Pregnant women at risk for miscarriage are no longer exposed to diethylstilbestrol, and thus fewer adolescent girls and young women are at risk for this unusual tumor.

A rare tumor occurring in the vagina of infants is the **endodermal sinus tumor**. This disease usually occurs in children younger than 2 yr of age, and survival rates are poor. Combination surgery and chemotherapy are appropriate. Benign papillomas can arise in the vagina of children and result in vaginal bleeding. Rarely, vaginal bleeding is secondary to leukemia or a hemangioma.

VULVA

Any questionable vulvar lesion should be biopsied and submitted for histologic examination. Lipoma, liposarcoma, and malignant melanoma of the vulva have been reported in young patients. The most common lesion is likely condyloma acuminata, associated with the human papilloma virus (HPV) (see Chapter 266). Diagnosis is usually made by visual inspection. Treatment consists of observation for spontaneous regression, topical trichloroacetic acid, local cryotherapy, electrocautery, excision, and laser ablation. Some products used to treat skin lesions in adults have not been approved for children, including provider application of podophyllin resin and home application of imiquimod, podofilox, and sinecatechins ointment.

CERVIX

Cervical cancer screening has been cytology based using the Papanicolaou (Pap) test and Bethesda Classification System (Table 553-4). Advances in epidemiologic research and molecular techniques have allowed the identification of the integral role of HPV in development of cervical cancer. HPV has become an important factor in the interpretation of cytologic results and subsequent management. The discovery of HPV presents a unique target for cervical cancer prevention, with the pediatric and adolescent population at the forefront of its implementation. Two HPV vaccines (bivalent HPV2 and quadrivalent HPV4) are currently available to protect against cervical cancer, and the HPV4 vaccine also protects against genital warts and cancers of the anus, vagina, and vulva. HPV vaccines offer the best protection if all three vaccine doses are administered before the patient is ever sexually active. The American Congress of Obstetrics and Gynecology recommends vaccination for all girls and women ages 9-26 yr, and The Advi-

Table 553-4 Management of Cytologic Abnormalities in Adolescents Who Are Screened in Error and Immunocompromised Women <21 Years of Age

CYTOLOGY RESULT	MANAGEMENT RECOMMENDATION	HPV TESTING?	COLPOSCOPY?
ASCUS	Repeat cytologic testing in 1 year	No	At 1 yr follow-up if HGSIL or greater result At 2 yr follow-up if persistent ASCUS or greater
LGSIL	Repeat cytologic testing in 1 year	No	At 1 yr follow-up if HGSIL or greater result At 2 yr follow-up if ASCUS or greater
HGSIL	If colposcopy is unsatisfactory or if CIN is ungraded: excisional procedure If colposcopy is satisfactory: • If no CIN1-3: Pap and colposcopy q6mo until 2 are negative. **If persistent HGSIL without CIN1-3 identified, then excisional procedure at 2 yr** • If CIN1: (ASCUS/LGSIL protocol) • If CIN2, CIN2-3: Pap or colposcopy q6mo until 2 are negative, or else rebiopsy at 1 yr, treat if persistent at 2 yr • If CIN3: excisional procedure	No	Yes, immediately
ASC-H or AGC	There are no specific recommendations in regard to adolescents; see ASCCP guidelines for adults Endometrial biopsy is not advised in adolescents	No	Yes, immediately

Note: Cryotherapy and laser ablation are acceptable treatment options only for biopsy-proven CIN2+ lesion and satisfactory colposcopic examination.
AGC, atypical glandular cells; ASCCP, American Society for Colposcopy and Cervical Pathology; ASC-H, atypical squamous cell changes, high grade; ASCUS, atypical squamous cell changes of undetermined significance; CIN, cervical dysplasia; HGSIL, high-grade squamous intraepithelial dysplasia; LGSIL, low-grade squamous intraepithelial dysplasia; Pap, Papanicolaou smear.

sory Committee on Immunization Practices (http://www.cdc.gov/vaccines/schedules/hcp/index.html) recommends routine vaccination of girls ages 11-12 yr with 3 doses of quadrivalent HPV vaccine, starting as early as age 9 yr. Catch-up vaccination is indicated for girls and women ages 13-26 yr who have not been fully vaccinated. Female patients should be vaccinated even if sexually exposed; vaccination prior to exposure is ideal. Pap testing and screening for HPV DNA or HPV antibody is not required before vaccination. The American Congress of Obstetrics and Gynecology recommends that cervical cancer screening of women who have been immunized against HPV-16 and HPV-18 should not differ from that of nonimmunized women and should follow the exact same regimen.

The adolescent population presents a unique challenge to cervical cancer screening, because the prevalence of HPV is high. In adolescents ages 15-19 yr, HPV cumulative incidence rates after initiation of sexual activity are reported as 17% at 1 yr and 35.7% at 3 yr. Correlating with the natural history of an HPV infection, >90% of low-grade intraepithelial lesions regress within this age group, giving the presence of HPV in this population little clinical significance. The overall incidence of a high-grade lesion on Pap test in the adolescent population remains low (0.7%); cervical cancer is uncommon in the age group. In the United States, the Surveillance, Epidemiology, and End Results Cancer Statistics Review 1975-2006 published by the National Cancer Institute reports an incidence of invasive cervical cancer as 0.1/100,000 in 15-19 yr olds, with no cases reported before the age of 15 yr; similar rates (≤0.3 cases per 100,000 among women ages 15-19 yr) have been reported by the Canadian Cancer Registry. Therefore, colposcopy for minor cytologic abnormalities within this age group should be highly discouraged, because it will result more often in harm than produce any clinical benefit. The American Society for Colposcopy and Cervical Pathology and the American College of Obstetricians and Gynecologists guidelines recommend that adolescents should be managed conservatively and should not receive Pap smear screening until age 21 yr regardless of age of onset of sexual intercourse. If an HPV test is done, the results should be ignored. However, sexually active immunocompromised (HIV-positive patients or organ transplant recipients) adolescents should undergo screening twice within the 1st yr after diagnosis and annually thereafter. Table 553-4 demonstrates management recommendations for abnormal cytologic results for adolescents who are screened in error and immunocompromised sexually active adolescents who are screened. Routine screening for cervical cancer in the general adolescent population (younger than age 21 yr) is *not* recommended.

Clinic protocols that require teenagers to undergo Pap smears before prescribing contraceptives should be reconsidered in light of these recommendations.

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Chapter 554
Vulvovaginal and Müllerian Anomalies

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EMBRYOLOGY

Cellular differentiation, duct elongation, fusion, resorption, canalization, and programmed cell death are all involved in the sequence of events that occur in a developing embryo and early fetus to create a normal reproductive system. Myriad gonadal, müllerian, and/or vulvovaginal anomalies can result from interruption of the intricate sequence or functions of any one of these processes during formation of the reproductive system (Table 554-1). Genetic, epigenetic, enzymatic, and environmental factors all have some role in the process (Table 554-2).

Table 554-1 Common Müllerian Anomalies

ANOMALY	DESCRIPTION
Hydrocolpos	Accumulation of mucus or nonsanguineous fluid in the vagina
Hemihematometra	Atretic segment of vagina with menstrual fluid accumulation
Hydrosalpinx	Accumulation of serous fluid in the fallopian tube, often an end result of pyosalpinx
Didelphic uterus	Two cervices, each associated with 1 uterine horn
Bicornuate uterus	One cervix associated with 2 uterine horns
Unicornuate uterus	Result of failure of 1 müllerian duct to descend

Phenotypic sexual differentiation, especially during formation of the vulvovaginal and müllerian systems, is determined from genetic (46,XX), gonadal, and hormonal influences (see Chapter 582). The genetic sex of the embryo is determined at fertilization when the gamete pronuclei fuse. The primordial germ cells (oogonia or spermatogonia) migrate from the yolk sac to the gonadal ridges. The primitive gonads are indistinguishable until about the 7th wk of development. Gonadal development determines the progression or regression of the genital ducts and subsequent hormonal production and, thus, the external genitalia. Critical areas in the SRY region (sex-determining region on the Y chromosome) are believed to be the factors that drive the development of a testis from a primitive gonad as well as spermatogenesis. The testis begins to develop between 6 and 7 wk of gestation, first with Sertoli cells followed by Leydig cells, and testosterone production begins at approximately 8 wk of gestation. The genital tract begins to differentiate later than the gonads. The differentiation of the wolffian ducts begins with an increase in testosterone, and the local action of testosterone activates development of the epididymis, vas deferens, and seminal vesicle. Further male genital duct and external genital structures depend on the conversion of testosterone to dihydrotestosterone.

In a 46,XX embryo, female sexual differentiation occurs about 2 wk later than gonadal differentiation in the male. Because the ovaries develop prior to and separately from the müllerian ducts, females with müllerian ductal anomalies usually have normal ovaries and steroid hormone production. The regression of the wolffian ducts results from the lack of local gonadal testosterone production, and the persistence of the **müllerian** (or paramesonephric) **ducts** results from the absence of **antimüllerian hormone** (or müllerian-inhibiting substance) production. The müllerian ducts continue to differentiate into the fallopian tubes, uterus, and upper vagina without interference from antimüllerian hormone. There are complex interactions among the mesonephric, paramesonephric, and metanephric ducts early in embryonic development, and normal development of the müllerian system depends on such interaction. If this process is interrupted, coexisting müllerian and renal anomalies are often discovered in the female patient at the time of evaluation. Differentiation along the female pathway is often referred to as the *default pathway,* but it is an extremely intricate process regulated by the absence, presence, or dosage compensation of numerous gene products (i.e., SRY, SF-1, WTI, SOX9, Wnt-4, GATA4, DAX-1, BMP4, HOX genes) and remains not entirely understood.

By 10 wk of gestation, the caudal portions of the müllerian ducts fuse together in the midline to form the uterus, cervix, and upper vagina, in a Y-shaped structure, with the open upper arms of the Y forming the primordial fallopian tubes. Initially the müllerian ducts are solid cords that gradually canalize as they grow along and cross

the mesonephric ducts ventrally and fuse in the midline. The mesonephric ducts caudally open into the **urogenital sinus**, and the müllerian ducts contact the dorsal wall of the urogenital sinus, where proliferation of the cells at the point of contact form the müllerian tubercle. Cells between the müllerian tubercle and the urogenital sinus continue to proliferate, forming the vaginal plate. At the same time of the midline fusion of the müllerian ducts, the medial walls begin to degenerate and resorption occurs to form the central cavity of the uterovaginal canal. Uterine septal resorption is thought to occur in a caudal to cephalad direction and to be complete at approximately 20 wk of gestation. This theory has been scrutinized because some anomalies do not fit the standard classification system. It is possible that septal resorption starts at some point in the middle and proceeds in both directions. At approximately 16 wk of gestation the central cells of the vaginal plate desquamate and resorption occurs, forming the vaginal lumen. The lumen of the vagina is initially separated from the urogenital sinus by a thin hymenal membrane. The hymenal membrane undergoes apoptosis and central resorption and is usually perforate before birth.

EPIDEMIOLOGY

Müllerian anomalies can include abnormalities in portions or all of the fallopian tubes, uterus, cervix, and vagina (Fig. 554-1). True estimates of prevalence are difficult because of the varied presentations and asymptomatic nature of some of the anomalies. Imaging techniques have made significant contributions to uterovaginal anomaly diagnoses, which has increased reporting of anomalies and led to additional combinations of anomalies. Most estimate that müllerian anomalies are present in 2-4% of the female population. The incidence increases in women with a history of adverse pregnancy outcomes or infertility: 5-10% of infertile women undergoing hysterosalpingogram, 5-10% of women with recurrent pregnancy loss, and 25% or more of women with late miscarriages and/or preterm delivery have müllerian defects.

CLINICAL MANIFESTATIONS

Vulvovaginal and müllerian anomalies can manifest at a variety of chronological time points during a female's life: from infancy, through childhood and adolescence, and adulthood (see Table 554-1). The majority of external genitalia malformations manifest at birth, and often even subtle deviations from normal in either a male or female newborn warrant evaluation. Structural reproductive tract abnormalities can be seen at birth or can cluster at menarche or any time during a woman's reproductive life. Some müllerian anomalies are asymptomatic, whereas others can cause gynecologic, obstetric, or infertility issues.

Clinical manifestations and treatments depend on the specific type of müllerian anomaly and are varied. There may be a pelvic mass, which may or may not be associated with symptoms. A mass bulging at the introitus or within the vagina indicates complete or partial

Table 554-2 Heritable Disorders Associated with Müllerian Anomalies

MODE OF INHERITANCE	DISORDER	ASSOCIATED MÜLLERIAN DEFECT
Autosomal dominant	Camptobrachydactyly Hand-foot-genital	Longitudinal vaginal septa Incomplete müllerian fusion
Autosomal recessive	McKusick-Kaufman Johanson-Blizzard Renal-genital-middle ear anomalies Fraser syndrome Uterine hernia syndrome	Transverse vaginal septa Longitudinal vaginal septa Vaginal atresia Incomplete müllerian fusion Persistent müllerian duct derivatives
Polygenic/multifactorial	Mayer-Rokitansky-Küster-Hauser syndrome	Müllerian aplasia
X-linked	Uterine hernia syndrome	Persistent müllerian duct derivatives

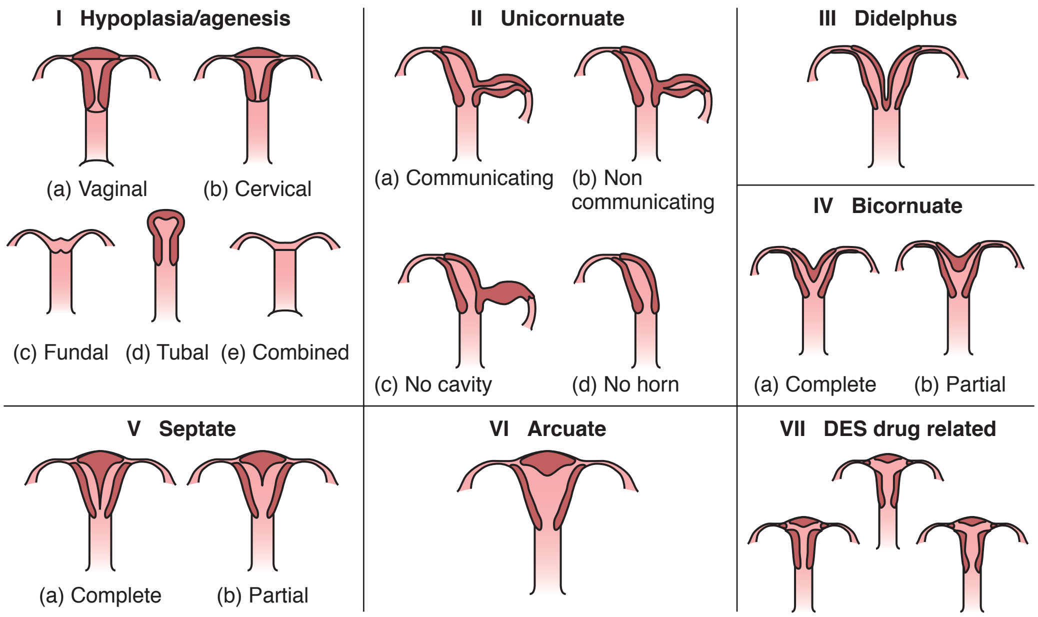

Figure 554-1 Classification system of müllerian duct anomalies developed by the American Fertility Society. *(From Gholoum S, Puligandla PS, Hui T, et al: Management and outcome of patients with combined vaginal septum, bifid uterus, and ipsilateral renal agenesis [Herlyn-Werner-Wunderlich syndrome].* J Pediatr Surg *41:987–992, 2006, Fig. 3.)*

outflow tract obstruction. An adolescent can present with pelvic pain either in association with primary amenorrhea or several months after the onset of menarche. Patients also may be asymptomatic until they present with miscarriage, pregnancy loss, or preterm delivery. When presentation is acutely symptomatic, emergency management may be required. Obstruction can result from a number of distinct anomalies including an **imperforate hymen**, **transverse vaginal septum**, and **noncommunicating rudimentary horn**. As menstrual fluid accumulates proximal to the obstruction, the resulting **hematocolpos** and **hematometra** cause cyclic pain or a pelvic mass.

Prenatal or neonatal presentation of hydrometrocolpos from distal vaginal obstruction produces fluid accumulation in the vagina and uterus and presents as a lower abdominal mass with or without associated acute urinary tract obstruction. **Hydrometrocolpos with polydactyly** may be a result of 2 disorders: McKusick-Kaufman syndrome (with associated congenital heart disease) and Bardet-Biedl syndrome (with obesity, learning disabilities, retinitis pigmentosa, renal anomalies). Both are autosomal recessive disorders.

Adolescent patients can present with acute obstruction of the outflow tract because of a müllerian anomaly, which requires emergency evaluation and surgical treatment. A small percentage of girls present with concomitant urinary retention caused by an altered urethral angle or pressure on the sacral plexus. Urinary hesitancy and incomplete emptying symptoms may be present before abdominopelvic pain from the obstruction in a patient of any age.

LABORATORY FINDINGS

Several radiographic studies have been used, often in combination, to aid in diagnosis including ultrasound, hysterosalpingogram, sonohysterography (saline-infusion sonography), and MRI. Laparoscopy and hysteroscopy were the gold standard for evaluation of müllerian anomalies, but the new standard may be MRI because of its noninvasive, high-quality capabilities. MRI is the most sensitive and specific imaging technique used for evaluating müllerian anomalies because it can image nearly all reproductive structures, blood flow, external contours, junctional zone resolution on T2-weighted images, and associated renal and other anomalies. MRI also has a high correlation with surgical findings because of its multiplanar capabilities and high spatial resolution. Three-dimensional ultrasound is another useful diagnostic tool and may be superior to traditional pelvic ultrasound and hysterosalpingogram. Three-dimensional ultrasound and MRI results are highly concordant in the diagnosis of uterine malformations. Evaluation of the external contour of the uterus is important for differentiating types of uterine anomalies. This often requires a combination of radiologic modalities for uterine cavity, external contour, and possible tubal patency. Diagnostic laparoscopy or hysteroscopy may be necessary depending on the presentation, but it is used less with the advancement of MRI and other imaging.

Diagnosis of müllerian anomalies should include a physical exam, pelvic ultrasound, possibly MRI, and renal and skeletal inspections for associated anomalies. Renal anomalies are noted in 30-40% and skeletal anomalies are associated in 10-15% of patients with müllerian anomalies. Unilateral renal agenesis occurs in 15% of patients. The most common skeletal anomalies are vertebral. Patients usually have a normal female karyotype (46,XX), but several familial segregations and gene mutations and/or abnormal karyotypes have been reported (see Table 554-2). Approximately 5-8% of patients with congenital müllerian anomalies have abnormal karyotypes. Most malformations are sporadic, with a polygenic mechanism and multifactorial etiology.

UTERINE ANOMALIES

Anomalous development of the uterus may be symmetric or asymmetric and/or obstructed or nonobstructed. Patients can present with primary amenorrhea or have either irregular or regular menstrual cycles. There may be an asymptomatic pelvic mass or dysmenorrhea. In adolescents and adults, pregnancy loss can cause the first suspicion of a uterine anomaly. Treatment is highly specific to the specific anomaly.

SEPTATE UTERUS

A **uterine septum** is the most common of all müllerian anomalies, accounting for just over half of all abnormalities, and it is the most common structural uterine anomaly. After the 2 müllerian ducts fuse in the midline, resorption must occur to unify the endometrial cavities; failure of this process results in some degree of uterine septum. It can vary in length from just below the fundus to beyond the cervix, depending on the amount of caudal resorption. A **septate uterus** has a normal external uterine contour, which is what distinguishes it from a bicornuate or didelphic uterus. An MRI can help delineate between a predominantly fibrous septum and a muscular or myometrial septum. Because the septum may be poorly vascularized, a septate uterus is the most significant anomaly associated with pregnancy loss, as well as other untoward pregnancy outcomes. Hysteroscopic metroplasty (septal excision) is generally recommended in the setting of a previous pregnancy loss. Controversy still exists regarding whether a woman should have such a surgical procedure without a previous pregnancy loss. Correction of uterine septum improves the prognosis in patients with a history of adverse obstetrical outcomes (i.e., spontaneous abortions, preterm delivery). The length of the septum might not correlate with the frequency or occurrence of untoward pregnancy outcomes. Differentiating precisely between bicornuate and septate uteri is extremely important to determine effective and safe treatment plans.

Bicornuate Uterus

Both müllerian ducts develop and elongate in this anomaly, but they do not completely fuse in the midline. The vagina and external cervix are normal, but the extent of division of the 2 endometrial cavities can vary depending on the extent of failed fusion between the cervix and the fundus. Bicornuate uteri are also associated with increased preterm labor and delivery, malpresentation, and miscarriage. This anomaly accounts for approximately 10-20% of müllerian anomalies and a significant percentage of uterine anomalies.

Unicornuate Uterus and Rudimentary Horns

A **unicornuate uterus** results from a normal creation of a fallopian tube, functional uterus, cervix and vagina from 1 müllerian duct. The other side fails to develop, resulting in either absence of the contralateral müllerian duct or a rudimentary horn. There is a 30-40% association of renal anomalies. If a rudimentary horn is identified, it is important to determine whether functional endometrium is present (usually with T2-weighted MRI images). About two-thirds of rudimentary horns are noncommunicating, some with a fibrous band connecting the 2 structures. Rudimentary horns can also communicate with the contralateral uterus. A fertilized ovum can implant and develop within a rudimentary horn. These pregnancies are incompatible with expectant gestation, and rupture of the horn could be life-threatening. Rupture tends to occur at a later gestation than with an ectopic pregnancy, and hemorrhage is severe. Patients with rudimentary horns with functioning endometrium can also present with pain caused by accumulating menses. Because the other horn has a normal outflow pathway, these patients present with pain, not primary amenorrhea. Pregnancies that arise in a unicornuate uterus are associated with increased preterm labor and delivery, malpresentation, and miscarriage.

Uterine Didelphys

A **uterine didelphys** is the result a complete failure of fusion and represents 5% of müllerian anomalies. There are 2 fallopian tubes, 2 completely separate uterine cavities, 2 cervices, and often 2 vaginal canals or 2 partial canals because of an associated longitudinal vaginal septum (75% of the time). Evaluation for renal anomalies should be pursued because they are common as well. At times, the longitudinal septum attaches to 1 sidewall and obstructs 1 side of the vagina (or hemivagina). The combination of uterine didelphys, obstructed hemivagina, and ipsilateral renal agenesis is a variant of the broad spectrum of müllerian anomalies that is referred to as the **Heryln-Werner-Wunderlich syndrome** or **obstructed hemivagina and ipsilateral**

renal anomaly syndrome in the literature. Adolescents with this disorder usually present with abdominal pain shortly after menarche. Although there still may be a risk of adverse pregnancy outcomes with a uterine didelphys (preterm labor, malpresentation), overall pregnancy outcomes are generally good and are associated with less risk than in other uterine anomalies.

Arcuate Uterus

An **arcuate uterus** is a uterine cavity that has a small midline septum, from lack of a small amount of resorption, and sometimes a slight indentation of the uterine fundus. An arcuate uterus might represent a variant of normal rather than a müllerian anomaly. Untoward pregnancy outcomes are rare and surgical correction is not warranted.

Uterine Anomalies in Diethylstilbestrol-Exposed Patients

Intrauterine diethylstilbestrol (DES) exposure is associated with an increased risk for development of uterine anomalies and clear cell adenocarcinoma of the vagina and cervix. DES was used to prevent preterm delivery, but this practice was discontinued in 1971. Commonly observed uterine features associated with DES exposure include the following: T-shaped uterus, cervical hypoplasia, fallopian tube irregularities, scalloped or irregularly shaped endometrial contour, constriction bands, and others. DES suppresses and/or alters *Wnt* and *HOX* genes in mice and thus might work by affecting gene expression in müllerian duct development, causing uterine abnormalities, vaginal adenosis, and potentially carcinoma.

Treatment

Treatment depends on the specific anomaly. Hysteroscopic surgical resection is widely supported for uterine septa. If a septate uterus extends through the cervical canal, many choose to leave this cervical portion of the septum because of concerns for future incompetence, although case reports indicate that incisions have been done with uneventful follow-up. Most would support the incision of a uterine septum in the clinical setting of pregnancy loss, but some would also support prophylactic metroplasty without a history of miscarriage, especially before in vitro fertilization.

A noncommunicating horn with functional endometrium should be resected to improve quality of life or prevent future complications; opinions vary as to whether resection of a communicating horn or one with no functional endometrium is warranted. Any surgical resection of a rudimentary horn requires careful surgical technique to protect the ipsilateral ovarian blood supply and the myometrium of the remaining unicornuate uterus.

Although metroplasty had been advocated with didelphic and bicornuate uteri and a history of poor pregnancy outcomes in the past, currently most clinicians feel there is not enough evidence to support such a complicated procedure. Any obstruction to the outflow tract must also be relieved; this can necessitate creation of a vaginal window or excision of a hemivaginal septum.

VAGINAL ANOMALIES

Abnormalities of the Hymen

An **imperforate hymen** is the most common obstructive anomaly, and familial occurrences have been reported. Its incidence is most often reported as approximately 1 in 1,000. In the newborn period and early infancy, it may be diagnosed by a bulging membrane caused by a mucocolpos from maternal estrogen stimulation of the vaginal mucosa. This can eventually reabsorb if it is not too large or symptomatic. More often it is diagnosed at the time of menarche, when menstrual fluid accumulates. The clinical manifestations often are a bulging blue-black membrane, pain, primary amenorrhea, and normal secondary sex characters. Depending on the circumstance, patients might have cyclic abdominal pain or a pelvic mass. Other hymenal abnormalities have been reported. A normal hymen can have various configurations (annular, crescentic). Some hymenal membranes do not undergo complete resorption or perforation, resulting in microperforate, cribriform, or septate-shaped hymen. Infants and children vary in age as to when these are recognized, but hymenal anomalies are often discovered after menarche when it is difficult for an adolescent to place a tampon, so resection is indicated.

Congenital Absence of the Vagina and Mayer-Rokitansky-Küster-Hauser Syndrome

Vaginal agenesis or **atresia** results when the vaginal plate fails to canalize. On physical exam it appears as an extremely foreshortened vagina, sometimes referred to as a *vaginal dimple*. Isolated (partial) vaginal agenesis involves an area of aplasia between the distal vaginal portion and a normal upper vagina, cervix, and uterus. On initial presentation it may be confused with a low transverse septum or imperforate hymen, and therefore clear delineation of the anomaly is critical before attempting surgical repair. It can also manifest with cyclic pain and a bulging mass just after menarche. Surgical repair and reconstruction are complicated and individualized and best performed with consultation of specialists.

Uterine and vaginal agenesis often occur together because of their close association during development, when müllerian ductal development fails early in the process. The most common cause of vaginal agenesis is **Mayer-Rokitansky-Küster-Hauser syndrome**, with an incidence reported at 1 in 4,000-10,000 female births. After gonadal dysgenesis, müllerian agenesis is the second most common cause of primary amenorrhea. The cause is unknown and likely has a multigenetic and multifactorial etiology. Mayer-Rokitansky-Küster-Hauser syndrome is characterized by primary amenorrhea, normal vulva, anomalies of the uterus (usually aplasia or agenesis), attenuated fallopian tubes, normal ovaries, normal female karyotype and phenotype, and associated anomalies (most commonly renal and skeletal). The vagina either is completely absent or only has a small dimpled opening. Although most patients with müllerian agenesis have small rudimentary müllerian bulbs, approximately 2-7% of patients can have active endometrium within these uterine structures. These patients will often present with cyclic pelvic pain. MRI imaging is often necessary to determine if any small uterine remnant is present (often located on the pelvic sidewall or near the ovaries and only a small fibromuscular remnant) and to clearly delineate the anomaly. Laparoscopy is not necessary to diagnosis müllerian agenesis but may be useful in the treatment of rudimentary uterine horns, particularly when removal of obstructed uterine structures or associated endometriosis is indicated for pelvic pain. Absence of the vagina and uterus has significant anatomic, physiologic, and psychologic implications for the patient and family. Any diagnosis of müllerian agenesis must be differentiated from androgen insensitivity (testicular feminization) as well; karyotype, serum testosterone levels, and pubic hair distribution usually help distinguish between the two.

Lesions involving other organ systems occur in association with the Mayer-Rokitansky-Küster-Hauser syndrome. The most common are urinary tract anomalies (15-40%) primarily involving unilateral absence of a kidney, a horseshoe or pelvic kidney, and skeletal anomalies (5-10%), which primarily involve vertebral development but can also include hearing impairment.

Longitudinal Vaginal Septa

Longitudinal vaginal septa represent failure of complete canalization of the vagina. These often occur in the presence of uterine anomalies as noted earlier.

Transverse Vaginal Septa (Vertical Fusion Defects)

Vertical fusion defects can result in a transverse septum, which may be imperforate and associated with hematocolpos or hematometra in adolescents or with mucocolpos in infants. These are much less common anomalies, reportedly found in 1 in 80,000 females. Most patients present with amenorrhea and cyclical pain around the time of menarche. Patients who have a small opening in the transverse septa might present with prolonged vaginal drainage and discharge. Transverse vaginal septa vary in location in the vagina (15-20% in the lower third, but most in the middle or upper third of the vagina) and thickness but

are generally ≤1 cm thick. High locations, thick septa, and narrow vaginal orifices present challenging surgical cases.

Transverse vaginal septa may be associated with other congenital anomalies, although this occurs less often than with müllerian agenesis. These patients have a functional normal uterus, unlike women with Mayer-Rokitansky-Küster-Hauser syndrome. There is also an increased incidence of endometriosis secondary to retrograde menstruation.

Evaluation of transverse vaginal septa includes careful pelvic examination and often pelvic imaging, usually with MRI and ultrasound, to delineate the anatomic abnormalities. MRI is especially helpful to determine the thickness of the septum and presence of a cervix and for surgical planning. Diagnosis and treatment plans should be made as soon as possible after menarche, because significant accumulation of hematometra and/or hematosalpinx could affect future reproductive success by negatively affecting uterine and/or tubal function.

Treatment

An imperforate hymen requires resection to prevent or relieve the outflow tract obstruction. Many approach it with a horizontal, lunate or cruciate incision, excision of excess tissue, and reanastomosis of the mucosal edges. Repair should be done at time of diagnosis, if the patient is symptomatic. Although the lesion may be repaired any time during infancy, childhood, or adolescence, surgery is facilitated by estrogen stimulation and thus is ideally performed in adolescence, either after puberty or menarche. Variants in the hymen with microperforations or hymenal septa may interfere with tampon use and resection of this tissue is usually electively performed.

Treatment of congenital absence of the vagina is usually delayed until the patient is ready to be sexually active. The nonsurgical approach is the most common first-line therapy owing to the high success rate and extremely low morbidity. It requires dedicated use of dilators to create a functional vagina. The series of dilators come in progressively increasing sizes and require a commitment and maturity on the part of the patient to comply with daily use (20-30 min daily). If done correctly it is possible to achieve a functional vaginal length (6-8 cm), width, and physiologic angle for intercourse in about 6-8 wk of therapy. When the ultimate size that accommodates coitus is reached, then the patient must use the dilator or have coitus with a frequency that maintains adequate length.

Surgical approaches require more expertise and often some postoperative vaginal dilation to ensure a functional result. Controversy exists among surgical subspecialties, because pediatric surgeons and pediatric urologists often recommend creating the neovagina in infancy. Pediatric gynecologists and reproductive endocrinologists believe better outcomes result from creating the neovagina when the young woman is interested in sexual activity and can participate in the decision to have surgery and in her own postoperative recovery. There is no consensus as to the best surgical option; the most-used procedures include 2 surgical approaches followed by dilators or an approach using a loop of bowel out of which to construct a vagina. Patients need to be counseled about the ability to use their own oocytes and a gestational carrier through in vitro fertilization to achieve pregnancy. These therapies can be quite complicated physically and emotionally. They are best approached in a multidisciplinary fashion, often with the assistance of psychologic counseling and surgeons with specialized training.

For transverse vaginal septa, treatment is surgical resection of the obstruction through a vaginal approach. Some surgeons advocate waiting for 1 or more menstrual cycles or using preoperative dilators from below to increase the depth and circumference of the distal vagina and to allow menstrual blood to accumulate and dilate the upper portion of the vagina. Complete resection of the septum, with primary anastomosis of the upper and lower mucosal segments, should be attempted. A vaginal stent is sometimes placed postoperatively in the vagina to maintain patency and allow squamous epithelization of the upper vagina and cervix. Follow-up dilation may be necessary after the stent is removed. Careful preoperative assessment is important because surgeons who begin a case believing they are operating on an imperforate hymen can find themselves in entirely different and more complex surgical planes. Regardless of the approach, vaginoplasty is often best deferred until the patient is mature and physically and psychologically prepared to participate in the healing process and postoperative dilator treatments.

Longitudinal vaginal septa themselves do not lead to adverse reproductive outcomes but may be symptomatic in a patient, causing dyspareunia, difficulties with tampon insertion, or impedance during vaginal birth. Such complaints can warrant a resection of the vaginal septa. In a small number of patients there may be unilateral obstruction of a hemivagina, which would require incision and resection.

CERVICAL ANOMALIES

Congenital atresia or complete agenesis of the uterine cervix is extremely rare and often manifests at puberty with amenorrhea and pelvic pain. It is associated with significant renal anomalies in 5-10% of patients. A pelvic MRI is often warranted to completely define the abnormality. Usually, pain and obstruction are significant and a hysterectomy is necessary. Attempts to reconnect the uterus to the vagina are rarely successful and associated with significant morbidity and reoperation rates. As with most müllerian anomalies, the ovaries usually remain normal and future reproduction can still occur through the use of in vitro fertilization and a gestational carrier.

VULVAR AND OTHER ANOMALIES

Complete Vulvar Duplication

Duplication of the vulva is a rare congenital anomaly that is seen in infancy and consists of 2 vulvas, 2 vaginas, and 2 bladders, a didelphic uterus, a single rectum and anus, and 2 renal systems.

Labial Asymmetry and Hypertrophy

With the onset of puberty the labia minora enlarge and grow to an adult size. A woman's labia can vary in size and shape. Asymmetry of the labia, where the right and left labia are different in size and appearance, is a normal variant. Some women are uncomfortable with what they perceive to be their asymmetric or enlarged labia minora and complain about self-consciousness and discomfort while wearing tight clothing, exercising, or having sex. The enlarged labia can have a protuberant and abnormal appearance that can be functionally or psychologically bothersome. Local irritation, problems of personal hygiene with bowel movements or menses, interference with sexual intercourse or while sitting or exercising have resulted in requests for labial reduction. Some surgeons are advertising procedures to reduce uneven or enlarged labia minora. The American College of Obstetricians and Gynecologists does not support performing such surgery unless there is significant impairment in function. Medically indicated surgical procedures can include reversal or repair of female genital cutting and treatment for labial hypertrophy or asymmetrical labial growth secondary to congenital conditions, chronic irritation, or excessive androgenic hormones. Complications of labial surgery include loss of sensation, keloid formation, and dyspareunia.

Clitoral Abnormalities

Agenesis of the clitoris is rare. Clitoral duplication has been reported, often associated with pelvic organ abnormalities, including agenesis of other genital tract structures and bladder exstrophy. Exposure to male hormones will result in clitoral enlargement, and is often a sign of a testosterone producing tumor or use of exogenous steroids.

Cloacal Anomalies

Cloacal anomalies are rare lesions representing a common urogenital sinus into which the gastrointestinal, urinary, and vaginal canals all exit. Usually there is an abnormality in all or some of the processes of fusion of the müllerian ducts, development of the sinovaginal bulbs, or development of the vaginal plate. The single opening (cloaca) requires surgical correction, preferably by a multidisciplinary pediatric surgical team.

Ductal Remnants

Even though the opposite duct regresses in both sexes, there can sometimes be a small portion of either the müllerian or wolffian duct that

remains in either the male or female, respectively. Such remnants can form cysts, which is what makes them clinically visible during surgery, examination, or imaging. Most do not cause pain, although torsion of some has been reported, and small asymptomatic ones usually do not require resection. The most commonly reported are hydatid of Morgagni cysts (remnant of a wolffian duct arising from the fallopian tube), cysts of the broad ligament, and Gartner's duct cysts, which can form an ectopic ureter or be found along the cervix or vaginal walls.

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Chapter 555

Gynecologic Care for Girls with Special Needs

Elisabeth H. Quint

Adolescence presents challenges for all children and their families, but particularly so for teens with special needs and their families. The start of menstrual periods, the mood changes associated with puberty and the concerns about sexual activity with possible unplanned pregnancies, and worries about safety and abuse may present teens with disabilities and their families with additional issues.

SEXUALITY AND SEXUAL EDUCATION

Adolescents with special needs can have physical and/or developmental disabilities. These young women are often seen as asexual by their families, care providers, and society and therefore sexual education might not have been provided or considered necessary. Physically disabled teens are as likely to be sexually active as nondisabled teens. The care provider needs to assess the teen's knowledge of anatomy and sexuality, her social knowledge of relationships, and her ability to consent to sexual activity. Education regarding HIV and other sexually transmitted infections, disease prevention, and contraception, including postcoital contraception, should be offered at a developmentally appropriate level. Teens with disabilities may be more at risk for isolation and depression during adolescence.

ABUSE

The risk for sexual abuse in teens with disabilities is difficult to estimate. Screening for abuse is mandatory. Studies show that teens with physical disabilities are just as sexually active as their nondisabled counterparts but that more of their activity is nonvoluntary. Patients with cognitive impairment are often taught to be cooperative, which may make them more vulnerable. Abuse prevention education can include the No! Go! Tell! model. For teens with limited verbal capacity or developmental delay, abuse may be very hard to detect. The care provider needs to be vigilant in looking for signs on physical exam, such as unexplained bruises or scratches, or changes in behavior, such as regression, which may be indications of sexual abuse in those adolescents (see Chapters 40.1 and 119).

PELVIC EXAMINATION

An internal pelvic exam is rarely indicated in teens that are not sexually active, as Papanicolaou smears are not recommended to start until age 21 yr. An external genital exam can be performed, if there are vulvar issues such as discharge, irregular bleeding, suspicion for abuse, or foreign body. The frogleg position is usually favored over the use of stirrups. If the vagina or cervix needs to be clearly visualized for a medical indication, an exam under anesthesia by a gynecologist should be considered. Testing for sexually transmitted infections can be accomplished by urine testing or vaginal swabs (see Chapter 120).

MENSTRUATION

Irregular menstruation is common in teenagers, especially during the 1st 5 yr after menarche, because of immaturity of the hypothalamic–pituitary–ovarian axis and subsequent anovulation (see Chapter 116). Several conditions in teens with disabilities are associated with an even higher risk of irregular cycles. Teens with Down syndrome have a higher incidence of thyroid disease. There is a higher incidence of reproductive issues, including polycystic ovarian syndrome in teens with epilepsy and on certain antiepileptic drugs (see Chapter 552). Antipsychotic medication can cause hyperprolactinemia, which can affect menstruation.

For teens with disabilities the main issue with menstrual cycles, whether they are regular, irregular, or heavy, is the impact of menstruation on the patient's life, her health, and her ability to perform her normal activities. The history should focus on this aspect, and menstrual calendars may be helpful to document the cycles, behavior, and the impact of treatments. Most adolescents who self-toilet can learn to use menstrual hygiene products appropriately.

The evaluation for abnormal bleeding is the same as for all teens. Areas requiring particular attention for the girl with special needs are the consideration of menstrual suppression for hygiene or cyclical behavioral issues, like crying, tantrums, or withdrawal. A request for birth control, especially coming from a caregiver and not from the teen, requires an evaluation of the teen's ability to consent to sexual activity and evaluate the safety of her environment. Guidelines for abnormal bleeding include menses that are too heavy (in excess of 1 pad/hr for several hours in a row), too long (longer than 10 days), or too frequent (fewer than 20 days apart).

Treatment of Menstruation

If after documenting the impact of the regular or irregular cycles on the patient's well-being (often through menstrual or behavioral charting for several months), the care provider, patient, and family decide on menstrual intervention, several options are available. Menstrual regulation is not different from that in the nondisabled teenager in general, although there are some special considerations. Goals for treatment can be to decrease the heaviness of flow, regulate cycles to predictable bleeding, relieve pain or cyclical behavior symptoms, provide contraception, and/or obtain amenorrhea. Menstrual suppression leading to complete amenorrhea is usually difficult to obtain and infrequent scheduled bleeds may be easier to manage than unpredictable spotting, a common side effect of any suppressive treatment, for certain patients. After treatment has started, continue to monitor cycles, ideally with continued menstrual or behavior calendars.

Nonhormonal Methods

If menorrhagia or dysmenorrhea (occasionally leading to cyclical behavior changes in nonverbal teens) is the main concern, the patient can be started on nonsteroidal antiinflammatory drugs. These can decrease the flow by up to 20% in adequate doses and can be used alone or in combination with other treatments.

Estrogen-Containing Methods

Oral Contraceptives

Cyclical oral contraceptives usually lead to regular, lighter cycles with less cramping. Extended cycling through the use of continuous use of oral contraceptives can suppress cycles, with amenorrhea rates improving with time. Some unpredictable spotting is usually unavoidable, and often teens with special needs prefer to have predictable cycles several times a year. A chewable oral contraceptive is available for those with swallowing issues.

Contraceptive Ring

The contraceptive ring is usually used in a pattern of 3 wk on and 1 wk off, but it can be used (off-label) in a continuous 4-wk pattern, which can lead to less bleeding. However, the contraceptive ring may be difficult to use for a teen with dexterity problems and help with placement has obvious privacy issues.

Contraceptive Patch

The weekly patch can also be used in a continuous fashion. Some teens with developmental disabilities remove their patch erratically, and placement out of reach (e.g., on buttocks or shoulder) is advised.

Estrogen Use, Venous Thromboembolism and Mobility Issues

Immobility per se is not a contraindication to estrogen-containing contraceptives, according to the Centers for Disease Control and Prevention medical eligibility criteria for contraception released in 2010. There are some data to support the concern that higher-dose oral estrogen, the combined estrogen patch, and the newer progestin preparations may have a higher risk for venous thromboembolism. However, there are minimal data on the risk of venous thromboembolism in teens with mobility issues in wheelchairs with or without extraneous estrogen. It is important to obtain a thorough and extended family history for hypercoagulability before initiating estrogen therapy. Careful use of lower-dose (30 or 20 µg) ethinyl estradiol preparations may be advisable and third-generation progestin combinations and the patch should only be used if other methods have failed.

Progestin-Only Methods

Intramuscular Medroxyprogesterone Acetate

Intramuscular medroxyprogesterone acetate (DMPA) has long been used for menstrual suppression. Two issues are particularly relevant to teens with disabilities. Studies documenting a decrease in bone density associated with longer-term use of DMPA and a black box warning by the FDA have raised concerns about use of these products in young women, although research indicates that the bone density improves after the medication is stopped. For teens with mobility issues or those with very low body weight who are already at risk for low bone density, decreased bone density is a real concern, although the risk of fractures is unclear. Adequate calcium and vitamin D is recommended. The second issue for teens with mobility issues is weight gain associated with DMPA, especially among obese teens, which can lead to transfer and mobility issues. If long-term DMPA is considered for a specific patient, calcium and vitamin D supplementation is recommended and bone density could be measured after several years of use, and weight should be monitored closely.

Oral Progestins

Continuous oral progestins can also be very effective to obtain amenorrhea. The progesterone-only minipill causes significant irregular spotting, so if full suppression is the goal, then other progestins can be used daily, such as norethindrone 2.5 or 5 mg or micronized progesterone 200 mg.

Progesterone Intrauterine Device

The 5 yr levonorgestrel-intrauterine device has now been used for many teenagers for contraception as well as heavy menses. Teens with special needs might require anesthesia for insertion if the exam is very difficult because of discomfort, contractures, or a narrow vagina. Checking for strings in a clinic setting may be challenging; however, the intrauterine device location can be confirmed by sonography. There may be a significant amount of irregular bleeding and spotting in the 1st several mo, but there is 20% amenorrhea after insertion and up to 50% amenorrhea after 1 year of use. The bleeding profile of the newer and smaller 3 year progesterone intrauterine device may not be as helpful for menstrual suppression as the amenorrhea rates from the initial studies by the manufacturer are 6% at 1 year, but more studies are needed.

Implants

Progestin subdermal implants have relatively low amenorrhea rates and high rates of unscheduled bleeding and therefore might not be ideal for teens with special needs, as they also require significant patient cooperation for insertion.

Hormones and Antiepileptic Drugs

Certain enzyme-inducing seizure medications can interfere with oral contraceptives, change their effectiveness, and/or lead to intermittent bleeding. Higher estrogen dose or shorter injection intervals for DMPA may be considered. The only antiepileptic medication that is affected by combined oral contraceptives is lamotrigine; consequently, the dose of that medication may need to be adjusted if used in conjunction with hormones.

Surgical Methods

Surgical procedures such as endometrial ablation, a procedure where the lining of the uterus is surgically removed, and hysterectomy are available for treatment of abnormal periods in adults, but they should only rarely be used in extreme situations for teenagers where all other methods have failed and the patient's health is severely compromised by her cycles. Endometrial ablation only leads to amenorrhea approximately 30% of the time and has a higher failure rate in women younger than 40 yr of age. Ethical considerations around these methods leading to infertility and consent issues are complicated, and state law varies on this topic.

CONTRACEPTION

See also Chapter 117.

The menstrual manipulation methods discussed above can also be used for contraception and if a request for birth control is made, an evaluation of the patient's ability to consent to sexual activity and the safety of her environment should be done. The method chosen should be the safest method for her situation with the highest protection rate. If she is dependent on others a long-acting reversible contraceptive method may be advisable. Sexually transmitted infections and condom use should be addressed with the teen and specific guidelines on how to obtain condoms and negotiate its use may be needed. A discussion about postcoital contraception is recommended, as well as ways to help the teen obtain this if indicated.

Bibliography is available at Expert Consult.

555.1 Female Genital Mutilation/Cutting

Robert M. Kliegman

Female genital mutilation/cutting (FGM/C) is a common practice in many parts of the world and is considered a form of child abuse and is illegal in most countries. It is estimated that more than 125 million women in 29 countries have undergone FGM/C (Fig. 555-1). FGM/C breaches international human rights laws and is considered a criminal act.

FGM/C has no health benefit. It threatens the health of girls and women having adverse effects on their psychologic, sexual, and reproductive well-being (Table 555-1). In addition, it increases the risk of HIV infection.

CLASSIFICATIONS

Type I: Partial or complete removal of the clitoris, prepuce, or both

Type II: Mutilation or cutting producing partial or complete removal of the clitoris and labia minora with or without excision of the labia majora

Type III: Infibulation; narrowing and sealing of the vaginal orifice by cutting and apposition of the labia minora or majora with or without excision of the clitoris

Type IV: All other harmful procedures

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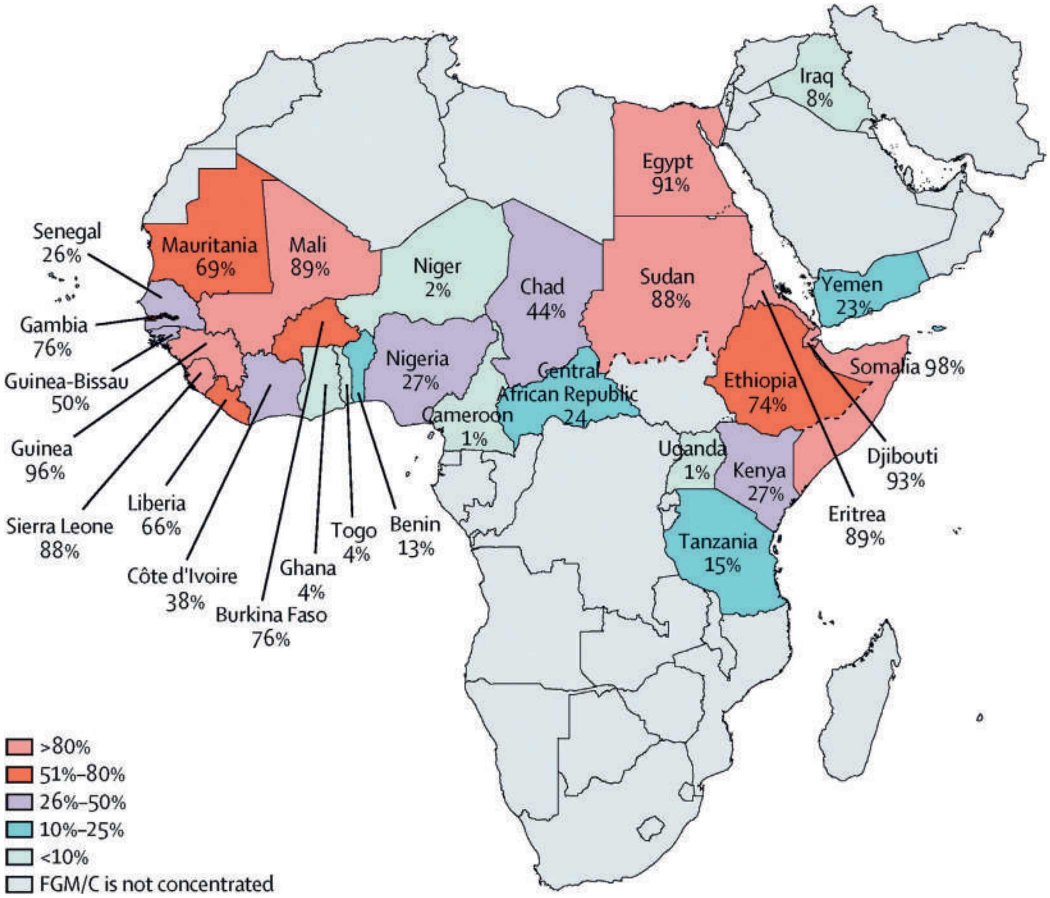

Figure 555-1 **Proportion of girls and women ages 15-49 yr who have undergone FGM/C, by country.** This map is stylized and not to scale; it does not indicate UNICEF's position on the legal status of any country or territory or the delimitation of any frontiers. The final boundary between Sudan and South Sudan has not yet been determined. FGM/C, female genital mutilation/cutting. *(Reproduced from Female genital mutilation/cutting: a statistical overview and exploration of the dynamics of change, by permission of UNICEF. Available at:* http://www.unicef.org/publications/index_69875.html*)*

Table 555-1	Health Consequences of Female Genital Mutilation
IMMEDIATE RISKS Pain, shock (caused by pain or hemorrhage, or both), excessive bleeding, difficulty passing urine or feces, infection (including tetanus inoculation and the transmission of bloodborne viruses such as HIV, hepatitis B, and hepatitis C), psychologic consequences (as a result of pain, shock, or physical restraint), unintended labial fusion, death (caused by hemorrhage or infection).	
LONG-TERM RISKS Pain (chronic neuropathic pain), keloid scarring, infections (including chronic pelvic infections, recurrent urinary tract infections, and an increased incidence of certain genital infections), birth complications (cesarean section, postpartum hemorrhage, and episiotomy), danger to the newborn (including death), decreased quality of sexual life, psychologic consequences (including posttraumatic stress disorder, depression, and anxiety)	
LONG-TERM RISKS PARTICULAR TO TYPE 3 FEMALE GENITAL MUTILATION Need for later surgery (deinfibulation), urinary and menstrual problems, painful sexual intercourse, and infertility	

From Simpson J, Robinson K, Creighton SM, Hodes D: Female genital mutilation: the role of health professionals in prevention, assessment, and management. BMJ *344:e1361, 2012, Box 3.*

West African women are at greater risk of type II FGM/C, while those in northeast and east Africa and the Middle East are subjected to type III FGM/C. Nonetheless because of migration, women and girls in the United States and Western Europe may undergo FGM/C by traditional practitioners or, rarely, ethnic minority obstetricians or other physicians. Many ethnic women at risk for FGM/C living in the United States or Western Europe are more ambivalent about the procedure demonstrating a conflict between 2 cultures.

MANAGEMENT

This is a complex ethnic minority issue that often goes undetected until complications develop, either acutely from the procedure or during pregnancy. Criminalization alone will not eliminate this practice because it is performed in secret, and women are reluctant to discuss this with their healthcare provider, but laws against these procedures are an important step in reducing the number of women subjected to FGM/C.

Surgical repair, such as clitoral reconstruction with removal of scar tissue has been quite beneficial in decreasing pain and enhancing pleasure, including orgasm. Furthermore, women report a positive effect on their self-image and female identity as well as a new sense of "completeness" after reconstructive surgery.

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The Endocrine System

PART XXVI

Section 1

Disorders of the Hypothalamus and Pituitary Gland

Chapter 556

Hormones of the Hypothalamus and Pituitary

Eric I. Felner and John S. Parks

The pituitary gland is the major regulator of an elaborate hormonal system. The pituitary gland receives signals from the hypothalamus and responds by sending pituitary hormones to target glands. The target glands produce hormones that provide negative feedback at the level of the hypothalamus and pituitary (Fig. 556-1). This feedback mechanism enables the pituitary to regulate the amount of hormone released into the bloodstream by the target glands. The pituitary's central role in this hormonal system and its ability to interpret and respond to a variety of signals have led to its designation as the "master gland." Table 556-1 lists hypothalamic and pituitary hormones and their functions.

ANATOMY

The pituitary gland is located at the base of the skull in a saddle-shaped cavity of the sphenoid bone called the *sella turcica.* The bony structure protects and surrounds the pituitary bilaterally and inferiorly. The dura, a dense layer of connective tissue, forms the roof of the sella. An external layer of the dura continues into the sella to form its lining. As a result, the pituitary is extradural and is not normally in contact with cerebrospinal fluid. The pituitary gland is connected to the hypothalamus by the pituitary stalk. The pituitary gland is composed of an anterior (adenohypophysis) and a posterior (neurohypophysis) lobe. The anterior lobe constitutes approximately 80% of the gland.

EMBRYOLOGY

The anterior pituitary gland originates from the Rathke pouch as an invagination of the oral ectoderm. It then detaches from the oral epithelium and becomes an individual structure of rapidly proliferating cells. By 6 wk of gestation, the connection between the Rathke pouch and the oropharynx is completely obliterated, and the pouch establishes a direct connection with the downward extension of the hypothalamus, which gives rise to the pituitary stalk. Persistent remnants of the original connection between the Rathke pouch and the oral cavity can develop into **craniopharyngiomas** (see Chapter 497), the most common type of tumor in this area.

VASCULAR SUPPLY

The arterial blood supply of the pituitary gland originates from the internal carotid via the inferior, middle, and superior hypophyseal arteries. This network of vessels forms a unique portal circulation connecting the hypothalamus and pituitary. The branches of the superior hypophyseal arteries penetrate the stalk and form a network of vessels that traverse the pituitary stalk and terminate in a network of capillaries within the anterior lobe. It is through this portal venous system that hypothalamic hormones are delivered to the anterior pituitary gland. Anterior pituitary hormones, in turn, are secreted into a secondary plexus of portal veins that drain into the dural venous sinuses.

ANTERIOR PITUITARY CELL TYPES

A series of sequentially expressed transcriptional activation factors directs the differentiation and proliferation of anterior pituitary cell types. These proteins are members of a large family of DNA-binding proteins resembling homeobox genes. The consequences of mutations in several of these genes are evident in human forms of multiple pituitary hormone deficiency. Five cell types in the anterior pituitary produce 6 peptide hormones. Somatotropes produce growth hormone (GH), lactotropes produce prolactin (PRL), thyrotropes make thyroid-stimulating hormone (TSH), corticotropes express proopiomelanocortin, the precursor of adrenocorticotropic hormone (ACTH), and gonadotropes express luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Growth Hormone

Human GH is a 191-amino-acid single-chain polypeptide that is synthesized, stored, and secreted by somatotropes in the pituitary. Its gene *(GH1)* is the first in a cluster of 5 closely related genes on the long arm of chromosome 17 (q22-24). The 4 other genes *(CS1, CS2, GH2,* and *CSP)* have >90% sequence identity with the *GH1* gene.

GH is secreted in a pulsatile fashion under the regulation of hypothalamic hormones. The alternating secretion of growth hormone–releasing hormone, which stimulates GH release, and somatostatin, which inhibits GH release, accounts for the rhythmic secretion of GH. Peaks of GH occur when peaks of growth hormone–releasing hormone coincide with troughs of somatostatin. **Ghrelin,** a peptide produced in the arcuate nucleus of the hypothalamus and in much greater quantities by the stomach, also stimulates GH secretion. In addition to the 3 hypothalamic hormones, physiologic factors play a role in stimulating and inhibiting GH. Sleep, exercise, physical stress, trauma, acute illness, puberty, fasting, and hypoglycemia stimulate the release of GH whereas hyperglycemia, hypothyroidism, and glucocorticoids inhibit GH release.

GH binds to receptor molecules on the surface of target cells. The GH receptor is a 620-amino-acid, single-chain molecule with an extracellular domain, a single membrane-spanning domain, and a cytoplasmic domain. Proteolytically cleaved fragments of the extracellular domain circulate in plasma and act as a GH-binding protein. As in other members of the cytokine receptor family, the cytoplasmic domain of the GH receptor lacks intrinsic kinase activity; instead, GH binding induces receptor dimerization and activation of a receptor-associated Janus kinase (Jak2). Phosphorylation of the kinase and other protein substrates initiates a series of events that leads to alterations in nuclear gene transcription. The signal transducer and activator of transcription 5b (STAT5b) plays a critical role in linking receptor activation to changes in gene transcription.

The biologic effects of GH include increases in linear growth, bone thickness, soft tissue growth, protein synthesis, fatty acid release from adipose tissue, insulin resistance, and blood glucose. The mitogenic actions of GH are mediated through increases in the synthesis of **insulin-like growth factor** 1 (IGF-1), formerly named *somatomedin C*, a 70-amino-acid single-chain peptide coded for by a gene on the long arm of chromosome 12. IGF-1 has considerable homology to

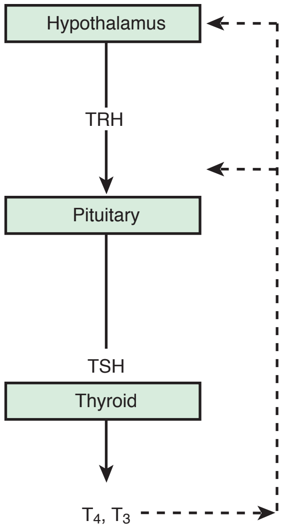

Figure 556-1 Hypothalamic–pituitary–thyroid (HPT) axis. Thyroid-releasing hormone (TRH) from the hypothalamus stimulates the pituitary gland to secrete thyroid-stimulating hormone (TSH). TSH stimulates the thyroid gland to produce and secrete thyroid hormones (T_4 and T_3). High circulating levels of T_3 and T_4 inhibit further TRH and TSH secretion and thyroid hormone production through a negative feedback mechanism *(dashed lines)*. T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (thyrotropin); <---, inhibits; ←, stimulates.

Table 556-1 Hormones of the Hypothalamus and Pituitary Gland

HORMONES	LOCATION	S/I	FUNCTION
ACTH	Anterior pituitary	S	Production and secretion of GCs, MCs, and androgens from adrenal gland
ADH	Posterior pituitary	S	Reabsorption of water into the bloodstream via renal collecting ducts
CRH	Hypothalamus	S	Secretion of ACTH
Dopamine	Hypothalamus	S	Secretion of PRL
FSH (females)	Anterior pituitary	I	Secretion of estrogen from ovary
FSH (males)	Anterior pituitary	S	Production of sperm from testis
GH	Anterior pituitary	S	Secretion of IGF-1
GHRH	Hypothalamus	S	Secretion of GH
Ghrelin	Hypothalamus	S	Secretion of GH
GnRH	Hypothalamus	S	Secretion of FSH and LH
LH (females)	Anterior pituitary	S	Ovulation and development of the corpus luteum
LH (males)	Anterior pituitary	S	Production and secretion of testosterone
Oxytocin	Posterior pituitary	S	Contractions of uterus at birth and release of milk from breast
PRL	Anterior pituitary	S	Promotion of milk synthesis
Somatostatin	Hypothalamus	I	Secretion of GH and TSH
TRH	Hypothalamus	S	Secretion of TSH and PRL
TSH	Anterior pituitary	S	Secretion of T_4 and T_3

ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GC, glucocorticoids; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-derived growth factor 1; LH, luteinizing hormone; MC, mineralocorticoids; PRL, prolactin; S/I, stimulate/inhibit; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (thyrotropin).

insulin. Circulating IGF-1 is synthesized primarily in the liver and formed locally in mesodermal and ectodermal cells, particularly in the growth plates of children, where its effect is exerted by paracrine or autocrine mechanisms. Circulating levels of IGF-1 are related to blood levels of GH and to nutritional status. IGF-1 circulates bound to several different binding proteins. The major one is a 150-kDa complex (IGF-BP3) that is decreased in GH-deficient children. Human recombinant IGF-1 might have therapeutic potential in conditions characterized by end organ resistance to GH such as Laron syndrome and the development of antibodies to administered GH. IGF-2 is a 67-amino-acid single-chain protein that is coded for by a gene on the short arm of chromosome 11. It has homology to IGF-1. Less is known about its physiologic role, but it appears to be an important mitogen in bone cells, where it occurs in a concentration many times higher than that of IGF-1.

Prolactin

PRL is a 199-amino-acid peptide made in pituitary lactotropes. The regulation of PRL is unique because PRL is consistently secreted unless it is actively inhibited by dopamine, a peptide produced by neurons in the hypothalamus. Disruption of the hypothalamus or pituitary stalk can result in elevated PRL levels. Dopamine antagonists, states of primary hypothyroidism, administration of thyrotropin-releasing hormone (TRH), and pituitary tumors result in increased serum levels of PRL. Dopamine agonists and processes causing destruction of the pituitary cause reduced levels of PRL.

The primary physiologic role for PRL is the initiation and maintenance of lactation. PRL prepares the breasts for lactation and stimulates milk production postpartum. During pregnancy, PRL stimulates the development of the milk-secretory apparatus, but lactation does not occur because of the high levels of estrogen and progesterone. After delivery, the estrogen and progesterone levels drop and physiologic stimuli such as suckling and nipple stimulation signal PRL release and initiate lactation.

Thyroid-Stimulating Hormone

TSH consists of 2 glycoprotein chains (α, β) linked by hydrogen bonding; the α-subunit, which is composed of 89 amino acids and is identical to other glycoproteins (FSH, LH, and human chorionic gonadotropin), and the β-subunit, composed of 112 amino acids, that is specific for TSH.

TSH is stored in secretory granules and released into circulation primarily in response to TRH, which is produced by the hypothalamus. TRH is released from the hypothalamus into the hypothalamic–pituitary portal system and ultimately stimulates TSH release from pituitary thyrotropes. TSH stimulates release of thyroxine (T_4) and triiodothyronine (T_3) from the thyroid gland through the formation of cyclic adenosine monophosphate and the G protein second messenger system. In addition to the negative feedback inhibition by T_3, the release of TRH and TSH is inhibited by dopamine, somatostatin, and glucocorticoids.

Deficiency of TSH results in inactivity and atrophy of the thyroid gland, whereas excess TSH results in hypertrophy and hyperplasia of the thyroid gland.

Adrenocorticotropic Hormone

ACTH is a 39-amino-acid single-chain peptide that is derived by proteolytic cleavage from proopiomelanocortin, a 240-amino-acid

precursor glycoprotein product of the pituitary gland. Proopiomelanocortin also contains the sequences for the lipotropins, melanocyte-stimulating hormones, and β-endorphin.

Secretion of ACTH is regulated by corticotropin-releasing hormone (CRH), a 41-amino-acid peptide found predominantly in the median eminence but also in other areas in and outside of the brain. ACTH is secreted in a diurnal pattern. It acts on the adrenal cortex to stimulate cortisol synthesis and secretion. ACTH and cortisol levels are highest in the morning at the time of waking, are low in the late afternoon and evening, and reach their nadir 1-2 hr after beginning sleep. ACTH also appears to be the principal pigmentary hormone in humans. Similar to TRH and TSH, CRH and ACTH function through the formation of cyclic adenosine monophosphate and the G protein second-messenger system. Although CRH is the primary regulator of ACTH secretion, other hormones play a role. Arginine vasopressin, oxytocin, angiotensin II, and cholecystokinin stimulate release of CRH and ACTH, whereas atrial natriuretic peptide and opioids inhibit release of CRH and ACTH. Similar to the feedback inhibition T_3 has on TRH and TSH, cortisol also inhibits CRH and ACTH. Physiologic conditions, such as stress, fasting, and hypoglycemia, also stimulate release of CRH and ACTH.

Luteinizing Hormone and Follicle-Stimulating Hormone

Gonadotropic hormones include 2 glycoproteins, LH and FSH. They contain the same α subunit as TSH and human chorionic gonadotropin but distinct β subunits. Receptors for FSH on the ovarian granulosa cells and on testicular Sertoli cells mediate FSH stimulation of follicular development in the ovary and of gametogenesis in the testis. On binding to specific receptors on ovarian theca cells and testicular Leydig cells, LH promotes luteinization of the ovary and Leydig cell function of the testis. The receptors for LH and FSH belong to a class of receptors with 7 membrane-spanning protein domains. Receptor occupancy activates adenylyl cyclase through the mediation of G proteins.

Luteinizing hormone–releasing hormone, a decapeptide, has been isolated, synthesized, and widely used in clinical studies. Because it leads to the release of LH and FSH from the same gonadotropic cells, it appears that it is the only gonadotropin-releasing hormone.

Secretion of LH is inhibited by androgens and estrogens, and secretion of FSH is suppressed by gonadal production of inhibin, a 31-kDa glycoprotein produced by the Sertoli cells. Inhibin consists of α and β subunits joined by disulfide bonds. The β-β dimer (activin) also occurs, but its biologic effect is to stimulate FSH secretion. The biologic features of these more recently identified hormones are being delineated. In addition to its endocrine effect, activin has paracrine effects in the testis. It facilitates LH-induced testosterone production, indicating a direct effect of Sertoli cells on Leydig cells.

POSTERIOR PITUITARY CELL TYPES

The posterior lobe of the pituitary is part of a functional unit, the neurohypophysis, that consists of the neurons of the supraoptic and paraventricular nuclei of the hypothalamus; neuronal axons, which form the pituitary stalk; and neuronal terminals in the median eminence or in the posterior lobe. Arginine vasopressin (antidiuretic hormone [ADH]) and oxytocin are the 2 hormones produced by neurosecretion in the hypothalamic nuclei and released from the posterior pituitary. They are octapeptides and differ by only 2 amino acids.

Antidiuretic Hormone

ADH regulates water conservation at the level of the kidney by increasing the permeability of the renal collecting duct to water. ADH stimulates translocation of water channels through its interaction with vasopressin 2 receptors in the collecting duct, which act through G proteins to increase adenylyl cyclase activity and increase permeability to water. V2 receptors also mediate the von Willebrand factor and tissue plasminogen activator. At higher concentrations, ADH activates V1 receptors in smooth muscle cells and hepatocytes and exerts pressor and glycogenolytic effects through mobilization of intracellular calcium stores. Separate V3 receptors mediate stimulation of ACTH secretion. These effects involve phosphatidylinositol hydrolysis rather than cyclic adenosine monophosphate production.

ADH and its accompanying protein neurophysin II are encoded by the same gene. A single preprohormone is cleaved and the 2 are transported to neurosecretory vesicles in the posterior pituitary. The 2 are released in equimolar amounts.

ADH has a short half-life and responds quickly to changes in hydration. The stimuli for its release are increased plasma osmolality, perceived by osmoreceptors in the hypothalamus, and decreased blood volume, perceived by baroreceptors in the carotid sinus of the aortic arch.

Oxytocin

Oxytocin stimulates uterine contractions at the time of labor and delivery in response to distention of the reproductive tract and stimulates smooth muscle contraction in the breast during suckling, which results in milk letdown. Studies suggest that oxytocin also plays a role in orgasm, social recognition, pair bonding, anxiety, trust, love, and maternal behavior. Most recently, through the interaction with its G-protein-coupled receptor in pancreatic and adipose tissue, oxytocin appears to play a significant role in appetite regulation and obesity by inducing anorexia.

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Chapter 557

Hypopituitarism

John S. Parks and Eric I. Felner

Hypopituitarism denotes underproduction of growth hormone (GH) alone or in combination with deficiencies of other pituitary hormones. Affected children have postnatal growth impairment that is specifically corrected by replacement of GH. The incidence of congenital hypopituitarism is thought to be between 1 in 4,000 and 1 in 10,000 live births. With expanding knowledge of the genes that direct pituitary development or hormone production, an increasing proportion of cases can be attributed to specific genetic disorders. Mutations in 7 candidate genes account for 13% of isolated growth hormone deficiency (IGHD) and 20% of multiple pituitary hormone deficiency (MPHD) cases. The likelihood of finding mutations is increased by consanguinity and occurrence in siblings or across generations. The genes, hormonal phenotypes, associated abnormalities, and modes of transmission for such established genetic disorders are shown in Tables 557-1 through 557-4. Acquired hypopituitarism usually has a later onset and different causes (Table 557-5).

MULTIPLE PITUITARY HORMONE DEFICIENCY

Genetic Forms

Sequentially expressed transcriptional activation factors direct the differentiation and proliferation of anterior pituitary cell types. These proteins are members of a large family of DNA-binding proteins resembling homeobox genes. Mutations produce different forms of MPHD. *PROP1* and *POU1F1* genes are expressed fairly late in pituitary development only in cells of the anterior pituitary and result in hypopituitarism without anomalies of other organ systems. The *HESX1, LHX3, LHX4,* and *PTX2* genes are expressed at earlier stages and are not restricted to the pituitary. Mutations in these genes tend to produce phenotypes that extend beyond hypopituitarism to include abnormalities in other organs.

Table 557-1 Etiologic Classification of Multiple Pituitary Hormone Deficiency

GENE OR LOCATION	PHENOTYPE	INHERITANCE
GENETIC FORMS		
POU1F1 (PIT1)	GH, TSH, PRL	R, D
PROP1	GH, TSH, PRL, LH, FSH, ±ACTH, variable AP	R
LHX3	GH, TSH, PRL, LH, FSH, variable AP, ±short neck	R
LHX4	GH, TSH, ACTH, small AP, EPP, ±Arnold-Chiari	D
TPIT	ACTH, severe neonatal form	R
HESX1	GH, variable for others, small AP, EPP	R, D
SOX3	Variable deficiencies, ±MR, EPP, small AP and stalk	XL
PTX2	Rieger syndrome	D
GLI2	Holoprosencephaly, midline defects	D
GLI3	Hall-Pallister syndrome	D
SHH (sonic hedgehog)	GH deficiency with single central incisor	D
ACQUIRED FORMS		
Idiopathic		
Irradiation	GH deficiency precedes other deficiencies	
Inflammation	Histiocytosis, sarcoidosis	
Autoimmune	Hypophysitis	
Postsurgical	Stalk section, vascular compromise	
Tumor	Craniopharyngioma, glioma, pinealoma	
Trauma	Battering, shaken baby, vehicular	
UNCERTAIN ETIOLOGY		
Idiopathic		
Congenital absence of pituitary		
Septooptic dysplasia		
Birth trauma		

ACTH, adrenocorticotropic hormone; AP, anterior pituitary; D, dominant; EPP, ectopic posterior pituitary; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; MR, mental retardation; PRL, prolactin; R, recessive; TSH, thyroid-stimulating hormone; XL, X-linked.

PROP1

PROP1 is found in the nuclei of somatotropes, lactotropes, and thyrotropes. Its roles include turning on *POU1F1* expression, hence its name prophet of *PIT1*. Mutations of *PROP1* are the most common explanation for recessive MPHD and are 10 times as common as the combined total of mutations in other pituitary transcription factor genes. Deletions of 1 or 2 base pairs in exon 2 are most common, followed by missense, nonsense, and splice-site mutations. Anterior pituitary hormone deficiencies are seldom evident in the neonatal period. The median age at diagnosis of GH deficiency is around 6 yr. Recognition of thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone, and adrenocorticotropin (ACTH) deficiencies is delayed relative to recognition of GH deficiency. Anterior pituitary size is small in most patients, but in others there is progressive enlargement of the pituitary.

POU1F1 (PIT1)

POU1F1 (formerly *PIT1*) was identified as a nuclear protein that binds to the GH and prolactin promoters. It is necessary for emergence and mature function of somatotropes, lactotropes, and thyrotropes. Dominant and recessive mutations in *POU1F1* are responsible for

Table 557-2 Established Genetic Defects of the GH-IGF Axis Resulting in IGF Deficiency

MUTANT GENE	INHERITANCE	PHENOTYPE
HPA		Developmental abnormalities
HESX1	AR	Septooptic dysplasia; variable involvement of pituitary hormones
PROP1	AR	GH, PRL, TSH, LH, FSH deficiencies; variable ACTH deficiency
POU1F1 (PIT1)	AR, AD	GH, PRL deficiency; variable degree of TSH deficiency
RIEG	AD	Rieger syndrome
LHX3	AR	GH, TSH, LH, FSH, prolactin deficiencies
LHX4	AD	GH, TSH, ACTH deficiencies
SOX3	XL	GH deficiency, mental retardation
GLI2	AD	Holoprosencephaly, hypopituitarism
GLI3	AD	Pallister-Hall syndrome, hypopituitarism
IGHD		
GHRHR	AR	IGHD, type IB form of IGHD
GHS-R	AD	GHD and ISS
GH1	AR AR AD XL AD	Type IA form of IGHD Type IB form of IGHD Type II form of IGHD Type III form of IGHD; hypogammaglobulinemia Bioinactive GH molecule
GHI		
GHR		
Extracellular domain	AR, AD	IGF-I deficiency; decreased or normal GHBP
Transmembrane	AR	IGF-I deficiency; normal or increased GHBP
Intracellular domain	AD	IGF-I deficiency; normal or increased GHBP
IGF		
IGF1	AR	IGF-1 deficiency; IUGR and postnatal growth failure
STAT5b	AR	IGF-1 deficiency, variable immune defect, hyperprolactinemia, chronic pulmonary infections, recurrent eczema
ALS	AR	IGF-1 deficiency; variable postnatal growth failure, delayed puberty

ACTH, adrenocorticotropic hormone (corticotropin); AD, autosomal dominant; ALS, acid labile subunit; AR, autosomal recessive; FSH, follicle-stimulating hormone; GH, growth hormone; GHBP, GH-binding protein; GHD, growth hormone deficiency; GHRHR, GH-releasing hormone receptor; HPA, hypothalamic pituitary; IGF, insulin-like growth factor; IGHD, isolated GHD; ISS, idiopathic short stature; IUGR, intrauterine growth retardation; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone; XL, X-linked.

From Sperling MA: Pediatric endocrinology, *ed 4, Philadelphia, 2014, Elsevier, Table 10-3, p. 333.*

Table 557-3 Clinical and Biochemical Features of Molecular Defects of the GH–IGF-1 Axis

GENE DEFECT/PHENOTYPE	*GHR*	*STAT5B*	*PTPN11*	*IGF1*	*IGFALS*	*IGFIR*	BIOINACTIVE GH	GH1 WITH ANTI-GH ANTIBODIES
Severe growth failure	+/–	+	–	+	–	–	–	+
Mild growth failure	–/+	–	+	–	+	+	+	–
Midface hypoplasia	+/–	+/–	–	–	–	–	–	+
Other facial dysmorphism	–	–	+	+	–	+	–	–
Deafness	–	–	–	+/–	–	–	–	–
Microcephaly	–	–	–	+	–	+	–	–
Intellectual delay	–	–	–/+	+	–	+/–	–	–
Puberty delay	+/–	+/–	+/–	–	+	–	–	–
Immune deficiency	–	+	–	–	–	–	–	–
Hypoglycemia	+	–/+	–	–	–	–	–	–
Hyperinsulinemia	–	–	–	+/–	+	–	–	–
IGF-1 deficiency	+	+	–/+	+/–	+	–	+	+
IGFBP-3 deficiency	+	+	–/+	–	+	–	+	+
ALS deficiency	+	+	–/+	–	+	–	+	+
GH excess	+	+	–	+/–	+	–	–	–
GHBP deficiency	+/–	–	–	–	–	–	–	–
Homozygous or compound heterozygous mutations	+	+	–	+	+	–	–/+	+
Heterozygous mutations	–	–	+	–/+	–	+	+/–	–

+, Positive; –, negative; +/–, predominantly positive; –/+, predominantly negative; ALS, acid labile subunit; GH, growth hormone; GHBP, growth hormone–binding protein; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor–binding protein.

From David A, Hwa V, Metherell L, et al: Evidence for a continuum of genetic, phenotypic, and biochemical abnormalities in children with growth hormone insensitivity. Endocr Rev *32:472–497, 2011, Table 2.*

Table 557-4 Proposed Classification of Growth Hormone Insensitivity

Primary GH insensitivity (hereditary defects)
- GH receptor defect (may be positive or negative for GH-binding protein)
  - Extracellular mutation (e.g., Laron syndrome)
  - Cytoplasmic mutation
  - Intracellular mutation
- GH signal transduction defects (distal to cytoplasmic domain of GH receptor)
  - Stat5b mutations
- Insulin-like growth factor-1 defects
  - IGF-1 gene deletion
  - IGF-1 transport defect (ALS mutation)
  - IGF-1 receptor defect
- Bioinactive GH molecule (responds to exogenous GH)

Secondary GH insensitivity (acquired defects)
- Circulating antibodies to GH that inhibit GH action
- Antibodies to the GH receptor
- GH insensitivity caused by malnutrition, liver disease, catabolic states, diabetes mellitus
- Other conditions that cause GH insensitivity

GH insensitivity: Clinical and biochemical features of IGF-1 deficiency and insensitivity to exogenous GH, associated with GH secretion that would not be considered abnormally low.

GH insensitivity syndrome: GH insensitivity associated with the recognizable dysmorphic features described by Laron.

Partial GH insensitivity: GH insensitivity in the absence of dysmorphic features described by Laron.

ALS, acid labile subunit; GH, growth hormone; IGF, insulin-like growth factor.

From Sperling MA: Pediatric endocrinology, *ed 4, Philadelphia, 2014, Elsevier, Box 10-4, p. 347.*

complete deficiencies of GH and prolactin and variable TSH deficiency. Affected patients exhibit nearly normal fetal growth but experience severe growth failure in the 1st yr of life. With normal production of LH and follicle-stimulating hormone, puberty develops spontaneously, though at a later than normal age. These patients are not at risk for development of ACTH deficiency. Anterior pituitary size is normal to small.

HESX1

The *HESX1* gene is expressed in precursors of all 5 cell types of the anterior pituitary early in embryologic development. Mutations result in a complex phenotype with defects in development of the optic nerve. Heterozygotes for loss-of-function mutations show the combinations of isolated GH deficiency and optic nerve hypoplasia. Homozygotes can have full expression of septooptic dysplasia. This condition combines incomplete development of the septum pellucidum with optic nerve hypoplasia and other midline abnormalities. Clinical observation of nystagmus and visual impairment in infancy leads to the discovery of optic nerve and brain abnormalities. Septooptic dysplasia is associated with anterior and/or posterior pituitary hormone deficiencies in approximately 25% of the cases. These patients often show the triad of a small anterior pituitary gland, an attenuated pituitary stalk, and an ectopic posterior pituitary bright spot. The great majority of patients with septooptic dysplasia do not have *HESX1* mutations. The etiology might involve mutations in another gene or a nongenetic explanation (see Chapters 591 and 631).

LHX3 and *LHX4*

The phenotype produced by recessive loss-of-function mutations of the *LHX3* gene resembles that produced by *PROP1* mutations. There are

Table 557-5	Causes of Acquired Hypopituitarism
BRAIN DAMAGE*	
Traumatic brain injury	
Subarachnoid hemorrhage	
Neurosurgery	
Irradiation	
Stroke	
PITUITARY TUMORS*	
Adenomas	
Others	
NONPITUITARY TUMORS	
Craniopharyngiomas	
Meningiomas	
Gliomas	
Chordomas	
Ependymomas	
Metastases	
INFECTION	
Abscess	
Hypophysitis	
Meningitis	
Encephalitis	
INFARCTION	
Apoplexy	
Sheehan syndrome	
AUTOIMMUNE DISORDER	
Lymphocytic hypophysitis	
OTHER	
Hemochromatosis, granulomatous diseases, histiocytosis	
Empty sella	
Perinatal insults	

*Pituitary tumors are classically the most common cause of hypopituitarism. However, new findings imply that causes related to brain damage might outnumber pituitary adenomas in causing hypopituitarism.

From Schneider HJ, Aimaretti G, Kreitschmann-Andermahr I, et al: Hypopituitarism, Lancet *369:1461–1470, 2007.*

deficiencies of GH, prolactin, TSH, LH, and follicle-stimulating hormone, but not ACTH. Some affected persons show enlargement of the anterior pituitary. The first patients to be described had the unusual findings of a short neck and a rigid cervical spine. They were only able to rotate their necks approximately 90 degrees compared with the normal rotation of 150-180 degrees. Dominantly inherited mutations in the structurally similar *LHX4* gene consistently produce GH deficiency, with the variable presence of TSH and ACTH deficiencies. Additional findings can include a very small V-shaped pituitary fossa, Chiari I malformation, and an ectopic posterior pituitary.

Other Congenital Forms

Pituitary hypoplasia can occur as an isolated phenomenon or in association with more extensive developmental abnormalities such as anencephaly or holoprosencephaly. Midfacial anomalies (cleft lip, palate; see Chapter 310) or the finding of a solitary maxillary central incisor indicates a high likelihood of GH or other anterior or posterior hormone deficiency. At least 12 genes have been implicated in the complex genetic etiology of holoprosencephaly (see Chapter 591.7). The Hall-Pallister syndrome is caused by dominant loss of function mutations in the *GLI3* gene. Absence of the pituitary gland is accompanied by hypothalamic hamartoblastoma, polydactyly, nail dysplasia, bifid epiglottis, imperforate anus, and anomalies of the heart, lungs, and kidneys. The combination of anophthalmia and hypopituitarism has been associated with mutations in the *SIX6, SOX2,* and *OTX2* genes.

Severe, early-onset MPHD including deficiency of ACTH is often associated with the triad of anterior pituitary hypoplasia, absence or attenuation of the pituitary stalk, and an ectopic posterior pituitary bright spot on MRI. Most cases are sporadic and there is a male predominance. Some are from abnormalities of the *SOX3* gene, located on the X chromosome. As with septooptic dysplasia, the majority of cases have not been explained at the genetic level.

Acquired Forms

Any lesion that damages the hypothalamus, pituitary stalk, or anterior pituitary can cause pituitary hormone deficiency (see Table 557-5). Because such lesions are not selective, multiple hormonal deficiencies are usually observed. Diabetes insipidus is more frequent in acquired than in congenital hypopituitarism. The most common lesion is the craniopharyngioma (see Chapter 497). Central nervous system germinoma, eosinophilic granuloma (histiocytosis), tuberculosis, sarcoidosis, toxoplasmosis, meningitis, and aneurysms can also cause hypothalamic-hypophyseal destruction. Trauma, including abusive head trauma (see Chapter 40), motor vehicle accidents, traction at delivery, anoxia, and hemorrhagic infarction, can also damage the pituitary, its stalk, or the hypothalamus.

ISOLATED GROWTH HORMONE DEFICIENCY AND INSENSITIVITY

Genetic Forms of Growth Hormone Deficiency

IGHD is caused by abnormalities of the GH-releasing hormone receptor, GH genes, and genes located on the X chromosome.

Growth Hormone–Releasing Hormone Receptor

Recessive loss-of-function mutations in the receptor for GH-releasing hormone interfere with proliferation of somatotropes during pituitary development and disrupt the most important signals for release of GH. The anterior pituitary is small, in keeping with the observation that somatotropes normally account for >50% of pituitary volume. There is some compromise of fetal growth followed by severe compromise of postnatal growth.

GH1

The *GH1* gene is one of a cluster of 5 genes on chromosome 17q22-24. This cluster arose through successive duplications of an ancestral GH gene. Unequal crossing over at meiosis has produced a variety of gene deletions. Small deletions (<10 kb) remove only the *GH1* gene, whereas large deletions (45 kb) remove 1 or more of the adjacent genes *(CSL, CS1, GH2,* and *CS2).* The growth phenotype is identical with deletion of *GH1* alone or *GH1* together with 1 or more of the adjacent genes. Loss of the *CS1, GH2,* and *CS2* genes without loss of *GH1* causes deficiency of chorionic somatomammotropin and placental GH in the maternal circulation, but it does not result in fetal or postnatal growth retardation. Most children with *GH1* gene deletions respond very well to recombinant GH treatment, but some develop antibodies to GH and cease growing.

Recessively transmitted mutations in the *GH1* gene produce a similar phenotype. Missense, nonsense, and frameshift mutations have been described. Autosomal dominant IGHD is also caused by mutations in *GH1.* The mutations usually involve splice-site errors in intron 3 and result in a variant protein that lacks the amino acids normally encoded by exon 3. Accumulation of this protein interferes with the processing, storage, and secretion of the normal GH protein and may result in additional deficiencies of TSH and/or ACTH. There are several reports of mutations in *GH1* that lead to variant proteins with reduced biological activity.

X-Linked Isolated Growth Hormone Deficiency

Two loci on the X chromosome have been associated with hypopituitarism. The first lies at Xq21.3-q22 in the region of the Bruton thymidine kinase *(BTK)* gene. Mutations in this region produce hypogammaglobulinemia as well as IGHD. The second locus maps farther out on the long arm, at Xq24-q27.1, a region containing the *SOX2* transcription factor gene. Abnormalities in this locus have been linked to IGHD with intellectual disability as well as to MPHD with the triad of pituitary hypoplasia, missing pituitary stalk, and ectopic posterior pituitary gland.

Acquired Forms

The GH axis is more susceptible to disruption by acquired conditions than are other hypothalamic-pituitary axes. Recognized causes of acquired GH deficiency include the use of radiotherapy for malignancy, meningitis, histiocytosis, and trauma.

Children who receive radiotherapy for central nervous system tumors or prevention of central nervous system malignancies (e.g., leukemia) are at risk for developing GH deficiency. Spinal irradiation contributes to disproportionately poor growth of the trunk. Growth typically slows during radiation therapy (see Chapter 718) or chemotherapy (see Chapter 494), improves for 1-2 yr, and then declines with the development of GH deficiency. The dose and frequency of radiotherapy are important determinants of hypopituitarism. GH deficiency is almost universal 5 yr after therapy with a total dose ≥35 Gy. More subtle defects are seen with doses around 20 Gy. Deficiency of GH is the most common defect, but deficiencies of TSH and ACTH can also occur. In contrast to other forms of hypopituitarism, puberty tends to be early rather than delayed (see Chapter 562.3). The clinician is likely to encounter children in the 8-10 yr age range who are growing at rates that are normal for chronological age but subnormal for stage of pubertal development.

GROWTH HORMONE INSENSITIVITY

Abnormalities of the Growth Hormone Receptor

GH insensitivity is caused by disruption of pathways distal to production of GH. Laron syndrome involves mutations of the GH receptor. Children with this condition clinically resemble those with severe IGHD. Birth length tends to be about 1 SD below the mean, and severe short stature with lengths >4 SD below the mean is present by 1 yr of age. Resting and stimulated GH levels tend to be high and insulin-like growth factor (IGF) 1 levels are low. The GH receptor has an extracellular GH-binding domain, a transmembrane domain, and an intracellular signaling domain. Mutations in the extracellular domain interfere with binding of GH. Serum GH-binding protein activity, representing the circulating form of the membrane receptor for GH, is generally low. Mutations in the transmembrane domain can interfere with anchoring of the receptor to the plasma membrane. In these cases, circulating GH-binding protein activity is normal or high. Mutations in the intracellular domain interfere with JAK/STAT signaling.

Postreceptor Forms of Growth Hormone Insensitivity

Some children with severe growth failure, high GH and low IGF-1 levels, and normal GH-binding protein levels have abnormalities distal to the GH binding and activation of the GH receptor. Several have been found to have mutations in the gene encoding signal transducer and activator of transcription 5b (STAT5b). Disruption of this key intermediate connecting receptor activation to gene transcription produces growth failure similar to that seen in Laron syndrome. These patients also suffer from chronic pulmonary infections, consistent with important roles for STAT5b in interleukin cytokine signaling.

IGF-1 Gene Abnormalities

Abnormalities of the *IGF-1* gene produce severe prenatal and postnatal growth impairment. Microcephaly, intellectual disability, and deafness are present in patients with exon deletion and a missense mutation. These patients can be expected to respond to recombinant IGF-1 treatment.

Insulin-Like Growth Factor–Binding Protein Abnormalities

Mutation of the gene encoding the acid labile subunit of the circulating 165-kDa IGF-1, IGF-BP3, acid labile subunit complex has been associated with short stature. Total IGF-1 levels were very low. The index case, with homozygosity for an acid labile subunit mutation, did not show an increase in IGF-1 levels or an increase in growth rate during GH treatment.

IGF-1 Receptor Gene Abnormalities

Mutations of the IGF-1 receptor also compromise prenatal and postnatal growth. The phenotype does not appear to be as severe as that seen with absence of IGF-1. Adult heights are closer to the normal range, and affected patients do not have intellectual disability or deafness.

CLINICAL MANIFESTATIONS

Congenital Hypopituitarism

The child with hypopituitarism is usually of normal size and weight at birth, although those with MPHD and genetic defects of the *GH1* or *GHR* gene have birth lengths that average 1 SD below the mean. Children with severe defects in GH production or action typically fall more than 4 SD below the mean for length by 1 yr of age. Those with less-severe deficiencies grow at rates below the 25th percentile for age and gradually diverge from normal height percentiles. Delayed closure of the epiphyses permits growth beyond the normal age when growth should be complete. Features of GH insensitivity are noted in Table 557-6.

Infants with congenital defects of the pituitary or hypothalamus may present with neonatal emergencies such as apnea, cyanosis, or severe hypoglycemia with or without seizures. Prolonged neonatal jaundice is common. It involves elevation of conjugated and unconjugated bilirubin and may be mistaken for neonatal hepatitis. Nystagmus can suggest septooptic dysplasia (see Chapter 591). Micropenis in boys provides an additional diagnostic clue. Deficiency of GH may be accompanied by hypoadrenalism (see Chapter 575) and hypothyroidism (see Chapter 565) as well as gonadotropin deficiency (see Chapters 583.2 and 586.2).

On physical examination, the head is round and the face is short and broad. The frontal bone is prominent, and the bridge of the nose is depressed and saddle shaped. The nose is small, and the nasolabial folds are well developed. The eyes are somewhat bulging. The mandible and the chin are underdeveloped, and the teeth, which erupt late, are often crowded. The neck is short and the larynx is small. The voice is high-pitched and remains high after puberty. The extremities are well proportioned, with small hands and feet. Weight for height is usually

Table 557-6	Clinical Features of Growth Hormone Insensitivity
Growth and development	
Birthweight: near-normal	
Birth length: may be slightly decreased	
Postnatal growth: severe growth failure	
Bone age: delayed, but may be advanced relative to height age	
Genitalia: micropenis in childhood; normal for body size in adults	
Puberty: delayed 3-7 yr	
Sexual function and fertility: normal	
Craniofacies	
Hair: sparse before the age of 7 yr	
Forehead: prominent; frontal bossing	
Skull: normal head circumference; craniofacial disproportion due to small facies	
Facies: small	
Nasal bridge: hypoplastic	
Orbits: shallow	
Dentition: delayed eruption	
Sclerae: blue	
Voice: high pitched	
Musculoskeletal/metabolic/miscellaneous	
Hypoglycemia: in infants and children; fasting symptoms in some adults	
Walking and motor milestones: delayed	
Hips: dysplasia; avascular necrosis of femoral head	
Elbow: limited extensibility	
Skin: thin, prematurely aged	
Osteopenia	

From Sperling MA: Pediatric endocrinology, *ed 4, Philadelphia, 2014, Elsevier, Table 10-5, p. 355.*

normal, but an excess of body fat and a deficiency of muscle mass contribute to a pudgy appearance. The genitals are usually small for age, and sexual maturation may be delayed or absent. Facial, axillary, and pubic hair usually is lacking, and the scalp hair is fine. Intelligence is usually normal for age and the children may seem precocious compared to children of a similar size.

Acquired Hypopituitarism

The child is normal initially, and manifestations similar to those seen in idiopathic pituitary growth failure gradually appear and progress. When complete or almost complete destruction of the pituitary gland occurs, signs of pituitary insufficiency are present. Atrophy of the adrenal cortex, thyroid, and gonads results in loss of weight, asthenia, sensitivity to cold, mental torpor, and absence of sweating. Sexual maturation fails to take place or regresses if already present. There may be atrophy of the gonads and genital tract with amenorrhea and loss of pubic and axillary hair. There is a tendency to hypoglycemia. Growth slows dramatically. Diabetes insipidus (see Chapter 558) may be present but tends to improve spontaneously with development of central adrenal insufficiency.

If the lesion is an expanding tumor, symptoms such as headache, vomiting, visual disturbances, pathologic sleep patterns, decreased school performance, seizures, polyuria, and growth failure can occur (see Chapter 497). Slowing of growth can antedate neurologic signs and symptoms, especially with craniopharyngiomas. Evidence of pituitary insufficiency may first appear after surgical intervention. In children with craniopharyngiomas, visual field defects, optic atrophy, papilledema, and cranial nerve palsy are common.

LABORATORY FINDINGS

GH deficiency should be suspected in children with severe postnatal growth failure (Table 557-7). Criteria for growth failure include height below the 1st percentile for age and sex or height >2 SD below sex-adjusted mid-parent height. Acquired GH deficiency can occur at any age, and when it is of acute onset, height may be within the normal range. A strong clinical suspicion is important in establishing the diagnosis because laboratory measures of GH sufficiency lack specificity. Observation of low serum levels of IGF-1 and the GH-dependent IGF-BP3 can be helpful, but IGF-1 and IGF-BP3 levels should be matched to normal values for skeletal age rather than chronological age. Values in the upper part of the normal range for age effectively exclude GH deficiency. IGF-1 values in normally growing children and those with hypopituitarism overlap during infancy and early childhood.

Definitive diagnosis of GH deficiency traditionally requires demonstration of absent or low levels of GH in response to stimulation. A variety of provocative tests have been devised that rapidly increase the level of GH in normal children. These include administration of insulin, arginine, clonidine, or glucagon. In chronic GH deficiency, the demonstration of subnormal linear growth, a delayed skeletal age, and low peak levels of GH (<10 ng/mL) in each of 2 provocative tests are compatible with GH deficiency. In acute GH deficiency, a high clinical suspicion of GH deficiency and low peak levels of GH (<10 ng/mL) in each of 2 provocative tests are compatible with GH deficiency. This rather arbitrary cutoff point is higher than the 3 or 5 ng/mL criteria used for diagnosis of adult GH deficiency. There is no consensus regarding adoption of criteria that take into account age, sex, and GH assay characteristics. Some studies indicate that a majority of normal prepubertal children fail to achieve GH values >10 ng/mL with 2 pharmacologic tests. The researchers suggest that 3 days of estrogen priming should be used before GH testing to achieve greater diagnostic specificity.

In addition to establishing the diagnosis of GH deficiency, it is necessary to examine other pituitary functions. Levels of TSH, free thyroxine, ACTH, cortisol, gonadotropins, and gonadal steroids might provide evidence of other pituitary hormonal deficiencies. Antidiuretic hormone deficiency may be established by appropriate studies.

Table 557-7 Evaluation of Suspected Growth Hormone Deficiency

Growth-related history and patient physical exam	• Infants and children with GHD have growth failure • Short stature and growth failure may be the only clinical features present • GHD affects ~1 in 3,500 children
Imaging and other evaluations	• Diagnosis is based on clinical, auxologic, and biochemical parameters • Radiologic evaluation of bone age • Central nervous system MRI or CT scan to evaluate the hypothalamic-pituitary region and to exclude other conditions • Evaluation and management by a pediatric endocrinologist
Laboratory evaluation	• Measurements of GH, IGF-1, and IGF-1–binding protein levels • Determination of peak GH levels after stimulation test
Special testing (if applicable)	• Family history and genetic analyses (e.g., search for *PROP1* and *POU1F1* mutations)
Rationale for treatment and treatment modalities	• Replacement therapy with rhGH (GHT) • Predictors of greater benefit with GHT in GHD include early initiation of treatment, higher rhGH dose, and IGF-1–guided dosing • GHT should be started as soon as GHD is diagnosed

GH, growth hormone; GHD, growth hormone deficiency; GHT, growth hormone therapy; IGF, insulin-like growth factor; *POU1F1,* POU class 1 homeobox 1; *PROP1,* homeobox protein prophet of Pit1; rhGH, human recombinant growth hormone.

From Rogol AD, Hayden GF: Etiologies and early diagnosis of short stature and growth failure in children and adolescents. J Pediatr *164(5):S1–S14, 2014, Table XIII, p. S10.*

RADIOLOGIC FINDINGS

Conventional x-ray films of the skull have been replaced by CT and MRI. CT is appropriate for recognizing suprasellar calcification associated with craniopharyngiomas and bony changes accompanying histiocytosis. MRI provides a much more detailed view of hypothalamic and pituitary anatomy. Many cases of severe early-onset MPHD show the triad of a small anterior pituitary gland, a missing or attenuated pituitary stalk, and an ectopic posterior pituitary bright spot at the base of the hypothalamus. Subnormal anterior pituitary height, implying a small anterior pituitary, is common in genetic and idiopathic causes of IGHD. Craniopharyngiomas are common and pituitary adenomas are rare in children with hypopituitarism. Both hypoplastic and markedly enlarged anterior pituitary glands are seen in patients with *PROP1* or *LHX3* mutations.

Skeletal maturation is delayed in patients with IGHD and may be even more delayed when there is combined GH and TSH deficiency. Dual-photon x-ray absorptiometry shows deficient bone mineralization, deficiencies in lean body mass, and a corresponding increase in adiposity.

DIFFERENTIAL DIAGNOSIS

The causes of growth disorders are legion. Systemic conditions, such as inflammatory bowel disease, celiac disease, occult renal disease, and anemia, must be considered. Patients with systemic conditions often have greater loss of weight than length. A few otherwise normal children are short (i.e., >3 SD below the mean for age) and grow 5 cm/yr or less but have normal levels of GH in response to provocative tests and normal spontaneous episodic secretion. Most of these children show increased rates of growth when treated with GH in doses comparable to those used to treat children with hypopituitarism. Plasma levels of IGF-1 in these patients may be normal or low. Several groups of treated children have achieved final or near-final adult heights. Different studies have found changes in adult height that range from −2.5 to +7.5 cm compared with pretreatment predictions. There are no methods that can reliably predict which of these children will become

taller in adulthood as a result of GH treatment and which will have compromised adult height.

Diagnostic strategies for distinguishing between permanent GH deficiency and other causes of impaired growth are imperfect. Children with a combination of genetic short stature and constitutional delay of growth have short stature, below-average growth rates, and delayed bone ages. Many of these children exhibit minimal GH secretory responses to provocative stimuli. When children in whom idiopathic or acquired GH deficiency is diagnosed are treated with human GH (hGH) and retested as adults, the majority have peak GH levels within the normal range.

Constitutional Growth Delay

Constitutional growth delay is one of the variants of normal growth commonly encountered by the pediatrician. Length and weight measurements of affected children are normal at birth, and growth is normal for the 1st 4-12 mo of life. Height is sustained at a lower percentile during childhood. The pubertal growth spurt is delayed, so their growth rates continue to decline after their classmates have begun to accelerate. Detailed questioning often reveals other family members (often 1 or both parents) with histories of short stature in childhood, delayed puberty, and eventual normal stature. IGF-1 levels tend to be low for chronological age but within the normal range for bone age. GH responses to provocative testing tend to be lower than in children with a more typical timing of puberty. The prognosis for these children to achieve normal adult height is guarded. Predictions based on height and bone age tend to overestimate eventual height to a greater extent in boys than in girls. Boys with >2 yr of pubertal delay can benefit from a short course of testosterone therapy to hasten puberty after 14 yr of age. The cause of this variant of normal growth is thought to be persistence of the relatively hypogonadotropic state of childhood (see Chapter 15).

Primary Hypothyroidism

Primary hypothyroidism (see Chapter 565) is more common than GH deficiency. Low total or free thyroxine and elevated TSH levels establish the diagnosis. Responses to GH provocative tests may be subnormal and the sella may be enlarged. Pituitary hyperplasia recedes during treatment with thyroid hormone. Because thyroid hormone is a necessary prerequisite for normal GH synthesis, it must always be assessed before GH evaluation.

Psychosocial Causes

Emotional deprivation is an important cause of retardation of growth and mimics hypopituitarism. The condition is known as *psychosocial dwarfism, maternal deprivation dwarfism*, or *hyperphagic short stature*. The mechanisms by which sensory and emotional deprivation interfere with growth are not fully understood. Functional hypopituitarism is indicated by low levels of IGF-1 and by inadequate responses of GH to provocative stimuli. Puberty may be normal or even premature. Appropriate history and careful observations reveal disturbed mother–child or family relations and provide clues to the diagnosis (see Chapter 40). Proof may be difficult to establish because the parents or caregivers often hide the true family situation from professionals, and the children rarely divulge their plight. Emotionally deprived children often have perverted or voracious appetites, enuresis, encopresis, insomnia, crying spasms, and sudden tantrums. The subgroup of children with hyperphagia and a normal body mass index tends to show catch-up growth when placed in a less stressful environment.

TREATMENT

Recombinant hGH has been available by prescription since 1982. There are currently 8 brands marketed in the United States. They are therapeutically equivalent, with the major differences consisting of proprietary devices for subcutaneous injection and availability of solubilized liquid forms or powders needing reconstitution before injection. At present none of the products are available in long-acting repository forms.

The FDA has approved 8 indications for GH treatment to promote growth. They are GH deficiency, Turner syndrome, chronic renal failure before transplantation, idiopathic short stature, small-for-gestational age short stature, Prader-Willi syndrome, *SHOX* gene abnormality, and Noonan syndrome. FDA approval for a given indication does not ensure that a patient's third-party insurance carrier will approve payment for the drug. The Pediatric Endocrine Society, the Academy of Pediatrics, and the GH Research Society have published guidelines for hGH treatment of children with classic GH deficiency. Treatment should be started as soon as possible to narrow the gap in height between patients and their classmates during childhood and to have the greatest effect on mature height. The recommended dose of hGH is 0.18-0.3 mg/kg/wk during childhood. Higher doses have been used during puberty. Recombinant GH is administered subcutaneously in 6 or 7 divided doses. Maximal response to GH occurs in the 1st yr of treatment. Growth velocity during this 1st yr is typically above the 95th percentile for age. With each successive yr of treatment, the growth rate tends to decrease. If growth rate drops below the 25th percentile, compliance should be evaluated before the dose is increased.

Concurrent treatment with GH and a gonadotropin-releasing hormone agonist has been used in the hope that interruption of puberty will delay epiphyseal fusion and prolong growth. This strategy can increase adult height. It can also increase the discrepancy in physical maturity between GH-deficient children and their age peers and can impair bone mineralization. There have also been attempts to forestall epiphyseal fusion in boys by giving drugs that inhibit aromatase, the enzyme responsible for converting androgens to estrogens. Therapy should be continued until near-final height is achieved. Criteria for stopping GH treatment include a decision by the patient that he or she is tall enough, a growth rate <1 inch/yr, and a bone age >14 yr in girls and >16 yr in boys.

Some patients develop either primary or central hypothyroidism while under treatment with GH. Similarly, there is a risk of developing adrenal insufficiency. If unrecognized, this can be fatal. Periodic evaluation of thyroid and adrenal function is indicated for all patients treated with GH.

Recombinant IGF-1 is approved for use in the United States. It is given subcutaneously twice a day. The risk of hypoglycemia is reduced by giving the injections concurrently with a meal or snack. In some situations its use is more efficacious than use of GH. These conditions include abnormalities of the GH receptor and *STAT5b* genes, as well as severe GH deficiency in patients who have developed antibodies to administered GH. Its utility in improving growth rate and adult stature in broader categories of short children is being explored.

The doses of GH used to treat children with classic GH deficiency usually enhance the growth of many non–GH-deficient children as well. Intensive investigation is in progress to determine the full spectrum of short children who may benefit from treatment with GH. The FDA approval for use of GH in idiopathic short stature specifies a height below the 1.2 percentile (–2.25 SD) for age and sex, a predicted height below the 5th percentile, and open epiphyses. Studies of the effect of GH treatment on adult height suggest a median gain of 2-3 inches, depending on dose and duration of treatment.

In children with MPHD, replacement should also be directed at other hormonal deficiencies. In TSH-deficient patients, thyroid hormone is given in full replacement doses. In ACTH-deficient patients, the optimal dose of hydrocortisone should not exceed 10 mg/m^2/24 hr. Increases of 2-3–fold are made to provide stress coverage during illness or in anticipation of surgical procedures. In patients with a deficiency of gonadotropins, gonadal steroids are given when bone age reaches the age at which puberty usually takes place. For infants with micropenis, 1 or 2 three-month courses of monthly intramuscular injections of 25 mg of testosterone cypionate or testosterone enanthate can bring the penis to normal size without an inordinate effect on osseous maturation.

COMPLICATIONS AND ADVERSE EFFECTS OF GH TREATMENT

GH treatment influences glucose homeostasis. Fasting and postprandial insulin levels are characteristically low before treatment, and they normalize during GH replacement. Recent studies indicate that GH

treatment is associated with a 6-fold increase in the risk for type 2 diabetes and no significant increase in the risk for type 1 diabetes.

Concerns have been raised about the safety of GH treatment in children who become deficient after treatment of brain tumors, leukemia, and other neoplasms. Long-term studies show no increase in risk of recurrence of craniopharyngioma, other brain tumors, or leukemia. At least 3 studies indicate an increased risk of second neoplasms in cancer survivors treated with GH. An unconfirmed study documents a 30% increase in mortality among young adults who received GH in childhood. There appears to be a correlation between risk of mortality and GH doses >0.35 mg/kg/wk.

Other reported side effects include pseudotumor cerebri, slipped capital femoral epiphysis, gynecomastia, and worsening of scoliosis, and in adults treated as a child there is an increased risk of hemorrhagic stroke. The risk of later development of Creutzfeldt-Jakob disease was limited to recipients of contaminated lots of extracted pituitary GH. No comparable risks have been seen with recombinant hGH.

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Chapter 558

Diabetes Insipidus

David T. Breault and Joseph A. Majzoub

Diabetes insipidus (DI) manifests clinically with polyuria and polydipsia and can result from either vasopressin deficiency (central DI) or vasopressin insensitivity at the level of the kidney (nephrogenic DI). Both central DI and nephrogenic DI can arise from inherited defects of congenital or neonatal onset or can be secondary to a variety of causes (Table 558-1).

PHYSIOLOGY OF WATER BALANCE

The control of extracellular tonicity (osmolality) and volume within a narrow range is critical for normal cellular structure and function (see Chapter 55.2). Extracellular fluid tonicity is regulated almost exclusively by water intake and excretion, whereas extracellular volume is regulated by sodium intake and excretion. The control of plasma tonicity and intravascular volume involves a complex integration of endocrine, neural, behavioral, and paracrine systems (Fig. 558-1). Vasopressin, secreted from the posterior pituitary, is the principal regulator of tonicity, with its release largely stimulated by increases in plasma tonicity. Volume homeostasis is largely regulated by the renin–angiotensin–aldosterone system, with contributions from both vasopressin and the natriuretic peptide family.

Vasopressin, a 9-amino-acid peptide, has both antidiuretic and vascular pressor activity and is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus. It is transported to the posterior pituitary via axonal projections, where it is stored awaiting release into the systemic circulation. The half-life of vasopressin in the circulation is 5 min. In addition to responding to osmotic stimuli, vasopressin is secreted in response to significant decreases in intravascular volume and pressure (minimum of 8% decrement) via afferent baroreceptor pathways arising from the aortic arch (carotid sinus) and volume receptor pathways in the cardiac atria and pulmonary veins. Osmotic and hemodynamic stimuli interact synergistically.

The sensation of thirst is regulated by cortical as well as hypothalamic neurons. The thirst threshold is approximately 10 mOsm/kg higher (i.e., 293 mOsm/kg) than the osmotic threshold for vasopressin release. Consequently, under conditions of hyperosmolality, vasopressin is released before thirst is initiated, allowing ingested water to be retained. Chemoreceptors present in the oropharynx rapidly downregulate vasopressin release following water ingestion.

Vasopressin exerts its principal effect on the kidney via V2 receptors located primarily in the collecting tubule, the thick ascending limb of the loop of Henle, and the periglomerular tubules. The human V2 receptor gene is located on the long arm of the X chromosome (Xq28) at the locus associated with **congenital, X-linked, vasopressin-resistant DI.** Activation of the V2 receptor results in increases in intracellular cyclic adenosine monophosphate, which leads to the insertion of the aquaporin-2 water channel into the apical (luminal) membrane. This allows water movement along its osmotic gradient into the hypertonic inner medullary interstitium from the tubule lumen and excretion of concentrated urine. In contrast to aquaporin-2,

Table 558-1	Differential Diagnosis of Polyuria and Polydipsia
Diabetes insipidus (DI)	
• Central DI	
Genetic (autosomal dominant)	
Acquired	
Trauma (surgical or accidental)	
Congenital malformations (holoprosencephaly, septooptic dysplasia, encephalocele)	
Neoplasms (craniopharyngioma, germinoma, metastasis)	
Infiltrative (Langerhans cell histiocytosis), autoimmune (lymphocytic infundibuloneurohypophysitis), and infectious diseases	
Drugs (chemotherapy)	
Idiopathic	
• Nephrogenic DI	
Genetic (X-linked, autosomal recessive, autosomal dominant)	
Acquired	
Hypercalcemia, hypokalemia	
Drugs (lithium, demeclocycline)	
Kidney disease	
Primary polydipsia	
Sickle cell anemia	
• Diabetes mellitus	

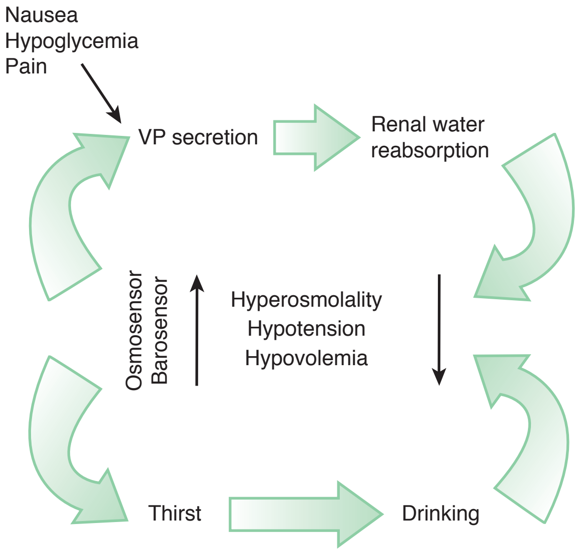

Figure 558-1 Regulation of vasopressin (VP) secretion and serum osmolality. Hyperosmolality, hypovolemia, and hypotension are sensed by osmosensors, volume sensors, and barosensors, respectively. These stimulate both VP secretion and thirst. VP, acting on the kidney, causes increased reabsorption of water (antidiuresis). Thirst causes increased water ingestion. The results of these dual negative feedback loops cause a reduction in hyperosmolality or in hypotension or hypovolemia. Additional stimuli for VP secretion include nausea, hypoglycemia, and pain. *(From Muglia LJ, Majzoub JA: Disorders of the posterior pituitary. In Sperling MA, editor:* Pediatric endocrinology, *ed 4, Philadelphia, 2014, Elsevier, Fig. 6.)*

aquaporin-3 and aquaporin-4 are expressed on the basolateral membrane of the collecting duct cells and aquaporin-1 is expressed in the proximal tubule. These channels may also contribute to urinary concentrating ability.

Atrial natriuretic peptide, initially isolated from cardiac atrial muscle, has a number of important effects on salt and water balance, including stimulation of natriuresis, inhibition of sodium resorption, and inhibition of vasopressin secretion. Atrial natriuretic peptide is expressed in endothelial cells and vascular smooth muscle, where it appears to regulate relaxation of arterial smooth muscle. Atrial natriuretic peptide is also expressed in the brain, along with other natriuretic family members; the physiologic role of these factors has yet to be defined.

APPROACH TO THE PATIENT WITH POLYURIA, POLYDIPSIA, AND HYPERNATREMIA

The cause of pathologic polyuria or polydipsia (exceeding 2 L/m^2/24 hr) may be difficult to establish in children. Infants can present with irritability, failure to thrive, and intermittent fever. Patients with suspected DI should have a careful history taken, which should quantify the child's daily fluid intake and output and establish the voiding pattern, nocturia, and primary or secondary enuresis. A complete physical examination should establish the patient's hydration status, and the physician should search for evidence of visual and central nervous system dysfunction, as well as for other pituitary hormone deficiencies.

If pathologic polyuria or polydipsia is present, the following should be obtained: serum for osmolality, sodium, potassium, blood urea nitrogen, creatinine, glucose, and calcium; urine for osmolality, specific gravity, and glucose determination. The diagnosis of DI is established if the serum osmolality is >300 mOsm/kg and the urine osmolality is <300 mOsm/kg. DI is unlikely if the serum osmolality is <270 mOsm/kg or the urine osmolality is >600 mOsm/kg. If the patient's serum osmolality is <300 mOsm/kg (but >270 mOsm/kg) and pathologic polyuria and polydipsia are present, a water deprivation test is indicated to establish the diagnosis of DI and to differentiate central from nephrogenic causes.

In the inpatient postneurosurgical setting, central DI is likely if hyperosmolality (serum osmolality >300 mOsm/kg) is associated with urine osmolality less than serum osmolality. It is important to distinguish between polyuria resulting from postsurgical central DI and polyuria resulting from the normal diuresis of fluids received intraoperatively. Both cases may be associated with a large volume (>200 mL/m^2/hr) of dilute urine, although in patients with DI, the serum osmolality is high in comparison with patients undergoing postoperative diuresis.

CAUSES OF HYPERNATREMIA

Hypernatremia is discussed in Chapter 55.3.

Central Diabetes Insipidus

Central DI can result from multiple etiologies, including genetic mutations in the vasopressin gene; trauma (accidental or surgical) to vasopressin neurons; congenital malformations of the hypothalamus or pituitary; neoplasms; infiltrative, autoimmune, and infectious diseases affecting vasopressin neurons or fiber tracts; and increased metabolism of vasopressin. In approximately 10% of children with central DI, the etiology is idiopathic. Other pituitary hormone deficiencies may be present (see Chapter 557). Over time, up to 35% of those with idiopathic central DI will develop other hormone deficiencies or have an underlying etiology identified.

Autosomal dominant central DI usually occurs within the 1st 5 yr of life and results from mutations in the vasopressin gene. A number of mutations can cause gene-processing defects in a subset of vasopressin-expressing neurons, which have been postulated to result in endoplasmic reticulum stress and cell death. **Wolfram syndrome,** which includes DI, diabetes mellitus, optic atrophy, and deafness, also results in vasopressin deficiency. Mutations in 2 genes, which give rise to endoplasmic reticulum proteins, are associated with this condition. Congenital brain abnormalities (see Chapter 591) such as **optic nerve hypoplasia syndrome** with agenesis of the corpus callosum, the Niikawa-Kuroki syndrome, holoprosencephaly, and familial pituitary hypoplasia with absent stalk may be associated with central DI and defects in thirst perception. Empty sella syndrome, possibly resulting from unrecognized pituitary infarction (see Chapter 557), can be associated with DI in children.

Trauma to the base of the brain and neurosurgical intervention in the region of the hypothalamus or pituitary are common causes of central DI. The **triphasic response** following surgery refers to an initial phase of transient DI, lasting 12-48 hr, followed by a 2nd phase of syndrome of inappropriate antidiuretic hormone secretion, lasting up to 10 days, which may be followed by permanent DI. The initial phase may be the result of local edema interfering with normal vasopressin secretion; the 2nd phase results from unregulated vasopressin release from dying neurons, whereas in the 3rd phase, permanent DI results if more than 90% of the neurons have been destroyed.

Given the anatomic distribution of vasopressin neurons over a large area within the hypothalamus, tumors that cause DI must either be very large and infiltrative or be strategically located near the base of the hypothalamus, where vasopressin axons converge before their entry into the posterior pituitary. Germinomas and pinealomas typically arise in this region and are among the most common primary brain tumors associated with DI. Germinomas can be very small and undetectable by MRI for several years following the onset of polyuria. Quantitative measurement of α-fetoprotein and β-human chorionic gonadotropin, often secreted by germinomas, should be performed in children with idiopathic or unexplained DI in addition to serial MRI scans. Craniopharyngiomas and optic gliomas can also cause central DI when they are very large, although this is more often a postoperative complication of the treatment for these tumors (see Chapter 497). Hematologic malignancies, such as acute myelocytic leukemia, can cause DI via infiltration of the pituitary stalk and sella.

Langerhans cell histiocytosis (see Chapter 507) and lymphocytic hypophysitis are common types of infiltrative disorders causing central DI, with **hypophysitis** as the cause in 50% of cases of "idiopathic" central DI. Infections involving the base of the brain (see Chapter 603), including meningitis (meningococcal, cryptococcal, listerial, toxoplasmal), congenital cytomegalovirus infection, and nonspecific inflammatory diseases of the brain may give rise to central DI that is often transient. Drugs associated with the inhibition of vasopressin release include ethanol, phenytoin, opiate antagonists, halothane, and α-adrenergic agents.

Nephrogenic Diabetes Insipidus

Nephrogenic (vasopressin-insensitive) DI (NDI) can result from genetic or acquired causes. Genetic causes are less common but more severe than acquired forms of NDI. The polyuria and polydipsia associated with genetic NDI usually occur within the 1st several wk of life, but may only become apparent after weaning or with longer periods of nighttime sleep. Many infants initially present with fever, vomiting, and dehydration. Failure to thrive may be secondary to the ingestion of large amounts of water, resulting in caloric malnutrition. Long-standing ingestion and excretion of large volumes of water can lead to nonobstructive hydronephrosis, hydroureter, and megabladder.

Congenital X-linked NDI results from inactivating mutations of the vasopressin V2 receptor. **Congenital autosomal recessive NDI** results from defects in the aquaporin-2 gene. An **autosomal dominant form of NDI** is associated with processing mutations of the aquaporin-2 gene.

Acquired NDI can result from hypercalcemia or hypokalemia and is associated with lithium, demeclocycline, foscarnet, clozapine, amphotericin, methicillin, and rifampin. Impaired renal concentrating ability can also be seen with ureteral obstruction, chronic renal failure, polycystic kidney disease, medullary cystic disease, Sjögren syndrome, and sickle cell disease. Decreased protein or sodium intake or excessive water intake, as in primary polydipsia, can lead to diminished tonicity of the renal medullary interstitium and NDI.

TREATMENT OF CENTRAL DIABETES INSIPIDUS

Fluid Therapy

With an intact thirst mechanism and free access to oral fluids, a person with complete DI can maintain plasma osmolality and sodium in the high normal range, although at great inconvenience. Neonates and young infants are often best treated solely with fluid therapy, given their requirement for large volumes (3 L/m^2/24 hr) of nutritive fluid. The use of vasopressin analogs in patients with obligate high fluid intake is difficult given the risk of life-threatening hyponatremia. Although not FDA approved, the use of diluted parenteral and lyophilized long-acting vasopressin analog DDAVP (desmopressin) has been successfully administered to infants with central DI both subcutaneously and orally without causing severe hyponatremia.

Vasopressin Analogs

Treatment of central DI in older children is best accomplished with the use of DDAVP. DDAVP is available in an intranasal preparation (onset 5-10 min) and as tablets (onset 15-30 min). The intranasal preparation of DDAVP (10 µg/0.1 mL) can be administered by rhinal tube (allowing dose titration) or by nasal spray. Use of DDAVP oral tablets requires at least a 10-fold increase in the dosage compared with the intranasal preparation. Oral dosages of 25-300 µg every 8-12 hr are safe and effective in children. The appropriate dosage and route of administration is determined empirically based on the desired length of antidiuresis and patient preference. The use of DDAVP nasal spray (10 µg/0.1 mL) for the treatment of primary enuresis in older children should be regarded as a temporizing measure, given it does not affect the underlying condition, and should be used with great caution given the risk of hyponatremia if water intake exceeds the capacity for renal clearance. To prevent water intoxication, patients should have at least 1 hr of urinary breakthrough between doses each day and be advised to drink in response to thirst sensation.

Aqueous Vasopressin

Central DI of acute onset following neurosurgery is best managed with continuous administration of synthetic aqueous vasopressin (Pitressin). Under most circumstances, total fluid intake must be limited to 1 L/m^2/24 hr during antidiuresis. A typical dosage for intravenous vasopressin therapy is 1.5 mU/kg/hr, which results in a blood vasopressin concentration of approximately 10 pg/mL. On occasion, following hypothalamic (but not transsphenoidal) surgery, higher initial concentrations of vasopressin may be required to treat acute DI, which has been attributed to the release of a vasopressin inhibitory substance. Vasopressin concentrations >1,000 pg/mL should be avoided because they can cause cutaneous necrosis, rhabdomyolysis, cardiac rhythm disturbances, and hypertension. Postneurosurgical patients treated with vasopressin infusion should be switched from intravenous to oral fluids as soon as possible to allow thirst sensation, if intact, to help regulate osmolality.

TREATMENT OF NEPHROGENIC DIABETES INSIPIDUS

The treatment of acquired NDI focuses on eliminating, if possible, the underlying disorder, such as offending drugs, hypercalcemia, hypokalemia, or ureteral obstruction. Congenital nephrogenic DI is often difficult to treat. The main goals are to ensure the intake of adequate calories for growth and to avoid severe dehydration. Foods with the highest ratio of caloric content to osmotic load (Na <1 mmol/kg/24 hr) should be ingested to maximize growth and to minimize the urine volume required to excrete the solute load. Even with the early institution of therapy, however, growth failure and developmental disabilities are common.

Pharmacologic approaches to the treatment of NDI include the use of thiazide diuretics and are intended to decrease the overall urine output. Thiazides appear to induce a state of mild volume depletion by enhancing sodium excretion at the expense of water and by causing a decrease in the glomerular filtration rate, which results in proximal tubular sodium and water reabsorption. Indomethacin and amiloride may be used in combination with thiazides to further reduce polyuria. High-dose DDAVP therapy, in combination with indomethacin, has been used in some subjects with NDI. This treatment could prove useful in patients with genetic defects in the V2 receptor associated with a reduced binding affinity for vasopressin.

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Chapter 559

Other Abnormalities of Arginine Vasopressin Metabolism and Action

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Hyponatremia (serum sodium <130 mEq/L) in children is usually associated with severe systemic disorders and is most often a result of intravascular volume depletion, excessive salt loss, or hypotonic fluid overload, especially in infants (see Chapter 55).

The initial approach to the patient with hyponatremia begins with determination of the volume status. A careful review of the patient's history, physical examination (including changes in weight), and vital signs helps determine whether the patient is hypovolemic or hypervolemic. Supportive evidence includes laboratory data such as serum electrolytes, blood urea nitrogen, creatinine, uric acid, urine sodium, specific gravity, and osmolality (see Chapter 55; Tables 559-1 and 559-2).

Table 559-1 Differential Diagnosis of Hyponatremia

DISORDER	INTRAVASCULAR VOLUME STATUS	URINE SODIUM
Systemic dehydration	Low	Low
Decreased effective plasma volume	Low	Low
Primary salt loss (nonrenal)	Low	Low
Primary salt loss (renal)	Low	High
SIADH	High	High
Cerebral salt wasting	Low	Very high
Decreased free water clearance	Normal or high	Normal or high
Primary polydipsia	Normal or high	Normal
Runner's hyponatremia	Low	Low
NSIAD	High	High
Pseudohyponatremia	Normal	Normal
Factitious hyponatremia	Normal	Normal

NSIAD, nephrogenic syndrome of inappropriate antidiuresis; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Table 559-2 Clinical Parameters to Distinguish Among SIADH, Cerebral Salt Wasting, and Central Diabetes Insipidus

CLINICAL PARAMETER	SIADH	CEREBRAL SALT WASTING	CENTRAL DI
Serum sodium	Low	Low	High
Urine output	Normal or low	High	High
Urine sodium	High	Very high	Low
Intravascular volume status	Normal or high	Low	Low
Vasopressin level	High	Low	Low

DI, diabetes insipidus; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

CAUSES OF HYPONATREMIA

Syndrome of Inappropriate Antidiuretic Hormone Secretion

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by hyponatremia, an inappropriately concentrated urine (>100 mOsm/kg), normal or slightly elevated plasma volume, normal-to-high urine sodium, and low serum uric acid. SIADH is uncommon in children, and most cases result from excessive administration of vasopressin in the treatment of central diabetes insipidus. It can also occur with encephalitis, brain tumors, head trauma, psychiatric disease, prolonged nausea, pneumonia, tuberculous meningitis, and AIDS and in the postictal phase following generalized seizures. SIADH is the cause of the hyponatremic second phase of the triphasic response seen after hypothalamic–pituitary surgery (see Chapter 558). It is found in up to 35% of patients 1 wk after surgery and can result from retrograde neuronal degeneration with cell death and vasopressin release. Common drugs that have been shown to increase vasopressin secretion or mimic vasopressin action, resulting in hyponatremia, include oxcarbazepine, carbamazepine, chlorpropamide, vinblastine, vincristine, and tricyclic antidepressants.

Nephrogenic Syndrome of Inappropriate Antidiuresis

Gain-of-function mutations in the V2 vasopressin receptor gene have been described in male infants presenting with an SIADH-like clinical picture with undetectable vasopressin levels. Activating mutations in the aquaporin-2 gene might also give rise to the same syndrome but have not yet been described.

Systemic Dehydration

The initial manifestation of systemic dehydration is often hypernatremia and hyperosmolality, which subsequently lead to the activation of vasopressin secretion and a decrease in water excretion. As dehydration progresses, hypovolemia and/or hypotension become a major stimulus for vasopressin release, further decreasing free water clearance. Excessive free water intake with ongoing salt loss can also produce hyponatremia. Urinary sodium excretion is low (usually <10 mEq/L) owing to a low glomerular filtration rate and concomitant activation of the renin–angiotensin–aldosterone system, unless primary renal disease or diuretic therapy is present.

Primary Salt Loss

Hyponatremia can result from the primary loss of sodium chloride as seen in specific disorders of the kidney (congenital polycystic kidney disease, acute interstitial nephritis, chronic renal failure), gastrointestinal tract (gastroenteritis), and sweat glands (cystic fibrosis). The hyponatremia is not solely caused by the salt loss, because the latter also causes hypovolemia, leading to an increase in vasopressin. Mineralocorticoid deficiency (hypoaldosteronism), pseudohypoaldosteronism (genetic or sometimes seen in children with urinary tract obstruction or infection), and diuretics can also result in loss of sodium chloride. Hypoaldosterone states are associated with salt wasting, hypovolemia, hyponatremia, hyperkalemia, and failure to thrive (Table 559-3).

Decreased Effective Plasma Volume

Hyponatremia can result from decreased effective plasma volume, as found in congestive heart failure, cirrhosis, nephrotic syndrome, positive pressure mechanical ventilation, severe burns, bronchopulmonary dysplasia in neonates, cystic fibrosis with obstruction, and severe asthma. The resulting decrease in cardiac output leads to reduced water and salt excretion, as with systemic dehydration, and an increase in vasopressin secretion. In patients with impaired cardiac output and elevated atrial volume (congestive heart failure, lung disease), atrial natriuretic peptide concentrations are elevated further, leading to hyponatremia by promoting natriuresis. However, owing to the marked elevation of aldosterone in these patients, their urine sodium remains low (<20 mEq/L) despite this. Unlike dehydrated patients, these patients also have excess total body sodium from activation of the renin–angiotensin–aldosterone system and can demonstrate peripheral edema as well.

Primary Polydipsia (Increased Water Ingestion)

In patients with normal renal function, the kidney can excrete dilute urine with an osmolality as low as 50 mOsm/kg. To excrete a daily solute load of 500 mOsm/m^2, the kidney must produce 10 L/m^2 of urine per day. Therefore, to avoid hyponatremia, the maximum amount of water a person with normal renal function can consume is 10 L/m^2. Neonates, however, cannot dilute their urine to this degree, putting them at risk for water intoxication if water intake exceeds 4 L/m^2/day (approximately 60 mL/hr in a newborn). Many infants develop transient but symptomatic hyponatremic seizures after being fed pure water without electrolytes rather than breast milk or formula.

Decreased Free Water Clearance

Hyponatremia as a consequence of decreased renal free water clearance, even in the absence of an increase in vasopressin secretion, can result from adrenal insufficiency or thyroid deficiency or can be related to a direct effect of drugs on the kidney. Both mineralocorticoids and glucocorticoids are required for normal free water clearance in a vasopressin-independent manner. In patients with unexplained hyponatremia, adrenal and thyroid insufficiency should be considered. In addition, patients with coexisting adrenal failure and diabetes insipidus might have no symptoms of the latter until glucocorticoid therapy unmasks the need for vasopressin replacement. Certain drugs can inhibit renal water excretion through direct effects on the nephron, thus causing hyponatremia; these drugs include high-dose cyclophosphamide, vinblastine, cisplatinum, carbamazepine, and oxcarbazepine.

Cerebral Salt Wasting

Cerebral salt wasting appears to be the result of hypersecretion of atrial natriuretic peptide and is seen primarily with central nervous system disorders including brain tumors, head trauma, hydrocephalus, neurosurgery, cerebrovascular accidents, and brain death. Hyponatremia is accompanied by elevated urinary sodium excretion (often >150 mEq/L), excessive urine output, hypovolemia, normal or high uric acid, suppressed vasopressin, and elevated atrial natriuretic

Table 559-3 Genetic Mutations Associated with Hypoaldosteronism/Pseudohypoaldosteronism (Type IV Renal Tubular Acidosis)

GENE CHROMOSOME OMIM	PATHOPHYSIOLOGY	MUTATION–CLINICAL MANIFESTATIONS–OMIM–INHERITANCE
PRIMARY HYPOALDOSTERONISM		
CYP21A2—cytochrome P450, subfamily XXIA, polypeptide 2 6p21.3 613815	P450c21—steroid 21-hydroxylase that converts 17 α-hydroxyprogesterone to 11-deoxycortisol and progesterone to 11-deoxycorticosterone in the adrenal zona fasciculata	Loss-of-function mutations decrease synthesis of cortisol and aldosterone, the latter resulting in the salt-losing form of classical congenital adrenal hyperplasia, AR–201910
CYP11B2—cytochrome P450, subfamily XIB, polypeptide 2 8q21 124080	P450c11B2—aldosterone synthase/corticosterone methyoxidase types I and II expressed only in the zona glomerulosa; hydroxylates deoxycorticosterone at carbon-11 and corticosterone at carbon-18 and oxidizes 18-hydroxycorticosterone to aldosterone	Loss-of-function mutations associated with severe salt loss and volume depletion but not with abnormalities of genital formation or glucocorticoid synthesis AR (CMOI 203400; CMOII 610600)
PSEUDOHYPOALDOSTERONISM TYPE I		
NR3C2—nuclear receptor subfamily 3, group C, member 2 (MR-mineralocorticoid receptor), 4q31.1 600983	Ligand-activated nuclear transcription factor that transmits aldosterone-mediated control of gene expression by binding to the mineralocorticoid response element in the promoter region of the target gene	Loss-of-function mutations lead to mineralocorticoid resistance and pseudohypoaldosteronism type I, AD–177735
SCNN1A—sodium channel, non–voltage-gated, α-subunit 12p13.31 600228	Inactivating mutation of α-subunit of the epithelial sodium channel	Pseudohypoaldosteronism type I, AR–264350
SCNN1B—sodium channel, non–voltage-gated, β-subunit 16p12.2 600760	Inactivating mutation of β-subunit of the epithelial sodium channel	Pseudohypoaldosteronism type I, AR–264350
SCNN1G—sodium channel, non–voltage-gated, γ-subunit 16p12.2 600761	Inactivating mutation of γ-subunit of the epithelial sodium channel	Pseudohypoaldosteronism type I, AR–264350
PSEUDOHYPOALDOSTERONISM TYPE II		
WNK4—protein kinase, lysine-deficient 4 17q21.31 601844	Multifunctional serine-threonine protein kinase whose substrate is SLC12A3, the thiazide-sensitive sodium/chloride cotransporter (NCCT)—OMIM 600968—that also regulates lysosomal degradation of NCCT and endocytosis of the KCNJ1 potassium channel	Pseudohypoaldosteronism type IIB, AD–614491
WNK1—protein kinase, lysine-deficient 1 12p13.33 605232	Serine-threonine protein kinase that inactivates WNK4 by phosphorylating its kinase domain	Pseudohypoaldosteronism type IIC, AD–614492
KLH3—Kelch-like 3 5q31.2 605775	Adaptor protein within the ubiquitination sequence that links WNK1 and WNK4 to CUL3	Pseudohypoaldosteronism type IID, AD/AR–614495
CUL3—Cullin 3 2q36.2 603136	Scaffold protein that links to RING-box E3 ligase facilitating WNK4 ubiquitination and proteasomal destruction of WNK4	Pseudohypoaldosteronism type IIE, AD–614496

AD, autosomal dominant; AR, autosomal recessive; CMO, corticosterone methyloxidase; OMIM, Online Mendelian Inheritance in Man.

From Root AW: Disorders of aldosterone synthesis, secretion, and cellular function. Curr Opin Pediatr *26:480–486, 2014, Table 1, p. 483.*

peptide concentrations (>20 pmol/L). Thus, it is distinguished from SIADH, in which normal or decreased urine output, euvolemia, only modestly elevated urine sodium concentration, and an elevated vasopressin level occur. The distinction between cerebral salt wasting and SIADH is important because the treatment of the 2 disorders differs markedly. However, its existence has been questioned, because few patients with the suspected syndrome have documented hypovolemia and thus might truly have SIADH.

Runners' Hyponatremia

Excess fluid ingestion during long-distance running (e.g., marathon running) can result in severe hyponatremia from hypovolemia-induced activation of arginine vasopressin secretion coupled with excessive water ingestion and is correlated with weight gain, long racing time, and extremes of body mass index.

Pseudohyponatremia and Other Causes of Hyponatremia

Pseudohyponatremia can result from hypertriglyceridemia (see Chapter 55). Elevated lipid levels result in a relative decrease in serum water content. As electrolytes are dissolved in the aqueous phase of the serum, they appear low when expressed as a fraction of the total serum volume. As a fraction of serum water, however, electrolyte content is normal. Modern laboratory methods that measure sodium concentration directly, independent of sample volume, do not cause this anomaly. Factitious hyponatremia can result from obtaining a blood sample proximal to the site of intravenous hypotonic fluid infusion.

Hyponatremia is also associated with hyperglycemia, which causes the influx of water into the intravascular space. Serum sodium decreases by 1.6 mEq/L for every 100 mg/dL increment in blood glucose >100 mg/dL. Glucose is not ordinarily an osmotically active agent and does not stimulate vasopressin release, probably because it can equilibrate freely across plasma membranes. In the presence of insulin deficiency and hyperglycemia, however, glucose acts as an osmotic agent, presumably because its normal intracellular access to osmosensor sites is prevented. Under these circumstances, an osmotic gradient exists, stimulating vasopressin release.

TREATMENT

Patients with systemic dehydration and hypovolemia should be rehydrated with salt-containing fluids such as normal saline or lactated Ringer solution. Because of activation of the renin–angiotensin–aldosterone system, the administered sodium is avidly conserved, and water diuresis quickly ensues as volume is restored and vasopressin concentrations decrease. Under these conditions, caution must be taken to prevent a too-rapid correction of hyponatremia, which can

result in central pontine myelinolysis characterized by discrete regions of axonal demyelination and the potential for irreversible brain damage.

Hyponatremia from a decrease in effective plasma volume caused by cardiac, hepatic, renal, or pulmonary dysfunction is more difficult to reverse. The most effective therapy is the least easily achieved: treatment of the underlying systemic disorder. For example, patients weaned from positive pressure ventilation undergo a prompt water diuresis and resolution of hyponatremia as cardiac output is restored and vasopressin concentrations decrease. Vaptans represent a new class of small-molecule arginine vasopressin V2 receptor antagonists (aquaretics) useful for the treatment of hypervolemic hyponatremia associated with severe congestive heart failure and chronic liver failure. Although these agents successfully increase plasma sodium, they also lead to increased thirst and plasma vasopressin levels, which can limit their effectiveness.

Patients with hyponatremia from primary salt loss require supplementation with sodium chloride and fluids. Initially, intravenous replacement of urine volume with fluid containing sodium chloride, 150-450 mEq/L depending on the degree of salt loss, may be necessary; oral salt supplementation may be required subsequently. This treatment contrasts with that of SIADH, in which water restriction without sodium supplementation is the mainstay.

Emergency Treatment of Hyponatremia

The development of acute hyponatremia (onset <12 hr) or a serum sodium concentration <120 mEq/L may be associated with lethargy, psychosis, coma, or generalized seizures, especially in younger children. Acute hyponatremia can cause cell swelling and lead to neuronal dysfunction or to cerebral herniation. The emergency treatment of cerebral dysfunction resulting from acute hyponatremia includes water restriction and can require rapid correction with hypertonic 3% sodium chloride. If hypertonic saline treatment is undertaken, the serum sodium should be raised only high enough to cause an improvement in mental status, and in no case faster than 0.5 mEq/L/hr or 12 mEq/L/24 hr.

Treatment of Syndrome of Inappropriate Antidiuretic Hormone

Chronic SIADH is best treated by oral fluid restriction. With full antidiuresis (urine osmolality of 1,000 mOsm/kg), a normal daily obligate renal solute load of 500 mOsm/m^2 would be excreted in 500 mL/m^2 water. This, plus a daily nonrenal water loss of 500 mL/m^2, would require that oral fluid intake be limited to 1,000 mL/m^2/24 hr to avoid hyponatremia. In young children, this degree of fluid restriction might not provide adequate calories for growth. In this situation, the creation of nephrogenic diabetes insipidus using demeclocycline therapy may be indicated to allow sufficient fluid intake for normal growth. Urea has also been safely used to induce an osmotic diuresis in infants and children.

Treatment of Cerebral Salt Wasting

Treatment of patients with cerebral salt wasting consists of restoring intravascular volume with sodium chloride and water, as for the treatment of other causes of systemic dehydration. The underlying cause of the disorder, which is usually due to acute brain injury, should also be treated if possible. Treatment involves the ongoing replacement of urine sodium losses volume for volume.

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Chapter 560

Hyperpituitarism, Tall Stature, and Overgrowth Syndromes

Omar Ali

HYPERPITUITARISM

Primary hypersecretion of pituitary hormones rarely occurs in the pediatric population and should be distinguished from **secondary hyperpituitarism,** which occurs in the setting of target hormone deficiencies resulting in decreased hormonal feedback, such as in hypogonadism, hypoadrenalism, or hypothyroidism. In secondary hyperpituitarism, chronic pituitary hypersecretion occurs in response to target hormone deficiencies and leads to pituitary hyperplasia, which can enlarge and erode the sella and, on rare occasions, increase intracranial pressure. Such enlargements should not be confused with primary pituitary tumors; they disappear when the underlying hormone deficiency is treated. The elevated pituitary hormone levels readily suppress to normal following replacement of end-organ hormones. Pituitary hyperplasia can also occur in response to stimulation by ectopic production of releasing hormones such as that seen occasionally in patients with Cushing syndrome secondary to corticotropin-releasing hormone excess or in children with acromegaly secondary to growth hormone–releasing hormone (GHRH) produced by a variety of systemic tumors.

Primary hypersecretion of pituitary hormones by adenoma is uncommon in childhood. The most commonly diagnosed adenoma during childhood is prolactinoma, followed by corticotropinoma, and then somatotropinoma, which secrete prolactin, corticotropin, and growth hormone, respectively. There are a handful of case reports of thyrotropinoma in children and adolescents. There are no pediatric reports of gonadotropinoma, but hypothalamic hamartomas that secrete excess gonadotropin-releasing hormone are responsible for a significant proportion of cases of precocious puberty.

The monoclonal nature of most pituitary adenomas implies that most originate from a clonal event in a single cell. It is suspected that some pituitary tumors result from stimulation with hypothalamic-releasing hormones and in other instances, as in McCune-Albright syndrome (MAS), the tumor is caused by activating mutations of the *GNAS1* gene that codes for the α subunit of $G_s\alpha$, a guanine nucleotide-binding protein. The clinical presentation typically depends on the pituitary hormone that is hypersecreted. Disruptions of growth regulation and/or sexual maturation are common, as a result of either hormone hypersecretion or local compression by the tumor. MAS also features polyostotic fibrous dysplasia of bone and café-au-lait spots in a distinct distribution.

TALL STATURE

The normal distribution of height predicts that 2.3% of the population will be taller than 2 SD (97.7%) above the mean. The social acceptability and even desirability of tallness (heightism) makes tall stature an uncommon complaint in clinical practice. It is exceptionally unusual for boys and men to seek medical attention regarding excessive height. Girls (or their parents) were historically more likely to approach a physician with concern about tall stature, but even in girls this complaint has become less frequent as tallness has become more acceptable and socially desirable in adult women. Concern about side effects of estrogen treatment and reports of dissatisfaction among adult women subjected to this treatment have also led to a decline in estrogen use.

Table 560-1 Differential Diagnosis of Tall Stature and Overgrowth Syndromes

FETAL OVERGROWTH
Maternal diabetes mellitus
Cerebral gigantism (Sotos syndrome)
Weaver syndrome
Beckwith-Wiedemann syndrome
Other IGF-2 excess syndromes
POSTNATAL OVERGROWTH LEADING TO CHILDHOOD TALL STATURE
Nonendocrine Causes
Familial (constitutional) tall stature
Exogenous obesity
Cerebral gigantism (Sotos syndrome)
Weaver syndrome
Marfan syndrome
Fragile X syndrome
Beckwith-Wiedemann syndrome
Klinefelter syndrome (XXY)
SHOX excess syndromes
Homocystinuria
XYY
Endocrine Causes
Excess GH secretion (pituitary gigantism)
McCune-Albright syndrome or MEN associated with excess GH secretion
Precocious puberty
Hyperthyroidism
POSTNATAL OVERGROWTH LEADING TO ADULT TALL STATURE
Familial (constitutional) tall stature
Marfan syndrome
Klinefelter syndrome (XXY)
XYY
Androgen or estrogen deficiency or estrogen resistance
Androgen insensitivity syndrome (testicular feminization)
ACTH or cortisol deficiency or resistance
Excess GH secretion (pituitary gigantism)

ACTH, adrenocorticotropic hormone; GH, growth hormone; IGF, insulin-like growth factor; MEN, multiple endocrine neoplasia.

Differential Diagnosis of Tall Stature

Unusual tall stature can have different causes in each age group. Table 560-1 lists the causes of tall stature in childhood and adolescence. Figure 560-1 shows an approach to diagnosis.

Overgrowth in the Fetus and Neonate

Maternal diabetes is the most common cause of infants large for gestational age. Even in the absence of clinical symptoms or a family history, the birth of a large-for-gestational-age infant should lead to evaluation for maternal (or gestational) diabetes.

A group of disorders associated with excessive somatic growth and growth of specific organs has been described and is collectively referred to as overgrowth syndromes. These disorders appear to be caused in many cases by excess production and availability of insulin-like growth factor 2 (IGF-2) encoded by the gene *Igf2.* The best described of these syndromes is the **Beckwith-Wiedemann syndrome** (BWS), which is an overgrowth malformation syndrome that occurs with an incidence of 1 : 14,000 births, equal in males and females. Approximately 15% of cases are familial, while the rest appear to be sporadic. Most cases of BWS are caused by deregulation of imprinted genes within the chromosome 11p15.5 region. Genetic disruptions affecting this region include gene duplication, loss of heterozygosity, and relaxation or loss of imprinting. The "imprinted" genes involved in BWS and associated childhood tumors include, in addition to *Igf2,* the gene *H19,* which is involved in *Igf2* suppression, as well as *WT-1* (the Wilms tumor gene), cyclin-dependent kinase inhibitor 1C (CDKN1C), potassium channel voltage-gated KQT-like subfamily member 1 (KCNQ1), and KCNQ1-overlapping transcript 1 (KCNQ1OT1, or long QT intronic transcript 1, LIT1).

Affected infants characteristically have macrosomia including macroglossia, hepatosplenomegaly, nephromegaly, and omphalocele. They also have hypoglycemia secondary to hyperinsulinemia as a result of pancreatic β-cell hyperplasia. Children with BWS are predisposed to a specific subset of childhood neoplasms (embryonal tumors), including Wilms tumor, hepatoblastoma, neuroblastoma, and adrenocortical carcinoma. Management focuses on omphalocele, airway issues (a result of macroglossia), and neonatal hypoglycemia. Cancer risk is high until 8 yr of age, and regular surveillance with abdominal ultrasound and measurement of α-fetoprotein is recommended every 3 mo until age 8 yr. Thereafter, renal ultrasound is recommended every 1-2 yr as medullary sponge kidney and nephrocalcinosis may develop later.

Mutations in *GPC3*, a glypican gene (which codes for an IGF-2-neutralizing membrane receptor), cause the related Simpson-Golabi-Behmel overgrowth syndrome. Other syndromic causes of fetal overgrowth include Costello syndrome, Weaver syndrome, Sotos syndrome, and Perlman syndrome.

Overgrowth in Childhood or Adolescence

Normal variant, familial, or constitutional tall stature is by far the most common cause of tall stature. Almost invariably, a family history of tall stature can be obtained, and no organic pathology is present. The child is often taller than the child's peers throughout childhood and enjoys excellent health. The parent of the constitutionally tall adolescent might reflect unhappily upon his or her own adolescence as a tall teenager. There are no abnormalities in the physical examination, and the laboratory studies, if obtained, are negative.

Exogenous obesity is a common condition in adolescence and may be associated with rapid linear growth and early onset of puberty. Bone age is accelerated leading to relative tall stature in childhood but adult height is typically normal.

Klinefelter syndrome (XXY syndrome) is a relatively common (1 in 500-1,000 live male births) abnormality associated with tall stature, learning disabilities (including requirement for speech therapy), gynecomastia, and decreased upper body:lower body segment ratio. Affected boys can have hypotonia, clinodactyly, and hypertelorism. The testes are invariably small, although androgen production by Leydig cells is often in the low-normal range. Spermatogenesis and Sertoli cell function are defective, and infertility results. Other genital abnormalities including relatively small phallus, hypospadias, and cryptorchidism may be present.

XYY syndrome is associated with tall stature, problems in motor and language development, and possible antisocial behavior.

Marfan syndrome is an autosomal dominant connective tissue disorder consisting of tall stature, arachnodactyly, thin extremities, increased arm span, and decreased upper body:lower body segment ratio (see Chapter 702). Additional abnormalities include ocular abnormalities (e.g., lens subluxation), hypotonia, kyphoscoliosis, cardiac valvular deformities, and aortic root dilation.

Homocystinuria is an autosomal recessive inborn error of amino acid metabolism, caused by a deficiency of the enzyme cystathionine synthetase. It is characterized by intellectual disability when untreated, and many of its clinical features resemble Marfan syndrome, particularly ocular manifestations (see Chapter 85).

SOTOS SYNDROME (CEREBRAL GIGANTISM)

Children with cerebral gigantism (also known as Sotos syndrome) are above the 90th percentile for both length and weight at birth; they can also have macrocrania at that time. Most cases of Sotos syndrome are caused by mutations in the *NSD1* (nuclear receptor SET domain-containing protein 1) gene, but in the Japanese population most cases are attributable to microdeletions of the 5q35 region that includes this gene. Inheritance is autosomal dominant, but 95% of cases are a result of new mutations. Incidence is estimated to be approximately 1 in 14,000 live births. The *NSD1* gene is thought to play a role in epigenetic regulation, but the mechanisms by which mutations lead to the features of Sotos syndrome are not clear at this time.

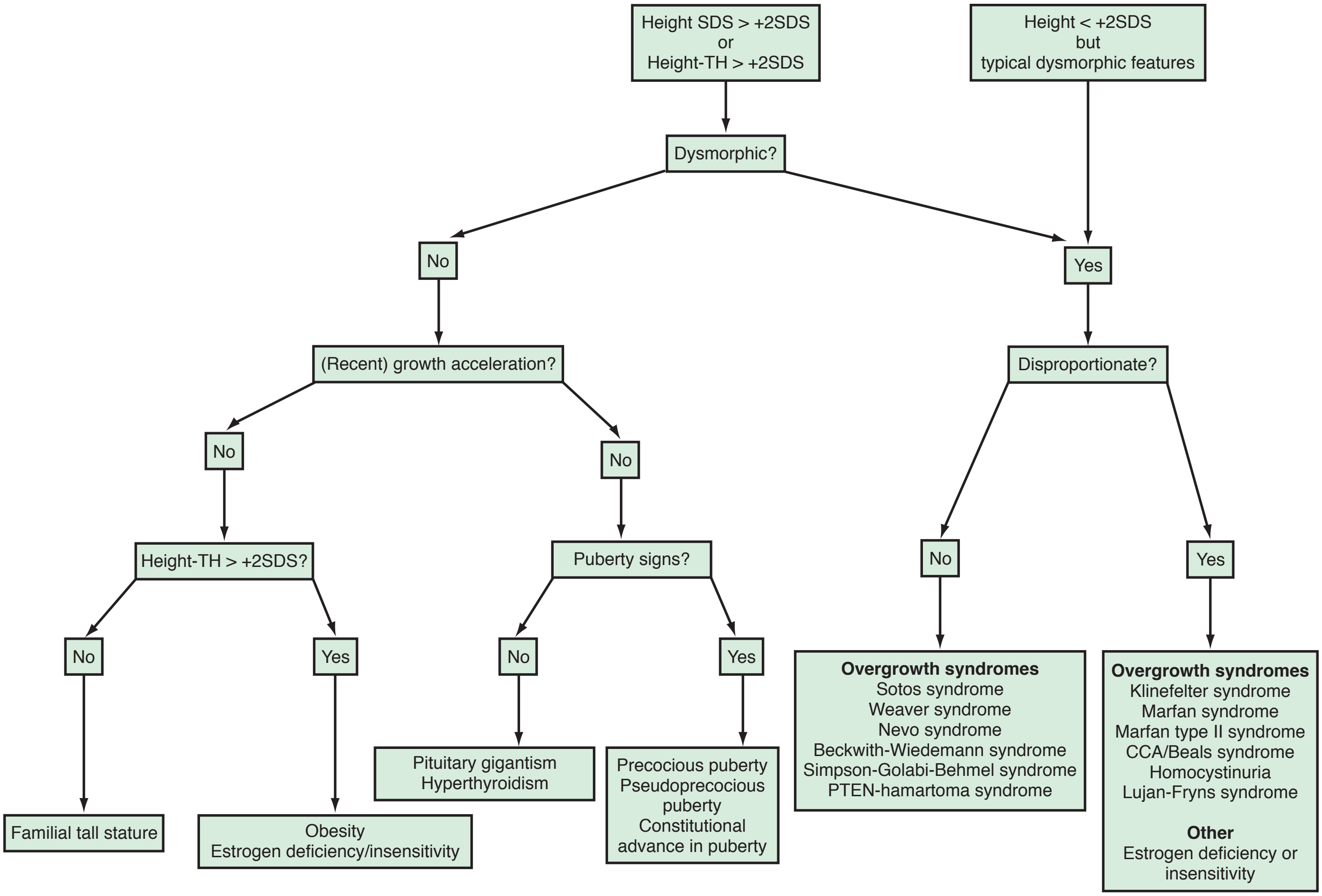

Figure 560-1 Diagnostic flow chart for the differential diagnosis of tall stature and overgrowth syndromes. Height-TH, current height percentile >2 SDS from target height percentile, the latter based on midparental height calculation; SDS, standard deviation score. *(From Neylon OM, Werther GA, Sabin MA: Overgrowth syndromes.* Curr Opin Pediatr *24:505–511, 2012, Fig. 1, p. 507.)*

Although it is characterized by rapid growth, there is no evidence that Sotos syndrome is caused by endocrine dysregulation. A hypothalamic defect has been suggested as a cause, but none has been demonstrated functionally or at necropsy. Growth is markedly rapid; by 1 yr of age, affected infants are taller than the 97th percentile in height. Accelerated growth continues for the 1st 4-5 yr and then returns to a normal rate (see Fig. 560-1). Puberty usually occurs at the expected time but may occur slightly early. Adult height is usually in the upper normal range.

Clinically the syndrome is characterized by a large (macrocephaly) dolichocephalic head, prominent forehead and jaw, hypertelorism, antimongoloid slant of the palpebral fissures, high-arched palate, and large hands and feet with thickened subcutaneous tissue. Clumsiness and awkward gait are also noted, and affected children have great difficulty in sports, in learning to ride a bicycle, and in other tasks requiring coordination. Some degree of developmental disability affects most patients; in some affected children perceptual deficiencies may predominate. Many different types of nonfebrile seizures have been reported and up to 25% of patients with Sotos syndrome have seizures at some point in their life. Affected patients may be at somewhat increased risk for neoplasms, including neuroblastoma, hepatoblastoma, and leukemia, with a lifetime risk of between 2% and 4%. Osseous maturation is usually compatible with the patient's height, although advanced bone age has been reported. Scoliosis develops in up to 30% of cases, usually starting in school-age children. Growth hormone (GH), IGF-1, and other endocrine studies are usually normal; there is no distinctive laboratory or radiologic marker for the syndrome. Abnormal electroencephalograms are common; imaging studies often reveal an enlarged ventricular system, but intracranial pressure is normal. Genetic testing for *NSD1* mutations (or fluorescence in situ hybridization for 5q35 microdeletions in Japanese patients) is available and should be routinely used. Management is symptomatic and includes paying special attention to developmental and behavioral problems (which tend to improve with age), scoliosis, and seizure disorder. No specific treatment is needed for the overgrowth itself. There is no consensus on the need for cancer surveillance at this time.

Table 560-2 notes additional features of overgrowth syndromes.

Hyperthyroidism in adolescents is associated with rapid growth but normal final adult height. It is almost always caused by Graves disease and is much more common in girls (see Chapter 568).

Precocious puberty, whether mediated centrally (increased gonadotropin secretion) or peripherally (increased secretion of androgens or estrogens, or both), results in accelerated linear growth during childhood, mimicking the pubertal growth spurt. Because skeletal maturation is also advanced, adult height is often compromised. Chapter 562 discusses the diagnostic evaluation and management of precocious puberty.

Although **delayed puberty** may be associated with short stature in childhood, as with constitutional delay, failure to eventually enter puberty and complete sexual maturation can result in sustained growth during adult life, with ultimate tall stature. The report of tall stature with open epiphyses resulting from a mutation of the estrogen receptor in a man with normal male sexual maturation underscores the fundamental role of estrogen in promoting epiphyseal fusion and termination of normal skeletal growth. Aromatase deficiency leads to tall stature through similar pathways.

Table 560-2 Genetic Overgrowth Syndromes

GENETIC SYNDROMES	CLINICAL FEATURES	INCIDENCE OF MALIGNANCY (%)	ETIOLOGY	INVESTIGATIONS AND MANAGEMENT
Beckwith-Wiedemann syndrome*	Hypoglycemia, large tongue, ear pits, omphalocele or umbilical hernia, hemihyperplasia	~7.5		US heart, kidneys Chromosomes 11p FISH and/ or MLPA, methylation studies Tumor surveillance justified
Perlman syndrome*	Macrosomia, unusual facies Nephroblastosis		Rare autosomal recessive	US brain (ACC), heart (coarctation), kidneys
Simpson-Golabi-Behmel syndrome*	Coarse facial features, macroglossia, central groove lower lip, supernumerary nipples	~7.5	X-linked recessive (glypican-3 mutations)	US heart, kidney X-ray spine (vertebral segmentation anomaly) Tumor surveillance justified
Sotos syndrome	Facial gestalt (long, thin face, broad forehead) Feeding difficulties Hypotonia	~4	Usually de novo dominant *NSD1* deletion or mutation Rare familial cases	US heart, kidneys Monitor development
PTEN-hamartoma syndrome (Bannayan-Ruvalcaba-Riley)	Macrocephaly (>97th percentile) often progressive from birth, hypotonia, pigmented skin, penile macules, lipomas	Uncertain	Sporadic or autosomal dominant *PTEN* mutation	US head, heart, and kidney Monitor development
Weaver syndrome	Broad forehead, hypertelorism, small chin, long philtrum, camptodactyly, fetal finger pads	~5-6	Rare, unknown	US heart, brain, kidney
Marfan syndrome type I	Facial gestalt, arachnodactyly, scoliosis, pectus carinatum or excavatum, aortic root dilation, lens dislocation		Autosomal dominant fibrillin-1 *(FBN1)*	Eye examination and follow-up Heart US and cardiology follow-up Monitor scoliosis
Marfan syndrome type II or Loeys-Dietz syndrome	Marfan-like habitus, aortic root dilation, aortic dissection, vasculopathy		Autosomal dominant, TGF-β pathway anomaly *TGFBR1* and *TGFBR2* genes	Eye examination usually normal Heart US and follow-up Monitor scoliosis
Beals syndrome	Congenital distal arthrogryposis Crumpled ears		Autosomal dominant fibrillin 2 *(FBN2)*	Eye examination and heart US usually normal
Homocystinuria	Marfan-like habitus Developmental delay Lens dislocation		Autosomal recessive Cystathionine β-synthase (CBS) mutation	Urine metabolic screen Eye examination Monitor development
Lujan syndrome	Marfanoid habitus plus intellectual disability		X-linked recessive *MED12* gene	Eye examination usually normal Heart US usually normal
Sex chromosome aneuploidy Klinefelter 47XXY, 47XYY, 47XXX	Tall stature, small testes, gynecomastia Tall stature, ± learning disability			Androgen replacement from puberty in Klinefelter syndrome Monitor development
Autosomal anomaly Tetrasomy 12p mosaicism,* pat 11pdup, 4pdub, 22q13del, 15q26-qter dup	Congenital overgrowth or childhood tall stature with intellectual disability			Monitor development

*Overgrowth often presenting at birth.

ACC, agenesis of the corpus callosum; FISH, fluorescence in situ hybridization; MLPA, multiple ligation probe amplification; PTEN, phosphatase and tensin homolog; TGF, transforming growth factor; TGFBR, transforming growth factor β receptor; US, ultrasound.

From Verge CF, Mowat D: Overgrowth, Arch Dis Child *95:458–463, 2010.*

The purpose of the diagnostic evaluation of tall stature is to distinguish the commonly occurring, normal variant, constitutional variety from the rare pathologic conditions. Often, when the history suggests familial tall stature and the physical examination is entirely normal, no laboratory tests are indicated. It is valuable to obtain a bone age radiograph to be able to predict adult height, which serves as a basis for discussions with the family and for management decisions. If the history suggests any of the aforementioned disorders or the physical examination reveals abnormalities, additional laboratory tests should be obtained. IGF-1 and IGF-binding protein-3 (IGFBP-3) are excellent screening tests for GH excess and can be verified with a glucose suppression test. Laboratory evidence of GH excess mandates MRI evaluation of the pituitary. Chromosome analysis is useful in boys, especially when the ratio of upper to lower body segment is decreased or when developmental disability is present, to rule out Klinefelter syndrome. If Marfan syndrome or homocystinuria is suspected from the physical examination, referral to a cardiologist and an ophthalmologist should be made. Thyroid function tests are

useful to diagnose or rule out hyperthyroidism when this disorder is suspected.

Treatment of Normal Variant Tall Stature

Reassurance of the family and the patients is the key to the management of normal variant tall stature. The use of the bone age to predict adult height might provide some comfort for them, as will general supportive discussions on the social acceptability of this condition. Although treatment is possible for girls and boys with excessive growth, its use should be restricted to patients with predicted adult height >3-4 SD above the mean (79 inches or 200 cm in boys, 73 inches or 185 cm in girls) and evidence of significant psychosocial impairment.

Sex steroids have been used in the treatment of tall stature and are designed to accelerate puberty and to promote epiphyseal fusion; these are therefore of little benefit when given in late puberty. The lack of extensive experience with this form of therapy and the risks of estrogen or androgen treatment for tall stature should be carefully weighed and discussed with the family and treatment should be discouraged except in the most extreme cases. Detailed discussion with the child at the child's level is also advisable as up to 40% of those who underwent such treatments are dissatisfied as adults and feel they were not sufficiently consulted about this course of action. Therapy is initiated ideally before puberty or in early puberty. In boys, treatment should begin before the bone age reaches 14 yr. In the extremely rare instances where treatment is desired, testosterone enanthate is used at a dose of 500 mg intramuscularly every 2 wk for 6 mo. In girls, oral estrogens in various doses have been used to reduce the predicted height, but average height reduction may be only 1.1-2.4 cm. Therapy must begin before the bone age has reached 12 yr. In the rare case where treatment is advised, oral ethinyl estradiol at a dose of 0.15-0.5 mg/day until cessation of growth occurs has been used. Short-term side effects have included benign breast disease, cholelithiasis, hypertension, menstrual irregularities, weight gain, nausea, limb pain, galactorrhea, and thrombosis. Reduced fertility later in life may be a potential long-term complication.

EXCESS GROWTH HORMONE SECRETION AND PITUITARY GIGANTISM

In young persons with open epiphyses, overproduction of GH results in **gigantism;** in persons with closed epiphyses, the result is **acromegaly.** Often some acromegalic features are seen with gigantism, even in children and adolescents. After closure of the epiphyses, the acromegalic features become more prominent.

Gigantism is rare, with only several hundred reported cases to date. Most cases are sporadic and are caused by pituitary adenomas or excessive GHRH secretion by the hypothalamus (and, rarely, by tumors in other parts of the body). **Syndromes associated with pituitary GH excess include** MAS, which is caused by mutations resulting in constitutively activated G-proteins, and can include somatotrophic tumors and excess GH secretion. Approximately 20% of patients with gigantism have MAS (commonly consisting of a triad of precocious puberty, café-au-lait spots, and fibrous dysplasia) and 20% of patients with MAS have some degree of GH hypersecretion. GH-secreting tumors are seen in approximately 60% of patients with **multiple endocrine neoplasia type 1,** but almost all these tumors develop in adult life and cause acromegaly rather than pituitary gigantism. Increased GH secretion and GH-secreting adenomas may also be seen in **neurofibromatosis, tuberous sclerosis**, and **Carney complex**.

The cardinal clinical feature of gigantism is longitudinal growth acceleration secondary to GH excess. The usual manifestations consist of coarse facial features and enlarging hands and feet. In young children, rapid growth of the head can precede linear growth. Some patients have behavioral and visual problems. In most recorded cases, the abnormal growth became evident at puberty, but the condition has been established as early as the newborn period in 1 child and at 21 mo of age in another. Giants have rarely been reported to grow to a height of over 8 ft. In some cases the patient may present with local effects of the pituitary tumor (headache, visual field defects, and other pituitary hormone deficiencies) as the main complaint, and there is at least 1 report of a patient presenting with diabetic ketoacidosis induced by GH excess. The presentation of gigantism is usually dramatic, unlike the insidious onset of acromegaly in adults.

Approximately 50% of the pituitary adenomas that cause gigantism also exhibit hyperprolactinemia because they secrete both GH and prolactin. This is because mammosomatotrophs are the most common type of GH-secreting cells involved in childhood gigantism. GH-secreting tumors of the pituitary are typically eosinophilic or chromophobic adenomas. Adenomas can compromise other anterior pituitary function through growth or cystic degeneration. Secretion of gonadotropins, thyrotropin, or corticotropin may be impaired. Delayed sexual maturation or hypogonadism can occur. When GH hypersecretion is accompanied by gonadotropin deficiency, accelerated linear growth can persist for decades. In some cases, the tumor spreads outside the sella, invading the sphenoid bone, optic nerves, and brain. GH-secreting tumors in pediatric patients are more likely to be locally invasive or aggressive than are those in adults.

Acromegalic features consist chiefly of enlargement of the distal parts of the body, but manifestations of abnormal growth involve all portions. The circumference of the skull increases, the nose becomes broad, and the tongue is often enlarged, with coarsening of the facial features. The mandible grows excessively, and the teeth become separated. Visual field defects and neurologic abnormalities are common; signs of increased intracranial pressure appear later. The fingers and toes grow chiefly in thickness. There may be dorsal kyphosis. Fatigue and lassitude are early symptoms. GH levels are elevated and occasionally exceed 100 ng/mL. There is usually no suppression of GH levels by the hyperglycemia of a glucose tolerance test and IGF-1 and IGFBP-3 levels are consistently elevated in acromegaly and pituitary gigantism.

Diagnosis

Most children with tall stature do not have pituitary gigantism and other etiologies of rapid linear growth such as genetic tall stature, precocious puberty, and hyperthyroidism should be carefully excluded. Coexisting findings (e.g., dysmorphic facial features, neurocognitive problems, hemihypertrophy) may suggest syndromic or chromosomal causes of tall stature, such as Sotos, Weaver, Klinefelter, or XYY syndrome. GH hypersecretion can be screened for by testing IGF-1 and IGFBP-3 levels. An excellent linear dose–response correlation between serum IGF-1 levels and 24 hr mean GH secretion has been demonstrated. An elevated IGF-1 level in a patient with appropriate clinical suspicion usually indicates GH excess. Potential confusion can arise in the evaluation of normal adolescents because significantly higher IGF-1 levels occur during puberty than in adulthood, so the IGF-1 level must be age and gender matched. Serum IGFBP-3 levels are also sensitive markers of GH elevations and will be elevated in almost all cases. If IGF-1 and/or IGFBP-3 levels are elevated, then the next step is to test for GH excess by doing an oral glucose-suppression test. The gold standard for the diagnosis of GH excess in adults is the failure to suppress serum GH levels to <1 ng/dL at any time during a 2 hr oral glucose tolerance test with 1.75 g/kg oral glucose challenge (maximum: 75 g). GH levels may not be suppressed to this level in normal adolescents and a cutoff of 5 ng/mL may be more appropriate in this age group. If laboratory findings suggest GH excess, the presence of a pituitary adenoma should be confirmed by MRI of the brain. In rare cases, a pituitary mass is not identified. This might be from an occult pituitary microadenoma or ectopic production of GHRH or GH. CT is acceptable when MRI is unavailable.

Treatment

The goals of therapy are to remove or shrink the pituitary mass, to restore GH and secretory patterns to normal, to restore IGF-1 and IGFBP-3 levels to normal, to retain the normal pituitary secretion of other hormones, and to prevent recurrence of disease.

For well-circumscribed pituitary adenomas, transsphenoidal surgery is the treatment of choice and may be curative. The tumor should be removed completely. The likelihood of surgical cure depends greatly on the surgeon's expertise as well as on the size and extension of the mass. Intraoperative GH measurements can improve the results of tumor resection. Transsphenoidal surgery to resect the tumors is as

safe in children as in adults. At times, a transcranial approach might be necessary. The primary goal of treatment is to normalize GH and IGF-1 levels. GH levels (<1 ng/mL within 2 hr after a glucose load) and serum IGF-1 levels (age-adjusted normal range) are the best tests to define a biochemical cure.

If GH secretion and IGF-1 levels are not normalized by surgery, the options include pituitary irradiation and medical therapy. Further growth of the tumor is prevented by irradiation in >99% of patients. The main disadvantage is the delayed efficacy in decreasing GH levels. GH is reduced by approximately 50% from the initial concentration by 2 yr, by 75% by 5 yr, and approaches 90% by 15 yr. Multiple pituitary hormone deficiency is a predictable outcome, occurring in 40-50% of patients 10 yr after irradiation.

Surgery fails to cure a significant number of patients and radiotherapy may not work fast enough, so medical therapy has an important role in treating patients with GH excess. Treatment is effective and well tolerated with long-acting somatostatin analogs and dopamine agonists, as well as by novel GH antagonists.

The **somatostatin analogs** are highly effective in the treatment of patients with GH excess. Octreotide suppresses GH to <2.5 ng/mL in 65% of patients with acromegaly and normalizes IGF-1 levels in 70%. The effects of octreotide are well sustained over time. Tumor shrinkage also occurs with octreotide but is generally modest. Consistent GH suppression can be obtained with a continuous SC pump infusion of octreotide or with long-acting formulations, including long-acting octreotide and lanreotide. These produce consistent GH and IGF-1 suppression in acromegalic patients with once-monthly or biweekly IM depot injections. These sustained-release preparations have not been formally tested in children. Octreotide injection in the pediatric population has been used at doses of 1-40 µg/kg/24 hr. In adults the long-acting form is used in a dose of 10-40 mg every mo, but no pediatric dose range has been established.

For patients with both GH and prolactin oversecretion, dopamine agonists, such as **bromocriptine and cabergoline,** which bind to pituitary dopamine type 2 receptors and may also suppress GH secretion, should be considered. Prolactin levels are often adequately suppressed, but GH levels and IGF-1 levels are rarely normalized with this treatment modality alone. Tumor shrinkage occurs in a minority of patients. The effectiveness of these agents may be additive to that of octreotide. Cabergoline therapy at doses of 0.25-4.0 mg/wk (given 1-2 times per wk) has been used in adults with acromegaly, and because of its less-frequent dosing and lower incidence of side effects as compared to bromocriptine, this is now considered the dopamine agonist of choice in both adults and children. Side effects can include nausea, vomiting, abdominal pain, arrhythmias, nasal stuffiness, orthostatic hypotension, sleep disturbances, and fatigue.

Pegvisomant is a GH-receptor antagonist that competes with endogenous GH for binding to the GH receptor. It effectively suppresses GH and IGF-1 levels in patients with acromegaly caused by pituitary tumors as well as ectopic GHRH hypersecretion. Normalization of IGF-1 levels occurs in up to 90% of patients treated daily with this drug for 3 mo or longer. The adult dosage is 10-40 mg via subcutaneous injection once daily, although twice-weekly protocols have also been reported as highly successful. IGF-1 levels and hepatic enzymes must be monitored. Combined therapy with somatostatin analogs and weekly pegvisomant injections also is effective. Pediatric experience is limited, but case reports indicate that it can successfully suppress IGF-1 levels when used in doses of 10-30 mg/day.

HYPERSECRETION OF OTHER PITUITARY HORMONES

Prolactinoma

Prolactin-secreting pituitary adenomas are the most common pituitary tumors in adolescents. With the advent of MRI, more of these tumors, particularly microadenomas (<1 cm in diameter), are being detected. The most common presenting manifestations are headache, primary or secondary amenorrhea, and galactorrhea. The disorder affects more than twice as many girls as boys; most patients have undergone normal puberty before becoming symptomatic. Only a few have delayed puberty. In some kindreds with type I multiple endocrine neoplasia, prolactinomas are the presenting feature during adolescence.

Prolactin levels may be elevated mildly (40-50 ng/mL) or markedly (10,000-15,000 ng/mL). Most prolactinomas in children are large (macroadenomas), cause the sella to enlarge, and in some cases cause visual field defects. Approximately 30% of patients with macroadenomas develop other pituitary hormone deficiencies, particularly GH deficiency. Alternatively, prolactin-secreting adenomas might also stain for and secrete excess GH and/or thyroid-stimulating hormone.

Prolactinomas should not be confused with the hyperprolactinemia and pituitary hyperplasia that can occur in patients with **primary hypothyroidism**, which is readily treated with thyroid hormone (see Chapter 565). Moderate elevations (<200 ng/mL) of prolactin are also associated with a variety of **medications** (antipsychotics, metoclopramide, phenothiazines, verapamil), with pituitary stalk dysfunction such as can occur with craniopharyngioma, with chronic stress (rarely >40 ng/mL), and with nipple stimulation.

In some cases, extreme hyperprolactinemia is associated with a "hook effect" that leads to factitiously low values on blood tests. In cases where clinical features are compatible with hyperprolactinemia, serial dilution of the lab specimen should be done to rule out this kind of measurement error. On the other hand, patients may have factitiously elevated prolactin levels on immunoassay as a result of the presence of prolactin polymers and dimers (macroprolactinemia). In cases where an elevated prolactin is detected in an asymptomatic patient, unnecessary diagnostic work-up and treatment can be avoided by performing polyethylene glycol precipitation to exclude the presence of macroprolactinemia, which is clinically benign.

In most patients where the hyperprolactinemia is secondary to an adenoma, it can be effectively treated with dopamine agonists. Treatment leads to lowering of prolactin levels and tumor shrinkage in the vast majority of patients. Because of its greater efficacy and lower incidence of side effects, cabergoline is considered the drug of choice for treatment of hyperprolactinemia in doses ranging from 0.125-1.0 mg twice weekly. Higher doses may be needed in some patients but carry the risk of inducing cardiac valvular abnormalities and should be carefully monitored.

When dopamine agonist treatment has been unsuccessful in lowering the serum prolactin concentration or the size of the adenoma, and when symptoms or signs attributable to hyperprolactinemia or adenoma size persist during treatment, transsphenoidal surgery should be considered.

Corticotropinoma

Corticotropinoma is very rare in children, and its peak occurrence is at age 14 yr. **Cushing disease** refers specifically to an adrenocorticotropic hormone–producing pituitary adenoma that stimulates excess cortisol production and secretion. It is more common than primary adrenal causes of Cushing syndrome, except in younger children (younger than 5 yr of age), in whom adrenal carcinomas and adrenal activating mutations of MAS are rare but dominant causes of the syndrome. Adenomas causing Cushing disease are almost always microadenomas with a diameter of <5 mm and are significantly smaller than all other types of adenomas at presentation. The most sensitive indicator of excess glucocorticoid secretion in children is growth failure, which generally precedes other manifestations. Patients develop weight gain that tends to be centripetal rather than generalized. Pubertal arrest, hypertension, large purplish striae, fatigue, and depression are also common. In prepubertal children, males are more frequently affected than females.

Midnight salivary cortisol measurements can be used as a screening test for cortisol excess, but confirmation requires at least 1 additional test (either 24 hr urinary free cortisol or an overnight dexamethasone suppression test). Location of the microadenoma is usually determined by MRI, and bilateral inferior petrosal sinus sampling may be needed in difficult cases. Transsphenoidal surgery is the treatment of choice for Cushing disease in children. Initial remission rates of 70-98% of patients and long-term success rates of 50-98% are reported. Residual transient hypoadrenalism is often observed after surgery, lasting as

long as 30 mo. Pituitary radiotherapy is used if cortisol levels remain elevated and/or adrenocorticotropic hormone levels continue to be detectable. Successful treatment may not correct the height deficit, and GH deficiency may be present after treatment and should be treated as required.

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Chapter 561

Physiology of Puberty

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Between early childhood and approximately 8-9 yr of age (prepubertal stage), the hypothalamic-pituitary-gonadal axis is dormant, as reflected by undetectable serum concentrations of luteinizing hormone (LH) and sex hormones (estradiol in girls, testosterone in boys). One to 3 yr before the onset of clinically evident puberty, low serum levels of LH during sleep become demonstrable. This sleep-entrained LH secretion occurs in a pulsatile fashion and reflects endogenous episodic discharge of hypothalamic gonadotropin-releasing hormone (GnRH). Nocturnal pulses of LH continue to increase in amplitude and, to a lesser extent, in frequency as clinical puberty approaches. This pulsatile secretion of gonadotropins is responsible for enlargement and maturation of the gonads and the secretion of sex hormones. The appearance of the secondary sex characteristics in early puberty is the visible culmination of the sustained, active interaction occurring among hypothalamus, pituitary, and gonads in the peripubertal period. By midpuberty, LH pulses become evident even during the daytime and occur at approximately 90-120 min intervals. A second critical event occurs in middle or late adolescence in girls in whom cyclicity and ovulation occur. A positive feedback mechanism develops whereby increasing levels of estrogen in midcycle cause a distinct increase of LH.

The increasing secretion of hypothalamic GnRH in a pulsatile fashion thus underlies the onset of pubertal development. The resulting "GnRH pulse generator" is regulated by multiple neuropeptides, including glutamic acid, kisspeptin, and neurokinin-B (stimulatory) and γ-aminobutyric acid, preproenkephalin, and dynorphin (inhibitory). GnRH secretion is also regulated by factors produced by the glial cells, such as transforming growth factor α. Loss-of-function mutations of the *KISS1 R*—also known as *GPR54*—gene (the gene encoding a G-protein–coupled receptor whose ligand is kisspeptin) cause an autosomal recessive form of hypogonadotropic hypogonadism, whereas gain-of-function mutations of the gene are associated with precocious puberty. Increased transforming growth factor α signaling is associated with the occurrence of central precocious puberty in patients with hypothalamic hamartoma.

The interpretation of the hormonal changes of puberty is complex. Issues in interpreting LH and follicle-stimulating hormone measurements include the presence of multiple gonadotropin isoforms, immunoassay-related variability, and problems inherent to their pulsatile secretion, which mandates serial sampling in plasma. In addition, important sex differences exist in the maturation of the hypothalamus and pituitary gland, and serum LH concentrations tend to increase earlier in the course of the pubertal process in boys than in girls. Adrenocortical androgens also have a role in sexual maturation. Serum levels of dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) begin to increase at approximately 6-8 yr of age, before any increase in LH or sex hormones and before the earliest physical changes of puberty are apparent; this process is called *adrenarche*. DHEAS is the most abundant adrenal C-19 steroid in the blood, and its serum concentration remains fairly stable over 24 hr. A single measurement of this hormone is commonly used as a marker of adrenal androgen secretion. Although adrenarche typically antedates the onset of gonadal activity (gonadarche) by a few years, the 2 processes do not seem to be causally related, because adrenarche and gonadarche are dissociated in conditions such as central precocious puberty and adrenocortical failure.

The effects of gonadal steroids (testosterone in boys, estradiol in girls) on bone growth and osseous maturation are critical. Both aromatase deficiency and estrogen receptor defects result in delayed epiphyseal fusion and tall stature in affected males. These observations suggest that estrogens, rather than androgens, are responsible for the process of bone maturation that ultimately leads to epiphyseal fusion and cessation of growth. Estrogens also mediate the increased production of growth hormone, which along with a direct effect of sex steroids on bone growth, is responsible for the pubertal growth spurt.

The age of onset of puberty varies and is more closely correlated with osseous maturation than with chronological age (see Chapter 14). In females, the **breast bud** (thelarche) is usually the first sign of **puberty** (10-11 yr of age), followed by the appearance of pubic hair (pubarche) 6-12 mo later. The interval to the onset of **menstrual activity** (menarche) is usually 2-2.5 yr, but may be as long as 6 yr. In the United States, at least 1 sign of puberty is present in approximately 95% of girls by 12 yr of age and in 99% of females by 13 yr of age. Peak height velocity occurs early (at breast stages II-III, typically between 11 and 12 yr of age) in girls and always precedes menarche. The mean age of menarche is approximately 12.75 yr. There are, however, wide variations in the sequence of changes involving growth spurt, breast bud, pubic hair, and maturation of the internal and external genitalia.

In males, **growth of the testes** (≥4 mL in volume or 2.5 cm in longest diameter) and thinning of the scrotum are the first signs of puberty (11-12 yr). These are followed by pigmentation of the scrotum and growth of the penis (see Chapter 14) and by **pubarche.** Appearance of **axillary hair** usually occurs in midpuberty. In males, unlike in females, acceleration of growth begins after puberty is well under way and is maximal at genital stages IV-V (typically between 13 and 14 yr of age). In males, the growth spurt occurs approximately 2 yr later than in females, and growth may continue beyond 18 yr of age.

Genetic and environmental factors affect the timing for the onset of puberty. Population-based studies in the United States and in Europe suggest secular trends for earlier onset of puberty over the past few decades in females and, to a lesser degree, in males. African-American and, to a lesser extent, Hispanic girls appear to be more advanced in the development of secondary sex characteristics for age than white females. The timing of menarche has, however, remained generally stable with only a marginal advancement (2.5-4 mo) reported in U.S.-based studies and no significant change reported in the Copenhagen Puberty Study. The latter also showed that the earlier onset of breast development observed in girls examined in 2006-2008 when compared to those seen in 1991-1993 (means: 10.88 yr vs 9.86 yr, $p < 0.0001$) was not associated with different levels of estradiol or gonadotropins when girls of similar chronological ages were compared between the 2 groups. Hence, earlier breast development may not necessarily reflect an earlier activation of the hypothalamic-pituitary-gonadal axis but could be the consequence of other factors such as increased adiposity or increased exposure to certain environmental agents. Positive correlations between the degree of adiposity and earlier pubertal development in girls have, indeed, been reported. Conversely, female athletes in whom leanness and strenuous physical activity have coexisted from early childhood frequently exhibit a marked delay in puberty or menarche, and they frequently have oligomenorrhea or amenorrhea as adults (see Chapter 691). Pubertal delay is also prevalent in males who are physically very active. These observations support the thesis that the energy balance is closely related to the activity of the GnRH pulse generator and the mechanisms initiating and sustaining puberty via hormonal signals such as leptin or other adipokines.

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Chapter 562

Disorders of Pubertal Development

Luigi R. Garibaldi and Wassim Chemaitilly

Precocious puberty is defined by the onset of secondary sexual characteristics before the age of 8 yr in girls and 9 yr in boys. The variation in the age of the onset of puberty in normal children, particularly of different ethnicities, makes this definition somewhat arbitrary. It remains in use by most clinicians.

Depending on the primary source of the hormonal production, precocious puberty may be classified as **central** (also known as **gonadotropin dependent,** or **true**) or **peripheral** (also known as **gonadotropin independent** or **precocious pseudopuberty**) (Table 562-1). **Central** precocious puberty is always isosexual and stems from hypothalamic-pituitary-gonadal activation with ensuing sex hormone secretion and progressive sexual maturation. In **peripheral** precocious puberty, some of the secondary sex characteristics appear, but there is no activation of the normal hypothalamic-pituitary-gonadal interplay. In this latter group, the sex characteristics may be isosexual or heterosexual (contrasexual) (see Chapters 583-588).

Peripheral precocious puberty can induce maturation of the hypothalamic-pituitary-gonadal axis and trigger the onset of central puberty. This mixed type of precocious puberty occurs commonly in conditions such as congenital adrenal hyperplasia, McCune-Albright syndrome, and familial male-limited precocious puberty, when the bone age reaches the pubertal range (10.5-12.5 yr).

Table 562-1 Conditions Causing Precocious Puberty
CENTRAL (GONADOTROPIN-DEPENDENT, TRUE PRECOCIOUS) PUBERTY
Idiopathic
Organic brain lesions
Hypothalamic hamartoma
Brain tumors, hydrocephalus, severe head trauma, myelomeningocele
Hypothyroidism, prolonged and untreated*
COMBINED PERIPHERAL AND CENTRAL
Treated congenital adrenal hyperplasia
McCune-Albright syndrome, late
Familial male precocious puberty, late
PERIPHERAL (GONADOTROPIN-INDEPENDENT, PRECOCIOUS) PSEUDOPUBERTY
GIRLS
Isosexual (feminizing) conditions
McCune-Albright syndrome
Autonomous ovarian cysts
Ovarian tumors
Granulosa–theca cell tumor associated with Ollier disease
Teratoma, chorionepithelioma
SCTAT associated with Peutz-Jeghers syndrome
Feminizing adrenocortical tumor
Exogenous estrogens
Heterosexual (masculinizing) conditions
Congenital adrenal hyperplasia
Adrenal tumors
Ovarian tumors
Glucocorticoid receptor defect
Exogenous androgens
BOYS
Isosexual (masculinizing) conditions
Congenital adrenal hyperplasia
Adrenocortical tumor
Leydig cell tumor
Familial male precocious puberty
Isolated
Associated with pseudohypoparathyroidism
hCG-secreting tumors
• Central nervous system
• Hepatoblastoma
Mediastinal tumor associated with Klinefelter syndrome
Teratoma
Glucocorticoid receptor defect
Exogenous androgen
Heterosexual (feminizing) conditions
Feminizing adrenocortical tumor
SCTAT associated with Peutz-Jeghers syndrome
Exogenous estrogens
INCOMPLETE (PARTIAL) PRECOCIOUS PUBERTY
Premature thelarche
Premature adrenarche
Premature menarche

*Central puberty without true gonadotropin dependency (see text).
hCG, human chorionic gonadotropin; SCTAT, sex-cord tumor with annular tubules.

562.1 Central Precocious Puberty

Luigi R. Garibaldi and Wassim Chemaitilly

Central precocious puberty is defined by the onset of breast development before the age of 8 yr in girls and by the onset of testicular development (volume ≥4 mL) before the age of 9 yr in boys, as a result of the early activation of the hypothalamic-pituitary-gonadal axis. It occurs 5-10–fold more frequently in girls than in boys and is usually sporadic. A high prevalence of idiopathic central precocious puberty has been reported in girls adopted from developing countries, with the limitation that the exact date of birth may be uncertain.

Although approximately 90% of girls have an idiopathic form, a structural central nervous system (CNS) abnormality can be demonstrated in up to 75% of boys with central precocious puberty. Beyond its etiology, which thus needs to be specifically addressed, central precocious puberty can impact linear growth and affect the child's growth potential.

CLINICAL MANIFESTATIONS

Sexual development may begin at any age and generally follows the sequence observed in normal puberty. In girls, early menstrual cycles may be more irregular than they are with normal puberty. The initial cycles are usually anovulatory, but pregnancy has been reported as early as 5.5 yr of age (Fig. 562-1). In boys, testicular biopsies have shown stimulation of all elements of the testes, and spermatogenesis has been observed as early as 5-6 yr of age. In affected girls and boys, height, weight, and osseous maturation are advanced. The increased rate of bone maturation results in early closure of the epiphyses, and the ultimate stature is less than it would have been otherwise. Without treatment, approximately 30% of girls and an even larger percentage of boys achieve a height less than the 5th percentile as adults. Mental development is usually compatible with chronological age. Emotional behavior and mood swings are common, but serious psychologic problems are rare.

Although the clinical course is variable, 3 main patterns of pubertal progression can be identified. Most girls (particularly those younger than 6 yr of age at the onset) and a large majority of boys have rapidly progressive puberty, characterized by rapid physical and osseous maturation, leading to a loss of height potential. An increasing percentage of girls (older than 6 yr of age at the onset with an idiopathic form) have a slowly progressive variant, characterized by parallel advancement of osseous maturation and linear growth, with preserved height potential. Spontaneously regressive or unsustained central precocious

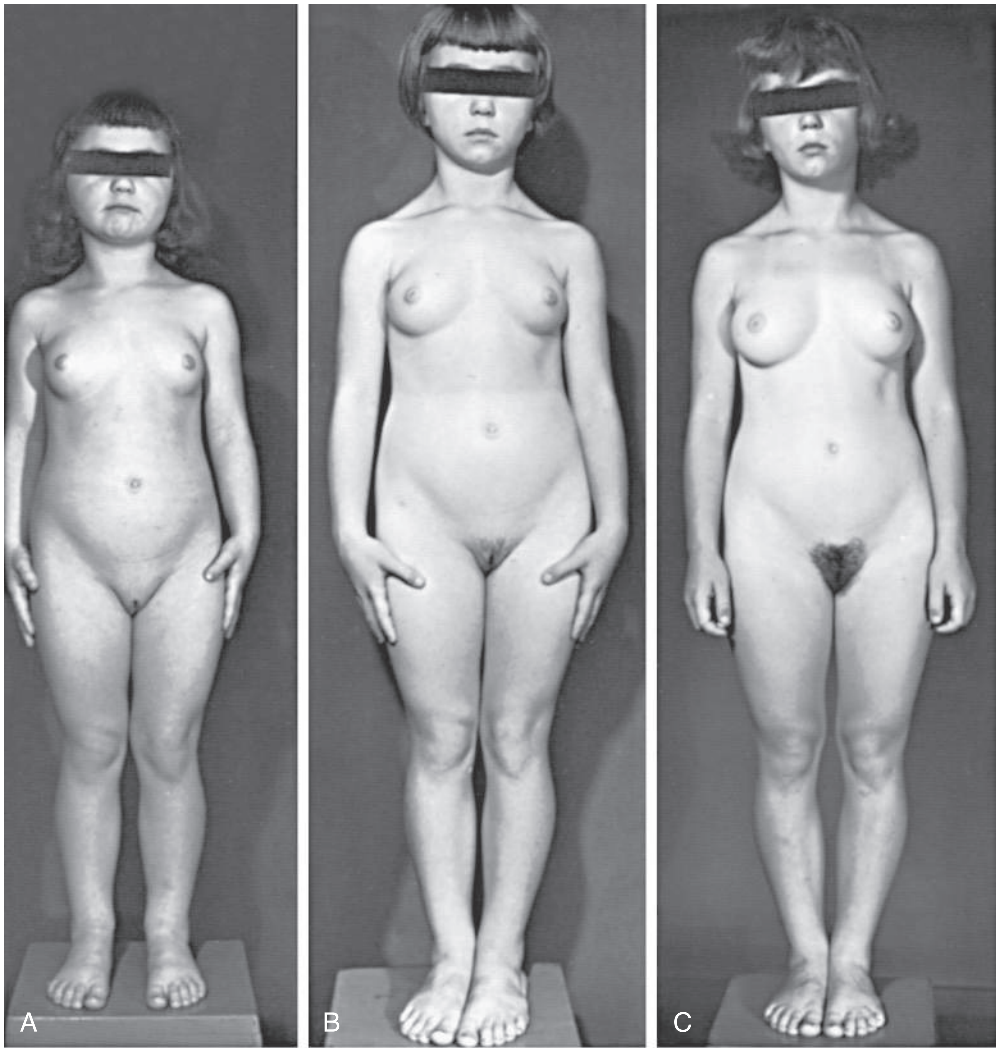

Figure 562-1 Natural course of idiopathic central precocious puberty. Patient **(A)** at $3\frac{11}{12}$, **(B)** at $5\frac{2}{3}$, and **(C)** at 8.5 yr of age. Breast development and vaginal bleeding began at 2.5 yr of age. Bone age was 7.5 yr at $3\frac{11}{12}$ yr of age, and 14 yr at 8 yr of age. Intelligence and dental age were normal for chronological age. Growth was completed at 10 yr; ultimate height was 142 cm (56 in). No effective therapy was available at the time this patient sought medical attention.

puberty is quite rare. This variability in the natural course of sexual precocity underscores the need for longitudinal observation at the onset of sexual development, before treatment is considered.

LABORATORY FINDINGS

Sex hormone concentrations are usually appropriate for the stage of puberty in both sexes. Despite the availability of sensitive and specific (liquid chromatography/tandem mass spectrometry) assays for sex hormones, serum estradiol concentrations are low or undetectable in the early phase of sexual precocity in girls, as they are in normal puberty. In boys, serum testosterone levels are usually detectable or clearly elevated by the time the parents seek medical attention, provided that an early morning blood sample is obtained. With the use of highly sensitive immunofluorometric and chemiluminescent assays, serum luteinizing hormone (LH) concentrations are undetectable in prepubertal children in random blood samples, but become detectable in 50-75% of girls and a higher percentage of boys with central sexual precocity. Unfortunately, a number of hospitals use only moderately sensitive immunoenzymatic assays for LH, and often insensitive assays for estradiol and testosterone, which decrease the diagnostic sensitivity of these measurements. Measurement of LH in serial blood samples obtained during sleep has greater diagnostic power than measurement in a single random sample, and it typically reveals a well-defined pulsatile secretion of LH. Intravenous administration of gonadotropin-releasing hormone (GnRH stimulation test) or a GnRH agonist (leuprolide stimulation test) is a helpful diagnostic tool, particularly for boys, in whom a "pubertal" LH response (LH peak >5 IU/L) with predominance of LH over follicle-stimulating hormone (FSH) tends to occur early in the course of precocious puberty. In girls with sexual precocity, however, the nocturnal LH secretion and the LH response to GnRH or GnRH agonist may be quite low at breast stages II to early III (immunometric LH peak, <5 IU/L), and the LH:FSH ratio may remain low until mid-advanced puberty. In such girls with "low" LH response, the central nature of sexual precocity can be proven by detecting pubertal levels of estradiol (>50 pg/mL), 20-24 hr after stimulation with leuprolide.

Osseous maturation is variably advanced, often by more than 2-3 SD. Pelvic ultrasonography in girls reveals progressive enlargement of the ovaries, followed by enlargement of the fundus and then of the whole uterus to pubertal size. An MRI scan usually demonstrates physiologic enlargement of the pituitary gland, as seen in normal puberty; it may also reveal CNS pathology (see Chapter 562.2).

DIFFERENTIAL DIAGNOSIS

Organic CNS causes of central sexual precocity are more likely in boys, and those girls who have rapid breast development, have estradiol

>30 pg/mL, or are younger than 6 yr of age. All children in these categories should undergo MRI scans of the brain and pituitary gland. Specific criteria for ordering brain imaging in girls older than age 6 yr are still lacking, although some authorities recommend MRI scans for all children with central precocious puberty.

Gonadotropin-independent causes of isosexual precocious puberty must be considered in the differential diagnosis (see Table 562-1). For girls, these include tumors of the ovaries, autonomously functioning ovarian cysts, feminizing adrenal tumors, McCune-Albright syndrome, and exogenous sources of estrogens. In boys, congenital adrenal hyperplasia, adrenal tumors, Leydig cell tumors, chorionic gonadotropin–producing tumors, exposure to exogenous androgens, and familial male precocious puberty should be considered.

TREATMENT

Virtually all boys and the large subgroup of girls with rapidly progressive precocious puberty are candidates for treatment. Girls with slowly progressive idiopathic central precocious puberty do not seem to benefit in terms of height prognosis from GnRH-agonist therapy. Former small-for-gestational-age infants may be at greater risk of short stature as adults and may require more aggressive treatment of precocious puberty, possibly in conjunction with human growth hormone therapy. Certain patients require treatment solely for psychologic or social reasons, including children with special needs and very young girls at risk of early menarche.

The observation that the pituitary gonadotropic cells require pulsatile, rather than continuous, stimulation by GnRH to maintain the ongoing release of gonadotropins provides the rationale for using GnRH agonists for treatment of central precocious puberty. By virtue of being more potent, and having a longer duration of action, than native GnRH, these GnRH agonists (after a brief period of stimulation) "desensitize" the gonadotropic cells of the pituitary to the stimulatory effect of endogenous GnRH and effectively halt the progression of central sexual precocity.

Long-acting formulations of GnRH agonists, which maintain fairly constant serum concentrations of the drug for weeks or months, constitute the preparations of choice for treatment of central precocious puberty. In the United States, the available preparations include: (1) leuprolide acetate (Lupron Depot-Ped), in a dose of 0.25-0.3 mg/kg (minimum 7.5 mg) intramuscularly once every 4 wk; (2) longer-acting preparations of depot leuprolide, allowing for injections (11.25-30.0 mg intramuscularly) every 90 days; and (3) histrelin (Supprelin LA), a subcutaneous 50 mg implant with effects lasting 12 mo. Other preparations (D-Trp6-GnRH [Decapeptyl], goserelin acetate [Zoladex]) are approved for treatment of precocious puberty in other countries. Recurrent sterile fluid collections at the sites of injections are an uncommon local side effect and occur in less than 1-3% of patients treated with depot leuprolide. Breakage or malfunction of the histrelin implant is very rare. Other available treatment options, usually reserved for children who cannot tolerate the products listed above, include subcutaneous injections of aqueous leuprolide, given once or twice daily (total dose 60 μg/kg/24 hr), or intranasal administration of the GnRH agonist nafarelin (Synarel), 800 μg bid. The potential for irregular compliance with daily administration, as well as the variable absorption of the intranasal route for nafarelin, may limit the long-term benefit of the latter preparations on adult height. GnRH antagonists have not been investigated sufficiently and are not FDA approved. Oral GnRH antagonists are also being investigated.

Treatment results in decrease of the growth rate, generally to age-appropriate values, and an even greater decrease of the rate of osseous maturation. Some children, particularly those with greatly advanced (pubertal) bone age, may show marked deceleration of their growth rate and a complete arrest in the rate of osseous maturation. Treatment results in enhancement of the predicted height, although the actual adult height of patients followed to epiphyseal closure is approximately 1 SD less than their midparental height. In girls, breast development may regress in those with Tanner stages II-III development. Most commonly, the size of the breasts remains unchanged in girls with stages III-V development, or may even increase slightly because of progressive adipose tissue deposition. The amount of glandular tissue decreases. Pubic hair usually remains stable in girls, or may progress slowly during treatment, reflecting the gradual increase in adrenal androgens. Menses, if present, cease. Pelvic sonography demonstrates a decrease of the ovarian and uterine size. In boys, there is decrease of testicular size, variable regression of pubic hair, and decrease in the frequency of erections. Except for a reversible decrease in bone density (of uncertain clinical significance), no serious adverse effects of GnRH analogs have been reported in children treated for sexual precocity. If treatment is effective, the serum sex hormone concentrations decrease to prepubertal levels (testosterone, <10-20 ng/dL in boys; estradiol, <5-10 pg/mL in girls). The serum LH and FSH concentrations, as measured by sensitive immunometric assays, decrease to less than 1 IU/L in most patients, although almost never does the LH return to truly prepubertal levels (<0.1 IU/L). Moreover, the incremental FSH and LH responses to GnRH stimulation decrease to less than 2-3 IU/L. Serum LH and sex hormone levels remain suppressed for as long as therapy is continued, but puberty resumes promptly when therapy is discontinued, typically at a "pubertal" chronological age. In girls, menarche generally appears at an average of 18 mo (range: 6-24 mo) of cessation of intramuscular therapy, and somewhat earlier after removal of the histrelin implant. The addition of human growth hormone to GnRH agonists has been used on an investigational basis in children with precocious puberty, markedly advanced bone age, and prediction of short stature. The available, albeit limited, data indicate that combined therapy may increase the adult height.

562.2 Precocious Puberty Resulting from Organic Brain Lesions

Wassim Chemaitilly and Luigi R. Garibaldi

ETIOLOGY

Hypothalamic hamartomas are the most common brain lesion causing central precocious puberty (Fig. 562-2). This congenital malformation consists of ectopically located neural tissue. Glial cells within the hamartoma have been shown to produce transforming growth factor α, which has the potential to activate the GnRH pulse generator. On MRI, it appears as a small pedunculated mass attached to the tuber cinereum or the floor of the third ventricle or, less often, as a sessile mass (Fig. 562-3) that remains static in size over years. Hypothalamic hamartomas, especially the sessile variant, can be associated with gelastic or psychomotor seizures.

A wide variety of other CNS lesions or insults, usually involving the hypothalamus by scarring, invasion, or pressure, are associated with gonadotropin-dependent sexual precocity. They include postencephalitic scars, tuberculous meningitis, tuberous sclerosis, severe head trauma, and hydrocephalus, either isolated or associated with myelomeningocele. Neoplasms causing precocious puberty include astrocytomas, ependymomas, and optic tract tumors. Tumors of the latter type (typically slowly progressive or indolent optic gliomas) are highly prevalent (15-20%) in children with neurofibromatosis type 1 and constitute the main etiologic factor for the central sexual precocity encountered in a small subset (approximately 3%) of children with neurofibromatosis type 1.

Approximately 50% of the tumors in the pineal region are germ cell tumors or astrocytomas; the remainder consist of a wide variety of histologically distinct tumor types. In boys, pineal or hypothalamic germ cell tumors can cause central precocious puberty by secreting human chorionic gonadotropin (hCG), which stimulates the LH receptors in the Leydig cells of the testes (see Chapter 562.5).

CLINICAL MANIFESTATIONS

Some of these tumors or malformations (hypothalamic hamartomas) remain static in size or grow slowly, producing no signs other than precocious puberty. For lesions causing neurologic symptoms, the neuroendocrine manifestations may be present for 1-2 yr before the tumor can be detected radiologically. Hypothalamic signs or symptoms such

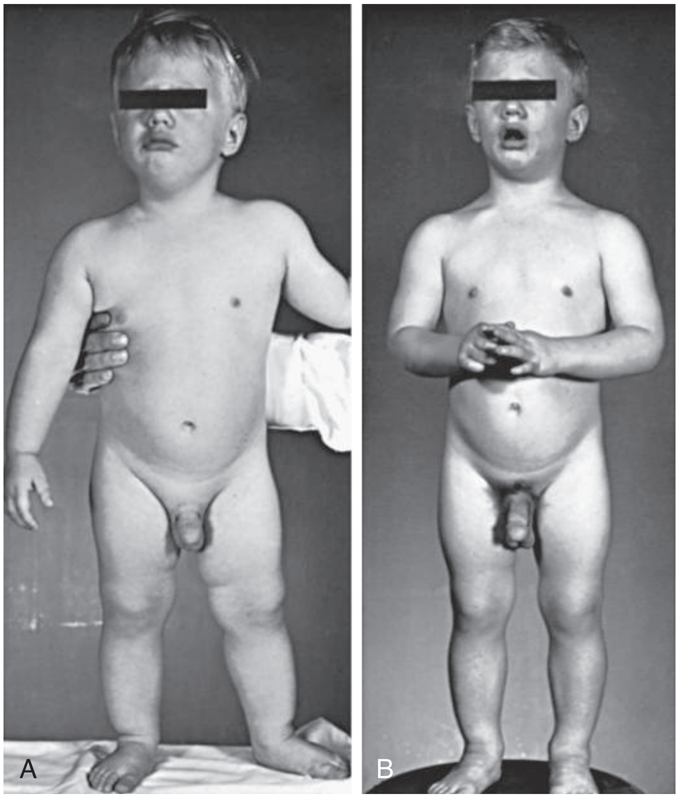

Figure 562-2 **Natural course of precocious puberty with central nervous system lesion.** Photographs at 1.5 **(A)** and 2.5 **(B)** yr of age. Accelerated growth, muscular development, osseous maturation, and testicular development were consistent with the degree of secondary sexual maturation. In early infancy, the patient began having frequent spells of rapid, purposeless motion; later in life, he had episodes of uncontrollable laughing with ocular movements. At 7 yr, he exhibited emotional lability, aggressive behavior, and destructive tendencies. Although a hypothalamic hamartoma had been suspected, it was not established until CT scanning became available when the patient was 23 yr of age. Epiphyses fused at 9 yr of age; final height was 142 cm (56 in). At 24 yr of age, he developed an embryonal cell carcinoma of the retroperitoneum.

as diabetes insipidus, adipsia, hyperthermia, unnatural crying or laughing (gelastic seizures), obesity, and cachexia should suggest the possibility of an intracranial lesion. Visual signs (proptosis, decreased visual acuity, visual field defects) may be the first manifestation of an optic glioma.

The sexual precocity is always isosexual, and the endocrine patterns are generally those found in children without demonstrable organic lesions. Rapidly progressive sexual precocity in very young children suggests the likelihood of a hypothalamic hamartoma. In conditions other than hypothalamic hamartoma, growth hormone deficiency can occur and may be masked by the growth-promoting effect of the increased sex hormone levels.

TREATMENT

Regardless of the cause, therapy with GnRH agonists is as effective in children with organic brain lesions causing central precocious puberty, and these analogs are the therapy of choice to halt premature sexual development. This includes patients with a hypothalamic hamartoma, if precocious puberty is its only manifestation. In patients with hypothalamic hamartoma and associated intractable gelastic or psychomotor seizures, however, stereotactic radiation therapy (gamma knife surgery) is effective and less risky than neurosurgical intervention. For other neurologic lesions, therapy depends on the nature and location of the pathologic process. Combined growth hormone therapy

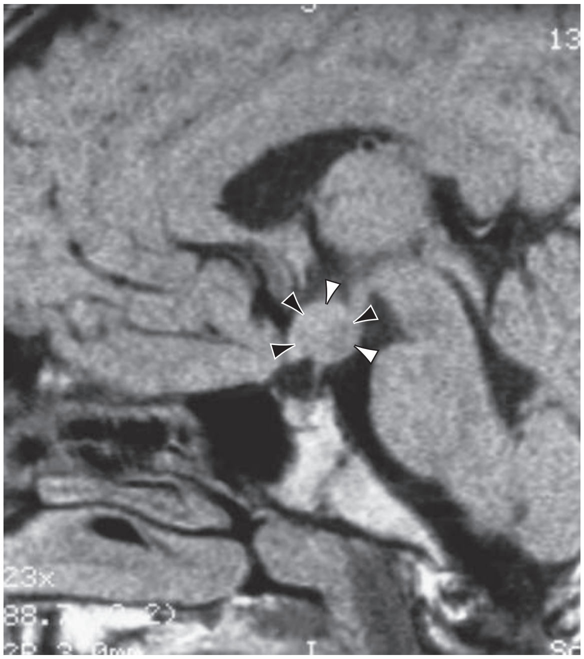

Figure 562-3 **MRI of a central nervous system lesion in a child with central precocious puberty.** A 6 yr old girl was referred for stage IV breast development and growth acceleration. Serum luteinizing hormone and estradiol concentrations were in the adult range. The midsagittal T1-weighted image shows an isointense hypothalamic mass *(arrowheads)*, typical of a hamartoma. *(From Sharafuddin M, Luisiri A, Garibaldi LR, et al: MR imaging diagnosis of central precocious puberty: importance of changes in the shape and size of the pituitary gland,* AJR Am J Roentgenol *162:1167–1173, 1994.)*

should be considered for patients with associated growth hormone deficiency.

562.3 Precocious Puberty Following Irradiation of the Brain

Wassim Chemaitilly and Luigi R. Garibaldi

Radiation therapy, generally for leukemia or intracranial tumors, increases the risk of precocious puberty considerably, whether the irradiation is directed to the hypothalamic area or to areas of the brain anatomically distant from the hypothalamus. Low-dose radiation (18-24 Gy) hastens the onset of puberty almost exclusively in girls. High-dose radiation (25-47 Gy), conversely, appears to trigger precocious sexual development in both sexes, and the risk of sexual precocity is inversely proportional to the age of the child at the time radiation was given.

This type of sexual precocity is often associated with growth hormone deficiency and may also be combined with other conditions (spinal irradiation, hypothyroidism) adversely affecting the prognosis for a reasonable adult height. Unless careful attention is paid to early signs of pubertal development in these children, the combination of growth hormone deficiency and the growth-promoting effect of sex steroids often results in a "normal" growth rate at the expense of a rapidly advancing bone age and impaired adult height potential.

TREATMENT

GnRH analogs are effective in arresting pubertal progression in this patient population. However, concomitant growth hormone deficiency (and/or thyroid hormone deficiency) should be diagnosed and treated promptly in order for the adult height prognosis to improve.

Paradoxically, hypopituitarism with gonadotropin deficiency may subsequently develop as a late effect of high-dose CNS irradiation in patients with or without a history of precocious puberty, and it may require substitution therapy with sex steroids.

562.4 Syndrome of Precocious Puberty and Hypothyroidism

Luigi R. Garibaldi and Wassim Chemaitilly

In children with untreated hypothyroidism, the onset of puberty is usually delayed until epiphyseal maturation reaches 12-13 yr of age. Precocious puberty in a child with untreated hypothyroidism and a prepubertal bone age presents a strikingly unphysiologic association, yet is common and may occur in as many as 50% of children with severe hypothyroidism of long duration. These children have the usual manifestations of hypothyroidism, including retardation of growth and of osseous maturation (see Chapter 565). The cause of the hypothyroidism is usually Hashimoto thyroiditis, which often goes undiagnosed, especially in children with special needs such as those with trisomy 21, in whom the symptoms of profound hypothyroidism may be more difficult to recognize. Sexual development in girls consists of breast enlargement and menstrual bleeding; the latter may occur even in girls with minimal breast enlargement. Pelvic sonography may reveal large, multicystic ovaries. Boys have testicular enlargement associated with modest or no penile enlargement. No pubic hair development occurs in either girls or boys. Enlargement of the sella, which is typical of long-standing primary hypothyroidism, may be demonstrated by skull film or MRI. Plasma levels of thyroid-stimulating hormone (TSH) are markedly elevated, often greater than 500 μU/mL, and those of prolactin and estradiol are mildly elevated. Although serum FSH is low and LH is undetectable, when measured by specific assays, the massively elevated concentrations of TSH appear to interact with the FSH receptor ("specificity spillover"), thus inducing FSH-like effects in the absence of LH effects on the gonads. The FSH-like effect suffices to induce estradiol secretion by the ovaries, while in boys testicular enlargement occurs without substantial testosterone secretion. Thus, the precocious puberty associated with hypothyroidism behaves as an incomplete form of gonadotropin-dependent puberty. Treatment of the hypothyroidism results in rapid return to normal of the biochemical and clinical manifestations. Possible progression to central puberty with rapid bone age advancement could occur in the months following the initiation of thyroid hormone replacement, a complication that would justify delaying puberty with GnRH analogs. Macroorchidism (testicular volume >30 mL) may persist in adult males despite adequate levothyroxine therapy.

562.5 Chorionic Gonadotropin-Secreting Tumors

Luigi R. Garibaldi and Wassim Chemaitilly

These are rare tumors, whose secretion of hCG stimulates the LH receptors in the Leydig cells. The testicles are only minimally enlarged, and the histology reveals interstitial cell hyperplasia with no spermatogenesis. Plasma levels of testosterone are elevated, while those of FSH and LH, as measured by specific immunometric assays, are low. These tumors induce puberty in boys but not in girls, as ovarian production of estrogens cannot take place in the absence of FSH stimulation.

HEPATIC TUMORS

All reported cases of **hepatoblastoma** causing isosexual precocious puberty have been in boys, with the average age of onset of 2 yr (range: 4 mo to 8 yr). An enlarged liver or mass in the right upper quadrant should suggest the diagnosis. Plasma levels of hCG and α-fetoprotein are usually markedly elevated and serve as useful markers for following the effects of therapy. Similarly to other carcinomas of the liver; the prognosis for survival beyond 1-2 yr from the time of diagnosis is poor.

INTRACRANIAL TUMORS

Nongerminomatous or mixed germ cell tumors, choriocarcinomas, teratomas, teratocarcinomas, and others account for <5% of intracranial tumors. They are usually located in the neurohypophyseal area or the pineal area and may cause precocious puberty in boys if they secrete hCG, and rarely in girls because of mass effect. Marked elevations of hCG and α-fetoprotein often occur in the cerebrospinal fluid, although elevations in the blood may be modest. Treatment includes radiation, chemotherapy, and debulking surgery.

TUMORS IN OTHER LOCATIONS

Very rare locations include the mediastinum, gonads, or even adrenal glands. Mediastinal tumors have been reported to cause precocious puberty in boys with Klinefelter syndrome.

PERIPHERAL PRECOCIOUS PUBERTY

The adrenal causes of pseudopuberty are discussed in Chapter 576, and the gonadal causes are discussed in Chapters 584 and 587.

562.6 McCune-Albright Syndrome (Precocious Puberty with Polyostotic Fibrous Dysplasia and Abnormal Pigmentation)

Wassim Chemaitilly and Luigi R. Garibaldi

This syndrome of endocrine dysfunction is associated with patchy cutaneous pigmentation and fibrous dysplasia of the skeletal system. It is a rare condition with a prevalence between 1 in 100,000 and 1 in 1,000,000 people. A classical cause of peripheral precocious puberty, it can also induce pituitary, thyroid, and adrenal aberrations. It is characterized by autonomous hyperfunction of many glands and is caused by a missense mutation in the gene encoding the α-subunit of G_S, the G protein that stimulates cyclic adenosine monophosphate formation, resulting in the formation of the putative gsp oncoprotein. Activation of receptors (corticotropin [adrenocorticotropic hormone (ACTH)], TSH, FSH, and LH receptors) that operate via a cyclic adenosine monophosphate–dependent mechanism, as well as cell proliferation, ensue. Because the mutation is somatic rather than genomic, it is expressed differently in different tissues; hence the variability of clinical expression. Precocious puberty has been described predominantly in girls (Fig. 562-4). The average age at onset in affected girls is about 3 yr, but vaginal bleeding has occurred as early as 4 mo of age and secondary sex characteristics have occurred as early as 6 mo. Young girls have suppressed levels of LH and FSH, and there is no response to GnRH or leuprolide stimulation. Estradiol levels vary from normal to markedly elevated (>900 pg/mL), are often cyclic, and may correlate with the size of the recurrent ovarian cysts. In boys, precocious puberty is less common but has been reported in several instances. Unlike ovarian enlargement in girls, testicular enlargement in boys is fairly symmetric. It is followed by the appearance of phallic enlargement and pubic hair, as in normal puberty. Testicular histology has demonstrated large seminiferous tubules and no or minimal Leydig cell hyperplasia; these findings may simply reflect the fact that biopsy specimens were obtained at an early stage of pubertal development. In girls and boys, when the bone age reaches the usual pubertal age range, gonadotropin secretion begins, and the response to GnRH becomes pubertal. Central precocious puberty overrides the antecedent (gonadotropin-independent) precocious pseudopuberty. In girls, menses become more regular, but often not completely so, and fertility has been documented.

Pubertal progression is variable in these patients. Functioning ovarian cysts often disappear spontaneously; aspiration or surgical excision of cysts is rarely indicated, but ovarian torsion may occur.

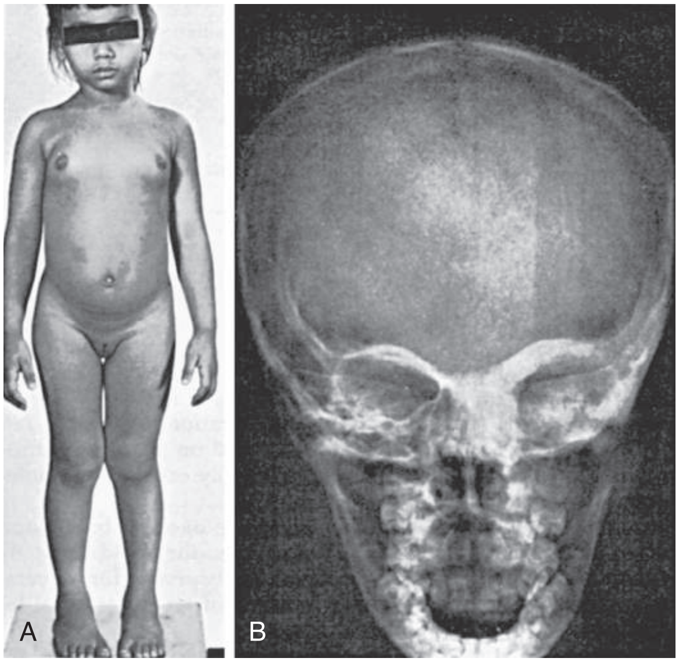

Figure 562-4 Precocious puberty associated with polyostotic fibrous dysplasia (McCune-Albright syndrome) in a girl 4.5 yr of age; at this time, her height age and bone age were normal. Menarche occurred at 4 yr of age. **A,** Note the bilateral breast development, hyperpigmented spots on the abdomen, and prominence of the left side of the face. **B,** Roentgenograms revealed fibrous dysplasia in the distal end of the left ulna and thickening of the bones about the left orbit and the maxillary portion of the frontal bones shown here.

For girls with persistent estradiol secretion, agents that interfere with the final step of estrogen biosynthesis (i.e., aromatase inhibitors such as letrozole [1.25-2.5 mg/day orally]) or antiestrogens (such as tamoxifen 5-20 mg/day orally) may limit, to a variable extent, the estrogen effects on pubertal and osseous maturation. The same compounds have also been used in boys, in combination with antiandrogens (such as spironolactone 50-100 mg bid, flutamide 125-250 mg bid, or bicalutamide 25-50 mg daily). These compounds are not approved by the FDA for this indication; tamoxifen, flutamide, and bicalutamide may be hepatotoxic, and high-dose spironolactone may (rarely) cause hyperkalemia. Associated therapy with long-acting analogs of GnRH is indicated only for patients whose puberty has shifted from a gonadotropin-independent to a predominantly gonadotropin-dependent mechanism.

EXTRAGONADAL MANIFESTATIONS

The hyperthyroidism that occurs in this condition differs from that characteristic of Graves disease. There is an equal distribution between male and female patients; the goiters are multinodular. Clinical hyperthyroidism is uncommon in children, but goiters, mildly elevated triiodothyronine levels, suppressed TSH levels, and abnormalities on ultrasound have been reported. Thyroidectomy is rarely necessary.

In patients with associated Cushing syndrome, bilateral nodular adrenocortical hyperplasia has occurred in early infancy, antedating the sexual precocity. ACTH levels are low, and adrenal function is not suppressed by large doses of dexamethasone. Treatment is bilateral adrenalectomy.

Increased secretion of growth hormone occurs uncommonly and is manifested clinically by gigantism or acromegaly or by increased rates of growth even in the absence of precocious puberty. Girls and boys are equally affected. Serum levels of growth hormone are elevated, increase during sleep, and are poorly inhibited by oral glucose. Serum levels of prolactin are increased in most patients, but fewer than 50% of the patients have a demonstrable pituitary tumor. Depot octreotide (Sandostatin LAR Depot 10-30 mg IM monthly) or Lanreotide (Somatuline Depot, 60-90 mg SC monthly), long-acting somatostatin analogs, can be used to treat the hypersomatotropism. The prognosis is favorable for longevity, but deformities, repeated fractures, pain, and occasional cranial nerve compression may result from the bony lesions.

Of the extraglandular manifestations, phosphaturia, leading to rickets or osteomalacia, is the most common. Cardiovascular and hepatic involvement is rare but may be life-threatening (severe neonatal cholestasis).

562.7 Familial Male Gonadotropin-Independent Precocious Puberty

Wassim Chemaitilly and Luigi R. Garibaldi

This rare, autosomal dominant form of peripheral precocious puberty is transmitted from affected males and unaffected female carriers of the gene to their male offspring. Signs of puberty appear by 2-3 yr of age. The testes are only slightly enlarged. Testicular biopsies show Leydig cell maturation and, sometimes, marked hyperplasia. Maturation of seminiferous tubules may be present. Testosterone levels are variably and often markedly elevated, even above the adult male range; however, baseline levels of LH are prepubertal, pulsatile secretion of LH is absent, and LH does not respond to stimulation with GnRH or GnRH agonist. The cause for activation of Leydig cells independently of gonadotropin stimulation is a missense mutation of the LH receptor leading to constitutive activation of cyclic adenosine monophosphate production. Osseous maturation may be markedly advanced; when it reaches the pubertal age range, hypothalamic maturation shifts the mechanism of pubertal development to a gonadotropin-dependent one. This sequence of events is similar to that occurring in children with McCune-Albright syndrome (see Chapter 562.6) or in those with congenital adrenal hyperplasia (see Chapter 576.1).

Gonadotropin-independent precocious puberty has been diagnosed in a few unrelated boys with type IA pseudohypoparathyroidism who had a single mutation of the $G_s\alpha$ protein. This mutation is inactivating at normal body temperature and causes pseudohypoparathyroidism, but in the cooler temperature of the testes, it is constitutionally activating, resulting in adenyl cyclase stimulation and production of testosterone. Although this mutation differs from the constitutive LH receptor mutation, which usually causes familial male gonadotropin-independent precocious puberty, the end result is the same.

TREATMENT

Young boys have been successfully treated with ketoconazole (600 mg/24 hr in 8 hr divided doses), an antifungal drug that inhibits C-17,20-lyase and testosterone synthesis. Other investigators use a combination of antiandrogens (such as spironolactone 50-100 mg twice a day, flutamide 125–250 mg twice a day, or bicalutamide 25-50 mg daily) and aromatase inhibitors (letrozole 2.5 mg/day, or anastrozole 1 mg/day), because estrogens derived from androgens stimulate bone maturation. These medications are unable to revert the serum testosterone to the normal (prepubertal) concentrations or completely offset the unfavorable effects of the elevated sex hormones. They slow down, but do not halt, the progression of puberty and may not improve the height prognosis. Boys whose GnRH pulse generator has matured require combined therapy with GnRH agonists.

562.8 Incomplete (Partial) Precocious Development

Luigi R. Garibaldi and Wassim Chemaitilly

Isolated manifestations of precocity without development of other signs of puberty are not unusual; development of the breasts in girls and growth of sexual hair in both sexes are the 2 most common forms.

PREMATURE THELARCHE

This term applies to a sporadic, transient condition of isolated breast development that most often appears in the 1st 2 yr of life. In some girls, breast development is present at birth and persists. It may be unilateral or asymmetric and often fluctuates in degree. Growth and osseous maturation are normal or slightly advanced. The genitalia show no evidence of estrogenic stimulation. Breast development may regress after 2 yr, often persists for 3-5 yr, and is rarely progressive. Menarche occurs at the expected age, and reproduction is normal. Basal serum levels of FSH and the FSH response to GnRH stimulation may be greater than that seen in normal controls. Plasma levels of LH and estradiol are consistently less than the limits of detection. Ultrasound examination of the ovaries reveals normal size, but a few small (<9 mm) cysts are not uncommon.

In some girls, breast development may be associated with definite evidence of systemic estrogen effects, such as growth acceleration or bone age advancement. Pelvic sonography may reveal enlarged ovaries or uterus. This condition, referred to as **exaggerated or atypical thelarche,** differs from central precocious puberty because it spontaneously regresses. Leuprolide or GnRH stimulation elicits a robust FSH response, a low LH response, and (after leuprolide only) a moderate estradiol increment at 24 hr (average: 60-90 pg/mL). The pathogenesis of typical and exaggerated forms of thelarche is unclear. Delayed inactivation of the hypothalamic-pituitary-ovarian axis, which is active during the prenatal and early postnatal period, increased peripheral sensitivity to estrogens, and other possibilities have been proposed, yet are unproven hypotheses. Premature thelarche is a benign condition but may be the first sign of true or peripheral precocious puberty, or it may be caused by exogenous exposure to estrogens. In addition to a detailed history, a bone age should be obtained if there are any unusual features. Random serum concentrations of FSH, LH, and estradiol are generally low and not diagnostic. Pelvic ultrasound examination or leuprolide stimulation testing is rarely indicated. Continued observation is important because the condition cannot be readily distinguished from true precocious puberty. Regression and recurrence suggest functioning follicular cysts. Occurrence of thelarche in children older than 3 yr of age most often is caused by a condition other than benign premature thelarche.

PREMATURE PUBARCHE (ADRENARCHE)

Premature adrenarche has traditionally applied to the appearance of sexual hair before the age of 8 yr in girls or 9 yr in boys without other evidence of maturation. It is much more frequent in girls than in boys. The higher prevalence of this condition in African-American and, to a smaller extent, Latino girls in comparison to white girls may suggest that the cutoff age for the definition of "premature" should be adjusted for different ethnic groups on the basis of epidemiologic data. Hair appears on the mons and labia majora in girls and perineal and scrotal area in boys; axillary hair generally appears later. Adult-type axillary odor is common. Affected children are often slightly advanced in height and osseous maturation. Premature adrenarche is an early maturational event of adrenal androgen production. This event coincides with precocious maturation of the zona reticularis, an associated decrease in 3β-hydroxysteroid dehydrogenase activity, and an increase in C-17,20-lyase activity. These enzymatic changes result in increased basal and ACTH-stimulated serum concentrations of the Δ^5-steroids (17-hydroxypregnenolone and dehydroepiandrosterone) and, to a lesser extent, of the Δ^4-steroids (particularly androstenedione) compared with age-matched control subjects. The levels of these steroids and of dehydroepiandrosterone sulfate are usually comparable to those of older children in the early stages of normal puberty. Idiopathic premature adrenarche is a slowly progressive condition that requires no therapy. However, a subset of patients with precocious pubarche has 1 or more features of systemic androgen effect, such as marked growth acceleration, clitoral (girls) or phallic (boys) enlargement, cystic acne, or advanced bone age (>2 SD above the mean for age). In these patients with **atypical premature adrenarche,** an ACTH stimulation test with measurement of steroid intermediates (mainly, serum 17-hydroxyprogesterone concentrations) is indicated to rule out nonclassical congenital adrenal hyperplasia caused by 21-hydroxylase deficiency. Epidemiologic and molecular genetic studies show that the prevalence of nonclassical 21-hydroxylase deficiency is approximately 3-6% of unselected children with precocious pubarche; the prevalence of other enzyme defects (i.e., 3β-hydroxysteroid dehydrogenase or 11β-hydroxylase deficiency) is extremely low. Although idiopathic premature adrenarche has been considered a benign condition, longitudinal observations suggest that approximately 50% of girls with premature adrenarche are at high risk for **hyperandrogenism** and **polycystic ovary syndrome,** alone or more often in combination with other components of the so-called metabolic syndrome (insulin resistance possibly progressing to type 2 diabetes mellitus, dyslipidemia, hypertension, increased abdominal fat) as adults. Whether the unfavorable progression to pubertal hyperandrogenism can be prevented by insulin-sensitizing agents (metformin 850-1,000 mg/day) or lifestyle interventions (diet, exercise) remains to be proven in large studies. An increased risk of premature adrenarche and the metabolic syndrome is documented in children born small for their gestational age. This appears to be associated with insulin resistance and decreased β-cell reserve, perhaps as a consequence of fetal undernutrition.

PREMATURE MENARCHE

This is a rare entity, much less frequent than premature thelarche or premature adrenarche, and is a diagnosis of exclusion. In girls with isolated vaginal bleeding in the absence of other secondary sexual characteristics, more common causes, such as vulvovaginitis, a foreign body (typically associated with malodorous discharge), or sexual abuse, and uncommon causes, such as urethral prolapse and sarcoma botryoides, must be carefully excluded. The majority of girls with idiopathic premature menarche have only 1-3 episodes of bleeding; puberty occurs at the usual time, and menstrual cycles are normal. Plasma levels of gonadotropins are low, but estradiol levels may be occasionally elevated, probably owing to episodic ovarian estrogen secretion associated with ovarian follicular cysts that can be detected on ultrasound.

562.9 Medicational Precocity

Luigi R. Garibaldi and Wassim Chemaitilly

A variety of medicaments can induce the appearance of secondary sexual characteristics that may be confused with precocious puberty. A careful history focused on exploring the possibility of accidental exposure to, or ingestion of, sex hormones is important. Peripheral precocious puberty has occurred in boys and girls from the accidental ingestion of estrogens (including contraceptive pills) and from the administration of anabolic steroids. The most common cause of medicational precocity is currently related to the widespread use of testosterone gels or creams that are applied to the skin for treatment of male hypogonadism. This has resulted in virilization of children and women following skin contact at, and systemic absorption from, the area where the gel/cream was applied by their family member.

Less commonly, estrogens in cosmetics, hair creams, and breast augmentation creams have caused breast development in girls and gynecomastia in boys, via percutaneous absorption. The high prevalence of premature thelarche and peripheral precocious puberty in Puerto Rico has been attributed to contamination of meats, particularly chicken, with estrogens used in animal husbandry, but has not been proved. Exogenous estrogens may produce a darkening of the areola that is not usually seen in endogenous types of precocity. The precocious changes disappear after cessation of exposure to the hormones.

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Section 2

Disorders of the Thyroid Gland

Chapter 563

Thyroid Development and Physiology

Stephen H. LaFranchi and Stephen A. Huang

FETAL DEVELOPMENT

The fetal thyroid arises from an outpouching of the foregut at the base of the tongue (foramen cecum). It migrates to its normal location over the thyroid cartilage by 8-10 wk of gestation. The thyroid bilobed shape is recognized by 7 wk of gestation, and characteristic thyroid follicle cell and colloid formation is seen by 10 wk. Thyroglobulin synthesis occurs from 4 wk, iodine trapping occurs by 8-10 wk, and thyroxine (T_4) and, to a lesser extent, triiodothyronine (T_3) synthesis and secretion occur from 12 wk of gestation. There is evidence that several transcription factors—TTF-1/NKX-2.1, TTF-2 (also termed FOXE1), NKX2.5, and PAX8—are important in thyroid gland morphogenesis and differentiation, and possibly also in its caudal migration to its final location. These factors also bind to the promoters of thyroglobulin and thyroid peroxidase genes and so influence thyroid hormone production. Hypothalamic neurons synthesize thyrotropin-releasing hormone (TRH) by 6-8 wk, the pituitary portal vessel system begins development by 8-10 wk, and thyroid-stimulating hormone (TSH) secretion is evident by 12 wk of gestation. Maturation of the hypothalamic-pituitary-thyroid axis occurs over the second half of gestation, but normal feedback relationships are not mature until approximately 3 mo of postnatal life. Other transcription factors, including PROP-1 and Pit-1, are important for differentiation and growth of thyrotrophs, along with somatotrophs and lactotrophs.

THYROID PHYSIOLOGY

The main function of the thyroid gland is to synthesize T_4 and T_3. The only known physiologic role of iodine (or iodide [I^-] in its ionized form) is in the synthesis of these hormones; the recommended dietary allowance of iodine is 30 µg/kg/24 hr for infants, 90-120 µg/24 hr for children, and 150 µg/24 hr for adolescents and adults.

The median iodine intake in the United States decreased by approximately 50% between the 1970s (320 µg/L) and the 1990s (145 µg/L), but it now appears to have stabilized (2009-2010 = 144 µg/L). Whatever the chemical form ingested, iodine eventually reaches the thyroid gland as iodide. Thyroid tissue has an avidity for iodide and is able to trap (with a gradient of 100 : 1), transport, and concentrate it in the follicular lumen for synthesis of thyroid hormone. Entry of iodide from the circulation into the thyroid is carried out by the sodium–iodide symporter. Iodide diffuses across the cell to the apical membrane where it is transported into the colloid via pendrin.

Before trapped iodide can react with tyrosine, it must be oxidized; this reaction is catalyzed by **thyroidal peroxidase.** Dual oxidase maturation factor 2 **(DUOXA2)** is required to express **DUOX2** enzymatic activity, which is required for H_2O_2 generation, a crucial step in iodide oxidation. The thyroid cells produce **thyroglobulin**, a large globular glycoprotein with a molecular weight of approximately 660,000, containing approximately 120 tyrosine units. Iodination of tyrosine forms monoiodotyrosine and diiodotyrosine; 2 molecules of diiodotyrosine then couple to form 1 molecule of T_4, or 1 molecule of diiodotyrosine and 1 of monoiodotyrosine to form T_3. Once formed, hormones are stored as thyroglobulin in the lumen of the follicle (colloid) until ready to be delivered to the body cells. T_4 and T_3 are liberated from thyroglobulin by activation of proteases and peptidases.

The metabolic potency of T_3 is 3-4 times that of T_4. In adults, the thyroid produces approximately 100 µg of T_4 and 20 µg of T_3 daily. Only 20% of circulating T_3 is secreted by the thyroid; the remainder is produced by deiodination of T_4 in the liver, kidney, and other extrathyroidal tissues by type I 5′-deiodinase. Selenocysteine is the active center of the iodothyronine deiodinases. Thus, selenium indirectly plays a role in normal growth and development. In the pituitary and brain, approximately 80% of required T_3 is produced locally from T_4 by a different enzyme, type II 5′-deiodinase. The level of T_3 in blood is one fiftieth that of T_4, but T_3 is the physiologically active thyroid hormone.

Thyroid hormones increase oxygen consumption, stimulate protein synthesis, influence growth and differentiation, and affect carbohydrate, lipid, and vitamin metabolism. Specific thyroid hormone transporters, of which the most important is monocarboxylate transporter 8, facilitate entry of T_4 and T_3 into cells. Once into the cell, T_4 is converted to T_3 by type I or II 5′-deiodinase. Intracellular T_3 then enters the nucleus, where it binds to thyroid hormone receptors. Thyroid hormone receptors are members of the steroid hormone receptor superfamily that includes glucocorticoids, estrogen, progesterone, vitamin D, and retinoids. Four different isoforms of the thyroid hormone receptor (α_1, α_2, β_1, and β_2) are expressed in different tissues; the protein product of the formerly designated c-*erb* A protooncogene *(THRA2)* is the α_2 thyroid hormone receptor in the brain and hypothalamus. Thyroid hormone receptors consist of a ligand-binding domain (binds T_3), hinge region, and DNA-binding domain (zinc finger). Binding of T_3 activates the thyroid hormone receptor response element, resulting in production of an encoded messenger RNA and protein synthesis specific for the target cell. In this manner, a single hormone, T_4, acting through tissue-specific thyroid hormone receptor isoforms and gene-specific thyroid response elements, can produce multiple effects in various tissues.

Approximately 70% of the circulating T_4 is firmly bound to T_4-binding globulin (TBG). Less-important carriers are T_4-binding prealbumin, called *transthyretin*, and albumin. Only 0.03% of T_4 in serum is not bound and comprises free T_4. Approximately 50% of circulating T_3 is bound to TBG, and 50% is bound to albumin; 0.30% of T_3 is unbound, or free, T_3. Because the concentration of TBG is altered in many clinical circumstances, its status must be considered when interpreting total T_4 or T_3 levels.

THYROID REGULATION

The thyroid is regulated by TSH, a glycoprotein produced and secreted by the anterior pituitary. This hormone activates adenylate cyclase in the thyroid gland and is important in all steps of thyroid hormone biosynthesis, from trapping of iodine to release of thyroid hormones. TSH is composed of 2 noncovalently bound subunits (chains): α and β. The α subunit is common to luteinizing hormone, follicle-stimulating hormone, and chorionic gonadotropin; the specificity of each hormone is conferred by the β subunit. TSH synthesis and release are stimulated by TRH, which is synthesized in the hypothalamus and secreted into the pituitary. TRH is found in other parts of the brain besides the hypothalamus and in many other organs; aside from its endocrine function, it may be a neurotransmitter. TRH is a simple tripeptide. In states of decreased production of thyroid hormone, TSH and TRH are increased. Exogenous thyroid hormone or increased thyroid hormone synthesis inhibits TSH and TRH production. Except in the neonate, levels of TRH in serum are very low.

Further control of the level of circulating thyroid hormones occurs in the periphery. In many nonthyroidal illnesses, extrathyroidal production of T_3 decreases; factors that inhibit T_4-type I 5′-deiodinase include fasting, chronic malnutrition, acute illness, and certain drugs. Such factors increase type III 5′-deiodinase conversion of T_4 to reverse T_3. Whereas levels of T_3 may be significantly decreased, levels of free

T_4 and TSH may remain normal. The decreased levels of T_3 may be a physiologic adaptation, resulting in decreased rates of oxygen production, of substrate use, and of other catabolic processes.

Bibliography is available at Expert Consult.

563.1 Thyroid Hormone Studies

Stephen H. LaFranchi

SERUM THYROID HORMONES

Methods are available to measure all the thyroid hormones in serum: T_4, free T_4, T_3, and free T_3. A metabolically inert T_3 (3,5′,3′-triiodothyronine), called reverse T_3, is also present in serum. Age must be considered in interpreting results, particularly in the neonate.

Thyroglobulin is a glycoprotein that is secreted through the apical surface of the thyroid follicular cell into the colloid. Small amounts escape into the circulation and are measurable in serum. Levels increase with TSH (also called *thyrotropin*) stimulation and decrease with TSH suppression. Serum thyroglobulin levels are increased in the neonate, in patients with Graves disease and other forms of autoimmune thyroid disease, and in those with endemic goiter. The most marked elevations of thyroglobulin occur in patients with differentiated carcinoma of the thyroid. Athyreotic infants have markedly reduced levels of thyroglobulin in serum.

Serum TSH levels are the most accurate test of thyroid function. Serum TSH levels are elevated in primary hypothyroidism and suppressed in hyperthyroidism. After the neonatal period, normal levels of TSH are <6 mIU/L. With central (secondary) hypothyroidism, serum TSH may be subnormal, though often it is "inappropriately" in the normal range, despite a low serum T_4 or free T_4 level. TSH appears to be less biologically active in central hypothyroidism. These sensitive (third-generation) TSH assays obviate the need for TRH stimulation in the diagnosis of most patients with thyroid disorders.

FETAL AND NEWBORN THYROID

Fetal serum T_4 and free T_4 increase progressively from midgestation to approximately 11.5 µg/dL and 1.5 ng/dL, respectively, at term. Fetal levels of T_3 are low before 20 wk and then gradually increase to approximately 45 ng/dL at term. Reverse T_3 levels (inactive form of T_3), however, are high in the fetus (250 ng/dL at 30 wk) and decrease to 150 ng/dL at term. Serum levels of TSH gradually increase to 10 mU/L at term. Approximately one third of maternal T_4 crosses the placenta to the fetus. Maternal T_4 plays a role in fetal development, especially that of the brain, before the synthesis of fetal thyroid hormone begins. The fetus of a hypothyroid mother may be at risk for neurologic injury, and a hypothyroid fetus may be partially protected by maternal T_4 until delivery. The amount of T_4 that crosses the placenta is not sufficient to interfere with a diagnosis of congenital hypothyroidism in the neonate.

At birth, there is an acute release of TSH; peak serum concentrations reach 60 mU/L 30 min following delivery in full-term infants. A rapid decline occurs in the ensuing 24 hr and a more gradual decline over the next 5 days to <10 mIU/L. The acute increase in TSH produces a dramatic increase in levels of T_4 to approximately 16 µg/dL and of T_3 to approximately 300 ng/dL in about 4 hr. This T_3 seems largely derived from increased peripheral conversion of T_4 to T_3. T_4 levels gradually decrease during the 1st 2 wk of life to 12 µg/dL. T_3 levels decline during the 1st wk of life to levels below 200 ng/mL. Serum free T_4 levels are 0.9-2.3 ng/dL in infancy and decline to 0.7-1.8 ng/dL in childhood. Serum free T_3 concentrations are approximately 180-760 pg/dL in infancy and decline to 230-650 pg/dL in childhood. Reverse T_3 levels are maintained for 2 wk (200 ng/dL) and decrease by 4 wk to around 50 ng/dL. In preterm infants, changes in thyroid function after birth are qualitatively similar to but quantitatively smaller than in full-term infants. Serum T_4 and T_3 levels are decreased in proportion to gestational age and birthweight.

SERUM THYROXINE-BINDING GLOBULIN

The thyroid hormones are transported in plasma bound to TBG, a glycoprotein synthesized in the liver. Estimation of TBG levels is occasionally necessary because TBG is increased or decreased in a variety of clinical situations, with effects on the level of total T_4 and T_3. TBG binds approximately 70% of T_4 and 50% of T_3. TBG levels increase in pregnancy, in the newborn period, with hepatitis, and with administration of estrogens (oral contraceptives), selective estrogen receptor modulators, heroin or methadone, mitotane, 5-fluorouracil, and perphenazine, and they decrease with androgens, anabolic steroids, glucocorticoids, nicotinic acid, and L-asparaginase. These effects are the results of modulation of hepatic synthesis of TBG. TBG levels may be markedly decreased owing to decreased production with hepatocellular disease or loss in the gut with protein-losing enteropathies or in urine, as in the congenital nephrotic syndrome. Decreased or increased levels of TBG also occur as genetic traits (see Chapter 564).

Some drugs, in particular phenytoin, carbamazepine, furosemide, salicylates, nonsteroidal antiinflammatory drugs, and heparin, also inhibit binding of T_4 and T_3 to TBG. In addition, phenytoin and carbamazepine cause abnormalities of thyroid function tests by another mechanism. They stimulate hepatic cytochrome P450 degradation of T_4 and accelerate transport of T_4 into tissues.

IN VIVO RADIONUCLIDE STUDIES

Markedly improved direct tests of thyroid function have made radioiodine uptake studies less necessary. The iodine trapping or concentrating mechanism of the thyroid can be evaluated by measuring the uptake of radioactive isotope ^{123}I (half-life: 13 hr). The technology allows doses of radioiodine (0.1-0.5 mCi) that are only a fraction of those used with ^{131}I. Technetium (^{99m}Tc) is a particularly useful radioisotope for children because in contrast to iodine, it is trapped but not organified by the thyroid and has a half-life of only 6 hr. Thyroid scanning may be indicated to assess the presence of thyroid tissue in questions of thyroid dysgenesis and to detect ectopic thyroid tissue, and thyroid uptake may be indicated to evaluate possible "hot" thyroid nodules. Diagnostic studies should be performed with ^{99m}Tc pertechnetate or ^{123}I because they have the advantages of lower radiation exposure and high-quality scintigrams. Radioiodine treatment, which may be used to treat children with Graves hyperthyroidism or differentiated thyroid cancer, employs administration of ^{131}I, which has a longer half-life (8 days) and greater killing effect.

THYROID ULTRASONOGRAPHIC STUDIES

Thyroid ultrasound examinations can determine the location, size, and shape of the thyroid gland, and they are useful for assessing the solid or cystic nature of nodules. Ultrasound is not as reliable as radionuclide studies in evaluating infants with suspected thyroid dysgenesis, particularly ectopic glands. Ultrasound examinations are useful in identifying normal thyroid gland position in children with suspected thyroglossal duct cysts. In children with autoimmune thyroiditis, ultrasound reveals scattered hypoechogenicity. Ultrasound examinations are more accurate than physical examination in estimating goiter size and assessing thyroid nodules. Certain characteristics of thyroid nodules, such as blurred margins, microcalcifications, hypoechogenicity, taller-than-wide shape, capsular extension, and increased vascularity, increase the likelihood of thyroid cancer, although none of these features is 100% sensitive or specific.

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Chapter **564**

Defects of Thyroxine-Binding Globulin

Stephen H. LaFranchi and Stephen A. Huang

Abnormalities in levels of thyroxine-binding globulin (TBG) are not associated with clinical disease and do not require treatment. They are usually uncovered by a chance finding of abnormally low or high levels of thyroxine (T_4) and may be a source of confusion in the diagnosis of hypothyroidism or hyperthyroidism.

TBG deficiency occurs as an X-linked dominant disorder. Congenital TBG deficiency is most often discovered through screening programs for neonatal hypothyroidism that measure levels of T_4 as the primary screening test. Affected patients have low levels of total T_4 and elevated resin triiodothyronine uptake, but levels of free T_4 and thyroid-stimulating hormone are normal. The diagnosis is confirmed by the finding of absent or low levels of TBG. TBG deficiency occurs in 1 in 2,400 male newborns, 36% of whom have TBG levels <1 mg/dL. Milder forms of TBG deficiency occur in approximately 1 in 42,000 heterozygous female newborns. Complete TBG deficiency (<5 µg/dL) occurs much less often. To date, more than 25 different mutations have been reported in the TBG gene, resulting in either decreased TBG levels or reduced affinity of TBG for T_4. Table 564-1 lists causes of acquired TBG deficiency.

TBG excess also is a harmless X-linked dominant anomaly, occurring in approximately 1 in 25,000 persons. It has been recognized primarily in adults, but newborn screening programs may uncover the condition in the neonate. The level of T_4 is elevated, triiodothyronine is variably elevated, thyroid-stimulating hormone and free T_4 are normal, and resin triiodothyronine uptake is decreased. The elevated levels of TBG confirm the diagnosis. In affected neonates, levels of T_4 as high as 95 µg/dL have been found, which decrease to 20-30 µg/dL after 2-3 wk. Such high levels of T_4 may be related in part to the normally elevated levels of TBG in neonates, presumably as an effect of maternal estrogens. Affected patients are euthyroid. Family studies may be indicated to alert other affected family members. Table 564-1 lists causes of acquired TBG excess.

Familial dysalbuminemic hyperthyroxinemia is an autosomal dominant disorder that may be confused with hyperthyroidism. Markedly increased binding of T_4 to an abnormal albumin variant leads to increased serum concentrations of T_4. However, the levels of free T_4, free triiodothyronine, and thyroid-stimulating hormone are normal. Levels of triiodothyronine are normal or only slightly elevated. Affected patients are euthyroid.

Table 564-1 Causes of Acquired Thyroxine-Binding Globulin (TBG) Deficiency and Excess

DECREASED TBG	INCREASED TBG
Androgens	Estrogens
Anabolic steroids	Selective estrogen receptor modulators
Glucocorticoids	Pregnancy
Hepatocellular disease	Hepatitis
Severe illness	Porphyria
Protein-losing nephropathies	Heroin, methadone
Protein-losing enteropathies	Mitotane
Nicotinic acid	5-Flurouracil
L-Asparaginase	Perphenazine

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Chapter 565

Hypothyroidism

Stephen H. LaFranchi and Stephen A. Huang

Hypothyroidism results from deficient production of thyroid hormone, either from a defect in the gland itself (primary hypothyroidism) or a result of reduced thyroid-stimulating hormone (TSH) stimulation (central or hypopituitary hypothyroidism; Table 565-1). The disorder may be manifested from birth (congenital) or acquired. When symptoms appear after a period of apparently normal thyroid function, the disorder may be truly acquired or might only appear so as a result of one of a variety of congenital defects in which the manifestation of the deficiency is delayed.

CONGENITAL HYPOTHYROIDISM

Most cases of congenital hypothyroidism are not hereditary and result from thyroid dysgenesis. Some cases are familial; these are usually caused by one of the inborn errors of thyroid hormone synthesis (dyshormonogenesis) and may be associated with a goiter. Most infants with congenital hypothyroidism are detected by newborn screening programs in the 1st few wk after birth, before obvious clinical symptoms and signs develop. In infants born in areas with no screening program, severe cases manifest features in the 1st few wk of life, but in cases of milder deficiency, manifestations may be delayed for months.

Epidemiology

The prevalence of congenital hypothyroidism based on nationwide programs for neonatal screening was initially reported at 1 in 4,000 infants worldwide. Over the last 2 decades, the prevalence has dropped to 1 in 2,000, likely the result of detection of milder cases of hypothyroidism. Studies from the United States report that the prevalence is lower in black Americans and higher in Asian-Americans and Pacific Islanders, Hispanics, and Native Americans as compared to white babies.

Etiology

See Table 565-1.

Primary Hypothyroidism

Thyroid Dysgenesis. Some form of thyroid dysgenesis (aplasia, hypoplasia, or an ectopic gland) is the most common cause of permanent congenital hypothyroidism, accounting for 80-85% of cases. In approximately 33% of cases of dysgenesis, even sensitive radionuclide scans can find no remnants of thyroid tissue (aplasia). In the other 66% of infants, rudiments of thyroid tissue are found in an ectopic location, anywhere from the base of the tongue (lingual thyroid) to the normal position in the neck (hypoplasia). Thyroid dysgenesis has a 2 : 1 female : male ratio.

The cause of thyroid dysgenesis is unknown in most cases. Thyroid dysgenesis occurs sporadically, but familial cases occasionally have been reported. The finding that thyroid developmental anomalies, such as thyroglossal duct cysts and hemiagenesis, are present in 8-10% of 1st-degree relatives of infants with thyroid dysgenesis supports an underlying genetic component.

Mutations in several transcription factors important for thyroid morphogenesis and differentiation (including TTF-1/NKX2.1, TTF-2 [also termed FOXE1], and PAX8) are monogenic causes of approximately 2% of the cases of thyroid dysgenesis. In addition, genetic

Table 565-1 Etiologic Classification of Congenital Hypothyroidism

PRIMARY HYPOTHYROIDISM
Defect of fetal thyroid development (dysgenesis)
- Aplasia
- Hypoplasia
- Ectopia

Defect in thyroid hormone synthesis (dyshormonogenesis)
- Iodide transport defect from blood into follicular cell: mutation in sodium–iodide symporter gene
- Defective iodide transport from follicular cell into colloid: mutation in Pendrin transport protein
- Thyroid organification, or coupling defect: mutation in thyroid peroxidase gene
- Defects in H_2O_2 generation: mutations in DUOXA2 maturation factor or *DUOX2* gene
- Thyroglobulin synthesis defect: mutation in thyroglobulin gene
- Deiodination defect: mutation in *DEHAL1* gene

TSH unresponsiveness
- Mutation in TSH receptor
- Defective TSH signaling: $G_s\alpha$ mutation (e.g., type IA pseudohypoparathyroidism)

Defect in thyroid hormone transport: mutation in monocarboxylate transporter 8 *(MCT8)* gene
Resistance to thyroid hormone
Maternal antibodies: thyrotropin receptor–blocking antibody (TRBAb, measured as *thyrotropin-binding inhibitor immunoglobulin*)
Iodine deficiency (endemic goiter)
Maternal medications
- Iodides, amiodarone
- Propylthiouracil, methimazole
- Radioiodine

CENTRAL (HYPOPITUITARY) HYPOTHYROIDISM
Isolated TSH deficiency: mutation in TSH β-subunit gene (depending on mutation, TSH may be undetectable, measurable ["normal"], or elevated)
Isolated TRH deficiency: mutation in TRH gene
TRH unresponsiveness: mutation in TRH receptor gene
Multiple congenital pituitary hormone deficiencies (e.g., septooptic dysplasia)
PIT-1 mutations
- Deficiency of TSH
- Deficiency of growth hormone
- Deficiency of prolactin

PROP-1 mutations
- Deficiency of TSH
- Deficiency of growth hormone
- Deficiency of prolactin
- Deficiency of LH
- Deficiency of FSH
- ±Deficiency of ACTH

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TRH, thyroid-releasing hormone; TSH, thyroid-stimulating hormone.

defects leading to absent or ineffective thyrotropin (TSH) receptor binding or signaling have been described.

The transcription factor TTF-1/NKX2.1 is expressed in the thyroid, lung, and central nervous system. Mutations in TTF-1/NKX2.1 are reported to result in congenital hypothyroidism, respiratory distress, and persistent neurologic problems, including chorea and ataxia, despite early thyroid hormone treatment. NKX2.5 is expressed in the thyroid and heart. Mutations in *NKX2.5* are associated with congenital hypothyroidism and cardiac malformations. PAX-8 is expressed in the thyroid and kidney. Mutations in *PAX-8* are associated with congenital hypothyroidism and kidney and ureteral malformations.

The common finding of thyroid dysgenesis confined to only 1 of a pair of monozygotic twins suggests the operation of a deleterious factor during intrauterine life. Maternal antithyroid antibodies might be that factor. Although thyroid peroxidase antibodies have been detected in some mother–infant pairs, there is little evidence of their pathogenicity. The demonstration of thyroid growth-blocking and cytotoxic antibodies in some infants with thyroid dysgenesis, as well as in their mothers, suggests a more likely pathogenetic mechanism.

Defective Synthesis of Thyroxine (Dyshormonogenesis). A variety of defects in the biosynthesis of thyroid hormone can result in congenital hypothyroidism; these account for 15% of cases detected by neonatal screening programs (1 in 30,000-50,000 live births). These defects are transmitted in an autosomal recessive manner. A **goiter** is almost always present. When the defect is incomplete, compensation occurs, and onset of hypothyroidism may be delayed for years.

Defect of Iodide Transport. Defect of iodide transport is rare and involves mutations in the sodium–iodide symporter. Among the several cases now reported, it has been found in 9 related infants of the Hutterite sect, and approximately 50% of the cases are from Japan. Consanguinity is a factor in approximately 30% of the families.

In the past, clinical hypothyroidism, with or without a goiter, often developed in the 1st few months of life; the condition has been detected in neonatal screening programs. In Japan, however, untreated patients acquire goiter and hypothyroidism after 10 yr of age, perhaps because of the very high iodine content (often 19 mg/24 hr) of the Japanese diet.

The energy-dependent mechanisms for concentrating iodide are defective in the thyroid and salivary glands. In contrast to other defects of thyroid hormone synthesis, uptake of radioiodine and pertechnetate is low; a reduced saliva : serum ratio of ^{123}I will support the diagnosis, confirmed by finding a mutation in the sodium–iodide symporter gene. This condition responds to treatment with large doses of potassium iodide, but treatment with L-thyroxine is preferable.

Thyroid Peroxidase Defects of Organification and Coupling. Thyroid peroxidase defects of organification and coupling are the most common of the thyroxine (T_4) synthetic defects. After iodide is trapped by the thyroid, it is rapidly oxidized to reactive iodine, which is then incorporated into tyrosine units on thyroglobulin. This process requires generation of H_2O_2, thyroid peroxidase, and hematin (an enzyme cofactor); defects can involve each of these components, and there is considerable clinical and biochemical heterogeneity. In the Dutch neonatal screening program, 23 infants were found with a complete organification defect (1 in 60,000 live births), but its prevalence in other areas is unknown. A characteristic finding in all patients with this defect is a marked "discharge" of thyroid radioactivity when perchlorate or thiocyanate is administered 2 hr after administration of a test dose of radioiodine. In these patients, perchlorate discharges 40-90% of radioiodine compared with <10% in normal persons. Several mutations in the thyroid peroxidase gene have been reported in children with congenital hypothyroidism.

Dual oxidase maturation factor 2 **(DUOXA2)** is required to express **DUOX2** enzymatic activity, which is required for H_2O_2 generation, a crucial step in iodide oxidation. Biallelic *DUOXA2* mutations produce permanent congenital hypothyroidism, whereas monoallelic mutations are associated with transient hypothyroidism. *DUOX2* mutations can also cause permanent or transient congenital hypothyroidism. *DUOX2* mutations are relatively common, present in 30% of cases of apparent dyshormonogenesis, whereas *DUOXA2* mutations are relatively rare, present in 2% of such cases.

Pendred syndrome is an autosomal recessive disorder caused by a mutation in the chloride–iodide transport protein common to the thyroid gland and the cochlea. Pendred syndrome is comprised of sensorineural deafness and goiter; it is the most common cause of syndromic deafness. Pendrin allows transport of iodide from the follicular cell into the colloid where it undergoes organification to iodine and incorporation into the tyrosine residues on thyroglobulin. Patients with a mutation in the pendrin gene have impaired iodide organification and a positive perchlorate discharge.

Defects of Thyroglobulin Synthesis. Defects of thyroglobulin synthesis are a heterogeneous group of disorders characterized by goiter, elevated serum TSH, low T_4 levels, and absent or low levels of thyroglobulin. It has been reported in approximately 100 patients. Molecular defects, primarily point mutations, have been described in several patients.

Defects in Deiodination. Monoiodotyrosine and diiodotyrosine released from thyroglobulin are normally deiodinated within the thyroid or in peripheral tissues by a deiodinase. The liberated iodine is recycled in the synthesis of thyroid hormones. The *DEHAL1* gene encodes iodotyrosine deiodinase in the thyroid. *DEHAL1* mutations are relatively rare; patients with deiodinase deficiency experience severe iodine loss from the constant urinary excretion of nondeiodinated tyrosines, leading to hormonal deficiency and goiter. The deiodination defect may be limited to thyroid tissue only or to peripheral tissue only, or it may be universal.

Thyrotropin Hormone Unresponsiveness. A mutation in the TSH receptor gene is a relatively uncommon autosomal recessive cause of congenital hypothyroidism. Both homozygous and compound heterozygous mutations in the TSH receptor gene have been reported. Infants with a severe defect have elevated TSH levels and will be detected by newborn screening, whereas other patients with a mild defect remain euthyroid without treatment. A study of infants with congenital hypothyroidism detected by newborn screening from Tokyo reported TSH receptor mutations in 4.3% of patients (1 in 118,000 live births), with a founder mutation (p.R450H) accounting for 70% of gene defects.

Mild congenital hypothyroidism has been detected in newborn infants who subsequently proved to have **type Ia pseudohypoparathyroidism.** The molecular cause of resistance to TSH in these patients is the generalized impairment of cyclic adenosine monophosphate activation caused by genetic defect of the α subunit of the guanine nucleotide regulatory protein G_s (see Chapter 572).

Defects in Thyroid Hormone Transport. Passage of thyroid hormone into the cell is facilitated by plasma membrane transporters. A mutation in one such transporter gene, monocarboxylate transporter 8 *(MCT8)*, located on the X chromosome **(Allan-Herndon-Dudley syndrome),** has now been reported in multiple patients. The defective transporter impairs passage of T_4 and triiodothyronine (T_3) into cells; this syndrome is characterized by elevated serum T_3 levels, low T_4 levels, and normal or mildly elevated TSH levels. Neurologic manifestations include severe developmental delay, reduced muscle mass, initial hypotonia that evolves into spastic paraplegia, dysarthria, and athetoid movements.

Resistance to Thyroid Hormone

This autosomal dominant disorder is caused by mutations in the thyroid hormone receptor. Most patients have a goiter, and levels of T_4, T_3, free T_4, and free T_3 are elevated. These findings often have led to the erroneous diagnosis of Graves disease, although most affected patients are clinically euthyroid. The unresponsiveness can vary among tissues. There may be subtle clinical features of hypothyroidism, including developmental delay, growth retardation, and delayed skeletal maturation. On the other hand, there may be clinical features compatible with hyperthyroidism, such as tachycardia and hyperreflexia. It is presumed that these patients have varying tissue resistance to thyroid hormone. One neurologic manifestation is an increased association of attention-deficit/hyperactivity disorder; the converse is not true because patients with attention-deficit/hyperactivity disorder do not have an increased risk of thyroid hormone resistance.

TSH levels are diagnostic in that they are not suppressed as in Graves disease but instead are moderately elevated or normal but inappropriate for the levels of T_4 and T_3. The failure of TSH suppression indicates that the resistance is generalized and affects the pituitary gland as well as peripheral tissues. More than 40 distinct point mutations in the hormone-binding domain of the β-thyroid receptor are identified. Different phenotypes do not correlate with genotypes. The same mutation has been observed in patients with generalized or isolated pituitary resistance, even in different members of the same family. A child homozygous for the receptor mutation showed unusually severe resistance. These cases support the dominant negative effect of mutant receptors, in which the mutant receptor protein inhibits normal receptor action in heterozygotes. Elevated levels of T_4 on neonatal thyroid screening should suggest the possibility of this diagnosis. No treatment is usually required unless growth and skeletal retardation are present.

Two infants of consanguineous matings are known to have an autosomal recessive form of thyroid resistance. These infants had manifestations of hypothyroidism early in life, and genetic studies revealed a major deletion of the β-thyroid receptor in 1 of them. The resistance appears to be more severe in this form of the entity.

Some patients have greater resistance to thyroid hormone in the pituitary gland as compared to peripheral tissues. Because the peripheral tissues are not resistant to thyroid hormones, the patient has a goiter and manifestations of hyperthyroidism. The laboratory findings are the same as those seen with generalized thyroid hormone resistance. This condition must be differentiated from a pituitary TSH-secreting tumor. Different treatments, including D-thyroxine, triiodothyroacetic acid, and tetraiodothyroacetic acid, have been successful in some patients. Bromocriptine administration, which interferes with TSH secretion, was reported to be successful in another patient. Whether isolated pituitary resistance to thyroid hormone exists as a distinct entity is controversial; it may be a variant of generalized resistance to thyroid hormone with varying tissue responsiveness.

Although the majority of patients with resistance have mutations in the thyroid hormone receptor β gene, a child with a mutation in the thyroid hormone receptor α gene has been reported. This patient presented at age 6 yr with growth retardation, delayed development, and constipation. Genetic analysis showed a heterozygous nonsense mutation in the thyroid hormone receptor α gene that, like β gene mutations, inhibited wild-type receptor action in a dominant negative manner.

Thyrotropin Receptor-Blocking Antibody. Maternal TSH receptor-blocking antibody (TRBAb) is an unusual cause of transitory congenital hypothyroidism. Transplacental passage of maternal TRBAb inhibits binding of TSH to its receptor in the neonate. Maternal TRBAb accounts for 2% of cases detected by neonatal screening programs (1 in 50,000-100,000 infants). It should be suspected whenever there is a history of maternal autoimmune thyroid disease, including Hashimoto thyroiditis or Graves disease, maternal hypothyroidism on replacement therapy, or recurrent congenital hypothyroidism of a transient nature in previous siblings. In these situations, maternal levels of TRBAb (measured as thyrotropin-binding inhibitor immunoglobulin) should be determined during pregnancy. Affected infants and their mothers also can have thyrotropin receptor–stimulating antibodies and thyroid peroxidase antibodies. Technetium pertechnetate and ^{123}I scans might fail to detect any thyroid tissue, mimicking thyroid agenesis, but ultrasonography will show a thyroid gland. After the condition remits, a normal thyroid gland is demonstrable by scanning following discontinuation of replacement therapy. The half-life of the antibody is 21 days, and remission of the hypothyroidism occurs in approximately 3-6 mo. Correct diagnosis of this cause of congenital hypothyroidism prevents unnecessary protracted treatment, alerts the clinician to possible recurrences in future pregnancies, and allows a favorable prognosis.

Radioiodine Administration. Hypothyroidism can occur as a result of inadvertent administration of radioiodine during pregnancy for treatment of Graves disease or cancer of the thyroid. The fetal thyroid is capable of trapping iodide by 70-75 days of gestation. Whenever radioiodine is administered to a woman of childbearing age, a pregnancy test must be performed before a therapeutic dose of ^{131}I is given, regardless of the menstrual history or putative history of contraception. Administration of radioactive iodine to lactating women also is contraindicated because it is readily excreted in milk.

Iodine Exposure. Congenital hypothyroidism can result from fetal exposure to excessive iodides. Perinatal exposure can occur with the use of iodine antiseptic to prepare the skin for caesarian section or painting of the cervix before delivery. It has also been reported in infants born to mothers who consumed large amounts of iodine daily (up to 12 mg) in the form of nutritional supplements and in mothers in Japan who consumed large quantities of iodine-rich seaweed. These conditions are transitory and must not be mistaken for the other forms of hypothyroidism. In the neonate, topical iodine-containing antiseptics used in nurseries and by surgeons can also cause transient congenital hypothyroidism, especially in low-birthweight infants, and can

lead to abnormal results on neonatal screening tests. In older children, the usual sources of iodides are proprietary preparations used to treat asthma. In a few instances, the cause of hypothyroidism was amiodarone, an antiarrhythmic drug with high iodine content. In most of these instances, goiter is present (see Chapter 567).

Iodine-Deficiency Endemic Goiter. See Chapter 567.3.

Iodine deficiency or endemic goiter is the most common cause of congenital hypothyroidism worldwide. The recommended intake of iodine in adults is 150 μg daily, increasing to 250 μg daily during pregnancy to allow for fetal iodine requirements. Despite efforts at universal iodization of salt in many countries, economic, political, and practical obstacles make achieving this objective difficult. While the U.S. population is iodine-sufficient as a whole, approximately 15% of women of reproductive age fall into the iodine-deficient category. Borderline iodine deficiency is more likely to cause problems in preterm infants who depend on a maternal source of iodine for normal thyroid hormone production.

Central (Hypopituitary) Hypothyroidism

Thyrotropin and Thyrotropin-Releasing Hormone Deficiency. Deficiency of TSH and central hypothyroidism can occur in any of the conditions associated with developmental defects of the pituitary or hypothalamus (see Chapter 557). More often in these conditions, the deficiency of TSH is secondary to a deficiency of thyrotropin-releasing hormone (TRH). TSH-deficient hypothyroidism is found in 1 in 30,000-50,000 infants; most screening programs are designed to detect primary hypothyroidism, so most of these cases are not detected by neonatal thyroid screening. The majority of affected infants have multiple pituitary deficiencies and present with hypoglycemia, persistent jaundice, and micropenis in association with septooptic dysplasia, midline cleft lip, midface hypoplasia, and other midline facial anomalies.

Mutations in genes coding for transcription factors essential to pituitary development, cell type differentiation, and hormone synthesis are associated with congenital TSH deficiency. *PIT-1* mutations include TSH deficiency associated with growth hormone and prolactin deficiency. Patients with *PROP-1* mutations ("prophet of pit-1") have not only TSH, growth hormone, and prolactin deficiency but also luteinizing hormone and follicle-stimulating hormone deficiency and variable adrenocorticotropic hormone deficiency. *HESX1* mutations are associated with TSH, growth hormone, prolactin, and adrenocorticotropic hormone deficiencies and are found in some patients with optic nerve hypoplasia (septooptic dysplasia syndrome; see Chapter 591).

Isolated deficiency of TSH is a rare autosomal recessive disorder that has been reported in several sibships. DNA studies in affected family members reveal defects in the TSH β-subunit gene, including point mutations, frame shifts causing a stop codon, and splice-site mutations. Depending on the specific mutation, serum TSH levels may be undetectable, measureable, or elevated. The diagnosis is usually delayed because the serum TSH level is not elevated in most cases, and so such patients are not detected by newborn screening programs.

Thyrotropin-Releasing Hormone Receptor Abnormality. Mutations in the TRH receptor gene, a rare cause of congenital central hypothyroidism, have now been reported in a few families. This condition, which results in isolated TSH deficiency and hypothyroidism, was suspected because of failure of both TSH and prolactin to respond to TRH stimulation.

Thyroid Function in Preterm Babies

Postnatal thyroid function in preterm babies is qualitatively similar but quantitatively reduced compared with that of term infants. The cord serum T_4 is decreased in proportion to gestational age and birthweight. The postnatal TSH surge is reduced, and the more premature, very-low-birthweight infants with complications of prematurity, such as respiratory distress syndrome, actually experience a decrease in serum T_4 in the 1st wk of life. As these complications resolve, the serum T_4 gradually increases so that generally by 6 wk of life it enters the T_4 range seen in term infants. Serum free T_4 concentrations seem less affected, and when measured by equilibrium dialysis, these levels are often normal. Preterm babies also have a higher incidence of "delayed" TSH elevation and apparent transient primary hypothyroidism. Premature infants of <28 wk of gestation might have problems resulting from a combination of immaturity of the hypothalamic-pituitary-thyroid axis and loss of the maternal contribution of thyroid hormone and so may be candidates for temporary thyroid hormone replacement; further studies are needed.

Clinical Manifestations

Most infants with congenital hypothyroidism are asymptomatic at birth, even if there is complete agenesis of the thyroid gland. This situation is attributed to partial transplacental passage of maternal T_4, which provides fetal levels that are approximately 33% of normal at birth. Despite this maternal contribution of T_4, hypothyroid infants still have a low serum T_4 and elevated TSH level and so will be identified by newborn screening programs.

The clinician depends on neonatal screening tests for the diagnosis of congenital hypothyroidism. Some babies escape newborn screening, and laboratory errors occur, so awareness of early symptoms and signs must be maintained. Congenital hypothyroidism caused by thyroid dysgenesis, the most common etiology, is twice as common in girls as in boys. Before neonatal screening programs, congenital hypothyroidism was rarely recognized in the newborn because the signs and symptoms are usually not sufficiently developed. It can be suspected and the diagnosis established during the early weeks of life if the initial, but less characteristic, manifestations are recognized. Birthweight and length are normal, but head size may be slightly increased because of myxedema of the brain. The anterior and posterior fontanels are open widely; observation of this sign at birth can serve as an initial clue to the early recognition of congenital hypothyroidism. *Only 3% of normal newborn infants have a posterior fontanel larger than 0.5 cm*. Prolongation of physiologic jaundice, caused by delayed maturation of glucuronide conjugation, may be the earliest sign. Feeding difficulties, especially sluggishness, lack of interest, somnolence, and choking spells during nursing, are often present during the 1st mo of life. Respiratory difficulties, partly caused by the large tongue, include apneic episodes, noisy respirations, and nasal obstruction. Some infants may develop respiratory distress syndrome. Affected infants cry little, sleep much, have poor appetites, and are generally sluggish. There may be constipation that does not usually respond to treatment. The abdomen is large, and an umbilical hernia is usually present. The temperature is subnormal, often <35°C (95°F), and the skin, particularly that of the extremities, may be cold and mottled. Edema of the genitals and extremities may be present. The pulse is slow, and heart murmurs, cardiomegaly, and asymptomatic pericardial effusion are common. Macrocytic anemia is often present and is refractory to treatment with hematinics. Because symptoms appear gradually, the clinical diagnosis is often delayed.

Approximately 10% of infants with congenital hypothyroidism have associated congenital anomalies. Cardiac anomalies are most common, but anomalies of the nervous system and eye have also been reported. Infants with congenital hypothyroidism may have associated hearing loss. As noted under "Etiology" above, specific mutations in genes involved in thyroid gland development result in "syndromic" congenital hypothyroidism. Mutations in *NKX2.1 (TTF-1)*, present in the thyroid gland, lungs, and brain, are characterized by congenital hypothyroidism, respiratory distress syndrome, and ataxia, or even choreoathetosis. Mutations in *NKX2.5* result in congenital hypothyroidism and associated congenital heart defects. Mutations in *TTF-2*, present in the thyroid gland, palate, and hair, include congenital hypothyroidism, cleft palate, and spiky hair. Mutations in *PAX-8*, present in the thyroid gland and kidneys, present with congenital hypothyroidism and genitourinary anomalies, including renal agenesis.

If congenital hypothyroidism goes undetected and untreated, these manifestations progress. Retardation of physical and mental development becomes greater during the following months, and by 3-6 mo of age the clinical picture is fully developed (Fig. 565-1). When there is only partial deficiency of thyroid hormone, the symptoms may be milder, the syndrome incomplete, and the onset delayed. Although breast milk contains significant amounts of thyroid hormones,

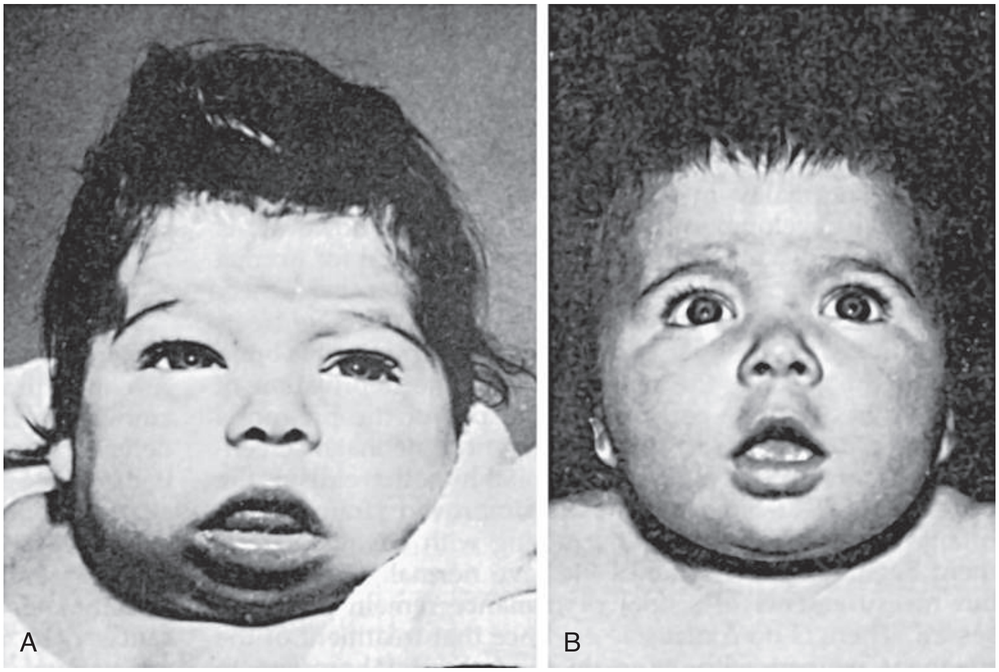

Figure 565-1 Congenital hypothyroidism in an infant 6 mo of age. The infant ate poorly in the neonatal period and was constipated. She had a persistent nasal discharge and a large tongue; she was very lethargic and had no social smile and no head control. **A,** Notice the puffy face, dull expression, and hirsute forehead. Tests revealed a negligible uptake of radioiodine. Osseous development was that of a newborn. **B,** Four mo after treatment, note the decreased puffiness of the face, the decreased hirsutism of the forehead, and the alert appearance.

particularly T_3, it is inadequate to protect the breastfed infant who has congenital hypothyroidism, and it has no effect on neonatal thyroid screening tests.

The child's growth will be stunted, the extremities are short, and the head size is normal or even increased. The anterior fontanel is large and the posterior fontanel may remain open. The eyes appear far apart, and the bridge of the broad nose is depressed. The palpebral fissures are narrow and the eyelids are swollen. The mouth is kept open, and the thick, broad tongue protrudes. Dentition will be delayed. The neck is short and thick, and there may be deposits of fat above the clavicles and between the neck and shoulders. The hands are broad and the fingers are short. The skin is dry and scaly, and there is little perspiration. Myxedema is manifested, particularly in the skin of the eyelids, the back of the hands, and the external genitals. The skin shows general pallor with a sallow complexion. Carotenemia can cause a yellow discoloration of the skin, but the sclerae remain white. The scalp is thickened, and the hair is coarse, brittle, and scanty. The hairline reaches far down on the forehead, which usually appears wrinkled, especially when the infant cries.

Development is usually delayed. Hypothyroid infants appear lethargic and are late in learning to sit and stand. The voice is hoarse, and they do not learn to talk. The degree of physical and intellectual delay increases with age. Sexual maturation may also be delayed or might not take place at all.

The muscles are usually hypotonic, but in rare instances generalized muscular pseudohypertrophy occurs **(Kocher-Debré-Sémélaigne syndrome).** Affected older children can have an athletic appearance because of pseudohypertrophy, particularly in the calf muscles. Its pathogenesis is unknown; nonspecific histochemical and ultrastructural changes seen on muscle biopsy return to normal with treatment. Boys are more prone to development of the syndrome, which has been observed in siblings born from a consanguineous mating. Affected patients have hypothyroidism of longer duration and severity.

Some infants with mild congenital hypothyroidism have normal thyroid function at birth and so are not identified by newborn screening programs. In particular, some children with ectopic thyroid tissue (lingual, sublingual, subhyoid) produce adequate amounts of thyroid hormone for many years, or it eventually fails in early childhood. Affected children come to clinical attention because of a growing mass at the base of the tongue or in the midline of the neck, usually at the level of the hyoid. Occasionally, ectopia is associated with **thyroglossal duct cysts**. It can occur in siblings. Surgical removal of ectopic thyroid tissue from a euthyroid patient usually results in hypothyroidism, because most such patients have no other thyroid tissue.

Laboratory Findings

In developed countries, infants with congenital hypothyroidism are identified by newborn screening programs. Blood obtained by heelprick between 2 and 5 days of life is placed on a filter paper card and sent to a central screening laboratory. The early approach to newborn screening in North America and Europe began with measure of levels of T_4, followed by measurement of TSH when T_4 is low. This approach identifies infants with primary hypothyroidism, some with central or hypopituitary hypothyroidism, and infants with a delayed elevation in TSH levels. Over time, many neonatal screening programs in North America, Europe, and elsewhere in the world have switched to an initial TSH measurement. This approach will detect infants with primary hypothyroidism and infants with milder, subclinical hypothyroidism (normal T_4, elevated TSH), but it may not detect infants with delayed TSH elevation or with central or hypopituitary hypothyroidism. With any of these tests, special care should be given to the normal range of values for age of the patient, particularly in the 1st weeks of life (Table 565-2). Regardless of the approach used for screening, some infants escape detection because of technical or human errors; clinicians must maintain their vigilance for clinical manifestations of hypothyroidism.

Serum levels of T_4 or free T_4 are low; serum levels of T_3 may be normal and are not helpful in the diagnosis. If the defect is primarily in the thyroid, levels of TSH are elevated, often to >100 mU/L. Serum levels of thyroglobulin are usually low in infants with thyroid agenesis or defects of thyroglobulin synthesis or secretion, whereas they are elevated with ectopic glands and other inborn errors of T_4 synthesis, but there is a wide overlap of ranges.

Special attention should be paid to identical twins; in several reported cases, neonatal screening failed to detect the affected twin with hypothyroidism, and the diagnosis was not made until the infants were 4-5 mo of age. In these cases, transfusion of euthyroid blood from the unaffected twin normalized the serum levels of T_4 and TSH in the

Table 565-2 Thyroid Function Tests

AGE	U.S. REFERENCE VALUE	CONVERSION FACTOR	SI REFERENCE VALUE
THYROID THYROGLOBULIN, SERUM			
Cord blood	14.7-101.1 ng/mL	×1	14.7-101.1 μg/L
Birth to 35 mo	10.6-92.0 ng/mL	×1	10.6-92.0 μg/L
3-11 yr	5.6-41.9 ng/mL	×1	5.6-41.9 μg/L
12-17 yr	2.7-21.9 ng/mL	×1	2.7-21.9 μg/L
THYROID-STIMULATING HORMONE, SERUM			
Premature Infants (28-36 wk)			
1st wk of life	0.7-27.0 mIU/L	×1	0.7-27.0 mIU/L
Term Infants			
Birth to 4 days	1.0-17.6 mIU/L	×1	1.0-17.6 mIU/L
2-20 wk	0.6-5.6 mIU/L	×1	0.6-5.6 mIU/L
5 mo-20 yr	0.5-5.5 mIU/L	×1	0.5-5.5 mIU/L
THYROXINE-BINDING GLOBULIN, SERUM			
Cord blood	1.4-9.4 mg/dL	×10	14-94 mg/L
1-4 wk	1.0-9.0 mg/dL	×10	10-90 mg/L
1-12 mo	2.0-7.6 mg/dL	×10	20-76 mg/L
1-5 yr	2.9-5.4 mg/dL	×10	29-54 mg/L
5-10 yr	2.5-5.0 mg/dL	×10	25-50 mg/L
10-15 yr	2.1-4.6 mg/dL	×10	21-46 mg/L
Adult	1.5-3.4 mg/dL	×10	15-34 mg/L
THYROXINE, TOTAL, SERUM			
Full-Term Infants			
1-3 days	8.2-19.9 μg/dL	×12.9	106-256 nmol/L
1 wk	6.0-15.9 μg/dL	×12.9	77-205 nmol/L
1-12 mo	6.1-14.9 μg/dL	×12.9	79-192 nmol/L
Prepubertal Children			
1-3 yr	6.8-13.5 μg/dL	×12.9	88-174 nmol/L
3-10 yr	5.5-12.8 μg/dL	×12.9	71-165 nmol/L
Pubertal Children and Adults			
>10 yr	4.2-13.0 μg/dL	×12.9	54-167 nmol/L
THYROXINE, FREE, SERUM			
Full-term (3 days)	2.0-4.9 ng/dL	×12.9	26-63.1 pmol/L
Infants	0.9-2.6 ng/dL	×12.9	12-33 pmol/L
Prepubertal children	0.8-2.2 ng/dL	×12.9	10-28 pmol/L
Pubertal children and adults	0.8-2.3 ng/dL	×12.9	10-30 pmol/L
THYROXINE, TOTAL, WHOLE BLOOD			
Newborn screen (filter paper)	6.2-22 μg/dL	×12.9	80-283 nmol/L
TRIIODOTHYRONINE, FREE, SERUM			
Cord blood	20-240 pg/dL	×0.01536	0.3-0.7 pmol/L
1-3 days	180-760 pg/dL	×0.01536	2.8-11.7 pmol/L
1-5 yr	185-770 pg/dL	×0.01536	2.8-11.8 pmol/L
5-10 yr	215-700 pg/dL	×0.01536	3.3-10.7 pmol/L
10-15 yr	230-650 pg/dL	×0.01536	3.5-10.0 pmol/L
>15 yr	210-440 pg/dL	×0.01536	3.2-6.8 pmol/L
TRIIODOTHYRONINE RESIN UPTAKE TEST (RT_3U), SERUM			
Newborn	26-36%	×0.01	0.26-0.36 fractional uptake
Thereafter	26-35%	×0.01	0.26-0.35 fractional uptake
TRIIODOTHYRONINE, TOTAL, SERUM			
Cord blood	30-70 ng/dL	×0.0154	0.46-1.08 nmol/L
1-3 days	75-260 ng/dL	×0.0154	1.16-4.00 nmol/L
1-5 yr	100-260 ng/dL	×0.0154	1.54-4.00 nmol/L
5-10 yr	90-240 ng/dL	×0.0154	1.39-3.70 nmol/L
10-15 yr	80-210 ng/dL	×0.0154	1.23-3.23 nmol/L
>15 yr	115-190 ng/dL	×0.0154	1.77-2.93 nmol/L

Adapted from Nicholson JF, Pesce MA: Reference ranges for laboratory tests and procedures. In Behrman RE, Kliegman RM, Jenson HB, editors: Nelson textbook of pediatrics, *ed 17, Philadelphia, 2004, WB Saunders, pp. 2412–2413; TSH from Lem AJ, de Rijke YB, van toor H, et al: Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age.* J Clin Endocrinol Metab *97:3170–3178, 2012; free T_3 from Elmlinger MW, Kuhnel W, Lambrecht H-G, Ranke MB: Reference intervals from birth to adulthood for serum thyroxine (T_4), triiodothyronine (T_3), free T_3, free T_4, thyroxine binding globulin (TBG), and thyrotropin (TSH).* Clin Chem Lab Med *39:973–979, 2001.*

affected twin at the initial screening. Many newborn screening programs perform a routine second test in same-sex twins.

Retardation of osseous development can be shown radiographically at birth in approximately 60% of congenitally hypothyroid infants and indicates some deprivation of thyroid hormone during intrauterine life. The distal femoral and proximal tibial epiphyses, normally present at birth, are often absent (Fig. 565-2*A*). In undetected and untreated patients, the discrepancy between chronologic age and osseous development increases. The epiphyses often have multiple foci of ossification (epiphyseal dysgenesis; Fig. 565-2*B*); deformity

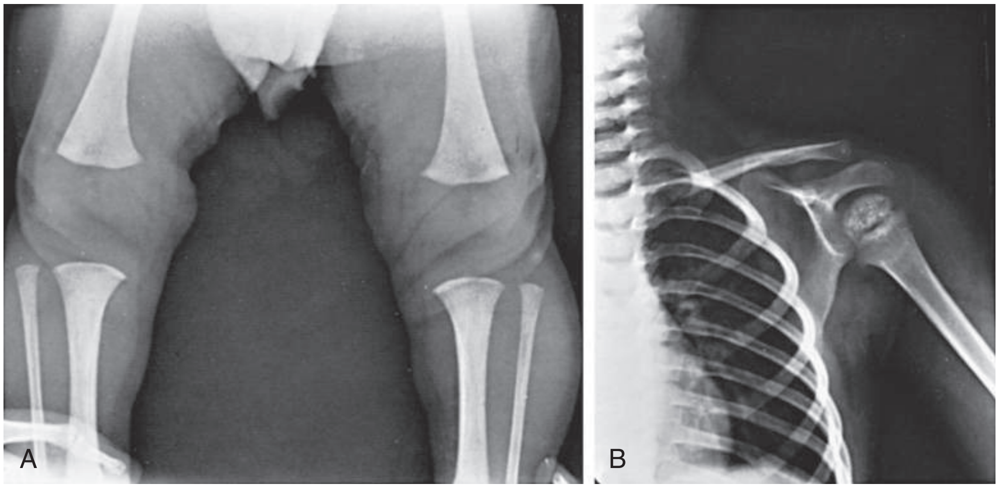

Figure 565-2 Congenital hypothyroidism. **A,** Absence of distal femoral epiphysis in a 3 mo old infant who was born at term. This is evidence for the onset of the hypothyroid state during fetal life. **B,** Epiphyseal dysgenesis in the head of the humerus in a 9 yr old girl who had been inadequately treated with thyroid hormone.

("beaking") of the 12th thoracic or 1st or 2nd lumbar vertebra is common. X-rays of the skull show large fontanels and wide sutures; intersutural (wormian) bones are common. The sella turcica is often enlarged and round; in rare instances, there may be erosion and thinning. Formation and eruption of teeth can be delayed. Cardiac enlargement or pericardial effusion may be present.

Scintigraphy can help to pinpoint the underlying cause in infants with congenital hypothyroidism, but treatment should not be unduly delayed for this study. ^{123}I-sodium iodide is superior to ^{99m}Tc-sodium pertechnetate for this purpose. Ultrasonographic examination of the thyroid is helpful, but studies show it can miss some ectopic glands shown by scintigraphy. Demonstration of ectopic thyroid tissue is diagnostic of thyroid dysgenesis and establishes the need for lifelong treatment with T_4. Failure to demonstrate any thyroid tissue suggests thyroid aplasia, but this also occurs in neonates with hypothyroidism caused by maternal TRBAb and in infants with the iodide-trapping defect. A normally situated thyroid gland with a normal or avid uptake of radionuclide indicates a defect in thyroid hormone biosynthesis. In the past, patients with goitrous hypothyroidism have required extensive evaluation, including radioiodine studies, perchlorate discharge tests, kinetic studies, chromatography, and studies of thyroid tissue, to determine the biochemical nature of the defect. Most can be evaluated by genetic studies looking for a suspected mutation in the steps along the T_4 biosynthetic pathway.

The electrocardiogram may show low-voltage P and T waves with diminished amplitude of QRS complexes and suggest poor left ventricular function and pericardial effusion. Echocardiography can confirm a pericardial effusion. The electroencephalogram often shows low voltage. In children older than 2 yr of age, the serum cholesterol level is usually elevated. Brain MRI before treatment is reportedly normal, although proton magnetic resonance spectroscopy shows high levels of choline-containing compounds, which can reflect blocks in myelin maturation.

Treatment

Levothyroxine (L-T_4) given orally is the treatment of choice. Although T_3 is the biologically active form of thyroid hormone, most of the T_3 in the brain is formed from local deiodination of T_4. Because 80% of circulating T_3 is formed by monodeiodination of T_4, serum levels of T_4 and T_3 return to normal with L-T_4 treatment alone. The recommended initial starting dose is 10-15 µg/kg/day (totaling 37.5-50.0 µg/day for most term infants). The starting dose can be tailored to the severity of hypothyroidism. Rapid normalization of thyroid function has been demonstrated to be important in achieving optimal neurodevelopmental outcome. Newborns with more severe hypothyroidism, as judged by a serum T_4 <5 µg/dL and/or imaging studies confirming aplasia, should be started at the higher end of the dosage range.

L-T_4 is available only in tablet form in the United States; there is an approved liquid L-T_4 preparation in Europe. The daily tablets should be crushed and mixed with a small volume of liquid. *L-T_4 tablets should not be mixed with soy protein formulas, concentrated iron, or calcium, because these can bind T_4 and inhibit its absorption*. Although it is recommended to administer L-T_4 on an empty stomach and avoid food for 30-60 min, this is not practical in an infant. As long as the method of administration is consistent day to day, dosing can be adjusted based on serum thyroid test results to achieve the desired treatment goals.

Levels of serum T_4 or free T_4 and TSH should be monitored at recommended intervals (every 1-2 mo in the 1st 6 mo of life, and then every 2-4 mo between 6 mo and 3 yr of age). The goals of treatment are to maintain the serum free T_4 or total T_4 in the upper half of the reference range for age (see Table 565-2), with serum TSH in the reference range for age, optimally 0.5-2.0 mU/L. The dose of L-T_4 on a weight basis gradually decreases with age.

Later, confirmation of the diagnosis may be necessary for some infants to rule out the possibility of transient hypothyroidism. This is unnecessary in infants with proven thyroid ectopia or in those who manifest elevated levels of TSH after 6-12 mo of therapy because of poor compliance or an inadequate dose of T_4. Discontinuation of therapy at about 3 yr of age for 3-4 wk results in a marked increase in TSH levels in children with permanent hypothyroidism.

Care should be taken to avoid prolonged undertreatment or overtreatment. The only untoward effects of L-T_4 are related to its dosage. Overtreatment can risk craniosynostosis and temperament problems.

Prognosis

Thyroid hormone is critical for normal cerebral development in the early postnatal months; biochemical diagnosis must be made soon after birth, and effective treatment must be initiated promptly to prevent irreversible brain damage. With the advent of neonatal screening programs for detection of congenital hypothyroidism, the prognosis for affected infants has improved dramatically. Early diagnosis and adequate treatment from the 1st weeks of life result in normal linear growth and development. Most studies report that psychometric testing in infants detected by newborn screening shows verbal, psychomotor, and global IQ scores similar to those of unaffected siblings or classmate controls. Some screening programs report that the most severely affected infants, as judged by the lowest T_4 levels and retarded skeletal maturation, have reduced IQs (by 5-20 points) and other neuropsychologic sequelae, such as incoordination, hypotonia or hypertonia, short attention span, and speech problems, even with early diagnosis and

adequate treatment. Psychometric testing can show problems with vocabulary and reading comprehension, arithmetic, and memory. Approximately 20% of children have a neurosensory hearing deficit. Outcome studies in adults, detected and treated as neonates, reveal delayed social development, lower self-esteem, and a lower health-related quality of life. The latter appears to be related to those individuals with lower neurocognitive outcome and associated congenital malformations.

Delay in diagnosis, failure to correct initial hypothyroxinemia rapidly, inadequate treatment, and poor compliance in the 1st 2-3 yr of life result in variable degrees of brain damage. Without treatment, affected infants are profoundly intellectually challenged and growth retarded. When onset of hypothyroidism occurs after 2 yr of age, the outlook for normal development is much better even if diagnosis and treatment have been delayed, indicating how much more important thyroid hormone is to the rapidly growing brain of the infant.

ACQUIRED HYPOTHYROIDISM

Epidemiology

Studies of school-age children report that hypothyroidism occurs in approximately 0.3% (1 in 333). Subclinical hypothyroidism (TSH >4.5 mU/L, normal T_4 or free T_4) is more common, occurring in approximately 2% of adolescents. Acquired hypothyroidism is most commonly a result of chronic lymphocytic thyroiditis; 6% of children age 12-19 yr have evidence of autoimmune thyroid disease, which occurs with a 2 : 1 female : male preponderance.

Etiology

The most common cause of acquired hypothyroidism (Table 565-3) is chronic lymphocytic (Hashimoto) thyroiditis (see Chapter 566). **Autoimmune thyroid disease** may be part of polyglandular syndromes; children with Down and Turner syndrome, possibly Klinefelter syndrome, and celiac disease or diabetes are at higher risk for associated autoimmune thyroid disease (see Chapter 566) as are those with **autoimmune polyglandular syndromes (APSs)** (Tables 565-4 and 565-5). APS has 4 types, but APS-1 and APS-2 are the most common. APS-1 includes 2 components of the triad of hypoparathyroidism, Addison disease (adrenal insufficiency) and mucocutaneous candidiasis ("HAM" syndrome). Commonly referred to by the acronym APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia), it is autosomal recessive, caused by a mutation in the *AIRE* (autoimmune regulator) gene. Less-common features include thyroiditis (~10%), type 1 diabetes mellitus, primary hypogonadism, pernicious anemia, vitiligo, alopecia, chronic active hepatitis, and malabsorption syndrome. APS-2 (Schmidt syndrome) most commonly consists of autoimmune thyroiditis (~70%), Addison disease, and type 1 diabetes mellitus. Less-common features include primary hypogonadism, pernicious anemia, and vitiligo. APS-2 occurs more commonly than APS-1, generally presents in early adulthood, and has a female preponderance. The underlying immunologic defect remains to be determined.

Table 565-4 Autoimmune Polyglandular Syndromes 1 and 2

	APS-1	APS-2
Incidence	<1 in 100,000 population/yr	1-2 in 10,000 population/yr
Onset	Infancy/early childhood	Late childhood/ adulthood
Male : female ratio	3 : 4	1 : 3
Inheritance	Monogenic (*AIRE* gene)	Polygenic (HLA-associated)
Mucocutaneous candidiasis	73-100%	None
Hypoparathyroidism	77-89%	None
Addison disease	60-86%	70-100%
Type 1 diabetes	4-18%	41-52%
Autoimmune thyroid disease	8-40%	70%
GONADAL FAILURE		
Male	7-17%	5%
Female	30-60%	3.5-10%
Ectodermal dysplasia	77%	None
Vitiligo	4-13%	4-5%
Pernicious anemia	12-15%	2-25%
Alopecia	27%	2%
Autoimmune hepatitis	10-15%	Rare
Malabsorption	10-18%	Rare

HLA, human leukocyte antigen.

From Nambam B, Winter WE, Schatz DA: IgG$_4$ antibodies in autoimmune polyglandular disease and IgG$_4$-related endocrinopathies: pathophysiology and clinical characteristics. Curr Opin Pediatr *26:493–499, 2014, Table 1, p. 494.*

Table 565-3 Etiologic Classification of Acquired Hypothyroidism

Autoimmune
- Hashimoto thyroiditis
- Autoimmune polyglandular syndromes types 1 and 2 (APS-1, APS-2)

Drug-induced
- Excess iodide: amiodarone, nutritional supplements, expectorants
- Anticonvulsants: phenytoin, phenobarbital, valproate
- Antithyroid drugs: methimazole, propylthiouracil
- Miscellaneous: lithium, tyrosine kinase inhibitors, interferon alfa, stavudine, thalidomide, aminoglutethimide

Postablative
- Irradiation
- Radioiodine
- Thyroidectomy

Systemic infiltrative disease
- Cystinosis
- Langerhans cell histiocytosis

Hemangiomas (large) of the liver (type 3 iodothyronine deiodinase)

Hypothalamic-pituitary disease with multiple pituitary hormone deficiencies
- Hypothalamic-pituitary tumors (e.g., craniopharyngioma)
- Meningoencephalitis
- Cranial radiation
- Head trauma
- Langerhans cell histiocytosis

Table 565-5 Organ-Specific Autoantigens in Autoimmune Polyglandular Syndromes

DISEASE	AUTOANTIGENS
Addison disease	P450c21, P450c17, P450scc
Hashimoto thyroiditis	Thyroid peroxidase, thyroglobulin
Graves disease	TSH receptor
Hypoparathyroidism	Calcium-sensing receptor, NALP 5 (NACHT leucine-rich-repeat protein 5)
Type 1 diabetes	Insulin, glutamic acid decarboxylase-65, IA-2A, ZnT8
Hypogonadism	P450c17, P450scc
Immune gastritis	H+, K+-ATPase
Pernicious anemia	Intrinsic factor
Celiac disease	Transglutaminase, gliadin
Immune hepatitis	P450D6, P4502C9, P4501A2
Alopecia areata	Tyrosine hydroxylase
Vitiligo	Tyrosinase

ATPase, adenosine triphosphatase; TSH, thyroid-stimulating hormone.

From Nambam B, Winter WE, Schatz DA: IgG$_4$ antibodies in autoimmune polyglandular disease and IgG$_4$-related endocrinopathies: pathophysiology and clinical characteristics. Curr Opin Pediatr *26:493–499, 2014, Table 2, p. 495.*

In children with **Down syndrome**, antithyroid antibodies develop in approximately 30%, and subclinical or overt hypothyroidism occurs in approximately 15-20%. In girls with **Turner syndrome**, antithyroid antibodies develop in approximately 40%, and subclinical or overt hypothyroidism occurs in approximately 15-30%, rising with increasing age. In children with **type 1 diabetes mellitus**, approximately 20% develop antithyroid antibodies and 5% become hypothyroid. Additional autoimmune diseases with an increased risk of hypothyroidism include immune dysregulation–polyendocrinopathy–enteropathy–X-linked syndrome (IPEX) and IPEX-like disorders, immunoglobulin G_4–related diseases, Sjögren syndrome, multiple sclerosis, pernicious anemia, Addison disease, and ovarian failure. Although typically seen in adolescence, it occurs as early as in the 1st yr of life. **Williams syndrome** is associated with subclinical hypothyroidism; this does not appear to be autoimmune, as antithyroid antibodies are negative.

Protracted ingestion of **medications** containing iodides—for example, expectorants or nutritional supplements—can cause hypothyroidism, usually accompanied by goiter (see Chapter 567). Amiodarone, a drug used for cardiac arrhythmias and consisting of 37% iodine by weight, causes hypothyroidism in approximately 20% of treated children. It affects thyroid function directly by its high iodine content as well as by inhibition of 5′-deiodinase, which converts T_4 to T_3. Children treated with this drug should have serial measurements of T_4, T_3, and TSH.

Anticonvulsants, including phenytoin, phenobarbital, and valproate, may cause thyroid dysfunction, usually mild, subclinical hypothyroidism. Certain anticonvulsants stimulate hepatic P450 metabolism and excretion of T_4. Children with Graves disease treated with antithyroid drugs (methimazole or propylthiouracil) can develop hypothyroidism. Additional drugs that can produce hypothyroidism include lithium, tyrosine kinase inhibitors, interferon-α, stavudine, thalidomide, and aminoglutethimide.

Children who receive craniospinal irradiation, as with treatment of Hodgkin disease or other head and neck malignancies or that is administered before bone marrow transplantation, are at risk for thyroid damage. Approximately 30% of such children acquire elevated TSH levels within a year after therapy, and another 15-20% progress to hypothyroidism within 5-7 yr. Central (hypopituitary) hypothyroidism may develop in approximately 10% of children receiving craniospinal irradiation.

Radioactive iodine ablative treatment or **thyroidectomy** for Graves disease or cancer results in hypothyroidism, as can removal of ectopic thyroid tissue. Thyroid tissue in a thyroglossal duct cyst usually constitutes the only source of thyroid hormone, and excision results in hypothyroidism. Ultrasonographic examination or a radionuclide scan before surgery is indicated in these patients.

Children with **nephropathic cystinosis,** a disorder characterized by intralysosomal storage of cystine in body tissues, acquire impaired thyroid function. Hypothyroidism may be overt, but subclinical forms are more common, and periodic assessment of TSH levels is indicated. By 13 yr of age, two thirds of these patients require T_4 replacement.

Histiocytic infiltration of the thyroid in children with **Langerhans cell histiocytosis** (see Chapter 507) can result in hypothyroidism.

Children with chronic **hepatitis C infection** are at risk for subclinical hypothyroidism; this does not appear to be autoimmune, because antithyroid antibodies are negative.

Hypothyroidism can occur in children with large **hemangiomas** of the liver, because of increased type 3 deiodinase activity, which catalyzes conversion of T_4 to reverse T_3 and T_3 to diiodothyronine. Thyroid secretion is increased, but it is not sufficient to compensate for the large increase in degradation of T_4 to reverse T_3.

Some patients with congenital thyroid dysgenesis and residual thyroid function or with incomplete genetic defects in thyroid hormone synthesis do not display clinical manifestations until childhood and appear to have acquired hypothyroidism. Although these conditions are usually now detected by newborn screening programs, very mild defects can escape detection.

Any **hypothalamic** or **pituitary** disease can cause acquired central hypothyroidism (see Chapter 557). TSH deficiency may be the result of a hypothalamic-pituitary tumor (craniopharyngioma is most common in children) or a result of treatment for the tumor. Other causes include cranial radiation, head trauma, or diseases infiltrating the pituitary gland, such as Langerhans cell histiocytosis.

Clinical Manifestations

Deceleration of growth is usually the first clinical manifestation, but this sign often goes unrecognized (Figs. 565-3 and 565-4). Goiter associated with Hashimoto thyroiditis, which may be a presenting feature, typically is nontender and firm, with a rubbery consistency and a pebbly surface. Weight gain is mostly fluid retention (myxedema), not true obesity. Myxedematous changes of the skin, constipation, cold intolerance, decreased energy, and an increased need for sleep develop insidiously. Surprisingly, schoolwork and grades usually do not suffer, even in severely hypothyroid children. Additional features include bradycardia, muscle weakness or cramps, nerve entrapment, and ataxia. Osseous maturation is delayed, often strikingly, which is an indication of the duration of the hypothyroidism. Adolescents typically have delayed puberty; older adolescent girls manifest menometrorrhagia. Younger children might present with galactorrhea or pseudoprecocious puberty. Galactorrhea is a result of increased TRH stimulating prolactin secretion. The precocious puberty, characterized by breast development and vaginal bleeding in girls and macroorchidism in boys, is thought to be the result of abnormally high TSH concentrations binding to the follicle-stimulating hormone receptor with subsequent stimulation.

Some children have headaches and vision problems; they usually have enlargement of the pituitary gland, sometimes with suprasellar extension, after long-standing primary hypothyroidism. This condition, believed to be the result of thyrotroph hyperplasia, may be mistaken for a pituitary tumor (see Chapter 557). Abnormal laboratory studies include hyponatremia, macrocytic anemia, hypercholesterolemia, and elevated creatine phosphokinase. Table 565-6 lists the complications seen in severe hypothyroidism. All these changes return to normal with adequate replacement of T_4.

Diagnostic Studies

Children with suspected hypothyroidism should undergo measurement of serum free T_4 and TSH. Because the normal range for thyroid tests is slightly higher in children than adults, it is important to compare results to age-specific reference ranges. Measurement of antithyroglobulin and antiperoxidase antibodies can pinpoint autoimmune thyroiditis as the cause. In cases with a goiter resulting from autoimmune thyroid disease, an ultrasound examination typically shows diffuse enlargement with scattered hypoechogenicity. However, generally, sonography is not indicated unless there is a suspicion of a thyroid nodule on neck palpation. In such cases, ultrasound examination is the most accurate study to confirm the presence of a nodule and determine if other, smaller nodules are present. In addition, an ultrasound examination can determine the nodule dimensions, texture (solid vs cystic nature), and presence or absence of other features that might influence a decision to undertake fine-needle aspiration, such as microcalcifications, blurred margins, "taller-than-wide" shape, intranodular vascular flow, and pathologic-appearing adjacent lymph nodes (see Chapter 569.1). In children with a nodule and suppressed TSH, a radioactive iodine uptake scan is indicated to determine if this is a "hot" or hyperfunctioning nodule. A bone age x-ray at diagnosis is useful, in that the degree of delay approximates duration and severity of hypothyroidism.

Treatment and Prognosis

L-T_4 is the treatment of choice in children with hypothyroidism. The dose on a weight basis gradually decreases with age. For children age 1-3 yr, the average L-T_4 dosage is 4-6 μg/kg/day; for age 3-10 yr, 3-5 μg/kg/day; and for age 10-16 yr, 2-4 μg/kg/day. Treatment should be monitored by measuring serum free T_4 and TSH every 4-6 mo as well as 6 wk after any change in dosage. In children with central hypothyroidism, where TSH levels are not helpful in monitoring treatment, the goal should be to maintain serum free T_4 in the upper half of the normal reference range for age.

During the 1st yr of treatment, deterioration of schoolwork, poor sleeping habits, restlessness, short attention span, and behavioral

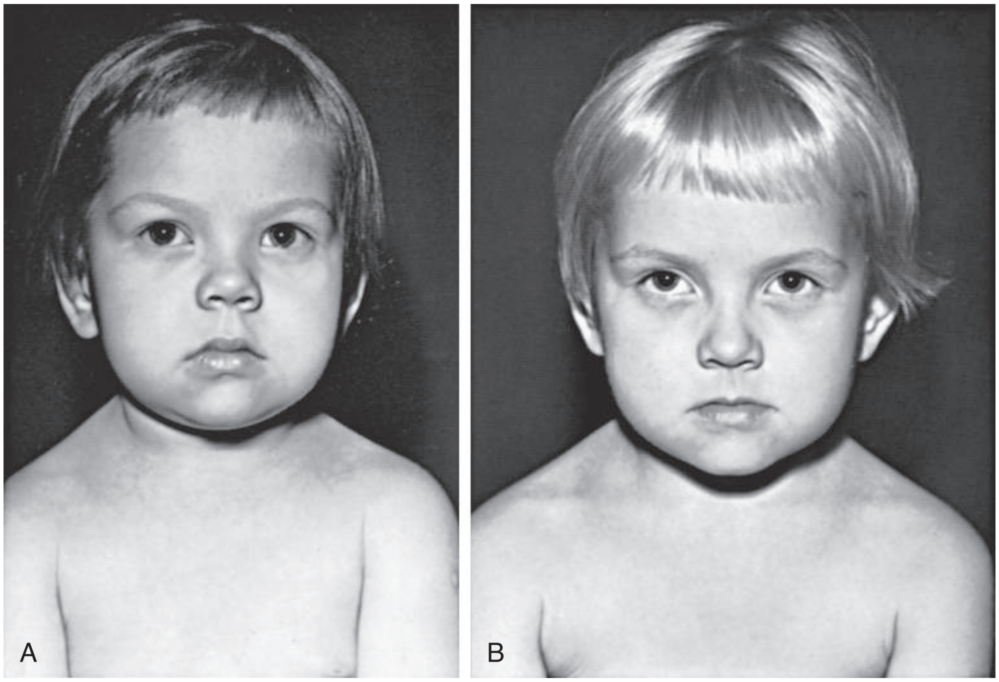

Figure 565-3 **A,** Acquired hypothyroidism in a girl 6 yr of age. She was treated with a wide variety of hematinics for refractory anemia for 3 yr. She had almost complete cessation of growth, constipation, and sluggishness for 3 yr. The height age was 3 yr; the bone age was 4 yr. She had a sallow complexion and immature facies with a poorly developed nasal bridge. Serum cholesterol, 501 mg/dL; radioiodine uptake, 7% at 24 hr; protein-bound iodine (PBI), 2.8 mg/dL. **B,** After therapy for 18 mo, note the nasal development, increased luster and decreased pigmentation of hair, and maturation of the face. The height age was 5.5 yr; the bone age was 7 yr. There was a decided improvement in her general condition. Menarche occurred at 14 yr. The ultimate height was 155 cm (61 in). She graduated from high school. The disorder was well controlled with sodium–L-thyroxine daily.

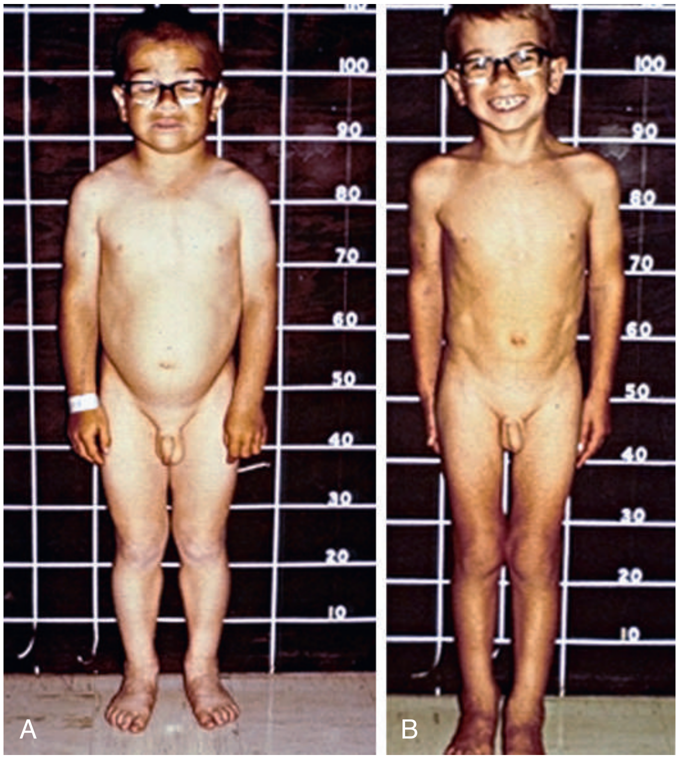

Figure 565-4 **A,** Short stature (108 cm, <3rd percentile), generalized myxedema, sleepy expression, protuberant abdomen, and coarse hair are signs of hypothyroidism in this 12 yr old boy. Body proportions are immature for his age (1.25 : 1). **B,** Same boy 4 mo after treatment. His height increased by 4 cm; note the marked change in body habitus owing to loss of generalized myxedema, improved muscle tone, and bright facial expression. *(From LaFranchi SH: Hypothyroidism,* Pediatr Clin North Am *26:33–51, 1979.)*

Table 565-6 Pathogenesis of General Complications in Management of Complicated Hypothyroidism

COMPLICATION	PATHOGENESIS
Heart failure	Impaired ventricular systolic and diastolic functions and increased peripheral vascular resistance
Ventilatory failure	Blunted hypercapnic and hypoxic ventilatory drives
Hyponatremia	Impaired renal free water excretion and syndrome of inappropriate antidiuretic hormone secretion
Ileus	Bowel hypomotility
Medication sensitivity	Reduced clearance rate and increased sensitivity to sedative, analgesic, and anesthetic agents
Hypothermia and lack of febrile response to sepsis	Decreased calorigenesis
Delirium, dementia, seizure, stupor, and coma	Decreased central nervous system thyroid hormone actions, and encephalopathy from hyponatremia and hypercapnia
Adrenal insufficiency	Associated intrinsic adrenal or pituitary disease, or reversible impairment of hypothalamic-pituitary-adrenal stress response
Coagulopathy	Acquired von Willebrand syndrome (type 1) and decreased factors VIII, VII, V, IX, and X

From Roberts CG, Landenson PW: Hypothyroidism, Lancet *363:793–803, 2004.*

problems might ensue, but these are transient; forewarning families about these manifestations enhances appropriate management. These may partially be ameliorated by starting at subreplacement T_4 doses and advancing slowly. The development of persistent headaches or vision changes should prompt an evaluation for papilledema associated with pseudotumor cerebri, a rare complication following initiation of L-T_4 treatment in older children (age 8-13 yr).

In older children, after catch-up growth is complete, the growth rate provides a good index of the adequacy of therapy. Periodic bone age x-rays are useful to monitor treatment and future growth potential. In children with long-standing hypothyroidism, catch-up growth may be incomplete (see Fig. 565-4). During the 1st 18 mo of treatment, skeletal maturation often exceeds expected linear growth, resulting in a loss of approximately 7 cm of predicted adult height.

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Chapter 566

Thyroiditis

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Stephen A. Huang

CHRONIC LYMPHOCYTIC THYROIDITIS (HASHIMOTO THYROIDITIS, AUTOIMMUNE THYROIDITIS)

Chronic lymphocytic thyroiditis is the most common cause of thyroid disease in children and adolescents and accounts for many of the enlarged thyroids formerly designated "adolescent" or "simple" goiter. It is also the most common cause of acquired hypothyroidism, with or without goiter.

One to 2% of younger school-age children and 6-8% of adolescents have positive antithyroid antibodies as evidence of autoimmune thyroid disease.

Etiology

This typical organ-specific autoimmune disease results from inheritance of susceptible genes involved in immunoregulation and environmental triggers, both as yet poorly characterized. Early in the course of the disease, there may be thyroid hyperplasia only; this is followed by infiltration of lymphocytes and plasma cells between the follicles and by atrophy of the follicles. Lymphoid follicle formation with germinal centers is almost always present; the degree of atrophy and fibrosis of the follicles varies from mild to moderate.

Intrathyroidal lymphocyte subsets differ from those in blood. Approximately 60% of infiltrating lymphoid cells are T cells, and approximately 30% express B-cell markers; the T-cell population is represented by helper ($CD4^+$) and cytotoxic ($CD8^+$) cells. The participation of cellular events in the pathogenesis is clear. Certain human leukocyte antigen (HLA) haplotypes (HLA-DR4, HLA-DR5) are associated with an increased risk of goiter and thyroiditis, and others (HLA-DR3) are associated with the atrophic variant of thyroiditis.

A variety of different thyroid antigen autoantibodies are also involved. Thyroid antiperoxidase antibodies (TPO-Abs) and antithyroglobulin antibodies (anti-Tg Abs) are demonstrable in the sera of 90% of children with chronic lymphocytic thyroiditis and in many patients with Graves disease. TPO-Abs are involved in activation of the complement cascade and in antibody-dependent, cell-mediated cytotoxicity. Anti-Tg Abs do not appear to play a role in the autoimmune destruction of the gland. Thyroid-stimulating hormone (TSH) receptor–blocking antibodies are related to the development of hypothyroidism and thyroid atrophy; they have been demonstrated in 18% of patients with severe hypothyroidism (TSH >20 mU/L) caused by autoimmune thyroiditis. Antibodies to pendrin, an apical protein on thyroid follicular cells, have been demonstrated in 80% of children with autoimmune thyroiditis. Antibodies also have been found against the sodium–iodide symporter, but their pathogenic role is unclear.

Clinical Manifestations

The disorder is 4-6 times more common in girls than in boys. It can occur during the 1st 3 yr of life, but becomes sharply more common after 6 yr of age and reaches a peak incidence during adolescence. The most common clinical manifestations are goiter and growth retardation. The goiter can appear insidiously and may be small or large. In most patients, the thyroid is diffusely enlarged, firm, and nontender. In approximately 30% of patients, the gland is asymmetric and can seem to be nodular. Most of the affected children are clinically euthyroid and asymptomatic; some may have symptoms of pressure in the neck, including difficulty swallowing and shortness of breath. Some children have clinical signs of hypothyroidism, but others who appear clinically euthyroid have laboratory evidence of hypothyroidism. A few children have manifestations suggesting hyperthyroidism, such as nervousness, irritability, increased sweating, and hyperactivity, but results of laboratory studies are not necessarily those of hyperthyroidism. Occasionally, the disorder coexists with Graves disease ("Hashitoxicosis"). Ophthalmopathy can occur in autoimmune thyroiditis in the absence of Graves disease.

The clinical course is variable. The goiter might become smaller or might disappear spontaneously, or it might persist unchanged for years while the patient remains euthyroid. Most children who are euthyroid at presentation remain euthyroid, although a percentage of patients acquire hypothyroidism gradually within months or years. In children who initially have mild or subclinical hypothyroidism (elevated serum TSH, normal free thyroxine [T_4] level), over several years approximately 40% revert to euthyroidism, 50% continue to have subclinical hypothyroidism, and approximately 10% develop overt hypothyroidism (elevated serum TSH, subnormal free T_4 level). Chronic lymphocytic thyroiditis is the cause of most cases of nongoitrous (atrophic) hypothyroidism.

Familial clusters of chronic lymphocytic thyroiditis are common; the incidence in siblings or parents of affected children may be as high as 25%. TPO-Abs and anti-Tg Abs in these families appear to be inherited in an autosomal dominant fashion, with reduced penetrance in males. The concurrence within families of patients with chronic lymphocytic thyroiditis, hypothyroidism, and Graves disease provides cogent evidence for a basic relationship among these 3 conditions.

The disorder is associated with many other autoimmune disorders. Autoimmune thyroiditis occurs in 10% of patients with type I autoimmune polyglandular syndrome (APS-1), characterized by autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia (APECED). APS-1 consists of 2 of the triad of hypoparathyroidism, Addison disease, and mucocutaneous candidiasis (HAM syndrome). This relatively rare autosomal recessive disorder occurs in childhood and is caused by mutations in the autoimmune regulator *(AIRE)* gene on chromosome 21q22.3.

Autoimmune thyroid disease occurs in 70% of patients with APS-2. APS-2 consists of the association of autoimmune thyroiditis and Addison disease (Schmidt syndrome) or autoimmune thyroiditis with type 1 diabetes mellitus (Carpenter syndrome). It typically occurs in later childhood or early adulthood; the etiology is unknown. Autoimmune thyroiditis has been described in children with immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, which includes early-onset diabetes and colitis. Autoimmune thyroid disease also tends to be associated with pernicious anemia, vitiligo, or alopecia. TPO-Abs are found in approximately 20% of white and 4% of black children with type 1 diabetes mellitus. Autoimmune thyroid disease has an increased incidence in children with congenital rubella.

Chronic lymphocytic thyroiditis also is associated with certain chromosomal disorders, particularly Turner syndrome and Down syndrome. In children with Down syndrome, one study reported that 28% had antithyroid antibodies (predominantly anti-TPOs), 7% had subclinical hypothyroidism, 7% had overt hypothyroidism, and 5% had

Table 566-1 Characteristics of Thyroiditis Syndromes

CHARACTERISTIC	HASHIMOTO THYROIDITIS	PAINLESS POSTPARTUM THYROIDITIS	PAINLESS SPORADIC THYROIDITIS	PAINFUL SUBACUTE THYROIDITIS	ACUTE SUPPURATIVE THYROIDITIS	RIEDEL THYROIDITIS
Sex ratio (F:M)	4-6:1	—	2:1	5:1	1:1	3-4:1
Cause	Autoimmune	Autoimmune	Autoimmune	Unknown (probably viral)	Infectious (bacterial)	Unknown
Pathologic findings	Lymphocytic infiltration, germinal centers, fibrosis	Lymphocytic infiltration	Lymphocytic infiltration	Giant cells, granulomas	Abscess formation	Dense fibrosis
Thyroid function	Usually euthyroidism; some hypothyroidism	Hyperthyroidism, hypothyroidism, or both	Hyperthyroidism, hypothyroidism, or both	Hyperthyroidism, hypothyroidism, or both	Usually euthyroidism	Usually euthyroidism
TPO antibodies	High titer, persistent	High titer, persistent	High titer, persistent	Low titer, or absent, or transient	Absent	Usually present
ESR	Normal	Normal	Normal	High	High	Normal
24 hr ^{123}I uptake	Variable	<5%	<5%	<5%	Normal	Low or normal

ESR, erythrocyte sedimentation rate; ^{123}I, iodine 123; TPO, thyroid peroxidase.
Data from Farwell AP, Braverman LE. Inflammatory thyroid disorders. Otolaryngol Clin North Am *4:541–556, 1996.*

hyperthyroidism. In a study of girls with Turner syndrome, 41% had antithyroid antibodies (again, predominantly anti-TPOs), 18% had goiter, and 8% had subclinical or overt hypothyroidism. Another study of 75 girls with Turner syndrome found that autoimmune thyroid disease increased from the 1st (15%) to the 3rd (30%) decade of life. Boys with Klinefelter syndrome appear to be at risk for autoimmune thyroid disease. Table 566-1 compares the characteristics of Hashimoto thyroiditis to other thyroiditis syndromes.

Laboratory Findings

Thyroid function tests (free T_4 and TSH) are often normal, although the level of TSH may be slightly or even moderately elevated in some patients, which is termed *subclinical hypothyroidism.* That many children with chronic lymphocytic thyroiditis do not have elevated levels of TSH indicates that the goiter is caused by the lymphocytic infiltrations or by thyroid growth-stimulating immunoglobulins. Young children with chronic lymphocytic thyroiditis have serum TPO-Abs, but the anti-Tg Abs are positive in <50%. TPO-Abs and anti-Tg Abs are found equally in adolescents with chronic lymphocytic thyroiditis. When both tests are used, approximately 95% of patients with thyroid autoimmunity are detected. Levels in children and adolescents are lower than those in adults with Hashimoto thyroiditis, and repeated measurements are indicated in questionable instances because titers might increase later in the course of the disease. In adolescent females with overt hypothyroidism, measurement of TSH receptor–blocking antibodies may identify patients at future risk of having babies with transient congenital hypothyroidism.

Thyroid scans and ultrasonography usually are not needed. If they are done, thyroid scans reveal irregular and patchy distribution of the radioisotope, and in approximately 60% or more, the administration of perchlorate results in a >10% discharge of iodide from the thyroid gland. Thyroid ultrasonography shows heterogeneous echogenicity in most patients, along with an increased number of benign-appearing hyperplastic lymph nodes in the neck. The definitive diagnosis can be established by biopsy of the thyroid; this procedure is rarely clinically indicated.

Antithyroid antibodies also may be found in almost 50% of the siblings of affected patients and in a significant percentage of the mothers of children with Down syndrome or Turner syndrome without demonstrable thyroid disease.

Treatment

If there is evidence of overt hypothyroidism (elevated TSH, low T_4 or free T_4), replacement treatment with levothyroxine (at doses specific for size and age) is indicated. The goiter usually shows some decrease in size but can persist for years. In a euthyroid patient, treatment with suppressive doses of levothyroxine is unlikely to lead to a significant decrease in size of the goiter. Antibody levels fluctuate in both treated and untreated patients and persist for years. Because the disease is self-limited in some instances, the need for continued therapy requires periodic reevaluation. Untreated patients should also be checked periodically. Although there is some controversy about treating patients with subclinical hypothyroidism (elevated TSH, normal T_4 or free T_4), many clinicians prefer to treat such children until growth and puberty are complete, and then reevaluate their thyroid function.

Prominent **nodules** (i.e., >1 cm) that persist despite suppressive therapy should be examined histologically using fine-needle aspiration, because thyroid carcinoma or lymphoma has occurred in patients with Hashimoto thyroiditis.

OTHER CAUSES OF THYROIDITIS

Subacute granulomatous thyroiditis (de Quervain disease) is rare in children. It is thought to have a viral cause and remits spontaneously. The disorder becomes manifested by an upper respiratory infection with vague tenderness over the thyroid and low-grade fever, followed by severe pain in the region of the thyroid gland. Inflammation results in leakage of preformed thyroid hormone from the gland into the circulation. Serum levels of T_4 and triiodothyronine are elevated while TSH is suppressed, and mild symptoms of hyperthyroidism may be present, but radioiodine uptake is depressed. The erythrocyte sedimentation rate is increased. The course is variable but usually characterized by 4 phases: hyperthyroidism, usually followed by a euthyroid phase and then a hypothyroid phase, and remission usually occurring in several months, with recovery to euthyroidism.

Acute suppurative thyroiditis is uncommon in children; it is usually preceded by a respiratory infection with pharyngitis. The left lower lobe is affected predominantly. Abscess formation can occur; anaerobic organisms, with or without aerobes, are the typical infectious agents. The most common organism is α-hemolytic streptococci (viridans) followed by *Staphylococcus aureus* and pneumococci. Recurrent episodes or detection of a mixed bacterial flora suggests that the infection arises from a **piriform sinus fistula** or, less commonly, from a **thyroglossal duct** remnant. Exquisite tenderness of the gland, swelling, erythema, dysphagia, and limitation of head motion are characteristic findings. Fever, chills, and sore throat are not uncommon, and leukocytosis is present. Scintigrams of the thyroid often reveal decreased uptake in the affected areas, and ultrasonography might show a complex echogenic mass. Thyroid function is usually normal, but hyperthyroidism caused by escape of thyroid hormone has been encountered in a child with suppurative thyroiditis resulting from *Aspergillus.* When abscesses form, incision and drainage and administration of parenteral antibiotics are indicated. After the infection

subsides, a barium esophagram or CT scan with contrast is indicated to search for a fistulous tract; if one is found, surgical excision is indicated.

Specific conditions such as tuberculosis, sarcoidosis, mumps, and cat-scratch disease are rare causes of thyroiditis in children. **Other forms of thyroiditis** seen in adults, such as painless sporadic thyroiditis and Riedel thyroiditis, are rare in children (see Table 566-1).

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Chapter 567
Goiter

Stephen A. Huang and Stephen H. LaFranchi

A goiter, or thyromegaly, is an enlargement of the thyroid gland. Persons with enlarged thyroids can have normal function of the gland **(euthyroidism),** thyroid deficiency **(hypothyroidism),** or overproduction of the hormones **(hyperthyroidism).** Goiter may be congenital or acquired, endemic or sporadic. Detection of a goiter should prompt an investigation of its cause and the assessment of thyroid function.

Goiter most often results from the increased pituitary secretion of thyroid-stimulating hormone (TSH) in response to decreased circulating levels of thyroid hormones. Activation of the TSH receptor from thyrotropin receptor–stimulating antibodies (in Graves disease), gain-of-function TSH receptor mutations, or inappropriate TSH secretion (from dominant negative thyroid hormone receptor mutations or TSH-secreting adenomas) can also cause thyromegaly. Thyroid enlargement can also result from infiltrative processes that may be inflammatory or neoplastic.

567.1 Congenital Goiter

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Congenital goiter is usually sporadic and can result from a fetal thyroxine (T_4) synthetic defect or from administration of antithyroid drugs or iodides during pregnancy for the treatment of maternal thyrotoxicosis. Goitrogenic drugs that cross the placenta at high doses can interfere with synthesis of thyroid hormone, resulting in goiter and hypothyroidism in the fetus. These effects are most severe when pharmacologic overtreatment with antithyroid drugs causes concomitant hypothyroidism in the mother and reduces the supply of maternal thyroid hormone available to the fetus. In women with Graves disease receiving antithyroid drugs, fetal effects can occur when the mother takes propylthiouracil at only 100-200 mg/24 hr; consequently, all infants born to women treated with antithyroid drugs in the 3rd trimester should undergo thyroid studies at birth. Even when the infant is clinically euthyroid, there may be retardation of osseous maturation, low levels of T_4, and elevated levels of TSH. Administration of thyroid hormone to affected infants may be indicated to treat clinical hypothyroidism, to hasten the disappearance of the goiter, and to prevent brain damage. Because the condition is rarely permanent, thyroid hormone may be safely discontinued after the antithyroid drug has been excreted by the neonate, usually after 1-2 wk. In addition to antithyroid medications, iodides are included in many proprietary cough preparations used to treat asthma; these preparations should be avoided during pregnancy because they have often been reported to cause congenital goiter. Amiodarone, an antiarrhythmic drug with 37% iodine content, has also caused congenital goiter with hypothyroidism.

Enlargement of the thyroid at birth may occasionally be sufficient to cause respiratory distress that interferes with nursing and can even cause death. The head may be maintained in extreme hyperextension. In pregnant women who are overtreated with antithyroid drugs, the prenatal diagnosis of even massive fetal goiter can often be corrected by withdrawal of the maternal medication, with or without intraamniotic thyroid hormone injection. When postnatal respiratory obstruction is severe, partial thyroidectomy rather than tracheostomy is indicated (Fig. 567-1).

Goiter is almost always present in the infant with neonatal Graves hyperthyroidism. Thyroid enlargement results from transplacental passage of maternal thyroid-stimulating immunoglobulin (see Chapter 568.2). These goiters usually are not large; the infant manifests clinical symptoms of hyperthyroidism. The mother often has a history of Graves disease, or the diagnosis of maternal Graves may be revealed through the evaluation of neonatal hyperthyroidism. TSH receptor–activating mutations are also a recognized cause of congenital goiter and hyperthyroidism.

When no causative factor is identifiable from the maternal or medication history, a **defect in synthesis** of thyroid hormone should be suspected. Neonatal screening programs find congenital hypothyroidism caused by such a defect in 1 in 30,000-50,000 live births. It is advisable to treat immediately with thyroid hormone and to postpone more-detailed studies for later in life. If a specific defect is suspected,

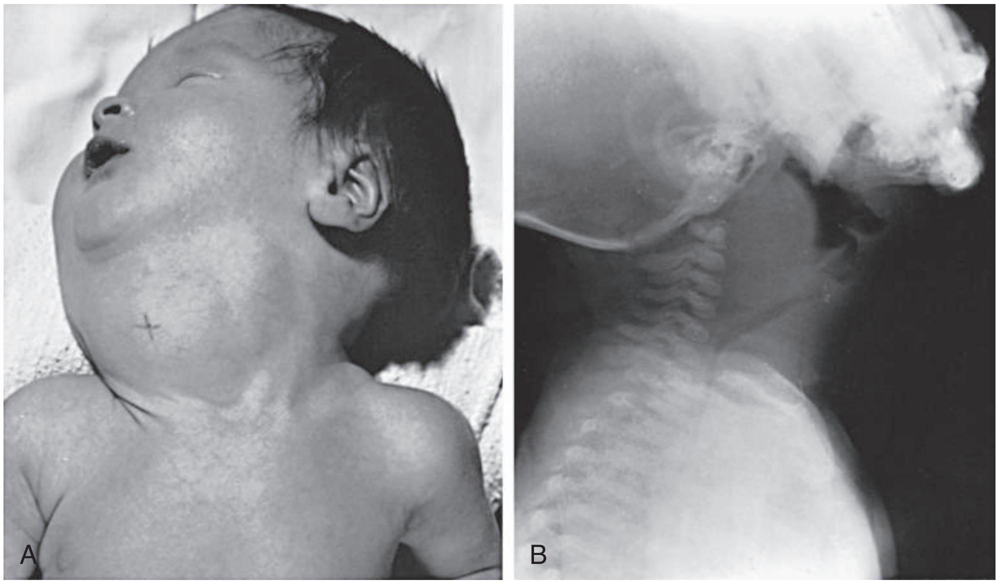

Figure 567-1 Congenital goiter in infancy. **A,** Large congenital goiter in an infant born to a mother with thyrotoxicosis who had been treated with iodides and methimazole during pregnancy. **B,** A different infant, 6 wk old, with increasing respiratory distress and cervical mass since birth. The operation revealed a large goiter that almost completely encircled the trachea. Notice the anterior deviation and posterior compression of the trachea. Partial thyroidectomy completely relieved the symptoms. It is apparent why a tracheostomy is not adequate treatment for these infants. The cause for the goiter was not found.

genetic tests to identify a mutation may be undertaken (see Chapter 565). Because these defects are often caused by recessive mutations, a precise diagnosis is helpful for genetic counseling. Monitoring subsequent pregnancies with ultrasonography can be useful in detecting fetal goiters (see Chapter 96).

Pendred syndrome, characterized by familial goiter and neurosensory deafness, is caused by a mutation in the *SLC26A4* gene, which encodes the pendrin chloride–iodide transport protein expressed in the thyroid gland and cochlea. This defect results in abnormal iodide organification in the thyroid and can cause a goiter at birth. The more common presentation is a euthyroid goiter and sensorineural hearing loss later in life.

Iodine deficiency as a cause of congenital goiter is rare in developed countries but persists in isolated endemic areas (see Chapter 567.3). More important is the recognition that severe iodine deficiency early in pregnancy can cause neurologic damage during fetal development, even in the absence of goiter. The iodine deficiency can result in combined maternal and fetal hypothyroidism, reducing the protective transfer of maternal thyroid hormones.

When the "goiter" is lobulated, asymmetric, firm, or large to an unusual degree, a teratoma within or in the vicinity of the thyroid must be considered in the differential diagnosis (see Chapter 569).

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567.2 Intratracheal Goiter

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One of the many ectopic locations of thyroid tissue is within the trachea. The intraluminal thyroid lies beneath the tracheal mucosa and is often continuous with the normally situated extratracheal thyroid gland. The thyroid is susceptible to goitrous enlargement, which involves both the eutopic and ectopic thyroid tissue. When there is obstruction of the airway associated with a goiter, it must be ascertained whether the obstruction is extratracheal or endotracheal. If obstructive manifestations are mild, administration of sodium L-thyroxine (levothyroxine) usually causes the goiter to decrease in size. When symptoms are severe, surgical removal of the endotracheal goiter is indicated.

567.3 Endemic Goiter and Cretinism

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ETIOLOGY

The association between dietary deficiency of iodine and the prevalence of goiter or cretinism is well established. A moderate deficiency of iodine can be overcome by increased efficiency in the synthesis of thyroid hormone. Iodine liberated in the tissues is returned rapidly to the gland, which resynthesizes triiodothyronine (T_3) preferentially at a higher rate than normal. This increased activity is achieved by compensatory hypertrophy and hyperplasia (goiter), which satisfy the demands of the tissues for thyroid hormone. In geographic areas where deficiency of iodine is severe, decompensation and hypothyroidism can result. Recent estimates from the World Health Organization indicate that nearly 2 billion individuals currently have insufficient iodine intake, including one third of the world's school-age children. Thus, despite great progress in the global effort to reduce iodine deficiency, it remains the leading cause of preventable intellectual disability worldwide.

Seawater is rich in iodine; the iodine content of fish and shellfish is also high. As a result, endemic goiter is rare in populations living along the coast. Iodine is deficient in the water and native foods in the Pacific West and the Great Lakes areas of the United States. Deficiency of dietary iodine is even greater in certain Alpine valleys, the Himalayas, the Andes, the Congo, and the highlands of Papua New Guinea. In areas such as the United States, where iodine is provided in foods from other areas and in iodized salt, endemic goiter has disappeared. Iodized salt in the United States contains potassium iodide (100 µg/g), which provides excellent prophylaxis. Further iodine intake in the United States is contributed by iodates used in baking, iodine-containing coloring agents, and iodine-containing disinfectants used in the dairy industry. The recommended daily allowance of iodine is as follows:

- Children younger than 2 yr: ≥100 µg/day
- School-age children: 100-299 µg/day
- Pregnant women: ≥150 µg/day
- Lactating women: ≥100 µg/day

While the overall dietary iodine intake in the United States is considered adequate, the most recent NHANES (National Health and Nutrition Examination Survey) from 2007-2010 reports that the median urinary iodine concentration among pregnant U.S. women has dropped to <150 µg/L. This indicates mild iodine deficiency and highlights the risk of iodine deficiency reemergence in industrialized countries as salt intake decreases. These risks can be mitigated by the continued monitoring of iodine status, the adjustment of salt iodization levels, and the targeted supplementation of vulnerable subpopulations (promotion of iodine-containing prenatal vitamins).

CLINICAL MANIFESTATIONS

If the deficiency of iodine is mild, thyroid enlargement does not become noticeable except when there is increased demand for the hormone during periods of rapid growth, as in adolescence and during pregnancy. In regions of moderate iodine deficiency, goiter observed in school children can disappear with maturity and reappear during pregnancy or lactation. Iodine-deficient goiters are more common in girls than in boys. In areas where iodine deficiency is severe, as in the hyperendemic highlands of Papua New Guinea, nearly half the population has large goiters, and endemic cretinism is common (Fig. 567-2).

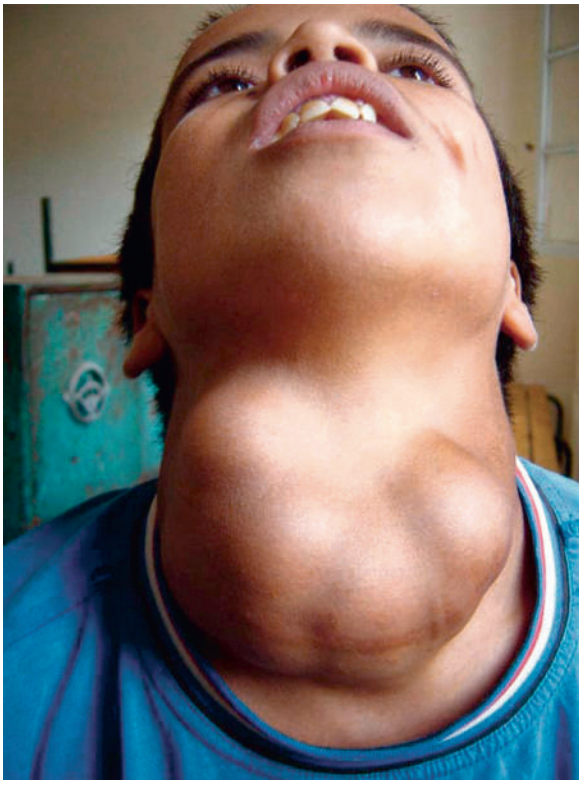

Figure 567-2 A 14 yr old boy with a large nodular goiter was seen in 2004, in an area of severe iodine-deficiency disorders in northern Morocco. He had tracheal and esophageal compression and hoarseness, probably as a result of damage to the recurrent laryngeal nerves. *(From Zimmernamm MB, Jooste PL, Pandav CS: Iodine-deficiency disorders,* Lancet *372:1251–1262, 2008, Fig 2.)*

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Serum T_4 levels are often low in persons with endemic goiter, although clinical hypothyroidism is rare. This is true in New Guinea, the Congo, the Himalayas, and South America. Despite low serum T_4 levels, serum TSH concentrations are often normal or only moderately increased. In such patients, circulating levels of T_3 are elevated. Moreover, T_3 levels are also elevated in patients with normal T_4 levels, indicating a preferential secretion of T_3 by the thyroid in this disease and an adaptive increase in peripheral T_4 to T_3 conversion.

Endemic cretinism is the most serious consequence of iodine deficiency; it occurs only in geographic association with endemic goiter. The term *endemic cretinism* includes 2 different but overlapping syndromes: a **neurologic type** and a **myxedematous type.** The incidence of the 2 types varies among different populations. In Papua New Guinea, the neurologic type occurs almost exclusively, whereas in the Congo, the myxedematous type predominates. Both types are found in all endemic areas, and some persons have intermediate or mixed features.

The **neurologic syndrome** is characterized by intellectual disability, deaf-mutism, disturbances in standing and gait, and pyramidal signs such as clonus of the foot, the Babinski sign, and patellar hyperreflexia. Affected persons are goitrous but euthyroid, have normal pubertal development and adult stature, and have little or no impaired thyroid function. Persons with the **myxedematous syndrome** also are intellectually challenged and deaf and have neurologic symptoms, but in contrast to the neurologic type, they have delayed growth and sexual development, myxedema, and absence of goiter. Serum T_4 levels are low and TSH levels are markedly elevated. Delayed skeletal maturation may extend into the 3rd decade or later. Ultrasonographic examination shows thyroid atrophy.

PATHOGENESIS

The pathogenesis of the **neurologic syndrome** is attributed to iodine deficiency and hypothyroxinemia during pregnancy, leading to fetal and postnatal hypothyroidism. Although some investigators have attributed brain damage to a direct effect of elemental iodine deficiency in the fetus, most believe the neurologic symptoms are caused by combined fetal and maternal hypothyroxinemia. There is evidence for the presence of thyroid hormone receptors in the fetal brain as early as 7 wk of gestation. Although the normal fetal thyroid gland does not begin to produce significant amounts of thyroid hormone until midgestation, there is measurable T_4 in the coelomic fluid as early as 6 wk, almost certainly of maternal origin. These lines of evidence support a role for maternal thyroid hormone in fetal brain development in the 1st trimester. In addition, there is evidence of transplacental passage of maternal thyroid hormone into the fetus, which normally might ameliorate the effects of fetal hypothyroidism on the developing nervous system in the second half of pregnancy. Thus, iodine deficiency in the mother affects fetal brain development both in the 1st trimester and throughout pregnancy. Intake of iodine after birth is often sufficient for normal or only minimally impaired thyroid function.

The pathogenesis of the **myxedematous syndrome** leading to thyroid atrophy is more bewildering. Searches for additional environmental factors that might provoke continuing postnatal hypothyroidism have led to incrimination of selenium deficiency, goitrogenic foods, thiocyanates, and *Yersinia* (Table 567-1). Studies from western China suggest that thyroid autoimmunity might play a role. Children with myxedematous cretinism with thyroid atrophy, but not children with euthyroid cretinism, were found to have thyroid growth-blocking immunoglobulins of the kind found in infants with sporadic congenital hypothyroidism. Others are skeptical about any role of thyroid growth-blocking immunoglobulins to explain these findings.

Table 567-1 Goitrogens and Their Mechanism

GOITROGEN	MECHANISM
FOODS	
Cassava, lima beans, linseed, sorghum, sweet potato	Contain cyanogenic glucosides that are metabolized to thiocyanates that compete with iodine for uptake by the thyroid
Cruciferous vegetables such as cabbage, kale, cauliflower, broccoli, turnips, rapeseed	Contain glucosinolates; metabolites compete with iodine for uptake by the thyroid
Soy, millet	Flavonoids impair thyroid peroxidase activity
INDUSTRIAL POLLUTANTS	
Perchlorate	Competitive inhibitor of the sodium–iodine symporter, decreasing iodine transport into the thyroid
Others (e.g., disulfides from coal processes)	Reduce thyroidal iodine uptake
Smoking	An important goitrogen; smoking during breastfeeding is associated with reduced iodine concentrations in breast milk; high serum concentration of thiocyanate from smoking might compete with iodine for active transport into the secretory epithelium of the lactating breast
NUTRIENTS	
Selenium deficiency	Accumulated peroxides can damage the thyroid, and deiodinase deficiency impairs thyroid hormone activation
Iron deficiency	Reduces heme-dependent thyroperoxidase activity in the thyroid and might blunt the efficacy of iodine prophylaxis
Vitamin A deficiency	Increases TSH stimulation and goiter through decreased vitamin A–mediated suppression of the pituitary TSH-β gene

TSH, thyroid-stimulating hormone.

From Zimmernamm MB, Jooste PL, Pandav CS: Iodine-deficiency disorders, Lancet 372:1251–1262, 2008, Table 1.

TREATMENT

In many developing countries, administration of a single intramuscular injection of iodinated poppy seed oil to women prevents iodine deficiency during future pregnancies for approximately 5 yr. This form of therapy given to children younger than 4 yr of age with myxedematous cretinism results in a euthyroid state in 5 mo. Older children respond poorly and adults not at all to iodized oil injections, indicating an inability of the thyroid gland to synthesize hormone; these patients require treatment with T_4. Through the efforts of the World Health Organization and its program of universal salt iodization, the number of households worldwide with access to adequately iodized salt has increased from <10% in 1990 to 70% in 2012. In the Xinjiang province of China, where the usual methods of iodine supplementation had failed, iodination of irrigation water has increased iodine levels in soil, animals, and human beings. In other countries, iodinated salt in school meal programs gives children the dietary iodine they need. Still, political, economic, and practical obstacles have limited penetration of iodized food into regular diets around the world.

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567.4 Acquired Goiter

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Most acquired goiters are sporadic and develop from a variety of causes; patients are usually euthyroid but may be hypothyroid or hyperthyroid. The most common cause of acquired goiter is

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lymphocytic thyroiditis (see Chapter 566). Rarer causes in children include painless sporadic thyroiditis and subacute painful thyroiditis (de Quervain disease; see Chapter 566). Other causes include excess iodide ingestion and certain drugs, including amiodarone and lithium. Intrinsic biochemical defects in the synthesis of thyroid hormone are almost always associated with goiter; thyromegaly from milder defects occurs later in childhood. The occurrence of the disorder in siblings, onset in early life, and possible association with hypothyroidism (goitrous hypothyroidism) are important clues to the diagnosis.

IODIDE GOITER

A small percentage of patients treated with iodide preparations for prolonged periods acquire goiters. Iodides are commonly included for their expectorant effect in cough medicines and in proprietary mixtures for asthma. Goiters resulting from iodide administration are firm and diffusely enlarged, and in some instances hypothyroidism develops. In normal persons, acute administration of large doses of iodide inhibits the organification of iodine and the synthesis of thyroid hormone (Wolff-Chaikoff effect). This effect is short-lived and does not lead to permanent hypothyroidism. When iodide administration continues, an autoregulatory mechanism in normal persons limits iodide trapping and permits the level of iodide in the thyroid to decrease and organification to proceed normally. In patients with iodide-induced goiter, this escape does not occur, because of an underlying abnormality of biosynthesis of thyroid hormone. The persons most susceptible to the development of iodide goiter are those with lymphocytic thyroiditis or with a subclinical inborn error in thyroid hormone synthesis and those who have had a partial thyroidectomy.

Lithium carbonate, which is used to treat bipolar disorder, also causes goiters and mild hypothyroidism. Lithium decreases T_4 and T_3 synthesis and release; the mechanism producing the goiter or hypothyroidism is similar to that described for iodide goiter. Lithium and iodide also act synergistically to produce goiter; their combined use should be avoided.

Amiodarone, a drug used to treat cardiac arrhythmias, can cause thyroid dysfunction with goiter because it is rich in iodine. It is also a potent inhibitor of 5′-deiodinase, preventing conversion of T_4 to T_3. It can cause hypothyroidism, particularly in patients with underlying autoimmune disease. In other patients, it can cause thyrotoxicosis through either transient thyroiditis or the Jod-Basedow effect.

SIMPLE GOITER (COLLOID GOITER)

A few children with euthyroid goiters have simple goiters, a condition of unknown cause not associated with hypothyroidism or hyperthyroidism and not caused by inflammation or neoplasia. The condition predominates in girls and has a peak incidence before and during the pubertal years. Histologic examination of the thyroid either is normal or reveals variable follicular size, dense colloid, and flattened epithelium. The goiter may be small or large. It is firm in half the patients and occasionally is asymmetric or nodular. Levels of TSH are normal or low, scintiscans are normal, and thyroid antibodies are absent. Differentiation from lymphocytic thyroiditis might not be possible without a biopsy, but biopsy is usually not indicated. Therapy with thyroid hormone can help prevent progression to a large multinodular goiter, although it is difficult to separate any treatment effects from the natural history, which is for the goiter to decrease in size. Patients should be reevaluated periodically, because some have antibody-negative lymphocytic thyroiditis and therefore are at risk for changes in thyroid function (see Chapter 566).

MULTINODULAR GOITER

Rarely, a firm goiter with a lobulated surface and single or multiple palpable nodules is encountered. Areas of cystic change, hemorrhage, and fibrosis may be present. The incidence of this condition has decreased markedly with the use of iodine-enriched salt. A mild goitrogenic stimulus, acting over a long time, is thought to be the cause. Ultrasonographic examination can reveal multiple nodules that are nonfunctioning on scintiscans. Thyroid studies are usually normal. Some children with chronic lymphocytic thyroiditis develop multinodular goiter; TSH may be elevated, and thyroid antibodies may be present.

Children can develop toxic multinodular goiter, characterized by a suppressed TSH and hyperthyroidism. The condition occurs in children with **McCune-Albright syndrome** (usually resulting in hyperthyroidism), with **TSH receptor–activating mutations,** and it has been described in 3 children (including 2 siblings) with digital anomalies and cystic kidney disease. If hypofunctioning nodules within a multinodular goiter grow to significant size (≥1 cm), fine-needle aspiration should be considered to rule out malignancy (see Chapter 569).

TOXIC GOITER (HYPERTHYROIDISM)

See Chapter 568.

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Chapter 568

Hyperthyroidism

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Hyperthyroidism results from excessive secretion of thyroid hormone; during childhood, with few exceptions, it is caused by Graves disease (Table 568-1). **Graves disease** is an autoimmune disorder; production of thyroid-stimulating immunoglobulin that binds to and activates the G-protein–coupled **thyroid-stimulating hormone (TSH) receptor** results in diffuse toxic goiter. Other causes of hyperthyroidism include gain-of-function germline mutations in the **TSH receptor**, which are found in both familial (autosomal dominant) and sporadic cases of non–autoimmune hyperthyroidism. These patients, whose disease can appear in the neonatal period or in later childhood, have thyroid hyperplasia with goiter and suppressed levels of TSH. Different activating mutations have been identified in some cases of thyroid adenomas. Hyperthyroidism occurs in some patients with **McCune-Albright syndrome** as a result of an activating mutation of the α subunit of the G-protein; these patients tend to have a multinodular goiter. Other rare causes of thyrotoxicosis that have been observed in children include painless sporadic thyroiditis, subacute painful thyroiditis, acute suppurative thyroiditis, thyrotoxicosis factitia, TSH-secreting adenomas, and hyperfunctioning thyroid carcinoma.

Suppression of plasma TSH indicates that the hyperthyroidism is not pituitary in origin. Hyperthyroidism caused by inappropriate thyrotropin secretion is rare and, in most cases, is caused by dominant negative thyroid hormone receptor mutations and pituitary resistance to thyroid hormone. TSH-secreting pituitary tumors are extremely rare in the pediatric population. In infants born to mothers with Graves disease, hyperthyroidism is almost always a transitory phenomenon; classic Graves disease during the neonatal period is rare. Choriocarcinoma, hydatidiform mole, and struma ovarii have caused hyperthyroidism in adults but have not been recognized as causes in children.

Studies have examined the health and quality of life of individuals with subclinical hyperthyroidism (i.e., with TSH <0.1 mU/L, but normal serum thyroxine [T_4] and triiodothyronine [T_3] concentrations) or who are euthyroid on antithyroid medication. These studies indicate that subclinical hyperthyroidism carries a risk of late-life atrial fibrillation, but no similar risks have been identified in the general pediatric population. There appears to be no difference in long-term quality of life among hyperthyroid patients treated with antithyroid medication, radioiodine ablation, or surgery. Quality of life was diminished relative to control persons in all 3 cases (see Chapter 568.1).

Table 568-1 Causes of Hyperthyroidism

CAUSES OF HYPERTHYROIDISM	PATHOPHYSIOLOGIC FEATURES	INCIDENCE
CIRCULATING THYROID STIMULATORS		
Graves disease	Thyroid-stimulating immunoglobulins	Common
Neonatal Graves disease	Thyroid-stimulating immunoglobulins	Rare
Thyrotropin-secreting tumor	Pituitary adenoma	Very rare
Choriocarcinoma	Human chorionic gonadotropin secretion stimulating the thyroid-stimulating hormone receptor	Rare
THYROIDAL AUTONOMY		
Toxic multinodular goiter	Activating mutations in thyrotropin receptor or G-protein	Common
Toxic solitary adenoma	Activating mutations in thyrotropin receptor or G-protein	Common
Congenital hyperthyroidism	Activating mutations in thyrotropin receptor	Very rare
Iodine-induced hyperthyroidism (Jod-Basedow phenomenon)	Unknown; excess iodine results in unregulated thyroid hormone production	Uncommon in United States and other iodine-sufficient areas
DESTRUCTION OF THYROID FOLLICLES (THYROIDITIS)		
Subacute painful thyroiditis	Probable viral infection	Uncommon
Painless sporadic thyroiditis (or postpartum thyroiditis)	Autoimmune	Common
Amiodarone-induced thyroiditis	Direct toxic drug effects	Uncommon
Acute (infectious) thyroiditis	Thyroid infection (e.g., bacterial, fungal) and release of preformed hormone	Uncommon
EXOGENOUS THYROID HORMONE		
Iatrogenic	Overtreatment with thyroid hormone	Common
Factitious	Excess ingestion of thyroid hormone	Rare
Hamburger thyrotoxicosis	Thyroid gland included in ground beef	Probably rare
ECTOPIC THYROID TISSUE		
Struma ovarii	Ovarian teratoma containing thyroid tissue	Rare
Metastatic follicular thyroid cancer	Large tumor mass capable of secreting thyroid hormone autonomously	Rare
Pituitary resistance to thyroid hormone	Mutated thyroid hormone receptor-β	Rare

Adapted from Cooper DS: Hyperthyroidism, Lancet *362:459–468, 2003.*

568.1 Graves Disease

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EPIDEMIOLOGY

Graves disease occurs in approximately 0.02% of children (1 : 5,000). It has a peak incidence in the 11-15 yr old age group; there is a 5 : 1 female : male ratio. Most children with Graves disease have a positive family history of some form of autoimmune thyroid disease. In Japan, familial Graves disease, defined as Graves disease in a 1st-degree relative, occurs in 2-3% of cases.

ETIOLOGY

Enlargement of the thymus, splenomegaly, lymphadenopathy, infiltration of the thyroid gland and retroorbital tissues with lymphocytes and plasma cells, and peripheral lymphocytosis are well-established findings in Graves disease. In the thyroid gland, T-helper cells ($CD4^+$) predominate in dense lymphoid aggregates; in areas of lower cell density, cytotoxic T cells ($CD8^+$) predominate. The percentage of activated B lymphocytes infiltrating the thyroid is higher than in peripheral blood. A postulated failure of T-suppressor cells allows expression of T-helper cells, sensitized to the TSH antigen, which interact with B cells. These cells differentiate into plasma cells, which produce thyrotropin receptor–stimulating antibody (TRSAb). TRSAb binds to the receptor for TSH and stimulates cyclic adenosine monophosphate, resulting in thyroid hyperplasia and unregulated overproduction of thyroid hormone. In addition to TRSAb, thyrotropin receptor–blocking antibody (TRBAb), which binds but does not activate the TSH receptor, may also be produced, and the clinical course of the disease usually correlates with the ratio between the 2 antibodies.

The ophthalmopathy occurring in Graves disease appears to be caused by antibodies against antigens shared by the thyroid and eye muscle. TSH receptors have been identified in retroorbital adipocytes and might represent a target for antibodies. The antibodies that bind to the extraocular muscles and orbital fibroblasts stimulate the synthesis of glycosaminoglycans by orbital fibroblasts and produce cytotoxic effects on muscle cells.

In whites, Graves disease is associated with human leukocyte antigen (HLA)-B8 and HLA-DR3; the latter carries a 7-fold relative risk for Graves disease. Graves disease is also associated with other HLA-D3–related disorders, such as Addison disease, type 1 diabetes mellitus, myasthenia gravis, and celiac disease. Systemic lupus erythematosus, rheumatoid arthritis, vitiligo, idiopathic thrombocytopenic purpura, and pernicious anemia have been described in children with Graves disease. In family clusters, the conditions associated most commonly with Graves disease are autoimmune lymphocytic thyroiditis and hypothyroidism. In Japanese children, Graves disease is associated with different HLA haplotypes: HLA-DRB1*0405 and HLA-DQB1*0401. In the Chinese population, the RNASET2-FGFR1OP-CCR6 region at 6q27 and an intergenic region at 4p14 are important susceptibility loci.

CLINICAL MANIFESTATIONS

Approximately 5% of all patients with hyperthyroidism are younger than 15 yr of age; the peak incidence in these children occurs during adolescence. Although rare, Graves disease has begun between 6 wk and 2 yr of age in children born to mothers without a history of hyperthyroidism. The incidence is approximately 5 times higher in girls than in boys.

The clinical course in children is highly variable but usually is not so fulminant as in many adults (Table 568-2). Symptoms develop gradually; the usual interval between onset and diagnosis is 6-12 mo and may be longer in prepubertal children compared with adolescents. The earliest signs in children may be emotional disturbances accompanied by motor hyperactivity. The children become irritable and excitable, and they cry easily because of emotional lability. They are restless sleepers and tend to kick their covers off. Their schoolwork suffers as a result of a short attention span and poor sleep. Tremor of the fingers can be

Table 568-2	Major Symptoms and Signs of Hyperthyroidism and of Graves Disease and Conditions Associated with Graves Disease

MANIFESTATIONS OF HYPERTHYROIDISM
Symptoms
Hyperactivity, irritability, altered mood, insomnia, anxiety, poor concentration
Heat intolerance, increased sweating
Palpitations
Fatigue, weakness
Dyspnea
Weight loss with increased appetite (weight gain in 10% of patients)
Pruritus
Increased stool frequency
Thirst and polyuria
Oligomenorrhea or amenorrhea
Signs
Sinus tachycardia, atrial fibrillation (rare in children), supraventricular tachycardia
Fine tremor, hyperkinesis, hyperreflexia
Warm, moist skin
Palmar erythema, onycholysis
Hair loss or thinning
Osteoporosis
Muscle weakness and wasting
High-output heart failure
Chorea
Periodic (hypokalemic) paralysis (primarily in Asian men)
Psychosis (rare)

MANIFESTATIONS OF GRAVES DISEASE
Diffuse goiter
Ophthalmopathy
A feeling of grittiness and discomfort in the eye
Retrobulbar pressure or pain
Eyelid lag or retraction
Periorbital edema, chemosis, scleral or conjunctival injection
Exophthalmos (proptosis)
Extraocular muscle dysfunction
Exposure keratitis
Optic neuropathy
Localized dermopathy (rare in children)
Lymphoid hyperplasia
Thyroid acropachy (rare in children)

CONDITIONS ASSOCIATED WITH GRAVES DISEASE
Type 1 diabetes mellitus
Addison disease
Vitiligo
Pernicious anemia
Alopecia areata
Myasthenia gravis
Celiac disease

Adapted from Weetman AP: Graves disease, N Engl J Med *343:1236–1248, 2000.*

Figure 568-1 A 15 yr old girl with classic Graves disease. Clinical features include a goiter and exophthalmos. She was treated with antithyroid drugs, to which she had a good response.

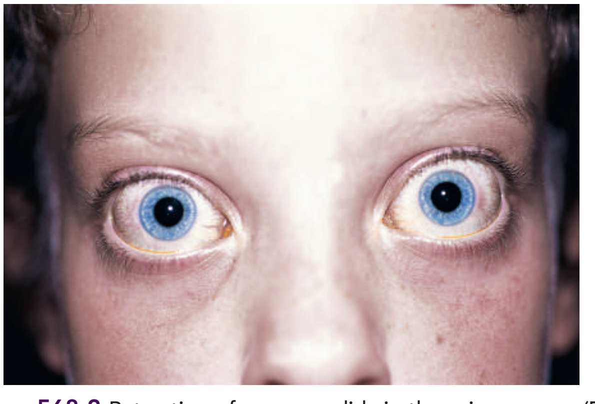

Figure 568-2 Retraction of upper eyelids in the primary gaze (Dalrymple sign). *(From Kanski JJ:* Systemic diseases and the eye: signs and differential diagnosis, *London, 2001, Mosby.)*

noticed if the arm is extended. There may be a voracious appetite combined with loss of or no increase in weight. Recent height measurements might show acceleration in growth velocity.

The size of the thyroid is variable. It may be so minimally enlarged that it initially escapes detection, but with careful examination, a diffuse goiter, soft with a smooth surface, is found in almost all patients. Exophthalmos is noticeable in most patients but is usually mild. Lagging of the upper eyelid as the eye looks downward, impairment of convergence, and retraction of the upper eyelid and infrequent blinking may be present (Figs. 568-1 and 568-2). Ocular manifestations can produce pain, lid erythema, chemosis, decreased extraocular muscle function, and decreased visual acuity (corneal or optic nerve involvement). The skin is smooth and flushed, with excessive sweating. Muscular weakness is uncommon but may be severe enough to result in clumsiness. Tachycardia, palpitations, dyspnea, and cardiac enlargement and insufficiency cause discomfort but rarely endanger the patient's life. Atrial fibrillation is a rare complication. Mitral regurgitation, probably resulting from papillary muscle dysfunction, is the cause of the apical systolic murmur present in some patients. The systolic blood pressure and the pulse pressure are increased. Reflexes are brisk, especially the return phase of the Achilles reflex. Many of the findings in Graves disease result from hyperactivity of the sympathetic nervous system.

Thyroid crisis, or thyroid storm, is a form of hyperthyroidism manifested by a severe biochemical derangement, acute onset, hyperthermia, tachycardia, heart failure, and restlessness. There may be rapid progression to delirium, coma, and death. Precipitating events include trauma, infection, radioactive iodine treatment, or surgery. **Apathetic**

(or **masked**) **hyperthyroidism** is another variety of hyperthyroidism characterized by extreme listlessness, apathy, and cachexia. A combination of both forms can occur. These symptom complexes are rare in children.

LABORATORY FINDINGS

Levels of TSH are suppressed to below the lower range of normal. Serum levels of T_4, T_3, free T_4, and free T_3 are typically elevated. In some patients, levels of T_3 may be more elevated than those of T_4. Antithyroid antibodies, including thyroid peroxidase antibodies, are often present. Most patients with newly diagnosed Graves disease have measurable TRSAb; the 2 methods to measure TRSAb are thyroid-stimulating immunoglobulin or thyrotropin-binding inhibitory immunoglobulin. Measurement of thyroid-stimulating immunoglobulin or thyrotropin-binding inhibitory immunoglobulin is useful in confirming the diagnosis of Graves disease. Children who experience an acceleration of growth might also have advanced skeletal maturation. Bone density may be reduced at diagnosis but returns to normal with treatment.

DIFFERENTIAL DIAGNOSIS

Diagnosis is rarely difficult once hyperthyroidism is considered. Elevated levels of T_4 or free T_4 and T_3 in association with suppressed levels of TSH are usually diagnostic (see Table 568-1). The combination of diffuse goiter and prolonged hyperthyroidism is nearly always caused by Graves disease, and the presence of characteristic eye or skin changes is diagnostic. Documentation of elevated TRSAb can confirm the diagnosis.

Other causes of hyperthyroidism are uncommon. In rare cases where clinical assessment cannot distinguish Graves hyperthyroidism from painless sporadic thyroiditis, ^{123}I radioiodine uptake can be measured and used to determine the appropriateness of antithyroid medication. If a discrete thyroid nodule is palpated, a ^{123}I scan should be performed to assess the possibility of a hyperfunctioning nodule(s). Some children with toxic multinodular goiter may have either a TSH receptor–activating mutation or McCune-Albright syndrome. If precocious puberty, polyostotic fibrous dysplasia, or café-au-lait pigmentation is present, the autonomous thyroid disorder of McCune-Albright syndrome is likely. Patients with generalized thyroid hormone resistance have elevated levels of free T_4 and free T_3, but levels of TSH are inappropriately elevated or normal. They must be differentiated from patients with TSH-secreting pituitary tumors who have elevated serum levels of the TSH α subunit. Most other causes of hyperthyroxinemia are uncommon but can result in erroneous diagnosis. Patients with elevated T_4-binding globulin levels or familial dysalbuminemic hyperthyroxinemia have normal levels of free T_4 and TSH. Rare patients with mutations in *SLC16A2* (encoding the MCT8 thyroid hormone transporter) or *THRA* (encoding thyroid hormone receptor α) can present with high serum T_3 and inappropriately normal or high TSH but low serum T_4 concentrations.

When hyperthyroxinemia is caused by **exogenous thyroid hormone (thyrotoxicosis factitia),** levels of free T_4 and TSH are the same as those seen in Graves disease but, in contrast to Graves hyperthyroidism, serum thyroglobulin is very low, thyroid size is small, and ^{123}I radioiodine uptake is suppressed.

TREATMENT

Most pediatric endocrinologists recommend initial medical therapy using antithyroid drugs rather than radioiodine or subtotal thyroidectomy, although radioiodine is gaining acceptance as initial treatment in children older than 10 yr of age. All therapeutic options have advantages and disadvantages (Table 568-3). The 2 antithyroid drugs used historically are propylthiouracil and methimazole (Tapazole). Both compounds inhibit incorporation of trapped inorganic iodide into organic compounds. However, there are important differences between the drugs. Methimazole is at least 10 times more potent than propylthiouracil on a weight basis and has a much longer serum half-life (6-8 hr vs 0.5 hr); propylthiouracil generally is administered 3 times daily, but methimazole can be given once daily. Unlike methimazole, propylthiouracil is heavily protein bound and has a lesser ability to cross the placenta and to pass into breast milk; theoretically, therefore, propylthiouracil is the preferred drug during pregnancy and for nursing mothers. Because of reports of **severe liver disease** in patients treated with **propylthiouracil,** with some patients requiring liver transplant or potentially suffering a fatal outcome, the consensus is to **use only methimazole** to treat children with Graves disease.

Adverse reactions occur with antithyroid drugs; most are mild, but some are life-threatening. Minor adverse effects occur in approximately 10-20%, and more-severe adverse effects occur in 2-5% of children. Reactions are unpredictable and can occur after therapy of any duration. Transient granulocytopenia (<2,000/mm^3) is common; it is asymptomatic and is not a harbinger of agranulocytosis, and it usually is not a reason to discontinue treatment. Transient urticarial rashes are common. They may be managed by a short period off therapy, and then restarting the antithyroid drug. The most severe reactions are hypersensitive and include agranulocytosis (0.1-0.5%), hepatitis (0.2-1.0%), a lupus-like polyarthritis syndrome, glomerulonephritis, and an antineutrophilic cytoplasmic antibody–positive vasculitis involving the skin and other organs. **Severe liver disease**, including liver failure requiring transplantation, have been reported **exclusively**

Table 568-3 Treatments for Hyperthyroidism Caused by Graves Disease

TREATMENT	ADVANTAGE	DISADVANTAGE	COMMENT
Antithyroid drugs	Noninvasive Less initial cost Low risk of permanent hypothyroidism Possible remission	Cure rate 30-80% (average: 40-50%) Adverse drug reactions Drug compliance required	First-line treatment in children and adolescents and in pregnancy Initial treatment in severe cases or preoperative preparation
Radioactive iodine (^{131}I)	Cure of hyperthyroidism Most cost-effective	Permanent hypothyroidism is almost inevitable Might worsen ophthalmopathy Pregnancy must be deferred for 6-12 mo, mother cannot breastfeed; small potential risk of exacerbation of hyperthyroidism	No evidence for infertility, birth defects, cancer when currently recommended doses are applied
Surgery	Rapid, effective treatment especially in patients with large goiter	Most invasive therapy Potential complications (recurrent laryngeal nerve damage, hypoparathyroidism) Most costly therapy Permanent hypothyroidism; pain; scarring	Potential use in pregnancy if major side effect from antithyroid drugs Useful when coexisting suspicious nodule is present or thyromegaly is massive Option for patients who refuse radioiodine

From Cooper DS: Hyperthyroidism, Lancet *362:459–468, 2003.*

with propylthiouracil. The most common liver disease associated with methimazole is cholestatic jaundice, reversible when the drug is discontinued. Patients with severe adverse effects should be treated with radioiodine or thyroidectomy. In rare instances where hyperthyroidism is severe and methimazole cannot be used, a short course of propylthiouracil may be offered to restore euthyroidism prior to definitive therapy. Cases of congenital skin defects (aplasia cutis) have been seen in infants exposed in fetal life to methimazole, but this association does not appear to be a strong one.

The initial dosage of methimazole is 0.25-1.0 mg/kg/24 hr given once or twice daily. Smaller initial dosages should be used in early childhood. Careful surveillance is required after treatment is initiated. Rising serum levels of TSH to greater than normal indicates overtreatment and leads to increased size of the goiter. Clinical response becomes apparent in 3-6 wk, and adequate control is evident in 3-4 mo. The dose is decreased to the minimal level required to maintain a euthyroid state.

Most studies report a remission rate of approximately 25% after 2 yr of antithyroid drug treatment in children. Some studies find that longer treatment is associated with higher remission rates, with 1 study reporting a 50% remission rate after 4.5 yr of drug treatment. If a relapse occurs, it usually appears within 3 mo and almost always within 6 mo after therapy has been discontinued. Therapy may be resumed in case of relapse. Patients older than 13 yr of age, boys, those with a higher body mass index, and those with small goiters and modestly elevated T_3 levels appear to have earlier remissions.

A β-adrenergic blocking agent such as propranolol (0.5-2.0 mg/kg/24 hr orally, divided 3 times daily) or atenolol (1-2 mg/kg orally given once daily) is a useful supplement to antithyroid drugs in the management of severely toxic patients. Table 568-4 lists additional therapies for **thyroid storm.** Thyroid hormones potentiate the actions of catecholamines, including tachycardia, tremor, excessive sweating, lid lag, and stare. These symptoms abate with the use of propranolol, which does not, however, alter thyroid function or exophthalmos.

Radioiodine treatment or surgery is indicated when adequate cooperation for medical management is not possible, when an adequate trial of medical management has failed to result in permanent remission, or when severe side effects preclude further use of antithyroid drugs. Either of these treatments may also be preferred by the patient or parent.

Table 568-4 Management of Thyroid Storm in Adolescents

GOAL	TREATMENT
Inhibition of thyroid hormone formation and secretion	Propylthiouracil, 400 mg every 8 hr PO or by nasogastric tube Saturated solution of potassium iodide, 3 drops every 8 hr
Sympathetic blockade	Propranolol, 20-40 mg every 4-6 hr or 1 mg IV slowly (repeat doses until heart rate slows); not indicated in patients with asthma or heart failure that is not rate related
Glucocorticoid therapy	Prednisone 20 mg bid
Supportive therapy	Intravenous fluids (depending on indication: glucose, electrolytes, multivitamins) Temperature control (cooling blankets, acetaminophen; avoid salicylates) O_2 if required Digitalis for heart failure and to slow ventricular response; pentobarbital for sedation Treatment of precipitating event (e.g., infection)

From Goldman L, Ausiello D, editors: Cecil textbook of medicine, *ed 22, Philadelphia, 2004, WB Saunders, p. 1401.*

Radioiodine is an effective therapy for Graves disease in children. In patients with severe thyrotoxicosis, euthyroidism should be restored with methimazole prior to radioablation in order to deplete the gland of preformed hormone and reduce the risk of thyrotoxic flare from radiation thyroiditis. If a patient is taking thionamides, they must be stopped 3-5 days before radioiodine administration to avoid inhibition of uptake. In children, the goal is to select a dose of radioiodine high enough to ensure complete ablation of thyroid tissue. Most centers obtain a diagnostic radioiodine uptake measurement before treatment and then use this to calculate a ^{131}I dose that delivers an absorbed thyroid dose of >150 μCi/g. Alternatively, an empirical fixed ^{131}I dose (usually 15 mCi) can be offered. The theoretical advantage of calculated doses is that they define for each individual patient the lowest administered dose that achieves the therapeutic target. This benefit is most important in small children, as the absorbed radiation dose to the bone marrow and other normal tissues is inversely proportional to body size. Based upon this concept and theoretical modeling of radiation exposure, current consensus guidelines recommend that ^{131}I therapy be avoided in very small children who are younger than 5 yr of age and that administered doses in children between 5 and 10 yr of age be <10 mCi. As with other Graves therapies, ^{131}I ablation has a low but obligate failure rate (5-20%). Patients with persistent hyperthyroidism more than 6 mo after their first ^{131}I therapy can be offered retreatment.

Thyroidectomy, a safe procedure when performed by an experienced surgeon, is done only after the patient has been brought to a euthyroid state. This may be accomplished with methimazole over 2-3 mo. After a euthyroid state has been attained, a saturated solution of potassium iodide, 3-5 drops 3 times per day, is added to the regimen for 2 wk before surgery to decrease the vascularity of the gland. In expert hands, complications of surgical treatment are rare and include hypoparathyroidism (transient or permanent) and paralysis of the vocal cords. The incidence of residual or recurrent hyperthyroidism or hypothyroidism depends on the extent of the surgery. Most recommend near-total thyroidectomy. The incidence of recurrence is low, and most patients become hypothyroid. Referral to a surgeon with extensive experience in thyroidectomy and a low personal complication rate is paramount.

The **ophthalmopathy** usually remits gradually and independently of the hyperthyroidism. Severe ophthalmopathy can require treatment with high-dose prednisone, orbital radiotherapy (of questionable value), or orbital decompression surgery. Cigarette smoking is a risk factor for thyroid eye disease and should be avoided or discontinued to avoid progression of eye involvement.

Bibliography is available at Expert Consult.

568.2 Congenital Hyperthyroidism

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ETIOLOGY AND PATHOGENESIS

Neonatal Graves disease is caused by transplacental passage of TRSAb, but the clinical onset, severity, and course may be modified by the concurrent presence of thyrotropin receptor–blocking antibody and by the transplacental passage of antithyroid drugs taken by the mother. Very high levels of TRSAb usually result in classic neonatal hyperthyroidism, but if the infant has been exposed to antithyroid drugs, onset of symptoms is delayed by 3-4 days as the maternally derived antithyroid drug is metabolized. If thyrotropin receptor–blocking antibody is also present, onset of hyperthyroid symptoms may be delayed for several weeks. The mothers of these infants have active Graves disease, Graves disease in remission, a past history of Graves disease managed by radioactive iodine ablation or surgery, or rarely hypothyroidism and a history of lymphocytic thyroiditis.

Neonatal hyperthyroidism occurs in only approximately 2% of infants born to mothers with a history of Graves disease. Fetal tachycardia and goiter can allow prenatal diagnosis and fetal ultrasound

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surveillance is recommended in mothers with uncontrolled hyperthyroidism, elevated serum titers of TRSAb (thyrotropin-binding inhibitory immunoglobulin more than 3 times the upper limit of normal), or the history of a prior child with neonatal thyroid dysfunction. Unlike Graves disease at all other ages, neonatal hyperthyroidism affects boys as often as girls. One would expect twins to be equally affected, but 1 case reported 1 twin to be hyperthyroid and the other twin to be hypothyroid. Both eventually recovered to euthyroidism.

The disorder usually remits spontaneously within 6-12 wk but can persist longer, depending on the levels of TRSAb. Mild asymptomatic hyperthyroxinemia also occurs. Rarely, classic neonatal Graves disease does not remit but persists for several years or longer. These children have impressive family histories of Graves disease. In these infants, TRSAb transfer from the mother apparently blends with the infantile onset of autonomous Graves disease.

CLINICAL MANIFESTATIONS

Many of the infants are premature and appear to have intrauterine growth restriction. Most have goiters. The infant is extremely restless, irritable, and hyperactive and appears anxious and unusually alert. Microcephaly and ventricular enlargement may be present. The eyes are opened widely and appear exophthalmic (Fig. 568-3). There may be extreme tachycardia and tachypnea, and the temperature is elevated. In severely affected infants, there is a progression of symptoms; weight loss occurs despite a ravenous appetite, hepatosplenomegaly increases, and jaundice can occur. Severe hypertension and cardiac decompensation can occur. The infant can die if therapy is not instituted promptly. The serum levels of T_4 or free T_4 and T_3 are markedly elevated, and TSH is suppressed. Advanced bone age, frontal bossing with triangular facies, and cranial synostosis are common, especially in infants with persistent clinical manifestations of hyperthyroidism.

TREATMENT

Treatment of the neonate consists of oral administration of propranolol (1-2 mg/kg/24 hr, orally in 3 divided doses) and methimazole (0.25-1.0 mg/kg/24 hr given every 12 hr); saturated solution of potassium iodide (1 drop per day) may be added. When propranolol is used during pregnancy to treat thyrotoxicosis, it crosses the placenta and can cause respiratory depression in the newborn infant. If the thyrotoxic state is severe, parenteral fluid therapy and corticosteroids may be indicated. If heart failure occurs, digitalization is indicated. After a euthyroid state is reached, antithyroid medications should be gradually tapered to keep the infant euthyroid. Most cases remit by 3-4 mo of age.

Figure 568-3 **Twin boys with neonatal hyperthyroidism confirmed by abnormal thyroid function tests.** Clinical features include lack of subcutaneous tissue owing to a hypermetabolic state and a wide-eyed, anxious stare. They were given the diagnosis of neonatal Graves disease, but, in fact, their mother did not have Graves disease; they had persistent, not transient, hyperthyroidism. At age 8 yr, they were treated with radioiodine. They are now believed to have had some other form of neonatal hyperthyroidism, such as a constitutive activation of the thyroid-stimulating hormone receptor.

Occasionally, neonatal hyperthyroidism does not remit but persists into childhood. These patients can have an impressive family history of hyperthyroidism. Neonatal hyperthyroidism, without evidence for autoimmune disease in mother or infant, may be caused by a mutation in the *TSHR* gene that produced constitutive activation of the receptor. Neonatal hyperthyroidism has also been reported in patients with McCune-Albright syndrome, a result of an activating mutation of the α subunit of the G-protein. Under these circumstances, hyperthyroidism recurs when antithyroid drugs are discontinued; these children eventually must be treated with radioiodine or surgery.

PROGNOSIS

Advanced osseous maturation, microcephaly, and cognitive impairment occur when treatment is delayed. Intellectual development is normal in most treated infants with neonatal Graves disease, though some manifest neurocognitive problems from in utero hyperthyroidism. In some infants, in utero hyperthyroidism appears to suppress the hypothalamic-pituitary-thyroid feedback mechanism, and they develop permanent central hypothyroidism, requiring lifelong thyroid hormone treatment.

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Chapter 569

Carcinoma of the Thyroid

Stephen A. Huang and
Stephen H. LaFranchi

EPIDEMIOLOGY

Carcinoma of the thyroid is rare in childhood; the annual incidence in children younger than 15 yr of age is approximately 2 in 100,000 cases, compared with an annual incidence at all ages around the world of 4-10 in 100,000 cases. In the last 2 decades, the incidence in children has increased 2-fold. Compared to adults, childhood thyroid cancers are characterized by dramatically higher rates of metastasis and recurrence. Despite being widespread at discovery, pediatric thyroid cancers usually have an indolent course and, with adequate treatment, most patients have a favorable outcome.

PATHOGENESIS

At all ages, the vast majority of differentiated thyroid cancers are of follicular cell origin and, in North America, **papillary carcinoma** (88%) is the most common subtype. Interestingly, while their histologic features are similar, the thyroid cancers of childhood are genetically distinct from their adult counterparts. Although up to 70% of adults with papillary thyroid cancer exhibit pathogenic somatic mutations in *BRAF* or *RAS,* these mutations are extremely rare in children with papillary cancer. In contrast, *RET-PTC* translocations, which result in chimeric proteins containing the tyrosine kinase domains of RET fused to the regulatory sequences of ubiquitously expressed genes such as *H1* and *ELE1,* are often found in childhood thyroid cancers. After papillary thyroid cancer, follicular cancer (10%) is the next most common type of childhood thyroid cancer. Medullary cancer (2%) and anaplastic thyroid cancers are relatively rare. Of note, only thyroid cancers of follicular cell origin (papillary and follicular carcinomas) respond to the adjunctive therapies of ^{131}I therapy and thyroid-stimulating hormone (TSH) suppression.

Up to 10% of cases of follicular cell–derived thyroid cancers are familial, and these are usually inherited in an autosomal dominant manner. Familial syndromes associated with an increased risk of thyroid neoplasia include Cowden syndrome (characterized by mucocutaneous

lesions, breast cancer, macrocephaly, and endometrial tumors) and familial adenomatous polyposis. Germline mutations in the *DICER-1* gene have also been recognized as a cause of thyroid neoplasia. The evaluation of a child with thyroid nodule should include a medical and family history to assess for features of these syndromes.

The thyroid gland of children is unusually sensitive to exposure to external radiation. There probably is no threshold dose; 1 Gy results in a 7.7 relative risk of thyroid cancer. In the past, approximately 80% of children with cancer of the thyroid had received inappropriate therapeutic irradiation of the neck and adjacent areas during infancy for benign conditions such as "enlarged" thymus, hypertrophied tonsils and adenoids, hemangiomas, nevi, eczema, tinea capitis, and "cervical adenitis." With the discontinuation of irradiation for benign conditions, this cause of thyroid cancer has vanished. The long-term survival of children who have received appropriate therapeutic irradiation of areas of the neck for neoplastic disease has made this cause of thyroid cancer and nodules increasingly prevalent; increased dose, younger age at time of treatment, and female sex are factors that increase the risk of thyroid cancer. Long-term risk data for cancer are sparse, but 15-50% of children who have received irradiation and chemotherapy for Hodgkin disease, leukemia, bone marrow transplantation, brain tumors, and other malignancies of the head and neck have elevated levels of TSH within the 1st yr of therapy, and 5-20% progress to hypothyroidism during the next 5-7 yr. Most large groups of treated children have a 10-30% incidence of benign thyroid nodules and an increased incidence of thyroid cancer. The latter begins to appear within 3-5 yr after radiation treatment and reaches a peak in 15-25 yr. It is unknown whether there is a period after which no more tumors develop. Administration of ^{131}I for diagnostic or therapeutic purposes does not appear to increase the risk of thyroid cancer.

Thyroid cancer has been reported in children with congenital goiter or ectopic thyroid tissue. In these patients, and also in children with autoimmune thyroiditis and hypothyroidism, chronic TSH stimulation appears to play a pathogenic role. It is unclear if the course of thyroid cancer differs in these patients compared to the general population. From a practical standpoint, nodules that are detected in the context of these disorders should be fully evaluated for cancer risk as in other children.

CLINICAL MANIFESTATIONS

The incidence of childhood thyroid cancer peaks in adolescence and girls are more commonly affected than boys. A painless nodule in the thyroid or in the neck is the usual presentation of disease. Rapid growth and large nodule size, firmness, fixation to adjacent tissues, hoarseness, dysphagia, and neck lymphadenopathy should heighten the concern for thyroid cancer. Cervical lymph node metastasis is common, so any unexplained cervical lymph node enlargement warrants examination of the thyroid. The lungs are the most common site of distant metastasis. There may be no clinical manifestations referable to them and formal pulmonary function testing may be normal even with widespread macroscopic metastases. Radiologically, they appear as diffuse miliary or nodular infiltrations, typically greatest in the posterior basal portions. They may be mistaken for tuberculosis, histoplasmosis, or sarcoidosis. Other sites of metastasis include the mediastinum, axilla, long bones, skull, and brain. Almost all children are euthyroid, but rarely, the carcinoma is functional and produces symptoms of hyperthyroidism.

DIAGNOSIS

As detailed in the following section, patients usually present with a neck mass and virtually all have a thyroid nodule of significant size upon ultrasound. While several imaging features are significantly associated with thyroid cancer risk, none have sufficient negative predictive value to forgo tissue diagnosis. Papillary thyroid cancer is characterized by nuclear abnormalities that are well identified by cytology and *fine-needle aspiration is the gold standard* in the evaluation of adults with nodules. Growing literature supports its use in the pediatric population. In most cases, operative pathology is required to confirm the diagnosis of thyroid cancer and to stage the extent of disease.

TREATMENT

The primary therapy for thyroid cancer is surgical resection. Because intrathyroidal spread is common in papillary thyroid, near-total thyroidectomy is the favored approach. Prior to this surgery, neck ultrasonography should be performed to screen for sonographically abnormal lymph nodes. Suspicious lymph nodes may be biopsied preoperatively to determine the appropriateness and extent of initial lymph node dissection. With the exception of very-low-risk patients, thyroidectomy is usually followed by adjunctive therapy with both TSH suppression (dosing levothyroxine to lower serum TSH and deprive residual thyroid cancer cells of this growth factor) and ^{131}I therapy (to ablate the normal thyroid remnant and/or to treat residual thyroid cancer).

PROGNOSIS

Although extrathyroidal invasion and distant metastasis are more common in the pediatric population, most children with thyroid cancer have a good outcome. Families should be counseled that the response to ^{131}I therapy is slow and that repeated treatments and years of care may be required to eliminate the disease. They should further be informed that many patients who are unable to achieve complete cure can be maintained in the well state with stable or slowly progressive cancer burden. For rare children with aggressive cancers that progress despite the optimization of conventional therapies, newer options, such as oral tyrosine kinase inhibitors, are available through research trials or on a compassionate basis. As with any cancer, psychosocial supports must be available, including access to social work and other mental health professionals.

Among solid tumors, thyroid cancer is unique in its capacity for late recurrence, sometimes occurring decades after initial presentation. For this reason, all children with thyroid cancer deserve lifelong monitoring for disease progression. For most patients, serum thyroglobulin is a sensitive and specific cancer marker. However, it must be recognized that about one fourth of patients have circulating antithyroglobulin autoantibodies that interfere with standard thyroglobulin assays and produce artifactually low measurements. Because of this, antithyroglobulin autoantibodies must always be measured whenever serum thyroglobulin is assayed to confirm the latter's reliability. As most thyroid cancer recurrences are local, surveillance should include serial neck ultrasounds. Patients with higher recurrence risk or documentation of distant metastases typically benefit from additional anatomic imaging studies and from extended surveillance studies performed during TSH stimulation.

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569.1 Solitary Thyroid Nodule

Stephen A. Huang and Stephen H. LaFranchi

The frequency of thyroid nodules increases with age. While sonographically detectable nodules are present in 19-67% of randomly selected adults, the estimated frequency of nodules in children is only 0.05-2.0%. Although early pediatric series cited extremely high rates of cancer in thyroid nodules (up to 70%), more recent studies of children report lower cancer prevalence (around 20-26%) that is similar to the 5-15% prevalence observed in adults. Thus, when a thyroid nodule is discovered in a child, parents should be counseled that the majority of nodules are benign.

Benign disorders that can occur as a solitary thyroid mass include benign adenomatous or colloid nodules, as well as a variety of congenital cysts (Table 569-1). A suddenly appearing or rapidly enlarging thyroid mass can indicate hemorrhage into a cyst or benign adenoma. When evaluating a child with a thyroid nodule, it is helpful to begin by measuring serum TSH.

In rare patients who present with a suppressed serum TSH, a thyroid scan, preferably using ^{123}I or ^{99m}Tc-pertechnetate, should be performed to assess the possibility of a benign hyperfunctioning thyroid nodule. All other patients should proceed directly to ultrasound and, if a

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Table 569-1	Etiologic Classification of Solitary Thyroid Nodules

Lymphoid follicle, as part of chronic lymphocytic thyroiditis
Thyroid developmental anomalies
  Intrathyroidal thyroglossal duct cyst
Thyroid abscess (acute suppurative thyroiditis)
Simple cyst
  Neoplasms
    Benign
    Colloid (adenomatous) nodule
    Follicular adenoma
    Toxic adenoma
    Nonthyroidal (e.g., lymphohemangioma)
  Malignant
    Papillary carcinoma
    Follicular carcinoma
    Mixed papillary-follicular carcinoma
    Undifferentiated (anaplastic)
    Medullary carcinoma
  Nonthyroidal
    Lymphoma
    Teratoma

discrete nodule(s) of significant size is documented by this imaging, it should be biopsied by ultrasound-guided fine-needle aspiration (FNA). FNA cytology may be interpreted as benign, positive for papillary thyroid cancer, indeterminate, or inadequate. When an initial biopsy is nondiagnostic, an adequate sample can usually be obtained by repeating aspiration. Multiple categorization systems exist and most North American centers follow the Bethesda Criteria for interpretation of thyroid cytology. The predictive value of thyroid FNA varies between institutions. In most high-volume centers, the "positive for papillary thyroid cancer" category corresponds to a >98% likelihood of cancer and, in that context, near-total thyroidectomy is appropriate. In children with indeterminate cytology and unilateral nodules, lobectomy is commonly performed. This is followed by completion thyroidectomy if lobectomy pathology shows a significant cancer. Patients with cytologically benign nodules can be offered the option of deferring surgery so long as they are willing to commit to careful surveillance with serial neck imaging.

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569.2 Medullary Thyroid Carcinoma

Stephen H. LaFranchi

Medullary thyroid carcinoma (MTC) arises from the parafollicular cells (C cells) of the thyroid and accounts for approximately 2% of thyroid malignancies in children. The majority of MTC cases are sporadic, but approximately 25% are familial, autosomal dominant disorders. Hereditary MTC is divided into 3 distinct syndromes: multiple endocrine neoplasia type 2A (MEN2A), multiple endocrine neoplasia type 2B (MEN2B), and familial MTC. In contrast to the somatic mutations associated with sporadic MTC, germline mutations in the *RET* protooncogene on chromosome 10q11.2 are inheritable and can cause familial medullary thyroid cancer. Once an index case is diagnosed in a family, it is important to pinpoint the specific *RET* mutation and then genotype all 1st-degree relatives for the mutation. Many *RET* mutations have been well studied and strong genotype–phenotype associations have been established to predict disease aggressiveness. In carriers, thyroidectomy before the MTC has spread outside the gland represents the best chance for a cure and the patient's specific genotype can be used to guide the timing of prophylactic surgery.

The most common presentation of sporadic MTC is an asymptomatic, palpable thyroid nodule. When the tumor occurs sporadically, it is usually unicentric, but in the familial form, it is usually multicentric, and it begins as hyperplasia of parafollicular cells. The diagnosis of MTC can often be made through routine FNA cytology, but documentation of high calcitonin in an FNA washing or in the patients' serum is helpful as confirmation. The diagnosis of MTC warrants genetic testing for *RET* mutation and screens for MEN2-associated pheochromocytoma and hyperparathyroidism should be obtained prior to anesthesia for thyroidectomy. No clinically recognizable manifestations result from the elevated serum levels of calcitonin or CEA. Nonetheless, these tests are helpful in screening and monitoring therapy.

MULTIPLE ENDOCRINE NEOPLASIA, TYPE 2A

MEN2A is an autosomal dominant disorder characterized by MTC, pheochromocytoma, and parathyroid hyperplasia. At least 19 different specific missense mutations of exon 10 or 11 of the extracellular domain of the *RET* gene have been described for MEN2A and for cases of familial MTC. DNA analysis permits unambiguous identification of carriers of the *RET* protooncogene mutation. Penetrance of MTC is close to 100%, but there is much variability in the other manifestations of MEN2A. C-cell hyperplasia or MTC usually appears earlier than pheochromocytoma. Pheochromocytomas are often bilateral and may be multiple. Adrenal medullary hyperplasia is known to precede pheochromocytoma, but the detectable latent period is short. Hypercalcemia is a late manifestation and indicates hyperparathyroidism. The parathyroid glands might reveal chief-cell hyperplasia or only hypercellularity.

MULTIPLE ENDOCRINE NEOPLASIA, TYPE 2B

MEN2B is an autosomal dominant disorder characterized by MTC and pheochromocytomas but not hyperparathyroidism. The distinguishing feature of MEN2B, also called the **mucosal neuroma syndrome,** is the occurrence of multiple neuromas and a characteristic phenotype that includes Marfan-like facies. A missense mutation of the *RET* protooncogene in exon 16, the tyrosine catalytic domain of *RET,* is found in 93% of families; all patients have had the same point mutation.

The neuromas most often occur on the tongue, buccal mucosa, lips, and conjunctivae. Peripheral neurofibromas and café-au-lait patches may be present, and intestinal ganglioneuromatosis is common. Diffuse proliferation of nerves and ganglion cells is found in mucosal, submucosal, myenteric, and subserosal plexus involving the small and large bowel as well as the esophagus. The patients may be tall, with arachnodactyly and a Marfan-like appearance. Scoliosis, pectus excavatum, pes cavus, and muscular hypotonia are common. The eyelids may be thickened and everted, the lips patulous and blubbery, the jaw prognathic. Feeding difficulties, poor sucking, diarrhea, constipation, and failure to thrive can begin in infancy or early childhood, many years before the appearance of neuromas or endocrine symptoms.

TREATMENT

Total thyroidectomy is indicated for all children who are shown by genetic studies to carry high-risk *RET* mutations. Recognition of familial forms of this tumor is critical to the early diagnosis and intervention in children at risk. MTC develops at an earlier age in patients with MEN2B and is more aggressive than in MEN2A. MTC has been seen in a 6 mo old child with MEN2B and in a 3 yr old child with MEN2A. In MEN2A, there is genotype–phenotype correlation between the specific mutation and the onset of C-cell hyperplasia or MTC. With codon 634 mutations, MTC occurs at an early age, whereas with mutations at codons 618, 620, and 804, MTC tends to occur at a later age. In young children, recommendations for the timing of prophylactic thyroidectomy are available for the common *RET* mutations. All these children should be screened for pheochromocytoma before surgery. Monitoring the serum levels of calcitonin and carcinoembryonic antigen is useful in following the course of the disease after operation and in detecting metastatic lesions. Periodic screening for the development of pheochromocytoma and hyperparathyroidism is indicated. Metastases to the regional lymph nodes and to the liver can occur. Early clinic studies support that prophylactic thyroidectomy is effective in preventing death from MTC.

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Section 3

Disorders of the Parathyroid Gland

Chapter 570

Hormones and Peptides of Calcium Homeostasis and Bone Metabolism

Daniel A. Doyle

Parathyroid hormone (PTH) and vitamin D are the principal regulators of calcium homeostasis (see Chapters 48 and 694). Calcitonin and PTH-related peptide (PTHrP) are important primarily in the fetus.

PARATHYROID HORMONE

PTH is an 84-amino-acid chain (95 kDa), but its biologic activity resides in the first 34 residues. In the parathyroid gland, a pre-pro-PTH (115-amino-acid chain) and a pro-PTH (90 amino acids) are synthesized. Pre-pro-PTH is converted to pro-PTH and pro-PTH to PTH. PTH (consisting of amino acids 1-84) is the major secretory product of the gland, but it is rapidly cleaved in the liver and kidney into smaller COOH-terminal, mid-region, and NH_2-terminal fragments.

The occurrence of these fragments in serum has led to the development of a variety of assays. The 1-34 aminoterminal (N-terminus) fragments possess biologic activity but are present in low amounts in the circulation; assay of these fragments is most useful for detecting acute secretory changes. The carboxyterminal (C-terminus) and midregion fragments, although biologically inert, are cleared more slowly from the circulation and represent 80% of plasma immunoreactive PTH; concentrations of the C-terminal fragment are 50-500 times the level of the active hormone. The C-terminal assays are effective in detecting hyperparathyroidism, but because C-terminal fragments are removed from the circulation by glomerular filtration, these assays are less useful for evaluating the secondary hyperparathyroidism characteristic of renal disease. Only certain sensitive radioimmunoassays for PTH can differentiate the subnormal concentrations that occur in hypoparathyroidism from normal levels.

When serum levels of calcium fall, the signal is transduced through the calcium-sensing receptor, and secretion of PTH increases (Fig. 570-1). PTH stimulates activity of 1α-hydroxylase in the kidney, enhancing production of 1,25-dihydroxycholecalciferol, also written $1,25(OH)_2D_3$. The increased level of $1,25(OH)_2D_3$ induces synthesis of a calcium-binding protein (calbindin-D) in the intestinal mucosa, with resultant absorption of calcium. PTH also mobilizes calcium by directly enhancing bone resorption, an effect that requires $1,25(OH)_2D_3$. The effects of PTH on bone and kidney are mediated through binding to specific receptors on the membranes of target cells and through activation of a transduction pathway involving a G-protein coupled to the adenylate cyclase system (see Chapter 572).

The calcium-sensing receptor regulates the secretion of PTH and the reabsorption of calcium by the renal tubules in response to alterations in serum calcium concentrations. The gene for the receptor is located on chromosome 3q13.3-q21 and encodes a cell surface protein that is expressed in parathyroid glands and kidneys and belongs to the family of G-protein–coupled receptors. In the normally functioning calcium-sensing receptor, hypocalcemia induces increased secretion of PTH and hypercalcemia depresses PTH secretion. Loss-of-function mutations cause an increased set point with respect to serum calcium, resulting in hypercalcemia and in the conditions of **familial hypocalciuric hypercalcemia** and neonatal severe hyperparathyroidism. Acquired hypocalciuric hypercalcemia may be a result of autoantibodies to the calcium-sensing receptor and manifests with hypercalcemia and hyperparathyroidism. Gain-of-function mutations result in depressed secretion of PTH in response to hypocalcemia, leading to the syndrome of familial hypocalcemia with hypercalciuria (see Fig. 570-1).

PARATHYROID HORMONE–RELATED PEPTIDE

PTHrP is homologous to PTH only in the first 13 amino acids of its amino terminus, 8 of which are identical to PTH. Its gene is on the short arm of chromosome 12 and that of PTH is on the short arm of chromosome 11.

PTHrP, like PTH, activates PTH receptors in kidney and bone cells and increases urinary cyclic adenosine monophosphate and renal production of $1,25(OH)_2D_3$. It is produced in almost every type of cell of the body, including every tissue of the embryo at some stage of development. PTHrP is critical for normal fetal development. Inactivating mutations of the receptor for PTH/PTHrP result in a lethal bone disorder characterized by short limbs and markedly advanced bone maturation known as *Blomstrand chondrodysplasia* (see Fig. 570-1). PTHrP appears to have a paracrine or autocrine role because serum levels are low except in a few clinical situations. Cord blood contains levels of PTHrP that are 3-fold higher than in serum from adults; it is produced by the fetal parathyroid glands and appears to be the main agent stimulating maternal-fetal calcium transfer. PTHrP appears to be essential for normal skeletal maturation of the fetus, which requires 30 g of calcium during a normal gestation. During pregnancy, maternal absorption of calcium increases from about 150 mg daily to 400 mg during the 2nd trimester.

As in cord blood, PTHrP levels are increased during lactation and in patients with benign breast hypertrophy. Breast milk and pasteurized bovine milk have levels of PTHrP that are 10,000 times higher than those of normal plasma. Most instances of the hormonal hypercalcemia syndrome of malignancy are caused by elevated concentrations of PTHrP.

VITAMIN D

See Chapter 51.

CALCITONIN

Calcitonin is a 32-amino-acid polypeptide. Its gene is on chromosome 11p and is tightly linked to that of PTH. The gene for calcitonin encodes 3 peptides: calcitonin, a 21-amino-acid carboxyterminal flanking peptide (katacalcin), and a calcitonin gene–related peptide. Katacalcin and calcitonin are cosecreted in equimolar amounts by the parafollicular cells (C cells) of the thyroid gland. Calcitonin appears to be of little consequence in children and adults because very high levels in patients with medullary carcinoma of the thyroid (a tumor arising from the C cells) do not cause hypercalcemia. In the fetus, however, circulating levels are high and appear to augment bone metabolism and skeletal growth; these high levels are probably stimulated by the normally high fetal calcium levels. Unlike the high levels in cord blood and circulating concentrations in young children, levels in older children and adults are low. Infants and children with congenital hypothyroidism (and presumed deficiency of C cells) have lower levels of calcitonin than do normal children.

Its action appears to be independent of PTH and vitamin D. Its main biologic effect appears to be the inhibition of bone resorption by decreasing the number and activity of bone-resorbing osteoclasts. This action of calcitonin is the rationale for its use in treatment of Paget disease. Calcitonin is synthesized in other organs, such as the gastrointestinal tract, pancreas, brain, and pituitary. In these organs, calcitonin is thought to behave as a neurotransmitter to impose a local inhibitory effect on cell function.

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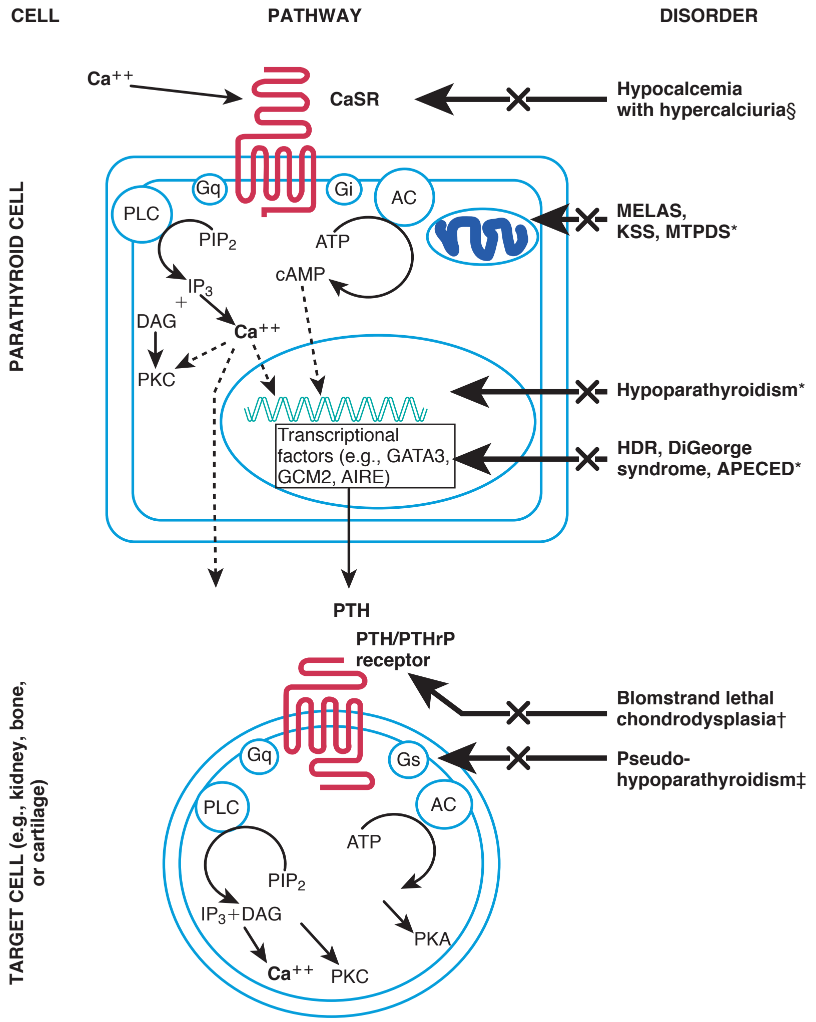

CaSR and PTH/PTHrP-receptor mediate their effects through G protein-coupled signaling pathways, which in turn activate the adenyl cyclase (AC) and phospholipase C (PLC) systems. Gq = G-pertussis-toxin-insensitive protein; Gi = G inhibitory protein; PIP_2 = phosphatidyl inositol 4,5-bisphosphate; IP_3 = inositol 1,4,5-triphosphate; DAG = diacylglycerol; PKC = protein kinase C.
*Disorders due to PTH deficiency.
†Defect due to defect in the PTH/PTHrP receptor.
‡Defect due to insensitivity to PTH caused by defects downstream of the PTH/PTHrP receptor.
§Defect due to altered set point in the Ca^{++}/PTH axis, associated with a gain-of-function mutation of the CaSR.
MELAS = mitochondrial encephalopathy, stroke-like episodes, and lactic acidosis.
KSS = Kearns Sayre syndrome (progressive external ophthalmoplegia, pigmentary retinopathy, heart block, and cardiomyopathy).
MTPDS = mitochondrial trifunctional protein deficiency syndrome.
HDR = hypoparathyroidism, deafness, and renal anomalies.
APECED = autoimmune polyendocrinopathy-candidosis-ectodermal dystrophy.

Figure 570-1 Some components involved in calcium homeostasis. The calcium-sensing receptor (CaSR) and PTH/PTHrP receptor mediate their effects through G-protein–coupled signaling pathways, which, in turn, activate the adenyl cyclase (AC) and phospholipase C (PLC) systems. *(From Thakker RV: Genetic development in hypoparathyroidism,* Lancet *357:974–976, 2001.)*

Chapter 571

Hypoparathyroidism

Daniel A. Doyle

ETIOLOGY

Hypocalcemia is common in neonates between 12 and 72 hr of life, especially in premature infants, in infants with asphyxia, and in infants of diabetic mothers (early neonatal hypocalcemia; see Chapter 106; Table 571-1 and Fig. 571-1). After the 2nd to 3rd day and during the 1st wk of life, the type of feeding also is a determinant of the level of serum calcium (late neonatal hypocalcemia). The role played by the parathyroid glands in these hypocalcemic infants remains to be clarified, although functional immaturity of the parathyroid glands is invoked as 1 pathogenetic factor. In a group of infants with transient idiopathic hypocalcemia (1-8 wk of age), serum levels of parathyroid hormone (PTH) are significantly lower than those in normal infants. It is possible that the functional immaturity is a manifestation of a delay in development of the enzymes that convert glandular PTH to secreted PTH; other mechanisms are possible.

APLASIA OR HYPOPLASIA OF THE PARATHYROID GLANDS

Aplasia or hypoplasia of the parathyroid glands is often associated with the **DiGeorge/velocardiofacial syndrome** (see Fig. 570-1). This syndrome occurs in 1 in 4,000 newborns. In 90% of patients, the condition is caused by a deletion of chromosome 22q11.2. Approximately 25%

Table 571-1 Causes of Hypocalcemia

I. Neonatal
  A. Maternal Disorders
    Diabetes mellitus
    Toxemia of pregnancy
    Vitamin D deficiency
    High intake of alkali or magnesium sulfate
    Use of anticonvulsants
    Hyperparathyroidism
  B. Neonatal Disorders
    Low birthweight: prematurity, intrauterine growth restriction
    Peripartum asphyxia, sepsis, critical illness
    Hyperbilirubinemia, phototherapy, exchange transfusion
    Hypomagnesemia, hypermagnesemia
    Acute/chronic renal failure
    Nutrients/medications: high phosphate intake, fatty acids, phytates, bicarbonate infusion, citrated blood, anticonvulsants, aminoglycosides
    Hypoparathyroidism
    Vitamin D deficiency or resistance
    Osteopetrosis type II
II. Hypoparathyroidism
  A. Congenital
    1. Transient neonatal
    2. Congenital hypoparathyroidism
      a. Familial isolated hypoparathyroidism
        (1) Autosomal recessive hypoparathyroidism (GCMB, PTH)
        (2) Autosomal dominant hypoparathyroidism (CaSR)
        (3) X-linked hypoparathyroidism *(SOX3)*
      b. DiGeorge syndrome *(TBX1)*
      c. Sanjad-Sakati syndrome (short stature, retardation, dysmorphism; HRD); Kenny-Caffey syndrome 1 (short stature, medullary stenosis) *(TBCE)*
      d. Barakat syndrome (sensorineural deafness, renal dysplasia; HDR) *(GATA3)*
      e. Lymphedema-hypoparathyroidism-nephropathy, nerve deafness
      f. Mitochondrial fatty acid disorders (Kearns-Sayre, Pearson, MELAS)
    3. Insensitivity to PTH
      a. Blomstrand chondrodysplasia *(PTHR1)*
      b. Pseudohypoparathyroidism type IA *(GNAS)*
        Pseudohypoparathyroidism type IB
        Pseudohypoparathyroidism type IC
        Pseudohypoparathyroidism type II
        Pseudopseudohypoparathyroidism
      c. Acrodysostosis with hormone resistance *(PRKAR1A)*
      d. Hypomagnesemia
    4. CaSR-activating mutation
      a. Sporadic
      b. Autosomal dominant (G protein subunit α11 mutation)
  B. Acquired
    1. Autoimmune polyglandular syndrome type I (*AIRE* gene mutation)
    2. Activating antibodies to the CaSR
    3. Postsurgical, radiation destruction
    4. Infiltrative—excessive iron (hemochromatosis, thalassemia) or copper (Wilson disease) deposition; granulomatous inflammation, neoplastic invasion; amyloidosis, sarcoidosis
    5. Maternal hyperparathyroidism
    6. Hypomagnesemia/hypermagnesemia
III. Vitamin D Deficiency
IV. Other Causes of Hypocalcemia
  A. Calcium Deficiency
    1. Nutritional deprivation
    2. Hypercalciuria
  B. Disorders of Magnesium Homeostasis
    1. Congenital hypomagnesemia
    2. Acquired
      a. Acute renal failure
      b. Chronic inflammatory bowel disease, intestinal resection
      c. Diuretics
  C. Hyperphosphatemia
    1. Renal failure
    2. Phosphate administration (intravenous, oral, rectal)
    3. Tumor cell lysis
    4. Muscle injuries (crush, rhabdomyolysis)
  D. Miscellaneous
    1. Hypoproteinemia
    2. Hyperventilation
    3. Drugs: furosemide, aminoglycosides, bisphosphonates, calcitonin, anticonvulsants, ketoconazole, antineoplastic agents (plicamycin, asparaginase, cisplatinum, cytosine arabinoside, doxorubicin), citrated blood products
    4. Hungry bone syndrome
    5. Acute and critical illness: sepsis, acute pancreatitis, toxic shock
      a. Organic acidemia: propionic, methylmalonic, isovaleric

HDR, hypoparathyroidism, sensorineural deafness, and renal anomaly; HRD, hypoparathyroidism, retardation, dysmorphism; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episode; PTH, parathyroid hormone.

Modified from Root AW, Diamond JR FB: Disorders of mineral homeostasis in children and adolescents. In Sperling MA, editor: Pediatric endocrinology, *ed 4, Philadelphia, 2014, Elsevier, Table 18-2A, p. 739.*

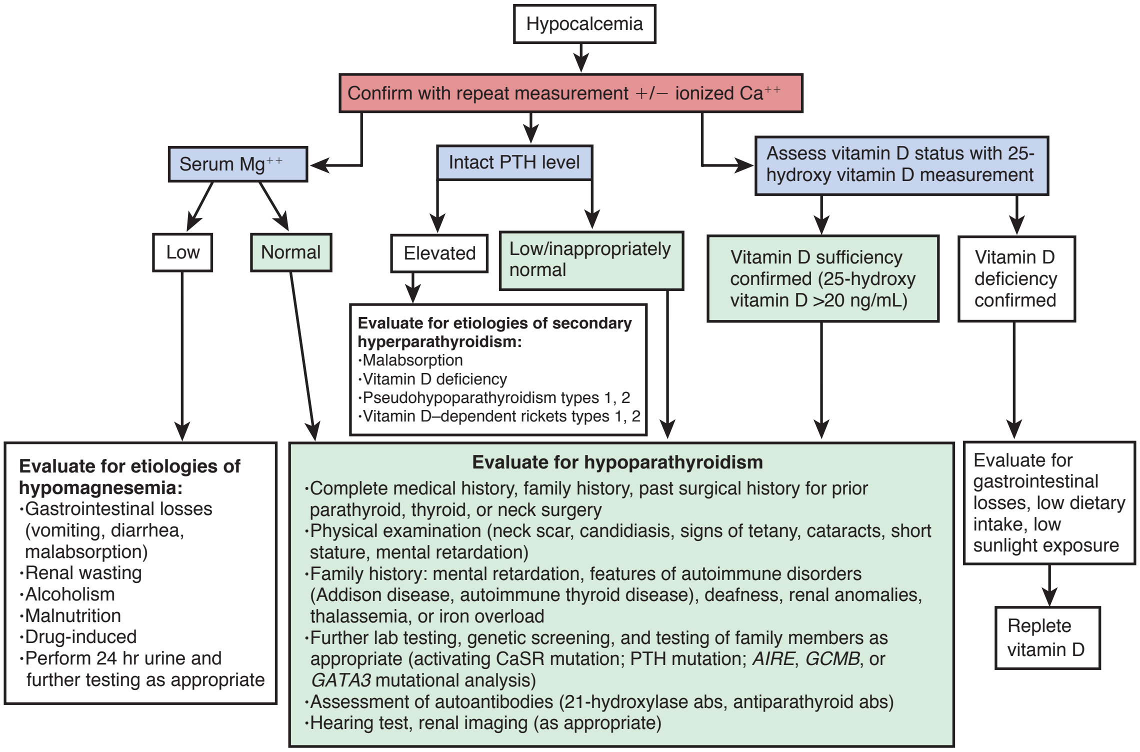

Figure 571-1 Evaluation of hypocalcemia. Abs, autoantibodies; CaSR, calcium-sensing receptor; PTH, parathyroid hormone. *(From Bilezikian JP, Khan A, Potts JT Jr, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research.* J Bone Miner Res *26:2317–2337, 2011, Fig. 1.)*

of these patients inherit the chromosomal abnormality from a parent. Neonatal hypocalcemia occurs in 60% of affected patients, but it is transitory in the majority; hypocalcemia can recur or can have its onset later in life. Associated abnormalities of the third and fourth pharyngeal pouches are common; these include conotruncal defects of the heart in 25%, velopharyngeal insufficiency in 32%, cleft palate in 9%, renal anomalies in 35%, and aplasia of the thymus with severe immunodeficiency in 1%. This syndrome has also been reported in a small number of patients with a deletion of chromosome 10p13, in infants of diabetic mothers, and in infants born to mothers treated with retinoic acid for acne early in pregnancy.

X-LINKED RECESSIVE HYPOPARATHYROIDISM

Familial clusters of hypoparathyroidism with various patterns of transmission have been described. In 2 large North American pedigrees, this disorder appears to be transmitted by an X-linked recessive gene located on Xq26-q27. In these families, the onset of afebrile seizures characteristically occurs in infants from 2 wk to 6 mo of age. The absence of parathyroid tissue after detailed examination of a boy with this condition suggests a defect in embryogenesis.

AUTOSOMAL RECESSIVE HYPOPARATHYROIDISM WITH DYSMORPHIC FEATURES

Autosomal recessive hypoparathyroidism with dysmorphic features has been described in Middle Eastern children. Parental consanguinity occurred for almost all of several dozen affected patients. Profound hypocalcemia occurs early in life, and dysmorphic features include microcephaly, deep-set eyes, beaked nose, micrognathia, and large floppy ears. Intrauterine and postnatal growth restriction are severe, and cognitive impairment is common. The putative gene is on chromosome 1q42-43. The autosomal recessive form of hypoparathyroidism that occurs with type I polyglandular autoimmune disease is described subsequently. In a few patients with autosomal recessive inheritance of isolated hypoparathyroidism, mutations of the *PTH* gene have been found.

HYPOPARATHYROIDISM, SENSORINEURAL DEAFNESS, AND RENAL ANOMALY SYNDROME

Hypoparathyroidism, sensorineural deafness, and renal anomaly occur owing to mutations of the *GATA3* gene. The protein encoded by this gene is essential in the development of the parathyroids, auditory system, and kidneys. The *GATA3* gene is located at chromosome 10p14 and is nonoverlapping with the DiGeorge critical region at 10p13 (see Fig. 570-1).

SUPPRESSION OF NEONATAL PARATHYROID HORMONE SECRETION BECAUSE OF MATERNAL HYPERPARATHYROIDISM

Neonatal PTH secretion can be suppressed by maternal hyperparathyroidism, resulting in transient hypocalcemia in the newborn infant. It appears that neonatal hypocalcemia results from suppression of the fetal parathyroid glands by exposure to elevated levels of calcium in maternal and hence fetal serum. Tetany usually develops within 3 wk but may be delayed by 1 mo or more if the infant is breastfed. Hypocalcemia can persist for weeks or months. When the cause of hypocalcemia in an infant is unknown, measurements of calcium, phosphorus, and PTH should be obtained from the mother. Most affected mothers are asymptomatic, and the cause of their hyperparathyroidism is usually a parathyroid adenoma.

AUTOSOMAL DOMINANT HYPOPARATHYROIDISM

Patients with autosomal dominant hypoparathyroidism have an activating (gain-of-function) mutation of the Ca^{2+}-sensing receptor, forcing the receptor to an “on” state with subsequent depression of PTH secretion even during hypocalcemia. The patients have hypercal-

ciuria. The hypocalcemia is usually mild and might not require treatment beyond childhood (see Fig. 570-1).

HYPOPARATHYROIDISM ASSOCIATED WITH MITOCHONDRIAL DISORDERS

Mitochondrial DNA mutations in Kearns-Sayre syndrome, MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndrome, and in mitochondrial trifunctional protein–deficiency syndrome are associated with hypoparathyroidism. A diagnosis of mitochondrial cytopathy should be considered in patients with unexplained symptoms, such as ophthalmoplegia, sensorineural hearing loss, cardiac conduction disturbances, and tetany (see Fig. 570-1).

SURGICAL HYPOPARATHYROIDISM

Removal or damage of the parathyroid glands can complicate thyroidectomy. Hypoparathyroidism has developed even when the parathyroid glands have been identified and left undisturbed at the time of operation. This may be the result of interference with the blood supply or of postoperative edema and fibrosis. Symptoms of tetany can occur abruptly postoperatively and may be temporary or permanent. In some instances, symptoms develop insidiously and go undetected until months after thyroidectomy. Occasionally, the first evidence of surgical hypoparathyroidism may be the development of cataract. The status of parathyroid function should be carefully monitored in all patients undergoing thyroidectomy.

Deposition of iron pigment or of copper in the parathyroid glands (thalassemia, Wilson disease) can produce hypoparathyroidism.

AUTOIMMUNE HYPOPARATHYROIDISM

An autoimmune mechanism for hypoparathyroidism is strongly suggested by the finding of parathyroid antibodies and by its frequent association with other autoimmune disorders or organ-specific antibodies. Autoimmune hypoparathyroidism is often associated with Addison disease and chronic mucocutaneous candidiasis. The association of at least 2 of these 3 conditions has been tentatively classified as **autoimmune polyglandular disease type I.** It is also known as autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy (APECED). This syndrome is inherited in an autosomal recessive fashion and is not related to any single human leukocyte antigen–associated haplotype. One third of patients with this syndrome have all 3 components; 66% have only 2 of 3 conditions. The candidiasis almost always precedes the other disorders (70% of cases occur in children younger than 5 yr of age); the hypoparathyroidism (90% of cases occur after 3 yr of age) usually occurs before Addison disease (90% of cases occur after 6 yr of age). A variety of other disorders, including alopecia areata or totalis, malabsorption disorder, pernicious anemia, gonadal failure, chronic active hepatitis, vitiligo, and insulin-dependent diabetes, occurs at various times. Some of these associations might not appear until adult life. Autoimmune thyroid disease is a rare concomitant finding.

Affected siblings can have the same or different constellations of disorders (hypoparathyroidism, Addison disease). The disorder is exceptionally prevalent among Finns and Iranian Jews. The gene for this disorder is designated *AIRE* (autoimmune regulator); it is located on chromosome 21q22. It appears to be a transcription factor that plays an essential role in the development of immunologic tolerance. Patients with Addison disease as part of polyendocrinopathy syndrome type I have demonstrated adrenal-specific autoantibody reactivity directed against the side-chain cleavage enzyme.

IDIOPATHIC HYPOPARATHYROIDISM

The term *idiopathic hypoparathyroidism* should be reserved for the small residuum of children with hypoparathyroidism for whom no causative mechanism can be defined. Most children in whom onset of hypoparathyroidism occurs after the 1st few yr of life have an **autoimmune condition.** Autoantibodies to the extracellular domain of the calcium-sensing receptor have been identified in some patients with acquired hypoparathyroidism. One should always consider incomplete forms of DiGeorge syndrome or an activating calcium-sensing receptor mutation in the differential diagnosis.

Clinical Manifestations

There is a spectrum of parathyroid deficiencies with clinical manifestations varying from no symptoms to those of complete and long-standing deficiency. Mild deficiency may be revealed only by appropriate laboratory studies. Muscular pain and cramps are early manifestations; they progress to numbness, stiffness, and tingling of the hands and feet. There may be only a positive Chvostek or Trousseau sign or laryngeal and carpopedal spasms. Convulsions with or without loss of consciousness can occur at intervals of days, weeks, or months. These episodes can begin with abdominal pain, followed by tonic rigidity, retraction of the head, and cyanosis. Hypoparathyroidism is often mistaken for epilepsy. Headache, vomiting, increased intracranial pressure, and papilledema may be associated with convulsions and might suggest a brain tumor.

In patients with long-standing hypocalcemia, the teeth erupt late and irregularly. Enamel formation is irregular, and the teeth may be unusually soft. The skin may be dry and scaly, and the nails might have horizontal lines. Mucocutaneous candidiasis, when present, antedates the development of hypoparathyroidism; the candidal infection most often involves the nails, the oral mucosa, the angles of the mouth, and less often, the skin; it is difficult to treat.

Cataracts in patients with long-standing untreated disease are a direct consequence of hypoparathyroidism; other autoimmune ocular disorders such as keratoconjunctivitis can also occur. Manifestations of Addison disease, lymphocytic thyroiditis, pernicious anemia, alopecia areata or totalis, hepatitis, and primary gonadal insufficiency may also be associated with those of hypoparathyroidism.

Permanent physical and mental deterioration occurs if initiation of treatment is long delayed.

Laboratory Findings

The serum calcium level is low (5-7 mg/dL), and the phosphorus level is elevated (7-12 mg/dL). Blood levels of ionized calcium (usually approximately 45% of the total) more nearly reflect physiologic adequacy but also are low. The serum level of alkaline phosphatase is normal or low, and the level of $1,25(OH)_2D_3$ is usually low, but high levels have been found in some children with severe hypocalcemia. The level of magnesium is normal but should always be checked in hypocalcemic patients. Levels of PTH are low when measured by immunometric assay. Radiographs of the bones occasionally reveal an increased density limited to the metaphyses, suggesting heavy metal poisoning, or an increased density of the lamina dura. Radiographs or CT scans of the skull can reveal calcifications in the basal ganglia. There is a prolongation of the QT interval on the electrocardiogram, which disappears when the hypocalcemia is corrected. The electroencephalogram usually reveals widespread slow activity; the tracing returns to normal after the serum calcium concentration has been within the normal range for a few weeks, unless irreversible brain damage has occurred or unless the parathyroid insufficiency is associated with epilepsy. When hypoparathyroidism occurs concurrently with Addison disease, the serum level of calcium may be normal, but hypocalcemia appears after effective treatment of the adrenal insufficiency.

Treatment

Emergency treatment of neonatal tetany consists of intravenous injections of 5-10 mL or 1-3 mg/kg of a 10% solution of calcium gluconate (elemental calcium 9.3 mg/mL) at the rate of 0.5-1.0 mL/min while the heart rate is monitored and a total dose not to exceed 20 mg of elemental calcium/kg. Additionally, 1,25-dihydroxycholecalciferol (calcitriol) should be given. The initial dosage is 0.25 µg/24 hr; the maintenance dosage ranges from 0.01-0.10 µg/kg/24 hr to a maximum of 1-2 µg/24 hr. Calcitriol has a short half-life and should be given in 2 equal divided doses; it has the advantages of rapid onset of effect (1-4 days) and rapid reversal of hypercalcemia after discontinuation in the

event of overdosage (calcium levels begin to fall in 3-4 days). Calcitriol is supplied as an oral solution.

An adequate intake of calcium should be ensured. Supplemental calcium can be given in the form of calcium gluconate or calcium glubionate to provide 800 mg of elemental calcium daily, but it is rarely essential. Foods with high phosphorus content such as milk, eggs, and cheese should be reduced in the diet.

Clinical evaluation of the patient and frequent determinations of the serum calcium levels are indicated in the early stages of treatment to determine the requirement for calcitriol or vitamin D_2. If hypercalcemia occurs, therapy should be discontinued and resumed at a lower dose after the serum calcium level has returned to normal. In long-standing cases of hypercalcemia, repair of cerebral and dental changes is not likely. Pigmentation, lowering of blood pressure, or weight loss can indicate adrenal insufficiency, which requires specific treatment. *Patients with autosomal dominant hypocalcemic hypercalciuria can develop nephrocalcinosis and renal impairment if treated with vitamin D.*

Differential Diagnosis

Magnesium deficiency must be considered in patients with unexplained hypocalcemia. Concentrations of serum magnesium <1.5 mg/dL (1.2 mEq/L) are usually abnormal. Familial hypomagnesemia with secondary hypocalcemia has been reported in approximately 50 patients, most of whom developed tetany and seizures at 2-6 wk of age. Administration of calcium is ineffective, but administration of magnesium promptly corrects both calcium and magnesium levels. Oral supplements of magnesium are necessary to maintain levels of magnesium in the normal range. Two genetic forms have been described. One is caused by an autosomal recessive gene on chromosome 9, resulting in a specific defect in absorption of magnesium. The other is caused by an autosomal dominant gene on chromosome 11q23, resulting in renal loss of magnesium.

Hypomagnesemia also occurs in malabsorption syndromes such as Crohn disease and cystic fibrosis. Patients with autoimmune polyglandular disease type I and hypoparathyroidism can also have concurrent steatorrhea and low magnesium levels. Therapy with aminoglycosides causes hypomagnesemia by increasing urinary losses.

It is not clear how low levels of magnesium lead to hypocalcemia. Evidence suggests that hypomagnesemia impairs release of PTH and induces resistance to the effects of the hormone, but other mechanisms also may be operative.

Poisoning with inorganic phosphate leads to hypocalcemia and tetany. Infants administered large doses of inorganic phosphates, either as laxatives or as sodium phosphate enemas, have had sudden onset of tetany, with serum calcium levels <5 mg/dL and markedly elevated levels of phosphate. Symptoms are quickly relieved by intravenous administration of calcium. The mechanism of the hypocalcemia is not clear (see Chapter 55.6).

Hypocalcemia can occur early in the course of treatment of acute lymphoblastic leukemia. Hypocalcemia is usually associated with hyperphosphatemia resulting from destruction of lymphoblasts.

Episodic symptomatic hypocalcemia occurs in the **Kenny-Caffey syndrome,** which is characterized by medullary stenosis of the long bones, short stature, delayed closure of the fontanel, delayed bone age, and eye abnormalities. Idiopathic hypoparathyroidism and abnormal PTH levels have been found. Autosomal dominant and autosomal recessive modes of inheritance have been reported. Mutations of the *TBCE* gene (1q 43-44) perturb microtubule organization in diseased cells.

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Chapter 572

Pseudohypoparathyroidism (Albright Hereditary Osteodystrophy)

Daniel A. Doyle

In contrast to the situation in hypoparathyroidism, in pseudohypoparathyroidism (PHP) the parathyroid glands are normal or hyperplastic and they can synthesize and secrete parathyroid hormone (PTH). Serum levels of immunoreactive PTH are elevated even when the patient is hypocalcemic and may be elevated when the patient is normocalcemic. Neither endogenous nor administered PTH raises the serum levels of calcium or lowers the levels of phosphorus. The genetic defects in the **hormone receptor adenylate cyclase system** are classified into various types depending on the phenotypic and biochemical findings.

TYPE IA

Type Ia accounts for the majority of patients with PHP. Affected patients have a genetic defect of the α subunit of the stimulatory guanine nucleotide-binding protein ($G_s\alpha$). This coupling factor is required for PTH bound to cell surface receptors to activate cyclic adenosine monophosphate (cAMP). Heterogeneous mutations of the $G_s\alpha$ gene have been documented; the gene is located on chromosome 20q13.2. Deficiency of the $G_s\alpha$ subunit is a generalized cellular defect and accounts for the association of other endocrine disorders with type Ia PHP. The defect is inherited as an autosomal dominant trait, and the paucity of father-to-son transmissions is thought to be a result of decreased fertility in males.

Tetany is often the presenting sign. Affected children have a short, stocky build and a round face. Brachydactyly with dimpling of the dorsum of the hand is usually present. The 2nd metacarpal is involved least often. As a result, the index finger occasionally is longer than the middle finger. Likewise, the 2nd metatarsal is only rarely affected. There may be other skeletal abnormalities such as short and wide phalanges, bowing, exostoses, and thickening of the calvaria. These patients often have calcium deposits and metaplastic bone formation subcutaneously. Moderate degrees of cognitive impairment, calcification of the basal ganglia, and lenticular cataracts are common in patients whose disease is diagnosed late.

Some members of affected kindreds may have the usual anatomic stigmata of PHP, but serum levels of calcium and phosphorus are normal despite reduced $G_s\alpha$ activity; however, PTH levels may be slightly elevated. Such patients have been labeled as having **pseudopseudohypoparathyroidism.** Transition from normocalcemia to hypocalcemia often occurs with increasing age of the patient. These phenotypically similar but metabolically dissimilar patients may be in the same family and have the same mutations of $G_s\alpha$ protein. It is not known what other factors cause clinically overt hypocalcemia in some affected patients and not in others. There is some evidence to suggest that the $G_s\alpha$ mutation is paternally transmitted in pseudopseudohypoparathyroidism and maternally transmitted in patients with type Ia disease. The gene may be imprinted in a tissue-specific manner.

In addition to resistance to PTH, resistance to other G-protein–coupled receptors for thyroid-stimulating hormone (TSH), gonadotropins, and glucagon can result in various metabolic effects. Clinical hypothyroidism is uncommon, but basal levels of TSH are elevated

and thyrotropin-releasing hormone–stimulated TSH responses are exaggerated. Moderately decreased levels of thyroxine and increased levels of TSH have been demonstrated by newborn thyroid-screening programs, leading to the detection of type Ia PHP in infancy. In adults, gonadal dysfunction is common, as manifested by sexual immaturity, amenorrhea, oligomenorrhea, and infertility. Each of these abnormalities can be related to deficient synthesis of cAMP secondary to a deficiency of $G_s\alpha$, but it is not clear why resistance to other G-protein–dependent hormones (corticotropin, vasopressin) is much less affected.

Serum levels of calcium are low, and those of phosphorus and alkaline phosphatase are elevated. Clinical diagnosis can be confirmed by demonstration of a markedly attenuated response in urinary phosphate and cAMP after intravenous infusion of the synthetic 1-34 fragment of human PTH (teriparatide acetate). Definitive diagnosis is established by demonstration of the mutated G protein.

Type Ia with Precocious Puberty

Two boys have been reported with both type Ia PHP and gonadotropin-independent precocious puberty (see Chapter 562.7). They were found to have a temperature-sensitive mutation of the G_s protein. Thus, at normal body temperature (37°C [98.6°F]), the G_s is degraded, resulting in PHP, but in the cooler temperature of the testes (33°C [91.4°F]) the G_s mutation results in constitutive activation of the luteinizing hormone receptor and precocious puberty.

TYPE IB

Affected patients have normal levels of G protein activity and a normal phenotypic appearance. These patients have tissue-specific resistance to PTH but not to other hormones. Serum levels of calcium, phosphorus, and immunoreactive PTH are the same as those in patients with type Ia PHP. These patients also show no rise in cAMP in response to exogenous administration of PTH. Bioactive PTH is not increased. The pathophysiology of the disorder in this group of patients is caused by paternal uniparental isodisomy of chromosome 20q and resulting *GNAS1* methylation. This, along with the loss of the maternal *GNAS1* gene, leads to PTH resistance in the proximal renal tubules, which leads to impaired mineral ion homeostasis.

ACRODYSOSTOSIS WITH HORMONE RESISTANCE

Patients with acrodysostosis resemble those with PHP type Ia, but defects in the $G_s\alpha$ subunit are not present. Instead, in 1 subgroup of patients there is a defect in the gene encoding *PRKAR1A*, the cAMP-dependent regulatory subunit of protein kinase A that confers resistance to multiple hormones, including PTH. Another subgroup has a defect in a phosphodiesterase gene *Pde4d*. This subgroup also carries the phenotype of PHP type Ia but rarely exhibits the hormone resistance.

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Chapter **573**

Hyperparathyroidism

Daniel A. Doyle

Excessive production of parathyroid hormone (PTH) can result from a primary defect of the parathyroid glands such as an adenoma or hyperplasia **(primary hyperparathyroidism).**

More often, the increased production of PTH is compensatory, usually aimed at correcting hypocalcemic states of diverse origins **(secondary hyperparathyroidism).** In vitamin D–deficient rickets and the malabsorption syndromes, intestinal absorption of calcium is deficient but hypocalcemia and tetany may be averted by increased activity of the parathyroid glands. In **pseudohypoparathyroidism,** PTH levels are elevated because a mutation in the $G_s\alpha$ protein interferes with response to PTH. Early in chronic renal disease, hyperphosphatemia results in a reciprocal fall in the calcium concentration with a consequent increase in PTH, but in advanced stages of renal failure, production of $1,25(OH)_2D_3$ is also decreased, leading to worsening hypocalcemia and further stimulation of PTH. In some instances, if stimulation of the parathyroid glands has been sufficiently intense and protracted, the glands continue to secrete increased levels of PTH for months or years after kidney transplantation, with resulting hypercalcemia.

ETIOLOGY

Childhood hyperparathyroidism is uncommon. Onset during childhood is usually the result of a single benign adenoma. It usually becomes manifested after 10 yr of age. There have been a number of kindreds in which multiple members have hyperparathyroidism transmitted in an autosomal dominant fashion. Most of the affected family members are adults, but children have been involved in approximately 30% of the pedigrees. Some affected patients in these families are asymptomatic, and disease is detected only by careful study. In other kindreds, hyperparathyroidism occurs as part of the constellation known as the **multiple endocrine neoplasia** (MEN) syndromes or of the hyperparathyroidism–jaw tumor syndrome.

Neonatal severe hyperparathyroidism is a rare disorder. Symptoms develop shortly after birth and consist of anorexia, irritability, lethargy, constipation, and failure to thrive. Radiographs reveal subperiosteal bone resorption, osteoporosis, and pathologic fractures. Symptoms may be mild, resolving without treatment, or can have a rapidly fatal course if diagnosis and treatment are delayed. Histologically, the parathyroid glands show diffuse hyperplasia. Affected siblings have been observed in some kindreds, and parental consanguinity has been reported in several kindreds. Most cases have occurred in kindreds with the clinical and biochemical features of **familial hypocalciuric hypercalcemia.** Infants with neonatal severe hyperparathyroidism may be homozygous or heterozygous for the mutation in the Ca^{2+}-sensing receptor gene, whereas most persons with 1 copy of this mutation exhibit autosomal dominant familial hypocalciuric hypercalcemia.

MEN type I is an autosomal dominant disorder characterized by hyperplasia or neoplasia of the endocrine pancreas (which secretes gastrin, insulin, pancreatic polypeptide, and occasionally glucagon), the anterior pituitary (which usually secretes prolactin), and the parathyroid glands. In most kindreds, hyperparathyroidism is usually the presenting manifestation, with a prevalence approaching 100% by 50 yr of age and occurring only rarely in children younger than 18 yr of age. With appropriate DNA probes, it is possible to detect carriers of the gene with 99% accuracy at birth, avoiding unnecessary biochemical screening programs.

The gene for MEN type I is on chromosome 11q13; it appears to function as a tumor-suppressor gene and follows the 2-hit hypothesis of tumor development. The first mutation (germinal) is inherited and is recessive to the dominant allele; this does not result in tumor formation. A second mutation (somatic) is required to eliminate the normal allele, which then leads to tumor formation.

Hyperparathyroidism–jaw tumor syndrome is an autosomal dominant disorder characterized by parathyroid adenomas and fibro-osseous jaw tumors. Affected patients can also have polycystic kidney disease, renal hamartomas, and Wilms tumor. Although the condition affects adults primarily, it has been diagnosed as early as age 10 yr.

MEN type II may also be associated with hyperparathyroidism (see Chapter 569.2).

Transient neonatal hyperparathyroidism has occurred in a few infants born to mothers with hypoparathyroidism (idiopathic or surgical) or with pseudohypoparathyroidism. In each case, the maternal disorder had been undiagnosed or inadequately treated during pregnancy. The cause of the condition is chronic intrauterine exposure to

hypocalcemia with resultant hyperplasia of the fetal parathyroid glands. In the newborn, manifestations involve the bones primarily, and healing occurs between 4 and 7 mo of age.

CLINICAL MANIFESTATIONS

At all ages, the clinical manifestations of hypercalcemia of any cause include muscle weakness, fatigue, headache, anorexia, abdominal pain, nausea, vomiting, constipation, polydipsia, polyuria, weight loss, and fever. When hypercalcemia is of long duration, calcium may be deposited in the renal parenchyma (nephrocalcinosis), with progressively diminished renal function. Renal calculi can develop and can cause renal colic and hematuria. Osseous changes can produce pain in the back or extremities, disturbances of gait, genu valgum, fractures, and tumors. Height can decrease from compression of vertebrae; the patient can become bedridden. Detection of completely asymptomatic patients is increasing with the advent of automated panel assays that include serum calcium determinations.

Abdominal pain is occasionally prominent and may be associated with **acute pancreatitis.** Parathyroid crisis can occur, manifested by serum calcium levels >15 mg/dL and progressive oliguria, azotemia, stupor, and coma. In infants, failure to thrive, poor feeding, and hypotonia are common.

Cognitive impairment, convulsions, and blindness can occur as sequelae of long-standing hypercalcemia. Psychiatric manifestations include depression, confusion, dementia, stupor, and psychosis.

LABORATORY FINDINGS

The serum calcium level is elevated; 39 of 45 children with adenomas had levels >12 mg/dL. The hypercalcemia is more severe in infants with parathyroid hyperplasia; concentrations ranging from 15-20 mg/dL are common, and values as high as 30 mg/dL have been reported. Even when the total serum calcium level is borderline or only slightly elevated, ionized calcium levels are often increased. The serum phosphorus level is reduced to approximately 3 mg/dL or less, and the level of serum magnesium is low. The urine can have a low and fixed specific gravity, and serum levels of nonprotein nitrogen and uric acid may be elevated. In patients with adenomas who have skeletal involvement, serum phosphatase levels are elevated, but in infants with hyperplasia the levels of alkaline phosphatase may be normal even when there is extensive involvement of bone.

Serum levels of intact PTH are elevated, especially in relation to the level of calcium. Calcitonin levels are normal. Acute hypercalcemia can stimulate calcitonin release, but with prolonged hypercalcemia, hypercalcitoninemia does not occur.

The most consistent and characteristic radiographic finding is resorption of subperiosteal bone, best seen along the margins of the phalanges of the hands. In the skull, there may be gross trabeculation or a granular appearance resulting from focal rarefaction; the lamina dura may be absent. In more advanced disease, there may be generalized rarefaction, cysts, tumors, fractures, and deformities. Approximately 10% of patients have radiographic signs of rickets. Radiographs of the abdomen can reveal renal calculi or nephrocalcinosis.

DIFFERENTIAL DIAGNOSIS

Other causes of hypercalcemia can result in a similar clinical pattern and must be differentiated from hyperparathyroidism (Table 573-1 and Fig. 573-1). A low serum phosphorus level with hypercalcemia is characteristic of primary hyperparathyroidism; elevated levels of PTH are also diagnostic. With hypercalcemia of any cause except hyperparathyroidism and familial hypocalciuric hypercalcemia, PTH levels are suppressed. Pharmacologic doses of corticosteroids lower the serum calcium level to normal in patients with hypercalcemia from other causes but generally do not affect the calcium level in patients with hyperparathyroidism.

TREATMENT

Surgical exploration is indicated in all instances. All glands should be carefully inspected; if an adenoma is discovered, it should be removed; very few instances of carcinoma are known in children. Most neonates with severe hypercalcemia require total parathyroidectomy; less-severe hypercalcemia remits spontaneously in others. Still others have been treated successfully with bisphosphonates and calcimimetics. The patient should be carefully observed postoperatively for the development of hypocalcemia and tetany; intravenous administration of calcium gluconate may be required for a few days. The serum calcium level then gradually returns to normal, and, under ordinary

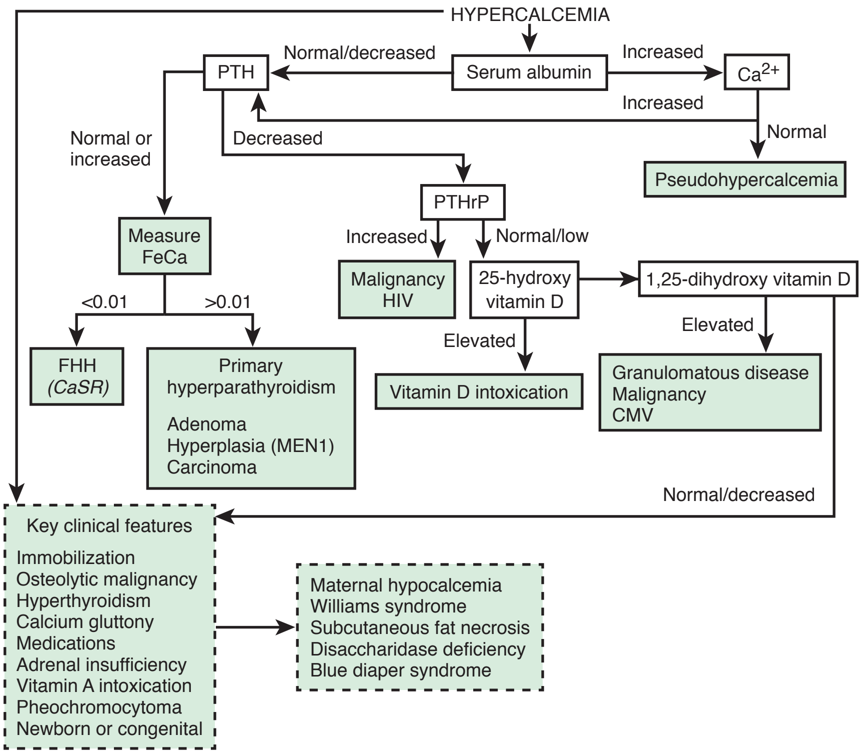

Figure 573-1 Evaluation of hypercalcemia. Ca^{2+}, calcium ions; CaSR, calcium-sensing receptor; CMV, cytomegalovirus; FeCa, fractional excretion of urinary calcium. *(From Lietman SA, Germain-Lee EL, Levine MA. Hypercalcemia in children and adolescents.* Curr Opin Pediatr *22:508–515, 2010.)*

Table 573-1 Causes of Hypercalcemia

I. Neonate/Infant
   A. Maternal Disorders
      1. Excessive vitamin D ingestion, hypoparathyroidism, pseudohypoparathyroidism
   B. Neonate/Infant
      1. Iatrogenic: excessive intake of calcium, vitamin D, vitamin A
      2. Phosphate depletion
      3. Subcutaneous fat necrosis
      4. Williams-Beuren syndrome (del7q11.23/*BAZ1B*) (transient receptor potential; 3-channel defect)
      5. Neonatal severe hyperparathyroidism *(CaSR)*
      6. Metaphyseal chondrodysplasia, Murk-Jansen type *(PTH1R)*
      7. Idiopathic infantile hypercalcemia *(CYP24A1)* (25-hydroxyvitamin D 24-hydroxylase)
      8. Persistent parathyroid hormone–related protein
      9. Lactase/disaccharidase deficiency *(LCT)*
      10. Infantile hypophosphatasia *(TNSALP)*
      11. Mucolipidosis type II *(GNPTAB)*
      12. Blue diaper syndrome
      13. Antenatal Bartter syndrome types 1 and 2 *(SLC12A1, KCNJ1)*
      14. Distal renal tubular acidosis
      15. IMAGe syndrome *(CDKN1C)*
      16. Post bone marrow transplantation for osteopetrosis
      17. Endocrinopathies: primary adrenal insufficiency, severe congenital hypothyroidism, hyperthyroidism
II. Hyperparathyroidism
   A. Sporadic
      1. Parathyroid hyperplasia, adenoma, carcinoma
   B. Familial
      1. Neonatal severe hyperparathyroidism *(CaSR)*
      2. Multiple endocrine neoplasia, type I *(MEN1)*
      3. Multiple endocrine neoplasia, type IIA *(RET)*
      4. Multiple endocrine neoplasia, type IIB *(RET)*
      5. Multiple endocrine neoplasia, type IV *(CDKN1B)*
      6. McCune-Albright syndrome *(GNAS)*
      7. Familial isolated hyperparathyroidism 1 *(CDC73)*
      8. Familial isolated hyperparathyroidism 2 (jaw tumor syndrome) *(CDC73)*
      9. Familial isolated hyperparathyroidism 3
      10. Jansen metaphyseal dysplasia *(PTH1R)*
   C. Secondary/Tertiary
      1. Postrenal transplantation
      2. Chronic hyperphosphatemia
   D. Hypercalcemia of Malignancy
      1. Ectopic production of parathyroid hormone–related peptide
      2. Metastatic dissolution of bone
III. Familial Hypocalciuric Hypercalcemia
   A. Familial Hypocalciuric Hypercalcemia I *(CaSR)*
      1. Loss-of-function mutations in *CaSR*
         a. Monoallelic: familial benign hypercalcemia
         b. Biallelic: neonatal severe hyperparathyroidism
   B. Familial Hypocalciuric Hypercalcemia II *(GNA11)*
   C. Familial Hypocalciuric Hypercalcemia III, Oklahoma Variant *(AP2S1)*
   D. *CaSR*-blocking autoantibodies
IV. Excessive Calcium or Vitamin D
   A. Milk-Alkali Syndrome
   B. Exogenous Ingestion of Calcium or Vitamin D or Topical Application of Vitamin D (calcitriol or analog)
   C. Ectopic Production of Calcitriol Associated with Granulomatous Diseases (sarcoidosis, cat-scratch fever; tuberculosis, histoplasmosis, coccidioidomycosis, leprosy; human immunodeficiency virus; cytomegalovirus; chronic inflammatory bowel disease)
   D. Neoplasia
      1. Primary bone tumors
      2. Metastatic tumors with osteolysis
      3. Lymphoma, leukemia
      4. Dysgerminoma
      5. Pheochromocytoma
      6. Tumors secreting parathyroid hormone–related peptide, growth factors, cytokines, prostaglandins, osteoclast-activating factors
   E. Williams-Beuren Syndrome (del7q11.23)
V. Immobilization
VI. Other Causes
   A. Drugs: Thiazides, Lithium, Vitamin A and Analogs, Calcium, Alkali, Antiestrogens, Aminophylline
   B. Total Parenteral Nutrition
   C. Endocrinopathies: Hyperthyroidism, Addison disease, Pheochromocytoma
   D. Vasoactive Intestinal Polypeptide–Secreting Tumor
   E. Acute or Chronic Renal Failure/Administration of Aluminum
   F. Hypophosphatasia
   G. Juvenile Rheumatoid Arthritis: Cytokine Mediated

Adapted from Lietman SA, Germain-Lee EL, Levine MA. Hypercalcemia in children and adolescents. Curr Opin Pediatr *22:508–515, 2010; Benjamin RW, Moats-Staats BM, Calikoglu A, et al. Hypercalcemia in children.* Pediatr Endocrinol Rev *5:778–784, 2008; Davies JH. A practical approach to the problems of hypercalcaemia.* Endocr Dev *16:93–114, 2009.*

circumstances, a diet high in calcium and phosphorus must be maintained for only several months after operation.

CT, real-time ultrasonography, and subtraction scintigraphy using sestamibi/technetium-pertechnetate alone and in combination have proved effective in localizing a single adenoma vs diffuse hyperplasia in 50-90% of adults. Parathyroid surgeons often rely on intraoperative selective venous sampling with intraoperative assay of PTH for localizing and removing the source of increased PTH secretion.

PROGNOSIS

The prognosis is good if the disease is recognized early and there is appropriate surgical treatment. When extensive osseous lesions are present, deformities may be permanent. A search for other affected family members is indicated.

573.1 Other Causes of Hypercalcemia

Daniel A. Doyle

FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FAMILIAL BENIGN HYPERCALCEMIA)

Patients with familial hypocalciuric hypercalcemia are usually asymptomatic, and the hypercalcemia is identified by chance during routine investigation for other conditions. The parathyroid glands are normal, PTH levels are inappropriately normal, and subtotal parathyroidectomy does not correct the hypercalcemia. Serum levels of magnesium are high normal or mildly elevated. The ratio of calcium-to-creatinine clearance is usually decreased despite hypercalcemia.

The disorder is inherited in an autosomal dominant manner and is caused by a mutant gene on chromosome 3q2. Penetrance is near 100%, and the disorder can be diagnosed early in childhood by serum and urinary calcium concentrations. Detection of other affected family members is important to avoid inappropriate parathyroid surgery. The defect is an inactivating mutation in the Ca^{2+}-sensing receptor gene. This G-protein–coupled receptor senses the level of free Ca^{2+} in the blood and triggers the pathway to increase extracellular Ca^{2+} in the face of hypocalcemia. This receptor functions in the parathyroid and kidney to regulate calcium homeostasis; inactivating mutations lead to an increased set point with respect to serum Ca^{2+}, resulting in mild to moderate hypercalcemia in heterozygotes.

GRANULOMATOUS DISEASES

Hypercalcemia occurs in 30-50% of children with sarcoidosis and less often in patients with other granulomatous diseases such as tuberculosis. Levels of PTH are suppressed, and levels of $1,25(OH)_2D_3$ are elevated. The source of **ectopic $1,25(OH)_2D_3$** is the activated macrophage, through stimulation by interferon-α from T lymphocytes, which are present in abundance in granulomatous lesions. Unlike renal tubular cells, the 1α-hydroxylase in macrophages is unresponsive to homeostatic regulation. Oral administration of prednisone (2 mg/kg/24 hr) lowers serum levels of $1,25(OH)_2D_3$ to normal and corrects the hypercalcemia.

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia often occurs in adults with a wide variety of solid tumors but is identified much less often in children. It has been reported in infants with malignant rhabdoid tumors of the kidney or congenital mesoblastic nephroma and in children with neuroblastoma, medulloblastoma, leukemia, Burkitt lymphoma, dysgerminoma, and rhabdomyosarcoma. Serum levels of PTH are rarely elevated. In most patients, the hypercalcemia associated with malignancy is caused by elevated levels of parathyroid hormone–related peptide and not PTH. Rarely, tumors produce $1,25(OH)_2D_3$ or PTH ectopically.

MISCELLANEOUS CAUSES OF HYPERCALCEMIA

Hypercalcemia can occur in infants with **subcutaneous fat necrosis.** Levels of PTH are normal. In 1 infant, the level of $1,25(OH)_2D_3$ was elevated and biopsy of the skin lesion revealed granulomatous infiltration, suggesting that the mechanism of the hypercalcemia was akin to that seen in patients with other granulomatous disease. In another infant, although the level of $1,25(OH)_2D_3$ was normal, PTH was suppressed, suggesting the hypercalcemia was not related to PTH. Treatment with prednisone is effective.

Hypophosphatasia, especially the severe infantile form, is usually associated with mild to moderate hypercalcemia (see Chapter 705). Serum levels of phosphorus are normal, and those of alkaline phosphatase are subnormal. The bones exhibit rachitic-like lesions on radiographs. Urinary levels of phosphoethanolamine, inorganic pyrophosphate, and pyridoxal 5′-phosphate are elevated; each is a natural substrate to a tissue-nonspecific (liver, bone, kidney) alkaline phosphatase enzyme. Missense mutations of the tissue-nonspecific alkaline phosphatase enzyme gene result in an inactive enzyme in this autosomal recessive disorder.

Idiopathic hypercalcemia of infancy is manifested by failure to thrive and hypercalcemia during the 1st yr of life, followed by spontaneous remission. Serum levels of phosphorus and PTH are normal. The condition has been defined as resulting from increased absorption of calcium from decreased degradation of $1,25(OH)_2D_3$. Mutations in the *CYP24A1* gene that encodes 25-hydroxyvitamin D 24-hydroxylase, the key enzyme in $1,25(OH)_2D_3$ degradation, cause excessive levels of the active vitamin D metabolite, which, in turn, causes hypercalcemia in a subset of infants who receive supplemental vitamin D. An excessive rise in the level of $1,25(OH)_2D_3$ in response to PTH administration has been reported years after the hypercalcemic phase.

Approximately 10% of patients with **Williams syndrome** also inconsistently exhibit associated infantile hypercalcemia. The phenotype consists of feeding difficulties, slow growth, elfin facies (small mandible, prominent maxilla, upturned nose), renovascular disorders, and a gregarious "cocktail party" personality. Cardiac lesions include supravalvular aortic stenosis, peripheral pulmonic stenosis, aortic hypoplasia, coronary artery stenosis, and atrial or ventricular septal defects. Nephrocalcinosis can develop if hypercalcemia persists. The IQ score of 50-70 is curiously accompanied by enhanced quantity and quality of vocabulary, auditory memory, and social use of language. A contiguous gene deletion syndrome with a submicroscopic deletion at chromosome 7q11.23, which includes deletion of 1 elastin allele, occurs in 90% of patients and seems to account for the vascular problems. Definitive diagnosis can be established by specific fluorescence in situ hybridization. The hypercalcemia and central nervous system symptoms may be caused by deletion of adjacent genes. Hypercalcemia has been successfully controlled with either prednisone or calcitonin.

Hypervitaminosis D resulting in hypercalcemia from drinking milk that has been incorrectly fortified with excessive amounts of vitamin D has been reported. Not all patients with hypervitaminosis D develop hypercalcemia. Affected infants can manifest failure to thrive, nephrolithiasis, poor renal function, and osteosclerosis. Serum levels of 25(OH)D are a better indicator of hypervitaminosis D than levels of $1,25(OH)_2D_3$ because 25(OH)D has a longer half-life.

Prolonged immobilization can lead to hypercalcemia and occasionally to decreased renal function, hypertension, and encephalopathy. Children who have hypophosphatemic rickets and undergo surgery with subsequent long-term immobilization are at risk for hypercalcemia and should therefore have their vitamin D supplementation decreased or discontinued.

Jansen-type metaphyseal chondrodysplasia is a rare genetic disorder characterized by short-limbed dwarfism and severe but asymptomatic hypercalcemia (see Chapter 704). Circulating levels of PTH and parathyroid hormone–related peptide are undetectable. These patients have an activating PTH–parathyroid hormone–related peptide receptor mutation that results in aberrant calcium homeostasis and abnormalities of the growth plate.

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Section 4
Disorders of the Adrenal Gland

Chapter 574
Physiology of the Adrenal Gland

574.1 Histology and Embryology

Perrin C. White

The adrenal gland is composed of 2 endocrine tissues: the medulla and the cortex. The chromaffin cells of the adrenal medulla are derived from neuroectoderm, whereas the cells of the adrenal cortex are derived from mesoderm. Mesodermal cells also contribute to the development of the gonads. The adrenal glands and gonads have certain common enzymes involved in steroid synthesis; an inborn error in steroidogenesis in one tissue can also be present in the other.

The adrenal cortex of the older child or adult consists of 3 zones: the zona glomerulosa, the outermost zone located immediately beneath the capsule; the zona fasciculata, the middle zone; and the zona reticularis, the innermost zone, lying next to the adrenal medulla. The zona fasciculata is the largest zone, constituting approximately 75% of the cortex; the zona glomerulosa constitutes approximately 15% and the zona reticularis approximately 10%. Glomerulosa cells are small, with a lower cytoplasmic : nuclear ratio, an intermediate number of lipid inclusions, and smaller nuclei containing more condensed chromatin than the cells of the other 2 zones. The cells of the zona fasciculata are large, with a high cytoplasmic : nuclear ratio and many lipid inclusions that give the cytoplasm a foamy, vacuolated appearance. The cells are arranged in radial cords. The cells of the zona reticularis are arranged in irregular anastomosing cords. The cytoplasmic: nuclear ratio is intermediate, and the compact cytoplasm has relatively little lipid content.

The zona glomerulosa synthesizes aldosterone, the most potent natural mineralocorticoid in humans. The zona fasciculata produces cortisol, the most potent natural glucocorticoid in humans, and the zona fasciculata and zona reticularis synthesize the adrenal androgens.

The adrenal medulla consists mainly of neuroendocrine (chromaffin) cells and glial (sustentacular) cells with some connective tissue and vascular cells. Neuroendocrine cells are polyhedral, with abundant cytoplasm and small, pale-staining nuclei. Under the electron microscope, the cytoplasm contains many large secretory granules that contain catecholamines. Glial cells have less cytoplasm and more basophilic nuclei.

The primordium of the fetal adrenal gland can be recognized at 3-4 wk of gestation just cephalad to the developing mesonephros. At 5-6 wk, the gonadal ridge develops into the steroidogenic cells of the gonads and adrenal cortex; the adrenal and gonadal cells separate, the adrenal cells migrate retroperitoneally, and the gonadal cells migrate caudad. At 6-8 wk of gestation, the gland rapidly enlarges, the cells of the inner cortex differentiate to form the fetal zone, and the outer subcapsular rim remains as the definitive zone. The primordium of the adrenal cortex is invaded at this time by sympathetic neural elements that differentiate into the chromaffin cells capable of synthesizing and storing catecholamines. Catechol *O*-methyltransferase, which converts norepinephrine to epinephrine, is expressed later in gestation. By the end of the 8th wk of gestation, the encapsulated adrenal gland is associated with the upper pole of the kidney. By 8-10 wk of gestation, the cells of the fetal zone are capable of active steroidogenesis.

In the full-term infant, the combined weight of both adrenal glands is 7-9 g. At birth, the inner fetal cortex makes up approximately 80% of the gland and the outer "true" cortex, 20%. Within a few days the fetal cortex begins to involute, undergoing a 50% reduction by 1 mo of age. Conversely, the adrenal medulla is relatively small at birth and undergoes a proportionate increase in size over the 1st 6 mo after birth. By 1 yr, the adrenal glands each weigh <1 g. Adrenal growth thereafter results in adult adrenal glands reaching a combined weight of 8 g. The zonae fasciculata and glomerulosa are fully differentiated by about 3 yr of age. The zona reticularis is not fully developed until puberty.

Adrenocorticotropic hormone (ACTH) is essential for fetal adrenal growth and maturation; feedback regulation of ACTH by cortisol is apparently established by 8-10 wk of gestation. Additional factors important in fetal growth and steroidogenesis include placental chorionic gonadotropins and a number of peptide growth factors produced by the placenta and fetus.

Several transcription factors are critical for the development of the adrenal glands. The 3 transcription factors associated with adrenal hypoplasia in humans are steroidogenic factor-1 (*SF-1;* NR5A1), *DAX-1* (dosage-sensitive sex reversal, adrenal hypoplasia congenita, X chromosome; NR0B1), and the *GLI3* oncogene. Disruption of *SF-1*, encoded on chromosome 9q33, results in gonadal and often adrenal agenesis, absence of pituitary gonadotropes, and an underdeveloped ventral medial hypothalamus. In-frame deletions and frameshift and missense mutations of this gene are associated with 46,XX ovarian insufficiency and 46,XY gonadal dysgenesis. Mutations in the *DAX1* gene, encoded on Xp21, result in adrenal hypoplasia congenita and hypogonadotropic hypogonadism (see Chapter 575.1). Mutations in *GLI3* on chromosome 7p13 cause Pallister-Hall syndrome, other features of which include hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly.

The postnatal adrenal cortex is not static but, in fact, is continually regenerated from a population of stem or progenitor cells under the adrenal capsule. These cells move radially inward (i.e., centripetally) and can differentiate into zona glomerulosa or fasciculata cells as needed in response to the appropriate trophic stimuli (see Chapter 574.3). Several signaling pathways, including sonic hedgehog and Wnt, regulate this process. Sonic hedgehog expression is restricted to the peripheral cortical cells that do not express high levels of steroidogenic genes but give rise to the underlying differentiated cells of the cortex. Wnt/β-catenin signaling maintains the undifferentiated state and adrenal fate of adrenocortical stem/progenitor cells, in part through induction of its target genes *DAX1* and inhibin-α, respectively. Adrenal tumors can result from constitutive activation of the Wnt signaling pathway (see Chapter 579), whereas mutations of *DAX1* lead to loss of the ability of the adrenal cortex to regenerate; this condition is termed *adrenal hypoplasia congenita* (see Chapter 575).

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574.2 Adrenal Steroid Biosynthesis

Perrin C. White

Cholesterol is the starting substrate for all steroid biosynthesis (Fig. 574-1). Although adrenal cortex cells can synthesize cholesterol de novo from acetate, circulating plasma lipoproteins provide most of the cholesterol for adrenal cortex hormone formation. Receptors for both low-density lipoprotein and high-density lipoprotein cholesterol are expressed on the surface of adrenocortical cells; the receptor is termed scavenger receptor class B, type I. Patients with familial hypercholesterolemia who lack low-density lipoprotein receptors have unimpaired adrenal steroidogenesis, suggesting that high-density lipoprotein is the more important source of cholesterol. Cholesterol is stored as cholesteryl esters in vesicles and subsequently hydrolyzed by cholesteryl ester hydrolases to liberate free cholesterol for steroid hormone synthesis.

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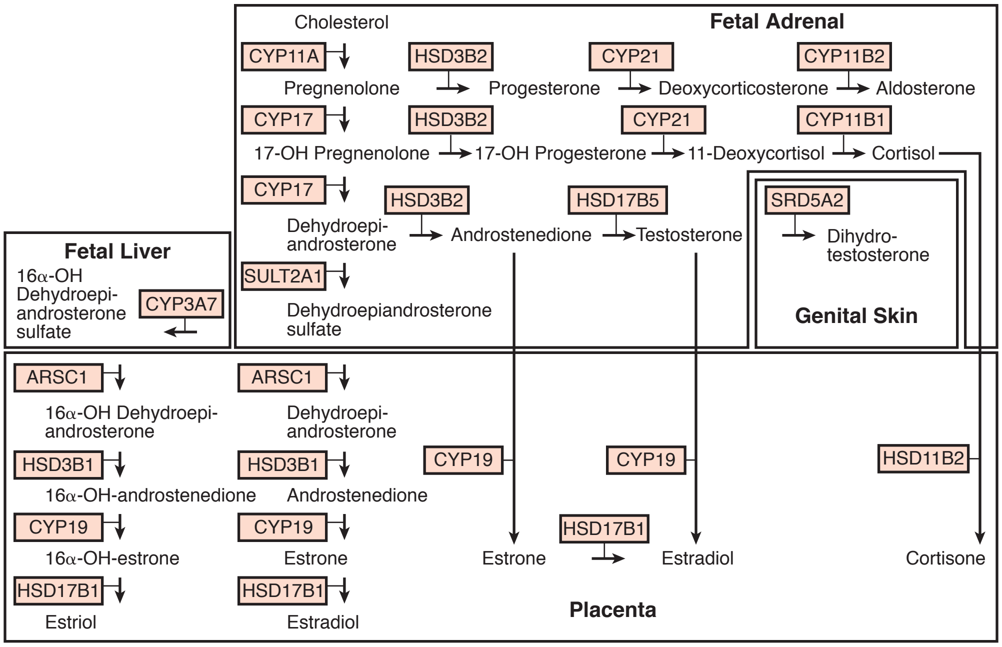

Figure 574-1 **Steroid biosynthesis and metabolism during gestation.** Conversions within the fetal adrenal cortex, fetal liver, male (i.e., testosterone-exposed) genital skin, and placenta are denoted by *arrows;* the enzyme mediating each conversion is also shown. Enzymatic conversions in the adrenal cortex are the same postnatally as prenatally, but cortisol and aldosterone biosynthesis are more prominent, and normally little testosterone is synthesized. Many of the involved enzymes are cytochromes P450 (CYPs). Adrenal enzymes include CYP 11A, cholesterol side-chain cleavage enzyme (P450scc in older terminology); HSD3B2, 3β-hydroxysteroid dehydrogenase/Δ5,Δ4 isomerase type 2; CYP 17, 17β-hydroxylase/17,20-lyase (P450c17); CYP 21, 21-hydroxylase (P450c21); CYP 11B1, 11β-hydroxylase (P450c11); CYP 11B2, aldosterone synthase (P450aldo; this enzyme mediates successive 11β-hydroxylase, 18-hydroxylase, and 18-oxidase reactions in the zona glomerulosa for the conversion of deoxycorticosterone to aldosterone). Other enzymes important in the fetoplacental unit include ARSC1, arylsulfatase; CYP 19, aromatase (P450arom); HSD3B1, 3β-hydroxysteroid dehydrogenase/Δ5,Δ4 isomerase type 1; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; HSD17B1 and HSD17B5 are 2 different 17-hydroxysteroid dehydrogenase enzymes; SRD5A2, steroid 5α-reductase type 2; SULT2A1, steroid sulfotransferase.

The rate-limiting step of adrenal steroidogenesis is importation of cholesterol across the mitochondrial outer and inner membrane. This requires several proteins, particularly the steroidogenic acute regulatory (StAR) protein. The steroidogenic acute regulatory protein has a very short half-life, and its synthesis is rapidly induced by trophic factors (corticotropin); thus, it is the main short-term (minutes to hours) regulator of steroid hormone biosynthesis.

At the mitochondrial inner membrane, the side chain of cholesterol is cleaved to yield pregnenolone. This is catalyzed by the cholesterol side-chain cleavage enzyme (cholesterol desmolase, side-chain cleavage enzyme, P450scc, CYP11A1; the last term is the current systematic nomenclature), a cytochrome P450 (CYP) enzyme. Like other P450s, this is a membrane-bound hemoprotein with a molecular mass of approximately 50 kDa. It accepts electrons from a nicotinamide adenine dinucleotide phosphate–dependent mitochondrial electron transport system consisting of 2 accessory proteins, adrenodoxin reductase (a flavoprotein) and adrenodoxin (a small protein containing nonheme iron). P450 enzymes use electrons and O_2 to hydroxylate the substrate and form H_2O. In the case of cholesterol side-chain cleavage, 3 successive oxidative reactions are performed to cleave the C20,22 carbon bond. Pregnenolone then diffuses out of mitochondria and enters the endoplasmic reticulum. The subsequent reactions that occur depend on the zone of the adrenal cortex.

ZONA GLOMERULOSA

In the zona glomerulosa, pregnenolone is converted to progesterone by 3β-hydroxysteroid dehydrogenase type 2, a nicotinamide adenine dinucleotide–positive–dependent enzyme of the short-chain dehydrogenase type. Progesterone is converted to 11-deoxycorticosterone by steroid 21-hydroxylase (P450c21, CYP21), which is another P450. Like other P450s in the endoplasmic reticulum, it uses an electron transport system with only 1 accessory protein, P450 oxidoreductase.

Deoxycorticosterone then reenters mitochondria and is converted to aldosterone by aldosterone synthase (P450aldo, CYP11B2), a P450 enzyme structurally related to cholesterol desmolase. Aldosterone synthase also carries out 3 successive oxidations: 11β-hydroxylation, 18-hydroxylation, and further oxidation of the 18-methyl carbon to an aldehyde.

ZONA FASCICULATA

In the endoplasmic reticulum of the zona fasciculata, pregnenolone and progesterone are converted by 17α-hydroxylase (P450c17, CYP17) to 17-hydroxypregenolone and 17-hydroxyprogesterone, respectively. This enzyme is not expressed in the zona glomerulosa, which consequently cannot synthesize 17-hydroxylated steroids. 17-Hydroxypregnenolone is converted to 17-hydroxyprogesterone and 11-deoxycortisol by the same 3β-hydroxysteroid and 21-hydroxylase enzymes, respectively, as are active in the zona glomerulosa. Thus, inherited disorders in these enzymes affect both aldosterone and cortisol synthesis (see Chapter 576). Finally, 11-deoxycortisol reenters mitochondria and is converted to cortisol by steroid 11β-hydroxylase (P450c11, CYP11B1). This enzyme is closely related to aldosterone synthase but has low 18-hydroxylase and nonexistent 18-oxidase activity. Thus, under normal circumstances the zona fasciculata cannot synthesize aldosterone.

ZONA RETICULARIS

In the zona reticularis and to some extent in the zona fasciculata, the 17-hydroxylase (CYP17) enzyme has an additional activity, cleavage of the 17,20 carbon–carbon bond. This converts 17-hydroxypregnenolone to dehydroepiandrosterone (DHEA). DHEA is converted to androstenedione by HSD3B. This may be further converted in other tissues to testosterone and estrogens.

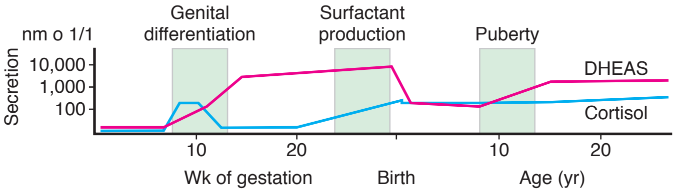

Figure 574-2 Relative levels of cortisol and dehydroepiandrosterone sulfate (DHEAS) secretion by the fetal adrenal cortex during gestation as well as postnatally. Approximate times of several events are shown. Vertical axis is logarithmic, but values are approximate. Horizontal axis is not to scale.

FETOPLACENTAL UNIT

Steroid synthesis in the fetal adrenal varies during gestation (see Figs. 574-1 and 574-2). Shortly after the fetal adrenal gland forms (wk 8-10), it efficiently secretes cortisol, which is able to negatively feedback on the fetal pituitary and hypothalamus to suppress ACTH secretion. This is critical time for differentiation of the external genitalia in both sexes (see Chapter 576.1); to prevent virilization, the female fetus must not be exposed to high levels of androgens of adrenal origin, and placental aromatase activity must remain low during this time to minimize conversion of testosterone to estradiol in male fetuses, which would interfere with masculinization. After wk 12, HSD3B activity in the fetal adrenal gland decreases and steroid sulfokinase activity increases. Thus, the major steroid products of the midgestation fetal adrenal gland are DHEA and DHEA sulfate (DHEAS) and, by 16α-hydroxylation in the liver, 16α-hydroxy DHEAS. Aromatase activity increases in the placenta at the same time, and steroid sulfatase activity is high as well. Thus, the placenta uses DHEA and DHEAS as substrates for estrone and estradiol and 16α-OH DHEAS as a substrate for estriol. Cortisol activity is low during the 2nd trimester, which might serve to prevent premature secretion of surfactant by the developing fetal lungs; surfactant levels can affect the timing of parturition. As term approaches, fetal cortisol concentration increases as a result of increased cortisol secretion and decreased conversion of cortisol to cortisone by 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2). Low levels of aldosterone are produced in mid-gestation, but aldosterone secretory capacity increases near term.

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574.3 Regulation of the Adrenal Cortex

Perrin C. White

REGULATION OF CORTISOL SECRETION

Glucocorticoid secretion is regulated mainly by ACTH (corticotropin), a 39-amino-acid peptide that is produced in the anterior pituitary. It is synthesized as part of a larger-molecular-weight precursor peptide known as proopiomelanocortin. This precursor peptide is also the source of β-lipotropin. ACTH and β-lipotropin are cleaved further to yield α- and β-melanocyte–stimulating hormone, corticotropin-like intermediate lobe peptide, γ-lipotropin, β- and γ-endorphin, and enkephalin (see Chapter 556).

ACTH is released in secretory bursts of varying amplitude throughout the day and night. The normal diurnal rhythm of cortisol secretion is caused by the varying amplitudes of ACTH pulses. Pulses of ACTH and cortisol occur every 30-120 min, are highest at about the time of waking, are low in late afternoon and evening, and reach their lowest point 1 or 2 hr after sleep begins.

Corticotropin-releasing hormone (CRH), synthesized by neurons of the parvicellular division of the hypothalamic paraventricular nucleus, is the most important stimulator of ACTH secretion. Arginine vasopressin (AVP) augments CRH action. Neural stimuli from the brain cause the release of CRH and AVP (see Chapter 556). AVP and CRH are secreted in the hypophyseal-portal circulation in a pulsatile manner. This pulsatile secretion appears to be responsible for the pulsatile (ultradian) release of ACTH. The circadian rhythm of corticotropin release is probably induced by a corresponding circadian rhythm of hypothalamic CRH secretion, regulated by the suprachiasmatic nucleus with input from other areas of the brain. Cortisol exerts a negative feedback effect on the synthesis and secretion of ACTH, CRH, and AVP. ACTH inhibits its own secretion, a feedback effect mediated at the level of the hypothalamus. Thus the secretion of cortisol is a result of the interaction of the hypothalamus, pituitary, and adrenal glands and other neural stimuli.

ACTH acts through a specific G-protein–coupled receptor (also termed melanocortin receptor-2, encoded by the *MCR2* gene) to activate adenylate cyclase and increase levels of cyclic adenosine monophosphate. Cyclic adenosine monophosphate has short-term (minutes to hours) effects on cholesterol transport into mitochondria by increasing expression of steroidogenic acute regulatory protein. The long-term effects (hours to days) of ACTH stimulation are to increase the uptake of cholesterol and the expression of genes encoding the enzymes required to synthesize cortisol. These transcriptional effects occur at least in part through increased activity of protein kinase A, which phosphorylates several transcriptional regulatory factors. MC2R trafficking and signaling are dependent on the MC2R accessory protein (MRAP). Mutations in either MC2R or MRAP can cause familial glucocorticoid deficiency (see Chapter 575).

REGULATION OF ALDOSTERONE SECRETION

The rate of aldosterone synthesis, which is normally 100- to 1,000-fold less than that of cortisol synthesis, is regulated mainly by the renin–angiotensin system and by potassium levels, with ACTH having only a short-term effect. In response to decreased intravascular volume, renin is secreted by the juxtaglomerular apparatus of the kidney. Renin is a proteolytic enzyme that cleaves angiotensinogen (renin substrate), an α_2-globulin produced by the liver, to yield the inactive decapeptide angiotensin I. Angiotensin-converting enzyme in the lungs and other tissues rapidly cleaves angiotensin I to the biologically active octapeptide angiotensin II. Cleavage of angiotensin II produces the heptapeptide angiotensin III. Angiotensins II and III are potent stimulators of aldosterone secretion; angiotensin II is a more potent vasopressor agent. Angiotensins II and III occupy a G-protein–coupled receptor activating phospholipase C. This protein hydrolyzes phosphatidylinositol bisphosphate to produce inositol triphosphate and diacylglycerol, which raise intracellular calcium levels and activate protein kinase C and calmodulin-activated kinases. Similarly, increased levels of extracellular potassium depolarize the cell membrane and increase calcium influx through voltage-gated L-type calcium channels. Phosphorylation of transcriptional regulatory factors by calmodulin-activated kinases increases transcription of the aldosterone synthase (CYP11B2) enzyme required for aldosterone synthesis.

REGULATION OF ADRENAL ANDROGEN SECRETION

The mechanisms by which the adrenal androgens DHEA and androstenedione are regulated are not completely understood. Adrenarche is a maturational process in the adrenal gland that results in increased adrenal androgen secretion between the ages of 5 and 20 yr. The process begins before the earliest signs of puberty and continues throughout the years when puberty is occurring. Histologically, it is associated with the appearance of the zona reticularis. Whereas ACTH stimulates adrenal androgen production acutely and clearly is the primary stimulus for cortisol release, additional factors have been implicated in the stimulation of the adrenal androgens. These include a relative decrease in expression of HSD3B in the zona reticularis and possibly increases in 17,20-lyase activity owing to phosphorylation of CYP17 or increased cytochrome b5 expression.

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574.4 Adrenal Steroid Hormone Actions

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Steroid hormones act through several distinct receptors corresponding to the known biologic activities of the steroid hormones: glucocorticoid, mineralocorticoid, progestin, estrogen, and androgen. These receptors belong to a larger superfamily of nuclear transcriptional factors that include, among others, thyroid hormone and retinoic acid receptors. They have a common structure that includes a carboxyterminal ligand-binding domain and a midregion DNA-binding domain. The latter domain contains 2 zinc fingers, each of which consists of a loop of amino acids stabilized by 4 cysteine residues chelating a zinc ion.

Unliganded glucocorticoid and mineralocorticoid receptors are found mainly in the cytosol. Hormone molecules diffuse through the cell membrane and bind receptors, changing their conformation and causing them to be translocated to the nucleus, where they bind DNA at specific hormone-response elements. Bound receptors can recruit other transcriptional coregulatory factors to DNA.

Whereas different steroids can share bioactivities because of their ability to bind to the same receptor, a given steroid can exert diverse biologic effects in different tissues. The diversity of hormonal responses is determined by the different genes that are regulated by each hormone in different tissues. Additionally, different combinations of coregulators are expressed in different tissues, allowing each steroid hormone to have many different effects. Moreover, enzymes can increase or decrease the affinity of steroids for their receptors and thus modulate their activity. 11β-Hydroxysteroid dehydrogenase type 1 (HSD11B1) converts cortisone, which is not a ligand for the glucocorticoid receptor, to cortisol, which is an active glucocorticoid. This increases local glucocorticoid concentrations in several tissues, especially the liver, where glucocorticoids maintain hepatic glucose output (see Chapter 575.4). Overexpression of this enzyme in adipose tissue can predispose to development of obesity. Conversely, HSD11B2 oxidizes cortisol to cortisone, particularly in the kidney, preventing mineralocorticoid receptors from being occupied by high levels of cortisol (see Chapter 575.4).

Although corticosteroid receptors mainly act in the nucleus, some responses to both glucocorticoids and mineralocorticoids begin within minutes, an interval too short to be accounted for by increased gene transcription and protein synthesis. Such "nongenomic" effects can in some cases be mediated by cell membrane–associated isoforms of the classic glucocorticoid and mineralocorticoid receptors, which can couple to a variety of rapid intracellular signaling pathways such as G proteins. Direct interactions with other proteins, such as ion channels, have been documented as well, particularly in the nervous system.

ACTIONS OF GLUCOCORTICOIDS

Glucocorticoids are essential for survival. The term *glucocorticoid* refers to the glucose-regulating properties of these hormones. However, glucocorticoids have multiple effects on carbohydrate, lipid, and protein metabolism. They also regulate immune, circulatory, and renal function. They influence growth, development, bone metabolism, and central nervous system activity.

In stress situations, glucocorticoid secretion can increase up to 10-fold. This increase is believed to enhance survival through increased cardiac contractility, cardiac output, sensitivity to the pressor effects of catecholamines and other pressor hormones, work capacity of the skeletal muscles, and capacity to mobilize energy stores.

Metabolic Effects

The primary action of the glucocorticoids on carbohydrate metabolism is to increase glucose production by increasing hepatic gluconeogenesis. Glucocorticoids also increase cellular resistance to insulin, thereby decreasing entry of glucose into the cell. This inhibition of glucose uptake occurs in adipocytes, muscle cells, and fibroblasts. In addition to opposing insulin action, glucocorticoids can work in parallel with insulin to protect against long-term starvation by stimulating glycogen deposition and production in liver. Both hormones stimulate glycogen synthetase activity and decrease glycogen breakdown. Glucocorticoid excess can cause hyperglycemia, and glucocorticoid deficiency can cause hypoglycemia.

Glucocorticoids increase free fatty acid levels by enhancing lipolysis, decreasing cellular glucose uptake, and decreasing glycerol production, which is necessary for reesterification of fatty acids. This increase in lipolysis is also stimulated through the permissive enhancement of lipolytic action of other factors such as epinephrine. This action affects adipocytes differently according to their anatomic locations. In the patient with glucocorticoid excess, fat is lost in the extremities but it is increased in the trunk (centripetal obesity), neck, and face (moon facies). This may involve effects on adipocyte differentiation.

Glucocorticoids generally exert a catabolic or antianabolic effect on protein metabolism. Proteolysis in fat, skeletal muscle, bone, lymphoid, and connective tissue increases amino acid substrates that can be used in gluconeogenesis. Cardiac muscle and the diaphragm are almost entirely spared from this catabolic effect.

Circulatory and Renal Effects

Glucocorticoids have a positive inotropic influence on the heart, increasing the left ventricular work index. Moreover, they have a permissive effect on the actions of epinephrine and norepinephrine on both the heart and the blood vessels. In the absence of glucocorticoids, decreased cardiac output and shock can develop; in states of glucocorticoid excess, hypertension is often observed. This may be a result of activation of the mineralocorticoid receptor (see Chapter 575.4), which occurs when renal HSD11B is saturated by excessive levels of glucocorticoids.

Growth

In excess, glucocorticoids inhibit linear growth and skeletal maturation in children, apparently through direct effects on the epiphyses. However, glucocorticoids are also necessary for normal growth and development. In the fetus and neonate, they accelerate the differentiation and development of various tissues, including the hepatic and gastrointestinal systems, as well as the production of surfactant in the fetal lung. Glucocorticoids are often given to pregnant women at risk for delivery of premature infants in an effort to accelerate these maturational processes (see Chapters 97.2 and 101.3).

Immunologic Effects

Glucocorticoids play a major role in immune regulation. They inhibit synthesis of glycolipids and prostaglandin precursors and the actions of bradykinin. They also block secretion and actions of histamine and proinflammatory cytokines (tumor necrosis factor-α, interleukin-1, and interleukin-6), thus diminishing inflammation. High doses of glucocorticoids deplete monocytes, eosinophils, and lymphocytes, especially T cells. They do so at least in part by inducing cell-cycle arrest in the G_1 phase and by activating apoptosis through glucocorticoid receptor–mediated effects. The effects on lymphocytes are primarily exerted on T-helper 1 cells and hence on cellular immunity, whereas the T-helper 2 cells are spared, leading to a predominantly humoral immune response. Pharmacologic doses of glucocorticoids can also decrease the size of immunologic tissues (spleen, thymus, and lymph nodes).

Glucocorticoids increase circulating polymorphonuclear cell counts, mostly by preventing their egress from the circulation. Glucocorticoids decrease diapedesis, chemotaxis, and phagocytosis of polymorphonuclear cells. Thus, the mobility of these cells is altered such that they do not arrive at the site of inflammation to mount an appropriate immune response. High levels of glucocorticoids decrease inflammatory and cellular immune responses and increase susceptibility to certain bacterial, viral, fungal, and parasitic infections.

Effects on Skin, Bone, and Calcium

Glucocorticoids inhibit fibroblasts, leading to increased bruising and poor wound healing through cutaneous atrophy. This effect explains

the thinning of the skin and striae that are seen in patients with Cushing syndrome.

Glucocorticoids have the overall effect of decreasing serum calcium and have been used in emergency therapy for certain types of hypercalcemia. This hypocalcemic effect probably results from a decrease in the intestinal absorption of calcium and a decrease in the renal reabsorption of calcium and phosphorus. Serum calcium levels, however, generally do not fall below normal because of a secondary increase in parathyroid hormone secretion.

The most significant effect of long-term glucocorticoid excess on calcium and bone metabolism is **osteoporosis.** Glucocorticoids inhibit osteoblastic activity by decreasing the number and activity of osteoblasts. Glucocorticoids also decrease osteoclastic activity but to a lesser extent, leading to low bone turnover with an overall negative balance. The tendency of glucocorticoids to lower serum calcium and phosphate levels causes secondary hyperparathyroidism. These actions decrease bone accretion and cause a net loss of bone mineral. Compliance with oral bisphosphonates, agents that are effective against glucocorticoid-induced osteoporosis, is poor, but evidence suggests that yearly treatment with intravenous zoledronic acid is just as effective.

Central Nervous System Effects

Glucocorticoids readily penetrate the blood–brain barrier and have direct effects on brain metabolism. They decrease certain types of central nervous system edema and are often used to treat increased intracranial pressure. They stimulate appetite and cause insomnia with a reduction in rapid eye movement sleep. There is an increase in irritability and emotional lability, with an impairment of memory and ability to concentrate. Mild to moderate glucocorticoid excess for a limited period often causes a feeling of euphoria or well-being, but glucocorticoid excess and deficiency can both be associated with clinical depression. Glucocorticoid excess produces **psychosis** in some patients.

Glucocorticoid effects in the brain are mediated largely through interactions with both the mineralocorticoid and glucocorticoid receptors (sometimes referred to in this context as type I and type II corticosteroid receptors, respectively). Activation of type II receptors increases sensitivity of hippocampal neurons to the neurotransmitter serotonin, which might help explain the euphoria associated with high doses of glucocorticoids. Glucocorticoids suppress release of CRH in the anterior hypothalamus, but they stimulate it in the central nucleus of the amygdala and lateral bed nucleus of the stria terminalis, where it can mediate fear and anxiety states. Glucocorticoids and other steroids might have nongenomic effects by modulating activities of both γ-aminobutyric acid and *N*-methyl-D-aspartate receptors.

ACTIONS OF MINERALOCORTICOIDS

The most important mineralocorticoids are aldosterone and, to a lesser degree, 11-deoxycorticosterone; corticosterone and cortisol are normally not important as mineralocorticoids unless secreted in excess. Mineralocorticoids have more limited actions than glucocorticoids. Their major function is to maintain intravascular volume by conserving sodium and eliminating potassium and hydrogen ions. They exert these actions in the kidney, gut, and salivary and sweat glands. Aldosterone can have distinct effects in other tissues. Mineralocorticoid receptors are found in the heart and vascular endothelium, and aldosterone increases myocardial fibrosis in heart failure.

Mineralocorticoids have their most important actions in the distal convoluted tubules and cortical collecting ducts of the kidney, where they induce reabsorption of sodium and secretion of potassium. In the medullary collecting duct, they act in a permissive fashion to allow vasopressin to increase osmotic water flux. Thus, patients with mineralocorticoid deficiency can develop weight loss, hypotension, hyponatremia, and hyperkalemia, whereas patients with mineralocorticoid excess can develop hypertension, hypokalemia, and metabolic alkalosis (see Chapters 575-578).

The mechanisms by which aldosterone affects sodium excretion are incompletely understood. Most effects of aldosterone are presumably due to changes in gene expression mediated by the mineralocorticoid receptor, and indeed levels of subunits of both the Na^+,K^+-adenosine triphosphatase and the epithelial sodium channel increase in response to aldosterone. Additionally, aldosterone increases expression of the serum and glucocorticoid-regulated kinase, which indirectly reduces turnover of epithelial sodium channel subunits and thus increases the number of open sodium channels.

The mineralocorticoid receptor has similar affinities in vitro for cortisol and aldosterone, yet cortisol is a weak mineralocorticoid in vivo. This discrepancy results from the action of HSD11B2, which converts cortisol to cortisone. Cortisone is not a ligand for the receptor, whereas aldosterone is not a substrate for the enzyme. Pharmacologic inhibition (as occurs with excessive consumption of licorice) or genetic deficiency of this enzyme allows cortisol to occupy renal mineralocorticoid receptors and produce sodium retention and hypertension; the genetic condition is termed *apparent mineralocorticoid excess syndrome*.

ACTIONS OF THE ADRENAL ANDROGENS

Many actions of adrenal androgens are exerted through their conversion to active androgens or estrogens such as testosterone, dihydrotestosterone, estrone, and estradiol. In men, <2% of the biologically important androgens are derived from adrenal production, whereas in women approximately 50% of androgens are of adrenal origin. The adrenal contribution to circulating estrogen levels is mainly important in pathologic conditions such as feminizing adrenal tumors. Adrenal androgens contribute to the physiologic development of pubic and axillary hair during normal puberty. They also play an important role in the pathophysiology of congenital adrenal hyperplasia, premature adrenarche, adrenal tumors, and Cushing syndrome (see Chapters 576, 577, and 579).

In humans, circulating levels of DHEA and DHEAS, the chief adrenal androgens, reach a peak in early adulthood and then decline. This has led to speculation that age-related physiologic changes might be reversed by DHEA administration, and beneficial effects have been suggested (but not proved) on insulin sensitivity, bone mineral density, muscle mass, cardiovascular risk, obesity, cancer risk, autoimmunity, and the central nervous system.

Synthetic Corticosteroids

Many synthetic analogs of cortisone and hydrocortisone are available. Prednisone and prednisolone are derivatives with an additional double bond in ring A. Like cortisone, prednisone is not an active steroid but it is converted to prednisolone by HSD11B1 in the liver. Prednisone and prednisolone are 4-5 times as potent in antiinflammatory and carbohydrate activity but have slightly less effect on retention of water and sodium than cortisol. Halogenated derivatives have different effects. Betamethasone and dexamethasone have 25-40 times the glucocorticoid potency of cortisol but have little mineralocorticoid effect. These analogs are usually used in pharmacologic doses for their antiinflammatory or immunosuppressive properties. The antiinflammatory activity of fludrocortisone is about 15 times that of hydrocortisone, but fludrocortisone is more than 125 times as active a mineralocorticoid; it is used to treat aldosterone deficiency.

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574.5 Adrenal Medulla

Perrin C. White

The principal hormones of the adrenal medulla are the physiologically active catecholamines: dopamine, norepinephrine, and epinephrine (Fig. 574-3). Catecholamine synthesis also occurs in the brain, in sympathetic nerve endings, and in chromaffin tissue outside the adrenal medulla. Metabolites of catecholamines are excreted in the urine, principally 3-methoxy-4-hydroxymandelic acid, metanephrine,

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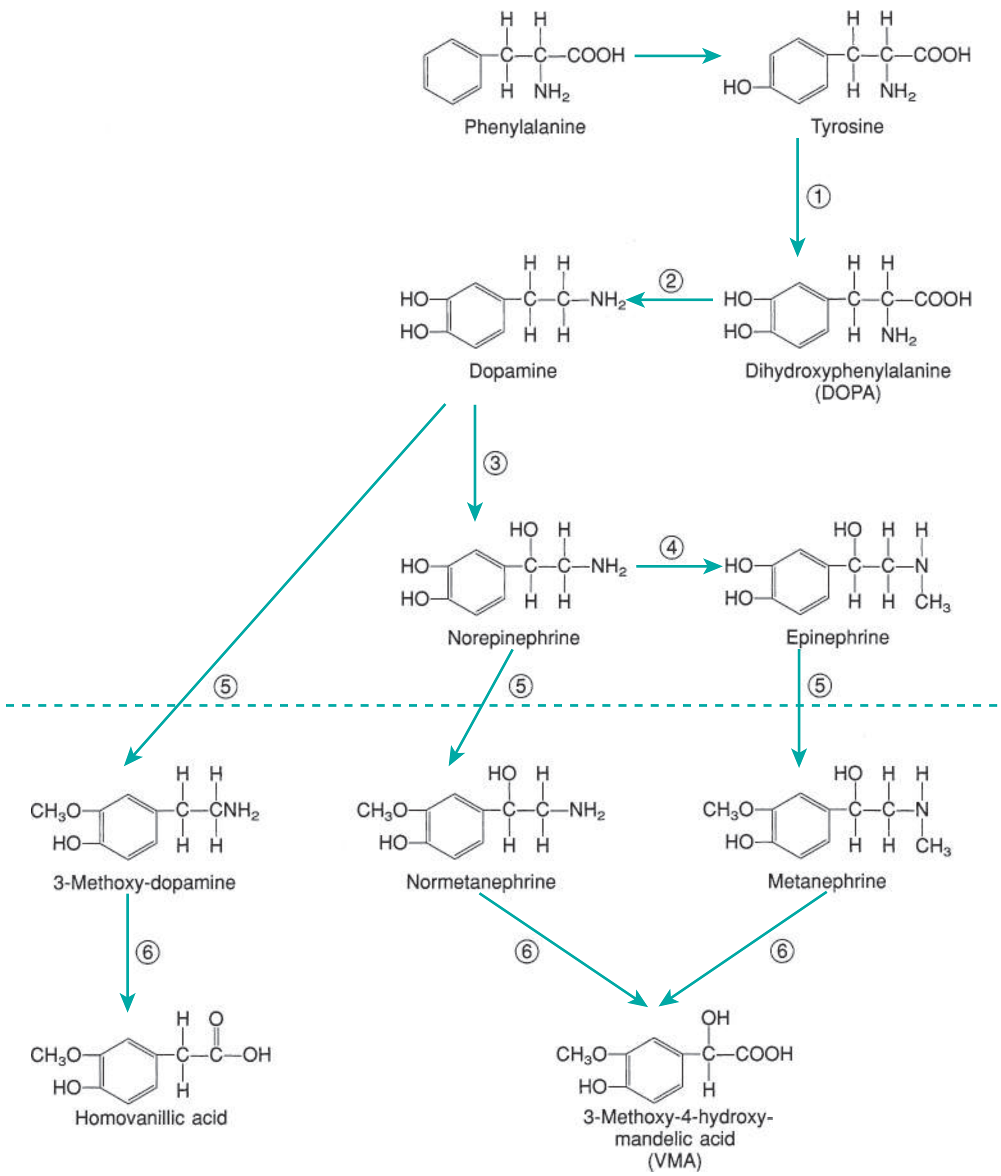

Figure 574-3 Biosynthesis (above *dashed line*) and metabolism (below *dashed line*) of the catecholamines norepinephrine and epinephrine. Enzymes: *1,* tyrosine hydroxylase; *2,* dopa decarboxylase; *3,* dopamine β-oxidase; *4,* phenylethanolamine-*N*-methyltransferase; *5,* catechol *O*-methyltransferase; *6,* monoamine oxidase.

and normetanephrine. Urinary metanephrines and catecholamines are measured to detect pheochromocytomas of the adrenal medulla and sympathetic nervous system (see Chapter 580).

The proportions of epinephrine and norepinephrine in the adrenal gland vary with age. In early fetal stages, there is practically no epinephrine; at birth, norepinephrine remains predominant. However in adults, norepinephrine accounts for only 10-30% of the pressor amines in the medulla.

The effects of catecholamines are mediated through a series of G-protein–coupled adrenergic receptors. Both epinephrine and norepinephrine raise the mean arterial blood pressure, but only epinephrine increases cardiac output. By increasing peripheral vascular resistance, norepinephrine increases systolic and diastolic blood pressures with only a slight reduction in the pulse rate. Epinephrine increases the pulse rate and, by decreasing the peripheral vascular resistance, decreases the diastolic pressure. The hyperglycemic and calorigenic effects of norepinephrine are much less pronounced than are those of epinephrine.

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Chapter 575

Adrenocortical Insufficiency

Perrin C. White

In primary adrenal insufficiency, congenital or acquired lesions of the adrenal cortex prevent production of cortisol and often aldosterone (Table 575-1). Acquired primary adrenal insufficiency is termed *Addison disease*. Dysfunction of the anterior pituitary gland or hypothalamus can cause a deficiency of corticotropin (adrenocorticotropic hormone [ACTH]) and lead to hypofunction of the adrenal cortex, termed *secondary adrenal insufficiency;* the term *tertiary adrenal insufficiency* is sometimes used to denote cases arising from hypothalamic dysfunction (Table 575-2).

Table 575-1 Causes of Primary Adrenal Insufficiency

	PATHOGENESIS OR GENETICS	CLINICAL FEATURES IN ADDITION TO ADRENAL INSUFFICIENCY
CONGENITAL ADRENAL HYPERPLASIA		
21-Hydroxylase deficiency	*CYP21A2* mutations	Hyperandrogenism
11β-Hydroxylase deficiency	*CYP11B1* mutations	Hyperandrogenism, hypertension
3β-Hydroxysteroid dehydrogenase type 2 deficiency	*HSD3B2* mutations	Ambiguous genitalia in boys, postnatal virilization in girls
17α-Hydroxylase deficiency	*CYP17A1* mutations	XY sex reversal, pubertal delay in both sexes, hypertension
P450 oxidoreductase deficiency	*POR* mutations	Skeletal malformation (Antley-Bixler syndrome), abnormal genitalia
P450 side-chain cleavage deficiency	*CYP11A1* mutations	XY sex reversal
Congenital lipoid adrenal hyperplasia	*STAR* mutations	XY sex reversal
OTHER GENETIC DISORDERS		
Adrenoleukodystrophy or adrenomyeloneuropathy	*ABCD1* mutations	Weakness, spasticity, dementia, blindness, quadriparesis. Adrenomyeloneuropathy is a milder variant of adrenoleukodystrophy with slower progression
Triple A syndrome (Allgrove syndrome)	*AAAS* mutations	Achalasia, alacrima, cognitive deficits, neuromuscular deficits, hyperkeratosis
Smith-Lemli-Opitz syndrome	*DHCR7* mutations	Craniofacial malformations, developmental delay growth failure, cholesterol deficiency
Wolman disease	*LIPA* mutations	Bilateral adrenal calcification, hepatosplenomegaly
Kearns-Sayre syndrome	Mitochondrial DNA deletions	External ophthalmoplegia, retinal degeneration, cardiac conduction defects, other endocrine disorders
Pallister-Hall syndrome	*GLI3* mutations	hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly
IMAGe syndrome	*CDKN1C* mutations	Intrauterine growth retardation, metaphyseal dysplasia, genital abnormalities
Adrenal Hypoplasia Congenita		
X-linked	*NR0B1* mutations	Hypogonadotropic hypogonadism in boys
Xp21 contiguous gene syndrome	Deletion of genes for Duchenne muscular dystrophy, glycerol kinase, and *NR0B1*	Duchenne muscular dystrophy, glycerol kinase deficiency, psychomotor retardation
SF-1 linked	*NR5A1* mutations	XY sex reversal
Familial Glucocorticoid Deficiency or Corticotropin Insensitivity Syndromes		
Type 1	*MC2R* mutations	Tall stature, characteristic facial features, such as hypertelorism and frontal bossing
Type 2	*MRAP* mutations	
Variant of familial glucocorticoid deficiency	*MCM4* mutations	Growth failure, increased chromosomal breakage, natural killer cell deficiency
Variant of familial glucocorticoid deficiency	*NNT* mutations	
AUTOIMMUNE		
Isolated	Sporadic; associations with *HLA-DR3-DQ2, HLA-DR4-DQ8, MICA, CTLA4, PTPN22, CIITA, CLEC16A*	None
APS type 1 (APECED)	*AIRE* mutations	Chronic mucocutaneous candidosis, hypoparathyroidism, other autoimmune diseases
APS type 2	Sporadic; associations with *HLA-DR3, HLA-DR4, CTLA4*	Thyroid autoimmune disease, type 1 diabetes, other autoimmune diseases
APS type 4	Sporadic; associations with *HLA-DR3, CTLA4*	Other autoimmune diseases (autoimmune gastritis, vitiligo, coeliac disease, alopecia), excluding thyroid disease and type 1 diabetes
INFECTIOUS		
Tuberculous adrenalitis	Tuberculosis	Tuberculosis-associated manifestations in other organs
AIDS	HIV-1	Other AIDS-associated diseases
Fungal adrenalitis	Histoplasmosis, cryptococcosis, coccidioidomycosis	Opportunistic infections
Meningococcal sepsis (Waterhouse-Friderichsen syndrome),	*Neisseria meningitidis*	
African trypanosomiasis	*Trypanosoma brucei*	Other trypanosomiasis-associated organ involvement
OTHER ACQUIRED CAUSES		
Bilateral adrenal hemorrhage	Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome, traumatic birth, anticoagulation	Symptoms and signs of underlying disease
Bilateral adrenal metastases	Mainly cancers of the lung, stomach, breast, and colon	Symptoms and signs of underlying disease
Bilateral adrenal infiltration	Primary adrenal lymphoma, amyloidosis, hemochromatosis, sarcoidosis (rare)	Symptoms and signs of underlying disease
Bilateral adrenalectomy		Symptoms and signs of underlying disease

Table 575-1 Causes of Primary Adrenal Insufficiency—cont'd

	PATHOGENESIS OR GENETICS	CLINICAL FEATURES IN ADDITION TO ADRENAL INSUFFICIENCY
DRUG-INDUCED		
Mitotane (o,p-DDD)	Cytotoxicity	None, unless related to drug
Aminoglutethimide	Inhibition of cholesterol side chain cleavage enzyme (CYP11A1)	None, unless related to drug
Trilostane	Inhibition of 3β-hydroxysteroid dehydrogenase type 2	None, unless related to drug
Etomidate	Inhibition of 11β-hydroxylase (CYP11B1)	None, unless related to drug
Ketoconazole, fluconazole	Inhibition of mitochondrial cytochrome P450 enzymes (e.g., CYP11A1, CYP11B1)	None, unless related to drug

AAAS, achalasia, adrenocortical insufficiency, alacrima syndrome; ABCD, ATP-binding cassette, subfamily D; ABCG5, ATP-binding cassette, subfamily G, member 5; ABCG8, ATP-binding cassette, subfamily G, member 8; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APS, autoimmune polyendocrinopathy syndrome; CIITA, class II transactivator; CTLA-4, cytotoxic T-lymphocyte antigen 4; DHCR7, 7-dehydrocholesterol reductase; HLA, human leukocyte antigen; IMAGe, *i*ntrauterine growth restriction (IUGR), *m*etaphyseal dysplasia, *a*drenal hypoplasia congenita (AHC), and *g*enitourinary abnormalities; LIPA, lipase A; MC2R, melanocortin 2 receptor; MCM4, minichromosome maintenance complex component 4; MICA, major histocompatibility complex class I chain-related gene A; MRAP, melanocortin 2 receptor accessory protein; PTPN22, protein tyrosine phosphatase, non-receptor type 22; StAR, steroidogenic acute regulatory protein.

Adapted from: Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet *383:2152–2164, 2014, Table 1, pp. 2153–2154.*

Table 575-2 Causes of Secondary Adrenal Insufficiency

	ETIOLOGIES	CLINICAL MANIFESTATIONS IN ADDITION TO ADRENAL INSUFFICIENCY
DRUG-INDUCED		
Abrupt cessation of glucocorticoid therapy (systemic or topical)	Suppression of CRH and ACTH secretion leading to atrophy of the adrenal cortex	Primary disease-associated symptoms
OTHER ACQUIRED CAUSES		
Hypothalamic or pituitary tumors	Adenomas, cysts, craniopharyngiomas, ependymomas, meningiomas, rarely carcinomas, metastasis	Panhypopituitarism*; primary disease-associated symptoms
Traumatic brain injury		Panhypopituitarism*; primary disease-associated symptoms
Hypothalamic or pituitary surgery or irradiation		Panhypopituitarism*; primary disease-associated symptoms
Infections or infiltrative processes	Lymphocytic hypophysitis, hemochromatosis, tuberculosis, meningitis, sarcoidosis, actinomycosis, histiocytosis X, Wegener granulomatosis	Panhypopituitarism*; primary disease-associated symptoms
Pituitary apoplexy (when occurring in a peripartum mother, termed Sheehan syndrome)	High blood loss or hypotension	Abrupt onset of severe headache, visual disturbance, nausea, vomiting; panhypopituitarism*; primary disease-associated symptoms
CONGENITAL OR GENETIC CAUSES		
Abnormal Central Nervous System Development		
Anencephaly	Multiple	Primary disease-associated symptoms
Holoprosencephaly	Multiple	Primary disease-associated symptoms
Combined Pituitary Hormone Deficiency (CPHD)†		
CPHD2	Mutations in *PROP1* (paired-like homeobox 1)	Panhypopituitarism; corticotropin deficiency occurs in adolescence
CPHD3	Mutations in *LHX3* (LIM homeobox 3)	Panhypopituitarism; deafness, short neck
CPHD4	Mutations in *LHX4* (LIM homeobox 4)	Panhypopituitarism; small sella, cerebellar defects
Septooptic dysplasia, CPHD5	Mutations in *HESX1* (HESX homeobox 1)	Panhypopituitarism; septooptic dysplasia (blindness owing to hypoplasic optic nerves, absence of the septum pellucidum); developmental delay
CPHD6	Mutations in *OTX2* (orthodenticle homeobox 2)	Panhypopituitarism; ectopic posterior pituitary gland
X-linked panhypopituitarism	Mutations in *SOX3* (SRY(sex-determining region Y) box 3)	Panhypopituitarism; infundibular hypoplasia, developmental delay
Other Genetic Syndromes Affecting Corticotropin Secretion		
Congenital proopiomelanocortin deficiency	Mutations in *POMC* (proopiomelanocortin)	Early-onset severe obesity, hyperphagia, red hair
Prohormone convertase 1/3 deficiency	Mutations in *PC1* (prohormone convertase 1/3)	Obesity, malabsorption or diarrhea, hypogonadotropic hypogonadism
Isolated ACTH (corticotropin) deficiency	Mutations in *TBX19* (T-box 19)	
Prader-Willi syndrome	Deletion or silencing of genes on the parental copy of genes within the imprinted chromosome region 15q11-q13 including *SNRPN* (small nuclear ribonucleoprotein polypeptide N) and *NDN* (necdin, melanoma antigen (MAGE) family member)	Dysmorphic features, hypotonia, developmental delay, obesity, growth hormone deficiency, hypogonadotropic hypogonadism

*The associated anterior and/or posterior hormone deficiencies may vary.

†CPHD1 (mutations in *POUF1*) is not associated with corticotropin deficiency.

575.1 Primary Adrenal Insufficiency

Perrin C. White

Primary adrenal insufficiency in children is most frequently caused by genetic conditions that are often but not always manifested in infancy and less often by acquired problems such as autoimmune conditions (Table 575-3). Susceptibility to autoimmune conditions often has a genetic basis, and so these distinctions are not absolute.

INHERITED ETIOLOGIES

Inborn Defects of Steroidogenesis

The most common causes of adrenocortical insufficiency in infancy are the salt-losing forms of congenital adrenal hyperplasia (see Chapter 576). Approximately 75% of infants with 21-hydroxylase deficiency, almost all infants with lipoid adrenal hyperplasia, and most infants with a deficiency of 3β-hydroxysteroid dehydrogenase manifest salt-losing symptoms in the newborn period because they are unable to synthesize either cortisol or aldosterone.

Adrenal Hypoplasia Congenita

Adrenal hypoplasia congenita (AHC) is a relatively frequent cause of adrenal failure in boys along with congenital adrenal hyperplasia, autoimmune disease, and adrenoleukodystrophy. The name of the disorder notwithstanding, AHC is predominantly a failure of development of the definitive zone of the adrenal cortex; the fetal zone may be relatively normal. Consequently, adrenal insufficiency generally becomes evident as the fetal zone involutes postnatally (see Chapter 574), with onset in infancy or in the 1st 2 yr of life, but occasionally in later childhood or even adulthood. In some cases, aldosterone deficiency becomes evident before cortisol deficiency.

The disorder is caused by mutation of the *DAX1 (NR0B1)* gene, a member of the nuclear hormone receptor family, located on Xp21. Boys with AHC often do not undergo puberty owing to hypogonadotropic hypogonadism caused by the same mutated *DAX1* gene. **Cryptorchidism,** sometimes noted in these boys, is probably an early manifestation of hypogonadotropic hypogonadism, but often testicular function in infants is normal, with a typical or even an unusually prolonged testosterone surge in the 1st mo of life.

AHC occasionally occurs as part of a **contiguous gene deletion** syndrome together with Duchenne muscular dystrophy, glycerol kinase deficiency, cognitive impairment, or a combination of these conditions.

Table 575-3 Frequencies of Etiologies of Primary Adrenal Insufficiency

ETIOLOGY		AGE AT DIAGNOSIS
Congenital adrenal hyperplasia	59%	Infancy
Autoimmune	16%	Childhood-adolescence
APECED (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy)	6%	Childhood-adolescence
Adrenoleukodystrophy	4%	Childhood-adolescence
Isolated glucocorticoid deficiency	4%	Infancy
Idiopathic	4%	Childhood
Syndromes	3%	Infancy
X-linked adrenal hypoplasia congenita	2%	Infancy-childhood
Hemorrhage	1%	Infancy

Data from Perry R, Kecha O, Paquette J, et al. Primary adrenal insufficiency in children: twenty years' experience at the Sainte-Justine Hospital, Montreal. J Clin Endocrinol Metab *90:3243–3250, 2005; Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood.* J Clin Endocrinol Metab *96:E925–E928, 2011.*

Other Genetic Causes of Adrenal Hypoplasia

The transcription factor SF-1 is required for adrenal and gonadal development (see Chapter 574). Males with a heterozygous mutation in SF-1 *(NR5A1)* have impaired development of the testes despite the presence of a normal copy of the gene on the other chromosome and can appear to be female, similar to patients with lipoid adrenal hyperplasia (see Chapter 576). Rarely, such patients have adrenal insufficiency as well.

Adrenal hypoplasia is also occasionally seen in patients with Pallister-Hall syndrome caused by mutations in the GLI3 oncogene (see Chapter 575).

Adrenoleukodystrophy

In adrenoleukodystrophy (ALD), adrenocortical deficiency is associated with demyelination in the central nervous system (see Chapters 86.2 and 599.3). High levels of very-long-chain fatty acids are found in tissues and body fluids, resulting from their impaired β-oxidation in the peroxisomes.

The most common form of ALD is an X-linked disorder with various presentations. The most common clinical picture is of a degenerative neurologic disorder appearing in childhood or adolescence and progressing to severe dementia and deterioration of vision, hearing, speech, and gait, with death occurring within a few years. Neurologic symptoms may be subtle at onset, sometimes consisting only of behavioral changes or deteriorating academic performance. Generalized but incomplete alopecia, resembling that of chemotherapy, is a characteristic but inconsistent finding. A milder form of X-linked ALD is adrenomyeloneuropathy, which begins in later adolescence or early adulthood. Patients may have evidence of adrenal insufficiency before, at the time of, or after neurologic symptoms develop, often with years separating their presentation. X-linked ALD is caused by mutations in the *ABCD1* gene located on Xq28. The gene encodes a transmembrane transporter involved in the importation of very-long-chain fatty acids into peroxisomes. More than 400 mutations have been described in patients with X-linked ALD. Clinical phenotypes can vary even within families, perhaps owing to modifier genes or other unknown factors. There is no correlation between the degree of neurologic impairment and severity of adrenal insufficiency. Prenatal diagnosis by DNA analysis and family screening by very-long-chain fatty acid assays and mutation analysis are available. Women who are heterozygous carriers of the X-linked ALD gene can develop symptoms in midlife or later; adrenal insufficiency is rare.

Neonatal ALD is a rare autosomal recessive disorder. Infants have neurologic deterioration and have or acquire evidence of adrenocortical dysfunction. Most patients have severe, progressive cognitive impairment and die before 5 yr of age. This disorder is a subset of Zellweger (cerebrohepatorenal) syndrome, in which peroxisomes do not develop at all owing to mutations in any of several genes (*PEX5, PEX1, PEX10, PEX13,* and *PEX26*) controlling the development of this organelle.

Familial Glucocorticoid Deficiency

Familial glucocorticoid deficiency is a form of chronic adrenal insufficiency characterized by isolated deficiency of glucocorticoids, elevated levels of ACTH, and generally normal aldosterone production, although salt-losing manifestations as are present in most other forms of adrenal insufficiency occasionally occur. Patients mainly have hypoglycemia, seizures, and increased pigmentation during the 1st decade of life. The disorder affects both sexes equally and is inherited in an autosomal recessive manner. There is marked adrenocortical atrophy with relative sparing of the zona glomerulosa. Mutations in the gene for the ACTH receptor *(MCR2)* have been described in approximately 25% of these patients, most of which affect trafficking of receptor molecules from the endoplasmic reticulum to the cell surface. Another 20% of cases are caused by mutations in *MRAP,* which encodes a melanocyte receptor accessory protein required for this trafficking. Recently, mutations at new genetic loci have been identified, including

the minichromosome maintenance-deficient 4 homolog *(MCM4)* and nicotinamide nucleotide transhydrogenase *(NNT)*. These genes are involved in DNA replication and antioxidant defense, respectively. Patients with *MCM4* mutations also have growth failure, increased chromosomal breakage, and natural killer cell deficiency.

Another syndrome of ACTH resistance occurs in association with **achalasia** of the gastric cardia and **alacrima (triple A** or **Allgrove syndrome).** These patients often have a progressive neurologic disorder that includes autonomic dysfunction, intellectual disability, motor neuropathy, and occasional deafness. This syndrome is also inherited in an autosomal recessive fashion, and the *AAAS* gene has been mapped to chromosome 12q13. The encoded protein, aladin, might help regulate nucleocytoplasmic transport of other proteins.

Type I Autoimmune Polyendocrinopathy

Although autoimmune Addison disease most often occurs sporadically (see "Autoimmune Addison Disease" in Chapter 575.1), it can occur as a component of 2 syndromes, each consisting of a constellation of autoimmune disorders (see Chapter 566). **Type I autoimmune polyendocrinopathy (APS-1),** also known as *autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy* (APECED) syndrome, is inherited in a mendelian autosomal recessive manner, whereas APS-2 (see "Autoimmune Addison Disease" in Chapter 575.1) has complex inheritance. **Chronic mucocutaneous candidiasis** is most often the first manifestation of APS-1, followed by hypoparathyroidism and then by Addison disease, which typically develops in early adolescence. Other closely associated autoimmune disorders include gonadal failure, alopecia, vitiligo, keratopathy, enamel hypoplasia, nail dystrophy, intestinal malabsorption, and chronic active hepatitis. Hypothyroidism and type 1 diabetes mellitus occur in less than 10% of affected patients. Some components of the syndrome continue to develop as late as the 5th decade. Patients with APS-1 may have autoantibodies to the adrenal cytochrome P450 enzymes CYP21, CYP17, and CYP11A1. The presence of such antibodies indicates a high likelihood of the development of Addison disease or, in female patients, ovarian failure. Adrenal failure can evolve rapidly in APS-1; death in patients with a previous diagnosis and unexplained deaths in siblings of patients with APS-1 have been reported, indicating the need to closely monitor patients with APS-1 and to thoroughly evaluate apparently unaffected siblings of patients with this disorder.

The gene affected in APS-1 is designated autoimmune regulator-1 *(AIRE1);* it has been mapped to chromosome 21q22.3. The *AIRE1* gene encodes a transcription factor that controls the expression of many proteins within the thymus, thus playing a critical role in the generation of immune tolerance. Many different mutations in the *AIRE1* gene have been described in patients with APS-1, with 2 mutations (R257X and a 3-bp deletion) being most common. There has been autosomal dominant transmission in 1 kindred owing to a specific missense mutation (G228W).

Disorders of Cholesterol Synthesis and Metabolism

Patients with disorders of cholesterol synthesis or metabolism, including abetalipoproteinemia with deficient lipoprotein B-containing lipoproteins, and familial hypercholesterolemia, with decreased or impaired low-density lipoprotein receptors, have limited adrenocortical function. Adrenal insufficiency has been reported in patients with **Smith-Lemli-Opitz syndrome**, an autosomal recessive disorder manifesting with facial anomalies, microcephaly, limb anomalies, and developmental delay (see Chapter 86.3). Mutations in the gene coding for sterol Δ^7-reductase, mapped to 11q12-q13, resulting in impairment of the final step in cholesterol synthesis with marked elevation of 7-dehydrocholesterol, abnormally low cholesterol, and adrenal insufficiency, have been identified in Smith-Lemli-Opitz syndrome. **Wolman disease** is a rare autosomal recessive disorder caused by mutations in the gene encoding human lysosomal acid lipase on chromosome 10q23.2-23.3. Cholesteryl esters accumulate in lysosomes in most organ systems, leading to organ failure. Infants during the 1st or 2nd mo of life have hepatosplenomegaly, steatorrhea, abdominal distention, and failure to thrive. Adrenal insufficiency and bilateral adrenal calcification are present, and death usually occurs in the 1st yr of life.

Corticosteroid-Binding Globulin Deficiency and Decreased Cortisol-Binding Affinity

Corticosteroid-binding globulin deficiency and decreased cortisol-binding affinity result in low levels of plasma cortisol but normal urinary free cortisol and normal plasma ACTH levels. A high prevalence of hypotension and fatigue has been reported in some adults with abnormalities of corticosteroid-binding globulin deficiency.

ACQUIRED ETIOLOGIES

Autoimmune Addison Disease

The most common cause of Addison disease is autoimmune destruction of the glands. The glands may be so small that they are not visible at autopsy, and only remnants of tissue are found in microscopic sections. Usually, the medulla is not destroyed, and there is marked lymphocytic infiltration in the area of the former cortex. In advanced disease, all adrenocortical function is lost, but early in the clinical course, isolated cortisol deficiency can occur. Most patients have **antiadrenal cytoplasmic antibodies** in their plasma; 21-hydroxylase (CYP21) is the most commonly occurring biochemically defined autoantigen.

Addison disease can occur as a component of 2 autoimmune polyendocrinopathy syndromes. Type I (APS-1) was discussed previously. **Type II autoimmune polyendocrinopathy (APS-2)** consists of Addison disease associated with autoimmune thyroid disease (Schmidt syndrome) or type 1 diabetes (Carpenter syndrome). Gonadal failure, vitiligo, alopecia, and chronic atrophic gastritis, with or without pernicious anemia, can occur. Frequencies of the human leukocyte antigen (HLA)-D3 and HLA-D4 alleles are increased in these patients and appear to confer an increased risk for development of this disease; particular alleles at the major histocompatibility complex class I chain–related genes A and B *(MICA* and *MICB)* also are associated with this disorder. Polymorphisms in genes involved in other autoimmune disorders have been inconsistently associated with primary adrenal insufficiency, and their contribution to its pathogenesis must be regarded as uncertain. These include the class II, major histocompatibility complex, transactivator (*CIITA*), C-type lectin domain family 16, member A (*CLEC16A*), and protein tyrosine phosphatase, nonreceptor type 22 (*PTPN22*). The disorder is most common in middle-aged women and can occur in many generations of the same family. Antiadrenal antibodies, specifically antibodies to the CYP21, CYP17, and CYP11A1 enzymes, are also found in these patients. Autoimmune adrenal insufficiency may also be seen in patients with celiac disease (see Chapter 338.2).

Infection

Tuberculosis was a common cause of adrenal destruction in the past but is much less prevalent now. The most common infectious etiology for adrenal insufficiency is meningococcemia (see Chapter 191); adrenal crisis from this cause is referred to as the Waterhouse-Friderichsen syndrome. Patients with AIDS can have a variety of subclinical abnormalities in the hypothalamic-pituitary-adrenal axis, but frank adrenal insufficiency is rare. However, drugs used in the treatment of AIDS can affect adrenal hormone homeostasis.

Drugs

Ketoconazole, an antifungal drug, can cause adrenal insufficiency by inhibiting adrenal enzymes. Mitotane (o,p′-DDD), used in the treatment of adrenocortical carcinoma and refractory Cushing syndrome (see Chapters 577 and 579), is cytotoxic to the adrenal cortex and can also alter extraadrenal cortisol metabolism. Signs of adrenal insufficiency occur in a substantial percentage of patients treated with mitotane. Etomidate, used in the induction and maintenance of general anesthesia, inhibits 11β-hydroxylase (CYP11B1), and a single induction dose can block cortisol synthesis for 4-8 hr or longer. This may be problematic in severely stressed patients, particularly if repeated doses

are used in a critical care setting. Atlhough not themselves a cause of adrenal insufficiency, rifampicin and anticonvulsive drugs such as phenytoin and phenobarbital reduce the effectiveness and bioavailability of corticosteroid replacement therapy by inducing steroid metabolizing enzymes in the liver.

Hemorrhage into Adrenal Glands

Hemorrhage into adrenal glands can occur in the neonatal period as a consequence of a difficult labor (especially breech presentation), or its etiology might not be apparent (Fig. 575-1). An incidence rate of 3 in 100,000 live births has been suggested. The hemorrhage may be sufficiently extensive to result in death from exsanguination or hypoadrenalism. An abdominal mass, anemia, unexplained jaundice, or scrotal hematoma may be the presenting sign. Often, the hemorrhage is asymptomatic initially and is identified later by calcification of the adrenal gland. Fetal adrenal hemorrhage has also been reported. Postnatally, adrenal hemorrhage most often occurs in patients being treated with anticoagulants. It can also occur as a result of child abuse.

Clinical Manifestations

Primary adrenal insufficiency leads to cortisol and often aldosterone deficiency. The signs and symptoms of adrenal insufficiency are most easily understood in the context of the normal actions of these hormones (see Chapter 574; Table 575-4).

Hypoglycemia is a prominent feature of adrenal insufficiency. It is often accompanied by ketosis as the body attempts to use fatty acids as an alternative energy source. Ketosis is aggravated by anorexia, nausea, and vomiting, all of which occur frequently.

Cortisol deficiency decreases cardiac output and vascular tone; moreover, catecholamines such as epinephrine have decreased inotropic and pressor effects in the absence of cortisol. These problems are initially manifested as orthostatic hypotension in older children and can progress to frank shock in patients of any age. They are exacerbated by aldosterone deficiency, which results in hypovolemia owing to decreased resorption of sodium in the distal nephron.

Hypotension and decreased cardiac output decrease glomerular filtration and thus decrease the ability of the kidney to excrete free water. Vasopressin (AVP) is secreted by the posterior pituitary in response to hypotension and also as a direct consequence of lack of inhibition by cortisol. These factors decrease plasma osmolality and lead in particular to hyponatremia. Hyponatremia is also caused by aldosterone deficiency and may be much worse when both cortisol and aldosterone are deficient.

In addition to hypovolemia and hyponatremia, aldosterone deficiency causes hyperkalemia by decreasing potassium excretion

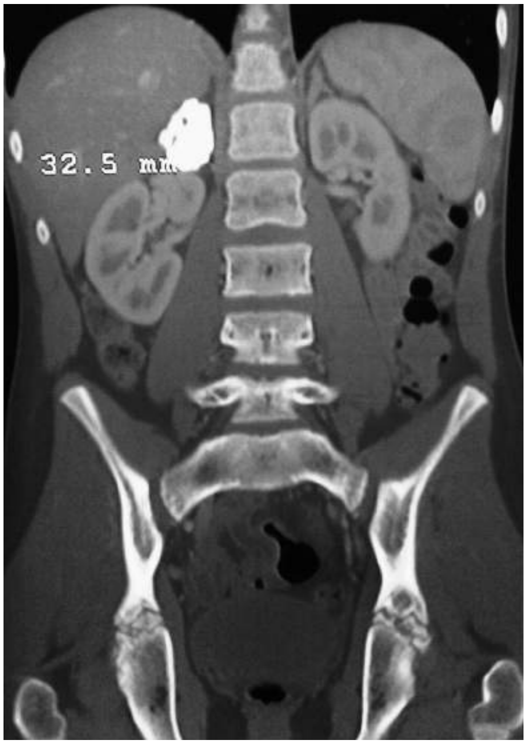

Figure 575-1 Coronal plane of contrast-enhanced computed tomography confirming intraadrenal localization of a round hyperdense lesion compatible with a large calcification. *(From Llano JP, Beaufils E, Nicolino M: Uncommon cause of large paravertebral calcification in a child.* J Pediatr *162:881, 2013, Fig. 2.)*

Table 575-4 Clinical Manifestations and Biochemical Findings in Adrenal Insufficiency

	PATHOPHYSIOLOGIC MECHANISM	PREVALENCE (%)*
SYMPTOMS		
Fatigue	Glucocorticoid deficiency	90
Anorexia, weight loss	Glucocorticoid deficiency	90
Nausea, vomiting	Glucocorticoid deficiency, mineralocorticoid deficiency	90
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency	20
Myalgia or joint pain	Glucocorticoid deficiency	
SIGNS		
Low blood pressure, orthostatic hypotension	Mineralocorticoid deficiency, glucocorticoid deficiency	70-100%
Skin or mucosal hyperpigmentation (primary adrenal insufficiency only)	Excess of proopiomelanocortin-derived peptides	70
LABORATORY FINDINGS		
Hyponatremia	Mineralocorticoid deficiency, glucocorticoid deficiency (leading to decreased free water excretion)	90
Hyperkalemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency	50
Hypoglycemia	Glucocorticoid deficiency	30
Ketosis	Glucocorticoid deficiency	30
Low random cortisol level	Glucocorticoid deficiency	80
Eosinophilia, lymphocytosis	Glucocorticoid deficiency	
High ACTH level (primary adrenal insufficiency only)	Glucocorticoid deficiency	100
High plasma renin activity (primary adrenal insufficiency only)	Mineralocorticoid deficiency	100

*Prevalence data are for primary insufficiency only. Blanks indicate that no pediatric prevalence data are available.

Data from Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood. J Clin Endocrinol Metab *96:E925–E928, 2011*

in the distal nephron. Cortisol deficiency alone does not cause hyperkalemia.

Cortisol deficiency decreases negative feedback on the hypothalamus and pituitary, leading to increased secretion of ACTH. Hyperpigmentation is caused by ACTH and other peptide hormones (γ-melanocyte–stimulating hormone) arising from the ACTH precursor proopiomelanocortin. In patients with a fair complexion, the skin can have a bronze cast. Pigmentation may be more prominent in skin creases, mucosa, and scars. In dark-skinned patients, it may be most readily appreciated in the gingival and buccal mucosa.

The clinical presentation of adrenal insufficiency depends on the age of the patient, whether both cortisol and aldosterone secretion are affected, and to some extent on the underlying etiology. The most common causes in early infancy are inborn errors of steroid biosynthesis, sepsis, AHC, and adrenal hemorrhage. Infants have a relatively greater requirement for aldosterone than do older children, possibly owing to immaturity of the kidney and also to the low sodium content of human breast milk and infant formula. Hyperkalemia, hyponatremia, and hypoglycemia are prominent presenting signs of adrenal insufficiency in infants. Ketosis is not consistently present because infants generate ketones less well than do older children. Hyperpigmentation is not usually seen because this takes weeks or months to develop, and orthostatic hypotension is obviously difficult to demonstrate in infants.

Infants can become ill very quickly. There may be only a few days of decreased activity, anorexia, and vomiting before critical electrolyte abnormalities develop.

In older children with Addison disease, symptoms include muscle weakness, malaise, anorexia, vomiting, weight loss, and orthostatic hypotension. These may be of insidious onset. It is not unusual to elicit, in retrospect, an episodic history spanning years with symptoms being noticeable only during intercurrent illnesses. Such patients can present with acute decompensation **(adrenal crisis)** during relatively minor infectious illnesses. *Some of these patients have been initially misdiagnosed with chronic fatigue syndrome, postmononucleosis syndrome, chronic Lyme disease, or psychiatric disorders (depression or anorexia nervosa).*

Hyperpigmentation is often, but not necessarily, present. Hyponatremia is present at diagnosis in almost 90% of patients. Hyperkalemia tends to occur later in the course of the disease in older children than in infants and is present in only half of patients at diagnosis. Normal potassium levels must never be presumed to rule out primary adrenal insufficiency.

Hypoglycemia and ketosis are common. Thus, the clinical presentation can be easily confused with gastroenteritis or other acute infections. Chronicity of symptoms can alert the clinician to the possibility of Addison disease, but this diagnosis should be considered in any child with orthostatic hypotension, hyponatremia, hypoglycemia, and ketosis. Salt craving is seen in primary adrenal insufficiency with mineralocorticoid deficiency. Fatigue, myalgias, fever, eosinophilia, lymphocytosis, hypercalcemia, and anemia may be noted with glucocorticoid deficiency.

LABORATORY FINDINGS

Hypoglycemia, ketosis, hyponatremia, and hyperkalemia have been discussed. An electrocardiogram is useful for quickly detecting hyperkalemia in a critically ill child. Acidosis is often present, and the blood urea nitrogen level is elevated if the patient is dehydrated.

Cortisol levels are sometimes at the low end of the normal range but are invariably low when the patient's degree of illness is considered. ACTH levels are high in primary adrenal insufficiency but can take time to be reported by the laboratory. Similarly, aldosterone levels may be within the normal range but inappropriately low considering the patient's hyponatremia, hyperkalemia, and hypovolemia. Plasma renin activity is elevated. Blood eosinophils may be increased in number, but this is rarely useful diagnostically.

Urinary excretion of sodium and chloride are increased and urinary potassium is decreased, but these are difficult to assess on random urine samples. Accurate interpretation of urinary electrolytes requires more-prolonged (24 hr) urine collections and knowledge of the patient's sodium and potassium intake.

The **most definitive** test for adrenal insufficiency is measurement of serum levels of cortisol before and after administration of ACTH; resting levels are low and do not increase normally after administration of ACTH. Occasionally, normal resting levels that do not increase after administration of ACTH indicate an absence of adrenocortical reserve. A low initial level followed by a significant response to ACTH can indicate secondary adrenal insufficiency. Traditionally, this test has been performed by measuring cortisol levels before and 30 or 60 min after giving 0.250 mg of cosyntropin (ACTH 1-24) by rapid intravenous infusion. Aldosterone will transiently increase in response to this dose of ACTH and may also be measured. A low-dose test (1 μg ACTH 1-24/1.73 m^2) is a more sensitive test of pituitary-adrenal reserve, but has somewhat lower specificity (more false-positive tests).

DIFFERENTIAL DIAGNOSIS

Upon presentation, Addison disease often needs to be distinguished from more acute illnesses such as gastroenteritis with dehydration or sepsis. Additional testing is directed at identifying the specific cause for adrenal insufficiency. When congenital adrenal hyperplasia is suspected, serum levels of cortisol precursors (17-hydroxyprogesterone) should be measured along with cortisol in an ACTH stimulation test (see Chapter 576). Elevated levels of very-long-chain fatty acids are diagnostic of ALD (see Chapter 599.3). Many genetic etiologies for primary adrenal insufficiency may be identified by direct genetic testing, but it can take many weeks for results to become available. The presence of antiadrenal antibodies suggests an autoimmune pathogenesis. Patients with autoimmune Addison disease must be closely observed for the development of other autoimmune disorders. In children, hypoparathyroidism is the most commonly associated disorder, and it is suspected if hypocalcemia and elevated phosphate levels are present.

Ultrasonography (which requires an experienced operator), CT, or MRI can help define the size of the adrenal glands.

TREATMENT

Treatment of acute adrenal insufficiency must be immediate and vigorous. If the diagnosis of adrenal insufficiency has not been established, a blood sample should be obtained before therapy to determine electrolytes, glucose, ACTH, cortisol, aldosterone, and plasma renin activity. If the patient's condition permits, an ACTH stimulation test can be performed while initial fluid resuscitation is under way. An intravenous solution of 5% glucose in 0.9% saline should be administered to correct hypoglycemia, hypovolemia, and hyponatremia. Hypotonic fluids (e.g., 5% glucose in water or 0.2% saline) must be avoided because they can precipitate or exacerbate hyponatremia. If hyperkalemia is severe, it can require treatment with intravenous calcium and/or bicarbonate, intrarectal potassium-binding resin (Kayexalate), or intravenous infusion of glucose and insulin. A water-soluble form of hydrocortisone, such as hydrocortisone sodium succinate, should be given intravenously. As much as 10 mg for infants, 25 mg for toddlers, 50 mg for older children, and 100 mg for adolescents should be administered as a bolus and a similar total amount given in divided doses at 6 hr intervals for the 1st 24 hr. These doses may be reduced during the next 24 hr if progress is satisfactory. Adequate fluid and sodium repletion is achieved by intravenous saline administration, aided by the mineralocorticoid effect of high doses of hydrocortisone.

Particular caution should be exercised in the rare patient with concomitant adrenal insufficiency and hypothyroidism, because thyroxine can increase cortisol clearance. Thus, an adrenal crisis may be precipitated if hypothyroidism is treated without first ensuring adequate glucocorticoid replacement.

After the acute manifestations are under control, most patients require chronic replacement therapy for their cortisol and aldosterone deficiencies. *Hydrocortisone (cortisol) may be given orally in daily doses of 10 mg/m^2/24 hr in 3 divided doses; some patients require 15 mg/m^2/24 hr to minimize fatigue,* especially in the morning.

Timed-release preparations of hydrocortisone are undergoing clinical trials but are not yet generally available. *Equivalent doses (20-25% of the hydrocortisone dose) of prednisone or prednisolone may be divided and given twice daily*. ACTH levels may be used to monitor adequacy of glucocorticoid replacement in primary adrenal insufficiency; in congenital adrenal hyperplasia, levels of precursor hormones are used instead (see Chapter 576). Blood samples for monitoring should be obtained at a consistent time of day and in a consistent relation to (i.e., before or after) the hydrocortisone dose. Normalizing ACTH levels is unnecessary and can require excessive doses of hydrocortisone; generally morning ACTH levels high in the normal range to 3-4 times normal are satisfactory. Because untreated or severely undertreated patients can acutely decompensate during relatively minor illnesses, assessment of symptoms (or lack thereof) must not be used as a substitute for biochemical monitoring. During situations of stress, such as periods of infection or minor operative procedures, the dose of hydrocortisone should be increased 2-3–fold. Major surgery under general anesthesia requires high intravenous doses of hydrocortisone similar to those used for acute adrenal insufficiency.

If aldosterone deficiency is present, *fludrocortisone, a synthetic mineralocorticoid, is given orally in doses of 0.05-0.2 mg daily.* Measurements of plasma renin activity are useful in monitoring the adequacy of mineralocorticoid replacement. Chronic overdosage with glucocorticoids leads to obesity, short stature, and osteoporosis, whereas overdosage with fludrocortisone results in hypertension and occasionally hypokalemia.

Replacement of dehydroepiandrosterone (DHEA) in adults remains controversial; prepubertal children do not normally secrete large amounts of DHEA. Many adults with Addison disease complain of having decreased energy, and replacing DHEA can improve this problem, particularly in women in whom adrenal androgens represent approximately 50% of total androgen secretion.

Additional therapy might need to be directed at the underlying cause of the adrenal insufficiency in regard to infections and certain metabolic defects. Therapeutic approaches to ALD include administration of glycerol trioleate and glycerol trierucate (Lorenzo's oil), bone marrow transplantation, and lovastatin (see Chapter 599.3).

Bibliography is available at Expert Consult.

575.2 Secondary and Tertiary Adrenal Insufficiency

Perrin C. White

ETIOLOGY

Abrupt Cessation of Administration of Corticosteroids

Secondary adrenal insufficiency most commonly occurs when the hypothalamic-pituitary-adrenal axis is suppressed by prolonged administration of high doses of a potent glucocorticoid and that agent is suddenly withdrawn or the dose is tapered too quickly. Patients at risk for this problem include those with leukemia, asthma (particularly when patients are transitioned from oral to inhaled corticosteroids), and collagen vascular disease or other autoimmune conditions and those who have undergone tissue transplants or neurosurgical procedures. The maximal duration and dosage of glucocorticoid that can be administered before encountering this problem is not known, but it is assumed that high-dose glucocorticoids (the equivalent of >10 times physiologic cortisol secretion) can be administered for at least 1 wk without requiring a subsequent taper of dose. On the other hand, when high doses of dexamethasone are given to children with leukemia, it can take up to 2 mo or longer after therapy is stopped before tests of adrenal function return to normal. Signs and symptoms of adrenal insufficiency are most likely in patients who are subsequently subjected to stresses such as severe infections or additional surgical procedures.

Corticotropin (Adrenocorticotropic Hormone) Deficiency

Pituitary or hypothalamic dysfunction can cause corticotropin deficiency (see Chapter 557), usually associated with deficiencies of other pituitary hormones such as growth hormone and thyrotropin. Destructive lesions in the area of the pituitary, such as craniopharyngioma and germinoma, are the most common causes of corticotropin deficiency. In many cases, the pituitary or hypothalamus is further damaged during surgical removal or radiotherapy of tumors in the midline of the brain. Traumatic brain injury (see Chapter 710) frequently causes pituitary dysfunction, especially in the first days after the injury. However, corticotropin deficiency is difficult to detect then owing to frequent use of high doses of dexamethasone to minimize brain swelling, and permanent corticotropin deficiency is unusual after traumatic brain injury. In rare instances, autoimmune hypophysitis is the cause of corticotropin deficiency.

Congenital lesions of the pituitary also occur. The pituitary alone may be affected, or additional midline structures may be involved, such as the optic nerves or septum pellucidum. The latter type of abnormality is termed **septooptic dysplasia,** or de Morsier syndrome (see Chapter 591.9). More-severe developmental anomalies of the brain, such as anencephaly and holoprosencephaly, can also affect the pituitary. These disorders are usually sporadic, although a few cases of autosomal recessive inheritance have occurred. Isolated deficiency of corticotropin has been reported, including in several sets of siblings. Patients with multiple pituitary hormone deficiencies caused by mutations in the *PROP1* gene have been described with progressive ACTH/cortisol deficiency. Isolated deficiency of corticotropin-releasing hormone has been documented in an Arab kindred as an autosomal recessive trait.

It was recently recognized that up to 60% of children with **Prader-Willi syndrome** (see Chapter 81.8) have some degree of secondary adrenal insufficiency as assessed by provocative testing with metyrapone (see "Laboratory Findings" in Chapter 575.2), although diurnal cortisol levels are normal. The clinical significance of this finding is uncertain, but it might contribute to the relatively high incidence of sudden death with infectious illness that occurs in this population. Although it is not yet a standard of care, some endocrinologists advocate treating patients who have Prader-Willi syndrome with hydrocortisone during febrile illness.

CLINICAL PRESENTATION

Aldosterone secretion is unaffected in secondary adrenal insufficiency because the adrenal gland is, by definition, intact and the renin–angiotensin system is not involved. Thus, signs and symptoms are those of cortisol deficiency. Newborns often have hypoglycemia. Older children can have orthostatic hypotension or weakness. Hyponatremia may be present.

When secondary adrenal insufficiency is the consequence of an inborn or acquired anatomic defect involving the pituitary, there may be signs of associated deficiencies of other pituitary hormones. The penis may be small in male infants if gonadotropins are also deficient. Infants with secondary hypothyroidism are often jaundiced. Children with associated growth hormone deficiency grow poorly after the 1st yr of life.

Some children with pituitary abnormalities have hypoplasia of the midface. Children with optic nerve hypoplasia can have obvious visual impairment. They usually have a characteristic wandering nystagmus, but this is often not apparent until several months of age.

LABORATORY FINDINGS

Because the adrenal glands themselves are not directly affected, the diagnosis of secondary adrenal insufficiency is sometimes challenging. Historical gold standard dynamic tests include insulin-induced hypoglycemia, which provides a potent stress to the entire hypothalamic-pituitary-adrenal (HPA) axis. This test requires constant attendance by a physician and is considered by many endocrinologists to be too dangerous for routine use. A second gold standard test uses metyrapone, a specific inhibitor of steroid 11β-hydroxylase (CYP11B1) to

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block cortisol synthesis, thus removing the normal negative feedback of cortisol on ACTH secretion. There are several protocols for this test; one version administers 30 mg/kg of metyrapone orally at midnight, with a blood sample obtained for cortisol and 11-deoxycortisol (the substrate for 11β-hydroxylase) at 8 AM. A low cortisol level (<5 µg/dL) demonstrates adequate suppression of cortisol synthesis, and an 11-deoxycortisol level >7 µg/dL indicates that ACTH has responded normally to the cortisol deficiency by stimulating the adrenal cortex. This test should be used with caution outside the research setting because it can precipitate adrenal crises in patients with marginal adrenal function; the drug is not available in all locales.

At present, the most commonly used test to diagnose secondary adrenal insufficiency is low-dose ACTH stimulation testing (1 µg/1.73 m^2 of cosyntropin given intravenously), the rationale being that there will be some degree of atrophy of the adrenal cortex if normal physiologic ACTH stimulation is lacking. Thus, this test may be falsely negative in cases of acute compromise of the pituitary (e.g., injury or surgery). Such circumstances rarely pose a diagnostic dilemma; in general, this test provides excellent sensitivity and specificity. Although assays vary somewhat, a threshold cortisol level of 18-20 µg/dL 30 min after cosyntropin administration may be used to dichotomize normal and abnormal responses.

At present, there seems to be little reason to use stimulation with corticotropin-releasing hormone instead of ACTH; although the corticotropin-releasing hormone test has the theoretical advantage of testing the ability of the anterior pituitary to respond to this stimulus by secreting ACTH (thus distinguishing secondary and tertiary adrenal insufficiency), in practice it does not provide improved sensitivity and specificity, and the agent is not as widely available.

TREATMENT

Iatrogenic secondary adrenal insufficiency (caused by chronic glucocorticoid administration) is best avoided by use of the smallest effective doses of systemic glucocorticoids for the shortest period of time. When a patient is thought to be at risk, tapering the dose rapidly to a level equivalent to or slightly less than the physiologic replacement (~10 mg/m^2/24 hr of hydrocortisone) and further tapering over several weeks can allow the adrenal cortex to recover without development of signs of adrenal insufficiency. Patients with anatomic lesions of the pituitary should be treated indefinitely with glucocorticoids. Mineralocorticoid replacement is not required. In patients with panhypopituitarism, treating cortisol deficiency can increase free water excretion, thus unmasking central diabetes insipidus. Electrolytes must be monitored carefully when initiating cortisol therapy in panhypopituitary patients.

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575.3 Adrenal Insufficiency in the Critical Care Setting

Perrin C. White

ETIOLOGY

Adrenal insufficiency in the context of critical illness is encountered in up to 20-50% of pediatric patients, often as a transient condition. In many cases, it is considered to be "functional" or "relative" in nature, meaning that cortisol levels are within normal limits but cannot increase sufficiently to meet the demands of critical illness. The causes are heterogeneous, and some were discussed in Chapter 575.1. They include adrenal hypoperfusion from shock, particularly septic shock, as is often seen in meningococcemia. Inflammatory mediators during septic shock, particularly interleukin-6, can suppress ACTH secretion, directly suppress cortisol secretion, or both. Etomidate, used as sedation for intubation, inhibits steroid 11β-hydroxylase and thus blocks cortisol biosynthesis. Neurosurgical patients with closed head trauma, or with tumors that involve the hypothalamus or pituitary, might have ACTH deficiency in the context of panhypopituitarism. Some children have been previously treated with systemic corticosteroids (e.g., children with leukemia) and have suppression of the HPA axis for that reason. In the intensive care nursery, premature infants have not yet developed normal cortisol biosynthetic capacity (see Chapter 574.2) and thus may not be able to secrete adequate amounts of this hormone when ill.

CLINICAL MANIFESTATIONS

Cortisol is required for catecholamines to have their normal pressor effects on the cardiovascular system (see Chapters 574.4 and 574.5). Accordingly, adrenal insufficiency is often suspected in hypotensive patients who do not respond to intravenous pressor agents. Patients may be at increased risk for hypoglycemia or a presentation resembling the syndrome of inappropriate antidiuretic hormone secretion, but these conditions commonly occur in the context of sepsis, and the contribution of adrenal insufficiency may be difficult to distinguish.

LABORATORY FINDINGS

Although low random cortisol levels in severely stressed patients are certainly abnormal, very high levels are also associated with a poor outcome in such patients; the latter situation presumably reflects a maximally stimulated adrenal cortex with diminished reserve. ACTH (cosyntropin) stimulation testing is generally considered the best way to diagnose adrenal insufficiency in this setting (see Chapter 575.1); evidence suggests that the low-dose (1 µg/1.73 m^2) test may be superior to the 250 µg standard dose test, although this remains controversial. Generally, a peak cortisol level <18 µg/dL or an increment of <9 µg/dL from baseline is considered suggestive for adrenal insufficiency in this context. In evaluating cortisol levels, it should be remembered that cortisol in the circulation is normally mostly bound to cortisol-binding globulin; in hypoproteinemic states total cortisol levels may be decreased, whereas free cortisol levels might be normal. It may be prudent to measure free cortisol before initiating treatment when total cortisol is low and albumin is <2.5 g/dL, but such measurements are not readily available in all institutions.

TREATMENT

There are limited data regarding treatment efficacy in critically ill children. Based on studies of both children and adults, it is likely that moderate stress doses of hydrocortisone (e.g., 50 mg/m^2/day) improve responses to pressor agents in patients with shock and documented adrenal insufficiency. It is uncertain if there is a beneficial effect on overall survival. There seems to be no benefit in using pharmacologic doses of potent synthetic glucocorticoids such as dexamethasone.

Bibliography is available at Expert Consult.

575.4 Altered End-Organ Sensitivity to Corticosteroids

Perrin C. White

Diseases can result from altered actions of hormones at their physiologic targets. These may be caused by abnormal metabolism of hormones, mutations in hormone receptors, or defects in cellular effectors (such as ion channels) that are targets of hormone action.

GENERALIZED GLUCOCORTICOID RESISTANCE

Etiology

Patients with generalized glucocorticoid resistance have target-tissue insensitivity to glucocorticoids. The condition is usually inherited in an autosomal dominant manner but sporadic cases occur. Impairment of normal negative feedback of cortisol at the levels of the hypothalamus and pituitary activates the HPA axis with consequent increases in ACTH and cortisol concentrations. Generalized glucocorticoid resistance is caused by mutations in the glucocorticoid receptor (encoded

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by the *NR3C1* gene) that impair its action by interfering with ligand binding, DNA binding, transcriptional activation, or some combination of these. Most mutations are heterozygous; glucocorticoid receptors usually bind DNA as dimers, and 3 out of every 4 dimers will contain at least 1 abnormal receptor molecule when a heterozygous mutation is present.

Clinical Manifestations

The excess ACTH secretion causes adrenal hyperplasia with increased production of adrenal steroids with mineralocorticoid activity, including cortisol, deoxycorticosterone, and corticosterone, and also androgens and precursors, including androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate. The high cortisol concentrations do not cause Cushing syndrome (see Chapter 577) because of the insensitivity to glucocorticoids; conversely, most signs and symptoms of adrenal insufficiency are absent except for the frequent occurrence of chronic fatigue and occasional anxiety (neonatal hypoglycemia was reported in 1 very unusual patient with a homozygous null mutation). On the other hand, the mineralocorticoid and androgen receptors are normally sensitive to their ligands. Signs of mineralocorticoid excess, such as hypertension and hypokalemic alkalosis, are frequently noted. The increased concentrations of adrenal androgens may cause ambiguous genitalia in girls and gonadotropin-independent precocious puberty in children of either gender; acne; hirsutism, and infertility in both sexes; menstrual irregularities in females; and oligospermia in males. Testicular adrenal rest tumors and ACTH-secreting pituitary adenomas occasionally occur.

Laboratory Findings

The diagnosis of generalized glucocorticoid resistance is suggested by elevated serum cortisol concentrations and increased 24 hr urinary free cortisol excretion in the absence of Cushing syndrome. Levels of other adrenal steroids are also increased. Plasma concentrations of ACTH may be normal or high. The circadian pattern of ACTH and cortisol secretion is preserved, although at higher-than-normal concentrations, and there is resistance of the HPA axis to dexamethasone suppression. Sequencing of the *NR3C1* gene can confirm the diagnosis, but is not routinely available.

Differential Diagnosis

Generalized glucocorticoid resistance should be distinguished from relatively mild cases of Cushing syndrome (whether caused by a pituitary adenoma or adrenal tumor, see Chapter 577); the latter is more likely to be associated with excessive weight gain or poor linear growth. Adrenocortical tumors may secrete mineralocorticoids such as deoxycorticosterone and also androgens, but ACTH levels are often suppressed and of course the tumor can usually be visualized with appropriate imaging techniques. Congenital adrenal hyperplasia (see Chapter 576), particularly 11β-hydroxylase deficiency, may present with hypertension and signs of androgen excess, but in that condition cortisol levels are low and levels of cortisol precursors (17-hydroxyprogesterone, 11-deoxycortisol) are elevated. Obese patients may be hypertensive and have hyperandrogenism, but cortisol secretion should be readily suppressed by dexamethasone.

Treatment

The goal of treatment is to suppress the excess secretion of ACTH, thereby suppressing the increased production of adrenal steroids with mineralocorticoid and androgenic activity. This requires administration of high doses of a pure glucocorticoid agonist such as dexamethasone (typically ~20-40 µg/kg/day) with careful titration to suppress endogenous corticosteroid secretion without causing signs of glucocorticoid excess such as excessive weight gain or suppression of linear growth.

CORTISONE REDUCTASE DEFICIENCY

Etiology

Levels of active glucocorticoids in target tissues are modulated by 2 isozymes of 11β-hydroxysteroid dehydrogenase. The 11-HSD2 isozyme converts cortisol to an inactive metabolite, cortisone; the 2 steroids differ in the presence of an 11β-hydroxyl vs an 11-oxo group, respectively. Mutations in this enzyme cause the syndrome of **apparent mineralocorticoid excess**. Conversely, the 11-HSD1 isozyme converts cortisone to cortisol, and so it is sometimes referred to as "cortisone reductase." This isozyme is expressed at high levels in glucocorticoid target tissues, particularly the liver, where it ensures adequate levels of active glucocorticoids (cortisol and corticosterone) to meet metabolic demands without requiring excessive adrenal cortisol secretion.

The 11-HSD1 isozyme is located in the endoplasmic reticulum (i.e., it is a "microsomal" enzyme) and functions as a dimer. It accepts electrons from reduced nicotine–adenine dinucleotide phosphate, which is generated within the endoplasmic reticulum by hexose-6-phosphate dehydrogenase, an enzyme distinct from cytoplasmic glucose-6-phosphate dehydrogenase.

Apparent cortisone reductase deficiency is caused by homozygous mutations in hexose-6-phosphate dehydrogenase that prevent generation of reduced nicotine–adenine dinucleotide phosphate within the endoplasmic reticulum and thus starve 11-HSD1 of its essential cofactor for the reductase reaction. Very rare patients have been reported to have heterozygous mutations in the *HSD11B1* gene encoding 11-HSD1 itself and thus have "true" cortisone reductase deficiency; because the enzyme functions as a homodimer, heterozygous mutations are able to impair three fourths of all dimmers.

Clinical Manifestations

Because circulating cortisone is not converted to cortisol, the circulating half-life of cortisol is decreased and the adrenal cortex must secrete additional cortisol to compensate. This leads to adrenocortical overactivity analogous to, but generally much milder than, that seen in generalized glucocorticoid resistance. This is usually not severe enough to cause hypertension, presenting instead with mild to moderate signs of androgen excess such as hirsutism, oligomenorrhea or amenorrhea, and infertility in females, and precocious pseudopuberty (axillary and pubic hair, and penile enlargement, but not testicular enlargement) in males.

Laboratory Findings

The ratio of cortisol to cortisone in blood is lower than usual. The same is true of urinary metabolites, typically measured as a ratio of the sum of the tetrahydrocortisol and allotetrahydrocortisol excretion to that of tetrahydrocortisone. These determinations are best accomplished by gas chromatography followed by mass spectrometry, and are available in specialized reference laboratories. Absolute levels of cortisol and ACTH are within normal limits.

Differential Diagnosis

Cortisone reductase deficiency has to be distinguished from, and is much less common than, other causes of androgen excess such as polycystic ovarian syndrome and nonclassical congenital adrenal hyperplasia as a result of 21-hydroxylase deficiency.

Treatment

Treatment is aimed at decreasing adrenal overactivity and thus reducing secretion of androgens. This can be accomplished by administration of hydrocortisone.

ALTERED END-ORGAN SENSITIVITY TO MINERALOCORTICOIDS

Pseudohypoaldosteronism

Etiology

Pseudohypoaldosteronism type 1 (PHA1) is a monogenic disease in which aldosterone action is deficient and patients are thus unable to resorb urinary sodium or excrete potassium properly. There are 2 forms. A relatively mild **autosomal dominant** form is caused by mutations in the *NR3C2* gene encoding the human mineralocorticoid receptor. As with generalized glucocorticoid resistance, a heterozygous mutation is sufficient to cause disease because the

mineralocorticoid receptor interacts with DNA as a dimer, and three fourths of the dimers are defective in individuals carrying heterozygous mutations (assuming mutant protein is synthesized). A more-severe **autosomal recessive** form is usually the result of homozygous mutations in the α (*SCNN1A*), β (*SCNN1B*), or γ (*SCNN1G*) subunits of the epithelial Na(+) channel, but 1 reported case of severe autosomal recessive disease was caused by homozygous mutations in *NR3C2*.

PHA1 should not be confused with pseudohypoaldosteronism type 2, a rare mendelian syndrome characterized by hyperkalemia and, in contrast to PHA1, by hypertension from excessive renal salt reabsorption. This disorder is caused by mutations in the renal regulatory kinases, WNK1 and WNK4, or components of an E3 ubiquitin ligase complex Kelch-like 3 (KLHL3) and Cullin 3 (CUL3).

Clinical Manifestations
Infants with PHA1 present with hyperkalemia, hyponatremia, hypovolemia, hypotension, and failure to thrive. In more-severe (usually autosomal recessive) cases, salt loss is not confined to the kidney but instead occurs from most epithelia. Mothers may report that the skin of their affected infants tastes salty. Some infants suffer from **cystic fibrosis–like pulmonary symptoms.** It is often difficult to control electrolyte abnormalities in patients with the autosomal recessive form, leading to frequent hospitalizations and a need for close clinical monitoring.

It is noteworthy that signs and symptoms of aldosterone deficiency tend to remit as the patients get older, particularly in the autosomal dominant form. This is similar to what is seen in actual aldosterone deficiency as occurs in the salt-losing forms of congenital adrenal hyperplasia or aldosterone synthase deficiency. The kidney matures after early infancy to become more efficient at excreting potassium, and whereas breast milk and infant formula are low in sodium, the normal adult Western diet is relatively high in sodium, thus compensating for the renal salt wasting.

Laboratory Findings
Infants have marked hyperkalemia and hyponatremia. Both plasma renin and aldosterone are markedly elevated. Levels of cortisol and ACTH are normal. If hypovolemia is severe, patients may develop prerenal azotemia. The electrocardiogram may include tall peaked T waves with severe hyperkalemia or ventricular tachycardia.

Differential Diagnosis
PHA in infants should be distinguished from other causes of hyperkalemia and hyponatremia. These include renal failure of any cause, congenital adrenal hyperplasia, aldosterone synthase deficiency, and other causes of adrenocortical insufficiency such as AHC. Patients with renal failure will have elevated blood urea nitrogen and creatinine, but these may be seen in severely dehydrated patients with PHA. Patients with any form of adrenal insufficiency in this clinical context will have low or low-normal aldosterone levels (with elevated plasma renin), in contrast to the elevated aldosterone levels seen in PHA. Patients with congenital adrenal hyperplasia have elevated levels of steroid precursors such as 17-hydroxyprogesterone (in patients with 21-hydroxylase deficiency), and patients with most forms of adrenal insufficiency have elevated ACTH levels.

Treatment
Infants must be given dietary sodium supplementation (initially intravenous and then oral), typically approximately 8 mEq/kg/day. Potassium levels in the infant formula often need to be reduced, which may be accomplished by mixing the formula with polystyrene resin (Kayexalate) and then decanting the formula prior to feeding. Fludrocortisone, a synthetic mineralocorticoid, may be efficacious in milder autosomal dominant cases if administered in high doses (titrating up to ~0.5 mg daily). Significant electrolyte abnormalities require treatment with intravenous normal saline and rectal polystyrene resin. Severe hyperkalemia may require glucose and insulin infusions to control.

APPARENT MINERALOCORTICOID EXCESS
Etiology
The syndrome of apparent mineralocorticoid excess is an autosomal recessive disorder caused by mutations in the *HSD11B2* gene encoding the 11-HSD2 isozyme of 11β-hydroxysteroid dehydrogenase. The mineralocorticoid receptor actually has nearly identical affinities for aldosterone (the main mineralocorticoid hormone) and cortisol, yet cortisol is normally only a weak mineralocorticoid in vivo. This is because 11-HSD2 is expressed along with the mineralocorticoid receptor in most target tissues such as the renal cortical collecting duct epithelium. It converts cortisol to cortisone, which is not an active steroid, thus preventing it from occupying the mineralocorticoid receptor. In contrast, aldosterone is not a substrate for the enzyme because its 11β-hydroxyl group forms a hemiketal with the 18-aldehyde group of the steroid and is thus not accessible to the enzyme. Thus, in the absence of 11-HSD2, cortisol is able to efficiently occupy the mineralocorticoid receptor, and because cortisol concentrations are normally far higher than those of aldosterone, this results in signs and symptoms of mineralocorticoid excess.

A similar clinical picture occurs with excessive consumption of licorice or licorice-flavored chewing tobacco; licorice contains compounds including glycyrrhetinic and glycyrrhizic acids that inhibit 11-HSD2. Carbenoxolone, an antihypertensive drug that is not marketed in the United States, has similar effects.

Clinical Manifestations
Affected infants often have some degree of intrauterine growth restriction with birth weights of 2 kg typical for term infants. Infants and children often fail to thrive. Severe hypertension (to ~200/120 mm Hg) is almost always present. In some patients, the hypertension tends to be labile or paroxysmal with severe emotional stress as a precipitating factor. Complications of hypertension have included cerebrovascular accidents. Several patients have died during infancy or adolescence, either from electrolyte imbalances leading to cardiac arrhythmias or from vascular sequelae of hypertension. Hypokalemic alkalosis can eventually cause nephrocalcinosis (often visible on renal ultrasound) and nephrogenic diabetes insipidus leading to polyuria and polydipsia. Deleterious effects on muscle range from elevations in serum creatine phosphokinase to frank rhabdomyolysis. Electrocardiograms show left ventricular hypertrophy.

Laboratory Findings
Hypokalemia and alkalosis are common but not persistent. Sodium levels are generally in the upper part of the reference range. Aldosterone and renin levels are very low because the hypertension and hypervolemia are independent of aldosterone concentrations. Serum cortisol and ACTH levels are generally within normal limits. The serum half-life of cortisol is increased, but the test for this requires a radioactive tracer and is not clinically available. Total urinary excretion of cortisol metabolites is markedly decreased. The urinary ratio of free cortisol to free cortisone is elevated, as is the ratio of urinary tetrahydrocortisol plus allotetrahydrocortisol to tetrahydrocortisone.

Differential Diagnosis
The differential diagnosis includes other forms of severe childhood hypertension such as renal artery anomalies, but relatively few conditions present with suppressed renin and aldosterone levels. Liddle syndrome has a similar presentation but no abnormalities in the steroid profile, typically has an autosomal dominant mode of inheritance, and does not respond to treatment with mineralocorticoid receptor antagonists. Hypertensive forms of congenital adrenal hyperplasia (see Chapter 576) also have suppressed renin and aldosterone levels, but they present with signs of androgen excess (11β-hydroxylase deficiency) or androgen deficiency (17α-hydroxylase deficiency); the latter can be difficult to appreciate in young children. The steroid profiles in congenital adrenal hyperplasia differ from those seen in apparent mineralocorticoid excess syndrome.

Patients with severe Cushing syndrome may have high enough cortisol levels to overwhelm renal 11-HSD2, leading to severe

hypertension with alterations in urinary cortisol-to-cortisone ratios. This occurs most often in patients with the ectopic ACTH syndrome. This generally does not present a diagnostic dilemma, because of the other signs of Cushing syndrome including high cortisol levels.

Treatment

Treatment includes a low-salt diet, potassium supplementation, and mineralocorticoid receptor blockade with spironolactone or eplerenone; a sodium channel blocker, such as amiloride or triamterene may work at least as well. In principle, suppression of cortisol secretion with dexamethasone (which does not bind the mineralocorticoid receptor) should work, but in practice it is much less effective than mineralocorticoid receptor blockade.

LIDDLE SYNDROME

Etiology

Liddle syndrome is a form of hypertension and hypokalemia that is clinically similar to the syndrome of apparent mineralocorticoid excess, but it is inherited in an autosomal dominant manner. It is caused by activating mutations in the β (*SCNN1B*) or γ (*SCNN1G*) subunits of the epithelial sodium channel. Most of these mutations prevent the channel subunits from being ligated to ubiquitin and targeted to the proteosome for degradation, a process that is normally regulated indirectly by aldosterone. The net effect is to increase the number of open channels at the apical surface of epithelial cells of the renal collecting duct, thus facilitating sodium resorption and potassium excretion. This disorder is thus the exact opposite of the autosomal recessive form of pseudohypoaldosteronism discussed previously.

Clinical Manifestations, Laboratory Findings, and Differential Diagnosis

Liddle syndrome is characterized by severe early-onset hypertension and by hypokalemia, which may not be persistent. Aldosterone and renin levels are suppressed but all steroid hormone levels are normal.

The differential diagnosis is the same as that for apparent mineralocorticoid excess.

Treatment

The mainstays of treatment are a low-salt diet, potassium supplementation, and a sodium channel blocker such as amiloride or triamterene. Mineralocorticoid receptor antagonists such as spironolactone are ineffective.

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Chapter 576

Congenital Adrenal Hyperplasia and Related Disorders

Perrin C. White

Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders of cortisol biosynthesis (normal adrenal steroidogenesis is discussed in Chapter 574). Cortisol deficiency increases secretion of corticotropin (adrenocorticotropic hormone [ACTH]), which, in turn, leads to adrenocortical hyperplasia and overproduction of intermediate metabolites. Depending on the enzymatic step that is deficient, there may be signs, symptoms, and laboratory findings of mineralocorticoid deficiency or excess; incomplete virilization or precocious puberty in affected males; and virilization or sexual infantilism in affected females (Figs. 576-1 and 576-2 and Table 576-1).

576.1 Congenital Adrenal Hyperplasia Caused by 21-Hydroxylase Deficiency

Perrin C. White

ETIOLOGY

More than 90% of CAH cases are caused by 21-hydroxylase deficiency. This P450 enzyme (CYP21, P450c21) hydroxylates progesterone and 17-hydroxyprogesterone to yield 11-deoxycorticosterone and 11-deoxycortisol, respectively (see Fig. 574-1 in Chapter 574). These conversions are required for synthesis of aldosterone and cortisol, respectively. Both hormones are deficient in the most-severe, "salt-wasting" form of the disease. Slightly less-severely affected patients are able to synthesize adequate amounts of aldosterone but have elevated levels of androgens of adrenal origin; this is termed "simple virilizing disease". These 2 forms are collectively termed classic 21-hydroxylase deficiency. Patients with nonclassic disease have relatively mildly elevated levels of androgens and may be asymptomatic or have signs of androgen excess at any time after birth. Clinical presentation is dependent, in part, on the genotype (see below, "Genetics,") (Table 576-2).

EPIDEMIOLOGY

Classic 21-hydroxylase deficiency occurs in approximately 1 in 15,000-20,000 births in most populations. Approximately 70% of affected infants have the salt-losing form, whereas 30% have the simple virilizing form of the disorder. In the United States, CAH is less common in African-Americans compared with white children (1 : 42,000 vs 1 : 15,500). Nonclassic disease has a prevalence of approximately 1 in 1,000 in the general population, but occurs more frequently in specific ethnic groups such as Ashkenazi Jews and Hispanics.

GENETICS

There are 2 steroid 21-hydroxylase genes—*CYP21P (CYP21A1P, CYP21A)* and *CYP21 (CYP21A2, CYP21B)*—which alternate in tandem with 2 genes for the fourth component of complement (C4A and C4B) in the human leukocyte antigen (HLA) major histocompatibility complex on chromosome 6p21.3 between the HLA-B and HLA-DR loci. Many other genes are located in this cluster. *CYP21* is the active gene; *CYP21P* is 98% identical in DNA sequence to *CYP21* but is a pseudogene because of 9 different mutations. More than 90% of mutations causing 21-hydroxylase deficiency are recombinations between *CYP21* and *CYP21P.* Approximately 20% are deletions generated by unequal meiotic crossing-over between *CYP21* and *CYP21P,* whereas the remainder are nonreciprocal transfers of deleterious mutations from *CYP21P* to *CYP21,* a phenomenon termed gene conversion.

The deleterious mutations in *CYP21P* have different effects on enzymatic activity when transferred to *CYP21.* Several mutations completely prevent synthesis of a functional protein, whereas others are missense mutations (they result in amino acid substitutions) that yield enzymes with 1-50% of normal activity. Disease severity correlates well with the mutations carried by an affected individual; for example, patients with salt-wasting disease usually carry mutations on both alleles that completely destroy enzymatic activity. Patients are frequently compound heterozygotes for different types of mutations (i.e., 1 allele is less-severely affected than the other), in which case the severity of disease expression is largely determined by the activity of the less-severely affected of the 2 alleles.

Closely adjacent to, but on the opposite DNA strand from, *CYP21* is the tenascin-X (*TNX)* gene, which encodes a connective tissue protein. Rarely, deletions of *CYP21* extend into *TNX.* Such patients may have a contiguous gene syndrome (see Chapter 81.1) consisting of CAH and **Ehlers-Danlos syndrome** (see Chapters 484 and 659).

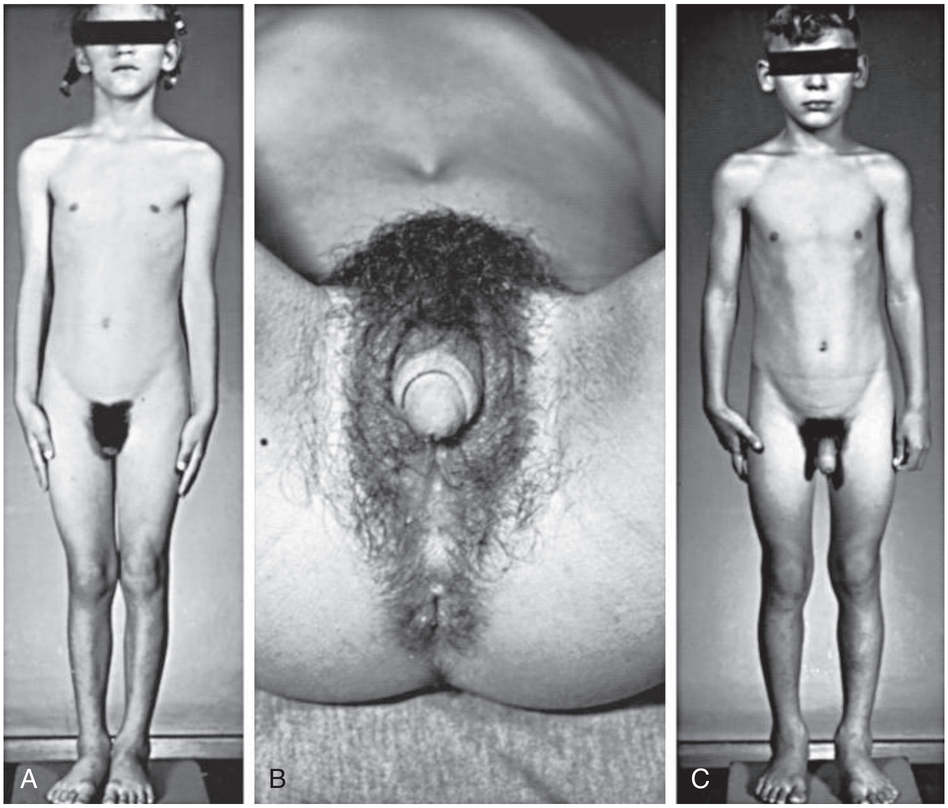

Figure 576-1 A, A 6-yr-old girl with congenital virilizing adrenal hyperplasia. The height age was 8.5 yr, and the bone age was 13 yr. **B,** Notice the clitoral enlargement and labial fusion. **C,** Her 5 yr old brother was not considered to be abnormal by the parents. The height age was 8 yr, and the bone age was 12.5 yr.

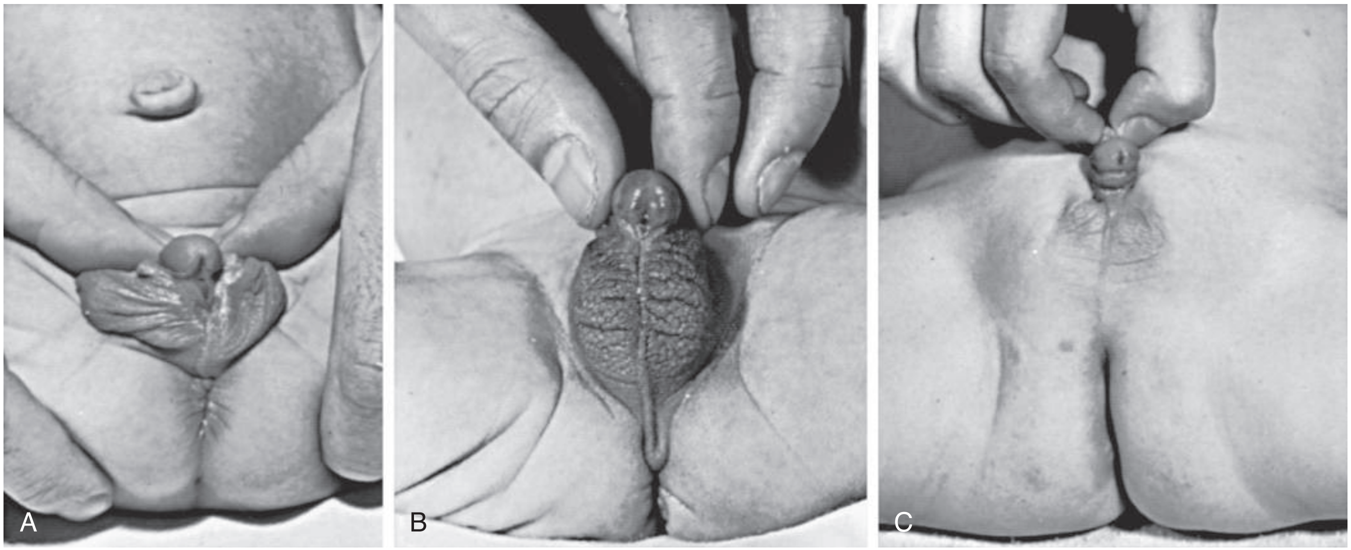

Figure 576-2 Three virilized females with untreated congenital adrenal hyperplasia. All were erroneously assigned male sex at birth, and each had a normal female sex-chromosome complement. Infants **A** and **B** had the salt-wasting form and received the diagnosis early in infancy. Infant **C** was referred at 1 yr of age because of bilateral cryptorchidism. Notice the completely penile urethra; such complete masculinization in females with adrenal hyperplasia is rare; most of these infants have the salt-wasting form.

Table 576-1 Diagnosis and Treatment of Congenital Adrenal Hyperplasia

DISORDER	AFFECTED GENE AND CHROMOSOME	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	THERAPEUTIC MEASURES
21-Hydroxylase deficiency, classic form	*CYP21* 6p21.3	Glucocorticoid deficiency	↓ Cortisol, ↑ACTH ↑↑ Baseline and ACTH-stimulated 17-hydroxy-progesterone	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
21-Hydroxylase deficiency, nonclassic form	*CYP21* 6p21.3	May be asymptomatic; precocious adrenarche, hirsutism, acne, menstrual irregularity, infertility	↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone ↑ Serum androgens	Suppression with glucocorticoids
11β-Hydroxylase deficiency	*CYP11B1* 8q24.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated 11-deoxycortisol and deoxycorticosterone	Glucocorticoid (hydrocortisone) replacement
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
		Hypertension	↓ Plasma renin, hypokalemia	Suppression with glucocorticoids
3β-Hydroxysteroid dehydrogenase deficiency, classic form	*HSD3B2* 1p13.1	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated Δ5 steroids (pregnenolone, 17-hydroxy-pregnenolone, DHEA)	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females and males	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Precocious adrenarche, disordered puberty	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Suppression with glucocorticoids
17α-Hydroxylase/17,20-lyase deficiency	*CYP17* 10q24.3	Cortisol deficiency (corticosterone is an adequate glucocorticoid)	↓ Cortisol, ↑ ACTH ↑ DOC, corticosterone Low 17α-hydroxylated steroids; poor response to ACTH	Glucocorticoid (hydrocortisone) administration
		Ambiguous genitalia in males	↓ Serum androgens; poor response to hCG	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Sexual infantilism	↓ Serum androgens or estrogens	Sex hormone replacement consonant with sex of rearing
		Hypertension	↓ Plasma renin; hypokalemia	Suppression with glucocorticoids
Congenital lipoid adrenal hyperplasia	*STAR* 8p11.2	Glucocorticoid deficiency	↑ ACTH Low levels of all steroid hormones, with decreased or absent response to ACTH	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↓ Aldosterone, ↑ plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in males	Decreased or absent response to hCG in males	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Poor pubertal development or premature ovarian failure in females	↑ FSH, ↑ LH, ↓ estradiol (after puberty)	Estrogen replacement

Table 576-1 Diagnosis and Treatment of Congenital Adrenal Hyperplasia—cont'd

DISORDER	AFFECTED GENE AND CHROMOSOME	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	THERAPEUTIC MEASURES
P450 oxidoreductase deficiency	*POR* 7q11.3	Glucocorticoid deficiency Ambiguous genitalia in males and females Maternal virilization Antley-Bixler syndrome	↓ Cortisol, ↑ ACTH ↑ Pregnenolone, ↑ progesterone ↑ Serum androgens prenatally, ↓ androgens and estrogens at puberty Decreased ratio of estrogens to androgens	Glucocorticoid (hydrocortisone) replacement Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing

↓, Decreased; ↑, increased; ↑↑, markedly increased; ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DOC, 11-deoxycorticosterone; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

Table 576-2 Genotype-Phenotype Correlations in Congenital Adrenal Hyperplasia Owing to 21-Hydroxylase Deficiency

MUTATION GROUP	A	B	C
Enzymatic activity, % normal	Nil	1-2%	20-50%
CYP21 mutations (phenotype generally corresponds to the least affected allele)	Gene deletion Exon 3 del 8 bp Exon 6 cluster Q318X R356W Intron 2 splice	I172N	P30L V281L P453S
Severity	Salt wasting	Simple virilizing	Nonclassic
Aldosterone synthesis	Low	Normal	Normal
Age at diagnosis (without newborn screening)	Infancy	Infancy (females) Childhood (males)	Childhood to adulthood, or asymptomatic
Virilization	Severe	Moderate to severe	None to Mild
Incidence	1/20,000	1/50,000	1/500

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Aldosterone and Cortisol Deficiency

Because both cortisol and aldosterone require 21-hydroxylation for their synthesis, both hormones are deficient in the most-severe, salt-wasting form of the disease. This form constitutes approximately 70% of cases of classic 21-hydroxylase deficiency. The signs and symptoms of cortisol and aldosterone deficiency, and the pathophysiology underlying them, are essentially those described in Chapter 575. These include progressive weight loss, anorexia, vomiting, dehydration, weakness, hypotension, hypoglycemia, hyponatremia, and hyperkalemia. These problems typically first develop in affected infants at approximately 10-14 days of age. Without treatment, shock, cardiac arrhythmias, and death may occur within days or weeks.

CAH differs from other causes of primary adrenal insufficiency in that precursor steroids accumulate proximal to the blocked enzymatic conversion. Because cortisol is not synthesized efficiently, ACTH levels are high, leading to hyperplasia of the adrenal cortex and levels of precursor steroids that may be hundreds of times normal. In the case of 21-hydroxylase deficiency, these precursors include 17-hydroxyprogesterone and progesterone. Progesterone and perhaps other metabolites act as antagonists of the mineralocorticoid receptor and thus may exacerbate the effects of aldosterone deficiency in untreated patients.

Prenatal Androgen Excess

The most important problem caused by accumulation of steroid precursors is that 17-hydroxyprogesterone is shunted into the pathway for androgen biosynthesis, leading to high levels of androstenedione that are converted outside the adrenal gland to testosterone. This problem begins in affected fetuses by 8-10 wk of gestation and leads to abnormal genital development in females (see Figs. 576-1 and 576-2).

The external genitalia of males and females normally appear identical early in gestation (see Chapter 582). Affected females who are exposed in utero to high levels of androgens of adrenal origin have masculinized external genitalia (see Figs. 576-1 and 576-2). This is manifested by enlargement of the clitoris and by partial or complete labial fusion. The vagina usually has a common opening with the urethra (urogenital sinus). The clitoris may be so enlarged that it resembles a penis; because the urethra opens below this organ, some affected females may be mistakenly presumed to be males with hypospadias and cryptorchidism. The severity of virilization is usually greatest in females with the salt-losing form of 21-hydroxylase deficiency (see Table 576-2). The internal genital organs are normal, because affected females have normal ovaries and not testes and thus do not secrete antimüllerian hormone.

Prenatal exposure of the brain to high levels of androgens may influence subsequent sexually dimorphic behaviors in affected females. Girls may demonstrate aggressive play behavior, tend to be interested in masculine toys such as cars and trucks, and often show decreased interest in playing with dolls. Women may have decreased interest in maternal roles. There is an increased frequency of homosexuality in affected females. Nonetheless, most function heterosexually and do not have gender identity confusion or dysphoria. It is unusual for affected females to assign themselves a male role except in some with the severest degree of virilization.

Male infants appear normal at birth. Thus, the diagnosis may not be made in boys until signs of adrenal insufficiency develop. Because

patients with this condition can deteriorate quickly, infant boys are more likely to die than infant girls. For this reason, all 50 American states and many countries have instituted newborn screening for this condition (see "Newborn Screening" in Chapter 576.2).

Postnatal Androgen Excess

Untreated or inadequately treated children of both sexes develop additional signs of androgen excess after birth. Boys with the simple virilizing form of 21-hydroxylase deficiency often have a delayed diagnosis because they appear normal and rarely develop adrenal insufficiency.

Signs of androgen excess include rapid somatic growth and accelerated skeletal maturation. Thus, affected patients are tall in childhood but premature closure of the epiphyses causes growth to stop relatively early, and adult stature is stunted (see Fig. 576-1). Muscular development may be excessive. Pubic and axillary hair may appear, and acne and a deep voice may develop. The penis, scrotum, and prostate may become enlarged in affected boys; however, the **testes are usually prepubertal** in size so that they appear relatively small in contrast to the enlarged penis. Occasionally, ectopic adrenocortical cells in the testes of patients become hyperplastic similarly to the adrenal glands, producing testicular adrenal rest tumors (see Chapter 584). The clitoris may become further enlarged in affected females (see Fig. 576-1). Although the internal genital structures are female, breast development and menstruation may not occur unless the excessive production of androgens is suppressed by adequate treatment.

Similar but usually milder signs of androgen excess may occur in **nonclassic 21-hydroxylase deficiency** (see Table 576-2). In this attenuated form, cortisol and aldosterone levels are normal and affected females have normal genitals at birth. Males and females may present with precocious pubarche and early development of pubic and axillary hair. Hirsutism, acne, menstrual disorders, and infertility may develop later in life, but many females and males are completely asymptomatic.

Adrenomedullary Dysfunction

Development of the adrenal medulla requires exposure to the extremely high cortisol levels normally present within the adrenal gland. Thus patients with classic CAH have abnormal adrenomedullary function, as evidenced by blunted epinephrine responses, decreased blood glucose, and lower heart rates with exercise. Ability to exercise is unimpaired and the clinical significance of these findings is uncertain. Adrenomedullary dysfunction may exacerbate the cardiovascular effects of cortisol deficiency in untreated or undertreated patients.

LABORATORY FINDINGS

See Table 576-1.

Patients with salt-losing disease have typical laboratory findings associated with cortisol and aldosterone deficiency, including hyponatremia, hyperkalemia, metabolic acidosis, and, often, hypoglycemia, but these abnormalities can take 10-14 days or longer to develop after birth. Blood levels of **17-hydroxyprogesterone** are markedly elevated. However, levels of this hormone are high during the 1st 2-3 days of life even in unaffected infants and especially if they are sick or premature. After infancy, once the circadian rhythm of cortisol is established, 17-hydroxyprogesterone levels vary in the same circadian pattern, being highest in the morning and lowest at night. Blood levels of cortisol are usually low in patients with the salt-losing type of disease. They are often normal in patients with simple virilizing disease but inappropriately low in relation to the ACTH and 17-hydroxyprogesterone levels. In addition to 17-hydroxyprogesterone, levels of androstenedione and testosterone are elevated in affected females; testosterone is not elevated in affected males, because normal infant males have high testosterone levels compared with those seen later in childhood. Levels of urinary 17-ketosteroids and pregnanetriol are elevated but are now rarely used clinically because blood samples are easier to obtain than 24 hr urine collections. ACTH levels are elevated but have no diagnostic utility over 17-hydroxyprogesterone levels. Plasma levels of renin are elevated, and serum aldosterone is inappropriately low for the renin level. However, renin levels are high in normal infants in the 1st few wk of life.

Diagnosis of 21-hydroxylase deficiency is most reliably established by measuring 17-hydroxyprogesterone before and 30 or 60 min after an intravenous bolus of 0.125-0.25 mg of cosyntropin (ACTH 1-24). Nomograms exist that readily distinguish normals and patients with nonclassic and classic 21-hydroxylase deficiency. Heterozygous carriers of this autosomal recessive disorder tend to have higher ACTH-stimulated 17-hydroxyprogesterone levels than genetically unaffected individuals, but there is significant overlap between subjects in these 2 categories. However, in infants with frank electrolyte abnormalities or circulatory instability, it may not be possible or necessary to delay treatment to perform this test, as levels of precursors will be sufficiently elevated on a random blood sample to make the diagnosis.

Genotyping is clinically available and may help confirm the diagnosis, but it is expensive and may take weeks. Because the gene conversions that generate most mutant alleles may transfer more than one mutation, at least one parent should be genotyped as well to determine which mutations lie on each allele.

DIFFERENTIAL DIAGNOSIS

Disorders of sexual development are discussed more generally in Chapter 588. The initial step in evaluating an infant with ambiguous genitals is a thorough physical examination to define the anatomy of the genitals, locate the urethral meatus, palpate the scrotum or labia and the inguinal regions for testes (palpable gonads almost always indicate the presence of testicular tissue and thus that the infant is a genetic male), and look for any other anatomic abnormalities. Ultrasonography is helpful in demonstrating the presence or absence of a uterus and can often locate the gonads. A rapid karyotype (such as fluorescence in situ hybridization of interphase nuclei for X and Y chromosomes) can quickly determine the genetic sex of the infant. These results are all likely to be available before the results of hormonal testing and together allow the clinical team to advise the parents as to the genetic sex of the infant and the anatomy of internal reproductive structures. Injection of contrast medium into the urogenital sinus of a virilized female demonstrates a vagina and uterus, and many surgeons utilize this information to formulate a plan for surgical management.

PRENATAL DIAGNOSIS

Prenatal diagnosis of 21-hydroxylase is possible late in the 1st trimester by analysis of DNA obtained by chorionic villus sampling or during the 2nd trimester by amniocentesis. This is usually done because the parents already have an affected child. Most often, the *CYP21* gene is analyzed for frequently occurring mutations; more rare mutations may be detected by DNA sequencing.

NEWBORN SCREENING

Because 21-hydroxylase deficiency is often undiagnosed in affected males until they have severe adrenal insufficiency, all states in the United States and many other countries have instituted newborn screening programs. These programs analyze **17-hydroxyprogesterone** levels in dried blood obtained by heelstick and absorbed on filter paper cards; the same cards are screened in parallel for other congenital conditions, such as hypothyroidism and phenylketonuria. Potentially affected infants are typically quickly recalled for additional testing (electrolytes and repeat 17-hydroxyprogesterone determination) at approximately 2 wk of age. Infants with salt-wasting disease often have abnormal electrolytes by this age but are usually not severely ill. Thus, screening programs are effective in preventing many cases of adrenal crisis in affected males. The nonclassic form of the disease is not reliably detected by newborn screening, but this is of little clinical significance because adrenal insufficiency does not occur in this type of 21-hydroxylase deficiency.

The main difficulty with current newborn screening programs is that to reliably detect all affected infants, the cutoff 17-hydroxyprogesterone levels for recalls are set so low that there is a very high frequency of false-positive results (i.e., the test has a low positive predictive value

of approximately 1%). This problem is worst in premature infants. Positive predictive value can be improved by using cutoff levels based on gestational age, and by utilizing more specific second-tier screening methods such as liquid chromatography followed by tandem mass spectrometry.

TREATMENT

Glucocorticoid Replacement

Cortisol deficiency is treated with glucocorticoids. Treatment also suppresses excessive production of androgens by the adrenal cortex and thus minimizes problems such as excessive growth and skeletal maturation and virilization. *This often requires larger glucocorticoid doses than are needed in other forms of adrenal insufficiency, typically 15-20 mg/m^2/24 hr of hydrocortisone daily administered orally in 3 divided doses.* Affected infants usually require dosing at the high end of this range. *Double or triple doses are indicated during* **periods of stress,** *such as infection or surgery.* Glucocorticoid treatment must be continued indefinitely in all patients with classic 21-hydroxylase deficiency but may not be necessary in patients with nonclassic disease unless signs of androgen excess are present. Therapy must be individualized. It is desirable to maintain linear growth along percentile lines; crossing to higher height percentiles may suggest undertreatment, whereas loss of height percentiles often indicates overtreatment with glucocorticoids. Overtreatment is also suggested by excessive weight gain. Pubertal development should be monitored by periodic examination, and skeletal maturation is evaluated by serial radiographs of the hand and wrist for bone age. Hormone levels, particularly 17-hydroxyprogesterone and androstenedione, should be measured early in the morning, before taking the morning medications, or at a consistent time in relation to medication dosing. In general, desirable 17- hydroxyprogesterone levels are in the high-normal range or several times normal; low-normal levels can usually be achieved only with excessive glucocorticoid doses.

Menarche occurs at the appropriate age in most girls in whom good control has been achieved; it may be delayed in girls with suboptimal control.

Children with simple virilizing disease, particularly males, are frequently not diagnosed until 3-7 yr of age, at which time skeletal maturation may be 5 yr or more in advance of chronological age. In some children, especially if the bone age is 12 yr or more, **spontaneous central (i.e., gonadotropin-dependent) puberty** may occur when treatment is instituted, because therapy with hydrocortisone suppresses production of adrenal androgens and thus stimulates release of pituitary gonadotropins if the appropriate level of hypothalamic maturation is present. *This form of superimposed true precocious puberty may be treated with a gonadotropin hormone–releasing hormone analog such as leuprolide* (see Chapter 562.1).

Males with 21-hydroxylase deficiency who have had inadequate corticosteroid therapy may develop **testicular adrenal rest tumors**, which usually regress with increased steroid dosage. Testicular MRI, ultrasonography, and color flow Doppler examination help define the character and extent of disease. Testis-sparing surgery for steroid-unresponsive tumors has been reported.

Mineralocorticoid Replacement

Patients with salt-wasting disease (i.e., aldosterone deficiency) require mineralocorticoid replacement with **fludrocortisone.** Infants may have very high mineralocorticoid requirements in the 1st few mo of life, usually 0.1-0.3 mg daily in 2 divided doses but occasionally up to 0.4 mg daily, and often require sodium supplementation (sodium chloride, 8 mmol/kg) in addition to the mineralocorticoid. Older infants and children are usually maintained with 0.05-0.1 mg daily of fludrocortisone. In some patients, simple virilizing disease may be easier to control with a low dose of fludrocortisone in addition to hydrocortisone even when these patients have normal aldosterone levels in the absence of mineralocorticoid replacement. Therapy is evaluated by monitoring of vital signs; tachycardia and hypertension are signs of overtreatment with mineralocorticoids. Serum electrolytes should be measured frequently in early infancy as therapy is adjusted. Plasma renin activity is a useful way to determine adequacy of therapy; it should be maintained in or near the normal range but not suppressed.

Additional approaches to improve outcome have been proposed but have not yet become the standard of care. These include an antiandrogen such as flutamide to block the effects of excessive androgen levels, and/or an aromatase inhibitor such as anastrozole, which blocks conversion of androgens to estrogen and thus retards skeletal maturation, a process that is sensitive to estrogens in both boys and girls. Aromatase inhibitors generally should not be used in pubertal girls because they will obviously retard normal puberty and may expose the ovaries to excessive levels of gonadotropins. Growth hormone, with or without luteinizing hormone–releasing hormone agonists to retard skeletal maturation, has been suggested to improve adult height.

Surgical Management of Ambiguous Genitals

Significantly virilized females usually undergo surgery between 2-6 mo of age. If there is severe clitoromegaly, the clitoris is reduced in size, with partial excision of the corporal bodies and preservation of the neurovascular bundle; however, moderate clitoromegaly may become much less noticeable even without surgery as the patient grows. Vaginoplasty and correction of the urogenital sinus usually are performed at the time of clitoral surgery; revision in adolescence is often necessary.

Risks and benefits of surgery should be fully discussed with parents of affected females. There is limited long-term follow-up of functional outcomes in patients who have undergone **modern** surgical procedures. It appears that female sexual dysfunction increases in frequency and severity in those with the most significant degrees of genital virilization and with the degree of enzymatic impairment (prenatal androgen exposure) caused by each patient's mutations (see Table 576-2). Sex assignment of infants with **disorders of sexual differentiation** (including CAH) is usually based on expected sexual functioning and fertility in adulthood with early surgical correction of the external genitals to conform with the sex assignment. Confused gender identity is not common with CAH; it occurs mostly in females with the salt-wasting form of the disease and the greatest degree of virilization.

Lay and medical opponents of genital surgery for other disorders of sexual differentiation state that it ignores any prenatally biased gender role predisposition from androgen exposure and precludes the patient from having any decision as to the patient's own preferred sexual identity and what surgical correction of the genitals should be performed. These individuals and groups say treatment should be aimed primarily at educating the patient, family, and others about the medical condition, its treatment, and how to deal with the intersex condition. They propose that surgery should be delayed until the patient decides on what, if any, correction should be performed. Severely virilized genotypic (XX) females raised as males have generally functioned well in the male gender as adults.

In adolescent and adult females with poorly controlled 21-hydroxylase deficiency (hirsutism, obesity, amenorrhea), bilateral laparoscopic adrenalectomy (with hormone replacement) may be an alternative to standard medical hormone replacement therapy, but patients treated in this way may be more susceptible to acute adrenal insufficiency if treatment is interrupted because the adrenal glands have been removed. Moreover, they may exhibit signs of elevated ACTH levels such as abnormal pigmentation.

Prenatal Treatment

Besides genetic counseling, the main goal of prenatal diagnosis is to facilitate appropriate prenatal treatment of affected females. Mothers with pregnancies at risk are given dexamethasone, a steroid that readily crosses the placenta, in an amount of 20 µg/kg prepregnancy maternal weight daily in 2 or 3 divided doses. This suppresses secretion of steroids by the fetal adrenal, including secretion of adrenal androgens. If started by 6 wk of gestation, it ameliorates virilization of the external

genitals in affected females. Chorionic villus biopsy is then performed to determine the sex and genotype of the fetus; therapy is continued only if the fetus is an affected female. DNA analysis of fetal cells isolated from maternal plasma for sex determination and *CYP21* gene analysis may permit earlier identification of the affected female fetus. Children exposed to this therapy have slightly lower birthweights. Effects on personality or cognition, such as increased shyness, have been suggested but not consistently observed. At present there is insufficient information to determine whether the long-term risks are acceptable, particularly in the males and unaffected females who derive no direct benefit from the treatment. Maternal side effects of prenatal treatment have included edema, excessive weight gain, hypertension, glucose intolerance, cushingoid facial features, and severe striae. Prenatal treatment is therefore carried out only under institutional protocols in some locales, but it is offered as an option outside the research setting by high-risk obstetricians in other communities.

Bibliography is available at Expert Consult.

576.2 Congenital Adrenal Hyperplasia Caused by 11β-Hydroxylase Deficiency

Perrin C. White

ETIOLOGY

Deficiency of 11β-hydroxylase is caused by a mutation in the *CYP11B1* gene located on chromosome 8q24. *CYP11B1* mediates 11-hydroxylation of 11-deoxycortisol to cortisol. Because 11-deoxycortisol is not converted to cortisol, levels of corticotropin are high. In consequence, precursors—particularly 11-deoxycortisol and deoxycorticosterone—accumulate and are shunted into androgen biosynthesis in the same manner as occurs in 21-hydroxylase deficiency. The adjacent *CYP11B2* gene encoding aldosterone synthase is generally unaffected in this disorder, so patients are able to synthesize aldosterone normally.

EPIDEMIOLOGY

11β-Hydroxylase deficiency accounts for approximately 5% of cases of adrenal hyperplasia; its incidence in the general population has been estimated as 1 in 250,000 to 1 in 100,000. The disorder occurs relatively frequently in Israeli Jews of North African origin (1 in 15,000-17,000 live births). In this ethnic group almost all alleles carry an Arg448 to His (R448H) mutation in *CYP11B1*, but many other mutations have been identified. This disorder presents in a classic, severe form and very rarely in a nonclassic, milder form.

CLINICAL MANIFESTATIONS

Although cortisol is not synthesized efficiently, aldosterone synthetic capacity is normal, and some corticosterone is synthesized from progesterone by the intact aldosterone synthase enzyme. Thus, it is unusual for patients to manifest signs of adrenal insufficiency such as hypotension, hypoglycemia, hyponatremia, and hyperkalemia. Approximately 65% of patients become **hypertensive,** although this can take several years to develop. Hypertension is probably a consequence of elevated levels of deoxycorticosterone, which has mineralocorticoid activity. Infants may transiently develop signs of mineralocorticoid deficiency after treatment with hydrocortisone is instituted. This is presumably from sudden suppression of deoxycorticosterone secretion in a patient with atrophy of the zona glomerulosa caused by chronic suppression of renin activity.

All signs and symptoms of androgen excess that are found in 21-hydroxylase deficiency may also occur in 11β-hydroxylase deficiency.

LABORATORY FINDINGS

Plasma levels of 11-deoxycortisol and deoxycorticosterone are elevated. Because deoxycorticosterone and metabolites have mineralocorticoid activity, plasma renin activity is suppressed. Consequently, aldosterone levels are low even though the ability to synthesize aldosterone is intact. Hypokalemic alkalosis occasionally occurs.

TREATMENT

Patients are treated with hydrocortisone in doses similar to those used for 21-hydroxylase deficiency. Mineralocorticoid replacement is sometimes transiently required in infancy but is rarely necessary otherwise. Hypertension often resolves with glucocorticoid treatment but may require additional therapy if it is of long standing. Calcium channel blockers may be beneficial under these circumstances.

Bibliography is available at Expert Consult.

576.3 Congenital Adrenal Hyperplasia Caused by 3β-Hydroxysteroid Dehydrogenase Deficiency

Perrin C. White

ETIOLOGY

Deficiency of 3β-hydroxysteroid dehydrogenase (3β-HSD) occurs in fewer than 2% of patients with adrenal hyperplasia. This enzyme is required for conversion of Δ5 steroids (pregnenolone, 17-hydroxypregnenolone, dehydroepiandrosterone [DHEA]) to Δ4 steroids (progesterone, 17-hydroxyprogesterone, and androstenedione). Thus, deficiency of the enzyme results in decreased synthesis of cortisol, aldosterone, and androstenedione but increased secretion of DHEA (see Fig. 574-1 in Chapter 574). The 3β-HSD isozyme expressed in the adrenal cortex and gonad is encoded by the *HSD3B2* gene located on chromosome 1p13.1. Over 30 mutations in the *HSD3B2* gene have been described in patients with 3β-HSD deficiency.

CLINICAL MANIFESTATIONS

Because cortisol and aldosterone are not synthesized in patients with the classic form of the disease, infants are prone to **salt-wasting crises.** Because androstenedione and testosterone are not synthesized, **boys are incompletely virilized.** Varying degrees of hypospadias may occur, with or without bifid scrotum or cryptorchidism. Because DHEA levels are elevated and this hormone is a weak androgen, girls are mildly virilized, with slight to moderate clitoral enlargement. Postnatally, continued excessive DHEA secretion can cause precocious adrenarche. During adolescence and adulthood, hirsutism, irregular menses, and polycystic ovarian disease occur in females. Males manifest variable degrees of hypogonadism, although appropriate male secondary sexual development may occur. A persistent defect of testicular 3β-HSD is demonstrated, however, by the high Δ5:Δ4 steroid ratio in testicular effluent.

LABORATORY FINDINGS

The hallmark of this disorder is the marked elevation of the Δ5 steroids (such as 17-hydroxypregnenolone and DHEA) preceding the enzymatic block. Patients may also have elevated levels of 17-hydroxyprogesterone because of the extraadrenal 3β-HSD activity that occurs in peripheral tissues; these patients may be mistaken for patients with 21-hydroxylase deficiency. The ratio of 17-hydroxypregnenolone:17-hydroxyprogesterone is markedly elevated in 3β-HSD deficiency, in contrast to the decreased ratio in 21-hydroxylase deficiency. Plasma renin activity is elevated in the salt-wasting form.

DIFFERENTIAL DIAGNOSIS

It is not unusual for children with premature adrenarche, or women with signs of androgen excess, to have mild to moderate elevations in DHEA levels. It has been suggested that such individuals have "nonclassic 3β-HSD deficiency." Mutations in the *HSD3B2* gene are usually not found in such individuals, and a nonclassic form of this deficiency must actually be quite rare. The activity of 3β-HSD in the adrenal zonae

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fasciculata and reticularis, relative to CYP17 (17-hydroxylase/17,20-lyase) activity, normally decreases during adrenarche to facilitate DHEA synthesis, and so modest elevations in DHEA in preteenage children or women usually represent a normal variant.

TREATMENT

Patients require glucocorticoid and mineralocorticoid replacement with hydrocortisone and fludrocortisone, respectively, as in 21-hydroxylase deficiency. Incompletely virilized genetic males in whom a male sex of rearing is contemplated may benefit from several injections of 25 mg every 4 wk of a depot form of testosterone early in infancy to increase the size of the phallus. They may also require testosterone replacement at puberty.

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576.4 Congenital Adrenal Hyperplasia Caused by 17-Hydroxylase Deficiency

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ETIOLOGY

Less than 1% of CAH cases are caused by 17-hydroxylase deficiency, but the condition is apparently more common in Brazil and China. A single polypeptide, CYP17, catalyzes 2 distinct reactions: 17-hydroxylation of pregnenolone and progesterone to 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, and the 17,20-lyase reaction mediating conversion of 17-hydroxypregnenolone to DHEA and, to a lesser extent, 17-hydroxyprogesterone to Δ4-androstenedione. DHEA and androstenedione are steroid precursors of testosterone and estrogen (see Fig. 574-1 in Chapter 574). The enzyme is expressed in both the adrenal cortex and the gonads and is encoded by a gene on chromosome 10q24.3. Most mutations affect both the hydroxylase and lyase activities, but rare mutations can affect either activity alone.

Mutations in genes other than *CYP17* can have the same phenotype as 17,20-lyase deficiency (i.e., deficient androgen synthesis with normal cortisol synthesis). These include an accessory electron transfer protein, cytochrome b_5, and mutations in 2 aldo-keto reductases, AKR1C2 and AKR1C4. These AKR1C isozymes normally catalyze 3α-hydroxysteroid dehydrogenase activity, which allows synthesis of the potent androgen dihydrotestosterone through an alternative "backdoor" biosynthetic pathway that does not include testosterone as an intermediate.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Patients with 17-hydroxylase deficiency cannot synthesize cortisol, but their ability to synthesize corticosterone is intact. Because corticosterone is an active glucocorticoid, patients do not develop adrenal insufficiency. Deoxycorticosterone, the immediate precursor of corticosterone, is synthesized in excess. This can cause **hypertension, hypokalemia,** and suppression of renin and aldosterone secretion, as occurs in 11β-hydroxylase deficiency. In contrast to 11β-hydroxylase deficiency, patients with 17-hydroxylase deficiency are unable to synthesize sex hormones. Affected **males are incompletely virilized** and present as phenotypic females (but gonads are usually palpable in the inguinal region or the labia) or with sexual ambiguity. Affected females usually present with **failure of sexual development** at the expected time of **puberty.** 17-Hydroxylase deficiency in females must be considered in the differential diagnosis of primary hypogonadism (see Chapter 586). Levels of deoxycorticosterone are elevated and renin and aldosterone are consequently suppressed. Cortisol and sex steroids are unresponsive to stimulation with ACTH and human chorionic gonadotropin, respectively.

Patients with isolated 17,20-lyase deficiency have deficient androgen synthesis with normal cortisol synthesis, and therefore do not become hypertensive.

TREATMENT

Patients with 17-hydroxylase deficiency require cortisol replacement to suppress secretion of deoxycorticosterone and thus control hypertension. Additional antihypertensive medication may be required. Females require estrogen replacement at puberty. Genetic males may require either estrogen or androgen supplementation depending on the sex of rearing. Because of the possibility of malignant transformation of abdominal testes with androgen insensitivity syndrome (see Chapter 588.2), genetic males with severe 17-hydroxylase deficiency being reared as females require gonadectomy at or before adolescence.

Bibliography is available at Expert Consult.

576.5 Lipoid Adrenal Hyperplasia

Perrin C. White

ETIOLOGY

Lipoid adrenal hyperplasia is a rare disorder, most frequently found in Japanese persons. Patients with this disorder exhibit marked accumulation of cholesterol and lipids in the adrenal cortex and gonads, associated with severe impairment of all steroidogenesis. Lipoid adrenal hyperplasia is usually caused by mutations in the gene for steroidogenic acute regulatory protein (StAR), a mitochondrial protein that promotes the movement of cholesterol from the outer to the inner mitochondrial membrane. However, mutations in the *CYP11A1* gene (which encodes the cholesterol side chain cleavage enzyme) have been reported in several patients.

Some cholesterol is able to enter mitochondria even in the absence of StAR, so it might be supposed that this disorder would not completely impair steroid biosynthesis. However, the accumulation of cholesterol in the cytoplasm is cytotoxic, eventually leading to death of all steroidogenic cells in which StAR is normally expressed. This occurs prenatally in the adrenals and testes. The ovaries do not normally synthesize steroids until puberty, so cholesterol does not accumulate and the ovaries can retain the capacity to synthesize estrogens until adolescence.

Although estrogens synthesized by the placenta are required to maintain pregnancy, the placenta does not require StAR for steroid biosynthesis. Thus, mutations of StAR are not prenatally lethal.

CLINICAL MANIFESTATIONS

Patients with lipoid adrenal hyperplasia are usually unable to synthesize any adrenal steroids. Thus, affected infants are likely to be confused with those with adrenal hypoplasia congenita. Salt-losing manifestations are typical, and many infants die in early infancy. Genetic males are unable to synthesize androgens and thus are **phenotypically female** but with gonads palpable in the labia majora or inguinal areas. Genetic females appear normal at birth and may undergo feminization at puberty with menstrual bleeding. They too, progress to hypergonadotropic hypogonadism when accumulated cholesterol kills granulosa (i.e., steroid synthesizing) cells in the ovary.

LABORATORY FINDINGS

Adrenal and gonadal steroid hormone levels are low in lipoid adrenal hyperplasia, with a decreased or absent response to stimulation (ACTH, human chorionic gonadotropin). Plasma renin levels are increased.

Imaging studies of the adrenal gland demonstrating massive adrenal enlargement in the newborn help establish the diagnosis of lipoid adrenal hyperplasia.

TREATMENT

Patients require glucocorticoid and mineralocorticoid replacement. Genetic males are usually assigned a female sex of rearing; thus both genetic males and females require estrogen replacement at the expected age of puberty.

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576.6 Deficiency of P450 Oxidoreductase (Antley-Bixler Syndrome)

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ETIOLOGY, PATHOGENESIS, AND CLINICAL MANIFESTATIONS

P450 oxidoreductase (POR, gene located on chromosome 7q11.3) is required for the activity of all microsomal cytochrome P450 enzymes (see Chapter 574) including the adrenal enzymes CYP17 and CYP21. Thus, complete POR deficiency abolishes all microsomal P450 activity. This is embryonically lethal in mice and presumably in humans as well. Patients with mutations that decrease but do not abolish POR activity have partial deficiencies of 17-hydroxylase and 21-hydroxylase activities in the adrenals. A single recurrent mutation, A287P (alanine-287 to proline) is found on approximately 40% of alleles.

Deficiency of 17-hydroxylase leads to incomplete masculinization in males; 21-hydroxylase deficiency may lead to virilization in females. Additionally, aromatase *(CYP19)* activity in the placenta is decreased, leading to unopposed action of androgens produced by the fetal adrenal. This exacerbates virilization of female fetuses and may **virilize the mother** of an affected fetus as well. Although it is puzzling that affected females could be virilized despite a partial deficiency in *CYP17* (which is required for androgen biosynthesis), an alternative ("back-door") biosynthetic pathway is utilized in which 17-hydroxyprogesterone is converted to 5α-pregnane-3α,17α-diol-20-one, a metabolite that is a much better substrate for the 17,20-lyase activity of *CYP17* than the usual substrate, 17-hydroxypregnenolone (see Chapter 574). The metabolite is then converted in several enzymatic steps to dihydrotestosterone, a potent androgen.

Because many other P450 enzymes are affected, patients often (but not invariably) have other congenital anomalies collectively referred to as **Antley-Bixler syndrome.** These include craniosynostosis; brachycephaly; frontal bossing; severe midface hypoplasia with proptosis and choanal stenosis or atresia; humeroradial synostosis; medial bowing of ulnas; long, slender fingers with camptodactyly; narrow iliac wings; anterior bowing of femurs; and malformations of the heart and kidneys. Studies of mutant mice suggest that the metabolic defects responsible for these anomalies include defective metabolism of retinoic acid, leading to elevated levels of this teratogenic compound, and deficient biosynthesis of cholesterol.

EPIDEMIOLOGY

The prevalence is not known with certainty. It must be rare compared with 21-hydroxylase deficiency but might occur at similar frequencies to the other forms of CAH.

LABORATORY FINDINGS

Serum steroids that are not 17- or 21-hydroxylated are most increased, including pregnenolone and progesterone. 17-Hydroxy, 21-deoxysteroids are also increased, including 17-hydroxypregnenolone, 17-hydroxyprogesterone, and 21-deoxycortisol. Urinary steroid metabolites may be determined by quantitative mass spectrometry. Metabolites excreted at increased levels include pregnanediol, pregnanetriol, pregnanetriolone, and corticosterone metabolites. Urinary cortisol metabolites are decreased. Genetic analysis demonstrates mutations in the *POR* gene.

DIFFERENTIAL DIAGNOSIS

This disorder must be distinguished from other forms of CAH, particularly 21-hydroxylase deficiency in females, which is far more common and has similar laboratory findings. Suspicion for *POR* deficiency may be raised if the mother is virilized or if the associated abnormalities of Antley-Bixler syndrome are present. Conversely, virilization of both the mother and her daughter can result from a luteoma of pregnancy, but in this case postnatal abnormalities of corticosteroid biosynthesis should not be observed. Antley-Bixler syndrome may also occur without abnormalities of steroid hormone biosynthesis, resulting from mutations in the fibroblast growth factor receptor FGFR2.

Bibliography is available at Expert Consult.

576.7 Aldosterone Synthase Deficiency

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ETIOLOGY

This is a rare autosomal recessive disorder in which conversion of corticosterone to aldosterone is impaired; a group of Iranian Jewish patients has been the most thoroughly studied. The majority of cases result from mutations in the *CYP11B2* gene coding for aldosterone synthase; however, linkage to *CYP11B2* has been excluded in other kindreds. When not caused by *CYP11B2* mutations, the disorder has been termed *familial hyperreninemic hypoaldosteronism type 2;* the causative gene or genes have not yet been identified.

Aldosterone synthase mediates the 3 final steps in the synthesis of aldosterone from deoxycorticosterone (11β-hydroxylation, 18-hydroxylation, and 18-oxidation). Although 11β-hydroxylation is required to convert deoxycorticosterone to corticosterone, this conversion can also be catalyzed by the related enzyme, CYP11B1, located in the fasciculata, which is unaffected in this disorder. For the same reason, these patients have normal cortisol biosynthesis.

The disease has been classified into 2 types, termed *corticosterone methyloxidase deficiency types I and II.* They differ only in levels of the immediate precursor of aldosterone, 18-hydroxycorticosterone; levels are low in type I deficiency and elevated in type II deficiency. These differences do not correspond in a simple way to particular mutations and are of limited clinical importance.

CLINICAL MANIFESTATIONS

Infants with aldosterone synthase deficiency may have severe electrolyte abnormalities with **hyponatremia, hyperkalemia,** and **metabolic acidosis.** Because cortisol synthesis is unaffected, infants rarely become as ill as untreated infants with salt-losing forms of CAH such as 21-hydroxylase deficiency. Thus, some infants escape diagnosis. Later in infancy or in early childhood they may exhibit failure to thrive and poor growth. Adults often are asymptomatic, although they may develop electrolyte abnormalities when depleted of sodium through procedures such as bowel preparation for a barium enema.

LABORATORY FINDINGS

Infants have elevated plasma renin activity. Aldosterone levels are decreased; they may be at the lower end of the normal range but are always inappropriately low for the degree of hyperkalemia or hyperreninemia. Corticosterone levels are often elevated.

Some, but not all, patients have marked elevation of 18-hydroxycorticosterone; however, low levels of this steroid do not exclude the diagnosis. In those kindreds in which 18-hydroxycorticosterone levels are elevated in affected individuals, this biochemical abnormality persists in adults even when they have no electrolyte abnormalities.

DIFFERENTIAL DIAGNOSIS

It is important to distinguish aldosterone synthase deficiency from primary adrenal insufficiency in which both cortisol and aldosterone are affected (including salt-wasting forms of CAH) because the latter condition is usually associated with a much greater risk of shock and hyponatremia. This becomes apparent after the appropriate laboratory studies. Adrenal hypoplasia congenita may initially present with aldosterone deficiency; all male infants with apparently isolated aldosterone deficiency should be carefully monitored for subsequent development of cortisol deficiency. **Pseudohypoaldosteronism** (see Chapter 575.4) may have similar electrolyte abnormalities and

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hyperreninemia, but aldosterone levels are high, and this condition usually does not respond to fludrocortisone treatment.

TREATMENT

Treatment consists of giving enough fludrocortisone (0.05-0.3 mg daily) or sodium chloride, or both, to return plasma renin levels to normal. With increasing age, salt-losing signs usually improve and drug therapy can often be discontinued.

Bibliography is available at Expert Consult.

576.8 Glucocorticoid-Suppressible Hyperaldosteronism

Perrin C. White

ETIOLOGY

Glucocorticoid-suppressible hyperaldosteronism (glucocorticoid-remediable aldosteronism, familial hyperaldosteronism type I) is an autosomal dominant form of **low-renin hypertension** in which hyperaldosteronism is rapidly suppressed by glucocorticoid administration. This unusual effect of glucocorticoids suggests that aldosterone secretion in this disorder is regulated by ACTH instead of by the renin–angiotensin system. In addition to abnormally regulated secretion of aldosterone, there is marked overproduction of 18-hydroxycortisol and 18-oxocortisol. The synthesis of these steroids requires both 17-hydroxylase (CYP17) activity, which is expressed only in the zona fasciculata, and aldosterone synthase (CYP11B2) activity, which is normally expressed only in the zona glomerulosa. Together, these features imply that aldosterone synthase is being expressed in a manner similar to the closely related enzyme steroid 11-hydroxylase *(CYP11B1).* The disorder is caused by unequal meiotic crossing-over events between the *CYP11B1* and *CYP11B2* genes, which are closely linked on chromosome 8q24. An additional "hybrid" gene is produced, having regulatory sequences of *CYP11B1* juxtaposed with coding sequences of *CYP11B2.* This results in the inappropriate expression of a *CYP11B2*-like enzyme with aldosterone synthase activity in the adrenal fasciculata.

CLINICAL MANIFESTATIONS

Some affected children have no symptoms, the diagnosis being established after incidental discovery of moderate hypertension, typically approximately 30 mm Hg higher than unaffected family members of the same age. Others have more symptomatic hypertension with headache, dizziness, and visual disturbances. A strong family history of early-onset hypertension or early strokes may alert the clinician to the diagnosis. Some patients have chronic hypokalemia, but this is not a consistent finding and is usually mild.

LABORATORY FINDINGS

Patients have elevated plasma and urine levels of aldosterone and suppressed plasma renin activity. Hypokalemia is not consistently present. Urinary and plasma levels of 18-oxocortisol and 18-hydroxycortisol are markedly increased. The hybrid *CYP11B1/CYP11B2* gene can be readily detected by molecular genetic methods.

DIFFERENTIAL DIAGNOSIS

This condition should be distinguished from primary aldosteronism based on bilateral hyperplasia or an aldosterone-producing adenoma (see Chapter 578). Most cases of primary aldosteronism are sporadic, although several affected kindreds have been reported. Patients with primary aldosteronism may also have elevated levels of 18-hydroxycortisol and 18-oxocortisol, and these biochemical tests should be used cautiously to distinguish primary and glucocorticoid-suppressible aldosteronism. A therapeutic trial of dexamethasone may be helpful if aldosterone secretion is suppressed, and genetic testing should identify the hybrid gene of glucocorticoid-suppressible hyperaldosteronism if it is present.

TREATMENT

Glucocorticoid-suppressible hyperaldosteronism is managed by daily administration of a glucocorticoid, usually dexamethasone, 25 µg/kg/day in divided doses. If necessary, effects of aldosterone can be blocked with a potassium-sparing diuretic such as spironolactone, eplerenone, or amiloride. Hypertension resolves in patients in whom the hypertension is not severe or of long standing. If hypertension is long standing, additional antihypertensive medication may be required, such as a calcium channel blocker.

GENETIC COUNSELING

Because of the autosomal dominant mode of inheritance, at-risk family members should be investigated for this easily treated cause of hypertension.

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Chapter 577

Cushing Syndrome

Perrin C. White

Cushing syndrome is the result of abnormally high blood levels of cortisol or other glucocorticoids. This can be iatrogenic or the result of endogenous cortisol secretion, a result of either an adrenal tumor or of hypersecretion of corticotropin (adrenocorticotropic hormone [ACTH]) by the pituitary (Cushing disease) or by a tumor (Table 577-1).

ETIOLOGY

The most common cause of Cushing syndrome is prolonged exogenous administration of glucocorticoid hormones, especially at the high doses used to treat lymphoproliferative disorders. This rarely represents a diagnostic challenge, but management of hyperglycemia, hypertension, weight gain, linear growth retardation, and osteoporosis often complicates therapy with corticosteroids.

Endogenous Cushing syndrome is most often caused in infants by a functioning adrenocortical tumor (see Chapter 579). Patients with these tumors often exhibit signs of hypercortisolism along with signs of hypersecretion of other steroids such as androgens, estrogens, and aldosterone.

Although extremely rare in infants, the most common etiology of endogenous Cushing syndrome in children older than 7 yr of age is **Cushing disease,** in which excessive ACTH secreted by a pituitary adenoma causes bilateral adrenal hyperplasia. Such adenomas are often too small to detect by imaging techniques and are termed microadenomas. They consist principally of chromophobe cells and frequently show positive immunostaining for ACTH and its precursor, proopiomelanocortin. Whereas the vast majority of such tumors are sporadic, a small number occur in kindreds with familial isolated pituitary adenoma syndrome. This syndrome, which is caused by mutations in the aryl hydrocarbon receptor interacting protein *(AIP)* gene, accounts for perhaps 2% of pituitary adenomas, but more commonly tumors with *AIP* mutations secrete growth hormone or prolactin, and only rarely do they secrete ACTH. Similarly, multiple endocrine neoplasia type 1 (MEN1) patients, who by definition have mutations in the MEN1 (menin) gene, may develop pituitary tumors, but these are typically prolactinomas.

ACTH-dependent Cushing syndrome may also result from ectopic production of ACTH, although this is uncommon in children. Ectopic

Table 577-1	Etiologic Classification of Adrenocortical Hyperfunction
EXCESS ANDROGEN Congenital adrenal hyperplasia 21-Hydroxylase (P450c21) deficiency 11β-Hydroxylase (P450c11) deficiency 3β-Hydroxysteroid dehydrogenase defect (deficiency or dysregulation) Tumor	
EXCESS CORTISOL (CUSHING SYNDROME) Bilateral adrenal hyperplasia Adenoma Hypersecretion of corticotropin (Cushing disease) Ectopic secretion of corticotropin Exogenous corticotropin Adrenocortical nodular dysplasia Pigmented nodular adrenocortical disease (Carney complex) Tumor McCune-Albright syndrome	
EXCESS MINERALOCORTICOID Primary hyperaldosteronism Aldosterone-secreting adenoma Bilateral micronodular adrenocortical hyperplasia Glucocorticoid-suppressible aldosteronism Tumor Deoxycorticosterone excess Congenital adrenal hyperplasia 11β-Hydroxylase (P450c11) 17α-Hydroxylase (P450c17) Tumor Apparent mineralocorticoid excess (deficiency of 11β-hydroxysteroid dehydrogenase type 2)	
EXCESS ESTROGEN Tumor	

ACTH secretion in children is associated with islet cell carcinoma of the pancreas, neuroblastoma or ganglioneuroblastoma, hemangiopericytoma, Wilms tumor, and thymic carcinoid. Hypertension is more common in the ectopic ACTH syndrome than in other forms of Cushing syndrome, because very high cortisol levels may overwhelm 11β-hydroxysteroid dehydrogenase in the kidney (see Chapter 575) and thus have an enhanced mineralocorticoid (salt-retaining) effect.

Several syndromes are associated with the development of multiple autonomously hyperfunctioning nodules of adrenocortical tissue, rather than single adenomas or carcinomas (which are discussed in Chapter 579). **Primary pigmented nodular adrenocortical disease** (PPNAD) is a distinctive form of ACTH-independent Cushing syndrome. It may occur as an isolated event or, more commonly, as a familial disorder with other manifestations. The adrenal glands are small and have characteristic multiple, small (<4 mm in diameter), pigmented (black) nodules containing large cells with cytoplasm and lipofuscin; there is cortical atrophy between the nodules. This adrenal disorder occurs as a component of **Carney complex,** an autosomal dominant disorder also consisting of centrofacial lentigines and blue nevi; cardiac and cutaneous myxomas; pituitary, thyroid, and testicular tumors; and pigmented melanotic schwannomas. Carney complex is inherited in an autosomal dominant manner, although sporadic cases occur. Genetic loci for Carney complex have been mapped to the gene for the type 1α regulatory subunit of protein kinase A (PRKAR1A) on chromosome 17q22-24 and less frequently to chromosome 2p16. Patients with Carney complex and PRKAR1A mutations generally develop PPNAD as adults, and those with the disorder mapping to chromosome 2 (and most sporadic cases) develop PPNAD less frequently and later. Conversely, children presenting with PPNAD as an isolated finding rarely have mutations in PRKAR1A, or subsequently develop other manifestations of Carney complex. Some patients with isolated PPNAD have mutations in the *PDE8B* or *PDE11A* genes encoding different phosphodiesterase isozymes.

ACTH-independent Cushing syndrome with nodular hyperplasia and adenoma formation occurs rarely in cases of **McCune-Albright syndrome,** with symptoms beginning in infancy or childhood. McCune-Albright syndrome is caused by a somatic mutation of the *GNAS* gene encoding the G protein, $G_s\alpha$, through which the ACTH receptor (MCR2) normally signals. This results in inhibition of guanosine triphosphatase activity and constitutive activation of adenylate cyclase, thus increasing levels of cyclic adenosine monophosphate. When the mutation is present in adrenal tissue, cortisol and cell division are stimulated independently of ACTH. Other tissues in which activating mutations may occur are bone (producing fibrous dysplasia), gonads, thyroid, and pituitary. Clinical manifestations depend on which tissues are affected.

Thus the genes causing nodular adrenocortical hyperplasia that have been identified thus far all produce overactivity of the ACTH signaling pathway either by constitutively activating $G_s\alpha$ (McCune-Albright syndrome), by reducing the breakdown of cyclic adenosine monophosphate and thus increasing its intracellular levels (mutations of *PDE8B* or *PDE11A*), or by disrupting the regulation of the cyclic adenosine monophosphate–dependent enzyme, protein kinase A (PRKAR1A mutations).

Additionally, adrenocortical lesions including diffuse hyperplasia, nodular hyperplasia, adenoma, and rarely carcinoma may occur as part of the MEN1 syndrome (see Chapter 573), an autosomal dominant disorder, in which there is homozygous inactivation of the menin **(MEN1)** tumor-suppressor gene on chromosome 11q13.

CLINICAL MANIFESTATIONS

Signs of Cushing syndrome have been recognized in infants younger than 1 yr of age. The disorder appears to be more severe and the clinical findings more flagrant in infants than in older children. The face is rounded, with prominent cheeks and a flushed appearance (moon facies). Generalized obesity is common in younger children. In children with adrenal tumors, signs of abnormal masculinization occur frequently; accordingly, there may be hirsutism on the face and trunk, pubic hair, acne, deepening of the voice, and enlargement of the clitoris in girls. Growth is impaired, with length falling below the 3rd percentile, except when significant virilization produces normal or even accelerated growth. Hypertension is common and may occasionally lead to heart failure. An increased susceptibility to infection may also lead to sepsis.

In older children, in addition to obesity, short stature is a common presenting feature. Gradual onset of obesity and deceleration or cessation of growth may be the only early manifestations. Older children most often have more severe obesity of the face and trunk compared with the extremities. Purplish striae on the hips, abdomen, and thighs are common. Pubertal development may be delayed, or amenorrhea may occur in girls past menarche. Weakness, headache, and emotional lability may be prominent. Hypertension and hyperglycemia usually occur; hyperglycemia may progress to frank diabetes. Osteoporosis is common and may cause pathologic fractures.

LABORATORY FINDINGS

Cortisol levels in blood are normally highest at 8 AM and decrease to less than 50% by midnight except in infants and young children in whom a diurnal rhythm is not always established. In patients with Cushing syndrome this circadian rhythm is lost; midnight cortisol levels >4.4 µg/dL strongly suggest the diagnosis. It is difficult to obtain diurnal blood samples as part of an outpatient evaluation, but cortisol can be measured in saliva samples, which can be obtained at home at the appropriate times of day. Elevated nighttime salivary cortisol levels raise suspicion for Cushing syndrome.

Urinary excretion of free cortisol is increased. This is best measured in a 24 hr urine sample and is expressed as a ratio of micrograms of cortisol excreted per gram of creatinine. This ratio is independent of body size and completeness of the urine collection.

A single-dose dexamethasone suppression test is often helpful; a dose of 25-30 μg/kg (maximum: 2 mg) given at 11 PM results in a plasma cortisol level of less than 5 μg/dL at 8 AM the next morning in normal individuals but not in patients with Cushing syndrome. It is prudent to measure the dexamethasone level in the same blood sample to ensure adequacy of dosing.

A glucose tolerance test is often abnormal but is of no diagnostic utility. Levels of serum electrolytes are usually normal, but potassium may be decreased, especially in patients with tumors that secrete ACTH ectopically.

After the diagnosis of Cushing syndrome has been established, it is necessary to determine whether it is caused by a pituitary adenoma, an ectopic ACTH-secreting tumor, or a cortisol-secreting adrenal tumor. ACTH concentrations are usually suppressed in patients with cortisol-secreting tumors and are very high in patients with ectopic ACTH-secreting tumors but may be normal in patients with ACTH-secreting pituitary adenomas. After an intravenous bolus of corticotropin-releasing hormone, patients with ACTH-dependent Cushing syndrome have an exaggerated ACTH and cortisol response, whereas those with adrenal tumors show no increase in ACTH and cortisol. The 2-step dexamethasone suppression test consists of administration of dexamethasone, 30 and 120 μg/kg/24 hr in 4 divided doses, on consecutive days. In children with pituitary/Cushing syndrome, the larger dose, but not the smaller dose, suppresses serum levels of cortisol. Typically, patients with ACTH-independent Cushing syndrome do not show suppressed cortisol levels with dexamethasone.

CT detects virtually all adrenal tumors larger than 1.5 cm in diameter. MRI may detect ACTH-secreting pituitary adenomas, but many are too small to be seen; the addition of gadolinium contrast increases the sensitivity of detection. Bilateral inferior petrosal blood sampling to measure concentrations of ACTH before and after corticotropin-releasing hormone administration may be required to localize the tumor when a pituitary adenoma is not visualized; this is not routinely available in many centers, and moreover may be of decreased specificity in children.

DIFFERENTIAL DIAGNOSIS

Cushing syndrome is frequently suspected in children with obesity, particularly when striae and hypertension are present. Children with simple obesity are usually tall, whereas those with Cushing syndrome are short or have a decelerating growth rate. Although urinary excretion of cortisol is often elevated in simple obesity, salivary nighttime levels of cortisol are usually normal and cortisol secretion is suppressed by oral administration of low doses of dexamethasone.

Elevated levels of cortisol and ACTH without clinical evidence of Cushing syndrome occur in patients with generalized glucocorticoid resistance (see Chapter 575.4). Affected patients may be asymptomatic or exhibit hypertension, hypokalemia, and precocious pseudopuberty; these manifestations are caused by increased mineralocorticoid and adrenal androgen secretion in response to elevated ACTH levels. Mutations in the glucocorticoid receptor have been identified.

TREATMENT

Transsphenoidal pituitary microsurgery is the treatment of choice in pituitary Cushing disease in children. The overall success rate with follow-up of less than 10 yr is 60-80%. Low postoperative serum or urinary cortisol concentrations predict long-term remission in the majority of cases. Relapses are treated with reoperation or pituitary irradiation.

Cyproheptadine, a centrally acting serotonin antagonist that blocks ACTH release, has been used to treat Cushing disease in adults; remissions are usually not sustained after discontinuation of therapy. This agent is rarely used in children. Inhibitors of adrenal steroidogenesis (metyrapone, ketoconazole, aminoglutethimide, etomidate) have been used preoperatively to normalize circulating cortisol levels and reduce perioperative morbidity and mortality. Mifepristone, a glucocorticoid receptor antagonist, has been used in a limited number of cases.

Pasireotide, a somatostatin analog, can inhibit ACTH secretion, and is approved for use in adults with persistent disease after surgery or in whom surgery is contraindicated.

If a pituitary adenoma does not respond to treatment or if ACTH is secreted by an ectopic metastatic tumor, the adrenal glands may need to be removed. This can often be accomplished laparoscopically. Adrenalectomy may lead to increased ACTH secretion by an unresected pituitary adenoma, evidenced mainly by marked hyperpigmentation; this condition is termed **Nelson syndrome.**

Management of patients undergoing adrenalectomy requires adequate preoperative and postoperative replacement therapy with a corticosteroid. Tumors that produce corticosteroids usually lead to atrophy of the normal adrenal tissue, and replacement with cortisol (10 mg/m^2/24 hr in 3 divided doses after the immediate postoperative period) is required until there is recovery of the hypothalamic-pituitary-adrenal axis. Postoperative complications may include sepsis, pancreatitis, thrombosis, poor wound healing, and sudden collapse, particularly in infants with Cushing syndrome. Substantial catch-up growth, pubertal progress, and increased bone density occur, but bone density remains abnormal and adult height is often compromised. The management of adrenocortical tumors is discussed in Chapter 579.

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Chapter 578

Primary Aldosteronism

Perrin C. White

Primary aldosteronism encompasses disorders caused by excessive aldosterone secretion independent of the renin–angiotensin system. These disorders are characterized by **hypertension, hypokalemia,** and suppression of the renin–angiotensin system.

ETIOLOGY

Aldosterone-secreting adenomas are unilateral and have been reported in children as young as 3.5 yr of age; they mainly affect girls. Adrenocortical tumors are discussed further in Chapter 579. Bilateral micronodular adrenocortical hyperplasia tends to occur in older children and is more frequent in males. Primary aldosteronism due to unilateral adrenal hyperplasia may also occur. Glucocorticoid-suppressible hyperaldosteronism is discussed in Chapter 576.8.

EPIDEMIOLOGY

These conditions are thought to be rare in children, but they may account for 5-10% of cases of hypertension in adults. Although usually sporadic, kindreds with several affected members have been reported. Genetic linkage to chromosome 7p22 has been identified in some of these kindreds, but the involved gene has not yet been identified. Mutations in the *KCNJ5* gene on chromosome 11q24 have been identified in several kindreds; these mutations (G151R and G151E) altered channel selectivity, producing increased Na^+ conductance and membrane depolarization, which increases aldosterone production and proliferation of adrenal glomerulosa cells. Moreover, such mutations have been identified in a subset of sporadic aldosterone-producing adenomas.

CLINICAL MANIFESTATIONS

Some affected children have no symptoms, the diagnosis being established after incidental discovery of moderate hypertension. Others have severe hypertension (up to 240/150 mm Hg), with headache, dizziness, and visual disturbances. Chronic hypokalemia, if present, may lead to polyuria, nocturia, enuresis, and polydipsia. Muscle weakness and discomfort, tetany, intermittent paralysis, fatigue, and growth failure affect children with severe hypokalemia.

LABORATORY FINDINGS

Hypokalemia occurs frequently. Serum pH and the carbon dioxide and sodium concentrations may be elevated and the serum chloride and magnesium levels decreased. Serum levels of calcium are normal, even in children who manifest tetany. The urine is neutral or alkaline, and urinary potassium excretion is high. Plasma levels of aldosterone may be normal or elevated. Aldosterone concentrations in 24 hr urine collections are always increased. Plasma levels of renin are persistently low.

The diagnostic test of choice for primary aldosteronism is controversial. Both renin and aldosterone levels may vary by time of day, posture, and sodium intake, making it difficult to establish consistent reference ranges. It is desirable to establish a consistent sampling protocol, for example, at midmorning after the patient has been sitting for 15 min. If possible, antihypertensive drugs or other medications that can affect aldosterone or renin secretion should be avoided for several weeks prior to testing, including diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, clonidine, and nonsteroidal antiinflammatory agents. Patients taking these agents may need to be changed to α-adrenergic blockers or calcium channel blockers that have smaller effects on the biochemical measurements. The ratio of plasma aldosterone concentration to renin activity is always high, and this represents a cost-effective screening test for primary aldosteronism. Aldosterone does not decrease with administration of saline solution or fludrocortisone, and renin does not respond to salt and fluid restriction. Urinary and plasma levels of 18-oxocortisol and 18-hydroxycortisol may be increased but not to the extent seen in glucocorticoid-suppressible hyperaldosteronism.

DIFFERENTIAL DIAGNOSIS

Primary aldosteronism should be distinguished from glucocorticoid-suppressible hyperaldosteronism (see Chapter 576.8), which is specifically treated with glucocorticoids. An autosomal dominant pattern of inheritance should raise suspicion for the latter disorder. Glucocorticoid-suppressible hyperaldosteronism is diagnosed by dexamethasone suppression tests or by specific genetic testing. More generally, primary aldosteronism should be distinguished from other forms of hypertension by means of the testing previously discussed.

TREATMENT

The treatment of an aldosterone-producing adenoma is surgical removal. This is performed primarily by laparotomy and adrenalectomy; successful enucleation of aldosterone-producing adenomas, as well as laparoscopic adrenalectomy, has been reported. *Hyperaldosteronism caused by bilateral adrenal hyperplasia is treated with the mineralocorticoid antagonists spironolactone (1-3 mg/kg/day to a maximum of 100 mg/day) or eplerenone (25-100 mg/day in 2 divided doses),* often normalizing blood pressure and serum potassium levels. There is greater experience with spironolactone, but this agent has antiandrogenic properties that may be unacceptable in pubertal males. Eplerenone is a more specific antimineralocorticoid that is safe in children, but there is little specific experience with primary aldosteronism in the pediatric age group. As an alternative, an epithelial sodium channel blocker, such as amiloride, may be used, with other antihypertensive agents added as necessary. In patients whose condition cannot be controlled medically, unilateral adrenalectomy may be considered.

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Chapter 579

Adrenocortical Tumors

Perrin C. White

EPIDEMIOLOGY

Adrenocortical tumors are rare in childhood, with an incidence of 0.3-0.5 cases per 1 million child-years. They occur in all age groups but most commonly in children younger than 6 yr of age, and are more frequent (1.6-fold) in girls. In 2-10% of cases, the tumors are bilateral. Almost half of childhood adrenocortical tumors are carcinomas.

Symptoms of endocrine hyperfunction are present in 80-90% of children with adrenal tumors (see Table 577-1 in Chapter 577). Tumors that secrete cortisol and aldosterone are also discussed in Chapters 577 and 578, respectively. Tumors may be associated with hemihypertrophy, usually occurring during the 1st few yr of life. They are also associated with other congenital defects, particularly genitourinary tract and central nervous system abnormalities and hamartomatous defects.

ETIOLOGY

The incidence of adrenocortical tumors is increased in several familial cancer syndromes resulting from abnormalities in genes that encode transcription factors implicated in cell proliferation, differentiation, senescence, apoptosis, and genomic instability. These include tumor protein 53 (*TP53*), menin (the *MEN1* gene involved in multiple endocrine neoplasia type 1), the *APC* gene involved in familial adenomatous polyposis coli, and the *PRKAR1A* gene encoding a cyclic adenosine monophosphate–dependent protein kinase regulatory subunit (also see Chapter 577).

Germline mutations in *TP53* (on chromosome 17p13.1) have been found in patients with isolated adrenal carcinoma as well as in patients with familial clustering of unusual malignancies; this latter condition is termed **Li-Fraumeni syndrome.** A 15-fold increased incidence of childhood adrenocortical tumors is found in southern Brazil, associated with a R337H mutation in *TP53*. Overexpression of insulin-like growth factor 2 (encoded by *IGF2*, on chromosome 11p15.5) occurs in 80% of sporadic childhood adrenocortical tumors, as well as in those associated with **Beckwith-Wiedemann syndrome,** in which there is loss of the normal imprinting of genes in this chromosomal region. Further implicating insulin-like growth factors (IGFs) in pathogenesis, many pediatric adrenocortical tumors overexpress the IGF receptor, IGF1R. Overexpression of steroidogenic factor-1 (SF1), a transcription factor required for adrenal development (see Chapter 574) is associated with decreased overall survival and recurrence-free survival when it occurs in adults with adrenocortical carcinomas, but it is seen in most pediatric adrenocortical tumors, where it does not seem to have prognostic significance. Conversely, the messenger RNA encoding the nephroblastoma overexpressed (NOV) protein (also termed cysteine-rich protein 61, or connective tissue growth factor, or nephroblastoma overexpressed gene-3) is significantly downregulated in childhood adrenocortical tumors. NOV is a selective proapoptotic factor for human adrenocortical cells, suggesting that abnormal apoptosis may play a role in childhood adrenocortical tumorigenesis.

Aldosterone-producing adenomas constitute a separate category from other adrenocortical tumors. They are very rarely malignant. The majority have mutations that activate the Wnt/β-catenin signaling pathway, either in β-catenin itself, or in the *APC* gene, which regulates this pathway. Additional, somatic mutations are often found in the potassium channel, KCNJ5, which probably first causes cell hypertrophy (see Chapter 576.8).

579.1 Virilizing and Feminizing Adrenal Tumors

Perrin C. White

CLINICAL MANIFESTATIONS

Virilization is the most common presenting symptom in children with adrenocortical tumors, occurring in 50-80%. In males, the clinical picture is similar to that of simple virilizing congenital adrenal hyperplasia: accelerated growth velocity and muscle development, acne, penile enlargement, and the precocious development of pubic and axillary hair. In females, virilizing tumors of the adrenal gland cause masculinization of a previously normal female with clitoral enlargement, growth acceleration, acne, deepening of the voice, and premature pubic and axillary hair development.

Conversely, adrenal tumors can occasionally (less than 10%) secrete high levels of estrogens as a result of overexpression of CYP19 (aromatase). Gynecomastia in males or premature thelarche in girls is often the initial manifestation. Growth and development may be otherwise normal, or concomitant virilization may occur.

In addition to virilization, 15-40% of children with adrenocortical tumors also have Cushing syndrome (see Chapter 577). Whereas isolated virilization occurs relatively frequently, children with adrenal tumors usually do not have Cushing syndrome alone.

In adults, adrenal tumors are frequently detected incident to CT or MRI imaging of the abdomen for other reasons; these are often referred to as **incidentalomas** (see Chapter 581.1). There are no published data on the frequency of the occurrence of such tumors in childhood. They are likely to be infrequent, being found in approximately 7% of autopsies of persons older than age 70 yr but in <1% of those younger than age 30 yr.

LABORATORY FINDINGS

Serum levels of dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione are usually elevated, often markedly. Serum levels of testosterone are often increased, usually as a result of peripheral conversion of androstenedione, but infants with predominantly testosterone-secreting adenomas have been reported. Levels of estrone and estradiol are elevated in tumors from patients with feminizing signs. Urinary 17-ketosteroids (sex steroid metabolites) are also increased but are no longer routinely measured. Many adrenocortical tumors have a relative deficiency of 11β-hydroxylase activity and secrete increased amounts of deoxycorticosterone; these patients are hypertensive, and their tumors are often malignant.

Tumors can usually be detected by ultrasonography, CT, or MRI. Preoperatively, the presence of metastatic disease should be determined by MRI or CT of the chest, abdomen, and pelvis. Radiochemical imaging of these tumors by positron emission tomography with 11C-metomidate or single photon emission CT with ^{123}I-iodometomidate have been proposed but are not routinely available.

PATHOLOGIC FINDINGS

Differentiation between benign and malignant tumors by histologic criteria (architecture, cytologic atypia, mitotic activity, atypical mitotic figures) is usually not possible; almost all pediatric adrenocortical tumors would be classified as malignant by the criteria used to classify adult tumors. Size is a useful prognostic factor, with tumors weighing less than 200 g, 200-400 g, and >400 g being classified as low, intermediate, and high risk (>10 cm diameter has also been suggested as a high-risk category). Incomplete resection and gross local invasion or metastasis are also associated with a poor prognosis. However, most tumors occurring in children younger than 4 yr of age fall into favorable prognostic categories.

DIFFERENTIAL DIAGNOSIS

For functioning tumors, the differential diagnoses are those of the main presenting signs and symptoms. The differential diagnosis for Cushing syndrome is discussed in Chapter 577. For virilizing signs, the differential includes virilizing forms of adrenal hyperplasia (see Chapter 576) and factitious exposure to androgens, such as topical testosterone preparations. The differential diagnosis for hormonally inactive adrenocortical adenomas includes pheochromocytomas, adrenocortical carcinoma, and metastasis from an extraadrenal primary carcinoma (very rare in children). Careful history, physical examination, and endocrine evaluation must be performed to seek evidence of autonomous cortisol, androgen, mineralocorticoid, or catecholamine secretion. Not infrequently, a low level of autonomous cortisol secretion is detected that does not cause clinically apparent symptoms; this condition is sometimes referred to as "subclinical" Cushing syndrome.

TREATMENT

Functioning adrenocortical tumors should be removed surgically. There are no data on which to base a recommendation regarding nonfunctioning childhood incidentalomas; in adults, such tumors may be closely observed with imaging and repeat biochemical studies if smaller than 4 cm in diameter, but it is not certain that this is prudent in small children. Adrenalectomy may be performed either transperitoneally or laparoscopically. Some adrenocortical neoplasms are highly malignant and metastasize widely, but cure with regression of masculinizing or Cushingoid features may follow removal of less malignant, encapsulated tumors. Postoperatively, patients should be closely monitored biochemically, with frequent determinations of adrenal androgen levels and imaging studies. Recurrent symptoms or biochemical abnormalities should prompt a careful search for metastatic disease. Metastases primarily involve liver, lung, and regional lymph nodes. The majority of metastatic recurrences appear within 1 yr of tumor resection. Repeat surgical resection of metastatic lesions should be performed if possible and adjuvant therapy instituted. Radiation therapy has not been generally helpful. Antineoplastic agents such as cisplatin and etoposide, ifosfamide and carboplatin, and 5-fluorouracil and leucovorin have had limited use in children, and their success is not established. Therapy with o,p′-DDD (mitotane), an adrenolytic agent, may relieve the symptoms of hypercortisolism or virilization in recurrent disease. Treatment with higher doses of mitotane for more than 6 mo is associated with improved survival. Other agents that interfere with adrenal steroid synthesis, such as ketoconazole, aminoglutethimide, and metyrapone, may also relieve symptoms of steroid excess but do not improve survival.

A neoplasm of 1 adrenal gland may produce atrophy of the other because excessive production of cortisol by the tumor suppresses adrenocorticotropic hormone stimulation of the normal gland. Consequently, adrenal insufficiency may follow surgical removal of the tumor. This situation can be avoided by giving 10-25 mg of hydrocortisone every 6 hr, starting on the day of operation and weaned over 3-4 days postoperatively. Adequate quantities of water, sodium chloride, and glucose also must be provided.

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Chapter 580
Pheochromocytoma
Perrin C. White

Pheochromocytomas are catecholamine-secreting tumors arising from chromaffin cells. The most common site of origin (approximately 90%) is the adrenal medulla; however, tumors may develop anywhere along the abdominal sympathetic chain and are likely to be located near the aorta at the level of the inferior mesenteric artery or at its bifurcation.

They also appear in the periadrenal area, urinary bladder or ureteral walls, thoracic cavity, and cervical region. Ten percent occur in children, in whom they present most frequently between 6 and 14 yr of age. Tumors vary from 1-10 cm in diameter; they are found more often on the right side than on the left. In more than 20% of affected children, the adrenal tumors are bilateral; in 30-40% of children, tumors are found in both adrenal and extraadrenal areas or only in an extraadrenal area.

ETIOLOGY

Pheochromocytomas may be associated with genetic syndromes such as **von Hippel-Lindau disease,** as a component of **multiple endocrine neoplasia** (MEN) syndromes MEN2A and MEN2B, and more rarely in association with **neurofibromatosis (type 1) or tuberous sclerosis.** The classic features of von Hippel-Landau syndrome, which occurs in 1 in 36,000 individuals, include retinal and central nervous system hemangioblastomas, renal clear cell carcinomas, and pheochromocytomas, but kindreds differ in their propensity to develop pheochromocytoma; in some kindreds, pheochromocytoma is the only tumor to develop. Germline mutations in the *VHL* tumor-suppressor gene on chromosome 3p25-26 have been identified in patients with this syndrome. Mutations of the *RET* protooncogene on chromosome 10q11.2 have been found in families with MEN2A and MEN2B. Patients with MEN2 are at risk of developing medullary thyroid carcinoma and parathyroid tumors; approximately 50% develop pheochromocytoma, with patients carrying mutations at codon 634 of the *RET* gene being at particularly high risk. Mutations are present in the *NF1* gene on chromosome 17q11.2 in neurofibromatosis type 1 patients.

Pheochromocytomas may occur in kindreds along with paragangliomas, particularly at sites in the head and neck. Such families typically carry mutations in the *SDHB*, *SDHD*, and, rarely, the *SDHC* genes encoding subunits of the mitochondrial enzyme succinate dehydrogenase.

Pheochromocytomas are also associated with tuberous sclerosis, Sturge-Weber syndrome, and ataxia-telangiectasia. Somatic mutations of the genes mentioned above, particularly *VHL,* have been found in some sporadic cases of pheochromocytoma (see Chapter 596).

CLINICAL MANIFESTATIONS

Pheochromocytomas detected by surveillance of patients who are known carriers of mutations in tumor-suppressor genes may be asymptomatic. Otherwise, patients are detected owing to hypertension, which results from excessive secretion of epinephrine and norepinephrine. All patients have hypertension at some time. Paroxysmal hypertension should particularly suggest pheochromocytoma as a diagnostic possibility, but in contrast to adults, the hypertension in children is more often sustained rather than paroxysmal. When there are paroxysms of hypertension, the attacks are usually infrequent at first, but become more frequent and eventually give way to a continuous hypertensive state. Between attacks of hypertension, the patient may be free of symptoms. During attacks, the patient complains of headache, palpitations, abdominal pain, and dizziness; pallor, vomiting, and sweating also occur. Convulsions and other manifestations of hypertensive encephalopathy may occur. In severe cases, precordial pains radiate into the arms; pulmonary edema and cardiac and hepatic enlargement may develop. Symptoms may be exacerbated by exercise, or with use of nonprescription medications containing stimulants such as pseudoephedrine. Patients have a good appetite but because of the hypermetabolic state may not gain weight, and severe cachexia may develop. Polyuria and polydipsia can be sufficiently severe to suggest diabetes insipidus. Growth failure may be striking. The blood pressure may range from 180-260 mm Hg systolic and from 120-210 mm Hg diastolic, and the heart may be enlarged. Ophthalmoscopic examination may reveal papilledema, hemorrhages, exudate, and arterial constriction.

LABORATORY FINDINGS

The urine may contain protein, a few casts, and occasionally glucose. Gross hematuria suggests that the tumor is in the bladder wall. Polycythemia is occasionally observed. The diagnosis is established by demonstration of elevated blood or urinary levels of catecholamines and their metabolites.

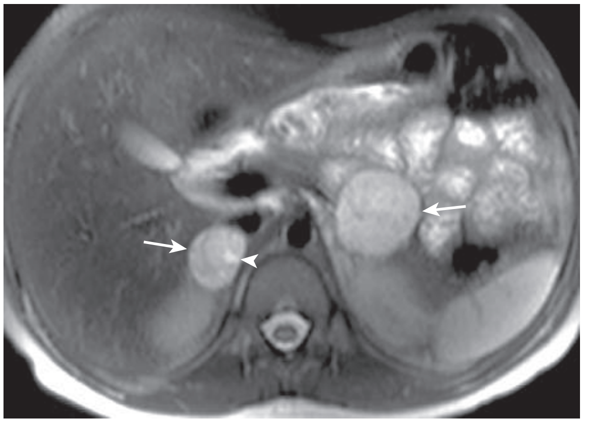

Figure 580-1 Bilateral pheochromocytoma in an 11 yr old boy with von Hippel-Lindau disease and arterial hypertension. An axial fat-suppressed T2-weighted magnetic resonance image shows bilateral adrenal masses *(arrows)*, larger on the left. The masses are hyperintense with small cystic change on the right medially. *(From Navarro OM, Daneman A. Acquired conditions. In Coley BD (ed):* Caffey's pediatric diagnostic imaging, *ed 12, Philadelphia, 2013, Elsevier, Fig. 123-9, p. 1283.)*

Pheochromocytomas produce norepinephrine and epinephrine. Normally, norepinephrine in plasma is derived from both the adrenal gland and adrenergic nerve endings, whereas epinephrine is derived primarily from the adrenal gland. In contrast to adults with pheochromocytoma in whom both norepinephrine and epinephrine are elevated, children with pheochromocytoma predominantly excrete norepinephrine in the urine. Total urinary catecholamine excretion usually exceeds 300 µg/24 hr. Urinary excretion of metanephrines (particularly normetanephrine) is also increased (see Fig. 574-3 in Chapter 574). Daily urinary excretion of these compounds by unaffected children increases with age. Although urinary excretion of vanillylmandelic acid (3-methoxy-4-hydroxymandelic acid), the major metabolite of epinephrine and norepinephrine, is increased, vanilla-containing foods and fruits can produce falsely elevated levels of this compound, which therefore is no longer routinely measured.

Elevated levels of free catecholamines and metanephrines can also be detected in plasma. In children, the best sensitivity and specificity are obtained by measuring plasma normetanephrine using gender-specific pediatric reference ranges, with plasma norepinephrine being next best. Plasma metanephrine and epinephrine are not reliably elevated in children. Additionally, the patient should be instructed to abstain from caffeinated drinks, and to avoid acetaminophen, which can interfere with plasma normetanephrine assays. If possible, the blood sample should be obtained from an indwelling intravenous catheter, to avoid acute stress associated with venipuncture.

Most tumors in the area of the adrenal gland are readily localized by CT or MRI (Fig. 580-1), but extraadrenal tumors may be difficult to detect. ^{123}I-metaiodobenzylguanidine is taken up by chromaffin tissue anywhere in the body and is useful for localizing small tumors. Venous catheterization with sampling of blood at different levels for catecholamine determinations is now only rarely necessary for localizing the tumor.

DIFFERENTIAL DIAGNOSIS

Various causes of hypertension in children must be considered, such as renal or renovascular disease; coarctation of the aorta; hyperthyroidism; Cushing syndrome; deficiencies of 11β-hydroxylase, 17α-hydroxylase, or 11β-hydroxysteroid dehydrogenase (type 2 isozyme); primary aldosteronism; adrenocortical tumors; and, rarely, essential hypertension (see Chapter 445). A nonfunctioning kidney may result

from compression of a ureter or of a renal artery by a pheochromocytoma. Paroxysmal hypertension may be associated with porphyria or familial dysautonomia. Cerebral disorders, diabetes insipidus, diabetes mellitus, and hyperthyroidism must also be considered in the differential diagnosis. Hypertension in patients with neurofibromatosis may be caused by renal vascular involvement or by concurrent pheochromocytoma.

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma frequently produce catecholamines, but urinary levels of most catecholamines are higher in patients with pheochromocytoma, although levels of dopamine and homovanillic acid are usually higher in neuroblastoma. Secreting neurogenic tumors often produce hypertension, excessive sweating, flushing, pallor, rash, polyuria, and polydipsia. Chronic diarrhea may be associated with these tumors, particularly with ganglioneuroma, and at times may be sufficiently persistent to suggest celiac disease.

TREATMENT

These tumors must be removed surgically, but careful preoperative, intraoperative, and postoperative management is essential. Preoperative **α- and β-adrenergic blockade** and **fluid loading** are required. Because these tumors are often multiple in children, a thorough transabdominal exploration of all the usual sites offers the best opportunity to find them all. Appropriate choice of anesthesia and expansion of blood volume with appropriate fluids during surgery are critical to avoid a precipitous drop in blood pressure during operation or within 48 hr postoperatively. Manipulation and excision of these tumors result in marked increases in catecholamine secretion that increase blood pressure and heart rate. Surveillance must continue postoperatively.

Although these tumors often appear malignant histologically, the only accurate indicators of malignancy are the presence of metastatic disease or local invasiveness that precludes complete resection, or both. Approximately 10% of all adrenal pheochromocytomas are malignant. Such tumors are rare in childhood; pediatric malignant pheochromocytomas occur more frequently in extraadrenal sites and are often associated with mutations in the *SDHB* gene encoding a subunit of succinate dehydrogenase. Prolonged follow-up is indicated because functioning tumors at other sites may be manifested many years after the initial operation. Examination of relatives of affected patients may reveal other individuals harboring unsuspected tumors that may be asymptomatic.

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Chapter 581

Adrenal Masses

581.1 Adrenal Incidentaloma

Perrin C. White

Adrenal masses are discovered with increasing frequency in patients undergoing abdominal imaging for reasons unrelated to the adrenal gland. The rate of detection of single adrenal masses has ranged from less than 1% to more than 4% of abdominal CT examinations in adults. The unexpected discovery of such a mass presents the clinician with a dilemma in terms of diagnostic steps to undertake and treatment interventions to recommend. The differential diagnosis of adrenal incidentaloma includes benign lesions such as cysts, hemorrhagic cysts, hematomas, and myelolipomas. These lesions can usually be identified on CT or MRI. If the nature of the lesion is not readily apparent, additional evaluation is required. Included in the differential diagnosis of lesions requiring additional evaluation are benign adenomas, pheochromocytomas, adrenocortical carcinoma, and metastasis from an extraadrenal primary carcinoma. Benign, hormonally inactive adrenocortical adenomas make up the majority of incidentalomas. Careful history, physical examination, and endocrine evaluation must be performed to seek evidence of autonomous cortisol, androgen, mineralocorticoid, or catecholamine secretion. Functional tumors require removal. If the adrenal mass is nonfunctional and larger than 4-6 cm, recommendations are to proceed with surgical resection of the mass. Lesions of 3 cm or less should be followed clinically with periodic reimaging. Treatment must be individualized; nonsecreting adrenal incidentalomas may enlarge and become hyperfunctioning. Nuclear scan, and occasionally fine-needle aspiration, may be helpful in defining the mass.

581.2 Adrenal Calcification

Perrin C. White

Calcification within the adrenal glands may occur in a wide variety of situations, some serious and others of no obvious consequence. Adrenal calcifications are often detected as incidental findings in radiographic studies of the abdomen in infants and children. The physician may elicit a history of anoxia or trauma at birth. Hemorrhage into the adrenal gland at or immediately after birth is probably the most common factor that leads to subsequent calcification (see Fig. 575-1 in Chapter 575). Although it is advisable to assess the adrenocortical reserve of such patients, there is rarely any functional disorder.

Neuroblastomas, ganglioneuromas, cortical carcinomas, pheochromocytomas, and cysts of the adrenal gland may be responsible for calcifications, particularly if hemorrhage has occurred within the tumor. Calcification in such lesions is almost always unilateral.

In the past, tuberculosis was a common cause both of calcification within the adrenals and of Addison disease. Calcifications may also develop in the adrenal glands of children who recover from the Waterhouse-Friderichsen syndrome; such patients are usually asymptomatic. Infants with Wolman disease, a rare lipid disorder caused by a deficiency of lysosomal acid lipase, have extensive bilateral calcifications of the adrenal glands (see Chapter 86.4).

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Section 5

Disorders of the Gonads

Chapter 582

Development and Function of the Gonads

Patricia A. Donohoue

GENETIC CONTROL OF EMBRYONIC GONADAL DIFFERENTIATION

Gonadal differentiation is a complex, multistep process that requires the sequential action and interaction of multiple gene products.

Early in the 1st trimester, the undifferentiated, bipotential fetal gonad begins as a thickening of the urogenital ridge, near the developing kidney and adrenal cortex. At 6 wk of gestation, the gonad contains germ cells, stromal cells that will become Leydig cells in testes, or theca, interstitial, or hilar cells in the ovary; and supporting cells that will develop into Sertoli cells in testes or granulosa cells in ovaries. In males, *SRY* (**s**ex-determining **r**egion on the **Y** chromosome) is transiently expressed, followed by a sequential upregulation of a number of testis-specific genes. SRY may also suppress a putative factor 2 that functions as repressor of male development. In the absence of SRY, the bipotential gonad will be able to develop into an ovary. Ovarian development is also characterized by expression of ovary-specific genes during the same time period. One such gene is *R-spondin1*. During the gestation time period of 6-9 wk, a number of genes are upregulated to the same degree in both the testis and the ovary, including *WNT4* and *CTNNB1*.

A chromosome complement of 46,XX is necessary for the development of **normal ovaries.** Both the long and short arms of the X chromosome contain genes for normal ovarian development. The DSS (**d**osage **s**ensitive/**s**ex reversal) locus associated with the *DAX1* (**D**SS **a**drenal hypoplasia on the **X** chromosome) gene, which is defective in patients with X-linked congenital adrenal hypoplasia and hypogonadotropic hypogonadism, is a member of the nuclear receptor superfamily and acts as a repressor of male gene expression. *DAX1* acts by binding to a related nuclear receptor SF-1 (**s**teroidogenic **f**actor-1). In vitro, the signaling gene *WNT4* stimulates expression of *DAX1,* resulting in the suppression of androgen synthesis in XX females. The WNTs are ligands that activate receptor-mediated signal transduction pathways and are involved in modulating gene expression as well as cell behavior, adhesion, and polarity. A key to its role in humans was elucidated by loss-of-function mutation of the *WNT4* gene that was found in an 18 yr old 46,XX woman. She had absence of müllerian-derived structures (uterus and fallopian tubes), unilateral renal agenesis, and clinical signs of androgen excess.

Mutations of the Wilms tumor 1 *(WT1)* gene, including alternative splicing, may also impact sex differentiation. *WT1* mutations are associated with the **Denys-Drash syndrome** (early-onset renal failure with abnormal external genitalia and Wilms tumor). Haploinsufficiency of a 3-amino-acid (KTS) form of *WT1* has been implicated in the gonadal dysgenesis of patients with **Fraser syndrome** (late-onset progressive glomerulopathy and 46,XY gonadal dysgenesis). Mutations in the *FOXL2* and *SF-1* genes are associated with ovarian failure. Mutation of the *R-spondin1* gene has been described in individuals with 46,XX DSD (**d**isorder of **s**ex **d**evelopment). Other autosomal genes also play a role in normal ovarian organogenesis and testicular development. Several conditions of gonadal dysgenesis are associated with gross abnormalities of both autosomes and sex chromosomes. A deletion affecting the short arm of the X chromosome produces the typical somatic anomalies of Turner syndrome.

Development of the testis requires the short arm of the Y chromosome; this contains the testis-determining factor *SRY* gene. During male meiosis, the Y chromosome must segregate from the X chromosome so that both X and Y chromosomes do not occur in the same spermatozoa. The major portion of the Y chromosome is composed of Y-specific sequences that do not pair with the X chromosome. However, a minor portion of the Y chromosome shares sequences with the X chromosome and pairing does occur in this region. The genes and sequences in this area recombine between the sex chromosomes, behaving like autosomal genes. Therefore, the term *pseudoautosomal region* is used to describe this portion of the chromosome, and the term indicates genetic behavior of these genes relative to pairing and recombinational events. The *SRY* gene is localized to the 35-kb portion proximal to the pseudoautosomal region of the Y chromosome. It contains a high-mobility group (HMG) nonhistone protein (HMG box), supporting SRY's role as a transcriptional regulator of other genes involved in sex differentiation. The gonadal ridge forms at around 33 days of gestation. SRY is detected at 41 days, peaks at 44 days when testis cords are first visible, and persists into adulthood.

Other genes that are found on autosomes are important in this process. *SOX9,* a *SRY*-related gene containing a region homologous with the HMG box 9 of *SRY,* is located on chromosome 17. Mutations of this gene result in XY sex reversal and camptomelic dysplasia. *SF-1* on chromosome 9q33 is important in adrenal and gonadal development, as well as the development of gonadotropin-releasing hormone–secreting neurons in the hypothalamus. *WTI,* especially the KST isoform on chromosome 11p13, is needed for early gonadal, adrenal, and renal development. Fibroblast growth factor-9, GATA-4, XH-2, and SOY9 are also important.

When genetic recombination events on sex chromosomes extend beyond the pseudoautosomal region, X- and Y-specific DNA may be transferred between the chromosomes. Such aberrant recombinations result in X chromosomes carrying *SRY*, resulting in **XX males**, or Y chromosomes that have lost *SRY*, resulting in **XY females.** SRY acts as a transcriptional regulator to increase cellular proliferation, attract interstitial cells from adjacent mesonephros into the genital ridge, and stimulate testicular Sertoli cell differentiation. Sertoli cells act as an organizer of steroidogenic and germ cell lines and produce **antimüllerian hormone** (AMH) that causes the female duct system to regress. Table 582-1 lists additional genes involved in sex development.

Development of the ovary was once thought to be a passive process in the absence of SRY. Although the morphologic changes in the developing ovary are less marked than in the testis, there are a number of sequentially expressed genes and pathways that are required for complete ovarian development as well as maintenance of ovarian integrity postnatally. One of these genes is *R-spondin1*, which if mutated can result in testicular or ovotesticular development in 46,XX individuals. Some peptides in the Wnt-signaling pathway may antagonize testicular development. This effect may be mediated by β-catenin signaling, which is required for suppressing testicular features. Once developed, the ovary requires FAX12 to preserve its differentiation and stability.

FUNCTION OF THE TESTES

Levels of placental chorionic gonadotropin peak at 8-12 wk of gestation and stimulate the fetal Leydig cells to secrete testosterone, the main hormonal product of the testis. In the classical androgen biosynthetic pathway, testosterone is then converted by the enzyme 5α-reductase to its more potent metabolite, dihydrotestosterone. This early period is critical for normal and complete virilization of the XY fetus. Defects in this process lead to different forms of atypical male development (see Chapter 588.2). After virilization occurs, fetal levels of testosterone decrease but are maintained at lower levels in the latter half of pregnancy by luteinizing hormone (LH) secreted by the fetal pituitary; this LH-mediated testosterone secretion is required for continued penile growth, and to some degree also for testicular descent.

As part of the normal transition from intrauterine to extrauterine life, perhaps related to the sudden withdrawal of maternal and placental hormones, newborns and young infants experience a transient surge of gonadotropins and sex steroids. This is the so-called minipuberty.

In males, LH and testosterone peak at 1-2 mo of age and then decline to reach prepubertal levels by 4-6 mo of age. Follicle-stimulating hormone (FSH), along with inhibin B, peak at 3 mo and decline to prepubertal levels by 9 and 15 mo, respectively. The LH rise is more dominant than that of FSH.

The neonatal surge may be important for postnatal maturation of the gonads, stabilization of male external genitalia, and perhaps also for gender identity and sexual behaviors. The postnatal surge in LH and testosterone is absent or blunted in infants with hypopituitarism, cryptorchidism, and complete androgen insensitivity syndrome. The development of nocturnal pulsatile secretion of LH marks the advent of puberty.

Within specific target cells, 6-8% of testosterone is converted by 5α-reductase to dihydrotestosterone, a more potent androgen (Fig. 582-1), and approximately 0.3% is acted on by aromatase to produce estradiol. Approximately half of circulating testosterone is bound to sex hormone–binding globulin and half to albumin; only 2% circulates in the free form. Plasma levels of sex hormone–binding globulin are low at birth, rise rapidly during the 1st 10 days of life, and then remain stable until the onset of puberty. Thyroid hormone may play a role in this

Table 582-1 Genes Known to Be Involved in Disorders of Sex Development (DSd)

GENE	PROTEIN	OMIM DATA BASE NO.	LOCUS	INHERITANCE	GONAD	MÜLLERIAN STRUCTURES	EXTERNAL GENITALS	ASSOCIATED FEATURES/VARIANT PHENOTYPES
46,XY DSD								
Disorders of Gonadal (Testicular) Development: Single-Gene Disorders								
WT1	TF	607102	11p13	AD	Dysgenetic testis	±	Female or ambiguous	Wilms tumor, renal abnormalities, gonadal tumors (WAGR, Denys-Drash, and Frasier syndromes)
SF-1 (NR5A1)	Nuclear receptor TF	184757	9q33	AD/AR	Dysgenetic testis	±	Female or ambiguous	More severe phenotypes include primary adrenal failure; milder phenotypes have isolated partial gonadal dysgenesis; mothers who carry SF-1 mutation have premature ovarian insufficiency
SRY	TF	480000	Yp11.3	Y	Dysgenetic testis or ovotestis	±	Female or ambiguous	
SOX9	TF	608160	17q24-25	AD	Dysgenetic testis or ovotestis	±	Female or ambiguous	Camptomelic dysplasia (17q24 rearrangements milder phenotype than point mutations)
DHH	Signaling molecule	605423	12q13.1	AR	Dysgenetic testis	+	Female	The severe phenotype of 1 patient included monofascicular neuropathy; other patients have isolated gonadal dysgenesis
ATRX	Helicase (?chromatin remodeling)	300032	Xq13.3	X	Dysgenetic testis	–	Female, ambiguous or male	α-Thalassemia, mental retardation
ARX	TF	3003382	Xp22.13	X	Dysgenetic testis	–	Ambiguous	X-linked lissencephaly, epilepsy, temperature instability
Disorders of Gonadal (Testicular) Development: Chromosomal Changes Involving Key Candidate Genes								
DMRT1	TF	602424	9p24.3	Monosomic deletion	Dysgenetic testis	±	Female or ambiguous	Mental retardation
DAX1 (NR0B1)	Nuclear receptor TF	300018	Xp21.3	dupXp21	Dysgenetic testis or ovary	±	Female or ambiguous	
WNT4	Signaling molecule	603490	1p35	dup1p35	Dysgenetic testis	+	Ambiguous	Mental retardation
Disorders in Hormone Synthesis or Action								
LHGCR	G-protein receptor	152790	2p21	AR	Testis	–	Female, ambiguous or micropenis	Leydig cell hypoplasia
DHCR7	Enzyme	602858	11q12-13	AR	Testis	–	Variable	Smith-Lemli-Opitz syndrome: coarse facies, 2nd-3rd toe syndactyly, failure to thrive, developmental delay, cardiac and visceral abnormalities
StAR	Mitochondrial membrane protein	600617	8p11.2	AR	Testis	–	Female	Congenital lipoid adrenal hyperplasia (primary adrenal failure), pubertal failure
CYP11A1	Enzyme	118485	15q23-24	AR	Testis	–	Female or ambiguous	CAH (primary adrenal failure), pubertal failure
HSD3B2	Enzyme	201810	1p13.1	AR	Testis	–	Ambiguous	CAH, primary adrenal failure, partial androgenization caused by ↑DHEA
CYP17A1	Enzyme	202110	10q24.3	AR	Testis	–	Female ambiguous or micropenis	CAH, hypertension caused by ↑corticosterone and 11-deoxycorticosterone (except in isolated 17,20-lyase deficiency)
POR (P450 oxidoreductase)	CYP enzyme electron donor	124015	7q11.2	AR	Testis	–	Male or ambiguous	Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency, and aromatase deficiency; sometimes associated with Antley-Bixler skeletal dysplasia

Continued

Table 582-1 Genes Known to Be Involved in Disorders of Sex Development (DSd)—cont'd

GENE	PROTEIN	OMIM DATA BASE NO.	LOCUS	INHERITANCE	GONAD	MÜLLERIAN STRUCTURES	EXTERNAL GENITALS	ASSOCIATED FEATURES/VARIANT PHENOTYPES
HSD17B3	Enzyme	605573	9q22	AR	Testis	–	Female or ambiguous	Partial androgenization at puberty, ↑androstenedione : testosterone ratio
SRD5A2	Enzyme	607306	2p23	AR	Testis	–	Ambiguous or micropenis	Partial androgenization at puberty, ↑testosterone : DHT ratio
AMH	Signaling molecule	600957	19p13.3-13.2	AR	Testis	+	Normal male	PMDS; male
AMH-receptor	Serine-threonine kinase transmembrane receptor	600956	12q13	AR	Testis	–	Normal male	External genitalia, bilateral cryptorchidism
Androgen receptor	Nuclear receptor TF	3130700	Xq11-12	X	Testis	–	Female, ambiguous, micropenis, or normal male	Phenotypic spectrum from complete androgen insensitivity syndrome (female external genitalia) and partial androgen insensitivity (ambiguous) to normal male genitalia/infertility
AKR1C2	3α-Hydroxysteroid dehydrogenase type III	600450	10p15.1	AR	Testis	–	Ambiguous or female	Originally thought that affected members of this family had isolated 17,20-lyase deficiency (CYP17A1)
46,XX DSD								
Disorders of Gonadal (Ovarian) Development								
SRY	TF	480000	Yp11.3	Translocation	Testis or ovotestis	–	Male or ambiguous	
SOX9	TF	608160	17q24	dup17q24	ND	–	Male or ambiguous	
R-spondin 1	R-spondin	609595	1p34.3		Ovotestis		Ambiguous	Palmoplantar hyperkeratosis
Androgen Excess								
HSD3B2	Enzyme	201810	1p13	AR	Ovary	+	Clitoromegaly	CAH, primary adrenal failure, partial androgenization caused by ↑DHEA
CYP21A2	Enzyme	201910	6p21-23	AR	Ovary	+	Ambiguous	CAH, phenotypic spectrum from severe salt-losing forms associated with adrenal failure to simple virilizing forms with compensated adrenal function, ↑17-hydroxyprogesterone
CYP11B1	Enzyme	20210	8q21-22	AR	Ovary	+	Ambiguous	CAH, hypertension caused by ↑11-deoxycortisol and 11-deoxycorticosterone
POR (P450 oxidoreductase)	CYP enzyme electron donor	124015	7q11.2	AR	Ovary	+	Ambiguous	Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency, and aromatase deficiency; associated with Antley-Bixler skeletal dysplasia
CYP19	Enzyme	107910	15q21	AR	Ovary	+	Ambiguous	Maternal virilization during pregnancy, absent breast development at puberty, except in partial cases
Glucocorticoid receptor	Nuclear receptor TF	138040	5q31	AR	Ovary	+	Ambiguous	↑ACTH, 17-hydroxyprogesterone and cortisol; failure of dexamethasone suppression (patient heterozygous for a mutation in CYP21)

Chromosomal rearrangements likely to include key genes are included.

↑, Increased; ACTH, adrenocorticotropin; AD, autosomal dominant (often de novo mutation); AMH, antimüllerian hormone; AR, autosomal recessive; CAH, congenital adrenal hyperplasia; *DAX1*, dosage sensitive/sex reversal adrenal hypoplasia on the X chromosome; DHEA, dehydroepiandrosterone; DHT, dehydrotestosterone; DSD, disorder of sex development; ND, not determined; PMDS, persistent müllerian duct syndrome; *SF-1*, steroidogenic factor-1; *SRY*, sex-determining region on the Y chromosome; *StAR*, steroidogenic acute regulatory; TF, transcription factor; WAGR, Wilms, aniridia, genital anomalies, and retardation; *WT1*, Wilms tumor 1; X, X-chromosomal; Y, Y-chromosomal.

From Lee PA, Houk CP, Ahmed SF, et al: International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex, Pediatrics *118:e488–e500, 2006.*

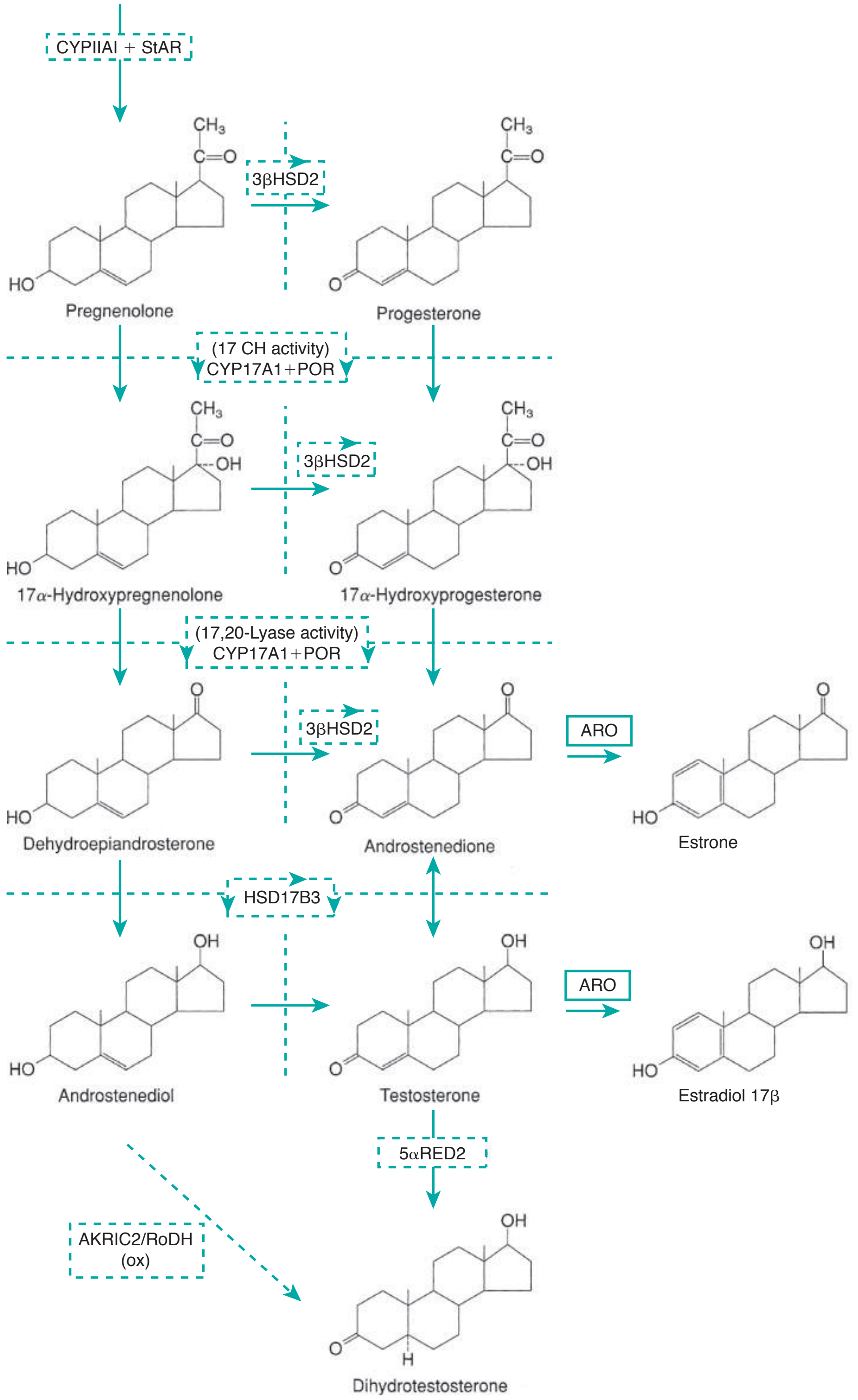

Figure 582-1 Biosynthesis of sex steroids. *Dashed lines* indicate enzymatic defects associated with 46,XY disorder of sex differentiation. *3β-HSD2*, 3β-hydroxysteroid dehydrogenase type 2; *AKR1C2/RoDH (Ox)*, one of the enzymes in the recently described alternative androgen biosynthetic pathway; *ARO*, aromatase; *CYP17A1*, the enzyme that catalyzes both 17α-hydroxylase (17-OH) and 17,20-lyase activities; *HSD17B3*, enzyme that catalyzes the 17-ketoreductase reaction; *POR*, P450 oxidoreductase; *StAR*, steroidogenic acute regulatory protein.

physiologic increase because neonates with athyreosis (absence of the thyroid gland) have very low levels of sex hormone–binding globulin.

AMH (antimüllerian hormone; previously referred to as *müllerian inhibitory substance*), **inhibin**, and **activin** are members of the transforming growth factor-β (TGF-β) superfamily of growth factors. This group, which has more than 45 members, also includes bone morphogenetic proteins. Members of the TGF-β superfamily are involved in the regulation of developmental processes and multiple diverse human disease states, including chondrodysplasias and cancer.

AMH, a homodimeric glycoprotein hormone encoded by a gene on chromosome 19, is the earliest secreted product of the Sertoli cells of the fetal testis. Produced as a prohormone, its carboxyterminal fragment is cleaved to make it active. *AMH* transcription is initiated by *SOX9* acting through the HMG box, while its expression is upregulated by SF-1 binding to its promoter and further interacting with *SOX9*, *WT1*, and *GATA4*. AMH binds to 2 distinct serine/threonine receptors, each having a single transmembrane domain. The activated type 1 receptor signals to the SMAD family of intracellular mediators.

The gene for the AMH receptor (on chromosome 12) is expressed in Sertoli cells. In the female, it is expressed in fetal müllerian duct cells and in fetal and postnatal granulosa cells. During sex differentiation in males, AMH causes involution of the müllerian ducts, which are embryologic precursors of the cervix and uterus. It works in concert with SF-1 to cause involution of the fallopian tubes.

AMH is secreted in males by Sertoli cells during both fetal and postnatal life. In females, it is secreted by granulosa cells from 36 wk of gestation to menopause but at lower levels. The serum concentration of AMH in males is highest at birth, whereas in females it is highest at puberty. After puberty, both sexes have similar serum concentrations of AMH. Its role in postnatal life is not yet fully characterized.

Inhibin is another glycoprotein hormone secreted by the Sertoli cells of the testes and granulosa and theca cells of the ovary. Inhibin A consists of an α-subunit disulfide linked to the β-A subunit, whereas inhibin B consists of the same α subunit linked to the β-B subunit. Activins are dimers of the B subunits, either homodimers (BA/BA, BB/BB) or heterodimers (BA/BB). Inhibins selectively inhibit whereas activins stimulate pituitary FSH secretion. By means of immunoassays specific for inhibin A or B, it has been shown that inhibin A is absent in males and is present mostly in the luteal phase in women. Inhibin B is the principal form of inhibin in males and in females during the follicular phase. Inhibin B may be used as a marker of Sertoli cell function in males. FSH stimulates inhibin B secretion in females and males, but only in males is there also evidence for gonadotropin-independent regulation. Levels of inhibin B are currently being studied in children with various forms of gonadal and pubertal disorders. In males with delayed puberty, inhibin B may be a useful screening test to differentiate between constitutional delay of puberty and hypogonadotropic hypogonadism. In hypogonadotropic hypogonadism, the serum inhibin B level is very low to undetectable.

Like inhibin and activin, follistatin (a single-chain glycosylated protein) is produced by gonads and other tissues such as the hypothalamus, kidney, adrenal gland, and placenta. Follistatin inhibits FSH secretion principally by binding activins, thereby blocking the effects of activins at the level of both ovary and pituitary.

Many additional peptides act as mediators of the development and function of the testis. They include neurohormones such as growth hormone–releasing hormone, gonadotropin-releasing hormone, corticotropin-releasing hormone, oxytocin, arginine vasopressin, somatostatin, substance P, and neuropeptide Y; growth factors such as insulin-like growth factors and insulin-like growth factor–binding proteins, TGF-β, and fibroblast, platelet-derived, and nerve growth factors; vasoactive peptides; and immune-derived cytokines such as tumor necrosis factor and interleukins 1, 2, 4, and 6.

Clinical patterns of pubertal changes vary widely (see Chapters 14 and 561 covering pubertal maturation). In 95% of boys, enlargement of the genitals begins between 9.5 and 13.5 yr of age, reaching maturity at 13-17 yr of age. In a minority of normal boys, puberty begins after 15 yr of age. In some boys, pubertal development is completed in less than 2 yr, but in others it may take longer than 4.5 yr. Pubertal development and the adolescent growth spurt occur at an older age in boys than in girls.

The median age of sperm production (spermarche) is 14 yr. This event occurs in midpuberty as judged by pubic hair, testis size, evidence of growth spurt, and testosterone levels. Nighttime levels of FSH are in the adult male range at the time of spermarche; the first conscious ejaculation occurs at about the same time.

FUNCTION OF THE OVARIES

In the normal female, the undifferentiated gonad can be identified histologically as an ovary by 10-11 wk of gestation, after the upregulation of *R-spondin1*. Oocytes are present from the 4th mo of gestation and reach a peak of 7 million by 5 mo of gestation. For normal maintenance, oocytes need granulosa cells to form primordial follicles. Functional FSH (but not LH) receptors are present in oocytes of primary follicles during follicular development. Normal X chromosomes are needed for maintenance of oocytes. In contrast to somatic cells, in which only 1 X chromosome is active, both Xs are active in germ cells. At birth, the ovaries contain approximately 1 million active follicles, which decrease to 0.5 million by menarche. Thereafter, they decrease at a rate of 1,000/mo, and at an even higher rate after the age of 35 yr.

The hormones of the fetal ovary are provided in most part by the fetoplacental unit. As in males, peak gonadotropin secretion occurs in fetal life and then again at 2-3 mo of life, with the lowest levels at about 6 yr of age. By contrast to males, the FSH surge predominates over LH in females. FSH peaks around 3-6 mo of age, declines by 12 mo, but remains detectable for 24 mo. Under LH influence, estradiol peaks at 2-6 mo of age. The inhibin B response is variable, peaking between 2 and 12 mo and remaining above prepubertal levels until 24 mo. In both infancy and childhood, gonadotropin levels are higher in females than in males.

The most important estrogens produced by the ovary are estradiol-17β (E_2) and estrone (E_1); estriol is a metabolic product of these 2, and all 3 estrogens may be found in the urine of mature females. Estrogens also arise from androgens produced by the adrenal gland and both the female and male gonads (see Fig. 574-1 in Chapter 574). This conversion explains why in certain types of disorders of sex differentiation in males, feminization occurs at puberty. In 17-ketosteroid reductase deficiency, for example, the enzymatic block results in markedly increased secretion of androstenedione, which is converted in the peripheral tissues to estradiol and estrone. These estrogens, in addition to those directly secreted by the testis, result in gynecomastia. Estradiol produced from testosterone in the complete androgen insensitivity syndrome causes complete feminization in XY individuals.

Estrogen regulates a host of functionally different activities in multiple tissues. There are at least 2 distinct estrogen receptors with different expression patterns. The ovary also synthesizes progesterone, the main progestational steroid; the adrenal cortex and testis also synthesize progesterone where it is a precursor for other adrenal and testicular hormones.

A host of other hormones with autocrine, paracrine, and intracrine effects have been identified in the ovary. They include inhibins, activins, relaxin, and growth factors insulin-like growth factor-1, TGF-α and TGF-β, and cytokines.

Plasma levels of estradiol increase slowly but steadily with advancing sexual maturation and correlate well with clinical evaluation of pubertal development, skeletal age, and rising levels of FSH. Levels of LH do not rise until secondary sexual characteristics are well developed. Estrogens, like androgens, inhibit secretion of both LH and FSH (negative feedback). In females, estrogens also provoke the surge of LH secretion that occurs in the mid–menstrual cycle. The capacity for this positive feedback is another maturational milestone of puberty.

The average age at menarche in American girls is approximately 12.5-13 yr, but the range of "normal" is wide, and 1-2% of normal girls have not menstruated by 16 yr of age. The age at onset of pubertal signs varies, with recent studies suggesting earlier ages than previously thought, especially in the U.S. African-American population (see Chapter 561). Menarche generally correlates closely with skeletal age. Maturation and closure of the epiphyses is at least partially estrogen dependent, as demonstrated by a very tall 28 yr old, normally masculinized male with continued growth as a result of incomplete closure of the epiphyses, who proved to have complete estrogen insensitivity caused by an estrogen-receptor defect.

DIAGNOSTIC TESTING

Improved, sensitive, and specific assays for pituitary and gonadal hormones that can be measured in small amounts of blood have contributed to rapid advances in the understanding of normal and abnormal hypothalamic-pituitary-gonadal interactions. In male infants, measurements of LH, FSH, and testosterone can detect pituitary and testicular defects. Leydig cell integrity in childhood can be determined by the testosterone response following human chorionic gonadotropin administration. (One protocol is to use 5,000 IU IM daily for 3 days; other protocols are available.) The integrity, as well as the maturity, of the hypothalamic-pituitary-gonadal axis in males and females can be assessed by measuring serial sex steroid, LH, and FSH levels after the subcutaneous administration of the gonadotropin-releasing hormone analog leuprolide. An ultrasensitive LH assay has been shown to

differentiate between boys with delayed puberty and those with complete, but not partial, hypogonadotropic hypogonadism.

The normal range for inhibin B levels has been established in infant boys. Inhibin B may be a marker of spermatogenesis and also of tumors such as granulosa cell tumors. Inhibin may be involved in tumor suppression. Estrogen-receptor assays may be clinically useful in the management of various ovarian cancers. AMH measurements are useful in the evaluation of children with nonpalpable gonads and disorders of sex development.

THERAPEUTIC USE OF SEX STEROIDS

The estrogenic effects of polyhalogenated aromatic hydrocarbons may in part be a result of inhibition of estradiol sulfation by estrogen sulfotransferase, an important pathway of estradiol inactivation. Naturally occurring estrogens administered orally are rapidly destroyed by gastrointestinal and liver enzymes; accordingly, they are usually given as conjugates or esters. The most widely used oral preparations are equine conjugated estrogens (Premarin) and ethinyl estradiol. Estrogen-containing skin patches for transdermal absorption are also used. With improvements in the understanding of estrogen and estrogen-receptor interactions, a new class of compounds called *selective estrogen-receptor modulators* has been synthesized. For example, raloxifene, a nonsteroidal benzothiophene derivative, acts as an estrogen agonist in bone and liver and as an estrogen antagonist in breast and uterus.

Androgens, such as testosterone, are generally injected intramuscularly as long-acting esters (enanthate or cypionate, most commonly) because of their potency and steady response. Transdermal testosterone patches and a cutaneously applied gel have to date been used mostly in adults with hypogonadism because of the difficulty in titrating the doses needed during childhood and adolescence. Oral preparations, such as methyltestosterone or fluoxymesterone, do not produce so potent an androgenic response and may be hepatotoxic. Testosterone undecenoate, another oral preparation, is used in Europe but not in the United States. Sublingual (microspheres or pellets) and buccal (absorption via the buccal mucosa) preparations of testosterone are in development.

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Chapter 583
Hypofunction of the Testes

Omar Ali and Patricia A. Donohoue

Testicular hypofunction during fetal life can be a component of some types of **disorders of sex development** (see Chapter 588.2) and may lead to varying degrees of ambiguous genitalia. After birth, neonates undergo "minipuberty" with relatively high levels of gonadotropins and sex steroids, but this phenomenon is transient and its absence does not lead to any obvious clinical findings. Because prepubertal children normally do not produce significant amounts of testosterone and are not yet producing sperm, there are no discernible effects of testicular hypofunction in this age group. Testicular hypofunction from the age of puberty onward may lead to testosterone deficiency, infertility, or both. Such hypofunction may be primary in the testes **(primary hypogonadism)** or secondary to deficiency of pituitary gonadotropic hormones **(secondary hypogonadism).** Both types may be caused by inherited genetic defects or acquired causes, and in some cases the etiology may be unclear, but the level of the lesion (primary or secondary) is usually well defined; patients with primary hypogonadism have elevated levels of gonadotropins (hypergonadotropic); those with secondary hypogonadism have inappropriately low or absent levels

Table 583-1	Etiologic Classification of Male Hypogonadism
HYPERGONADOTROPIC HYPOGONADISM (PRIMARY HYPOGONADISM; TESTES) ***Congenital*** Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) resistance Mutations in steroid synthetic pathways Gonadal dysgenesis Klinefelter syndrome (47,XXY) Noonan syndrome (*PTPN-11* gene mutation in many cases) Cystic fibrosis (infertility) ***Acquired*** Cryptorchidism (some cases) Vanishing testes Chemotherapy Radiation Infection (e.g., mumps) Infarction (testicular torsion) Trauma	
HYPOGONADOTROPIC HYPOGONADISM (SECONDARY HYPOGONADISM; HYPOTHALAMIC-PITUITARY) ***Congenital*** Genetic defects causing Kallmann syndrome and/or normosmic hypogonadotropic hypogonadism (HH) Other genetic disorders associated with HH: leptin gene, leptin receptor, DAX1 (dosage-sensitive/sex-reversal adrenal hypoplasia on the X chromosome), SF-1 (steroidogenic factor-1) Inherited syndromes: Prader-Willi, Bardet-Biedl, Laurence-Moon-Biedl, Alström Isolated HH at pituitary level (gonadotropin-releasing hormone receptor, FSH and LH β-subunit) Multiple pituitary hormone deficiencies: septooptic dysplasia (*HESX-1* in some cases) and other disorders of pituitary organogenesis (e.g., *PROP1, LHX3, LHX4, SOX-3*) Idiopathic ***Acquired*** Anorexia nervosa Drug use Malnutrition Chronic illness, especially Crohn disease Hyperprolactinemia Pituitary tumors Pituitary infarction Infiltrative disorders (e.g., histiocytosis, sarcoidosis) Hemosiderosis and hemochromatosis Radiation	

(hypogonadotropic). Table 583-1 details the etiologic classification of male hypogonadism.

583.1 Hypergonadotropic Hypogonadism in the Male (Primary Hypogonadism)

Omar Ali and Patricia A. Donohoue

ETIOLOGY

Some degree of testicular function is essential in the development of phenotypically male newborns. If testicular function is present, sex differentiation is normally complete by the 14th wk of intrauterine life. Hypogonadism may occur after phenotypically male genitalia have developed for a variety of reasons; genetic or chromosomal anomalies may lead to testicular hypofunction that does not become apparent until the time of puberty, when these boys may have delayed or incomplete pubertal development. In other cases, normally developed testes may be damaged by infarction, trauma, radiation, chemotherapy, infections, infiltration, or other causes after sexual differentiation has occurred. In some cases, genetic defects may predispose to atrophy or maldescent; or torsion or infarction or may lead to progressive testicular damage and atrophy after a period of normal development. If testicular compromise is global, both testosterone secretion and fertility

(sperm production) are likely to be affected. Even when the primary defect is in testosterone production, low levels of intratesticular testosterone will frequently lead to infertility. The reverse is not necessarily true. Defects in sperm production and in the storage and transit of sperm may not be associated with low testosterone levels; infertility may thus be seen in patients with normal testosterone levels, normal libido, and normal secondary sexual characteristics.

Various degrees of primary hypogonadism also occur in a significant percentage of patients with chromosomal aberrations as in **Klinefelter syndrome, males with more than one X chromosome**, and **XX males.** These chromosomal anomalies are associated with other characteristic findings. Noonan syndrome is associated with cryptorchidism and infertility, but other (nongonadal) features dominate its clinical picture.

Congenital Anorchia or Testicular Regression Syndrome

Boys in whom the external genitalia have developed normally (or nearly normally) and müllerian duct derivatives (uterus, fallopian tubes) are absent have obviously had testicular function for at least some part of gestation. If their testes cannot be palpated at birth, they are said to have **cryptorchidism.** In most such cases, the testes are undescended or retractile, but in some cases no testes are found in any location, even after extensive investigation. This syndrome of absence of testes in a phenotypic male with normal 46,XY karyotype (indicating that there was some period of testicular function in intrauterine life) is known as "vanishing testes," "congenital anorchia," or **"testicular regression syndrome."**

Testicular regression syndrome is not uncommon. Cryptorchidism occurs in 1.5-9% of male births and in 10-20% of these cases, the testes are impalpable. Of children with impalpable testes, up to 50% may have no detectable testes after extensive investigation. Most cases appear to be sporadic and are thought to be a result of torsion or vascular accidents. The incompletely descended testis may be more prone to torsion and this may be one of the causes of "vanishing testes." Most cases are sporadic but in a subset of patients testicular regression syndrome occurs in monozygotic twins or in families with other affected individuals, suggesting a genetic etiology. Some cases are associated with micropenis and in these cases the testicular loss probably occurred after the 14th wk, but well before the time of birth, or this may indicate a preexisting dysfunction of male hormonal development. Low levels of testosterone (<10 ng/dL) and markedly elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are found in the early postnatal months; thereafter, levels of gonadotropins tend to decrease even in agonadal children, rising to very high levels again as the pubertal years approach. Stimulation with human chorionic gonadotropin (hCG) fails to evoke an increase in the level of testosterone. Serum levels of antimüllerian hormone (AMH) are undetectable or low. All patients with undetectable testes should be tested for AMH and should undergo an hCG stimulation test. If the results indicate that no testicular tissue is present (absent AMH and no rise in testosterone after hCG stimulation), then the diagnosis of testicular regression syndrome is confirmed. If testosterone secretion is demonstrated, then imaging with abdominal MRI and/or surgical exploration is indicated. A small fibrotic nodule may be found at the end of the spermatic cord in many cases of testicular regression syndrome. Treatment of male hypogonadism (primary or secondary) is discussed in Chapter 583.2. There is no possibility of normal fertility in these patients.

Chemotherapy and Radiation-Induced Hypogonadism

Testicular damage is a frequent consequence of **chemotherapy** and **radiotherapy** for cancer. The frequency and extent of damage depend on the agent used, total dose, duration of therapy, and posttherapy interval of observation. Another important variable is age at therapy; germ cells are less vulnerable in prepubertal than in pubertal and postpubertal boys. **Chemotherapy** is most damaging if more than 1 agent is used. The use of alkylating agents such as cyclophosphamide in prepubertal children does not impair pubertal development, even though there may be biopsy evidence of germ cell damage. High doses of cyclophosphamide and ifosfamide are associated with infertility. Cisplatin causes transient azoospermia or oligospermia at lower doses, while higher doses (400-600 mg/m^2) can cause permanent infertility. Interleukin 2 can depress Leydig cell function, whereas interferon-α does not seem to affect gonadal function. Most chemotherapeutic agents produce azoospermia and infertility; Leydig cell damage (leading to low testosterone levels) is less common. In many cases, the damage is transient and sperm counts recover after 12-24 mo. Both chemotherapy and radiotherapy are associated with an increase in the percentage of abnormal gametes, but data concerning the outcomes of pregnancies after such therapy have *not* shown any increase in genetically mediated birth defects, possibly because of selection bias against abnormal sperm.

Radiation damage is dose dependent. Temporary oligospermia can be seen with doses as low as 0.1 Gy, with permanent azoospermia seen with doses greater than 2 Gy. Recovery of spermatogenesis can be seen as long as 5 yr (or more) after irradiation, with higher doses leading to slower recovery. Leydig cells are more resistant to irradiation. Mild damage as determined by elevated LH levels can be seen with up to 6 Gy; doses greater than 30 Gy cause hypogonadism in most patients. Whenever possible, testes should be shielded from irradiation. Testicular function should be carefully evaluated in adolescents after multimodal treatment for cancer in childhood. Replacement therapy with testosterone and counseling concerning fertility may be indicated. The storage of sperm prior to chemotherapy or radiation treatment in postpubertal males is an option. Even in those cases where sperm counts are abnormal, recovery is possible, though the chances of recovery decline with increasing dose of radiation. If sperm counts remain low, fertility is still possible in some cases with testicular sperm extraction and intracytoplasmic sperm injection.

Sertoli Cell–Only Syndrome

Small testes and azoospermia are seen in patients with the extremely rare Sertoli cell–only syndrome (germ cell aplasia, or **Del Castillo syndrome**). These patients have no germ cells in the testes, but usually have normal testosterone production, and present as adults with the complaint of infertility. Most cases are sporadic and idiopathic, but deletions involving the azoospermia factor (AZF) region of the Y chromosome (Yq11) may be found in some cases.

Other Causes of Testicular Hypofunction

Atrophy of the testes may follow damage to the vascular supply as a result of manipulation of the testes during surgical procedures for correction of cryptorchidism or as a result of bilateral torsion of the testes. **Acute orchitis** is common in pubertal or adult males with mumps and may lead to subfertility in 13% of cases, though infertility is rare. Testosterone secretion usually remains normal. The incidence of mumps orchitis in postpubertal males has increased in some areas as a result of decrease in measles, mumps, and rubella vaccination uptake. Autoimmune polyendocrinopathy may be associated with primary hypogonadism (associated with anti-P450scc antibodies) but this appears to be more common in females.

Testicular Dysgenesis Syndrome

The incidence of testicular cancer has increased in many developed societies while the incidence of cryptorchidism, hypospadias, low sperm counts, and sperm abnormalities also appears to have increased in some, but not all, studies. It has been proposed that all these trends are linked by prenatal testicular dysgenesis. The hypothesis is that some degree of testicular dysgenesis develops in intrauterine life from genetic as well as environmental factors, and is associated with increased risk of cryptorchidism, hypospadias, hypofertility, and testicular cancer. The environmental influences that have been implicated in this syndrome include environmental chemicals that act as endocrine disruptors, such as bisphenol A and phthalates (components of many types of plastics), several pesticides, phytoestrogens or mycoestrogens, and other chemicals. The fact that these lesions can be reproduced in some animal models by environmental chemicals has led to efforts to remove

these chemicals from products used by infants and pregnant mothers, and from the environment in general. Nonetheless, the evidence is only suggestive and is not conclusive.

CLINICAL MANIFESTATIONS

Primary hypogonadism may be suspected at birth if the testes and penis are abnormally small. Normative data are available for different populations. The condition often is not noticed until puberty, when secondary sex characteristics fail to develop. Facial, pubic, and axillary hair is scant or absent; there is neither acne nor regression of scalp hair; and the voice remains high pitched. The penis and scrotum remain infantile and may be almost obscured by pubic fat; the testes are small or not palpable. Fat accumulates in the region of the hips and buttocks and sometimes in the breasts and on the abdomen. The epiphyses close later than normal; therefore, extremities are long. The span may be several inches longer than the height, and the distance from the symphysis pubis to the soles of the feet (lower segment) is much greater than that from the symphysis to the vertex (upper segment). The proportions of the body are described as **eunuchoid.** The upper to lower segment ratio is considerably less than 0.9. Many individuals with milder degrees of hypogonadism may be detected only by appropriate studies of the pituitary-gonadal axis. Examination of the testes should be performed routinely by pediatricians; testicular volumes as determined by comparison with standard orchidometers or by measurement of linear dimensions should be recorded.

DIAGNOSIS

Levels of serum FSH and, to a lesser extent, of LH are elevated to greater than age-specific normal values in early infancy (when "minipuberty" normally occurs and the gonadotropins are normally disinhibited). This is followed by a period of time when even agonadal children may not exhibit significant elevation in gonadotropins, indicating that the gonadotropins are also suppressed at this stage by some mechanism independent of feedback inhibition by gonadal hormones. In the latter half of childhood and several years prior to the onset of puberty, this inhibition is released and gonadotropin levels again rise above age-matched normals in subjects with primary hypogonadism. These elevated levels indicate that even in the prepubertal child there is an active hypothalamic-gonadal feedback relationship. After the age of 11 yr, FSH and LH levels rise significantly, reaching the castrate range. Measurements of random plasma testosterone levels in prepubertal boys are not helpful because they are ordinarily low in normal prepubertal children, rising during puberty to attain adult levels. During puberty, these levels, when measured in an early-morning blood sample, correlate better with testicular size, stage of sexual maturity, and bone age than with chronological age. In patients with primary hypogonadism, testosterone levels remain low at all ages. There is an attenuated rise or no rise at all after administration of hCG, in contrast to normal males in whom hCG produces a significant rise in plasma testosterone at any stage of development.

AMH is secreted by the Sertoli cells and this secretion is suppressed by testosterone. As a result, AMH levels are elevated in prepubertal boys and suppressed at onset of puberty. Boys with primary hypogonadism continue to have elevated AMH levels in puberty. Detection of AMH may be used in prepubertal years as an indicator of the presence of testicular tissue (e.g., in patients with bilateral cryptorchidism). Inhibin B is also secreted by the Sertoli cells, is present throughout childhood, and rises at onset of puberty (more in boys than in girls). It may be used as another marker of the presence of testicular tissue in bilateral cryptorchidism and as a marker of spermatogenesis (e.g., in delayed puberty, cancer survivors, and patients with Noonan syndrome). Bone age x-rays are useful to document delayed bone age in patients with constitutional growth delay as well as primary hypogonadism.

NOONAN SYNDROME

Etiology

The term *Noonan syndrome* has been applied to males and females with normal karyotypes who have certain phenotypic features that occur also in females with Turner syndrome (although the genetic causes are completely distinct) (see Chapter 81.4). Noonan syndrome occurs in 1 in 1,000-2,500 live births. Approximately 20% of the cases are familial and exhibit autosomal dominant inheritance. Males and females are equally affected. It is now thought that several mutations in the renin–angiotensin system (RAS)–mitogen-activated protein kinase (MAPK) pathway can cause Noonan syndrome and other related disorders and such mutations are currently detected in approximately 70% of the cases of Noonan syndrome. Missense mutations in *PTPN11*—a gene on chromosome 12q24.1 encoding the nonreceptor protein tyrosine phosphatase SHP-2—are seen in about half the cases. Mutations in other genes in this pathway, including *SHOC2*, *CBL*, *SOS1*, *KRAS*, *NRAS*, *BRAF*, and *RAF1*, as well as duplications of the 12q24 region, are also seen. Phenotypic features of Noonan syndrome therefore overlap with other syndromes involving the RAS-MAPK pathway, such as Leopard syndrome and cardiofaciocutaneous syndrome.

Clinical Manifestations

The most common abnormalities are short stature, webbing of the neck, pectus carinatum or pectus excavatum, cubitus valgus, right-sided congenital heart disease, and characteristic facies. Hypertelorism, epicanthus, downward-slanting palpebral fissures, ptosis, micrognathia, and ear abnormalities are common. Other abnormalities such as clinodactyly, hernias, and vertebral anomalies occur less frequently. As opposed to Turner syndrome, the mean IQ of school-age children with Noonan syndrome is subnormal at 86, with a range of 53-127. Verbal IQ tends to be better than performance IQ. High-frequency sensorineural hearing loss is common. The cardiac defect is most often pulmonary valvular stenosis, hypertrophic cardiomyopathy, or atrial septal defect. Hepatosplenomegaly and several hematologic diseases, including low clotting factors XI and XII, acute lymphoblastic leukemia, and chronic myelomonocytic leukemia, are noted. Noonan-like features can be part of the phenotypic variation of the *NF1* (neurofibromatosis) gene mutation, possibly as a result of common involvement of the RAS-MAPK pathway in both diseases. Males frequently have cryptorchidism and small testes. Testosterone secretion may be low or normal, but spermatogenesis may be affected even in those with normal testosterone (and normal secondary sexual characteristics). Serum inhibin-B is a useful marker of Sertoli cell function in these patients. Puberty is delayed and adult height is achieved by the end of the 2nd decade and usually reaches the lower limit of the normal population. Prenatal diagnosis should be suspected in fetuses with normal karyotype, edema, or hydrops and short femur length.

Treatment

Human growth hormone results in improvement in growth velocity in many Noonan syndrome patients, comparable to that seen in patients with Turner syndrome, and studies show a mean increase in height standard deviation score ranging from 1.3-1.7, corresponding to 9.5-13 cm for boys and 9.0-9.8 cm for girls. Many patients with Noonan syndrome reach normal height without growth hormone therapy, but treatment is recommended for those who fall below the 3rd percentile for height. The recommended dose is up to 66 µg/kg/day of recombinant growth hormone. Patients with Noonan syndrome and demonstrable *PTNP11* mutations grow less well and are less responsive to growth hormone treatment than those without mutations. They have lower insulin-like growth factor-1 and higher growth hormone levels, suggesting partial growth hormone resistance because of post–receptor-signaling defects. Treatment of male hypogonadism is discussed in Chapter 583.2.

KLINEFELTER SYNDROME

See also Chapter 81.

Etiology

Klinefelter syndrome is the most common sex chromosomal aneuploidy in males, with an incidence of 0.1-0.2% in the general population (1 in 500-1,000) and rising to 4% among infertile males and 10-11% in those with oligospermia or azoospermia. Approximately 80% of them have a 47,XXY chromosome complement, while mosaics

and higher degrees of polyX are seen in the remaining 20%. Even with as many as 4 X chromosomes, the Y chromosome determines a male phenotype. The chromosomal aberration most often results from meiotic nondisjunction of an X chromosome during parental gametogenesis; the extra X chromosome is maternal in origin in 54% and paternal in origin in 46% of patients. A national study in Denmark revealed a prenatal prevalence of 213 per 100,000 male fetuses, but in adult men the prevalence was only 40 per 100,000, suggesting that only 1 in 4 of adult males with Klinefelter syndrome was diagnosed.

Clinical Manifestations

In patients who do not have a prenatal diagnosis, the diagnosis is rarely made before puberty because of the paucity or subtleness of clinical manifestations in childhood. Behavioral or psychiatric disorders may be apparent long before defects in sexual development. These children tend to have learning disabilities and deficits in "executive function" (concept formation, problem solving, task switching, and planning), and the condition should be considered in boys with psychosocial, learning, or school adjustment problems. Affected children may be anxious, immature, or excessively shy and tend to have difficulty in social interactions throughout life. In a prospective study, a group of children with 47,XXY karyotypes identified at birth exhibited relatively mild deviations from normal during the 1st 5 yr of life. None had major physical, intellectual, or emotional disabilities; some were inactive, with poorly organized motor function and mild delay in language acquisition. Problems often first become apparent after the child begins school. Full-scale IQ scores may be normal, with verbal IQ being somewhat decreased. Verbal cognitive defects and underachievement in reading, spelling, and mathematics are common. By late adolescence, many boys with Klinefelter syndrome have generalized learning disabilities, most of which are language based. Despite these difficulties, most complete high school.

The patients tend to be tall, slim, and have a specific tendency to have long legs (disproportionate to the arms, and longer than those seen with other causes of hypogonadism), but body habitus can vary markedly. The testes tend to be small for age, but this sign may become apparent only after puberty, when normal testicular growth fails to occur. The phallus tends to be smaller than average, and cryptorchidism is more common than in the general population. Bone mineral density may be low in adults with Klinefelter syndrome and this correlates with lower testosterone levels.

Pubertal development may be delayed, although some children undergo apparently normal or nearly normal virilization. Despite normal testosterone levels, serum LH and FSH concentrations and their responses to gonadotropin-releasing hormone (GnRH) stimulation are elevated starting at around 13 yr of age. Approximately 80% of adults have **gynecomastia;** they have sparser facial hair, most shaving less often than daily. The most common testicular lesions are spermatogenic arrest and Sertoli cell predominance. The sperm have a high incidence of sex chromosomal aneuploidy. Azoospermia and infertility are usual, although rare instances of fertility are known. It is now clear that germ cell numbers and sperm counts are higher in early puberty and decline with age. Testicular sperm extraction followed by intracytoplasmic sperm injection can result in the birth of healthy infants, with success rates declining with increasing age. In nonmosaic Klinefelter patients, most testicular sperm (94%) have a normal pattern of sex chromosome segregation, indicating that meiotic checkpoints can remove most aneuploid cells. Antisperm antibodies have been detected in 25% of tested specimens.

There is an increased incidence in adulthood of central adiposity, metabolic syndrome, pulmonary disease, varicose veins, and cancer of the breast. Among 93 unselected **male breast cancer** patients, 7.5% were found to have Klinefelter syndrome. Mediastinal germ cell tumors have been reported; some of these tumors produce hCG and cause precocious puberty in young boys. They may also be associated with leukemia, lymphoma, and other hematologic neoplasia. The highest cancer risk (relative risk: 2.7) occurs in the 15-30 yr age group. A large cohort study in Britain demonstrated an overall significantly increased standardized mortality ratio (1.5), with particular increases in deaths from diabetes, epilepsy, peripheral and intestinal vascular sufficiency, pulmonary embolism, and renal disease. Mortality from ischemic heart disease was decreased. In adults, structural brain abnormalities correlate with cognitive deficits.

In adults with XY/XXY mosaicism, the features of Klinefelter syndrome are decreased in severity and frequency. Children with mosaicism have a better prognosis for virilization, fertility, and psychosocial adjustment.

Klinefelter Variants and Other Poly-X Syndromes

When the number of X chromosomes exceeds 2, the clinical manifestations, including mental retardation and impairment of virilization, are more severe. Height decreases with increasing number of X chromosomes. The XXYY variant is the most common variant (1 in 18,000-40,000 male births). In most, mental retardation occurs with IQ scores between 60 and 80, but 10% have IQs greater than 110. The XXYY male phenotype is not distinctively different from that of the XXY patient, except that XXYY adults tend to be taller than the average XXY patient. The 49,XXXXY variant is sufficiently distinctive to be detected in childhood. Its incidence is estimated to be 1 in 80,000-100,000 male births. The disorder arises from sequential nondisjunction in meiosis. Affected patients are severely cognitively impaired and have short necks and typical coarse facies with wide-set eyes with a mild upward slant of the fissures, epicanthus, strabismus, a wide and flat upturned nose, a large open mouth, and large malformed ears. The testes are small and may be undescended, the scrotum is hypoplastic, and the penis is very small. Defects suggestive of Down syndrome (short, incurved terminal 5th phalanges, single palmar creases, and hypotonia) and other skeletal abnormalities (including defects in the carrying angle of the elbows and restricted supination) are common. The most frequent radiographic abnormalities are radioulnar synostosis or dislocation, elongated radius, pseudoepiphyses, scoliosis or kyphosis, coxa valga, and retarded osseous age. Most patients with such extensive changes have a 49,XXXXY chromosome karyotype; several mosaic patterns have also been observed: 48,XXXY/49,XXXXY; 48,XXXY/49,XXXXY/50,XXXXXY; and 48,XXXY/49,XXXXY/50,XXXXYY. Prenatal diagnosis of a 49,XXXXY infant has been reported. The fetus had intrauterine growth retardation, edema, and cystic hygroma colli.

The 48,XXXY variant is relatively rare. The characteristic features are generally less severe than those of patients with 49,XXXXY and more severe than those of 47,XXY patients. Mild intellectual disability, delayed speech and motor development, and immature but passive and pleasant behavior are associated with this condition.

Very few patients have been described with 49,XYYY and 49,XXYYY karyotypes. Dysmorphic features and cognitive impairment are common to both.

Laboratory Findings

Most males with Klinefelter syndrome go through life undiagnosed. The chromosomes should be examined in all patients suspected of having Klinefelter syndrome, particularly those attending child guidance, psychiatric, and cognitive disability clinics. In infancy, inhibin B and AMH levels are normal but testosterone levels are lower than in controls. Before 10 yr of age, boys with 47,XXY Klinefelter syndrome have normal basal plasma levels of FSH and LH. Responses to gonadotropin-stimulating hormone and to hCG are normal. The testes show normal growth early in puberty, but by midpuberty the testicular growth stops, gonadotropins become elevated, and testosterone levels are slightly low. Inhibin B levels are normal in early puberty, decrease in late puberty, and are low in adults with the syndrome. Elevated levels of estradiol, resulting in a high estradiol to testosterone ratio, account for the development of gynecomastia during puberty. Sex hormone–binding globulin levels are elevated, further decreasing free testosterone levels. Long androgen receptor polyglutamine (CAG) repeat length is associated with the more-severe phenotype, including gynecomastia, small testes, and short penile length.

Testicular biopsy before puberty may reveal only deficiency or absence of germinal cells. After puberty, the seminiferous tubular membranes are hyalinized, and there is adenomatous clumping of Leydig cells. Sertoli cells predominate. Azoospermia is characteristic, and infertility is the rule.

Management

Boys known to have Klinefelter syndrome should be monitored closely for speech, learning, and behavioral problems, and referred for early evaluation and treatment as needed. Testosterone, LH, and FSH levels should be checked at 11-12 yr of age and replacement therapy with a testosterone preparation is recommended once FSH and LH begin to rise above normal. Fasting glucose, lipids, and hemoglobin A_{1C} should also be obtained as these children are at risk for central adiposity and metabolic syndrome. A baseline dual-energy x-ray absorptiometry scan to assess bone density is also recommended by some authorities. Although testosterone treatment will normalize testosterone levels, stimulate the development of secondary sexual characteristics, increase bone mass and muscle mass, and improve body composition, it will *not* improve fertility (and will, in fact, suppress spermatogenesis). There is some evidence that it also improves mood and may have a positive effect on cognition and social functioning but the findings are not conclusive at this time. Either long-acting testosterone injections or daily application of testosterone gel may be used (testosterone patches have a high incidence of skin rash and are not frequently used in pediatrics). Testosterone enanthate or cypionate ester may be used in a starting dose of 25-50 mg injected intramuscularly every 3-4 wk, with 50-mg increments every 6-9 mo until a maintenance dose for adults (200-250 mg every 3-4 wk) is achieved. At that time, testosterone patches or testosterone gel may be substituted for the injections. Depending on patient and physician preference, transdermal testosterone may also be used as initial treatment instead of injections. For older boys, larger initial doses and increments can achieve more rapid virilization. The various transdermal preparations differ somewhat from each other and standard references should be consulted for recommendations regarding dosage and mode of application.

Gynecomastia may be treated with aromatase inhibitors (which will also increase endogenous testosterone levels) but medical treatment is not always successful and plastic surgery may be needed. Fertility is usually not an issue in the pediatric age group, but adults can father children using testicular sperm extraction followed by intracytoplasmic sperm injection. Because sperm counts decrease rapidly after onset of puberty in children with Klinefelter syndrome, sperm banking during early puberty is an option that can be discussed with a fertility specialist. Sperm counts can be stimulated using hCG treatment prior to testicular sperm extraction. Therapy, counseling and psychiatric services should be provided as needed for learning difficulties and psychosocial disabilities.

XX MALES

This disorder is thought to occur in 1 in 20,000 newborn males. Affected individuals have a male phenotype, small testes, a small phallus, and no evidence of ovarian or müllerian duct tissue. They appear, therefore, to be distinct from the ovotesticular disorder of sexual development. Undescended testes and hypospadias occur in a minority of patients. Infertility occurs in practically all cases and the histologic features of the testes are essentially the same as in Klinefelter syndrome. Patients with the condition usually come to medical attention in adult life because of hypogonadism, gynecomastia, or infertility. Hypergonadotropic hypogonadism occurs secondary to testicular failure. A few cases have been diagnosed perinatally as a result of discrepancies between prenatal ultrasonography and karyotype findings.

In 90% of XX males with normal male external genitalia, 1 of the X chromosomes carries the *SRY* (sex-determining region on the Y chromosome) gene. The exchange from the Y to the X chromosome occurs during paternal meiosis, when the short arms of the Y and X chromosomes pair. XX males inherit 1 maternal X chromosome and 1 paternal X chromosome containing the translocated male-determining gene. A few cases of 46,XX males with 9P translocations have also been identified. Most XX males who are identified before puberty have hypospadias or micropenis; this group of patients may lack Y-specific sequences, suggesting other mechanisms for virilization. Fluorescent in situ hybridization and primed in situ labeling have been used to identify small *SRY* DNA segments. Yp fragment abnormalities may result in sexually ambiguous phenotypes.

45,X MALES

In a few male patients recognized with a 45,X karyotype, Yp sequences are translocated to an autosomal chromosome. In 1 instance, the terminal short arm of the Y chromosome was translocated onto an X chromosome. In another, *SRY/autosomal* translocation was postulated. A male with 45,X karyotype and Leri-Weill dyschondrosteosis, *SHOX* gene loss, and SRY to Xp translocation also has been described.

47,XXX MALES

A Japanese male with poor pubic hair development, hypoplastic scrotal testes (4 mL), normal penis and normal height, gynecomastia, and severe cognitive impairment had 47,XXX karyotype caused by an abnormal X-Y interchange during paternal meiosis and X-X nondisjunction during maternal meiosis.

Bibliography is available at Expert Consult.

583.2 Hypogonadotropic Hypogonadism in the Male (Secondary Hypogonadism)

Omar Ali and Patricia A. Donohoue

In hypogonadotropic hypogonadism, lack of gonadal function is secondary to deficiency of 1 or both gonadotropins: FSH or LH. The primary defect may lie either in the anterior pituitary or in the hypothalamus. Hypothalamic etiologies result in deficiency of GnRH. The testes are normal but remain in the prepubertal state because stimulation by gonadotropins is lacking. The disorder may be recognized in infancy but is much more commonly recognized because of marked pubertal delay. Rarely, patients with an inherited form of hypogonadotropic hypogonadism (HH) may go through puberty and may present with hypogonadism as adults.

ETIOLOGY

HH may be genetic or acquired. Several different genes can cause inherited forms of HH; the affected genes may be upstream of GnRH, at the level of GnRH receptors, or at the level of gonadotropin production. In addition, various genetic defects in transcription factors such as POUF-1, LHX-3, LHX-4, and HESX-1 lead to defects in pituitary development and multiple pituitary hormone deficiencies, including deficiency of gonadotropins. Acquired pituitary gonadotropin deficiency may develop from various lesions in the hypothalamic-pituitary region (e.g., tumors, infiltrative disease, autoimmune disease, trauma, stroke).

Isolated Gonadotropin Deficiency

Isolated gonadotropin deficiency in which other pituitary hormone levels are normal is more likely to be from defects in the secretion of GnRH from the hypothalamus rather than defects in gonadotropin synthesis in the pituitary. It affects approximately 1 in 10,000 males and 1 in 50,000 females and encompasses a heterogeneous group of entities. Many cases are associated with anosmia and this combination of anosmia and HH defines Kallmann syndrome.

Kallmann syndrome is the most common form of HH and is genetically heterogeneous, with autosomal recessive, X-linked, and autosomal dominant forms of inheritance. Clinically, it is characterized by its association with **anosmia** or **hyposmia;** 85% of the cases are autosomal and 15% are X-linked. The X-linked form (KAL1) is caused by mutations of the *KAL1* gene at Xp22.3. This leads to failure of olfactory axons and GnRH-expressing neurons to migrate from their common origin in the olfactory placode to the brain. The *KAL* gene product anosmin-1, an extracellular 95 kDa matrix glycoprotein, facilitates neuronal growth and migration. The *KAL* gene is also expressed in various parts of the brain, facial mesenchyme, and mesonephros and metanephros, thus explaining some of the associated findings in patients with Kallmann syndrome, such as synkinesia (mirror movements), hearing loss, midfacial defects, and renal agenesis.

Some kindreds contain anosmic individuals with or without hypogonadism; others contain hypogonadal individuals who are anosmic.

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Cleft lip and palate, hypotelorism, median facial clefts, sensorineural hearing loss, unilateral renal aplasia, neurologic deficits, and other findings occur in some affected patients. When Kallmann syndrome is caused by terminal or interstitial deletions of the Xp22.3 region, it may be associated with other contiguous gene syndromes, such as steroid sulfatase deficiency, chondrodysplasia punctata, X-linked ichthyosis, or ocular albinism.

The autosomal dominant form of Kallmann syndrome (KAL2) occurs in up to 10% of patients, and is caused by a loss of function mutation in the fibroblast growth factor receptor 1 *(FGFR1)* gene. Cleft lip and palate are associated with KAL2 but not with KAL1. Oligodontia and hearing loss may occur with both KAL1 and KAL2.

A variety of other genes, including *FGF8*, *PROK2/PROKR2*, *NELF*, *CHD7* (responsible for CHARGE [coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies] syndrome, which includes hypogonadism in its phenotype), *HS6ST1*, *WDR11*, and *SEMA3A*, are associated with defects in neuronal migration that can result in Kallmann syndrome, but in most patients the affected gene remains undefined.

Hypogonadotropic Hypogonadism Without Anosmia

A specific genetic defect is not found in most cases of normosmic idiopathic hypogonadotropic hypogonadism (IHH) but the list of genes associated with this disorder is growing; mutations in the genes *KISS1/KISS1R*, *TAC3/TACR3*, and*GNRH1/GNRHR* lead to abnormalities in the secretion and action of GnRH and are seen exclusively in patients with normosmic IHH. Mutations in *FGFR1*, *FGF8*, *PROKR2*, *CHD7*, and *WDR11* more commonly present with anosmia/hyposmia (Kallmann syndrome), but are also associated with normosmic IHH in some cases. It appears that kisspeptin (the gene product of the *KISS1* gene) and its G-protein–coupled receptor (GPCR54) play an important role in triggering puberty in humans and act downstream of the leptin receptor in this pathway. Rare cases of leptin deficiency and leptin receptor defects are also associated with HH. In addition, starvation and anorexia are associated with hypogonadism, most likely acting via the leptin pathway.

There are no known human mutations of the *GnRH* gene, but several families with mutations in the GnRH receptor have been described. These mutations account for 2-14% of idiopathic HH without anosmia. The severity of the defect is variable and many patients will respond to high-dose GnRH with increased gonadotropin secretion, indicating that the receptor defect is partial and not complete.

Mutations in gonadotropin genes are extremely rare. Mutations in the common α-subunit are not known in humans. Mutations in the LH-β subunit have been described in a few individuals and may lead to low, absent, or elevated LH levels, depending on the mutation. Defects in the FSH-β subunit may be the cause of azoospermia in a few rare cases.

Children with **X-linked congenital adrenal hypoplasia** have associated HH as a result of impaired GnRH secretion. In these patients, there is a mutation of the *DAX1* gene at Xp21.2-21.3. Conditions occasionally associated with these patients because of the **contiguous gene syndrome** include glycerol kinase deficiency, Duchenne muscular dystrophy, and ornithine transcarbamoyltransferase deficiency. Most boys with *DAX1* mutations develop HH in adolescence, although a patient with adult-onset adrenal insufficiency and partial HH and 2 females with HH and delayed puberty also have been described, the latter as part of extended families with males with classic HH. The *DAX1* gene defect is, however, rare in patients with delayed puberty or HH without at least a family history of adrenal failure (see Chapter 576).

It should be noted that genotype–phenotype correlations in IHH appear to be complex and pedigrees with digenic or oligogenic inheritance have been described. The same genetic defect may be associated with Kallmann syndrome, normosmic IHH, additional birth defects, delayed normal puberty, or an apparently normal phenotype. This variability has been observed more frequently in kindreds with mutations in *FGF8/FGFR1* and in *PROK2/PROKR2* ligand-receptor pairs, and may be from other interacting genes, epigenetic effects, or environmental factors.

Other Disorders with Hypogonadotropic Hypogonadism

HH has been observed in a few patients with polyglandular autoimmune syndrome, in some with elevated melatonin levels, and in those with a variety of other syndromes such as Bardet-Biedl, Prader-Willi, multiple lentigines, and several ataxia syndromes. In rare cases, HH is associated with complex chromosomal abnormalities.

Hypogonadotropic Hypogonadism Associated with Other Pituitary Hormone Deficiencies

Defects in pituitary transcription factors such as PROP-1, HESX-1, LHX-4, SOX-3, and LHX-3 lead to multiple pituitary deficiencies, including HH. Most of these present with multiple pituitary hormone deficiency in infancy, but some cases (especially with *PROP-1* mutations) may present with hypogonadism or hypoadrenalism in adult life. Growth hormone is almost always affected in multiple pituitary hormone deficiency, but thyroid-stimulating hormone and adrenocorticotropic hormone may be spared in some cases. In patients with organic lesions in or near the pituitary, the gonadotropin deficiency is usually pituitary in origin. Microphallus (<2.5 cm at term) in the newborn male with growth hormone deficiency suggests the possibility of gonadotropin deficiency.

DIAGNOSIS

Levels of gonadotropins and gonadal steroids are elevated for up to 6 mo after birth (minipuberty), and if the diagnosis of HH is suspected in early infancy these levels will be found to be inappropriately low. By the second half of the 1st yr of life these levels normally decline to near zero and remain suppressed until late childhood. Therefore, routine lab tests cannot distinguish HH from normal suppression of gonadotropins in this age group. At the normal age of puberty, these patients fail to show clinical signs of puberty or normal increase in LH and FSH levels. Children with constitutional delay of growth and puberty will have the same clinical picture and similar lab findings (and these cases are far more common than true HH, especially in males), and their differentiation from patients with HH is extremely difficult. Dynamic testing with GnRH or hCG may *not* be able to distinguish these groups in a reliable manner. A testosterone level greater than 50 ng/dL (1.7 nmol/L) generally indicates that normal puberty is likely, but a lower level does not reliably distinguish these groups. At least 1 study shows that an inhibin B level of <35 pg/mL in Tanner stage 1 and <65 pg/mL in Tanner stage 2 may be able to distinguish IHH from constitutional delay in males.

Insulin-like growth factor-1, thyroid-stimulating hormone, free thyroxine, and morning cortisol levels should be checked to assess the status of other anterior pituitary hormones; dynamic testing for growth hormone deficiency and adrenal insufficiency may be necessary if these are abnormal or equivocal. HH is very likely if the patient has evidence of another pituitary deficiency, such as a deficiency of growth hormone, particularly if it is associated with adrenocorticotropic hormone deficiency. **Hyperprolactinemia** is a known cause of delayed puberty and should be excluded by determination of serum prolactin levels in all patients. The presence of **anosmia** usually indicates permanent gonadotropin deficiency, but occasional instances of markedly delayed puberty (18-20 yr of age) have been observed in anosmic individuals. Although anosmia may be present in the family or in the patient from early childhood, its existence is rarely volunteered, and direct questioning is necessary in all patients with delayed puberty. Formal olfactometry, such as the University of Pennsylvania Smell Identification Test, is advisable to determine if partial degrees of hyposmia are present because IHH patients display a broad spectrum of olfactory function.

In the absence of family history, it may not be possible to make the diagnosis of HH with certainty, but the diagnosis will become more and more likely as puberty is delayed further beyond the normal age. If pubertal delay persists beyond age 18 yr with low 8 AM testosterone levels and inappropriately low gonadotropins (normal values are inappropriately low in this setting), then the patient can be presumptively diagnosed with HH. An MRI of the brain is indicated to look for

tumors and other anomalies in the hypothalamic-pituitary region. Genetic testing for pituitary transcription factors and several of the genes involved in isolated HH is also available and should be performed when possible. A renal ultrasound is recommended in patients with Kallmann syndrome because of its association with unilateral renal agenesis. Some authorities also recommend obtaining a baseline bone-density evaluation.

Treatment

Constitutional delay of puberty should be ruled out before a diagnosis of HH is established and treatment is initiated. Testicular volume of less than 4 mL by 14 yr of age occurs in approximately 3% of boys, but true HH is a rare condition. Even relatively moderate delays in sexual development and growth may result in significant psychologic distress and require attention. Initially, an explanation of the variations characteristic of puberty and reassurance suffice for the majority of boys. If by 15 yr of age no clinical evidence of puberty is beginning and the testosterone level is <50 ng/dL, a brief course of testosterone may be recommended. Various regimens are used, including testosterone enanthate 100 mg intramuscularly once monthly for 4-6 mo or 150 mg once monthly for 3 mo. Some practitioners use oral oxandrolone, which may have the theoretical advantage that it is not aromatized and may have less effect on bone age advancement (though definitive evidence of advantage is lacking). Oral oxandrolone may cause hepatic dysfunction and liver function tests should be monitored if it is used. Treatment is not necessary in all cases of constitutional delay, but if used, it is usually followed by normal progression through puberty and this may differentiate constitutional delay in puberty from isolated gonadotropin deficiency. The age of initiation of this treatment must be individualized.

Once a diagnosis of HH is made, treatment with testosterone will induce secondary sexual characteristics but will *not* stimulate testicular growth or spermatogenesis. Treatment with gonadotropins (either as a combination of hCG and human menopausal gonadotropins or using GnRH pulse therapy) will lead to testicular development, including spermatogenesis, but is much more complex to manage, so in most cases testosterone treatment is the best option. Either long-acting testosterone injections or daily application of testosterone gel may be used (testosterone patches have a high incidence of skin rash and are infrequently used in pediatrics). Testosterone enanthate or cypionate ester may be used in a starting dose of 25-50 mg injected intramuscularly every 3-4 wk, with 50 mg increments every 6-9 mo until a maintenance dose for adults (200-250 mg every 3-4 wk) is achieved. At that time, testosterone patches or testosterone gel may be substituted for the injections. Depending on patient and physician preference, transdermal testosterone may also be used as initial treatment instead of injections. For older boys, larger initial doses and increments can achieve more rapid virilization.

Treatment with gonadotropins is more physiologic but is expensive and complex, so it is less commonly used in adolescence. This treatment may be attempted in adult life when fertility is desired. The treatment schedule varies from 1,250-5,000 IU hCG in combination with 12.5-150 IU human menopausal gonadotropins 3 times per wk intramuscularly. It may require up to 2 yr of treatment to achieve adequate spermatogenesis in adults. Recombinantly produced gonadotropins (LH and FSH) are also able to stimulate gonadal growth and function but are much more expensive. Treatment with GnRH (when available) is the most physiologically appropriate, but it requires the use of a subcutaneous infusion pump to deliver appropriately pulsed therapy because continuous exposure to GnRH will suppress gonadotropins rather than stimulate them. In some cases, patients with GnRH defects also have pituitary or testicular dysfunction (a "dual defect") and may fail to respond adequately to GnRH or gonadotropin treatment. The rare patient with isolated LH deficiency can be treated effectively using hCG injections.

It has been found that up to 10% of patients diagnosed with HH (with or without anosmia) may exhibit spontaneous reversal of hypogonadism with sustained normal gonadal function when treatment has been discontinued; this may occur in patients with known genetic mutations in various genes, including *FGFR1*, *PROK2*, *GNRH*, *CHD7*, and *TAC/TACR3*. Such recovery is more likely in patients who show an increase in testicular volume during treatment or when treatment has been discontinued. Therefore, a brief trial of interruption of treatment is justified in patients with idiopathic HH. However, the recovery of gonadal function may not be lifelong.

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Chapter 584

Pseudoprecocity Resulting from Tumors of the Testes

Omar Ali and Patricia A. Donohoue

Leydig cell tumors of the testes are rare causes of precocious pseudopuberty (gonadotropin-independent) and cause asymmetric enlargement of the testes. Leydig cells are sparse before puberty and tumors derived from them are more common in the adult, but rare cases do occur in children and the youngest reported case was in a 1 yr old boy. Although up to 10% of adult tumors may be malignant, metastasizing malignant tumors have not been reported in children, and pediatric Leydig cell tumors are usually unilateral and benign. Some tumors may be due to somatic activating mutations of the luteinizing hormone receptor.

The clinical manifestations are those of puberty in the male; onset usually occurs at 5-9 yr of age. Gynecomastia has been described. The tumor of the testis can usually be readily felt; the contralateral unaffected testis is normal in size for the age of the patient.

Plasma levels of testosterone are markedly elevated, and follicle-stimulating hormone and luteinizing hormone levels are suppressed. Ultrasonography may aid in the detection of small nonpalpable tumors. Fine-needle aspiration biopsy may help define the diagnosis.

Treatment consists of surgical removal of the affected testis. These tumors are generally resistant to chemotherapy. Progression of virilization ceases after removal of the tumor, and partial reversal of the signs of precocity may occur.

Testicular adrenal rests may develop into tumors that mimic Leydig cell tumors. Adrenal rest tumors are usually bilateral and occur in children with inadequately controlled congenital adrenal hyperplasia, usually of the salt-losing variety, during adolescence or young adult life. The stimulus for the growth of the adrenal rests is inadequate corticosteroid suppressive therapy causing excess adrenocorticotropic hormone secretion, and treatment with adequate doses almost always results in their regression. These tumors are histologically similar to primary Leydig cell tumors, but definite evidence of the origin of these may be achieved by demonstrating their 21-hydroxylase activity. Misdiagnosis of these tumors as primary Leydig cell tumors may lead to unnecessary orchidectomy and should be avoided.

Fragile X syndrome (see Chapter 81.5) is caused by the amplification of a polymorphic CGG repeat in the 5′ untranslated region of the *FMRI* gene at Xp17.3. The gene encodes an RNA binding protein that is highly expressed in the brain and the testis. In otherwise normal individuals, 6-50 CGG repeats are present in the gene; the presence of 50-200 repeats (permutation) is associated with mild intellectual disability and other abnormalities, and the presence of more than 200 repeats (fragile X mutation) is associated with the classic fragile X syndrome. Permutations are present in 1 in 1,000 white males, and

mutations are found in 1 in 4,000-8,000. A cardinal characteristic of the condition is testicular enlargement **(macroorchidism),** reaching 40-50 mL after puberty. Although the condition has been recognized in a child as young as 5 mo of age, affected boys younger than 6 yr of age rarely have testicular enlargement; by 8-10 yr of age, most have testicular volumes greater than 3 mL. The testes are enlarged bilaterally, are not nodular, and are histologically normal. Results of hormonal studies are normal. Direct DNA analysis searching for CGG repeat sequences permits definitive diagnosis.

Large-cell calcifying Sertoli cell tumors of the testes and **sex cord tumors with annular tubules** are extremely rare Sertoli cell tumors that may be a cause of breast development in young boys. These tumors are usually associated with Peutz-Jeghers syndrome or Carney complex; they often occur bilaterally, are multifocal, and are detectible by ultrasonography. Excessive production of aromatase (P450arom), the enzyme that converts testosterone to estradiol, causes feminization of these boys. Because they are usually benign, they may be left in place if they are not causing pain; the gynecomastia can be treated with aromatase inhibitors.

In boys with **unilateral cryptorchidism,** the contralateral testis is approximately 25% larger than normal for age. Testicular enlargement has also been noted in boys with Henoch-Schönlein purpura and lymphangiectasia. Epidermoid and dermoid cysts of the testes have been reported rarely.

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Chapter 585
Gynecomastia

Omar Ali and Patricia A. Donohoue

Gynecomastia, the proliferation of mammary glandular tissue in the male, is a common condition. True gynecomastia (the presence of glandular breast tissue) needs to be distinguished from pseudogynecomastia, which is the result of accumulation of adipose tissue in the area of the breast that is commonly seen in overweight boys. True gynecomastia is characterized by the presence of a palpable fibroglandular mass at least 0.5 cm in diameter, located concentrically beneath the nipple and areolar region.

PHYSIOLOGIC FORMS OF GYNECOMASTIA

Gynecomastia occurs in many newborn males as a result of normal stimulation by maternal estrogen; the effect usually disappears in a few weeks. It is then extremely rare in prepubertal boys, in whom it should always be investigated to identify the cause, but again becomes common during normal puberty.

Neonatal Gynecomastia

Transient gynecomastia occurs in 60-90% of male newborns secondary to exposure to estrogens during pregnancy. Breast development may be asymmetrical and galactorrhea is seen in approximately 5%. Most cases resolve within 4-8 wk of birth, but a few can last as long as 12 mo.

Pubertal Gynecomastia

During early puberty to midpuberty, up to 70% of boys develop various degrees of subareolar hyperplasia of the breasts. Incidence peaks at 14 yr of age, at Tanner stage 3-4 and at a testicular volume of 5-10 mL. Physiologic pubertal gynecomastia may involve only 1 breast; it is not unusual for both breasts to enlarge at disproportionate rates or at different times. Tenderness of the breast is common but transitory. Spontaneous regression may occur within a few months; it rarely persists longer than 2 yr. Significant psychosocial distress may be present, especially in obese boys with relatively large breasts.

The cause is thought to be an imbalance between estrogen and androgen action at the level of breast tissue. Testing usually fails to reveal any significant difference in circulating estrogen and androgen levels between affected and unaffected males, but minor degrees of imbalance in free hormone levels may still be present. Other hormones, including leptin and luteinizing hormone, may directly stimulate breast development and may play a role in pubertal gynecomastia. Some cases may be caused by an increased sensitivity to estrogens and/or relative androgen resistance in the affected tissue. As androgen levels continue to rise in later puberty, most cases resolve.

Pathologic Gynecomastia

See Table 585-1.

Monogenic forms of gynecomastia are extremely rare, but do exist. Familial gynecomastia has occurred in several kindreds as an X-linked or autosomal dominant sex-limited trait. Some of these cases were found to be caused by constitutive activation of the P450 aromatase enzyme (*CYP19A1* gene), leading to increased peripheral conversion of C-19 steroids to estrogens (increased aromatization). A report of this syndrome in a father and his son and daughter suggests autosomal dominant inheritance. Excess aromatase activity was shown in skin fibroblasts and transformed lymphocytes in vitro.

Exogenous sources of estrogens are an important cause of gynecomastia in prepubertal children. Very small amounts of estrogens can cause gynecomastia in male children and accidental exposure may occur by inhalation, percutaneous absorption, or ingestion. Common sources of estrogens include oral contraceptive pills and oral and transdermal estrogen preparations. Gynecomastia has been reported in workers involved in the manufacture of estrogens and even in the children of such workers. Gynecomastia can also occur secondary to exposure to medications that decrease the level of androgens (especially free androgens), increase estradiol, or displace androgens from breast androgen receptors. Spironolactone, alkylating agents, anabolic steroids, human chorionic gonadotropin, ketoconazole, cimetidine, and androgen inhibitors such as flutamide are all associated with the occurrence of gynecomastia. Weaker associations are seen with a large number of other medications and drugs of abuse, including opiates, alcohol, and marijuana, although the association with marijuana may not be as strong as previously thought. Lavender, tea oils, and excessive consumption of soy are also implicated as causes of prepubertal gynecomastia.

Klinefelter syndrome and other causes of **male hypogonadism** are strongly associated with gynecomastia. Significant gynecomastia is seen in 50% of adolescents with Klinefelter syndrome; it is also seen in other conditions characterized by male undervirilization, including partial androgen insensitivity syndrome and 17-ketosteroid reductase deficiency. Gynecomastia has also been observed in children with congenital virilizing adrenal hyperplasia (11β-hydroxylase deficiency) and with Leydig cell tumors of the testis or with feminizing tumors of the adrenal gland. Several boys with Peutz-Jeghers syndrome and gynecomastia had sex cord tumors of the testes. The testes may not be enlarged in these cases and the tumor is usually multifocal and bilateral. Excessive aromatase production accounts for the gynecomastia. When gynecomastia is associated with galactorrhea, a prolactinoma should be considered. Hyperthyroidism alters the androgen to estrogen ratio by increasing bound androgen and decreasing the free testosterone and may result in gynecomastia in up to 40% of cases. Gynecomastia is also seen in malnourished patients after restoration of normal nutrition (refeeding syndrome), in whom it may be from hepatic dysfunction or abnormal activation of the gonadotropin axis.

EVALUATION OF GYNECOMASTIA

In pubertal cases a detailed history and physical examination may be all that is needed to exclude rare pathologic causes. Historical evaluation should include family history of male relatives with gynecomastia, history of liver or renal disease, use of medications or drugs of abuse, and exposure to herbal and cosmetic products that may contain phytoestrogens. Physical examination should include special attention to the breasts (looking for overlying skin changes, fixation, local lymphadenopathy, and nipple discharge) as well as a testicular exam. No

Table 585-1 Causes of Gynecomastia	
SYMPTOMS	**SIGNS**
FETAL ANDROGEN DEFICIENCY	
Ambiguous genitalia	Ambiguous genitalia (47,XY disorders of sex development) Normal female genitalia Microphallus (resembling clitoromegaly) Pseudovaginal perineoscrotal hypospadias Bifid scrotum Cryptorchidism
PREPUBERTAL ANDROGEN DEFICIENCY	
Delayed puberty	Eunuchoidism
Lack of sexual interest or desire (libido)	Infantile genitalia Small testes
Reduced nighttime or morning spontaneous erections	Lack of male hair pattern growth, no acne
Breast enlargement and tenderness	Disproportionately long arms and legs relative to height
Reduced motivation and initiative	Pubertal fat distribution Poorly developed muscle mass
Diminished strength and physical performance	High-pitched voice Reduced peak bone mass, osteopenia, or osteoporosis
No ejaculate or ejaculation (spermarche)	Gynecomastia
Inability to father children (infertility)	Small prostate gland Aspermia, severe oligozoospermia, or azoospermia
ADULT ANDROGEN DEFICIENCY	
Incomplete sexual development	Eunuchoidism
Lack of sexual interest or desire (libido)	Small or shrinking testes Loss of male hair (axillary and pubic hair)
Reduced nighttime or morning spontaneous erections	Gynecomastia
Breast enlargement and tenderness	Aspermia or azoospermia or severe oligozoospermia
Inability to father children (infertility)	Low bone mineral density (osteopenia or osteoporosis)
Height loss, history of minimal-trauma fracture	Height loss, minimal-trauma or vertebral compression fracture
Hot flushes, sweats	
Reduced shaving frequency	Unexplained reduction in prostate size or prostate-specific antigen
Less-Specific Symptoms	**Less-Specific Signs**
Decreased energy, vitality	Mild normocytic, normochromic anemia (normal female range)
Decreased motivation, self-confidence	Depressed mood, mild depression or dysthymia
Feeling sad or blue, irritability	Reduced muscle bulk and strength
Weakness, decreased physical or work performance	Increased body fat or body mass index
Poor concentration and memory	Fine facial skin wrinkling (lateral to orbits and mouth)
Increased sleepiness	

From Matsumoto AM, Bremner WJ: Testicular disorders. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: Williams textbook of endocrinology, *ed 12, Philadelphia, 2011, WB Saunders, Table 19-3, p. 719.*

laboratory evaluation is indicated in routine cases with no other associated abnormality but all prepubertal cases, as well as pubertal cases with suspicious features, should be investigated; initial laboratory evaluation should include thyroid function tests (to rule out hyperthyroidism), testosterone, estradiol, human chorionic gonadotropin, luteinizing hormone, and prolactin levels. Most cases of hyperprolactinemia are associated with galactorrhea, but there are a few reports of hyperprolactinemia causing gynecomastia without associated galactorrhea. Because of circadian variation, these levels should ideally be obtained in the morning. Other tests that may be indicated in selected cases include a karyotype, dehydroepiandrosterone sulfate, and liver and renal function tests. Gonadotropin levels may be a useful screen for Klinefelter syndrome and will be elevated in pubertal boys with this condition. If elevated, a karyotype should be performed.

TREATMENT

Treatment in case of benign pubertal gynecomastia usually consists of reassuring the boy and his family of the physiologic and transient nature of the phenomenon. When the enlargement is striking and persistent and causes serious emotional disturbance to the patient, specific treatment may be justified. Unfortunately, medical treatment is generally ineffective in long-standing cases. Early cases respond better to medical treatment but it is harder to justify treatment as most cases will resolve spontaneously. Agents that have been used for medical treatment include androgens, aromatase inhibitors, and estrogen antagonists. The effectiveness of synthetic androgens is variable and side effects are a concern, so these are rarely used in pediatrics. Aromatase inhibitors make physiologic sense, but placebo-controlled trials have been disappointing. Estrogen antagonists like tamoxifen and raloxifene are more effective, with raloxifene being the superior agent in at least 1 well-designed trial. If medical treatment is attempted, it should be in early cases (<12 mo standing) using raloxifene (in a dose of 60 mg/day) or tamoxifen (10-20 mg/day) for 3-9 mo, with the understanding that success rates are generally low in severe cases and mild cases will likely resolve on their own without treatment.

In those cases where breast development is excessive (Tanner stages 3-5), causes significant psychologic distress, and fails to regress in 18-24 mo, surgical removal of the enlarged breast tissue may be indicated, particularly in boys who have completed or nearly completed pubertal development. Careful examination and laboratory testing to exclude nonphysiologic causes are advisable before proceeding to surgery.

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Chapter 586

Hypofunction of the Ovaries

Alvina R. Kansra and Patricia A. Donohoue

Hypofunction of the ovaries can be either primary or central in etiology. It may be caused by congenital failure of development, postnatal destruction (primary or hypergonadotropic hypogonadism), or lack of central stimulation by the pituitary and/or hypothalamus (secondary or tertiary hypogonadotropic hypogonadism). **Primary ovarian insufficiency** (hypergonadotropic hypogonadism), which is also termed *premature ovarian failure*, is characterized by the arrest of normal ovarian function before the age of 40 yr. Certain genetic mutations can result in primary ovarian insufficiency. Hypofunction of the ovaries because of a lack of central stimulation (hypogonadotropic hypogonadism) can be associated with other processes, such as multiple pituitary hormone deficiencies and some chronic diseases. Table 586-1 details the etiologic classification of ovarian hypofunction.

586.1 Hypergonadotropic Hypogonadism in the Female (Primary Hypogonadism)

Alvina R. Kansra and Patricia A. Donohoue

Diagnosis of hypergonadotropic hypogonadism before puberty is difficult. Except in the case of Turner syndrome, most affected patients have no prepubertal clinical manifestations.

Table 586-1 Etiologic Classification of Ovarian Hypofunction

HYPOGONADOTROPIC HYPOGONADISM

Hypothalamic

Genetic defects

- Kallmann syndrome *KAL1, FGFR1, FGF8, PROK2, PROKR2, CHD7, WDR11, NELF, SEMA3A*
- Other gene defects: leptin, leptin receptor, *KISS-1* (deficiency of kisspeptin), *DAX-1, TAC3* (deficiency of neurokinin B), *TACR3, SEMA7A*
- Inherited syndromes: Prader-Willi, Bardet-Biedl, and others
- Marked constitutional growth delay

Acquired defects (reversible)

- Anorexia nervosa
- Drug use
- Malnutrition
- Chronic illness, especially Crohn disease
- Hyperprolactinemia

Pituitary

Genetic defects

- Isolated gonadotropin deficiency (GnRH receptor, FSH, and LH β-subunit)
- Septooptic dysplasia (*HESX-1* in some cases)
- Disorders of pituitary organogenesis (*PROP1, LHX3, LHX4, SOX-3*, etc.)

Acquired defects

- Pituitary tumors
- Pituitary infarction
- Infiltrative disorders (histiocytosis, sarcoidosis)
- Hemosiderosis and hemochromatosis
- Radiation

HYPERGONADOTROPIC HYPOGONADISM

Genetic

Follicle-stimulating hormone and luteinizing hormone resistance
Mutations in steroidogenic pathways
46,XX gonadal dysgenesis
Turner syndrome and its variants
Noonan syndrome (*PTPN-11* gene)
SF-1 gene mutations
Galactosemia
Fragile X–associated disorders
Bloom syndrome
Werner syndrome
Ataxia-telangiectasia
Fanconi anemia

Acquired

Chemotherapy
Radiation
Autoimmune ovarian failure from autoimmune polyendocrine syndromes 1 and 2

TURNER SYNDROME

Turner described a syndrome consisting of sexual infantilism, webbed neck, and cubitus valgus in adult females (see Chapter 81). Ullrich described a girl with short stature and many of the same phenotypic features. The term *Ullrich-Turner syndrome* is frequently used in Europe, but is infrequently used in the United States where the condition is called Turner syndrome. The syndrome is defined as the combination of the characteristic phenotypic features accompanied by complete or partial absence of the second X chromosome with or without mosaicism.

Pathogenesis

Half the patients with Turner syndrome have a 45,X chromosomal complement. Approximately 15% of patients are mosaics for 45,X and a normal cell line (45,X/46,XX). Other mosaics with isochromosomes, 45,X/46,X,i(Xq); with rings, 45,X/46,X,r(X); or with fragments, 45,X/46fra, occur less often. Mosaicism is detected most commonly when more than 1 tissue is examined. The single X is of maternal origin in nearly 80% of 45,X patients. The mechanism of chromosome loss is unknown, and the risk for the syndrome does not increase with maternal age. The genes involved in the Turner phenotype are X-linked genes that escape inactivation. A major locus involved in the control of linear growth has been mapped within the pseudoautosomal region of the X chromosome (PAR1). *SHOX*, a homeobox-containing gene of 170 kb of DNA within the PAR1, is thought to be important for controlling growth in children with Turner syndrome, Leri-Weill syndrome, and, rarely, in patients having idiopathic short stature. Genes for the control of normal ovarian function are postulated to be on Xp and perhaps 2 "supergenes" on Xq.

Turner syndrome occurs in approximately 1 in 1,500-2,500 liveborn females. The frequency of the 45,X karyotype at *conception* is approximately 3%, but 99% of these are spontaneously aborted, accounting for 5-10% of all abortuses. Mosaicism (45,X/46,XX) occurs in a proportion higher than that seen with any other aneuploid state, but the mosaic Turner constitution is rare among the abortuses; these findings indicate preferential survival for mosaic forms.

The normal fetal ovary contains approximately 7 million oocytes, but these begin to disappear rapidly after the 5th mo of gestation. At birth, there are only 2 million (1 million active follicles); by menarche, there are 400,000-500,000; and at menopause, 10,000 remain. In the absence of 1 X chromosome, this process is accelerated, and nearly all oocytes are gone by 2 yr of age. In aborted 45,X fetuses, the number of primordial germ cells in the gonadal ridge appears to be normal, suggesting that the normal process is accelerated in patients with Turner syndrome. Eventually, the ovaries are described as "streaks" and consist only of connective tissue, with very few germ cells present.

Clinical Manifestations

Many patients with Turner syndrome are recognizable at birth because of a characteristic edema of the dorsa of the hands and feet and loose skinfolds at the nape of the neck. Low birthweight and decreased birth length are common (see Chapter 81). Clinical manifestations in childhood include webbing of the neck, a low posterior hairline, small mandible, prominent ears, epicanthal folds, high arched palate, a broad chest presenting the illusion of widely spaced nipples, cubitus valgus, and hyperconvex fingernails. The diagnosis is often first suspected at puberty when breast development fails to occur.

Short stature, the cardinal finding in virtually all girls with Turner syndrome, may be present with little in the way of other clinical manifestations. The linear growth deceleration begins in infancy and young childhood, gets progressively more pronounced in later childhood and adolescence, and results in significant adult short stature. Sexual maturation (breast development) fails to occur at the expected age; however, signs of adrenarche (pubic hair) are normally present. Among untreated patients with Turner syndrome, the mean adult height is 143-144 cm in the United States and most of northern Europe, but 140 cm in Argentina and 147 cm in Scandinavia (Fig. 586-1). The height is well correlated with the midparental height (average of the parents' heights). Specific growth curves for height have been developed for girls with Turner syndrome.

Associated **cardiac defects** are common. In the girls with Turner syndrome, life-threatening consequences of X-chromosome haploinsufficiency involve the cardiovascular system. There is a 4-5–fold increased rate of premature mortality secondary to congenital heart disease and premature coronary heart disease in adults with Turner syndrome. Clinically silent cardiac defects, mainly bicuspid aortic valve but also ascending aortic dilation, coarctation of the aorta, and partial anomalous pulmonary venous connections, are present in patients with Turner syndrome. Regardless of the age, all patients with Turner syndrome at the time of diagnosis need comprehensive cardiovascular evaluation by a cardiologist specializing in congenital heart disease. Complete cardiologic evaluation, including echocardiography, reveals isolated nonstenotic bicuspid aortic valves in one third to one half of patients. In later life, bicuspid aortic valve disease can progress to dilation of the aortic root. Less-frequent defects include aortic coarctation (20%), aortic stenosis, mitral valve prolapse, and anomalous pulmonary venous drainage. In 1 study, 38% of patients with 45,X chromosomes had cardiovascular malformations compared with 11%

Figure 586-1 Turner syndrome in a 15 yr old girl exhibiting failure of sexual maturation, short stature, cubitus valgus, and a goiter. There is no webbing of the neck. Karyotyping revealed 45,X/46,XX chromosome complement.

of those with mosaic monosomy X; the most common were aortic valve abnormalities and aortic coarctation. *Webbed neck in patients with or without recognized chromosome syndromes is associated with both flow-related and non–flow-related heart defects.* Among patients with Turner syndrome, those with webbed necks have a much greater chance of having coarctation of the aorta than do those without webbed necks. Transthoracic echocardiogram in young girls is adequate if cardiac anatomy is clearly seen; otherwise magnetic resonance angiographic screening studies should be considered in asymptomatic individuals with Turner syndrome. During adolescence, and certainly before pregnancy (when possible) is contemplated, repeat cardiac evaluation should be considered even in those without prior findings of cardiac abnormalities. Blood pressure should be routinely monitored even in the absence of cardiac or renal lesions and especially in those with suggestions of aortic root dilation. Cardiac MRI is a valuable tool to detect and monitor aortic root dilation.

Renal ultrasound should be performed in all girls with Turner syndrome at diagnosis. One fourth to one third of patients have **renal malformations** on ultrasonographic examination (50% of those with 45,X karyotypes). The more serious defects include pelvic kidney, horseshoe kidney, double collecting system, complete absence of 1 kidney, and ureteropelvic junction obstruction. Some of the malformations may increase the risk of hypertension and urinary tract infection. Idiopathic hypertension is also common. Girls with Turner syndrome who had normal baseline renal ultrasound findings did not develop renal disease during a follow-up period averaging 6 yr.

When the ovaries were examined by ultrasonography, older studies found a significant decrease in percentage of detectable ovaries from infancy to later childhood. A subsequent report found no such age-related differences in a cross-sectional and longitudinal study; 27-46% of patients had detectable ovaries at various ages; 76% of those with X mosaicism and 26% of those with 45,X karyotypes had detectable ovaries.

Sexual maturation usually fails to occur, but 10-20% of girls have spontaneous breast development, and a small percentage may have menstrual periods. Primary gonadal failure is associated with early onset of adrenarche (elevation in dehydroepiandrosterone sulfate) but delayed pubarche (pubic hair development). Spontaneous pregnancies have been reported in menstruating patients with Turner syndrome. Premature menopause, increased risk of miscarriage, and offspring with increased risk of trisomy 21 have been reported. A woman with a 45,X/46,X,r(X) karyotype treated with hormone replacement therapy had 3 pregnancies, resulting in a normal 46,XY male infant, a spontaneous abortion, and a healthy term female with Turner syndrome 45,X/46,Xr(X).

Antithyroid antibodies (thyroid peroxidase, and/or thyroglobulin antibodies) occur in 30-50% of patients. The prevalence increases with advancing age. **Autoimmune thyroid disease,** with or without the presence of a goiter, occurs in 10-30% of patients. Age-dependent abnormalities in carbohydrate metabolism characterized by abnormal glucose tolerance and insulin resistance and, only rarely, frank type 2 diabetes occur in older patients with Turner syndrome. Impaired insulin secretion has been described in 45,X women. Cholesterol levels are elevated in adolescence, regardless of body mass index or karyotype.

Inflammatory bowel disease, both Crohn disease and ulcerative colitis, gastrointestinal bleeding because of abnormal mesenteric vasculature, and delayed gastric emptying time have all been reported. Screening for celiac disease is recommended by recent guidelines, as the risk of celiac disease is increased in Turner syndrome, with 4-6% of individuals affected. Although autoimmune diseases have been associated with Turner syndrome, the prevalence of type 1 diabetes with Turner syndrome is not very high.

Sternal malformations can be detected by lateral chest radiography. An increased carrying angle at the elbow is usually not clinically significant. Scoliosis occurs in approximately 10% of adolescent girls. Congenital hip dysplasia occurs more commonly than in the general population. Reported eye findings include anterior segment dysgenesis and keratoconus. Pigmented nevi become more prominent with age; melanocytic nevi are common. Essential hyperhidrosis, torus mandibularis, and alopecia areata occur rarely.

Recurrent bilateral otitis media develops in approximately 75% of patients. Sensorineural hearing deficits are common, and the frequency increases with age. Problems with gross and fine motor-sensory integration, failure to walk before 15 mo of age, and early language dysfunction often raise questions about developmental delay, but intelligence is normal in most patients. However, cognitive impairment does occur in patients with 45,X/46,X,r(X); the ring chromosome is unable to undergo inactivation and leads to 2 functional X chromosomes.

Special attention should be given to psychosocial development in girls with Turner syndrome. In general, the behavior function is normal in girls with Turner syndrome, but they are at an increased risk for social isolation, immaturity, and anxiety. Other conditions, such as dyslexia, nonverbal learning disability, and attention deficit disorder, have been reported in girls with Turner syndrome. In adults, deficits in perceptual spatial skills are more common than they are in the general population. Some unconfirmed data suggest the existence of an imprinted X-linked locus that affects cognitive function such as verbal and higher-order executive function skills. These functions are apparently better when the X is paternal in origin.

The prevalence of mosaicism depends in large part on the techniques used for studying chromosomal patterns. The use of fluorescent in situ hybridization and reverse transcription–polymerase chain reaction (PCR) has increased the reported prevalence of mosaic patterns to as high as 60-74%.

Mosaicism involving the Y chromosome occurs in 5%. A population study using PCR with 5 different primer sets found Y chromosome material in 12.2%. **Gonadoblastoma** among Y-positive patients occurred in 7-10%. Therefore, the recommendation is that prophylactic gonadectomy should be performed even in the absence of MRI or CT evidence of tumors. The recommended timing of this procedure is

at the time of diagnosis, but this may need to be reevaluated in the future. The gonadoblastoma locus on the Y chromosome (GBY) maps close to the Y centromere. The presence of only the SRY (sex-determining region on the Y chromosome) locus is not sufficient to confer increased susceptibility for the development of gonadoblastoma. A detailed study of 53 patients with Turner syndrome by nested PCR excluded low-level Y mosaicism in almost all cases. A second round of PCR detected SRY on the distal short arm of the Y chromosome in only 2 subjects. Therefore, routine PCR for Y chromosome detection for the purpose of assigning gonadoblastoma risk is not indicated. High-throughput quantitative genotyping may provide an effective and inexpensive method for the identification of X chromosome abnormalities and Y chromosome material identification.

In patients with 45,X/46,XX mosaicism, the clinical abnormalities are attenuated and fewer; short stature is as frequent as it is in the 45,X patient and may be the only manifestation of the condition other than ovarian failure (see Fig. 586-1).

Laboratory Findings

Chromosomal analysis must be considered routinely in short girls. In a systematic search, using Southern blot analysis of leukocyte DNA, Turner syndrome was detected in 4.8% of girls referred to an endocrinology service because of short stature. Patients with a marker chromosome in some or all cells should be tested for DNA sequences at or near the centromere of the Y chromosome for GBY.

Ultrasonography of the heart, kidneys, and ovaries is indicated after the diagnosis is established. The most common skeletal abnormalities are shortening of the 4th metatarsal and metacarpal bones, epiphyseal dysgenesis in the joints of the knees and elbows, Madelung deformity, scoliosis, and in older patients, inadequate osseous mineralization.

Plasma levels of gonadotropins, particularly follicle-stimulating hormone (FSH), are markedly elevated to greater than those of age-matched controls during infancy; at 2-3 yr of age, a progressive decrease in levels occurs until they reach a nadir at 6-8 yr of age, and by 10-11 yr of age, they rise to adult castrate levels.

Antithyroid peroxidase and antithyroglobulin antibodies should be checked periodically, and if positive, levels of thyroxine and thyroid-stimulating hormone should be obtained. Turner syndrome girls should be screened for **celiac disease** by measuring tissue transglutaminase immunoglobulin A antibodies. Initial testing should be done around age 4 yr and repeated every 2-5 yr. Extensive studies have failed to establish that growth hormone deficiency plays a primary role in the pathogenesis of the growth disorder. Defects in normal secretory patterns of growth hormone are seen in adolescents because of a lack of gonadal steroids, but not in younger girls with Turner syndrome. In vitro, monocytes and lymphocytes show decreased sensitivity to insulin-like growth factor 1.

Treatment

Treatment with recombinant human growth hormone increases height velocity and ultimate stature in most, but not all, children with Turner syndrome. Many girls achieve heights of greater than 150 cm with early initiation of treatment. In a large, multicenter, placebo-controlled clinical trial, 99 patients with Turner syndrome who started receiving growth hormone at a mean age of 10.9 yr at doses between 0.27 and 0.36 mg/kg/wk achieved a mean height of 149 cm, with nearly one third reaching heights greater than 152.4 cm (60 in). In the Netherlands, higher doses of growth hormone (up to 0.63 mg/kg/wk in the 3rd yr of treatment) resulted in 85% of the subjects reaching adult heights in the normal range for the Dutch reference population. Growth hormone treatment should be initiated in early childhood and/or when there is evidence of height velocity attenuation on specific Turner syndrome growth curves. The average starting dose of growth hormone is 0.375 mg/kg/wk. Growth hormone therapy does not significantly aggravate carbohydrate tolerance and does not result in marked adverse events in patients with Turner syndrome. Serum levels of insulin-like growth factor 1 should be monitored if the patient is receiving high doses of growth hormone. If the insulin-like growth factor 1 levels are significantly elevated, the dose of growth hormone may need to be reduced. Treatment with growth hormone can cause excessive growth of the hands and feet in some girls with Turner syndrome.

Oxandrolone has also been used to treat the short stature associated with Turner syndrome, either alone or in combination with growth hormone. This synthetic anabolic steroid has weak androgenic effects, and patients should be monitored for signs of pubarche, as well as hepatotoxicity. The latter is rare.

Replacement therapy with estrogens is indicated, but there is little consensus about the optimal age at which to initiate treatment. The psychologic preparedness of the patient to accept therapy must be taken into account. The improved growth achieved by girls treated with growth hormone in childhood permits initiation of estrogen replacement at 12-13 yr. Delaying estrogen therapy to optimize height potential until 15 yr of age, as previously recommended, seems unwarranted. This change to starting earlier estrogen therapy was considered because of the psychologic importance of age-appropriate pubertal maturation. Also, delaying estrogen therapy could be deleterious for bone health and other aspects of the child's health. Low-dose estrogen replacement at 12 yr of age permits a normal pace of puberty without interfering with the positive effect of growth hormone on the final adult height. Estrogen therapy improves verbal and nonverbal memory in girls with Turner syndrome. In young women with age-appropriate pubertal development who achieve normal height, health-related quality-of-life questionnaires have yielded normal results.

Although many forms of estrogen are available, oral estrogens have been mostly used. Even though transdermal and injectable depot forms of estradiol may be alternative physiologic options, transdermal patches are increasing in popularity. This is because transdermal patches bypass the first hepatic metabolism, thereby requiring only a small amount of estrogen to attain the adequate levels for its function. For oral preparation a conjugated estrogen (Premarin), 0.15-0.625 mg daily, or micronized estradiol (Estrace), 0.5 mg given daily for 3-6 mo, is usually effective in inducing puberty. The recommendations for transdermal patch are 6.25 µg daily that is gradually increased over 2 yr to the adult dose of 100-200 µg daily. The estrogen then is cycled (taken on days 1-23) and a progestin (Provera) is added (taken on days 10-23) in a dose of 5-10 mg daily. In the remainder of the calendar month, during which no treatment is given, withdrawal bleeding usually occurs.

Prenatal chromosome analysis for advanced maternal age has revealed a frequency of 45,X/46,XX that is 10 times higher than when diagnosed postnatally. Most of these patients have no clinical manifestations of Turner syndrome, and levels of gonadotropins are normal. Awareness of this mild phenotype is important in counseling patients.

Psychosocial support for these girls is an integral component of treatment. A comprehensive psychologic education evaluation is recommended either at the time of Turner syndrome diagnosis, depending on the patient's age, when any of the components of behavior or cognition become obvious, or immediately preceding school entry. The Turner Syndrome Society, which has local chapters in the United States, and similar groups in Canada and other countries provide a valuable support system for these patients and their families in addition to that given by the healthcare team.

Successful pregnancies have been carried to term using ovum donation and in vitro fertilization. Adolescents with few signs of spontaneous puberty may have ovaries with follicles. There remains a future possibility of using cryopreserved ovarian tissue with immature oocytes before the regression of the ovaries for the future pregnancies. In adult women with Turner syndrome, there seems to be a high prevalence of undiagnosed bone mineral density, lipid, and thyroid abnormalities. Glucose intolerance, diminished 1st-phase insulin response, elevated blood pressure, and lowered fat-free mass are common. Glucose tolerance worsens, but fat-free mass and blood pressure and general physical fitness improve with sex hormone replacement. The neurocognitive profile of adult women is unaffected by estrogen status.

XX GONADAL DYSGENESIS

Some phenotypically and genetically normal females have gonadal lesions identical to those in 45,X patients but without somatic features

of Turner syndrome; their condition is termed **pure gonadal dysgenesis** or **pure ovarian dysgenesis**.

The disorder is rarely recognized in prepubertal children because the external genitals are normal, no other abnormalities are visible, and growth is normal. At pubertal age, sexual maturation fails to take place. Plasma gonadotropin levels are elevated. Delay of epiphyseal fusion may result in a **eunuchoid** habitus. Pelvic ultrasonography reveals streak ovaries.

Affected siblings, parental consanguinity, and failure to uncover mosaicism all point to female-limited autosomal recessive inheritance. The disorder appears to be especially frequent in Finland (1 in 8,300 liveborn girls). In this population, several mutations in the FSH receptor gene (on chromosome 2p) were demonstrated as the cause of the condition. FSH receptor gene mutations were not detected in Mexican women with 46,XX gonadal dysgenesis. In some patients, XX gonadal dysgenesis has been associated with sensorineural deafness (**Perrault syndrome**). A patient with this condition and concomitant growth hormone deficiency and virilization has also been reported. There may be distinct genetic forms of this disorder. **Müllerian agenesis,** or the **Mayer-Rokitansky-Küster-Hauser** syndrome, which is second to gonadal dysgenesis as the most common cause of primary amenorrhea, occurring in 1 in 4,000-5,000 females, has been reported in association with 46,XX gonadal dysgenesis in a 17 yr old adolescent with primary amenorrhea and lack of breast development. One case of dysgerminoma with syncytiotrophoblastic giant cells was reported. An 18 yr old woman with primary amenorrhea and an absence of müllerian-derived structures, unilateral renal agenesis, and clinical signs of androgen excess, a phenotype resembling the Mayer-Rokitansky-Küster-Hauser syndrome, was found to have a loss-of-function mutation in the *WNT4* gene. Treatment consists of estrogen replacement therapy.

45,X/46,XY GONADAL DYSGENESIS

45,X/46,XY gonadal dysgenesis, also called **mixed gonadal dysgenesis,** has extreme phenotypic variability postnatally that may extend from a Turner-like syndrome to a male phenotype with a penile urethra; it is possible to delineate 3 major clinical phenotypes. Short stature is a major finding in all affected children. Ninety percent of prenatally diagnosed cases have a normal male phenotype.

Some patients have no evidence of virilization; they have a female phenotype and often have the somatic signs of Turner syndrome. The condition is discovered prepubertally when chromosomal studies are made in short girls, or later when chromosomal studies are made because of failure of sexual maturation. Fallopian tubes and uterus are present. The gonads consist of intraabdominal undifferentiated streaks; chromosomal study of the streak often reveals an XY cell line. The streak gonad differs somewhat from that in girls with Turner syndrome; in addition to wavy connective tissue, there are often tubular or cordlike structures, occasional clumps of granulosa cells, and frequently, mesonephric or hilar cells.

Some children have mild virilization manifested only by prepubertal clitoromegaly. Normal müllerian structures are present, but at puberty virilization occurs. These patients usually have an intraabdominal testis, a contralateral streak gonad, and bilateral fallopian tubes.

Many 45,X/46,XY children present with frank ambiguity of the genitals in infancy. A testis and vas deferens are found on one side in the labioscrotal fold, and a streak gonad is identified on the contralateral side. Despite the presence of a testis, fallopian tubes are often present bilaterally. An infantile or rudimentary uterus is almost always present.

Other genotypes and phenotypes have been described in mixed gonadal dysgenesis. Approximately 25% of 200 analyzed patients have a dicentric Y chromosome (45,X/46,X,dic Y). In some patients, the Y chromosome may be represented by only a fragment (45,X/45,X +fra); application of Y-specific probes can establish the origin of the fragment. It is not clear why the same genotype (45,X/46,XY) can result in such diverse phenotypes. Mutations in the *SRY* gene have been described in some patients.

Children with a female phenotype present no problem in gender of rearing. Patients who are only slightly virilized are usually assigned a female gender of rearing before a diagnosis is established. Patients with ambiguity of the genitals are readily often clinically indistinguishable from patients with various types of 46,XY disorders of sex development (46,XY DSD). In some instances, there may need to be careful consideration regarding sex of rearing. Factors that may influence this decision include short stature, the need for surgical genital reconstruction, the presence of müllerian structures, and the need for gonadectomy because of predisposition of the gonad to the development of malignancy. In some patients followed to adulthood, the putative normal testis proves to be dysgenetic with eventual loss of Leydig and Sertoli cell function (see Chapter 583). In an analysis of 22 patients with mixed gonadal dysgenesis, no significant associations or correlations were found between internal and external phenotypes or endocrine function and gonadal morphologic features. The sex of rearing was determined by the appearance of the external genitalia. In 11 patients, basal and human chorionic gonadotropin–stimulated testosterone levels were lower than in control subjects.

Gonadal tumors, usually **gonadoblastomas,** occur in approximately 25% of these children. As described above, a gonadoblastoma locus has been localized to a region near the centromere of the Y chromosome (GBY). These germ cell tumors are preceded by the changes of carcinoma in situ. Accordingly, both gonads should be removed in all patients reared as girls, and the undifferentiated gonad should be removed in the patients reared as boys.

There is no correlation among the proportion of 45,X/46,XY cell lines in either blood or fibroblasts with the phenotype. In the past, all patients came to clinical attention because of their abnormal phenotypes. However, 45,X/46,XY mosaicism is found in approximately 7% of fetuses, with true chromosome mosaicism encountered prenatally. Of 76 infants with 45,X/46,XY mosaicism diagnosed prenatally, 72 had a normal male phenotype, 1 had a female phenotype, and only 3 males had hypospadias. Of 12 males whose gonads were examined, only 3 were abnormal. These data must be taken into account when counseling a family in which a 45,X/46,XY infant is discovered prenatally.

XXX, XXXX, AND XXXXX FEMALES

XXX Females

The 47,XXX (trisomy) chromosomal constitution is the most frequent extra–X chromosome abnormality in females, occurring in almost 1 in 1,000 liveborn females. In 68%, this condition is caused by maternal meiotic nondisjunction, but most 45,X and half of 47,XXY constitutions are caused by paternal sex chromosome errors. The phenotype is that of a normal female; affected infants and children are not recognized based on the genital appearance.

Sexual development and menarche are normal. Most pregnancies have resulted in normal infants. By 2 yr of age, delays in speech and language become evident and lack of coordination, poor academic performance, and immature behavior are seen in some. These girls tend to be tall and gangly, manifest behavior disorders, and are placed in special education classes. Using high-resolution MRI, 10 47,XXX subjects had lower amygdala volumes than 20 euploid controls; 10 47,XXY subjects had even lower amygdala volumes. In a review of 155 girls, 62% were physically normal. There is marked variability within the syndrome, and a small proportion of affected girls are well coordinated, socially outgoing, and academically superior.

XXXX and XXXXX Females

The great majority of females with these rare karyotypes have been intellectually challenged. Commonly associated defects are epicanthal folds, hypertelorism, clinodactyly, transverse palmar creases, radioulnar synostosis, and congenital heart disease. Sexual maturation is often incomplete and may not occur at all. Nevertheless, 3 women with the tetra-X syndrome gave birth, but no pregnancies were reported in 49,XXXXX women. Most 48,XXXX women tend to be tall, with an average height of 169 cm, whereas short stature is a common feature of the 49,XXXXX phenotype.

NOONAN SYNDROME

Girls with Noonan syndrome show certain anomalies that also occur in girls with 45,X Turner syndrome, but they have normal 46,XX chromosomes (see Chapter 81.4). The most common abnormalities are

the same as those described for males with Noonan syndrome (see Chapter 583.1). Short stature is one of the cardinal signs of this syndrome. The phenotype differs from Turner syndrome in several respects. Cognitive impairment is often present, the cardiac defect is most often pulmonary valvular stenosis or an atrial septal defect rather than an aortic defect, normal sexual maturation usually occurs but is delayed by 2 yr on average, and premature ovarian failure has been reported. Growth hormone therapy is approved by the FDA for use in Noonan syndrome patients with short stature.

OTHER OVARIAN DEFECTS

Some young women with no chromosomal abnormality are found to have streak gonads that may contain only occasional or no germ cells. Gonadotropins are increased. Cytotoxic drugs, especially alkylating agents such as cyclophosphamide and busulfan, procarbazine, etoposide, and exposure of the ovaries to irradiation for the treatment of malignancy are frequent causes of ovarian failure. Young women with Hodgkin disease demonstrate that combination chemotherapy and pelvic irradiation may be more deleterious than either therapy alone. Teenagers are more likely than older women to retain or recover ovarian function after irradiation or combined chemotherapy; normal pregnancies have occurred after such treatment. Treatment regimens may result in some ovarian damage in most girls treated for cancer. The median lethal dose for the human oocyte is estimated to be approximately 4 Gy; doses as low as 6 Gy have produced primary amenorrhea. Ovarian transposition before abdominal and pelvic irradiation in childhood can preserve ovarian function by decreasing the ovarian exposure to less than 4-7 Gy.

Autoimmune ovarian failure occurs in 60% of children older than 13 yr of age with type I autoimmune polyendocrinopathy (Addison disease, hypoparathyroidism, candidiasis). This condition, also known as *polyglandular autoimmune disease* type 1 is rare worldwide but not in Finland, where, as a result of a founder gene effect, it occurs in 1 in 25,000 people. The gene for this disorder is located on chromosome 21 and is associated with human leukocyte antigen (HLA) DR5. In patients with polyglandular autoimmune disease type 1 and ovarian failure, an association with HLA-A3 has been described. Affected girls may not develop sexually, or secondary amenorrhea may occur in young women. The ovaries may have lymphocytic infiltration or appear simply as streaks. Most affected patients have circulating steroid cell antibodies and autoantibodies to 21-hydroxylase. Among patients with polyglandular autoimmune syndromes, 5% were found to have hypogonadism.

The condition also occurs in young women as an isolated event or in association with other autoimmune disorders, leading to secondary amenorrhea (premature ovarian failure [POF]). It occurs in 0.2-0.9% of women younger than 40 yr of age. Premature ovarian failure is a heterogeneous disorder with many causes: chromosomal, genetic, enzymatic, infectious, and iatrogenic. When associated with autoimmune adrenal disease, steroid cell autoantibodies are always present. These antibodies react with P450scc, 17α-OH, or 21-OH enzymes. When associated with an entire host of endocrine and nonendocrine autoimmune diseases and not adrenal autoimmunity, steroid cell autoantibodies are rarely found. A second autoimmune disorder, often subclinical, is found in 10-39% of adult patients with POF. One 17 yr old with idiopathic thrombocytopenic purpura and 47,XXX chromosomes had autoimmune POF. Patients with POF do not have the neurocognitive defects found in Turner syndrome patients.

Galactosemia, particularly the classical form of the disease, usually results in ovarian damage, beginning during intrauterine life. Levels of FSH and luteinizing hormone (LH) are elevated early in life. Ovarian damage may be caused by deficient uridine diphosphate-galactose (see Chapter 87). The **Denys-Drash syndrome,** caused by a *WT1* mutation, can result in ovarian dysgenesis.

Ataxia-telangiectasia may be associated with ovarian hypoplasia and elevated gonadotropins; the cause is unknown. Gonadoblastomas and dysgerminomas have occurred in a few girls.

Hypergonadotropic hypogonadism has been postulated to also occur because of the resistance of the ovary to both endogenous and exogenous gonadotropins (Savage syndrome). This condition occurs also in women with POF. Antiovarian antibodies or FSH receptor abnormalities may cause this condition. Mutation of the FSH receptor gene has been reported as an autosomal recessive condition (see Chapter 582). A few females with 46,XX chromosomes presenting in primary amenorrhea with elevated gonadotropin levels were found to have inactivating mutations of the LH receptor gene. This suggests that LH action is needed for normal follicular development and ovulation. Other genetic defects associated with ovarian failure include mutations in *FOXL2, GNAS, CYP17,* and *CYP19.* Some data also suggest that mutations within the gene encoding transcription factor SF-1 are associated with early ovarian failure.

Bibliography is available at Expert Consult.

586.2 Hypogonadotropic Hypogonadism in the Female (Secondary Hypogonadism)

Alvina R. Kansra and Patricia A. Donohoue

Hypofunction of the ovaries can result from failure to secrete normal pulses of the gonadotropins LH (luteinizing hormone) and FSH. Hypogonadotropic hypogonadism may occur if the hypothalamic-pituitary-gonadal axis is interrupted either at the hypothalamic or pituitary level. The mechanisms that result in hypogonadotropic hypogonadism include failure of the hypothalamic luteinizing hormone–releasing hormone (also known as *gonadotropin-releasing hormone*) pulse generator or inability of the pituitary to respond with secretion of LH and FSH. It is often difficult to distinguish between marked constitutional delay and hypogonadotropic hypogonadism.

ETIOLOGY

Hypopituitarism

Hypogonadotropic hypogonadism is most commonly seen with multiple pituitary hormone deficiencies resulting from malformations (e.g., septooptic dysplasia, other midline defects), pituitary transcription factor defects such as in PROP-1, or lesions of the pituitary that are acquired postnatally. Familial isolated gonadotropin deficiency associated with anosmia (Kallmann syndrome) was described in 1944. Many other genetic causes for hypogonadotropic hypogonadism have been identified. A gene important in luteinizing hormone–releasing hormone secretion is named *KISS* (encoding the protein kisspeptin), which is suggested to play a significant role in the development of the luteinizing hormone–releasing hormone–secreting cells. Another set of genes recently implicated in hypogonadotropic hypogonadism are the genes for neurokinin B *(TAC3)* and its receptor *(TAC3R).*

In children with idiopathic hypopituitarism, the defect is usually found in the hypothalamus. In these patients, administration of gonadotropin-releasing hormone results in increased plasma levels of FSH and LH, establishing the integrity of the pituitary gland.

Hypogonadotropic hypogonadism is less common than hypergonadotropic hypogonadism. The latter condition, when associated with LH excess, underlies polycystic ovarian syndrome (Stein-Leventhal syndrome; see Chapter 552).

Isolated Deficiency of Gonadotropins

This heterogeneous group of disorders is characterized more fully with the use of the gonadotropin-releasing hormone analog stimulation test. In most children, the pituitary gland is normal, and the defect causing gonadotropin deficiency resides in the hypothalamus. Patients with hyperprolactinemia, most often caused by a pituitary prolactin-secreting adenoma, often have suppression of gonadotropin secretion. If breast development has occurred, then galactorrhea and amenorrhea are frequently seen.

Several sporadic instances of anosmia with hypogonadotropic hypogonadism have been reported. **Anosmic** hypogonadal females have

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also been reported in kindreds with Kallmann syndrome, but hypogonadism more frequently affects the males in these families. Mutations in the gene for the β-subunit of FSH and LH have been reported.

Some autosomal recessive disorders, such as the Laurence-Moon-Biedl, multiple lentigines, and Carpenter syndromes, appear in some instances to include gonadotropic hormone deficiency. Patients with Prader-Willi syndrome usually have some degree of hypogonadotropic hypogonadism. Girls with severe thalassemia may have gonadotropin deficiency from pituitary damage caused by chronic iron overload secondary to multiple transfusions. Anorexia nervosa frequently results in hypogonadotropic hypogonadism. The rare patients described with leptin deficiency or leptin receptor defects have failure of pubertal maturation because of gonadotropin deficiency.

DIAGNOSIS

The diagnosis may be apparent in patients with other deficiencies of pituitary tropic hormones, but, as in males, it is difficult to differentiate isolated hypogonadotropic hypogonadism from physiologic delay of puberty. Repeated measurements of FSH and LH, particularly during sleep, may reveal the rising levels that herald the onset of puberty. Stimulation testing with gonadotropin-releasing hormone or one of its analogs may help establish the diagnosis. Morbidity for both men and women with hypogonadism includes infertility and an increased risk of osteoporosis.

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Chapter 587

Pseudoprecocity Resulting from Lesions of the Ovary

Alvina R. Kansra and Patricia A. Donohoue

Girls with signs of early puberty may, in rare circumstances, have a lesion of the ovary as the etiology. These include tumors or cysts that secrete estrogenic, androgenic, or both types of hormones. In these patients the sex steroid production is not mediated by pituitary gonadotropin secretion, and thus they are said to produce pseudoprecocity.

Ovarian tumors are rare in the pediatric population, occurring at a rate of less than 3 in 100,000. Most ovarian masses are benign, but 10-30% may be malignant. If they occur before 8 yr of age they may cause signs of puberty. Ovarian malignancies, the most common genital neoplasms in adolescence, account for only 1% of childhood cancers. More than 60% are germ cell tumors, most of which are dysgerminomas that can secrete tumor markers as well as sex hormones (see Chapter 503). Five to 10% of germ cell tumors occur in phenotypic females with abnormal gonads associated with the presence of a Y chromosome. Next most common are epithelial cell tumors (20%), and nearly 10% are sex cord/stromal tumors (granulosa, Sertoli cell, and mesenchymal tumors). Multiple tumor markers can be seen in ovarian tumors, including α-fetoprotein, human chorionic gonadotropin, carcinoembryonic antigen, oncoproteins, p105, p53, *KRAS* mutations, cyclin D_1, epidermal growth factor–related proteins and receptors, cathepsin B, and others. Variable levels of inhibin–activin subunit gene expression have been detected in ovarian tumors.

Functioning lesions of the ovary consist of benign cysts or malignant tumors. The majority synthesize estrogens; a few synthesize androgens. The most common estrogen-producing ovarian tumor causing precocious puberty is the granulosa cell tumor. Other tumors that can cause precocious puberty are thecomas, luteomas, mixed types, theca-lutein and follicular cysts, and ovarian tumors (i.e., teratoma, choriocarcinoma, and dysgerminoma).

ESTROGENIC LESIONS OF THE OVARY

These lesions cause isosexual precocious sexual development but account for only a small percentage of all cases of precocity. Benign ovarian follicular cysts are the most common tumors associated with isosexual precocious puberty in girls; they may rarely be gonadotropin dependent. Gonadotropin-independent follicular cysts that produce estrogen are often associated with the McCune-Albright syndrome.

Juvenile Granulosa Cell Tumor

In childhood, the most common neoplasm of the ovary with estrogenic manifestations is the granulosa cell tumor, although it makes up only 1-10% of all ovarian tumors. These tumors have distinctive histologic features that differ from those encountered in older women (adult granulosa cell tumor). The cells have high mitotic activity, follicles are often irregular, Call-Exner bodies are rare, and luteinization is frequent. The tumor may be solid or cystic, or both. It usually is benign. In a few instances, this tumor has been associated with multiple enchondromas **(Ollier disease)** and, in fewer still, with multiple subcutaneous hemangiomas **(Maffucci syndrome).**

Clinical Manifestations and Diagnosis

The juvenile granulosa cell tumor has been observed in newborns and may manifest with sexual precocity at 2 yr of age or younger; about half these tumors occurred before 10 yr of age. The mean age at diagnosis is 7.5 yr. The tumors are almost always unilateral. The breasts become enlarged, rounded, and firm, and the nipples prominent. The external genitals resemble those of a normal girl at puberty, and the uterus is enlarged. A white vaginal discharge is followed by irregular or cyclic menstruation. Ovulation, however, does not occur. The presenting manifestation may be abdominal pain or swelling. Pubic hair is usually absent unless there is mild virilization.

A mass is readily palpable in the lower portion of the abdomen in most children by the time sexual precocity is evident. The tumor may be small, however, and escape detection even on careful rectal and abdominal examination; the tumors may be detected by ultrasonography, but multidetector CT scans are most sensitive. Most such tumors (90%) are diagnosed at very early stages of malignancy.

Plasma estradiol levels are markedly elevated. Plasma levels of gonadotropins are suppressed and do not respond to gonadotropin-releasing hormone analog stimulation. Levels of antimüllerian hormone, inhibin B, and α-fetoprotein may be elevated. Activating mutations of $G_S\alpha$ are seen in 30%, and GATA-4 expression is retained in the more aggressive tumors while antimüllerian hormone levels are inversely proportional to tumor size. Osseous development is moderately advanced. Several case reports showing the association of 45,X/46,XY karyotype and ambiguous genitalia with ovarian granulosa tumor have been published in literature.

Treatment and Prognosis

The tumor should be removed as soon as the diagnosis is established. Prognosis is excellent because fewer than 5% of these tumors in children are malignant. Advanced-stage tumors, however, behave aggressively and require difficult decisions regarding surgical approaches as well as the use of irradiation and chemotherapy. In adults with granulosa cell tumors, p53 expression is associated with unfavorable prognosis. Vaginal bleeding immediately after removal of the tumor is common. Signs of precocious puberty abate and may disappear within a few months after the operation. The secretion of estrogens returns to normal.

Sex cord tumor with annular tubules is a distinctive tumor, thought to arise from granulosa cells, that occurs primarily in patients with Peutz-Jeghers syndrome. These tumors are multifocal, bilateral, and usually benign. The presence of calcifications aids ultrasonographic detection. Increased aromatase production by these tumors results in gonadotropin-independent precocious puberty. Inhibin A and B levels

are elevated and decrease after tumor removal. In 1 study, 9 of 13 sex cord/stromal tumors exhibited follicle-stimulating hormone receptor mutations, suggesting a role for such mutation in the development of these tumors.

Chorioepithelioma has been reported only rarely. This highly malignant tumor is thought to arise from a preexisting teratoma. The usually unilateral tumor produces large amounts of human chorionic gonadotropin, which stimulates the contralateral ovary to secrete estrogen. Elevated levels of human chorionic gonadotropin are diagnostic.

Follicular Cyst

Small ovarian cysts (<0.7 cm in diameter) are common in prepubertal children. At puberty and in girls with true isosexual precocious puberty, larger cysts (1-6 cm) are often seen; these are secondary to stimulation by gonadotropins. However, similar larger cysts occur occasionally in young girls with precocious puberty in the absence of luteinizing hormone and follicle-stimulating hormone. Because surgical removal or spontaneous involution of these cysts results in regression of pubertal changes, there is little doubt that they are its cause. The mechanism of production of these autonomously functioning cysts is unknown. Such cysts may form only once, or they may disappear and recur, resulting in waxing and waning of the signs of precocious puberty. They may be unilateral or bilateral. The sexual precocity that occurs in young girls with **McCune-Albright syndrome** is usually associated with autonomous follicular cysts caused by a somatic-activating mutation of the $G_S\alpha$-protein occurring early in development (see Chapter 562.6). Gonadotropins are suppressed, and estradiol levels are often markedly elevated, but they may fluctuate widely and even temporarily may return to normal. Gonadotropin-releasing hormone analog stimulation fails to evoke an increase in gonadotropins. Ultrasonography is the method of choice for the detection and monitoring of such cysts. Aromatase inhibitors are shown to be the mainstay of the therapy in females with McCune-Albright syndrome and persistent estradiol elevation. A short period of observation to ascertain the lack of spontaneous resolution is advisable before cyst aspiration or cystectomy is considered. Cystic neoplasms must be considered in the differential diagnosis.

ANDROGENIC LESIONS OF THE OVARY

Virilizing ovarian tumors are rare at all ages but particularly so in prepubertal girls. **Arrhenoblastoma** has been reported as early as 14 days of age, but few cases have been reported in girls younger than 16 yr of age.

The **gonadoblastoma** occurs exclusively in dysgenetic gonads, particularly in phenotypic females who have a Y chromosome or a Y fragment in their genotype (46,XY; 45,X/46,XY; 45,X/46,X-fra). As noted above, there is a proposed gonadoblastoma locus on the Y chromosome (GBY). The tumors may be bilateral. Virilization occurs with some but not all tumors. The clinical features are the same as those seen in patients with virilizing adrenal tumors and include accelerated growth, acne, clitoral enlargement, and growth of sexual hair. A palpable, abdominal mass is found in about 50% of patients. Plasma levels of testosterone and androstenedione are elevated, and gonadotropins are suppressed. Ultrasonography, CT, and MRI usually localize the lesion. The dysgenetic gonad of phenotypic females with a Y chromosome or fragment of Y chromosome containing GBY should be removed prophylactically. When a unilateral tumor is removed, the contralateral dysgenetic gonad should also be removed. Association of gonadoblastoma and WAGR (Wilms, aniridia, genitourinary anomalies, mental retardation) syndrome is also reported in the literature. In an immunohistochemical study of 2 gonadoblastomas, expressions of *WT1, p53,* and *MIS*, as well as inhibin, were all demonstrated.

Virilizing manifestations occur occasionally in girls with **juvenile granulosa cell tumors.** Adrenal rests and hilum cell tumors rarely lead to virilization. Activating mutations of G-protein genes have been described in ovarian (and testicular) tumors. $G_S\alpha$ mutations, usually seen in gonadal tumors associated with **McCune-Albright syndrome,** were also noted in 4 of 6 Leydig cell tumors (3 ovarian, 1 testicular). Two granulosa cell tumors and 1 thecoma of 10 ovarian tumors studied were found to have *GIP-2* mutations.

Sertoli-Leydig cell tumors, rare sex cord/stromal neoplasms, constitute less than 1% of ovarian tumors. The average age at diagnosis is 25 yr; less than 5% of these tumors occur before puberty. α-Fetoprotein levels may be mildly elevated. In one 12 mo old with Sertoli-Leydig cell tumor presenting with isosexual precocity the only detectable tumor marker was the serum inhibin level, with elevations in both A and B subunits. Five-year survival rates are 70-90%.

Of 102 consecutive patients who underwent surgery because of ovarian masses over a 15 yr period, the presenting symptoms were acute abdominal pain in 56% and abdominal or pelvic mass in 22%. Of 9 children whose cause for surgery was presumed malignancy, 3 had dysgerminomas, 2 had teratomas, 2 had juvenile granulosa cell tumors, 1 had a Sertoli-Leydig cell tumor, and 1 had a yolk sac tumor.

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Chapter 588

Disorders of Sex Development

Patricia A. Donohoue

SEX DIFFERENTIATION

See also Chapter 582.

In normal differentiation, the final form of all sexual structures is consistent with normal sex chromosomes (either XX or XY). A 46,XX complement of chromosomes as well as genetic factors such as DAX1 (dosage-sensitive/sex-reversal adrenal hypoplasia on the X chromosome), the signaling molecule WNT-4, and R-Spondin1 are among the many needed for the development of normal ovaries. Development of the male phenotype is potentially more complex. It requires a Y chromosome and, specifically, an intact *SRY* (sex-determining region on the Y chromosome) gene, which, in association with other genes such as *SOX9, SF-1* (steroidogenic factor-1), *WT1* (Wilms tumor 1), and others (see Chapter 582), directs the undifferentiated gonad to become a testis. Aberrant recombinations may result in X chromosomes carrying *SRY,* resulting in XX males, or Y chromosomes that have lost *SRY,* resulting in XY females. Epigenetic causes of abnormal sex differentiation have been shown in plants, invertebrates, and vertebrates, and will likely contribute to human disorders of sex development (DSDs) as well.

Antimüllerian hormone (AMH) causes the müllerian ducts to regress; in its absence, they persist as the uterus, fallopian tubes, cervix, and upper vagina. AMH activation in the testes may require the *SF-1* gene. By about 8 wk of gestation, the Leydig cells of the testis begin to produce testosterone. During this critical period of male differentiation, testosterone secretion is stimulated by placental human chorionic gonadotropin (hCG), which peaks at 8-12 wk. In the latter half of pregnancy, lower levels of testosterone are maintained by luteinizing hormone (LH) secreted by the fetal pituitary. Testosterone produced locally initiates development of the ipsilateral wolffian duct into the epididymis, vas deferens, and seminal vesicle. Development of the external genitalia also requires dihydrotestosterone (DHT), the more active metabolite of testosterone. DHT is produced largely from circulating testosterone and is necessary to fuse the genital folds to form the penis and scrotum. DHT is also produced via an alternative biosynthetic pathway from androstanediol, and this pathway must be intact for normal and complete prenatal virilization to occur. A functional androgen receptor, produced by an X-linked gene, is required for testosterone and DHT to induce these androgen effects.

In the XX fetus with normal long and short arms of the X chromosome, the bipotential gonad develops into an ovary by about the 10th-11th wk. This occurs only in the absence of SRY, testosterone, and AMH and requires a normal gene in the dosage-sensitive/sex-reversal

Table 588-1 Revised Nomenclature

PREVIOUS	CURRENTLY ACCEPTED
Intersex	Disorders of sex development (DSD)
Male pseudohermaphrodite	46,XY DSD
Undervirilization of an XY male	46,XY DSD
Undermasculinization of an XY male	46,XY DSD
46,XY intersex	46,XY DSD
Female pseudohermaphrodite	46,XX DSD
Overvirilization of an XX female	46,XX DSD
Masculinization of an XX female	46,XX DSD
46,XX intersex	46,XX DSD
True hermaphrodite	Ovotesticular DSD
Gonadal intersex	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

From Lee PA, Houk CP, Ahmed SF, et al: Consensus statement on management of intersex disorders, Pediatrics *118:e488–e500, 2006.*

locus DAX1, the WNT-4 molecule, and R-Spondin1. A female external phenotype develops in the absence of fetal gonads. However, the male phenotype development requires androgen production and action. Estrogen is unnecessary for normal prenatal sexual differentiation, as demonstrated by 46,XX patients with aromatase deficiency and by mice without estradiol receptors.

Chromosomal aberrations may result in ambiguity of the external genitalia. Conditions of aberrant sex differentiation may also occur with the XX or XY genotype. The appropriate term for what was previously called *intersex* is **DSD.** This term defines a condition "in which development of chromosomal, gonadal, or anatomical sex is atypical." It is increasingly preferable to use the term "atypical genitalia" rather than "ambiguous genitalia." Tables 588-1 and 588-2 compare previous terms with their revised etiologic classification nomenclature. Table 582-1 in Chapter 582 lists some of the genes that are mutated in various forms of DSD.

The definition of atypical or ambiguous genitalia, in a broad sense, is any case in which the external genitalia do not appear completely male or completely female. Although there are standards for genital size dimensions, variations in size of these structures do not always constitute ambiguity.

Development of the external genitalia begins with the potential to be either male or female (Fig. 588-1). Virilization of a female, the most common form of DSD, results in varying phenotypes (Fig. 588-2), that develop from the basic bipotential genital appearances of the embryo (Fig. 588-1).

DIAGNOSTIC APPROACH TO THE PATIENT WITH ATYPICAL OR AMBIGUOUS GENITALIA

The appearance of the external genitalia is rarely diagnostic of a particular disorder, and thus does not often allow distinction among the various forms of DSD. The most common forms of 46,XX DSD are virilizing forms of congenital adrenal hyperplasia. It is important to note that in 46,XY DSD, the specific diagnosis is not found in up to 50% of cases; partial androgen insensitivity syndrome and pure gonadal dysgenesis are common identifiable etiologies in XY DSD. At 1 center with a large experience, the etiologies of DSD in 250 patients over 25 yr were compiled. The 6 most common diagnoses accounted for 50% of the cases. These included virilizing congenital adrenal hyperplasia (14%), androgen insensitivity syndrome (10%), mixed gonadal dysgenesis (8%), clitoral/labial anomalies (7%), hypogonadotropic hypogonadism (6%), and 46,XY small-for-gestational-age males with hypospadias (6%).

Table 588-2 Etiologic Classification of Disorders of Sex Development (DSD)

46,XX DSD
Androgen Exposure
Fetal/Fetoplacental Source
21-Hydroxylase (P450c21 or CYP21) deficiency
11β-Hydroxylase (P450c11 or CYP11B1) deficiency
3β-Hydroxysteroid dehydrogenase II (3β-HSD II) deficiency
Cytochrome P450 oxidoreductase (POR)
Aromatase (P450arom or CYP19) deficiency
Glucocorticoid receptor gene mutation
Maternal Source
Virilizing ovarian tumor
Virilizing adrenal tumor
Androgenic drugs
Disorder of Ovarian Development
XX gonadal dysgenesis
Testicular DSD (SRY+, SOX9 duplication)
Undetermined Origin
Associated with genitourinary and gastrointestinal tract defects

46,XY DSD
Defects in Testicular Development
Denys-Drash syndrome (mutation in *WT1* gene)
WAGR syndrome (Wilms tumor, aniridia, genitourinary malformation, retardation)
Deletion of 11p13
Campomelic syndrome (autosomal gene at 17q24.3-q25.1) and *SOX9* mutation
XY pure gonadal dysgenesis (Swyer syndrome)
Mutation in *SRY* gene
XY gonadal agenesis
Unknown cause
Deficiency of Testicular Hormones
Leydig cell aplasia
Mutation in LH receptor
Lipoid adrenal hyperplasia (P450scc or CYP11A1) deficiency; mutation in StAR (steroidogenic acute regulatory protein)
3β-HSD II deficiency
17-Hydroxylase/17,20-lyase (P450c17 or CYP17) deficiency
Persistent müllerian duct syndrome because of antimüllerian hormone gene mutations or receptor defects for antimüllerian hormone
Defect in Androgen Action
Dihydrotestosterone deficiency because of 5α-reductase II mutations or *AKR1C2/AKR1C4* mutations
Androgen receptor defects:
Complete androgen insensitivity syndrome
Partial androgen insensitivity syndrome
(Reifenstein and other syndromes)
Smith-Lemli-Opitz syndrome (defect in conversion of 7-dehydrocholesterol to cholesterol, DHCR7)
Ovotesticular DSD
XX
XY
XX/XY chimeras
Sex Chromosome DSD
45,X (Turner syndrome and variants)
47,XXY (Klinefelter syndrome and variants)
45,X/46,XY (mixed gonadal dysgenesis, sometimes a cause of ovotesticular DSD)
46,XX/46,XY (chimeric, sometimes a cause of ovotesticular DSD)

From Lee PA, Houk CP, Ahmed SF, et al: Consensus statement on management of intersex disorders, Pediatrics *118:e488–e500, 2006.*

The relative lack of established diagnoses in 46,XY DSD and the resulting lack of specific management emphasizes the need for thorough diagnostic evaluations. These include biochemical characterization of possible steroidogenic enzymatic defects in each patient with genital ambiguity. The parents need counseling about the potentially complex nature of the baby's condition, and guidance as to how to deal with their well-meaning but curious friends and family members. The

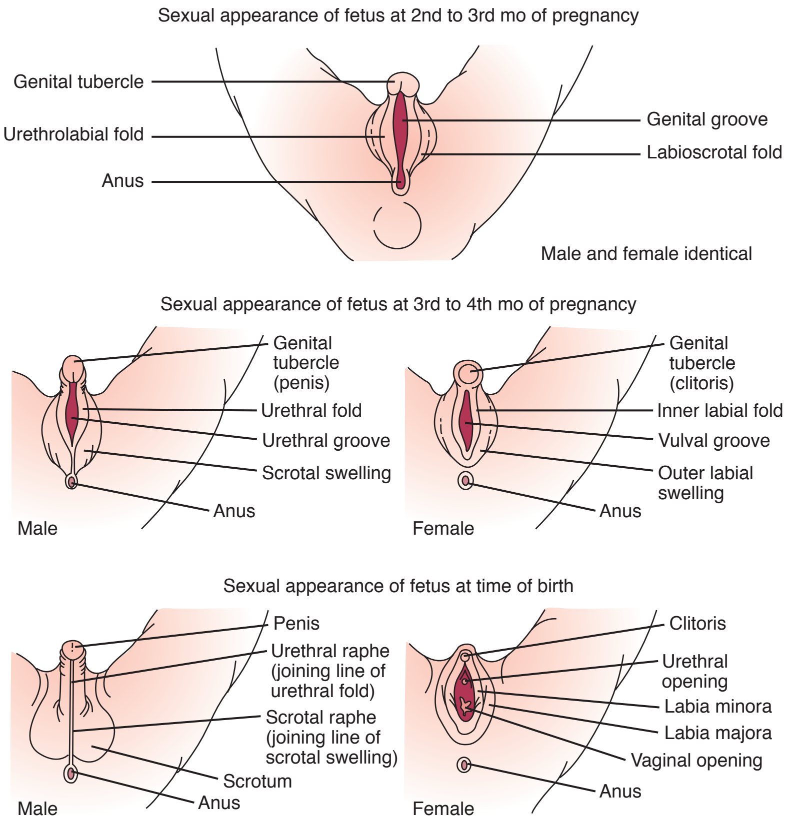

Figure 588-1 Schematic demonstration of differentiation of normal male and female genitalia during embryogenesis. *(From Zitelli BJ, Davis HW: Atlas of pediatric physical diagnosis, ed 4, St. Louis, 2002, Mosby, p. 328.)*

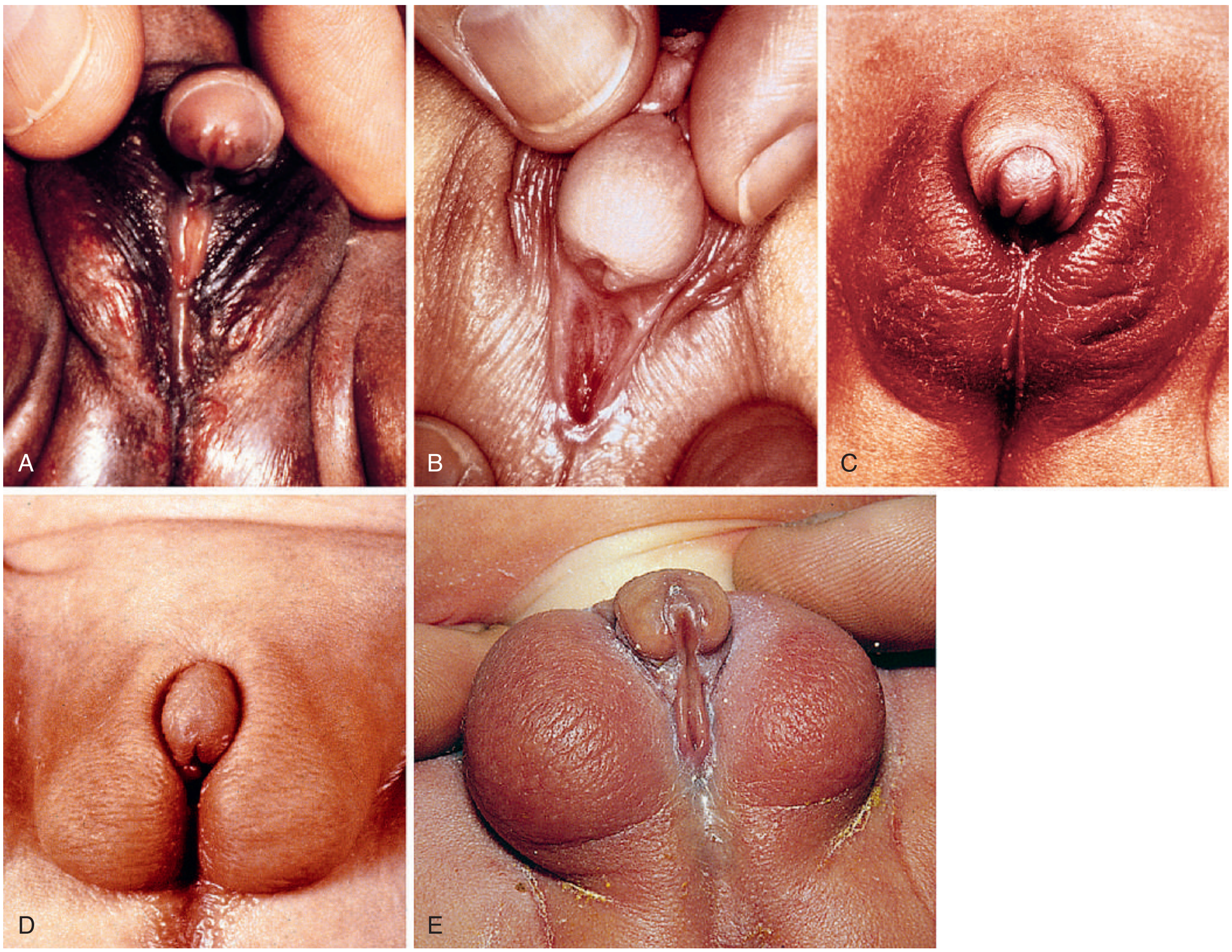

Figure 588-2 Examples of atypical genitalia. These cases include ovotesticular disorder of sexual development **(A)** and congenital virilizing adrenal hyperplasia **(B-E)**. *(**B-D** courtesy of D. Becker, MD, Pittsburgh. From Zitelli BJ, Davis HW:* Atlas of pediatric physical diagnosis, *ed 4, St. Louis, 2002, Mosby, p. 329.)*

Table 588-3 Ambiguous Genitalia: Steps in Establishing the Diagnosis

	21-OH DEFICIENCY	GONADAL DYSGENESIS WITH Y CHROMOSOME	OVOTESTICULAR DSD	PARTIAL ANDROGEN INSENSITIVITY	BLOCK IN TESTOSTERONE SYNTHESIS
CLINICAL FEATURE					
Palpable gonad(s)	–	±	±	+	+
Uterus present*	+	+	Usually	–	–
Increased skin pigmentation	±	–	–	–	–
Sick baby	±	–	–	–	±
Dysmorphic features	–	±	–	–	–
DIAGNOSTIC CONSIDERATIONS					
Serum 17-OHP	Elevated	Normal	Normal	Normal	Normal
Electrolytes	Possibly abnormal	Normal	Normal	Normal	Possibly abnormal
Karyotype	46,XX	45,X/46,XY or others	46,XX	46,XY	46,XY
Testosterone response to hCG	NA	Positive	Normal or reduced	Positive response	Reduced or absent
Gonadal biopsy	NA	Dysgenetic gonad	Ovotestis	Normal testis with ± Leydig cell hyperplasia	Normal testis
Other testing				Genital skin fibroblast culture For AR assay Or DNA screening for AR mutations in blood cells	Measure Testosterone Precursors

*As determined by ultrasound or rectal examination.

AR, androgen receptor; DSD, disorders of sex development; hCG, human chorionic gonadotropin; 21-OH, 21-hydroxylase; 17-OHP, 17-hydroxyprogesterone; NA, not applicable.

Adapted from Donohoue PA, Saenger PH: Ambiguous genitalia. In Finberg L, Kleinman RE, editors: Saunders manual of pediatric practice, *Philadelphia, 2002, WB Saunders, p. 874.*

evaluation and management should be carried out by a multidisciplinary team of experts that includes pediatric endocrinology, pediatric surgery/urology, pediatric radiology, newborn medicine, genetics, and psychology. Once the sex of rearing has been agreed on by the family and team, treatment can be organized. Genetic counseling should be offered when the specific diagnosis is established.

After a complete history and physical exam, the common diagnostic approach includes multiple steps, described in the following outline. These steps are usually performed simultaneously rather than waiting for results of 1 test prior to performing another, because of the sensitive and sometimes urgent nature of the condition. Careful attention to the presence of physical features other than the genitalia is crucial, to determine if a diagnosis of a particular multisystem syndrome is possible. These are described in more detail in Chapters 588.1, 588.2, and 588.3 below. Table 588-3 summarizes many of the features of commonly encountered causes of DSD.

Diagnostic tests include the following:

1. Karyotype, with rapid determination of sex chromosomes (in many centers this is available within 24-48 hr)
2. Other blood tests
   a. Screen for congenital adrenal hyperplasia: cortisol biosynthetic precursors and adrenal androgens (particularly 17-hydroxyprogesterone and androstenedione for 21-hydroxylase deficiency, the most common form)
   b. Screen for androgens and their biosynthetic precursors
   c. Screen for gonadal response to gonadotropin in patients suspected of having testicular gonads: stimulation with injections of hCG; measure testosterone and DHT before and after hCG
   d. Molecular genetic analyses for SRY and other Y-specific loci
   e. Gonadotropin levels
3. The internal anatomy of patients with ambiguous genitalia can be defined with 1 or more of the following studies:
   a. Voiding cystourethrogram
   b. Endoscopic examination of the genitourinary tract
   c. Pelvic ultrasound; renal and adrenal ultrasound
   d. Pelvic CT or MRI
   e. Exploratory laparoscopy

588.1 46,XX DSD

Patricia A. Donohoue

In this condition, the genotype is XX and the gonads are ovaries but the external genitalia are virilized. There is no significant AMH production because the gonads are ovaries. Thus the uterus, fallopian tubes, and cervix develop. The varieties and causes of this condition are relatively few. Most instances result from exposure of the female fetus to excessive exogenous or endogenous androgens during intrauterine life. The changes consist principally of virilization of the external genitalia (clitoral hypertrophy and labioscrotal fusion).

CONGENITAL ADRENAL HYPERPLASIA

See Chapter 576.1.

This is the most common cause of genital ambiguity and of 46,XX DSD. Females with the 21-hydroxylase and 11-hydroxylase defects are the most highly virilized, although minimal virilization also occurs with the type II 3β-hydroxysteroid dehydrogenase defect (see Fig. 588-1). Female patients with salt-losing congenital adrenal hyperplasia tend to have more virilization than do non–salt-losing patients. Masculinization may be so intense that a complete penile urethra results, and the patient may appear to be a male with bilateral cryptorchidism.

AROMATASE DEFICIENCY

In genotypic females, the rare condition of aromatase deficiency during fetal life leads to 46,XX DSD and results in hypergonadotropic hypogonadism at puberty because of ovarian failure to synthesize estrogen.

Two 46,XX infants had enlargement of the clitoris and posterior labial fusion at birth. In 1 instance, maternal serum and urinary levels of estrogen were very low and serum levels of androgens were high. Cord serum levels of estrogen were also extremely low, but those of androgen were elevated. The second patient also had virilization of unknown cause since birth, but the aromatase deficiency was not diagnosed until 14 yr of age, when she had further virilization and failed to go into puberty. At that time, she had elevated levels of gonadotropins and androgens but low estrogen levels, and ultrasonography

revealed large ovarian cysts bilaterally. These 2 patients demonstrate the important role of aromatase in the conversion of androgens to estrogens. Additional female and male patients with aromatase deficiency as a consequence of mutations in the *aromatase gene (CYP19)* are known. Two siblings were described. The 28 yr old XX proband was 177.6 cm tall (+2.5 SD) after having received hormonal replacement therapy; her 24 yr old brother was 204 cm tall (+3.7 SD), and had a bone age of 14 yr. Low-dose estradiol replacement, carefully adjusted to maintain normal age-appropriate levels, may be indicated for affected females, even prepubertally.

GLUCOCORTICOID RECEPTOR GENE MUTATION

A 9 yr old girl with 46,XX disorder of sexual development, thought to be caused by 21-hydroxylase deficiency (congenital adrenal hyperplasia) since the age of 5 yr, had elevated cortisol levels both at baseline and after dexamethasone, hypertension, and hypokalemia, suggestive of the diagnosis of generalized glucocorticoid resistance. A novel homozygous mutation in exon 5 of the glucocorticoid receptor was demonstrated. In this Brazilian family, the condition was autosomal recessive.

Cytochrome P450 oxidoreductase, encoded by a gene on 7q11.2, is a cofactor implicated in combined P450C17 and P450C21 steroidogenic defects. Girls are born with ambiguous genitalia, but the virilization does not progress postnatally and androgen levels are normal or low. Boys may be born undervirilized. Both may exhibit bony abnormalities seen in **Antley-Bixler syndrome**. Conversely, in a series of Antley-Bixler syndrome patients, those with ambiguous genitalia and disordered steroidogenesis had cytochrome P450 oxidoreductase deficiency. Those without genital ambiguity with normal steroidogenesis had fibroblast growth factor receptor 2 (*FGFR2)* mutations. The cardinal features of Antley-Bixler syndrome include craniosynostosis, severe midface hypoplasia, proptosis, choanal atresia/stenosis, frontal bossing, dysplastic ears, depressed nasal bridge, radiohumeral synostosis, long bone fractures and femoral bowing, and urogenital abnormalities.

VIRILIZING MATERNAL TUMORS

Rarely, the female fetus has been virilized during fetal life by a maternal androgen-producing tumor. In a few cases, the lesion was a benign adrenal adenoma, but all others were ovarian tumors, particularly androblastomas, luteomas, and Krukenberg tumors (Table 588-4). **Maternal virilization** may be manifested by enlargement of the clitoris, acne, deepening of the voice, decreased lactation, hirsutism, and elevated levels of androgens. In the infant, there is enlargement of the clitoris of varying degrees, often with labial fusion. Mothers of children with unexplained 46,XX DSD should undergo physical examination and measurements of their own levels of plasma testosterone, dehydroepiandrosterone sulfate, and androstenedione.

Table 588-4 Sources of Maternal-Derived Androgens

ENDOGENOUS	EXOGENOUS
BENIGN	SYNTHETIC ANDROGENS
Luteoma of pregnancy	Danazol
Adrenal adenoma	Progestins (medroxyprogesterone acetate)
Hyperreactio luteinalis	Potassium-sparing diuretics
Thecoma/fibroma	
Stromal hyperthecosis	
Brenner tumor	
Serous cystadenoma	
Mature cystic teratoma (dermoid cyst)	
MALIGNANT	
Metastatic carcinomas (Krukenberg tumor)	
Sex-cord stromal tumors—granulosa cell and Sertoli-Leydig tumors	
Adrenal cortical carcinoma	
Cystadenocarcinoma	
Hilar cell tumor	

From Auchus RJ, Chang AY: 46,XX DSD: the masculinised female. Best Pract Res Clin Endocrinol Metab *24:219–242, 2010, Table 2, p. 237.*

ADMINISTRATION OF ANDROGENIC DRUGS TO WOMEN DURING PREGNANCY

Testosterone and 17-methyltestosterone have been reported to cause 46,XX DSD in some instances (see Table 588-4). The greatest number of cases has resulted from the use of certain progestational compounds for the treatment of threatened abortion. These progestins have been replaced by nonvirilizing ones.

Infants with virilization and 46,XX chromosomes and caudal anomalies have been reported for whom no virilizing agent could be identified. In such instances, the disorder is usually associated with other congenital defects, particularly of the urinary and gastrointestinal tracts. Y-specific DNA sequences, including SRY, are absent. In 1 case, a scrotal raphe and elevated testosterone levels were found, but the cause remains unknown.

Bibliography is available at Expert Consult.

588.2 46,XY DSD

Patricia A. Donohoue

In this condition, the genotype is XY but the external genitalia are either not completely virilized, are ambiguous (atypical), or are completely female. When gonads can be found, they invariably contain testicular elements; their development ranges from rudimentary to normal. Because the process of normal virilization in the fetus is so complex, it is not surprising that there are many varieties and causes of 46,XY DSD. As noted earlier, the etiology of 46,XY DSD is not identified in approximately 50% of cases.

DEFECTS IN TESTICULAR DIFFERENTIATION

The first step in male differentiation is conversion of the bipotential gonad into a testis. In the XY fetus, if there is a deletion of the short arm of the Y chromosome or of the *SRY* gene, male differentiation does not occur. The phenotype is female; müllerian ducts are well developed because of the absence of AMH, and gonads consist of undifferentiated streaks. By contrast, even extreme deletions of the long arm of the Y chromosome (Yq−) have been found in normally developed males, most of whom are azoospermic and have short stature. This indicates that the long arm of the Y chromosome normally has genes that prevent these manifestations. In many syndromes in which the testes fail to differentiate, Y chromosomes are morphologically normal.

Denys-Drash Syndrome

The constellation of nephropathy with ambiguous genitalia and **bilateral Wilms tumor** is the major phenotype of this syndrome. Most reported cases have been 46,XY. Müllerian ducts are often present, indicating a global deficiency of fetal testicular function. Patients with a 46,XX karyotype have normal external genitalia. The onset of proteinuria in infancy progresses to **nephrotic syndrome** and end-stage renal failure by 3 yr of age, with focal or diffuse mesangial sclerosis being the most consistent histopathologic finding. Wilms tumor usually develops in children younger than 2 yr of age and is frequently bilateral. Gonadoblastomas have also been reported.

Several mutations of the *WT1* gene, located on chromosome 11p13, have been found. *WT1* functions as a tumor-suppressor gene and a transcriptional factor, and is expressed in the genital ridge and fetal gonads. Nearly all reported mutations have been near or within the zinc finger–coding region. One report found a zinc finger domain mutation in the *WT1* alleles of a patient with no genitourinary abnormalities, suggesting that some cases of sporadic Wilms tumor may carry the *WT1* mutation. Different mutations of the *WT1* gene, con-

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stitutional heterozygote mutations at intron 9, have been described in **Fraser syndrome,** a condition of nonspecific focal and segmental glomerulosclerosis, 46,XY gonadal dysgenesis, and frequent gonadoblastoma, but **without** Wilms tumor.

WAGR Syndrome

This acronymic contiguous gene syndrome consists of Wilms tumor, aniridia, genitourinary malformations, and retardation (WAGR). These children have a deletion of 1 copy of chromosome 11p13, which may be visible on karyotype analysis. The deleted region encompasses the aniridia gene *(PAX6)* and the Wilms tumor-suppressor gene *(WT1).* Only the 46,XY males have genital abnormalities, ranging from cryptorchidism to severe deficiency of virilization. Gonadoblastomas have developed in the dysgenetic gonads. Wilms tumor usually occurs by 2 yr of age. Some cases also had unexplained obesity, raising the question of an obesity-associated gene in this region of chromosome 11 and naming the syndrome **WAGRO.**

Campomelic Syndrome

See Chapter 704.

This form of **short-limbed dysplasia** is characterized by anterior bowing of the femur and tibia, small, bladeless scapulae, small thoracic cavities, and 11 pairs of ribs, along with malformations of other organs. It is usually lethal in early infancy. Approximately 75% of reported 46,XY patients exhibit a completely **female phenotype;** the external and internal genitalia are female. Some 46,XY patients have ambiguous genitals. The gonads appear to be ovaries but histologically may contain elements of both ovaries and testes.

The gene responsible for the condition is *SOX9* (SRY-related HMG [high-mobility group]-box gene) and is on 17q24-q25. This gene is structurally related to *SRY* and also directly regulates development of the type II collagen gene *(COL2A1).* The same mutations may result in different gonadal phenotypes. Gonadoblastoma was reported in a patient with this condition. The inheritance is autosomal dominant. Adrenal insufficiency and 46,XY gonadal dysgenesis has been described in patients with mutations of the *SF-1* gene. In some of these patients, if the mother shares the *SF-1* mutation, she has premature ovarian insufficiency.

46,XY sex reversal has been described in patients with deletions of parts of autosomal loci on chromosomes 2q, 9p, and 10q.

XY Pure Gonadal Dysgenesis (Swyer Syndrome)

The designation "pure" distinguishes this condition from forms of gonadal dysgenesis that are of chromosomal origin and associated with somatic anomalies. Affected patients have normal stature and a **female phenotype,** including vagina, uterus, and fallopian tubes, but at pubertal age, breast development and menarche fail to occur. None of the other phenotypic features associated with 45,X are present. Patients present at puberty with hypergonadotropic primary amenorrhea. Familial cases suggest an X-linked or a sex-limited dominant autosomal transmission. Most of the patients examined have had mutations of the *SRY* gene. None had a *SOX9* gene mutation. The gonads consist of almost totally undifferentiated streaks despite the presence of a cytogenetically normal Y chromosome. The primitive gonad cannot accomplish any testicular function, including suppression of müllerian ducts. There may be hilar cells in the gonad capable of producing some androgens; accordingly, some virilization, such as clitoral enlargement, may occur at the age of puberty. The streak gonads may undergo neoplastic changes, such as gonadoblastomas and dysgerminomas, and should be removed as soon as the diagnosis is established, regardless of the age of the patient.

Pure gonadal dysgenesis also occurs in XX individuals (see Chapter 586).

XY Gonadal Agenesis Syndrome (Embryonic Testicular Regression Syndrome)

In this rare syndrome, the external genitalia are slightly ambiguous but more nearly **female.** Hypoplasia of the labia; some degree of labioscrotal fusion; a small, clitoris-like phallus; and a perineal urethral opening are present. No uterus, no gonadal tissue, and usually no vagina can be found. At the age of puberty, no sexual development occurs and gonadotropin levels are elevated. Most children have been reared as females. In several patients with XY gonadal agenesis in whom no gonads could be found on exploration, significant rises in testosterone followed stimulation with hCG, indicating Leydig cell function somewhere. Siblings with the disorder are known.

It is presumed that testicular tissue was active long enough during fetal life for AMH to inhibit development of müllerian ducts but not long enough for testosterone production to result in virilization. In 1 patient, no deletion of the Y chromosome was found by means of Y-specific DNA probes. Testicular degeneration seems to occur between the 8th and the 12th fetal wk. Regression of the testis before the 8th wk of gestation results in Swyer syndrome; between the 14th and the 20th wk of gestation, it results in the rudimentary testis syndrome; and after the 20th wk, it results in anorchia.

In **bilateral anorchia,** sometimes referred to as *vanishing testes syndrome*, testes are absent, but the **male phenotype** is complete; it is presumed that tissue with fetal testicular function was active during the critical period of genital differentiation but that sometime later it was damaged. Bilateral anorchia in identical twins and unilateral anorchia in identical twins and in siblings suggest a genetic predisposition. Coexistence of anorchia and the gonadal agenesis syndrome in a sibship is evidence for a relationship between the disorders. *SRY* defects have not yet been reported for patients with anorchia.

A retrospective review of urologic explorations revealed absent testes in 21% of 691 testes. Of those, 73% had blind-ending cord structures with the suggested site of the vanishing testes being the inguinal canal (59%), abdomen (21%), superficial inguinal ring (18%), and scrotum (2%). It was suggested that the presence of cord structures on laparoscopy should prompt inguinal exploration because viable testicular tissue was found in 4 of these children. No hormonal data (hCG stimulation tests, AMH levels) were reported.

DEFECTS IN TESTICULAR HORMONES

Five genetic defects have been delineated in the enzymatic synthesis of testosterone by the fetal testis, and a defect in Leydig cell differentiation has been described. These defects produce 46,XY males with inadequate masculinization (see Fig. 582-1 in Chapter 582). Because levels of testosterone are normally low before puberty, an hCG stimulation test may be needed in children to assess the ability of the testes to synthesize testosterone.

Leydig Cell Aplasia

Patients with aplasia or hypoplasia of the Leydig cells usually have **female phenotypes,** but there may be mild virilization. Testes, epididymis, and vas deferens are present; the uterus and fallopian tubes are absent because of normal production of AMH. There are no secondary sexual changes at puberty, but pubic hair may be normal. Plasma levels of testosterone are low and do not respond to hCG; LH levels are elevated. The Leydig cells of the testes are absent or markedly deficient. The defect may involve a lack of receptors for LH. In children, hCG stimulation is necessary to differentiate the condition from the androgen insensitivity syndromes (AISs). There is male-limited autosomal recessive inheritance. The human LH receptor is a member of the G-protein–coupled superfamily of receptors that contains 7 transmembrane domains. Several inactivating mutations of the LH receptor have been described in males with hypogonadism suspected of having Leydig cell hypoplasia or aplasia.

High serum LH and low follicle-stimulating hormone were noted in 1 male with hypogonadism owing to a mutation in the gene for the β-subunit of follicle-stimulating hormone (see Table 583-1 in Chapter 583).

Lipoid Adrenal Hyperplasia

See Chapter 576.

The most severe form of congenital adrenal hyperplasia derives its name from the appearance of the enlarged adrenal glands resulting from accumulation of cholesterol and cholesterol esters. The rate-limiting process in steroidogenesis is the transport of free cholesterol

through the cytosol to the inner mitochondrial membrane, where the P450 side-chain cleavage enzyme (P450scc; CYP11A1) acts. Cholesterol transport into mitochondria is mediated by the steroidogenetic acute regulatory protein (StAR) whose synthesis occurs via cyclic adenosine monophosphate through a cyclic adenosine monophosphate response element–binding protein. StAR is a 30 kDa protein essential for steroidogenesis and is encoded by a gene on chromosome 8p11.2. The mitochondrial content of StAR increases between 1 and 5 hr after adrenocorticotropic hormone stimulation, long after the acute adrenocorticotropic hormone–induced increase in steroidogenesis. This has led some to suggest that extramitochondrial StAR might also be involved in the acute response to adrenocorticotropic hormone.

All serum steroid levels are low or undetectable, whereas corticotropin and plasma renin levels are quite elevated. The phenotype is female in both genetic females and males. Genetic males have no müllerian structures because the testes can produce normal AMH but no steroid hormones. These children present with acute adrenal crisis and salt wasting in infancy. Most patients are 46,XY. In a few patients, ovarian steroidogenesis is present at puberty.

The regulatory role of StAR-independent steroidogenesis is illustrated by 46,XX 4 mo old twins with lipoid adrenal hyperplasia. One died at 15 mo because of cardiac complications related to coarctation of the aorta. The adrenal glands had characteristic lipid deposits. The surviving twin had spontaneous puberty with feminization at 11.5 yr and menarche at 13.8 yr. When restudied at the age of 15 yr, a homozygous frameshift-inactivating mutation in her *StAR* gene was discovered. This and the fact that she survived as an infant until 4 mo of age without replacement therapy with detectable serum aldosterone levels supports the hypothesis that StAR-independent steroidogenesis was able to proceed until enough intracellular lipid accumulated to destroy steroidogenic activity. Partial defects in only partially virilized males and delayed onset of salt wasting have been described. Complete P450scc defects may be incompatible with life because only this enzyme can convert cholesterol to pregnenolone, which then becomes progesterone, a hormone essential for the maintenance of normal mammalian pregnancy. Heterozygous mutation in *CYP11A1* was described in a 4 yr old with 46,XY sex reversal and late-onset form of lipoid adrenal hyperplasia. At 6-7 wk of gestation, when maternal corpus luteum progesterone synthesis stops, the placenta, which does not express StAR, produces progesterone by StAR-independent steroidogenesis using the CYP11A1 enzyme system.

3β-Hydroxysteroid Dehydrogenase Deficiency

Males with this form of congenital adrenal hyperplasia (see Chapter 576) have various degrees of **hypospadias,** with or without bifid scrotum and cryptorchidism and, rarely, a complete female phenotype. Affected infants usually develop salt-losing manifestations shortly after birth. Incomplete defects, occasionally seen in boys with premature pubarche, as well as late-onset nonclassic forms, have been reported. These children have point mutations of the gene for type II 3β-hydroxysteroid enzyme, resulting in impairment of steroidogenesis in the adrenals and gonads; the impairment may be unequal between adrenals and gonads. Normal pubertal changes in some boys could be explained by the normally present type I 3β-hydroxysteroid dehydrogenase present in many peripheral tissues. Infertility is frequent. There is no correlation between degree of salt wasting and degree of phenotypic abnormality.

Deficiency of 17-Hydroxylase/17,20-Lyase

A single enzyme (CYP17A1) encoded by a single gene on chromosome 10q24.3 has both 17-hydroxylase and 17,20-lyase activities in adrenal and gonadal tissues (see Chapter 576). Many different genetic lesions have been reported. Genetic males usually have a complete female phenotype or, less often, various degrees of undervirilization from labioscrotal fusion to perineal hypospadias and cryptorchidism. Pubertal development fails to occur in both genetic sexes.

In the classical disorder, there is decreased synthesis of cortisol by the adrenals and of sex steroids by the adrenals and gonads. Levels of deoxycorticosterone and corticosterone are markedly increased and lead to the hypertension and hypokalemia characteristic of this form of male DSD. Although levels of cortisol are low, the elevated corticotropin and corticosterone levels prevent symptomatic cortisol deficiency. The renin–aldosterone axis is suppressed because of the strong mineralocorticoid effect of elevated deoxycorticosterone. Virilization does not occur at puberty; levels of testosterone are low, and those of gonadotropins are increased. Because fetal production of AMH is normal, no müllerian duct remnants are present. In phenotypic XY females, gonadectomy and replacement therapy with hydrocortisone and sex steroids are indicated.

The defect follows autosomal recessive inheritance. Affected XX females are usually not detected until young adult life, when they fail to experience normal pubertal changes and are found to have hypertension and hypokalemia. This condition should be suspected in patients presenting with primary amenorrhea and hypertension whose chromosomal complement is either 46,XX or 46,XY.

Deficiency of 17-Ketosteroid Reductase

This enzyme, also called *17β-hydroxysteroid dehydrogenase*, catalyzes the final step in testosterone biosynthesis. It is necessary to convert androstenedione to testosterone and also dehydroepiandrosterone to androstenediol and estrone to estradiol. Enzymatic defects in the fetal testis give rise to males with complete or near-complete female phenotype in 46,XY males. Müllerian ducts are absent, and a shallow vagina is present. The diagnosis is based on the ratio of androstenedione to testosterone; in prepubertal children, stimulation with hCG may be necessary to make the diagnosis.

The defect is inherited in an autosomal recessive fashion. At least 4 different types of 17β-hydroxysteroid dehydrogenase are recognized, each coded by a different gene or different chromosomes. Type III is the enzyme defect that is especially common in a highly inbred Arab population in Gaza. The gene for the disorder is at 9q22 and is expressed only in the testes, where it converts androstenedione to testosterone. Most patients are diagnosed at puberty because of virilization and the failure to menstruate. Testosterone levels at puberty may approach normal, presumably as a result of peripheral conversion of androstenedione to testosterone; at this time, some patients spontaneously adopt a male gender role.

Type I 17β-hydroxysteroid dehydrogenase, encoded by a gene on chromosome 17q21, converts estrone to estradiol and is found in placenta, ovary, testis, liver, prostate, adipose tissue, and endometrium. Type II, whose gene is on chromosome 16q24, reverses the reactions of types I and III (converting testosterone to androstenedione and estrone to estradiol, respectively). Type IV is similar in action to type II. A late-onset form of 17-ketosteroid reductase deficiency presents as gynecomastia in young adult males.

Persistent Müllerian Duct Syndrome

In this disorder, there is persistence of müllerian duct derivatives in otherwise completely virilized males. Cases have been reported in siblings and identical twins. **Cryptorchidism** is present in 80% of affected males; and during surgery for this or inguinal hernia, the condition is uncovered when a fallopian tube and uterus are found. The degree of müllerian development is variable and may be asymmetric. Testicular function is normal in most, but testicular degeneration has been reported. Some affected males acquire testicular tumors after puberty. In a study of 38 families, 16 families had defects in the AMH gene, located on the short arm of chromosome 19. They had low AMH levels. In 16 families with high AMH levels, the defect was in the AMH type II receptor gene, with 10 of 16 having identical 27-bp deletions on exon 10 in at least 1 allele.

Treatment consists of removal of as many of the müllerian structures as possible without causing damage to the testis, epididymis, or vas deferens.

DEFECTS IN ANDROGEN ACTION

In the following group of disorders, fetal synthesis of testosterone is normal and defective virilization results from inherited abnormalities in androgen action.

Dihydrotestosterone Deficiency

Decreased production of DHT in utero results in marked ambiguity of external genitalia of affected males. Biosynthesis and peripheral action of testosterone are normal.

The phenotype most commonly associated with this condition results in boys who have a small phallus, bifid scrotum, urogenital sinus with perineal hypospadias, and a blind vaginal pouch (Fig. 588-3). Testes are in the inguinal canals or labioscrotal folds and are normal histologically. There are no müllerian structures. Wolffian structures—the vas deferens, epididymis, and seminal vesicles—are present. Most affected patients have been identified as females. At puberty, virilization occurs; the phallus enlarges, the testes descend and grow normally, and spermatogenesis occurs. There is no gynecomastia. Beard growth is scanty, acne is absent, the prostate is small, and recession of the temporal hairline fails to occur. Virilization of the wolffian duct is caused by the action of testosterone itself, although masculinization of the urogenital sinus and external genitals depends on the action of DHT during the critical period of fetal masculinization. Growth of facial hair and of the prostate also appears to be DHT dependent.

The adult height reached is close to that of the father and other male siblings. There is significant phenotypic heterogeneity. This has led to a classification of such patients into 5 types of steroid 5α-reductase deficiency (SRD).

Several different gene defects of SRD5A2 (the 5α-reductase type 2 gene leading to SRD) have been identified, located on the short arm of chromosome 2, in patients from throughout the world. Familial clusters have been reported from the Dominican Republic, Turkey, Papua New Guinea, Brazil, Mexico, and the Middle East. There is no reliable correlation between genotype and phenotype.

The disorder is inherited as an autosomal recessive trait but is limited to males; normal homozygous females with normal fertility indicate that in females DHT has no role in sexual differentiation or in ovarian function later in life. The clinical diagnosis should be made as early as possible in infancy. It is important to distinguish this from partial androgen insensitivity syndrome (PAIS), as patients with PAIS are far less sensitive to androgen than are patients with SRD. The biochemical diagnosis of SRD is based on finding normal serum testosterone levels, normal or low DHT levels with markedly increased basal and especially hCG-stimulated testosterone: DHT ratios (>17), and high ratios of urinary etiocholanolone to androsterone. Children with androgen insensitivity have normal hepatic 5α reduction and, thus, a normal ratio of tetrahydrocortisol to 5α-tetrahydrocortisol, as opposed to those with SRD.

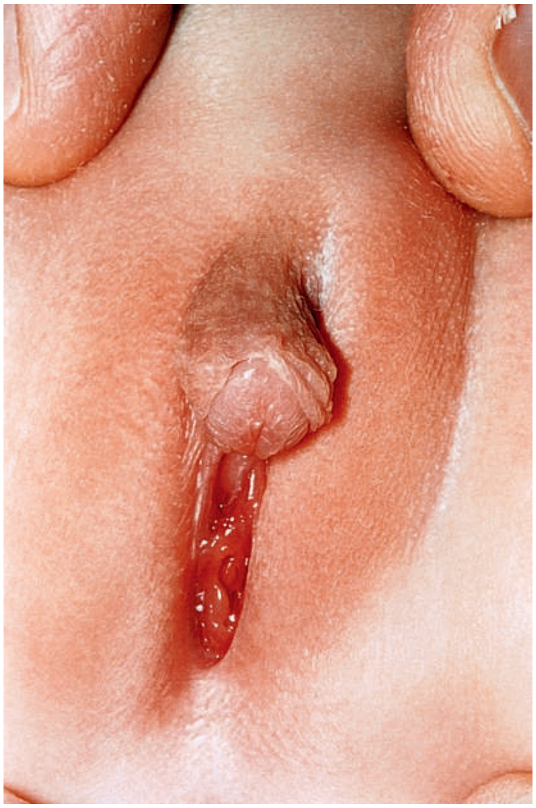

Figure 588-3 5α-Reductase deficiency. *(From Wales JKH, Wit JM, Rogol AD:* Pediatric endocrinology and growth, *ed 2, Philadelphia, 2003, WB Saunders, p. 165.)*

It is important to note that most but not all children with SRD reared as females in childhood have changed to male around the time of puberty. It appears that exposures to testosterone in utero, neonatally, and at puberty have variable contributions to the formation of male gender identity. Much more needs to be learned about the influences of hormones such as androgens as well as the influences of cultural, social, psychologic, genetic, and other biologic factors in gender identity and behavior. Infants with this condition should be reared as boys whenever practical. Treatment of male infants with DHT results in phallic enlargement.

Another cause of DHT deficiency is a block in an alternative pathway of DHT synthesis. Patients previously thought to have 46,XY DSD because of isolated 17,20-lyase deficiency have subsequently been characterized as having mutations in the *AKR1C2* gene (3α-reductase type 3) or both the *AKR1C2* and *AKR1C4* (3α-reductase type 4) genes. These findings showed that both the classical and alternative pathways to DHT must be intact for normal prenatal virilization.

Androgen Insensitivity Syndromes

The AISs are the most common forms of male DSD, occurring with an estimated frequency of 1/20,000 genetic males. This group of heterogeneous X-linked recessive disorders is caused by more than 150 different mutations in the androgen receptor gene, located on Xq11-12: single point mutations resulting in amino acid substitutions or premature stop codons, frameshift and premature terminations, gene deletions, and splice-site mutations.

Clinical Manifestations

The clinical spectrum of patients with AISs, all of whom have a 46,XY chromosomal complement, range from phenotypic females (in complete AIS) to males with various forms of ambiguous genitalia and undervirilization (partial AIS, or clinical syndromes such as **Reifenstein syndrome**) to phenotypically normal-appearing males with infertility. In addition to normal 46,XY chromosomes, the presence of testes and normal or elevated testosterone and LH levels are common to all such children (Figs. 588-4 and 588-5).

In **complete androgen insensitivity syndrome (CAIS),** an extreme form of failure of virilization, genetic males appear female at birth and are invariably reared accordingly. The external genitalia are female. The vagina ends blindly in a pouch, and the uterus is absent as a result of the normal production and effect of AMH by the testes. In about one third of patients, unilateral or bilateral fallopian tube remnants are found. The testes are usually intraabdominal but may descend into the inguinal canal; they consist largely of seminiferous tubules. At puberty, there is normal development of breasts and the habitus is female, but menstruation does not occur and sexual hair is absent. Adult heights of these women are commensurate with those of normal males despite profound congenital deficiency of androgenic effects.

The testes of affected adult patients produce normal male levels of testosterone, which are converted to normal levels of DHT. Failure of normal male differentiation during fetal life reflects a defective response to androgens at that time. The absence of androgenic effects is caused by a striking resistance to the action of endogenous or exogenous testosterone at the cellular level.

Prepubertal girls with this disorder are often detected when inguinal masses prove to be testes or when a testis is unexpectedly found during herniorrhaphy. Approximately 1-2% of girls with an inguinal hernia prove to have this disorder. In infants, elevated LH levels should suggest the diagnosis. In older girls and adults, **amenorrhea** is the usual presenting symptom. In prepubertal children, the condition must

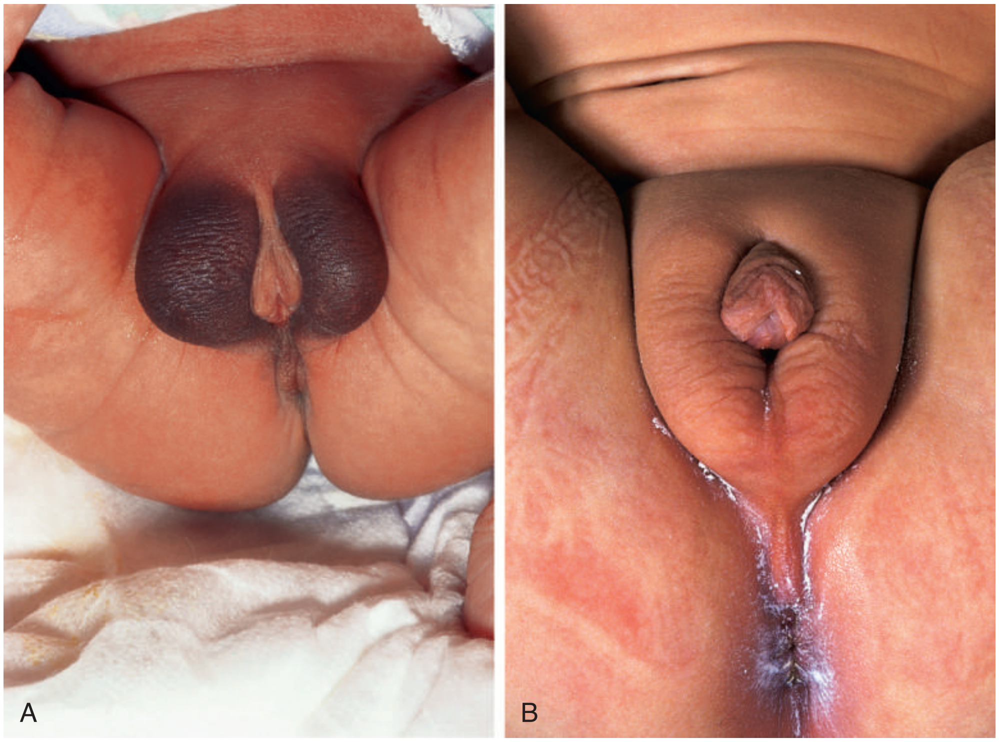

Figure 588-4 **A,** Partial androgen insensitivity with descended testes in bifid labioscrotal folds. **B,** Less-severe partial androgen insensitivity with severe hypospadias and maldescent of testes. *(From Wales JKH, Wit JM, Rogol AD:* Pediatric endocrinology and growth*, ed 2, Philadelphia, 2003, WB Saunders, p. 165.)*

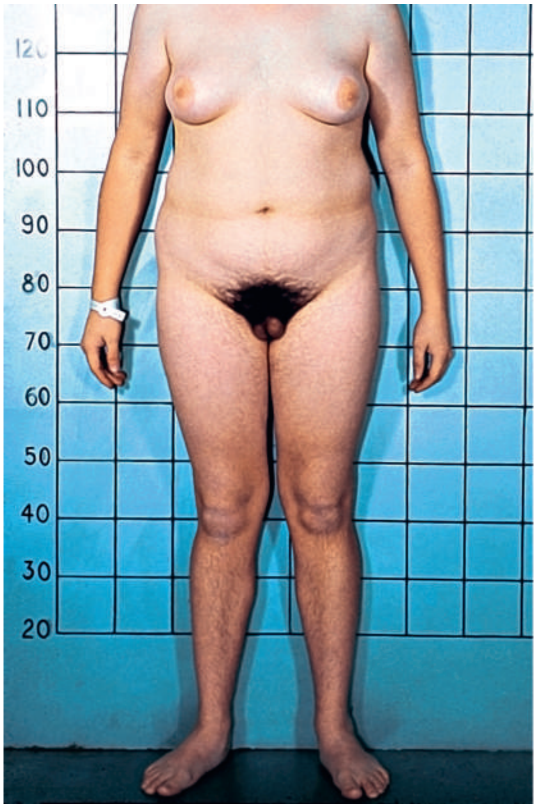

Figure 588-5 **Partial androgen insensitivity syndrome at adolescence, male sex of rearing.** Note gynecomastia from peripheral aromatase conversion of testosterone to estrogen. Abundant pubic hair implies only partial resistance. *(From Wales JKH, Wit JM, Rogol AD:* Pediatric endocrinology and growth*, ed 2, Philadelphia, 2003, WB Saunders, p. 165.)*

be differentiated from other types of XY undervirilized males in which there is complete feminization. These include XY gonadal dysgenesis (Swyer syndrome), true agonadism, Leydig cell aplasia including LH receptor defects, and 17-ketosteroid reductase deficiency; all these conditions, unlike CAIS, are characterized by **low levels of testosterone** as neonates and during adult life and by failure to respond to hCG during the prepubertal years.

Although patients with CAIS have unambiguously female external genitals at birth, those with **PAIS** have a wide variety of phenotypic presentations, ranging from **perineoscrotal hypospadias,** bifid scrotum, and cryptorchidism to extreme undervirilization appearing as clitoromegaly and labial fusion. Some forms of PAIS are known as specific syndromes. Patients with **Reifenstein syndrome** have incomplete virilization characterized by hypogonadism, severe hypospadias, and gynecomastia (see Fig. 588-5). **Gilbert-Dreyfus** and **Lubs** syndromes are also classified as PAISs. In all cases, abnormalities in the androgen receptor gene have been identified. Table 588-5 lists other causes of a PAIS-like syndrome.

Diagnosis

The diagnosis of patients with PAIS may be particularly difficult in infancy. The postnatal surge in testosterone and LH is diminished in those with CAIS but not in those with PAIS. In some, especially those sufficiently virilized in infancy, the diagnosis is not suspected until puberty when there is inadequate virilization with lack of facial hair or voice change and the appearance of gynecomastia. Azoospermia and infertility are common. Increasingly, androgen receptor defects are being recognized in adults who have a small phallus and testes and infertility. A single-amino-acid substitution in the androgen receptor was reported in a large Chinese family in whom some affected members were fertile while others had gynecomastia and/or hypospadias. Production of insulin-like growth factor 2 and insulin-like growth factor–binding protein-2, but not insulin-like growth factor–binding protein-3, by genital skin fibroblasts is decreased in CAIS compared with normal genital skin fibroblasts, suggesting a possible role for the insulin-like growth factor system in modulating androgen action.

Table 588-5	Causes of a PAIS-Like Phenotype
DEFECTS IN ANDROGEN PRODUCTION • Partial gonadal dysgenesis • Mutations in *SRY, NR5A1, WT1* • Mutations of the luteinizing hormone receptor • Biosynthetic enzyme deficiencies • 17,20-Lyase deficiency • P450 oxidoreductase deficiency • 17β-hydroxysteroid dehydrogenase deficiency type 3 • 5α-Reductase deficiency type 2	
GENETIC • Klinefelter syndrome • Smith-Lemli-Opitz syndrome • Denys-Drash syndrome • Frasier syndrome	
PAIS • Mutations of the androgen receptor gene • Normal androgen receptor gene with fetal growth restriction	

NR5A1, nuclear receptor subfamily 5 A1; PAIS, partial androgen insensitivity syndrome; SRY, sex-determining region Y; WT1, Wilms tumor 1.

From Hughes IA, Davies JD, Bunch TI, et al: Androgen insensitivity syndrome. Lancet *380:1419–1428, 2012, Panel 1, p. 1421.*

Treatment and Prognosis

In patients with CAIS whose sexual orientation is unambiguously female, the testes should be removed as soon as they are discovered. Laparoscopic removal of Y chromosome–bearing gonads has been performed in patients with AIS and in those with gonadal dysgenesis. In one third of patients, malignant tumors, usually seminomas, develop by 50 yr of age. Several teenage girls have acquired seminomas. Replacement therapy with estrogens is indicated at the age of puberty.

Normal breasts develop in affected girls who have not had their testes removed by the age of puberty. In these individuals, production of estradiol results from aromatase activity on testicular testosterone. The absence of androgenic activity also contributes to the feminization of these women.

The psychosexual and surgical management of patients with PAIS is extremely complex and depends in large part on the presenting phenotype. Osteopenia is recognized as a late feature of AIS.

Molecular analyses have suggested that phenotype may depend in part on somatic mosaicism of the androgen receptor gene. This was based on the case of a 46,XY patient who had a premature stop codon in exon 1 of the androgen receptor gene, but who also had evidence of virilization (pubic hair and clitoral enlargement) explained by the discovery of the wild-type alleles on careful examination of the sequencing gel. The presence of mosaicism shifts the phenotype to a higher degree of virilization than expected from the genotype of the mutant allele alone.

Genetic counseling is difficult in families with androgen receptor gene mutation. In addition to lack of genotype–phenotype correlations, there is a high rate (27%) of de novo mutations in families.

Sex hormone–binding globulin reduction after exogenous androgen administration (stanozolol) correlates with the severity of the receptor defect and may become a useful clinical tool. Successful therapy with supplemental androgens has been reported in patients with PAIS and various mutations of the androgen receptor in the DNA-binding domain and the ligand-binding domain.

Mutated androgen receptors are also reported in patients with spinal and bulbar muscular atrophy in whom clinical manifestations including testicular atrophy, infertility, gynecomastia, and elevated LH, follicle-stimulating hormone, and estradiol levels usually manifest between the 3rd and 5th decades of life. Androgen receptor mutations have also been described in patients with prostate cancer.

UNDETERMINED CAUSES

Other XY undervirilized males display great variability of the external and internal genitalia and various degrees of phallic and müllerian development. Testes may be histologically normal or rudimentary, or there may only be 1. No recognized cause is identified in up to 50% of children with 46,XY DSD. Some ambiguity of the genitalia is associated with a wide variety of chromosomal aberrations, which must always be considered in the differential diagnosis, the most common being the 45,X/46,XY syndrome (see Chapter 586.1). It may be necessary to karyotype several tissues to establish mosaicism. Other complex genetic syndromes, many resulting from single gene mutations, are associated with varying degrees of ambiguity of the genitalia, particularly in the male. These entities must be identified on the basis of the associated extragenital malformations.

Smith-Lemli-Opitz syndrome is an autosomal recessive disorder caused by mutations in the sterol Δ7-reductase gene located on chromosome 11q12-q13. It is characterized by prenatal and postnatal growth retardation, microcephaly, ptosis, anteverted nares, broad alveolar ridges, syndactyly of the 2nd-3rd toes, and severe cognitive impairment (see Chapter 86.3). Its incidence is 1 in 20,000 to 30,000 live births in populations of northern and central European origin; 70% are male. Genotypic males usually have genital ambiguity and, occasionally, partial sex reversal with female genital ambiguity or complete sex reversal with female external genitals. Müllerian duct derivatives are usually absent. Affected 46,XX patients have normal genitalia. Two types of Smith-Lemli-Opitz syndrome have been recognized. The **classical form** (type I) described earlier and the acrodysgenital syndrome, which is usually lethal within 1 yr and is associated with severe malformations, postaxial polydactyly, and extremely abnormal external genitalia (type II). Pyloric stenosis is associated with Smith-Lemli-Opitz syndrome type I and Hirschsprung disease with type II. Cleft palate, skeletal abnormalities, and 1 case of a lipoma of the pituitary gland have been seen in **type II** cases. Some authors believe in a spectrum of disease severity rather than in the above classification. Low plasma cholesterol with elevated 7-dehydrocholesterol, its precursor, are found in types I and II, and the levels do not correlate with severity. Maternal apolipoprotein E values do seem to correlate with severity. The most common prenatal expression of Smith-Lemli-Opitz syndrome is intrauterine growth retardation (see Chapter 86.3 for treatment).

46,XY DSD subjects also have been described in siblings with the α-thalassemia/mental retardation syndrome.

Bibliography is available at Expert Consult.

588.3 Ovotesticular DSD

Patricia A. Donohoue

In ovotesticular DSD, both ovarian and testicular tissues are present, either in the same or in opposite gonads. Affected patients have ambiguous genitalia, varying from normal female with only slight enlargement of the clitoris to almost normal male external genitalia (see Fig. 588-2*A*).

Approximately 70% of all patients have a 46,XX karyotype. Ninety-seven percent of affected patients of African descent are 46,XX. Fewer than 10% of persons with ovotesticular DSD are 46,XY. Approximately 20% have 46,XX/46,XY mosaicism. Half of these are derived from more than 1 zygote and are chimeras (chi 46,XX/46,XY). The presence of paternal and both maternal alleles for some blood groups is demonstrated. An ovotesticular DSD chimera, 46,XX/46,XY, was reported as resulting from embryo amalgamation after in vitro fertilization. Each embryo was derived from an independent, separately fertilized ovum.

Examination of 46,XX ovotesticular DSD patients with Y-specific probes has detected fewer than 10% with a portion of the Y chromosome including the *SRY* gene. Ovotesticular DSD is usually sporadic, but a number of siblings have been reported. The cause of most cases of ovotesticular DSD is unknown.

The most frequently encountered gonad in ovotesticular DSD is an ovotestis, which may be bilateral. If unilateral, the contralateral gonad

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is usually an ovary but may be a testis. The ovarian tissue is normal, but the testicular tissue is dysgenetic. The presence and function of testicular tissue can be determined by measuring basal and hCG-stimulated testosterone levels as well as AMH levels. Patients who are highly virilized and have had adequate testicular function with no uterus are usually reared as males. If a uterus exists, virilization is often mild and testicular function minimal; assignment of female sex may be indicated. Selective removal of gonadal tissue inconsistent with sex of rearing may be indicated. In a few families, 46,XY ovotesticular DSD subjects and 44,XX males have been described in the same sibship.

Defects in R-Spondin1, encoded by the *RSPO1* gene, have been described in 46,XX ovotesticular DSD.

Pregnancies with living offspring have been reported in 46,XX ovotesticular DSD individuals reared as females, but very few males with ovotesticular DSD have fathered children. Approximately 5% of patients will develop gonadoblastomas, dysgerminomas, or seminomas.

DIAGNOSIS AND MANAGEMENT OF DISORDERS OF SEX DEVELOPMENT

In the neonate, ambiguity of the genitals requires immediate attention to decide on the sex of rearing as early in life as possible. The family of the infant needs to be informed of the child's condition as early, completely, compassionately, and honestly as possible. Caution must be used to avoid feelings of guilt, shame, and discomfort. Guidance needs to be provided to alleviate both short-term and long-term concerns and to allow the child to grow up in a completely supportive environment. The initial care is best provided by a team of professionals that include neonatologists and pediatric specialists, endocrinologists, radiologists, urologists, psychologists, and geneticists, all of whom remain focused foremost on the needs of the child. Management of the potential psychologic upheaval that these disorders can generate in the child or the family is of paramount importance and requires physicians and other healthcare professionals with sensitivity, training, and experience in this field.

While awaiting the results of chromosomal analysis, pelvic ultrasonography is indicated to determine the presence of a uterus and ovaries. Presence of a uterus and absence of palpable gonads usually suggests a virilized XX female. A search for the source of virilization should be undertaken; this includes studies of adrenal hormones to rule out varieties of congenital adrenal hyperplasia, and studies of androgens and estrogens occasionally may be necessary to rule out aromatase deficiency. Virilized XX females are generally (but not always) reared as females even when highly virilized.

The absence of a uterus, with or without palpable gonads, often indicates an undervirilized male and an XY karyotype. Measurements of levels of gonadotropins, testosterone, AMH, and DHT are necessary to determine whether testicular production of androgen is present and is normal. Undervirilized males who are totally feminized may be reared as females. Certain significantly feminized infants, such as those with 5α-reductase deficiency, may be reared as males because these children virilize normally at puberty. Sixty percent of individuals with 5α-reductase deficiency assigned as female in infancy live as males as adults. An infant with a comparable degree of feminization resulting from an androgen receptor defect, such as CAIS, is best reared as a female.

When receptor disorders are suspected in the XY male with a small phallus (micropenis), a course of 3 monthly intramuscular injections of testosterone enanthate (25-50 mg) may assist in the differential diagnosis of androgen insensitivity, as well as in treatment.

In some mammals, the female exposed to androgens prenatally or in early postnatal life exhibits nontraditional sexual behavior in adult life. Most, but not all, girls who have undergone fetal masculinization from congenital adrenal hyperplasia or from maternal progestin therapy have female sexual identity, although during childhood they may appear to prefer male playmates and activities over female playmates and feminine play with dolls in mothering roles.

In the past it was thought that surgical treatment of ambiguous genitalia to create a female appearance, particularly when a vagina is present, was more successful than construction of male genitalia. Considerable controversy exists regarding these decisions. Sexual functioning is to a large extent more dependent on neurohormonal and behavioral factors than the physical appearance and functional ability of the genitalia. Similarly, controversy exists regarding the timing of the performance of invasive and definitive procedures, such as surgery. Whenever possible without endangering the physical or psychologic health of the child, an expert multidisciplinary team should consider deferring elective surgical repairs and gonadectomies until the child can participate in the informed consent for the procedure. One study of children (n = 59 boys and 18 girls) with gender dysphoria but without documentation of genomic or enzymologic abnormalities indicated that most of these children no longer have gender dysphoria after completion of puberty. Among those who do, homosexuality and bisexuality are the most frequent diagnoses.

For patients with DSD who have Y-chromosome material and intraabdominal gonads, gonadectomy is generally recommended because of the risk of gonadal tumors, many of which are malignant.

The pediatrician, pediatric endocrinologist, and psychologist, along with the appropriate additional specialists, should provide ongoing compassionate, supportive care to the patient and the patient's family throughout childhood, adolescence, and adulthood. Support groups are available for families and patients with many of the conditions discussed.

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Section 6

Diabetes Mellitus in Children

Chapter 589 Diabetes Mellitus

589.1 Classification

Britta M. Svoren and Nicholas Jospe

Diabetes mellitus (DM) is a common, chronic, metabolic disease characterized by hyperglycemia as a cardinal biochemical feature. The major forms of diabetes are differentiated by insulin deficiency vs insulin resistance: type 1 diabetes mellitus (T1DM) results from deficiency of insulin secretion because of pancreatic β-cell damage; type 2 diabetes mellitus (T2DM) is a consequence of insulin resistance occurring at the level of skeletal muscle, liver, and adipose tissue, with various degrees of β-cell impairment. T1DM is the most common endocrine-metabolic disorder of childhood and adolescence, with important consequences for physical and emotional development. Individuals with T1DM confront serious lifestyle alterations, including an absolute daily requirement for exogenous insulin, the need to monitor their own glucose level, and the need to pay attention to dietary intake. Morbidity and mortality stem from a constant potential for acute metabolic derangements and from long-term **complications** (usually in adulthood) that affect small and large blood vessels resulting in retinopathy, nephropathy, neuropathy, ischemic heart disease, and arterial obstruction with gangrene of the extremities. The acute clinical manifestations are caused by hypoinsulinemic hyperglycemic ketoacidosis; the genesis of T1DM owes to autoimmune mechanisms; and the long-term complications are related to metabolic disturbances (hyperglycemia).

Table 589-1 Etiologic Classifications of Diabetes Mellitus

I. Type 1 diabetes (β-cell destruction ultimately leading to complete insulin deficiency)
  A. Immune mediated
  B. Idiopathic
II. Type 2 diabetes (variable combinations of insulin resistance and insulin deficiency)
  A. Typical
  B. Atypical
III. Genetic defects of β-cell function
  A. MODY (maturity-onset diabetes of the young) syndromes
    1. MODY 1 chromosome 20, HNF4α
    2. MODY 2 chromosome 7, glucokinase
    3. MODY 3 chromosome 12, HNF1α, TCF-1
    4. MODY 4 chromosome 13, IPF-1
    5. MODY 5 chromosome 17, HNF1β, TCF-2
    6. MODY 6 chromosome 2q32, neuro-D_1/β_2
  B. Mitochondrial DNA mutations (includes 1 form of Wolfram syndrome, Pearson syndrome, Kearns-Sayre, diabetes mellitus, deafness)
  C. Wolfram syndrome—DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness): WFS1-Wolframin—chromosome 4p
    1. Wolfram locus 2—chromosome 4q22-24
    2. Wolfram mitochondrial
  D. Thiamine responsive megaloblastic anemia and diabetes
IV. Drug or chemical induced
  A. Antirejection—cyclosporine, sirolimus
  B. Glucocorticoids (with impaired insulin secretion; e.g., cystic fibrosis)
  C. L-Asparaginase
  D. β-Adrenergic blockers
  E. Vacor (rodenticide)
  F. Phenytoin (Dilantin)
  G. α-Interferon
  H. Diazoxide
  I. Nicotinic acid
  J. Pentamidine
V. Diseases of exocrine pancreas
  A. Cystic fibrosis–related diabetes
  B. Trauma—pancreatectomy
  C. Pancreatitis—ionizing radiation
  D. Others
VI. Infections
  A. Congenital rubella
  B. Cytomegalovirus
  C. Hemolytic-uremic syndrome
VII. Variants of type 2 diabetes
  A. Genetic defects of insulin action
    1. Rabson-Mendenhall syndrome
    2. Leprechaunism
    3. Lipoatrophic diabetes syndromes
    4. Type A insulin resistance—acanthosis
  B. Acquired defects of insulin action
    1. Endocrine tumors—rare in childhood
  C. Pheochromocytoma
  D. Cushing
  E. Others
    1. Antiinsulin receptor antibodies
VIII. Genetic syndromes with diabetes and insulin resistance/insulin deficiency
  A. Prader-Willi syndrome, chromosome 15
  B. Down syndrome, chromosome 21
  C. Turner syndrome
  D. Klinefelter syndrome
  E. Others
    1. Bardet-Biedel
    2. Alström
    3. Werner
  F. IPEX (immunodysfunction, polyendocrinopathy, enteropathy, X-linked)
  G. Celiac disease
  H. Autoimmune polyendocrinopathy
IX. Gestational diabetes
X. Neonatal diabetes
  A. Transient—chromosome 6q24, KCNJ11, ABCC8, INS, HNF1β, others
  B. Permanent—agenesis of pancreas—glucokinase deficiency, homozygous, KCNJ11, ABCC8, others

Modified from Sperling MA, Tamborlane WV, Battelino T, Weinzimer SA, Phillip M: Diabetes mellitus. In Sperling MA, editor: Pediatric endocrinology, *ed 4, Philadelphia, 2014, Elsevier, Box 19-1.*

DM is not a single entity but rather a heterogeneous group of disorders in which there are distinct genetic patterns as well as other etiologic and pathophysiologic mechanisms that lead to impairment of glucose tolerance. Table 589-1 presents a classification of diabetes and other categories of glucose intolerance. Three major forms of diabetes and several forms of carbohydrate intolerance are identified.

TYPE 1 DIABETES MELLITUS

Formerly called *insulin-dependent diabetes mellitus* (IDDM) or *juvenile diabetes*, T1DM is characterized by low or absent levels of endogenously produced insulin and by dependence on exogenous insulin to prevent development of ketoacidosis, an acute life-threatening complication of T1DM. The natural history includes 4 distinct stages: (1) preclinical β-cell autoimmunity with progressive defect of insulin secretion, (2) onset of clinical diabetes, (3) transient remission "honeymoon period," and (4) established diabetes during which there may occur acute and/or chronic complications and decreased life expectancy. The onset occurs predominantly in childhood, with a median age of 7-15 yr, but it may present at any age. The incidence of T1DM has steadily increased in nearly all parts of the world (Fig. 589-1). T1DM is characterized by autoimmune destruction of pancreatic islet β cells. Both genetic susceptibility and environmental factors contribute to the pathogenesis. Susceptibility to T1DM is genetically controlled by alleles of the major histocompatibility complex class II genes expressing human leukocyte antigens (HLAs). Autoantibodies to β-cell antigens such as islet cell cytoplasm (ICA), insulin autoantibody (IAA), antibodies to glutamic acid decarboxylase, and ICA512 are detected in serum from affected subjects. These can be detected months to years prior to clinical onset of T1DM. T1DM is associated with other **autoimmune** diseases such as thyroiditis, celiac disease, and Addison disease. In some children and adolescents with apparent T1DM, the β-cell destruction is not immune mediated. This subtype of diabetes occurs in patients of African or Asian origin and is distinct from known causes of β-cell destruction such as drugs or chemicals, viruses, mitochondrial gene defects, pancreatectomy, and ionizing radiation. These individuals may have ketoacidosis, but they have extensive periods of remission with variable insulin deficiency, similar to patients with T2DM.

TYPE 2 DIABETES MELLITUS

Children and adolescents with this type of diabetes are usually obese but are not insulin dependent and infrequently develop ketosis. Some subjects with T2DM may present with or develop ketosis during severe infections or other stresses and may then need insulin for correction of symptomatic hyperglycemia. This category includes the most prevalent form of diabetes in adults, which is characterized by insulin

resistance and often a progressive defect in insulin secretion. This type of diabetes was formerly known as *adult-onset diabetes mellitus or non–insulin-dependent diabetes mellitus*.

The presentation of T2DM is typically more insidious than that with T1DM. In contrast to patients with T1DM who are usually ill at the time of diagnosis and whose presentation rarely spans more than a few weeks, children with T2DM often seek medical care because of excessive weight gain and fatigue as a result of insulin resistance and/or the incidental finding of glycosuria during routine physical examination. A history of polyuria and polydipsia is not always a cardinal clinical feature in these patients. The incidence of T2DM in children has increased by more than 10-fold, depending on geography and mostly as a result of the epidemic of childhood obesity (see Chapter 47). Pediatric T2DM may account for as many as 80% of the new cases of diabetes, especially in obese African-American and Mexican-American adolescents. **Acanthosis nigricans** (dark pigmentation of skin creases in the nape of the neck especially), a sign of insulin resistance, is present in the majority of patients with T2DM and is accompanied by a relative hyperinsulinemia at the time of the diagnosis (see Chapter 652). However, the serum insulin elevation is usually disproportionately lower than that of age-, weight-, and sex-matched nondiabetic children and adolescents, suggesting a state of insulin insufficiency. In some individuals, it may represent slowly evolving T1DM.

In some children with a strong family history of diabetes, impaired glucose tolerance (IGT) may occur in a pattern implying dominant inheritance. This pattern of diabetes has been termed **maturity-onset diabetes of the young (MODY):** it may require insulin treatment, can be treated with sulfonylureas with varying degrees of success, and is often now referred to as monogenic diabetes. MODY may present with hyperglycemia, and consequent polyuria and polydipsia, or may be diagnosed simply by routine screening. In MODY, there is no autoimmune destruction of β cells and no HLA association. MODY results from specific genetic disorders involving mutations in the gene encoding either pancreatic β-cell and liver glucokinase or in the nuclear transcription factors hepatocyte nuclear factor (1α, 4α, or 1β). A defect in the gene regulating glucose transport into the pancreatic β cell, the GLUT2 transporter, may be responsible for other forms of T2DM. The genetic basis of T2DM also includes defects in glycogen synthase, insulin receptors, Rad (Ras associated with diabetes), and possibly apolipoprotein C-III. A recent metaanalysis suggests that the incidence of T2DM has a complexly inverse relationship with birthweight in some populations, depending on ethnic and genetic factors.

OTHER SPECIFIC TYPES OF SECONDARY DIABETES

Examples include diabetes secondary to exocrine pancreatic diseases (cystic fibrosis), other endocrine diseases (Cushing syndrome), and ingestion of certain drugs or poisons (the rodenticide Vacor). In organ transplantation survivors, there is a linkage between cyclosporine and tacrolimus and posttransplantation DM, ascribed to a number of mechanisms. Certain genetic syndromes, including those with abnormalities of the insulin receptor, also are included in this category. There are no associations with HLA types, autoimmunity, or islet cell antibodies among the entities in this subdivision.

Table 589-2 details the current criteria for the diagnosis of type 1 and type 2 DM. It should be noted that a fasting blood glucose that exceeds 125 mg/dL (6.9 mmol/L) is the accepted criterion for the diagnosis of diabetes.

IMPAIRED GLUCOSE TOLERANCE

The term *impaired glucose tolerance* (IGT) refers to a metabolic stage that is intermediate between normal glucose homeostasis and diabetes. A fasting glucose concentration of 99 mg/dL (5.5 mmol/L) is the upper limit of "normal." This choice is near the level above which acute-phase insulin secretion is lost in response to intravenous administration of glucose and is associated with a progressively greater risk of the development of microvascular and macrovascular complications.

Many individuals with IGT (fasting glucose 100-125 mg/dL) are euglycemic in their daily lives and may have normal or nearly normal glycated hemoglobin levels. Individuals with IGT often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized oral glucose tolerance test.

In the absence of pregnancy, IGT is not a clinical entity but rather a risk factor for future diabetes and cardiovascular disease. This may be observed as an intermediate stage in any of the disease processes listed in Table 589-1. IGT is often associated with the **insulin**

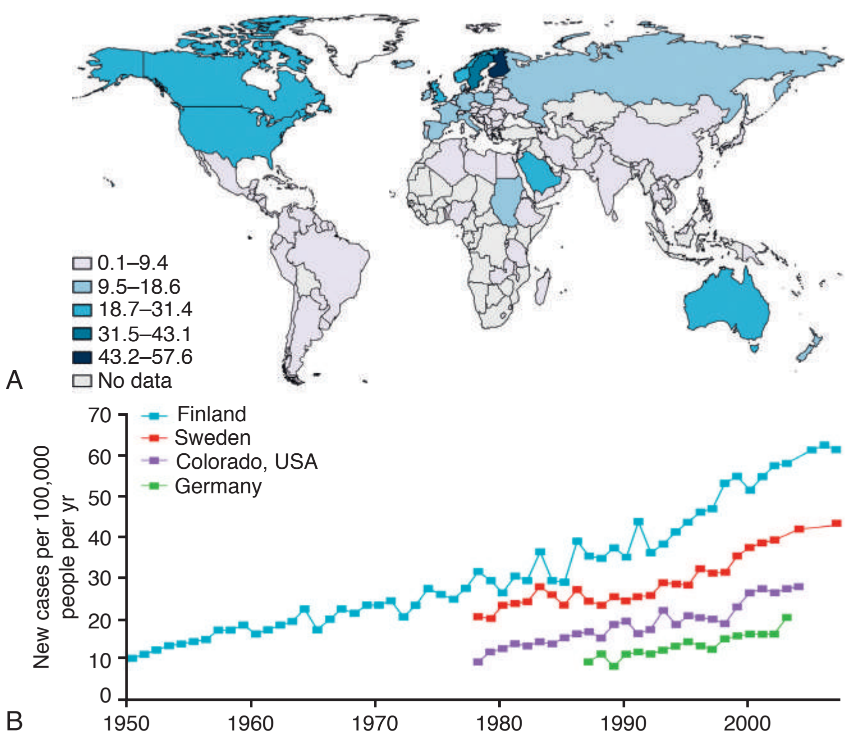

Figure 589-1 Incidence of type 1 diabetes in children ages 0-14 yr, by geographical region and over time. **A,** Estimated global incidence of type 1 diabetes, by region, in 2011. **B,** Time-based trends for the incidence of type 1 diabetes in children ages 0-14 yr in areas with high or high-intermediate rates of disease. *(From Atkinson MA, Eisenbarth GS, Michels AW: Type 1 diabetes.* Lancet *383:69–78, 2014, Fig. 1, p. 70.)*

Table 589-2	Diagnostic Criteria for Impaired Glucose Tolerance and Diabetes Mellitus
IMPAIRED GLUCOSE TOLERANCE	**DIABETES MELLITUS**
Fasting glucose 100-125 mg/dL (5.6-7.0 mmol/L)	Symptoms* of diabetes mellitus plus random or casual plasma glucose ≥200 mg/dL (11.1 mmol/L)
	or
2-hr plasma glucose during the OGTT ≥140 mg/dL, but <200 mg/dL (11.1 mmol/L)	Fasting (at least 8 hr) plasma glucose ≥126 mg/dL (7.0 mmol/L) *or* 2 hr plasma glucose during the OGTT ≥200 mg/dL *or* Hemoglobin A_{1C} ≥6.5%[†]

*Symptoms include polyuria, polydipsia, and unexplained weight loss with glucosuria and ketonuria.
[†]Results should be confirmed by repeat testing if in absence of unequivocal hyperglycemia.
OGTT, oral glucose tolerance test.
From Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, Diabetes Care *20(Suppl 1):S5, 1999; and from Chaing J, Kirkman S, Laffel L, et al: Type 1 diabetes through the life span: A position statement of the American Diabetes Association,* Diabetes Care *37:2034–2054, 2014.*

resistance syndrome (also known as *syndrome X* or *metabolic syndrome*), which consists of insulin resistance, compensatory hyperinsulinemia to maintain glucose homeostasis, obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride or low- or high-density lipoprotein type, or both, and hypertension (see Chapter 47). Insulin resistance is directly involved in the pathogenesis of T2DM. IGT appears as a risk marker for this type of diabetes at least in part because of its correlation with insulin resistance. Table 589-2 presents the diagnostic criteria for IGT.

589.2 Type 1 Diabetes Mellitus (Immune Mediated)

Britta M. Svoren and Nicholas Jospe

EPIDEMIOLOGY

T1DM accounts for approximately 10% of all cases of diabetes, affecting up to 3 million people in the United States and more than 15 million people in the world. Using population-based estimates of diabetes incidence and prevalence, a recent study indicates that approximately 15,000 youths are diagnosed with type 1 diabetes each year. While it accounts for most cases of diabetes in childhood, it is not limited to this age group; new cases continue to occur in adult life and approximately 50% of individuals with T1DM present as adults. The incidence of T1DM is highly variable among different ethnic groups (see Fig. 589-1). The overall age-adjusted incidence of T1 DM varies from 0.7 in 100,000 per yr in Karachi (Pakistan) to more than 40 in 100,000 per yr in Finland. The incidence of T1DM is increasing in most (but not all) populations and this increase appears to be most marked in populations where the incidence of autoimmune diseases was historically low. Data from Western European diabetes centers suggest that the annual rate of increase in T1DM incidence is 2-5%, whereas some central and eastern European countries demonstrate an even more rapid increase—up to 9%. The rate of increase is greatest among the youngest children. In the United States, the overall prevalence of diabetes among school-age children is approximately 1.9 in 1,000, increasing from a prevalence of 1 in 1,430 children at 5 yr of age to 1 in 360 children at 16 yr of age. Among African-Americans, the occurrence of T1DM is 30-60% of that seen in American whites. The annual incidence of new cases in the United States is now approximately 19.7 in 100,000 among youth younger than 10 yr and 18.6 in 100,000 of those older than 10 yr, It is estimated that 30,000 new cases occur each year in the United States, affecting 1 in 300 children and as many as 1 in 100 adults during the life span. Rates are similar or higher in most Western European countries and significantly lower in Asia and Africa.

Girls and boys are almost equally affected, but there is a modest female preponderance in some low-risk populations (e.g., the Japanese); there is no apparent correlation with socioeconomic status. Peaks of presentation occur in 2 age groups: at 5-7 yr of age and at the time of puberty. The first peak may correspond to the time of increased exposure to infectious agents coincident with the beginning of school; the second peak may correspond to the pubertal growth spurt induced by gonadal steroids and the increased pubertal growth hormone secretion (which antagonizes insulin). The understanding of the cause of diabetes or of its increased incidence remains elusive. A growing number of cases are presenting between 1 and 2 yr of age, especially in high-risk groups; the average age of presentation is older in low-risk populations. Low-risk groups that migrate to a high-risk country seem to acquire the increased risk of that country. On the other hand, there can be marked differences in incidence rates in various ethnic groups within the same country; for example, incidence rates in the 10-14 yr age group in the United States range from a low of 7.1 in Native Americans, to 17.6 in Hispanics, 19.2 in African-Americans, and 32.9 in whites. These variations also remain unexplained at this time.

GENETICS

There is a clear familial clustering of T1DM, with prevalence in siblings approaching 6%, whereas the prevalence in the general population in the United States is only 0.4%. Risk of diabetes is also increased when a parent has diabetes and this risk differs between the 2 parents; the risk is 3-4% if the mother has diabetes but 5-6% when the father has diabetes. In monozygotic twins, the concordance rate ranges from 30-65%, whereas dizygotic twins have a concordance rate of 6-10%. Because the concordance rate of dizygotic twins is higher than the sibling risk, factors other than the shared genotypes (e.g., the shared intrauterine environment) may play a role in increasing the risk in dizygotic twins. Furthermore, the genetic susceptibility for T1DM in the parents of a child with diabetes is estimated at 3%. It should be kept in mind that although there is a large genetic component in T1DM, 85% of newly diagnosed type 1 diabetic patients do not have a family member with T1DM. Thus, we cannot rely on family history to identify patients who may be at risk for the future development of T1DM as most cases will develop in individuals with no such family history.

Monogenic Type 1 Diabetes Mellitus

Classic single-gene defects are an extremely rare cause of type 1 diabetes, and more than 20 genes have been linked to monogenic diabetes, in children and in adults. In 2 rare syndromes (IPEX and APS-1) the genetic susceptibility that leads to diabetes is caused by a classic single-gene defect. The IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndrome is caused by mutations of the *FOXP3* and other genes. The *FOXP3* (forkhead box P3) is a gene involved in immune system responses. A member of the FOX protein family, *FOXP3* appears to function as the master regulator in the development and function of regulatory T cells. These mutations lead to the lack of a major population of regulatory T lymphocytes with resulting overwhelming autoimmunity and development of diabetes (as early as 2 days of age) in approximately 80% of the children with this disorder.

APS-1 (autoimmune polyendocrinopathy syndrome type 1) is caused by mutations of the *AIRE* (autoimmune regulator) gene, leading to abnormalities in expression of peripheral antigens within the thymus and/or abnormalities of negative selection in the thymus. This results in widespread autoimmunity. Approximately 18% of children with this syndrome develop type 1 diabetes.

Genes Altering the Risk of Autoimmune Type 1 Diabetes Mellitus

For most patients with T1DM, their risk of developing T1DM is modified by the influence of several risk loci. The genomic region with by

far the greatest contribution to the risk of T1DM is the major histocompatibility complex on chromosome 6. The region with the next highest odds ratio is the promoter region 5′ of the insulin gene on chromosome 11. Studies have identified more than 50 other risk loci. These loci include insulin *(INS)*, protein tyrosine phosphatase nonreceptor type 22 *(PTPN22)*, protein tyrosine phosphatase nonreceptor type 2 *(PTPN2)*, interleukin (IL)-2 receptor *(CD25)*, a lectin-like gene *(KIAA0350)*, v-erb-b2 erythroblastic leukemia viral oncogene homolog 3e *(ERBB3e)*, cytotoxic T-lymphocyte antigen 4 *(CTLA4)*, and interferon-induced with helicase C domain 1 *(IFIH1)*. However, except for *PTPN22*, their contribution is relatively small, thus making them less useful for predicting the genetic risk of T1DM in a given individual. On balance, the known functions of these genes suggest the primary etiologic pathways of diabetes, namely, HLA class II and class I molecules binding, T and B cell activation, innate pathogen viral responses, chemokine and cytokine signaling, and T regulatory and antigen-presenting cell functions.

Major Histocompatibility Complex/Human Leukocyte Antigen Encoded Susceptibility to Type 1 Diabetes Mellitus

The major histocompatibility complex is a large genomic region that contains a number of genes related to immune system function in humans. These genes are further divided into HLA classes I, II, III, and IV genes. Class II genes are the ones most strongly associated with risk of T1DM, but some of the risk associated with various HLA types is a result of variation in genes in HLA classes other than class II. Overall, genetic variation in the HLA region can explain 40-50% of the genetic risk of T1DM (Fig. 589-2).

Some of the known associations include the HLA DR3/4-DQ2/8 genotype; compared to a population prevalence of T1DM of approximately 1 in 300, DR3/4-DQ2/8 newborns from the general population have a 1 in 20 genetic risk. This risk of development of T1DM is even higher when the high-risk HLA haplotypes are shared with a sibling or parent with T1DM. Thus, if 1 sibling has T1DM and shares the same high-risk DR3/4-DQ2/8 haplotype with another sibling, then the risk of autoimmunity in the other sibling is 50%. And this risk approaches 80% when siblings share both HLA haplotypes identical by descent. This is known as the *relative paradox* and points to the existence of other shared genetic risk factors (most likely in the extended HLA haplotype).

With advances in genotyping, further discrimination is possible and we can identify more specific risk ratios for specific haplotypes. For example, the DRB1*0401-DQA1*0301g-DQB1*0302 haplotype has an odds ratio (OR) of 8.39 whereas the DRB1*0401-DQA1*0301g-DQB1*0301 has an OR of 0.35, implicating the DQB1*0302 allele as a critical susceptibility allele. There are some dramatically protective

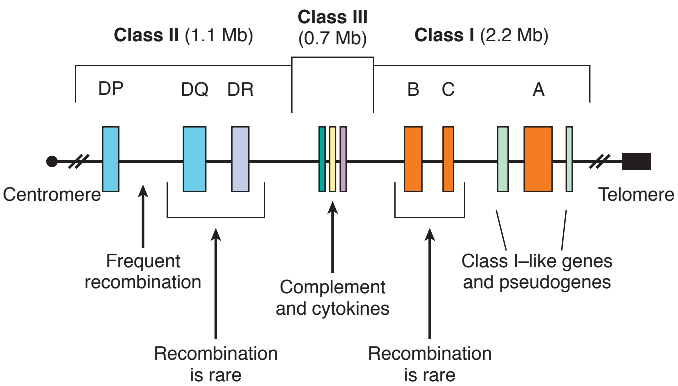

Figure 589-2 The human leukocyte antigen (HLA) complex (6p21.31). Graphic representation of the HLA complex, showing the relative locations of the 3 classes of HLA genes. *(Courtesy of Dr. George Eisenbarth.)*

DR-DQ haplotypes (e.g., DRB1*1501-DQA1*0102-DQB1*0602 [OR = 0.03], DRB1*1401-DQA1*0101-DQB1*0503 [OR = 0.02], and DRB1*0701-DQA1*0201-DQB1*0303 [OR = 0.02]). The DR2 haplotype (DRB1*1501-DQA1*0102-DQB1*0602) is dominantly protective and is present in 20% of the general population but is seen in only 1% of patients with T1DM.

Role of Aspartate at Position 57 in DQB1

DQB1*0302 (high risk for diabetes) differs from DQB1*0301 (protective against diabetes) only at position 57, where it lacks an aspartic acid residue. The DQB1*0201 allele (increased risk for diabetes) also lacks aspartic acid at position 57, and it has been proposed that the presence of aspartate at this position alters the protein recognition and protein binding characteristics of this molecule. Although the absence of aspartate at this position appears to be important in most studies on white individuals, it does not have the same role in Korean and Japanese populations. Moreover, certain low-risk DQB1 genotypes also lack aspartic acid at position 57, including DQB1*0302/DQB1*0201 (DR7) and DQB1*0201 (DR3)/DQB1*0201 (DR7). Thus, the presence of aspartate at this position is usually, but not always, protective in white populations but not necessarily in other populations.

Role of Human Leukocyte Antigen Class I

Although the alleles of class II HLA genes appear to have the strongest associations with diabetes, recent genotyping studies and analyses of pooled data have identified associations with other elements in the HLA complex, especially HLA-A and HLA-B. The most significant association is with HLA-B39, which confers high risk for T1DM in 3 different populations, makes up the majority of the signal from HLA-B, and is associated with a lower age of onset of the disease.

Insulin Gene Locus, *IDDM2*

The second locus found to be associated with risk of T1DM was labeled IDDM2 and has been localized to a region upstream of the insulin gene (i.e., 5′ of the insulin gene). It is estimated that this locus accounts for approximately 10% of the familial risk of T1DM. Susceptibility in this region has been primarily mapped to a variable number of tandem repeats approximately 500 bp upstream of the insulin gene. This highly polymorphic region consists of anywhere from 30 to several hundred repeats of a 14-15 bp unit sequence (ACAGGGGTCTGGGG). A shorter number of repeats is associated with increased risk of T1DM.

PTPN22 (Lymphoid Tyrosine Phosphatase)

A single-nucleotide polymorphism in the *PTPN22* gene on chromosome 1p13 that encodes lymphoid tyrosine phosphatase correlates strongly with the incidence of T1DM in 2 independent populations. This gene has an association with several other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, vitiligo, and Graves disease.

Cytotoxic T Lymphocyte Antigen 4

The cytotoxic T lymphocyte antigen 4 *(CTLA-4)* gene is located on chromosome 2q33 and is associated with T1DM as well as Graves disease, Hashimoto thyroiditis, celiac disease, and systemic lupus erythematosus. This gene is a negative regulator of T-cell activation.

Interleukin-2 Receptor

Single-nucleotide polymorphisms in or near the gene for the IL-2 receptor have been found to have an association with T1DM risk. Studies with IL-2 in T1DM to date have not been successful in halting progression.

Interleukin-1 Receptor

IL-1 receptor activation and chemokines involved in monocyte/macrophage and neutrophil chemotaxis have been also identified as critical steps in nitric oxide–induced islet necrosis and subsequent apoptosis. Indeed, inhibition of the activation of IL-1β–dependent inflammatory pathways by an IL-1 receptor antagonist in cultured rat islets exposed to nitric oxide prevented necrosis and apoptosis

supporting evaluation in human islets in vitro and potentially as a posttransplantation therapy. **IL-1 blockade in patients with T1DM has not halted progression.**

Interferon-Induced Helicase

Another gene identified as having a modest effect on the risk of T1DM is the interferon-induced helicase *(IFIH1)* gene. Significant association exists with T1DM as well as Graves disease and multiple sclerosis. This gene is thought to play a role in protecting the host from viral infections and given the specificity of different helicases for different RNA viruses, it is possible that knowledge of this gene locus will help to narrow down the list of viral pathogens that may have a role in T1DM.

CYP27B1

Cytochrome P450, subfamily 27, polypeptide 1 gene encodes vitamin D 1α-hydroxylase. Because of the known role of vitamin D in immune regulation and because of epidemiologic evidence that vitamin D may play a role in T1DM, this gene was examined as a candidate gene and 2 single-nucleotide polymorphisms were found to be associated.

ENVIRONMENTAL FACTORS

That 50% or so of monozygotic twins are discordant for T1DM, the variation seen in urban and rural areas populated by the same ethnic group, the change in incidence that occurs with migration, the increase in incidence that has been seen in almost all populations in the last few decades, and the occurrence of seasonality all provide evidence that environmental factors also play a significant role in the causation of T1DM.

Viral Infections

It is possible that various viruses do play a role in the pathogenesis of T1DM, but no single virus, and no single pathogenic mechanism, stands out in the environmental etiology of T1DM. Instead, a variety of viruses and mechanisms may contribute to the development of diabetes in genetically susceptible hosts. Invoked mechanisms involved direct infection of β cells by viruses resulting in lysis and release of self-antigens, direct viral infection of antigen-presenting cells causing increased expression of cytokines, and "molecular mimicry," the notion that viral antigens exhibit homology to self-epitopes.

Congenital Rubella Syndrome

The clearest evidence of a role for viral infection in human T1DM is seen in congenital rubella syndrome. Prenatal infection with rubella is associated with β-cell autoimmunity in up to 70%, with development of T1DM in up to 40% of infected children. The time lag between infection and development of diabetes may be as high as 20 yr. T1DM after congenital rubella is more likely in patients that carry the higher-risk genotypes. Interestingly, there appears to be no increase in risk of diabetes when rubella infection develops after birth or when live-virus rubella immunization is used.

Enteroviruses

Studies show an increase in evidence of enteroviral infection in patients with T1DM and an increased prevalence of enteroviral RNA in prenatal blood samples from children who subsequently develop T1DM. In addition, there are case reports of association between enteroviral infection and subsequent T1DM. But the true significance of these infections remains unknown at this time.

Mumps Virus

It has been variably observed that mumps infection leads to the development of β-cell autoimmunity with high frequency and to T1DM in some cases. Although mumps may play a role in some cases of diabetes, the fact that T1DM diabetes incidence has increased steadily in several countries after universal mumps vaccination was introduced and that the incidence is extremely low in several populations where mumps is still prevalent indicates that mumps alone is not a major causal factor in diabetes.

The Hygiene Hypothesis: Possible Protective Role of Infections

Although some viral infections may increase the risk of T1DM, infectious agents may also play a protective role against diabetes. The hygiene hypothesis states that T1DM is a disease of industrialized countries, where the observation that there are fewer infections implies that the immune system is less-well trained for its main task, namely host defense. Some call this theory the "microbial deprivation hypothesis." The hygiene hypothesis states that lack of exposure to childhood infections may increase an individual's chances of developing autoimmune diseases, including T1DM. Rates of T1DM and other autoimmune disorders are generally lower in underdeveloped nations with a high prevalence of childhood infections and tend to increase as these countries become more developed. The incidence of T1DM differs almost 6-fold between Russian Karelia and Finland, even though both are populated by a genetically related population and are adjacent to each other and at the same latitude. The incidence of autoimmunity in the 2 populations varies inversely with immunoglobulin (Ig) E antibody levels, and IgE is involved in the response to parasitic infestation. All these observations indicate that decreased exposure to certain parasites and other microbes in early childhood may lead to an increased risk of autoimmunity in later life, including autoimmune diabetes. On the other hand, retrospective case-control studies have been equivocal at best and direct evidence of protection by childhood infections is still lacking.

Diet

Breastfeeding may lower the risk of T1DM, either directly or by delaying exposure to cow's milk protein. Early introduction of cow's milk protein and early exposure to gluten are implicated in the development of autoimmunity and it has been suggested that this is a result of the "leakiness" of the immature gut to protein antigens. Implicated antigens include β-lactoglobulin, a major lipocalin protein in bovine milk, which is homologous to the human protein glycodelin (PP14), a T-cell modulator. Other studies focused on bovine serum albumin as the inciting antigen, but the data are contradictory and not yet conclusive. In addition, milk and milk products are also indicators of the level of contamination of persistent organic pollutants, polychlorinated biphenyls, dioxin, and others. One large study in infants who are at high risk for T1DM did not demonstrate a reduced incidence of diabetes-associated autoantibodies when fed an extensively hydrolyzed vs cow milk–based formula. A smaller study demonstrated a reduced incidence of autoantibody production in infants fed a whey-based formula that was free of bovine insulin. Additional studies are underway and should be available in 2017.

Other dietary factors that have been suggested at various times as playing a role in diabetes risk include omega-3 fatty acids, vitamin D, ascorbic acid, zinc, and vitamin E. Vitamin D is biologically plausible (it has a role in immune regulation), deficiency is more common in northern countries like Finland, and there is some epidemiologic evidence that decreased vitamin D levels in pregnancy or early childhood may be associated with diabetes risk; but the evidence is not yet conclusive and it is hoped that ongoing studies like TEDDY (The Environmental Determinants of Diabetes in the Young) will help to resolve some of the uncertainties in this area.

Psychologic Stress

Several studies show an increased prevalence of stressful psychologic situations among children who subsequently developed T1DM. Whether these stresses only aggravate preexisting autoimmunity or whether they can actually trigger autoimmunity through epigenetic mechanisms remains unknown.

PATHOGENESIS AND NATURAL HISTORY OF TYPE 1 DIABETES MELLITUS

In T1DM, a genetically susceptible host develops autoimmunity against the host's own β cells. What triggers this autoimmune response remains unclear at this time. In some (but not all) patients, this autoimmune process results in progressive destruction of β cells until a critical mass

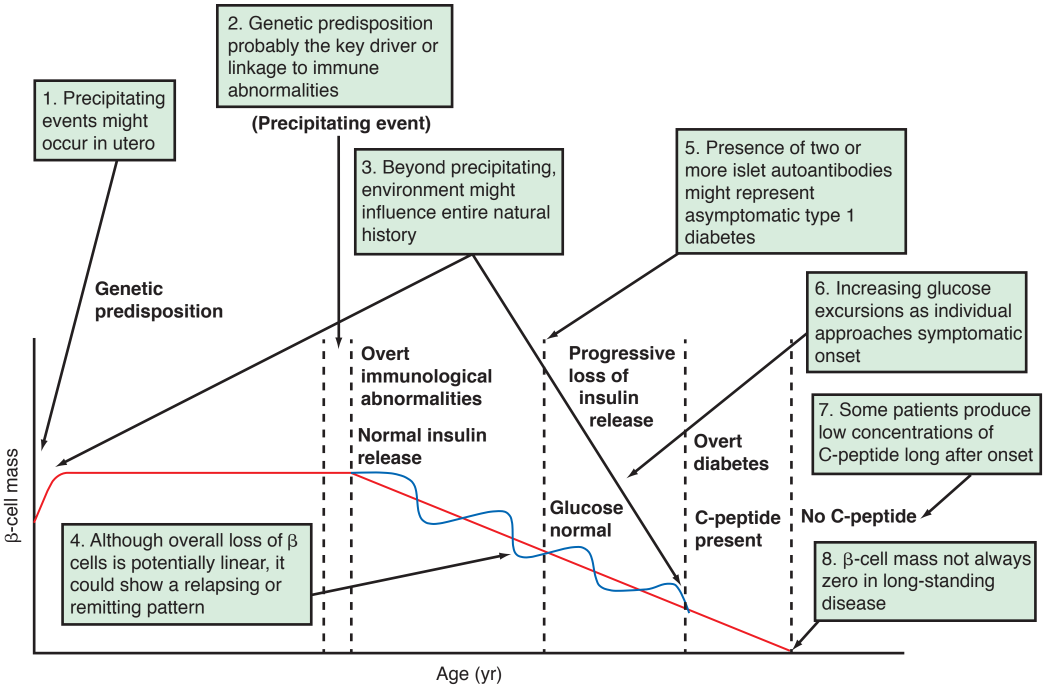

Figure 589-3 **The natural history of type 1 diabetes—a 25 yr old concept revisited.** A recreation of the model of type 1 diabetes, originally proposed in 1986, is shown in *black*. Additions and conjectures based on recent knowledge gains are shown in *green*. *(From Atkinson MA, Eisenbarth GS, Michels AW: Type 1 diabetes.* Lancet *383:69–78, 2014, Fig. 4, p. 73.)*

of β cells is lost and insulin deficiency develops. Insulin deficiency, in turn, leads to the onset of clinical signs and symptoms of T1DM. At the time of diagnosis, some viable β cells are still present and these may produce enough insulin to lead to a partial remission of the disease (honeymoon period) but over time, almost all β cells are destroyed and the patient becomes totally dependent on exogenous insulin for survival (Fig. 589-3). Over time, some of these patients develop secondary complications of diabetes that appear to be related to how well-controlled the diabetes has been. Thus, the natural history of T1DM involves some or all of the following stages:

1. Initiation of autoimmunity
2. Preclinical autoimmunity with progressive loss of β-cell function
3. Onset of clinical disease
4. Transient remission
5. Established disease
6. Development of complications

Initiation of Autoimmunity

Genetic susceptibility to T1DM is determined by several genes (see "Genetics" below), with the largest contribution coming from variants in the HLA system. But it is important to keep in mind that even with the highest-risk haplotypes, most carriers will *not* develop T1DM. Even in monozygotic twins, the concordance is 30-65%. The observed rise in incidence of T1DM within an essentially genetically stable patient population implies that something has accordingly changed in the environment or the way children are raised. A number of factors, including prenatal influences, diet in infancy, viral infections, lack of exposure to certain infections, even psychologic stress, are implicated in the pathogenesis of T1DM, but their exact role and the mechanism by which they trigger or aggravate autoimmunity remains uncertain (Fig. 589-4). What is clear is that markers of autoimmunity are much more prevalent than clinical T1DM, indicating that initiation of autoimmunity is a necessary but not a sufficient condition for T1DM. Whatever the triggering factor, it seems that in most cases of T1DM that are diagnosed in childhood, the onset of autoimmunity occurs very early in life. In a majority of the children diagnosed before age 10 yr, the first signs of autoimmunity appear before age 2 yr. Development of autoimmunity is associated with the appearance of several

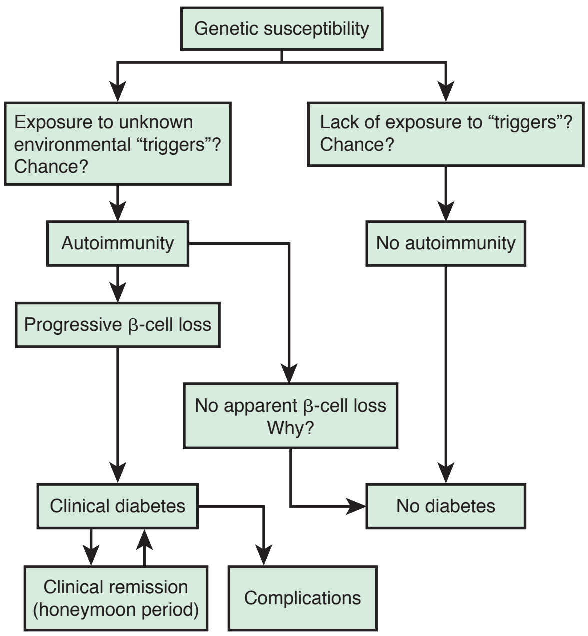

Figure 589-4 **Schematic of the natural history of type 1 diabetes mellitus.** Unknown triggers act upon a genetically susceptible host to trigger autoimmunity. Some proportion of those with autoimmunity develop progressive β-cell loss that eventually leads to clinical diabetes. This is followed by temporary clinical remission (honeymoon period) in most patients. Over time, insulin secretion is almost completely lost and complications may develop in some patients (in direct proportion to the occurrence of hyperglycemia).

autoantibodies. IAAs are usually the first to appear in young children, followed by glutamic acid decarboxylase 65 kDa, and later by tyrosine phosphatase insulinoma–associated 2 and zinc transporter 8 antibodies. The earliest antibodies are predominantly of the IgG_1 subclass. Not only is there "spreading" of autoimmunity to more antigens (IAA, and

then glutamic acid decarboxylase 65 and insulinoma-associated 2 and zinc transporter 8) but there is also epitope spreading within 1 antigen. Initial glutamic acid decarboxylase 65 antibodies tend to be against the middle region or the carboxyl-terminal region, whereas aminoterminal antibodies usually appear later and are less common in children.

Preclinical Autoimmunity with Progressive Loss of β-Cell Function

In some, but not all, patients, the appearance of autoimmunity is followed by progressive destruction of β cells. Antibodies are a marker for the presence of autoimmunity, but the actual damage to the β cells is primarily T-cell mediated (Fig. 589-5). Histologic analysis of the pancreas from patients with recent-onset T1DM reveals insulitis, with an infiltration of the islets of Langerhans by mononuclear cells, including T and B lymphocytes, monocytes/macrophages, and natural killer cells. In the nonobese diabetic mouse, a similar cellular infiltrate is followed by linear loss of β cells until they completely disappear. But it appears that the process in human T1DM is not necessarily linear and there may be an undulating downhill course, with remissions and relapses, in the development of T1DM.

Role of Autoantibodies

Even though T1DM does not occur as a direct consequence of autoantibody formation, the risk of developing clinical disease increases dramatically with an increase in the number of antibodies; only 30% of children with 1 antibody will progress to diabetes, but this risk increases to 70% when 2 antibodies are present and 90% when 3 are present. The risk of progression also varies with the intensity of the antibody response and those with higher antibody titers are more likely to progress to clinical disease. Another factor that appears to influence progression of β-cell damage is the age at which autoimmunity develops; children in whom IAAs appeared within the 1st 2 yr of life rapidly developed anti–islet cell antibodies and progressed to diabetes more frequently than children in whom the first antibodies appeared between ages 5 and 8 yr.

Role of Genetics in Disease Progression

Genetics plays a role in progression to clinical disease. In a large study of healthy children, the appearance of single antibodies is relatively common and usually transient, and does not correlate with the presence of high-risk HLA alleles, but those carrying high-risk HLA alleles are more likely to develop multiple antibodies and progress to disease. Similarly, the appearance of antibodies is more likely to predict diabetes in those with a family history of diabetes vs those with no family history of T1DM. Thus, it may be the case that environmental factors can induce transient autoimmunity in many children, but those with genetic susceptibility are more likely to see progression of autoimmunity and eventual development of diabetes.

Role of Environmental Factors

In addition to genetic factors, environmental factors may also act as accelerators of T1DM after the initial appearance of autoimmunity. This is evident from the fact that the incidence of T1DM can vary several-fold between populations that have the same prevalence of autoimmunity. For instance, the incidence of T1DM in Finland is almost 4-fold higher than in Lithuania, but the incidence of autoimmunity is similar in both countries.

The fact that all children with evidence of autoimmunity and of autoreactive T cells do not progress to diabetes indicates that there are "checkpoints" at which the autoimmune process can be halted or

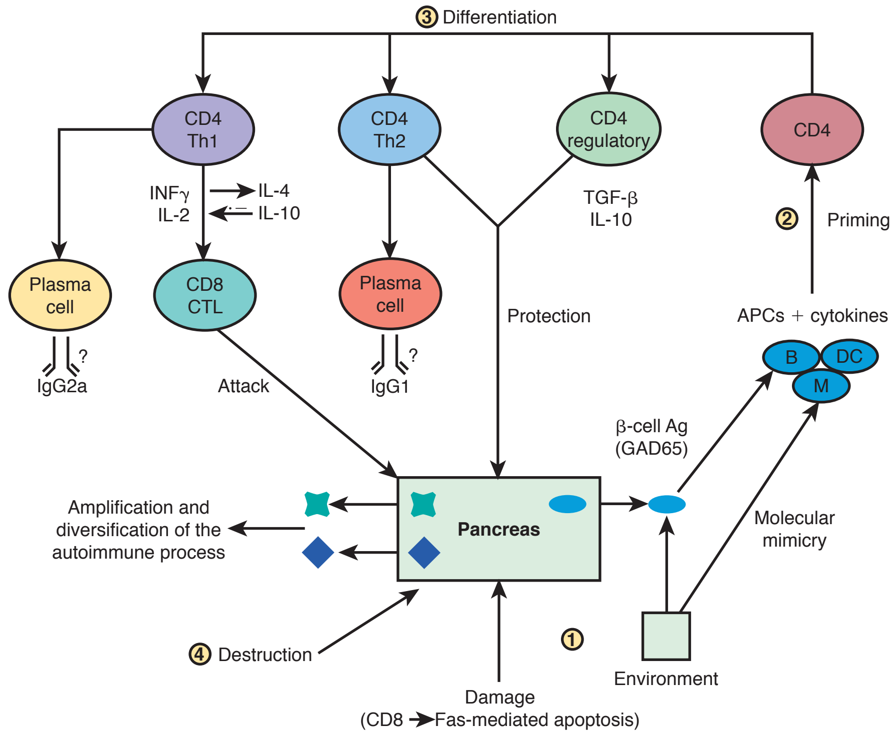

Figure 589-5 **Schematic of the autoimmune response against pancreatic β cells.** An insult to the pancreas leads to the release of β-cell antigens (GAD65), which are taken up by antigen-presenting cells (APCs) and the epitopes presented to the CD4 T cells. Type and stage of activation of APCs as well as the cytokine environment, in which the CD4 T-cell priming takes place, dictate the differentiation of autoreactive T cells toward diabetogenic T-helper type 1 (Th1) cells, T-helper type 2 (Th2) cells, or antigen-specific regulatory T cells. A predominant Th1 autoimmune response results in the recruitment and differentiation of cytotoxic CD8 cells, which attack the pancreatic β cells, leading to a massive release of β-cell antigens (Ag), epitope spreading, and destruction of the pancreatic islets. B, B lymphocyte; CTL, cytotoxic cell; DC, dendritic cell; IL, interleukin; INFγ, interferon-γ; M, macrophage; TGF-β, tumor growth factor β. *(Adapted from Casares S, Brumeanu TD: Insights into the pathogenesis of T1DM: a hint for novel immunospecific therapies,* Curr Mol Med *1:357–378, 2001.)*

reversed before it progresses to full-blown diabetes. This has raised the possibility of preventing T1DM by intervening in the preclinical stage.

Onset of Clinical Disease

Patients with progressive β-cell destruction will eventually present with clinical T1DM. It was thought that 90% of the total β-cell mass is destroyed by the time clinical disease develops, but later studies have revealed that this is not always the case. It now appears that β-cell destruction is more rapid and more complete in younger children, while in older children and adults the proportion of surviving β cells is greater (10-20% in autopsy specimens) and some β cells (about 1% of the normal mass) survive up to 30 yr after the onset of diabetes. As autopsies are usually done on patients who died of diabetic ketoacidosis, these figures may underestimate the actual β-cell mass present at diagnosis. Functional studies indicate that up to 40% of the insulin secretory capacity may be preserved in adults at the time of presentation of T1DM. Ultrasensitive assays indicate that C-peptide production is measurable decades after onset of T1DM. The fact that newly diagnosed diabetic individuals may still have a significant surviving β-cell mass is important because it raises the possibility of secondary prevention of T1DM. Similarly, the existence of viable β cells years or decades after initial presentation indicates that even patients with long-standing diabetes may be able to exhibit some recovery of β-cell function if the autoimmune destructive process can be halted and islet cell regeneration occurs.

PREDICTION AND PREVENTION

Autoimmunity precedes clinical T1DM, and indicators of maturing autoimmune responses may be useful markers for disease prediction. Individuals at risk for T1DM can be identified by a combination of genetic, immunologic, and metabolic markers. The most informative genetic locus, HLA class II, confers about half of the total genetic risk but has a low positive predictive value (PPV) when used in the general population. Autoantibodies provide a practical readout of β-cell autoimmunity, are easily sampled in venous blood, and have become the mainstay of T1DM prediction efforts. In the 1st-degree relatives of patients with T1DM, the number of positive autoantibodies can help estimate the risk of developing T1DM: low risk (single autoantibodies: PPV of 2-6%), moderate risk (2 autoantibodies: PPV of 21-40%), and high risk (>2 autoantibodies: PPV of 59-80%) over a 5 yr period. In children carrying the T1DM highest-risk genotype (HLA-DQB1*0201-DQA1*05/DQB1*0302-DQA1*03), insulitis is almost 10 times more frequent (PPV 21%) than in children with other genotypes (PPV 2.2%). But while autoantibodies are useful for the prediction of T1DM in the relatives of patients with T1DM, outside of that obvious population, the screening of the general population would be required in order to identify healthy subjects at risk of T1DM. Indeed, close to 9 of 10 individuals with new-onset T1DM have no family background of T1DM. This has been difficult, in part, because the observed autoantibody prevalence greatly exceeds the low disease prevalence in nonrelatives, leading to high false-positive rates.

Primary Prevention of Type 1 Diabetes Mellitus

A safe, effective, inexpensive, and easily administered intervention could theoretically be targeted at all newborns, but no such universally effective intervention is yet available. Delaying the introduction of cow's milk protein, delaying introduction of cereals, and increasing the duration of breastfeeding are all potentially beneficial but of unproven value.

In high-risk populations (relatives of individuals with T1DM, especially those with high-risk genotypes), it is feasible to test more targeted interventions. Parenteral insulin and nasal insulin proved similarly ineffective in preventing diabetes, but oral insulin appeared to delay the incidence of diabetes in only some of autoantibody-positive but still prediabetic patients. In the approach to the newly diagnosed patient with T1DM, antigen-specific immunotherapy trials studying the effect of glutamic acid decarboxylase formulated in aluminum hydroxide, IL-1β inhibition, or intranasal insulin have been negative, and anti-CD3 antibodies have been inconclusive.

Secondary Prevention

Immunosuppressants like cyclosporine have been tested after the onset of T1DM, but while they may prolong the honeymoon period, they are associated with significant side effects and are only effective as long as they are being administered, so their use for this purpose has been abandoned.

The possibility of using glucagon-like peptide (GLP)-1 agonists (e.g., exenatide) alone or in combination with immunomodulatory therapies is also being explored as these agents are capable of increasing β-cell mass in animals.

PATHOPHYSIOLOGY

Insulin performs a critical role in the storage and retrieval of cellular fuel. Its secretion in response to feeding is exquisitely modulated by the interplay of neural, hormonal, and substrate-related mechanisms to permit controlled disposition of ingested foodstuff as energy for immediate or future use. Insulin levels must be lowered to then mobilize stored energy during the fasted state. Thus, in normal metabolism, there are regular swings between the postprandial, high-insulin anabolic state and the fasted, low-insulin catabolic state that affect liver, muscle, and adipose tissue (Table 589-3). T1DM is a progressive low-insulin catabolic state in which feeding does not reverse, but rather exaggerates, these catabolic processes. With moderate insulinopenia, glucose utilization by muscle and fat decreases and postprandial hyperglycemia appears. At even lower insulin levels, the liver produces excessive glucose via glycogenolysis and gluconeogenesis, and fasting hyperglycemia begins. Hyperglycemia produces an osmotic diuresis (glycosuria) when the renal threshold is exceeded (180 mg/dL; 10 mmol/L). The resulting loss of calories and electrolytes, as well as the worsening dehydration, produces a physiologic stress with hypersecretion of stress hormones (epinephrine, cortisol, growth hormone, and glucagon). These hormones, in turn, contribute to the metabolic decompensation by further impairing insulin secretion (epinephrine), by antagonizing its action (epinephrine, cortisol, growth hormone), and by promoting glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis (glucagon, epinephrine, growth hormone, and cortisol) while decreasing glucose utilization and glucose clearance (epinephrine, growth hormone, cortisol).

Table 589-3 Influence of Feeding (High Insulin) or of Fasting (Low Insulin) on Some Metabolic Processes in Liver, Muscle, and Adipose Tissue*

	HIGH PLASMA INSULIN (POSTPRANDIAL STATE)	LOW PLASMA INSULIN (FASTED STATE)
Liver	Glucose uptake Glycogen synthesis Absence of gluconeogenesis Lipogenesis Absence of ketogenesis	Glucose production Glycogenolysis Gluconeogenesis Absence of lipogenesis Ketogenesis
Muscle	Glucose uptake Glucose oxidation Glycogen synthesis Protein synthesis	Absence of glucose uptake Fatty acid and ketone oxidation Glycogenolysis Proteolysis and amino acid release
Adipose tissue	Glucose uptake Lipid synthesis Triglyceride uptake	Absence of glucose uptake Lipolysis and fatty acid release Absence of triglyceride uptake

*Insulin is considered to be the major factor governing these metabolic processes. Diabetes mellitus may be viewed as a permanent low-insulin state that, untreated, results in exaggerated fasting.

The combination of insulin deficiency and elevated plasma values of the counterregulatory hormones is also responsible for accelerated lipolysis and impaired lipid synthesis, with resulting increased plasma concentrations of total lipids, cholesterol, triglycerides, and free fatty acids. The hormonal interplay of insulin deficiency and glucagon excess shunts the free fatty acids into ketone body formation; the rate of formation of these ketone bodies, principally β-hydroxybutyrate and acetoacetate, exceeds the capacity for peripheral utilization and renal excretion. Accumulation of these keto acids results in metabolic acidosis (diabetic ketoacidosis [DKA]) and compensatory rapid deep breathing in an attempt to excrete excess CO_2 (Kussmaul respiration). Acetone, formed by nonenzymatic conversion of acetoacetate, is responsible for the characteristic fruity odor of the breath. Ketones are excreted in the urine in association with cations and thus further increase losses of water and electrolyte and bicarbonate regenerating ability. With progressive dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen utilization, consciousness becomes impaired, and the patient ultimately becomes comatose.

CLINICAL MANIFESTATIONS

In diabetes the decreasing β-cell mass with worsening insulinopenia, progressive hyperglycemia, and eventual ketoacidosis all imply that symptoms steadily increase, from early intermittent polyuria to DKA and coma, over weeks usually, rather than months. Initially, when only insulin reserve is limited, occasional postprandial hyperglycemia occurs. When the serum glucose increases above the renal threshold, intermittent polyuria or nocturia begins. With further β-cell loss, chronic hyperglycemia causes a more persistent diuresis, often with nocturnal enuresis, and polydipsia becomes more apparent. Female patients may develop monilial vaginitis from the chronic glycosuria. Calories are lost in the urine (glycosuria), triggering a compensatory hyperphagia. If this hyperphagia does not keep pace with the glycosuria, loss of body fat ensues, with clinical weight loss and diminished subcutaneous fat stores. An average, healthy 10 yr old child consumes approximately 50% of 2,000 daily calories as carbohydrate. As that child becomes diabetic, daily losses of water and glucose may be 5 L and 250 g, respectively, representing 1,000 calories, or 50%, of the average daily caloric intake. Despite the child's compensatory increased intake of food, the body starves because unused calories are lost in the urine.

When extremely low insulin levels are reached, ketoacids accumulate. At this point, the child quickly deteriorates. Ketoacids produce abdominal discomfort or true pain, nausea, and emesis, preventing oral replacement of urinary water losses. Dehydration accelerates, causing weakness or orthostasis—but polyuria persists. As in any hyperosmotic state, the degree of dehydration may be clinically underestimated because intravascular volume is conserved at the expense of intracellular volume. Ketoacidosis exacerbates prior symptoms and leads to Kussmaul respirations (deep, heavy, nonlabored rapid breathing), fruity breath odor (acetone), prolonged corrected Q-T interval, diminished neurocognitive function, and possible coma. Approximately 20-40% of children with new-onset diabetes progress to DKA before diagnosis.

This entire progression happens much more quickly (over a few weeks) in younger children, owing to either more aggressive autoimmune destruction of β cells and/or to lower β-cell mass compared to older subjects. In infants, most of the weight loss is acute water loss because they will not have had prolonged urinary loss of calories from glycosuria, and there will be an increased incidence of DKA at diagnosis. In adolescents, the course is usually more prolonged (over a few months), and most of the weight loss represents fat loss from prolonged starvation. Additional weight loss from acute dehydration may occur just before diagnosis. In any child, the progression of symptoms may be accelerated by the stress of an intercurrent illness or trauma, when counterregulatory (stress) hormones overwhelm the limited insulin secretory capacity.

DIAGNOSIS

The diagnosis of T1DM is usually straightforward (see Table 589-2). Although most symptoms are nonspecific, the most important clue is an inappropriate polyuria in any child with dehydration, poor weight gain, or "the flu." Hyperglycemia, glycosuria, and ketonuria can be determined quickly. Nonfasting blood glucose greater than 200 mg/dL (11.1 mmol/L) with typical symptoms is diagnostic with or without ketonuria. In the obese child, T2DM must be considered (see "Type 2 Diabetes Mellitus" below). Once hyperglycemia is confirmed, it is prudent to determine whether DKA is present (especially if ketonuria is found) and to evaluate electrolyte abnormalities—even if signs of dehydration are minimal. A baseline hemoglobin A_{1c} (HbA_{1c}) will be confirmatory and allows an estimate of the duration of hyperglycemia and provides an initial value by which to compare the effectiveness of subsequent therapy. Falsely low HbA_{1c} levels are noted in hemolytic anemias, pure red cell aplasia, blood transfusions, and anemias associated with hemorrhage, cirrhosis, myelodysplasias, or renal disease treated with erythropoietin.

In the nonobese child, testing for autoimmunity to β cells is not commonly necessary. Other autoimmunities associated with T1DM should be sought, including celiac disease (by tissue transglutaminase IgA and total IgA) and thyroiditis (by antithyroid peroxidase and antithyroglobulin antibodies). Fifteen to 30% of subjects with T1DM have elevated thyroid-stimulating hormone (TSH) and antithyroid antibodies and close to 5-10% have evidence for celiac disease. These diseases share common genes and likely the same interplay between environmental and immunologic factors. Because significant physiologic distress can disrupt the pituitary–thyroid axis, free thyroxine and TSH levels should be checked after the child is stable for a few weeks.

Rarely, a child has transient hyperglycemia with glycosuria while under substantial physical stress. This usually resolves permanently during recovery from the stressors. Stress-produced hyperglycemia can reflect a limited insulin reserve temporarily revealed by counterregulatory hormones. A child with temporary hyperglycemia should therefore be monitored for the development of symptoms of persistent hyperglycemia and tested if such symptoms occur. Formal testing in a child who remains clinically asymptomatic is not necessary; if there is concern for T1DM or T2DM a hemoglobin A_{1c} may be of value.

Routine screening procedures, such as postprandial determinations of blood glucose or screening oral glucose tolerance tests have yielded low detection rates in healthy, asymptomatic children, even among those considered at risk, such as siblings of diabetic children. Accordingly, such screening procedures are not recommended in children.

Diabetic Ketoacidosis

DKA is the end result of the metabolic abnormalities resulting from a severe deficiency of insulin or insulin effectiveness. The latter occurs during stress as counterregulatory hormones block insulin action. DKA occurs in 20-40% of children with new-onset diabetes and in children with known diabetes who omit insulin doses or who do not successfully manage an intercurrent illness. DKA may be arbitrarily classified as mild, moderate, or severe (Table 589-4), and the range of symptoms depends on the depth of ketoacidosis. There is a large amount of ketonuria, an increased ion gap, a decreased serum bicarbonate (or total CO_2) and pH, and an elevated effective serum osmolality, indicating hypertonic dehydration.

TREATMENT

Therapy is tailored to the degree of insulinopenia at presentation. Most children with new diabetes have mild to moderate symptoms, have minimal dehydration with no history of emesis, and have not progressed to ketoacidosis. Once DKA has resolved in the newly diagnosed child, therapy is transitioned to that described for children with nonketotic onset. Children with previously diagnosed diabetes who develop DKA are usually transitioned to their previous insulin regimen.

NEW-ONSET DIABETES WITHOUT KETOACIDOSIS

Excellent diabetes control involves many goals: to maintain a balance between tight glucose control and avoiding hypoglycemia, to eliminate polyuria and nocturia, to prevent ketoacidosis, and to permit normal growth and development with minimal effect on lifestyle. Therapy

Table 589-4 Classification of Diabetic Ketoacidosis

	NORMAL	MILD	MODERATE	SEVERE*
CO_2 (mEq/L, venous)[†]	20-28	16-20	10-15	<10
pH (venous)[†]	7.35-7.45	7.25-7.35	7.15-7.25	<7.15
Clinical	No change	Oriented, alert but fatigued	Kussmaul respirations; oriented but sleepy; arousable	Kussmaul or depressed respirations; sleepy to depressed sensorium to coma

*Severe hypernatremia (corrected Na >150 mEq/L) would also be classified as severe diabetic ketoacidosis.
[†]CO_2 and pH measurement are method dependent; normal ranges may vary.

Table 589-5 Starting Doses of Insulin (units/kg/day)

	NO DIABETIC KETOACIDOSIS	DIABETIC KETOACIDOSIS
Prepubertal	0.25-0.50	0.75-1.0
Pubertal	0.50-0.75	1.0-1.2
Postpubertal	0.25-0.50	0.8-1.0

encompasses initiation and adjustment of insulin, extensive teaching of the child and caretakers, and reestablishment of the life routines. Each aspect should be addressed early in the overall care.

Insulin Therapy

Several factors influence the initial daily insulin dose per kilogram of body weight. The dose is usually higher in pubertal children. It is also higher in those who are in DKA at the time of presentation. Table 589-5 shows the recommended starting total daily dose (units/kg/day) of insulin in children.

The optimal insulin dose can only be determined empirically, with frequent self-monitored blood glucose levels and insulin adjustment by the diabetes team. Many children with new-onset diabetes have some residual β-cell function (the honeymoon period), which is associated with reduced exogenous insulin needs shortly after starting on treatment. Residual β-cell function usually fades within a few months and is reflected as a steady increase in insulin requirements and wider glucose excursions.

The initial insulin schedule should be directed toward the optimal degree of glucose control in an attempt to duplicate the activity of the β cell. There are inherent limits to our ability to mimic the β cell. Exogenous insulin does not have a first pass to the liver, whereas 50% of pancreatic portal insulin is taken up by the liver, a key organ for the disposal of glucose; absorption of an exogenous dose continues despite hypoglycemia, whereas endogenous insulin release ceases and serum levels quickly lower with a normally rapid clearance. The absorption rate from an injection varies by injection site and patient activity level, whereas endogenous insulin is secreted directly into the portal circulation. Despite these fundamental physiologic differences, acceptable glucose control can be obtained with insulin analogs used in a basal-bolus regimen, that is, with slow-onset, long-duration background insulin for between-meal glucose control and rapid-onset insulin at each meal.

All preanalog insulins form hexamers, which must dissociate into monomers subcutaneously before being absorbed into the circulation. Thus, a detectable effect for **regular insulin** is delayed by 30-60 min after injection. This, in turn, requires delaying the meal 30-60 min after the injection for optimal effect—a delay rarely attained in a busy child's life. Regular insulin has a wide peak and a long tail for bolus insulin (Figs. 589-6 and 589-7). This profile limits postprandial glucose control, produces prolonged peaks with excessive hypoglycemic effects between meals, and increases the risk of nighttime hypoglycemia. These unwanted between-meal effects often necessitate "feeding the insulin" with snacks and limiting the overall degree of blood glucose control. **Neutral protamine Hagedorn (NPH) and Lente insulins** also have inherent limits because they do not create a peakless background insulin level (see Fig. 589-7*C-E*). This produces a significant hypoglycemic effect during the midrange of their duration. Thus, it is often difficult to predict their interaction with fast-acting insulins. When regular insulin is combined with NPH or Lente (see Fig. 589-7*E*), the composite insulin profile poorly mimics normal endogenous insulin secretion. Lente and Ultralente insulins have been discontinued and are no longer available.

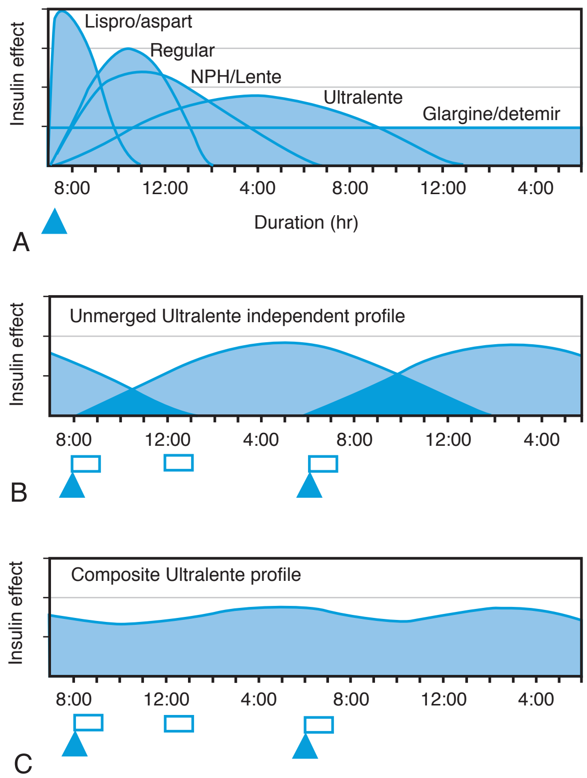

Figure 589-6 Approximate insulin effect profiles. Meals are shown as rectangles below time axis. **A,** The following relative peak effect and duration units are used: lispro/aspart, peak 20 for 4 hr; regular, peak 15 for 7 hr; neutral protamine Hagedorn/Lente, peak 12 for 12 hr; Ultralente, peak 9 for 18 hr; glargine, peak 5 for 24 hr. Although Lente and Ultralente are no longer manufactured, they are shown to give historical comparison to newer insulin analogs. ▲, Injection time. **B,** Two Ultralente injections given at breakfast and supper. Note overlap of profiles. **C,** Composite curve showing approximate cumulative insulin effect for the 2 Ultralente injections. This composite view is much more useful to the patient, parents, and medical personnel because it shows important combined effects of multiple insulin injections with variable absorption characteristics and overlapping durations.

Lispro and aspart, insulin analogs, are absorbed much quicker because they do not form hexamers. They provide discrete pulses with little if any overlap and short tail effect. This allows better control of postmeal glucose increase and reduces between-meal or nighttime

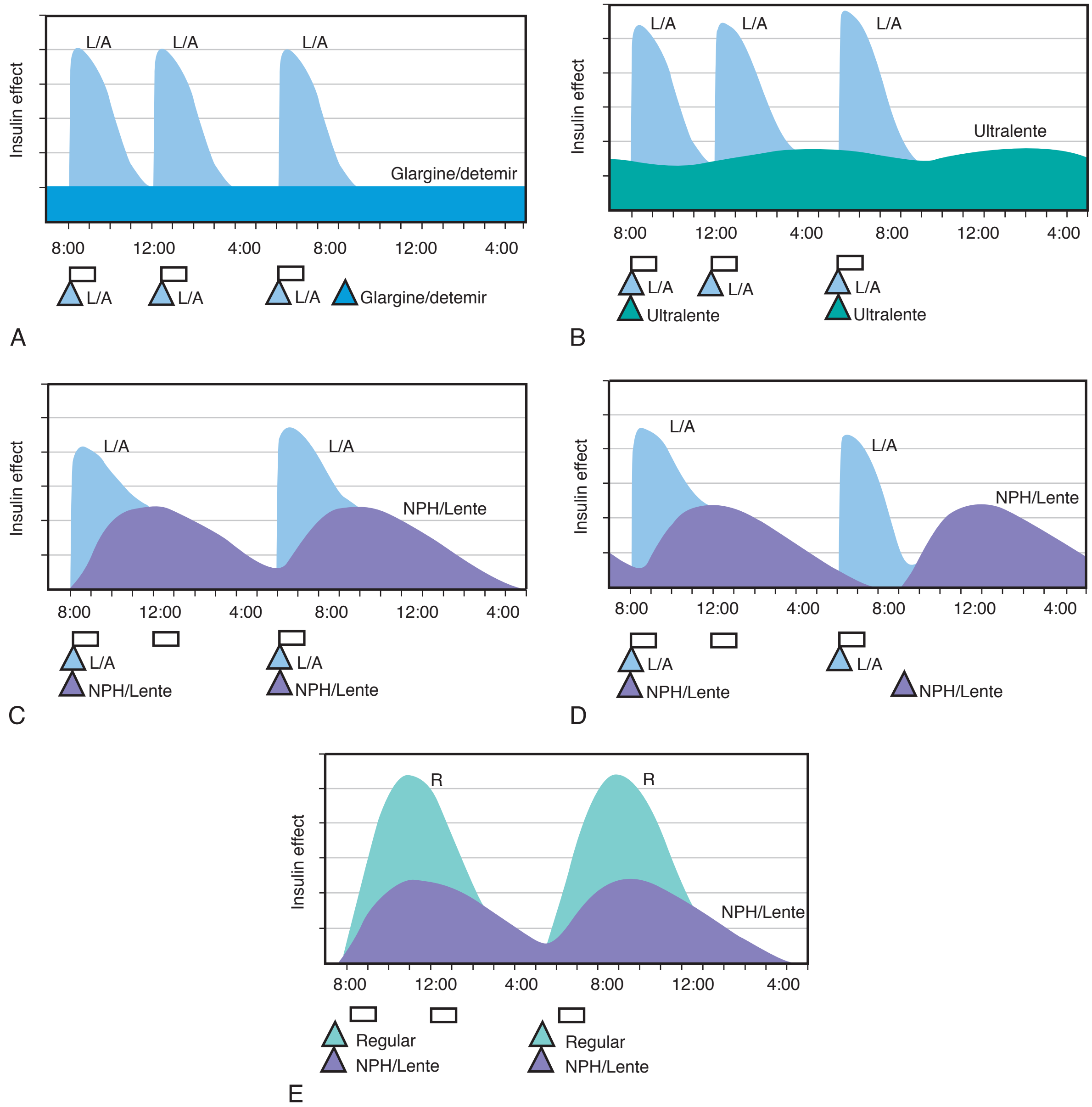

Figure 589-7 **Approximate composite insulin effect profiles.** Meals are shown as rectangles below time axis. Injections are shown as labeled *triangles; L/A,* lispro or aspart. Even though the fast- and long-acting insulins are shaded differently to show the addition of 1 insulin effect to another, the profile is changed to show the combined effect. For example, in the breakfast injection in **C,** the quick decline of L/A effect is blunted by the rising neutral protamine Hagedorn (NPH)/Lente effect, producing a broad tail, which slowly declines to baseline at supper. All profiles are idealized using average absorption and clearance rates. In typical clinical situations, these profiles vary among patients. A given patient has varying rates of absorption depending on the injection site, physical activity, and other variables. **A,** L or A premeal; glargine at bedtime. The rapid onset and short duration of L or A reduce overlap between premeal injections, and there is no extended nighttime action. This reduces the risk of hypoglycemia. Glargine provides a steady basal profile that simplifies prediction of bolus insulin effect. **B,** L or A premeal; Ultralente at breakfast and supper. Ultralente produces a basal profile similar to that seen with glargine. Some excessive insulin effect, however, is seen before supper and at nighttime. **C,** L or A premeal; NPH or Lente at breakfast and supper. The broad peak of NPH or Lente produces substantial risk of hypoglycemia before lunch and during the early hours of the night. The waning insulin effect before supper and breakfast may also allow breakthrough hyperglycemia. **D,** L or A premeal; NPH or Lente at breakfast and bedtime. Moving the evening long-acting insulin helps to cover the prebreakfast hours, but the risk of nighttime lows persists. **E,** Regular and NPH or Lente at breakfast and supper. This produces the least physiologic profile, with large excesses before lunch and during the early night, combined with poor coverage before supper and breakfast. Although Lente and Ultralente are no longer manufactured, they are shown to give historical comparison to newer insulin analogs.

hypoglycemia (see Fig. 589-7*A*). The **long-acting analog glargine** creates a much flatter 24 hr profile, making it easier to predict the combined effect of a rapid bolus (lispro or aspart) on top of the basal insulin, producing a more physiologic pattern of insulin effect (see Fig. 589-7*A*). Postprandial glucose elevations are better controlled, and between-meal and nighttime hypoglycemia are reduced.

Glargine may be given every 12 hr in young children if a single daily dose of glargine does not produce complete 24 hr basal coverage. The basal insulin glargine should be 25-30% of the total dose in toddlers and 40-50% in older children. The remaining portion of the total daily dose is provided as bolus insulin that is dosed by both the carbohydrate content of the meal as well as the preprandial glucose value.

Frequent blood glucose monitoring and insulin adjustment are necessary in the 1st weeks as the child returns to routine activities and adapts to a new nutritional schedule, and as the total daily insulin requirements are determined. The major physiologic limit to tight control is hypoglycemia. Use of insulin analogs moderates but does not eliminate this problem.

Some families may be unable to administer 4 daily injections. In these cases, a compromise may be needed. A 3 injection regimen combining NPH with a rapid analog bolus at breakfast, a rapid-acting analog bolus at supper, and glargine at bedtime may provide fair glucose control. Further compromise to a 2 injection regimen may occasionally be needed and frequently involves use of premix insulin (e.g., 70/30).

Insulin Pump Therapy

Continuous subcutaneous insulin infusion (CSII) via battery-powered pumps provides a closer approximation of normal plasma insulin profiles and increased flexibility regarding timing of meals and snacks compared with conventional insulin injection regimens. Insulin pump models can be programmed with a patient's personal insulin dose algorithms, including the insulin to carbohydrate ratio and the correction scale for premeal glucose levels. The patient can enter the patient's blood glucose level and the carbohydrate content of the meal, and the pump computer will calculate the proper insulin bolus dose. Although CSII frequently improves metabolic control, this may not always be the case. The degree of glycemic control is mainly dependent on how closely patients adhere to the principles of diabetes self-care, regardless of the type of intensive insulin regimen. One benefit of pump therapy may be a reduction in severe hypoglycemia and associated seizures. Randomized trials comparing multiple daily insulin regimens using glargine insulin and CSII in children with T1DM demonstrate similar metabolic control and frequency of hypoglycemic events.

Continuous Glucose Monitoring Systems

Subcutaneous glucose sensors that continuously measure interstitial fluid glucose levels are available and approved for use in children. The 1st generation of continuous glucose monitors provided blood glucose data only after downloading by the physician, and did not provide real-time feedback to the patient. This type of device did not appear to improve glycemic control in children, although there was some educational value in detecting patterns of blood glucose fluctuations and episodes of hypoglycemia during periods of sleep.

The newer generation of continuous monitors report blood glucose levels to the patient in real time. Short-term studies indicate clinical benefits of these devices as compared to conventional methods of blood glucose monitoring, when used by motivated and well-informed patients. These devices do not directly control insulin administration but provide glucose readings to permit finer control of insulin administration by patients and families. To avoid hypoglycemia the glucose sensor sounds an alarm; many episodes of hypoglycemia occur at night and unfortunately the parent may sleep through the alarm. Studies are currently evaluating the efficacy of a fully automated closed-loop system of insulin delivery based on continuous glucose sensing, sometimes mistakenly known as an "artificial pancreas" (Fig. 589-8). Some automated glycemic systems employ a bihormonal approach (insulin, glucagon) or have an automated insulin suspension program to ensure normal glycemia while avoiding hypoglycemia. The latter hypoglycemia threshold insulin suspension feature greatly reduces the incidence of hypoglycemia, especially at night. The FDA has approved an insulin pump in combination with a continuous glucose monitoring system that will stop insulin delivery when interstitial glucose levels fall below a predetermined level.

Amylin-Based Adjunct Therapy

Pramlintide acetate, a synthetic analog of amylin, may be of therapeutic value combined with insulin therapy. In adolescents it has been shown to decrease postprandial hyperglycemia, insulin dosage, gastric emptying, and HbA_{1c} levels. It is given as a subcutaneous dose before meals.

Basic and Advanced Diabetes Education

Therapy consists not only of initiation and adjustment of insulin dose but also of education of the patient and family. Teaching is most efficiently provided by experienced diabetes educators and nutritionists.

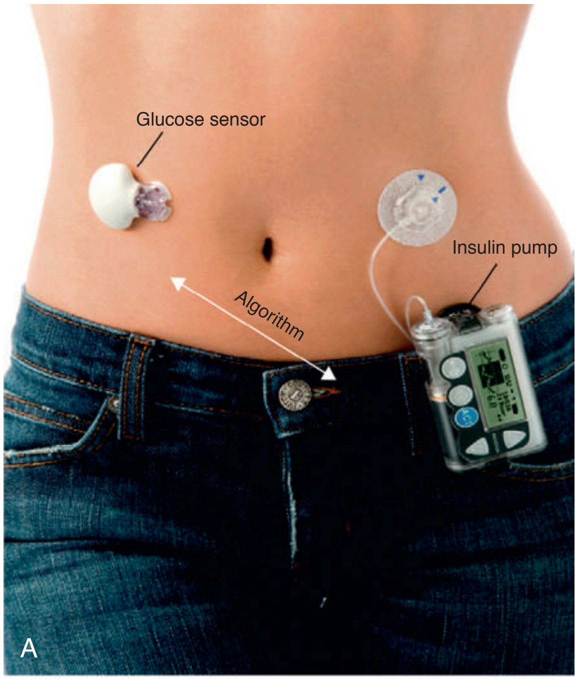

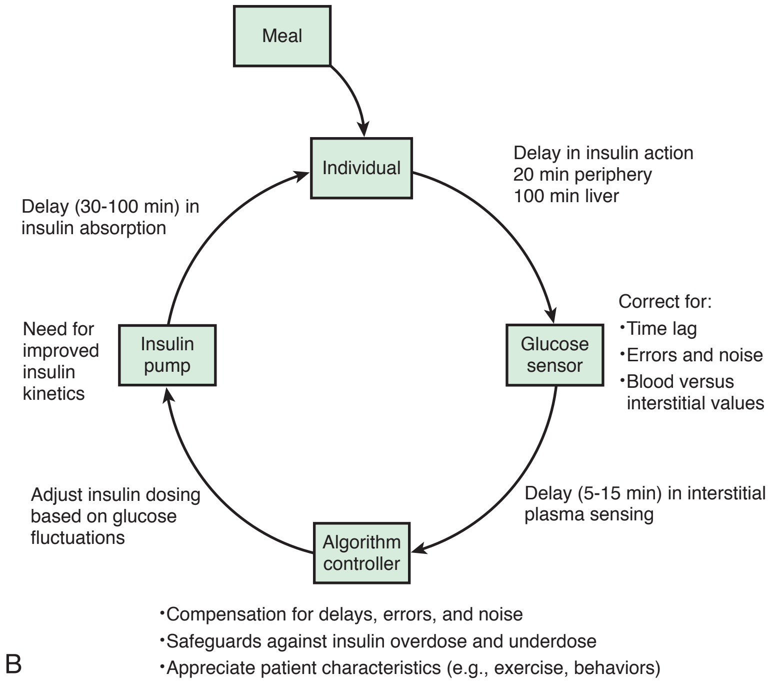

Figure 589-8 Closed-loop system for type 1 diabetes (artificial pancreas). **A,** Prototype of a closed-loop system. **B,** Components of a closed-loop system. Three potential delays in the system include glucose sensing in interstitial fluid, insulin absorption (depends on use of rapid vs regular insulin), and insulin action in peripheral tissues and liver. *(From Atkinson MA, Eisenbarth GS, Michels AW: Type 1 diabetes.* Lancet *383:69–78, 2014, Fig. 5, p. 75.)*

In the acute phase, the family must learn the "basics," which includes monitoring the child's blood glucose and urine and/or blood ketones, preparing and injecting the correct insulin dose subcutaneously at the proper time, recognizing and treating low blood glucose reactions, and having a basic meal plan. Most families are trying to adjust psychologically to the new diagnosis of diabetes in their child and thus have a limited ability to retain new information. Written materials covering these basic topics help the family during the 1st few days.

Children and their families are also required to complete advanced self-management classes in order to facilitate implementation of flexible insulin management. These educational classes will help patients and their families acquire skills for managing diabetes during athletic activities and sick days.

Ketoacidosis

Severe insulinopenia (or lack of effective insulin action) results in a physiologic cascade of events in 3 general pathways:

1. Excessive glucose production coupled with reduced glucose utilization raises serum glucose. This produces an osmotic diuresis, with loss of fluid and electrolytes, dehydration, and activation of the renin–angiotensin–aldosterone axis with accelerated potassium loss. If glucose elevation and dehydration are severe and persist for several hours, the risk of cerebral edema increases.
2. Increased catabolic processes result in cellular losses of sodium, potassium, and phosphate.
3. Increased release of free fatty acids from peripheral fat stores supplies substrate for hepatic ketoacid production. When ketoacids accumulate, buffer systems are depleted and a metabolic acidosis ensues. Therapy must address both the initiating event in this cascade (insulinopenia) and the subsequent physiologic disruptions.

Reversal of DKA is associated with inherent risks that include hypoglycemia, hypokalemia, and cerebral edema. Any protocol must be used with caution and close monitoring of the patient. Adjustments based on sound medical judgment may be necessary for any given level of DKA (Table 589-6).

Hyperglycemia and Dehydration

Insulin must be given at the beginning of therapy to accelerate movement of glucose into cells, to subdue hepatic glucose production, and to halt the movement of fatty acids from the periphery to the liver. An initial insulin bolus does not speed recovery and may increase the risk of hypokalemia and hypoglycemia. Therefore, insulin infusion is typically begun **without** a bolus at a rate of 0.1 units/kg/hr. This approximates maximal insulin output in normal subjects during an oral glucose tolerance test. Rehydration also lowers glucose levels by improving renal perfusion and enhancing renal excretion. The combination of these therapies usually causes a rapid initial decline in serum glucose levels. Once glucose goes below 180 mg/dL (10 mmol/L), the osmotic diuresis stops and rehydration accelerates without further increase in the infusion rate.

Repair of hyperglycemia occurs well before correction of acidosis. Therefore, insulin is still needed to control fatty acid release and ketosis after normal glucose levels are reached. To continue the insulin infusion without causing hypoglycemia, glucose must be added to the infusion. We typically recommend that glucose be added as a 5% solution when the serum glucose has decreased <300 mg/dL and as a 10% solution when the serum glucose has decreased <200 mg/dL. The insulin infusion can also be lowered from the initial maximal rate if, despite the above outlined interventions, the serum glucose falls further.

Repair of fluid deficits must be tempered by the potential risk of cerebral edema. It is prudent to approach any child in any hyperosmotic state with cautious rehydration. The effective serum osmolality ($E_{osm} = 2 \times [Na_{uncorrected}] + [glucose]$) is an accurate index of tonicity of the body fluids, reflecting intracellular and extracellular hydration better than measured plasma osmolality. It is calculated with sodium and glucose in mmol/L. This value is usually elevated at the beginning of therapy and should steadily normalize. A rapid decline, or a slow decline to a subnormal range, may indicate an excess of free water entering the vascular space and an increasing risk of cerebral edema. Therefore, patients should not be allowed oral fluids until rehydration is well underway and significant electrolyte shifts are no longer likely. Limited ice chips may be given as a minimal oral intake. All fluid intake and output should be closely monitored.

Calculation of fluid deficits using clinical signs is difficult in children with DKA because intravascular volume is better maintained in the hypertonic state. For any degree of tachycardia, delayed capillary refill, decreased skin temperature, or orthostatic blood pressure change, the child with DKA will be more dehydrated than the child with a normotonic fluid deficit. The protocol in Table 589-6 corrects a deficit of 85 mL/kg (8.5% dehydration) for all patients in the 1st 24 hr. Children with mild DKA rehydrate earlier and can be switched to oral intake,

Table 589-6 Diabetic Ketoacidosis Treatment Protocol

TIME	THERAPY	COMMENTS
1st hr	10-20 mL/kg IV bolus 0.9% NaCl or LR Insulin drip at 0.05 to 0.10 units/kg/hr	Quick volume expansion; may be repeated. NPO. Monitor I/O, neurologic status. Use flow sheet. Have mannitol at bedside; 1 g/kg IV push for cerebral edema
2nd hr until DKA resolution	0.45% NaCl: plus continue insulin drip 20 mEq/L KPhos and 20 mEq/L KAc 5% glucose if blood sugar >250 mg/dL (14 mmol/L)	$\text{IV rate} = \frac{85\ \text{mL/kg} + \text{maintenance} - \text{bolus}}{23\ \text{hr}}$ If K <3 mEq/L, give 0.5-1.0 mEq/kg as oral K solution *or* increase IV K to 80 mEq/L
Variable	Oral intake with subcutaneous insulin	No emesis; CO_2 ≥16 mEq/L; normal electrolytes
Note that the initial IV bolus is considered part of the total fluid allowed in the 1st 24 hr and is subtracted before calculating the IV rate.		
Maintenance (24 hr) = 100 mL/kg (for the first 10 kg) + 50 mL/kg (for the second 10 kg) + 25 mL/kg (for all remaining kg)		
Sample calculation for a 30-kg child: 1st hr = 300 mL IV bolus 0.9% NaCl or LR $\text{2nd and subsequent hr} = \frac{(85\ \text{mL} \times 30) + 1750\ \text{mL} - 300\ \text{mL}}{23\ \text{hr}} = \frac{175\ \text{mL}}{\text{hr}}$ (0.45% NaCl with 20 mEq/L Kphos and 20 mEq/L KAc)		

DKA, diabetic ketoacidosis; I/O, input and output (urine, emesis); K, potassium; KAc, potassium acetate; KPhos, potassium phosphate; LR, lactated Ringer solution; NaCl, sodium chloride; NPO, nothing by mouth.

whereas those with severe DKA and a greater volume deficit require 30-36 hr with this protocol. This more gradual rehydration of the child with severe DKA is an inherent safety feature. The initial intravenous bolus (20 mL/kg of glucose-free isotonic sodium salt solution such as Ringer lactate or 0.9% sodium chloride) for all patients ensures a quick volume expansion and may be repeated if clinical improvement is not quickly seen. This bolus is given as isotonic saline because the patient is inevitably hypertonic, keeping most of the initial infusion in the intravascular space. Subsequent fluid is hypotonic to repair the free water deficit, to allow intracellular rehydration, and to allow a more appropriate replacement of ongoing hypotonic urine losses.

The initial serum sodium is usually normal or low because of the osmolar dilution of hyperglycemia and the effect of an elevated sodium-free lipid fraction. An estimate of the reconstituted, or "true," serum sodium for any given glucose level above 100 mg/dL (5.6 mmol/L) is calculated as follows:

$[Na^+] + (1.6\ mEq/L\ Na^+$ for every 100 mg/dL glucose in excess of 100)

or

$[Na^+] + (1.6\ mEq/L\ Na^+$ for every 5.6 mmol/L glucose in excess of 5.6)

The sodium should increase by approximately 1.6 mmol/L for each 100 mg/dL decline in the glucose. The corrected sodium is usually normal or slightly elevated and indicates moderate hypernatremic dehydration. If the corrected value is greater than 150 mmol/L, severe hypernatremic dehydration may be present and may require slower fluid replacement. The sodium should steadily increase with therapy. *Declining sodium may indicate excessive free water accumulation and increased risk of cerebral edema.*

Catabolic Losses

Both the metabolic shift to a catabolic predominance and the acidosis move potassium and phosphate from the cell to the serum. The osmotic diuresis, the kaliuretic effect of the hyperaldosteronism, and the ketonuria then accelerate renal losses of potassium and phosphate. Sodium is also lost with the diuresis, but free water losses are greater than isotonic losses. With prolonged illness and severe DKA, total body losses can approach 10-13 mEq/kg of sodium, 5-6 mEq/kg of potassium, and 4-5 mEq/kg of phosphate. These losses continue for several hours during therapy until the catabolic state is reversed and the diuresis is controlled. For example, 50% of infused sodium may be lost in the urine during IV therapy. Even though the sodium deficit may be repaired within 24 hr, intracellular potassium and phosphate may not be completely restored for several days.

Although patients with DKA have a total body potassium deficit, the initial serum level is often normal or elevated. This is caused by the movement of potassium from the intracellular space to the serum, both as part of the ketoacid buffering process and as part of the catabolic shift. These effects are reversed with therapy, and potassium returns to the cell. Improved hydration increases renal blood flow, allowing for increased excretion of potassium in the elevated aldosterone state. The net effect is often a dramatic decline in serum potassium levels, especially in severe DKA, and can precipitate changes in cardiac conductivity, flattening of T waves, and prolongation of the QRS complex and can cause skeletal muscle weakness or ileus. The risk of myocardial dysfunction is increased with shock and acidosis. Potassium levels must be closely followed and electrocardiographic monitoring continued until DKA is substantially resolved. If needed, the parenteral potassium can be increased to 80 mEq/L or an oral supplement can be given if there is no emesis. Rarely, the IV insulin must be temporarily stopped.

It is unclear whether phosphate deficits contribute to symptoms of DKA such as generalized muscle weakness. In pediatric patients, a deficit has not been shown to compromise oxygen delivery via a deficiency of 2,3-diphosphoglycerate. Because the patient will receive an excess of chloride, which may aggravate acidosis, it is prudent to use potassium phosphate rather than potassium chloride as a potassium source. Potassium acetate is also used, because it provides an additional buffer.

Pancreatitis is occasionally seen with DKA, especially if prolonged abdominal distress is present; serum amylase may be elevated. If the serum lipase is not elevated, the amylase is likely nonspecific or salivary in origin. Serum creatinine adjusted for age may be falsely elevated owing to interference by ketones in the autoanalyzer methodology. An initial elevated value rarely indicates renal failure and should be rechecked when the child is less ketonemic. Blood urea nitrogen may be elevated with prerenal azotemia and should be rechecked as the child is rehydrated. Mildly elevated creatine or blood urea nitrogen is not a reason to withhold potassium therapy if good urinary output is present.

Keto Acid Accumulation

Low insulin infusion rates (0.02-0.05 units/kg/hr) are usually sufficient to stop peripheral release of fatty acids, thereby eliminating the flow of substrate for ketogenesis. Therefore, the initial infusion rate may be decreased if blood glucose levels go below 150 mg/dL (8 mmol/L) despite the addition of glucose to the infusion. Ketogenesis continues until fatty acid substrates already in the liver are depleted, but this production declines much more quickly without new substrate inflow. Bicarbonate buffers, regenerated by the distal renal tubule and by metabolism of ketone bodies, steadily repair the acidosis once ketoacid production is controlled. *Bicarbonate therapy is rarely necessary and may even increase the risk of hypokalemia and cerebral edema.*

There should be a steady increase in pH and serum bicarbonate as therapy progresses. Kussmaul respirations should abate and abdominal pain resolve. Persistent acidosis may indicate inadequate insulin or fluid therapy, infection, or rarely lactic acidosis. Urine ketones may be positive long after ketoacidosis has resolved because the nitroprusside reaction routinely used to measure urine ketones by dipstick measures only acetoacetate. During DKA, most excess ketones are β-hydroxybutyrate, which increases the normal ratio to acetoacetate from 3 : 1 to as high as 8 : 1. With resolution of the acidosis, β-hydroxybutyrate converts to acetoacetate, which is excreted into the urine and detected by the dipstick test. Therefore, persistent ketonuria may not accurately reflect the degree of clinical improvement and should not be relied on as an indicator of therapeutic failure.

All patients with DKA should be checked for initiating events that may have triggered the metabolic decompensation.

Diabetic Ketoacidosis Protocol

See Table 589-6.

Even though DKA can be of variable severity, a common approach to all cases simplifies the therapeutic regimen and can be safely used for most children. Fluids are best calculated based on weight, not body surface area (m^2), because heights are rarely available for the acutely critically ill child. A standard water deficit (85 mL/kg) is assumed. This amount, when added to maintenance, yields approximately 4 L/m^2 for children of all sizes. Children with milder DKA recover in 10-20 hr (and need less total IV fluid before switching to oral intake), whereas those with more severe DKA require 30-36 hr with this protocol. Any child can be easily transitioned to oral intake and subcutaneous insulin when DKA has resolved (total CO_2 >15 mEq/L; pH >7.30; sodium stable between 135 and 145 mEq/L; no emesis). The first dose of short-acting subcutaneous insulin is given with a meal, and the insulin drip is discontinued approximately 30 min later.

A flow sheet is mandatory for accurate monitoring of changes in acidosis, electrolytes, fluid balance, and clinical status, especially if the patient is transferred from the emergency department to an inpatient setting with new caretakers. This flow sheet is best implemented by a central computer system, which allows for rapid update and wide availability of results, as well as rule-driven highlighting of critical values. A paper flow sheet suffices if it stays with the patient, is kept current, and is reviewed frequently by the physician. Any flow sheet should include columns for serial electrolytes, pH, glucose, and fluid balance. Blood testing should occur every 1-2 hr for children with severe DKA and every 3-4 hr for those with mild to moderate DKA.

Cerebral Edema

Cerebral edema complicating DKA remains the major cause of morbidity and mortality in children and adolescents with T1DM. However, its etiology remains unknown. A case-control study of DKA suggested that baseline acidosis and abnormalities of sodium, potassium, and blood urea nitrogen concentrations were important predictors of risk of cerebral edema. Early bolus administration of insulin and high volumes of fluid were also identified as risk factors. The incidence of cerebral edema in children with DKA has not changed over the past 15-20 yr, despite the widespread introduction of gradual rehydration protocols during this interval. Radiographic imaging is frequently unhelpful in making the diagnosis of cerebral edema. Consequently, each patient must be closely monitored. For all but the mildest cases, this includes frequent neurologic checks for any signs of increasing intracranial pressure, such as a change of consciousness, depressed respiration, worsening headache, bradycardia, apnea, pupillary changes, papilledema, posturing, and seizures. Mannitol must be readily available for use at the earliest sign of cerebral edema. The physician must also keep informed of the laboratory changes; hypokalemia or hypoglycemia can occur rapidly. Children with moderate to severe DKA have a higher overall risk and should be treated in an intensive care environment.

Nonketotic Hyperosmolar Coma

This syndrome is characterized by severe hyperglycemia (blood glucose >800 mg/dL), absence of or only slight ketosis, nonketotic acidosis, severe dehydration, depressed sensorium or frank coma, and various neurologic signs that may include grand mal seizures, hyperthermia, hemiparesis, and positive Babinski signs. Respirations are usually shallow, but coexistent metabolic (lactic) acidosis may be manifested by Kussmaul breathing. Serum osmolarity is commonly 350 mOsm/kg or greater. This condition is uncommon in children; among adults, mortality rates are high, possibly in part because of delays in recognition and institution of appropriate therapy. In children, there has been a high incidence of preexisting neurologic damage. Profound hyperglycemia may develop over a period of days and, initially, the obligatory osmotic polyuria and dehydration may be partially compensated for by increasing fluid intake. With progression of disease, thirst becomes impaired, possibly because of alteration of the hypothalamic thirst center by hyperosmolarity and, in some instances, because of a preexisting defect in the hypothalamic osmoregulating mechanism.

The low production of ketones is attributed mainly to the hyperosmolarity, which in vitro blunts the lipolytic effect of epinephrine and the antilipolytic effect of residual insulin; blunting of lipolysis by the therapeutic use of β-adrenergic blockers may contribute to the syndrome. Depression of consciousness is closely correlated with the degree of hyperosmolarity in this condition as well as in DKA. Hemoconcentration may also predispose to cerebral arterial and venous thromboses.

Treatment of nonketotic hyperosmolar coma is directed at rapid repletion of the vascular volume deficit and very slow correction of the hyperosmolar state. One-half isotonic saline (0.45% NaCl; some use normal saline) is administered at a rate estimated to replace 50% of the volume deficit in the 1st 12 hr, and the remainder is administered during the ensuing 24 hr. The rate of infusion and the saline concentration are titrated to result in a slow decline of serum osmolality. When the blood glucose concentration approaches 300 mg/dL, the hydrating fluid should be changed to 5% dextrose in 0.2 normal saline. Approximately 20 mEq/L of potassium chloride should be added to each of these fluids to prevent hypokalemia. Serum potassium and plasma glucose concentrations should be monitored at 2 hr intervals for the 1st 12 hr and at 4 hr intervals for the next 24 hr to permit appropriate adjustments of administered potassium and insulin.

Insulin can be given by continuous intravenous infusion beginning with the 2nd hr of fluid therapy. Blood glucose may decrease dramatically with fluid therapy alone. The IV insulin dosage should be 0.05 units/kg/hr rather than 0.1 units/kg/hr as advocated for patients with DKA.

Nutritional Management

Nutrition plays an essential role in the management of patients with T1DM. This is of critical importance during childhood and adolescence, when appropriate energy intake is required to meet the needs for energy expenditure, growth, and pubertal development. There are no special nutritional requirements for the diabetic child other than those for optimal growth and development. In outlining nutritional requirements for the child on the basis of age, sex, weight, and activity, food preferences, including cultural and ethnic ones, must be considered.

Total recommended caloric intake is based on size or surface area and can be obtained from standard tables (Tables 589-7 and 589-8). The caloric mixture should comprise approximately 55% carbohydrate, 30% fat, and 15% protein. Approximately 70% of the carbohydrate content should be derived from complex carbohydrates such as starch; intake of sucrose and highly refined sugars should be limited. Complex carbohydrates require prolonged digestion and absorption so that plasma glucose levels increase slowly, whereas glucose from refined sugars, including carbonated beverages, is rapidly absorbed and may cause wide swings in the metabolic pattern; carbonated beverages should be sugar free. Priority should be given to total calories and total carbohydrate consumed rather than its source. Carbohydrate counting has become a mainstay in the nutrition education and management of patients with DM. Patients and their families are provided with information regarding the carbohydrate contents of different foods and food label reading. This allows patients to adjust their insulin dosage to their mealtime carbohydrate intake. The use of carbohydrate counting and insulin to carbohydrate ratios and the use of fast-acting insulin analogs and long-acting basal insulin (detemir and glargine) provide many children with less rigid meal planning. Flexibility in the use of insulin in relation to carbohydrate content of food improves the quality of life.

Although in children there is concern about the potential cumulative effect of saccharin, available data do not support an association of moderate amounts with bladder cancer. Other nonnutritive sweeteners such as aspartame are used in a variety of products.

Diets with high fiber content are useful in improving control of blood glucose. Moderate amounts of sucrose consumed with fiber-rich foods such as whole-grain bread may have no more glycemic effect than their low-fiber, sugar-free equivalents.

The intake of fat is adjusted so that the polyunsaturated:saturated ratio is increased to approximately 1.2 :1.0, in contrast to the estimated American average of 0.3 :1.0. Dietary fats derived from animal sources are, therefore, reduced and replaced by polyunsaturated fats from vegetable sources. Substituting margarine for butter, vegetable oil for

Table 589-7 Calorie Needs for Children and Young Adults

AGE	KCAL REQUIRED/KG BODY WEIGHT*
CHILDREN	
0-12 mo	120
1-10 yr	100-75
YOUNG WOMEN	
11-15 yr	35
≥16 yr	30
YOUNG MEN	
11-15 yr	80-55 (65)
16-20 yr	
Average activity	40
Very physically active	50
Sedentary	30

Numbers in parentheses are means.

*Gradual decline in calories per unit weight as age increases.

From Nutrition guide for professionals: diabetes education and meal planning, *Alexandria, VA, and Chicago, IL, 1988, The American Diabetes Association and The American Dietetic Association.*

Table 589-8 Summary of Nutrition Guidelines for Children and/or Adolescents with Type 1 Diabetes Mellitus

NUTRITION CARE PLAN

Promotes optimal compliance.

Incorporates goals of management: normal growth and development, control of blood glucose, maintenance of optimal nutritional status, and prevention of complications. Uses staged approach.

NUTRIENT RECOMMENDATIONS AND DISTRIBUTION

NUTRIENT	(%) OF CALORIES	RECOMMENDED DAILY INTAKE
Carbohydrate	Will vary	High fiber, especially soluble fiber; optimal amount unknown
Fiber	>20 g/day	
Protein	12-20	
Fat	<30	
Saturated	<10	
Polyunsaturated	6-8	
Monounsaturated	Remainder of fat allowance	
Cholesterol		300 mg
Sodium		Avoid excessive; limit to 3,000-4,000 mg if hypertensive

ADDITIONAL RECOMMENDATIONS

Energy: If using measured diet, reevaluate prescribed energy level at least every 3 mo.

Protein: High-protein intakes may contribute to diabetic nephropathy. Low intakes may reverse preclinical nephropathy. Therefore, 12-20% of energy is recommended; lower end of range is preferred. In guiding toward the end of the range, a staged approach is useful.

Alcohol: Safe use of moderate alcohol consumption should be taught as routine anticipatory guidance as early as junior high school.

Snacks: Snacks vary according to individual needs (generally 3 snacks per day for children; midafternoon and bedtime snacks for junior high children or teens).

Alternative sweeteners: Use of a variety of sweeteners is suggested.

Educational techniques: No single technique is superior. Choice of educational method used should be based on patient needs. Knowledge of variety of techniques is important. Follow-up education and support are required.

Eating disorders: Best treatment is prevention. Unexplained poor control or severe hypoglycemia may indicate a potential eating disorder.

Exercise: Education is vital to prevent delayed or immediate hypoglycemia and to prevent worsened hyperglycemia and ketosis.

From Connell JE, Thomas-Doberson D: Nutritional management of children and adolescents with insulin-dependent diabetes mellitus: a review by the Diabetes Care and Education Dietetic Practice Group, J Am Diet Assoc 91:1556, 1991.

animal oils in cooking, and lean cuts of meat, poultry, and fish for fatty meats is advisable. The intake of cholesterol is also reduced by these measures and by limiting the number of egg yolks consumed. These simple measures reduce serum low-density lipoprotein cholesterol, a predisposing factor to atherosclerotic disease. Less than 10% of calories should be derived from saturated fats and up to 10% from polyunsaturated fats; the remaining fat-derived calories should be derived from monounsaturated fats. Table 589-8 summarizes current nutritional guidelines.

Each child/family can and should select a diet based on personal taste with the help of the physician or dietitian (or both). Emphasis should be placed on regularity of food intake and on constancy of carbohydrate intake. Occasional excesses ("treats") for birthdays and other parties are permissible and tolerated to not foster rebellion and stealth in obtaining desired food. Cakes and even candies are permissible on special occasions as long as the food carbohydrate content is adjusted in the meal plan. Adjustments in meal planning must constantly be made to meet the needs as well as the desires of each child. A consistent eating pattern with appropriate supplements for exercise, the pubertal growth spurt, and pregnancy in an adolescent with diabetes is important for metabolic control.

Monitoring

Success in the daily management of the child with diabetes can be measured by the competence acquired by the family, and subsequently by the child, in assuming responsibility for daily self-care. Their initial and ongoing instruction in conjunction with their supervised experience can lead to a sense of confidence in making adjustments in insulin dosage for dietary deviations, for unusual physical activity, and even for some minor intercurrent illnesses. Such acceptance of responsibility should make them relatively independent of the physician for their ordinary care. The physician must maintain ongoing interested supervision and shared responsibility with the family and the child.

Self-monitoring of blood glucose is an essential component of managing diabetes. Monitoring often also needs to include insulin dose, unusual physical activity, dietary changes, hypoglycemia, intercurrent illness, and other items that may influence the blood glucose. These items may be valuable in interpreting the self-monitoring of blood glucose record, prescribing appropriate adjustments in insulin doses, and teaching the family. If there are discrepancies in the self-monitoring of blood glucose and other measures of glycemic control (such as the HbA_{1c}), the clinician should attempt to clarify the situation in a manner that does not undermine their mutual confidence.

Daily blood glucose monitoring has been markedly enhanced by the availability of strips impregnated with glucose oxidase that permit blood glucose measurement from a drop of blood. A portable calibrated reflectance meter can approximate the blood glucose concentration accurately. Many meters contain a memory "chip" enabling recall of each measurement, its average over a given interval, and the ability to display the pattern on a computer screen. Such information is a useful educational tool for verifying degree of control and modifying recommended regimens. A small, spring-loaded device that automates capillary bloodletting (lancing device) in a relatively painless fashion is commercially available. Parents and patients should be taught to use these devices and measure blood glucose at least 4 times daily—before breakfast, lunch, and supper, and at bedtime. When insulin therapy is initiated and when adjustments are made that may affect the overnight glucose levels, self-monitoring of blood glucose should also be performed at 12 midnight and 3 AM to detect nocturnal hypoglycemia. Ideally, the blood glucose concentration should range from approximately 80 mg/dL in the fasting state to 140 mg/dL after meals. In practice, however, a range is acceptable, based on age of the patient (Table 589-9). Blood glucose measurements that are consistently at or outside these limits, in the absence of an identifiable cause such as exercise or dietary indiscretion, are an indication for a change in the insulin dose. If the fasting blood glucose is high, the evening dose of long-acting insulin is increased by 10-15% and/or additional fast-acting insulin (lispro or aspart) coverage for bedtime snack may be considered. If the noon glucose level exceeds set limits, the morning fast-acting insulin (lispro or aspart) is increased by 10-15%. If the presupper glucose is high, the noon dose of fast-acting insulin is increased by 10-15%. If the prebedtime glucose is high, the presupper dose of fast-acting insulin is increased by 10-15%. Similarly, reductions in the insulin type and dose should be made if the corresponding blood glucose measurements are consistently below desirable limits.

A minimum of 4 daily blood glucose measurements should be performed. However, some children and adolescents may need to have more frequent blood glucose monitoring based on their level of physical activity and history of frequent hypoglycemic reactions. Families should be encouraged to become sufficiently knowledgeable about managing diabetes. They can maintain near-normal glycemia for prolonged periods by self-monitoring of blood glucose levels before and

Table 589-9 Target Premeal and 30-Day Average Blood Glucose Ranges and the Corresponding Hemoglobin A_{1c} for Each Age Group

AGE GROUP (yr)	TARGET PREMEAL BG RANGE (mg/dL)	30-DAY AVERAGE BG RANGE (mg/dL)	TARGET HbA_{1c} (%)
<5	100-200	180-250	7.5-9.0
5-11	80-150	150-200	6.5-8.0
12-15	80-130	120-180	6.0-7.5
16-18	70-120	100-150	5.5-7.0

In our laboratory, the nondiabetic reference range for HbA_{1c} is 4.5-5.7% (95% confidence interval).
BG, blood glucose; HbA_{1c}, hemoglobin A_{1c}.

2 hr after meals, and in conjunction with multiple daily injections of insulin, adjusted as necessary.

A continuous glucose monitoring system (CGMS) records data obtained from a subcutaneous sensor every 5 min for up to 72 hr and provides the clinician with a continuous profile of tissue glucose levels. The interstitial glucose levels lag about 13 min behind the blood glucose values at any given level. The CGMS values tend to have a high correlation coefficient for blood glucose values ranging between 40 and 400 mg/dL. CGMS is minimally invasive and entails the placement of a small, subcutaneous catheter that can be easily worn by adults and children. The system provides information that allows the patient and healthcare team to adjust the insulin regimen and the nutrition plan to improve glycemic control. CGMS can be helpful in detecting asymptomatic nocturnal hypoglycemia as well as in lowering HbA_{1c} values without increasing the risk for severe hypoglycemia. Although there are potential pitfalls in CGMS use, including suboptimal compliance, human error, incorrect technique, and sensor failure, the implementation of CGMS in ambulatory diabetes practice allows the clinician to diagnose abnormal glycemic patterns in a more precise manner.

Real-Time Continuous Glucose Monitoring

Real-time continuous glucose monitoring is a technology with the potential of transforming current concepts of glycemic control and optimal diabetes management. In addition to displaying real-time glucose data, newer generations of continuous glucose monitors also have alarms that can be set at below or above predetermined blood glucose thresholds. This safety feature can help parents of young children to recognize nocturnal hypoglycemia. In addition, continuous glucose monitoring shows the rate and direction of glucose change and alerts patients to trends that could lead to dangerous hypoglycemia or hyperglycemia. However, the use of continuous glucose monitoring without clinical decision-making algorithms and guidelines has not been proven to be very effective in improving glycemic control.

Glycosylated Hemoglobin

A reliable index of long-term glycemic control is provided by measurement of glycosylated hemoglobin. HbA_{1c} represents the fraction of hemoglobin to which glucose has been nonenzymatically attached in the bloodstream. The formation of HbA_{1c} is a slow reaction that is dependent on the prevailing concentration of blood glucose; it continues irreversibly throughout the red blood cell's life span of approximately 120 days. The higher the blood glucose concentration and the longer the red blood cell's exposure to it, the higher is the fraction of HbA_{1c}, which is expressed as a percentage of total hemoglobin. Because a blood sample at any given time contains a mixture of red blood cells of varying ages, exposed for varying times to varying blood glucose concentrations, an HbA_{1c} measurement reflects the average blood glucose concentration from the preceding 2-3 mo. When measured by standardized methods to remove labile forms, the fraction of HbA_{1c} is not influenced by an isolated episode of hyperglycemia.

It is recommended that HbA_{1c} measurements be obtained 3-4 times/yr to obtain a profile of long-term glycemic control. The lower the HbA_{1c} level, the more likely it is that microvascular complications such as retinopathy and nephropathy will be less severe, delayed in appearance, or even avoided altogether. Depending on the method used for determination, HbA_{1c} values may be spuriously elevated in thalassemia (or other conditions with elevated hemoglobin F) and spuriously lower in sickle cell disease (or other conditions with high red blood cell turnover). Although values of HbA_{1c} may vary according to the method used for measurement, in individuals without diabetes, the HbA_{1c} fraction is usually less than 6%; in individuals with diabetes, values of 6-7.5% represent good metabolic control, values of 7.6-9.9%, fair control, and values of 10% or higher, poor control. The target HbA_{1c} of <7.5% is the same regardless of the patient's age (see Table 589-9).

Exercise

No form of exercise, including competitive sports, should be forbidden to the child with diabetes. A major complication of exercise in patients with diabetes is the presence of a hypoglycemic reaction during or within hours after exercise. If hypoglycemia does not occur with exercise, adjustments in diet or insulin are not necessary, and glucoregulation is likely to be improved through the increased utilization of glucose by muscles. The major contributing factor to hypoglycemia with exercise is an increased rate of absorption of insulin from its injection site. Higher insulin levels dampen hepatic glucose production so that it is inadequate to meet the increased glucose utilization of exercising muscle. Regular exercise also improves glucoregulation by increasing insulin receptor number. In patients who are in poor metabolic control, vigorous exercise may precipitate ketoacidosis because of the exercise-induced increase in the counterregulatory hormones.

Benefits of Improved Glycemic Control

The Diabetes Control and Complications Trial (DCCT) established conclusively the association between higher glucose levels and long-term microvascular complications. Intensive management produced dramatic reductions of retinopathy, nephropathy, and neuropathy by 47-76%. The data from the adolescent cohort demonstrated the same degree of improvement and the same relationship between the outcome measures of microvascular complications.

The beneficial effect of intensified treatment was determined by the degree of blood glucose normalization, independently of the type of intensified treatment used. Frequent blood glucose monitoring was considered an important factor in achieving better glycemic control for the intensively treated adolescents and adults. Patients who were intensively treated had individualized glucose targets, frequent adjustments based on ongoing capillary blood glucose monitoring, and a team approach that focused on the person with diabetes as the prime initiator of ambulatory care. Care was constantly adjusted toward reaching normal or near-normal glycemic goals while avoiding or minimizing severe episodes of hypoglycemia. Teaching emphasized a preventive approach to blood glucose fluctuations with constant readjustment to counterbalance any high or low blood glucose readings. Target blood glucose goals were adjusted upward if hypoglycemia could not be prevented.

Total duration of diabetes contributes to development and severity of complications. Nonetheless, many professionals have concerns

about applying the results of the DCCT to preschool-age children, who often have hypoglycemia unawareness with unique safety issues, and to prepubertal school-age children, who were not included in the DCCT. When the DCCT ended in 1993, researchers continued to study more than 90% of participants. The follow-up study, called Epidemiology of Diabetes Interventions and Complications (EDIC), was assessing the incidence and predictors of cardiovascular disease events such as heart attack, stroke, or needed heart surgery, as well as diabetic complications related to the eye, kidney, and nerves. The EDIC demonstrated that **intensive blood glucose control reduced risk** of any cardiovascular disease event by 42%. In addition, intensive therapy reduced risk of nonfatal heart attack, stroke, or death from cardiovascular causes by 57%.

Current Intensive Insulin Replacement Regimens

The goal of physiologic insulin replacement for T1DM is accomplished with short-acting insulins that more closely mimic the sharp increase and short duration of pancreatic insulin secreted with nutrient intake. The rapid-acting insulin analog lispro has superior pharmacokinetic properties for the control of postprandial glucose. Improved postprandial glucose responses occur with twice-daily injections (conventional insulin), multiple daily insulin injections, or CSII. The use of lispro or aspart insulin reduces the frequency of between-meal hypoglycemic events, especially when it is carefully balanced with the carbohydrate content of meal.

The carbohydrate content of food does not influence glycemic control if premeal rapid-acting insulin (bolus) is adjusted to the carbohydrate content of the meal. Wide variations in carbohydrate intake do not modify long-acting (detemir or glargine) or basal insulin requirements. Insulin replacement strategies stress the importance of administering smaller doses of insulin throughout the day. This approach allows insulin doses to be changed as needed to correct hyperglycemia, supplement for additional anticipated carbohydrate intake, or subtract for exercise. Indeed, bolus-basal treatment with multiple injections is better adapted to the physiologic profiles of insulin and glucose and can therefore provide better glycemic control than the conventional 2-3 dose regimen. Age-adjusted and individualized insulin to carbohydrate ratios and insulin dosage adjustment algorithms have been developed to normalize elevated blood glucose levels and to compensate for alterations in carbohydrate intake. The use of flexible multiple daily injections and CSII in children with T1DM improves glycemic control without an increase in the incidence of severe hypoglycemia.

Hypoglycemic Reactions

Hypoglycemia is the major limitation to tight control of glucose levels. Once injected, insulin absorption and action are independent of the glucose level, thus creating a unique risk of hypoglycemia from an unbalanced insulin effect. Insulin analogs may help reduce but cannot eliminate this risk. Most children with T1DM can expect mild hypoglycemia each week, moderate hypoglycemia a few times each year, and severe hypoglycemia every few years. These episodes are usually not predictable, although exercise, delayed meals or snacks, and wide swings in glucose levels increase the risk. Infants and toddlers are at higher risk for hypoglycemia because they have more variable meals and activity levels, are unable to recognize early signs of hypoglycemia, and are limited in their ability to seek a source of oral glucose to reverse the hypoglycemia. The very young have an increased risk of permanently reduced cognitive function as a long-term sequela of severe hypoglycemia. For this reason, a more relaxed degree of glucose control is necessary until the child matures (see Table 589-9).

Hypoglycemia can occur at any time of day or night. Early symptoms and signs (mild hypoglycemia) may occur with a sudden decrease in blood glucose to levels that do not meet standard criteria for hypoglycemia in children without diabetes. The child may show pallor, sweating, apprehension or fussiness, hunger, tremor, and tachycardia, all as a result of the surge in catecholamines as the body attempts to counter the excessive insulin effect. Behavioral changes such as tearfulness, irritability, and aggression are more prevalent in children. As glucose levels decline further, cerebral glucopenia occurs with drowsiness, personality changes, mental confusion, and impaired judgment (moderate hypoglycemia), progressing to inability to seek help and seizures or coma (severe hypoglycemia). Prolonged severe hypoglycemia can result in a depressed sensorium or stroke-like focal motor deficits that persist after the hypoglycemia has resolved. Although permanent sequelae are rare, severe hypoglycemia is frightening for the child and family and can result in significant reluctance to attempt even moderate glycemic control afterward.

Important counterregulatory hormones in children include growth hormone, cortisol, epinephrine, and glucagon. The latter 2 seem more critical in the older child. Many older patients with long-standing T1DM lose their ability to secrete glucagon in response to hypoglycemia. In the young adult, epinephrine deficiency may also develop as part of a general autonomic neuropathy. This substantially increases the risk of hypoglycemia because the early warning signals of a declining glucose level are as a result of catecholamine release. Recurrent hypoglycemic episodes associated with tight metabolic control may aggravate partial counterregulatory deficiencies, producing a syndrome of hypoglycemia unawareness and reduced ability to restore euglycemia (hypoglycemia-associated autonomic failure). Avoidance of hypoglycemia allows some recovery from this unawareness syndrome.

The most important factors in the management of hypoglycemia are an understanding by the patient and family of the symptoms and signs of the reaction and an anticipation of known precipitating factors such as gym or sports activities. Tighter glucose control increases the risk. Families should be taught to look for typical hypoglycemic scenarios or patterns in the home blood glucose log, so that they may adjust the insulin dose and avert predictable episodes. A source of emergency glucose should be available at all times and places, including at school and during visits to friends. If possible, it is important to document the hypoglycemia before treating, because some symptoms may not always be from hypoglycemia. Any child suspected of having a moderate to severe hypoglycemic episode should be treated before testing. It is important not to give too much glucose; 5-10 g should be given as juice or a sugar-containing carbonated beverage or candy, and the blood glucose checked 15-20 min later. Patients, parents, and teachers should also be instructed in the administration of glucagon when the child cannot take glucose orally. An injection kit should be kept at home and school. The intramuscular dose is 0.5 mg if the child weighs less than 20 kg and 1.0 mg if more than 20 kg. This produces a brief release of glucose from the liver. Glucagon often causes emesis, which precludes giving oral supplementation if the blood glucose declines after the glucagon effects have waned. Caretakers must then be prepared to take the child to the hospital for IV glucose administration, if necessary. Minidose glucagon (10 µg/yr of age up to a maximum of 150 µg subcutaneously) is effective in treating hypoglycemia in children with blood glucose less than 60 mg/dL who fail to respond to oral glucose and remain symptomatic.

Dawn Phenomenon and Somogyi Phenomenon

There are several reasons that blood glucose levels increase in the early morning hours before breakfast. The most common is a simple decline in insulin levels. This usually results in routinely elevated morning glucose. The **dawn phenomenon** is thought to be mainly caused by overnight growth hormone secretion and increased insulin clearance. It is a normal physiologic process seen in most adolescents without diabetes, who compensate with more insulin output. A child with T1DM cannot compensate. The dawn phenomenon is usually recurrent and modestly elevates most morning glucose levels.

Rarely, high morning glucose is caused by the **Somogyi phenomenon,** a theoretical rebound from late-night or early-morning hypoglycemia, thought to be from an exaggerated counterregulatory response. It is unlikely to be a common cause, in that most children remain hypoglycemic (do not rebound) once nighttime glucose levels decline. Continuous glucose monitoring systems may help clarify ambiguously elevated morning glucose levels.

Behavioral/Psychologic Aspects and Eating Disorders

Diabetes in a child affects the lifestyle and interpersonal relationships of the entire family. Feelings of anxiety and guilt are common in parents. Similar feelings, coupled with denial and rejection, are equally common in children, particularly during the rebellious teenage years. Family conflict has been associated with poor treatment adherence and poor metabolic control among youths with T1DM. On the other hand, it has been shown that shared responsibility is consistently associated with better psychologic health, good self-care behavior, and good metabolic control, whereas responsibility assumed by either the child or parent alone does not have outcomes that are equally successful. In some cases, links of shared responsibility to health outcomes were stronger among older adolescents. However, no specific personality disorder or psychopathology is characteristic of diabetes; similar feelings are observed in families with other chronic disorders.

COGNITIVE FUNCTION

There is increasing agreement that children with T1DM are at higher risk of developing small differences in cognitive abilities compared to healthy age-matched peers. Evidence suggests that early-onset diabetes (younger than 7 yr) is associated with cognitive difficulties compared to late-onset diabetes and healthy controls. The cognitive difficulties observed were primarily learning and memory skills (both verbal and visual) and attention/executive function skills. It is likely that the impact of diabetes on pediatric cognition appears shortly after diagnosis. Indeed, it has been observed that early-onset diabetes and longer duration of diabetes in children with diabetes adversely affect their school performance and educational achievements.

COPING STYLES

Children and adolescents with T1DM are faced with a complex set of developmental changes as well as shifting burdens of the disease. Adjustment problems might affect psychologic well-being and the course of the disease by impacting self-management and leading to poor metabolic control. Coping styles refer to typical habitual preferences for ways of approaching problems and might be regarded as strategies that people generally use to cope across a wide range of stressors. Problem-focused coping refers to efforts directed toward rational management of a problem, and it is aimed at changing the situation causing distress. On the other hand, emotion-focused coping implies efforts to reduce emotional distress caused by the stressful event and to manage or regulate emotions that might accompany or result from the stressor. In adolescents with diabetes, avoidance coping and venting emotions have been found to predict poor illness-specific self-care behavior and poor metabolic control. Patients who use more mature defenses and exhibit greater adaptive capacity are more likely to adhere to their regimen. Coping strategies seem to be age dependent, with adolescents using more avoidance coping than younger children with diabetes.

NONADHERENCE

Family conflict, denial, and feelings of anxiety or loss of control find expression in nonadherence to instructions regarding nutritional and insulin therapy and in noncompliance with self-monitoring. When adolescents perceive their parents' involvement as criticism, or when they externalize behavior problems, such behaviors interfere with adherence and may result in deterioration of glycemic control. Such behaviors are very common, whereas episodes of deliberate overdosage with insulin resulting in hypoglycemia, or omission of insulin resulting in ketoacidosis, are far less prevalent. They may, however, be pleas for psychologic help or be manipulative attempts to escape an environment perceived as undesirable or intolerable; occasionally, they may be manifestations of suicidal intent. Frequent admissions to the hospital for ketoacidosis or hypoglycemia should arouse suspicion of an underlying emotional conflict. Overprotection on the part of parents is common and often is not in the best interest of the adolescent patient. Feelings of being different or of being alone, or both, are common and must be acknowledged, but may be addressed by tailoring the insulin administration and timing of meals and blood sugar testings in order to allow for a more individualized lifestyle. Families and patients worry about the risk of complications from diabetes, aggregating what they know about type 1 and type II diabetes, and worry about the decreased life span. Unfortunately, misinformation abounds about the risks of the development of diabetes in siblings or offspring and of pregnancy in young diabetic women. Even appropriate information may cause further anxiety.

All of these issues must be spoken about at the outset, and many of these problems can be averted through continued empathic counseling based on correct information, focusing on normality and on planning to be a productive member of society. Recognizing the potential impact of these problems, peer discussion groups have been organized in many locales; feelings of isolation and frustration tend to be lessened by the sharing of common problems. Summer camps for diabetic children afford an excellent opportunity for learning and sharing under expert supervision. Education about the pathophysiology of diabetes, insulin dose, technique of administration, nutrition, exercise, and hypoglycemic reactions can be reinforced by medical and paramedical personnel. The presence of numerous peers with similar problems offers new insights to the diabetic child. Residential treatment for children and adolescents with difficult to manage T1DM is an option available only in some centers.

ANXIETY AND DEPRESSION

It has been shown that there are significant correlations between poor metabolic control and depressive symptoms, a high level of anxiety, or a previous psychiatric diagnosis. In a similar way, poor metabolic control is related to higher levels of personal, social, school maladjustment, or family environment dissatisfaction. It is estimated that 20-26% of adolescent patients may develop major depressive disorder. The prevalence of depression is 2-fold greater than controls in children with diabetes and 3-fold greater in adolescents. The course characteristics of depression in young diabetic subjects and psychiatric control subjects appear to be similar; however, eventual propensity of diabetic youths for more protracted depressions is greater and there is a higher risk of recurrence among young diabetic females. On balance, anxiety and depression play an important and complex role in T1DM; their relationship to metabolic control does not yet appear clear. Therefore, the healthcare providers managing a child or adolescent with diabetes should be aware of their pivotal role as counselor and advisor and should closely monitor the mental health of patients with diabetes.

FEAR OF SELF-INJECTING AND SELF-TESTING

Extreme fear of self-injecting insulin (injection phobia) is likely to compromise glycemic control as well as emotional well-being. Likewise, fear of finger pricks can be a source of distress and may seriously hamper self-management. Children and adolescents may either omit insulin dosing or refuse to rotate their injection sites because repeated injection in the same site is associated with less pain sensation. Failure to rotate injection sites results in subcutaneous scar formation (lipohypertrophy). Insulin injection into the lipohypertrophic skin is usually associated with poor insulin absorption and/or insulin leakage with resultant suboptimal glycemic control. Children and adolescents with injection phobia and fear of self-testing can be counseled by a trained behavioral therapist and benefit from such techniques as desensitization and biofeedback to attenuate pain sensation and psychologic distress associated with these procedures. Another possibility is to consider using an indwelling subcutaneous soft cannula to minimize the discomfort of repeated injections.

EATING DISORDERS

Treatment of T1DM involves constant monitoring of food intake. In addition, improved glycemic control is sometimes associated with increased weight gain. In adolescent females, these 2 factors, along with individual, familial, and socioeconomic factors, can lead to an increased incidence of both nonspecific and specific eating disorders, which can disrupt glycemic control and increase the risk of long-term complications. Eating disorders and subthreshold eating disorders are almost

twice as common in adolescent females with T1DM as in their nondiabetic peers. The reports of the frequencies of specific (anorexia or bulimia nervosa) eating disorders vary from 1.0-6.9% among female patients with T1DM. The prevalence of nonspecific and subthreshold eating disorders is 9% and 14%, respectively. Approximately 11% of T1DM adolescent females take less insulin than prescribed in order to lose weight. Among adolescent females with an eating disorder, approximately 42% of patients misuse insulin, whereas the estimates of insulin misuse prevalence in subthreshold and nondisordered eating groups are 18% and 6%, respectively. Although there is little information regarding the prevalence of eating disorders among male adolescents with T1DM, available data suggest normal eating attitudes in most. Among healthy adolescent males who participate in wrestling, however, the drive to lose weight has led to the seasonal, transient development of abnormal eating attitudes and behaviors, which may lead to insulin dose omission in order to lose weight.

When behavioral/psychologic problems and/or eating disorders are assumed to be responsible for poor adherence with the medical regimen, referral for psychologic evaluation and management is indicated. Behavioral therapists and psychologists usually form part of the pediatric diabetes team in most centers and can help assess and manage emotional and behavioral disorders in diabetic children. Evaluation of nurse-delivered motivational enhancement with and without cognitive behavior therapy in adults revealed the combined therapy resulted in modest improvement in glycemic control. However, motivational enhancement therapy alone did not improve glycemic control. While in some studies the effect of therapist-delivered motivational enhancement therapy on glycemic control in adolescents with T1DM lasted as long as intensive individualized counseling continued, in other studies, motivational interviewing was shown to be an effective method of facilitating changes in a teenager's behavior with T1DM with corresponding improvement in glycemic control.

Management During Infections

Although infections are no more common in diabetic children than in nondiabetic ones, they can often disrupt glucose control and may precipitate DKA. In addition, the diabetic child is at increased risk of dehydration if hyperglycemia causes an osmotic diuresis or if ketosis causes emesis. Counterregulatory hormones associated with stress blunt insulin action and elevate glucose levels. If anorexia occurs from ketosis, lack of caloric intake increases the risk of hypoglycemia. Although children younger than 3 yr of age tend to become hypoglycemic and older children tend toward hyperglycemia, the overall effect is unpredictable. Therefore, frequent blood glucose monitoring and adjustment of insulin doses are essential elements of sick day guidelines (Table 589-10).

The overall goals are to maintain hydration, control glucose levels, and avoid ketoacidosis. This can usually be done at home if proper sick day guidelines are followed and with telephone contact with healthcare providers. The family should seek advice if home treatment does not control ketonuria, hyperglycemia, or hypoglycemia, or if the child shows signs of dehydration. A child with large ketonuria and emesis should be seen in the emergency department for a general examination, to evaluate hydration, and to determine whether ketoacidosis is present by checking serum electrolytes, glucose, pH, and total CO_2. A child whose blood glucose declines to less than 50-60 mg/dL (2.8-3.3 mmol/L) and who cannot maintain oral intake may need IV glucose, especially if further insulin is needed to control ketonemia.

Management During Surgery

Surgery can disrupt glucose control in the same way as can intercurrent infections. Stress hormones associated with the underlying condition as well as with surgery itself cause insulin resistance. This increases glucose levels, exacerbates fluid losses, and may initiate DKA. On the other hand, caloric intake is usually restricted, which decreases glucose levels. The net effect is as difficult to predict as during an infection. Vigilant monitoring and frequent insulin adjustments are required to maintain euglycemia and avoid ketosis.

Maintaining glucose control and avoiding DKA are best accomplished with IV insulin and fluids. A simple insulin adjustment scale based on the patient's weight and blood glucose level can be used in most situations (Table 589-11). The IV insulin is continued after surgery as the child begins to take oral fluids; the IV fluids can be steadily decreased as oral intake increases. When full oral intake is achieved, the IV may be capped and subcutaneous insulin begun. When surgery is elective, it is best performed early in the day, allowing the patient maximal recovery time to restart oral intake and subcutaneous insulin therapy. When elective surgery is brief (less than 1 hr) and full oral intake is expected shortly afterward, one may simply monitor the blood glucose hourly and give a dose of insulin analog according to the child's home glucose correction scale. If glargine or detemir is used as the basal insulin, a full dose is given the evening before planned surgery. If NPH or Lente is used, one half of the morning dose is given before surgery. The child should not be discharged until blood glucose levels are stable and oral intake is tolerated.

Table 589-11 Guidelines for Intravenous Insulin Coverage During Surgery

BLOOD GLUCOSE LEVEL (mg/dL)	INSULIN INFUSION (units/kg/hr)	BLOOD GLUCOSE MONITORING
<120	0.00	1 hr
121-200	0.03	2 hr
200-300	0.06	2 hr
300-400	0.08	1 hr*
400	0.10	1 hr*

An infusion of 5% glucose and 0.45% saline solution with 20 mEq/L of potassium acetate is given at 1.5 times maintenance rate.
*Check urine ketones.

Table 589-10 Guidelines for Sick Day Management

URINE KETONE STATUS	GLUCOSE TESTING AND EXTRA RAPID-ACTING INSULIN: Insulin	GLUCOSE TESTING AND EXTRA RAPID-ACTING INSULIN: Correction Doses*	COMMENT
Negative or small†	q2hr	q2hr for glucose >250 mg/dL	Check ketones every other void
Moderate to large‡	q1hr	q1hr for glucose >250 mg/dL	Check ketones each void; go to hospital if emesis occurs

Basal insulin: glargine or detemir basal insulin should be given at the usual dose and time. NPH and Lente should be reduced by half if blood glucose <150 mg/dL and the oral intake is limited.
Oral fluids: sugar-free if blood glucose >250 mg/dL (14 mmol/L); sugar-containing if blood glucose <250 mg/dL.
Call physician or nurse if blood glucose remains elevated after 3 extra doses; if blood glucose remains less than 70 mg/dL and child cannot take oral supplement; if dehydration occurs.
*Give insulin based on individualized dosing schedule. Also give usual dose for carbohydrate intake if glucose >150 mg/dL.
†For home serum ketones <1.5 mmol/L per commercial kit.
‡For home serum ketones >1.5 mmol/L.

LONG-TERM COMPLICATIONS: RELATION TO GLYCEMIC CONTROL

Complications of DM can be divided into 3 major categories: (1) microvascular complications, specifically, retinopathy and nephropathy; (2) macrovascular complications, particularly accelerated coronary artery disease, cerebrovascular disease, and peripheral vascular disease; and (3) neuropathies, both peripheral and autonomic, affecting a variety of organs and systems (Table 589-12). In addition, cataracts may occur more frequently.

Diabetic retinopathy is the leading cause of blindness in the United States in adults age 20-65 yr. The risk of diabetic retinopathy after 15 yr duration of diabetes is 98% for individuals with T1DM and 78% for those with T2DM. Rates for diabetic retinopathy range from close to 15% to up to 30%. Lens opacities (caused by glycation of tissue proteins and activation of the polyol pathway) are present in at least 5% of those younger than age 19 yr. The metabolic control has an impact on the development of this complication, as prevalence rates are substantially higher with increased duration of diabetes, and higher HbA_{1c}, blood pressure, and cholesterol. Independent of duration, the prevalence of diabetic retinopathy is higher in T1DM. However, genetic factors also have a role, because only 50% of patients develop proliferative retinopathy. The earliest clinically apparent manifestations of diabetic retinopathy are classified as nonproliferative or background diabetic retinopathy—microaneurysms, dot and blot hemorrhages, hard and soft exudates, venous dilation and beading, and intraretinal microvascular abnormalities. These changes do not impair vision. The more severe form is proliferative diabetic retinopathy, which manifests by neovascularization, fibrous proliferation, and preretinal and vitreous hemorrhages. Proliferative retinopathy, if not treated, is relentlessly progressive and impairs vision, leading to blindness. The mainstay of treatment is panretinal laser photocoagulation. In advanced diabetic eye disease—manifested by severe vitreous hemorrhage or fibrosis, often with retinal detachment—vitrectomy is an important therapeutic modality. Eventually, the eye disease becomes quiescent, a stage termed involutional retinopathy. A separate subtype of retinopathy is diabetic maculopathy, which is manifested by severe macular edema impairing central vision, for which focal laser photocoagulation may be effective.

Guidelines suggest that diabetic patients have an initial dilated and comprehensive examination by an ophthalmologist shortly after the diagnosis of diabetes is made in patients with T2DM, and within 3-5 yr after the onset of T1DM (but not before age 10 yr). Any patients with visual symptoms or abnormalities should be referred for ophthalmologic evaluation. Subsequent evaluations for both T1DM and T2DM patients should be repeated annually by an ophthalmologist who is experienced in diagnosing the presence of diabetic retinopathy and is knowledgeable about its management (see Table 589-12).

Diabetic nephropathy is the leading known cause of end-stage renal disease (ESRD) in the United States. Most ESRD from diabetic nephropathy is preventable. Diabetic nephropathy affects 20-30% of patients with T1DM and 15-20% of T2DM patients 20 yr after onset. The mean 5 yr life expectancy for patients with diabetes-related ESRD is less than 20%. The increased mortality risk in long-term T1DM may be due to nephropathy, which may account for approximately 50% of deaths. The risk of nephropathy increases with duration of diabetes (up until 25-30 yr duration, after which this complication rarely begins), degree of metabolic control, and genetic predisposition to essential hypertension. Only 30-40% of patients affected by T1DM eventually experience ESRD. The glycation of tissue proteins results in glomerular basement membrane thickening. The course of diabetic nephropathy is slow. An increased urinary albumin excretion rate of 30-300 mg/24 hr (20-200 µg/min)—*microalbuminuria*—can be detected and constitutes an early stage of nephropathy from intermittent to persistent (incipient), which is commonly associated with glomerular hyperfiltration and blood pressure elevation. As nephropathy evolves to early overt stage with proteinuria (albumin excretion rate >300 mg/24 hr, or >200 µg/min), it is accompanied by hypertension. Advanced-stage nephropathy is defined by a progressive decline in renal function (declining glomerular filtration rate and elevation of serum blood urea and creatinine), progressive proteinuria, and

Table 589-12 Screening Guidelines

	WHEN TO COMMENCE SCREENING	FREQUENCY	PREFERRED METHOD OF SCREENING	OTHER SCREENING METHODS	POTENTIAL INTERVENTION
Retinopathy	After 5 yr duration in prepubertal children, after 2 yr in pubertal children	1-2 yearly	Fundal photography	Fluorescein angiography, mydriatic ophthalmoscopy	Improved glycemic control, laser therapy
Nephropathy	After 5 yr duration in prepubertal children, after 2 yr in pubertal children	Annually	Spot urine sample for albumin : creatinine ratio	24 hr excretion of albumin, urinary albumin : creatinine ratio	Improved glycemic control, blood pressure control, ACE inhibitors
Neuropathy	Unclear in children; adults at diagnosis in T2DM and 5 yr after diagnosis in T1DM	Unclear	Physical examination	Nerve conduction, thermal and vibration threshold, pupillometry, cardiovascular reflexes	Improved glycemic control
Macrovascular disease	After age 2 yr	Every 5 yr	Lipids	Blood pressure	Statins for hyperlipidemia Blood pressure control
Thyroid disease	At diagnosis	Every 2-3 yr or more frequently based on symptoms or the presence of antithyroid antibodies	TSH	Thyroid peroxidase, thyroglobulin antibodies	Thyroxine
Celiac disease	At diagnosis	Every 2-3 yr	Tissue transglutaminase, endomysial antibody	Transglutaminase antibodies	Gluten-free diet

ACE, angiotensin-converting enzyme; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TSH, thyroid-stimulating hormone.

From Glastras SJ, Mohsin F, Donaghue KC: Complications of diabetes mellitus in childhood, Pediatr Clin North Am *52:1735–1753, 2005.*

hypertension. Progression to ESRD is recognized by the appearance of uremia, the nephritic syndrome, and the need for renal replacement (transplantation or dialysis).

Screening for diabetic nephropathy is a routine aspect of diabetes care (see Table 589-12). The American Diabetes Association recommends yearly screening for individuals with T2DM and yearly screening for those with T1DM after 5 yr duration of disease (but not before puberty). A random spot urine sample for albumin to creatinine ratio is obtained. Abnormal results should be confirmed by 2 additional specimens on separate days because of the high variability of albumin excretion in patients with diabetes. Short-term hyperglycemia, strenuous exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness can cause transient elevation urinary albumin excretion. There is marked day-to-day variability in albumin excretion, so at least 2 of 3 collections done in a 3-6 mo period should show elevated levels before microalbuminuria is diagnosed and treatment is started. Once albuminuria is diagnosed, a number of factors attenuate the effect of hyperfiltration on kidneys: (1) meticulous control of hyperglycemia, (2) aggressive control of systemic blood pressure, (3) selective control of arteriolar dilation by use of angiotensin-converting enzyme inhibitors (thus decreasing transglomerular capillary pressure), and (4) dietary protein restriction (because high protein intake increases the renal perfusion rate). Tight glycemic control will delay the progression of microalbuminuria and slow the progression of diabetic nephropathy. Previous extensive therapy of diabetes has a persistent benefit for 7-8 yr and may delay or prevent the development of diabetic nephropathy.

DIABETIC NEUROPATHY

Both the peripheral and autonomic nervous systems can be involved, and adolescents with diabetes can show early evidence of neuropathy. This complication can be traced to the metabolic effects of hyperglycemia and/or other effects of insulin deficiency on the various constituents of the peripheral nerve. The polyol pathway, nonenzymatic glycation, and/or disturbances of myoinositol metabolism affecting 1 or more cell types in the multicellular constituents of the peripheral nerve appear likely to have an inciting role. The role of other factors, such as possible direct neurotrophic effects of insulin, insulin-related growth factors, nitric oxide, and stress proteins, seems to be relevant. Peripheral neuropathy may first present in some adolescents with a long-standing history of diabetes. Using quantitative sensory testing, abnormal cutaneous thermal perception is a common finding in both upper and lower limbs in neurologically asymptomatic young diabetic patients. Heat-induced pain threshold in the hand is correlated with the duration of the diabetes. There is no correlation between quantitative sensory testing scores and metabolic control. Subclinical motor nerve impairment as manifested by reduced sensory nerve conduction velocity and sensory nerve action potential amplitude can be detected during late puberty and after puberty in approximately 10% of adolescents. Poor metabolic control during puberty appears to induce deteriorating peripheral neural function in young patients. An early sign of autonomic neuropathy such as decreased heart rate variability may present in adolescents with a history of long-standing disease and poor metabolic control. A number of therapeutic strategies have been attempted with variable results. These treatment modalities include (1) improvement in metabolic control, (2) use of aldose reductase inhibitors to reduce by-products of the polyol pathway, (3) use of α-lipoic acid (an antioxidant) that enhances tissue nitric oxide and its metabolites, (4) use of anticonvulsants (e.g., lorazepam, valproate, gabapentin, carbamazepine, pregabalin, phenytoin, tiagabine, and topiramate) for treatment of neuropathic pain, and (5) antidepressants (amitriptyline, imipramine, and selective serotonin reuptake inhibitors). Additional medications include antiarrhythmics such as lidocaine, topical analgesics, and nonsteroidal antiinflammatory drugs.

Other quite rarely noted complications in diabetic children include dwarfism associated with a glycogen-laden enlarged liver **(Mauriac syndrome),** osteopenia, and a syndrome of limited joint mobility associated with tight, waxy skin; growth impairment; and maturational delay. The Mauriac syndrome is related to chronic underinsulinization; it is much less common since longer-acting insulins have become available. Clinical features of Mauriac syndrome include moon face, protuberant abdomen, proximal muscle wasting, and enlarged liver from fat and glycogen infiltration. The syndrome of limited joint mobility is frequently associated with the early development of diabetic microvascular complications, such as retinopathy and nephropathy, which may appear before 18 yr of age. In the past decade or two, the prevalence of limited joint mobility has significantly decreased, which is attributed to the improved overall metabolic control of children and adolescents with T1DM.

PROGNOSIS

T1DM is a serious, chronic disease. It has been estimated that the average life span of individuals with diabetes is approximately 10 yr shorter than that of the nondiabetic population. Although diabetic children eventually attain a height within the normal adult range, puberty may be delayed, and the final height may be less than the genetic potential. From studies in identical twins, it is apparent that despite seemingly satisfactory control, the diabetic twin manifests delayed puberty and a substantial reduction in height when onset of disease occurs before puberty. These observations indicate that, in the past, conventional criteria for judging control were inadequate and that adequate control of T1DM was almost never achieved by routine means.

The introduction of portable devices (insulin pumps) that can be programmed to provide CSII with meal-related boluses is 1 approach to the resolution of these long-term problems. In selected individuals, nearly normal patterns of blood glucose and other indices of metabolic control, including HbA_{1c}, have been maintained for several years. This approach, however, should be reserved for highly motivated persons committed to rigorous self-monitoring of blood glucose who are alert to the potential complications, such as mechanical failure of the infusion device causing hyperglycemia or hypoglycemia and to infection at the site of catheter insertion.

The changing pattern of metabolic control is having a profound influence on reducing the incidence and the severity of certain complications. For example, after 20 yr of diabetes, there is a decline in the incidence of nephropathy in T1DM in Sweden among children whose disease was diagnosed in 1971-1975 compared with in the preceding decade. In addition, in most patients with microalbuminuria in whom it was possible to obtain good glycemic control, microalbuminuria disappeared. This improved prognosis is directly related to metabolic control.

PANCREAS AND ISLET TRANSPLANTATION AND REGENERATION

In an attempt to cure T1DM, transplantation of a segment of the pancreas or of isolated islets has been performed in adults. These procedures are both technically demanding and associated with the risks of disease recurrence and complications of rejection or its treatment by immunosuppression. Long-term complications of immunosuppression include the development of malignancy. Some antirejection drugs, notably cyclosporine and tacrolimus, are toxic to the islets of Langerhans, impairing insulin secretion and even causing diabetes. Hence, segmental pancreas transplantation is generally only performed in association with transplantation of a kidney for a patient with ESRD due to diabetic nephropathy in which the immunosuppressive regimen is indicated for the renal transplantation. Several thousand such transplants have been performed in adults. With experience and newer immunosuppressive agents, functional survival of the pancreatic graft may be achieved for up to several years, during which time patients may be in metabolic control with no or minimal exogenous insulin and reversal of some of the microvascular complications. However, because children and adolescents with DM are not likely to have ESRD from their diabetes, pancreas transplantation as a primary treatment in children cannot be recommended.

Islet cell transplantation is challenging because of limited survival of the transplanted cells and because of rejection. Research continues to improve techniques for the yield, viability, and reduction of

immunogenicity of the islets of Langerhans for transplantation. An islet transplantation strategy **(Edmonton protocol)** infused isolated pancreatic islets into the portal vein of a group of adults with T1DM, along with immunosuppressive medications that had lower side-effect profiles than other drugs. While lasting insulin independence was initially low, engraftment and insulin independence have improved over the last decade, and over a thousand patients having undergone the procedure. There has been improved islet engraftment by the use of improved induction and maintenance immunosuppression. Still, in 5-yr follow-up studies, only 1 in 10 maintain insulin independence, with an average duration of insulin independence in all of only about 15 mo. Long-term challenges remain the toxicity of immunosuppression, the limited procurement of viable tissue, and funding and limitations of engraftment itself.

Alternative means of generating β cells are being sought from islet expansion, encapsulated islet xenografts, human islet cell-lines, and stem cells. Regeneration of islets is an approach that could potentially cure T1DM because β-cell mass is actually dynamically regulated.

589.3 Type 2 Diabetes Mellitus

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Formerly known as non–insulin dependent diabetes or adult-onset diabetes, T2DM is a heterogeneous disorder, characterized by peripheral insulin resistance and failure of the β cell to keep up with increasing insulin demand. Patients with T2DM have relative rather than absolute insulin deficiency. Generally, they are not ketosis prone, but ketoacidosis may develop in some circumstances. The specific etiology is not known, but these patients do not have autoimmune destruction of β cells, nor do they have any of the known causes of secondary diabetes.

NATURAL HISTORY

T2DM is considered a polygenic disease aggravated by environmental factors, such as low physical activity and excessive caloric intake. Most patients are obese, although the disease can occasionally be seen in normal weight individuals. Asians in particular appear to be at risk for T2DM at lower degrees of total adiposity. Some patients may not necessarily meet overweight or obese criteria for age and gender despite abnormally high percentage of body fat in the abdominal region. Obesity, in particular, central obesity, is associated with the development of insulin resistance. In addition, patients who are at risk for developing T2DM exhibit decreased glucose-induced insulin secretion. Obesity does not lead to the same degree of insulin resistance in all individuals and even those who develop insulin resistance do not necessarily exhibit impaired β-cell function. Thus, many obese individuals have some degree of insulin resistance but compensate for it by increasing insulin secretion. Those individuals who are unable to adequately compensate for insulin resistance by increasing insulin secretion, develop IGT and impaired fasting glucose (usually, although not always, in that order). Hepatic insulin resistance leads to excessive hepatic glucose output (failure of insulin to suppress hepatic glucose output), while skeletal muscle insulin resistance leads to decreased glucose uptake in a major site of glucose disposal. Over time hyperglycemia worsens, a phenomenon that has been attributed to the deleterious effect of chronic hyperglycemia (glucotoxicity) or chronic hyperlipidemia (lipotoxicity) on β-cell function and is often accompanied by increased triglyceride content and decreased insulin gene expression. At some point, blood glucose elevation meets the criteria for diagnosis of T2DM (see Table 589-2), but most patients with T2DM remain asymptomatic for months to years after this point because hyperglycemia is moderate and symptoms are not as dramatic as the polyuria and weight loss accompanying T1DM. Weight gain may even continue. The prolonged hyperglycemia may be accompanied by the development of microvascular and macrovascular complications. In time, β-cell function can decrease to the point that the patient has absolute insulin deficiency and becomes dependent on exogenous insulin. In T2DM, insulin deficiency is rarely absolute, so patients usually do not need insulin to survive. Nevertheless, glycemic control can be improved by exogenous insulin. Although DKA is uncommon in patients with T2DM, it can occur and is usually associated with the stress of another illness such as severe infection. DKA tends to be more common in African-American patients than in other ethnic groups. Although it is generally believed that autoimmune destruction of pancreatic β cells does not occur in T2DM, autoimmune markers of T1DM—namely, glutamic acid decarboxylase antibody, ICA512, and insulin-associated autoantibody—may be positive in up to one third of the cases of adolescent T2DM. The presence of these autoimmune markers does not rule out T2DM in children and adolescents. At the same time, because of the general increase in obesity, the presence of obesity does not preclude the diagnosis of T1DM. Although the majority of newly diagnosed children and adolescents can be confidently assigned a diagnosis of T1DM or T2DM, a few exhibit features of both types and are difficult to classify.

EPIDEMIOLOGY

National Health and Nutritional Examination Surveys data (from 1999-2002) show that the prevalence of T2DM in 12-19 yr olds in the United States is 1.46 in 1,000. The Southeastern Aerosol Research and Characterization (SEARCH) study found that the prevalence of type 2 diabetes in the 10-19 yr old age group in the United States was 15% in 2001 and it is likely that this proportion has increased over time. Certain ethnic groups appear to be at higher risk; for example, Native Americans, Hispanic Americans, and African-Americans (in that order) have higher incidence rates than white Americans. Although a majority of children presenting with diabetes still have T1DM, the percentage of children presenting with T2DM is increasing and represents up to 50% of the newly diagnosed children in some centers.

Prevalence in the rest of the world varies widely and accurate data are not available for many countries, but it is clear that the prevalence is increasing in every part of the world. Asians in general seem to develop T2DM at lower body mass index levels than Europeans. In conjunction with their low incidence of type 1 diabetes, this means that T2DM accounts for a higher proportion of childhood diabetes in many Asian countries.

The epidemic of T2DM in children and adolescents parallels the emergence of the obesity epidemic. Although obesity itself is associated with insulin resistance, diabetes does not develop until there is some degree of failure of insulin secretion. Thus, when measured, insulin secretion in response to glucose or other stimuli is always lower in persons with T2DM than in control subjects matched for age, sex, weight, and equivalent glucose concentration.

GENETICS

T2DM has a strong genetic component; concordance rates among identical twins are in the 60-90% range. It should be kept in mind, however, that twinning itself increases the risk of T2DM (because of intrauterine growth restriction) and this may distort estimates of genetic risk. In at least 1 study from Denmark, both monozygotic and dizygotic twins have a lifetime concordance of T2DM of around 70%, indicating that shared environmental factors (including the prenatal environment) may play a large role in the development of T2DM. The genetic basis for T2DM is complex and incompletely defined; no single identified defect predominates as does the HLA association with T1DM. Genomewide association studies have now identified certain genetic polymorphisms that are associated with increased T2DM risk in most populations studied; the most consistently identified are variants of the TCF7L2 (transcription factor 7–like 2) gene, which may have a role in β-cell function. Other identified risk alleles include variants in *PPARG* and *KCNJ11* as well as many others. But to date, all these identified variants explain only a small portion (probably less than 20%) of the population risk of diabetes and in many cases the mechanism by which these polymorphisms confer risk of T2DM is not clear.

EPIGENETICS AND FETAL PROGRAMMING

Low birthweight and intrauterine growth restriction are associated with increased risk of T2DM. This risk appears to be higher in

low-birthweight infants who gain weight more rapidly in the 1st few years of life. These findings have led to the formulation of the "thrifty phenotype" hypothesis, which postulates that poor fetal nutrition somehow programs these children to maximize storage of nutrients and makes them more prone to future weight gain and development of diabetes. Epigenetic modifications may play a role in this phenomenon, but the detailed molecular mechanisms involved have yet to be determined. Whatever the exact mechanism, prenatal and early childhood environments play an important role in the pathogenesis of T2DM and may do so by epigenetic modification of the DNA (in addition to other factors).

ENVIRONMENTAL AND LIFESTYLE-RELATED RISK FACTORS

Obesity is the most important lifestyle factor associated with development of T2DM. This, in turn, is associated with the intake of high-energy foods, physical inactivity, TV viewing ("screen time"), and low socioeconomic status (in developed countries). Maternal smoking also increases the risk of diabetes and obesity in the offspring. Interestingly, smoking by young adults also increases their own risk of diabetes by as yet unknown mechanisms. In addition, sleep deprivation and psychosocial stress are associated with increased risk of obesity in childhood and with IGT in adults, possibly via overactivation of the hypothalamic-pituitary-adrenal axis. Many antipsychotics (especially the atypical antipsychotics like olanzapine and quetiapine) and antidepressants (both tricyclic antidepressants and newer antidepressants like fluoxetine and paroxetine) induce weight gain. In addition to the risk conferred by increased obesity, some of these medications may also have a direct role in causing insulin resistance, β-cell dysfunction, leptin resistance, and activation of inflammatory pathways. To complicate matters further, there is evidence that schizophrenia and depression themselves increase the risk of T2DM and the metabolic syndrome, independent of the risk conferred by drug treatment. As a result, both obesity and T2DM are more prevalent in this population, and with increasing use of antipsychotics and antidepressants in the pediatric population, this association is likely to become stronger.

CLINICAL FEATURES

In the United States, T2DM in children is more likely to be diagnosed in Native American, Hispanic American, and African-American youth, with the highest incidence being reported in Pima Indian youth. While cases may be seen as young as 6 yr of age, most are diagnosed in adolescence and incidence increases with increasing age. Family history of T2DM is present in practically all cases. Typically, patients are obese and present with mild symptoms of polyuria and polydipsia, or are asymptomatic and detected on screening tests. Presentation with DKA occurs in up to 10% of cases. Physical examination frequently reveals the presence of acanthosis nigricans, most commonly on the neck and in other flexural areas. Other findings may include striae and an increased waist : hip ratio. Laboratory testing reveals elevated HbA_{1c} levels. Hyperlipidemia characterized by elevated triglycerides and low-density lipoprotein cholesterol levels is commonly seen in patients with T2DM at diagnosis. Consequently, lipid screening is indicated in all new cases of T2DM. Because hyperglycemia develops slowly and patients may be asymptomatic for months or years after they develop T2DM, screening for T2DM is recommended in high-risk children (Table 589-13). The American Diabetes Association recommends that all youth who are overweight and have at least 2 other risk factors be tested for T2DM beginning at age 10 yr or at the onset of puberty and every 2 yr after that. Risk factors include family history of T2DM in 1st- or 2nd-degree relatives, history of gestational diabetes in the mother, belonging to certain ethnic groups (i.e., Native American, African-American, Hispanic, or Asian/Pacific Islander groups) and having signs of insulin resistance (e.g., acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome). The current recommendation is to use fasting blood glucose as a screening test, but some authorities now recommend that HbA_{1c} be used as a screening tool. In borderline or asymptomatic cases, the diagnosis may be confirmed using a standard oral glucose tolerance test, but this test is not required

Table 589-13 Testing for Type 2 Diabetes in Children

- Criteria*
  - Overweight (body mass index >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
  - *Plus*
  - Any 2 of the following risk factors:
    - Family history of type 2 diabetes in 1st- or 2nd-degree relative
    - Race/ethnicity (Native American, African-American, Hispanic, Asian/Pacific Islander)
    - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome)
- Age of initiation: age 10 yr or at onset of puberty if puberty occurs at a younger age
- Frequency: every 2 yr
- Test: fasting plasma glucose preferred

*Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria.

From Type 2 diabetes in children and adolescents. American Diabetes Association, Diabetes Care *23:386, 2000. Reproduced by permission.*

if typical symptoms are present or fasting plasma glucose or HbA_{1c} is clearly elevated on 2 separate occasions.

TREATMENT

Type 2 diabetes is a progressive syndrome that gradually leads to complete insulin deficiency during the patient's life. A systematic approach for treatment of T2DM should be implemented according to the natural course of the disease, including adding insulin when hypoglycemic oral agent failure occurs. Nevertheless, lifestyle modification (diet and exercise) is an essential part of the treatment regimen, and consultation with a dietitian is usually necessary.

There is no particular dietary or exercise regimen that has been conclusively shown to be superior but most centers recommend a low-calorie, low-fat diet and 30-60 min of physical activity at least 5 times/wk. Screen time should be limited to 1-2 hr/day. Children with T2DM often come from household environments with a poor understanding of healthy eating habits. Commonly observed behaviors include skipping meals, heavy snacking, and excessive daily television viewing, video game playing, and computer use. Adolescents engage in non–appetite-based eating (i.e., emotional eating, television-cued eating, boredom) and cyclic dieting ("yo-yo" dieting). Treatment in these cases is frequently challenging and may not be successful unless the entire family buys into the need to change their unhealthy lifestyle.

It is recommended that oral hypoglycemic agents be introduced at the time of diagnosis (Table 589-14). Patients who present with DKA or with markedly elevated HbA_{1c} (>9.0%) will require treatment with insulin using protocols similar to those used for treating T1DM. Once blood glucose levels are under control, most cases can be managed with oral hypoglycemic agents and lifestyle interventions, but some patients will continue to require insulin therapy.

The most commonly used and the only FDA-approved oral agent for the treatment of T2DM in children and adolescents is metformin. Renal function must be assessed before starting metformin as impaired renal function has been associated with potentially fatal lactic acidosis. Significant hepatic dysfunction is also a contraindication to metformin use, although mild elevations in liver enzymes may not be an absolute contraindication. The usual starting dose is 500 mg once daily. This may be increased to a maximum dose of 2,000 mg/day. Abdominal symptoms are common early in the course of treatment, but in most cases they will resolve with time.

Other agents such as thiazolidinediones, sulfonylureas, acarbose, pramlintide, and incretin mimetics are being used routinely in adults but are not used as commonly in pediatrics. Sulfonylureas are widely used in adults, but experience in pediatrics is limited. Sulfonylureas cause insulin release by closing the potassium channel (K_{ATP}) on β

Table 589-14 Oral Hypoglycemic Agents

DRUG	MECHANISM OF ACTION	DURATION OF BIOLOGIC EFFECT (hr)	USUAL DAILY DOSE (mg)	DOSES/DAY	SIDE EFFECTS	CAUTION
Biguanide	Insulin sensitizer				Gastrointestinal disturbance, lactic acidosis	Avoid in hepatic or renal impairment
Metformin			1500-2500	2-3		
Sulfonylureas						
1st generation						
Acetohexamide		12-18	500-750	1 or divided		
Chlorpropamide		27-72	250-500	1		
Tolbutamide		14-16	1000-2000	1 or divided		
2nd generation						
Glipizide		14-16	2.5-10 XL: 5-10	1 or divided 1		
Glyburide		20-24+	2.5-10	1 or divided		
Glimepiride		24+	2-4	1		
Glitinides	Promote insulin secretion					Titrate carefully in renal or hepatic dysfunction
Repaglinide		≤24	2-16	3		
Nateglinide		4	360	3		
α-Glucosidase inhibitors	Slow hydrolysis and absorption of complex carbohydrates		150-300	3 (with meals)	Transient gastrointestinal disturbances	
Acarbose			150-300	3 (with meals)		
Miglitol						
Thiazolidinedione	Peripheral insulin sensitizer				Upper respiratory tract infection, headache, edema, weight gain	
Rosiglitazone			4-8	1 or divided		
Pioglitazone			15-45	1		
Sitagliptin	GLP-1 receptor agonist	24	50-100	1	Upper respiratory tract infection, sore throat, diarrhea	No data in children or adolescents

From Jacobson-Dickman E, Levistky L: Oral agents in managing diabetes mellitus in children and adolescents, Pediatr Clin North Am *52:1689–1703, 2005.*

cells. They are occasionally used when metformin monotherapy is unsuccessful or contraindicated for some reason (use in certain forms of neonatal diabetes is discussed in the section on neonatal diabetes). Thiazolidinediones are not approved for use in pediatrics. Pramlintide (Symlin) is an analog of IAPP (islet amyloid polypeptide), which is a peptide that is cosecreted with insulin by the β cells and acts to delay gastric emptying, suppress glucagon, and possibly suppress food intake. It is not yet approved for pediatric use. Incretins are gut-derived peptides like GLP-1, GLP-2, and GIP (glucose-dependent insulinotropic peptide, previously known as gastric inhibitory protein) that are secreted in response to meals and act to enhance insulin secretion and action, suppress glucagon production, and delay gastric emptying (among other actions). GLP-1 analogs (e.g., exenatide) and agents that prolong endogenous GLP-1 action (e.g., sitagliptin) are now available for use in adults but are not yet approved for use in children; they may be associated with side effects such as hepatic injury and pancreatitis.

COMPLICATIONS

In the SEARCH study of diabetes in youth, 92% of the patients with T2DM had 2 or more elements of the metabolic syndrome (hypertension, hypertriglyceridemia, decreased high-density lipoprotein, increased waist circumference), including 70% with hypertension. In addition, the incidence of microalbuminuria and diabetic retinopathy appears to be higher in T2DM than it is in T1DM. In the SEARCH study, the incidence of microalbuminuria among patients who had T2DM of less than 5 yr duration was 7-22%, while retinopathy was present in 18.3%. Thus, all adolescents with T2DM should be screened for hypertension and lipid abnormalities and screening for microalbuminuria and retinopathy may be indicated even earlier than it is in T1DM. Sleep apnea and fatty liver disease are being diagnosed with increasing frequency and may necessitate referral to the appropriate specialists. Complications associated with all forms of diabetes and recommendations for screening are noted in Table 589-12; Table 589-15 lists additional conditions particularly associated with T2DM.

PREVENTION

The difficulties in achieving good glucose control and preventing diabetes complications make prevention a compelling strategy. This is particularly true for T2DM, which is clearly linked to modifiable risk factors (obesity, a sedentary lifestyle). The Diabetes Prevention Program was designed to prevent or delay the development of T2DM in adult individuals at high risk by virtue of IGT. The Diabetes Prevention Program results demonstrated that intensified lifestyle or drug intervention in individuals with IGT prevented or delayed the onset of T2DM. The results were striking. Lifestyle intervention reduced the diabetes incidence by 58%; metformin reduced the incidence by 31% compared with placebo. The effects were similar for men and women and for all racial and ethnic groups. Lifestyle interventions are believed to have similar beneficial effects in obese adolescents with IGT. Screening is indicated for at-risk patients (see Table 589-13).

Table 589-15 Monitoring for Complications and Comorbidities

CONDITION	SCREENING TEST	COMMENT
Hypertension	Blood pressure	
Fatty liver	Aspartate aminotransferase, alanine aminotransferase, possibly liver ultrasound	
Polycystic ovary syndrome	Menstrual history, assessment for androgen excess with free/total testosterone, dehydroepiandrosterone	
Microalbuminuria	Urine albumin concentration and albumin : creatinine ratios	
Dyslipidemia	Fasting lipid profile (total, low-density lipoprotein, high-density lipoprotein cholesterol, triglycerides)	Obtain at diagnosis and every 2 yr
Sleep apnea	Sleep study to assess overnight oxygen saturation	

From Liu L, Hironaka K, Pihoker C: Type 2 diabetes in youth, Curr Probl Pediatr Adolesc Health Care *34:249–280, 2004.*

589.4 Other Specific Types of Diabetes

Britta M. Svoren and Nicholas Jospe

Most cases of diabetes in children as well as adults fall into the 2 broad categories of type 1 and type 2 diabetes, but up to 4% of cases are caused by single-gene disorders. These disorders include hereditary defects of β-cell function and insulin action, as well as rare forms of mitochondrial diabetes.

GENETIC DEFECTS OF β-CELL FUNCTION

Maturity-Onset Diabetes of Youth

Several forms of diabetes are associated with monogenic defects in β-cell function. Before these genetic defects were identified, this subset of diabetics was diagnosed on clinical grounds and described by the term MODY. This subtype of DM consists of a group of heterogeneous clinical entities that are characterized by onset before 25 yr, autosomal dominant inheritance, and a primary defect in insulin secretion. Strict criteria for the diagnosis of MODY include diabetes in at least 3 generations with autosomal dominant transmission and diagnosis before age 25 yr in at least 1 affected subject. Mutations have been found in at least in 10 different genes, accounting for the dominantly inherited monogenic defects of insulin secretion, for which the term MODY is used. The American Diabetes Association groups these disorders together under the broader category of “genetic defects of β-cell function.” Eleven of these defects typically meet the clinical criteria for the diagnosis of MODY and are listed in Table 589-16. Just 3 of them (MODY2 and MODY3 and MODY5) account for 90% of the cases in this category in European populations, but the distribution may be different in other ethnic groups. Except for MODY2 (which is caused by mutations in the enzyme glucokinase), all other forms are caused by genetic defects in various transcription factors (Table 589-16).

MODY2

This is the second most common form of MODY and accounts for approximately 15-30% of all patients diagnosed with MODY. Glucokinase plays an essential role in β-cell glucose sensing and heterozygous mutations in this gene lead to mild reductions in pancreatic β-cell response to glucose. Homozygotes with the same mutations are completely unable to secrete insulin in response to glucose and develop a form of permanent neonatal diabetes. Patients with heterozygous mutations have a higher threshold for insulin release but are able to secrete insulin adequately once blood glucose rises above 7 mmol/L. This results in a relatively mild form of diabetes (HbA_{1c} is usually less than 7%), with mild fasting hyperglycemia and IGT in the majority of patients. MODY2 may be misdiagnosed as type 1 diabetes in children, gestational diabetes in pregnant women, or well-controlled type 2 diabetes in adults (Table 589-17). An accurate diagnosis is important because most cases are not progressive, and except for gestational diabetes, may not require treatment. When needed, they can usually be treated with small doses of exogenously administered insulin. Treatment with oral agents (sulfonylureas and related drugs) can be successful and may be more acceptable to many patients.

MODY3

Patients affected with mutations in the transcription factor hepatocyte nuclear factor-1α show abnormalities of carbohydrate metabolism varying from IGT to severe diabetes and often progressing from a mild to a severe form over time. They are also prone to the development of vascular complications. This is the most common MODY subtype and accounts for 50-65% of all cases. These patients are very sensitive to the action of sulfonylureas and can usually be treated with relatively low doses of these oral agents, at least in the early stages of the disease. In children, this form of MODY is sometimes misclassified as T1DM and treated with insulin. Evaluation of autoimmune markers will rule out T1DM, and genetic testing for this form of MODY is now available and is indicated in patients with relatively mild diabetes and a family history suggestive of autosomal dominant inheritance. On the other hand, even patients with relatively mild and gradual onset of diabetes may have T1DM, and in the absence of a family history suggestive of autosomal dominant inheritance, the diagnosis of MODY is not warranted. Accurate diagnosis can lead to avoidance of unnecessary insulin treatment and specific genetic counseling.

Hepatocyte nuclear factor-4α (MODY1), insulin promoter factor (IPF)-1, also known as (PDX-1) (MODY4), hepatocyte nuclear factor 1β/TCF2 (MODY5), and NeuroD1 (MODY6) are all transcription factors that are involved in β-cell development and function and mutations in these lead to various rare forms of MODY. In addition to diabetes they can also have specific findings unrelated to hyperglycemia; for example, MODY1 is associated with low triglyceride and lipoprotein levels and MODY5 is associated with renal cysts and renal dysfunction. In terms of treatment, MODY1 and MODY4 may respond to oral sulfonylureas, but MODY5 does not respond to oral agents and requires treatment with insulin. NeuroD1 defects are extremely rare and not much is known about their natural history.

Primary or secondary defects in the glucose transporter-2, which is an insulin-independent glucose transporter, may also be associated with diabetes. Diabetes may also be a manifestation of a polymorphism in the glycogen synthase gene. This enzyme is crucially important for storage of glucose as glycogen in muscle. Patients with this defect are notable for marked insulin resistance and hypertension, as well as a strong family history of diabetes.

Mitochondrial Gene Defects

Maternally Inherited Diabetes and Deafness. Point mutations in mitochondrial DNA are sometimes associated with maternally inherited DM and deafness. The most common mitochondrial DNA mutation in these cases is the point mutation m.3243A>G in the transfer RNA leucine gene. This mutation is identical to the

Table 589-16 Summary of MODY Types and Special Clinical Characteristics

	GENE MUTATED	FUNCTION	SPECIAL FEATURE
MODY1	*HNF4α*	Transcription factor	Decreased levels of triglycerides, apolipoproteins AII and CIII (5-10% of MODY), neonatal hypoglycemia, very sensitive to sulfonylureas
MODY2	Glucokinase *(GCK)*	Enzyme, glucose sensor	Hyperglycemia of early onset but mild and nonprogressive; common (30-70% MODY)
MODY3	*HNF1α*	Transcription factor	Decreased renal absorption of glucose and consequent glycosuria; common (30-70% of cases of MODY); very sensitive to sulfonylureas
MODY4	*IPF-1*	Necessary for pancreatic development	Homozygous mutation causes pancreatic agenesis
MODY5	*HNF1β*	Transcription factor	Renal malformations; associated with uterine abnormalities, hypospadias, joint laxity, and learning difficulties, pancreatic atrophy, pancreatic exocrine insufficiency; 5-10% of MODY
MODY6	*NEUROD1*	Differentiation factor in the development of pancreatic islets	Extremely rare
MODY7	*KFL11*	Zinc finger transcription factor	Early-onset type II diabetes mellitus
MODY8	*CEL*	Bile salt–dependent lipase	Hyperglycemia; fecal elastase deficiency; exocrine pancreatic atrophy
MODY9	*PAX4*	Transcription factor	
MODY10	*INS*	Insulin gene	Usually associated with neonatal diabetes
MODY11	*BLK*	B-lymphocyte tyrosine kinase	Early-onset T1DM without autoantibodies

MODY, maturity-onset diabetes of the young.
From Nakhla M, Polychronakos C: Monogenic and other unusual causes of diabetes mellitus, Pediatr Clin North Am *52:1637–1650, 2005.*

Table 589-17 Clinical and Biochemical Features Associated with Type 1 Diabetes, Type 2 Diabetes and the Common Subtypes of Maturity-Onset Diabetes of the Young

FEATURES	TYPE 1 DIABETES	TYPE 2 DIABETES	GCK-MODY	HNF1A/4A-MODY
Typical age of diagnosis (yr)	10-30	>25	Present from birth; presents at any age	15-45
Diabetic ketoacidosis	Common	Rare	Rare	Rare
Insulin dependent	Yes	No	No	No
Parental history of diabetes	<15%	>50% in young onset type 2 diabetes	If tested, 1 parent usually has impaired fasting glycemia (may not be previously known)	60-90%*
Obesity	Uncommon	Common	Uncommon	Uncommon
Insulin resistance	Uncommon	Common	Uncommon	Uncommon
Presence of β-cell antibodies	>90%	Negative	Rare	Rare
C-peptide concentrations	Undetectable/low	Normal/high	Normal	Normal
Optimal first-line treatment	Insulin	Metformin	None	Sulfonylurea

*Family history is often part of the criteria for testing. Some reports cite a parental history of 60-70%.
GCK, glucokinase; HNF1A/4A, hepatocyte nuclear factor 1α/4α; MODY, maturity-onset diabetes of the young.
From Thanabalasingham G, Owen KR: Diagnosis and management of maturity onset diabetes of the young (MODY), BMJ *343:d6044, 2011, Table 2, p. 838.*

mutation in MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome), but this syndrome is not associated with diabetes; the phenotypic expression of the same defect varies. Diabetes in most of these cases presents insidiously but approximately 20% of patients have an acute presentation resembling T1DM. The mean age of diagnosis of diabetes is 37 yr but cases have been reported as young as 11 yr. This mutation has been estimated to be present in 1.5% of Japanese diabetics, which may be higher than the prevalence in other ethnic groups. Metformin should be avoided in these patients because of the theoretical risk of severe lactic acidosis in the presence of mitochondrial dysfunction.

Another form of IDDM, sometimes associated with mitochondrial mutations, is the **Wolfram syndrome**. **Wolfram syndrome 1** is characterized by diabetes insipidus, DM, optic atrophy, and deafness—thus, the acronym DIDMOAD. Some patients with diabetes appear to have severe insulinopenia, whereas others have significant insulin secretion as judged by C-peptide. The overall prevalence is 1 in 770,000 live births. The sequence of appearance of the stigmata is as follows: nonautoimmune IDDM in the 1st decade, central diabetes insipidus and sensorineural deafness in two thirds to three fourths of the patients in the 2nd decade, renal tract anomalies in about one half of the patients in the 3rd decade, and neurologic complications such as cerebellar ataxia and myoclonus in one half to two thirds of the patients in the 4th decade. Other features include primary gonadal atrophy in the majority of males and a progressive neurodegenerative course with neurorespiratory death at a median age of 30 yr. Some (but not all) cases are caused by mutations in the *WFS-1* (wolframin) gene on chromosome 4p. **Wolfram syndrome 2** has early-onset optic atrophy, DM, deafness, and a shortened life span but no diabetes insipidus; the associated gene is *CISD2*.

DIABETES MELLITUS OF THE NEWBORN

Neonatal DM is exceedingly rare. Onset of classic autoimmune T1DM before the age of 6 mo is most unusual and most cases of diabetes in this age range are caused by genetic mutations.

Transient Neonatal Diabetes Mellitus

Neonatal diabetes is transient in approximately 50% of cases, but after an interim period of normal glucose tolerance, 50-60% of these patients develop permanent diabetes (at an average age of 14 yr). There are also reports of patients with classic T1DM who formerly had transient diabetes of the newborn. It remains to be determined whether this association of transient diabetes in the newborn followed much later in life by classic T1DM is a chance occurrence or causally related.

The syndrome of transient DM in the newborn infant has its onset in the 1st wk of life and persists several weeks to months before spontaneous resolution. Median duration is 12 wk. It occurs most often in infants who are small for gestational age and is characterized by hyperglycemia and pronounced glycosuria, resulting in severe dehydration and, at times, metabolic acidosis, but with only minimal or no ketonemia or ketonuria. There may also be findings such as umbilical hernia or large tongue. Insulin responses to glucose or tolbutamide are low to absent; basal plasma insulin concentrations are normal. After spontaneous recovery, the insulin responses to these same stimuli are brisk and normal, implying a functional delay in β-cell maturation with spontaneous resolution. Occurrence of the syndrome in consecutive siblings has been reported. About 70% of cases are due to a**bnormalities of an imprinted locus on chromosome 6q24,** resulting in overexpression of paternally expressed genes such as pleomorphic adenoma gene–like 1 (PLAGL1/ZAC) and hydatidiform mole associated and imprinted (HYMAI). Most of the remaining cases are caused by mutations in K_{ATP} channels. Mutations in K_{ATP} channels also cause many cases of permanent neonatal diabetes, but there is practically no overlap between the mutations that lead to transient neonatal DM and those causing permanent neonatal DM. This syndrome of transient neonatal DM should be distinguished from the severe hyperglycemia that may occur in hypertonic dehydration; that usually occurs in infants beyond the newborn period and responds promptly to rehydration with minimal or no requirement for insulin.

Administration of insulin is mandatory during the active phase of DM in the newborn. One to 2 units/kg/24 hr of an intermediate-acting insulin in 2 divided doses usually results in dramatic improvement and accelerated growth and gain in weight. Attempts at gradually reducing the dose of insulin may be made as soon as recurrent hypoglycemia becomes manifested or after 2 mo of age. Genetic testing is now available for 6q24 abnormalities as well as potassium channel defects and should be obtained on all patients and recurrence risk assessment by a genetic counselor is recommended.

Permanent Neonatal Diabetes Mellitus

Permanent DM in the newborn period is caused in approximately 50% of the cases by mutations in the *KCNJ11* (potassium inwardly-rectifying channel J, member 11) and *ABCC8* (adenosine triphosphate–binding cassette, subfamily C, member 8) genes. These genes code for the Kir6.2 and SUR1 subunits of the adenosine triphosphate–sensitive potassium channel, which is involved in an essential step in insulin secretion by the β cell. Some cases are caused by pancreatic agenesis as a result of homozygous mutations in the *IPF-1* gene (where heterozygous mutations cause MODY4); homozygous mutations in the glucokinase gene (where heterozygous mutations cause MODY2); and mutations in the insulin gene. Almost all these infants are small at birth because of the role of insulin as an intrauterine growth factor. Instances of affected twins and families with more than 1 affected infant have been reported. Infants with permanent neonatal DM may be initially euglycemic and typically present between birth and 6 mo of life (mean age of presentation is 5 wk). There is a spectrum of severity and up to 20% have neurologic features. The most severely affected patients have the syndrome of *d*evelopmental delay, *e*pilepsy and *n*eonatal *d*iabetes (DEND syndrome). Less-severe forms of DEND are labeled intermediate DEND or i-DEND.

Activating mutations in the *KCNJ11* gene (encoding the adenosine triphosphate–sensitive potassium channel subunit Kir6.2) are associated with both transient neonatal DM and permanent neonatal DM, with particular mutations being associated with each phenotype. More than 90% of these patients respond to sulfonylureas (at higher doses than those used in T2DM), but patients with severe neurologic disease may be less responsive. Mutations in the *ABCC8* gene (encoding the SUR1 subunit of this potassium channel) were thought to be less likely to respond to sulfonylureas (because this is the subunit that binds sulfonylurea drugs), but some of these mutations are reported to respond and patients have been successfully switched from insulin to oral therapy. Several protocols for switching the patient from insulin to glibenclamide are available and patients are usually stabilized on doses ranging from 0.4-1 mg/kg/day. Because approximately 50% of neonatal diabetics have K-channel mutations that can be switched to sulfonylurea therapy, with dramatic improvement in glycemic control and quality of life, *all* patients with diabetes diagnosed before 6 mo of age (and perhaps even those diagnosed before 12 mo of age) should now be screened for these mutations by genetic testing.

IPEX Syndrome

IPEX means immunodysregulation, polyendocrinopathy, and enteropathy, X-linked. In most patients with IPEX, mutations in the *FOXP3* (Forkhead box P3) gene, a specific marker of natural and adaptive regulatory T cells, leads to severe immune dysregulation and rampant autoimmunity. Autoimmune diabetes develops in >90% of cases, usually within the 1st few wk of life and is accompanied by enteropathy, failure to thrive, and other autoimmune disorders (see Chapter 126.5).

Abnormalities of the Insulin Gene

Diabetes of variable degrees may also result from defects in the insulin gene that lead to various amino acid substitutions that impair the effectiveness of insulin at the receptor level. Insulin gene defects are exceedingly rare and may be associated with relatively mild diabetes or even normal glucose tolerance. Diabetes may also develop in patients with faulty processing of proinsulin to insulin (an autosomal dominant defect). These defects are notable for the high concentration of insulin as measured by radioimmunoassay, whereas MODY and glucose transporter-2 defects are characterized by relative or absolute deficiency of insulin secretion for the prevailing glucose concentrations.

GENETIC DEFECTS OF INSULIN ACTION

Various genetic mutations in the insulin receptor can impair the action of insulin at the insulin receptor or impair postreceptor signaling, leading to insulin resistance.

The mildest form of the syndrome with mutations in the insulin receptor was previously known as *type A insulin resistance*. This is associated with hirsutism, hyperandrogenism, and cystic ovaries in females, without obesity. Acanthosis nigricans may be present and life expectancy is not significantly impaired. More-severe forms of insulin resistance are seen in 2 mutations in the insulin receptor gene that cause the pediatric syndromes of Donohue syndrome (formerly called leprechaunism) and Rabson-Mendenhall syndrome.

Donohue Syndrome

This is a syndrome characterized by intrauterine growth restriction, fasting hypoglycemia, and postprandial hyperglycemia in association with profound resistance to insulin; severe hyperinsulinemia is seen compared to age-matched infants during an oral glucose tolerance test. Various defects of the insulin receptor have been described, thereby attesting to the important role of insulin and its receptor in fetal growth and possibly in morphogenesis. Most of these patients die in the 1st yr of life.

Rabson-Mendenhall Syndrome

This entity is defined by clinical manifestations that appear to be intermediate between those of acanthosis nigricans with insulin resistance type A and Donohue syndrome. The features include extreme insulin

Table 589-18 Clinical and Biochemical Features of Inherited Lipodystrophies

	CONGENITAL GENERALIZED LIPODYSTROPHY		FAMILIAL PARTIAL LIPODYSTROPHY	
Subtype	**BSCL1**	**BSCL2**	**FPLD2**	**FPLD3**
Defective gene	*AGPAT2*	*BSCL2*	*LMNA*	*PPARG*
Clinical onset	Soon after birth	Soon after birth	Puberty	Usually puberty, but may present in younger children
Fat distribution	Generalized absence	Generalized absence	Loss of limb and gluteal fat; typically excess facial and nuchal fat; trunk fat often lost	Loss of limb and gluteal fat; preserved facial and trunk fat
Cutaneous features	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women
Musculoskeletal	Acromegaloid features common	Acromegaloid features common	Frequent muscle hypertrophy; some have overlap features of muscular dystrophy	Nil specific
Nonalcoholic fatty liver disease	Severe	Severe	Yes	Yes
Dyslipidemia	Severe associated with pancreatitis	Severe associated with pancreatitis	Yes, may be severe	Yes, may be severe
Insulin resistance	Severe early onset	Severe early onset	Severe	Severe; early onset in some
Diabetes onset	<20 yr	<20 yr	Variable; generally later in men than women	Variable; generally later in men than women
Hypertension	Common	Common	Common	Very common
Other		Mild mental retardation possible		

From Semple RK, Savage DB, Halsall DJ, O'Rahilly S: Syndromes of severe insulin resistance and/or lipodystrophy. In Weiss RE, Refetoff S, editors: Genetic diagnosis of endocrine disorders, *Philadelphia, 2010, Elsevier, Table 4.2.*

resistance, acanthosis nigricans, abnormalities of the teeth and nails, and pineal hyperplasia. It is not clear whether this syndrome is entirely distinct from Donohue syndrome; however, by comparison, patients with Rabson-Mendenhall tend to live significantly longer. Therapies with modest benefit have included insulin-like growth factor-1 and leptin.

Lipoatrophic Diabetes

Various forms of lipodystrophy are associated with insulin resistance and diabetes (Table 589-18). Familial partial lipoatrophy is associated with mutations in the *LMNA* gene, encoding nuclear envelope proteins lamin A and C. Severe generalized lipoatrophy is associated with mutations in the seipin and *AGPAT2* genes, but the mechanism by which these mutations lead to insulin resistance and diabetes is not known.

Stiff-Person Syndrome

This is an extremely rare autoimmune central nervous system disorder that is characterized by progressive stiffness and painful spasms of the axial muscles and very high titers of glutamic acid decarboxylase antibodies. About one third of the patients also develop T1DM.

Systemic Lupus Erythematosus

In rare cases, patients with systemic lupus erythematosus may develop autoantibodies to the insulin receptor, leading to insulin resistance and diabetes.

CYSTIC FIBROSIS–RELATED DIABETES

See Chapter 403.

As patients with cystic fibrosis (CF) live longer, an increasing number are being diagnosed with cystic fibrosis–related diabetes (CFRD). Females appear to have a somewhat higher risk of CFRD than males and prevalence increases with increasing age until age 40 yr (there is a decline in prevalence after that, presumably because only the healthiest CF patients survive beyond that age). There is an association with pancreatic insufficiency and there may be a higher risk in patients with class I and class II CF transmembrane conductance regulator mutations. A large multicenter study in the United States reported prevalence (in all ages) of 17% in females and 12% in males. Cross-sectional studies indicate that the prevalence of IGT may be significantly higher than this and up to 65% of children with CF have diminished 1st phase insulin secretion, even when they have normal glucose tolerance. In Denmark, oral glucose tolerance screening of the entire CF population demonstrated no diabetes in patients younger than 10 yr, diabetes in 12% of patients age 10-19 yr, and diabetes in 48% of adults age 20 yr and older. At a Midwestern center where routine annual oral glucose tolerance screening is performed, only about one half of children and one fourth of adults have normal glucose tolerance.

Patients with CFRD have features of both T1DM and T2DM. In the pancreas, exocrine tissue is replaced by fibrosis and fat and many of the pancreatic islets are destroyed. The remaining islets demonstrate diminished numbers of β-, α-, and pancreatic polypeptide-secreting cells. Secretion of the islet hormones insulin, glucagon, and pancreatic polypeptide is impaired in patients with CF in response to a variety of secretagogs. This pancreatic damage leads to slowly progressive insulin deficiency, of which the earliest manifestation is an impaired 1st phase insulin response. As patients age, this response becomes progressively delayed and less robust than normal. At the same time, these patients develop insulin resistance due to chronic inflammation and the intermittent use of corticosteroids. Insulin deficiency and insulin resistance lead to a very gradual onset of IGT that eventually evolves into diabetes. In some cases, diabetes may wax and wane with disease exacerbations and the use of corticosteroids. The clinical presentation is similar to that of T2DM in that the onset of the disease is insidious and the occurrence of ketoacidosis is rare. Islet antibody titers are negative. Microvascular complications do develop but may do so at a slower rate than in typical T1DM or T2DM. Macrovascular complications do not appear to be of concern in CFRD, perhaps because of the shortened

life span of these patients. Several factors unique to CF influence the onset and the course of diabetes. For example: (1) frequent infections are associated with waxing and waning of insulin resistance; (2) energy needs are increased because of infection and pulmonary disease; (3) malabsorption is common, despite enzyme supplementation; (4) nutrient absorption is altered by abnormal intestinal transit time; (5) liver disease is frequently present; (6) anorexia and nausea are common; (7) there is a wide variation in daily food intake based on the patient's acute health status; and (8) both insulin and glucagon secretion are impaired (in contrast to autoimmune diabetes, in which only insulin secretion is affected).

Impaired glucose tolerance and CFRD are associated with poor weight gain and there is evidence that treatment with insulin improves weight gain and slows the rate of pulmonary deterioration. Because of these observations, the CF Foundation recommends routine diabetes screening of all children with CF, starting at age 12 yr. Despite debate over the ideal screening modality, the current recommendation is the 2 hr glucose tolerance test, though it is possible that simply obtaining a single 2 hr postprandial glucose value may be sufficient. When hyperglycemia develops, the accompanying metabolic derangements are usually mild, and relatively low doses of insulin usually suffice for adequate management. Basal insulin may be started initially, but basal-bolus therapy similar to that used in T1DM will eventually be needed. Dietary restrictions are minimal as increased energy needs are present and weight gain is usually desired. Ketoacidosis is very uncommon but may occur with progressive deterioration of islet cell function. Impaired glucose tolerance is not necessarily an indication for treatment, but patients who have poor growth and inadequate weight gain may benefit from the addition of basal insulin even if they do not meet the criteria for diagnosis of diabetes.

AUTOIMMUNE DISEASES

Chronic lymphocytic thyroiditis (Hashimoto thyroiditis) is frequently associated with T1DM in children (see Chapter 566). As many as 1 in 5 insulin-dependent diabetic patients have thyroid antibodies in their serum; the prevalence is 2-20 times greater than in control populations. Only a small proportion of these patients, however, acquire clinical hypothyroidism; the interval between diagnosis of diabetes and thyroid disease averages about 5 yr. Periodic palpation of the thyroid gland is indicated in all diabetic children; if the gland feels firm or enlarged, serum measurements of thyroid antibodies and TSH should be obtained. A confirmed TSH level of greater than 10 μU/mL indicates existing or incipient thyroid dysfunction that warrants replacement with thyroid hormone. Deceleration in the rate of growth may also be caused by thyroid failure and is, in itself, a reason for securing serum measurements of thyroxine and TSH concentrations.

When diabetes and thyroid disease coexist, the possibility of autoimmune adrenal insufficiency should be considered. It may be heralded by decreasing insulin requirements, increasing pigmentation of the skin and buccal mucosa, salt craving, weakness, asthenia and postural hypotension, or even frank Addisonian crisis. This syndrome is most unusual in the 1st decade of life, but it may become apparent in the 2nd decade or later.

Celiac disease, which is caused by hypersensitivity to dietary gluten, is another autoimmune disorder that occurs with significant frequency in children with T1DM (see Chapter 338.2). It is estimated that approximately 7-15% of children with T1DM develop celiac disease within the 1st 6 yr of diagnosis, and the incidence of celiac disease is significantly higher in children younger than 4 yr of age and in girls. Young children with T1DM and celiac disease usually present with gastrointestinal symptoms (abdominal cramping, diarrhea, and gastroesophageal reflux), growth failure as a consequence of suboptimal weight gain, and unexplained hypoglycemic reactions because of nutrient malabsorption, including vitamin D; adolescents may remain asymptomatic. The diagnosis of celiac disease is considered if serum tissue transglutaminase antibody titers are elevated in the presence of normal serum total IgA levels. The diagnosis is confirmed on endoscopic evaluation and biopsy of small bowel revealing characteristic atrophy of intestinal villi. Therapy consists of a gluten-free diet, which will alleviate gastrointestinal symptoms and may reduce glycemic excursions.

Circulating antibodies to gastric parietal cells and to intrinsic factor are 2-3 times more common in patients with T1DM than in control subjects. The presence of antibodies to gastric parietal cells is correlated with atrophic gastritis and antibodies to intrinsic factor are associated with malabsorption of vitamin B_{12}. However, megaloblastic anemia is rare in children with T1DM.

A variant of the multiple endocrine deficiency syndrome is characterized by T1DM, idiopathic intestinal mucosal atrophy with associated inflammation and severe malabsorption, IgA deficiency, and circulating antibodies to multiple endocrine organs including the thyroid, adrenal, pancreas, parathyroid, and gonads. In addition, nondiabetic family members have an increased frequency of vitiligo, Graves disease, and multiple sclerosis as well as low complement levels and antibodies to endocrine tissues.

ENDOCRINOPATHIES

The endocrinopathies listed in Table 589-1 are only rarely encountered as a cause of diabetes in childhood. They may accelerate the manifestations of diabetes in those with inherited or acquired defects in insulin secretion or action.

DRUGS

High-dose oral or parenteral steroid therapy usually results in significant insulin resistance leading to glucose intolerance and overt diabetes. The immunosuppressive agents cyclosporin and tacrolimus are toxic to β cells, causing IDDM in a significant proportion of patients treated with these agents. Their toxicity to pancreatic β cells was 1 of the factors that limited their usefulness in arresting ongoing autoimmune destruction of β cells. Streptozotocin and the rodenticide Vacor are also toxic to β cells, causing diabetes.

There are no consensus guidelines regarding treatment of steroid-induced hyperglycemia in children. Many patients on high-dose steroids have elevated blood glucose during the day and evening, but become normoglycemic late at night and early in the morning. In general, significant hyperglycemia in an inpatient setting is treated with short-acting insulin on an as-needed basis. Basal insulin may be added when fasting hyperglycemia is significant. Outpatient treatment can be more difficult, but when treatment is needed, protocols similar to the basal-bolus regimens used in T1DM are used.

GENETIC SYNDROMES ASSOCIATED WITH DIABETES MELLITUS

A number of rare genetic syndromes associated with IDDM or carbohydrate intolerance have been described (see Table 589-1). These syndromes represent a broad spectrum of diseases, ranging from premature cellular aging, as in the Werner and Cockayne syndromes (see Chapter 90) to excessive obesity associated with hyperinsulinism, resistance to insulin action, and carbohydrate intolerance, as in the Prader-Willi syndrome (see Chapters 80 and 81). Some of these syndromes are characterized by primary disturbances in the insulin receptor or in antibodies to the insulin receptor without any impairment in insulin secretion. Although rare, these syndromes provide unique models to understand the multiple causes of disturbed carbohydrate metabolism from defective insulin secretion or from defective insulin action at the cell receptor or postreceptor level.

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The Nervous System

PART XXVII

Chapter 590

Neurologic Evaluation

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HISTORY

A detailed history is the cornerstone of any neurologic assessment. Although parents may be the primary informants, most children older than 3-4 yr are capable of contributing to their history and should be questioned directly.

The history should begin with the chief complaint, as well as a determination of the complaint's relative significance within the context of normal development (see Chapters 9-16). The latter step is critical because a 13 mo old who cannot walk may be perfectly normal, whereas a 4 yr old who cannot walk might have a serious neurologic condition.

Next, the history of present illness should provide a chronological outline of the patient's symptoms, with attention paid to location, quality, intensity, duration, associated features, and alleviating or exacerbating factors. It is essential to perform a review of systems, because abnormalities of the central nervous system (CNS) often manifest with vague, nonfocal symptoms that may be misattributed to other organ systems (e.g., vomiting, constipation, urinary incontinence). A detailed history might suggest that vomiting is as a result of increased intracranial pressure (ICP) rather than gastritis or that constipation and urinary incontinence are caused by a spinal cord tumor rather than behavioral stool withholding. In addition, a systemic illness may produce CNS manifestations such as lupus erythematosus (seizures, psychosis, demyelination) or mitochondrial disorders (developmental delay, strokes, hypotonia).

Following the chief complaint and history of present illness, the physician should obtain a complete birth history, particularly if a congenital disorder is suspected. The birth history should begin with a review of the pregnancy, including specific questions about common complications, such as pregnancy-induced hypertension, preeclampsia, gestational diabetes, vaginal bleeding, infections, and falls. It is important to quantify any cigarette, alcohol, or drug (prescription, herbal, illicit) use. Inquiring about fetal movement might provide clues to an underlying diagnosis, because decreased or absent fetal activity can be associated with chromosomal anomalies and CNS or neuromuscular disorders. Finally, any abnormal ultrasound or amniocentesis results should be noted.

A labor history should address the gestational age at delivery and mode of delivery (spontaneous vaginal, vacuum- or forceps-assisted, cesarean section) and should comment on the presence or absence of fetal distress. If delivery was by cesarean section, it is essential to record the indication for surgery.

The birth weight, length, and head circumference provide useful information about the duration of a given problem, as well as insights into the uterine environment. Parents can usually provide a reliable history of their child's postnatal course; however, if the patient was resuscitated or had a complicated hospital stay, it is often helpful to obtain the hospital records. The physician should inquire about the infant's general well-being, feeding and sleeping patterns, activity level, and the nature of the infant's cry. If the infant had jaundice, it is important to determine both the degree of jaundice and how it was managed. Historical markers of neurologic dysfunction include full-term infants who are unable to breathe spontaneously; have poor, uncoordinated sucks; need an inordinate amount of time to feed; or require gavage feeding. Again, it is important to consider the developmental context, because all of these issues would be expected in premature infants, particularly those with a very-low birthweight. Double-checking the state newborn screening results may provide a clue to abnormal neurologic manifestation in an infant.

The most important component of a neurologic history is the **developmental assessment** (see Chapters 9-14 and 16). Careful evaluation of a child's social, cognitive, language, fine motor, and gross motor skills is required to distinguish normal development from either isolated or global (i.e., in 2 or more domains) developmental delay. An abnormality in development from birth suggests an intrauterine or perinatal cause, but a loss of skills **(regression)** over time strongly suggests an underlying degenerative disease of the CNS, such as an inborn error of metabolism. The ability of parents to recall the precise timing of their child's developmental milestones is extremely variable. It is often helpful to request old photographs of the child or to review the baby book, where the milestones may have been dutifully recorded. In general, parents are aware when their child has a developmental problem, and the physician should show appropriate concern. Table 590-1 outlines the upper limits of normal for attaining specific developmental milestones. Chapter 16 includes a comprehensive review of developmental screening tests and their interpretation.

Family history is extremely important in the neurologic evaluation of a child. Most parents are extremely cooperative in securing medical information about family members, particularly if it might have relevance for their child. The history should document the age and history of neurologic disease, including developmental delay, epilepsy, migraine, stroke, and inherited disorders, for all 1st- and 2nd-degree relatives. It is important to inquire directly about miscarriages or fetal deaths in utero and to document the sex of the embryo or fetus, as well as the gestational age at the time of demise. When available, the results of postmortem examinations should be obtained, as they can have a direct bearing on the patient's condition. The parents should be questioned about their ethnic backgrounds, because some genetic disorders occur more commonly within specific populations (e.g., Tay-Sachs disease in the Ashkenazi Jewish population). They should also be asked if there is any chance that they could be related to each other, because the incidence of metabolic and degenerative disorders of the CNS is increased significantly in children of **consanguineous** marriages.

The social history should detail the child's current living environment, as well as the child's relationship with other family members. It is important to inquire about recent stressors, such as divorce, remarriage, birth of a sibling, or death of a loved one, because they can affect the child's behavior. If the child is in daycare or school, one should document the child's academic and social performance, paying particular attention to any abrupt changes. Academic performance can be assessed by asking about the child's latest report card, and peer relationships can be evaluated by having the child name his or her "best friends." Any child who is unable to name at least 2 or 3 playmates might have abnormal social development. In some cases, discussions with the daycare worker or teacher provide useful ancillary data.

NEUROLOGIC EXAMINATION

The neurologic examination begins at the outset of the interview. Indirect observation of the child's appearance and movements can yield valuable information about the presence of an underlying disorder. For instance, it may be obvious that the child has dysmorphic facies, an

Table 590-1 Screening Scheme for Developmental Delay: Upper Range

AGE (mo)	GROSS MOTOR	FINE MOTOR	SOCIAL SKILLS	LANGUAGE
3	Supports weight on forearms	Opens hands spontaneously	Smiles appropriately	Coos, laughs
6	Sits momentarily	Transfers objects	Shows likes and dislikes	Babbles
9	Pulls to stand	Pincer grasp	Plays pat-a-cake, peek-a-boo	Imitates sounds
12	Walks with 1 hand held	Releases an object on command	Comes when called	1-2 meaningful words
18	Walks upstairs with assistance	Feeds from a spoon	Mimics actions of others	At least 6 words
24	Runs	Builds a tower of 6 blocks	Plays with others	2-3–word sentences

unusual posture, or an abnormality of motor function manifested by a hemiparesis or gait disturbance. The child's behavior while playing and interacting with his or her parents may also be telling. A normal child usually plays independently early in the visit, but then engages in the interview process. A child with attention-deficit/hyperactivity disorder might display impulsive behavior in the examining room, and a child with neurologic impairment might exhibit complete lack of awareness of the environment. Finally, note should be made of any unusual odors about the patient, because some metabolic disorders produce characteristic scents (e.g., the "musty" smell of phenylketonuria or the "sweaty feet" smell of isovaleric acidemia). If such an odor is present, it is important to determine whether it is persistent or transient, occurring only with illnesses.

The examination should be conducted in a nonthreatening, child-friendly setting. The child should be allowed to sit where the child is most comfortable, whether it be on a parent's lap or on the floor of the examination room. The physician should approach the child slowly, reserving any invasive or painful tests (e.g., measurement of head circumference, gag reflex) for the end of the examination. In the end, the more that the examination seems like a game, the more the child will cooperate. Because the neurologic examination of an infant requires a somewhat modified approach from that of an older child, the 2 groups are considered separately (see Chapters 9, 10, and 94 vs Chapters 11-14).

Mental Status

Age aside, the neurologic examination should include an assessment of the patient's mental status in terms of both level of arousal and interaction with the environment. Premature infants born at <28 wk of gestation do not have consistent periods of alertness, whereas slightly older infants arouse from sleep with gentle physical stimulation. Sleep–wake patterns are well developed at term. Because the level of alertness of a neonate depends on many factors, including the time of the last feeding, room temperature, and gestational age, serial examinations are critical when evaluating for changes in neurologic function. Older children's mental status can be assessed by watching them play. Having them tell a story, draw a picture, or complete a puzzle can also be helpful in assessing cognitive function. Memory can be evaluated informally as patients recount their personal information, as well as more formally by asking them to register and recall 3 objects or perform a digit span.

Head

Correct measurement of the **head circumference** is important. It should be performed at every visit for patients younger than 3 yr and should be recorded on a suitable head growth chart. To measure, a nondistensible plastic measuring tape is placed over the mid-forehead and extended circumferentially to include the most prominent portion of the occiput. If the patient's head circumference is abnormal, it is important to document the head circumferences of the parents and siblings. Errors in the measurement of a newborn skull are common owing to scalp edema, overriding sutures, and the presence of cephalohematomas. The average rate of head growth in a healthy premature infant is 0.5 cm in the 1st 2 wk, 0.75 cm in the 3rd wk, and 1.0 cm in the 4th wk and every week thereafter until the 40th wk of development. The head circumference of an average term infant measures 34-35 cm at birth, 44 cm at 6 mo, and 47 cm at 1 yr of age (see Chapters 9 and 10).

Figure 590-1 Congenital hydrocephalus. Note the enlarged cranium and prominent scalp veins.

If the brain is not growing, the skull will not grow; therefore, a small head frequently reflects a small brain, or **microcephaly**. Conversely, a large head may be associated with a large brain, or **macrocephaly**, which is most commonly familial but may be from a disturbance of growth, neurocutaneous disorder (e.g., neurofibromatosis), chromosomal defect (e.g., Klinefelter syndrome), or storage disorder. Alternatively, the head size may be increased secondary to hydrocephalus (Fig. 590-1) or chronic subdural hemorrhages. In the latter case, the skull tends to assume a square or box-like shape, because the long-standing presence of fluid in the subdural space causes enlargement of the middle fossa.

The shape of the head should be documented carefully. Plagiocephaly, or flattening of the skull, can be seen in normal infants but may be particularly prominent in hypotonic or weak infants, who are less mobile. A variety of abnormal head shapes can be seen when cranial sutures fuse prematurely, as in the various forms of inherited **craniosynostosis** (see Chapter 591.12).

An infant has 2 **fontanels** at birth: a diamond-shaped anterior fontanel at the junction of the frontal and parietal bones that is open at birth, and a triangular posterior fontanel at the junction of the parietal and occipital bones that can admit the tip of a finger or may be closed at birth. If the posterior fontanel is open at birth, it should close over the ensuing 6-8 wk; its persistence suggests underlying hydrocephalus or congenital hypothyroidism. The anterior fontanel varies greatly in size, but it usually measures approximately 2×2 cm. The average time of closure is 18 mo, but the fontanel can close normally as early as 9 mo. A very small or absent anterior fontanel at birth might indicate craniosynostosis or microcephaly, whereas a very large fontanel can

signify a variety of problems. The fontanel is normally slightly depressed and pulsatile and is best evaluated by holding the infant upright while the infant is asleep or feeding. A bulging fontanel is a potential indicator of increased ICP, but vigorous crying can cause a protuberant fontanel in a normal infant.

Inspection of the head should include observation of the venous pattern, because increased ICP and thrombosis of the superior sagittal sinus can produce marked venous distention. Dysmorphic facial features can indicate a neurodevelopmental aberration. Likewise, cutaneous abnormalities, such as cutis aplasia or abnormal hair whorls, can suggest an underlying brain malformation or genetic disorder.

Palpation of a newborn's skull characteristically reveals **molding** of the skull accompanied by **overriding sutures**—a result of the pressures exerted on the skull during its descent through the pelvis. Marked overriding of the sutures beyond the early neonatal period is cause for alarm, because it suggests an underlying brain abnormality. Palpation additionally might reveal bony bridges between sutures **(craniosynostosis),** cranial defects, or, in premature infants, softening of the parietal bones **(craniotabes).**

Auscultation of the skull is an important adjunct to the neurologic examination. **Cranial bruits** may be noted over the anterior fontanel, temporal region, or orbits, and are best heard using the diaphragm of the stethoscope. Soft symmetric bruits may be discovered in normal children younger than 4 yr of age or in association with a febrile illness. Demonstration of a loud or localized bruit is usually significant and warrants further investigation, because they may be associated with severe anemia, increased ICP, or arteriovenous malformations of the middle cerebral artery or vein of Galen. It is important to exclude murmurs arising from the heart or great vessels, because they may be transmitted to the cranium.

Cranial Nerves

Olfactory Nerve (Cranial Nerve I)

Anosmia, loss of smell, most commonly occurs as a transient abnormality in association with an upper respiratory tract infection or allergies. Permanent causes of anosmia include head trauma with damage to the ethmoid bone or shearing of the olfactory nerve fibers as they cross the cribriform plate, tumors of the frontal lobe, intranasal drug use, and exposure to toxins (acrylates, methacrylates, cadmium). Occasionally, a child who recovers from purulent meningitis or develops hydrocephalus has a diminished sense of smell. Rarely, anosmia is congenital, in which case it can occur as an isolated deficit or as part of Kallmann syndrome, a familial disorder characterized by hypogonadotropic hypogonadism and congenital anosmia. Although not a routine component of the examination, smell can be tested reliably as early as the 32nd wk of gestation by presenting a stimulus and observing for an alerting response, withdrawal, or both. Care should be taken to use appropriate stimuli, such as coffee or peppermint, as opposed to strongly aromatic substances (e.g., ammonia inhalants) that stimulate the trigeminal nerve. Each nostril should be tested individually by pinching shut the opposite side.

Optic Nerve (Cranial Nerve II)

Assessment of the optic disc and retina is a critical component of the neurologic examination. Although the retina is best visualized by dilating the pupil, most physicians do not have ready access to mydriatic agents at the bedside; therefore, it may be necessary to consult an ophthalmologist in some cases. Mydriatics should not be administered to patients whose pupillary responses are being followed as a marker for impending herniation or to patients with cataracts. When mydriatics are used, both eyes should be dilated, because unilateral papillary fixation and dilation can cause confusion and worry in later examiners unaware of the pharmacologic intervention. Examination of an infant's retina may be facilitated by providing a nipple or soother and by turning the head to one side. The physician gently strokes the patient to maintain arousal, while examining the closer eye. An older child should be placed in the parent's lap and should be distracted by bright objects or toys. The color of the optic nerve is salmon-pink in a child but may be gray-white in a newborn, particularly if the newborn has fair coloring. This normal finding can cause confusion and can lead to the improper diagnosis of optic atrophy.

Disc edema refers to swelling of the optic disc, and **papilledema** specifically refers to swelling that is secondary to increased ICP. Papilledema rarely occurs in infancy because the skull sutures can separate to accommodate the expanding brain. In older children, papilledema may be graded according to the Frisen scale (Fig. 590-2). Disc edema must be differentiated from **papillitis**, or inflammation of the optic nerve. Both conditions manifest with enlargement of the blind spot, but visual acuity and color vision tend to be spared in early papilledema in contrast to what occurs in optic neuritis.

Retinal hemorrhages occur in 30-40% of all full-term newborn infants. The hemorrhages are more common after vaginal delivery than after Cesarean section and are not associated with birth injury or with neurologic complications. They disappear spontaneously by 1-2 wk of age. The presence of retinal hemorrhages beyond the early neonatal period should raise a concern for nonaccidental trauma.

Vision

At 28 wk of corrected gestational age, a premature infant blinks in response to a bright light, and at 32 wk, the infant maintains eye closure until the light source is removed. A normal 37 wk infant turns the head and eyes toward a soft light, and a term infant is able to fix on and follow a target, such as the examiner's face. **Optokinetic nystagmus** (OKN), which is conjugate nystagmus that occurs during attempted fixation on a series of rapidly moving objects, can also be used as a crude assessment of the visual system in infants. OKN is elicited by moving an OKN tape—usually a strip of material with alternating 2-inch black and white strips—across the patient's visual field. Although OKN responses can be tested monocularly in neonates, they do not become symmetric until 4-6 mo of age.

Visual fields can be tested in an infant or young child by advancing a brightly colored object from behind the patient's head into the peripheral visual field and noting when the patient first looks at the object. Suspension of the object by a string prevents the patient from focusing on the examiner's hand and arm. The examiner should be certain that the patient is responding to seeing, not hearing, the object.

Visual acuity in term infants approximates 20/150 and reaches the adult level of 20/20 by about 6 mo of age. Children who are too young to read the standard letters on a Snellen eye chart may learn the "E game," which entails pointing to indicate the direction that the E is facing. Children as young as 2.5-3 yr of age can identify the objects on a pediatric eye chart (Allen chart) at a distance of 15-20 ft.

The pupil reacts to light by 29-32 wk of corrected gestational age; however, the pupillary response is often difficult to evaluate, because premature infants resist eye opening and have poorly pigmented irises. Pupillary size, symmetry, and reactivity may be affected by drugs, space-occupying brain lesions, metabolic disorders, and abnormalities of the optic nerves and midbrain. A small pupil may be seen as part of the **Horner syndrome**—characterized by ipsilateral **ptosis** (droopy eyelid), **miosis** (constricted pupil), and **anhidrosis** (lack of sweating) of the face. Horner syndrome may be congenital or may be caused by a lesion of the sympathetic pathway in the hypothalamus, brainstem, cervical spinal cord, or sympathetic plexus. Localization of the lesion within the sympathetic nervous system may be obvious given the other signs present or may be uncertain. In the latter case, serial testing with cocaine drops followed by hydroxyamphetamine drops may be helpful.

During the examination of the pupil, any abnormalities of the iris should also be noted (e.g., heterochromia, Brushfield spots). The physician should also assess the posterior segment of the eye using the **red reflex** test, which is performed in a darkened room using a direct ophthalmoscope held close to the examiner's eye and 12-18 inches from the infant's eyes. If the posterior segment of the eye is normal, the examiner should see symmetric reddish-pink retinal reflections. The absence of any red reflex or the presence of a blunted reflex, white reflex (**leukocoria**), or red reflex with dark spots all signal pathology and should prompt referral to an ophthalmologist.

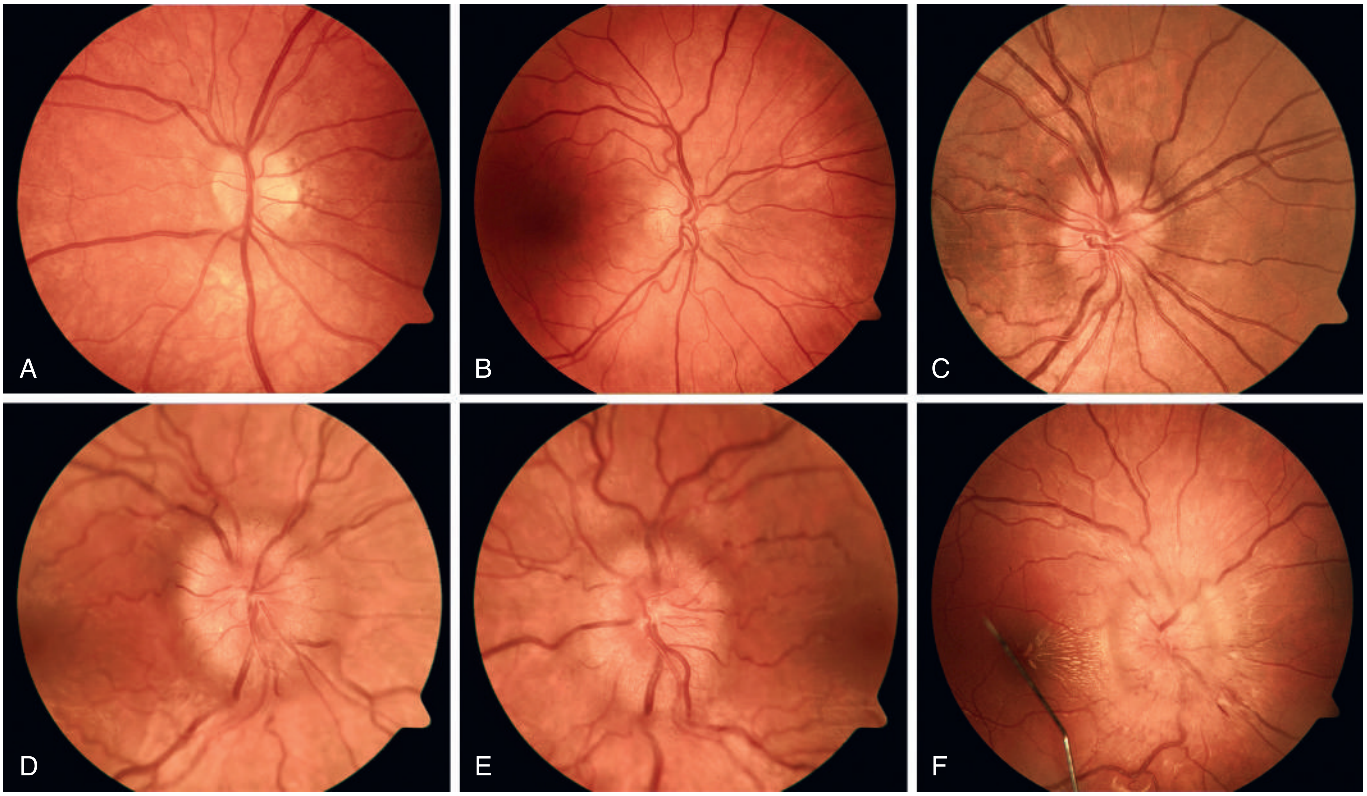

Figure 590-2 Stages of papilledema (Frisen scale). **A,** Stage 0: Normal optic disc. **B,** Stage 1: Very early papilledema with obscuration of the nasal border of the disc only, without elevation of the disc borders. **C,** Stage 2: Early papilledema showing obscuration of all borders, elevation of the nasal border, and a complete peripapillary halo. **D,** Stage 3: Moderate papilledema with elevation of all borders, increased diameter of the optic nerve head, obscuration of vessels at the disc margin, and a peripapillary halo with finger-like extensions. **E,** Stage 4: Marked papilledema characterized by elevation of the entire nerve head and total obscuration a segment of a major blood vessel on the disc. **F,** Stage 5: Severe papilledema with obscuration of all vessels and obliteration of the optic cup. Note also the nerve fiber layer hemorrhages and macular exudate. *(**A-C** courtesy Dr. Deborah Friedman; **D-F** courtesy Flaum Eye Institute, University of Rochester.)*

Oculomotor (Cranial Nerve III), Trochlear (Cranial Nerve IV), and Abducens Nerves (Cranial Nerve VI)

The globe is moved by 6 extraocular muscles, which are innervated by the oculomotor, trochlear, and abducens nerves. These muscles and nerves can be assessed by having the patient follow an interesting toy or the examiner's finger in the 6 cardinal directions of gaze. The physician observes the range and nature (conjugate vs dysconjugate, smooth vs choppy or saccadic) of the eye movements, particularly noting the presence and direction of any abnormal eye movements. Premature infants older than 25 wk of gestational age and comatose patients can be evaluated using the oculocephalic (doll's eye) maneuver, in which the patient's head is quickly rotated to evoke reflex eye movements. If the brainstem is intact, rotating the patient's head to the right causes the eyes to move to the left and vice versa. Similarly, rapid flexion and extension of the head elicits vertical eye movement.

Disconjugate gaze can result from extraocular muscle weakness; cranial nerve (CN) III, IV, or VI palsies; or brainstem lesions that disrupt the medial longitudinal fasciculus. Infants who are younger than 2 mo old can have slightly disconjugate gaze at rest, with 1 eye horizontally displaced from the other by 1 or 2 mm **(strabismus)**. Vertical displacement of the eyes requires investigation, as it can indicate trochlear nerve (CN IV) palsy or **skew deviation** (supranuclear ocular malalignment that is often associated with lesions of the posterior fossa). Strabismus is discussed further in Chapter 623.

The oculomotor nerve innervates the superior, inferior, and medial recti, as well as the inferior oblique and the levator palpebrae superioris muscles. Complete paralysis of the oculomotor nerve causes ptosis, dilation of the pupil, displacement of the eye outward and downward, and impairment of adduction and elevation. The trochlear nerve supplies the superior oblique muscle, which depresses and intorts the globe during activities such as reading and walking downstairs. Patients with an isolated paralysis of the trochlear nerve often have a compensatory head tilt away from the affected side, which helps to alleviate their diplopia. The abducens nerve innervates the lateral rectus muscle; its paralysis causes medial deviation of the eye with an inability to abduct beyond the midline. Patients with increased ICP often respond positively when questioned about double vision (**diplopia**) and exhibit incomplete abduction of the eyes on lateral gaze as a result of partial VIth nerve palsies. This false-localizing sign occurs because CN VI has a long intracranial course, making it particularly susceptible to being stretched. **Internuclear ophthalmoplegia,** caused by a lesion in the medial longitudinal fasciculus of the brainstem, that functionally serves conjugate gaze by connecting CN VI on one side to CN III on the other, results in paralysis of medial rectus function in the adducting eye and nystagmus in the abducting eye.

When there is a subtle eye movement abnormality, the **red glass test** may be helpful in localizing the lesion. To perform this test, a red glass is placed over one of the patient's eyes and the patient is instructed to follow a white light in all directions of gaze. The child sees 1 red/white light in the direction of normal muscle function but notes a separation of the red and white images that is greatest in the plane of action of the affected muscle.

In addition to gaze palsies, the examiner might encounter a variety of adventitious movements. **Nystagmus** is an involuntary, rapid movement of the eye that may be subclassified as being **pendular**, in which the 2 phases have equal amplitude and velocity, or **jerk**, in which there is a fast and slow phase. Jerk nystagmus can be further characterized by the direction of its fast phase, which may be left-, right-, up-, or downbeating; rotatory; or mixed. Many patients have a few beats of nystagmus with extreme lateral gaze **(end-gaze nystagmus),** which is

of no consequence. Pathologic horizontal nystagmus is most often congenital, drug-induced (e.g., alcohol, anticonvulsants), or a result of vestibular system dysfunction. By contrast, vertical nystagmus is often associated with structural abnormalities of the brainstem and cerebellum. **Ocular bobbing** is characterized by a downward jerk followed by a slow drift back to primary position and is associated with pontine lesions. **Opsoclonus** describes involuntary, chaotic oscillations of the eyes, which are often seen in the setting of neuroblastoma or viral infection.

Trigeminal Nerve (Cranial Nerve V)

The 3 divisions of the trigeminal nerve—ophthalmic, maxillary, and mandibular—convey information about facial protopathic (pain, temperature) and epicritic (vibration, proprioception) sensation. Each modality should be tested and compared to the contralateral side. In patients who are uncooperative or comatose, the integrity of the trigeminal nerve can be assessed by the corneal reflex, elicited by touching the cornea with a small pledget of cotton and observing for symmetric eye closure, and nasal tickle, obtained by stimulating the nasal passage with a cotton swab and observing for symmetric grimace. An absent reflex may be because of a sensory defect (trigeminal nerve) or a motor deficit (facial nerve). The motor division of the trigeminal nerve can be tested by examining the masseter, pterygoid, and temporalis muscles during mastication, as well as by evaluation of the jaw jerk.

Facial Nerve (Cranial Nerve VII)

The facial nerve is a predominantly motor nerve that innervates the muscles of facial expression, buccinator, platysma, stapedius, stylohyoid, and posterior belly of the digastric. It also has a separate division, called the chorda tympani, that contains sensory, special sensory (taste), and parasympathetic fibers. Because the portion of the facial nucleus that innervates the upper face receives bilateral cortical input, lesions of the motor cortex or corticobulbar tract have little effect on upper face strength. Rather, such lesions manifest with flattening of the contralateral nasolabial fold or drooping of the corner of the mouth. Conversely, lower motor neuron or facial nerve lesions tend to involve upper and lower facial muscles equally. Facial strength can be evaluated by observing the patient's spontaneous movements and by asking the patient to mimic a series of facial movements (e.g., smiling, raising the eyebrows, inflating the cheeks). A facial nerve palsy may be congenital; idiopathic (**Bell palsy**); or secondary to trauma, demyelination (Guillain-Barré syndrome), infection (Lyme disease, herpes simplex virus, HIV), granulomatous disease, neoplasm, or meningeal inflammation or infiltration. Facial nerve lesions that are proximal to the junction with the chorda tympani will result in an inability to taste substances with the anterior two-thirds of the tongue. If necessary, taste can be tested by placing a solution of saline or glucose on 1 side of the extended tongue. Normal children can identify the test substance in <10 sec. Other findings that may be associated with facial nerve palsy include hyperacusis, resulting from stapedius muscle involvement, and impaired tearing.

Vestibulocochlear Nerve (Cranial Nerve VIII)

The vestibulocochlear nerve has 2 components within a single trunk: the vestibular nerve, which innervates the semicircular canals of the inner ear and is involved with equilibrium, coordination, and orientation in space, and the cochlear nerve, which innervates the cochlea and subserves hearing.

Dysfunction of the vestibular system results in **vertigo**, the sensation of environmental motion. On examination, patients with vestibular nerve dysfunction typically have nystagmus, in which the fast component is directed away from the affected nerve. With their arms outstretched and eyes closed, their limbs tend to drift toward the injured side. Likewise, if they march in place, they slowly pivot toward the lesion (**Fukuda stepping test**). On Romberg and tandem gait testing, they tend to fall toward the abnormal ear. Vestibular function can be further evaluated with **caloric testing**. Before testing, the tympanic membrane should be visualized to ensure that it is intact and unobstructed. In an obtunded or comatose patient, 30-50 mL of ice water is then delivered by syringe into the external auditory canal with the patient's head elevated 30 degrees. If the brainstem is intact, the eyes deviate toward the irrigated side. A much smaller quantity of ice water (2 mL) is used in awake, alert patients to avoid inducing nausea. In normal subjects, introduction of ice water produces eye deviation toward the stimulated labyrinth followed by nystagmus with the fast component away from the stimulated labyrinth.

Because hearing is integral to normal language development, the physician should inquire directly about hearing problems. Parents' concern is often a reliable indicator of hearing impairment and warrants a formal audiologic assessment with either audiometry or brainstem auditory evoked potential testing (see Chapter 637). Even in the absence of parents' concern, certain children warrant formal testing within the 1st mo of life, including those with a family history of early life or syndromic deafness or a personal history of prematurity, severe asphyxia, exposure to ototoxic drugs, hyperbilirubinemia, congenital anomalies of the head or neck, bacterial meningitis, and congenital TORCH (*t*oxoplasmosis, *o*ther infections, *r*ubella, *c*ytomegalovirus, *h*erpes simplex virus) infections. For all other infants and children, a simple bedside assessment of hearing is usually sufficient. Newborns might have subtle responses to auditory stimuli, such as changes in breathing, cessation of movement, or opening of the eyes and/or mouth. If the same stimulus is presented repeatedly, normal neonates cease to respond, a phenomenon known as *habituation.* By 3-4 mo of age, infants begin to orient to the source of sound. Hearing-impaired toddlers are visually alert and appropriately responsive to physical stimuli but might have more frequent temper tantrums and abnormal speech and language development.

Glossopharyngeal Nerve (Cranial Nerve IX)

The glossopharyngeal nerve conveys motor fibers to the stylopharyngeus muscle; general sensory fibers from the posterior third of the tongue, pharynx, tonsil, internal surface of the tympanic membrane, and skin of the external ear; special sensory (taste) fibers from the posterior third of the tongue; parasympathetic fibers to the parotid gland; and general visceral sensory fibers from the carotid bodies. The nerve is tested by stimulating 1 side of the lateral oropharynx or soft palate with a tongue blade and observing for symmetric elevation of the palate **(gag reflex).** An isolated lesion of CN IX is rare, because it runs in close proximity to CN X. Potential causes of injury and/or dysfunction include birth trauma, ischemia, mass lesions, motor neuron disease, retropharyngeal abscess, and Guillain-Barré syndrome.

Vagus Nerve (Cranial Nerve X)

The vagus nerve has 10 terminal branches: meningeal, auricular, pharyngeal, carotid body, superior laryngeal, recurrent laryngeal, cardiac, pulmonary, esophageal, and gastrointestinal. The pharyngeal, superior laryngeal, and recurrent laryngeal branches contain motor fibers that innervate all of the muscles of the pharynx and larynx, with the exception of the stylopharyngeus (CN IX) and tensor veli palatini (CN V) muscles. Thus, unilateral injury of the vagus nerve results in weakness of the ipsilateral soft palate and a hoarse voice; bilateral lesions can produce respiratory distress as a result of vocal cord paralysis, as well as nasal regurgitation of fluids, pooling of secretions, and an immobile, low-lying soft palate. Isolated lesions to the vagus nerve may be a complication of thoracotomies or may be seen in neonates with type II Chiari malformations. If such a lesion is suspected, it is important to visualize the vocal cords. In addition to motor information, the vagus nerve carries somatic afferents from the pharynx, larynx, ear canal, external surface of the tympanic membrane, and meninges of the posterior fossa; visceral afferents; taste fibers from the posterior pharynx; and preganglionic parasympathetics.

Accessory Nerve (Cranial Nerve XI)

The accessory nerve innervates the sternocleidomastoid (SCM) and trapezius muscles. The left SCM acts to turn the head to the right side and vice versa; acting together, the SCMs flex the neck. The trapezius

acts to elevate the shoulder. Lesions to the accessory nerve result in atrophy and paralysis of the ipsilateral SCM and trapezius muscles, with resultant depression of the shoulder. Because several cervical muscles are involved in head rotation, unilateral SCM paresis might not be evident unless the patient is asked to rotate the head against resistance. Skull base fractures or lesions, motor neuron disease, myotonic dystrophy, and myasthenia gravis commonly produce atrophy and weakness of these muscles; congenital torticollis is associated with SCM hypertrophy.

Hypoglossal Nerve (Cranial Nerve XII)

The hypoglossal nerve innervates the tongue. Examination of the tongue includes assessment of its bulk and strength, as well as observation for adventitious movements. Malfunction of the hypoglossal nucleus or nerve produces atrophy, weakness, and fasciculations of the tongue. If the injury is unilateral, the tongue deviates toward the side of the injury; if it is bilateral, tongue protrusion is not possible and the patient can have difficulty swallowing (**dysphagia**). Werdnig-Hoffmann disease (infantile spinal muscular atrophy, or spinal muscular atrophy type 1) and congenital anomalies in the region of the foramen magnum are the principal causes of hypoglossal nerve dysfunction.

Motor Examination

The motor examination includes assessment of muscle bulk, tone, and strength, as well as observation for involuntary movements that might indicate central or peripheral nervous system pathology.

Bulk

Decreased muscle bulk **(atrophy)** may be secondary to disuse or to diseases of the lower motor neuron, nerve root, peripheral nerve, or muscle. In most cases, neurogenic atrophy is more severe than myogenic atrophy. Increased muscle bulk **(hypertrophy)** is usually physiologic (e.g., body builders). **Pseudohypertrophy** refers to muscle tissue that has been replaced by fat and connective tissue, giving it a bulky appearance with a paradoxical reduction in strength, as in Duchenne muscular dystrophy.

Tone

Muscle tone, which is generated by an unconscious, continuous, partial contraction of muscle, creates resistance to passive movement of a joint. Tone varies greatly based on a patient's age and state. At 28 wk of gestation, all 4 extremities are extended and there is little resistance to passive movement. Flexor tone is visible in the lower extremities at 32 wk and is palpable in the upper extremities at 36 wk; a normal-term infant's posture is characterized by flexion of all 4 extremities.

There are 3 key tests for assessing postural tone in neonates: the traction response, vertical suspension, and horizontal suspension (Fig. 590-3; see Chapters 94 and 97). To evaluate the **traction response**, the physician grasps the infant's hands and gently pulls the infant to a sitting position. Normally, the infant's head lags slightly behind the infant's body and then falls forward upon reaching the sitting position. To test **vertical suspension**, the physician holds the infant by the axillae without gripping the thorax. The infant should remain suspended with the infant's lower extremities held in flexion; a hypotonic infant will slip through the physician's hands. With **horizontal suspension**, the physician holds the infant prone by placing a hand under the infant's abdomen. The head should rise and the limbs should flex, but a hypotonic infant will drape over the physician's hand, forming a U shape. Assessing tone in the extremities is accomplished by observing the infant's resting position and passively manipulating the infant's limbs. When the upper extremity of a normal-term infant is pulled gently across the chest, the elbow does not quite reach the mid-sternum **(scarf sign),** whereas the elbow of a hypotonic infant extends beyond the midline with ease. Measurement of the **popliteal angle** is a useful method for documenting tone in the lower extremities. The examiner flexes the hip and extends the knee. Normal-term infants allow

Figure 590-3 Normal tone in a full-term neonate. **A,** Flexed resting posture. **B,** Traction response. **C,** Vertical suspension. **D,** Horizontal suspension.

extension of the knee to approximately 80 degrees. Similarly, tone can be evaluated by flexing the hip and knee to 90 degrees and then internally rotating the leg, in which case the heel should not pass the umbilicus.

Abnormalities of tone include spasticity, rigidity, and hypotonia. (Paratonia, which is rarely seen in the pediatric population, is not discussed here.) **Spasticity** is characterized by an initial resistance to passive movement, followed by a sudden release, referred to as the **clasp-knife** phenomenon. Because spasticity results from upper motor neuron dysfunction, it disproportionately affects the upper-extremity flexors and lower-extremity extensors and tends to occur in conjunction with disuse atrophy, hyperactive deep tendon reflexes, and extensor plantar reflexes **(Babinski sign).** In infants, spasticity of the lower extremities results in scissoring of the legs upon vertical suspension. Older children can present with prolonged commando crawling or toe-walking. **Rigidity,** seen with lesions of the basal ganglia, is characterized by resistance to passive movement that is equal in the flexors and extensors regardless of the velocity of movement **(lead pipe).** Patients with either spasticity or rigidity might exhibit **opisthotonos**, defined as severe hyperextension of the spine caused by hypertonia of the paraspinal muscles (Fig. 590-4), although similar posturing can be seen in patients with Sandifer syndrome (gastroesophageal reflux or hiatal hernia associated with torsional dystonia). **Hypotonia** refers to abnormally diminished tone and is the most common abnormality of tone in neurologically compromised neonates. A hypotonic infant is floppy and often assumes a frog-leg posture at rest. Hypotonia can reflect pathology of the cerebral hemispheres, cerebellum, spinal cord, anterior horn cell, peripheral nerve, neuromuscular junction, or muscle.

Figure 590-4 Opisthotonus in a brain-injured infant.

Strength

Older children are usually able to cooperate with formal strength testing, in which case muscle power is graded on a scale of 0-5 as follows: 0 = no contraction; 1 = flicker or trace of contraction; 2 = active movement with gravity eliminated; 3 = active movement against gravity; 4 = active movement against gravity and resistance; 5 = normal power. An examination of muscle power should include all muscle groups, including the neck flexors and extensors and the muscles of respiration. It is important not only to assess individual muscle groups, but also to determine the pattern of weakness (i.e., proximal vs distal; segmental vs regional). Testing for **pronator drift** can be helpful in localizing the lesion in a patient with weakness. This test is accomplished by having the patient extend his or her arms away from the body with the palms facing upward and the eyes closed. *Together, pronation and downward drift of an arm indicate a lesion of the contralateral corticospinal tract.*

Because infants and young children are not able to participate in formal strength testing, they are best assessed with functional measures. Proximal and distal strength of the upper extremities can be tested by having the child reach overhead for a toy and by watching the child manipulate small objects. In infants younger than 2 mo old, the physician can also take advantage of the palmar grasp reflex in assessing distal power and the Moro reflex in assessing proximal power. Infants with decreased strength in the lower extremities tend to have diminished spontaneous activity in their legs and are unable to support their body weight when held upright. Older children may have difficulty climbing or descending steps, jumping, or hopping. They might also use their hands to "climb up" their legs when asked to rise from a prone position, a maneuver called **Gowers sign** (Fig. 590-5).

Involuntary Movements

Patients with lower motor neuron or peripheral nervous system lesions might have **fasciculations**, which are small, involuntary muscle contractions that result from the spontaneous discharge of a single motor unit and create the illusion of a "bag of worms" under the skin. Because most infants have abundant body fat, muscle fasciculations are best observed in the tongue in this age group.

Most other involuntary movements, including tics, dystonia, chorea, and athetosis, stem from disorders of the basal ganglia. Tremor seems

Figure 590-5 A-D, Gowers sign in a boy with hip girdle weakness because of Duchenne muscular dystrophy. When asked to rise from a prone position, the patient uses his hands to walk up his legs to compensate for proximal lower-extremity weakness.

Table 590-2 Timing of Selected Primitive Reflexes

REFLEX	ONSET	FULLY DEVELOPED	DURATION
Palmar grasp	28 wk gestation	32 wk gestation	2-3 mo postnatal
Rooting	32 wk gestation	36 wk gestation	Less prominent after 1 mo postnatal
Moro	28-32 wk gestation	37 wk gestation	5-6 mo postnatal
Tonic neck	35 wk gestation	1 mo postnatal	6-7 mo postnatal
Parachute	7-8 mo postnatal	10-11 mo postnatal	Remains throughout life

to be an exception, as it is thought to be mediated by cerebellothalamocortical pathways. Further detail on the individual movement disorders is provided in Chapter 597.

Sensory Examination

The sensory examination is difficult to perform on an infant or uncooperative child and has a relatively low yield in terms of the information that it provides. A gross assessment of sensory function can be achieved by distracting the patient with an interesting toy and then touching the patient with a cotton swab in different locations. Normal infants and children indicate an awareness of the stimulus by crying, withdrawing the extremity, or pausing briefly; however, with repeated testing, they lose interest in the stimulus and begin to ignore the examiner. It is critical, therefore, that any areas of concern are tested efficiently and, if necessary, reexamined at an appropriate time.

Fortunately, isolated disorders of the sensory system are less common in the very young pediatric population than in the adult population, so detailed sensory testing is rarely warranted. Furthermore, most patients who are old enough to voice a sensory complaint are also old enough to cooperate with formal testing of light touch, pain, temperature, vibration, proprioception, and corticosensation (e.g., stereognosis, 2-point discrimination, extinction to double simultaneous stimulation). A notable exception is when the physician suspects a spinal cord lesion in an infant or young child and needs to identify a sensory level. In such situations, observation might suggest a difference in color, temperature, or perspiration, with the skin cool and dry below the level of injury. Lightly touching the skin above the level can evoke a squirming movement or physical withdrawal. Other signs of spinal cord injury include decreased anal sphincter tone and strength and absence of the superficial abdominal, anal wink, and cremasteric reflexes.

Reflexes

Deep Tendon Reflexes and the Plantar Response

Deep tendon reflexes are readily elicited in most infants and children. In infants, it is important to position the head in the midline when assessing reflexes, because turning the head to 1 side can alter reflex tone. Reflexes are graded from 0 (absent) to 4+ (markedly hyperactive), with 2+ being normal. Reflexes that are 1+ or 3+ can be normal as long as they are symmetrical. Sustained clonus is always pathologic, but infants younger than 3 mo old can have 5-10 beats of clonus, and older children can have 1-2 beats of clonus, provided that it is symmetrical.

The ankle jerk is hardest to elicit, but it can usually be obtained by passively dorsiflexing the foot and then tapping on either the Achilles tendon or the ball of the foot. The knee jerk is evoked by tapping the patellar tendon. If this reflex is exaggerated, extension of the knee may be accompanied by contraction of the contralateral adductors **(crossed adductor response).** Hypoactive reflexes reflect lower motor neuron or cerebellar dysfunction, whereas hyperactive reflexes are consistent with upper motor neuron disease. The plantar response is obtained by stimulation of the lateral aspect of the sole of the foot, beginning at the heel and extending to the base of the toes. The **Babinski sign,** indicating an upper motor neuron lesion, is characterized by extension of the great toe and fanning of the remaining toes. Too vigorous stimulation may produce withdrawal, which may be misinterpreted as a Babinski sign. Plantar responses have limited diagnostic utility in neonates, because they are mediated by several competing reflexes and can be either flexor or extensor, depending on how the foot is positioned. Asymmetry of the reflexes or plantar response is a useful lateralizing sign in infants and children.

Primitive Reflexes

Primitive reflexes appear and disappear at specific times during development (Table 590-2), and their absence or persistence beyond those times signifies CNS dysfunction. Although many primitive reflexes have been described, the Moro, grasp, tonic neck, and parachute reflexes are the most clinically relevant. The **Moro reflex** is elicited by supporting the infant in a semierect position and then allowing the infant's head to fall backwards onto the examiner's hand. A normal response consists of symmetric extension and abduction of the fingers and upper extremities, followed by flexion of the upper extremities and an audible cry. An asymmetric response can signify a fractured clavicle, brachial plexus injury, or hemiparesis. Absence of the Moro reflex in a term newborn is ominous, suggesting significant dysfunction of the CNS. The **grasp response** is elicited by placing a finger in the open palm of each hand; by 37 wk of gestation, the reflex is strong enough that the examiner can lift the infant from the bed with gentle traction. The **tonic neck reflex** is produced by manually rotating the infant's head to 1 side and observing for the characteristic fencing posture (extension of the arm on the side to which the face is rotated and flexion of the contralateral arm). An obligatory tonic neck response, in which the infant becomes "stuck" in the fencing posture, is always abnormal and implies a CNS disorder. The **parachute reflex**, which occurs in slightly older infants, can be evoked by holding the infant's trunk and then suddenly lowering the infant as if he or she were falling. The arms will spontaneously extend to break the infant's fall, making this reflex a prerequisite to walking.

Coordination

Ataxia refers to a disturbance in the smooth performance of voluntary motor acts and is usually the result of cerebellar dysfunction. Lesions to the cerebellar vermis result in unsteadiness while sitting or standing **(truncal ataxia).** Affected patients might have a wide-based gait or may be unable to perform tandem gait testing. Lesions of the cerebellar hemispheres cause appendicular ataxia, which may be apparent as the patient reaches for objects and performs finger-to-nose and heel-to-shin movements. Other features of cerebellar dysfunction include errors in judging distance **(dysmetria),** inability to inhibit a muscular action **(rebound),** impaired performance of rapid alternating movements **(dysdiadochokinesia),** intention tremor, nystagmus, scanning dysarthria, hypotonia, and decreased deep tendon reflexes. Acute ataxia suggests an infectious or postinfectious, endocrinologic, toxic, traumatic, vascular, or psychogenic process, and chronic symptoms suggest a metabolic, neoplastic, or degenerative process.

Station and Gait

Observation of a child's station and gait is an important aspect of the neurologic examination. Normal children can stand with their feet close together without swaying; however, children who are unsteady may sway or even fall. On gait testing, the heels should strike either side of an imaginary line, but children with poor balance tend to walk with their legs farther apart to create a more stable base. Tandem gait

testing forces patients to have a narrow base, which highlights subtle balance difficulties.

There are a variety of abnormal gaits, many of which are associated with a specific underlying etiology. Patients with a **spastic** gait appear stiff-legged like a soldier. They may walk on tiptoe as a result of tightness or contractures of the Achilles tendons, and their legs may scissor as they walk. A **hemiparetic** gait is associated with spasticity and circumduction of the leg, as well as decreased arm swing on the affected side. **Cerebellar ataxia** results in a wide-based, reeling gait like a drunk person, whereas **sensory ataxia** results in a wide-based **steppage gait,** in which the patient lifts the legs up higher than usual in the swing phase and then slaps the foot down. A **myopathic,** or waddling, gait is associated with hip girdle weakness. Affected children often develop a compensatory lordosis and have other signs of proximal muscle weakness, such as difficulty climbing stairs. During gait testing, the examiner might also note hypotonia or weakness of the lower extremities; extrapyramidal movements, such as dystonia or chorea; or orthopedic deformities, such as pelvic tilt, genu recurvatum, varus or valgus deformities of the knee, pes cavus (high arches) or pes planus (flat feet), and scoliosis.

GENERAL EXAMINATION

Examination of other organ systems is essential because myriad systemic diseases affect the nervous system. Dysmorphic features can indicate a genetic syndrome (see Chapter 108). Heart murmurs may be associated with rheumatic fever (Sydenham chorea), cardiac rhabdomyoma (tuberous sclerosis), cyanotic heart disease (cerebral abscess or thrombosis), and endocarditis (cerebral vascular occlusion). Hepatosplenomegaly can suggest an inborn error of metabolism, storage disease, HIV, or malignancy. Cutaneous lesions may be a feature of a neurocutaneous syndrome (see Chapter 596).

SPECIAL DIAGNOSTIC PROCEDURES

Lumbar Puncture and Cerebrospinal Fluid Examination

Examination of the cerebrospinal fluid (CSF) and measurement of the pressure it creates in the subarachnoid space are essential in confirming the diagnosis of meningitis, encephalitis, and idiopathic intracranial hypertension (previously referred to as pseudotumor cerebri), and it is often helpful in assessing subarachnoid hemorrhage; demyelinating, degenerative, and collagen vascular diseases; and intracranial neoplasms. Having an experienced assistant who can position, restrain, and comfort the patient is critical to the success of the procedure.

The patient should be situated in a lateral decubitus or seated position with the neck and legs flexed to enlarge the intervertebral spaces. As a rule, sick neonates should be maintained in a seated position to prevent problems with ventilation and perfusion. Regardless of the position chosen, it is important to make sure that the patient's shoulders and hips are straight to prevent rotating the spine.

Once the patient is situated, the physician identifies the appropriate interspace by drawing an imaginary line from the iliac crest downward perpendicular to the vertebral column. In adults, lumbar punctures are usually performed in the L3-L4 or L4-L5 interspaces. Next, the physician dons a mask, gown, and sterile gloves. The skin is thoroughly prepared with a cleansing agent, and sterile drapes are applied. The skin and underlying tissues are anesthetized by injecting a local anesthetic (e.g., 1% lidocaine) at the time of the procedure or by applying a eutectic mixture of lidocaine and prilocaine (EMLA) to the skin 30 minutes before the procedure. A 22-gauge, 1.5-3.0 in, sharp, beveled spinal needle with a properly fitting stylet is introduced in the midsagittal plane and directed slightly cephalad. The physician should pause frequently, remove the stylet, and assess for CSF flow. Although a pop can occur as the needle penetrates the dura, it is more common to experience a subtle change in resistance.

Once CSF has been detected, a manometer and 3-way stopcock can be attached to the spinal needle to obtain an opening pressure. If the patient was seated as the spinal needle was introduced, the patient should be moved carefully to a **lateral decubitus position** with the head and legs extended before the manometer is attached. Normal opening pressures are 90-120 mm H_2O in newborns, 60-180 mm H_2O in young children, and 12-120 mm H_2O in older children and adults. The 90th percentile in children has been reported to be 250 mm of H_2O. The most common cause of an elevated opening pressure is an agitated patient. Sedation and high body mass index can also increase the opening pressure.

Contraindications to performing a lumbar puncture include suspected mass lesion of the brain, especially in the posterior fossa or above the tentorium and causing shift of the midline; suspected mass lesion of the spinal cord; symptoms and signs of impending cerebral herniation in a child with probable meningitis; critical illness (on rare occasions); skin infection at the site of the lumbar puncture; and thrombocytopenia with a platelet count $<20 \times 10^9$/L. If disc edema or focal findings suggest a mass lesion, a head CT should be obtained before proceeding with lumbar puncture to prevent uncal or cerebellar herniation as the CSF is removed. In the absence of these findings, routine head imaging is not warranted. The physician should also be alert to clinical signs of impending herniation, including alterations in the respiratory pattern (e.g., hyperventilation; Cheyne-Stokes respirations, ataxic respirations, respiratory arrest), abnormalities of pupil size and reactivity, loss of brainstem reflexes, and decorticate or decerebrate posturing. If any of these signs are present or the child is so ill that the lumbar puncture might induce cardiorespiratory arrest, blood cultures should be drawn and supportive care, including antibiotics, should be initiated. Once the patient has stabilized, it may be possible to perform a lumbar puncture safely.

Normal CSF contains up to 5/mm^3 white blood cells, and a newborn can have as many as 15/mm^3. Polymorphonuclear cells are always abnormal in a child, but 1-2/mm^3 may be present in a normal neonate. An elevated polymorphonuclear count suggests bacterial meningitis or the early phase of aseptic meningitis (see Chapter 603). CSF lymphocytosis can be seen in aseptic, tuberculous, or fungal meningitis; demyelinating diseases; brain or spinal cord tumor; immunologic disorders, including collagen vascular diseases; and chemical irritation (following myelogram, intrathecal methotrexate).

Normal CSF contains no red blood cells; thus, their presence indicates a traumatic tap or a subarachnoid hemorrhage. Progressive clearing of the blood between the first and last samples indicates a traumatic tap. Bloody CSF should be centrifuged immediately. A clear supernatant is consistent with a bloody tap, whereas **xanthochromia** (yellow color that results from the degradation of hemoglobin) suggests a subarachnoid hemorrhage. Xanthochromia may be absent in bleeds <12 hr old, particularly when laboratories rely on visual inspection rather than spectroscopy. Xanthochromia can also occur in the setting of hyperbilirubinemia, carotenemia, and markedly elevated CSF protein.

The normal CSF protein is 10-40 mg/dL in a child and as high as 120 mg/dL in a neonate. The CSF protein falls to the normal childhood range by 3 mo of age. The CSF protein may be elevated in many processes, including infectious, immunologic, vascular, and degenerative diseases, blockage of CSF flow, as well as tumors of the brain (primary CNS tumors, systemic tumors metastatic to the CNS, infiltrative acute lymphoblastic leukemia) and spinal cord. With a traumatic tap, the CSF protein is increased by approximately 1 mg/dL for every 1,000 red blood cells/mm^3. Elevation of CSF immunoglobulin G, which normally represents approximately 10% of the total protein, is observed in subacute sclerosing panencephalitis, in postinfectious encephalomyelitis, and in some cases of multiple sclerosis. If the diagnosis of multiple sclerosis is suspected, the CSF should be tested for the presence of oligoclonal bands.

The CSF glucose content is approximately 60% of the blood glucose in a healthy child. To prevent a spuriously elevated blood:CSF glucose ratio in a case of suspected meningitis, it is advisable to collect the blood glucose before the lumbar puncture when the child is relatively calm. Hypoglycorrhachia is found in association with diffuse meningeal disease, particularly bacterial and tubercular meningitis. Widespread neoplastic involvement of the meninges, subarachnoid hemorrhage, disorders involving the glucose transporter protein type 1, fungal meningitis, and, occasionally, aseptic meningitis can produce low CSF glucose as well.

A Gram stain of the CSF is essential if there is a suspicion for bacterial meningitis; an acid-fast stain and India ink preparation can be used to assess for tuberculous and fungal meningitis, respectively. CSF is then plated on different culture media depending on the suspected pathogen. When indicated by the clinical presentation, it can also be helpful to assess for the presence of specific antigens (e.g., latex agglutination for *Neisseria meningitidis*, *Haemophilus influenzae* type b, or *Streptococcus pneumoniae*) or to obtain antibody or polymerase chain reaction studies (e.g., herpes simplex virus-1 and -2, West Nile virus, enteroviruses). In noninfectious cases, levels of CSF metabolites, such as lactate, amino acids, and enolase, can provide clues to the underlying metabolic disease.

Neuroradiologic Procedures

Skull roentgenograms have limited diagnostic utility. They can demonstrate fractures, bony defects, intracranial calcifications, or indirect evidence of increased ICP. Acutely increased ICP causes separation of the sutures, whereas chronically increased ICP is associated with erosion of the posterior clinoid processes, enlargement of the sella turcica, and increased convolutional markings.

Cranial ultrasonography is the imaging method of choice for detecting intracranial hemorrhage, periventricular leukomalacia, and hydrocephalus in infants with patent anterior fontanels. Ultrasound is less sensitive than either CT or MRI for detecting hypoxic–ischemic injury, but the use of color Doppler or power Doppler sonography, both of which show changes in regional cerebral blood flow, improve its sensitivity. In general, ultrasound is not a useful technique in older children, although it can be helpful intraoperatively when placing shunts, locating small tumors, and performing needle biopsies.

CT is a valuable diagnostic tool in the evaluation of many neurologic emergencies, as well as some nonemergent conditions. It is a noninvasive, rapid procedure that can usually be performed without sedation. CT scans use conventional x-ray techniques, meaning that they produce ionizing radiation. Because children younger than 10 yr of age are several times more sensitive to radiation than adults, it is important to consider the whether imaging is actually indicated and, if it is, whether an ultrasound or MRI might be the more appropriate study. In the emergency setting, a noncontrast CT scan can demonstrate skull fractures, pneumocephalus, intracranial hemorrhages, hydrocephalus, and impending herniation. If the noncontrast scan reveals an abnormality and an MRI cannot be performed in a timely fashion, nonionic contrast should be used to highlight areas of breakdown in the blood–brain barrier (e.g., abscesses, tumors) and/or collections of abnormal blood vessels (e.g., arteriovenous malformations). CT is less useful for diagnosing acute infarcts in children, because radiographic changes might not be apparent for up to 24 hr. Some subtle signs of early (<24 hr) infarction include sulcal effacement, blurring of the gray–white junction, and the hyperdense middle cerebral artery sign (increased attenuation in the middle cerebral artery that is often associated with thrombosis). In the routine setting, CT imaging can be used to demonstrate intracranial calcifications or, with the addition of 3-dimensional reformatting, to evaluate patients with craniofacial abnormalities or craniosynostosis. Although other pathologic processes may be visible on CT scan, *MR is generally preferred because it provides a more-detailed view of the anatomy without exposure to ionizing radiation* (Table 590-3).

CT angiography is a useful tool for visualizing vascular structures and is accomplished by administering a tight bolus of iodinated contrast through a large-bore intravenous catheter and then acquiring CT images as the contrast passes through the arteries.

MRI is a noninvasive procedure that is well suited for detecting a variety of abnormalities, including those of the posterior fossa and spinal cord. MR scans are highly susceptible to patient motion artifact; consequently, many children younger than age 8 yr require sedation to ensure an adequate study. (The need for sedation is beginning to change in some centers as MRI technology improves and allows for faster performance of studies.) Because the American Academy of Pediatrics recommends that infants be kept nothing by mouth (NPO) for 4 hr or longer and older children for 6 hr or longer before deep sedation, it is often difficult to obtain an MRI on an infant or young child in the acute setting. MRI can be used to evaluate for congenital or acquired brain lesions, migrational defects, dysmyelination or demyelination, posttraumatic gliosis, neoplasms, cerebral edema, and acute stroke (see Table 590-3). Paramagnetic MR contrast agents (e.g., gadolinium-diethylenetriaminepentaacetic acid [DTPA]) are efficacious in identifying areas of disruption in the blood–brain barrier, such as those occurring in primary and metastatic brain tumors, meningitis, cerebritis, abscesses, and active demyelination. **MR angiography** and **MR venography** provide detailed images of major intracranial vasculature structures and assist in the diagnosis of conditions such as stroke, vascular malformations, and cerebral venous sinus thrombosis. MR angiography is the procedure of choice for infants and young children owing to the lack of ionizing radiation and contrast; however, CT angiography may be preferable in older children because it is faster and can eliminate the need for sedation; it is particularly useful for looking at blood vessels in the neck, where there is less interference from bone artifact than in the skull-encased brain.

Functional MRI is a noninvasive technique used to map neuronal activity during specific cognitive states and/or sensorimotor functions. Data are usually based on blood oxygenation, although they can also be based on local cerebral blood volume or flow. Functional MRI is useful for presurgical localization of critical brain functions and has several advantages over other functional imaging techniques. Specifically, functional MRI produces high-resolution images without exposure to ionizing radiation or contrast, and it allows coregistration of functional and structural images.

Proton MR spectroscopy (MRS) is a molecular imaging technique in which the unique neurochemical profile of a preselected brain region is displayed in the form of a spectrum. Many metabolites can be detected, the most common of which are *N*-acetylaspartate, creatine and phosphocreatine, choline, myoinositol, and lactate. Changes in the spectral pattern of a given area can yield clues to the underlying pathology, making MRS useful in the diagnosis of inborn errors of metabolism, as well as the preoperative and posttherapeutic assessment of intracranial tumors. MRS can also detect areas of cortical dysplasia in patients with epilepsy, because these patients have low *N*-acetylaspartate:creatine ratios. Finally, MRS may be useful in detecting hypoxic–ischemic injury in newborns in the 1st day of life, because the lactate peak enlarges and the *N*-acetylaspartate peak diminishes before MRI sequences become abnormal.

Catheter angiography is the gold standard for diagnosing vascular disorders of the CNS, such as arteriovenous malformations, aneurysms, arterial occlusions, and vasculitis. A 4-vessel study is accomplished by introducing a catheter into the femoral artery and then injecting contrast media into each of the internal carotid and vertebral arteries. Because catheter angiography is invasive and requires general anesthesia, it is typically reserved for treatment planning of endovascular or open procedures and for cases in which noninvasive imaging results are not diagnostic.

Positron emission tomography provides unique information on brain metabolism and perfusion by measuring blood flow, oxygen uptake, and/or glucose consumption. Positron emission tomography is an expensive technique that is gaining a following in some pediatric centers, particularly those with active epilepsy surgery programs. **Single-photon emission CT** using ^{99m}Tc hexamethylpropyleneamine oxime is a sensitive and inexpensive technique to study regional cerebral blood flow. Single-photon emission CT is particularly useful in assessing for vasculitis, herpes encephalitis, dysplastic cortex, and recurrent brain tumors. Positron emission tomography MRI is only available in a few pediatric centers in the United States; it provides better resolution and tissue definition than single-photon emission CT.

Electroencephalography

An electroencephalogram (EEG) provides a continuous recording of electrical activity between reference electrodes placed on the scalp. Although the genesis of the electrical activity is not certain, it likely originates from postsynaptic potentials in the dendrites of cortical neurons. Even with amplification of the electrical activity, not all potentials are recorded because there is a buffering effect of the scalp, muscles, bone, vessels, and subarachnoid fluid. EEG waves are

Table 590-3 Preferred Imaging Procedures in Neurologic Diseases

ISCHEMIC INFARCTION OR TRANSIENT ISCHEMIC ATTACK CT/CTA (head and neck) ± CT perfusion for patients who are unstable or are potential candidates for tissue plasminogen activator or other acute interventions Otherwise, MRI/MRA (head and neck) with and without gadolinium and with diffusion-weighted images If the examination findings localize to the anterior circulation, carotid ultrasound should be performed rather than neck CTA or MRA Obtain an MRV if the infarct does not follow an arterial distribution CT or MRI can detect infarcts more than 24 hr old, although MRI is generally preferred to avoid exposure to ionizing radiation	HEADACHE CT with and without contrast or MRI with and without gadolinium if a structural disorder is suspected (MRI is preferred in nonemergent situations as it does not involve ionizing radiation and provides a better view of the parenchyma)
INTRAPARENCHYMAL HEMORRHAGE CT if <24 hr; MRI if >24 hr MRI and MRA to assess for underlying vascular malformation, tumor, etc. Catheter angiography if MRA is nondiagnostic	HEAD TRAUMA CT without contrast initially MRI after initial assessment and treatment if clinically indicated. Diffusion tensor imaging and/or diffusion kurtosis sequences may be useful to detect subtle white matter abnormalities
ARTERIOVENOUS MALFORMATION CT for acute hemorrhage; MRI and MRA with and without gadolinium as early as possible Catheter angiography if noninvasive imaging is nondiagnostic	EPILEPSY MRI with and without gadolinium. Thin slices through the mesial temporal lobes may be helpful if a temporal focus is suspected PET Interictal SPECT
CEREBRAL ANEURYSM CT without contrast for acute subarachnoid hemorrhage MRA or CTA to identify the aneurysm Catheter angiography may be necessary in some cases TCD to detect vasospasm	BRAIN TUMOR MRI with and without gadolinium MRS PET
HYPOXIC–ISCHEMIC BRAIN INJURY Ultrasound in infants If ultrasound is negative or there is a discrepancy between the clinical course and the sonogram, obtain an MRI In older children, CT if unstable; otherwise, MRI MRS can show a lactate peak even in the absence of structural abnormalities and can be useful for prognostication purposes	MULTIPLE SCLEROSIS MRI with and without gadolinium Obtain sagittal FLAIR images
METABOLIC DISORDERS MRI, particularly T2-weighted and FLAIR images Diffusion-weighted images may be useful in distinguishing acute and chronic changes MRS, SPECT, and PET may be useful in certain disorders	MENINGITIS OR ENCEPHALITIS CT without and with contrast before lumbar puncture if there are signs of increased ICP on examination MRI with and without gadolinium after initial assessment and treatment for patients with complicated meningitis or encephalitis
HYDROCEPHALUS Ultrasound (in infants), CT with and without contrast, or MR with and without gadolinium for diagnosis of communicating hydrocephalus MR with and without gadolinium for diagnosis of noncommunicating hydrocephalus Ultrasound (in infants) or CT to follow ventricular size in response to treatment	BRAIN ABSCESS MRI with and without gadolinium Diffusion-weighted images and MRS can help to differentiate abscess from necrotic tumor If the patient is unstable, CT with and without contrast followed by MRI with and without contrast when feasible MOVEMENT DISORDERS MRI with and without gadolinium PET DaTscan (SPECT scan using ioflupane iodine-123 as the contrast agent for detecting dopamine transporters in suspected parkinsonian syndromes)

CTA, computed tomographic angiography; FLAIR, fluid-attenuated inversion recovery; ICP, intracranial pressure; MRA, magnetic resonance angiography; MRS, magnetic resonance spectroscopy; MRV, magnetic resonance venography; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TCD, transcranial Doppler ultrasonography.

classified according to their frequency as delta (1-3/sec), theta (4-7/sec), alpha (8-12/sec), and beta (13-20/sec). These waves are altered by many factors, including age, level of alertness, eye closure, drugs, and disease states.

The normal waking EEG is characterized by the posterior dominant rhythm—a sinusoidal, 8-12 Hz rhythm that is most prominent over the occipital region in a state of relaxed wakefulness with the eyes closed. This rhythm first becomes apparent at 3-4 mo old, and most children have achieved the adult frequency of 8-12 Hz by age 8 yr.

Normal sleep is divided into 3 stages of non–rapid eye movement sleep—designated N1, N2, and N3—and rapid eye movement sleep. N1 corresponds to drowsiness, and N3 represents deep, restorative, slow-wave sleep. Rapid eye movement sleep is rarely captured during a routine EEG but may be seen on an overnight recording. The American Electroencephalography Society Guideline and Technical Standards states that "sleep recordings should be obtained whenever possible"; however, it appears that sleep deprivation—not sleep during the EEG—is what increases the yield of the study, particularly in children with 1 or more clinically diagnosed seizures and in children older than 3 yr of age.

EEG abnormalities can be divided into 2 general categories: epileptiform discharges and slowing. Epileptiform discharges are paroxysmal spikes or sharp waves, often followed by slow waves, which interrupt the background activity. They may be focal, multifocal, or generalized. Focal discharges are often associated with cerebral dysgenesis or irritative lesions, such as cysts, slow-growing tumors, or glial scar tissue; generalized discharges typically occur in children with structurally normal brains. Generalized discharges can occur as an epilepsy trait in children who have never had a seizure and, by themselves, are not an indication for treatment. Epileptiform activity may be enhanced by activation procedures, including hyperventilation and photic stimulation.

As with epileptiform discharges, slowing can be either focal or diffuse. Focal slowing should raise a concern for an underlying functional or structural abnormality, such as an infarct, hematoma, or tumor. Diffuse slowing is the hallmark of encephalopathy and is usually secondary to a widespread disease process or toxic–metabolic insult.

Long-term video EEG monitoring provides precise characterization of seizure types, which allows specific medical or surgical management. It facilitates more accurate differentiation of epileptic seizures

from paroxysmal events that mimic epilepsy, including psychogenic nonepileptiform attacks. Long-term EEG monitoring can also be useful during medication adjustments.

Evoked Potentials

An evoked potential is an electrical signal recorded from the CNS following the presentation of a specific visual, auditory, or sensory stimulus. Stimulation of the visual system by a flash or patterned stimulus, such as a black-and-white checkerboard, produces **visual evoked potentials** (VEPs), which are recorded over the occiput and averaged in a computer. Abnormal VEPs can result from lesions to the visual pathway anywhere from the retina to the visual cortex. Many demyelinating disorders and neurodegenerative diseases, such as Tay-Sachs, Krabbe, or Pelizaeus-Merzbacher disease, or neuronal ceroid lipofuscinoses, show characteristic VEP abnormalities. Flash VEPs can also be helpful in evaluating infants who have sustained an anoxic injury; however, detection of an evoked potential does not necessarily mean that the infant will have functional vision.

Brainstem auditory evoked responses (BAERs) provide an objective measure of hearing and are particularly useful in neonates and in children who have failed, or are uncooperative with, audiometric testing. BAERs are abnormal in many neurodegenerative diseases of childhood and are an important tool in evaluating patients with suspected tumors of the cerebellopontine angle. BAERs can be helpful in assessing brainstem function in comatose patients, because the waveforms are unaffected by drugs or by the level of consciousness; however, they are not accurate in predicting neurologic recovery and outcome.

Somatosensory evoked potentials (SSEPs) are obtained by stimulating a peripheral nerve (peroneal, median) and then recording the electrical response over the cervical region and contralateral parietal somatosensory cortex. SSEPs determine the functional integrity of the dorsal column–medial lemniscal system and are useful in monitoring spinal cord function during operative procedures for scoliosis, aortic coarctation, and myelomeningocele repair. SSEPs are abnormal in many neurodegenerative disorders and are the most accurate evoked potential in the assessment of neurologic outcome following a severe CNS insult.

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Chapter 591
Congenital Anomalies of the Central Nervous System

Stephen L. Kinsman and Michael V. Johnston

Central nervous system (CNS) malformations are grouped into neural tube defects and associated spinal cord malformations; encephaloceles; disorders of structure specification (gray matter structures, neuronal migration disorders, disorders of connectivity, and commissure and tract formation); disorders of the posterior fossa, brainstem, and cerebellum; disorders of brain growth and size; and disorders of skull growth and shape. Classification of these conditions into syndromic, nonsyndromic, and single-gene etiologies is also important. These disorders can also be seen as isolated findings or as being a consequence of environmental exposures. Elucidation of single-gene causes has outpaced our understanding of the epigenetic and environmental mechanisms causing these malformations.

These disorders are heterogeneous in their presentation. Common presentations and clinical problems include disorders of head size and/or shape; hydrocephalus; fetal ultrasonographic brain abnormalities; neonatal encephalopathy and seizures; developmental delay, cognitive impairment, and intellectual disability; hypotonia, motor impairment, and cerebral palsy; seizures, epilepsy, and drug-resistant epilepsy; cranial nerve dysfunction; and spinal cord dysfunction.

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591.1 Neural Tube Defects

Stephen L. Kinsman and Michael V. Johnston

Neural tube defects (NTDs) account for the largest proportion of congenital anomalies of the CNS and result from failure of the neural tube to close spontaneously between the 3rd and 4th wk of in utero development. Although the precise cause of NTDs remains unknown, evidence suggests that many factors, including hyperthermia, drugs (valproic acid), malnutrition, low red cell folate levels, chemicals, maternal obesity or diabetes, and genetic determinants (mutations in folate-responsive or folate-dependent enzyme pathways) can adversely affect normal development of the CNS from the time of conception. In some cases, an abnormal maternal nutritional state or exposure to radiation before conception increases the likelihood of a congenital CNS malformation. The major NTDs include spina bifida occulta, meningocele, myelomeningocele, encephalocele, anencephaly, caudal regression syndrome, dermal sinus, tethered cord, syringomyelia, diastematomyelia, and lipoma involving the conus medullaris and/or filum terminale and the rare condition iniencephaly.

The human nervous system originates from the primitive ectoderm that also develops into the epidermis. The ectoderm, endoderm, and mesoderm form the three primary germ layers that are developed by the 3rd wk. The endoderm, particularly the notochordal plate and the intraembryonic mesoderm, induces the overlying ectoderm to develop the neural plate in the 3rd wk of development (Fig. 591-1*A*). Failure of normal induction is responsible for most of the NTDs, as well as disorders of prosencephalic development. Rapid growth of cells within the neural plate causes further invagination of the neural groove and differentiation of a conglomerate of cells, the neural crest, which migrate laterally on the surface of the neural tube (Fig. 591-1*B*). The notochordal plate becomes the centrally placed notochord, which acts as a foundation around which the vertebral column ultimately develops. With formation of the vertebral column, the notochord undergoes involution and becomes the nucleus pulposus of the intervertebral disks. The neural crest cells differentiate to form the peripheral nervous system, including the spinal and autonomic ganglia and the ganglia of cranial nerves V, VII, VIII, IX, and X. In addition, the neural crest forms the leptomeninges, as well as Schwann cells, which are responsible for myelination of the peripheral nervous system. The dura is thought to arise from the paraxial mesoderm. In the region of the embryo destined to become the head, similar patterns exist. In this region, the notochord is replaced by the prechordal mesoderm.

In the 3rd wk of embryonic development, invagination of the neural groove is completed and the neural tube is formed by separation from the overlying surface ectoderm (see Fig. 591-1*C*). Initial closure of the neural tube is accomplished in the area corresponding to the future junction of the spinal cord and medulla and moves rapidly both caudally and rostrally. For a brief period, the neural tube is open at both ends, and the neural canal communicates freely with the amniotic cavity (see Fig. 591-1*D*). Failure of closure of the neural tube allows excretion of fetal substances (α-fetoprotein [AFP], acetylcholinesterase) into the amniotic fluid, serving as biochemical markers for a NTD. Prenatal screening of maternal serum for AFP in the 16th-18th wk of gestation is an effective method for identifying pregnancies at risk for fetuses with NTDs in utero. Normally, the rostral end of the neural

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tube closes on the 23rd day and the caudal neuropore closes by a process of secondary neurulation by the 27th day of development, before the time that many women realize they are pregnant.

The embryonic neural tube consists of 3 zones: ventricular, mantle, and marginal (see Fig. 591-1*E*). The ependymal layer consists of pluripotential, pseudostratified, columnar neuroepithelial cells. Specific neuroepithelial cells differentiate into primitive neurons or neuroblasts that form the mantle layer. The marginal zone is formed from cells in the outer layer of the neuroepithelium, which ultimately becomes the white matter. Glioblasts, which act as the primitive supportive cells of the CNS, also arise from the neuroepithelial cells in the ependymal zone. They migrate to the mantle and marginal zones and become future astrocytes and oligodendrocytes. The importance of other pathways of progenitor cell generation and migration are also being elucidated. It is likely that microglia originate from mesenchymal cells at a later stage of fetal development when blood vessels begin to penetrate the developing nervous system.

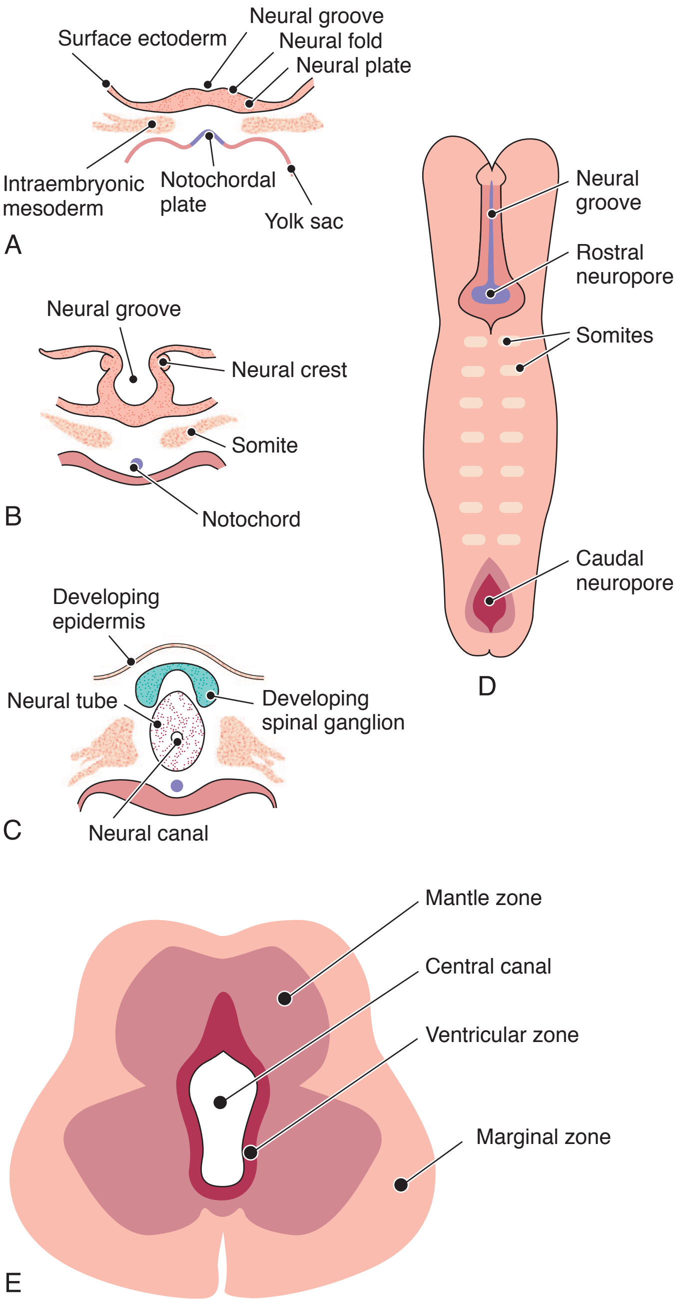

Figure 591-1 Diagrammatic illustration of the developing nervous system. **A,** Transverse sections of the neural plate during the 3rd wk. **B,** Formation of the neural groove and the neural crest. **C,** The neural tube is developed. **D,** Longitudinal drawing showing the initial closure of the neural tube in the central region. **E,** Cross-sectional drawing of the embryonic neural tube (primitive spinal cord).

591.2 Spina Bifida Occulta (Occult Spinal Dysraphism)

Stephen L. Kinsman and Michael V. Johnston

Spina bifida occulta is a common anomaly consisting of a midline defect of the vertebral bodies without protrusion of the spinal cord or meninges. Most patients are asymptomatic and lack neurologic signs, and the condition is usually of no consequence. Some consider the term *spina bifida occulta* to denote merely a posterior vertebral body fusion defect. This simple defect does not have an associated spinal cord malformation. Other clinically more significant forms of this closed spinal cord malformation are more correctly termed *occult spinal dysraphism.* In most of these cases, there are cutaneous manifestations such as a hemangioma, discoloration of the skin, pit, lump, dermal sinus, or hairy patch (Fig. 591-2). A spine roentgenogram in simple spina bifida occulta shows a defect in closure of the posterior vertebral arches and laminae, typically involving L5 and S1; there is no abnormality of the meninges, spinal cord, or nerve roots. Occult spinal dysraphism is often associated with more significant developmental abnormalities of the spinal cord, including syringomyelia, diastematomyelia, lipoma, fatty filum, dermal sinus, and/or a tethered cord. A spine x-ray in these cases might show bone defects or may be normal. All cases of occult spinal dysraphism are best investigated with MRI (Fig. 591-3). Initial screening in the neonate may include ultrasonography, but MRI is more accurate at any age.

A dermoid sinus usually forms a small skin opening, which leads into a narrow duct, sometimes indicated by protruding hairs, a hairy patch, or a vascular nevus. Dermoid sinuses occur in the midline at the sites where meningoceles or encephaloceles can occur: the lumbosacral region or occiput, respectively and occasionally in the cervical or thoracic area. Dermoid sinus tracts can pass through the dura, acting as a conduit for the spread of infection. Recurrent meningitis of occult origin should prompt careful examination for a small sinus tract in the posterior midline region, including the back of the head. Lower back sinuses are usually above the gluteal fold and are directed cephalad. Tethered spinal cord syndrome may also be an associated problem. Diastematomyelia commonly has bony abnormalities that require surgical intervention along with untethering of the spinal cord.

An approach to imaging of the spine in patients with cutaneous lesions is noted in Table 591-1.

Table 591-1	Cutaneous Lesions Associated with Occult Spinal Dysraphism
IMAGING INDICATED Subcutaneous mass or lipoma Hairy patch Dermal sinus Atypical dimples (deep, >5 mm, >25 mm from anal verge) Vascular lesion, e.g., hemangioma or telangiectasia Skin appendages or polypoid lesions, e.g., skin tags, tail-like appendages Scar-like lesions	
IMAGING UNCERTAIN Hyperpigmented patches Deviation of the gluteal fold	
IMAGING NOT REQUIRED Simple dimples (<5 mm, <25 mm from anal verge) Coccygeal pits	

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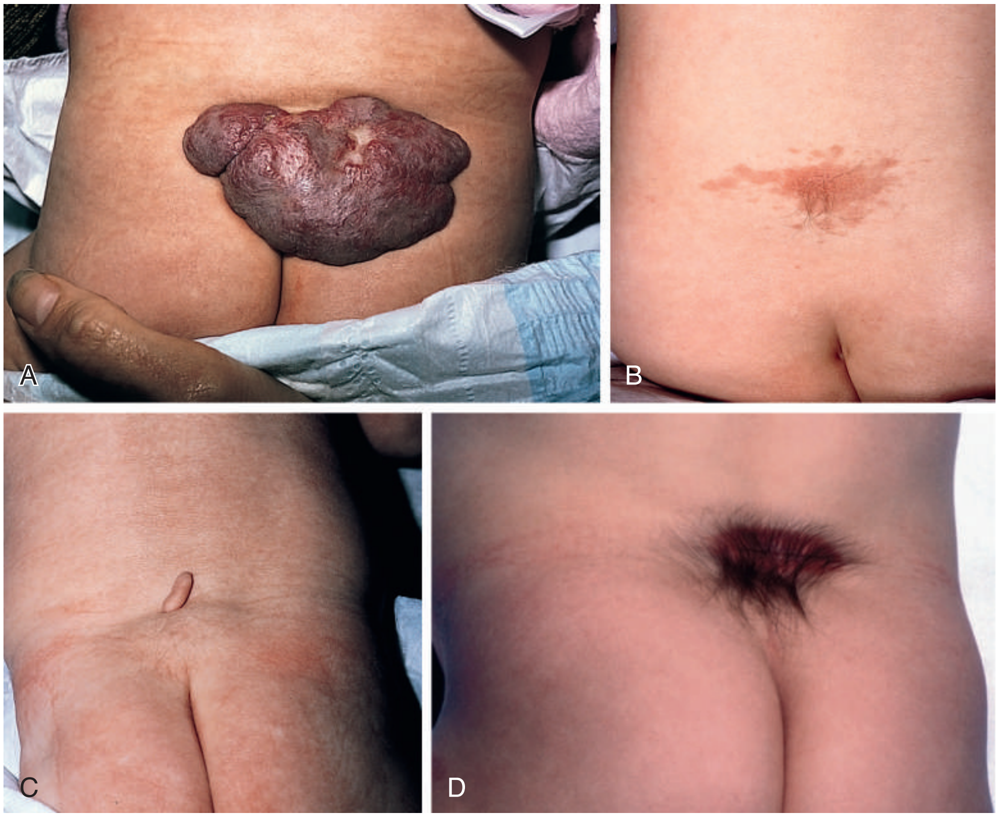

Figure 591-2 Clinical aspects of congenital median lumbosacral cutaneous lesions. **A,** Midline sacral hemangioma in a patient with an occult lipomyelomeningocele. **B,** Capillary malformation with a subtle patch of hypertrichosis in a patient with a dermal sinus. **C,** Human tail with underlying lipoma in an infant with lipomyelomeningocele. **D,** Midline area of hypertrichosis (faun tail) overlying a patch of hyperpigmentation. (**A-C** from Kos L, Drolet BA: Developmental abnormalities. In Eichenfield LF, Frieden IJ, Esterly NB, editors: *Neonatal dermatology*, ed 2, Philadelphia, 2008, WB Saunders. **D** from Spine and spinal cord: developmental disorders. In Schapira A, editor: *Neurology and clinical neuroscience*, Philadelphia, 2007, Mosby.)

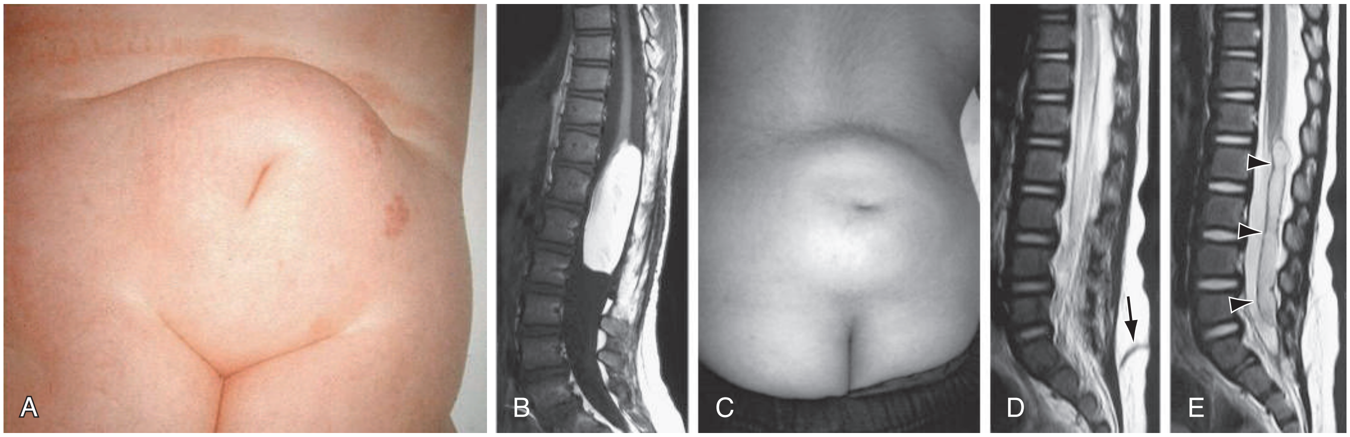

Figure 591-3 Clinical features and imaging findings associated with occult spinal dysraphism. **A,** Lumbosacral lipoma. The subcutaneous lipoma is in continuity with the spinal cord via a defect in the underlying muscles bone and dura. **B,** Sagittal T1-weighted image shows huge intradural lipoma, merging with the conus medullaris superiorly. **C,** Lipoma and central dermal sinus. **D** and **E,** Dermal sinus with dermoid on an 8 yr old girl. Slightly parasagittal T2-weighted image shows sacral dermal sinus coursing obliquely downward in subcutaneous fat *(arrow)* **(D).** Midsagittal T2-weighted image shows huge dermoid in the thecal sac *(arrowheads)*, extending upward to the tip of the conus medullaris **(E).** The mass gives a slightly lower signal than cerebrospinal fluid and is outlined by a thin low-signal rim. *(**A** from Thompson DNP: Spinal dysraphic anomalies: classification, presentation and management.* Paed Child Health *24:431–438, 2014, Fig. 4; **B, D,** and **E** from Rossi A, Biancheri R, Cama A, et al: Imaging in spine and spinal cord malformations,* Eur J Radiol *50(2):177–200, 2004, Fig. 9a; and **C,** from Jaiswal AK, Garg A, Mahapatra AK: Spinal ossifying lipoma,* J Clin Neurosci *12:714–717, 2005, Fig. 1.)*

591.3 Meningocele

Stephen L. Kinsman and Michael V. Johnston

A meningocele is formed when the meninges herniate through a defect in the posterior vertebral arches or the anterior sacrum. The spinal cord is usually normal and assumes a normal position in the spinal canal, although there may be tethering of the cord, syringomyelia, or diastematomyelia. A fluctuant midline mass that might transilluminate occurs along the vertebral column, usually in the lower back. Most meningoceles are well covered with skin and pose no immediate threat to the patient. Careful neurologic examination is mandatory. Orthopedic and urologic examination should also be considered. In asymptomatic children with normal neurologic findings and full-thickness skin covering the meningocele, surgery may be delayed or sometimes not performed.

Before surgical correction of the defect, the patient must be thoroughly examined with the use of plain x-rays, ultrasonography, and MRI to determine the extent of neural tissue involvement, if any, and associated anomalies, including diastematomyelia, lipoma, and possible clinically significant tethered spinal cord. Urologic evaluation usually includes cystometrogram to identify children with neurogenic bladder who are at risk for renal deterioration. Patients with leaking cerebrospinal fluid (CSF) or a thin skin covering should undergo immediate surgical treatment to prevent meningitis. A CT scan or MRI of the head is recommended for children with a meningocele because of the association with hydrocephalus in some cases. An anterior meningocele projects into the pelvis through a defect in the sacrum. Symptoms of constipation and bladder dysfunction develop due to the increasing size of the lesion. Female patients might have associated anomalies of the genital tract, including a rectovaginal fistula and vaginal septa. Plain x-rays demonstrate a defect in the sacrum, and CT scanning or MRI outlines the extent of the meningocele and any associated anomalies.

591.4 Myelomeningocele

Stephen L. Kinsman and Michael V. Johnston

Myelomeningocele represents the most severe form of dysraphism, a so-called aperta or open form, involving the vertebral column and spinal cord, which occurs with an incidence of approximately 1 in 4,000 live births.

ETIOLOGY

The cause of myelomeningocele is unknown, but as with all neural tube closure defects, including anencephaly, a genetic predisposition exists; the risk of recurrence after 1 affected child is 3-4% and increases to 10% with 2 prior affected children. Both epidemiologic evidence and the presence of substantial familial aggregation of anencephaly, myelomeningocele, and craniorachischisis indicate heredity, on a polygenic basis, as a significant contributor to the etiology of NTDs. Nutritional and environmental factors have a role in the etiology of myelomeningocele as well.

Folate is intricately involved in the prevention and etiology of NTDs. Folate functions in single-carbon transfer reactions and exists in many chemical forms. Folic acid (pteroylmonoglutamic acid), which is the most oxidized and stable form of folate, occurs rarely in food but is the form used in vitamin supplements and in fortified food products, particularly flour. Most naturally occurring folates (food folate) are pteroylpolyglutamates, which contain 1-6 additional glutamate molecules joined in a peptide linkage to the γ-carboxyl of glutamate. Folate coenzymes are involved in DNA synthesis, purine synthesis, generation of formate into the formate pool, and amino acid interconversion; the conversion of homocysteine to methionine provides methionine for the synthesis of *S*-adenosylmethionine (SAMe, an agent important for in vivo methylation). Mutations in the genes encoding the enzymes involved in homocysteine metabolism may play a role in the pathogenesis of meningomyelocele. These enzymes include 5,10-methylenetetrahydrofolate reductase, cystathionine β-synthase, and methionine synthase. An association between a thermolabile variant of 5,10-methylenetetrahydrofolate reductase and mothers of children with NTDs might account for up to 15% of preventable NTDs. Maternal periconceptional use of folic acid supplementation reduces the incidence of NTDs in pregnancies at risk by at least 50%. To be effective, folic acid supplementation should be initiated before conception and continued until at least the 12th wk of gestation, when neurulation is complete. The mechanisms by which folic acid prevents NTDs remain poorly understood.

PREVENTION

The U.S. Public Health Service has recommended that all women of childbearing age and who are capable of becoming pregnant take 0.4 mg of folic acid daily. If, however, a pregnancy is planned in high-risk women (previously affected child), supplementation should be started with 4 mg of folic acid daily, beginning 1 mo before the time of the planned conception. The modern diet provides about half the daily requirement of folic acid. To increase folic acid intake, fortification of flour, pasta, rice, and cornmeal with 0.15 mg folic acid per 100 g was mandated in the United States and Canada in 1998. The added folic acid is insufficient to maximize the prevention of preventable NTDs. Therefore, informative educational programs and folic acid vitamin supplementation remain essential for women planning a pregnancy and possibly for all women of childbearing age. In addition, women should also strive to consume food folate from a varied diet. Certain drugs, including drugs that antagonize folic acid, such as trimethoprim and the anticonvulsants carbamazepine, phenytoin, phenobarbital, and primidone, increase the risk of myelomeningocele. The anticonvulsant valproic acid causes NTDs in approximately 1-2% of pregnancies when administered during pregnancy. Some epilepsy clinicians recommend that all female patients of childbearing potential who take anticonvulsant medications also receive folic acid supplements. There may be a threshold for ideal red blood cell folate levels (900-1,000 nmol/L), which is associated with a markedly reduced risk of NTDs.

CLINICAL MANIFESTATIONS

Myelomeningocele produces dysfunction of many organs and structures, including the skeleton, skin, and gastrointestinal and genitourinary tracts, in addition to the peripheral nervous system and the CNS. A myelomeningocele may be located anywhere along the neuraxis, but the lumbosacral region accounts for at least 75% of the cases. The extent and degree of the neurologic deficit depend on the location of the myelomeningocele and the associated lesions. A lesion in the low sacral region causes bowel and bladder incontinence associated with anesthesia in the perineal area but with no impairment of motor function. Newborns with a defect in the midlumbar or high lumbothoracic region typically have either a sac-like cystic structure covered by a thin layer of partially epithelialized tissue (Fig. 591-4) or an exposed flat

Figure 591-4 A lumbar myelomeningocele is covered by a thin layer of skin.

neural placode without overlying tissues. When a cyst or membrane is present, remnants of neural tissue are visible beneath the membrane, which occasionally ruptures and leaks CSF.

Examination of the infant shows a flaccid paralysis of the lower extremities, an absence of deep tendon reflexes, a lack of response to touch and pain, and a high incidence of lower-extremity deformities (clubfeet, ankle and/or knee contractures, and subluxation of the hips). Some children have constant urinary dribbling and a relaxed anal sphincter. Other children do not leak urine and in fact have a high-pressure bladder and sphincter dyssynergy. Thus, a myelomeningocele above the midlumbar region tends to produce lower motor neuron signs because of abnormalities and disruption of the conus medullaris and above spinal cord structures.

Infants with myelomeningocele typically have increased neurologic deficit as the myelomeningocele extends higher into the thoracic region. These infants sometimes have an associated kyphotic gibbus that requires neonatal orthopedic correction. Patients with a myelomeningocele in the upper thoracic or cervical region usually have a very minimal neurologic deficit and, in most cases, do not have hydrocephalus. They can have neurogenic bladder and bowel.

Hydrocephalus in association with a type II Chiari malformation develops in at least 80% of patients with myelomeningocele. Generally, patients with sacral myelomeningocele have a very low risk of hydrocephalus. The possibility of hydrocephalus developing after the neonatal period should always be considered, no matter what the spinal level. Ventricular enlargement may be indolent and slow growing or may be rapid causing a bulging anterior fontanel, dilated scalp veins, setting-sun appearance of the eyes, irritability, and vomiting in association with an increased head circumference. Approximately 15% of infants with hydrocephalus and Chiari II malformation develop symptoms of hindbrain (brainstem) dysfunction, including difficulty feeding, choking, stridor, apnea, vocal cord paralysis, pooling of secretions, and spasticity of the upper extremities, which, if untreated, can lead to death. This Chiari crisis is caused by downward herniation of the medulla and cerebellar tonsils through the foramen magnum, as well as endogenous malformations in the cerebellum and brainstem, causing dysfunction.

TREATMENT

Management and supervision of a child and family with a myelomeningocele require a multidisciplinary team approach, including surgeons, other physicians, and therapists, with 1 individual (often a pediatrician) acting as the advocate and coordinator of the treatment program. The news that a newborn child has a devastating condition such as myelomeningocele causes parents to feel considerable grief and anger. They need time to learn about the condition and its associated complications and to reflect on the various procedures and treatment plans. A knowledgeable individual in an unhurried and nonthreatening setting must give the parents the facts, along with general prognostic information and management strategies and timelines. If possible, discussions with other parents of children with NTDs are helpful in resolving important questions and issues.

Surgery is often done within a day or so of birth but can be delayed for several days (except when there is a CSF leak) to allow the parents time to begin to adjust to the shock and to prepare for the multiple procedures and inevitable problems that lie ahead. Evaluation of other congenital anomalies and renal function can also be initiated before surgery. Most pediatric centers aggressively treat the majority of infants with myelomeningocele. After repair of a myelomeningocele, most infants require a shunting procedure for hydrocephalus. If symptoms or signs of hindbrain dysfunction appear, early surgical decompression of the posterior fossa is indicated. Clubfeet can require taping or casting, and dislocated hips may require operative procedures.

Careful evaluation and reassessment of the genitourinary system are some of the most important components of the management. Teaching the parents, and, ultimately, the patient, to regularly catheterize a neurogenic bladder is a crucial step in maintaining a low residual volume and bladder pressure that prevents urinary tract infections and reflux leading to pyelonephritis, hydronephrosis, and bladder damage. Latex-free catheters and gloves must be used to prevent development of latex allergy. Periodic urine cultures and assessment of renal function, including serum electrolytes and creatinine as well as renal scans, vesiculourethrograms, renal ultrasonography, and cystometrograms, are obtained according to the risk status and progress of the patient and the results of the physical examination. This approach to urinary tract management has greatly reduced the need for urologic diversionary procedures and significantly decreased the morbidity and mortality associated with progressive renal disease in these patients. Some children can become continent with surgical implantation of an artificial urinary sphincter (these are used less often) or bladder augmentation at a later age.

Although incontinence of fecal matter is common and is socially unacceptable during the school years, it does not pose the same organ-damaging risks as urinary dysfunction, but occasionally fecal impaction and/or megacolon develop. Many children can be bowel-trained with a regimen of timed enemas or suppositories that allows evacuation at a predetermined time once or twice a day. Special attention to low anorectal tone and enema administration and retention is often required. Appendicostomy for antegrade enemas may also be helpful (see Chapter 23.4).

Functional ambulation is the wish of each child and parent and may be possible, depending on the level of the lesion and on intact function of the iliopsoas muscles. Almost every child with a sacral or lumbosacral lesion obtains functional ambulation; approximately half the children with higher defects ambulate with the use of braces, other orthotic devices, and canes. Ambulation is often more difficult as adolescence approaches and body mass increases. Deterioration of ambulatory function, particularly during earlier years, should prompt referral for evaluation of tethered spinal cord and other neurosurgical issues.

In utero surgical closure of a spinal lesion has been successful in a few centers. Preliminary reports suggest a lower incidence of hindbrain abnormalities and hydrocephalus (fewer shunts) as well as improved motor outcomes. This suggests that the defects may be progressive in utero and that prenatal closure might prevent the development of further loss of function. In utero diagnosis is facilitated by maternal serum AFP screening and by fetal ultrasonography (see Chapter 96).

PROGNOSIS

For a child who is born with a myelomeningocele and who is treated aggressively, the mortality rate is 10-15%, and most deaths occur before age 4 yr, although life-threatening complications occur at all ages. At least 70% of survivors have normal intelligence, but learning problems and seizure disorders are more common than in the general population. Previous episodes of meningitis or ventriculitis adversely affect intellectual and cognitive function. Because myelomeningocele is a chronic disabling condition, periodic and consistent multidisciplinary follow-up is required for life. Renal dysfunction is one of the most important determinants of mortality.

Bibliography is available at Expert Consult.

591.5 Encephalocele

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Two major forms of dysraphism affect the skull, resulting in protrusion of tissue through a bony midline defect, called cranium bifidum. A cranial meningocele consists of a CSF-filled meningeal sac only, and a cranial encephalocele contains the sac plus cerebral cortex, cerebellum, or portions of the brainstem. Microscopic examination of the neural tissue within an encephalocele often reveals abnormalities. The cranial defect occurs most commonly in the occipital region at or

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below the inion, but in certain parts of the world, frontal or nasofrontal encephaloceles (transethmoidal, sphenoethmoidal, sphenomaxillary, sphenoorbital, transsphenoidal) are more common. Some frontal lesions are associated with a cleft lip and palate. These abnormalities are one-tenth as common as neural tube closure defects involving the spine. The etiology is presumed to be similar to that for anencephaly and myelomeningocele; examples of each are reported in the same family.

Infants with a cranial encephalocele are at increased risk for developing hydrocephalus because of **aqueductal stenosis**, **Chiari malformation**, or the **Dandy-Walker syndrome**. Examination might show a small sac with a pedunculated stalk or a large cyst-like structure that can exceed the size of the cranium. The lesion may be completely covered with skin, but areas of denuded lesion can occur and require urgent surgical management. Transillumination of the sac can indicate the presence of neural tissue. A plain x-ray of the skull and cervical spine is indicated to define the anatomy of the cranium and vertebrae. Ultrasonography is most helpful in determining the contents of the sac. MRI or CT further helps define the spectrum of the lesion. Children with a cranial meningocele generally have a good prognosis, whereas patients with an encephalocele are at risk for vision problems, microcephaly, intellectual disability, and seizures. Generally, children with neural tissue within the sac and associated hydrocephalus have the poorest prognosis.

Cranial encephalocele is often part of a syndrome. Meckel-Gruber syndrome is a rare autosomal recessive condition that is characterized by an occipital encephalocele, cleft lip or palate, microcephaly, microphthalmia, abnormal genitalia, polycystic kidneys, and polydactyly. Determination of maternal serum AFP levels and ultrasound measurement of the biparietal diameter, as well as identification of the encephalocele itself, can diagnose encephaloceles in utero. Fetal MRI can help define the extent of associated CNS anomalies and the degree of brain herniated into the encephalocele.

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591.6 Anencephaly

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An anencephalic infant presents a distinctive appearance with a large defect of the calvarium, meninges, and scalp associated with a rudimentary brain, which results from failure of closure of the rostral neuropore, the opening of the anterior neural tube. The primitive brain consists of portions of connective tissue, vessels, and neuroglia. The cerebral hemispheres and cerebellum are usually absent, and only a residue of the brainstem can be identified. The pituitary gland is hypoplastic, and the spinal cord pyramidal tracts are missing owing to the absence of the cerebral cortex. Additional anomalies include folding of the ears, cleft palate, and congenital heart defects in 10-20% of cases. Most anencephalic infants die within several days of birth.

The incidence of anencephaly approximates 1 in 1,000 live births; the greatest incidence is in Ireland, Wales, and Northern China. The recurrence risk is approximately 4% and increases to 10% if a couple has had 2 previously affected pregnancies. Many factors, in addition to genetics, are implicated as a cause of anencephaly, including low socioeconomic status, nutritional and vitamin deficiencies, and a large number of environmental and toxic factors. It is very likely that several noxious stimuli interact on a genetically susceptible host to produce anencephaly. The incidence of anencephaly has been decreasing since the 1990s. Approximately 50% of cases of anencephaly have associated polyhydramnios. Couples who have had an anencephalic infant should have successive pregnancies monitored, including amniocentesis, determination of AFP levels, and ultrasound examination between the 14th and 16th wk of gestation. Prenatal folic acid supplementation decreases the risk of this condition.

591.7 Disorders of Neuronal Migration

Stephen L. Kinsman and Michael V. Johnston

Disorders of neuronal migration can result in minor abnormalities with little or no clinical consequence (small heterotopia of neurons) or devastating abnormalities of CNS structure and/or function (intellectual disability, seizures, lissencephaly, and schizencephaly, particularly the open-lip form) (Fig. 591-5). One of the most important mechanisms in the control of neuronal migration is the radial glial fiber system that guides neurons to their proper site. Migrating neurons attach to the radial glial fiber and then disembark at predetermined sites to form, ultimately, the precisely designed 6-layered cerebral cortex. Another important mechanism is the tangential migration of progenitor neurons destined to become cortical interneurons. The severity and the extent of the disorder are related to numerous factors, including the timing of a particular insult and a host of environmental and genetic contributors. Some cortical malformations may be from somatic mutations, as exemplified by kinesin gene mutations in patients with pachygyria.

LISSENCEPHALY

Lissencephaly, or agyria, is a rare disorder that is characterized by the absence of cerebral convolutions and a poorly formed sylvian fissure, giving the appearance of a 3-4 mo fetal brain. The condition is probably a result of faulty neuroblast migration during early embryonic life and is usually associated with enlarged lateral ventricles and heterotopias in the white matter. In some forms, there is a 4-layered cortex, rather than the usual 6-layered one, with a thin rim of periventricular white matter and numerous gray heterotopias visible by microscopic examination. Milder forms of lissencephaly also exist.

Figure 591-5 T1-weighted MRI scan demonstrating band heterotopia. A thin layer of white matter *(black arrow)* lies between the band of heterotopic gray matter and the cortical surface. Failure of cortical organization with lissencephaly is present in both frontal lobes *(white arrow)*.

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These infants present with failure to thrive, microcephaly, marked developmental delay, and a severe seizure disorder. Ocular abnormalities are common, including hypoplasia of the optic nerve and microphthalmia. Lissencephaly can occur as an isolated finding, but it is associated with Miller-Dieker syndrome in approximately 15% of cases. These children have characteristic facies, including a prominent forehead, bitemporal hollowing, anteverted nostrils, a prominent upper lip, and micrognathia. Approximately 70% of children with Miller-Dieker syndrome have visible or submicroscopic chromosomal deletions of 17p13.3.

The gene *LIS-1* (lissencephaly 1) that maps to chromosome region 17p13.3 is deleted in patients with Miller-Dieker syndrome. CT and MRI scans typically show a smooth brain with an absence of sulci (Fig. 591-6). *Doublecortin* is an X chromosome gene that causes lissencephaly when mutated in males and subcortical band heterotopia when mutated in females. Other important forms of lissencephaly include the Walker-Warburg variant and other cobblestone cortical malformations.

SCHIZENCEPHALY

Schizencephaly is the presence of unilateral or bilateral clefts within the cerebral hemispheres owing to an abnormality of morphogenesis (Fig. 591-7). The cleft may be fused or unfused and, if unilateral and large, may be confused with a porencephalic cyst. Not infrequently, the borders of the cleft are surrounded by abnormal brain, particularly microgyria. MRI is the study of choice for elucidating schizencephaly and associated malformations.

When the clefts are bilateral, many patients are severely intellectually challenged, with seizures that are difficult to control, and microcephalic, with spastic quadriparesis. Some cases of bilateral schizencephaly are associated with septooptic dysplasia and endocrinologic disorders. Unilateral schizencephaly is a common cause of congenital hemiparesis. It remains controversial whether genetic causes of schizencephaly exist. Some gene mutations are seen in cases of familial schizencephaly.

NEURONAL HETEROTOPIAS

Subtypes of neuronal heterotopias include periventricular nodular heterotopias, subcortical heterotopia (including band-type), and marginal glioneuronal heterotopias. Intractable seizures are a common feature. Several genes have been identified that are a cause of these conditions.

POLYMICROGYRIAS

Polymicrogyria is characterized by an augmentation of small convolutions separated by shallow enlarged sulci. Epilepsy, including drug-resistant forms, is a common feature. Truncation of the *KBP* gene has been implicated in a family with multiple members with polymicrogyria.

Figure 591-6 MRI of an infant with lissencephaly. Note the absence of cerebral sulci and the maldeveloped sylvian fissures associated with enlarged ventricles.

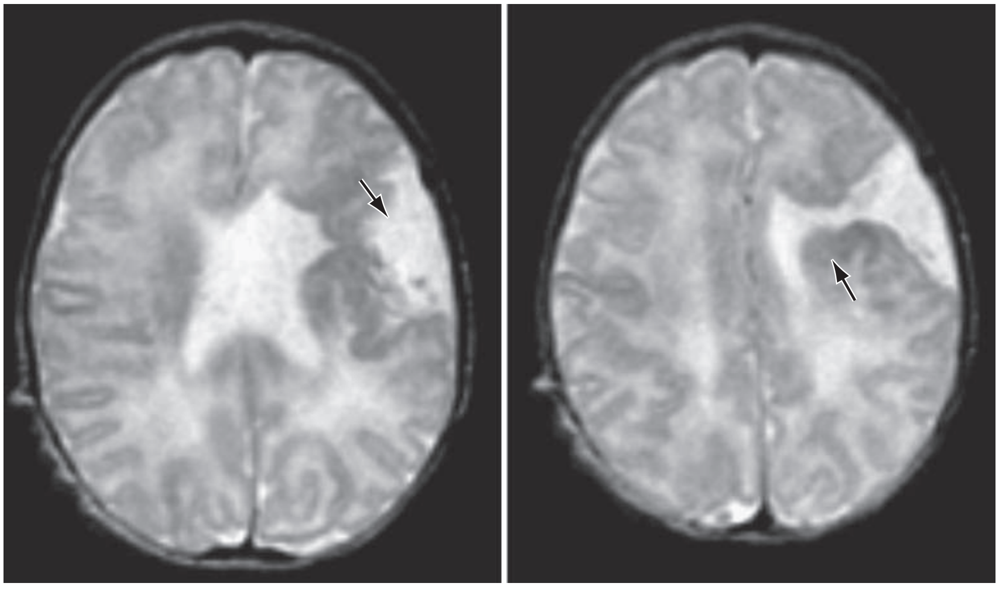

Figure 591-7 Unilateral schizencephaly shown on axial MR images of the brain. Example of an open-lip schizencephaly with a cleft communicating between the ventricle and the extraaxial cranial space *(arrow on left panel)*. Many of these clefts are lined with abnormal gray matter *(arrow on right panel)*.

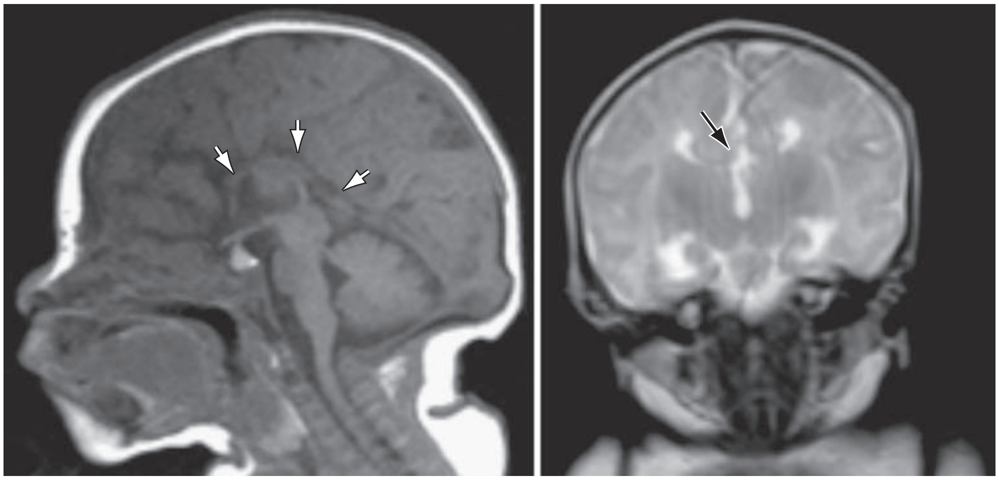

Figure 591-8 Agenesis of the corpus callosum shown on MR images of the brain. Sagittal *(left panel)* and coronal *(right panel)* views of an infant show the total absence of a midsagittal white matter structure *(left panel, arrows)*. The coronal view *(right panel)* demonstrates (despite some motion artifact) the absence of a structure bridging the 2 hemispheres *(area under arrow)*.

FOCAL CORTICAL DYSPLASIAS

Focal cortical dysplasias consist of abnormal cortical lamination in a discrete area of cortex. High-resolution, thin-section MRI can reveal these areas sometimes in the setting of drug-resistant epilepsy.

PORENCEPHALY

Porencephaly is the presence of cysts or cavities within the brain that result from developmental defects or acquired lesions, including infarction of tissue. True porencephalic cysts are most commonly located in the region of the sylvian fissure and typically communicate with the subarachnoid space, the ventricular system, or both. They represent developmental abnormalities of cell migration and are often associated with other malformations of the brain, including microcephaly, abnormal patterns of adjacent gyri, and encephalocele. Affected infants tend to have many problems, including intellectual disability, spastic hemiparesis or quadriparesis, optic atrophy, and seizures.

Several risk factors for porencephalic cyst formation have been identified, including hemorrhagic venous infarctions; various thrombophilias such as protein C deficiency and factor V Leiden mutations; perinatal alloimmune thrombocytopenia; von Willebrand disease; maternal warfarin use; maternal cocaine use; congenital infections; trauma such as amniocentesis; and maternal abdominal trauma. Mutations in the *COL4A1* gene have been described in cases of familial porencephaly.

Pseudoporencephalic cysts characteristically develop during the perinatal or postnatal period and result from abnormalities (infarction, hemorrhage) of arterial or venous circulation. These cysts tend to be unilateral, do not communicate with a fluid-filled cavity, and are not associated with abnormalities of cell migration or CNS malformations. Infants with pseudoporencephalic cysts present with hemiparesis and focal seizures in the 1st yr of life and sometimes present with neonatal encephalopathy or as a floppy newborn or infant.

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591.8 Agenesis of the Corpus Callosum

Stephen L. Kinsman and Michael V. Johnston

Agenesis of the corpus callosum consists of a heterogeneous group of disorders that vary in expression from severe intellectual and neurologic abnormalities to the asymptomatic and normally intelligent patient (Fig. 591-8). The corpus callosum develops from the commissural plate that lies in proximity to the anterior neuropore. Either a direct insult to the commissural plate or disruption of the genetic signaling that specifies and organizes this area during early embryogenesis causes agenesis of the corpus callosum.

It is often said that the outcome of agenesis of the corpus callosum is dictated by *the company it keeps*. When agenesis of the corpus callosum is an isolated phenomenon, the patient may be normal. When it is accompanied by brain anomalies from cell migration defects, such as heterotopias, polymicrogyria, and pachygyria (broad, wide gyri), patients often have significant neurologic abnormalities, including intellectual disability, microcephaly, hemiparesis, diplegia, and seizures.

The anatomic features of agenesis of the corpus callosum are best depicted on MRI or CT scan and include widely separated frontal horns with an abnormally high position of the third ventricle between the lateral ventricles. MRI precisely outlines the extent of the corpus callosum defect.

Absence of the corpus callosum may be inherited as an X-linked recessive trait or as an autosomal dominant trait and on occasion as an autosomal recessive trait. The condition may be associated with specific chromosomal disorders, particularly trisomy 8 and trisomy 18. Single-gene mutations have also been identified, usually in association with other anomalies. Agenesis of the corpus callosum is also seen in some metabolic disorders (Table 591-2).

Aicardi syndrome represents a complex disorder that affects many systems and is typically associated with agenesis of the corpus callosum, distinctive chorioretinal lacunae, and infantile spasms. Patients are almost all female, suggesting a genetic abnormality of the X chromosome (it may be lethal in males during fetal life). Seizures become evident during the 1st few mo and are typically resistant to anticonvulsants. An electroencephalogram shows independent activity recorded from both hemispheres as a result of the absent corpus callosum and shows often hemihypsarrhythmia. All patients have severe intellectual disability and can have abnormal vertebrae that may be fused or only partially developed (hemivertebra). Abnormalities of the retina, including circumscribed pits or lacunae and coloboma of the optic disc, are the most characteristic findings of Aicardi syndrome.

Colpocephaly refers to an abnormal enlargement of the occipital horns of the ventricular system and can be identified as early as the fetal period. It is often associated with agenesis of the corpus callosum, but it can occur in isolation. It is also associated with microcephaly. It can also be seen in anatomic megalencephaly, such as is associated with Sotos syndrome.

HOLOPROSENCEPHALY

Holoprosencephaly is a developmental disorder of the brain that results from defective formation of the prosencephalon and

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Table 591-2 Disorders Associated with Agenesis of the Corpus Callosum*

DISORDER	SALIENT FEATURES
WITH IDENTIFIED GENES†	
Andermann syndrome (*KCC3*)	ACC, progressive neuropathy, and dementia
Donnai-Barrow syndrome (*LRP2*)	Diaphragmatic hernia, exomphalos, ACC, deafness
Frontonasal dysplasia (*ALX1*)	ACC, bilateral extreme microphthalmia, bilateral oblique facial cleft
XLAG (*ARX*)	Lissencephaly, ACC, intractable epilepsy
Microcephaly (*TBR2*)	ACC, polymicrogyria
Microcephaly with simplified gyral pattern and ACC (*WDR62*)	
Mowat-Wilson syndrome (*ZFHX1B*)	Hirschsprung disease, ACC
Pyridoxine-dependent epilepsy (*ALDH7A1*)	ACC, seizures, other brain malformations
Pyruvate dehydrogenase deficiency (*PDHA1, PDHB, PDHX*)	ACC with other brain changes
ACC with fatal lactic acidosis (*MRPS16*)	Complexes I and IV deficiency, ACC, brain malformations
HSAS/MASA syndromes (*L1CAM*)	Hydrocephalus, adducted thumbs, ACC, MR
ACC SEEN CONSISTENTLY (NO GENE YET IDENTIFIED)	
Acrocallosal syndrome	ACC, polydactyly, craniofacial changes, MR
Aicardi syndrome	ACC, chorioretinal lacunae, infantile spasms, MR
Chudley-McCullough syndrome	Hearing loss, hydrocephalus, ACC, colpocephaly
FG syndrome	MR, ACC, craniofacial changes, macrocephaly
Genitopatellar syndrome	Absent patellae, urogenital malformations, ACC
Temtamy syndrome	ACC, optic coloboma, craniofacial changes, MR
Toriello-Carey syndrome	ACC, craniofacial changes, cardiac defects, MR
Vici syndrome	ACC, albinism, recurrent infections, MR
ACC SEEN OCCASIONALLY (PARTIAL LIST)‡	
ACC with spastic paraparesis (*SPG11; SPG15*)	Progressive spasticity and neuropathy, thin corpus callosum
Craniofrontonasal syndrome	Coronal craniosynostosis, facial asymmetry, bifid nose
Fryns syndrome	CDH, pulmonary hypoplasia, craniofacial changes
Marden-Walker syndrome	Blepharophimosis, micrognathia, contractures, ACC
Meckel-Gruber syndrome	Encephalocele, polydactyly, polycystic kidneys
Nonketotic hyperglycinemia (*GLDC, GCST, GCSH*)	ACC, cerebral and cerebellar atrophy, myoclonus, progressive encephalopathy
Microphthalmia with linear skin defects	Microphthalmia, linear skin markings, seizures
Opitz G syndrome	Pharyngeal cleft, craniofacial changes, ACC, MR
Orofaciodigital syndrome	Tongue hamartoma, microretrognathia, clinodactyly
Pyruvate decarboxylase deficiency	Lactic acidosis, seizures, severe MR and spasticity
Rubinstein-Taybi syndrome	Broad thumbs and great toes, MR, microcephaly
Septooptic dysplasia (de Morsier syndrome)	Hypoplasia of septum pellucidum and optic chiasm
Sotos syndrome	Physical overgrowth, MR, craniofacial changes
Warburg micro syndrome	Microcephaly, microphthalmia, microgenitalia, MR
Wolf-Hirschhorn syndrome	Microcephaly, seizures, cardiac defects, 4p–

*Reliable incidence data are unavailable for these very rare syndromes.
†Gene symbols in parentheses.
‡Many of these also may consistently have a thin of dysplastic corpus callosum, such as Sotos' syndrome or agenesis of the corpus callosum (ACC) with spastic paraparesis (SPG11). The overlap between ACC and these conditions is still under investigation. Other gene symbols are omitted from this section.
4p–, deletion of the terminal region of the short arm of chromosome 4, defines the genotype for Wolf-Hirschhorn patients; ACC, agenesis of the corpus callosum; ARX, Aristaless-related homeobox gene; CDH, congenital diaphragmatic hernia; HSAS/MASA, X-linked hydrocephalus/mental retardation, aphasia, shuffling gait, and adducted thumbs; KCC3, KCl cotransporter 3; L1CAM, L1 cell adhesion molecule; MR, mental retardation; MRPS16, mitochondrial ribosomal protein S16; SPG11, spastic paraplegia 11; XLAG, X-linked lissencephaly with absent corpus callosum and ambiguous genitalia; ZFHX1B, zinc finger homeobox 1b.
From Sherr EH, Hahn JS: Disorders of forebrain development. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *5th ed. Philadelphia, 2012, WB Saunders, Table 23-2.*

inadequate induction of forebrain structures. The abnormality, which represents a spectrum of severity, is classified into 3 groups: alobar, semilobar, and lobar, depending on the degree of the cleavage abnormality (Fig. 591-9). A fourth type, the middle interhemispheric fusion variant or syntelencephaly, involves a segmental area of noncleavage, actually a nonseparation, of the posterior frontal and parietal lobes. Facial abnormalities, including cyclopia, synophthalmia, cebocephaly, single nostril, choanal atresia, solitary central incisor tooth, and premaxillary agenesis are common in severe cases, because the prechordal mesoderm that induces the ventral prosencephalon is also responsible for induction of the median facial structures. Milder facial abnormalities are seen in milder forms. Alobar holoprosencephaly is characterized by a single ventricle, an absent falx, and nonseparated deep cerebral nuclei. Care must be taken not to overdiagnose holoprosencephaly based on ventricular abnormalities alone. Evidence of nonseparated midline deep-brain structures, such as caudate, putamen, globus pallidus, and hypothalamus, is the critical element for diagnosis.

Affected children with the alobar type have high mortality rates, but some live for years. Mortality and morbidity with milder types are more variable, and morbidity is less severe. Care must be taken not to prognosticate severe outcomes in all cases. The incidence of holoprosencephaly ranges from 1 in 5,000-16,000 live births. A prenatal diagnosis can be confirmed by ultrasonography after the 10th wk of gestation for more severe types, but fetal MRI at later gestational ages gives far greater anatomic, and therefore diagnostic, precision.

The cause of holoprosencephaly is often not identified. There appears to be an association with maternal diabetes. Chromosomal abnormalities, including deletions of chromosomes 7q and 3p, 21q, 2p, 18p, and 13q, as well as trisomy 13 and 18, account for upwards of 50% of all cases. Mutations in the *sonic hedgehog* gene at 7q have been shown to cause holoprosencephaly. *Gene Reviews* lists 14 single-gene causes. Clinically, it is important to look for associated anomalies, because many syndromes are associated with holoprosencephaly.

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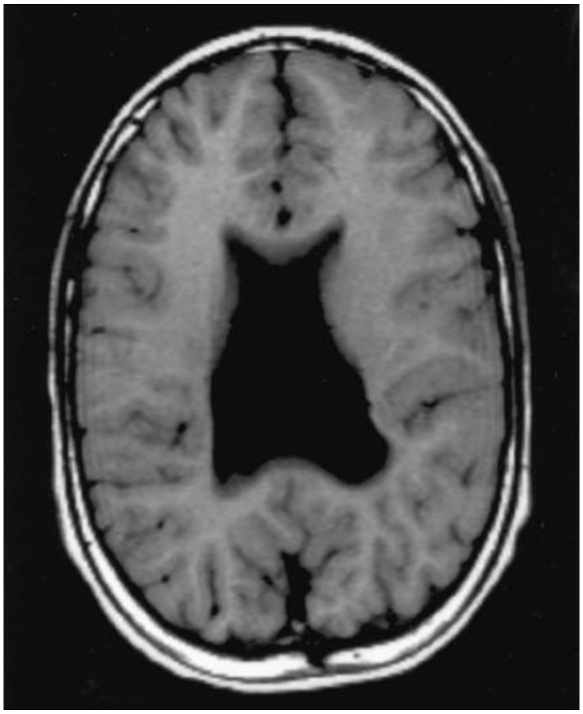

Figure 591-9 Lobar holoprosencephaly. T1-weighted MRI scan demonstrates failure of separation of the hemispheres and a persistent fused ventricle.

591.9 Agenesis of the Cranial Nerves and Dysgenesis of the Posterior Fossa

Stephen L. Kinsman and Michael V. Johnston

Classification of disorders of cranial nerve, brainstem, and cerebellum development remains anatomic, but future classification systems will likely be based on the molecular biology of brain development based on the genes involved and the roles they play in orchestrating brain architecture.

CONGENITAL CRANIAL DYSINNERVATION DISORDERS

Absence of the cranial nerves or the corresponding central nuclei has been described in several conditions and includes the optic nerve defects, congenital ptosis, Marcus Gunn phenomenon (sucking jaw movements causing simultaneous eyelid blinking; this congenital synkinesis results from abnormal innervation of the trigeminal and oculomotor nerves), trigeminal and auditory nerves defects, and cranial nerves IX, X, XI, and XII defects. Increased understanding of these disorders and their genetic causes has led to the term *congenital cranial dysinnervation disorders*.

Optic nerve hypoplasia can occur in isolation or as part of the septooptic dysplasia complex (de Morsier syndrome). Septooptic dysplasia can be caused by a mutation in the *HESX1* gene.

Möbius syndrome is characterized by bilateral facial weakness, which is often associated with paralysis of the abducens nerve. Hypoplasia or agenesis of brainstem nuclei, as well as absent or decreased numbers of muscle fibers, has been reported. Affected infants present in the newborn period with facial weakness, causing feeding difficulties owing to a poor suck. The immobile, dull facies might give the incorrect impression of intellectual impairment; the prognosis for normal development is excellent in most cases. The facial appearance of Möbius syndrome has been improved by facial surgery.

Duane retraction syndrome is characterized by congenital limitation of horizontal globe movement and some globe retraction on attempted adduction and is believed to be the result of abnormal innervation by the oculomotor nerve of the lateral rectus muscle. Abnormalities of cranial nerve development have been demonstrated in this condition.

Less common than Duane retraction syndrome and Möbius syndrome are the group of disorders known as **congenital fibrosis of the extraocular muscles**. Congenital fibrosis of the extraocular muscles is characterized by severe restriction of eye movements and ptosis from abnormal oculomotor and trochlear nerve development and/or from abnormalities of extraocular muscle innervation.

BRAINSTEM AND CEREBELLAR DISORDERS

Disorders of the posterior fossa structures include abnormalities of not only the brainstem and cerebellum, but also the CSF spaces. Commonly encountered malformations include Chiari malformation, Dandy-Walker malformation, arachnoid cysts, mega cisterna magna, persisting Blake pouch, Joubert syndrome, rhombencephalosynapsis, Lhermitte-Duclos disease, and the pontocerebellar hypoplasias.

Chiari malformation is the most common malformation of the posterior fossa and hindbrain. It consists of herniation of the cerebellar tonsils though the foramen magnum. Often, there is also an associated developmental abnormality of the bones of the skull base leading to a small posterior fossa. Cases can be either asymptomatic or symptomatic. When symptoms develop, they often do not do so until late childhood. Symptoms include headaches that are worse with straining and other maneuvers that increase intracranial pressure. Symptoms of brainstem compression such as diplopia, oropharyngeal dysfunction, spasticity, tinnitus, and vertigo can occur. Obstructive hydrocephalus and/or syringomyelia can also occur.

Dandy-Walker malformation is part of a continuum of posterior fossa anomalies that include cystic dilation of the fourth ventricle, hypoplasia of the cerebellar vermis, hydrocephalus, and an enlarged posterior fossa with elevation of the lateral venous sinuses and the tentorium. Extracranial anomalies are also seen. Variable degrees of neurologic impairment are usually present. The etiology of Dandy-Walker malformation includes chromosomal abnormalities, single gene disorders, and exposure to teratogens.

Arachnoid cysts of the posterior fossa can be associated with hydrocephalus. Mega cisterna magna is characterized by an enlarged CSF space inferior and dorsal to the cerebellar vermis and when present in isolation may be considered a normal variant. Persisting Blake pouch is a cyst that obstructs the subarachnoid space and is associated with hydrocephalus.

Joubert syndrome is an autosomal recessive disorder (ciliopathy) with significant genetic heterogeneity that is associated with cerebellar vermis hypoplasia and the pontomesencephalic **molar tooth sign** (a deepening of the interpeduncular fossa with thick and straight superior cerebellar peduncles) (Fig. 591-10). It is associated with hypotonia, ataxia (as toddler), characteristic breathing abnormalities including episodic apnea and hyperpnea (which improves with age), global developmental delay, nystagmus, strabismus, ptosis, and oculomotor apraxia. There can be many associated systemic features (Joubert syndrome and related disorders) including progressive retinal dysplasia (Leber congenital amaurosis), coloboma, congenital heart disease, microcystic kidney disease, liver fibrosis, polydactyly, tongue protrusion, and soft tissue tumors of the tongue (Fig. 591-11).

Rhombencephalosynapsis is an absent or small vermis associated with a nonseparation or fusion of the deep midline cerebellar structures. Ventriculomegaly or hydrocephalus is often seen. There is variable clinical presentation from normal to cognitive and language impairments, epilepsy, and spasticity. **Lhermitte-Duclos** disease is a dysplastic gangliocytoma of the cerebellum leading to focal enlargement of the cerebellum and macrocephaly, cerebellar signs, and seizures.

Pontocerebellar hypoplasias are a group of disorders characterized by impairment of cerebellar and pontine development together with histopathologic features of neuronal death and glial replacement. Clinical features tend to be nonspecific and include hypotonia, feeding difficulties, developmental delay, and breathing difficulties. Classification, associations, and causes include type I (with features of anterior

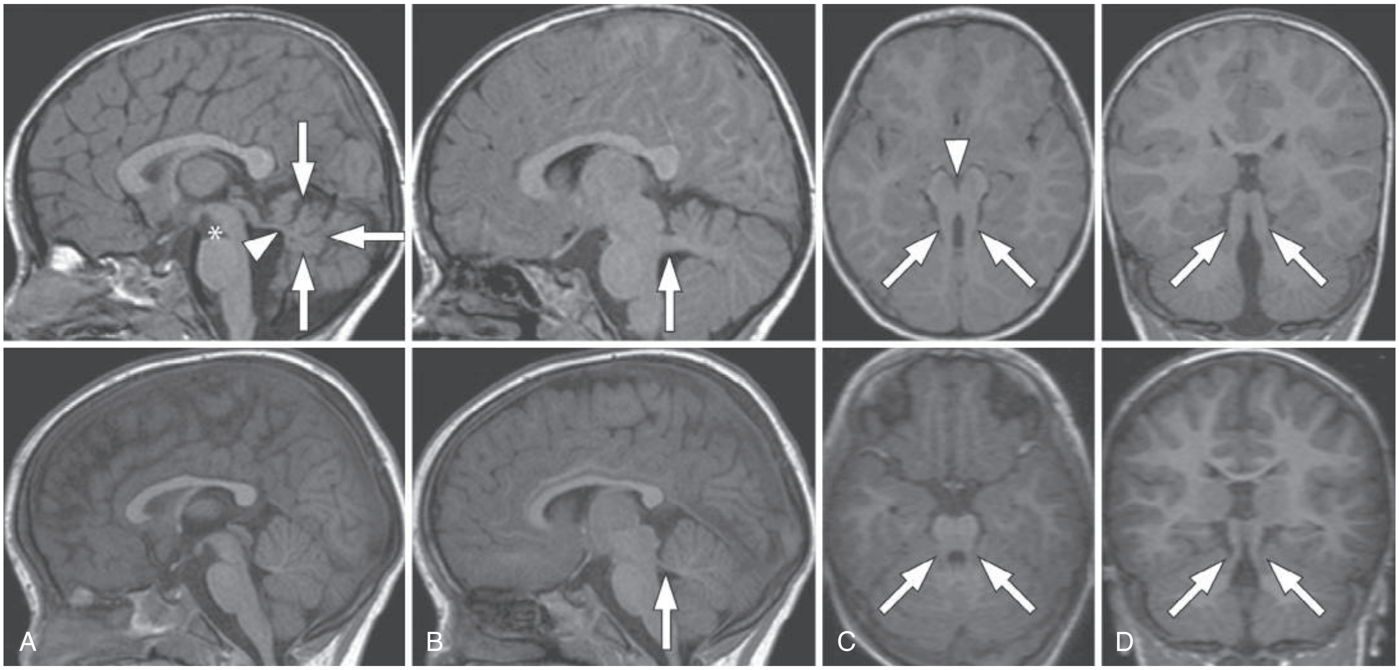

Figure 591-10 Neuroimaging findings in a 2-yr-old child with pure Joubert syndrome *(upper panels)* compared to a healthy control *(lower panels)*. **A,** Parasagittal T1-weighted image shows the thickened, elongated, and horizontally orientated superior cerebellar peduncles *(white arrow)*. **B,** Midsagittal T1-weighted image demonstrates a moderate hypoplasia and dysplasia of the cerebellar vermis *(white arrows)* with secondary distortion and enlargement of the fourth ventricle with rostral shifting of the fastigium *(white arrowhead)*. A deepened interpeduncular fossa is also noted. **C,** Axial T1-weighted image at the level of the pontomesencephalic junction shows the molar tooth sign with a deepened interpeduncular fossa *(white arrowhead)* and elongated, thickened, and horizontally orientated superior cerebellar peduncles *(white arrows)*. Additionally, the cerebellar vermis appears to be hypoplastic and its remnants dysplastic. **D,** Coronal T1-weighted image reveals the thickened superior cerebellar peduncles *(white arrows)*. *(From Romani M, Micalizzi A, Valente EM: Joubert syndrome: congenital cerebellar ataxia with the molar tooth.* Lancet Neurol *12:894–905, 2013, Fig. 1.)*

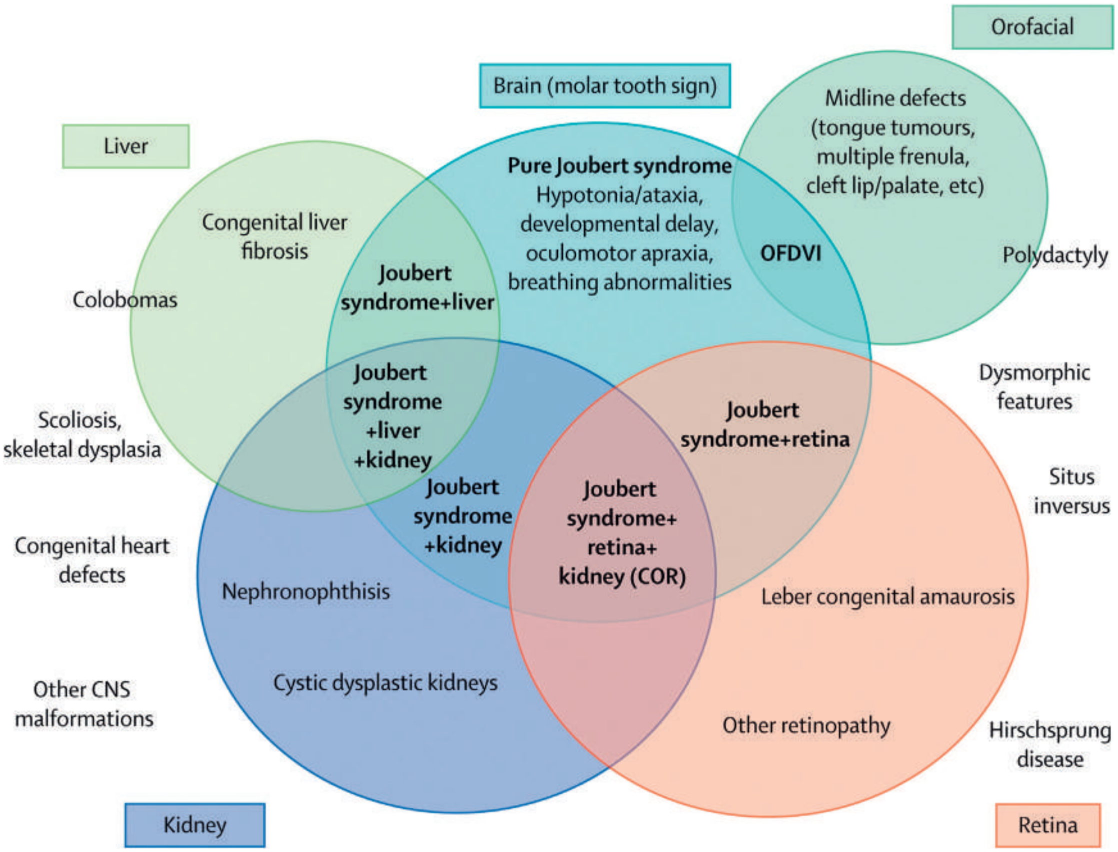

Figure 591-11 Spectrum of organ involvement in Joubert syndrome and classification in clinical subgroups *(in bold)*. Chorioretinal colobomas are more frequently found in the subgroup of Joubert syndrome with liver involvement but can be present also in other subgroups. Similarly, polydactyly (especially if preaxial or mesoaxial) is invariably present in the Orofaciodigital type VI subgroup, but postaxial polydactyly is frequently observed also in association with other Joubert syndrome phenotypes. Other clinical features outside the circles occur more rarely, without a specific association to a clinical subgroup. *CNS,* central nervous system; *COR,* cerebello oculorenal; K, kidney involvement; L, liver involvement; MTS, molar tooth sign; *OFDVI,* orofaciodigital type VI syndrome. *(From Romani M, Micalizzi A, Valente EM: Joubert syndrome: congenital cerebellar ataxia with the molar tooth.* Lancet Neurol *12:894–905, 2013, Fig. 3.)*

horn cell involvement), type II (with extrapyramidal features, seizures, and acquired microcephaly), Walker-Warburg syndrome, muscle-eye-brain disease, congenital disorders of glycosylation type 1A, mitochondrial cytopathies, teratogen exposure, congenital cytomegalovirus infection, 3-methylglutaconic aciduria, PEHO syndrome (progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy), autosomal recessive cerebellar hypoplasia in the Hutterite population, lissencephaly with cerebellar hypoplasia, and other subtypes of pontocerebellar hypoplasia.

Bibliography is available at Expert Consult.

591.10 Microcephaly

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Microcephaly is defined as a head circumference that measures more than 3 SD below the mean for age and sex. This condition is relatively common, particularly among developmentally delayed children. Although there are many causes of microcephaly, abnormalities in neuronal migration during fetal development, including heterotopias of neuronal cells and cytoarchitectural derangements, are often found. Microcephaly may be subdivided into 2 main groups: primary (genetic) microcephaly and secondary (nongenetic) microcephaly. A precise diagnosis is important for genetic counseling and for prediction for future pregnancies.

ETIOLOGY

Primary microcephaly refers to a group of conditions that usually have no associated malformations and follow a mendelian pattern of inheritance or are associated with a specific genetic syndrome. Affected infants are usually identified at birth because of a small head circumference. The more common types include familial and autosomal dominant microcephaly and a series of chromosomal syndromes that are summarized in Table 591-3. Primary microcephaly is also associated with at least 7 gene loci, and 7 single etiologic genes have been identified. It is known as autosomal recessive primary microcephaly and has autosomal inheritance. Many X-linked causes of microcephaly are caused by gene mutations that lead to severe structural brain

Table 591-3 Causes of Microcephaly

CAUSES	CHARACTERISTIC FINDINGS
PRIMARY (GENETIC)	
Familial (autosomal recessive)	Incidence 1 in 40,000 live births Typical appearance with slanted forehead, prominent nose and ears; severe mental retardation and prominent seizures; surface convolutional markings of the brain, poorly differentiated and disorganized cytoarchitecture
Autosomal dominant	Nondistinctive facies, upslanting palpebral fissures, mild forehead slanting, and prominent ears Normal linear growth, seizures readily controlled, and mild or borderline mental retardation
Syndromes	
Down (trisomy 21)	Incidence 1 in 800 live births Abnormal rounding of occipital and frontal lobes and a small cerebellum; narrow superior temporal gyrus, propensity for Alzheimer neurofibrillary alterations, ultrastructure abnormalities of cerebral cortex
Edward (trisomy 18)	Incidence 1 in 6,500 live births Low birthweight, microstomia, micrognathia, low-set malformed ears, prominent occiput, rocker-bottom feet, flexion deformities of fingers, congenital heart disease, increased gyri, heterotopias of neurons
Cri-du-chat (5 p-)	Incidence 1 in 50,000 live births Round facies, prominent epicanthic folds, low-set ears, hypertelorism, characteristic cry No specific neuropathology
Cornelia de Lange	Prenatal and postnatal growth delay; synophrys; thin, downturning upper lip Proximally placed thumb
Rubinstein-Taybi	Beaked nose, downward slanting of palpebral fissures, epicanthic folds, short stature, broad thumbs and toes
Smith-Lemli-Opitz	Ptosis, scaphocephaly, inner epicanthic folds, anteverted nostrils Low birthweight, marked feeding problems
SECONDARY (NONGENETIC)	
Congenital Infections	
Cytomegalovirus	Small for dates, petechial rash, hepatosplenomegaly, chorioretinitis, deafness, mental retardation, seizures Central nervous system calcification and microgyria
Rubella	Growth retardation, purpura, thrombocytopenia, hepatosplenomegaly, congenital heart disease, chorioretinitis, cataracts, deafness Perivascular necrotic areas, polymicrogyria, heterotopias, subependymal cavitations
Toxoplasmosis	Purpura, hepatosplenomegaly, jaundice, convulsions, hydrocephalus, chorioretinitis, cerebral calcification
Drugs	
Fetal alcohol	Growth retardation, ptosis, absent philtrum and hypoplastic upper lip, congenital heart disease, feeding problems, neuroglial heterotopia, disorganization of neurons
Fetal hydantoin	Growth delay, hypoplasia of distal phalanges, inner epicanthic folds, broad nasal ridge, anteverted nostrils
Other Causes	
Radiation	Microcephaly and mental retardation most severe with exposure before 15th wk of gestation
Meningitis/encephalitis	Cerebral infarcts, cystic cavitation, diffuse loss of neurons
Malnutrition	Controversial cause of microcephaly
Metabolic	Maternal diabetes mellitus and maternal hyperphenylalaninemia
Hyperthermia	Significant fever during 1st 4-6 wk has been reported to cause microcephaly, seizures, and facial anomalies Pathologic studies show neuronal heterotopias Further studies show no abnormalities with maternal fever
Hypoxic–ischemic encephalopathy	Initially diffuse cerebral edema; late stages characterized by cerebral atrophy and abnormal signals on MRI

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malformations such as lissencephaly, holoprosencephaly, polymicrogyria, cobblestone dysplasia, neuronal heterotopia, pontocerebellar hypoplasia; these should be sought on MRI. Secondary microcephaly results from a large number of noxious agents that can affect a fetus in utero or an infant during periods of rapid brain growth, particularly the 1st 2 yr of life.

Acquired microcephaly can be seen in conditions such as Rett, Seckel, and Angelman syndromes and in encephalopathy syndromes associated with severe seizure disorders.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

A thorough family history should be taken, seeking additional cases of microcephaly or disorders affecting the nervous system. It is important to measure a patient's head circumference at birth to diagnose microcephaly as early as possible. A very small head circumference implies a process that began early in embryonic or fetal development. An insult to the brain that occurs later in life, particularly beyond the age of 2 yr, is less likely to produce severe microcephaly. Serial head circumference measurements are more meaningful than a single determination, particularly when the abnormality is minimal. The head circumference of each parent and sibling should be recorded.

Laboratory investigation of a microcephalic child is determined by the history and physical examination. If the cause of the microcephaly is unknown, the mother's serum phenylalanine level should be determined. High phenylalanine serum levels in an asymptomatic mother can produce marked brain damage in an otherwise normal nonphenylketonuric infant. A karyotype and/or array comparative genomic hybridization study is obtained if a chromosomal syndrome is suspected or if the child has abnormal facies, short stature, and additional congenital anomalies. MRI is useful in identifying structural abnormalities of the brain such as lissencephaly, pachygyria, and polymicrogyria, and CT scanning is useful to detect intracerebral calcification. Additional studies include a fasting plasma and urine amino acid analysis; serum ammonia determination; *to*xoplasmosis, *r*ubella, *c*ytomegalovirus, and *h*erpes simplex (TORCH) titers as well as HIV testing of the mother and child; and a urine sample for the culture of cytomegalovirus. Single-gene mutations as a cause of both primary microcephaly and syndromic microcephaly are being increasingly identified.

TREATMENT

Once the cause of microcephaly has been established, the physician must provide accurate and supportive genetic and family counseling. Because many children with microcephaly are also intellectually challenged, the physician must assist with placement in an appropriate program that will provide for maximal development of the child (see Chapter 36).

Bibliography is available at Expert Consult.

591.11 Hydrocephalus

Stephen L. Kinsman and Michael V. Johnston

Hydrocephalus is not a specific disease; it represents a diverse group of conditions that result from impaired circulation and/or absorption of CSF or, in rare circumstances, from increased production of CSF by a choroid plexus papilloma (Table 591-4). Because megalencephaly is often discovered as part of an evaluation for hydrocephalus in children with macrocephaly, it is included in this section.

PHYSIOLOGY

The CSF is formed primarily in the ventricular system by the choroid plexus, which is situated in the lateral, third, and fourth ventricles. Although most CSF is produced in the lateral ventricles, approximately 25% originates from extrachoroidal sources, including the capillary endothelium within the brain parenchyma. There is active neurogenic control of CSF formation because adrenergic and cholinergic nerves innervate the choroid plexus. Stimulation of the adrenergic system diminishes CSF production, whereas excitation of the cholinergic nerves may double the normal CSF production rate. In a normal child, approximately 20 mL/hr of CSF is produced. The total volume of CSF approximates 50 mL in an infant and 150 mL in an adult. Most of the CSF is extraventricular. The choroid plexus forms CSF in several stages; through a series of intricate steps, a plasma ultrafiltrate is ultimately processed into a secretion, the CSF.

Table 591-4 Causes of Hydrocephalus
COMMUNICATING
Achondroplasia
Basilar impression
Benign enlargement of subarachnoid space
Choroid plexus papilloma
Meningeal malignancy
Meningitis
Posthemorrhagic
NONCOMMUNICATING
Aqueductal stenosis
Infectious*
X-linked
Mitochondrial
Autosomal recessive
Autosomal dominant
L1CAM mutations
Chiari malformation
Dandy-Walker malformation
Klippel-Feil syndrome
Mass lesions
Abscess
Hematoma
Tumors and neurocutaneous disorders
Vein of Galen malformation
Walker-Warburg syndrome
HYDRANENCEPHALY
Holoprosencephaly
Massive hydrocephalus
Porencephaly

*Toxoplasmosis, neurocysticercosis mumps.

From Fenichel GM: Clinical pediatric neurology, *ed 5, Philadelphia, 2005, Elsevier, p. 354.*

CSF flow results from the pressure gradient that exists between the ventricular system and venous channels. Intraventricular pressure may be as high as 180 mm H_2O in the normal state, whereas the pressure in the superior sagittal sinus is in the range of 90 mm H_2O. Normally, CSF flows from the lateral ventricles through the foramina of Monro into the 3rd ventricle. It then traverses the narrow aqueduct of Sylvius, which is approximately 3 mm long and 2 mm in diameter in a child, to enter the fourth ventricle. The CSF exits the fourth ventricle through the paired lateral foramina of Luschka and the midline foramen of Magendie into the cisterns at the base of the brain. Hydrocephalus resulting from obstruction within the ventricular system is called obstructive or noncommunicating hydrocephalus. The CSF then circulates from the basal cisterns posteriorly through the cistern system and over the convexities of the cerebral hemispheres. CSF is absorbed primarily by the arachnoid villi through tight junctions of their endothelium by the pressure forces that were noted earlier. CSF is absorbed to a much lesser extent by the lymphatic channels directed to the paranasal sinuses, along nerve root sleeves, and by the choroid plexus itself. Hydrocephalus resulting from obliteration of the subarachnoid cisterns or malfunction of the arachnoid villi is called nonobstructive or communicating hydrocephalus.

PATHOPHYSIOLOGY AND ETIOLOGY

Obstructive or noncommunicating hydrocephalus develops most commonly in children because of an abnormality of the aqueduct of Sylvius or a lesion in the fourth ventricle. Aqueductal stenosis results from an abnormally narrow aqueduct of Sylvius that is often associated with

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branching or forking. In a small percentage of cases, aqueductal stenosis is inherited as a sex-linked recessive trait. These patients occasionally have minor neural tube closure defects, including spina bifida occulta. Rarely, aqueductal stenosis is associated with neurofibromatosis. Aqueductal gliosis can also give rise to hydrocephalus. As a result of neonatal meningitis or a subarachnoid hemorrhage in a premature infant, the ependymal lining of the aqueduct is interrupted and a brisk glial response results in complete obstruction. Intrauterine viral infections can also produce aqueductal stenosis followed by hydrocephalus, and mumps meningoencephalitis has been reported as a cause in a child. A vein of Galen malformation can expand to become large and, because of its midline position, obstruct the flow of CSF. Lesions or malformations of the posterior fossa are prominent causes of hydrocephalus, including posterior fossa brain tumors, Chiari malformation, and the Dandy-Walker syndrome.

Nonobstructive or communicating hydrocephalus most commonly follows a subarachnoid hemorrhage, which is usually a result of intraventricular hemorrhage in a premature infant. Blood in the subarachnoid spaces can cause obliteration of the cisterns or arachnoid villi and obstruction of CSF flow. Pneumococcal and tuberculous meningitis have a propensity to produce a thick, tenacious exudate that obstructs the basal cisterns, and intrauterine infections can also destroy the CSF pathways. Leukemic infiltrates can seed the subarachnoid space and produce communicating hydrocephalus.

CLINICAL MANIFESTATIONS

The clinical presentation of hydrocephalus is variable and depends on many factors, including the age at onset, the nature of the lesion causing obstruction, and the duration and rate of increase of the intracranial pressure (ICP). In an infant, an accelerated rate of enlargement of the head is the most prominent sign. In addition, the anterior fontanel is wide open and bulging, and the scalp veins are dilated. The forehead is broad, and the eyes might deviate downward because of impingement of the dilated suprapineal recess on the brainstem tectum, producing the setting-sun eye sign. Long-tract signs, including brisk tendon reflexes, spasticity, clonus (particularly in the lower extremities), and Babinski sign, are common owing to stretching and disruption of the corticospinal fibers originating from the leg region of the motor cortex. In an older child, the cranial sutures are less accommodating so that the signs of hydrocephalus may be subtler. Irritability, lethargy, poor appetite, and vomiting are common to both age groups, and headache is a prominent symptom in older patients. A gradual change in personality and deterioration in academic productivity suggest a slowly progressive form of hydrocephalus. With regard to other clinical signs, serial measurements of the head circumference often indicate an increased velocity of growth. Percussion of the skull might produce a cracked pot sound or Macewen sign, indicating separation of the sutures. A foreshortened occiput suggests Chiari malformation, and a prominent occiput suggests the Dandy-Walker malformation. Papilledema, abducens nerve palsies, and pyramidal tract signs, which are most evident in the lower extremities, are apparent in many cases.

Chiari malformation consists of 2 major subgroups. Type I typically produces symptoms during adolescence or adult life and is usually not associated with hydrocephalus. Patients complain of recurrent headache, neck pain, urinary frequency, and progressive lower-extremity spasticity. The deformity consists of displacement of the cerebellar tonsils into the cervical canal (Fig. 591-12). Syrinx of the spinal cord, especially the cervical region should be looked for on MRI imaging. Although the pathogenesis is unknown, a prevailing theory suggests that obstruction of the caudal portion of the fourth ventricle during fetal development is responsible. Other theories include tethering of the cord or additional anomalies (syrinx).

The type II Chiari malformation is characterized by progressive hydrocephalus with a myelomeningocele. This lesion represents an anomaly of the hindbrain, probably owing to a failure of pontine flexure development during embryogenesis, and results in elongation of the fourth ventricle and kinking of the brainstem, with displacement of the inferior vermis, pons, and medulla into the cervical canal

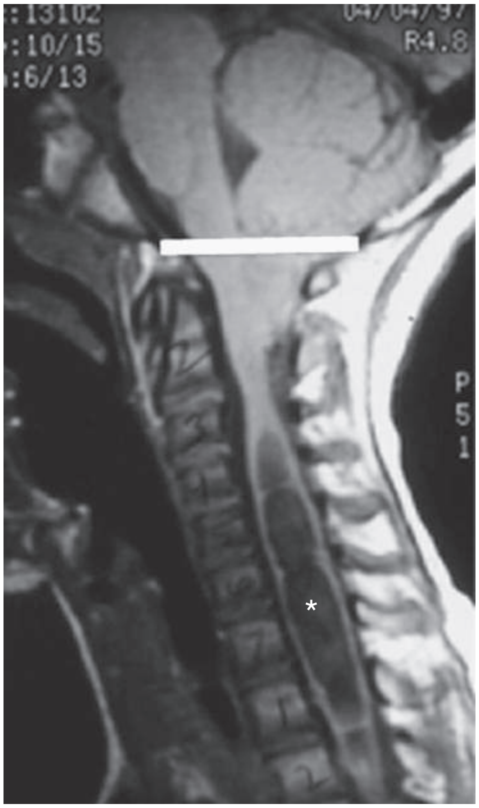

Figure 591-12 Sagittal MR scan of a patient with Chiari malformation type I. Cerebellar tonsils are displaced through the foramen magnum *(white bar)* to the lower aspect of C2 with clear crowding at the foramen. A syrinx *(white asterisk)* is visible extending from C3 to T2. *(From Yassari R, Frim D: Evaluation and management of the Chiari malformation type 1 for the primary care pediatrician,* Pediatr Clin North Am *51:477–490, 2004.)*

(Fig. 591-13). Approximately 10% of type II malformations produce symptoms during infancy, consisting of stridor, weak cry, and apnea, which may be relieved by shunting or by decompression of the posterior fossa. A more indolent form consists of abnormalities of gait, spasticity, and increasing incoordination (including the arms and hands) during childhood.

Plain skull radiographs show a small posterior fossa and a widened cervical canal. CT scanning with contrast and MRI display the cerebellar tonsils protruding downward into the cervical canal and the hindbrain abnormalities. The anomaly is treated by surgical decompression, but asymptomatic or mildly symptomatic patients may be managed conservatively.

The Dandy-Walker malformation consists of a cystic expansion of the fourth ventricle in the posterior fossa and midline cerebellar hypoplasia, which results from a developmental failure of the roof of the fourth ventricle during embryogenesis (Fig. 591-14). Approximately 90% of patients have hydrocephalus, and a significant number of children have associated anomalies, including agenesis of the posterior cerebellar vermis and corpus callosum. Infants present with a rapid increase in head size and a prominent occiput. Transillumination of the skull may be positive. Most children have evidence of long-tract signs, cerebellar ataxia, and delayed motor and cognitive milestones, probably due to the associated structural anomalies. The Dandy-Walker malformation is managed by shunting the cystic cavity (and on occasion the ventricles as well) in the presence of hydrocephalus.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Investigation of a child with hydrocephalus begins with the history. Familial cases suggest X-linked or autosomal hydrocephalus secondary to aqueductal stenosis. A past history of prematurity with intracranial

hemorrhage, meningitis, or mumps encephalitis is important to ascertain. Multiple café-au-lait spots and other clinical features of neurofibromatosis point to aqueductal stenosis as the cause of hydrocephalus.

Examination includes careful inspection, palpation, and auscultation of the skull and spine. The occipitofrontal head circumference is recorded and compared with previous measurements. The size and configuration of the anterior fontanel are noted, and the back is inspected for abnormal midline skin lesions, including tufts of hair, lipoma, or angioma that might suggest spinal dysraphism. The presence of a prominent forehead or abnormalities in the shape of the occiput can suggest the pathogenesis of the hydrocephalus. A cranial bruit is audible in association with many cases of vein of Galen arteriovenous malformation. Transillumination of the skull is positive with massive dilation of the ventricular system or in the Dandy-Walker syndrome. Inspection of the eyegrounds is mandatory because the finding of chorioretinitis suggests an intrauterine infection, such as toxoplasmosis, as a cause of the hydrocephalus. Papilledema is observed in older children but is rarely present in infants because the cranial sutures separate as a result of the increased pressure.

Plain skull films typically show separation of the sutures, erosion of the posterior clinoids in an older child, and an increase in convolutional markings (beaten-silver appearance) on the inside of the skull with long-standing increased ICP. The CT scan and/or MRI along with ultrasonography in an infant are the most important studies to identify the specific cause and severity of hydrocephalus.

The head might appear enlarged (and can be confused with hydrocephalus) secondary to a thickened cranium resulting from chronic anemia, rickets, osteogenesis imperfecta, and epiphyseal dysplasia. Chronic subdural collections can produce bilateral parietal bone prominence. MRI has revealed the common occurrence of benign external hydrocephalus, a growth-limited condition where intervention is rarely required. Various metabolic and degenerative disorders of the CNS produce megalencephaly as a result of abnormal storage of substances within the brain parenchyma. These disorders include lysosomal diseases (Tay-Sachs disease, gangliosidosis, and the mucopolysaccharidoses), the aminoacidurias (maple syrup urine disease), and the leukodystrophies (metachromatic leukodystrophy, Alexander disease, Canavan disease). In addition, cerebral gigantism (Sotos syndrome), other overgrowth syndromes and neurofibromatosis are characterized by increased brain mass. Familial megalencephaly is inherited as an autosomal dominant trait and is characterized by delayed motor milestones and hypotonia but normal or near-normal intelligence. Measurement of parents' head circumferences is necessary to establish the diagnosis.

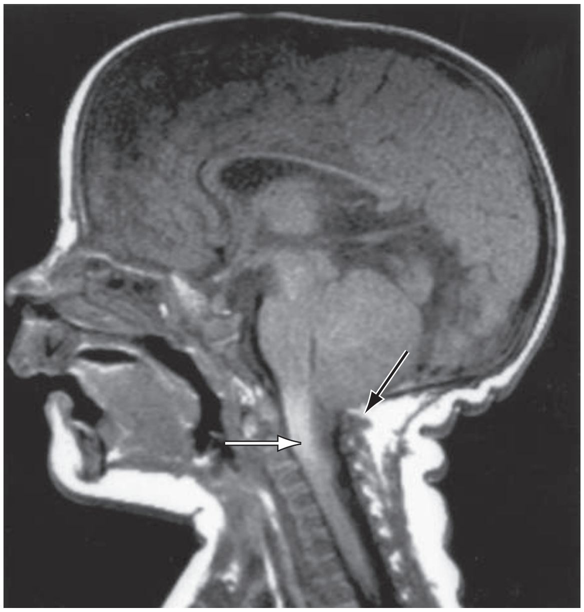

Figure 591-13 A midsagittal T1-weighted MRI of a patient with type II Chiari malformation. The cerebellar tonsils *(white arrow)* have descended below the foramen magnum *(black arrow)*. Note the small, slitlike fourth ventricle, which has been pulled into a vertical position.

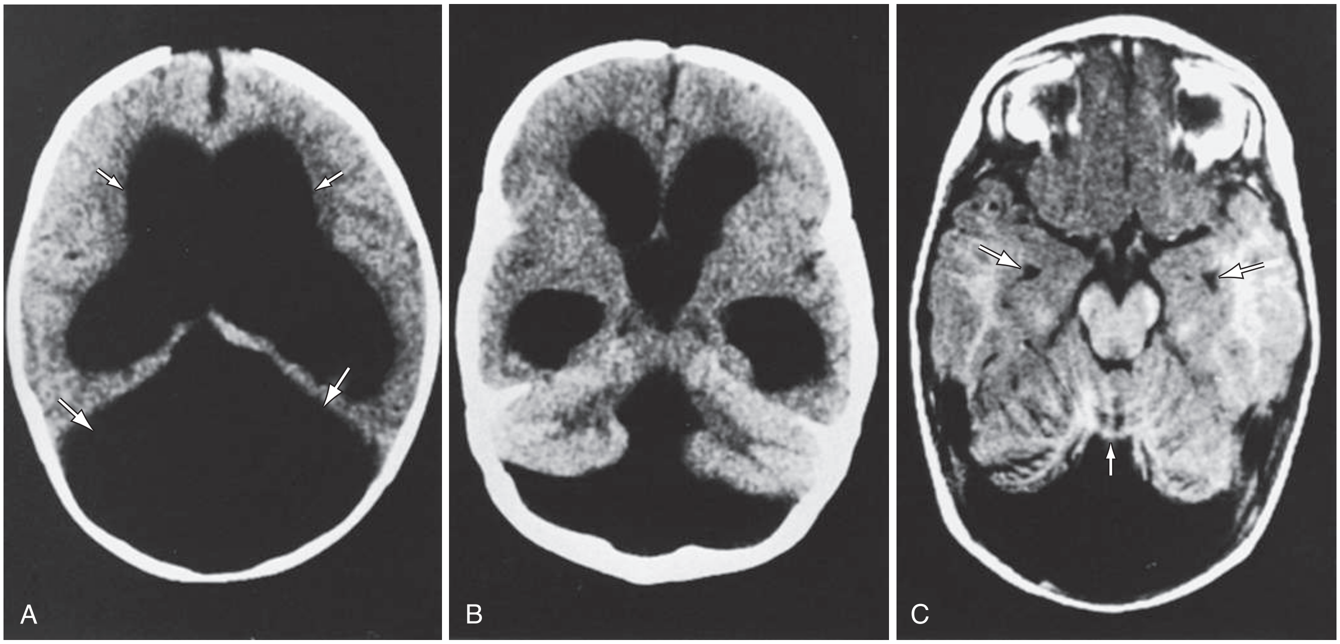

Figure 591-14 Dandy-Walker cyst. **A,** Axial CT scan (preoperative) showing large posterior fossa cyst (Dandy-Walker cyst; *large arrows*) and dilated lateral ventricles *(small arrows)*, a complication secondary to cerebrospinal fluid (CSF) pathway obstruction at the fourth ventricular outlet. **B,** Same patient, with a lower axial CT scan showing splaying of the cerebellar hemispheres by the dilated fourth ventricle (Dandy-Walker cyst). The dilated ventricles proximal to the fourth ventricle again show CSF obstruction caused by the Dandy-Walker cyst. **C,** MRI of the same patient showing decreased size of the Dandy-Walker cyst and temporal horns *(arrows)* after shunting. The incomplete vermis *(small arrow)* now becomes recognizable.

MEGALENCEPHALY

Megalencephaly is an anatomic disorder of brain growth defined as a brain weight : volume ratio >98th percentile for age (or ≥2 SD above the mean) that is usually accompanied by macrocephaly (an occipitofrontal circumference >98th percentile). Various storage and degenerative diseases are associated with megalencephaly, but anatomic and genetic causes exist as well. The most common cause of anatomic megalencephaly is benign familial megalencephaly. This condition is easily diagnosed by careful family history and measurement of the parents' head circumferences (occipitofrontal circumferences). On the other hand, macrocephaly is a known feature of more than 100 syndromes.

Anatomic megalencephaly is usually apparent at birth, and head growth continues to run parallel to the upper percentiles. Sometimes, in some syndromes, increased occipitofrontal circumference is the presenting sign. Neuroimaging is critical in identifying the various structural and gyral abnormalities seen in syndromic macrocephaly and determining whether anatomic megalencephaly exists.

Common megalencephaly-associated macrocephaly syndromes include syndromes with prenatal and/or postnatal somatic overgrowth such as Sotos, Simpson-Golabi-Behmel, fragile X, Weaver, macrocephaly-cutis marmorata telangiectatica congenita, and Bannayan-Ruvalcaba-Riley syndromes, and syndromes without somatic overgrowth such as FG, Greig cephalopolysyndactyly, acrocallosal, and Gorlin.

Sotos syndrome (cerebral gigantism) is the most common megalencephalic syndrome, with 50% of patients having prenatal macrocephaly and 100% of patients having macrocephaly by age 1 yr. Early postnatal overgrowth normalizes by adulthood. Facial features include high forehead with frontal bossing, sparse hair in the frontoparietal region, downslanting palpebral fissures, apparent hypertelorism, long narrow face, prominent mandible, and malar flushing. Hypotonia, poor coordination, and speech delay are common. Most children show cognitive impairment, ranging from mild to severe.

HYDRANENCEPHALY

Hydranencephaly may be confused with hydrocephalus. The cerebral hemispheres are absent or represented by membranous sacs with remnants of frontal, temporal, or occipital cortex dispersed over the membrane. The midbrain and brainstem are relatively intact (Fig. 591-15).

Figure 591-15 Hydranencephaly. MRI scan showing the brainstem and spinal cord with remnants of the cerebellum and the cerebral cortex. The remainder of the cranium is filled with cerebrospinal fluid.

The cause of hydranencephaly is unknown, but bilateral occlusion of the internal carotid arteries during early fetal development would explain most of the pathologic abnormalities. Affected infants can have a normal or enlarged head circumference at birth that grows at an excessive rate postnatally. Transillumination shows an absence of the cerebral hemispheres. The child is irritable, feeds poorly, develops seizures and spastic quadriparesis, and has little or no cognitive development. A ventriculoperitoneal shunt prevents massive enlargement of the cranium.

TREATMENT

Therapy for hydrocephalus depends on the cause. Medical management, including the use of acetazolamide and furosemide, can provide temporary relief by reducing the rate of CSF production, but long-term results have been disappointing. Most cases of hydrocephalus require extracranial shunts, particularly a ventriculoperitoneal shunt. Endoscopic third ventriculostomy has evolved as a viable approach and criteria have been developed for its use, but the procedure might need to be repeated to be effective. Ventricular shunting may be avoided with this approach. The major complications of shunting are occlusion (characterized by headache, papilledema, emesis, mental status changes) and bacterial infection (fever, headache, meningismus), usually caused by *Staphylococcus epidermidis*. With meticulous preparation, the shunt infection rate can be reduced to <5%. The results of intrauterine surgical management of fetal hydrocephalus have been poor (possibly because of the high rate of associated cerebral malformations in addition to the hydrocephalus) except for some promise in cases of hydrocephalus associated with fetal meningomyelocele.

PROGNOSIS

Prognosis depends on the cause of the dilated ventricles and not on the size of the cortical mantle at the time of operative intervention, except in cases in which the cortical mantle has been severely compressed and stretched. Hydrocephalic children are at increased risk for various developmental disabilities. The mean intelligence quotient is reduced compared with the general population, particularly for performance tasks as compared with verbal abilities. Many children have abnormalities in memory function. Vision problems are common, including strabismus, visuospatial abnormalities, visual field defects, and optic atrophy with decreased acuity secondary to increased ICP. The visual evoked potential latencies are delayed and take some time to recover after correction of the hydrocephalus. Although most hydrocephalic children are pleasant and mild mannered, some children show aggressive and delinquent behavior. Accelerated pubertal development in patients with shunted hydrocephalus or myelomeningocele is relatively common, possibly because of increased gonadotropin secretion in response to increased ICP. It is imperative that hydrocephalic children receive long-term follow-up in a multidisciplinary setting.

Bibliography is available at Expert Consult.

591.12 Craniosynostosis

Stephen L. Kinsman and Michael V. Johnston

Craniosynostosis is defined as premature closure of the cranial sutures and is classified as primary or secondary. It is associated with varying types of abnormal skull shape. Primary craniosynostosis refers to closure of 1 or more sutures owing to abnormalities of skull development, whereas secondary craniosynostosis results from failure of brain growth and expansion and is not discussed here. The incidence of primary craniosynostosis approximates 1 in 2,000 live births. The cause is unknown in the majority of children; however, genetic syndromes account for 10-20% of cases. Deformational forces appear important in occipital and frontal plagiocephaly in many cases. Early detection of posterior skull shape is critical and allows successful intervention to be offered in the form of physical therapy for torticollis and other positional asymmetries that lead to plagiocephaly.

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DEVELOPMENT AND ETIOLOGY

The bones of the cranium are well developed by the 5th mo of gestation (frontal, parietal, temporal, and occipital) and are separated by sutures and fontanels. The brain grows rapidly in the 1st several yr of life and is normally not impeded because of equivalent growth along the suture lines. The cause of craniosynostosis is unknown, but the prevailing hypothesis suggests that abnormal development of the base of the skull creates exaggerated forces on the dura that act to disrupt normal cranial suture development. Genetic factors have been identified for some isolated and for many syndromic causes of craniosynostosis (Table 591-5).

Table 591-5 Commonly Used Clinical Genetic Classifications of Craniosynostoses

DISORDER	CAUSE
ISOLATED CRANIOSYNOSTOSIS	
Morphologically described	Unknown, uterine constraint, or *FGFR3* mutation
SYNDROMIC CRANIOSYNOSTOSIS	
Antler-Bixler syndrome	Unknown
Apert syndrome	Usually 1 of 2 mutations in *FGFR2*
Beare-Stevenson syndrome	Mutation in *GFGR2* or *FGFR3*
Baller-Gerold syndrome	Mutation in *TWIST* heterogenous
Carpenter syndrome	Unknown
Craniofrontonasal dysplasia	Unknown gene at *Xp22*
Crouzon syndrome	Numerous different mutations at *FGFR2*
Crouzonomesodermoskeletal syndrome	Mutation in *FGFR3*
Jackson-Weiss syndrome	Mutation in *FGFR2*
Muenke syndrome	Mutation in *FGFR3*
Pfeiffer syndrome	Mutation in *FGFR1* or numerous mutation in *FGFR2*
Saethre-Chotzen syndrome	Mutation in *TWIST*
Shprintzen-Goldberg syndrome	Mutation in *FBEN1*

From Ridgway EB, Weiner HL: Skull deformities, Pediatr Clin North Am *51:359–387, 2004.*

CLINICAL MANIFESTATIONS AND TREATMENT

Most cases of craniosynostosis are evident at birth and are characterized by a skull deformity that is a direct result of premature suture fusion. Palpation of the suture reveals a prominent bony ridge, and fusion of the suture may be confirmed by plain skull roentgenograms, CT scan, or bone scan in ambiguous cases (Table 591-6).

Premature closure of the sagittal suture produces a long and narrow skull, or **scaphocephaly,** the most common form of craniosynostosis. Scaphocephaly is associated with a prominent occiput, a broad forehead, and a small or absent anterior fontanel. The condition is sporadic, is more common in males, and often causes difficulties during labor because of cephalopelvic disproportion. Scaphocephaly does not produce increased ICP or hydrocephalus, and results of neurologic examination of affected patients are normal.

Frontal plagiocephaly is the next most common form of craniosynostosis and is characterized by unilateral flattening of the forehead, elevation of the ipsilateral orbit and eyebrow, and a prominent ear on the corresponding side. The condition is more common in females and is the result of premature fusion of a coronal and sphenofrontal suture. Surgical intervention produces a cosmetically pleasing result. When imaging does not reveal a closed suture, positional factors are of primary importance.

Occipital plagiocephaly is most often a result of positioning during infancy and is more common in an immobile child or a child with a disability, but fusion or sclerosis of the lambdoid suture can cause unilateral occipital flattening and bulging of the ipsilateral frontal bone. **Trigonocephaly** is a rare form of craniosynostosis caused by premature fusion of the metopic suture. These children have a keel-shaped forehead and hypotelorism and are at risk for associated developmental abnormalities of the forebrain. Milder forms of metopic ridging are more common. **Turricephaly** refers to a cone-shaped head from premature fusion of the coronal, and often sphenofrontal and frontoethmoidal, sutures. The **kleeblattschädel deformity** is a peculiarly shaped skull that resembles a cloverleaf. Affected children have very prominent temporal bones, and the remainder of the cranium is constricted. Hydrocephalus is a common complication.

Premature fusion of only 1 suture rarely causes a neurologic deficit. In this situation, the sole indication for surgery is to enhance the child's cosmetic appearance, and the prognosis depends on the suture involved

Table 591-6 Epidemiology and Clinical Characteristics of the Common Craniosynostoses

TYPE	EPIDEMIOLOGY	SKULL DEFORMITY	CLINICAL PRESENTATION
Sagittal	Most common CSO affecting a single suture, 80% male	Dolicocephaly or scaphocephaly (boat-shaped)	Frontal bossing, prominent occiput, palpable keel ridge. OFC normal and reduced biparietal diameter
Coronal	18% of CSO, more common in girls Associated with Apert syndrome (with syndactyly) and Crouzon disease, which includes abnormal sphenoid, orbital, and facial bones (hypoplasia of the midface)	Unilateral: plagiocephaly Bilateral: brachycephaly, acrocephaly	Unilateral: flattened forehead on affected side, flat checks, nose deviation on normal side; higher supraorbital margin leading to harlequin sign on radiograph and outward rotation of orbit can result in amblyopia Bilateral: broad, flattened forehead. In Apert syndrome accompanied by syndactyly and in Crouzon disease by hypoplasia of the midface and progressive proptosis
Lambdoid	10-20% of CSO, M:F ratio 4:1	Lambdoid/occipital plagiocephaly; right side affected in 70% of cases	Unilateral: flattening of occiput, indentation along synostotic suture, bulging of ipsilateral forehead leading to rhomboid skull, ipsilateral ear is anterior and inferior Bilateral: brachycephaly with bilateral anteriorly and inferiorly displaced ears
Metopic	Association with 19p chromosome abnormality	Trigonocephaly	Pointed forehead and midline ridge, hypotelorism
Multiple		Oxycephaly	Tower skull with undeveloped sinuses and shallow orbits, and elevated intercranial pressure

CSO, craniosynostosis; OFC, occipital-frontal circumference.

From Ridgway EB, Weiner HL: Skull deformities, Pediatr Clin North Am *51:359–387, 2004.*

and on the degree of disfigurement. Neurologic complications, including hydrocephalus and increased ICP, are more likely to occur when 2 or more sutures are prematurely fused, in which case operative intervention is essential. The role of early repositioning efforts and therapy for torticollis and the use of cranial molding devices are beyond the scope of this review.

The most prevalent genetic disorders associated with craniosynostosis include Crouzon, Apert, Carpenter, Chotzen, and Pfeiffer syndromes. Crouzon syndrome is characterized by premature craniosynostosis and is inherited as an autosomal dominant trait. The shape of the head depends on the timing and order of suture fusion but most often is a compressed back-to-front diameter or brachycephaly resulting from bilateral closure of the coronal sutures. The orbits are underdeveloped, and ocular proptosis is prominent. Hypoplasia of the maxilla and orbital hypertelorism are typical facial features.

Apert syndrome has many features in common with Crouzon syndrome. Apert syndrome is usually a sporadic condition, although autosomal dominant inheritance can occur. It is associated with premature fusion of multiple sutures, including the coronal, sagittal, squamosal, and lambdoid sutures. The facies tend to be asymmetric, and the eyes are less proptotic than in Crouzon syndrome. Apert syndrome is characterized by syndactyly of the 2nd, 3rd, and 4th fingers, which may be joined to the thumb and the 5th finger. Similar abnormalities often occur in the feet. All patients have progressive calcification and fusion of the bones of the hands, feet, and cervical spine.

Carpenter syndrome is inherited as an autosomal recessive condition, and the many fusions of sutures tend to produce the kleeblattschädel skull deformity. Soft tissue syndactyly of the hands and feet is always present, and intellectual disability is common. Additional but less common abnormalities include congenital heart disease, corneal opacities, coxa valga, and genu valgum.

Chotzen syndrome is characterized by asymmetric craniosynostosis and plagiocephaly. The condition is the most prevalent of the genetic syndromes and is inherited as an autosomal dominant trait. It is associated with facial asymmetry, ptosis of the eyelids, shortened fingers, and soft tissue syndactyly of the 2nd and 3rd fingers.

Pfeiffer syndrome is most often associated with turricephaly. The eyes are prominent and widely spaced, and the thumbs and great toes are short and broad. Partial soft-tissue syndactyly may be evident. Most cases appear to be sporadic, but autosomal dominant inheritance has been reported.

Mutations of the fibroblast growth factor receptor (FGFR) gene family have been shown to be associated with phenotypically specific types of craniosynostosis. Mutations of the *FGFR1* gene located on chromosome 8 result in Pfeiffer syndrome; a similar mutation of the *FGFR2* gene causes Apert syndrome. Identical mutations of the *FGFR2* gene can result in both Pfeiffer and Crouzon phenotypes.

Each of the genetic syndromes poses a risk of additional anomalies, including hydrocephalus, increased ICP, papilledema, optic atrophy resulting from abnormalities of the optic foramina, respiratory problems secondary to a deviated nasal septum or choanal atresia, and disorders of speech and deafness. Craniectomy is mandatory for management of increased ICP, and a multidisciplinary craniofacial team is essential for the long-term follow-up of affected children. Craniosynostosis may be surgically corrected with good outcomes and relatively low morbidity and mortality, especially for nonsyndromic infants.

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Chapter 592 Deformational Plagiocephaly

René P. Myers, Aubrey N. Duncan, and John A. Girotto

Deformational plagiocephaly (DP), also known as positional plagiocephaly, is the development of cranial flattening and asymmetry in the infant *as a result of extrinsic molding forces placed on the skull, such as consistently sleeping on the same area of the head*. Since the suggestion to place sleeping infants on their backs to sleep for the prevention of the **sudden infant death syndrome**, the incidence of DP has risen dramatically, and this has caused concern for parents and clinicians in the primary care setting.

EPIDEMIOLOGY AND ETIOLOGY

Incidence

The incidence is frequent at 6 wk of age (16%), greatest at 4 mo of age (up to 20%), and then decreases over the next 3 yr (7% at 12 mo and 3.3% at 24 mo). It generally resolves completely by 2-3 yr of age. The American Academy of Pediatrics started a campaign in the 1990s that resulted in the recommendation to place infants on their backs or sides while sleeping, which resulted in a 40% decrease in sudden infant death syndrome cases. Within 4 yr, craniofacial centers and primary care offices reported a 600% increase in referrals for plagiocephaly, which was previously reported to be approximately 1 in 300 infants. This may be a result of increasing awareness or early referral, as point prevalence has not changed in the past 40 yr.

Infants cannot reposition their heads in the 1st few wk of life and are not able to hold their own heads up until about 4 mo of age. It is for this reason that DP is most severe around 4 mo of age. It is also during this time that an infant's head circumference is rapidly increasing: about 2 cm/month in the 1st 3 mo, 1 cm/month from 4-6 mo of age, and 0.5 cm/month after 6 mo of age. Around 6 mo of age, an infant has developed head control, and this ability to actively reposition their own head allows for the gradual improvement of the cranial shape because of pressure offloading and continued brain growth.

Risk Factors

Congenital torticollis, positional preference when sleeping, and lower levels of activity are especially prominent in patients with DP. Table 592-1 delineates other risk factors. Many of these risk factors cannot be prevented, but sleeping supine with the head always turned to the same side has been found to predict DP independent of the other factors, and this *can* be prevented. There may be an association between developmental delay and DP. Although not causal, studies have found significant differences in gross motor development such as sitting up, crawling, and rolling back to side, between babies with and without DP.

Table 592-1	Factors That Increase Risk for Deformational Plagiocephaly
Male	
Firstborn child	
Limited passive neck rotation at birth (e.g., congenital torticollis)	
Developmental delay	
Sleep position is supine at birth and at 6 weeks	
Bottle feeding only	
Tummy time <3 times/day	
Lower activity level, slower milestone achievement	
Sleeping with head to same side, positional preference	

Causes

Prenatal causes of DP include uterine compression and intrauterine constraint, such as occurs with oligohydramnios or multifetus gestation. Postnatal causes of DP include infant sleeping position and congenital muscular torticollis.

Muscular torticollis is a condition that is present in as many as 1 in 6 newborns and causes continuous tightening of muscles in the neck preventing passive rotation. It is thought that this condition typically precedes the development of cranial deformity. However, head position preference may result from cervical asymmetry that leads to torticollis and later flattening of a side of the skull from acquired positional preference (see Chapter 680.1).

Sleeping position plays a major role in the incidence of DP. When an infant continuously sleeps with the same part of the skull resting on a flat surface, a continuous force is placed in this area. During this time of rapid skull development, the growth is inhibited at the area where it rests on a hard surface, causing a "flat spot." Because of this inhibition, growth is increased in opposite directions causing a deformation that can be distinguished from other types of plagiocephaly.

EXAMINATION AND DIFFERENTIATING BETWEEN DEFORMATIONAL PLAGIOCEPHALY AND CRANIOSYNOSTOSIS

Abnormal head shape in an infant is distressing for parents. DP is a clinical diagnosis. Management also requires accurate counseling about its cause and treatment. It is especially important to be able to rule out **craniosynostosis** as a primary cause for cranial asymmetry in infants, as management of this condition is very different from that of DP and requires immediate referral to a craniofacial surgeon for evaluation (see Chapter 591.12). Craniosynostosis occurs in approximately 1 in 2,000 live births and results in plagiocephaly as a consequence of the early closure of skull sutures. Craniosynostosis must be distinguished from DP because the management is different. Lambdoidal craniosynostosis, although extremely rare (1 in 300,000 live births), presents with features most similar to those of DP. It can be distinguished from DP by a variety of historical and physical findings. Bilateral coronal synostosis also presents very similarly to posterior DP.

History and Physical Exam

Tables 592-2 and 592-3 outline the key components of history and physical examination.

Observation of the cranial shape as well as ear displacement are the first steps. It is critical to observe the child anteriorly, laterally, and from a vertex view. When cranial shape is viewed from above, DP typically looks like a **parallelogram**, and the ear on the same side of the flat or bald spot is **displaced anteriorly**. In lambdoidal craniosynostosis, the head has a trapezoid shape and the ear on the same side as the flat spot is posteriorly displaced (Fig. 592-1).

Palpation will help to differentiate these 2 conditions. Craniosynostosis presents with palpable ridges along the suture, whereas DP does not. Additionally, patients with craniosynostosis will not have mobile calvarial bones. This can be tested by applying gentle pressure on 2

Table 592-2 Important Historical and Physical Factors in the Evaluation of a Patient with Plagiocephaly

	DEFORMATIONAL	SYNOSTOTIC
Birth history	• Intrauterine compression • Firstborn child	• Typically no complications
Head shape at birth	• Typically normal	• Can be irregular
Age first noticed shape irregularity	• Usually in 1st few mo of life	• Can be at birth
How patient prefers to sleep	• Same side, same position • Same even during naps	• Variable
Bald spot	• Yes	• No
Motor development for age	• If age atypical for deformational plagiocephaly, typically slow motor development for age • Torticollis present • History of limited activity or mobility	• Varies depending on presence of concomitant syndrome
Tummy time	• Decreased	• Suggested time
Signs/symptoms of increasing intracranial pressure	• No	• Possible

Table 592-3 Key Differences Between Synostotic (Craniosynostosis) and Deformational Plagiocephaly

	DEFORMATIONAL PLAGIOCEPHALY	CRANIOSYNOSTOSIS
Causes	External forces applied to the skull • Prenatal: uterine compression, intrauterine constrained • Postnatal: congenital torticollis, sleeping position	Premature fusion of 1 or more cranial sutures
Common types	• Lateral • Posterior	• Bilateral coronal • Sagittal • Metopic
Common distinguishing features	• Normal round head shape at birth • Parallelogram shape to head • Ipsilateral ear anteriorly displaced • No palpable bony ridges	• Can have abnormal head shape at birth • Trapezoid shape to head • Ipsilateral ear posteriorly displaced • Palpable bony ridges
Management	• Repositioning • Physical therapy • Helmet in some cases	• Surgery • Helmet in some cases

Adapted from Nield LS, Brunner MD, Kamat D: The infant with a misshapen head. Clin Pediatr (Phila) *46:292–298, 2007, Tables 1 and 2.*

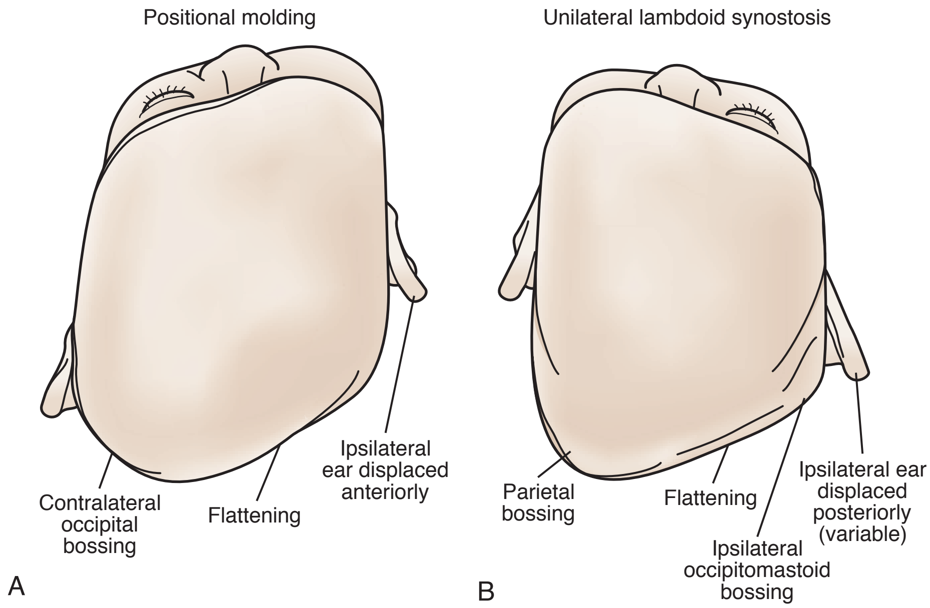

Figure 592-1 **Differentiating physical findings between deformational plagiocephaly and craniosynostosis.** Vertex views. **A,** Right-sided deformational plagiocephaly exhibiting a parallelogram head shape. **B,** Right-sided lambdoid craniosynostosis exhibiting a trapezoid-like head shape. *(From Lin AY, Losee JE: Pediatric plastic surgery. In Zitelli BJ, McIntire SC, Norwalk AJ, editors:* Zitelli and Davis' atlas of pediatric physical diagnosis, *ed 6, Philadelphia, 2012, Elsevier,* Fig. 22-5.*)*

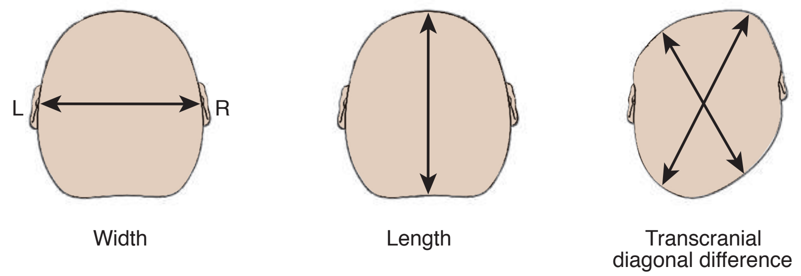

Figure 592-2 **Cranial measurements.** *(Modified from Looman WS, Flannery AB: Evidence-based care of the child with deformational plagiocephaly, part I: assessment and diagnosis.* J Pediatr Health Care *26:242–250, 2012, Table 1.)*

adjacent skull bones separated by a suspected synostotic suture. If the plates do not move relative to each other, then the suspicion for craniosynostosis is raised.

Verifying neck muscle tone and range of motion is a key part of the exam because it helps in evaluating motor development and in diagnosing congenital torticollis. Resistance to passive motion raises the concern for torticollis. Decreased tone should prompt further evaluation of motor development. Infants do not gain the muscle control to turn or lift their heads until approximately 4 mo of age, and delays in motor development could increase the infant's risk of DP at later ages than those at which it usually occurs. Decreased range of motion can also be seen in cervical spine abnormalities, although this is rare. Early recognition of these conditions is critical in treatment, management, and outcome.

Accurate and consistent measurements will help to distinguish etiologies and manage infants presenting with an abnormal-shape skull. Along with the usual head circumference measurements, the clinician should also measure cranial width, length, and transcranial diameter (as shown in Figure 592-2), which is best performed with calipers. These measurements allow the clinician to diagnose, determine severity, and monitor the plagiocephaly.

- *Cranial length:* Distance from the most prominent point between the eyebrows to the most prominent point of the occiput
- *Width:* Maximum transverse diameter, horizontal
- *Cephalic index* (cranial index): Ratio of the cranial width to the cranial length
- *Occipital-frontal transcranial diameter*: Find the points on either side of the head where the deformation is the worst (2 on the right, 2 on the left), then measure the **diagonal distances** between these points
- *Transdiagonal difference* (transcranial diagonal difference): The difference between 2 transcranial diameters
- *Cranial vault asymmetry:* Ratio of oblique measurements. This is difficult to implement because different physicians and authors propose varying points to use for these measurements

One technology for the evaluation of the severity and improvement over time of DP is the 3-dimensional photographic system. Advantages of this system include an easy and comfortable ability to image in an unbiased manner. Similarly, the use of laser scanners for the prefabrication scans for helmets is frequently employed by orthotists.

After observations and measurements the clinician can determine the type and severity of the DP (Table 592-4 and Fig. 592-3). For *lateral DP*, bossing of the occiput occurs opposite the flattened deformity and the ear on the same side as the flat area can be anteriorly displaced. This type of DP is typically associated with infants who have torticollis or a head position preference to 1 side. Transdiagonal diameter is typically abnormal in this type of plagiocephaly, and this measurement is the gold standard for determining severity.

In *posterior DP*, the occiput is uniformly flattened, temporal bossing can occur, and the ears are normal. It is usually associated with large head size and a history of limited activity or mobility. Cephalic index is increased with posterior DP.

Time and accurate exam records can help in management. If deformation is worsening when DP typically begins to demonstrate improving head shape, craniosynostosis should be suspected.

TREATMENT

Prevention

Sleep position should be monitored and varied. Alternating the infant's head to face the head and foot of the crib on alternate nights will allow the infant to sleep facing into the room without always lying on the same side of the head. Consistently alternating sleeping position early on allows the infant to have equal time on both sides of the occiput, and this will become a pattern the infant is used to. Infants who have

Table 592-4 Diagnostic Guide for Determining Type and Severity of Lateral and Posterior Deformational Plagiocephaly

TYPE

CLINICAL FINDINGS	LATERAL DEFORMATIONAL PLAGIOCEPHALY	POSTERIOR DEFORMATIONAL PLAGIOCEPHALY (BRACHYCEPHALY)
Occiput (vertex view)	Ipsilateral occipital flattening; contralateral occipital bossing	Uniform occipital flattening
Ear position (vertex view)	Ipsilateral ear may be anteriorly displaced	Normal
Face, forehead (anterior, lateral, and vertex views)	May be normal; more-severe cases may present with the following: mandibular asymmetry, ipsilateral frontal bossing, contralateral forehead flattening, ipsilateral cheek anteriorly displaced	Temporal bossing, increase in vertical height in severe cases
Other	Torticollis, head position preference	Large size, history of limited activity or limited mobility

SEVERITY

	LATERAL DEFORMATIONAL PLAGIOCEPHALY			POSTERIOR DEFORMATIONAL PLAGIOCEPHALY (BRACHYCEPHALY)	
Mild	TDD 3-10 mm	Type I	Flattening restricted to the back of the skull	CI: 0.82-0.9	Central posterior deformity ("ping-pong ball depression")
Moderate	TDD 10-12 mm	Type II	Malposition of ear	CI: 0.9-1.0	Central posterior deformity and widening of posterior skull
		Type III	Forehead deformity		
Severe	TDD >12 mm	Type IV	Malar deformity	CI: >1.0	Vertical head, head growth, or temporal bossing
		Type V	Vertical or temporal skull growth		

CI, cephalic index (cranial index); TDD, transcranial diameter difference.

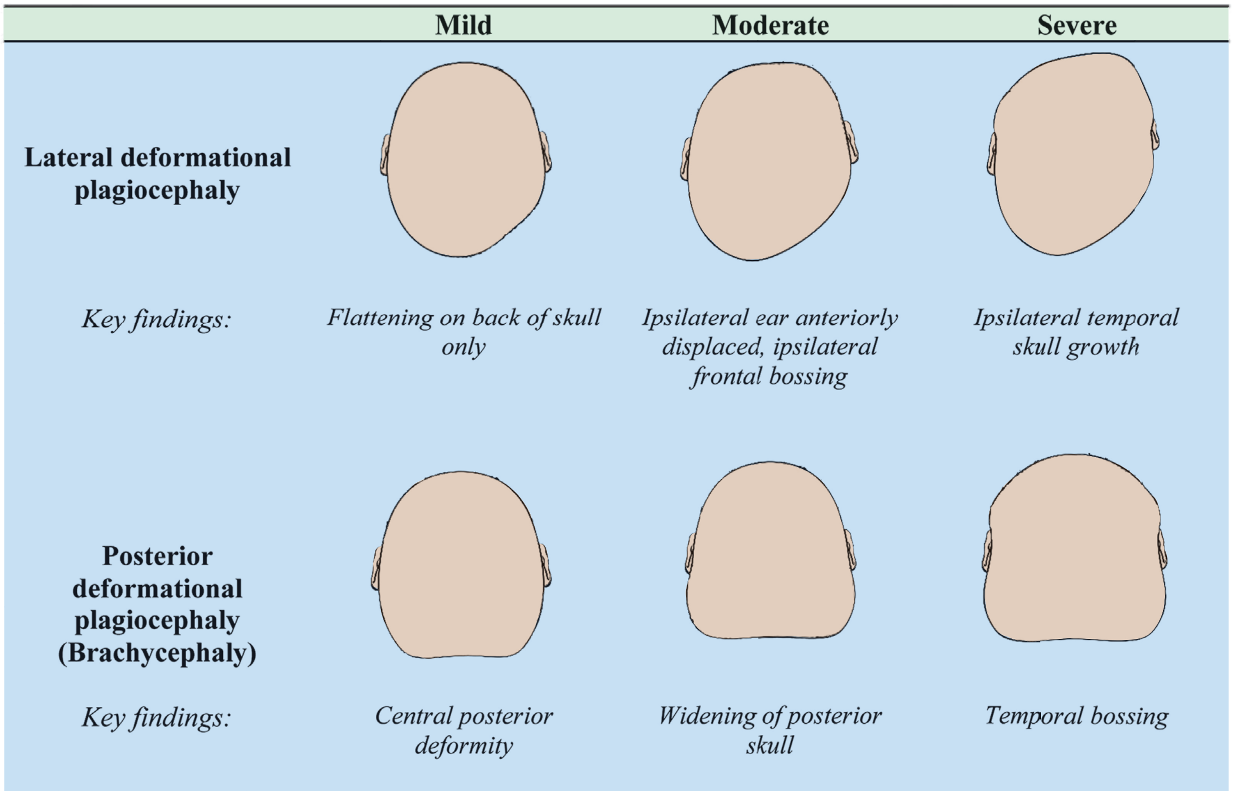

Figure 592-3 Types of deformational plagiocephaly. *(From Looman WS, Flannery AB: Evidence-based care of the child with deformational plagiocephaly, part I: assessment and diagnosis.* J Pediatr Health Care *26:242–250, 2012, Fig. 1.)*

an obvious positional preference to a particular side will take more time and effort in purposefully repositioning them counter to their preference. Parents must be counseled in the benefit of this strategy in preventing bald spots or flat spots that can progress to cranial deformity.

"Tummy time" is the term used to describe the infant's awake time spent lying on their stomach. The suggested amount of tummy time is **10-15 minutes at least 3 times a day**. Reassure parents that sleep is the only time during which the prone position should be avoided, and educate the parents as to the benefits for the infant of awake prone positioning to help progression of motor development.

Treatment Options

Cranial asymmetry from DP does not usually spontaneously improve, nor do the more-severe manifestations of facial and ear asymmetry disappear. Once a flat spot develops, it is unlikely that the infant will be able to overcome the pull to lie on the same spot in time to allow for reversal of the asymmetry.

"Watch-and-wait" management is not recommended in infants with DP. Evidence suggests that, at a minimum, repositioning and physiotherapy should be initiated as soon as asymmetry is observed.

Repositioning and physiotherapy (RPPT) include the counseling and teaching for parents as to positional changes and tummy time in their child as well as **referral to physical therapy in the case of congenital torticollis.** RPPT is the optimal treatment choice for patients younger than 4 mo of age who have mild or moderately severe DP. The earliest types of behavioral modifications can be as simple as increasing tummy time, or repositioning the infant's crib such that everything interesting in the room is on the side opposite the DP.

Molding therapy (helmet therapy) is the use of an orthotic helmet to promote the resolution of cranial asymmetry while the infant's head is still rapidly growing. Orthotic helmets do not actively mold the skull; rather, they protect the areas that are flat and allow the child to "grow into" the flat spot. Studies have shown helmet therapy to achieve correction 3 times faster and better than repositioning alone. This therapy is still debated because of its expense, time requirements, coverage and side effects (irritation, rashes, and pressure sores). The most recent studies suggest that **combined treatment with helmet therapy and RPPT is the most beneficial management of infants older than 4 mo with severe DP or with worsening of mild/moderate DP trialed on RPPT.** Infants with severe DP should be considered for helmet therapy at any age.

Studies suggest helmet therapy should be started for significant DP between 4 and 8 mo and continued for 7-8 mo. Parents should be counseled on the commitment involved in this treatment as helmets need to be worn more than 20 hr a day.

Patients with craniosynostosis require surgery. Sometimes, a molding helmet can be used as an adjunctive therapy after surgery but never as monotherapy.

OUTCOMES

Outcomes may be better when helmet therapy is started before 6 mo of age, and infants starting therapy later than that do not achieve the same degree of normal head measurements as those whose helmet therapy is started before 6 mo of age do. Significant improvements in asymmetry are usually obvious at 4-11 wk after initiation of helmet therapy.

Studies in patients with a median follow-up age of 9 yr old found that 75% of cases had a what both parents and patients considered to be a normal head appearance. Nine percent of patients and 4% of parents noted residual asymmetry that they considered significant.

Cognitive and academic outcomes may be different depending on the side of deformity. Poorer academic performance and greater speech abnormalities were found in patients with left-sided deformities compared to those with right-sided deformities. This manifested as double the number of patients with expressive speech abnormalities and triple the number of special education needs. It is unclear what the underlying mechanism is; treatment differences were apparently not a factor. In general, children with DP and without comorbid conditions are usually developmentally normal, healthy children. This is in contrast to craniosynostosis, in which increases in intracranial pressure may have deleterious effects on central nervous system function.

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Chapter 593

Seizures in Childhood

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A seizure is a transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain. The International Classification of Epileptic Seizures divides epileptic seizures into 2 large categories: In **focal (formerly known as partial) seizures,** the first clinical and electroencephalographic (EEG) changes suggest initial activation of a system of neurons limited to part of 1 cerebral hemisphere. The term *simple partial seizures* is an outdated classification that refers to focal seizures with no alteration in consciousness whereas complex partial seizures, currently also referred to as focal dyscognitive, denote focal seizures with altered awareness of the surroundings. In **generalized seizures,** the first clinical and EEG changes indicate synchronous involvement of all of both hemispheres (Table 593-1). Approximately 30% of patients who have a first afebrile seizure have later epilepsy; the risk is approximately 20% if neurologic exam, EEG, and neuroimaging are normal. **Febrile seizures** are a separate category. **Acute symptomatic seizures** occur secondary to an acute problem affecting brain excitability such as electrolyte imbalance. Most children with these types of seizures do well. However, sometimes these seizures signify major structural, inflammatory, or metabolic disorders of the brain, such as meningitis, encephalitis, acute stroke, or brain tumor. Consequently, the prognosis depends on the underlying disorder, including its reversibility or treatability and the likelihood of developing epilepsy from it. An **unprovoked seizure** is one that is not an acute symptomatic seizure. **Remote symptomatic seizure** is one that is considered to be secondary to a distant brain injury, such as an old stroke. **Reflex seizures** are usually precipitated by a sensory stimulus such as flashing lights (see Chapter 593.9).

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate seizures and by the neurobiologic, cognitive, psychologic, and social consequences of this condition. The clinical diagnosis of epilepsy usually requires the occurrence of at least 1 unprovoked epileptic seizure with either a second such seizure or enough EEG and clinical information to convincingly demonstrate an enduring predisposition to develop recurrences. For epidemiologic and commonly for clinical purposes, epilepsy is considered to be present when 2 or more unprovoked seizures occur in a time frame of longer than 24 hr. Approximately 4-10% of children experience at least 1 seizure (febrile or afebrile) in the 1st 16 yr of life. The cumulative lifetime incidence of epilepsy is 3%, and more than half of the cases start in childhood. The annual prevalence is 0.5-1.0%. Thus, the occurrence of a single seizure or of febrile seizures does not necessarily imply the diagnosis of epilepsy. **Seizure disorder** is a general term that is usually used to include any 1 of several disorders, including epilepsy, febrile seizures, and possibly single seizures and symptomatic seizures secondary to metabolic, infectious, or other etiologies (e.g., hypocalcemia, meningitis).

An **epileptic syndrome** is a disorder that manifests 1 or more specific seizure types and has a specific age of onset and a specific prognosis. Several types of epileptic syndromes can be distinguished

Table 593-1 Types of Epileptic Seizures

SELF-LIMITED SEIZURE TYPES	CONTINUOUS SEIZURE TYPES
Focal Seizures	***Generalized Status Epilepticus***
Focal sensory seizures	Generalized tonic-clonic status epilepticus
• With elementary sensory symptoms (e.g., occipital and parietal lobe seizures)	Clonic status epilepticus
• With experiential sensory symptoms (e.g., temporoparietooccipital junction seizures)	Absence status epilepticus
Focal motor seizures	Tonic status epilepticus
• With elementary clonic motor signs	Myoclonic status epilepticus
• With asymmetrical tonic motor seizures (e.g., supplementary motor seizures)	***Focal Status Epilepticus***
• With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures)	Epilepsia partialis continua of Kojevnikov
• With hyperkinetic automatisms	Aura continua
• With focal negative myoclonus	Limbic status epilepticus (psychomotor status)
• With inhibitory motor seizures	Hemiconvulsive status with hemiparesis
Gelastic seizures	PRECIPITATING STIMULI FOR REFLEX SEIZURES
Hemiclonic seizures	Visual stimuli
Secondarily generalized seizures	• Flickering light—color to be specified when possible
Reflex seizures in focal epilepsy syndromes	• Patterns
Generalized Seizures	• Other visual stimuli
Tonic-clonic seizures (includes variations beginning with a clonic or myoclonic phase)	Thinking
Clonic seizures	Music
• Without tonic features	Eating
• With tonic features	Praxis
Typical absence seizures	Somatosensory
Atypical absence seizures	Proprioceptive
Absence with special features:	Reading
• Eyelid myoclonia	Hot water
• Myoclonic absence	Startle
Tonic seizures	
Myoclonic seizures	
Myoclonic atonic seizures	
Negative myoclonus	
Atonic seizures	
Reflex seizures in generalized epilepsy syndromes	
Unknown	
Epileptic Spasms	

Modified from Berg AT, Berkovic SF, Brodie MJ et al: Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia *51(4):676–685, 2010.*

(Tables 593-2 to 593-5). This classification has to be distinguished from the classification of epileptic seizures that refers to single events rather than to clinical syndromes. In general, seizure type is the primary determinant of the type of medications the patient is likely to respond to, and the epilepsy syndrome determines the type of prognosis one could expect. An **epileptic encephalopathy** is an epilepsy syndrome in which there is a severe EEG abnormality which is thought to result in cognitive and other impairments in the patient. **Idiopathic epilepsy** is an older term that refers to an epilepsy syndrome that is genetic or presumed genetic and in which there is no underlying disorder affecting development or other neurologic function (e.g., petit mal epilepsy). In the International League Against Epilepsy (ILAE) classification of etiology of epilepsy, idiopathic epilepsy was replaced by the term **genetic epilepsy**, which implies that the epilepsy syndrome is the direct result of a known or presumed genetic defect(s) in which the genetic defect is not causative of a brain structural or metabolic disorder other than the epilepsy. **Symptomatic epilepsy** is also an older term referring to an epilepsy syndrome caused by an underlying brain disorder that may or may not be genetic (e.g., epilepsy secondary to tuberous sclerosis or to an old stroke); this is referred to as **structural/metabolic epilepsy**, which would be caused by a distinct structural or metabolic entity that increases the risk for seizures and causes the epilepsy. The older terms of **cryptogenic epilepsy** or of presumed **symptomatic epilepsy** refer to an epilepsy syndrome in which there is a presumed underlying brain disorder causing the epilepsy and affecting neurologic function, but the underlying disorder is not known; this is referred to as the **unknown epilepsy**, designating that the underlying cause of the epilepsy is as yet unknown.

EVALUATION OF THE FIRST SEIZURE

Initial evaluation of an infant or child during or shortly after a suspected seizure should include an assessment of the adequacy of the airway, ventilation, and cardiac function, as well as measurement of temperature, blood pressure, and glucose concentration. For acute evaluation of the first seizure, the physician should search for potentially life-threatening causes of seizures such as meningitis, systemic sepsis, unintentional or nonaccidental intentional head trauma, and ingestion of drugs of abuse or accidental ingestion of drugs or of other toxins. The history should attempt to define factors that might have promoted the convulsion and to provide a detailed description of the seizure and the child's postictal state (see Chapter 593.9). Most parents vividly recall their child's initial convulsion and can describe it in detail.

The subsequent step in an evaluation is to determine whether the seizure has a focal onset or is generalized. **Focal seizures** may be characterized by motor or sensory symptoms, which could include forceful turning of the head and eyes to 1 side, unilateral clonic movements beginning in the face or extremities, or a sensory disturbance, such as paresthesias or pain localized to a specific area. Focal seizures in an adolescent or adult usually indicate a localized lesion, whereas these seizures during childhood are often, but not always, secondary to a

Text continued on p. 2829

Table 593-2 Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options

SPECIFIC SYNDROMES	AGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON*	POSSIBLE ADD-ON†	SURGERY†
EPILEPSIES OF UNKNOWN CAUSE OF INFANCY AND CHILDHOOD						
Benign infantile seizures (nonfamilial)	Infant	Infant	Good	PB	—	No
Benign childhood epilepsy with centrotemporal spikes	3-13 yr	16 yr	Good	CBZ, LEV, OXC, VPA	—	No
Early and late-onset idiopathic occipital epilepsy	2-8 yr; 6-17 yr	12 yr or younger; 18 yr	Good	CBZ, LEV, OXC, VPA	—	No
FAMILIAL (AUTOSOMAL DOMINANT) EPILEPSIES						
Benign familial neonatal convulsions	Newborn to young infant	Newborn to young infant	Good	PB	—	No
Benign familial infantile convulsions	Infant	Infant	Good	CBZ, PB	—	No
Autosomal dominant nocturnal frontal lobe epilepsy	Childhood		Variable	CBZ, GBP, OXC, PHT, TPM	CLB, LEV, PB, PHT	No
Familial lateral temporal lobe epilepsy	Childhood to adolescence		Variable	CBZ, GBP, OXC, PHT, TPM, VPA	CLB, LEV, PB, PHT	No
Generalized epilepsies with febrile seizures plus	Childhood to adolescence		Variable	ESM, LTG, TPM, VPA	CLB, LEV	No
STRUCTURAL–METABOLIC FOCAL EPILEPSIES						
Limbic Epilepsy						
Mesial temporal lobe epilepsy with hippocampal sclerosis	School-age or earlier	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	CLB, GBP, LAC, PB, PHT, ZON	Temporal resection
Mesial temporal lobe epilepsy defined by specific causes	Variable	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	CLB, GBP, LAC, PB, PHT, ZON	Temporal resection
Other types defined by location and causes	Variable	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	CLB, FBM, GBP, LAC, PB, PHT, ZON	Lesionectomy ± temporal resection
Neocortical Epilepsies						
Rasmussen syndrome	6-12 yr	Progressive	Ominous	Plasmapheresis, immunoglobulins	CBZ, LAC, PB, PHT, TPM	Functional hemispherectomy
Hemiconvulsion-hemiplegia syndrome	1-5 yr	Chronic	Severe	CBZ, LEV, OXC, TPM, VPA	CLB, GBP, LAC, PB, PHT, ZON	Functional hemispherectomy
Other types defined by location and cause	Variable	Long lasting	Variable	CBZ, LEV, OXC, TPM, VPA	PHT, PB, CLB, GBP, LAC, ZON	Lesionectomy ± cortical resection
Migrating partial seizures of early infancy	Infant	No remission	Ominous	Bromides, CBZ, LEV, PB, PHT, TPM, VPA	BDZ, LAC, ZON	No
GENERALIZED EPILEPSIES OF UNKNOWN CAUSE						
Benign myoclonic epilepsy in infancy	3 mo-3 yr	3-5 yr	Variable	LEV, TPM, VPA	BDZ, ZON	No
Epilepsy with myoclonic astatic seizures	3-5 yr	Variable	Variable	ESM, TPM, VPA	BDZ, ketogenic diet, LEV, LTG, steroids, ZON	No
Childhood absence epilepsy	5-6 yr	10-12 yr	Good	ESM, LTG, VPA	Acetazolamide, ketogenic diet, ZON	No
Epilepsy with myoclonic absences	1-12 yr	Variable	Guarded	ESM, VPA	BDZ, ZON	No

*Reflects current trends in practice, which may be off-label and may not be FDA approved for that indication. See Table 593-10 for FDA indications.

†May apply to selected cases only. Vagus nerve stimulation has been used for all types of refractory seizures and epilepsy types.

ACTH, adrenocorticotropic hormone; BDZ, benzodiazepine; CBZ, carbamazepine; CLB, clobazam; DZP: diazepam; ESM, ethosuximide; FBM: felbamate; GBP, gabapentin; IVIG, intravenous immunoglobulin; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; n/a, not applicable; OXC: oxcarbazepine; PB, phenobarbital; PHT, phenytoin; PRM, primidone; RFD, rufinamide; TPM, topiramate; VGB: vigabatrin; VPA, valproic acid; ZON, zonisamide.

Continued

Table 593-2 Classification for Epilepsy Syndromes with an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options—cont'd

SPECIFIC SYNDROMES	AGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON*	POSSIBLE ADD-ON†	SURGERY†
GENERALIZED EPILEPSIES OF UNKNOWN CAUSE WITH VARIABLE PHENOTYPES						
Juvenile absence epilepsy	10-12 yr	Usually lifelong	Good	ESM, LTG, VPA	BDZ	No
Juvenile myoclonic epilepsy	12-18 yr	Usually lifelong	Good	LEV, TPM, VPA	BDZ, LTG, PB, PRM, ZON	No
Epilepsy with generalized tonic-clonic seizures only	12-18 yr	Usually lifelong	Good	LEV, LTG, TPM, VPA	BDZ, CBZ, ZON	No
REFLEX EPILEPSIES						
Idiopathic photosensitive occipital lobe epilepsy	10-12 yr	Unclear	Variable	VPA	BDZ, LEV, LTG, ZON	No
Other visual sensitive epilepsies	2-5 yr	Unclear	Variable	VPA	BDZ, LEV, LTG, ZON	No
Startle epilepsy	Variable	Long lasting	Guarded	CBZ, GBP, OXC, PHT, TPM, VPA	CLB, LEV, PB, PHT, ZON	Lesionectomy ± cortical resection in some
EPILEPTIC ENCEPHALOPATHIES						
Early myoclonic encephalopathy and Ohtahara syndrome	Newborn-infant	Poor, Ohtahara syndrome evolves into West syndrome	Ominous	PB, steroids, VGB	BDZ, ZON	No
West syndrome	Infant	Variable	Variable	ACTH, steroids, VGB	BDZ, FBM, IVIG, TPM, ZON	Lesionectomy ± cortical resection
Dravet syndrome (severe myoclonic epilepsy in infancy)	Infant	No remission	Severe	CLB, stiripentol, TPM, VPA	BDZ, ZON	No
Lennox-Gastaut syndrome	3-10 yr	No remission	Severe	CLB, LTG, RFD, TPM, VPA	BDZ, FBM, IVIG, steroids, ZON	Callosotomy
Landau-Kleffner syndrome	3-6 yr	8-12 yr	Guarded	LEV, nocturnal DZP, steroids, VPA	BDZ, ESM, IVIG, LTG	Multiple subpial transections, rarely lesionectomy
Epilepsy with continuous spike waves during slow-wave sleep	4-7 yr	8-12 yr	Guarded	LEV, nocturnal DZP, steroids, VPA	BDZ, ESM, IVIG, LTG	No
PROGRESSIVE MYOCLONUS EPILEPSIES						
Unverricht-Lundborg, Lafora, ceroid lipofuscinoses, etc.	Late infant to adolescent	Progressive	Ominous	TPM, VPA, ZON	BDZ, PB	No
OTHER EPILEPSIES AND SEIZURE DISORDERS OF UNKNOWN OR OTHER CAUSES						
Benign neonatal seizures	Newborn	Newborn	Good	LEV, PB	—	No
Febrile seizures	3-5 yr	3-6 yr	Good	PB or VPA if repeated and prolonged	—	No
Reflex seizures	Variable	n/a		LEV, VPA	LTG, ZON	No
Drug or other chemically induced seizures	Variable	n/a		Withdraw offending agent	—	No
Immediate and early posttraumatic seizures	Variable	n/a		LEV, PHT	—	No

Modified from Guerrini R: Epilepsy in children, Lancet *367:499–524, 2006; and Parisi P, Verrotti A, Paolino MC, et al. "Electro-clinical syndromes" with onset in the pediatric age group: the highlights of the clinical-EEG, genetic and therapeutic advances.* Ital J Pediatr *37:58, 2011.*

Table 593-3 Identified Genes for Epilepsy Syndromes*†

EPILEPSY TYPE	GENE	PROTEIN
INFANTILE ONSET		
Benign familial neonatal seizures	*KCNQ2*	Potassium voltage-gated channel
	KCNQ3	Potassium voltage-gated channel
Benign familial neonatal infantile seizures	*SCN2A*	Sodium channel protein type 2α
Early familial neonatal infantile seizures	*SCN2A*	Sodium channel protein type 2α
Early infantile epileptic encephalopathy (EIEE)	*CDKL5 (EIEE2)*	Cyclin-dependent kinase-like 5
	ARX (EIEE1)	Aristaless-related homeobox
	TSC1	Hamartin
	TSC2	Tuberin
	SCN1A (EIEE6)	Sodium channel protein type 1α
	PCDH19(EIEE9)	Protocadherin-19
	KCNQ2 (EIEE7)	Potassium voltage-gated channel
	STXBP1 (EIEE4)	Syntaxin binding protein 1
	SLC2A1	Solute carrier family 2, facilitated glucose transporter member 1
	ALDH7A1	α-Aminoadipic semialdehyde dehydrogenase (antiquitin)
	POLG	DNA polymerase subunit gamma-1
	SCN2A (EIEE11)	Sodium channel protein type 2α
	PLCβ1 (EIEE12)	Phospholipase C β1
	ATP6AP2	Renin receptor
	SPTAN1 (EIEE5)	α_2-Spectrin
	SLC25A22 (EIEE3)	Mitochondrial glutamate carrier 1
	PNPO	Pyridoxine-5′-phosphate oxidase
Generalized epilepsy with febrile seizures plus (early onset)	*SCN1A*	Sodium channel protein type 1α
	SCN1B	Sodium channel protein type 1β
	GABRG2	γ-Aminobutyric acid receptor subunit γ2
	SCN2A	Sodium channel protein type 1α
CHILDHOOD ONSET		
Childhood onset epileptic encephalopathies	*SCN1A*	Sodium channel protein type 1α
	PCDH19	Protocadherin-19
	SLC2A1	Solute carrier family 2, facilitated GTM1
	POLG	DNA polymerase subunit γ1
	SCN2A	Sodium channel protein type 2α
Early onset absence seizures, refractory epilepsy of multiple types at times with movement disorder	*GLUT-1* deficiency syndrome, *SLC2A1*gene	Solute carrier family 2, facilitated GTM1
Generalized epilepsy with febrile seizure plus	*SCN1A*	Sodium channel protein type 1α
	SCN1B	Sodium channel protein type 1β
	GABRG2	γ-Aminobutyric acid receptor subunit γ2
	SCN2A	Sodium channel protein type 1α
Juvenile myoclonic epilepsy (more commonly presents in adolescence)	*EFHC1*	EF-hand domain-containing protein 1
	CACNB4	Voltage-dependent L-type calcium channel
	GABRA1	γ-Aminobutyric acid receptor subunit α1
Progressive myoclonic epilepsy (different forms present from infancy through adulthood)	*EPM2A*	Laforin
	NHLRC1	NHL repeat-containing protein 1 (Malin)
	CSTB	Cystatin-B
	PRICKLE1	Prickle-like protein 1
	PPT1, TPP1,CLN3, CLN5, CLN6, CLN8, CTSD, DNAJC5, MFSD8	Multiple proteins causing neuronal ceroid lipofuscinosis
Autosomal dominant nocturnal frontal lobe epilepsies (presents in childhood through adulthood)	*CHRNA4*	Neuronal acetylcholine receptor α4
	CHRNB2	Neuronal acetylcholine receptor β2
	CHRNA2	Neuronal acetylcholine receptor α2
ADOLESCENT ONSET		
Juvenile myoclonic epilepsy (JME)	See Childhood Onset JME	
Progressive myoclonic epilepsy (PME)	See Childhood Onset PME	
Autosomal dominant nocturnal frontal lobe epilepsies (AD-NFLE)	See Childhood Onset AD-NFLE	
Autosomal dominant lateral temporal lobe epilepsy (AD-LTLE)	See Childhood Onset AD-LTLE	
Autosomal dominant lateral temporal lobe epilepsy (usually presents in adulthood)	*LGI1*	Leucine-rich glioma-inactivated protein 1

*Note that the same gene (different mutations) often appears as causing different epilepsy syndromes.

†Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or though exome sequencing (http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=genetests).

Table 593-4 Identified Genes for Syndromic Epilepsy Syndromes*

SYNDROME	GENE	PROTEIN
Rett/atypical Rett syndromes	*MECP2* *CDKL5* *FOXG1* *MBD5* *MEF2C*	Methyl CpG binding protein 2 Cyclin-dependent kinase-like 5 Forkhead box protein G1 Methyl-CpG-binding domain protein 5 Myocyte-specific enhancer factor 2C
Angelman/Angelman-like/Pitt-Hopkins syndromes	*UBE3A* *SLC9A6* *MBD5* *TCF4* *NRXN1* *CNTNAP2*	Ubiquitin protein ligase E3A Sodium/hydrogen exchanger 6 Methyl-CpG-binding domain protein 5 Transcription factor 4 Neurexin-1 Contactin-associated protein-like 2
Mowat-Wilson syndrome	*ZEB2*	Zinc finger E-box-binding homeobox 2
Creatine deficiency syndromes	*GAMT* *GATM*	Guanidinoacetate *N*-methyltransferase Glycine amidinotransferase, mitochondrial
Neuronal ceroid lipofuscinosis (NCL)	*PPT1 (CLN1)* *TPP1 (CLN2)* *CLN3* *CLN5* *CLN6* *MFSD8 (CLN7)* *CLN8* *CTSD (CLN10)* *KCTD7 (CLN14)*	Palmitoyl-protein thioesterase 1 Tripeptidyl-peptidase 1 Battenin Ceroid-lipofuscinosis neuronal protein 5 Ceroid-lipofuscinosis neuronal protein 6 Major facilitator superfamily domain-containing protein 8 Ceroid-lipofuscinosis neuronal protein 8 Cathepsin D BTB/POZ domain-containing protein KCTD7
Adenosuccinate lyase deficiency	*ADSL*	Adenylosuccinate lyase
Cerebral folate deficiency	*FOLR1*	Folate receptor alpha
Epilepsy with variable learning and behavioral disorders	*GRIN2A* *SYN1*	Glutamate receptor ionotropic, *N*-methyl-D-aspartate (NMDA) 2A Synapsin-1
17q21.31 microdeletion syndrome	*KANSL1*	KAT8 regulatory nonspecific lethal (NSL) complex subunit 1
Microcephaly with early-onset intractable seizures and developmental delay (MCSZ)	*PNKP*	Bifunctional polynucleotide phosphatase/kinase

*Most of these genes can be tested for through commercially available targeted single-gene sequencing or through commercially available gene panels or though exome sequencing.

Table 593-5 Childhood Epileptic Syndromes with Generally Good Prognosis

SYNDROME	COMMENT
Benign neonatal familial convulsions	Dominant, may be severe and resistant for a few days Febrile or afebrile seizures (benign) occur later in a minority
Infantile familial convulsions	Dominant; seizures often in clusters
Febrile convulsions plus syndromes (see Table 593-2)	Febrile and afebrile generalized convulsions, absence and myoclonic seizures occur in different members. Seizures usually generalized (GEFS+) but in some families may be focal
Benign myoclonic epilepsy of infancy	Often seizures during sleep; 1 rare variety with reflex myoclonic seizures (touch, noise)
Partial idiopathic epilepsy with rolandic spikes (benign epilepsy with centrotemporal spikes)	Seizures with falling asleep or on awakening; focal sharp waves with centrotemporal location on EEG
Idiopathic occipital partial epilepsy	Early childhood form with seizures during sleep and ictal vomiting; can occur as status epilepticus Later form with occipital spikes that block on eye opening; migrainous symptoms and seizures; not always benign
Petit mal absence epilepsy	Cases with absences only; some have generalized seizures In most cases, absences disappear on therapy but there are resistant cases (unpredictable); 60-80% full remission
Juvenile myoclonic epilepsy	Adolescence onset, with early morning myoclonic seizures and generalized seizures during sleep or upon awakening; often history of absences in childhood

EEG, electroencephalogram; GEFS+, generalized epilepsy with febrile seizures plus.

Modified from Deonna T: Management of epilepsy, Arch Dis Child *90:5–9, 2005; and Seneviratne U: The prognosis of idiopathic generalized epilepsy,* Epilepsia *53(12):2079–2090, 2012.*

lesion or the result of a genetic, idiopathic, epilepsy. Focal seizures in a neonate may be seen because of focal lesions like perinatal stroke or because of a metabolic abnormality like hypocalcemia caused by immaturity of the brain connections. Focal and generalized motor seizures may be tonic–clonic, tonic, clonic, myoclonic, or atonic. **Tonic seizures** are characterized by increased tone or rigidity, and **atonic seizures** are characterized by flaccidity or lack of movement during a convulsion. **Clonic seizures** consist of rhythmic fast muscle contractions and slightly longer relaxations; **myoclonus** is a "shock-like" contraction of a muscle of <50 msec that is often repeated. The duration of the seizure and state of consciousness (retained or impaired) should be documented. The history should determine whether an **aura** preceded the convulsion and the behavior of the child immediately preceding the seizure. The most common aura experienced by children consists of epigastric discomfort or pain and a feeling of fear. The posture of the patient, presence or absence and distribution of cyanosis, vocalizations, loss of sphincter control (particularly of the urinary bladder), and postictal state (including sleep, headache, and hemiparesis) should be noted.

In addition to the assessment of cardiorespiratory and metabolic status, examination of a child with a seizure disorder should be geared toward the search for an organic cause. The child's head circumference, length, and weight are plotted on a growth chart and compared with previous measurements. A careful general and neurologic examination should be performed. The **eyegrounds** must be examined for the presence of papilledema, optic neuritis, retinal hemorrhages, uveitis, chorioretinitis, coloboma, or macular changes, as well as retinal phakoma. The finding of unusual facial features or of associated physical findings such as hepatosplenomegaly point to an underlying metabolic or storage disease as the cause of the neurologic disorder. The presence of a **neurocutaneous disorder** may be indicated by the presence of vitiliginous ash leaf–type lesions using an ultraviolet light (Wood lamp), of adenoma sebaceum, shagreen patches, or of retinal phakomas (tuberous sclerosis), of multiple café-au-lait spots (neurofibromatosis), or of V1 or V2 distribution nevus flammeus (Sturge-Weber syndrome).

Localizing neurologic signs, such as a subtle **hemiparesis** with hyperreflexia, an equivocal Babinski sign, and a downward-drifting of an extended arm with eyes closed, might suggest a contralateral hemispheric structural lesion, such as a slow-growing glioma, as the cause of the seizure disorder. Unilateral growth arrest of the thumbnail, hand, or extremity in a child with a focal seizure disorder suggests a chronic condition, such as a porencephalic cyst, arteriovenous malformation, or cortical atrophy of the opposite hemisphere.

After the initial acute investigation, which often includes metabolic and CT scanning, depending on the clinical presentation in emergency room, in a child with a first nonfebrile seizure, it is recommended to obtain an EEG to help predict the risk of seizure recurrence. Subsequent imaging studies with MRI should be seriously considered in any child with a significant cognitive or motor impairment of unknown etiology, unexplained abnormalities on neurologic or psychiatric examination, a seizure of focal onset with or without secondary generalization, an EEG that does not represent a benign partial epilepsy of childhood or primary generalized epilepsy, or in children younger than 1 year of age. Other laboratory tests or lumbar punctures may be pursued depending on the specific clinical settings. Further details regarding the approach to a first seizure are included in Chapter 593.2.

593.1 Febrile Seizures

Mohamad A. Mikati and Abeer J. Hani

Febrile seizures are seizures that occur between the age of 6 and 60 mo with a temperature of 38°C (100.4°F) or higher, that are not the result of central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures. A **simple febrile seizure** is a primary generalized, usually tonic–clonic, attack associated with fever, lasting for a maximum of 15 min, and not recurrent within a 24-hr period. A **complex febrile seizure** is more prolonged (>15 min), is focal, and/or reoccurs within 24 hr. **Febrile status epilepticus** is a febrile seizure lasting longer than 30 min. Some use the term **simple febrile seizure plus** for those with recurrent febrile seizures within 24 hr. Most patients with simple febrile seizures have a very short postictal state and usually return to their baseline normal behavior and consciousness within minutes of the seizure.

Between 2% and 5% of neurologically healthy infants and children experience at least 1, usually simple, febrile seizure. Simple febrile seizures do not have an increased risk of mortality even though they are, understandably, concerning to the parents when they first witness them. Complex febrile seizures may have an approximately 2-fold long-term increase in mortality, as compared to the general population, over the subsequent 2 yr, probably secondary to coexisting pathology. There are no long-term adverse effects of having 1 or more simple febrile seizures. Compared with age-matched controls, patients with febrile seizures do not have any increase in the incidence of abnormalities of behavior, scholastic performance, neurocognitive function, or attention. Children who develop later epilepsy, however, might experience such difficulties. Febrile seizures recur in approximately 30% of those experiencing a first episode, in 50% after 2 or more episodes, and in 50% of infants younger than 1 yr old at febrile seizure onset. Several factors affect recurrence risk (Table 593-6). Although approximately 15% of children with epilepsy have had febrile seizures, only 2-7% of children who experience febrile seizures proceed to develop epilepsy later in life. There are several predictors of epilepsy after febrile seizures (Table 593-7).

GENETIC FACTORS

The genetic contribution to the incidence of febrile seizures is manifested by a positive family history for febrile seizures in many patients. In some families, the disorder is inherited as an autosomal dominant

Table 593-6 Risk Factors for Recurrence of Febrile Seizures

MAJOR
Age <1 yr
Duration of fever <24 hr
Fever 38-39°C (100.4-102.2°F)
MINOR
Family history of febrile seizures
Family history of epilepsy
Complex febrile seizure
Daycare
Male gender
Lower serum sodium at time of presentation

Having no risk factors carries a recurrence risk of approximately 12%; 1 risk factor, 25-50%; 2 risk factors, 50-59%; 3 or more risk factors, 73-100%.

Table 593-7 Risk Factors for Occurrence of Subsequent Epilepsy After a Febrile Seizure

RISK FACTOR	RISK FOR SUBSEQUENT EPILEPSY
Simple febrile seizure	1%
Recurrent febrile seizures	4%
Complex febrile seizures (more than 15 min duration or recurrent within 24 hr)	6%
Fever <1 hr before febrile seizure	11%
Family history of epilepsy	18%
Complex febrile seizures (focal)	29%
Neurodevelopmental abnormalities	33%

trait, and multiple single genes that cause the disorder have been identified in such families. However, in most cases the disorder appears to be polygenic, and the genes predisposing to it remain to be identified. Identified single genes include *FEB 1, 2, 3, 4, 5, 6, 7, 8, 9,* and *10* genes on chromosomes 8q13-q21, 19p13.3, 2q24, 5q14-q15, 6q22-24, 18p11.2, 21q22, 5q34, 3p24.2-p23, and 3q26.2-q26.33. Only the function of *FEB 2* is known: it is a sodium channel gene, *SCN1A*.

Almost any type of epilepsy can be preceded by febrile seizures, and a few epilepsy syndromes typically start with febrile seizures. These are **generalized epilepsy with febrile seizures plus** (GEFS+), **severe myoclonic epilepsy of infancy** (also called **Dravet syndrome**), and, in many patients, temporal lobe epilepsy secondary to mesial temporal sclerosis.

GEFS+ is an autosomal dominant syndrome with a highly variable phenotype. Onset is usually in early childhood and remission is usually in mid-childhood. It is characterized by multiple febrile seizures and by several subsequent types of afebrile generalized seizures, including generalized tonic–clonic, absence, myoclonic, atonic, or myoclonic astatic seizures with variable degrees of severity. A focal febrile seizures plus epilepsy variant, in which the seizures are focal rather than generalized, has also been described.

Dravet syndrome is the most severe of the phenotypic spectrum of febrile seizure-associated epilepsies. It constitutes a distinct entity in the onset of which is in infancy. Its onset is characterized by febrile and afebrile unilateral clonic seizures recurring every 1 or 2 mo. These early seizures are typically induced by fever, but they differ from the usual febrile convulsions in that they are more prolonged, are more frequent, are focal and come in clusters. Seizures subsequently start to occur with lower fevers and then without fever. During the 2nd yr of life, myoclonus, atypical absences, and partial seizures occur frequently and developmental delay usually follows. This syndrome is usually caused by a de novo mutation, although rarely it is inherited in an autosomal dominant manner. The mutated gene is located on 2q24-31 and encodes for *SCN1A*, the same gene mutated in GEFS+ spectrum. However, in Dravet syndrome the mutations lead to loss of function and thus to a more severe phenotype. There are several milder variants of Dravet syndrome that manifest some but not all of the above features and that are referred to as Dravet syndrome spectrum or Borderland. Mutations in other genes may also cause Dravet syndrome or GEFS+ phenotypes.

The majority of patients who had prolonged febrile seizures and encephalopathy after vaccination and who had been presumed to have suffered from **vaccine encephalopathy** (seizures and psychomotor regression occurring after vaccination and presumed to be caused by it) turn out to have Dravet syndrome mutations, indicating that their disease is caused by the mutation and not secondary to the vaccine. This has raised doubts about the very existence of the entity termed vaccine encephalopathy.

EVALUATION

Figure 593-1 delineates the general approach to the patient with febrile seizures. Each child who presents with a febrile seizure requires a detailed history and a thorough general and neurologic examination. Febrile seizures often occur in the context of otitis media, roseola and human herpesvirus (HHV) 6 infection, shigella, or similar infections, making the evaluation more demanding. In patients with febrile status, HHV-6B (more frequently) and HHV-7 infections were found to account for one-third of the cases. Several laboratory studies need to be considered in evaluating the patient with febrile seizures.

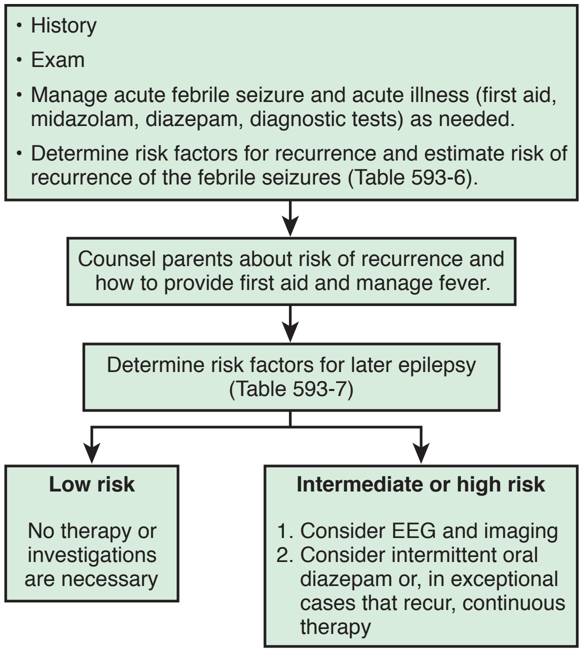

Figure 593-1 Management of febrile seizures. *(Modified from Mikati MA, Rahi A: Febrile seizures: from molecular biology to clinical practice,* Neurosciences (Riyadh) *10:14–22, 2004.)*

Lumbar Puncture

Meningitis should be considered in the differential diagnosis, and lumbar puncture should be performed for all infants younger than 6 mo of age who present with fever and seizure, or if the child is ill-appearing or at any age if there are clinical signs or symptoms of concern. A lumbar puncture is an option in a child 6-12 mo of age who is deficient in *Haemophilus influenzae* type b and *Streptococcus pneumoniae* immunizations or for whom immunization status is unknown. A lumbar puncture is an option in children who have been pretreated with antibiotics. *In patients presenting with febrile status epilepticus in the absence of a central nervous system infection, a nontraumatic lumbar puncture rarely shows cerebrospinal fluid (CSF) pleocytosis (96% have <3 nucleated cells in the CSF) and the CSF protein and glucose are usually normal.*

Electroencephalogram

If the child is presenting with the first simple febrile seizure and is otherwise neurologically healthy, an EEG need not normally be performed as part of the evaluation. An EEG would not predict the future recurrence of febrile seizures or epilepsy even if the result is abnormal. Spikes during drowsiness are often seen in children with febrile seizures, particularly those older than age 4 yr, and these do not predict later epilepsy. EEGs performed within 2 wk of a febrile seizure often have nonspecific slowing, usually posteriorly. Thus, in many cases, if an EEG is indicated, it is delayed until or repeated after more than 2 wk have passed. An EEG should, therefore, generally be restricted to special cases in which epilepsy is highly suspected, and, generally, it should be used to delineate the type of epilepsy rather than to predict its occurrence. If an EEG is done, it should be performed for at least 20 min in wakefulness and in sleep according to international guidelines to avoid misinterpretation and drawing of erroneous conclusions. At times, if the patient does not recover immediately from a seizure, then an EEG can help distinguish between ongoing seizure activity and a prolonged postictal period, sometimes termed a **nonepileptic twilight state.** EEG can also be helpful in patients who present with febrile status epilepticus because the presence of focal slowing present on the EEG obtained within 72 hr of the status has been shown to be highly associated with MRI evidence of acute hippocampal injury.

Blood Studies

Blood studies (serum electrolytes, calcium, phosphorus, magnesium, and complete blood count) are not routinely recommended in the work-up of a child with a first simple febrile seizure. Blood glucose should be determined in children with prolonged postictal obtundation or with poor oral intake (prolonged fasting). Serum electrolyte values may be abnormal in children after a febrile seizure, but this should be suggested by precipitating or predisposing conditions elicited in the history and reflected in abnormalities of the physical examination. If clinically indicated (e.g., in a history or physical examination

suggesting dehydration), these tests should be performed. A low sodium level is associated with higher risk of recurrence of the febrile seizure within the following 24 hr.

Neuroimaging

A CT or MRI is not recommended in evaluating the child after a first simple febrile seizure. The work-up of children with complex febrile seizures needs to be individualized. This can include an EEG and neuroimaging, particularly if the child is neurologically abnormal. Approximately 11% of children with febrile status epilepticus are reported to have (usually) unilateral swelling of their hippocampus acutely, which is followed by subsequent long-term hippocampal atrophy. Whether these patients will ultimately develop temporal lobe epilepsy remains to be determined.

TREATMENT

In general, antiepileptic therapy, continuous or intermittent, is not recommended for children with 1 or more simple febrile seizures. Parents should be counseled about the relative risks of recurrence of febrile seizures and recurrence of epilepsy, educated on how to handle a seizure acutely, and given emotional support. If the seizure lasts for longer than 5 min, acute treatment with diazepam, lorazepam, or midazolam is needed (see Chapter 593.8 for acute management of seizures and status epilepticus). Rectal diazepam is often prescribed to be given at the time of reoccurrence of a febrile seizure lasting longer than 5 min (see Table 593-12 for dosing). Alternatively, buccal or intranasal midazolam may be used and is often preferred by parents. Intravenous benzodiazepines, phenobarbital, phenytoin, or valproate may be needed in the case of febrile status epilepticus. If the parents are very anxious concerning their child's seizures, intermittent oral diazepam (0.33 mg/kg every 8 hr during fever) or intermittent rectal diazepam (0.5 mg/kg administered as a rectal suppository every 8 hr), can be given during febrile illnesses. Intermittent oral nitrazepam, clobazam, and clonazepam (0.1 mg/kg/day) have also been used. Such therapies help reduce, but do not eliminate, the risks of recurrence of febrile seizures. Other therapies have included continuous phenobarbital (4-5 mg/kg/day in 1 or 2 divided doses), and continuous valproate (20-30 mg/kg/day in 2 or 3 divided doses). *In the vast majority of cases, it is not justified to use continuous therapy owing to the risk of side effects and lack of demonstrated long-term benefits, even if the recurrence rate of febrile seizures is expected to be decreased by these drugs.*

Antipyretics can decrease the discomfort of the child but do not reduce the risk of having a recurrent febrile seizure, probably because the seizure often occurs as the temperature is rising or falling. Chronic antiepileptic therapy may be considered for children with a high risk for later epilepsy. Currently available data indicate that the possibility of future epilepsy does not change with or without antiepileptic therapy. Iron deficiency is associated with an increased risk of febrile seizures, and thus screening for that problem and treating it appears appropriate.

Bibliography is available at Expert Consult.

593.2 Unprovoked Seizures

Mohamad A. Mikati and Abeer J. Hani

HISTORY AND EXAMINATION

Acute evaluation of a first seizure includes assessment of vital signs and respiratory and cardiac function, and institution of measures to normalize and stabilize them as needed. Signs of head trauma, abuse, drug intoxication, poisoning, meningitis, sepsis, focal abnormalities, increased intracranial pressure, herniation, neurocutaneous stigmata, brainstem dysfunction, and/or focal weakness should all be sought because they could suggest an underlying etiology for the seizure.

The **history** should also include details of the seizure manifestations, particularly those that occurred at its initial onset. These could give clues to the type and brain localization of the seizure. One should also probe for previous signs or symptoms of other seizures in the preceding weeks, or longer, that the parents may have overlooked and did not report. In some instances, if the events have been going on for a time and there is a question about their nature (e.g., sleep myoclonus vs seizures), then the family could video record the patient and make the video available to the healthcare provider. Having the parents imitate the seizure can also be helpful. Seizure patterns (e.g., clustering), precipitating conditions (e.g., sleep or sleep deprivation, television, visual patterns, mental activity, stress), exacerbating conditions (e.g., menstrual cycle, medications), frequency, duration, time of occurrence, and other characteristics need to be carefully documented (see Chapter 593.9). Parents often overlook, do not report, or underreport absence, complex partial, or myoclonic seizures. A history of personality change or symptoms of increased intracranial pressure can suggest an intracranial tumor. Similarly, a history of cognitive regression can suggest a degenerative or metabolic disease. Certain medications such as stimulants or antihistamines, particularly sedating ones, can precipitate seizures. A history of prenatal or perinatal distress or of developmental delay can suggest etiologic congenital or perinatal brain dysfunction. Details of the spells can suggest nonepileptic paroxysmal disorders that mimic seizures (see Chapter 594).

DIFFERENTIAL DIAGNOSIS

This involves consideration of nonepileptic paroxysmal events (see Chapter 594), determination of the seizure type, as classified by the new ILAE system (see Table 593-1) and consideration of potential underlying etiologies. Some seizures might begin with **auras**, which are sensory experiences reported by the patient and not observed externally. These can take the form of visual (e.g., flashing lights or seeing colors or complex visual hallucinations), somatosensory (tingling), olfactory, auditory, vestibular, or experiential (e.g., déjà vu, déjà vécu feelings) sensations, depending upon the precise localization of the origin of the seizures.

Motor seizures can be **tonic** (sustained contraction), **clonic** (rhythmic contractions), **myoclonic** (rapid shock-like contractions, usually <50 msec in duration, that may be isolated or may repeat but usually are not rhythmic), **atonic**, or **astatic**. **Astatic** seizures often follow myoclonic seizures and cause a very momentary loss of tone with a sudden fall. **Atonic** seizures, on the other hand, are usually longer and the loss of tone often develops more slowly. Sometimes it is difficult to distinguish among tonic, myoclonic, atonic, or astatic seizures based on the history alone when the family reports only that the patient "falls"; in such cases, the seizure may be described as a **drop attack**. Loss of tone or myoclonus in only the neck muscles results in a milder seizure referred to as a **head drop**. Tonic, clonic, myoclonic, and atonic seizures can be focal (including 1 limb or 1 side only), focal with secondary generalization, or primary generalized. Epileptic **spasms** (axial spasms, these terms being preferred over infantile spasms because they can occur beyond infancy) consist of flexion or extension of truncal and extremity musculature that is sustained for 1-2 sec, shorter than what is seen in tonic seizures, which last longer than 2 sec. Focal motor clonic and/or myoclonic seizures that persist for days, months, or even longer are termed **epilepsia partialis continua**.

Absence seizures are generalized seizures consisting of staring, unresponsiveness, and eye flutter lasting usually for few seconds. **Typical absences** are associated with 3 Hz spike–and–slow-wave discharges and with petit mal epilepsy, which has a good prognosis. **Atypical absences** are associated with 1-2 Hz spike–and–slow-wave discharges, and with head atonia and myoclonus during the seizures. They occur in Lennox-Gastaut syndrome, which has a poor prognosis. **Juvenile absences** are similar to typical absences but are associated with 4-5 Hz spike-and-slow waves and occur in juvenile myoclonic epilepsy. Seizure type and other EEG and clinical manifestations determine the type of **epilepsy syndrome** with which a particular patient is afflicted (Table 593-8; see Chapter 593.3 and 593.4).

Family history of certain forms of epilepsy, like benign neonatal seizures, can suggest the specific epilepsy syndrome. More often, however, different members of a family with a positive history of epilepsy have different types of epilepsy. Head circumference can indicate

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Table 593-8	Selected Epilepsy Syndromes by Age of Onset
NEONATAL PERIOD Benign familial neonatal seizures (BFNS) Early myoclonic encephalopathy (EME) Ohtahara syndrome	
INFANCY Epilepsy of infancy with migrating focal seizures West syndrome Myoclonic epilepsy in infancy (MEI) Benign infantile seizures Benign familial infantile epilepsy Dravet syndrome Myoclonic encephalopathy in nonprogressive disorders	
CHILDHOOD Febrile seizures plus (FS+) (can start in infancy; this can be with generalized [GEFS+] or with focal seizures) Early-onset benign childhood occipital epilepsy (Panayiotopoulos type) Epilepsy with myoclonic atonic (previously astatic) seizures Benign epilepsy with centrotemporal spikes (BCECTS) Late-onset childhood occipital epilepsy (Gastaut type) Autosomal dominant nocturnal frontal lobe epilepsy (AD-NFLE) Epilepsy with myoclonic absences Lennox-Gastaut syndrome Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) Landau-Kleffner syndrome Childhood absence epilepsy (CAE)	
ADOLESCENCE–ADULT Juvenile absence epilepsy (JAE) Juvenile myoclonic epilepsy (JME) Epilepsy with generalized tonic–clonic seizures alone Progressive myoclonus epilepsies (PME) Autosomal dominant epilepsy with auditory features (ADEAF) Other familial temporal lobe epilepsies	
AGE-RELATED (AGE OF ONSET LESS SPECIFIC) Familial focal epilepsy with variable foci (childhood to adult) Reflex epilepsies	
SEIZURE DISORDERS THAT ARE NOT TRADITIONALLY GIVEN THE DIAGNOSIS OF EPILEPSY Benign neonatal seizures (BNS) Febrile seizures (FS)	
EPILEPTIC ENCEPHALOPATHIES EME Ohtahara syndrome Migrating partial seizures of infancy West syndrome Dravet syndrome Myoclonic encephalopathy in nonprogressive disorders Epilepsy with myoclonic astatic seizures Lennox-Gastaut syndrome Epileptic encephalopathy with CSWS Landau-Kleffner syndrome	
OTHER SECONDARY GENERALIZED EPILEPSIES Generalized epilepsy secondary to neurodegenerative disease Progressive myoclonus epilepsies	

Modified from Berg AT, Berkovic SF, Bordie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia *51:676–685, 2010.*

the presence of microcephaly or of macrocephaly. Eye exam may show optic disc edema, retinal hemorrhages, chorioretinitis, colobomata (associated with brain malformations), a cherry-red spot, optic atrophy, macular changes (associated with genetic neurodegenerative and storage diseases), or phakomas (associated with tuberous sclerosis). Skin exam could show a trigeminal V_1 distribution capillary hemangioma (associated with Sturge-Weber syndrome), hypopigmented lesions (sometimes associated with tuberous sclerosis and detected more reliably by viewing the skin under UV light), or other neurocutaneous manifestations such as Shagreen patches and adenoma sebaceum (associated with tuberous sclerosis), or whorl-like hypopigmented areas (hypomelanosis of Ito, associated with hemimegalencephaly). Subtle asymmetries on the exam such as drift of 1 of the extended arms, posturing of an arm on stress gait, slowness in rapid alternating movements, small hand or thumb and thumb nail on 1 side, or difficulty in hopping on 1 leg relative to the other can signify a subtle hemiparesis associated with a lesion on the contralateral side of the brain.

Table 593-9	Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy
Epileptic seizures and epilepsy syndromes are to be described and categorized according to a system that uses standardized terminology and that is sufficiently flexible to take into account the practical and dynamic aspects of epilepsy diagnosis: • Axis 1: Ictal phenomenology, used to describe ictal events with any degree of detail needed. • Axis 2: Seizure type, from the List of types of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate. • Axis 3: Syndrome, from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible. • Axis 4: Etiology, from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathologic substrates for symptomatic focal epilepsies. • Axis 5: Impairment; this is often useful to make sure one does not overlook the consequences of epilepsy, such as medication side effects, and learning and socialization difficulties.	

Modified from Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. Epilepsia. 2001;42:796–803.

Guidelines on the evaluation of a **first unprovoked nonfebrile** seizure include a careful history and physical examination and brain imaging by head CT or MRI. Emergency head CT in the child presenting with a first unprovoked nonfebrile seizure is often useful for acute management of the patient. Laboratory studies are recommended in specific clinical situations: Spinal tap is considered in patients with suspected meningitis or encephalitis, in children without brain swelling or papilledema, and in children in whom a history of intracranial bleeding is suspected without evidence of such on head CT. In the second of these, examination of the CSF for xanthochromia is essential. Electrocardiography (ECG) to rule out long QT or other cardiac dysrhythmias and other tests directed at disorders that could mimic seizures may be needed (see Chapter 594). EEG is highly recommended to assess for focal abnormalities and predict seizure recurrence.

LONG-TERM APPROACH TO THE PATIENT AND ADDITIONAL TESTING

The approach to the patient with epilepsy is based on the diagnostic scheme proposed by the ILAE Task Force on Classification and Terminology and presented in Table 593-9. This emphasizes the total approach to the patient, including identification, if possible, of the underlying etiology of the epilepsy and the impairments that result from it. The impairments are very often just as important as, if not more important than, the seizures themselves. Most epilepsy syndromes are potentially caused by any 1 of multiple underlying or still undetermined etiologies. However, in addition, there are many epilepsy syndromes that are associated with specific gene mutations (see Table 593-2). Different mutations of the same gene can result in different epilepsy syndromes, and mutations of different genes can cause the same epilepsy syndrome phenotype. The clinical use of gene testing in the diagnosis and management of childhood epilepsy has been limited to patients manifesting specific underlying malformational, metabolic, or degenerative disorders, patients with severe named epilepsy syndromes (such as West and Dravet syndromes and progressive

myoclonic epilepsies), and to patients with syndromes of mendelian inheritance (see Table 593-2).

Patients with **recurrent seizures**, specifically with 2 seizures spaced apart by longer than 24 hr, warrant further work-up directed at the underlying etiology. In patients with drug-resistant epilepsy, or in infants with new-onset epilepsy in whom the initial testing did not reveal an underlying etiology, a full metabolic work-up, including amino acids, organic acids, biotinidase, and CSF studies, is needed. Additional testing can include, depending on the case, some or most of the following:

1. Measurement of serum lactate, pyruvate, acyl carnitine profile, creatine, very-long-chain fatty acids, and guanidino-acetic acid.
2. Blood and serum sometimes need to be tested for white blood cell lysosomal enzymes, serum coenzyme Q levels, and serum copper and ceruloplasmin levels (for Menkes syndrome).
3. Serum immune isoelectric focusing is performed for carbohydrate-deficient transferrin.
4. CSF glucose testing looks for glucose transporter deficiency, and CSF can be examined for cells and proteins (for parainfectious and postinfectious syndromes, and for Aicardi-Goutières syndrome, which also shows cerebral calcifications and has a specific gene defect test available).
5. Other laboratory studies include immunoglobulin (Ig) G index, NMDA (*N*-methyl-D-aspartate) receptor antibodies, and measles titers.
6. CSF tests can also confirm with, the appropriate clinical setup, the diagnosis of cerebral folate deficiency, pyridoxine dependency, pyridoxal dependency, mitochondrial disorders, nonketotic hyperglycinemia, neopterin/biopterin metabolism disorders, adenylosuccinate lyase deficiency, and neurotransmitter deficiencies. In infants who do not respond immediately to antiepileptic therapy, vitamin B_6 (100 mg intravenously) is given as a therapeutic trial to help diagnose pyridoxine-responsive seizures, with precautions to guard against possible apnea. The trial is best done with continuous EEG monitoring, including a preadministration baseline recording period. Prior to the vitamin B_6 trial, a pipecolic acid level and urine and CSF α-aminoadipic acid semialdehyde levels should be drawn, because they often elevated in this rare syndrome and the therapeutic trial result may not be definitive. Some patients are pyridoxal phosphate, rather than pyridoxine, dependent. Also patients with cerebral folate deficiency can have intractable seizures. Thus trials of pyridoxal phosphate given orally (up to 50 mg/kg) and folinic acid (up to 3 mg/kg) over several weeks can help diagnose these rare disorders while waiting for the definitive diagnosis from CSF or genetic testing for these disorders. Certain EEG changes such as continuous spike–and–slow-wave seizure activity and burst-suppression patterns may also suggest these vitamin-responsive syndromes.
7. Urine may also need to be tested for urinary sulfites indicating molybdenum cofactor deficiency and for oligosaccharides and mucopolysaccharides. MR spectroscopy is performed for lactate and creatine peaks to rule out mitochondrial disease and creatine transporter deficiency.
8. Gene testing looks for specific disorders that can manifest with seizures, including *SCN1A* mutations in Dravet syndrome; *ARX* gene for West syndrome in boys; *MECP2, CDKL5,* and protocadherin 19 for Rett syndrome and similar presentations; syntaxin binding protein for Ohtahara syndrome; and polymerase G for West syndrome and other seizures in infants. Gene testing can also be performed for other dysmorphic or metabolic syndromes.
9. Muscle biopsy can be performed for mitochondrial enzymes and coenzyme Q10 levels, and skin biopsy for inclusion bodies seen in neuronal ceroid lipofuscinosis and Lafora body disease is sometimes needed.
10. Genetic panels are available that include multiple genes that can cause epilepsy at specific ages; whole-exome sequencing is also available. These can be helpful in selected patients.

Most patients do not require a work-up anywhere near the above described extensive testing. The pace and extent of the work-up must depend critically upon the clinical epileptic and nonepileptic features, the family and antecedent personal history of the patient, the medication responsiveness of the seizures, the likelihood of identifying a treatable condition, and the wishes and need of the family to assign a specific diagnosis to the child's illness.

Bibliography is available at Expert Consult.

593.3 Partial Seizures and Related Epilepsy Syndromes

Mohamad A. Mikati and Abeer J. Hani

Partial (now referred to as focal) seizures account for approximately 40% of seizures in children and can be divided into **simple partial seizures** (currently referred to in the most recent ILAE classification as **focal seizures without impairment of consciousness**), in which consciousness is not impaired, and **complex partial seizures** (currently referred to as **focal seizures with impairment of consciousness**, also called **focal dyscognitive seizures**), in which consciousness is affected. Simple and complex partial seizures can each occur in isolation, one can temporally lead to the other (usually simple to complex), and/or each can progress into **secondary generalized seizures** (tonic, clonic, atonic, or most often tonic–clonic).

FOCAL SEIZURES WITHOUT IMPAIRMENT OF CONSCIOUSNESS

These can take the form of sensory seizures (auras) or brief motor seizures, the specific nature of which gives clues as to the location of the seizure focus. Brief motor seizures are the most common and include focal tonic, clonic, or atonic seizures. Often there is a motor (jacksonian) march from face to arm to leg, adversive head and eye movements to the contralateral side, or postictal (Todd) paralysis that can last minutes or hours, and sometimes longer. Unlike tics, motor seizures are not under partial voluntary control; seizures are more often stereotyped and less likely than tics to manifest different types in a given patient.

FOCAL SEIZURES WITH IMPAIRMENT OF CONSCIOUSNESS

These seizures usually last 1-2 min and are often preceded by an **aura**, such as a rising abdominal feeling, déjà vu or déjà vécu, a sense of fear, complex visual hallucinations, micropsia or macropsia (temporal lobe), generalized difficult-to-characterize sensations (frontal lobe), focal sensations (parietal lobe), or simple visual experiences (occipital lobe). Children younger than 7 yr old are less likely than older children to report auras, but parents might observe unusual preictal behaviors that suggest the experiencing of auras. Subsequent manifestations consist of decreased responsiveness, staring, looking around seemingly purposelessly, and automatisms. **Automatisms** are automatic semipurposeful movements of the mouth (oral, alimentary such as chewing) or of the extremities (manual, such as manipulating the sheets; leg automatisms such as shuffling, walking). Often there is salivation, dilation of the pupils, and flushing or color change. The patient might appear to react to some of the stimulation around him or her but does not later recall the epileptic event. At times, walking and/or marked limb flailing and agitation occur, particularly in patients with frontal lobe seizures. Frontal lobe seizures often occur at night and can be very numerous and brief, but other complex partial seizures from other areas in the brain can also occur at night, too. There is often contralateral dystonic posturing of the arm and, in some cases, unilateral or bilateral tonic arm stiffening. Some seizures have these manifestations with minimal or no automatisms. Others consist of altered consciousness with contralateral motor, usually clonic, manifestations. After the seizure, the patient can have postictal automatisms, sleepiness, and/or other transient focal deficits such as weakness (Todd paralysis) or aphasia.

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SECONDARY GENERALIZED SEIZURES

Seizures of this type were previously known as focal seizures with impairment of consciousness evolving to bilateral convulsive seizures. Secondary generalized seizures can start with generalized clinical phenomena (from rapid spread of the discharge from the initial focus), or as simple or complex partial seizures with subsequent clinical generalization. There is often adversive eye and head deviation to the side contralateral to the side of the seizure focus followed by generalized tonic, clonic, or tonic–clonic activity. Tongue biting, urinary and stool incontinence, vomiting with risk of aspiration, and cyanosis are common. Fractures of the vertebrae or humerus are rare complications. Most such seizures last 1-2 min. Tonic focal or secondary generalized seizures often manifest adversive head deviation to the contralateral side, or fencing, hemi- or full figure-of-four arm, or Statue of Liberty postures. These postures often suggest frontal origin, particularly when consciousness is preserved during them, indicating that the seizure originated from the medial frontal supplementary motor area.

EEG in patients with focal/partial seizures usually shows focal spikes or sharp waves in the lobe where the seizure originates. A sleep-deprived EEG with recording during sleep increases the diagnostic yield and is advisable in all patients whenever possible (Fig. 593-2). Despite that, approximately 15% of children with epilepsy initially have normal EEGs because the discharges are relatively infrequent or the focus is deep. If repeating the test does not detect paroxysmal findings, then longer recordings in the laboratory or using ambulatory EEG or even inpatient 24-hr video EEG monitoring may be helpful. The latter is particularly helpful if the seizures are frequent enough, because it then can allow visualization of the clinical events and the corresponding EEG tracing.

Brain imaging is critical in patients with focal seizures. In general, MRI is preferable to CT, which misses subtle but occasionally potentially clinically significant lesions. MRI can show pathologies such as changes as a result of previous strokes or hypoxic injury, malformations, medial temporal sclerosis, arteriovenous malformations, inflammatory pathologies, or tumors (Fig. 593-3).

BENIGN EPILEPSY SYNDROMES WITH FOCAL SEIZURES

The most common such syndrome is **benign childhood epilepsy with centrotemporal spikes** which typically starts during childhood (ages 3-10 yr) and is outgrown in adolescence. The child typically wakes up at night owing to a focal (simple partial) seizure causing buccal and throat tingling and tonic or clonic contractions of 1 side of the face, with drooling and inability to speak but with preserved consciousness and comprehension. Dyscognitive focal (complex partial) and secondary generalized seizures can also occur. EEG shows typical broad-based centrotemporal spikes that are markedly increased in frequency during drowsiness and sleep. MRI is normal. Patients respond very well to antiepileptic drugs (AEDs) such as carbamazepine. In some patients who only have rare and mild seizures treatment might not be needed.

Benign epilepsy with occipital spikes can occur in early childhood (**Panayiotopoulos type**) and manifests with complex partial seizures with ictal vomiting, or they appear in later childhood (**Gastaut type**) with complex partial seizures, visual auras, and migraine headaches. Both are typically outgrown in a few years. Manifestations may include visual hallucinations and postictal headache (epilepsy–migraine sequence).

In infants, several less-common **benign infantile familial convulsion syndromes** have been reported. For some of these, the corresponding gene mutation and its function are known (see Tables 593-2 and 593-5), but for others, the genetic underpinnings are yet to be determined. Specific syndromes include benign infantile familial convulsions with parietooccipital foci linked to chromosomal loci 19q and 2q, benign familial infantile convulsions with associated choreoathetosis linked to chromosomal locus 16p12-q12, and benign

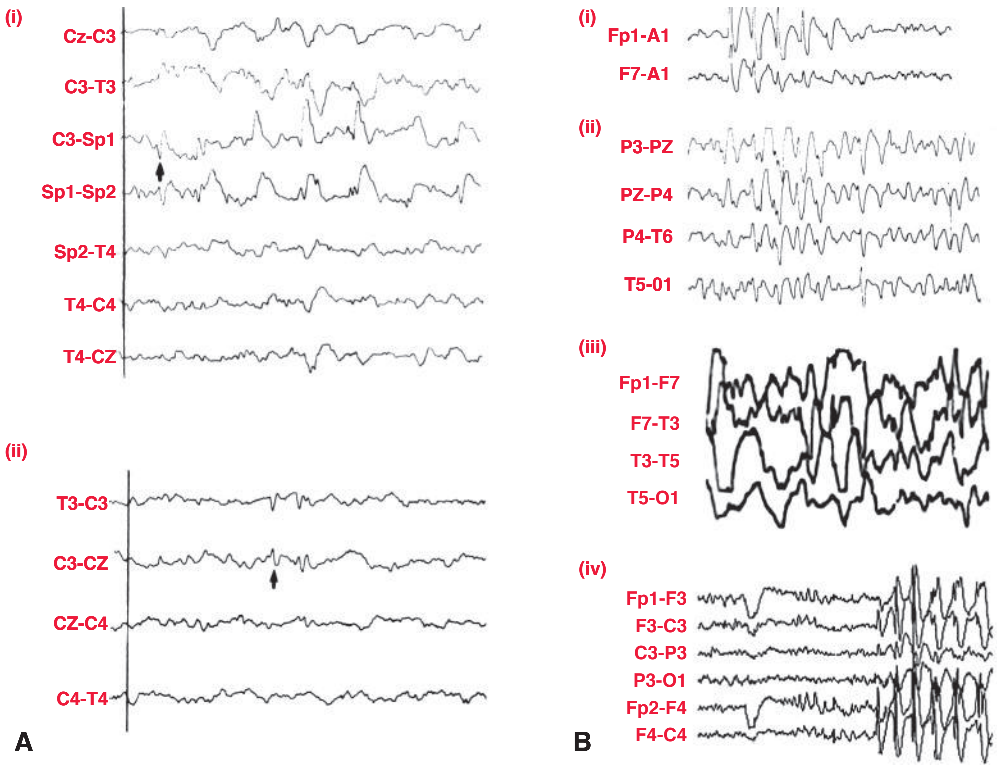

Figure 593-2 **A,** Representative EEG associated with partial seizures: (i) Spike discharges from the left temporal lobe *(arrow)* in a patient with complex partial seizures caused by mesial temporal sclerosis; (ii) left central-parietal spikes *(arrow)* characteristic of benign partial epilepsy with centrotemporal spikes. **B,** Representative EEGs associated with generalized seizures: (i) 3/sec spike-and-wave discharge of absence seizures with normal background activity; (ii) 1-2/sec interictal slow spike waves in a patient with Lennox-Gastaut syndrome; (iii) hypsarrhythmia with an irregular multifocal high-voltage spike and wave activity with chaotic high-voltage slow background; (iv) juvenile myoclonic epilepsy EEG showing 4-6/sec spike and waves enhanced by photic stimulation.

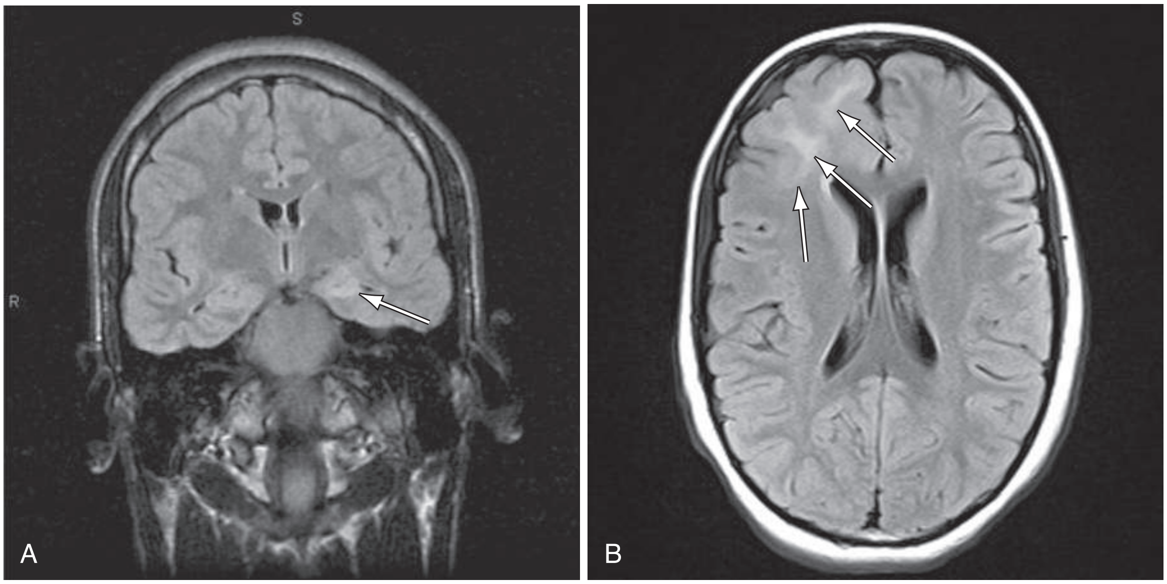

Figure 593-3 **A,** Coronal fluid-attenuated inversion-recovery (FLAIR) MRI scan of a 13 yr old with intractable seizures and mesial temporal sclerosis (MTS). The *arrow* points at the hippocampus with the high-intensity signal characteristic of MTS. **B,** Axial FLAIR MRI of a 7 yr old with intractable seizures and right frontal cortical dysplasia. The *arrows* point at the high-intensity signal corresponding to the dysplasia. (***A*** *from Lee JYK, Adelson PD: Neurosurgical management of pediatric epilepsy,* Pediatr Clin North Am *51:441–456, 2004.)*

infantile familial convulsions with hemiplegic migraine linked to chromosome 1. A number of **benign infantile nonfamilial syndromes** have been reported, including dyscognitive focal (complex partial) seizures with temporal foci, secondary generalized tonic–clonic seizures with variable foci, tonic seizures with midline foci, and partial seizures in association with mild gastroenteritis. All of these have a good prognosis and respond to treatment promptly, often necessitating only short-term (e.g., 6 mo), if any, therapy. **Nocturnal autosomal dominant frontal lobe epilepsy** has been linked to acetylcholine-receptor gene mutations and manifests with nocturnal seizures with dystonic posturing and agitation, screaming, kicking that respond promptly to carbamazepine. Several other less-frequent familial benign epilepsy syndromes with different localizations have also been described, some of which occur exclusively or predominantly in adults (see Table 593-2).

SEVERE EPILEPSY SYNDROMES WITH FOCAL SEIZURES

Symptomatic structural/metabolic epilepsy secondary to focal brain lesions has a higher chance of being severe and refractory to therapy than idiopathic genetic epilepsy. It is important to note that many patients with focal lesions, for example, old strokes or brain tumors, either never have seizures or have well-controlled epilepsy. In infants, drug-resistant epilepsy with focal seizures is often caused by severe metabolic problems, hypoxic–ischemic injury, or congenital malformations. In addition, in this age group, a syndrome of multifocal severe partial seizures with progressive mental regression and cerebral atrophy called **migrating partial seizures of infancy** has been described. In infants and older children, several types of lesions, which can occur in any lobe, can cause intractable epilepsy and seizures and some cases may be secondary to mutations in the calcium sensitive potassium channel KCNT1. Brain malformations causing focal epilepsy include focal cortical dysplasia, hemimegalencephaly, Sturge-Weber hemangioma, tuberous sclerosis, and congenital tumors such as ganglioglioma, and dysembryoplastic neuroepithelial tumors, as well as others. The intractable seizures can be simple partial, complex partial, secondary generalized, or combinations thereof. If secondary generalized seizures predominate and take the form of absence-like seizures and drop attacks, the clinical picture can mimic the generalized epilepsy syndrome of Lennox-Gastaut syndrome and has been termed by some **pseudo–Lennox-Gastaut syndrome**.

Temporal lobe epilepsy can be caused by any temporal lobe lesion. A common cause is **mesial** (also termed **medial**) **temporal sclerosis**, a condition often preceded by febrile seizures and, rarely, genetic in origin. Pathologically, these patients have atrophy and gliosis of the hippocampus and, in some, of the amygdala. It is the most common cause of surgically remediable partial epilepsy in adolescents and adults. Occasionally, in patients with other symptomatic or cryptogenic partial or generalized epilepsies, the focal discharges are so continuous that they cause an epileptic encephalopathy. Activation of temporal discharges in sleep can lead to loss of speech and verbal auditory agnosia (**Landau-Kleffner epileptic aphasia syndrome**). Activation of frontal and secondary generalized discharges in sleep leads to more global delay secondary to the **syndrome of continuous spike waves in slow-wave sleep** (>85% of slow-wave sleep recording dominated by discharges).

The syndrome of **Rasmussen encephalitis** is a form of chronic encephalitis that manifests with unilateral intractable partial seizures, epilepsia partialis continua, and progressive hemiparesis of the affected side, with progressive atrophy of the contralateral hemisphere. The etiology is usually unknown. Some cases have been attributed to cytomegalovirus and others to anti-NMDA receptor autoantibodies.

593.4 Generalized Seizures and Related Epilepsy Syndromes

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ABSENCE SEIZURES

Typical absence seizures usually start at 5-8 yr of age and are often, owing to their brevity, overlooked by parents for many months even though they can occur up to hundreds of times per day. Unlike complex partial seizures they do not have an aura, usually last for only a few seconds, and are accompanied by eye lid flutter or upward rolling of the eyes but typically not by the usually more florid automatisms of complex partial seizures (absence seizures can have simple automatisms like lip-smacking or picking at clothing and the head can minimally fall forward). Absence seizures do not have a postictal period and are characterized by immediate resumption of what the patient was doing before the seizure. Hyperventilation for 3-5 min can precipitate the seizures and the accompanying 3 Hz spike–and–slow-wave

discharges. The presence of periorbital, lid, perioral or limb myoclonic jerks with the typical absence seizures usually predicts difficulty in controlling the seizures with medications. Early onset absence seizures (before the age of 4 yr) should trigger evaluation for glucose transporter defect that is often associated with low CSF glucose levels and an abnormal sequencing test of the transporter gene.

Atypical absence seizures have associated myoclonic components and tone changes of the head (head drop) and body and are also usually more difficult to treat. They are precipitated by drowsiness and are usually accompanied by 1-2 Hz spike–and–slow-wave discharges.

Juvenile absence seizures are similar to typical absences but occur at a later age and are accompanied by 4-6 Hz spike–and–slow-wave and polyspike–and–slow-wave discharges. These are usually associated with juvenile myoclonic epilepsy (see "Benign Generalized Epilepsies").

GENERALIZED MOTOR SEIZURE

The most common generalized motor seizures are generalized tonic–clonic seizures that can be either primarily generalized (bilateral) or secondarily generalized (as described in Chapter 593.3) from a unilateral focus. If there is no partial component, then the seizure usually starts with loss of consciousness and, at times, with a sudden cry, upward rolling of the eyes, and a generalized tonic contraction with falling, apnea, and cyanosis. In some, a clonic or myoclonic component precedes the tonic stiffening. The tonic phase is followed by a clonic phase that, as the seizure progresses, shows slowing of the rhythmic contractions until the seizure stops usually 1-2 min later. Incontinence and a postictal period often follow. The latter usually lasts for 30 min to several hours with semicoma or obtundation and postictal sleepiness, weakness, ataxia, hyper- or hyporeflexia, and headaches. There is a risk of aspiration and injury. First aid measures include positioning the patient on his or her side, clearing the mouth if it is open, loosening tight clothes or jewelry, and gently extending the head and, if possible, insertion of an airway by a trained professional. The mouth should not be forced open with a foreign object (this could dislodge teeth, causing aspiration) or with a finger in the mouth (this could result in serious injury to the examiner's finger). Many patients have single **idiopathic generalized tonic–clonic seizures** that may be associated with intercurrent illness or with a cause that cannot be ascertained (see Chapter 593.2). Generalized tonic, atonic, and astatic seizures often occur in severe generalized pediatric epilepsies. Generalized myoclonic seizures can occur in either benign or difficult-to-control generalized epilepsies (see "Benign Generalized Epilepsies" and "Severe Generalized Epilepsies").

BENIGN GENERALIZED EPILEPSIES

Petit mal epilepsy typically starts in mid-childhood, and most patients outgrow it before adulthood. Approximately 25% of patients also develop generalized tonic–clonic seizures, half before and half after the onset of absences. **Benign myoclonic epilepsy of infancy** consists of the onset of myoclonic and other seizures during the 1st yr of life, with generalized 3 Hz spike–and–slow-wave discharges. Often, it is initially difficult to distinguish this type from more-severe syndromes, but follow-up clarifies the diagnosis. **Febrile seizures plus syndrome** manifests febrile seizures and multiple types of generalized seizures in multiple family members, and at times different individuals within the same family manifest different generalized and febrile seizure types (see Chapter 593.1).

Juvenile myoclonic epilepsy (Janz syndrome) is the most common generalized epilepsy in young adults, accounting for 5% of all epilepsies. It has been linked to mutations in many genes including *CACNB4; CLNC2; EJM2, 3, 4, 5, 6, 7, 9; GABRA1; GABRD;* and *Myoclonin1/EFHC1* (see Table 593-2). Typically, it starts in early adolescence with 1 or more of the following manifestations: myoclonic jerks in the morning, often causing the patient to drop things; generalized tonic–clonic or clonic–tonic–clonic seizures upon awakening; and juvenile absences. Sleep deprivation, alcohol (in older patients), and photic stimulation, or, rarely, certain cognitive activities can act as precipitants. The EEG usually shows generalized 4-5 Hz polyspike–and–slow-wave discharges. There are other forms of generalized epilepsies such as **photoparoxysmal epilepsy**, in which generalized tonic–clonic, absence or myoclonic generalized seizures are precipitated by photic stimuli such as strobe lights, flipping through TV channels and viewing video games. Other forms of **reflex** (i.e., **stimulus-provoked**) **epilepsy** can occur; associated seizures are usually generalized, although some may be focal (see Table 593-1 and Chapter 593.9).

SEVERE GENERALIZED EPILEPSIES

Severe generalized epilepsies are associated with intractable seizures and developmental delay. **Early myoclonic infantile encephalopathy** starts during the 1st 2 mo of life with severe myoclonic seizures and burst suppression pattern on EEG. It is usually caused by inborn errors of metabolism such as non-ketotic hyperglycinemia. **Early infantile epileptic encephalopathy (Ohtahara syndrome)** has similar age of onset and EEG but manifests tonic seizures and is usually caused by brain malformations or syntaxin binding protein 1 mutations. Severe **myoclonic epilepsy of infancy (Dravet syndrome)** starts as focal febrile status epilepticus or focal febrile seizures and later manifests myoclonic and other seizure types (see Chapter 593.1).

West syndrome starts between the ages of 2 and 12 mo and consists of a triad of infantile epileptic spasms that usually occur in clusters (particularly in drowsiness or upon arousal), developmental regression, and a typical EEG picture called **hypsarrhythmia** (see Fig. 593-2). Hypsarrhythmia is a high-voltage, slow, chaotic background with multifocal spikes. Patients with cryptogenic (sometimes called idiopathic, now referred to as unknown etiology) West syndrome have normal development before onset, while patients with symptomatic West syndrome have preceding developmental delay owing to perinatal encephalopathies, malformations, underlying metabolic disorders, or other etiologies (see Chapter 593.2). In boys, West syndrome can also be caused by *ARX* gene mutations (often associated with ambiguous genitalia and cortical migration abnormalities). West syndrome, especially in cases of unknown etiology (cryptogenic cases, i.e., cases that are not symptomatic of metabolic or structural brain disorder), is a medical emergency because diagnosis delayed for 3 wk or longer can affect long-term prognosis. The spasms are often overlooked by parents and by physicians, being mistaken for startles caused by colic or for other benign paroxysmal syndromes (see Chapter 594).

Lennox-Gastaut syndrome typically starts between the ages of 2 and 10 yr and consists of a triad of developmental delay, multiple seizure types that as a rule include atypical absences, myoclonic, astatic, and tonic seizures. The tonic seizures occur either in wakefulness (causing falls and injuries) or also, typically, in sleep. The third component is the EEG findings (see Fig. 593-2): 1-2 Hz spike–and–slow waves, polyspike bursts in sleep, and a slow background in wakefulness. Patients commonly have myoclonic, atonic, and other seizure types that are difficult to control, and most are left with long-term cognitive impairment and intractable seizures despite multiple therapies. Some, but not all, patients start with Ohtahara syndrome, develop West syndrome, and then progress to Lennox-Gastaut syndrome. **Myoclonic astatic epilepsy** is a syndrome similar to, but milder than, Lennox-Gastaut syndrome that usually does not have tonic seizures or polyspike bursts in sleep. The prognosis is more favorable than that for Lennox-Gastaut syndrome. Another syndrome characterized by atonic seizures causing head nodding as well as tonic, clonic and stimulus sensitive seizures is the **nodding syndrome**, which is a recently described epidemic type of epilepsy seen in some African countries and often associated with encephalopathy, stunted growth, and variable degrees of cognitive deficits. The underlying etiology is unknown.

Progressive myoclonic epilepsies are a group of epilepsies characterized by progressive dementia and worsening myoclonic and other seizures. **Type I** or **Unverricht-Lundborg disease** (secondary to a cystatin B mutation) is more slowly progressive than the other types and usually starts in adolescence. **Type II** or **Lafora body disease** can have an early childhood onset but usually starts in adolescence, is more quickly progressive, and is usually fatal within the 2nd or 3rd decade. It can be associated with photosensitivity, manifests periodic acid–Schiff-positive Lafora inclusions on muscle or skin biopsy (in eccrine

sweat gland cells), and has been shown to be caused by laforin *(EPM2A)* or malin *(EPM2B)* gene mutations. Other causes of progressive myoclonic epilepsy include myoclonic epilepsy with ragged red fibers, sialidosis type I, neuronal ceroid lipofuscinosis, juvenile neuropathic Gaucher disease, dentatorubral-pallidoluysian atrophy, and juvenile neuroaxonal dystrophy.

Myoclonic encephalopathy in nonprogressive disorders is an epileptic encephalopathy that occurs in some congenital disorders affecting the brain, such as Angelman syndrome, and consists of almost continuous and difficult-to-treat myoclonic and, at times, other seizures.

Landau-Kleffner syndrome is a rare condition of unknown cause characterized by loss of language skills attributed to auditory agnosia in a previously normal child. At least 70% have associated clinical seizures, but some do not. The seizures when they occur are of several types, including focal, generalized tonic–clonic, atypical absence, partial complex, and, occasionally, myoclonic seizures. High-amplitude spike-and-wave discharges predominate and tend to be bitemporal. In the later evolutionary stages of the condition, the EEG findings may be normal. The spike discharges are always more apparent during non–rapid eye movement sleep; thus, a child in whom Landau-Kleffner syndrome is suspected should have an EEG during sleep, particularly if the awake record is normal. CT and MRI studies typically yield normal results. In the related but clinically distinct epilepsy syndrome with **continuous spike waves in slow-wave sleep**, the discharges are more likely to be frontal or generalized and the delays more likely to be global. The approach and therapy to the 2 syndromes are similar. Valproic acid is often the anticonvulsant that is used first to treat the clinical seizures and may help the aphasia. Some children respond to clobazam, to the combination of valproic acid and clobazam, or to levetiracetam. For therapy of the aphasia, nocturnal diazepam therapy (0.2-0.5 mg/kg PO at bedtime for several months) is often used as first- or second-line therapy, as are oral steroids. Oral prednisone is started at 2 mg/kg/24 hr for 1 mo and decreased to 1 mg/kg/24 hr for an additional month. With clinical improvement, the prednisone is reduced further to 0.5 mg/kg/24 hr for up to 6-12 mo. Long-term therapy is often needed irrespective of what the patient responds to. If the seizures and aphasia persist after diazepam and steroids trials, then a course of intravenous immunoglobulins should be considered. It is imperative to initiate speech therapy and maintain it for several years, because improvement in language function occurs over a prolonged period.

Amenably treatable metabolic epilepsies are becoming increasingly recognized. **Pyridoxine-dependent epilepsy** typically presents as neonatal encephalopathy shortly after birth with, at times, report of increased fetal movements (seizure) in utero. There are associated gastrointestinal symptoms with emesis and abdominal distention, neurologic irritability, sleepless and facial grimacing along with recurrent partial motor seizure, generalized tonic seizures, and myoclonus. Seizures are usually refractory and may progress to status epilepticus if no pyridoxine is used. Some cases start in infancy or in childhood. Diagnosis is confirmed by the presence of elevated plasma, urine and CSF α-aminoadipic semialdehyde and elevated plasma and CSF pipecolic acid levels. The presence of either homozygous or compound heterozygous mutations in ALDH7A1 alleles (which encode the protein antiquitin) confirms the diagnosis. The use of pyridoxine 100 mg daily orally (up to 600 mg/day) or intravenously helps stop the seizures. **Pyridoxal phosphate responsive neonatal epileptic encephalopathy** (Pyridox[am]ine 5′-phosphate oxidase [PNPO] deficiency) may present similarly in the absence of gastrointestinal symptoms. Diagnostically, there are reduced pyridoxal phosphate levels in the CSF with increased levels of CSF levodopa and 3-methoxytyrosine along with decreased CSF homovanillic acid and 5-hydroxyindolacetic acid. The EEG may show a burst suppression pattern and treatment is by enteral administration of pyridoxal phosphate (up to 60 mg/kg/day). **Folinic acid–responsive seizures** may also present with neonatal epileptic encephalopathy and intractable seizures. These patients have a similar diagnostic profile as pyridoxine-dependent epilepsy patients and are caused by the same gene mutations but respond to folinic acid supplementation in addition to pyridoxine use. **Cerebral folate deficiency**, which also responds to high doses of folinic acid (2-3 mg/kg/day), may manifest with epilepsy, intellectual disability, developmental regression, dyskinesias, and autism. CSF 5-methyltetrahydrofolate levels are decreased with normal plasma and red blood cell folate levels. There are usually mutations in the folate receptor *(FOLR1)* gene or blocking autoantibodies against membrane-associated folate receptors of the choroid plexus. **Tetrahydrobiopterin deficiencies** with or without hyperphenylalaninemia may present with epilepsies, and symptoms resulting from deficiencies of dopamine (parkinsonism, dystonia), noradrenaline (axial hypotonia), serotonin (depression, insomnia, temperature changes) and folate (myelin formation, basal ganglia calcifications, and seizures). Treatment is by substitution therapy with tetrahydrobiopterin and neurotransmitter precursors started as early as possible. **Creatine deficiency syndromes** present typically with developmental delay, seizures, autistic features, and movement disorders and are diagnosed by abnormal levels of urine creatine and guanidinoacetic acid and/or, depending on the type of underlying genetic etiology, with absent creatine peak on MR spectroscopy of the brain. Use of creatine monohydrate and dietary restrictions are helpful. **Biotinidase deficiency** presenting as developmental delay, seizures, ataxia, alopecia, and skin rash and often associated with intermittent metabolic acidosis and organic profile of lactic and propionic acidemia, responds to the use of biotin. Serine biosynthesis defects with low serine levels in plasma or CSF amino acids often present with congenital microcephaly, intractable seizures, and psychomotor retardation and respond to supplemental serine and glycine use. **Developmental delay, epilepsy, and neonatal diabetes** is caused by activating mutations in the adenosine triphosphate-sensitive potassium channels. Sulfonylurea drugs that block the potassium channel treat the neonatal diabetes and probably also favorably affect the central nervous system (CNS) symptoms and affect seizures. Hyperinsulinism-hyperammonemia syndrome is caused by activating mutations of the glutamate dehydrogenase encoded by the *GLUD1* gene. Patients present with hypoglycemic seizures after a protein-rich meal with hyperammonemia (ammonia levels 80-150 µmol/L). They are managed with a combination of protein restriction, AEDs, and diazoxide (a potassium channel agonist that inhibits insulin release). **GLUT-1 deficiency syndrome** classically presents with infantile-onset epilepsy, developmental delay, acquired microcephaly, and complex movement disorders. It causes impaired glucose transport to the brain typically diagnosed by genetic testing or finding of low CSF lactate and CSF glucose, or low CSF to serum glucose ratios (less than 0.4). The manifestations of the disease are usually responsive to ketogenic diet.

593.5 Mechanisms of Seizures

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One can distinguish in the pathophysiology of epilepsy 4 distinct, often sequential, mechanistic processes. First is the **underlying etiology**, which is any pathology or pathologic process that can disrupt neuronal function and connectivity and that eventually leads to the second process (epileptogenesis) which makes the brain epileptic. The underlying etiologies of epilepsy are diverse and include, among other entities, brain tumors and malformations, strokes, scarring, or mutations of specific genes. These mutations can involve voltage-gated channels (Na^+, K^+, Ca^{2+}, Cl^-, and HCN [hydrogen cyanide]), ligand-gated channels (nicotinic acetylcholine and γ-aminobutyric acid A receptors [$GABA_A$]) or other proteins. In some but not in all such mutations, the molecular and cellular deficits caused by the mutations have been identified. For example, in Dravet syndrome, the loss of function mutation in the *SCN1A* gene causes decreased excitability in inhibitory GABAergic interneurons, leading to increased excitability and epilepsy. In human cortical dysplasia, the expression of the NR2B subunit of the NMDA receptor is increased, leading to excessive depolarizing currents. In many other epileptic conditions, a clear etiology is still lacking and in others the etiology may be known, but it is still not

known how the identified underlying genetic etiology or brain insult results in epileptogenesis.

Second, **epileptogenesis** is the mechanism through which the brain, or part of it, turns epileptic. The presence of this process explains why some patients with the above pathologies develop epilepsy and some do not. **Kindling** is an animal model for human focal epilepsy in which repeated electrical stimulation of selected areas of the brain with a low-intensity current initially causes no apparent changes but with repeated stimulation results in epilepsy. This repetitive stimulation can lead to temporal lobe epilepsy, for example, through activation of metabotropic and ionotropic glutamate receptors (by glutamate), as well as the tropomyosin-related kinase B receptor (by brain-derived neurotrophic factor and neurotrophin-4). This leads to an increase in the intraneuronal calcium, which, in turn, activates calcium calmodulin–dependent protein kinase and calcineurin, a phosphatase, resulting eventually in calcium-dependent epileptogenic gene expression (e.g., c-fos) and promotion of mossy fiber sprouting. **Mossy fibers** are excitatory fibers that connect the granule cells to the CA3 region within the hippocampus, and their pathologic sprouting underlies increased excitability in medial temporal lobe epilepsy associated with mesial temporal sclerosis in humans and in animal models. The cell loss in the CA3 region that is a characteristic of mesial temporal sclerosis (presumably resulting from an original insult such as a prolonged febrile status epilepticus episode or hypoxia) leads to a pathologic attempt at compensation by sprouting of the excitatory mossy fibers. Consequently, mossy fiber sprouting, which has been demonstrated in humans also, leads to increased excitability and to epilepsy. Complex febrile seizures in rats induce hyperactivation of, paradoxically excitatory, $GABA_A$ receptors leading to granule cell ectopia and to subsequent temporal lobe epilepsy. Possibly similar yet to be fully characterized epileptogenesis mechanisms may underlie other focal epilepsies.

Lately, the role of large-scale molecular cell signaling pathways in epileptogenesis, namely the mammalian target of rapamycin (mTOR), the Ras/ERK, and repressor element 1 (RE1)-silencing transcription factor (REST; also known as neuron-restrictive silencer factor) pathways have been implicated in the mechanisms leading to epilepsy. The mTOR pathway in tuberous sclerosis, hemimegalencephaly and cortical dysplasia-related epilepsies, Ras/ERK in a number of syndromes, and REST in epileptogenesis after acute neuronal injury.

The third process is the resultant **epileptic state of increased excitability** that is present in all patients irrespective of the underlying etiology or mechanism of epileptogenesis. In a seizure focus, each neuron has a stereotypic synchronized response called **paroxysmal depolarization shift** that consists of a sudden depolarization phase, resulting from glutamate and calcium channel activation, with a series of action potentials at its peak followed by an after-hyperpolarization phase, resulting from activation of potassium channels and GABA receptors that open chloride channels. When the after-hyperpolarization is disrupted in a sufficient number of neurons, the inhibitory surround is lost and a population of neurons fire at the same rate and time, resulting in a seizure focus. In childhood absence epilepsy, the discharging neurons also develop a paroxysmal depolarization shift similar to the one found in partial epilepsy. However, the mechanism of paroxysmal depolarization shift generation is different because it involves thalamocortical connections bilaterally. T-type calcium channels on thalamic relay neurons are activated during hyperpolarization by GABAergic interneurons in the reticular thalamic nucleus, which results in enhancement of synchronization in the thalamocortical loop and consequently in the typical generalized spike-wave pattern. In tumor-related epilepsy, particularly in that related to oligodendroglioma, the voltage-gated sodium channels are present on the surface of tumor cells at a higher density than on normal cells, and their inactivation is impaired by the alkaline pH present in this condition. In hypothalamic hamartoma causing gelastic seizures, clusters of GABAergic interneurons spontaneously fire, thus synchronizing the output of the hypothalamic hamartoma neurons projecting to the hippocampus.

The fourth process is **seizure-related neuronal injury** as demonstrated by MRI in patients after prolonged febrile and afebrile status epilepticus. Many such patients show acute swelling in the hippocampus and long-term hippocampal atrophy with sclerosis on MRI. Nonetheless in most patients with seizure-related MRI abnormalities, the findings are transient. In experimental models, the mechanisms of such injuries have been shown to involve both apoptosis and necrosis of neurons in the involved regions. There is evidence from surgically resected epileptic tissue that apoptotic pathways are activated in foci of intractable epilepsy.

In infantile spasms, recently developed animal models suggest that increases in stress-related corticotropin-releasing hormone, sodium channel blockade, and NMDA receptor stimulation are contributing mechanisms. Prior positron emission tomography data suggest that an interaction between focal cortical lesions and the brainstem raphe nuclei is important at least in some infantile spasms patients.

Bibliography is available at Expert Consult.

593.6 Treatment of Seizures and Epilepsy

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DECIDING ON LONG-TERM THERAPY

After a *first seizure*, if the risk of recurrence is low, such as when the patient has normal neurodevelopmental status, EEG, and MRI (risk approximately 20%), then treatment is usually not started. If the patient has abnormal EEG, MRI, development, and/or neurologic exam, and/or a positive family history of epilepsy, then the risk is higher and often treatment is started. Other considerations are also important, such as motor vehicle driving status and type of employment in older patients or the parents' ability to deal with recurrences or AED drug therapy in children. The decision is therefore always individualized. All aspects of this decision-making process should be discussed with the family. Figure 593-4 presents an overview of the approach to the treatment of seizures and epilepsy.

COUNSELING

An important part of the management of a patient with epilepsy is educating the family and the child about the disease, its management, and the limitations it might impose and how to deal with them. It is important to establish a successful therapeutic alliance. Restrictions on driving (in adolescents) and on swimming are usually necessary (Table 593-10). In most states, the physician is not required to report the epileptic patient to the motor vehicle registry; this is the responsibility of the patient. The physician then is requested to complete a specific form for patients who are being cleared to drive. Also in most states, a seizure-free period of 6 mo, and in some states longer, is required before driving is allowed. Often swimming in rivers, lakes, or sea, and underwater diving are prohibited, but swimming in swimming pools may be allowable. When swimming, even patients with epilepsy that is under excellent control should be under the continuous supervision of an observer who is aware of their condition and capable of lifeguard-level rescue.

The physician, parents, and child should jointly evaluate the risk of involvement in athletic activities. To participate in athletics, proper medical management, good seizure control, and proper supervision are crucial to avoid significant risks. Any activity where a seizure might cause a dangerous fall should be avoided; these activities include rope climbing, use of the parallel bars, and high diving. Participation in collision or contact sports depends on the patient's condition. Epileptic children should not automatically be banned from participating in hockey, baseball, basketball, football, or wrestling. Rather, individual consideration should be based on the child's specific case (see Table 593-10).

Counseling is helpful to support the family and to educate them about the resources available in the community. Educational and, in some cases, psychologic evaluation may be necessary to evaluate for possible learning disabilities or abnormal behavioral patterns that might coexist with the epilepsy. Epilepsy does carry a risk of increased

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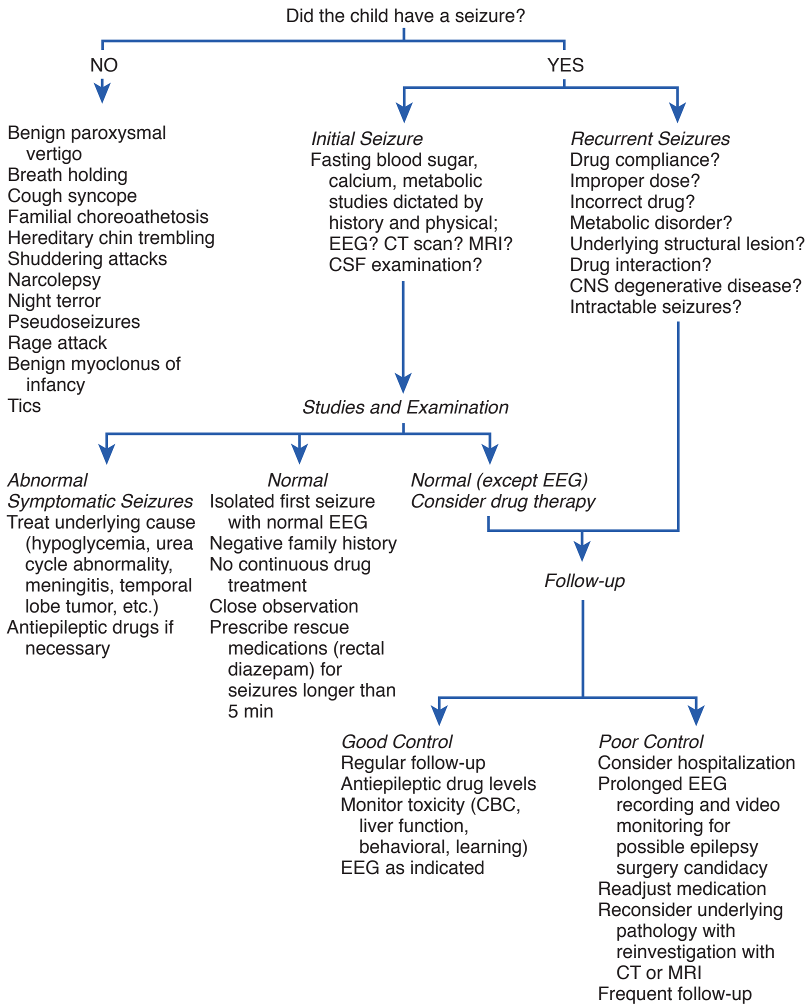

Figure 593-4 Approach to the child with a suspected convulsive disorder.

Table 593-10 Sports and Special Considerations for the Child with Epilepsy*

SPORTS TYPE	SPECIAL CONSIDERATIONS
Body contact sports	If there are more than occasional seizures, physician evaluation of benefits and risks of participation should be made based on the child's condition. No contraindications in general except for boxing.
Noncontact sports	Generally recommended. Anxiety and fatigue can cause a problem in some children. Individualization based on clinical history must be the rule.
Gymnastics	A fall can result if the child experiences a sudden seizure, especially with trampolines, parallel bars, and rope climbing, which should be avoided. Individual consideration remains the basic determinant.
Swimming	The child should always be under supervision, and scuba diving should be discouraged in poorly controlled epileptics.

*Specific advice should be individualized depending on the patient's clinical condition. Many patients actually have fewer seizures when they are active than when they are idle.

Modified from Committee on Children with Handicaps: The epileptic child and competitive school athletics, Pediatrics *42:700–702, 1968; and Knowles BD: Athletes with seizure disorders,* Curr Sports Med Rep *11(1):16–20, 2012, Table 1.*

mortality (2 or more times the standardized mortality rates of the general population) and of sudden unexpected death. This is mostly related to the conditions associated with or underlying the epilepsy (e.g., tumor, metabolic diseases), to poor seizure control (e.g., in patients with severe epileptic encephalopathies, or drug-resistant seizures), and to poor compliance with prescribed therapies. Thus, family members can usually be informed about this increased risk without inappropriately increasing their anxiety. Many family members feel they need to observe the patient continuously in wakefulness and sleep and have the patient sleep in the parents' room to detect seizures. There are currently advertised seizure-detection equipment that use motion sensors placed under the mattress to detect seizures. Some are disappointing and ineffective in detecting seizures, whereas data from other equipment are encouraging in that they were useful in detecting a majority of generalized tonic–clonic seizures during sleep (see bibliography for details). Whether such measures can reduce sudden unexpected death in epilepsy (SUDEP) risk remains to be seen and the parents need to guard against being overprotective to avoid adversely affecting the psychology of the child. Education about what to do in case of seizures, the choices of treatment or no treatment and of medications and their side effects, and potential complications of epilepsy should be provided to the parents and, if the child is old enough, to the child.

MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

AEDs reduce excitability by interfering with the sodium, potassium or calcium ion channels, by reducing excitatory neurotransmitter release

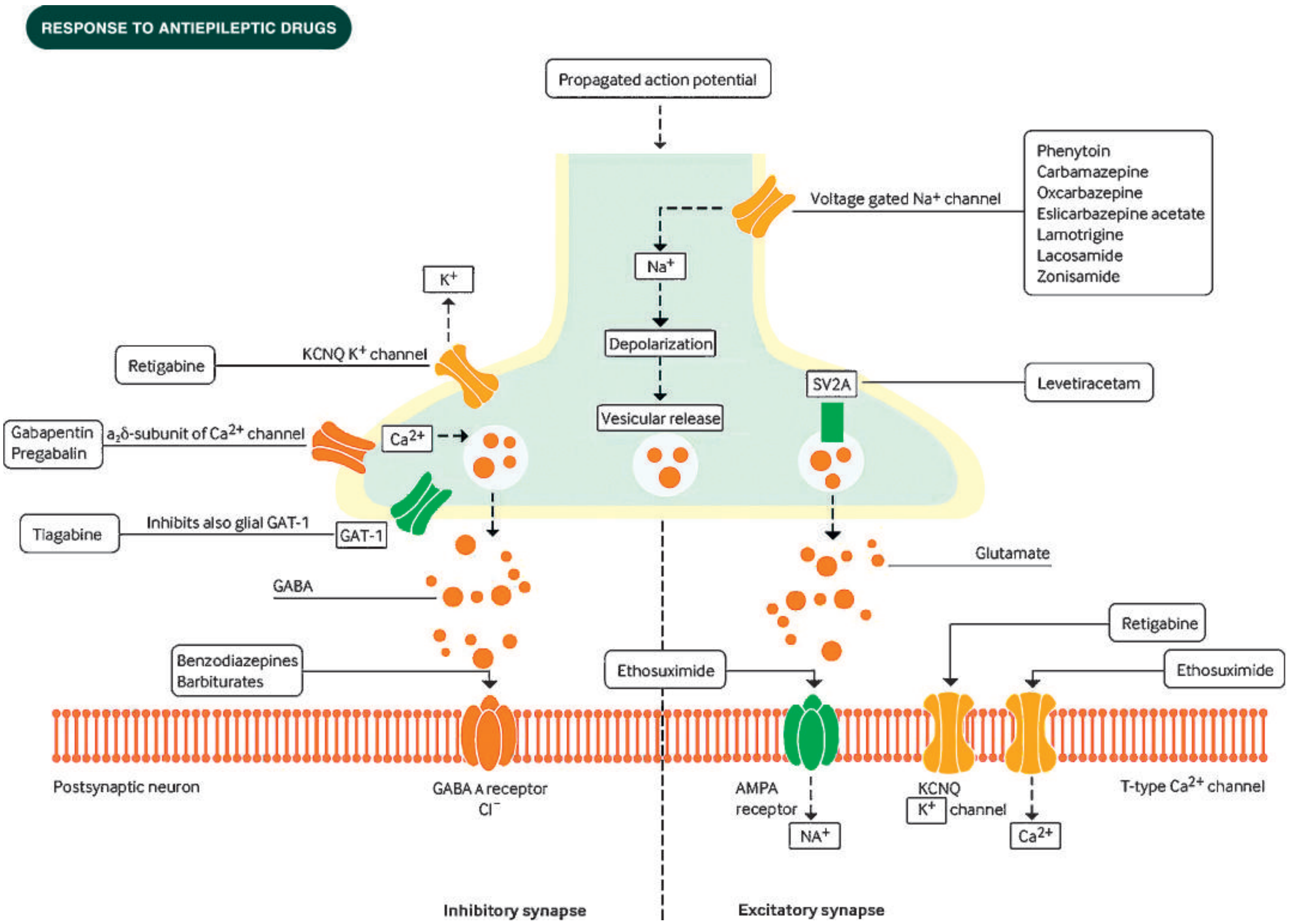

Figure 593-5 Mechanisms of action of antiepileptic drugs, which act by diverse mechanisms, mainly involving modulation of voltage activated ion channels, potentiation of GABA, and inhibition of glutamate. Approved antiepileptic drugs have effects on inhibitory *(left hand side)* and excitatory *(right hand side)* nerve terminals. The antiepileptic efficacy in trials of most of these drugs as initial add-on does not differ greatly, indicating that seemingly similar antiseizure activity can be obtained by mechanisms aimed at diverse targets. However, putative mechanisms of action were determined only after discovering the antiseizure effects; mechanism driven drug discovery has been largely ignored. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ-aminobutyric acid; GAT-1, sodium-dependent and chloride-dependent GABA transporter 1; SV2A, synaptic vesicle glycoprotein 2A. *(From Schmidt D, Schachter SC: Drug treatment of epilepsy in adults.* BMJ, *348:bmj.g254, 2014.)*

or function, or by enhancing GABAergic inhibition (Fig. 593-5). Most medications have multiple mechanisms of action, and the exact mechanism responsible for their activity in human epilepsy is usually not fully understood. Often, medications acting on sodium channels are effective against partial seizures, and medications acting on T-type calcium channels are effective against absence seizures. Voltage-gated sodium channels are blocked by felbamate, valproate, topiramate, carbamazepine, oxcarbazepine, lamotrigine, phenytoin, rufinamide, lacosamide, and zonisamide. T-type calcium channels, found in the thalamus area, are blocked by valproate, zonisamide, and ethosuximide. Voltage-gated calcium channels are inhibited by gabapentin, pregabalin, lamotrigine, and felbamate. N-type calcium channels are inhibited by levetiracetam. Ezogabine/retigabine opens KCNQ/Kv7 voltage-gated potassium channels.

$GABA_A$ receptors are activated by phenobarbital, benzodiazepines, topiramate, felbamate, and levetiracetam. Tiagabine, by virtue of its binding to GABA transporters 1 (GAT-1) and 3 (GAT-3), is a GABA reuptake inhibitor. GABA levels are increased by vigabatrin via its irreversible inhibition of GABA transaminases. Valproate inhibits GABA transaminases, acts on $GABA_B$ presynaptic receptors (also done by gabapentin), and activates glutamic acid decarboxylase (the enzyme that forms GABA).

Glutaminergic transmission is decreased by felbamate that blocks NMDA and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid)/kainate receptors. Topiramate also blocks AMPA/kainate receptors. Levetiracetam binds to the presynaptic vesicle protein SV2A found in all neurotransmitter vesicles and possibly results in inhibition of presynaptic neurotransmitter release in a use-dependent manner. Perampanel blocks glutamate AMPA receptors.

CHOICE OF DRUG ACCORDING TO SEIZURE TYPE AND EPILEPSY SYNDROME

Drug therapy should be based on the type of seizure and the epilepsy syndrome as well as on other individual factors. In general, the **drugs of first choice** for focal seizures and epilepsies are oxcarbazepine and carbamazepine; for absence seizures, ethosuximide; for juvenile myoclonic epilepsy, valproate and lamotrigine; for Lennox-Gastaut syndrome, clobazam, valproate, topiramate, lamotrigine, and, most recently, as add on, rufinamide; and for infantile spasms, adrenocorticotropic hormone (ACTH). There is significant controversy about these choices, and therapy should always be individualized (see Choice of Drug: Other Considerations below and Table 593-10).

West syndrome is best treated with ACTH. There are several protocols that range in dose from high to intermediate to low. The recommended regimen of ACTH (80 mg/mL) is a daily dose of 150 units/m^2 (divided into twice-daily intramuscular injections of 75 units/m^2, the lot number is recorded) administered over a 2-wk period with a subsequent gradual taper over a 2-wk period (30 units/m^2 in the morning

for 3 days; 15 units/m^2 in the morning for 3 days; 10 units/m^2 in the morning for 3 days; and 10 units/m^2 every other morning for 6 days, then stop). The increase in price of ACTH gel in the United States has led many physicians to use the lower-dose regimen because it may be just as effective (initial: 20 units/day for 2 wk, if patient responds, taper and discontinue over a 1-wk period; if patient does not respond, increase dose to 30 units/day for 4 wk then taper and discontinue over a 1-wk period). Response is usually observed within the 1st 7 days; however, if no response is observed within 2 wk, the lot is changed. During the tapering period of any regimen, and especially in symptomatic patients, relapse can occur. Remediation entails increasing the dose to the previously effective dose for 2 wk and then beginning the taper again. Synthetic ACTH has also been used: Synacthen Depot intramuscular 0.25 mg/mL or 1 mg/mL is used; 1 mg is considered to have the potency of 100 IU in stimulating the adrenal gland.

Awake and asleep EEGs are often done 1, 2, and 4 wk after the initiation of ACTH to monitor the patient's response, with the aim of clearing the EEG from hypsarrhythmia and of stopping the seizures. Side effects, more common with the higher doses, include hypertension, electrolyte imbalance, infections, hyperglycemia and/or glycosuria, and gastric ulcers. All should be carefully monitored for and prophylactic therapy for ulcers is desirable. ACTH is generally thought to offer an added advantage, particularly in cryptogenic cases, over vigabatrin and possibly over prednisone and other steroids.

Vigabatrin is considered by some as a drug of second choice for infantile spasms and by some even as an alternative to ACTH as a drug of first choice. Its principal side effect is retinal toxicity that is seen in approximately 30% of the patients, with resultant visual field defects that persist despite withdrawal of the drug. The level of evidence for its efficacy is weaker than that for ACTH but stronger than that of other alternative medications, including valproate, benzodiazepines like nitrazepam and clonazepam, topiramate, lamotrigine, zonisamide, pyridoxine, ketogenic diet, and intravenous gamma globulin (IVIG). None of these alternative drugs offers uniformly satisfactory results. However, they are useful for decreasing the frequency and severity of seizures in patients with symptomatic infantile spasms and as adjunctive therapy in patients with cryptogenic infantile spasms who do not respond completely to ACTH or vigabatrin.

Lennox-Gastaut syndrome is another difficult-to-treat epilepsy syndrome. Treatment of seizures in Lennox-Gastaut syndrome varies according to the preponderant seizure type. For drop attacks (tonic, atonic, or myoclonic astatic seizures), valproate, lamotrigine, topiramate, clobazam, felbamate, and rufinamide are considered to be effective. Felbamate is used as a last resort medication because of its potential toxicity. These drugs might control other types of seizures (partial, generalized tonic–clonic, atypical absence, other tonic, myoclonic) as well. For patients who have a preponderance of atypical absence seizures, lamotrigine or ethosuximide are often suitable drugs to try because they are relatively less toxic than many of the alternative drugs. Valproate is helpful against these seizures, too. Clonazepam is often helpful but produces significant sedation, hyperactivity, and drooling, and often tolerance to its antiepileptic effects develops in a few months. Consequently, clonazepam is often used as a rescue medication for clusters of seizures (disintegrating tablet preparation). In resistant cases of Lennox-Gastaut syndrome and related epilepsies, zonisamide, levetiracetam, acetazolamide, methsuximide, corticosteroids, ketogenic diet, or IVIG can be used.

Dravet syndrome is usually treated with valproate and benzodiazepines such as clobazam or clonazepam. The ketogenic diet can also be useful in patients with this syndrome, including cases with refractory status. Stiripentol, which is available in some countries, is useful, particularly if used in combination with valproate and clobazam, but doses need to be adjusted, since stirpentol can increase clobazam levels and valproate can increase stirpentol levels. Other medications include zonisamide and topiramate. Lamotrigine, carbamazepine, and phenytoin are reported to exacerbate seizures. Barbiturate use during status epilepticus in this syndrome is suspected to be associated with adverse outcomes; consequently, alternative acute therapies in such cases need to be considered.

Very rare cases of patients who have neonatal, infantile, or early childhood seizures who have **pyridoxine-dependent epilepsy** (demonstrated to be caused by antiquitin gene mutation) respond to pyridoxine 10-100 mg/day orally (up to 600 mg/day has been used) within 3-7 days of the initiation of oral therapy and almost immediately if given parenterally. Some patients have seizures that are intractable from onset, but others have seizures that show an initial but transient response to traditional AEDs. Some of these patients also require concurrent folinic acid (5-15 mg/day). Other patients require the active form of vitamin B_6, specifically, pyridoxal phosphate (50 mg/day initial dose that can be increased gradually up to 15 mg/kg every 6 hr) owing to their deficiency of **PNPO**. In both the PNPO-deficient/pyridoxal phosphate–dependent and the pyridoxine-dependent forms, hypotonia and hypopnea can occur after initiation of vitamin therapy. Pyridoxine has also been used by some, specifically in Japan, early in the treatment of West syndrome. Patients with **cerebral folate deficiency** can respond to folinic acid supplementation (usually at doses of 2-3 mg/kg/day). Traditionally these entities have been diagnosed by giving the vitamin B_6 or folinic acid in therapeutic trials, but currently laboratory testing is available to confirm the diagnosis (see Chapter 593.4).

Absence seizures are most often initially treated with ethosuximide, which is, as effective as, but less toxic than, valproate and more effective than lamotrigine. Alternative drugs of first choice are lamotrigine and valproate, especially if generalized tonic–clonic seizures coexist with absence seizures, as these 2 medications are effective against the latter seizures whereas ethosuximide is not. Patients resistant to ethosuximide might still respond to valproate or to lamotrigine. In absence seizures, the EEG is usually helpful in monitoring the response to therapy and is often more sensitive than the parents' observations in detecting these seizures. The EEG often normalizes when complete seizure control is achieved. This is usually not true for partial epilepsies. Other medications that could be used for absence seizures include acetazolamide, zonisamide, or clonazepam.

Benign myoclonic epilepsies are often best treated with valproate, particularly when patients have associated generalized tonic–clonic and absence seizures. Benzodiazepines, clonazepam, lamotrigine, and topiramate are alternatives for the treatment of benign myoclonic epilepsy. **Severe myoclonic epilepsies** are treated with medications effective for Lennox-Gastaut syndrome such topiramate, clobazam, and valproate, as well as zonisamide. Levetiracetam may also have efficacy in myoclonic epilepsies.

Partial and secondary generalized tonic and clonic seizures can be treated with oxcarbazepine, levetiracetam, carbamazepine, phenobarbital, topiramate, valproic acid, lamotrigine, clobazam, or clonazepam (see Table 593-8). Oxcarbazepine, levetiracetam, carbamazepine (United States), or valproate (Europe) are often being used first. One study favored lamotrigine as initial monotherapy for partial seizures and valproate for generalized seizures. Almost any of these medications has been used as first or second choice. depending on the individualization of the therapy.

CHOICE OF DRUG: OTHER CONSIDERATIONS

Because there are many options for each patient, the choice of which drug to use is always an individualized decision based on comparative effectiveness data from randomized controlled trials and on several other considerations delineated below.

Comparative effectiveness (Table 593-11) and **potential for paradoxical seizure aggravation** by some AEDs (e.g., precipitation of myoclonic seizures by lamotrigine in Dravet syndrome and exacerbation of absence seizures by carbamazepine and tiagabine) must be considered.

- **Comparative tolerability** (see Table 593-14): Adverse effects can vary according to the profile of the patient. The most prominent example is the increased risk of liver toxicity for valproate therapy in children who are younger than 2 yr of age, on polytherapy, and/or have metabolic disorders. Thus, if metabolic disorders are suspected, other drugs should be considered first and valproate should not be started until the metabolic disorders are ruled out by normal amino acids, organic acids, acylcarnitine profile, lactate,

Table 593-11 Comparison of Recommendations for the Treatment of Pediatric Epilepsy

SEIZURE TYPE OR EPILEPSY SYNDROME	FDA APPROVED	SIGN (2005)	NICE (2012)	AAN (2004)	ILAE (2013)*	PEDIATRIC EXPERT CONSENSUS SURVEY (NORTH AMERICA–2005)	PEDIATRIC EXPERT CONSENSUS SURVEY (EUROPE–2007)
Partial-onset	CBZ, ezogabine, lacosamide, LEV, LTG, OXC, PB, perampanel, PHT, TPM, VGB	CBZ, CLB, LTG, OXC, PHT, TPM, VGB, VPA	CBZ, LEV, LTG, OXC, VPA	CBZ, GBP, LTG, OXC, PB, PHT, TPM	A: OXC B: None C: CBZ, PB, PHT, TPM, VGB, VPA D: CLB, CZP, LTG, ZNS	CBZ, OXC	CBZ, OXC
BCECT	None	Not specifically mentioned	CBZ, LEV, LTG, OXC, VPA	Not surveyed	A, B: None C: CBZ, VPA D: GBP, LEV, OXC, STM	CBZ, OXC	VPA
Childhood absence epilepsy	ESM, VPA	ESM, LTG, VPA	ESM, LTG, VPA	LTG	A: ESM, VPA B: None C: LTG D: None	ESM	VPA
Juvenile myoclonic epilepsy	LEV, LTG, TPM	VPA	LEV, LTG, TPM, VPA	Not surveyed	A, B, C: None D: TPM, VPA	LTG, VPA	VPA
Lennox-Gastaut syndrome	CLB, FLB, LTG, rufinamide (atonic), TPM	CLB, LTG, VPA	VPA	Not surveyed	Not reviewed	LTG, VPA	VPA
Infantile spasms	VGB	Nitrazepam, TPM, VGB, VPA	Corticosteroids, VGB	ACTH, VGB (updated IS guidelines 2012)	Not reviewed	ACTH, VGB	VGB
Primary generalized tonic-clonic seizures	LEV, LTG, TPM	TPM, VPA	LTG, TPM, VPA	No evidence given	A: None B: None C: CBZ, PB, PHT, TPM, VPA D: OXC		

*ILAE recommendations are listed according to levels of evidence supporting the efficacy of the options. Level A: ≥1 class I randomized controlled trial (RCT) or ≥2 class II RCTs; Level B: 1 class II RCT or ≥2 class III RCTs; Level C: ≥2 class III RCTs; Level D: 1 class III double-blind or open-label study *or* 1 class IV clinical study *or* data from expert committee reports, opinions from experienced clinicians.

AAN, American Academy of Neurology; ACTH, adrenocorticotropic hormone; BCECT, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; FDA, Food and Drug Administration; FLB, felbamate; GBP, gabapentin; ILAE, International League against Epilepsy; LEV, levetiracetam; LTG, lamotrigine; NICE, National Institute for Clinical Excellence; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; SIGN, Scottish Intercollegiate Guidelines Network; STM, sulthiame; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

Modified and updated from Wheless JW, Clarke DF, Arzimanoglou A, et al: Treatment of pediatric epilepsy: European expert opinion, Epileptic Disord *9:353–412, 2007; and Perucca E, Tomson T; ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes.* Epilepsia *54(3):551–563, 2013.*

pyruvate, liver function tests, and perhaps other tests. The choice of an AED can also be influenced by the likelihood of occurrence of nuisance side effects such as weight gain (valproate, carbamazepine), gingival hyperplasia (phenytoin), alopecia (valproate), hyperactivity (benzodiazepines, barbiturates, levetiracetam, valproate, gabapentin). Children with behavior problems and/or with attention-deficit disorder can become particularly hyperactive with GABAergic drugs mentioned above. This often affects the choice of medications.

- **Cost and availability:** The cost of the newer AEDs often precludes their use, particularly in developing countries where cost is a major issue. Also, many drugs are not available in many countries either because they are too expensive, because, paradoxically, they are too inexpensive (lower profit margin), or because of regulatory restrictions. AEDs have a narrow therapeutic range and thus switching from brand name to generic formulations, or from one generic to another, can result in changes in levels that could result in breakthrough seizures or side effects. Thus, generic substitution is generally best avoided, particularly in fragile patients, if a brand name drug has already proved efficacious.
- **Ease of initiation** of the AED: Medications that are started very gradually such as lamotrigine and topiramate should not be chosen in situations when there is a need to achieve a therapeutic level quickly. In such situations, medications that have intravenous preparations or that can be started and titrated more quickly, such as valproate, phenytoin, or levetiracetam, should be considered instead.
- **Drug interactions** and presence of background medications: An example is the potential interference of enzyme-inducing drugs with many chemotherapeutic agents. In those cases, medications like gabapentin or levetiracetam are used. Also, valproate inhibits the metabolism and increases the levels of lamotrigine, phenobarbital, and felbamate. It also displaces protein-bound phenytoin from protein-binding sites, increasing the free fraction, and, thus, the free and not the total level needs to be checked when both medications are being used together. Enzyme inducers like phenobarbital, carbamazepine, phenytoin, and primidone reduce levels of lamotrigine, valproate, and, to a lesser extent, topiramate and zonisamide. Medications exclusively excreted by the kidney like levetiracetam and gabapentin are not subject to such interactions.

Table 593-12 Teratogenesis and Perinatal Outcomes of Antiepileptic Drugs

FINDING	RECOMMENDATION	LEVEL OF RECOMMENDATION
VPA as part of polytherapy and possibly monotherapy probably contributes to the development of major congenital malformations and adverse cognitive outcome	If possible, avoidance of valproate polytherapy during the 1st trimester of pregnancy should be considered so as to decrease the risk of major congenital malformations and adverse cognitive outcome	B
AED polytherapy, as compared to monotherapy, regimens probably contribute to the development of major congenital malformations and to adverse cognitive outcomes	If possible, avoidance of AED polytherapy during the 1st trimester of pregnancy should be considered to decrease the risk of major congenital malformations and adverse cognitive outcome	B
Monotherapy exposure to phenytoin or phenobarbital possibly increases the likelihood of adverse cognitive outcomes	If possible, avoidance of phenytoin and phenobarbital during pregnancy may be considered to prevent adverse cognitive outcomes	C
Neonates of women with epilepsy taking AEDs probably have an increased risk of being small for gestational age and possibly have an increased risk of a 1 min Apgar score of <7	Pregnancy risk stratification should reflect that the offspring of women with epilepsy taking AEDs are probably at increased risk for being small for gestational age (level B) and possibly at increased risk of 1 min Apgar scores of <7	C

Levels of recommendation: A: strongest recommendation; based on class 1 evidence; B and C: lower levels of recommendations.

Types of malformations: Prior studies had reported the occurrence of spina bifida with valproate and carbamazepine therapy, and of cardiac malformation and cleft palate after carbamazepine, phenytoin, and phenobarbital exposure. There is variability from study to study. However, in general the relative incidence of major malformations of approximately 10% for valproate monotherapy, higher with valproate polytherapy, and in the range of 5% for monotherapy with the other above 3 AEDs and higher with polytherapy.

FDA categories: Valproate, phenobarbital, carbamazepine, and phenytoin are classified by the FDA as category D. Ethosuximide, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide are category C. Category C: Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women. Category D: Studies, adequate, well-controlled, or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy might outweigh the potential risk.

AED, antiepileptic drug; VPA, valproate.

Data from Harden CI, Meador KJ, Pennell PB, et al: Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and American Epilepsy Society, Neurology *73(2):133–141, 2009.*

- **The presence of comorbid conditions:** For example, the presence of migraine in a patient with epilepsy can lead to the choice of a medication that is effective against both conditions such as valproate or topiramate. In an obese patient, a medication such as valproate might be avoided, and a medication that decreases appetite such as topiramate might be used instead. In adolescent girls of child-bearing potential, enzyme-inducing AEDs are often avoided because they can interfere with birth control pills; other AEDs, particularly valproate, can increase risks for fetal malformations (Table 593-12). Valproic acid may unmask or exacerbate certain underlying metabolic disorders; these include nonketotic hyperglycinemia, DNA polymerase γ mutations *(POLG)* with mitochondrial DNA depletion (also known as Alpers-Huttenlocher syndrome), other mitochondrial disorders (Leigh syndrome; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]; myoclonic epilepsy with ragged red fibers; myoclonic epilepsy-myopathy-sensory ataxia syndrome), and hyperammonemic encephalopathies. Manifestations may include hepatotoxicity or encephalopathy.
- **Coexisting seizures:** In a patient with both absence and generalized tonic–clonic seizures, a drug that has a broad spectrum of antiseizure effects such as lamotrigine or valproate could be used rather than medications that have a narrow spectrum of efficacy, such as phenytoin and ethosuximide.
- **History of prior response** to specific AEDs: For example, if a patient or a family member with the same problem had previously responded to carbamazepine, carbamazepine could be a desirable choice.
- **Mechanism of drug actions:** At present, the current understanding of the pathophysiology of epilepsy does not allow specific choice of AEDs based on the assumed pathophysiology of the epilepsy. However, in general, it is believed that it is better to avoid combining medications that have similar mechanisms of action, such as phenytoin and carbamazepine (both work on sodium channels). A number of medications, such as lamotrigine and valproate or topiramate and lamotrigine, are reported to have synergistic effects, possibly because they have different mechanisms of action.
- **Ease of use:** Medications that are given once or twice a day are easier to use than medications that are given 3 or 4 times a day. Availability of a pediatric liquid preparation, particularly if palatable, also plays a role.
- **Ability to monitor the medication** and adjust the dose: Some medications are difficult to adjust and to follow, requiring frequent blood levels. The prototype of such medications is phenytoin, but many of the older medications also require blood level monitoring for optimal titration. However, monitoring in itself can represent a practical or patient satisfaction disadvantage for the older drugs as compared to the newer AEDs, which generally do not require blood-level monitoring except to check for compliance.
- **Patient's and family's preferences:** All things being equal, the choice between 2 or more acceptable alternative AEDs might also depend on the patient's or family's preferences. For example, some patients might want to avoid gingival hyperplasia and hirsutism as side effects but might tolerate weight loss, or vice versa.
- **Genetics** and genetic testing: A genetic predisposition to developing AED-induced side effects is another factor that may be a consideration. For example, there is a strong association between the human leukocyte antigen HLA-B*1502 allele and severe cutaneous reactions induced by carbamazepine, phenytoin, or lamotrigine in Chinese Han patients and, to a lesser extent, South East Asian populations; hence these AEDs should be avoided in genetically susceptible persons after testing for the allele. The testing for other alleles that predispose to such allergies in other populations is not yet clinically useful. Mutations of the *SCN1A* sodium channel gene indicating Dravet syndrome could also lead to avoiding lamotrigine, carbamazepine, and phenytoin, and to the use of the more appropriate valproate, clobazam, or stiripentol.

- **Teratogenic profiles:** Some AEDs, including valproate and to a lesser extent carbamazepine, phenobarbital, and phenytoin, are associated with teratogenic effects (see Table 593-12).

Some of these considerations can be addressed by resorting to expert opinion surveys (see Table 593-11) or to guidelines developed by concerned societies such as the ILAE, National Institute for Clinical Excellence (NICE) in England, Scottish Intercollegiate Guidelines Network (SIGN), or the American Academy of Neurology (AAN). Some guidelines are totally evidence based (AAN, ILAE), and others (NICE, SIGN) incorporate other considerations as well. However, no guideline is able to incorporate all the considerations relevant to each patient.

INITIATING AND MONITORING THERAPY

In nonemergency situations, or when loading is not necessary, the **maintenance dose** of the chosen AED is started (Table 593-13). With some medications (e.g., carbamazepine and topiramate), even smaller doses are initially started then **gradually increased** up to the maintenance dose to build tolerance to adverse effects such as sedation. For example, the starting dose of carbamazepine is usually 5-10 mg/kg/day. Increments of 5 mg/kg/day can be added every 3 days until a therapeutic level is achieved and a therapeutic response is established or until unacceptable adverse effects occur. With other medications such as zonisamide, phenobarbital, phenytoin, or valproate, starting at the maintenance dose is usually tolerated. With some, such as levetiracetam and gabapentin, either approach can be used. Patients should be counseled about potential adverse effects, and these should be monitored during follow-up visits (Table 593-14).

Titration

Levels of many AEDs should usually be determined after initiation to ensure compliance and therapeutic concentrations. Monitoring is most helpful for the older AEDs such as phenytoin, carbamazepine, valproate, phenobarbital, and ethosuximide. After starting the maintenance dosage or after any change in the dosage, a steady state is not reached until 5 half-lives have elapsed, which, for most AEDs, is 2-7 days (half-life: 6-24 hr). For phenobarbital, it is 2-4 wk (mean half-life: 69 hr). For zonisamide it is 14 days during monotherapy and less than that during polytherapy with enzyme inducers (half-life: 63 hr in monotherapy and 27-38 hr during combination therapy with enzyme inducers). If a therapeutic level has to be achieved faster, a **loading dose** may be used for some drugs, usually with a single dose that is twice the average maintenance dose per half-life. For valproate it is 25 mg/kg, for phenytoin it is 20 mg/kg, and for phenobarbital it is 10-20 mg/kg. A lower loading dosage of phenobarbital is sometimes given in older children (5 mg/kg, which may be repeated once or more in 24 hr), to avoid excessive sedation.

Only 1 drug should be used initially and the dose increased until complete control is achieved or until side effects prohibit further increases. Then, and only then, may another drug be added and the initial drug subsequently tapered. Control with 1 drug (**monotherapy**) should be the goal, although some patients eventually need to take

Table 593-13 Dosages of Selected Antiepileptic Drugs

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATIONS
Acetazolamide	Absence seizures (adults)	1-12 mo; 10 <1 yr: 20-30	bid or tid	10-15 mg/L	125, 250, 500 mg tabs
Bromide		50-100	bid or qd	10-15 mEq/L	Supplied as triple bromide soln (240 mg/mL of bromide salt)
Carbamazepine*	Partial and GTC (all ages)	10-20	tid or qid SR usually bid	3-12 mg/L	150, 300 mg ER caps 100, 200, 400 mg ER tabs 100 mg chewable tabs 200 mg tabs 100 mg/5 mL susp
Clobazam[†]	LGS (all ages above 2 yr)	10-20 mg/day	bid or tid	60-200 µg/L	5 mg, 10 mg, 20 mg tabs 2.5 mg/mL soln
Clonazepam[†]	Absence sz, LGS, myoclonic sz (all ages)	0.05-0.2	bid or tid	25-85 µg/L	0.5, 1, 2 mg tabs 0.125, 0.25, 0.5 mg orally disintegrating tabs
Diazepam	Partial sz (all ages >6 mo)	0.25-1.5 0.01-0.25 IV 0.2-0.5 mg/kg rectal (according to age; see Table 593-15)	bid or tid	100-700 µg/L	2, 5, 10 mg tabs 5 mg/mL, 5 mg/5 mL soln Rectal gel that can be dialed to dispense 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 mg
Ethosuximide	Absence sz (>3 yr)	20-30	bid or tid	40-100 mg/L	250 mg caps 250 mg/5 mL syrup, soln
Ezogabine	Partial sz (adults)	No pediatric dose approved	tid	—	50, 200, 300, 400 mg tabs
Felbamate	LGS (>2 yr) Partial sz (>14 yr)	15-45	bid or tid	50-110 mg/L	400, 600 mg tabs 600 mg/5 mL susp
Gabapentin[‡]	Partial sz (>3 yr)	30-60	tid	2-20 mg/L	100, 300, 400 mg caps, 600, 800 mg tabs
Lacosamide	Partial sz (>17 yr)	No FDA approved dose. 4-12	bid	<= 15 µg/L	50, 100, 150, 200 mg tabs 10 mg/mL oral soln

Table 593-13 Dosages of Selected Antiepileptic Drugs—cont'd

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATIONS
Lamotrigine	LGS, partial and tonic–clonic sz (age >2 yr)	5-15[§] 1-5[¶]	tid bid	1-15 mg/L	25, 100, 150, 200 mg tabs 5, 25 mg chewable dispersible tabs 25, 50, 100, 200 mg ODTs 25, 50, 100, 200, 250, 300 mg ER tabs
Levetiracetam[†]	Myoclonic, partial and tonic–clonic sz (age >4-6 yr)	20-40	bid or tid	6-20 mg/L	250, 500, 750 mg tabs 100 mg/mL soln 500, 750 mg SR (ER) tabs
Lorazepam	Status epilepticus (all ages)	0.05-0.1	bid or tid	20-30 μg/L	0.5, 1, 2 mg tabs 2 mg/mL soln
Methsuximide (or methsuximide)	Absence sz (children and older)	10-30	bid or tid	10-50 mg/L	150, 300 mg caps
Nitrazepam	–	0.25-1	bid or tid	<200 μg/L	5 mg tabs
Oxcarbazepine*	Partial sz (>2 yr)	20-40	bid	13-28 mg/L	150, 300, 600 mg tabs 300 mg/5 mL susp
Perampanel	Partial sz (>12 yr)	2-12 mg per day (older than 12 yr)	qhs	-	2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg tabs
Phenobarbital	Myoclonic, partial, and tonic–clonic sz and status (all ages)	<5 yr, 3-5 >5 yr, 2-3	bid or qd	10-40 mg/L	15, 30, 60, 90, 100 mg tabs 4 mg/mL soln
Phenytoin	Partial, tonic–clonic sz and status (all ages)	<3 yr, 8-10 >3 yr, 4-7	tabs, susp: tid caps: qd	5-20 mg/L	50 mg tabs 30,100 mg caps 125 mg/5 mL susp
Pregabalin	Partial sz (adults)	2-14	bid	Up to 10 μg/mL	25, 50, 75, 100, 150, 200, 225, 300 mg caps 20 mg/mL soln
Primidone	Partial and tonic–clonic sz (all ages)	10-20	bid or tid	4-13 mg/L	50, 250 mg tabs, susp
Rufinamide[†]	LGS (age >4 yr)	30-45	bid	<60 μg/mL	200, 400 mg tabs
Sulthiame[‖]		5-15	bid or tid	1.5-20 μg/mL	50, 200 mg caps Not available in all countries
Tiagabine	Partial sz (age >2 yr)	0.5-2	bid, tid, qid	80-450 μg/L	2, 4, 12, 16 mg tabs
Topiramate[†]	LGS, partial and tonic–clonic sz (all ages)	3-9, slow titration	bid or tid	2-25 mg/L	25, 100, 200 mg tabs 15, 25 mg sprinkle caps
Valproate	Absence, myoclonic, partial and tonic–clonic sz (age >2 yr)	15-40. Higher doses are used if the patient is on enzyme inducers (up to 60 kg/day)	Sprinkle caps: bid Soln: tid	50-100 mg/L	250 mg caps 125 mg sprinkle caps 125, 250, 500 mg tabs 250 mg/5 mL soln
Vigabatrin	Infantile spasms and partial sz (age >1 mo)	50-150	bid	20-160 μg/mL	500 mg tabs 500 mg powder for soln
Zonisamide	Partial sz (age >16 yr)	4-8	bid or qd	10-40 mg/L	100 mg caps

Unless specified otherwise, as above, one would usually target the lower range of therapeutic dose then adjust as needed depending on response and/or levels. Dosing schedule (e.g., bid or tid) can depend on if a sustained release preparation is available and if the patient is on enzyme inducers (e.g., carbamazepine) or inhibitors (e.g., valproic acid) that could affect that drug (as indicated in the dosing in the table and in the text).

*Usually start by one-fourth maintenance dose and increase by one-fourth every 2-3 days to full dose.

[†]Usually start with one-fourth maintenance dose and increase by one-fourth every 7 days to full dose.

[‡]Usually start with one-fourth maintenance dose and increase by one-fourth every day to full dose.

[§]Child on enzyme inducers.

[‖]Available in some European countries.

[¶]Child on valproate.

cap, capsule; ER, extended release; GTC, generalized tonic–clonic; LGS, Lennox-Gastaut syndrome; ODT, orally disintegrating tablet; soln, solution; SR, sustained release; susp, suspension; sz, seizure(s); tab, tablet.

Table 593-14 Some Common Adverse Effects of Antiepileptic Drugs*

ANTIEPILEPTIC DRUG	SIDE EFFECT(S)
Acetazolamide	Nuisance: dizziness, polyuria, electrolyte imbalance Serious: Stevens-Johnson syndrome
Benzodiazepines	Nuisance: dose-related neurotoxicity (drowsiness, sedation, ataxia), hyperactivity, drooling, increased secretions Serious: apnea
Bromide	Nuisance: irritability, spurious hyperchloremia (falsely high chloride owing to bromide) Serious: psychosis, rash, toxicity developing slowly owing to the very long half-life
Carbamazepine	Nuisance: tics, transient leukopenia; hyponatremia, weight gain, nausea; dizziness Serious: Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, liver toxicity
Ezogabine	Nuisance: dizziness, somnolence tremor, abnormal coordination, disturbance in attention, memory impairment, blurred vision, gait disturbance, and dysarthria Serious: blue discoloration of the skin and retinal pigmentation that requires close ophthalmologic monitoring in follow up, urinary retention
Felbamate	Nuisance: anorexia, vomiting, insomnia, hyperactivity, dizziness Serious: major risks for liver and hematologic toxicity requiring close monitoring (1 in 500 in children >2 yr with complex neurological disorders)
Gabapentin	In children: acute onset of aggression, hyperactivity In adults: euphoria and behavioral disinhibition, weight gain
Lacosamide	Nuisance: diplopia, headache, dizziness, nausea Serious: possibly cardiac arrhythmias (if predisposed)
Lamotrigine	Nuisance: CNS side effects: headache, ataxia, dizziness, tremor, but usually less than other AEDs Serious: Stevens-Johnson syndrome, rarely liver toxicity
Levetiracetam	CNS adverse events: somnolence, asthenia, dizziness, but usually less than other AEDs In children: behavioral symptoms are common In adults: depressive mood
Oxcarbazepine	Somnolence, headache, dizziness, nausea, apathy, rash, hypertrichosis, gingival hypertrophy, hyponatremia
Perampanel	Dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder
Phenobarbital and other barbiturates	Nuisance: neurotoxicity, insomnia, hyperactivity, signs of distractibility, fluctuation of mood, aggressive outbursts Serious: liver toxicity, Stevens-Johnson syndrome
Phenytoin and other hydantoins	Nuisance: gingival hyperplasia, coarsening of the facies, hirsutism, cerebellovestibular symptoms (nystagmus and ataxia) Serious: Stevens-Johnson syndrome, liver toxicity
Pregabalin	Nuisance: dizziness, peripheral edema, blurred vision, weight gain, thrombocytopenia Serious: hypersensitivity reactions, rhabdomyolysis
Primidone	Nuisance: CNS toxicity (dizziness, slurred speech, giddiness, drowsiness, depression) Serious: liver toxicity, Stevens-Johnson syndrome
Rufinamide	Nuisance: somnolence, vomiting Serious: contraindicated in familial short QT interval
Succinimides	Nuisance: nausea, abdominal discomfort, anorexia, hiccups Serious: Stevens-Johnson syndrome, drug-induced lupus
Tiagabine	Nuisance: dizziness, somnolence, asthenia, headache and tremor, precipitation of absence or myoclonic seizures Serious: precipitation of nonconvulsive status epilepticus
Topiramate	Nuisance: cognitive dysfunction, weight loss, renal calculi, hypohidrosis, fever Serious: precipitation of glaucoma
Valproic acid	Nuisance: weight gain; hyperammonemia tremor, alopecia, menstrual irregularities Serious: hepatic and pancreatic toxicity
Vigabatrin	Nuisance: hyperactivity Serious: irreversible visual field deficits, retinopathy that requires frequent ophthalmologic evaluations and follow up
Zonisamide	Fatigue, dizziness, anorexia, psychomotor slowing, ataxia, rarely hallucinations, hypohidrosis and fever

*Essentially all AEDs can cause CNS toxicity and potentially rashes and serious allergic reactions.
AED, antiepileptic drug; CNS, central nervous system.

multiple drugs. When appropriate, levels should also be checked upon addition (or discontinuation) of a second drug because of potential drug interactions. During follow-up, repeating the EEG every few months may be helpful to evaluate changes in the predisposition to seizures. This is especially true in situations where tapering off of medication is contemplated in any seizure type and during follow-up to assess response for absence seizures, as the EEG mirrors response in such patients.

Monitoring

For the older AEDs, before starting treatment, **baseline laboratory studies,** including complete blood count, platelets, liver enzymes, and possibly kidney function tests and urinalysis, are often obtained and repeated periodically. Laboratory monitoring is more relevant early on, because idiosyncratic adverse effects such as allergic hepatitis and agranulocytosis are more likely to occur in the 1st 3-6 mo of therapy. These laboratory studies are usually initially checked once or twice during the 1st mo, then every 3-4 mo thereafter. Serious concerns have been raised about the real usefulness of routine monitoring (in the absence of clinical signs) because the yield of significant adverse effects is low and the costs may be high. There are currently many advocates of less-frequent routine monitoring.

In approximately 10% of patients, a reversible dose-related leukopenia may occur in patients on carbamazepine or on phenytoin. This adverse effect responds to decreasing the dose or to stopping the medication and should be distinguished from the much-less-common idiosyncratic aplastic anemia or agranulocytosis. One exception requiring frequent (even weekly) monitoring of liver function and of blood counts throughout the therapy is felbamate, owing to the high incidence of liver and hematologic toxicity (1 in 500 children under 2 yr of age with complex neurological disorders who are on the drug). The gum hyperplasia that is seen with phenytoin necessitates good oral hygiene (brushing teeth at least twice per day and rinsing the mouth after taking the phenytoin); in a few cases, it may be severe enough to warrant surgical reduction and/or change of medication. Allergic rash can occur with any medication, but is probably most common with lamotrigine, carbamazepine, and phenytoin.

SIDE EFFECTS

During follow-up the patient should be monitored for **side effects**. Occasionally, a Stevens-Johnson–like syndrome develops, probably most commonly with lamotrigine; it also has been found to be particularly common in Chinese patients who have the allele HLA-B*1502 and are taking carbamazepine and lamotrigine.

Other potential side effects are rickets from phenytoin, phenobarbital, primidone, and carbamazepine (enzyme inducers that reduce 25-hyrdroxy-vitamin D level by inducing its metabolism) and hyperammonemia from valproate. Skeletal monitoring is warranted in patients on chronic AED therapy because it is often associated with vitamin D abnormalities (low bone density, rickets, and hypocalcemia) in children and adults, particularly those on enzyme-inducing medications. Thus, counseling the patient about sun exposure and vitamin D intake, monitoring its levels, and, in most cases, vitamin D supplementation are recommended. There is currently no consensus on the dose to be used for supplementation or prophylaxis, but starting doses of 400-2,000 IU/day with follow-up of the levels are reasonable.

Irreversible hepatic injury and death are particularly feared in young children (<2 yr old) who are on valproate in combination with other AEDs, particularly those who might have inborn errors of metabolism such as acidopathies and mitochondrial disease. Virtually all AEDs can produce sleepiness, ataxia, nystagmus, and slurred speech with toxic levels.

The FDA has determined that the use of AEDs may be associated with an increased risk of suicidal ideation and action and has recommended counseling about this side effect before starting these medications. This is obviously more applicable to adolescents and adults.

When adding a new AED, the doses used are often affected by the background medications. For example, if the patient is on enzyme inducers, the doses needed of valproate and lamotrigine are often double the usual maintenance doses. On the other hand, if the patient is on valproate, the doses of phenobarbital or lamotrigine are approximately half of what is usually needed. Thus, changes in the dosing of the background medication are often done as the interacting medication is being started. Genetic variability in enzymes that metabolize AEDs, and in the presence of inducible multidrug resistance genes, **pharmacogenomics**, might account for some of the variation among individuals in responding to certain AEDs. Although numerous variants of the cytochrome P450 enzymes have been characterized and although several multidrug resistance genes have been identified, the use of this new knowledge is currently largely restricted to research investigations, and it has yet to be applied in routine clinical practice.

Additional Treatments

The principles of monotherapy indicate that a second medication needs to be considered after the first either is pushed as high as tolerated and still does not control the seizures or results in intolerable adverse effects. In those cases, a second drug is started and the first is tapered and then discontinued. The second drug is then again pushed to the dose that controls the seizure or that results in intolerable side effects. If the second drug fails, monotherapy with a third drug or **dual (combination) therapy** is considered.

Patients with **drug-resistant** (previously referred to as intractable or refractory) **epilepsy** (those who have failed at least 2 fair trials of appropriate medications) warrant a careful diagnostic reevaluation to look for degenerative, metabolic, or inflammatory underlying disorders (e.g., mitochondrial disease, Rasmussen encephalitis; see Chapter 593.2) and to investigate them for candidacy for epilepsy surgery. Treatable metabolic disorders that can manifest as intractable epilepsy include pyridoxine-dependent and pyridoxal-responsive epilepsy; folinic acid–responsive seizures (demonstrated to be the same disorder as pyridoxine-dependent epilepsy); cerebral folate deficiency; neurotransmitter disorders; biotinidase deficiency; glucose transporter 1 deficiency (responds to the ketogenic diet); serine synthesis defects; creatine deficiency syndromes; untreated phenylketonuria; developmental delay, epilepsy and neonatal diabetes; and hyperinsulinemia–hyperammonia. Often patients who do not respond to AEDs are candidates for steroids, IVIG, or the ketogenic diet.

Steroids, usually given as ACTH (see the discussion of West syndrome in "Severe Generalized Epilepsies" in Chapter 593.4) or as prednisone 2 mg/kg/day (or equivalent), are often used in epileptic encephalopathies such as West, Lennox-Gastaut, myoclonic astatic, continuous spike-waves in slow-wave sleep, and Landau-Kleffner syndromes. The course usually is for 2-3 mo with a taper over a similar period. Because relapses occur commonly during tapering, and in such syndromes as Landau-Kleffner and continuous spike-waves in slow-wave sleep, therapy for longer than 1 yr is often needed.

IVIG has also been reported to be similarly effective in non–immunodeficient patients with West, Lennox-Gastaut, Landau-Kleffner, and continuous spike-waves in slow-wave sleep syndromes and may also have efficacy in partial seizures. One should check the IgA levels before starting the infusions (to assess the risk for allergic reactions, because these are increased in patients with complete IgA deficiency) and guard against allergic reactions during the infusion. Low IgA, low IgG_2, and male sex are reported to possibly predict favorable response. The usual regimen is 2 g/kg divided over 4 consecutive days followed by 1 g/kg once a month for 6 mo. The mechanism of action of steroids and of IVIG are not known but is presumed to be antiinflammatory, because it has been demonstrated that seizures increase cytokines and that these, in turn, increase neuronal excitability by several mechanisms, including activation of glutamate receptors. Steroids and ACTH might also stimulate brain neurosteroid receptors that enhance GABA activity and might reduce corticotrophin-releasing hormone, which is known to be epileptogenic.

The **ketogenic diet** is believed to be effective in glucose transporter protein 1 deficiency, pyruvate dehydrogenase deficiency, myoclonic–astatic epilepsy, tuberous sclerosis complex, Rett syndrome, severe myoclonic epilepsy of infancy (Dravet syndrome), and infantile spasms. There is also suggestion of possible efficacy in selected

mitochondrial disorders—glycogenosis type V, Landau-Kleffner syndrome, Lafora body disease, and subacute sclerosing panencephalitis. The diet is absolutely contraindicated in carnitine deficiency (primary); carnitine palmitoyltransferase I or II deficiency; carnitine translocase deficiency; β-oxidation defects; medium-chain acyl dehydrogenase deficiency; long-chain acyl dehydrogenase deficiency; short-chain acyl dehydrogenase deficiency; long-chain 3-hydroxyacyl-coenzyme A deficiency; medium-chain 3-hydroxyacyl-coenzyme A deficiency; pyruvate carboxylase deficiency; and porphyrias. Thus, an appropriate metabolic work-up, depending on the clinical picture, usually needs to be performed before starting the diet (e.g., acyl carnitine profile, total and free carnitine levels). The diet has been used for refractory seizures of various types (partial or generalized) and consists of an initial period of fasting followed by a diet with a 3 : 1 or 4 : 1 fat : nonfat ratio, with fats consisting of animal fat, vegetable oils, or medium-chain triglycerides. Many patients do not tolerate it owing to diarrhea, vomiting, hypoglycemia, dehydration, or lack of palatability. Diets such as the low-glycemic-index diet and the Atkins diet are easier to institute, do not require hospitalization, and are also useful, but it is not known yet if they are as effective as the classic diet.

APPROACH TO EPILEPSY SURGERY

If a patient has failed 3 drugs, the chance of achieving seizure freedom using AEDs is generally <10%. Therefore, proper evaluation for surgery is necessary as soon as patients fail 2 or 3 AEDs, usually within 2 yr of the onset of epilepsy and often sooner than 2 yr. Performing epilepsy surgery in children at an earlier stage (e.g., <5 yr of age) allows transfer of function in the developing brain. Candidacy for epilepsy surgery requires proof of resistance to AEDs used at maximum, tolerably nontoxic doses; absence of expected unacceptable adverse consequences of surgery, and a properly defined **epileptogenic zone** (area that needs to be resected to achieve seizure freedom). The epileptogenic zone is identified by careful analysis, by an expert team of epilepsy specialists in an epilepsy center, of the following parameters: seizure semiology, interictal EEG, video-EEG long-term monitoring, neuropsychologic profile, and MRI. Other techniques, such as invasive EEG (depth electrodes, subdurals), single-photon emission CT, magnetoencephalography, and positron emission tomography are also often needed when the epileptogenic zone is difficult to localize or when it is close to eloquent cortex. To avoid resection of eloquent cortex, several techniques can be used, including the **Wada test**. In this test, intracarotid infusion of amobarbital is used to anesthetize 1 hemisphere to lateralize memory and speech by testing them during that unilateral anesthesia. Other tests to localize function include functional MRI, magnetoencephalography, and subdural electrodes with cortical stimulation. Developmental delay or psychiatric diseases must be considered in assessing the potential impact of surgery on the patient. The usual minimal presurgical evaluation includes EEG monitoring, imaging, and age-specific neuropsychologic assessment.

Epilepsy surgery is often used to treat refractory epilepsy of a number of etiologies, including cortical dysplasia, tuberous sclerosis, polymicrogyria, hypothalamic hamartoma, Landau-Kleffner syndrome, and hemispheric syndromes, such as Sturge-Weber syndrome, hemimegalencephaly, and Rasmussen encephalitis. Patients with intractable epilepsy resulting from metabolic or degenerative problems are not candidates for resective epilepsy surgery. **Focal resection** of the epileptogenic zone is the most common procedure. **Hemispherectomy** is used for diffuse hemispheric lesions; **multiple subpial transection**, a surgical technique in which the horizontal connections of the epileptic focus are partially cut without resecting it, is sometimes used for unresectable foci located in eloquent cortex such as in Landau-Kleffner syndrome. In Lennox-Gastaut syndrome, **corpus callosotomy** is used for drop attacks. **Vagal nerve stimulation** is often used for intractable epilepsies of various types and for seizures of diffuse focal or multifocal anatomic origin that do not yield themselves to resective surgery. Focal resection and hemispherectomy result in a high rate (50-80%) of seizure freedom. Corpus callosotomy and vagal nerve stimulation result in lower rates (5-10%) of seizure freedom; however, these procedures do result in significant reductions in the frequency and severity of seizures, decrease in medication requirements, and meaningful improvements in the patient's quality of life in approximately half or more of eligible patients.

DISCONTINUATION OF THERAPY

Discontinuation of AEDs is usually indicated when children are free of seizures for at least 2 yr. In more-severe syndromes, such as temporal lobe epilepsy secondary to mesial temporal sclerosis, Lennox-Gastaut syndrome, or severe myoclonic epilepsy, a prolonged period of seizure freedom on treatment is often warranted before AEDs are withdrawn, if withdrawal is attempted at all. In self-limited (benign) epilepsy syndromes, the duration of therapy can often be as short as 6 mo.

Many factors should be considered before discontinuing medications, including the likelihood of remaining seizure-free after drug withdrawal based on the type of epilepsy syndrome and etiology; the risk of injury in case of seizure recurrence (e.g., if the patient drives); and the adverse effects of AED therapy. Most children who have not had a seizure for 2 yr or longer and who have a normal EEG when AED withdrawal is initiated, remain free of seizures after discontinuing medication, and most relapses occur within the 1st 6 mo.

Certain risk factors can help the clinician predict the prognosis after AED withdrawal. The most important risk factor for seizure relapse is an abnormal EEG before medication is discontinued. Children who have remote structural (symptomatic) epilepsy are less likely to be able to stop AEDs than are children who have a benign genetic (idiopathic) epilepsy. In patients with absences or in patients treated with valproate for primary generalized epilepsy, the risk of relapse might still be high despite a normal EEG because valproate can normalize EEGs with generalized spike-wave abnormalities. Thus, in these patients, repeating the EEG during drug taper can help identify recurrence of the EEG abnormality and associated seizure risk before clinical seizures recur. Older age of epilepsy onset, longer duration of epilepsy, presence of multiple seizure types, and need to use more than 1 AED are all factors associated with a higher risk of seizure relapse after AED withdrawal.

AED therapy should be discontinued gradually; often over a period of 3-6 mo. Abrupt discontinuation can result in withdrawal seizures or status epilepticus. Withdrawal seizures are especially common with phenobarbital and benzodiazepines; consequently, special attention must be given to a prolonged tapering schedule during the withdrawal of these AEDs. Seizures that occur more than 2-3 mo after AEDs are completely discontinued indicate relapse, and resumption of treatment is usually warranted.

The decision to attempt AED withdrawal must be assessed mutually among the clinician, the parents, and the child depending on the child's age. Risk factors should be identified and precautionary measures should be taken. The patient and family should be counseled fully on what to expect, what precautions to take (including cessation of driving for a period of time), and what to do in case of relapse. A prescription for rectal diazepam or of intranasal midazolam to be given at the time of seizures that might occur during and after tapering is usually warranted (see Table 593-12 for dosing).

Sudden Unexpected Death in Epilepsy

SUDEP is the most common epilepsy related mortality in patients with chronic epilepsy; the incidence is unknown but ranges from 1-5 per 1,000 people with epilepsy. Although the precise etiology is unknown, risk factors include polypharmacology, poorly controlled generalized tonic–clonic seizures, male gender, age younger than 16 yr, long duration of epilepsy, and frequent seizures. Patients are usually found dead in their bed in a prone position with evidence suggesting a recent seizure. Potential mechanisms of SUDEP include respiratory arrest or dysfunction, drug-induced cardiac toxicity, CNS dysfunction (hypoventilation, arrhythmia, suppression of brain electrical activity), or pulmonary edema. Table 593-15 lists possible preventive measures.

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Table 593-15	Measures in Clinical Practice to Reduce the Risk of SUDEP

- **Reduction of tonic–clonic seizures:** optimum treatment, good drug compliance, lifestyle advice (e.g., alcohol intake, sleep deprivation)
- **Treatment changes:** change in a gradual staged manner; when switching drugs, introduce the new drug before withdrawing the old drug; the patients should have access to immediate advice in the event of worsening seizures during periods of change
- **Supervision at night for patients at high risk:** attendance, use of alarms (balancing the benefits of independent living and the penalties of intrusive monitoring)
- **Choice of drugs:** caution with antiepileptic drugs with potential cardiorespiratory adverse effects
- **Act on ictal warning signs:** tonic–clonic seizures that are prolonged, associated with marked cyanosis, severe bradycardia or apnea, and postictal EEG suppression; complex partial seizures with marked atonia (drop attacks); seizure in those with preexisting cardiac or respiratory impairment
- **Supervision after a tonic–clonic seizure:** continuous attendance until full consciousness is restored; call emergency services for high-risk seizures
- **Counseling on the risks:** lifestyle and treatment decisions are the patient's prerogative and the physician's role is to provide a risk-vs-benefit analysis

EEG, electroencephalogram; SUDEP, sudden unexpected death in epilepsy.
From Shorvan S, Tomson T: Sudden unexpected death in epilepsy. Lancet *378:2028–2036, 2011.*

593.7 Neonatal Seizures

Mohamad A. Mikati and Abeer J. Hani

Seizures are possibly the most important and common indicator of significant neurologic dysfunction in the neonatal period. Seizure incidence is higher during this period than in any other period in life: 57.5 per 1,000 in infants with birth weights <1,500 g and 2.8 per 1,000 in infants weighing between 2,500 and 3,999 g have seizures.

PATHOPHYSIOLOGY

The immature brain has many differences from the mature brain that render it more excitable and more likely to develop seizures. Based predominantly on animal studies, these are delay in Na^+, K^+-adenosine triphosphatase maturation and increased NMDA and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor density. In addition, the specific types of these receptors that are increased are those that are permeable to calcium (GLUR2 AMPA receptors). This contributes to increased excitability and to the long-term consequences associated with seizures, particularly those resulting from perinatal hypoxia. Medications that block AMPA receptors, such as topiramate, may thus prove useful in this clinical setup.

Another difference is delay in the development of inhibitory GABAergic transmission. In fact, GABA in the immature brain has an excitatory function as the chloride gradient is reversed relative to the mature brain, with higher concentrations of chloride being present intracellularly than extracellularly. Thus, opening of the chloride channels in the immature brain results in depolarizing the cell and not in hyperpolarizing it. This phenomenon appears to be more prominent in male neonates, perhaps explaining their greater predisposition to seizures. The reason for this is that the Cl^- transporter, NKCC1, is predominantly expressed in the neonatal period, leading to transport of Cl^- into the cell at rest, and then to cellular depolarization upon activation of $GABA_A$ receptors and opening of Cl^- channels with chloride efflux. This is important for neuronal development but renders the neonatal brain hyperexcitable. With maturation, expression of NCCK1 decreases and KCC2 increases. KCC2 transports Cl^- out of the cell, resulting in reduction of intracellular chloride concentration so that when $GABA_A$ receptors are activated, Cl^- influx and hyperpolarization occur. Bumetanide, a diuretic that blocks NKCC1, can prevent excessive GABA depolarization and avert the neuronal hyperexcitability underlying neonatal seizures. It also prevents, in rats, complex febrile seizure induced hyperactivation of excitatory $GABA_A$ receptors and the resultant granule cell ectopia and temporal lobe epilepsy.

Although it is susceptible to developing seizures, the immature brain appears to be more resistant to the deleterious effects of seizures than the mature brain, as a result of increases in calcium binding proteins that buffer injury-related increases in calcium, increased extracellular space, decreased levels of the second messenger inositol triphosphate, and the immature brain's ability to tolerate hypoxic conditions by resorting to anaerobic energy metabolism.

Many animal studies indicate that seizures are detrimental to the immature brain. Human studies also suggest harmful effects of seizures as shown by MRI and by the association of worse prognosis in neonates with seizures even when correcting for confounding factors. Even electrographic seizures without clinical correlates have been shown to be associated with worse prognosis. However, it is not definite that this association is causal: It is difficult in human studies to distinguish among effects of seizures, of the underlying insult responsible for the seizures (clinical or electrographic), and of the AEDs used to stop the seizures. Most physicians currently believe that it is favorable to control clinical as well as electrographic seizures.

TYPES OF NEONATAL SEIZURES

There are 5 main neonatal seizure types: subtle, clonic, tonic, spasms, and myoclonic. Spasms, focal clonic, focal tonic, and generalized myoclonic seizures are, as a rule, associated with electrographic discharges (epileptic seizures), whereas motor automatisms, the subtle, generalized tonic and multifocal myoclonic episodes are frequently not associated with discharges and thus are thought to often represent release phenomena with abnormal movements secondary to brain injury rather than true epileptic seizures (Table 593-16). To determine clinically whether such manifestations are seizures or release phenomena is often difficult, but precipitation of such manifestations by stimulation and aborting them by restraint or manipulation would suggest that they are not seizures. One needs to keep in mind, however, that epileptic seizures can also be induced by stimulation. Thus, in many cases, specifically in sick neonates with history of neurologic insults, continuous bedside EEG monitoring helps make this distinction. Such monitoring has become the standard of care in most intensive care nurseries.

Subtle Seizures

Subtle seizures include transient eye deviations, nystagmus, blinking, mouthing, abnormal extremity movements (rowing, swimming, bicycling, pedaling, and stepping), fluctuations in heart rate, hypertension episodes, and apnea. Subtle seizures occur more commonly in premature than in full-term infants.

Clonic Seizures

Clonic seizures can be focal or multifocal. Multifocal clonic seizures incorporate several body parts and are migratory in nature. The migration follows a nonjacksonian trend; for example, jerking of the left arm can be associated with jerking of the right leg. Generalized clonic seizures that are bilateral, symmetric, and synchronous are uncommon in the neonatal period presumably due to decreased connectivity associated with incomplete myelination at this age.

Tonic Seizures

Tonic seizures can be focal or generalized (generalized are more common). Focal tonic seizures include persistent posturing of a limb or posturing of trunk or neck in an asymmetric way often with persistent horizontal eye deviation. Generalized tonic seizures are bilateral tonic limb extension or tonic flexion of upper extremities often associated with tonic extension of lower extremities.

Spasms

Spasms are sudden generalized jerks lasting 1-2 sec that are distinguished from generalized tonic spells by their shorter duration and by

Table 593-16 Clinical Characteristics, Classification, and Presumed Pathophysiology of Neonatal Seizures

CLASSIFICATION	CHARACTERIZATION
Focal clonic	Repetitive, rhythmic contractions of muscle groups of the limbs, face, or trunk May be unifocal or multifocal May occur synchronously or asynchronously in muscle groups on 1 side of the body May occur simultaneously but asynchronously on both sides Cannot be suppressed by restraint Pathophysiology: epileptic
Focal tonic	Sustained posturing of single limbs Sustained asymmetrical posturing of the trunk Sustained eye deviation Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic
Generalized tonic	Sustained symmetrical posturing of limbs, trunk, and neck May be flexor, extensor, or mixed extensor/flexor May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic
Myoclonic	Random, single, rapid contractions of muscle groups of the limbs, face, or trunk Typically not repetitive or may recur at a slow rate May be generalized, focal, or fragmentary May be provoked by stimulation Presumed pathophysiology: may be epileptic or nonepileptic
Spasms	May be flexor, extensor, or mixed extensor/flexor May occur in clusters Cannot be provoked by stimulation or suppressed by restraint Pathophysiology: epileptic
Motor automatisms	
Ocular signs	Random and roving eye movements or nystagmus (distinct from tonic eye deviation) May be provoked or intensified by tactile stimulation Presumed pathophysiology: nonepileptic
Oral-buccal-lingual movements	Sucking, chewing, tongue protrusions May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic
Progression movements	Rowing or swimming movements Pedaling or bicycling movements of the legs May be provoked or intensified by stimulation May be suppressed by restraint or repositioning Presumed pathophysiology: nonepileptic
Complex purposeless movements	Sudden arousal with transient increased random activity of limbs May be provoked or intensified by stimulation Presumed pathophysiology: nonepileptic

From Mizrahi EM, Kellaway P. Diagnosis and management of neonatal seizures. *Philadelphia, 1998, Lippincott-Raven. Tab 4, p. 21.*

the fact that spasms are usually associated with a single, very brief, generalized discharge.

Myoclonic Seizures

Myoclonic seizures are divided into focal, multifocal, and generalized types. Myoclonic seizures can be distinguished from clonic seizures by the rapidity of the jerks (<50 msec) and by their lack of rhythmicity. Focal myoclonic seizures characteristically affect the flexor muscles of the upper extremities and are sometimes associated with seizure activity on EEG. Multifocal myoclonic movements involve asynchronous twitching of several parts of the body and are not commonly associated with seizure discharges on EEG. Generalized myoclonic seizures involve bilateral jerking associated with flexion of upper and occasionally lower extremities. The latter type of myoclonic jerks is more commonly correlated with EEG abnormalities than the other types.

Seizures vs Jitteriness

Jitteriness can be defined as rapid motor activities, such as a tremor or shake, that can be ended by flexion or holding the limb. Seizures, on the other hand, generally do not end with tactile or motor suppression. Jitteriness, unlike most seizures, is usually induced by a stimulus. Also unlike jitteriness, seizures often involve eye deviation and autonomic changes.

ETIOLOGY

Table 593-17 lists causes of neonatal seizures.

Hypoxic–Ischemic Encephalopathy

This is the most common cause of neonatal seizures, accounting for 50-60% of patients. Seizures secondary to this encephalopathy occur within 12 hr of birth.

Vascular Events

These include intracranial bleeds and ischemic strokes and account for 10-20% of patients. Three types of hemorrhage can be distinguished: primary subarachnoid hemorrhage, germinal matrix–intraventricular hemorrhage, and subdural hemorrhage. Patients with arterial strokes or venous sinus thrombosis can present with seizure and these can be

Table 593-17 Causes of Neonatal Seizures According to Common Age of Presentation

AGES 1-4 DAYS Hypoxic–ischemic encephalopathy Drug withdrawal, maternal drug use of narcotic or barbiturates Drug toxicity: lidocaine, penicillin Intraventricular hemorrhage Acute metabolic disorders • Hypocalcemia • Sepsis • Maternal hyperthyroidism, or hypoparathyroidism • Hypoglycemia • Perinatal insults, prematurity, small for gestational age • Maternal diabetes • Hyperinsulinemic hypoglycemia • Hypomagnesemia • Hyponatremia or hypernatremia • Iatrogenic or inappropriate antidiuretic hormone secretion Inborn errors of metabolism • Galactosemia • Hyperglycinemia • Urea cycle disorders Pyridoxine deficiency and pyridoxal-5-phosphate deficiency (must be considered at any age)
AGES 4-14 DAYS Infection • Meningitis (bacterial) • Encephalitis (enteroviral, herpes simplex) Metabolic disorders • Hypocalcemia • Diet, milk formula • Hypoglycemia, persistent • Inherited disorders of metabolism • Galactosemia • Fructosemia • Leucine sensitivity • Hyperinsulinemic hypoglycemia, hyperinsulinism, hyperammonemia syndrome • Anterior pituitary hypoplasia, pancreatic islet cell tumor • Beckwith syndrome Drug withdrawal, maternal drug use of narcotics or barbiturates Benign neonatal convulsions, familial and nonfamilial Kernicterus, hyperbilirubinemia Developmental delay, epilepsy, neonatal diabetes syndrome
AGES 2-8 WK Infection • Herpes simplex or enteroviral encephalitis • Bacterial meningitis Head injury • Subdural hematoma • Child abuse Inherited disorders of metabolism • Aminoacidurias • Urea cycle defects • Organic acidurias • Neonatal adrenoleukodystrophy Malformations of cortical development • Lissencephaly • Focal cortical dysplasia Tuberous sclerosis Sturge-Weber syndrome

diagnosed by neuroimaging. Venous sinus thrombosis could be missed unless MR or CT venography studies are requested.

Intracranial Infections

Bacterial and nonbacterial infections account for 5-10% of the cases of neonatal seizures and include bacterial meningitis, TORCH (*t*oxoplasmosis, *o*ther infections, *r*ubella, *c*ytomegalovirus, *h*erpes simplex virus) infections, particularly herpes simplex encephalitis.

Brain Malformations

Brain malformations account for 5-10% of neonatal seizure cases. An example is **Aicardi syndrome**, which affects girls only and consists of retinal lacunae, agenesis of the corpus callosum, and severe seizures including subsequent infantile spasms with hypsarrhythmia that is sometimes initially unilateral on EEG.

Metabolic Disturbances

Metabolic disturbances include disturbances in glucose, calcium, magnesium, other electrolytes, amino acids, or organic acids and pyridoxine dependency.

Hypoglycemia can cause neurologic disturbances and is very common in small neonates and neonates whose mothers are diabetic or prediabetic. The duration of hypoglycemia is very critical in determining the incidence of neurologic symptoms.

Hypocalcemia occurs at 2 peaks. The first peak corresponds to low-birthweight infants and is evident in the 1st 2-3 days of life. The second peak occurs later in neonatal life and often involves large, full-term babies who consume milk that has an unfavorable ratio of phosphorus to calcium and phosphorus to magnesium. **Hypomagnesemia** is often associated with hypocalcemia. **Hyponatremia** can cause seizures and is often secondary to inappropriate antidiuretic hormone secretion.

Local anesthetic intoxication seizures can result from neonatal intoxication with local anesthetics administered into the infant's scalp.

Neonatal seizures can also result from disturbances in **amino acid or organic acid** metabolism. These are usually associated with acidosis and/or hyperammonemia. However, even in the absence of these findings, if a cause of the seizures is not immediately evident, then ruling out metabolic causes requires a full metabolic work-up (see Chapter 593.2) including examination of serum amino acids, acyl carnitine profile, lactate, pyruvate, ammonia, very-long-chain fatty acids (for neonatal adrenoleukodystrophy and Zellweger syndrome), examination of urine for organic acids, α-aminoadipic acid semialdehyde and sulfocysteine, as well as examination of CSF for glucose, protein, cells, amino acids, lactate, pyruvate, α-aminoadipic acid semialdehyde, pyridoxal phosphate, 5-MTHF (5-methyltetrahydrofolate), succinyladenosine, and CSF neurotransmitter metabolites. This is because many inborn errors of metabolism, such as nonketotic hyperglycinemia, can manifest with neonatal seizures (often mistaken initially for hiccups that these patients also have) and can be detected only by performing these tests. Definitive diagnosis of **nonketotic hyperglycinemia**, for example, requires measuring the ratio of CSF glycine to plasma glycine.

Pyridoxine and **pyridoxal dependency disorders** can cause severe seizures. These seizures, which are often multifocal clonic, usually start during the 1st few hr of life. Cognitive impairment is often associated if therapy is delayed (see Chapter 593.6).

Drug Withdrawal

Seizures can rarely be caused by the neonate's passive addiction and then drug withdrawal. Such drugs include narcotic analgesics, sedative–hypnotics, and others. The associated seizures appear during the 1st 3 days of life.

Neonatal Seizure Syndromes

Seizure syndromes include **benign idiopathic neonatal seizures (fifth day fits)**, which are usually apneic and focal motor seizures that start around the fifth day of life. Interictal EEG shows a distinctive pattern called *theta pointu alternant* (runs of sharp 4-7 Hz activity), and ictal EEG shows multifocal electrographic seizures. Patients have a good response to medications and a good prognosis. Autosomal dominant **benign familial neonatal seizures** have onset at 2-4 days of age and usually remit at 2-15 wk of age. The seizures consist of ocular deviation, tonic posturing, clonic jerks, and, at times, motor automatisms. Interictal EEG is usually normal. These are caused by mutations in the *KCNQ2* and *KCNQ3* genes. Approximately 16% of patients develop later epilepsy. **Early myoclonic encephalopathy** and **early infantile epileptic encephalopathy (Ohtahara syndrome)** are discussed in Chapter 593.4.

Miscellaneous Conditions

Miscellaneous conditions include benign neonatal sleep myoclonus and hyperekplexia, which are nonepileptic conditions (see Chapter 594).

DIAGNOSIS

Some cases can be correctly diagnosed by simply taking the prenatal and postnatal history and performing an adequate physical examination. Depending on the case, additional tests or procedures can be performed. EEG is considered the main tool for diagnosis. It can show paroxysmal activity (e.g., sharp waves) in between the seizures and electrographic seizure activity if a seizure is captured. However, some neonatal seizures might not be associated with EEG abnormalities as noted above either because they are "release phenomena" or alternatively because the discharge is deep and is not detected by the scalp EEG. Additionally, electrographic seizures can occur without observed clinical signs **(electroclinical dissociation).** This is presumed to be caused by the immaturity of cortical connections, resulting, in many cases, in no or minimal motor manifestations. Continuously monitoring the EEG at the bedside in the neonatal intensive care unit for neonates at risk for neonatal seizures and brain injury is part of routine clinical practice in most centers, providing real-time measurements of the brain's electrical activity and identifying seizure activity. Many centers apply EEG monitoring to at-risk babies even before seizures develop, which is often desirable; others monitor patients who have manifested or are suspected of having seizures. In addition, there are currently attempts to develop methods for continuous monitoring of cerebral activity with automated detection and background analysis of neonatal seizures, similar to the continuous ECG monitoring in intensive care facilities. In infants started on hypothermia protocols following suspected hypoxic–ischemic injuries, it is recommended to continuously monitor the EEG during the cooling and rewarming periods to detect clinical and subclinical events in this high-risk population. The American Clinical Neurophysiology Society recommends continuous EEG monitoring in the neonatal intensive care unit to monitor evolution of EEG background to help with prognostication, to guide titration of anticonvulsant therapy for infants with established seizures, to screen for seizures among infants deemed to be at risk (hypoxic ischemic encephalopathy, stroke, meningitis, intraventricular hemorrhage, metabolic disorders, and congenital cerebral malformations), to screen for seizures among infants who are paralyzed, to characterize clinical events suspected to represent seizures, and to detect impending cerebral ischemia or hemorrhage.

Careful neurologic examination of the infant might uncover the cause of the seizure disorder. Examination of the **retina** might show the presence of chorioretinitis, suggesting a congenital TORCH infection, in which case titers of mother and infant are indicated. The **Aicardi syndrome** is associated with coloboma of the iris and retinal lacunae. Inspection of the **skin** might show hypopigmented lesions characteristic of tuberous sclerosis (seen best on UV light examination) or the typical crusted vesicular lesions of incontinentia pigmenti; both neurocutaneous syndromes are often associated with generalized myoclonic seizures beginning early in life. An unusual body or urine odor suggests an inborn error of metabolism.

Blood should be obtained for determinations of glucose, calcium, magnesium, electrolytes, and blood urea nitrogen. If hypoglycemia is a possibility, serum glucose testing is indicated so that treatment can be initiated immediately. Hypocalcemia can occur in isolation or in association with hypomagnesemia. A lowered serum calcium level is often associated with birth trauma or a CNS insult in the perinatal period. Additional causes include maternal diabetes, prematurity, DiGeorge syndrome, and high-phosphate feedings. Hypomagnesemia (<1.5 mg/dL) is often associated with hypocalcemia and occurs particularly in infants of malnourished mothers. In this situation, the seizures are resistant to calcium therapy but respond to intramuscular magnesium, 0.2 mL/kg of a 50% solution of $MgSO_4$. Serum electrolyte measurement can indicate significant hyponatremia (serum sodium <115 mEq/L) or hypernatremia (serum sodium >160 mEq/L) as a cause of the seizure disorder.

A **lumbar puncture** is indicated in virtually all neonates with seizures, unless the cause is obviously related to a metabolic disorder such as hypoglycemia or hypocalcemia. The latter infants are normally alert interictally and usually respond promptly to appropriate therapy. The CSF findings can indicate a bacterial meningitis or aseptic encephalitis. Prompt diagnosis and appropriate therapy improve the outcome for these infants. Bloody CSF indicates a traumatic tap or a subarachnoid or intraventricular bleed. Immediate centrifugation of the specimen can assist in differentiating the 2 disorders. A clear supernatant suggests a traumatic tap, and a xanthochromic color suggests a subarachnoid bleed. Mildly jaundiced normal infants can have a yellowish discoloration of the CSF that makes inspection of the supernatant less reliable in the newborn period.

Many **inborn errors of metabolism** cause generalized convulsions in the newborn period. Because these conditions are often inherited in an autosomal recessive or X-linked recessive fashion, it is imperative that a careful family history be obtained to determine if there is consanguinity or whether siblings or close relatives developed seizures or died at an early age. Serum ammonia determination is useful for screening for the hypoglycemic hyperammonemia syndrome and for suspected urea cycle abnormalities. In addition to having generalized clonic seizures, these latter infants present during the 1st few days of life with increasing lethargy progressing to coma, anorexia and vomiting, and a bulging fontanel. If the blood gases show an anion gap and a metabolic acidosis with the hyperammonemia, urine organic acids should be immediately determined to investigate the possibility of methylmalonic or propionic acidemia.

Maple syrup urine disease should be suspected when a metabolic acidosis occurs in association with generalized clonic seizures, vomiting, bulging fontanel, and muscle rigidity during the 1st wk of life. The result of a rapid screening test using 2,4-dinitrophenylhydrazine that identifies keto derivatives in the urine is positive in maple syrup urine disease.

Additional metabolic causes of neonatal seizures include nonketotic hyperglycinemia, an intractable condition characterized by markedly elevated plasma and CSF glycine levels, prominent hiccups, persistent generalized seizures, and lethargy rapidly leading to coma; ketotic hyperglycinemia in which seizures are associated with vomiting, fluid and electrolyte disturbances, and a metabolic acidosis; and Leigh disease suggested by elevated levels of serum and CSF lactate or an increased lactate : pyruvate ratio. Biotinidase deficiency should also be considered. A comprehensive description of the diagnosis and management of these metabolic diseases is discussed in Part XI, Metabolic Disorders.

Unintentional **injection of a local anesthetic** into a fetus during labor can produce intense tonic seizures. These infants are often thought to have had a traumatic delivery because they are flaccid at birth, have abnormal brainstem reflexes, and show signs of respiratory depression that sometimes require ventilation. Examination may show a needle puncture of the skin or a perforation or laceration of the scalp. An elevated serum anesthetic level confirms the diagnosis. The treatment consists of supportive measures and promotion of urine output by administering intravenous fluids with appropriate monitoring to prevent fluid overload.

Benign familial neonatal seizures, an autosomal dominant condition, begins on the 2nd-3rd day of life, with a seizure frequency of 10-20/day. Patients are normal between seizures, which stop in 1-6 mo. These are caused by mutations in the voltage-sensitive potassium channel genes *Kv7.2*, and *Kv7.3* (*KCNQ2* and *KCNQ3*). Other mutations in the *Kv7.2* gene cause severe neonatal epileptic encephalopathy. **Fifth-day fits** occur on day 5 of life (4-6 days) in normal-appearing neonates. The seizures are multifocal and are often present for <24 hr. The diagnosis requires exclusion of other causes of seizures and sequencing of the above genes. The prognosis is good for the benign form.

Pyridoxine dependency, a rare disorder, must be considered when seizures begin shortly after birth with signs of fetal distress in utero and are resistant to conventional anticonvulsants such as phenobarbital or phenytoin. The history may suggest that similar seizures

occurred in utero. When pyridoxine-dependent seizures are suspected, 100-200 mg of pyridoxine or pyridoxal phosphate should be administered intravenously during the EEG, which should be promptly performed once the diagnosis is considered. The seizures abruptly cease, and the EEG often normalizes in the next few hours or longer. Not all cases of pyridoxine dependency respond dramatically to the initial bolus of IV pyridoxine. Therefore, a 6-wk trial of oral pyridoxine (100-200 mg/day) or preferably pyridoxal phosphate (as pyridoxine does not help infants with the related but distinct syndrome of pyridoxal dependency) is recommended for infants in whom a high index of suspicion continues after a negative response to IV pyridoxine. Measurement of serum pipecolic acid and α-aminoadipic acid semialdehyde (elevated) and CSF pyridoxal-5-phosphate (decreased) needs to be performed before initiation of the trials without delay. These children require lifelong supplementation of oral pyridoxine (100 mg/day at times with folinic acid) or pyridoxal phosphate (15-60 mg/kg/day). Cerebral folate deficiency should also be ruled out by medication trial (folinic acid 1-3 mg/kg/day) and by CSF levels of 5-methyltetrahydrofolate assay. Gene sequencing can confirm the diagnosis (see Chapter 593.4). The earlier the therapy is initiated in these vitamin responsive disorders, the more favorable the outcome.

Drug-withdrawal seizures can occur in the newborn nursery but can take several weeks to develop because of prolonged excretion of the drug by the neonate. The incriminated drugs include barbiturates, benzodiazepines, heroin, and methadone. The infant may be jittery, irritable, and lethargic, and can have myoclonus or frank clonic seizures. The mother might deny the use of drugs; a serum or urine drug screen might identify the responsible agent.

Infants with focal seizures, suspected stroke or intracranial hemorrhage, and severe **cytoarchitectural abnormalities** of the brain (including lissencephaly and schizencephaly) who clinically may appear normal or microcephalic should undergo MRI or CT scan. Indeed, it is appropriate to recommend imaging of all neonates with seizures unexplained by serum glucose, calcium, or electrolyte disorders. Infants with chromosome abnormalities and adrenoleukodystrophy are also at risk for seizures and should be evaluated with investigation of a karyotype and serum very-long-chain fatty acids, respectively.

PROGNOSIS

Over the last few decades, prognosis of neonatal seizures has improved owing to advancements in obstetric and intensive neonatal care. Mortality has decreased from 40% to 20%. The correlation between EEG and prognosis is very clear. Although neonatal EEG interpretation is very difficult, EEG was found to be highly associated with the outcome in premature and full-term infants. An abnormal background is a powerful predictor of less-favorable later outcome. In addition, prolonged electrographic seizures (>10 min/hr), multifocal periodic electrographic discharges, and spread of the electrographic seizures to the contralateral hemisphere also correlate with poorer outcome. The underlying etiology of the seizures is the main determinant of outcome. For example, patients with seizures secondary to hypoxic–ischemic encephalopathy have a 50% chance of developing normally, whereas those with seizures caused by primary subarachnoid hemorrhage or hypocalcemia have a much better prognosis.

TREATMENT

A mainstay in the therapy of neonatal seizures is the diagnosis and treatment of the underlying etiology (e.g., hypoglycemia, hypocalcemia, meningitis, drug withdrawal, trauma), whenever one can be identified. There are conflicting approaches regarding the control of neonatal seizures. Most experts advocate complete control of clinical as well electrographic seizures. Others argue for treating clinical seizures only. Most centers favor the first approach. An important consideration before starting anticonvulsants is deciding, based on the severity duration and frequency of the seizures if the patient needs to receive intravenous therapy and loading with an initial bolus or can simply be started on maintenance doses of a long-acting drug. Patients often require assisted ventilation after receiving intravenous or oral loading doses of AEDs, and thus precautions for observations and for needed interventions are necessary.

Lorazepam

The initial drug used to control acute seizures is usually lorazepam. Lorazepam is distributed to the brain very quickly and exerts its anticonvulsant effect in <5 min. It is not very lipophilic and does not clear out from the brain very rapidly. Its action can last 6-24 hr. Usually, it does not cause hypotension or respiratory depression. The dose is 0.05 mg/kg (range: 0.02-0.10 mg/kg) every 4-8 hr.

Diazepam

Diazepam can be used as an alternative initial drug. It is highly lipophilic, so it distributes very rapidly into the brain and then is cleared very quickly out, carrying the risk of recurrence of seizures. Like other intravenous benzodiazepines, it carries a risk of apnea and hypotension, particularly if the patient is also on a barbiturate, so patients need to be observed for 3-8 hr after administration. The usual dose is 0.1-0.3 mg/kg IV over 3-5 min, given every 15-30 min to a maximum total dose of 2 mg. However, because of the respiratory and blood pressure limitations and because the intravenous preparation contains sodium benzoate and benzoic acid, it is currently not recommended as a first-line agent.

Midazolam

Midazolam can be used as an initial drug as a bolus or as a second- or third-line drug as a continuous drip for patients who did not respond to phenobarbital and/or to phenytoin. The doses used have been in the range of 0.05-0.1 mg/kg IV initial bolus, with a continuous infusion of 0.5-1 µg/kg/min IV that can then be gradually titrated upward, if tolerated, every 5 min or longer, to a maximum of approximately 33 µg/kg/min (2 mg/kg/hr).

Phenobarbital

Phenobarbital is considered by many as the first choice long-acting drug in neonatal seizures. Whether to use a benzodiazepine first depends on the clinical situation. The usual loading dose is 20 mg/kg. If this dosage is not effective, then additional doses of 5-10 mg/kg can be given until a dose of 40 mg/kg is reached. Respiratory support may be needed after phenobarbital loading. Twenty-four hours after starting the loading dose, maintenance dosing can be started at 3-6 mg/kg/day usually administered in 2 separate doses. Phenobarbital is metabolized in the liver and is excreted through kidneys. Thus, any abnormality in the function of these organs alters the drug's metabolism and can result in toxicity. In infants with acidosis or critical illness that might alter serum protein content, free (i.e., not protein bound) levels of the drug should be followed carefully.

Phenytoin and Fosphenytoin

For ongoing seizures, if a total loading dose of 40 mg/kg of phenobarbital was not effective, then a loading dose of 15-20 mg/kg of phenytoin can be administered intravenously. The rate at which the dose should be given must not exceed 0.5-1.0 mg/kg/min so as to prevent cardiac problems, and the medication needs to be avoided in patients with significant heart disease. Heart rate should be monitored while administrating the drug. It is not possible to mix phenytoin or fosphenytoin with dextrose solutions. Owing to its reduced solubility, potentially severe local cutaneous reactions, interaction with other drugs, and possible cardiac toxicity, intravenous phenytoin is not widely used.

Fosphenytoin, which is a phosphate ester prodrug, is preferable. It is highly soluble in water, and can be administered very safely intravenously and intramuscularly, without causing injury to tissues. Fosphenytoin is administered in phenytoin equivalents (PE). The usual loading dose of fosphenytoin is 15-20 PE/kg administered over 30 min. Maintenance doses of 4-8 PE/kg/day can be given. As is the case for phenobarbital, free levels of the drug should be monitored in neonates whose serum pH or protein content might not be normal.

Other Medications

Approximately 45% of neonates respond to the first drug used if it is phenobarbital or phenytoin and an additional 15% respond to the second agent. Levetiracetam (which can be given intravenously with later convenient conversion to oral solution) and topiramate (oral) are reported to be the drugs of second and third choice for approximately half of surveyed pediatric neurologists and some have used them even before phenobarbital or phenytoin in selected cases. The dosages used are 10-30 mg/kg/day of levetiracetam, at times higher, and up to 20 mg/kg/day of topiramate. Bumetanide has been used as an adjunct drug, particularly with phenobarbital, because of its effect on the chloride gradient, as discussed above. Lidocaine is another medication used for resistant cases. Primidone, carbamazepine, valproate, and lamotrigine use, although reported in some studies, is rarely warranted. Valproate, for example, is more likely to be toxic in children younger than 2 yr of age than in older children.

Duration of Therapy

Duration of therapy is related to the risk of developing later epilepsy in infants suffering from neonatal seizures, which ranges from 10-30% and depends on the individual neurologic examination, the etiology of the seizures, and the EEG at the time of discharge from the hospital. In general, if the EEG at the time of discharge does not show evidence of epileptiform activity, then medications are usually tapered at that time. If the EEG remains paroxysmal, then the decision is usually delayed for several months after discharge.

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593.8 Status Epilepticus

Mohamad A. Mikati and Abeer J. Hani

Status epilepticus is a medical emergency that should be anticipated in any patient who presents with an acute seizure. It is defined as continuous seizure activity or recurrent seizure activity without regaining of consciousness lasting for more than 5 min as part of an operational definition put forth within the past few years. In the past, the cutoff time was 30 min, but this has been reduced to emphasize the risks involved with the longer durations. The ILAE defines status epilepticus as “a seizure which shows no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients or recurrent seizures without resumption of baseline central nervous system function interictally.” The measures used to treat status epilepticus have to be started in any patient with acute seizures that do not stop within a few minutes. The most common type is **convulsive status epilepticus** (generalized tonic, clonic, or tonic–clonic), but other types do occur, including **nonconvulsive status** (complex partial, absence), myoclonic status, epilepsia partialis continua, and neonatal status epilepticus. The incidence of status epilepticus ranges between 10 and 60 per 100,000 population in various studies. Status epilepticus is most common in children younger than 5 yr of age, with an incidence in this age group of >100 per 100,000 children.

Approximately 30% of patients presenting with status epilepticus are having their first seizure, and approximately 40% of these later develop epilepsy. Febrile status epilepticus is the most common type of status epilepticus in children. In the 1950s and 1960s, mortality rates of 6-18% were reported after status epilepticus; currently, with the recognition of status epilepticus as a medical emergency, a lower mortality rate of 4-5% is observed, most of it secondary to the underlying etiology rather than to the seizures. Status epilepticus carries an approximately 14% risk of new neurologic deficits, most of this (12.5%) secondary to the underlying pathology.

Nonconvulsive status epilepticus manifests as a confusional state, dementia, hyperactivity with behavioral problems, fluctuating impairment of consciousness with at times unsteady sitting or walking, fluctuating mental status, confusional state, hallucinations, paranoia, aggressiveness catatonia, and or psychotic symptoms. It should be considered in any of these situations, especially in an unresponsive or encephalopathic child. Epilepsia partialis continua has been defined previously and can be caused by tumor, vascular etiologies, mitochondrial disease (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]), and Rasmussen encephalitis.

Refractory status epilepticus is status epilepticus that has failed to respond to therapy, usually with at least 2 (such as a benzodiazepine and another medication) medications. Currently, the trend is not to assign a minimum duration, whereas in the past a minimum duration of 30 min, 60 min, or even 2 hr was cited. **New-onset refractory status epilepticus** has been identified as a distinct entity that can be caused by almost any of the causes of status epilepticus in a patient without prior epilepsy. It also is often of unknown etiology, presumed to be encephalitic or postencephalitic, can last several weeks or longer, and often, but not always, has a poor prognosis. Devastating epileptic encephalopathy in school-age children, also called **fever-induced refractory epileptic encephalopathy in school age children (FIRES)** is a syndrome of refractory status epilepticus that is associated with acute febrile infections, appears to be parainfectious in nature, and to be highly drug resistant but responsive to the ketogenic diet.

ETIOLOGY

Etiologies include new-onset epilepsy of any type; drug intoxication (e.g., tricyclic antidepressants) in children and drug and alcohol abuse in adolescents; drug withdrawal or overdose in patients on AEDs; hypoglycemia; hypocalcemia; hyponatremia; hypomagnesemia; acute head trauma; encephalitis; meningitis; autoimmune encephalitis (such as anti-NMDA receptor and anti–voltage-gated potassium channel complex antibody syndromes); ischemic (arterial or venous) stroke; intracranial hemorrhage; folinic acid and pyridoxine and pyridoxal phosphate dependency (these usually present in infancy but childhood onset is also possible); inborn errors of metabolism (see Chapter 593.2) such as nonketotic hyperglycinemia in neonates and mitochondrial encephalopathy with lactic acidosis (MELAS) in infants, children, and adolescents; ion channel–related epilepsies (e.g., sodium and potassium channel mutations reviewed in the sections above); hypoxic–ischemic injury (e.g., after cardiac arrest); systemic conditions (such as hypertensive encephalopathy, posterior reversible encephalopathy, renal or hepatic encephalopathy); brain tumors; and any other disorders that can cause epilepsy (such as brain malformations, neurodegenerative disorders, different types of progressive myoclonic epilepsy, storage diseases).

A rare condition called **hemiconvulsion-hemiplegia-epilepsy syndrome** consists of prolonged febrile status epilepticus presumably caused by focal acute encephalitis with resultant atrophy in the involved hemisphere, contralateral hemiplegia, and chronic epilepsy. It should be suspected early on to attempt to control the seizures as early as possible. This and the somewhat similar condition mentioned above called FIRES are likely to be have a parainfectious-autoimmune etiology. Rasmussen encephalitis often causes epilepsia partialis continua (see Chapter 593.3) and sometimes convulsive status epilepticus. Several types of infections are more likely to cause encephalitis with status epilepticus, such as herpes simplex (complex partial and convulsive status), *Bartonella* (particularly nonconvulsive status), Epstein-Barr virus, and mycoplasma (postinfectious encephalomyelitis with any type of status epilepticus). Postinfectious encephalitis and acute disseminated encephalomyelitis are common causes of status epilepticus, including refractory status epilepticus. HHV6 can cause a distinct epileptic syndrome with limbic status epilepticus in immune-suppressed patients.

MECHANISMS

The mechanisms leading to the establishment of sustained seizure activity seen in status epilepticus appear to involve (1) failure of desensitization of AMPA glutamate receptors, thus persistence of increased excitability, and (2) reduction of GABA-mediated inhibition as a result of intracellular internalization of $GABA_A$ receptors. This explains the

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clinical observation that status epilepticus is often less likely to stop in the next specific period of time the longer the seizure has lasted and why benzodiazepines appear to be decreasingly effective the longer seizure activity lasts. During status epilepticus there is increased cerebral metabolic rate and a compensatory increase in cerebral blood flow that, after approximately 30 min, is not able to keep up with the increases in cerebral metabolic rate. This leads to a transition from adequate to inadequate cerebral oxygen tensions and, together with other factors, contributes to neuronal injury resulting from status epilepticus. Status epilepticus can cause both neuronal necrosis and apoptosis. The mechanisms of apoptosis are thought to be related to increases in intracellular calcium and proapoptotic factors such as ceramide, Bax, and apoptosis-inducing factor. In addition, inflammation through the cytokines (such as interleukin-1β) released during seizure activity can modify neuronal excitability by modifying neurotransmitter function in a number of ways, such as through phosphorylation of the NR2B subunit rendering the NMDA receptors more permeable to calcium influx, increased expression of highly calcium-permeable AMPA receptors, and induction of endocytosis of $GABA_A$ receptors. Prostaglandins (such as prostaglandin E_2) can increase glutamate release and reduce potassium currents leading to increased excitability.

THERAPY

Status epilepticus is a medical emergency that requires initial and continuous attention to securing airway, breathing, and circulation (with continuous monitoring of vital signs including ECG) and determination and management of the underlying etiology (e.g., hypoglycemia). Laboratory studies, including glucose, sodium, calcium, magnesium, complete blood count, basic metabolic panel, CT scan, and continuous EEG, are needed for all patients. Blood and spinal fluid cultures, toxic screens, and tests for inborn errors of metabolism are often needed. AED levels need to be determined in all patients known already to be taking these drugs. Lumbar puncture, comprehensive toxicologic screens, MRI, and other laboratory tests are performed depending on clinical suspicion and need. EEG is helpful in ruling out **pseudo–status epilepticus** (psychologic conversion reaction mimicking status epilepticus) or other movement disorders (chorea, tics), rigors, clonus with stimulation, and decerebrate/decorticate posturing. The EEG can also be helpful in identifying the type of status epilepticus (generalized vs focal), which can guide further testing for the underlying etiology and further therapy. EEG can also help distinguish between postictal depression and later stages of status epilepticus in which the clinical manifestations are subtle (e.g., minimal myoclonic jerks) or absent (electroclinical dissociation), and can help in monitoring the therapy, particularly in patients who are paralyzed and intubated. Neuroimaging must be considered after the child has been stabilized, especially if it is indicated by the clinical manifestations, by an asymmetric or focal nature of the EEG abnormalities, or by lack of knowledge of the underlying etiology. The EEG manifestations of status epilepticus show several stages that consist of initial distinct electrographic seizures (stage I) followed by waxing and waning electrographic seizures (stage II), continuous electrographic seizures (stage III; many patients start with this directly), continuous ictal discharges punctuated by flat periods (stage IV), and periodic epileptiform discharges on flat background (stage V). The last 2 stages are often associated with subtle clinical manifestations and with a lower chance of response to medications.

The initial **emergent** therapy usually involves intravenous diazepam, lorazepam, or midazolam. Diazepam is at least as effective as intravenous lorazepam but has fewer side effects (Table 593-18). The use of midazolam autoinjector as initial therapy for acute seizures was found to be at least as useful and safe as the use intravenous lorazepam and results in earlier response. If intravenous access is not available, buccal or intranasal midazolam, intranasal lorazepam, or rectal diazepam are effective options. Intramuscular midazolam is equally effective as intravenous lorazepam. With all options, respiratory depression is a potential side effect for which the patient should be monitored and managed as needed. In some infants, a trial of pyridoxine may be warranted. The strongest evidence for initial and emergent therapy is for diazepam or

Table 593-18 Doses of Commonly Used Antiepileptic Drugs in Status Epilepticus

DRUG*	ROUTE	DOSAGE
Lorazepam	Intravenous Intranasal	0.1 mg/kg up to 4 mg total, may repeat in 5-10 min 0.1 mg/kg
Midazolam	Intravenous Intramuscular Intranasal Buccal	0.2 mg/kg up to 10 mg total dose, may repeat in 5-10 min 0.08-0.23 mg/kg/hr maintenance 0.2 mg/kg 0.2 mg/kg 0.5 mg/kg
Diazepam	Intravenous Rectal	0.15 mg/kg up to a max total dose of 10 mg, may repeat in 5-10 min 2-5 yr: 0.5 mg/kg 6-11 yr: 0.3 mg/kg ≥12 yr: 0.2 mg/kg
Fosphenytoin	Intravenous	20 mg/kg PE, then 3-6 mg/kg/24 hr, loading rate up to 50 mg PE per min
Phenobarbital†	Intravenous	5-20 mg/kg
Pentobarbital coma†	Intravenous	13.0 mg/kg, then 1-5 mg/kg/hr
Propofol†	Intravenous	1 mg/kg (bolus), then 1-15 mg/kg/hr (infusion)
Thiopental†	Intravenous	5 mg/kg/1st hr, then 1-2 mg/kg/hr
Valproate†	Intravenous	Loading: 25 mg/kg, then 30-60 mg/kg/24 hr
Lacosamide†	Intravenous	Loading: 4 mg/kg then 4-12 mg/kg/24 hr
Levetiracetam	Intravenous	20-60 mg/kg
Topiramate	Enterally	5-10 mg/kg/24 hr (loading dose) then same or lower for maintenance

*Reflects current trends in use which may not be FDA approved. For FDA indications, see Table 593-13.
†May cause PR prolongation.
PE, phenytoin sodium equivalents.

lorazepam, followed by phenytoin/fosphenytoin and phenobarbital, then valproate and levetiracetam.

After the emergent therapy usually with a benzodiazepine, the subsequent **urgent therapy** medication is usually fosphenytoin, and the loading dose is usually 15-20 PE/kg. A level is usually taken 2 hr later to ensure achievement of a therapeutic concentration. Depending on the level, maintenance dose can be started right away or, more commonly, in 6 hr. With phenytoin and phenobarbital, each 1 mg/kg (1 PE/kg for fosphenytoin) increases the serum concentration by approximately 1 µg/mL; for valproate, each 1 mg/kg increases the serum concentration by approximately 4 µg/mL. Precautions about the rate of infusion of fosphenytoin and phenytoin (not >0.5-1.0 mg/kg/min) and the other medications need to be followed because side effects often depend on infusion rate. The subsequent medication is often phenobarbital. The dose used in neonates is usually 20 mg/kg loading dose, but in infants and children the dose is often 5-10 mg/kg (to avoid respiratory depression), with the dose repeated if there is not an adequate response. Current evidence for the urgent therapy is strongest for valproate, followed by phenytoin/fosphenytoin and midazolam continuous infusion, followed by phenobarbital and levetiracetam, the last of which are currently being increasingly used.

After the second or third medication is given, and sometimes before that, the patient might need to be intubated. All patients with status epilepticus, even the ones who respond, need to be admitted to the ICU for completion of therapy and monitoring. Ideally, emergent and urgent therapies should have been received within less than 30 min so as to initiate the subsequent therapy soon, thus reducing the chances of sequelae. For **refractory status epilepticus treatment**, an intravenous bolus followed by continuous infusion of midazolam, propofol, pentobarbital, or thiopental is used. This is done in the ICU. Subsequent boluses and adjustment of the rate of the infusion are usually made depending on clinical and EEG responses. Because most of these patients need to be intubated and paralyzed, the EEG becomes the method of choice by which to follow them. The goal is to stop electrographic seizure activity before reducing the therapy. Usually this implies achievement of complete flattening of the EEG. Some consider that achieving a burst suppression pattern may be enough, and the periods of flattening in such a case need to be 8-20 sec to ensure interruption of electrographic seizure activity. However, this is an area that is in need of further study. Currently, the level of the evidence for refractory treatment is strongest for midazolam and valproate, followed by propofol and pentobarbital/thiopental, followed by levetiracetam, phenytoin/fosphenytoin, lacosamide, topiramate, and phenobarbital.

Patients on these therapies require careful attention to blood pressure and to systemic complications, and some develop multiorgan failure. It is not unusual for patients put into pentobarbital coma to have to be on multiple pressors to maintain their blood pressure during therapy.

The choice among the above options to treat refractory status epilepticus often depends on the experience of the specific center. Midazolam probably has fewer side effects, but is less effective, and barbiturate coma is more effective, but carries a higher risk of side effects. On propofol, some patients develop a propofol infusion syndrome with lactic acidosis, hemodynamic instability, and rhabdomyolysis with higher infusion rates (>67 µg/kg/min). Thus electrolytes, creatine phosphokinase, and organ function studies need to be monitored. Often, barbiturate coma and similar therapies are maintained for 1 or more days before it is possible to gradually taper the therapy, usually over a few days. However, in some cases, including cases of new-onset refractory status epilepticus (new-onset refractory status epilepticus), such therapies need to be maintained for several weeks or even months. Even though the prognosis in new-onset refractory status epilepticus cases is often poor and many patients do not survive, meaningful recovery despite a prolonged course is still possible. This also appears to apply to the FIRES syndrome. Occasionally, inhalational anesthetics are useful. Probably isoflurane is preferable because halothane can increase intracranial pressure and enflurane can induce seizures. Other therapies have included ketamine, corticosteroids (e.g., for Rasmussen encephalitis, Hashimoto encephalopathy, or other autoimmune encephalitides), immunoglobulins, and plasma exchange (e.g., in Rasmussen or other autoimmune encephalitides), ketogenic diet (in patients with FIRES and Landau-Kleffner syndrome), vagus nerve stimulation in catastrophic epilepsy in infants, hypothermia, electroconvulsive therapy, magnetic transcranial stimulation, and surgical management with focal resection. Another potential therapy under study for convulsive status epilepticus is induction of acidosis (e.g., by hypercapnia), which could reduce neuronal excitability.

For nonconvulsive status epilepticus and epilepsia partialis continua, therapy needs to be tailored according to the clinical manifestations and often consists of trials of sequential oral or sometimes parenteral AEDs without resorting to barbiturate coma or overmedication that could result in respiratory compromise. The approach to complex partial status epilepticus is sometimes similar to the approach to convulsive status epilepticus and sometimes intermediate between the approach for epilepsia partialis and that for convulsive status, depending on severity. Long-term consequences after complex partial status epilepticus do occur, but the complications are often less severe than those after convulsive status epilepticus of similar duration. Prolonged nonconvulsive complex partial status epilepticus can last for as long as 12 wk, with patients manifesting psychotic symptoms and confusional states. These cases can be resistant to therapy. Despite that, patients still can have a full recovery. Some of these cases appear to improve with the use of steroids or IVIG, which are used if an autoimmune, parainfectious etiology is suspected.

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593.9 Reflex Seizures (Stimulus Precipitated Seizures)

Robert M. Kliegman

Many patients with epilepsy can identify precipitating or provoking events that predispose them to having a seizure. Common events in patients with epilepsy include stress, lack of sleep, fever, or fatigue.

There is another group of patients who have seizures in response to a very specific, identifiable sensory stimulus or activity and are considered to have reflex seizures. Although no known "reflex" may be involved, more appropriate terms may be sensory precipitated or stimulus sensitive seizures (see Table 593-1). Stimuli may be external (light, patterns, music, brushing teeth) or internal (math, reading, thinking, self-induced). Reflex seizures may be generalized, partial, nonconvulsive, absence or myoclonic. One common pattern is photomyoclonic seizures characterized by forehead muscle twitching or repetitive eye opening or closing.

Photosensitive or pattern-induced seizures are a well-recognized disorder stimulated by bright or flashing lights (TV, video games, discotheques, concert light shows) or by patterns (TV, video games, lines on the road while traveling). Visual sensitivity may occur in 0.3-3% of the population, while photosensitive or pattern-induced seizures may occur in 1 in 4,000 people in the at-risk age group of 5-25 yr. When Japanese children were exposed to a Pokémon cartoon that induced seizures, only 24% had a history of spontaneous seizures. Patients tend to outgrow photosensitive or pattern-induced seizures in their 30s. Photoparoxysmal responses, with an abnormal EEG response to photic stimulation may be more common than photic-induced seizures. There are some photo-induced responses that do not demonstrate EEG abnormalities (nonconvulsive).

For patients with isolated photosensitive or pattern-induced seizures, avoidance or modification of stimuli is the initial approach. Such activities may include blue or polarized sunglasses, avoiding high-contrast flashing-light video games, avoiding discotheques, use a TV remote or watch TV in a well-lit room at a distance of >8 feet, and covering 1 eye when in a provocative situation.

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Table 593-19	Consensus Case Definition and Modified Consensus Case Definition for Nodding Syndrome—Uganda, 2012-2013*	
TYPE OF CASE	**CONSENSUS CASE DEFINITION**	**MODIFIED CONSENSUS CASE DEFINITION**
Suspected case	Reported head nodding (repetitive involuntary drops of the head toward the chest on 2 or more occasions) in a previously normal person	Reported head nodding (repetitive involuntary drops of the head toward the chest on 2 or more occasions) in a previously normal person
Probable case	Suspected case of head nodding, with both major criteria: • Age of onset of nodding ranging from 3-18 yr • Frequency of nodding 5-20 per minute Plus at least 1 of the following minor criteria: • Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) • Clustering in space or time with similar cases • Triggering by food or cold weather • Stunting or wasting • Delayed sexual or physical development • Psychiatric symptoms	Suspected case of head nodding, with 1 major criterion: • Age of onset of nodding ranging from 3-18 yr Plus at least 1 of the following minor criteria: • Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) • Clustering in space or time with similar cases • Triggering by food or cold weather • Stunting or wasting • Psychiatric symptoms
Confirmed case	Probable case, with documented nodding episode • Observed and recorded by a trained healthcare worker, *or* • Videotaped nodding episode, *or* • Video/EEG/EMG documenting head nodding as atonic seizures	Probable case, with documented nodding episode • Observed and recorded by a trained healthcare worker, *or* • Videotaped nodding episode, *or* • Video/EEG/EMG documenting head nodding as atonic seizures

*The consensus case definition was drafted at the first International Scientific Meeting on Nodding Syndrome, held July 30–August 1, 2012, in Kampala, Uganda. Meeting report available at http://www.who.int/neglected_diseases/diseases/Nodding_syndrom_Kampala_Report_2012.pdf. The modified consensus case definition was developed during the March 2013 single-stage cluster survey conducted by Centers for Disease Control and Prevention (CDC) and the Ugandan Ministry of Health to assess prevalence of nodding syndrome in Uganda.

EEG, electroencephalographic; EMG, electromyographic.

From Iyengar PJ, Wamala J, Ratto J, et al: Prevalence of nodding syndrome–Uganda, 2012-2013. MMWR Morb Mortal Wkly Rep *63:603–606, 2014, Table 1.*

593.10 Nodding Syndrome

Robert M. Kliegman

Nodding syndrome appears to be an epidemic progressive epilepsy encephalopathy syndrome of unknown etiology seen predominantly in Uganda, Liberia, Tanzania, and the southern Sudan, with a prevalence of approximately 6.8 per 1,000 children. Age of onset is 6-13 yr. Nodding episodes are characterized by at least daily, rapid, paroxysmal forward head bobbling spells lasting several minutes; some patients are unresponsive whereas others may respond to commands or continue what they were doing before the episode. Children were previously healthy, although there may be a family history of seizures. In addition to episodes of nodding, there may be associated definable generalized tonic–clonic or absence seizures. Furthermore, patients go on to demonstrate severe and global cognitive impairment (see Table 593-19 for case definitions).

The EEG demonstrates a disorganized slow background and interictal generalized 2.5-3.0 Hz spike and slow waves. During a nodding episode, the EEG demonstrates generalized electrodecrement and paraspinal electromyography dropout suggestive of an atonic seizure. Cerebral spinal fluid analysis is usually negative, while the MRI shows cerebral and cerebellar atrophy.

Nodding episodes may be triggered during meals while eating hot foods or drinking cold liquids; cold environmental temperature may also trigger a nodding episode.

Treatment of seizures are indicated; however, the response to treatment is poor.

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Chapter 594

Conditions That Mimic Seizures

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The misdiagnosis of epilepsy is estimated to be as high as 5-40%, implying that many patients may be subjected to unnecessary therapy and tests. Often all that is needed to differentiate nonepileptic paroxysmal disorders from epilepsy is a careful and detailed history in addition to a thorough exam; but sometimes an electroencephalogram (EEG) or more advanced testing may be necessary. The ready availability of video recording on mobile phones and other devices at home or at school can provide invaluable information. Nonepileptic paroxysmal disorders can be classified according to the age of presentation and the clinical manifestations: (1) syncope and other generalized paroxysms, (2) movement disorders and other abnormal movements and postures, (3) oculomotor abnormalities and visual hallucinations, and (4) sleep-related disorders (Table 594-1).

SYNCOPE AND OTHER GENERALIZED PAROXYSMS

Apnea

Apneic episodes in neonates are usually associated with bradycardia as is usually apnea resulting from brainstem compression. In contrast, apnea associated with seizures is usually accompanied by tachycardia. Of note, exceptions do occur as bradycardia can occur during epileptic seizures, and severe apnea of any cause can be followed by anoxic seizures.

Table 594-1 Conditions That Mimic Seizures According to Age of Presentation

AGE	SYNCOPE AND OTHER GENERALIZED PAROXYSMS	MOVEMENT DISORDERS AND OTHER ABNORMAL MOVEMENTS	OCULOMOTOR ABNORMALITIES	SLEEP DISORDERS
Neonate	Apnea Paroxysmal extreme pain disorder	Jitteriness Hyperekplexia Paroxysmal dystonic choreoathetosis	Paroxysmal tonic up gaze Alternating hemiplegia of childhood	Benign neonatal sleep myoclonus Sleep transition disorders
Infants	Reflex anoxic seizures Breath-holding spells Benign paroxysmal vertigo Paroxysmal extreme pain disorder	Jitteriness Sandifer Paroxysmal dystonic choreoathetosis Benign myoclonus of early infancy Pathologic startle Shuddering attacks Benign paroxysmal torticollis Psychologic disorders Alternating hemiplegia of childhood Jactatio capitis head banging Drug reactions	Paroxysmal tonic upgaze Oculomotor apraxia Spasmus nutans Opsoclonus myoclonus syndrome	Non-REM partial arousal disorders REM sleep disorders Narcolepsy Sleep transition disorders (somnambulism, somniloquy)
Children and adolescents	Benign paroxysmal vertigo Compulsive Valsalva Familial hemiplegic migraine Syncope (long QT, vasovagal, vagovagal, orthostatic, migraine-induced) Psychogenic seizures Transient global amnesia Hyperventilation spells	Tics Tremor Pathologic startle Paroxysmal dyskinesias Alternating hemiplegia of childhood Benign paroxysmal torticollis Episodic ataxia Psychologic disorders including factitious disorder imposed on another, malingering Masturbation Psychogenic seizures Cataplexy Jactatio capitis (head banging) Episodic rage Drug reactions	Daydreaming Drug reactions	Non-REM partial-arousal disorders REM sleep disorders Narcolepsy Sleep transition disorders (somnambulism, somniloquy) Sleep myoclonus Restless legs syndrome

REM, rapid eye movement.

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Breath-Holding Spells

The term *breath-holding spells* is actually a misnomer, as these are not self-induced, but result from the immaturity of the autonomic system and occur in 2 different forms. The first type is the **pallid breath-holding spell**, which is caused by reflex vagal–cardiac bradycardia and asystole. The second type is the **cyanotic,** or **"blue," breath-holding spell**, which does not occur during inspiration, but results from prolonged expiratory apnea and intrapulmonary shunting. Episodes usually start with a cry (often, in the case of the pallid type, a "silent" cry with marked pallor), and progress to apnea and cyanosis. Spells usually begin between 6 and 18 mo of age. Syncope, tonic posturing, and even reflex anoxic seizures may follow the more-severe episodes, particularly in breath-holding spells of the pallid type. Injury, anger, and frustration, particularly with surprise, are common triggers. Education and reassurance of the parents is usually all that is needed, as these episodes are, as a rule, self-limited and are outgrown within a few years. However, treatment of coexisting iron deficiency is needed if it is present as the spells are made worse by iron-deficiency anemia. Anticholinergic drugs (e.g., atropine sulfate 0.01 mg/kg/24 hr in divided doses with a maximum daily dose of 0.4 mg), or antiepileptic drug therapy for coexisting anoxic seizures that are recurrent and not responding to other measures may, rarely, be needed. It is important also to educate parents on how to handle more-severe spells by first-aid measures, or even basic CPR when needed. In severe cases of asystole, a cardiac pacemaker implantation may be needed. All parents should be taught not to provide secondary gain when the episodes occur, because this can reinforce the episodes. Also, preparation for unpleasant experiences (such as receiving a shot) rather than surprising the child with them, can help limit the number of spells (see Chapter 69).

Compulsive Valsalva

In children with intellectual disability, including Rett syndrome, syncopal convulsions may be self-induced by maneuvers like Valsalva. In this case, true breath-holding occurs, and it usually lasts for approximately 10 sec during inspiration. Some clinicians advocate the use of naloxone in such cases.

Neurally Mediated Syncope

Syncope can present with drop attacks and can also lead to generalized convulsions, termed *anoxic seizures*. These convulsions, triggered by a sudden reduction of oxygen to the brain, are clinically similar to and can be misdiagnosed as generalized epileptic seizures. **Vasovagal (neurocardiogenic) syncope** is one of the most common mimickers of generalized tonic–clonic seizures and is usually triggered by dehydration, heat, standing for a long time without movement, hot showers, the sight of blood, pain, swallowing, vomiting, and or sudden stress. History is usually the clue to distinguishing syncope from epileptic seizures: There is initially pallor and sweating followed by blurring of vision, dizziness, nausea, and then gradual collapse with loss of consciousness. These symptoms are present in most, although not necessarily all patients with syncope and can sometimes be manifestations of complex partial seizures. Much more important is the fact that such prodromal features have an insidious onset and build up gradually, often arising from a state of malaise when they precede syncope. However when they precede an epileptic convulsion, such features usually start suddenly are short in duration, paroxysmal and are followed by other manifestations of complex partial seizures such as stereotyped automatisms. Abdominal pain, a common aura in temporal lobe epilepsy, occurs in vasovagal syncope, and can be a trigger or a consequence of that process (intestinal vagal discharge). Urinary incontinence and a brief period of convulsive jerks are not uncommon in vasovagal syncope. These occur with a frequency of 10% and 50%, respectively. Postictal confusion only rarely occurs, and the rule is the occurrence of only brief postictal tiredness with a subsequent remarkable ability to resume planned activities. Most children with vasovagal syncope have an affected 1st-degree relative; reports demonstrate

autosomal dominant inheritance at least in some families. The EEG is normal and the tilt test has been used for diagnostic purposes in selected cases. In most cases with typical history, this test is not needed. **Vagovagal syncope** can progress to convulsive seizure if the asystole is sufficiently prolonged. Sudden cold exposure to the face or to the body can also trigger vagal syncope. Syncope has been reported (rarely) to occur in association with cough, tight hair braiding, and hair combing. **Orthostatic hypotension and orthostatic intolerance** manifest symptoms that develop during upright standing and can be relieved by recumbence. **Postural tachycardia syndrome,** the pathophysiology of which presumably involves an excessive sympathetic discharge resulting in increased heart rate and vasoconstriction that can lead to decreased peripheral perfusion, is usually a disease of adolescent females that is characterized by upright syncope/near syncope, and tachycardia with normal or even increased blood pressure during the episode. Primary autonomic failure is rare in children, and familial dysautonomia is the only relatively common form. **Familial dysautonomia** is a disease common in Ashkenazi Jews and is characterized by absence of overflow emotional tears, depressed patellar reflexes, and lack of a flare reaction following intradermal histamine. **Dopamine β-hydroxylase deficiency** is a very rare cause of primary autonomic failure, and is characterized by a complicated perinatal course (hypotension, hypotonia, hypothermia), ptosis, highly arched palate, hyperflexible joints, impaired ejaculation, and nocturia. The tilt test causes a drop in both blood pressure and heart rate in patients with classic vasovagal syncope. It results in a blood pressure drop with minimal change in heart rate in autonomic failure, and in blood pressure drop and an increase in heart rate in postural tachycardia syndrome. Management of syncope centers on avoidance of precipitating factors (maintenance of hydration, avoidance of standing still, rising slowly from sitting, first-aid measures, raising of the legs, positioning) and treatment of any accompanying or underlying medical conditions (anemia, adrenal insufficiency, cardiac, etc.). In addition, **salt supplementation (2-4 g/day),** β-blockers (e.g., metoprolol at a starting dose of 1-2 mg/kg once per day up to a maximum of 6 mg/kg/day), or fluorohydrocortisone (0.05-0.1 mg/day) therapy may be needed in selected cases.

Cardiac Syncope

See Chapter 435.5.

Long QT syndromes (LQT) can cause life-threatening “pallid” or white syncope. Accompanying this are ventricular arrhythmias, usually torsades de pointes or even ventricular fibrillation. There are more than 10 types of prolonged QT syndrome. When accompanied by congenital deafness, it is part of the autosomal recessive Jervell and Lange-Nielson syndrome (type 1, LQT 1, associated with *KvLQT1* potassium channel mutation). The Romano-Ward syndrome is an autosomal dominant syndrome with incomplete penetrance that is characterized by episodes of lying still like a dead body for several seconds before the anoxic convulsive episode (LQT 2 associated with an *HERG* potassium channel mutation). LQT 3 is associated with an *SCN1A* sodium channel mutation, LQT 4 with ankyrin protein mutation, LQT 5 (milder form) with *KCNE1* mutations, LQT 6 with *KCNE2* potassium gene mutations, LQT 9 with caveolin sodium channel–related protein mutations, and LQT 10 with *SCN4B* sodium channel mutations. LQT 7 and LQT 8 are of particular interest because of associated clinical and neurologic manifestations. LQT 7 (Andersen-Tawil) syndrome is associated with periodic paralysis, skeletal developmental abnormalities, clinodactyly, low-set ears, and micrognathia (mutations in *KCNJ2* gene). LQT 8 or the Timothy syndrome (mutations in the calcium channel gene *CACNA1c*) manifests congenital heart disease, autism, syndactyly, and immune deficiency. All family members of an affected LQT syndrome individual should be investigated. Affected individuals need insertion of cardiac defibrillators, and their families should be taught CPR. As a rule, children with new-onset seizure disorder should get an electrocardiogram to rule out LQT syndrome masquerading as seizure disorder. Cardiac syncope is usually sudden without the gradual onset and the symptoms that accompany vagal syncope. Aortic stenosis can cause sudden syncope at the height of the exercise (usually hypertrophic), or directly at the end (usually valvular) and, if suspected, warrants an echocardiogram.

Other Causes of Syncope

Syncope that is not neurally mediated or cardiac in origin is caused by a decrease in blood volume, or a mechanical disruption of brain perfusion. Systemic diseases that lead to syncope by affecting blood volume (e.g., adrenal insufficiency) are usually first brought to medical attention by other accompanying signs and symptoms. In **stretch syncope**, which occurs mostly in adolescents while stretching the neck and the trunk backward and the arms outward, or during flexion of the neck, the presumed mechanism is mechanical disruption of brain perfusion caused by compression of the vertebral arteries. In some cases, this may be associated with an abnormally prolonged stylomastoid process compressing the carotids. If the latter condition is suspected, then neuroimaging (CT, MRI) is required for proper diagnosis of the stylomastoid anomaly.

Sporadic and Familial Hemiplegic Migraine

This is a rare type of migraine with a motor aura of weakness. Attacks begin as early as 5-7 yr of age. In a genetically susceptible person, attacks may be precipitated by head trauma, exertion, or emotional stress. The 3 genes so far identified are *SCN1A* (neuronal sodium channel subunit), *CACNA1*A (neuronal calcium channel subunit), and *ATP1A2* (sodium potassium adenosine triphosphatase subunit). However at least a quarter of the affected families, and most of the sporadic cases do not carry a mutations in these 3 genes. Headaches occur in all attacks in most patients. The presence of negative phenomena (e.g., numbness, visual scotomas) in addition to positive phenomena (pins and needles, flickering lights), and the progressive and successive occurrence of visual, sensory, motor, aphasic, and basilar signs and symptoms, in that order, help differentiate these attacks from epileptic seizures. Persistent cerebellar deficits (e.g., nystagmus, ataxia) may be present. Verapamil, acetazolamide, and lamotrigine have been successfully used to prevent attacks and verapamil and ketamine have been used for the acute episode, while ergot derivatives, nimodipine, Midrin (isometheptene mucate, dichloralphenazone, and paracetamol), and probably triptans and propranolol are to be avoided because of concerns of exacerbating the attacks. Interestingly, the co-occurrence of epileptic seizures has been reported in a minority of patient with hemiplegic migraine. It is important also to note that recurrent attacks akin to hemiplegic migraine can be symptomatic of Sturge-Weber syndrome or various metabolic diseases (e.g., mitochondrial encephalopathy with lactic acidosis and stroke-like episodes).

Benign Paroxysmal Vertigo of Childhood

This is a common migraine equivalent that consists of brief seconds-to-minutes episodes of vertigo that is often accompanied by postural imbalance and nystagmus. It is important to note that vertigo does not always refer to a spinning motion; it can also refer to a backward or forward motion (vertigo titubant) where children sometimes report that objects are moving toward them. The child appears frightened during the episode. Diaphoresis, nausea, vomiting, and, rarely, tinnitus may be present. Episodes usually remit by 6 yr of age. MRI and EEG are normal, but caloric testing, if done, can show abnormal vestibular function. Diphenhydramine, 5 mg/kg/day (maximum of 300 mg/day) may be used for a cluster of attacks. Preventive therapy with cyproheptadine may be rarely needed for frequent attacks.

Cyclic Vomiting Syndrome

This syndrome is another related periodic migraine variant that can respond to antimigraine or antiepileptic drugs. This and other periodic syndromes have been associated with mutations that also can cause hemiplegic migraine.

The “Alice in Wonderland” Syndrome

This is the episodic experience of transient distortions of body image or visual images that, most often, constitute a migraine equivalent. It also can be an epileptic phenomenon.

Migraine-Induced Syncope

Migraine, usually of the basilar variety, can trigger vasovagal syncope and, less commonly, epileptic seizures. Careful elicitation of the history of a migrainous prelude to the syncope helps in identifying these phenomena.

Psychologic Disorders

Psychogenic nonepileptic seizures are conversion reactions that are usually suspected clinically based on the characteristics of the spells (Table 594-2). The diagnosis can be confirmed by video EEG with capture of an episode to eliminate any residual doubts about their nature, as they can often occur in patients who also have epileptic seizures. They are best managed acutely by reassurance about their relatively benign nature and by a supportive attitude while at the same time avoiding positive reinforcement of the episodes. Psychiatric evaluation and follow-up are needed to uncover underlying psychopathology, and to establish continued support as psychogenic seizures can persist over long periods of time. **Malingering** and **factitious disorder imposed on another (formerly called Munchausen syndrome by proxy)** are often difficult to diagnose but an approach similar to that for psychogenic seizures, including video-EEG monitoring, is often helpful.

Paroxysmal Extreme Pain Disorder

Paroxysmal extreme pain disorder was previously called familial rectal pain syndrome. This syndrome (caused by the *SCN9A* sodium channel gene mutation) usually starts in the neonatal period or infancy and persists throughout life. Autonomic manifestations predominate initially, with skin flushing in all cases and harlequin color change and tonic attacks in most. Dramatic syncope with bradycardia and sometimes asystole are common. Later, the disorder is characterized by attacks of excruciating deep burning pain often in the rectal, ocular, or jaw areas, but also diffusely in some. Attacks are triggered by defecation, cold, wind, eating, and emotion. Carbamazepine is used, but the response is often incomplete. Gain-of-function Na(v)1.7 mutations are known to cause two neuropathic **pain** syndromes: inherited **erythromelalgia** and **paroxysmal extreme pain syndrome**. These syndromes are inherited in a dominant trait; they usually begin in childhood or infancy, and are characterized by attacks of severe neuropathic **pain** accompanied with autonomic symptoms. In addition, small fiber neuropathy and chronic nonparoxysmal **pain** have been described in patients harboring gain-of-function mutations in Na(v)1.7 channel. Loss-of-function mutations in Na(v)1.7 are extremely rare and invariably cause **congenital inability to perceive pain.**

Autonomic Storms (Diencephalic Seizures)

Spells of hyperhidrosis, changes in blood pressure, temperature and autonomic instability occur in patients with severe diffuse brain injury or localized hypothalamic injury and have been termed autonomic storms. The term *diencephalic seizures* is discouraged as these are not truly seizures. Therapy is difficult and has included, with mixed results, clonidine, anticonvulsants, cyproheptadine, morphine, and sympathectomy. Serotonin syndrome caused by antidepressants, stimulants, opioids, certain herbs like St. John's Wart and some other medications can produce similar symptoms, and if not recognized, can at times be fatal as can be the similar neuroleptic malignant syndrome caused by antipsychotic medications.

MOVEMENT DISORDERS AND OTHER ABNORMAL MOVEMENTS AND POSTURES

Neonatal Jitteriness and Clonus

Jitteriness consists of equal backward and forward movements of limbs, occurring spontaneously, or triggered by touch or loud sounds. Movement suppression by stimulus removal or by relaxing the affected limbs, the lack of autonomic symptoms, and the clear difference from the 2-phased (fast contraction, slow relaxation) clonic activity and the very quick myoclonic jerks, point to a nonepileptic event.

Table 594-2 Comparison of Generalized Seizures and Some Disorders That Can Mimic Them

CONDITION	PRECIPITANTS (MAY NOT APPLY TO ALL PATIENTS)	PRODROME	ICTAL SYMPTOMS	POSTICTAL SYMPTOMS
Generalized seizures	Sleep deprivation, television, video games, visual patterns, and photic stimulation	Rarely irritability or nonspecific behavioral changes	Usually 2-3 min Consciousness might be preserved if atonic, or in some, tonic seizures Synchronous bilateral movements Tongue biting	Delayed recovery with postictal depression, incontinence (may be ictal also)
Syncope: vasovagal Syncope with reflex anoxic seizures Syncope: trigeminal vagal Syncope: orthostatic	Fatigue, emotional stress, dehydration, vomiting, choking, swallowing Minor bump to head, upsetting surprises Cold water on face Standing up, bathing, awakening	Blurring of vision, tinnitus, dizziness Crying in breath-holding spells	Loss of consciousness for seconds, pallor and rarely reflex anoxic seizures	Rapid recovery with no postictal depression
Hyperekplexia	Auditory and tactile stimuli	None	Tonic stiffening, cyanosis if severe, nonfatigable nose-tap–induced startles	Depending on severity, may have postictal depression
Cardiac	Exercise	None	Loss of consciousness, often only few seconds, pallor	Rarely
Psychogenic	Suggestion, stress	None	Eyes closed Asynchronous flailing limb movements that vary between attacks No injury, closed eyelids May respond to suggestion during "loss of consciousness" Usually longer than 2-3 min	No postictal depression

Adapted from Obeid M, Mikati MA: Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy, Pediatr Neurol *37(5):309–316, 2007.*

Hypocalcemia, hypoglycemia, drug withdrawal, and hypoxic–ischemic encephalopathy are possible etiologies. **Clonus** as a result of corticospinal tract injury usually occurs in later infancy and childhood and can be stopped by change in position.

Hyperekplexia (Stiff Baby Syndrome) and Pathologic Startles

Hyperekplexia is a rare, sporadic or dominantly inherited disorder with neonatal onset of life-threatening episodes of tonic stiffening that precipitate apnea and convulsive hypoxic seizures.

Stiffness may result in difficulty in swallowing, choking spells, hip dislocations, umbilical or inguinal hernias, and delayed motor development. Stiffness in the neonatal form improves by 1 yr of age and may disappear during sleep.

The genetic cause is a defect in the α or β subunits of the strychnine-sensitive glycine receptors. It is characterized by a triad of generalized stiffness, nocturnal myoclonus, and later a pathologic startle reflex. A specific diagnostic sign can be elicited by tapping the nose, which produces a nonfatigable startle reflex with head retraction. Bathing, sudden awakening, and auditory or tactile stimuli can induce attacks. The differential diagnosis includes congenital stiff person syndrome, startle epilepsy, myoclonic seizures, neonatal tetany, phenothiazine toxicity, and Schwartz-Jampel syndrome. Making a prompt diagnosis is extremely important to initiate treatment with clonazepam as hypoxic brain injury can result from a prolonged episode. Other antiepileptics have also been effective. Repeatedly flexing the baby at the neck and hips (the Vigevano maneuver) can abort the episodes.

In other children after brain injury, and in many patients with cerebral palsy, an exaggerated startle reflex can occur. This is more common than hyperekplexia. In Tay-Sachs disease and similar gangliosidoses, exaggerated startle to sound occurs and has been, inappropriately, interpreted as hyperacusis.

Benign Paroxysmal Torticollis of Infancy

This condition typically presents as morning episodes of painless retrocollis, and later, torticollis, often triggered by changes in posture. Attacks may start with abnormal ocular movements, and progress to stillness in an abnormal posture. This usually lasts for minutes or hours and, at times, days. Neurologic exam between attacks, EEG, and neuroimaging are normal. It affects girls more than boys (3:1), often begins before 3 mo of age, and spontaneously remits before the age of 5 yr. Medical therapy is not needed. It is considered to be a migraine equivalent and cosegregates with migraine in families.

Sandifer Syndrome

Gastroesophageal reflux in infants may cause paroxysmal episodes of generalized stiffening and opisthotonic posturing that may be accompanied by apnea, staring, and minimal jerking of the extremities. Episodes often occur 30 min after a feed. In older children, this syndrome manifests with episodic dystonic or dyskinetic movements consisting of latero-, retro-, or torticollis, the exact pathophysiology of which remains elusive.

Alternating Hemiplegia of Childhood

This is a rare, often severe, disorder that consists of attacks of flaccid hemiplegia affecting 1 or both sides lasting minutes to days, starting in the 1st 18 mo of life. Earlier manifestations include paroxysmal nystagmus, which is often monocular and ipsilateral to the hemiplegia. Dystonic and tonic spells often occur and can be confused with seizures and the hemiplegia with Todd paralysis. Attacks can be triggered by bathing, cold, fatigue, hyperthermia, and emotional stress, and they remit during sleep and for about 15 minutes or so after waking up. Most cases are caused by mutations in the *ATP1A3* gene while, rarely, a similar clinical picture can occur as a result of mutations in *ATP1A2* or in the glucose transporter 1 *(GLUT1/SLC2AI)* gene mutations. Flunarizine 2.5-15 mg/day reduces the frequency of the attacks. Most children ultimately develop ataxia, developmental delay, and persistent choreoathetosis.

Paroxysmal Dyskinesias and Other Movement Disorders

These disorders are characterized by sudden attacks that consist of choreic, dystonic, ballistic, or mixed movements (Table 594-3). A sensation of fatigue or weakness confined to 1 side may herald an attack. Consciousness is preserved and patients may be able perform a motor activity, like walking, despite the attack. The variability in the pattern of severity and localization between different attacks may also help in differentiating them from seizures. The frequency of attacks increases in adolescence, and steadily decreases in the 3rd decade. Neurologic exam between attacks, EEG, laboratory investigations, and imaging studies are normal. These dyskinesias often respond to phenytoin, carbamazepine, clonazepam, or to antidopaminergic drugs such as haloperidol. **Drug reactions** can result in abnormal movements such as **oculogyric crisis** with many antiemetics, choreoathetosis with phenytoin, dystonia and facial dyskinesias with antidopaminergic drugs, and tics with carbamazepine. Strokes, focal brain lesions, connective tissue disorders (e.g., systemic lupus erythematosus), vasculitis, or metabolic and genetic disorders can also cause movement disorders. Mutations of the glucose transporter 1 *(GLUT1/SLC2AI)* gene have been described in patients with **exercise-induced dyskinesia**.

Motor Tics

These are movements that are under partial control, and are associated with an urge to do them and with a subsequent relief. They are usually exacerbated by emotions, and often change in character over time. In patients with tics who have Tourette syndrome, there is often a family history of tics and/or obsessive compulsive disorder or personality traits.

Episodic Ataxias

Episodic ataxia encompasses 7 clinically and genetically heterogeneous syndromes, only 2 of which (types 1 and 2) have been described in a large number of families. Type 1 is caused by mutations in the voltage-gated potassium channel Kv1.1. It consists of brief episodes (seconds to minutes) of cerebellar ataxia, and occasional partial seizures with interictal myokymia as a main diagnostic feature. Type 2 is characterized by longer attacks (minutes to hours) and interictal cerebellar signs. It is caused by mutations in the voltage-gated calcium channel gene *CACNA1A*. This type is more responsive than type 1 to acetazolamide that reduces the frequency and severity of attacks, but not the interictal signs and symptoms.

Benign Myoclonus of Early Infancy, Shuddering Attacks, and Chin Trembling

Benign myoclonus consists of myoclonic jerks of the extremities in wakefulness and sometimes also in sleep. It has been suggested by some that these attacks are in the same spectrum as shuddering attacks. **Shuddering attacks** are characterized by rapid tremor of the head, shoulder, and trunk, lasting a few seconds, often associated with eating, and recurring many times a day. Others have considered shuddering as an early manifestation of essential tremor as family history of essential tremor is often present. The clinical events in either of these can be mistaken for infantile spasms, but ictal and interictal EEG, MRI, and development are normal. Spontaneous remission occurs in both usually within a few months. **Hereditary chin trembling** at a frequency faster than 3 Hz starting shortly after birth and precipitated by stress has been described in several families.

A novel type of nonepileptic attack with infantile onset characterized in 3 patients as clusters of repeated head drops, mimicking epileptic negative myoclonus of the neck, accompanied by crying. The episodes occurred for 5 or 6 mo and disappeared by the end of the 1st yr. Language and cognition were normal This is a different form of myoclonic activity that may complicate the diagnosis of infantile spasms and West syndrome; thorough EEG investigation is needed in such cases.

Brainstem Dysfunction

Decorticate or decerebrate posturing that mimics epileptic tonic seizures may be secondary to decompensated hydrocephalus,

Table 594-3 Differential Diagnoses of Various Types of Paroxysmal Dyskinesia

Features	PKD	PNKD MR1+	PNKD MR1–	PED	PHD
Nomenclature	PKC	PDC, FPC	PDC, FPC	PEDt	ADNFLE
Inheritance	AD–16q	AD–2q35	AD–2q13	AD/AR	AD–20q13, 15q24, 1q21, 8p21
Age at onset (yr)	1-20	<1-12	1-23	Usually childhood	Usually childhood
Triggers	Sudden whole-body movement	Coffee, alcohol, stress	Exercise	After 10-15 minutes of exercise	Sleep
Clinical features	Chorea, athetosis, ballismus, dystonia	Chorea, athetosis, dystonia, ballismus	Chorea, athetosis, dystonia, ballismus	Mainly leg dystonia	Wakes up with dystonic posture
Usual duration	<1-5 min	10 min to 1 hr	10 min to 2-3 hr	10-15 min	<1 min
Frequency	1-20/day	1/week	1/week	Unclear	Several/night
Associations	Infantile seizures, migraine, writer's cramp, essential tremor	Migraine	Epilepsy	RE-PED-WC	
Medication	Carbamazepine Phenytoin Oxcarbazepine	Clonazepam Benzodiazepine	Clonazepam Benzodiazepine	Acetazolamide L-DOPA	Carbamazepine Oxcarbazepine
Prognosis	Excellent	Excellent, worse than PKD	Minimally worse than PNKD MR1+	Poor medication response	Excellent

AD, autosomal-dominant; ADNFLE, autosomal-dominant nocturnal frontal lobe epilepsy; AR, autosomal-recessive; FPC, familial paroxysmal choreoathetosis; MR1+, myofibrillogenesis regulator 1-positive; MR1–, myofibrillogenesis regulator 1-negative; PDC, paroxysmal dystonic choreoathetosis; PED, paroxysmal exercise-induced dyskinesia; PEDt, paroxysmal exercise-induced dystonia; PHD, paroxysmal hypnogenic dyskinesia; PKC, paroxysmal kinesigenic choreoathetosis; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; RE-PED-WC, rolandic epilepsy–paroxysmal exercise-induced dystonia–writer's cramp.

From Friedman NR, Ghosh D, Moodley M: Syncope and paroxysmal disorders other than epilepsy. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Table 65-1.*

hemorrhage, or other causes of sudden rises in intracranial pressure that lead to brainstem dysfunction. In addition, crowding of the posterior fossa and near herniation, the so-called cerebellar fits can also lead to abnormal extensor posturing, drop attacks, and varying degrees of altered consciousness and respiratory compromise. Historically secondary to undiagnosed posterior fossa tumors in the preneuroimaging era, "cerebellar fits" mostly occur in the context of Chiari I malformations.

Psychologic Disorders

Many psychologic disorders can be mistaken for epileptic seizures. Pleasurable behavior similar to masturbation may occur from infancy onward, and may consist of rhythmical rocking movement in a sitting or lying position, or rhythmic hip flexion and adduction. **Masturbation** may occur in girls 2-3 yr of age and is often associated with perspiration, irregular breathing, and grunting, but no loss of consciousness. Occasionally this is associated with child abuse or with other psychopathology. **Stereotypies,** or repetitive movements that are more complex than tics and do not change and wax and wane like tics (e.g., head banging, head rolling, body rocking, and hand flapping), usually occur in neurologically impaired children. **A mannerism** is a pattern of socially acceptable, situational behavior that is seen in particular situations such as gesturing when talking. Mannerisms should not be confused with stereotypies which are generally pervasive over almost every other activity such as head-shaking or hand-flapping in multiple situations. Stereotypies, unlike mannerisms, increase with stress. Unlike tics and mannerisms, stereotypies usually start before the age of 3 yr, involve more body parts, are more rhythmic and most importantly occur with engrossment with an object or activity of interest and do not have a premonitory urge that increases with attempts to suppress them as children rarely try to suppress stereotypies. **Panic and anxiety attacks** have been described in children; at times, these may be clinically indistinguishable from actual epileptic seizures, and therefore may necessitate video-EEG monitoring. **Rage attacks** usually occur in patients with personality disorder and are usually not seizures although rare cases of partial seizures can manifest as rage attacks. **Hyperventilation spells** can be precipitated by anxiety and are associated with dizziness, tingling, and, at times, carpopedal spasm. **Transient global amnesia** consists of isolated short-term memory loss for minutes to hours that occurs mostly in the elderly. The etiology can be epileptic, vascular, or drug related.

OCULOMOTOR ABNORMALITIES AND VISUAL HALLUCINATIONS

Paroxysmal Tonic Upgaze of Childhood

This usually starts before 3 mo of age, and consists of protracted attacks (hours to days) of continuous or episodic upward gaze deviation, during which horizontal eye movements are preserved. A downbeating nystagmus occurs on downward gaze. Symptoms are reduced or relieved by sleep, exacerbated by fatigue and infections, and spontaneously remit after a few years. Up to 50% of patients may have psychomotor and language delay. Imaging, laboratory, and neuropsychologic examinations are usually nonrevealing. Therapy with low-dose levodopa/carbidopa may be helpful.

Oculomotor Apraxia and Saccadic Intrusions

In oculomotor apraxia saccadic eye movements are impaired. Sudden head turns compensating for lateral gaze impairment mimic seizures. This disorder may be idiopathic (Cogan oculomotor apraxia) or may occur in the context of ataxia telangiectasia or lysosomal storage diseases. Genetic defects in DNA repair mechanisms have been implicated in at least 4 spinocerebellar ataxia disorders that are accompanied by oculomotor apraxia. A selective loss of Purkinje cells required to suppress omnipause neurons and initiate saccadic eye movement is believed to occur in those disorders. Saccadic intrusions are involuntary sudden conjugate eye movements away from the desired eye position. These are not necessarily pathologic.

Spasmus Nutans

This disorder presents with a triad of nystagmus, head tilt, and head nodding. If diurnal fluctuation occurs, symptoms may look like epileptic seizures. Brain MRI should be performed, as the triad has been

associated with masses in the optic chiasm and third ventricle. Retinal disease should also be ruled out. In the absence of these associations, remission occurs before 5 yr of age.

Opsoclonus Myoclonus Syndrome

The so-called dancing eyes refers to continuous, random, irregular, and conjugate eye movements that may fluctuate in intensity. They usually accompany myoclonus and ataxia ("dancing feet"). Encephalitis and neuroblastoma are possible causes. Therapy is by treating the underlying etiology, but adrenocorticotropic hormone (ACTH), corticosteroids, and clonazepam may be needed. Rituximab has been studied and preliminary trials suggest it may be effective as well.

Daydreaming and Behavioral Staring

Staring may be a manifestation of absence seizures, which should be differentiated from daydreaming, behavioral staring because of fatigue, and inattention. Episodes of staring only in certain settings (e.g., school) are unlikely to be seizures. In addition, responsiveness to stimulation such as touch and lack of interruption of playing activity characterizes nonepileptic staring.

Visual Hallucinations

Visual perceptions in the absence of external stimuli, or visual hallucinations, are usually accompanied by other neurologic signs and symptoms when they occur in the context of seizures. An exception is occipital seizures, which can manifest with isolated and unformed visual hallucinations and may be accompanied by headache and nausea, making them difficult to differentiate from migraine. However, occipital seizures are characterized by colorful, shapes, circles and spots lasting seconds and confined to 1 hemifield, while migrainous auras usually last minutes, and consist of black-and-white lines, scotomas, and or fortification spectra that start in the center of vision. Hallucinations can also be secondary to drug exposure, midbrain lesions, and psychiatric illnesses. In addition, retinal-associated hallucinations can occur in the form of flashes of light in the context of inflammatory etiologies, trauma, or optic nerve edema.

SLEEP DISORDERS

Paroxysmal nonepileptic sleep events are more common in epileptic patients than in the general population, which makes their diagnosis difficult. Semiology, timing of events, and if needed video-EEG and polysomnography help in distinguishing epileptic from nonepileptic events. Parasomnias typically occur less than once or twice a night; more frequent episodes suggest epileptic seizures. Of note, the EEG pattern of frontal lobe epileptic seizures may be similar to the one seen in a normal arousals, making their diagnosis challenging, especially that they have nonspecific hypermotor manifestations such as thrashing, body rocking, kicking, boxing, pedaling, bending, running, and various vocalizations. The diagnosis of such epileptic seizures is made on the basis of highly stereotyped events arising several times a night from nonrapid eye movement sleep.

Benign Sleep Myoclonus and Neonatal Sleep Myoclonus

Neonatal sleep myoclonus consists of repetitive, usually bilateral rhythmic jerks involving the upper and lower limbs during nonrapid eye movement sleep, sometimes mimicking clonic seizures. A slow (1 Hz) rocking of the infant in a head-to-toe direction is a specific diagnostic test that may reproduce the myoclonus. The lack of autonomic changes, occurrence only in sleep, and suppression by awakenings may help in differentiating these events from epileptic seizures. Remission is spontaneous at 2-3 mo of age. In older children and adults, sleep myoclonus consists of random myoclonic jerks of the limbs.

Nonrapid Eye Movement Partial Arousal Disorders

Brief **nocturnal confusional arousals** occurring 1-2 hr after sleep in stage 4 sleep are normal in children. Such episodes can vary from chewing, sitting up, and mumbling to agitated sleep walking, and usually last for 10-15 min. **Night terrors** similarly occur a few hours after going to sleep in stage 3 or 4 of sleep, most often at 2-7 yr of age and more so in boys. The child screams; appears terrified; has dilated pupils, tachycardia, tachypnea, unresponsiveness, agitation, and thrashing that increase with attempts to be consoled; is difficult to arouse; and may have little or no vocalization. In older children with persistent night terrors, an underlying psychologic etiology may be present. Diagnosis is based on the history. However, rarely, video EEG monitoring may be needed. At times, the use of bedtime diazepam (0.2-0.3 mg/kg) or clonazepam (0.01 mg/kg) may help control the problem while psychologic factors are being investigated. **Restless leg syndrome** can cause painful leg dysesthesias that cause nocturnal arousals and insomnia. It can be either genetic or associated with iron deficiency, systemic illness, or some drugs. Therapy depends upon treating the underlying cause and, if needed, on dopaminergic drugs such as levodopa/carbidopa, or antiepileptics like gabapentin.

Rapid Eye Movement Sleep Disorders

Nightmares and **sleep paralysis** are common disorders. Unlike night terrors, nightmares tend to occur later during the night and the child has a memory of the event.

Sleep Transition Disorders

Nocturnal head banging **(jactatio capitis nocturna)**, rolling, or body rocking often occurs in infants and toddlers as they are trying to fall asleep. These usually remit spontaneously by 5 yr of age. No specific therapy is needed.

Narcolepsy-Cataplexy Syndrome

Narcolepsy is characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, hypnogogic hallucinations, and disturbed nighttime sleep. The persistence of rapid eye movement sleep atonia upon awakening or its intrusion during wakefulness lead to sleep paralysis or cataplexy, respectively. Loss of tone in cataplexy occurs in response to strong emotions, and spreads from the face downwards leading to a fall in a series of stages rather than a sudden one. Consciousness is maintained in cataplexy. A selective loss of hypocretin-secreting neurons in the hypothalamus is at the origin of this disorder. The fact that DQB1*0602 is a predisposing HLA allele identified in 85-95% of patients with narcolepsy-cataplexy suggests an autoimmune-mediated neuronal loss. Diagnosis is based on the **multiple sleep latency test**, and therapy relies on scheduled naps, amphetamines, methylphenidate, tricyclic antidepressants, and counseling about precautions in work and driving.

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Chapter 595

Headaches

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Headache is a common complaint in children and adolescents. Headaches can be a primary problem or occur as a symptom of another disorder, representing a secondary problem. Recognizing this difference is essential for choosing the appropriate evaluation and treatment to ensure successful management of the headache. Primary headaches are most often recurrent, episodic headaches and for most children are sporadic in their presentation.

The most common forms of primary headache of childhood are migraine and tension-type headaches (Table 595-1). Other forms of

Table 595-1 Classification of Headaches (ICHD-3 Beta Code Diagnosis)

MIGRAINE
Migraine with or without aura
Migraine with typical aura (with or without headache)
Migraine with brainstem aura
Hemiplegic migraine (sporadic or familial types 1, 2, 3, or other genetic loci)
Retinal migraine
Chronic migraine
Complications of Migraine
Status migrainosus
Persistent aura without infarction
Migrainous infarction
Migraine aura-triggered seizure
Episodic Syndromes That May Be Associated with Migraine
Recurrent gastrointestinal disturbance
Cyclical vomiting syndrome
Abdominal migraine
Benign paroxysmal vertigo
Benign paroxysmal torticollis

TENSION-TYPE HEADACHE (TTH)
Infrequent episodic tension-type headache associated with or without pericranial tenderness
Frequent episodic tension-type headache associated with or without pericranial tenderness
Chronic tension-type headache associated with or without pericranial tenderness
Probable tension-type headaches

TRIGEMINAL AUTONOMIC CEPHALALGIAS (TACS)
Cluster headache (episodic or cluster)
Paroxysmal hemicrania (episodic or cluster)
Short-lasting unilateral neuralgiform headache attacks with or without conjunctival injection and tearing (SUNCT)
Episodic SUNCT
Chronic SUNCT
Short-lasting unilateral neuralgiform headache attacks with or without cranial autonomic symptoms (SUNA)
Episodic SUNA
Chronic SUNA
Hemicrania continua
Probable trigeminal autonomic cephalalgias

OTHER PRIMARY HEADACHE DISORDERS
Primary cough headache
Primary exercise headache
Primary headache associated with sexual activity
Primary thunderclap headache
Cold-stimulus headache (external application, ingestion, or inhalation)
External-pressure headache
External-compression headache
External-traction headache
Primary stabbing headache
Nummular headache
Hypnic headache
New daily persistent headache (NDPH)

HEADACHE ATTRIBUTED TO TRAUMA OR INJURY TO THE HEAD AND/OR NECK
Acute headache attributed to traumatic (mild, moderate, or severe) injury to the head
Persistent headache attributed to traumatic (mild, moderate, or severe) injury to the head
Acute or persistent headache attributed to whiplash
Acute or persistent headache attributed to craniotomy

HEADACHE ATTRIBUTED TO CRANIAL OR CERVICAL VASCULAR DISORDER
Headache attributed to ischemic stroke or transient ischemic attack
Headache attributed to nontraumatic intracerebral hemorrhage
Headache attributed to nontraumatic subarachnoid hemorrhage (SAH)
Headache attributed to nontraumatic acute subdural hemorrhage (ASDH)
Headache attributed to unruptured vascular malformation
Headache attributed to unruptured saccular aneurysm
Headache attributed to arteriovenous malformation (AVM)
Headache attributed to dural arteriovenous fistula (DAVF)
Headache attributed to cavernous angioma
Headache attributed to encephalotrigeminal or leptomeningeal angiomatosis (Sturge-Weber syndrome)
Headache attributed to arteritis
Headache attributed to giant cell arteritis (GCA)
Headache attributed to primary angiitis of the central nervous system (PACNS)
Headache attributed to secondary angiitis of the central nervous system (SACNS)
Headache attributed to cervical carotid or vertebral artery disorder
Headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection
Post-endarterectomy headache
Headache attributed to carotid or vertebral angioplasty
Headache attributed to cerebral venous thrombosis (CVT)
Headache attributed to other acute intracranial arterial disorder
Headache attributed to an intracranial endovascular procedure
Angiography headache
Headache attributed to reversible cerebral vasoconstriction syndrome (RCVS)
Headache attributed to intracranial arterial dissection
Headache attributed to genetic vasculopathy
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS)
Headache attributed to another genetic vasculopathy
Headache attributed to pituitary apoplexy

HEADACHE ATTRIBUTED TO NONVASCULAR INTRACRANIAL DISORDER
Headache attributed to increased cerebrospinal fluid pressure
Headache attributed to idiopathic intracranial hypertension (IIH)
Headache attributed to intracranial hypertension secondary to metabolic, toxic, or hormonal causes
Headache attributed to intracranial hypertension secondary to hydrocephalus
Headache attributed to low cerebrospinal fluid pressure
Postdural puncture headache
Cerebrospinal fluid fistula headache
Headache attributed to spontaneous intracranial hypotension
Headache attributed to noninfectious inflammatory disease
Headache attributed to neurosarcoidosis
Headache attributed to aseptic (noninfectious) meningitis
Headache attributed to other noninfectious inflammatory disease
Headache attributed to lymphocytic hypophysitis
Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL)
Headache attributed to intracranial neoplasm
Headache attributed to colloid cyst of the third ventricle
Headache attributed to carcinomatous meningitis
Headache attributed to hypothalamic or pituitary hyper- or hyposecretion
Headache attributed to intrathecal injection
Headache attributed to epileptic seizure
Hemicrania epileptica
Postictal headache
Headache attributed to Chiari malformation type I (CM1)
Headache attributed to other nonvascular intracranial disorder

Table 595-1 Classification of Headaches (ICHD-3 Beta Code Diagnosis)—cont'd

HEADACHE ATTRIBUTED TO A SUBSTANCE OR ITS WITHDRAWAL Headache attributed to use of or exposure to a substance Nitric oxide (NO) donor-induced headache Phosphodiesterase (PDE) inhibitor-induced headache Carbon monoxide (CO)-induced headache Alcohol-induced headache Monosodium glutamate (MSG)-induced headache Cocaine-induced headache Histamine-induced headache Calcitonin gene-related peptide (CGRP)-induced headache Headache attributed to exogenous acute pressor agent Headache attributed to occasional or long-term use of nonheadache medication Headache attributed to exogenous hormone *Medication-Overuse Headache (MOH)* Ergotamine-overuse headache Triptan-overuse headache Simple analgesic-overuse headache Paracetamol (acetaminophen)-overuse headache Acetylsalicylic acid-overuse headache Other non-steroidal antiinflammatory drug (NSAID)-overuse headache Opioid-overuse headache Combination analgesic-overuse headache *Headache Attributed to Substance Withdrawal* Caffeine-withdrawal headache Opioid-withdrawal headache Estrogen-withdrawal headache	**HEADACHE OR FACIAL PAIN ATTRIBUTED TO DISORDER OF THE CRANIUM, NECK, EYES, EARS, NOSE, SINUSES, TEETH, MOUTH, OR OTHER FACIAL OR CERVICAL STRUCTURE** Headache attributed to disorder of cranial bone Headache attributed to retropharyngeal tendonitis Headache attributed to craniocervical dystonia Headache attributed to acute glaucoma Headache attributed to refractive error Headache attributed to heterophoria or heterotropia (latent or persistent squint) Headache attributed to ocular inflammatory disorder Headache attributed to trachelitis Headache attributed to disorder of the ears Headache attributed to acute or chronic or recurring rhinosinusitis Headache attributed to temporomandibular disorder (TMD) Head or facial pain attributed to inflammation of the stylohyoid ligament Headache or facial pain attributed to other disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure
HEADACHE ATTRIBUTED TO INFECTION Acute or chronic headache attributed to bacterial meningitis or meningoencephalitis Persistent headache attributed to past bacterial meningitis or meningoencephalitis Acute or chronic headache attributed to intracranial fungal or other parasitic infection Headache attributed to brain abscess Headache attributed to subdural empyema Headache attributed to systemic infection (acute or chronic)	**HEADACHE ATTRIBUTED TO PSYCHIATRIC DISORDER** Headache attributed to somatization disorder Headache attributed to psychotic disorder
HEADACHE ATTRIBUTED TO DISORDER OF HOMEOSTASIS Headache attributed to hypoxia and/or hypercapnia High-altitude headache Headache attributed to airplane travel Diving headache Sleep apnea headache Dialysis headache Headache attributed to arterial hypertension Headache attributed to pheochromocytoma Headache attributed to hypertensive crisis with or without hypertensive encephalopathy Headache attributed to preeclampsia or eclampsia Headache attributed to autonomic dysreflexia Headache attributed to hypothyroidism Headache attributed to fasting Cardiac cephalalgia Headache attributed to other disorder of homoeostasis	**PAINFUL CRANIAL NEUROPATHIES AND OTHER FACIAL PAINS** Classical trigeminal neuralgia Classical trigeminal neuralgia, purely paroxysmal or with concomitant persistent facial pain Painful trigeminal neuropathy Painful trigeminal neuropathy attributed to acute herpes zoster Postherpetic trigeminal neuropathy Painful posttraumatic trigeminal neuropathy Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque Painful trigeminal neuropathy attributed to space-occupying lesion Painful trigeminal neuropathy attributed to other disorder Glossopharyngeal neuralgia Classical nervus intermedius (facial nerve) neuralgia Nervus intermedius neuropathy attributed to herpes zoster Occipital neuralgia Optic neuritis Headache attributed to ischemic ocular motor nerve palsy Tolosa-Hunt syndrome Paratrigeminal oculosympathetic (Raeder) syndrome Recurrent painful ophthalmoplegic neuropathy Burning mouth syndrome (BMS) Persistent idiopathic facial pain (PIFP) Central neuropathic pain Central neuropathic pain attributed to multiple sclerosis (MS) Central post-stroke pain (CPSP)

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013.*

primary headache, including the trigeminal autonomic cephalalgias, occur much less commonly. Primary headache can progress to very frequent or even daily headaches with chronic migraine and chronic tension-type headaches being increasingly recognized. These more frequent headaches can have an enormous impact on the life of the child and adolescent, as reflected in school absences and decreased school performance, social withdrawal, and changes in family interactions. To reduce this impact, a treatment strategy that incorporates acute treatments, preventive treatments, and biobehavioral therapies must be implemented.

Secondary headache involves headaches that are a symptom of an underlying illness (see Table 595-1). The underlying illness should be clearly present as a direct cause of the headaches. This is often difficult when 2 or more common conditions occur in close temporal association. This frequently leads to the misdiagnosis of a primary headache as a secondary headache. This is, for example, the case when migraine is misdiagnosed as a sinus headache. In general, the key components of a secondary headache are the likely direct cause-and-effect relationship between the headache and the precipitating condition, and the lower likelihood in a specific patient and circumstance of the headaches being the result of a recurrent headache disorder. In addition, once the underlying suspected cause is treated, the secondary headache should resolve. If this does not occur, either the diagnosis must be reevaluated or the effectiveness of the treatment reassessed. *One key clue that additional investigation is warranted is the presence of an abnormal neurologic examination or unusual neurologic symptoms.*

595.1 Migraine

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Migraine is the most frequent type of recurrent headache that is brought to the attention of parents and primary care providers, but it remains underrecognized and undertreated, particularly in children. Migraine is characterized by episodic attacks that may be moderate to severe in intensity, focal in location on the head, have a throbbing quality, and may be associated with nausea, vomiting, light sensitivity, and sound sensitivity. Compared to adults, pediatric migraine is shorter in duration and has a bilateral, often bifrontal, location. Migraine can also be associated with an aura that may be typical (visual, sensory, or dysphasic) or atypical (i.e., hemiplegic, "Alice in Wonderland" syndrome) (Tables 595-2 to 595-6). In addition, a number of migraine variants have been described and, in children, include abdominal related symptoms without headache, and components of the painless periodic syndromes of childhood (see Table 595-1). Treatment of migraine requires the incorporation of an acute treatment plan, a preventive treatment plan if the migraine occurs frequently or is disabling, and a biobehavioral plan to help cope with both the acute attacks and frequent or persistent attacks if present.

EPIDEMIOLOGY

Up to 75% of children report having a significant headache by the time they are 15 yr old. Recurrent headaches are less common, but remain highly frequent. Migraine has been reported to occur in up to 10.6% of children between the ages of 5 and 15 yr, and up to 28% of older

Table 595-2 Migraine Without Aura

A. At least 5 attacks fulfilling criteria B to D
B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following 4 characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least 1 of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 4.*

Table 595-3 Migraine with Typical Aura

A. At least 2 attacks fulfilling criteria B and C
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor, brainstem or retinal symptoms
C. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 minutes
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 6.*

Table 595-4 Migraine with Brainstem Aura

A. At least 2 attacks fulfilling criteria B to D
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor or retinal symptoms
C. At least 2 of the following brainstem symptoms:
   1. Dysarthria
   2. Vertigo
   3. Tinnitus
   4. Hypacusis
   5. Diplopia
   6. Ataxia
   7. Decreased level of consciousness
D. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 minutes
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes, by headache
E. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 7.*

Table 595-5 Vestibular Migraine with Vertigo

A. At least 5 episodes fulfilling criteria C and D
B. A current or past history of 1.1 *Migraine without aura* or 1.2 *Migraine with aura*
C. Vestibular symptoms of moderate or severe intensity, lasting between 5 min and 72 hr
D. At least 50% of episodes are associated with at least 1 of the following 3 migrainous features:
   1. Headache with at least 2 of the following 4 characteristics:
      a. Unilateral location
      b. Pulsating quality
      c. Moderate or severe intensity
      d. Aggravation by routine physical activity
   2. Photophobia and phonophobia
   3. Visual aura
E. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013 (Table 8).*

Table 595-6 Chronic Migraine

A. Headache (tension-type-like and/or migraine-like) on 15 or more days per month for more than 3 mo and fulfilling criteria B and C
B. Occurring in a patient who has had at least 5 attacks fulfilling criteria B to D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*
C. On 8 or more days per month for more than 3 mo, fulfilling any of the following:
   1. Criteria C and D for 1.1 *Migraine without aura*
   2. Criteria B and C for 1.2 *Migraine with aura*
   3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 9.*

adolescents. When the headaches become frequent, they convert into chronic daily headaches in up to 1% of children. When headaches are occurring more than 15 days a month the risk of conversion to a daily headache becomes more prominent. This explains the necessity to treat the headaches aggressively or prevent the headaches altogether, trying to block transformation to chronic daily headaches.

Migraine can impact a patient's life through school absences, limitation of home activities, and restriction of social activities. As headaches become more frequent, their negative impact increases in magnitude. This can lead to further complications including anxiety and school avoidance, requiring a more extensive treatment plan.

CLASSIFICATION AND CLINICAL MANIFESTATIONS

Criteria have been established to guide the clinical and scientific study of headaches; these are summarized in *The International Classification of Headache Disorders*, 3rd edition (ICHD-3 beta). Table 595-1 contrasts the different clinical types of migraine; Tables 595-2 to 595-6 list the specific criteria for migraine types.

Migraine Without Aura

Migraine without aura is the most common form of migraine in both children and adults. The ICHD-3 beta (see Table 595-2) requires this to be recurrent (at least 5 headaches that meet the criteria, but there is no time limit over which this must occur). The recurrent episodic nature helps differentiate this from a secondary headache, as well as separates migraine from tension-type headache, but may limit the diagnosis in children as they may just be beginning to have headaches.

The duration of the headache is defined as 4-72 hr for adults. It has been recognized that children may have shorter-duration headaches, so an allowance has been made to reduce this duration to 2-72 hr or 1-72 hr with diary confirmation. Note that this duration is for the untreated or unsuccessfully treated headache. Furthermore, if the child falls asleep with the headache, the entire sleep period is considered part of the duration. These duration limits help differentiate migraine from both short-duration headaches, including the trigeminal autonomic cephalalgias, and prolonged headaches, like those caused by idiopathic intracranial hypertension (pseudotumor cerebri). Some prolonged headaches may still be migraine, but a migraine that persists beyond 72 hr is classified as a variant termed **status migrainosus.**

The quality of migraine pain is often, but not always, throbbing or pounding. This may be difficult to elicit in young children and drawings or demonstrations may help confirm the throbbing quality.

The location of the pain has classically been described as **unilateral (hemicrania)**; in young children it is more commonly bilateral. A more appropriate way to think of the location would therefore be focal, to differentiate it from the diffuse pain of tension-type headaches. Of particular concern is the exclusively occipital headache because although these can be migraines, they are more frequently secondary to another more proximate etiology such as posterior fossa abnormalities.

Migraine, when allowed to fully develop, often worsens in the face of and secondarily results in altered activity level. For example, worsening of the pain occurs classically in adults when going up or down stairs. This history is often not elicited in children. A change in the child's activity pattern can be easily observed as a reduction in play or physical activity. Older children may limit or restrict their sports activity or exercise during a headache attack.

Migraine may have a variety of associated symptoms. In younger children, nausea and vomiting may be the most obvious symptoms and often outweigh the headache itself. This often leads to the overlap with several of the gastrointestinal periodic diseases, including recurrent abdominal pain, recurrent vomiting, cyclic vomiting, and abdominal migraine. The common feature among all of these related conditions is an increased propensity among children with them for the later development of migraine. Oftentimes, early childhood recurrent vomiting may in fact be migraine, but the child is not asked about or is unable to describe headache pain. Once this becomes clear, the earlier diagnosis of a gastrointestinal disorder is no longer appropriate. When headache is present, vomiting raises the concern of a secondary headache, particularly related to increased intracranial pressure. *One of the red flags for this is the daily or near daily early morning vomiting, or headaches waking the child up from sleep.* When the headaches associated with vomiting episodes are sporadic and not worsening, it is more likely that the diagnosis is migraine. Vomiting and headache caused by increased intracranial pressure are frequently present on first awakening and remit with maintenance of upright posture. In contrast, if a migraine is present on first awakening *(a relatively infrequent occurrence in children)*, getting up and going about normal, upright activities usually makes the headache and vomiting worse.

As the child matures, light and sound sensitivity (**photophobia** and **phonophobia**) may become more apparent. This is either by direct report of the patient, or the interpretation by the parents of the child's activity. These symptoms are likely a component of the hypersensitivity that develops during an acute migraine attack and may also include smell sensitivity **(osmophobia)** and touch sensitivity **(cutaneous allodynia with central sensitization).** Although only the photophobia and phonophobia are components of the ICHD-3 beta criteria, these other symptoms are helpful in confirming the diagnosis and may be helpful in understanding the underlying pathophysiology and determining the response to treatment. The final ICHD-3 beta requirement is the exclusion of causes of secondary headaches, and this should be an integral component of the headache history.

Migraine typically runs in families with reports up to 90% of children having a 1st- or 2nd-degree relative with recurrent headaches. Given the underdiagnosis and misdiagnosis in adults, this is often not recognized by the family and a headache family history is required. When a family history is not identified, this may be the result of either a lack of awareness of migraine within the family or an underlying secondary headache in the child. Any child whose family, upon close and both direct and indirect questioning, does not include individuals with migraine or related syndromes (e.g., motion sickness, cyclic vomiting, menstrual headache) should have an imaging procedure performed to look for anatomic etiologies for headache.

In addition to the classifying features, there may additional markers of a migraine disorder. These include such things as triggers (skipping meals, inadequate or irregular sleep, dehydration and weather changes are the most common), pattern recognition (associated with menstrual periods in adolescents or Monday-morning headaches resulting from changes in sleep patterns over the weekend and nonphysiologic early waking on Monday mornings for school), and premonitory symptoms (a feeling of irritability, tiredness, and food cravings prior to the start of the headache). Although these additional features may not be consistent, they do raise the index of suspicion for migraine and provide a potential mechanism of intervention. In the past, food triggers were considered widely common, but the majority have either been discredited with scientific study or represent such a small number of patients that they only need to be addressed when consistently triggering the headache.

Migraine with Aura

The aura associated with migraine is a neurologic warning that a migraine is going to occur. In the common forms this can be the start of a typical migraine or a headache without migraine, or it may even occur in isolation. For a typical aura, the aura needs to be visual, sensory, or dysphasic, lasting longer than 5 min and less than 60 min with the headache starting within 60 min (see Table 595-3). The importance of the aura lasting longer than 5 min is to differentiate the migraine aura from a seizure with a postictal headache, while the 60 min maximal duration is to separate migraine aura from the possibility of a more prolonged neurologic event such as a transient ischemic attack.

The most common type of visual aura in children and adolescents is **photopsia** (flashes of light or light bulbs going off everywhere). These photopsias are often multicolored and when gone, the child may report not being able to see where the flash occurred. Less likely in children are the typical adult auras including *fortification spectra* (brilliant white

zigzag lines resembling a starred pattern castle) or *shimmering scotoma* (sometimes described as a shining spot that grows or a sequined curtain closing). In adults, the auras typically involve only half the visual field, whereas in children they may be randomly dispersed. Blurred vision is often confused as an aura but is difficult to separate from photophobia or difficulty concentrating during the pain of the headache.

Sensory auras are less common. They typically occur unilaterally. Many children describe this sensation as insects are worms crawling from their hand, up their arm to their face with a numbness following this sensation. Once the numbness occurs, the child may have difficulty using the arm as they have lost sensory input, and a misdiagnosis of hemiplegic migraine may be made.

Dysphasic auras are the least-common type of typical aura and have been described as an inability or difficulty to respond verbally. The patient afterwards will describe an ability to understand what is being asked, but cannot answer back. This may be the basis of what in the past has been referred to as confusional migraine and special attention needs to be paid to asking the child about this possibility and their degree of understanding during the initial phases of the attack. Most of the time, these episodes are described as a motor aphasia and they are often associated with sensory or motor symptoms.

Much less commonly, *atypical forms of aura can occur,* including hemiplegia (true weakness, not numbness, and may be familial), vertigo or lower cranial nerve symptoms (basilar-type, formerly thought to be caused by basilar artery dysfunction, now thought to be more brainstem based) (see Table 595-4), and distortion ("Alice in Wonderland" syndrome). Whenever these rarer forms of aura are present, further investigation is warranted. Not all motor auras can be classified as hemiplegic migraine spectrum and they should be differentiated from those very specific migrainous events, as the diagnosis of hemiplegic migraine has genetic, pathophysiologic, and therapeutic implications.

Hemiplegic migraine is one of the better known forms of rare auras. This transient unilateral weakness usually lasts only a few hours but may persist for days. Both familial and sporadic forms have been described. The familial hemiplegic migraine is an autosomal dominant disorder with mutations described in 3 separate genes: (1) *CACNA1A*, (2) *ATP1A2*, and (3) *SCN1A*. Some patients with familial hemiplegic migraine have other yet-to-be-identified genetic mutations. Multiple polymorphisms have been described for these genes. Hemiplegic migraines may be triggered by minor head trauma, exertion, or emotional stress. The motor weakness is usually associated with another aura symptom and may progress slowly over 20-30 min first with visual and then followed in sequence by sensory, motor, aphasic, and then basilar auras. Headache is present in more than 95% of patients and usually begins during the aura; headache may be unilateral or bilateral and may have no relationship to the motor weakness. Some patients may develop attacks of coma with encephalopathy, cerebrospinal fluid (CSF) pleocytosis, and cerebral edema. Long-term complications may include seizures, repetitive daily episodes of blindness, cerebellar signs with the development of cerebellar atrophy, and mental retardation.

Basilar-type migraine was formerly considered a disease of the basilar artery as many of the unique symptoms were attributed to dysfunction in this area of the brainstem. Some of the symptoms described include vertigo, tinnitus, diplopia, blurred vision, scotoma, ataxia, and an occipital headache. The pupils may be dilated, and ptosis may be evident.

Syndrome of transient headache and neurological deficits with CSF lymphocytosis (HaNDL) describes transient headaches associated with neurologic deficits, and CSF showing pleocytosis. It is considered a self-limited migraine-like syndrome, and is rarely reported in the pediatric population.

Childhood periodic syndromes are a group of potentially related symptoms that occur with increased frequency in children with migraine. The hallmark of these symptoms is the recurrent episodic nature of the events. Some of these have included gastrointestinal-related symptoms (motion sickness, recurrent abdominal pain, recurrent vomiting including cyclic vomiting, and abdominal migraine), sleep disorders (sleepwalking, sleeptalking, and night terrors), unexplained recurrent fevers, and even seizures.

The gastrointestinal symptoms span the spectrum from the relatively mild (motion sickness on occasional long car rides) to severe episodes of uncontrollable vomiting that may lead to dehydration and the need for hospital admission to receive fluids. These latter episodes may occur on a predictable time schedule and hence have been called cyclic vomiting. During these attacks, the child may appear pale and frightened but does not lose consciousness. After a period of deep sleep, the child awakens and resumes normal play and eating habits as if the vomiting had not occurred. Many children with cyclic vomiting have a positive family history of migraine, and as they grow older have a higher than average likelihood of developing migraine. Cyclic vomiting may be responsive to migraine-specific therapies with careful attention to fluid replacement if the vomiting is excessive. Cyclic vomiting of migraine must be differentiated from gastrointestinal disorders including intestinal obstruction (malrotation, intermittent volvulus, duodenal web, duplication cysts, superior mesenteric artery compression, and internal hernias), peptic ulcer, gastritis, giardiasis, chronic pancreatitis, and Crohn disease. Abnormal gastrointestinal motility and pelviureteric junction obstruction can also cause cyclic vomiting. Metabolic causes include disorders of amino acid metabolism (heterozygote ornithine transcarbamylase deficiency), organic acidurias (propionic acidemia, methylmalonic acidemia), fatty acid oxidation defects (medium-chain acyl-coenzyme A dehydrogenase deficiency), disorders of carbohydrate metabolism (hereditary fructose intolerance), acute intermittent porphyria, and structural central nervous system lesions (posterior fossa brain tumors, subdural hematomas or effusions). The diagnosis is a diagnosis of exclusion and children will need a full work up prior to be labeled of cyclic vomiting syndrome. Cyclic vomiting syndrome is more frequent in younger children and will gradually transform into a typical migraine attack by puberty.

The diagnosis of **abdominal migraine** can be confusing but can be thought of as a migraine without the headache. Like a migraine, it is an episodic disorder characterized by midabdominal pain with pain-free periods between attacks. At times this pain is associated with nausea and vomiting (thus crossing into the recurrent abdominal pain or cyclic vomiting spectrum). The pain is usually described as "dull" and may be moderate to severe. The pain may persist from 1-72 hr and, although usually midline, may be periumbilical or poorly localized by the child. To meet the criteria of abdominal migraine, the child must complain at the time of the abdominal pain of at least 2 of the following: anorexia, nausea, vomiting, or pallor. As with cyclic vomiting, a thorough history and physical examination with appropriate laboratory studies must be completed to rule out an underlying gastrointestinal disorder as a cause of the abdominal pain. Careful questioning about the presence of headache or head pain needs to be addressed directly with the child, as many times this is truly a migraine, but in the child's mind (as well as the parents' observation) the abdominal symptoms are paramount.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A thorough history and physical examination including a neurologic examination with special focus on headache has been shown to be the most sensitive indicator of an underlying etiology. The history needs to include a thorough evaluation of the premonitory symptoms, any potential triggering events or timing of the headaches, associated neurologic symptoms, and a detailed characterization of the headache attacks, including frequency, severity, duration, associated symptoms, use of medication, and disability. The disability assessment should include the impact on school, home, and social activities and can easily be assessed with tools such as PedMIDAS. Family history of headaches and any other neurologic, psychiatric, and general health conditions is also important both for identification of migraine within the family as well as the identification of possible secondary headache disorders. The familial penetrance of migraine is so robust that the absence of a family history of migraine or its equivalent phenomena should trigger obtaining of an imaging procedure. When headaches are refractory, a history of potential comorbid conditions, which includes mood disorders and

illicit substance use, especially in teenagers, that may influence adherence and acceptability of the treatment plan, may also need to be addressed.

Neuroimaging is warranted when the neurologic examination is abnormal or unusual neurologic features occur during the migraine; when the child has headaches that awaken the child from sleep or that are present on first awakening and remit with upright posture; when the child has brief headaches that only occur with cough or bending over; when the headache is mostly in the occipital area; and when the child has migrainous headache with an absolutely negative family history of migraine or its equivalent (e.g., motion sickness, cyclic vomiting; Table 595-7). In this case, an MRI is the imaging of choice as it provides the highest sensitivity for detecting posterior fossa lesions and does not expose the child to radiation.

In the child with a headache that is instantaneously at its worst at onset, a CT scan looking for blood is the best initial test; and, if it is negative, a lumbar puncture should be done looking especially for xanthochromia of the CSF. There is no evidence that laboratory studies or an electroencephalogram is beneficial in a typical migraine without aura or migraine with aura.

TREATMENT

Table 595-8 outlines the drugs used to manage migraine headaches in children.

The American Academy of Neurology established useful practice guidelines for the management of migraine as follows:

1. Reduction of headache frequency, severity, duration, and disability
2. Reduction of reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
3. Improvement in quality of life
4. Avoidance of acute headache medication escalation
5. Education and enabling of patients to manage their disease to enhance personal control of their migraine
6. Reduction of headache-related distress and psychologic symptoms

Table 595-7 Indications for Neuroimaging in a Child with Headaches

Abnormal neurologic examination
Abnormal or focal neurologic signs or symptoms
- Focal neurologic symptoms or signs developing during a headache (i.e., complicated migraine)
- Focal neurologic symptoms or signs (except classic visual symptoms of migraine) develop during the aura, with fixed laterality; focal signs of the aura persisting or recurring in the headache phase

Seizures or very brief auras (<5 min)
Unusual headaches in children
- Atypical auras including basilar-type, hemiplegic
- Trigeminal autonomic cephalalgia including cluster headaches in child or adolescent
- An acute secondary headache (i.e., headache with known underlying illness or insult)

Headache in children younger than 6 yr old or any child who cannot adequately describe his or her headache
Brief cough headache in a child or adolescent
Headache worst on first awakening or that awakens the child from sleep
Migrainous headache in the child with no family history of migraine or its equivalent

Table 595-8 Drugs Used in the Management of Migraine Headaches in Children

DRUG	DOSE	MECHANISM	SIDE EFFECTS	COMMENTS
ACUTE MIGRAINE				
Analgesics				
Acetaminophen	15 mg/kg/dose	Analgesic effects	Overdose, fatal hepatic necrosis	Effectiveness limited in migraine
Ibuprofen	7.5-10 mg/kg/dose	Antiinflammatory and analgesic	GI bleeding stomach upset, kidney injury	Avoid overuse (2-3 times per wk)
Triptans				
Almotriptan* (ages 12-17 yr)	12.5 mg	$5\text{-HT}_{1b/1d}$ agonist	Vascular constriction, serotonin symptoms such as flushing, paresthesias, somnolence, GI discomfort	Avoid overuse (more than 4-6 times per mo)
Eletriptan	40 mg	Same	Same	Avoid overuse (more than 4-6 times per mo)
Frovatriptan	2.5 mg	Same	Same	May be effective for menstrual migraine prevention Avoid overuse (more than 4-6 times per mo)
Naratriptan	2.5 mg	Same	Same	May be effective for menstrual migraine prevention Avoid overuse (more than 4-6 times per mo)
Rizatriptan* (ages 6-17 yr)	5 mg for child weighing <40 kg, 10 mg	Same	Same	Available in tablets and melts Avoid overuse (more than 4-6 times per mo)
Sumatriptan	Oral: 25 mg, 50 mg, 100 mg Nasal: 10 mg SC: 6 mg	Same	Same	Avoid overuse (more than 4-6 times per mo)
Zolmitriptan	Oral: 2.5 mg, 5 mg Nasal: 5 mg	Same	Same	Available in tablets and melts Avoid overuse (more than 4-6 times per mo)

Continued

Table 595-8 Drugs Used in the Management of Migraine Headaches in Children—cont'd

DRUG	DOSE	MECHANISM	SIDE EFFECTS	COMMENTS
PROPHYLAXIS (NONE APPROVED BY FDA FOR CHILDREN)				
Calcium Channel Blockers				
Flunarizine[†]	5 mg hs	Calcium channel blocking agent	Headache, lethargy, dizziness	May ↑ to 10 mg hs
Anticonvulsants				
Valproic acid	20 mg/kg/24 hr (begin 5 mg/kg/24 hr)	↑ Brain GABA	Nausea, pancreatitis, fatal hepatotoxicity	↑ 5 mg/kg every 2 wk
Topiramate	100-200 mg divided bid	↑ Activity of GABA	Fatigue, nervousness	Increase slowly over 12-16 wk
Levetiracetam	20-60 mg/kg divided bid	Unknown	Irritability, fatigue	Increase every 2 wk starting at 20 mg/kg divided bid
Gabapentin	900-1800 mg divided bid	Unknown	Somnolence, fatigue aggression, weight gain	Begin 300 mg, ↑ 300 mg/wk
Antidepressants				
Amitriptyline	1 mg/kg/day	↑ CNS serotonin and norepinephrine	Cardiac conduction, abnormalities and dry mouth, constipation, drowsiness, confusion	Increase by 0.25 mg/kg every 2 wk Morning sleepiness reduced by administration at dinnertime
Antihistamines				
Cyproheptadine	0.2-0.4 mg/kg divided bid; max: 0.5 mg/kg/24 hr	H_1-receptor and serotonin agonist	Drowsiness, thick bronchial secretions	Preferred in children who cannot swallow pills; not well tolerated in adolescents
Antihypertensive				
Propranolol	10-20 mg tid	Nonselective β-adrenergic blocking agent	Dizziness, lethargy	Begin 10 mg/24 hr ↑ 10 mg/wk (contraindicated in asthma and depression)
Others				
Coenzyme Q10	1-3 mg/kg/day	Increases fatty acid oxidation in mitochondria	No adverse effects reported	Fat soluble; ensure brand contains small amount of vitamin E to help absorption
Riboflavin	50-400 mg daily	Cofactor in energy metabolism	Bright yellow urine, polyuria and diarrhea	
Magnesium	9 mg/kg divided tid	Cofactor in energy metabolism	Diarrhea or soft stool	
Butterbur	50-150 mg daily	May act similar to a calcium channel blocker	Burping	
OnabotulinumtoxinA	100 units (age 11-17 yr)	Inhibits acetylcholine release from nerve endings	Ptosis, blurred vision, hematoma at injection site	Used off label in children
SEVERE INTRACTABLE				
Prochlorperazine	0.15 mg/kg/IV; max dose 10 mg	Dopamine antagonist	Agitation, drowsiness, muscle stiffness, akinesia and akathisia	May have increased effectiveness when combined with ketorolac and fluid hydration
Metoclopramide	0.2 mg/kg IV; 10 mg max dose	Dopamine antagonist	Drowsiness, urticaria, agitation, akinesia and akathisia	Caution in asthma patients
Ketorolac	0.5 mg/kg IV; 15 mg max dose	Antiinflammatory and analgesic	GI upset, bleeding	
Valproate sodium injection	15 mg/kg IV: 1,000 mg max dose	↑ Brain GABA	Nausea, vomiting, somnolence, thrombocytopenia	Would avoid in hepatic disease
Dihydroergotamine IV	0.5 mg/dose every 8 hr (<40 kg) 1.0 mg/dose every 8 hr (>40 kg)		Nausea, vomiting, vascular constriction, phlebitis	Dose may need to be adjusted for side effects (decrease) or limited effectiveness (increase).
Nasal spray	0.5-1.0 mg/dose 0.5 mg/spray			

*FDA approved in the pediatric population.
[†]Available in Europe.
↑, Increase; CNS, central nervous system; GABA, γ-aminobutyric acid; GI, gastrointestinal; hs, at night; SC, subcutaneous.

To accomplish these goals, 3 components need to be incorporated into the treatment plan:

1. An acute treatment strategy should be developed for stopping a headache attack on a consistent basis with return to function as soon as possible with the goal being 2 hr maximum.
2. A preventive treatment strategy should be considered when the headaches are frequent (1 or more per week) and disabling.
3. Biobehavioral therapy should be started, including a discussion of adherence, elimination of barriers to treatment, and healthy habit management.

Acute Treatment

Management of an acute attack is to provide headache freedom as quickly as possible with return to normal function. This mainly includes 2 groups of medicines: nonsteroidal antiinflammatory drugs (NSAIDs) and triptans. Most migraine headaches in children will respond to appropriate doses of NSAIDs when administered at the onset of the headache attack. Ibuprofen has been well documented to be effective at a dose of 7.5-10.0 mg/kg and is often preferred; however, acetaminophen (15 mg/kg) can be effective in those with a contraindication to NSAIDs. Special concern for the use of ibuprofen or other NSAIDs includes ensuring that the children can recognize and respond to onset of the headache. This means discussing with the child the importance of telling the teacher when the headache starts at school and ensuring that proper dosing guidelines and permission have been provided to the school. In addition, overuse needs to be avoided, limiting the NSAID (or any combination of nonprescription analgesics) to not more than 2-3 times per week. The limitation of any analgesic to not more than 3 headaches a week is necessary to prevent the transformation of the migraines into medication overuse headaches. If a patient has maximized the weekly allowance of analgesics, the patient's next step is to only use hydrating fluids for the rest of the week as an abortive approach. If ibuprofen is not effective, naproxen sodium also may be tried in similar doses. Aspirin is also a reasonable option but is usually reserved for older children (older than age 15 yr). Use of other NSAIDs have yet to be studied in pediatric migraine. The goal of the primary acute medication should be headache relief within 1 hr with return to function in 10 of 10 headaches.

When a migraine is especially severe, NSAIDs alone may not be sufficient. In this case, a triptan may be considered. Multiple studies have demonstrated their effectiveness and tolerability. There are currently 2 triptans that are approved by the FDA for the treatment of episodic migraine in the pediatric population. Almotriptan is approved for the treatment of acute migraine in adolescents (ages 12-17 yr). Rizatriptan is approved for the treatment of migraine in children as young as age 6 yr. The combination of naproxen sodium and sumatriptan has been studied and may be effective in children. Controlled clinical trials demonstrate that intranasal sumatriptan is safe and effective in children older than age 8 yr with moderate to severe migraine. At present, pediatric studies showing the effectiveness of oral sumatriptan are lacking and there is insufficient evidence to support the use of subcutaneous sumatriptan in children. For most adolescents, dosing is the same as for adults; a reduction in dose is made for children weighing less than 40 kg. The triptans vary by rapidity of onset and biologic half-life. This is related to both their variable lipophilicity and dose. Clinically, 60-70% of patients respond to the first triptan tried, with 60-70% of the patients who did not respond to the first triptan responding to the next triptan. Therefore, in the patient who does not respond to the first triptan in the desired way (rapid reproducible response without relapse or side effects), it is worthwhile to try a different triptan. The most common side effects of the triptans are caused by their mechanism of action—tightness in the jaw, chest, and fingers as a result of vascular constriction and a subsequent feeling of grogginess and fatigue from the central serotonin effect. The vascular constriction symptoms can be alleviated through adequate fluid hydration during an attack.

The most effective way to administer abortive treatment is to use NSAIDs first in mild to severe cases, restricting their use to fewer than 2-3 attacks per week, and adding the triptan for moderate to severe, or attacks that have failed NSAID use, restricting to not more than 4-6 attacks per month. For an acute attack, the NSAIDs can be repeated once in 3-4 hr if needed for that specific attack, and the triptans can be repeated once in 2 hr if needed. It is important to consider the various formulations available and a discussion of these options should be made with pediatric patients and their parents, especially if a child is unable to swallow pills or take an oral dose because of nausea.

As vascular dilation is a common feature of migraine that may be responsible for some of the facial flushing followed by paleness and the lightheaded feeling accompanying the attacks, fluid hydration should be integrated into the acute treatment plan. For oral hydration this can include the sports drinks that combine electrolytes and sugar to provide the intravascular rehydration.

Antiemetics were used for acute treatment of the nausea and vomiting. Further study has identified that their unique mechanism of effectiveness in headache treatment is related to their antagonism of dopaminergic neurotransmission. Therefore, the antiemetics with the most robust dopamine antagonism (i.e., prochlorperazine and metoclopramide) have the best efficacy. These can be very effective for status migrainosus or a migraine that is unresponsive to the NSAIDs and triptans. They require intravenous administration, as other forms of administration of these drugs are less effective than the NSAIDs or triptans. When combined with ketorolac and intravenous fluids in the emergency department or an acute infusion center, intravenous antiemetics can be very effective. When they are not effective, further inpatient treatment may be required using dihydroergotamine (DHE) which will mean an admission to an inpatient unit for more aggressive therapy of an intractable attack.

Emergency Department Treatments for Intractable Headaches

When an acute migraine attack does not respond to an outpatient regimen and is disabling, other therapeutic approaches are available and may be necessary to prevent further increases in the frequency of headaches. These migraines fall into the classification of status migrainosus and need infusion therapy and admission to the emergency room department or to an inpatient unit.

Available specific treatments for migraine headache in an emergency room setting include the following: antidopaminergic medications such as prochlorperazine and metoclopramide; NSAIDs such as ketorolac and DHE; antiepileptic drugs such as sodium valproate; and triptans.

Antidopaminergic Drugs: Prochlorperazine and Metoclopramide. The use of these medications is not limited to controlling the nausea and vomiting often present during a migraine headache. Their potential pharmacologic effect may be a result of their antidopamine property and the underlying pathologic process involving the dopaminergic system during a migraine attack. Prochlorperazine is very effective in aborting an attack in the emergency room when given intravenously with a bolus of IV fluid. Results show a 75% improvement with 50% headache freedom at 1 hr and 95% improvement with 60% headache freedom at 3 hr. Prochlorperazine may be more effective than metoclopramide. The average dose of metoclopramide use is 0.13-0.15 mg/kg with a maximum dose of 10 mg given intravenously over 15 min. The average dose of prochlorperazine is 0.15 mg/kg with a maximum dose of 10 mg. These medications are usually well tolerated, but *extrapyramidal reactions* are more frequent in children compared to the older population. An acute extrapyramidal reaction can be controlled in the emergency room with 25-50 mg of diphenhydramine given IV.

Nonsteroidal Antiinflammatory Drugs: Ketorolac. It is known that an aseptic inflammation occurs in the central nervous system as a result of the effect of multiple reactive peptides in patients with migraines. Ketorolac is often used in the emergency department as monotherapy for a migraine attack or in combination with other drugs. In monotherapy, the response to ketorolac is 55.2% improvement. When combined to prochlorperazine, the response rate jumps to 93%.

Antiepileptic Drugs: Sodium Valproate. Antiepileptic drugs have been used as prophylactic treatment for migraine headache for years with adequate double-blinded, controlled studies on their efficacy in adults. The mechanism in which sodium valproate acutely aborts migraine headaches is not well understood. Sodium valproate is given as a bolus of 15-20 mg/kg push (over 10 min). This intravenous load is followed by an oral dose (15-20 mg/day) in the 4 hr after the injection. Patients may benefit from a short-term preventive treatment with an extended release form after discharge from the emergency room. Sodium valproate is usually well tolerated. Patients should be receiving a fluid load during the procedure to prevent a possible hypotensive episode.

Triptans. Subcutaneous sumatriptan (0.06 mg/kg) has an overall efficacy of 72% at 30 min and 78% at 2 hr, with a recurrence rate of 6%. Because children tend to have a shorter duration of headache, a recurrence rate of 6% would seem appropriate for this population. DHE, if recommended for the recurrences, should not be given in the 24 hr after triptan use. Triptans are contraindicated in patients treated with ergotamine within 24 hr and within 2 wk of treatment with monoamine oxidase inhibitors. Triptans may potentially produce a serotonin syndrome in patients taking a serotonin syndrome reuptake inhibitor. Both triptans and ergotamine are contraindicated in hemiplegic migraines.

Dihydroergotamine. DHE is an old migraine medication used as a vasoconstrictor to abort the vascular phase of migraine headache. The effectiveness is discussed in detail in the section "Inpatient Management of Intractable Migraine and Status Migrainosus" below. One dose of DHE can be effective for abortive treatment in the emergency department. Emergency room treatment of migraine shows a recurrence rate of 29% at 48-72 hr, with 6% who need more aggressive therapy in an inpatient unit.

Inpatient Management of Intractable Migraine and Status Migrainosus

Six percent to 7% of patients fail acute treatment in the emergency department. These patients are usually admitted for a 3-5 day stay and receive extensive parenteral treatment. A child should be admitted to the hospital for a primary headache when the child is in status migrainous, has an exacerbation of a chronic severe headache, or is in an analgesic rebound headache. The goal of inpatient treatment is to control a disabling headache that has been unresponsive to other abortive therapy and is disabling to the child. Treatment protocols include the use of DHE, antiemetics, sodium valproate and other drugs.

Dihydroergotamine. Ergots are one of the oldest treatments for migraine headache. DHE is a parenteral form used for acute exacerbations. Its effect is because of the $5HT_{1A\text{-}1B\text{-}1D\text{-}1F}$ receptor agonist affinity and central vasoconstriction. DHE has a greater α-adrenergic antagonist activity and is less vasoconstrictive peripherally. Before initiation of an IV ergot protocol, a full history and neurologic examination should be obtained. Girls of childbearing age should be evaluated for pregnancy before administering ergots.

The DHE protocol consists of the following: Patients are premedicated with 0.13-0.15 mg/kg of prochlorperazine 30 min prior to the DHE dose (maximum of 3 prochlorperazine doses to prevent extrapyramidal syndrome, then other types of antiemetics should be used, such as ondansetron). A dose of 0.5-1.0 mg of DHE is used (depending on age and tolerability) every 8 hr until headache freedom. When headache ceases, an extra dose is given in an attempt to prevent recurrence after discharge. The response to this protocol is a 97% improvement and 77% headache freedom. Response starts being noticeable by the fifth dose and can reach its maximum effects after the 10th dose. Side effects of DHE include nausea, vomiting, abdominal discomfort, flushed face, increased blood pressure. The maximum dose used in this protocol is 15 mg total of DHE. During the hospital admission the patient is usually started on migraine prophylaxis depending on the patient's history and comorbid problems.

Sodium Valproate. Sodium valproate is used when DHE is contraindicated or has been ineffective. One adult study recommends the use of valproate sodium as follows: Bolus with 15 mg/kg (maximum of 1,000 mg), followed by 5 mg/kg every 8 hr until headache freedom or up to a maximum of 10 doses. Always give an extra dose after headache ceases. This protocol was studied in adults with chronic daily headaches and showed an 80% improvement. It is well tolerated and is useful in children when DHE is ineffective, contraindicated, or not tolerated.

Preventive Therapy

When the headaches are frequent (more than 1 headache/wk) or there are more than 1 disabling headache a month (missing school, home, or social activities, or a PedMIDAS score higher than 20), preventive or **prophylactic therapy** is warranted. The goal of this therapy should to be to reduce frequency (1-2 headaches or fewer per month) and disability (PedMIDAS score <10). Prophylactic agents should be given for at least 4-6 mo at an adequate dose and then weaned over several weeks. Evidence in adult studies has begun to demonstrate that persistent frequent headaches foreshadow an increased risk of progression with decreased responsiveness and increased risk of refractoriness in the future. It is unclear whether this also occurs in children and/or adolescents and whether early treatment of headache in childhood prevents development of refractory headache in adulthood.

Multiple preventive medications have been utilized for migraine prophylaxis in children. When analyzed as part of a practice parameter, only 1 medication, **flunarizine** (a calcium channel blocking agent), demonstrated a level of effectiveness viewed as substantial; it is not available in the United States. Flunarizine is typically dosed at 5 mg orally daily and increased after 1 mo to 10 mg orally daily, with a month off of the drug every 4-6 mo.

The most commonly used preventive therapy for headache and migraine is amitriptyline. Typically, a dose of 1 mg/kg daily at dinner or in the evening is effective. However, this dose needs to be reached slowly (i.e., over weeks: with an increase every 2 wk until goal is reached) to minimize side effects and improve tolerability. The most common side effects are sleepiness and those related to amitriptyline's anticholinergic activity. Weight gain has been observed in adults using amitriptyline but is a less frequent occurrence in children. Amitriptyline does have the potential to exacerbate prolonged QT syndrome, so it should be avoided in patients with this diagnosis and looked for in patients on the drug who complain of rapid or irregular heart rate.

Antiepileptic medications are also used for migraine prophylaxis, with topiramate, valproic acid, and levetiracetam having been demonstrated to be effective in adults. There are limited studies in children for migraine prevention, but all of these medications have been assessed for safety and tolerability in children with epilepsy.

Topiramate has become widely used for migraine prophylaxis in adults. Topiramate was also demonstrated to be effective in an adolescent study. This study demonstrated that a 25 mg dose twice a day was equivalent to placebo, whereas a 50 mg dose twice a day was superior. Thus it appears that the adult dosing schedule is also effective in adolescents with an effective dosage range or 50 mg twice a day to 100 mg twice a day. This dose needs to be reached slowly to minimize the cognitive slowing associated with topiramate use. Additional side effects include weight loss, paresthesias, kidney stones, lowered bicarbonate levels, decreased sweating, and rarely glaucoma and changes in serum transaminases. In addition, in adolescent girls taking birth control pills, the lowering of the effectiveness of the birth control by topiramate needs to be discussed.

Valproic acid has long been used for epilepsy in children and has been demonstrated to be effective in migraine prophylaxis in adults. The effective dose in children appears to be 10 mg/kg orally twice a day. Side effects of weight gain, ovarian cysts, and changes in serum transaminases and platelet counts need to be monitored. Other antiepileptics, including lamotrigine, levetiracetam, zonisamide, gabapentin, and pregabalin, are also used for migraine prevention.

β-Blockers have long been used for migraine prevention. The studies on β-blockers have a mixed response pattern with variability both between β-blockers and between patients with a given β-blocker. Propranolol is the best studied for pediatric migraine prevention with unequivocally positive results. The contraindication for use of

propranolol in children with asthma or allergic disorders or diabetes and the increased incidence of depression in adolescents using propranolol limit its use somewhat. It may be very effective for a mixed subtype of migraine (basilar-type migraine with postural orthostatic tachycardia syndrome). This syndrome has been reported to be responsive to propranolol. α-Blockers and calcium channel blockers, aside from flunarizine, also have been used in pediatric migraine; their effectiveness, however, remains unclear.

In very young children, cyproheptadine may be effective in prevention of migraine or the related variants. Young children tend to tolerate the increased appetite induced by the cyproheptadine and tend not to be subject to the lethargy seen in older children and adults; the weight gain is limiting once children start to enter puberty. Typical dosing is 0.1-0.2 mg/kg orally twice a day.

Nutraceuticals have become increasingly popular over the past few years, especially among families who prefer a more "natural" approach to headache treatment. Despite studies showing success of these therapies in adults, few studies have shown effectiveness in pediatric headaches. Riboflavin (vitamin B_2), at doses ranging from 25-400 mg, is the most widely studied with good results. Side effects are minimal and include bright yellow urine, diarrhea, and polyuria. Coenzyme Q10 supplementation may be effective in reducing migraine frequency at doses of 1-2 mg/kg/day. Butterbur is also effective in reducing headaches with minimal side effects, including burping. Use in children has been limited to avoid the potential toxicity of butterbur containing pyrrolizidine alkaloids, which are naturally contained and are a known carcinogen and toxic to the liver.

OnabotulinumtoxinA is the first medication FDA-approved for chronic migraine in adults. There are studies in children indicating its effectiveness; use in children is considered off-label. The limited available studies revealed the following: Average dose used was 188.5 units ± 32 units with a minimum dose of 75 units and maximum of 200 units. The average age of patients receiving the treatment was 16.8 ± 2.0 yr (minimum: 11; maximum: 21 yr old). OnabotulinumtoxinA injections improved disability scores (PedMIDAS) and headache frequency in pediatric chronic daily headache patients and chronic migraine in this age group. OnabotulinumtoxinA not only had a positive effect on the disability scoring for these young patients with headache, but was also able to transform the headaches from chronic daily to intermittent headache in more than 50% of the patients.

Biobehavioral Therapy

Biobehavioral evaluation and therapy is essential for effective migraine management. This includes identification of behavioral barriers to treatment, like a child's shyness or limitation in notifying a teacher of the start of a migraine or a teacher's unwillingness to accept the need for treatment. Additional barriers include a lack of recognition of the significance of their headache problem and reverting to "bad habits" once the headaches have responded to treatment. Adherence is equally important for acute and preventive treatment. The need to have a sustained response for long enough to prevent relapse (i.e., to stay on preventive medication) is often difficult when the child starts to feel better. Establishing a defined treatment goal (1-2 or fewer headaches per month for 4-6 mo) helps with acceptance.

As many of the potential triggers for frequent migraines (skipping meals, dehydration, decreased or altered sleep) are related to a child's daily routine, a discussion of healthy habits is a component of biobehavioral therapy. This should include adequate fluid intake without caffeine, regular exercise, not skipping meals and making healthy food choices, and adequate (8-9 hr) sleep on a regular basis. Sleep is often difficult in adolescents, as middle and high schools often have very early start times, and the adolescent's sleep architecture features a shift to later sleep onset and waking. This has been one of the explanations for worsening headaches during the school year in general and at the beginning of the school year and week.

Biofeedback-assisted relaxation and cognitive behavioral therapy (usually in combination with amitriptyline) are effective for both acute and preventive therapy and may be incorporated into this multiple treatment strategy. This provides the child with a degree of self-control over the headaches and may further help the child cope with frequent headaches.

Bibliography is available at Expert Consult.

595.2 Secondary Headaches

Andrew D. Hershey, Marielle A. Kabbouche, and Hope L. O'Brien

Headaches can be a common symptom of other underlying illnesses. In recognition of this, the ICHD-3 beta has classified the potential secondary headaches (see Table 595-1). The key to the diagnosis of a secondary headache is to recognize the underlying cause and demonstrate a direct cause and effect. Until this has been demonstrated the diagnosis is speculative. This is especially true when the suspected etiology is common.

Common causes or suspected causes of secondary headaches in children include the sequelae of head trauma and sinusitis. **Posttraumatic headaches** sometimes occur in children who have not had a prior history of headaches and are temporally related to the initiating head injury. Frequently, though, these children have a family history of migraine or its equivalent. The head injury may be minor or major and the subsequent headache may be acute (resolves within 3 mo, most typically within 10 days) or chronic (longer than 15 days per month for more than 3 mo). Bed rest appears to be the most effective treatment for acute posttraumatic headache; magnesium supplementation and migraine prophylaxis may also be effective. When a child has a history of episodic headaches, the head trauma or the overuse of daily medications may lead to status migrainosus or chronic migraine and the diagnosis may be difficult to sort out.

Sinus headache is the most overdiagnosed form of recurrent headaches. Although no studies have evaluated the frequency of misdiagnosis of an underlying migraine as a sinus headache in children, in adults, it has been found that up to 90% of adults diagnosed as having a sinus headache by either themselves or their physician appear to have migraine. When headaches are recurrent and respond within hours to analgesics, migraine should be considered first. In the absence of purulent nasal discharge, fever, or chronic cough, the diagnosis of sinus headache should not be made.

Medication overuse headaches frequently complicate primary and secondary headaches. A medication overuse headache is defined as a headache present for more than 15 days/mo for longer than 3 mo and intake of a simple analgesic on more than 15 days/mo and/or prescription medications including triptans or combination medications on more than 10 days/mo. Some of the signs that should raise suspicion of medication overuse are the increasing use of analgesics (nonprescription or prescription) with either decreased effectiveness or frequently wearing off (i.e., analgesic rebound). This can be worsened by using ineffective medications and underdosing or misdiagnosing the headache. Patients should be cautioned against the frequent use of antimigraine medications, including combination analgesics or triptans.

Serious causes of secondary headaches are likely to be related to increased intracranial pressure. This can be caused by a mass (tumor, vascular malformation, cystic structure) or an intrinsic increase in pressure (idiopathic intracranial hypertension also known as pseudotumor cerebri). In the former case, the headache is caused by the mass effect and local pressure on the dura; in the latter case, the headache is caused by diffuse pressure on the dura. The etiology of idiopathic intracranial hypertension may be the intake of excessive amounts of fat-soluble compounds (e.g., vitamin A, retinoic acid, and minocycline), hormonal changes (increased incidence in females) or blockage of venous drainage (as with inflammation of the transverse venous sinus from mastoiditis). When increased pressure is suspected, either by historical suspicion or the presence of papilledema, an MRI with magnetic resonance angiography and magnetic resonance venography should be performed, followed by a lumbar puncture if no mass or

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vascular anomaly is noted. The lumbar puncture can be diagnostic and therapeutic of idiopathic intracranial hypertension but must be performed with the patient in a relaxed recumbent position with legs extended, as abdominal pressure can artificially raise intracranial pressure. If headache persists or there are visual field changes, pharmaceutical treatment with a carbonic anhydrase inhibitor, optic nerve fenestration, or a shunt needs to be considered.

Additional causes of secondary headaches in children that may not be associated with increased intracranial pressure include arteriovenous malformations, berry aneurysm, collagen vascular diseases affecting the central nervous system, hypertensive encephalopathy, infectious or autoimmune etiologies, acute subarachnoid hemorrhage, and stroke. The management of secondary headache depends on the cause. Helpful laboratory tests and neuroradiologic procedures depend on the clues provided by the history and physical examination. By definition, a secondary headache has a specific cause and should resolve once this cause is treated. If the headache persists, the diagnosis and treatment should be questioned as either the diagnosis, which may include a primary headache, and/or treatment may be incorrect.

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595.3 Tension-Type Headaches

Andrew D. Hershey, Marielle A. Kabbouche, and Hope L. O'Brien

Tension-type headaches (TTHs) may be very common in children and adolescents with prevalence in some studies shown as high as 48%, with those having a combination of migraine and TTH around 20%. Because of their mild to moderate nature, relative lack of associated symptoms and lower degree of associated disability they are often ignored or have a minimal impact. The ICHD-3 beta subclassifies TTHs as infrequent (<12 times/yr) (Table 595-9), frequent (1-15 times/mo), and chronic (>15 headaches/mo). They can further be separated into headaches with or without pericranial muscle tenderness. The classification of TTH can be likened to the opposite of migraine. Whereas migraines are typically moderate to severe, are focal in location, are worsened by physical activity or limit physical activity, and have a throbbing quality, TTH are mild to moderate in severity, are diffuse in location, are not affected by activity (although the patient may not feel like being active), and are nonthrobbing (often described as a constant pressure). TTH is much less frequently associated with nausea, photophobia, or phonophobia and is never associated with more than 1 of these at a time or with vomiting. TTH must be recurrent, but at least 10 headaches are required and the duration can be 30 min to 7 days. Secondary headaches with other underlying etiologies must be ruled out.

Table 595-9	Infrequent Episodic Tension-Type Headache

A. At least 10 episodes of headache occurring on <1 day per month on average (<12 days per year) and fulfilling criteria B to D
B. Lasting from 30 min to 7 days
C. At least 2 of the following 4 characteristics:
   1. Bilateral location
   2. Pressing or tightening (nonpulsating) quality
   3. Mild or moderate intensity
   4. Not aggravated by routine physical activity such as walking or climbing stairs
D. Both of the following:
   1. No nausea or vomiting
   2. No more than 1 of photophobia or phonophobia
E. Not better accounted for by another ICHD-3 beta diagnosis

From Headache Classification Committee on the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version). Cephalalgia *33(9):629–808, 2013, Table 10.*

Evaluation of patients with suspected TTHs requires a detailed headache history and complete general and neurologic examination. This is to establish the diagnosis and ensure exclusion of secondary etiologies. When secondary headaches are suspected, further, directed evaluation is indicated.

Treatment of TTHs can require acute therapy to stop attacks, preventive therapy when frequent or chronic, and behavioral therapy. It is often suspected that there may be underlying psychologic stressors (hence the misnomer as a "stress" headache), but this is often difficult to identify in children, and although it may be suspected by the parents, it cannot be confirmed in the child. Studies of and conclusive evidence to guide the treatment of TTH in children are lacking, but the same general principles and medications used in migraine can be applied to children with TTHs (see Chapter 595.1). Oftentimes, simple analgesics (ibuprofen or acetaminophen) can be effective for acute treatment. Flupirtine is a nonopioid analgesic that has been approved in Europe for the treatment of TTH in children as young as age 6 yr, but is not available in the United States. Amitriptyline has the most evidence of effective prevention of TTH; biobehavioral intervention, including biofeedback-assisted relaxation training and coping skills, can be useful as well.

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Chapter 596

Neurocutaneous Syndromes

Mustafa Sahin

The neurocutaneous syndromes include a heterogeneous group of disorders characterized by abnormalities of both the integument and central nervous system. Many of the disorders are familial and believed to arise from a defect in differentiation of the primitive ectoderm. Disorders classified as neurocutaneous syndromes include neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, von Hippel-Lindau disease, PHACE (posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of aorta, cardiac defects, eye abnormalities) syndrome, ataxia telangiectasia, linear nevus syndrome, hypomelanosis of Ito, and incontinentia pigmenti.

596.1 Neurofibromatosis

Mustafa Sahin

Neurofibromatoses are autosomal dominant disorders that cause tumors to grow on nerves and result in other abnormalities such as skin changes and bone deformities. It was believed that there were 2 types of neurofibromatosis (type 1 and type 2), but it is recognized that they are clinically and genetically distinct diseases and should be considered separate entities: neurofibromatosis type 1 (NF-1) and neurofibromatosis type 2 (NF-2).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

NF-1 is the most prevalent type, with an incidence of 1 in 3,000 live births, and is caused by dominant loss-of-function mutations in the *NF-1* gene. The disease is clinically diagnosed when any 2 of the following 7 features are present: (1) six or more café-au-lait macules larger than 5 mm in greatest diameter in prepubertal individuals and larger than 15 mm in greatest diameter in postpubertal individuals (Fig. 596-1). Café-au-lait spots are the hallmark of neurofibromatosis

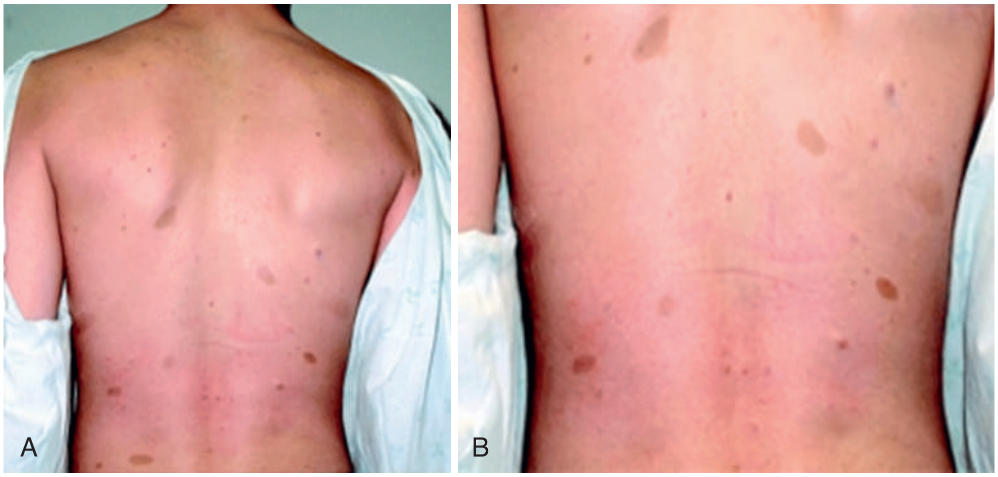

Figure 596-1 **A** and **B,** Multiple café-au-lait spots over the back. Note the dermal neurofibromas below the right scapula and right side of the lower back. *(From Hersh JH, Committee on Genetics: Health supervision for children with neurofibromatosis,* Pediatrics *121:633–642, 2008, Fig. 1.)*

Table 596-1 Diseases Associated with Multiple Café-Au-Lait Spots

DISEASE	MAJOR FEATURES
Ataxia telangiectasia	Progressive ataxia, lymphoreticular malignancy
Bannayan-Riley-Ruvalcaba syndrome	Macrosomia, megalencephaly, lipomas, intestinal polyps
Basal cell nevus syndrome	Multiple basal cell epitheliomas, jaw cysts, skeletal anomalies
Bloom syndrome	Short stature, photosensitivity, chromosome breaks, malignancy
Fanconi anemia	Limb anomalies, renal anomalies, pancytopenia
Gaucher disease	Jewish predilection, ataxia, mental retardation
Hunter syndrome	Thickened skin, coarse facies, skin papules, joint contractures
Jaffe-Campanacci syndrome	Fibromas of long bones, hypogonadism, mental retardation, ocular/cardiac anomalies
Maffucci syndrome	Venous malformations, enchondromas
McCune-Albright syndrome	Polyostotic fibrous dysplasia, precocious puberty
Multiple lentigines syndrome	Multiple lentigines, hypertelorism, pulmonic stenosis
Multiple mucosal neuroma syndrome	Mucosal neuromas, thyroid carcinoma, pheochromocytoma, parathyroid adenoma, dysautonomia
Neurofibromatosis	Neurofibromas, central nervous system tumors, iris hamartomas, axillary freckles, skeletal anomalies
Russell-Silver syndrome	Short stature, asymmetry, limb anomalies
Tuberous sclerosis	White macules, multiple hamartomas, central nervous system anomalies
Watson syndrome	Pulmonic stenosis, axillary freckles, low intelligence
Legius syndrome	Axillary freckling macrocephaly, a Noonan-like facial dysmorphism, lipomas

From Marcoux DA, Duran-McKinster C, Baselga E, et al: Pigmentary abnormalities. In: Schachner LA, Hansen RC, editors: Pediatric dermatology, *ed 4, Philadelphia, 2011, Mosby, Table 10-2.*

and are present in almost 100% of patients. They are present at birth but increase in size, number, and pigmentation, especially during the 1st few yr of life. The spots are scattered over the body surface, with predilection for the trunk and extremities but sparing the face. (2) Axillary or inguinal freckling consisting of multiple hyperpigmented areas 2-3 mm in diameter. Skinfold freckling usually appears between 3 and 5 yr of age. The frequency of axillary and inguinal freckling is reported to be >80% by 6 yr of age. Café-au-lait macules are not specific for NF-1; they may be seen in Noonan syndrome, constitutional mismatch repair deficiency syndrome, Legius syndrome, Peutz-Jeghers syndrome, Carney complex, and those diseases listed in Table 596-1. (3) Two or more iris Lisch nodules. Lisch nodules are hamartomas located within the iris and are best identified by a slit-lamp examination (Fig. 596-2). They are present in more than 74% of patients with NF-1 but are not a characteristic of NF-2. The prevalence of Lisch nodules increases with age, from only 5% of children younger than 3 yr of age, to 42% among children 3-4 yr of age, and virtually 100% of adults older than 21 yr of age. (4) Two or more neurofibromas or 1 plexiform neurofibroma. Neurofibromas typically involve the skin, but they may be situated along peripheral nerves and blood vessels and within viscera including the gastrointestinal tract. These lesions appear characteristically during adolescence or pregnancy, suggesting a hormonal influence. They are usually small, rubbery lesions with a slight purplish discoloration of the overlying skin. Plexiform neurofibromas are usually evident at birth and result from diffuse thickening of nerve trunks that are frequently located in the orbital or temporal region of the face. The skin overlying a plexiform neurofibroma may be hyperpigmented to a greater degree than a café-au-lait macule. Plexiform

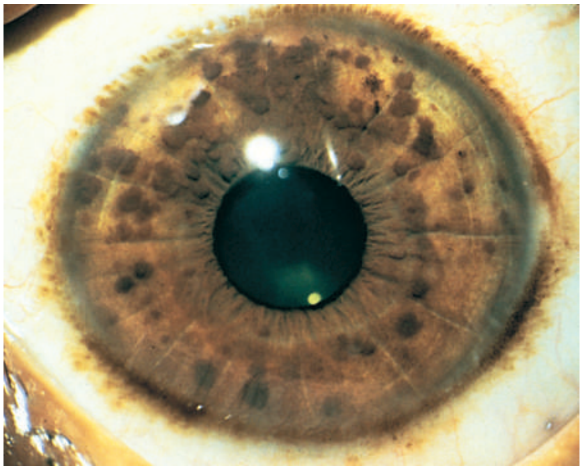

Figure 596-2 Neurofibromatosis type 1 (NF-1). Pigmented hamartomas of the iris (Lisch nodules). *(From Zitelli BJ, McIntire S, Nowalk AJ, editors:* Zitelli and Davis' atlas of pediatric physical diagnosis, *ed 6, Philadelphia, 2012, Mosby, Fig. 15-9.)*

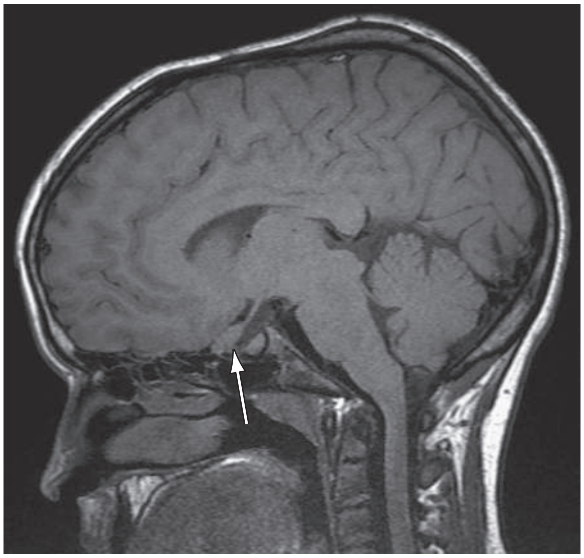

Figure 596-3 Optic glioma. Sagittal T1-weighted MRI scan of a patient with NF-1 shows thickening of the optic nerve *(arrow)*.

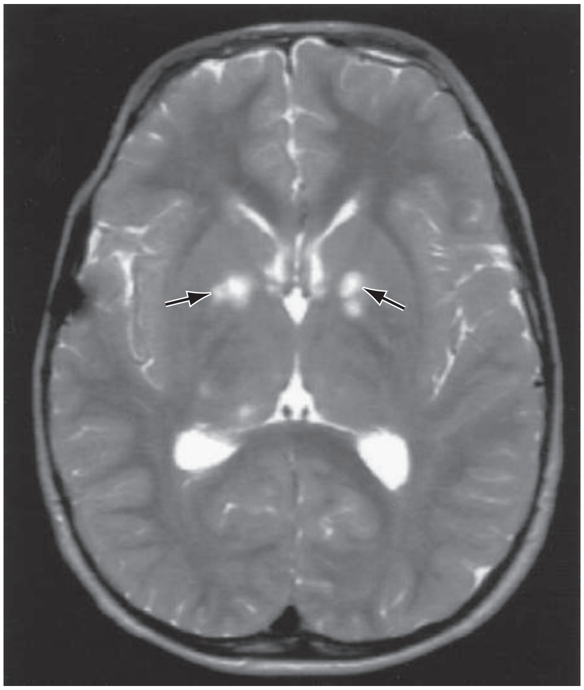

Figure 596-4 T2-weighted MRI scan of a patient with NF-1. Note the high-signal areas (unidentified bright objects) in the basal ganglia *(black arrows)*.

neurofibromas may produce overgrowth of an extremity and a deformity of the corresponding bone. (5) A distinctive osseous lesion such as sphenoid dysplasia (which may cause pulsating exophthalmos) or cortical thinning of long bones with or without pseudoarthrosis (e.g., tibia). (6) Optic gliomas are present in approximately 15% of patients with NF-1 and represent mostly low-grade astrocytomas. They are the main central nervous system tumor with a marked increased frequency in NF-1. Because of their growth, it is recommended that all children age 10 yr or younger with NF-1 undergo annual ophthalmologic examinations. When they progress, visual symptoms occur because the tumors enlarge and put pressure on the optic nerves and chiasm resulting in impaired visual acuity and visual fields. Extension into the hypothalamus can lead to endocrine deficiencies or failure to thrive. The MRI findings of an optic glioma include diffuse thickening, localized enlargement, or a distinct focal mass originating from the optic nerve or chiasm (Fig. 596-3). (7) A 1st-degree relative with NF-1 whose diagnosis was based on the aforementioned criteria.

Children with NF-1 are susceptible to **neurologic complications.** MRI studies of selected children have shown abnormal hyperintense T2-weighted signals in the optic tracts, brainstem, globus pallidus, thalamus, internal capsule, and cerebellum (Fig. 596-4). These signals, **"unidentified bright objects,"** tend to disappear with age; most have disappeared by 30 yr of age. It is unclear what the unidentified bright objects represent pathologically, and there is disagreement as to the relationship between the presence and number of unidentified bright objects and the occurrence of learning disabilities, attention-deficit disorders, behavioral and psychosocial problems, and abnormalities of speech among affected children. Therefore, imaging studies such as brain MRIs should be reserved for patients with clinical symptoms only.

One of the most common complications is learning disability affecting approximately 30% of children with NF-1. Seizures are observed in approximately 8% of NF-1 patients. The cerebral vessels may develop aneurysms or stenosis resulting in moyamoya syndrome (see Chapter 601). Neurologic sequelae of these vascular abnormalities include transient cerebrovascular ischemic attacks, hemiparesis, and cognitive defects. Precocious puberty may become evident in the presence or absence of lesions of the optic pathway tumors. Malignant neoplasms are also a significant problem in patients with NF-1, affecting approximately 3% of patients. A neurofibroma occasionally differentiates into a malignant peripheral nerve sheath tumor. The incidence of pheochromocytoma, rhabdomyosarcoma, leukemia, and Wilms tumor is higher than in the general population. Scoliosis is a common complication found in approximately 10% of the patients. Patients with NF-1 are at risk for hypertension, which may result from renal vascular stenosis or a pheochromocytoma.

MANAGEMENT

Because of the diverse and unpredictable complications associated with NF-1, close multidisciplinary follow-up is necessary. Patients with NF-1 should have regular clinical assessments at least yearly, focusing the history and examination on the potential problems for which they are at increased risk. These assessments include yearly ophthalmologic examination, neurologic assessment, blood pressure monitoring, and scoliosis evaluation. Neuropsychologic and educational testing should be considered as needed. The National Institutes of Health (NIH) Consensus Development Conference has advised against routine imaging studies of the brain and optic tracts because treatment in these

Table 596-2 Frequency of Lesions Associated with Neurofibromatosis Type 2

	FREQUENCY OF ASSOCIATION WITH NF-2
NEUROLOGIC LESIONS	
Bilateral vestibular schwannomas	90-95%
Other cranial nerve schwannomas	24-51%
Intracranial meningiomas	45-58%
Spinal tumors	63-90%
Extramedullary	55-90%
Intramedullary	18-53%
Peripheral neuropathy	Up to 66%
OPHTHALMOLOGIC LESIONS	
Cataracts	60-81%
Epiretinal membranes	12-40%
Retinal hamartomas	6-22%
CUTANEOUS LESIONS	
Skin tumors	59-68%
Skin plaques	41-48%
Subcutaneous tumors	43-48%
Intradermal tumors	Rare

From Asthagiri AR, Parry DM, Butman JA, et al: Neurofibromatosis type 2, Lancet 373:1974–1984, 2009, Table 1.

asymptomatic NF-1 children is rarely required. However, all symptomatic cases (i.e., those with visual disturbance, proptosis, increased intracranial pressure) must be studied without delay.

GENETIC COUNSELING

Although NF-1 is an autosomal dominant disorder, more than half the cases are sporadic, representing de novo mutations. The *NF-1* gene on chromosome region 17q11.2 encodes for a protein also known as neurofibromin. Neurofibromin acts as an inhibitor of the oncogene Ras. The diagnosis of NF-1 is based on the clinical features. However, molecular testing for the *NF-1* gene mutations is available and can be useful in a number of cases. Some scenarios in which genetic testing is helpful include for patients who meet only 1 of the criteria for clinical diagnosis, those with unusually severe disease, and those seeking prenatal/preimplantation diagnosis.

NF-2 is a rarer condition, with an incidence of 1 in 25,000 births, and may be diagnosed when 1 of the following 4 features is present: (1) bilateral vestibular schwannomas; (2) a parent, sibling, or child with NF-2 and either unilateral vestibular schwannoma or any 2 of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities; (3) unilateral vestibular schwannoma and any 2 of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities; or (4) multiple meningiomas (2 or more) and unilateral vestibular schwannoma or any 2 of the following: schwannoma, glioma, neurofibroma, cataract. Symptoms of tinnitus, hearing loss, facial weakness, headache, or unsteadiness may appear during childhood, although signs of a cerebellopontine angle mass are more commonly present in the 2nd and 3rd decades of life. Although café-au-lait macules and skin neurofibromas are classic findings in NF-1, they are much less common in NF-2. Posterior subcapsular lens opacities are identified in approximately 50% of patients with NF-2. The NF-2 gene (which codes for a protein known as merlin or schwannomin) is located on chromosome 22q1.11. Table 596-2 notes the frequency of lesions in NF-2.

Legius syndrome (caused by *SPRED1* mutations) resembles a mild form of NF-1. Patients with Legius syndrome present with multiple café-au-lait macules and macrocephaly, with and without skinfold freckling. However, other typical features of NF-1, such as Lisch nodules, neurofibromas, optic nerve gliomas, and malignant peripheral nerve sheath tumors, are not seen with *SPRED1* mutations.

Bibliography is available at Expert Consult.

596.2 Tuberous Sclerosis

Mustafa Sahin

Tuberous sclerosis complex (TSC) is inherited in an autosomal dominant manner with variable expression and a prevalence of 1 in 6,000 newborns. Spontaneous genetic mutations occur in 65% of the cases. Molecular genetic studies have identified 2 foci for TSC: the *TSC1* gene is located on chromosome 9q34, and the *TSC2* gene is on chromosome 16p13. The *TSC1* gene encodes a protein called *hamartin,* while the *TSC2* gene encodes the protein *tuberin.* Within a cell, these 2 proteins bind to one another and work together. Consequently, a mutation in either the *TSC1* gene or the *TSC2* gene results in a similar disease in patients. The *TSC1* and *TSC2* genes are tumor-suppressor genes. The loss of either tuberin or hamartin protein results in the formation of numerous benign tumors (hamartomas). Tuberin and hamartin are involved in a key pathway in the cell that regulates protein synthesis and cell size. One of the ways cells regulate their growth is by controlling the rate of protein synthesis. A protein called mTOR (mammalian target of rapamycin) was identified as one of the master regulators of cell growth. mTOR, in turn, is controlled by rheb, a small cytoplasmic guanosine triphosphatase. When rheb is activated, the protein synthesis machinery is turned on, most likely via mTOR, and the cell grows in size. Of interest in TSC, rheb is activated by the protein complex formed by hamartin and tuberin.

TSC is an extremely heterogeneous disease with a wide clinical spectrum varying from severe intellectual disability and intractable epilepsy to normal intelligence and a lack of seizures; this variation is often seen within the same family, thus with individuals carrying the same mutation. The disease affects many organ systems other than the skin and brain, including the heart, kidney, eyes, lungs, and bone (Fig. 596-5).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Definite TSC is diagnosed when at least 2 major or one major plus 2 minor features are present (Tables 596-3 and 596-4 list the major and minor features).

The hallmark of TSC is the involvement of the central nervous system. Retinal lesions consist of two types: hamartomas (elevated mulberry lesions or plaque-like lesions; Fig. 596-6) and white depigmented patches (similar to the hypopigmented skin lesions). The characteristic brain lesion is a cortical tuber (Fig. 596-7). Brain MRI is the best way of identifying cortical tubers, which can form before birth.

Subependymal nodules are lesions found along the wall of the lateral ventricles where they undergo calcification and project into the ventricular cavity, producing a candle-dripping appearance. These lesions do not cause any problems; however, in 5-10% of cases, these benign lesions can grow into subependymal giant cell astrocytomas (SEGAs). These tumors can grow and block the circulation of cerebrospinal fluid around the brain and cause hydrocephalus, which requires immediate neurosurgical intervention. Thus, it is recommended that all asymptomatic TSC patients undergo brain MRI every 1-3 yr to monitor for new occurrence of SEGA. Patients with large or growing SEGA, or with SEGA causing ventricular enlargement but yet are still asymptomatic, should undergo MRI scans more frequently and the patients and their families should be educated regarding the potential of new symptoms due to increased intracranial pressure. Surgical resection should be performed for acutely symptomatic SEGA. For growing but otherwise asymptomatic SEGA, either surgical resection or medical treatment with an mTOR inhibitor may be used. Presymptomatic treatment with everolimus is effective in slowing the growth or even reducing the size of SEGAs. Everolimus is also effective in treating refractory seizures and reducing the volume of renal angiomyolipomas and lymphangioleiomyomatosis as well as facial angiofibromas.

The most common neurologic manifestations of TSC consist of epilepsy, cognitive impairment, and autism spectrum disorders. TSC may present during infancy with infantile spasms and a hypsarrhythmic electroencephalogram pattern. However, it is important to remember

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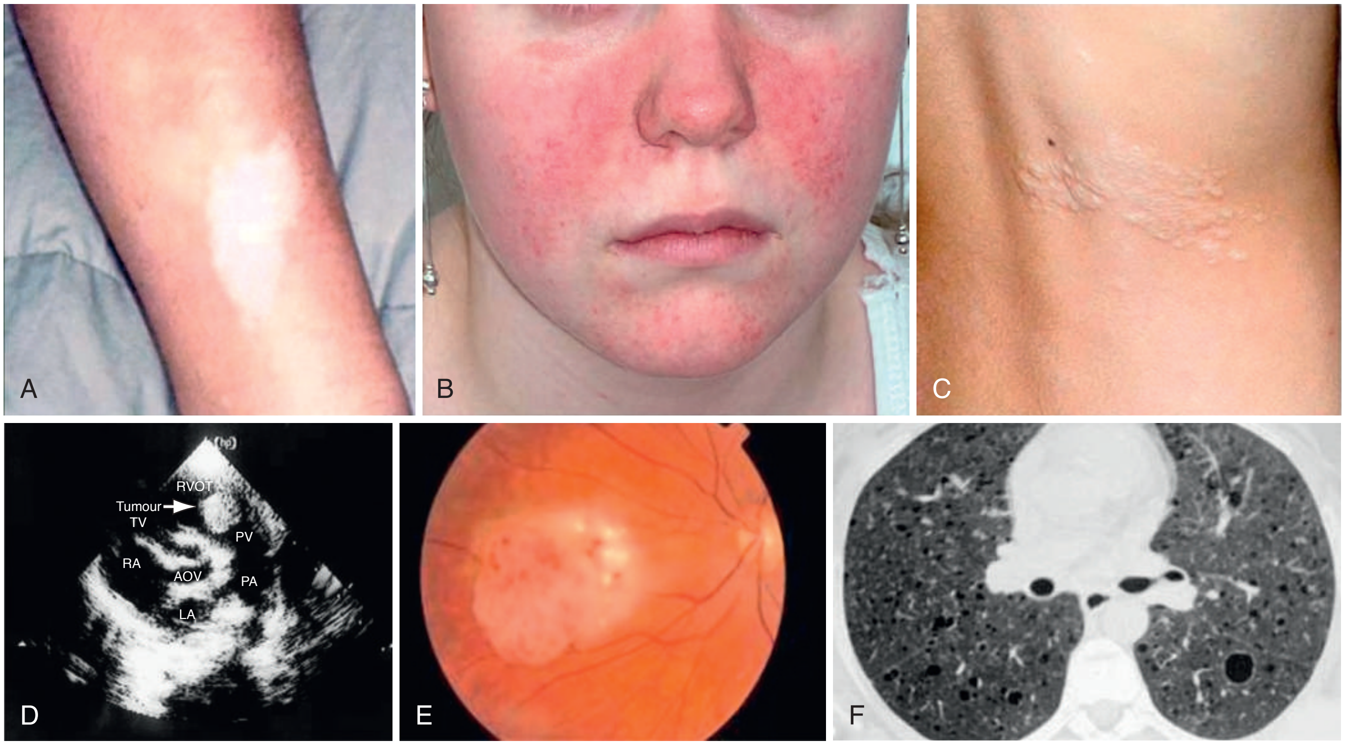

Figure 596-5 Dermatologic, cardiac, and pulmonary manifestations of tuberous sclerosis. **A,** Hypomelanotic macules. **B,** Facial angiofibromas. **C,** Shagreen patch. **D,** Hyperechoic rhabdomyoma detected by echocardiography. **E,** Retinal hamartoma. **F,** Lymphangioleiomyomatosis. *(From Curatolo P, Bombardieri R, Jozwiak S: Tuberous sclerosis,* Lancet *372:657–668, 2008, Fig. 7.)*

Table 596-3	Major Features of TSC
Cortical tuber	
Subependymal nodule	
Subependymal giant cell astrocytoma	
Facial angiofibroma or forehead plaque	
Ungual or periungual fibroma (non-traumatic)	
Hypomelanotic macules (>3)	
Shagreen patch	
Multiple retinal hamartomas	
Cardiac rhabdomyoma	
Renal angiomyolipoma	
Pulmonary lymphangioleiomyomatosis	

Table 596-4	Minor Features of TSC
Cerebral white matter migration lines	
Multiple dental pits	
Gingival fibromas	
Bone cysts	
Retinal achromatic patch	
Confetti skin lesions	
Nonrenal hamartomas	
Multiple renal cysts	
Hamartomatous rectal polyps	

that you can have infantile spasms without hypsarrhythmia in TSC patients. The seizures may be difficult to control and, at a later age, they may develop into myoclonic epilepsy (see Chapter 593). Vigabatrin is the first-line therapy for infantile spasms. ACTH can be used if treatment with vigabatrin fails. Anticonvulsant therapy of other seizure types in TSC should generally follow that of other epilepsies, and epilepsy surgery should be considered for medically refractory TSC patients.

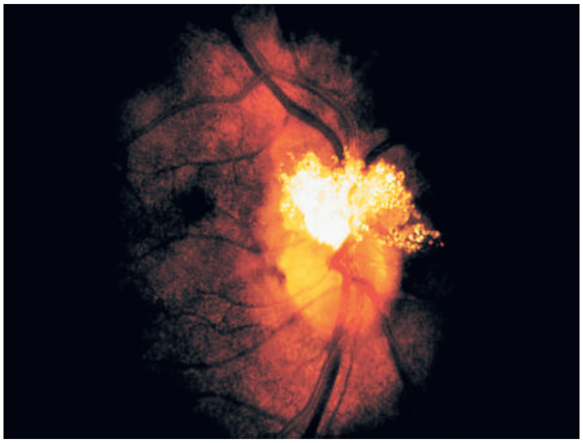

Figure 596-6 A mulberry lesion involving the superior part of the optic nerve in a patient with tuberous sclerosis. *(From Yanoff M, Sassani JW:* Ocular pathology, *ed 7, Philadelphia, 2015, WB Saunders, Fig. 2-7.)*

SKIN LESIONS

More than 90% of patients show the typical hypomelanotic macules that have been likened to an ash leaf on the trunk and extremities. Visualization of the hypomelanotic macule is enhanced by the use of a Wood ultraviolet lamp (see Chapter 653). To count as a major feature, at least three hypomelanotic macules must be present (see Fig. 596-5). Facial angiofibromas develop between 4 and 6 yr of age; they appear as tiny red nodules over the nose and cheeks and are sometimes confused with acne (see Fig. 596-5). Later, they enlarge, coalesce, and assume a fleshy appearance. A shagreen patch is also characteristic of TSC and consists of a roughened, raised lesion with an orange-peel consistency located primarily in the lumbosacral region (see Fig. 596-5). During adolescence or later, small fibromas or nodules

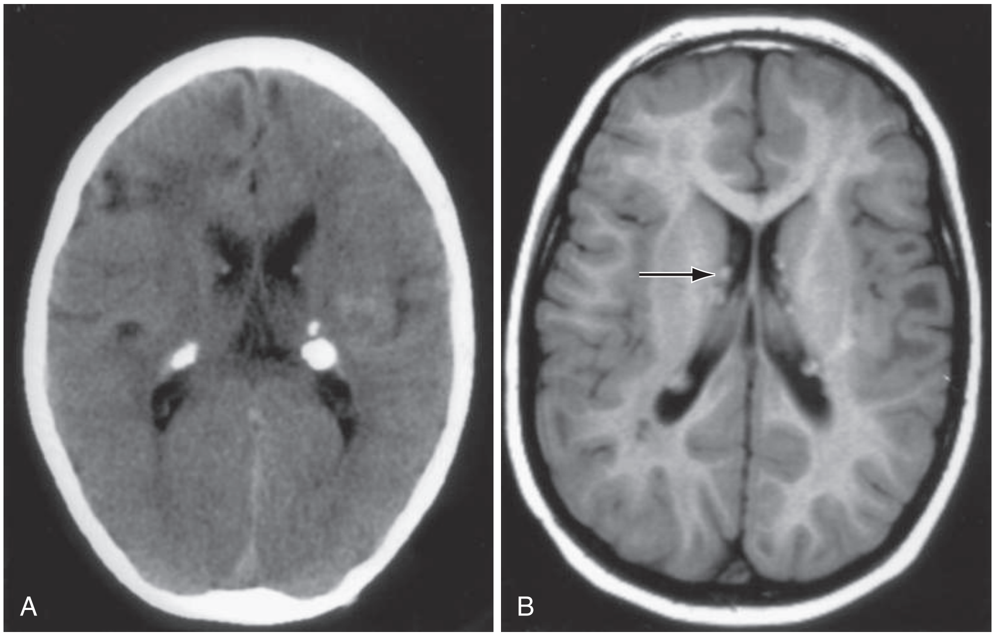

Figure 596-7 Tuberous sclerosis. **A,** CT scan with subependymal calcifications characteristic of tuberous sclerosis. **B,** The MRI demonstrates multiple subependymal nodules in the same patient *(black arrow)*. Parenchymal tubers are also visible on both the CT and the MRI scan as low-density areas in the brain parenchyma.

Figure 596-8 Periungual fibroma in a patient tuberous sclerosis complex (TSC).

of skin may form around fingernails or toenails in 15-20% of the TSC patients (Fig. 596-8).

OTHER ORGAN INVOLVEMENT

Approximately 50% of children with TSC have cardiac rhabdomyomas, which may be detected in the fetus at by an echocardiogram. The rhabdomyomas may be numerous or located at the apex of the left ventricle, and although they can cause congestive heart failure and arrhythmias in a minority of patients, they tend to slowly resolve spontaneously. In 75-80% of patients older than 10 yr of age, the kidneys display angiomyolipomas that are usually benign tumors. Angiomyolipomas begin in childhood in many individuals with TSC, but they may not be problematic until young adulthood. By the third decade of life, they may cause lumbar pain and hematuria from slow bleeding, and rarely they may result in sudden retroperitoneal bleeding. Embolization followed by corticosteroids is first-line therapy for angiomyolipoma presenting with acute hemorrhage. Nephrectomy should be avoided. For asymptomatic, growing angiomyolipomas measuring larger than 3 cm in diameter, an mTOR inhibitor, everolimus, is FDA-approved for treatment. Selective embolization or kidney-sparing resection is alternative therapies for asymptomatic angiomyolipoma. The current recommendation is to follow the angiomyolipoma by yearly imaging, and when the size of the lesion reaches more than 4 cm, to use transcatheter tumor embolization for treatment. Single or multiple renal cysts are also commonly present in TSC. Lymphangioleiomyomatosis is the classical pulmonary lesion in TSC and only affects women after the age of 20 yr.

Diagnosis of TSC relies on a high index of suspicion when assessing a child with infantile spasms. A careful evaluation for the typical skin and retinal lesions should be completed in all patients with a seizure disorder or autism spectrum disorder. Brain MRI confirms the diagnosis in most cases. Genetic testing for *TSC1* and *TSC2* mutations is available and may be considered when the individual patient does not meet all the clinical criteria. Prenatal testing may be offered when a known TSC mutation exists in that family.

MANAGEMENT

As for routine follow-up of individuals with TSC, the following are recommended in addition to physical examination: brain MRI every 1-3 yr, renal imaging (US, CT or MRI) every 1-3 yr and neurodevelopmental testing at the time of beginning 1st grade. Based on the complications of the disease, additional follow-up testing may be required for each individual. Symptoms and signs of increased intracranial pressure suggest obstruction of the foramen of Monro by a SEGA and warrant immediate investigation and surgical intervention.

Bibliography is available at Expert Consult.

596.3 Sturge-Weber Syndrome

Mustafa Sahin

Sturge-Weber syndrome (SWS) is a sporadic vascular disorder and consists of a constellation of symptoms and signs including a facial capillary malformation (port-wine stain), abnormal blood vessels of the brain (leptomeningeal angioma) and abnormal blood vessels of the eye leading to glaucoma. Patients present with seizures, hemiparesis, stroke-like episodes, headaches, and developmental delay. Approximately 1 in 50,000 live births are affected with SWS.

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ETIOLOGY

The sporadic incidence and focal nature of SWS suggests the presence of somatic mutations. Whole-genome sequencing from affected and unaffected skin of 3 patients with SWS identified a single-nucleotide variant (c.548G→A, p.Arg183Gln) in the *GNAQ* gene. This mutation has been confirmed in samples of affected tissue from 88% of a larger cohort of SWS patients as well as 92% of the participants with apparently nonsyndromic port-wine stains. Brain tissue from SWS patients also demonstrated the same change in the *GNAQ* gene. These results strongly suggest that SWS occurs as a result of mosaic mutations in *GNAQ*.

The condition is thought to result from anomalous development of the embryonic vascular bed in the early stages of facial and cerebral development. There are hypotheses about aberrant sympathetic innervation, increased vascular growth factors and defects in extracellular matrix, but these remain to be tested. Low flow angiomatosis of the leptomeninges appears to result in a chronic hypoxic state leading to cortical atrophy and calcifications.

CLINICAL MANIFESTATIONS

The facial port-wine stain is present at birth, tends to be unilateral, and always involves the upper face and eyelid, in a distribution consistent with the ophthalmic division of the trigeminal nerve (Fig. 596-9). The capillary malformation may also be evident over the lower face, trunk, and in the mucosa of the mouth and pharynx. It is important to note that not all children with facial port-wine stain have SWS even though the genetic defect appears to be the same. In fact, the overall incidence of SWS has been reported to be 8-33% in those with a port-wine stain. Buphthalmos and glaucoma of the ipsilateral eye are common complications. The incidence of epilepsy in patients with SWS is 75-90%, and seizures develop in most patients in the 1st yr of life. They are typically focal tonic–clonic and contralateral to the side of the facial capillary malformation. The seizures may become refractory to anticonvulsants and are associated with a slowly progressive hemiparesis in many cases. Transient stroke-like episodes or visual defects persisting for several days and unrelated to seizure activity are common and probably result from thrombosis of cortical veins in the affected region. Although neurodevelopment appears to be normal in the 1st yr of life, intellectual disability or severe learning disabilities are present in at least 50% in later childhood, probably the result of intractable epilepsy and increasing cerebral atrophy.

DIAGNOSIS

MRI with contrast is the imaging modality of choice for demonstrating the leptomeningeal angioma in SWS (Fig. 596-10). White matter abnormalities are common and are thought to be a result of chronic hypoxia. Often, atrophy is noted ipsilateral to the leptomeningeal angiomatosis. Calcifications can be seen best with a head CT (Fig. 596-11).

Figure 596-10 Gadolinium-enhanced axial T1 fluid-attenuated inversion recovery (FLAIR) images of a 15 mo old with Sturge-Weber syndrome shows leptomeningeal enhancement in left hemisphere.

Figure 596-9 Port-wine stain involving both V1 and V2 dermatomes. *(Courtesy of Dr. Anne W. Lucky, Cincinnati Children's Hospital.)*

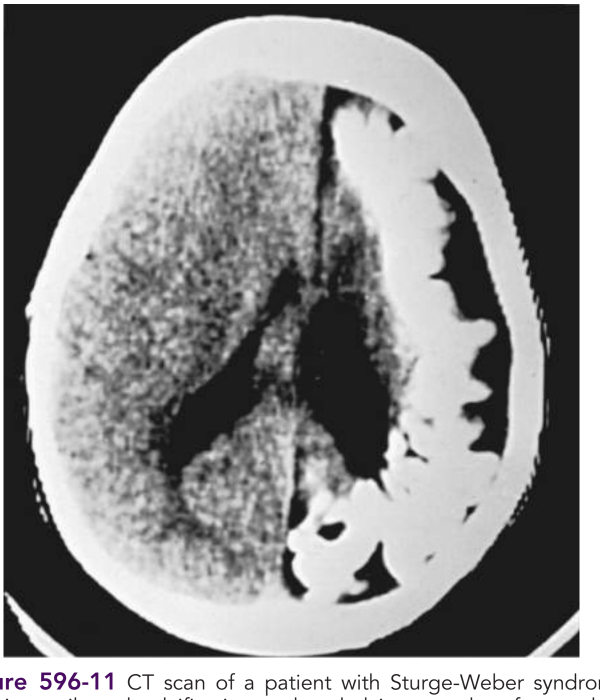

Figure 596-11 CT scan of a patient with Sturge-Weber syndrome showing unilateral calcification and underlying atrophy of a cerebral hemisphere.

Ophthalmologic evaluation examining for glaucoma is also necessary. Based on the involvement of the brain and the face, there are 3 types of SWS according to the Roach Scale:

1. Type I—Both facial and leptomeningeal angiomas; may have glaucoma
2. Type II—Facial angioma alone (no central nervous system involvement); may have glaucoma
3. Type III—Isolated leptomeningeal angiomas; usually no glaucoma

MANAGEMENT

Management of SWS is symptomatic and multidisciplinary but not well studied by prospective studies. It is aimed at seizure control, treatment of headaches, and prevention of stroke-like episodes, as well as monitoring of glaucoma and laser therapy for the cutaneous capillary malformations. Seizures beginning in infancy are not always associated with a poor neurodevelopmental outcome. For patients with well-controlled seizures and normal or near-normal development, management consists of anticonvulsants and surveillance for complications including glaucoma, buphthalmos, and behavioral abnormalities. If the seizures are refractory to anticonvulsant therapy, especially in infancy and the 1st 1-2 yr, and arise from primarily 1 hemisphere, most medical centers advise a hemispherectomy. Because of the risk of glaucoma, regular measurement of intraocular pressure is indicated. The facial port-wine stain is often a target of ridicule by classmates, leading to psychologic trauma. Pulsed-dye laser therapy often provides excellent clearing of the port-wine stain, particularly if it is located on the forehead.

Bibliography is available at Expert Consult.

596.4 Von Hippel-Lindau Disease

Mustafa Sahin

von Hippel-Lindau disease affects many organs, including the cerebellum, spinal cord, retina, kidney, pancreas, and epididymis. Its incidence is around 1 in 36,000 newborns. It results from an autosomal-dominant mutation affecting a tumor suppressor gene, *VHL*. Approximately 80% of individuals with von Hippel-Lindau syndrome have an affected parent, and approximately 20% have a de novo gene mutation. Molecular testing is available and detects mutations in almost 100% of probands.

The major neurologic features of the condition include cerebellar hemangioblastomas and retinal angiomas. Patients with cerebellar hemangioblastoma present in early adult life with symptoms and signs of increased intracranial pressure. A smaller number of patients have hemangioblastoma of the spinal cord, producing abnormalities of proprioception and disturbances of gait and bladder dysfunction. A CT or MRI scan typically shows a cystic cerebellar lesion with a vascular mural nodule. Total surgical removal of the tumor is curative.

Approximately 25% of patients with cerebellar hemangioblastoma have retinal angiomas. Retinal angiomas are characterized by small masses of thin-walled capillaries that are fed by large and tortuous arterioles and venules. They are usually located in the peripheral retina so that vision is unaffected. Exudation in the region of the angiomas may lead to retinal detachment and visual loss. Retinal angiomas are treated with photocoagulation and cryocoagulation, and both have produced good results.

Cystic lesions of the kidneys, pancreas, liver, and epididymis as well as pheochromocytoma are frequently associated with von Hippel-Lindau disease. Renal carcinoma is the most common cause of death. Regular follow-up and appropriate imaging studies are necessary to identify lesions that may be treated at an early stage.

Bibliography is available at Expert Consult.

596.5 Linear Nevus Syndrome

Mustafa Sahin

This sporadic condition is characterized by a facial nevus and neurodevelopmental abnormalities. The nevus is located on the forehead and nose and tends to be midline in its distribution. It may be quite faint during infancy but later becomes hyperkeratotic, with a yellow-brown appearance. Two thirds of the patients with linear nevus syndrome demonstrate associated neurologic findings, including cortical dysplasia, glial hamartomas, and low-grade gliomas. Cerebral and cranial anomalies, predominantly hemimegalencephaly and enlargement of the lateral ventricles, were reported in 72% of cases. The incidence of epilepsy has been reported as high as 75% and intellectual disability as high as 60%. Focal neurologic signs including hemiparesis and homonymous hemianopia may also be seen.

Bibliography is available at Expert Consult.

596.6 PHACE Syndrome

Mustafa Sahin

See also Chapter 650.

The syndrome denotes *p*osterior fossa malformations, *h*emangiomas, *a*rterial anomalies, *c*oarctation of the aorta and other cardiac defects, and *e*ye abnormalities. It is also referred to as *PHACES syndrome* when ventral developmental defects, including *s*ternal clefting and/or a *s*upraumbilical raphe, are present. Large facial hemangiomas may be associated with a Dandy-Walker malformation, vascular anomalies (coarctation of aorta, aplasia or hypoplastic carotid arteries, aneurysmal carotid dilation, aberrant left subclavian artery), glaucoma, cataracts, microphthalmia, optic nerve hypoplasia, and ventral defects (sternal clefts). The facial hemangioma is typically ipsilateral to the aortic arch. The Dandy-Walker malformation is the most common developmental abnormality of the brain. Other anomalies include hypoplasia or agenesis of the cerebellum, cerebellar vermis, corpus callosum, cerebrum, and septum pellucidum. Cerebrovascular anomalies can result in acquired, progressive vessel stenosis and acute ischemic stroke. According to a case series of 29 children with PHACE syndrome, 44% had language delay, 36% gross motor delay, and 8% fine motor delay; 52% had an abnormal neurologic exam, with speech abnormalities as the most common finding. Overall, there is a female predominance. The underlying pathogenesis of PHACE syndrome remains unknown. Propranolol is starting to be used for treatment of the infantile hemangiomas associated with PHACE syndrome.

Bibliography is available at Expert Consult.

596.7 Incontinentia Pigmenti

Mustafa Sahin

This rare, heritable, multisystem ectodermal disorder features dermatologic, dental, and ocular abnormalities. The phenotype is produced by functional mosaicism caused by random X-inactivation of an X-linked dominant gene that is lethal in males (*IKBKG [inhibitor of kappa B kinase gamma,* previously *NEMO]* gene). The paucity of affected males, the occurrence of female-to-female transmission, and an increased frequency of spontaneous abortions in carrier females support this supposition.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

This disease has 4 phases, not all of which may occur in a given patient. The **1st phase** is evident at birth or in the 1st few wk of life and consists of erythematous linear streaks and plaques of vesicles (Fig. 596-12) that are most pronounced on the limbs and circumferentially

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Figure 596-12 Whorled vesicular phase of incontinentia pigmenti.

on the trunk. The lesions may be confused with those of herpes simplex, bullous impetigo, or mastocytosis, but the linear configuration is unique. Histopathologically, epidermal edema and eosinophil-filled intraepidermal vesicles are present. Eosinophils also infiltrate the adjacent epidermis and dermis. Blood eosinophilia as high as 65% of the white blood cell count is common. The **1st stage** generally resolves by 4 mo of age, but mild, short-lived recurrences of blisters may develop during febrile illnesses. In the **2nd phase**, as blisters on the distal limbs resolve, they become dry and hyperkeratotic, forming verrucous plaques. The verrucous plaques rarely affect the trunk or face and generally involute within 6 mo. Epidermal hyperplasia, hyperkeratosis, and papillomatosis are characteristic. The **3rd or pigmentary stage** is the hallmark of incontinentia pigmenti. It generally develops over weeks to months and may overlap the earlier phases, be evident at birth, or, more commonly, begin to appear in the 1st few wk of life. Hyperpigmentation is more often apparent on the trunk than the limbs and is distributed in macular whorls, reticulated patches, flecks, and linear streaks that follow Blaschko lines. The axillae and groin are invariably affected. The sites of involvement are not necessarily those of the preceding vesicular and warty lesions. The pigmented lesions, once present, persist throughout childhood. They generally begin to fade by early adolescence and often disappear by age 16 yr. Occasionally, the pigmentation remains permanently, particularly in the groin. The lesion, histopathologically, shows vacuolar degeneration of the epidermal basal cells and melanin in melanophages of the upper dermis as a result of incontinence of pigment. In the **4th stage**, hairless, anhidrotic, hypopigmented patches or streaks occur as a late manifestation of incontinentia pigmenti; they may develop, however, before the hyperpigmentation of stage 3 has resolved. The lesions develop mainly on the flexor aspect of the lower legs and less often on the arms and trunk.

Approximately 80% of affected children have other defects. Alopecia, which may be scarring and patchy or diffuse, is most common on the vertex and occurs in up to 40% of patients. Hair may be lusterless, wiry, and coarse. Dental anomalies, which are present in up to 80% of patients and are persistent throughout life, consist of late dentition, hypodontia, conical teeth, and impaction. Central nervous system manifestations, including seizures, intellectual disability, hemiplegia, hemiparesis, spasticity, microcephaly, and cerebellar ataxia, are found in up to 30% of affected children. Ocular anomalies, such as neovascularization, microphthalmos, strabismus, optic nerve atrophy, cataracts, and retrolenticular masses, occur in >30% of children. Nonetheless, >90% of patients have normal vision. Less common abnormalities include dystrophy of nails (ridging, pitting) and skeletal defects.

Diagnosis of incontinentia pigmenti is made on clinical grounds, although major and minor criteria have been established to aid in diagnosis. Wood's lamp examination may be useful in older children and adolescents to highlight pigmentary abnormalities. Clinical molecular testing is available, and in 80% of the affected patients a deletion that removes exons 4 through 10 of *IKBKG* gene can be detected. Differential diagnosis includes hypomelanosis of Ito, which presents with similar skin manifestations and is often associated with chromosomal mosaicism.

MANAGEMENT

The choice of investigative studies and the plan of management depend on the occurrence of particular noncutaneous abnormalities since the skin lesions are benign. The high incidence of associated major anomalies warrants genetic counseling.

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Chapter 597

Movement Disorders

Jonathan W. Mink

Movement disorders are characterized by abnormal or excessive involuntary movements that may result in abnormalities in posture, tone, balance, or fine motor control. Most movement disorders in children are characterized by involuntary movements. These involuntary movements can represent the sole disease manifestation, or they may be one of many signs and symptoms.

Evaluation of movement disorders begins with a comprehensive history and careful neurologic examination. It is often difficult for children and caregivers to describe abnormal movements, which makes observation of the movements by the clinician an essential component of the evaluation. If the movements are not apparent at the time of the examination, video examples from home or school can be invaluable. With the increasing availability of high quality video capability on cellular phones, obtaining a short video is feasible for most families. Resources are available to guide families in gathering useful video data.

There is no specific diagnostic test to differentiate among movement disorders. The category of movement assists in localizing the pathologic process, whereas the onset, age, and degree of abnormal motor activity and associated neurologic findings help organize the investigation.

When considering the type of movement disorder, the following questions concerning the history and examination of the movement are helpful.

- What is the distribution of the movements across body parts?
- Are the movements symmetric?
- What is the speed of the involuntary movements? Are they rapid and fast or slow and sustained?
- When do the movements occur? Are they present at rest? Are they present with maintained posture or with voluntary actions?
- Are the movements seen in relation to certain postures or boy positions?
- Do the abnormal movements occur only with specific tasks?
- Can the child voluntarily suppress the movements, even for a short time?
- Are the movements stereotyped?
- Are the movements rhythmic?
- What is the temporal pattern of the movements? Are they continuous or intermittent? Do they occur in discrete episodes?
- Are the involuntary movements preceded by an urge to make the movement?
- Do the movements persist during sleep?
- Are the movements associated with impairment of motor function?
- What factors aggravated or alleviate the movements?

Table 597-1 Selected Types of Involuntary Movement in Childhood

TYPE	CHARACTERISTICS
Stereotypies (see Chapter 24)	Involuntary, patterned, coordinated, repetitive, rhythmic movements that occur in the same fashion with each repetition
Tics (see Chapter 24)	Involuntary, sudden, rapid, abrupt, repetitive, nonrhythmic, simple or complex motor movements or vocalizations (phonic productions). Tics are usually preceded by an urge that is relieved by carrying out the movement
Tremor	Oscillating, rhythmic movements about a fixed point, axis, or plane
Dystonia (see Chapter 597.3)	Intermittent and sustained involuntary muscles contractions that produce abnormal postures and movements of different parts of the body, often with a twisting quality
Chorea (see Chapter 597.2)	Involuntary, continual, irregular movements or movement fragments with variable rate and direction that occur unpredictably and randomly
Ballism	Involuntary, high amplitude, flinging movements typically occurring proximally. Ballism is essentially a large amplitude chorea
Athetosis	Slow, writhing, continuous, involuntary movements
Myoclonus	Sudden, quick, involuntary muscle jerks

The first decision to be made is whether the movement disorder is "hyperkinetic"(characterized by excessive and involuntary movements) or "hypokinetic" (characterized by slow voluntary movements and a general paucity of movement). Hyperkinetic movement disorders are much more common than hypokinetic disorders in children. Once the category of movement disorder is recognized, etiology can be considered. Clinical history, including birth history, medication/toxin exposure, trauma, infections, family history, progression of the involuntary movements, developmental progress, and behavior should be explored as the underlying cause is established. Table 597-1 lists types and clinical characteristics of selected hyperkinetic movement disorders.

597.1 Ataxias

Denia Ramirez-Montealegre and Jonathan W. Mink

Ataxia is the inability to make smooth, accurate, and coordinated movements, usually because of a dysfunction of the cerebellum, its inputs or outputs, sensory pathways in the posterior columns of the spinal cord, or a combination of these. Ataxias may be generalized or primarily affect gait or the hands and arms or trunk; they may be acute or chronic; acquired or genetic (Tables 597-2 to 597-5).

Signs and symptoms of ataxia include clumsiness, difficulty walking or sitting, falling to 1 side, slurred speech, hypotonia, intention tremor, dizziness, and delayed motor development. Genetic or chronic causes of cerebellar ataxia are often characterized by a long duration of symptoms, a positive family history, muscle weakness and abnormal gait, abnormal tone and strength, abnormal deep tendon reflexes, pes cavus, and sensory defects. Distinguishing ataxia from vestibular dysfunction may be difficult; however, labyrinth disorders are often characterized by severe vertigo, nausea and vomiting, position-induced vertigo, and a severe sense of unsteadiness.

Congenital anomalies of the posterior fossa, including the Dandy-Walker malformation, Chiari malformation, and encephalocele, are prominently associated with ataxia because of their destruction or replacement of the cerebellum (see Chapter 591.9). *MRI is the method of choice for investigating congenital abnormalities of the cerebellum, vermis, and related structures.* **Agenesis of the cerebellar vermis** presents in infancy with generalized hypotonia and decreased deep-tendon reflexes. Delayed motor milestones and truncal ataxia are typical. **Joubert syndrome and related disorders** are autosomal recessive disorders marked by developmental delay, hypotonia, abnormal eye movements, abnormal respirations, and a distinctive malformation of the cerebellum and brainstem that manifests as the "molar tooth sign" on MRI. Mutations in more than 21 different genes are associated with Joubert syndrome, but only approximately 50% of cases have a demonstrated causal mutation (see Chapter 591).

The major **infectious causes of ataxia** include cerebellar abscess, acute labyrinthitis, and acute cerebellar ataxia. **Acute cerebellar ataxia** occurs primarily in children 1-3 yr of age and is a diagnosis of exclusion. The condition often follows a viral illness, such as varicella virus, coxsackievirus, or echovirus infection by 2-3 wk and is thought to represent an autoimmune response to the viral agent affecting the cerebellum (see Chapters 250, 253, and 603). The onset is sudden, and the truncal ataxia can be so severe that the child is unable to stand or sit. Vomiting may occur initially, but fever and nuchal rigidity are absent. Horizontal nystagmus is evident in approximately 50% of cases and, if the child is able to speak, dysarthria may be impressive. Examination of the cerebrospinal fluid is typically normal at the onset of ataxia but a mild lymphocytic pleocytosis (10-30/mm^3) is not unusual. Later in the course, the cerebrospinal fluid protein undergoes a moderate elevation. The ataxia begins to improve in a few weeks but may persist for as long as 3 mo and rarely longer than that. The incidence of acute cerebellar ataxia appears to have declined with increased rates of vaccination against varicella. The prognosis for complete recovery is excellent; a small number have long-term sequelae, including behavioral and speech disorders as well as ataxia and incoordination. **Acute cerebellitis** in contrast is a more severe form of cerebellar ataxia demonstrating abnormal MRI scans, more severe symptoms, and a poorer long-term prognosis. Infectious agents include Epstein-Barr virus, mycoplasma, mumps, and influenza virus, although in many the etiology is unknown; autoimmune cerebellitis may represent some of these unknown cases. Patients may present with ataxia, increased intracranial pressure from obstructive hydrocephalus, headache and fever. **Acute labyrinthitis** may be difficult to differentiate from acute cerebellar ataxia in a toddler. The condition is associated with middle-ear infections and presents with intense vertigo, vomiting, and abnormalities in labyrinthine function.

Toxic causes of ataxia include alcohol, thallium (which is used occasionally in homes as a pesticide), and the anticonvulsants, particularly phenytoin and carbamazepine when serum levels exceed the usual therapeutic range.

Brain tumors (see Chapter 497), including tumors of the cerebellum and frontal lobe, as well as peripheral nervous system neuroblastoma, may present with ataxia. Cerebellar tumors cause ataxia because of direct disruption of cerebellar function or indirectly because of increased intracranial pressure from compression of the fourth ventricle. Frontal lobe tumors may cause ataxia as a consequence of destruction of the association fibers connecting the frontal lobe with the cerebellum or because of increased intracranial pressure. Neuroblastoma (see Chapter 498) may be associated with a paraneoplastic encephalopathy characterized by progressive ataxia, myoclonic jerks,

Table 597-2 Selected Causes of Ataxia in Childhood

CONGENITAL
- Agenesis of vermis of the cerebellum
- Aplasia or dysplasia of the cerebellum
- Basilar impression
- Cerebellar dysplasia with microgyria, macrogyria, or agyria
- Cervical spinal bifida with herniation of the cerebellum (Chiari malformation type 3)
- Chiari malformation
- Dandy-Walker syndrome
- Encephalocele
- Hydrocephalus (progressive)
- Hypoplasia of the cerebellum

DEGENERATIVE AND/OR GENETIC
- Acute intermittent cerebellar ataxia
- Ataxia, retinitis pigmentosa, deafness, vestibular abnormality, and intellectual deterioration
- Ataxia-telangiectasia
- Biemond posterior column ataxia
- Cerebellar ataxia with deafness, anosmia, absent caloric responses, nonreactive pupils, and hyporeflexia
- Cockayne syndrome
- Dentate cerebellar ataxia (dyssynergia cerebellaris progressiva)
- Familial ataxia with macular degeneration
- Friedreich ataxia
- Hereditary cerebellar ataxia, intellectual retardation, choreoathetosis, and eunuchoidism
- Hereditary cerebellar ataxia with myotonia and cataracts
- Hypertrophic interstitial neuritis
- Marie ataxia
- Marinesco-Sjögren syndrome
- Multiple-system atrophy
- Pelizaeus-Merzbacher disease
- Periodic attacks of vertigo, diplopia, and ataxia–autosomal-dominant inheritance
- Posterior and lateral column difficulties, nystagmus, and muscle atrophy
- Progressive cerebellar ataxia and epilepsy
- Ramsay Hunt syndrome (myoclonic seizures and ataxia)
- Roussy-Lévy disease
- Spinocerebellar ataxia (SCA); olivopontocerebellar ataxias
- Vanishing white matter syndrome

ENDOCRINOLOGIC
- Acquired hypothyroidism
- Cretinism

INFECTIOUS, POSTINFECTIOUS, INFLAMMATORY
- Acute cerebellar ataxia
- Acute disseminated encephalomyelitis
- Autoimmune (anti-glutamic acid decarboxylase, anti–γ-aminobutyric $acid_B$ receptor antibodies)
- Cerebellar abscess
- Cerebellitis
- Coxsackievirus
- Diphtheria
- Echovirus
- Fisher syndrome
- Infectious mononucleosis (Epstein-Barr virus infection)
- Infectious polyneuropathy
- Japanese B encephalitis
- Mumps encephalitis
- *Mycoplasma* pneumonia
- Paraneoplastic (opsoclonus-myoclonus-ataxia syndrome)
- Pertussis
- Polio
- Postbacterial meningitis
- Rubeola
- Tuberculosis
- Typhoid
- Varicella

METABOLIC
- Abetalipoproteinemia
- Argininosuccinic aciduria
- Ataxia with vitamin E deficiency (AVED)
- Congenital disorders of glycosylation
- GM_2 gangliosidosis (late)
- Hartnup disease
- Hyperalaninemia
- Hyperammonemia I and II (urea cycle defects)
- Hypoglycemia
- Kearns-Sayre syndrome
- Leigh disease
- Maple syrup urine disease (intermittent)
- Myoclonic epilepsy with ragged red fibers (MERRF)
- Metachromatic leukodystrophy
- Mitochondrial complex defects (I, III, IV)
- Multiple carboxylase deficiency (biotinidase deficiency)
- Neuronal ceroid-lipofuscinosis
- Neuropathy, ataxia, retinitis pigmentosa (NARP)
- Niemann-Pick disease (late infantile)
- 5-Oxoprolinuria
- Pyruvate decarboxylase deficiency
- Refsum disease
- Sialidosis
- Triose-phosphate isomerase deficiency
- Tryptophanuria
- Wernicke encephalopathy

NEOPLASTIC
- Frontal lobe tumors
- Hemispheric cerebellar tumors
- Midline cerebellar tumors
- Neuroblastoma
- Pontine tumors (primarily gliomas)
- Spinal cord tumors

PRIMARY PSYCHOGENIC
- Conversion reaction

TOXIC
- Alcohol
- Benzodiazepines
- Carbamazepine
- Clonazepam
- Lead encephalopathy
- Neuroblastoma
- Phenobarbital
- Phenytoin
- Primidone
- Tic paralysis poisoning

TRAUMATIC
- Acute cerebellar edema
- Acute frontal lobe edema

VASCULAR
- Angioblastoma of cerebellum
- Basilar migraine
- Cerebellar embolism
- Cerebellar hemorrhage
- Cerebellar thrombosis
- Posterior cerebellar artery disease
- Vasculitis
- von Hippel-Lindau disease

Modified from Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Box 67-1.*

Table 597-3 Treatable Causes of Inherited Ataxia

DISORDER	METABOLIC ABNORMALITY	DISTINGUISHING CLINICAL FEATURES	TREATMENT
Acute disseminated encephalomyelitis	Demyelination	Positive MRI findings	Steroids, IVIG, rituximab
Ataxia with vitamin E deficiency	Mutation in α-tocopherol transfer protein	Ataxia, areflexia, retinopathy	Vitamin E
Bassen-Kornzweig syndrome	Abetalipoproteinemia	Acanthocytosis, retinitis pigmentosa, fat malabsorption	Vitamin E
Hartnup disease	Tryptophan malabsorption	Pellagra rash, intermittent ataxia	Niacin
Familial episodic ataxia type 1 and type 2	Mutations in potassium channel (KCNA1) and α_{1A} voltage-gated calcium channel, respectively	Episodic attacks, worse with pregnancy or birth control pills	Acetazolamide
Multiple carboxylase deficiency	Biotinidase deficiency	Alopecia, recurrent infections, variable organic aciduria	Biotin
Mitochondrial complex defects	Complexes I, III, IV	Encephalomyelopathy	Possibly riboflavin, CoQ10, dichloroacetate
Opsoclonus-myoclonus-ataxia syndrome	Paraneoplastic or spontaneous autoimmune	Underlying neuroblastoma or autoantibodies	Steroids, IVIG, rituximab
Pyruvate dehydrogenase deficiency	Block in E-M and Krebs cycle interface	Lactic acidosis, ataxia	Ketogenic diet, possibly dichloroacetate
Refsum disease	Phytanic acid, α-hydroxylase	Retinitis pigmentosa, cardiomyopathy, hypertrophic neuropathy, ichthyosis	Dietary restriction of phytanic acid
Urea cycle defects	Urea cycle enzymes	Hyperammonemia	Protein restriction, arginine, benzoate, α-ketoacids

CoQ10, Coenzyme Q10; E-M, mitochondrial electron transport; IVIG, intravenous immunoglobulin.

Modified from Stumpf DA: The inherited ataxias. Pediatr Neurol *1:129-133, 1985, Table 1; and from Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors:* Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Table 67-1.*

Table 597-4 Autosomal-Recessive Cerebellar Ataxias

ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (yr)
Friedreich ataxia	9q13	*X25*	Frataxin	GAA repeat	2-51
Friedreich ataxia 2	9p23–p11	Unknown	Unknown	Unknown	5-20
AVED	8q13	*TTP1*	TTPA	Missense mutation, deletion, insertion	2-52
Ataxia-telangiectasia	11q22.3	*ATM*	ATM	Missense and deletion mutations	Infancy
ATLD	11q21	*hMRE11*	MRE11A	Missense and deletion mutations	9-48 mo
Ataxia-ocular apraxia 1	9p13.3	*APTX*	Aprataxin	Frameshift, missense, nonsense mutations	2-18
SCAR1	9q34	*SETX*	Senataxin	Frameshift, missense, nonsense mutations	9-22
SCAR2	9q34–qter	Unknown	Unknown	Unknown	Congenital
SCAR3	6p23–p21	Unknown	Unknown	Unknown	3-52
SCAR4	1p36	Unknown	Unknown	Unknown	23-39
SCAR5	15q24–q26	Unknown	Unknown	Unknown	1-10
SCAR6	20q11–q13	Unknown	Unknown	Unknown	Infancy
SCAR7	11p15	Unknown	Unknown	Unknown	Childhood
SCAR8	11p15	*SYNE1*	SYNE1	Splice site mutation, nonsense mutations	17-46

Continued

Table 597-4 Autosomal-Recessive Cerebellar Ataxias—cont'd

ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (yr)
SCAR9	1q41	*ADCK3*	ADCK3	Splice site mutation, missense, nonsense mutations	3-11
Ataxia, Cayman type	19q13.3	*ATCAY*	Caytaxin	Missense mutation	Birth
IOSCA	10q24	*C10orf2*	Twinkle	Missense, silent mutations	9-24 mo
Progressive myoclonic epilepsy	21q22.3	*CST6*	Cystatin B	5′ dodecamer repeat	6–13
ARSACS	13q12	*SACS*	Sacsin	Frameshift and nonsense mutations	1–20
Congenital disorders of glycosylation	Multiple	Multiple	Multiple		Birth

ARSACS, autosomal-recessive spastic ataxia of Charlevoix-Saguenay; ATLD, ataxia-telangiectasia-like disorder; AVED, ataxia with vitamin E deficiency; IOSCA, infantile-onset spinocerebellar ataxia; SCAR, spinocerebellar ataxia, autosomal-recessive.

From Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Table 67-2.*

Table 597-5 Autosomal-Dominant Cerebellar Ataxias

ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (yr)	NORMAL REPEAT	EXPANDED REPEAT	DURATION OF EPISODES
POLYGLUTAMINE EXPANSION								
SCA1	6p23	*SCA1*	Ataxin-1	CAG repeat	6-60	6-44*	39-82*	
SCA2	12q24	*SCA2*	Ataxin-2	CAG repeat	2-65	15-24	35-59	
SCA3/MJD	14q24.3-q31	*MJD1*	Ataxin-3	CAG repeat	11-70	13-47*	45-84*	
SCA6	19q13	*CACNA1A*	CACNA1A	CAG repeat	16-v73	4-20	21-33	
SCA7	3p21.1-p12	*SCA7*	Ataxin-7	CAG repeat	Birth-53	4-35	37-460	
SCA17	6q27	*SCA17*	TBP	CAG repeat	3-48	25-42	45-66	
DRPLA	12p13.31	*DRPLA*	Atrophin-1	CAG repeat	4-55 mo	7-34	53-93	
NONCODING EXPANSION								
SCA8	13q21	*SCA8*	SCA8 RNA	CTG repeat in 3′ UTR	18-72	2-91*	110-155*	
SCA10	22q13	*SCA10*	Ataxin-10	ATTCT repeat in intron 9	14-45	10-29	750-4500	
SCA12	5q31-q33	*SCA12*	P2R2B	CAG repeat in 5′ UTR	8-55	7-32	55-78	
SCA31	16q22.1	*BEAN/TK2*	BEAN/TK2	TGGAA repeat insertion in intron of BEAN and TK	45-72	Rarely (0.23%) 1.5-2.0 kb	2.5-3.8 kb	
OTHER MUTATIONS								
SCA14	19q13.4	*PKC-γ*	PKC-γ	Missense mutation	10-69			
SCA27	13q34	*FGF14*	FGF14	Fibroblast growth factor deficiency	15-20			
SCA5	11p11-q11	*SPTBN2*	β-3 spectrin	Deletion, missense mutations	10-68			
SCA11	15q14-q21.3	*TTBK2*	TTBK2	Truncation mutation	15-43			
SCA13	19q13.3-q13.4	*KCNC3*	KCNC3	Missense mutations	<1-60			
SCA15	3p24.2-3pter	*ITPR1*	ITPR1	Deletion, missense mutation	Child–adult			
SCA28	18p11.22-q11.2.	*AFG3L2*	AFG3L2	Missense mutations	12-36			

Table 597-5 Autosomal-Dominant Cerebellar Ataxias—cont'd

ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (yr)	NORMAL REPEAT	EXPANDED REPEAT	DURATION OF EPISODES
MUTATION UNKNOWN								
SCA4	16q22	Unknown	Unknown	Unknown	19-59			
SCA18/SMNA	7q31-q32	Unknown	Unknown	Unknown	12-25			
SCA19	1p21-q21	Unknown	Unknown	Unknown	10-45			
SCA20	11	Unknown	Unknown	Unknown	19-64			
SCA21	7p21.3–p15.1	Unknown	Unknown	Unknown	6-30			
SCA22	1p21-q23	Unknown	Unknown	Unknown	10-46			
SCA23	20p13-p12.2	Unknown	Unknown	Unknown	43-56			
SCA25	2p	Unknown	Unknown	Unknown	1.5-39			
SCA26	19p13.3	Unknown	Unknown	Unknown	26-60			
SCA30	4q34.3-q35.1	Unknown	Unknown	Unknown	45-76			
SAX1	12p13	Unknown	Unknown	Unknown	Early childhood to early 20s			
SPAR	Unknown	Unknown	Unknown	Unknown	15-35			
EPISODIC ATAXIA								
EA1	12p13	*EA1*	KCNA1	Channelopathy	Early childhood			Secs to mins
EA2/FHM	19p13	*CACNA1A*	CACNA1A	Channelopathy: missense and nonsense mutations	4-30			Hours
EA3	1q42	Unknown	Unknown	Unknown	1-42			1 min to 6 h
EA4	Unknown	Unknown	Unknown	Unknown	23-42			Short to constant
EA5	2q22-q23	*CACNB4*	CACNB4	Channelopathy: missense and nonsense mutations	Juvenile			Hours
EA6	5p13	*SLC1A3*	EAAT1	Missense mutation	5			Hours to days
EA7	19q13	Unknown	Unknown	Unknown	<20			Hours to days

*Some overlap of pathogenic and nonpathogenic repeat length.

DRPLA, dentatorubral-pallidoluysian atrophy; EA, episodic ataxia; FHM, familial hemiplegic migraine; MJD, Machado-Joseph disease; SAX, spastic ataxia; SCA, spinocerebellar ataxia; SMNA, sensorimotor neuropathy with ataxia; SPAR, spastic paraplegia, ataxia, and mental retardation; TBP, TATA-binding protein, UTR, untranslated region.

From Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, WB Saunders, Table 67-3.*

and opsoclonus (nonrhythmic, conjugate horizontal and vertical oscillations of the eyes).

Several **metabolic disorders** are characterized by ataxia, including abetalipoproteinemia, arginosuccinic aciduria, and Hartnup disease. **Abetalipoproteinemia** (Bassen-Kornzweig disease) begins in childhood with steatorrhea and failure to thrive (see Chapters 86.3 and 600). A blood smear shows acanthocytosis. Serum chemistries reveal decreased levels of cholesterol and triglycerides; serum β-lipoproteins are absent. Neurologic signs become evident by late childhood and consist of ataxia, retinitis pigmentosa, peripheral neuritis, abnormalities of position and vibration sense, muscle weakness, and intellectual disability. Vitamin E is undetectable in the serum of patients with neurologic symptoms.

Degenerative diseases of the central nervous system represent an important group of ataxic disorders of childhood because of the genetic consequences and poor prognosis. **Ataxia-telangiectasia,** an autosomal recessive condition, is the most common of the degenerative ataxias and is heralded by ataxia beginning at approximately age 2 yr and progressing to loss of ambulation by adolescence. Ataxia-telangiectasia is caused by mutations in the *ATM* gene located at 11q22-q23. ATM is a phosphytidylinositol-3 kinase that phosphorylates proteins involved in DNA repair and cell-cycle control. Oculomotor apraxia of horizontal gaze, defined as difficulty shifting gaze from one object to another and overshooting the target with lateral movement of the head, followed by refixating the eyes, is a frequent finding, as is strabismus, hypometric saccade pursuit abnormalities, and nystagmus. Ataxia-telangiectasia may present with chorea (see Chapter 597.2) rather than ataxia. The telangiectasia becomes evident by mid-childhood and is found on the bulbar conjunctiva, over the bridge of the nose, and on the ears and exposed surfaces of the extremities. Examination of the skin shows a loss of elasticity. Abnormalities of immunologic function that lead to frequent sinopulmonary infections include decreased serum and secretory immunoglobulin (Ig) A as well as diminished IgG_2, IgG_4, and IgE levels in more than 50% of patients. Children with ataxia-telangiectasia have a 50-100–fold increased risk of developing lymphoreticular tumors (lymphoma, leukemia, and Hodgkin disease) as well as brain tumors. Additional laboratory abnormalities include an increased incidence of chromosome breaks, particularly of chromosome 14, and elevated levels of α-fetoprotein. Death results from infection or tumor dissemination.

Friedreich ataxia is inherited as an autosomal-recessive disorder involving the spinocerebellar tracts, dorsal columns in the spinal cord, the pyramidal tracts, and the cerebellum and medulla. The majority of patients are homozygous for a GAA repeat expansion in the noncoding region of the gene coding for the mitochondrial protein frataxin. Mutations cause oxidative injury associated with excessive iron deposits in mitochondria. The onset of ataxia is somewhat later than in ataxia-telangiectasia, but usually occurs before age 10 yr. The ataxia is slowly progressive and involves the lower extremities to a greater degree than the upper extremities. The Romberg test result is positive; the deep-tendon reflexes are absent (particularly at the ankle), and the plantar response is typically extensor (Babinski sign). Patients develop

a characteristic explosive, dysarthric speech, and nystagmus is present in most children. Although patients may appear apathetic, their intelligence is preserved. They may have significant weakness of the distal musculature of the hands and feet. Marked loss of vibration and joint position sense is common and is caused by degeneration of the posterior columns. Friedreich ataxia is also characterized by skeletal abnormalities, including high-arched feet (pes cavus) and hammertoes, as well as progressive kyphoscoliosis. Results of electrophysiologic studies, including visual, auditory brainstem, and somatosensory-evoked potentials, are often abnormal. Hypertrophic cardiomyopathy with progression to intractable congestive heart failure is the cause of death for most patients.

Several forms of **spinocerebellar ataxia** are similar to Friedreich ataxia but are less common. **Roussy-Levy disease** has, in addition to ataxia, atrophy of the muscles of the lower extremity with a pattern of wasting similar to that observed in Charcot-Marie-Tooth disease; **Ramsay Hunt syndrome** has an associated myoclonic epilepsy.

There are more than 20 dominantly inherited spinocerebellar ataxias, some of which present in childhood. These include those associated with CAG (polyglutamine) repeats and noncoding microsatellite expansions. Dominantly inherited episodic ataxias caused by potassium or calcium channel dysfunction present as episodes of ataxia and muscle weakness. Some of these disorders may respond to acetazolamide. The dominantly inherited **olivopontocerebellar atrophies** include ataxia, cranial nerve palsies, and abnormal sensory findings in the 2nd or 3rd decade, but can present in children with rapidly progressive ataxia, nystagmus, dysarthria, and seizures.

Additional degenerative ataxias include **Pelizaeus-Merzbacher disease, neuronal ceroid lipofuscinoses,** and late-onset **GM_2 gangliosidosis** (see Chapters 86.4 and 600). Rare forms of progressive cerebellar ataxia have been described in association with **vitamin E deficiency.** A number of autosomal-dominant progressive spinocerebellar ataxias have been defined at the molecular level, including those caused by unstable trinucleotide repeat expansions.

597.2 Chorea, Athetosis, Tremor

Rebecca K. Lehman and Jonathan W. Mink

Chorea, meaning "dance-like" in Greek, refers to rapid, chaotic movements that seem to flow from 1 body part to another. Affected individuals exhibit motor impersistence, with difficulty keeping the tongue protruded ("darting tongue") or maintaining grip ("milkmaid grip"). Chorea tends to occur both at rest and with action. Patients often attempt to incorporate the involuntary movements into more purposeful movements, making them appear fidgety. *Chorea increases with stress and disappears in sleep.* Chorea can be divided into primary (i.e., disorders in which chorea is the dominant symptom and the etiology is presumed to be genetic) and secondary forms, with the vast majority of pediatric cases falling into the latter category (Tables 597-6 and 597-7).

Sydenham chorea (St. Vitus dance) is the most common acquired chorea of childhood. It occurs in 10-20% of patients with **acute rheumatic fever,** typically weeks to months after a group A β-hemolytic streptococcal infection (see Chapter 183.1). Peak incidence is at age 8-9 yr, with a female predominance of 2:1. There is evidence that group A β-hemolytic streptococci promote the generation of cross-reactive or polyreactive antibodies through molecular mimicry between streptococcal and host antigens. Specifically, antibodies against the *N*-acetyl-β-D-glucosamine epitope (GlcNAc) of streptococcal group A carbohydrate target intracellular β-tubulin and extracellular lysoganglioside GM_1 in human caudate-putamen preparations. These antibodies are also capable of directing calcium/calmodulin–dependent protein kinase II activation, which may cause the neurologic manifestations of Sydenham chorea by increasing dopamine release into the synapse.

The clinical hallmarks of Sydenham chorea are chorea, hypotonia, and emotional lability. Onset of the chorea is usually insidious but may be abrupt. Most patients have generalized chorea but the majority have asymmetric manifestations and up to 20% have hemichorea. Hypotonia manifests with the "pronator sign" (arms and palms turn outward when held overhead) and the "choreic hand" (spooning of the extended hand by flexion of the wrist and extension of the fingers). When chorea and hypotonia are severe, the child may be incapable of feeding, dressing, or walking without assistance. Speech is often involved, sometimes to the point of being unintelligible. Periods of uncontrollable crying and extreme mood swings are characteristic and may precede the onset of the movement disorder.

Table 597-6 Etiologic Classification of Choreic Syndromes

GENETIC CHOREAS
Huntington disease (rarely presents with chorea in childhood)
Huntington disease–like 2 and other Huntington disease –like syndromes
Dentatorubropallidoluysian atrophy
Neuroacanthocytosis
Leigh syndrome and other mitochondrial disorders
Ataxia telangiectasia
Benign hereditary chorea
Wilson disease
Spinocerebellar ataxia (types 2, 3, or 17)
Pantothene kinase–associated neurodegeneration (PKAN)
Paroxysmal kinesigenic choreoathetosis
Paroxysmal nonkinesigenic choreoathetosis
Fahr syndrome
Rett syndrome
STRUCTURAL BASAL-GANGLIA LESIONS
Vascular chorea in stroke, vasculitis, Moyamoya disease
Mass lesions (e.g., central nervous system lymphoma, metastatic brain tumors)
Joubert syndrome and related disorders
Multiple sclerosis plaques
Extrapontine myelinolysis
Trauma
PARAINFECTIOUS AND AUTOIMMUNE DISORDERS
Sydenham chorea
Systemic lupus erythematosus
Chorea gravidarum
Antiphospholipid antibody syndrome
Postinfectious or postvaccinal encephalitis
Anti–N-methyl-D-aspartate (NMDA)–receptor antibody syndrome (Limbic encephalitis)
Paraneoplastic choreas
INFECTIOUS CHOREA
HIV encephalopathy
Toxoplasmosis
Cysticercosis
Diphtheria
Bacterial endocarditis
Neurosyphilis
Scarlet fever
Viral encephalitis (mumps, measles, varicella)
METABOLIC DRUG OR TOXIC ENCEPHALOPATHIES
Acute intermittent porphyria
Hypo-/hypernatremia
Hypocalcemia
Hyperthyroidism
Hypoparathyroidism
Hepatic/renal failure
Carbon monoxide poisoning
Manganese poisoning
Mercury poisoning
Organophosphate poisoning
Pheochromocytoma
DRUG-INDUCED CHOREA (see Table 597-8)

Modified from Cardoso F, Seppi K, Mair KJ, et al: Seminar on choreas, Lancet Neurol *5:589–602, 2006.*

Table 597-7 Genetic Choreas

	MODE OF INHERITANCE	GENE, LOCATION	PROTEIN PRODUCT	USUAL AGE AT ONSET (yr)	CLINICAL SIGNS
HDL2*	AD†	*JPH3*, 16q	Junctophilin-3	20-40	Huntington disease phenotype, sometimes acanthocytosis; almost exclusively African ethnicity
SCA17	AD†	*TBP*, 6q	TBP	10-30	Cerebellar ataxia, chorea, dystonia, hyperreflexia, cognitive decline
DRPLA	AD†	*DRPLA*, 12p	Atrophin-1	About 20	Variable phenotypic picture including chorea, ataxia, seizures, psychiatric disturbances, dementia; more common in Japan than in Europe or United States
SCA3/MJD	AD†	*MJD*, 14q	Ataxin-3	35-40	Wide phenotypic variability with cerebellar ataxia, protruded eyes, chorea, dystonia, parkinsonian features, neuropathy, pyramidal tract features
SCA2	AD†	*Ataxin-2*, 12q	Ataxin-2	30-35	Cerebellar ataxia, chorea, markedly reduced velocity of saccadic eye movements, hyporeflexia
Chorea-acanthocytosis	AR	*VPS13A* (formerly *CHAC*), 9q	Chorein	20-50	Orofacial self-mutilation, dystonia, neuropathy, myopathy, seizures, acanthocytosis
McLeod syndrome	X-linked, recessive	*XK*, Xp	XK-protein	40-70	Dystonia, neuropathy, myopathy, cardiomyopathy, seizures, acanthocytosis, raised creatine kinase, weak expression of Kell antigen
Neuroferritinopathy	AD	*FTL*, 19q	FTL	20-55	Chorea, dystonia, parkinsonian features; usually reduced serum ferritin; MR abnormalities with cyst formation and increased T2 signal in globus pallidus and putamen
AT and ATLD	AR	*ATM*, 11q *(AT)* *MRE11*, 11q *(ATLD)*	ATM (AT) MRE11 (ATLD)	Childhood	Ataxia, neuropathy, oculomotor apraxia, other extrapyramidal manifestations including chorea, dystonia, and myoclonus In AT: oculocutaneous telangiectasias; predisposition to malignancies, IgA and IgG deficiency, high α-fetoprotein in serum and high concentrations of carcinoembryonic antigen
AOA 1 and 2	AR	*APTX*, 9p *(AOA 1)* *SETX*, 9q *(AOA 2)*	Aprataxin (AOA 1) Senataxin (AOA 2)	Childhood or adolescence (later onset in AOA 2)	Ataxia, neuropathy, oculomotor apraxia, other extrapyramidal manifestations including chorea and dystonia; ataxia with oculomotor apraxia type 1: hypoalbuminemia and hypercholesterolemia; ataxia with oculomotor apraxia type 2: raised α-fetoprotein in serum
Pantothenate kinase associated neurodegeneration (formerly Hallervorden-Spatz syndrome)	AR	*PANK2*, 20p	Pantothenate kinase 2	Childhood, but also adult-onset subtype	Chorea, dystonia, parkinsonian features, pyramidal tract features; MR abnormalities with decreased T2 signal in the globus pallidus and substantia nigra, "eye of the tiger" sign (hyperintense area within the hypointense area); sometimes acanthocytosis, abnormal cytosomes in lymphocytes

Continued

Table 597-7 Genetic Choreas—cont'd

	MODE OF INHERITANCE	GENE, LOCATION	PROTEIN PRODUCT	USUAL AGE AT ONSET (yr)	CLINICAL SIGNS
Lesch-Nyhan syndrome	X-linked, recessive	*HPRT*, Xq	Hypoxanthine-guanine phosphoribosyl-transferase	Childhood	Chorea, dystonia, hypotonia, self-injurious behavior with biting of fingers and lips, mental retardation; short stature, renal calculi, hyperuricemia
Wilson disease	AR	*ATP7B*, 13q	Copper transporting P-type adenosine triphosphatase (ATPase)	<40	Parkinsonian features, dystonia, tremor, rarely chorea, behavioral and cognitive change, corneal Kayser-Fleischer rings, liver disease
PKC syndrome and ICCA syndrome	AD	Unknown, 16p	Unknown	<1-40	Paroxysmal movement disorders presenting with recurrent brief episodes of abnormal involuntary movements with dramatic response to low-dose carbamazepine (PKC); recurrent brief episodes of abnormal involuntary movements in association with infantile convulsions (ICCA)
Benign hereditary chorea	AD	*TITF-1*, 14q; other	Thyroid transcription factor 1	Childhood	Chorea, mild ataxia; genetically heterogeneous

*HDL1, HDL3, and HDL4 are very rare conditions (only 1 family known) and therefore not included in the table.
†Disorders based on expanded CAG repeats (HDL2 based on CAG/CTG repeats; SCA 17 based on CAG/CAA repeats); age of symptom onset inversely related to repeat size.
AD, autosomal dominant; AOA, ataxia with oculomotor apraxia (types 1 or 2); AR, autosomal recessive; AT, ataxia telangiectasia; ATLD, ataxia telangiectasia–like disorder; DRPLA, dentatorubropallidoluysian atrophy; ICCA, infantile convulsions and paroxysmal choreoathetosis syndrome; MJD, Machado-Joseph disease; PKC, paroxysmal kinesigenic choreoathetosis; SCA, spinocerebellar ataxia (types 2, 3, or 17).
Modified from Cardoso F, Seppi K, Mair KJ, et al: Seminar on choreas, Lancet Neurol *5:589–602, 2006.*

Sydenham chorea is a clinical diagnosis; a combination of acute *and* convalescent serum antistreptolysin O titers may help to confirm an acute streptococcal infection. Negative titers do not exclude the diagnosis. All patients with Sydenham chorea should be evaluated for carditis and started on long-term antibiotic prophylaxis (e.g., penicillin G benzathine 1.2 million units IM every 4 wk or penicillin V 250 mg PO twice daily) to decrease the risk of rheumatic heart disease with recurrence. For patients with chorea that is impairing, treatment options include valproate, carbamazepine, and dopamine receptor antagonists. Historically, there have been conflicting data regarding the efficacy of prednisone, intravenous immunoglobulin, and other immunomodulatory agents in Sydenham chorea, making it difficult to recommend their routine use. A more recent randomized, double-blinded study of 37 children with Sydenham chorea compared high-dose prednisone (2 mg/kg/day, max: 60 mg) for 4 wk vs a placebo and found that steroids significantly reduced time to remission (54.3 days vs 119.9 days in controls). There is no evidence that treatment with prednisone alters recurrence rate or long-term outcome.

Sydenham chorea usually resolves spontaneously within 6-9 mo, although it can persist for up to 2 yr and, in rare cases, can remain a lifelong condition. Relapse in the 1st few yr is relatively common, occurring in 37.9% of patients in 1 series. Remote recurrence of chorea is rare, but may be provoked by streptococcal infections, pregnancy **(chorea gravidarum),** or oral contraceptive use.

Although much rarer than Sydenham chorea, **systemic lupus erythematosus** (see Chapter 158) is a well-known cause of chorea in children. In some cases, chorea may be the presenting sign of systemic lupus erythematosus. A recent retrospective study of a large pediatric lupus cohort examined the prevalence of antiphospholipid antibodies and evaluated their association with neuropsychiatric symptoms. There was a significant association between a persistently positive lupus anticoagulant and chorea ($p = 0.02$); however, only 2 of the 137 patients in the cohort had chorea. Regardless, a child with chorea of unknown cause should be investigated for the presence of antiphospholipid antibodies.

Table 597-8 Drugs That Can Induce Chorea

DOPAMINE RECEPTOR BLOCKING AGENTS (UPON WITHDRAWAL OR AS A TARDIVE SYNDROME) Phenothiazines Butyrophenones Benzamides	**CALCIUM CHANNEL BLOCKERS** Cinnarizine Flunarizine Verapamil
ANTIPARKINSONIAN DRUGS L-DOPA Dopamine agonists Anticholinergics	**OTHERS** Lithium Baclofen Digoxin Tricyclic antidepressants Cyclosporine Steroids/oral contraceptives Theophylline Propofol
ANTIEPILEPTIC DRUGS Phenytoin Carbamazepine Valproic acid	
PSYCHOSTIMULANTS Amphetamines Methylphenidate Cocaine	

Modified from Cardoso F, Seppi K, Mair KJ, et al: Seminar on choreas, Lancet Neurol *5:589–602, 2006.*

Additional causes of secondary chorea include metabolic (hyperthyroidism, hypoparathyroidism), infectious (Lyme disease), immune-mediated (systemic lupus erythematosus; anti–*N*-methyl-D-aspartate receptor antibody syndrome), vascular (stroke, moyamoya disease), heredodegenerative disorders (Wilson disease), and drugs (Table 597-8). Although chorea is a hallmark of Huntington disease in adults, children who develop Huntington disease tend to present with rigidity and bradykinesia **(Westphal variant)** or dystonia rather than chorea.

Athetosis is characterized by slow, continuous, writhing movements that repeatedly involve the same body part(s), usually the distal

extremities, face, neck, or trunk. Like chorea, athetosis may occur at rest and is often worsened by voluntary movement. Because athetosis tends to co-occur with other movement disorders, such as chorea **(choreoathetosis)** and dystonia, it is often difficult to distinguish as a discrete entity. Choreoathetosis is associated with cerebral palsy, kernicterus, and other forms of basal ganglia injury; therefore, it is often seen in conjunction with **rigidity**—increased muscle tone that is equal in the flexors and extensors in all directions of passive movement regardless of the velocity of the movement. This is to be differentiated from **spasticity,** a velocity-dependent ("clasp-knife") form of hypertonia that is seen with upper motor neuron dysfunction. As with chorea, athetosis/choreoathetosis can also be seen with hypoxic-ischemic injury and dopamine-blocking drugs.

Tremor is a rhythmic, oscillatory movement around a central point or plane that results from the action of antagonist muscles. Tremor can affect the extremities, head, trunk, or voice and can be classified by both its frequency (slow [4 Hz], intermediate [4-7 Hz], and fast [>7 Hz]) and by the context in which it is most pronounced. **Rest tremor** is maximal when the affected body part is inactive and supported against gravity, whereas **postural tremor** is most notable when the patient sustains a position against gravity. **Action tremor** occurs with performance of a voluntary activity and can be subclassified into **simple kinetic tremor**, which occurs with limb movement, and **intention tremor**, which occurs as the patient's limb approaches a target and is a feature of cerebellar disease.

Essential tremor (ET) is the most common movement disorder in adults, and 50% of persons diagnosed with ET report an onset in childhood; thus ET may be the most common tremor disorder in children as well. Clinical experience in pediatric movement disorders clinic suggests that ET is more common in the pediatric population than the literature would suggest. ET is an autosomal-dominant condition with variable expressivity but complete penetrance by the age of 60 yr. Although the genetics of ET are not fully understood, at least 3 different genes—*EMT1* on chromosome 3q13, *EMT2* on chromosome 2p22-25, and *LINGO1* on chromosome 15q24—are linked to the condition. Based on functional imaging studies, the defect is thought to localize to cerebellar circuits.

ET is characterized by a slowly progressive, bilateral, 4-9 Hz postural tremor that involves the upper extremities and occurs in the absence of other known causes of tremor. Mild asymmetry is common, but ET is rarely unilateral. ET may be worsened by actions, such as trying to pour water from cup to cup. Affected adults may report a history of ethanol responsiveness. Most young children present for evaluation because a parent, teacher, or therapist has noticed the tremor, rather than because the tremor causes impairment. Most children with ET do not require pharmacologic intervention. If they are having difficulty with their handwriting or self-feeding, an occupational therapy evaluation and/or assistive devices, such as wrist weights and weighted silverware, may be helpful. Teenagers tend to report more impairment from ET. Teenagers who do require pharmacotherapy usually respond to the same medications that are used in adults—propranolol and primidone. Propranolol, which is generally considered the first-line treatment, can be started at 20–40 mg daily and titrated to effect, with most patients responding to doses of 60-80 mg/day. Propranolol should not be used in patients with reactive airway disease. Primidone can be started at 12.5-25 mg at bedtime and increased gradually in a twice daily schedule. Most patients respond to doses of 50-200 mg/day. Other treatments options for ET reported in the adult literature include atenolol, gabapentin, topiramate, and alprazolam. Surgical treatments, which include deep brain stimulation of the thalamus and unilateral thalamotomy, are generally reserved for adults with medically refractory disabling tremor.

In addition to ET, there are numerous secondary etiologies of tremor in children (Table 597-9). **Holmes tremor,** previously referred to as midbrain or rubral tremor, is characterized by a slow frequency, high-amplitude tremor that is present at rest and with intention. It is a symptomatic tremor, which usually results from lesions of the brainstem, cerebellum, or thalamus. **Psychogenic tremor** is distinguished by its variable appearance, abrupt onset and remission, nonprogressive course, and association with selective but not task-specific disabilities. In some cases, tremor may even occur as a manifestation of another movement disorder, as is seen with position- or task-specific tremor (e.g., writing tremor), dystonic tremor, and myoclonic tremor.

When evaluating a child with tremor, it is important to screen for common metabolic disturbances, including electrolyte abnormalities and thyroid disease, assess the child's caffeine intake, and review the child's medication list for known tremor-inducing agents. It is also critical to exclude Wilson disease in teenagers with characteristic "wing-beating" tremor, as this is a treatable condition.

Table 597-9 Selected Causes of Tremor in Children
BENIGN
Enhanced physiologic tremor
Shuddering attacks
Jitteriness
Spasmus nutans
STATIC INJURY/STRUCTURAL
Cerebellar malformation
Stroke (particularly in the midbrain or cerebellum)
Multiple sclerosis
HEREDITARY/DEGENERATIVE
Familial essential tremor
Fragile X premutation
Wilson disease
Huntington disease
Juvenile parkinsonism (tremor is rare)
Pallidonigral degeneration
METABOLIC
Hyperthyroidism
Hyperadrenergic state (including pheochromocytoma and neuroblastoma)
Hypomagnesemia
Hypocalcemia
Hypoglycemia
Hepatic encephalopathy
Vitamin B_{12} deficiency
Inborn errors of metabolism
Mitochondrial disorders
DRUGS/TOXINS
Valproate, phenytoin, carbamazepine, lamotrigine, gabapentin, lithium, tricyclic antidepressants, stimulants (cocaine, amphetamine, caffeine, thyroxine, bronchodilators), neuroleptics, cyclosporine, toluene, mercury, thallium, amiodarone, nicotine, lead, manganese, arsenic, cyanide, naphthalene, ethanol, lindane, serotonin reuptake inhibitors
PERIPHERAL NEUROPATHIES
PSYCHOGENIC

597.3 Dystonia

Erika F. Augustine and Jonathan W. Mink

Dystonia is a disorder of movement characterized by sustained muscle contraction, frequently causing twisting and repetitive movements or abnormal postures. Major causes of dystonia include primary generalized dystonia, medications, metabolic disorders, and perinatal asphyxia (Tables 597-10 and 597-11).

INHERITED PRIMARY DYSTONIAS

Primary generalized dystonia, also referred to as primary torsion dystonia or *dystonia musculorum deformans*, is caused by a group of genetic disorders with onset in childhood. One form, which occurs more commonly in the Ashkenazi Jewish population, is caused by a dominant mutation in the ***DYT1*** gene coding for the adenosine

Table 597-10 Causes of Dystonia in Childhood

STATIC INJURY/STRUCTURAL DISORDERS
Cerebral palsy
Hypoxic–ischemic injury
Kernicterus
Head trauma
Encephalitis
Tumors
Stroke in the basal ganglia (which may be a result of vascular abnormalities or varicella)
Congenital malformations

HEREDITARY/DEGENERATIVE DISORDERS
DYT1 (9q34, encodes torsinA)
DYT2 (autosomal-recessive)
DYT3 (X-linked dystonia-parkinsonism syndrome of Lubag–Xq13)
DYT4
DYT5 (14q22.1-2, encodes GTP cyclohydrolase I, leading to dopa-responsive dystonia or Segawa disease)
DYT6 (8p21-q22)
DYT7 (18p)
DYT8 (2q33-q35, causing paroxysmal nonkinesigenic choreoathetosis [PNKC])
DYT9 (1p, causing paroxysmal nonkinesigenic dyskinesia [PNKD] and spasticity)
DYT10 (16p11.2-q12.1, causing paroxysmal kinesigenic choreoathetosis [PKC])
DYT11 (heterogeneous, causing familial myoclonus-dystonia)
Rapid-onset dystonia-parkinsonism (DYT12)
Fahr disease (often caused by hypoparathyroid disease)
Pantothenate kinase-associated neurodegeneration (PKAN; neuronal brain iron accumulation type 1, formerly Hallervorden-Spatz disease, caused by mutations in PANK2)
Huntington disease (particularly the Westphal variant, IT15-4p16.3)
Spinocerebellar ataxias (SCAs, including SCA3/Machado-Joseph disease)
Neuronal ceroid-lipofuscinoses (NCL)
Rett syndrome
Striatal necrosis
Leigh disease
Neuroacanthocytosis
HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration)
Ataxia-telangiectasia
Tay-Sachs disease
Sandhoff's disease
Niemann-Pick type C
GM_1 gangliosidosis
Metachromatic leukodystrophy (MLD)
Lesch-Nyhan disease

METABOLIC DISEASE
Glutaric aciduria types 1 and 2
Acyl-coenzyme A (CoA) dehydrogenase deficiencies
Dopa-responsive dystonia (tyrosine hydroxylase deficiency, guanosine triphosphate [GTP] cyclohydrolase 1 deficiency, DYT5)
Dopamine agonist-responsive dystonia (aromatic l-amino acid decarboxylase deficiency, aminolevulinic acid dehydrase [ALAD])
Biotin responsive basal ganglia disease
Mitochondrial disorders
Wilson disease
Vitamin E deficiency
Homocystinuria
Methylmalonic aciduria
Tyrosinemia

DRUGS/TOXINS
Neuroleptic and antiemetic medications (haloperidol, chlorpromazine, olanzapine, risperidone, prochlorperazine)
Calcium channel blockers
Stimulants (amphetamine, cocaine, ergot alkaloids)
Anticonvulsants (carbamazepine, phenytoin)
Thallium
Manganese
Carbon monoxide
Ethylene glycol
Cyanide
Methanol
Wasp sting

PAROXYSMAL DISORDERS
Paroxysmal kinesigenic choreoathetosis (PKC)
Paroxysmal nonkinesigenic choreoathetosis (PNKC)
Exercise-induced dystonia
Complex migraine
Alternating hemiplegia of childhood (AHC)
Paroxysmal torticollis of infancy

DISORDERS THAT MIMIC DYSTONIA
Tonic seizures (including paroxysmal nocturnal dystonia caused by nocturnal frontal lobe seizures)
Arnold-Chiari malformation type II
Atlantoaxial subluxation
Syringomyelia
Posterior fossa mass
Cervical spine malformation (including Klippel-Feil syndrome)
Skew deviation with vertical diplopia causing neck twisting
Juvenile rheumatoid arthritis
Sandifer syndrome (associated with hiatal hernia in infants)
Spasmus nutans
Tics
Infant masturbation
Spasticity
Myotonia
Rigidity
Stiff-person syndrome
Isaac syndrome (neuromyotonia)
Startle disease (hyperekplexia)
Neuroleptic malignant syndrome
Central herniation with posturing
Psychogenic dystonia

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Table 597-11 Examples of Primary and Secondary Dystonia in Childhood

DIAGNOSIS	ADDITIONAL CLINICAL FEATURES
Aicardi-Goutières syndrome	Encephalopathy, developmental regression Acquired microcephaly Sterile pyrexias Lesions on the digits, ears (chilblain) Epilepsy CT: calcification of the basal ganglia
Alternating hemiplegia of childhood	Episodic hemiplegia/quadriplegia Abnormal ocular movements Autonomic symptoms Epilepsy Global developmental impairment Environmental triggers for spells
Aromatic amino acid decarboxylase deficiency (AADC)	Developmental delay Oculogyric crises Autonomic dysfunction Hypotonia
ARX gene mutation (X-linked)	Male Cognitive impairment Infantile spasms, epilepsy Brain malformation
Benign paroxysmal torticollis of infancy	Episodic Cervical dystonia only Family history of migraine
Complex regional pain syndrome	Lower limb involvement Prominent pain
Dopa-responsive dystonia (DRD)	Diurnal variation
Drug-induced dystonia	
Dystonia-deafness optic neuropathy syndrome	Sensorineural hearing loss in early childhood Psychosis Optic atrophy in adolescence
DYT1 dystonia	Lower limb onset followed by generalization
Glutaric aciduria type 1	Macrocephaly Encephalopathic crises MRI: striatal necrosis
GM_1 gangliosidosis type 3	Short stature, skeletal dysplasia Orofacial dystonia Speech/swallowing disturbance Parkinsonism MRI: putaminal hyperintensity
Huntington disease	Parkinsonism Epilepsy Family history of Huntington disease
Kernicterus	Jaundice in infancy Hearing loss Impaired upgaze Enamel dysplasia MRI: hyperintense lesions in the globus pallidus
Leigh syndrome	Motor delays, weakness, hypotonia Ataxia, tremor Elevated lactate MRI: bilateral symmetric hyperintense lesions in the basal ganglia or thalamus
Lesch-Nyhan syndrome (X-linked)	Male Self-injurious behavior Hypotonia Oromandibular dystonia, inspiratory stridor Oculomotor apraxia Cognitive impairment Elevated uric acid
Myoclonus dystonia	Myoclonus Head, upper limb involvement
Niemann-Pick type C	Hepatosplenomegaly Hypotonia Supranuclear gaze palsy Ataxia, dysarthria Epilepsy Psychiatric symptoms
Neuroacanthocytosis	Oromandibular and lingual dystonia
Neurodegeneration with brain iron accumulation	Cognitive impairment Retinal pigmentary degeneration, optic atrophy
Rapid onset dystonia parkinsonism (DYT12)	Acute onset Distribution face > arm > leg Prominent bulbar signs
Rett syndrome	Female Developmental regression following a period of normal development Stereotypic hand movements Acquired microcephaly Epilepsy
Spinocerebellar ataxia 17 (SCA17)	Ataxia Dementia, psychiatric symptoms Parkinsonism
Tics	Stereotyped movements Premonitory urge, suppressible
Tyrosine hydroxylase deficiency	Infantile encephalopathy, hypotonia Oculogyric crises, ptosis Autonomic symptoms Less diurnal fluctuation than DRD

triphosphate (ATP) binding protein torsinA. The initial manifestation of *DYT1* dystonia is often intermittent unilateral posturing of a lower extremity, which assumes an extended and rotated position. Ultimately, all 4 extremities and the axial musculature can be affected, but the dystonia may also remain localized to one limb. Cranial involvement can occur in *DYT1* dystonia, but it is uncommon compared to non-*DYT1* dystonias. There is a wide clinical spectrum, varying even within families. If a family history of dystonia is absent, the diagnosis should still be considered, given the intrafamilial variability in clinical expression.

More than a dozen loci for genes for torsion dystonia have been identified (*DYT1-DYT24*). One is the autosomal dominant disorder **dopa-responsive dystonia (DRD, *DYT5a*),** also called Segawa syndrome. The gene for DRD codes for guanosine triphosphate cyclohydrolase 1, the rate-limiting enzyme for tetrahydrobiopterin synthesis, which is a cofactor for synthesis of the neurotransmitters dopamine

and serotonin. Thus, the genetic mutation results in dopamine deficiency. The hallmark of the disorder, particularly in adolescents and adults, is diurnal variation: symptoms worsen as the day progresses and may transiently improve with sleep. Early-onset patients, who tend to present with delayed or abnormal gait from dystonia of a lower extremity, can easily be confused with patients with dystonic cerebral palsy. It should be noted that in the presence of a progressive dystonia, diurnal fluctuation, or if loss of previously achieved motor skills occurs, a prior diagnosis of cerebral palsy should be reexamined. DRD responds dramatically to small daily doses of levodopa. The responsiveness to levodopa is a sustained benefit, even if the diagnosis is delayed several years, as long as contractures have not developed.

Myoclonus dystonia (DYT11), caused by mutations in the epsilon-sarcoglycan *(SCGE)* gene, is characterized by dystonia involving the upper extremities, head, and/or neck, as well as myoclonic movements in these regions. Although a combination of myoclonus and dystonia typically occurs, each manifestation can present in isolation. When repetitive, the myoclonus may take on a tremor-like appearance, termed *dystonic tremor*. Improvement in symptoms following alcohol ingestion, reported by affected adult family members, may be a helpful clue to this diagnosis.

Common to the inherited dystonias, there is considerable intrafamilial variability in clinical manifestations, distribution, and severity of dystonia. In primary dystonias, although the main clinical features are motor, there may be an increased risk for major depression. Anxiety, obsessive-compulsive disorder, and depression have all been reported in the myoclonus–dystonia syndrome. Screening for psychiatric comorbidities cannot be overlooked in this population.

DRUG-INDUCED DYSTONIAS

A number of medications are capable of inducing involuntary movements, drug-induced movement disorders, in children and adults. Dopamine-blocking agents, including antipsychotics (e.g., haloperidol) and antiemetics (e.g., metoclopramide, prochlorperazine), as well as atypical antipsychotics (e.g., risperidone) can produce acute dystonic reactions or delayed (tardive) drug-induced movement disorders. **Acute dystonic reactions,** occurring in the 1st days of exposure, typically involve the face and neck, manifesting as torticollis, retrocollis, oculogyric crisis, or tongue protrusion. Life-threatening presentations with laryngospasm and airway compromise can also occur, requiring prompt recognition and treatment of this entity. Intravenous diphenhydramine, 1-2 mg/kg/dose, may rapidly reverse the drug-related dystonia. The high potency of the dopamine blocker, young age, and prior dystonic reactions may be predisposing factors. Acute dystonic reactions have also been described with cetirizine.

Severe rigidity combined with high fever, autonomic symptoms (tachycardia, diaphoresis), delirium, and dystonia are signs of **neuroleptic malignant syndrome**, which typically occurs a few days after starting or increasing the dose of a neuroleptic drug, or in the setting of withdrawal from a dopaminergic agent. In contrast to acute dystonic reactions, which take place within days, neuroleptic malignant syndrome occurs within a month of medication initiation or dose increase.

Delayed onset involuntary movements, **tardive dyskinesias,** develop in the setting of chronic (>3 mo duration) neuroleptic use. Involvement of the face, particularly the mouth, lips, and/or jaw with chewing or tongue thrusting is characteristic. The risk of tardive dyskinesia, which is much less frequent in children compared to adults, increases as medication dose and duration of treatment increase. There are data to suggest that children with autism spectrum disorders may also be at increased risk for this drug-induced movement disorders. Unlike acute dystonic reactions and neuroleptic malignant syndrome, discontinuation of the offending agent may not result in clinical improvement. In these patients, use of dopamine-depletors, such as reserpine or tetrabenazine, may prove helpful.

Therapeutic doses of phenytoin or carbamazepine rarely cause progressive dystonia in children with epilepsy, particularly in those who have an underlying structural abnormality of the brain.

During evaluation of new onset dystonia, a careful history of prescriptions and potential medication exposures is critical.

CEREBRAL PALSY

See Chapter 598.

METABOLIC DISORDERS

Disorders of monamine neurotransmitter metabolism, of which DRD is one, present in infancy and early childhood with dystonia, hypotonia, oculogyric crises, and/or autonomic symptoms. The more common disorders among this group of rare diseases include DRD, tyrosine hydroxylase deficiency, and aromatic amino acid decarboxylase deficiency. Abnormalities of the dopamine transporter (DAT) can also present in infancy with dystonia. Detailed discussion is beyond the scope of this chapter; reviews, however, are available for reference.

Wilson disease is an autosomal recessive inborn error of copper transport characterized by cirrhosis of the liver and degenerative changes in the central nervous system, particularly the basal ganglia (see Chapter 357.2). It has been determined that there are multiple mutations in the Wilson disease gene (*WND*), accounting for the variability in presentation of the condition. The neurologic manifestations of Wilson disease rarely appear before age 10 yr, and the initial sign is often progressive dystonia. Tremors of the extremities develop, unilaterally at first, but they eventually become coarse, generalized, and incapacitating. Other neurologic signs of Wilson disease relate to progressive basal ganglia disease, such as parkinsonism, dysarthria, dysphonia, and choreoathetosis. Less frequent are ataxia and pyramidal signs. The MRI or CT scan shows ventricular dilation in advanced cases with atrophy of the cerebrum, cerebellum, and/or brainstem, along with signal intensity change in the basal ganglia, thalamus, and/or brainstem, particularly the midbrain.

Pantothenate kinase–associated neurodegeneration (formerly known as *Hallervorden-Spatz disease*) is a rare autosomal recessive neurodegenerative disorder. Many patients have mutations in pantothenate kinase 2 *(PANK2)* localized to mitochondria in neurons. The condition usually begins before 6 yr of age and is characterized by rapidly progressive dystonia, rigidity, and choreoathetosis. Spasticity, extensor plantar responses, dysarthria, and intellectual deterioration become evident during adolescence, and death usually occurs by early adulthood. MRI shows lesions of the globus pallidus, including low signal intensity in T2-weighted images (corresponding to iron pigments) and an anteromedial area of high signal intensity (tissue necrosis and edema), or "eye-of-the-tiger" sign (Fig. 597-1). Neuropathologic examination indicates excessive accumulation of iron-containing pigments in the globus pallidus and substantia nigra. More recently, similar disorders of high brain iron content without *PANK2* mutations, including infantile neuroaxonal dystrophy, neuroferritinopathy, and aceruloplasminemia, have been grouped as disorders of neurodegeneration with brain iron accumulation. Patterns of iron deposition visualized by brain MRI have shown utility in differentiating these disorders.

Biotin-responsive basal ganglia disease manifests with episodes of acute dystonia, external ophthalmoplegia and encephalopathy. *SLC19A3* is the responsible mutated gene. MRI demonstrates involvement of the basal ganglia, with vasogenic edema and the "bat-wing" sign (Fig. 597-2). Treatment with biotin and thiamine results in improvement in 2-4 days.

Although dystonia may present in isolation as the first sign of a metabolic or neurodegenerative disorder, this group of diseases should be considered mainly in those who demonstrate signs of systemic disease, (e.g., organomegaly, short stature, hearing loss, vision impairment, epilepsy), those with episodes of severe illness, evidence of regression, or cognitive impairment. Table 597-11 outlines additional features suggestive of specific disorders.

OTHER DISORDERS

Although uncommon, movement disorders, including dystonia, may be part of the presenting symptoms of **complex regional pain syndrome**. Onset of involuntary movements within 1 yr of the traumatic event, affected lower limb, pain disproportionate to inciting event, and changes in the overlying skin and blood flow to the affected area suggest complex regional pain syndrome. Although sustained dystonia

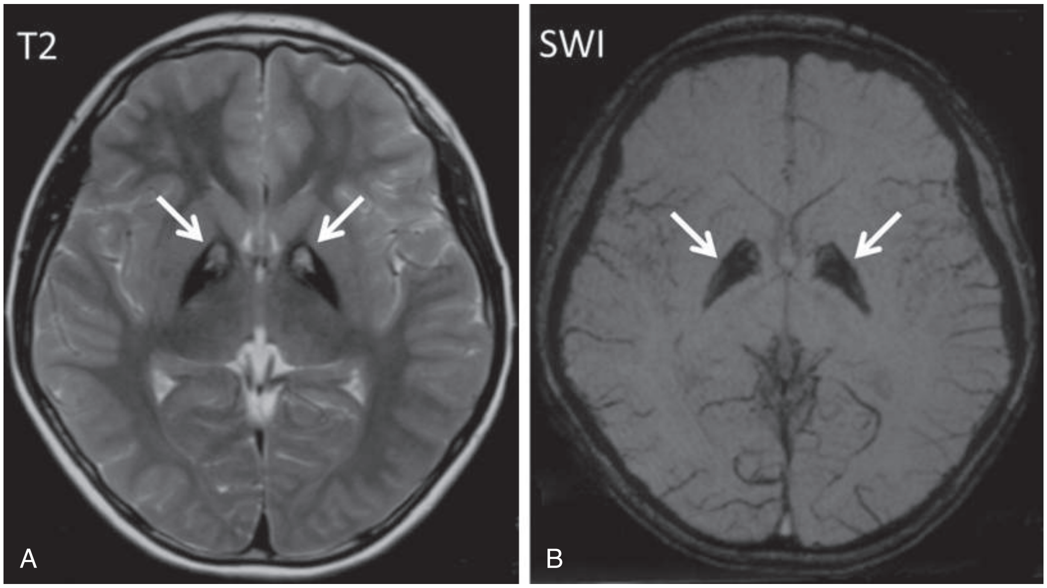

Figure 597-1 Pantothenate kinase–associated neurodegeneration (PKAN). **A,** Axial T2-weighted image showing symmetric hypointensity in the bilateral globi pallidi with central hyperintensity ("eye-of-the-tiger sign," *arrows*). **B,** Axial susceptibility-weighted image (SWI) image showing hypointensity in the globi pallidi representing increased iron accumulation *(arrows). (From From Bosemani T, Meoded A, Poretti A: Susceptibility-weighted imaging in pantothenate kinase-associated neurodegeneration.* J Pediatr *164:212, 2014.)*

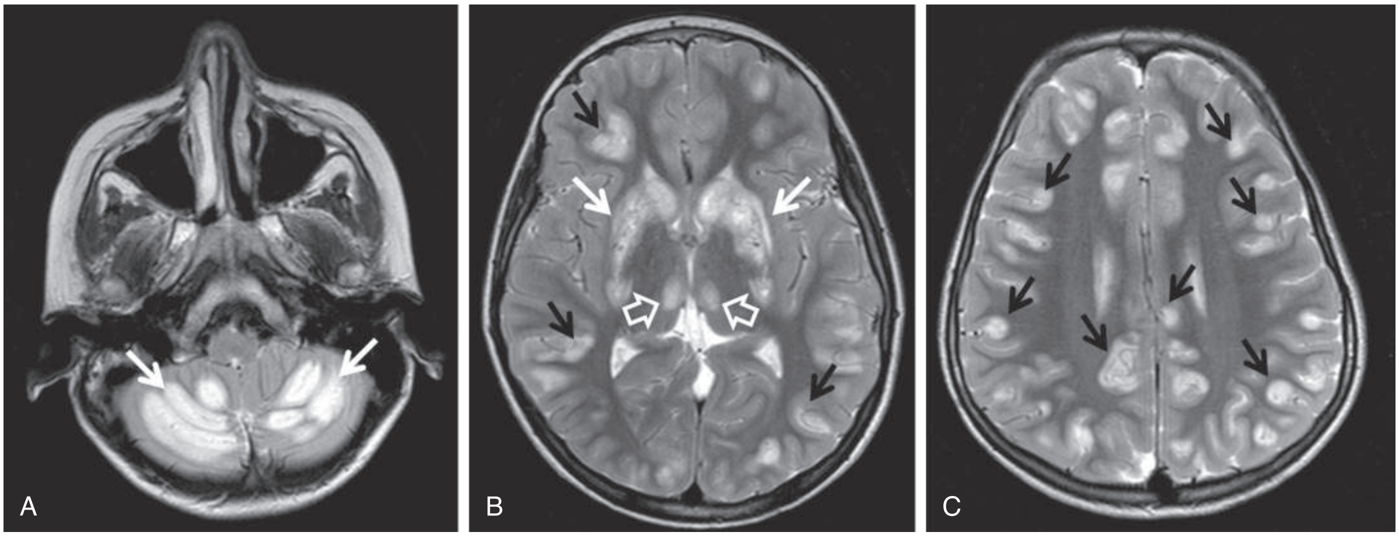

Figure 597-2 Biotin-responsive basal ganglia disease. An initial brain MRI showed high-signal intensity alterations on T2-weighted images bilaterally involving the **(A)** cerebellum *(arrows)*, **(B)** basal ganglia *(white arrows)*, and medial nucleus of the thalamus *(open arrows)*, and **(B, C)** cerebral cortex *(black arrows). (Modified from Tabarki B, Al-Sheikh F, Al-Shahwan S, Zuccoli G: Bilateral external ophthalmoplegia in biotin-responsive basal ganglia disease.* J Pediatr *162:1291–1292, 2013.)*

can produce pain or discomfort, complex regional pain syndrome should be considered in those who have a prominent component of pain and recent history of trauma to the affected limb.

There are disorders unique to childhood that warrant exploration in this section. **Benign paroxysmal torticollis of infancy** is characterized by recurrent episodes of cervical dystonia beginning in the 1st few mo of life. The torticollis may alternate sides from 1 episode to the next and may also persist during sleep. Associated signs and symptoms include irritability, pallor, vomiting, vertigo, ataxia, and occasionally limb dystonia. Family history is often notable for migraine and/or motion sickness in 1st-degree relatives. Despite the high frequency of spells, imaging studies are normal, and the outcome is uniformly benign with resolution by 3 yr of age.

In **alternating hemiplegia of childhood**, episodic hemiplegia affecting either side of the body is the hallmark of the disorder. However, patients are also affected by episodes of dystonia, ranging from minutes to days in duration. On average, both features of the disorder commence at approximately 6 mo of age. Episodic abnormal eye movements are observed in a large proportion of patients (93%) with onset as early as the 1st wk of life. Alternating hemiplegia of childhood is associated with mutations in the *ATP1A2* and *ATP1A3* genes. Alternating hemiplegia of childhood can similarly be triggered by fluctuations in temperature, certain foods, or water exposure. Over time, epilepsy and cognitive impairment emerge, and the involuntary movements change from episodic to constant. Infantile onset and the paroxysmal nature of symptoms early in the disease course are key features to this diagnosis.

Finally, although a diagnosis of exclusion, the presence of odd movements or selective disability may indicate a psychogenic dystonia in older children. There is considerable overlap in features of organic and

psychogenic movement disorders, making the diagnosis difficult to establish. For instance, both organic and psychogenic movement disorders have the potential to worsen in the setting of stress and may dissipate with relaxation or sleep. History should include review of recent stressors, psychiatric symptoms, and exposure to others with similar disorders. On examination, a changing movement disorder, inconsistent motor or sensory exam, or response to suggestion, are supportive of a possible psychogenic movement disorder. Early recognition of this disorder may lessen morbidity caused by unnecessary diagnostic and interventional procedures.

TREATMENT

Children with generalized dystonia, including those with involvement of the muscles of swallowing, may respond to the anticholinergic agent trihexyphenidyl (Artane). Titration occurs slowly over the course of months in an effort to limit untoward side effects, such as urinary retention, mental confusion, or blurred vision. Additional drugs that have been effective include levodopa and diazepam. Segmental dystonia, such as torticollis, often responds well to botulinum toxin injections. Intrathecal baclofen delivered through implantable constant infusion pump may be helpful in some patients. Deep brain stimulation with leads implanted in the globus pallidus is most helpful for children with severe primary generalized dystonia. Recent data suggest, however, that deep brain stimulation may also be of benefit in children with secondary dystonias, such as cerebral palsy.

In the case of drug-induced dystonias, removal of the offending agent and treatment with intravenous diphenhydramine typically suffices. For neuroleptic malignant syndrome, dantrolene may be indicated.

Bibliography is available at Expert Consult.

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Chapter 598
Encephalopathies

Michael V. Johnston

Encephalopathy is a generalized disorder of cerebral function that may be acute or chronic, progressive, or static. The etiologies of the encephalopathies in children include infectious, toxic (carbon monoxide, drugs, lead), metabolic, genetic, and ischemic causes. Hypoxic–ischemic encephalopathy is discussed in Chapter 99.5.

598.1 Cerebral Palsy

Michael V. Johnston

See Chapters 36, 97.2, and 597.3.

Cerebral palsy (CP) is a diagnostic term used to describe a group of permanent disorders of movement and posture causing activity limitation, that are attributed to nonprogressive disturbances in the in the developing fetal or infant brain. The motor disorders are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior as well as by epilepsy and secondary musculoskeletal problems. CP is caused by a broad group of developmental, genetic, metabolic, ischemic, infectious, and other acquired etiologies that produce a common group of neurologic phenotypes. CP has historically been considered a static encephalopathy, but some of the neurologic features of CP, such as movement disorders and orthopedic complications, including scoliosis and hip dislocation, can change or progress over time. Many children and adults with CP function at a high educational and vocational level, without any sign of cognitive dysfunction.

EPIDEMIOLOGY AND ETIOLOGY

CP is the most common and costly form of chronic motor disability that begins in childhood; data from the Centers for Disease Control and Prevention indicate that the incidence is 3.6 per 1,000 children with a male : female ratio of 1.4 : 1. The Collaborative Perinatal Project, in which approximately 45,000 children were regularly monitored from in utero to the age of 7 yr, found that most children with CP had been born at term with uncomplicated labors and deliveries. In 80% of cases, features were identified pointing to antenatal factors causing abnormal brain development. A substantial number of children with CP had congenital anomalies external to the central nervous system (CNS). Fewer than 10% of children with CP had evidence of intrapartum asphyxia. Intrauterine exposure to maternal infection (chorioamnionitis, inflammation of placental membranes, umbilical cord inflammation, foul-smelling amniotic fluid, maternal sepsis, temperature >38°C [100.4°F] during labor, urinary tract infection) was associated with a significant increase in the risk of CP in normal birthweight infants. Elevated levels of inflammatory cytokines have been reported in heelstick blood collected at birth from children who later were identified with CP. Genetic factors may contribute to the inflammatory cytokine response, and a functional polymorphism in the interleukin-6 gene is associated with a higher rate of CP in term infants.

The prevalence of CP has increased somewhat as a result of the enhanced survival of very premature infants weighing <1,000 g, who go on to develop CP at a rate of approximately 15 per 100. However, the gestational age at birth-adjusted prevalence of CP among 2 yr old former premature infants born at 20-27 wk of gestation has decreased over the past decade. The major lesions that contribute to CP in preterm infants are **intracerebral hemorrhage** and **periventricular leukomalacia** (PVL). Although the incidence of intracerebral hemorrhage has declined significantly, PVL remains a major problem. PVL reflects the enhanced vulnerability of immature oligodendroglia in premature infants to oxidative stress caused by ischemia or infectious/inflammatory insults. White matter abnormalities (loss of volume of periventricular white matter, extent of cystic changes, ventricular dilation, thinning of the corpus callosum) present on MRI at 40 wk of gestational age among former preterm infants are a predictor of later CP.

In 2006, the European Cerebral Palsy Study examined prenatal and perinatal factors as well as clinical findings and results of MRI in a contemporary cohort of more than 400 children with CP. In agreement with the Collaborative Perinatal Project study, more than half the children with CP in this study were born at term, and less than 20% had clinical or brain imaging indicators of possible intrapartum factors such as asphyxia. The contribution of intrapartum factors to CP is higher in some underdeveloped regions of the world. Also in agreement with earlier data, antenatal infection was strongly associated with CP and 39.5% of mothers of children with CP reported having an infection during the pregnancy, with 19% having evidence of a urinary tract infection and 11.5% reporting taking antibiotics. Multiple pregnancy was also associated with a higher incidence of CP and 12% of the cases in the European CP study resulted from a multiple pregnancy, in contrast to a 1.5% incidence of multiple pregnancy in the study. Other studies have also documented a relationship between multiple births and CP, with a rate in twins that is 5-8 times greater than in singleton pregnancies and a rate in triplets that is 20-47 times greater. Death of a twin in utero carries an even greater risk of CP that is 8 times that of a pregnancy in which both twins survive and approximately 60 times the risk in a singleton pregnancy. Infertility treatments are also associated with a higher rate of CP, probably because these treatments are often associated with multiple pregnancies. Among children from multiple pregnancies, 24% were from pregnancies after infertility treatment compared with 3.4% of the singleton pregnancies in the study. CP is more common and more severe in boys compared to girls and this effect is enhanced at the extremes of body weight. Male infants with intrauterine growth retardation and a birthweight less than the 3rd percentile are 16 times more likely to have CP than males with optimal growth, and infants with weights above the 97th percentile are 4 times more likely to have CP.

Table 598-1 Classification of Cerebral Palsy and Major Causes

MOTOR SYNDROME (APPROX. % OF CP)	NEUROPATHOLOGY/MRI	MAJOR CAUSES
Spastic diplegia (35%)	Periventricular leukomalacia Periventricular cysts or scars in white matter, enlargement of ventricles, squared off posterior ventricles	Prematurity Ischemia Infection Endocrine/metabolic (e.g., thyroid)
Spastic quadriplegia (20%)	Periventricular leukomalacia Multicystic encephalomalacia Cortical malformations	Ischemia, infection Endocrine/metabolic, genetic/ developmental
Hemiplegia (25%)	Stroke: in utero or neonatal Focal infarct or cortical, subcortical damage Cortical malformations	Thrombophilic disorders Infection Genetic/developmental Periventricular hemorrhagic infarction
Extrapyramidal (athetoid, dyskinetic) (15%)	Asphyxia: symmetric scars in putamen and thalamus Kernicterus: scars in globus pallidus, hippocampus Mitochondrial: scaring globus pallidus, caudate, putamen, brainstem No lesions: ? dopa-responsive dystonia	Asphyxia Kernicterus Mitochondrial Genetic/metabolic

CLINICAL MANIFESTATIONS

CP is generally divided into several major motor syndromes that differ according to the pattern of neurologic involvement, neuropathology, and etiology (Table 598-1). The physiologic classification identifies the major motor abnormality, whereas the topographic taxonomy indicates the involved extremities. CP is also commonly associated with a spectrum of developmental disabilities, including intellectual impairment, epilepsy, and visual, hearing, speech, cognitive, and behavioral abnormalities. The motor handicap may be the least of the child's problems.

Infants with **spastic hemiplegia** have decreased spontaneous movements on the affected side and show hand preference at a very early age. The arm is often more involved than the leg and difficulty in hand manipulation is obvious by 1 yr of age. Walking is usually delayed until 18-24 mo, and a circumductive gait is apparent. Examination of the extremities may show growth arrest, particularly in the hand and thumbnail, especially if the contralateral parietal lobe is abnormal, because extremity growth is influenced by this area of the brain. Spasticity refers to the quality of increased muscle tone, which increases with the speed of passive muscle stretching and is greatest in antigravity muscles. It is apparent in the affected extremities, particularly at the ankle, causing an equinovarus deformity of the foot. An affected child often walks on tiptoe because of the increased tone in the antigravity gastrocnemius muscles, and the affected upper extremity assumes a flexed posture when the child runs. Ankle clonus and a Babinski sign may be present, the deep tendon reflexes are increased, and weakness of the hand and foot dorsiflexors is evident. About one-third of patients with spastic hemiplegia have a seizure disorder that usually develops in the 1st yr or 2; approximately 25% have cognitive abnormalities including mental retardation. MRI is far more sensitive than CT for most lesions seen with CP, although a CT scan may be useful for detecting calcifications associated with congenital infections. In the European CP study, 34% of children with hemiplegia had injury to the white matter that probably dated to the in utero period and 27% had a focal lesion that may have resulted from a stroke. Other children with hemiplegic CP had had malformations from multiple causes including infections (e.g., cytomegalovirus), lissencephaly, polymicrogyria, schizencephaly, or cortical dysplasia. Focal cerebral infarction (stroke) secondary to intrauterine or perinatal thromboembolism related to thrombophilic disorders, like the presence of anticardiolipin antibodies, is an important cause of hemiplegic CP (see Chapter 601). Family histories suggestive of thrombosis and inherited clotting disorders, such as factor V Leiden mutation, may be present and evaluation of the mother may provide information valuable for future pregnancies and other family members.

Spastic diplegia is bilateral spasticity of the legs that is greater than in the arms. Spastic diplegia is strongly associated with damage to the immature white matter during the vulnerable period of immature oligodendroglia between 20-34 wk of gestation. However, approximately 15% of cases of spastic diplegia result from in utero lesions in infants who go on to delivery at term. The first clinical indication of spastic diplegia is often noted when an affected infant begins to crawl. The child uses the arms in a normal reciprocal fashion but tends to drag the legs behind more as a rudder (commando crawl) rather than using the normal 4-limbed crawling movement. If the spasticity is severe, application of a diaper is difficult because of the excessive adduction of the hips. If there is paraspinal muscle involvement, the child may be unable to sit. Examination of the child reveals spasticity in the legs with brisk reflexes, ankle clonus, and a bilateral Babinski sign. When the child is suspended by the axillae, a scissoring posture of the lower extremities is maintained. Walking is significantly delayed, the feet are held in a position of equinovarus, and the child walks on tiptoe. Severe spastic diplegia is characterized by disuse atrophy and impaired growth of the lower extremities and by disproportionate growth with normal development of the upper torso. The prognosis for normal intellectual development for these patients is good, and the likelihood of seizures is minimal. Such children often have learning disabilities and deficits in other abilities, such as vision, because of disruption of multiple white matter pathways that carry sensory as well as motor information.

The most common neuropathologic finding in children with spastic diplegia is PVL, which is visualized on MRI in more than 70% of cases. MRI typically shows scarring and shrinkage in the periventricular white matter with compensatory enlargement of the cerebral ventricles. However, neuropathology has also demonstrated a reduction in oligodendroglia in more widespread subcortical regions beyond the periventricular zones, and these subcortical lesions may contribute to the learning problems these patients can have. MRI with diffusion tensor imaging is being used to map white matter tracks more precisely in patients with spastic diplegia, and this technique has shown that thalamocortical sensory pathways are often injured as severely as motor corticospinal pathways (Fig. 598-1). These observations have led to greater interest in the importance of sensory deficits in these patients, which may be important for designing rehabilitative techniques.

Spastic quadriplegia is the most severe form of CP because of marked motor impairment of all extremities and the high association with intellectual disability and seizures. Swallowing difficulties are common as a result of supranuclear bulbar palsies, often leading to aspiration pneumonia. The most common lesions seen on pathologic examination or on MRI scanning are severe PVL and multicystic cortical encephalomalacia. Neurologic examination shows increased tone and spasticity in all extremities, decreased spontaneous movements, brisk reflexes, and plantar extensor responses. Flexion contractures of the knees and elbows are often present by late childhood. Associated

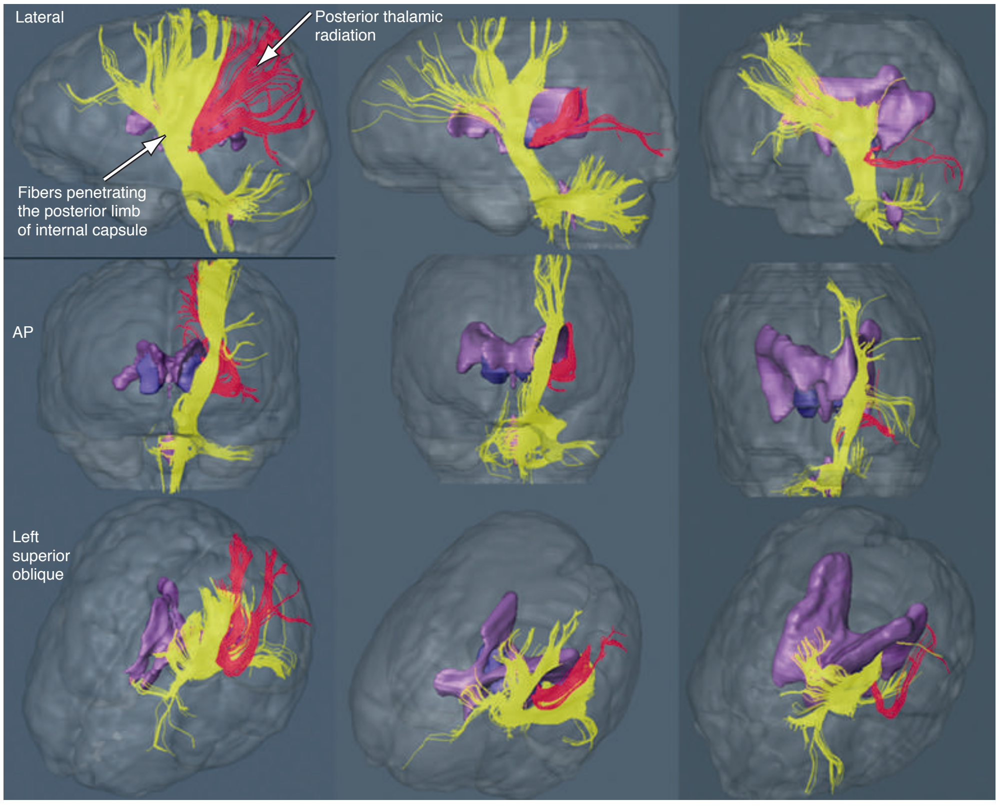

Figure 598-1 Diffusion tensor image of white matter pathways in the brains of 2 patients with spastic diplegia on the right compared to a normal child on the far left. Yellow fibers are corticospinal pathways projected from the motor cerebral cortex at the top downward into the brainstem, whereas the red fibers are thalamocortical sensory fibers projected from the thalamus upward to the cortex. In the children with spastic diplegia, both the corticospinal and thalamocortical pathways are reduced in size, but the ascending thalamocortical pathways are more affected. *(From Nagae LM, Hoon AH Jr, Stashinko E, et al: Diffusion tensor imaging in children with periventricular leukomalacia: variability of injuries to white matter tracts,* AJNR Am J Neuroradiol *28:1213–1222, 2007.)*

developmental disabilities, including speech and visual abnormalities, are particularly prevalent in this group of children. Children with spastic quadriparesis often have evidence of athetosis and may be classified as having mixed CP.

Athetoid CP, also called **choreoathetoid, extrapyramidal,** or **dyskinetic** CP, is less common than spastic CP and makes up approximately 15-20% of patients with CP. Affected infants are characteristically hypotonic with poor head control and marked head lag and develop variably increased tone with rigidity and dystonia over several years. The term *dystonia* refers to the abnormality in tone in which muscles are rigid throughout their range of motion and involuntary contractions can occur in both flexors and extensors leading to limb positioning in fixed postures. Unlike spastic diplegia, the upper extremities are generally more affected than the lower extremities in extrapyramidal CP. Feeding may be difficult, and tongue thrust and drooling may be prominent. Speech is typically affected because the oropharyngeal muscles are involved. Speech may be absent or sentences are slurred, and voice modulation is impaired. Generally, upper motor neuron signs are not present, seizures are uncommon, and intellect is preserved in many patients. This form of CP is also referred to in Europe as dyskinetic CP and is the type most likely to be associated with **birth asphyxia.** In the European CP study, 76% of patients with this form of CP had lesions in the basal ganglia and thalamus. Extrapyramidal CP secondary to acute intrapartum near-total asphyxia is associated with bilaterally symmetric lesions in the posterior putamen and ventrolateral thalamus. These lesions appear to be the correlate of the neuropathologic lesion called *status marmoratus* in the basal ganglia. Athetoid CP can also be caused by **kernicterus** secondary to high levels of bilirubin, and in this case the MRI scan shows lesions in the globus pallidus bilaterally. Extrapyramidal CP can also be associated with lesions in the basal ganglia and thalamus caused by metabolic genetic disorders such as mitochondrial disorders and glutaric aciduria. MRI scanning and possibly metabolic testing are important in the evaluation of children with extrapyramidal CP to make a correct etiologic diagnosis. In patients with dystonia who have a normal MRI, it is important to have a high level of suspicion for dihydroxyphenylalanine (DOPA)-responsive dystonia (Segawa disease), which causes prominent dystonia that can resemble CP. These patients typically have diurnal variation in their signs with worsening dystonia in the legs during the day; however, this may not be prominent. These patients can be tested for a response to small doses of L-dopa and/or cerebrospinal fluid can be sent for neurotransmitter analysis.

Associated comorbidities are common and include pain (in 75%), cognitive disability (50%), hip displacement (30%), seizures (25%), behavioral disorders (25%), sleep disturbances (20%), visual impairment (19%), and hearing impairment (4%).

DIAGNOSIS

A thorough history and physical examination should preclude a **progressive disorder** of the CNS, including degenerative diseases, metabolic disorders, spinal cord tumor, or muscular dystrophy. The possibility of anomalies at the base of the skull or other disorders affecting the cervical spinal cord needs to be considered in patients with little involvement of the arms or cranial nerves. An MRI scan of the brain is indicated to determine the location and extent of structural lesions or associated congenital malformations; an MRI scan of the spinal cord is indicated if there is any question about spinal cord pathology. Additional studies may include tests of hearing and visual function. Genetic evaluation should be considered in patients with congenital malformations (chromosomes) or evidence of metabolic disorders (e.g., amino acids, organic acids, MR spectroscopy). In addition to the genetic disorders mentioned earlier that can present as CP,

the urea cycle disorder arginase deficiency is a rare cause of spastic diplegia and a deficiency of sulfite oxidase or molybdenum cofactor can present as CP caused by perinatal asphyxia. Tests to detect inherited thrombophilic disorders may be indicated in patients in whom an in utero or neonatal stroke is suspected as the cause of CP.

Because CP is usually associated with a wide spectrum of developmental disorders, a multidisciplinary approach is most helpful in the assessment and treatment of such children.

TREATMENT

Some progress has been made in both prevention of CP before it occurs and treatment of children with the disorder. Preliminary results from controlled trials of magnesium sulfate given intravenously to mothers in premature labor with birth imminent before 32 wk gestation showed significant reduction in the risk of CP at 2 yr of age. Nonetheless, one study that followed preterm infants whose mothers received magnesium sulfate demonstrated no benefit in terms of the incidence of CP and abnormal motor, cognitive, or behavioral function at school age. Furthermore, several large trials have shown that cooling term infants with hypoxic–ischemic encephalopathy to 33.3°C (91.9°F) for 3 days, starting within 6 hr of birth, reduces the risk of dyskinetic or spastic quadriplegia form of CP.

For children who have a diagnosis of CP, a team of physicians, including neurodevelopmental pediatricians, pediatric neurologists, and physical medicine and rehabilitation specialists, as well as occupational and physical therapists, speech pathologists, social workers, educators, and developmental psychologists, is important to reduce abnormalities of movement and tone and to optimize normal psychomotor development. Parents should be taught how to work with their child in daily activities such as feeding, carrying, dressing, bathing, and playing in ways that limit the effects of abnormal muscle tone. They also need to be instructed in the supervision of a series of exercises designed to prevent the development of contractures, especially a tight Achilles tendon. Physical and occupational therapies are useful for promoting mobility and the use of the upper extremities for activities of daily living. Speech language pathologists promote acquisition of a functional means of communications. These therapists help children to achieve their potential and often recommend further evaluations and adaptive equipment.

Children with spastic diplegia are treated initially with the assistance of adaptive equipment, such as walkers, poles, and standing frames. If a patient has marked spasticity of the lower extremities or evidence of hip dislocation, consideration should be given to performing surgical soft-tissue procedures that reduce muscle spasm around the hip girdle, including an adductor tenotomy or psoas transfer and release. A rhizotomy procedure in which the roots of the spinal nerves are divided produces considerable improvement in selected patients with severe spastic diplegia (Fig. 598-2). A tight heel cord in a child with spastic hemiplegia may be treated surgically by tenotomy of the Achilles tendon. Quadriplegia is managed with motorized wheelchairs, special feeding devices, modified typewriters, and customized seating arrangements. The function of the affected extremities in children with **hemiplegic CP** can often be improved by therapy in which movement of the good side is constrained with casts while the impaired extremities perform exercises which induce improved hand and arm functioning. This constraint-induced movement therapy is effective in patients of all ages.

Several drugs have been used to **treat spasticity,** including the benzodiazepines and baclofen. These medications have beneficial effects in some patients but can also cause side effects such as sedation for benzodiazepines and lowered seizure threshold for baclofen. Several drugs can be used to **treat spasticity,** including oral diazepam (0.01-0.3 mg/kg/day, divided bid or qid), baclofen (0.2-2 mg/kg/day, divided bid or tid) or dantrolene (0.5-10 mg/kg/day, bid). Small doses of levodopa (0.5-2 mg/kg/day) can be used to treat dystonia or DOPA-responsive dystonia. Artane (trihexyphenidyl, 0.25 mg/day, divided bid or tid and titrated upward) is sometimes useful for treating dystonia and can increase use of the upper extremities and vocalizations. Reserpine (0.01-0.02 mg/kg/day, divided bid to a maximum of 0.25 mg daily) or tetrabenazine (12.5-25.0 mg, divided bid or tid) can be useful for hyperkinetic movement disorders including athetosis or chorea.

Intrathecal baclofen delivered with an implanted pump has been used successfully in many children with severe spasticity, and can be useful because it delivers the drug directly around the spinal cord where it reduces neurotransmission of afferent nerve fibers. Direct delivery to the spinal cord overcomes the problem of CNS side effects caused by the large oral doses needed to penetrate the blood–brain barrier. This therapy requires a team approach and constant follow-up for complications of the infusion pumping mechanism and infection. **Botulinum toxin** injected into specific muscle groups for the management of spasticity shows a very positive response in many patients. Botulinum toxin injected into salivary glands may also help reduce the severity of drooling, which is seen in 10-30% of patients with CP and has been traditionally treated with anticholinergic agents. Patients with rigidity, dystonia, and spastic quadriparesis sometimes respond to levodopa, and children with dystonia may benefit from carbamazepine or trihexyphenidyl. Hyperbaric oxygen has not been shown to improve the condition of children with CP.

Communication skills may be enhanced by the use of Bliss symbols, talking typewriters, electronic speech generating devices, and specially adapted computers including artificial intelligence computers to augment motor and language function. Significant behavior problems may substantially interfere with the development of a child with CP; their early identification and management are important, and the assistance of a psychologist or psychiatrist may be necessary. Learning and attention deficit disorders and mental retardation are assessed and managed by a psychologist and educator. Strabismus, nystagmus, and optic atrophy are common in children with CP; an ophthalmologist should be included in the initial assessment. Lower urinary tract dysfunction should receive prompt assessment and treatment.

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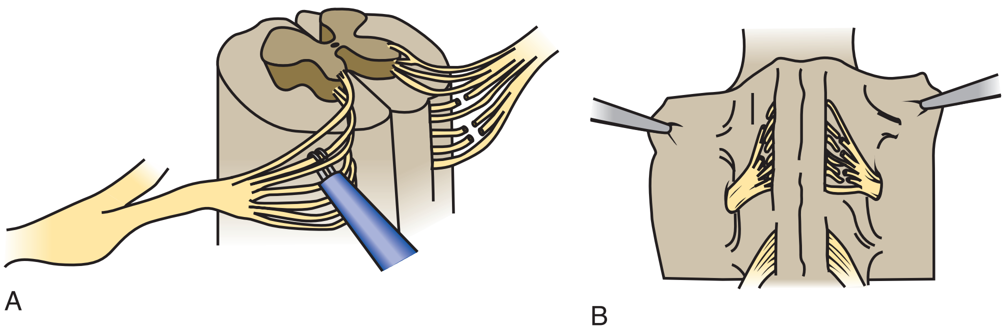

Figure 598-2 Schematic of the technique of selected dorsal rhizotomy. **A,** After laminectomy, the dura is opened and the dorsal spinal rootlets are exposed. The rootlets are stimulated so that abnormal rootlet activity can be identified. **B,** A proportion of rootlets are transected. *(From Koman LA, Smith BP, Shilt JS: Cerebral palsy,* Lancet *363:1619–1631, 2004. Reproduced with permission from Wake Forest University Orthopaedic Press.)*

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598.2 Mitochondrial Encephalomyopathies

Michael V. Johnston

See Chapters 87.4 and 611.4.

Mitochondrial encephalomyopathies are a heterogeneous group of clinical syndromes caused by genetic lesions that impair energy production through oxidative phosphorylation. The signs and symptoms of these disorders reflect the vulnerability of the nervous system, muscles, and other organs to energy deficiency. Signs of brain and muscle dysfunction (seizures, weakness, ptosis, external ophthalmoplegia, psychomotor regression, hearing loss, movement disorders, and ataxia) in association with lactic acidosis are prominent features of mitochondrial disorders. Cardiomyopathy and diabetes mellitus can also result from mitochondrial disorders.

Children with mitochondrial disorders often have multifocal signs that are intermittent or relapsing–remitting, often in association with intercurrent illness. Many of these disorders were described as clinical syndromes before their genetics were understood. Children with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) present with developmental delay, weakness, and headaches, as well as focal signs that suggest a stroke. Brain imaging indicates that injury does not fit within the usual vascular territories. Children with myoclonic epilepsy with ragged red fibers (MERRF) present with myoclonus and myoclonic seizures as well as intermittent muscle weakness. The ragged red fibers referred to in the name of this disorder are clumps of abnormal mitochondria seen within muscle fibers in sections from a muscle biopsy stained with Gomori trichrome stain. NARP syndrome (neuropathy, ataxia, and retinitis pigmentosa), Kearns-Sayre syndrome (KSS; ptosis, ophthalmoplegia, heart block), Leigh disease (subacute necrotizing encephalomyelopathy), and Leber hereditary optic neuropathy (LHON) are also defined as relatively homogeneous clinical subgroups (Table 598-2). It is important to keep in mind that mitochondrial disorders can be difficult to diagnose. They often present with novel combinations of signs and symptoms as a consequence of high mutation rates for mitochondrial DNA (mtDNA), and the severity of disease varies from person to person.

Mitochondrial diseases can be caused by mutations of nuclear DNA (nDNA) or mtDNA (see Chapters 80, 86, and 87). Oxidative phosphorylation in the respiratory chain is mediated by 4 intramitochondrial enzyme complexes (complexes I-IV) and 2 mobile electron carriers (coenzyme Q and cytochrome c) that create an electrochemical proton gradient utilized by complex V (adenosine triphosphate [ATP] synthase) to create the ATP required for normal cellular function. The maintenance of oxidative phosphorylation requires coordinated regulation of nuclear DNA and mtDNA genes. Human mtDNA is a small (16.6 kb), circular, double-stranded molecule that has been completely sequenced and encodes 37 genes including 13 structural proteins, all of which are subunits of the respiratory chain complexes, as well as 2 ribosomal RNAs and 22 transfer RNAs (tRNAs) needed for translation. The nuclear DNA is responsible for synthesizing approximately 70 subunits, transporting them to the mitochondria via chaperone proteins, ensuring their passage across the inner mitochondrial membrane, and coordinating their correct processing and assembly. Diseases of mitochondrial oxidative phosphorylation can be divided into 3 groups: (1) defects of mtDNA, (2) defects of nDNA, and (3) defects of communication between the nuclear and mitochondrial genome. mtDNA is distinct from nDNA for the following 4 reasons: (1) its genetic code differs from nDNA, (2) it is tightly packed with information because it contains no introns, (3) it is subject to spontaneous mutations at a higher rate than nDNA, (4) it has less efficient repair mechanisms.

Inheritance of mutations present on mtDNA is nonmendelian and can be complex. At fertilization, mtDNA is present in hundreds or thousands of copies per cell and is transmitted by maternal inheritance from her oocyte to all her children, but only her daughters can pass it on to their children. Through the process called heteroplasmy or threshold effect, mtDNA containing mutations can be distributed unequally between cells in specific tissues. Some cells receive few or no mutant genomes (**normal** or **wild-type homoplasmy**), whereas

Table 598-2 Clinical Manifestations of Mitochondrial Encephalomyopathies

TISSUE	SYMPTOMS/SIGNS	MELAS	MERRF	NARP	KSS	LEIGH	LHON
CNS	Regression	+	+		+	+	
	Seizures	+	+				
	Ataxia	+	+	+	+		
	Cortical blindness	+					
	Deafness	+		+			
	Migraine	+					
	Hemiparesis	+					
	Myoclonus	+	+				
	Movement disorder	+					+
Nerve	Peripheral neuropathy	+	+	+	+		
Muscle	Ophthalmoplegia				+		
	Weakness	+	+	+	+	+	
	RRF on muscle biopsy	+	+		+		
	Ptosis				+		
Eye	Pigmentary retinopathy			+	+		
	Optic atrophy				+	+	+
	Cataracts						
Heart	Conduction block				+		+
	Cardiomyopathy				+		
Blood	Anemia	+					
	Lactic acidosis		+		+	+	
Endocrine	Diabetes mellitus				+		
	Short stature	+	+		+		
Kidney	Fanconi syndrome	+	+		+		

KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; NARP, neuropathy, ataxia and retinitis pigmentosa; RRF, ragged red fibers.

others receive a mixed population of **mutant** and **wild-type** mtDNAs **(heteroplasmy),** and still others receive primarily or exclusively **mutant** genomes **(mutant homoplasmy).** The important implications of maternal inheritance and heteroplasmy are as follows: (1) inheritance of the disease is maternal, but both sexes are equally affected; (2) phenotypic expression of an mtDNA mutation depends on the relative proportions of mutant and wild-type genomes, with a minimum critical number of mutant genomes being necessary for expression **(threshold effect);** (3) at cell division, the proportional distribution may shift between daughter cells (mitotic segregation), leading to a corresponding phenotypic change; and (4) subsequent generations are affected at a higher rate than in autosomal dominant diseases. The critical number of mutant mtDNAs required for the threshold effect may vary, depending on the vulnerability of the tissue to impairments of oxidative metabolism as well as on the vulnerability of the same tissue over time that may increase with aging. In contrast to maternally inherited disorders caused by mutations in mtDNA, diseases resulting from defects in nDNA follow mendelian inheritance. Mitochondrial diseases caused by defects in nDNA include defects in substrate transport (plasmalemmal carnitine transporter, carnitine palmitoyltransferases I and II, carnitine acylcarnitine translocase defects), defects in substrate oxidation (pyruvate dehydrogenase complex, pyruvate carboxylase, intramitochondrial fatty acid oxidation defects), defects in the Krebs cycle (α-ketoglutarate dehydrogenase, fumarase, aconitase defects), and defects in the respiratory chain (complexes I-V), including defects of oxidation/phosphorylation coupling (Luft syndrome), and defects in mitochondrial protein transport.

Diseases caused by defects in mtDNA can be divided into those associated with point mutations that are maternally inherited (e.g., LHON, MELAS, MERRF, and NARP syndromes) and those caused by deletions or duplications of mtDNA that reflect altered communication between the nucleus and the mitochondria (KSS; Pearson syndrome, a rare severe encephalopathy with anemia and pancreatic dysfunction; and progressive external ophthalmoplegia). These disorders can be inherited by sporadic, autosomal dominant or recessive mechanisms and mutations in multiple genes, including mitochondrial mtDNA polymerase γ catalytic subunit (POLG), have been identified. **POLG mutations** have also been identified in patients with Alpers-Huttenlocher syndrome, which causes a refractory seizure disorder and hepatic failure as well as autosomal dominant and recessive progressive external ophthalmoplegia, childhood myocerebrohepatopathy spectrum disorders, myoclonic epilepsy myopathy sensory ataxia syndrome, and *POLG*-related ataxia neuropathy spectrum disorders. Other genes that regulate the supply of nucleotides for mtDNA synthesis are associated with severe encephalopathy and liver disease, and new disorders are being identified that result from defects in the interactions between mitochondria and their milieu in the cell.

MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKELIKE EPISODES

Children with MELAS may be normal for the 1st several yr, but they gradually display delayed motor and cognitive development and short stature. The clinical syndrome is characterized by (1) recurrent stroke-like episodes of hemiparesis or other focal neurologic signs with lesions most commonly seen in the posterior temporal, parietal, and occipital lobes (CT or MRI evidence of focal brain abnormalities); (2) lactic acidosis, ragged red fibers (RRF), or both; and (3) at least 2 of the following: focal or generalized seizures, dementia, recurrent migraine headaches, and vomiting. In 1 series, onset was before age 15 yr in 62% of patients, and hemianopia or cortical blindness was the most common manifestation. Cerebrospinal fluid protein is often increased. The MELAS 3243 mutation on mtDNA is the most common mutation to produce MELAS and can also be associated with different combinations of exercise intolerance, myopathy, ophthalmoplegia, pigmentary retinopathy, hypertrophic or dilated cardiomyopathy, cardiac conduction defects, deafness, endocrinopathy (diabetes mellitus), and proximal renal tubular dysfunction. A number of other mutations have been reported, and 2 patients have been described with bilateral rolandic lesions and epilepsia partialis continua associated with mtDNA mutations at 10158T>C and 10191T>C. MELAS is a progressive disorder that has been reported in siblings. However, most maternal relatives of MELAS patients are mildly affected or unaffected. MELAS is punctuated with episodes of stroke leading to dementia (see Chapter 611.4).

Regional cerebral hypoperfusion can be detected by single-photon emission CT studies and MR spectroscopy can detect focal areas of lactic acidosis in the brain. Neuropathology may show cortical atrophy with infarct-like lesions in both cortical and subcortical structures, basal ganglia calcifications, and ventricular dilation. Muscle biopsy specimens usually show RRF. Mitochondrial accumulations and abnormalities have been shown in smooth muscle cells of intramuscular vessels and of brain arterioles and in the epithelial cells and blood vessels of the choroid plexus, producing a mitochondrial angiopathy. Muscle biochemistry shows complex I deficiency in many cases; however, multiple defects have also been documented involving complexes I, III, and IV. Targeted molecular testing for specific mutations or sequence analysis and mutation scanning are generally used to make a diagnosis of MELAS when clinical evaluation suggests the diagnosis. Because the number of mutant genomes is lower in blood than in muscle, muscle is the preferable tissue for examination. Inheritance is maternal, and there is a highly specific, although not exclusive, point mutation at nt 3243 in the $tRNA^{Leu(UUR)}$ gene of mtDNA in approximately 80% of patients. An additional 7.5% have a point mutation at nt 3271 in the $tRNA^{Leu(UUR)}$ gene. A third mutation has been identified at nt 3252 in the $tRNA^{Leu(UUR)}$ gene. The prognosis in patients with the full syndrome is poor. Therapeutic trials reporting some benefit have included corticosteroids, coenzyme Q10, nicotinamide, carnitine, creatine, riboflavin and various combinations of these; L-arginine and preclinical studies reported some success with resveratrol.

MYOCLONUS EPILEPSY AND RAGGED RED FIBERS

MERRF syndrome is characterized by progressive myoclonic epilepsy, mitochondrial myopathy, and cerebellar ataxia with dysarthria and nystagmus. Onset may be in childhood or in adult life, and the course may be slowly progressive or rapidly downhill. Other features include dementia, sensorineural hearing loss, optic atrophy, peripheral neuropathy, and spasticity. Because some patients have abnormalities of deep sensation and pes cavus, the condition may be confused with Friedreich ataxia. A significant number of patients have a positive family history and short stature. This condition is maternally inherited.

Pathologic findings include elevated serum lactate concentrations, RRF on muscle biopsy, and marked neuronal loss and gliosis affecting, in particular, the dentate nucleus and inferior olivary complex with some dropout of Purkinje cells and neurons of the red nucleus. Pallor of the posterior columns of the spinal cord and degeneration of the gracile and cuneate nuclei occur. Muscle biochemistry has shown variable defects of complex III, complexes II and IV, complexes I and IV, or complex IV alone. More than 80% of cases are caused by a heteroplasmic G to A point mutation at nt 8344 of the $tRNA^{Lys}$ gene of mtDNA. Additional patients have been reported with a T to C mutation at nt 8356 in the $tRNA^{Lys}$ gene. Targeted mutation analysis or mutation analysis after sequencing of the mitochondrial genome is used to diagnosis MERRF.

There is no specific therapy, although coenzyme Q10 appeared to be beneficial in a mother and daughter with the MERRF mutation. The anticonvulsant levetiracetam is reported to help reduce myoclonus and myoclonic seizures in this disorder.

NEUROPATHY, ATAXIA, AND RETINITIS PIGMENTOSA SYNDROME

This maternally inherited disorder presents with either Leigh syndrome or with neurogenic weakness and NARP syndrome, as well as seizures. It is caused by a point mutation at nt 8993 within the ATPase subunit 6 gene. The severity of the disease presentation appears to have close correlation with the percentage of mutant mtDNA in leukocytes.

Two clinical patterns are seen in patients with NARP syndrome: (1) neuropathy, ataxia, retinitis pigmentosa, dementia, and ataxia, and (2) severe infantile encephalopathy resembling Leigh syndrome with lesions in the basal ganglia on MRI.

LEBER HEREDITARY OPTIC NEUROPATHY

LHON is characterized by onset usually between the ages of 18 and 30 yr of acute or subacute visual loss caused by severe bilateral optic atrophy, although children as young as 5 yr have been reported to have LHON. Three mtDNA mutations account for most cases of LHON and at least 85% of patients are young men. An X-linked factor may modulate the expression of the mtDNA point mutation. The classic ophthalmologic features include circumpapillary telangiectatic microangiopathy and pseudoedema of the optic disc. Variable features may include cerebellar ataxia, hyperreflexia, Babinski sign, psychiatric symptoms, peripheral neuropathy, or cardiac conduction abnormalities (preexcitation syndrome). Some cases are associated with widespread white matter lesions as seen with multiple sclerosis. Lactic acidosis and RRF tend to be conspicuously absent in LHON. More than 11 mtDNA point mutations have been described, including a usually homoplasmic G to A transition at nt 11,778 of the ND4 subunit gene of complex I. The latter leads to replacement of a highly conserved arginine residue by histidine at the 340th amino acid and accounts for 50-70% of cases in Europe and more than 90% of cases in Japan. Certain LHON pedigrees with other point mutations are associated with complex neurologic disorders and may have features in common with MELAS syndrome and with infantile bilateral striatal necrosis. One family has been reported with pediatric onset of progressive generalized dystonia with bilateral striatal necrosis associated with a homoplasmic G14459A mutation in the mtDNA *ND6* gene, which is also associated with LHON alone and LHON with dystonia.

KEARNS-SAYRE SYNDROME

KSS is a characteristic multiorgan disorder involving external ophthalmoplegia, heart block, and retinitis pigmentosa with onset before age 20 yr caused by single deletions in mtDNA. There must also be at least 1 of the following: heart block, cerebellar syndrome, or cerebrospinal fluid protein >100 mg/dL. Other nonspecific but common features include dementia, sensorineural hearing loss, and multiple endocrine abnormalities, including short stature, diabetes mellitus, and hypoparathyroidism. The prognosis is guarded, despite placement of a pacemaker, and progressively downhill, with death resulting by the 3rd or 4th decade. Unusual clinical presentations can include renal tubular acidosis and Lowe syndrome. There are also a few overlap cases of children with KSS and stroke-like episodes. Muscle biopsy shows RRF and variable cytochrome c oxidase (COX)-negative fibers. Most patients have mtDNA deletions, and some have duplications. These may be new mutations accounting for the generally sporadic nature of KSS. A few pedigrees have shown autosomal dominant transmission. Patients should be monitored closely for endocrine abnormalities, which can be treated. Coenzyme Q is reported anecdotally to have some beneficial effect; a positive effect of folinic acid for low folate levels also is reported. A report of positive effects of a cochlear implant for deafness is also reported.

Sporadic progressive external ophthalmoplegia with ragged red fibers is a clinically benign condition characterized by adolescent or young adult–onset ophthalmoplegia, ptosis, and proximal limb girdle weakness. It is slowly progressive and compatible with a relatively normal life. The muscle biopsy material demonstrates RRF and COX-negative fibers. Approximately 50% of patients with progressive external ophthalmoplegia have mtDNA deletions, and there is no family history.

REVERSIBLE INFANTILE CYTOCHROME C OXIDASE DEFICIENCY MYOPATHY

Mutations in mtDNA are also responsible for a reversible form of severe neuromuscular weakness and hypotonia in infants that is the result of a maternally inherited homoplasmic m.14674T>C mt-tRNA^{Glu} mutation associated with a deficiency of COX. Affected children present within the 1st few wk of life with hypotonia, severe muscle weakness, and very elevated serum lactate levels, and they often require mechanical ventilation. However, feeding and psychomotor development are not affected. Muscle biopsies taken from these children in the neonatal period show RRF and deficient COX activity, but these findings disappeared within 5-20 mo when the infants recovered spontaneously. It is difficult to distinguish these infants from those with lethal mitochondrial disorders without waiting for them to improve. The mechanism for this recovery is not established, but it may reflect a developmental switch in mitochondrial RNAs later in infancy. This reversible disorder is observed only in COX deficiency associated with the 14674T>C mt-tRNA^{Glu} mutation, so it is suggested that infants with this type of severe weakness in the neonatal period be tested for this mutation to help with prognosis.

LEIGH DISEASE (SUBACUTE NECROTIZING ENCEPHALOMYOPATHY)

Leigh disease is a progressive degenerative disorder presenting in infancy with feeding and swallowing problems, vomiting, and failure to thrive associated with lactic acidosis and lesions seen in the brainstem and/or basal ganglia on MRI (Table 598-3). There are several genetically determined causes of Leigh disease that result from nuclear DNA mutations in genes that code for components of the respiratory chair: pyruvate dehydrogenase complex deficiency, complex I or II deficiency, complex IV (COX) deficiency, complex V (ATPase) deficiency, and deficiency of coenzyme Q10. These defects may occur sporadically or be inherited by autosomal recessive transmission, as in the case of COX deficiency; by X-linked transmission, as in the case of pyruvate dehydrogenase $E_1\alpha$ deficiency; or by maternal transmission, as in complex V (ATPase 6 nt 8993 mutation) deficiency. Approximately 30% of cases are caused by mutations in mtDNA. Delayed motor and language milestones may be evident, and generalized seizures, weakness, hypotonia, ataxia, tremor, pyramidal signs, and nystagmus are prominent findings. Intermittent respirations with associated sighing or sobbing are characteristic and suggest brainstem dysfunction. Some patients have external ophthalmoplegia, ptosis, retinitis pigmentosa, optic atrophy, and decreased visual acuity. Abnormal results on CT or MRI scan consist of bilaterally symmetric areas of low attenuation in the basal ganglia and brainstem as well as elevated lactic acid on MR spectroscopy (Fig. 598-3). Pathologic changes consist of focal symmetric areas of necrosis in the thalamus, basal ganglia, tegmental gray matter, periventricular and periaqueductal regions of the brainstem, and posterior columns of the spinal cord. Microscopically, these spongiform lesions show cystic cavitation with neuronal loss, demyelination, and vascular proliferation. Elevations in serum lactate levels are characteristic and hypertrophic cardiomyopathy, hepatic failure and rental tubular dysfunction can occur. The overall outlook is poor, but a few patients experience prolonged periods of remission. There is no definitive treatment for the underlying disorder, but a range of vitamins including riboflavin, thiamine, and coenzyme Q are often given to try to improve mitochondrial function. Biotin, creatine, succinate, and idebenone, as well as a high-fat diet have also been used, but phenobarbital and valproic acid should be avoided because of their inhibitory effect on the mitochondrial respiratory chain.

REYE SYNDROME

This encephalopathy, which has become uncommon, is associated with pathologic features characterized by fatty degeneration of the viscera (microvesicular steatosis) and mitochondrial abnormalities and biochemical features consistent with a disturbance of mitochondrial metabolism (see Chapter 361).

Recurrent Reye-like syndrome is encountered in children with genetic defects of fatty acid oxidation, such as deficiencies of the plasmalemmal carnitine transporter, carnitine palmitoyltransferases I and II, carnitine acylcarnitine translocase, medium- and long-chain acyl-coenzyme A dehydrogenase, multiple acyl-coenzyme A dehydrogenase, and long-chain L-3 hydroxyacyl-coenzyme A dehydrogenase or trifunctional protein. These disorders are manifested by recurrent hypoglycemic and hypoketotic encephalopathy, and they are inherited

Table 598-3 Clinical Features of Congenital Leigh Syndrome or Leigh-Like Syndrome

NEUROLOGIC MANIFESTATIONS	NONNEUROLOGIC MANIFESTATIONS
Brainstem	*Dysmorphic Features*
Bradypnea, hypopnea, episodes of apnea	Lip cleft
Bradycardia	Short distal phalanges
Tetraparesis	Single palmar crease
Hypotonia (floppy infant)	Rostral vertebrae
Failure to thrive, poor sucking	Round face
Swallowing difficulties, dysphagia, poor feeding, poor sucking	Frontal bossing
Vomiting	Flat nasal root
Spasticity, brisk tendon reflexes	Microcephaly
Dysphasia, dysarthria	Thin lips
Squint	Small chin
Absence of optic or acoustic blink	Long, featureless philtrum
Other Cerebral Manifestations	Hypospadia
Stroke-like episodes	*Others*
Delay of developmental milestones	Inguinal hernia
Paralysis of vertical gaze	Stiff neck
Myoclonic jerks of limbs or eyelids	Retinal dystrophy, retinopathy
Hypothermia	Deafness, hypoacusis
Drowsiness, dizziness	Hypertrophic, dilated cardiomyopathy
Psychomotor (mental) retardation	Pancreatitis
Ataxia, tremor	Diarrhea
Seizures, convulsions	Urinary excretion of Krebs-cycle intermediates
Growth retardation	Intrauterine growth retardation
Dystonia	Hypertrichosis
Clumsiness, dullness	Villous atrophy
Nystagmus, uncoordinated eye movement, slow saccades	Nephrotic syndrome
Optic atrophy	Nephropathy
Visual loss	Hyperhidrosis
Facial dyskinesia	Scoliosis
Ocular apraxia	
Drooling	
Gaze fixation difficulty	
Peripheral Nervous System Manifestations	
Cranial nerve palsies	
Generalized wasting	
Bilateral ptoses	
Chronic progressive external ophthalmoplegia, strabismus	
Reduced tendon reflexes	
Polyneuropathy	
Muscle weakness	
Myopathy	

From Finsterer J: Leigh and Leigh-like syndrome in children and adults. Pediatr Neurol *39:223–235, 2008, Table 1.*

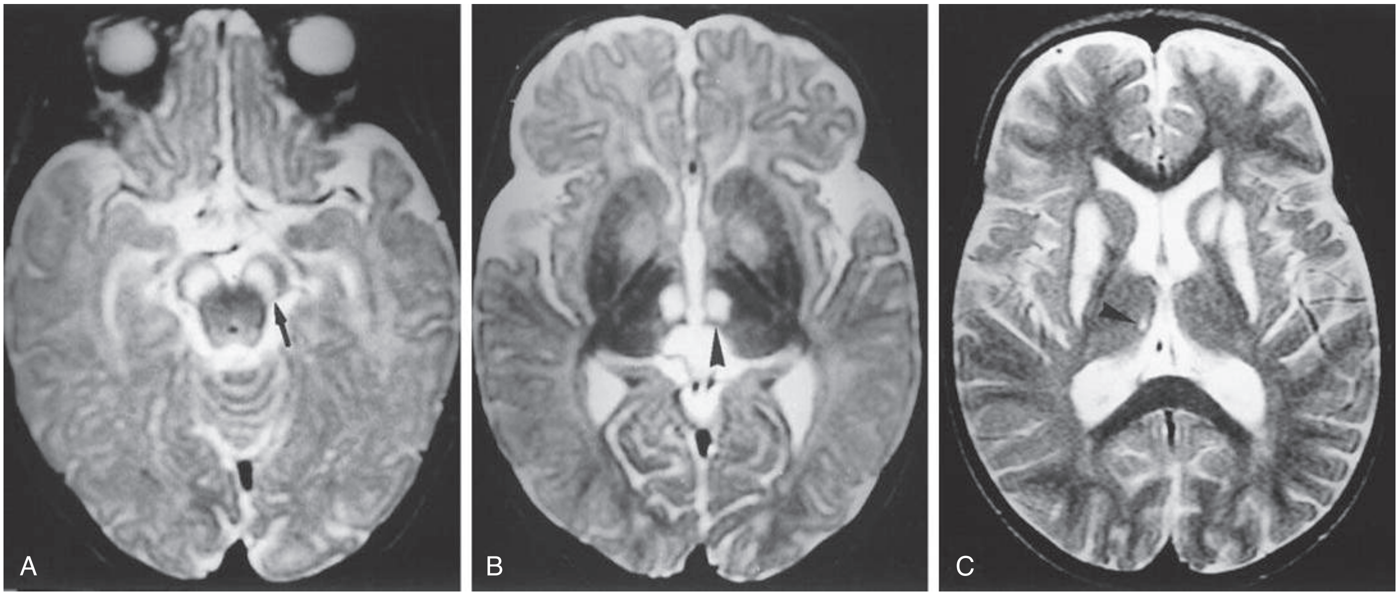

Figure 598-3 **Leigh syndrome.** Axial T2-weighted magnetic resonance images (TR/TE/NEX = 3,000/120/1 msec) of 8 mo old girl with Leigh syndrome because of a *SURF1* mutation indicate hyperintense lesions in substantia nigra and medial thalamic nuclei **(A, B).** Follow-up images (TR/TE/NEX = 2,028/120/2 msec) at age 26 mo **(C)** indicate hyperintense putamina and hyperintense left caudate nucleus. *(From Farina L, Chiapparini L, Uziel G, et al: MR findings in Leigh syndrome with COX deficiency and* SURF-1 *mutations,* AJNR Am J Neuroradiol *23:1095–1100, 2002, Fig. 2.)*

in an autosomal recessive pattern. Other potential inborn errors of metabolism presenting with Reye syndrome include urea cycle defects (ornithine transcarbamylase, carbamyl phosphate synthetase) and certain of the organic acidurias (glutaric aciduria type I), respiratory chain defects, and defects of carbohydrate metabolism (fructose intolerance).

Bibliography is available at Expert Consult.

598.3 Other Encephalopathies

Michael V. Johnston

HIV ENCEPHALOPATHY

Encephalopathy is an unfortunate and common manifestation in infants and children with HIV infection (see Chapter 276).

LEAD ENCEPHALOPATHY

See Chapter 721.

BURN ENCEPHALOPATHY

An encephalopathy develops in approximately 5% of children with significant burns in the 1st several wk of hospitalization (see Chapter 75). There is no single cause of burn encephalopathy but rather a combination of factors that include anoxia (smoke inhalation, carbon monoxide poisoning, laryngospasm), electrolyte abnormalities, bacteremia and sepsis, cortical vein thrombosis, a concomitant head injury, cerebral edema, drug reactions, and emotional distress. Seizures are the most common clinical manifestation of burn encephalopathy, but altered states of consciousness, hallucinations, and coma may also occur. Management of burn encephalopathy is directed to a search for the underlying cause and treatment of hypoxemia, seizures, specific electrolyte abnormalities, or cerebral edema. The prognosis for complete neurologic recovery is generally excellent, particularly if seizures are the primary abnormality.

HYPERTENSIVE ENCEPHALOPATHY

Hypertensive encephalopathy is most commonly associated with renal disease in children, including acute glomerulonephritis, chronic pyelonephritis, and end-stage renal disease (see Chapters 445 and 535). In some cases, hypertensive encephalopathy is the initial manifestation of underlying renal disease. Marked systemic hypertension produces vasoconstriction of the cerebral vessels, which leads to vascular permeability, causing areas of focal cerebral edema and hemorrhage. The onset may be acute, with seizures and coma, or more indolent, with headache, drowsiness and lethargy, nausea and vomiting, blurred vision, transient cortical blindness, and hemiparesis. Examination of the eyegrounds may be nondiagnostic in children, but papilledema and retinal hemorrhages may occur. MRI often shows increased signal intensity in the occipital lobes on T2-weighted images, which is known as **posterior reversible leukoencephalopathy (PRES)** and may be confused with cerebral infarctions. These high signal areas may appear in other regions of the brain as well. PRES may also be seen in children without hypertension. In all circumstances, PRES manifests with generalized motor seizures, headache, mental status changes, and visual disturbances. CT may be normal in PRES; MRI is the study of choice. Treatment is directed at restoration of a normotensive state and control of seizures with appropriate anticonvulsants.

RADIATION ENCEPHALOPATHY

Acute radiation encephalopathy is most likely to develop in young patients who have received large daily doses of radiation. Excessive radiation injures vessel endothelium, resulting in enhanced vascular permeability, cerebral edema, and numerous hemorrhages. The child may suddenly become irritable and lethargic, complain of headache, or present with focal neurologic signs and seizures. Patients occasionally develop hemiparesis as the result of an infarct secondary to vascular occlusion of the cerebral vessels. Steroids are often beneficial in reducing the cerebral edema and reversing the neurologic signs. Late-radiation encephalopathy is characterized by headaches and slowly progressive focal neurologic signs, including hemiparesis and seizures. Exposure of the brain to radiation for treatment of childhood cancer increases the risk of later cerebrovascular disease, including stroke, moyamoya disease, aneurysm, vascular malformations, mineralizing microangiopathy, and stroke-like migraines. Some children with acute lymphocytic leukemia treated with a combination of intrathecal methotrexate and cranial irradiation develop neurologic signs months or years later; signs consist of increasing lethargy, loss of cognitive abilities, dementia, and focal neurologic signs and seizures (see Chapter 494). The CT scan shows calcifications in the white matter, and the postmortem examination demonstrates a necrotizing encephalopathy. This devastating complication of the treatment of leukemia has prompted re-evaluation and reduction in the use of cranial radiation in the treatment of these children.

Table 598-4	Diagnostic Criteria for Acute Necrotizing Encephalopathy of Childhood

1. Acute encephalopathy following (1-3 days) a febrile disease. Rapid deterioration in the level of consciousness. Seizures.
2. No cerebrospinal fluid pleocytosis. Increase in cerebrospinal fluid protein.
3. CT or MRI evidence of symmetric, multifocal brain lesions. Involvement of the bilateral thalami. Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum and cerebellar medulla. No involvement of other central nervous system regions.
4. Elevation of serum aminotransferases of variable degrees. No increase in blood ammonia.
5. Exclusion of resembling diseases.
   A. Differential diagnosis from clinical viewpoints.
   Overwhelming bacterial and viral infections, and fulminant hepatitis; toxic shock, hemolytic uremic syndrome, and other toxin-induced diseases; Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke.
   B. Differential diagnosis from radiologic viewpoints.
   Leigh encephalopathy and related mitochondrial cytopathies; glutaric acidemia, methylmalonic acidemia, and infantile bilateral striatal necrosis; Wernicke encephalopathy and carbon monoxide poisoning; acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, other types of encephalitis, and vasculitis; arterial or venous infection, and the effects of severe hypoxia or head trauma

Modified from Hoshino A, Saitoh M, Oka, et al: Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. Brain Dev *34:337–343, 2012, Table 1.*

ACUTE NECROTIZING ENCEPHALOPATHY

Acute necrotizing encephalopathy is a rare, severe encephalopathy seen more commonly in Asian countries. It is thought to be triggered by a viral infection (influenza, HHV-6) in a genetically susceptible host. Table 598-4 lists the diagnostic criteria. The elevation of hepatic enzymes without hyperammonemia is a unique feature. A familial or recurrent form is associated with mutations in the *RANBP2* gene and is designated ANE1. MRI finding are characterized by symmetric lesions that must be present in the thalami (Fig. 598-4). The prognosis is usually poor, however some patients have responded to steroids and intravenous immunoglobulin (IVIG).

CYSTIC LEUKOENCEPHALOPATHY

An autosomal recessive disorder caused by mutations of RNASET2 proteins produces a brain MRI study that closely resembles congenital cytomegalovirus infection. Cystic leukoencephalopathy is manifest as a static encephalopathy without megalencephaly.

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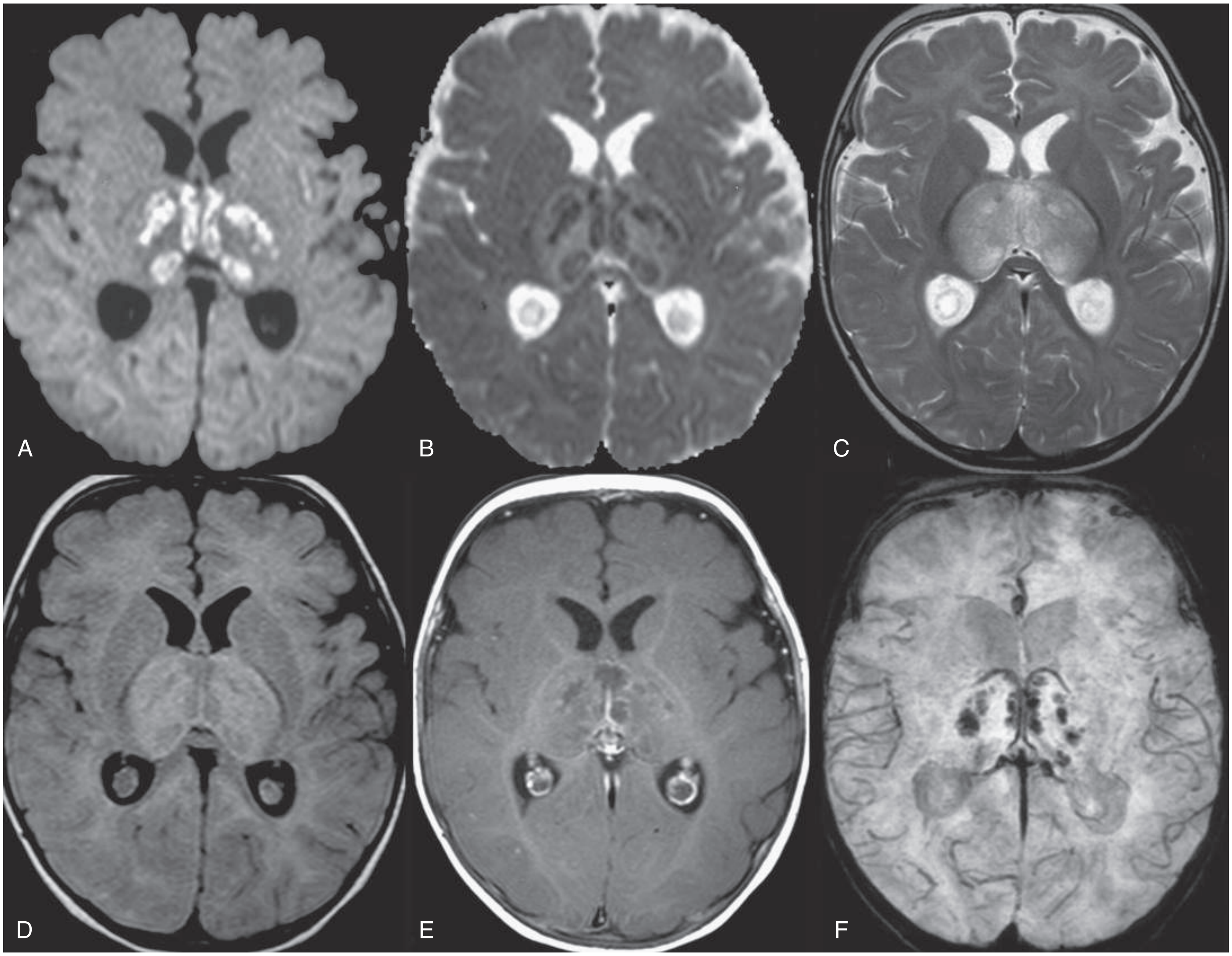

Figure 598-4 **Acute necrotizing encephalopathy.** MRI at presentation. **A,** Axial diffusion-weighted image; **B,** axial apparent diffusion coefficient (ADC) map; **C,** axial T2-weighted image; **D,** axial fluid-attenuated inversion recovery (FLAIR) image; **E,** contrast-enhanced axial T1-weighted image; **F,** axial susceptibility weighted image. Diffusion-weighted images **(A)** and corresponding ADC map **(B)** clearly show multiple areas of restricted diffusion against a background of increased diffusion involving both thalami, which are swollen. On T2-weighted **(C)** and FLAIR **(D)** images, the thalami are markedly swollen and hyperintense. On T1-weighted images obtained after intravenous gadolinium chelate injection **(E),** multiple necrotic portions are well delineated by peripheral faint, linear enhancement. Incidental choroid plexus cysts are detected. Susceptibility weighted image **(F)** shows multiple hypointense spots, consistent with petechial hemorrhage. *(From Bergamino L, Capra V, Biancheri R, et al: Immunomodulatory therapy in recurrent acute necrotizing encephalopathy ANE1: is it useful?* Brain Dev *34:384–391, 2012, Fig. 1.)*

598.4 Autoimmune Encephalitis

Thaís Armangué and Josep O. Dalmau

Autoimmune encephalitis comprises an expanding group of clinical syndromes that can occur at all ages (<1 yr to adult) but preferentially affect younger adults and children (Table 598-5). These disorders associate with antibodies against neuronal cell surface proteins and synaptic receptors involved in synaptic transmission, plasticity, or neuronal excitability. The syndromes vary according to the associated antibody with phenotypes that resemble those in which the function of the target antigen is pharmacologically or genetically modified.

Most of these disorders are severe and potentially fatal but patients frequently respond to immunotherapy with good outcomes. Moreover, because of the broad spectrum of symptoms—including alterations of behavior, psychosis, catatonia, memory deficits, seizures, abnormal movements, and autonomic dysregulation—patients usually require a multidisciplinary treatment approach often in an intensive care unit.

The identification of these disorders provides a definitive diagnosis to many cases of encephalitis previously considered idiopathic, infectious, or postinfectious, although no causative agents were found. Because the etiology and pathogenic mechanisms were unknown, some of these disorders were previously defined with descriptive terms. More than half of cases under the ill-defined term "encephalitis lethargica" and some cases of "choreoathetosis post–herpes simplex encephalitis" are known to be anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.

The mechanisms that trigger the production of the antibodies are unknown. In a small subgroup of adolescent or young adult patients, the presence of a tumor that expresses the target neuronal antigen likely contributes in triggering the immune response. In addition, the high prevalence of prodromal viral-like symptoms has suggested that nonspecific viral infections may contribute to breaking immune tolerance and increase the permeability of the blood–brain barrier to antibodies. Nonetheless in many of these disorders the blood–brain barrier appears intact and there is evidence that the autoantibodies are

Table 598-5 Autoimmune Encephalitis in Children

	MECHANISMS	TUMOR ASSOCIATION	SYNDROME	ANCILLARY TEST	TREATMENT/ PROGNOSIS
DEMONSTRATED IMMUNE MECHANISMS					
Anti-NMDAR encephalitis	Antibodies against NR1 subunit of NMDAR, disrupt function by crosslinking and internalization of receptors	Age and gender related: 41% in females older than 12 yr; <6% in girls younger than 12 yr. No tumors identified in young boys	Psychiatric symptoms, seizures, orofacial dyskinesias and other abnormal movements, autonomic dysfunction	EEG: almost always abnormal; it may show "extreme delta brush" pattern Brain MRI: nonspecific findings in ~35% CSF: pleocytosis and/or increased protein in >80%	80% complete recovery after immunotherapy and tumor removal (if appropriate). Frequently second-line drug* immunotherapy is required. Relapses in ~15% of patients
Limbic encephalitis	**Antibodies against intraneuronal antigens:** Hu, Ma2, amphiphysin, GAD **Antibodies against synaptic antigens:** $GABA_BR$, mGluR5	Extremely rare in children (see text)	Severe short-term memory loss, seizures	EEG: temporal lobe epileptic activity; focal or generalized slowing MRI: increased T2 and FLAIR signal in limbic region CSF: pleocytosis and increased proteins	If autoantigens are intracellular, poor response to immunotherapy If autoantigens are on the cell surface, ~80% are responsive to immunotherapy
STRONGLY SUSPECTED IMMUNE MECHANISMS					
Opsoclonus-myoclonus and other cerebellar-brainstem encephalitis	Most patients do not have detectable antibodies (a few patients have Hu antibodies)	Neuroblastoma occurs in 50% of children <2 year old; teratoma in teenagers and young adults	Opsoclonus often accompanied by irritability, ataxia, falling, myoclonus, tremor, and drooling	CSF abnormalities suggesting B-cell activation MRI: in some cases cerebellar atrophy	Partial response to immunotherapy in neuroblastoma-related opsoclonus High response to immunotherapy in teratoma-associated opsoclonus
Bickerstaff encephalitis	GQ1b antibodies	No tumor association	Ophthalmoplegia, ataxia, hyperreflexia. May overlap with Miller-Fisher syndrome	MRI: abnormal in ~30% (T2-signal abnormalities in the brainstem, thalamus, and cerebellum) Nerve conduction studies: abnormal in ~44% (predominant axonal degeneration, less frequent demyelination)	Often good outcome with steroids, IVIG and/or plasma exchange
Hashimoto encephalitis	TPO antibodies	No tumor association	Stroke-like symptoms, tremor, myoclonus, aphasia, sleep and behavioral problems seizures, ataxia	48% hypothyroidism, MRI often normal EEG: slow activity CSF: elevated protein	Steroid-responsive. Partial responses are frequent
Rasmussen encephalitis	Most likely immune mediated (unclear mechanism)	No tumor association	Progressive refractory partial seizures, cognitive decline, focal deficits, and brain hemiatrophy	MRI: progressive unilateral hemispheric atrophy	Limited response to immunotherapy. Patients may need functional hemispherectomy
Basal ganglia encephalitis	Antibodies to D2R in some cases	No tumor association	Abnormal movement and behavior disorder	Variable basal ganglia T2/FLAIR abnormalities	Mostly monophasic, can relapse
POSSIBLE IMMUNE MECHANISMS					
CLIPPERS	No antibodies	No tumor association	Episodic diplopia or facial paresthesias with subsequent development of symptoms of brainstem and occasionally spinal cord dysfunction	MRI: symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, midbrain, and, occasionally, spinal cord	Steroid-responsive but may require chronic steroid or other immunosuppressive therapy
ROHHAD	Unknown. Autoimmune and genetic origin postulated.	Neural crest tumor in ~50% of cases†	Rapid onset obesity, hyperphagia, abnormal behavior, autonomic dysfunction, and central hypoventilation	Brain MRI, usually normal	Symptomatic; in some patients limited response to immunotherapy

*Includes rituximab and cyclophosphamide.

†Exact frequency is unknown.

CLIPPERS, Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CSF, cerebrospinal fluid; D2R, dopamine 2 receptor; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; $GABA_BR$, γ-aminobutyric acid-B receptor, GAD, glutamic acid decarboxylase; IVIG, intravenous immunoglobulin; mGluR5, metabotropic glutamate receptor 5; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; ROHHAD, rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; TPO, thyroid peroxidase.

synthesized within the CNS by plasma cells that form part of local brain and meningeal inflammatory infiltrates.

ANTI-*N*-METHYL-D-ASPARTATE RECEPTOR ENCEPHALITIS

In this disorder, the antibodies target the NR1 subunit of the NMDA receptor. The exact frequency of this syndrome is unknown but it is considered the second most common cause of autoimmune encephalitis after acute disseminated encephalomyelitis in children and adolescents. Overall, the disorder predominates in females (80%), although in patients younger than 12 yr the frequency of males is higher (40%). The resulting syndrome is highly predictable and usually evolves in stages. In teenagers and young adults, the disorder usually presents with prominent psychiatric manifestations that may include rapidly progressive anxiety, agitation, delusional thoughts, bizarre behavior, labile affect, mood disturbances (mania), catatonic features, memory deficit, language disintegration, aggression, and insomnia or other sleep disturbances. In many cases, these symptoms had been preceded by a few days of prodromal headache, fever or viral-like symptoms. As a result of this symptom presentation, patients are often misdiagnosed with new-onset psychosis or a primary psychiatric disorder. However, in a few days or weeks, additional symptoms occur, including a decreased level of consciousness, seizures (including status epilepticus), limb or oral dyskinesias, choreoathetoid movements, and autonomic instability which usually includes tachycardia, bradycardia, fluctuations of blood pressure, hypoventilation, hyperthermia and sialorrhea. In rare instances, bradycardia and cardiac pauses occur, at times requiring the transient use of a pacemaker. The disorder also occurs in toddlers and infants (the youngest patient identified to date was 6 mo old), and although the evolution of the syndrome is similar to that of adults, young patients more frequently present with motor or complex seizures and movement disorders. Because of their age, the psychiatric–behavioral features may be missed. In this young age group, behavior changes include irritability, new-onset temper tantrums, agitation, aggression, reduced speech, mutism, and autistic-like regression. Moreover, compared with adults some children also develop cerebellar ataxia and hemiparesis; in contrast, autonomic dysfunction is usually milder and less severe in children. There is often an abrupt on–off phenomenon in alterations of responsiveness or level of consciousness.

Brain MRI is abnormal in approximately 35% of cases, usually showing nonspecific cortical and subcortical T2–fluid-attenuated inversion recovery (FLAIR) signal abnormalities, sometimes with transient cortical or meningeal enhancement; nonspecific white matter abnormalities are common. Lesions may also involve the spinal cord producing symptoms of myelitis. The cerebrospinal fluid (CSF) is initially abnormal in approximately 80% of cases, showing moderate lymphocytic pleocytosis and less frequently increased protein synthesis and oligoclonal bands. The electroencephalogram (EEG) is abnormal in virtually all patients, and usually shows focal or diffuse slow activity in the delta and theta range, which does not correlate with abnormal movements. In addition, many patients develop epileptic activity, requiring video-monitoring for adequate clinical management. A characteristic EEG pattern called "extreme delta brush" characterized by beta-delta complexes occurs in 30% of adults and has been described in children (Fig. 598-5).

The diagnosis of the disorder is established by demonstrating NMDAR antibodies in CSF or serum. The sensitivity is higher in CSF compared with serum (100% vs 85%), and the levels of antibodies in CSF appear to correlate better with outcome. Antibodies may remain detectable, albeit at lower titers, after patients recover.

The presence of an underlying tumor, mostly teratomas, is age and sex dependent. Whereas 40% of females older than 12 yr have an underlying teratoma of the ovary, less than 6% of females younger than 12 yr have a tumor. In young boys with anti-NMDAR encephalitis, the presence of an underlying tumor is exceptional; in young adults, the presence of a testicular teratoma is also rare (<15% of cases). In children, MRI of abdomen and pelvis and abdominal and testicular ultrasound are the preferred tumor screening tests.

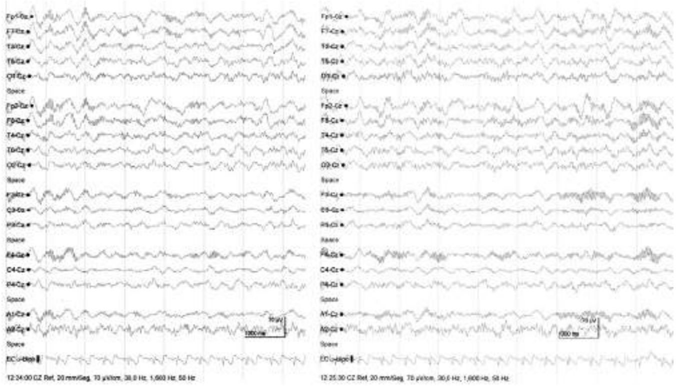

Figure 598-5 **Electroencephalogram showing a pattern named "extreme delta brush" in a 14 yr old girl with anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.** This pattern has been found to be characteristic of anti-NMDAR encephalitis. It consists of a nearly continuous combination of delta activity with superimposed fast activity, usually in the beta range, symmetrically involving all head regions, with a frontal preference in patients who are not under effects of sedation or anesthetics. *(From Armangue T, Titulaer MJ, Málaga I, et al: Pediatric anti-*N*-methyl-*D*-aspartate receptor encephalitis—clinical analysis and novel findings in a series of 20 patients.* J Pediatr *162:850–856, 2012, Fig. 2.)*

In a small number of patients, anti-NMDAR encephalitis occurs simultaneously or after infections with a variety of pathogens, including *Mycoplasma pneumoniae*, human herpes simplex viruses 1 and 6 (HSV), enterovirus, and influenza. A pathogenic link with most of these infections has not established; there is evidence that some patients with HSV encephalitis develop antibodies against the NR1 subunit of the NMDAR. These patients may progress to develop relapsing neurologic symptoms post-HSV encephalitis. In a subgroup of patients with noninfectious relapsing neurologic symptoms post-HSV encephalitis, or "choreoathetosis post-HSV encephalitis," the disorder is in fact anti-NMDAR encephalitis (see Videos 598-1, 598-2, and 598-3).

Although no prospective clinical trials have been done, there is evidence that tumor removal, when appropriate, and prompt immunotherapy improve outcome. Most children receive first-line immunotherapies, including corticosteroids, IVIG, or plasma exchange. However, because these treatments fail in almost 50% of patients, and with an increasing number of reports showing that rituximab can be effective, this treatment is increasingly being used in combination with IVIG and steroids, or after first-line immunotherapies. Cyclophosphamide can be effective when there has been no response to these treatments.

Although anti-NMDAR encephalitis has a mortality rate of 7%, approximately 80% of patients have substantial or full recovery. Recovery is usually slow and can take as long as 2 yr after symptom onset. The last symptoms to improve are social interactions, and language and executive functions. Relapses occur in approximately 15% of patients; they can develop as partial syndromes, are usually milder than the initial episode and respond equally to immunotherapy. Initial comprehensive immunotherapy appears to prevent or reduce the number of relapses. The efficacy of chronic immunosuppression with drugs such as azathioprine or mycophenolate mofetil in preventing relapses is unknown.

The differential diagnosis of anti-NMDAR encephalitis is extensive and varies according to the stage of the disease (Table 598-6). The most frequently considered disorders are viral encephalitis, neuroleptic malignant syndrome, acute psychosis, and drug abuse.

LIMBIC ENCEPHALITIS

This disorder refers to an inflammatory process of the limbic system including, the medial temporal lobes, amygdala, and cingulate gyri. In adults, the most frequent immune-mediated limbic encephalitis occurs

Table 598-6 Differential Diagnosis of Anti-NMDAR Encephalitis in Children

DISORDER	COMMENTS
Viral encephalitis	Viral encephalitis is often suggested by the acute onset of symptoms, CSF pleocytosis, and hyperthermia. Most viral encephalitides (except rabies) occur with higher levels of CSF pleocytosis and protein concentration. Psychosis and dyskinesias are significantly less frequent in viral encephalitis than in anti-NMDAR encephalitis.
Relapsing post–herpes simplex virus encephalitis	Occurs ~4-6 wk after successful treatment of herpes simplex encephalitis. This may represent a true viral relapse of encephalitis (CSF PCR-positive, progression of necrotic MRI changes, response to acyclovir), or an autoimmune disorder (CSF PCR-negative, no new necrotic lesions on MRI, lack of response to acyclovir). In a proportion of the latter patients, the disorder is anti-NMDAR encephalitis.
New-onset psychosis	Because most patients with anti-NMDAR encephalitis present with psychosis, a primarily psychiatric disorder is frequently considered. As the disease evolves, the development of neurological symptoms usually reveals the diagnosis.
Drugs/toxins	The acute development of personality and behavioral changes, and symptoms suggesting involvement of dopaminergic pathways (rigidity, dystonia, orofacial movements) usually leads to a suspicion of drug abuse (e.g., ketamine, phencyclidine, among others). Carbon monoxide.
Neuroleptic malignant syndrome	The occurrence of altered level of consciousness, episodes of rigidity, hyperthermia, and autonomic instability often suggest NMS. In addition, some patients with anti-NMDAR encephalitis have elevated serum creatine kinase and rhabdomyolysis (in the absence of antipsychotic medication). The frequent use of neuroleptics to control the abnormal behavior adds further confusion between both syndromes. The presence of dyskinesias and catatonia suggest anti-NMDAR encephalitis.
Limbic encephalitis	Criteria of LE are well defined. Patients with LE do not have dyskinesias or central hypoventilation; the MRI usually shows abnormalities restricted to the medial temporal lobes, and the EEG findings (epileptic or slow activity) are largely restricted to the temporal lobes.
Encephalitis lethargica	This is an ill-defined entity, likely representing multiple disorders. Criteria include: acute or subacute encephalitis with at least 3 of the following: signs of basal ganglia involvement; oculogyric crises; ophthalmoplegia; obsessive-compulsive behavior; akinetic mutism; central respiratory irregularities; and somnolence and/or sleep inversion. Approximately, 50% of patients categorized as encephalitis lethargica hyperkinetica have anti-NMDAR encephalitis.
Childhood disintegrative disorder/late-onset autism	Children with anti-NMDAR encephalitis often show cognitive regression, rapid loss of language function, autistic features, and seizures, suggesting a childhood disintegrative disorder. While the prognosis of CDD is poor, most patients with anti-NMDAR encephalitis respond to immunotherapy and have substantial clinical recovery.
Kleine-Levin syndrome	Symptoms of hypersomnia, compulsive hyperphagia, hypersexuality, apathy, and child-like behavior, which are typical components of Kleine-Levin syndrome, may occur transiently during the process of recovery of anti-NMDAR encephalitis, or as permanent sequelae.
Inborn errors of metabolism	Glutaric aciduria type I can present in previously asymptomatic patients as episodes of encephalopathy with dystonia, coinciding with an infection or febrile process. Several inborn errors of metabolism can also occur with acute or subacute encephalopathy with extrapyramidal signs, including 3-methylglutaconic aciduria, creatine transport deficiency, mitochondrial disorders (Leigh syndrome), Wilson, and Lesch-Nyhan syndromes. Pantothenate kinase associated neurodegeneration, porphyria, and urea cycle defects should also be considered.
Monoamine neurotransmitter disorders	Deficiency of dopamine, serotonin or both can result in encephalopathy, epilepsy, and pyramidal and extrapyramidal symptoms. The diagnosis is established by examining the CSF for levels of these neurotransmitters.
Demyelinating disorders	Acute disseminated encephalomyelitis and neuromyelitis optica are immune-mediated inflammatory and demyelinating disorders of the central nervous system. These disorders should be considered in the differential diagnosis of multifocal neurologic abnormalities and encephalopathy in children. As with anti-NMDAR encephalitis these disorders may be preceded by an infection and can show pleocytosis. The diagnosis is suggested by the MRI findings. In NMO the presence of aquaporin 4 antibodies in serum or CSF is associated with relapses and poor prognosis.
CNS vasculitis	CNS vasculitis results in neurologic deficits and psychiatric manifestations. The diagnosis is established by angiography in large vessel angiitis, and brain biopsy in small vessel angiitis. In the latter, serum inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, Complement 3, von Willebrand factor antigen) are usually elevated, and the MRI shows FLAIR/T2 abnormalities in the white and/or gray matter, not restricted to vascular territories with frequent leptomeningeal and/or local enhancement.
Systemic rheumatic disorders	Systemic lupus erythematosus and other rheumatic disorders can result in encephalopathy and multifocal neurologic and psychiatric manifestations. These disorders are usually suggested by the presence of signs and symptoms of involvement of systemic organs: skin, joints, kidneys, blood-forming cells, and blood vessels.

CDD, childhood disintegrative disorder; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; LE, limbic encephalitis; MRI, magnetic resonance imaging; NMDAR, *N*-methyl-D-aspartate receptor; NMO, neuromyelitis optica; NMS, neuroleptic malignant syndrome; PCR, polymerase chain reaction.

in association with antibodies against proteins that were once thought to be voltage-gated potassium channels (VGKC), but which, in fact, target a secreted neuronal protein called leucine-rich glioma-inactivated 1 (LGI1), and a protein called Caspr2 expressed in brain and juxtaparanodal regions of myelinated nerves. Patients with LGI1 antibody associated limbic encephalitis often develop *hyponatremia*; in some patients the disorder is preceded by short-lasting episodes of distinctive dystonic or myoclonic-like movements, described as *faciobrachial dystonic seizures*, but with EEG features of tonic seizures. Patients with antibodies to Caspr2 usually develop Morvan syndrome, which includes encephalopathy, seizures, autonomic dysfunction, and neuromyotonia. How the clinical significance of antibodies called "VGKC-complex proteins" differs from LGI1 and Caspr2 is unknown.

Other less frequent types of autoimmune limbic encephalitis in adults are paraneoplastic and may occur with antibodies against intracellular antigens (e.g., Hu, CRMP5, Ma2) or neuronal cell surface and synaptic proteins (e.g., AMPA, $GABA_B$ receptor, mGluR5). While the disorders associated with antibodies against intracellular antigens appear to be mediated by cytotoxic T-cell responses and are poorly responsive to treatment, those associated with antibodies to cell surface and synaptic antigens are likely mediated by the antibodies and treatment responsive.

In children, autoimmune or paraneoplastic limbic encephalitis is exceptional. Unfortunately, any type of encephalopathy resulting in seizures and alteration of memory and behavior is frequently labeled as "limbic encephalitis," making data based on literature searches using the term "limbic encephalitis" unreliable. Fewer than 30 children with limbic encephalitis have been described in the English literature, some of them with antibodies against intracellular or cell surface antigens (Hu, Ma2, GAD, amphiphysin, $GABA_B$, and VGKC-complex proteins different from LGI1 and Caspr2). In some cases an underlying tumor was identified and included, leukemia, ganglioneuroblastoma, neuroblastoma, and small-cell carcinoma of the ovary.

The **Ophelia syndrome** is a form of limbic encephalitis that occurs in association with Hodgkin's lymphoma and predominantly affects young adults, teenagers or children. Some patients develop antibodies against mGluR5, a receptor involved in learning and memory; symptoms are usually responsive to chemotherapy.

HASHIMOTO ENCEPHALOPATHY

Hashimoto encephalopathy is defined by the detection of thyroid peroxidase (TPO) antibodies in patients with acute or subacute encephalitis that responds to corticosteroids. Since almost 50% of patients have normal thyroid function and not all patients respond to steroids, the term "encephalopathy associated with autoimmune thyroid disease" is considered more accurate than the previous term "steroid-responsive encephalopathy associated with autoimmune thyroiditis." Clinical features are not specific and may include stroke-like symptoms, tremor, myoclonus, transient aphasia, sleep and behavior abnormalities, hallucinations, seizures, and ataxia. The CSF usually shows elevated protein level with less-frequent pleocytosis. EEG studies almost always are abnormal frequently showing generalized slowing. Brain MRI is usually normal, although it may show diffuse white matter abnormalities and meningeal enhancement that can resolve with steroid therapy. As TPO antibodies occur in approximately 10% of asymptomatic children (nonencephalopathic and most cases euthyroid), as well as in patients who have more relevant antibody-associated disorders, such as $GABA_B$, LGI1, or NMDAR antibodies, TPO antibodies should be viewed as a marker of autoimmunity rather than a neurologic disease-specific or pathogenic antibody. Importantly the presence of TPO antibodies should not prevent testing for more relevant antibodies.

OPSOCLONUS–MYOCLONUS AND OTHER BRAINSTEM–CEREBELLAR ENCEPHALITIDES

Opsoclonus-myoclonus occurs in infants, teenagers and adults, although it probably represents different diseases and pathogenic mechanisms. In infants, the syndrome usually develops in the 1st 2 yr of life (mean: 20 mo), and at least 50% of patients have an underlying neuroblastoma. The child often presents with irritability, ataxia, falling, myoclonus, tremor, and drooling. Additional symptoms may include refusal to walk or sit, speech problems, hypotonia, and the typical features of opsoclonus characterized by rapid, chaotic, multidirectional eye movements without saccadic intervals. Because opsoclonus may be absent at symptom presentation, patients may initially be diagnosed with acute cerebellitis or labyrinthitis. Typically CSF abnormalities suggest B-cell activation, and the presence of antibodies against neuronal proteins has been demonstrated in several studies, although the identification of a specific autoantigen has been elusive.

Immunosuppressive treatment, including corticosteroids, IVIG, rituximab, and cyclophosphamide often improves the abnormal eye movements, but residual behavioral, language, and cognitive problems persist in the majority of patients, often requiring special education. In addition, insomnia and abnormal response to pain are common. Relapses occur in 50% of the patients, usually as a result of an intercurrent infection or drug tapering. Delay in treatment appears to associate with a poorer neurologic outcome; therefore, in cases with neuroblastoma, removal of the tumor should not delay the start of immunotherapy.

In teenagers and young adults, opsoclonus–myoclonus and brainstem–cerebellar encephalitis without opsoclonus are often considered "idiopathic" or "postinfectious"; however, there is evidence that some of these patients have an underlying teratoma, usually in the ovaries. These patients do not harbor NMDAR antibodies, and compared with those with anti-NMDAR encephalitis are less likely to initially present with psychosis and behavioral changes, and rarely develop dyskinesias. Although these patients do not appear to have neuronal antibodies, the CSF often shows pleocytosis and elevated protein concentration. Identification of this subphenotype of opsoclonus–myoclonus is important because patients usually have full recovery after treatment with immunotherapy (corticosteroids, IVIG, and/or plasma exchange) and if present, removal of the ovarian teratoma. The prognosis of this disorder seems better than that of neuroblastoma-associated opsoclonus, or the paraneoplastic opsoclonus of older patients, usually related to breast, ovarian, or lung cancer.

BICKERSTAFF ENCEPHALITIS

This term is used to describe patients with subacute progressive ophthalmoplegia and ataxia in addition to drowsiness or hyperreflexia. Although this entity has been described more frequently in adults, children as young as 3 yr old have been identified. Most patients are treated with steroids, IVIG, and/or plasma exchange, and often have good outcome. Serum GQ1b immunoglobulin G antibodies are found in 66% of patients. Brain MRI abnormalities occur in 30% of the patients and usually include increased T2-signal abnormalities in the brainstem, thalamus, cerebellum, and sometimes cerebral white matter. Some patients develop hyporeflexia and limb weakness, with predominant axonal involvement, overlapping with symptoms of the Miller-Fisher syndrome and the axonal subtype of the Guillain-Barré syndrome.

CHRONIC LYMPHOCYTIC INFLAMMATION WITH PONTINE PERIVASCULAR ENHANCEMENT RESPONSIVE TO STEROIDS

This is a clinically and radiologically distinct pontine-predominant encephalomyelitis. To date fewer than 30 patients have been reported and two of them were children (13 and 16 yr). Patients usually present with episodic diplopia or facial paresthesias with subsequent development of symptoms of brainstem and occasionally spinal cord dysfunction. Brain MRI shows symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, midbrain and occasionally spinal cord. The clinical and radiological findings usually respond to high dose steroids but may worsen after the steroid taper, requiring chronic steroid or other immunosuppressive therapy. The differential diagnosis is extensive and includes infections, granulomatous disease, lymphoma or vasculitis. Biopsy studies may be needed to exclude these and other conditions.

AUTOIMMUNE ENCEPHALOPATHIES ASSOCIATED WITH EPILEPSY AND STATUS EPILEPTICUS

Rasmussen encephalitis is an inflammatory encephalopathy characterized by progressive refractory partial seizures, cognitive deterioration, and focal deficits that occur with gradual atrophy of 1 brain hemisphere. The disorder frequently presents in 6-8 yr old children, although adolescents and adults can be affected. The etiology is unknown and, therefore, multiple theories are proposed, including the presence of antibodies against the GluR3 subunit of the AMPA receptor and T-cell mediated mechanisms triggered by a viral infection. None of these mechanisms satisfactorily explains the unilateral brain involvement characteristic of the disorder. Treatment with high-dose steroids, plasma exchange, or IVIG can ameliorate symptoms in early stages of the disease. Rituximab and intraventricular γ-interferon have been effective in a few isolated cases. In a small series, patients treated with tacrolimus showed better outcomes of neurologic function and slower progression of cerebral hemiatrophy, but not improved seizure control. The only definitive treatment is functional hemispherectomy that consists in surgical disconnection of the affected hemisphere.

The discovery of treatment-responsive encephalitis associated with antibodies against cell surface or synaptic proteins has resumed the interest for a potential autoimmune basis of several devastating encephalopathies with refractory seizures. Some well-defined autoimmune encephalitis such as **anti-NMDAR encephalitis** can present in children with refractory seizures or status epilepticus. In these patients, the development over a short period of time of the characteristic spectrum of symptoms (altered behavior, orofacial dyskinesias, and autonomic dysfunction) and demonstration of NMDAR antibodies leads to the correct diagnosis and initiation of immunotherapy.

A devastating epileptic encephalopathy associated with fever named **fever-induced refractory epileptic encephalopathy syndrome,** among other terms, is suspected to be an infection-triggered autoimmune process because of its biphasic clinical course and the occasional finding of neuronal antibodies in a few patients. However, the lack of response to most treatments including immunotherapy, and the rare and inconsistent association to different types of antibodies cast doubts on an autoimmune pathogenesis. Other investigators suggest a genetic error in metabolism.

Antibodies to VGKC-complex proteins different from LGI1 and Caspr2 have been described in a few children with encephalitis with or without status epilepticus. Given that the target antigens are unknown and the response to immunotherapy is unpredictable, the significance of these antibodies is unclear.

OTHER SUSPECTED AUTOIMMUNE ENCEPHALITIDES

Demyelinating disorders, vasculitis of the CNS, and rheumatic diseases associate with autoimmune mechanisms can result in encephalitis.

Rapid onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (**ROHHAD**) usually affects children who had normal development until 2-4 yr of age and then develop rapid onset of hyperphagia, weight gain, and abnormal behavior (social disinhibition, irascibility, impulsivity, lethargy, outburst of euphoria and laughing, impaired concentration), followed by autonomic dysfunction (abnormal pupillary responses, thermal dysregulation, gastrointestinal dysmotility), and central hypoventilation. An autoimmune or paraneoplastic etiology of ROHHAD syndrome is supported by the frequent association to neural crest tumors, the identification in some patients of genetic factors predisposing to autoimmunity, and the finding of intrathecal oligoclonal bands and infiltrates of lymphocytes and histiocytes in the hypothalamus of some patients. Furthermore, responses to immunotherapy have been described in a few patients. A possible genetic origin is suggested because of the similarities of this syndrome with the congenital central hypoventilation syndrome (Ondine curse) related to a *PHOX2B* mutation, which presents in the neonatal period and also associates with autonomic problems (Hirschsprung disease) and neural crest tumors (see Chapter 418.2). However, no mutations in *PHOX2B* and other candidate genes have been found in patients with ROHHAD.

The term **basal ganglia encephalitis** is used to describe patients with predominant or isolated involvement of the basal ganglia. These patients typically have abnormal movements and neuropsychiatric disease. Although these disorders probably have multiple etiologies, including metabolic, toxic, genetic, and infectious processes, an immune-mediated etiology has been postulated in some patients. There have been no clinical trials, but case reports and small noncontrolled case series describe the potential benefit of immunotherapy. Antibodies against the dopamine-2 receptor have been identified in some of these patients as well as in patients with Sydenham chorea and Tourette syndrome.

Pseudomigraine syndrome with CSF pleocytosis (**PMP**) or **headache with neurologic deficits and CSF lymphocytosis** (**HaNDL**) is an ill-defined entity that predominantly affects young male adults with a family history of migraine, although adolescents can be affected. This syndrome is characterized by repeated episodes of severe headache with transient neurologic deficits, accompanied by aseptic CSF lymphocytosis and normal brain MRI. Patients frequently show high CSF opening pressure, elevated CSF protein concentration, and focal EEG slowing, which normalize after the episodes of headache. Because of the inflammatory characteristics of the CSF and the high prevalence of prodromal viral-like symptoms, an infectious-autoimmune mediated mechanism has been proposed. Other theories include spreading cortical depression and trigeminal-vascular activation.

An immune-mediated mechanism and trigeminal-vascular activation are also considered as possible mechanisms of **ophthalmoplegic migraine,** also named **recurrent cranial neuralgia.** This disorder predominantly affects young children and is characterized by recurrent bouts of head pain in addition to cranial nerves III, IV, and/or VI involvement. In contrast to PMP/HaNDL, CSF studies do not show pleocytosis, and in approximately 75% of cases, the MRI shows focal nerve thickening and contrast enhancement. Observational data suggest that treatment with steroids may be beneficial. In this syndrome, as well as in PMP/HaNDL, the differential diagnosis includes structural, neoplastic, traumatic, metabolic, and infectious disorders.

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Chapter 599

Neurodegenerative Disorders of Childhood

Jennifer M. Kwon

Neurodegenerative disorders of childhood encompass a large, heterogeneous group of diseases that result from specific genetic and biochemical defects, chronic viral infections, and varied unknown causes. Children with suspected neurodegenerative disorders were once subjected to brain and rectal (neural) biopsies, but with modern neuroimaging techniques and specific biochemical and molecular diagnostic tests, these invasive procedures are rarely necessary. The most important component of the diagnostic investigation continues to be a thorough history and physical examination. The hallmark of a neurodegenerative disease is **regression and progressive deterioration** of neurologic function with loss of speech, vision, hearing, or locomotion, often associated with seizures, feeding difficulties, and impairment of intellect. The age of onset, rate of progression, and principal

Table 599-1 Neurometabolic Conditions Associated with Developmental Regression

AGE AT ONSET (yr)	CONDITIONS	COMMENTS
<2 with hepatomegaly	Fructose intolerance	Vomiting, hypoglycemia, poor feeding, failure to thrive (when given fructose)
	Galactosemia	Lethargy, hypotonia, icterus, cataract, hypoglycemia (when given lactose)
	Glycogenosis (glycogen storage disease) types I-IV	Hypoglycemia, cardiomegaly (type II)
	Mucopolysaccharidosis types I and II	Coarse facies, stiff joints
	Niemann-Pick disease, infantile type	Gray matter disease, failure to thrive
	Tay-Sachs disease	Seizures, cherry-red macula, edema, coarse facies
	Zellweger syndrome	Hypotonia, high forehead, flat facies
	Gaucher disease (neuronopathic form)	Extensor posturing, irritability
	Carbohydrate-deficient glycoprotein syndromes	Dysmyelination, cerebellar hypoplasia
<2, without hepatomegaly	Krabbe disease	Irritability, extensor posturing, optic atrophy, and blindness
	Rett syndrome	Girls with deceleration of head growth, loss of hand skills, hand wringing, impaired language skills, gait apraxia
	Maple syrup urine disease	Poor feeding, tremors, myoclonus, opisthotonos
	Phenylketonuria	Light pigmentation, eczema, seizures
	Menkes kinky hair disease	Hypertonia, irritability, seizures, abnormal hair
	Subacute necrotizing encephalopathy of Leigh disease	White matter disease
	Canavan disease	White matter disease, macrocephaly
	Neurodegeneration with brain iron accumulation disease	White matter disease, movement disorder
2-5	Niemann-Pick disease types III and IV	Hepatosplenomegaly, gait difficulty
	Wilson disease	Liver disease, Kayser-Fleischer ring; deterioration of cognition is late
	Gangliosidosis type II	Gray matter disease
	Neuronal ceroid lipofuscinosis	Gray matter disease
	Mitochondrial encephalopathies (e.g., myoclonic epilepsy with ragged red fibers [MERRF])	Gray matter disease
	Ataxia-telangiectasia	Basal ganglia disease
	Huntington disease (chorea)	Basal ganglia disease
	Neurodegeneration with brain iron accumulation syndrome	Basal ganglia disease
	Metachromatic leukodystrophy	White matter disease
	Adrenoleukodystrophy	White matter disease, behavior problems, deteriorating school performance, quadriparesis
5-15	Adrenoleukodystrophy	Same as for adrenoleukodystrophy in 2-5 yr olds
	Multiple sclerosis	White matter disease
	Neuronal ceroid lipofuscinosis, juvenile and adult (Spielmeyer-Vogt and Kufs disease)	Gray matter disease
	Schilder disease	White matter disease, focal neurologic symptoms
	Refsum disease	Peripheral neuropathy, ataxia, retinitis pigmentosa
	Sialidosis II, juvenile form	Cherry-red macula, myoclonus, ataxia, coarse facies
	Subacute sclerosing panencephalitis	Diffuse encephalopathy, myoclonus; may occur years after measles

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, WB Saunders, p. 542.*

neurologic findings determine whether the disease affects primarily the white or the gray matter. Upper motor neuron signs and progressive spasticity are the hallmarks of white matter disorders; convulsions and intellectual and visual impairments that occur early in the disease course are the hallmarks of gray matter disorders. A precise history confirms regression of developmental milestones, and the neurologic examination localizes the process within the nervous system. Although the outcome of a neurodegenerative condition is usually fatal and available therapies are often limited in effect, it is important to make the correct diagnosis so that genetic counseling may be offered and prevention strategies can be implemented. Bone marrow transplantation and other novel therapies may prevent the progression of disease in certain individuals who are either presymptomatic or very early in their disease course. For all conditions in which the specific enzyme defect is known, prevention by prenatal diagnosis (chorionic villus sampling or amniocentesis) is possible. Carrier detection is also often possible by enzyme assay. Table 599-1 summarizes selected inherited neurodegenerative and metabolic disorders by their usual age of onset.

599.1 Sphingolipidoses

Jennifer M. Kwon

The sphingolipidoses are characterized by intracellular storage of lipid substrates resulting from defective catabolism of the sphingolipids comprising cellular membranes (Fig. 599-1). The sphingolipidoses are subclassified into 6 categories: Niemann-Pick disease, Gaucher disease, GM_1 gangliosidosis, GM_2 gangliosidosis, Krabbe disease, and metachromatic leukodystrophy. Niemann-Pick disease and Gaucher disease are discussed in Chapter 86.4.

GANGLIOSIDOSES

See also Chapter 86.4.

Gangliosides are glycosphingolipids, normal constituents of the neuronal and synaptic membranes. The basic structure of GM_1 ganglioside consists of an oligosaccharide chain attached to a hydroxyl group of ceramide and sialic acid bound to galactose. The gangliosides are catabolized by sequential cleavage of the sugar molecules

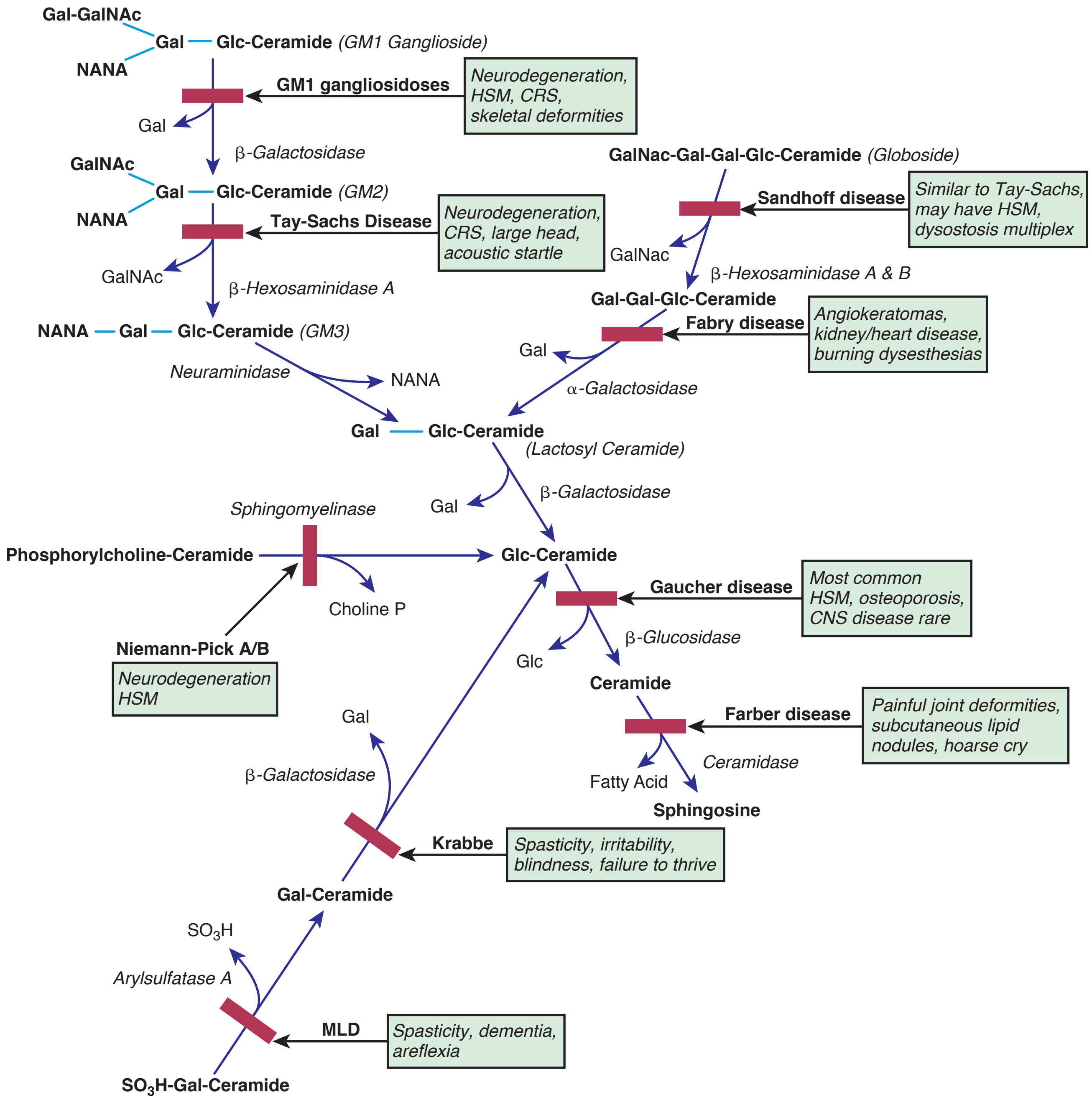

Figure 599-1 **Sphingolipid degradation pathway showing the sites of enzyme deficiencies and their associated disorders.** Sphingolipids are composed of a ceramide backbone with oligosaccharide side chains. CRS, cherry-red spot (retinal); Gal-, galactosyl-; GalNAc, N-acetyl-galactose; Glc-, glucosyl-; HSM, hepatosplenomegaly; MLD, metachromatic leukodystrophy; NANA, N-acetyl-neuraminic acid.

by specific exoglycosidases. Abnormalities in catabolism result in an accumulation of the ganglioside within the cell. Defects in ganglioside degradation can be classified into 2 groups: the GM_1 gangliosidoses and the GM_2 gangliosidoses.

GM_1 Gangliosidoses

The 3 subtypes of GM_1 gangliosidoses are classified according to age at presentation: infantile (type 1), juvenile (type 2), and adult (type 3). The condition is inherited as an autosomal recessive trait and results from a marked deficiency of acid β-galactosidase. This enzyme may be assayed in leukocytes and cultured fibroblasts. The acid β-galactosidase gene has been mapped to chromosome 3p14.2. Prenatal diagnosis is possible by measurement of acid β-galactosidase in cultured amniotic cells.

Infantile GM_1 gangliosidosis presents at birth or during the neonatal period with anorexia, poor sucking, and inadequate weight gain. Development is globally delayed, and generalized seizures are prominent. The phenotype is striking and shares many characteristics with Hurler syndrome. The facial features are coarse, the forehead is prominent, the nasal bridge is depressed, the tongue is large (macroglossia), and the gums are hypertrophied. Hepatosplenomegaly is present early in the course as a result of accumulation of foamy histiocytes, and kyphoscoliosis is evident because of anterior beaking of the vertebral bodies. The neurologic examination is dominated by apathy, progressive blindness, deafness, spastic quadriplegia, and decerebrate rigidity. A cherry-red spot in the macular region is visualized in approximately 50% of cases. The **cherry-red spot** is characterized by an opaque ring (sphingolipid-laden retinal ganglion cells) encircling the normal red fovea (Fig. 599-2). Children rarely survive beyond age 2-3 yr, and death may be from aspiration pneumonia.

Juvenile GM_1 gangliosidosis has a delayed onset beginning about 1 yr of age. The initial symptoms consist of incoordination, weakness,

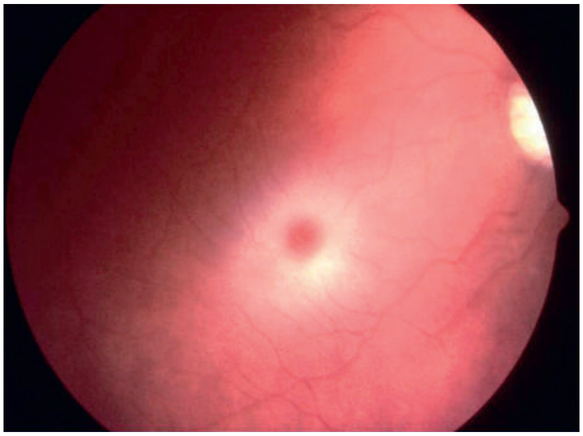

Figure 599-2 A cherry-red spot in a patient with GM_1 gangliosidosis. Note the whitish ring of sphingolipid-laden ganglion cells surrounding the fovea. *(From Leavitt JA, Kotagal S: The "cherry red" spot.* Pediatr Neurol *37(1):74–75, 2007, Fig. 1.)*

ataxia, and regression of language. Thereafter, convulsions, spasticity, decerebrate rigidity, and blindness are the major findings. Unlike the infantile type, this type is not usually marked by coarse facial features and hepatosplenomegaly. Radiographic examination of the lumbar vertebrae may show minor beaking. Children rarely survive beyond 10 yr of age. **Adult GM_1 gangliosidosis** is a slowly progressive disease consisting of spasticity, ataxia, dysarthria, and a gradual loss of cognitive function.

GM_2 Gangliosidoses

The GM_2 gangliosidoses are a heterogeneous group of autosomal recessive inherited disorders that consist of several subtypes, including Tay-Sachs disease (TSD), Sandhoff disease, juvenile GM_2 gangliosidosis, and adult GM_2 gangliosidosis. **TSD** is most prevalent in the Ashkenazi Jewish population and has an approximate carrier rate of 1 in 30 Jews in the United States. TSD is caused by mutations in the *HEXA* gene located on chromosome 15q23-q24. Affected infants appear normal until approximately 6 mo of age, except for a marked startle reaction to noise that is evident soon after birth. Affected children then begin to lag in developmental milestones and, by 1 yr of age, they lose the ability to stand, sit, and vocalize. Early hypotonia develops into progressive spasticity, and relentless deterioration follows, with convulsions, blindness, deafness, and cherry-red spots in almost all patients (see Fig. 599-2). Macrocephaly becomes apparent by 1 yr of age and results from the 200-300–fold normal content of GM_2 ganglioside deposited in the brain. Few children live beyond 3-4 yr of age, and death is usually associated with aspiration or bronchopneumonia. A deficiency of the isoenzyme hexosaminidase A is found in tissues of patients with TSD. Mass screening for prenatal diagnosis of TSD is a reliable and cost-effective method of prevention because the condition occurs most frequently in a defined population (Ashkenazi Jews). Targeted screening is responsible for the fact that currently, the rare children with TSD born in the United States are most commonly born to non-Jewish parents who are not routinely screened. An accurate and inexpensive carrier detection test is available (serum or leukocyte hexosaminidase A), and the disease can be reliably diagnosed by chorionic villus sampling in the 1st trimester of pregnancy in couples at risk (heterozygote parents).

Sandhoff disease is very similar to TSD in the mode of presentation, including progressive loss of motor and language milestones beginning at 6 mo of age. Seizures, cherry-red spots, macrocephaly, and doll-like facies are present in most patients; however, children with Sandhoff disease may also have splenomegaly. The visual evoked potentials (VEPs) are normal early in the course of Sandhoff disease and TSD, but become abnormal or absent as the disease progresses. The auditory brainstem responses show prolonged latencies. The diagnosis of Sandhoff disease is established by finding deficient levels of hexosaminidases A and B in serum and leukocytes. Children usually die by 3 yr of age. Sandhoff disease is caused by mutations in the *HEXB* gene located on chromosome 5q13.

Juvenile GM_2 gangliosidosis develops in mid-childhood, initially with clumsiness followed by ataxia. Signs of spasticity, athetosis, loss of language, and seizures gradually develop. Progressive visual loss is associated with optic atrophy, but cherry-red spots rarely occur in juvenile GM_2 gangliosidosis. A deficiency of hexosaminidase is variable (total deficiency to near normal) in these patients. Death occurs around 15 yr of age.

Adult GM_2 gangliosidosis is characterized by a myriad neurologic signs, including slowly progressive gait ataxia, spasticity, dystonia, proximal muscle atrophy, and dysarthria. Generally, visual acuity and intellectual function are unimpaired. Hexosaminidase A activity alone or hexosaminidases A and B activity is reduced significantly in the serum and leukocytes.

Krabbe Disease (Globoid Cell Leukodystrophy)

Krabbe disease (KD) is a rare autosomal recessive neurodegenerative disorder characterized by severe myelin loss and the presence of globoid bodies in the white matter. The gene for KD *(GALC)* is located on chromosome 14q24.3-q32.1. The disease results from a marked deficiency of the lysosomal enzyme galactocerebroside β-galactosidase. KD is a disorder of myelin destruction rather than abnormal myelin formation. Normally, myelination begins in the 3rd trimester, corresponding with a rapid increase of galactocerebroside β-galactosidase activity in the brain. In patients with KD, galactocerebroside cannot be metabolized during the normal turnover of myelin because of deficiency of galactocerebroside β-galactosidase. When galactocerebroside is injected into the brains of experimental animals, a globoid cell reaction ensues. It is postulated that a similar phenomenon occurs in humans; nonmetabolized galactocerebroside stimulates the formation of globoid cells that reflect the destruction of oligodendroglial cells. Because oligodendroglial cells are responsible for the elaboration of myelin, their loss results in myelin breakdown, thus producing additional galactocerebroside and causing a vicious circle of myelin destruction.

The symptoms of KD become evident in the 1st few mo of life and include excessive irritability and crying, unexplained episodes of hyperpyrexia, vomiting, and difficulty feeding. In the initial stage of KD, children are often treated for colic or milk allergy with frequent formula changes. Generalized seizures may appear early in the course of the disease. Alterations in body tone with rigidity and opisthotonos and visual inattentiveness as a result of optic atrophy become apparent as the disease progresses. In the later stages of the illness, blindness, deafness, absent deep-tendon reflexes, and decerebrate rigidity constitute the major physical findings. Most patients die by 2 yr of age. MRI and magnetic resonance spectroscopy are useful for evaluating the extent of demyelination in KD. Umbilical cord blood (stem cell) transplantation from unrelated donors in asymptomatic babies may favorably alter the natural history but will not help patients who already have neurologic symptoms.

Late-onset KD has been described beginning in childhood or adolescence. Patients present with optic atrophy and cortical blindness, and their condition may be confused with adrenoleukodystrophy. Slowly progressive gait disturbances, including spasticity and ataxia, are prominent. As with classic KD, globoid cells are abundant in the white matter, and leukocytes are deficient in galactocerebroside β-galactosidase. An examination of the cerebrospinal fluid shows an elevated protein content, and the nerve conduction velocities are markedly delayed as a result of segmental demyelination of the peripheral nerves. The VEPs decrease gradually in amplitude with no response in the late stages of the disease, and the auditory brainstem responses are characterized by the presence of only waves I and II. CT scans and MRI studies highlight the marked decrease in white matter, especially of the cerebellum and centrum semiovale, with sparing of the subcortical U fibers. Prenatal diagnosis is possible by the assay of galactocerebroside β-galactosidase activity in chorionic villi or in cultured amniotic fluid cells. Newborn screening may identify patients at risk for late onset disease.

Metachromatic Leukodystrophy

This disorder of myelin metabolism is inherited as an autosomal recessive trait and is characterized by a deficiency of arylsulfatase A activity. The *ARSA* gene is located on chromosome 22q13-13qter. The absence or deficiency of arylsulfatase A leads to accumulation of cerebroside sulfate within the myelin sheath of the central nervous system (CNS) and peripheral nervous system because of the inability to cleave sulfate from galactosyl-3-sulfate ceramide. The excessive cerebroside sulfate is thought to cause myelin breakdown and destruction of oligodendroglia. Prenatal diagnosis of metachromatic leukodystrophy (MLD) is made by assaying of arylsulfatase A activity in chorionic villi or cultured amniotic fluid cells. Cresyl violet applied to tissue specimens produces metachromatic staining of the sulfatide granules, giving the disease its name. Some individuals with low arylsulfatase A enzyme activity are clinically normal and have a pseudodeficiency state that can only be confirmed by additional genetic or biochemical tests. Those affected with MLD are generally classified according to age of onset: late infantile, juvenile, and adult.

Late infantile MLD begins with insidious onset of gait disturbances between 1 and 2 yr of age. The child initially appears awkward and frequently falls, but locomotion is gradually impaired significantly and support is required to walk. The extremities are hypotonic, and the deep-tendon reflexes are absent or diminished. Within the next several months, the child can no longer stand, and deterioration in intellectual function becomes apparent. The speech is slurred and dysarthric, and the child appears dull and apathetic. Visual fixation is diminished, nystagmus is present, and examination of the retina shows optic atrophy. Within 1 yr from the onset of the disease, the child is unable to sit unsupported, and progressive decorticate postures develop. Feeding and swallowing are impaired because of pseudobulbar palsies, and a feeding gastrostomy is required. Patients ultimately become stuporous and die of aspiration or bronchopneumonia by age 5-6 yr. Neurophysiologic evaluation shows slowing of peripheral nerve conduction velocities and progressive changes in the VEPs, auditory brainstem responses, and somatosensory evoked potentials. CT and MRI images of the brain indicate diffuse symmetric attenuation of the cerebellar and cerebral white matter, and examination of the cerebrospinal fluid shows an elevated protein content. Bone marrow transplantation is a promising experimental therapy for the management of late infantile MLD, and early trials of enzyme replacement are being conducted. As with KD, favorable outcomes have been reported only in patients treated with less-severe disease or those identified very early in the course of the disease.

Juvenile MLD has many features in common with late infantile MLD, but the onset of symptoms is delayed to 5-10 yr of age. Deterioration in school performance and alterations in personality may herald the onset of the disease. This is followed by incoordination of gait, urinary incontinence, and dysarthria. Muscle tone becomes increased, and ataxia, dystonia, or tremor may be present. In the terminal stages, generalized tonic–clonic convulsions are prominent and are difficult to control. Patients rarely live beyond mid-adolescence.

Adult MLD occurs from the 2nd to 6th decade. Abnormalities in memory, psychiatric disturbances, and personality changes are prominent features. Slowly progressive neurologic signs, including spasticity, dystonia, optic atrophy, and generalized convulsions, lead eventually to a bedridden state characterized by decorticate postures and unresponsiveness.

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599.2 Neuronal Ceroid Lipofuscinoses

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The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited, neurodegenerative, lysosomal storage disorders characterized by visual loss, progressive dementia, seizures, motor deterioration, and early death. The NCLs are so named because of the intracellular accumulation of fluorescent lipopigments, ceroid and lipofuscin. They comprise a genetically and phenotypically heterogeneous group of disorders (currently there are at least 9 NCL types) that have traditionally been subclassified by age of onset, among other clinical features. They differ from one another in the associated ultrastructural patterns of the inclusions as seen by electron microscopy. Evaluation of neuronal biopsies (either brain, rectal, conjunctival, or skin) was once required for diagnosis. With the advent of enzymatic and molecular testing methods, clinicians can make specific NCL diagnoses using less-invasive methods (Table 599-2).

Infantile-type neuronal ceroid lipofuscinose (INCL, Haltia-Santavuori) begins in the 1st yr of life with myoclonic seizures, intellectual deterioration, and blindness. Optic atrophy and brownish discoloration of the macula are evident on examination of the retina, and cerebellar ataxia is prominent. The electroretinogram typically shows small-amplitude or absent waveforms. Death occurs during childhood. The infantile form is caused by recessive mutations of the gene for the lysosomal enzyme palmitoyl-protein thioesterase-1 (PPT1) on chromosome 1p32. A number of cell types in INCL patients show characteristic intracellular fine granular osmiophilic deposits discernible by electron microscopy.

Table 599-2 Clinical and Genetic Characteristics of the Neuronal Ceroid Lipofuscinoses (NCL)

NCL TYPE	GENE*	PROTEIN	AGE OF ONSET	CLINICAL PRESENTATION
Congenital	*CLN10*	Cathepsin[‡]	Birth (but can present later)	Severe seizures, blindness, rigidity, early death Can also present similar to late infantile forms
Infantile	*CLN1*	Palmitoyl-protein thioesterase-1 (PPT1)[‡]	6-24 months	Early onset, often rapid progression of seizures; cognitive and motor decline with visual loss
Variant infantile	*CLN1*		3 yr to adulthood	Chronic course Initial visual loss followed then by slow mental and motor decline and seizures
Late infantile	*CLN2*	Tripeptidyl peptidase-1 (TPP1)[‡]	2-8 yr	Seizures, often severe and intractable; cognitive and motor decline; and visual loss
	CLN5	Partially soluble protein		
	CLN6	Membrane protein		
	CLN7	Membrane protein		
	CLN8	Membrane protein	5-10 yr	Severe epilepsy, progressive with mental retardation
Juvenile	*CLN3*	Membrane protein	4-10 yr	Visual loss is usually the initial presenting complaint Also have mental, motor disorder and seizures

*Note that all the NCL genes have the prefix CLN. The adult form (also called Kufs disease, with locus CLN4, caused by mutations in DNAJC5) is not well characterized and is not included in the table.

[†]Direct genetic testing is available for all.

[‡]Enzyme testing available.

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A subset of children with PPT1 enzyme deficiency has a much less-severe course with clinical features resembling those of the juvenile-onset NCL patients. Clinically, these variant INCL patients have a course that is often quite distinct from the typical, classic rapidly degenerating infantile form. Yet they have PPT1 deficiency and granular osmiophilic deposits on pathology. There is no clear *CLN1* genotype that predicts severity of phenotype.

Late infantile-type neuronal ceroid lipofuscinose (LINCL, Jansky-Bielschowsky) generally presents with myoclonic seizures beginning between 2 and 4 yr of age in a previously normal child. Dementia and ataxia are combined with a progressive loss of visual acuity and microcephaly. Examination of the retina shows marked attenuation of vessels, peripheral black bone spicule pigmentary abnormalities, optic atrophy, and a subtle brown pigment in the macular region. The electroretinogram and VEP are abnormal early in the course of disease. The autofluorescent material is deposited in neurons, fibroblasts, and secretory cells. Electron microscopic examination of the storage material in skin or conjunctival biopsy material typically shows curvilinear profiles. LINCL can be caused by autosomal recessive mutations of several different genes: *CLN2* gene, which codes for a tripeptidyl peptidase-1 (TPP1) that is essential for the degradation of cholecystokinin-8, as well as the *CLN5, CLN6,* and *CLN8* genes that code for membrane proteins that have not been completely characterized. *CLN8* is also known as the locus of Northern epilepsy syndrome, which is often called progressive epilepsy with mental retardation.

Juvenile type neuronal ceroid lipofuscinose (JNCL, Spielmeyer-Vogt or Batten disease) is the most common form of NCL disease and is generally caused by autosomal-recessive mutations in *CLN3*. (Patients who present clinically with JNCL but have PPT1 or TPP1 deficiency are said to have variant INCL or LINCL, respectively.) Children affected with JNCL tend to develop normally for the 1st 5 yr of life. Their initial symptom is usually progressive visual loss and their retinal pigmentary changes often results in an initial diagnosis of retinitis pigmentosa. The funduscopic changes are similar to those for the late infantile type. After disease onset, there may be rapid decline with changes in cognition and personality, motor incoordination, and seizures. Myoclonic seizures are not as prominent as in LINCL, but parkinsonism can develop and impair ambulation. Patients die in their late twenties to early thirties. In JNCL caused by *CLN3*, the electron microscopy of tissues show deposits called fingerprint profiles, and routine light microscopy of a peripheral blood smear may show lymphocyte vacuoles.

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599.3 Adrenoleukodystrophy

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See Chapter 86.2.

599.4 Sialidosis

Jennifer M. Kwon

Sialidosis is the result of lysosomal sialidase deficiency, secondary to autosomal recessive mutations in the sialidase (α-neuraminidase, *NEU1*) gene on chromosome 6p21.3. The accumulation of sialic acid–oligosaccharides with markedly increased urinary excretion of sialic acid–containing oligosaccharides is associated with clinical presentations that range from the milder sialidosis type I to the more severe sialidosis type II associated with both neurologic and somatic features.

Sialidosis type I, the **cherry-red spot myoclonus syndrome**, usually presents in the 2nd decade of life, when a patient complains of visual deterioration. Inspection of the retina shows a cherry-red spot, but, unlike patients with TSD, visual acuity declines slowly in individuals with cherry-red spot myoclonus syndrome. Myoclonus of the extremities is gradually progressive and often debilitating and eventually renders patients nonambulatory. The myoclonus is triggered by voluntary movement, touch, and sound and is not controlled with anticonvulsants. Generalized convulsions responsive to antiepileptic drugs occur in most patients.

Sialidosis type II patients present at a younger age and have cherry-red spots and myoclonus, as well as somatic involvement, including coarse facial features, corneal clouding (rarely), and dysostosis multiplex, producing anterior beaking of the lumbar vertebrae. Type II patients may be further subclassified into congenital and infantile (childhood) forms, depending on the age at presentation. Examination of lymphocytes shows vacuoles in the cytoplasm, biopsy of the liver demonstrates cytoplasmic vacuoles in Kupffer cells, and membrane-bound vacuoles are found in Schwann cell cytoplasm, all attesting to the multiorgan nature of sialidosis type II. No distinctive neuroimaging findings or abnormalities in electrophysiologic studies are noted in this group of disorders. Patients with sialidosis have been reported to live beyond the 5th decade.

Some cases of what appears to be sialidosis type II are the result of combined deficiencies of β-galactosidase and α-neuraminidase resulting from deficiency of protective protein/cathepsin A that prevents premature intracellular degradation of these 2 enzymes. These patients have galactosialidosis and they are clinically indistinguishable from those with sialidosis type II. Consequently, patients who have features of sialidosis type II with marked urinary excretion of oligosaccharides should be tested for protective protein/cathepsin A deficiency as well as sialidase deficiency.

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599.5 Miscellaneous Disorders

Jennifer M. Kwon

PELIZAEUS-MERZBACHER DISEASE

Pelizaeus-Merzbacher disease (PMD) is an X-linked recessive disorder characterized by nystagmus and abnormalities of myelin. PMD is caused by mutations in the proteolipid protein *(PLP1)* gene, on chromosome Xq22, which is essential for CNS myelin formation and oligodendrocyte differentiation. Mutations in the same gene can cause familial spastic paraparesis (progressive spastic paraparesis type 2, SPG2). *PLP1* mutations causing disease include point mutations, deletions, gene duplications, and other gene dosage changes.

Clinically, classic PMD is recognized by nystagmus and roving eye movements with head nodding during infancy. Developmental milestones are delayed; ataxia, choreoathetosis, and spasticity ultimately develop. Optic atrophy and dysarthria are associated findings, and death occurs in the 2nd or 3rd decade. The major pathologic finding is a loss of myelin with intact axons, suggesting a defect in the function of oligodendroglia. An MRI scan shows a symmetric pattern of delayed myelination. Multimodal-evoked potential studies demonstrate early in the course a pattern consisting of loss of waves III-V on the auditory brainstem response. This finding is useful in the investigation of nystagmus in infant boys. VEPs show prolonged latencies, and somatosensory evoked potentials show absent cortical responses or delayed latencies. It is now recognized that a broad spectrum of phenotypes, including SPG2 and peripheral nerve abnormalities, can also result from mutations in the *PLP1* gene.

There is a PMD-like syndrome caused by autosomal recessive mutations in the gap junction protein alpha 12 (*GJA12*, or connexin 47). Individuals with *GJA12* mutations have a clinical and radiologic phenotype like PMD including hypomyelinating leukodystrophy.

ALEXANDER DISEASE

This is a rare disorder that causes progressive macrocephaly and leukodystrophy. Alexander disease is caused by dominant mutations in the glial fibrillary acidic protein *(GFAP)* gene, on chromosome 17q21

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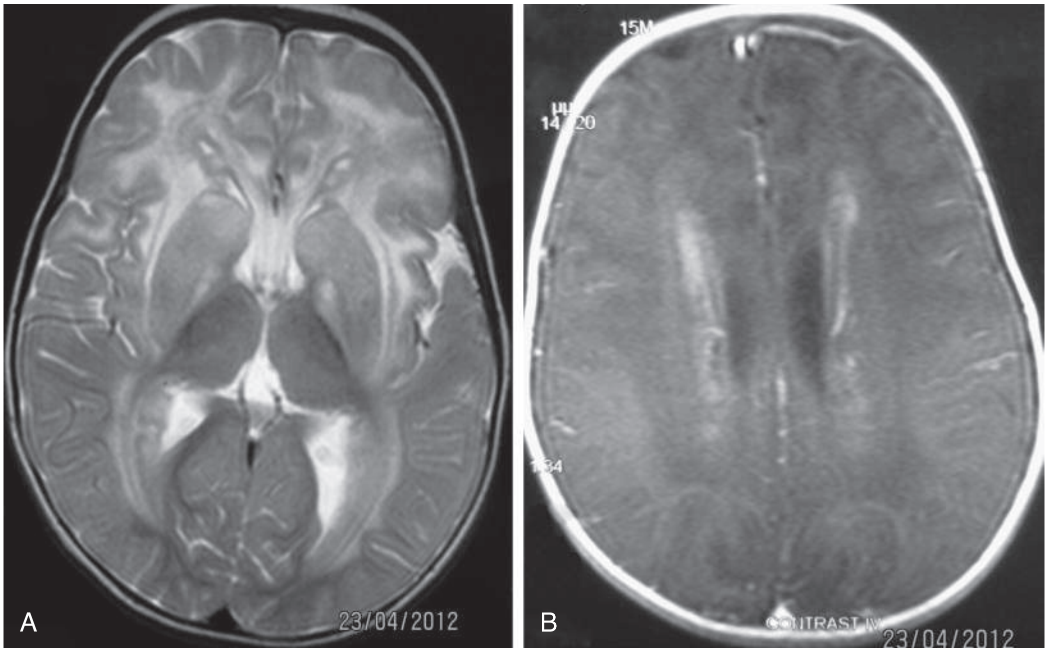

Figure 599-3 Alexander disease. MRI of the index patient at the age of 15 mo. **A,** Axial T2-weighted sequences (TR/TE: 4000/99) at the basal ganglia and thalamus level demonstrating diffuse bilateral, symmetric increased signal predominantly of the frontal periventricular, but also of the subcortical white matter and of the basal ganglia. **B,** Significant periventricular rim after intravenous gadolinium infusion (T1-weighted sequences; TR/TE: 400/88). *(From Zafeiriou DI, Dragoumi P, Vargiami E: Alexander disease.* J Pediatr *162:648, 2013.)*

and cases are usually sporadic in their families. Pathologic examination of the brain discloses deposition of eosinophilic hyaline bodies called Rosenthal fibers in astrocyte processes. These accumulate in a perivascular distribution throughout the brain. In the classic infantile form of Alexander disease, degeneration of white matter is most prominent frontally. Diagnosis may be suggested by MRI (Fig. 599-3) and MR spectroscopy demonstrating abnormal metabolic substrates. Affected children develop progressive loss of intellect, spasticity, and unresponsive seizures causing death by 5 yr of age. However, there are milder forms that present later in life and that may not have the characteristic frontal predominance or megalencephaly.

CANAVAN SPONGY DEGENERATION

See Chapter 85.15.

OTHER LEUKODYSTROPHIES

Metabolic and degenerative disorders can present with significant cerebral white matter changes, such as some mitochondrial disorders (see Chapters 86.1 and 598.2) and glutaric aciduria type 1 (see Chapter 85.14). In addition, the broader use of MRI has brought to light new leukodystrophies. One example is vanishing white matter disease or childhood ataxia with CNS hypomyelination characterized by ataxia and spasticity. Some patients also have optic atrophy, seizures, and cognitive deterioration. The age of presentation and the rapidity of decline can be quite variable. In the early-onset forms, decline is usually rapid and followed quickly by death; in the later-onset forms, mental decline is usually slower and milder. Interestingly, acute demyelination in these disorders can be triggered by fever or fright. The diagnosis of vanishing white matter disease or childhood ataxia with CNS hypomyelination is based on clinical findings, characteristic abnormalities on cranial MRI, and autosomal recessive mutations in 1 of 5 causative genes (*EIF2B1, EIF2B2, EIF2B3, EIF2B4,* and *EIF2B5*) encoding the 5 subunits of the eucaryotic translation initiation factor, eIF2B.

MENKES DISEASE

Menkes disease (kinky hair disease) is a progressive neurodegenerative condition inherited as a X-linked recessive trait. The Menkes gene codes for a copper-transporting, P-type adenosine triphosphatase, and mutations in the protein are associated with low serum copper and ceruloplasmin levels, as well as a defect in intestinal copper absorption and transport. Symptoms begin in the 1st few mo of life and include hypothermia, hypotonia, and generalized myoclonic seizures. The facies are distinctive, with chubby, rosy cheeks and kinky, colorless, friable hair. Microscopic examination of the hair shows several abnormalities, including trichorrhexis nodosa (fractures along the hair shaft) and pili torti (twisted hair). Feeding difficulties are prominent and lead to failure to thrive. Severe mental retardation and optic atrophy are constant features of the disease. Neuropathologic changes include tortuous degeneration of the gray matter and marked changes in the cerebellum with loss of the internal granule cell layer and necrosis of the Purkinje cells. Death occurs by 3 yr of age in untreated patients.

Copper-histidine therapy may be effective in preventing neurologic deterioration in some patients with Menkes disease, particularly when treatment is begun in the neonatal period or, preferably, with the fetus. These presymptomatic children are currently identified because of a family history of an affected brother. Copper is essential in the early stages of CNS development, and its absence probably accounts for the neuropathologic changes. Infants diagnosed presymptomatically in the 1st 10 days of life can be started on an experimental protocol of daily copper-histidine subcutaneous injections (as of 2015, only available at NIH under a program supervised by Dr. Stephen Kaler). Optimal response to copper-histidine injection treatment appears to occur only in patients who are identified in the newborn period and whose mutations permit residual copper-transport activity.

The **occipital horn syndrome,** a skeletal dysplasia caused by different mutations in the same gene as that involved in Menkes disease, is a relatively mild disease. The 2 diseases are often confused, because the biochemical abnormalities are identical. Resolution of the uncertainty about treatment of patients with Menkes disease will require careful genotype-phenotype correlation, along with further clinical trials of copper therapy.

RETT SYNDROME

This syndrome is not strictly speaking a degenerative disease, but a disorder of early brain development marked by a period of developmental regression and deceleration of brain growth after a relatively

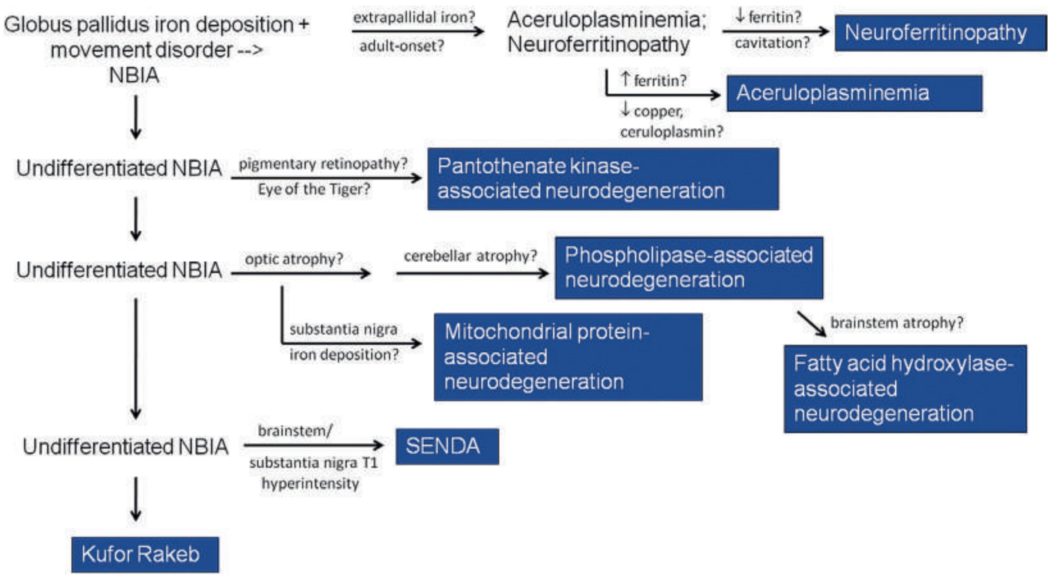

Figure 599-4 **Clinical and radiographic approach to neurodegeneration with brain iron accumulation.** NBIA, neurodegeneration with brain iron accumulation; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood. *(From Kruer MC, Boddaert N: Neurodegeneration with brain iron accumulation: a diagnostic algorithm.* Semin Pediatr Neurol *19:67–74, 2012, Fig. 1.)*

normal neonatal course. It occurs predominantly in girls. The frequency is approximately 1 in 15,000-22,000 children. Rett syndrome is caused by mutations in *MeCP2,* a transcription factor that binds to methylated CpG islands and silences transcription. Development may proceed normally until 1 yr of age, when regression of language and motor milestones and acquired microcephaly become apparent. An ataxic gait or fine tremor of hand movements is an early neurologic finding. Most children develop peculiar sighing respirations with intermittent periods of apnea that may be associated with cyanosis. The hallmark of Rett syndrome is repetitive hand-wringing movements and a loss of purposeful and spontaneous use of the hands; these features may not appear until 2-3 yr of age. Autistic behavior is a typical finding in all patients. Generalized tonic-clonic convulsions occur in the majority and are usually well controlled by anticonvulsants. Feeding disorders and poor weight gain are common. After the initial period of neurologic regression, the disease process appears to plateau, with persistence of the autistic behavior. Cardiac arrhythmias may result in sudden, unexpected death at a rate that is higher than the general population. Generally girls survive into adulthood.

Postmortem studies show significantly reduced brain weight (60-80% of normal) with a decrease in the number of synapses, associated with a decrease in dendritic length and branching. The phenotype may be related to failure to suppress expression of genes that are normally silent in the early phases of postnatal development. Although very few males survive with the classic Rett syndrome phenotype, genotyping of boys without the classic Rett syndrome phenotype but with intellectual disability and other atypical neurologic features has detected a significant number with mutations in *MeCP2*. Mutations in *MeCP2* have been demonstrated in normal female carriers, females with Angelman syndrome, and in males with fatal encephalopathy, Klinefelter (47 XXY) syndrome, and familial X-linked mental retardation.

Some girls have an atypical Rett phenotype associated with severe myoclonic seizures in infancy, slowing of head growth, and developmental arrest and have mutations in another X-linked gene encoding for cyclin-dependent kinase–like 5 (CDKL5), which may interact with MeCP2 and other proteins regulating gene expression.

SUBACUTE SCLEROSING PANENCEPHALITIS

This is a rare, progressive neurologic disorder caused by persistent measles virus infection of the CNS (see Chapter 246). The number of reported cases has decreased dramatically to 0.06 cases/million population, paralleling the decline in reported measles cases. The initial clinical manifestations include personality changes, aggressive behavior, and impaired cognitive function in individuals who have been exposed to natural measles virus in early childhood. Myoclonic seizures soon dominate the clinical picture. Later, generalized tonic–clonic convulsions, hypertonia, and choreoathetosis become evident, followed by progressive bulbar palsy, hyperthermia, and decerebrate postures. Funduscopic examination early in the course of the disease reveals papilledema in approximately 20% of the cases. Optic atrophy, chorioretinitis, and macular pigmentation are observed in most patients. The diagnosis is established by the typical clinical course and 1 of the following: (1) measles antibody detected in the cerebrospinal fluid, (2) a characteristic electroencephalogram consisting of bursts of high-voltage slow waves interspersed with a normal background that occur with a constant periodicity in the early stages of the disease, and (3) typical histologic findings in the brain biopsy or postmortem specimen. Treatment with a series of antiviral agents has been attempted without success. Death occurs usually within 1-2 yr from the onset of symptoms.

NEURODEGENERATION WITH BRAIN IRON ACCUMULATION

Neurodegeneration with brain iron accumulation represents multiple, age-of-onset-dependent disorders characterized by extrapyramidal symptoms, intellectual deterioration and regression, with iron deposition in the basal ganglia. There is significant phenotype variability of these disorders; however, a characteristic finding on MRI demonstrates symmetric T2 signal homogeneous *hypointensity*. Common neurodegeneration with brain iron accumulation disorders are distinguished in Table 599-3 and an approach to their diagnosis is noted in Figure 599-4. Clinical features, which are highly variable, may include dystonia, parkinsonism, ataxia, spasticity, psychiatric symptoms, and intellectual impairment. Treatment should focus on the specific disorder and is usually symptomatic relief rather than curative. Iron chelation has been attempted without major long-term benefit.

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Table 599-3 Overview of Neurodegeneration with Brain Iron Accumulation Conditions and Genes (if Known)

					CHILDHOOD-ONSET VARIANT		LATE-ONSET VARIANT	
CONDITION (ACRONYM)	**SYNONYM**	**GENE**	**CHROMOSOMAL POSITION**	**LB PATHOLOGY**	**AGE OF ONSET**	**CLINICAL PRESENTATION**	**AGE OF ONSET**	**CLINICAL PRESENTATION**
PKAN	NBIA1	PANK2	20p13	No	Early childhood, around age 3	Typical PKAN	Teens or early adulthood	Atypical PKAN
PLAN	NBIA2, PARK14	PLA2G6	22q12	√	Infancy	Infantile neuroaxonal dystrophy	Teens or early adulthood	Dystonia parkinsonism
FAHN	SPG35	FA2H	16q23	Not known	Childhood	Leukodystrophy, hereditary spastic paraplegia	Adulthood (age range up to 30 yr)	May resemble idiopathic PD
MPAN	—	C19orf12	19q12	√	—	Pyramidal extrapyramidal syndrome		
Kufor-Rakeb disease	PARK9	ATP13A2	1p36	√	Childhood-teens	Parkinsonism, pyramidal tract signs, eye movement disorder		
BPAN	SENDA syndrome	WDR45	Xp11.23	Not known	Childhood	Encephalopathy with psychomotor regression, then static	Then: 20s to 30s	Sudden onset progressive dystonia parkinsonism
Aceruloplasminemia	—	CP	3q23	No	—	—	50s (range: 16-70)	Extrapyramidal, diabetes, dementia
Neuroferritinopathy	—	FTL	19q13	No	—	—	40s	Chorea, dystonia, dementia
Idiopathic late-onset cases	—	Probably heterogeneous	Probably heterogeneous	Heterogeneous	—	—	Heterogeneous	Parkinsonism, in may resemble idiopathic PD

√, Present; BPAN, beta-propeller associated neurodegeneration; CP, ceruloplasmin; FA2H, fatty acid 2-hydroxylase; FAHN, fatty acid 2-hydroxylase-associated neurodegeneration; FTL, ferritin light chain; MPAN, mitochondrial membrane-associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; PANK2, pantothenate kinase 2; PD, Parkinson disease; PKAN, pantothenate kinase-associated neurodegeneration; PLA2G6, phospholipase A2; PLAN, PLA2G6-associated neurodegeneration; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood; SPG, spastic paraplegia.

From Schneider SA, Zorzi G, Nardocci N: Pathophysiology and treatment of neurodegeneration with brain iron accumulation in the pediatric population, Curr Treat Option Neurol *15:652-667, 2013, Table 1.*

Chapter 600

Demyelinating Disorders of the Central Nervous System

Jayne M. Ness

Acquired demyelinating disorders of the central nervous system (CNS) result in neurologic dysfunction caused by immune-mediated attacks on white matter insulating the brain, optic nerves and spinal cord. The white matter insulation is formed by myelin contained within oligodendrocytes wrapping around nerve axons. In contrast to genetically determined leukodystrophies (sometimes called dysmyelinating disorders) that produce disrupted white matter, acquired demyelinating disorders generally target normally formed white matter. Pediatric demyelinating syndromes are characterized clinically by (1) localization of neurologic deficits (i.e., single site, such as spinal cord [transverse myelitis], optic nerves [optic neuritis] or brainstem, vs polyregional demyelination); (2) the presence vs absence of encephalopathy; and (3) disease course (i.e., monophasic vs repeated attacks involving either the same or new CNS regions). Major demyelinating disorders in childhood include acute disseminated encephalomyelitis (ADEM), typically a self-limited disorder, and relapsing–remitting multiple sclerosis (MS). MRI of brain and spine is useful to initially characterize symptomatic and clinically silent demyelinating lesions, but serial MRI is often required to distinguish self-limited vs chronic demyelinating syndromes, especially in the younger child. Additional studies, such as cerebrospinal fluid (CSF) analysis, autoimmune and genetic testing, and sometimes even brain biopsy, may be required to evaluate for mimickers of demyelination, such as neoplasm, infection, systemic rheumatologic disorders, isolated CNS angiitis, mitochondrial disease, and leukodystrophies (Tables 600-1 and 600-2).

Table 600-1	Differential Diagnosis of Demyelinating Disorders
Acute disseminated encephalomyelitis (ADEM)	
Multiple sclerosis (including tumefactive MS)	
Acute hemorrhagic leukoencephalopathy	
Clinically isolated syndrome (CIS)	
Neuromyelitis optica spectrum disorder	
N-methyl-D-aspartate receptor (NMDAR) antibody and other autoimmune encephalitis	
Vasculitis/angiopathies	
Hashimoto encephalitis (anti–thyroid peroxidase [TPO] antibody)	
Familial hemophagocytic lymphohistiocytosis	
Langerhans cell histiocytosis	
Lymphoma	
Gliomatosis cerebri	
Glioma	
Sarcoidosis	
Mitochondrial disorders (Leigh syndrome)	
Vitamin E deficiency	
Vitamin B_{12} deficiency	
Celiac disease	
Herpes simplex virus (HSV), enterovirus, arbovirus, Powassan and other viral encephalitides	
Rabies	
Subacute sclerosing pan-encephalitis (SSPE) (chronic measles)	
Charcot-Marie-Tooth syndrome	
Leukoencephalopathies (Aicardi-Goutières syndrome)	
Vanishing white matter disease	
Schilder disease (possibly an adrenoleukodystrophy)	
X-linked adrenoleukodystrophy	
Griscelli syndrome type 2	

600.1 Multiple Sclerosis

Jayne M. Ness

Pediatric MS is a chronic demyelinating disorder of the brain, spinal cord, and optic nerves characterized by a relapsing–remitting course of neurologic events without encephalopathy separated in time and space.

EPIDEMIOLOGY

Pediatric MS is rare, with an estimated 2-5% of MS patients experiencing their first symptoms before age 18 yr. Pediatric MS has a slight male predominance when disease onset is before age 6 yr, but by age 12 yr, females outnumber males 2 : 1.

PATHOGENESIS

A complex interplay of environmental, infectious, and genetic factors influence MS susceptibility. Immune system dysregulation involving T and B lymphocytes triggers inflammation, axonal demyelination, axonal loss, and regeneration within both white and gray matter. Inflammatory infiltrates within actively demyelinating lesions of relapsing-remitting MS are targets for disease modifying agents (DMAs). Neurodegenerative changes predominate in progressive forms of MS.

CLINICAL MANIFESTATIONS

Presenting symptoms in pediatric MS include hemiparesis or paraparesis; unilateral or, less often, bilateral optic neuritis; focal sensory loss; ataxia; diplopia; dysarthria; or bowel/bladder dysfunction (Table 600-3). Polyregional symptoms are reported in 30% of patients. Encephalopathy is less common and suggests consideration of ADEM or possibly neuromyelitis optica (NMO).

LABORATORY FINDINGS

Cranial MRI exhibits discrete T2 lesions in cerebral white matter, particularly periventricular regions as well as brainstem, cerebellum, and juxtacortical and deep gray matter. Alternatively, large tumefactive T2 lesions may be seen. Spine MRI typically shows partial-width cord lesions restricted to 1-2 spine segments. CSF may be normal or exhibit mild pleocytosis, particularly in younger children. Abnormal MS profiles (increased immunoglobulin [Ig] G index, and/or CSF oligoclonal bands) increase likelihood of MS but may be negative in 10-60% of pediatric MS patients, particularly prepubertal children; they also may be occasionally positive in ADEM or autoimmune encephalitis (Fig. 600-1). Abnormal evoked potential studies can localize disruptions in visual, auditory, or somatosensory pathways.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Pediatric MS can usually be diagnosed following 2 demyelinating episodes without encephalopathy localizing to distinct CNS regions, lasting longer than 24 hr and separated by more than 30 days, provided no other plausible explanation exists. Current MS diagnostic criteria use MRI to serve as a surrogate for recurrent demyelination, enabling MS diagnosis after the first event. For adults and children >12 yr, the initial MRI may be sufficient to diagnose MS if it demonstrates dissemination in space (≥2 T2 lesions involving juxtacortical, periventricular, infratentorial, or spine regions) and time (presence of asymptomatic gadolinium-enhancing lesion and nonenhancing T2 lesion in same scan). Alternatively, MS can be diagnosed with a follow-up MRI at any time interval exhibiting accumulation of T2 or gadolinium-enhancing lesions in the brain or spine. Challenges arise in distinguishing pediatric MS from other acquired demyelinating

Table 600-2 IPMSSG 2012 Definitions for Pediatric Acute Demyelinating Disorders of the Central Nervous System

DISORDER	IPMSSG 2012
CIS	• A first monofocal or multifocal CNS demyelinating event; encephalopathy is absent, **unless caused by fever**
Monophasic ADEM	• A first polyfocal clinical CNS event with presumed inflammatory cause • Encephalopathy that **cannot be explained by fever** is present MRI typically shows **diffuse, poorly demarcated, large, >1-2 cm lesions** involving predominantly the cerebral white matter; **T1 hypointense white matter lesions are rare**; deep gray-matter lesions (e.g., thalamus or basal ganglia) can be present • No new symptoms, signs or MRI findings after 3 mo of the incident ADEM
Recurrent ADEM	• **See multiphasic ADEM**
Multiphasic ADEM	• New event of ADEM 3 mo or more after the initial event that can be associated with **new or reemergence of prior clinical and MRI findings. Timing in relation to steroids is no longer pertinent**
MS	Any of the following: • Two or more nonencephalopathic CNS clinical events separated by more than 30 days, involving more than 1 area of the CNS • Single clinical event and MRI features rely on 2010 Revised McDonald criteria for DIS and DIT (but criteria relative for DIT for a single attack and single MRI only apply to children ages 2-12 yr and only apply to cases without an ADEM onset)
NMO	All are required: • Optic neuritis • Acute myelitis At least 2 of 3 supportive criteria • Contiguous spinal cord MRI lesion S3 vertebral segments • **Brain MRI not meeting diagnostic criteria for MS** • Anti–aquaporin-4 immunoglobulin G–seropositive status • ADEM followed 3 mo later by a nonencephalopathic clinical event with new lesions on brain MRI consistent with MS

The 2001 McDonald MRI criteria for DIS require 3 of the following 4 MRI features: 29 T2 lesions or 1 gadolinium-enhancing lesion; 23 periventricular lesions; 21 infratentorial lesion(s); 21 juxtacortical lesion(s). The DIT criteria require subsequent white-matter lesions whose timing depends on the temporal relation of the initial MRI with the onset of the clinical symptoms.

The 2010 Revised McDonald MRI criteria for DIS require the presence of at least 2 of the following 4 criteria: 21 lesions in each of the 4 locations; periventricular, juxtacortical, infratentorial, and spinal cord. The 2010 Revised McDonald MRI criteria for DIT can be satisfied either by the emergence of newT2 lesions (with or without enhancement) on serial scan(s) or can be met on a single baseline scan if there exists simultaneous presence of a clinically silent gadolinium-enhancing lesion and a nonenhancing lesion.

ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; CNS, central nervous system; DIS, dissemination in space; DIT, dissemination in time; IPMSSG, International Pediatric Multiple Sclerosis Study Group; MS, multiple sclerosis; NMO, neuromyelitis optica.

Modified from Krupp LB, Tardieu M, Amato MP, et al: International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revision to the 2007 definitions. Mult Scler 19(10):1261–1267, 2013, Appendix 1, p. 1266.

Table 600-3 Symptoms and Signs of Multiple Sclerosis by Site

	SYMPTOMS	SIGNS
Cerebrum	Cognitive impairment Hemisensory and motor Affective (mainly depression) Epilepsy (rare) Focal cortical deficits (rare)	Deficits in attention, reasoning, and executive function (early); dementia (late) Upper motor neuron signs
Optic nerve	Unilateral painful loss of vision	Scotoma, reduced visual acuity, color vision, and relative afferent papillary defect
Cerebellum and cerebellar pathways	Tremor Clumsiness and poor balance	Postural and action tremor, dysarthria Limb incoordination and gait ataxia
Brainstem	Diplopia, oscillopsia Vertigo Impaired swallowing Impaired speech and emotional lability Paroxysmal symptoms	Nystagmus, internuclear and other complex ophthalmoplegias Dysarthria Pseudobulbar palsy
Spinal cord	Weakness Stiffness and painful spasms Bladder dysfunction Erectile impotence Constipation	Upper motor neuron signs Spasticity
Other	Pain Fatigue Temperature sensitivity and exercise intolerance	

Modified from Compston A, Coles A: Multiple sclerosis, Lancet *372:1502–1517, 2008, p. 1503.*

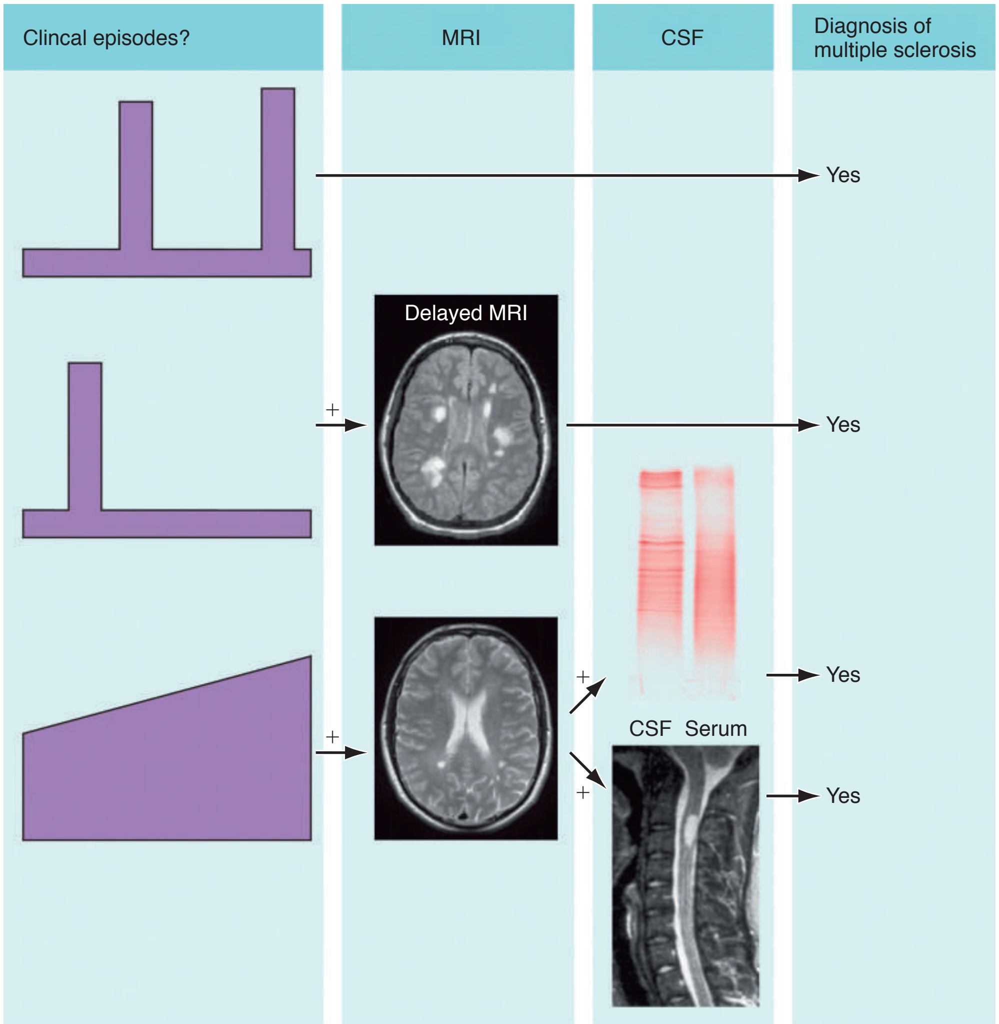

Figure 600-1 **Criteria for the diagnosis of multiple sclerosis.** The principle is to establish dissemination in time and place of lesions, meaning that episodes affecting separate sites within the central nervous system have occurred at least 30 days apart. MRI can substitute for 1 of these clinical episodes. Dissemination in time of magnetic resonance lesions requires simultaneous presence of asymptomatic gadolinium-enhancing and asymptomatic lesions or followup MRI showing accumulation of a new gadolinium-enhancing lesion or T2 lesion. Criteria for MRI definition of dissemination in space require 2 or more lesions in periventricular, juxtacortical, or infratentorial regions or spine. Primary progressive MS is very rare in childhood but can be diagnosed after 1 yr of a progressive deficit and 2 of the following: (1) a positive brain MRI; (2) a positive spinal cord MRI; and (3) positive oligoclonal bands. Patients having an appropriate clinical presentation but who do not meet all of the diagnostic criteria can be classified as having possible MS. CSF, cerebrospinal fluid. *(From Compston A, Coles A: Multiple sclerosis,* Lancet *372:1502–1517, 2008, Fig. 1.)*

syndromes such as ADEM or NMO, especially in the prepubertal child. ADEM is a self-limited syndrome characterized by encephalopathy, polyregional neurologic deficits, and diffuse multifocal MRI T2 abnormalities followed by subsequent clinical improvement and resolution of MRI T2 lesions (see Tables 600-1, 600-2, 600-4, and 600-5). However, a subset of pediatric MS patients (10-25%) presents with an ADEM phenotype and then experiences multiple relapses with accumulation of MRI T2 lesions. NMO, traditionally thought of as a combined myelitis and optic neuritis with normal brain MRI, now has a broader phenotype with the identification of the NMO antibody against the CNS water channel aquaporin-4 and MRI lesions in the brain. The NMO spectrum includes isolated bilateral optic neuritis or longitudinally extensive transverse myelitis even in the presence of brain MRI abnormalities or encephalopathy.

COMPLICATIONS

Similar to adults with MS, pediatric MS patients can acquire fixed neurologic deficits affecting vision and other cranial nerves, motor and sensory function, balance, and bowel/bladder function. Cognitive impairment can impede academic achievement.

TREATMENT

Relapses causing functional disability may be treated with methylprednisolone, 20-30 mg/kg/day (max: 1,000 mg/day) for 3-5 days, with or without prednisone taper. DMAs reduce relapse frequency and T2 lesion load, mainly by targeting the inflammatory response that predominates during the relapsing-remitting phase of MS (Table 600-6). There are 4 injectable DMAs, 3 oral DMAs, and 2 infused DMAs approved by the FDA for adult MS, but to date, none of these agents has a pediatric MS indication. Injectable agents, first approved in the mid-1990s (interferon-beta1α SC or IM or interferon-beta1β SC; glatiramer acetate SC) have some side effects such as flu-like side effects and risk of transaminase elevation with interferon-beta or requirement for daily injections with glatiramer acetate but otherwise have an excellent safety record so are still recommended as first-line therapy in pediatric MS. Three oral DMAs (fingolimod, teriflunomide, dimethyl fumarate) have been FDA-approved since 2010, but despite ease of oral administration, enthusiasm is tempered by reports of severe side effects or even death from reactivation of latent viruses (fingolimod, dimethyl fumarate) and potential of severe birth defects (teriflunomide). Intravenous DMAs (natalizumab, mitoxantrone) are second-line agents

used only after failure of first-line injectable or oral agents. Natalizumab therapy is associated with the risk of developing progressive multifocal encephalopathy (CNS infection with human polyomavirus JC). Mitoxantrone has a lifetime dose limit because of cardiotoxicity and is associated with subsequent development of acute myelogenous lymphoma in 2 of 802 MS patients (0.25%).

PROGNOSIS

Retrospective studies of patients diagnosed with MS prior to widespread dimethyltryptamine use suggest slower disease progression in pediatric MS patients compared to adults. Despite a longer time to irreversible disability (20-30 yr), pediatric MS patients acquire irreversible disability at a younger age than adults.

Bibliography is available at Expert Consult.

Table 600-4 Clinical Features That May Distinguish ADEM from First Attack of MS

	ADEM	MS
Age	<10 yr	>10 yr
Stupor/coma	+	–
Encephalopathy	+	–
Fever/vomiting	+	–
Family history	No	20%
Sensory complaints	+	+
Optic neuritis	Bilateral	Unilateral
Manifestations	Polysymptomatic	Monosymptomatic
CSF	Pleocytosis (lymphocytosis)	Oligoclonal bands
Response to steroids	+	+
Follow-up	No new lesions	New lesions

Some features that may help distinguish an initial acute episode of demyelination from a first attack of MS in children. Final diagnosis of MS is based on follow-up evaluation and possibly MRI.

+, More likely to be present; –, less likely to be present; ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; MS, multiple sclerosis.

600.2 Neuromyelitis Optica

Jayne M. Ness

NMO (Devic disease) is a demyelinating disorder characterized by monophasic or polyphasic episodes of optic neuritis and/or transverse myelitis. It was once thought that NMO was a variant of MS; but identification of the NMO antibody against the aquaporin-4 water channel has broadened the spectrum of NMO to include brainstem syndromes and recurrent forms of optic neuritis and transverse myelitis (see Table 600-2). **NMO spectrum disorder** frequently involves symptomatic or silent MRI lesions demonstrating demyelination of the cerebral cortex and other regions of the brain.

EPIDEMIOLOGY

NMO has an age of onset of 31.2 ± 11 yr. In 1 study, in monophasic patients, the range of age of onset was 1-54 yr; in polyphasic patients, the range was 6-72 yr. NMO is more common in females than in males; 65% of monophasic and 80-85% of polyphasic NMO patients are female. It is also more common in Asians than in blacks or whites and appears to have a higher mortality rate in individuals of African descent than in others.

PATHOGENESIS

NMO is associated with IgG antibodies against the aquaporin-4 water channel, which is most abundant on astrocyte foot processes within periventricular regions, brainstem, optic nerves, and spinal cord. Antibody binding to aquaporin-4 activates the classical complement pathway with C5b-C9 components leading to leukocytes attraction and degranulation, causing astrocyte death. Chemokines from dying astrocytes and activated leukocytes attract macrophages, leading to death of oligodendrocytes and neurons with subsequent necrosis or even cavitation in affected tissues. Although most cases of NMO are idiopathic and only occasional familial cases have been reported, there have been reports of postinfectious NMO. HIV, syphilis, chlamydia, varicella, cytomegalovirus, and Epstein-Barr virus are associated with subsequent development of NMO. Aquaporin-4 antibody–positive NMO may follow or occur simultaneously with *N*-methyl-D-aspartate receptor antibody autoimmune encephalitis.

CLINICAL MANIFESTATIONS

NMO presents with optic neuritis or transverse myelitis or brainstem symptoms such as intractable vomiting or hiccups, diplopia, facial

Table 600-5 MRI Characteristics for Dissemination in Space That Increase the Likelihood of a Pediatric Multiple Sclerosis Diagnosis

BARKHOF*	MIKAELOFF (KIDMUS)†	CALLEN (MS VS ADEM)‡	CALLEN (DIAGNOSTIC MS)§	VERHEY (DIFFERENTIAL)‖	POLMAN (2010 REVISED MCDONALD CRITERIA)¶
3 of 4: ≥9 T2 lesions or 1 gadolinium enhancing ≥3 Periventricular ≥1 Infratentorial ≥1 Juxtacortical	1 of 2: Lesions perpendicular to long axis of the corpus callosum Sole presence of well-defined lesions	2 of 3: Absence of a diffuse bilateral lesion pattern Presence of black holes ≥2 Periventricular lesions	2 of 3: ≥5 Lesions on T2-weighted images 2 Periventricular lesions ≥1 Brainstem lesions	2 of 2: ≥1 Periventricular lesions ≥1 Hypointense lesions on T1 images	2 of 4: ≥1 Periventricular ≥1 Juxtacortical ≥1 Infratentorial ≥1 Spinal cord

*Barkhof F, Filippi M, Miller DH, et al: Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 120:2059–2069, 1997.

†Mikaeloff Y, Adamsbaum C, Husson HM, et al: MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood. Brain 127:1942–1947, 2004.

‡Callen DJ, Shroff MM, Branson HM, et al: Role of MRI in the differentiation of ADEM from MS in children. *Neurology* 72:968–973, 2009.

§Callen DJ, Shroff MM, Branson HM, et al: MRI in the diagnosis of pediatric multiple sclerosis. *Neurology* 72:961–967, 2009.

‖Verhay LH, Branson HM, Shroff MM, et al: MRI parameters for prediction of multiple sclerosis diagnosis in children with acute CNS demyelination: a prospective national cohort study. *Lancet Neurol* 10:1065–1073, 2011.

¶Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 69:292–302, 2011.

ADEM, acute disseminated encephalomyelitis; MS, multiple sclerosis.

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Table 600-6 Overview of Available and Emerging Therapies in Pediatric Multiple Sclerosis

MEDICATION	MEDICATION CLASS	MECHANISM IN MS	SIDE EFFECTS	STUDIES DESCRIBING DRUG EFFICACY IN PEDIATRIC MS
FIRST-LINE THERAPIES				
Interferon-α or β	Immunomodulator	Modulates T cells and cytokine production	Flu-like symptoms; transaminitis; leukopenia; tissue necrosis at injection site (rare)	Retrospective Prospective multicenter
Glatiramer acetate*	Immunomodulator	Modulates T cells and reduces antigen presentation	Flushing, lipodystrophy at injection sites	Prospective single center Prospective multicenter
SECOND-LINE THERAPIES				
Natalizumab*	Monoclonal antibody	Targets α_4-integrin; prevents T-cell migration into CNS and other tissues	Overall PML rate ~1 in 500 patients, but lower in subgroups; immune reconstitution syndrome after discontinuation; melanoma; infusion reaction; transaminitis (rare)	Retrospective Prospective multicenter
Cyclophosphamide	Chemotherapeutic	DNA alkylation; effects include cytotoxic immune cell depletion	Hemorrhagic cystitis; bladder cancer; late-onset malignancy; infection; infertility	Retrospective multicenter
Mitoxantrone*	Chemotherapeutic	Disrupts DNA synthesis; effects include cytotoxic immune cell depletion	Significant long-term safety risks, including cardiotoxicity (1 in 200 patients) and secondary leukemia (1 in 125 patients); opportunistic infections	Retrospective single center
Daclizumab	Monoclonal antibody	Targets/inactivates interleukin-2 receptor; inhibits activated T cells	Glucose intolerance; pulmonary edema; infusion reaction; gastrointestinal upset; skin reactions	Retrospective multicenter
Rituximab	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	PML (rate undefined); infusion-related side effects	No efficacy assessments available in pediatric MS
Azathioprine	Chemotherapeutic	Disrupts purine metabolism; effects include cytotoxic immune cell depletion	Transaminitis; leukopenia; lymphoma	No efficacy assessments available in pediatric MS
Fingolimod*†	Immunomodulator	Sphingosine-1-phosphate agonist; causes T-cell sequestration in lymphoid compartments	Systemic viral infection; cardiac arrhythmia; macular edema; transaminitis	FDA approved for adult MS in September 2010; no reports of use in pediatric MS to date
Teriflunomide*†	Immunomodulator	Impairs immune cell proliferation via pyrimidine synthesis inhibition	Infections; headaches; diarrhea; transaminitis; alopecia; teratogenicity	FDA approved for adult MS in September 2012; no reports of use in pediatric MS to date
EMERGING THERAPIES				
Vitamin D†	Vitamin/hormone	Modulates immune cell expression	Hypercalcemia and kidney stones at a serum 25(OH) vitamin D level >100 ng/mL	Prospective trials in pediatric and adult MS are currently underway
Ocrelizumab	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	Headache; infusion-related side effects; theoretical risk of PML (undefined)	Recently completed phase III trial in adult MS; no use in pediatric MS to date
Dimethyl fumarate†	Immunomodulator	Neuroprotectant; antioxidant	Flushing reaction; gastrointestinal upset; headache	FDA approved for adult MS in March 2013; no use in pediatric MS to date
Alemtuzumab	Monoclonal antibody	Anti-CD52 antibody target; depletes mature T cells	Opportunistic infection, autoimmune thyroiditis (20-30% risk), immune thrombocytopenia (1%)	Recently completed phase III trial in adult MS; no use in pediatric MS to date
Laquinimod†	Immunomodulator	Modulates T cell and cytokine production	Transaminitis	Recently completed phase III trial in adult MS; no use in pediatric MS to date

*FDA approved for the treatment of adult MS.
†Orally administered therapy.
CNS, central nervous system; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy.

weakness or numbness or dysphagia. Optic neuritis or transverse myelitis may occur simultaneously or may be separated in time by weeks or even years. Some present with an encephalopathy mimicking ADEM. Others exhibit endocrinopathies such as the syndrome of inappropriate antidiuretic hormone secretion, diabetes insipidus, or disrupted puberty. The symptoms and signs of transverse myelitis depend on the spinal level and completeness of the inflammatory changes. NMO differs from MS in that recovery of visual and spinal cord function is generally not as complete after each episode; optic neuritis is more frequently bilateral in NMO than in MS.

LABORATORY FINDINGS

CSF in patients with NMO often has 50 or more white blood cells per microliter. Unlike MS, it is devoid of oligoclonal bands. Serum positivity for anti–aquaporin-4 antibodies (so-called NMO antibodies) has a sensitivity of 73% and a specificity of 91% for NMO. Neuroimaging studies should include the entire spine, optic nerves as well as the cortex that may reveal lesions in the brainstem or thalami or hazy ill-defined lesions in the hemispheres in contrast to the discrete, well-defined oval lesions in the periventricular white matter seen in MS.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical diagnosis of NMO currently requires optic neuritis and transverse myelitis plus at least 2 of 3 supporting criteria: (1) brain MRI not diagnostic of MS, (2) seropositivity for anti–aquaporin-4 antibody, or (3) spine MRI with longitudinally extensive transverse myelitis involving at least 3 spinal segments (see Table 600-2). NMO spectrum disorder may be diagnosed in relapsing forms of transverse myelitis or optic neuritis with aquaporin-4 seropositivity. The differential diagnosis includes MS; ADEM (see Chapter 600.3); rheumatologic etiologies producing transverse myelitis, and/or optic neuritis, including systemic lupus erythematosus, Behçet disease, and neurosarcoidosis (usually accompanied by other nonneurologic manifestations); idiopathic transverse myelitis, tropical spastic paraparesis, and viral encephalomyelitis (none of which have NMO antibodies in the serum or CSF); and metabolic and idiopathic causes of isolated optic neuritis or other acute monocular or binocular visual loss (see Chapter 631). Additional considerations depending on the location of the lesions include lymphoma, Langerhans cell histiocytosis, tuberculosis, and vitamin B_{12} or E deficiencies.

COMPLICATIONS

Similar to adults with NMO, pediatric NMO patients often are left with fixed neurologic deficits affecting visual acuity, visual fields, color vision, motor and sensory function, balance, and bowel/bladder function.

TREATMENT

Initial episodes and relapses may be treated acutely with methylprednisolone, 20-30 mg/kg/day (max: 1,000 mg/day) for 3-5 days, followed by a slow prednisone taper. Rituximab is effective in preventing relapses of NMO and NMO spectrum disorder. Preliminary evidence suggests that eculizumab also reduced recurrences and may improve disability in patients with severe NMO spectrum disorder.

PROGNOSIS

The prognosis is generally poor for patients with NMO. In 1 study, approximately 20% remained functionally blind (i.e., 20/200 vision or worse) in at least 1 eye and 31% had permanent monoplegia or paraplegia. Five-year survival of the patients with paraplegia is approximately 90%.

Bibliography is available at Expert Consult.

600.3 Acute Disseminated Encephalomyelitis

Jayne M. Ness

ADEM is an initial inflammatory, demyelinating event with multifocal neurologic deficits, typically accompanied by encephalopathy (see Table 600-2).

EPIDEMIOLOGY

ADEM can occur at any age but most series report a mean age between 5 and 8 yr with a slight male predominance. Reported incidence ranges from 0.07-0.4 per 100,000 per year in the pediatric population.

PATHOGENESIS

Molecular mimicry induced by infectious exposure or vaccine may trigger production of CNS autoantigens. Many patients experience a transient febrile illness in the month prior to ADEM onset. Preceding infections associated with ADEM include influenza, Epstein-Barr virus, cytomegalovirus, varicella, enterovirus, measles, mumps, rubella, herpes simplex, and *Mycoplasma pneumoniae.* Postvaccination ADEM has been reported following immunizations for rabies, smallpox, measles, mumps, rubella, Japanese encephalitis B, pertussis, diphtheria-polio-tetanus, and influenza.

CLINICAL MANIFESTATIONS

Initial symptoms of ADEM may include lethargy, fever, headache, vomiting, meningeal signs, and seizures, including status epilepticus. **Encephalopathy** is a hallmark of ADEM, ranging from ongoing confusion to persistent irritability to coma. Focal neurologic deficits can be difficult to ascertain in the obtunded or very young child but common neurologic signs in ADEM include visual loss, cranial neuropathies, ataxia, motor and sensory deficits, plus bladder/bowel dysfunction with concurrent spinal cord demyelination.

NEUROIMAGING

Head CT may be normal or show hypodense regions. Cranial MRI, the imaging study of choice, typically exhibits large, multifocal and sometimes confluent or large edematous mass-like tumefactive T2 lesions with variable enhancement within white and often gray matter of the cerebral hemispheres, cerebellum, and brainstem (Fig. 600-2). Deep gray-matter structures (thalami, basal ganglia) are often involved, although this may not be specific to ADEM. Spinal cord may have abnormal T2 signal or enhancement, with or without clinical signs of myelitis. MRI lesions of ADEM typically appear to be of similar age but their evolution may lag behind the clinical presentation. Serial MRI imaging 3-12 mo following ADEM shows improvement and often complete resolution of T2 abnormalities, although residual gliosis may remain.

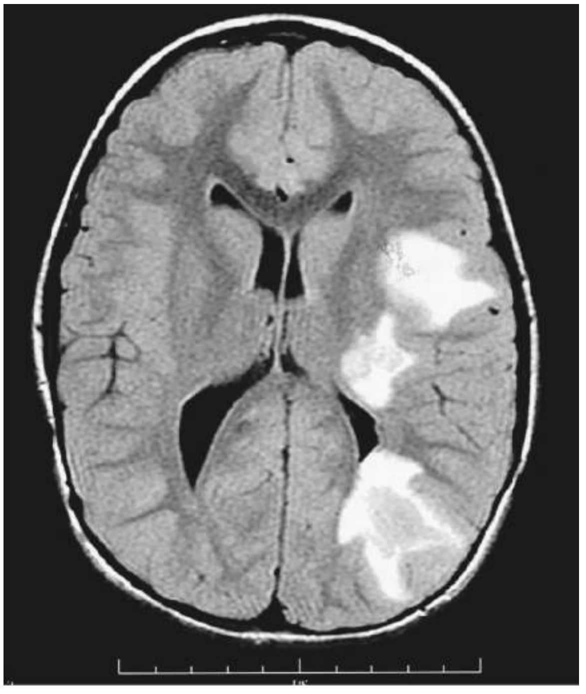

Figure 600-2 Axial T2-weighted fluid-attenuated inversion recovery MRI of the brain in a child with acute disseminated encephalomyelitis. High signal (white) lesions in the T2-weighted image reflect areas of demyelination and edema in deep subcortical and periventricular white matter as well as the basal ganglia and thalamus on the left side.

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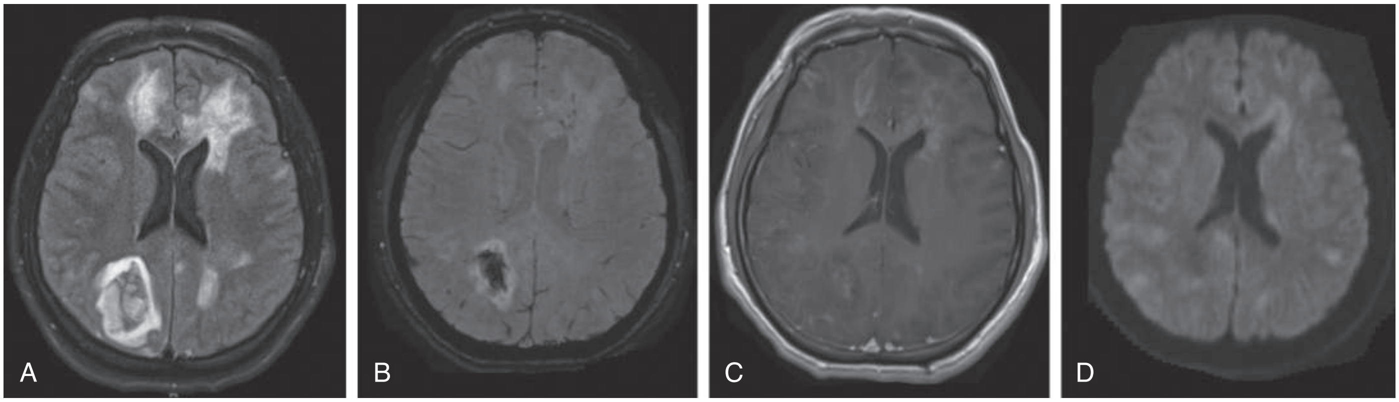

Figure 600-3 **MRI findings in acute disseminated encephalomyelitis.** Multiple scattered T2 hyperintensities are appreciated on fluid-attenuated inversion recovery images **(A)** with evidence of hemorrhage on susceptibility-weighted images **(B),** contrast enhancement on T1 postgadolinium images **(C),** and without diffusion restriction on diffusion-weighted imaging **(D).** *(From Virmani T, Agarwal A, Klawiter EC: Clinical reasoning: a young adult presents with focal weakness and hemorrhagic brain lesions.* Neurology *76:e105–e109, 2011, Fig. 2.)*

Severe involvement may progress to an **acute hemorrhagic leukoencephalopathy (Hurst disease)** with large lesions, edema, mass affect, and a polymorphonucleated cell pleocytosis (in contrast to lymphocytic pleocytosis in the CSF noted in typical ADEM) (Fig. 600-3).

LABORATORY FINDINGS

There is no biologic marker for ADEM and laboratory findings can vary widely. CSF studies often exhibit pleocytosis with lymphocytic or monocytic predominance. CSF protein can be elevated, especially on repeat studies. Up to 10% of patients with ADEM have oligoclonal bands in the CSF and/or elevated CSF immune globulin production. Patients with ADEM may occasionally demonstrate antibodies against myelin oligodendrocyte glycoprotein, or anti–*N*-methyl-D-aspartate receptor antibodies. Electroencephalograms often show generalized slowing, consistent with encephalopathy, although polyregional demyelination of ADEM can also cause focal slowing or epileptiform discharges.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for ADEM is broad but can be narrowed by careful history, appropriate laboratory evaluations, and MRI (see Table 600-1). Empirical antibiotic and antiviral treatment should be considered while infectious evaluations are pending. Follow-up MRI examinations 3-12 mo after ADEM should show improvement; new or enlarging T2 lesions should prompt reevaluation for other etiologies such as MS, leukodystrophies, tumor, vasculitis, or mitochondrial, metabolic, or rheumatologic disorders (see Table 600-1 and Table 600-5).

TREATMENT

Although there are no randomized controlled trials to compare acute treatments for ADEM or other demyelinating disorders of childhood, high-dose intravenous steroids are commonly employed (typically methylprednisolone 20-30 mg/kg per day for 5 days with a maximum dose of 1,000 mg per day). An oral prednisone taper over 1 mo may prevent relapse. Other treatment options include intravenous immune globulin (usually 2 g/kg administered over 2-5 days) or plasmapheresis (typically 5-7 exchanges administered every other day). In severe cases of suspected ADEM, rituximab or cyclophosphamide have been used. There is no consensus about timing of these treatments for ADEM.

PROGNOSIS

Many children experience full recovery after ADEM but some are left with residual motor and/or cognitive deficits. ADEM is usually a monophasic illness but demyelinating symptoms can fluctuate for several months. Repeated bouts of demyelination more than 3 mo after ADEM later raise the question of MS vs repeated ADEM.

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Chapter 601
Pediatric Stroke
Adam Kirton and Gabrielle A. deVeber

Stroke is an important cause of acquired brain injury in newborns and children. The ischemic varieties of arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) are more common than brain malignancy (incidence approximately 5 in 100,000 children per year). Perinatal stroke is even more common and is the leading cause of hemiparetic cerebral palsy. A similar number of children suffer from hemorrhagic stroke (HS) and other forms of cerebrovascular disease. Acute stroke is a neurologic emergency; however, delays in recognition are common and delayed treatment worsens outcomes. In contrast to stroke in adults, there are a diverse group of disorders producing stroke in neonates and children.

601.1 Arterial Ischemic Stroke
Adam Kirton and Gabrielle A. deVeber

Arterial blood reaches the brain via the anterior (internal carotid) and posterior (vertebrobasilar) circulations, converging at the circle of Willis. Strokes most often involve the middle cerebral artery territory but can occur in any cerebral artery of any size. AIS is the focal brain infarction that results from occlusion of these arteries and is a leading cause of acquired brain injury in children with the perinatal period carrying the highest risk.

The diagnosis of stroke in children is frequently delayed. This is a consequence of subtle and nonspecific clinical presentations, poor awareness by primary care pediatric physicians, a complicated differential diagnosis (see Chapter 601.4), and a high frequency (>50%) of negative initial CT scan. **The acute onset of a focal neurologic deficit in a child is stroke until proven otherwise.** The most common focal presentation is hemiparesis, but acute visual, speech, sensory, or balance deficits also occur. Children with these presentations require urgent neuroimaging and consultation with a child neurologist, as emergency interventions may be indicated. AIS is a clinical and radiographic diagnosis. Although CT imaging can demonstrate mature AIS and exclude hemorrhage, MRI is required to identify early and small infarcts. **Diffusion-weighted MRI** demonstrates AIS within minutes of onset and up to 7 days postonset; MR angiography can confirm vascular occlusion and suggest possible arteriopathy (Fig. 601-1). Diffusion-weighted MRI can also demonstrate wallerian degeneration

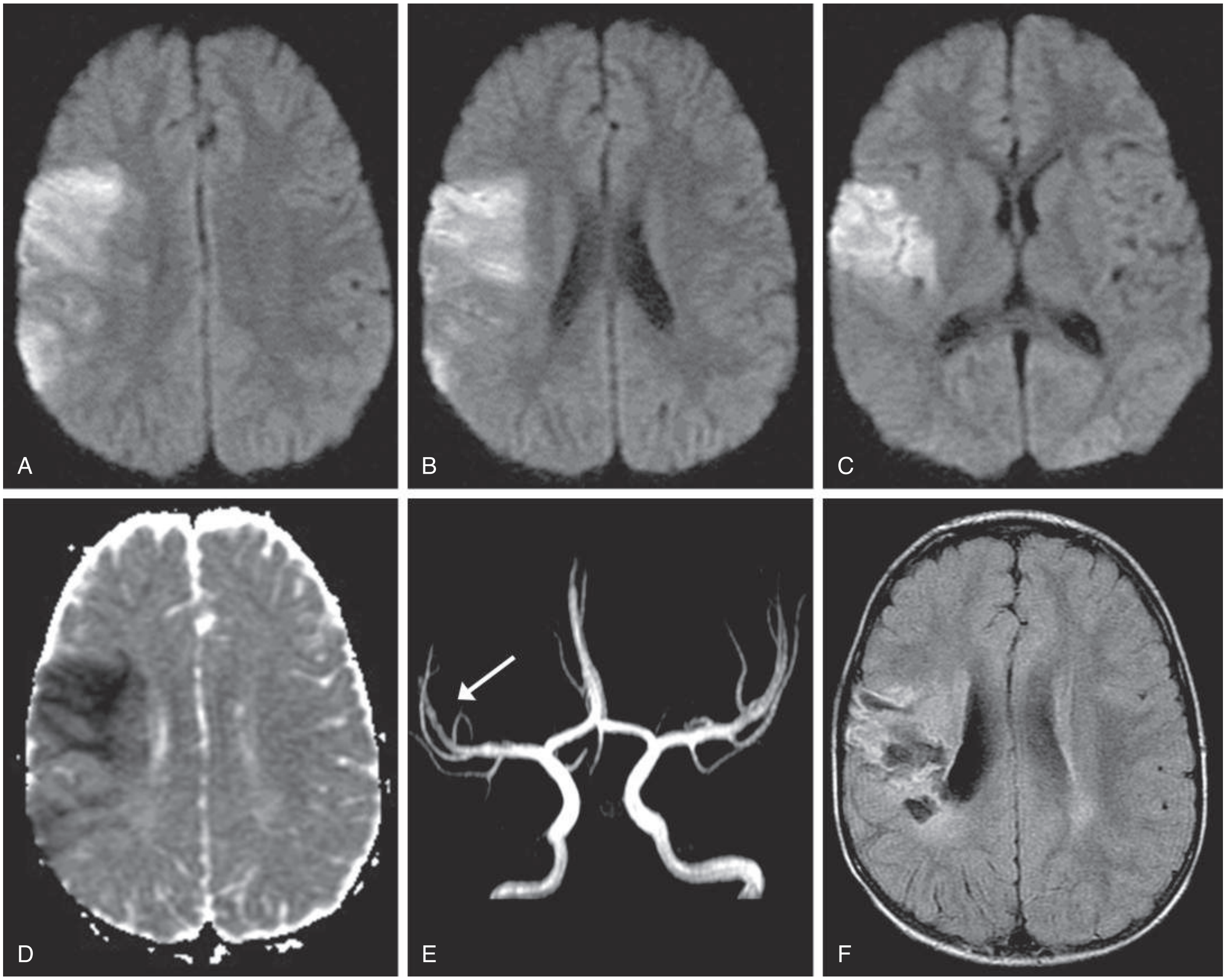

Figure 601-1 Arterial ischemic stroke. A healthy 3 yr old boy had sudden onset of left-sided weakness. Examination also demonstrated left-sided hemisensory loss and neglect. **A** to **C,** Diffusion-weighted MRI shows focal increased signal in the right temporal–parietal region in the territory of the middle cerebral artery (MCA). **D,** Apparent diffusion coefficient map confirms restricted diffusion consistent with infarction (ischemic stroke). **E,** MR angiogram shows decreased flow in the corresponding branch of the MCA. **F,** Follow-up MRI at 3 mo shows atrophy and gliosis in the same region.

in the descending corticospinal tract, which correlates with chronic hemiparesis.

Many possible risk factors for AIS are recognized (Table 601-1), although the specific pathophysiologic mechanisms are often poorly understood. Three main categories of etiology should be considered: **arteriopathy, cardiac,** and **hematologic;** full investigation, however, often reveals multiple risk factors per individual.

Arteriopathy refers to disorders of the cerebral arteries and is a leading cause of childhood AIS, present in more than 50% of children. A common syndrome affecting healthy school-age children features unilateral irregular stenosis of the proximal middle cerebral artery and neighboring arteries presenting with basal ganglia infarction. The description of this entity has been published under multiple names—**transient cerebral arteriopathy**, postvaricella angiopathy, nonprogressive childhood primary angiitis of the central nervous system, and focal cerebral arteriopathy—reflecting uncertainty regarding the pathogenesis.

This entity may represent focal inflammation or intracranial dissection or early moyamoya disease, although it is nearly always self-limited. Diffuse, bilateral, progressive **vasculitis** is rare and can represent progressive childhood primary angiitis of the central nervous system or be associated with systemic vasculitides (Table 601-2). Cranial infections (e.g., bacterial meningitis) also produce arteritis and thrombophlebitis of surface vessels. A**rterial dissection** can be spontaneous or post-traumatic and can affect extra- or intracranial arteries. **Moyamoya syndrome** may be idiopathic or associated with other conditions (neurofibromatosis type 1, trisomy 21, Alagille syndrome, sickle cell anemia, chromosomal microdeletions/microduplications, postirradiation) and demonstrates progressive occlusion of the distal internal carotid arteries. Congenital malformations of the craniocervical arteries, including PHACES (posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities) syndrome, or fibromuscular dysplasia may predispose to AIS. Vasospasm as occurs in migraine, subarachnoid hemorrhage or reversible cerebral vasoconstriction syndrome (sometimes called Call-Fleming syndrome) can cause AIS.

Cardioembolic stroke makes up approximately 25% of childhood AIS with maximal embolic risk concurrent with catheterization, surgical repair, or ventricular assistive device use. AIS complicates approximately 0.5% of pediatric cardiac surgeries and reoperation increases the risk. Although **complex congenital heart diseases** are most frequently associated with AIS, acquired conditions, including arrhythmia, cardiomyopathy, and infective endocarditis, also should be considered. A patent foramen ovale provides the possibility of paradoxical venous thromboembolism but is not likely an independent risk factor. All children with suspected AIS require thorough cardiovascular examination, electrocardiogram, and echocardiogram.

Table 601-1 Risk Factors for Arterial Ischemic Stroke in Children

MAJOR CATEGORY	EXAMPLES
Arteriopathy	Transient cerebral arteriopathy (TCA) (synonyms: childhood primary angiitis of the central nervous system [cPACNS]; focal cerebral arteriopathy [FCA]) Postvaricella and other viruses angiopathy (PVA) Systemic/secondary vasculitis (e.g., Takayasu arteritis) Moyamoya disease/syndrome Arterial infection (e.g., bacterial meningitis, tuberculosis) Fibromuscular dysplasia Traumatic or spontaneous carotid or vertebral artery dissection Vasospasm (e.g., Call-Fleming syndrome) Migraine (migrainous infarction?) Congenital arterial hypoplasia (e.g., PHACES syndrome)
Cardiac	Complex congenital heart diseases (cyanotic ≫ acyanotic) Cardiac catheterization/procedure (e.g., balloon atrial septostomy) Ventricular assistive device use Cardiac surgery Arrhythmia Valvular heart disease Endocarditis Cardiomyopathy, severe ventricular dysfunction Intracardiac lesions (e.g., atrial myxoma) Septal defects (atrial septal defect, ventricular septal defect, patent foramen ovale [possible paradoxical emboli])
Hematologic	Sickle cell anemia Iron-deficiency anemia Inherited prothrombotic (e.g., factor V Leiden, prothrombin gene mutation 20210A) Acquired prothrombotic (e.g., protein C/S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies, oral contraceptives, pregnancy)

Other including metabolic/genetic etiologies	Acute systemic illness (e.g., dehydration, sepsis, diabetic ketoacidosis)
	Chronic systemic illness (e.g., systemic lupus erythematosus, leukemia)
	Illicit drugs and toxins (e.g., cocaine)
	Extracorporeal membrane oxygenation (ECMO)
	Hereditary dyslipoproteinemia
	  Familial hypoalphalipoproteinemia
	  Familial hypercholesterolemia
	  Type IV, type III hyperlipoproteinemia
	  Tangier disease
	  Progeria
	Fabry disease (α-galactosidase A deficiency)
	Subacute necrotizing encephalomyelopathy (Leigh disease)
	Sulfite oxidase deficiency
	11β-Ketoreductase deficiency
	17α-Hydroxylase deficiency
	Purine nucleoside phosphorylase deficiency
	Ornithine transcarbamylase deficiency
	Neurofibromatosis type 1
	HERNS
	Heritable disorders of connective tissue
	  Ehlers-Danlos syndrome (type IV)
	  Marfan syndrome
	  Pseudoxanthoma elasticum
	  Homocystinuria (cystathionine β-synthase deficiency, or 5,20-methylenetetrahydrofolate reductase)
	  Menkes syndrome
	Organic acidemias
	  Methylmalonic academia
	  Propionic academia
	  Isovaleric academia
	  Glutaric aciduria type II
	Mitochondrial encephalomyopathies
	  MELAS
	  MERRF
	  MERRF/MELAS overlap syndrome
	  Kearns-Sayre syndrome
	See also: stroke mimics (see Chapter 601.4)

HERNS, hereditary endotheliopathy with retinopathy, nephropathy, and stroke; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; PHACES, posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities.

Modified from Roach ES, Golomb MR, Adams R, et al: Management of stroke in infants and children. Stroke *39:2644–2691, 2008, Table 2, p. 6.*

Table 601-2	Classification of Cerebral Vasculitis
Infectious vasculitis	
Bacterial, fungal, parasitic	
Spirochetal (syphilis, Lyme disease, leptospirosis)	
Viral, rickettsial, mycobacterial, free-living amebae, cysticercosis, other helminths	
Necrotizing vasculitides	
Classic polyarteritis nodosa	
Wegener granulomatosis	
Allergic angiitis and granulomatosis (Churg-Strauss syndrome)	
Necrotizing systemic vasculitis overlap syndrome	
Lymphomatoid granulomatosis	
Vasculitis associated with collagen vascular disease	
Systemic lupus erythematosus	
Rheumatoid arthritis	
Scleroderma	
Sjögren syndrome	
Vasculitis associated with other systemic diseases	
Behçet disease	
Ulcerative colitis	
Sarcoidosis	
Relapsing polychondritis	
Kohlmeier-Degos disease	
Takayasu arteritis	
Hypersensitivity vasculitides	
Henoch-Schönlein purpura	
Drug-induced vasculitides	
Chemical vasculitides	
Essential mixed cryoglobulinemia	
Miscellaneous	
Vasculitis associated with neoplasia	
Vasculitis associated with radiation	
Cogan syndrome	
Dermatomyositis-polymyositis	
X-linked lymphoproliferative syndrome	
Kawasaki disease	

Primary central nervous system vasculitis

From Roach ES, Golomb MR, Adams R, et al: Management of stroke in infants and children, Stroke *39:2644–2691, 2008, Table 5, p. 8.*

Prothrombotic coagulation disorders and infection at index stroke increase stroke recurrence risk.

Hematologic disorders associated with AIS include **sickle cell anemia,** in which stroke risk is increased 400-fold, although effective screening (transcranial Doppler) and treatments (transfusions) have reduced the incidence. Iron-deficiency anemia also increases the risk and is easily treatable. Coagulation disorders are associated with childhood AIS. They include hereditary (e.g., factor V Leiden) and acquired (e.g., antiphospholipid antibodies, lipoprotein-a elevation) **prothrombotic states** and **prothrombotic medications,** including oral contraceptives and asparaginase chemotherapy. Additional AIS risk factors include migraine, acute childhood illnesses, chronic systemic illnesses, illicit drugs and toxins, and rare inborn errors of metabolism.

Treatment of childhood AIS is multifaceted and multiple consensus-based guidelines are available. Given the inadequate safety data, emergency thrombolysis is not recommended for children, but safety studies are underway. Early initiation of **antithrombotic strategies** is paramount to prevent early reinfarction. Depending on the suspected cause, this includes anticoagulation with heparins or antiplatelet strategies, usually aspirin. Hyperacute **neuroprotective strategies** are essential to initiate with suspected stroke as they prevent progressive ischemic brain injury. These include control of blood glucose, temperature and seizures and maintenance of cerebral perfusion pressure. Early malignant cerebral edema is life-threatening, more common in children and predictable, and emergency surgical decompression can be life-saving. Disease-specific treatments include transfusion therapy in sickle cell disease, immunosuppression in vasculitis, and revascularization surgery in moyamoya. Long-term treatment goals include **secondary stroke prevention**, including antiplatelet therapy in arteriopathy and anticoagulation in cardiogenic causes. Multimodal, family-centered **rehabilitation** programs are required for most survivors, targeting motor deficits, language and intellectual impairments, behavioral and social disabilities, and epilepsy. Long-term attention to arterial health lifestyle factors may also be important. Outcomes after childhood stroke include recurrent stroke ranging from 10-50% depending on cause and preventative treatment, death in 6-10%, neurologic deficits in 60-70%, and seizure disorders in up to 30%.

PERINATAL ARTERIAL ISCHEMIC STROKE

Perinatal stroke is very common, differs from childhood stroke, and has 2 distinct clinical presentations. Acute symptomatic neonatal AIS presents with focal seizures at 24-28 hr of life (Fig. 601-2). MRI diffusion

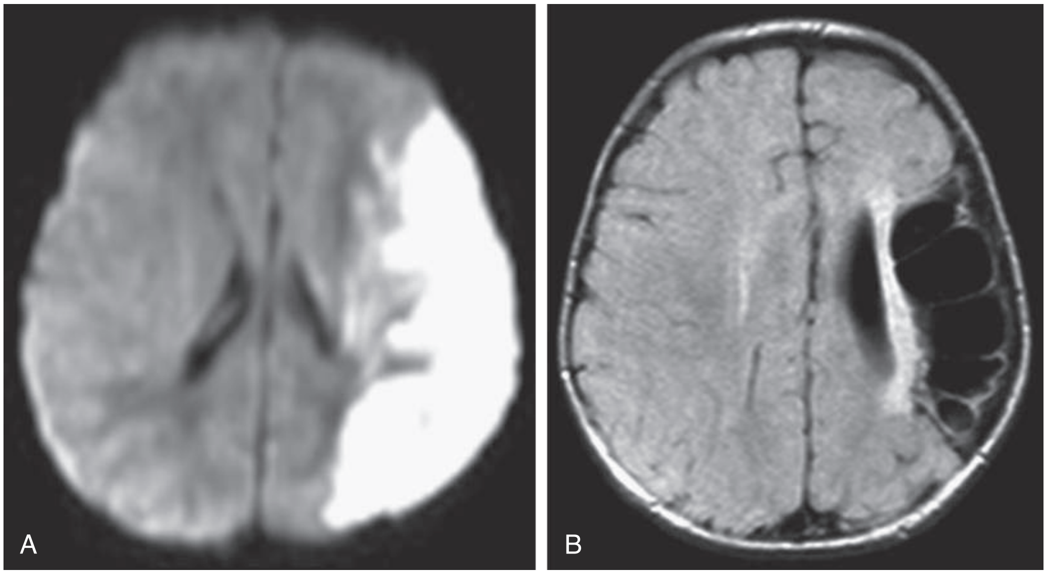

Figure 601-2 Perinatal arterial ischemic stroke. A term newborn developed focal right-sided seizures at 16 hr of life. **A,** Diffusion-weighted MRI on day 2 diagnoses neonatal arterial ischemic stroke by demonstrating restricted diffusion in the left middle cerebral artery territory. **B,** Repeat MRI at 12 mo shows cystic encephalomalacia and scarring in the same territory, a similar appearance to children diagnosed with presumed perinatal arterial ischemic stroke later in infancy.

abnormalities in an arterial territory confirm recent infarction. Alternatively, infants are asymptomatic at birth and present in later infancy with signs of early hand preference and congenital hemiparesis. Hand dominance within the 1st yr of life is abnormal and may be the result of perinatal stroke. Imaging reveals focal encephalomalacia in an arterial territory, typically large middle cerebral artery lesions.

In acute neonatal AIS, seizure control is important, but antithrombotic agents are rarely required (exception: cardiac embolism). Pathophysiology is complex and poorly understood. Most are idiopathic, although established causes include congenital heart disease, thrombotic placentopathy, and other prothrombotic disorders and meningitis. Many other maternal, prenatal, perinatal, obstetrical, and neonatal factors have been investigated with several strong associations found (e.g., infertility, primiparity, multiple gestation). Outcomes are poor, with most children having lifelong disability. Perinatal stroke accounts for most cases of hemiparetic cerebral palsy (congenital hemiplegia, see Chapter 598.1). Additional morbidity, seen in approximately 25%, includes disorders of language, learning, cognition, and behavior and longer-term epilepsy. Stroke recurrence rates for both the child and subsequent pregnancies are extremely low.

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601.2 Cerebral Sinovenous Thrombosis

Adam Kirton and Gabrielle A. deVeber

Cerebral venous drainage occurs via the cerebral sinovenous system. This includes superficial (cortical veins, superior sagittal sinus) and deep (internal cerebral veins, straight sinus) systems that converge at the torcula to exit via the paired transverse and sigmoid sinuses and jugular veins. In CSVT, thrombotic occlusion of these venous structures can create increased intracranial pressure, cerebral edema, and, in 50% of cases, venous infarction or hemorrhage (stroke). CSVT may be more common in children than in adults, and risk is greatest risk in the neonatal period.

Clinical presentations are typically gradual, variable, and nonspecific compared to AIS. Neonates often present with encephalopathy and seizures. Children may present with symptoms mimicking idiopathic intracranial hypertension, including progressive headache, papilledema, diplopia secondary to 6th nerve palsy, or with acute focal deficits. Seizures, lethargy, and confusion are common. Diagnosis requires a high clinical suspicion and purposeful imaging of the cerebral venous system. Nonenhanced CT is very insensitive for CSVT, and contrast **CT venography** or MR venography is necessary to demonstrate filling defects in the cerebral venous system (Fig. 601-3). MRI offers superior parenchymal imaging compared to CT.

Table 601-3 lists the risk factors for CSVT. **Prothrombotic states** associated with childhood CSVT include inherited (e.g., prothrombin gene 20210A mutation) and acquired (e.g., antiphospholipid antibodies) conditions, prothrombotic medications (asparaginase, oral contraceptives) and common childhood illnesses including otitis media, iron-deficiency anemia, and **dehydration. Systemic diseases** associated with increased CSVT risk include leukemia, inflammatory bowel disease, and nephrotic syndrome.

Head and neck disorders can directly involve cerebral veins and sinuses causing CSVT. Common **infections,** including meningitis, otitis media, and mastoiditis, can cause **septic thrombophlebitis** of venous channels. CSVT can complicate head **trauma** especially adjacent to skull fractures. Neurosurgical procedures in proximity to cerebral venous structures may lead to injury and CSVT. Finally, obstruction of the jugular veins and proximal stasis may result in CSVT. In neonates, the unfused status of cranial sutures enables mechanical distortion of underlying venous sinuses during delivery, or postnatally occipital bone compression of the posterior sagittal sinus during supine lying predisposing to CSVT.

Anticoagulation therapy plays an important role in childhood CSVT treatment. Substantial indirect evidence has led to consensus to recommend anticoagulation with unfractionated or low-molecular-weight heparins in most children. Hemorrhagic transformation of venous infarcts is not an absolute contraindication. Treatment is usually planned for 6 mo, although if reimaging at 3 mo confirms recanalization, treatment is usually discontinued. However anticoagulation of neonates is more controversial and guidelines differ. Evidence suggests that 30% of untreated neonates and children will extend their thrombosis in the 1st wk postdiagnosis and additional venous infarction can result. Therefore, if anticoagulation is withheld, early (e.g., 5-7

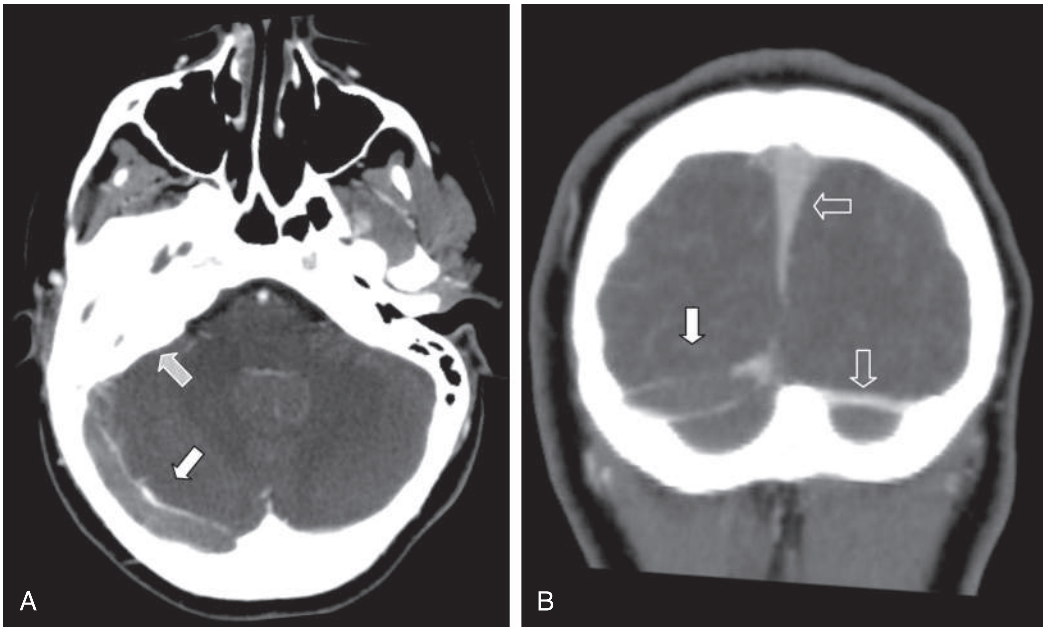

Figure 601-3 **Cerebral sinovenous thrombosis.** A 9 yr old girl presented with fever and progressive right-sided headache. She complained of double vision and had papilledema on examination. Axial **(A)** and coronal **(B)** CT venography demonstrates a large thrombus in the right transverse sinus that fails to opacify with contrast *(full arrows).* Note normal filling in superior sagittal and in smaller left transverse sinuses *(empty arrows, right)* and opacification of the mastoid air cells *(hatched arrow, left).* Cause was otitis media/mastoiditis with septic thrombophlebitis of transverse sinus.

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Table 601-3 Common Risk Factors for Cerebral Sinovenous Thrombosis in Children

MAJOR CATEGORIES	EXAMPLES
Blood coagulation	Prothrombotic conditions Factor V Leiden, prothrombin gene mutation 20210A, protein C deficiency, protein S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies), pregnancy/puerperium Dehydration (e.g., gastroenteritis, neonatal failure to thrive) Iron-deficiency anemia Drugs and toxins (e.g., L-asparaginase, oral contraceptives) Acute systemic illness (e.g., sepsis, disseminated intravascular coagulation) Chronic systemic illness (e.g., inflammatory bowel disease, systemic lupus erythematosus, leukemia) Nephrotic syndrome Inborn errors of metabolism (e.g., homocystinuria)
Blood vessel	Infection/thrombophlebitis Otitis media, mastoiditis, bacterial meningitis, sinusitis, dental abscess, pharyngitis Lemierre syndrome Sepsis Trauma: skull fractures, closed hear trauma Compression: birth, occipital bone compression in neonates in supine lying Iatrogenic: neurosurgery, jugular lines, extracorporeal membrane oxygenation Venous malformations (e.g., dural arteriovenous fistulas)

days) repeat venous imaging is paramount. Protocols supporting initial anticoagulation recommend shorter treatment durations (i.e., 6 wk to 3 mo) in neonates. Children with persistent risk factors may require prophylactic long-term anticoagulation. At initial diagnosis, supportive interventions include management of infection, detection and treatment of seizures, and neuroprotective measures (normothermia, normotension, normovolemia, normoglycemia). **Optic neuropathy** secondary to increased intracranial pressure is an important and easily missed complication of CSVT. Regular funduscopic examination by an ophthalmologist and measures to reduce intracranial pressure (e.g., acetazolamide, serial lumbar puncture) may be required to avoid visual loss. Most neurologic morbidity is suffered by those incurring venous infarction and children with bilateral venous infarction can be devastated. Consistent with other forms of childhood stroke, a comprehensive neurorehabilitation program is required.

Bibliography is available at Expert Consult.

601.3 Hemorrhagic Stroke

Adam Kirton and Gabrielle A. deVeber

HS includes nontraumatic intracranial hemorrhage and is classified by the intracranial compartment containing the hemorrhage. Intraparenchymal bleeds may occur in any location, whereas intraventricular hemorrhage may be isolated or an extension of intraparenchymal hemorrhage. Bleeding outside the brain may occur in the subarachnoid, subdural, or epidural spaces.

Clinical presentations vary according to location, cause, and rate of bleeding. Acute hemorrhages may feature instantaneous or **thunderclap headache,** loss of consciousness, and nuchal rigidity in addition to focal neurologic deficits and seizures. HS can be rapidly fatal. In bleeds associated with vascular malformations, pulsatile tinnitus, cranial bruit, macrocephaly, and high-output heart failure may be present. Diagnosis relies on imaging and CT is highly sensitive to acute HS. However, lumbar puncture may be required to exclude subarachnoid hemorrhage. MRI is highly sensitive to even small amounts of both acute and chronic hemorrhage and offers improved diagnostic accuracy (Fig. 601-4). Angiography by CT, MR, or conventional catheter means is often required to exclude underlying vascular abnormalities (e.g., vascular malformations, aneurysms).

Abusive head trauma with intracranial bleeding in children may present as primary subdural or parenchymal hemorrhage with no apparent history of trauma. Subtle scalp, suborbital, or ear bruising; retinal hemorrhages in multiple layers; and chronic failure to thrive should always be sought, and in infants with subdural bleeds, x-rays performed to rule out fractures. Epidural hematoma is nearly always caused by trauma, including middle meningeal artery injury typically associated with skull fracture. Subdural hematoma can occur spontaneously in children with brain atrophy because of stretching of bridging veins.

Causes of and risk factors for HS (Table 601-4) include vascular malformations and systemic disorders. **Arteriovenous malformations**

Table 601-4 Potential Risk Factors for Hemorrhagic Stroke in Children

MAJOR CATEGORIES	EXAMPLES
Vascular disorder	Arteriovenous malformations Cavernous malformations ("cavernomas") Venous angiomas and other venous anomalies Hereditary hemorrhagic telangiectasia Intracranial aneurysm Choroid plexus angiomas (pure intraventricular hemorrhage) Moyamoya disease/syndrome Inflammatory vasculitis (see Chapter 601.1) Neoplastic lesions with unstable vasculature Drugs/toxins (cocaine, amphetamine) Cerebral sinovenous thrombosis
Blood disorder	Idiopathic thrombocytopenic purpura Hemolytic uremic syndrome Hepatic disease/failure coagulopathy Vitamin K deficiency (hemorrhagic disease of the newborn) Disseminated intravascular coagulopathy
Trauma	Middle meningeal artery injury (epidural hematoma) Bridging vein injury (subdural hematoma) Subarachnoid hemorrhage Hemorrhagic contusions (coup and contrecoup) Nonaccidental trauma (subdural hematomas of different ages) Iatrogenic (neurosurgical procedures, angiography) Rupture of arachnoid cyst

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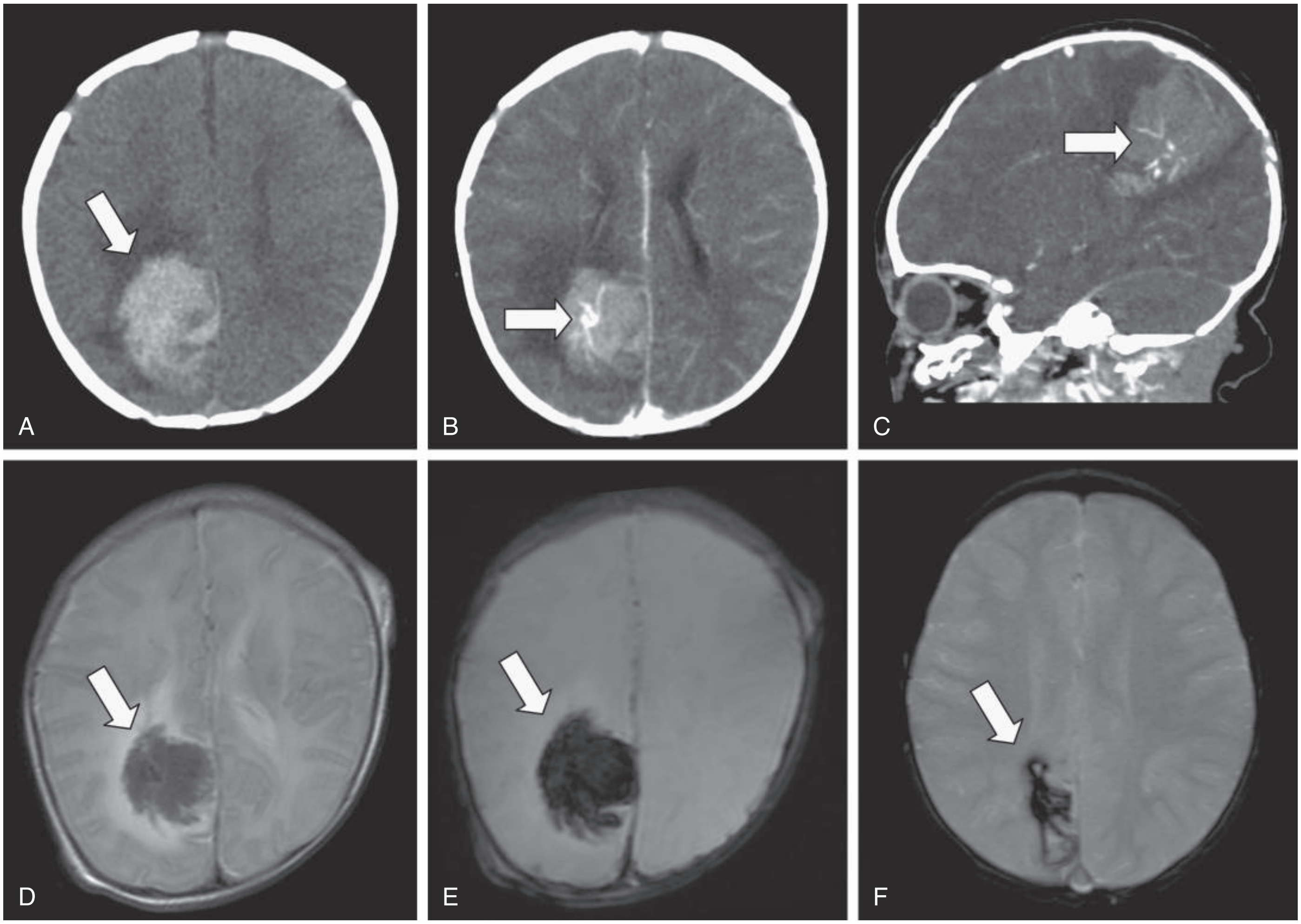

Figure 601-4 Hemorrhagic stroke. A healthy 1 mo old presented with sudden-onset irritability followed by focal left body seizures. Plain CT head demonstrates a large hyperdense lesion in the right parietal region with surrounding edema consistent with acute hemorrhage **(A).** Axial **(B)** and sagittal **(C)** contrast CT scans suggest an abnormal cluster of vessels in the center of the hemorrhage consistent with an AVM. T2-weighted MRI differentiates the acute hemorrhage from surrounding edema **(D).** Gradient echo MRI, both acutely **(E)** and at 3 mo **(F),** demonstrates the presence of blood product.

are the most common cause of childhood subarachnoid and intraparenchymal HS and may occur anywhere. Neonates with vein of Galen malformations may present with heart failure, progressive macrocephaly, or, rarely, hemorrhage. In older children with arteriovenous malformations, the risk of bleeding is approximately 2-4% per year throughout life. Other vascular malformations leading to HS include cavernous angiomas **("cavernomas"),** dural arteriovenous fistulas, and vein of Galen malformations. Cerebral aneurysms are an uncommon cause of subarachnoid hemorrhage in children and may suggest an underlying disorder (e.g., polycystic kidney disease, infective endocarditis). A common cause for HS is bleeding from a preexisting brain tumor. Arterial diseases that usually cause ischemic stroke, including fibromuscular dysplasia, vasculitis, and moyamoya, can also predispose to HS. Additional causes of parenchymal HS include hypertensive hemorrhage and hematologic disorders such as thrombocytopenic purpura, hemophilia, acquired coagulopathies (e.g., disseminated intravascular coagulopathy, liver failure), anticoagulant therapy (e.g., warfarin), or illicit drug use. Ischemic infarcts may undergo hemorrhagic transformation, particularly in CSVT, and may be difficult to differentiate from primary HS.

Management of acute childhood HS may require emergent neurosurgical intervention for large or rapidly expanding hemorrhage. The same principles of neuroprotection for vulnerable brain suggested in the ischemic stroke sections also apply to HS. Reversal of anticoagulant therapy (with, for example, vitamin K, fresh-frozen plasma) may be required, but the role of other medical interventions, such as factor VII, are unstudied in children. Recurrence risk for those with structural lesions is significant and serial imaging may be required. Definitive repair or removal of the vascular malformation may require a combined approach with interventional endovascular methods or neurosurgery. Outcomes from childhood HS are not well studied but likely depend on lesion size, location, and etiology. Compared with ischemic stroke, HS mortality is higher while long-term deficits are less common.

Neonatal HSs have unique features. Cranial ultrasound can detect many neonatal parenchymal bleeds, especially In the preterm infant where bleeds are located centrally within the cranium and include germinal matrix bleeding and intraventricular hemorrhage (see Chapter 99.3). Germinal matrix injury or bleeding may also occur in utero, resulting in periventricular venous infarction that becomes symptomatic in later infancy as congenital hemiparesis. Subarachnoid and subdural blood may be imaged in up to 25% of normal term newborns. Term HS is poorly studied and includes the etiologies listed above, although HS may be idiopathic in more than 50% of cases. Term intraventricular bleeding is often secondary to deep CSVT with specific management implications.

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601.4 Differential Diagnosis of Stroke-Like Events

Adam Kirton and Gabrielle A. deVeber

The diagnosis of stroke in childhood requires a high index of suspicion balanced with awareness of the differential diagnosis for stroke-like events (Table 601-5). Acute onset of a focal neurologic deficit should be considered stroke until proven otherwise and assessed with neuroimaging. However, pediatric stroke must be differentiated from other stroke-like disorders that may require their own urgent specific treatment.

MIGRAINE

Careful history and examination can often suggest migraine as the cause of acute focal deficits. Migraine auras should last between 5 and 60 min and resolve completely. Neurologic deficits associated with migraine typically evolve slowly compared with stroke, with sensory disturbance or weakness "marching" across body areas over minutes. Although evolution into a migrainous headache is expected, headache may also accompany acute infarction. Furthermore, a group of uncommon migraine subtypes can occur without headache and can more closely mimic stroke in children. These include familial hemiplegic migraine, basilar migraine, and migraine aura without headache. Migraine can also (rarely) cause a stroke, referred to as migrainous infarction.

SEIZURE

Prolonged focal seizure activity is frequently followed by a period of focal neurologic deficit ("Todd's paresis") which typically resolves within an hour. Very rarely, focal seizures can manifest with only "negative" symptoms producing acute onset, focal neurologic deficits. A history of clonic jerks or tonic posturing at onset, a known past history of seizures, and electroencephalogram findings may be helpful. Imaging is required in all new cases of seizure with persisting Todd's paresis because stroke in children is often associated with seizures at onset.

INFECTION

Life-threatening and treatable brain infections, including bacterial meningitis and herpes encephalitis, can be mistaken for stroke. However, symptom onset in primary central nervous system infection is typically more gradual and less focal with fever as a consistent feature. Children with bacterial meningitis are at risk for both venous and arterial stroke.

DEMYELINATION

Acute disseminated encephalomyelitis, clinically isolated syndrome, multiple sclerosis, and other demyelinating conditions can present

Table 601-5 Differential Diagnosis of Stroke-Like Episodes in Children

DISORDER	CLINICAL DISTINCTION FROM STROKE	IMAGING DISTINCTION FROM STROKE
Migraine	Evolving or "marching" symptoms, short duration, complete resolution, headache, personal or family history of migraine	Typically normal Migrainous infarction is rare
Seizure	Positive symptoms, Todd paralysis is postseizure and limited	Normal or may identify source of seizures (e.g., malformation, old injury, etc.)
Infection	Fever, encephalopathy, gradual onset, meningismus	Normal or signs of encephalitis/cerebritis, which are typically diffuse and bilateral. Arterial ischemic stroke and cerebral sinovenous thrombosis can occur in bacterial meningitis
Demyelination	Gradual onset, multifocal symptoms, encephalopathy Accompanying optic neuritis or transverse myelitis	Multifocal lesions, characteristic appearance (e.g., patchy in acute disseminated encephalomyelitis, ovoid in multiple sclerosis), typical locations (e.g., pericallosal in multiple sclerosis), less likely to show restricted diffusion
Hypoglycemia	Risk factor (e.g., insulin therapy), related to meals, additional systemic symptoms	Bilateral, symmetrical May see restricted diffusion Posterior dominant pattern
Watershed infarction caused by global hypoxic–ischemic encephalopathy	Risk factor (e.g., hypotension, sepsis, heart disease), bilateral deficits	Bilateral, symmetric restricted diffusion in border zones between major arteries (watershed zones)
Hypertensive encephalopathy (posterior reversible leukoencephalopathy)	Documented hypertension, bilateral visual symptoms, encephalopathy	Posterior dominant, bilateral, patchy lesions involving gray and white matter, usually no restricted diffusion
Inborn errors of metabolism	Preexisting delays/regression, multisystem disease, abnormal biochemical profiles	May have restricted diffusion lesions but bilateral, symmetrical, not within vascular territories. MR spectroscopy changes (e.g., high lactate in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes)
Vestibulopathy	Symptoms limited to vertigo, imbalance (i.e., no weakness). Gradual onset	Normal
Acute cerebellar ataxia	Sudden-onset bilaterally symmetric ataxia; postviral	Normal
Channelopathy	Syndromic cluster of symptoms not localizing to single lesion. Gradual onset, progressive evolution	Normal
Alternating hemiplegia	History contralateral events Choreoathetosis/dystonia	Normal

with acute focal neurologic deficits. Symptom onset and initial progression is more gradual (typically hours or days) compared with stroke onset (minutes). Multifocal deficits, or concurrent encephalopathy in the case of acute disseminated encephalomyelitis, would decrease the probability of stroke.

HYPOGLYCEMIA

Acute lowering of blood glucose levels can produce focal deficits mimicking stroke. New-onset hypoglycemia in otherwise healthy children is rare, but predisposing conditions include insulin-dependent diabetes, adrenal insufficiency, steroid withdrawal, and ketogenic diet.

GLOBAL HYPOXIC–ISCHEMIC ENCEPHALOPATHY

Generalized decreases in cerebral perfusion can produce focal areas of watershed brain infarction which can be asymmetric and mimic stroke. Watershed ischemic injury should be accompanied by recognized hypotension or conditions predisposing to low cerebral perfusion such as sepsis, dehydration, or cardiac dysfunction. Clinical presentations would involve more generalized and bilateral cerebral dysfunction compared to stroke and the anatomic location of the infarct is in typical bilateral watershed zones rather than a single arterial territory.

HYPERTENSIVE ENCEPHALOPATHY

The posterior reversible leukoencephalopathy syndrome is seen in children with hypertension, often in the context of an acute rise in blood pressure. Posterior regions are selectively involved, possibly resulting in symptoms of bilateral cortical visual dysfunction in addition to encephalopathy and seizures.

INBORN ERRORS OF METABOLISM

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS; see Chapter 598.2) are the classic examples, though other mitochondrial disease can mimic stroke. Features favoring MELAS would include a history of developmental regression, posterior (and often bilateral) lesions not respecting vascular territories on MRI, and elevated serum or cerebrospinal fluid lactate (MR spectroscopy). In contrast to these types of "metabolic infarction," children with Fabry disease (see Chapter 613.6) and homocystinuria (see Chapter 85.4) are at risk of true ischemic stroke.

VESTIBULOPATHY/ATAXIA

Acute onset vertigo and/or ataxia can be confused with brainstem or cerebellar stroke. Simple bedside tests of vestibular function with otherwise intact brainstem functions are reassuring. This differential diagnosis includes acute vestibular neuronopathy, viral labyrinthitis, and the benign paroxysmal vertigos as well as acute cerebellar ataxia and episodic ataxias.

CHANNELOPATHIES

An increasing number of nervous system ion channel mutations are described that feature sudden focal neurological deficits thereby mimicking stroke. These include the migraine syndromes mentioned above as well as a growing list of episodic ataxias. A strong family history raises suspicion but most require additional investigation.

ALTERNATING HEMIPLEGIA OF CHILDHOOD

Alternating hemiplegia of childhood typically presents in infancy with acute intermittent episodes of hemiplegia that alternate from 1 side of the body to the other. The hemiplegia persists for minutes to weeks and then resolves spontaneously. Choreoathetosis and dystonic movements are commonly observed in the hemiparetic extremity. Signs spontaneously regress with sleep but recur with awakening. Neuroimaging including MRA should be completed to exclude moyamoya disease. Alternating hemiplegia of childhood is linked to mutations in the *ATP1A3* gene.

Chapter 602

Central Nervous System Vasculitis

Heather A. Van Mater, William B. Gallentine, and Susanne M. Benseler

Autoimmune-mediated inflammatory brain diseases are recognized as an etiology for neurologic and neuropsychiatric symptoms in children and adults and include primary central nervous system (CNS) vasculitis, secondary CNS vasculitis, and autoimmune encephalitis (Fig. 602-1; see Chapter 598.4).

Primary angiitis of the CNS (PACNS) is recognized as the underlying etiology of a broad spectrum of neurologic and psychiatric symptoms in children. Criteria characteristic of childhood CNS vasculitis (cPACNS) include (1) newly acquired focal and/or diffuse neurologic deficits and/or psychiatric symptoms in a child 18 yr of age or younger, **plus** (2) angiographic and/or histologic evidence of vasculitis **in the absence of** (3) a systemic underlying condition known to cause or mimic the findings. Two broad categories of cPACNS are recognized based on the predominant vessel size affected: large/medium-vessel cPACNS and small-vessel cPACNS. Large/medium-vessel cPACNS is diagnosed on angiography demonstrating features of vessel wall inflammation, wall swelling and edema, and resulting luminal stenosis. Based on the clinical course and the corresponding distribution of vessel stenosis within the vascular tree of the CNS, children with large/medium-vessel cPACNS are classified as a monophasic, nonprogressive (NPcPACNS) or a progressive subtype (PcPACNS). The latter is characterized by chronic, progressive vessel wall inflammation affecting both proximal and distal vessel segments in 1 or both hemispheres. In contrast, NPcPACNS is a monophasic illness; vessel inflammation occurs in a characteristic distribution and is limited to the proximal vessel segments of the anterior and/or middle cerebral artery and/or distal internal carotid artery of 1 hemisphere. Small vessel cPACNS (SVcPACNS) is considered a progressive illness; the diagnosis is confirmed on brain biopsies because angiography is normal.

Secondary childhood CNS vasculitis can affect all cerebral vessel segments and can occur in the context of infections, rheumatic or other inflammatory conditions or as a result of systemic or local vascular irritation (Table 602-1). The neuropsychiatric manifestations of secondary CNS vasculitis are the same as those of primary CNS vasculitis. Secondary CNS vasculitis is distinguished from primary CNS vasculitis largely by the non-CNS manifestations of the underlying systemic vasculitic disease.

EPIDEMIOLOGY

The incidence and prevalence of primary CNS vasculitis is undetermined. In the past, the majority of children have been diagnosed at autopsy. Increased physician awareness, improved diagnostic markers, sensitive neuroimaging techniques, and brain biopsies have led to dramatically increased recognition and decreased mortality. Exploring the epidemiology of primary CNS vasculitis remains a challenge: the disease has many names including isolated angiitis of the CNS, transient cerebral angiitis, postvaricella angiopathy, and focal cerebral arteriopathy. Furthermore, children are frequently diagnosed with their presenting clinical phenotype, such as stroke, movement disorder, hallucination, or cognitive decline. Within clinical phenotypes, such as arterial ischemic stroke or status epilepticus in children without preexisting epilepsy, cPACNS should be considered an important etiology.

CLINICAL MANIFESTATIONS

Recognition of childhood CNS vasculitis requires a very high level of suspicion; any neurologic or psychiatric presentation can be the result

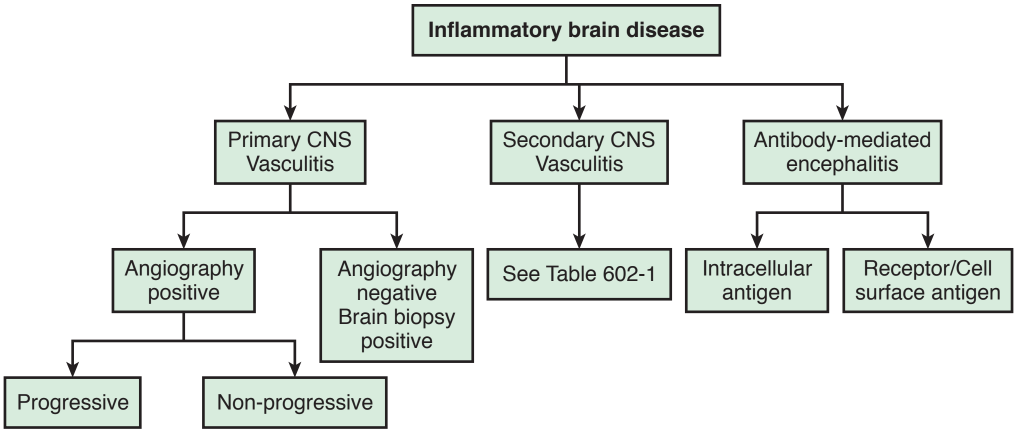

Figure 602-1 CNS vasculitis within the spectrum of immune-mediated inflammatory brain diseases.

Table 602-1 Causes of Secondary CNS Vasculitis
VIRAL INFECTIONS Varicella zoster virus, HIV, hepatitis C virus, cytomegalovirus, parvovirus B19
BACTERIAL INFECTIONS *Treponema pallidum, Borrelia burgdorferi, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Bartonella henselae, Rickettsia* spp.
FUNGAL INFECTIONS Aspergillosis, mucormycosis, coccidioidomycosis, candidosis
PARASITIC INFECTIONS Cysticercosis
SYSTEMIC VASCULITIDES Wegener granulomatosis, Churg-Strauss syndrome, Behçet disease, polyarteritis nodosa, Henoch-Schönlein purpura, Kawasaki disease, giant-cell arteritis, Takayasu arteritis
CONNECTIVE TISSUE DISEASES Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, dermatomyositis, mixed connective tissue disease
MISCELLANEOUS Antiphospholipid antibodies syndrome, Hodgkin and non-Hodgkin lymphomas, neurosarcoidosis, inflammatory bowel disease, graft-versus-host disease, bacterial endocarditis, acute bacterial meningitis, drug-induced CNS vasculitis (cocaine, amphetamine, ephedrine, phenylpropanolamine)

From Salvarani C, Brown Jr. RD, Hunder GG: Adult primary central nervous system vasculitis. Lancet *380:767–776, 2012, Panel, p. 768.*

of an underlying CNS vasculitis. The clinical phenotype may provide clues to the size of the primarily affected vessel segments and resulting cPACNS subtype: the majority of children with large/medium cPACNS present with arterial ischemic stroke features. Focal neurologic deficits, such as hemiparesis, facial droop, aphasia or any other distinct gross or fine motor deficits, may be the result of large vessel inflammation causing stenosis and decreased blood supply to the specific functional areas of the brain. Initially, these focal deficits wax and wane; they may even briefly resolve without therapeutic intervention and can therefore be easily overlooked. Headaches are a symptom of vascular disease in general and are commonly reported in cPACNS. New onset of vascular-type (e.g., migraine) headaches in children without any family history of migraine can serve as a diagnostic clue. Cognitive dysfunction in cPACNS often includes loss of higher executive function, concentration difficulties, learning and memory problems, atypical behavior or personality changes, and loss of social and emotional control. Seizures are a hallmark of SVcPACNS, as more than 80% of children with SVcPACNS present with seizures; all seizure types are seen. Often there is a disconnection between the clinical presentation and the child's electroencephalogram findings. In many centers, refractory status epilepticus is increasingly recognized as the presenting phenotype of SVcPACNS. Optic neuritis and spinal cord disease are also recognized in SVcPACNS.

Constitutional features of fever or fatigue may point toward an underlying systemic illness causing a secondary CNS vasculitis. All children with suspected or confirmed CNS vasculitis require a careful assessment for a systemic illness.

DIAGNOSIS

The first step is considering vasculitis as a possible underlying etiology of newly acquired neurologic deficits and/or psychiatric symptoms (Table 602-2). The likelihood of CNS vasculitis in general and a specific subtype of CNS vasculitis in particular depends on the demographic characteristics of the patient, the CNS and non-CNS features of the clinical presentation, the preceding symptoms, and the mode of onset of the disease. SVcPACNS is more commonly seen in girls of all ages, whereas large/medium cPACNS has a clear male preponderance. Seizures are a hallmark of SVcPACNS, whereas strokes often reflect large/medium-vessel inflammation. Laboratory markers of vasculitis typically include C-reactive protein, erythrocyte sedimentation rate, and complete blood counts. But inflammatory markers lack sensitivity and specificity in cPACNS, particularly when the CNS is involved in isolation. More than 50% of children with large/medium-vessel cPACNS have normal inflammatory markers at diagnosis. In contrast, the majority of children with SVcPACNS present with mild-moderately raised markers. Von Willebrand factor antigen, an endothelial cell–derived protein, is a proposed biomarker of vasculitis correlating closely with disease activity in cPACNS. It may be of particular importance for distinguishing SVcPACNS from demyelinating diseases. Cerebrospinal fluid (CSF) analysis is abnormal in up to 90% of SVcPACNS patients and less than half of large/medium-vessel cPACNS. Within the latter group, children with the progressive subtype have a higher likelihood of presenting with abnormal CSF findings, including high opening pressure, raised CSF cell count, typically with lymphocyte predominance, and raised CSF protein. Oligoclonal bands are seen in 20% of children with SVcPACNS. They are rarely seen in other subtypes. Autoimmune encephalitis (see Chapter 598.4) is one of the key differential diagnoses of SVcPACNS.

Neuroimaging is a valuable diagnostic modality for cPACNS. Parenchymal lesions may be inflammatory or ischemic in nature and are best viewed on MRI including T2/fluid attenuated inversion recovery (FLAIR) sequences and diffusion-weighted images (DWI) (Fig. 602-2). CNS lesions in children with large/medium-vessel cPACNS are predominantly ischemic in nature and restricted to large vascular territories. In contrast, MRI lesions in children with SVcPACNS are not restricted to major vascular territories; lesions are primarily inflammatory and may enhance with contrast. In this subtype, focal or

Table 602-2	Proposed Diagnostic Evaluation of Suspected Childhood Primary CNS Vasculitis

1. Clinical evaluation: Newly acquired symptom or deficit in a previously healthy child
   - Focal neurologic deficit: hemiparesis, hemisensory loss, aphasia, ataxia, movement abnormality, paresthesia, facial droop, ataxia, vision loss, spinal cord symptoms, others
   - Seizures or (refractory) seizure status
   - Diffuse neurologic deficit including cognitive decline with loss of higher executive function, concentration difficulties, learning or memory problems, behavior or personality changes, loss of social skills or emotional/impulse control, others
   - Headaches
   - Meningitis symptoms, abnormal level of consciousness
   - Psychiatric symptoms including hallucinations, pseudoseizures

   Differential diagnosis approach:
   - Underlying illness known to cause, be associated or mimic CNS vasculitis: check all potential clinical features
2. Laboratory tests
   - Blood inflammatory markers: C-reactive protein, erythrocyte sedimentation rate and complete blood counts
   - Endothelial markers: von Willebrand factor (vWF) antigen
   - Cerebrospinal fluid (CSF) inflammatory markers: opening pressure, cell count, protein, oligoclonal bands

   Differential diagnosis approach:
   - Infections/postinfectious inflammation: cultures, serologies, Gram stains
   - Autoimmune encephalitis: check neuronal antibodies in CSF and blood
   - Systemic inflammation/rheumatic disease: characteristic laboratory markers such as complement, autoantibodies
   - Thromboembolic conditions: procoagulatory profile
3. Neuroimaging
   - Parenchymal imaging on MRI:
     - Inflammatory lesions: T2/fluid attenuated inversion recovery sequences plus gadolinium contrast (lesion enhancement)
     - Ischemic lesions: diffusion-weighted images/apparent diffusion coefficient mapping
   - Vessel imaging
4. Brain biopsy

generalized meningeal enhancement is commonly seen if children are imaged prior to immunosuppressive therapy. Spinal cord parenchymal imaging is challenging; defining the nature of lesions is often difficult.

Evidence of vessel stenosis confirms the diagnosis in large/medium-vessel cPACNS subtypes; brain biopsies are not required. Important information about the disease activity can be obtained from post–gadolinium contrast studies of the vascular wall. The vessel wall of an inflamed cerebral vessel in active large/medium-vessel cPACNS subtypes is thickened and enhances contrast. Conventional angiography when compared to MR angiography has a higher sensitivity in detecting vessel stenosis in the distal vessel segments, the posterior circulation, and in very young children. Vessel wall imaging is often normal in children with SVcPACNS, sometimes mandating an elective brain biopsy to definitively make the diagnosis. Studies of regional blood flow or therapeutic trials of antiinflammatory or immunosuppressive agents are nonsurgical alternatives that do not afford specific diagnostic information. Biopsies should target low-risk, nonfunctional areas identified on MRI. In the appropriate clinical context, nonlesional biopsies have a high yield for confirming the diagnosis of SVcPACNS. Characteristic findings in SVcPACNS include an intramural and/or perivascular mononuclear infiltrate, evidence of endothelial activation, and reactive astrocyte activation. Gliosis and perivascular demyelination are hallmarks of long-standing disease. Findings typically seen in adult PACNS, including granulomas or vessel wall necrosis, are rarely seen in children with SVcPACNS. In children, the diagnostic yield of brain biopsies is 70%. Biopsy-related complications are rarely seen.

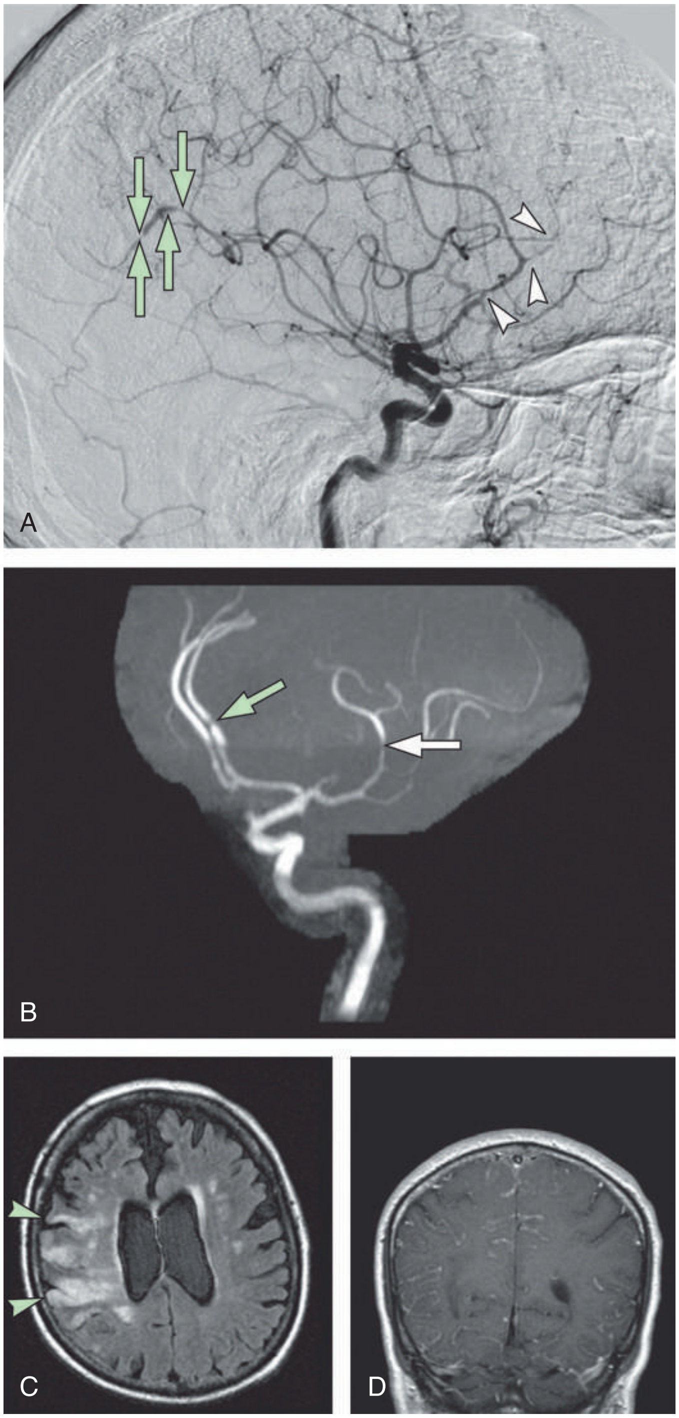

Figure 602-2 Imaging of patients with primary CNS vasculitis. **A,** Cerebral angiogram shows alternating stenosis and dilation of the distal middle cerebral artery *(arrows)* and the anterior cerebral artery *(arrowheads).* **B,** Magnetic resonance angiography of the brain shows a short-segment stenosis of the anterior cerebral artery *(green arrow)* and stenosis of the distal middle cerebral artery *(white arrow).* **C,** Fluid attenuation inversion recovery–weighted MRI shows a large abnormality within the right cerebral hemisphere consistent with ischemia *(arrowheads).* **D,** MRI shows diffuse, asymmetric, nodular, and linear leptomeningeal enhancement, with dura only slightly affected. *(From Salvarani C, Brown Jr. RD, Hunder GG: Adult primary central nervous system vasculitis.* Lancet *380:767–776, 2012, Fig. 2.)*

Table 602-3 Characteristics of Primary CNS Vasculitis and Reversible Cerebral Vasoconstriction Syndrome

	PCNSV	RCVS
Precipitating factor	None	Postpartum onset or onset after exposure to vasoactive substances
Onset	More insidious, progressive course	Acute onset followed by a monophasic course
Headaches	Chronic and progressive	Acute, thunderclap type
CSF findings	Abnormal (leucocytosis and high total protein concentration)	Normal to near normal
MRI	Abnormal in almost all patients	Normal in 70% of patients
Angiography	Possibly normal; otherwise, diffuse abnormalities are often indistinguishable from RCVS; irregular and asymmetrical arterial stenoses or multiple occlusions are more suggestive of PCNSV; abnormalities might be irreversible	Always abnormal, strings of beads appearance of cerebral arteries; abnormalities reversible within 6-12 wk
Cerebral biopsy	Vasculitis	No vasculitic changes
Drug treatment	Prednisone with or without cytotoxic agents	Nimodipine

CSF, cerebrospinal fluid; PCNSV, primary CNS vasculitis; RCVS, reversible cerebral vasoconstriction syndrome.
From Salvarani C, Brown Jr. RD, Hunder GG: Adult primary central nervous system vasculitis. Lancet *380:767–776, 2012, Table 2.*

Disorders that may be seen in adolescents and young adults that produce the reversible vasoconstriction syndrome must also be considered. These include migraine, drug-induced vasospasm, and postpartum angiopathy. Differentiating vasculitis is important for therapy and prognosis (Table 602-3).

TREATMENT

Corticosteroids are the mainstay of acute immunosuppressive management of cPACNS. Usually IV pulse therapy is initially given. Antithrombotic therapy is equally important, particularly in large/medium-vessel cPACNS subtypes, because children are at high risk for recurrent ischemic events. For the distinct cPACNS subtypes, different treatment regimens should be considered. Nonprogressive cPACNS is a monophasic inflammatory attack with the highest risk of poor neurologic outcome. Vessel wall inflammation causes severe proximal stenosis and a high restroke risk. High-dose corticosteroid pulses are commonly given followed by a 6-12 wk course of oral steroids at tapering doses. Second-line immunosuppressive agents are uncommonly used. All children require antithrombotic therapy. No unifying regimen exists. Many centers initially use low-molecular-weight heparin followed by long-term antiplatelet therapy. When reimaged at 3 mo follow-up, children should have stable or improved vessel disease, no newly affected vessel segments, and no evidence of contrast wall enhancement. At this point the immunosuppressive therapy is commonly discontinued and children are only kept on antiplatelet agents.

Progressive cPACNS and SVcPACNS are considered chronic progressive vasculitis subtypes requiring a prolonged course of combination immunosuppression. High-dose corticosteroids are initially used followed by long-term oral corticosteroids with slow taper. Many centers use an induction-maintenance protocol adding IV cyclophosphamide to the corticosteroids as the induction medication, followed by mycophenolate mofetil or other oral second-line agents during maintenance therapy. Symptomatic therapy is essential including anticonvulsants or psychotropic medication if required. Supportive therapy includes bone protection with calcium and vitamin D, prophylaxis against pneumocystis pneumonia, and gastric mucosal protection as required.

PROGNOSIS

The mortality rate of cPACNS has significantly improved. Some treatment protocols for SVcPACNS report a good outcome, defined as no functional neurologic deficits in two-thirds of children. Children presenting with status epilepticus and SVcPACNS have the poorest cognitive outcome.

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Chapter 603

Central Nervous System Infections

Charles G. Prober, Nivedita S. Srinivas, and Roshni Mathew

Infection of the central nervous system (CNS) is the most common cause of fever associated with signs and symptoms of CNS disease in children. Many microorganisms can cause infection. Nonetheless, specific pathogens are identifiable and are influenced by the age and immune status of the host and the epidemiology of the pathogen. In general, viral infections of the CNS are much more common than bacterial infections, which, in turn, are more common than fungal and parasitic infections. Infections caused by rickettsiae (Rocky Mountain spotted fever, *Ehrlichia*) are relatively uncommon but assume important roles under certain epidemiologic circumstances. *Mycoplasma* spp. can also cause infections of the CNS, although their precise contribution is often difficult to determine.

Regardless of etiology, most patients with CNS infection have similar clinical manifestations. **Common symptoms** include headache, nausea, vomiting, anorexia, restlessness, altered state of consciousness, and irritability; most of these symptoms are nonspecific. **Common signs** of CNS infection, in addition to fever, include photophobia, neck pain and rigidity, obtundation, stupor, coma, seizures, and focal neurologic deficits. The severity and constellation of signs are determined by the specific pathogen, the host, and the area of the CNS affected.

Infection of the CNS may be diffuse or focal. Meningitis and encephalitis are examples of diffuse infection. Meningitis implies primary involvement of the meninges, whereas encephalitis indicates brain parenchymal involvement. Because these anatomic boundaries are often not distinct, many patients have evidence of both meningeal and parenchymal involvement and should be considered to have meningoencephalitis. Brain abscess is the best example of a focal infection of the CNS. The neurologic expression of this infection is determined by the site and extent of the abscess(es) (see Chapter 604).

The diagnosis of diffuse CNS infections depends on examination of cerebrospinal fluid (CSF) obtained by lumbar puncture (LP). Table 603-1 provides an overview of the expected CSF abnormalities with various CNS disorders.

Table 603-1 Cerebrospinal Fluid Findings in Central Nervous System Disorders

CONDITION	PRESSURE (mm H_2O)	LEUKOCYTES (mm^3)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	COMMENTS
Normal	50-80	<5, ≥75% Lymphocytes	20-45	>50 (or 75% serum glucose)	
COMMON FORMS OF MENINGITIS					
Acute bacterial meningitis	Usually elevated (100-300)	100-10,000 or more; usually 300-2,000; PMNs predominate	Usually 100-500	Decreased, usually <40 (or <50% serum glucose)	Organisms usually seen on Gram stain and recovered by culture
Partially treated bacterial meningitis	Normal or elevated	5-10,000; PMNs usual but mononuclear cells may predominate if pretreated for extended period of time	Usually 100-500	Normal or decreased	Organisms may be seen on Gram stain Pretreatment may render CSF sterile. Antigen may be detected by agglutination test
Viral meningitis or meningoencephalitis	Normal or slightly elevated (80-150)	Rarely >1,000 cells. Eastern equine encephalitis and lymphocytic choriomeningitis may have cell counts of several thousand. PMNs early but mononuclear cells predominate through most of the course	Usually 50-200	Generally normal; may be decreased to <40 in some viral diseases, particularly mumps (15-20% of cases)	HSV encephalitis is suggested by focal seizures or by focal findings on CT or MRI scans or EEG. Enteroviruses and HSV infrequently recovered from CSF. HSV and enteroviruses may be detected by PCR of CSF
UNCOMMON FORMS OF MENINGITIS					
Tuberculous meningitis	Usually elevated	10-500; PMNs early, but lymphocytes predominate through most of the course	100-3,000; may be higher in presence of block	<50 in most cases; decreases with time if treatment is not provided	Acid-fast organisms almost never seen on smear. Organisms may be recovered in culture of large volumes of CSF. *Mycobacterium tuberculosis* may be detected by PCR of CSF
Fungal meningitis	Usually elevated	5-500; PMNs early but mononuclear cells predominate through most of the course. Cryptococcal meningitis may have no cellular inflammatory response	25-500	<50; decreases with time if treatment is not provided	Budding yeast may be seen. Organisms may be recovered in culture. Cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection
Syphilis (acute) and leptospirosis	Usually elevated	50-500; lymphocytes predominate	50-200	Usually normal	Positive CSF serology. Spirochetes not demonstrable by usual techniques of smear or culture; dark-field examination may be positive
Amebic (*Naegleria*) meningoencephalitis	Elevated	1,000-10,000 or more; PMNs predominate	50-500	Normal or slightly decreased	Mobile amebas may be seen by hanging-drop examination of CSF at room temperature
BRAIN ABSCESSES AND PARAMENINGEAL FOCUS					
Brain abscess	Usually elevated (100-300)	5-200; CSF rarely acellular; lymphocytes predominate; if abscess ruptures into ventricle, PMNs predominate and cell count may reach >100,000	75-500	Normal unless abscess ruptures into ventricular system	No organisms on smear or culture unless abscess ruptures into ventricular system
Subdural empyema	Usually elevated (100-300)	100-5,000; PMNs predominate	100-500	Normal	No organisms on smear or culture of CSF unless meningitis also present; organisms found on tap of subdural fluid
Cerebral epidural abscess	Normal to slightly elevated	10-500; lymphocytes predominate	50-200	Normal	No organisms on smear or culture of CSF
Spinal epidural abscess	Usually low, with spinal block	10-100; lymphocytes predominate	50-400	Normal	No organisms on smear or culture of CSF
Chemical (drugs, dermoid cysts, myelography dye)	Usually elevated	100-1,000 or more; PMNs predominate	50-100	Normal or slightly decreased	Epithelial cells may be seen within CSF by use of polarized light in some children with dermoids

Continued

Table 603-1 Cerebrospinal Fluid Findings in Central Nervous System Disorders—cont'd

CONDITION	PRESSURE (mm H_2O)	LEUKOCYTES (mm^3)	PROTEIN (mg/dL)	GLUCOSE (mg/dL)	COMMENTS
NONINFECTIOUS CAUSES					
Sarcoidosis	Normal or elevated slightly	0-100; mononuclear	40-100	Normal	No specific findings
Systemic lupus erythematosus with CNS involvement	Slightly elevated	0-500; PMNs usually predominate; lymphocytes may be present	100	Normal or slightly decreased	No organisms on smear or culture. Positive neuronal and ribosomal P protein antibodies in CSF
Tumor, leukemia	Slightly elevated to very high	0-100 or more; mononuclear or blast cells	50-1,000	Normal to decreased (20-40)	Cytology may be positive
Acute disseminated encephalomyelitis	Normal or elevated	~100 lymphocytes	Normal to elevated	Normal	MRI adds to diagnosis
Autoimmune encephalitis	Normal	~100 lymphocytes	Normal to elevated	Normal	Anti-NMDAR antibody–positive

CSF, cerebrospinal fluid; EEG, electroencephalogram; HSV, herpes simplex virus; NMDAR, *N*-methyl-D-aspartate receptor; PCR, polymerase chain reaction; PMN, polymorphonuclear neutrophils.

603.1 Acute Bacterial Meningitis Beyond the Neonatal Period

Charles G. Prober and Roshni Mathew

Bacterial meningitis is one of the most potentially serious infections occurring in infants and older children. This infection is associated with a high rate of acute complications and risk of long-term morbidity. The incidence of bacterial meningitis is sufficiently high in febrile infants that it should be included in the differential diagnosis of those with altered mental status and other evidence of neurologic dysfunction.

ETIOLOGY

The most common causes of bacterial meningitis in children older than 1 mo of age in the United States are *Streptococcus pneumoniae and Neisseria meningitidis.* Bacterial meningitis caused by *S. pneumoniae* and *Haemophilus influenzae* type b has become much less common in developed countries since the introduction of universal immunization against these pathogens beginning at 2 mo of age. Demonstrating the importance of vaccination, invasive *H. influenzae* disease was reported in Minnesota in 2008 in 5 children with no relationship to one another and who were partially or not immunized. It is the largest number of children with invasive *H. influenzae* in Minnesota since 1992. Infection caused by *S. pneumoniae* or *H. influenzae* type b must be considered in incompletely vaccinated individuals or those in developing countries. Those with certain underlying immunologic (HIV infection, immunoglobulin [Ig] G subclass deficiency) or anatomic (splenic dysfunction, cochlear defects or implants) disorders also may be at increased risk of infection caused by these bacteria.

Alterations of host defense resulting from anatomic defects or immune deficits also increase the risk of meningitis from less-common pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus aureus,* coagulase-negative staphylococci, *Salmonella* spp., anaerobes, and *Listeria monocytogenes.*

EPIDEMIOLOGY

A major risk factor for meningitis is the lack of immunity to specific pathogens associated with young age. Additional risks include recent colonization with pathogenic bacteria, close contact (household, daycare centers, college dormitories, military barracks) with individuals having invasive disease caused by *N. meningitidis* or *H. influenzae* type b, crowding, poverty, black or Native American race, and male gender. The mode of transmission is probably person-to-person contact through respiratory tract secretions or droplets. The risk of meningitis is increased among infants and young children with occult bacteremia; the odds ratio is greater for meningococcus (85 times) and *H. influenzae* type b (12 times) relative to that for pneumococcus.

Specific host defense defects as a result of altered immunoglobulin production in response to encapsulated pathogens may be responsible for the increased risk of bacterial meningitis in Native Americans and Eskimos. Defects of the complement system (C5-C8) are associated with recurrent meningococcal infection, and defects of the properdin system are associated with a significant risk of lethal meningococcal disease. Splenic dysfunction (sickle cell anemia) or asplenia (caused by trauma or congenital defect) is associated with an increased risk of pneumococcal, *H. influenzae* type b (to some extent), and, rarely, meningococcal sepsis and meningitis. T-lymphocyte defects (congenital or acquired by chemotherapy, AIDS, or malignancy) are associated with an increased risk of *L. monocytogenes* infections of the CNS.

A congenital or acquired CSF leak across a mucocutaneous barrier, such as a lumbar dural sinus, cranial or midline facial defects (cribriform plate), and middle ear (stapedial foot plate) or inner ear fistulas (oval window, internal auditory canal, cochlear aqueduct), or CSF leakage through a rupture of the meninges as a result of a basal skull fracture into the cribriform plate or paranasal sinus, is associated with an increased risk of pneumococcal meningitis. The risk of bacterial meningitis, caused by *S. pneumoniae,* in children with cochlear implants, used for the treatment of hearing loss, is more than 30 times the risk in the general U.S. population. Lumbosacral dermal sinus and meningomyelocele are associated with staphylococcal, anaerobic, and Gram-negative enteric bacterial meningitis. CSF shunt infections increase the risk of meningitis caused by staphylococci (especially coagulase-negative species) and other low-virulence bacteria that typically colonize the skin.

Streptococcus pneumoniae

See Chapter 182.

The 7-valent pneumococcal protein polysaccharide conjugate vaccine (PCV7) was introduced into the routine vaccination schedule in 2000 and contained the serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. These serotypes caused most of the invasive pneumococcal infections in the United States at that time. The vaccine led to a dramatic decrease in rates of invasive pneumococcal disease. However, an increase in invasive disease caused by serotypes not contained in the original vaccine, such as serotype 19A, was observed. As a result, a 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13) was licensed in the United States in February 2010. PCV13 contains the serotypes in PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A. This vaccine is recommended for routine administration to all children 2-59 mo of age. The PCV13 vaccine is given as a 4-dose series at 2, 4, 6, and 12-15 mo of age. The incidence of invasive pneumococcal infections

peaks in the 1st 2 yr of life, reaching rates of 228 per 100,000 in children 6-12 mo of age. Children with anatomic or functional asplenia secondary to sickle cell disease and those infected with HIV have infection rates that are 20-100–fold higher than in those of healthy children in the 1st 5 yr of life. Additional risk factors for contracting pneumococcal meningitis include otitis media, sinusitis, pneumonia, CSF otorrhea or rhinorrhea, the presence of a cochlear implant, and chronic graft-versus-host disease following bone marrow transplantation.

Neisseria meningitidis

See Chapter 191.

Five serogroups of meningococcus—A, B, C, Y, and W-135—are responsible for disease. Meningococcal meningitis may be sporadic or may occur in epidemics. In the United States, serogroups B, C, and Y each account for approximately 30% of cases, although serogroup distribution varies by location and time. Epidemic disease, especially in developing countries, is usually caused by serogroup A. Cases occur throughout the year but may be more common in the winter and spring and following influenza virus infections. Nasopharyngeal carriage of *N. meningitidis* occurs in 1-15% of adults. Colonization may last weeks to months; recent colonization places nonimmune younger children at greatest risk for meningitis. The incidence of disease occurring in association with an index case in the family is 1%, a rate that is 1,000-fold the risk in the general population. The risk of secondary cases occurring in contacts at daycare centers is approximately 1 in 1,000. Most infections of children are acquired from a contact in a daycare facility, a colonized adult family member, or an ill patient with meningococcal disease. Children younger than 5 yr have the highest rates of meningococcal infection. A second peak in incidence occurs in persons between 15 and 24 yr of age. College freshmen living in dormitories have an increased incidence of infection compared to non–college-attending, age-matched controls.

The Centers for Disease Control and Prevention (CDC) recommends vaccination against meningococcus (types A, C, W, and Y) with 1 dose of a quadrivalent conjugate meningococcal vaccine between the ages of 11 and 12 yr and for persons 2 mo to 18 yr who are at increased risk for meningococcal disease. The CDC also has specific recommendations for meningococcal vaccination of infants at high risk of meningococcal infection as a consequence of complement pathway deficiencies. College freshmen living in dormitories who have not been previously vaccinated should also be vaccinated.

Haemophilus influenzae Type B

See Chapter 194.

Before universal *H. influenzae* type b vaccination in the United States, approximately 70% of cases of bacterial meningitis occurring in the 1st 5 yr of life were caused by this pathogen. Invasive infections occurred primarily in infants 2 mo to 2 yr of age; peak incidence was at 6-9 mo of age, and 50% of cases occurred in the 1st yr of life. The risk to children was markedly increased among family or daycare center contacts of patients with *H. influenzae* type b disease. Incompletely vaccinated individuals, those in underdeveloped countries who are not vaccinated, and those with blunted immunologic responses to vaccine (such as children with HIV infection) remain at risk for *H. influenzae* type b meningitis.

PATHOLOGY AND PATHOPHYSIOLOGY

A meningeal purulent exudate of varying thickness may be distributed around the cerebral veins, venous sinuses, convexity of the brain, and cerebellum, and in the sulci, sylvian fissures, basal cisterns, and spinal cord. Ventriculitis with bacteria and inflammatory cells in ventricular fluid may be present (more often in neonates), as may subdural effusions and, rarely, empyema. Perivascular inflammatory infiltrates also may be present, and the ependymal membrane may be disrupted. Vascular and parenchymal cerebral changes characterized by polymorphonuclear infiltrates extending to the subintimal region of the small arteries and veins, vasculitis, thrombosis of small cortical veins, occlusion of major venous sinuses, necrotizing arteritis producing subarachnoid hemorrhage, and, rarely, cerebral cortical necrosis in the absence of identifiable thrombosis have been described at autopsy. **Cerebral infarction,** resulting from vascular occlusion because of inflammation, vasospasm, and thrombosis, is a frequent sequela. Infarct size ranges from microscopic to involvement of an entire hemisphere.

Inflammation of spinal nerves and roots produces meningeal signs, and inflammation of the cranial nerves produces cranial neuropathies of optic, oculomotor, facial, and auditory nerves. Increased intracranial pressure (ICP) also produces oculomotor nerve palsy because of the presence of temporal lobe compression of the nerve during tentorial herniation. Abducens nerve palsy may be a nonlocalizing sign of elevated ICP.

Increased ICP is a result of cell death (cytotoxic cerebral edema), cytokine-induced increased capillary vascular permeability (vasogenic cerebral edema), and, possibly, increased hydrostatic pressure (interstitial cerebral edema) after obstructed reabsorption of CSF in the arachnoid villus or obstruction of the flow of fluid from the ventricles. ICP may exceed 300 mm H_2O; cerebral perfusion may be further compromised if the cerebral perfusion pressure (mean arterial pressure minus ICP) is <50 cm H_2O as a result of systemic hypotension with reduced cerebral blood flow. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) may produce excessive water retention and potentially increase the risk of elevated ICP (see Chapter 559). Hypotonicity of brain extracellular spaces may cause cytotoxic edema after cell swelling and lysis. Tentorial, falx, or cerebellar herniation does not usually occur because the increased ICP is transmitted to the entire subarachnoid space and there is little structural displacement. Furthermore, if the fontanels are still patent, increased ICP is not always dissipated.

Hydrocephalus can occur as an acute complication of bacterial meningitis. It most often takes the form of a communicating hydrocephalus caused by adhesive thickening of the arachnoid villi around the cisterns at the base of the brain. Thus, there is interference with the normal resorption of CSF. Less often, obstructive hydrocephalus develops after fibrosis and gliosis of the aqueduct of Sylvius or the foramina of Magendie and Luschka.

Raised CSF protein levels are partly a result of increased vascular permeability of the blood–brain barrier and the loss of albumin-rich fluid from the capillaries and veins traversing the subdural space. Continued transudation may result in subdural effusions, usually found in the later phase of acute bacterial meningitis. **Hypoglycorrhachia** (reduced CSF glucose levels) is attributable to decreased glucose transport by the cerebral tissue.

Damage to the cerebral cortex may be a result of the focal or diffuse effects of vascular occlusion (infarction, necrosis, lactic acidosis), hypoxia, bacterial invasion (cerebritis), toxic encephalopathy (bacterial toxins), elevated ICP, ventriculitis, and transudation (subdural effusions). These pathologic factors result in the clinical manifestations of impaired consciousness, seizures, cranial nerve deficits, motor and sensory deficits, and later psychomotor retardation.

PATHOGENESIS

Bacterial meningitis most commonly results from hematogenous dissemination of microorganisms from a distant site of infection; **bacteremia** usually precedes meningitis or occurs concomitantly. Bacterial colonization of the nasopharynx with a potentially pathogenic microorganism is the usual source of the bacteremia. There may be prolonged carriage of the colonizing organisms without disease or, more likely, rapid invasion after recent colonization. Prior or concurrent viral upper respiratory tract infection may enhance the pathogenicity of bacteria producing meningitis.

N. meningitidis and *H. influenzae* type b attach to mucosal epithelial cell receptors by pili. After attachment to epithelial cells, bacteria breach the mucosa and enter the circulation. *N. meningitidis* may be transported across the mucosal surface within a phagocytic vacuole after ingestion by the epithelial cell. Bacterial survival in the bloodstream is enhanced by large bacterial capsules that interfere with opsonic phagocytosis and are associated with increased virulence. Host-related developmental defects in bacterial opsonic phagocytosis also contribute to the bacteremia. In young, nonimmune hosts, the

defect may be from an absence of preformed IgM or IgG anticapsular antibodies, whereas in immunodeficient patients, various deficiencies of components of the complement or properdin system may interfere with effective opsonic phagocytosis. Splenic dysfunction may also reduce opsonic phagocytosis by the reticuloendothelial system.

Bacteria gain entry to the CSF through the choroid plexus of the lateral ventricles and the meninges and then circulate to the extracerebral CSF and subarachnoid space. Bacteria rapidly multiply because the CSF concentrations of complement and antibody are inadequate to contain bacterial proliferation. Chemotactic factors then incite a local inflammatory response characterized by polymorphonuclear cell infiltration. The presence of bacterial cell wall lipopolysaccharide (endotoxin) of Gram-negative bacteria (*H. influenzae* type b, *N. meningitidis*) and of pneumococcal cell wall components (teichoic acid, peptidoglycan) stimulates a marked inflammatory response, with local production of tumor necrosis factor, interleukin 1, prostaglandin E, and other inflammatory mediators. The subsequent inflammatory response is characterized by neutrophilic infiltration, increased vascular permeability, alterations of the blood–brain barrier, and vascular thrombosis. Meningitis-associated brain injury is not simply caused by viable bacteria but occurs as a consequence of the host reaction to the inflammatory cascade initiated by bacterial components.

Rarely, meningitis may follow bacterial invasion from a contiguous focus of infection such as paranasal sinusitis, otitis media, mastoiditis, orbital cellulitis, or cranial or vertebral osteomyelitis or may occur after introduction of bacteria via penetrating cranial trauma, dermal sinus tracts, or meningomyeloceles.

CLINICAL MANIFESTATIONS

The onset of acute meningitis has 2 predominant patterns. The more dramatic and, fortunately, less common presentation is sudden onset with rapidly progressive manifestations of shock, purpura, disseminated intravascular coagulation, and reduced levels of consciousness often resulting in progression to coma or death within 24 hr. More often, meningitis is preceded by several days of fever accompanied by upper respiratory tract or gastrointestinal symptoms, followed by nonspecific signs of CNS infection, such as increasing lethargy and irritability.

The signs and symptoms of meningitis are related to the nonspecific findings associated with a systemic infection and to manifestations of meningeal irritation. Nonspecific findings include fever, anorexia and poor feeding, headache, symptoms of upper respiratory tract infection, myalgias, arthralgias, tachycardia, hypotension, and various cutaneous signs, such as petechiae, purpura, or an erythematous macular rash. Meningeal irritation is manifested as nuchal rigidity, back pain, **Kernig sign** (flexion of the hip 90 degrees with subsequent pain with extension of the leg), and **Brudzinski sign** (involuntary flexion of the knees and hips after passive flexion of the neck while supine). In children, particularly in those younger than 12-18 mo, Kernig and Brudzinski signs are not consistently present. Indeed fever, headache, and nuchal rigidity are present in only 40% of adults with bacterial meningitis. Increased ICP is suggested by headache, emesis, bulging fontanel or diastasis (widening) of the sutures, oculomotor (anisocoria, ptosis) or abducens nerve paralysis, hypertension with bradycardia, apnea or hyperventilation, decorticate or decerebrate posturing, stupor, coma, or signs of herniation. Papilledema is uncommon in uncomplicated meningitis and should suggest a more chronic process, such as the presence of an intracranial abscess, subdural empyema, or occlusion of a dural venous sinus. Focal neurologic signs usually are a result of vascular occlusion. Cranial neuropathies of the ocular, oculomotor, abducens, facial, and auditory nerves may also be the result of focal inflammation. Overall, approximately 10-20% of children with bacterial meningitis have focal neurologic signs.

Seizures (focal or generalized) caused by cerebritis, infarction, or electrolyte disturbances occur in 20-30% of patients with meningitis. Seizures that occur on presentation or within the 1st 4 days of onset are usually of no prognostic significance. Seizures that persist after the 4th day of illness and those that are difficult to treat may be associated with a poor prognosis.

Alterations of mental status are common among patients with meningitis and may be the consequence of increased ICP, cerebritis, or hypotension; manifestations include irritability, lethargy, stupor, obtundation, and coma. Comatose patients have a poor prognosis. Additional manifestations of meningitis include photophobia and tache cérébrale, which is elicited by stroking the skin with a blunt object and observing a raised red streak within 30-60 sec.

DIAGNOSIS

The diagnosis of acute pyogenic meningitis is confirmed by analysis of the CSF, which typically reveals microorganisms on Gram stain and culture, a neutrophilic pleocytosis, elevated protein, and reduced glucose concentrations (see Table 603-1). LP should be performed when bacterial meningitis is suspected. **Contraindications** for an immediate LP include (1) evidence of increased ICP (other than a bulging fontanel), such as 3rd or 6th cranial nerve palsy with a depressed level of consciousness, or hypertension and bradycardia with respiratory abnormalities (see Chapter 590); (2) severe cardiopulmonary compromise requiring prompt resuscitative measures for shock or in patients in whom positioning for the LP would further compromise cardiopulmonary function; and (3) infection of the skin overlying the site of the LP. Thrombocytopenia is a relative contraindication for LP. If an LP is delayed, empirical antibiotic therapy should be initiated. CT scanning for evidence of a brain abscess or increased ICP should not delay therapy. LP may be performed after increased ICP has been treated or a brain abscess has been excluded.

Blood cultures should be performed in all patients with suspected meningitis. Blood cultures reveal the responsible bacteria in up to 80-90% of cases of meningitis. Elevations of the C-reactive protein, erythrocyte sedimentation rate, and procalcitonin have been used to differentiate bacterial (usually elevated) from viral causes of meningitis.

Lumbar Puncture

See Chapter 590.

The CSF leukocyte count in bacterial meningitis usually is elevated to >1,000/mm^3 and, typically, there is a neutrophilic predominance (75-95%). Turbid CSF is present when the CSF leukocyte count exceeds 200-400/mm^3. Normal healthy neonates may have as many as 30 leukocytes/mm^3 (usually <10), but older children without viral or bacterial meningitis have <5 leukocytes/mm^3 in the CSF; in both age groups there is a predominance of lymphocytes or monocytes.

A CSF leukocyte count <250/mm^3 may be present in as many as 20% of patients with acute bacterial meningitis; pleocytosis may be absent in patients with severe overwhelming sepsis and meningitis and is a poor prognostic sign. Pleocytosis with a lymphocyte predominance may be present during the early stage of acute bacterial meningitis; conversely, neutrophilic pleocytosis may be present in patients in the early stages of acute viral meningitis. The shift to lymphocytic-monocytic predominance in viral meningitis invariably occurs within 8-24 hr of the initial LP. The Gram stain is positive in 70-90% of patients with untreated bacterial meningitis.

A diagnostic conundrum in the evaluation of children with suspected bacterial meningitis is the analysis of CSF obtained from children already receiving antibiotic (usually oral) therapy. This is an important issue, because 25-50% of children being evaluated for bacterial meningitis are receiving oral antibiotics when their CSF is obtained. CSF obtained from children with bacterial meningitis, after the initiation of antibiotics, may be negative on Gram stain and culture. Pleocytosis with a predominance of neutrophils, elevated protein level, and a reduced concentration of CSF glucose usually persist for several days after the administration of appropriate intravenous antibiotics. Therefore, despite negative cultures, the presumptive diagnosis of bacterial meningitis can be made. Some clinicians test CSF for the presence of bacterial antigens if the child has been pretreated with antibiotics and the diagnosis of bacterial meningitis is in doubt. These tests have technical limitations. Polymerase chain reactions using broad-based bacterial 16S ribosomal RNA gene patterns may be useful in diagnosing the

cause of culture-negative meningitis because of prior antibiotic therapy or the presence of a nonculturable fastidious pathogen.

A traumatic LP may complicate the diagnosis of meningitis. Repeat LP at a higher interspace may produce less hemorrhagic fluid, but this fluid usually also contains red blood cells. Interpretation of CSF leukocytes and protein concentration are affected by LPs that are traumatic, although the Gram stain, culture, and glucose level may not be influenced. Although methods for correcting for the presence of red blood cells have been proposed, it is prudent to rely on the bacteriologic results rather than attempt to interpret the CSF leukocyte and protein results of a traumatic LP. Children with seizure, particularly those with fever associated status epilepticus *do not* have a CSF pleocytosis in the absence of CNS infection or inflammatory disease.

Differential Diagnosis

In addition to *S. pneumoniae, N. meningitidis,* and *H. influenzae* type b, many other microorganisms can cause generalized infection of the CNS with similar clinical manifestations. These organisms include less-typical bacteria, such as *Mycobacterium tuberculosis, Nocardia* spp., *Treponema pallidum* (syphilis), and *Borrelia burgdorferi* (Lyme disease); fungi, such as those endemic to specific geographic areas (*Coccidioides, Histoplasma,* and *Blastomyces*) and those responsible for infections in compromised hosts (*Candida, Cryptococcus,* and *Aspergillus*); parasites, such as *Toxoplasma gondii* and those that cause cysticercosis and, most frequently, viruses (see Chapter 603.2; Table 603-2). Focal infections of the CNS including brain abscess and parameningeal abscess (subdural empyema, cranial and spinal epidural abscess) may also be confused with meningitis. In addition, noninfectious illnesses can cause generalized inflammation of the CNS. Relative to infections, these disorders are uncommon and include malignancy, collagen vascular syndromes, and exposure to toxins (Table 603-2).

Determining the specific cause of CNS infection is facilitated by careful examination of the CSF with specific stains (Kinyoun carbol fuchsin for mycobacteria, India ink for fungi), cytology, antigen detection *(Cryptococcus),* serology (syphilis, West Nile virus, arboviruses), viral culture (enterovirus), and polymerase chain reaction (herpes simplex, enterovirus, and others). Other potentially valuable diagnostic tests include blood cultures, CT or MRI of the brain, serologic tests, and, rarely, meningeal or brain biopsy. A unique MRI finding in patients suspected of CNS infection is pachymeningitis (Fig. 603-1). In addition to bacterial, tuberculous, or fungal infection (Fig. 603-1), the differential diagnosis also includes immune or inflammatory diseases such as Sweet syndrome, CNS vasculitis, sarcoidosis, lymphoma, and neonatal-onset multisystem inflammatory disease.

Acute viral meningoencephalitis is the most likely infection to be confused with bacterial meningitis (see Tables 603-2 and 603-3). Although, in general, children with viral meningoencephalitis appear less ill than those with bacterial meningitis, both types of infection have a spectrum of severity. Some children with bacterial meningitis may have relatively mild signs and symptoms, whereas some with viral meningoencephalitis may be critically ill. Although classic CSF profiles associated with bacterial vs viral infection tend to be distinct (see Table 603-1), specific test results may have considerable overlap.

TREATMENT

The therapeutic approach to patients with presumed bacterial meningitis depends on the nature of the initial manifestations of the illness. A child with rapidly progressing disease of less than 24 hr duration, in the absence of increased ICP, should receive antibiotics as soon as possible after an LP is performed. If there are signs of increased ICP or focal neurologic findings, antibiotics should be given without performing an LP and before obtaining a CT scan. Increased ICP should be treated simultaneously (see Chapter 68). Immediate treatment of associated multiple organ system failure, shock (see Chapter 70), and acute respiratory distress syndrome (see Chapter 71) is also indicated.

Patients who have a more protracted subacute course and become ill over a 4-7 day period should also be evaluated for signs of increased ICP and focal neurologic deficits. Unilateral headache, papilledema, and other signs of increased ICP suggest a focal lesion, such as a brain or epidural abscess, or subdural empyema. Under these circumstances, antibiotic therapy should be initiated before LP and CT scanning. If signs of increased ICP and/or focal neurologic signs are present, CT scanning should be performed first to determine the safety of performing an LP.

Initial Antibiotic Therapy

The initial (empirical) choice of therapy for meningitis in immunocompetent infants and children is primarily influenced by the antibiotic susceptibilities (Table 603-4) of *S. pneumoniae.* Selected antibiotics should achieve bactericidal levels in the CSF. Although there are substantial geographic differences in the frequency of resistance of *S. pneumoniae* to antibiotics, rates are increasing throughout the world. In the United States, 25-50% of strains of *S. pneumoniae* are currently resistant to penicillin; relative resistance (minimal inhibitory concentration = 0.1-1.0 μg/mL) is more common than high-level resistance (minimal inhibitory concentration = 2.0 μg/mL). Resistance to cefotaxime and ceftriaxone is also evident in up to 25% of isolates. In contrast, most strains of *N. meningitidis* are sensitive to penicillin and cephalosporins, although rare resistant isolates have been reported. Approximately 30-40% of isolates of *H. influenzae* type b produce β-lactamases and, therefore, are resistant to ampicillin. These β-lactamase–producing strains are sensitive to the extended-spectrum cephalosporins.

Based on the substantial rate of resistance of *S. pneumoniae* to β-lactam drugs, vancomycin (60 mg/kg/24 hr, given every 6 hr) is recommended as part of initial empirical therapy. Because of the efficacy of third-generation cephalosporins in the therapy of meningitis caused by sensitive *S. pneumoniae, N. meningitidis,* and *H. influenzae* type b, cefotaxime (300 mg/kg/24 hr, given every 6 hr) or ceftriaxone (100 mg/kg/24 hr administered once per day or 50 mg/kg/dose, given every 12 hr) should also be used in initial empirical therapy. Patients allergic to β-lactam antibiotics and >1 mo of age can be treated with chloramphenicol, 100 mg/kg/24 hr, given every 6 hr. Another option for patients with allergy to β-lactam antibiotics is a combination of vancomycin and rifampin. Alternatively, patients can be desensitized to the antibiotic (see Chapter 152).

If *L. monocytogenes* infection is suspected, as in young infants or those with a T-lymphocyte deficiency, ampicillin (200 mg/kg/24 hr, given every 6 hr) also should also be given because cephalosporins are inactive against *L. monocytogenes.* Intravenous trimethoprim-sulfamethoxazole is an alternative treatment for *L. monocytogenes.*

If a patient is immunocompromised and Gram-negative bacterial meningitis is suspected, initial therapy might include ceftazidime and an aminoglycoside or meropenem.

DURATION OF ANTIBIOTIC THERAPY

Therapy for uncomplicated penicillin-sensitive *S. pneumoniae* meningitis should be for 10-14 days with a third-generation cephalosporin or intravenous penicillin (400,000 units/kg/24 hr, given every 4-6 hr). If the isolate is resistant to penicillin and the third-generation cephalosporin, therapy should be completed with vancomycin. Intravenous penicillin (300,000 units/kg/24 hr) for 5-7 days is the treatment of choice for uncomplicated *N. meningitidis* meningitis. Uncomplicated *H. influenzae* type b meningitis should be treated for 7-10 days. Patients who receive intravenous or oral antibiotics before LP and who do not have an identifiable pathogen, but do have evidence of an acute bacterial infection on the basis of their CSF profile, should continue to receive therapy with ceftriaxone or cefotaxime for 7-10 days. If focal signs are present or the child does not respond to treatment, a parameningeal focus may be present and a CT or MRI scan should be performed.

A routine repeat LP is not indicated in all patients with uncomplicated meningitis caused by antibiotic-sensitive *S. pneumoniae, N. meningitidis,* or *H. influenzae* type b. Repeat examination of CSF is indicated in some neonates, in all patients with Gram-negative bacillary meningitis, or in infection caused by a β-lactam–resistant *S. pneumoniae.* The CSF should be sterile within 24-48 hr of initiation of appropriate antibiotic therapy.

Table 603-2 Clinical Conditions and Infectious Agents Associated with Aseptic Meningitis

VIRUSES
Enteroviruses (coxsackievirus, echovirus, poliovirus, enterovirus)
Arboviruses: Eastern equine, Western equine, Venezuelan equine, St. Louis encephalitis, Powassan and California encephalitis, West Nile virus, Colorado tick fever
Parechovirus
Herpes simplex (types 1, 2)
Human herpesvirus type 6
Varicella-zoster virus
Epstein-Barr virus
Parvovirus B19
Cytomegalovirus
Adenovirus
Variola (smallpox)
Measles
Mumps
Rubella
Influenza A and B
Parainfluenza
Rhinovirus
Rabies
Lymphocytic choriomeningitis
Rotaviruses
Coronaviruses
Human immunodeficiency virus type 1

BACTERIA
Mycobacterium tuberculosis (early and late)
Leptospira species (leptospirosis)
Treponema pallidum (syphilis)
Borrelia species (relapsing fever)
Borrelia burgdorferi (Lyme disease)
Nocardia species (nocardiosis)
Brucella species
Bartonella species (cat-scratch disease)
Rickettsia rickettsii (Rocky Mountain spotted fever)
Rickettsia prowazekii (typhus)
Ehrlichia canis
Coxiella burnetii
Mycoplasma pneumoniae
Mycoplasma hominis
Chlamydia trachomatis
Chlamydia psittaci
Chlamydia pneumoniae
Partially treated bacterial meningitis

BACTERIAL PARAMENINGEAL FOCUS
Sinusitis
Mastoiditis
Brain abscess
Subdural-epidural empyema
Cranial osteomyelitis

FUNGI
Coccidioides immitis (coccidioidomycosis)
Blastomyces dermatitidis (blastomycosis)
Cryptococcus neoformans (cryptococcosis)
Histoplasma capsulatum (histoplasmosis)
Candida species
Other fungi *(Alternaria, Aspergillus, Cephalosporium, Cladosporium, Drechslera hawaiiensis, Paracoccidioides brasiliensis, Petriellidium boydii, Sporotrichum schenckii, Ustilago* spp.*, Zygomycetes)*

PARASITES (EOSINOPHILIC)
Angiostrongylus cantonensis
Gnathostoma spinigerum
Baylisascaris procyonis
Strongyloides stercoralis
Trichinella spiralis
Toxocara canis
Taenia solium (cysticercosis)
Paragonimus westermani
Schistosoma spp.
Fasciola spp.

PARASITES (NONEOSINOPHILIC)
Toxoplasma gondii (toxoplasmosis)
Acanthamoeba spp.
Naegleria fowleri
Malaria

POSTINFECTIOUS
Vaccines: rabies, influenza, measles, poliovirus
Demyelinating or allergic encephalitis

SYSTEMIC OR IMMUNOLOGICALLY MEDIATED
Acute Disseminated Encephalomyelitis (ADEM)
Autoimmune Encephalitis
Bacterial endocarditis
Kawasaki disease
Systemic lupus erythematosus
Vasculitis, including polyarteritis nodosa
Sjögren syndrome
Mixed connective tissue disease
Rheumatoid arthritis
Behçet syndrome
Wegener granulomatosis
Lymphomatoid granulomatosis
Granulomatous arteritis
Sarcoidosis
Familial Mediterranean fever
Vogt-Koyanagi-Harada syndrome

MALIGNANCY
Leukemia
Lymphoma
Metastatic carcinoma
Central nervous system tumor (e.g., craniopharyngioma, glioma, ependymoma, astrocytoma, medulloblastoma, teratoma)

DRUGS
Intrathecal infections (contrast media, serum, antibiotics, antineoplastic agents)
Nonsteroidal antiinflammatory agents
OKT3 monoclonal antibodies
Carbamazepine
Azathioprine
Intravenous immune globulins
Antibiotics (trimethoprim-sulfamethoxazole, sulfasalazine, ciprofloxacin, isoniazid)

MISCELLANEOUS
Heavy metal poisoning (lead, arsenic)
Foreign bodies (shunt, reservoir)
Subarachnoid hemorrhage
Postictal state
Postmigraine state
Mollaret syndrome (recurrent)
Intraventricular hemorrhage (neonate)
Familial hemophagocytic syndrome
Postneurosurgery
Dermoid–epidermoid cyst
Headache, neurologic deficits
CSF lymphocytosis (syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis [HaNDL])

Compiled from Cherry JD: Aseptic meningitis and viral meningitis. In Feigin RD, Cherry JD, editors: *Textbook of pediatric infectious diseases*, ed 4, Philadelphia, 1998, WB Saunders, p. 450; Davis LE: Aseptic and viral meningitis. In Long SS, Pickering LK, Prober CG, editors: *Principles and practice of pediatric infectious disease*, New York, 1997, Churchill Livingstone, p. 329; and Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis therapy*, ed 2, Philadelphia, 2004, Elsevier, p. 961.

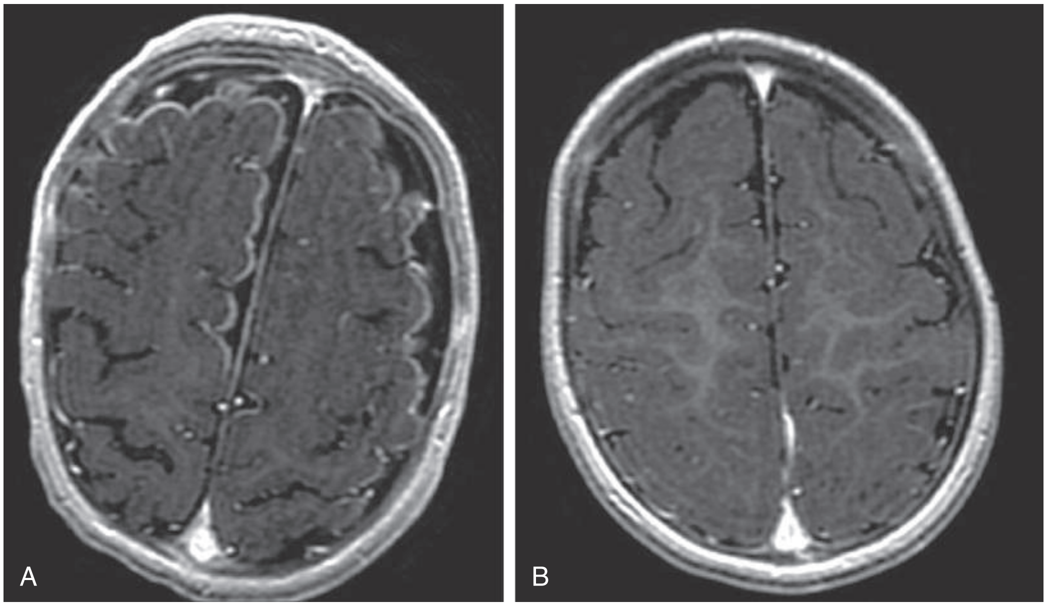

Figure 603-1 Cerebral MRI. Three-dimensional T1 sequence with fast-spoiled gradient-echo gadolinium injection. **A,** Day 11 following meningococcal infection. **B,** Day 9 following meningococcal infection. *(From Toubiana J, Heilbronner C, Gitiaux C, et al: Pachymeningitis after meningococcal infection.* Lancet *381:1596–1597, 2013.)*

Meningitis caused by *Escherichia coli* or *P. aeruginosa* requires therapy with a third-generation cephalosporin active against the isolate in vitro. Most isolates of *E. coli* are sensitive to cefotaxime or ceftriaxone, and most isolates of *P. aeruginosa* are sensitive to ceftazidime. Gram-negative bacillary meningitis should be treated for 3 wk or for at least 2 wk after CSF sterilization, which may occur after 2-10 days of treatment.

Side effects of antibiotic therapy of meningitis include phlebitis, drug fever, rash, emesis, oral candidiasis, and diarrhea. Ceftriaxone may cause reversible gallbladder pseudolithiasis, detectable by abdominal ultrasonography. This is usually asymptomatic but may be associated with emesis and upper right quadrant pain.

Corticosteroids

Rapid killing of bacteria in the CSF effectively sterilizes the meningeal infection but releases toxic cell products after cell lysis (cell wall endotoxin) that precipitate the cytokine-mediated inflammatory cascade. The resultant edema formation and neutrophilic infiltration may produce additional neurologic injury with worsening of CNS signs and symptoms. Therefore, agents that limit production of inflammatory mediators may be of benefit to patients with bacterial meningitis.

Data support the use of intravenous dexamethasone, 0.15 mg/kg/dose given every 6 hr for 2 days, in the treatment of children older than 6 wk with acute bacterial meningitis caused by *H. influenzae* type b. Among children with meningitis caused by *H. influenzae* type b, corticosteroid recipients have a shorter duration of fever, lower CSF protein and lactate levels, and a reduction in sensorineural hearing loss. Data in children regarding benefits, if any, of corticosteroids in the treatment of meningitis caused by other bacteria are inconclusive. Early steroid treatment of adults with bacterial meningitis, especially those with pneumococcal meningitis, results in improved outcome.

Corticosteroids appear to have maximum benefit if given 1-2 hr before antibiotics are initiated. They also may be effective if given concurrently with or soon after the first dose of antibiotics. Complications of corticosteroids include gastrointestinal bleeding, hypertension, hyperglycemia, leukocytosis, and rebound fever after the last dose.

Supportive Care

Repeated medical and neurologic assessments of patients with bacterial meningitis are essential to identify early signs of cardiovascular, CNS, and metabolic complications. Pulse rate, blood pressure, and respiratory rate should be monitored frequently. Neurologic assessment, including pupillary reflexes, level of consciousness, motor strength, cranial nerve signs, and evaluation for seizures, should be made frequently in the 1st 72 hr, when the risk of neurologic complications is greatest. Important laboratory studies include an assessment of blood urea nitrogen; serum sodium, chloride, potassium, and bicarbonate levels; urine output and specific gravity; complete blood and platelet counts; and, in the presence of petechiae, purpura, or abnormal bleeding, measures of coagulation function (fibrinogen, prothrombin, and partial thromboplastin times).

Patients should initially receive nothing by mouth. If a patient is judged to be normovolemic, with normal blood pressure, intravenous fluid administration should be restricted to one-half to two-thirds of maintenance, or 800-1,000 mL/m^2/24 hr, until it can be established that increased ICP or SIADH is not present. Fluid administration may be returned to normal (1,500-1,700 mL/m^2/24 hr) when serum sodium levels are normal. Fluid restriction is not appropriate in the presence of systemic hypotension because reduced blood pressure may result in reduced cerebral perfusion pressure and CNS ischemia. Therefore, shock must be treated aggressively to prevent brain and other organ dysfunction (acute tubular necrosis, acute respiratory distress syndrome). Patients with shock, a markedly elevated ICP, coma, and refractory seizures require intensive monitoring with central arterial and venous access and frequent vital signs, necessitating admission to a pediatric intensive care unit. Patients with septic shock may require fluid resuscitation and therapy with vasoactive agents such as dopamine and epinephrine. The goal of such therapy in patients with meningitis is to avoid excessive increases in ICP without compromising blood flow and oxygen delivery to vital organs.

Neurologic complications include increased ICP with subsequent herniation, seizures, and an enlarging head circumference because of a subdural effusion or hydrocephalus. Signs of increased ICP should be treated emergently with endotracheal intubation and hyperventilation (to maintain the pCO_2 at approximately 25 mm Hg). In addition, intravenous furosemide (Lasix, 1 mg/kg) and mannitol (0.5-1.0 g/kg) osmotherapy may reduce ICP (see Chapter 68). Furosemide reduces brain swelling by venodilation and diuresis without increasing intracranial blood volume, whereas mannitol produces an osmolar gradient between the brain and plasma, thus shifting fluid from the CNS to the plasma, with subsequent excretion during an osmotic diuresis. Another approach to treating reductions of cerebral perfusion pressure caused by elevations of intracranial pressure is to increase systemic blood

Table 603-3 Classification of Encephalitis by Cause and Source

I. INFECTIONS: VIRAL
- A. Spread: person to person only
  1. Mumps: frequent in an unimmunized population; often mild
  2. Measles: may have serious sequelae
  3. Enteroviruses: frequent at all ages; more serious in newborns
  4. Parechovirus
  5. Rubella: uncommon; sequelae rare except in congenital rubella
  6. Herpesvirus group
     - a. Herpes simplex (types 1 and 2, possibly 6): relatively common; sequelae frequent; devastating in newborns
     - b. Varicella-zoster virus: uncommon; serious sequelae not rare
     - c. Cytomegalovirus, congenital or acquired: may have delayed sequelae in congenital type
     - d. Epstein-Barr virus (infectious mononucleosis): not common
  7. Pox group
     - a. Vaccinia and variola: uncommon, but serious CNS damage occurs
  8. Parvovirus (erythema infectiosum): not common
  9. Influenzas A and B
  10. Adenovirus
  11. Other: reoviruses, respiratory syncytial, parainfluenza, hepatitis B
- B. Arthropod-borne agents
- C. Arboviruses: spread to humans by mosquitoes or ticks; seasonal epidemics depend on ecology of the insect vector; the following occur in the United States:

Eastern equine	California
Western equine	Powassan
Venezuelan equine	Dengue
St. Louis	Colorado tick fever
West Nile	

- D. Spread by warm-blooded mammals
  1. Rabies: saliva of many domestic and wild mammalian species
  2. Herpesvirus simiae ("B" virus): monkeys' saliva
  3. Lymphocytic choriomeningitis: rodents' excreta

II. INFECTIONS: NONVIRAL
- A. Rickettsial: in Rocky Mountain spotted fever and typhus; encephalitic component from cerebral vasculitis
- B. *Mycoplasma pneumoniae:* interval of some days between respiratory and CNS symptoms
- C. Bacterial: tuberculous and other bacterial meningitis; often has encephalitic component
- D. Spirochetal: syphilis, congenital or acquired; leptospirosis; Lyme disease
- E. Cat-scratch disease
- F. Fungal: immunologically compromised patients at special risk: cryptococcosis; histoplasmosis; aspergillosis; mucormycosis; candidosis; coccidioidomycosis
- G. Protozoal: *Plasmodium*, *Trypanosoma*, *Naegleria*, and *Acanthamoeba* spp.; Toxoplasma gondii
- H. Metazoal: trichinosis; echinococcosis; cysticercosis; schistosomiasis

III. PARAINFECTIOUS: POSTINFECTIOUS, ALLERGIC, AUTOIMMUNE

Patients in whom an infectious agent or 1 of its components plays a contributory role in etiology, but the intact infectious agent is not isolated in vitro from the nervous system; it is postulated that in this group, the influence of cell-mediated antigen–antibody complexes plus complement is especially important in producing the observed tissue damage
- A. Associated with specific diseases (these agents may also cause direct CNS damage; see I and II)
  - Measles
  - Rickettsial infections
  - Rubella
  - Influenzas A and B
  - Mumps
  - Varicella-zoster
  - M. *pneumoniae*
- B. Associated with vaccines
  - Rabies
  - Measles
  - Vaccinia
  - Yellow fever
- C. Autoimmune encephalitis
- D. Acute disseminated encephalomyelitis (ADEM)
  - Paraneoplastic
  - Idiopathic

IV. HUMAN SLOW-VIRUS DISEASES

Accumulating evidence that viruses frequently acquired earlier in life, not necessarily with detectable acute illness, participate in later chronic neurologic disease (similar events also known to occur in animals)
- A. Subacute sclerosing panencephalitis; measles; rubella?
- B. Creutzfeldt-Jakob disease (spongiform encephalopathy)
- C. Progressive multifocal leukoencephalopathy
- D. Kuru (Fore tribe in New Guinea only)
- E. Human immunodeficiency virus

V. UNKNOWN: COMPLEX GROUP

This group constitutes more than two-thirds of the cases of encephalitis reported to the Centers for Disease Control and Prevention, Atlanta, Georgia; the yearly epidemic curve of these undiagnosed cases suggests that the majority are probably caused by enteroviruses and/or arboviruses.

There is also a miscellaneous group that is based on clinical criteria: Reye syndrome is 1 current example; others include the extinct von Economo encephalitis (epidemic during 1918-1928); myoclonic encephalopathy of infancy; retinomeningoencephalitis with papilledema and retinal hemorrhage; recurrent encephalomyelitis (? allergic or autoimmune); pseudotumor cerebri; and epidemic neuromyasthenia (Iceland disease).

An encephalitic clinical pattern may follow ingestion or absorption of a number of known and unknown toxic substances; these include ingestion of lead and mercury, and percutaneous absorption of hexachlorophene as a skin disinfectant and gamma benzene hexachloride as a scabicide.

CNS, central nervous system.

Modified from Behrman RE, editor: Nelson textbook of pediatrics, ed 14, Philadelphia, 1992, WB Saunders, p. 667. From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, Elsevier, p. 967.

pressure using fluids (normal saline) and vasopressor agents (dopamine, norepinephrine). This method reduces the risk of systemic hypotension and may improve survival and reduce disability.

Seizures are common during the course of bacterial meningitis. Immediate therapy for seizures includes intravenous diazepam (0.1-0.2 mg/kg/dose) or lorazepam (0.05-0.10 mg/kg/dose), and careful attention paid to the risk of respiratory suppression. Serum glucose, calcium, and sodium levels should be monitored. After immediate management of seizures, patients should receive phenytoin (15-20 mg/kg loading dose, 5 mg/kg/24 hr maintenance) to reduce the likelihood of recurrence. Phenytoin is preferred to phenobarbital because it produces less CNS depression and permits assessment of a patient's level of consciousness. Serum phenytoin levels should be monitored to maintain them in the therapeutic range (10-20 µg/mL).

COMPLICATIONS

During the treatment of meningitis, acute CNS complications can include seizures, increased ICP, cranial nerve palsies, stroke,

Table 603-4 Antibiotics Used for the Treatment of Bacterial Meningitis*

DRUGS	Neonates 0-7 DAYS	Neonates 8-28 DAYS	INFANTS AND CHILDREN
Amikacin[†‡]	15-20 divided q12h	30 divided q8h	20-30 divided q8h
Ampicillin	150 divided q8h	200 divided q6h or q8h	300 divided q6h
Cefotaxime	100-150 divided q8h or q12h	150-200 divided q6h or q8h	225-300 divided q6h or q8h
Ceftriaxone[§]	—	—	100 divided q12h or q24h
Ceftazidime	100-150 divided q8h or q12h	150 divided q8h	150 divided q8h
Gentamicin[†‡]	5 divided q12h	7.5 divided q8h	7.5 divided q8h
Meropenem	—	—	120 divided q8h
Nafcillin	75 divided q8h or q12h	100-150 divided q6h or q8h	200 divided q6h
Penicillin G	150,000 divided q8h or q12h	200,000 divided q6h or q8h	300,000 divided q4h or q6h
Rifampin	—	10-20 divided q12h	10-20 divided q12h or q24h
Tobramycin[†‡]	5 divided q12h	7.5 divided q8h	7.5 divided q8h
Vancomycin[†‡]	20-30 divided q8h or q12h	30-45 divided q6h or q8h	60 divided q6h

*Dosages in mg/kg (units/kg for penicillin G) per day.
[†]Smaller doses and longer dosing intervals, especially for aminoglycosides and vancomycin for very-low-birthweight neonates, may be advisable.
[‡]Monitoring of serum levels is recommended to ensure safe and therapeutic values.
[§]Use in neonates is not recommended because of inadequate experience in neonatal meningitis.
Adapted from Tunkel AR, Hartman BJ, Kaplan SL, et al: Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 39(9):1267–1284, 2004, Table 6.

cerebral or cerebellar herniation, and thrombosis of the dural venous sinuses.

Collections of fluid in the subdural space develop in 10-30% of patients with meningitis and are asymptomatic in 85-90% of patients. **Subdural effusions** are especially common in infants. Symptomatic subdural effusions may result in a bulging fontanel, diastasis of sutures, enlarging head circumference, emesis, seizures, fever, and abnormal results of cranial transillumination. CT or MRI scanning confirms the presence of a subdural effusion. In the presence of increased ICP or a depressed level of consciousness, symptomatic subdural effusion should be treated by aspiration through the open fontanel (see Chapters 68 and 590). Fever alone is not an indication for aspiration.

SIADH occurs in some patients with meningitis, resulting in hyponatremia and reduced serum osmolality. This may exacerbate cerebral edema or result in hyponatremic seizures (see Chapter 55).

Fever associated with bacterial meningitis usually resolves within 5-7 days of the onset of therapy. **Prolonged fever** (>10 days) is noted in approximately 10% of patients. Prolonged fever is usually caused by intercurrent viral infection, nosocomial or secondary bacterial infection, thrombophlebitis, or drug reaction. Secondary fever refers to the recrudescence of elevated temperature after an afebrile interval. Nosocomial infections are especially important to consider in the evaluation of these patients. Pericarditis or arthritis may occur in patients being treated for meningitis, especially that caused by *N. meningitidis*. Involvement of these sites may result either from bacterial dissemination or from immune complex deposition. In general, infectious pericarditis or arthritis occurs earlier in the course of treatment than does immune-mediated disease.

Thrombocytosis, eosinophilia, and anemia may develop during therapy for meningitis. Anemia may be a result of hemolysis or bone marrow suppression. Disseminated intravascular coagulation is most often associated with the rapidly progressive pattern of presentation and is noted most commonly in patients with shock and purpura. The combination of endotoxemia and severe hypotension initiates the coagulation cascade; the coexistence of ongoing thrombosis may produce symmetric peripheral gangrene.

PROGNOSIS

Appropriate antibiotic therapy and supportive care have reduced the mortality of bacterial meningitis after the neonatal period to <10%. The highest mortality rates are observed with pneumococcal meningitis. Severe neurodevelopmental sequelae may occur in 10-20% of patients recovering from bacterial meningitis, and as many as 50% have some, albeit subtle, neurobehavioral morbidity. The prognosis is poorest among infants younger than 6 mo and in those with high concentrations of bacteria/bacterial products in their CSF. Those with seizures occurring more than 4 days into therapy or with coma or focal neurologic signs on presentation have an increased risk of long-term sequelae. There does not appear to be a correlation between duration of symptoms before diagnosis of meningitis and outcome.

The most common neurologic sequelae include hearing loss, cognitive impairment, recurrent seizures, delay in acquisition of language, visual impairment, and behavioral problems. **Sensorineural hearing** loss is the most common sequela of bacterial meningitis and, usually, is already present at the time of initial presentation. It is a result of cochlear infection and occurs in as many as 30% of patients with pneumococcal meningitis, 10% with meningococcal, and 5-20% of those with *H. influenzae* type b meningitis. Hearing loss may also be caused by direct inflammation of the auditory nerve. All patients with bacterial meningitis should undergo careful audiologic assessment before or soon after discharge from the hospital. Frequent reassessment on an outpatient basis is indicated for patients who have a hearing deficit.

PREVENTION

Vaccination and antibiotic prophylaxis of susceptible at-risk contacts represent the 2 available means of reducing the likelihood of bacterial meningitis. The availability and application of each of these approaches depend on the specific infecting bacteria.

Neisseria meningitidis

Chemoprophylaxis is recommended for all close contacts of patients with meningococcal meningitis regardless of age or immunization status. Close contacts should be treated with rifampin 10 mg/kg/dose every 12 hr (maximum dose of 600 mg) for 2 days as soon as possible after identification of a case of suspected meningococcal meningitis or sepsis. Close contacts include household, daycare center, and nursery school contacts, and healthcare workers who have direct exposure to oral secretions (mouth-to-mouth resuscitation, suctioning, intubation). Exposed contacts should be treated immediately on suspicion of

infection in the index patient; bacteriologic confirmation of infection should not be awaited. In addition, all contacts should be educated about the early signs of meningococcal disease and the need to seek prompt medical attention if these signs develop.

Two quadrivalent (A, C, Y, W-135), conjugated vaccines (MCV-4; Menactra and Menveo) are licensed by the FDA. The Advisory Committee on Immunization Practices (ACIP) to the CDC recommends routine administration of this vaccine to 11-12 yr old adolescents. Menactra is licensed for use in infants older than 9 mo of age, and Menveo for use in children older than 2 yr of age. There is also a bivalent meningococcal polysaccharide protein conjugate vaccine that provides protection against serogroups C and Y along with *H. influenzae* type b. This vaccine is licensed for use in children ages 6 wk through 18 mo. High-risk patients include those with anatomic or functional asplenia or deficiencies of terminal complement proteins. Use of meningococcal vaccine should be considered for college freshmen, especially those who live in dormitories, because of an observed increased risk of invasive meningococcal infections compared to the risk in non–college-attending, age-matched controls.

Haemophilus influenzae Type B

Rifampin prophylaxis should be given to all household contacts of patients with invasive disease caused by *H. influenzae* type b, if any close family member younger than 48 mo has not been fully immunized or if an immunocompromised person, of any age, resides in the household. A household contact is one who lives in the residence of the index case or who has spent a minimum of 4 hr with the index case for at least 5 of the 7 days preceding the patient's hospitalization. Family members should receive rifampin prophylaxis immediately after the diagnosis is suspected in the index case because >50% of secondary family cases occur in the 1st wk after the index patient has been hospitalized.

The dose of rifampin is 20 mg/kg/24 hr (maximum dose of 600 mg) given once each day for 4 days. Rifampin colors the urine and perspiration red-orange, stains contact lenses, and reduces the serum concentrations of some drugs, including oral contraceptives. Rifampin is contraindicated during pregnancy.

The most striking advance in the prevention of childhood bacterial meningitis followed the development and licensure of conjugated vaccines against *H. influenzae* type b. Three conjugate vaccines are licensed in the United States. Although each vaccine elicits different profiles of antibody response in infants immunized at 2-6 mo of age, all result in protective levels of antibody with an efficacy rate against invasive infections after primary series at 93%. Efficacy is not as consistent in Native American populations, a group recognized as having an especially high incidence of disease. All children should be immunized with *H. influenzae* type b conjugate vaccine beginning at 2 mo of age (see Chapter 172).

Streptococcus pneumoniae

Routine administration of conjugate vaccine against *S. pneumoniae* is recommended for children younger than 5 yr of age. The initial dose is given at about 2 mo of age. Children who are at high risk of invasive pneumococcal infections, including those with functional or anatomic asplenia and those with underlying immunodeficiency (such as infection with HIV, primary immunodeficiency, and those receiving immunosuppressive therapy) should also receive the vaccine.

Bibliography is available at Expert Consult.

603.2 Viral Meningoencephalitis

Charles G. Prober and Nivedita S. Srinivas

Viral meningoencephalitis is an acute inflammatory process involving the meninges and, to a variable degree, brain tissue. These infections are relatively common and may be caused by a number of different agents. The CSF is characterized by pleocytosis and the absence of microorganisms on Gram stain and routine bacterial culture. In most instances, the infections are self-limited. In some cases, substantial morbidity and mortality occur.

ETIOLOGY

Enteroviruses are the most common cause of viral meningoencephalitis. As of 2014, more than 70 serotypes of these small RNA viruses have been identified. The severity of infection caused by enteroviruses ranges from mild, self-limited illness with primarily meningeal involvement to severe encephalitis resulting in death or significant sequelae. Human enterovirus 68 has been associated with neurologic symptoms including flaccid paralysis. **Parechoviruses** may be an important cause of aseptic meningitis or encephalitis in infants. The clinical manifestations are similar to that of the enteroviruses with the exception of more severe MRI lesions of the cerebral cortex and at times an absence of a CSF pleocytosis.

Arboviruses are arthropod-borne agents, responsible for some cases of meningoencephalitis during summer months. Mosquitoes and ticks are the most common vectors, spreading disease to humans and other vertebrates, such as horses, after biting infected birds or small animals. Encephalitis in horses ("blind staggers") may be the first indication of an incipient epidemic. Although rural exposure is most common, urban and suburban outbreaks also are frequent. The most common arboviruses responsible for CNS infection in the United States are West Nile virus (WNV), La Crosse, Powassan, and St. Louis encephalitis viruses (see Chapter 267). WNV made its appearance in the Western hemisphere in 1999. It has gradually made its way from the east to the west coast over successive summers. Cumulatively, from 1999 through 2008, a total of 47 states reported roughly 30,000 human infections caused by WNV. WNV may also be transmitted by blood transfusion, organ transplantation, or vertically across the placenta. Most children with WNV are either asymptomatic or have a nonspecific viral-like illness. Approximately 1% develop CNS disease; adults are more severely affected than children.

Several members of the **herpes family** of viruses can cause meningoencephalitis. Herpes simplex virus (HSV) type 1 is an important cause of severe, sporadic encephalitis in children and adults. Brain involvement usually is focal; progression to coma and death occurs in 70% of cases without antiviral therapy. Severe encephalitis with diffuse brain involvement is caused by HSV type 2 in neonates who usually contract the virus from their mothers at delivery. A mild transient form of meningoencephalitis may accompany genital herpes infection in sexually active adolescents; most of these infections are caused by HSV type 2. Varicella-zoster virus may cause CNS infection in close temporal relationship with chickenpox. The most common manifestation of CNS involvement is cerebellar ataxia, and the most severe is acute encephalitis. After primary infection, varicella-zoster virus becomes latent in spinal and cranial nerve roots and ganglia, expressing itself later as herpes zoster, sometimes with accompanying mild meningoencephalitis. Cytomegalovirus infection of the CNS may be part of congenital infection or disseminated disease in immunocompromised hosts, but it does not cause meningoencephalitis in normal infants and children. Epstein-Barr virus is associated with myriad CNS syndromes (see Chapter 254). Human herpes virus 6 can cause encephalitis, especially among immunocompromised hosts.

Mumps is a common pathogen in regions where mumps vaccine is not widely used. Mumps meningoencephalitis is mild, but deafness from damage of the 8th cranial nerve may be a sequela. Meningoencephalitis is caused occasionally by respiratory viruses (adenovirus, influenza virus, parainfluenza virus), rubeola, rubella, or rabies; it may follow live virus vaccinations against polio, measles, mumps, or rubella.

EPIDEMIOLOGY

The epidemiologic pattern of viral meningoencephalitis is primarily determined by the prevalence of enteroviruses, the most common etiology. Infection with enteroviruses is spread directly from person

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to person, with a usual incubation period of 4-6 days. Most cases in temperate climates occur in the summer and fall. Epidemiologic considerations in aseptic meningitis due to agents other than enteroviruses also include season, geography (travel), climatic conditions, animal exposures, mosquito or tick bites, and factors related to the specific pathogen.

PATHOGENESIS AND PATHOLOGY

Neurologic damage is caused by direct invasion and destruction of neural tissues by actively multiplying viruses or by a host reaction to viral antigens. Tissue sections of the brain generally are characterized by meningeal congestion and mononuclear infiltration, perivascular cuffs of lymphocytes and plasma cells, some perivascular tissue necrosis with myelin breakdown, and neuronal disruption in various stages, including, ultimately, neuronophagia and endothelial proliferation or necrosis. A marked degree of demyelination with preservation of neurons and their axons is considered to represent predominantly "postinfectious" or an autoimmune encephalitis.

The cerebral cortex, especially the temporal lobe, is often severely affected by HSV; the arboviruses tend to affect the entire brain; rabies has a predilection for the basal structures. Involvement of the spinal cord, nerve roots, and peripheral nerves is variable.

CLINICAL MANIFESTATIONS

The progression and severity of disease are determined by the relative degree of meningeal and parenchymal involvement, which, in part, is determined by the specific etiology. The clinical course resulting from infection with the same pathogen varies widely. Some children may appear to be mildly affected initially, only to lapse into coma and die suddenly. In others, the illness may be ushered in by high fever, violent convulsions interspersed with bizarre movements, and hallucinations alternating with brief periods of clarity, followed by complete recovery.

The onset of illness is generally acute, although CNS signs and symptoms are often preceded by a nonspecific febrile illness of a few days' duration. The presenting manifestations in older children are headache and hyperesthesia, and in infants, irritability and lethargy. Headache is most often frontal or generalized; adolescents frequently complain of retrobulbar pain. Fever, nausea and vomiting, photophobia, and pain in the neck, back, and legs are common. As body temperature increases, there may be mental dullness, progressing to stupor in combination with bizarre movements and convulsions. Focal neurologic signs may be stationary, progressive, or fluctuating. WNV and nonpolio enteroviruses may cause anterior horn cell injury and a flaccid paralysis. For those reported with WNV, encephalitis is more common than aseptic meningitis; acute flaccid paralysis may be noted in approximately 5% of patients. Nonetheless, many patients have a nonspecific febrile illness "West Nile fever" and may never seek medical attention. Loss of bowel and bladder control and unprovoked emotional outbursts may occur.

Exanthems often precede or accompany the CNS signs, especially with echoviruses, coxsackieviruses, varicella-zoster virus, measles, rubella, and, occasionally, WNV. Examination often reveals nuchal rigidity without significant localizing neurologic changes, at least at the onset.

Specific forms or complicating manifestations of CNS viral infection include Guillain-Barré syndrome, transverse myelitis, hemiplegia, and cerebellar ataxia.

DIAGNOSIS

The diagnosis of viral encephalitis is usually made on the basis of the clinical presentation of nonspecific prodrome followed by progressive CNS symptoms. The diagnosis is supported by examination of the CSF, which usually shows a mild mononuclear predominance (see Table 603-1). Other tests of potential value in the evaluation of patients with suspected viral meningoencephalitis include an electroencephalogram (EEG) and neuroimaging studies. The EEG typically shows diffuse slow-wave activity, usually without focal changes. Neuroimaging studies (CT or MRI) may show swelling of the brain parenchyma. Focal seizures or focal findings on EEG, CT, or MRI, especially involving the temporal lobes, suggest HSV encephalitis.

Differential Diagnosis

A number of clinical conditions that cause CNS inflammation mimic viral meningoencephalitis (see Table 603-2). The most important group of alternative infectious agents to consider is bacteria. Most children with acute bacterial meningitis appear more critically ill than those with CNS viral infection. Parameningeal bacterial infections, such as brain abscess or subdural or epidural empyema, may have features similar to viral CNS infections. Infections caused by *M. tuberculosis, T. pallidum* (syphilis), *B. burgdorferi* (Lyme disease), and *Bartonella henselae,* the bacillus associated with cat scratch disease, tend to result in indolent courses. Analysis of CSF and appropriate serologic tests are necessary to differentiate these various pathogens.

Infections caused by fungi, rickettsiae, mycoplasma, protozoa, and other parasites may also need to be included in the differential diagnosis. Consideration of these agents usually arises as a result of accompanying symptoms, geographic locality of infection, or host immune factors.

Various noninfectious disorders may be associated with CNS inflammation and have manifestations overlapping with those associated with viral meningoencephalitis. Some of these disorders include malignancy, autoimmune diseases, intracranial hemorrhage, and exposure to certain drugs or toxins. Attention to history and other organ involvement usually allow elimination of these diagnostic possibilities. Autoimmune encephalitis owing to anti–*N*-methyl-D-aspartate receptor antibodies is an important cause of noninfectious encephalitis in children. Detection of these antibodies in the serum or CSF confirms this diagnosis. Acute disseminated encephalomyelitis may also initially be confused with encephalitis.

Laboratory Findings

The CSF contains from a few to several thousand cells per cubic millimeter. Early in the disease, the cells are often polymorphonuclear; later, mononuclear cells predominate. This change in cellular type is often demonstrated in CSF samples obtained as little as 8-12 hr apart. The protein concentration in CSF tends to be normal or slightly elevated, but concentrations may be very high if brain destruction is extensive, such as that accompanying HSV encephalitis. The glucose level is usually normal, although with certain viruses, for example, mumps, a substantial depression of CSF glucose concentrations may be observed. The CSF may be normal with parechovirus and in those who have encephalitis in the absence of meningeal involvement.

The success of isolating viruses from the CSF of children with viral meningoencephalitis is determined by the time in the clinical course that the specimen is obtained, the specific etiologic agent, whether the infection is a meningitic as opposed to a localized encephalitic process, and the skill of the diagnostic laboratory staff. Isolating a virus is most likely early in the illness, and the enteroviruses tend to be the easiest to isolate, although recovery of these agents from the CSF rarely exceeds 70%. To increase the likelihood of identifying the putative viral pathogen, specimens for culture should also be obtained from nasopharyngeal swabs, feces, and urine. Although isolating a virus from 1 or more of these sites does not prove causality, it is highly suggestive. *Detection of viral DNA or RNA by polymerase chain reaction is the test of choice in the diagnosis of CNS infection caused by HSV, parechovirus and enteroviruses, respectively.* CSF serology is the diagnostic test of choice for WNV.

A serum specimen should be obtained early in the course of illness and, if viral cultures are not diagnostic, again 2-3 wk later for serologic studies. Serologic methods are not practical for diagnosing CNS infections caused by the enteroviruses because there are too many serotypes. This approach may be useful, however, in confirming that a case is caused by a known circulating serotype. Serologic tests may also be of value in determining the etiology of nonenteroviral CNS infection, such as arboviral infection.

TREATMENT

With the exception of the use of acyclovir for HSV encephalitis (see Chapter 252), treatment of viral meningoencephalitis is supportive. Treatment of mild disease may require only symptomatic relief. Headache and hyperesthesia are treated with rest, non–aspirin-containing analgesics, and a reduction in room light, noise, and visitors. Acetaminophen is recommended for fever. Opioid agents and medications to reduce nausea may be useful, but if possible, their use in children should be minimized because they may induce misleading signs and symptoms. Intravenous fluids are occasionally necessary because of poor oral intake. More-severe disease may require hospitalization and intensive care.

It is important to monitor patients with severe encephalitis closely for convulsions, cerebral edema, inadequate respiratory exchange, disturbed fluid and electrolyte balance, aspiration and asphyxia, and cardiac or respiratory arrest of central origin. In patients with evidence of increased ICP, placement of a pressure transducer in the epidural space may be indicated. The risks of cardiac and respiratory failure or arrest are high with severe disease. All fluids, electrolytes, and medications are initially given parenterally. In prolonged states of coma, parenteral alimentation is indicated. SIADH is common in acute CNS disorders; monitoring of serum sodium concentrations is required for early detection (see Chapter 559). Normal blood levels of glucose, magnesium, and calcium must be maintained to minimize the likelihood of convulsions. If cerebral edema or seizures become evident, vigorous treatment should be instituted.

PROGNOSIS

Supportive and rehabilitative efforts are very important after patients recover from the acute phase of illness. Motor incoordination, convulsive disorders, total or partial deafness, and behavioral disturbances may follow viral CNS infections. Visual disturbances from chorioretinopathy and perceptual amblyopia may also occur. Special facilities and, at times, institutional placement may become necessary. Some sequelae of infection may be very subtle. Therefore, neurodevelopmental and audiologic evaluations should be part of the routine follow-up of children who have recovered from viral meningoencephalitis.

Most children completely recover from viral infections of the CNS, although the prognosis depends on the severity of the clinical illness, the specific causative organism, and the age of the child. If the clinical illness is severe and substantial parenchymal involvement is evident, the prognosis is poor, with potential deficits being intellectual, motor, psychiatric, epileptic, visual, or auditory in nature. Severe sequelae should also be anticipated in those with infection caused by HSV. Although some literature suggests that infants who contract viral meningoencephalitis have a poorer long-term outcome than older children, most other data refute this observation. Approximately 10% of children younger than 2 yr of age with enteroviral CNS infections suffer an acute complication such as seizures, increased ICP, or coma. Almost all have favorable long-term neurologic outcomes.

PREVENTION

Widespread use of effective viral vaccines for polio, measles, mumps, rubella, and varicella has almost eliminated CNS complications from these diseases in the United States. The availability of domestic animal vaccine programs against rabies has reduced the frequency of rabies encephalitis. Control of encephalitis caused by arboviruses has been less successful because specific vaccines for the arboviral diseases that occur in North America are not available. Control of insect vectors by suitable spraying methods and eradication of insect breeding sites, however, reduces the incidence of these infections. Furthermore, minimizing mosquito bites through the application of *N,N*-diethyl-3-methylbenzamide (DEET)-containing insect repellents on exposed skin and wearing long-sleeved shirts, long pants, and socks when outdoors, especially at dawn and dusk, reduces the risk of arboviral infection.

Bibliography is available at Expert Consult.

603.3 Eosinophilic Meningitis

Charles G. Prober and Nivedita S. Srinivas

Eosinophilic meningitis is defined as 10 or more eosinophils/mm^3 of CSF. The most common cause worldwide of eosinophilic pleocytosis is CNS infection with helminthic parasites. In countries such as the United States, where helminthic infestation is uncommon, however, the differential diagnosis of CSF eosinophilic pleocytosis is broad.

ETIOLOGY

Although any tissue-migrating helminth may cause eosinophilic meningitis, the most common cause is human infection with the rat lungworm, *Angiostrongylus cantonensis* (see Chapter 297). Other parasites that can cause eosinophilic meningitis include *Gnathostoma spinigerum* (dog and cat roundworm) (see Chapter 297), *Baylisascaris procyonis* (raccoon roundworm), *Ascaris lumbricoides* (human roundworm), *Trichinella spiralis, Toxocara canis, T. gondii, Paragonimus westermani, Echinococcus granulosus, Schistosoma japonicum, Onchocerca volvulus,* and *Taenia solium.* Eosinophilic meningitis may also occur as an unusual manifestation of more common viral, bacterial, or fungal infections of the CNS. Noninfectious causes of eosinophilic meningitis include multiple sclerosis, malignancy, hypereosinophilic syndrome, or a reaction to medications or a ventriculoperitoneal shunt.

EPIDEMIOLOGY

A. cantonensis is found in Southeast Asia, the South Pacific, Japan, Taiwan, Egypt, Ivory Coast, and Cuba. Infection is acquired by eating raw or undercooked freshwater snails, slugs, prawns, or crabs containing infectious 3rd-stage larvae. *Gnathostoma* infections are found in Japan, China, India, Bangladesh, and Southeast Asia. Gnathostomiasis is acquired by eating undercooked or raw fish, frog, bird, or snake meat.

CLINICAL MANIFESTATIONS

When eosinophilic meningitis results from helminthic infestation, patients become ill 1-3 wk after exposure. This reflects the transit time for parasites to migrate from the gastrointestinal tract to the CNS. Common concomitant findings include fever, peripheral eosinophilia, vomiting, abdominal pain, creeping skin eruptions, or pleurisy. Neurologic symptoms may include headache, meningismus, ataxia, cranial nerve palsies, and paresthesias. Paraparesis or incontinence can result from radiculitis or myelitis.

DIAGNOSIS

The presumptive diagnosis of helminth-induced eosinophilic meningitis is most often based on travel and exposure history in the presence of typical clinical and laboratory findings. Direct visualization of helminths in CSF is affected by the relatively low organism burden, resulting in limited diagnostic sensitivity. Serologic assays for helminthic infections are also of limited utility because they are not readily available commercially and there is substantial cross-reactivity between different helminth species.

TREATMENT

Treatment is supportive, because infection is self-limited and anthelmintic drugs do not appear to influence the outcome of infection. Analgesics should be given for headache and radiculitis, and CSF removal or shunting should be performed to relieve hydrocephalus, if present. Steroids may decrease the duration of headaches in adults with eosinophilic meningitis.

PROGNOSIS

The prognosis is good; 70% of patients improve sufficiently to leave the hospital in 1-2 wk. Mortality associated with eosinophilic meningitis is <1%.

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Chapter 604

Brain Abscess

Charles G. Prober and Roshni Mathew

Brain abscesses can occur in children of any age but are most common in children between 4 and 8 yr old and in neonates. The causes of brain abscess include embolization as a result of congenital heart disease with right-to-left shunts (especially tetralogy of Fallot), endocarditis, meningitis, chronic otitis media and mastoiditis, sinusitis, soft-tissue infection of the face or scalp, orbital cellulitis, dental infections, severe complicated pneumonia, penetrating head injuries, immunodeficiency states, and infection of ventriculoperitoneal shunts.

PATHOLOGY

Cerebral abscesses are evenly distributed between the 2 hemispheres, and 80% of cases are divided equally between the frontal, parietal, and temporal lobes. Brain abscesses in the occipital lobe, cerebellum, and brainstem account for approximately 20% of the cases. Most brain abscesses are single, but 30% are multiple and may involve more than 1 lobe. The pathogenesis is undetermined in 10-15% of cases. An abscess in the frontal lobe is often caused by extension from sinusitis or orbital cellulitis, whereas abscesses located in the temporal lobe or cerebellum are frequently associated with chronic otitis media and mastoiditis. Abscesses resulting from penetrating injuries tend to be singular and caused by *Staphylococcus aureus,* whereas those resulting from septic emboli, congenital heart disease, or meningitis often have several causal organisms.

Figure 604-1 **CT with contrast.** Note the large, wall-enhancing abscess in the left frontal lobe causing a shift of the brain to the right. The patient had no neurologic signs until just before the CT scan because the abscess is located in the frontal lobe, a "silent" area of the brain.

ETIOLOGY

The predominant organisms causing brain abscesses in children are aerobic and anaerobic streptococci (60-70% of the cases) with *Streptococcus milleri* gp (*Streptococcus anginosus, Streptococcus constellatus,* and *Streptococcus intermedius*) being increasingly isolated from surgically drained brain abscesses. Other important streptococci include group A and *B streptococci*, *Streptococcus pneumoniae,* and *Enterococcus faecalis.* Other bacteria isolated from brain abscesses include anaerobic organisms (Gram-positive cocci, *Bacteroides* spp., *Fusobacterium* spp., *Prevotella* spp., *Actinomyces* spp.) and Gram-negative aerobic bacilli (*Haemophilus aphrophilus, Haemophilus parainfluenzae, Haemophilus influenzae, Enterobacter, Escherichia coli, Proteus* spp.). *Citrobacter* is most common in neonates. One organism is cultured in 70% of abscesses, 2 in 20%, and 3 or more in 10% of cases. Abscesses associated with mucosal infections (sinusitis) frequently have anaerobic bacteria. Fungi *(Aspergillus, Candida)*, *Nocardia, Mycobacterium*, and *Listeria* spp. are more common in children with impaired host defenses.

CLINICAL MANIFESTATIONS

The early stages of cerebritis and abscess formation are associated with nonspecific symptoms, including low-grade fever, headache, and lethargy. The significance of these symptoms is generally not recognized, and an oral antibiotic is often prescribed with resultant transient relief. As the inflammatory process proceeds, vomiting, severe headache, seizures, papilledema, focal neurologic signs (hemiparesis), and coma may develop. A cerebellar abscess is characterized by nystagmus, ipsilateral ataxia and dysmetria, vomiting, and headache. If the abscess ruptures into the ventricular cavity, overwhelming shock and death usually ensue.

DIAGNOSIS

The peripheral white blood cell count can be normal or elevated, and the blood culture is positive in 10% of cases. Examination of the cerebrospinal fluid shows variable results; the white blood cells and protein may be minimally elevated or normal, and the glucose level may be low. Cerebrospinal fluid cultures are rarely positive; culture of pus from the neurosurgical drainage is the key to establishing a bacteriologic diagnosis. However, the culture can be sterile in a substantial number of cases and 16S bacterial ribosomal RNA polymerase chain reaction amplification and sequencing may be used to identify unculturable bacteria in brain abscesses. Because examination of the cerebrospinal fluid is seldom useful and a lumbar puncture may cause herniation of the cerebellar tonsils, the procedure should not be undertaken in a child suspected of having a brain abscess. The electroencephalogram shows corresponding focal slowing, and the radionuclide brain scan indicates an area of enhancement caused by disruption of the blood–brain barrier in more than 80% of cases. CT with contrast and MRI are the most reliable methods of demonstrating cerebritis and abscess formation (Fig. 604-1). MRI is the diagnostic test of choice. The CT findings of cerebritis are characterized by a parenchymal low-density lesion, and MRI T2-weighted images indicate increased signal intensity. An abscess cavity shows a ring-enhancing lesion by contrast CT, and the MRI also demonstrates an abscess capsule with gadolinium administration.

TREATMENT

The initial management of a brain abscess includes prompt diagnosis and institution of an antibiotic regimen that is based on the probable pathogenesis and the most likely organism. When the cause is unknown, the combination of vancomycin, a third-generation cephalosporin, and metronidazole is commonly used. The same regimen is initiated when otitis media, sinusitis, or mastoiditis is the likely cause. If there is a history of penetrating head injury, head trauma, or neurosurgery, vancomycin plus a third-generation cephalosporin is appropriate. When cyanotic congenital heart disease is the predisposing factor, ampicillin-sulbactam alone or a third-generation cephalosporin plus metronidazole may be used. Meropenem has good activity against Gram-negative bacilli, anaerobes, staphylococci, and streptococci,

including most antibiotic-resistant pneumococci, and may be used alone to replace the combination of metronidazole and a β-lactam in the previous regimens. Notably, meropenem does not provide activity against methicillin-resistant *S. aureus* and may have decreased activity against penicillin-resistant strains of *S. pneumoniae,* indicating that vancomycin should remain a part of the initial regimen when these organisms are suspected. Abscesses secondary to an infected ventriculoperitoneal shunt may be initially treated with vancomycin and ceftazidime. When *Citrobacter* meningitis (often in neonates) leads to abscess formation, a third-generation cephalosporin is used, typically in combination with an aminoglycoside. *Listeria monocytogenes* may cause a brain abscess in the neonate and if suspected, ampicillin should be added to the cephalosporin. In immunocompromised patients, broad-spectrum antibiotic coverage is used, and amphotericin B therapy should be considered.

A brain abscess can be treated with antibiotics without surgery if the abscess is <2 cm in diameter, the illness is of short duration (<2 wk), there are no signs of increased intracranial pressure, and the child is neurologically intact. If the decision is made to treat with antibiotics alone, the child should have follow-up neuroimaging studies to ensure the abscess is decreasing in size. An encapsulated abscess, particularly if the lesion is causing a mass effect or increased intracranial pressure, should be treated with a combination of antibiotics and aspiration. Surgical excision of an abscess is rarely required, because the procedure may be associated with greater morbidity compared with aspiration of a cavity. Surgery is indicated when the abscess is >2.5 cm in diameter, gas is present in the abscess, the lesion is multiloculated, the lesion is located in the posterior fossa, or a fungus is identified. Associated infectious processes, such as mastoiditis, sinusitis, or a periorbital abscess, may require surgical drainage. The duration of antibiotic therapy depends on the organism and response to treatment but is usually 4-6 wk.

PROGNOSIS

Mortality rates prior to 1980s ranged from 11-53%. More recent mortality rates accompanying wider use of CT and MRI, improved microbiologic techniques and prompt antibiotic and surgical management, range from 5-10%. Factors associated with high mortality rate at the time of admission include age younger than 1 yr, multiple abscesses and coma. Long-term sequelae occur in about one-third of the survivors and include hemiparesis, seizures, hydrocephalus, cranial nerve abnormalities, and behavior and learning problems.

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Chapter 605

Idiopathic Intracranial Hypertension/ Pseudotumor Cerebri

Misha L. Pless

Idiopathic intracranial hypertension, also known as pseudotumor cerebri, is a clinical syndrome that mimics brain tumors and is characterized by increased intracranial pressure ≥280 mm Hg in sedated or obese children; ≥250 mm Hg in nonobese, nonsedated children with a normal cerebrospinal fluid (CSF) cell count and protein content and normal to slightly decreased ventricular size, and normal ventricular anatomy and position documented by MRI. Papilledema is universally present in children old enough to have a closed fontanel (Fig. 605-1).

ETIOLOGY

Table 605-1 lists the many causes of pseudotumor cerebri. There are many explanations for the development of pseudotumor cerebri, including alterations in CSF absorption and production, subtle cerebral edema, abnormalities in vasomotor control and cerebral blood flow, and venous obstruction. The causes of pseudotumor are numerous and include metabolic disorders (galactosemia, hypoparathyroidism, pseudohypoparathyroidism, hypophosphatasia, prolonged corticosteroid therapy or rapid corticosteroid withdrawal, possibly growth hormone treatment, refeeding of a significantly malnourished child, hypervitaminosis A, severe vitamin A deficiency, Addison disease, obesity, menarche, oral contraceptives, and pregnancy), infections (roseola infantum, sinusitis, chronic otitis media and mastoiditis, Guillain-Barré syndrome), drugs (nalidixic acid, doxycycline, minocycline, tetracycline, nitrofurantoin, isotretinoin used for acne therapy especially when combined with tetracycline), hematologic disorders (polycythemia, hemolytic and iron-deficiency anemias [see Fig. 605-1],

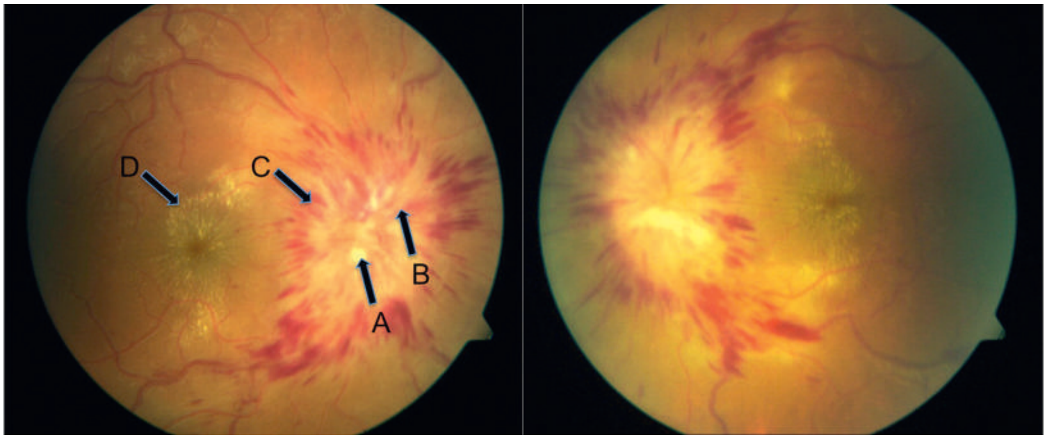

Figure 605-1 Optic nerve photos of the right and left eyes, respectively, demonstrating grade 5 optic nerve head edema with characteristics, including **(A)** total obscuration of the optic cup; **(B)** total obscuration of a segment of a major blood vessel; **(C)** total obscuration of disc margin; and **(D)** macular star. *(From Vickers AL, El-Dairi MA: Subacute vision loss in young, obese female.* J Pediatr *163:1518–1519, 2013, Fig. 1.)*

Table 605-1 Etiology of Childhood Pseudotumor Cerebri

HEMATOLOGIC	**NUTRITIONAL**
Wiskott-Aldrich syndrome	Hypovitaminosis A
Iron-deficiency anemia	Vitamin A intoxication
Aplastic anemia	Hyperalimentation in malnourished patient
Sickle cell disease	Vitamin D–dependent rickets
Polycythemia?	**CONNECTIVE TISSUE DISORDERS**
Bone marrow transplantation and associated treatments?	Antiphospholipid antibody syndrome
Prothrombotic states	Systemic lupus erythematosus?
Fanconi anemia	Behçet disease
INFECTIONS	**ENDOCRINE**
Acute sinusitis	Menarche
Otitis media (lateral sinus thrombosis)	Polycystic ovarian syndrome
Mastoiditis	Hypothyroidism
Tonsillitis	Hypoparathyroidism/ hyperparathyroidism
Measles	Congenital adrenal hyperplasia
Roseola	Addison disease
Varicella, recurrent varicella-zoster virus infection	Recombinant growth hormone
Lyme disease?	**OTHER**
HIV or associated treatment complications?	Dural sinus thrombosis
DRUGS	Obesity (in pubertal patients)
Tetracyclines	Bariatric surgery
Sulfonamides	Head trauma
Nalidixic acid	Superior vena cava syndrome
Fluoroquinolones	Arteriovenous malformation
Corticosteroid therapy and withdrawal	Sleep apnea
Nitrofurantoin	Guillain-Barré syndrome
Cytarabine	Crohn disease
Cyclosporine	Ulcerative colitis?
Phenytoin	Turner syndrome
Mesalamine	**POSSIBLE ASSOCIATIONS**
Isotretinoin	Cystic fibrosis
Amiodarone?	Cystinosis
1-Deamino-8-D-arginine vasopressin (DDAVP)?	Down syndrome
Lithium?	Hypomagnesemia–hypercalciuria
Levonorgestrel implants?	Galactokinase deficiency
Oral contraceptive pills	Galactosemia
RENAL	Atrial septal defect repair
Nephrotic syndrome	Moebius syndrome
Chronic renal insufficiency?	Sarcoidosis?
Post–renal transplantation?	
Peritoneal dialysis?	

Wiskott-Aldrich syndrome), obstruction of intracranial drainage by venous thrombosis (lateral sinus or posterior sagittal sinus thrombosis), head injury, and obstruction of the superior vena cava. When a cause is not identified, the condition is classified as idiopathic intracranial hypertension.

CLINICAL MANIFESTATIONS

The most frequent symptom is chronic (weeks to months), progressive, frontal headache that may worsen with postural changes or a Valsalva maneuver, and although vomiting also occurs, the vomiting is rarely as persistent and insidious as that associated with a posterior fossa tumor. Transient visual obscuration lasting seconds and diplopia (secondary to dysfunction of the abducens nerve) may also occur as may pulsatile tinnitus. Most patients are alert and lack constitutional symptoms. Examination of the infant with pseudotumor cerebri characteristically reveals a bulging fontanel and a "cracked pot sound" or Macewen sign (percussion of the skull produces a resonant sound) resulting from separation of the cranial sutures. **Papilledema** with an enlarged blind spot is the most consistent sign in a child beyond infancy. Papilledema may be absent or mild in infants with pseudotumor cerebri because high CSF pressure may be transmitted to the soft fontanels earlier than the optic nerves. Early optic nerve edema may be noted with orbit ultrasonography. Inferior nasal or peripheral visual field defects may be detected on formal tangent screen testing. The presence of focal neurologic signs should prompt an investigation to uncover a process other than pseudotumor cerebri. Any patient suspected of pseudotumor cerebri should undergo an MRI. MR angiography/MR venography should be considered in patients suspected of having dural sinus thrombosis.

TREATMENT

The key objective in management is recognition and treatment of the underlying cause. There are no randomized clinical trials to guide the treatment of pseudotumor cerebri. Pseudotumor cerebri can be a self-limited condition, but optic atrophy and blindness are the most significant complications of untreated pseudotumor cerebri (Fig. 605-2). The obese patient should be treated with a weight-loss regimen, and if a drug is thought to be responsible, it should be discontinued. For most patients old enough to participate in such testing, serial monitoring of visual function is required. Serial determination of visual acuity, color vision, and visual fields is critical in this disease. Serial optic nerve examination is essential as well. Optical coherence tomography is useful to serially follow changes in papilledema. Serial visual-evoked potentials are useful if the visual acuity cannot be reliably documented. The initial lumbar tap that follows a CT or MRI scan is diagnostic and may be therapeutic. The spinal needle produces a small rent in the dura that allows CSF to escape the subarachnoid space, thus reducing the intracranial pressure. Several additional lumbar taps and the removal

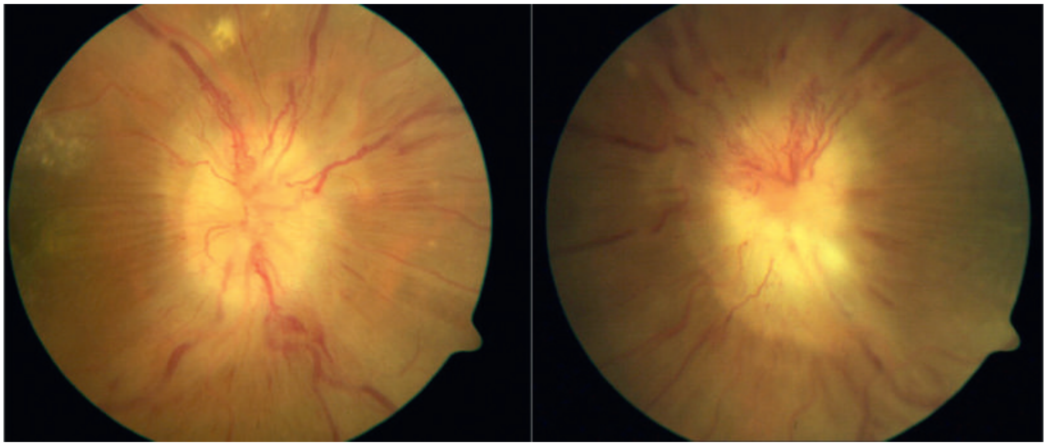

Figure 605-2 Bilateral optic atrophy is evident upon resolution of the papilledema, 1 mo after bilateral optic nerve sheath fenestrations. *(From Vickers AL, El-Dairi MA: Subacute vision loss in young, obese female.* J Pediatr *163:1518–1519, 2013, Fig. 2.)*

of sufficient CSF to reduce the opening pressure by 50% occasionally lead to resolution of the process. Acetazolamide, 10-30 mg/kg/24 hr, is an effective regimen. Corticosteroids are not routinely administered, although they may be used in a patient with severe intracranial pressure elevation who is at risk of losing visual function and is awaiting a surgical decompression. Sinus thrombosis is typically addressed by anticoagulation therapy. Rarely, a ventriculoperitoneal shunt or subtemporal decompression is necessary, if the aforementioned approaches are unsuccessful and optic nerve atrophy supervenes. Some centers perform optic nerve sheath fenestration to prevent visual loss. Any patient whose intracranial pressure proves to be refractory to treatment warrants consideration for repeat neuroradiologic studies. A **slow-growing tumor** or **obstruction of a venous sinus** may become evident by the time of reinvestigation.

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Chapter 606

Spinal Cord Disorders

Harold L. Rekate

606.1 Tethered Cord

Harold L. Rekate

Beyond infancy the spinal cord in humans ends in the conus medullaris at about the level of L1. The position of the conus below L2 is consistent with a congenital tethered spinal cord. For normal humans as the spine flexes and extends, the spinal cord is free to move up and down within the spinal canal. If the spinal cord is fixed at any point, this movement is restricted and the spinal cord and nerve roots become stretched. This fixing of the spinal cord, regardless of the underlying cause of the fixation, is called a tethered cord. When severe pain or neurologic deterioration occurs in response to the fixation, it is called the **tethered cord syndrome.**

In its simplest form the tethered cord syndrome results from a thickened filum terminale, which normally extends as a thin, very mobile structure from the tip of the conus to the sacrococcygeal region where it attaches. When this structure is thickened and shortened, the conus is found to end at levels below L2. This stretching between 2 points is likely to cause symptoms later in life. Fatty infiltration is often seen in the thickened filum (Fig. 606-1).

Figure 606-1 Sagittal MRI showing thickening of the filum terminale in a patient with a symptomatic tethered spinal cord. *(Used with permission from Barrow Neurological Institute.)*

Any condition that fixes the spinal cord can be the cause of the tethered cord syndrome. Conditions that are well established to cause symptomatic tethering include various forms of occult dysraphism such as lipomyelomeningocele, myelocystocele, and diastematomyelia. These conditions are associated with cutaneous manifestations such as midline lipomas often with asymmetry of the gluteal fold (Fig. 606-2), and hairy patches called hypertrichosis (Fig. 606-3). Probably the most common type of symptomatic tethered cord involves patients who had previously undergone closure of an open myelomeningocele and later become symptomatic with pain or neurologic deterioration. Tethered cord syndrome can also be associated with attachment of the spinal cord in patients who undergo surgical procedures that disrupt the pial surface of the spinal cord.

Figure 606-2 Child with a lipomyelomeningocele demonstrating an extraspinal mass and an asymmetry of the gluteal fold indicative of underlying occult dysraphism. *(Used with permission from Barrow Neurological Institute.)*

It is possible that a patient can be suffering from a tethered cord with the conus medullaris in a completely normal position. Although this concept remains controversial, recent reports suggest that half of children with new onset of incontinence found to be neurologic in nature by urodynamic measurements can be successfully treated by sectioning of the filum terminale in the context of normal radiology. This concept will require a randomized controlled trial to evaluate the efficacy of this approach.

CLINICAL MANIFESTATIONS

Patients at risk for the subsequent development of the tethered cord syndrome can often be identified at birth by the presence of an open myelomeningocele or by cutaneous manifestations of dysraphism. It is important to examine the back of the newborn for cutaneous midline lesions (lipoma, dermal sinus, tail, or hairy patch) that may signal an

Figure 606-3 Hairy patch or hypertrichosis usually associated with diastematomyelia. *(Used with permission from Barrow Neurological Institute.)*

Figure 606-4 Example of the neuroorthopedic syndrome involving a larger left foot than right foot, a high arch, and absent ankle jerk frequently associated with tethered cord regardless of the etiology. *(Used with permission from Barrow Neurological Institute.)*

underlying form of occult dysraphism. Dermal sinuses are usually located above the gluteal fold. Cutaneous abnormalities are not found in patients with an isolated thickened filum terminale. Patients who become symptomatic later in life often exhibit an asymmetry of the feet (i.e., 1 is smaller than the other). The smaller foot will show a high arch and clawing of the toes (Fig. 606-4). Characteristically, there is no ankle jerk on the involved side and the calf is atrophied. This condition is termed the **neuroorthopedic syndrome**.

Three clinical syndromes can occur at the time of deterioration. The most likely clinical presentation is increasing urinary urgency and, finally, incontinence. Deterioration of motor and sensory function in the lower extremities is a compelling reason for intervention. Finally, severe generalized back pain, often radiating into the lower extremities, can occur, particularly in older adolescents and adults.

DIAGNOSTIC EVALUATION

When patients present with symptoms related to the tethered cord syndrome, a thorough motor and sensory examination of the patient must be documented. Assessment of bladder function with an ultrasound of the bladder and urodynamic studies is useful in analyzing bladder innervation. MRI is the diagnostic study of choice to reflect the anatomy of the tethering lesion and to provide information about the risks of surgical intervention.

TREATMENT

There are no nonsurgical options for the management of tethered cord syndrome. Because the presence of tethering is most likely to be at least suspected in the newborn, prophylactic surgery to prevent late deterioration has been advocated by some neurosurgeons. This strategy remains controversial and depends to some extent on a careful assessment of the risks compared to the benefits. If surgical intervention is chosen, microsurgical dissection with release of the spinal cord attachment to the overlying dura is the goal of treatment.

OUTCOME

The outcome of releasing a thickened filum terminale or detethering of patients with diastematomyelia is routinely good, and the chance of recurrent symptoms is very low. Patients with symptomatic tethered cord who undergo repair of a myelomeningocele or a lipomyelomeningocele have a significant possibility of recurrent tethering and recurrent symptoms.

Bibliography is available at Expert Consult.

606.2 Diastematomyelia

Harold L. Rekate

DIASTEMATOMYELIA: SPLIT-CORD MALFORMATION

Diastematomyelia is a relatively rare form of occult dysraphism in which the spinal cord is divided into 2 halves. In type 1 split-cord malformation, there are 2 spinal cords, each in its own dural tube and separated by a spicule of bone and cartilage (Fig. 606-5*A*). In a type 2 split-cord malformation, the 2 spinal cords are enclosed in a single dural sac with a fibrous septum between the 2 spinal segments (Fig. 606-5*B*). In both cases the anatomy of the outer half of the spinal cord is essentially normal while the medial half is extremely underdeveloped. Undeveloped nerve roots and dentate ligaments terminate medially into the medial dural tube in type 1 cases and terminate in the membranous septum in type 2 cases. Both types have an associated defect in the bony spinal segment. In the case of type 2 lesions, this defect can be quite subtle.

CLINICAL MANIFESTATIONS

Patients with both type 1 and type 2 split-cord malformations may have subtle signs of neurologic involvement such as unilateral calf atrophy and a high arch to 1 or both feet early in life, but they are more likely to be neurologically normal. These patients are tethered by the adherence of the spinal cord to the median membrane or dural sac. Later they may develop progressive loss of bowel and bladder function and sensory and motor difficulties in the lower extremities. Back pain is a common symptom in adolescents and adults with split-cord malformation but is uncommon in small children.

Cutaneous manifestations of dysraphism are present in 90% of patients with split-cord malformations. Large, hairy, midline patches called hypertrichosis, the most common cutaneous manifestations, are present in approximately 60% of the cases.

DIAGNOSTIC EVALUATION

MRI, the study of choice, shows the 2 spinal cords. The frequent association of bony abnormalities in this condition may require further evaluation with radiography or computed tomography.

TREATMENT

The treatment of split-cord malformations is surgical. This abnormality is a form of tethered cord syndrome, and its treatment is to release the spinal cord to move freely with movement of the spine. In type 1 split-cord malformations, the 2 half cords are in separate dural sacs with medial attachment to the dura and bony septum. In this case the dura needs to be opened, the bony septum removed, the medial attachments to the dura lysed, and a single dural tube created. For type 2 lesions,

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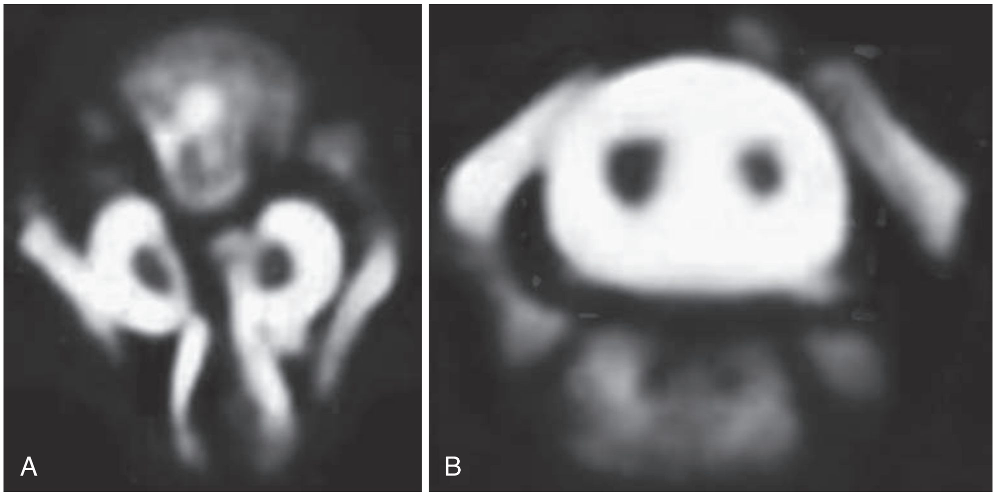

Figure 606-5 **A,** T2-weighted axial MRI of a type 1 split cord malformation showing the 2 spinal cords within 2 separate dural compartments. **B,** Type 2 split cord malformation with 2 spinal cords sharing a single dural compartment. *(**A** and **B** used with permission from Barrow Neurological Institute.)*

the membranous septum should be lysed. An attachment of this membrane to the anterior dura should be explored and lysed as well. Retethering of this type is rare as there is no reason to disrupt the pial layer of the spinal cord.

Bibliography is available at Expert Consult.

606.3 Syringomyelia

Harold L. Rekate

Syringomyelia is a cystic distention of the spinal cord caused by obstruction of the flow of spinal fluid from within the spinal cord to its point of absorption. There are 3 recognized forms of syringomyelia depending on the underlying cause. Communicating syringomyelia implies that cerebrospinal fluid (CSF) from within the ventricles communicates with the fluid within the spinal cord and is assumed to be the source of the CSF that distends the spinal cord. Noncommunicating syringomyelia implies that ventricular CSF does not communicate with the fluid within the spinal cord. It primarily occurs in the context of intramedullary tumors and obstructive lesions. In the final form of syringomyelia, that is, posttraumatic syringomyelia, spinal cord injury results in damage and subsequent softening of the spinal cord. This softening, combined with the scarring of the surrounding spinal cord tissue, results in progressive distention of the cyst. Syringomyelia has been associated with Chiari anomalies and in patients with Ehlers-Danlos syndrome; most are isolated findings unassociated with syndromes.

CLINICAL MANIFESTATIONS

Signs and symptoms of syringomyelia develop insidiously over years or decades. The classic presentation is the **central cord syndrome.** In this situation the patient develops numbness beginning in the shoulder in a cape-like distribution followed by the development of atrophy and weakness in the upper extremities. Trophic ulcers of the hands are characteristic of advanced cases. The central cord syndrome results from damage to the central spinal cord and the orientation of spinal tracts from proximal to distal leading to selective involvement of the upper rather than the lower extremities.

Other forms of presentation include scoliosis that may be rapidly progressive and often can be presumed from the absence of superficial abdominal reflexes. Urgency and bladder dysfunction as well as lower extremity spasticity also may be part of the presentation.

In patients with syringomyelia related to spinal cord injury, the presentation is usually severe pain in the area of the spinal cord distention above the level of the initial injury. There is also an ascending level of motor and sensory dysfunction.

Figure 606-6 Sagittal MRI of patient with a Chiari I malformation and a holocord syrinx. *(Used with permission from Barrow Neurological Institute.)*

DIAGNOSTIC EVALUATION

MRI is the radiologic study of choice (Figs. 606-6 and 606-7). The study should include the entire spine and should include gadolinium-enhanced sequences. Specific attention should be paid to the craniovertebral junction because of the frequent association of syringomyelia with Chiari I and II malformations. Obstruction to the flow of CSF from the fourth ventricle can cause syringomyelia; therefore, most patients also should undergo imaging of the brain.

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TREATMENT

The treatment of syringomyelia should be tailored to the underlying cause. If that cause can be removed or ameliorated, the syrinx should improve. Traumatic syrinxes result from hematomyelia in the substance of the spinal cord coupled with severe arachnoidal scarring around the circumference of the spinal cord. When progressive this form of syringomyelia is treated by exploration and lysis of the adhesions that fix the spinal cord to the overlying dura. In cases of complete spinal cord injury, as is usually found in the thoracic spinal cord, the most effective treatment is the transection of the spinal cord, which would both drain the syrinx and detether the spinal cord. Doing so drains the fluid from the spinal cord. In cases of incomplete spinal cord injury, functioning neurologic elements must be protected. Microscopic lysis of the scar surrounding the spinal cord at the point of injury allows the spinal cord to collapse and prevents it from being distorted by a hydrostatic column.

Communicating syringomyelia is most frequently seen in the context of abnormalities at the craniovertebral junction caused by inflammatory conditions such as chronic meningitis as seen in tuberculosis or meningeal carcinomatosis. There is frequently a causative association with hindbrain herniation as in Chiari malformations (see Fig. 606-6). In such cases decompression of the craniovertebral junction is usually effective in the management of the syringomyelia. In the context of the Chiari II malformation associated with spina bifida, syringomyelia usually results from an insidious failure of the shunt used to treat the hydrocephalus. This distention of the spinal cord results in a rapid development of scoliosis and occasionally spasticity in the lower extremities. Repair of the shunt is effective treatment.

Noncommunicating syringomyelia results from blocking the flow of spinal cord extracellular fluid or CSF within the central canal by an intramedullary spinal cord tumor or severe external compression of the spinal cord. In such cases, management should be directed to tumor resection or to decompression of constricting elements.

Drainage procedures can result in symptomatic and radiographic improvement. Syrinx-to-subarachnoid shunting with a small piece of shunt tubing is 1 form of treatment. Syrinx-to-pleural or syrinx-to-peritoneal shunting is more likely to result in improvement in the radiographic appearance of the syrinx. In patients with syringomyelia that extends to the conus medullaris, remnants of the central canal can be found in the filum terminale. Lysis of this structure near the conus can provide effective drainage.

Some children who show no testable neurologic findings are being referred to pediatric neurosurgeons with the diagnosis of syringomyelia. Many of these children were scanned because of back pain or as part of a screening for scoliosis. They are found on MRI to have a **persistent central canal** and the diagnosis of syringomyelia is made. Some have been scanned sequentially for follow up and banned from athletic activities. These syrinxes are 1-3 mm in diameter and extend over 2 segments (see Fig. 606-7). There is no distortion of the spinal cord in the region and no change in signal of the surrounding spinal cord. These syrinxes have been called "idiopathic" syrinxes. Follow-up of significant numbers of such children has shown them to be benign in nature and probably represent a normal variant. There does not seem to be a need for routine follow-up imaging without new symptoms. They need no treatment and do not require limitations of activity.

Bibliography is available at Expert Consult.

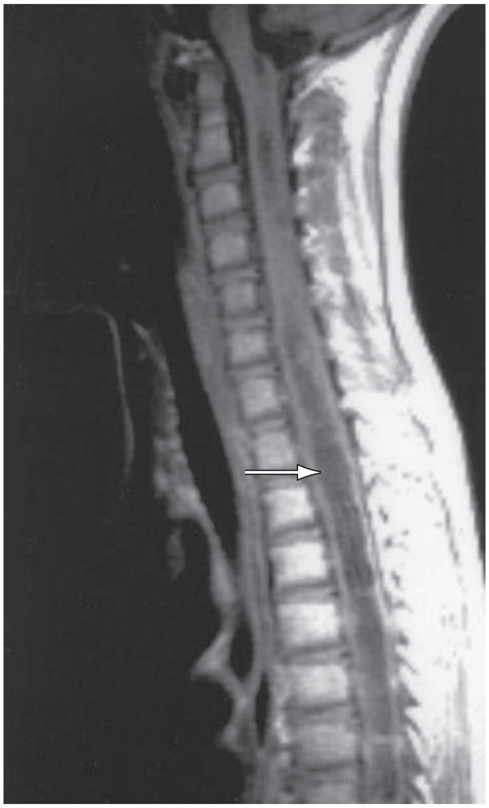

Figure 606-7 T1-weighted MRI scan of upper spinal cord showing an extensive syringomyelia *(arrow).*

606.4 Spinal Cord Tumors

Harold L. Rekate

Tumors of the spine and spinal cord are rare in children. Different types of tumors have different relationships with the spinal cord, meninges, and bony elements of the spine (Fig. 606-8). Intramedullary spinal cord tumors arise within the substance of the spinal cord itself (Fig. 606-9). They represent between 5% and 15% of primary central nervous system tumors. This percentage may well reflect the total volume of spinal cord as opposed to brain. Approximately 10% of intramedullary spinal cord tumors are malignant astrocytic tumors, but most are World Health Organization grade I or II tumors of glial or ependymal origin. In children, low-grade astrocytomas and gangliogliomas represent the most common tumor types with ependymomas being less common than in adults. Ependymomas in children are frequently associated with neurofibromatosis (NF-2).

Except in the context of NF-1 and NF-2, intradural extramedullary tumors are extremely rare in children. Most are nerve sheath tumors,

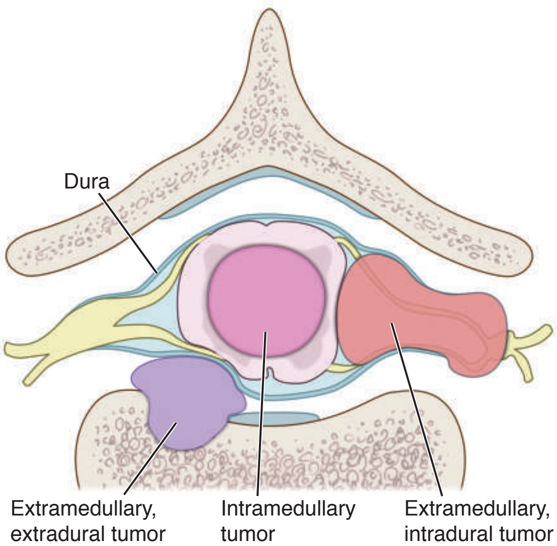

Figure 606-8 Diagram of the relationship of various tumors to the spine, nerve roots, and spinal cord. *(Used with permission from Barrow Neurological Institute.)*

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Figure 606-9 T1-weighted MRI scan of a spinal cord tumor *(arrow)*. The fusiform expansion of the cervical cord enhances after intravenous gadolinium injection.

either schwannomas or, in the case of NF-2, neurofibromas. Intraspinal meningiomas in children are essentially found only in patients with NF-2. The intradural extramedullary compartment is also a site for metastatic tumors from primary cancers such as leukemia or primitive neuroectodermal tumors.

Extradural spinal tumors characteristically begin in the bones of the spine. Primary tumors in this location include aneurysmal bone cysts, Langerhans cell histiocytosis (formerly called eosinophilic granuloma), and giant cell tumors. In infants, the extradural space is often the site of neuroblastomas or ganglioneuroblastomas, which tend to be present in the epidural space and in the paraspinous tissue through the intervertebral foramen. In older patients, the bones of the spine may be the site of multiple myeloma and metastases from common malignant tumors.

CLINICAL MANIFESTATIONS

With the exception of the uncommon malignant glial tumors of the spinal cord, which tend to present precipitously, intramedullary spinal cord tumors present in a very insidious manner. Back pain related to the level of the tumor is a common presenting complaint. It is likely that this pain will awaken the child from sleep and improve as the day progresses. Before the use of MRI became routine, the time from the first onset of symptoms to diagnosis of the tumor could be as long as 9 yr. Weakness, gait disturbance, and sensory deficits are usually minor and are often found when formal neurologic examinations are performed. Scoliosis, urinary urgency, and incontinence may be the presenting complaints associated with intramedullary spinal cord tumors.

Extramedullary extradural tumors have a propensity to cause an acute block of the CSF pathways owing to rapid growth within a confined space. Such children present with a flaccid paraplegia, urinary retention, and a patulous anus. Some extramedullary tumors produce the *Brown-Séquard syndrome,* which consists of ipsilateral weakness, spasticity, and ataxia, with contralateral loss of pain and temperature sensation. Papilledema is observed in a few patients, usually in association with markedly elevated CSF protein levels that presumably interfere with normal CSF flow dynamics.

Nerve sheath tumors primarily arise from the sensory rootlet of the exiting spinal nerve. They are very slow-growing tumors and present with symptoms and signs relative to the nerve root involved. Pain in a band-like distribution around the chest or into an extremity is the most common presenting complaint. Tumor growth eventually leads to spinal cord compression and involvement of adjacent nerve roots.

Tumors rarely arise in the fat of the epidural space; most epidural tumors arise in the bony compartment of the spine. They can present abruptly with severe pain and neurologic deficit at the time of pathologic fracture of the vertebral body. Benign tumors such as giant cell tumors and aneurysmal bone cysts present more insidiously as the tumor slowly grows and begins to compress neural structures.

DIAGNOSTIC EVALUATION

MRI with and without gadolinium enhancement of the spinal cord is the diagnostic study of choice and is essential in the diagnosis of spinal cord tumors, especially intramedullary spinal cord tumors. Most astrocytic tumors of the spinal cord and most ependymomas show diffuse enhancement and will distend the spinal cord focally. These tumors may involve the entire length of the spinal cord (holocord astrocytomas). MRI also shows the relationship between the normal spinal cord and tumor embedded within spinal cord tissue. These tumors are frequently associated with a syrinx, which is usually distal to the tumor. Nerve sheath tumors characteristically enhance and are focal. They may exit through the neural foramen and distend the canal as can be seen on MRI. They also may be visualized on plain radiographs of the affected area of the spine.

Plain radiographs of the spine are helpful in defining the relationship of extradural tumors to the bony spine and in documenting evidence of instability in the case of pathologic compression fractures. When a pathologic fracture occurs, CT is essential to determine the effect of the tumor on the bone. Because many of these tumors occur as metastatic lesions, a general staging of the extent of disease is essential. In the case of Langerhans cell histiocytosis, a thorough bone survey should be conducted to look for other lesions. Radionucleotide bone scanning is also useful in determining the extent of the disease.

TREATMENT

The primary treatment of both intramedullary and extramedullary intradural tumors is surgical removal. For both low-grade astrocytomas and ependymomas, microsurgical removal with the intent of total removal is the treatment of choice. This goal should be attainable in all patients with ependymomas and in most patients with low-grade astrocytomas and gangliogliomas. Adjunctive treatment of these tumors is unwarranted in patients treated with adequate surgical resection. Likewise, schwannomas should be resectable. Occasionally, however, the nerve root must be resected. Doing so may be of no consequence in the thoracic spinal cord, but an attempt to remove the tumor while salvaging the motor root in the cervical and lumbosacral region is critical to preserve movement. Malignant astrocytic tumors cannot be resected without major morbidity and, in any case, carry an extremely poor prognosis. In the case of grades III and IV astrocytomas of the spinal cord, decompression and biopsy followed by radiation therapy and possibly chemotherapy are utilized.

The diagnosis and treatment of extramedullary spinal cord tumors must be individualized. Patients with distention of the vertebral body or with unstable pathologic fractures benefit from extensive resection of the involved vertebral bodies and will likely need fusion. For extramedullary tumors with soft-tissue components such as neuroblastomas, treatment is determined by the nature of the tumor and degree of spinal cord compression, and directed following needle biopsy of the lesion. In the absence of significant neurologic compression, surgical intervention is rarely indicated.

OUTCOME

The prognosis for patients with benign intramedullary spinal cord tumors depends, to some extent, on the patient's condition at the time of surgical intervention. It is very unlikely that nonambulatory patients will improve after surgery. If, however, patients are ambulatory at the time of surgery, they may experience increased weakness after surgery.

They are likely to recover at least their preoperative level of function. Malignant spinal cord tumors are usually lethal with death resulting from diffuse metastases via the CSF pathways. Successful resection of nerve sheath tumors should be curative. In the context of neurofibromatosis, however, many more tumors can be found at other levels or can be expected to develop later in life. Surgical intervention in the context of neurofibromatoses should be performed only on clearly symptomatic lesions.

The outcome of treatment of extramedullary tumors depends on the cell type and, in most cases, on the efficacy of nonsurgical, adjunctive therapies. For aneurysmal bone cysts and giant cell tumors, resection of the tumor and fusion of the spine are the treatments of choice.

The significant majority of spinal cord tumors in children are benign (World Health Organization grades 2 and 3). The intramedullary low-grade glial tumors for the most part act the same as the same histology in the brain. The evidence would point to the fact that intramedullary ependymomas act in a more benign fashion than they do in the fourth ventricle. Gross total removal without adjuvant treatment is the preferred method of treatment and carries not only much longer progression free survival but improved quality of life as well.

Bibliography is available at Expert Consult.

606.5 Spinal Cord Injuries in Children

Harold L. Rekate

Spine and spinal cord injuries are very rare in children, particularly in young children. The spine of a small child is very mobile, and fractures of the spine are exceedingly rare. This increased mobility is not always a positive feature. Transfer of energy leading to spinal distortion can maintain the structural integrity of the spine but lead to significant injuries of the spinal cord. Spinal cord injury without radiographic bone (vertebral) abnormalities, called **SCIWORA,** is more common in children than adults. There seem to be 2 distinct forms. The infantile form involves severe injury of the cervical or thoracic spine. These patients have a poor likelihood of complete recovery. In older children and adolescents, SCIWORA is more likely to cause a less-severe injury and the likelihood of complete recovery over time is high. The adolescent form is assumed to be a spinal cord concussion or mild contusion as opposed to the severe spinal cord injury related to the mobility of the spine in small children.

Although the mechanisms of spinal cord injury in children include birth trauma, falls, and child abuse, the major cause of morbidity and mortality remains motor vehicle injuries. Although the mechanisms of injury and diagnosis are distinct in very small children, adolescents incur spinal cord injuries with epidemiology similar to that of adults, including significant male predominance and a high likelihood of fracture dislocations of the lower cervical spine or thoracolumbar region. In infants and children younger than age 5 yr, fractures and mechanical disruption of spinal elements are limited to the upper cervical spine between the occiput and C3.

CLINICAL MANIFESTATIONS

One in 3 patients with significant trauma to the spine and spinal cord will have a concomitant severe head injury, which makes early diagnosis challenging. For these patients clinical evaluation may be difficult. They need to be maintained in a protective environment such as a collar until the appropriate radiographs can be obtained. A careful neurologic examination is necessary for infants with suspected spinal cord injuries. Complete spinal cord injury will lead to **spinal shock** with early areflexia. Severe cervical spinal cord injuries will usually lead to paradoxical respiration in patients who are breathing spontaneously. Paradoxical respiration occurs when the diaphragm functions because the phrenic nerves from C3, C4, and C5 are functioning normally but the intercostal musculature innervated by the thoracic spinal cord is paralyzed. In this situation, inspiration fails to expand of the chest wall but distends the abdomen.

The *mildest injury* to the spinal cord is transient quadriparesis evident for seconds or minutes with complete recovery in 24 hr. This injury follows a concussion of the cord.

A transverse injury in the high cervical cord level (C1-C2) causes respiratory arrest and death in the absence of ventilatory support. *Fracture dislocations at the C5-C6 level* resulting in spinal cord injuries are characterized by flaccid quadriparesis, loss of sphincter function, and a sensory level corresponding to the upper sternum. Fractures or dislocations in the low thoracic (T12-L1) region may produce the **conus medullaris syndrome,** which includes a loss of urinary and rectal sphincter control, flaccid weakness, and sensory disturbances of the legs. A **central cord lesion** may result from contusion and hemorrhage and typically involves the upper extremities to a greater degree than the legs. There are lower motor neuron signs in the upper extremities and upper motor neuron signs in the legs, bladder dysfunction, and loss of sensation caudal to the lesion. There may be considerable recovery, particularly in the lower extremities.

Thoracolumbar injuries are usually fracture–dislocations such as occur in severe motor vehicle accidents when children are wearing lap belts but not shoulder harnesses. These injuries lead to a conus medullaris syndrome. These patients exhibit a loss of bowel and bladder function and lower motor neuron injuries involving the innervation of the lower extremities.

CLEARING THE CERVICAL SPINE IN CHILDREN

The management of children following major trauma is challenging. Clearing the cervical spine in children carries some of the same issues as it does in comatose adults in that with small children you cannot count on their cooperation with positioning for radiographs and complaints of pain are difficult to assess. There has been an increasing emphasis on the use of MRI for the evaluation of potential cervical spine instability but in small children this study requires sedation and, in most centers, the presence of an anesthesiologist. Despite the radiation dose, it is clear that the CT scan is the most important study with 100% sensitivity and 95% specificity. A multiply injured child is likely to be in the scanner having other anatomic studies done in any case and no other study has been shown to be better for detection of unstable cervical spine injury. This test detects all significant injuries to the cervical spine and has very few false-positives as opposed to MRI scanning, which overcalls the injury 1 in 4 times.

TREATMENT

The initial management of spine and spinal cord injuries in children is similar to that in adults. The cervical spine should be immobilized in the field by the emergency medical technicians. In cases of acute spinal cord injury, some data support the acute infusion of a bolus of high-dose (30 mg/kg) methylprednisolone followed by a 23 hr infusion (5.4 mg/kg/hr). The data for this treatment in children are controversial.

Surgical management of unstable spinal injuries must be tailored to the patient's age. For occipitocervical dislocations, early surgery with fusion from the occiput to C2 or C3 should be performed, even in babies older than 6 mo. Fixation of the subaxial spine must be tailored to the size of the pedicles and other osseus structures of the developing axial skeleton.

PREVENTION

The most important aspect of the care of spinal cord injuries in children relates to injury prevention. In this regard, the use of appropriate child restraints in automobiles is the most important precaution. In older children and adolescents, rules against spear tackling in football and the "Feet First, First Time Program" from the Think First Foundation aimed at adolescents diving into swimming pools and natural water areas are important ways to help prevent severe cervical spinal cord injuries.

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606.6 Transverse Myelitis

Harold L. Rekate

Transverse myelitis (TM) is a condition characterized by rapid development of both motor and sensory deficits at any level of the spinal cord. TM presents acutely as either partial or complete cord involvement and is defined as evidence of spinal cord inflammation by an MRI-documented enhancing lesion, or CSF pleocytosis (>10 cells), or increased immunoglobulin G index. The progression is rapid and the time to maximal disability is more than 4 hr and fewer than 21 days. It has multiple causes and tends to occur in 2 distinct contexts. Small children, 3 yr of age and younger, develop spinal cord dysfunction over hours to a few days. They have a history of an infectious disease, usually of viral origin, or of an immunization within the few weeks preceding the development of their neurologic difficulties. The clinical loss of function is often severe and may seem complete. Although a slow recovery (weeks to months) is common in these cases, it is likely to be incomplete. The likelihood of independent ambulation in these small children is approximately 40%. The pathologic findings of perivascular infiltration with mononuclear cells imply an infectious or inflammatory basis. Overt necrosis of spinal cord may rarely be seen.

In older children, the syndrome is somewhat different. Although the onset is also rapid with a nadir in neurologic function occurring between 2 days and 2 wk, recovery is more rapid and more likely to be complete. Pathologic or imaging examination shows acute demyelination.

CLINICAL MANIFESTATIONS

TM is often preceded within the previous 1-3 wk by a mild nonspecific illness, minimal trauma, or perhaps an immunization. In both forms the patient shows or complains of discomfort or overt pain in the neck or back, depending on the level of the lesion. The most common involved segments are in the thoracic region. Depending on its severity, the condition progresses to numbness, anesthesia, ataxia, areflexia, and motor weakness in the truncal and appendicular musculature at or distal to the lesion. Paralysis begins as flaccidity (paraparesis, tetraparesis), but over a few weeks spasticity develops and is evident by hyperreflexia and clonus. Rarely is the weakness unilateral. Urinary retention is an early finding; incontinence occurs later in the course. Most have sensory loss manifest as anesthesia, paresthesia, or allodynia. Other findings may include priapism and vision loss (neuromyelitis optica), as well as spinal shock and subsequent autonomic dysreflexia.

The differential diagnosis includes demyelinating disorders, overt meningitis, spinal cord infarction, or mass lesions such as bony distortion, abscess, and spine and spinal cord tumors (Table 606-1).

DIAGNOSTIC EVALUATION

MRI with and without contrast enhancement is essential to rule out a mass lesion requiring neurosurgical intervention. In both conditions, T1-weighted images of the spine at the anatomic level of involvement may be normal or may show distention of the spinal cord. In the infantile form, T2-weighted images show high signal intensity that extends over multiple segments. In the adolescent form, the high signal intensity may be limited to 1 or 2 segments. A limited degree of contrast enhancement after the administration of gadolinium is expected, especially in the infantile form, and denotes an inflammatory condition (Fig. 606-10). MRI of the brain is also indicated and shows evidence of other foci of demyelination in at least 30% of patients; in these patients and those with encephalopathy, acute disseminated encephalomyelitis must be considered (Fig. 606-11).

After a mass lesion associated with spinal cord compression or complete subarachnoid column block from spinal cord swelling have been ruled out, a lumbar puncture is indicated. In both forms of disease, the number of mononuclear cells is usually elevated. The level of CSF protein maybe elevated or normal. CSF should be analyzed for myelin basic protein and immunoglobulin levels, which are usually elevated in TM. The presence of inflammatory cells is essential for the diagnosis of TM.

Because one of the most important possibilities for this condition is neuromyelitis optica (NMO; Devic syndrome) the serum of all patients should be analyzed for the NMO antibody. This test is positive in most patients with NMO (see Chapter 600.2). NMO is associated with bilateral optic neuritis and recurrent or long segment TM (≥3 segments). NMO may involve any spinal segment in addition to the brainstem or conus medullaris and cauda equina (myeloradiculitis). As in adults with

Table 606-1 Clinical and Radiologic Mimics of Transverse Myelitis

EXTRAAXIAL COMPRESSION DISEASE	SPINAL CORD DISORDERS
1. Vertebral spine disorders	1. Congenital malformation
a. Trauma	a. Neurenteric cysts
i. Blunt	b. Spinal cord tethering
ii. Penetrating	2. Infection
iii. Surfing	a. Nonpolio enteroviruses
b. Atlantoaxial subluxation	b. West Nile virus
i. Trisomy 21	c. Human T-lymphocyte virus 1
ii. Mucopolysaccharidosis type IV	d. Neurocysticercosis
iii. Grisel syndrome	3. Vascular disorders
c. Destructive lesions	a. Arteriovenous malformation
i. Tuberculosis	b. Cavernomas
ii. Lymphoma	c. Cobb syndrome
iii. Langerhans cell histiocytosis	d. Fibrocartilaginous embolization
d. Scheuermann disease	e. Spinal cord infarction
2. Epidural disease	4. Vasculitis
a. Tumor	a. Systemic lupus erythematosus
i. Neuroblastoma	b. Behçet disease
ii. Wilms tumor	5. Nutritional disorders
iii. Ewing sarcoma	a. Vitamin B_{12} deficiency (Subacute combined degeneration)
b. Abscess	6. Toxic injury
i. Associated dermal sinus, vertebral body infection	a. Chemotherapy (e.g., methotrexate)
c. Hematoma	b. Radiation
3. Arachnoiditis	7. Immune mediated
a. Tuberculosis	a. Acute disseminated encephalomyelitis
b. Cryptococcosis	b. Neuromyelitis optica
c. Carcinomatous infiltration	c. Multiple sclerosis
4. Spinal nerve root inflammation	
a. Guillain-Barré syndrome	

Modified from Thomas T, Branson HM: Childhood transverse myelitis and its mimics. Neuroimaging Clin N Am *23:267–278, 2013, Box 11.*

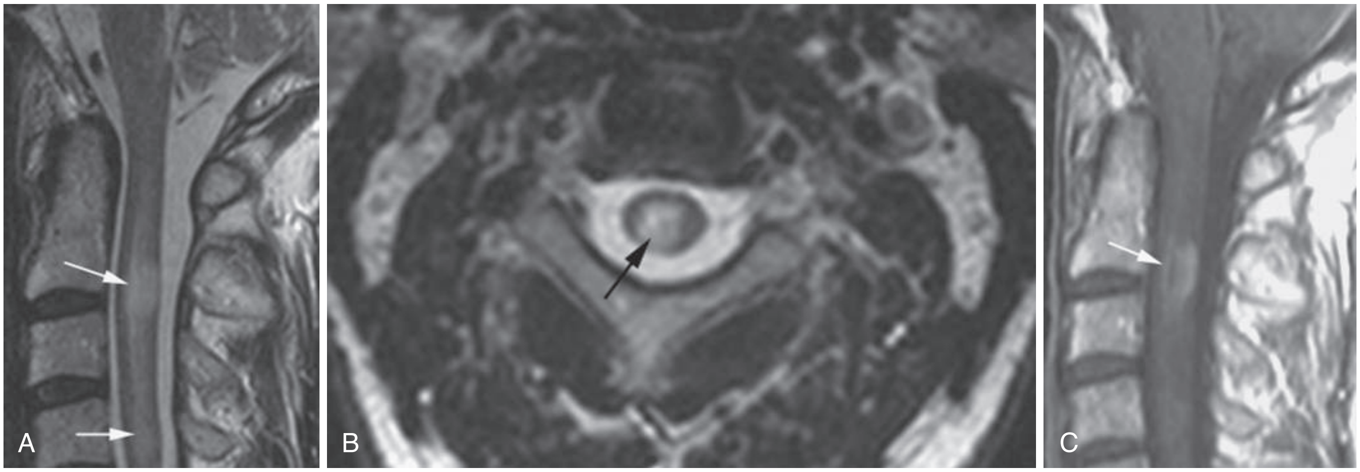

Figure 606-10 Transverse myelitis. **A,** Sagittal T2-weighted image demonstrates a longitudinal hyperintense spinal cord lesion spanning three vertebral segments *(arrows).* **B,** On an axial T2-weighted image, the lesion involves more than two-thirds of the cord's cross-sectional area *(arrow).* **C,** Sagittal T1-weighted postcontrast image shows an enhancing area within the lesion *(arrow). (From Ajtai B, Lindzen E, Masdeu JC: Structural imaging: magnetic resonance imaging and computed tomography. In Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors:* Bradley's neurology in clinical practice, *ed 6. Philadelphia, 2012, WB Saunders,* Fig. 33A.96.*)*

Figure 606-11 Acute disseminated encephalomyelitis. Sagittal T2-weighted image shows a diffuse hyperintense lesion spanning the length of the cervical cord *(arrows).* Note the enlarged caliber of the cord, which is a result of swelling. *(From Ajtai B, Lindzen E, Masdeu JC: Structural imaging: magnetic resonance imaging and computed tomography. In Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors:* Bradley's neurology in clinical practice, *ed 6. Philadelphia, 2012, WB Saunders,* Fig. 33A.95.*)*

TM, older children with the condition should have serum studies sent for autoimmune disorders, especially systemic lupus erythematosus.

TREATMENT

There are no standards for the treatment of TM. Available evidence suggests that modulation of the immune response may be effective in decreasing the severity and duration of the condition. The use of high-dose steroids, particularly methylprednisolone, is the initial approach to treatment of childhood forms of TM. If there is a poor response to high-dose steroids, other therapeutic approaches include intravenous immunoglobulin, plasma exchanges, rituximab, and cyclophosphamide.

Follow-up of children with TM often reveals poor ambulation, continued bowel or bladder symptoms and dysesthesias.

Bibliography is available at Expert Consult.

606.7 Spinal Arteriovenous Malformations

Harold L. Rekate

Arteriovenous malformations of the spinal cord are rare lesions in children. Only about 60 patients younger than age 18 yr are treated in the United States each year. These lesions are complex. Despite their rarity there are multiple subtypes, which require different treatment strategies. Patients commonly present with back or neck pain, depending on the segments of the spinal cord involved, and they may experience the insidious onset of motor and sensory disturbances. Sudden onset of paraplegia secondary to hemorrhage has been reported. Occasionally, patients present with subarachnoid hemorrhage without overt neurologic deficits, similar to the presentation associated with cerebral aneurysms. In some cases, bruits are audible upon auscultation over the bony spine.

DIAGNOSTIC EVALUATION

When a spinal arteriovenous malformation is suspected, MRI of the spinal cord is first needed to make the diagnosis and to obtain a general idea of the location of the lesion. MR angiography or CT angiography may provide further information, but formal catheter angiography of the spinal cord is needed to obtain an adequate understanding of the complex anatomy of the lesion and to plan the intervention.

TREATMENT

Open microsurgery had been the mainstay of treatment for spinal cord arteriovenous fistulas and arteriovenous malformations. With the rapid development of interventional techniques, the percentage of patients undergoing microsurgery has decreased from 70% to approximately 30%. Stereotactic radiosurgery may be used adjunctively. Treatment of these complex lesions requires the commitment of an organized neurovascular treatment program.

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Neuromuscular Disorders

PART XXVIII

Chapter 607
Evaluation and Investigation

Harvey B. Sarnat

The term **neuromuscular disease** defines disorders of the motor unit and excludes influences on muscular function from the brain, such as spasticity. The motor unit has 4 components: a motor neuron in the brainstem or ventral horn of the spinal cord; its axon, which together with other axons forms the peripheral nerve; the neuromuscular junction; and all muscle fibers innervated by a single motor neuron. The size of the motor unit varies among different muscles and with the precision of muscular function required. In large muscles, such as the glutei and quadriceps femoris, hundreds of muscle fibers are innervated by a single motor neuron; in small, finely tuned muscles, such as the stapedius or the extraocular muscles, a 1 : 1 ratio can prevail. The motor unit is influenced by suprasegmental or upper motor neuron control that alters properties of muscle tone, precision of movement, reciprocal inhibition of antagonistic muscles during movement, and sequencing of muscle contractions to achieve smooth, coordinated movements. Suprasegmental impulses also augment or inhibit the monosynaptic stretch reflex; the corticospinal tract is inhibitory upon this reflex.

Diseases of the motor unit are common in children. These neuromuscular diseases may be genetically determined, congenital or acquired, acute or chronic, and progressive or static. Because specific therapy is available for many diseases and because of genetic and prognostic implications, precise diagnosis is important; laboratory confirmation is required for most diseases because of overlapping clinical manifestations.

Many chromosomal loci are identified with specific neuromuscular diseases as a result of genetic linkage studies and the isolation and cloning of a few specific genes. In some cases, such as Duchenne muscular dystrophy, the genetic defect is a deletion of nucleotide sequences and is associated with a defective protein product, dystrophin. In other cases, such as myotonic muscular dystrophy, the genetic defect is an expansion or repetition, rather than a deletion, in a codon (a set of 3 consecutive nucleotide repeats that encodes for a single amino acid), with many copies of a particular codon (in this example they are also associated with abnormal messenger RNA). Some diseases manifest as autosomal dominant and autosomal recessive traits in different pedigrees; these distinct mendelian genotypes can result from different genetic mutations on different chromosomes (nemaline myopathy) or from small differences in the same gene at the same chromosomal locus (myotonia congenita), despite many common phenotypic features and shared histopathologic findings in a muscle biopsy specimen. Among the several clinically defined mitochondrial myopathies, specific mitochondrial DNA deletions and transfer RNA point mutations are recognized. The inheritance patterns and chromosomal and mitochondrial loci of common neuromuscular diseases affecting infants and children are summarized in Table 608-1 in Chapter 608.

CLINICAL MANIFESTATIONS

Examination of the neuromuscular system includes an assessment of muscle bulk, tone, and strength. Tone and strength should not be confused: **Passive tone** is range of motion around a joint; **active tone** is physiologic resistance to movement. Head lag when an infant is pulled to a sitting position from supine is a sign of weakness, not of low tone. Hypotonia may be associated with normal strength or with weakness; enlarged muscles may be weak or strong; thin, wasted muscles may be weak or have unexpectedly normal strength. The distribution of these components is of diagnostic importance. In general, myopathies follow a proximal distribution of weakness and muscle wasting (with the notable exception of myotonic muscular dystrophy); neuropathies are generally distal in distribution (with the notable exception of juvenile spinal muscular atrophy; Table 607-1). Involvement of the face, tongue, palate, and extraocular muscles provides an important distinction in the differential diagnosis. **Tendon stretch reflexes** are generally lost in neuropathies and in motor neuron diseases and are diminished but preserved in myopathies (Table 607-1). A few specific clinical features are important in the diagnosis of some neuromuscular diseases. **Fasciculations** of muscle, which are often best seen in the tongue, are a sign of denervation. Sensory abnormalities indicate neuropathy. Fatigable weakness is characteristic of neuromuscular junctional disorders. Myotonia is specific for a few myopathies.

Some features do not distinguish myopathy from neuropathy. Muscle pain or **myalgias** are associated with acute disease of either myopathic or neurogenic origin. Acute dermatomyositis and acute polyneuropathy (Guillain-Barré syndrome) are characterized by myalgias. Muscular dystrophies and spinal muscular atrophies are not associated with muscle pain. Myalgias also occur in several metabolic diseases of muscle and in ischemic myopathy, including vascular diseases such as dermatomyositis. Myalgias denote the acuity, rather than the nature, of the process, so that progressive but chronic diseases, such as muscular dystrophy and spinal muscular atrophy, are not painful but acute stages of inflammatory myopathies and acute denervation of muscle often do present with muscular pain and tenderness to palpation. **Contractures** of muscles, whether present at birth or developing later in the course of an illness, occur in both myopathic and neurogenic diseases.

Infant boys who are weak in late fetal life and in the neonatal period often have **undescended testes**. The testes are actively pulled into the scrotum from the anterior abdominal wall by a pair of cords that consist of smooth and striated muscle called the gubernacula. The gubernacula are weakened in many congenital neuromuscular diseases, including spinal muscular atrophy, myotonic muscular dystrophy, and many congenital myopathies.

The thorax of infants with congenital neuromuscular disease often has a funnel shape, and the ribs are thin and radiolucent as a result of intercostal muscle weakness during intrauterine growth. This phenomenon is characteristically found in infantile spinal muscular atrophy but also occurs in myotubular myopathy, neonatal myotonic dystrophy, and other disorders (Fig. 607-1). Because of the small muscle mass, birthweight may be low for gestational age.

Generalized hypotonia and motor developmental delay are the most common presenting manifestations of neuromuscular disease in infants and young children (Table 607-2). These features can also be expressions of neurologic disease, endocrine and systemic metabolic diseases, and Down syndrome, or they may be nonspecific neuromuscular expressions of malnutrition or chronic systemic illness (Table 607-3). A prenatal history of decreased fetal movements and intrauterine growth retardation is often found in patients who are symptomatic at birth. Developmental disorders tend to be of slow onset and are progressive. Acute flaccid paralysis in older infants and children has a different differential diagnosis (Table 607-4).

LABORATORY FINDINGS

Serum Enzymes

Several lysosomal enzymes are released by damaged or degenerating muscle fibers and may be measured in serum. The most useful of these enzymes is **creatine kinase (CK)**, which is found in only 3 organs and may be separated into corresponding isozymes: MM for skeletal muscle, MB for cardiac muscle, and BB for brain. Serum CK determination is not a universal screening test for neuromuscular disease because many diseases of the motor unit are not associated with elevated enzymes. The CK level is characteristically elevated in certain diseases, such as Duchenne muscular dystrophy, and the magnitude of increase is characteristic for particular diseases.

Table 607-1 Distinguishing Features of Disorders of the Motor System

LOCUS OF LESION	WEAKNESS: Face	Arms	Legs	Proximal–Distal	DEEP TENDON REFLEXES	ELECTRO-MYOGRAPHY	MUSCLE BIOPSY	OTHER
Central	0	+	+	≥	Normal or ↑	Normal	Normal	Seizures, hemiparesis, and delayed development
Ventral horn cell	Late	++++	++++	≥	0	Fasciculations and fibrillations	Denervation pattern	Fasciculations (tongue)
Peripheral nerve	0	+++	+++	<	↓	Fibrillations	Denervation pattern	Sensory deficit, elevated cerebrospinal fluid protein, depressed nerve biopsy
Neuromuscular junction	+++	+++	+++	=	Normal	Decremental response (myasthenia); incremental response and BSAP (botulism)	Normal	Response to neostigmine or edrophonium (myasthenia); constipation and fixed pupils (botulism)
Muscle	Variable (+ to ++++)	++	+	>	↓	Short duration, small-amplitude motor unit potentials and myopathic polyphasic potentials	Myopathic pattern*	Elevated muscle enzyme levels (variable)

*Can also show unique features, such as in central core disease, nemaline myopathy, myotubular myopathy, and congenital fiber type disproportion.
+ to ++++, varying degrees of severity; BSAP, brief duration, small amplitude, overly abundant motor unit potentials.
From Volpe J: Neurology of the newborn, *ed 4, Philadelphia, 2001, WB Saunders, p. 706.*

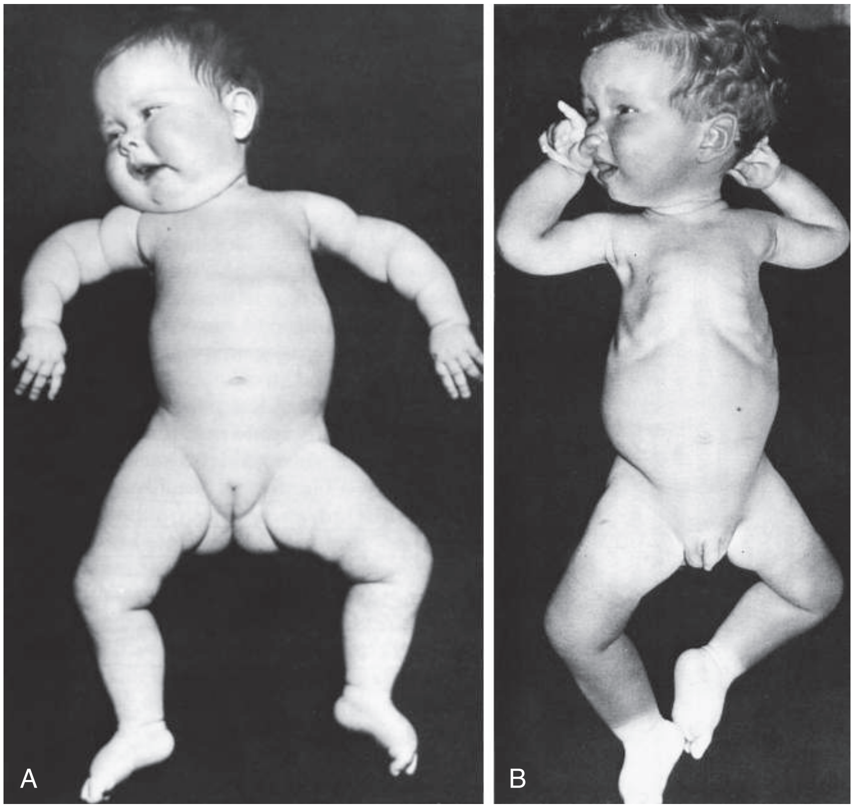

Figure 607-1 **Type 1 spinal muscular atrophy (Werdnig-Hoffmann disease).** Characteristic postures in 6 wk old **(A)** and 1 yr old **(B)** infants with severe weakness and hypotonia from birth. Note the frogleg posture of the lower limbs and internal rotation ("jug handle") **(A)** or external rotation **(B)** at the shoulders. Note also intercostal recession, especially evident in **B,** and normal facial expressions. *(From Volpe J:* Neurology of the newborn, *ed 4, Philadelphia, 2001, WB Saunders, p. 645.)*

Table 607-2 Pattern of Weakness and Localization in the Floppy Infant

ANATOMIC REGION OF HYPOTONIA	CORRESPONDING DISORDERS	PATTERN OF WEAKNESS AND INVOLVEMENT
Central nervous system	Chromosomal disorders Inborn errors of metabolism Cerebral dysgenesis Cerebral, spinal cord trauma	Central hypotonia Axial hypotonia more prominent Hyperactive reflexes
Motor neuron	Spinal muscular atrophy	Generalized weakness; often spares the diaphragm, facial muscles, pelvis, and sphincters
Nerve	Peripheral neuropathies	Distal muscle groups involved Weakness with wasting
Neuromuscular junction	Myasthenia syndromes Infantile botulism	Bulbar, oculomotor muscles exhibit greater degree of involvement
Muscle	Congenital myopathies Metabolic myopathies Congenital muscular dystrophy Congenital myotonic dystrophy	Weakness is prominent Proximal musculature Hypoactive reflexes Joint contractures

From Prasad AN, Prasad C: The floppy infant: contribution of genetic and metabolic disorders, Brain Dev *27:457–476, 2003.*

Molecular Genetic Markers

Many DNA markers of hereditary myopathies, including the muscular dystrophies, and neuropathies are available from leukocytes in blood samples. If the clinical manifestations suggest a particular disease, these tests can provide a definitive diagnosis and not subject the child to more-invasive procedures, such as muscle biopsy. Other molecular markers are available only in muscle biopsy tissue.

Nerve Conduction Velocity

Motor and sensory nerve conduction velocity may be measured electrophysiologically by using surface electrodes. Neuropathies of various types are detected by decreased conduction. The site of a traumatic nerve injury may also be localized. The nerve conduction value at birth is about half of the mature value achieved by age 2 yr. Tables are available for normal values at various ages in infancy, including for preterm infants. Because the nerve conduction velocity study measures only the fastest conducting fibers in a nerve, 80% of the total nerve fibers must be involved before slowing in conduction is detected.

Electromyography

Electromyography (EMG) requires insertion of a needle into the belly of a muscle and recording of the electric potentials in various states of contraction. It is less useful in pediatrics than in adult medicine, in part because of technical difficulties in recording these potentials in young children and in part because the best results require the patient's cooperation for full relaxation and maximal voluntary contraction of a muscle. Many children are too frightened to provide such cooperation. Characteristic EMG patterns distinguish denervation from myopathic involvement. The specific type of myopathy is not usually definitively diagnosed, but certain specialized myopathic conditions, such as myotonia, may be demonstrated. An EMG can transiently raise the serum CK level.

EMG combined with repetitive electrical stimulation of a motor nerve supplying a muscle to produce tetany is useful in demonstrating myasthenic decremental responses. Small muscles, such as the abductor digiti quinti of the hypothenar eminence, are used for such studies. Additional specialized tests, such as single myofiber EMG, may provide supplementary evidence in selected cases, but are performed only in large neuromuscular centers.

Imaging of Muscle and Central Nervous System

Ultrasonography, CT scans, and, more often, MRI are used to image muscle in many neuromuscular diseases. Although these methods are not always definitively diagnostic, in experienced hands, they provide a supplementary means of following the progression of disease over time. MRI is quite useful in identifying inflammatory myopathies of immune (dermatomyositis) or infectious (viral, bacterial, parasitic) origin. MRI is the study of choice to image the spinal cord, if a tumor or other structural lesion of the spinal cord is suspected as the cause of muscular dysfunction, and nerve roots and plexus (e.g., brachial plexus). Brain MRI is indicated in some myopathies, such as the congenital muscular dystrophies, in which cerebral malformations often accompany the myopathy because the mutated gene responsible is expressed in both muscle and the developing brain.

Muscle Biopsy

The muscle biopsy is traditionally the most important and specific diagnostic study of most neuromuscular disorders, if the definitive diagnosis of a hereditary disease is not provided by molecular genetic testing in blood. Not only are neurogenic and myopathic processes distinguished, but also the type of myopathy and specific enzymatic deficiencies may be determined. The vastus lateralis (quadriceps femoris) is the muscle that is most commonly sampled. The deltoid muscle should be avoided in most cases because it normally has a 60-80% predominance of type I fibers so that the distribution patterns of fiber types are difficult to recognize. Muscle biopsy is a simple outpatient procedure that may be performed under local anesthesia with or without femoral nerve block. Needle biopsies are preferred in some centers but are not percutaneous and require an incision in the skin similar to open biopsy; numerous samples must be taken to conduct an adequate examination of the tissue, and they provide inferior specimens. The volume of tissue from a needle biopsy is usually not adequate for all required studies, including supplementary biochemical studies, such as mitochondrial respiratory chain enzymes; a small, clean, open biopsy is therefore advantageous.

Histochemical studies of frozen sections of the muscle are obligatory in all pediatric muscle biopsies because many congenital and metabolic myopathies cannot be diagnosed from paraffin sections using conventional histologic stains. Immunohistochemistry is a useful supplement in some cases, such as for demonstrating dystrophin in suspected Duchenne muscular dystrophy or merosin in congenital muscular dystrophy. A portion of the biopsy specimen should be fixed for potential electron microscopy, but ultrastructure has additional diagnostic value only in selected cases. Interpretation of muscle biopsy samples is complex and should be performed by an experienced pathologist. A portion of frozen muscle tissue should also be routinely saved for possible biochemical analysis (mitochondrial cytopathies, carnitine palmitoyltransferase, acid maltase).

Immunocytochemical reactivities can be applied to formalin-fixed, paraffin-embedded sections and do not require frozen sections. Some reactivities, such as slow and fast myosin, can distinguish fiber types and hence substitute for myofibrillar adenosine triphosphatase histochemical stains in frozen sections. An increasing number of sarcolemmal regional proteins can be demonstrated that are specific for

Table 607-3	Differential Diagnosis of Infantile Hypotonia

Cerebral hypotonia
- Benign congenital hypotonia
- Chromosome disorders
- Prader-Willi syndrome
- Trisomy
- Chronic nonprogressive encephalopathy
- Cerebral malformation
- Perinatal distress
- Postnatal disorders
- Peroxisomal disorders
- Cerebrohepatorenal syndrome (Zellweger syndrome)
- Neonatal adrenoleukodystrophy
- Other genetic defects
- Familial dysautonomia
- Oculocerebrorenal syndrome (Lowe syndrome)
- Other metabolic defects
- Acid maltase deficiency (see "Metabolic Myopathies")
- Infantile G_M gangliosidosis

Spinal cord disorders

Spinal muscular atrophies
- Acute infantile
  - Autosomal dominant
  - Autosomal recessive
- Cytochrome-c oxidase deficiency
- X-linked
- Chronic infantile
  - Autosomal dominant
  - Autosomal recessive
- Congenital cervical spinal muscular atrophy
- Infantile neuronal degeneration
- Neurogenic arthrogryposis

Polyneuropathies
- Congenital hypomyelinating neuropathy
- Giant axonal neuropathy
- Hereditary motor-sensory neuropathies

Disorders of neuromuscular transmission
- Familial infantile myasthenia
- Infantile botulism
- Transitory myasthenia gravis

Fiber-type disproportion myopathies
- Central core disease
- Congenital fiber-type disproportion myopathy
- Myotubular (centronuclear) myopathy
- Acute
- Chronic
- Nemaline (nemaline rod) myopathy
- Autosomal dominant
- Autosomal recessive

Metabolic myopathies
- Acid maltase deficiency (Pompe disease)
- Cytochrome-c oxidase deficiency
- Other mitochondrial disorders
- Muscular dystrophies
- Bethlem myopathy
- Congenital dystrophinopathy
- Congenital muscular dystrophy
- Merosin deficiency primary
- Merosin deficiency secondary
- Merosin positive
- Congenital myotonic dystrophy

From Fenichel GM: The hypotonic infant. In Fenichel GM, editor: Clinical pediatric neurology: a signs and symptoms approach, *ed 5, Philadelphia, 2005, Saunders, p. 150.*

each of the various muscular dystrophies and include the dystrophins, merosin, sarcoglycans, and dystroglycans. Ryanodine receptors, important in myasthenia gravis and in malignant hyperthermia, also now can be demonstrated. In addition, immunocytochemical reactivities can distinguish the various types of inflammatory cells in autoimmune myopathies, including T and B lymphocytes and macrophages.

Table 607-4	Differential Diagnosis of Acute Flaccid Paralysis

Brainstem stroke

Brainstem encephalitis

Acute anterior poliomyelitis
- Caused by poliovirus
- Caused by other neurotropic viruses

Acute myelopathy
- Space-occupying lesions
- Acute transverse myelitis

Peripheral neuropathy
- Guillain-Barré syndrome
- Post–rabies vaccine neuropathy
- Diphtheritic neuropathy
- Heavy metals, biologic toxins, or drug intoxication
- Acute intermittent porphyria
- Vasculitic neuropathy
- Critical illness neuropathy
- Lymphomatous neuropathy

Disorders of neuromuscular transmission
- Myasthenia gravis
- Biologic or industrial toxins
- Tic paralysis

Disorders of muscle
- Hypokalemia
- Hypophosphatemia
- Inflammatory myopathy
- Acute rhabdomyolysis
- Trichinosis
- Familial periodic paralyses (normokalemic, hypokalemic, hyperkalemic)

From Hughes RAC, Camblath DR: Guillain-Barré syndrome, Lancet *366:1653–1666, 2005.*

Nerve Biopsy

The most commonly sampled nerve is the sural nerve, a pure sensory nerve that supplies a small area of skin on the lateral surface of the foot. Whole or fascicular biopsy specimens of this nerve may be taken. When the sural nerve is severed behind the lateral malleolus of the ankle, regeneration of the nerve occurs in more than 90% of cases, so that permanent sensory loss is not experienced. The sural nerve is often involved in many neuropathies whose clinical manifestations are predominantly motor.

Electron microscopy is performed on most nerve biopsy specimens because many morphologic alterations cannot be appreciated at the resolution of a light microscope. Teased fiber preparations are sometimes useful in demonstrating segmental demyelination, axonal swellings, and other specific abnormalities, but these time-consuming procedures are not done routinely. Special stains may be applied to ordinary frozen or paraffin sections of nerve biopsy material to demonstrate myelin, axoplasm, and metabolic products.

The molecular genetic identification of the specific mutation in many of the hereditary motor and sensory neuropathies, determined from blood samples, has rendered the nerve biopsy much less often performed than in the past, but it retains a great value in selected cases for which the etiology remains elusive despite genetic and electrophysiological testing.

Cardiac Assessment

Cardiac evaluation is important if myopathy is suspected because of involvement of the heart in muscular dystrophies and in inflammatory and metabolic myopathies. Electrocardiography often detects early cardiomyopathy or conduction defects that are clinically asymptomatic. At times, a more complete cardiac work-up, including echocardiography and consultation with a pediatric cardiologist, is indicated. Serial pulmonary function tests also should be performed in muscular dystrophies and in other chronic or progressive diseases of the motor unit.

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Chapter 608

Developmental Disorders of Muscle

Harvey B. Sarnat

A heterogeneous group of congenital neuromuscular disorders is known as the **congenital myopathies** (Tables 608-1 and 608-2). Most of these disorders have subcellular abnormalities that can be demonstrated only by muscle biopsy, by means of histochemistry and electron microscopy. In others, the muscle biopsy abnormality is not a subcellular anatomic defect but an aberration in the ratio and sizes of specific myofiber types. A genetic basis is demonstrated in many of the congenital myopathies, and molecular genetic testing from blood samples may confirm the diagnosis without muscle biopsy.

Most congenital myopathies are nonprogressive conditions, but some patients show slow clinical deterioration accompanied by additional changes in their muscle histology. In some congenital myopathies, such as severe neonatal nemaline myopathy, the clinical expression can be life-threatening because of dysphagia and respiratory and/or cardiac insufficiency. *Cardiomyopathy develops in some patients with congenital myopathies* (Table 608-3). Most of the diseases in the category of congenital myopathies are hereditary; others are sporadic. Although clinical features, including phenotype, can raise a strong suspicion of a congenital myopathy, the definitive diagnosis is determined by the histopathologic findings in the muscle biopsy specimen. In conditions for which the defective gene has been identified, the diagnosis may be established by the specific molecular analysis of the suspected gene expressed in lymphocytes. The morphologic and histochemical abnormalities differ considerably from those of the muscular dystrophies, spinal muscular atrophies, and neuropathies. Many are reminiscent of the embryologic development of muscle, thus suggesting possible defects in the genetic regulation of muscle development.

Congenital myopathies often show closer genetic relationships than previously appreciated between entities that have quite distinct pathologic phenotypes in the muscle biopsy and also distinctiveness in clinical expression with a degree of overlap. For example, mutation of the *tropomyosin-3* (*TPM3*) gene is one of the well-documented etiologies of nemaline myopathy, but identical genetic mutations of this gene are more recently also shown to be capable of causing isolated congenital fiber-type disproportion without nemaline rods, cap myopathy, centronuclear ("myotubular") myopathy, and central core/minicore disease.

MYOGENIC REGULATORY GENES AND GENETIC LOCI OF INHERITED DISEASES OF MUSCLE

A family of 4 myogenic regulatory genes shares encoding transcription factors of "basic helix-loop-helix" proteins associated with common DNA nucleotide sequences. These genes direct the differentiation of striated muscle from any undifferentiated mesodermal cell. The earliest basic helix-loop-helix gene to program the differentiation of myoblasts is myogenic factor 5 *(MYF5)*. The second gene, *myogenin,* promotes

Text continued on p. 2970

Table 608-1 Classification of Muscular Dystrophies

	INHERITANCE	OMIM NUMBER	LOCUS	GENE SYMBOL	PROTEIN	MAIN LOCALIZATION
Duchenne or Becker muscular dystrophy	X-R	310200 (Duchenne); 300376 (Becker)	Xq21·2	*DMD*	Dystrophin	Sarcolemma-associated protein
LIMB-GIRDLE MUSCULAR DYSTROPHY						
Type 1A	AD	159000	5q31	*MYOT*	Myotilin	Sarcomere-associated protein (Z disc)
Type 1B	AD	159001	1q21·2	*LMNA*	Lamin A/C	Nuclear lamina-associated protein
Type 1C	AD	607780	3p25	*CAV3*	Caveolin-3	Sarcolemma-associated protein
Type 1D	AD	603511	7q	*DNAJB6*	Co-chaperone DNAJB6	Sarcomere-associated protein (Z disc)
Type 1E	AD	602067	6q23	*DES*	Desmin	Intermediate filament protein
Type 1F	AD	608423	7q32	Unknown	Unknown	Unknown
Type 1G	AD	609115	4p21	Unknown	Unknown	Unknown
Type 1H	AD	613530	3p23–p25	Unknown	Unknown	Unknown
Type 2A	AR	253600	15q15·1	*CAPN3*	Calpain-3	Myofibril-associated proteins
Type 2B	AR	253601	2p13	*DYSF*	Dysferlin	Sarcolemma-associated protein
Type 2C	AR	253700	13q12	*SGCG*	γ-Sarcoglycan	Sarcolemma-associated protein
Type 2D	AR	608099	17q12–q21·33	*SGCA*	α-Sarcoglycan	Sarcolemma-associated protein
Type 2E	AR	604286	4q12	*SGCB*	β-Sarcoglycan	Sarcolemma-associated protein
Type 2F	AR	601287	5q33	*SGCD*	δ-Sarcoglycan	Sarcolemma-associated protein

Table 608-1 Classification of Muscular Dystrophies—cont'd

	INHERITANCE	OMIM NUMBER	LOCUS	GENE SYMBOL	PROTEIN	MAIN LOCALIZATION
Type 2G	AR	601954	17q12	*TCAP*	Titin cap (telethonin)	Sarcomere-associated protein (Z disc)
Type 2H	AR	254110	9q31–q34	*TRIM32*	Tripartite motif-containing 32 (ubiquitin ligase)	Sarcomeric-associated protein (Z disc)
Type 2I	AR	607155	19q13·3	*FKRP*	Fukutin-related protein	Putative glycosyltransferase enzymes
Type 2J	AR	608807	2q31	*TTN*	Titin	Sarcomeric protein
Type 2K	AR	609308	9q34	*POMT1*	Protein-1-O-mannosyltransferase 1	Glycosyltransferase enzymes
Type 2L	AR	611307	11p14·3	*ANO5*	Anoctamin 5	Transmembrane protein, possible sarcoplasmic reticulum
Type 2M	AR	611588	9q31	*FKTN*	Fukutin	Putative glycosyltransferase enzymes
Type 2N	AR	613158	14q24	*POMT2*	Protein-O-mannosyltransferase 2	Glycosyltransferase enzymes
Type 2O	AR	613157	1p34	*POMGNT1*	Protein-O-linked mannose β 1,2-N-aminyltransferase 1	Glycosyltransferase enzymes
Type 2P	AR	613818	3p21	*DAG1*	Dystrophin-associated glycoprotein 1	Sarcomeric-associated protein
Type 2Q	AR	613723	8q24	*PLEC1*	Plectin 1	Sarcolemma-associated protein (Z disc)
FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY						
Type 1	AD	158900	4q35	Unknown	DUX4 and chromatin rearrangement	Nuclear
Type 2	AD	158901	18	Unknown	SMCHD1	Structural maintenance of chromosome's flexible hinge domain containing 1
EMERY-DREIFUSS MUSCULAR DYSTROPHY						
X-linked type 1	X-R	310300	Xq28	*EMD*	Emerin	Nuclear membrane protein
X-linked type 2	X-R	300696	Xq27·2	*FHL1*	Four and a half LIM domain 1	Sarcomere and sarcolemma
Autosomal dominant	AD	2181350	1q21·2	*LMNA*	Lamin A/C	Nuclear membrane protein
Autosomal recessive	AR	604929	1q21·2	*LMNA*	Lamin A/C	Nuclear membrane protein
With nesprin-1 defect	AD	612998	6q25	*SYNE1*	Spectrin repeat containing, nuclear envelope 1 (nesprin-1)	Nuclear membrane protein
With nesprin-2 defect	AD	5612999	4q23	*SYNE2*	Spectrin repeat containing, nuclear envelope 2 (nesprin-2)	Nuclear membrane protein
Congenital muscular dystrophy with merosin deficiency (MDC1A)	AR	607855	6q2	*LAMA2*	Laminin α_2 chain of merosin	Extracellular matrix proteins
Congenital muscular dystrophy	AR	604801	1q42	Unknown	Unknown	Unknown
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (MDC1C)	AR	606612	19q13	*FKRP*	Fukutin-related protein	Putative glycosyltransferase enzymes
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (MDC1D)	AR	608840	22q12	*LARGE*	Like-glycosyl transferase	Putative glycosyltransferase enzymes
Fukuyama congenital muscular dystrophy	AR	253800	9q31–q33	*FCMD*	Fukutin	Putative glycosyltransferase enzymes

Continued

Table 608-1 Classification of Muscular Dystrophies—cont'd

	INHERITANCE	OMIM NUMBER	LOCUS	GENE SYMBOL	PROTEIN	MAIN LOCALIZATION
WALKER–WARBURG SYNDROME						
With fukutin defect	AR	236670	9q31–q33	*FCMD*	Fukutin	Putative glycosyltransferase enzymes
With protein-O-mannosyltransferase 1 defect	AR	236670	9q34	*POMT1*	Protein-1-O-mannosyltransferase 1	Glycosyltransferase enzymes
With protein-O-mannosyltransferase 2 defect	AR	236670	14q24	*POMT2*	Protein-O-mannosyltransferase 2	Glycosyltransferase enzymes
With protein-O-linked mannose β 1,2-N-aminyltransferase 1 defect	AR	236670	1p34	*POMGNT1*	Protein-O-linked mannose β 1,2-N-aminyltransferase 1	Glycosyltransferase enzymes
With fukutin-related protein defect	AR	236670	19q13	*FKRP*	Fukutin-related protein	Putative glycosyltransferase enzymes
MUSCLE-EYE-BRAIN DISEASE						
With protein-O-linked mannose β 1,2-N-aminyltransferase 1 defect	AR	253280	1p34	*POMGNT1*	Protein-O-linked mannose β 1,2-N-aminyltransferase 1	Glycosyltransferase enzymes
With fukutin-related protein defect	AR	253280	19q13	*FKRP*	Fukutin-related protein	Putative glycosyltransferase enzymes
With protein-O-mannosyltransferase 2 defect	AR	253280	14q24	*POMT2*	Protein-O-mannosyltransferase 2	Glycosyltransferase enzymes
Congenital muscular dystrophy caused by glycosylation disorder	AR	NA	9q34·1	*DPM2*	Dolichyl-phosphate mannosyltransferase polypeptide 2	Glycosyltransferase enzymes
Congenital muscular dystrophy caused by glycosylation disorder	AR	NA	1q21·3	*DPM3*	Dolichyl-phosphate mannosyltransferase polypeptide 3	Glycosyltransferase enzymes
Congenital muscular dystrophy with mitochondrial structural abnormalities	mtDNA	602541	22q13	*CHKB*	Choline kinase	Sarcolemmal and mitochondrial membrane
Congenital muscular dystrophy with rigid spine syndrome	AR	602771	1p36	*SEPN1*	Selenoprotein N1	Endoplasmic reticulum protein
ULLRICH SYNDROME						
With collagen type VI subunit α_1 defect	AR	254090	21q22·3	*COL6A1*	Collagen type VI, subunit α_1	Extracellular matrix proteins
With collagen type VI subunit α_2 defect	AR	254090	21q22·3	*COL6A2*	Collagen type VI, subunit α_2	Extracellular matrix proteins
With collagen type VI subunit α_3 defect	AR	254090	2q37	*COL6A3*	Collagen type VI, subunit α_3	Extracellular matrix proteins
Congenital muscular dystrophy with integrin α_7 defect	AR	613204	12q13	*ITGA7*	Integrin α_7	External sarcolemmal protein
Congenital muscular dystrophy with integrin α_9 defect	AR	NA	3p21·3	*ITGA9*	Integrin α_9	External sarcolemmal protein
Muscular dystrophy with generalized lipodystrophy	AR	NA	17q21–q23	*PTRF*	Polymerase I and transcript release factor (cavin-1)	T tubules and sarcolemma
Oculopharyngeal muscular dystrophy	AD or AR	164300	14q11·2	*PABPN1*	Polyadenylate-binding protein nuclear 1	Unknown

AD, autosomal dominant; AR, autosomal recessive; NA, not assigned; OMIM, Online Mendelian Inheritance in Man; X-R, X-linked recessive.

From Mercuri E, Muntoni F: Muscular dystrophies. Lancet *381:845–858, 2013, Table 1.*

Table 608-2 Clinical Signs of Muscular Dystrophy

	MOTOR FUNCTION	DISTRIBUTION OF WEAKNESS	RIGID SPINE	CARDIOMYOPATHY	RESPIRATORY IMPAIRMENT	DISEASE COURSE	INCREASED CK	OTHER SIGNS
CONGENITAL-ONSET MUSCULAR DYSTROPHY								
Congenital muscular dystrophy with merosin deficiency	Independent ambulation generally not achieved in patients with absent merosin	Upper limbs > lower limbs	–	Not frequent	++	Slowly progressive	++	White matter changes on brain MRI
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (Walker-Warburg syndrome, muscle-eye-brain disease, congenital muscular dystrophy type 1C, etc.)	Independent ambulation generally not achieved	Upper limbs > lower limbs	–	Not frequent	+	Slowly progressive	++	Frequent structural brain changes
Congenital muscular dystrophy with rigid spine syndrome type 1 (SEPN1)	Ambulation achieved	Axial muscles > limbs	++	–	Early respiratory failure	Progression of respiratory signs > motor signs	N or +	Scoliosis
Ullrich syndrome	Ambulation achieved in ~50% but lost by middle teens	Proximal and axial	++	–	Early respiratory failure	Progression of respiratory and motor signs	N or +	Distal laxity
FROM EARLY-ONSET TO CHILDHOOD-ONSET MUSCULAR DYSTROPHY								
Duchenne muscular dystrophy	Independent ambulation achieved, but lost before age of 13 yr	Proximal > distal (pattern A)	–	++	++	Progression of motor, cardiac, and respiratory signs	++	Mental retardation in 30%
Emery-Dreifuss muscular dystrophy with lamin AC deficiency (type 2)	Ambulation achieved in all cases except for rare cases with congenital onset	Scapuloperoneal (pattern B)	++	++	In adulthood in the typical form, but also in childhood (congenital variants)	Slowly progressive	+ (+)	Frequent association with Dunningham-type lipodystrophy
Limb-girdle muscular dystrophy with lamin AC deficiency (type 1B)	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	+	++	In adulthood	Progression of cardiac signs > motor signs	+ (+)	None
Limb-girdle muscular dystrophy with calpain deficiency (type 2A)	Ambulation achieved	Proximal > distal (pattern A)	+	–	Not frequent	Slow progression	++	None

Continued

Table 608-2 Clinical Signs of Muscular Dystrophy—cont'd

	MOTOR FUNCTION	DISTRIBUTION OF WEAKNESS	RIGID SPINE	CARDIOMYOPATHY	RESPIRATORY IMPAIRMENT	DISEASE COURSE	INCREASED CK	OTHER SIGNS
CHILDHOOD-ONSET AND ADULTHOOD-ONSET MUSCULAR DYSTROPHY								
Becker muscular dystrophy	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	–	++	Not frequent	Progressive with substantial variability	++	None
Limb-girdle muscular dystrophy with sarcoglycan deficiency (types 2C, 2D, 2E, 2F)	Independent ambulation achieved, generally lost in the 2nd decade	Proximal > distal (pattern A)	–	++	++	Progression of motor, cardiac, and respiratory signs	++	None
Limb-girdle muscular dystrophy with abnormal glycosylation of dystroglycan (types 2I, 2K, 2L, 2M, 2N, 2O)	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	–	++	+(+)	Progressive	++	Mental retardation reported in some cases
Limb-girdle muscular dystrophy with dysferlin deficiency (type 2B)	Independent ambulation always achieved	Both pattern A and pattern E	–	–	–	Progressive in adulthood	++	None
Limb-girdle muscular dystrophy with telethonin deficiency (type 2G)	Independent ambulation achieved, generally lost in the 4th decade	Proximal > distal (pattern A); in some pattern B	–	+	+	Progressive in adulthood	+ (+)	None
Limb-girdle muscular dystrophy with titin deficiency (type 2J)	Independent ambulation achieved	Proximal > distal (pattern A) but also pattern E	–	–	–	Roughly half lose ambulation in adulthood	++	None
Facioscapulohumeral dystrophy	Independent ambulation achieved, variable progression	Pattern D	–	–	Uncommon and mild	Slowly progressive	N or +	Neurosensory hearing loss and retinal degeneration
Emery-Dreifuss muscular dystrophy with merin deficiency (type 1)	Independent ambulation achieved, variable progression	Scapuloperoneal (pattern B)	+	++	Not frequent	Progression of cardiac signs > motor signs	+ (+)	None
ADULT-ONSET MUSCULAR DYSTROPHY								
Limb-girdle muscular dystrophy with anoctamin deficiency (type 2L)	Onset in adulthood, 8:1 ratio of men to women	Mainly lower limbs pattern A, rarely pattern E	–	–	–	Slowly progressive in adulthood	++	None
Limb-girdle muscular dystrophy type 1A (myotilin)	Independent ambulation achieved	Proximal > distal (pattern A)	–	–	–	Generally slowly progressive in adulthood	+	Dysarthria in some cases
Limb-girdle muscular dystrophy with caveolin deficiency (type 1C)	Independent ambulation achieved; rippling might be seen before weakness	Proximal and distal	–	+	–	Slowly progressive, variable	++	Cramps, rippling, percussion-induced repetitive contractions

–, Absent; +, mild; ++, severe; +(+), variable; CK, creatine kinase; N, normal.
From Mercuri E, Muntoni F: Muscular dystrophies. Lancet *381:845–858, 2013, Table 2.*

Table 608-3 Cardiac Involvement in Muscular Dystrophies

	ONSET AND FIRST SIGNS	PROGRESSION	CARDIAC DEATH	SURVEILLANCE
Duchenne muscular dystrophy	Dilated cardiomyopathy with reduced left-ventricular ejection fraction after 10 yr of age	Dilated cardiomyopathy in almost all patients by 18 yr of age. Ventricular dysrhythmias occur in older patients	Congestive heart failure or sudden death in 20% of patients, although the contribution of heart to death of ventilated patients is now well established	Echocardiography every 2 yr in the 1st decade of life and annually after 10 yr of age (or more frequently if abnormalities are identified)
Becker muscular dystrophy	Dilated cardiomyopathy, generally after 10 yr of age	Present in 40% of patients older than 18 yr and more than 80% of those older than 40 yr. Most patients develop dilated cardiomyopathy followed by ventricular arrhythmias	Death from congestive heart failure and arrhythmias is estimated to occur in up to 50% of cases. Cardiac transplants reported	Echocardiography at least every 5 yr
Myotonic dystrophy	Cardiac abnormalities can occur as early as the 2nd decade of life	Conduction deficits occur in about 65% of adult patients	20-30% of patients; mean 54 yr of age. Sudden death is mainly caused by conduction blocks, but ventricular tachyarrhythmias are also a possible cause of death	ECG yearly. Holter monitoring is recommended in patients with ECG abnormalities to detect asymptomatic conduction blocks and arrhythmias
EMERY-DREIFUSS MUSCULAR DYSTROPHY				
X-linked recessive Emery-Dreifuss muscular dystrophy (type 1)	Conduction disturbances generally in the 2nd decade	Ventricular myocardium might become involved, leading to mild ventricular dilation and low-to-normal systolic function	Sudden death is by far the most common cause of death and can be very unpredictable	ECG and yearly Holter monitoring are indicated. Pacemaker implantation should be considered if sinus node or atrioventricular node disease develops. Defibrillator might be needed in some patients
Emery-Dreifuss muscular dystrophy 2 and limb-girdle muscular dystrophy 1B	Conduction disease and cardiac failure	Dysrhythmias (sinus bradycardia, atrioventricular conduction block, or atrial arrhythmias) present in 92% of patients older than 30 yr	Sudden death reported also in patients with pacemaker. Rare death with defibrillator also reported. Cardiac failure. Cardiac transplants reported	ECG and yearly Holter monitoring are indicated. Defibrillator implantation should be considered as pacemaker does not have a substantial effect on mortality
LIMB-GIRDLE MUSCULAR DYSTROPHY				
Sarcoglycanopathies	ECG and/or echocardiographic abnormalities reported in 20-30% of patients (especially β and δ variants; less common in α variant)	Severe dilated cardiomyopathy and lethal ventricular arrhythmias might occur in patients with Duchenne muscular dystrophy–like dystrophy	Typically by cardiac failure. Cardiac transplants reported	No evidence-based standards of care exist, but experts have made recommendations
Limb-girdle muscular dystrophy 2I	Cardiac involvement reported in 29-62% of limb-girdle muscular dystrophy 2I. Dilated cardiomyopathy may start in teenage yr	Symptomatic cardiac failure over time, at a mean age of 38 yr (range: 18-58 yr)	Cardiac failure. Cardiac transplants reported	No evidence-based standards of care exist, but experts have made recommendations
Limb-girdle muscular dystrophy 1E	Dilated, restrictive, hypertrophic cardiomyopathies and arrhythmias. Cardiac involvement can precede muscle weakness in some patients	Major cardiac signs, such as atrioventricular block, can be the presenting symptom or occur within a decade of onset of muscle weakness	Life-threatening cardiac complications in roughly 50% of patients, at a mean age of 40 yr, including sudden death, end-stage heart failure, atrioventricular block, and syncope	No evidence-based standards of care exist, but experts have made recommendations

Continued

Table 608-3 Cardiac Involvement in Muscular Dystrophies—cont'd

	ONSET AND FIRST SIGNS	PROGRESSION	CARDIAC DEATH	SURVEILLANCE
CONGENITAL MUSCULAR DYSTROPHY				
Congenital muscular dystrophy merosin muscular dystrophy type C1A	Occasional reports of reduced left ventricular systolic function	Not well characterized	Rare by cardiac failure	No evidence-based standards of care exist, but experts have made recommendations
Fukuyama congenital muscular dystrophy	Systolic left-ventricular dysfunction may develop in the 2nd decade	Symptomatic cardiac failure over time	Death from congestive heart failure might occur by the age of 20 yr	No evidence-based standards of care exist, but experts have made recommendations
Muscular dystrophy type C1C	Dilated cardiomyopathy reported in young children	Not well characterized	Not reported	No evidence-based standards of care exist, but experts have made recommendations
Facioscapulohumeral muscular dystrophy	Uncommon	Not well characterized	Not reported	No evidence-based standards of care exist, but experts have made recommendations

ECG, electrocardiogram.
From Mercuri E, Muntoni F: Muscular dystrophies. Lancet *381:845–858, 2013, Table 3.*

fusion of myoblasts to form myotubes. *Herculin* (also known as *MYF6*) and *MYOD1* are the other 2 myogenic genes. *Myf5* cannot support myogenic differentiation without myogenin, *MyoD,* and *MYF6.* Each of these 4 genes can activate the expression of at least 1 other and, under certain circumstances, can autoactivate as well. Another recently discovered gene known as **myomaker** also facilitates myoblast fusion. The expression of *MYF5* and of *herculin* is transient in early ontogenesis but returns later in fetal life and persists into adult life.

The human locus of the *MYOD1* gene is on chromosome 11, very near to the domain associated with embryonal rhabdomyosarcoma. The genes *Myf5* and *herculin* are on chromosome 12, and *myogenin* is on chromosome 1.

The myogenic genes are activated during muscle regeneration, recapitulating the developmental process; *MyoD* in particular is required for myogenic stem cell (satellite cell) activation in adult muscle. *PAX3, PAX7,* and *WNT3a* genes also play important roles in myogenesis and interact with each of the 4 basic genes mentioned above. Another gene, *myostatin,* is a negative regulator of muscle development by preventing myocytes from differentiating. The precise integrative roles of the myogenic genes in developmental myopathies are not yet fully defined.

The myogenic genes are important not only for fetal myogenesis but also for regeneration of muscle at any age, particularly in degenerative diseases such as muscular dystrophies and autoimmune inflammatory myopathies and in injuries of muscle secondary to trauma or to toxins. Satellite cells in mature muscle that mediate regeneration have the same somitic origin as embryonic muscle progenitor cells, but the genes that regulate them differ. *Pax3* and *Pax7* mediate the migration of primitive myoblast progenitors from the myotomes of the somites to their peripheral muscle sites in the embryo, but only 1 of 2 *Pax7* genes continues to act postnatally for satellite cell survival. Then it, too, no longer is required after the juvenile period for muscle satellite (i.e., stem) cells to become activated for muscle regeneration.

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608.1 Myotubular Myopathy (Centronuclear Myopathy)

Harvey B. Sarnat

The term **myotubular myopathy** is a misnomer because it implies maturational arrest of fetal muscle during the myotubular stage of development at 8-15 wk of gestation. It was based on the morphologic appearance of myofibers as a row of central nuclei and mitochondria within a core of cytoplasm, with contractile myofibrils forming a cylinder around this core (Fig. 608-1). These morphologically abnormal myofibers are not true fetal myotubes, however; hence the more neutral and descriptive term **centronuclear myopathy** is preferred.

PATHOGENESIS

The common pathogenesis involves loss of myotubularin protein, leading to structural and functional abnormalities in the organization of T-tubules and sarcoplasmic reticulum and defective excitation-contraction coupling.

CLINICAL MANIFESTATIONS

Fetal movements can decrease in late gestation. Polyhydramnios is a common complication because of pharyngeal weakness of the fetus and inability to swallow amniotic fluid.

At birth, affected infants have a thin muscle mass involving axial, limb girdle, and distal muscles; severe generalized hypotonia; and diffuse weakness. Respiratory efforts may be ineffective, requiring ventilatory support. Gavage feeding may be required because of weakness of the muscles of sucking and deglutition. The testes are often undescended. Facial muscles may be weak, but infants do not have the characteristic facies of myotonic dystrophy. Ptosis may be a prominent feature. Ophthalmoplegia is observed in a few cases. The palate may be high. The tongue is thin, but fasciculations are not seen. Tendon stretch reflexes are weak or absent.

Myotubular myopathy is not associated with cardiomyopathy (mature cardiac muscle fibers normally have central nuclei), but one report describes complete atrioventricular block without cardiomyopathy in a patient with confirmed X-linked myotubular myopathy. Congenital anomalies of the central nervous system or of other systems are not associated. A single patient with progressive dementia was reported, who had a mutation removing the start signal of exon 2. Patients with much milder symptoms or a much later age of onset with mutations in the same gene are now known. Some of these are manifesting carriers.

LABORATORY FINDINGS

Serum levels of creatine kinase (CK) are normal. Electromyography does not show evidence of denervation; results are usually normal or show minimal nonspecific myopathic features in early infancy. Nerve conduction velocity may be slow but is usually normal. The

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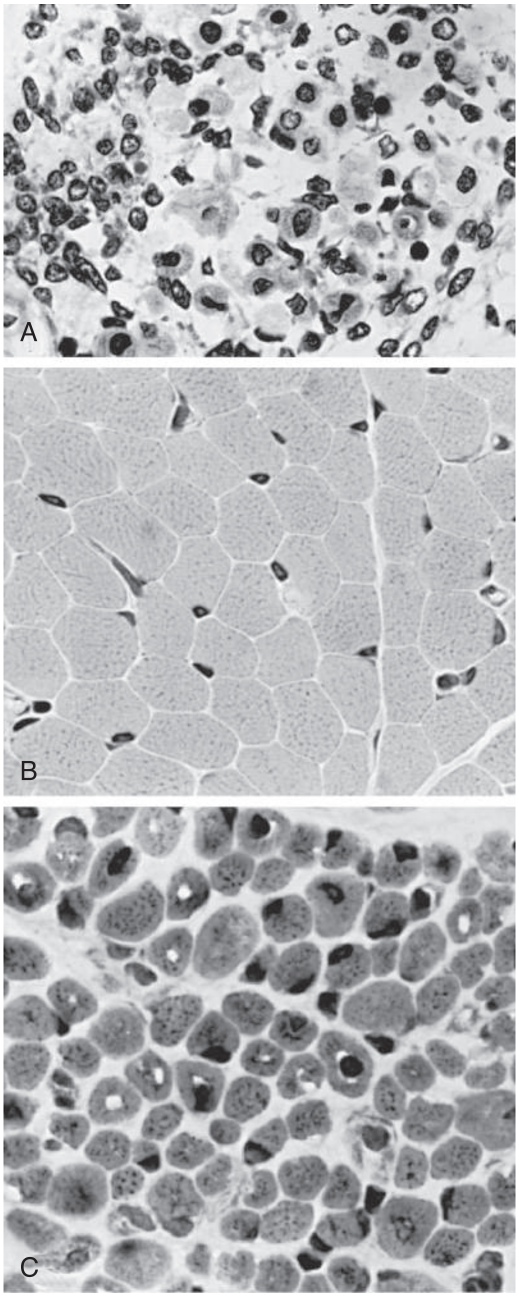

Figure 608-1 Cross section of muscle from a 14 wk old human fetus **(A),** a normal full-term neonate **(B),** and a term neonate with X-linked recessive myotubular myopathy **(C).** Myofibers have large central nuclei in the fetus and in myotubular myopathy patient, and nuclei are at the periphery of the muscle fiber in the term neonate as in the adult (hematoxylin and eosin, ×500).

electrocardiogram appears normal. Chest radiographs show no cardiomegaly; the ribs may be thin.

DIAGNOSIS

If the diagnosis is strongly suspected from the clinical presentation, especially if this diagnosis was confirmed in a sibling, genetic tests can be performed in the neonatal period. In most cases the diagnosis is not so evident, but the muscle biopsy findings are diagnostic at birth, even in premature infants. More than 90% of muscle fibers are small and have centrally placed, large vesicular nuclei in a single row. Spaces between nuclei are filled with sarcoplasm containing mitochondria. Histochemical stains for oxidative enzymatic activity and glycogen reveal a central distribution as in fetal myotubes. The cylinder of myofibrils shows mature histochemical differentiation with adenosine triphosphatase stains. The connective tissue of muscle spindles, blood vessels, intramuscular nerves, and motor end plates is mature. Ultrastructural features other than those that define the disease are also mature. Electron microscopy shows disorganized triads and focal loss of myofilaments. Vimentin and desmin show strong immunoreactivity in muscle fibers in congenital centronuclear myopathy and no demonstrable activity in normal term neonatal muscle. The molecular genetic marker in blood is available also for early prenatal diagnosis if suspicion is strong because of family history. Table 608-4 distinguishes centronuclear myopathy from other congenital myopathies.

GENETICS

At least 5 genes are involved in this disorder and account for approximately 80% of patients. These include mutations in myotubularin (*MTM1* gene) with X-linked severe manifestations; dynamin 2 (*DNM2*) with autosomal dominant or sporadic occurrence; amphiphysin 2 (*BIN1*) and titin (*TTN*) mutations with autosomal recessive inheritance and ryanodine receptor 1 (*RYR1*), with autosomal recessive or sporadic occurrence.

X-linked recessive inheritance is the most common trait in this disease affecting boys. The mothers of affected infants are clinically asymptomatic, but their muscle biopsy specimens show minor alterations. Genetic linkage on the X chromosome has been localized to the Xq28 site, a locus different from the Xp21 gene of Duchenne and Becker muscular dystrophies. A deletion in the responsible *MTM1* gene has been identified. It encodes a protein called myotubularin. This gene belongs to a family of similar genes encoding enzymatically active and inactive forms of phosphatidylinositol-3-phosphatases that form dimers. *MTM1*, dynamin-2, and amphiphysin all are localized to the T-tubule wall in triads. This crucial region is where the action potential releases a signal to the ryanodine receptor to release calcium. The pathogenesis is in the regulation of enzymatic activity and binding to other proteins induced by dimer interactions. Although only a single *MTM1* gene is involved, 5 distinct point mutations and many different alleles, as well as large duplications, can produce the same clinical disease. Mutations in the dynamin-2 protein result in an autosomal dominant form of centronuclear myopathy and may account for up to half of all patients with centronuclear myopathy, but these cases usually are mild and might not manifest clinically until adult life as diffuse, slowly progressive weakness and generalized muscular pseudohypertrophy.

Other **rarer centronuclear myopathies** also are known; some are autosomal recessive and affect both sexes and others are sporadic and of unknown genetic origin. The recessive forms are sometimes divided into an early-onset form with or without ophthalmoplegia and a late-onset form without ophthalmoplegia.

TREATMENT

Only supportive and palliative treatment is presently available. Progressive scoliosis may be treated by long posterior fusion. Genetic and neuropathologic studies of X-linked centronuclear ("myotubular") myopathy have led to effective gene therapy in mice and in dogs, so that even after a single dose the animals are more ambulatory and have much improved weakness. Gene replacement therapy in this disease is now being studied in humans.

PROGNOSIS

Approximately 75% of severely affected neonates with the X-linked disease die within the 1st few wk or mo of life. Survivors do not experience a progressive course but have major physical handicaps, rarely walk, and remain severely hypotonic. Late-onset and especially autosomal dominant forms have a much better prognosis, often with mild static weakness.

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Table 608-4 Specific Congenital Myopathies: Distinguishing Clinical Features

MYOPATHY	NEONATAL HYPOTONIA AND WEAKNESS	SEVERE FORM WITH NEONATAL DEATH	FACIAL WEAKNESS	PTOSIS	EXTRAOCULAR MUSCULAR WEAKNESS
Central core disease	+	0	±	0	0
Nemaline myopathy	+	+	+	0	0
Myotubular myopathy (centronuclear myopathy)	+	+	+	+	+
Congenital fiber-type disproportion	+	±	±	0	+

+, Often a prominent feature; ±, variably a prominent feature; 0, not a prominent feature.
From Volpe JJ: Neurology of the newborn, *ed 5, Philadelphia, 2008, Elsevier Saunders, p. 820.*

608.2 Congenital Muscle Fiber-Type Disproportion

Harvey B. Sarnat

Congenital muscle fiber-type disproportion (CMFTD) occurs as an isolated congenital myopathy but also develops in association with various unrelated disorders that include nemaline rod disease, Krabbe disease (globoid cell leukodystrophy) early in the course before expression of the neuropathy, cerebellar hypoplasia and certain other brain malformations, fetal alcohol syndrome, some glycogenoses, multiple sulfatase deficiency, Lowe syndrome, rigid spine myopathy, and some infantile cases of myotonic muscular dystrophy. CMFTD should, therefore, be regarded as a syndrome, unless a specific genetic mutation is confirmed.

PATHOGENESIS

The association of CMFTD with cerebellar hypoplasia suggests that the pathogenesis may be an abnormal suprasegmental influence on the developing motor unit during the stage of histochemical differentiation of muscle between 20 and 28 wk of gestation. Muscle fiber types and growth are determined by innervation and are mutable even in adults. Although CMFTD does not actually correspond with any normal stage of development, it appears to be an embryologic disturbance of fiber type differentiation and growth.

CLINICAL MANIFESTATIONS

As an isolated condition not associated with other diseases, CMFTD is a nonprogressive disorder present at birth. Patients have generalized hypotonia and weakness, but the weakness is usually not severe and respiratory distress and dysphagia are rare. Contractures are present at birth in 25% of patients. Poor head control and developmental delay for gross motor skills are common in infancy. Walking is usually delayed until 18-24 mo but is eventually achieved. Because of the hypotonia, subluxation of the hips can occur. Muscle bulk is reduced. The muscle wasting and hypotonia are proportionately greater than the weakness, and the child may be stronger than expected during examination. Cardiomyopathy is a rare complication.

The facies of children with CMFTD often raise suspicion, especially if the child is referred for assessment of developmental delay and hypotonia. The head is dolichocephalic, and facial weakness is present. The palate is usually high arched. Thin muscles of the trunk and extremities give a thin, wasted appearance. The phenotype is very similar to that of nemaline myopathy that also includes CMFTD as part of the pathologic picture. Patients do not complain of myalgias. The clinical course is nonprogressive.

LABORATORY FINDINGS

Serum CK, electrocardiogram, electromyography, and nerve conduction velocity results are normal in simple CMFTD. If other diseases are associated, laboratory investigation of those conditions discloses the specific features.

DIAGNOSIS

CMFTD is diagnosed by muscle biopsy that shows disproportion in size and relative ratios of histochemical fiber types: Type I fibers are uniformly small, and type II fibers are hypertrophic; type I fibers are more numerous than type II fibers. Degeneration of myofibers and other primary myopathic features are absent. The biopsy is diagnostic at birth. Table 608-2 lists the features that distinguish CMFTD from other congenital myopathies.

GENETICS

Many cases of simple CMFTD are sporadic, although autosomal recessive inheritance is well documented in some families and an autosomal dominant trait is suspected in others. The genetic basis is heterogeneous in hereditary forms; a mutation in the insulin receptor gene at 19p13.2 is reported. Translocation t(10;17) was seen in 1 family. X-linked transmission with linkage to Xp23.12-p11.4 and Xq13.1-q22.1 also is described. In 3 unrelated families with CMFTD, a heterozygous missense mutation of the skeletal muscle α-actin gene (*ACTA1*) was demonstrated, but this genetic defect represents a minority; mutations in *TPM3* are a more common genetic finding. As with X-linked myotubular myopathy, large duplications in the *TPM3* gene can cause CMFTD. In CMFTD associated with cerebellar hypoplasia, the genetic effect is on cerebellar development and the muscular expression is secondary.

TREATMENT

No drug therapy is available. Physiotherapy may be helpful for some patients in strengthening muscles that do not receive sufficient exercise in daily activities. Mild congenital contractures often respond well to gentle range-of-motion exercises and rarely require plaster casting or surgery.

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608.3 Nemaline Rod Myopathy

Harvey B. Sarnat

Nemaline rods (derived from the Greek *nema*, meaning "thread") are rod-shaped, inclusion-like abnormal structures within muscle fibers. They are difficult to demonstrate histologically with conventional hematoxylin-and-eosin stain, but are easily seen with special stains. They are not foreign inclusion bodies but rather consist of excessive Z-band material with a similar ultrastructure (Fig. 608-2). Chemically, the rods are composed of actin, α-actinin, tropomyosin-3, and the protein nebulin. Nemaline rod formation may be an unusual reaction of muscle fibers to injury because these rod structures have rarely been found in other diseases. They are most abundant in the congenital myopathy known as *nemaline rod disease.* Most rods are within the myofibrils, but intranuclear rods are occasionally demonstrated by electron microscopy. Intranuclear rods occur mainly in neonates with

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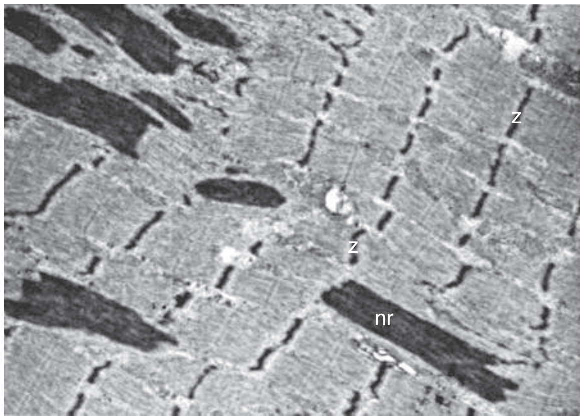

Figure 608-2 Electron micrograph of the muscle from a patient shown in Figure 608-4. Nemaline rods *(nr)* are seen within many myofibrils. They are identical in composition to the normal Z bands *(z)* (×6,000).

Figure 608-3 Back of a 13 yr old girl with the juvenile form of nemaline rod disease. The paraspinal muscles are very thin, and winging of the scapulas is evident. The muscle mass of the extremities is also greatly reduced proximally and distally.

severe weakness; they usually indicate *ACTA1* mutations and may coexist with the more usual cytoplasmic rods. Nemaline myopathy caused by *ACTA1* mutation is one of a spectrum of "actinopathies."

Mutations in tropomyosin-2 (*TPM2*) can cause a congenital myopathy related to nemaline rod myopathy, designated **cap myopathy**, in which accumulations of distorted myofilaments are focally present on the periphery of fibers. They may coexist with myofibrillar nemaline rods. Somatic mosaicism is demonstrated in *TPM2*-related nemaline myopathy with cap structures.

CLINICAL MANIFESTATIONS

Neonatal, infantile, and juvenile forms of the disease are known. The neonatal form is severe and usually fatal because of respiratory failure since birth. In the infantile form, generalized hypotonia and weakness, which can include bulbar-innervated and respiratory muscles, and a very thin muscle mass are characteristic (Fig. 608-3).

Figure 608-4 Infantile form of nemaline rod disease in a 6 yr old boy. Facial weakness and generalized muscle wasting are severe. The head is dolichocephalic. The mouth is usually open because the masseters are too weak to lift the mandible against gravity for more than a few seconds.

The head is dolichocephalic, and the palate high arched or even cleft. Muscles of the jaw may be too weak to hold it closed (Fig. 608-4). Decreased fetal movements are reported by the mother, and neonates suffer from hypoxia and dysphagia; arthrogryposis may be present. Infants with severe neonatal and infantile nemaline myopathy have facies and phenotype that are nearly indistinguishable from those of neonatal myotonic dystrophy, but their mothers have normal facies. The juvenile form is the mildest and is not associated with respiratory failure, but the phenotype, including facial involvement, is similar.

LABORATORY FINDINGS

Serum CK level is normal or mildly elevated. The muscle biopsy is diagnostic. In addition to the characteristic nemaline rods, it also shows CMFTD or at least fiber type I predominance. In some patients, uniform type I fibers are seen with few or no type II fibers. Focal myofibrillar degeneration and an increase in lysosomal enzymes have been found in a few severe cases associated with progressive symptoms. Intranuclear nemaline rods, demonstrated by electron microscopy, correlate with the most severe neonatal manifestations. Because nemaline bodies can occur in other myopathies, their presence in the muscle biopsy is not pathognomonic in the absence of the supportive clinical manifestations. Adult-onset cases may be associated with monoclonal gammopathy.

GENETICS

Autosomal dominant and autosomal recessive forms of nemaline rod disease occur, and an X-linked dominant form in girls also can occur. Nemaline myopathy can be caused by mutation in at least 7 genes, including α-actin, α-tropomyosin, β-tropomyosin, troponin-T, nebulin, cofilin-2, and Kelch-like family member *(KLML40)*. The latter causes severe neonatal autosomal recessive nemaline myopathy. The proteins encoded for by all these genes are related to the thin filaments of myofibrils. Dominant nemaline myopathy is most often caused by mutations in *ACTA-1* or α-tropomyosin (*TPM3* at the 1q21-q23 locus); recessive mutations most frequently result from nebulin mutations (2q21.2-q22 locus), which account for about half the cases of nemaline myopathy and are particularly prevalent in Ashkenazi Jews. Some

mutations in the α-actin gene give rise to a severe neonatal myopathy with masses of exclusively thin filaments, with or without rods. Mutations in tropomyosin-2 can cause a congenital myopathy with nonspecific findings. In α-actin defects both autosomal dominant and recessive varieties occur at the same 1q42.1 locus. The autosomal dominantly inherited defect of β-tropomyosin at 9q13 and the α-tropomyosin defects are rare and account for only 3% of patients with nemaline myopathy. An autosomal recessive troponin-T defect is at locus 19q13 and has been found only in the Amish population, in whom the incidence of nemaline myopathy is as high as 1 in 500, whereas in Australia in non-Amish ethnic groups it is estimated at 1 in 500,000.

TREATMENT AND PROGNOSIS

Therapy is supportive. Survivors are confined to an electric wheelchair and are usually unable to overcome gravity. Both proximal and distal muscles are involved. Congenital arthrogryposis can occur and predicts a poor prognosis. Gastrostomy may be needed for chronic dysphagia. In the juvenile form, patients are ambulatory and are able to perform most tasks of daily living. Weakness is not usually progressive, but some patients have more difficulty over time or enter a phase of progressive weakness. Cardiomyopathy is an uncommon complication. Death usually results from respiratory insufficiency, with or without superimposed pneumonia.

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608.4 Central Core, Minicore, and Multicore Myopathies

Harvey B. Sarnat

Central core disease most often manifests itself in children with slow motor development who are hypotonic and have mild weakness especially in the hip girdle; congenital dislocation or dysplasia of the hips may be diagnosed in the neonatal period. In older children, central core disease is an important differential diagnosis of progressive thoracolumbar scoliosis. Central core myopathies are transmitted as either an autosomal dominant or recessive trait and are caused by the same abnormal gene at the 19q13.1 locus. This gene programs the ryanodine receptor *(RYR1)*, a tetrameric receptor that contains a non–voltage-gated calcium channel; it is prevalent in the sarcoplasmic reticulum and especially at the junction of the T-tubule with the cisternae of the sarcoplasmic reticulum. It contains the channel by which calcium is released among the myofilaments. Mutations in the *RYR1* gene are also the cause of **malignant hyperthermia**.

Infantile hypotonia, proximal weakness, muscle wasting, and involvement of facial muscles and neck flexors are the typical features in both the dominant and recessive forms. Contractures of the knees, hips, and other joints are common, and kyphoscoliosis and pes cavus often develop, even without much axial or distal muscle weakness. There is a high incidence of cardiac abnormalities. The course is not progressive, except for the contractures. In one variant, external ophthalmoplegia also is present. Rare cases of minicore myopathy also show hypertrophic cardiomyopathy associated with short-chain acyl-coenzyme A dehydrogenase deficiency.

The disease is characterized pathologically by central cores within muscle fibers in which only amorphous, granular cytoplasm is found with an absence of myofibrils and organelles. Histochemical stains show a lack of enzymatic activities of all types within these cores, as well as absence of contractile proteins (actin and myosin) that form the thin and thick myofilaments. Variants of central cores, called *minicores* and *multicores*, are described in some families.

Minicores or multicores are small areas, usually multiple within muscle fibers, that lack mitochondria and show Z-disc streaming. They can be caused by mutations in the gene (*SEPN1*) for the selenoprotein N, localized to triads, but *RYR1* mutations also are reported. The distinction previously made between single and multiple cores in myofibers is now believed to be of little importance and they represent the same basic disease process.

The serum CK value is normal in central core disease except during crises of malignant hyperthermia, which can result in rhabdomyolysis or extensive acute myofiber necrosis (see Chapter 611.2). Central core disease is consistently associated with malignant hyperthermia, which can precede the diagnosis of central core disease. All patients should have special precautions with pretreatment with dantrolene before an anesthetic agent is administered.

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608.5 Myofibrillar Myopathies

Harvey B. Sarnat

Most myofibrillar myopathies are not symptomatic in childhood, but occasionally older children and adolescents show early symptoms of nonspecific proximal and distal weakness. An infantile form also occurs and can cause mild neonatal hypotonia and weakness with disproportionately severe dysphagia and respiratory insufficiency, at times leading to early death. It is not progressive, however, and some patients show improvement in later infancy and early childhood, acquiring the ability to swallow by 3 yr of age. Cardiomyopathy is a complication in a minority.

The diagnosis is by muscle biopsy: some sarcomeres of myofibers have disorganization or dissolution of myofibrils adjacent to other areas of normal sarcomeres within the same fiber. These zones are associated with streaming of the Z bands and focally increased desmin intermediate filaments, myotilin, and αB-crystallin. Immunocytochemical and ultrastructural study of the muscle biopsy tissue is required. Mutation in the desmin gene is implicated as a contributory factor in the etiology of both adult-onset and childhood myofibrillar myopathies, but the primary defect is a mutation in, not just an upregulation of, the αB-crystallin molecule. An associated secondary mitochondrial defect is detected in some patients.

A unique autosomal recessive myopathy in Cree native infants is characterized by severe generalized muscular hypertonia that is not relieved by neuromuscular blockade and hence is myopathic in origin. Most die in infancy of respiratory insufficiency as a result of diaphragmatic involvement. The muscle biopsy shows findings similar to many other myofibrillar myopathies (Fig. 608-5); a novel αB-crystallin gene mutation is the cause.

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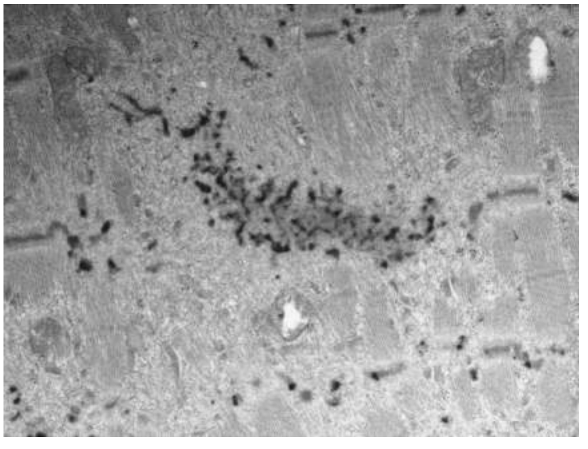

Figure 608-5 Electron micrograph of quadriceps femoris muscle biopsy of a 1 mo old native girl with Cree myofibrillar myopathy. Within the same myofiber, some sarcomeres are well formed and others exhibit disarray of the thick and thin myofilaments and fragmentation of Z bands. Mitochondria appear normal (×21,400).

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608.6 Brain Malformations and Muscle Development

Harvey B. Sarnat

Infants with **cerebellar hypoplasia** are hypotonic and developmentally delayed, especially in gross motor skills. Muscle biopsy is sometimes performed to exclude a congenital myopathy. A biopsy specimen can show delayed maturation of muscle, fiber-type predominance, or CMFTD. Other malformations of the brain may also be associated with abnormal histochemical patterns, but supratentorial lesions are less likely than brainstem or cerebellar lesions to alter muscle development. Abnormal descending impulses along bulbospinal pathways probably alter discharge patterns of lower motor neurons that determine the histochemical differentiation of muscle at 20-28 wk of gestation. The corticospinal tract does not participate because it is not yet functional during this period of fetal life.

In several congenital muscular dystrophies (see Chapter 609.6), including the Walker-Warburg syndrome, Fukuyama disease, and muscle-eye-brain disease of Santavuori, major cerebral malformations, such as pachygyria and lissencephaly, are present. It is clear that in at least some of these cases, the abnormal protein implicated in pathogenesis of the syndrome is expressed in both muscle and brain and is important for both stabilization of muscle and migration of central neurons.

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608.7 Amyoplasia

Harvey B. Sarnat

Congenital absence of individual muscles is common and is often asymmetric. A common aplasia is the *palmaris longus muscle* of the ventral forearm, which is absent in 30% of normal subjects and is fully compensated for by other flexors of the wrist. Unilateral absence of a *sternocleidomastoid muscle* is one cause of congenital torticollis. Absence of 1 *pectoralis major muscle* is part of the **Poland anomalad**.

When innervation does not develop, as in the lower limbs in severe cases of *myelomeningocele*, muscles can fail to develop. In *sacral agenesis*, the abnormal somites that fail to form bony vertebrae can also fail to form muscles from the same defective mesodermal plate, a disorder of induction resulting in segmental amyoplasia. Skeletal muscles of the extremities fail to differentiate from embryonic myomeres if the long bones do not form. Absence of 1 long bone, such as the radius, is associated with variable aplasia or hypoplasia of associated muscles, such as the flexor carpi radialis. End-stage neurogenic atrophy of muscle is sometimes called **amyoplasia**, but this use is semantically incorrect.

Generalized amyoplasia usually results in fetal death, and liveborn neonates rarely survive. A mutation in 1 of the myogenic genes is the suspected etiology because of genetic knockout studies in mice, but it has not been proven in humans.

608.8 Muscular Dysgenesis (Proteus Syndrome Myopathy)

Harvey B. Sarnat

Proteus syndrome is a disturbance of cellular growth involving ectodermal and mesodermal tissues, representing a cellular mosaicism. The genetic defect is a mutation in the *AKT1* gene, of the same genetic family as *AKT3*, which causes hemimegalencephaly; indeed many cases of Proteus syndrome also have hemimegalencephaly. These genes participate in the mammalian target of rapamycin pathway. Proteus syndrome also manifests as asymmetric overgrowth of the extremities, verrucous cutaneous lesions, angiomas of various types, thickening of bones, and excessive growth of muscles without weakness. Severe seizures, beginning in neonates, are uncommon. Histologically, the muscle demonstrates a unique *muscular dysgenesis.* Abnormal zones are adjacent to zones of normal muscle formation and do not follow anatomic boundaries.

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608.9 Benign Congenital Hypotonia

Harvey B. Sarnat

Benign congenital hypotonia is not a disease, but it is a descriptive term for infants or children with nonprogressive hypotonia of unknown origin. The hypotonia is not usually associated with weakness or developmental delay, although some children acquire gross motor skills more slowly than normal. Tendon stretch reflexes are normal or hypoactive. There are no cranial nerve abnormalities, and intelligence is normal.

The **diagnosis** is one of exclusion (see Table 607-2 in Chapter 607) after results of laboratory studies, including muscle biopsy and imaging of the brain with special attention to the cerebellum, are normal. Muscle biopsy is deferred in some mild cases to follow the clinical evolution over time, but the diagnosis in these infants is more provisional. No known molecular genetic basis for this syndrome has been identified. Table 607-3 in Chapter 607 lists the differential diagnosis.

The **prognosis** is generally good; no specific therapy is required. Contractures do not develop. Physical therapy might help achieve motor milestones (walking) sooner than expected. Hypotonia persists into adult life. The disorder is not always as "benign" as its name implies because a common complication is recurrent dislocation of joints, especially the shoulders. Excessive motility of the spine can result in stretch injury, compression, or vascular compromise of nerve roots or of the spinal cord. These are particular hazards for patients who perform gymnastics or who become circus performers because of agility of joints without weakness or pain.

Bibliography is available at Expert Consult.

608.10 Arthrogryposis

Harvey B. Sarnat

Arthrogryposis multiplex congenita is not a disease but is a descriptive term that signifies multiple congenital contractures and is heterogeneous in etiology (see Chapter 682).

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Chapter 609

Muscular Dystrophies

Harvey B. Sarnat

The term *dystrophy* means abnormal growth, derived from the Greek *trophe,* meaning "nourishment." A muscular dystrophy is distinguished from all other neuromuscular diseases by 4 obligatory criteria: It is a primary myopathy, it has a genetic basis, the course is progressive, and degeneration and death of muscle fibers occur at some stage in the

disease. This definition excludes neurogenic diseases such as spinal muscular atrophy, nonhereditary myopathies such as dermatomyositis, nonprogressive, and nonnecrotizing congenital myopathies such as congenital muscle fiber-type disproportion, and nonprogressive inherited metabolic myopathies. Some metabolic myopathies can fulfill the definition of a progressive muscular dystrophy but are not traditionally classified as dystrophies (muscle carnitine deficiency).

All muscular dystrophies might eventually be reclassified as metabolic myopathies once the biochemical defects are better defined. Muscular dystrophies are a group of unrelated diseases, each transmitted by a different genetic trait and each differing in its clinical course and expression. Some are severe diseases at birth that lead to early death; others follow very slow progressive courses over many decades, may be compatible with normal longevity, and might not even become symptomatic until late adult life. Some categories of dystrophies, such as limb-girdle muscular dystrophy (LGMD), are not homogeneous diseases but rather syndromes encompassing several distinct myopathies. Relationships among the various muscular dystrophies are resolved by molecular genetics rather than by similarities or differences in clinical and histopathologic features.

609.1 Duchenne and Becker Muscular Dystrophies

Harvey B. Sarnat

Duchenne muscular dystrophy (DMD) is the most common hereditary neuromuscular disease affecting all races and ethnic groups. Its characteristic clinical features are progressive weakness, intellectual impairment, hypertrophy of the calves, and proliferation of connective tissue in muscle. The incidence is 1 in 3,600 liveborn infant boys. This disease is inherited as an X-linked recessive trait. The abnormal gene is at the Xp21 locus and is one of the largest genes. **Becker muscular dystrophy** (BMD) is a disease that is fundamentally similar to DMD, with a genetic defect at the same locus, but clinically it follows a milder and more protracted course.

CLINICAL MANIFESTATIONS

Infant boys are rarely symptomatic at birth or in early infancy, although some are mildly hypotonic. Early gross motor skills, such as rolling over, sitting, and standing, are usually achieved at the appropriate ages or may be mildly delayed. Poor head control in infancy may be the first sign of weakness. Distinctive facies are not an early feature because facial muscle weakness is a late event; in later childhood, a "transverse" or horizontal smile may be seen. Walking is often accomplished at the normal age of approximately 12 mo, but hip girdle weakness may be seen in subtle form as early as the 2nd yr. Toddlers might assume a lordotic posture when standing to compensate for gluteal weakness. An early Gowers sign is often evident by age 3 yr and is fully expressed by age 5 or 6 yr (see Fig. 590-5 in Chapter 590). A Trendelenburg gait, or hip waddle, appears at this time. Common presentations in toddlers include delayed walking, falling, toe walking, and trouble running or walking upstairs, developmental delay, and, less often, malignant hyperthermia after anesthesia.

The length of time a patient remains ambulatory varies greatly. Some patients are confined to a wheelchair by 7 yr of age; most patients continue to walk with increasing difficulty until age 10 yr without orthopedic intervention. With orthotic bracing, physiotherapy, and sometimes minor surgery (Achilles tendon lengthening), most are able to walk until age 12 yr. Ambulation is important not only for postponing the psychologic depression that accompanies the loss of an aspect of personal independence but also because scoliosis usually does not become a major complication as long as a patient remains ambulatory, even for as little as 1 hr per day; scoliosis often becomes rapidly progressive after confinement to a wheelchair.

The relentless progression of **weakness** continues into the 2nd decade. The function of distal muscles is usually relatively well enough preserved, allowing the child to continue to use eating utensils, a pencil, and a computer keyboard. Respiratory muscle involvement is expressed as a weak and ineffective cough, frequent pulmonary infections, and decreasing respiratory reserve. Pharyngeal weakness can lead to episodes of aspiration, nasal regurgitation of liquids, and an airy or nasal voice quality. The function of the extraocular muscles remains well preserved. Incontinence due to anal and urethral sphincter weakness is an uncommon and very late event.

Contractures most often involve the ankles, knees, hips, and elbows. **Scoliosis** is common. The thoracic deformity further compromises pulmonary capacity and compresses the heart. Scoliosis usually progresses more rapidly after the child becomes nonambulatory and may be uncomfortable or painful. Enlargement of the calves (pseudohypertrophy) and wasting of thigh muscles are classic features. The enlargement is caused by hypertrophy of some muscle fibers, infiltration of muscle by fat, and proliferation of collagen. After the calves, the next most common site of muscular hypertrophy is the tongue, followed by muscles of the forearm. Fasciculations of the tongue do not occur. The voluntary sphincter muscles rarely become involved.

Unless ankle contractures are severe, ankle deep tendon reflexes remain well preserved until terminal stages. The knee deep tendon reflexes may be present until about 6 yr of age but are less brisk than the ankle jerks and are eventually lost. In the upper extremities, the brachioradialis reflex is usually stronger than the biceps or triceps brachii reflexes.

Cardiomyopathy, including persistent tachycardia and myocardial failure, is seen in 50-80% of patients with this disease. The severity of cardiac involvement does not necessarily correlate with the degree of skeletal muscle weakness. Some patients die early of severe cardiomyopathy while still ambulatory; others in terminal stages of the disease have well-compensated cardiac function. Smooth muscle dysfunction, particularly of the gastrointestinal tract, is a minor, but often overlooked, feature.

Intellectual impairment occurs in all patients, although only 20-30% have an IQ <70. The majority have learning disabilities that still allow them to function in a regular classroom, particularly with remedial help. A few patients are profoundly intellectually impaired, but there is no correlation with the severity of the myopathy. Epilepsy is slightly more common than in the general pediatric population. Autism-like behavior may develop but is uncommon. Dystrophin is expressed in brain and retina, as well as in striated and cardiac muscle, though the level is lower in brain than in muscle. This distribution might explain some of the central nervous system manifestations. Abnormalities in cortical architecture and of dendritic arborization may be detected neuropathologically; cerebral atrophy is demonstrated by MRI late in the clinical course. The degenerative changes and fibrosis of muscle constitute a painless process. Myalgias and muscle spasms do not occur. Calcinosis of muscle is rare.

Death occurs usually at about 18-20 yr of age. The causes of death are respiratory failure during sleep, intractable heart failure, pneumonia, or, occasionally, aspiration and airway obstruction.

In **BMD,** boys remain ambulatory until late adolescence or early adult life. Calf pseudohypertrophy, cardiomyopathy, and elevated serum levels of creatine kinase (CK) are similar to those of patients with DMD. Learning disabilities are less common. The onset of weakness is later in BMD than in DMD. Death often occurs in the mid to late 20s; fewer than half of patients are still alive by age 40 yr; these survivors are severely disabled.

LABORATORY FINDINGS

The serum CK level is consistently greatly elevated in DMD, even in presymptomatic stages, including at birth. The usual serum concentration is 15,000-35,000 IU/L (normal <160 IU/L). A normal serum CK level is incompatible with the diagnosis of DMD, although in terminal stages of the disease, the serum CK value may be considerably lower than it was a few years earlier because there is less muscle to degenerate. Other lysosomal enzymes present in muscle, such as aldolase and aspartate aminotransferase, are also increased but are less specific.

Cardiac assessment by echocardiography, electrocardiography (ECG), and radiography of the chest is essential and should be repeated

periodically. After the diagnosis is established, patients should be referred to a pediatric cardiologist for long-term cardiac care.

Electromyography (EMG) shows characteristic myopathic features but is not specific for DMD. No evidence of denervation is found. Motor and sensory nerve conduction velocities are normal.

DIAGNOSIS

Polymerase chain reaction (PCR) for the dystrophin gene mutation is the primary test, if the clinical features and serum CK are consistent with the diagnosis. If the blood PCR is diagnostic, muscle biopsy may be deferred, but if it is normal and clinical suspicion is high, the more specific dystrophin immunocytochemistry performed on muscle biopsy sections detects the 30% of cases that do not show a PCR abnormality. Immunohistochemical staining of frozen sections of muscle biopsy tissue detects differences in the rod domain, the carboxyl-terminus (that attaches to the sarcolemma), and the aminoterminus (that attaches to the actin myofilaments) of the large dystrophin molecule, and may be prognostic of the clinical course as Duchenne or Becker disease. More-severe weakness occurs with truncation of the dystrophin molecule at the carboxyl-terminus than at the aminoterminus. The diagnosis should be confirmed by blood PCR or muscle biopsy in every case. Dystroglycans and other sarcolemmal regional proteins, such as merosin and sarcoglycans, also can be measured because they may be secondarily decreased.

The **muscle biopsy** is diagnostic and shows characteristic changes (Figs. 609-1 and 609-2). Myopathic changes include endomysial connective tissue proliferation, scattered degenerating and regenerating myofibers, foci of mononuclear inflammatory cell infiltrates as a reaction to muscle fiber necrosis, mild architectural changes in still-functional muscle fibers, and many dense fibers. These hypercontracted fibers probably result from segmental necrosis at another level, allowing calcium to enter the site of breakdown of the sarcolemmal membrane and trigger a contraction of the whole length of the muscle fiber. Calcifications within myofibers are correlated with secondary β-dystroglycan deficiency.

The decision about whether muscle biopsy should be performed to establish the diagnosis sometimes presents problems. If there is a family history of the disease, particularly in the case of an involved brother whose diagnosis has been confirmed, a patient with typical

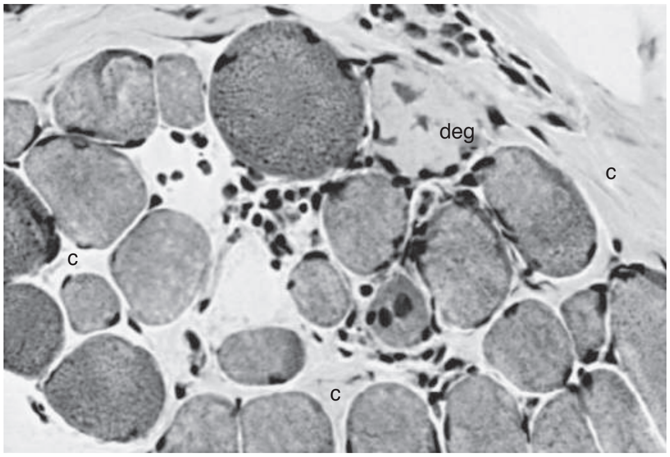

Figure 609-1 **Muscle biopsy of a 4 yr old boy with Duchenne muscular dystrophy.** Both atrophic and hypertrophic muscle fibers are seen, and some fibers are degenerating *(deg)*. Connective tissue *(c)* between muscle fibers is increased (hematoxylin and eosin, ×400).

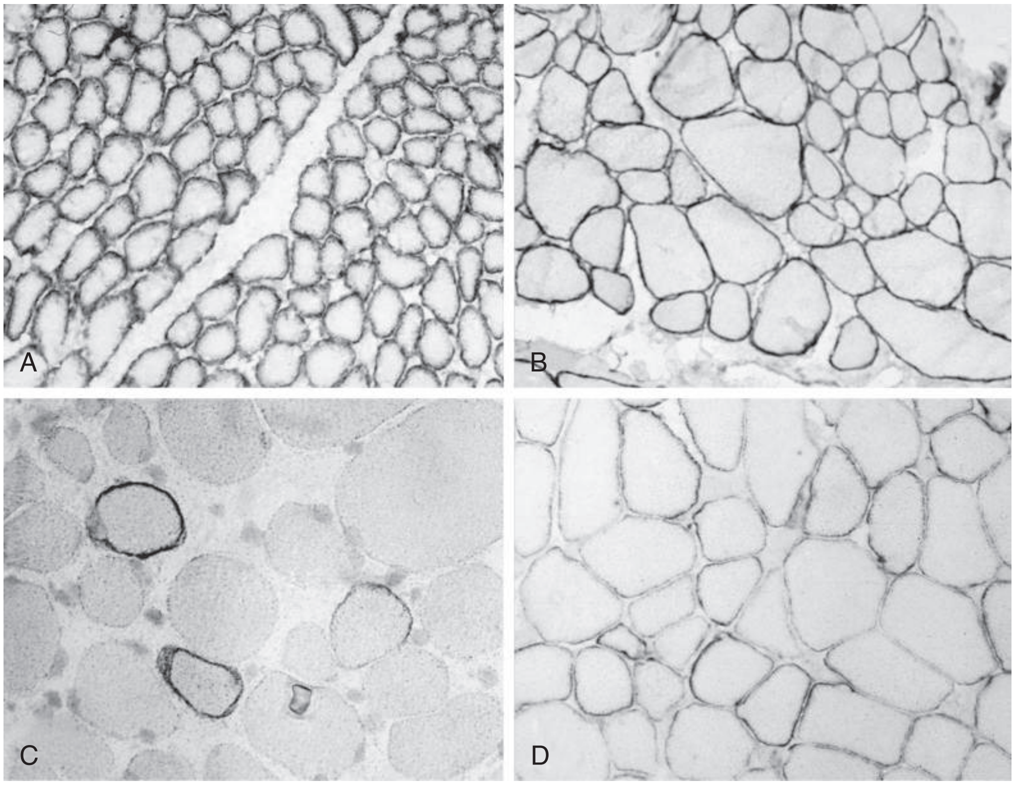

Figure 609-2 Dystrophin is demonstrated by immunohistochemical reactivity in the muscle biopsies of a normal term male neonate **(A),** a 10 yr old boy with limb-girdle muscular dystrophy **(B),** a 6 yr old boy with Duchenne muscular dystrophy **(C),** and a 10 yr old boy with Becker muscular dystrophy **(D).** In the normal condition, and also in non–X-linked muscular dystrophies in which dystrophin is not affected, the sarcolemmal membrane of every fiber is strongly stained, including atrophic and hypertrophic fibers. In Duchenne dystrophy, most myofibers express no detectable dystrophin, but a few scattered fibers known as revertant fibers show near-normal immunoreactivity. In Becker muscular dystrophy, the abnormal dystrophin molecule is thin, with pale staining of the sarcolemma, in which reactivity varies not only between myofibers but also along the circumference of individual fibers (×250).

clinical features of DMD and high concentrations of serum CK probably does not need to undergo biopsy. The result of the PCR might also influence whether to perform a muscle biopsy. A first case in a family, even if the clinical features are typical, should have the diagnosis confirmed to ensure that another myopathy is not masquerading as DMD. The most common muscles sampled are the vastus lateralis (quadriceps femoris) and the gastrocnemius.

GENETIC ETIOLOGY AND PATHOGENESIS

Despite the X-linked recessive inheritance in DMD, approximately 30% of cases are new mutations, and the mother is not a carrier. The female carrier state usually shows no muscle weakness or any clinical expression of the disease, but affected girls are occasionally encountered, usually having much milder weakness than boys. These symptomatic girls are explained by the Lyon hypothesis in which the normal X chromosome becomes inactivated and the one with the gene deletion is active (see Chapter 80). The full clinical picture of DMD has occurred in several girls with Turner syndrome in whom the single X chromosome must have had the Xp21 gene deletion.

The asymptomatic carrier state of DMD is associated with elevated serum CK values in 80% of cases. The level of increase is usually in the magnitude of hundreds or a few thousand but does not have the extreme values noted in affected males. Prepubertal girls who are carriers of the dystrophy also have increased serum CK values, with highest levels at 8-12 yr of age. Approximately 20% of carriers have normal serum CK values. If the mother of an affected boy has normal CK levels, it is unlikely that her daughter can be identified as a carrier by measuring CK. Muscle biopsy of suspected female carriers can detect an additional 10% in whom serum CK is not elevated; a specific genetic diagnosis using PCR on peripheral blood is definitive. Some female carriers suffer cardiomyopathy without weakness of striated muscles.

A 427-kDa cytoskeletal protein known as *dystrophin* is encoded by the gene at the Xp21.2 locus. This gene contains 79 exons of coding sequence and 2.5 Mb of DNA, 10 times larger than the next largest gene yet identified. This subsarcolemmal protein attaches to the sarcolemmal membrane overlying the A and M bands of the myofibrils and consists of 4 distinct regions or domains: the aminoterminus contains 250 amino acids and is related to the *N*-actin binding site of α-actinin; the second domain is the largest, with 2,800 amino acids, and contains many repeats, giving it a characteristic rod shape; a third, cysteine-rich domain is related to the carboxyl-terminus of α-actinin; and the final carboxyl-terminal domain of 400 amino acids is unique to dystrophin and to a dystrophin-related protein encoded by chromosome 6. "Dystrophin deficiency" at the sarcolemma disrupts the membrane cytoskeleton and leads to loss secondarily of other components of the cytoskeleton.

The molecular defects in the dystrophinopathies vary and include intragenic deletions, duplications, or point mutations of nucleotides. Approximately 65% of patients have deletions; approximately 10% exhibit duplications while approximately 10% have point mutations or smaller rearrangements. The site or size of the intragenic abnormality does not always correlate well with the phenotypic severity; in both Duchenne and Becker forms the mutations are mainly near the middle of the gene, involving deletions of exons 46-51. Phenotypic or clinical variations are explained by the alteration of the translational reading frame of messenger RNA (mRNA), which results in unstable, truncated dystrophin molecules and severe, classic DMD; mutations that preserve the reading frame still permit translation of coding sequences further downstream on the gene and produce a semifunctional dystrophin, expressed clinically as BMD. An even milder form of adult-onset disease, formerly known as **quadriceps myopathy,** is also caused by an abnormal dystrophin molecule. The clinical spectrum of the dystrophinopathies not only includes the classic Duchenne and Becker forms but also ranges from a severe neonatal muscular dystrophy to asymptomatic children with persistent elevation of serum CK levels >1,000 IU/L.

Analysis of the dystrophin protein requires a muscle biopsy and is demonstrated by Western blot analysis or in tissue sections by immunohistochemical methods using either fluorescence or light microscopy of antidystrophin antisera (see Fig. 609-2). In classic DMD, levels of <3% of normal are found; in BMD, the molecular weight of dystrophin is reduced to 20-90% of normal in 80% of patients, but in 15% of patients the dystrophin is of normal size but reduced in quantity, and 5% of patients have an abnormally large protein caused by excessive duplications or repeats of codons. Selective immunoreactivity of different parts of the dystrophin molecule in sections of muscle biopsy material distinguishes the Duchenne and Becker forms (Fig. 609-3). The demonstration of deletions and duplications also can be made from blood samples by the more rapid PCR, which identifies as many as 98% of deletions by amplifying 18 exons but cannot detect duplications. The diagnosis can thus be confirmed at the molecular genetic level from either the muscle biopsy material or from peripheral blood, although as many as 30% of boys with DMD or BMD have a false-normal blood PCR; all cases of dystrophinopathy are detected by muscle biopsy.

The same methods of DNA analysis from blood samples may be applied for carrier detection in female relatives at risk, such as sisters and cousins, and to determine whether the mother is a carrier or whether a new mutation occurred in the embryo. Prenatal diagnosis is possible as early as the 12th wk of gestation by sampling chorionic villi for DNA analysis by Southern blot or PCR and is confirmed in aborted fetuses with DMD by immunohistochemistry for dystrophin in muscle.

TREATMENT

There is no medical cure for this disease. Much can be done to treat complications and to improve the quality of life of affected children. **Cardiac decompensation** often responds initially well to digoxin. **Pulmonary infections** should be promptly treated. Patients should avoid contact with children who have obvious respiratory or other contagious illnesses. Immunizations for influenza virus and other routine vaccinations are indicated.

Preservation of a good **nutritional state** is important. DMD is not a vitamin-deficiency disease, and excessive doses of vitamins should be avoided. Adequate calcium intake is important to minimize osteoporosis in boys confined to a wheelchair, and fluoride supplements may also be given, particularly if the local drinking water is not fluoridated. Because sedentary children burn fewer calories than active children and because depression is an additional factor, these children tend to eat excessively and gain weight. Obesity makes a patient with myopathy even less functional because part of the limited reserve muscle strength is dissipated in lifting the weight of excess subcutaneous adipose tissue. Dietary restrictions with supervision may be needed.

Physiotherapy delays but does not always prevent contractures. At times, contractures are actually useful in functional rehabilitation. If contractures prevent extension of the elbow beyond 90 degrees and the muscles of the upper limb no longer are strong enough to overcome gravity, the elbow contractures are functionally beneficial in fixing an otherwise flail arm and in allowing the patient to eat and write. Surgical correction of the elbow contracture may be technically feasible, but the result may be deleterious. Physiotherapy contributes little to muscle strengthening because patients usually are already using their entire reserve for daily function, and exercise cannot further strengthen involved muscles. Excessive exercise can actually accelerate the process of muscle fiber degeneration.

Special vigilance should be maintained in watching for progressive scoliosis, which should be treated early by orthopedists using external braces or corsets and occasionally by surgeons. Scoliosis often becomes rapidly progressive once the patient is confined to a wheelchair.

Another recommended treatment of patients with DMD involves the use of prednisone, prednisolone, deflazacort, or other steroids. Glucocorticoids decrease the rate of apoptosis or programmed cell death of myotubes during ontogenesis and can decelerate the myofiber necrosis in muscular dystrophy. Strength usually improves initially, but the long-term complications of chronic steroid therapy, including

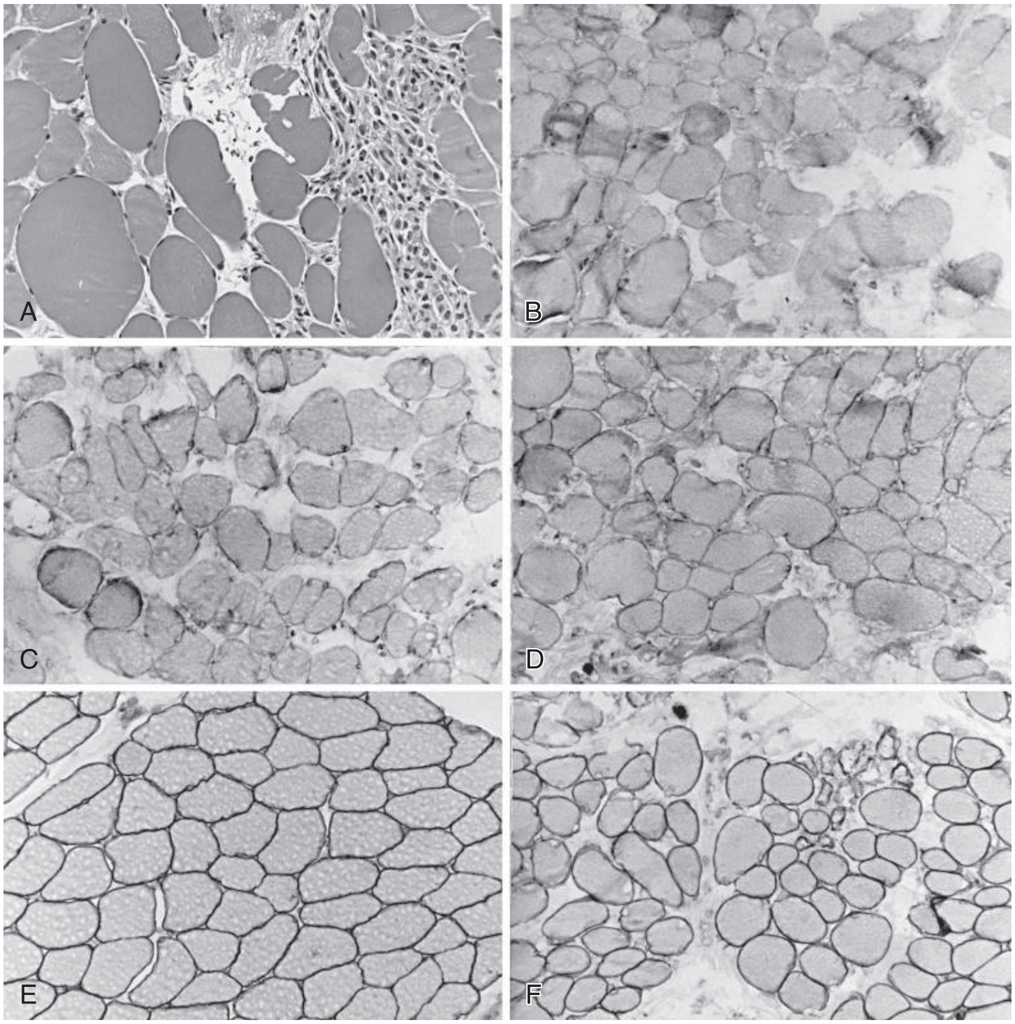

Figure 609-3 Quadriceps femoris muscle biopsy specimens from a 4 yr old boy with Becker muscular dystrophy. **A,** Myofibers vary greatly in size, with both atrophic and hypertrophic forms; at the right is a zone of degeneration and necrosis infiltrated by macrophages, similar to Duchenne muscular dystrophy (hematoxylin and eosin, ×250). Immunoreactivity using antibodies against the dystrophin molecule in the rod domain **(B),** carboxyl-terminus **(C),** and aminoterminus **(D)** all show deficient but not totally absent dystrophin expression; most fibers of all sizes retain some dystrophin in parts of the sarcolemma but not around the entire circumference in cross section. Alternatively, the prominence of dystrophin is less, appearing weak, when compared with the simultaneously incubated normal control from another child of similar age **(E). F,** Merosin expression is normal in this patient with Becker dystrophy, in both large and small myofibers, and is lacking only in frankly necrotic fibers. Compare with classic Duchenne muscular dystrophy illustrated in Figure 609-2C and with Figure 609-6.

considerable weight gain and osteoporosis, can offset this advantage or even result in greater weakness than might have occurred in the natural course of the disease. Nevertheless, some patients with DMD treated early with steroids appear to have an improved long-term prognosis in muscle and myocardial outcome, as well as short-term improvement in muscle strength, and steroids can help keep patients ambulatory for more years than expected without treatment. One protocol gives prednisone (0.75 mg/kg/day) for the 1st 10 days of each month to avoid chronic complications. Deflazacort, administered as 0.9 mg/kg/day, may be more effective than prednisone. Fluorinated steroids, such as dexamethasone or triamcinolone, should be avoided because they induce myopathy by altering the myotube abundance of ceramide. The American Academy of Neurology and the Child Neurology Society recommend administering corticosteroids during the ambulatory stage of the disease.

Another potential treatment still under investigation is intravenous or subcutaneous injection of antisense oligonucleotide drugs that induce exon skipping during mRNA splicing in patients with susceptible mutations (~15% of patients) to restore the open reading frame in the DMD gene. Drisapersen and eteplirsen are exon 51 skipping antisense oligonucleotides that bind RNA and skip (bridge) over the defective exon, thus producing a shorter but potentially functional dystrophin protein. The shortened protein has been demonstrated to appear in muscle biopsies after treatment with these agents.

Bibliography is available at Expert Consult.

609.2 Emery-Dreifuss Muscular Dystrophy

Harvey B. Sarnat

Emery-Dreifuss muscular dystrophy, also known as **scapuloperoneal or scapulohumeral muscular dystrophy,** is a rare X-linked recessive dystrophy. The usual locus of its associated genetic abnormality is on the long arm within the large Xq28 region that includes other mutations that cause myotubular myopathy, neonatal adrenoleukodystrophy, and the Bloch-Sulzberger type of incontinentia pigmenti; it is far from the gene for DMD on the short arm of the X chromosome. Another, rarer form of Emery-Dreifuss dystrophy is transmitted as an autosomal dominant trait and is localized at 1q. This form can manifest quite late, in adolescence or early adult life, although the muscular and cardiac symptoms and signs are similar, and sudden death from ventricular fibrillation is a risk.

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Clinical manifestations begin at between 5 and 15 yr of age, but many patients survive to late adult life because of the slow progression of the disease's course. A rarer severe infantile presentation also is documented. Muscles do not exhibit pseudohypertrophy. Contractures of elbows and ankles develop early, and muscle becomes wasted in a scapulohumeroperoneal distribution. Facial weakness does not occur; this disease is thus distinguished clinically from autosomal dominant scapulohumeral and scapuloperoneal syndromes of neurogenic origin. Myotonia is absent. Intellectual function is normal. Dilated cardiomyopathy is severe and is often the cause of death, more commonly from conduction defects such as atrial fibrillation/flutter and sudden ventricular fibrillation than from intractable myocardial failure. Stroke is another complication, secondary to the cardiac arrhythmia. The serum CK value is only mildly to moderately elevated, further distinguishing this disease from other X-linked recessive muscular dystrophies.

Nonspecific myofiber necrosis and endomysial fibrosis are seen in the muscle biopsy. Many centronuclear fibers and selective histochemical type I muscle fiber atrophy can cause confusion with myotonic dystrophy.

GENETICS

The defective gene in the X-linked form is called *EMD* or *EDMD* and encodes a protein, emerin. Unlike other dystrophies in which the defective gene is expressed at the sarcolemmal membrane, emerin is expressed at the inner nuclear membrane; this protein stabilizes the nuclear membrane against the mechanical stresses that occur during muscular contraction. It interacts with *Nesprin-1* and *Nesprin-2* genes, also critical for nuclear membrane integrity. Complete deletion of *EDMD* occurs in approximately 25% of cases and results from an inversion in the Xq28 region; total absence of emerin is demonstrated by both Western blotting and immunoreactivity in tissue sections. Another gene, *LMNA*, at the 1q21 locus, is linked to the nuclear envelope and encodes lamins A and C, sometimes termed *laminopathy*. This genetic mutation causes an identical clinical phenotype to EMD defects, except that both sexes are affected and it is transmitted as either an autosomal dominant or recessive trait. Most *EDMD* deletions are null mutations, whereas most *LMNA* alterations are mainly missense mutations with a minority being nonsense or out-of-frame mutations. Desmin protein also may be mutated and seen to be abnormally expressed in the muscle biopsy. Homozygous nonsense mutations in these *lamin A/C* genes are lethal owing to cardiomyopathy and conduction disturbances.

DIAGNOSIS AND INVESTIGATIONS

In suspected cases, emerin deficiency may be demonstrated not only in the muscle biopsy by immunoreactivity and Western blotting techniques but also in a variety of other tissues, including circulating lymphocytes in peripheral blood, exfoliative buccal mucosal cells, and skin fibroblasts. Emerin is absent in varying proportions in female carriers. Genetic testing of the specific genes also is available. Patients should all have careful cardiac evaluation, including electrocardiogram and echocardiogram. Serum CK should be measured because it may be moderately elevated; though nonspecific, it provides a baseline for comparison with future measurements. Muscle MRI of the glutei and lower extremities may be helpful, particularly in *LMNA* mutations. EMG is not definitively diagnostic, but it provides a serial means of following the progression of the myopathy. Muscle biopsy is diagnostic from the onset of symptoms. In the differential diagnosis, an Emery-Dreifuss–like syndrome with joint contractures, mild weakness, and later-onset cardiac symptoms is caused by *FHL1* mutations of myofibrillar myopathy, but reducing bodies are absent.

Treatment should be supportive, with special attention to cardiac conduction defects, and can require medications or a pacemaker. Implantable cardioverter-defibrillators are now available and have prevented sudden death in some patients with Emery-Dreifuss muscular dystrophy.

Bibliography is available at Expert Consult.

609.3 Myotonic Muscular Dystrophy

Harvey B. Sarnat

Myotonic dystrophy (Steinert disease) is the second most common muscular dystrophy in North America, Europe, and Australia, having an incidence varying from 1 in 100,000 to 1 in 300,000 in the general population. It is inherited as an autosomal dominant trait. Classic myotonic dystrophy (type 1) (DM1) is caused by a CTG trinucleotide expansion on chromosome 19q13.3 in the 3′ untranslated region of *DMPK*, the gene that encodes a serine-threonine protein kinase. Type 2 (DM2) is associated with unstable CCTG tetranucleotide repeat expansion on chromosome 3q21 of an intron of the zinc finger 9 protein gene. A third, late form (DM3) is identified, at locus 15q21-q24.

Myotonic dystrophy is an example of a genetic defect causing dysfunction in multiple organ systems. Not only is striated muscle severely affected, but smooth muscle of the alimentary tract and uterus is also involved, cardiac function is altered, and patients have multiple and variable endocrinopathies, immunologic deficiencies, cataracts, dysmorphic facies, increased risk for malignancies, intellectual impairment, and other neurologic abnormalities.

CLINICAL MANIFESTATIONS

DM1 becomes symptomatic at any age, but DM2 is rarely expressed in infancy or early childhood. In the usual clinical course, **excluding the severe neonatal** form, DM1 infants can appear almost normal at birth, or facial wasting and hypotonia can already be early expressions of the disease. The facial appearance is characteristic, consisting of an inverted V-shaped upper lip, thin cheeks, and scalloped, concave temporalis muscles (Fig. 609-4). The head may be narrow, and the palate is high and arched because the weak temporal and pterygoid muscles in late fetal life do not exert sufficient lateral forces on the developing head and face.

Weakness is mild in the 1st few yr. Progressive wasting of distal muscles becomes increasingly evident, particularly involving intrinsic muscles of the hands. The thenar and hypothenar eminences are flattened, and the atrophic dorsal interossei leave deep grooves between the fingers. The dorsal forearm muscles and anterior compartment muscles of the lower legs also become wasted. The tongue is thin and atrophic. Wasting of the sternocleidomastoids gives the neck a long, thin, cylindrical contour. Proximal muscles also eventually undergo atrophy, and scapular winging appears. Difficulty with climbing stairs

Figure 609-4 Facial weakness, inverted V–shaped upper lip, and loss of muscle mass in the temporal fossae are characteristic of myotonic muscular dystrophy, even in infancy, as seen in this 8 mo old girl.

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and Gowers sign are progressive. Tendon stretch reflexes are usually preserved.

The distal distribution of muscle wasting in myotonic dystrophy is an *exception* to the general rule of myopathies having proximal and neuropathies having distal distribution patterns. The muscular atrophy and weakness in myotonic dystrophy are slowly progressive throughout childhood and adolescence and continue into adulthood. It is rare for patients with myotonic dystrophy to lose the ability to walk even in late adult life, although splints or bracing may be required to stabilize the ankles.

Myotonia, a characteristic feature shared by few other myopathies, does not occur in infancy and is usually not clinically or even electromyographically evident until about age 5 yr. Exceptional patients develop it as early as age 3 yr. Myotonia is a very slow relaxation of muscle after contraction, regardless of whether that contraction was voluntary or was induced by a stretch reflex or electrical stimulation. During physical examination, myotonia may be demonstrated by asking the patient to make tight fists and then to quickly open the hands (grip myotonia; Fig. 609-5). It may be induced by striking the thenar eminence with a rubber percussion hammer (percussion myotonia), and it may be detected by watching the involuntary drawing of the thumb across the palm. Myotonia can also be demonstrated in the tongue by pressing the edge of a wooden tongue blade against its dorsal surface and by observing a deep furrow that disappears slowly. The severity of myotonia does not necessarily parallel the degree of weakness, and the weakest muscles often have only minimal myotonia. *Myotonia is not a painful muscle spasm*. Myalgias do not occur in myotonic dystrophy.

The **speech** of patients with myotonic dystrophy is often articulated poorly and is slurred because of the involvement of the muscles of the face, tongue, and pharynx. Difficulties with swallowing sometimes occur. Aspiration pneumonia is a risk in severely involved children. Incomplete external ophthalmoplegia sometimes results from extraocular muscle weakness.

Smooth muscle involvement of the **gastrointestinal tract** results in slow gastric emptying, poor peristalsis, and constipation. Some patients have encopresis associated with anal sphincter weakness. Women with myotonic dystrophy can have ineffective or abnormal uterine contractions during labor and delivery.

Cardiac involvement is usually manifested as heart block in the Purkinje conduction system and arrhythmias (and sudden death) rather than as cardiomyopathy, unlike most other muscular dystrophies. Atrial or ventricular tachyarrhythmias have also resulted in sudden death in adults and older children.

Endocrine abnormalities involve many glands and appear at any time during the course of the disease so that endocrine status must be reevaluated annually. Hypothyroidism is common; hyperthyroidism occurs rarely. Adrenocortical insufficiency can lead to an addisonian crisis even in infancy. Diabetes mellitus is common in patients with myotonic dystrophy; some children have a disorder of insulin release rather than defective insulin production. Onset of puberty may be precocious or, more often, delayed. Testicular atrophy and testosterone deficiency are common in adults and are responsible for a high incidence of male infertility. Ovarian atrophy is rare. Frontal baldness is also characteristic in male patients and often begins in adolescence.

Figure 609-5 The patient was asked to squeeze with both of his hands for several seconds and then suddenly release his grasp, and several seconds passed before full relaxation was achieved, an exam finding known as grip myotonia. *(From Hughes BN, Hogue JS, Hsieh DT: Grip and percussion myotonia in myotonic dystrophy type 1,* J Pediatr *164:1234, 2014.)*

Immunologic deficiencies are common in myotonic dystrophy. The plasma immunoglobulin G level is often low.

Cataracts often occur in myotonic dystrophy. They may be congenital, or they can begin at any time during childhood or adult life. Early cataracts are detected only by slit-lamp examination; periodic examination by an ophthalmologist is recommended. Visual evoked potentials are often abnormal in children with myotonic dystrophy and are unrelated to cataracts. They are not usually accompanied by visual impairment.

About half of the patients with myotonic dystrophy are **intellectually impaired,** but severe intellectual impairment is unusual. The remainder are of average or occasionally above-average intelligence. Epilepsy is not common. Cognitive impairment might result from accumulations of mutant *DMPK* mRNA and aberrant alternative splicing in cerebral cortical neurons. A higher than expected incidence of autism occurs in children with DM1.

A severe **congenital form** of myotonic dystrophy appears in a minority of involved infants born to mothers with symptomatic myotonic dystrophy. All patients with this severe congenital disease to date have had the DM1 form. Clubfoot deformities alone or more extensive congenital contractures of many joints can involve all extremities (arthrogryposis multiplex congenita) and even include the cervical spine. Generalized hypotonia and weakness are present at birth. Facial wasting is prominent. Infants can require gavage feeding or ventilator support for respiratory muscle weakness or apnea. Those requiring ventilation for <30 days often survive, and those with prolonged ventilation have an infant mortality of 25%. Children ventilated for <30 days have better motor, language, and daily activity skills than those requiring prolonged ventilation. One or both leaves of the diaphragm may be nonfunctional. The abdomen becomes distended with gas in the stomach and intestine because of poor peristalsis from smooth muscle weakness. The distention further compromises respiration. Inability to empty the rectum can compound the problem.

LABORATORY FINDINGS

The classic myotonic electromyogram is not found in infants but can appear in toddlers or children in the early school years. The levels of serum CK and other serum enzymes from muscle may be normal or only mildly elevated in the hundreds (never the thousands).

ECG should be performed annually in early childhood. Ultrasound imaging of the abdomen may be indicated in affected infants to determine diaphragmatic function. Radiographs of the chest and abdomen and contrast studies of gastrointestinal motility may be needed.

Endocrine assessment should be undertaken to determine thyroid and adrenal cortical function and to verify carbohydrate metabolism (glucose tolerance test). Immunoglobulins should be examined, and, if needed, more extensive immunologic studies should be performed.

DIAGNOSIS

The primary diagnostic test is a DNA analysis of blood to demonstrate the abnormal expansion of the CTG or CCTG repeat. Prenatal diagnosis also is feasible. The muscle biopsy specimen in older children shows many muscle fibers with central nuclei and selective atrophy of histochemical type I fibers, but degenerating fibers are usually few and widely scattered, and there is little or no fibrosis of muscle. Intrafusal fibers of muscle spindles are also abnormal. In young children with the common form of the disease, the biopsy specimen can even appear normal or at least not show myofiber necroses, which is a striking contrast with DMD. In the severe neonatal form of myotonic dystrophy, the muscle biopsy reveals maturational arrest in various stages of

development in some and congenital muscle fiber-type disproportion in others. It is likely that the sarcolemmal membrane of muscle fibers not only has abnormal properties of electrical polarization but is also incapable of responding to trophic influences of the motor neuron. Muscle biopsy is not usually required for diagnosis, which in typical cases can be based on the clinical manifestations, including family history. **Neonatal myotonic dystrophy** must be distinguished from amyoplasia, congenital muscular dystrophy with or without merosin expression, congenital myasthenia gravis, spinal muscular atrophy, and arthrogryposis secondary to oligohydramnios.

GENETICS

The genetic defect in myotonic muscular dystrophy is on chromosome 19 at the 19q13 locus. It consists of an expansion of the *DM* gene that encodes a serine-threonine kinase *(DMPK),* with numerous repeats of the CTG codon. Expansions range from 50 to >2,000, with the normal alleles of this gene ranging in size from 5-37; the larger the expansion, the more severe the clinical expression, with the largest expansions seen in the severe neonatal form. Rarely, the disease is associated with no detectable repeats, perhaps a spontaneous correction of a previous expansion but a phenomenon still incompletely understood. Another myotonic dystrophy (proximal myotonic myopathy) is a clinical entity linked to at least 2 different chromosomal loci than classic myotonic dystrophy but to 1 locus that shares a common unique pathogenesis in being mediated by a mutant mRNA. Defects in RNA splicing explain the insulin resistance in myotonic dystrophies as well as the myotonia.

Clinical and genetic expression can vary between siblings or between an affected parent and child. In the severe neonatal form of the disease, the mother is the transmitting parent in 94% of cases, a fact not explained by increased male infertility alone. Several cases of paternal transmission have been reported. Genetic analysis reveals that symptomatic neonates usually have many more repeats of the CTG codon than do patients with the more classic form of the disease, regardless of which parent is affected. Myotonic dystrophy often exhibits a pattern of **anticipation** in which each successive generation has a tendency to be more severely involved than the previous generation. Prenatal genetic diagnosis of myotonic dystrophy is available.

Treatment

There is no specific medical treatment, but the cardiac, endocrine, gastrointestinal, and ocular complications can often be treated. Physiotherapy and orthopedic treatment of contractures in the neonatal form of the disease may be beneficial. Myotonia may improve with exercise (warm-up phenomenon). Cardiac pacemaker implantation might be considered for heart block and antiarrhythmic drugs might be indicated but are needed only rarely in children.

Myotonia may be diminished, and function may be restored by drugs that raise the depolarization threshold of muscle membranes, such as mexiletine, phenytoin, carbamazepine, procainamide, and quinidine sulfate. These drugs also have cardiotropic effects; thus, cardiac evaluation is important before prescribing them. Phenytoin and carbamazepine are used in doses similar to their use as antiepileptics (see Chapter 593.6); serum concentrations of 10-20 µg/mL for phenytoin and 5-12 µg/mL for carbamazepine should be maintained. If a patient's disability is caused mainly by weakness rather than by myotonia, these drugs will be of no value.

OTHER MYOTONIC SYNDROMES

Most patients with myotonia have myotonic dystrophy. However, myotonia is not specific for this disease and occurs in several rarer conditions.

Myotonic chondrodystrophy (Schwartz-Jampel disease) is a rare congenital disease characterized by generalized muscle hypertrophy and weakness. Dysmorphic phenotypical features and the radiographic appearance of long bones are reminiscent of Morquio disease (see Chapter 88), but abnormal mucopolysaccharides are not found. Dwarfism, joint abnormalities, and blepharophimosis are present. Several patients have been the products of consanguinity, suggesting autosomal recessive inheritance. The muscle protein perlecan, encoded by the *SJS1* gene, a large heparan sulfate proteoglycan of basement membranes and cartilage, is defective in some cases of Schwartz-Jampel disease and explains both the muscular hyperexcitability and the chondrodysplasia.

EMG reveals continuous electrical activity in muscle fibers closely resembling or identical to myotonia. Muscle biopsy reveals nonspecific

Table 609-1 Channelopathies and Related Disorders

DISORDER	PATTERN OF CLINICAL FEATURES	INHERITANCE	CHROMOSOME	GENE
CHLORIDE CHANNELOPATHIES				
Myotonia Congenita				
Thomsen disease	Myotonia	Autosomal dominant	7q35	*CLC1*
Becker disease	Myotonia and weakness	Autosomal recessive	7q35	*CLC1*
SODIUM CHANNELOPATHIES				
Paramyotonia congenita	Paramyotonia	Autosomal dominant	17q13.1-13.3	*SCNA4A*
Hyperkalemic periodic paralysis	Periodic paralysis with myotonia and paramyotonia	Autosomal dominant	17q13.1-13.3	*CNA4A*
Hypokalemic periodic paralysis	Periodic paralysis	Autosomal dominant	17q13.1-13.3	*SCNA4A*
POTASSIUM-AGGRAVATED MYOTONIAS				
Myotonia fluctuans	Myotonia	Autosomal dominant	17q13.1-13.3	*SCNA4A*
Myotonia permanens	Myotonia	Autosomal dominant	17q13.1-13.3	*SCNA4A*
Acetazolamide-responsive myotonia	Myotonia	Autosomal dominant	17q13.1-13.3	*SCNA4A*
CALCIUM CHANNELOPATHIES				
Hypokalemic periodic paralysis	Periodic paralysis	Autosomal dominant	1q31-32	Dihydropyridine receptor
Schwartz-Jampel syndrome (chondrodystrophic myotonia)	Myotonia; dysmorphic	Autosomal recessive	1q34.1-36.1	*Perlecan*
Rippling muscle disease	Muscle mounding, stiffness	Autosomal dominant	1q41	*Caveolin-3*
Anderson syndrome	Periodic paralysis, cardiac arrhythmia, distinctive facies	Autosomal dominant	17q23	*KCNJ2-Kir2.1*
Brody disease	Delayed relaxation, no electromyogram myotonia	Autosomal recessive	16p12	Calcium adenosine triphosphatase
Malignant hyperthermia	Anesthetic-induced delayed relaxation	Autosomal dominant	19q13.1	Ryanodine receptor

From Goldman L, Ausiello D: Cecil textbook of medicine, *ed 22, Philadelphia, 2004, WB Saunders.*

myopathic features, which are minimal in some cases and pronounced in others. The sarcotubular system is dilated.

Myotonia congenita (Thomsen disease) is a channelopathy (Table 609-1) and is characterized by weakness and generalized muscular hypertrophy so that affected children resemble bodybuilders. Myotonia is prominent and can develop at age 2-3 yr, earlier than in myotonic dystrophy. The disease is clinically stable and is apparently not progressive for many years. Muscle biopsy specimens show minimal pathologic changes, and the EMG demonstrates myotonia. Various families are described as showing either autosomal dominant (Thomsen disease) or recessive (Becker disease, not to be confused with BMD or DMD) inheritance. Rarely, myotonic dystrophy and myotonia congenita coexist in the same family. The autosomal dominant and autosomal recessive forms of myotonia congenita have been mapped to the same 7q35 locus. This gene is important for the integrity of chloride channels of the sarcolemmal and T-tubular membranes.

Paramyotonia is a temperature-related myotonia that is aggravated by cold and alleviated by warm external temperatures. Patients have difficulty when swimming in cold water or if they are dressed inadequately in cold weather. *Paramyotonia congenita* (Eulenburg disease) is a defect in a gene at the 17q13.1-13.3 locus, the identical locus identified in hyperkalemic periodic paralysis. By contrast with myotonia congenita, paramyotonia is a disorder of the voltage-gated sodium channel caused by a mutation in the α subunit. Myotonic dystrophy also is a sodium channelopathy (see Table 609-1).

In sodium channelopathies, exercise produces increasing myotonia, whereas in chloride channelopathies, exercise reduces the myotonia. This is easily tested during examination by asking patients to close the eyes forcefully and open them repeatedly; it becomes progressively more difficult in sodium channel disorders and progressively easier in chloride channel disorders.

Bibliography is available at Expert Consult.

609.4 Limb-Girdle Muscular Dystrophies

Harvey B. Sarnat

Limb-girdle muscular dystrophies (LGMDs) encompass a heterogeneous group of progressive hereditary muscular dystrophies that mainly affect muscles of the hip and shoulder girdles (Table 609-2). Distal muscles also eventually become atrophic and weak. Hypertrophy of the calves and ankle contractures develop in some forms, causing potential confusion with BMD. Sixteen genetic forms of LGMD are now described, each at a different chromosomal locus and expressing different protein defects. Some include diseases classified with other traditional groups, such as the lamin-A/C defects of the nuclear membrane (see Emery-Dreifuss muscular dystrophy, above), and some forms of congenital muscular dystrophy. LGMD1 denotes autosomal dominant inheritance and LGMD2 implies an autosomal recessive trait, but neither term defines the genetic etiology. LGMD2 is mainly a group of several sarcoglycanopathies, calpainopathy resulting from a mutation in the *calpain-3* gene (*CAPN3*), or dysferlinopathies that include Miyoshi myopathy, which usually does not become symptomatic until adult life.

The initial **clinical manifestations** rarely appear before middle or late childhood or may be delayed until early adult life. Low back pain may be a presenting complaint because of the lordotic posture resulting from gluteal muscle weakness. Confinement to a wheelchair usually becomes obligatory at about 30 yr of age. The rate of progression varies from one pedigree to another but is uniform within a kindred. Although weakness of neck flexors and extensors is universal, facial, lingual, and other bulbar-innervated muscles are rarely involved. As weakness and muscle wasting progress, tendon stretch reflexes become diminished. Cardiac involvement is unusual. Intellectual function is generally normal. The clinical **differential diagnosis** of LGMD includes juvenile spinal muscular atrophy (Kugelberg-Welander disease), myasthenia gravis, and metabolic myopathies.

The EMG and muscle biopsy show confirmatory evidence of muscular dystrophy, but none of the findings is specific enough to make the definitive **diagnosis** without additional clinical criteria. In some cases, α-sarcoglycan (formerly known as *adhalin*), a dystrophin-related glycoprotein of the sarcolemma, is deficient; this specific defect may be demonstrated in the muscle biopsy by immunocytochemistry, as may deficiency of 3 other forms of sarcoglycan as well. Increased serum CK level is usual, but the magnitude of elevation varies among families. The ECG is usually unaltered.

In one autosomal dominant form of LGMD, a genetic defect has been localized to the long arm of chromosome 5. In the autosomal recessive disease, it is on the long arm of chromosome 15. A mutated dystrophin-associated protein in the sarcoglycan complex (sarcoglycanopathy; LGMD types 2C, 2E, and 2F) is responsible for some cases of autosomal recessive LGMD. Most sarcoglycanopathies result from a mutation in α-sarcoglycan; other LGMDs resulting from deficiencies in β-, γ-, and δ-sarcoglycan also occur. In normal smooth muscle, α-sarcoglycan is replaced by ε-sarcoglycan, and the others are the same. A dystroglycan mutation also is implicated in some cases.

Another group of LGMDs (type 2B) are caused by allelic mutations of the dysferlin *(DYSF)* gene, another gene expressing a protein essential to structural integrity of the sarcolemma, though not associated with the dystrophin-glycoprotein complex. *DYSF* interacts with caveolin-3 or calpain-3, and *DYSF* deficiency may be secondary to defects in these other gene products. Primary calpain-3 defect (type 2A) is reported in Amish families and in families from French Reunion Island and from Brazil. Autosomal recessive (Miyoshi myopathy) and autosomal dominant traits are documented. Both are slowly progressive myopathies with onset in adolescence or young adult life and can affect distal as well as proximal muscles. Cardiomyopathy is rare. Chronically elevated serum CK in the thousands is found in dysferlinopathies. Ultrastructure shows a thickened basal lamina over defects in the sarcolemma and replacement of the sarcolemma by multiple

Table 609-2 Autosomal Recessive Limb-Girdle Muscular Dystrophies

TYPE	LOCATION	GENE PRODUCT	CLINICAL FEATURES
LGMD2A	15q	Calpain 3	Onset at 8-15 yr, progression variable
LGMD2B	2p13-16	Dysferlin	Onset at adolescence, mild weakness; gene site is the same as for Miyoshi myopathy
LGMD2C	13q12	Sarcoglycan	Duchenne-like, severe childhood autosomal recessive muscular dystrophy (SCARMD1)
LGMD2D	17q12	α-Sarcoglycan (adhalin)	Duchenne-like, severe childhood autosomal recessive muscular dystrophy (SCARMD2)
LGMD2E	4q12	β-Sarcoglycan	Phenotype between Duchenne and Becker muscular dystrophies
LGMD2F	5q33-34	Sarcoglycan	Slowly progressive, growth retardation

LGMD, limb-girdle muscular dystrophy.

From Fenichel GM: Clinical pediatric neurology: a signs and symptoms approach, *ed 5, Philadelphia, 2005, Elsevier Saunders, p. 176, Table 7-5.*

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layers of small vesicles. Regenerating myofibers outnumber degenerating myofibers. These disorders were formerly called *hyperCKemia* and *rippling muscle disease,* the latter sometimes confused with myotonia. An autosomal recessive mutation in the calcium-activated chloride channel anoctamin-5 can cause proximal LGMD2.

There is overlap of the group of LGMDs with the congenital muscular dystrophies, such as Walker-Warburg syndrome with *POMT*, Fukuyama muscular dystrophy with *FKRP* genetic defects, and Ullrich muscular dystrophy of collagen VI subunits.

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609.5 Facioscapulohumeral Muscular Dystrophy

Harvey B. Sarnat

Facioscapulohumeral muscular dystrophy, also known as **Landouzy-Dejerine disease,** is probably not a single disease entity but a group of diseases with similar clinical manifestations. Autosomal dominant inheritance is the rule; genetic anticipation is often found within several generations of a family, the succeeding more severely involved at an earlier age than the preceding. The frequency is 1 : 20,000 population. Though the clinical onset is generally in later childhood or adult life, early molecular defects arising during myogenesis are demonstrated in the human fetus. The genetic mechanism in autosomal dominant facioscapulohumeral dystrophy involves integral deletions of a 3.3-kb tandem repeat (D4Z4) in the subtelomeric region at the 4q35 locus. Several other genes clustered at the 4q35 locus are upregulated in fetuses with facioscapulohumeral dystrophy. D4Z4 acts as a lamins-dependent insulator exhibiting both enhancer-blocking and barrier activities and displaces the telomere toward the nuclear periphery. A 3.3-kb repeat array at the subtelomeric locus 10q26 is closely homologous, with chromosomal translocation or sequence conversion between these 2 regions, possibly predisposing to the DNA rearrangement causing facioscapulohumeral dystrophy. Approximately 10% of families with this phenotype do not map to the 4q35 locus.

CLINICAL MANIFESTATIONS

Facioscapulohumeral dystrophy shows the earliest and most severe weakness in facial and shoulder girdle muscles. The facial weakness differs from that of myotonic dystrophy; rather than an inverted V–shaped upper lip, the mouth in facioscapulohumeral dystrophy is rounded and appears puckered because the lips protrude. Inability to close the eyes completely in sleep is a common expression of upper facial weakness; some patients have extraocular muscle weakness, although ophthalmoplegia is rarely complete. Facioscapulohumeral dystrophy has been associated with Möbius syndrome on rare occasions. Pharyngeal and tongue weakness may be absent and is never as severe as the facial involvement. Hearing loss, which may be subclinical, and retinal vasculopathy (indistinguishable from Coats disease) are associated features, particularly in severe cases of facioscapulohumeral dystrophy with early-childhood onset.

Scapular winging is prominent, often even in infants. Flattening or even concavity of the deltoid contour is seen, and the biceps and triceps brachii muscles are wasted and weak. Muscles of the hip girdle and thighs also eventually lose strength and undergo atrophy, and Gowers sign and a Trendelenburg gait appear. Contractures of the extremities are rare. Finger and wrist weakness occasionally is the first symptom. Weakness of the anterior tibial and peroneal muscles can lead to footdrop; this complication usually occurs only in advanced cases with severe weakness. Lumbar lordosis and kyphoscoliosis are common complications of axial muscle involvement. Calf pseudohypertrophy is not a usual feature but is described rarely.

Facioscapulohumeral muscular dystrophy can also be a mild disease causing minimal disability. Clinical manifestations might not be expressed in childhood and are delayed into middle adult life. Unlike most other muscular dystrophies, asymmetry of weakness is common. About 30% of affected patients are asymptomatic or show only mild scapular winging and decreased tendon stretch reflexes, of which they were unaware until formal neurologic examination was performed.

LABORATORY FINDINGS

Serum levels of CK and other enzymes vary greatly, ranging from normal or near-normal to elevations of several thousand. An ECG should be performed, although the anticipated findings are usually normal. EMG reveals nonspecific myopathic muscle potentials. Diagnostic molecular testing in individual cases and within families is indicated for prediction.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Molecular genetic diagnosis is the most specific confirmation if clinical suspicion is high, with or without a family history of the disease. Muscle biopsy distinguishes more than one form of facioscapulohumeral dystrophy, consistent with clinical evidence that several distinct diseases are embraced by the term *facioscapulohumeral dystrophy.* Muscle biopsy and EMG also distinguish the primary myopathy from a neurogenic disease with a similar distribution of muscular involvement. The general histopathologic findings in the muscle biopsy material are extensive proliferation of connective tissue between muscle fibers, extreme variation in fiber size with many hypertrophic as well as atrophic myofibers, and scattered degenerating and regenerating fibers. An "inflammatory" type of facioscapulohumeral muscular dystrophy is also distinguished, characterized by extensive lymphocytic infiltrates within muscle fascicles. Despite the resemblance of this form to inflammatory myopathies, such as polymyositis, there is no evidence of autoimmune disease, and steroids and immunosuppressive drugs do not alter the clinical course. A precise histopathologic diagnosis has important therapeutic implications. Mononuclear cell "inflammation" in a muscle biopsy sample of infants younger than 2 yr old is usually facioscapulohumeral dystrophy or, less often, a congenital muscular dystrophy.

TREATMENT

Physiotherapy is of no value in regaining strength or in retarding progressive weakness or muscle wasting. Footdrop and scoliosis may be treated by orthopedic measures. In selected cases, surgical wiring of the scapulas to the thoracic wall provides improved shoulder stability and abduction of the arm, but brachial plexopathy, frozen shoulder, and scapular fractures are reported complications. Cosmetic improvement of the facial muscles of expression may be achieved by reconstructive surgery, which grafts a fascia lata to the zygomatic muscle and to the zygomatic head of the quadratus labii superioris muscle. Exercise of facial muscles can help minimize secondary disuse atrophy. No effective pharmacologic or genetic treatment is presently available.

Bibliography is available at Expert Consult.

609.6 Congenital Muscular Dystrophies

Harvey B. Sarnat

The term *congenital muscular dystrophy* is misleading because all muscular dystrophies are genetically determined. It is used to encompass several distinct diseases that have a common characteristic of severe involvement at birth but that, ironically, often follow a more benign clinical course than the early onset and the histopathological changes in the muscle biopsy would suggest. A distinguishing feature of the congenital dystrophies, by contrast with other muscular dystrophies, is a high association with brain malformations, particularly disorders of cortical development such as lissencephaly/pachygyria and polymicrogyria, often complicated by severe epilepsy. Autosomal recessive inheritance is the rule.

CLINICAL MANIFESTATIONS

In several distinct clinical and genetic diseases grouped under the umbrella term *congenital muscular dystrophies*, infants often have

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contractures or arthrogryposis at birth and are diffusely hypotonic. The muscle mass is thin in the trunk and extremities. Head control is poor. Facial muscles may be mildly involved, but ophthalmoplegia, pharyngeal weakness, and weak sucking are not common. A minority has severe dysphagia and requires gavage or gastrostomy. Tendon stretch reflexes may be hypoactive or absent. Arthrogryposis is common in all forms of congenital muscular dystrophy (see Chapter 608.10). Congenital contractures of the elbows have a high association with the **Ullrich type of congenital muscular dystrophy** owing to a defect in 1 or more of the 3 collagen VI genes, each at a different locus.

The congenital muscular dystrophies can be classified according to the type of protein altered by the specific genetic mutations. Diseases of extracellular matrix proteins include merosin deficiency (*LAMA2* mutation at locus 6q22-q23) and Ullrich disease (*COL6A1*, *-A2* and *-A3* mutations at 21q22 and 2q37 loci). A protein of the endoplasmic reticulum (*SEPN1* mutation at 1p35) is the basis of rigid spine syndrome. Abnormal glycosylation of α-dystroglycan causes Walker-Warburg syndrome (*POMT1* mutation at 9q34), muscle-eye-brain disease of Santavuori (*POMGnT1* mutation at 1p32), Fukuyama muscular dystrophy (*FCMD* mutation at 8q31-q33 and 9q31), and congenital muscular dystrophy with secondary merosin deficiency (*FKRP* mutation at 19q13). Glycosylation defects (dystroglycanopathies) result in defective neuroblast migration in the fetal brain and also can cause dilated cardiomyopathy. The dystroglycan molecule interacts with both proteins of the plasma (sarcolemmal) membrane and those of the extracellular matrix and basal lamina not only in muscle but also in brain, where defective dystroglycan and poor glycosylation result in gaps in the pial limiting membrane, a discontinuous glia limitans, causing cobblestone lissencephaly and glioneuronal heterotopia of overmigrated neural cells during formation of the cerebral cortex.

The **Fukuyama type** of congenital muscular dystrophy is the second most common muscular dystrophy in Japan (after DMD); it has also been reported in children of Dutch, German, Scandinavian, and Turkish ethnic backgrounds. In the Fukuyama variety, severe cardiomyopathy and malformations of the brain usually accompany the skeletal muscle involvement. Signs and symptoms related to these organs are prominent: cardiomegaly and heart failure, intellectual disability, seizures, microcephaly, and failure to thrive.

Central neurologic disease can accompany forms of congenital muscular dystrophy other than Fukuyama disease. Mental and neurologic status is the most variable feature; an apparently normal brain and normal intelligence do not preclude the diagnosis if other manifestations indicate this myopathy. The cerebral malformations that occur are not consistently of one type and vary from severe dysplasias (holoprosencephaly, lissencephaly) to milder conditions (agenesis of the corpus callosum, focal heterotopia of the cerebral cortex and subcortical white matter, cerebellar hypoplasia). Seizures are a frequent complication, as early as the neonatal period, and may include infantile spasms and other severe infantile epilepsies.

Congenital muscular dystrophy is a constant association with cerebral dysgenesis in the **Walker-Warburg syndrome** and in **muscle-eye-brain disease of Santavuori.** The neuropathologic findings are those of neuroblast migratory abnormalities in the cerebral cortex, cerebellum, and brainstem. Studies indicate considerably more genetic overlap between Walker-Warburg, Fukuyama, and muscle-eye-brain forms of congenital muscular dystrophy that explain mixed and transitional phenotypes, so that, for example, a *Fukutin*-related (*FKRP*) gene can cause a Walker-Warburg or muscle-eye-brain presentation, or *POMGnT1* also can produce phenotypes other than classic Walker-Warburg disease.

LABORATORY FINDINGS

Serum CK level is usually moderately elevated from several hundred to many thousand IU/L; only marginal increases are sometimes found. EMG shows nonspecific myopathic features. Investigation of all forms of congenital muscular dystrophy should include cardiac assessment and an imaging study of the brain. Muscle biopsy is essential for the diagnosis, but if there is a high degree of suspicion (e.g., a confirmed genetic defect in a sibling), specific genetic testing might avoid the muscle biopsy.

DIAGNOSIS

Muscle biopsy is diagnostic in the neonatal period or thereafter. An extensive proliferation of endomysial collagen envelops individual muscle fibers even at birth, also causing them to be rounded in cross-sectional contour by acting as a rigid sleeve, especially during contraction. The perimysial connective tissue and fat are also increased, and the fascicular organization of the muscle may be disrupted by the fibrosis. Tissue cultures of intramuscular fibroblasts exhibit increased collagen synthesis, but the structure of the collagen is normal. Muscle fibers vary in diameter, and many show central nuclei, myofibrillar splitting, and other cytoarchitectural alterations. Scattered degenerating and regenerating fibers are seen. No inflammation or abnormal inclusions are found.

Immunocytochemical reactivity for merosin (α_2 chain of laminin) at the sarcolemmal region is absent in approximately 40% of cases and normally expressed in the others (Figs. 609-6 and 609-7).

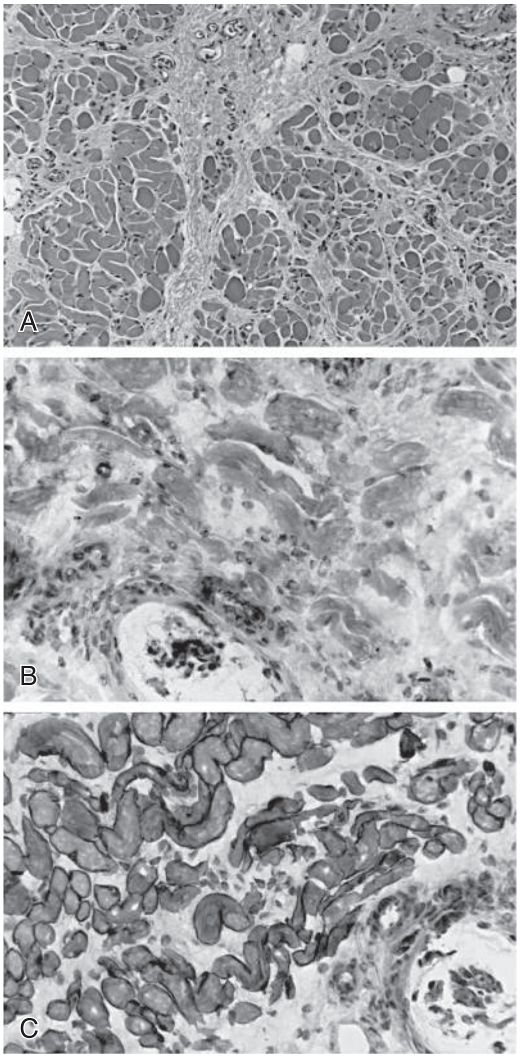

Figure 609-6 Quadriceps femoris muscle biopsy of a 6 mo old girl with congenital muscular dystrophy associated with merosin (α_2-laminin) deficiency. **A,** Histologically, the muscle is infiltrated by a great proliferation of collagenous connective tissue; myofibers vary in diameter, but necrotic fibers are rare. **B,** Immunocytochemical reactivity for merosin (α_2-laminin) is absent in all fibers, including the intrafusal myofibers of a muscle spindle seen at bottom. **C,** Dystrophin expression (rod domain) is normal. Compare with Figures 609-2, 609-3, and 609-7.

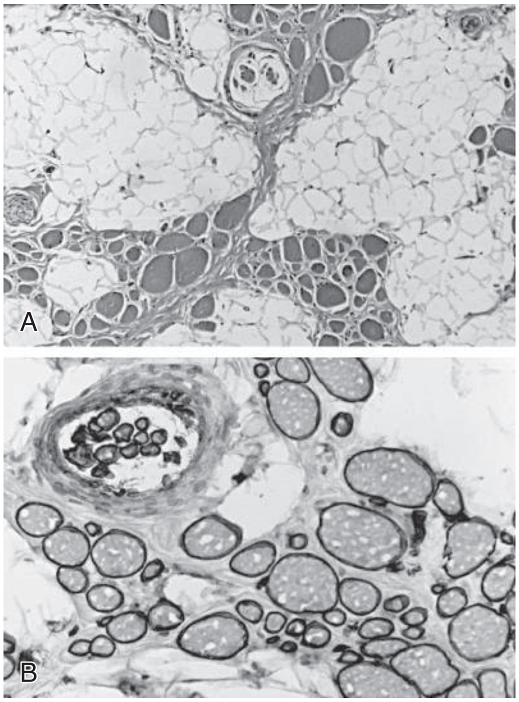

Figure 609-7 Quadriceps femoris muscle biopsy specimen of a 2 yr old girl with congenital muscular dystrophy. **A,** The fascicular architecture of the muscle is severely disrupted, and muscle is replaced by fat and connective tissue; the remaining small groups of myofibers of variable size are seen, including a muscle spindle at top. **B,** Merosin expression is normal in both extrafusal fibers of all sizes and in intrafusal spindle fibers. The severity of the myopathy does not relate to the presence or absence of merosin in congenital muscular dystrophy. Compare with Figure 609-6.

Merosin is a protein that binds the sarcolemmal membrane of the myofiber to the basal lamina or basement membrane. Merosin also is expressed in brain and in Schwann cells. The presence or absence of merosin does not always correlate with the severity of the myopathy or predict its course, but cases with merosin deficiency tend to have more severe cerebral involvement. Adhalin (α-dystroglycan) may be secondarily reduced in some cases. Collagen VI is selectively reduced or absent in Ullrich disease because of a mutation in the *COL6A* gene. Mitochondrial dysfunction may be another secondary defect.

TREATMENT

Only supportive therapy is available in general. Cyclosporine might correct the mitochondrial dysfunction and muscular apoptosis in collagen VI myopathy. Though no curative treatment is presently available for the congenital muscular dystrophies, a consensus statement on the standard of supportive care was issued at a special workshop in 2009 and published the following year. It covers aspects of various organ systems that could be involved, including neurologic, pulmonary, gastroenterologic, cardiac, orthopedic/rehabilitation, and palliative care.

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Chapter 610

Endocrine and Toxic Myopathies

Harvey B. Sarnat

THYROID MYOPATHIES

See also Chapters 563-568.

Thyrotoxicosis causes proximal weakness and wasting accompanied by myopathic electromyographic changes. Thyroxine binds to myofibrils and, if in excess, impairs contractile function. **Hyperthyroidism** can also induce myasthenia gravis and hypokalemic periodic paralysis, the latter mainly affecting East Asian males who have a genetic predisposition. Mutation in the gene *KCNJ18* may be responsible for altering the potassium channel Kir2.6 in up to one third of cases. Potassium supplementation and propranolol are useful in treating thyrotoxic periodic paralysis.

Hypothyroidism, whether congenital or acquired, consistently produces hypotonia and a proximal distribution of weakness. Although muscle wasting is most characteristic, one form of cretinism, the Kocher-Debré-Sémélaigne syndrome, is characterized by generalized pseudohypertrophy of weak muscles. Infants can have a Herculean appearance reminiscent of myotonia congenita. The serum creatine kinase (CK) level is elevated in hypothyroid myopathy and returns to normal after thyroid replacement therapy.

Results of muscle biopsy in hypothyroidism reveal acute myopathic changes, including myofiber necrosis and sometimes central cores. In hyperthyroidism, the muscle biopsy specimen shows only mild, nonspecific myopathic changes without necrosis of myofibers.

The clinical and pathologic features of hyperthyroid myopathy and hypothyroid myopathy resolve after appropriate treatment of the thyroid disorder. Many of the systemic symptoms of hyperthyroidism, including myopathic weakness and ophthalmoparesis, improve with the administration of β-blockers.

Most patients with primary **hyperparathyroidism** (see Chapter 573) develop weakness, fatigability, fasciculations, and muscle wasting that is reversible after removal of the parathyroid adenoma. The serum creatine kinase and muscle biopsy remain normal, but the electromyography can show nonspecific myopathic features. A minority of patients develop myotonia that could be confused with myotonic dystrophy.

STEROID-INDUCED MYOPATHY

Natural Cushing disease and iatrogenic Cushing syndrome from exogenous corticosteroid administration can cause painless, symmetric, progressive proximal weakness, increased serum creatine kinase levels, and a myopathic electromyogram and muscle biopsy specimen (see Chapter 577). Myosin filaments may be selectively lost. The 9α-fluorinated steroids, such as dexamethasone, betamethasone, and triamcinolone, are the most likely to produce *steroid myopathy.* Dexamethasone alters the abundance of ceramides in myotubes in developing muscle. In patients with dermatomyositis or other myopathies treated with steroids, it is sometimes difficult to distinguish refractoriness of the disease from steroid-induced weakness, especially after long-term steroid administration. Vitamin D is another factor altering muscle metabolism and particularly its sensitivity to insulin; vitamin D deficiency may be accentuated and contribute to steroid myopathy, especially in type 2 diabetic patients and insulin resistance.

All patients who have been taking steroids for long periods develop reversible type II myofiber atrophy; this is a *steroid effect* but is not steroid myopathy unless it progresses to become a necrotizing myopathy. At greatest risk in the pediatric age group are children requiring long-term steroid therapy for asthma, rheumatoid arthritis, dermatomyositis, lupus, and other autoimmune or inflammatory diseases or who are being treated for leukemia or other hematologic diseases.

Table 610-1 Toxic Myopathies

INFLAMMATORY Cimetidine D-Penicillamine Procainamide L-Tryptophan L-DOPA	**MALIGNANT HYPERTHERMIA** Halothane Ethylene Diethyl ether Methoxyflurane Ethyl chloride Trichloroethylene Gallamine Succinylcholine
NONINFLAMMATORY NECROTIZING OR VACUOLAR Cholesterol-lowering agents Chloroquine Colchicine Emetine ε-Aminocaproic acid Labetalol Cyclosporine and tacrolimus Isoretinoic acid (vitamin A analog) Vincristine Alcohol	**MITOCHONDRIAL** Zidovudine **MYOTONIA** 2,4-*d*-Chlorophenoxyacetic acid Anthracene-9-carboxycyclic acid Cholesterol-lowering drugs Chloroquine Cyclosporine
RHABDOMYOLYSIS AND MYOGLOBINURIA Cholesterol-lowering drugs (especially statins) Alcohol Heroin Amphetamine Toluene Cocaine ε-Aminocaproic acid Pentazocine Phencyclidine	**MYOSIN LOSS** Nondepolarizing neuromuscular blocking agents Intravenous glucocorticoids

From Goldman L, Ausiello D: Cecil textbook of medicine, *ed 22, Philadelphia, 2004, WB Saunders, p. 2399.*

In addition to steroids, the drugs listed in Table 610-1 can cause acute or chronic toxic myopathies. An incompletely understood entity known as critical illness myopathy is a progressive weakness of patients with extended illnesses who remain in the intensive care unit; it is associated pathologically with selective loss of thick (myosin) myofilaments; immobility and excessive steroid treatment are believed to be important factors. Various steroids are sometimes used chronically in the treatment of Duchenne muscular dystrophy; they may actually exaggerate the weakness because of steroid myopathy superimposed on the dystrophic process (see Chapter 609).

Hyperaldosteronism (Conn syndrome) is accompanied by episodic and reversible weakness similar to that of periodic paralysis. The proximal myopathy can become irreversible in chronic cases. Elevated creatine kinase levels and even myoglobinuria sometimes occur during acute attacks. Arterial hypertension is a frequent manifestation and, in children, aldosterone-secreting adenomas should be considered in the differential diagnosis of idiopathic hypertension. Hereditary primary aldosteronism is due to a mutation in one of the potassium channel genes *KCNJ5* and *GIRK4*.

Chronic growth hormone excess (sometimes illicitly acquired by adolescent athletes or seen in acromegaly) produces atrophy of some myofibers and hypertrophy of others, and scattered myofiber degeneration. Despite the augmented protein synthesis induced by growth hormone, it impairs myofibrillar adenosine triphosphatase activity and reduces sarcolemmal excitability, with resultant diminished, rather than increased, strength corresponding to the larger muscle mass. It has been used therapeutically in muscular dystrophy with both a positive effect and complications. *Ghrelin* is an intestinal hormone that activates a growth hormone secretagog receptor and stimulates growth hormone release. In addition to its effect as a "hunger hormone" that involves food intake and fat deposition, it also prevents muscular atrophy by inducing myodifferentiation and myoblast fusion.

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Chapter 611

Metabolic Myopathies

Harvey B. Sarnat

Table 611-1 describes the differential diagnosis of metabolic myopathies.

611.1 Periodic Paralyses (Potassium-Related) and Other Muscle Channelopathies

Harvey B. Sarnat

Episodic, reversible weakness or paralysis, known as **periodic paralysis,** is associated with transient alterations in serum potassium levels, usually hypokalemia but occasionally hyperkalemia. All familial forms of periodic paralysis are caused by mutations in genes encoding voltage-gated ion channels in muscle: sodium, calcium, and potassium. Mutations in the *CACNA1S* voltage-gated calcium (not potassium) channel are the etiology of hypokalemic periodic paralysis. Nonhereditary causes of periodic paralysis are caused by a diverse group of disorders that affect potassium balance (Table 611-2). During

Table 611-1 Metabolic and Mitochondrial Myopathies
GLYCOGEN METABOLISM DEFICIENCIES
Type II: α-1,4-Glucosidase (acid maltase)
Type III: Debranching
Type IV: Branching
Type V: Phosphorylase (McArdle disease)*
Type VII: Phosphofructokinase (Tarui disease)*
Type VIII: Phosphorylase B kinase*
Type IX: Phosphoglycerate kinase*
Type X: Phosphoglycerate mutase*
Type XI: Lactate dehydrogenase*
LIPID METABOLISM DEFICIENCIES
Carnitine palmitoyltransferase*
Primary systemic/muscle carnitine deficiency
Secondary carnitine deficiency
β-Oxidation defects
Medications (valproic acid)
PURINE METABOLISM DEFICIENCIES
Myoadenylate deaminase deficiency
MITOCHONDRIAL MYOPATHIES
Alpers-Huttenlocher syndrome
Chronic progressive external ophthalmoplegia
Kearns-Sayre syndrome
Pearson syndrome
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)
Myoclonic epilepsy with ragged red fibers (MERRF)
Leber hereditary optic neuropathy
Leigh syndrome
Infantile myopathy and lactic acidosis

*Deficiency can produce exercise intolerance and myoglobinuria.
From Chinnery PF: Muscle diseases. In Goldman L, Schafer AI, editors: Goldman's Cecil medicine, *ed 24, Philadelphia, 2012, Elsevier, Table 429-7, p. 2413.*

Table 611-2	Secondary Causes of Periodic Paralysis
HYPOKALEMIC	
Thyrotoxic	
Primary hyperaldosteronism (Conn syndrome)	
Renal tubular acidosis (e.g., Fanconi syndrome)	
Juxtaglomerular apparatus hyperplasia (Bartter syndrome)	
Gastrointestinal potassium wastage	
Villous adenoma	
Laxative abuse	
Pancreatic non–insulin-secreting tumors with diarrhea	
Nontropical sprue	
Barium intoxication	
Potassium-depleting diuretics	
Amphotericin B	
Licorice	
Corticosteroids	
Toluene toxicity	
p-Aminosalicylic acid	
Carbenoxolone	
HYPERKALEMIC	
Addison disease	
Hypoaldosteronism	
Excessive potassium supplementation	
Potassium-sparing diuretics	
Chronic renal failure	

From Chinnery PF: Muscle diseases. In Goldman L, Schafer AI, editors: Goldman's Cecil medicine, *ed 24, Philadelphia, 2012, Elsevier, Table 429-8, p. 2415.*

attacks, myofibers are electrically unexcitable, although the contractile apparatus can respond normally to calcium. The genetic disorder is inherited as an autosomal dominant trait. It is precipitated in some patients by a heavy carbohydrate meal, insulin, epinephrine including that induced by emotional stress, hyperaldosteronism or hyperthyroidism, administration of amphotericin B, or ingestion of licorice. The defective genes are at the 17q13.1-13.3 locus in **hyperkalemic periodic paralysis,** the same as in paramyotonia congenita, and at the 1q31-32 locus in **hypokalemic periodic paralysis.**

Attacks often begin in infancy, particularly in the hyperkalemic form, and the disease is nearly always symptomatic by 10 yr of age, affecting both sexes equally. Late childhood or adolescence is the more typical age of onset of the hypokalemic form, Andersen-Tawil syndrome, and paramyotonia congenita. Periodic paralysis is an episodic event; patients are unable to move after awakening and gradually recover muscle strength during the next few minutes or hours. All 4 extremities are involved. Muscles that remain active in sleep, such as the diaphragm, extraocular muscles (rapid eye movements), and cardiac muscle, are not affected. Patients are normal between attacks, but in adult life the attacks become more frequent, and the disorder causes progressive myopathy with permanent weakness even between attacks. The usual frequency of attacks in childhood is once a week. The differential diagnosis includes thyrotoxic periodic paralysis, myotonia congenita, and paramyotonia congenita. A triad of periodic paralysis, potentially fatal cardiac ventricular ectopy (caused by a defect in Kir2.1 channels for terminal repolarization), and characteristic physical features is known as **Andersen-Tawil syndrome.**

Alterations in serum potassium levels occur only during acute episodes and are accompanied by T-wave changes in the electrocardiogram. Hypokalemia may be caused by alterations in calcium gradients. The creatine kinase (CK) level may be mildly elevated at those times. Plasma phosphate levels often decrease during symptomatic periods. Muscle biopsy findings are often normal between attacks, but during an attack a vacuolar myopathy is demonstrated. Pathologic changes in the periodic paralyses are similar, whether the disease is the result of a sodium or a potassium channel defect, suggesting that the changes might result from the recurrent paralytic state rather than the specific channelopathy. The vacuoles are dilated sarcoplasmic reticulum and invaginations of the extracellular space into the cytoplasm, and they may be filled with glycogen. Muscle biopsy is not essential to diagnose periodic paralysis, however. Hypoglycemia does not occur. Loci for the majority of periodic paralyses have been demonstrated and the genes at least partially characterized, but many patients with the same clinical phenotype exhibit no mutations in the identified genes.

TREATMENT

Paralytic attacks of hypokalemic periodic paralysis are best treated by the oral administration of potassium or even fruit juices that contain potassium. A low sodium intake and the administration of acetazolamide, 125-250 mg bid or tid in school-age children, often is effective in abolishing attacks or at least reducing their frequency and severity. Spironolactone, in a dose of 100-200 mg/day PO in school-age children, may be beneficial as well.

OTHER MUSCLE CHANNELOPATHIES

Disorders of ion channels other than the well-documented potassium channelopathies also are recognized. A rare, severe **neonatal myotonia** is secondary to a mutation of the voltage-gated sodium-channel *SCN4A* gene; it is unrelated to neonatal myotonic dystrophy, myotonia congenita, or infantile myofibrillar myopathies. This same gene also is responsible for severe neonatal episodic laryngospasm. Mexiletine is effective treatment of the myotonia, but the long-term prognosis remains poor, with death by 2 yr of age. Sodium channel blockers, such as carbamazepine, phenytoin, and procainamide, are alternatives.

Neuromyotonia, a continuous muscle activity of neurogenic origin, may be caused by mutations in genes encoding or antibodies against potassium channels, but is rare in childhood. **Schwartz-Jampel disease**, resulting from, an autosomal recessive trait, involves severe muscle stiffness, myotonia, blepharospasm, and chondroplasia. It becomes symptomatic in the 1st yr of life and is slowly progressive until midadolescence, after which it is stable. It is no longer considered a variant of myotonic dystrophy and is caused by mutation in the *HSPG2* gene that encodes perlecan, the major heparin sulphate proteoglycan of basement membranes. Sodium channel blockers may be useful.

Bibliography is available at Expert Consult.

611.2 Malignant Hyperthermia

Harvey B. Sarnat

See also Chapters 61 and 608.4.

This syndrome is usually inherited as an autosomal dominant trait. It occurs in all patients with central core disease but is not limited to that particular myopathy. The gene is at the 19q13.1 locus in both central core disease and malignant hyperthermia without this specific myopathy. At least 15 separate mutations in this gene are associated with malignant hyperthermia. The gene programs the ryanodine receptor, a tetrameric calcium release channel in the sarcoplasmic reticulum, in apposition to the voltage-gated calcium channel of the transverse tubule. It occurs rarely in Duchenne and other muscular dystrophies, in various other myopathies, in some children with scoliosis, and in an isolated syndrome not associated with other muscle disease. Affected children sometimes have peculiar facies. All ages are affected, including premature infants whose mothers underwent general anesthesia for cesarean section.

Acute episodes are precipitated by exposure to general anesthetics and occasionally to local anesthetic drugs. Patients suddenly develop extreme fever, rigidity of muscles, and metabolic and respiratory acidosis; the serum CK level rises to as high as 35,000 IU/L. Myoglobinuria can result in tubular necrosis and acute renal failure.

The muscle biopsy specimen obtained during an episode of malignant hyperthermia or shortly afterward is not indicated but shows widely scattered necrosis of muscle fibers known as **rhabdomyolysis**. Between attacks, the muscle biopsy specimen is normal unless there is an underlying chronic myopathy.

It is important to recognize patients at risk of malignant hyperthermia because the attacks may be prevented by administering dantrolene

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sodium before an anesthetic is given. Patients at risk, such as siblings, are identified by the caffeine contracture test: a portion of fresh muscle biopsy tissue in a saline bath is attached to a strain gauge and exposed to caffeine and other drugs; an abnormal spasm is diagnostic. The syndrome-associated receptor also may be demonstrated by immunochemistry in frozen sections of the muscle biopsy. The gene defect of the ryanodine receptor is present in 50% of patients; gene testing is available only for this genetic group. This receptor also may be seen in the muscle biopsy by immunoreactivity. Another candidate gene is at the 1q31 locus.

Apart from the genetic disorder of malignant hyperthermia, some drugs can induce acute rhabdomyolysis with myoglobinuria and potential renal failure, but this usually occurs in patients who are predisposed by some other metabolic disease (mitochondrial myopathies). Valproic acid can induce this process in children with mitochondrial cytopathies or with carnitine palmitoyltransferase deficiency.

611.3 Glycogenoses

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See also Chapter 87.1.

Glycogenosis I (von Gierke disease) is not a true myopathy because the deficient liver enzyme glucose-6-phosphatase is not normally present in muscle. Nevertheless, children with this disease are hypotonic and mildly weak for unknown reasons.

Glycogenosis II (Pompe disease) is an autosomal recessively inherited deficiency of the glycolytic lysosomal enzyme α-glucosidase (formerly known as acid maltase) that cleaves the α-1,4 and α-1,6 glycosidic linkages. Of the 12 known glycogenoses, type II is the only one with a defective lysosomal enzyme. The defective gene is at locus 17q23, with more than 200 distinct mutations identified. Two clinical forms are described. The **infantile** form is a severe generalized myopathy and cardiomyopathy. Patients have cardiomegaly and hepatomegaly and are diffusely hypotonic and weak. The serum CK level is greatly elevated. A muscle biopsy specimen reveals a vacuolar myopathy with abnormal lysosomal enzymatic activities such as acid and alkaline phosphatases. Evidence of a secondary mitochondrial cytopathy is often demonstrated; it includes electron microscopic demonstration of paracrystallin structures within muscle mitochondria and low concentrations of respiratory chain enzymes. Death in infancy or early childhood is usual; however, enzyme replacement therapy has improved the outcome.

The **late childhood** or **adult** form is a much milder myopathy without cardiac or hepatic enlargement. It might not become clinically expressed until later childhood or early adult life but may be symptomatic as myopathic weakness and hypotonia even in early infancy. Even in late adult-onset acid maltase deficiency, >50% of the patients report difficulties with muscle strength dating from childhood. Ultrastructural evidence of secondary mitochondrial cytopathy also occurs, as with infantile Pompe disease. MRI of muscle may show distinctive changes that differ from other myopathies.

The serum CK level is greatly elevated, and the muscle biopsy findings are diagnostic even in the presymptomatic stage. The diagnosis of glycogenosis II is confirmed by quantitative assay of acid maltase activity in muscle or liver biopsy specimens. A rare variant of the milder form of acid maltase deficiency can show muscle acid maltase activity in the low normal range with only intermittent decreases to subnormal values; the muscle biopsy findings are similar although milder. In another form, **Danon disease,** transmitted as an X-linked recessive trait at the Xq24 locus, the primary deficiency is lysosomal membrane protein-2 (LAMP2) and results in hypertrophic cardiomyopathy, proximal myopathy, and intellectual disability.

Glycogenosis III (Cori-Forbes disease), a deficiency of debrancher enzyme (amylo-1,6-glucosidase), is more common than is usually diagnosed, and it is generally the least severe. Hypotonia, weakness, hepatomegaly, and fasting hypoglycemia in infancy are common, but these features often resolve spontaneously, and patients become asymptomatic in childhood and adult life. Others experience slowly progressive distal muscle wasting, hepatic cirrhosis, recurrent hypoglycemia, and heart failure. This more serious chronic course is particularly seen in the Inuit population. Minor myopathic findings including vacuolation of muscle fibers are found in the muscle biopsy specimen.

Glycogenosis IV (Andersen disease) is a deficiency of brancher enzyme, resulting in the formation of an abnormal glycogen molecule, amylopectin, in the liver, reticuloendothelial cells, and skeletal and cardiac muscle. Hypotonia, generalized weakness, muscle wasting, and contractures are the usual signs of myopathic involvement. Most patients die before age 4 yr because of hepatic or cardiac failure. A few children without neuromuscular manifestations have been described.

Glycogenosis V (McArdle disease) is caused by muscle glycogen phosphorylase deficiency inherited as an autosomal recessive trait at locus 11q13, encoded by the *PMGM* gene. Exercise intolerance is the cardinal clinical feature. Physical exertion results in cramps, weakness, and myoglobinuria, but strength is normal between attacks. The serum CK level is elevated only during exercise. A characteristic clinical feature is lack of the normal rise in serum lactate levels during ischemic exercise because of inability to convert pyruvate to lactate under anaerobic conditions in vivo. Myophosphorylase deficiency may be demonstrated histochemically and biochemically in the muscle biopsy tissue. Some patients have a defect in adenosine monophosphate–dependent muscle phosphorylase β-kinase, a phosphorylase enzyme activator. Muscle phosphorylase deficiency was the first neuromuscular disease to be diagnosed by MR spectroscopy, which shows that the intramuscular pH does not decrease with exercise and there is no depletion of adenosine triphosphatase but that the phosphocreatine concentration falls excessively. This noninvasive technique may be useful in some patients if the radiologist is experienced with the disease.

A rare **neonatal form of myophosphorylase deficiency** causes feeding difficulties in early infancy, may be severe enough to result in neonatal death, or can follow a course of slowly progressive weakness resembling a muscular dystrophy. The long-term prognosis is good. Patients must learn to moderate their physical activities, but they do not develop severe chronic myopathic handicaps or cardiac involvement.

Glycogenosis VII (Tarui disease) is muscle phosphofructokinase deficiency. Although this disease is rarer than glycogenosis V, the symptoms of exercise intolerance, clinical course, and inability to convert pyruvate to lactate are identical. The distinction is made by biochemical study of the muscle biopsy specimen. It is transmitted as an autosomal recessive trait at the 1cenq32 locus and some mutations are particularly prevalent in the Ashkenazi Jewish population.

Bibliography is available at Expert Consult.

611.4 Mitochondrial Myopathies

Harvey B. Sarnat

See also Chapters 87.4 and 598.2.

Several diseases involving muscle, brain, and other organs are associated with structural and functional abnormalities of mitochondria, producing defects in aerobic cellular metabolism, the electron transport chain, and the Krebs cycle. Because mitochondria are found in all cells, except mature erythrocytes, the term **mitochondrial cytopathy** is used preferentially to emphasize the multisystemic nature of these diseases. The structural aberrations are best demonstrated by electron microscopy of the muscle biopsy sample, revealing a proliferation of abnormally shaped cristae, including stacked or whorled cristae and paracrystallin structures that occupy the space between cristae and are formed from CK. Muscle biopsies of neonates, infants, and toddlers show more severe involvement of endothelial cells of intramuscular capillaries than of myofibers, unlike the reverse in adults, but endothelial paracrystallin structures are globular rather than brick shaped as in myofibers. The endoplasmic reticulum becomes abnormally adherent to mitochondria. Similar endothelial mitochondrial alterations are seen in brain in Leigh and other infantile mitochondrial encephalopathies. Histochemical study of the muscle biopsy specimen reveals abnormal clumping of oxidative enzymatic activity and scattered myofibers, with

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loss of cytochrome-c oxidase activity and with increased neutral lipids within myofibers. Ragged red muscle fibers occur in some mitochondrial myopathies, particularly those with a combination of respiratory chain complexes I and IV deficiencies. Accumulations of this membranous material beneath the muscle fiber membrane are best demonstrated by special stains, such as modified Gomori trichrome.

These characteristic histochemical and ultrastructural changes are most consistently seen with point mutations in mitochondrial transfer RNA. The large mitochondrial DNA (mtDNA) deletions of 5 or 7.4 kb (the single mitochondrial chromosome has 16.5 kb) are associated with defects in mitochondrial respiratory oxidative enzyme complexes, if as few as 2% of the mitochondria are affected, but minimal or no morphologic or histochemical changes may be noted in the muscle biopsy specimen, even by electron microscopy; hence, quantitative biochemical studies of the muscle tissue are needed to confirm the diagnosis. Because most of the subunits of the respiratory chain complexes are encoded by nuclear DNA (nDNA) rather than mtDNA, mendelian autosomal inheritance is possible, rather than maternal transmission as with pure mtDNA point mutations. Complex II (succinate dehydrogenase) is the only enzyme complex in which all of its subunits are encoded by nDNA; hence it is histochemically reactive in all mitochondrial diseases with mtDNA point mutations. Serum lactate is elevated in some diseases, and cerebrospinal fluid lactate is more consistently elevated, even if serum concentrations are normal.

Several distinct mitochondrial diseases that primarily affect striated muscle or muscle and brain are identified. These can be divided into the ragged red fiber diseases and non–ragged fiber diseases. The ragged red fiber diseases include Kearns-Sayre, MELAS (*m*itochondrial *e*ncephalopathy, *l*actic *a*cidosis, and *s*troke-like episodes) syndrome, MERRF (*m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers) syndrome, and progressive external ophthalmoplegia syndromes, which are associated with a combined defect in respiratory chain complexes I and IV. The non–ragged fiber diseases include Leigh encephalopathy and Leber hereditary optic atrophy; they involve complex I or IV alone or, in children, the common combination of defective complexes III and V. **Kearns-Sayre syndrome** is characterized by the triad of progressive external ophthalmoplegia, pigmentary degeneration of the retina, and onset before age 20 yr. Heart block, cerebellar deficits, and high cerebrospinal fluid protein content are often associated. Visual evoked potentials are abnormal. Patients usually do not experience weakness of the trunk or extremities or dysphagia. Most cases are sporadic.

Chronic progressive external ophthalmoplegia may be isolated or accompanied by limb muscle weakness, dysphagia, and dysarthria. A few patients described as having *ophthalmoplegia plus* have additional central nervous system involvement. Autosomal dominant inheritance is found in some pedigrees, but most cases are sporadic.

MERRF and **MELAS syndromes** are other mitochondrial disorders affecting children. The latter is characterized by stunted growth, episodic vomiting, seizures, and recurring cerebral insults causing hemiparesis, hemianopia, or even cortical blindness, and dementia. The disease behaves as a degenerative disorder, and children die within a few years.

Other "degenerative" diseases of the central nervous system that also involve myopathy with mitochondrial abnormalities include **Leigh subacute necrotizing encephalopathy** (see Chapter 87.4) and **cerebrohepatorenal (Zellweger) disease, primarily a peroxisomal disease with secondary mitochondrial alterations** (see Chapter 86.2). Another recognized mitochondrial myopathy is **cytochrome-c oxidase deficiency. Oculopharyngeal muscular dystrophy** is also fundamentally a mitochondrial myopathy.

Mitochondrial depletion syndrome of early infancy is characterized by severely decreased oxidative enzymatic activities in most or all 5 of the complexes; in addition to diffuse muscle weakness, neonates and young infants can show multisystemic involvement and the syndrome occurs in several forms: myopathic; encephalomyopathic; hepatoencephalopathic; and intestinal encephalopathic. Cardiomyopathy and sometimes bullous skin lesions or generalized edema also can occur. **Alpers syndrome** is genetically homogeneous and is caused by mtDNA depletion and mutations in the *POLG1* gene. Several other genes are identified, mostly in later-onset forms; hence mitochondrial depletion is a syndrome and not a single disease. **Barth syndrome** is an X-linked recessive mitochondrial disorder characterized by cardiomyopathy, myopathy of striated muscle, growth retardation, neutropenia, and high serum and urinary concentrations of 3-methylglutaconic acid.

Many rare diseases with only a few case reports are suspected of being mitochondrial disorders. It is also now recognized that secondary mitochondrial defects occur in a wide range of nonmitochondrial diseases, including inflammatory autoimmune myopathies, Pompe disease, and some cerebral malformations, and also may be induced by certain drugs and toxins, so that interpretation of mitochondrial abnormalities as primary defects must be approached with caution.

mtDNA is distinct from the DNA of the cell nucleus and is inherited exclusively from the mother; mitochondria are present in the cytoplasm of the ovum but not in the head of the sperm, the only part that enters the ovum at fertilization. The rate of mutation of mtDNA is 10 times higher than that of nDNA. The mitochondrial respiratory enzyme complexes each have subunits encoded either in mtDNA or nDNA. Complex II (succinate dehydrogenase, a Krebs cycle enzyme) has 4 subunits, all encoded in nDNA; complex III (ubiquinol or cytochrome-b oxidase) has 9 subunits, only 1 of which is encoded by mtDNA and 8 of which are programmed by nDNA; complex IV (cytochrome-c oxidase) has 13 subunits, only 3 of which are encoded by mtDNA. For this reason, mitochondrial diseases of muscle may be transmitted as autosomal recessive traits rather than by strict maternal transmission, even though all mitochondria are inherited from the mother.

In Kearns-Sayre syndrome, a single large mtDNA deletion has been identified, but other genetic variants are known; in MERRF and MELAS syndromes of mitochondrial myopathy, point mutations occur in transfer RNA.

INVESTIGATIONS

Investigation for mitochondrial cytopathies begins with serum lactate. Lactic acid is not increased in all mitochondrial cytopathies, so that a normal result is not necessarily reassuring; cerebrospinal fluid lactate is increased in some cases in which serum lactate is normal, particularly if there are clinical signs of encephalopathy. Serum 3-methylglutaconic acid often is increased in mitochondrial cytopathies in general, demonstrated in more than 50 different genetic mutations, and hence is a good screening measurement; it rarely is increased in other metabolic diseases. This product also may be increased in urine. Hepatic enzymes (transaminases) should be measured in blood. Cardiac evaluation often is warranted. Molecular markers in blood for the common diseases with known mtDNA point mutations identify many of the mitochondrial cytopathies presenting in adult life or adolescence, but less frequently in children and least in young infants. MRI of the brain may reveal hyperintense lesions of the basal ganglia and MR spectroscopy can demonstrate an increased lactate peak. The muscle biopsy provides the best evidence of all mitochondrial myopathies and should include histochemistry for oxidative enzymes, electron microscopy, and quantitative biochemical assay of respiratory chain enzyme complexes and coenzyme-Q10; muscle tissue also can be analyzed for mtDNA. Many mitochondrial disorders also can affect the Schwann cells and axons of peripheral nerves and present clinically with neuropathy; hence motor and sensory nerve conduction velocities can be measured in selected patients; sural nerve biopsy is required only rarely if neuropathy is the predominant finding and the diagnosis is not evident from other studies.

TREATMENT

There is no effective treatment of mitochondrial cytopathies, but various "cocktails" are often used empirically to try to overcome the metabolic deficits. These include oral carnitine supplements, riboflavin, coenzyme-Q10, ascorbic acid (vitamin C), vitamin E, and other antioxidants. Although some anecdotal reports are encouraging, no controlled studies that prove efficacy have been published.

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611.5 Lipid Myopathies

Harvey B. Sarnat

See Chapter 86.4.

Considered as metabolic organs, skeletal muscles are the most important sites in the body for long-chain fatty acid metabolism because of their large mass and their rich density of mitochondria where fatty acids are metabolized. They are the major source of energy for skeletal muscle during sustained exercise or fasting. Hereditary disorders of lipid metabolism that cause progressive myopathy are an important, relatively common, and often treatable group of muscle diseases. Increased lipid within myofibers is seen in the muscle biopsy of some mitochondrial myopathies and is a constant, rather than an unpredictable, feature of specific diseases. Among the ragged red fiber diseases, Kearns-Sayre syndrome always shows increased neutral lipid, whereas MERRF and MELAS syndromes do not, a useful diagnostic marker for the pathologist. Free fatty acids are converted to acyl-coenzyme A by fatty acyl-coenzyme A synthetases; the resulting long-chain fatty acids bind to carnitine and are transported into mitochondria where β-oxidation is carried out. Disorders of lipid fuel utilization and lipid storage disorders can be divided into defects of transport and oxidation of exogenous fatty acids within mitochondria and defects of endogenous triglyceride catabolism.

Muscle carnitine deficiency is an autosomal recessive disease caused by mutations in the *SLC22A5* gene, involving deficient transport of dietary carnitine across the intestinal mucosa. Carnitine is acquired from dietary sources but is also synthesized in the liver and kidneys from lysine and methionine; it is the obligatory carrier of long- and medium-chain fatty acids into muscle mitochondria.

The clinical course may be one of sudden exacerbations of weakness or can resemble a progressive muscular dystrophy with generalized proximal myopathy and sometimes facial, pharyngeal, and cardiac involvement. Symptoms usually begin in late childhood or adolescence or may be delayed until adult life. Progression is slow but can end in death.

Serum CK level is mildly elevated. Muscle biopsy material shows vacuoles filled with lipid within muscle fibers in addition to nonspecific changes suggestive of a muscular dystrophy. Mitochondria can appear normal or abnormal. Carnitine measured in muscle biopsy tissue is reduced, but the serum carnitine level is normal.

Treatment stops the progression of the disease and can even restore lost strength if the disease is not too advanced. It consists of special diets low in long-chain fatty acids. Steroids can enhance fatty acid transport. Specific therapy with L-carnitine taken orally in large doses overcomes the intestinal barrier in some patients. Some patients also improve when given supplementary riboflavin, and other patients seem to improve with propranolol.

Systemic carnitine deficiency is a disease of impaired renal and hepatic synthesis of carnitine rather than a primary myopathy. Patients with this autosomal recessive disease experience progressive proximal myopathy and show muscle biopsy changes similar to those of muscle carnitine deficiency; however, the onset of weakness is earlier and may be evident at birth. Endocardial fibroelastosis also can occur. Episodes of acute hepatic encephalopathy resembling Reye syndrome can occur. Hypoglycemia and metabolic acidosis complicate acute episodes. Cardiomyopathy may be the predominating feature in some cases and result in death.

Cerebral infarctions and myopathy occur in children, particularly when accompanied by hypoglycemia. Mean age at presentation is approximately 9 yr. Brain MRI shows distinctive changes related to multiple infarcts of various sizes.

The concentration of carnitine is reduced in serum as well as in muscle and liver. L-Carnitine deficiency can be corrected by oral administration of carnitine on a daily basis.

A similar clinical syndrome may be a complication of renal Fanconi syndrome because of excessive urinary loss of carnitine or loss during chronic hemodialysis.

Treatment with L-carnitine improves the maintenance of blood glucose and serum carnitine levels but does not reverse the ketosis or acidosis or improve exercise capacity.

Muscle carnitine palmitoyltransferase (CPT) deficiency manifests as episodes of rhabdomyolysis, coma, and elevated serum CK levels that may be indistinguishable from Reye syndrome. It is the most common identified cause of recurrent myoglobinuria in adults, but myoglobinuria is not a constant feature in all. CPT transfers long-chain fatty acid acyl-coenzyme A residues to carnitine on the outer mitochondrial membrane for transport into the mitochondria. Exercise intolerance and myoglobinuria resemble glycogenoses V and VII. The degree of exercise that triggers an attack varies among individuals, ranging from casual walking to strenuous exercise. Fasting hypoglycemia can occur. Some patients present only in late adolescence or adult life with myalgias. Genetic transmission is autosomal recessive and is caused by a defect on chromosome 1 at the 1p32 locus. Administration of valproic acid can precipitate acute rhabdomyolysis with myoglobinuria in patients with CPT deficiency; it should be avoided in the treatment of seizures or migraine if they occur. *Very long-chain acyl-coenzyme A dehydrogenase deficiency* has a similar clinical presentation but mainly with adult onset.

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611.6 Vitamin E Deficiency Myopathy

Harvey B. Sarnat

In experimental animals, deficiency of vitamin E (α-tocopherol, an antioxidant also important in mitochondrial superoxide generation) produces a progressive myopathy closely resembling a muscular dystrophy. Myopathy and neuropathy are recognized in humans who lack adequate intake of this antioxidant. Patients with chronic malabsorption, those undergoing long-term dialysis, and premature infants who do not receive vitamin E supplements are particularly vulnerable. Treatment with high doses of vitamin E can reverse the deficiency. Myopathy caused by chronic hypervitaminosis E also occurs.

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Chapter 612

Disorders of Neuromuscular Transmission and of Motor Neurons

Harvey B. Sarnat

612.1 Myasthenia Gravis

Harvey B. Sarnat

AUTOIMMUNE MYASTHENIA GRAVIS

Myasthenia gravis is a chronic autoimmune disease of neuromuscular blockade, characterized clinically by rapid fatigability of striated muscle, particularly extraocular and palpebral muscles and those of swallowing. It must be distinguished from congenital myasthenic

syndrome, a genetic disorder of receptors on the postsynaptic membrane of the neuromuscular junction and toxin-induced myasthenia, such as botulism (see below). The release of acetylcholine (ACh) into the synaptic cleft by the axonal terminal is normal, but the postsynaptic muscle membrane (i.e., *sarcolemma*) or *motor end plate* is less responsive than normal. A decreased number of available ACh receptors is as a result of circulating receptor-binding antibodies in most cases of autoimmune myasthenia.

A rare **familial** myasthenia gravis is an autosomal recessive trait not associated with increased plasma anti-ACh antibodies. One familial form is a deficiency of motor end plate acetylcholinesterase (AChE). Most congenital (familial) forms are postsynaptic defects. Infants born to myasthenic mothers can have a **transient neonatal myasthenic syndrome** secondary to placentally transferred anti-ACh receptor antibodies, distinct from congenital myasthenic syndromes (Tables 612-1 and 612-2).

Clinical Manifestations

In juvenile autoimmune myasthenia gravis, unilateral or bilateral but usually asymmetrical ptosis and some degree of extraocular muscle weakness are the earliest and most constant signs. Extraocular weakness is not confined to muscles innervated by just 1 or 2 of the 3 corresponding brainstem nuclei and is progressive. Older children might complain of diplopia, and young children might hold open their eyes with their fingers or thumbs if the ptosis is severe

Table 612-1 Classification of the Congenital Myasthenic Syndromes

PRESYNAPTIC DEFECTS
- Paucity of synaptic vesicles and decreased quantal release
- Congenital myasthenic syndromes with episodic apnea (choline acetyltransferase deficiency)
- Lambert-Eaton syndrome–like form

SYNAPTIC DEFECTS
- End plate acetylcholinesterase deficiency

POSTSYNAPTIC DEFECTS
- Primary acetylcholine receptor deficiency
- Reduced receptor expression as a result of acetylcholine receptor mutations
- Reduced receptor expression because of rapsyn mutations
- Reduced receptor expression with plectin deficiency
- Primary acetylcholine receptor kinetic abnormality with or without acetylcholine receptor deficiency
- Slow-channel syndrome
- Fast-channel syndrome
- Sodium-channel mutations
- *Dok7* mutations

From Muppidi S, Wolfe GI, Barhon RJ: Diseases of the neuromuscular junction. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, Elsevier, Box 91-3.*

Table 612-2 Distinctive Clinical and Electrodiagnostic Features of Congenital Myasthenic Syndromes

	Presynaptic		Synaptic	Postsynaptic			
	CHOLINE ACETYLTRANSFERASE DEFICIENCY	LEMS-LIKE FORM	AChE DEFICIENCY	PRIMARY AChR DEFICIENCY	SLOW-CHANNEL CMS	FAST-CHANNEL CMS	*DOK7* MUTATIONS
Autosomal dominant inheritance					X (most mutations)		
Episodic apnea triggered by stressors	X						
Neonatal hypotonia and respiratory insufficiency	X	X	X (in severe cases)	X (in severe cases)			
Skeletal deformities			X	X		X (in severe cases)	
Delayed pupillary light responses			X				
Prominent neck, wrist, and finger extensor weakness					X		
Repetitive CMAPs after single stimulus			X		X		
Progressive decrement with prolonged exercise or repetitive stimulation	X			X			
Marked increment (>200%) with high-frequency repetitive stimulation		X					
Decrement repairs with AChE inhibitors				X		X	
Clinical improvement with AChE inhibitors						X	
Clinical worsening with AChE inhibitors			X		X		X

AChE, acetylcholinesterase; AChR, acetylcholine receptor; CMAPs, compound muscle action potentials; CMS, congenital myasthenic syndrome; LEMS, Lambert-Eaton myasthenic syndrome.

From Muppidi S, Wolfe GI, Barhon RJ: Diseases of the neuromuscular junction. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, *ed 5, Philadelphia, 2012, Elsevier, Table 91-3.*

enough to obstruct vision. Pupillary responses to light are preserved. Dysphagia and facial weakness also are common and, in early infancy, feeding difficulties are frequent as the cardinal sign of myasthenia; in severe cases, aspiration and airway obstruction may occur. Poor head control because of weakness of the neck flexors may be prominent. Involvement initially may appear to be limited to bulbar-innervated muscles, but the disease is systemic and progressive weakness eventually involves limb-girdle muscles and distal muscles of the hands in most cases. Fasciculations of muscle, myalgias, and sensory symptoms do not occur. Tendon stretch reflexes may be diminished but rarely are lost. Ocular myasthenia gravis may prove to be transitory over time, but in some patients weakness never progresses to involve axial or appendicular muscles. This group accounts for approximately 25% of all juvenile myasthenia gravis patients and is most frequent in children of Chinese and southeastern Asian descent, suggesting an ethnic genetic predisposition.

Rapid fatigue of muscles is a characteristic feature of myasthenia gravis that distinguishes it from most other neuromuscular diseases. Ptosis increases progressively as patients are asked to sustain an upward gaze for 30-90 sec. Holding the head up from the surface of the examining table while lying supine is very difficult, and gravity cannot be overcome for more than a few seconds. Repetitive opening and closing of the fists produces rapid fatigue of hand muscles, and patients cannot elevate their arms for more than 1-2 min because of fatigue of the deltoids. Patients are more symptomatic late in the day or when tired. Dysphagia can interfere with eating, and the muscles of the jaw soon tire when an affected child chews. Reviewing activities of daily living helps determine the severity of symptoms (Table 612-3).

Left untreated, myasthenia gravis is usually progressive and can become life-threatening because of respiratory muscle involvement and the risk of aspiration, particularly at times when the child is otherwise unwell, such as with an upper respiratory tract infection. Familial myasthenia gravis usually is not progressive.

Myasthenic crisis is an acute or subacute severe increase in weakness in patients with myasthenia gravis, usually precipitated by an intercurrent infection, surgery, or even emotional stress. It may require intravenous cholinesterase inhibitors, immunoglobulin, plasma exchange, gavage feeding, and even transitory ventilator support. It must be distinguished from **cholinergic crisis** secondary to overdosing with anticholinesterase medications. The muscarinic effects include abdominal cramps, diarrhea, profuse sweating, salivation, bradycardia, increased weakness, and miosis. Cholinergic crisis requires only supportive care and withholding of further doses of cholinergic drugs, and it passes within a few hours; the dose of medication to be restarted should be reconsidered, unless the patient had taken an overdose that was not prescribed.

Approximately 30% of affected adolescents show elevations, but anti-AChR antibodies are only occasionally demonstrated in the plasma of prepubertal children. Some with negative titers of AChE exhibit anti–muscle-specific tyrosine kinase (MuSK) circulating antibodies. MuSK is localized at the neuromuscular junction and appears essential to fetal development of this junction. MuSK myasthenia usually occurs in female infants and toddlers and severe bulbar involvement with dysphagia is frequent, but clinical features alone cannot distinguish between these 2 different antibody forms of the disease.

Infants born to myasthenic mothers can have respiratory insufficiency, inability to suck or swallow, and generalized hypotonia and weakness. They might show little spontaneous motor activity for several days to weeks. Some require ventilatory support and feeding by gavage during this period. After the abnormal antibodies disappear from the blood and muscle tissue, these infants regain normal strength and are not at increased risk of developing myasthenia gravis in later childhood. A small minority develop *fetal akinesia sequence* with multiple joint contractures (*arthrogryposis*) that develop in utero from lack of fetal movement. AChR antibodies can usually be demonstrated in maternal blood, but at times maternal antibodies may not be detected.

CONGENITAL MYASTHENIC SYNDROMES

A heterogeneous group of genetic diseases of neuromuscular transmission is collectively called **congenital myasthenic syndromes.** The etiology and pathogenesis of these syndromes are unrelated to either transitory neonatal myasthenia caused by placental transfer of maternal antibodies or to autoimmune myasthenia gravis, despite overlap of clinical symptoms. Congenital myasthenic syndromes are nearly always permanent static disorders without spontaneous remission (see Tables 612-1 and 612-2). Several distinct genetic forms are recognized, all with onset at birth or in early infancy with hypotonia, external ophthalmoplegia, ptosis, dysphagia, weak cry, facial weakness, easy muscle fatigue generally, and sometimes respiratory insufficiency or failure, the last often precipitated by a minor respiratory infection. Cholinesterase inhibitors have a favorable effect in most, but in some forms the symptoms and signs are actually worsened. Most congenital myasthenic syndromes are transmitted as autosomal recessive traits, but the slow channel syndrome is autosomal dominant.

Mutations responsible for congenital myasthenic syndromes have been identified in 18 different genes. The genetic mutations are known in less than half of children with congenital myasthenic syndromes. Of

Table 612-3 Myasthenia Gravis Activities of Daily Living Scale (MG-ADL)

GRADE	0	1	2	3
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube
Swallowing	Normal	Rare episode of choking	Frequent choking, necessitating changes in diet	Gastric tube
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do 1 of these functions
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant
TOTAL MG-ADL SCORE				

From Wolfe GI, Herbelin L, Nations SP, et al: Myasthenia gravis activities of daily living profile. Neurology *52:1487–1489, 1999.*

known genetic defects, *rapsyn* and *downstream-of-kinase-7* (*DOK7*) are demonstrated in 85% of cases. Acetylcholine receptor deficiencies have more than 60 identified genetic mutations. Basal lamina–associated synaptic defects from mutations of the *COLQ* gene that encodes the collagen tail of AChR account for another 10% of cases. Another 5% of cases are presynaptic, attributed to mutations in *ChAT*, encoding choline acetyltransferase. Anti-AChR and anti-MuSK antibodies are usually, but not always, absent in serum, unlike in autoimmune forms of myasthenia gravis affecting older children and adults.

Three **presynaptic congenital myasthenic syndromes** are recognized, all as autosomal recessive traits; some of these have anti-MuSK antibodies. These children exhibit weakness of extraocular, pharyngeal, and respiratory muscles and later show shoulder girdle weakness as well. **Episodic apnea** is a problem in congenital myasthenia gravis. Another synaptic form is caused by congenital absence or marked deficiency of motor end plate AChE in the synaptic basal lamina; this was the first form recognized as caused by an enzymatic deficiency at the neuromuscular junction. Postsynaptic forms of congenital myasthenia are caused by mutations in ACh receptor subunit genes that alter the synaptic response to ACh. An abnormality of the ACh receptor channels appearing as high conductance and excessively fast closure may be the result of a point mutation in a subunit of the receptor affecting a single amino acid residue. Children with congenital myasthenia gravis do not experience myasthenic crises and rarely exhibit elevations of anti-ACh antibodies in plasma.

RARE OTHER CAUSES OF MYASTHENIA

Myasthenia gravis is occasionally associated with hypothyroidism, usually as caused by **Hashimoto thyroiditis.** Other collagen vascular diseases may also be associated with myasthenia gravis. Thymomas, noted in some adults, rarely coexist with myasthenia gravis in children, nor do carcinomas of the lung occur, which produce a unique form of myasthenia in adults called **Eaton-Lambert syndrome.** The Eaton-Lambert syndrome in children is rare but is reported with lymphoproliferative disorders and with neuroblastoma. Postinfectious myasthenia gravis in children is transitory and usually follows a varicella-zoster infection by 2-5 wk as an immune response.

Laboratory Findings and Diagnosis

Myasthenia gravis is one of the few neuromuscular diseases in which electromyography (EMG) is more specifically diagnostic than a muscle biopsy. A *decremental response* is seen to repetitive nerve stimulation; the muscle potentials diminish rapidly in amplitude until the muscle becomes refractory to further stimulation. Motor nerve conduction velocity remains normal. This unique EMG pattern is the electrophysiologic correlate of the fatigable weakness observed clinically and is reversed after a cholinesterase inhibitor is administered. A myasthenic decrement may be absent or difficult to demonstrate in muscles that are not involved clinically. This feature may be confusing in early cases or in patients showing only weakness of extraocular muscles. Microelectrode studies of end plate potentials and currents reveal whether the transmission defect is presynaptic or postsynaptic. Special electrophysiologic studies are required in the classification of congenital myasthenic syndromes and involve estimating the number of ACh receptors per end plate and in vitro study of end plate function. These special studies and patch-clamp recordings of kinetic properties of channels are performed on special biopsy samples of intercostal muscle strips that include both origin and insertion of the muscle but are only performed in specialized centers. If myasthenia is limited to the extraocular, levator palpebrae, and pharyngeal muscles, evoked-potential EMG of the muscles of the extremities and spine, diagnostic in the generalized disease, usually is normal.

Anti-AChR antibodies should be assayed in the plasma but are inconsistently demonstrated. Antibodies against the MuSK receptor should be sought in children without circulating AChR antibodies, a diagnostic finding when elevated, which further delineates the etiology. Many cases of congenital myasthenia gravis result from failure to synthesize or release ACh at the presynaptic membrane. In some cases, the gene that mediates the enzyme choline acetyltransferase for the synthesis of ACh is mutated. In others, there is a defect in the quantal release of vesicles containing ACh. The treatment of such patients with cholinesterase inhibitors is futile. Assays of anti-rapsyn, anti-*Dok7*, *COLQ*, and *ChAT* antibodies are available in a few specialized laboratories.

Other serologic tests of autoimmune disease, such as antinuclear antibodies and abnormal immune complexes, should also be sought. If these are positive, more extensive autoimmune disease involving vasculitis or tissues other than muscle is likely. A thyroid profile should always be examined. The serum creatine kinase level is normal in myasthenia gravis.

The heart is not involved, and electrocardiographic findings remain normal. Radiographs of the chest often reveal an enlarged thymus, but the hypertrophy is not a thymoma. It may be further defined by tomography or by CT or MRI of the anterior mediastinum if the radiographic findings are uncertain, but these imaging modalities are not recommended routinely because of radiation exposure and anesthetic risk, which is higher in myasthenic patients than in normal children.

The role of conventional muscle biopsy in myasthenia gravis is limited. It is not required in most cases, but approximately 17% of patients show inflammatory changes, sometimes called *lymphorrhages*, that are interpreted by some physicians as a mixed myasthenia-polymyositis immune disorder. Muscle biopsy tissue in myasthenia gravis shows nonspecific type II muscle fiber atrophy, similar to that seen with disuse atrophy, steroid effects on muscle, polymyalgia rheumatica, and many other conditions. The ultrastructure of motor end plates shows simplification of the membrane folds; the ACh receptors are located in these postsynaptic folds, as shown by bungarotoxin (snake venom), which binds specifically to the ACh receptors.

A **clinical test for myasthenia gravis** is administration of a short-acting cholinesterase inhibitor, usually edrophonium chloride. Ptosis and ophthalmoplegia improve within a few seconds, and fatigability of other muscles decreases.

Recommendations on the Use of Cholinesterase Inhibitors as a Diagnostic Test for Myasthenia Gravis in Infants and Children

Children 2 Yr and Older

- The child should have a specific fatigable weakness that can be measured, such as ptosis of the eyelids, dysphagia, or inability of the cervical muscles to support the head. Nonspecific generalized weakness without cranial nerve motor deficits is not a criterion.
- An IV infusion should be started to enable the administration of medications in the event of an adverse reaction.
- Electrocardiographic monitoring is recommended during the test.
- A dose of atropine sulfate (0.01 mg/kg) should be available in a syringe, ready for IV administration at the bedside during the edrophonium test, to block acute muscarinic effects of the cholinesterase inhibitor, mainly abdominal cramps and/or sudden diarrhea from increased peristalsis, profuse bronchotracheal secretions that can obstruct the airway, or, rarely, cardiac arrhythmias. Some physicians pretreat all patients with atropine before administering edrophonium, but this is not recommended unless there is a history of reaction to tests. Atropine can cause the pupils to be dilated and fixed for as long as 14 days after a single dose, and the pupillary effects of homatropine can last 4-7 days.
- Edrophonium chloride (Tensilon) is administered IV. Initially, a test dose of 0.01 mg/kg is given to ensure that the patient does not have an allergic reaction or is otherwise very sensitive to muscarinic side effects. In children weighing <30 kg, 0.1 mg/kg is the maximum total delivered dose; in children weighing >30 kg, the total delivered dose is 0.2 mg/kg. After the test dose, intravenous injection of 0.01-0.02 mg is administered every 30-45 sec, as long as dosing does not exceed the recommended maximum dose. In adults, the average edrophonium dose to show positive responses is approximately 3.3 mg for ptosis and

approximately 2.6 mg for oculomotor symptoms. Side effects include nausea and emesis; light-headedness from bradycardia (atropine is the antidote) and bronchospasm are less common side effects. These doses may be given IM or subcutaneously, but these routes are not recommended because the results are much more variable owing to unpredictable absorption, and the test may be ambiguous or falsely negative.

- Effects should be seen within 10 sec and disappear within 120 sec. Weakness is measured as, for example, distance between upper and lower eyelids before and after administration, degree of external ophthalmoplegia, or ability to swallow a sip of water.
- Long-acting cholinesterase inhibitors, such as pyridostigmine (Mestinon), are generally not as useful for the acute assessment of myasthenic weakness. The Prostigmin test may be used (as outlined later) but might not be as definitively diagnostic as the edrophonium test.

For Children Younger Than 2 Yr

- Infants ideally should have a specific fatigable weakness that can be measured, such as ptosis of the eyelids, dysphagia, and inability of cervical muscles to support the head. Nonspecific generalized weakness without cranial nerve motor deficits makes it less easy to assess results but may be a criterion at times.
- An IV infusion should be started as a rapid route for medications in the event of an adverse effect of the test medication.
- Electrocardiographic monitoring is recommended during the test.
- Pretreatment with atropine sulfate to block the muscarinic effects of the test medication is not recommended, but atropine sulfate should be available at the bedside in a prepared syringe. If needed, it should be administered IV in a dose of 0.01 mg/kg.
- Edrophonium is not recommended for use in infants; its effect is too brief for objective assessment and an increased incidence of acute cardiac arrhythmias is reported in infants, especially neonates, with this drug.
- Prostigmin methylsulfate (neostigmine) is administered IM at a dose of 0.04 mg/kg. If the result is negative or equivocal, another dose of 0.04 mg/kg may be administered 4 hr after the first dose (a typical dose is 0.5-1.5 mg). The peak effect is seen in 20-40 min. IV Prostigmin is contraindicated because of the risk of cardiac arrhythmias, including fatal ventricular fibrillation, especially in young infants.
- Long-acting cholinesterase inhibitors administered orally, such as pyridostigmine (Mestinon), are generally not as useful for the acute assessment of myasthenic weakness because onset and duration are less predictable.

The test should be performed in the emergency department, hospital ward, or intensive care unit; the important issue is preparation for potential complications such as cardiac arrhythmia or cholinergic crisis, as outlined.

Treatment

Some patients with mild myasthenia gravis require no treatment. **Cholinesterase-inhibiting drugs** are the primary therapeutic agents. Neostigmine methylsulfate (0.04 mg/kg) may be given IM every 4-6 hr, but most patients tolerate oral neostigmine bromide, 0.4 mg/kg every 4-6 hr. If dysphagia is a major problem, the drug should be given approximately 30 min before meals to improve swallowing. Pyridostigmine is an alternative; the dose required is approximately 4 times greater than that of neostigmine, but it may be slightly longer acting. Overdoses of cholinesterase inhibitors produce cholinergic crises; atropine blocks the muscarinic effects but does not block the nicotinic effects that produce additional skeletal muscle weakness. In the rare familial myasthenia gravis caused by absence of end plate AChE, cholinesterase inhibitors are not helpful and often cause increased weakness; these patients can be treated with ephedrine or diaminopyridine, both of which increase ACh release from terminal axons.

Because of the autoimmune basis of the disease, long-term **steroid treatment** with prednisone may be effective. **Thymectomy** should be considered and might provide a cure. Thymectomy is most effective in patients who have high titers of anti-ACh receptor antibodies in the plasma and who have been symptomatic for <2 yr. Thymectomy is ineffective in congenital and familial forms of myasthenia gravis. Treatment of hypothyroidism usually abolishes an associated myasthenia without the use of cholinesterase inhibitors or steroids.

If the specific genetic mutation can be identified in a patient with one of the congenital myasthenic syndromes, specific therapeutic approaches are available for some that differ from the treatments listed above; these are well outlined by Eyemard et al (2013).

Plasmapheresis is effective treatment in some children, particularly those who do not respond to steroids, but plasma exchange therapy provides only temporary remission. **IV immunoglobulin** is beneficial and should be tried before plasmapheresis because it is less invasive. Plasmapheresis and IV immunoglobulin appear to be most effective in patients with high circulating levels of anti-ACh receptor antibodies. Refractory patients might respond to rituximab, a monoclonal antibody to the B-cell CD20 antigen.

Neonates with transient maternally transmitted myasthenia gravis require cholinesterase inhibitors for only a few days or occasionally for a few weeks, especially to allow feeding. No other treatment is usually necessary. In non–maternally transmitted congenital myasthenia gravis, identification of the specific molecular defect is important for treatment; Table 612-4 summarizes specific therapies for each type.

Complications

Children with myasthenia gravis do not tolerate neuromuscular-blocking drugs, such as succinylcholine and pancuronium, and may be paralyzed for weeks after a single dose. An anesthesiologist should carefully review myasthenic patients who require a surgical anesthetic and such anesthetics should be administered only by an experienced physician/anesthesiologist. Also, certain antibiotics can potentiate myasthenia and should be avoided; these include the aminoglycosides (gentamicin and others).

Prognosis

Some patients with autoimmune myasthenia gravis experience spontaneous remission after a period of months or years; others have a permanent disease extending into adult life. Immunosuppression, thymectomy, and treatment of associated hypothyroidism might provide a cure. Genetically determined congenital myasthenic syndromes may show initial worsening in infancy but then remain static throughout childhood and into adult life.

Other Causes of Neuromuscular Blockade

Organophosphate chemicals, commonly used as insecticides, can cause a myasthenia-like syndrome in children exposed to these toxins (see Chapter 63).

Botulism results from ingestion of food containing the toxin of *Clostridium botulinum,* a Gram-positive, spore-bearing, anaerobic bacillus (see Chapter 210). The mechanism is cleavage by the botulinum toxin of several of the structural glycoproteins of the wall (i.e., membrane) of synaptic vesicles within axonal terminals. These glycoproteins include synaptobrevin and synaptotagmin, but synaptophysin is resistant. Honey is a common source of contamination. The incubation period is short, only a few hours, and symptoms begin with nausea, vomiting, and diarrhea. Cranial nerve involvement soon follows, with diplopia, dysphagia, weak suck, facial weakness, and absent gag reflex. Generalized hypotonia and weakness then develop and can progress to respiratory failure. Neuromuscular blockade is documented by EMG with repetitive nerve stimulation. Respiratory support may be required for days or weeks until the toxin is cleared from the body. No specific antitoxin is available. Guanidine, 35 mg/kg/24 hr, may be effective for extraocular and limb muscle weakness but not for respiratory muscle involvement.

Tick paralysis is a disorder of ACh release from axonal terminals due to a neurotoxin that blocks depolarization. It also affects large

Table 612-4	Potential Therapies in Congenital Myasthenic Syndromes
AChE	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults Avoid AChE inhibitors
AChR deficiency	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
AChR fast channel	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
AChR slow channel	Quinidine sulfate • Adults: Begin for 1 wk with 200 mg tid; gradual increase to maintain a serum level of 1-25 μg/mL • Children: 15-60 mg/kg/day in 4-6 divided doses; not available in several countries If quinidine sulfate is not available, fluoxetine 80-100 mg/day in adults Avoid AChE inhibitors
ChAT	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
Dok7	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults Avoid AChE inhibitors
Laminin β_2	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries Avoid AChE inhibitors
MuSK	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses 3,4-Diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
Rapsyn	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults

Modified from Eyemard B, Hantaï D, Estounet B: Congenital myasthenic syndromes, Handb Clin Neurol *113:1469-1480, 2013.*

myelinated motor and sensory nerve fibers. This toxin is produced by the wood tick or dog tick, insects common in the Appalachian and Rocky Mountains of North America. The tick embeds its head into the skin, usually the scalp, and neurotoxin production is maximal about 5-6 days later. Motor symptoms include weakness, loss of coordination, and sometimes an ascending paralysis resembling Guillain-Barré syndrome. Tendon reflexes are lost. Sensory symptoms of tingling paresthesias can occur in the face and extremities. The diagnosis is confirmed by EMG and nerve conduction studies and by identifying the tick. The tick must be removed completely and the buried head not left beneath the skin. Patients then recover completely within hours or days.

Bibliography is available at Expert Consult.

612.2 Spinal Muscular Atrophies

Harvey B. Sarnat

Spinal muscular atrophies (SMAs) are degenerative diseases of motor neurons that begin in fetal life and continue to be progressive in infancy and childhood. The progressive denervation of muscle is compensated for in part by reinnervation from an adjacent motor unit, but giant motor units are thus created with subsequent atrophy of muscle fibers when the reinnervating motor neuron eventually becomes involved. Motor neurons of cranial nerves III, IV, and VI to extraocular muscles, as well as those of the sacral spinal cord innervating striated muscle of the urethral and anal sphincters, are selectively spared. Upper motor neurons (layer 5 pyramidal neurons in the cerebral cortex) also remain normal.

SMA is classified clinically into a severe infantile form, also known as **Werdnig-Hoffmann disease** or SMA type 1; a late infantile and more slowly progressive form, SMA type 2; and a more chronic or juvenile form, also called **Kugelberg-Welander disease,** or SMA type 3. A severe fetal form that is usually fatal in the perinatal period has been described as SMA type 0, with motor neuron degeneration demonstrated in the spinal cord as early as midgestation. These distinctions of types are based upon age at onset, severity of weakness, and clinical course; muscle biopsy does not distinguish types 1 and 2, though type 3 shows a more adult than perinatal pattern of denervation and reinnervation. Type 0 can show biopsy features more similar to myotubular myopathy because of maturational arrest; scattered myotubes and other immature fetal fibers also are demonstrated in the muscle biopsies of patients with types 1 and 2, but they do not predominate. Approximately 25% of patients have type 1, 50% type 2, and 25% type 3; type 0 is rare and accounts for <1%. Some patients are transitional between types 1 and 2 or between types 2 and 3 in terms of clinical function. A variant of SMA, **Fazio-Londe disease,** is a progressive bulbar palsy resulting from motor neuron degeneration more in the brainstem than the spinal cord, but cranial nerves of extraocular muscles also are spared in this form. Table 612-5 lists other variants.

Autonomic motor neurons of both the sympathetic and parasympathetic systems are not spared, but usually do not show clinical manifestations until late stages. Autonomic deficits may involve the detrusor muscle of the urinary bladder or the smooth muscle urethral and anal sphincters, in all 3 forms of SMA. In some patients with type 1 SMA and respiratory distress there may be severe autonomic dysregulation with dysautonomia and cardiovascular collapse leading to death or to severe ischemic brain damage.

ETIOLOGY

The cause of SMA is genetic as an autosomal recessive mendelian trait. Neuropathologically it appears to be a pathologic continuation of a process of programmed cell death (apoptosis) that is normal in embryonic life. A surplus of motor neuroblasts and other neurons is generated from primitive neuroectoderm, but only about half survive and mature to become neurons; the excess cells have a limited life cycle and degenerate. If the process that arrests physiologic cell death fails to intervene by a certain stage, neuronal death can continue in late fetal life and postnatally. The survivor motor neuron gene *(SMN)* arrests apoptosis of motor neuroblasts. Unlike most genes that are highly conserved in evolution, *SMN* is a uniquely mammalian gene. An additional function of *SMN*, both centrally and peripherally, is to transport RNA-binding proteins to the axonal growth cone to ensure an adequate

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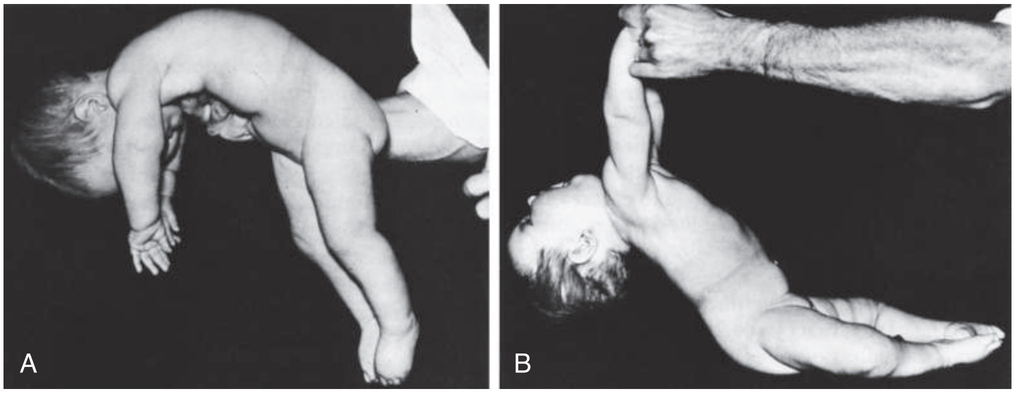

Figure 612-1 Type 1 spinal muscular atrophy (Werdnig-Hoffmann disease). Clinical manifestations of weakness of limb and axial musculature in a 6 wk old infant with severe weakness and hypotonia from birth. Note the marked weakness of the limbs and trunk on ventral suspension **(A)** and of neck on pull to sit **(B).** *(From Volpe JJ:* Neurology of the newborn*, ed 4, Philadelphia, 2001, WB Saunders, p. 644.)*

Table 612-5 Spinal Muscular Atrophy Variants: Progressive or Severe Neonatal Anterior Horn Cell Disease Not Linked to *SMN*

VARIANT	MAJOR FEATURES
SMA with respiratory distress type 1 (SMARD1)	Mild hypotonia, weak cry, distal contractures initially Respiratory distress from diaphragmatic paralysis 1-6 mo, progressive distal weakness Autosomal recessive, locus 11q13.2, gene: immunoglobulin mu-binding protein 2 (IGHMBP2)
Pontocerebellar hypoplasia type 1	Arthrogryposis, hypotonia, weakness, bulbar deficits early; later, microcephaly, extraocular defects, cognitive deficits: pontocerebellar hypoplasia Molecular defect unknown Likely autosomal recessive
X-linked infantile SMA with bone fractures	Arthrogryposis, hypotonia, weakness, congenital bone fractures, respiratory failure Lethal course as in severe type 1 SMA Most cases X-linked (X9/11.3-q11.2), a few cases likely autosomal recessive
Congenital SMA with predominant lower limb involvement	Arthrogryposis, hypotonia, weakness, especially distal lower limbs early Nonprogressive but severe disability Autosomal dominant or sporadic; locus 12q23-24

SMA, spinal muscular atrophy; *SMN*, survivor motor neuron gene.
From Volpe JJ: Neurology of the newborn*, ed 5, Philadelphia, 2008, Saunders Elsevier, Table 18-7, p. 775.*

amount of protein-encoding transcripts essential for growth cone mobility both during fetal development and in postnatal synaptic remodeling.

CLINICAL MANIFESTATIONS

The cardinal features of **SMA type 1** are severe hypotonia (Fig. 612-1); generalized weakness; thin muscle mass; absent tendon stretch reflexes; involvement of the tongue, face, and jaw muscles; and sparing of extraocular muscles and sphincters. Diaphragmatic involvement is late. Infants who are symptomatic at birth can have respiratory distress and are unable to feed. Congenital contractures, ranging from simple clubfoot to generalized arthrogryposis, occur in approximately 10% of severely involved neonates. Infants lie flaccid with little movement, unable to overcome gravity (see Fig. 607-1 in Chapter 607). They lack head control. More than 65% of children die by 2 yr of age, and many die early in infancy.

In **type 2 SMA,** affected infants are usually able to suck and swallow, and respiration is adequate in early infancy. These children show progressive weakness, but many survive into the school years or beyond, although confined to an electric wheelchair and severely handicapped. Nasal speech and problems with deglutition develop later. Scoliosis becomes a major complication in many patients with long survival. Gastroesophageal reflux may lead to malnutrition or to aspiration with acute airway obstruction or pneumonia.

Kugelberg-Welander disease is the mildest **SMA (type 3),** and patients can appear normal in infancy. The progressive weakness is proximal in distribution, particularly involving shoulder girdle muscles. Patients are ambulatory. Symptoms of bulbar muscle weakness are rare. Approximately 25% of patients with this form of SMA have muscular hypertrophy rather than atrophy, and it may easily be confused with a muscular dystrophy. Longevity can extend well into middle adult life. Fasciculations are a specific clinical sign of denervation of muscle. In thin children, they may be seen in the deltoid and biceps brachii muscles and occasionally the quadriceps femoris muscles, but the continuous, involuntary, worm-like movements may be masked by a thick pad of subcutaneous fat. Fasciculations are best observed in the tongue, where almost no subcutaneous connective tissue separates the muscular layer from the epithelium. If the intrinsic lingual muscles are contracted, such as in crying or when the tongue protrudes, fasciculations are more difficult to see than when the tongue is relaxed. Cramps and myalgias of appendicular and axial muscles are common, especially in later stages, and problems of micturition may present, though adolescent patients may be too embarrassed to state them unless the physician directly inquires.

The outstretched fingers of children with SMA often show a characteristic tremor owing to fasciculations and weakness. It should not be confused with a cerebellar tremor.

The heart is not involved in SMA. Intelligence is normal, and children often appear brighter than their normal peers because the effort they cannot put into physical activities is redirected to intellectual development, and they are often exposed to adult speech more than to juvenile language because of the social repercussions of the disease. Progressive deterioration of ambulation and the high risk of falling and fracturing long bones or the pelvis eventually require use of a

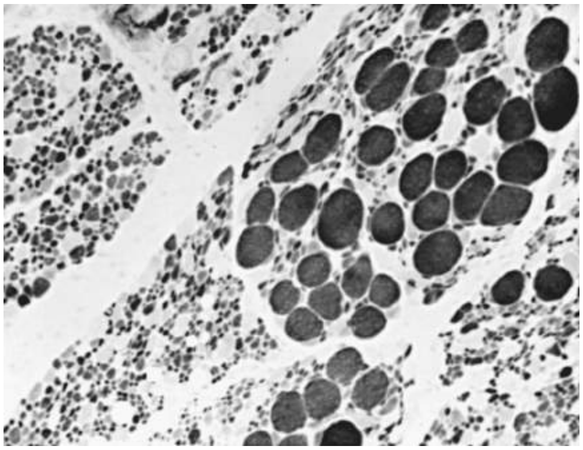

Figure 612-2 **Muscle biopsy of neonate with infantile spinal muscular atrophy.** Groups of giant type I (darkly stained) fibers are seen within muscle fascicles of severely atrophic fibers of both histochemical types. This is the characteristic pattern of perinatal denervation of muscle. Myofibrillar adenosine triphosphatase, preincubated at pH 4.6 (×400).

wheelchair; an electric wheelchair often is needed because weakness of the upper extremities does not allow the patient to manually push the wheels. Progressive scoliosis is another serious complication and may have a further adverse effect on respiration.

LABORATORY FINDINGS

The serum creatine kinase level may be normal but more commonly is mildly elevated in the hundreds. A creatine kinase level of several thousand is rare. The chest x-ray in early-onset disease demonstrates thin ribs. Results of motor nerve conduction studies are normal, except for mild slowing in terminal stages of the disease, an important feature distinguishing SMA from peripheral neuropathy. EMG shows fibrillation potentials and other signs of denervation of muscle. A secondary mitochondrial DNA depletion is sometimes demonstrated in the muscle biopsy of infants with SMA. The molecular genetic test of the *SMN* gene provides definite confirmation of the diagnosis.

DIAGNOSIS

The simplest, most definitive diagnostic test is a molecular genetic marker in blood for the *SMN* gene. Muscle biopsy used to be the diagnostic test before the genetic marker from blood samples became available, and muscle biopsy now is used more selectively in patients showing equivocal or negative genetic findings. The muscle biopsy in infancy reveals a characteristic pattern of perinatal denervation that is unlike that of mature muscle. Groups of giant type I fibers are mixed with fascicles of severely atrophic fibers of both histochemical types (Fig. 612-2). Scattered immature myofibers resembling myotubes also are demonstrated. In juvenile SMA, the pattern may be more similar to adult muscle that has undergone many cycles of denervation and reinnervation. Neurogenic changes in muscle also may be demonstrated by EMG, but the results are less definitive than by muscle biopsy in infancy. Sural nerve biopsy is now performed only occasionally, but shows mild sensory neuropathic changes, and sensory nerve conduction velocity may be slowed; hypertrophy of unmyelinated axons also is seen. At autopsy, mild degenerative changes are seen in sensory neurons of dorsal root ganglia and in somatosensory nuclei of the thalamus, but these alterations are not perceived clinically as sensory loss or paresthesias. The most pronounced neuropathologic lesions are the extensive neuronal degeneration and gliosis in the ventral horns of the spinal cord and brainstem motor nuclei, especially the hypoglossal nucleus.

GENETICS

Molecular genetic diagnosis by DNA probes in blood samples or in muscle biopsy or chorionic villi tissues is available for diagnosis of suspected cases and for prenatal diagnosis. Most cases are inherited as an autosomal recessive trait. The incidence of SMA is 10-15 in 100,000 live births, affecting all ethnic groups; it is the second most common neuromuscular disease, following Duchenne muscular dystrophy. The incidence of heterozygosity for autosomal recessive SMA is 1 in 50.

The genetic locus for all 3 of the common forms of SMA is on chromosome 5, a deletion at the 5q11-q13 locus, indicating that they are variants of the same disease rather than different diseases. The affected *SMN1* gene has a molecular weight of 38 kDa and contains 8 exons that span 20 kb and telomeric and centromeric exons that differ only by 5bp and produce a transcript encoding 294 amino acids. *SMN1* is duplicated in a highly homologous gene called *SMN2* and both genes are transcribed. *SMN2* remains present in all patients with SMA, but cannot fully compensate the *SMN1* defect. However, a molecular basis for correlation between the SMN2 copy number and clinical severity of the SMA is the capability of *SMN2* to encode a small amount of an identical *SMN* protein. The critical difference between *SMN1* and *SMN2* genes is a cytosine (C) to thymine (T) transition in exon 7 of *SMN2*. Another gene, the *neuronal apoptosis inhibitory gene (NAIP),* is located next to the *SMN* gene and in many cases there is an inverted duplication with 2 copies, telomeric and centromeric, of both genes; isolated mutations or deletions of *NAIP* do not produce clinical SMA and generate a mostly nonfunctional isoform lacking the carboxy-terminus amino acids encoded by exon 7. Milder forms of SMA have more than 2 copies of *SMN2*, and in late-onset patients with homozygous deletion of the *SMN1* gene, there are 4 copies of *SMN2.* An additional gene mapped to 11q13-q21 in SMA may help explain early respiratory failure in some patients. Nucleotide expansions account for only 5-10% of cases of SMA, and deletions or splicing out of exons 7 and 8 are the genetic mechanism in the great majority of cases. Another pair of genes adjacent to the *SMN1* and *SMN2* genes, *SERF1* and *SERF2*, also may play a secondary role. The *SMN* gene product modulates axonal growth and localization of β-actin messenger RNA in growth cones of motor neurons.

Infrequent families with autosomal dominant inheritance are described, and a rare X-linked recessive form also occurs. Carrier testing by dose analysis is available.

TREATMENT

No medical treatment is able to delay the progression. Supportive therapy includes orthopedic care with particular attention to scoliosis and joint contractures, mild physiotherapy, and mechanical aids for assisting the child to eat and to be as functionally independent as possible. Most children learn to use a computer keyboard with great skill but cannot use a pencil easily. Valproic acid is sometimes administered because it increases SMN2 protein, and gabapentin and oral phenylbutyrate also may slow the progression, but these treatments do not alter the course in all patients. A benefit of antioxidants is unproved. Gene replacement and protein replacement therapies remain theoretical and experimental. Potential therapeutic genetic strategies in SMA include upregulation of *SMN2* gene expression, preventing exon 7 skipping of SMN2 transcripts and improving the stability of the protein lacking the amino acid sequence encoded by exon 7.

Bibliography is available at Expert Consult.

612.3 Other Motor Neuron Diseases

Harvey B. Sarnat

Motor neuron diseases other than SMA are rare in children. *Poliomyelitis* used to be a major cause of chronic disability, but with the routine use of polio vaccine, this viral infection is now rare (see Chapter 249). Other enteroviruses, such as coxsackievirus and echovirus, or the live polio vaccine virus can also cause an acute infection of motor neurons with symptoms and signs similar to poliomyelitis, although usually

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milder. Specific polymerase chain reaction tests and viral cultures of cerebrospinal fluid are diagnostic. Motor neuron infection with the West Nile virus also occurs.

A **juvenile form of amyotrophic lateral sclerosis** is rare. Upper and lower motor neuron loss is evident clinically, unlike in SMA. The course is progressive and ultimately fatal.

Pena-Shokeir and **Marden-Walker syndromes** are progressive motor neuron degenerations associated with severe arthrogryposis and congenital anomalies of many organ systems. **Pontocerebellar hypoplasias** are progressive degenerative diseases of the central nervous system that begin in fetal life; type 1 also involves motor neuron degeneration resembling an SMA, but the *SMN* gene on chromosome 5 is normal.

Motor neurons become involved in several metabolic diseases of the nervous system, such as gangliosidosis (Tay-Sachs disease), ceroid lipofuscinosis (Batten disease), and glycogenosis II (Pompe disease), but the signs of denervation may be minor or obscured by the more prominent involvement of other parts of the central nervous system or of muscle.

Chapter 613

Hereditary Motor-Sensory Neuropathies

Harvey B. Sarnat

The hereditary motor-sensory neuropathies (HMSNs) are a group of progressive diseases of peripheral nerves (Table 613-1). Motor components generally dominate the clinical picture, but sensory and autonomic involvement is expressed later. Sural nerve biopsy used to be the most definitive means of diagnosis, but with the expanded knowledge

Text continued on p. 3003

Table 613-1 Hereditary Peripheral Neuropathies

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
CMT1 (DEMYELINATING)			
CMT1 A-F (HMSN type I)	Autosomal dominant. Onset 1st-4th decade. Predominant distal weakness, decreased DTRs, mild distal sensory loss, hypertrophy of nerves common	Delayed motor and sensory conduction studies. Motor studies typically <38 m/s	
1A (118220)	Commonest form recognized, seen in all ages (but more adults)		*PMP22* duplication or point mutation
1B (118200)	Approximately 5% of CMT1 group		*MPZ*
1C (601098)	Childhood onset, starts with abnormal gait, then distal weakness and wasting, occasional nerve hypertrophy. Rarely, early-onset hearing loss		*LITAF*
1D (607678)	Possible cranial nerve involvement. Late onset in childhood or early adulthood		*EGR2*
1E (118300)	Associated with deafness (29-45%)		*PMP22*
1F (607734)			*NEFL*
Hereditary neuropathy with liability to pressure palsies (tomaculous neuropathy) (162500)	Autosomal dominant. Recurrent mononeuropathy simplex or multiplex frequently related to trauma	Significant slowing of motor and sensory conduction velocities in clinically affected nerves but also in unaffected nerves	*PMP 22* deletion
Slowed NCVs Asymptomatic	Often a miscellaneous group. Incidentally detected with no clinical symptoms. Autosomal dominant	Moderately slowed conduction velocities	*ARHGEF10*
CMT2 (AXONAL)			
CMT2 A-L (HMSN type II)	Autosomal dominant (A, B, D, E, F, G, I) Autosomal recessive (BI, B2, H, K) Clinically similar to CMT type 1, except for later onset, absence of peripheral nerve enlargement, and less marked weakness	Nerve conduction velocities greater than HMSN type I (>38 m/s) but below normal range occasionally	
2A1 (118210) 2A2 (609260)	CMT2A: prominent distal weakness, proximal weakness also present in 60%. Optic atrophy and central involvement reported. Main form related to *MFN2* mutations		2A1: *KIF1B* (one family) 2A2: *MFN2*
2B (600882) 2B1 (605588)	CMT2B: severe sensory loss: often complications with infections, arthropathy, amputations, foot ulcers, distal weakness		2B: *RAB7* 2B1: *LMNA*
2B2 (605589)	Average onset 34 yr (Costa Rican family)		?*MED25*
2C (606071)	Vocal cord, diaphragm, and respiratory involvement, decreased longevity. Allelic with congenital dSMA (600175) and scapuloperoneal muscular atrophy (181405)		*TRP4* 12q23–q24 *TRP4*
2D (601472) (allelic to dSMA)	Upper limb predominance		*GARS*
2E (607684) (1F dominant is allelic to CMT2E)	30% associated with deafness, early childhood onset with gait abnormalities, occasional hyperkeratosis, increased sensory involvement	Intermediate/slow nerve conduction studies	*NEFL*

Continued

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
2F (606595)	Trophic changes feet and knees		*HSPB1* (*HSP27*)
2G (608591)	Onset age 9-76 yr, average age 20 yr, large Spanish family. Also severe form with early onset		12q12–q13
2H (607731) 2H (allelic to CMT4A–CMT4C2 in original publication)	Pyramidal involvement, vocal cord involvement	Intermediate/slow nerve conduction studies	*GDAP1*
2I (607677)	CMT I and J: possible late onset, pupillary anomalies, pain, hearing loss, dysphagia		*MPZ*
2J (607736)	Vocal cord paralysis, more severe early-onset form		*MPZ*
2K (607831)	Occasional proximal leg weakness (like dHMN II), large Chinese family, with onset at age 15-33 yr. Scoliosis		*GDAP1*
2L (608673)			*HSPB8* 12q24
HMSN II with onset in early childhood (EOHMSN) Severe early-onset axonal neuropathy (SEOAN)	Autosomal dominant or recessive. Weakness within 1st 5 yr, rapid progression of weakness, usually complete paralysis below elbows and knees by teens, absent DTRs, moderate sensory changes in most cases. Normal CSF protein. Occasional optic atrophy or spasticity	Axonal pattern with axonal-degenerative polyneuropathy. Absent SNAPs, no response to stimulation in cerebral palsy nerve, upper limb nerves normal or mildly slowed. EMG: denervation	*MFN2*; *GDAP1* Heterogeneous
Spinal muscular atrophy with respiratory distress type 1 (SMARD1)/severe infantile axonal neuropathy with respiratory failure (SIANR) Allelic to dHMN6 dSMA1 (604320)	Autosomal recessive. Onset in infancy (3-6 mo), respiratory failure, progressive distal weakness, eventual plateau. No recovery	Absent conduction in most cases	*IGHMBP2*
Hereditary motor and sensory neuropathy (HMSN-P) (Okinawa type)	Adult onset (after 30 yr). Autosomal dominant. Slowly progressive proximal dominant area of weakness. Fasciculations of extremities and trunk. Raised creatine kinase, hyperlipidemia, diabetes mellitus, eventual loss of ambulation, absent DTRs, sensory disturbances. Most patients described from Japan	Motor and sensory axonal neuropathy. SNAPs, CMAPs, MNCVs, and SNCVs reduced or absent EMG: fasciculations, fibrillations, and neuromyotonic picture early on	3q13
CMT3* AND 4			
CMT3 (Dejerine-Sottas syndrome) (145900)	Onset 1st 2 yr, overall disability ?less severe than CMT4. Hypotonia, motor delay by 1st yr, poor coordination, ataxia, distal weakness (max. lower limbs), short stature. By 2nd decade, proximal weakness, hand and foot deformities. Nerve hypertrophy. Moderate to severe sensory loss. Scoliosis. Common cranial nerve involvement, nystagmus, deafness, and mild bifacial weakness. Raised CSF protein	Motor conduction velocities usually <10 m/s. SAPs absent. EMG: chronic denervation	*PMP22*, *MPZ*, *PRX*, *EGR2*, *FIG4*
CMT4 (A-J) Autosomal recessive	Clinical picture similar to or slightly more severe than in CMT1 form, increased ataxia, areflexia, scoliosis. Nerve hypertrophy rare	Moderate slowing of nerve conduction studies	
4A (214400)	Onset <2 yr, Tunisian and Moroccan families. Severe progressive. Less-severe European phenotypes	25-35 m/s	*GDAP1*
4B1 (601382)	Ophthalmoplegia, vocal cord paralysis, facial, bulbar weakness (all infrequent). Weakness below 5 yr, proximal and distal weakness, absent DTRs	9-20 m/s	*MTMR2*, (*MPZ*)
4B2 (604563)	Early onset: 1st decade; glaucoma and deafness sometimes. Recorded in Tunisia, Japan, and Turkey	15-30 m/s	*SBF2*, *MTMR13*
4C (601596)	Early-onset scoliosis, commoner in Algerians, glaucoma and neutropenia. 1st and 2nd decades	4-37 m/s	*SH3TC2* (*KIAA1985*)
4D (601455) (HMSN-Lom)	Closed gypsy pedigree; onset <10 yr. Deafness (by 2nd-3rd decade). Tongue atrophy	10-20 m/s	*NDRG1*
4E (605253)	Congenital hypomyelinating neuropathy	5-20 m/s	*ERG2/KROX 20*, *MPZ*

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
4F (145900)	Severely affected at birth or by 7 yr; arthrogryposis multiplex congenita common; respiratory and feeding difficulties; often die young	<5 m/s	*PRX*
4G (605285)	Type Russe. Onset 8-16 yr. Origin Bulgaria	30-35 m/s	10q22
4H (609311)	Increased in Lebanese/Turkish. Onset infancy to childhood (1-2 yr). Delayed motor milestones. Occasional scoliosis, increased distal weakness, usually absent DTRs	<10 m/s or absent	*FDG4*
4J (611228)	Onset by 5 yr. Severe disorder. Similarities to motor neuron disease	2-7 m/s; some cases higher	*FIG4*
CCFDN (604168)	Congenital cataract, microcornea, facial dysmorphism, mental retardation, distal motor peripheral neuropathy	19-33 m/s	*CTDP1*
MIXED PATHOLOGY (AXONAL AND DEMYELINATING)			
CMT X X-linked CMT X1 (302800)	X-linked dominant. Onset 1st-2nd decade. Progressive wasting and weakness of distal limb musculature, especially hands, more marked in affected males than carrier females	Median nerve motor conduction studies <40 m/s (but faster than CMT1A). Intermediate slowing less uniform along nerves with dispersion more pronounced	*GJB1*
X2 (302801)	X-linked recessive. Rare infantile onset, intellectual disability, females very mildly affected	Mixed demyelinating/axonal	Xp22.2
X3 (302802)	X-linked recessive. ± Spasticity. Females unaffected	Mixed demyelinating/axonal	Xq26
X4 (310490)	X-linked (Cowchock syndrome). Severe neuropathy, females very mildly affected. Isolated case reports. Onset birth to early childhood. Slowly progressive. Many develop deafness by 5 yr. Mental retardation commonly seen. Occasional optic atrophy	Axonal neuropathy. Motor conduction velocities: mild delay (33-56 m/s). Sensory very abnormal. EMG: denervation, large motor unit potential, and fasciculation	Xq24–26.1
X5 (311070)	X-linked. Mild to moderate neuropathy, deafness, optic atrophy. Allelic with Rosenberg-Chutorian (opticoacoustic neuropathy) and Arts syndromes	Axonal neuropathy–mild demyelinating changes	Xq21.32–q24 *PRPS1*
Intermediate forms of CMT	Patients have neurophysiologic results that fall between axonal and demyelinating ranges	"Intermediate values" 30-40 m/s–most accurate from median motor nerves. Some forms have normal nerve conduction studies (DI-CMTB)	
DI-CMTA	Italian family		10q24.1–q25.1
DI-CMTB (606482)	American family		*DNM2*
DI-CMTC (608323)			*YARS*
DI-CMTD (607791)	Myelin protein zero		*MPZ*
A–autosomal recessive form (608340)	Overlap conditions: Recessive CMT with *GADP1* mutations: (CMT2K and 4A) Spanish and Tunisian family–severe childhood forms reported. Also called DI-CMTA autosomal recessive form CMT with NF-L: (CMT1F and 2E)		Overlap: *GJB1* *NF-L* *GDAP1*
OTHER HMSN AND HMN SYNDROMES			
HMSN V/spastic paraplegia with HMSN type V/CMT5 (CMT with pyramidal signs) (600631)	Variable inheritance. Spasticity in lower limbs causing difficulty walking and toe walking. Autosomal recessive form associated with mental retardation. Lower limb marked spasticity with little weakness, increased DTRs, extensor plantars, pes cavus, often distal amyotrophy. Expanding field with multiple subforms, n = 37. Not all associated with peripheral neuropathy CMT with pyramidal signs: part of HMSN V but described without spasticity	Small/absent SNAPs. Motor studies axonal in type	*SPG3A, SPAST, NIPA1, BSCL2, SPG4, SPG7, SPG20, SPG21, SPG30, PLP1* CMT with pyramidal signs: *MFN2*
HMSN VI (allelic CMT2A)	Visual impairment due to optic atrophy. Dominant and recessive forms. Onset in 1st decade. Distal weakness, often proximal involvement too. Less sensory involvement. Scoliosis	No response or motor conduction around 45 m/s. Sensory nerves often cannot be stimulated	*MFN2*
HMSN VII	HMSN with retinitis pigmentosa. CSF protein raised. Usually adult onset. Rare entity described in a few families, mainly of adult onset		

Continued

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
DISTAL HEREDITARY MOTOR NEURONOPATHIES (DHMN)			
dHMNI (182960)	Autosomal dominant. Juvenile onset. Distal weakness and wasting	Normal nerve conduction studies, occasional mild slowing. EMG neurogenic	*HSPB1* 7q34–q36
dHMNII (608634)	Autosomal dominant. Adult onset, distal weakness and wasting		*HSPB8, HSPB3*
dHMNIIjuv (158590)	(Allelic CMT2F, CMT2L)		*HSPB1*
dHMNIII	Autosomal recessive. Infantile to adult onset. Slow, progressive muscle wasting and weakness, variable diaphragmatic paralysis		11q13.3
dHMNIV (607088) Distal SMA type 3	Autosomal recessive. Juvenile onset. Severe muscle wasting and weakness and diaphragmatic paralysis		11q13
dHMNV (600794)	(Allelic CMT2D) Autosomal dominant. Upper limb predominance, occasional pyramidal features		*GARS*
dHMN type V (Silver syndrome) (270685)	Autosomal dominant. Prominent hand muscle weakness and wasting, mild to severe spasticity of lower limbs		*BSCL2*
dHMNVI (604320)	(Allelic SMARD1) Autosomal recessive. Severe infantile form with respiratory distress		*IGHMBP2*
dHMNVIIA (158580)	Autosomal dominant. Onset with vocal cord paralysis		*DCTN1*
dHMNVIIB (607641)	Autosomal dominant. Onset with vocal cord paralysis and facial weakness		2q14
X-linked dHMN			Xq13–q21
dHMN/ALS4 (602433)	X-linked recessive. Juvenile onset with distal wasting and weakness		*SETX*
dHMN-J (Jerash)	Autosomal dominant. Early onset symptomatic in 2nd decade with pyramidal tract signs		9p21.1–p12
Congenital distal SMA (600175)	Autosomal recessive. Onset from 6-10 yr with pyramidal features in 1 Jordanian family Autosomal dominant congenital nonprogressive distal HMN with contractures		12q23–q24
Peripheral neuropathy with agenesis of corpus callosum (Charlevoix disease or Andermann syndrome) (218000)	Autosomal recessive. Increased in French Canadian populations. Progressive axonal neuropathy. CNS malformations—absence/hypoplasia of corpus callosum in most, early onset, developmental delay, areflexia, dysmorphology. Later, increased motor disability, hallucinatory psychosis. Death by 3rd decade	EMG: denervation. Axonal neuropathy	*SLC12A6 (KCC3)*
Hereditary neuralgic amyotrophy (brachial plexus neuropathy) (162100)	Autosomal dominant. Episodes of paralysis and muscle weakness initiated by severe pain. Onset can be from birth or later childhood but usually adult onset. Outcome usually good but some left with residual dysfunction. Episodes often triggered by infections, immunizations, and stress. Some pedigrees dysmorphic with hypotelorism	Normal or mildly prolonged MNCVs distal to affected brachial plexus	*SEPT9*
HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES			
HSN (HSAN) 1 (162400)	Type 1: Autosomal dominant. Onset 2nd–5th decade. Predominant loss of pain and temperature sensation, preservation of vibration sense, lancinating pain, variable distal motor involvement	Normal to low-normal MNCVs, disturbance of sensory conduction of variable severity Type 1B: Autosomal dominant. Predominantly sensory neuropathy with cough and gastroesophageal reflux, rarely foot ulcers. More often adult onset. Hearing often abnormal	*SPTLC1* *RAB7* 3p24–p22
HSN (HSAN) 2(A) (201300)	Autosomal recessive. Onset in infancy/early childhood–1st 2 decades. Mutilating acropathy. Often unrecognized fractures. Marked sensory loss affecting all cutaneous modalities, most marked distally in all limbs. Autonomic dysfunction less marked. Absent or decreased DTRs	Normal MNCVs; SNAPs are absent	*WNK1*
HSN (HSAN) 2B (223900)	Autosomal recessive. Impaired sensation, ulcers, and arthropathy develop in childhood		*FAM134B*

Table 613-1 Hereditary Peripheral Neuropathies—cont'd

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
HSN (HSAN) 3 (Riley-Day syndrome, familial dysautonomia) (223900)	Autosomal recessive. History of neurologic abnormality and of difficult feeding from birth. Failure to produce tears regularly. Absent or reduced DTRs. Absent corneal reflexes, postural hypotension, emotional lability. Relative indifference to pain, absence of fungiform papillae on tongue, absence of flare with intradermal histamine. Normal intelligence	Motor conduction velocities usually slightly below control values. Sensory conduction normal or decreased	*IKBAP*
HSN (HSAN) 4 (congenital insensitivity to pain with anhidrosis, CIPA) (256800)	Autosomal recessive. Onset from infancy, often high fevers due to truncal anhidrosis during hot weather. Painless injuries of extremities and oral structures, often self-mutilation. Lack of pain sensation, both peripheral and visceral, inability to distinguish hot and cold. Preservation of DTRs. Mild mental retardation. Hyperactivity and emotional lability common	Nerve conduction studies normal. Sympathetic skin responses are absent (histamine test)	*NTRK1*
HSN (HSAN) 5 (608654)	Autosomal recessive. Onset in early life. Rare disorder. Painless injuries of the extremities. Lack of pain and thermal sensitivity in the limbs but preservation of response to tactile and mechanical stimuli. Preservation of muscle strength and DTRs. Distal anhidrosis. Bone and joint fractures; arthropathy. Normal intelligence	Normal motor and sensory nerve conduction studies	*NGFβ*

*The term CMT3 should be reserved for hereditary neuropathies in which hypomyelination is the dominant feature. This would include congenital hypomyelinating neuropathy, Dejerine-Sottas disease, and congenital amyelinating neuropathy.

CCFDN, congenital cataract, microcornea, facial dysmorphism, mental retardation, distal motor peripheral neuropathy; CIPA, congenital insensitivity to pain with anhidrosis; CMAP, compound motor unit action potential; CMT, Charcot-Marie-Tooth disease; CP, common peroneal; CSF, cerebrospinal fluid; dHMN, distal hereditary motor neuronopathy; DI, dominant intermediate; dSMA, distal spinal muscular atrophy; DTR, deep tendon reflex; EMG, electromyography; EOHMSN, early-onset HMSN; HMN, hereditary motor neuropathy; HMSN, hereditary motor and sensory neuropathy; HSAN, hereditary sensory and autonomic neuropathy; HSN, hereditary sensory neuropathy; MNCV, motor nerve conduction velocity; OMIM, Online Mendelian Inheritance in Man; SAP, sensory action potential; SEOAN, severe early-onset axonal neuropathy; SMA, spinal muscular atrophy; SNAP, sensory nerve action potential.

From Wilmshurst JM, Ouvrier R: Hereditary peripheral neuropathies of childhood: an overview for clinicians, Neuromuscul Disord *21(11):763–775, 2011.*

of the molecular genetics of this group of diseases, the diagnosis of most can be confirmed by less invasive genetic testing. Electromyography (EMG) remains a useful adjunct to clinical diagnosis and helps distinguish between **demyelinating** or **hypomyelinating** and **axonal** forms.

Classification of HMSNs is difficult because no simple unifying scheme is capable of incorporating all the clinical presentations and overlapping genetics (see Table 613-1). In some neuropathies, a diverse genotype of mutations of different genes at different chromosomal loci may produce a similar phenotype. One classification identifies: I. Hereditary neuropathies secondary to general diseases; II. Primary neuropathies as: IIa. Hereditary motor sensory neuropathies; IIb. Distal hereditary motor neuropathies; IIc. Hereditary sensory ± autonomic neuropathies; III. Syndromic neuropathies including congenital hypomyelinating neuropathies; and IV. Hereditary sensory neuropathy (Refsum disease).

613.1 Peroneal Muscular Atrophy (Charcot-Marie-Tooth Disease, Hereditary Motor-Sensory Neuropathy Type IIa)

Harvey B. Sarnat

Charcot-Marie-Tooth disease is the most common genetically determined neuropathy and has an overall prevalence of 3.8/100,000 population. It is transmitted as an autosomal dominant trait with 83% expressivity; the 17p11.2 locus is the site of the abnormal gene. Autosomal recessive transmission also is described but is rarer. The gene product is peripheral myelin protein 22 (PMP22). A much rarer X-linked HMSN type I results from a defect at the Xq13.l locus, causing mutations in the gap junction protein connexin-32. Other forms have been reported (see Table 613-1).

CLINICAL MANIFESTATIONS

Most patients are asymptomatic until late childhood or early adolescence, but young children sometimes manifest gait disturbance as early as the 2nd yr of life. The peroneal and tibial nerves are the earliest and most severely affected. Children with the disorder are often described as being clumsy, falling easily, or tripping over their own feet. Application of the Cumberland Ankle Instability Tool for Youth is a means of objectively documenting and following this manifestation. The onset of symptoms may be delayed until after the 5th decade.

Muscles of the anterior compartment of the lower legs become wasted, and the legs have a characteristic stork-like contour. The muscular atrophy is accompanied by progressive weakness of dorsiflexion of the ankle and eventual footdrop. The process is bilateral but may be slightly asymmetric. Pes cavus deformities invariably develop as a result of denervation of intrinsic foot muscles, further destabilizing the gait. Atrophy of muscles of the forearms and hands is usually not as severe as that of the lower extremities, but in advanced cases contractures of the wrists and fingers produce a claw hand. Proximal muscle weakness is a late manifestation and is usually mild. Axial muscles are not involved.

The disease is slowly progressive throughout life, but patients occasionally show accelerated deterioration of function over a few years. Most patients remain ambulatory and have normal longevity, although orthotic appliances are required to stabilize the ankles.

Sensory involvement mainly affects large myelinated nerve fibers that convey proprioceptive information and vibratory sense, but the threshold for pain and temperature can also increase. Some children complain of tingling or burning sensations of the feet, but pain is rare. Because the muscle mass is reduced, the nerves are more vulnerable to trauma or compression. Autonomic manifestations may be expressed as poor vasomotor control with blotching or pallor of the skin of the feet and inappropriately cold feet.

Nerves often become palpably enlarged. Tendon stretch reflexes are lost distally. Cranial nerves are not affected. Sphincter control remains well preserved. Autonomic neuropathy does not affect the heart, gastrointestinal tract, or bladder. Intelligence is normal. A unique point mutation in *PMP22* causes progressive auditory nerve deafness in addition, but this is usually later in onset than the peripheral neuropathy.

Davidenkow syndrome is a variant of HMSN type I with a scapuloperoneal distribution.

LABORATORY FINDINGS AND DIAGNOSIS

Motor and sensory nerve conduction velocities are greatly reduced, sometimes as slow as 20% of normal conduction time. In new cases without a family history, both parents should be examined, and nerve conduction studies should be performed.

EMG and muscle biopsy are not usually required for diagnosis, but they show evidence of many cycles of denervation and reinnervation. Serum creatine kinase level is normal. Cerebrospinal fluid (CSF) protein may be elevated, but no cells appear in the CSF.

Sural nerve biopsy is diagnostic. Large- and medium-size myelinated fibers are reduced in number, collagen is increased, and characteristic **onion bulb formations** of proliferated Schwann cell cytoplasm surround axons. This pathologic finding is called **interstitial hypertrophic neuropathy.** Extensive segmental demyelination and remyelination also occur.

The definitive molecular genetic diagnosis may be made in blood.

TREATMENT

Stabilization of the ankles is a primary concern. In early stages, stiff boots that extend to the midcalf often suffice, particularly when patients walk on uneven surfaces such as ice and snow or stones. As the dorsiflexors of the ankles weaken further, lightweight plastic splints may be custom made to extend beneath the foot and around the back of the ankle. They are worn inside the socks and are not visible, reducing self-consciousness. External short-leg braces may be required when footdrop becomes complete. Surgical fusion of the ankle may be considered in some cases.

The leg should be protected from traumatic injury. In advanced cases, compression neuropathy during sleep may be prevented by placing soft pillows beneath or between the lower legs. Burning paresthesias of the feet are not common but are often abolished by phenytoin, carbamazepine, or gabapentin. No medical treatment is available to arrest or slow the progression.

613.2 Peroneal Muscular Atrophy (Axonal Type)

Harvey B. Sarnat

Peroneal muscular atrophy is clinically similar to HMSN type I, but the rate of progression is slower and the disability is less. EMG shows denervation of muscle. Sural nerve biopsy reveals axonal degeneration rather than the demyelination and whorls of Schwann cell processes typical in type I. The locus is on chromosome 1 at 1p35-p36; this is a different disease than HMSN type I, although both diseases are transmitted as autosomal dominant traits. An autosomal recessive infantile motor axonal neuropathy can closely mimic infantile spinal muscular atrophy.

613.3 Congenital Hypomyelinating Neuropathy and Dejerine-Sottas Disease (Hereditary Motor-Sensory Neuropathy Type III)

Harvey B. Sarnat

Congenital hypomyelinating neuropathy is an interstitial hypertrophic neuropathy of autosomal dominant transmission, clinically similar to HMSN type I but more severe. Symptoms develop in early infancy and are rapidly progressive, with hypotonia and breathing and feeding difficulties. Pupillary abnormalities, such as lack of reaction to light and *Argyll Robertson pupil,* are common. Kyphoscoliosis and pes cavus deformities complicate approximately 35% of cases. Nerves become palpably enlarged at an early age. Dejerine-Sottas disease is a more slowly progressive variant with onset usually before age 5 yr.

An autosomal recessive form of congenital hypomyelinating neuropathy also is known and may be caused by various genetic mutations, including *MTMR2*, *PMP22*, *EGR2*, and *MPZ*. Neonatal hypotonia and developmental delay in infancy are hallmark clinical features. Many patients exhibit congenital insensitivity to pain. Cranial nerves are inconsistently involved, and respiratory distress and dysphagia are rare complications. Tendon reflexes are absent. **Arthrogryposis** is present at birth in at least half the cases.

The onion bulb formations seen in the sural nerve biopsy specimen are pronounced. Hypomyelination also occurs. In the recessive form, hypomyelination may not be accompanied by interstitial hypertrophy in all cases.

The genetic locus of 17p11.2 is identical to that of HMSN type I or Charcot-Marie-Tooth disease. Monoallelic mutations in *MPZ* (myelin protein zero), *PMP22,* or *EGR2* (early grow response 2) are the most frequent genetic causes. The clinical and pathologic differences may be phenotypical variants of the same disease, analogous to the situation in Duchenne and Becker muscular dystrophies. An autosomal recessive form of Dejerine-Sottas disease is incompletely documented.

613.4 Roussy-Lévy Syndrome

Harvey B. Sarnat

Roussy-Lévy syndrome is defined as a combination of HMSN type II and cerebellar deficit resembling Friedreich ataxia, but it does not have cardiomyopathy.

613.5 Refsum Disease (Hereditary Sensory Neuropathy Type IV) and Infantile Refsum Disease

Harvey B. Sarnat

See Chapter 86.2.

Refsum disease is a rare autosomal recessive disease caused by an enzymatic block in β-oxidation of phytanic acid to pristanic acid. Phytanic acid is a branched-chain fatty acid that is derived mainly from dietary sources: spinach, nuts, and coffee. Levels of phytanic acid are greatly elevated in plasma, CSF, and brain tissue. The CSF shows an albuminocytologic dissociation, with a protein concentration of 100-600 mg/dL. Genetic linkage studies identify 2 distinct loci at 10p13 and 6q22-q24 with *PHYH* and *PEX7* genetic mutations, respectively. The infantile form also can be caused by *PEX1*, *PEX2,* or *PEX26* genes, which produce both clinical and biochemical differences from the classical form, and include minor facial dysmorphism, retinitis pigmentosa, sensorineural hearing loss, hypercholesterolemia, hepatomegaly, and failure to thrive. Phytanic acid accumulation in infantile Refsum disease is secondary to a primary peroxisomal disorder; hence autosomal recessive Refsum disease is really a different disease.

Clinical onset of classical Refsum disease is usually between 4 and 7 yr of age, with intermittent motor and sensory neuropathy. Ataxia, progressive neurosensory hearing loss, retinitis pigmentosa with loss of night vision, ichthyosis, and liver dysfunction also develop in various degrees. Skeletal malformations from birth and cardiac findings of conduction disturbances and cardiomyopathy appear in the majority. Motor and sensory nerve conduction velocities are delayed. Sural nerve biopsy shows loss of myelinated axons. Treatment is by dietary management and periodic plasma exchange. With careful management, life expectancy can be normal.

613.6 Fabry Disease

Harvey B. Sarnat

See Chapter 86.4.

Fabry disease, a rare X-linked recessive trait, results in storage of ceramide trihexose because of deficiency of the enzyme ceramide trihexosidase, which cleaves the terminal galactose from ceramide trihexose (ceramide-glucose-galactose-galactose), resulting in tissue accumulation of this trihexose lipid in central nervous system neurons, Schwann cells and perineurial cells, ganglion cells of the myenteric plexus, skin, kidneys, blood vessel endothelial and smooth muscle cells, heart, sweat glands, cornea, and bone marrow. It results from a missense mutation disrupting the crystallographic structure of α-galactosidase A.

CLINICAL MANIFESTATIONS

The presentation is in late childhood or adolescence, with recurrent episodes of burning pain and paresthesias of the feet and lower legs so severe that patients are unable to walk. These episodes are often precipitated by fever or by physical activity. Objective sensory and motor deficits are not demonstrated on neurologic examination, and reflexes are preserved. Characteristic skin lesions are seen in the perineal region, scrotum, buttocks, and periumbilical zone as flat or raised red-black telangiectases known as **angiokeratoma corporis diffusum.** Hypohidrosis may be present. Corneal opacities, cataracts, and necrosis of the femoral heads are inconstant features. Tortuosity of retinal vessels and of the vertebral and basilar arteries can occur. The disease is progressive. Hypertension and renal failure are usually delayed until early adult life. Recurrent strokes result from vascular wall involvement. Death often occurs in the 5th decade owing to cerebral infarction or renal insufficiency, but a significant morbidity already occurs in childhood despite the absence of major organ failure. Heterozygous female carriers may be asymptomatic or, rarely, are as affected as males; corneal opacities involve 70-80%, though cataracts are rare.

LABORATORY FINDINGS

Motor and sensory nerve conduction velocities are normal to only mildly slow, showing preservation of large myelinated nerve fibers. CSF protein is normal. Proteinuria is present early in the course.

Calcifications often are seen in pulvinar of the thalamus, as demonstrated by CT or MRI and are specific imaging findings, believed caused by cerebral hyperperfusion. Positron tomography, by contrast, shows reduced cerebral blood flow velocity and impaired autoregulation because of the glycosphingolipid storage in vascular endothelial cells.

Pathologic features are usually first detected in skin or sural nerve biopsy specimens. Electron microscopy demonstrates crystalline glycosphingolipids, appearing as *zebra bodies*, in lysosomes of endothelial cells, in smooth myocytes of arterioles, and in Schwann cells. Nerves show a selective loss of small myelinated fibers and relative preservation of large and medium-sized axons, contrasting to most axonal neuropathies in which large myelinated fibers are most involved.

Assay for the deficient enzyme, α-galactosidase-A, may be performed from skin fibroblasts, leukocytes, and other tissues. This test permits detection of the female carrier state and provides a reliable means of prenatal diagnosis.

TREATMENT

See Chapter 86.4 for specific therapy of Fabry disease, including enzyme replacement.

Medical therapy of painful neuropathies includes management of the initiating disease and therapy directed to the neuropathic pain independent of etiology. Pain may be burning or associated with paresthesia, hyperalgesia (abnormal response to noxious stimuli), or allodynia (induced by non–noxious stimuli; see Chapter 62). Neuropathic pain is often successfully managed by tricyclic antidepressants; selective serotonin reuptake inhibitors are less effective. Anticonvulsants (carbamazepine, phenytoin, gabapentin, lamotrigine) are effective, as are narcotic and nonnarcotic analgesics. Enzyme replacement therapy has improved the short- and long-term prognosis of the clinical neuropathy and also reverses the increased blood flow velocity in the brain.

613.7 Giant Axonal Neuropathy

Harvey B. Sarnat

Giant axonal neuropathy is a rare autosomal recessive disease with onset in early childhood. It is a progressive mixed peripheral neuropathy and degeneration of central white matter, similar to the leukodystrophies. Ataxia and nystagmus are accompanied by signs of progressive peripheral neuropathy. A large majority of affected children have frizzy hair, which microscopically shows variation in diameter of the shaft and twisting, similar to that in Menkes disease; hence, microscopic examination of a few scalp hairs provides a simple screening tool in suspected cases. Focal axonal enlargements are seen in both the peripheral nervous system and the central nervous system, but the myelin sheath is intact. The disease is a general proliferation of intermediate filaments, including neurofilaments in axons, glial filaments (i.e., Rosenthal fibers) in brain, cytokeratin in hair, and vimentin in Schwann cells and fibroblasts.

Nonsense and missense mutations or deletions occur in the *GAN* gene, with allelic heterogeneity, at 16q24. These mutations are responsible for defective synthesis of the protein gigaxonin, a member of the cytoskeletal BTB/kelch superfamily, crucial to linkage between intermediate proteins and the cell membrane. MRI shows white matter lesions of the brain similar to leukodystrophies, and MR spectroscopy demonstrates increased ratios of choline : creatine and myoinositol : creatine, with a normally preserved ratio of *N*-acetyl aspartate : creatine, indicating demyelination and glial proliferation without axonal loss. Gigaxonin is expressed in a wide variety of neuronal cell types and is localized to the Golgi apparatus and endoplasmic reticulum.

The diagnosis is established by microscopy of scalp hair and by MRI and MR spectroscopy of the brain; it is confirmed by sural nerve biopsy and/or by genetic studies, if available, of the *GAN* gene. A mutation of *BAG3*, one of several genes associated with myofibrillar myopathy (see Chapter 608.5), also can cause giant axonal neuropathy as another genetic etiology not associated with the more frequent *GAN* gene.

613.8 Tomaculous (Hypermyelinating) Neuropathy; Hereditary Neuropathy with Liability to Pressure Palsies

Harvey B. Sarnat

This hereditary neuropathy is characterized by redundant overproduction of myelin around each axon in an irregular segmental fashion so that tomaculous (sausage-shaped) bulges occur in the individual myelinated nerve fibers. Other sections of the same nerve can show loss of myelin. Such nerves are particularly prone to pressure palsies, and patients, usually beginning in adolescence, present with recurrent or intermittent mononeuropathies secondary to minor trauma or entrapment neuropathies, such as carpal tunnel syndrome, peroneal palsies, and even "writer's cramp." It is transmitted as an autosomal dominant trait, with loci identified at 17p11.2 and 17p12, deletion of exons in the *PMP22* gene, in some patients only microdeletions. Duplication of the same 17p12 locus leads to Charcot-Marie-Tooth disease type 1A, myelin protein zero *(MPZ)* gene mutation. Sural nerve biopsy is diagnostic, but special teased fiber preparations should be made to demonstrate the myelin abnormalities most clearly. Skin or conjunctival biopsies also may be diagnostic. Electrophysiologic nerve conduction studies are abnormal but nonspecific. Genetic studies are definitive.

Treatment is supportive and includes avoiding trauma and prolonged nerve compression, including postures when sitting or lying.

Surgical release of entrapped nerves is indicated at times, particularly of the ulnar nerve.

613.9 Leukodystrophies

Harvey B. Sarnat

Several hereditary degenerative diseases of white matter of the central nervous system also cause peripheral neuropathy. The most important are Krabbe disease (globoid cell leukodystrophy), metachromatic leukodystrophy, and adrenoleukodystrophy (see Chapters 86 and 599).

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Chapter 614
Toxic Neuropathies

Harvey B. Sarnat

Table 614-1 Toxic and Metabolic Neuropathies	
METALS Arsenic (insecticide, herbicide) Lead (paint, batteries, pottery) Mercury (metallic, vapor) Thallium (rodenticides) Gold	Nitrofurantoin Nitrous oxide Nucleosides (antiretroviral agents dideoxycytidine [ddC], didanosine [ddI], d4T, others) Penicillamine Pentamidine Phenytoin Pyridoxine (excessive) Statins Stilbamidine Suramin Tacrolimus Taxanes (paclitaxel, docetaxel) Thalidomide Tryptophan (eosinophilia-myalgia syndrome) Vincristine
OCCUPATIONAL OR INDUSTRIAL CHEMICALS Acrylamide (grouting, flocculation) Carbon disulfide (solvent) Cyanide Dichlorophenoxyacetate Dimethylaminopropionitrite Ethylene oxide (gas sterilization) Hexacarbons (glue, solvents) Organophosphates (insecticides, petroleum additive) Polychlorinated biphenyls Tetrachlorbiphenyl Trichloroethylene	**METABOLIC DISORDERS** Fabry disease Krabbe disease Leukodystrophies Porphyria Tangier disease Tyrosinemia Uremia
DRUGS Amiodarone Chloramphenicol Chloroquine Cisplatin Colchicine Dapsone Ethambutol Ethanol Fluoroquinolones Gold Hydralazine Isoniazid Metronidazole	**BIOLOGIC AND INFECTIOUS NEUROPATHIES** Diphtheria Herpesviruses HIV Leprosy Lyme disease Rabies West Nile virus

Many chemicals (organophosphates), toxins, and drugs can cause peripheral neuropathy (Table 614-1). Heavy metals are well-known neurotoxins. Lead poisoning, especially if chronic, causes mainly a motor neuropathy selectively involving large nerves, such as the common peroneal, radial, and median nerves, a condition known as **mononeuritis multiplex** (see Chapter 721). Arsenic produces painful burning paresthesias and motor polyneuropathy. Exposure to industrial and agricultural chemicals is a less-common cause of toxic neuropathy in children than in adults, but insecticides are neurotoxins for both insects and humans, and if they are used as sprays in closed spaces, they may be inhaled and induce lethargy, vomiting, seizures, and neuropathy, particularly with recurrent or long-term exposure. Working adolescents and children in developing countries are also at risk. Puffer fish poisoning, which can be acquired even when fish contaminated with the venom has been cooked, produces a Guillain-Barré–like syndrome. Ethanol abuse can be neurotoxic and particularly affects the optic nerves, but optic neuritis is not a true peripheral neuropathy.

The most frequent cause of toxic neuropathies in children is prescribed medications, though street drugs also can be neurotoxic. Antimetabolic and immunosuppressive drugs, such as vincristine, cisplatin, and paclitaxel, produce polyneuropathies as complications of chemotherapy for neoplasms and immunologic disorders, such as juvenile idiopathic arthritis. This "iatrogenic" cause is usually an axonal degeneration rather than primary demyelination, unlike primary autoimmune neuropathies. Excessive vitamin intake ("megavitamins") can be neurotoxic.

Chronic uremia is associated with toxic neuropathy and myopathy. The neuropathy is caused by excessive levels of circulating parathyroid hormone. Reduction in serum parathyroid hormone levels is accompanied by clinical improvement and a return to normal of nerve conduction velocity. Peripheral nerve axonal damage, particularly of small fibers, can be secondary to mitochondrial loss or dysfunction in toxic neuropathies. Abnormal toxic complex lipids, generated in Schwann cells by deficient mitochondrial respiration, are capable of damaging or destroying neighboring axons, a secondary mitochondrial toxic neuropathy. Small heat-shock proteins can be provoked that also may contribute to toxic neuropathy.

Biologic neurotoxins associated with diphtheria, Lyme disease, West Nile virus disease, leprosy, herpesviruses (Bell palsy), and rabies also produce peripheral nerve– or ventral horn cell–induced weakness or paralysis. HIV infections also produce neuropathy and this infection is particularly prevalent in children in several African countries, including those who immigrate to western countries as refugees. Tick paralysis, botulism, and paralytic shellfish poisoning cause neuromuscular junction blockade rather than true neuropathy. Various inborn errors of metabolism are also associated with peripheral neuropathy from metabolite toxicity or deficiencies (see Part XI and Table 614-1).

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Chapter 615

Autonomic Neuropathies

Harvey B. Sarnat

Involvement of small, lightly or unmyelinated autonomic nerve fibers may be seen in many peripheral neuropathies; the autonomic manifestations are usually mild or subclinical. Certain autonomic neuropathies are more symptomatic and demonstrate varying degrees of involvement of the autonomic nervous system regulation of the cardiovascular, gastrointestinal, genitourinary, thermoregulatory, sudomotor, and pupillomotor systems. Figure 615-1 shows the classification of autonomic disorders (dysautonomias).

The differential diagnosis is noted in Tables 613-1 (in Chapter 613) and 615-1; Table 615-2 compares the neonatal-infantile onset

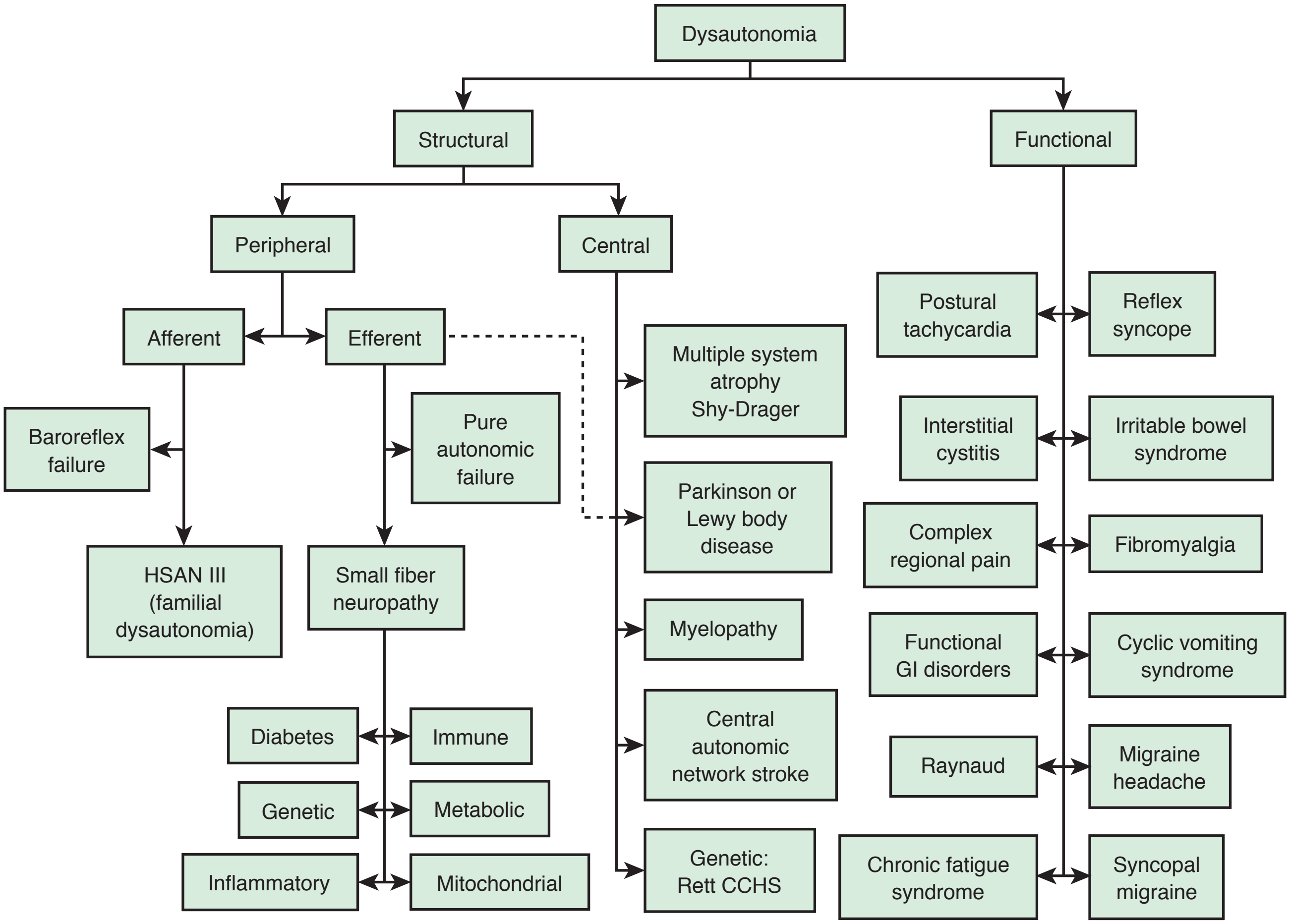

Figure 615-1 Classification of autonomic disorders or dysautonomias. The first conceptual division is between a structural and functional disorder. The word "functional" is being used in its true meaning of a disturbance in autonomic function, without clear evidence of structural damage to the autonomic nervous system, akin to the use of the word "functional" in functional gastrointestinal disorders, and without implication of a psychiatric etiology. In the absence of any evidence of consistent structural abnormalities functional disorders clearly cannot be localized in the nervous system. In contrast, structural disorders can be further divided into those localized in the central and peripheral nervous systems, with the division point usually taken at the sympathetic ganglion. Finally, peripheral nervous system disorders can be further classified based on whether they primarily involve afferent or efferent nerves. It should be emphasized that there is overlap between these groups, for example, diabetes will often involve afferent nerve fibers, but this classification emphasizes the predominant fiber involvement. A *dotted line* links Parkinson disease to a peripheral efferent group as Lewy bodies are present in the both parasympathetic and sympathetic ganglia, impairing peripheral autonomic function. See below for discussion of specific disorders. *CCHS*, Congenital central hypoventilation syndrome; *HSAN*, hereditary sensory autonomic neuropathy. *(From Chelimsky T, Robertson D, Chelimsky G: Disorders of the autonomic nervous system. In Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors:* Bradley's neurology in clinical practice, *ed 6, Philadelphia, 2012, WB Saunders, Fig. 77-1, p. 2018.)*

Table 615-1 Autonomic Neuropathies

Guillain-Barré syndrome (see Chapter 608)
Non–Guillain-Barré syndrome autoimmunity
- Paraneoplastic (type I antineuronal nuclear antibody)
- Lambert-Eaton syndrome
- Antibodies to neuronal nicotinic acetylcholine receptors
- Antibodies to P/Q-type calcium channels
- Other autoantibodies
- Systemic lupus erythematosus

Hereditary sensory and autonomic neuropathies
- Type I autosomal dominant
- Type II autosomal recessive (Morvan disease)
- Type III autosomal recessive (Riley-Day)
- Type IV autosomal recessive (congenital insensitivity to pain with anhidrosis)
- Type V absence of pain

Metabolic
- Fabry disease
- Diabetes mellitus
- Tangier disease
- Porphyria

Infectious
- HIV
- Chagas disease
- Botulism
- Leprosy
- Diphtheria

Other
- Triple A (Allgrove) syndrome
- Navajo Indian neuropathy
- Multiple endocrine neoplasia type 2b

Toxins (see Table 614-1 in Chapter 614)

Table 615-2 Major Clinical Features of Hereditary Sensory-Autonomic Neuropathy Types II, III, and IV

CLINICAL FEATURES	HSAN TYPE II	HSAN TYPE III	HSAN TYPE IV
Onset	Birth	Birth	Birth
Initial symptoms (from birth to age 3 yr)	Swallowing problems Self-mutilation (65%) Delayed development	Swallowing problems Aspiration pneumonia Breech presentation (37%) Hypothermia Delayed development	Fevers Self-mutilation (88%)
Unique features	No axon flare Lack of fungiform papilla Hearing loss (30%)	No axon flare Lack of fungiform papilla Alacrima	No axon flare Anhidrosis Consanguinity 50%
Sensory dysfunction			
Depressed deep tendon reflexes	Frequent (71%)	Almost consistent (99%)	Infrequent (9%)
Pain perception	Absent	Mild to moderate decrease	Absent
Temperature perception	Severe decrease	Mild to moderate decrease	Absent
Vibration sense	Normal	Normal	Normal to moderate decrease
Autonomic			
Gastroesophageal reflux	Frequent (71%)	Frequent (67%)	Uncommon (24%)
Postural hypotension	Uncommon (25%)	Almost consistent (99%)	Uncommon (29%)
Episodic hypertension	Rare	Frequent	Rare
Ectodermal features			
Dry skin	No	No	Consistent
Fractures	29%	40%	71%
Scoliosis	59%	85%	23%
Intelligence			
IQ <65	Common (38%)	Uncommon (10%)	Common (33%)
Hyperactivity	Common (41%)	Uncommon	Common (54%)

Frequency definitions: rare = <1%; infrequent = <10%; uncommon = <30%; common = 30-65%; frequent = >65%.

From Axelrod FB, Gold-von Simson G: Hereditary sensory and autonomic neuropathies: types II, III, and IV, Orphanet J Rare Dis *2:39, 2007, Table 2.*

Table 615-3 Autonomic Function Testing

Sympathetic and parasympathetic divisions of the autonomic nervous system are involved in all tests of autonomic function
CARDIAC PARASYMPATHETIC NERVOUS SYSTEM FUNCTION Heart rate variability with deep respiration (respiratory sinus arrhythmia); time-domain and frequency-domain assessments Heart rate response to Valsalva maneuver Heart rate response to standing
SYMPATHETIC ADRENERGIC FUNCTION Blood pressure response to upright posture (standing or tilt table) Blood pressure response to Valsalva maneuver Microneurography
SYMPATHETIC CHOLINERGIC FUNCTION Thermoregulatory sweat testing Quantitative sudomotor-axon reflex test Sweat imprint methods Sympathetic skin response

From Freeman R: Autonomic peripheral neuropathy, Lancet *365:1259–1270, 2005.*

Table 615-4 Management of Autonomic Neuropathies

PROBLEM	TREATMENT
Orthostatic hypotension	Volume and salt supplements Fluorohydrocortisone (mineralocorticoid) Midodrine (α agonist)
Gastroparesis	Prokinetic agents (metoclopramide, domperidone, erythromycin)
Hypomotility	Fiber, laxatives
Urinary dysfunction	Timed voiding; bladder catheterization
Hyperhidrosis	Anticholinergic agents (glycopyrrolate, propantheline) Intracutaneous botulism toxin

hereditary sensory-autonomic neuropathies (HSANs). Table 615-3 lists autonomic nervous system functional tests. The general treatment of acquired autonomic dysfunction includes treating the primary disorder (systemic lupus erythematosus, diabetes) and long-term management of specific organ system manifestations (Table 615-4). Acute fluctuations of autonomic symptoms may be seen in Guillain-Barré syndrome. Rapid fluctuations of hypertension or tachycardia changing to hypotension or bradycardia should be managed carefully and with very short-acting medications.

615.1 Familial Dysautonomia

Harvey B. Sarnat

Familial dysautonomia (Riley-Day syndrome) is an autosomal recessive disorder that is common in Eastern European Jews, among whom the incidence is 1 in 10,000-20,000, and the carrier state is estimated to be 1%. It is rare in other ethnic groups but is the most common HSAN. The defective gene is at the 9q31-q33 locus. The familial dysautonomia gene is identified as *IKBKAP* (IκB kinase–associated protein), with aberrant splicing and a truncated protein (see Table 615-2). This and other autonomic neuropathies are often regarded as **neurocristopathies** because the abnormal target tissues are largely derived from neural crest.

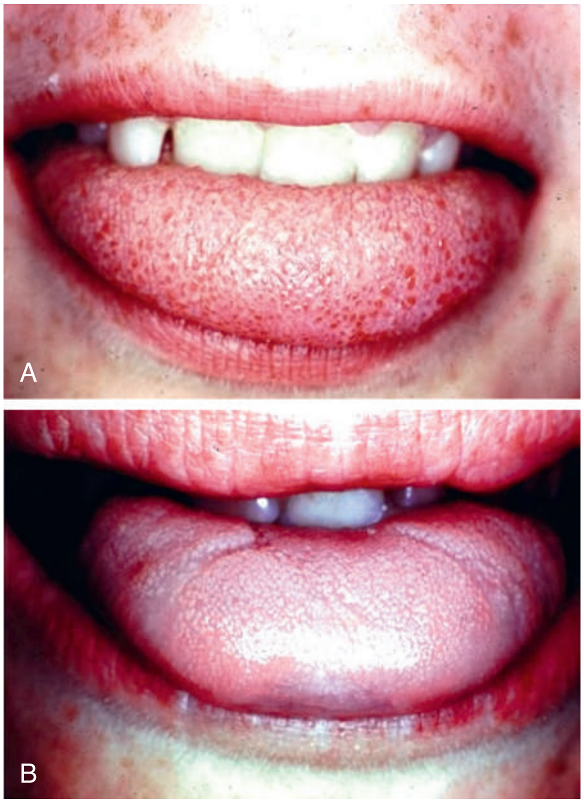

Figure 615-2 **A,** Normal tongue with fungiform papillae present on the tip. **B,** Dysautonomic tongue. Note the absence of the highly vascularized fungiform papillae from the tongue tip, which gives the appearance of a smooth tongue. *(From Axelrod FB, Gold-von Simson G: Hereditary sensory and autonomic neuropathies: types II, III, and IV,* Orphanet J Rare Dis *2:39, 2007, Fig. 4.)*

PATHOLOGY

This disease of the peripheral nervous system is characterized pathologically by a reduced number of small unmyelinated nerve fibers that carry pain, temperature, and taste sensations and that mediate autonomic functions including baroreceptors. Large myelinated afferent nerve fibers that relay impulses from muscle spindles and Golgi tendon organs also are deficient. The degree of demonstrable anatomic change in peripheral and especially autonomic nerves is variable. Optic neuropathy with predominant loss of papillomacular nerve fibers may impair visual acuity. Fungiform papillae of the tongue (taste buds) are absent or reduced in number (Fig. 615-2). The number of parasympathetic ganglion cells in the myenteric plexuses is reduced. There is terminal vessel hyperperfusion in tissues, despite an overall hypoperfusion of organs and extremities.

CLINICAL MANIFESTATIONS

Clinical manifestations are highly variable between individuals. The disease is expressed in infancy by poor sucking and swallowing. Aspiration pneumonia can occur. Feeding difficulties with oral incoordination is a major symptom throughout childhood. Vomiting crises can occur, and indeed nausea, retching, and hyperemesis (dysautonomic crisis) are the most disabling symptoms in some children. Apart from dysphagia, esophageal dysmotility can contribute to these symptoms. Episodic somnolence can occur in infants, as does hypotonia. Excessive sweating and blotchy erythema of the skin are common, especially at mealtime or when the child is excited. Infants are vulnerable to heatstroke. Episodic hyperhidrosis is caused by chemical hypersensitivity of the remaining sudomotor axons rather than of the sweat gland secretory cells. Breathholding spells followed by syncope are common in the 1st 5 yr of life. Episodic arterial hypertension and hypotension may be related to loss of baroreceptor modulation of muscle vasoconstrictor drive, and an acute fall in blood pressure manifests as orthostatic hypotension. Chronic and progressive renal disease may result from renal hypoperfusion. Responses to hypoxia are reduced.

As affected children become older, insensitivity to pain becomes evident and traumatic injuries are frequent. Pain and temperature sensation is reduced but is not as severe as in other HSANs (see Table 615-2). Corneal ulcerations are common partly as a result of decreased corneal reflexes and perhaps because of alacrima (absence of tears with emotional crying), which is a universal finding. Newly erupting teeth cause tongue ulcerations and, in older children, dental trauma and oral soft tissue mutilation may be prominent. Walking is delayed or clumsy or appears ataxic because of poor sensory feedback from muscle spindles. The ataxia is probably related more to deficient muscle spindle feedback and to vestibular nerve dysfunction than to cerebellar involvement, but defective ocular saccades also may indicate cerebellar dysfunction and cerebellar atrophy. Tendon stretch reflexes are absent. Scoliosis or kyphosis is a serious complication in the majority of patients and usually is progressive. Overflow tearing with crying does not normally develop until 2-3 mo of age but fails to develop after that time or is severely reduced or absent in children with familial dysautonomia. There is an increased incidence of urinary incontinence. Bradycardia and other cardiac arrhythmias can occur, and some patients require a cardiac pacemaker.

Approximately 40% of patients have generalized major motor seizures; some of these are associated with acute hypoxia during breathholding and some with extreme fevers, but most do not have an apparent precipitating event. Body temperature is poorly controlled; both hypothermia and extreme fevers occur. Impaired intellectual function is not secondary to epilepsy. Emotional lability and learning disabilities are common in school-age children with the disorder. Puberty is often delayed, especially in girls. Short stature can occur, but growth velocity can be accelerated by treatment with growth hormone. Speech is often slurred or nasal.

After 3 yr of age, autonomic crises begin, usually with attacks of cyclic vomiting lasting 24-72 hr or even several days. Retching and vomiting occur every 15-20 min and are associated with hypertension, profuse sweating, blotching of the skin, apprehension, and irritability. Prominent gastric distention can occur, causing abdominal pain and even respiratory distress. Hematemesis can complicate pernicious vomiting. Activation of dopamine receptors may explain the cyclic vomiting and retching.

Allgrove syndrome (triple A syndrome) is a clinical variant, involving early-onset alacrima, feeding difficulties and achalasia, autonomic dysfunction with orthostatic hypotension, altered heart rate variability, hyperreflexia, ataxia, muscle weakness, sensorimotor polyneuropathy, and adrenocorticotropic hormone–resistant adrenal insufficiency (develops in 1st decade). The gene *AAAS* (alacrima-achalasia-adrenal insufficiency neurologic disorder) is located on chromosome 12q13.

LABORATORY FINDINGS

Electrocardiography discloses prolonged corrected QT intervals with lack of appropriate shortening with exercise, a reflection of the aberration in autonomic regulation of cardiac conduction. Chest radiographs show atelectasis and pulmonary changes resembling cystic fibrosis. Urinary vanillylmandelic acid level is decreased, and the homovanillic acid level is increased. Plasma level of dopamine β-hydroxylase (the enzyme that converts dopamine to epinephrine) is diminished. Sural nerve biopsy shows a decreased number of unmyelinated fibers. Electroencephalography is useful for evaluating seizures.

DIAGNOSIS

Slow IV infusion of norepinephrine produces an exaggerated pressor response. The hypotensive response to infusion of methacholine is increased. Intradermal injection of 1 : 1,000 histamine phosphate fails to produce a normal axon flare, and local pain is absent or diminished.

Because the skin of a normal infant reacts more intensely to histamine, a 1 : 10,000 dilution should be used. Instillation of 2.5% methacholine into the conjunctival sac produces miosis in patients with familial dysautonomia and no detectable effect on a normal pupil; this is a nonspecific sign of parasympathetic denervation from any cause. Methacholine is applied to only 1 eye in this test, with the other eye serving as a control; the pupils are compared at 5 min intervals for 20 min. The combination of alacrima, absent fungiform papillae, decreased patellar reflexes, and an abnormal histamine test with Ashkenazi Jewish lineage is diagnostic. Because of variable expression and potential overlap with other HSANs, genetic testing should be used to confirm the diagnosis.

TREATMENT

Symptomatic treatment includes special attention to the respiratory and gastrointestinal systems to prevent aspiration and malnutrition, methylcellulose eyedrops or topical ocular lubricants to replace tears and prevent corneal ulceration, orthopedic management of scoliosis and joint problems, and appropriate anticonvulsants for epilepsy. Chlorpromazine is an effective antiemetic and may be given as rectal suppositories during autonomic crises; however, clonidine may be more effective. It also reduces apprehension and lowers the blood pressure. Diazepam has also been effective in some cases. Dehydration and electrolyte disturbances should be anticipated. A more specific and promising approach is the administration of carbidopa, an inhibitor of dopa-decarboxylase, particularly for the hyperemesis that is so prominent and disabling in many patients. Blockers of dopamine receptors are alternative drugs for cyclic vomiting. It is also useful for enuresis, another common complication, and augments tear production. Protection from injuries is important because of the lack of pain as a protective mechanism. Scoliosis often requires surgical treatment. Antiepileptic drugs may be required. A cardiac pacemaker may be required by some children. Blood pressure monitoring may be important in some cases. A promising genetic approach to treatment, which corrects the splicing defect, is the use of oral kinetin to regulate the expression of *IKBKAP* transcripts. Specific compounds identified from stem cells obtained from dysautonomia patients provide a potential therapy to rescue IKBKAP expression.

PROGNOSIS

Sixty percent of patients die in childhood before the age of 20 yr, usually of chronic pulmonary failure or aspiration. Treatment in a center familiar with the diverse complications greatly extends the life expectancy; some have survived to age 40 yr. Prevention of aspiration with fundoplication, gastrostomy, and tube feeding reduces the risk of aspiration. Newer measures to better control vasomotor stability and vomiting improve the quality of life, but whether they change longevity is not yet known.

Bibliography is available at Expert Consult.

615.2 Other Autonomic Neuropathies

Harvey B. Sarnat

CONGENITAL INSENSITIVITY TO PAIN AND ANHIDROSIS

Congenital insensitivity to pain and anhidrosis is an autosomal recessive disorder HSAN type IV (see Table 615-2). Onset is in infancy. Patients have episodes of extreme fevers related to warm environmental temperatures because they have absent or reduced sweating. Frequent burns and traumatic injuries result from apparent lack of pain perception. Poor healing of fractures occurs, as does osteomyelitis. Neonatal hypotonia improves with growth but learning problems may develop. Intelligence is normal. Nerve biopsy reveals an almost total absence of unmyelinated nerve fibers that convey impulses of pain, temperature, and autonomic functions. Some cases of hypomyelinating neuropathy manifest clinically as congenital insensitivity to pain (see Chapter 613.3). The sympathetic skin response as an electrophysiologic study is a reliable diagnostic test in cases associated with a mutation in the TrKA receptor for nerve growth factor.

REFLEX SYMPATHETIC DYSTROPHY

Reflex sympathetic dystrophy is a form of local causalgia, usually involving a hand or foot but not corresponding to the anatomic distribution of a peripheral nerve (see Chapter 168.2). A continuous burning pain and hyperesthesia are associated with vasomotor instability in the affected zone, resulting in increased skin temperature, erythema, and edema caused by vasodilation and hyperhidrosis. In the chronic state, atrophy of skin appendages, cool and clammy skin, and disuse atrophy of underlying muscle and bone occur. More than 1 extremity is occasionally involved. The pain is disabling and is exacerbated by the movement of an associated joint, although no objective signs of arthritis are seen; immobilization provides some relief. The most common preceding event is local trauma in the form of a contusion, laceration, sprain, or fracture that occurred days or weeks earlier.

Several theories of pathogenesis have been proposed to explain this phenomenon. The most widely accepted is reflexive overactivity of autonomic nerves in response to injury, and regional sympathetic blockade often affords temporary relief. Physiotherapy also is helpful. Some cases resolve spontaneously after weeks or months, but others continue to be symptomatic and require sympathectomy. A psychogenic component is suspected in some cases but is difficult to prove.

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Chapter 616

Guillain-Barré Syndrome

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Guillain-Barré syndrome is an autoimmune disorder often considered a postinfectious polyneuropathy involving mainly motor but also sensory and sometimes autonomic nerves. This syndrome affects people of all ages and is not hereditary. Most patients in the United States and Europe have a demyelinating neuropathy, but primarily axonal degeneration is documented in some cases, mainly in China, Mexico, Bangladesh, and Japan.

CLINICAL MANIFESTATIONS

The paralysis usually follows a nonspecific gastrointestinal or respiratory infection by approximately 10 days. The original infection might have caused only gastrointestinal (especially *Campylobacter jejuni,* but also *Helicobacter pylori*) or respiratory tract (especially *Mycoplasma pneumoniae*) symptoms. Consumption of undercooked poultry, unpasteurized milk, and contaminated water are the main sources of gastrointestinal infections. West Nile virus also can mimic Guillain-Barré–like syndrome, but more often it causes motor neuron disease similar to poliomyelitis. Guillain-Barré syndrome is reported following administration of vaccines against rabies, influenza, and poliomyelitis (oral) and following administration of conjugated meningococcal vaccine, particularly serogroup C. Additional infectious precursors of Guillain-Barré syndrome include mononucleosis, Lyme disease, cytomegalovirus, and *Haemophilus influenzae* (for the Miller-Fisher syndrome).

Initial symptoms include numbness and paresthesia, followed by weakness. There may be associated neck, back, buttock, and leg pain. Weakness usually begins in the lower extremities and progressively involves the trunk, the upper limbs, and, finally, the bulbar muscles, a pattern known as **Landry ascending paralysis.** Proximal and distal muscles are involved relatively symmetrically, but asymmetry is found in 9% of patients. The onset is gradual and progresses over days or weeks; the process plateaus in 1-28 days. Particularly in cases with an abrupt onset, tenderness on palpation and pain in muscles are common in the initial stages. Affected children are irritable. Weakness can progress to inability or refusal to walk and later to flaccid tetraplegia. Maximal severity of weakness is usually reached by 4 wk after onset. The differential diagnosis of acute weakness is noted in Table 607-3 (in Chapter 607) and of Guillain-Barré syndrome in Table 616-1.

Bulbar involvement occurs in about half of cases. Respiratory insufficiency can result. Dysphagia and facial weakness are often impending signs of respiratory failure. They interfere with eating and increase the risk of aspiration. The facial nerves may be involved. Some young patients exhibit symptoms of viral meningitis or meningoencephalitis. Extraocular muscle involvement is rare, but in an uncommon variant, oculomotor and other cranial neuropathies are severe early in the course.

Miller-Fisher syndrome (MFS) consists of acute external and occasionally internal ophthalmoplegia, ataxia, and areflexia. The 6th cranial nerve is most often involved in MFS. Papilledema may precede or follow MFS and suggests a diagnosis of pseudotumor; optic neuritis may also be noted. Although areflexia is seen in MFS, patients do not have significant lower extremity weakness compared with Guillain-Barré syndrome. Distal paresthesias are noted in MFS. Urinary incontinence or retention of urine is a complication in approximately 20% of cases but is usually transient. MFS overlaps with Bickerstaff brainstem encephalitis, which also shares many features with Guillain-Barré syndrome with lower motor neuron involvement.

Tendon reflexes in Guillain-Barré syndrome are lost, usually early in the course, but are sometimes preserved until later; areflexia is common but hyporeflexia may be seen; 10% may have normal reflexes. This variability can cause confusion when attempting early diagnosis. The **autonomic nervous system** is also involved in some cases. Lability of blood pressure and cardiac rate, postural hypotension, episodes of profound bradycardia, or tachycardia and occasional asystole occur. Cardiovascular monitoring is important. A few patients require insertion of a temporary venous cardiac pacemaker.

Subtypes of Guillain-Barré syndrome include an acute inflammatory demyelinating polyneuropathy and an acute motor axonal neuropathy; these are distinguished by nerve conduction studies, geography, and the pattern of antiganglioside antibodies (Table 616-2). Localized forms also occur and include a pattern of facial diplegia with paresthesias and a pattern of pharyngeal-cervical-brachial weakness.

Chronic inflammatory demyelinating polyradiculoneuropathies (CIDPs, sometimes called *chronic inflammatory relapsing polyneuritis* or *chronic unremitting polyradiculoneuropathy*) are chronic varieties of Guillain-Barré syndrome that recur intermittently, or do not improve, or progress slowly and relentlessly for periods of months to years. Approximately 7% of children with Guillain-Barré syndrome suffer an acute relapse. Patients are usually severely weak and can have a flaccid tetraplegia with or without bulbar and respiratory muscle involvement. Hyporeflexia or areflexia is almost universal. Motor deficits occur in 94% of cases, sensory paresthesias in 64%, and cranial nerve involvement in less than a third of patients. Autonomic and micturitional involvement is variable. Cerebrospinal fluid (CSF) shows no pleocytosis and protein is variably normal or mildly elevated. Nerve conduction

Table 616-1 Differential Diagnosis of Childhood Guillain-Barré Syndrome

SPINAL CORD LESIONS
Acute transverse myelitis
Epidural abscess
Tumors
Poliomyelitis (natural or live virus)
Enteroviruses
Hopkins syndrome
Vascular malformations
Cord infarction
Fibrocartilaginous embolism
Cord compression from vertebral subluxation related to congenital abnormalities or trauma
Acute disseminated encephalomyelitis
Bickerstaff brainstem encephalitis for Miller-Fisher syndrome
PERIPHERAL NEUROPATHIES
Toxic
• Vincristine
• Glue sniffing
• Heavy metal: gold, arsenic, lead, thallium
• Organophosphate pesticides
• Fluoroquinolones
Infections
• HIV
• Diphtheria
• Lyme disease
Inborn errors of metabolism
• Leigh disease
• Tangier disease
• Porphyria
Critical illness: polyneuropathy/myopathy
Vasculitis syndromes
Porphyria
Mitochondrial neurogastrointestinal encephalomyopathy
CD59 deficiency
NEUROMUSCULAR JUNCTION DISORDERS
Tick paralysis
Myasthenia gravis
Botulism
Hypercalcemia
Myopathies
Periodic paralyses
Dermatomyositis
Critical illness myopathy/polyneuropathy

From Agrawal S, Peake D, Whitehouse WP: Management of children with Guillain Barré syndrome, Arch Dis Child Educ Pract Ed *92:161–168, 2007.*

Table 616-2 Classification of Guillain-Barré Syndrome and Related Disorders and Typical Antiganglioside Antibodies By Pathology

DISORDER	ANTIBODIES
Acute inflammatory demyelinating polyradiculoneuropathy	Unknown
Acute motor and sensory axonal neuropathy	GM_1, GM_{1b}, GD_{1a}
Acute motor axonal neuropathy	GM_1, GM_{1b}, GD_{1a}, GalNac-GD_{1a}
Acute sensory neuronopathy	GD_{1b}
ACUTE PANDYSAUTONOMIA	
Regional Variants	
Fisher syndrome	GQ_{1b}, GT_{1a}
Oropharyngeal	GT_{1a}
Overlap	
Fisher/Guillain-Barré overlap syndrome	GQ_{1b}, GM_1, GM_{1b}, GD_{1a}, GalNac-GD_{1a}

From Hughes RAC: Treatment of Guillain-Barré syndrome with corticosteroids: lack of benefit? Lancet *363:181–182, 2004.*

velocity studies and sural nerve biopsy are abnormal. Polymorphic nucleotide repeats in the *SH2D2A* gene are associated with a predisposition to CIDP.

Congenital Guillain-Barré syndrome is described rarely, manifesting as generalized hypotonia, weakness, and areflexia in an affected neonate, fulfilling all electrophysiologic and CSF criteria and in the absence of maternal neuromuscular disease. Treatment might not be required, and there is gradual improvement over the 1st few mo and no evidence of residual disease by 1 yr of age. In 1 case, the mother had ulcerative colitis treated with prednisone and mesalamine from the 7th mo of gestation until delivery at term.

LABORATORY FINDINGS AND DIAGNOSIS

CSF studies are essential for diagnosis. The CSF protein is elevated to more than twice the upper limit of normal, the glucose level is normal, and there is no pleocytosis. Fewer than 10 white blood cells/mm^3 may be found. The results of bacterial cultures are negative, and viral cultures rarely isolate specific viruses. The dissociation between high CSF protein and a lack of cellular response in a patient with an acute or subacute polyneuropathy is diagnostic of Guillain-Barré syndrome. MRI of the spinal cord may be indicated to rule out disorders listed in Table 616-1. MRI findings include thickening of the cauda equina and intrathecal nerve roots with gadolinium enhancement. These finds are fairly sensitive and are present in >90% of patients (Fig. 616-1). Imaging in CIDP is similar but demonstrates greater enhancement of spinal nerve roots (Fig. 616-2).

Motor nerve conduction velocities are greatly reduced, and sensory nerve conduction time is often slow. Electromyography shows evidence of acute denervation of muscle. *Serum creatine kinase level may be mildly elevated or normal.* Antiganglioside antibodies, mainly against GM_1 and GD_1, are sometimes elevated in the serum in Guillain-Barré syndrome, particularly in cases with primarily axonal rather than demyelinating neuropathy, and suggest that they might play a role in disease propagation and/or recovery in some cases (see Table 616-1). Muscle biopsy is not usually required for diagnosis; specimens appear normal in early stages and show evidence of denervation atrophy in chronic stages. Sural nerve biopsy tissue shows segmental demyelination, focal inflammation, and wallerian degeneration but also is usually not required for diagnosis.

Serologic testing for *Campylobacter* and *Helicobacter* infections helps establish the cause if results are positive but does not alter the course of treatment. Results of stool cultures are rarely positive because

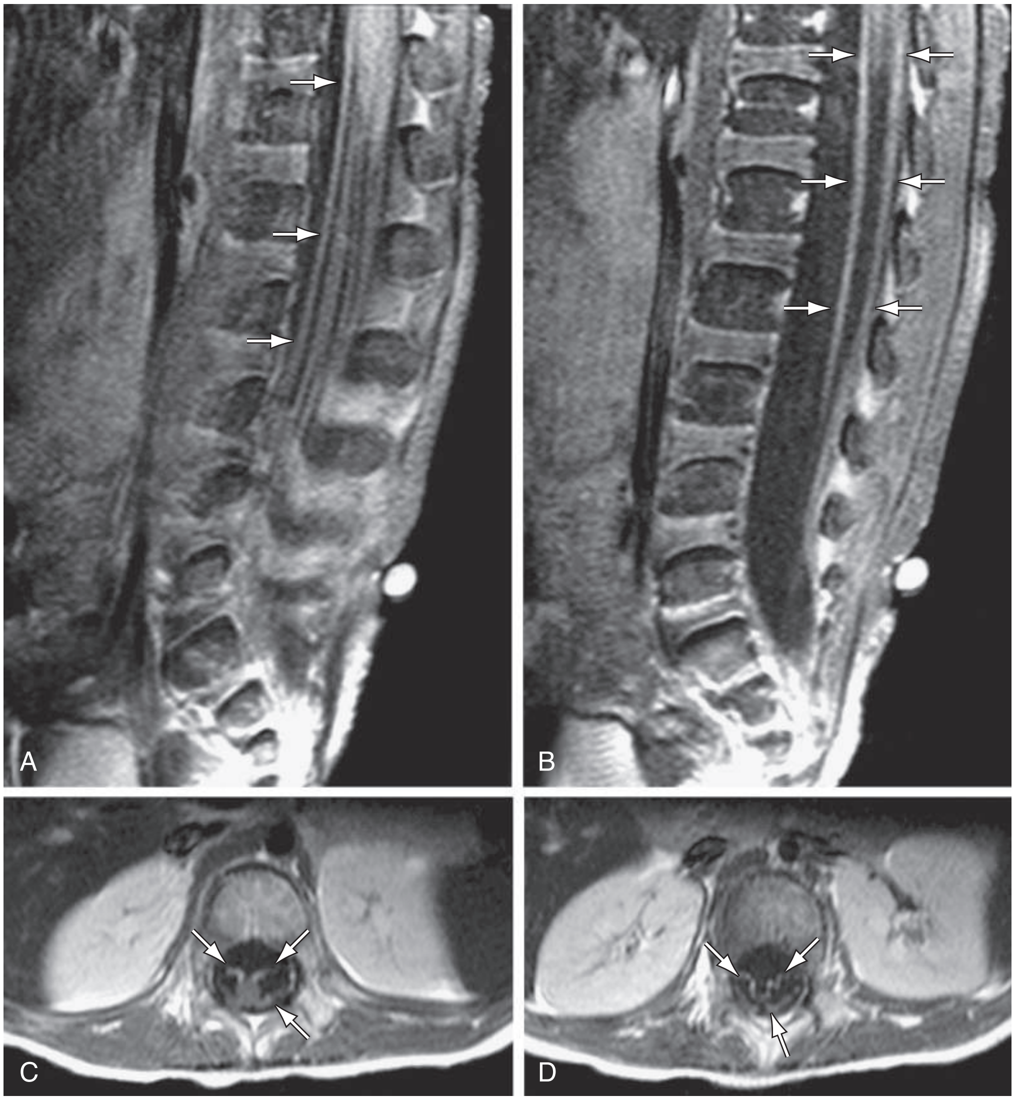

Figure 616-1 **Guillain-Barré syndrome.** Sagittal off-midline **(A)** and midline **(B)** postgadolinium T1-weighted fat-saturated images through the lumbar spine of a patient who could not ambulate. **C** and **D,** Axial postcontrast T1-weighted images through the conus medullaris and proximal lumbar nerve roots, respectively. The images show extensive contrast enhancement of nerve roots (*arrows* in **A-D**), in keeping with changes of Guillain-Barré. *(From Slovis TL, editor:* Caffey's pediatric diagnostic imaging*, ed 11, Philadelphia, 2008, Mosby, Fig. 65-6.)*

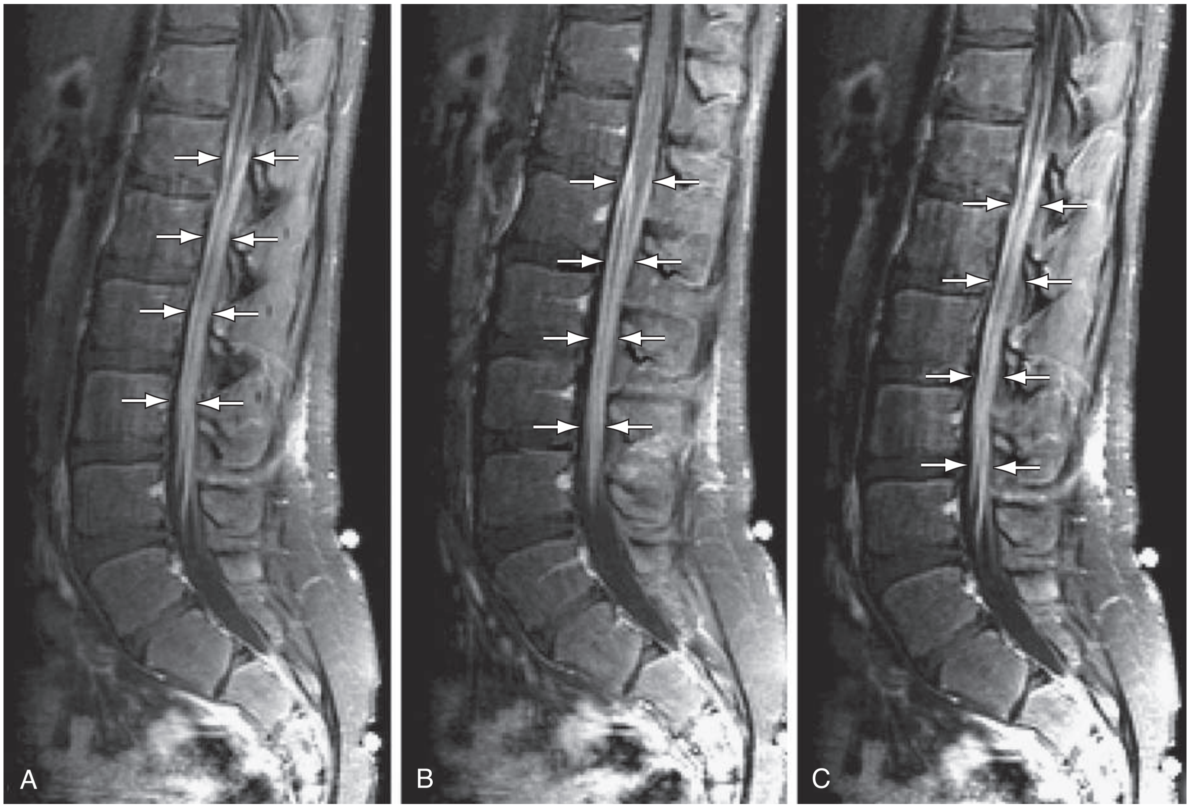

Figure 616-2 Chronic inflammatory demyelinating polyneuropathy (CIDP) in a 13 yr old boy with peripheral neuropathy and gait disturbance. Sagittal fat-saturated T1-weighted images off the midline to the right **(A),** at the midline **(B),** and off the midline to the left **(C).** *(From Slovis TL, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, Fig. 65-7.)*

the infection is self-limited and only occurs for about 3 days, and the neuropathy follows the acute gastroenteritis.

TREATMENT

Patients in early stages of this acute disease should be admitted to the hospital for observation because the ascending paralysis can rapidly involve respiratory muscles during the next 24 hr. Respiratory effort (negative inspiratory force, spirometry) **must** be monitored to prevent respiratory failure and respiratory arrest. Patients with slow progression might simply be observed for stabilization and spontaneous remission without treatment. Rapidly progressive ascending paralysis is treated with intravenous immunoglobulin (IVIG), administered for 2, 3, or 5 days. A commonly recommended protocol is IVIG 0.4 g/kg/day for 5 consecutive days, but some studies suggest that larger doses are more effective (1 g/kg/day for 2 consecutive days) and related to improved outcome. Plasmapheresis and/or immunosuppressive drugs are alternatives if IVIG is ineffective. Steroids are not effective. Supportive care, such as respiratory support, prevention of decubiti in children with flaccid tetraplegia, nutritional support, pain management, prevention of deep vein thrombosis, and treatment of secondary bacterial infections, is important.

CIDPs, whether relapsing-remitting or unremitting, also are treated with oral or pulsed steroids and IVIG. Subcutaneous immunoglobulin infusion may be an alternative to the intravenous route. Plasma exchange, sometimes requiring as many as 10 exchanges daily, is an alternative. Remission in these cases may be sustained, but relapses can occur within days, weeks, or even after many months; relapses usually respond to another course of plasmapheresis. Steroid and immunosuppressive drugs are another alternative, but their effectiveness is less predictable. High-dose pulsed methylprednisolone given intravenously is successful in some cases. The prognosis in chronic forms of the Guillain-Barré syndrome is more guarded than in the acute form, and many patients are left with major residual handicaps.

Even if *C. jejuni* infection is documented by stool culture or serologic tests, treatment of the infection is not necessary because it is self-limited, and the use of antibiotics does not alter the course of the polyneuropathy.

For the treatment of chronic neuropathic pain following Guillain-Barré syndrome, gabapentin is more effective than carbamazepine, and the requirement for fentanyl is reduced. But no pharmacologic treatments for neuropathic pain in this disease are wholly effective.

PROGNOSIS

The clinical course is usually benign, and spontaneous recovery begins within 2-3 wk. Most patients regain full muscular strength, although some are left with residual weakness. The tendon reflexes are usually the last function to recover. Improvement usually follows a gradient opposite the direction of involvement: bulbar function recovering first, and lower extremity weakness resolving last. Bulbar and respiratory muscle involvement can lead to death if the syndrome is not recognized and treated. Although prognosis is generally good and the majority of children recover completely, 3 clinical features are predictive of poor outcome with sequelae: cranial nerve involvement, intubation, and maximum disability at the time of presentation. The electrophysiologic features of conduction block are predictive of good outcome. Long-term follow-up studies of patients who recover from an attack of Guillain-Barré syndrome reveal that many do have some permanent axonal loss, with or without residual clinical signs of chronic neuropathy. Easy fatigue is one of the most common chronic symptoms, but it is not the rapid fatigability of muscles seen in myasthenia gravis. Most patients with the axonal form of Guillain-Barré syndrome had a slow recovery over the 1st 6 mo and could eventually walk, although some required years to recover. Electromyography and nerve conduction velocity electrophysiologic studies do not necessarily predict the long-term outcome.

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Chapter 617

Bell Palsy

Harvey B. Sarnat

Bell palsy is an acute unilateral peripheral facial nerve palsy that is not associated with other cranial neuropathies or brainstem dysfunction. It is a common disorder at all ages from infancy through adolescence and usually develops abruptly about 2 wk after a systemic viral infection. The preceding infection is caused by the herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, Lyme disease, mumps virus, *Toxocara*, *Rickettsia*, *Mycoplasma*, or HIV infection (Table 617-1). Ramsay Hunt syndrome (herpes zoster oticus) is associated with vesicles in the external auditory canal or auricle and an ipsilateral facial palsy. Active or reactivation of herpes simplex or varicella-zoster virus may be the most common cause of Bell palsy (Fig. 617-1). The disease is occasionally a postinfectious allergic or immune demyelinating facial neuritis. It also may be a focal toxic or inflammatory neuropathy and has been associated with ribavirin and interferon-α therapy for hepatitis C. Hereditary forms are rare, but it may be associated with other genetic polyneuropathies. Rarely, Bell palsy occurs in the context of hypertension or juvenile type 1 diabetes mellitus, most often associated with concomitant viral infections.

Table 617-1 Etiologies of Acute Peripheral Facial Palsy

COMMON	OTHER LESS-COMMON CONDITIONS
Idiopathic Herpes simplex virus type 1* Varicella-zoster virus* LESS-COMMON INFECTIONS Otitis media ± cholesteatoma Lyme disease Epstein-Barr virus Cytomegalovirus Mumps Human herpesvirus 6 Intranasal influenza vaccine *Mycoplasma* *Toxocara* *Rickettsia* AIDS/HIV	Trauma Schwannoma of facial nerve Infiltrative tumor Aneurysm or vascular malformation Anomalous narrowing of facial canal Hypertension Sjögren syndrome Diabetes mellitus, type 1 Guillain-Barré syndrome Sarcoidosis Melkersson-Rosenthal syndrome† Ribavirin Interferon

*Implicated in idiopathic Bell palsy.
†Noncaseating granulomas with facial (lips, eyelids) edema, recurrent alternating facial paralysis, family history, migraines, or headaches.

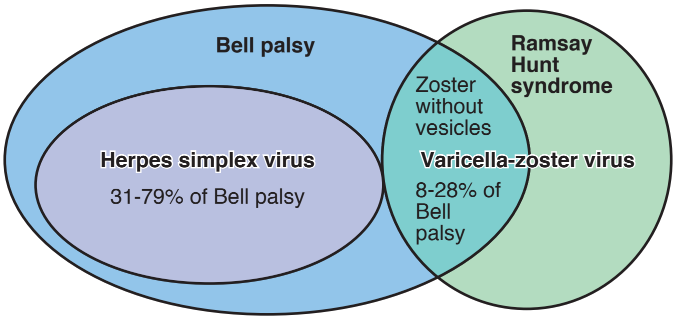

Figure 617-1 Involvement of herpes simplex and varicella-zoster viruses in acute facial palsy. *(Modified from Hato N, Murakami S, Gyo K: Steroid and antiviral treatment for Bell's palsy,* Lancet *371:1818–1820, 2008.)*

CLINICAL MANIFESTATIONS

The upper and lower portions of the face are paretic, and the corner of the mouth droops. Patients are unable to close the eye on the involved side and can develop an exposure keratitis at night. Taste on the anterior two thirds of the tongue is lost on the involved side in approximately 50% of cases; this finding helps to establish the anatomic limits of the lesion as being proximal or distal to the chorda tympani branch of the facial nerve. Numbness and paresthesias do not usually occur, but ipsilateral numbness of the face is reported in a few cases and probably is caused by viral (especially herpes) or postviral immunologic impairment of the trigeminal and the facial nerves. Pain behind the ear may precede weakness. Acute hearing loss may occur in Bell palsy associated with *Rickettsia* infection. Several grading systems have been devised for Bell palsy, including the Sunnybrook, House-Brackmann, and Yanagihara systems.

IMAGING THE FACIAL NERVE AND ITS BONY CANAL

Modern high-resolution MRI, particularly with multiplanar reconstruction, is able to visualize the facial nerve within its canal and determine whether there are bony anomalies, compressive aneurysms, vascular malformations, or nerve sheath or infiltrative tumors that might explain a palsy anatomically. The two sides can be compared and, in particular, the labyrinthine segment within the petrous bone, which is the narrowest site in the facial nerve canal, can be examined. Ultrasound of the facial nerve also has been used, in part as a predictor of functional outcome in Bell palsy. More recently, diffusion tensor tractography enables a tridimensional display of facial nerve axons.

TREATMENT

Oral prednisone (1 mg/kg/day for 1 wk, followed by a 1 wk taper) started within the 1st 3-5 days results in improved outcome and is a traditional treatment, its efficacy confirmed in a recent long-term prospective study in the United Kingdom. Because of the recovery of herpes simplex virus in the neural fluid of the 7th nerve, some also recommend adding oral acyclovir or valacyclovir to the prednisone therapy. Alone, antiviral agents are not effective in reducing adverse sequelae (synkinesis, autonomic dysfunction), but added to prednisone may be associated with an additional small benefit. If a specific infection can be identified as a predisposing cause, specific antiviral or antibacterial treatment is more justified. Surgical decompression of the facial canal, theoretically to provide more space for the swollen facial nerve, is not of value unless imaging provides evidence of nerve compression or an anatomic lesion. Both high- and low-level laser therapy has been used with good results in some cases as a form of physiotherapy. Traditional physiotherapy to the facial muscles is recommended in some chronic cases with poor recovery, but the efficacy of this treatment is uncertain. Protection of the cornea with methylcellulose eyedrops or an ocular lubricant is especially important at night. Botulinum toxin has been applied in adults to the contralateral normal facial muscles for cosmetic purposes to minimize the apparent asymmetry or to treat chronic unilateral ptosis, but this has little application in pediatric patients.

PROGNOSIS

The prognosis for functional recovery is excellent. More than 85% of patients recover spontaneously with no residual facial weakness. Another 10% have mild facial weakness as a sequela, often perceived only as a mild facial asymmetry, and only 5% are left with permanent severe facial weakness. In patients who do not recover within a few weeks (chronic), electrophysiologic examination of the facial nerve helps to determine the degree of neuropathy and regeneration. In chronic cases, other causes of facial neuropathy should be considered, including facial nerve tumors such as schwannomas and neurofibromas, infiltration of the facial nerve by leukemic cells or by a rhabdomyosarcoma of the middle ear, brainstem infarcts or tumors, and traumatic injury of the facial nerve.

Nerve regrowth may be misdirected and result in **synkinesis**, where activation of one muscle group may produce activation of another

inappropriate muscle group; blinking may result in mouth twitching, smiling may cause eye blinking, and lacrimation (crocodile tears) may occur while eating.

FACIAL PALSY AT BIRTH

Facial palsy at birth is usually a compression neuropathy from forceps application during delivery and recovers spontaneously in a few days or weeks in most cases. **Congenital absence of the depressor angularis oris muscle** causes facial asymmetry, especially when an affected infant cries, and is often associated with other congenital anomalies, especially of the heart. It is not a facial nerve lesion but is a cosmetic defect that does not interfere with feeding. Infants with **Möbius syndrome** can have bilateral or, less commonly, unilateral facial palsy; this syndrome is usually caused by symmetric calcified infarcts in the tegmentum of the pons and medulla oblongata during midgestation or late fetal life, although it rarely is a developmental anomaly of the brainstem.

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Disorders of the Eye

PART XXIX

Chapter 618

Growth and Development

Scott E. Olitsky, Denise Hug, Laura S. Plummer, Erin D. Stahl, Michelle M. Ariss, and Timothy P. Lindquist

The eye of a normal full-term infant at birth is approximately 65% of adult size. Postnatal growth is maximal during the 1st yr, proceeds at a rapid, but decelerating rate until the 3rd yr, and continues at a slower rate thereafter until puberty, after which little change occurs. The anterior structures of the eye are relatively large at birth but thereafter grow proportionately less than the posterior structures. This results in a progressive change in the shape of the globe such that it becomes more spherical.

In an infant, the sclera is thin and translucent, with a bluish tinge. The cornea is relatively large in newborns (averaging 10 mm) and attains adult size (nearly 12 mm) by the age of 2 yr or earlier. Its curvature tends to flatten with age, resulting in a progressive change in the refractive properties of the eye. A normal cornea is perfectly clear. In infants born prematurely, however, the cornea may have a transient opalescent haze. The anterior chamber in a newborn appears shallow, and the angle structures, important in the maintenance of normal intraocular pressure, must undergo further differentiation after birth. The iris, typically light blue or gray at birth in white individuals, undergoes progressive change of color as the pigmentation of the stroma increases in the 1st 6 mo of life. The pupils of a newborn infant tend to be small and are often difficult to dilate. This is the result of an immature iris dilator muscle. Remnants of the **pupillary membrane** (anterior vascular capsule) are often evident on ophthalmoscopic examination, appearing as cobweb-like lines crossing the pupillary aperture, especially in preterm infants.

The lens of a newborn infant is more spherical than that of an adult; its greater refractive power helps to compensate for the relative shortness of the young eye. The lens continues to grow throughout life; new fibers added to the periphery continually push older fibers toward the center of the lens. With age, the lens becomes progressively denser and more resistant to change of shape during accommodation.

The fundus of a newborn's eye is less pigmented than that of an adult; the choroidal vascular pattern is highly visible, and the retinal pigment pattern often has a fine peppery or mottled appearance. In some darkly pigmented infants, the fundus has a gray or opalescent sheen. In a newborn, the macular landmarks, particularly the foveal light reflex, are less-well defined and may not be readily apparent. The peripheral retina appears pale or grayish, and the peripheral retinal vasculature is immature, especially in premature infants. The optic nerve head color varies from pink to slightly pale, sometimes grayish. Within 4-6 mo, the appearance of the fundus approximates that of the mature eye.

Superficial retinal hemorrhages may be observed in many newborn infants. These are usually absorbed promptly and rarely leave any permanent effect. The majority of birth-related **retinal hemorrhages** resolve within 2 wk, with complete resolution of all such hemorrhages within 4-6 wk of birth. Conjunctival hemorrhages also may occur at birth and are resorbed spontaneously without consequence.

Remnants of the **primitive hyaloid vascular** system may also be seen as small tufts or wormlike structures projecting from the disc (Bergmeister papilla) or as a fine strand traversing the vitreous; in some cases, only a small dot (Mittendorf dot) remains on the posterior aspect of the lens capsule.

An infant's eye is somewhat hyperopic **(farsighted).** The general trend is for hyperopia to increase from birth until age 7 yr. Thereafter, the level of hyperopia tends to decrease rapidly until age 14 yr. Elimination of the hyperopic state may occur during this time. If the process continues, myopia (nearsightedness) develops. A slower continuation of the decrease in hyperopia, or increase in myopia, continues into the 3rd decade of life. The refractive state at any time in life depends on the net effect of many factors: the size of the eye, the state of the lens, and the curvature of the cornea.

Newborn infants tend to keep their eyes closed much of the time, but normal newborns can see, respond to changes in illumination, and fixate points of contrast. The visual acuity in newborns is estimated to be approximately 20/400. This poor vision is a result of the immature, multilayered foveal anatomy. Retinal development continues postnatally, maturing completely during the 1st few yr of life. One of the earliest responses to a formed visual stimulus is an infant's regard for the mother's face, evident especially during feeding. By 2 wk of age, an infant shows more sustained interest in large objects, and by 8-10 wk of age, a normal infant can follow an object through an arc of 180 degrees. The acuity improves rapidly and may reach 20/30-20/20 by the age of 2-3 yr.

Many normal infants may have imperfect coordination of the eye movements and alignment during the early days and weeks, but proper coordination should be achieved by 3-6 mo, usually sooner. Persistent deviation of an eye in an infant at 6 mo of age requires evaluation.

Tears often are not present with crying until after 1-3 mo. Preterm infants have reduced reflex and basal tear secretion, which may allow topically applied medications to become concentrated and lead to rapid drying of their corneas.

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Chapter 619

Examination of the Eye

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The eye exam is a routine part of the pediatric wellness evaluation, which begins in the newborn period. The primary care physician plays a critical role in the detection of both obvious and insidious, asymptomatic eye diseases. School and community screening programs can also be effective in identifying problems at an early age. The American Academy of Ophthalmology recommends preschool vision screening as a means of reducing preventable visual loss (Table 619-1). The screening process begins with the pediatrician during well child visits. Referrals to an ophthalmologist should be made when a significant ocular abnormality or visual acuity deficit is suspected. An

Table 619-1 Vision Screening Guidelines

FUNCTION	RECOMMENDED TESTS	REFERRAL CRITERIA	COMMENTS
AGES 3-5 YR			
Distance visual acuity	Snellen letters Snellen numbers Tumbling E test HOTV test	<4 of 6 correct on 20-ft line with either eye tested at 10 ft monocularly (i.e., <10/20 or 20/40), or Two-line difference between eyes, even within the passing range (i.e., 10/12.5 and 10/20 or 20/25 and 20/40)	Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used; in general, the tumbling E or the HOTV test should be used for ages 3-5 yr and Snellen letters or numbers for ages 6 yr and older.
	Picture tests -Allen figures -Lea symbols		Testing distance of 3 m (10 ft) is recommended for all visual acuity tests. A line of figures is preferred over a single figure. The nontested eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to eye; the examiner must ensure that it is not possible to peek with the nontested eye.
Ocular alignment	Cross cover test at 3 m (10 ft) or Random dot E stereo test at 40 cm (630 sec of arc)	Any eye movement <4 of 6 correct	
	Simultaneous red reflex test (Bruckner test)	Any asymmetry of pupil color, size, brightness	Direct ophthalmoscope used to view both red reflexes simultaneously in a darkened room from 2-3 ft away; detects asymmetric refractive errors as well.
Ocular media clarity (cataracts, tumors, etc.)	Red reflex	White pupil, dark spots, absent reflex	Direct ophthalmoscope, darkened room. View eyes separately at 12-18 inches; white reflex indicates possible retinoblastoma.
AGES 6 YR AND OLDER			
Distance visual acuity	Snellen letters Snellen numbers Tumbling E test HOTV test	<4 of 6 correct on 4.5 m (15 ft) line with either eye tested at 3 m (10 ft) monocularly (i.e., <10/15 or 20/30)	Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used; in general, the tumbling E or the HOTV test should be used for ages 3-5 yr and Snellen letters or numbers for ages 6 yr and older.
	Picture tests -Allen figures -Lea symbols	Two-line difference between eyes, even within the passing range (i.e., 10/10 and 10/15 or 20/20 and 20/30)	Testing distance of 3 m (10 ft) is recommended for all visual acuity tests. A line of figures is preferred over a single figure. The nontested eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to the eye; the examiner must ensure that it is not possible to peek with the nontested eye.
Ocular alignment	Cross cover test at 3 m (10 ft) or Random dot E stereo test at 40 cm (630 sec of arc)	Any eye movement <4 of 6 correct	

ophthalmologist should also examine high-risk children, such as those with a family history of eye disease, or various systemic or genetic disorders, such as Down syndrome.

The basic eye exam, whether performed by a pediatrician or an ophthalmologist, must include: visual acuity and visual field testing, assessment of pupils, ocular motility and alignment, a general external/facial examination, and finally, examination of the media and fundus via ophthalmoscopy. When indicated, biomicroscopy (slit-lamp examination), cycloplegic refraction, and tonometry are performed by an ophthalmologist. Special diagnostic procedures, such as ultrasound, fluorescein angiography, electroretinography, or visual evoked response testing, are also indicated for specific conditions.

VISUAL ACUITY

There are various means of assessing visual acuity in the pediatric population. A child's age and ability to cooperate, as well as clinician preference, all factor in deciding which test to use. The most common visual acuity test in infants is an assessment of their ability to fixate and follow a target. If appropriate targets are used, this response can be demonstrated by approximately 6 wk of age.

The test begins by seating the child comfortably in the caretaker's lap. The object of visual interest, usually a bright-colored toy, or target with lights, is slowly moved to the right and to the left. The examiner observes whether the infant's eyes turn toward the object and follow its movements. The examiner can use a thumb or palm of the hand to

occlude one of the infant's eyes, in order to test each eye separately. Although a sound-producing object might compromise the purity of the visual stimulus, in practice, toys that squeak or rattle heighten an infant's awareness and interest in the test.

The human face is a better target than test objects. The examiner can exploit this by moving his or her face slowly in front of the infant's face. If the appropriate following movements are not elicited, the test should be repeated with the caretaker's face as the test stimulus. It should be remembered that even children with poor vision can follow a large object without apparent difficulty, especially if only 1 eye is affected.

An objective measurement of visual acuity is usually possible when children reach the age of 2.5-3 yr. Children this age are tested using a schematic picture or other illiterate eye chart. Examples include Allen or Lea symbols and tumbling E. Each eye should be tested separately. It is essential to prevent peeking. The examiner should hold the occluder in place and observe the child throughout the test. The child should be reassured and encouraged throughout the test as many children are intimidated by the process and fear a "bad grade" or punishment for errors.

The tumbling **E test,** in which the child indicates which direction the E is facing, is the most widely used visual acuity test for preschool children. Right–left presentations are more confusing than up–down presentations. With pretest practice, the test can be performed by most children ages 3-4 yr.

An adult-type **Snellen acuity chart** can be used at 5-6 yr of age if the child knows letters. A visual acuity of 20/40 is generally accepted as normal for 3 yr old children. At 4 yr of age, 20/30 is acceptable. By 5 or 6 yr of age, most children attain 20/20 vision.

Optokinetic nystagmus (the response to a sequence of moving targets; "railroad" nystagmus) can also be used to assess vision; this can be calibrated by targets of various sizes (stripes or dots) or by a rotating drum (known as an OKN drum) at specified distances.

The visual evoked response, an electrophysiologic method of evaluating the response to light and special visual stimuli, such as calibrated stripes or a checkerboard pattern, can also be used to study visual function in selected cases.

Preferential looking tests are used for evaluating vision in infants and children who cannot respond verbally to standard acuity tests. This is a behavioral technique based on the observation that, given a choice, an infant prefers to look at patterned rather than unpatterned stimuli. Because these tests require the presence of a skilled examiner, their use is often limited to research protocols involving preverbal children.

VISUAL FIELD ASSESSMENT

Like visual acuity testing, visual field assessment must be geared to a child's age and abilities. Formal visual field examination (perimetry and scotometry) can often be accomplished in school-age children. In younger children and in the pediatrician's office, the examiner must often rely on confrontation techniques and finger counting in quadrants of the visual field. In many such children, only testing by attraction can be accomplished; the examiner observes a child's response to familiar objects brought into each of the 4 quadrants of the visual field of each eye in turn. The child's bottle, a favorite toy, and lollipops are particularly effective attention-getting items. These gross methods can often detect diagnostically significant field changes such as the bitemporal hemianopia of a chiasmal lesion or the homonymous hemianopia of a cerebral lesion.

COLOR VISION TESTING

Color vision testing can be accomplished when a child is able to name or trace the test symbols, which include numbers, shapes, or other symbols. The common color vision testing tools include Ishihara color plates or Hardy Rand Littler. Color vision testing is not frequently necessary in young children; however, parents may request testing, particularly if their child seems to be slow in learning colors or if there is a family history of color vision deficiency. It is important to keep in mind, and reassure parents that "color-deficient" children do not misname colors, and that true "color blindness" is very rare and not compatible with normal vision. Defective color vision is common in male patients but rare in females, as the gene is transmitted in an X-linked manner. Achromatopsia, which may be encountered occasionally, is a condition of complete color blindness associated with subnormal visual acuity, nystagmus, and photophobia.

Color discrimination is a means of assessing the intensity of a hue, typically red. Patients describe the intensity of red depicted from the test object. A change in color discrimination (often referred to as color "desaturation") can be a sign of optic nerve or retinal disease.

PUPILLARY EXAMINATION

The pupil exam includes evaluations of both the direct and consensual responses to light, accommodation (a near target), and reduced illumination, noting the size and symmetry of the pupils under each testing condition. Special care must be taken to differentiate the reaction to light from the reaction to near gaze. A child's natural tendency is to look directly at the approaching light, inducing the near gaze reflex when one is attempting to test only the reaction to light; accordingly, every effort must be made to control fixation on a distance target. The swinging flashlight test is especially useful for detecting unilateral or asymmetric prechiasmatic afferent defects in children (see "Marcus Gunn Pupil" section in Chapter 622).

OCULAR MOTILITY

Ocular motility testing assesses alignment and extraocular muscle function. This is tested by having a child follow an object in various positions of gaze, known as the cardinal positions. The cardinal positions are those in which one extraocular muscle predominantly functions and a deficit can be identified if present. Movements of each eye individually (ductions) and of the 2 eyes together (versions, conjugate movements, and convergence) are assessed.

Alignment can be assessed in 2 ways. The first is symmetry of the corneal light reflexes. The second method is to occlude each eye in an alternating fashion and observe for a change in fixation of the viewing eye (see discussion on cover testing for strabismus in Chapter 623).

BINOCULAR VISION

Attaining binocular visual function is one of the primary goals of amblyopia therapy and ocular realignment surgery. Just as there are multiple methods for assessing visual acuity, there are various means of testing the level of binocular vision. The Titmus test is probably the most frequently used test; a series of three-dimensional images are shown to the child while he or she wears a set of polarized glasses. The level of difficulty with which these images can be detected correlates with the degree of binocular vision present.

EXTERNAL EXAMINATION

The external examination begins with general inspection, in good illumination of the face, paying close attention to the orbits and lids, noting the size, shape, and symmetry of the orbits; position and movement of the lids; and position and symmetry of the globes. Viewing the eyes and lids in such a manner aids in detecting orbital asymmetry, lid masses, proptosis **(exophthalmos),** and abnormal pulsations. Palpation is also important in detecting orbital and lid masses. Orbital dermoids and capillary hemangiomas are frequently evaluated during the external examination.

The lacrimal system is assessed by looking for evidence of tear deficiency, overflow of tears **(epiphora),** erythema, and swelling in the region of the tear sac or gland. The lacrimal gland is located in the superotemporal orbit, beneath the eyebrow. The tear drain system, which includes the lacrimal sac, is located within the medial wall of the orbit, where the eyelids meet the bridge of the nose. The sac is massaged to check for reflux when obstruction is suspected. The presence and position of the puncta are also checked.

The lids and conjunctivae are specifically examined for focal lesions, foreign bodies, and inflammatory signs; loss and misdirection of lashes should also be noted. When necessary, the lids can be everted in the following manner: (1) instruct the patient to look down; (2) grasp the lashes of the patient's upper lid between the thumb and index finger of 1 hand; (3) place a probe, a cotton-tipped applicator, or the thumb of

the other hand at the upper margin of the tarsal plate; and (4) pull the lid down and outward and evert it over the probe, using the instrument as a fulcrum. Foreign bodies commonly lodge in the concavity just above the lid margin and are exposed only by fully everting the lid.

The anterior segment of the eye is then evaluated with oblique focal illumination, noting the luster and clarity of the cornea, the depth and clarity of the anterior chamber, and the features of the iris. Transillumination of the anterior segment aids in detecting opacities and in demonstrating atrophy or hypopigmentation of the iris; these latter signs are important when ocular albinism is suspected. When necessary, fluorescein dye can be used to aid in diagnosing abrasions, ulcerations, and foreign bodies.

BIOMICROSCOPY (SLIT-LAMP EXAMINATION)

The slit-lamp exam provides a highly magnified view of the various structures of the eye and an optical section through the media of the eye—the cornea, aqueous humor, lens, and vitreous. Lesions can be identified and localized according to their depth within the eye; the resolution is sufficient to detect individual inflammatory cells in the aqueous and anterior vitreous. With the addition of special lenses and prisms, the angle of the anterior chamber and components of the fundus also can be examined with a slit lamp. Biomicroscopy is often crucial in trauma and in examining for iritis. It is also helpful in diagnosing many metabolic and genetic diseases of childhood.

FUNDUS EXAMINATION (OPHTHALMOSCOPY)

The ideal setting for ophthalmoscopy is with a well-dilated pupil, unless there are neurologic or other contraindications. Tropicamide (Mydriacyl) 0.5-1% and phenylephrine (Neo-Synephrine) 2.5% are recommended as mydriatics of short duration. These are safe for most children, but the possibility of adverse systemic effects must be recognized. For very small infants, especially 6 mo or younger, more dilute preparations may be advisable. Beginning with posterior landmarks, the disc and the macula, the 4 quadrants are systematically examined by following each of the major vessel groups to the periphery. Retinal hemorrhages, vascular anomalies, and posterior uveitis are often appreciated during this segment of the examination. Color, cup, and contour of the optic nerve should be noted as well. Abnormalities are frequently followed with further imaging studies such as a CT or MRI or diagnostic testing such as automated perimetry (see "Visual Field Assessment" above). The midperipheral retina can be seen if a child is directed to look up and down and to the right and left. Even with care, only a limited fraction of the fundus can be seen with a direct or handheld ophthalmoscope. For examination of the far periphery, an indirect ophthalmoscope is used, and full dilation of the pupil is essential.

REFRACTION

Refraction determines the focusing power of the eye: the degree of nearsightedness (hypermetropia), farsightedness (myopia), or astigmatism. Retinoscopy provides an objective determination of the amount of correction needed and can be performed at any age, including the newborn period. In young children, it is best done with cycloplegia using cyclopentolate 1% eyedrops in an ophthalmologist's office. Subjective refinement of refraction involves asking patients for preferences in the strength and axis of corrective lenses; it can be accomplished in many school-age children. Refraction and determination of visual acuity with appropriate corrective lenses in place are essential steps in deciding whether a patient has a visual defect or amblyopia. Photoscreening cameras aid ancillary medical personnel in screening for refractive errors in preverbal children. The accuracy and practical usefulness of these devices are still being investigated.

TONOMETRY

Tonometry is the method of assessing intraocular pressure. It may be performed with a portable, stand-alone instrument or by the applanation method during slit-lamp examination. Alternative methods are pneumatic, electronic, or rebound tonometry. When accurate measurement of the pressure is necessary in a child who cannot cooperate, it may be performed with sedation or general anesthesia. A gross estimate of pressure can be made by palpating the globe with the index fingers placed side by side on the upper lid above the tarsal plate.

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Chapter 620

Abnormalities of Refraction and Accommodation

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Emmetropia is the state in which parallel rays of light come to focus on the retina with the eye at rest (nonaccommodating). Even though such an ideal optical state is common, the opposite condition, ametropia, often occurs. Three principal types of **ametropia** exist: **hyperopia** (farsightedness), **myopia** (nearsightedness), and **astigmatism** (Fig. 620-1). The majority of children are physiologically hyperopic at birth. Yet a significant number, especially those born prematurely, are myopic and often have some degree of astigmatism. With growth the refractive state tends to change and should be evaluated periodically.

Measurement of the refractive state of the eye (refraction) can be accomplished both objectively and subjectively. The objective method involves directing a beam of light from a retinoscope onto a patient's retina. Using loose lenses of various strengths held in front of the eye, the retinal light reflex (viewed through the pupil) can be neutralized, yielding a precise refraction. An objective refraction is obtainable at any age because it requires no response from the patient. In infants and children, it is generally more accurate to perform a refraction after instillation of eyedrops that produce mydriasis (dilation of the pupil) and cycloplegia (paralysis of accommodation); those used most commonly are tropicamide (Mydriacyl), cyclopentolate (Cyclogyl), and atropine sulfate. A subjective refraction involves placing lenses in front of the eye and having the patient report which lenses provide the clearest image of the letters on a chart. This method is dependent on a patient's ability to discriminate and communicate, but can be used for some children and can be helpful in determining the best refractive correction for children who are developmentally capable.

HYPEROPIA

If parallel rays of light come to focus posterior to the retina with the eye in a neutral state, hyperopia or farsightedness exists. This may result from a shorter anteroposterior diameter of the eye or a lower refractive power of the cornea or lens.

In hyperopia, the additional refracting power needed to bring objects into focus at distance and near is generated through the accommodative mechanism. If the accommodative effort required for focus is within that child's accommodative amplitude, the vision is clear. In high degrees of hyperopia requiring greater accommodative effort, vision may be blurred, and the child may complain of eyestrain, headaches, or fatigue. Squinting, eye rubbing, and lack of interest in reading are frequent manifestations. If the induced discomfort is great enough, a child may not make an effort to focus and may develop bilateral amblyopia (ametropic amblyopia). Esotropia may also be associated (see discussion on convergent strabismus, accommodative esotropia in Chapter 623). Convex lenses (spectacles or contact lenses) of sufficient

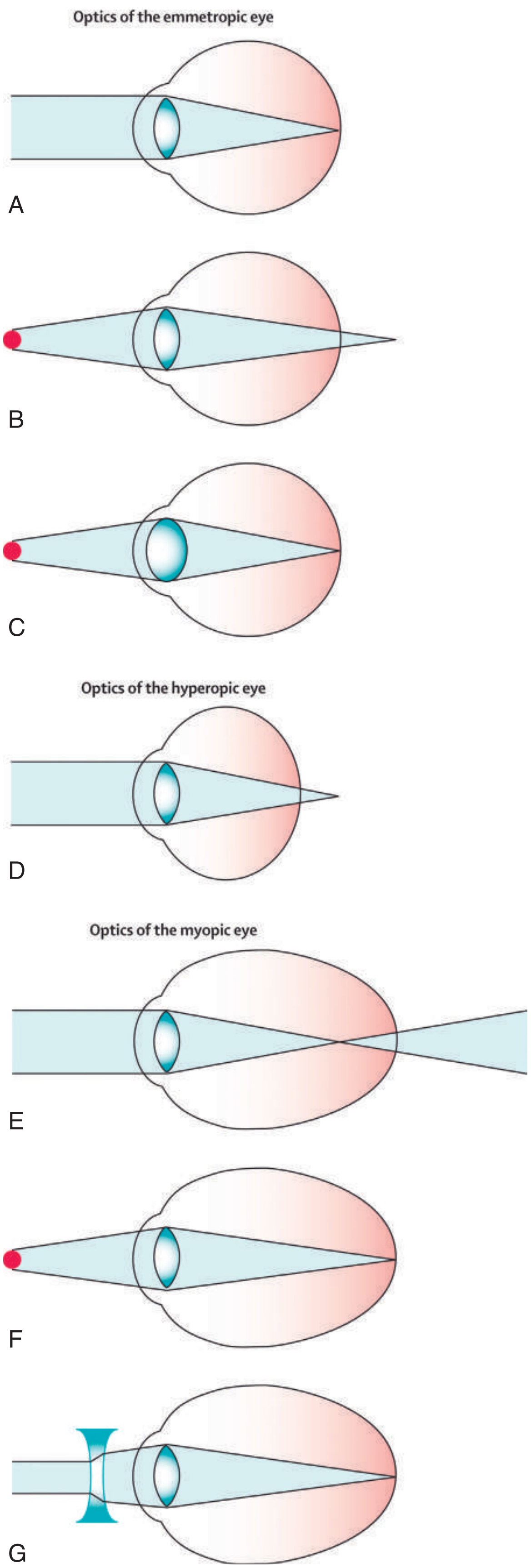

Figure 620-1 Schematic optics of the eye. **A, B,** and **C,** Emmetropic eyes. **D,** Hyperopic eyes. **E, F,** and **G,** Myopic eyes. **A,** In emmetropic eyes, the parallel rays of a distant object are focused on the photoreceptors. **B,** When a closer object is viewed, the image is in focus behind the photoreceptors. The image can be brought forward into focus on the photoreceptors by the process of accommodation—increasing the optical power of the lens **(C).** In hyperopic eyes **(D),** the eye is too short, and the image of a distant object is focused behind the photoreceptors, and can be brought into focus by accommodation. Myopic eyes are eyes that have grown too long **(E),** and the image of a distant object falls in front of the photoreceptors, and cannot be brought into focus by accommodation. When closer objects are viewed, the image moves back toward the photoreceptors, and at a certain distance (the far point), which is related inverse to the severity of the myopia, it comes into focus **(F)**. Closer objects can then be brought into focus using accommodation. Optical correction for myopia is achieved with concave (diverging) lenses, which move the image into focus on the photoreceptors **(G)**. Contact lenses work in a similar way, whereas refractive surgery reduces the power of the cornea to bring the image of distant objects into focus. For equal corneal power, myopic eyes have longer axial lengths than emmetropic eyes, with deeper anterior and vitreal chambers. Their lenses tend to be thinner and of lower power than those of emmetropic eyes. *(From Morgan IG, Ohno-Matusi K, Saw SM: Myopia.* Lancet *379:1739–1746, 2012, Fig. 1, p. 1740.)*

strength to provide clear vision and comfort are prescribed when indicated. Even children who have high degrees of hyperopia but who have good vision will happily wear glasses because they provide comfort by eliminating the excessive accommodation required to see well. Preverbal children should also be given glasses for high levels of hyperopia to prevent the development of esotropia or amblyopia. Children with normal levels of hyperopia do not require correction in the majority of cases.

MYOPIA

In myopia, parallel rays of light come to focus anterior to the retina. This is a result of either a long anteroposterior diameter of the eye or a higher refractive power of the cornea or lens. The principal symptom is blurred vision for distant objects. The far point of clear vision varies inversely with the degree of myopia; as the myopia increases, the far point of clear vision moves closer to the eye. With myopia of 1 diopter, for example, the far point of clear focus is 1 m from the eye; with myopia of 3 diopters, the far point of clear vision is only ⅓ m from the eye. Thus, myopic children tend to hold objects and reading material closer, prefer to be close to the blackboard, and may be uninterested in distant activities. Squinting is common because the visual acuity is improved when the lid aperture is reduced, also known as the pinhole effect.

Myopia is infrequent in infants and preschool-age children. It is more common in infants with a history of **retinopathy of prematurity.** A hereditary tendency to myopia is also observed, and children of myopic parents should be examined at an early age. The incidence of myopia increases during the school years, especially during the preteen and teen years. The degree of myopia also increases with age during the growing years.

Concave lenses (spectacles or contact lenses) of appropriate strength to provide clear vision and comfort are prescribed. Changes are usually needed periodically, from every few months to every 1-2 yr. Excessive accommodation during near work has been considered by some to lead to progression of myopia. Based on this philosophy, some practitioners advocate the use of cycloplegic agents, bifocals, intentional undercorrection of myopic refractive errors, or mandatory removal of myopic glasses for near work in an effort to retard the progression of myopia. The value of such treatment has not been scientifically proven.

Excimer laser correction for myopia has been approved for adults since 1995. The laser is applied to the corneal stroma to reshape the cornea, changing its refractive power. LASIK (laser-assisted in situ keratomileusis) uses either a microkeratome or a femtosecond laser to produce an epithelial-stromal flap permitting the underlying corneal

tissue to be ablated. The flap is then reseated and assumes the altered corneal shape. Photorefractive keratectomy (PRK) uses manual removal of the epithelium following treatment with alcohol to expose the Bowman layer and stroma, which is then treated by the excimer laser. The epithelium regenerates to cover the defect over a period of 4-10 days. Visual improvement is usually significant and remains stable over time. Risks are greatest with high degrees of myopia (>10 diopters) and include starbursts, halos, and distorted images or multiple images (usually at night). Refractive surgery is not approved for pediatric patients but is being used off-label to treat of some forms of amblyopia and certain circumstances of myopia and astigmatism, usually by PRK.

In most cases, myopia is not a result of pathologic alteration of the eye and is referred to as simple or physiologic myopia. Some children may have pathologic myopia, a rare condition caused by a pathologically abnormal axial length of the eye; this is usually associated with thinning of the sclera, choroid, and retina and often with some degree of uncorrectable visual impairment. Tears or breaks in the retina may occur as it becomes increasingly thin, leading to the development of retinal detachments. Myopia may also occur as a result of other ocular abnormalities, such as keratoconus, ectopia lentis, congenital stationary night blindness, and glaucoma. Myopia is also a major feature of Stickler syndrome, a genetic disorder of connective tissue involving problems with vision, hearing, and facial and skeletal development.

ASTIGMATISM

In astigmatism, the refractive powers of the various meridians of the eye differ. Most cases are caused by irregularity in the curvature of the cornea, although some astigmatism results from changes in the lens. Mild degrees of astigmatism are common and may produce no symptoms. With greater degrees, distortion of vision can occur. To achieve a clearer image, a person with astigmatism uses accommodation or squints to obtain a pinhole effect. Symptoms include eyestrain, headache, and fatigue. Cylindrical or spherocylindrical lenses are used to provide optical correction when indicated. Glasses may be needed constantly or only part time, depending on the degree of astigmatism and the severity of the attendant symptoms. In some cases, contact lenses are used.

Infants and children with corneal irregularity resulting from injury, ptosis, or hemangiomas of the periorbita or eyelid are at increased risk of astigmatism and associated amblyopia.

ANISOMETROPIA

When the refractive state of one eye is significantly different from the refractive state of the other eye, anisometropia exists. If uncorrected, 1 eye may always be out of focus, leading to the development of amblyopia. Early detection and correction are essential if normal visual development in both eyes is to be achieved.

ACCOMMODATION

During accommodation, the ciliary muscle contracts, the suspensory fibers of the lens relax, and the lens assumes a more rounded shape, adding power to the lens. The amplitude of accommodation is greatest during childhood and gradually diminishes with age. The physiologic decrease in accommodative ability that occurs with age is called presbyopia.

Disorders of accommodation in children are relatively rare. Premature presbyopia is occasionally encountered in young children. The most common cause of paralysis of accommodation in children is intentional or inadvertent use of cycloplegic substances, topically or systemically; included are all the anticholinergic drugs and poisons, as well as plants and plant substances having these effects. Neurogenic causes of accommodative paralysis include lesions affecting the oculomotor nerve (3rd cranial nerve) in any part of its course. Differential diagnoses include tumors, degenerative diseases, vascular lesions, trauma, and infectious etiologies. Systemic disorders that may cause impairment of accommodation include botulism, diphtheria, Wilson disease, diabetes mellitus, and syphilis. Adie tonic pupil may also lead to a deficiency of accommodation after some viral illnesses (see Chapter 622). An apparent defect in accommodation may be psychogenic in origin; it is common for a child to feign inability to read when it can be demonstrated that visual acuity and ability to focus are normal.

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Chapter 621

Disorders of Vision

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Severe visual impairment (corrected vision poorer than **6/60**) and blindness in children have many etiologies and may be caused by multiple defects affecting any structure or function along the visual pathways (Table 621-1). The overall incidence is approximately 2.5 per 100,000 children; the incidence is higher in developing countries, in low birthweight infants, and in the 1st yr of life. The most common causes occur during the prenatal and perinatal time periods; the cerebral-visual pathways, optic nerve, and retinal sites are most often affected. Important prenatal causes include autosomal recessive (most common), autosomal dominant, and X-linked genetic disorders as well as hypoxia and chromosomal syndromes. Perinatal/neonatal causes include retinopathy of prematurity, hypoxia–ischemia, and infection. Severe visual impairment starting in older children may be due to central nervous system or retinal tumors, infections, hypoxia–ischemia, injuries, neurodegenerative disorders, or juvenile idiopathic arthritis.

AMBLYOPIA

This is a decrease in visual acuity, unilateral or bilateral, that occurs in visually immature children as a result of a lack of a clear image projecting onto the retina. The unformed retinal image may occur secondary to a deviated eye **(strabismic amblyopia),** an unequal need for vision correction between the eyes **(anisometropic amblyopia),** a high refractive error in both eyes **(ametropic amblyopia),** or a media opacity within the visual axis **(deprivation amblyopia).**

The development of visual acuity normally proceeds rapidly in infancy and early childhood. Anything that interferes with the formation of a clear retinal image during this early developmental period can produce amblyopia. Amblyopia occurs only during the critical period of development before the cortex has become visually mature, within the 1st decade of life. The younger the child, the more susceptible he or she is to the development of amblyopia.

The **diagnosis** of amblyopia is confirmed when a complete ophthalmologic examination reveals reduced acuity that is unexplained by an organic abnormality. If the history and ophthalmologic examination do not support the diagnosis of amblyopia in a child with poor vision, consideration must be given to other causes (neurologic, psychologic). Amblyopia is usually asymptomatic and can avoid detection until vision screening, which may delay diagnosis as screening programs often target school-age children. This is problematic as amblyopia is more resistant to treatment at an older age, being reversed more rapidly in younger children whose visual system is less mature. Thus, one key to the successful treatment of amblyopia is early detection and prompt intervention.

Most often **treatment** first consists of removing any media opacity or prescribing appropriate glasses, if needed, so that a well-focused retinal image can be produced in each eye. The sound eye is then

Table 621-1 Causes of Childhood Severe Visual Impairment or Blindness

CONGENITAL Optic nerve hypoplasia or aplasia Septooptic dysplasia Optic coloboma Congenital hydrocephalus Hydranencephaly Porencephaly Micrencephaly Encephalocele, particularly occipital Morning glory disc Aniridia Microphthalmia/anophthalmia Peters anomaly Rieger anomaly Persistent pupillary membrane Glaucoma Cataracts Persistent hyperplastic primary vitreous	Special types: Dawson disease, Leigh disease, the Bassen-Kornzweig syndrome, Refsum disease Retinal degenerations: retinitis pigmentosa and its variants and Leber congenital type Optic atrophies: congenital autosomal recessive type, infantile and congenital autosomal dominant types, Leber disease, and atrophies associated with hereditary ataxias—the types of Behr, of Marie, and of Sanger-Brown
PHAKOMATOSES Tuberous sclerosis Neurofibromatosis (special association with optic glioma) Sturge-Weber syndrome von Hippel-Lindau disease	INFECTIOUS/INFLAMMATORY PROCESSES Encephalitis, especially in the prenatal infection syndromes caused by *Toxoplasma gondii*, cytomegalovirus, rubella virus, *Treponema pallidum*, herpes simplex virus Meningitis; arachnoiditis Chorioretinitis Endophthalmitis Trachoma Keratitis Uveitis
TUMORS Retinoblastoma Optic glioma Perioptic meningioma Craniopharyngioma Cerebral glioma Astrocytoma Posterior and intraventricular tumors when complicated by hydrocephalus Pseudotumor cerebri	HEMATOLOGIC DISORDERS Leukemia with central nervous system involvement
	VASCULAR AND CIRCULATORY DISORDERS Collagen vascular diseases Arteriovenous malformations—intracerebral hemorrhage, subarachnoid hemorrhage Central retinal occlusion
	TRAUMA Contusion or avulsion of optic nerves, chiasm, globe, cornea Cerebral contusion or laceration Intracerebral, subarachnoid, or subdural hemorrhage Retinal detachment Laser injury
NEURODEGENERATIVE DISEASES Cerebral storage disease Gangliosidoses, particularly Tay-Sachs disease, Sandhoff variant, generalized gangliosidosis Other lipidoses and ceroid lipofuscinoses, particularly the late-onset disorders such as those of Jansky-Bielschowsky and of Batten-Mayou-Spielmeyer-Vogt Mucopolysaccharidoses, particularly Hurler syndrome and Hunter syndrome Leukodystrophies (dysmyelination disorders), particularly metachromatic leukodystrophy and Canavan disease Demyelinating sclerosis (myelinoclastic diseases), especially Schilder disease and Devic neuromyelitis optica	DRUGS AND TOXINS Quinine Ethambutol Methanol Many others
	OTHER Retinopathy of prematurity Sclerocornea Conversion reaction Optic neuritis Osteopetrosis

Modified from Kliegman R: Practical strategies in pediatric diagnosis and therapy. *Philadelphia, 1996, WB Saunders.*

covered (occlusion therapy) or blurred with glasses (fogging) or drops (penalization therapy) to stimulate proper visual development of the more severely affected eye. Occlusion therapy may provide a more rapid improvement in vision, but some children may better tolerate atropine penalization. The best treatment for any one patient should be selected on an individual basis. The goals of treatment should be thoroughly understood, and the treatment carefully supervised. Close monitoring of amblyopia therapy by an ophthalmologist is essential, especially in the very young, to avoid deprivation amblyopia in the good eye. Many families need reassurance and support throughout the trying course of treatment. Although full-time occlusion has historically been considered the best way to treat children with amblyopia, a series of prospective studies has shown that some children can achieve similar results with part-time patching or through the use of atropine drops. Historical thought was that older children would not respond to amblyopia therapy. Recent studies now suggest children deemed visually mature who demonstrate amblyopia, particularly refractive or anisometropic in etiology, can demonstrate improvement in vision with appropriate therapy.

DIPLOPIA

Diplopia, or double vision, is generally a result of a misalignment of the visual axes. Occluding either eye relieves the diplopia if it is binocular in origin. Affected children commonly squint, cover 1 eye with a hand, or assume an abnormal head posture (a face turn or head tilt) to alleviate the bothersome sensation. These behaviors, especially in preverbal children, are important clues to diplopia. *The onset of diplopia in any child warrants prompt evaluation; it may signal the onset of a serious problem such as increased intracranial pressure, a brain tumor, infection (Lyme disease), migraine, Guillain-Barré syndrome, or an orbital mass.*

Monocular diplopia results from dislocation of the lens, cataract, dry eyes, or some defect in the media or macula. With this type of diplopia, occluding the nondiplopic eye will not relieve the symptoms. *Monocular diplopia may often have psychological causes.*

SUPPRESSION

In the presence of strabismus, diplopia occurs secondary to the same image falling on different regions of the retina in each eye. In a visually

immature child, a process may occur in the cortex that eliminates the disability of seeing double. This is an active process and is termed *suppression*. It develops only in children. Although suppression eliminates the annoying symptom of diplopia, it is the potential awareness of a second image that tends to keep our eyes properly aligned. Once suppression develops, it may allow an intermittent strabismus to become constant or strabismus to redevelop later in life, even after successful treatment during childhood.

AMAUROSIS

Amaurosis is partial or total loss of vision; the term is usually reserved for profound impairment, blindness, or near blindness. When amaurosis exists from birth, primary consideration in the differential diagnosis must be given to developmental malformations, damage consequent to gestational or perinatal infection, anoxia or hypoxia, perinatal trauma, and the genetically determined diseases that can affect the eye itself or the visual pathways. Often, the reason for amaurosis can be readily determined by objective ophthalmic examination; examples are severe microphthalmia, corneal opacification, dense cataracts, chorioretinal scars, macular defects, retinal dysplasia, and severe optic nerve hypoplasia. In other cases, an intrinsic retinal disease may not be apparent on initial ophthalmoscopic examination or the defect may involve the brain and not the eye. Neuroradiologic (MRI or CT) and electrophysiologic (electroretinography) evaluation may be especially helpful in these cases.

Amaurosis that develops in a child who once had useful vision has different implications. In the absence of obvious ocular disease (cataract, chorioretinitis, retinoblastoma, retinitis pigmentosa), consideration must be given to many neurologic and systemic disorders that can affect the visual pathways. Amaurosis of rather rapid onset may indicate an encephalopathy (hypertension), infectious or parainfectious processes, vasculitis, migraine, leukemia, toxins, or trauma. It may be caused by acute demyelinating disease affecting the optic nerves, chiasm, or cerebrum. In some cases, precipitous loss of vision is a result of increased intracranial pressure, rapidly progressive hydrocephalus, or dysfunction of a shunt. More slowly progressive visual loss suggests tumor or neurodegenerative disease. Gliomas of the optic nerve and chiasm and craniopharyngiomas are primary diagnostic considerations in children who show progressive loss of vision.

Clinical manifestations of impairment of vision vary with the age and abilities of a child, the mode of onset, and the laterality and severity of the deficit. The first clue to amaurosis in an infant may be **nystagmus** or **strabismus,** with the vision deficit itself passing undetected for some time. Timidity, clumsiness, or behavioral change may be the initial clues in the very young. Deterioration in school progress and indifference to school activities are common signs in an older child. School-age children often try to hide their disability and, in the case of very slowly progressive disorders, may not themselves realize the severity of the problem; some detect and promptly report small changes in their vision.

Any evidence of loss of vision requires prompt and thorough ophthalmic evaluation. Complete delineation of childhood amaurosis and its cause may require extensive investigation involving neurologic evaluation, electrophysiologic tests, neuroradiologic procedures, and sometimes metabolic and genetic studies. Furthermore, attendant special educational, social, and emotional needs must be met.

NYCTALOPIA

Nyctalopia, or night blindness, is vision that is defective in reduced illumination. It generally implies impairment in function of the rods, particularly in dark adaptation time and perceptual threshold. Stationary congenital night blindness may occur as an autosomal dominant, autosomal recessive, or X-linked recessive condition. It may be associated with myopia and nystagmus. Children may have excessive problems going to sleep in a dark room, which may be mistaken for a behavioral problem. Progressive night blindness usually indicates primary or secondary retinal, choroidal, or vitreoretinal degeneration (see Chapter 630); it occurs also in vitamin A deficiency or as a result of retinotoxic drugs such as quinine.

PSYCHOGENIC DISTURBANCES

Vision problems of psychogenic origin are common in school-age children. Both conversion reactions and willful feigning are encountered. The usual manifestation is a report of reduced visual acuity in 1 or both eyes. Another common manifestation is constriction of the visual field. In some cases, the symptom is diplopia or polyopia (see Chapters 22 and 25).

Important clues to the diagnosis are inappropriate affect, excessive grimacing, inconsistency in performance, and suggestibility. A thorough ophthalmologic examination is essential to differentiate organic from functional visual disorders.

Affected children usually fare well with reassurance and positive suggestions. In some cases, psychiatric care is indicated. In all cases, the approach must be supportive and nonpunitive.

DYSLEXIA

This is the inability to develop the capability to read at an expected level despite an otherwise normal intellect. The terms *reading disability* and *dyslexia* are often used interchangeably. Most dyslexic individuals also display poor writing ability. Dyslexia is a primary reading disorder and should be differentiated from secondary reading difficulties caused by intellectual disability, environmental or educational deprivation, and systemic physical or other organic brain or eye diseases. Because there is no one standard test for dyslexia, the diagnosis is usually made by comparing reading ability with intelligence and standard reading expectations. Dyslexia is a language-based disorder and is not caused by any defect in the eye or visual acuity per se, nor is it attributable to a defect in ocular motility or binocular alignment. Although ophthalmologic evaluation of children with a reading problem is recommended to diagnose and correct any concurrent ocular problems such as a refractive error, amblyopia, or strabismus, treatment directed to the eyes themselves cannot be expected to correct developmental dyslexia (see Chapter 34).

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Chapter 622

Abnormalities of Pupil and Iris

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ANIRIDIA

The term *aniridia* is a misnomer because iris tissue is usually present, although it is hypoplastic (Fig. 622-1). Two thirds of the cases are dominantly transmitted with a high degree of penetrance. The other third of cases are sporadic and are considered to be new mutations. The condition is bilateral in 98% of all patients, regardless of the means of transmission, and is found in approximately 1/50,000 persons. *PAX6* is the mutated gene at the chromosome 11p3 region.

Aniridia is a panocular disorder and should not be thought of as an isolated iris defect. Macular and optic nerve hypoplasias are commonly present and lead to decreased vision and sensory nystagmus. The visual acuity is measured as 20/200 in most patients, although the vision may occasionally be better. Other ocular deformities are common and may involve the lens and cornea. The cornea may be small, and a cellular infiltrate (pannus) occasionally develops in the superficial layers of

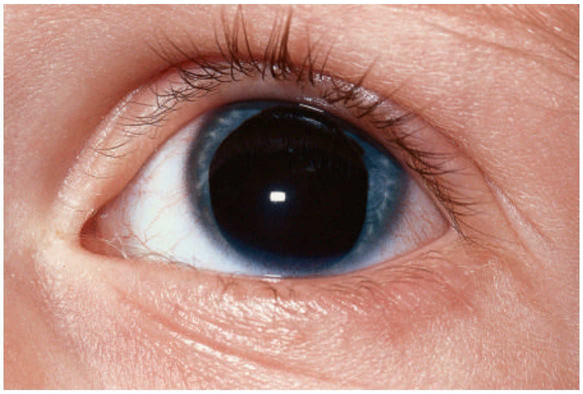

Figure 622-1 Partial aniridia in a member of an autosomal dominant pedigree. *(From Hoyt CS, Taylor D, editors:* Pediatric ophthalmology and strabismus, *ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 32.22, p. 304.)*

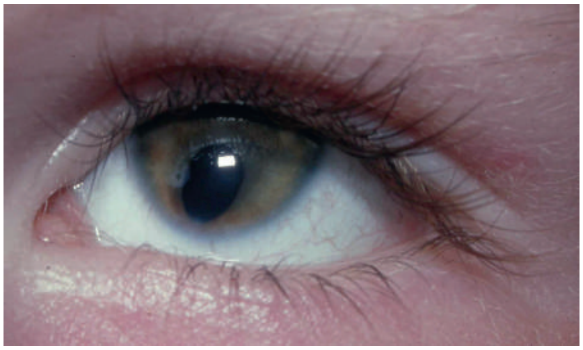

Figure 622-2 Coloboma ("keyhole pupil"). *(From Hoyt CS, Taylor D, editors:* Pediatric ophthalmology and strabismus, *ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 38.11, p. 372.)*

the peripheral cornea. Clinically, this appears as a gray opacification. Lens abnormalities include cataract formation and partial or total lens dislocation. **Glaucoma** develops in as many as 75% of individuals with aniridia.

One fifth of **sporadic** aniridic patients may develop **Wilms tumor** (see Chapter 499.1).

The gene for aniridia is very close to the Wilms tumor gene; deletions in this area cause the association. Of particular interest is the association of aniridia, genitourinary anomalies, mental retardation, and a partial deletion of the short arm of chromosome 11. Among individuals thus affected, the appearance of Wilms tumor is more common. It is thought that only patients with sporadic aniridia are at risk for developing Wilms tumor, although Wilms tumor has occurred in a patient with familial aniridia. Wilms tumor usually presents before the 5th yr. Therefore, these children should be screened using renal ultrasonography every 3-6 mo until approximately 5 yr of age if there is an 11p13 region deletion placing the child at risk for Wilms tumor.

COLOBOMA OF THE IRIS

This developmental defect may present as a defect in a sector of the iris, a hole in the substance of the iris, or a notch in the pupillary margin (Fig. 622-2). Simple colobomas are frequently transmitted as an autosomal dominant trait and may occur alone or in association with other anomalies. A coloboma is formed when the embryonic fissure fails to close completely. Because of the anatomic location of the embryonic fissure, an iris coloboma is always located inferiorly, giving the iris a keyhole appearance. An iris coloboma may be the only externally visible part of an extensive malclosure of the embryonic fissure that also involves the fundus and optic nerve. When this occurs, vision is likely to be severely affected. Therefore, all children with an iris coloboma should undergo a full ophthalmologic examination.

MICROCORIA

Microcoria (congenital miosis) appears as a small pupil that does not react to light or accommodation and that dilates poorly, if at all, with medication. The condition may be unilateral or bilateral. In bilateral cases, the degree of miosis may be different in each eye. The eye may be otherwise normal or may demonstrate other abnormalities of the anterior segment. Congenital microcoria is usually transmitted as an autosomal dominant trait, although it may occur sporadically.

CONGENITAL MYDRIASIS

In this disorder, the pupils appear dilated, do not constrict significantly to light or near gaze, and respond minimally to miotic agents. The iris is otherwise normal, and affected children are usually healthy. Trauma, pharmacologic mydriasis, and neurologic disorders should be considered. Many apparent cases of congenital mydriasis show abnormalities of the central iris structures and may be considered a form of aniridia.

DYSCORIA AND CORECTOPIA

Dyscoria is abnormal shape of the pupil, and corectopia is abnormal pupillary position. They may occur together or independently as congenital or acquired anomalies.

Congenital corectopia is usually bilateral and symmetric and rarely occurs as an isolated anomaly; it is usually accompanied by dislocation of the lens (ectopia lentis et pupillae), and the lens and pupil are commonly dislocated in opposite directions. Ectopia lentis et pupillae is transmitted as an autosomal recessive disorder; consanguinity is common. It is associated with mutations in ADAMTSL4, a secreted glycoprotein widely distributed in the eye, which binds fibrillin-1 microfibrils and accelerates microfibril biogenesis.

When acquired, distortion and displacement of the pupil are frequently a result of trauma or intraocular inflammation. Prolapse of the iris after perforating injuries of the eye leads to peaking of the pupil in the direction of the perforation. Posterior synechiae (adhesions of the iris to the lens) are commonly seen when inflammation due to any cause occurs in the anterior segment.

ANISOCORIA

This is inequality of the pupils. The difference in size may be a result of local or neurologic disorders. As a rule, if the inequality is more pronounced in the presence of bright focal illumination or on near gaze, there is a defect in pupillary constriction and the larger pupil is abnormal. If the anisocoria is worse in reduced illumination, a defect in dilation exists and the smaller pupil is abnormal. Neurologic causes of anisocoria (parasympathetic or sympathetic lesions) must be differentiated from local causes such as synechiae (adhesions), congenital iris defects (colobomas, aniridia), and pharmacologic effects. **Horner syndrome** is an important cause of anisocoria (see below). Simple central anisocoria may occur in otherwise healthy individuals.

DILATED FIXED PUPIL

Differential diagnosis of a dilated unreactive pupil includes internal ophthalmoplegia caused by a central or peripheral lesion, Hutchinson pupil of transtentorial herniation, tonic pupil, pharmacologic blockade, and iridoplegia secondary to ocular trauma.

The most common cause of a dilated unreactive pupil is purposeful or accidental instillation of a cycloplegic agent, particularly atropine and related substances. Central nervous system lesions, such as a pinealoma, may cause internal ophthalmoplegia in children. Because the external surface of the oculomotor nerve carries the fibers responsible for pupillary constriction, compression of the nerve along its intracranial course may be associated with internal ophthalmoplegia, even before the development of ptosis or an ocular motility deficit. Although

ophthalmoplegic migraine is a common cause of a 3rd nerve palsy with pupillary involvement in children, an intracranial aneurysm must also be considered in the differential diagnosis. The **blown pupil** of transtentorial herniation, occurring with increasing intracranial pressure, is generally unilateral, and patients usually are obviously ill. The pilocarpine test can help differentiate neurologic iridoplegia from pharmacologic blockade. In the case of neurologic iridoplegia, the dilated pupil constricts within minutes after instillation of 1 or 2 drops of 0.5–1% pilocarpine; if the pupil has been dilated with atropine, pilocarpine has no effect. Because pilocarpine is a long-acting drug, this test is not to be used in acute situations in which pupillary signs must be carefully monitored. Because of the consensual pupil response to light, even complete uniocular blindness does not cause a unilaterally dilated pupil.

TONIC PUPIL

This is typically a large pupil that reacts poorly to light (the reaction may be very slow or essentially nil), reacts poorly and slowly to accommodation, and redilates in a slow, tonic manner. The features of tonic pupil are explained by cholinergic supersensitivity of the sphincter after peripheral (postganglionic) denervation and imperfect reinnervation. A distinctive feature of a tonic pupil is its sensitivity to dilute cholinergic agents. Instillation of 0.125% pilocarpine causes significant constriction of the involved pupil and has little or no effect on the unaffected side. The condition is usually unilateral.

Tonic pupil may develop after the acute stage of a partial or complete iridoplegia. It can be seen after trauma to the eye or orbit and may occur in association with toxic or infectious conditions. For those in the pediatric age group, tonic pupil is uncommon. Infectious processes (primarily viral syndromes) and trauma are the primary causes. Features of tonic pupil may also be seen in infants and children with familial dysautonomia (Riley-Day syndrome), although the significance of these findings has been questioned. Tonic pupil has also been reported in young children with Charcot-Marie-Tooth disease. The occurrence of tonic pupil in association with decreased deep tendon reflexes in young women is referred to as **Adie syndrome.**

MARCUS GUNN PUPIL

This relative afferent pupillary defect indicates an asymmetric, prechiasmatic, afferent conduction defect. It is best demonstrated by the swinging flashlight test, which allows comparison of the direct and consensual pupillary responses in both eyes. With patients fixing on a distant target (to control accommodation), a bright focal light is directed alternately into each eye in turn. In the presence of an afferent lesion, both the direct response to light in the affected eye and the consensual response in the other eye are subnormal. Swinging the light to the better or normal eye causes both pupils to react (constrict) normally. Swinging the light back to the affected eye causes both pupils to redilate to some degree, reflecting the defective conduction. This is a very sensitive and useful test for detecting and confirming optic nerve and retinal disease. This test is only abnormal if there is a "relative" difference in the conduction properties of the optic nerves. Therefore, patients with bilateral and symmetrical optic nerve disease will not demonstrate an afferent pupillary defect. A subtle relative afferent defect may be found in some children with amblyopia.

HORNER SYNDROME

The principal signs of oculosympathetic paresis (Horner syndrome) are homolateral miosis, mild ptosis, and apparent enophthalmos with slight elevation of the lower lid as a result of the slight ptosis. Patients may also have decreased facial sweating, increased amplitude of accommodation, and transient decrease in intraocular pressure. If paralysis of the ocular sympathetic fibers occurs before the age of 2 yr, heterochromia iridis with hypopigmentation of the iris may occur on the affected side (Fig. 622-3).

Oculosympathetic paralysis may be caused by a lesion (tumor, trauma, infarction) in the midbrain, brainstem, upper spinal cord, neck, middle fossa, or orbit. Congenital oculosympathetic paresis, often as part of Klumpke brachial palsy, is common, although the ocular signs, particularly the anisocoria, may pass undetected for years. Horner syndrome is also seen in some children after thoracic surgery. Congenital Horner syndrome may occur in association with vertebral anomalies and with enterogenous cysts. In some infants and children, Horner syndrome is the presenting sign of tumor in the mediastinal or cervical region, particularly neuroblastoma. Rare causes of Horner syndrome, such as vascular lesions, also occur in the pediatric age group. In many cases, no cause of congenital Horner syndrome can be identified. Occasionally, the condition is familial.

When the cause of Horner syndrome is in question, investigative procedures should be implemented and may include imaging of the head, neck, and chest as well as 24-hr urinary catecholamine assay. Examining old photographs and old records can sometimes be helpful in establishing the age at onset of Horner syndrome.

The cocaine test is useful in diagnosing oculosympathetic paralysis; a normal pupil dilates within 20–45 min after instillation of 1 or 2 drops of 4% cocaine, whereas the miotic pupil of an oculosympathetic paresis dilates poorly, if at all, with cocaine. In some cases, there is denervation supersensitivity to dilute phenylephrine; 1 or 2 drops of a 1% solution dilates the affected pupil but not the normal one. Furthermore, instillation of 1% hydroxyamphetamine hydrobromide dilates the pupil only if the postganglionic sympathetic neuron is intact.

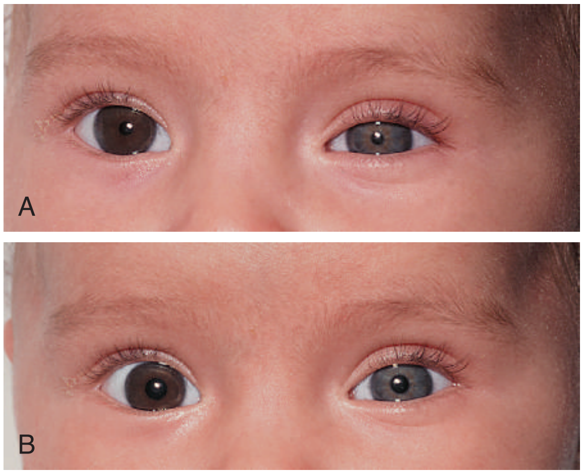

Figure 622-3 Left congenital Horner syndrome showing upper- and lower-lid ptosis and an iris heterochromia, with the lighter eye being the affected eye. **A,** In bright light and **(B)** in the dark. *(From Hoyt CS, Taylor D, editors:* Pediatric ophthalmology and strabismus, *ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 63.9, p. 661.)*

PARADOXICAL PUPIL REACTION

Some children exhibit paradoxical constriction of the pupils to darkness. An initial brisk constriction of the pupils occurs when the light is turned off, followed by slow redilation of the pupils. The response to direct light stimulation and the near response are normal. The mechanism is not clear, but paradoxical constriction of the pupils in reduced light can be a sign of retinal or optic nerve abnormalities. The phenomenon has been observed in children with congenital stationary night blindness, albinism, retinitis pigmentosa, Leber congenital retinal amaurosis, and Best disease. It has also been observed in those with optic nerve anomalies, optic neuritis, optic atrophy, and possibly amblyopia. Thus, children with paradoxical pupillary constriction to darkness should have a thorough ophthalmologic examination.

PERSISTENT PUPILLARY MEMBRANE

Involution of the pupillary membrane and anterior vascular capsule of the lens is usually completed during the 5th–6th mo of fetal development. It is common to see some remnants of the pupillary membrane in newborns, particularly in premature infants. These membranes are

nonpigmented strands of obliterated vessels that cross the pupil and may secondarily attach to the lens or cornea. The remnants tend to atrophy in time and usually present no problem. In some cases, however, significant remnants that remain obscure the pupil and interfere with vision. Rarely, there is patency of the vascular elements; hyphema may result from rupture of persistent vessels.

Intervention must be considered to minimize amblyopia in infants with extensive persistent pupillary membrane of sufficient degree to interfere with vision in the early months of life. In some cases, mydriatics and occlusion therapy may be effective, but in others, surgery may be needed to provide an adequate pupillary aperture.

HETEROCHROMIA

In heterochromia, the 2 irides are of different color (heterochromia iridium) or a portion of an iris differs in color from the remainder (heterochromia iridis). Simple heterochromia may occur as an autosomal dominant characteristic. Congenital heterochromia is also a feature of Waardenburg syndrome, an autosomal dominant condition characterized principally by lateral displacement of the inner canthi and puncta, pigmentary disturbances (usually a median white forelock and patches of hypopigmentation of the skin), and defective hearing. Change in the color of the iris may occur as a result of trauma, hemorrhage, intraocular inflammation (iridocyclitis, uveitis), intraocular tumor (especially retinoblastoma), intraocular foreign body, glaucoma, iris atrophy, oculosympathetic palsy (Horner syndrome), melanosis oculi, previous intraocular surgery, and some glaucoma medications.

OTHER IRIS LESIONS

Discrete nodules of the iris, referred to as **Lisch nodules,** are commonly seen in patients with neurofibromatosis (see Chapter 596.1). Lisch nodules represent melanocytic hamartomas of the iris and vary from slightly elevated pigmented areas to distinct ball-like excrescences. The nodules cause no visual disturbance. Lisch nodules are found in 92-100% of individuals older than 5 yr of age who have neurofibromatosis. Slit-lamp identification of these nodules may help to fulfill the criteria required to confirm the diagnosis of neurofibromatosis.

In leukemia (see Chapter 495), there may be infiltration of the iris, sometimes with **hypopyon,** an accumulation of white blood cells in the anterior chamber, which may herald relapse or involvement of the central nervous system.

The lesion of **juvenile xanthogranuloma** (nevoxanthoendothelioma; see Chapter 670) may occur in the eye as a yellowish fleshy mass or plaque of the iris. Spontaneous hyphema (blood in the anterior chamber), glaucoma, or a red eye with signs of uveitis may be associated. A search for the skin lesions of xanthogranuloma should be made in any infant or young child with spontaneous hyphema. In many cases, the ocular lesion responds to topical corticosteroid therapy.

LEUKOCORIA

This includes any white pupillary reflex, or so-called cat's-eye reflex. Primary diagnostic considerations in any child with leukocoria are cataract, persistent hyperplastic primary vitreous, cicatricial retinopathy of prematurity, retinal detachment and retinoschisis, larval granulomatosis, and retinoblastoma (Fig. 622-4). Also to be considered are endophthalmitis, organized vitreous hemorrhage, leukemic ophthalmopathy, exudative retinopathy (as in Coats disease), and less-common conditions such as medulloepithelioma, massive retinal gliosis, the retinal pseudotumor of Norrie disease, the so-called pseudoglioma of the Bloch-Sulzberger syndrome, retinal dysplasia, and the retinal lesions of the phakomatoses. A white reflex may also be seen with fundus coloboma, large atrophic chorioretinal scars, and ectopic medullation of retinal nerve fibers. Leukocoria is an indication for prompt and thorough evaluation.

Figure 622-4 Leukocoria. White pupillary reflex in a child with retinoblastoma.

The diagnosis can often be made by direct examination of the eye by ophthalmoscopy and biomicroscopy. Ultrasonographic and radiologic examinations are often helpful. In some cases, the final diagnosis rests with a pathologist.

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Chapter 623

Disorders of Eye Movement and Alignment

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STRABISMUS

Strabismus, or misalignment of the eyes, is one of the most common eye problems encountered in children, affecting approximately 4% of children younger than 6 yr of age. Strabismus can result in vision loss (amblyopia) and can have significant psychological effects. Early detection and treatment of strabismus are essential to prevent permanent visual impairment. Of children with strabismus, 30-50% develop amblyopia. Restoration of proper alignment of the visual axis must occur at an early stage of visual development to allow these children a chance to develop normal binocular vision. The word strabismus means "to squint or to look obliquely." Many terms are used in discussing and characterizing strabismus.

Orthophoria is the ideal condition of exact ocular balance. It implies that the oculomotor apparatus is in perfect equilibrium so that the eyes remain coordinated and aligned in all positions of gaze and at all distances. Even when binocular vision is interrupted, as by occlusion of one eye, truly orthophoric individuals maintain perfect alignment. Orthophoria is seldom encountered because the majority of individuals have a small latent deviation (heterophoria).

Heterophoria is a latent tendency for the eyes to deviate. This latent deviation is normally controlled by fusional mechanisms that provide binocular vision or avoid diplopia (double vision). The eye deviates only under certain conditions, such as fatigue, illness, or stress, or during tests that interfere with maintenance of these normal fusional abilities (such as covering one eye). If the amount of heterophoria is large, it may give rise to bothersome symptoms, such as transient diplopia (double vision), headaches, or asthenopia (eyestrain). Some degree of heterophoria is found in normal individuals; it is usually asymptomatic.

Heterotropia is a misalignment of the eyes that is constant. It occurs because of an inability of the fusional mechanism to control the deviation. Tropias can be alternating, involving both eyes, or unilateral. In an alternating tropia, there is no preference for fixation of either eye, and both eyes drift with equal frequency. Because each eye is used periodically, vision usually develops normally. A unilateral tropia is a more serious situation because only 1 eye is constantly misaligned. The undeviated eye becomes the preferred eye, resulting in loss of vision or amblyopia of the deviated eye.

It is common in ocular misalignments to describe the type of deviation. This helps to make decisions on the cause and treatment of the strabismus. The prefixes *eso-, exo-, hyper-,* and *hypo-* are added to the terms *phoria* and *tropia* to further delineate the type of strabismus. Esophorias and esotropias are inward or convergent deviations of the eyes, commonly known as crossed eyes. Exophorias and exotropias are divergent or outward-facing eye deviations, walleyed being the lay term. Hyperdeviations and hypodeviations designate upward or downward, respectively, deviations of an eye. In cases of unilateral strabismus, the deviating eye is often part of the description of the misalignment (left esotropia).

Diagnosis

Many techniques are used to assess ocular alignment and movement of the eyes to aid in diagnosing strabismic disorders. In a child with strabismus or any other ocular disorder, assessment of visual acuity is mandatory. Decreased vision in 1 eye requires evaluation for a strabismus or other ocular abnormalities, which may be difficult to discern on a brief screening evaluation. Even strabismic deviations of only a few degrees in magnitude, too small to be evident by gross inspection, may lead to amblyopia and significant vision loss.

Corneal light reflex tests are perhaps the most rapid and easily performed diagnostic tests for strabismus. They are particularly useful in children who are uncooperative and in those who have poor ocular fixation. To perform the **Hirschberg corneal reflex test,** the examiner projects a light source onto the cornea of both eyes simultaneously as a child looks directly at the light. Comparison should then be made of the placement of the corneal light reflex in each eye. In straight eyes, the light reflection appears symmetric and, because of the relationship between the cornea and the macula, slightly nasal to the center of each pupil. If strabismus is present, the reflected light is asymmetric and appears displaced in one eye. The Krimsky method of the corneal reflex test uses prisms placed over one or both eyes to align the light reflections. The amount of prism needed to align the reflections is used to measure the degree of deviation. Although it is a useful screening test, corneal light reflex testing may not detect a small angle or an intermittent strabismus.

Cover tests for strabismus require a child's attention and cooperation, good eye movement capability, and reasonably good vision in each eye. If any of these are lacking, the results of these tests may not be valid. These tests consist of the cover–uncover test and the alternate cover test. In the cover–uncover test, a child looks at an object in the distance, preferably 6 m away. An eye chart is commonly used for fixation in children older than 3 yr of age. For younger children, a noise-making toy or movie helps hold their attention for the test. As the child looks at the distant object, the examiner covers 1 eye and watches for movement of the uncovered eye. If no movement occurs, there is no apparent misalignment of that eye. After 1 eye is tested, the same procedure is repeated on the other eye. When performing the alternate cover test, the examiner rapidly covers and uncovers each eye, shifting back and forth from one eye to the other. If the child has an ocular deviation, the eye rapidly moves as the cover is shifted to the other eye. Both the cover–uncover test and the alternate cover test should be performed at both distance and near fixation. The cover–uncover test differentiates tropias, or manifest deviations, from latent deviations, called phorias.

Clinical Manifestations and Treatment

The etiologic classification of strabismus is complex, and the causative types must be distinguished; there are comitant and noncomitant forms of strabismus.

Comitant Strabismus

Comitant strabismus is the most common type of strabismus. The individual extraocular muscles usually have no defect. The amount of deviation is constant, or relatively constant, in the various directions of gaze.

Pseudostrabismus (pseudoesotropia) is one of the most common reasons a pediatric ophthalmologist is asked to evaluate an infant. This condition is characterized by the false appearance of strabismus when the visual axes are aligned accurately. This appearance may be caused by a flat, broad nasal bridge, prominent epicanthal folds, or a narrow interpupillary distance. The observer may see less white sclera nasally than would be expected, and the impression is that the eye is turned in toward the nose, especially when the child gazes to either side. Parents frequently comment that when their child looks to the side, the eye almost disappears from view. Pseudoesotropia can be differentiated from a true misalignment of the eyes when the corneal light reflex is centered in both eyes and when the cover–uncover test shows no refixation movement. Once pseudoesotropia has been confirmed, parents can be reassured that the child will outgrow the appearance of esotropia. As the child grows, the bridge of the nose becomes more prominent and displaces the epicanthal folds, and the medial sclera becomes proportional to the amount visible on the lateral aspect. It is the appearance of crossing that the child will outgrow. Some parents of children with pseudoesotropia erroneously believe that their child has an actual esotropia that will resolve on its own. Because true esotropia can develop later in children with pseudoesotropia, parents and pediatricians should be cautioned that reassessment is required if the apparent deviation does not improve.

Esodeviations are the most common type of ocular misalignment in children and represent >50% of all ocular deviations. *Congenital esotropia* is a confusing term. Few children who are diagnosed with this disorder are actually born with an esotropia. Most reports in the literature have, therefore, considered infants with confirmed onset earlier than 6 mo as having the same condition, which some observers have designated **infantile esotropia**.

Between 2 and 4 mo of age, many infants have infantile esotropia (neonatal misalignments), which in most resolve spontaneously. Those that resolve without treatment do so before 10-12 wk of age and had intermittent or variable deviations, while those who may benefit from active treatment have persistent esotropia (10 weeks–6 mo of age), a constant esotropia (40 PD), a refractive error $\leq$ +3.00 D, and the absence of prematurity, developmental delay, meningitis, nystagmus, eye anomalies, and incomitant or paralytic strabismus. The evaluation is noted in Figure 623-1.

The characteristic angle of congenital esodeviations is large and constant (Fig. 623-2). Because of the large deviation, cross-fixation is frequently encountered. This is a condition in which the child looks to the right with the left eye and to the left with the right eye. With cross-fixation, there is no need for the eye to turn away from the nose (abduction) as the adducting eye is used in side gaze; this condition simulates a 6th nerve palsy. Abduction can be demonstrated by the doll's-head maneuver or by patching 1 eye for a short time. Children with congenital esotropia tend to have refractive errors similar to those of normal children of the same age. This contrasts with the characteristic high level of farsightedness associated with accommodative esotropia. **Amblyopia** is common in children with congenital esotropia.

The primary goal of treatment in congenital esotropia is to eliminate or reduce the deviation as much as possible. Ideally, this results in normal sight in each eye, in straight-looking eyes, and in the development of binocular vision. Early treatment is more likely to lead to the development of binocular vision, which helps to maintain long-term ocular alignment. Once any associated amblyopia is treated, surgery is performed to align the eyes. Even with successful surgical alignment, it is common for vertical deviations to develop in children with a history of congenital esotropia. The 2 most common forms of vertical deviations to develop are inferior oblique muscle overaction and dissociated vertical deviation. In inferior oblique muscle overaction, the overactive inferior oblique muscle produces an upshoot of the eye closest to the nose when the patient looks to the side (Fig. 623-3). In dissociated vertical deviation, 1 eye drifts up slowly with no movement of the other eye. Surgery may be necessary to treat either or both of these conditions.

It is important that parents realize that early successful surgical alignment is only the beginning of the treatment process. Because many children may redevelop strabismus or amblyopia, they need to be monitored closely during the visually immature period of life.

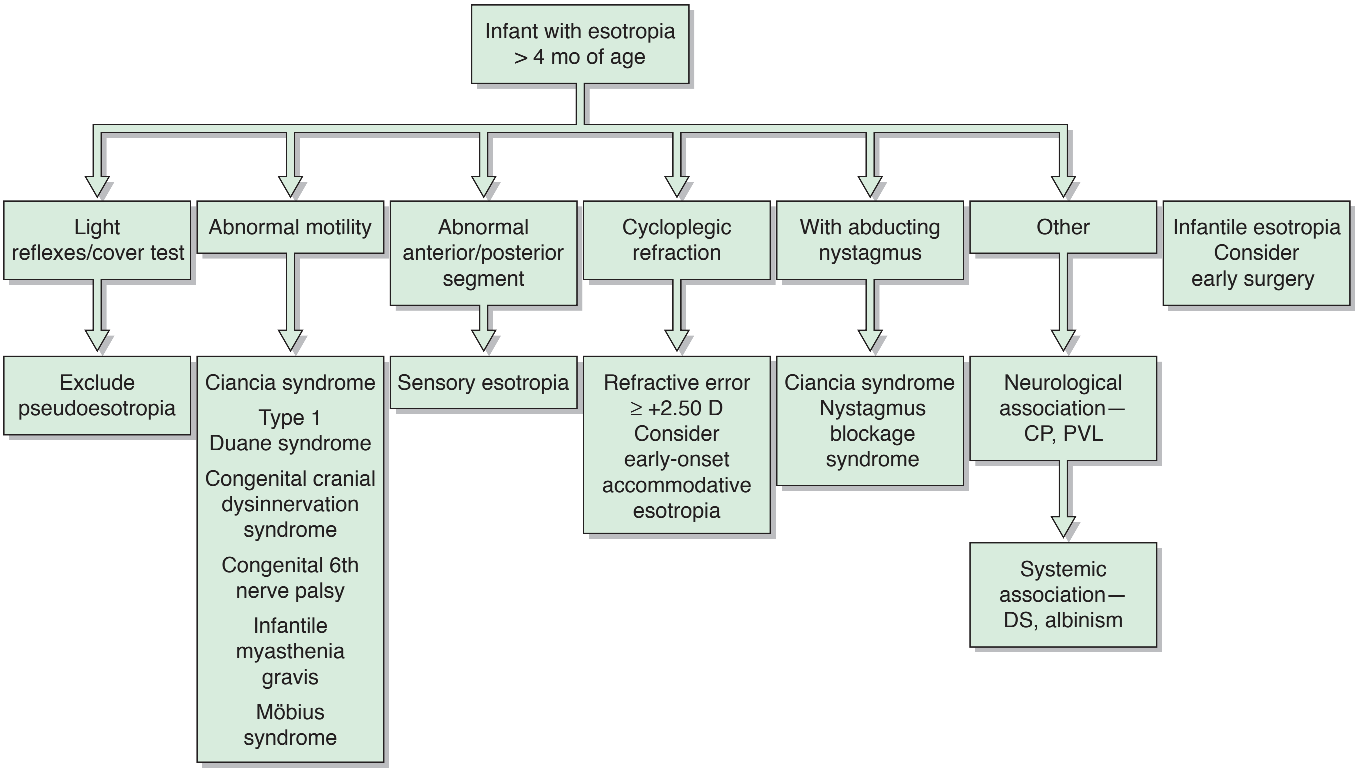

Figure 623-1 **Work-up of infant ≥4 mo of age with esotropia.** *CP*, cerebral palsy; *DS*, Down syndrome; *PVL*, periventricular leukomalacia. *(From Hoyt CS, Taylor D, editors:* Pediatric ophthalmology and strabismus, *ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 74.4, p. 767.)*

Figure 623-2 **Congenital esotropia.** Note the large angle of crossing.

Accommodative esotropia is defined as a "convergent deviation of the eyes associated with activation of the accommodative (focusing) reflex." It usually occurs in a child who is between 2 and 3 yr of age and who has a history of acquired intermittent or constant crossing. Amblyopia occurs in the majority of cases.

The mechanism of accommodative esotropia involves uncorrected hyperopia, accommodation, and accommodative convergence. The image entering a hyperopic (farsighted) eye is blurred. If the amount of hyperopia is not significant, the blurred image can be sharpened by accommodating (focusing of the lens of the eye). Accommodation is closely linked with convergence (eyes turning inward). If a child's hyperopic refractive error is large or if the amount of convergence that occurs in response to each unit of accommodative effort is great, esotropia may develop.

Figure 623-3 Inferior oblique muscle overaction.

Figure 623-4 **Accommodative esotropia.** Control of deviation with corrective lenses.

To treat accommodative esotropia, the full hyperopic (farsighted) correction is initially prescribed. These glasses eliminate a child's need to accommodate and therefore correct the esotropia (Fig. 623-4). Although many parents are initially concerned that their child will not want to wear glasses, the benefits of binocular vision and the decrease in the focusing effort required to see clearly provide a strong stimulus to wear glasses, and they are generally accepted well. The full hyperopic correction sometimes straightens the eye position at distance fixation but leaves a residual deviation at near fixation; this may be observed or treated with bifocal lenses or surgery.

It is important to warn parents of children with accommodative esotropia that the esodeviation may appear to increase without glasses after the initial correction is worn. Parents frequently state that before wearing glasses, their child had a small esodeviation, whereas after removal of the glasses, the esodeviation becomes quite large. Parents often blame the increased esodeviation on the glasses. This apparent increase is a result of a child's using the appropriate amount of accommodative effort after the glasses have been worn. When these children remove their glasses, they continue to use an accommodative effort to bring objects into proper focus and increase the esodeviation.

Most children maintain straight eyes once initially treated. Because hyperopia generally decreases with age, patients may outgrow the need to wear glasses to maintain alignment. In some patients, a residual esodeviation persists even when wearing their glasses. This condition commonly occurs when there is a delay between the onset of accommodative esotropia and treatment. In others, the esotropia may initially be eliminated with glasses but crossing redevelops and is not correctable with glasses. The crossing that is no longer correctable with glasses is the deteriorated or nonaccommodative portion. Surgery for this portion of the crossing may be indicated to restore binocular vision.

Exodeviations are the second most common type of misalignment. The divergent deviation may be intermittent or constant. Intermittent exotropia is the most common exodeviation in childhood. It is characterized by outward drifting of 1 eye, which usually occurs when a child is fixating at distance. The deviation is generally more frequent with fatigue or illness. Exposure to bright light may cause reflex closure of the exotropic eye. Because the eyes initially can be kept straight most of the time, visual acuity tends to be good in both eyes and binocular vision is initially normal.

The age at onset of intermittent exotropia varies but is often between age 6 mo and 4 yr. The decision to perform eye muscle surgery is based on the amount and frequency of the deviation. If the deviation is small and infrequent, it is reasonable to observe the child. If the exotropia is large or increasing in frequency, surgery is indicated to maintain normal binocular vision.

Constant exotropia may rarely be congenital. Congenital exotropia may be associated with neurologic disease or abnormalities of the bony orbit, as in Crouzon syndrome. Exotropia that occurs later in life may represent a deterioration of an intermittent exotropia that was present in childhood. Surgery can restore binocular vision even in long-standing cases.

Noncomitant Strabismus

When an eye muscle is paretic, palsied, or restricted, a muscle imbalance occurs in which the deviation of the eye varies according to the direction of gaze. Recent onset of a paretic muscle can be suggested by the symptom of double vision that increases in one direction, the findings of an ocular deviation that increases in the field of action of the paretic muscle, and an increase in the deviation when the child fixates with the paretic eye. It is important to differentiate a noncomitant strabismus from a comitant deviation because noncomitant forms of strabismus are often associated with trauma, systemic disorders, or neurologic abnormalities.

3rd Nerve Palsy

In the pediatric population, 3rd nerve palsies are usually congenital. The congenital form is often associated with a developmental anomaly or birth trauma. Acquired 3rd nerve palsies in children can be an ominous sign and may indicate a neurologic abnormality such as an intracranial neoplasm or an aneurysm. Other less-serious causes include an inflammatory or infectious lesion, head trauma, postviral syndromes, and migraines.

A 3rd nerve palsy, whether congenital or acquired, usually results in an exotropia and a hypotropia, or downward deviation of the affected eye, as well as complete or partial ptosis of the upper lid. This characteristic strabismus results from the action of the normal, unopposed muscles, the lateral rectus muscle, and the superior oblique muscle. If the internal branch of the 3rd nerve is involved, pupillary dilation may be noted as well. Eye movements are usually limited nasally in elevation and in depression. In addition, clinical findings and treatment may be complicated in congenital and traumatic cases of 3rd nerve palsy owing to misdirection of regenerating nerve fibers, referred to as aberrant regeneration. This results in anomalous and paradoxical eyelid, eye, and pupil movement such as elevation of the eyelid, constriction of the pupil, or depression of the globe on attempted medial gaze.

4th Nerve Palsy

These palsies can be congenital or acquired. Because the 4th nerve has a long intracranial course, it is susceptible to damage resulting from head trauma. In children, however, 4th nerve palsies are more frequently congenital than traumatic. A palsied 4th nerve results in weakness in the superior oblique muscle, which causes an upward deviation of the eye, a hypertropia. Because the antagonist muscle, the inferior oblique, is relatively unopposed, the affected eye demonstrates an upshoot when looking toward the nose. Children typically present with a head tilt to the shoulder opposite the affected eye, their chin down, and their face turned away from the affected side. This head position places the eye away from the area of greatest action of the affected muscle and therefore minimizes the deviation and the associated double vision. Long-standing head tilts may lead to facial asymmetry. Because the abnormal head posture maintains the child's ocular alignment, amblyopia is uncommon. Because no abnormality exists in the neck muscles, attempts to correct the head tilt by exercises and neck muscle surgery are ineffective. Recognition of a superior oblique paresis can be difficult because deviation of the head and the eye may be minimal. Eye muscle surgery can be performed to improve the ocular alignment and eliminate the abnormal head posture.

6th Nerve Palsy

These palsies produce markedly crossed eyes with limited ability to move the afflicted eye laterally. Children frequently present with their head turned toward the palsied muscle, a position that helps preserve binocular vision. The esotropia is largest when the eye is moved toward the affected muscle.

Congenital 6th nerve palsies are rare. Decreased lateral gaze in infants is often associated with other disorders, such as congenital esotropia or Duane retraction syndrome. In neonates, a transient 6th nerve paresis can occur; it usually clears spontaneously by 6 wk. It is believed that increased intracranial pressure associated with labor and delivery is the contributing factor.

Acquired 6th nerve palsies in childhood are often an ominous sign because the 6th nerve is susceptible to increased intracranial pressure associated with hydrocephalous and intracranial tumors. Other causes of 6th nerve defects in children include trauma, vascular malformations, meningitis, and Gradenigo syndrome. A benign 6th nerve palsy, which is painless and acquired, can be noted in infants and older children. This is frequently preceded by a febrile illness or upper respiratory tract infection and may be recurrent. Complete resolution of the palsy is usual. Although not uncommon, other causes of an acute 6th nerve palsy should be eliminated before this diagnosis is made.

Strabismus Syndromes

Special types of strabismus have unusual clinical features. Most of these disorders are caused by structural anomalies of the extraocular muscles or adjacent tissues. Most strabismus syndromes produce noncomitant misalignments.

Monocular Elevation Deficiency

A monocular elevation deficit in both abduction and adduction is referred to as monocular elevation deficiency (previously called double-elevator palsy). It may represent a paresis of both elevators, the superior rectus and inferior oblique muscles, or a possible restriction to elevation from a fibrotic inferior rectus muscle. When an affected child fixates with the nonparetic eye, the paretic eye is hypotropic and the ipsilateral upper eyelid may appear ptotic. Fixation with the paretic eye causes a hypertropia of the nonparetic eye and a disappearance of the ptosis (Fig. 623-5). Because the apparent ptosis is actually secondary to the strabismus, correction of the hypotropia treats the pseudoptosis.

Duane Syndrome

This congenital disorder of ocular motility is characterized by retraction of the globe on adduction. This is attributed to the absence of the 6th nerve nucleus and anomalous innervation of the lateral rectus muscle, which results in cocontraction of the medial and lateral rectus muscles on attempted adduction of the affected eye. Within the spectrum of Duane syndrome, patients may exhibit impairment of abduction, impairment of adduction, or upshoot or downshoot of the involved eye on adduction. They may have esotropia, exotropia, or relatively straight eyes. Many exhibit a compensatory head posture to maintain single vision. Some develop amblyopia. Surgery to improve alignment or to reduce a noticeable face turn can be helpful in selected cases. Duane syndrome usually occurs sporadically. It is sometimes inherited as an autosomal dominant trait. It usually occurs as an isolated condition but may occur in association with various other ocular and systemic anomalies.

Figure 623-5 Double-elevator palsy of the right eye. Note the disappearance of the apparent ptosis when fixating with the involved eye.

Möbius Syndrome

The distinctive features of Möbius syndrome are congenital facial paresis and abduction weakness. The facial palsy is commonly bilateral, frequently asymmetric, and often incomplete, tending to spare the lower face and platysma. Ectropion, epiphora, and exposure keratopathy may develop. The abduction defect may be unilateral or bilateral. Esotropia is common. The cause is unknown. Whether the primary defect is maldevelopment of cranial nerve nuclei, hypoplasia of the muscles, or a combination of central and peripheral factors is unclear. Some familial cases have been reported. Associated developmental defects may include ptosis, palatal and lingual palsy, hearing loss, pectoral and lingual muscle defects, micrognathia, syndactyly, supernumerary digits, and the absence of hands, feet, fingers, or toes. Surgical correction of the esotropia is indicated and any attendant amblyopia should be treated.

Brown Syndrome

In this syndrome, elevation of the eye in the adducted position is restricted (Fig. 623-6). An associated downward deviation of the affected eye in adduction may also occur. A compensatory head posture may be evident. Brown syndrome occurs as a result of restriction of the superior oblique tendon as it moves through the trochlea. Cases may be congenital or acquired. Acquired Brown syndrome may follow trauma to the orbit involving the region of the trochlea or sinus surgery. It may also occur with inflammatory processes, particularly sinusitis and juvenile idiopathic arthritis.

Acquired inflammatory Brown syndrome may respond to treatment with either nonsteroidal medications or corticosteroids. Surgery may be helpful for selected cases of Brown syndrome.

Parinaud Syndrome

This eponym designates a palsy of vertical gaze, isolated or associated with pupillary or nuclear oculomotor (3rd cranial nerve) paresis. It indicates a lesion affecting the mesencephalic tegmentum. The ophthalmic signs of midbrain disease include vertical gaze palsy, dissociation of the pupillary responses to light and to near focus, general pupillomotor paralysis, corectopia, dyscoria, accommodative disturbances, pathologic lid retraction, ptosis, extraocular muscle paresis, and convergence paralysis. Some cases have associated spasms of convergence, convergent retraction nystagmus, and vertical nystagmus, particularly on attempted vertical gaze. Combinations of these signs are referred to as the sylvian aqueduct syndrome.

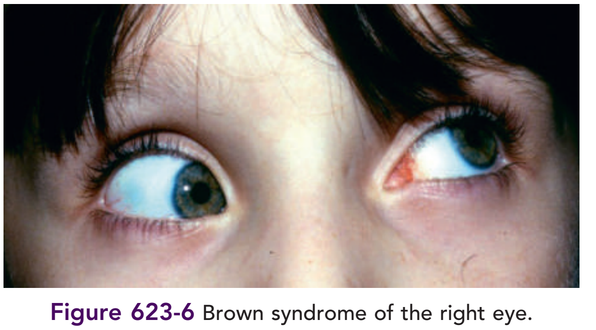

Figure 623-6 Brown syndrome of the right eye.

A principal cause of vertical gaze palsy and associated mesencephalic signs in children is tumor of the pineal gland or third ventricle. Differential diagnosis includes trauma and demyelinating disease. In children with hydrocephalus, impairment of vertical gaze and pathologic lid retraction are referred to as the setting-sun sign. A transient supranuclear disorder of gaze is sometimes seen in healthy neonates.

CONGENITAL OCULAR MOTOR APRAXIA

This congenital disorder of conjugate gaze is characterized by a defect in voluntary horizontal gaze, compensatory jerking movement of the head, and retention of slow pursuit and reflexive eye movements. Additional features are absence of the fast (refixation) phase of optokinetic nystagmus and obligate contraversive deviation of the eyes on rotation of the body. Affected children typically are unable to look quickly to either side voluntarily in response to a command or in response to an eccentrically presented object but may be able to follow a slowly moving target to either side. To compensate for the defect in purposive lateral eye movements, children jerk their head to bring the eyes into the desired position and may also blink repetitively in an attempt to change fixation. The signs tend to become less conspicuous with age.

The pathogenesis of congenital ocular motor apraxia is unknown. It may be a result of delayed myelination of the ocular motor pathways. Structural abnormalities of the central nervous system have been found in a few patients, including agenesis of the corpus callosum and cerebellar vermis, porencephaly, hamartoma of the foramen of Monro, and macrocephaly. Many children with congenital ocular motor apraxia show delayed motor and cognitive development.

NYSTAGMUS

Nystagmus (rhythmic oscillations of 1 or both eyes) may be caused by an abnormality in any one of the 3 basic mechanisms that regulate position and movement of the eyes: the fixation, conjugate gaze, or vestibular mechanism. In addition, physiologic nystagmus may be elicited by appropriate stimuli (Table 623-1).

Congenital sensory nystagmus is generally associated with ocular abnormalities that lead to decreased visual acuity; common disorders that lead to early-onset nystagmus include albinism, aniridia, achromatopsia, congenital cataracts, congenital macular lesions, and congenital optic atrophy. In some instances, nystagmus occurs as a dominant or X-linked characteristic without obvious ocular abnormalities.

Congenital idiopathic motor nystagmus is characterized by horizontal jerky oscillations with gaze preponderance; the nystagmus is coarser in one direction of gaze than in the other, with the jerk toward the direction of gaze. There are no ocular anatomic defects that cause the nystagmus, and the visual acuity is generally near normal. There may be a null point in which the nystagmus lessens and the vision improves; a compensatory head posture will develop that places the eyes into the position of least nystagmus. The cause of congenital idiopathic motor nystagmus is unknown; in some instances, it is familial. Eye muscle surgery may be performed to eliminate an abnormal head posture by bringing the point of best vision into straight-ahead gaze.

Acquired nystagmus requires prompt and thorough evaluation. Worrisome pathologic types are the gaze-paretic or gaze-evoked oscillations of cerebellar, brainstem, or cerebral disease.

Nystagmus retractorius or **convergent nystagmus** is repetitive jerking of the eyes into the orbit or toward each other. It is usually seen with vertical gaze palsy as a feature of Parinaud (sylvian aqueduct) syndrome. The causal condition may be neoplastic, vascular, or inflammatory. In children, nystagmus retractorius suggests particularly the presence of pinealoma or hydrocephalus.

A diagnostic approach to nystagmus is noted in Figures 623-7 and 623-8.

Spasmus nutans is a special type of acquired nystagmus in childhood (see also Chapter 597). In its complete form, it is characterized by the **triad** of pendular nystagmus, head nodding, and torticollis. The nystagmus is characteristically very fine, very rapid, horizontal, and pendular; it is often asymmetric, sometimes unilateral. Signs usually develop within the 1st yr or 2 of life. Components of the triad may develop at various times. In many cases, the condition is benign and self-limited, usually lasting a few months, sometimes years. The cause of this classic type of spasmus nutans, which usually resolves spontaneously, is unknown. Some children exhibiting signs resembling those of spasmus nutans have underlying brain tumors, particularly hypothalamic and chiasmal optic gliomas. Appropriate neurologic and neuroradiologic evaluation and careful monitoring of infants and children with nystagmus are therefore recommended.

Table 623-1 Specific Patterns of Nystagmus

PATTERN	DESCRIPTION	ASSOCIATED CONDITIONS
Latent nystagmus	Conjugate jerk nystagmus toward viewing eye	Congenital vision defects, occurs with occlusion of eye
Manifest latent nystagmus	Fast jerk to viewing eye	Strabismus, congenital idiopathic nystagmus
Periodic alternating	Cycles of horizontal or horizontal-rotary that change direction	Caused by both visual and neurologic conditions
Seesaw nystagmus	One eye rises and intorts as other eye falls and extorts	Usually associated with optic chiasm defects
Nystagmus retractorius	Eyes jerk back into orbit or toward each other	Caused by pressure on mesencephalic tegmentum (Parinaud syndrome)
Gaze-evoked nystagmus	Jerk nystagmus in direction of gaze	Caused by medications, brainstem lesion, or labyrinthine dysfunction
Gaze-paretic nystagmus	Eyes jerk back to maintain eccentric gaze	Cerebellar disease
Downbeat nystagmus	Fast phase beating downward	Posterior fossa disease, drugs
Upbeat nystagmus	Fast phase beating upward	Brainstem and cerebellar disease; some visual conditions
Vestibular nystagmus	Horizontal-torsional or horizontal jerks	Vestibular system dysfunction
Asymmetric or monocular nystagmus	Pendular vertical nystagmus	Disease of retina and visual pathways
Spasmus nutans	Fine, rapid, pendular nystagmus	Torticollis, head nodding; idiopathic or gliomas of visual pathways

From Kliegman R: Practical strategies in pediatric diagnosis and therapy. *Philadelphia, 1996, WB Saunders.*

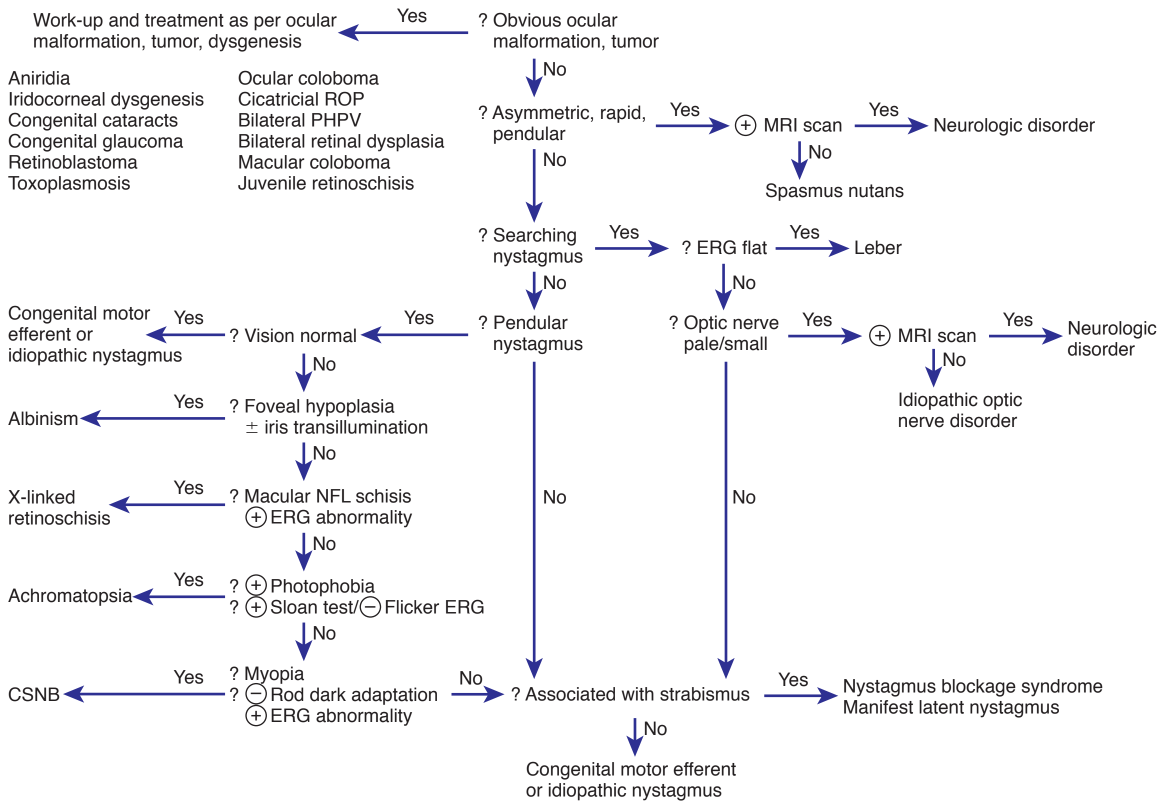

Figure 623-7 Algorithm for the work-up of an infant with nystagmus. ⊕, positive; ⊖, negative; CSNB, congenital stationary night blindness; ERG, electroretinogram; NFL, nerve fiber layer; PHPV, persistent hyperplastic primary vitreous; ROP, retinopathy of prematurity. *(From Nelson LB:* Harley's pediatric ophthalmology, *ed 4, Philadelphia, 1998, WB Saunders, p. 470.)*

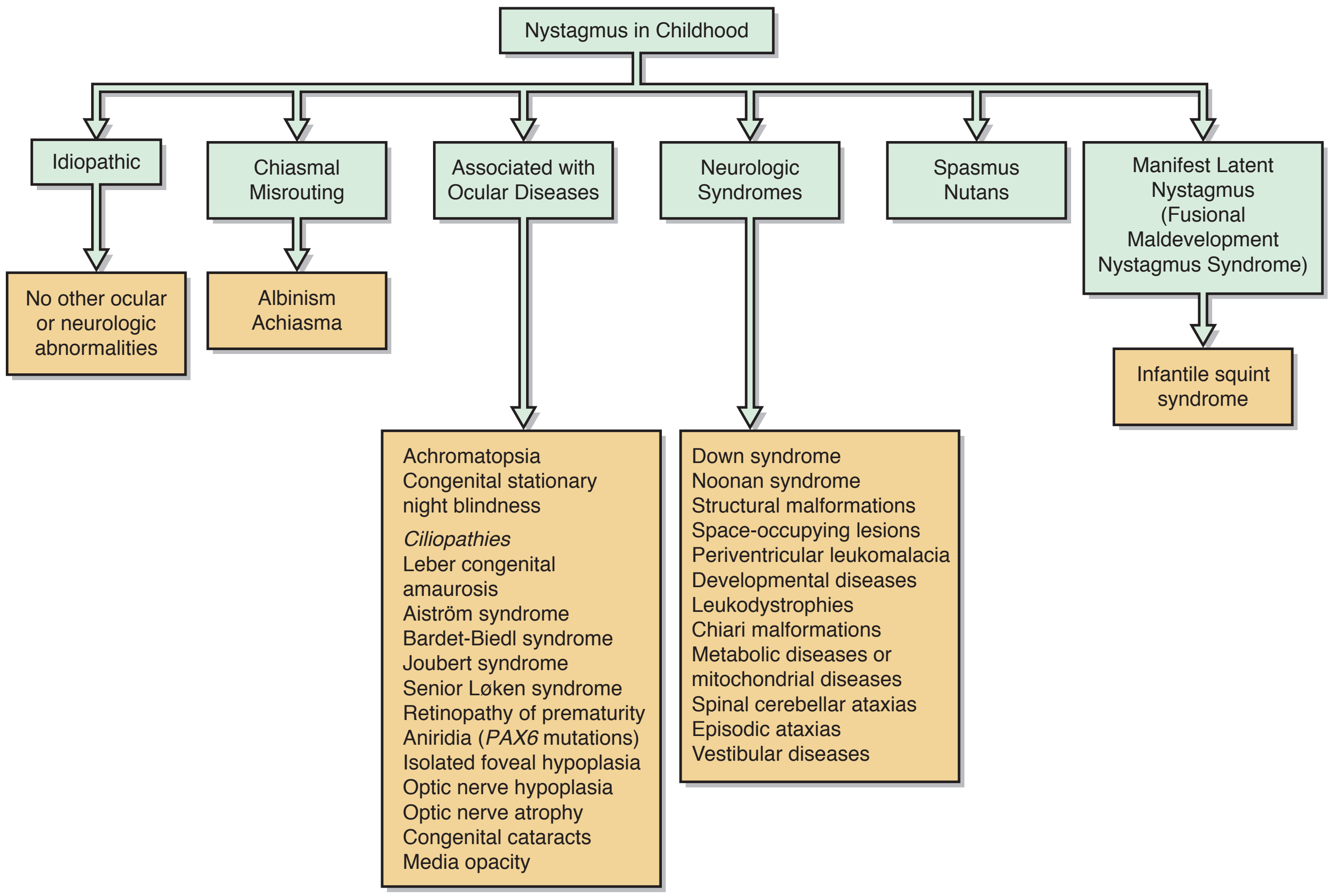

Figure 623-8 Classification of nystagmus based on associated diseases. *(From Hoyt CS, Taylor D, editors:* Pediatric ophthalmology and strabismus, *ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 89.2, p. 910.)*

Table 623-2 Specific Patterns of Nonnystagmus Eye Movements

PATTERN	DESCRIPTION	ASSOCIATED CONDITIONS
Opsoclonus	Multidirectional conjugate movements of varying rate and amplitude	Hydrocephalus, diseases of brainstem and cerebellum, neuroblastoma, paraneoplasia syndrome
Ocular dysmetria	Overshoot of eyes on rapid fixation	Cerebellar dysfunction
Ocular flutter	Horizontal oscillations with forward gaze and sometimes with blinking	Cerebellar disease, hydrocephalus, or central nervous system neoplasm
Ocular bobbing	Downward jerk from primary gaze, remains for a few sec, then drifts back	Pontine disease
Ocular myoclonus	Rhythmic to-and-fro pendular oscillations of the eyes, with synchronous nonocular muscle movement	Damage to red nucleus, inferior olivary nucleus, and ipsilateral dentate nucleus

From Kliegman R: Practical strategies in pediatric diagnosis and therapy. *Philadelphia, 1996, WB Saunders.*

OTHER ABNORMAL EYE MOVEMENTS

To be differentiated from true nystagmus are certain special types of abnormal eye movements, particularly opsoclonus, ocular dysmetria, and flutter (Table 623-2).

Opsoclonus

Opsoclonus and ataxic conjugate movements are spontaneous, non-rhythmic, multidirectional, chaotic movements of the eyes. The eyes appear to be in agitation, with bursts of conjugate movement of varying amplitude in varying directions. Opsoclonus is most often associated with infectious or autoimmune encephalitis. It may be the first sign of neuroblastoma or other tumors producing a paraneoplastic syndrome.

Ocular Motor Dysmetria

This is analogous to dysmetria of the limbs. Affected individuals show a lack of precision in performing movements of refixation, characterized by an overshoot (or undershoot) of the eyes with several corrective to-and-fro oscillations on looking from one point to another. Ocular motor dysmetria is a sign of cerebellar or cerebellar pathway disease.

Flutter-Like Oscillations

These intermittent to-and-fro horizontal oscillations of the eyes may occur spontaneously or on change of fixation. They are characteristic of cerebellar disease.

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Chapter 624

Abnormalities of the Lids

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PTOSIS

In blepharoptosis, the upper eyelid droops below its normal level. Congenital ptosis is usually a result of a localized dystrophy of the levator muscle in which the striated muscle fibers are replaced with fibrous tissue. The condition may be unilateral or bilateral and can be familial, transmitted as a dominant trait.

Parents often comment that the eye looks smaller because of the drooping eyelid. The lid crease is decreased or absent where the levator muscle would normally insert below the skin surface. Because the levator is replaced by fibrous tissue, the lid does not move downward fully in downgaze (lid lag). If the ptosis is severe, affected children often attempt to raise the lid by lifting their brow or adapting a chin-up head posture to maintain binocular vision. **Marcus Gunn jaw-winking ptosis** accounts for 5% of ptoses in children. In this syndrome, an abnormal synkinesis exists between the 5th and 3rd cranial nerves; this causes the eyelid to elevate with movement of the jaw. The wink is produced by chewing or sucking and may be more noticeable than the ptosis itself.

Although ptosis in children is often an isolated finding, it may occur in association with other ocular or systemic disorders. Systemic disorders include myasthenia gravis, muscular dystrophy, and botulism. Ocular disorders include mechanical ptosis secondary to lid tumors, blepharophimosis syndrome, congenital fibrosis syndrome, combined levator/superior rectus maldevelopment, and congenital or acquired 3rd nerve palsy. A small degree of ptosis is seen in Horner syndrome (see Chapter 622). A complete ophthalmic and systemic examination is therefore important in the evaluation of a child with ptosis.

Amblyopia may occur in children with ptosis. The amblyopia may be secondary to the lid's covering the visual axis (deprivation) or induced astigmatism (anisometropia). When amblyopia occurs, it should generally be treated before treating the ptosis.

Treatment of ptosis in a child is indicated for elimination of an abnormal head posture, improvement in the visual field, prevention of amblyopia, and restoration of a normal eyelid appearance. The timing of surgery depends on the degree of ptosis, its cosmetic and functional severity, the presence or absence of compensatory posturing, the wishes of the parents, and the discretion of the surgeon. Surgical treatment is determined by the amount of levator function that is present. A levator resection may be used in children with moderate to good function. In patients with poor or absent function, a frontalis suspension procedure may be necessary. This technique requires that a suspension material be placed between the frontalis muscle and the tarsus of the eyelid. It allows patients to use their brow and frontalis muscle more effectively to raise their eyelid. Amblyopia remains a concern even after surgical correction and should be monitored closely.

EPICANTHAL FOLDS

These vertical or oblique folds of skin extend on either side of the bridge of the nose from the brow or lid area, covering the inner canthal region. They are present to some degree in most young children and become less apparent with age. The folds may be sufficiently broad to cover the medial aspect of the eye, making the eyes appear crossed (pseudoesotropia). Epicanthal folds are a common feature of many syndromes, including chromosomal aberrations (trisomies) and disorders of single genes.

LAGOPHTHALMOS

This is a condition in which complete closure of the lids over the globe is difficult or impossible. It may be paralytic because of a facial palsy

involving the orbicularis muscle, or spastic, as in thyrotoxicosis. It may be structural when retraction or shortening of the lids results from scarring or atrophy consequent to injury (burns) or disease. For example, children with various craniosynostosis syndromes can have problematic lagophthalmos. Infants with collodion membrane may have temporary lagophthalmos caused by the restrictive effect of the membrane on the lids. Lagophthalmos may accompany proptosis or buphthalmos (enlarged cornea because of elevated intraocular pressure) when the lids, although normal, cannot effectively cover the enlarged or protuberant eye. A degree of physiologic lagophthalmos may occur normally during sleep, but functional lagophthalmos in an unconscious or debilitated patient can be a problem.

In patients with lagophthalmos, exposure of the eye may lead to drying, infection, corneal ulceration, or perforation of the cornea; the result may be loss of vision, even loss of the eye. In lagophthalmos, protection of the eye by artificial tear preparations, ophthalmic ointment, or moisture chambers is essential. Gauze pads are to be avoided because the gauze may abrade the cornea. In some cases, surgical closure of the lids (tarsorrhaphy) may be necessary for long-term protection of the eye.

LID RETRACTIONS

Pathologic retraction of the lid may be myogenic or neurogenic. Myogenic retraction of the upper lid occurs in thyrotoxicosis, in which it is associated with 3 classic signs: a staring appearance (Dalrymple sign), infrequent blinking (Stellwag sign), and lag of the upper lid on downward gaze (von Graefe sign).

Neurogenic retraction of the lids may occur in conditions affecting the anterior mesencephalon. Lid retraction is a feature of the syndrome of the sylvian aqueduct. In children, it is commonly a sign of hydrocephalus. It may occur with meningitis. Paradoxical retraction of the lid is seen in the Marcus Gunn jaw-winking syndrome. It may also be seen with attempted eye movement after recovery from a 3rd nerve palsy, if aberrant regeneration of the oculomotor nerve fibers has occurred.

Simple staring and the physiologic or reflexive lid retraction ("eye popping"), in contrast to pathologic lid retractions, occur in infants in response to a sudden reduction in illumination or as a startle reaction.

ECTROPION, ENTROPION, AND EPIBLEPHARON

Ectropion is eversion of the lid margin; it may lead to overflow of tears (epiphora) and subsequent maceration of the skin of the lid, inflammation of exposed conjunctiva, or superficial exposure keratopathy. Common causes are scarring consequent to inflammation, burns, or trauma and weakness of the orbicularis muscle as a result of facial palsy; these forms may be corrected surgically. Protection of the cornea is essential. Ectropion is also seen in certain children who have faulty development of the lateral canthal ligament; this may occur in Down syndrome.

Entropion is inversion of the lid margin, which may cause discomfort and corneal damage because of the inward turning of the lashes (trichiasis). A principal cause is scarring secondary to inflammation such as occurs in trachoma or as a sequela of Stevens-Johnson syndrome. There is also a rare congenital form. Surgical correction is effective in many cases.

Epiblepharon is commonly seen in childhood and may be confused with entropion. In epiblepharon, a roll of skin beneath the lower eyelid lashes causes the lashes to be directed vertically and to touch the cornea (Fig. 624-1). Unlike entropion, the eyelid margin itself is not rotated toward the cornea. Epiblepharon usually resolves spontaneously. If corneal scarring begins to occur, surgical correction may be necessary.

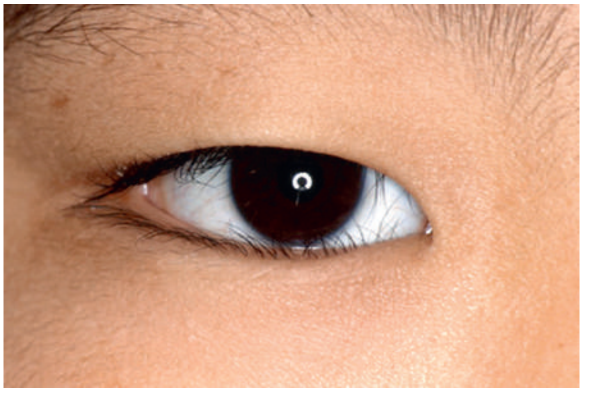

Figure 624-1 Epiblepharon.

BLEPHAROSPASM

This spastic or repetitive closure of the lids may be caused by irritative disease of the cornea, conjunctiva, or facial nerve; fatigue or uncorrected refractive error; or common tic. Thorough ophthalmic examination for pathologic causes, such as trichiasis, keratitis, conjunctivitis, or foreign body, is indicated. Local injection of botulinum toxin may give relief, but frequently must be repeated.

BLEPHARITIS

This inflammation of the lid margins is characterized by erythema and crusting or scaling; the usual symptoms are irritation, burning, and itching. The condition is commonly bilateral and chronic or recurrent. The 2 main types are **staphylococcal** and **seborrheic.** In staphylococcal blepharitis, ulceration of the lid margin is common, the lashes tend to fall out, and conjunctivitis and superficial keratitis are often associated. In seborrheic blepharitis, the scales tend to be greasy, the lid margins are less red, and ulceration usually does not occur. The blepharitis is often of mixed type.

Thorough daily cleansing of the lid margins with a cloth or moistened cotton applicator to remove scales and crusts is important in the **treatment** of both forms. Staphylococcal blepharitis is treated with an antistaphylococcal antibiotic applied directly to the lid margins. When a child also has seborrhea, concurrent treatment of the scalp is important.

Pediculosis of the eyelashes may produce a clinical picture of blepharitis. The lice can be smothered with ophthalmic-grade petrolatum ointment applied to the lid margin and lashes. Nits should be mechanically removed from the lashes. It should be remembered that pediculosis can represent a sexually transmitted disease. Molluscum virus involvement of the lids can also cause blepharitis.

HORDEOLUM (STYE)

Infection of the glands of the lid may be acute or subacute; tender focal swelling and redness are noted. The usual agent is *Staphylococcus aureus.* When the meibomian glands are involved, the lesion is referred to as an internal hordeolum; the abscess tends to be large and may point through either the skin or the conjunctival surface. When the infection involves the glands of Zeis or Moll, the abscess tends to be smaller and more superficial and points at the lid margin; it is then referred to as an external hordeolum or stye.

Treatment is frequent warm compresses and, if necessary, surgical incision and drainage. In addition, topical antibiotic preparations are often used. Untreated, the infection may progress to cellulitis of the lid or orbit, requiring the use of systemic antibiotics.

CHALAZION

A chalazion is a granulomatous inflammation of a meibomian gland characterized by a firm, nontender nodule in the upper or lower lid. This lesion tends to be chronic and differs from internal hordeolum in the absence of acute inflammatory signs. Although many chalazia subside spontaneously, excision may be necessary if they become large enough to distort vision (by inducing astigmatism by exerting pressure on the globe) or to be a cosmetic blemish. Patients who experience frequent chalazia formation, or those who have significant corneal changes secondary to the underlying blepharitis,

may benefit from systemic, low-dose erythromycin or azithromycin treatment.

COLOBOMA OF THE EYELID

This cleft-like deformity may vary from a small indentation or notch of the free margin of the lid to a large defect involving almost the entire lid. If the gap is extensive, ulceration and corneal opacities may result from exposure. Early surgical correction of the lid defect is recommended. Other deformities frequently associated with lid colobomas include dermoid cysts or dermolipomas on the globe; they often occur in a position corresponding to the site of the lid defect. Lid colobomas may also be associated with extensive facial malformation, as in mandibulofacial dysostosis (Franceschetti or Treacher Collins syndrome).

TUMORS OF THE LID

A number of lid tumors arise from surface structures (the epithelium and sebaceous glands). Nevi may appear in early childhood; most are junctional. Compound nevi tend to develop in the prepubertal years and dermal nevi at puberty. Malignant epithelial tumors (basal cell carcinoma, squamous cell carcinoma) are rare in children, but the basal cell nevus syndrome and the malignant lesions of xeroderma pigmentosum and of Rothmund-Thomson syndrome may develop in childhood.

Other lid tumors arise from deeper structures (the neural, vascular, and connective tissues). Capillary hemangiomas are especially common in children (Fig. 624-2). Many tend to regress spontaneously, although they may show alarmingly rapid growth in infancy. In many cases, the best management of such hemangiomas is patient observation, allowing spontaneous regression to occur (see Chapter 650). In the case of a rapidly expanding lesion, which may cause amblyopia by obstructing the visual axis or inducing astigmatism, corticosteroid, interferon, or surgical treatment should be considered. Systemic propranolol has been shown to be an effective treatment without the risks associated with corticosteroid use. Other treatment options include corticosteroids, systemically or by direct injection, and surgical excision. Nevus flammeus (port-wine stain), a noninvoluting hemangioma, occurs as an isolated lesion or in association with other signs of Sturge-Weber syndrome. Affected patients should be monitored for the development of glaucoma. Lymphangiomas of the lid appear as firm masses at or soon after birth and tend to enlarge slowly during the growing years. Associated conjunctival involvement, appearing as a clear, cystic, sinuous conjunctival mass, may provide a clue to the diagnosis. In some cases, there is also orbital involvement. The **treatment** is surgical excision.

Figure 624-2 Capillary hemangioma of the eyelid. *(Courtesy of Amy Nopper, MD, and Brandon Newell, MD.)*

Plexiform neuromas of the lids occur in children with neurofibromatosis, often with ptosis as the first sign. The lid may take on an S-shaped configuration. The lids may also be involved by other tumors, such as retinoblastoma, neuroblastoma, and rhabdomyosarcoma of the orbit; these conditions are discussed elsewhere.

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Chapter 625

Disorders of the Lacrimal System

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THE TEAR FILM

This film, which bathes the eye, is actually a complex structure composed of 3 layers. The innermost mucin layer is secreted by the goblet and epithelial cells of the conjunctiva and the acinar cells of the lacrimal gland. It adds stability and provides an attachment for the tear film to the conjunctiva and cornea. The middle aqueous layer constitutes 98% of the tear film and is produced by the main lacrimal gland and accessory lacrimal glands. It contains various electrolytes and proteins as well as antibodies. The outermost lipid layer is produced largely from the sebaceous meibomian glands of the eyelid and retards evaporation of the tear film. Tears drain medially into the punctal openings of the lid margin and flow through the canaliculi into the lacrimal sac and then through the nasolacrimal duct into the nose (Fig. 625-1). Preterm infants have reduced tear secretion. This may mask the diagnosis of a nasolacrimal duct obstruction and concentrate topically applied medications. Tear production reaches adult levels near term.

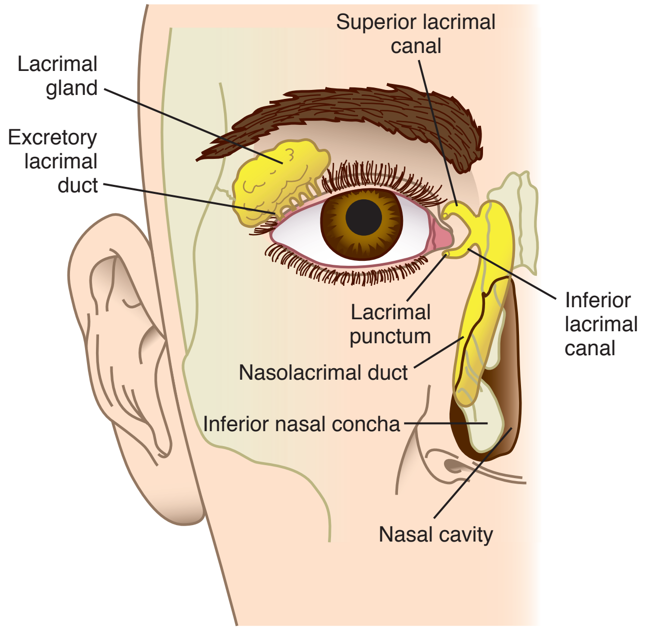

Figure 625-1 The lacrimal apparatus.

DACRYOSTENOSIS

Congenital nasolacrimal duct obstruction (CNLDO), or dacryostenosis, is the most common disorder of the lacrimal system, occurring in up to 20% of newborn infants. It is usually caused by a failure of canalization of the epithelial cells that form the nasolacrimal duct as it enters the nose (valve of Hasner). Signs of CNLDO may be present at the time of birth, although the condition may not become evident until normal tear production develops. Signs of CNLDO include an excessive tear lake, overflow of tears onto the lid and cheek, and reflux of mucoid material that is produced in the lacrimal sac. Erythema or maceration of the skin may result from irritation and rubbing produced by dripping of tears and discharge. If the blockage is complete, these signs may be severe and continuous. If obstruction is only partial, the nasolacrimal duct may be capable of draining the basal tear film that is produced. However, under periods of increased tear production (exposure to cold, wind, sunlight) or increased closure of the distal end of the nasolacrimal duct (nasal mucosal edema), tear overflow may become evident or may increase.

Infants at increased risk for CNLDO include those with trisomy 21, EEC (ectrodactyly, ectodermal dysplasia, clefting) syndrome, branchiooculofacial syndrome, craniometaphyseal or craniodiaphyseal dysplasias, LADD (lacrimo-auriculo-dento-digital) syndrome, CHARGE (coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies) syndrome, and Goldenhar syndrome.

Infants with CNLDO may develop acute infection and inflammation of the nasolacrimal sac **(dacryocystitis),** inflammation of the surrounding tissues **(pericystitis),** or, rarely, periorbital cellulitis. With dacryocystitis, the sac area is swollen, red, and tender, and patients may have systemic signs of infection such as fever and irritability.

The primary **treatment** of uncomplicated nasolacrimal duct obstruction is a regimen of nasolacrimal massage, usually 2-3 times daily, accompanied by cleansing of the lids with warm water. Topical antibiotics are used for control of mucopurulent drainage. A bland ophthalmic ointment may be used on eyelids if the skin is macerated. Most cases of CNLDO resolve spontaneously; 96% before 1 yr of age. For cases that do not resolve by 1 yr, the nasolacrimal duct may be probed in the office with topical anesthesia, with a cure rate of approximately 80%. Some ophthalmologists intubate the nasolacrimal system at the same time as this has been shown to improve the outcome of the procedure.

Acute dacryocystitis or cellulitis requires prompt treatment with systemic antibiotics. In such cases, some form of definitive surgical intervention is usually indicated.

A **dacryocystocele** (mucocele) is an unusual presentation of a nonpatent nasolacrimal sac that is obstructed both proximally and distally. Dacryocystoceles can be seen at birth or shortly after birth as a bluish subcutaneous mass just below the medial canthal tendon (Fig. 625-2). Initial treatment of dacryocystocele is usually conservative, involving massage/digital decompression of the lacrimal sac. If resolution of the dacryocystocele is not achieved with conservative management, the surgical probing may be beneficial. At times, the intranasal portion of the nasolacrimal duct becomes distended, causing respiratory compromise. In a recent study, 9.5% of infants with dacryocystocele had related respiratory compromise. These infants benefit from early probing. Another associated complication of dacryocystocele is that of dacryocystitis/cellulitis. This requires systemic antibiotics, often with hospitalization. In the aforementioned study, 65% of infants with dacryocystocele developed dacryocystitis/cellulitis. Once the cellulitis has improved, the nasolacrimal system should be probed if spontaneous resolution has not occurred.

Figure 625-2 Dacryocystocele below inner canthus of the right eye.

Not all tearing in infants and children is caused by nasolacrimal obstruction. Tearing may also be a sign of glaucoma, intraocular inflammation, or external irritation, such as that from a corneal abrasion or foreign body.

ALACRIMA AND "DRY EYE"

Alacrima refers to a wide spectrum of disorders with reduced or absent tear secretion. Occasionally, normal basal tearing occurs with an absence of emotional tearing. Etiologies can be divided into syndromes that have a pathologic association or are inherited. Associated syndromes include familial dysautonomia (Riley-Day syndrome), anhidrotic ectodermal dysplasia, and triple-A syndrome (Allgrove syndrome). Examples of pathologic association include aplasia of cranial nerve nuclei and lacrimal gland aplasia/hypoplasia. Both autosomal recessive and autosomal dominant inheritance has been reported in isolated congenital alacrima. In addition, medications with anticholinergic side effects can decrease tear production. The patients with alacrima have variable presentation including no symptoms, photophobia, foreign body sensation, eye pain, and decreased vision. The symptoms, if present, often occur early in life. Because the dryness can be severe, damage to the cornea and subsequent loss of vision may occur. The goal of treatment is to minimize corneal irritation, corneal scarring, and loss of vision. Aggressive ocular lubrication is used to prevent these sequelae.

An acquired abnormality of any layer of the tear film may produce a dry eye. Commonly acquired disorders that may lead to a decreased or unstable tear film include Sjögren syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, vitamin A deficiency, viral infections of the lacrimal gland, ocular pemphigoid, trachoma, chemical burns, irradiation, isotretinoin treatment of acne, graft-versus-host disease, and meibomian gland dysfunction. Exposure as a consequence of poor lid closure or other pathologic states can quickly lead to pathologically dry eyes. Examples of conditions leading to such exposure include ichthyosis, xeroderma pigmentosum, and certain craniosynostoses syndromes such as Crouzon, Apert, or Pfeiffer. Any tear deficiency can lead to corneal ulceration, scarring, or infection. **Treatment** includes correction of the underlying disorder when possible and frequent instillation of an ocular lubricant. In some cases, occlusion of the lacrimal puncta is helpful. In severe cases, tarsorrhaphy may be necessary to protect the cornea.

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Chapter 626

Disorders of the Conjunctiva

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CONJUNCTIVITIS

The conjunctiva reacts to a wide range of bacterial and viral agents, allergens, irritants, toxins, and systemic diseases. Conjunctivitis is common in childhood and may be infectious or noninfectious. The differential diagnosis of a red-appearing eye includes conjunctival as well as other ocular sites (Table 626-1).

Table 626-1 The Red Eye

CONDITION	ETIOLOGY	SIGNS AND SYMPTOMS	TREATMENT
Bacterial conjunctivitis	*Haemophilus influenzae, Haemophilus aegyptius, Streptococcus pneumoniae, Staphylococcus aureus, Moraxella catarrhalis*	Mucopurulent unilateral or bilateral discharge, normal vision, photophobia	Topical antibiotics, parenteral ceftriaxone for gonococcus, *H. influenzae*
Hyperacute bacterial conjunctivitis	*Neisseria gonorrhoeae, Neisseria meningitides*	Conjunctival injection and edema (chemosis); gritty sensation	
Viral conjunctivitis	Adenovirus, ECHO virus, coxsackievirus, herpes simplex virus	As above; may be hemorrhagic, unilateral	Self-limited
Neonatal conjunctivitis	*Chlamydia trachomatis*, gonococcus, chemical (silver nitrate), *S. aureus*	Palpebral conjunctival follicle or papillae; as above	Ceftriaxone for gonococcus and erythromycin for *C. trachomatis*
Allergic conjunctivitis	Seasonal pollens or allergen exposure	Itching, incidence of bilateral chemosis (edema) greater than that of erythema, tarsal papillae	Antihistamines, topical mast cell stabilizers or prostaglandin inhibitors, steroids
Keratitis	Herpes simplex virus, adenovirus, *S. pneumoniae, S. aureus, Pseudomonas, Acanthamoeba*, chemicals	Severe pain, corneal swelling, clouding, limbus erythema, hypopyon, cataracts; contact lens history with amebic infection	Specific antibiotics for bacterial/fungal infections; keratoplasty, acyclovir for herpes
Endophthalmitis	*S. aureus, S. pneumoniae, Candida albicans*, associated surgery or trauma	Acute onset, pain, loss of vision, swelling, chemosis, redness; hypopyon and vitreous haze	Antibiotics
Anterior uveitis (iridocyclitis)	JIA, postinfectious with arthritis and rash, sarcoidosis, Behçet disease, Kawasaki disease, inflammatory bowel disease	Unilateral/bilateral; erythema, ciliary flush, irregular pupil, iris adhesions; pain, photophobia, small pupil, poor vision	Topical steroids, plus therapy for primary disease
Posterior uveitis (choroiditis)	Toxoplasmosis, histoplasmosis, *Toxocara canis*	No signs of erythema, decreased vision	Specific therapy for pathogen
Episcleritis/scleritis	Idiopathic autoimmune disease (e.g., SLE, Henoch-Schönlein purpura)	Localized pain, intense erythema, unilateral; blood vessels bigger than in conjunctivitis; scleritis may cause globe perforation	Episcleritis is self-limiting; topical steroids for fast relief
Foreign body	Occupational exposure	Unilateral, red, gritty feeling; visible or microscopic size	Irrigation, removal; check for ulceration
Blepharitis	*S. aureus, Staphylococcus epidermidis*, seborrheic, blocked lacrimal duct; rarely molluscum contagiosum, *Phthirus pubis, Pediculus capitis*	Bilateral, irritation, itching, hyperemia, crusting, affecting lid margins	Topical antibiotics, warm compresses, lid hygiene
Dacryocystitis	Obstructed lacrimal sac: *S. aureus, H. influenzae,* pneumococcus	Pain, tenderness, erythema, and exudates in area of lacrimal sac (inferomedial to inner canthus); tearing (epiphora); possible orbital cellulitis	Systemic, topical antibiotics; surgical drainage
Dacryoadenitis	*S. aureus, Streptococcus*, CMV, measles, EBV, enteroviruses; trauma, sarcoidosis, leukemia	Pain, tenderness, edema, erythema over gland area (upper temporal lid); fever, leukocytosis	Systemic antibiotics; drainage of orbital abscesses
Orbital cellulitis (postseptal cellulitis)	Paranasal sinusitis: *H. influenzae, S. aureus, S. pneumoniae*, streptococci Trauma: *S. aureus* Fungi: *Aspergillus, Mucor* spp. if immunodeficient	Rhinorrhea, chemosis, vision loss, painful extraocular motion, proptosis, ophthalmoplegia, fever, lid edema, leukocytosis	Systemic antibiotics, drainage of orbital abscesses
Periorbital cellulitis (preseptal cellulitis)	Trauma: *S. aureus*, streptococci Bacteremia: pneumococcus, streptococci, *H. influenzae, S. aureus*	Cutaneous erythema, warmth, normal vision, minimal involvement of orbit; fever, leukocytosis, toxic appearance	Systemic antibiotics

CMV, cytomegalovirus; EBV, Epstein-Barr virus; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.
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Ophthalmia Neonatorum

This form of conjunctivitis, occurring in infants younger than 4 wk of age, is the most common eye disease of newborns. Its many different causal agents vary greatly in their virulence and outcome. Silver nitrate instillation may result in a mild self-limited chemical conjunctivitis, whereas *Neisseria gonorrhoeae* and *Pseudomonas* are capable of causing corneal perforation, blindness, and death. The risk of conjunctivitis in newborns depends on frequencies of maternal infections, prophylactic measures, circumstances during labor and delivery, and postdelivery exposure to microorganisms.

Epidemiology

Conjunctivitis during the neonatal period is usually acquired during vaginal delivery and reflects the sexually transmitted infections prevalent in the community. In 1880, 10% of European children developed gonococcal conjunctivitis at birth. Ophthalmia neonatorum was the leading cause of blindness during that period. The epidemiology of this condition changed dramatically in 1881, when Crede reported that 2% silver nitrate solution instilled in the eyes of newborns reduced the incidence of gonococcal ophthalmia from 10% to 0.3%.

During the 20th century, the incidence of gonococcal ophthalmia neonatorum decreased in industrialized countries secondary to widespread use of silver nitrate prophylaxis and prenatal screening and treatment of maternal gonorrhea. Gonococcal ophthalmia neonatorum has an incidence of 0.3/1,000 live births in the United States. In comparison, *Chlamydia trachomatis* is the most common organism causing ophthalmia neonatorum in the United States, with an incidence of 8.2/1,000 births.

Clinical Manifestations

The clinical manifestations of the various forms of ophthalmia neonatorum are not specific enough to allow an accurate diagnosis. Although the timing and character of the signs are somewhat typical for each cause of this condition, there is considerable overlap and physicians should not rely solely on clinical findings. Regardless of its cause, ophthalmia neonatorum is characterized by redness and chemosis (swelling) of the conjunctiva, edema of the eyelids, and discharge, which may be purulent.

Neonatal conjunctivitis is a potentially blinding condition. The infection may also have associated systemic manifestations that require treatment. Therefore, any newborn infant who develops signs of conjunctivitis needs a prompt and comprehensive systemic and ocular evaluation to determine the agent causing the infection and the appropriate treatment.

The onset of inflammation caused by silver nitrate drops usually occurs within 6-12 hr after birth, with clearing by 24-48 hr. The usual incubation period for conjunctivitis caused by *N. gonorrhoeae* is 2-5 days, and for that caused by *C. trachomatis,* 5-14 days. Gonococcal infection may be present at birth or be delayed beyond 5 days of life owing to partial suppression by ocular prophylaxis. Gonococcal conjunctivitis may also begin in infancy after inoculation by the contaminated fingers of adults. The time of onset of disease with other bacteria is highly variable.

Gonococcal conjunctivitis begins with mild inflammation and a serosanguineous discharge. Within 24 hr, the discharge becomes thick and purulent, and tense edema of the eyelids with marked chemosis occurs. If proper treatment is delayed, the infection may spread to involve the deeper layers of the conjunctivae and the cornea. Complications include corneal ulceration and perforation, iridocyclitis, anterior synechiae, and rarely panophthalmitis. Conjunctivitis caused by *C. trachomatis* (inclusion blennorrhea) may vary from mild inflammation to severe swelling of the eyelids with copious purulent discharge. The process involves mainly the tarsal conjunctivae; the corneas are rarely affected. Conjunctivitis caused by *Staphylococcus aureus* or other organisms is similar to that produced by *C. trachomatis.* Conjunctivitis caused by *Pseudomonas aeruginosa* is uncommon, acquired in the nursery, and a potentially serious process. It is characterized by the appearance on days 5-18 of edema, erythema of the lids, purulent discharge, pannus formation, endophthalmitis, sepsis, shock, and death.

Diagnosis

Conjunctivitis appearing after 48 hr should be evaluated for a possibly infectious cause. Gram stain of the purulent discharge should be performed and the material cultured. If a viral cause is suspected, a swab should be submitted in tissue culture media for virus isolation. In chlamydial conjunctivitis, the diagnosis is made by examining Giemsa-stained epithelial cells scraped from the tarsal conjunctivae for the characteristic intracytoplasmic inclusions, by isolating the organisms from a conjunctival swab using special tissue culture techniques, by immunofluorescent staining of conjunctival scrapings for chlamydial inclusions, or by tests for chlamydial antigen or DNA. The differential diagnosis of ophthalmia neonatorum includes dacryocystitis caused by congenital nasolacrimal duct obstruction with lacrimal sac distention (dacryocystocele; see Chapter 625).

Treatment

Treatment of infants in whom gonococcal ophthalmia is suspected and the Gram stain shows the characteristic intracellular Gram-negative diplococci should be initiated immediately with ceftriaxone, 50 mg/kg/24 hr for 1 dose, not to exceed 125 mg. The eye should also be irrigated initially with saline every 10-30 min, gradually increasing to 2-hr intervals until the purulent discharge has cleared. An alternative regimen includes cefotaxime (100 mg/kg/24 hr given IV or IM every 12 hr for 7 days or 100 mg/kg as a single dose). Treatment is extended if sepsis or other extraocular sites are involved (meningitis, arthritis). Neonatal conjunctivitis secondary to chlamydial infections is treated with oral erythromycin (50 mg/kg/24 hr in 4 divided doses) for 2 wk. This cures conjunctivitis and may prevent subsequent chlamydial pneumonia. *Pseudomonas* neonatal conjunctivitis is treated with systemic antibiotics, including an aminoglycoside, plus local saline irrigation and gentamicin ophthalmic ointment. Staphylococcal conjunctivitis is treated with parenteral methicillin and local saline irrigation.

Prognosis and Prevention

Before the institution of topical ophthalmic prophylaxis at birth, gonococcal ophthalmia was a common cause of blindness or permanent eye damage. If properly applied, this form of prophylaxis is highly effective unless infection is present at birth. Drops of 0.5% erythromycin or 1% silver nitrate are instilled directly into the open eyes at birth using wax or plastic single-dose containers. Saline irrigation after silver nitrate application is unnecessary. Silver nitrate is ineffective against active infection and may have limited use against *Chlamydia*. Povidone-iodine (2% solution) may also be an effective prophylactic agent, especially in developing countries.

Identification of maternal gonococcal infection and appropriate treatment has become a standard element of routine prenatal care. An infant born to a woman who has untreated gonococcal infection should receive a single dose of ceftriaxone, 50 mg/kg (maximum 125 mg) IV or IM, in addition to topical prophylaxis. The dose should be reduced for premature infants. Penicillin (50,000 units) should be used if the mother's gonococcal isolate is known to be penicillin sensitive.

Neither topical prophylaxis nor topical treatment prevents the afebrile pneumonia that occurs in 10-20% of infants exposed to *C. trachomatis.* Although chlamydial conjunctivitis is often a self-limiting disease, chlamydial pneumonia may have serious consequences. It is important that infants with chlamydial disease receive systemic treatment. Treatment of colonized pregnant women with erythromycin may prevent neonatal disease.

Acute Purulent Conjunctivitis

This is characterized by more or less generalized (bilateral in 50-75%) conjunctival hyperemia, edema, mucopurulent exudate, glued eyes (lids stuck together after sleeping), and various degrees of ocular pain and discomfort. It is usually a result of bacterial infection. In addition, there is usually little or no pruritus or periauricular lymph node enlargement; the peak season is between December and April. Bacterial conjunctivitis is more common in young children (<5 yr), whereas viral conjunctivitis is more common among adults. The most frequent causes are nontypeable *Haemophilus influenzae* (60-80%) (associated

Table 626-2 Topical Antibiotics Used to Treat Bacterial Conjunctivitis: Adult Dosages

DRUG	DOSAGE
Bacitracin (AK-Tracin, Bacticin) ointment	Apply 0.5 inch in eye q3-4h
Ciprofloxacin (Ciloxan) 0.3% ophthalmic solution	1-2 gtt in eye q15min × 6h, then q30min × 18h, then q1h × 1 day, then q4h × 12 days*
Gatifloxacin (Zymar) 0.3% ophthalmic solution	1 gt in eye q2h up to 8 × per day × 2 days, then 1 gt qid × 5 days
Gentamicin (Gentak, Gentasol) 0.3% ophthalmic solution or ointment	Ointment: 0.5 inch applied to eye 2-3 × per day Solution: 1-2 gtt in eye q4h
Levofloxacin (Quixin) 0.5% ophthalmic solution	1-2 gtt in eye q2h × 2 days while awake, then q4h × 5 days while awake
Moxifloxacin (Vigamox) 0.5% ophthalmic solution	1 gt in eye tid × 7 days
Neomycin/polymyxin B/gramicidin (Neosporin) ophthalmic solution	1-2 gtt in eye q4h × 7-10 days
Ofloxacin (Ocuflox) 0.3% ophthalmic solution	1-2 gtt in eye q2-4h × 2 days, then 1-2 gtt in eye qid × 5 days
Polymyxin B and trimethoprim (Polytrim) ophthalmic solution	1 gt in eye q3h × 7-10 days
Sulfacetamide (Isopto Cetamide, Ocusulf-10, Sodium Sulamyd, Sulf-10, AK-Sulf) 10% ophthalmic solution, ointment	Ointment: 0.5-inch ribbon in eye q3-4h and qhs × 7 days Solution: 1-2 gtt in eye q2-3h × 7-10 days
Tobramycin (AK-Tob, Tobrex) 0.3% ophthalmic solution	1-2 gtt in eye q4h

*Exceeds dosage recommended by the manufacturer.
From: Bope ET, Kellerman RD, editors: Conn's current therapy, *Philadelphia, 2014, Elsevier/Saunders, Table 2, p. 321.*

with ipsilateral otitis media), pneumococci (20%), and staphylococci (5-10%). Bacterial purulent conjunctivitis, especially that caused by pneumococcus or *H. influenzae,* may occur in epidemics. Conjunctival smear and culture are helpful in differentiating specific types. These common forms of acute purulent conjunctivitis usually respond well to warm compresses and topical instillation of antibiotic drops, which shortens the duration of illness and hastens return to school. Topical antibiotics include aminoglycosides (gentamicin, tobramycin), quinolones (ciprofloxacin, ofloxacin, moxifloxacin), and combinations of antibiotics and chloramphenicol (Table 626-2). Brazilian purpuric fever caused by *Haemophilus aegyptius* manifests as conjunctivitis and sepsis. **Hyperacute bacterial conjunctivitis** is caused by gonococcal or meningococcal infection and requires systemic, not topical, antimicrobial therapies. Concerning symptoms that should require an ophthalmology referral include vision loss, severe purulent discharge, corneal involvement, conjunctival scarring, cutaneous-conjunctival involvement (Stevens-Johnson syndrome), recurrent symptoms, severe pain, herpes simplex virus infection, severe photophobia, and involvement with a contact (cosmetic or prescription) lens.

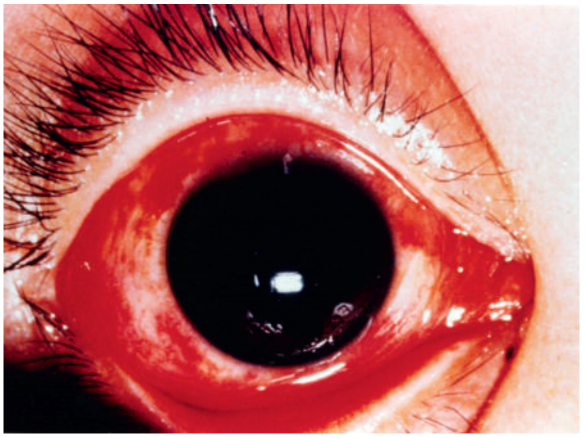

Figure 626-1 Hemorrhagic conjunctivitis caused by enterovirus 70. *(From Kono R, Uchida Y. Acute haemorrhagic conjunctivitis. Ophthalmol Dig 39:14, 1977.)*

Viral Conjunctivitis

This is generally characterized by a watery discharge. Follicular changes (small aggregates of lymphocytes) are often found in the palpebral conjunctiva. Involvement is often unilateral and associated with periauricular nodes. Viral conjunctivitis occurs more often in the summer and in older children (>5 yr). Conjunctivitis resulting from adenovirus infection is relatively common, sometimes with corneal involvement as well as pharyngitis or pneumonia. Outbreaks of conjunctivitis caused by enterovirus are also encountered; this type may be hemorrhagic (Fig. 626-1). Acute hemorrhagic conjunctivitis may be epidemic because of enterovirus CA24 or 70 and is characterized by red, swollen, and painful eyes with a hemorrhagic watery discharge. Conjunctivitis is commonly associated with such systemic viral infections as the childhood exanthems, particularly measles. Viral conjunctivitis is usually self-limited.

Epidemic Keratoconjunctivitis

This is caused by adenovirus type 8 and is transmitted by direct contact. It initially presents as a sensation of a foreign body beneath the lids, with itching and burning. Edema (chemosis) and photophobia develop rapidly, and large oval follicles appear within the conjunctiva. Preauricular adenopathy and a pseudomembrane on the conjunctival surface occur frequently. Subepithelial corneal infiltrates may develop and may cause blurring of vision; these usually disappear but may permanently reduce visual acuity. Corneal complications are less common in children than in adults. Children may have associated upper respiratory tract infection and pharyngitis. No specific medical therapy is available to decrease the symptoms or shorten the course of the disease. Emphasis must be placed on prevention of spread of the disease. Replicating virus is present in 95% of patients 10 days after the appearance of symptoms.

Pharyngoconjunctival fever presents with high fever, pharyngitis, bilateral conjunctivitis, and periauricular lymphadenopathy. It is highly contagious.

Membranous and Pseudomembranous Conjunctivitis

These types of conjunctivitis can be encountered in a number of diseases. The classic membranous conjunctivitis is that of diphtheria, accompanied by a fibrin-rich exudate that forms on the conjunctival surface and permeates the epithelium; the membrane is removed with difficulty and leaves raw bleeding areas. In pseudomembranous conjunctivitis, the layer of fibrin-rich exudate is superficial and can often be stripped easily, leaving the surface smooth. This type occurs with many bacterial and viral infections, including staphylococcal, pneumococcal, streptococcal, or chlamydial conjunctivitis, and in epidemic keratoconjunctivitis. It is also found in vernal conjunctivitis and in Stevens-Johnson disease.

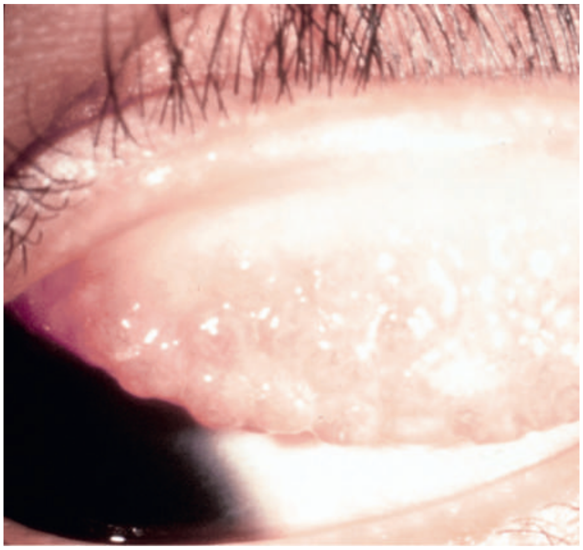

Figure 626-2 Vernal conjunctivitis.

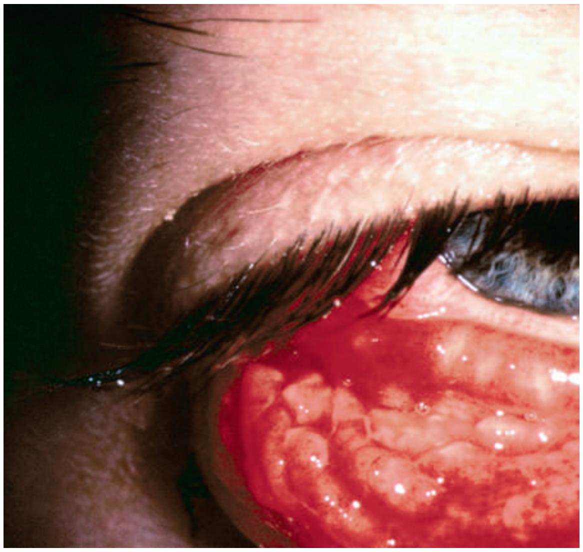

Figure 626-3 Conjunctival granulomas in Parinaud oculoglandular syndrome.

Allergic Conjunctivitis

This is usually accompanied by intense itching, clear watery discharge, and conjunctival edema (chemosis). It is commonly seasonal (spring-summer). Cold compresses and topical antihistamine drops give symptomatic relief. Topical mast cell stabilizers or prostaglandin inhibitors may also help. In selected cases, topical corticosteroids are used under an ophthalmologist's supervision but should not be used routinely or for a long time.

Vernal Conjunctivitis

This usually begins in the prepubertal years and may recur for many years. Atopy appears to have a role in its origin, but the pathogenesis is uncertain. Extreme itching and tearing are the usual complaints. Large, flattened, cobblestone-like papillary lesions of the palpebral conjunctivae are characteristic (Fig. 626-2). A stringy exudate and a milky conjunctival pseudomembrane are frequently present. Small elevated lesions of the bulbar conjunctiva adjacent to the limbus (limbal form) may be found. Smear of the conjunctival exudate reveals many eosinophils. Topical corticosteroid therapy and cold compresses afford some relief. Topical mast cell stabilizers or prostaglandin inhibitors are useful when long-term control is needed. The long-term use of corticosteroids should be avoided.

Parinaud Oculoglandular Syndrome

This represents a form of cat-scratch disease and is caused by *Bartonella henselae,* which is transmitted from cat to cat by fleas (see Chapter 209). Kittens are more likely than adult cats to be infected. Humans can become infected when they are scratched by a cat. In addition, bacteria may pass from a cat's saliva to its fur during grooming. The bacteria can then be deposited on the conjunctiva after rubbing one's eyes after handling the cat. Lymphadenopathy and conjunctivitis are hallmarks of the disease. Conjunctival granulomas may develop (Fig. 626-3). The course is generally self-limited, but antibiotics may be used in some cases.

Chemical Conjunctivitis

This can result when an irritating substance enters the conjunctival sac (as in the acute but benign conjunctivitis caused by silver nitrate in newborns). Other common offenders are household cleaning substances, sprays, smoke, smog, and industrial pollutants. Alkalis tend to linger in the conjunctival tissues and continue to inflict damage for hours or days. Acids precipitate the proteins in tissues and so produce their effect immediately. In either case, prompt, thorough, and copious irrigation is crucial. Extensive tissue damage, even loss of the eye, can result, especially if the offending agent is an alkali.

Other Conjunctival Disorders

Subconjunctival hemorrhage is manifested by bright or dark red patches in the bulbar conjunctiva and may result from injury or inflammation. It commonly occurs spontaneously. It may occasionally result from severe sneezing or coughing. Rarely, it may be a manifestation of a blood dyscrasia. Subconjunctival hemorrhages are self-limiting and require no treatment.

Pinguecula is a yellowish-white, slightly elevated mass on the bulbar conjunctiva, usually in the interpalpebral region. It represents elastic and hyaline degenerative changes of the conjunctiva. No treatment is required except for cosmetic reasons, in which case simple excision suffices.

Pterygium is a fleshy triangular conjunctival lesion that may encroach on the cornea. It typically occurs in the nasal interpalpebral region. The pathologic findings are similar to those of a pinguecula. The development of pterygia is related to exposure to ultraviolet light, and it therefore is more commonly found among people who live near the equator. Removal is suggested when the lesion encroaches far onto the cornea. Recurrence after removal is common.

Dermoid cyst and **dermolipoma** are benign lesions, clinically similar in appearance. They are smooth, elevated, round to oval lesions of various sizes. The color varies from yellowish white to fleshy pink. The most frequent site is the upper outer quadrant of the globe; they also commonly occur near or straddling the limbus. Dermolipoma is composed of adipose and connective tissue. Dermoid cysts may also contain glandular tissue, hair follicles, and hair shafts. Excision for cosmetic reasons is feasible. Dermolipomas are often connected to the extraocular muscles, making their complete removal impossible without sacrificing ocular motility.

Conjunctival nevus is a small, slightly elevated lesion that may vary in pigmentation from pale salmon to dark brown. It is usually benign, but careful observation for progressive growth or changes suggestive of malignancy is advised.

Symblepharon is a cicatricial adhesion between the conjunctiva of the lid and the globe; the lower lid is usually affected. It follows operation or injuries, especially burns from lye, acids, or molten metals. It is a serious complication of Stevens-Johnson syndrome. It may interfere with motion of the eyeball and may cause diplopia. The adhesions should be separated and the raw surfaces kept from uniting during healing. Grafts of oral mucous membrane may be necessary.

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Chapter 627

Abnormalities of the Cornea

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MEGALOCORNEA

This is a nonprogressive symmetric condition characterized by an enlarged cornea (>12 mm in diameter) and an anterior segment in which there is no evidence of previous or concurrent ocular hypertension. High myopia is frequently present and may lead to reduced vision. A frequent complication is the development of lens opacities in adult life. All modes of inheritance have been described, although X-linked recessive is the most common; therefore, this disorder more commonly affects males. Systemic abnormalities that may be associated with megalocornea include Marfan syndrome, craniosynostosis, and Alport syndrome. The cause of the enlargement of the cornea and the anterior segment is unknown, but possible explanations include a defect in the growth of the optic cup and an arrest of congenital glaucoma. The region on the X chromosome responsible for this disorder has been identified.

Pathologic corneal enlargement caused by glaucoma is to be differentiated from this anomaly. Any progressive increase in the size of the cornea, especially when accompanied by photophobia, lacrimation, or haziness of the cornea, requires prompt ophthalmologic evaluation.

MICROCORNEA

Microcornea, or anterior microphthalmia, is an abnormally small cornea in an otherwise relatively normal eye. It may be familial, with transmission being dominant more often than recessive. More commonly, a small cornea is just one feature of an otherwise developmentally abnormal or microphthalmic eye; associated defects include colobomas, microphakia, congenital cataract, glaucoma, and aniridia.

KERATOCONUS

This is a disease of unclear pathogenesis characterized by progressive thinning and bulging of the central cornea, which becomes cone shaped. Although familial cases are known, most cases are sporadic. It is a common ocular condition with an incidence of 1 in 2,000 adults. Eye rubbing and contact lens wear have been implicated as pathogenic, but the evidence to support this is equivocal. The incidence is increased in individuals with atopy, Down syndrome, Marfan syndrome, and retinitis pigmentosa.

Most cases are bilateral, but involvement may be asymmetric. The disorder usually presents and progresses rapidly during adolescence; progression slows and stabilizes when patients reach full growth. Descemet membrane may occasionally be stretched beyond its elastic breaking point, causing an acute rupture in the membrane with resultant sudden and marked corneal edema (acute hydrops, Fig. 627-1) and decrease in vision. The corneal edema resolves as endothelial cells cover the defective area. Some degree of corneal scarring occurs, but the visual acuity is often better than before the initial incident. Signs of keratoconus include Munson sign (bulging of the lower eyelid on looking downward) and the presence of a Fleischer ring (a deposit of iron in the epithelium at the base of the cone). Glasses and contact lenses are the first step in treating the visual distortion caused by keratoconus. Emerging research now suggests that a corneal cross-linking procedure using riboflavin and UV light may arrest the progression of keratoconus. If the cornea vaults too severely for the vision to be corrected with contact lenses then a corneal transplant must be performed to restore vision.

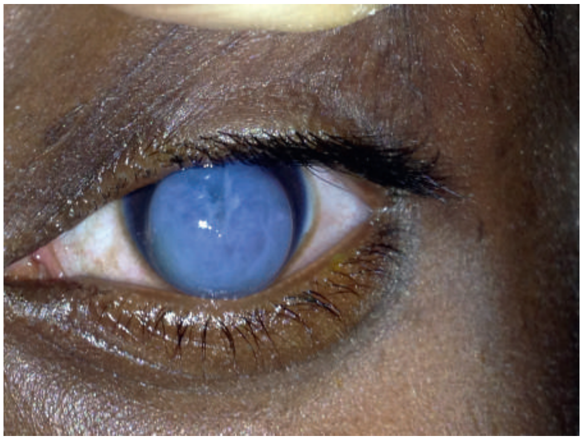

Figure 627-1 Acute hydrops from keratoconus with significant corneal edema.

NEONATAL CORNEAL OPACITIES

Loss of the normal transparency of the cornea in neonates may occur secondary to either intrinsic hereditary or extrinsic environmental causes (Table 627-1).

SCLEROCORNEA

In sclerocornea, the normally translucent cornea is replaced by sclera-like tissue. Instead of a clearly demarcated cornea, white, feathery, often ill-defined and vascularized tissue develops in the peripheral cornea, appearing to blend with and extend from the sclera. The central cornea is usually clearer, but total replacement of the cornea with sclera may occur. The curvature of the cornea is often flatter, similar to the sclera. Potentially coexisting abnormalities include a shallow anterior chamber, iris abnormalities, and microphthalmos. This condition is usually bilateral. In approximately 50% of cases, a dominant or recessive inheritance has been described. Sclerocornea has been reported in association with numerous systemic abnormalities including limb deformities, craniofacial defects, and genitourinary disorders. In generalized sclerocornea, especially if bilateral, early corneal transplantation should be considered in an effort to provide vision.

Sclerocornea is classified into one of the congenital corneal opacity disorders with cornea plana if it involves peripheral scleralization or total sclerocornea disorders such as Peters anomaly.

PETERS ANOMALY

Peters anomaly is a central corneal opacity (leukoma) that is present at birth (Fig. 627-2). It is often associated with iridocorneal adhesions that extend from the iris collarette to the border of the corneal opacity. Approximately 50% of patients have other ocular abnormalities, which may include cataracts, glaucoma, and microcornea. As many as 80% of cases may be bilateral and 60% are associated with systemic malformations (Peters plus syndrome) that may include short stature, developmental delay, dysmorphic facial features, and cardiac, genitourinary, and central nervous system malformations. Some investigators have divided Peters anomaly into 2 types: a mesodermal or neuroectodermal form (type I), which does not show associated lens changes, and a surface ectodermal form (type II), which does. Histologic findings include a focal absence of Descemet membrane and corneal endothelium in the region of the opacity. Peters anomaly may be caused by incomplete migration and differentiation of the precursor cells of the central corneal endothelium and Descemet membrane or a defective separation between the primitive lens and cornea during embryogenesis.

Table 627-1 STUMPED: Differential Diagnosis of Neonatal Corneal Opacities

DIAGNOSIS	LATERALITY	OPACITY	OCULAR PRESSURE	OTHER OCULAR ABNORMALITIES	NATURAL HISTORY	INHERITANCE
S—Sclerocornea	Unilateral or bilateral	Vascularized, blends with sclera, clearer centrally	Normal (or elevated)	Cornea plana	Nonprogressive	Sporadic
T—Tears in endothelium and Descemet membrane						
Birth trauma	Unilateral	Diffuse edema	Normal	Possible hyphema, periorbital ecchymoses	Spontaneous improvement in 1 mo	Sporadic
Infantile glaucoma	Bilateral	Diffuse edema	Elevated	Megalocornea, photophobia and tearing, abnormal angle	Progressive unless treated	Autosomal recessive
U—Ulcers						
Herpes simplex keratitis	Unilateral	Diffuse with geographic epithelial defect	Normal	None	Progressive	Sporadic
Congenital rubella	Bilateral	Disciform or diffuse edema, no frank ulceration	Normal or elevated	Microphthalmos, cataract, pigment epithelial mottling	Stable, may clear	Sporadic
Neurotrophic exposure	Unilateral or bilateral	Central ulcer	Normal	Lid anomalies, congenital sensory neuropathy	Progressive	Sporadic
M—Metabolic (rarely present at birth) (mucopolysaccharidoses IH, IS; mucolipidosis type IV)*	Bilateral	Diffuse haze, denser peripherally	Normal	Few	Progressive	Autosomal dominant
P—Posterior corneal defect	Unilateral or bilateral	Central, diffuse haze or vascularized leukoma	Normal or elevated	Anterior chamber cleavage syndrome	Stable, sometimes early clearing or vascularization	Sporadic, autosomal recessive
E—Endothelial dystrophy						
Congenital hereditary endothelial dystrophy	Bilateral	Diffuse corneal edema, marked corneal thickening	Normal	None	Stable	Autosomal dominant or recessive
Posterior polymorphous dystrophy	Bilateral	Diffuse haze, normal corneal thickness	Normal	Occasional peripheral anterior synechiae	Slowly progressive	Autosomal dominant
Congenital hereditary stromal dystrophy	Bilateral	Flaky, feathery stromal opacities; normal corneal thickness	Normal	None	Stable	Autosomal dominant
D—Dermoid	Unilateral or bilateral	White vascularized mass, hair, lipid arc	Normal	None	Stable	Sporadic

*Mucopolysaccharidosis IH (Hurler syndrome); mucopolysaccharidosis IS (Scheie syndrome).

From Nelson LB, Calhoun JH, Harley RD: Pediatric ophthalmology, *ed 3, Philadelphia, 1991, WB Saunders, p. 210.*

CORNEAL DYSTROPHIES

These are rare inherited disorders that may present during childhood or early adulthood with bilateral involvement (although severity may be asymmetric) that progresses with time. In most, inheritance is autosomal dominant with variable expression; the most common mutation is in *TGFB1*, which is associated with the granular corneal dystrophy types 1 and 2, as well as lattice corneal dystrophy. Congenital hereditary endothelial dystrophy is both an autosomal recessive (*SLC4A11*) and dominant (unknown gene) disorder; the recessive form presents at birth and is more severe.

Figure 627-2 Peters anomaly. Central opacity in a patient with Peters anomaly.

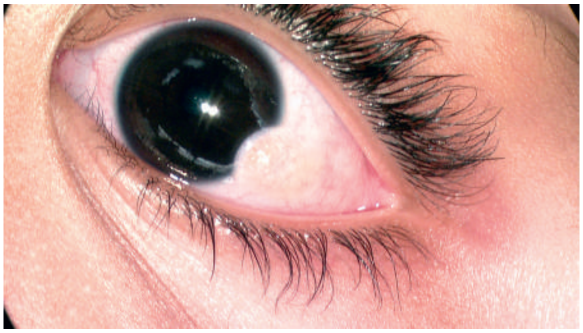

Figure 627-3 Limbal dermoid. Inferotemporal lesion in a patient with Goldenhar syndrome.

DERMOIDS

Epibulbar dermoids are choristomas. They are often present at birth and may increase in size with age. They occur most frequently in the lower temporal quadrant. They most commonly straddle the limbus and extend into the peripheral cornea (Fig. 627-3). Rarely, they may be confined entirely to the cornea or conjunctiva. Epibulbar (or limbal) dermoids may cause visual disturbance by encroaching on the visual axis or by contributing to the development of astigmatism, which may lead to amblyopia.

A dermoid usually appears as a well-circumscribed rounded or oval, gray or pinkish-yellow mass with a dry surface from which short hairs may protrude. It may affect only the superficial layers of the cornea, although full-thickness involvement is common. Associated ocular anomalies include eyelid and iris colobomas, microphthalmos, and retinal and choroidal defects. A total of 30% of dermoids are associated with systemic abnormalities. Many of the associated anomalies involve developmental defects of the first branchial arch (vertebral anomalies, dysostosis of the facial bones, ear anomalies and dental anomalies, and Goldenhar syndrome). Epibulbar dermoids are found in 75% of cases of Goldenhar syndrome.

DENDRITIC KERATITIS

Infection of the cornea with the herpes simplex virus produces a characteristic lesion of the corneal epithelium, referred to as a dendrite; it has a branching tree-like pattern that can be demonstrated by fluorescein staining. The acute episode is accompanied by pain, photophobia, tearing, blepharospasm, and conjunctival injection. Specific treatment may include mechanical debridement of the involved corneal epithelium to remove the source of infection and eliminate an antigenic stimulus to inflammation in the adjacent stroma. Medical treatment involves the use of trifluridine, topical ganciclovir, or systemic acyclovir. In addition, a cycloplegic agent is useful to relieve pain from spasm of the ciliary muscle. Overly aggressive topical antiviral treatment itself can be toxic to the cornea and should be avoided. Recurrent infection and deep stromal involvement can lead to corneal scarring and loss of vision.

Topical use of corticosteroids causes exacerbation of superficial herpetic disease of the eye and may lead to corneal perforation; eyedrops combining steroids and antibiotics are therefore to be avoided in treatment of red eye unless there are clear-cut indications for their use and close supervision during therapy.

Infants born to mothers infected with herpes simplex virus should be examined carefully for signs of ocular involvement. Intravenous acyclovir is required for treatment of ocular herpes in newborns.

CORNEAL ULCERS

The usual signs and symptoms are focal or diffuse corneal haze, hyperemia, lid edema, pain, photophobia, tearing, and blepharospasm. Hypopyon (pus in the anterior chamber) is common. Corneal ulcers require prompt treatment. They result most frequently from contact lens wear and traumatic lesions that become secondarily infected. Many organisms are capable of infecting the cornea. One of the most serious is *Pseudomonas aeruginosa;* it can rapidly destroy stromal tissue and lead to corneal perforation. *Neisseria gonorrhoeae* also is particularly damaging to the cornea. Indolent ulcers may be caused by fungi, often in association with the use of contact lenses. In each case, scrapings of the cornea must be studied in an effort to identify the infectious agent and to determine the best therapy. Although aggressive local treatment is generally needed to save the eye, systemic treatment may be necessary in some cases as well. Perforation or scarring resulting from corneal ulceration is an important cause of blindness throughout the world and is estimated to be responsible for 10% of blindness in the United States.

Unexplained corneal ulcers in infants and young children should raise the question of a sensory defect, as in Riley-Day or Goldenhar-Gorlin syndrome, or of a metabolic disorder such as tyrosinemia (Fig. 627-4). Corneal ulceration can also occur as a consequence of severe vitamin deficiencies, such as those seen with cystic fibrosis.

PHLYCTENULES

These are small, yellowish, slightly elevated lesions usually located at the corneal limbus; they may encroach on the cornea and extend centrally. A small corneal ulcer is often found at the head of the advancing lesion, with a fascicle of blood vessels behind the head of the lesion. Although once thought to represent a sign of systemic tuberculin infection, phlyctenular keratoconjunctivitis is now accepted as a morphologic expression of delayed hypersensitivity to diverse antigens. In children, it commonly occurs as a result of a hypersensitivity reaction to nonpathogenic staphylococcal strains at the eyelid margin. Treatment usually consists of eliminating the underlying disorder, usually staphylococcal blepharitis or meibomianitis, and suppressing the immune response with the use of topical corticosteroid therapy. A superficial stromal pannus and scarring sometimes remain after treatment.

INTERSTITIAL KERATITIS

This denotes nonulcerative inflammation of the corneal stroma. There is a diverse list of causes of interstitial keratitis (IK), including bacterial, viral, parasitic, and inflammatory etiologies. In the United States, herpesvirus infections and congenital syphilis account for the majority of cases of IK. Although the corneal findings may regress with time, "ghost vessels," which represent the previous vascular changes, and patchy corneal scarring remain and serve as permanent stigmata of the disease.

Cogan syndrome is IK associated with hearing loss and vestibular symptoms. Although its cause is unknown, a systemic vasculitis is

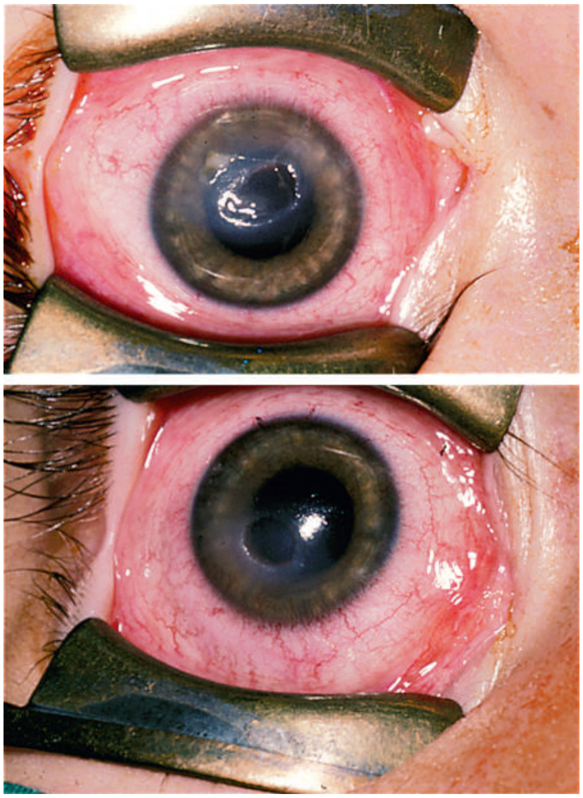

Figure 627-4 Riley-Day syndrome. This child had a combination of anesthetic corneas and dry eyes that had been treated for several months by topical wetting agents without success. He responded well to a bilateral tarsorrhaphy and lubricant ointment. Later, punctal occlusion allowed enough wetting of his eyes to allow the tarsorrhaphies to be undone. *(From Hoyt CS, Taylor D, editors:* Pediatric ophthalmology and strabismus, *ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 33-9, p. 315.)*

suspected. Prompt treatment is required to avoid permanent hearing loss. Both the corneal changes and the auditory involvement may respond to the use of immunosuppressive agents.

CORNEAL MANIFESTATIONS OF SYSTEMIC DISEASE

Several metabolic diseases produce distinctive corneal changes in childhood. Refractile polychromatic crystals are deposited throughout the cornea in cystinosis (see Chapter 85.4). Corneal deposits producing various degrees of corneal haze also occur in certain types of mucopolysaccharidosis (MPS; see Chapter 88), particularly MPS IH (Hurler), MPS IS (Scheie), MPS I H/S (Hurler-Scheie compound), MPS IV (Morquio), MPS VI (Maroteaux-Lamy), and sometimes MPS VII (Sly). Corneal deposits may develop in patients with GM_1 (generalized) gangliosidosis (see Chapter 86.4). In Fabry disease, fine opacities radiating in a whorl or fan-like pattern occur, and corneal changes can be important in identifying the carrier state (see Chapter 86.4). A spray-like pattern of corneal opacities may also be seen in the Bloch-Sulzberger syndrome (incontinentia pigmenti; see Chapter 596.7). In Wilson disease (see Chapter 357.2), the distinctive corneal sign is the Kayser-Fleischer ring, a golden brown ring in the peripheral cornea resulting from changes in Descemet's membrane. Pigmented corneal rings may develop in neonates with cholestatic liver disease. Corneal changes may occur in autoimmune hypoparathyroidism and band keratopathy in patients with hypercalcemia (see Chapter 570). Transient keratitis may occur with rubeola and sometimes with rubella (see Chapter 247).

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Chapter 628

Abnormalities of the Lens

Scott E. Olitsky, Denise Hug, Laura S. Plummer, Erin D. Stahl, Michelle M. Ariss, and Timothy P. Lindquist

CATARACTS

A cataract is any opacity of the lens (Fig. 628-1). Some are clinically unimportant; others significantly affect visual function. The incidence of infantile cataracts is approximately 2-13/10,000 live births. An epidemiologic study of infantile cataracts published in 2003 suggests that approximately 60% of cataracts are an isolated defect; 22% are part of a syndrome; and the remainder are associated with other unrelated major birth defects. Cataracts are more common in low birthweight infants. Infants who weigh at or below 2,500 g have 3-4–fold increased odds of developing infantile cataracts. Some cataracts are associated with other ocular or systemic diseases.

Differential Diagnosis

The differential diagnosis of cataracts in infants and children includes a wide range of developmental disorders, infectious and inflammatory processes, metabolic diseases, and toxic and traumatic insults (Table 628-1). Cataracts may also develop secondary to intraocular processes, such as retinopathy of prematurity, persistent hyperplastic primary vitreous, retinal detachment, retinitis pigmentosa, and uveitis. Finally, a fraction of cataracts in children are inherited (Fig. 628-2).

Developmental Variants

Early developmental processes may lead to various congenital lens opacities. Discrete dots or white plaque-like opacities of the lens capsule are common and sometimes involve the contiguous subcapsular region. Small opacities of the posterior capsule may be associated with persistent remnants of the primitive hyaloid vascular system (the common Mittendorf dot), whereas those of the anterior capsule may be associated with persistent strands of the pupillary membrane or vascular sheath of the lens. Congenital cataracts of this type are usually stationary and rarely interfere with vision, but in some cases, progression occurs.

Prematurity

A special type of lens change seen in some preterm newborn infants is the so-called cataract of prematurity. The appearance is of a cluster of tiny vacuoles in the distribution of the Y sutures of the lens. They

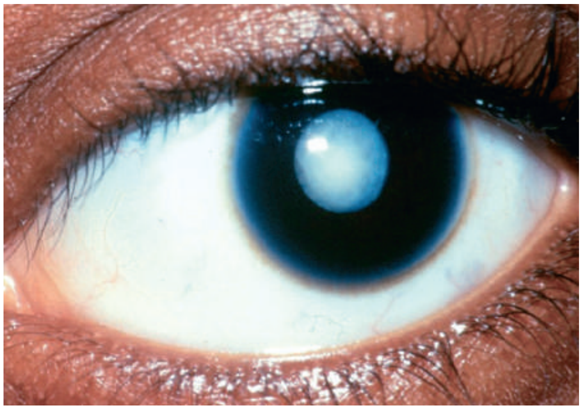

Figure 628-1 Leukocoria secondary to cataract.

Table 628-1 Differential Diagnosis of Cataracts

Differential Diagnosis of Cataracts
DEVELOPMENTAL VARIANTS
Prematurity (Y-suture vacuoles) with or without retinopathy of prematurity
Mittendorf dot (remnant of hyaloid artery)
Persistent pupillary membrane (remnant of embryonic lens vasculature)
GENETIC DISORDERS
Simple Mendelian Inheritance
Autosomal dominant (most common)
Autosomal recessive
X-linked
Major Chromosomal Defects
Trisomy disorders (13, 18, 21)
Turner syndrome (45X)
Deletion syndromes (11p13, 18p, 18q)
Duplication syndromes (3q, 20p, 10q)
Multisystem Genetic Disorders
Alport syndrome (hearing loss, renal disease)
Alström syndrome (nerve deafness, diabetes mellitus)
Apert disease (craniosynostosis, syndactyly)
Cerebrooculofacial syndrome
Cockayne syndrome (premature senility, skin photosensitivity)
Conradi disease (chondrodysplasia punctata)
Crouzon disease (dysostosis craniofacialis)
Ectodermal dysplasia
Hallermann-Streiff syndrome (microphthalmia, small pinched nose, skin atrophy, and hypotrichosis)
Hypohidrotic ectodermal dysplasia (anomalous dentition, hypohidrosis, hypotrichosis)
Ichthyosis (keratinizing disorder with thick, scaly skin)
Incontinentia pigmenti (dental anomalies, mental retardation, cutaneous lesions)
Lowe syndrome (oculocerebrorenal syndrome: hypotonia, renal disease)
Marfan syndrome
Meckel-Gruber syndrome (renal dysplasia, encephalocele)
Myotonic dystrophy
Nail–patella syndrome (renal dysfunction, dysplastic nails, hypoplastic patella)
Marinesco-Sjögren syndrome (cerebellar ataxia, hypotonia)
Nevoid basal cell carcinoma syndrome (autosomal dominant, basal cell carcinoma erupts in childhood)
Peters anomaly (corneal opacifications with iris-corneal dysgenesis)
Progeria
Rieger syndrome (iris dysplasia, myotonic dystrophy)
Rothmund-Thomson syndrome (poikiloderma: skin atrophy)
Rubinstein-Taybi syndrome (broad great toe, mental retardation)
Smith-Lemli-Opitz syndrome (toe syndactyly, hypospadias, mental retardation)
Sotos syndrome (cerebral gigantism)
Spondyloepiphyseal dysplasia (dwarfism, short trunk)
Werner syndrome (premature aging in 2nd decade of life)
Inborn Errors of Metabolism
Abetalipoproteinemia (absent chylomicrons, retinal degeneration)
Fabry disease (α-galactosidase A deficiency)
Galactokinase deficiency
Galactosemia (galactose-1-phosphate uridyltransferase deficiency)
Homocystinemia (subluxation of lens, mental retardation)
Infantile neuronal ceroid lipofuscinosis
Mannosidosis (acid α-mannosidase deficiency)
Niemann-Pick disease (sphingomyelinase deficiency)
Refsum disease (phytanic acid α-hydrolase deficiency)
Wilson disease (accumulation of copper leads to cirrhosis and neurologic symptoms)
Zellweger syndrome
ENDOCRINOPATHIES
Hypocalcemia (hypoparathyroidism)
Hypoglycemia
Diabetes mellitus
CONGENITAL INFECTIONS
Toxoplasmosis
Cytomegalovirus infection
Syphilis
Rubella
Perinatal herpes simplex infection
Measles (rubeola)
Poliomyelitis
Influenza
Varicella-zoster
OCULAR ANOMALIES
Microphthalmia
Coloboma
Aniridia
Mesodermal dysgenesis
Persistent pupillary membrane
Posterior lenticonus
Persistent fetal vasculature
Primitive hyaloid vascular system
Retinitis pigmentosa
MISCELLANEOUS DISORDERS
Atopic dermatitis
Drugs (corticosteroids)
Radiation
Trauma
Juvenile idiopathic arthritis
Retinopathy of prematurity
IDIOPATHIC

can be visualized with an ophthalmoscope and are best seen with the pupil well dilated. The pathogenesis is unclear. In most cases, the opacities disappear spontaneously, often within a few weeks.

Mendelian Inheritance

Many cataracts unassociated with other diseases are hereditary. The most common mode of inheritance is autosomal dominant. Penetrance and expressivity vary. Autosomal recessive inheritance occurs less frequently; it is sometimes found in populations with high rates of consanguinity. X-linked inheritance of cataracts unassociated with disease is relatively rare.

Congenital Infection Syndrome

Cataracts in infants and children can be a result of prenatal infection. Lens opacity may occur in any of the major congenital infection syndromes (e.g., toxoplasmosis, cytomegalovirus, syphilis, rubella, herpes simplex virus). Cataracts may also occur secondary to other perinatal infections, including measles, poliomyelitis, influenza, varicella-zoster, and vaccinia.

Metabolic Disorders

Cataracts are a prominent manifestation of many metabolic diseases, particularly certain disorders of carbohydrate, amino acid, calcium, and copper metabolism. A primary consideration in any infant with cataracts is the possibility of **galactosemia** (see Chapter 87.2). In classic infantile galactosemia, galactose-1-phosphate uridyl transferase deficiency, the cataract is typically of the zonular type, with haziness or opacification of 1 or more of the perinuclear layers of the lens. Haziness or clouding of the nucleus also often occurs. In its early stages, the cataract generally has a distinctive oil droplet appearance and is best

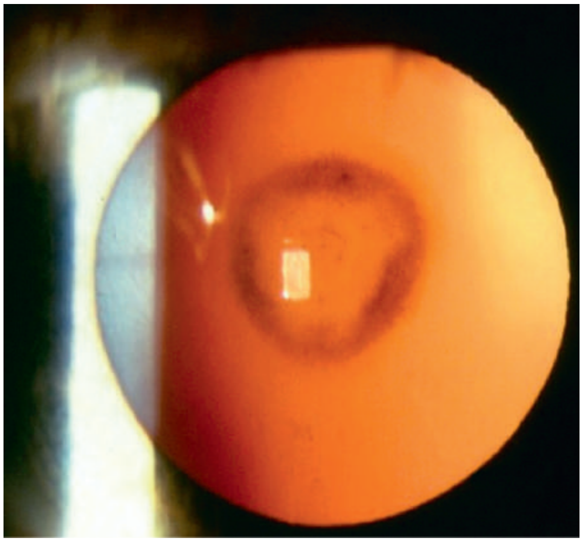

Figure 628-2 Central lamellar cataract.

detected with the pupil fully dilated. Progression to complete opacification of the lens may occur within weeks. With early treatment (galactose-free diet), the lens changes may be reversible.

In **galactokinase deficiency,** cataracts are the sole clinical manifestation. The cataracts are usually zonular and may appear in the 1st few mo of life, 1st few yr of life, or later in childhood.

In children with juvenile-onset diabetes mellitus, lens changes are uncommon. Some develop snowflake-like white opacities and vacuoles of the lens. Others develop cataracts that may progress and mature rapidly, sometimes in a matter of days, especially during adolescence. An antecedent event may be the sudden development of myopia caused by changes in the optical density of the lens. Congenital lens opacities may be seen in children of diabetic and prediabetic mothers (see Chapter 107.1).

Hypoglycemia in neonates can also be associated with early development of cataracts. Ketotic hypoglycemia is also associated with cataracts.

An association between cataracts and hypocalcemia is well established. Various lens opacities may be seen in patients with hypoparathyroidism (see Chapter 570).

The **oculocerebral renal syndrome of Lowe** is associated with cataracts in infants. Affected male children frequently have dense bilateral cataracts at birth, often in association with glaucoma and miotic pupils. Punctate lens opacities are frequently present in heterozygous females.

The distinctive sunflower cataract of **Wilson disease** is not commonly seen in children. Various lens opacities may be seen in children with certain of the sphingolipidoses, mucopolysaccharidoses, and mucolipidoses, particularly Niemann-Pick disease, mucosulfatidosis, Fabry disease, and aspartylglycosaminuria (see Chapter 86).

Chromosomal Defects

Lens opacities of various types may occur in association with chromosomal defects, including trisomies 13, 18, and 21; Turner syndrome; and a number of deletion (11p13, 18p, 18q) and duplication (3q, 20p, 10q) syndromes.

Drugs, Toxic Agents, and Trauma

Of the various drugs and toxic agents that may produce cataracts, corticosteroids are of major importance in the pediatric age group. Steroid-related cataracts characteristically are posterior subcapsular lens opacities. The incidence and severity vary. The relative significance of dose, mode of administration, duration of treatment, and individual susceptibility is controversial, and the pathogenesis of steroid-induced cataracts is unclear. The effect on vision depends on the extent and density of the opacity. In many cases, the acuity is only minimally or moderately impaired. Reversibility of steroid-induced cataracts may occur in some cases. All children receiving long-term steroid treatment should have periodic eye examinations.

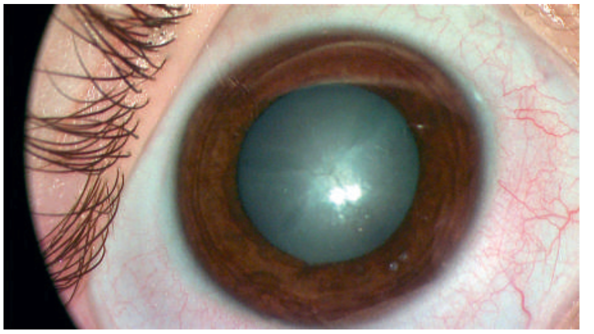

Figure 628-3 Diffuse cataract related to blunt trauma.

Trauma to the eye is a major cause of cataracts in children (Fig. 628-3). Opacification of the lens may result from blunt or penetrating injury. Cataracts can be an important manifestation of child abuse.

Cataract formation after exposure to radiation is dose and duration dependent. Adult research shows 50% occurrence in lens dose of 15 Gy. Delayed onset is the rule.

Miscellaneous Disorders

The list of multisystem syndromes and diseases associated with lens opacities and other eye anomalies is extensive (see Table 628-1).

Treatment

The treatment of cataracts that significantly interfere with vision includes the following: (1) surgical removal of lens material to provide an optically clear visual axis; (2) correction of the resultant aphakic refractive error with spectacles, contact lenses, or intraocular lens implantation; and (3) correction of any associated sensory deprivation amblyopia. Because the use of spectacles may not be possible in children after cataract removal, the use of contact lenses for visual rehabilitation is sometimes a medical necessity. Intraocular lens implantation has become a mainstay for visual rehabilitation in children 2 yr or older. A multicenter trial is underway to try to determine visual outcomes in very young children treated with a contact lens versus an intraocular lens implant. One yr after treatment, the children randomized into the intraocular lens implant group had more statistically significant intraoperative complications, adverse events, and need for additional intraocular surgery. Grating visual acuity at 1 yr was measured and 86% of patients in the contact lens group and 77% in the intraocular lens group had 20/200 vision or better. The median visual acuity between the groups was analyzed and although the median acuity was better in the contact lens group, the difference did not reach statistical significance. Final outcome will be the comparison of visual acuity at 4.5 yr of age. Treatment of the amblyopia may be the most demanding and difficult step in the visual rehabilitation of infants or children with cataracts. Not all cataracts require surgical intervention. Cataracts that are not visually significant should be monitored for change and the child should be monitored for development of amblyopia.

Prognosis

Prognosis depends on many factors, including the nature of the cataract, the underlying disease, age at onset, age at intervention, duration and severity of any attendant amblyopia, and presence of any associated ocular abnormalities (e.g., microphthalmia, retinal lesions, optic atrophy, glaucoma, nystagmus, and strabismus). Persistent amblyopia is the most common cause of poor visual recovery after cataract surgery in children. Secondary conditions and complications may develop in children who have had cataract surgery, including inflammatory sequelae, secondary membranes, glaucoma, retinal detachment, and changes in the axial length of the eye. All of these should be considered in planning treatment.

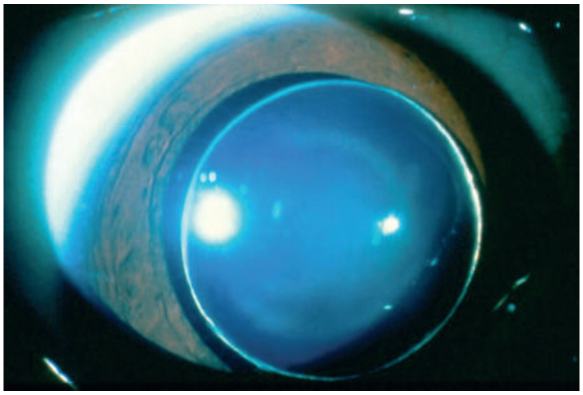

Figure 628-4 Complete dislocation of lens into the anterior chamber seen in Weill-Marchesani syndrome.

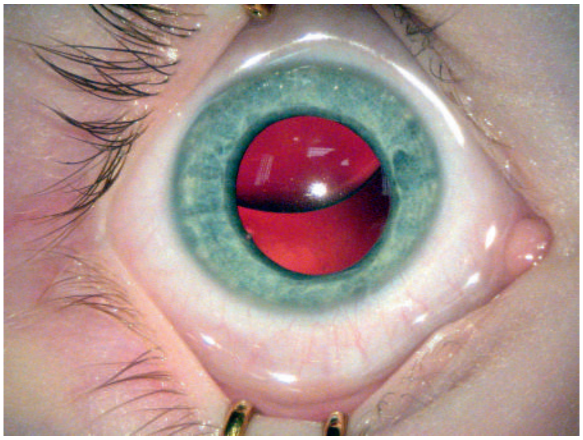

Figure 628-5 Marfan syndrome. Upward lens subluxation. *(From Hoyt CS, Taylor D:* Pediatric ophthalmology and strabismus, *ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 35.9A, p. 333.)*

Ectopia Lentis

Normally, the lens is suspended in place behind the iris diaphragm by the zonular fibers of the ciliary body. Abnormalities of the suspensory system resulting from a developmental defect, disease, or trauma may result in instability or displacement of the lens. Displacement of the lens is classified as luxation, which is complete displacement of the lens (also known as dislocation) (Fig. 628-4), or as subluxation, which is a partial displacement (Fig. 628-5). Symptoms include blurring of vision, which is often the result of refractive changes such as myopia, astigmatism, or aphakic hyperopia. Some patients experience diplopia (double vision). An important sign of displacement is iridodonesis, a tremulousness of the iris caused by the loss of its usual support. Also, the anterior chamber may appear deeper than normal. Sometimes the equatorial region ("edge") of the displaced lens may be visible in the pupillary aperture. On ophthalmoscopy, this may appear as a black crescent. Also, the difference between the phakic and aphakic portions can be appreciated when focusing on the fundus.

Differential Diagnosis

A major cause of lens displacement is trauma. Displacement may also occur as a result of ocular disease such as uveitis, intraocular tumor, congenital glaucoma, high myopia, megalocornea, or aniridia or in association with cataract. Ectopia lentis may also be inherited or associated with systemic disease.

Displacement of the lens occurring as a heritable ocular condition unassociated with systemic abnormalities is referred to as simple ectopia lentis. Simple ectopia lentis is usually transmitted as an autosomal dominant condition. The lens is generally displaced upward and temporally. The ectopia may be present at birth or may appear later in life. Another form of heritable dislocation is ectopia lentis et pupillae (see Chapter 622). In this condition, both the lens and pupil are displaced, usually in opposite directions. This condition is generally bilateral, with 1 eye being almost a mirror image of the other. Ectopia lentis et pupillae is an autosomal recessive condition, although variable expression with some intermingling with simple ectopia lentis has been reported.

Systemic disorders associated with displacement of the lens include Marfan syndrome, homocystinuria, Weill-Marchesani syndrome, and sulfite oxidase deficiency. Ectopia lentis occurs in approximately 80% of patients with Marfan syndrome. In approximately 50% of patients with Marfan syndrome, the ectopia is evident by 5 yr of age. In most cases, the lens is displaced superiorly and temporally; it is almost always bilateral and relatively symmetric. In homocystinuria, the lens is usually displaced inferiorly and somewhat nasally. The subluxation of the lens occurs early in life and is often evident by 5 yr of age. In Weill-Marchesani syndrome, the displacement of the lens is often downward and forward, and the lens tends to be small and round.

Ectopia lentis is also associated occasionally with other conditions, including Ehlers-Danlos, Sturge-Weber, Crouzon, and Klippel-Feil syndromes; oxycephaly; and mandibulofacial dysostosis. A syndrome of dominantly inherited blepharoptosis, high myopia, and ectopia lentis has also been described.

Treatment and Prognosis

Displacement of the lens often results only in optical problems. In some cases, however, more serious complications may develop, such as glaucoma, uveitis, retinal detachment, or cataract. Management must be individualized according to the type of displacement, its cause, and the presence of any complicating ocular or systemic conditions. For many patients, optical correction by spectacles or contact lenses can be provided. Manipulation of the iris diaphragm with mydriatic or miotic drops may sometimes help improve vision. In selected cases, the best treatment is surgical removal of the lens. In many children, treatment of any associated amblyopia must be instituted early. In addition, for children with ectopia lentis, safety precautions should be taken to prevent injury to the eye.

Microspherophakia

The term microspherophakia refers to a small, round lens that may occur as an isolated anomaly (probably autosomal recessive) or in association with other ocular abnormalities, such as ectopia lentis, myopia, or retinal detachment (possibly autosomal dominant). Microspherophakia may also occur in association with various systemic disorders, including Marfan syndrome, Weill-Marchesani syndrome, Alport syndrome, mandibulofacial dysostosis, and Klinefelter syndrome.

Anterior Lenticonus

Anterior lenticonus is a rare bilateral condition in which the anterior capsule of the lens thins, allowing the lens to bulge forward centrally. It may be accompanied by lens opacities or other eye anomalies and is a prominent feature of Alport syndrome. The increased curvature of the central area may cause high myopia. Spontaneous rupture of the anterior capsule may occur, requiring prompt surgical intervention.

Posterior Lenticonus

Posterior lenticonus, which occurs more commonly than anterior lenticonus, is characterized by a circumscribed round or oval bulge of the posterior lens capsule and cortex, involving the central region of the lens. In the early stages, by the red reflex test, this may look like an oil droplet. It occurs in infants and young children and tends to increase with age. Usually the lens material within and surrounding the capsular bulge eventually becomes opacified. Posterior lenticonus usually occurs as an isolated ocular anomaly. It is generally unilateral but may be bilateral. It is believed to be sporadic, although autosomal dominant and X-linked inheritance has been suggested in some cases. Infants or children with posterior lenticonus may require optical correction, amblyopia treatment, and surgery for progressive cataract.

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Chapter 629

Disorders of the Uveal Tract

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UVEITIS (IRITIS, CYCLITIS, CHORIORETINITIS)

The uveal tract (the inner vascular coat of the eye, consisting of the iris, ciliary body, and choroid) is subject to inflammatory involvement in a number of systemic diseases, both infectious and noninfectious, and in response to exogenous factors, including trauma and toxic agents (Table 629-1). Inflammation may affect any one portion of the uveal tract preferentially or all parts together.

Table 629-1 Uveitis in Childhood
ANTERIOR UVEITIS
Juvenile idiopathic arthritis (pauciarticular)
Sarcoidosis
Trauma
Tuberculosis
Kawasaki disease
Ulcerative colitis
Crohn syndrome
Postinfectious (enteric or genital) with arthritis and rash
Spirochetal (syphilis, leptospiral)
Brucellosis
Heterochromic iridocyclitis (Fuchs)
Viral (herpes simplex, herpes zoster)
Ankylosing spondylitis
Stevens-Johnson syndrome
Chronic infantile neurologic cutaneous arthritis syndrome (CINCA)
Familial Mediterranean fever
Hyperimmunoglobulin D syndrome
Tumor necrosis factor receptor–associated periodic syndrome
Muckle-Wells syndrome
Blau syndrome
Psoriasis
Multiple sclerosis
Cyclic neutropenia
Chronic granulomatous disease
X-linked lymphoproliferative disease
Hypocomplementemic vasculitis
Idiopathic
Drugs
POSTERIOR UVEITIS (CHOROIDITIS—MAY INVOLVE RETINA)
Toxoplasmosis
Toxocariasis
Parasites (toxocariasis)
Sarcoidosis
Cat-scratch disease
Tuberculosis
Viral (rubella, herpes simplex, HIV, cytomegalovirus, West Nile)
Subacute sclerosing panencephalitis
Tubulointestinal nephritis and uveitis syndrome
Idiopathic
ANTERIOR AND/OR POSTERIOR UVEITIS
Sympathetic ophthalmia (trauma to other eye)
Vogt-Koyanagi-Harada syndrome (uveootocutaneous syndrome: poliosis, vitiligo, deafness, tinnitus, uveitis, aseptic meningitis, retinitis)
Behçet syndrome
Lyme disease

Iritis may occur alone or in conjunction with inflammation of the ciliary body as iridocyclitis or in association with pars planitis. Pain, photophobia, and lacrimation are the characteristic symptoms of acute anterior uveitis, but the inflammation may develop insidiously without disturbing symptoms. Signs of anterior uveitis include conjunctival hyperemia, particularly in the perilimbal region (ciliary flush), and cells and protein ("flare") in the aqueous humor (Fig. 629-1). Inflammatory deposits on the posterior surface of the cornea (keratic precipitates) and congestion of the iris may also be seen. More chronic cases may show degenerative changes of the cornea (band keratopathy), lenticular opacities (cataract), development of glaucoma, and impairment of vision. The cause of anterior uveitis is often obscure; primary considerations in children are rheumatoid disease, particularly pauciarticular arthritis, Kawasaki disease, Reiter syndrome, and sarcoidosis. Iritis may be secondary to corneal disease, such as herpetic keratitis or a bacterial or fungal corneal ulcer, or to a corneal abrasion or foreign body. Traumatic iritis and iridocyclitis are especially common in children.

Iridocyclitis that occurs in children with arthritis deserves special mention. Unlike most forms of anterior uveitis, it rarely creates pain, photophobia, or conjunctival hyperemia. Loss of vision may not be noticed until severe and irreversible damage has occurred. Because of the lack of symptoms and the high incidence of uveitis in these children, routine periodic screening is necessary. Ophthalmic screening guidelines are based on 3 factors that predispose children with arthritis to uveitis:

1. Type of arthritis
2. Age of onset of arthritis
3. Antinuclear antibody (ANA) status

Table 629-2 has been developed by the American Academy of Pediatrics for children with juvenile idiopathic arthritis without known iridocyclitis.

Choroiditis, inflammation of the posterior portion of the uveal tract, invariably also involves the retina; when both are obviously affected, the condition is termed chorioretinitis. The causes of posterior uveitis are numerous; the more common are toxoplasmosis, histoplasmosis, cytomegalic inclusion disease, sarcoidosis, syphilis, tuberculosis, and toxocariasis (Fig. 629-2). Depending on the etiology, the inflammatory signs may be diffuse or focal. Vitreous reaction often occurs as well. With many types, the result is atrophic chorioretinal scarring demarcated by pigmentation, often with visual impairment. Secondary complications include retinal detachment, glaucoma, and phthisis.

Panophthalmitis is inflammation involving all parts of the eye. It is frequently suppurative, most often as a result of a perforating injury or of septicemia. It produces severe pain, marked congestion of the eye, inflammation of the adjacent orbital tissues and eyelids, and loss of vision. In many cases, the eye is lost despite intensive treatment of the infection and inflammation. Enucleation of the eye or evisceration of the orbit may be necessary.

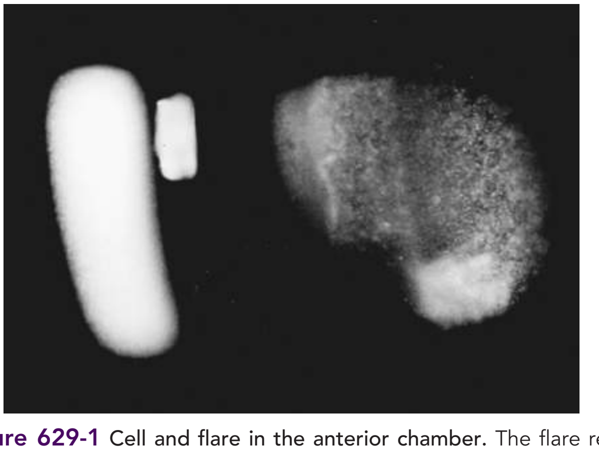

Figure 629-1 Cell and flare in the anterior chamber. The flare represents protein leakage. *(Courtesy of Peter Buch, CRA.)*

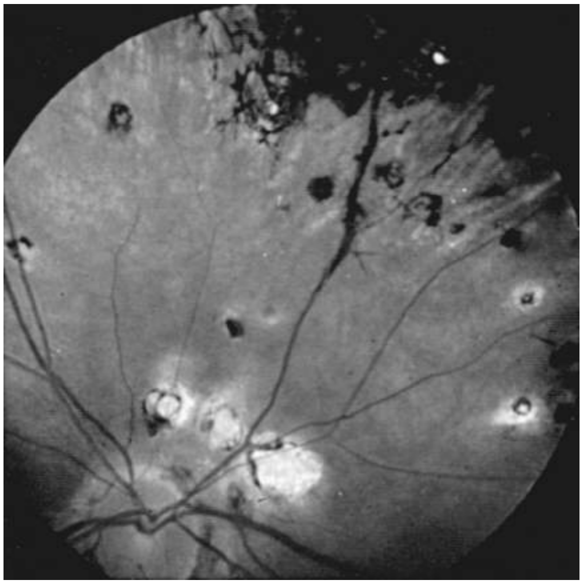

Figure 629-2 Focal atrophic and pigmented scars of chorioretinitis.

Table 629-2 Examination Schedule for Children with JIA Without Known Iridocyclitis

	AGE OF ONSET	
JIA SUBTYPE	**≤6 yr**	**>6 yr**
OLIGOARTHRITIS OR POLYARTHRITIS		
Positive ANA		
Less than 4 yr duration	Every 3 mo	Every 6 mo
4-7 yr duration	Every 6 mo	Annually
More than 7 yr duration	Annually	Annually
Negative ANA		
Less than 4 yr duration	Every 6 mo	Annually
4-7 yr duration	Annually	Annually
More than 7 yr duration	Annually	Annually
Systemic	Annually regardless of duration	Annually regardless of duration

ANA, antinuclear antibody; JIA, juvenile idiopathic arthritis; JRA, juvenile rheumatoid arthritis.

Sympathetic ophthalmia is a rare type of inflammatory response that affects the uninjured eye after a perforating injury. It may occur weeks, months, or even years after the injury. A hypersensitivity phenomenon is the most probable cause. Loss of vision in the uninjured (sympathizing) eye may result. Removal of the injured eye prevents the development of sympathetic ophthalmia but does not stop the progression of the disease once it has occurred. Therefore, early enucleation should be considered if there is no hope of visual recovery after a severe injury.

Treatment

The various forms of intraocular inflammation are treated according to their underlying systemic causal factors. When infection is proved or suspected, appropriate systemic antimicrobial or antiviral therapy is used. In some cases, intravitreal injection is indicated.

Elimination of the intraocular inflammation is important to reduce the risk of severe, and often permanent, vision loss. Untreated, the inflammatory process may lead to the development of band keratopathy (calcium deposition in the cornea), cataracts, glaucoma, and irreversible retinal damage. Anterior inflammation may respond well to topical corticosteroid treatment. Posterior cases often require systemic therapy. The use of topical and systemic corticosteroids can lead to the development of glaucoma and cataracts. To reduce the need for topical and systemic corticosteroids, systemic immunosuppression is often used in patients requiring long-term treatment. Commonly used immunosuppressive agents include methotrexate, cyclosporine, and tumor necrosis factor inhibitors. Multiple agents may be needed in recalcitrant cases. Cycloplegic agents, particularly atropine, are also used to reduce inflammation and to prevent adhesion of the iris to the lens (posterior synechiae), especially in anterior uveitis. Extensive posterior synechiae formation can lead to acute angle closure glaucoma.

Surgery may be required for patients who develop glaucoma because of the underlying disease process or the need for corticosteroid treatment. Cataract surgery should be delayed until the inflammation has been under control for a period of time. Cataract surgery in children with a history of prolonged uveitis can carry significant risk. There is no universal agreement concerning the use of intraocular lenses in these patients.

Pars planitis is an uncommon idiopathic form of intermediate uveitis characterized by anterior chamber involvement, anterior vitreous cells and condensations, and peripheral retinal vasculitis. The average age of onset is 9 yr. It is predominately bilateral and seen more frequently in males. Painless decreased vision is the usual presenting sign. The prognosis is good when adequate medical treatment is sought early in the course of the disease.

Masquerade syndromes can sometimes mimic intraocular inflammation. Retinoblastoma, leukemia, retained intraocular foreign body, juvenile xanthogranuloma, and peripheral retinal detachments may produce signs similar to those seen in uveitis. These syndromes should be kept in mind when evaluating a patient with suspected uveitis or if a patient does not respond as anticipated to antiinflammatory treatment.

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Chapter 630

Disorders of the Retina and Vitreous

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RETINOPATHY OF PREMATURITY

Retinopathy of prematurity (ROP) is a complex disease of the developing retinal vasculature in premature infants. It may be acute (early stages) or chronic (late stages). Clinical manifestations range from mild, usually transient changes of the peripheral retina to severe progressive vasoproliferation, scarring, and potentially blinding retinal detachment. ROP includes all stages of the disease and its sequelae. Retrolental fibroplasia, the previous name for this disease, described only the cicatricial stages.

Pathogenesis

Beginning at 16 wk of gestation, retinal angiogenesis normally proceeds from the optic disc to the periphery, reaching the outer rim of the retina (ora serrata) nasally at about 36 wk and extending temporally by approximately 40 wk. Injury to this process results in various pathologic and clinical changes. The first observation in the acute phase is cessation of vasculogenesis. Rather than a gradual transition

from vascularized to avascular retina, there is an abrupt termination of the vessels, marked by a line in the retina. The line may then grow into a ridge composed of mesenchymal and endothelial cells. Cell division and differentiation may later resume, and vascularization of the retina may proceed. Alternatively, there may be progression to an abnormal proliferation of vessels out of the plane of the retina, into the vitreous, and over the surface of the retina. Cicatrization and traction on the retina may follow, leading to retinal detachment.

The risk factors associated with ROP are not fully known, but prematurity and the associated retinal immaturity at birth represent the major factors. Oxygenation, respiratory distress, apnea, bradycardia, heart disease, infection, hypercarbia, acidosis, anemia, and the need for transfusion are thought by some to be contributory factors. Generally, the lower the gestational age, the lower the birthweight, and the sicker the infant are, the greater the risk is for ROP.

The basic pathogenesis of ROP is still unknown. Exposure to the extrauterine environment, including the necessarily high inspired oxygen concentrations, produces cellular damage, perhaps mediated by free radicals. Later in the course of the disease, peripheral hypoxia develops and vascular endothelial growth factors (VEGFs) are produced in the nonvascularized retina. These growth factors stimulate abnormal vasculogenesis, and neovascularization may occur. Because of poor pulmonary function, a state of relative retinal hypoxia occurs. This causes upregulation of VEGF, which, in susceptible infants, can cause abnormal fibrovascular growth. This neovascularization may then lead to scarring and vision loss.

Classification

The currently used international classification of ROP describes the location, extent, and severity of the disease. To delineate location, the retina is divided into 3 concentric zones, centered on the optic disc (Fig. 630-1). Zone I, the posterior or inner zone, extends twice the disc-macular distance, or 30 degrees in all directions from the optic disc. Zone II, the middle zone, extends from the outer edge of zone I to the ora serrata nasally and to the anatomic equator temporally. Zone III, the outer zone, is the residual crescent that extends from the outer border of zone II to the ora serrata temporally. The extent of involvement is described by the number of circumferential clock hours involved.

The phases and severity of the disease process are classified into 5 stages. Stage 1 is characterized by a demarcation line that separates vascularized from avascular retina. This line lies within the plane of the retina and appears relatively flat and white. Often noted is abnormal branching or arcading of the retinal vessels that lead into the line. Stage 2 is characterized by a ridge; the demarcation line has grown, acquiring height, width, and volume and extending up and out of the plane of the retina. Stage 3 is characterized by the presence of a ridge and by the development of extraretinal fibrovascular tissue (Fig. 630-2*A*). Stage 4 is characterized by subtotal retinal detachment caused by traction from the proliferating tissue in the vitreous or on the retina. Stage 4 is subdivided into 2 phases: (a) subtotal retinal detachment not involving the macula and (b) subtotal retinal detachment involving the macula. Stage 5 is total retinal detachment.

When signs of posterior retinal vascular changes accompany the active stages of ROP, the term *plus disease* is used (see Fig. 630-2*B* and *C*). Patients reaching the point of dilation and tortuosity of the retinal vessels also frequently demonstrate the associated findings of engorgement of the iris, pupillary rigidity, and vitreous haze.

Clinical Manifestations and Prognosis

In more than 90% of at-risk infants, the course is one of spontaneous arrest and regression, with little or no residual effects or visual disability. Fewer than 10% of infants have progression toward severe disease, with significant extraretinal vasoproliferation, cicatrization, detachment of the retina, and impairment of vision.

Some children with arrested or regressed ROP are left with demarcation lines, undervascularization of the peripheral retina, or abnormal branching, tortuosity, or straightening of the retinal vessels. Some are left with retinal pigmentary changes, dragging of the retina (so-called dragged disc), ectopia of the macula, retinal folds, or retinal breaks. Others proceed to total retinal detachment, which commonly assumes a funnel-like configuration. The clinical picture is often that of a retrolental membrane, producing leukokoria (a white reflex in the pupil). Some patients develop cataract, glaucoma, and signs of inflammation. The end stage is often a painful blind eye or a degenerated phthisical eye. The spectrum of ROP also includes myopia, which is often progressive and of significant degree in infancy. The incidence of anisometropia, strabismus, amblyopia, and nystagmus may also be increased.

Diagnosis

Systematic serial screening ophthalmologic examinations of infants at risk are recommended. Infants with a birthweight of less than 1,500 g or gestational age of 32 wk or less, and selected infants with a birthweight between 1,500 and 2,000 g or gestational age of more than

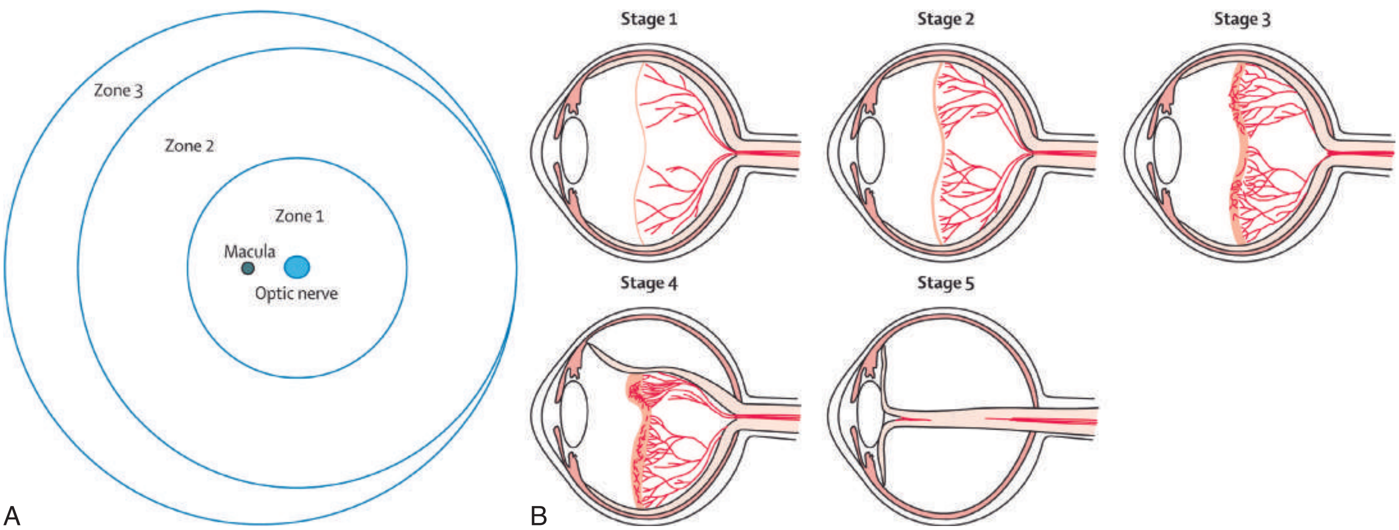

Figure 630-1 The retina is divided into 3 zones (**A,** diagram shows right eye) and the extent or severity of retinopathy in these zones is classified as stages **(B).** Stage 1 is characterized by a thin demarcation line between vascularized and nonvascularized retina, stage 2 by a ridge, stage 3 by extraretinal fibrovascular proliferation, stage 4 by partial retinal detachment, and stage 5 by total retinal detachment. In stage 3, extraretinal neovascularization can become severe enough to cause retinal detachment (stages 4-5), which usually leads to blindness. *(**B** courtesy Lisa Hård. From Hellström A, Smith LEH, Dammann O: Retinopathy of prematurity.* Lancet *382:1445-1454, 2013, Fig. 3, p. 1450.)*

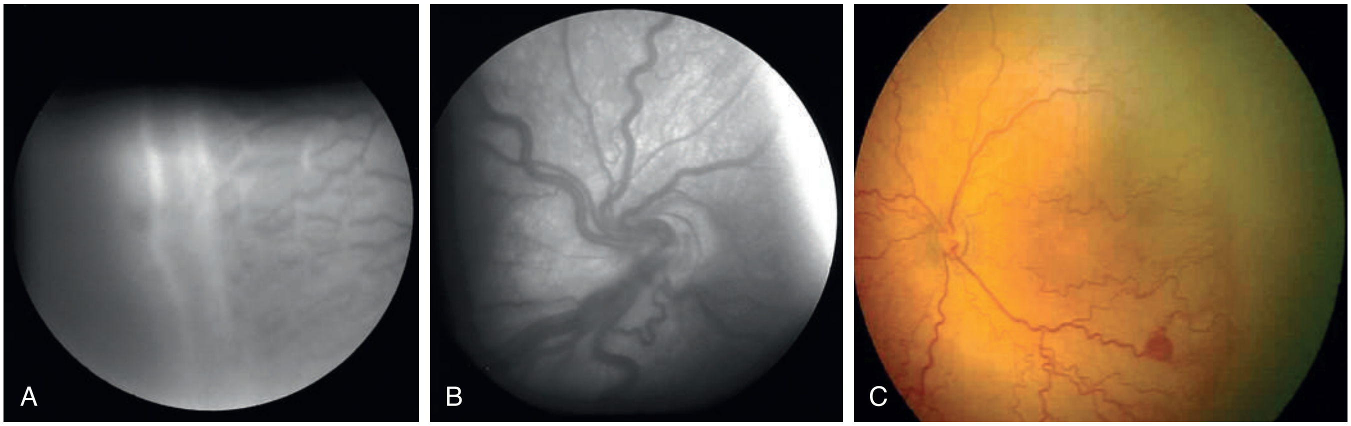

Figure 630-2 Retinopathy of prematurity (ROP). **A,** In stage 3, there is a ridge and extraretinal vascular tissue. **B,** Retinal vessels are dilated and tortuous in active zone 1 ROP with plus disease. **C,** Zone 1 ROP with plus disease.

Table 630-1 Timing of First Eye Examination Based on Gestational Age at Birth

GESTATIONAL AGE AT BIRTH	AGE AT INITIAL EXAMINATION IN WEEKS	
	POSTMENSTRUAL	CHRONOLOGIC
22	31	9
23	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4

32 wk with an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their attending pediatrician or neonatologist to be at high risk, should have retinal screening examinations. The timing of the initial screening exam is based on the infant's age. Table 630-1 was developed from an evidence-based analysis of the Multicenter Trial of Cryotherapy for ROP. The examination can be stressful to fragile preterm infants, and the dilating drops can have untoward side effects. Infants must be carefully monitored during and after the examination. Some neonatologists and ophthalmologists advocate the use of topical tetracaine and/or oral sucrose to reduce the discomfort and stress to the infant. Follow-up is based on the initial findings and risk factors but is usually 2 wk or less.

Treatment

In selected cases, cryotherapy or laser photocoagulation of the avascular retina reduces the more severe complications of progressive ROP. Advances in vitreoretinal surgical techniques have led to limited success in reattaching the retina in infants with total retinal detachment (stage 5 ROP), but the visual results are often disappointing. The Early Treatment for Retinopathy of Prematurity Cooperative study did find improved structural and visual outcomes with the redefined threshold for treatment. It demonstrated the importance of plus disease and the presence of posterior retinal involvement in the determination of when to treat ROP. This study also supported the fact that laser is the **treatment modality of choice.** Peripheral retinal ablation should be considered for any eye with type 1 ROP. Serial examinations are indicated for any eye with type 2 ROP; treatment is considered if type 2 progresses to type 1 or if threshold ROP develops.

Clinical trials using systemic propranolol or intravitreal VEGF antagonists are ongoing and being evaluated for efficacy and risk.

Prevention

Prevention of ROP ultimately depends on prevention of premature birth and its attendant problems (see Chapters 95 and 97.2). However, a number of other potential factors have been studied in order to decrease the occurrence of ROP in these premature infants. Ambient light had been considered by some to be a potential agent that could hopefully be manipulated. The LIGHT-ROP study definitively found that ambient light reduction had no impact on ROP. The association between ROP and oxygen saturation has been studied for decades. Recent research has focused on maintaining oxygen saturation levels for severely premature infants at levels sufficiently low to minimize the risk of ROP and sufficiently high to optimize survival.

PERSISTENT FETAL VASCULATURE

Persistent fetal vasculature (PFV; formerly called persistent hyperplastic primary vitreous) includes a spectrum of manifestations caused by the persistence of various portions of the fetal hyaloid vascular system and associated fibrovascular tissue.

Pathogenesis

During development of the eye, the hyaloid artery extends from the optic disc to the posterior aspect of the lens; it sends branches into the vitreous and ramifies to form the posterior portion of the vascular capsule of the lens. The posterior portion of the hyaloid system normally regresses by the 7th fetal mo and the anterior portion by the 8th fetal mo. Small remnants of the system, such as a tuft of tissue at the disc (Bergmeister papilla) or a tag of tissue on the posterior capsule of the lens (Mittendorf dot), are common findings in healthy persons. More extensive remnants and associated complications constitute PFV. Two major forms are described, anterior PFV and posterior PFV. Variability is great, and mixed or intermediate forms occur.

Clinical Manifestations

The usual clinical feature of anterior PFV is the presence of a vascularized plaque of tissue on the back surface of the lens in an eye that is microphthalmic or slightly smaller than normal. The condition is usually unilateral and may occur in infants with no other abnormalities and no history of prematurity. The fibrovascular tissue tends to undergo gradual contracture. The ciliary processes become elongated, and the anterior chamber may become shallow. The lens usually is smaller than normal and may be clear but often becomes cataractous and may swell or absorb fluid. Large or anomalous vessels of the iris may be present.

The anterior chamber angle may have abnormalities. In time, the cornea may become cloudy.

Anterior PFV is usually noted in the 1st wk or mo of life. The most frequent presenting signs are leukocoria (white pupillary reflex), strabismus, and nystagmus. The course is usually progressive and the outcome poor. Major complications are spontaneous intraocular hemorrhage, swelling of the lens caused by rupture of the posterior capsule, and glaucoma. The eye may eventually deteriorate. The spectrum of posterior PFV includes fibroglial veils around the disc and macula, vitreous membranes and stalks containing hyaloid artery remnants projecting from the disc, and meridional retinal folds. Traction detachment of the retina may occur. Vision may be impaired, but the eye is usually retained.

Treatment

Surgery is performed in an effort to prevent complications, to preserve the eye and a reasonably good cosmetic appearance, and, in some cases, to salvage vision. Surgical treatment usually involves aspirating the lens and excising the abnormal tissue. If useful vision is to be attained, refractive correction and aggressive amblyopia therapy are required. In some cases, the affected eye is enucleated because distinguishing between this white mass and retinoblastoma can be difficult. Ultrasonography and CT are valuable diagnostic aids.

RETINOBLASTOMA

Also see Chapter 502.

Retinoblastoma (Fig. 630-3) is the most common primary malignant intraocular tumor of childhood. It occurs in approximately 1/15,000 live births; 250-300 new cases are diagnosed in the United States annually. Hereditary and nonhereditary patterns of transmission occur; there is no gender or race predilection. The hereditary form occurs earlier and is usually bilateral and multifocal, whereas the nonhereditary form is generally unilateral and unifocal. Fifteen percent of unilateral cases are hereditary. Bilateral cases often present earlier than unilateral cases. Unilateral tumors are often large by the time they are discovered. The average age at diagnosis is 15 mo for bilateral cases, compared with 27 mo for unilateral cases. It is unusual for a child to present with a retinoblastoma after 3 yr of age. Rarely, the tumor is discovered at birth, during adolescence, or even in early adulthood.

Clinical Manifestations

The clinical manifestations of retinoblastoma vary, depending on the stage at which the tumor is detected. The initial sign in the majority of patients is a white pupillary reflex (leukocoria). Leukocoria results because of the reflection of light off the white tumor. The second most frequent initial sign of retinoblastoma is strabismus. Less-frequent presenting signs include pseudohypopyon (tumor cells layered inferiorly in front of the iris) caused by tumor seeding in the anterior chamber of the eye, hyphema (blood layered in front of the iris) secondary to iris neovascularization, vitreous hemorrhage, and signs of orbital cellulitis. On examination, the tumor appears as a white mass, sometimes small and relatively flat, sometimes large and protuberant. It may appear nodular. Vitreous haze or tumor seeding may be evident.

The retinoblastoma gene is a recessive suppressor gene located on chromosome 13 at the 13q14 region. Because of the hereditary nature of retinoblastoma, family members of affected children should undergo

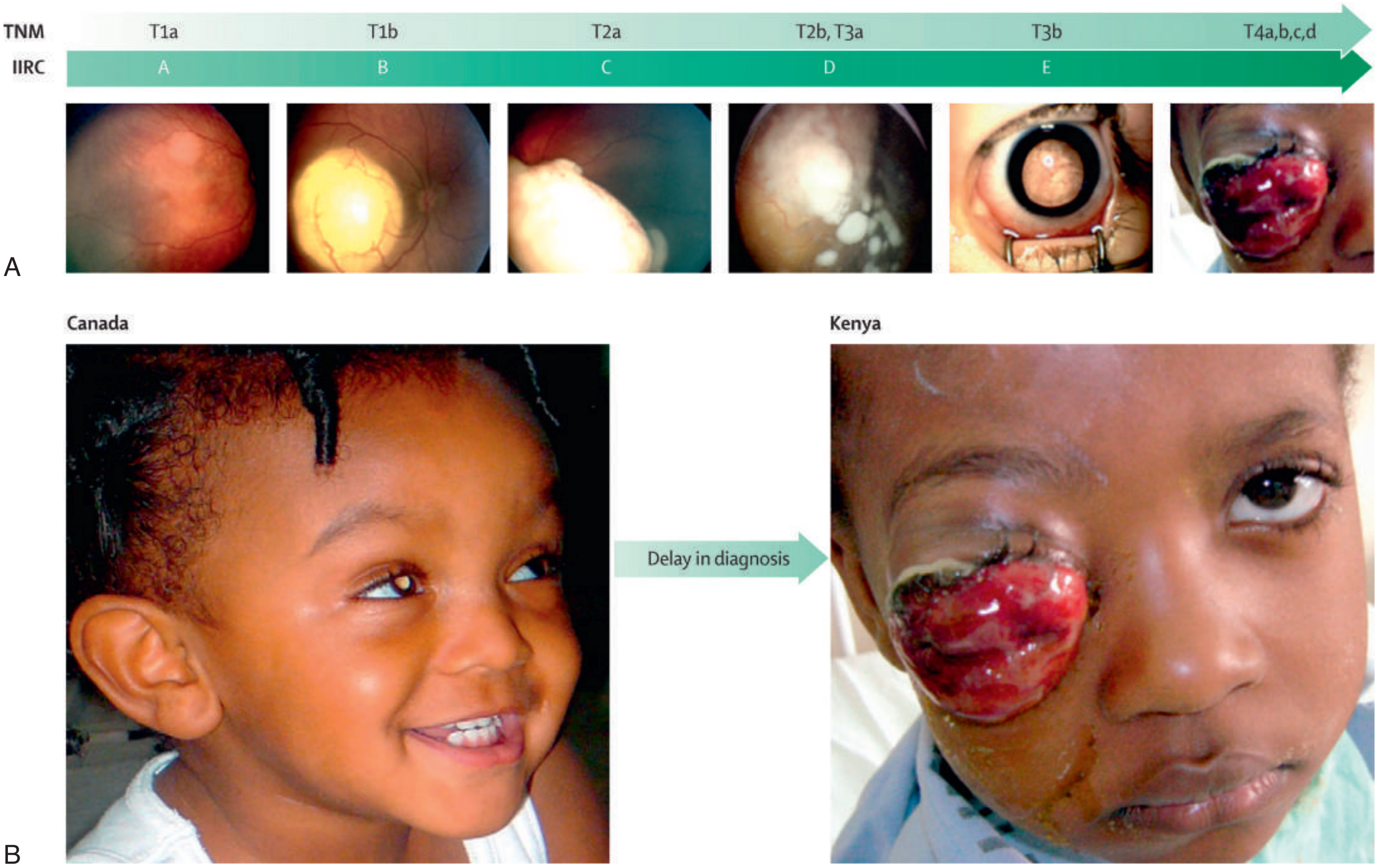

Figure 630-3 Progression of retinoblastoma from small intraretinal tumors to massive orbital retinoblastoma probably extending into the brain. Progression of retinoblastoma **(A)** from small intraretinal tumors that can be cured by laser treatment and cryotherapy (TNM T1a, IIRC A) to massive orbital retinoblastoma probably extending into the brain (TNM T4a-b). A difference in age at diagnosis recorded between Canada and Kenya could be the difference between possible cure and certain death **(B).** The Canadian child with leukocoria was diagnosed because of the left-hand image, which was taken by his sister with his mother's mobile phone. *IIRC,* International Intraocular Retinoblastoma Classification; *TNM,* Tumor Node Metastasis Cancer Staging. *(From Dimaras H, Kimani K, Dimba EAO, et al: Retinoblastoma.* Lancet *379:1436-1444, 2012, Fig. 1, p. 1438.)*

a complete ophthalmologic examination and genetic counseling. Newborn siblings and children of affected patients should be referred to an ophthalmologist shortly after birth, when the peripheral retina can be evaluated without the need for an examination under anesthesia.

Diagnosis

This is made by direct observation by an experienced ophthalmologist. Ancillary testing such as CT or ultrasonography may help to confirm the diagnosis and demonstrate calcification within the mass. MRI may better detect the presence of an associated pineoblastoma (trilateral retinoblastoma). A definitive diagnosis occasionally cannot be made, and removal of the eye must be considered to avoid the possibility of lethal metastasis of the tumor. Because a biopsy can lead to spread of the tumor, histologic confirmation before enucleation is not possible in most cases. Therefore, removal of a blind eye in which the diagnosis of retinoblastoma is likely may be appropriate.

Treatment

Therapy varies, depending on the size and location of the tumor as well as whether it is unilateral or bilateral. Advanced tumors may be treated by enucleation. Other treatment modalities include the use of external beam irradiation, radiation plaque therapy, laser or cryotherapy, and chemotherapy. During the last decade there has been a dramatic shift in the treatment of retinoblastomas. Chemoreduction (systemic chemotherapy) followed by local therapies (i.e., laser therapy, cryotherapy, and brachytherapy) has markedly reduced the use of external beam radiation and is a more vision-sparing technique. Those children who are irradiated during their 1st yr of life are 2-8 times more likely to develop second cancers as those irradiated after 1 yr of age. Patients treated with radiation tend to develop brain tumors and sarcomas of the head and neck. Secondary cataracts can also develop from radiation.

Nonocular secondary tumors are common in patients with germinal mutations estimated to occur with an incidence of 1% per yr of life. The most common secondary tumor is osteogenic sarcoma of the skull and long bones; the risk is higher in patients treated with radiation. Other malignancies include lung, brain, soft tissue, and skin.

The prognosis for children with retinoblastoma depends on the size and extension of the tumor. When confined to the eye, most tumors can be cured. The prognosis for long-term survival is poor when the tumor has extended into the orbit or along the optic nerve.

RETINITIS PIGMENTOSA

This progressive retinal degeneration is characterized by pigmentary changes, arteriolar attenuation, usually some degree of optic atrophy, and progressive impairment of visual function. Dispersion and aggregation of the retinal pigment produce various ophthalmoscopically visible changes, ranging from granularity or mottling of the retinal pigment pattern to distinctive focal pigment aggregates with the configuration of bone spicules (Fig. 630-4). Other ocular findings include subcapsular cataract, glaucoma, and keratoconus.

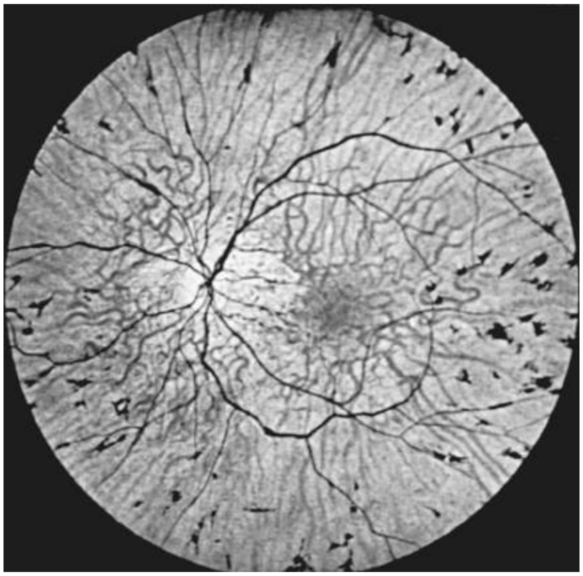

Figure 630-4 Retinitis pigmentosa.

Impairment of night vision or dark adaptation is often the first clinical manifestation. Progressive loss of peripheral vision, often in the form of an expanding ring scotoma or concentric contraction of the field, is usual. There may be loss of central vision. Retinal function, as measured by electroretinography (ERG), is characteristically reduced. The disorder may be autosomal recessive, autosomal dominant, or X linked. Children with autosomal recessive retinitis pigmentosa are more likely to become symptomatic at an earlier age (median age 10.7 yr). Those with autosomal dominant retinitis pigmentosa are more likely to present in their 20s. Only supportive treatment is available.

A special form of retinitis pigmentosa is **Leber congenital retinal amaurosis,** in which the retinal changes tend to be pleomorphic, with various degrees of pigment disorder, arteriolar attenuation, and optic atrophy. The retina may appear normal during infancy. Vision impairment, nystagmus, and poor pupillary reaction are usually evident soon after birth, and the ERG findings are abnormal early and confirm the diagnosis. Retinal pigment epithelium–specific 65-kDa deficiency is the cause of autosomal recessive disease. Gene replacement therapy (subretinal injection) presently shows early promise for people affected with Leber congenital retinal amaurosis.

Usher syndrome, an autosomal recessive disorder, is the most common cause of retinitis pigmentosa and sensorineural deafness (incidence 1 : 25,000). Type 1 Usher syndrome presents at birth with profound hearing loss and poor balance; visional loss progresses more slowly and begins during adolescence. Patients with type 3 disease have normal hearing at birth but develop hearing loss and night blindness around puberty. To date, 11 genetic loci have been located (5 for type 1; 3 for type 2; 1 for type 3).

Clinically similar, secondary pigmentary retinal degenerations that need to be differentiated from retinitis pigmentosa occur in a wide variety of metabolic diseases, neurodegenerative processes, and multifaceted syndromes. Examples include the progressive retinal changes of the mucopolysaccharidoses (particularly Hurler, Hunter, Scheie, and Sanfilippo syndromes; see Chapter 88) and certain of the late-onset gangliosidoses (Batten-Mayou, Spielmeyer-Vogt, and Jansky-Bielschowsky diseases; see Chapters 86.4 and 599.2), the progressive retinal degeneration that is associated with progressive external ophthalmoplegia (Kearns-Sayre syndrome; see Chapter 598.2), and the retinitis pigmentosa–like changes in the Laurence-Moon and Bardet-Biedl syndromes. The retinal manifestations of abetalipoproteinemia (Bassen-Kornzweig syndrome; see Chapter 86) and Refsum disease (see Chapter 86.2) are also similar to those found in retinitis pigmentosa. The diagnosis of these latter two disorders in a patient with presumed retinitis pigmentosa is important because treatment is possible. There is also an association of retinitis pigmentosa and congenital hearing loss, as in Usher syndrome.

STARGARDT DISEASE (FUNDUS FLAVIMACULATUS)

This autosomal recessive retinal disorder is characterized by slowly progressive bilateral macular degeneration and vision impairment. It usually appears at 8-14 yr of age, and affected children are often initially misdiagnosed as having functional visual loss. The foveal reflex becomes obtunded or appears grayish, pigment spots develop in the macular area, and macular depigmentation and chorioretinal atrophy eventually occur. Macular hemorrhages also may develop. Some patients also have white or yellow spots beyond the macula or pigmentary changes in the periphery; the term *fundus flavimaculatus* is commonly used for this condition. It is now recognized that Stargardt disease and fundus flavimaculatus represent different entities on the spectrum of the same disease. Central visual acuity is reduced, often to 20/200, but total loss of vision does not occur. ERG findings vary. The condition is not associated with central nervous system abnormalities and is to be

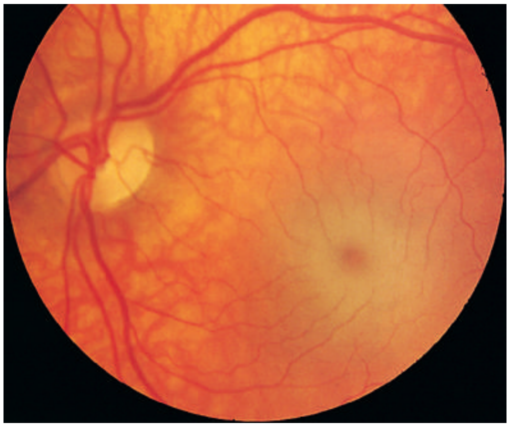

Figure 630-5 Cherry-red spot seen in a case of Tay-Sachs disease. Because the parafoveal area has many retinal ganglion cells and the fovea has none, the fovea retains its orange-red color but is surrounded by retina that is whitish. This produces the cherry-red spot in the macula. *(From Cheng KP, Biglan AW: Ophthalmology. In Zitelli BJ, McIntire S, Nowalk AJ (eds): Zitelli and Davis' atlas of pediatric physical diagnosis, ed 6, Philadelphia: Saunders, 2012. Fig. 19-102.)*

differentiated from the macular changes of many progressive metabolic neurodegenerative diseases. The genetic mutation responsible for Stargardt macular dystrophy has been identified.

BEST VITELLIFORM DEGENERATION

This macular dystrophy is characterized by a distinctive yellow or orange discoid subretinal lesion in the macula, resembling the intact yolk of a fried egg. Diagnosis is usually made at 3-15 yr of age with a mean age of presentation of 6 yr. Vision is usually normal at this stage. The condition may be progressive; the yolk-like lesion may eventually degenerate ("scramble") and result in pigmentation, chorioretinal atrophy, and vision impairment. The condition is usually bilateral. There is no association with systemic abnormalities. Inheritance is usually autosomal dominant. The vitelliform macular dystrophy gene *(VMD2)* has been identified and DNA testing is available. In vitelliform macular degeneration, the ERG response is normal. Electrooculographic findings are abnormal in affected patients and carriers, and this test is useful in diagnosis and in genetic counseling.

CHERRY-RED SPOT

Because of the special histologic features of the macula, certain pathologic processes affecting the retina produce an ophthalmoscopically visible sign referred to as a cherry-red spot, a bright to dull red spot at the center of the macula surrounded and accentuated by a grayish-white or yellowish halo (Fig. 630-5). The halo is a result of a loss of transparency of the retinal ganglion cell layer secondary to edema or lipid accumulation, or both. Because ganglion cells are not present in the fovea, the retina surrounding the fovea is opacified but the fovea transmits the normal underlying choroidal color (red), accounting for the presence of the cherry-red spot. A cherry-red spot typically occurs in certain sphingolipidoses, principally in Tay-Sachs disease (GM_2 type 1), in the Sandhoff variant (GM_2 type 2), and in generalized gangliosidosis (GM_1 type 1). Similar but less distinctive macular changes occur in some cases of metachromatic leukodystrophy (sulfatide lipidosis), in some forms of neuronopathic Niemann-Pick disease, galactosialidosis, and in certain mucolipidoses. The cherry-red spot that characteristically occurs as a result of retinal ischemia secondary to vasospasm, ocular contusion, or occlusion of the central retinal artery must be differentiated from the cherry-red spot of neurodegenerative disease (see Chapters 86.4 and 599).

PHAKOMAS

See also Chapter 596.

These are the herald lesions of the hamartomatous disorders. In Bourneville disease (tuberous sclerosis), the distinctive ocular lesion is a refractile, yellowish, multinodular cystic lesion arising from the disc or retina; the appearance of this typical lesion is often compared with that of an unripe mulberry (Fig. 630-6). Equally characteristic and more common in tuberous sclerosis are flatter, yellow to whitish retinal lesions, varying in size from minute dots to large lesions approaching the size of the disc. These lesions are benign astrocytic proliferations. Rarely, similar retinal phakomas occur in von Recklinghausen disease (neurofibromatosis). In von Hippel-Lindau disease (angiomatosis of the retina and cerebellum), the distinctive fundus lesion is a hemangioblastoma; this vascular lesion usually appears as a reddish globular mass with large paired arteries and veins passing to and from the lesion. In Sturge-Weber syndrome (encephalofacial angiomatosis), the fundus abnormality is a choroidal hemangioma; the hemangioma may impart a dark color to the affected area of the fundus, but the lesion is best seen with fluorescein angiography.

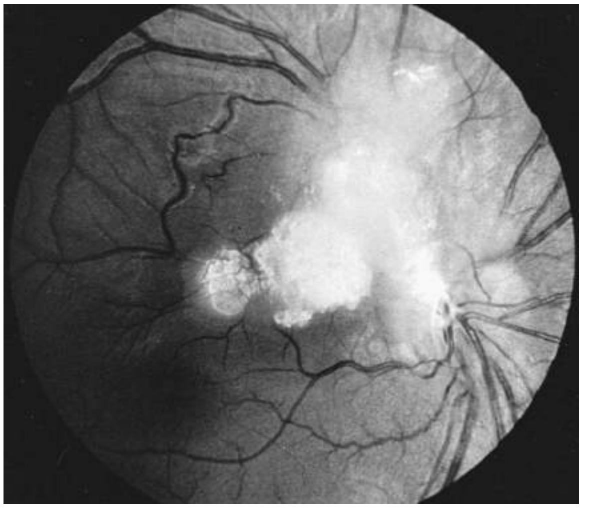

Figure 630-6 Retinal phakoma of tuberous sclerosis.

RETINOSCHISIS

Congenital hereditary retinoschisis, also referred to as juvenile X-linked retinoschisis, is a bilateral vitreoretinal dystrophy that has a bimodal age of presentation. The first group presents with strabismus and nystagmus at a mean age of 1.5-2 yr and is the most severely affected group. The second group presents at 6-7 yr with poor vision. It is characterized by splitting of the retina into inner and outer layers. The usual ophthalmoscopic finding in affected males is an elevation of the inner layer of the retina, most commonly in the inferotemporal quadrant of the fundus, often with round or oval holes visible in the inner layer. Schisis of the fovea is virtually pathognomonic and is found in almost 100% of patients. Ophthalmoscopically, this appears in early stages as small, fine striae in the internal limiting membrane. These striae radiate outward in a petaloid or spoke wheel configuration. In some cases, frank retinal detachment or vitreous hemorrhage occurs.

Vision impairment varies from mild to severe; visual acuity may worsen with age, but good vision is often retained. Carrier females are asymptomatic, but linkage studies may be useful to help detect carriers.

RETINAL DETACHMENT

A retinal detachment is a separation of the outer layers of the retina from the underlying retinal pigment epithelium (RPE). During embryogenesis, the retina and RPE are initially separated. During ocular development, they join together and are held in apposition to each other by various physiologic mechanisms. Pathologic events leading to a retinal detachment return the retina–RPE to its former separated state. The detachment can occur as a congenital anomaly but more commonly arises secondary to other ocular abnormalities or trauma. Three types of detachment are described; each may occur in children. Rhegmatogenous detachments result from a break in the

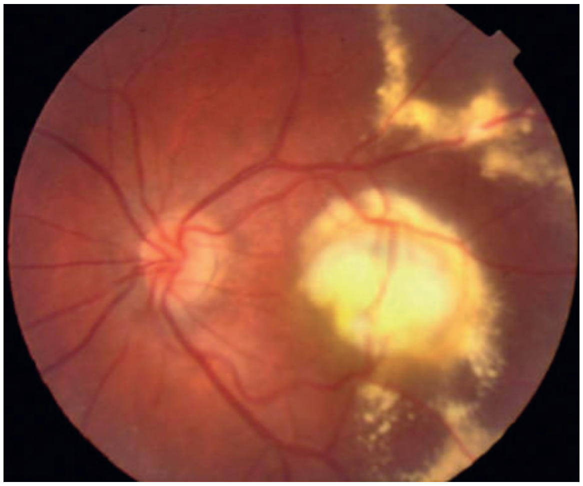

Figure 630-7 Coats disease with massive retinal exudation.

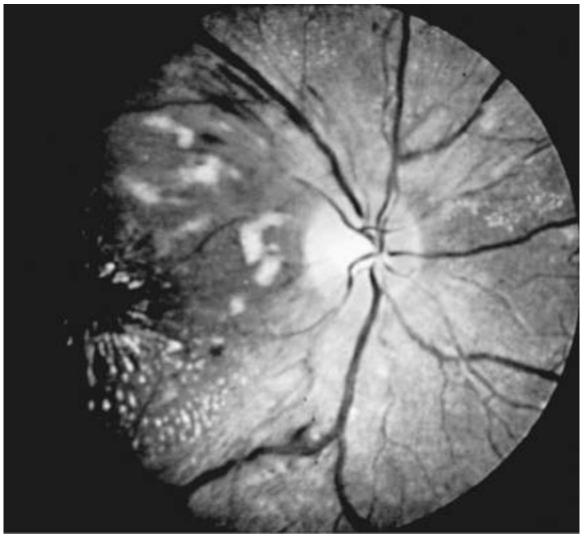

Figure 630-8 Hypertensive retinopathy.

retina that allows fluid to enter the subretinal space. In children, these are usually a result of trauma (such as child abuse) but may occur secondary to myopia or ROP or after congenital cataract surgery. Tractional retinal detachments result when vitreoretinal membranes pull on the retina. They can occur in diabetes, sickle cell disease, and ROP. Exudative retinal detachments result when exudation exceeds absorption. This can be seen in Coats disease, retinoblastoma, and ocular inflammation.

The presenting sign of retinal detachment in an infant or child may be loss of vision, secondary strabismus or nystagmus, or leukocoria (white pupillary reflex). In addition to direct examination of the eye, special diagnostic studies such as ultrasonography and neuroimaging (CT, MRI) may be necessary to establish the cause of the detachment and the appropriate treatment. Prompt treatment is essential if vision is to be salvaged.

COATS DISEASE

This exudative retinopathy of unknown cause is characterized by telangiectasia of retinal vessels with leakage of plasma to form intraretinal and subretinal exudates and by retinal hemorrhages and detachment (Fig. 630-7). The condition is usually unilateral. It predominantly affects boys, usually appearing in the 1st decade. The condition is nonfamilial and for the most part occurs in otherwise healthy children. The most frequent presenting signs are blurring of vision, leukocoria, and strabismus. Rubeosis of the iris, glaucoma, and cataract may develop. **Treatment** with photocoagulation or cryotherapy may be helpful.

FAMILIAL EXUDATIVE VITREORETINOPATHY

This progressive retinal vascular disorder is of unknown cause, but clinical and angiographic findings suggest an aberration of vascular development. Avascularity of the peripheral temporal retina is a significant finding in most cases, with abrupt cessation of the retinal capillary network in the region of the equator. The avascular zone often has a wedge- or V-shaped pattern in the temporal meridian. Glial proliferation or well-marked retinochoroidal atrophy may be found in the avascular zone. Excessive branching of retinal arteries and veins, dilation of the capillaries, arteriovenous shunt formation, neovascularization, and leakage from retinal vessels of the farthest vascularized retina occur. Vitreoretinal adhesions are usually present at the peripheral margin of the vascularized retina. Traction, retinal dragging and temporal displacement of the macula, falciform retinal folds, and retinal detachment are common. Intraretinal or subretinal exudation, retinal hemorrhage, and recurrent vitreous hemorrhages may develop. Patients may also develop cataracts and glaucoma. Vision impairment of varying severity occurs. The condition is usually bilateral. Familial exudative vitreoretinopathy (FEVR) is usually an autosomal dominant condition with incomplete penetrance. Asymptomatic family members often display a zone of avascular peripheral retina.

The findings in FEVR may resemble those of ROP in the cicatricial stages, but unlike ROP, the neovascularization of FEVR seems to develop years after birth and most patients with FEVR have no history of prematurity, oxygen therapy, prenatal or postnatal injury or infection, or developmental abnormalities. FEVR is also to be differentiated from Coats disease, angiomatosis of the retina, peripheral uveitis, and other disorders of the posterior segment.

HYPERTENSIVE RETINOPATHY

In the early stages of hypertension, no retinal changes may be observable. Generalized constriction and irregular narrowing of the arterioles are usually the first signs in the fundus. Other alterations include retinal edema, flame-shaped hemorrhages, cotton-wool spots (retinal nerve fiber layer infarcts), and papilledema (Fig. 630-8). These changes are reversible if the hypertension can be controlled in the early stages, but in long-standing hypertension, irreversible changes may occur. Thickening of the vessel wall may produce a silver- or copper-wire appearance. Hypertensive retinal changes in a child should alert the physician to renal disease, pheochromocytoma, collagen disease, and cardiovascular disorders, particularly coarctation of the aorta.

DIABETIC RETINOPATHY

The retinal changes of diabetes mellitus are classified as nonproliferative or proliferative. Nonproliferative diabetic retinopathy is characterized by retinal microaneurysms, venous dilation, retinal hemorrhages, and exudates. The microaneurysms appear as tiny red dots. The hemorrhages may be of both the dot and blot type, representing deep intraretinal bleeding, and the splinter or flame-shaped type, involving the superficial nerve fiber layer. The exudates tend to be deep and to appear waxy. There may also be superficial nerve fiber infarcts called cytoid bodies or cotton-wool spots, as well as retinal edema. These signs may wax and wane. They are seen primarily in the posterior pole, around the disc and macula, well within the range of direct ophthalmoscopy. Involvement of the macula may lead to decreased vision.

Proliferative retinopathy, the more serious form, is characterized by neovascularization and proliferation of fibrovascular tissue on the retina, extending into the vitreous. Neovascularization may occur on the optic disc, elsewhere on the retina, or on the iris and in the anterior chamber angle (or rubeosis irides) (Fig. 630-9). Traction on these new vessels leads to hemorrhage and, eventually, scarring. The vision-threatening complications of proliferative diabetic retinopathy are retinal and vitreous hemorrhages, cicatrization, traction, and retinal detachment. Neovascularization of the iris may lead to secondary glaucoma if not treated promptly.

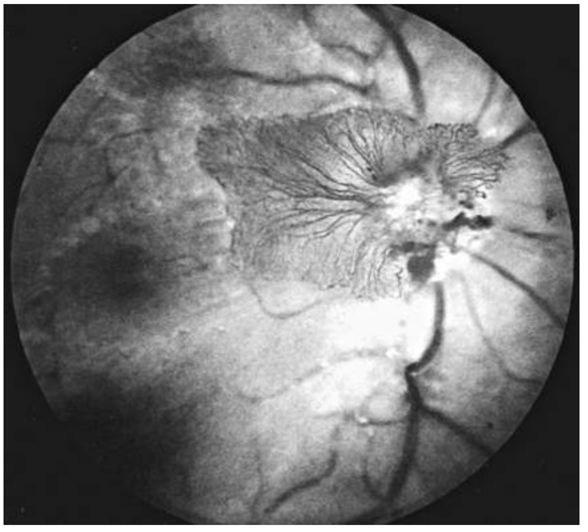

Figure 630-9 Proliferative diabetic retinopathy with neovascularization of the disc.

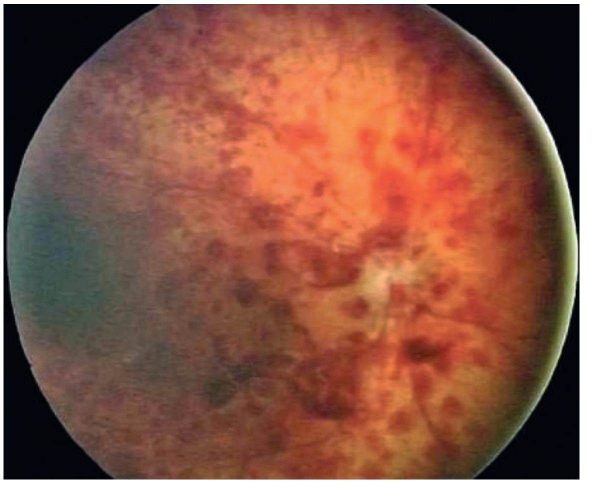

Figure 630-10 Shaken baby syndrome (inflicted neurotrauma). Retinal hemorrhages in multiple layers too numerous to count into far periphery.

Diabetic retinopathy involves the alteration and nonperfusion of retinal capillaries, retinal ischemia, and neovascularization, but its pathogenesis is not yet completely understood, either in terms of location of the primary pathogenetic mechanism (retinal vessels vs surrounding neuronal or glial tissue) or the specific biochemical factors involved. The better the degree of long-term metabolic control, the lower the risk of diabetic retinopathy.

Clinically, the prevalence and course of retinopathy relate to a patient's age and to disease duration. Detectable microvascular changes are rare in prepubertal children, with the prevalence of retinopathy increasing significantly after puberty, especially after the age of 15 yr. The incidence of retinopathy is low during the 1st 5 yr of disease and increases progressively thereafter, with the incidence of proliferative retinopathy becoming substantial after 10 yr and with increased risk of visual impairment after 15 yr or more.

Ophthalmic examination guidelines have been proposed by the American Academy of Pediatrics. An initial exam is recommended at age 9 yr if the diabetes is poorly controlled. If the diabetes is well controlled, an initial exam 3 yr after puberty with annual follow-up is recommended.

In addition to retinopathy, patients with juvenile-onset diabetes may develop optic neuropathy, characterized by swelling of the disc and blurring of vision. Patients with diabetes may also develop cataracts, even at an early age, sometimes with rapid progression.

Treatment

Macular edema is the leading cause of visual loss in diabetic persons. Photocoagulation may be used to decrease the risk of continued vision loss in patients with macular edema.

Proliferative retinopathy causes the most severe vision loss and can lead to total loss of vision and even loss of the eye. Patients who have proliferative disease and who display certain high-risk characteristics should undergo panretinal photocoagulation to preserve their central vision. Neovascularization of the iris is also treated with panretinal photocoagulation to stop the development of neovascular glaucoma.

Vitrectomy and other intraocular surgery may be necessary in patients with nonresolving vitreous hemorrhage or traction retinal detachment. The value of technologic advances, such as insulin infusion pumps and pancreatic transplants, in preventing ocular complications is under investigation (see Chapter 589).

SUBACUTE BACTERIAL ENDOCARDITIS

At some time during the course of the disease, retinopathy is present in approximately 40% of cases of subacute bacterial endocarditis. The lesions include hemorrhages, hemorrhages with white centers (Roth spots), papilledema, and, rarely, embolic occlusion of the central retinal artery.

BLOOD DISORDERS

In primary and secondary anemias, retinopathy in the form of hemorrhages and cotton-wool patches may occur. Vision can be affected if hemorrhage occurs in the macular area. The hemorrhages may be light and feathery or dense and preretinal. In polycythemia vera, the retinal veins are dark, dilated, and tortuous. Retinal hemorrhages, retinal edema, and papilledema may be observed. In leukemia, the veins are characteristically dilated, with sausage-shaped constrictions; hemorrhages, particularly white-centered hemorrhages and exudates, are common during the acute stage. In the sickling disorders, fundus changes include vascular tortuosity, arterial and venous occlusions, "salmon patches," refractile deposits, pigmented lesions, arteriolar-venous anastomoses, and neovascularization (with "sea-fan" formations), sometimes leading to vitreous hemorrhage and retinal detachment. Individuals with sickle cell hemoglobin C and sickle cell hemoglobin β-thalassemia hemoglobinopathies are at a higher risk of the development of retinopathy than are those with homozygous hemoglobin S disease. It is thought that the more anemic state of those patients with homozygous hemoglobin S disease offers protection from vascular occlusions in the retina.

TRAUMA-RELATED RETINOPATHY

Retinal changes may occur in patients who suffer trauma to other parts of the body. The occurrence of retinal hemorrhages in infants who have been physically abused is well documented (Fig. 630-10; see Chapter 40). Retinal, subretinal, subhyaloid, and vitreous hemorrhages have been described in infants and young children with inflicted neurotrauma. Often there are no signs of direct trauma to the eye, periocular region, or head. Such cases may result from violent shaking of an infant, and permanent retinal damage may result.

In patients with severe head or chest compressive trauma, a traumatic retinal angiopathy known as **Purtscher retinopathy** may occur. This is characterized by retinal hemorrhage, cotton-wool spots, possible disc swelling, and decreased vision. The pathogenesis is unclear, but there is evidence of arteriolar obstruction in this condition. A Purtscher-like fundus picture may also occur in several nontraumatic settings, such as acute pancreatitis, lupus erythematosus, and childbirth.

MYELINATED NERVE FIBERS

Myelination of the optic nerve fibers normally terminates at the level of the disc, but in some individuals, ectopic myelination extends to nerve fibers of the retina. The condition is most commonly seen adjacent to the disc, although more peripheral areas of the retina may be

involved. The characteristic ophthalmoscopic picture is a focal white patch with a feathered edge or brushstroke appearance. Because the macula is generally unaffected, the visual prognosis is good. A relative or absolute visual field defect corresponding to areas of ectopic myelination is usually the only associated ocular abnormality. Extensive unilateral involvement, however, is associated with ipsilateral myopia, amblyopia, and strabismus. If unilateral high myopia and amblyopia are present, appropriate optical correction and occlusion therapy should be instituted. For unknown reasons, the disorder is more commonly encountered in patients with craniofacial dysostosis, oxycephaly, neurofibromatosis, and Down syndrome.

COLOBOMA OF THE FUNDUS

The term *coloboma* describes a defect such as a gap, notch, fissure, or hole. The typical fundus coloboma is a result of malclosure of the embryonic fissure, which leaves a gap in the retina, RPE, and choroid, thus baring the underlying sclera. The defect may be extensive, involving the optic nerve, ciliary body, and iris and even the lens, or it may be localized to 1 or more portions of the fissure. The usual appearance is of a well-circumscribed, wedge-shaped white area extending inferonasally below the disc, sometimes involving or engulfing the disc. In some cases, there is ectasia or cyst formation in the area of the defect. Less-extensive colobomatous defects may appear as only single or multiple focal punched-out chorioretinal defects or anomalous pigmentation of the fundus in the line of the embryonic fissure. Colobomas may occur in 1 or both eyes. A visual field defect usually corresponds to the chorioretinal defect. Visual acuity may be impaired, particularly if the defect involves the disc or macula.

Fundus colobomas may occur in isolation as sporadic defects or as an inherited condition. Isolated colobomatous anomalies are commonly inherited in an autosomal dominant manner with highly variable penetrance and expressivity. Family members of affected patients should receive appropriate genetic counseling. Colobomas may also be associated with such abnormalities as microphthalmia, glioneuroma of the eye, cyclopia, or encephalocele. They occur in children with various chromosomal disorders, including trisomies 13 and 18, triploidy, cat's-eye syndrome, and 4p–. Ocular colobomas also occur in many multisystem disorders, including the CHARGE (*C,* coloboma; *H,* heart disease; *A,* atresia choanae; *R,* retarded growth and development and/or central nervous system anomalies; *G,* genetic anomalies and/or hypogonadism; *E,* ear anomalies and/or deafness) association; Joubert, Aicardi, Meckel, Warburg, and Rubinstein-Taybi syndromes; linear sebaceous nevus; Goldenhar and Lenz microphthalmia syndromes; and Goltz focal dermal hypoplasia.

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Chapter 631

Abnormalities of the Optic Nerve

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OPTIC NERVE APLASIA

This rare congenital anomaly is typically unilateral. The optic nerve, retinal ganglion cells, and retinal blood vessels are absent. A vestigial dural sheath usually connects with the sclera in a normal position, but no neural tissue is present within this sheath. Optic nerve aplasia typically occurs sporadically in an otherwise healthy person.

OPTIC NERVE HYPOPLASIA

Hypoplasia of the optic nerve is a nonprogressive condition characterized by a subnormal number of optic nerve axons with normal mesodermal elements and glial supporting tissue. In typical cases, the nerve head is small and pale, with a pale or pigmented peripapillary halo or double-ring sign.

This anomaly is associated with defects of vision and of visual fields of varying severity, ranging from blindness to normal or near-normal vision. It may be associated with systemic anomalies that most commonly involve the central nervous system (CNS). Protean CNS defects such as hydranencephaly or anencephaly or more focal lesions compatible with continued development of a patient may accompany optic nerve hypoplasia, but unilateral or bilateral optic nerve hypoplasia may be found without any concomitant defects.

Optic nerve hypoplasia is a principal feature of **septooptic dysplasia of de Morsier,** a developmental disorder characterized by the association of anomalies of the midline structures of the brain with hypoplasia of the optic nerves, optic chiasm, and optic tracts; typically noted are agenesis of the septum pellucidum, partial or complete agenesis of the corpus callosum, and malformation of the fornix, with a large chiasmatic cistern. Patients may have hypothalamic abnormalities and endocrine defects, ranging from panhypopituitarism to isolated deficiency of growth hormone, hypothyroidism, or diabetes insipidus. Neonatal hypoglycemia and seizures are important presenting signs in affected infants.

MRI is preferred for evaluating CNS abnormalities in patients with optic nerve hypoplasia. During MRI, special attention should be directed to the pituitary infundibulum, where ectopia of the posterior pituitary may be found. Posterior pituitary ectopia appears on MRI as an absence of the pituitary infundibulum with an abnormal bright spot at the upper infundibulum area. This abnormality is present in approximately 15% of patients and suggests posterior pituitary hormone deficiency, requiring further endocrinologic work-up. Endocrine function should be watched closely in patients with optic nerve hypoplasia. The cause of optic nerve hypoplasia remains unclear.

Children with **periventricular leukomalacia** display an unusual form of optic nerve hypoplasia. The optic nerves demonstrate a large cup within a normal-size optic disc. This form of optic nerve hypoplasia occurs secondary to transsynaptic degeneration of optic axons caused by the primary bilateral lesion in the optic radiation (periventricular leukomalacia).

OPTIC NERVE COLOBOMA

Optic nerve colobomas can be unilateral or bilateral. The visual acuity can range from normal to complete blindness. The coloboma develops secondary to incomplete closure of the embryonic fissure. The defect may produce a partial or total excavation of the optic disc (Fig. 631-1).

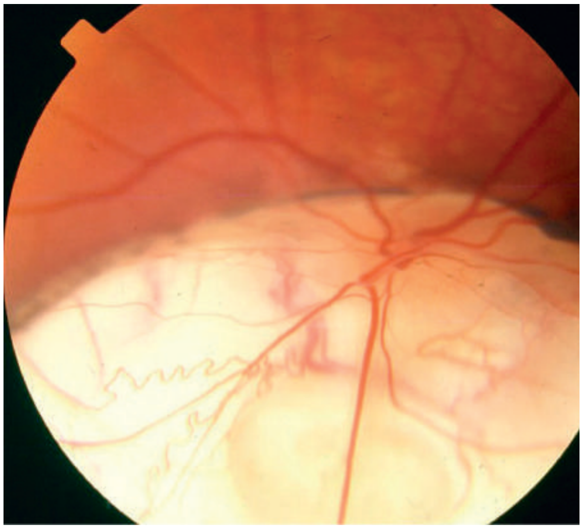

Figure 631-1 Optic nerve coloboma.

Chorioretinal and iris colobomas may also occur. Optic nerve colobomas may be seen in a multitude of ocular and systemic abnormalities including the CHARGE (*C,* coloboma; *H,* heart disease; *A,* atresia choanae; *R,* retarded growth and development and/or CNS anomalies; *G,* genetic anomalies and/or hypogonadism; *E,* ear anomalies and/or deafness) association.

MORNING GLORY DISC ANOMALY

This term describes a congenital malformation of the optic nerve characterized by an enlarged, excavated, funnel-shaped disc with an elevated rim, resembling a morning glory flower. White glial tissue is present in the central part of the disc. The retinal vessels are abnormal and appear at the peripheral disc and course over the elevated pink rim in a radial fashion. Pigmentary mottling of the peripapillary region is usually seen. Most cases are unilateral. Females are affected twice as often as males. Visual acuity is usually severely reduced. Morning glory disc anomaly has been associated with basal encephalocele in patients with midfacial anomalies. Abnormalities of the carotid circulation can also be seen in patients with morning glory anomaly. Moyamoya disease is a well-described associated finding.

TILTED DISC

In this congenital anomaly, the vertical axis of the optic disc is directed obliquely, so that the upper temporal portion of the nerve head is more prominent and anterior to the lower nasal portion of the disc. The retinal vessels emerge from the upper temporal portion of the disc rather than from the nasal side. Often noted is a peripapillary crescent or conus. Associated visual field defects and myopic astigmatism may be found. Clinical recognition of the tilted disc syndrome is important to avoid confusion of its disc and visual field signs with those of papilledema and intracranial tumor.

DRUSEN OF THE OPTIC NERVE

These globular, acellular bodies are thought to arise from axoplasmic derivatives of disintegrating nerve fibers. Drusen may be buried within the optic nerve, producing elevation of the optic nerve head (which can be confused with papilledema), or they may be partially or completely exposed, appearing as refractile bodies at the surface of the disc. Visual field defects and spontaneous peripapillary nerve fiber layer hemorrhages may occur in association with drusen. Drusen may occur as an autosomal dominant condition. B scan ultrasonography can help positively identify drusen suspected on clinical ophthalmic exam (Fig. 631-2).

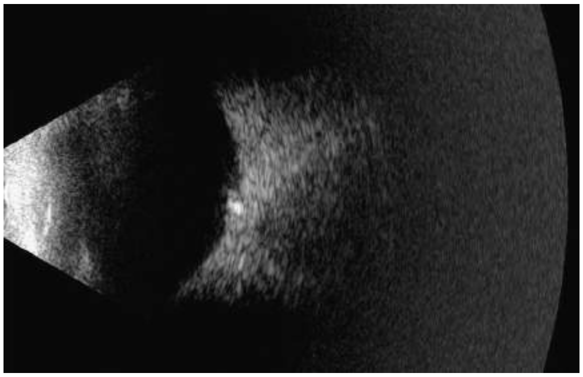

Figure 631-2 Optic nerve drusen seen on B scan ultrasonography.

PAPILLEDEMA

The term *papilledema* is reserved to describe swelling of the nerve head secondary to increased intracranial pressure (ICP). Clinical manifestations of papilledema include edematous blurring of the disc margins, fullness or elevation of the nerve head, partial or complete obliteration of the disc cup, capillary congestion and hyperemia of the nerve head, generalized engorgement of the veins, loss of spontaneous venous pulsation, nerve fiber layer hemorrhages around the disc, and peripapillary exudates (see Fig. 590-1 in Chapter 590). In some cases, edema extending into the macula may produce a fan- or star-shaped figure. In addition, concentric peripapillary retinal wrinkling (Paton lines) may be noted. Transient obscuration of vision may occur, lasting seconds and associated with postural changes. Vision, however, is usually normal in acute papilledema. Normally, when the ICP is relieved, the papilledema resolves and the disc returns to a normal or nearly normal appearance within 6-8 wk. Sustained chronic papilledema or long-standing unrelieved increased ICP may, however, lead to permanent nerve fiber damage, atrophic changes of the disc, macular scarring, and impairment of vision.

The *pathophysiology* of papilledema is probably as follows: elevation of intracranial subarachnoid cerebrospinal fluid (CSF) pressure, elevation of CSF pressure in the sheath of the optic nerve, elevation of tissue pressure in the optic nerve, stasis of axoplasmic flow and swelling of the nerve fibers in the optic nerve head, and secondary vascular changes and the characteristic ophthalmoscopic signs of venous stasis. Associated neuroophthalmic signs of increased ICP in infants and children include 6th cranial nerve palsy and attendant esotropia, lid retraction, paresis of upward gaze, tonic downward deviation of the eyes, and convergent nystagmus.

The common **etiologies** of papilledema in childhood are intracranial tumors and obstructive hydrocephalus, intracranial hemorrhage, the cerebral edema of trauma, meningoencephalitis, toxic encephalopathy, and certain metabolic diseases. Whatever the cause, the optic disc signs of increased ICP in early childhood may occasionally be modified by the distensibility of the young skull. In the absence of conditions associated with early closure of sutures and early obliteration of the fontanel (craniosynostosis, Crouzon disease, and Apert syndrome), infants with increased ICP may not develop papilledema.

The **differential diagnosis** of papilledema includes structural changes of the disc (pseudopapilledema, pseudoneuritis, drusen, and myelinated nerve fibers), with which it may be confused, and the disc swelling of papillitis associated with optic neuritis in addition to the disc changes of hypertension and diabetes mellitus. Unless retinal hemorrhage or edema involves the macular area, the preservation of good central vision and the absence of an afferent pupillary defect (Marcus Gunn pupil) help to differentiate acute papilledema from the edema of the optic nerve head found in acute optic neuritis.

Papilledema is a neurologic emergency. It can be accompanied by other signs of increased ICP, including headaches, nausea, and vomiting. Neuroimaging should be performed; if no intracranial masses are detected, a lumbar puncture and determination of CSF pressure should follow.

OPTIC NEURITIS

This is any inflammation or demyelinization of the optic nerve with attendant impairment of function. The process is usually acute, with rapidly progressive loss of vision. It may be unilateral or bilateral. Pain on movement of the globe or pain on palpation of the globe may precede or accompany the onset of visual symptoms. There is decreased visual activity, decreased color vision and contrast sensitivity, a relative afferent pupillary defect, and a normal macula and peripheral retina.

When the retrobulbar portion of the nerve is affected without ophthalmoscopically visible signs of inflammation at the disc, the term *retrobulbar optic neuritis* is applied. When there is ophthalmoscopically visible evidence of inflammation of the nerve head, the term *papillitis* or *intraocular optic neuritis* is used. When there is involvement of both the retina and the papilla, the term optic *neuroretinitis* is used.

In childhood, optic neuritis may occur as an isolated condition or as a manifestation of a neurologic or systemic disease. Optic neuritis may be secondary to inflammatory diseases (systemic lupus erythematosus, sarcoidosis, Behçet disease, autoimmune optic neuritis); infections (tuberculosis, syphilis, Lyme disease, meningitis, viral encephalitis, HIV, or postinfectious disease); and toxic or nutritional disorders (methanol, ethambutol, vitamin B_{12} deficiency). It may

signify one of the many demyelinating diseases of childhood (see Chapter 600). Although a significant percentage of adults who experience an episode of optic neuritis eventually develop other symptoms associated with multiple sclerosis (MS), young children with optic neuritis are seemingly at less risk (risk of MS is 19% within 20 yr). High-risk features suggestive of MS include visual acuity better than no light perception, periocular pain, acutely normal-appearing optic nerve, no retinal abnormalities, and abnormal MRI suggesting a demyelinating disease. Bilateral optic neuritis in children may be associated with acute disseminated encephalomyelitis or **neuromyelitis optica (NMO or Devic disease).** NMO is characterized by rapid and severe bilateral visual loss accompanied by transverse myelitis and paraplegia. Brainstem and occasionally involvement of the cortex may be seen on MRI. NMO-specific immunoglobulin G (directed to the aquaporin 4 water channel) is the diagnostic test of choice for Devic syndrome. Optic neuritis may also be secondary to an exogenous toxin or drug, such as with lead poisoning or as a complication of long-term high-dose treatment with chloramphenicol or vincristine. Extensive pediatric neurologic and ophthalmic investigation, including MRI and lumbar puncture, is usually required. Idiopathic NMO is associated with antiaquaporin 4 antibodies, otherwise known as NMO antibodies.

In most cases of acute optic neuritis, some improvement in vision begins within 1-4 wk after onset, and vision may improve to normal or near normal within weeks or months. The course varies with cause. Although central vision may fully recover, it is common to find permanent defects in other areas of visual function (contrast sensitivity, color, brightness sense, and motion perception). Recurrences may occur especially, but not universally, in patients who go on to develop MS.

A **treatment** trial demonstrated that high-dose intravenous methylprednisolone may help to speed the visual recovery in young adults, and it may prevent the development of MS in those at risk. Orally administered corticosteroids should not be used because they are associated with a significant increase in the recurrence rate of optic neuritis. It is unknown to what degree the results of the aforementioned trial may be extrapolated to optic neuritis in childhood. Eculizumab, an inhibitor of complement C5, has had some success in reducing relapses in patients with NMO.

LEBER OPTIC NEUROPATHY

This entity is characterized by sudden loss of central vision occurring in the 2nd and 3rd decades of life, and primarily affects young males. A characteristic peripapillary telangiectatic microangiopathy occurs not only in the presymptomatic phase of involved eyes but also in a high number of asymptomatic offspring in the female line. Disc hyperemia and edema mark the acute phase of visual loss. One eye is usually affected before the other. Visual field loss and impaired color vision are also present. In time, progressive optic atrophy and vision loss usually ensue. The tortuous angiopathy becomes less obvious. Although visual function after the initial loss generally remains stable, a significant and sometimes complete recovery may occur in as many as 30% of affected individuals. This recovery may take place years or decades after the initial episode of acute vision loss. The peripapillary angiopathy, the lack of short-term remission, and the degree of symmetry serve to distinguish most cases of Leber disease from the optic neuritis of MS.

Leber optic neuropathy is maternally inherited and is caused by defective cytoplasmic mitochondrial DNA. Multiple point mutations in the mitochondrial DNA that lead to the development of the disorder have been found. Because of the mitochondrial nature of the disorder, skeletal and cardiac muscle disorders, including electrocardiographic abnormalities, may also be encountered in affected individuals.

OPTIC ATROPHY

This term denotes degeneration of optic nerve axons, with attendant loss of function. The ophthalmoscopic signs of optic atrophy are pallor of the disc and loss of substance of the nerve head, sometimes with enlargement of the disc cup. The associated vision defect varies with the nature and site of the primary disease or lesion.

Optic atrophy is the common expression of a wide variety of congenital or acquired pathologic processes. The cause may be traumatic, inflammatory, degenerative, neoplastic, or vascular; intracranial tumors and hydrocephalus are principal causes of optic atrophy in children. In some cases, progressive optic atrophy is hereditary. **Dominantly inherited infantile optic atrophy** is a relatively mild heredodegenerative type that tends to progress through childhood and adolescence. **Autosomal recessively inherited congenital optic atrophy** is a rare condition that is evident at birth or develops at a very early age; the visual defect is usually profound. **Behr optic atrophy** is a hereditary type associated with hypertonia of the extremities, increased deep tendon reflexes, mild cerebellar ataxia, some degree of mental deficiency, and possibly external ophthalmoplegia. This disorder afflicts principally boys age 3-11 yr. Some forms of heredodegenerative optic atrophy are associated with sensorineural hearing loss, as may occur in some children with juvenile-onset (insulin-dependent) diabetes mellitus. In the absence of an obvious cause, optic atrophy in an infant or child warrants extensive etiologic investigation.

OPTIC NERVE GLIOMA

Optic nerve glioma, more properly referred to as **juvenile pilocytic astrocytoma,** is the most frequent tumor of the optic nerve in childhood. This neuroglial tumor may develop in the intraorbital, intracanalicular, or intracranial portion of the nerve; the chiasm is often involved.

The tumor is a cytologic benign hamartoma that is generally stationary or only slowly progressive. The principal *clinical manifestations* when the tumor occurs in the intraorbital portion of the nerve are unilateral loss of vision, proptosis, and deviation of the eye; optic atrophy or congestion of the optic nerve head may occur. Chiasmal involvement may be attended by defects of vision and visual fields (often bitemporal hemianopia), increased ICP, papilledema or optic atrophy, hypothalamic dysfunction, pituitary dysfunction, and sometimes nystagmus or strabismus. Juvenile pilocytic astrocytomas occur with increased frequency in patients with neurofibromatosis.

Treatment of optic pathway gliomas is controversial. The best management is usually periodic observation with serial radiography (preferably MRI). Only symptomatic and radiographically progressing optic nerve gliomas require strong consideration for treatment. Surgical removal may be appropriate when the tumor is confined to the intraorbital, intracanalicular, or prechiasmal portion of the nerve if a patient has unsightly proptosis with complete or nearly complete loss of vision of the affected eye. When the chiasm is involved, resection is not usually indicated and radiation and chemotherapy may be necessary.

TRAUMATIC OPTIC NEUROPATHIES

Injury to the optic nerve may result from both direct and indirect trauma. Direct trauma to the optic nerve is a result of a penetrating injury to the orbit with transection or contusion of the nerve. Blunt trauma to the orbit may also lead to severe visual loss if the traumatic force is transmitted to the optic canal and causes disruption of the blood supply to the intracanalicular portion of the nerve. Treatment with high-dose corticosteroids has not been proven to be effective, and similar regimens have shown there is an increased relative risk of death when such regimens are given to patients after significant head injury.

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Chapter 632

Childhood Glaucoma

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Glaucoma is a general term used to indicate damage to the optic nerve with visual field loss that is caused by or related to elevated pressure within the eye. It is classified according to the age of the affected individual at presentation and the association of other ocular or systemic conditions. Glaucoma that begins within the 1st 3 yr of life is called infantile (congenital); that which begins between the ages of 3 and 30 yr is called juvenile.

Primary glaucoma indicates that the cause is an isolated anomaly of the drainage apparatus of the eye (trabecular meshwork). More than 50% of infantile cases are primary glaucoma. In secondary glaucoma, other ocular or systemic abnormalities are associated, even if a similar developmental defect of the trabecular meshwork is also present. Primary infantile glaucoma occurs with an incidence of 0.03% (Table 632-1).

CLINICAL MANIFESTATIONS

The symptoms of infantile glaucoma include the classic triad of epiphora (tearing), photophobia (sensitivity to light), and blepharospasm (eyelid squeezing; Fig. 632-1). Each can be attributed to corneal irritation. Only approximately 30% of affected infants demonstrate the classic symptom complex. Signs of glaucoma include corneal edema, corneal and ocular enlargement, and conjunctival injection (Fig. 632-2).

Table 632-1 Primary and Secondary Childhood Glaucomas

I. PRIMARY GLAUCOMAS
- A. Congenital open-angle glaucoma
  - 1. Congenital
  - 2. Infantile
  - 3. Late recognized
- B. Autosomal dominant juvenile glaucoma
- C. Primary angle-closure glaucoma
- D. Associated with systemic abnormalities
  - 1. Sturge-Weber syndrome
  - 2. Neurofibromatosis type 1 (NF-1)
  - 3. Stickler syndrome
  - 4. Oculocerebrorenal (Lowe) syndrome
  - 5. Rieger syndrome
  - 6. Hepatocerebrorenal syndrome
  - 7. Marfan syndrome
  - 8. Rubinstein-Taybi syndrome
  - 9. Infantile glaucoma associated with mental retardation and paralysis
  - 10. Oculodentodigital dysplasia
  - 11. Open-angle glaucoma associated with microcornea and absence of frontal sinuses
  - 12. Mucopolysaccharidosis
  - 13. Trisomy 13
  - 14. Cutis marmorata telangiectasia congenita
  - 15. Warburg syndrome
  - 16. Kniest syndrome (skeletal dysplasia)
  - 17. Michel syndrome
  - 18. Nonprogressive hemiatrophy
- E. Associated with ocular abnormalities
  - 1. Congenital glaucoma with iris and pupillary abnormalities
  - 2. Aniridia
    - a. Congenital glaucoma
    - b. Acquired glaucoma
  - 3. Congenital ocular melanosis
  - 4. Sclerocornea
  - 5. Iridotrabecular dysgenesis
  - 6. Peters syndrome
  - 7. Iridotrabecular dysgenesis and ectropion uveae
  - 8. Posterior polymorphous dystrophy
  - 9. Idiopathic or familial elevated episcleral venous pressure
  - 10. Anterior corneal staphyloma
  - 11. Congenital microcornea with myopia
  - 12. Congenital hereditary endothelial dystrophy
  - 13. Congenital hereditary iris stromal hypoplasia

II. SECONDARY GLAUCOMAS
- A. Traumatic glaucoma
  - 1. Acute glaucoma
    - a. Angle concussion
    - b. Hyphema
    - c. Ghost cell glaucoma
  - 2. Late-onset glaucoma with angle recession
  - 3. Arteriovenous fistula
- B. Secondary to intraocular neoplasm
  - 1. Retinoblastoma
  - 2. Juvenile xanthogranuloma
  - 3. Leukemia
  - 4. Melanoma
  - 5. Melanocytoma
  - 6. Iris rhabdomyosarcoma
  - 7. Aggressive nevi of the iris
- C. Secondary to uveitis
  - 1. Open-angle glaucoma
  - 2. Angle-blockage glaucoma
    - a. Synechial angle closure
    - b. Iris bombé with pupillary block
- D. Lens-induced glaucoma
  - 1. Subluxation–dislocation and pupillary block
    - a. Marfan syndrome
    - b. Homocystinuria
  - 2. Spherophakia and pupillary block
  - 3. Phacolytic glaucoma
- E. Secondary to surgery for congenital cataract
  - 1. Lens material blockage of the trabecular meshwork (acute or subacute)
  - 2. Pupillary block
  - 3. Chronic open-angle glaucoma associated with angle defects
- F. Steroid-induced glaucoma
- G. Secondary to rubeosis
  - 1. Retinoblastoma
  - 2. Coats disease
  - 3. Medulloepithelioma
  - 4. Familial exudative vitreoretinopathy
- H. Secondary angle-closure glaucoma
  - 1. Retinopathy of prematurity
  - 2. Microphthalmos
  - 3. Nanophthalmos
  - 4. Retinoblastoma
  - 5. Persistent hyperplastic primary vitreous
  - 6. Congenital pupillary iris–lens membrane
- I. Glaucoma associated with increased venous pressure
  - 1. Carotid or dural-venous fistula
  - 2. Orbital disease
- J. Secondary to maternal rubella
- K. Secondary to intraocular infection
  - 1. Acute recurrent toxoplasmosis
  - 2. Acute herpetic iritis

From Nelson LB: Harley's pediatric ophthalmology, *ed 4, Philadelphia, 1998, WB Saunders, p. 294.*

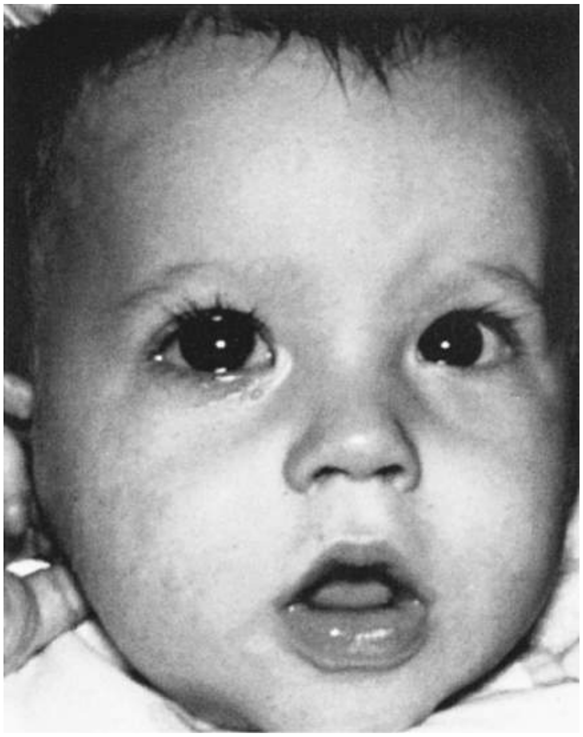

Figure 632-1 Tearing of the right eye caused by glaucoma. Note the increased corneal diameter of the right eye. *(From Nelson LB:* Harley's pediatric ophthalmology, *ed 4, Philadelphia, 1998, WB Saunders, p. 285.)*

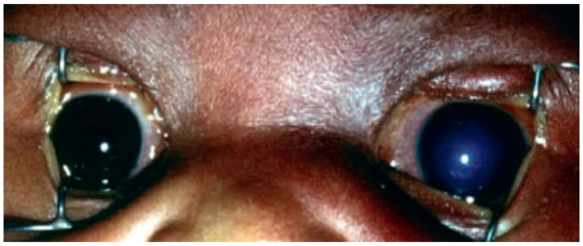

Figure 632-2 Infantile glaucoma. The left cornea is enlarged and edematous.

The sclera and cornea are more elastic in early childhood than later in life. An increase in intraocular pressure (IOP), therefore, leads to an expansion of the globe, including the cornea, and the development of buphthalmos ("ox eye"). If the cornea continues to enlarge, breaks occur in the endothelial basement membrane (Descemet membrane) and may lead to permanent corneal scarring. These breaks in Descemet membrane (Haab striae) are visible as horizontal edematous lines that cross or curve around the central cornea. They rarely occur beyond 3 yr of age or in corneas <12 mm in diameter. The cornea also becomes edematous and cloudy, with increased IOP. The corneal edema leads to tearing and photophobia. Glaucoma should be considered in a child suspected of having a nasolacrimal duct obstruction if any of these other signs or symptoms are present.

Children with unilateral glaucoma generally present early because the difference in the corneal size between the eyes can be noticed. When the disease is bilateral, parents may not recognize the increased corneal size. Many parents view the large eyes as attractive and do not seek help until other symptoms develop.

Cupping of the optic nerve head is detected by ocular examination. The optic nerve of an infant is easily distended by excessive pressure. Deep, central cupping readily occurs and may regress with normalization of pressure.

Some infants and children with early-onset glaucoma have more extensive maldevelopment of the anterior segment of the eye. The neurocristopathies comprise a spectrum of conditions relating to abnormal embryologic development of the anterior segment. They are usually bilateral and may include abnormalities of the iris, cornea, and lens. Other ocular anomalies that may be associated with glaucoma in infants and children are aniridia, cataract, spherophakia, and ectopia lentis. Glaucoma may also develop secondary to persistent hyperplastic primary vitreous or retinopathy of prematurity.

Trauma, intraocular hemorrhage, ocular inflammatory disease, and intraocular tumor are also important causes of glaucoma in the pediatric population. Systemic disorders associated with glaucoma in infants and children are Sturge-Weber syndrome (see Chapter 596.3), neurofibromatosis (see Chapter 596.1), Lowe syndrome, Marfan syndrome (see Chapter 702), congenital rubella (see Chapters 109.6 and 247), and a number of chromosomal syndromes (see Chapter 81).

Glaucoma occurs frequently in children with a history of congenital cataracts. Glaucoma may develop in up to 25% of children who have undergone cataract surgery early in life. The cause of aphakic glaucoma is not known but is thought to be the result of a coexistent anterior chamber deformity. Children treated for cataracts need to be monitored closely for this complication that may threaten vision.

DIAGNOSIS AND TREATMENT

The diagnosis of infantile glaucoma is made on recognition of the signs and symptoms. Once the diagnosis is established, treatment is started promptly. Unlike adult glaucoma, in which medication is often the first line of therapy, for infantile glaucoma, the treatment is primarily surgical. Procedures used to treat glaucoma in children include surgery to establish a more normal anterior chamber angle (goniotomy and trabeculotomy), to create a site for aqueous fluid to exit the eye (trabeculectomy and seton surgery), or to reduce aqueous fluid production (cyclocryotherapy and cyclophotocoagulation). Many children frequently require several operations to lower and maintain their IOP adequately, and long-term medical therapy may be necessary as well. Patients with multiple ocular abnormalities and those with aphakic glaucoma generally require more surgeries to achieve and maintain adequate IOP control. Although vision may be reduced secondary to glaucomatous optic nerve damage or corneal scarring, amblyopia is the most common cause of loss of vision in these children.

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Chapter 633
Orbital Abnormalities

Scott E. Olitsky, Denise Hug, Laura S. Plummer, Erin D. Stahl, Michelle M. Ariss, and Timothy P. Lindquist

HYPERTELORISM AND HYPOTELORISM

Hypertelorism is wide separation of the eyes or an increased interorbital distance, which may occur as a morphogenetic variant, a primary deformity, or a secondary phenomenon in association with developmental abnormalities, such as frontal meningocele or encephalocele or the persistence of a facial cleft. Often associated are strabismus, generally exotropia, and sometimes optic atrophy.

Hypotelorism refers to narrowness of the interorbital distance, which may occur as a morphogenetic variant alone or in association with other anomalies, such as epicanthus or holoprosencephaly, or secondary to a cranial dystrophy, such as scaphocephaly.

EXOPHTHALMOS AND ENOPHTHALMOS

Protrusion of the eye is referred to as exophthalmos or proptosis and is a common indicator of orbital disease. It may be caused by shallowness of the orbits, as in many craniofacial malformations, or by increased tissue mass within the orbit, as with neoplastic, vascular, and inflammatory disorders. Ocular complications include exposure keratopathy, ocular motor disturbances, and optic atrophy with loss of vision.

Posterior displacement or sinking of the eye back into the orbit is referred to as enophthalmos. This may occur with orbital fracture or with atrophy of orbital tissue.

ORBITAL INFLAMMATION

Inflammatory disease involving the orbit may be primary or secondary to systemic disease. Idiopathic orbital inflammation **(orbital pseudotumor)** represents a wide spectrum of clinical entities. Symptoms at the time of presentation may include pain, eyelid swelling, proptosis, a red eye, and fever. The inflammation may involve a single extraocular muscle (myositis) or the entire orbit. Orbital apex syndrome is a serious condition that may also involve the cavernous sinus and may compress or displace the optic nerve. Confusion with orbital cellulitis is common but can be differentiated by the lack of associated sinus disease, its appearance on CT scan, and lack of improvement with systemic antibiotics. Orbital pseudotumor is associated with systemic lupus erythematosus, Crohn disease, myasthenia gravis, and lymphoma. **Treatment** includes the use of high-dose systemic corticosteroids. Often, the symptoms improve dramatically shortly after treatment is initiated. Bilateral involvement, associated uveitis, disc edema, and recurrence of inflammation are not uncommon in the pediatric population. Immunotherapy or radiation treatment may be necessary for resistant or recurrent cases.

Thyroid-related ophthalmopathy (see also Chapter 563) is believed to be secondary to an immune mechanism, leading to inflammation and deposition of mucopolysaccharides and collagen in the extraocular muscles and orbital fat. Involvement of the extraocular muscles may lead to a restrictive strabismus. Lid retraction and exophthalmos may cause corneal exposure and infection or perforation. Involvement of the posterior orbit can compress the optic nerve. Treatment of thyroid-related ophthalmopathy may include the use of systemic corticosteroids, radiation of the orbit, eyelid surgery, strabismus surgery, or orbital decompression to eliminate symptoms and protect vision. The degree of orbital involvement is often independent of the status of the systemic disease.

Other systemic disorders that may cause inflammatory disease within the orbit include lymphoma (see Chapter 496), sarcoidosis (see Chapter 165), amyloidosis (see Chapter 164), polyarteritis nodosa (see Chapter 167.3), systemic lupus erythematosus (see Chapter 158), dermatomyositis (see Chapter 159), Wegener granulomatosis (see Chapter 167), and juvenile xanthogranuloma (see Chapter 507).

TUMORS OF THE ORBIT

Various tumors occur in and about the orbit in childhood. Among benign tumors, the most common are vascular lesions (principally hemangiomas) (Fig. 633-1) and dermoids. Among malignant neoplasms, rhabdomyosarcoma, lymphosarcoma, and metastatic neuroblastoma are the most frequent. Optic nerve gliomas (see Chapter 631) are most commonly seen in patients with neurofibromatosis and may present with poor vision or proptosis. Retinoblastoma (see Chapter 502) may extend into the orbit if it is discovered late or goes untreated. Teratomas are rare tumors that typically grow rapidly after birth and exhibit explosive proptosis.

The effects of orbital tumors vary with their locations and growth patterns. The principal signs are proptosis, resistance to retroplacement of the eye, and impairment of eye movement. A palpable mass may be found. Other significant signs are ptosis, optic nerve head congestion, optic atrophy, and loss of vision. Bruit and visible pulsation of the globe are important clues to vascular lesions.

Evaluation of orbital tumors includes ultrasonography, MRI, and CT. Pseudotumor of the orbit also must be considered in children with signs of a mass lesion. In selected cases, an incisional or excisional biopsy of the lesion may be warranted.

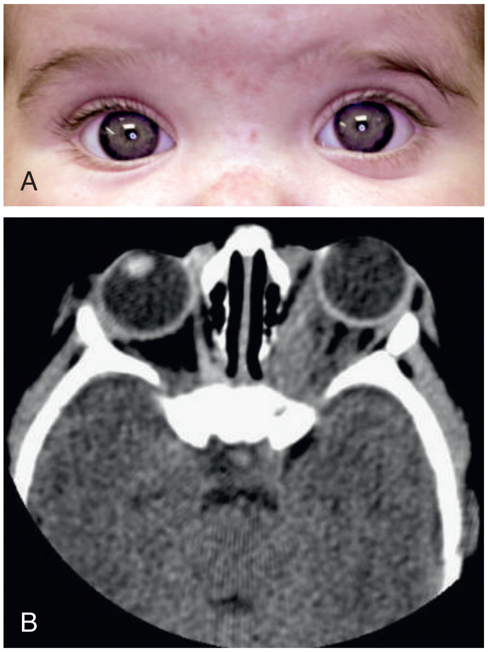

Figure 633-1 Orbital hemangioma. **A,** Note the proptosis. **B,** CT scan. *(Courtesy of Amy Nopper, MD, and Brandon Newell, MD.)*

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Chapter 634

Orbital Infections

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Orbital infections are common in children. It is important to be able to distinguish the different forms of infection that occur in the orbital region to allow rapid diagnosis and treatment to prevent loss of vision or spread of the infection to the nearby intracranial structures (Table 634-1).

DACRYOADENITIS

Dacryoadenitis, or inflammation of the lacrimal gland, is uncommon in childhood. It may occur with mumps (in which case it is usually acute and bilateral, subsiding in a few days or weeks) or with infectious mononucleosis. *Staphylococcus aureus* may produce a suppurative dacryoadenitis. Chronic dacryoadenitis is associated with certain systemic diseases, particularly sarcoidosis, tuberculosis, and syphilis. Some systemic diseases may produce enlargement of the lacrimal and salivary glands (Mikulicz syndrome).

DACRYOCYSTITIS

Dacryocystitis is an infection of the lacrimal sac. Dacryocystitis generally requires obstruction of the nasolacrimal system to allow its development. Acute dacryocystitis presents with redness and swelling over the region of the lacrimal sac (Fig. 634-1). It is treated with warm compresses and systemic antibiotics. This helps to control the

Figure 634-1 Dacrycystitis in a child previously treated for nasolacrimal duct obstruction.

Figure 634-2 CT scan of a patient with preseptal cellulitis.

Table 634-1 Chandler Classification of Orbital Complications of Sinusitis, a Clinical Description

CHANDLER CLASS	STAGE	CLINICAL DESCRIPTION AND DEFINITION
I	Inflammatory edema	Eyelid edema and erythema Normal extraocular movement Normal visual acuity
II	Orbital cellulitis	Diffuse edema of orbital contents without discrete abscess formation
III	Subperiosteal abscess	Collection of purulent exudate* beneath periosteum of lamina papyracea Displacement of globe downward/laterally
IV	Orbital abscess	Purulent collection within orbit* Proptosis Chemosis Ophthalmoplegia Decreased vision
V	Cavernous sinus thrombosis	Bilateral eye findings Prostration Meningismus

*The radiographic correlation of a subperiosteal or orbital abscess seen with CT is a contrast-enhancing mass in the extraconal or intraconal space, possibly with areas of cavitation, because purulence cannot be determined with CT scanning.

From Rudloe TF, Harper M, Prabhu SP, et al: Acute periorbital infections: who needs emergent imaging? Pediatrics *125:e719–e726, 2010.*

infection, but the obstruction usually requires definitive treatment to reduce the risk of recurrence.

Dacryocystitis may occur in newborns as a complication of a congenital dacryocystocele (see Chapter 625). If present, systemic antibiotics and digital pressure for decompression are recommended. The obstruction of the nasolacrimal system may resolve once the infection clears. If spontaneous resolution does not occur, probing should be considered within a short time frame. An intranasal cyst may be present in conjunction with the dacryocystocele. If this occurs, marsupialization of the cyst may be needed at the time of the probing.

PRESEPTAL CELLULITIS

Inflammation of the lids and periorbital tissues without signs of true orbital involvement (such as proptosis or limitation of eye movement) is generally referred to as periorbital or preseptal cellulitis and is a form of facial cellulitis. This is common in young children and may be caused by bacteremia, sinusitis, trauma, an infected wound, or an abscess of the lid or periorbital region (pyoderma, hordeolum, conjunctivitis, dacryocystitis, insect bite). Patients present with eyelid swelling; the edema may be so intense as to make it difficult to evaluate the globe. Prior to the *Haemophilus influenzae* type B vaccine, the most common cause of pediatric preseptal (facial) cellulitis was bacteremia caused by *H. influenzae* type B. Group A streptococcus, *S. aureus*, and pneumococcus are common etiologic agents. Clinical examination will show lack of proptosis, normal ocular movement, and normal pupil function. CT examination will demonstrate edema of the lids and subcutaneous tissues anterior to the orbital septum (Fig. 634-2). Antibiotic therapy and careful monitoring for signs of sepsis and local progression are essential.

ORBITAL CELLULITIS

This is a condition involving inflammation of the tissues of the orbit, with proptosis, limitation of movement of the eye, edema of the conjunctiva (chemosis), and inflammation and swelling of the eyelids with potentially decreased visual acuity (see Table 634-1). The mean age is approximately 7 yr but the range is 10 mo–18 yr. Patients often feel ill with general symptoms of toxicity, fever, and leukocytosis (also see Chapter 194).

Orbital cellulitis may follow direct infection of the orbit from a wound, metastatic deposition of organisms during bacteremia, or **more often** direct extension or venous spread of infection from contiguous sites such as the lids, conjunctiva, globe, lacrimal gland, or nasolacrimal sac or, **more commonly**, from the paranasal (ethmoid) sinuses. In some cases, primary or metastatic tumor in the orbit can produce the clinical picture of orbital cellulitis. The most common cause of orbital cellulitis in children is paranasal sinusitis. The spread of infection to the orbit from the sinuses is more prevalent in children because of their thinner bony septa and sinus wall, greater porosity of bones, open suture lines, and larger vascular foramina. The spread of infection is also facilitated by the venous and lymphatic communication between the sinuses and surrounding structures, which allow flow in either direction, facilitating retrograde thrombophlebitis. Frequent pathogenic organisms include *S. aureus*, including methicillin-resistant *S. aureus*, streptococcus species (*Streptococcus anginosus)*, and *Haemophilus* species.

The potential for complications is great. Visual loss can occur secondary to an increase in orbital pressure that causes retinal artery occlusion or optic neuritis. This is more likely to occur in the presence of an orbital abscess. Extension of infection from the orbit into the cranial cavity may lead to cavernous sinus thrombosis or meningitis, epidural or subdural empyema, or brain abscesses. Additional complications include optic atrophy, exposure keratitis, and retinal or choroidal ischemia. The **differential diagnosis** includes idiopathic orbital

inflammation, myositis, sarcoidosis, granulomatous vasculitis, leukemia, lymphoma, histiocytic disorders, rhabdomyosarcoma, ruptured dermoid cyst, orbital trauma, and orbital foreign body.

Orbital cellulitis must be recognized promptly and treated aggressively. Hospitalization and systemic antibiotic therapy are usually indicated. All patients require CT imaging of the orbit, including the surrounding central nervous system, preferably with intravenous contrast to detect a subperiosteal abscess, orbital abscess, or intracranial extension. Parenteral antibiotics must be started immediately. Antimicrobial agents should begin with vancomycin and cefotaxime (or ceftriaxone); some include metronidazole. If there is no evidence of improvement or if there are signs of progression, sinus drainage may be required. The presence of an orbital or subperiosteal abscess (Figs. 634-3 and 634-4) may require urgent drainage of the orbit. The clinical presentation and course of each individual patient should dictate the need and timing of abscess drainage.

Children <9 yr of age with a medial **subperiosteal abscess** can initially be managed with a trial of intravenous antibiotics, which usually is sufficient for resolution of the abscess. They must be examined frequently (every 6 hr until improvement) for signs of visual deterioration or pupillary abnormalities. Most will become afebrile within 48 hr and have exam improvement by 72 hr. If there are pupillary abnormalities, decreased vision, or failure to improve, the subperiosteal abscess should be drained. Many recommend routine drainage for a subperiosteal abscess in children >9 yr of age. If there is an **orbital abscess** with an abnormal physical exam, the recommendation is that drainage be performed and antibiotics given at the time of diagnosis. The use of adjunctive corticosteroids and anticoagulation for cavernous venous thrombosis and or superior ophthalmic vein thrombosis is controversial.

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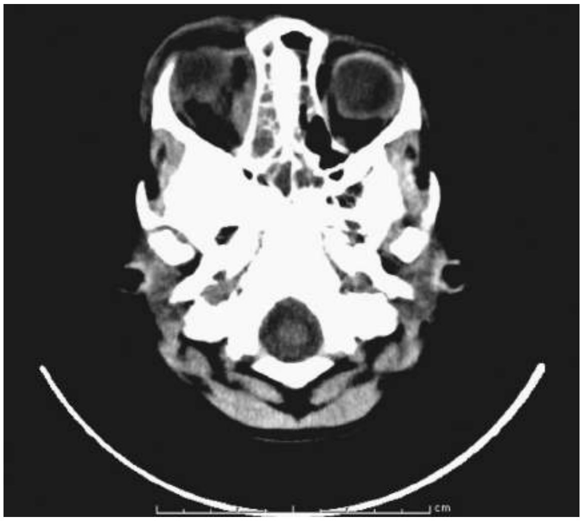

Figure 634-3 CT scan demonstrating a subperiosteal abscess along the medial wall of the orbit.

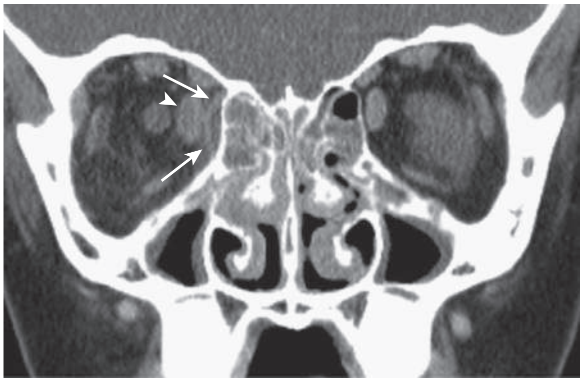

Figure 634-4 An orbital subperiosteal abscess in a 9 yr old girl. A coronal contrast-enhanced computed tomography image shows a small, low-attenuation, rim-enhancing fluid collection consistent with an abscess *(arrows)* in the medial aspect of the orbit with mass effect on the medial rectus muscle *(arrowhead)*, which is thickened. Bilateral ethmoid sinus disease with infiltration of the right retroorbital fat is demonstrated. *(From Coley BD, editor: Caffey's* Pediatric diagnostic imaging, *ed 12, Vol 1, Philadelphia, 2013, Elsevier Saunders, Fig. 8-17, p. 80.)*

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Chapter 635

Injuries to the Eye

Scott E. Olitsky, Denise Hug, Laura S. Plummer, Erin D. Stahl, Michelle M. Ariss, and Timothy P. Lindquist

Approximately 30% of all blindness in children results from trauma. Children and adolescents account for a disproportionate number of episodes of ocular trauma. Boys ages 11-15 yr are the most vulnerable; their injuries outnumber those in girls by a ratio of about 4 : 1. The majority of injuries are related to sports, sticks, stones, fireworks, paint balls, air-powered BB guns, and other projectiles. High-velocity projectiles and fireworks cause particularly devastating ocular and orbital injuries. Much of the trauma is avoidable (see Chapter 5.1). Any part of the orbit or globe may be affected (Fig. 635-1).

ECCHYMOSIS AND SWELLING OF THE EYELIDS

Ecchymosis and edema of the eyelids are common after blunt trauma (Fig. 635-2). These disorders are self-limiting, absorb spontaneously, and can be treated with iced compresses and analgesics. Periorbital ecchymosis should prompt careful examination of the eye and surrounding structures for more serious injuries such as orbital bone fracture, intraocular hemorrhage, or rupture of the globe.

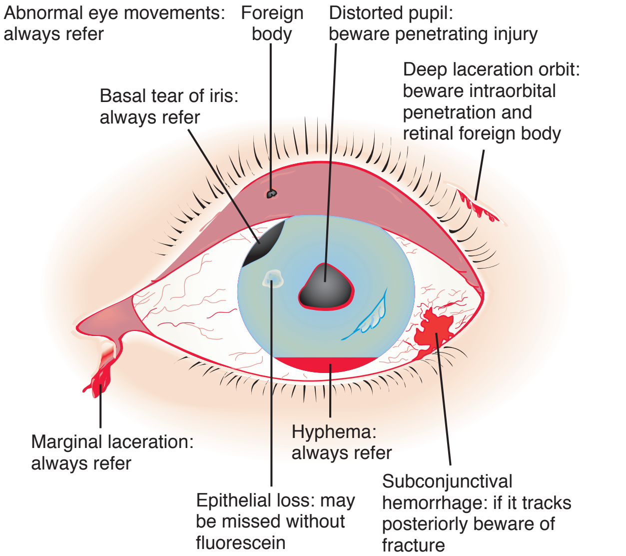

Figure 635-1 The injured eye. *(From Khaw PT, Shah P, Elkington AR: Injury to the eye.* BMJ *2004;328:36–38.)*

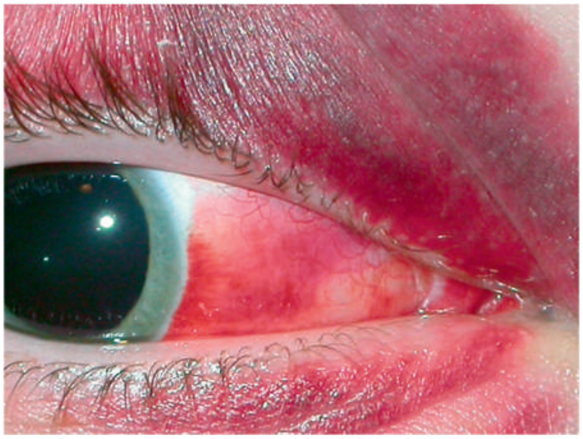

Figure 635-2 Eyelid ecchymosis and subconjunctival hemorrhage.

Figure 635-3 Eyelid margin laceration.

LACERATIONS OF THE EYELIDS

Eyelid lacerations may vary from simple to complex. When evaluating an eyelid laceration, key findings include depth of the laceration, its location, and whether there is involvement of the canaliculus. Most superficial eyelid lacerations may be closed by the primary caregiver, but if a laceration is deep, involves the lid margin, or involves the canaliculus, it should be evaluated by an ophthalmologist. The levator muscle is responsible for elevation of the upper eyelid and runs deep to the skin and orbicularis oculi muscle. If the levator muscle is compromised and not recognized at initial repair, ptosis will occur. Therefore, if orbital fat is visible in the laceration, the laceration has compromised the skin, orbicularis oculi and levator muscles, and orbital septum and must be meticulously repaired to avoid ptosis. Eyelid margin involvement (Fig. 635-3) also requires careful repair to avoid lid malposition and notch formation. These can lead to ocular surface problems in the future, resulting in corneal scarring and loss of vision. Lacerations involving the canaliculus require intubation of the nasolacrimal system in addition to repair of the laceration of the eyelid to avoid future tearing problems. Proper primary repair of eyelid lacerations often achieves a superior outcome to secondary repair at a later date. As with any eyelid injury, careful examination of the eye and surrounding tissue is required.

SUPERFICIAL ABRASIONS OF THE CORNEA

When the corneal epithelium is scratched, abraded, or denuded, it exposes the underlying epithelial basement layer and superficial corneal nerves. This is accompanied by pain, tearing, photophobia, and decreased vision. Corneal abrasions are detected by instilling fluorescein dye and inspecting the cornea using a blue-filtered light (Fig. 635-4). A slit lamp is ideal for this examination, but a direct ophthalmoscope with blue filter or a handheld Wood lamp is adequate for young children.

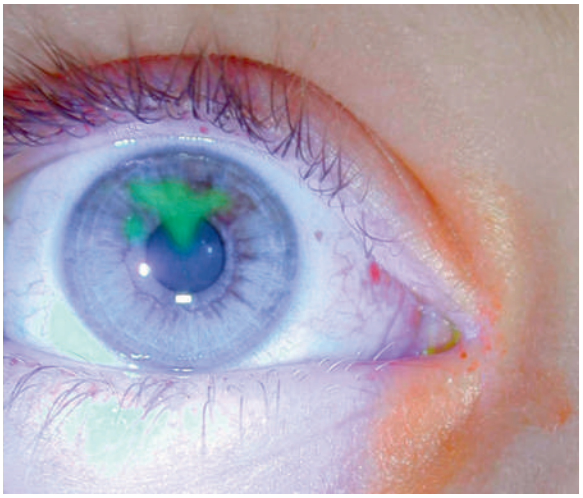

Figure 635-4 Corneal abrasion with fluorescein staining.

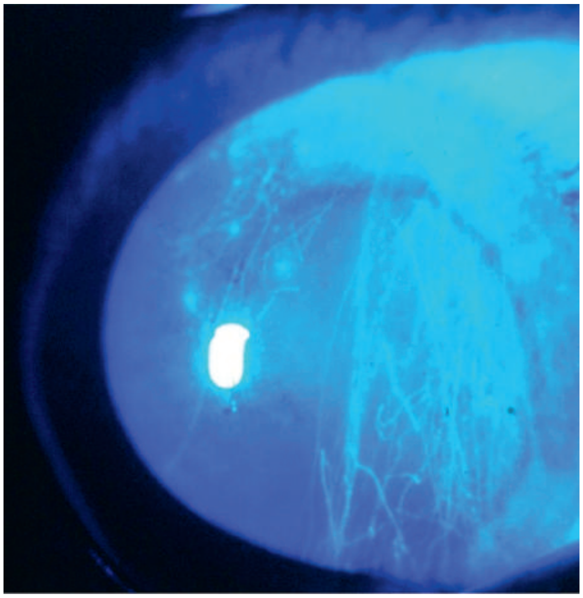

Figure 635-5 Vertically oriented linear corneal abrasions secondary to a foreign body underneath the upper eyelid.

Treatment of a corneal abrasion is directed at promoting healing and relieving pain. Abrasions are treated with frequent applications of a topical antibiotic ointment until the epithelium is completely healed. The use of a semipressure patch does not improve healing time or decrease pain. An improperly applied patch may itself abrade the cornea. A topical cycloplegic agent (cyclopentolate hydrochloride 1%) can relieve the pain from ciliary spasm in patients with large abrasions. Topical anesthetics should not be given at home because they retard epithelial healing and inhibit the natural blinking reflex.

FOREIGN BODY INVOLVING THE OCULAR SURFACE

This usually produces acute discomfort, tearing, and inflammation. Most foreign bodies can be detected by examination in good light with the aid of magnification (Fig. 635-5) or a direct ophthalmoscope set on a high plus lens (+10 or +12). In many cases, slit-lamp examination is necessary, especially if the particle is deep or metallic. Some

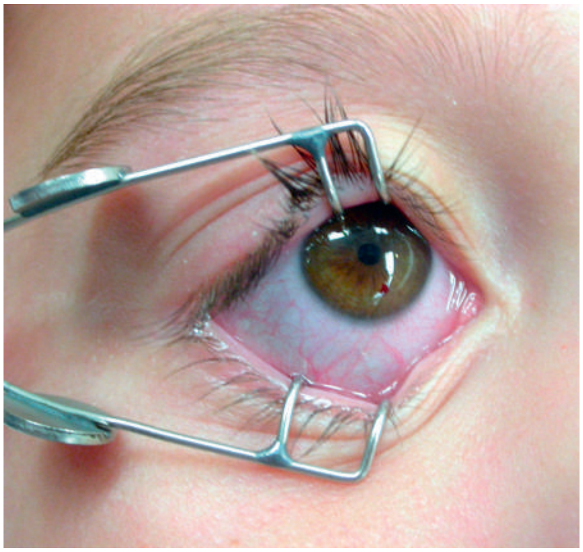

Figure 635-6 Superficial corneal foreign body.

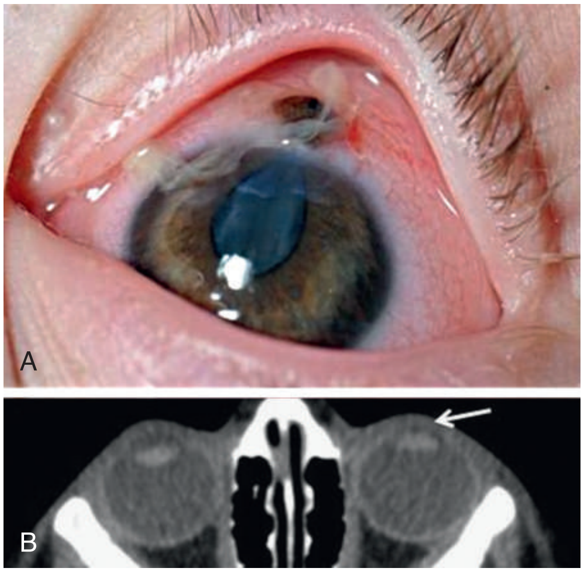

Figure 635-7 **A,** External photograph of an open globe injury with a peaked pupil because of iris prolapse through the sclera, a shallow anterior chamber, and a traumatic cataract. **B,** CT imaging demonstrating a shallow left anterior chamber when compared with the right, but without evidence of an intraocular foreign body. *(From Hwang RY, Schoenberger SD: Imaging a peaked pupil in a traumatic open globe injury.* J Pediatr *163:1517, 2013, Figs. A and B, p. 1517.)*

conjunctival foreign bodies tend to lodge under the upper eyelid, causing the sensation of corneal foreign body as they come into contact with the globe on eyelid movement; they may also produce vertically oriented linear corneal abrasions (Fig. 635-6). Finding these abrasions should lead to a suspicion of such a foreign body, and eversion of the lid may be necessary (see Chapter 619). If a foreign body is suspected but not found, further examination is indicated. If the history suggests injury with a high-velocity particle, radiologic examination of the eye may be needed to explore the possibility of an intraocular foreign body.

Removal of a foreign body can be facilitated by instillation of a drop of topical anesthetic. Many foreign bodies can be removed by irrigation or by gently wiping them away with a moistened cotton-tipped applicator. Embedded foreign bodies or foreign bodies in the central cornea should be treated by an ophthalmologist. Removal of corneal foreign bodies may leave epithelial defects, which are treated as corneal abrasions. Metallic foreign bodies may cause rust to form in the corneal tissues; examination by an ophthalmologist 1 or 2 days after removal of a foreign body is recommended because a rust ring might require further treatment.

HYPHEMA

This is the presence of blood in the anterior chamber of the eye. It may occur with either a blunt or perforating injury and represents a situation that may threaten vision. Hyphema appears as a bright or dark red fluid level between the cornea and iris or as a diffuse murkiness of the aqueous humor. Children with hyphema present with acute loss of vision, with or without pain. The treatment of hyphema involves efforts to minimize the vision-threatening sequelae such as rebleeding, glaucoma, and corneal blood staining. Bedrest is necessary, with elevation of the head of the bed to 30 degrees. A shield (without underlying patch) is placed on the affected eye, and a cycloplegic agent is used to immobilize the iris. Additionally, topical or systemic steroids are used to minimize intraocular inflammation. Antiemetics should be considered if the patient is experiencing nausea. All nonsteroidal anti-inflammatories and aspirin must be avoided. Rarely, hospitalization and sedation may be necessary to ensure compliance in some children. If the intraocular pressure is elevated, topical and systemic pressure-lowering medications are used. If the pressure is not controllable by such measures, then surgical evacuation of the clot may be required to minimize the risk of permanent vision loss. Patients with sickle cell disease or trait are at higher risk of acute loss of vision secondary to elevated intraocular pressure or optic nerve infarction and may require more aggressive intervention. Individuals with a history of traumatic hyphema have an increased incidence of glaucoma later in life and should be monitored on a regular basis throughout their lives.

OPEN GLOBE

A penetrating, perforating, or blunt injury resulting in compromise of the cornea or sclera of the eye is one of the most sight-threatening injuries that can be sustained (Fig. 635-7). This is known as an open globe. An open globe is a true ophthalmologic emergency that requires prompt, careful evaluation and immediate repair to minimize vision loss. Permanent vision loss can result from corneal scarring, loss of intraocular contents, or infection. Evaluation involves careful history including time and mechanism of the injury, as well as visual acuity and inspection of the eye. A full-thickness corneal wound will often present with prolapsed iris tissue through the wound. If this is not immediately evident, a peaked or irregular pupil may be a sign of full-thickness laceration. Scleral compromise may be more difficult to identify because of overlying structures. The thinnest part of the sclera is at the corneoscleral junction (the limbus) and just posterior to the insertion of the rectus muscles. When an open globe is caused by blunt force injury, these are the 2 areas most likely involved. The overlying conjunctiva may not be compromised but a subconjunctival hemorrhage may be present, obscuring the view. In these cases, look for a shallow anterior chamber, low intraocular pressure, or pigment within the involved area. If the patient has been diagnosed with an open globe, the examination should be stopped, an eye shield placed immediately, and the ophthalmologist contacted to minimize further ocular compromise.

OPTIC NERVE TRAUMA

The optic nerve may be injured in both penetrating and blunt trauma. The injury may occur at any point between the globe and the chiasm. Traumatic injury to the optic nerve, regardless of cause or location, results in reduced vision and a pupillary defect. Direct trauma to the intraorbital optic nerve may cause transection, partial transection, or optic sheath hemorrhage. Fractures involving the skull base may cause injury to the intracranial portions of the optic nerve. Treatment decisions are difficult because there are no universally accepted guidelines, and the prognosis for good visual outcome is often poor. Medical management involves observation and the use of high-dose corticosteroids, although the use of corticosteroids has not been proven to improve visual outcomes and has been shown to increase the risk of death in patients with significant head injury. Surgical intervention

involves optic nerve sheath decompression for nerve sheath hemorrhages. If compression of the optic nerve is secondary to orbital hemorrhage, prompt lateral canthotomy and cantholysis should be performed to relieve intraorbital pressure. Decompression of the optic canal may be performed if there is compression of the optic nerve by a bone fragment. Optic canal decompression is controversial in the absence of direct bone compression.

CHEMICAL INJURIES

Chemical burns of the cornea and adnexal tissue are among the most urgent of ocular emergencies. Alkali burns are usually more destructive than acid burns because they react with fats to form soaps, which damage cell membranes, allowing further penetration of the alkali into the eye. Acids generally cause less severe, more localized tissue damage. The corneal epithelium offers moderate protection against weak acids, and little damage occurs unless the pH is 2.5 or less. Most stronger acids precipitate tissue proteins, creating a physical barrier against their further penetration.

Mild acid or alkali burns are characterized by conjunctival injection and swelling and mild corneal epithelial erosions. The corneal stroma may be mildly edematous, and the anterior chamber may have mild to moderate cell and flare reactions. With strong acids, the cornea and conjunctiva rapidly become white and opaque. The corneal epithelium may slough, leaving a relatively clear stroma; this appearance may initially mask the severity of the burn. Severe alkali burns are characterized by corneal opacification.

Emergency treatment of a chemical burn begins with immediate, copious irrigation with water or saline. Local debridement and removal of foreign particles should be performed as irrigation continues. If the nature of the chemical injury is unknown, the use of pH test paper is helpful in determining whether the agent was basic or acidic. Irrigation should continue for at least 30 min or until 2 L of irrigant has been instilled in mild cases and for 2-4 hr or until 10 L of irrigant has been instilled in severe cases. At the end of irrigation, the pH should be within a normal range (7.3-7.7). The pH should be checked again approximately 30 min after irrigation to ensure that it has not changed. The goal of treatment is to minimize sequelae that may threaten vision, such as conjunctival scarring, corneal scarring/opacification, glaucoma, cataract, and phthisis.

ORBITAL FRACTURES

The orbit is the bony structure surrounding the eye. Any of these bones may fracture in a traumatic incident. Superior and lateral wall fractures are the least common of the fracture sites, but superior orbital fracture is the most significant because of the potential of intracranial injury. The medial wall of the orbit is very susceptible to fracture because of the thin nature of the lamina papyracea. Perhaps the most common site of fracture from blunt trauma is the orbital floor. This is often referred to as blowout fracture. At times, the fracture may act as a trapdoor, entrapping orbital contents within the fracture site.

The patient often presents with a recent history of periorbital trauma and pain. Diplopia, eyelid swelling, eye movement restriction, or hypesthesia may or may not be present. Eye symptoms may be associated with nausea and bradycardia if the inferior rectus is entrapped in the fracture site. A complete ophthalmic examination, including, visual acuity, examination of the pupil for ocular alignment, ocular motility, anterior segment and fundus status, as well as the history of the injury, is required because there are often accompanying ocular injuries. The diagnosis of fracture is suspected if eye misalignment, eye movement restriction, or enophthalmos (sunken eye) is present. The diagnosis is verified by orbital CT scan.

Medical management includes iced compresses to the orbit and elevation for the head of the bed for the 1st 24-48 hr. Broad-spectrum antibiotics are sometimes recommended for 14 days because of the exposure of the orbital contents to the sinus cavity. In medial wall fractures, instructions not to blow one's nose should be given to the patient to avoid orbital emphysema and subsequent optic nerve compression. Consider neurosurgical consultation in orbital roof fractures. Indications for surgical repair of orbital fractures are diplopia in primary gaze or downgaze that persists for 2 wk, enophthalmos, or fracture of the orbital floor involving more than half of the floor. Extraocular muscle entrapment often requires prompt surgical repair because affected patients have significant pain, nausea, and vomiting that are difficult to control. Rarely, extraocular muscle entrapment can cause activation of the oculocardiac reflex, requiring urgent fracture repair.

PENETRATING WOUNDS OF THE ORBIT

These demand careful evaluation for possible damage to the eye, optic nerve, orbital contents, or brain. Examination should include investigation for a retained foreign body. Orbital hemorrhage and infection are common with penetrating wounds of the orbit; such injuries must be treated as emergencies.

CHILD ABUSE

See Chapter 40.

This is a major cause of injuries to the eye and orbital region. The possibility of nonaccidental trauma must be considered in any child with ecchymosis or laceration of the lids, hemorrhage in or about the eye, cataract or dislocated lens, retinal detachment, or fracture of the orbit. Inflicted childhood neurotrauma (shaken baby syndrome) occurs secondary to violent, nonaccidental, repetitive, unrestrained acceleration-deceleration head and neck movements, with or without blunt head trauma in children typically younger than 3 yr of age. Inflicted childhood neurotrauma accounts for approximately 10% of all cases of child abuse and carries a mortality rate of up to 25%. Detection of abuse is not only important in order to treat the pathology that is discovered but also to prevent further abuse or even death. The ocular manifestations are numerous and may have a prominent role in recognition of this syndrome. Retinal hemorrhage is the most common ophthalmic finding and occurs at all levels of the retina. The pattern of hemorrhage helps to distinguish this disorder from other causes of retinal hemorrhage or from accidental injuries (Fig. 635-8). Retinal hemorrhages can occur without associated intracranial pathology.

FIREWORKS-RELATED INJURIES

Injuries related to the use of fireworks can be the most devastating of all ocular traumas that occur in children. At least 20% of emergency department visits for fireworks-related injuries are for ocular trauma. In the United States, a majority of these injuries take place around Independence Day, and most occur despite adult supervision.

SPORTS-RELATED OCULAR INJURIES AND THEIR PREVENTION

Although sports injuries occur in all age groups, far more children and adolescents participate in high-risk sports than do adults. The

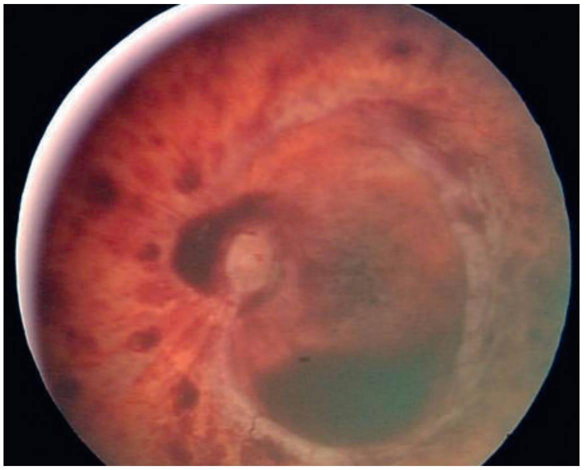

Figure 635-8 Retinal hemorrhages in an abused child.

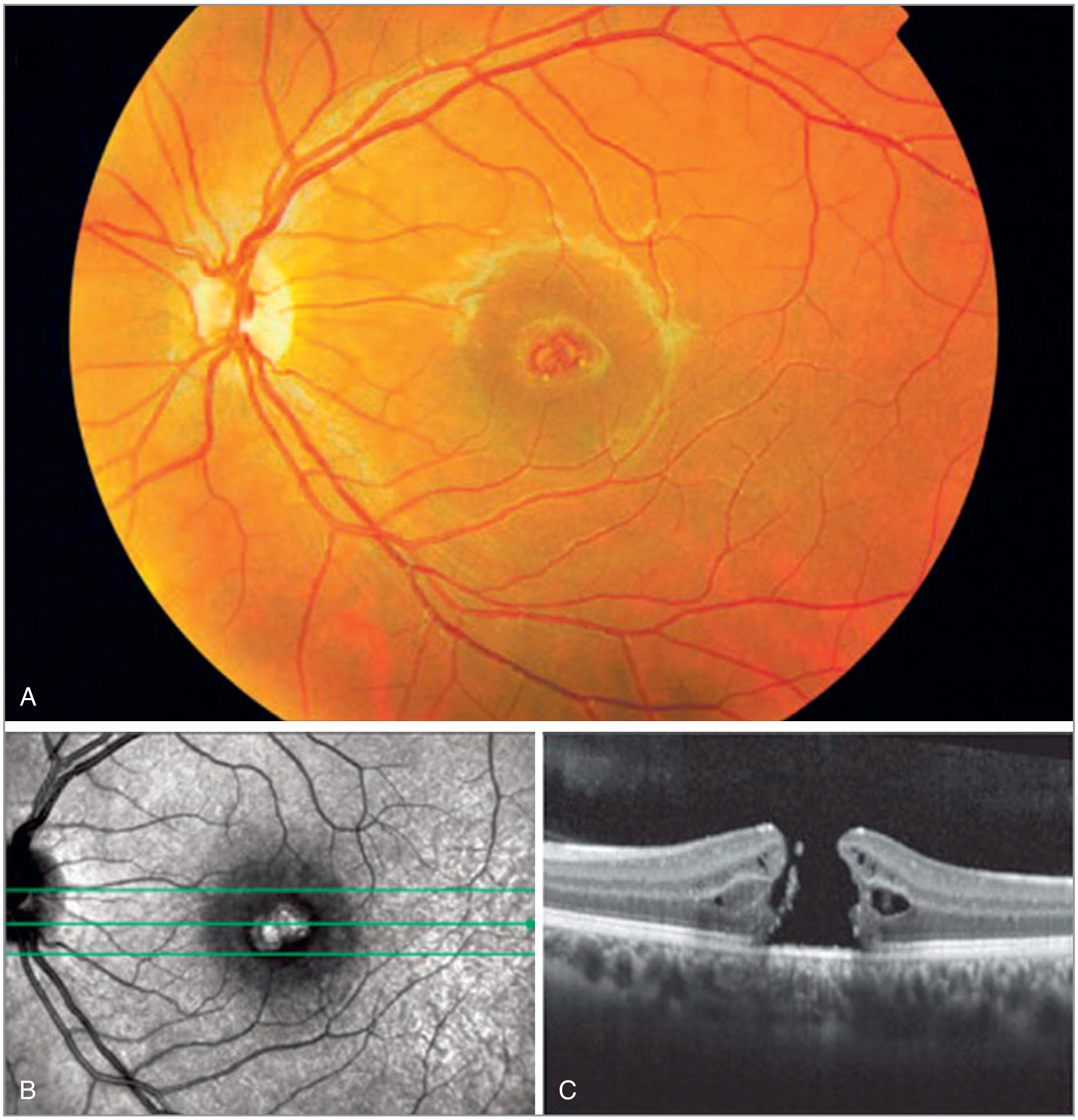

Figure 635-9 Laser damage to the left eye. **A,** Color photo of the fundus of the left eye showing a macular hole. Note the changes at the retinal pigment epithelium. **B,** Infrared photo of the left fundus. **C,** Optical coherence tomography (OCT) of the left eye showing the macular hole. *(From Petrou P, Patwary S, Banerjee PJ, et al: Bilateral macular hole from a handheld laser pointer,* Lancet *383:1780, 2014.)*

greater number of participating children, their athletic immaturity, and the increased likelihood of their using inadequate or improper eye protection account for their disproportionate share of sports-related eye injuries (see Chapters 688 and 693).

The sports with the highest risk of eye injury are those in which no eye protection can be worn, including boxing, wrestling, and martial arts. Other high-risk sports include those that use a rapidly moving ball or puck, bat, stick, racquet, or arrow (baseball, hockey, lacrosse, racquet sports, and archery) or involve aggressive body contact (football and basketball). Related to both risk and frequency of participation, the highest percentage of eye injuries are in basketball and baseball.

Protective eyewear, designed for a specific activity, is available for most sports. For basketball, racquet sports, and other recreational activities that do not require a helmet or face mask, molded polycarbonate sports goggles that are secured to the head by an elastic strap are suggested. For hockey, football, lacrosse, and baseball (batter), specific helmets with polycarbonate face shields and guards are available. Children should also wear sports goggles under the helmets. For baseball, goggles and helmets should be worn for batting, catching, and base running; goggles alone are usually sufficient for other positions.

HANDHELD LASER RETINAL INJURY

Handheld laser pointers, often purchased to light cigarettes or for other purposes, may produce significant retinal damage if the power output is ≥150 mW. If a person looks directly at the light, direct foveal injury may occur before he or she has time to blink. Central (foveal) blurring and decreased visual activity are the chief complaints. Retinal injuries include retinal disruption, subretinal edema, and macular holes (Fig. 635-9), which usually require surgical repair.

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The Ear

PART XXX

Chapter 636

General Considerations and Evaluation

Joseph Haddad Jr. and Sarah Keesecker

CLINICAL MANIFESTATIONS

Diseases of the ear and temporal bone typically manifest with 1 or more of 8 clinical signs and symptoms.

Otalgia usually is associated with inflammation of the external or middle ear, but it can represent pain referred from involvement of the teeth, temporomandibular joint, or pharynx. In young infants, pulling or rubbing the ear along with general irritability or poor sleep, especially when associated with fever, may be the only signs of ear pain. Ear pulling alone is not diagnostic of ear pathology.

Purulent otorrhea is a sign of otitis externa, otitis media with perforation of the tympanic membrane (TM), drainage from the middle ear through a patent tympanostomy tube, or, rarely, drainage from a first branchial cleft sinus. Bloody drainage may be associated with acute or chronic inflammation (often with granulation tissue and/or an ear tube), trauma, neoplasm, foreign body, or blood dyscrasia. Clear drainage suggests a perforation of the TM with a serous middle-ear effusion or, rarely, a cerebrospinal fluid leak draining through defects (congenital or traumatic) in the external auditory canal or from the middle ear.

Hearing loss results either from disease of the external or middle ear (conductive hearing loss) or from pathology in the inner ear, retrocochlear structures, or central auditory pathways (sensorineural hearing loss). The most common cause of hearing loss in children is otitis media (OM).

Swelling around the ear most commonly is a result of inflammation (e.g., external otitis, perichondritis, mastoiditis), trauma (e.g., hematoma), benign cystic masses, or neoplasm.

Vertigo is a specific type of dizziness that is defined as any illusion or sensation of motion. **Dizziness** is less specific than vertigo and refers to a sensation of altered orientation in space. Vertigo is an uncommon complaint in children; the child or parent might not volunteer information about balance unless asked specifically. The most common cause of dizziness in young children is eustachian tube–middle-ear disease, but true vertigo also may be caused by labyrinthitis, perilymphatic fistula between the inner and middle ear as a result of trauma or a congenital inner ear defect, cholesteatoma in the mastoid or middle ear, vestibular neuronitis, benign paroxysmal vertigo, Ménière disease, or disease of the central nervous system. Older children might describe a feeling of the room spinning or turning; younger children might express the dysequilibrium only by falling, stumbling, or clumsiness.

Nystagmus may be unidirectional, horizontal, or jerk nystagmus. It is vestibular in origin and usually is associated with vertigo.

Tinnitus rarely is described spontaneously by children, but it is common, especially in patients with eustachian tube–middle-ear disease or sensorineural hearing loss (SNHL). Children can describe tinnitus if asked directly about it, including laterality and the quality of the sound.

FACIAL PARALYSIS

The facial nerve may be dehiscent in its course through the middle ear in as many as 50% of patients. Infection with local inflammation, most commonly in acute OM, can lead to a temporary paralysis of the facial nerve. It also can result from Lyme disease, cholesteatoma, Bell palsy, Ramsay Hunt syndrome (herpes zoster oticus), fracture, neoplasm, or infection of the temporal bone. Congenital facial paralysis can result from birth trauma or congenital abnormality of the 7th nerve or from a syndrome such as Möbius or CHARGE (coloboma, heart defects, atresia choanae, retarded growth, genital hypoplasia, and ear anomalies), or it may be associated with other cranial nerve abnormalities and craniofacial anomalies.

PHYSICAL EXAMINATION

Complete examination with special attention to the head and neck can reveal a condition that can predispose to or be associated with ear disease in children. The facial appearance and the character of speech can give clues to an abnormality of the ear or hearing. Many craniofacial anomalies, such as cleft palate, mandibulofacial dysostosis (Treacher Collins syndrome), and trisomy 21 (Down syndrome), are associated with disorders of the ear and eustachian tube. Mouth breathing and hyponasality can indicate intranasal or postnasal obstruction. **Hypernasality** is a sign of velopharyngeal insufficiency. Examining the oropharyngeal cavity might uncover an overt cleft palate or a submucous cleft (usually associated with a bifid uvula), both of which predispose to OM with effusion. A nasopharyngeal tumor with nasal and eustachian tube blockage may be associated with OM.

The position of the patient for examination of the ear, nose, and throat depends on the patient's age and ability to cooperate, the clinical setting, and the examiner's preference. The child can be examined on an examination table or in the parent's lap. The presence of a parent or assistant usually is necessary to minimize movement and provide better examination results (Fig. 636-1). An examining table may be desirable for uncooperative older infants or when a procedure, such as microscopic evaluation or tympanocentesis, is performed. Wrapping the child in a sheet or using a papoose board can help to minimize movement. Lap examination is adequate and preferable in most infants and young children; the parent may assist in restraining the child by folding the child's wrists and arms over the child's own abdomen with one hand and holding the child's head against the parent's chest with the other hand. If necessary, the child's legs can be held between the parent's knees. To avoid ear trauma with movement, the examiner should hold the otoscope with the hand placed firmly against the child's head or face, so that the otoscope moves with the head. Pulling up and out on the pinna straightens the ear canal and allows better exposure of the TM.

When examining the ear, inspecting the auricle and external auditory meatus for infection can aid in evaluating complications of OM. External otitis can result from acute OM with discharge, or inflammation of the posterior auricular area can indicate a periostitis or subperiosteal abscess extending from the mastoid air cells. The presence of preauricular pits or skin tags also should be noted because affected children have a slightly higher incidence of sensorineural hearing loss; ear pits can develop chronic infection.

Cerumen is a protective, waxy, water-repellent coating in the ear canal that can interfere with examination. Cerumen usually is removed using the surgical head of the otoscope, which allows passage of a wire loop or a blunt curette under direct visualization. Other methods include gentle irrigation of the ear canal with warm water, which should be performed only if the TM is intact, or instillation of a solution such as diluted hydrogen peroxide in the ear canal (with intact TM only) for a few minutes to soften the wax for suction removal or

irrigation. Some commercial preparations such as trolamine polypeptide oleate–condensate (Cerumenex) can cause dermatitis of the external canal with chronic use and should be used only under a physician's supervision.

Inflammation of the ear canal with associated pain often indicates external otitis. Abnormalities of the external auditory canal include stenosis (common in children with trisomy 21), bony exostoses, otorrhea, and the presence of foreign bodies. Cholesteatoma of the middle ear can manifest in the canal as intermittent foul-smelling drainage, sometimes associated with white debris; cholesteatoma of the external canal can appear as a white, pearl-like mass in the canal skin. White or gray debris of the canal suggests fungal external otitis. Newborn ear canals are filled with vernix caseosa, which is soft and pale yellow and should disappear shortly after birth.

The TM and its mobility are best assessed with a pneumatic otoscope. The normal TM is in a neutral position; a bulging TM may be caused by increased middle-ear air pressure, with or without pus or effusion in the middle ear; a bulging drum can obscure visualization of the malleus and annulus. Retraction of the TM usually indicates negative middle-ear pressure, but it also can result from previous middle-ear disease with fixation of the ossicles, ossicular ligaments, or TM. When retraction is present, the bony malleus appears more prominent, and the incus may be more visible posterior to the malleus.

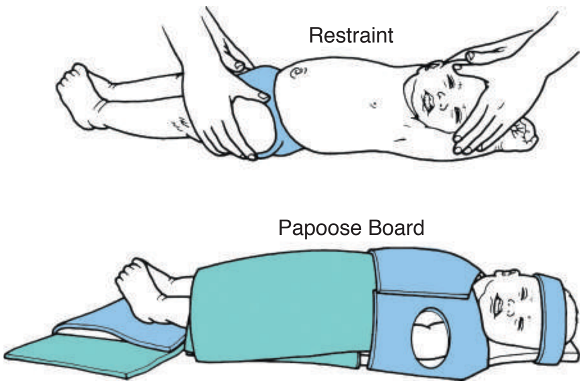

Figure 636-1 Methods of restraining an infant for examination and for procedures such as tympanocentesis or myringotomy. *(From Bluestone CD, Klein JO:* Otitis media in infants and children, *ed 2, Philadelphia, 1995, WB Saunders, p. 91.)*

The normal TM has a silvery-gray, "waxed paper" appearance (Fig. 636-2). A white or yellow TM can indicate a middle-ear effusion. A red TM alone might not indicate pathology, because the blood vessels of the membrane may be engorged as a result of crying, sneezing, or nose blowing. A normal TM is translucent, allowing the observer to visualize the middle-ear landmarks: incus, promontory, round window niche, and, often, the chorda tympani nerve. If a middle-ear effusion is present, an air–fluid level or bubbles may be visible (Fig. 636-2). Inability to visualize the middle-ear structures indicates opacification of the drum, usually caused by thickening of the TM or a middle-ear effusion, or both. Assessment of the light reflex often is not helpful, because a middle ear with effusion reflects light as well as a normal ear.

TM mobility is helpful in assessing middle-ear pressures and the presence or absence of fluid (see Fig. 636-2). To best perform pneumatic otoscopy, a speculum of adequate size is used to obtain a good seal and allow air movement in the canal. A rubber ring around the tip of the speculum can help to obtain a better canal seal. Normal middle-ear pressure is characterized by a neutral TM position and brisk TM movement to both positive and negative pressures.

Eardrum retraction is most common when negative middle-ear pressure is present; with even moderate negative middle-ear pressure there is no visible inward movement with applied positive pressure in the ear canal (see Fig. 636-1). However, negative canal pressure, which is produced by releasing the rubber bulb of the pneumatic otoscope, can cause the TM to bounce out toward the neutral position. The TM can retract in both the presence and absence of middle-ear fluid, and if the middle-ear fluid is mixed with air, the TM might still have some mobility. Outward eardrum movement is less likely in the presence of severe negative middle-ear pressure or middle-ear effusion.

The TM that exhibits fullness (bulging) moves to applied positive pressure but not to applied negative pressure if the pressure within the middle ear is positive. A full TM and positive middle-ear pressure without an effusion may be seen in young infants who are crying during the otoscopic examination, in older infants and children with nasal obstruction, and in the early stage of acute OM. When the middle-ear–mastoid air cell system is filled with an effusion and little or no air is present, the mobility of the TM is severely decreased or absent in response to both applied positive and negative pressures.

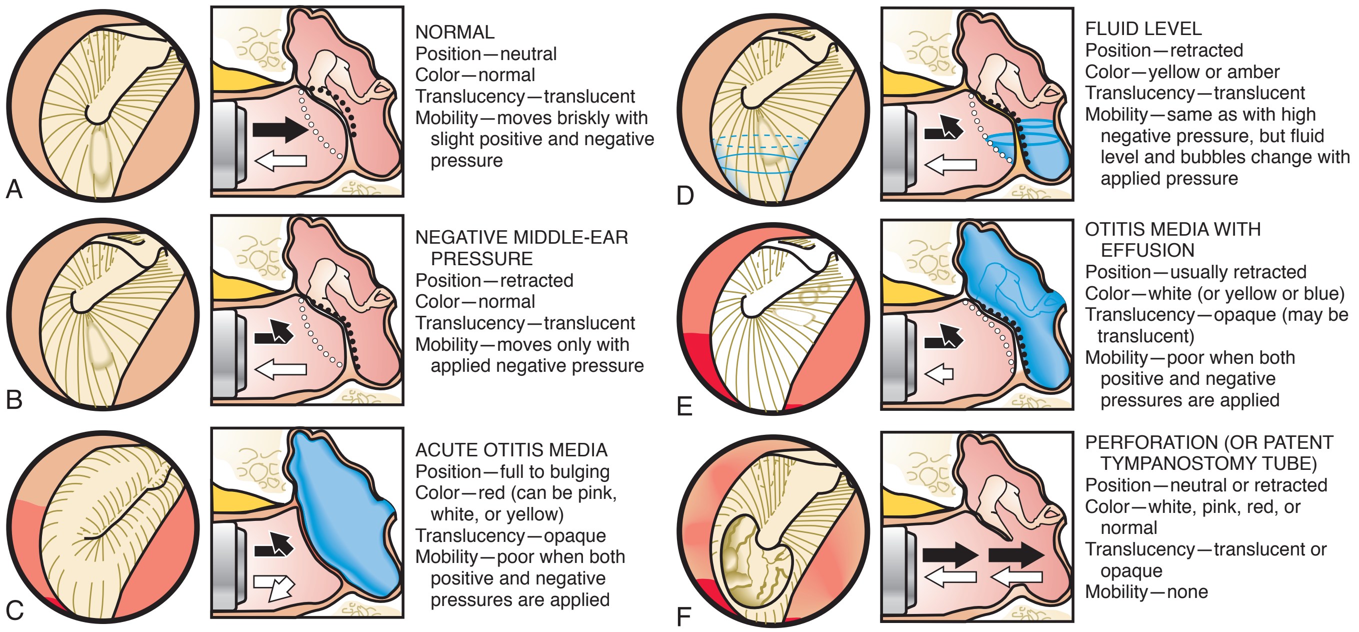

Figure 636-2 A-F, Common conditions of the middle ear, as assessed with the otoscope. *(From Bluestone CD, Klein JO:* Otitis media in infants and children, *ed 3, Philadelphia, 2001, WB Saunders, p. 131.)*

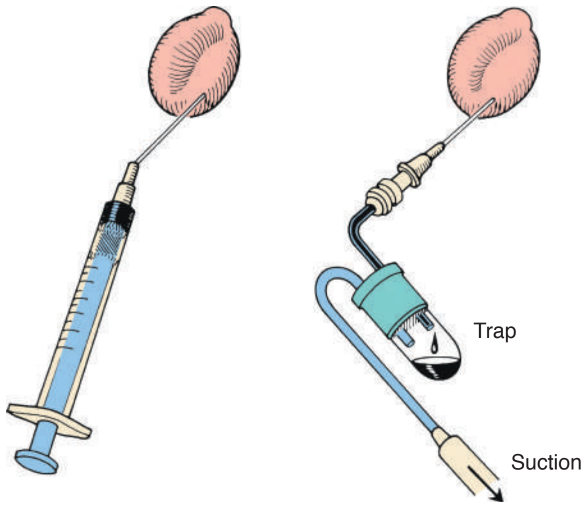

Figure 636-3 Tympanocentesis can be performed with a needle attached to a tuberculin syringe *(left)* or by using an Alden-Senturia collection trap (Storz Instrument Co, St. Louis). *(From Bluestone CD, Klein JO:* Otitis media in infants and children, *ed 2, Philadelphia, 1995, WB Saunders, p. 127.)*

Tympanocentesis, or aspiration of the middle ear, is the definitive method of verifying the presence and type of a middle-ear effusion and is performed by inserting, through the inferior portion of the TM, an 18-gauge spinal needle attached to a syringe or a collection trap (Fig. 636-3). Culturing of the ear canal and alcohol cleansing should precede tympanocentesis and culture of the middle-ear aspirate; a canal culture is taken first to help determine whether organisms cultured from the middle ear are contaminants from the external canal or true middle-ear pathogens.

Further diagnostic studies of the ear and hearing include audiometric evaluation, impedance audiometry (tympanometry), acoustic reflectometry, and specialized eustachian tube function studies. Diagnostic imaging studies, including CT and MRI, often provide further information about anatomic abnormalities and the extent of inflammatory processes or neoplasms. Specialized assessment of labyrinthine function should be considered in the evaluation of a child with a suspected vestibular disorder (see Chapter 641).

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Chapter 637

Hearing Loss

Joseph Haddad Jr. and Sarah Keesecker

INCIDENCE AND PREVALENCE

Bilateral neural hearing loss is categorized as mild (20-30 dB), moderate (30-50 dB), severe (50-70 dB), or profound (>70 dB). The World Health Organization estimates that approximately 360 million people (5% of the world's population, including 32 million children) have disabling hearing loss. An additional 364 million people have mild hearing loss. Half of these cases could have been prevented. In the United States, the average incidence of neonatal hearing loss is 1.1 in 1,000 infants; the rate by state varies from 0.22-3.61 in 1,000. Among children and adolescents, the rate of mild or greater hearing loss is 3.1% and is higher among Latin Americans, African-Americans, and persons from lower-income families.

The onset of hearing loss among children can occur at any time in childhood. When less-severe hearing loss or the transient hearing loss that commonly accompanies middle-ear disease in young children is considered, the number of affected children increases substantially.

TYPES OF HEARING LOSS

Hearing loss can be peripheral or central in origin. Peripheral hearing loss can be conductive, sensorineural, or mixed. **Conductive hearing loss (CHL)** commonly is caused by dysfunction in the transmission of sound through the external or middle ear or by abnormal transduction of sound energy into neural activity in the inner ear and the 8th nerve. CHL is the most common type of hearing loss in children and occurs when sound transmission is physically impeded in the external and/or middle ear. Common causes of CHL in the *ear canal* include atresia or stenosis, impacted cerumen, or foreign bodies. In the *middle ear*, perforation of the tympanic membrane (TM), discontinuity or fixation of the ossicular chain, otitis media (OM) with effusion, otosclerosis, and cholesteatoma can cause CHL.

Damage to or maldevelopment of structures in the inner ear can cause **sensorineural hearing loss (SNHL).** Causes include hair cell destruction from noise, disease, or ototoxic agents; cochlear malformation; perilymphatic fistula of the round or oval window membrane; and lesions of the acoustic division of the 8th nerve. A combination of CHL and SNHL is considered a **mixed hearing loss.**

An auditory deficit originating along the central auditory nervous system pathways from the proximal 8th nerve to the cerebral cortex usually is considered **central** (or **retrocochlear**) **hearing loss.** Tumors or demyelinating disease of the 8th nerve and cerebellopontine angle can cause hearing deficits but spare the outer, middle, and inner ear. These causes of hearing loss are rare in children. Other forms of central auditory deficits, known as **central auditory processing disorders,** include those that make it difficult even for children with normal hearing to listen selectively in the presence of noise, to combine information from the 2 ears properly, to process speech when it is slightly degraded, and to integrate auditory information when it is delivered faster although they can process it when delivered at a slow rate. These deficits can manifest as poor attention or as academic or behavior problems in school. Strategies for coping with such disorders are available for older children, and identification and documentation of the central auditory processing disorder often is valuable so that parents and teachers can make appropriate accommodations to enhance learning.

ETIOLOGY

Most CHL is acquired, with middle-ear fluid the most common cause. Congenital causes include anomalies of the pinna, external ear canal, TM, and ossicles. Rarely, congenital cholesteatoma or other masses in the middle ear manifest as CHL. TM perforation (e.g., trauma, OM), ossicular discontinuity (e.g., infection, cholesteatoma, trauma), tympanosclerosis, acquired cholesteatoma, or masses in the ear canal or middle ear (Langerhans cell histiocytosis, salivary gland tumors, glomus tumors, rhabdomyosarcoma) also can manifest as CHL. Uncommon diseases that affect the middle ear and temporal bone and can manifest with CHL include otosclerosis, osteopetrosis, fibrous dysplasia, and osteogenesis imperfecta.

SNHL may be congenital or acquired. Acquired SNHL may be caused by genetic, infectious, autoimmune, anatomic, traumatic, ototoxic, and idiopathic factors (Tables 637-1, 637-2, 637-3, and 637-4). The recognized risk factors account for approximately 50% of cases of moderate to profound SNHL.

Sudden SNHL in a previously healthy child is uncommon but may be from OM or other middle-ear pathologies such as autoimmunity. Usually these causes are obvious from the history and physical examination. Sudden loss of hearing in the absence of obvious causes often is the result of a vascular event affecting the cochlear apparatus or nerve, such as embolism or thrombosis (secondary to prothrombotic conditions), or an autoimmune process. Additional causes include perilymph fistula, drugs, trauma, and the first episode of Ménière syndrome. In adults, sudden SNHL is often idiopathic and unilateral;

Table 637-1 Indicators Associated with Hearing Loss

INDICATORS ASSOCIATED WITH SENSORINEURAL AND/OR CONDUCTIVE HEARING LOSS

Neonates (Birth-28 Days) When Universal Screening Is Not Available

Family history of hereditary childhood sensorineural hearing loss

In utero infection, such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis

Craniofacial anomalies, including those with morphologic abnormalities of the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies

Birthweight <1500 g (3.3 lb)

Hyperbilirubinemia at a serum level requiring exchange transfusion

Ototoxic medications, including but not limited to the aminoglycosides, used in multiple courses or in combination with loop diuretics

Bacterial meningitis

Apgar scores of 0-4 at 1 min or 0-6 at 5 min

Mechanical ventilation lasting ≥5 days; extracorporeal membrane oxygenation

Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss; white forelock

Infants and Toddlers (Age 29 Days-2 Yr) When Certain Health Conditions Develop That Require Rescreening

Parent or caregiver concern regarding hearing, speech, language, and/or developmental delay

Bacterial meningitis and other infections associated with sensorineural hearing loss

Head trauma associated with loss of consciousness or skull fracture

Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss; neurofibromatosis, osteopetrosis, and Usher Hunter, Waardenburg, Alport, Pendred, or Jervell and Lange-Nielsen syndrome

Ototoxic medications, including but not limited to chemotherapeutic agents or aminoglycosides used in multiple courses or in combination with loop diuretics

Recurrent or persistent otitis media with effusion for 3 mo or longer

Skeletal dysplasia

Infants and Toddlers (Age 29 Days-3 Yr) Who Require Periodic Monitoring of Hearing

Some newborns and infants pass initial hearing screening but require periodic monitoring of hearing to detect delayed-onset sensorineural and/or conductive hearing loss. Infants with these indicators require hearing evaluation at least every 6 mo until age 3 yr, and at appropriate intervals thereafter

INDICATORS ASSOCIATED WITH DELAYED-ONSET SENSORINEURAL HEARING LOSS

Family history of hereditary childhood hearing loss

In utero infection, such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis

Neurofibromatosis type 2 and neurodegenerative disorders

Cogan syndrome (vasculitis: keratitis, uveitis, vertigo, arthritis, dermatitis)

INDICATORS ASSOCIATED WITH CONDUCTIVE HEARING LOSS

Recurrent or persistent otitis media with effusion

Anatomic deformities and other disorders that affect eustachian tube function

Neurodegenerative disorders

Note: At all ages, parents' concern about hearing loss must be taken seriously even in the absence of risk factors.

Adapted from American Academy of Pediatrics, Joint Committee on Infant Hearing: Joint Committee on Infant Hearing 1994 position statement, Pediatrics *95:152, 1995.*

Table 637-2 Common Types of Early-Onset Hereditary Nonsyndromic Sensorineural Hearing Loss

LOCUS	GENE	AUDIO PHENOTYPE
DFN3	*POU3F4*	Conductive hearing loss as a result of stapes fixation mimicking otosclerosis; superimposed progressive SNHL
DFNA1	*DIAPH1*	Low-frequency loss beginning in the 1st decade and progressing to all frequencies to produce a flat audio profile with profound losses throughout the auditory range
DFNA2	*KCNQ4*	Symmetric high-frequency sensorineural loss beginning in the 1st decade and progressing over all frequencies
	GJB3	Symmetric high-frequency sensorineural loss beginning in the 3rd decade
DFNA3	*GJB2*	Childhood-onset, progressive, moderate-to-severe high-frequency sensorineural hearing impairment
	GJB6	Childhood-onset, progressive, moderate-to-severe high-frequency sensorineural hearing impairment
DFNA6, 14, and 38	*WFS1*	Early-onset low-frequency sensorineural loss; approximately 75% of families dominantly segregating this audio profile carry missense mutations in the C-terminal domain of wolframin
DFNA8, and 12	*TECTA*	Early-onset stable bilateral hearing loss, affecting mainly mid to high frequencies
DFNA10	*EYA4*	Progressive loss beginning in the 2nd decade as a flat to gently sloping audio profile that becomes steeply sloping with age
DFNA11	*MYO7A*	Ascending audiogram affecting low and middle frequencies at young ages and then affecting all frequencies with increasing age
DFNA13	*COL11A2*	Congenital midfrequency sensorineural loss that shows age-related progression across the auditory range
DFNA15	*POU4F3*	Bilateral progressive sensorineural loss beginning in the 2nd decade

Table 637-2 Common Types of Early-Onset Hereditary Nonsyndromic Sensorineural Hearing Loss—cont'd

LOCUS	GENE	AUDIO PHENOTYPE
DFNA20, and 26	*ACTG1*	Bilateral progressive sensorineural loss beginning in the 2nd decade; with age, the loss increases with threshold shifts in all frequencies, although a sloping configuration is maintained in most cases
DFNA22	*MYO6*	Postlingual, slowly progressive, moderate to severe hearing loss
DFNB1	*GJB2*, *GJB6*	Hearing loss varies from mild to profound. The most common genotype, 35delG/35delG, is associated with severe to profound SNHL in about 90% of affected children; severe to profound deafness is observed in only 60% of children who are compound heterozygotes carrying 1 35delG allele and any other *GJB2* SNHL-causing allele variant; in children carrying 2 *GJB2* SNHL-causing missense mutations, severe to profound deafness is not observed
DFNB3	*MYO7A*	Severe to profound sensorineural hearing loss
DFNB4	*SLC26A4*	DFNB4 and Pendred syndrome (see Table 637-3) are allelic. DFNB4 hearing loss is associated with dilation of the vestibular aqueduct and can be unilateral or bilateral. In the high frequencies, the loss is severe to profound; in the low frequencies, the degree of loss varies widely. Onset can be congenital (prelingual), but progressive postlingual loss also is common
DFNB7, and 11	*TMC1*	Severe-to-profound prelingual hearing impairment
DFNB9	*OTOF*	*OTOF*-related deafness is characterized by 2 phenotypes: prelingual nonsyndromic hearing loss and, less frequently, temperature-sensitive nonsyndromic auditory neuropathy. The nonsyndromic hearing loss is bilateral severe-to-profound congenital deafness
DFNB12	*CDH23*	Depending on the type of mutation, recessive mutations of *CDH23* can cause nonsyndromic deafness or type 1 Usher syndrome (USH1), which is characterized by deafness, vestibular areflexia, and vision loss as a result of retinitis pigmentosa
DFNB16	*STRC*	Early-onset nonsyndromic autosomal recessive sensorineural hearing loss
mtDNA 1555A > G	*12S rRNA*	Degree of hearing loss varies from mild to profound but usually is symmetric; high frequencies are preferentially affected; precipitous loss in hearing can occur after aminoglycoside therapy

SNHL, sensorineural hearing loss.
Adapted from Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children, Lancet *365:879–890, 2005.*

Table 637-3 Common Types of Syndromic Sensorineural Hearing Loss

SYNDROME	GENE	PHENOTYPE
DOMINANT		
Waardenburg (WS1)	*PAX3*	Major diagnostic criteria include dystopia canthorum, congenital hearing loss, heterochromic irises, white forelock, and an affected 1st-degree relative. Approximately 60% of affected children have congenital hearing loss; in 90%, the loss is bilateral.
Waardenburg (WS2)	*MITF*, others	Major diagnostic criteria are as for WS1 but without dystopia canthorum. Approximately 80% of affected children have congenital hearing loss; in 90%, the loss is bilateral.
Branchiootorenal	*EYA1*	Diagnostic criteria include hearing loss (98%), preauricular pits (85%), and branchial (70%), renal (40%), and external-ear (30%) abnormalities. The hearing loss can be conductive, sensorineural, or mixed, and mild to profound in degree.
CHARGE syndrome	*CHD7*	Choanal atresia, colobomas, heart defect, retardation, genital hypoplasia, ear anomalies, deafness. Can lead to sensorineural or mixed hearing loss. Can be autosomal dominant or isolated cases.
Goldenhar syndrome	Unknown	Part of the hemifacial microsomia spectrum. Facial hypoplasia, ear anomalies, hemivertebrae, parotid gland dysfunction. Can cause conductive or mixed hearing loss. Can be autosomal dominant or sporadic.
RECESSIVE		
Pendred syndrome	*SLC26A4*	Diagnostic criteria include sensorineural hearing loss that is congenital, nonprogressive, and severe to profound in many cases, but can be late-onset and progressive; bilateral dilation of the vestibular aqueduct with or without cochlear hypoplasia; and an abnormal perchlorate discharge test or goiter.
Alport syndrome	*COL4A3*, *COL4A4*, and *COL4A5*	Nephritis, deafness, lens defects, retinitis. Can lead to bilateral sensorineural hearing loss in the 2,000-8,000 Hz range. The hearing loss develops gradually and is not generally present in early infancy.
Usher syndrome type 1 (USH1)	*USH1A*, *MYO7A*, *USH1C*, *CDH23*, *USH1E*, *PCDH15*, *USH1G*	Diagnostic criteria include congenital, bilateral, and profound hearing loss, vestibular areflexia, and retinitis pigmentosa (commonly not diagnosed until tunnel vision and nyctalopia become severe enough to be noticeable).
Usher syndrome type 2 (USH2)	*USH2A*, *USH2B*, *USH2C*, others	Diagnostic criteria include mild to severe, congenital, bilateral hearing loss and retinitis pigmentosa; hearing loss may be perceived as progressing over time because speech perception decreases as diminishing vision interferes with subconscious lip reading.
Usher syndrome type 3 (USH3)	*USH3*	Diagnostic criteria include postlingual, progressive sensorineural hearing loss, late-onset retinitis pigmentosa, and variable impairment of vestibular function.

Adapted from Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children, Lancet *365:879–890, 2005.*

Table 637-4	Infectious Pathogens Implicated in Sensorineural Hearing Loss in Children
CONGENITAL INFECTIONS	
Cytomegalovirus	
Lymphocytic choriomeningitis virus	
Rubella virus	
Toxoplasma gondii	
Treponema pallidum	
ACQUIRED INFECTIONS	
Borrelia burgdorferi	
Epstein-Barr virus	
Haemophilus influenzae	
Lassa virus	
Measles virus	
Mumps virus	
Neisseria meningitidis	
Nonpolio enteroviruses	
Plasmodium falciparum	
Streptococcus pneumoniae	
Varicella-zoster virus	

From Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children, Lancet *365:879–890, 2005.*

it may be associated with tinnitus and vertigo. Identifiable causes of sudden SNHL include infections (Epstein-Barr virus, varicella-zoster virus, herpes simplex virus), vascular injury to the cochlea, endolymphatic hydrops, and autoimmune inflammatory diseases. In most patients with sudden SNHL, no etiology is discovered, and it is termed **idiopathic sudden SNHL**.

Infectious Causes

The most common infectious cause of congenital SNHL is **cytomegalovirus (CMV),** which infects 1 in 100 newborns in the United States (see Chapters 255 and 638). Of these, 6,000-8,000 infants each yr have clinical manifestations, including approximately 75% with SNHL. Congenital CMV warrants special attention because it is associated with hearing loss in its symptomatic and asymptomatic forms, and the hearing loss may be progressive. Some children with congenital CMV have suddenly lost residual hearing at 4-5 yr of age. Much less common congenital infectious causes of SNHL include toxoplasmosis and syphilis. Congenital CMV, toxoplasmosis, and syphilis also can manifest with delayed onset of SNHL months to years after birth. Rubella, once the most common viral cause of congenital SNHL, is very uncommon because of effective vaccination programs. In utero infection with herpes simplex virus is rare, and hearing loss is not an isolated manifestation.

Other postnatal infectious causes of SNHL include neonatal group B streptococcal sepsis and bacterial meningitis at any age. *Streptococcus pneumoniae* is the most common cause of bacterial meningitis that results in SNHL after the neonatal period and has become less common with the routine administration of pneumococcal conjugate vaccine. *Haemophilus influenzae* type b, once the most common cause of meningitis resulting in SNHL, is rare owing to the *H. influenzae* type b conjugate vaccine. Uncommon infectious causes of SNHL include Lyme disease, parvovirus B19, and varicella. Mumps, rubella, and rubeola, all once common causes of SNHL in children, are rare owing to vaccination programs.

Genetic Causes

Genetic causes of SNHL probably are responsible for as many as 50% of SNHL cases (see Tables 637-2 and 637-3). These disorders may be associated with other abnormalities, may be part of a named syndrome, or can exist in isolation. SNHL often occurs with abnormalities of the ear and eye and with disorders of the metabolic, musculoskeletal, integumentary, renal, and nervous systems.

Autosomal dominant hearing losses account for approximately 10% of all cases of childhood SNHL. Waardenburg (types I and II) and branchiootorenal syndromes represent 2 of the most common autosomal dominant syndromic types of SNHL. Types of SNHL are coded with a 4 letter code and a number, as follows: **DFN** = deafness, A = dominant, B = recessive, and number = order of discovery, for example, DFNA 13. Autosomal dominant conditions in addition to those just discussed include DFNA 1-18, 20-25, 30, 36, 38, and mutations in the crystallin gene *(CRYM).*

Autosomal recessive genetic SNHL, both syndromic and nonsyndromic, accounts for approximately 80% of all childhood cases of SNHL. Usher syndrome (types 1, 2, and 3: all associated with blindness, retinitis pigmentosa), Pendred syndrome, and the Jervell and Lange-Nielsen syndrome (one form of the long Q-T syndrome) are 3 of the most common syndromic recessive types of SNHL. Other autosomal recessive conditions include Alström syndrome, type 4 Bartter syndrome, biotinidase deficiency, and DFNB 1-18, 20-23, 26-27, 29-33, 35-40, 42, 44, 46, 48, 49, 53, and 55.

Unlike children with an easily identified syndrome or with anomalies of the outer ear, who may be identified as being at risk for hearing loss and consequently monitored adequately, children with nonsyndromic hearing loss present greater diagnostic difficulty. Mutations of the connexin-26 and -30 genes have been identified in autosomal recessive (DNFB 1) and autosomal dominant (DNFA 3) SNHL and in sporadic patients with nonsyndromic SNHL; up to 50% of nonsyndromic SNHLs may be related to a mutation of connexin-26. Mutations of the *GJB2* gene colocalize with DFNA 3 and DFNB 1 loci on chromosome 13, are associated with autosomal nonsyndromic susceptibility to deafness, and are associated with as many as 30% of cases of sporadic severe to profound congenital deafness and 50% of cases of autosomal recessive nonsyndromic deafness. In addition, mutations in *GJB6* are associated with approximately 5% of recessive nonsyndromic deafness. Sex-linked disorders associated with SNHL, thought to account for 1-2% of SNHLs, include Norrie disease, the otopalatal digital syndrome, Nance deafness, and Alport syndrome. Chromosomal abnormalities such as trisomy 13-15, trisomy 18, and trisomy 21 also can be accompanied by hearing impairment. Patients with Turner syndrome have monosomy for all or part of 1 X chromosome and can have CHL, SNHL, or mixed hearing loss. The hearing loss may be progressive. Mitochondrial genetic abnormalities also can result in SNHL (see Table 637-2).

Many genetically determined causes of hearing impairment, both syndromic and nonsyndromic, do not express themselves until sometime after birth. Alport, Alström, Down, and Hunter-Hurler syndromes and von Recklinghausen disease are genetic diseases that can have SNHL as a late manifestation.

Physical Causes

Agenesis or malformation of cochlear structures, including the Scheibe, Mondini (Fig. 637-1), Alexander, and Michel anomalies, enlarged vestibular aqueducts (which may be associated with Pendred syndrome), and semicircular canal anomalies, may be genetic. These anomalies probably occur before the 8th wk of gestation and result from arrest in normal development or aberrant development, or both. Many of these anomalies also have been described in association with other congenital conditions such as intrauterine CMV and rubella infections. These abnormalities are quite common; in as many as 20% of children with SNHL, obvious or subtle temporal bone abnormalities are seen on high-resolution CT scanning or MRI.

Conditions, diseases, or syndromes that include craniofacial abnormalities may be associated with CHL and possibly with SNHL. Pierre Robin, Treacher Collins, Klippel-Feil, Crouzon, and branchiootorenal syndromes and osteogenesis imperfecta often are associated with hearing loss. Congenital anomalies causing CHL include malformations of the ossicles and middle-ear structures and atresia of the external auditory canal.

SNHL also can occur secondary to exposure to toxins, chemicals, and antimicrobials. Early in pregnancy, the embryo is particularly vulnerable to the effects of toxic substances. Ototoxic drugs, including aminoglycosides, loop diuretics, and chemotherapeutic agents (cisplatin) also can cause SNHL. Congenital SNHL can occur secondary to

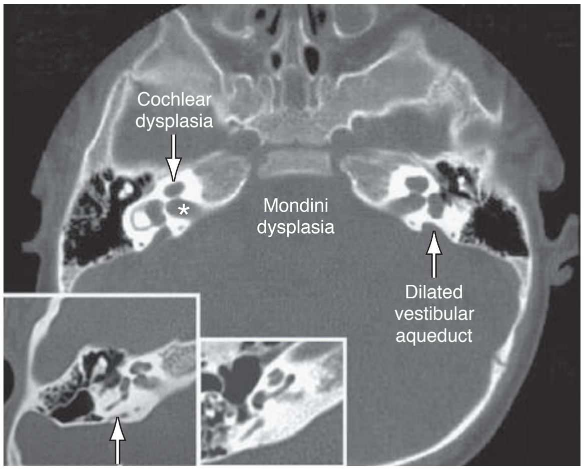

Figure 637-1 Mondini dysplasia shown by CT of the temporal bone in a child with Pendred syndrome. Both dilation of the vestibular aqueduct and cochlear dysplasia are present in this section. In the larger of the 2 inset images of a normal temporal bone, the vestibular aqueduct is visible but much smaller *(arrow)*. The cochlea appears normal, and in the smaller inset image of a more inferior axial section, the expected number of cochlear turns can be clearly counted. *Internal auditory canal. *(From Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children,* Lancet *365:879–890, 2005.)*

exposure to these drugs as well as to thalidomide and retinoids. Certain chemicals, such as quinine, lead, and arsenic, can cause hearing loss both prenatally and postnatally.

Trauma, including temporal bone fractures, inner ear concussion, head trauma, iatrogenic trauma (e.g., surgery, extracorporeal membrane oxygenation), radiation exposure, and noise, also can cause SNHL. Other uncommon causes of SNHL in children include immune disease (systemic or limited to the inner ear), metabolic abnormalities, and neoplasms of the temporal bone.

EFFECTS OF HEARING IMPAIRMENT

The effects of hearing impairment depend on the nature and degree of the hearing loss and on the individual characteristics of the child. Hearing loss may be unilateral or bilateral, conductive, sensorineural, or mixed; mild, moderate, severe, or profound; of sudden or gradual onset; stable, progressive, or fluctuating; and affecting a part or all of the audible spectrum. Other factors, such as intelligence, medical or physical condition (including accompanying syndromes), family support, age at onset, age at time of identification, and promptness of intervention, also affect the impact of hearing loss on a child.

Most hearing-impaired children have some usable hearing. Only 6% of those in the hearing-impaired population have bilateral profound hearing loss. Hearing loss very early in life can affect the development of speech and language, social and emotional development, behavior, attention, and academic achievement. Some cases of hearing impairment are misdiagnosed because affected children have sufficient hearing to respond to environmental sounds and can learn some speech and language but when challenged in the classroom cannot perform to full potential.

Even mild or unilateral hearing loss can have a detrimental effect on the development of a young child and on school performance. Children with such hearing impairments have greater difficulty when listening conditions are unfavorable (e.g., background noise and poor acoustics), as can occur in a classroom. The fact that schools are auditory-verbal environments is unappreciated by those who minimize the impact of hearing impairment on learning. Hearing loss should be considered in any child with speech and language difficulties or below-par performance, poor behavior, or inattention in school (Table 637-5).

Children with moderate, severe, or profound hearing impairment and those with other handicapping conditions often are educated in classes or schools for children with special needs. The auditory management and choices regarding modes of communication and education for children with hearing handicaps must be individualized, because these children are not a homogeneous group. A team approach to individual case management is essential, because each child and family unit has unique needs and abilities.

HEARING SCREENING

Hearing impairment can have a major impact on a child's development, and because early identification improves prognosis, screening programs have been widely and strongly advocated. The National Center for Hearing Assessment and Management estimates that the detection and treatment at birth of hearing loss saves $400,000 per child in special education costs; screening costs approximately $8-50/child. Data from the Colorado newborn screening program suggest that if hearing-impaired infants are identified and treated by age 6 mo, these children (with the exception of those with bilateral profound impairment) should develop the same level of language as their age-matched peers who are not hearing impaired. This is compelling support for the establishment of mandated newborn hearing screening programs for all children. The American Academy of Pediatrics endorses the goal of universal detection of hearing loss in infants before 3 mo of age, with appropriate intervention no later than 6 mo of age. Newborn screening rates in the United States have increased significantly; the Centers for Disease Control and Prevention estimates that of the approximately 4 million infants born in the United States in 2009, 97% were screened for hearing loss.

Until mandated screening programs are established universally, many hospitals will continue to use other criteria to screen for hearing loss. Some use the high-risk criteria (see Table 637-1) to decide which infants to screen; some screen all infants who require intensive care; and some do both. The problem with using high-risk criteria to screen is that 50% of cases of hearing impairment will be missed, either because the infants are hearing impaired but do not meet any of the high-risk criteria or because they develop hearing loss after the neonatal period.

The recommended hearing screening techniques are either otoacoustic emissions (OAE) testing or auditory brainstem evoked responses (ABRs). The ABR test, an auditory evoked electrophysiologic response that correlates highly with hearing, has been used successfully and cost-effectively to screen newborns and to identify further the degree and type of hearing loss. OAE tests, used successfully in most universal newborn screening programs, are quick, easy to administer, and inexpensive, and they provide a sensitive indication of the presence of hearing loss. Results are relatively easy to interpret. OAE tests elicit no response if hearing is worse than 30-40 dB, no matter what the cause; children who fail OAE tests undergo an ABR for a more definitive evaluation. Screening methods such as observing behavioral responses to uncalibrated noisemakers or using automated systems such as the Crib-o-gram (Canon) or the auditory response cradle (in which movement of the infant in response to sound is recorded by motion sensors) are not recommended.

Many children become hearing impaired after the neonatal period and therefore are not identified by newborn screening programs. Often it is not until children are in preschool or kindergarten that further hearing screening takes place. Primary care physicians and pediatricians should be alert to the signs and symptoms of childhood hearing impairment, so that children with hearing impairment who have not been screened formally can be identified as early as possible. Figure 637-2 identifies recommendations for postneonatal screening.

IDENTIFICATION OF HEARING IMPAIRMENT

The impact of hearing impairment is greatest on an infant who has yet to develop language; consequently, identification, diagnosis, description, and treatment should begin as soon as possible. In general, infants with a prenatal or perinatal history that puts them at risk (see Table 637-2) or those who have failed a formal hearing screening should be monitored closely by an experienced clinical audiologist until a reliable

assessment of auditory function has been obtained. Pediatricians should encourage families to cooperate with the follow-up plan. Infants who are born at risk but who were not screened as neonates (often because of transfer from one hospital to another) should have a hearing screening by age 3 mo.

Hearing-impaired infants, who are born at risk or are screened for hearing loss in a neonatal hearing screening program, account for only a portion of hearing-impaired children. Children who are congenitally deaf because of autosomal recessive inheritance or subclinical congenital infection often are not identified until 1-3 yr of age. Usually, those

Table 637-5 Hearing Handicap as a Function of Average Hearing Threshold Level of the Better Ear

AVERAGE THRESHOLD LEVEL (dB) AT 500-2,000 Hz (ANSI)	DESCRIPTION	COMMON CAUSES	WHAT CAN BE HEARD WITHOUT AMPLIFICATION	DEGREE OF HANDICAP (IF NOT TREATED IN 1ST YR OF LIFE)	PROBABLE NEEDS
0-15	Normal range	Conductive hearing loss	All speech sounds	None	None
16-25	Slight hearing loss	Otitis media, TM perforation, tympanosclerosis; eustachian tube dysfunction; some SNHL	Vowel sounds heard clearly, may miss unvoiced consonant sounds	Mild auditory dysfunction in language learning Difficulty in perceiving some speech sounds	Consideration of need for hearing aid, speech reading, auditory training, speech therapy, appropriate surgery, preferential seating
26-30	Mild	Otitis media, TM perforation, tympanosclerosis, severe eustachian dysfunction, SNHL	Hears only some speech sounds, the louder voiced sounds	Auditory learning dysfunction Mild language retardation Mild speech problems Inattention	Hearing aid Lip reading Auditory training Speech therapy Appropriate surgery
31-50	Moderate hearing loss	Chronic otitis, ear canal/middle ear anomaly, SNHL	Misses most speech sounds at normal conversational level	Speech problems Language retardation Learning dysfunction Inattention	All of the above, plus consideration of special classroom situation
51-70	Severe hearing loss	SNHL or mixed loss due to a combination of middle-ear disease and sensorineural involvement	Hears no speech sound of normal conversations	Severe speech problems Language retardation Learning dysfunction Inattention	All of the above; probable assignment to special classes
71+	Profound hearing loss	SNHL or mixed	Hears no speech or other sounds	Severe speech problems Language retardation Learning dysfunction Inattention	All of the above; probable assignment to special classes or schools

ANSI, American National Standards Institute; SNHL, sensorineural hearing loss; TM, tympanic membrane.
Modified from Northern JL, Downs MP: Hearing in children, *ed 4, Baltimore, 1991, Williams & Wilkins.*

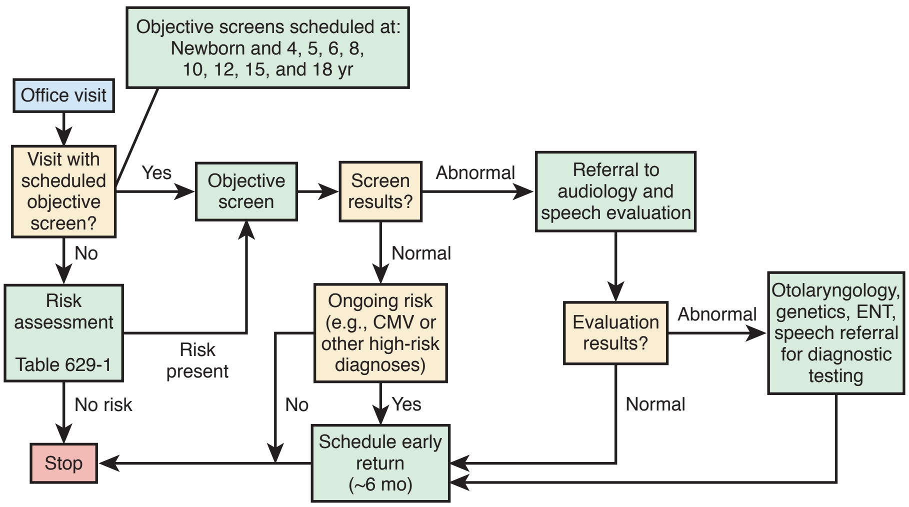

Figure 637-2 Hearing-assessment algorithm within an office visit. CMV, cytomegalovirus; ENT, ear, nose, and throat. *(From Harlor AD Jr, Bower C: Clinical report—hearing assessment in infants and children: recommendations beyond neonatal screening,* Pediatrics *124:1252–1263, 2009, Fig. 1, p. 1254.)*

Table 637-6 Criteria for Referral for Audiologic Assessment

AGE (mo)	REFERRAL GUIDELINES FOR CHILDREN WITH "SPEECH" DELAY
12	No differentiated babbling or vocal imitation
18	No use of single words
24	Single-word vocabulary of ≤10 words
30	<100 words; no evidence of 2 word combinations; unintelligible
36	<200 words; no use of telegraphic sentences; clarity <50%
48	<600 words; no use of simple sentences; clarity ≤80%

From Matkin ND: Early recognition and referral of hearing-impaired children, Pediatr Rev 6:151–156, 1984. Reproduced by permission of Pediatrics.

Table 637-7 Guidelines for Referral of Children with Suspected Hearing Loss

AGE (mo)	NORMAL DEVELOPMENT
0-4	Should startle to loud sounds, quiet to mother's voice, momentarily cease activity when sound is presented at a conversational level
5-6	Should correctly localize to sound presented in a horizontal plane, begin to imitate sounds in own speech repertoire or at least reciprocally vocalize with an adult
7-12	Should correctly localize to sound presented in any plane Should respond to name, even when spoken quietly
13-15	Should point toward an unexpected sound or to familiar objects or persons when asked
16-18	Should follow simple directions without gestural or other visual cues; can be trained to reach toward an interesting toy at midline when a sound is presented
19-24	Should point to body parts when asked; by 21-24 mo, can be trained to perform play audiometry

From Matkin ND: Early recognition and referral of hearing-impaired children, Pediatr Rev 6:151–156, 1984.

with more-severe hearing loss are identified at an earlier age, but identification often occurs later than the age at which intervention can provide an optimal outcome. Children who hear normally develop an extensive language by 3-4 yr of age (Table 637-6) and exhibit behavior reflecting normal auditory function (Table 637-7). Failure to fulfill these criteria should be the reason for an audiologic evaluation. Parents' concern about hearing and any delayed development of speech and language should alert the pediatrician, because parents' concern usually precedes formal identification and diagnosis of hearing impairment by 6 mo to 1 yr of age.

CLINICAL AUDIOLOGIC EVALUATION

Even the youngest infants can be evaluated for auditory function. When hearing impairment is suspected in a young child, reliable and valid estimates of auditory function can be obtained. Successful treatment strategies for hearing-impaired children rely on prompt identification and ongoing assessment to define the dimensions of auditory function. Cooperation among the pediatrician and specialists in areas such as audiology, speech and language pathology, education, and child development is necessary to optimize auditory-verbal development.

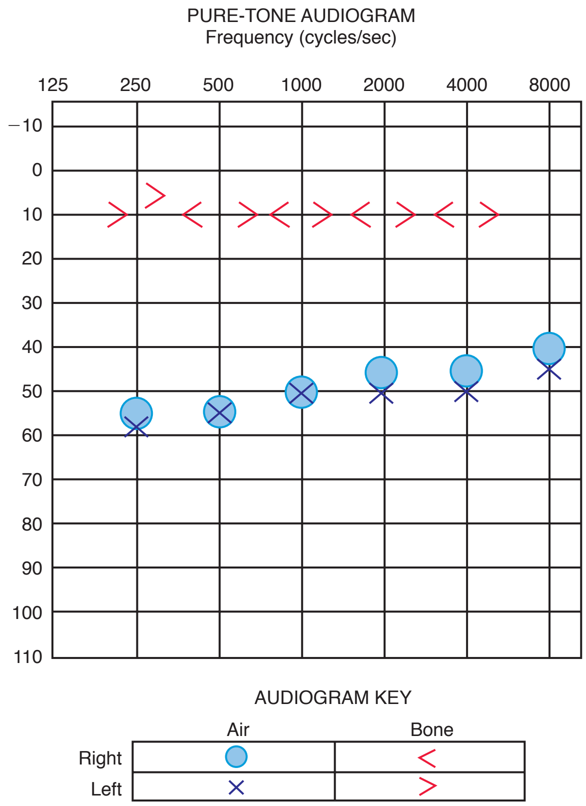

Figure 637-3 Audiogram showing bilateral conductive hearing loss.

Therapy for hearing-impaired children includes considering and often fitting an amplification device, using a **frequency modulation** system in the classroom, monitoring hearing and auditory skills, counseling parents and families, advising teachers, and dealing with public agencies.

Audiometry

The technique of the audiologic evaluation varies as a function of the age or developmental level of the child, the reason for the evaluation, and the child's otologic condition or history. An audiogram provides the fundamental description of hearing sensitivity (Fig. 637-3). Hearing thresholds are assessed as a function of frequency using pure tones (sine waves) at octave intervals from 250-8,000 Hz. Earphones typically are used when age-appropriate, and hearing is assessed independently for each ear. **Air-conducted signals** are presented through earphones (or loudspeakers) and are used to provide information about the sensitivity of the auditory system. These same test sounds can be delivered to the ear through an oscillator that is placed on the head, usually on the mastoid. Such signals are considered bone-conducted because the bones of the skull transmit vibrations as sound energy directly to the inner ear, essentially bypassing the outer and middle ears. In a normal ear, and also in children with SNHL, the air- and bone-conduction thresholds are the same. In those with CHL, the air- and bone-conduction thresholds differ. This is called the **air–bone gap,** which indicates the amount of hearing loss attributable to dysfunction in the outer and/or middle ear. With mixed hearing loss, both the bone- and air-conduction thresholds are abnormal, and there is an air–bone gap.

Speech-Recognition Threshold

Another measure useful for describing auditory function is the **speech-recognition threshold (SRT)**, which is the lowest intensity level at which a score of approximately 50% correct is obtained on a task of recognizing spondee words. Spondee words are 2 syllable words or phrases that have equal stress on each syllable, such as baseball, hotdog,

and pancake. Listeners must be familiar with all the words for a valid test result to be obtained. The SRT should correspond to the average of pure-tone thresholds at 500, 1,000, and 2,000 Hz, the pure-tone average. The SRT is relevant as an indicator of a child's potential for development and use of speech and language; it also serves as a check of the validity of a test because children with nonorganic hearing loss (malingerers) might show a discrepancy between the pure-tone average and SRT.

The basic battery of hearing tests concludes with an assessment of a child's ability to understand monosyllabic words when presented at a comfortable listening level. Performance on such word intelligibility tests assists in the differential diagnosis of hearing impairment and provides a measure of how well a child performs when speech is presented at loudness levels similar to those encountered in the environment.

Play Audiometry

Hearing testing is age dependent. For children at or above the developmental level of a 5-6 yr old, conventional test methods can be used. For children 30 mo to 5 yr of age, play audiometry can be used. Responses in play audiometry usually are conditioned motor activities associated with a game, such as dropping blocks in a bucket, placing rings on a peg, or completing a puzzle. The technique can be used to obtain a reliable audiogram for a preschool child. For those who will not or cannot repeat words clearly for the SRT and word intelligibility tasks, pictures can be used with a pointing response.

Visual Reinforcement Audiometry

For children between the ages of about 6 mo and 30 mo, **visual reinforcement audiometry (VRA)** commonly is used. In this technique, the child is observed for a head-turning response on activation of an animated (mechanical) toy reinforcer. If infants are properly conditioned, by giving sounds associated with the visual toy cue, VRA can provide reliable estimates of hearing sensitivity for tones and speech sounds. In most applications of VRA, sounds are presented by loudspeakers in a sound field, so no *ear-specific* information is obtained. Assessment of an infant often is designed to rule out hearing loss that would affect the development of speech and language. Normal sound-field response levels of infants indicate sufficient hearing for this purpose despite the possibility of different hearing levels in the 2 ears.

Behavioral Observation Audiometry

Used as a screening device for infants <5 mo of age, **behavioral observation audiometry** is limited to unconditioned, reflexive responses to complex (not frequency-specific) test sounds such as noise, speech, or music presented using calibrated signals from a loudspeaker or uncalibrated noisemakers. Response levels can vary widely within and among infants and usually do not provide a reliable estimate of sensitivity.

Assessment of a child with suspected hearing loss is not complete until pure-tone hearing thresholds and SRTs (a reliable audiogram) have been obtained in each ear. Behavioral observation audiometry and VRA in sound-field testing give estimates of hearing responsivity in the *better-hearing ear*.

Acoustic Immittance Testing

Acoustic immittance testing is a standard part of the clinical audiologic test battery and includes tympanometry. It is a useful objective assessment technique that provides information about the status of the middle ear. Tympanometry can be performed in a physician's office and is helpful in the diagnosis and management of OM with effusion, a common cause of mild to moderate hearing loss in young children.

Tympanometry

Tympanometry provides a graph of the middle ear's ability to transmit sound energy (admittance, or compliance) or impede sound energy (impedance) as a function of air pressure in the external ear canal. Because most immittance test instruments measure acoustic admittance, the term *admittance* is used here. The principles apply to whatever units of measurement are used.

A probe is inserted into the entrance of the external ear canal so that an airtight seal is obtained. The probe varies air pressure, presents a tone, and measures sound pressure level in the ear canal through the probe assembly. The sound pressure measured in the ear canal relative to the known intensity of the probe signal is used to estimate the acoustic admittance of the ear canal and middle-ear system. Admittance can be expressed in a unit called a millimho (mmho) or as a volume of air (mL) with equivalent acoustic admittance. The test is performed so that an estimate can be made of the volume of air enclosed between the probe tip and TM. The acoustic admittance of this volume of air is deducted from the overall admittance measure to obtain a measure of the admittance of the middle-ear system alone. Estimating ear canal volume also has a diagnostic benefit, because an abnormally large value is consistent with the presence of an opening in the TM (perforation or tube).

Once the admittance of the air mass in the external auditory canal has been eliminated, it is assumed that the remaining admittance measure accurately reflects the admittance of the entire middle-ear system. Its value is controlled largely by the dynamics of the TM. Abnormalities of the TM can dictate the shape of tympanograms, thus obscuring abnormalities medial to the TM. In addition, the frequency of the probe tone, the speed and direction of the air pressure change, and the air pressure at which the tympanogram is initiated can all influence the outcome.

When air pressure in the ear canal is equal to that in the middle ear, the middle-ear system is functioning optimally. Therefore, the ear canal pressure at which there is the greatest flow of energy (admittance) should be a reasonable estimate of the air pressure in the middle-ear space. This pressure is determined by finding the maximum or **peak admittance** on the tympanogram and obtaining its value on the x-axis. The value on the y-axis at the tympanogram peak is an estimate of peak admittance based on admittance tympanometry (Table 637-8). This peak measure sometimes is referred to as **static acoustic admittance,** even though it is estimated from a dynamic measure.

Tympanometry in Otitis Media with Effusion

Children who have OM with effusion often have reduced peak admittance or high negative tympanometric peak pressures (see Fig. 640-5*C* in Chapter 640). However, in the diagnosis of effusion, the tympanometric measure with the greatest sensitivity and specificity is the shape of the tympanogram rather than its peak pressure or admittance. This shape sometimes is referred to as the tympanometric gradient or width; it measures the degree of roundness or **peakedness** of the tympanogram. The more rounded the peak (or, in an absent peak, a flat

Table 637-8 Norms for Peak (Static) Admittance Using a 226-Hz Probe Tone for Children and Adults

AGE GROUP	ADMITTANCE (mL)	Speed of Air Pressure Sweep	
		≤50 daPa/sec*	200 daPa/sec†
Children (3-5 yr)	Lower limit	0.30	0.36
	Median	0.55	0.61
	Upper limit	0.90	1.06
Adults	Lower limit	0.56	0.27
	Median	0.85	0.72
	Upper limit	1.36	1.38

*Ear canal volume measurement based on admittance at lowest tail of tympanogram.

†Ear canal measurement based on admittance at lowest tail of tympanogram for children and at +200 daPa for adults.

daPa, decaPascals.

Adapted from Margolis RH, Shanks JE: Tympanometry: basic principles of clinical application. In Rintelman WS, editor: Hearing assessment, *ed 2, Austin, 1991, PRODED, pp. 179–245.*

tympanogram), the higher is the probability that an effusion is present (see Fig. 640-5*B* in Chapter 640). It is important to know which instrument is used, because some compute gradient automatically but others do not.

Acoustic Reflex Test

The **acoustic reflex test** also is part of the immittance test battery. With a properly functioning middle-ear system, admittance at the TM changes on activation of the stapedius and tensor tympani muscles. In healthy ears, the stapedial reflex occurs after exposure to loud sounds. Admittance instruments are designed to present reflex activating signals (pure tones of various frequencies or noise), either to the same ear or the contralateral ear, while monitoring admittance. Very small admittance changes that are time locked to presentations of the signal are considered to be a result of middle-ear muscle reflexes. Admittance changes may be absent when the hearing loss is sufficient to prevent the signal from reaching the loudness level necessary to elicit the reflex or when a middle-ear condition affects the ear's ability to monitor a small admittance change. Reflexes usually are absent in patients with CHL because of the presence of an abnormal transfer system; thus, the acoustic reflex test is useful in the differential diagnosis of hearing impairment. The acoustic reflex test also is used in the assessment of SNHL and the integrity of the neurologic components of the reflex arc, including cranial nerves VII and VIII.

Auditory Brainstem Response

The auditory brainstem response (ABR) test is used to screen newborn hearing, confirm hearing loss in young children, obtain ear-specific information in young children, and test children who cannot, for whatever reason, cooperate with behavioral test methods. It also is important in the diagnosis of auditory dysfunction and of disorders of the auditory nervous system. The ABR test is a far-field recording of minute electrical discharges from numerous neurons. The stimulus, therefore, must be able to cause simultaneous discharge of the large numbers of neurons involved. Stimuli with very rapid onset, such as clicks or tone bursts, must be used. Unfortunately, the rapid onset required to create a measurable ABR also causes energy to be spread in the frequency domain, reducing the frequency-specificity of the response.

The ABR result is not affected by sedation or general anesthesia. Infants and children from about 4 mo to 4 yr of age routinely are sedated to minimize electrical interference caused by muscle activity during testing. The ABR also can be performed in the operating room when a child is anesthetized for another procedure. Children younger than 4 mo of age might sleep for a long enough period of time after feeding to allow an ABR to be done.

The ABR is recorded as 5-7 waves. Waves I, III, and V can be obtained consistently in all age groups; waves II and IV appear less consistently. The latency of each wave (time of occurrence of the wave peak after stimulus onset) increases, and the amplitude decreases with reductions in stimulus intensity or loudness; latency also decreases with increasing age, with the earliest waves reaching mature latency values earlier in life than the later waves.

The ABR test has 2 major uses in a pediatric setting. As an audiometric test, it provides information on the ability of the peripheral auditory system to transmit information to the auditory nerve and beyond. It also is used in the differential diagnosis or monitoring of central nervous system pathology. For audiometry, the goal is to find the minimum stimulus intensity that yields an observable ABR. Plotting latency vs intensity for various waves also aids in the differential diagnosis of hearing impairment. A major advantage of auditory assessment using the ABR test is that ear-specific threshold estimates can be obtained on infants or patients who are difficult to test. ABR thresholds using click stimuli correlate best with behavioral hearing thresholds in the higher frequencies (1,000-4,000 Hz); responsivity in the low frequencies requires different stimuli (tone bursts or filtered clicks) or the use of masking, neither of which isolates the low-frequency region of the cochlea in all cases, and this can affect interpretation.

The ABR test does not assess "hearing." It reflects auditory neuronal electrical responses that can be correlated to behavioral hearing thresholds, but a normal ABR result only suggests that the auditory system, up to the level of the midbrain, is responsive to the stimulus used. Conversely, a failure to elicit an ABR indicates an impairment of the system's synchronous response but does not necessarily mean that there is no "hearing." The behavioral response to sound sometimes is normal when no ABR can be elicited, such as in neurologic demyelinating disease. The ABR test may be used to infer whether and at what level of the auditory system impairment exists.

Hearing losses that are sudden, progressive, or unilateral are indications for ABR testing. Although it is believed that the different waves of the ABR reflect activity in increasingly rostral levels of the auditory system, the neural generators of the response have not been precisely determined. Each ABR wave beyond the earliest waves probably is the result of neural firing at many levels of the system, and each level of the system probably contributes to several ABR waves. High-intensity click stimuli are used for the neurologic application. The morphology of the response and wave and interwave latencies are examined in respect to age-appropriate forms. Delayed or missing waves in the ABR result often have diagnostic significance.

The ABR and other electrical responses are extremely complex and difficult to interpret. A number of factors, including instrumentation design and settings, environment, degree and configuration of hearing loss, and patients' characteristics, can influence the quality of the recording. Therefore, testing and interpretation of electrophysiologic activity as it possibly relates to hearing should be carried out by trained audiologists to avoid the risk that unreliable or erroneous conclusions will affect a patient's care.

Otoacoustic Emissions

During normal hearing, OAEs originate from the hair cells in the cochlea and are detected by sensitive amplifying processes. They travel from the cochlea through the middle ear to the external auditory canal, where they can be detected using miniature microphones. Transient evoked OAEs (TEOAEs) may be used to check the integrity of the cochlea. In the neonatal period, detection of OAEs can be accomplished during natural sleep, and TEOAEs can be used as screening tests in infants and children for hearing at the 30 dB level of hearing loss. They are less time consuming and elaborate than ABRs and are more sensitive than behavioral tests in young children. TEOAEs are reduced or absent owing to various dysfunctions in the middle and inner ears. They are absent in patients with >30 dB of hearing loss and are not used to determine the hearing threshold; rather, they provide a screen for whether hearing is present at >30-40 dB. Diseases such as OM or congenitally abnormal middle-ear structures reduce the transfer of TEOAEs and may incorrectly indicate a cochlear hearing disorder. If a hearing loss is suspected based on the absence of OAEs, the ears should be examined for evidence of pathology, and then ABR testing should be used for confirmation and identification of the type, degree, and laterality of hearing loss.

Acoustic Reflectometry

In acoustic reflectometry, a handheld instrument is placed next to the opening of a child's ear canal and an 80 dB sound is delivered that varies in frequency from 2,000-4,500 Hz in a 100 msec period. The instrument measures the total level of reflected and transmitted sound. Some physicians have found this device useful to help gauge the presence or absence of middle-ear fluid, and a commercial version is marketed to parents as a way to monitor ear fluid. The instrument does not provide any information about hearing; if the presence of chronic fluid is suggested, audiometric evaluation should be obtained.

TREATMENT

With the use of universal hearing screening in the majority of states within the United States, the early diagnosis and treatment of children with hearing loss is common. Testing for hearing loss is possible even in very young children, and it should be done if parents suspect a

Table 637-9 Recommended Pneumococcal Vaccination Schedule for Persons with Cochlear Implants

AGE AT FIRST PCV13 DOSE (mo)*	PCV12 PRIMARY SERIES	PCV13 ADDITIONAL DOSE	PPV23 DOSE
2-6	3 doses, 2 mo apart†	1 dose at 12-15 mo of age‡	Indicated at ≥24 mo of age§
7-11	2 doses, 2 mo apart†	1 dose at 12-15 mo of age‡	Indicated at ≥24 mo of age§
12-23	2 doses, 2 mo apart¶	Not indicated	Indicated at ≥24 mo of age§
24-59	2 doses, 2 mo apart¶	Not indicated	Indicated§
≥60	Not indicated‖	Not indicated‖	Indicated

*A schedule with a reduced number of total 13-valent pneumococcal conjugate vaccine (PCV13) doses is indicated if children start late or are incompletely vaccinated. Children with a lapse in vaccination should be vaccinated according to the catch-up schedule (see Chapter 182).

†For children vaccinated at younger than age 1 yr, minimum interval between doses is 4 wk.

‡The additional dose should be administered 8 wk or more after the primary series has been completed.

§Children younger than age 5 yr should complete the PCV13 series first; 23-valent pneumococcal polysaccharide vaccine (PPV23) should be administered to children 24 mo of age or older 8 wk or more after the last dose of PCV13 (see Chapter 182). (Centers for Disease Control and Prevention Advisory Committee on Immunization Practices: Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR Recomm Rep* 49[RR-9]:1–35, 2000, and Licensure of a 13-valent pneumococcal conjugate vaccine [PCV13] and recommendations for use among children—Advisory Committee on Immunization Practices [ACIP], 2010, *MMWR Morb Mortal Wkly Rep* 59(9);258–261, 2010.)

¶Minimum interval between doses is 8 wk.

‖PCV13 is not recommended generally for children age 5 yr or older.

PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.

From Centers for Disease Control and Prevention Advisory Committee on Immunization Practices: Pneumococcal vaccination for cochlear implant candidates and recipients: Updated recommendations of the Advisory Committee on Immunization Practices, MMWR Morb Mortal Wkly Rep *52(31):739–740, 2003.*

problem. Any child with a known risk factor for hearing loss should be evaluated in the 1st 6 mo of life.

Once a hearing loss is identified, a full developmental and speech and language evaluation is needed. Counseling and involvement of parents are required in all stages of the evaluation and treatment or rehabilitation. A CHL often can be corrected through treatment of a middle-ear effusion (i.e., ear tube placement) or surgical correction of the abnormal sound-conducting mechanism. Children with SNHL should be evaluated for possible hearing aid use by a pediatric audiologist. Hearing aids may be fitted for children as young as 2 mo of age. Compelling evidence from the hearing screening program in Colorado shows that identification and amplification before age 6 mo makes a very significant difference in the speech and language abilities of affected children, compared with cases identified and amplified after the age of 6 mo. In these children, repeat audiologic testing is needed to reliably identify the degree of hearing loss and to fine-tune the use of hearing aids.

Infants and young children with profound congenital or prelingual onset of deafness have benefited from **multichannel cochlear implants** (Fig. 637-4). These implants bypass injury to the organ of Corti and provide neural stimulation by way of an external microphone and a signal processor that digitizes auditory stimuli into digital radiofrequency impulses. Cochlear implantation before age 2 yr (and even 1 yr) improves hearing and speech, enabling more than 90% of children to be in mainstream education. Most develop age-appropriate auditory perception and oral language skills.

A serious complication of cochlear implants is an excessively high incidence of pneumococcal meningitis. All children receiving a cochlear implant must be vaccinated with the pneumococcal polyvalent vaccine PCV13 (Table 637-9).

The best approach to the education of children with significant hearing loss is a subject of ongoing controversy. Because we live in a predominantly speaking world, some have advocated a pure auditory and oral approach to hearing therapy. However, because affected children often are slow to develop communication skills, many advocate a total communication approach; depending on the individual child's needs, this technique uses a mixture of sign language, lip reading, hearing aids, and speech. The appropriate program for each child depends on the patient, family, and available resources.

Management of **idiopathic sudden SNHL** is controversial and has included oral prednisone, intratympanic (also called transtympanic) dexamethasone perfusion, or a combination of both; the latter combination may be the most useful, although the data are not conclusive.

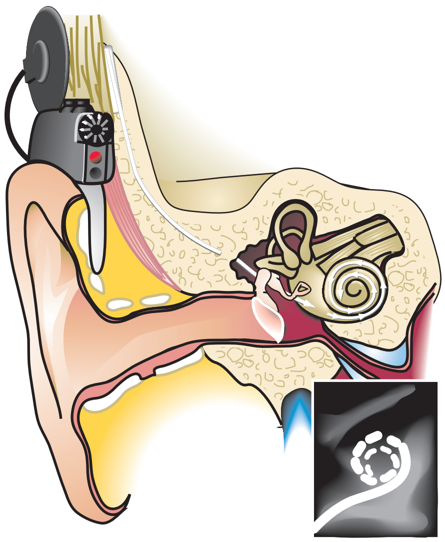

Figure 637-4 All cochlear implants share key components, including a microphone, speech processor, and transmitter coil, shown in a behind-the-ear position in this diagram. The microphone and speech processor pick up environmental sounds and digitize them into coded signals. The signals are sent to the transmitter coil and relayed through the skin to the internal device imbedded in the skull. The internal device converts the code to electronic signals, which are transmitted to the electrode array wrapping around the cochlea. The inset shows the radiographic appearance of the stimulating electrode array. *(Reproduced with permission from MED-EL Corporation, Innsbruck, Austria. From Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children,* Lancet *365:879–890, 2005.)*

GENETIC COUNSELING

Families of children with the diagnosis of SNHL or a syndrome associated with SNHL and/or CHL should consider genetic counseling, which will allow a discussion of the likelihood of similar diagnoses in future pregnancies. The geneticist also can help in the evaluation and further testing of the patient with hearing loss to establish a diagnosis.

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Chapter 638
Congenital Malformations

Joseph Haddad Jr. and Sarah Keesecker

The external and middle ears, derived from the first and second branchial arches and grooves, grow throughout puberty, but the inner ear, which develops from the otocyst, reaches adult size and shape by midfetal development. The ossicles are derived from the first and second arches (malleus and incus), and the stapes arises from the second arch and the otic capsule. The malleus and incus achieve adult size and shape by the 15th wk of gestation, and the stapes achieves adult size and shape by the 18th wk of gestation. Although the pinna, ear canal, and tympanic membrane (TM) continue to grow after birth, congenital abnormalities of these structures develop during the first half of gestation. Malformed external and middle ears may be associated with serious renal anomalies, mandibulofacial dysostosis, hemifacial microsomia, and other craniofacial malformations. Facial nerve abnormalities may be associated with any of the congenital abnormalities of the ear and temporal bone. Malformations of the external and middle ears also may be associated with abnormalities of the inner ear and both conductive (CHL) and sensorineural hearing loss (SNHL).

Congenital ear problems may be minor and mainly cosmetic, or major, affecting both appearance and function. Any child born with an abnormality of the pinna, external auditory canal, or TM should have a complete audiologic evaluation in the neonatal period. Imaging studies are necessary for evaluation and treatment; in the patient with other craniofacial abnormalities a team approach with other specialists can assist in guiding therapy.

PINNA MALFORMATIONS

Severe malformations of the external ear are rare, but minor deformities are common. Isolated abnormalities of the external ear occur in approximately 1% of children. A pit-like depression just in front of the helix and above the tragus may represent a cyst or an epidermis-lined fistulous tract. These are common, with an incidence of approximately 8 in 1,000 children, and may be unilateral or bilateral and familial. The pits require surgical removal only if there is recurrent infection. Accessory skin tags, with an incidence of 1-2/1,000 live births, can be removed for cosmetic reasons by simple ligation if they are attached by a narrow pedicle. If the pedicle is broad based or contains cartilage, the defect should be corrected surgically. An unusually prominent or "lop" ear results from lack of bending of the cartilage that creates the antihelix. It may be improved cosmetically in the neonatal period by applying a firm framework (sometimes soldering wire is used) attached by Steri-Strips to the pinna and worn continuously for weeks to months. Otoplasty for cosmetic correction can be considered in children older than 5 yr of age, when the pinna has reached approximately 80% of its adult size.

The term **microtia** may indicate subtle abnormalities of the size, shape, and location of the pinna and ear canal, or major abnormalities with only small nubbins of skin and cartilage and the absence of the ear canal opening; **anotia** indicates complete absence of the pinna and ear canal. Microtia can have a genetic or environmental predisposition. Several hereditary forms of microtia have been identified that exhibit either autosomal dominant or recessive mendelian inheritance. In addition, some forms due to chromosomal aberrations have been reported. Most of the responsible genes that have been identified are homeobox genes. Microtic ears often are more anterior and inferior in placement than normal auricles, and the location and function of the facial nerve may be abnormal. Surgery to correct microtia is considered for both cosmetic and functional reasons; children who have some pinna can wear regular glasses, a hearing aid, and earrings and feel more normal in appearance. If the microtia is severe, some patients may opt for creation and attachment of a prosthetic ear, which cosmetically closely resembles a real ear. Surgery to correct severe microtia may involve a multistage procedure, including carving and transplantation of autogenous cartilage rib grafts and local soft tissue flaps. Cosmetic reconstruction of the auricle usually is performed between 5-7 yr of age and is performed before canal atresia repair in children deemed appropriate for this surgery.

CONGENITAL STENOSIS OR ATRESIA OF THE EXTERNAL AUDITORY CANAL

Stenosis or atresia of the ear canal often occurs in association with malformation of the auricle and middle ear. Malformations can occur in isolation or as part of a genetic syndrome. For example, the ear canal is narrow in trisomy 21 and external canal stenosis or atresia is common in branchiooculofacial syndrome, leading to CHL. Audiometric evaluation of these children should be undertaken as early in life as possible. Most children with significant CHL secondary to bilateral atresia wear bone conduction hearing aids for the 1st several yr of life. Diagnosis, evaluation, and surgical planning often are aided by CT, and sometimes MRI, of the temporal bone. Mild cases of ear canal stenosis do not require surgical enlargement unless the patient develops chronic external otitis or severe cerumen impaction that affects hearing.

Reconstructive ear canal and middle-ear surgery for atresia usually is considered for children older than 5 yr of age who have bilateral deformities resulting in a significant CHL. The aim of reconstructive surgery is to improve hearing to a point where the child may not need a hearing aid or to provide an ear canal and pinna so that the child can derive improved benefit from an air-conduction hearing aid. Hearing results for atresiaplasty range from fair to excellent. CT evidence of an adequate middle-ear cleft, ossicles, and mastoid is required to perform the surgery; the position of the facial nerve, which often is in an abnormal location in these children, also must be considered (Fig. 638-1). The use of bone-anchored hearing aids is a safe, reliable, and low-risk alternative to atresiaplasty and hearing results are generally excellent. Bone-anchored hearing aids may also be useful for rehabilitation of nonoptimal atresiaplasty hearing results. These devices are approved by the U.S. Food and Drug Administration for surgical placement in children age 5 yr and older; prior to age 5 yr, they can be worn with a soft band around the head. Disadvantages include the fact that cosmesis is not very good (a bone-anchored hearing aid has a visible titanium abutment and snap-on hearing aid) and frequent wound care is required.

CONGENITAL MIDDLE-EAR MALFORMATIONS

Children may have congenital abnormalities of the middle ear as an isolated defect or in association with other abnormalities of the temporal bone, especially the ear canal and pinna, or as part of a syndrome. Affected children usually have CHL but may have mixed CHL and SNHL. Most malformations involve the ossicles, with the incus most commonly affected. Other less-common abnormalities of the middle ear include persistent stapedial artery, high-riding jugular bulb, and abnormalities of the shape and volume of the aerated portion of the middle ear and mastoid; all present problems for a surgeon. Depending on the type of abnormality and the presence of other anomalies, surgery may be considered to improve hearing.

CONGENITAL INNER EAR MALFORMATIONS

Congenital inner ear malformations have been identified and classified as a result of improvements in imaging modalities, especially CT and MRI. As many as 20% of children with SNHL may have anatomic abnormalities identified on CT or MRI. Congenital malformations of the inner ear usually are associated with SNHL of various degrees, from mild to profound. These malformations may occur as isolated anomalies or in association with other syndromes, genetic abnormalities, or structural abnormalities of the head and neck. Enlarged vestibular

Figure 638-1 External auditory canal atresia on CT scans. **A,** Coronal scan of right ear shows absent external auditory canal with thick bony atresia plate *(white arrows)*. Malleus neck is rotated and fused to superior portion of atresia plate *(black arrow)*. **B,** Axial scan through attic shows fused ossicular mass *(arrow)*. **C,** Coronal scan more posterior to **A** shows mastoid segment of facial nerve canal positioned more anteriorly than normal *(arrows)*. **D,** Axial scan more inferior to **B** shows anterior-posterior mastoid segment of the facial nerve en face *(arrow)*. Note abnormally close relationship to mandibular condoyle. *(From Faerber EN, Booth TN, Swartz JD. Temporal bone and ear. In Slovis TL, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, Fig. 44-7, p. 584.)*

aqueducts have been identified on imaging studies in association with SNHL; although no therapy exists for this condition, it may be associated with progressive SNHL in some children, and, therefore, diagnosis may have some prognostic value.

Congenital perilymphatic fistula of the oval or round window membrane may present as a rapid-onset, fluctuating, or progressive SNHL with or without vertigo and often is associated with congenital inner ear abnormalities. Middle-ear exploration may be required to confirm this diagnosis, because no reliable nonoperative diagnostic test exists. It may be necessary to repair a perilymphatic fistula to prevent possible spread of infection from the middle ear to the labyrinth, to stabilize hearing loss, and to improve vertigo when present.

CONGENITAL CHOLESTEATOMA

A congenital cholesteatoma (approximately 2% of all cholesteatomas) is a nonneoplastic, destructive, cystic lesion that usually appears as a white, round, cyst-like structure medial to an intact TM. Cysts are seen most commonly in the anterior-superior portion of the middle ear, although they can present in other locations and within the TM or in the skin of the ear canal. Affected children often have no prior history of otitis media. One theory for the pathogenesis is that the cyst derives from a congenital rest of epithelial tissue that persists beyond 33 wk of gestation, when it ordinarily would disappear. Other theories include squamous metaplasia of the middle ear, entrance of squamous epithelium through a nonintact eardrum into the middle ear, ectodermal implants between the first and second branchial arch remnants, and residual amniotic fluid squamous debris. Congenital or acquired cholesteatoma should be suspected when deep retraction pockets, keratin debris, chronic drainage, aural granulation tissue, or a mass behind or involving the TM is present. Besides acting as a benign tumor causing local bone destruction, the keratinaceous debris of a cholesteatoma is a good culture medium and may become a focus of infection for chronic otitis media. Complications include ossicular erosion with hearing loss, bone erosion into the inner ear with dizziness, or exposure of the dura, with consequent meningitis or a brain abscess. Cholesteatoma should be removed surgically after CT scan (Fig. 638-2) and hearing evaluation, and appropriate antibiotic therapy. A second-look procedure 6-9 mo after primary surgery is often recommended to prevent further recurrence. Higher initial stage of disease, erosion of ossicles, cholesteatoma abutting or enveloping the incus or stapes, and need for removal of the ossicles are associated with increased likelihood of residual cholesteatoma. In addition, more extensive disease at initial surgery is associated with poorer hearing outcomes. Recurrence rates vary and are related to the extent of involvement at the time of surgery. In a large case series, recurrence rates were found to be as follows: 14% when disease was confined to 1 quadrant, 33% when more than 1 quadrant was involved but the ossicles and mastoids were not, 41% with ossicular involvement, and 67% with mastoid involvement. Overall recurrence may be as high as 57%. Congenital cholesteatoma is an aggressive disease, and early surgical

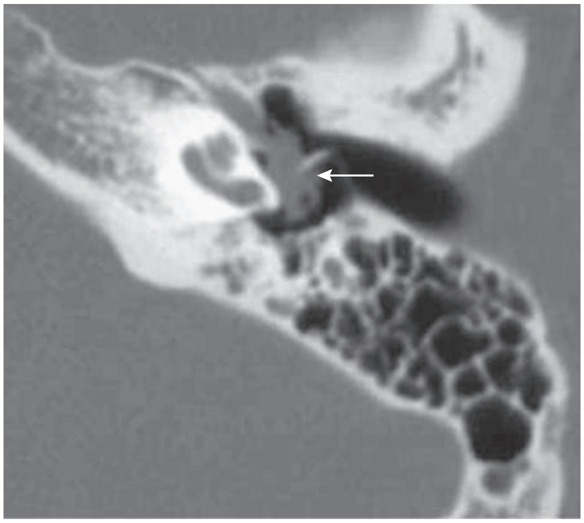

Figure 638-2 **Congenital cholesteatoma.** Axial CT of left ear shows soft tissue mass *(arrow)* in the middle ear. This mass was noted otoscopically behind an intact membrane. *(From Faerber EN, Booth TN, Swartz JD. Temporal bone and ear. In Slovis TL, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, Fig. 44-31, p. 598.)*

removal and close monitoring will help prevent permanent damage to the middle and inner ear.

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Chapter 639
External Otitis (Otitis Externa)

Joseph Haddad Jr. and Sarah Keesecker

In an infant, the outer two thirds of the ear canal is cartilaginous and the inner one third is bony. In an older child and adult the outer one third is cartilaginous and the inner two thirds is bony. The epithelium is thinner in the bony portion than in the cartilaginous portion, there is no subcutaneous tissue, and epithelium is tightly applied to the underlying periosteum; hair follicles, sebaceous glands, and apocrine glands are scarce or absent. The skin in the cartilaginous area has well-developed dermis and subcutaneous tissue and contains hair follicles, sebaceous glands, and apocrine glands. The highly viscid secretions of the sebaceous glands and the watery, pigmented secretions of the apocrine glands in the outer portion of the canal combine with exfoliated surface cells of the skin to form **cerumen,** a protective, waxy, water-repellent coating.

The normal flora of the external canal consists mainly of aerobic bacteria and includes coagulase-negative staphylococci (see Chapter 181.3), *Corynebacterium* (diphtheroids) (see Chapter 187), *Micrococcus,* and, occasionally, *Staphylococcus aureus* (see Chapter 181.1), viridans streptococci (see Chapter 185), and *Pseudomonas aeruginosa* (see Chapter 205.1). **Excessive wetness** (swimming, bathing, increased environmental humidity), **dryness** (dry canal skin and lack of cerumen), the presence of other skin pathologic conditions (previous infection, eczema, or other forms of dermatitis), and trauma (due to digital or foreign body, use of cotton-tip applicators [Q-tips]) make the skin of the canal vulnerable to infection by the normal flora or exogenous bacteria.

ETIOLOGY

External otitis (**swimmer's ear,** although it can occur without swimming) is caused most commonly by *P. aeruginosa,* but *S. aureus, Enterobacter aerogenes, Proteus mirabilis, Klebsiella pneumoniae,* streptococci, coagulase-negative staphylococci, diphtheroids, and fungi such as *Candida* and *Aspergillus* also may be isolated. External otitis results from chronic irritation and maceration from excessive moisture in the canal. The loss of protective cerumen may play a role, as may trauma, but cerumen impaction with trapping of water also can cause infection. Inflammation of the ear canal due to herpesvirus, varicella-zoster virus, other skin exanthems, and eczema also may predispose to external otitis.

CLINICAL MANIFESTATIONS

The predominant symptom is acute rapid onset of ear pain (otalgia), often severe, accentuated by manipulation of the pinna or by pressure on the tragus and by jaw motion. The severity of the pain and tenderness (tragus or pinna, or both) may be disproportionate to the degree of inflammation, because the skin of the external ear canal is tightly adhered to the underlying perichondrium and periosteum. Itching often is a precursor of pain and usually is characteristic of chronic inflammation of the canal or resolving acute otitis externa. Conductive hearing loss (CHL) may result from edema of the skin and tympanic membrane (TM), serous or purulent secretions, or the canal skin thickening associated with chronic external otitis.

Edema of the ear canal, erythema, and thick, clumpy otorrhea are prominent signs of the acute disease. The cerumen usually is white and soft in consistency, as opposed to its usual yellow color and firmer consistency. The canal often is so tender and swollen that the entire ear canal and TM cannot be adequately visualized, and complete otoscopic examination may be delayed until the acute swelling subsides. If the TM can be visualized, it may appear either normal or opaque. TM mobility may be normal or, if the TM is thickened, mobility may be reduced in response to positive and negative pressure.

Other physical findings may include palpable and tender lymph nodes in the periauricular region, and erythema and swelling of the pinna and periauricular skin. Rarely, facial paralysis, other cranial nerve abnormalities, vertigo, and/or sensorineural hearing loss are present. If these occur, **necrotizing (malignant) otitis externa** is probable. This invasive infection of the temporal bone and skull base requires immediate culture, intravenous antibiotics, and imaging studies to evaluate the extent of the disease. Surgical intervention to obtain cultures or debride devitalized tissue may be necessary. *P. aeruginosa* (see Chapter 205.1) is the most common causative organism of necrotizing otitis externa. Fortunately, this disease is rare in children and is seen only in association with immunocompromise or severe malnourishment. In adults, it is associated with diabetes mellitus.

DIAGNOSIS

Diffuse external otitis may be confused with **furunculosis, otitis media (OM),** and **mastoiditis.** Furuncles occur in the lateral hair-bearing part of the ear canal; furunculosis usually causes a localized swelling of the canal limited to 1 quadrant, whereas external otitis is associated with concentric swelling and involves the entire ear canal. In OM, the TM may be perforated, severely retracted, or bulging and immobile; hearing usually is impaired. If the middle ear is draining through a perforated TM or tympanostomy tube, secondary external otitis may occur; if the TM is not visible owing to drainage or ear canal swelling, it may be difficult to distinguish acute OM with drainage from an acute external otitis. Pain on manipulation of the auricle and significant lymphadenitis are not common features of OM, and these findings assist in the differential diagnosis. In some patients with external otitis, the periauricular edema is so extensive that the auricle is pushed forward, creating a condition that may be confused with acute mastoiditis and a subperiosteal abscess. In mastoiditis, the postauricular fold is obliterated, whereas in external otitis, the fold is usually

better preserved. In acute mastoiditis, a history of OM and hearing loss is usual; tenderness is noted over the mastoid and not on movement of the auricle; and otoscopic examination may show sagging of the posterior canal wall.

Referred otalgia may come from disease in the paranasal sinuses, teeth, pharynx, parotid gland, neck and thyroid, and cranial nerves (trigeminal neuralgia) (herpes simplex virus, varicella-zoster virus).

TREATMENT

Topical otic preparations containing acetic acid with or without hydrocortisone, or neomycin (active against Gram-positive organisms and some Gram-negative organisms, notably *Proteus* spp.), polymyxin (active against Gram-negative bacilli, notably *Pseudomonas* spp.), and hydrocortisone are highly effective in treating most forms of acute external otitis. *Other preparations of eardrops (e.g., ofloxacin, ciprofloxacin with hydrocortisone or dexamethasone) are preferable and do not contain potentially ototoxic antibiotics.* If canal edema is marked, the patient may need referral to a specialist for cleaning and possible wick placement. An otic antibiotic and corticosteroid eardrop is often recommended. A wick can be inserted into the ear canal and topical antibiotics applied to the wick 3 times a day for 24-48 hr. The wick can be removed after 2-3 days, at which time the edema of the ear canal usually is markedly improved, and the ear canal and TM are better seen. Topical antibiotics are then continued by direct instillation. When the pain is severe, oral analgesics (e.g., ibuprofen, codeine) may be necessary for a few days. Careful evaluation for underlying conditions should be undertaken in patients with severe or recurrent otitis externa. Figure 639-1 outlines an approach to managing acute external otitis.

As the inflammatory process subsides, cleaning the canal with a suction or cotton-tipped applicator to remove the debris enhances the effectiveness of the topical medications. In subacute and chronic infections, periodic cleansing of the canal is essential. In severe, acute external otitis associated with fever and lymphadenitis, oral or parenteral antibiotics may be indicated; an ear canal culture should be done, and empirical antibiotic treatment can then be modified if necessary, based on susceptibility of the organism cultured. A fungal infection of the external auditory canal, or **otomycosis,** is characterized by fluffy white debris, sometimes with black spores seen; treatment includes cleaning and application of antifungal solutions such as clotrimazole or nystatin; other antifungal agents include m-cresyl acetate 25%, gentian violet 2%, and thimerosal 1 : 1,000.

PREVENTION

Preventing external otitis may be necessary for individuals susceptible to recurrences, especially children who swim. The most effective prophylaxis is instillation of dilute alcohol or acetic acid (2%) immediately after swimming or bathing. During an acute episode of otitis externa, patients should not swim and the ears should be protected from excessive water during bathing. A hair dryer may be used to clear moisture from the ear after swimming as a method of prevention.

OTHER DISEASES OF THE EXTERNAL EAR

Furunculosis

Furunculosis is caused by *S. aureus* and affects only the hair-containing outer third of the ear canal. Mild forms are treated with oral antibiotics active against *S. aureus.* If an abscess develops, incision and drainage may be necessary.

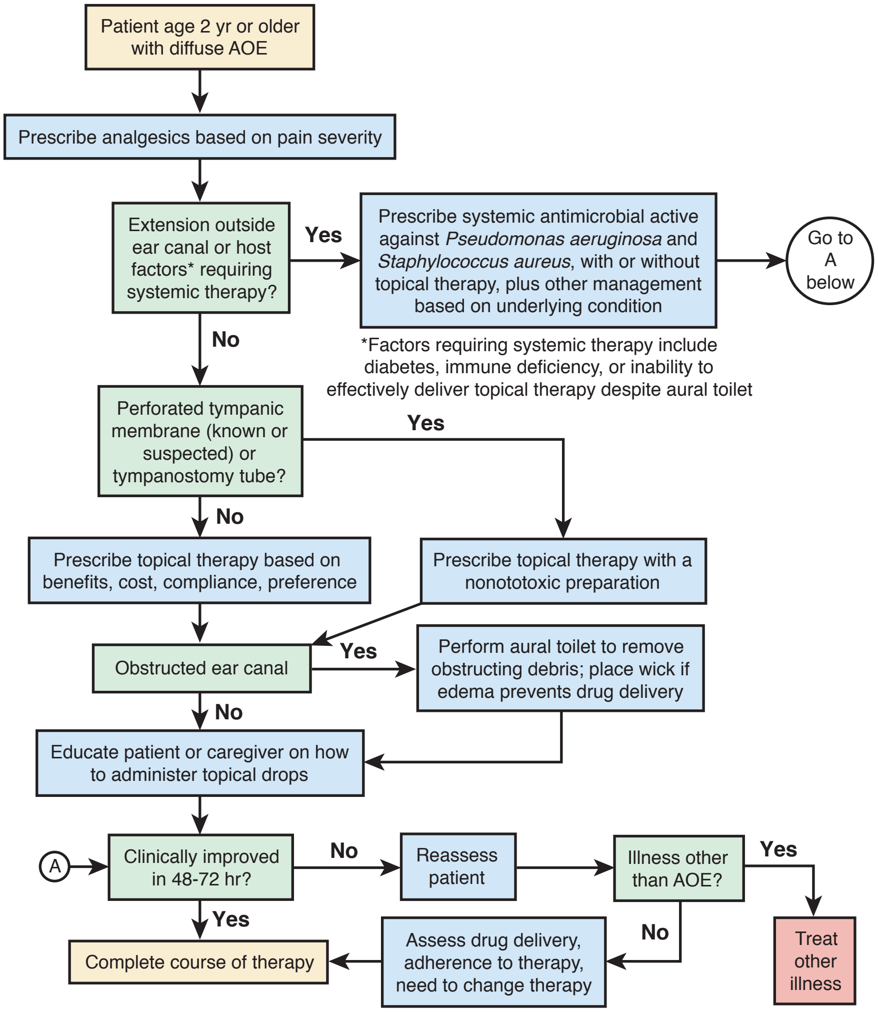

Figure 639-1 Flow chart for managing acute otitis externa (AOE). *(From Rosenfeld RM, Brown L, Cannon CR, et al: Clinical practice guideline: acute otitis externa,* Otolaryngol Head Neck Surg *134:S4–S23, 2006. Copyright 2006 American Academy of Otolaryngology-Head and Neck Surgery Foundation, Inc.)*

Acute Cellulitis

Acute cellulitis of the auricle and external auditory canal usually is caused by group A streptococcus and occasionally by *S. aureus.* The skin is red, hot, and indurated, without a sharply defined border. Fever may be present with little or no exudate in the canal. Parenteral administration of penicillin G or a penicillinase-resistant penicillin is the therapy of choice.

Perichondritis and Chondritis

Perichondritis is an infection involving the skin and perichondrium of the auricular cartilage; extension of infection to the cartilage is termed **chondritis.** The ear canal, especially the lateral aspect, also may be involved. Early perichondritis may be difficult to differentiate from cellulitis because both are characterized by skin that is red, edematous, and tender. The main cause of perichondritis/chondritis and cellulitis is trauma (accidental or iatrogenic, laceration or contusion), including ear piercing, especially when done through the cartilage. The most commonly isolated organism in perichondritis and chondritis is *P. aeruginosa,* although other Gram-negative and, occasionally, Gram-positive organisms may be found. Treatment involves systemic, often parenteral, antibiotics; surgery to drain an abscess or remove nonviable skin or cartilage may also be needed. Removal of all ear jewelry is mandatory in the presence of infection.

Dermatoses

Various dermatoses (seborrheic, contact, infectious eczematoid, or neurodermatoid) are common causes of inflammation of the external canal; scratching and the introduction of infecting organisms cause acute external otitis in these conditions.

Seborrheic dermatitis is characterized by greasy scales that flake and crumble as they are detached from the epidermis; associated changes in the scalp, forehead, cheeks, brow, postauricular areas, and concha are usual.

Contact dermatitis of the auricle or canal may be caused by earrings or by topical otic medications such as neomycin, which may produce erythema, vesiculation, edema, and weeping. Poison ivy, oak, and sumac also may produce contact dermatitis. Hair care products have been implicated in sensitive individuals.

Infectious eczematoid dermatitis is caused by a purulent infection of the external canal, middle ear, or mastoid; the purulent drainage infects the skin of the canal or auricle, or both. The lesion is weeping, erythematous, or crusted.

Atopic dermatitis occurs in children with a familial or personal history of allergy; the auricle, particularly the postauricular fold, becomes thickened, scaly, and excoriated.

Neurodermatitis is recognized by intense itching and erythematous, thickened epidermis localized to the concha and orifice of the meatus.

Treatment of these dermatoses depends on the type but should include application of an appropriate topical medication, elimination of the source of infection or contact when identified, and management of any underlying dermatologic problem. In addition to topical antibiotics (or antifungals), topical steroids are helpful if contact dermatitis, atopic dermatitis, or eczematoid dermatitis is suspected.

Herpes Simplex Virus

See Chapter 252.

Herpes simplex virus may appear as vesicles on the auricle and lips. The lesions eventually become encrusted and dry and may be confused with impetigo. Topical application of a 10% solution of carbamide peroxide in anhydrous glycerol is symptomatically helpful. The **Ramsay Hunt syndrome** (herpes zoster oticus with facial paralysis) may present with herpes vesicles in the ear canal and on the pinna and with facial paralysis and pain. Other cranial nerves may be affected as well, especially the 8th nerve. The current recommended treatment of herpes zoster oticus includes systemic antiviral agents, such as acyclovir, and corticosteroids. As many as 50% of patients with Ramsay Hunt syndrome do not completely recover their facial nerve function.

Bullous Myringitis

Commonly associated with an acute upper respiratory tract infection, bullous myringitis presents as an ear infection with more severe pain than usual. On examination, hemorrhagic or serous blisters (bullae) may be seen on the TM. The disease sometimes is difficult to differentiate from acute OM, because a large bulla may be confused with a bulging TM. The organisms involved are the same as those that cause acute OM, including both bacteria and viruses. Treatment consists of empiric antibiotic therapy and pain medications. In addition to ibuprofen or codeine for severe pain, a topical anesthetic eardrop may also provide some relief. Incision of the bullae, although not necessary, promptly relieves the pain.

Exostoses and Osteomas

Exostoses represent benign hyperplasia of the perichondrium and underlying bone. Those involving the auditory canal tend to be found in people who swim often in cold water. Exostoses are broad based, often multiple, and bilateral. Osteomas are benign bony growths in the ear canal of uncertain cause (see Chapter 501.2). They usually are solitary and attached by a narrow pedicle to the tympanosquamous or tympanomastoid suture line. Both are more common in males; exostoses are more common than osteomas. Surgical treatment is recommended when large masses cause cerumen impaction, ear canal obstruction, or hearing loss.

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Chapter 640

Otitis Media

Joseph E. Kerschner and Diego Preciado

The term **otitis media (OM)** has 2 main categories: acute infection, which is termed suppurative or **acute otitis media (AOM),** and inflammation accompanied by **middle-ear effusion (MEE),** termed nonsuppurative or **secretory OM,** or **otitis media with effusion (OME).** These 2 main types of OM are interrelated: acute infection usually is succeeded by residual inflammation and effusion that, in turn, predispose children to recurrent infection. MEE is a feature of both AOM and of OME and is an expression of the underlying middle-ear mucosal inflammation. MEE results in the conductive hearing loss (CHL) associated with OM, ranging from none to as much as 50 dB of hearing loss.

The peak incidence and prevalence of OM is during the 1st 2 yr of life. More than 80% of children will have experienced at least 1 episode of OM by the age of 3 yr. OM is a leading reason for physician visits and for use of antibiotics and figures importantly in the differential diagnosis of fever. OM often serves as the sole or the main basis for undertaking the most frequently performed operations in infants and young children: myringotomy with insertion of tympanostomy tubes and adenoidectomy. OM is also the most common cause of hearing loss in children. OM has a propensity to become chronic and recur. The earlier in life a child experiences the first episode, the greater the degree of subsequent difficulty the child is likely to experience in terms of frequency of recurrence, severity, and persistence of middle-ear effusion.

Accurate diagnosis of AOM in infants and young children may be difficult (Table 640-1). Symptoms may not be apparent, especially in early infancy and in chronic stages of the disease. Accurate visualization of the tympanic membrane and middle-ear space may be difficult because of anatomy, patient cooperation, or blockage by cerumen, removal of which may be arduous and time consuming. Abnormalities of the eardrum may be subtle and difficult to appreciate. In the face of these difficulties, both underdiagnosis and overdiagnosis occur.

Table 640-1 Treatments for Otalgia in Acute Otitis Media

TREATMENT MODALITY	COMMENTS
Acetaminophen, ibuprofen	Effective analgesia for mild to moderate pain. Readily available. Mainstay of pain management for AOM
Home remedies (no controlled studies that directly address effectiveness) Distraction External application of heat or cold Oil drops in external auditory canal	May have limited effectiveness
Benzocaine, procaine, lidocaine (topical)	Additional, but brief, benefit over acetaminophen in patients older than 5 yr
Naturopathic agents	Comparable to amethocaine/phenazone drops in patients older than 6 yr
Homeopathic agents	No controlled studies that directly address pain
Narcotic analgesia with codeine or analogs	Effective for moderate or severe pain. Requires prescription; risk of respiratory depression, altered mental status, gastrointestinal tract upset, and constipation
Tympanostomy/myringotomy	Requires skill and entails potential risk

From Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics *131:e964-e999, 2013, Table 3.*

EPIDEMIOLOGY

Several factors have been demonstrated to affect the occurrence of OM, including age, gender, race, genetic background, socioeconomic status, breast milk feeding, degree of exposure to tobacco smoke, degree of exposure to other children, presence or absence of respiratory allergy, season of the yr, and vaccination status. Children with certain types of congenital craniofacial anomalies are particularly prone to OM.

Age

The age of onset of OM is an important predictor of the development of recurrent and chronic OM, with earlier age of onset having an increased risk for exhibiting these difficulties later in life. The development of at least 1 episode of OM has been reported as 63-85% by 12 mo and 66-99% by 24 mo of age. The percentage of days with MEE has been reported as 5-27% during the 1st yr of life and 6-18% during the 2nd yr of life. Across groups, rates were highest at 6-20 mo of age. After the age of 2 yr, the incidence and prevalence of OM decline progressively, although the disease remains relatively common into the early school-age years. The most likely reasons for the higher rates in infants and younger children include less-well–developed immunologic defenses and less-favorable eustachian tubal factors involving both the structure and function of the tube.

Gender

Epidemiologic data suggest an incidence of OM greater in boys than in girls, although some studies have found no gender-related differences in the occurrence of OM.

Race

OM is especially prevalent and severe among Native American, Inuit, and indigenous Australian children. Studies comparing the occurrence of OM in white children and black children have given conflicting results.

Genetic Background

That middle-ear disease tends to run in families is a commonplace observation, suggesting that OM has a heritable component. The degree of concordance for the occurrence of OM is much greater among monozygotic than among dizygotic twins.

Socioeconomic Status

Poverty has long been considered an important contributing factor to both the development and the severity of OM. Elements contributing to this relationship include crowding, limited hygienic facilities, suboptimal nutritional status, limited access to medical care, and limited resources for complying with prescribed medical regimens.

Breast Milk Compared to Formula Feeding

Most studies have found a protective effect of breast milk feeding against OM. This protective effect may be greater in socioeconomically disadvantaged than in more advantaged children. The protective effect is attributable to the milk itself rather than to the mechanics of breastfeeding.

Exposure to Tobacco Smoke

Exposure to tobacco smoke is thought to be an important preventable risk factor in the development of OM. Studies that have used objective measures to determine infant exposure to second-hand tobacco smoke, such as cotinine levels, have more consistently identified a significant linkage between tobacco smoke and OM.

Exposure to Other Children

Many studies have established that a strong, positive relationship exists between the occurrence of OM and the extent of repeated exposure to other children—measured mainly by the number of other children involved—whether at home or in out-of-home group daycare. Together, but independently, family socioeconomic status and the extent of exposure to other children appear to constitute 2 of the most important identifiable risk factors for developing OM.

Season

In keeping with the pattern of occurrence of upper respiratory tract infections in general, highest rates of occurrence of OM are observed during cold weather months and lowest rates during warm weather months. In OM, it is likely that these findings strongly depend on the significant association of OM with viral respiratory illnesses.

Congenital Anomalies

OM is universal among infants with unrepaired palatal clefts, and is also highly prevalent among children with submucous cleft palate, other craniofacial anomalies, and Down syndrome (see Chapter 81.2). The common feature in these congenital anomalies is a deficiency in the functioning of the eustachian tubes, which predisposes these children to middle-ear disease.

Vaccination Status

See "Immunoprophylaxis" below.

Other Factors

Pacifier use is linked with an increased incidence of OM and recurrence of OM, although the effect is small. Neither maternal age nor birthweight nor season of birth appears to influence the occurrence of OM once other demographic factors are taken into account. Very limited data are available regarding the association of OM with bottle feeding in the recumbent position.

ETIOLOGY

Acute Otitis Media

Pathogenic bacteria can be isolated by standard culture techniques from middle-ear fluid in a majority of well-documented AOM cases. Three pathogens predominate in AOM: *Streptococcus pneumoniae* (see Chapter 182), nontypeable *Haemophilus influenzae* (see Chapter 194), and *Moraxella catarrhalis* (see Chapter 196). The overall incidence of these organisms has changed with the use of the conjugate pneumococcal vaccine. In countries where this vaccine is employed, nontypeable *H. influenzae* initially overtook *S. pneumoniae* as the most common pathogen, being found in 40-50% of cases. However, over time, *S. pneumoniae* serotypes not covered in the conjugate vaccine have emerged, with *S. pneumoniae* again overtaking nontypeable *H. influenzae* as the most common pathogen in many studies. *M. catarrhalis* represents the majority of the remaining cases. Other pathogens include group A streptococcus (see Chapter 183), *Staphylococcus aureus* (see Chapter 181), and Gram-negative organisms. *S. aureus* and Gram-negative organisms are found most commonly in neonates and very young infants who are hospitalized; in outpatient settings, the distribution of pathogens in these young infants is similar to that in older infants. Molecular techniques to identify nonculturable bacterial pathogens have suggested the importance of other bacterial species such as *Alloiococcus otitidis.*

Evidence of respiratory viruses also may be found in middle-ear exudates of children with AOM, either alone or, more commonly, in association with pathogenic bacteria. Of these viruses, rhinovirus and respiratory syncytial virus are found most often. AOM is a known complication of bronchiolitis; middle-ear aspirates in children with bronchiolitis regularly contain bacterial pathogens, suggesting that respiratory syncytial virus is rarely, if ever, the sole cause of their AOM. Using more precise measures of viable bacteria than standard culture techniques, such as polymerase chain reaction assays, a much higher rate of bacterial pathogens can be demonstrated. It remains uncertain whether viruses alone can cause AOM, or whether their role is limited to setting the stage for bacterial invasion, and perhaps also to amplifying the inflammatory process and interfering with resolution of the bacterial infection. Viral pathogens have a negative impact on eustachian tube function, can impair local immune function, and increase bacterial adherence, and can change the pharmacokinetic dynamics, reducing the efficacy of antimicrobial medications.

Otitis Media with Effusion

Using standard culture techniques, the pathogens typically found in AOM are recoverable in only 30% of children with OME. However, in studies of children with OME using polymerase chain reaction assays, middle-ear effusions have been found to contain evidence of bacterial DNA and viral RNA in much larger proportions of these children. These studies suggest that these patients do not have sterile effusions as previously thought. Biofilms of pathogenic bacteria have been demonstrated to be present on the middle-ear mucosa and adenoid pad in a majority of children with chronic OM. Biofilms consist of aggregated and adherent bacteria, embedded in an extracellular matrix, allowing for protection against antimicrobials, and their presence may contribute to the persistence of pathogens and the recalcitrance of chronic OM to antibiotic treatment (see Chapter 171).

PATHOGENESIS

A multifactorial disease process, risk profile, and host–pathogen interactions have become recognized as playing important roles in the pathogenesis of OM. Such events as alterations in mucociliary clearance through repeated viral exposure experienced in daycare settings or through exposure to tobacco smoke may tip the balance of pathogenesis in less-virulent OM pathogens in their favor, especially in children with a unique host predisposition.

Anatomic Factors

Patients with significant craniofacial abnormalities affecting the eustachian tube function have an increased incidence of OM. During the pathogenesis of OM the eustachian tube demonstrates decreased effectiveness in ventilating the middle-ear space.

Under usual circumstances the eustachian tube is passively closed and is opened by contraction of the tensor veli palatini muscle. In relation to the middle ear, the tube has 3 main functions: ventilation, protection, and clearance. The middle-ear mucosa depends on a continuing supply of air from the nasopharynx delivered by way of the eustachian tube. Interruption of this ventilatory process by tubal obstruction initiates an inflammatory response that includes secretory metaplasia, compromise of the mucociliary transport system, and effusion of liquid into the tympanic cavity. Measurements of eustachian tube function have demonstrated that the tubal function is suboptimal during the events of OM with increased opening pressures.

Eustachian tube obstruction may result from extraluminal blockage via hypertrophied nasopharyngeal adenoid tissue or tumor, or may result from intraluminal obstruction via inflammatory edema of the tubal mucosa, most commonly as a consequence of a viral upper respiratory tract infection. Progressive reduction in tubal wall compliance with increasing age may explain the progressive decline in the occurrence of OM as children grow older. The protection and clearance functions of the eustachian tube may also be involved in the pathogenesis of OM. Thus, if the eustachian tube is patulous or excessively compliant, it may fail to protect the middle ear from reflux of infective nasopharyngeal secretions, whereas impairment of the mucociliary clearance function of the tube might contribute to both the establishment and persistence of infection. The shorter and more horizontal orientation of the tube in infants and young children may increase the likelihood of reflux from the nasopharynx and impair passive gravitational drainage through the eustachian tube.

In special patient populations with craniofacial abnormalities there exists an increased incidence of OM that has been associated with the abnormal eustachian tube function. In children with cleft palate, where OM is a universal finding, a main factor underlying the chronic middle-ear inflammation appears to be impairment of the opening mechanism of the eustachian tube. Possible factors include muscular changes, tubal compliance factors, and defective velopharyngeal valving, which may result in disturbed aerodynamic and hydrodynamic relationships in the nasopharynx and proximal portions of the eustachian tubes. In children with other craniofacial anomalies and with Down syndrome, the high prevalence of OM has also been attributed to structural and/or functional eustachian tubal abnormalities.

Host Factors

The effectiveness of a child's immune system in response to the bacterial and viral insults of the upper airway and middle ear during early childhood probably is the most important factor in determining which children are otitis prone. The maturation of this immune system during early childhood is most likely the primary event leading to the decrease in incidence of OM as children move through childhood. Immunoglobulin (Ig) A deficiency is found in some children with recurrent AOM, but the significance is questionable, inasmuch as IgA deficiency is also found not infrequently in children without recurrent AOM. Selective IgG subclass deficiencies (despite normal total serum IgG) may be found in children with recurrent AOM in association with recurrent sinopulmonary infection, and these deficiencies probably underlie the susceptibility to infection. Children with HIV infection have recurrent and difficult to treat episodes of AOM in the 1st and 2nd yr of life. Children with recurrent OM that is not associated with recurrent infection at other sites rarely have a readily identifiable immunologic deficiency. Evidence that subtle immune deficits play a role in the pathogenesis of recurrent AOM is provided by studies involving antibody responses to various types of infection and

immunization; by the observation that breast milk feeding, as opposed to formula feeding, confers some protection against the occurrence of OM in infants with cleft palate; and by studies in which young children with recurrent AOM achieved a measure of protection from intramuscularly administered bacterial polysaccharide immune globulin or intravenously administered polyclonal immunoglobulin. This evidence, along with the documented decrease in incidence of upper respiratory tract infections and OM as children's immune systems develop and mature, is indicative of the importance of a child's innate immune system in the pathogenesis of OM (see Chapter 124).

Viral Pathogens

Although OM may develop and certainly may persist in the absence of apparent respiratory tract infection, many, if not most, episodes are initiated by viral or bacterial upper respiratory tract infection. In children in group daycare, AOM was observed in approximately 30-40% of children with respiratory illness caused by respiratory syncytial virus (see Chapter 260), influenzaviruses (see Chapter 258), or adenoviruses (see Chapter 262), and in approximately 10-15% of children with respiratory illness caused by parainfluenza viruses (see Chapter 259), rhinoviruses (see Chapter 263), or enteroviruses (see Chapter 250). Viral infection of the upper respiratory tract results in release of cytokines and inflammatory mediators, some of which may cause eustachian tube dysfunction.

Respiratory viruses also may enhance nasopharyngeal bacterial colonization and adherence and impair host immune defenses against bacterial infection.

Allergy

Evidence that respiratory allergy is a primary etiologic agent in OM is not convincing; however, in children with both conditions it is possible that the otitis is aggravated by the allergy.

CLINICAL MANIFESTATIONS

Symptoms of AOM are variable, especially in infants and young children. In young children, evidence of ear pain may be manifested by irritability or a change in sleeping or eating habits and occasionally, holding or tugging at the ear. *Pulling at the ear alone has a low sensitivity and specificity.* Fever may also be present and may occasionally be the only sign. Rupture of the tympanic membrane with purulent otorrhea is uncommon. Systemic symptoms and symptoms associated with upper respiratory tract infections also occur; occasionally there may be no symptoms, the disease having been discovered at a routine health examination. OME often is not accompanied by overt complaints of the child but can be accompanied by hearing loss. This hearing loss may manifest as changes in speech patterns but often goes undetected if unilateral or mild in nature, especially in younger children. Balance difficulties or disequilibrium can also be associated with OME and older children may complain of mild discomfort or a sense of fullness in the ear (see Chapter 636).

EXAMINATION OF THE TYMPANIC MEMBRANE

Otoscopy

Two types of otoscope heads are available: **surgical** or **operating**, and **diagnostic** or **pneumatic**. The surgical head embodies a lens that can swivel over a wide arc and an unenclosed light source, thus providing ready access of the examiner's instruments to the external auditory canal and tympanic membrane. Use of the surgical head is optimal for removing cerumen or debris from the canal under direct observation, and is necessary for satisfactorily performing tympanocentesis or myringotomy. The diagnostic head incorporates a larger lens, an enclosed light source, and a nipple for the attachment of a rubber bulb and tubing. When an attached speculum is fitted snugly into the external auditory canal, an airtight chamber is created comprising the vault of the otoscope head, the bulb and tubing, the speculum, and the proximal portion of the external canal. Although examination of the ear in young children is a relatively invasive procedure that is often met with lack of cooperation by the patient, this task can be enhanced if done with as little pain as possible. The outer portion of the ear canal contains hair-bearing skin and subcutaneous fat and cartilage that allow a speculum to be placed with relatively little discomfort. Closer to the tympanic membrane the ear canal is made of bone and is lined only with skin and no adnexal structures or subcutaneous fat; a speculum pushed too far forward and placed in this area often causes skin abrasion and pain. Using a rubber-tipped speculum or adding a small sleeve of rubber tubing to the tip of the plastic speculum may serve to minimize patient discomfort and enhance the ability to achieve a proper fit and an airtight seal, facilitating pneumatic otoscopy.

Learning to perform pneumatic otoscopy is a critical skill in being able to assess a child's ear and in making an accurate diagnosis of AOM. By observing as the bulb is alternately squeezed gently and released, the degree of tympanic membrane mobility in response to both positive and negative pressure can be estimated, providing a critical assessment of middle-ear fluid, which is a hallmark sign of both AOM and OME (Fig. 640-1). With both types of otoscope heads, bright illumination is also critical for adequate visualization of the tympanic membrane.

Clearing the External Auditory Canal

Many children's ears are "self-cleaning" because of squamous migration of ear canal skin. Parental cleaning of cerumen with cotton swabs often complicates cerumen impaction by pushing cerumen deeper into the canal compacting it. If the tympanic membrane is obscured by cerumen, the cerumen should be removed. This can be accomplished through

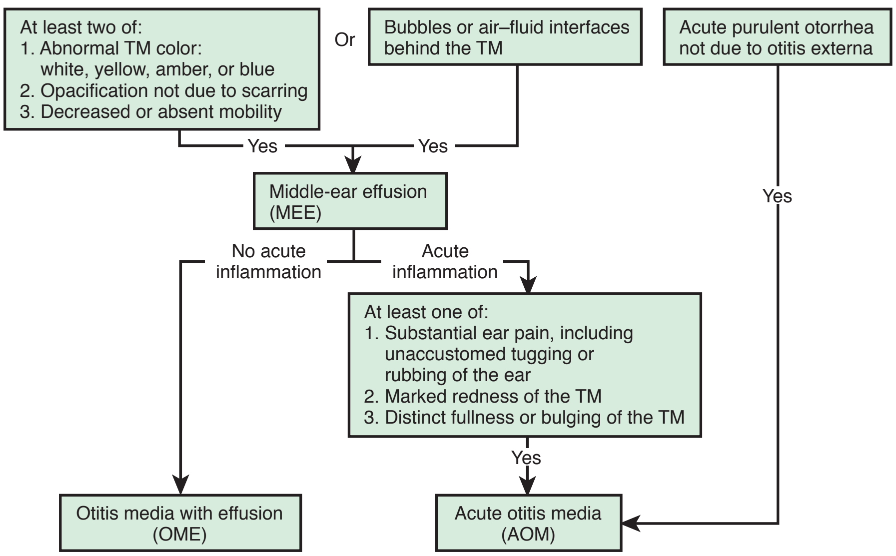

Figure 640-1 Algorithm for distinguishing between acute otitis media and otitis media with effusion. TM, tympanic membrane.

direct visualization using a headlight or through the surgical head of the otoscope by using an ear curette or gentle suction with a No. 5 or 7 French ear suction tube. During this procedure it may be most advantageous to restrain the infant or young child in the prone position, turning the child's head to the left or right as each ear is cleared. In children old enough to cooperate, usually beginning at about 5 yr of age, clearing of the external canal may be achieved more easily and less traumatically by lavage than by mechanical removal, provided one can be certain that a tympanic membrane perforation is not present.

Tympanic Membrane Findings

Important characteristics of the tympanic membrane (TM) consist of contour, color, translucence, structural changes if any, and mobility. The TM is anatomically divided into the pars tensa and pars flaccida. The pars tensa comprises the lower two thirds of the drum inferior to the lateral process of the malleus. Its contour is normally **slightly concave;** abnormalities consist of fullness or bulging or, conversely, extreme retraction. The normal color of the pars tensa is **pearly gray**, with the pars flaccida being slightly more vascular in nature. Erythema may be a sign of inflammation or infection, but unless intense, erythema alone may result from crying or vascular flushing. Abnormal whiteness of the membrane may result from either scarring or the presence of effusion in the middle-ear cavity; this effusion also may impart an amber, pale yellow, or, rarely, bluish color. Rarely a persistent focal white area may be indicative of a congenital cholesteatoma in the middle-ear space. Normally, the membrane is translucent, although some degree of opacity may be normal in the 1st few mo of life; later, opacification denotes either scarring or, more commonly, underlying effusion. Structural changes include scars, perforations, and retraction pockets. Retractions or perforations, especially in the posterior-superior quadrant, or pars flaccida, of the TM may be a sign of cholesteatoma formation. Of all the visible characteristics of the TM, mobility is the most sensitive and specific in determining the presence or absence of MEE. Mobility is generally not an all-or-none phenomenon. A total absence of mobility does exist with a TM perforation that can develop following a substantial increase in middle-ear pressure associated with effusion. When a perforation is not present, substantial impairment of mobility is the more common finding with MEE. Bulging of the TM is the most specific finding of AOM (97%) but has lower specificity (51%) (Fig. 640-2).

Diagnosis

The 2013 guidelines from the American Academy of Pediatrics for diagnosis of AOM are more restrictive than were the earlier (2004) guidelines. The 2004 guidelines employed a 3-part definition: (1) acute onset of symptoms; (2) presence of an MEE; and (3) signs of acute middle-ear inflammation. This definition was thought by the 2013 American Academy of Pediatrics to lack sufficient precision and thereby liable to include cases of OME and/or enable the diagnosis of AOM to be made without visualizing the TM.

A diagnosis of AOM according to the 2013 guideline should be made in children who present with:

- moderate to severe bulging of the TM or new-onset otorrhea not caused by otitis externa
- mild bulging of the TM and recent (<48 hr) onset of ear pain or intense TM erythema

A **diagnosis of AOM should *not*** be made in children without MEE.

AOM and OME may evolve into the other without any clearly differentiating physical findings; any schema for distinguishing between them is to some extent arbitrary. In an era of increasing bacterial resistance, distinguishing between AOM and OME is important in determining treatment, because OME in the absence of acute infection does not require antimicrobial therapy. Purulent otorrhea of recent onset is indicative of AOM; thus, difficulty in distinguishing clinically between AOM and OME is limited to circumstances in which purulent otorrhea is not present. Both AOM without otorrhea and OME are accompanied by physical signs of MEE, namely, the presence of at least 2 of 3 TM abnormalities: white, yellow, amber, or (rarely) blue discoloration; opacification other than that caused by scarring; and decreased or absent mobility. Alternatively in OME, either air–fluid levels or air

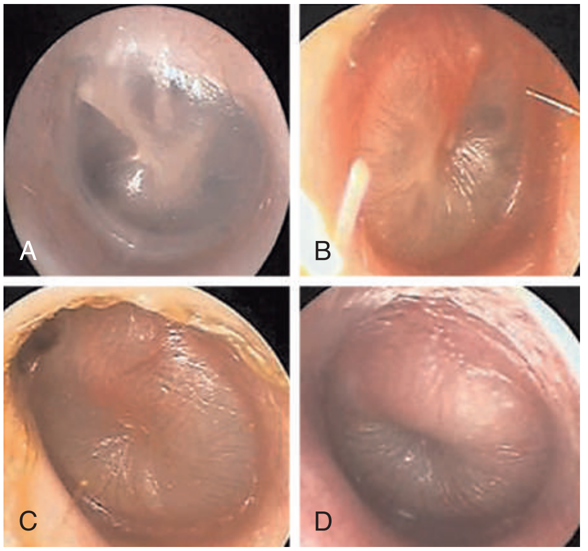

Figure 640-2 Examples of normal tympanic membrane **(A)** and of mild bulging **(B),** moderate bulging **(C),** and severe bulging **(D)** of the tympanic membrane from middle-ear effusion. *(Courtesy of Alejandro Hoberman, MD.)*

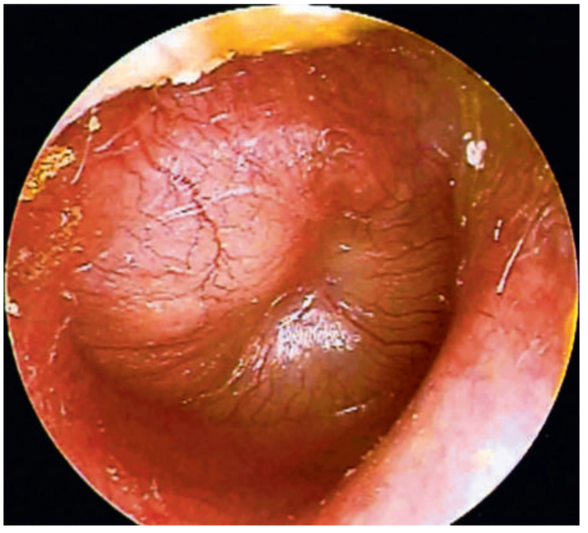

Figure 640-3 Tympanic membrane in acute otitis media.

bubbles outlined by small amounts of fluid may be visible behind the TM, a condition often indicative of impending resolution (Fig. 640-3).

To support a diagnosis of AOM instead of OME in a child with MEE, distinct fullness or bulging of the TM may be present, with or without accompanying erythema, or, at a minimum, MEE should be accompanied by ear pain that appears clinically important. Unless intense, erythema alone is insufficient because erythema, without other abnormalities, may result from crying or vascular flushing. In AOM, the malleus may be obscured and the TM may resemble a bagel without a hole but with a central depression (see Fig. 640-3). Rarely, the TM may be obscured by surface bullae or may have a cobblestone appearance. Bullous myringitis is a physical manifestation of AOM and not an etiologically discrete entity. Within days after onset, fullness of the membrane may diminish, even though infection may still be present.

In OME, bulging of the TM is absent or slight or the membrane may be retracted (Fig. 640-4); erythema also is absent or slight, but may increase with crying or with superficial trauma to the external auditory canal incurred in clearing the canal of cerumen.

Both before and after episodes of OM and also in the absence of OM, the TM may be retracted as a consequence of negative middle-ear air pressure. The presumed cause is diffusion of air from the middle-ear cavity more rapidly than it is replaced via the eustachian tube. Mild

retraction is generally self-limited, although in some children it is accompanied by mild conductive hearing loss. More extreme retraction is of concern, as discussed later in the section on sequelae of OM.

Conjunctivitis-Associated Otitis Media

Simultaneous appearance of purulent and erythematous conjunctivitis with an ipsilateral OM is a well-recognized presentation, caused by nontypeable *H. influenzae* in most children.

The disease often is present in multiple family members and affects young children and infants. Topical ocular antibiotics are ineffective. In an era of resistant organisms, this clinical association can be important in antibiotic selection, with oral antibiotics (see later) effective against resistant forms of nontypeable *H. influenzae.*

Asymptomatic Purulent Otitis Media

Rarely, a child will present during a routine exam without fever, irritability, or other overt signs of infection, but on exam, the patient will demonstrate an obvious purulent MEE and bulging TM. Although an uncommon presentation of "acute" OM, the bulging nature of the TM and the obvious purulence of the effusion do warrant antimicrobial therapy.

Tympanometry

Tympanometry, or **acoustic immittance testing,** is a simple, rapid, atraumatic test that, when performed correctly, offers objective evidence of the presence or absence of MEE. The tympanogram provides information about **TM compliance** in electroacoustic terms that can be thought of as roughly equivalent to TM mobility as perceived visually during pneumatic otoscopy. The absorption of sound by the TM varies inversely with its stiffness. The stiffness of the membrane is least, and accordingly its compliance is greatest, when the air pressures impinging on each of its surfaces—middle-ear air pressure and external canal air pressure—are equal. In simple terms, anything tending to stiffen the TM, such as TM scarring or middle-ear fluid, reduces the TM compliance, which is recorded as a flattening of the curve of the tympanogram. An ear filled with middle-ear fluid generally has a very noncompliant TM and, therefore, a flattened tympanogram tracing.

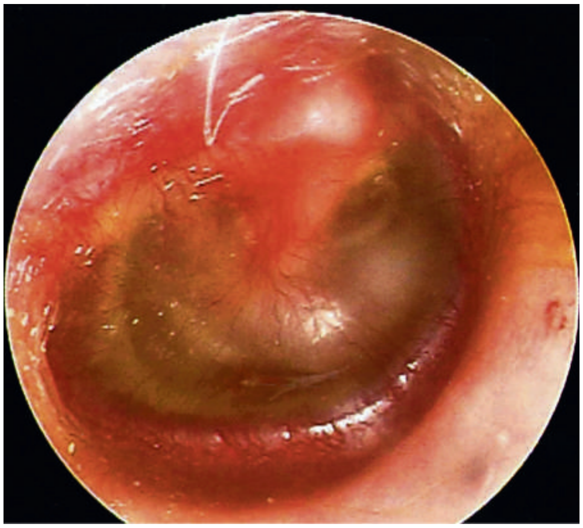

Figure 640-4 Tympanic membrane in otitis media with effusion.

Tympanograms may be grouped into 1 of 3 categories (Fig. 640-5). Tracings characterized by a relatively steep gradient, sharp-angled peak, and middle-ear air pressure (location of the peak in terms of air pressure) that approximates atmospheric pressure (Fig. 640-5*A*) (type A curve) are assumed to indicate normal middle-ear status. Tracings characterized by a shallow peak or no peak are often termed "flat" or type B (Fig. 640-5*B*), and usually are assumed to indicate the presence of a middle-ear abnormality that is causing decreased TM compliance. The most common such abnormality in infants and children is MEE. Tracings characterized by intermediate findings—somewhat shallow peak, often in association with a gradual gradient (obtuse-angled peak) or negative middle-ear air pressure peak (often termed type "C"), or combinations of these features (Fig. 640-5*C*)—may or may not be associated with MEE, and must be considered nondiagnostic or equivocal with respect to OM. However, type C tympanograms do suggest eustachian tube dysfunction and some ongoing pathology in the middle ear and warrant follow-up.

When reading a tympanogram it is important to look at the volume measurement. The type B tympanometric response has to be analyzed within the context of the recorded volume. A flat, "low"-volume (≤1 mL) tracing typically reflects the volume of the ear canal only, representing MEE, which impedes the movement of an intact ear drum. A flat, high-volume (>1 mL) tracing typically reflects the volume of the ear canal and middle-ear space, representing a perforation (or patent tympanostomy tube) in the TM. In a child with a tympanostomy tube present, a flat tympanogram with a volume <1 mL would suggest a plugged or nonfunctioning tube and middle-ear fluid, whereas a flat tympanogram with a volume >1 mL would suggest a patent tympanostomy tube.

Although tympanometry is quite sensitive in detecting MEE, it can be limited by patient cooperation, the skill of the individual administering the test, and the age of the child, with less-reliable results in very young children. Use of tympanometry may be helpful in office screening, may supplement the examination of difficult to examine patients, and may help identify patients who require further attention because their tympanograms are abnormal. Tympanometry also may be used to help confirm, refine, or clarify questionable otoscopic findings; to objectify the follow-up evaluation of patients with known middle-ear disease; and to validate otoscopic diagnoses of MEE. Even

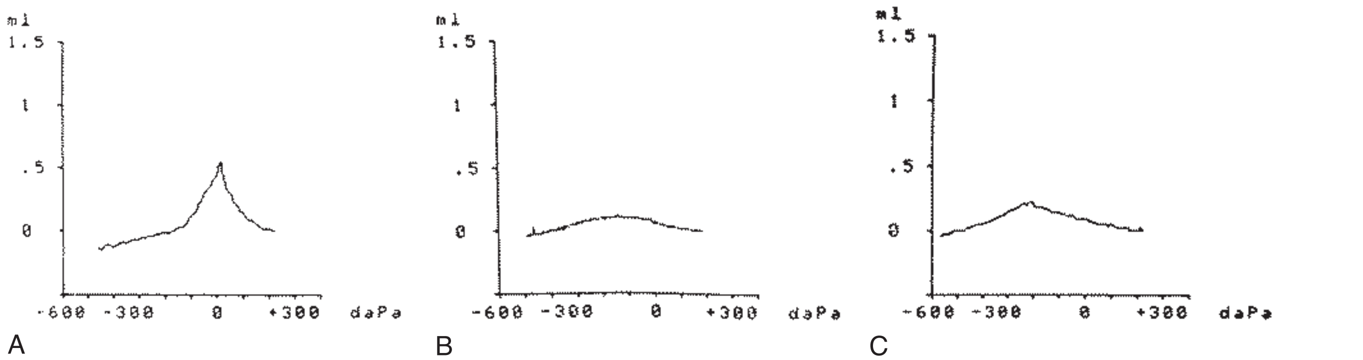

Figure 640-5 Tympanograms obtained with a Grason-Stadler GSI 33 Middle Ear Analyzer, exhibiting **(A)** high admittance, steep gradient (i.e., sharp-angled peak), and middle-ear air pressure approximating atmospheric pressure (0 decaPascals [daPa]); **(B)** low admittance and indeterminate middle-ear air pressure; and **(C)** somewhat low admittance, gradual gradient, and markedly negative middle-ear air pressure.

though tympanometry can predict the probability of MEE, it cannot distinguish the effusion of OME from that of AOM.

PREVENTION

General measures to prevent OM that have been supported by a number of investigations include avoiding exposure to individuals with respiratory infection; appropriate vaccination strategies against pneumococci and influenzae; avoiding environmental tobacco smoke; and breast milk feeding.

IMMUNOPROPHYLAXIS

Heptavalent pneumococcal conjugate vaccine (PCV7) reduced the overall number of episodes of AOM by only 6-8% but with a 57% reduction in serotype-specific episodes. Reductions of 9-23% are seen in children with histories of frequent episodes, and a 20% reduction is seen in the number of children undergoing tympanostomy tube insertion. A 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13) was licensed by the FDA in 2010. PCV13 contains the 7 serotypes included in PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and 6 additional serotypes (serotypes 1, 3, 5, 6A, 7F, and 19A). The effects of PCV13 on AOM incidence reduce pneumococcal nasopharyngeal carriage, including serotypes 19A, 7F, and 6C, in young children (younger than age 2 yr) with AOM. Given that 19A is a particularly invasive pneumococcal serotype, the effect of PCV13 on reducing complicated AOM will hopefully be of significance. Early data indicate a significant reduction in the number of invasive pneumococcal mastoiditis cases since the introduction of PCV13. With the widespread use of PCV13, continued surveillance will be necessary to detect other emerging serotypes, which are also demonstrating increasing resistance. Although the influenza vaccine also provides a measure of protection against OM, the relatively limited time during which individuals and even communities are exposed to influenzaviruses limits the vaccine's effectiveness in broadly reducing the incidence of OM. Limitation of OM disease is only a portion of the benefit realized from the vaccinations for pneumococci and influenza viruses. Support for these vaccination programs requires an understanding of the preventive benefit for OM in concert with the other benefits.

TREATMENT

Management of Acute Otitis Media

AOM can be very painful. Whether or not antibiotics are employed for treatment, pain should be assessed and if present, treated (see Table 640-1).

Individual episodes of AOM have traditionally been treated with antimicrobial drugs. Concern about increasing bacterial resistance has prompted some clinicians to recommend withholding antimicrobial treatment in some or most cases unless symptoms persist for 2 or 3 days, or worsen (Table 640-2). Three factors argue in favor of routinely prescribing antimicrobial therapy for children who have documented AOM using the diagnostic criteria outlined previously (see "Diagnosis" above). First, pathogenic bacteria cause a large majority of cases. Second, symptomatic improvement and resolution of infection occur more promptly and more consistently with antimicrobial treatment than without, even though most untreated cases eventually resolve. Third, prompt and adequate antimicrobial treatment may prevent the development of suppurative complications. The sharp decline in such complications during the last half-century seems likely attributable, at least in part, to the widespread routine use of antimicrobials for AOM. In the Netherlands, where initial antibiotic treatment is routinely withheld from most children older than 6 mo of age, and where only approximately 30% of children with AOM receive antibiotics at all, the incidence of acute mastoiditis, although low (in children younger than age 14 yr, 3.8 per 100,000 person-years), appears slightly higher than rates in other countries with higher antibiotic prescription rates by about 1-2 episodes per 100,000 person-years. Groups in other countries where initial conservative management of AOM is the standard in children older than 6 mo, such as Denmark, report acute mastoiditis rates similar to those of the Netherlands (4.8 per 100,000 person-years).

Given that most episodes of OM will spontaneously resolve, consensus guidelines have been published by the American Academy of Pediatrics to assist clinicians who wish to consider a period of "watchful waiting" or observation prior to treating AOM with antibiotics (see Tables 640-2 and 640-3; Fig. 640-6). The most important aspect of these guidelines is that close follow-up of the patient must be ensured to assess for lack of spontaneous resolution or worsening of symptoms and that patients should be provided with adequate analgesic medications (acetaminophen, ibuprofen) during the period of observation. When pursuing the practice of watchful waiting in patients with AOM, the certainty of the diagnosis, the patient's age, and the severity of the disease should be considered. For younger patients, <2 yr of age, it is recommended to treat all confirmed diagnoses of AOM. In very young patients, <6 mo of age, even presumed episodes of AOM should be treated because of the increased potential of significant morbidity from infectious complications. In children between 6 and 24 mo of age who have a questionable diagnosis of OM but severe disease, defined as temperature of >39°C (102°F), significant otalgia, or toxic appearance, antibiotic therapy is also recommended. Children in this age group with a questionable diagnosis and nonsevere disease can be observed for a period of 2-3 days with close follow-up. In children older than 2 yr of age, observation might be considered in all episodes of nonsevere OM or episodes of questionable diagnosis, while antibiotic therapy is reserved for confirmed, severe episodes of AOM. Information from Finland suggests that the "watchful waiting" or delayed treatment approach does not worsen the recovery from AOM, or increase the complication rates. However, watchful waiting may be associated with transient worsening of the child's condition and longer overall duration of symptoms.

Accurate diagnosis is the most crucial aspect of the treatment of OM. In studies utilizing stringent criteria for diagnosis of AOM the benefit of antimicrobial treatment is enhanced. Additionally, subpopulations of patients clearly receive more benefit from oral antimicrobial

Table 640-2 Recommendations for Initial Management for Uncomplicated Acute Otitis Media*

AGE	OTORRHEA WITH AOM*	UNILATERAL OR BILATERAL AOM* WITH SEVERE SYMPTOMS†	BILATERAL AOM* WITHOUT OTORRHEA	UNILATERAL AOM* WITHOUT OTORRHEA
6 mo to 2 yr	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation
≥2 yr	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation	Antibiotic therapy or additional observation‡

*Applies only to children with well-documented AOM with high certainty of diagnosis.

†A toxic-appearing child, persistent otalgia more than 48 hr, temperature ≥39°C (102.2°F) in the past 48 hr, or if there is uncertain access to follow-up after the visit.

‡This plan of initial management provides an opportunity for shared decision making with the child's family for those categories appropriate for additional observation. If observation is offered, a mechanism must be in place to ensure follow-up and begin antibiotics if the child worsens or fails to improve within 48-72 hr of AOM onset.

NOTE: For infants younger than age 6 mo, a suspicion of AOM should result in antibiotic therapy.

From Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics *131:e964–e999, 2013, Table 4.*

Table 640-3 Recommended Antibiotics for (Initial or Delayed) Treatment and for Patients Who Have Failed Initial Antibiotic Treatment

Initial Immediate or Delayed Antibiotic Treatment		Antibiotic Treatment After 48-72 hr of Failure of Initial Antibiotic Treatment	
RECOMMENDED FIRST-LINE TREATMENT	**ALTERNATIVE TREATMENT (IF PENICILLIN ALLERGY)**	**RECOMMENDED FIRST-LINE TREATMENT**	**ALTERNATIVE TREATMENT**
Amoxicillin (80-90 mg/kg/day in 2 divided doses)	Cefdinir[‡] (14 mg/kg/day in 1 or 2 doses)	Amoxicillin-clavulanate* (90 mg/kg/day of amoxicillin, with 6.4 mg/kg/day of clavulanate in 2 divided doses)	Ceftriaxone (50 mg IM or IV for 3 days, every other day until clinical improvement; max 3 doses) Clindamycin (30-40 mg/kg/day in 3 divided doses), with or without third-generation cephalosporin
or	Cefuroxime[‡] (30 mg/kg/day in 2 divided doses)	or	Failure of second antibiotic
Amoxicillin-clavulanate* (90 mg/kg/day of amoxicillin, with 6.4 mg/kg/day of clavulanate [amoxicillin : clavulanate ratio, 14 : 1] in 2 divided doses) or Ceftriaxone (50 mg IM or IV for 3 days, every other day until improvement; max 3 doses)	Cefpodoxime[‡] (10 mg/kg/day in 2 divided doses) Ceftriaxone[‡] (50 mg IM or IV per day for 1 or 3 days)	Ceftriaxone (50 mg IM or IV for 3 days, every other day until clinical improvement or for a maximum of 3 doses)	Clindamycin (30-40 mg/kg/day in 3 divided doses) with or without third-generation cephalosporin Tympanocentesis[†] Consult specialist[†]

IM, intramuscular; IV, intravenous.

*May be considered in patients who have received amoxicillin in the previous 30 days or who have the otitis–conjunctivitis syndrome.

[†]Perform tympanocentesis/drainage if skilled in the procedure, or seek a consultation from an otolaryngologist for tympanocentesis/drainage. If the tympanocentesis reveals multidrug-resistant bacteria, seek an infectious disease specialist consultation.

[‡]Cefdinir, cefuroxime, cefpodoxime, and ceftriaxone are highly unlikely to be associated with cross reactivity with penicillin allergy on the basis of their distinct chemical structures.

From Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics *131:e964–e999, 2013, Table 5.*

therapy than others. *Younger children, children with otorrhea, and children with bilateral AOM have a significantly enhanced benefit from antimicrobial therapy in comparison to older children, children without otorrhea, or children with unilateral AOM.*

Bacterial Resistance

Persons at greatest risk of harboring resistant bacteria are those who are younger than 2 yr of age, who are in regular contact with large groups of other children, especially in daycare settings, or who recently have received antimicrobial treatment. Bacterial resistance is a particular problem in relation to OM. The development of resistant bacterial strains and their rapid spread have been fostered and facilitated by selective pressure resulting from extensive use of antimicrobial drugs, the most common target of which, in children, is OM. Many strains of each of the pathogenic bacteria that commonly cause AOM are resistant to commonly used antimicrobial drugs.

Although antimicrobial resistance rates vary between countries, in the United States approximately 40% of strains of nontypeable *H. influenzae* and almost all strains of *M. catarrhalis* are resistant to aminopenicillins (e.g., ampicillin and amoxicillin). In most cases, the resistance is attributable to production of β-lactamase and can be overcome by combining amoxicillin with a β-lactamase inhibitor (clavulanate) or by using a β-lactamase–stable antibiotic. Occasional strains of nontypeable *H. influenzae* that do not produce β-lactamase are resistant to aminopenicillins and other β-lactam antibiotics by virtue of alterations in their penicillin-binding proteins. It is worth noting that bacterial resistance rates in northern European countries where antibiotic usage is less are comparatively exceedingly lower (β-lactamase resistance in 6-10% of isolates) than in the United States.

In the United States, approximately 50% of strains of *S. pneumoniae* are penicillin-nonsusceptible, divided approximately equally between penicillin-intermediate and, even more difficult to treat, penicillin-resistant strains. A much higher incidence of resistance is seen in children attending daycare. Resistance by *S. pneumoniae* to the penicillins and other β-lactam antibiotics is mediated not by β-lactamase production but by alterations in penicillin-binding proteins. This mechanism of resistance can be overcome if higher concentrations of β-lactam antibiotics at the site of infection can be achieved for a sufficient time interval. Many penicillin-resistant strains of *S. pneumoniae* are also resistant to other antimicrobial drugs, including sulfonamides, macrolides, and cephalosporins. In general, as penicillin resistance increases, so also does resistance to other antimicrobial classes. Resistance to macrolides, including azithromycin and clarithromycin, by *S. pneumoniae* has increased rapidly, rendering these antimicrobials far less effective in treating AOM. One mechanism of resistance to macrolides also results in resistance to clindamycin, which otherwise is generally effective against resistant strains of *S. pneumoniae*. Unlike resistance to β-lactam antibiotics, macrolide resistance cannot be overcome by increasing the dose.

First-Line Antimicrobial Treatment

Amoxicillin remains the drug of first choice for uncomplicated AOM under many circumstances because of its excellent record of safety, relative efficacy, palatability, and low cost. In particular, amoxicillin is the most efficacious of available oral antimicrobial drugs against both penicillin-susceptible and penicillin-nonsusceptible strains of *S. pneumoniae*. Increasing the dose from the traditional 40-45 mg/kg/24 hr to 80-90 mg/kg/24 hr will generally provide efficacy against penicillin-intermediate and some penicillin-resistant strains. This higher dose should be used particularly in children younger than 2 yr of age, in children who have recently received treatment with β-lactam drugs, and in children who are exposed to large numbers of other children because of their increased likelihood of an infection with a nonsusceptible strain of *S. pneumoniae*. A limitation of amoxicillin is that it may be inactivated by the β-lactamases produced by many strains of nontypeable *H. influenzae* and most strains of *M. catarrhalis*. Episodes of AOM caused by these pathogens often resolve spontaneously. Allergies to penicillin antibiotics should be categorized into type I hypersensitivity, consisting of urticaria or anaphylaxis, and those that fall short of type I reactions, such as rash formation. For children with a non–type I reaction in which cross reactivity with cephalosporins is less of a concern, first-line therapy with cefdinir would be an appropriate choice. In children with a type I reaction or known sensitivity to cephalosporin antibiotics there are far fewer choices. Resistance to

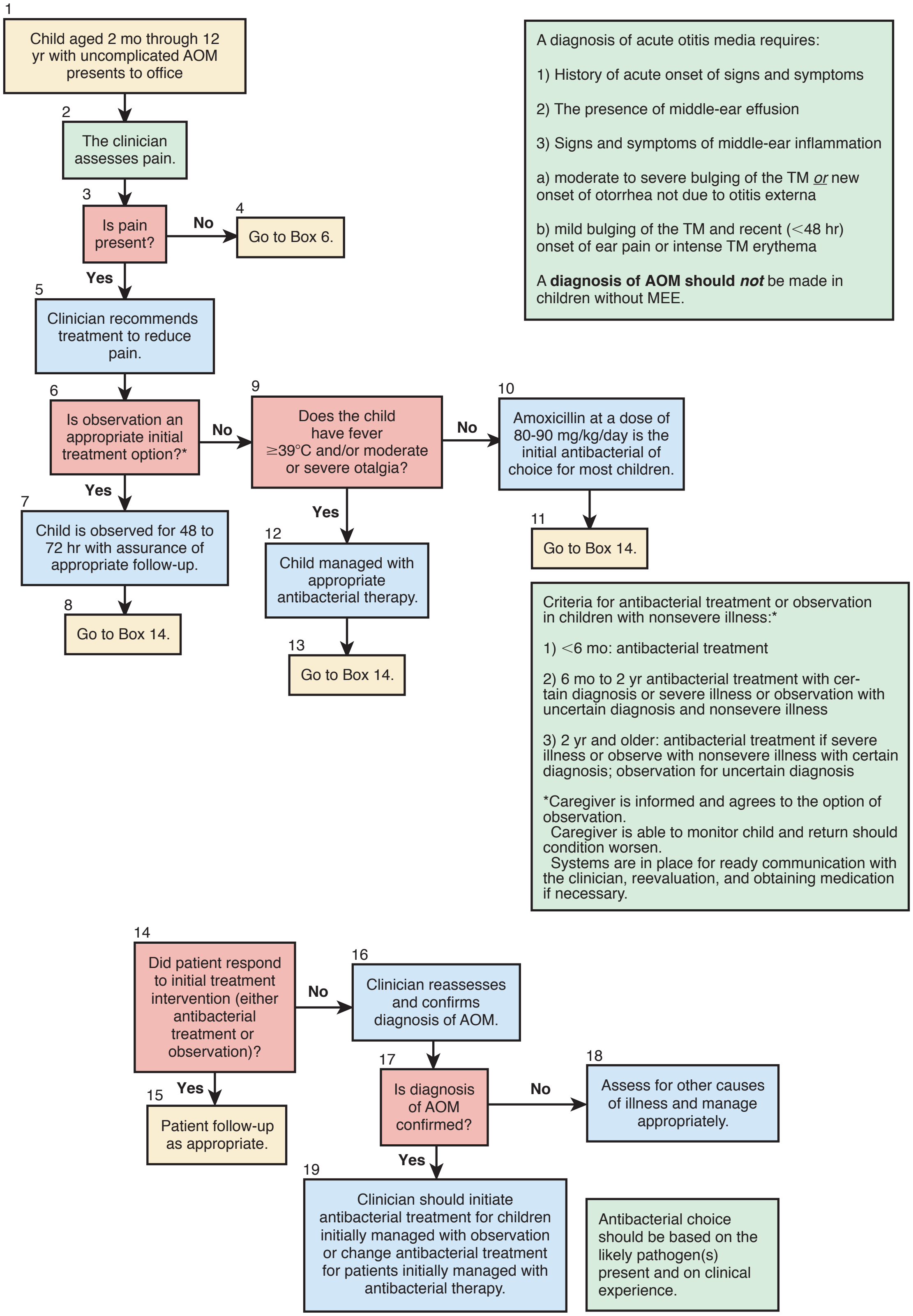

Figure 640-6 Management of acute otitis media. *(From Subcommittee on Management of Acute Otitis Media: Diagnosis and management of acute otitis media,* Pediatrics *113:1451–1465, 2004.)*

trimethoprim-sulfamethoxazole by many strains of both nontypeable *H. influenzae* and *S. pneumoniae* and a reported high clinical failure rate in children with AOM treated initially with this antimicrobial argue against its use. Similarly, increasing rates of macrolide resistance argue against the efficacy of azithromycin. Although not approved by the FDA for use in children, many clinicians have employed quinolones in this patient population. Early alternative management in these allergic patients with tympanostomy tubes can allow for lessening of the severity of their disease and the utilization of topical antimicrobials.

Duration of Treatment

The duration of treatment of AOM has historically been set at 10 days and most efficacy studies examining antimicrobial treatment in AOM have utilized this duration as a benchmark. Studies comparing shorter with longer durations of treatment suggest that short-course treatment will often prove inadequate in children younger than 6 yr of age and particularly in children younger than 2 yr of age. Thus, for most episodes in most children, treatment that provides tissue concentrations of an antimicrobial for at least 10 days is advisable. Treatment for longer than 10 days may be required for children who are very young or are having severe episodes or whose previous experience with OM has been problematic.

Follow-Up

The principal goals of follow-up are to assess the outcome of treatment and to differentiate between inadequate response to treatment and early recurrence. The appropriate interval for follow-up should be individualized. Follow-up within days is advisable in the young infant with a severe episode or in a child of any age with continuing pain. Follow-up within 2 wk is appropriate for the infant or young child who has been having frequent recurrences. At that point, the TM is not likely to have returned to normal, but substantial improvement in its appearance should be evident. In the child with only a sporadic episode of AOM and prompt symptomatic improvement, follow-up 1 mo after initial examination is early enough, or in older children, no follow-up may be necessary. The continuing presence of MEE alone following an episode of AOM is not an indication for additional or second-line antimicrobial treatment. However, persisting MEE does warrant additional follow-up to ensure that this resolves and does not lead to persisting hearing loss or other complications.

Unsatisfactory Response to First-Line Treatment

AOM is essentially a closed-space infection and its resolution depends both on eradication of the offending organism and restoration of middle-ear ventilation. Factors contributing to unsatisfactory response to first-line treatment, in addition to inadequate antimicrobial efficacy, include poor compliance with treatment regimens; concurrent or intercurrent viral infection; persistent eustachian tube dysfunction and middle-ear underaeration; reinfection from other sites or from incompletely eradicated middle-ear pathogens; and immature or impaired host defenses. The identification of biofilm formation in the middle ear of children with chronic OM also indicates that, in some children, eradication with standard antimicrobial therapy is likely to be unsuccessful. Despite these many potential factors, switching to an alternative or second-line drug is reasonable when there has been inadequate improvement in symptoms or in middle-ear status as reflected in the appearance of the TM, or when the persistence of purulent nasal discharge suggests that the antimicrobial drug being used has less-than-optimal efficacy. Second-line drugs may also appropriately be used when AOM develops in a child already receiving antimicrobial therapy, or in an immunocompromised child, or in a child with severe symptoms whose previous experience with OM has been problematic.

Second-Line Treatment

When treatment of AOM with a first-line antimicrobial drug has proven inadequate, a number of second-line alternatives are available (see Table 640-3). Drugs chosen for second-line treatment should be effective against β-lactamase–producing strains of nontypeable *H. influenzae* and *M. catarrhalis* and against susceptible and most nonsusceptible strains of *S. pneumoniae.* Only 4 antimicrobial agents meet these requirements: amoxicillin-clavulanate, cefdinir, cefuroxime axetil, and intramuscular ceftriaxone. Because high-dose amoxicillin (80-90 mg/kg/24 hr) is effective against most strains of *S. pneumoniae* and because the addition of clavulanate extends the effective antibacterial spectrum of amoxicillin to include β-lactamase–producing bacteria, high-dose amoxicillin-clavulanate is particularly well-suited as a second-line drug for treating AOM. The 14 : 1 amoxicillin-clavulanate formulation contains twice as much amoxicillin as the previously available 7 : 1 formulation. Diarrhea, especially in infants and young children, is a common adverse effect, but may be ameliorated in some cases by feeding active culture yogurt, and usually is not severe enough to require cessation of treatment. Cefdinir has demonstrated broad efficacy in treatment, is generally well tolerated with respect to taste, and can be given as a once-daily regimen. The ability to also utilize cefdinir in most children with mild type 1 hypersensitivity reactions has further added to its favorable selection as a second-line agent. Both cefuroxime axetil and intramuscular ceftriaxone have important limitations for use in young children. The currently available suspension of cefuroxime axetil is not palatable and its acceptance is low. Ceftriaxone treatment entails both the pain of intramuscular injection and substantial cost, and the injection may need to be repeated once or twice at 2 day intervals to achieve the desired degree of effectiveness. Nonetheless, use of ceftriaxone is appropriate in severe cases of AOM when oral treatment is not feasible, or in highly selected cases after treatment failure using orally administered second-line antimicrobials (i.e., amoxicillin-clavulanate or cefuroxime axetil), or when highly resistant *S. pneumoniae* is found in aspirates obtained from diagnostic tympanocentesis.

Clarithromycin and azithromycin have only limited activity against nonsusceptible strains of *S. pneumoniae* and against β-lactamase–producing strains of nontypeable *H. influenzae.* Macrolide use also appears to be a major factor in causing increases in rates of resistance to macrolides by group A streptococcus and *S. pneumoniae*. Clindamycin is active against most strains of *S. pneumoniae,* including resistant strains, but is not active against nontypeable *H. influenzae* or *M. catarrhalis.*

Other antimicrobial agents that have been traditionally utilized in the management of AOM have such significant lack of effectiveness against resistant organisms that employment seldom outweighs the potential side effects or complications possible from the medications. This includes cefprozil, cefaclor, loracarbef, cefixime, trimethoprim-sulfamethoxazole, and erythromycin-sulfisoxazole. Cefpodoxime has demonstrated reasonable effectiveness in some investigations but is generally poorly tolerated because of its taste.

ANTIMICROBIAL PROPHYLAXIS

In children who have developed frequent episodes of AOM, antimicrobial prophylaxis with subtherapeutic doses of an aminopenicillin or a sulfonamide has been utilized in the past to provide protection against recurrences of AOM (although not of OME). However, because of the increased incidence of resistant organisms and the contribution of antimicrobial usage to bacterial resistance, the risks of sustained antimicrobial prophylaxis clearly outweigh potential benefits.

Myringotomy and Tympanocentesis

Myringotomy is a long-standing treatment for AOM but is not commonly needed in children receiving antimicrobials. **Indications for myringotomy** in children with AOM include severe, refractory pain; hyperpyrexia; complications of AOM such as facial paralysis, mastoiditis, labyrinthitis, or central nervous system infection; and immunologic compromise from any source. Myringotomy should be considered as third-line therapy in patients that have failed 2 courses of antibiotics for an episode of AOM. In children with AOM in whom clinical response to vigorous, second-line treatment has been unsatisfactory, either diagnostic tympanocentesis or myringotomy is indicated to enable identification of the offending organism and its sensitivity profile. Either procedure may be helpful in effecting relief of pain. Tympanocentesis with culture of the middle-ear aspirate may also be indicated as part of the sepsis work-up in very young infants with AOM who show systemic signs of illness such as fever, vomiting, or lethargy, and whose illness accordingly cannot be presumed to be limited to infection of the middle ear. Performing tympanocentesis can be facilitated by use of a specially designed tympanocentesis aspirator. Studies reporting the usage of strict, individualized criteria for the diagnosis of AOM that include office tympanocentesis with bacterial culture followed by culture-guided antimicrobial therapy demonstrate significant reduction in the frequency of recurrent AOM episodes and

tympanostomy tube surgery. However, many primary care physicians do not feel comfortable performing this procedure, there is the potential for complications, and parents may view this procedure as traumatic. Often children requiring this intervention have a strong enough history of recurrent OM to warrant the consideration of tympanostomy tube placement, so that the procedure can be performed under general anesthesia.

Early Recurrence After Treatment

Recurrence of AOM after apparent resolution may be caused by either incomplete eradication of infection in the middle ear or upper respiratory tract reinfection by the same or a different bacteria or bacterial strain. Recent antibiotic therapy predisposes patients to an increased incidence of resistant organisms, which should also be considered in choosing therapy, and, generally, initiating therapy with a second-line agent is advisable (see Table 640-3).

Myringotomy and Insertion of Tympanostomy Tubes

When AOM is recurrent, despite appropriate medical therapy, consideration of surgical management of AOM with tympanostomy tube insertion is warranted. This procedure is effective in reducing the rate of AOM in patients with recurrent OM and in significantly improving the quality of life in patients with recurrent AOM. Individual patient factors, including the risk profile, severity of AOM episodes, child's development and age, presence of a history of adverse drug reactions, concurrent medical problems, and parental wishes, will affect the timing of a decision to consider referral for this procedure. When a patient experiences 3 episodes of AOM in a 6 mo period or 4 episodes in a 12 mo period with 1 episode in the preceding 6 mo, potential surgical management of the child's AOM should be discussed with the parents. Additionally, often patients with recurrent AOM may have persisting MEE between episodes with accompanying hearing loss, which may add to the indication for tympanostomy tube placement.

Tube Otorrhea

Although tympanostomy tubes often reduce the incidence of AOM in most children, patients with tympanostomy tubes may still develop AOM. One advantage of tympanostomy tubes in children with recurrent AOM is that if patients do develop an episode of AOM with a functioning tube in place, these patients will manifest purulent drainage from the tube. By definition, children with functioning tympanostomy tubes without otorrhea do not have bacterial AOM as a cause for a presentation of fever or behavioral changes and should not be treated with oral antibiotics. If tympanostomy tube otorrhea develops, ototopical treatment should be considered as first-line therapy. With a functioning tube in place, the infection is able to drain, there is usually negligible pain associated with the infection, and the possibility of developing a serious complication from an episode of AOM is extremely remote. The current quinolone otic drops approved by the U.S. Food and Drug Administration for use in the middle-ear space in children are formulated with ciprofloxacin/dexamethasone (Ciprodex) and ofloxacin (Floxin). The topical delivery of these otic drops allows them to utilize a higher antibiotic concentration than can be tolerated by administering oral antibiotics and they have excellent coverage of even the most resistant strains of common middle-ear pathogens as well as coverage of *S. aureus* and *Pseudomonas aeruginosa*. The high rate of success of these topical preparations, their broad coverage, the lower likelihood of their contributing to the development of resistant organisms, the relative ease of administration, the lack of significant side effects, and the lack of ototoxicity makes them the first choice for tube otorrhea. Oral antibiotic therapy should generally be reserved for cases of tube otorrhea that have other associated systemic symptoms, patients who have difficulty in tolerating the use of topical preparations, or, possibly, patients who have failed an attempt at topical otic drops. Despite these advantages of ototopical therapy, survey data have indicated that, compared to otolaryngologists, primary care practitioners are less likely to prescribe ototopicals as first-line therapy in tympanostomy tube otorrhea. As a result of the relative ease in obtaining fluid for culture and the possibility of the development of fungal otitis, which has shown an increase with the utilization of broad-spectrum quinolone ototopicals, patients that fail topical therapy should also have culture performed to rule out the development of fungal otitis. Other otic preparations are available; although these either have some risk of ototoxicity or have not received approval for use in the middle ear, many of these preparations were widely used prior to the development of the current quinolone drops and were generally considered reasonably safe and effective. In all cases of tube otorrhea, attention to aural toilet (e.g., cleansing the external auditory canal of secretions, and avoidance of external ear water contamination) is important. In some cases with very thick, tenacious discharge, topical therapy may be inhibited due to lack of delivery of the medication to the site of infection. Suctioning and removal of the secretions, often done through referral to an otolaryngologist, may be quite helpful. When children with tube otorrhea fail to improve satisfactorily with conventional outpatient management, they may require tube removal, or hospitalization to receive parenteral antibiotic treatment, or both.

MANAGEMENT OF OTITIS MEDIA WITH EFFUSION

Management of OME depends on an understanding of its natural history and its possible complications and sequelae. Most cases of OME resolve without treatment within 3 mo. To distinguish between persistence and recurrence, examination should be conducted monthly until resolution; hearing should be assessed if effusion has been present for longer than 3 mo. When MEE persists for longer than 3 mo, consideration of referral to an otolaryngologist may be appropriate. For young children, this referral is warranted for the assessment of hearing levels. In older children (generally older than age 4 yr), and depending upon the expertise in the primary care physician's office, hearing screening may be achieved by the primary care physician. For any child who fails a hearing screening in the primary care physician's office, referral to an otolaryngologist is warranted. In considering the decision to refer the patient for consultation, the clinician should attempt to determine the impact of the OME on the child. Although hearing loss may be of primary concern, OME causes a number of other difficulties in children that should also be considered. These include predisposition to recurring AOM, pain, disturbance of balance, and tinnitus. In addition, long-term sequelae that have been demonstrated to be associated with OME include pathologic middle-ear changes; atelectasis of the TM and retraction pocket formation; adhesive OM; cholesteatoma formation and ossicular discontinuity; and conductive and sensorineural hearing loss. Long-term adverse effects on speech, language, cognitive, and psychosocial development have also been demonstrated. This impact is related to the duration of effusion present, whether the effusion is unilateral or bilateral, the degree of underlying hearing loss, and other developmental and social factors affecting the child. In considering the impact of OME on development, it is especially important to take into consideration the overall presentation of the child. Although it is unlikely that OME causing unilateral hearing loss in the mild range will have long-term negative effects on an otherwise healthy and developmentally normal child, even a mild hearing loss in a child with other developmental or speech delays certainly has the potential to compound this child's difficulties (Table 640-4). At a minimum, children with OME persisting longer than 3 mo deserve close monitoring of their hearing levels with skilled audiologic evaluation; frequent assessment of developmental milestones, including speech and language assessment; and attention paid to their rate of recurrent AOM.

Variables Influencing Otitis Media with Effusion Management Decisions

Patient-related variables that affect decisions on how to manage OME include the child's age; the frequency and severity of previous episodes of AOM and the interval since the last episode; the child's current speech and language development; the presence of a history of adverse drug reactions, concurrent medical problems, or risk factors such as daycare attendance; and the parental wishes. In considering surgical management of OME with tympanostomy tubes, particular benefit is

Table 640-4	Sensory, Physical, Cognitive, or Behavioral Factors That Place Children Who Have Otitis Media with Effusion at an Increased Risk for Developmental Difficulties (Delay or Disorder)
Permanent hearing loss independent of otitis media with effusion	
Suspected or diagnosed speech and language delay or disorder	
Autism-spectrum disorder and other pervasive developmental disorders	
Syndromes (e.g., Down) or craniofacial disorders that include cognitive, speech, and language delays	
Blindness or uncorrectable visual impairment	
Cleft palate with or without associated syndrome	
Developmental delay	

From American Academy of Family Physicians; American Academy of Otolaryngology-Head and Neck Surgery; American Academy of Pediatrics Subcommittee on Otitis Media with Effusion: Otitis media with effusion, Pediatrics *113(5):1412–1429, 2004, Table 3, p. 1416.*

seen in patients with persisting OME punctuated by episodes of AOM, as the tubes generally provide resolution of both conditions. Disease-related variables that most otolaryngologists consider in the treatment of OME include whether the effusion is unilateral or bilateral; the apparent quantity of effusion; the duration, if known; the degree of hearing impairment; the presence or absence of other possibly related symptoms, such as tinnitus, vertigo, or disturbance of balance; and the presence or absence of mucopurulent or purulent rhinorrhea, which, if sustained for longer than 2 wk, would suggest that concurrent nasopharyngeal or paranasal sinus infection is contributing to continuing compromise of middle-ear ventilation.

Medical Treatment

In some studies, antimicrobials have demonstrated some efficacy in resolving OME, presumably because they help eradicate nasopharyngeal infection or unapparent middle-ear infection, or both. The most significant effects of antibiotics for OME have been shown with treatment durations of 4 wk and 3 mo. However, in the current era of bacterial antimicrobial resistance, the small potential benefit of antimicrobial therapy is outweighed by the negative potential of treatment and is not recommended. Instead, treatment should be limited to cases in which there is evidence of associated bacterial upper respiratory tract infection or untreated middle-ear infection. For this purpose, the most broadly effective drug available should be used as recommended for AOM.

The efficacy of corticosteroids in the treatment of OME is probably short term. The risk: benefit ratio for steroids would argue against their use. Antihistamine-decongestant combinations are not effective in treating children with OME. Antihistamines alone, decongestants alone, and mucolytic agents are unlikely to be effective. The risk profile for decongestants and antihistamines in children suggests that they are not indicated in the treatment of OME. Allergic management, including antihistamine therapy, might prove helpful in children with problematic OME who also have evidence of environmental allergies, although supporting data specifically analyzing this patient population are not conclusive. Recent randomized controlled trials do not support the usage of topical intranasal steroid sprays to treat the manifestations of eustachian tube dysfunction. Inflation of the eustachian tube by the Valsalva maneuver or other means has not demonstrated long-term efficacy but is unlikely to lead to significant harm. Other "alternative" therapies, including spinal manipulation, currently have no demonstrated efficacy or role in children with OME.

Myringotomy and Insertion of Tympanostomy Tubes

When OME persists despite an ample period of watchful waiting, generally 3-6 mo or perhaps longer in children with unilateral effusion, consideration of surgical intervention with tympanostomy tubes is appropriate. Myringotomy alone, without tympanostomy tube insertion, permits evacuation of middle-ear effusion and may sometimes be effective, but often the incision heals before the middle-ear mucosa returns to normal and the effusion soon reaccumulates. Inserting a tympanostomy tube offers the likelihood that middle-ear ventilation will be sustained for at least as long as the tube remains in place and functional. Tympanostomy tubes have a variable duration of efficacy based on design. Tubes that are designed for a shorter duration, 6-12 mo, have a lesser impact on disease-free middle-ear spaces in children. Some studies comparing the efficacy of tympanostomy tube types, including shorter-acting tubes, with watchful waiting provide a less helpful assessment of the differences between these approaches. Tubes that are somewhat longer acting, effective for 12-18 mo, are generally more appropriate for most children undergoing tube placement. Regardless of type, tympanostomy tube placement nearly uniformly reverses the conductive hearing loss associated with OME. Occasional episodes of obstruction of the tube lumen and premature tube extrusion may limit the effectiveness of tympanostomy tubes, and tubes can also be associated with otorrhea. However, placement of tympanostomy tubes is generally quite effective in providing resolution of OME in children. Tympanostomy tubes generally extrude on their own but rarely require surgical removal after several years in place. Sequelae following tube extrusion include residual perforation of the eardrum, tympanosclerosis, localized or diffuse atrophic scarring of the eardrum that may predispose to the development of atelectasis or a retraction pocket, or both, residual conductive hearing loss, and cholesteatoma. The more serious of these sequelae are quite infrequent. Recurrence of middle-ear effusion following the extrusion of tubes does develop, especially in younger children; most children without underlying craniofacial abnormalities only require 1 set of tympanostomy tubes, with developmental changes providing improved middle-ear health and resolution of chronic OME by the time of tube extrusion. Because even previously persistent OME often clears spontaneously during the summer mo, watchful waiting through the summer season is also advisable in most children with OME who are otherwise well. In considering surgical management of OME in children, primarily in those with bilateral disease and hearing loss, it has been demonstrated that placement of tympanostomy tubes results in a significant improvement in their quality of life.

Adenoidectomy

Adenoidectomy is efficacious to some extent in reducing the risk of subsequent recurrences of both AOM and OME in children who have undergone tube insertion and in whom, after extrusion of tubes, OM continues to be a problem. Efficacy appears to be independent of adenoid size and probably derives from removal of the focus of infection in the nasopharynx as a site of biofilm formation, chronic inflammation impacting eustachian tube function, and recurrent seeding of the middle ear via the eustachian tube. In younger children with recurrent AOM who have not previously undergone tube insertion, adenoidectomy is usually not recommended along with tube insertion, unless significant nasal airway obstruction or recurrent rhinosinusitis is associated, in which case, performing adenoidectomy might be considered.

Complications of Acute Otitis Media

Most complications of AOM consist of the spread of infection to adjoining or nearby structures or the development of chronicity, or both. Suppurative complications are relatively uncommon in children in developed countries but occur not infrequently in disadvantaged children whose medical care is limited. The complications of AOM may be classified as either intratemporal or intracranial.

Intratemporal Complications

Direct but limited extension of AOM leads to complications within the local region of the ear and temporal bone. These complications include dermatitis, TM perforation, chronic suppurative OM (CSOM), mastoiditis, hearing loss, facial nerve paralysis, cholesteatoma formation, and labyrinthitis.

Infectious Dermatitis

This is an infection of the skin of the external auditory canal resulting from contamination by purulent discharge from the middle ear. The skin is often erythematous, edematous, and tender. Management consists of proper hygiene combined with systemic antimicrobials and ototopical drops as appropriate for treating AOM and tube otorrhea.

Tympanic Membrane Perforation

Rupture of the TM can occur with episodes of either AOM or OME. Although damage to the TM from these episodes generally heals spontaneously, chronic perforations can develop in a small number of cases and require further surgical intervention in the future.

Chronic Suppurative Otitis Media

CSOM consists of persistent middle-ear infection with discharge through a TM perforation. The disease is initiated by an episode of AOM with rupture of the membrane. The mastoid air cells are invariably involved. The most common etiologic organisms are *P. aeruginosa* and *S. aureus;* however, the typical AOM bacterial pathogens may also be the cause, especially in younger children or in the winter months. Treatment is guided by the results of microbiologic investigation. If an associated cholesteatoma is not present, parenteral antimicrobial treatment combined with assiduous aural cleansing is likely to be successful in clearing the infection, but in refractory cases, tympanomastoidectomy can be required.

Acute Mastoiditis

Technically, all cases of AOM are accompanied by mastoiditis by virtue of the associated contiguous inflammation of the mastoid air cells. However, early in the course of the disease, no signs or symptoms of mastoid infection are present, and the inflammatory process usually is readily reversible, along with the AOM, in response to antimicrobial treatment. Spread of the infection to the overlying periosteum, but without involvement of bone, constitutes **acute mastoiditis with periosteitis.** In such cases, signs of mastoiditis are usually present, including redness and swelling in the postauricular area, often with protrusion and displacement of the pinna inferiorly and anteriorly (Fig. 640-7 and Table 640-5). Treatment with myringotomy and parenteral antibiotics, if instituted promptly, usually provides satisfactory resolution.

In acute mastoid osteitis, or **coalescent mastoiditis,** infection has progressed further to cause destruction of the bony trabeculae of the mastoid. Frank signs and symptoms of mastoiditis are usually, but not always, present. In acute **petrositis,** infection has extended further to involve the petrous portion of the temporal bone. Eye pain, a result of irritation of the ophthalmic branch of cranial nerve V, is a prominent symptom. Cranial nerve VI palsy is a later finding, suggesting further extension of the infectious process along the cranial base. **Gradenigo syndrome** is the triad of suppurative OM, paralysis of the external rectus muscle, and pain in the ipsilateral orbit. Rarely, mastoid infection spreads external to the temporal bone into the neck musculature that attaches to the mastoid tip, resulting in an abscess in the neck, termed a **Bezold abscess.**

When mastoiditis is suspected or diagnosed clinically, CT scanning of the temporal bones can be considered to further clarify the nature and extent of the disease. Bony destruction of the mastoid must be differentiated from the simple clouding of mastoid air cells that is found often in uncomplicated cases of OM. The most common causative organisms in all variants of acute mastoiditis are *S. pneumoniae,* group A streptococcus, and nontypeable *H. influenzae. P. aeruginosa* is also a causative agent, primarily in patients with CSOM. Children with acute mastoid osteitis generally require intravenous antimicrobial treatment and mastoidectomy, with the extent of the surgery dependent on the extent of the disease process. Early cases of mastoid osteitis may respond to myringotomy and parenteral antibiotics. Insofar as possible, choice of the antimicrobial regimen should be guided by the findings of microbiologic examination from cultures.

Each of the variants of mastoiditis may also occur in subacute or chronic form. Symptoms are correspondingly less prominent. Chronic mastoiditis is always accompanied by CSOM, and occasionally will respond to the conservative regimen recommended for that condition. In most cases, mastoidectomy also is required.

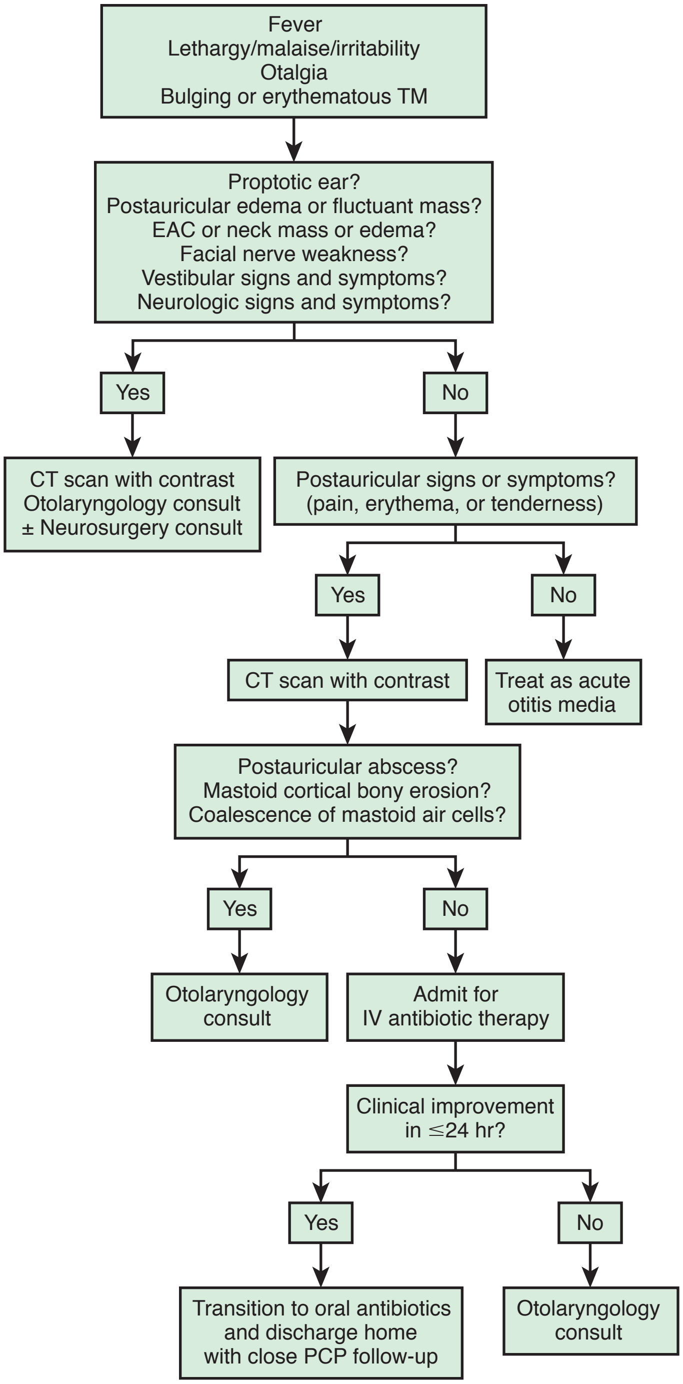

Figure 640-7 Diagnosis and treatment algorithm for cases of suspected acute mastoiditis. *(From Lin HW, Shargorodsky J, Gopen Q. Clinical strategies for the management of acute mastoiditis in the pediatric population.* Clin Pediatr (Phila) *49(2):110–115, 2010, Fig. 5.)*

Facial Paralysis

The facial nerve, as it traverses the middle ear and mastoid bone, may be affected by adjacent infection. Facial paralysis occurring as a complication of AOM is uncommon, and often resolves after myringotomy and parenteral antibiotic treatment. Facial paralysis in the presence of AOM requires urgent attention as prolonged infection can result in the development of permanent facial paralysis, which can have a devastating effect on a child. Facial paralysis in an infant or child requires complete and unequivocal examination of the TM and middle-ear

Table 640-5 Differential Diagnosis of Postauricular Involvement of Acute Mastoiditis with Periosteitis/Abscess

DISEASE	Postauricular Signs and Symptoms: CREASE*	ERYTHEMA	MASS	TENDERNESS	EXTERNAL CANAL INFECTION	MIDDLE-EAR EFFUSION
Acute mastoiditis with periosteitis	May be absent	Yes	No	Usually	No	Usually
Acute mastoiditis with subperiosteal abscess	Absent	Maybe	Yes	Yes	No	Usually
Periosteitis of pinna with postauricular extension	Intact	Yes	No	Usually	No	No
External otitis with postauricular extension	Intact	Yes	No	Usually	Yes	No
Postauricular lymphadenitis	Intact	No	Yes (circumscribed)	Maybe	No	No

*Postauricular crease (fold) between pinna and postauricular area.
From Bluestone CD, Klein JO, editors: Otitis media in infants and children, *ed 3, Philadelphia, 2001, WB Saunders, p. 333.*

Figure 640-8 A retraction pocket cholesteatoma of the posterosuperior quadrant. The incus long process is eroded, which leaves the drum adherent to the stapes head *(S)*. An effusion is present in the middle ear, and squamous debris emanates from the attic. *(From Isaacson G: Diagnosis of pediatric cholesteatoma,* Pediatrics *120:603–608, 2007, Fig. 9, p. 607.)*

space. Any difficulty in examination requires urgent consultation with an otolaryngologist. Any examination that demonstrates an ear abnormality also requires urgent referral to an otolaryngologist. If facial paralysis develops in a child with mastoid osteitis or with chronic suppurative OM, mastoidectomy should be undertaken urgently.

Cholesteatoma

Cholesteatoma is a cyst-like growth originating in the middle ear, lined by keratinized, stratified squamous epithelium and containing desquamated epithelium and/or keratin (see Chapter 638; Fig. 640-8).

Acquired cholesteatoma develops most often as a complication of long-standing chronic OM. The condition also may develop from a deep retraction pocket of the TM or as a consequence of epithelial implantation in the middle-ear cavity from traumatic perforation of the TM or insertion of a tympanostomy tube. Cholesteatomas tend to expand progressively, causing bony resorption, often extend into the mastoid cavity, and may extend intracranially with potentially life-threatening consequences. Acquired cholesteatoma commonly presents as a chronically draining ear in a patient with a history of previous ear disease. Cholesteatoma should be suspected if otoscopy demonstrates an area of TM retraction or perforation with white, caseous debris persistently overlying this area. Along with otorrhea from this area, granulation tissue or polyp formation identified in conjunction with this history and presentation should prompt suspicion of cholesteatoma. The most common location for cholesteatoma development is in the superior portion of the TM *(pars flaccida)*. Most patients also present with conductive hearing loss on audiologic evaluation. When cholesteatoma is suspected, otolaryngology consultation should be sought immediately. Delay in recognition and treatment can have significant long-term consequences, including the need for more extensive surgical treatment, permanent hearing loss, facial nerve injury, labyrinthine damage with loss of balance function, and intracranial extension. The required treatment for cholesteatoma is tympanomastoid surgery.

Congenital cholesteatoma is an uncommon condition generally identified in younger patients (Fig. 640-9). The etiology of congenital cholesteatoma is thought to be a result of epithelial implantation in the middle-ear space during otologic development in utero. Congenital cholesteatoma most commonly presents in the anterior-superior quadrant of the TM but can be found elsewhere. Congenital cholesteatoma appears as a discrete, white opacity in the middle-ear space on otoscopy. Unlike patients with acquired cholesteatoma, there is generally not a strong history of OM or chronic ear disease, history of otorrhea, or changes in the TM anatomy such as perforation or retraction. Similar to acquired cholesteatoma many patients do have some degree of abnormal findings on audiologic evaluation, unless identified very early. Congenital cholesteatoma also requires surgical resection.

Labyrinthitis

This occurs uncommonly as a result of the spread of infection from the middle ear and/or mastoid to the inner ear (see Chapter 641). Cholesteatoma or CSOM is the usual source. Symptoms and signs include vertigo, tinnitus, nausea, vomiting, hearing loss, nystagmus, and clumsiness. Treatment is directed at the underlying condition and must be undertaken promptly to preserve inner-ear function and prevent the spread of infection.

INTRACRANIAL COMPLICATIONS

Meningitis, epidural abscess, subdural abscess, focal encephalitis, brain abscess (see Chapters 603 and 604), sigmoid sinus thrombosis (also called *lateral sinus thrombosis*), and otitic hydrocephalus each may develop as a complication of acute or chronic middle-ear or mastoid infection, through direct extension, hematogenous spread, or thrombophlebitis. Bony destruction adjacent to the dura is often involved, and a cholesteatoma may be present. In a child with middle-ear or mastoid infection, the presence of any systemic symptom, such as high

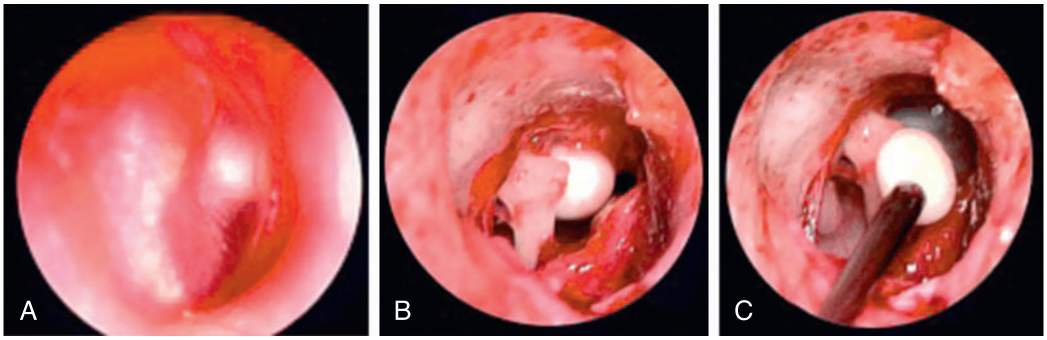

Figure 640-9 **A,** Congenital cholesteatoma of the anterosuperior quadrant. **B,** The eardrum is reflected downward to reveal a white spherical lesion. **C,** Removal of the lesion. *(From Isaacson G: Diagnosis of pediatric cholesteatoma,* Pediatrics *120:603–608, 2007, Fig. 3, p. 605.)*

spiking fevers, headache, or lethargy of extreme degree, or a finding of meningismus or of any central nervous system sign on physical examination should prompt suspicion of an intracranial complication.

When an intracranial complication is suspected, lumbar puncture should be performed only after imaging studies establish that there is no evidence of mass effect or hydrocephalus. In addition to examination of the cerebrospinal fluid, culture of middle-ear exudate obtained via tympanocentesis may identify the causative organism, thereby helping guide the choice of antimicrobial medications. Myringotomy should be performed to permit middle-ear drainage. Concurrent tympanostomy tube placement is preferable to allow for continued decompression of the "infection under pressure" that is the causative event leading to intracranial spread of the infection.

Treatment of intracranial complications of OM requires urgent, otolaryngologic, and, often, neurosurgical consultation, intravenous antibiotic therapy, drainage of any abscess formation, and tympanomastoidectomy in patients with coalescent mastoiditis.

Sigmoid sinus thrombosis may be complicated by dissemination of infected thrombi with resultant development of septic infarcts in various organs. With prompt recognition and wide availability of MRI, which facilitates diagnosis, this complication is exceedingly rare. Mastoidectomy may be required even in the absence of osteitis or coalescent mastoiditis, especially in the case of propagation or embolization of infected thrombi. In the absence of coalescent mastoiditis, sinus thrombosis can often be treated with tympanostomy tube placement and intravenous antibiotics. Anticoagulation therapy may also be considered in the treatment of sigmoid sinus thrombosis; however, otolaryngology consultation should be obtained before initiating this therapy to coordinate the possible need for surgical intervention prior to anticoagulation.

Otitic hydrocephalus, a form of **pseudotumor cerebri** (see Chapter 605), is an uncommon condition that consists of increased intracranial pressure without dilation of the cerebral ventricles, occurring in association with acute or chronic OM or mastoiditis. The condition is commonly also associated with lateral sinus thrombosis, and the pathophysiology is thought to involve obstruction by thrombus of intracranial venous drainage into the neck, producing a rise in cerebral venous pressure and a consequent increase in cerebrospinal fluid pressure. Symptoms are those of increased intracranial pressure. Signs may include, in addition to evidence of OM, paralysis of 1 or both lateral rectus muscles and papilledema with or without visual acuity loss. MRI can confirm the diagnosis. Treatment measures include the use of antimicrobials and medications such as acetazolamide or furosemide to reduce intracranial pressure, mastoidectomy, repeated lumbar puncture, lumboperitoneal shunt, and ventriculoperitoneal shunt. If left untreated, otitic hydrocephalus may result in loss of vision secondary to optic atrophy.

PHYSICAL SEQUELAE

The physical sequelae of OM consist of structural middle-ear abnormalities resulting from long-standing middle-ear inflammation. In most instances, these sequelae are consequences of severe and/or chronic infection, but some may also result from the noninfective inflammation of long-standing OME. The various sequelae may occur singly, or interrelatedly in various combinations.

Tympanosclerosis consists of whitish plaques in the TM and nodular deposits in the submucosal layers of the middle ear. The changes involve hyalinization with deposition of calcium and phosphate crystals. Uncommonly, there may be associated conductive hearing loss. In developed countries, probably the most common cause of tympanosclerosis is tympanostomy tube insertion.

Atelectasis of the TM is a descriptive term applied to either severe retraction of the TM caused by high negative middle-ear pressure or loss of stiffness and medial prolapse of the membrane as a consequence of long-standing retraction or severe or chronic inflammation. A **retraction pocket** is a localized area of atelectasis. Atelectasis is often transient and usually unaccompanied by symptoms, but a deep retraction pocket may lead to erosion of the ossicles and adhesive otitis, and may serve as the nidus of a cholesteatoma. For a deep retraction pocket, and for the unusual instance in which atelectasis is accompanied by symptoms such as otalgia, tinnitus, or conductive hearing loss, the required treatment is tympanostomy tube insertion and, at times, tympanoplasty. Patients with persisting atelectasis and retraction pockets should have referral to an otolaryngologist.

Adhesive OM consists of proliferation of fibrous tissue in the middle-ear mucosa, which may, in turn, result in severe TM retraction, conductive hearing loss, impaired movement of the ossicles, ossicular discontinuity, and cholesteatoma. The hearing loss may be amenable to surgical correction.

Cholesterol granuloma is an uncommon condition in which the TM may appear to be dark blue secondary to middle-ear fluid of this color. Cholesterol granulomas are rare, benign cysts that occur in the temporal bone. They are expanding masses that contain fluids, lipids, and cholesterol crystals surrounded by a fibrous lining and generally require surgical removal. Tympanostomy tube placement will not provide satisfactory relief. This lesion requires differentiation from bluish middle-ear fluid, which can also rarely develop in patients with the more common OME.

Chronic perforation may rarely develop after spontaneous rupture of the TM during an episode of AOM or from acute trauma, but more commonly results as a sequelae of CSOM or as a result of failure of closure of the TM following extrusion of a tympanostomy tube. Chronic perforations are generally accompanied by conductive hearing loss. Surgical repair of a TM perforation is recommended to restore hearing, prevent infection from water contamination in the middle-ear space, and prevent cholesteatoma formation. Chronic perforations are almost always amenable to surgical repair, usually after the child has been free of OM for an extended period.

Permanent **conductive hearing loss** (see Chapter 637) may result from any of the conditions just described. Rarely, permanent sensorineural hearing loss may occur in association with acute or chronic OM, secondary to spread of infection or products of inflammation through the round window membrane, or as a consequence of suppurative labyrinthitis.

POSSIBLE DEVELOPMENTAL SEQUELAE

Permanent hearing loss in children has a significant negative impact on development, particularly in speech and language. The degree to which OM impacts long-term development in children is difficult to assess and there have been conflicting studies examining this question. Developmental impact is most likely to be significant in children that have greater levels of hearing loss, hearing loss that is sustained for longer periods of time, or hearing loss that is bilateral and in those children that have other developmental difficulties or risk factors for developmental delay (see Table 640-4).

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Chapter 641

The Inner Ear and Diseases of the Bony Labyrinth

Joseph Haddad Jr. and Sarah Keesecker

Genetic factors can impact the anatomy and function of the inner ear. Infectious agents, including viruses, bacteria, and protozoa, also can cause abnormal function, most commonly as sequelae of congenital infection or bacterial meningitis. Other acquired diseases of the labyrinthine capsule include otosclerosis, osteopetrosis, Langerhans cell histiocytosis, fibrous dysplasia, and other types of bony dysplasia. All of these can cause both conductive hearing loss (CHL) and sensorineural hearing loss (SNHL) as well as vestibular dysfunction. Use of currently available vaccines reduces the risk for bacterial meningitis and the associated sensorineural hearing loss.

VIRUSES

The most common cause of childhood sensorineural hearing loss (SNHL) is congenital cytomegalovirus (CMV) infection (see Chapter 255). Although the pathogenesis of hearing loss has not been elucidated, there is histologic evidence of infection in the cells of both the cochlear and vestibular endolabyrinth. The strongest predictor of delayed hearing loss appears to be the presence of symptoms at birth; prolonged viral shedding may also be a risk factor. In one large study, children who passed initial audiologic examinations but who had CMV-related symptoms at birth were approximately 6 times more likely to develop hearing loss than those who were asymptomatic. Stabilization (or even reversal) of the hearing loss may be possible by using ganciclovir in very young infants with congenital CMV infection. Administering ganciclovir for 6 wk improved hearing outcomes in neonates with symptomatic congenital CMV infections involving the central nervous system.

Other viral causes of SNHL include congenital rubella as well as acquired mumps (see Chapter 248), rubella (see Chapter 247), rubeola (measles; see Chapter 246), and fifth disease, caused by parvovirus B19 (see Chapter 251). Many other viruses also occasionally are associated with SNHL. In as many as 50% of cases, hearing loss, which usually is bilateral and often is asymmetric, progresses and worsens over weeks to years.

Before an effective vaccine was introduced, rubella was responsible for as many as 60% of cases of childhood SNHL. Vaccination in developed countries has reduced the rate of rubella by >97%. Similarly, measles and mumps are now uncommon causes of SNHL in the United States because of successful vaccination programs.

Herpes simplex encephalitis can also be associated with SNHL, which is more common in children with congenital herpesvirus infection. Acyclovir and other antiviral agents can help the hearing loss and other central nervous system manifestations (see Chapter 245).

TOXOPLASMOSIS

See Chapter 290.

Toxoplasma gondii is a protozoan that can cause congenital SNHL. In an estimated 1-10 per 10,000 live births in the United States, 1 per 3,000 live births in France, and 1 per 770 live births in southeast Brazil, infants are born each year with congenital toxoplasmosis; approximately 25% of untreated patients have SNHL. If maternal infection is documented during the fetal period, medical therapy may be able to prevent some of the clinical manifestations, including SNHL of the offspring.

BACTERIAL MENINGITIS

Since the *Haemophilus influenzae* type b vaccine was introduced, *Streptococcus pneumoniae* (see Chapter 182) and *Neisseria meningitidis* (see Chapter 191) have become the leading causes of bacterial meningitis in children in the United States. Hearing loss occurs more commonly with *S. pneumoniae,* with an estimated incidence of 15-20%. Approximately 60% of the associated hearing loss is bilateral, although it often is asymmetric. If hearing loss is present at the time of presentation with meningitis, and especially if it is severe to profound, the likelihood of significant improvement is low. However, if the hearing loss develops after admission for treatment and is not severe, stabilization or improvement is possible. Late progression of SNHL also has been noted in some children years after meningitis. In the United States and many other developed countries, bacterial meningitis is one of the major causes of profound deafness leading to cochlear implantation in children. Gadolinium-enhanced MRI could be utilized to detect meningitic labyrinthitis and therefore to predict which patients are at high risk for postmeningitic hearing loss. Gadolinium-enhanced MRI was found to be 87% sensitive and 100% specific for predicting which ears would develop permanent SNHL. The introduction of pneumococcal conjugate vaccine is expected to lead to a reduction in SNHL caused by pneumococcal meningitis, although pneumococcal strains not sensitive to the vaccine appear to be associated with rates of deafness equivalent to those that are sensitive.

Studies have shown favorable trends in the course and outcome after administration of dexamethasone for hearing loss and other neurologic deficits associated with bacterial meningitis (see Chapter 603.1), although its effectiveness, especially for *S. pneumoniae* and *N. meningitidis* meningitis, generally has not reached statistical significance because of the small number of cases in the trials. A metaanalysis of 2,029 patients from randomized, double-blinded, placebo-controlled trials of dexamethasone for bacterial meningitis found that adjunctive dexamethasone does not seem to significantly reduce death or neurologic disability but does reduce hearing loss among survivors. Dexamethasone has been shown to reduce severe hearing loss associated with *H. influenzae* type b meningitis regardless of the timing of administration of dexamethasone (before or with antibiotics vs later) or of the antibiotic used. For pneumococcal meningitis, dexamethasone might confer benefit only when given early and only for protection against severe hearing loss.

SYPHILIS

See Chapter 218.

Congenital syphilis, caused by *Treponema pallidum,* causes SNHL in 3-38% of affected children. The exact incidence is difficult to ascertain, because the hearing loss might not develop until adolescence or even adulthood. When the condition is identified, treatment with antibiotics and corticosteroids can improve the hearing loss.

OTHER DISEASES OF THE INNER EAR

Labyrinthitis (also called **vestibular neuritis**) may be a complication of direct spread of infection from acute or chronic otitis media or mastoiditis and also can complicate bacterial meningitis as a result of organisms entering the labyrinth through the internal auditory meatus, endolymphatic duct, perilymphatic duct, vascular channels, or

hematogenous spread. Clinical manifestations of vestibular neuritis can include a sudden onset of rotatory vertigo, dysequilibrium, postural imbalance (furniture walking) with falls to the affected side, deep-seated ear pain, nausea, vomiting, and spontaneous horizontal (occasionally rotary) nystagmus.

The dizziness may last a few days, but balance issues, particularly following rapid head movements toward the affected ear, may last for mo. Vestibular neuritis is usually unilateral and is not associated with other neurologic defects; subjective hearing loss is unusual in vestibular neuritis. If hearing loss is present, idiopathic SNHL should be considered, as well as classical labyrinthitis (vestibular and cochlear nerves). Treatment of vestibular neuritis may include prednisone and vestibular rehabilitative exercises. Recurrent episodes should suggest another diagnosis such as vestibular migraine or benign paroxysmal positional vertigo.

In children, viral labyrinthitis is often associated with hearing loss. Acute suppurative labyrinthitis, characterized by abrupt, severe onset of these symptoms, requires intensive antimicrobial therapy. Vestibular suppressants (dimenhydrinate 1-2 mg/kg) can also be used in the acute stage but should not be given for more than 3 days. If it is secondary to otitis media, otologic surgery may be required to remove underlying cholesteatoma or drain the middle ear and mastoid, in addition to antibiotics. Acute serous labyrinthitis, with milder symptoms of vertigo and hearing loss, can develop secondary to middle-ear infection as well. It usually responds well to antibiotics and corticosteroids, with improvement in both vertigo and hearing. Chronic labyrinthitis, most commonly associated with cholesteatoma, manifests with SNHL and vestibular dysfunction that develops over time; surgery is required to remove the cholesteatoma. Chronic labyrinthitis also occurs uncommonly secondary to long-standing otitis media, with the slow development of SNHL, usually starting in the higher frequencies, and possibly with vestibular dysfunction. Additionally, and more commonly, children with chronic middle-ear fluid often are unsteady or off balance, a situation that improves immediately when the fluid resolves.

Vertigo and dizziness are common among older children and adolescents. Benign **paroxysmal vertigo** is common and is characterized by short periods of vertigo or dizziness lasting seconds to a few min and is associated with imbalance and nystagmus; tinnitus or hearing loss is unusual. **Basilar/vestibular migraine** is a common cause of episodic vertigo or dizziness and is associated with headache (50-70% of patients), rotary or to and fro nystagmus, and sensitivity to noise and bright light (see Chapter 595.1). **Benign paroxysmal positional vertigo** is less common in young children and more common with increasing age into adulthood. Particles form in the semicircular canals (canalolithiasis), most often the posterior canal; symptoms occur with position changes of the head and may last sec to min. Vertigo and nystagmus may be demonstrated by changing position (sitting to lying down on the right or left). Treatment involves canalith repositioning maneuvers to shift the debris from the canals into the utricle.

Otosclerosis, an autosomal dominant disease that affects only the temporal bones, causes abnormal bone growth that can result in fixation of the stapes in the oval window, leading to progressive hearing loss. In one series in North America, otosclerosis was found in 0.6% of temporal bones of children younger than 5 yr of age and 4% of those ages 5-18 yr. The hearing loss is usually conductive at first, but SNHL can develop. White girls and women are affected most commonly, with onset of otosclerosis in teenagers or young adults, often associated with pregnancy. Corrective surgery to replace the stapes with a mobile prosthesis often is successful.

Osteogenesis imperfecta is a systemic disease that can involve both the middle and inner ears (see Chapter 701). Hearing loss occurs in approximately 20% of young children and as many as 90% of adults with this disease. The hearing loss most commonly is conductive because of abnormalities of the ossicles, but SNHL can occur if other areas of the otic capsule become affected. Hearing loss may be the result of clinical or cochlear otosclerosis, fracture or atrophy of the ossicles, and/or cochlear degeneration due to an unidentified mechanism. An association between bone mineral density and hearing loss in osteogenesis imperfecta has been demonstrated, suggesting that patients with lower bone mineral density are more susceptible to microfractures, which may lead to the conductive hearing loss component. If the hearing loss is severe enough, a hearing aid may be a preferable alternative to surgical correction of the fixed stapes, because stapedectomy in children with osteogenesis imperfecta can be technically very difficult, and the disease and the hearing loss may be progressive.

Osteopetrosis, a very uncommon skeletal dysplasia, can involve the temporal bone, including the middle ear and ossicles, resulting in a moderate to severe, usually conductive hearing loss. Recurrent facial nerve paralysis also can occur as a result of excess bone deposition; with each recurrence, less facial function might return (see Chapter 699).

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Chapter 642

Traumatic Injuries of the Ear and Temporal Bone

Joseph Haddad Jr. and Sarah Keesecker

AURICLE AND EXTERNAL AUDITORY CANAL

Auricle trauma is common in certain sports. Hematoma, with accumulation of blood between the perichondrium and the cartilage, can follow trauma to the pinna and is especially common in teenagers related to wrestling or boxing. Prompt drainage of a hematoma can prevent irreversible damage. Immediate needle aspiration or, when the hematoma is extensive or recurrent, incision and drainage and a pressure dressing are necessary to prevent perichondritis, which can result in cartilage loss and a "cauliflower ear deformity." Sports helmets should be worn when appropriate during activities when head trauma is possible.

Frostbite of the auricle should be managed by rapidly rewarming the exposed pinna with warm irrigation or warm compresses.

Foreign bodies in the external canal are common in childhood. Often these can be removed in the office setting without general anesthesia if the child is mature enough to understand and cooperate and is properly restrained; if an adequate headlight, surgical head otoscope, or otomicroscope is used for visualizing the object; and if appropriate instruments such as alligator forceps, wire loops or a blunt cerumen curette, or suction are used, depending on the shape of the object. Gentle irrigation of the ear canal with body temperature water or saline may be used to remove very small objects, but only if the tympanic membrane (TM) is intact. Attempts to remove an object from a struggling child or with poor visualization and inadequate tools result in a terrified child with a swollen and bleeding ear canal and can then mandate general anesthesia to remove the object. Difficult foreign bodies, especially those that are large, deeply embedded, or associated with canal swelling, are best removed by an otolaryngologist and/or under general anesthesia. Disk batteries are removed emergently because they leach a basic fluid that can cause severe tissue destruction. Insects in the canal are first killed with mineral oil or lidocaine and are then removed under otomicroscopic examination.

After a foreign body is removed from the external canal, the TM should be inspected carefully for possible traumatic perforation or for a preexisting middle-ear effusion. If a foreign body has resulted in acute inflammation of the canal, ear drop treatment as described for acute external otitis should be instituted (see Chapter 639).

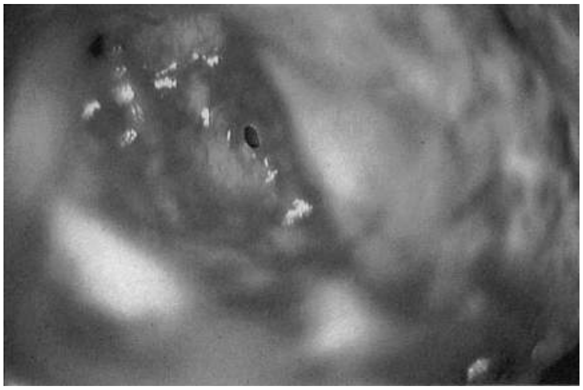

Figure 642-1 Intraoperative view of traumatic oval window perilymphatic fistula. *(From Kim SH, Kazahaya K, Handler SD. Traumatic perilymphatic fistulas in children: etiology, diagnosis and management.* Int J Pediatr Otorhinolaryngol *60(2):147–153, 2001, Fig. 2.)*

TYMPANIC MEMBRANE AND MIDDLE EAR

Traumatic perforation of the TM usually occurs as a result of a sudden external compression, such as a slap, or penetration by a foreign object such as a stick or cotton-tipped applicator. The perforation may be linear or stellate. It is most commonly in the anterior portion of the pars tensa when it is caused by compression, and it may be in any quadrant of the TM when caused by a foreign object. Systemic antibiotics and topical otic medications are not required unless suppurative otorrhea is present. Traumatic TM perforations often heal spontaneously, but it is important to evaluate and monitor the patient's hearing to ensure that spontaneous healing occurs. If the TM does not heal within several mo, surgical graft repair should be considered. As long as the perforation is present, otorrhea can occur from water entering the middle ear from the ear canal, which can occur during swimming or bathing; appropriate precautions should be taken. Perforations resulting from penetrating foreign bodies are less likely to heal than those caused by compression. Audiometric examination reveals a conductive hearing loss, with larger air–bone gaps seen in larger perforations. Immediate surgical exploration may be indicated if the injury is accompanied by 1 or more of the following: vertigo, nystagmus, severe tinnitus, moderate to severe hearing loss, or cerebrospinal fluid (CSF) otorrhea. At the time of exploration, it is necessary to inspect the ossicles, especially the stapes, for possible dislocation or fracture and to clear sharp objects that might have penetrated the oval or round windows. SNHL results if the stapes subluxates or dislocates into the oval window or if either the oval or round window is penetrated. Children should not be given access to cotton-tipped applicators, because the applicators commonly cause ear trauma. Contact with small objects should be limited to times of parental supervision.

Perilymphatic fistula can occur after barotrauma or an increase in CSF pressure. It should be suspected in a child who develops a sudden SNHL or vertigo after physical exertion, deep water diving, air travel, playing a wind instrument, or significant head trauma. The leak characteristically is at the oval (Fig. 642-1) or the round window and may be associated with congenital abnormalities of these structures or an anatomic abnormality of the cochlea or semicircular canals. Perilymphatic fistulas occasionally close spontaneously, but immediate surgical repair of the fistula is recommended to control vertigo and to stop any progression of the SNHL; even timely surgery does not usually restore the SNHL. No reliable test is known for perilymphatic fistula, so middle-ear exploration is required for diagnosis and treatment.

TEMPORAL BONE FRACTURES

Children are particularly prone to basilar skull fractures, which usually involve the temporal bone. Temporal bone trauma should be considered in head injuries, and the status of the ear and hearing should be evaluated. Temporal bone fractures are divided into longitudinal (70-80%), transverse, and mixed. Longitudinal fractures (Fig. 642-2) are commonly manifested by bleeding from a laceration of the external canal or TM; postauricular ecchymosis **(Battle sign); hemotympanum** (blood behind an intact TM); conductive hearing loss resulting from TM perforation, hemotympanum, or ossicular injury; delayed onset of facial paralysis (which usually improves spontaneously); and temporary CSF otorrhea or rhinorrhea (from CSF running down the eustachian tube). Transverse fractures of the temporal bone have a graver prognosis than longitudinal fractures and are often associated with immediate facial paralysis. Facial paralysis might improve if caused by edema, but surgical decompression of the nerve is often recommended if there is no evidence of clinical recovery and facial nerve studies are unfavorable. If the facial nerve has been transected, surgical decompression and anastomosis offer the possibility of some functional recovery. Transverse fractures are also associated with severe SNHL, vertigo, nystagmus, tinnitus, nausea, and vomiting associated with loss of cochlear and vestibular function; hemotympanum; rarely, external canal bleeding; and CSF otorrhea, either in the external auditory canal or behind the TM, which can exit the nose via the eustachian tube.

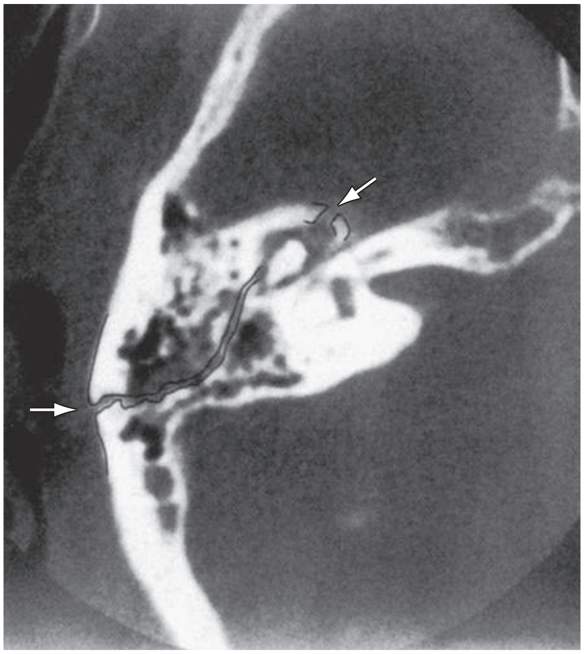

Figure 642-2 High-resolution axial CT of uncomplicated longitudinal fracture *(arrows).* A hematoma is present. The course of the fracture has been touched. *(From Schubiger O, Valavanis A, Stuckman G, et al: Temporal bone fractures and their complications: examination with high resolution CT.* Neuroradiology *28:93–99, 1986.)*

If temporal bone fracture is suspected or seen on radiographs, gentle examination of the pinna and ear canal is indicated; lacerations or avulsion of soft tissue is common with temporal bone fractures. Vigorous removal of external auditory canal blood clots or tympanocentesis is not indicated, because removing the clot can further dislodge the ossicles or reopen CSF leaks. The effectiveness of prophylactic antibiotics to prevent meningitis in patients with basilar skull fractures and CSF otorrhea or rhinorrhea cannot be determined because studies to date are flawed by biases. If a patient is afebrile and the drainage is not cloudy, watchful waiting without antibiotics is indicated. Surgical intervention is reserved for children who require repair of a nonhealing TM perforation, who have suffered dislocation of the ossicular chain, or who need decompression of the facial nerve. SNHL can also follow a blow to the head without an obvious fracture of the temporal bone (labyrinthine concussion).

ACOUSTIC TRAUMA

Acoustic trauma results from exposure to high-intensity sound (fireworks, gunfire, loud music, heavy machinery) and is initially

manifested by a temporary decrease in the hearing threshold, most commonly at 4,000 Hz on an audiometric examination, and tinnitus. If the sound is between 85 and 140 dB, the loss is usually temporary (after a rock concert), but both the hearing loss and the tinnitus can become permanent with chronic noise exposure; the frequencies from 3,000-6,000 Hz are most often involved. Sudden, extremely loud (>140 dB), short-duration noises with loud peak components (gunfire, bombs) can cause permanent hearing loss after a single exposure. Noise-induced hearing loss results from interactions between genes and the environment. Ear protection and avoidance of chronic exposure to loud noise are preventive measures. Hearing loss from chronic noise exposure should be entirely preventable. Parents should be made aware of the dangers of acoustic trauma, from the environment and from the use of headphones, and should take measures to minimize exposure. Treatment with high-dose steroids for 1-2 wk should be considered to treat acute hearing loss related to noise trauma.

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Chapter 643

Tumors of the Ear and Temporal Bone

Joseph Haddad Jr. and Sarah Keesecker

Benign tumors of the external canal include osteomas and monostotic and polyostotic fibrous dysplasia. Osteomas manifest as bony masses in the canal and require removal only if hearing is impaired or external otitis results; osteomas may be confused clinically with exostoses (see Chapter 501.2). Masses occurring over the mastoid bone, such as first branchial cysts, dermoid cysts, and lipomas, may be confused with primary mastoid tumors; imaging can help with the diagnosis and treatment plan.

Eosinophilic granuloma, which can occur in isolation or as part of the systemic Langerhans cell histiocytosis (see Chapter 507), should be suspected in patients with otalgia, otorrhea (sometimes bloody), hearing loss, abnormal tissue within the middle ear or ear canal, and roentgenographic findings of a sharply delineated destructive lesion of the temporal bone. Definitive diagnosis is made by biopsy. Treatment depends on the site of the lesion and histology. Depending on the site, it may be treated by surgical excision, curettage, or local radiation. If the lesion is part of a systemic presentation of Langerhans cell histiocytosis, chemotherapy in addition to local therapy (surgery with or without radiation) is indicated. Long-term follow-up is necessary whether the temporal bone lesion is a single isolated lesion or part of a multisystem disease.

Symptoms and signs of rhabdomyosarcoma (see Chapter 500) originating in the middle ear or ear canal include a mass or polyp in the middle ear or ear canal, bleeding from the ear, otorrhea, otalgia, facial paralysis, and hearing loss. Other cranial nerves also may be involved. Diagnosis is based on biopsy, but the extent of disease is determined by both CT and MRI of the temporal and facial bones, skull base, and brain (Fig. 643-1). Management usually involves a combination of chemotherapy, radiation, and surgery.

Non-Hodgkin lymphoma (see Chapter 496.2) and leukemia (see Chapter 495) also occur rarely in the temporal bone. Although primary neoplasms of the middle ear are very uncommon in children, they include adenoid cystic carcinoma, adenocarcinoma, and squamous cell carcinoma. Benign tumors of the temporal bone include glomus tumors. The initial signs and symptoms of the more common nasopharyngeal neoplasms (angiofibroma, rhabdomyosarcoma, epidermoid carcinoma) may be associated with insidious onset of chronic otitis media with effusion (often unilateral). A high index of suspicion is needed for diagnosing these tumors early.

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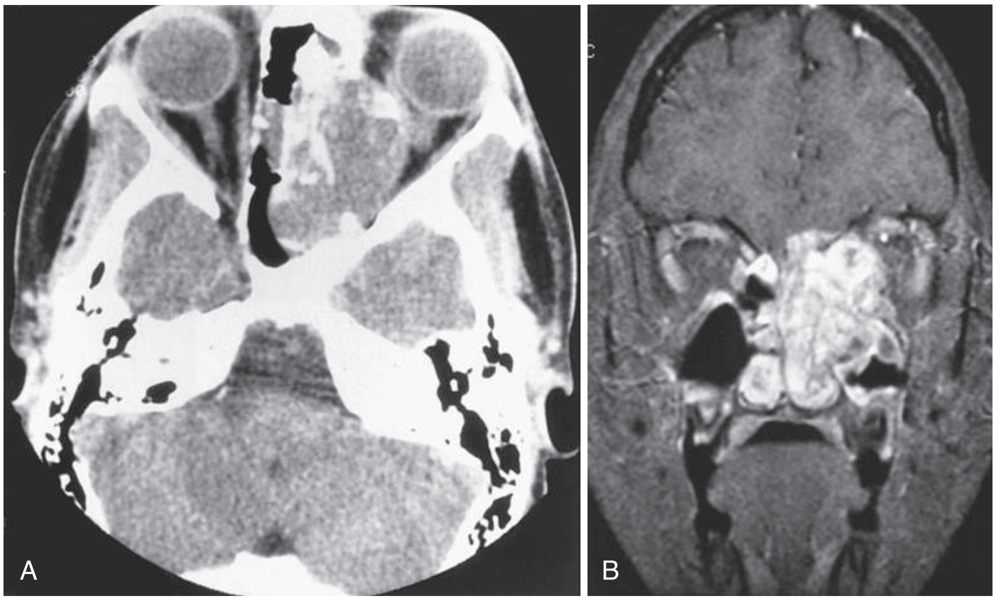

Figure 643-1 Rhabdomyosarcoma in a 2 yr old child presenting with a large mass in the nose. **A,** CT scan of the head shows destruction of the nose and lamina papyracea; a large soft tissue mass is present. **B,** MRI shows enhancement of the mass. *(From Slovis T, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, p. 560.)*

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The Skin

PART XXXI

Chapter 644

Morphology of the Skin

Brianne Z. Dickey and Yvonne E. Chiu

EPIDERMIS

The mature epidermis is a stratified epithelial tissue composed predominantly of keratinocytes. The function of the epidermis is protection of the organism from the external environment, through physical, chemical, and immunologic barrier functions, and the prevention of water loss. The process of epidermal differentiation results in the formation of a functional barrier to the external world. The epidermis comprises four histologically recognizable layers, described here from deepest to most superficial. The first or basal layer consists of columnar cells that rest on the dermal–epidermal junction. Basal keratinocytes are connected to the dermal–epidermal junction by hemidesmosomes. Basal keratinocytes are attached to themselves and to the cells in the spinous layer by desmosomal, tight, gap, and adherens junctions. The role of the basal keratinocyte is to serve as a continuing supply of keratinocytes for the normally differentiating epidermis as well as a reservoir of cells to repair epidermal damage. The second layer is the spinous layer, composed of 3-4 layers of spinous cells. Their role is to synthesize keratin, which makes up the keratin intermediate filament network. The third layer is the granular layer, which consists of 2-3 layers of granular cells. Granular cells contain keratohyalin and lamellar granules, containing the protein and lipid components that make up the cornified layer. The fourth layer, or cornified layer, is composed of multiple layers of dead, highly compacted cells. The dead cells are composed mainly of disulfide-bonded keratins crosslinked by filaggrins. The intercellular spaces are composed of hydrophobic lipids, predominantly ceramides, cholesterol, and fatty acids, serving as an effective barrier against water and salt loss as well as permeation of water-soluble substances. As the cornified layer is replenished, the oldest or most superficial layer is shed in a highly regulated process. The normal process of epidermal differentiation from basal cell to shedding of cornified layer takes 28 days.

The epidermis also contains 3 other cell types. The **melanocytes** are pigment-forming cells, which are responsible for skin color and protection from ultraviolet radiation. Epidermal melanocytes are derived from the neural crest and migrate to the skin during embryonic life. They reside in the interfollicular epidermis and in the hair follicles. Melanocytes produce intracellular organelles (melanosomes) containing melanin, which they transfer via dendrites to the keratinocytes to protect the keratinocyte nucleus from ultraviolet damage. **Merkel** cells are type I slow-adapting mechanosensory receptors for touch that differentiate within the epidermis from epidermal progenitor cells. **Langerhans** cells are dendritic cells of the mononuclear phagocyte system. They are recognized electron microscopically by a specific organelle, the Birbeck granule. These cells are derived from bone marrow and participate in immune reactions in the skin, playing an active part in antigen presentation and processing.

The junction of the epidermis and dermis is the basement membrane zone. This complex structure is a result of contributions from both epidermal and mesenchymal cells. The dermal-epidermal junction extends from the basal cell plasma membrane to the uppermost region of the dermis. Ultrastructurally, the basement membrane appears as a trilaminar structure, consisting of a lamina lucida immediately adjacent to the basal cell plasma membrane, a central lamina densa, and the subbasal lamina on the dermal side of the lamina densa. Several structures within this zone act to anchor the epidermis to the dermis. The plasma membrane of basal cells contains electron-dense plates known as hemidesmosomes; tonofilaments course within basal cells to insert at these sites. The **hemidesmosomes** are composed of 180- and 230-kDa bullous pemphigoid antigens (BP180 [type XVII collagen] and BP230, respectively), $\alpha_6\beta_4$ and $\alpha_3\beta_1$ integrins, and plectin. Anchoring filaments originate in the plasma membrane, primarily near the hemidesmosomes, and insert into the lamina densa. Anchoring fibrils, composed predominantly of type VII collagen, extend from the lamina densa into the uppermost dermis, where they loop through collagen fibrils before reinserting into the lamina densa.

DERMIS

The dermis provides the skin with most of its mechanical properties. The dermis forms a tough, pliable, fibrous supporting structure between the epidermis and the subcutaneous fat. The predominant dermal cell is a spindle-shaped fibroblast that is responsible for the synthesis of collagen, elastic fibers, and mucopolysaccharides. Phagocytic histiocytes, mast cells, and motile leukocytes are also present. Within the dermis are blood vessels, lymphatics, neural structures, eccrine and apocrine sweat glands, hair follicles, sebaceous glands, and smooth muscle. Morphologically, the dermis can be divided into 2 layers: the superficial papillary layer that interdigitates with the rete ridges of the epidermis and the deeper reticular layer that lies beneath the papillary dermis. The papillary layer is less dense and more cellular, whereas the reticular layer appears more compact because of the coarse network of interlaced collagen and elastic fibers.

The extracellular matrix of the dermis consists of collagen and elastic fibers embedded in an amorphous ground substance. Collagen provides strength and stability to the dermis, while elastic fibers allow for elasticity. The gelatinous ground substance serves as a supporting medium for the fibrillar and cellular components and as a storage place for a substantial portion of body water.

SUBCUTANEOUS TISSUE

The **panniculus,** or subcutaneous tissue, consists of fat cells and fibrous septa that divide it into lobules and anchor it to the underlying fascia and periosteum. Blood vessels and nerves are also present in this layer, which serves as a storage depot for lipid, an insulator to conserve body heat, and a protective cushion against trauma.

APPENDAGEAL STRUCTURES

Appendageal structures are derived from aggregates of epidermal cells that become specialized during early embryonic development. Small buds (primary epithelial germs) appear in the 3rd fetal mo and give rise to hair follicles, sebaceous and apocrine glands, and the attachment bulges for the arrector pili muscles. Eccrine sweat glands are derived from separate epidermal downgrowths that arise in the 2nd fetal mo and are completely formed by the 5th mo. Formation of nails is initiated in the 3rd intrauterine mo.

Hair Follicles

The pilosebaceous unit includes the hair follicle, sebaceous gland, arrector pili muscle, and, in areas such as the axillae, an apocrine gland. Hair follicles are distributed throughout the skin, except in the palms, soles, lips, and glans penis. Individual follicles extend from the surface of the epidermis to the deep dermis. The hair follicle is divided into 4 segments: the infundibulum, which extends from the skin surface to

the opening of the sebaceous duct; the isthmus, extending from the sebaceous duct opening to the bulge; the lower follicle between the bulge and the hair bulb; and the hair bulb. The bulge is at the insertion of the arrector pili muscle and is a focus of epidermal stem cells. The bulb is where the matrix cells and the dermal papilla are involved in formation and maintenance of the hair. The growing hair consists of the hair shaft, made of dead keratinocytes, and its supporting inner and outer root sheaths.

Human hair growth is cyclic, with alternate periods of growth (anagen), transition (catagen), and rest (telogen). The length of the anagen phase varies from months to years. At birth, all hairs are in the anagen phase. Subsequent generative activity lacks synchrony, so an overall random pattern of growth and shedding prevails. At any time, approximately 85% of hairs are in the anagen phase. Scalp hair usually grows about 1 cm per month.

The types of hair are lanugo, terminal, and vellus hairs. Lanugo hair is thin and short; this hair is shed in utero and is replaced by vellus hair by 36-40 wk of gestation. Vellus hair is short, soft, and frequently unpigmented and is distributed over the rest of the body. Terminal hair is long and coarse and is found on the scalp, beard, eyebrows, eyelashes, and axillary and pubic areas. During puberty, androgenic hormone stimulation causes pubic, axillary, and beard hair to change from vellus hair to terminal hair.

Sebaceous Glands

Sebaceous glands occur in all areas except the palms, soles, and dorsal feet and are most numerous on the face, upper chest, and back. Their ducts open into the hair follicles except on the lips, prepuce, and labia minora, where they emerge directly onto the mucosal surface. These holocrine glands are saccular structures that are often branched and lobulated and consist of a proliferative basal layer of small flat cells peripheral to the central mass of lipidized cells. The latter cells disintegrate as they move toward the duct and form the lipid secretion known as sebum, which consists of triglycerides, wax esters, squalene, and cholesterol esters. The purpose of sebum production likely relates to hydrophobic skin barrier function. Sebaceous glands depend on hormonal stimulation and are activated by androgens at puberty. Fetal sebaceous glands are stimulated by maternal androgens, and their lipid secretion, together with desquamated stratum corneum cells, constitutes the vernix caseosa.

Apocrine Glands

The apocrine glands are located in the axillae, areolae, perianal and genital areas, and the periumbilical region. These large, coiled, tubular structures continuously secrete an odorless milky fluid that is discharged in response to adrenergic stimuli, usually as a result of emotional stress. Bacterial biotransformation of apocrine sweat components (fatty acids, thioalcohols, and steroids) accounts for the unpleasant odor associated with perspiration. Apocrine glands remain dormant until puberty, when they enlarge and secretion begins in response to androgenic activity. The secretory coil of the gland consists of a single layer of cells enclosed by a layer of contractile myoepithelial cells. The duct is lined with a double layer of cuboidal cells and opens into the pilosebaceous complex. Although apocrine glands do not function in thermoregulation, they are involved in certain disease processes.

Eccrine Sweat Glands

Eccrine sweat glands are distributed over the entire body surface and are most abundant on the palms and soles. Those on the hairy skin respond to thermal stimuli and serve to regulate body temperature by delivering water to the skin surface for evaporation; in contrast, sweat glands on the palms and soles respond mainly to psychophysiologic stimuli.

Each eccrine gland consists of a secretory coil located in the reticular dermis or subcutaneous fat and a secretory duct that opens onto the skin surface. Sweat pores can be identified on the epidermal ridges of the palm and fingers with a magnifying lens but are not readily visualized elsewhere. Two types of cells constitute the single-layered secretory coil: small dark cells and large clear cells. These rest on a layer of contractile myoepithelial cells and a basement membrane. The glands are supplied by sympathetic nerve fibers, but the pharmacologic mediator of sweating is acetylcholine rather than epinephrine. Sweat from these glands consists of water, sodium, potassium, calcium, chloride, phosphorus, lactate, and small quantities of iron, glucose, and protein. The composition varies with the rate of sweating but is always hypotonic in normal children.

Nails

Nails are specialized protective epidermal structures that form convex, translucent, tight-fitting plates on the distal dorsal surfaces of the fingers and toes. The nail plate, which is derived from a metabolically active matrix of multiplying cells situated beneath the posterior nail fold, is composed of anucleate keratinocytes. Nail growth is relatively slow; complete fingernail regrowth takes 6 mo, while complete toenail regrowth requires 12-18 mo. The nail plate is bounded by the lateral and posterior nail folds; a thin eponychium (the cuticle) protrudes from the posterior fold over a crescent-shaped white area called the lunula. The eponychium serves as a sealant barrier to protect the germinal matrix of the nail plate. The pink color beneath the nail reflects the underlying vascular bed. Nail health relies on several factors, including nutrition, hydration, local infection/irritation, and systemic disease.

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Chapter 645

Evaluation of the Patient

Brianne Z. Dickey and Yvonne E. Chiu

HISTORY AND PHYSICAL EXAMINATION

Although many skin disorders are easily recognized by simple inspection, the history and physical examination are often necessary for accurate assessment. The skin examination should be performed under adequate illumination. In addition to the skin covering the entire body surface, mucous membranes (conjunctiva, oropharynx, nasal mucosa, anogenital mucosa), hair, and nails should be examined when appropriate. The color, turgor, texture, temperature, and moisture of the skin and the growth, texture, caliber, and luster of the hair and nails should be noted. Skin lesions should be palpated, inspected, and classified on the bases of morphology, size, color, texture, firmness, configuration, location, and distribution. One must also decide whether the changes are those of the *primary* lesion itself or whether the clinical pattern has been altered by a *secondary* factor such as infection, trauma, or therapy.

Primary lesions are classified as macules, papules, patches, plaques, nodules, tumors, vesicles, bullae, pustules, wheals, and cysts. A **macule** represents an alteration in skin color but cannot be felt. When the lesion is >1 cm, the term **patch** is used. **Papules** are palpable solid lesions <1 cm. **Plaques** are palpable lesions >1 cm in size and have a flat surface. **Nodules** are palpable lesions >1 cm with a rounded surface. The word **tumor** may be used for a large nodule that is suspected to be neoplastic in origin. Vesicles are raised, fluid-filled lesions <1 cm in diameter; when larger, they are called **bullae. Pustules** contain purulent material. **Wheals** are flat-topped, palpable lesions of variable size, duration, and configuration that represent dermal collections of edema fluid. **Cysts** are circumscribed, thick-walled lesions; they are covered by a normal epidermis and contain fluid or semisolid material.

Primary lesions may change into secondary lesions, or secondary lesions may develop over time where no primary lesion existed.

Primary lesions are usually more helpful for diagnostic purposes than secondary lesions. Secondary lesions include scales, purpura, petechiae, ulcers, erosions, excoriations, fissures, crusts, and scars. **Scales** consist of compressed layers of stratum corneum cells that are retained on the skin surface. **Purpura** are the result of bleeding into the skin and have a red-purple color; they may be flat or palpable. **Petechiae** are small purpura <2-3 mm. **Erosions** involve focal loss of the epidermis, and they heal without scarring. **Ulcers** extend into the dermis and tend to heal with scarring. Ulcerated lesions inflicted by scratching are often linear or angular in configuration and are called **excoriations.** **Fissures** are caused by splitting or cracking. **Crusts** consist of matted, retained accumulations of blood, serum, pus, and epithelial debris on the surface of a weeping lesion. **Scars** are end-stage lesions that can be thin, depressed, and atrophic; raised and hypertrophic; or flat and pliable. **Lichenification** is a thickening of skin with accentuation of normal skin lines that is caused by chronic irritation (rubbing, scratching) or inflammation.

If the diagnosis is not clear after a thorough examination, 1 or more diagnostic procedures may be indicated.

BIOPSY OF SKIN

Biopsy of skin is occasionally required for diagnosis. Punch biopsy is a simple, relatively painless procedure and usually provides adequate tissue for examination if the appropriate lesion is sampled. The selection of a fresh, well-developed primary lesion is extremely important to obtain an accurate diagnosis. The site of the biopsy should have relatively low risk for damage to underlying dermal structures. After cleansing of the site, the skin is anesthetized by intradermal injection of 1-2% lidocaine, with or without epinephrine, with a 27- or 30-gauge needle. A punch, 3 or 4 mm in diameter, is pressed firmly against the skin and rotated until it sinks to the proper depth. All 3 layers (epidermis, dermis, subcutis) should be contained in the plug. The plug should be lifted gently with forceps or extracted with a needle and separated from the underlying tissue with iris scissors. Bleeding abates with firm pressure and with suturing. The biopsy specimen should be placed in 10% formaldehyde solution (Formalin) for appropriate processing.

WOOD LAMP

A Wood lamp emits ultraviolet light mainly at a wavelength of 365 nm. The examination, which is performed in a darkened room, is useful in accentuating changes in pigmentation and detecting fluorescence in certain infectious disorders. Discrete areas of altered pigment can often be visualized more clearly by using a Wood lamp, particularly if the pigmentary change is epidermal. Hyperpigmented lesions appear darker, and hypopigmented lesions (e.g., those seen in **tuberous sclerosis**), lighter than the surrounding skin. Blue-green fluorescence is detectable at the base of each infected hair shaft in ectothrix infections, such as tinea capitis caused by *Microsporum* species. Scales and crusts may appear pale yellow, but this color is not evidence of a fungal infection. Dermatophyte lesions of the skin (tinea corporis) do not fluoresce; macules of tinea versicolor have a golden fluorescence under a Wood lamp. **Erythrasma**, an intertriginous infection caused by *Corynebacterium minutissimum,* may fluoresce pink-orange, whereas *Pseudomonas aeruginosa* is yellow-green under a Wood lamp.

POTASSIUM HYDROXIDE PREPARATION

Potassium hydroxide (KOH) preparation is a rapid and reliable method for detecting fungal elements of both yeasts and dermatophytes. Scaly lesions should be scraped at the active border for optimal recovery of mycelia and spores. Vesicles should be unroofed, and the blister roof should be clipped and placed on a slide for examination. In tinea capitis, infected hairs must be plucked from the follicle; scales from the scalp do not usually contain mycelia. A few drops of 20% KOH are added to the specimen. Dimethyl sulfoxide is usually in solution with the KOH, negating the need to heat the specimen. If using KOH without dimethyl sulfoxide, the specimen is gently heated over an alcohol lamp or on a hot plate until the KOH begins to bubble. Alternatively, sufficient time (10-20 min) can be allowed for dissolution of the keratin at room temperature. The preparation is examined under low-intensity light microscopy for fungal elements.

TZANCK SMEAR

Tzanck smear is useful in the diagnosis of infections caused by herpes simplex virus or varicella zoster virus and for the detection of acantholytic cells in pemphigus. An intact, fresh vesicle is ruptured and drained of fluid. The roof and base of the blister are then carefully scraped with a no. 15 scalpel blade, with care taken to avoid drawing a significant amount of blood; the material is smeared on a clear glass slide and air dried. Staining with Giemsa stain is preferable, but Wright stain is acceptable. Balloon cells and multinucleated giant cells are diagnostic of herpesvirus infection; acantholytic epidermal cells are characteristic of pemphigus.

Direct fluorescent assay and polymerase chain reaction tests have largely replaced Tzanck smears in the diagnosis of herpes simplex and varicella zoster infections. Both of these are rapid, sensitive, and specific, with the polymerase chain reaction even more so. When obtaining specimens for these tests, the vesicles should be ruptured prior to sample collection with the swab.

IMMUNOFLUORESCENCE STUDIES

Immunofluorescence studies of skin can be used to detect tissue-fixed antibodies to skin components and complement; characteristic staining patterns are specific for certain skin disorders (Table 645-1). Direct immunofluorescence detects autoantibodies bound to cutaneous antigens in the skin, while indirect immunofluorescence detects circulating autoantibodies present in the serum.

Skin biopsy specimens for direct immunofluorescence should be obtained from involved sites except in those diseases for which perilesional skin or uninvolved skin is required. A punch biopsy sample is obtained, and the tissue is placed in a special transport medium or immediately frozen in liquid nitrogen for transport or storage. Thin cryostat sections of the specimen are incubated with fluorescein-conjugated antibodies to the specific antigens.

Serum of patients can be examined by indirect immunofluorescence techniques using sections of normal human skin, guinea pig lip, or monkey esophagus as substrate. The substrate is incubated with fresh or thawed frozen serum and then with fluorescein-conjugated antihuman globulin. If the serum contains antibody to epithelial components, its specific staining pattern can be seen on fluorescence microscopy. By serial dilution, the titer of circulating antibody can be estimated.

645.1 Cutaneous Manifestations of Systemic Diseases

Brianne Z. Dickey and Yvonne E. Chiu

Selected diseases have signature skin findings, often as the presenting signs of illness, that can facilitate the assessment of patients with complex medical states (Table 645-2).

CONNECTIVE TISSUE DISEASES

Lupus Erythematosus

Lupus erythematosus (LE; see Chapter 158) is an idiopathic autoimmune inflammatory disease that may be multisystemic (i.e., systemic LE or SLE) or confined to the skin. Distinct cutaneous lupus subtypes seen in children include acute cutaneous LE, subacute cutaneous LE, chronic cutaneous LE (including discoid LE, discussed under “Discoid Lupus Erythematosus”), and neonatal LE (discussed under “Neonatal Lupus Erythematosus”).

Systemic Lupus Erythematosus

SLE is a chronic inflammatory multisystem disease. It is diagnosed when 4 of 11 well-defined criteria are present (see Chapter 158). Three of the criteria are skin findings. Criterion 1 is the classic malar or “butterfly” rash (Fig. 645-1). It must be distinguished from other causes of a “red face,” most notably seborrheic dermatitis, atopic dermatitis, and

Table 645-1 Immunofluorescence Findings in Immune-Mediated Cutaneous Diseases

DISEASE	INVOLVED SKIN	UNINVOLVED SKIN	DIRECT IF FINDINGS	INDIRECT IF FINDINGS	CIRCULATING ANTIBODIES
Dermatitis herpetiformis	Negative	Positive	Granular IgA ± C in papillary dermis	None	IgA antiendomysial and transglutaminase antibodies
Bullous pemphigoid	Positive	Positive	Linear IgG and C band in BMZ, occasionally IgM, IgA, IgE	IgG to BMZ	IgG anti-BP180 and anti-BP230
Pemphigus (all variants)	Positive	Positive	IgG in intercellular spaces of epidermis between keratinocytes	IgG to intercellular spaces of epidermis between keratinocytes	IgG antidesmoglein 1 and 3 (pemphigus vulgaris and foliaceus). IgA antidesmocollin 1 (IgA pemphigus).
Linear IgA bullous dermatosis (chronic bullous dermatosis of childhood)	Positive	Positive	Linear IgA at BMZ, occasionally C	Low titer, rare IgA, anti-BP180	None
Discoid lupus erythematosus	Positive	Negative	Linear IgG, IgM, IgA, and C3 at BMZ (lupus band)	None	Usually ANA-negative
Systemic lupus erythematosus	Positive	Variable; exposed to sun, 30-50%; nonexposed, 10-30%	Linear IgG, IgM, IgA, and C3 at BMZ (lupus band)	None	ANA Anti-Ro (SSA), anti-La (SSB) Anti-RNP Anti-dsDNA Anti-Sm
Henoch-Schönlein purpura	Positive	Positive	IgA around vessel walls	None	None

ANA, antinuclear antibody; BMZ, basement membrane zone at the dermal–epidermal junction; BP, bullous pemphigoid; C, complement; dsDNA, double-stranded deoxyribonucleic acid; IF, immunofluorescence; Ig, immunoglobulin; Sm, Smith; SSA/SSB, Sjögren syndrome A/B; RNP, ribonucleoprotein.

rosacea. Criterion 2 is discoid lupus lesions. Criterion 3 is a photosensitive erythematous macular or papular eruption (Fig. 645-2). Other associated but not diagnostic cutaneous findings include purpuric lesions, livedo reticularis, mucosal ulcerations, Raynaud phenomenon, urticaria, and nonscarring alopecia.

On histology, cutaneous LE demonstrates varying degrees of epidermal atrophy, plugging of hair follicles, and a vacuolar alteration at an inflamed dermal-epidermal junction. Deposition of immunoglobulins (IgM, IgG) and complement in lesional skin may help confirm the diagnosis. Immune deposits in nonlesional sun-exposed skin are found in the majority of patients with SLE (lupus band test), although clinical use of this test has been mostly abandoned in favor of serologic testing.

The skin lesions often respond to treatment of the SLE with systemic agents. Oral hydroxychloroquine is used most commonly, but many other systemic therapies are effective, including both classic and biologic immunosuppressants. Low- to mid-potency topical corticosteroids, topical calcineurin inhibitors, and intralesional corticosteroid injection may be considered for adjunctive therapy.

Neonatal Lupus Erythematosus

Neonatal LE (see Chapter 158.1) manifests at birth or during the 1st few wk of life as annular, erythematous, scaly plaques, typically on the head, neck, and upper trunk (Fig. 645-3). Telangiectasias are also common. Ultraviolet light may exacerbate or initiate cutaneous lesions. Passive transplacental transfer of maternal anti-Ro/SSA and anti-La/SSB antibodies causes the transient skin lesions, though most infants are born to mothers without a known rheumatologic diagnosis. Antibody levels wane by 6 mo, generally resulting in clearance of the rash. Congenital heart block occurs in 30% of affected infants, but only 10% of affected infants have both skin and cardiac abnormalities. Noncardiac extracutaneous manifestations, such as anemia, thrombocytopenia, and cholestatic liver disease are less common. Neonatal LE is often misdiagnosed as infantile eczema, seborrheic dermatitis, or tinea corporis. Skin lesions are typically managed conservatively given the transient nature of neonatal LE, and strict sun avoidance and protection are important. If necessary, low- to mid-potency topical corticosteroids may be used. Systemic agents should be avoided. Maternal antinuclear antibody testing is indicated.

Discoid Lupus Erythematosus

Discoid LE (DLE) is uncommon in early childhood and manifests in late adolescence. The signature skin findings in DLE are chronic, erythematous, scaly, atrophic plaques (Fig. 645-4) on sun-exposed skin that frequently heal with scarring and dyspigmentation. Extracutaneous features may include involvement of the nasal and oral mucosa, eyes, and nails. The differential diagnosis includes other photodermatoses, such as polymorphous light eruption, juvenile springtime eruption, and juvenile dermatomyositis. There is a distinct overlap between SLE and DLE, with common histopathologic features and photoexacerbation; most patients with DLE have normal laboratory results and do not progress to systemic disease.

First-line treatment of DLE consists of low- to mid-potency topical corticosteroids. Other topical options include calcineurin inhibitors, retinoids, and topically-applied R-salbutamol. Intralesional corticosteroid injection is also effective for severe localized lesions. Oral hydroxychloroquine is used first-line for severe skin disease or as a second-line agent when lesions are not controlled with topical or local agents. Strict ultraviolet light avoidance is important.

Juvenile Dermatomyositis

Characteristic skin findings are often the presenting sign of juvenile dermatomyositis (JDM; see Chapter 159). An ill-defined, erythematous to violaceous, scaly, minimally pruritic eruption occurs in photodistributed areas such as the face, upper trunk, and extensor extremities. Circumscribed periocular involvement of this **heliotrope** rash involving the eyelids may take the appearance of "raccoon eyes," particularly in young children. Distinctive erythematous, scaly papules overlying the knuckles and other joints **(Gottron papules)** are helpful in suggesting the diagnosis in the absence of associated muscle weakness (Fig. 645-5). Other cutaneous features include nail fold and gingival margin telangiectasia, palmar hyperkeratosis ("mechanic's hands"),

Table 645-2 Characteristics of Cutaneous Signs of Systemic Diseases

DISEASE	AGE OF ONSET	SKIN LESIONS	DISTRIBUTION	DIAGNOSTIC EVALUATION(S) AND FINDINGS	ASSOCIATED SYMPTOMS/SIGNS	DIFFERENTIAL DIAGNOSIS
Systemic lupus erythematosus	Any	Erythematous patches; palpable purpura; livedo reticularis; Raynaud phenomenon; thrombocytopenic and nonthrombocytopenic purpura	Photodistribution; "malar" face	ANA panel Anti–dsDNA Leukopenia/lymphopenia Thrombocytopenia Complement levels Urinalysis	Arthritis Nephritis Cerebritis Serositis	Seborrheic dermatitis Atopic dermatitis Juvenile dermatomyositis
Discoid lupus erythematosus	Any	Annular, scaly plaques; atrophy; dyspigmentation	Photodistribution	ANA	Scarring	Subacute cutaneous lupus Polymorphous light eruption Juvenile dermatomyositis
Neonatal lupus erythematosus	Newborn	Annular, erythematous, scaly plaques	Head/neck	ANA Anti-Ro (SSA), anti-La (SSB)	Heart block Thrombocytopenia	Tinea capitis Atopic dermatitis Seborrheic dermatitis
Juvenile dermatomyositis	Any	Erythematous to violaceous scaly, macules; discrete papules overlying knuckles	Periocular face; shoulder girdle; extensor extremities; knuckles; palms	ANA AST ALT Aldolase Creatine kinase Lactate dehydrogenase	Proximal muscle weakness Calcifications Vasculopathy	Atopic dermatitis Allergic contact dermatitis Lupus erythematosus
Henoch-Schönlein purpura	Childhood and adolescence	Purpuric papules and plaques	Buttocks; lower extremities	Urinalysis Blood urea nitrogen/creatinine ratio Skin biopsy	Abdominal pain Arthritis	Vasculitis Drug eruption Infantile hemorrhagic edema Viral exanthem
Kawasaki disease	Infancy, childhood	Erythematous maculopapular to urticarial plaques; acral and groin erythema, edema, desquamation	Diffuse	Leukocytosis ESR C-reactive protein Thrombocytosis	Strawberry tongue Conjunctivitis Lymphadenopathy Cardiovascular complications	Viral syndrome Drug eruption Staphylococcal/ streptococcal illness
Inflammatory bowel disease	Childhood and adolescence	Aphthae; erythema nodosum; pyoderma gangrenosum; thrombophlebitis	Oral ulcers; perianal fissures	Skin biopsy	Abdominal pain Diarrhea Cramping Arthritis Conjunctivitis	Behçet syndrome Vasculitis *Yersinia* colitis
Sweet syndrome	Any	Infiltrated erythematous, edematous plaques	Diffuse	Skin biopsy Leukocytosis ESR	Fever Flu-like illness Conjunctivitis	Infection Urticaria Erythema multiforme Urticarial vasculitis
Graft-versus-host disease	Any	Acute: erythema, papules, vesicles, bulla	Head and neck; palms/soles; diffuse	Skin biopsy Liver function	Fever Mucositis Hepatitis	Drug eruption Infectious exanthem
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)	Any	Erythema; urticarial macules and plaques	Diffuse	Liver function Eosinophilia Atypical lymphocytosis	Perioral edema Lymphadenopathy Fever Hepatitis	Stevens-Johnson syndrome Infectious exanthem
Serum sickness–like reaction (SSLR)	Any	Edematous, urticarial plaques	Acral; diffuse	None	Fever Lymphadenopathy Arthritis, nephritis	Kawasaki disease Urticaria

ANA, antinuclear antibodies; ALT, alanine aminotransferase; AST, aspartate aminotransferase; dsDNA, double-stranded deoxyribonucleic acid; ESR, erythrocyte sedimentation rate; SSA/SSB, Sjögren's syndrome A/B.

Figure 645-1 Malar rash of systemic lupus erythematosus.

Figure 645-2 Photosensitive rash of systemic lupus erythematosus.

Figure 645-3 Annular plaque in neonatal lupus erythematosus.

ulceration resulting from vasculopathy or underlying calcinosis, lipodystrophy, and a poikilodermatous (dyspigmentation and telangiectasia) eruption over the shoulder girdle ("shawl sign"). Cutaneous features may precede the systemic illness, which is primarily characterized by muscle weakness and pain. The differential diagnosis includes atopic dermatitis, other connective tissue diseases, lichen planus, medication reactions, and infectious exanthems. Lesional skin demonstrates epidermal atrophy and vacuolar degeneration at the

Figure 645-4 Erythematous scaly plaque of discoid lupus erythematosus.

Figure 645-5 Gottron papules in juvenile dermatomyositis.

dermal-epidermal junction, often similar to LE. JDM is distinct from adult dermatomyositis in both presentation and prognosis. Pediatric patients have more difficulty with gastrointestinal vasculopathy and cutaneous calcifications, and JDM is not a paraneoplastic phenomenon as in adults. A rare clinical variant known as **amyopathic dermatomyositis** occurs when only skin, and not muscle, is involved.

Skin lesions benefit from systemic immunosuppressive therapy as discussed in detail in Chapter 159. Additional treatment options for localized skin disease include topical corticosteroids and calcineurin inhibitors. In case reports, the cutaneous calcinosis of JDM has been difficult to manage with a variety of agents, and no treatment consensus exists. Strict photoprotection and sunlight avoidance are vital to prevent cutaneous exacerbations.

Systemic Sclerosis

Systemic sclerosis frequently manifests as acral (sclerodactyly, ulceration, nail fold telangiectasia, or Raynaud phenomenon) and facial changes (pinched nose, furrowed perioral skin, or "scleroderma facies") (see Chapter 160). Overlap syndromes such as **mixed connective tissue disease** may include some physical and laboratory features of scleroderma.

VASCULITIDES

The vasculitides (see Chapter 167) encompass a broad group of disorders having considerable overlap with connective tissue diseases. Immune-mediated inflammation of blood vessels of varying size may be caused by an underlying inflammatory state, infection, medication, or malignancy. Common clinical features include **palpable**

Figure 645-6 Purpura of the lower leg in Henoch-Schönlein purpura.

nonthrombocytopenic purpuric skin lesions, arthritis, fever, myalgia, fatigue, and weight loss as well as an elevated erythrocyte sedimentation rate. Extracutaneous organs that may be involved include the joints, lungs, kidneys, and central nervous system.

Henoch-Schönlein Purpura (Immunoglobulin A Vasculitis)

Henoch-Schönlein purpura (see Chapter 167.1) is a vasculitis that manifests in school-age children as palpable purpuric lesions in gravity dependent areas, predominantly the buttocks and lower extremities (Fig. 645-6). **Infantile hemorrhagic edema (IHE;** also called acute hemorrhagic edema of infancy) shares some clinical features with Henoch-Schönlein purpura but appears in infants and toddlers. Infantile hemorrhagic edema is characterized by the sudden onset of circumscribed edema with purpuric papules and plaques on the trunk and extremities but, unlike Henoch-Schönlein purpura, commonly affects the face and lacks other organ involvement. Henoch-Schönlein purpura must also be differentiated from infectious causes of purpuric skin lesions, such as meningococcemia, Rocky Mountain spotted fever, and purpuric viral exanthems such as those caused by enteroviruses, as well as from juvenile rheumatoid arthritis and other vasculitides. Diagnosis is confirmed by histologic confirmation of a small vessel vasculitis with the immunofluorescence finding of IgA in blood vessel walls. Skin lesions are generally managed conservatively and self-resolve in 3-4 wk. Systemic treatment is discussed in detail in Chapter 167.1.

Kawasaki Disease

Kawasaki disease (see Chapter 166) is a clinical diagnosis based on both cutaneous and extracutaneous features in children younger than age 5 yr. The skin eruption of Kawasaki disease may be polymorphic, manifesting variously as maculopapular or morbilliform patches and plaques or rarely urticarial on the trunk and extremities. Early involvement with erythema and peeling in the perineum/inguinal region may be an initial clue to the diagnosis. Acral edema and desquamation are also prominent features but typically occur later. Classic mucocutaneous features include erythematous cracked lips, nonpurulent conjunctivitis with sparing of the limbus, and lingual plaques ("white strawberry tongue") that shed to produce denuded, erythematous patches with prominent papilla ("strawberry tongue"). Extracutaneous features include high fever, cervical lymphadenopathy, arthritis, and occasionally cardiac or gastrointestinal disease. First-line treatment is with aspirin and intravenous immunoglobulin, as discussed in Chapter 166.

Behçet Disease

Behçet disease (see Chapter 161) is a multisystem disease that includes oral and genital ulceration and ocular disease (uveitis, relapsing iridocyclitis) in older children and adults. Recurrent aphthous stomatitis is present in almost all patients and is commonly the presenting symptom. Genital ulcerations may resemble aphthae; can occur on the penis, scrotum, or vulva; and may be particularly painful in females. Perianal ulceration is more common in children than adults. Additional skin findings may include folliculitis, purpuric lesions, erythema nodosum, and pustule formation after venipuncture or skin trauma **(pathergy).** Differential diagnosis of oral lesions includes recurrent aphthous stomatitis, herpes simplex, and rare oculocutaneous syndromes (e.g., MAGIC [mouth and genital ulcers with inflamed cartilage] syndrome). Skin biopsy demonstrates nongranulomatous vasculitis in all vessel sizes. Oral lesions may respond to swish and spit/swallow preparations variably including corticosteroids, antihistamines, antibiotics, and analgesics. Skin lesions are managed with topical corticosteroids, topical anesthetics such as sucralfate, and systemic agents as outlined in Chapter 161.

GASTROINTESTINAL DISEASES

Inflammatory Bowel Disease

Inflammatory bowel disease includes ulcerative colitis (see Chapter 336.1) and Crohn disease (see Chapter 336.2). Skin lesions of inflammatory bowel disease are classified as specific or reactive. Specific cutaneous manifestations have the same histologic features and pathologic mechanism as the underlying inflammatory bowel disease lesions and include aphthous ulcers, perianal fistulas and fissures, and metastatic Crohn disease (discussed below). Reactive cutaneous manifestations occur secondary to immune-mediated antigen cross-reactivity between gut and skin components; examples include erythema nodosum and pyoderma gangrenosum.

Up to 30% of patients with **ulcerative colitis** present with cutaneous manifestations. Aphthous ulcers are common and may worsen with gastrointestinal exacerbations. Erythema nodosum, occurring in up to 10% of patients, manifests as warm, erythematous nodules, often on the distal lower extremities. Pyoderma gangrenosum is a focal, ulcerative process that has distinctive, inflamed, undermined borders and a purulent, boggy center. Thrombophlebitis also occurs at an increased rate in patients with ulcerative colitis.

Crohn disease classically manifests as perianal fissures and skin tags, abscesses, sinuses, and fistulas; these may be presenting signs. A cobblestone appearance of oral mucosa may also be present. As in ulcerative colitis, aphthae, erythema nodosum, and pyoderma gangrenosum occur at increased frequency and may improve with treatment of the underlying disease. Noncaseating granulomatous inflammation is seen on routine histopathology, and when found in skin not contiguous with the intestinal tract, is labeled **metastatic Crohn disease.** Metastatic lesions may appear as solitary or multiple, localized plaques or nodules and may be located on perianal, perioral, or other cutaneous surfaces, including scars and ileostomy sites. In most cases of inflammatory bowel disease–associated skin disease, treatment of the underlying condition improves the cutaneous sequelae. Azathioprine, a common treatment, causes increased risk for nonmelanoma skin cancers.

CUTANEOUS MANIFESTATIONS OF MALIGNANCY

Skin disease associated with malignancy has a wide variety of presentations, including both metastatic lesions and nonmalignant paraneoplastic conditions. Cutaneous metastases manifest as firm nodules and occur at any cutaneous site. Paraneoplastic reaction patterns are often distinctive and can aid in the diagnosis of the underlying malignancy. Some genetic syndromes have an increased malignancy risk that may be suggested initially by cutaneous signs. Other cutaneous findings that may signal an underlying malignancy include pruritus, ichthyosis, acanthosis nigricans, urticaria, pemphigus, and erythroderma.

Sweet Syndrome

Also known as **acute febrile neutrophilic dermatosis**, Sweet syndrome (see Chapter 169) occurs in several forms, including classical (usually idiopathic or infection-related, Fig. 645-7), malignancy-associated, immunodeficiency-related, and drug-induced; pathogenesis

Figure 645-7 Clinical picture of idiopathic Sweet syndrome. *(From Prat L, Bouaziz JD, Wallach D, et al: Neutrophilic dermatoses as systemic diseases.* Clin Dermatol *32:376–388, 2014, Fig. 1.)*

Figure 645-8 Lichenoid eruption in chronic graft-versus-host disease.

for all 3 forms remains unclear. Malignancy-associated Sweet syndrome is most commonly associated with hematologic malignancies, especially **acute myelogenous leukemia**. It manifests abruptly before, during, or after the malignancy course and is characterized by tender, erythematous, edematous plaques or nodules that may be pustular or targetoid, often accompanied by fever, anemia, and leukocytosis. Oral ulcers are more common in malignancy-associated Sweet syndrome than in other forms of the disease, and extracutaneous manifestations involving various organ systems may also occur. Diagnosis is confirmed by the presence of a dense neutrophilic infiltrate without evidence of vasculitis. The differential diagnosis includes other neutrophilic dermatoses-like pyoderma gangrenosum as well as cellulitis, erythema multiforme, Behçet disease, and erythema nodosum. First-line treatment for both malignancy-associated and nonmalignancy-associated Sweet syndrome is oral glucocorticoids (prednisone 1-2 mg/kg/day for 2-4 wk) in combination with high-potency topical or intralesional corticosteroids. Systemic steroid-sparing agents include colchicine and dapsone.

Necrolytic Migratory Erythema (Glucagonoma Syndrome)

Necrolytic migratory erythema is a distinctive migratory erythema that often signals an underlying neoplasm, usually an α-cell pancreatic tumor. Polycyclic, weeping, erythematous patches and plaques on the face, extremities, and groin occur in association with glossitis and cheilitis. The lesions are painful or pruritic, enlarge and coalesce over time and may develop central clearing with vesicles, crusts, and scales peripherally. Skin biopsy reveals superficial necrolysis with perivascular infiltrate. Elevated glucagon levels, hyperglycemia, and hypoaminoacidemia confirm the diagnosis, and tumor resection leads to resolution of the rash. Other treatments for necrolytic migratory erythema include somatostatin analogs (octreotide) and nutritional support; however, these measures do not affect the underlying tumor burden.

CUTANEOUS REACTIONS IN THE SETTING OF IMMUNOSUPPRESSION

Medication reactions, infectious etiologies, and graft-versus-host disease (GVHD) are included in the differential diagnosis in immunosuppressed patients; cutaneous and histologic similarities can be confounding.

Medication Reactions

The majority of medication reactions are mild morbilliform or exanthematous eruptions of little clinical consequence. Identifying the suspect medication may be difficult owing to the many medications used in immunosuppressed patients. Features that may help identify suspect medications include rash onset relative to exposure, character of distribution and spread, associated symptoms, and laboratory data. Medication eruptions begin on the trunk 7-10 days after exposure; they spread peripherally and are associated with pruritus and, less commonly, with fever, arthralgia, and lymphadenopathy. Eosinophilia may support a diagnosis of drug eruption but may be absent in the setting of bone marrow suppression. Penicillins, sulfa drugs, cephalosporins, nonsteroidal antiinflammatory drugs, anticonvulsants, and aminoglycosides are common offenders. Medication eruptions may resolve despite continued use of the offending agent, or they may progress to more severe involvement. A careful drug history, elimination of all nonessential, suspect medications or change to medications of dissimilar class, and treatment of pruritus with emollients, topical steroids, antihistamines, and antipruritics are indicated. Skin biopsies are rarely useful in distinguishing medication eruptions from infectious exanthems, although GVHD, if sufficiently advanced, may have signature histopathologic findings.

Graft-Versus-Host Disease

GVHD (see Chapter 137) may have florid cutaneous expression in addition to characteristic extracutaneous features such as fever, mucositis, diarrhea, and hepatitis. It may be either acute or chronic. **Acute GVHD** occurs in 20-70% of hematopoietic stem cell transplants, depending on histocompatibility differences. It may be mistaken for a medication reaction or infectious exanthem because of the nonspecific erythematous maculopapular (morbilliform) eruption that often starts focally and then generalizes. Features that suggest acute GVHD include timing of eruption (typically 1-3 wk after transplantation, at the time of hematopoietic reconstitution), initial involvement of the head and neck including the ears, and subsequent spread to the trunk, extremities, palms, and soles. In severe cases of acute GVHD, blistering, necrolysis, and erythroderma occur. **Chronic GVHD** occurs in approximately 65% of long-term transplant survivors who may or may not have experienced prior acute GVHD. Cutaneous manifestations of chronic GVHD are distinctive, with sclerotic, poikilodermic scaly plaques and lichen planus-like papules predominating on the trunk and distal extremities (Fig. 645-8). Sclerotic areas are prone to contracture and chronic wound development. Involvement of the hair, nails, and oral mucosa is also common in chronic GVHD. First-line treatment for GVHD includes systemic glucocorticoids and other immunosuppressants supplemented by mid- to high-potency topical corticosteroids. In mild disease, topical corticosteroids or topical calcineurin inhibitors alone may be effective. Second-line treatment approaches include phototherapy (narrow band UVB or UVA1) and extracorporeal photopheresis. All patients with GVHD benefit from sunlight protection, emollient use, and topical or oral antipruritics.

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645.2 Multisystem Medication Reactions

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See also Chapter 152.

Most cutaneous reactions that result from the use of systemic medications are confined to the skin and resolve without sequelae after discontinuation of the offending agent (Table 645-3). More severe drug eruptions may be life-threatening, making rapid recognition vital (see Chapter 654). Genetics and, particularly, ethnicity appear to play a major role in determination of the occurrence of multisystem medication reactions, particularly to anticonvulsants.

DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS SYNDROME)

DRESS syndrome, or drug rash with eosinophilia and systemic symptoms, is also called drug hypersensitivity syndrome or anticonvulsant hypersensitivity syndrome. It is classically seen 2-6 wk after initial exposure to an anticonvulsant (carbamazepine, phenobarbital, phenytoin, lamotrigine) or other drugs (allopurinol, minocycline, sulfonamides [dapsone, sulfasalazine], other antibiotics) and often manifests as the triad of **fever, rash,** and **hepatitis.** The skin rash is initially located on the head, upper trunk, and arms. A diffuse exanthem of pruritic, morbilliform papules is most common, though any morphology may be present (Fig. 645-9). Exfoliation early in the course, as seen in toxic epidermal necrolysis, is uncommon. If mucous membrane involvement occurs, it is usually mild. Prominent periocular or facial edema, cervical lymphadenopathy, pharyngitis, and malaise accompany this dramatic cutaneous eruption. *Eosinophilia (≥500/µL) and atypical lymphocytosis are common but not always present.* Hepatitis ranging from mild elevation of liver transaminase values to frank hepatic failure may also be accompanied by interstitial nephritis, pneumonitis, myocarditis, shock, and encephalitis; mortality rate from these complications approaches 10%. Late-onset thyroiditis and hypothyroidism may occur months later as a result of antimicrosomal antibodies directed against thyroid peroxidases involved in drug metabolism.

The proposed pathogenesis of anticonvulsant-induced DRESS syndrome relates to a heritable defect in the epoxide hydrolase pathway leading to accumulation of toxic metabolites and subsequent

Table 645-3 Drug Eruptions in Pediatric Patients

ERUPTION	KEY DRUGS	LESIONAL PATTERN	MUCOSAL CHANGES
Urticaria	Penicillins, cephalosporins, sulfonamides, aspirin/NSAIDs, radiocontrast media, TNF inhibitors	Pruritic erythematous wheals	None
Angioedema	Aspirin/NSAIDs, angiotensin-converting enzyme inhibitors	Swelling of subcutaneous and deep dermal tissues	May be present
Serum sickness–like reaction	Cephalosporins, penicillins, minocycline, bupropion, sulfonamides	Annular urticarial plaques	None
Exanthematous	Any drug	Erythematous macules and/or papules	None
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)	Phenytoin, phenobarbital, carbamazepine, lamotrigine, allopurinol, sulfonamides, dapsone, minocycline	Edema; erythematous macules and/or papules; sometimes vesicles or bullae	May be present
Lichenoid	Captopril, enalapril, β-blockers, gold salts, hydrochlorothiazide, hydroxychloroquine, penicillamine, griseofulvin, tetracycline, carbamazepine, phenytoin, NSAIDs	Discrete flat-topped, reddish purple papules and plaques	May be present
Fixed drug	Sulfonamides, ibuprofen, acetaminophen, tetracyclines, pseudoephedrine, barbiturates, lamotrigine, metronidazole, penicillin	Solitary to few erythematous, hyperpigmented plaques	Unusual
Pustular (acute generalized exanthematous pustulosis)	β-Lactam antibiotics, macrolides, clindamycin, terbinafine, calcium channel blockers, antimalarials	Generalized small pustules and papules	Unusual
Acneiform	Corticosteroids, androgens, lithium, iodides, phenytoin, isoniazid, tetracycline, B vitamins, azathioprine	Follicle-based inflammatory papules and pustules predominate	None
Pseudoporphyria	NSAIDs, cyclooxygenase-2 inhibitors, tetracyclines, furosemide	Photodistributed blistering and skin fragility	None
Vasculitis	Penicillins, NSAIDs, sulfonamides, cephalosporins	Purpuric papules, especially on the lower extremities; urticaria, hemorrhagic bullae, digital necrosis, pustules, ulcers	Rarely
Stevens-Johnson/toxic epidermal necrolysis	Sulfonamides, anticonvulsants, NSAIDs, allopurinol, dapsone	Target lesions, bullae, epidermal necrosis with detachment	Present
Drug-induced lupus	Minocycline, procainamide, hydralazine, isoniazid, penicillamine, carbamazepine, chlorpromazine, infliximab	Rarely has skin manifestations but may be urticarial, vasculitic, erythematous	Rare

NSAIDs, nonsteroidal antiinflammatory drugs; TNF, tumor necrosis factor.

Adapted from Paller AS, Mancini AJ, editors: Hurwitz clinical pediatric dermatology, *ed 3, Philadelphia, 2006, Elsevier/Saunders, p. 526.*

Figure 645-9 A 9 yr old boy with cerebral palsy and seizures treated with carbamazepine. Seventeen days after start of therapy he demonstrated fever, rash (exanthematous), lymphadenopathy, and nephritis, all part of a drug-induced hypersensitivity syndrome. *(From Schachner LA, Hansen RC, editors:* Pediatric dermatology, *ed 3, Philadelphia, 2003, Mosby, p. 1269.)*

Figure 645-10 Acute generalized exanthematous pustulosis is characterized by the acute onset of fever and generalized erythema with numerous, small, discrete, sterile, nonfollicular pustules. Pustules may appear in a few days after the drug therapy is started. Pustules resolve in less than 15 days, followed by desquamation. *(From Habif TP, editor:* Clinical dermatology, *ed 4, Philadelphia, 2004, Mosby, p. 490.)*

lymphocyte activation. Reactivation of herpesviruses, especially human herpesvirus 6, is also commonly associated with DRESS syndrome via an unknown pathogenic mechanism. The differential diagnosis includes Stevens-Johnson syndrome, viral exanthem, macrophage activation, and hemophagocytic syndromes, and GVHD in the appropriate clinical setting. DRESS syndrome is often distinguished from other medication reactions by its later onset following drug exposure and more persistent course. In addition to anticonvulsants, sulfonamides may cause similar symptoms on first exposure because of abnormalities in glutathione *S*-transferase pathways.

Withdrawal of the medication is the primary therapeutic intervention. Lymphocyte transformation tests and patch testing are helpful for identifying the offending drug when multiple suspect agents are present, but drug discontinuation should not be delayed while awaiting results. Symptomatic treatment of pruritus and pain can be accomplished with emollients and mid- to high-potency topical corticosteroids (twice daily for 1 wk). Oral corticosteroid therapy is necessary in the setting of rapidly evolving or severe hepatic or renal involvement. Counseling about increased risk with similar medications and in siblings is important. DRESS syndrome can have a relapsing course, both in the skin and other organ systems, well after the medication has been withdrawn and initial improvement achieved, necessitating close follow-up for several months.

SERUM SICKNESS–LIKE REACTION

Serum sickness–like reaction (SSLR) manifests as annular, urticarial, sharply marginated, coalescing plaques; these often have a lavender hue to the center. In addition, acral erythema/edema, arthritis/arthralgia, lymphadenopathy, and fever are often present. Unlike with true serum sickness (see Chapter 150), laboratory evidence of circulating immune complexes and multisystem involvement of vasculitis are typically absent. The differential diagnosis includes Kawasaki disease, connective tissue diseases, acute annular urticaria, and DRESS syndrome. SSLR is most commonly seen after exposure to various drugs (especially cefaclor and other antibiotics), as well as after certain infections and vaccinations. The cause of drug-related SSLR is unknown, but a toxic metabolite is suspected. In contrast to DRESS syndrome, SSLR typically occurs after repeated drug exposures. Medication withdrawal and symptomatic treatment with oral antihistamines and analgesics are recommended. Systemic glucocorticoids are indicated for severe joint involvement or extensive rashes.

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis is often drug-related (most commonly aminopenicillins, macrolides, sulfonamides), occurring within hours to days after drug exposure. It is characterized by many nonfollicular sterile pustules with underlying edema and erythema, typically beginning on the face and intertriginous regions (Fig. 645-10). Neutrophilia and fever are common, whereas eosinophilia is less common than in DRESS syndrome. The rash may burn or itch; mucous membrane involvement is rare and often mild. Internal organ involvement is not common and often is asymptomatic. A pustular smear is always indicated to rule out infection in the setting of leukocytosis, fever, and a pustular rash. Therapy consists of stopping the causative drug and offering symptomatic relief with moist dressings, emollients, and mid-potency topical corticosteroids (applied twice daily for 1 wk).

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Chapter 646

Principles of Therapy

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Competent skin care requires an appreciation of primary vs secondary lesions, a specific diagnosis, and knowledge of the natural course of the disease. If the diagnosis is uncertain, it is better to err on the side of less-aggressive rather than more-aggressive treatment.

In the use of topical medication, consideration of vehicle is as important as the specific therapeutic agent. Acute **weeping lesions** respond best to wet compresses, followed by lotions or creams. For **dry, thickened,** scaly skin, or for treatment of a contact allergic reaction possibly the consequence of a component of a topical medication, an ointment base is preferable, as it helps to occlude and moisten the affected area. Gels and solutions are most useful for the scalp and other hairy areas because of their faster absorption. The site of involvement is of considerable importance because the most desirable vehicle may not be cosmetically or functionally appropriate, such as an ointment on the face or hands. A patient's preference should also play a part in the choice of vehicle because compliance is poor if a medication is not acceptable to a patient. Ointments tend to sting less and are the least irritating. Cosmetically acceptable foam delivery systems have been developed, and the number of products and formulations available is increasing.

Most **lotions** are mixtures of water and oil that can be poured. After the water evaporates, the small amount of remaining oil covers the skin. Some shake lotions are a suspension of water and insoluble powder; as the water evaporates, cooling the skin, a thin film of powder covers the skin. **Creams** are emulsions of oil and water that are viscous and do not pour (more oil than in lotions). **Ointments** have oils and a small amount of water or no water at all; they feel greasy, lubricate dry skin, trap water, and aid in occlusion. Ointments without water usually require no preservatives because microorganisms require water to survive. Because of this, ointments often have the lowest number and concentration of ingredients, decreasing the risk of sensitizing the skin.

Therapy should be kept as simple as possible, and specific written instructions about the frequency and duration of application should be provided. Physicians should become familiar with one or two preparations in each category and should learn to use them appropriately. Prescribing nonspecific proprietary medications that may contain sensitizing agents should be avoided. Certain preparations, such as topical antihistamines and sensitizing anesthetics, are never indicated.

WET DRESSINGS

Wet dressings cool and dry the skin by evaporation and cleanse it by removing crusts and exudate, which would cause further irritation if permitted to remain. The dressings decrease pruritus, burning, and stinging sensations and are indicated for acutely inflamed moist or oozing dermatitis. Although various astringent and antiseptic substances may be added to the solution, cool or tepid tap water compresses are just as effective. Dressings of multiple layers of Kerlix, gauze, or soft cotton material may be saturated with water and remoistened as often as necessary. Compresses should be applied for 10-20 min at least every 4 hr and should usually be continued for 24-48 hr.

Alternatively, cotton long johns can be soaked in water and then wrung as dry as possible. These are placed on the child and covered with dry pajamas, preferably sleeper pajamas with feet. The child should sleep in these overnight. This type of dressing can be used nightly for up to 1 wk.

Wet dressings or wet wraps in conjunction with topical steroids may also be used in more severe cases of dermatitis (e.g., atopic dermatitis). In this method, a thin layer of the topical steroid is applied to the affected areas, which are then covered with warm, wet wraps for approximately 30 min to 1 hr 2-3 times daily. This method is especially effective in children with extensive and severe dermatitis.

BATH OILS, COLLOIDS, SOAPS

Bath oil has little benefit in the treatment of children. It offers little moisturizing effect but increases the risk of injury during a bath. Bath oil may lubricate the surface of the bathtub, causing an adult or child to fall when stepping into the tub. Tar bath solutions can be prescribed and may be helpful for psoriasis and atopic dermatitis. Colloids such as starch powder and colloidal oatmeal are soothing and antipruritic for some patients when added to the bathwater. Oilated colloidal oatmeal contains mineral oil and lanolin derivatives for lubrication if the skin is dry. These can also lubricate the bathtub surface. Ordinary bath soaps may be irritating and drying if patients have dry skin or dermatitis. Synthetic soaps are much less irritating. Fragrance-free soaps and cleansers are often better tolerated and less likely to irritate skin. When skin is acutely inflamed, avoidance of soap is advised.

LUBRICANTS

Lubricants, such as lotions, creams, and ointments, can be used as moisturizers for dry skin and as vehicles for topical agents such as corticosteroids and keratolytics. In general, ointments are the most effective emollients. Numerous commercial preparations are available. Some patients do not tolerate ointments, and some may be sensitized to a component of the lubricant; some preservatives in creams are also sensitizers. These preparations can be applied several times a day if necessary and tolerated. Maximal effect is achieved when they are applied to dry skin 2 or 3 times daily. Lotions containing menthol and camphor in an emollient vehicle can help control pruritus and dryness, but the use of moisturizers in addition to these products is best to decrease skin dryness.

SHAMPOOS

Special shampoos containing sulfur, salicylic acid, zinc, and selenium sulfide are useful for conditions in which there is scaling of the scalp, such as seborrheic dermatitis or psoriasis. Tar-containing shampoos are useful in these conditions. Most shampoos also contain surfactants and detergents. They should be used as frequently as necessary to control scaling. Patients should be instructed to leave the lathered shampoo in contact with the scalp for 5-10 minutes before thorough rinsing.

SHAKE LOTIONS

Shake lotions are useful antipruritic agents; they consist of a suspension of powder in a liquid vehicle. Water-dispersible oil may be added for lubrication. These preparations can be used effectively in combination with wet dressings for exudative dermatitis. Cooling occurs as the lotion evaporates and the powder deposited on the skin absorbs moisture.

POWDERS

Powders are hygroscopic and serve as absorptive agents in areas of excessive moisture. When dry, powders decrease friction between 2 surfaces. They are most useful in the intertriginous areas and between the toes, where maceration and abrasion may result from friction on movement. Coarse powders may cake; therefore, they should be of fine particle size and inert, unless medication has been incorporated in the formulation. The use of cornstarch-based powders in inflamed or broken skin may serve as a good growth environment for microorganisms and should be avoided.

PASTES

Pastes contain fine powder in ointment vehicles and are not often prescribed in current dermatologic therapy; in certain situations, however, they can be used effectively to protect vulnerable or damaged skin. A stiff zinc oxide paste is bland and inert and can be applied to the diaper area to prevent further irritation due to diaper dermatitis. Zinc oxide paste should be applied in a thick layer completely

obscuring the skin and is removed more easily with mineral oil than with soap and water.

KERATOLYTIC AGENTS

Urea-containing agents are hydrophilic; they hydrate the stratum corneum and make the skin more pliable. In addition, because urea dissolves hydrogen bonds and epidermal keratin, it is effective in treating scaling disorders. Concentrations of 10-40% are available in several commercial lotions and creams, which can be applied once or twice daily as tolerated. Salicylic acid is an effective keratolytic agent and can be incorporated into various vehicles in concentrations up to 6% to be applied 2 or 3 times daily. Salicylic acid preparations should not be used in treating small infants or on large surface areas or denuded skin; percutaneous absorption may result in salicylism. The α-hydroxy acids, particularly lactic acid and glycolic acid, are available in commercial preparations or can be incorporated in an ointment vehicle in concentrations up to 12%. Some creams contain both urea and lactic acid. The α-hydroxy acid preparations are useful for the treatment of keratinizing disorders and may be applied once or twice daily. Some patients complain of burning with the use of these agents; in such cases, the frequency of application should be decreased.

TAR COMPOUNDS

Tars are obtained from bituminous coal, shale, petrolatum (coal tars), and wood. They are antipruritic and astringent and appear to promote normal keratinization. They may be useful for chronic eczema and psoriasis, and their efficacy may be increased if the affected area is exposed to UV light after the tar has been removed. Tars should not be used for acute inflammatory lesions. Tars are often messy and unacceptable because they may stain and they have an odor. They may be incorporated into shampoos, bath oils, lotions, and ointments. A useful preparation for pediatric patients is liquor carbonis detergens 2-5% in a cream or ointment vehicle. Tar gel and tar in light body oil are relatively pleasant cosmetic preparations that cause minimal staining of skin and fabrics. Tars can also be incorporated into a vehicle with a topical corticosteroid. The frequency of application varies from 1-3 times daily, according to tolerance. Many children refuse to use tar preparations because of their odor and staining characteristics.

ANTIFUNGAL AGENTS

Antifungal agents are available as powders, lotions, creams, and ointments for the treatment of dermatophyte and yeast infections. Nystatin, naftifine, and amphotericin B are specific for *Candida albicans* and are ineffective in other fungal disorders. Tolnaftate is effective against dermatophytes but not against yeast. The spectrum for ciclopirox olamine includes the dermatophytes, *Malassezia furfur,* and *C. albicans.* The azoles clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, and sulconazole have a similar broad spectrum. Butenafine has a similar broad spectrum and also has antiinflammatory properties. Terbinafine has greater activity against dermatophytes but poorer activity against yeasts than the azoles. The topical antifungal agents should be applied 1-2 times a day for most fungal infections. All have low sensitizing potential; additives such as preservatives and stabilizers in the vehicles may cause allergic contact dermatitis. Ointments containing 6% benzoic acid and 3% salicylic acid are potent keratolytic agents that have also been used for the treatment of dermatophyte infections. Irritant reactions are common.

TOPICAL ANTIBIOTICS

Topical antibiotics have been used for many years to treat local cutaneous infections, although their efficacy, with the exception of mupirocin, fusidic acid and retapamulin, has been questioned. Ointments are the preferred vehicles (except in the treatment of acne vulgaris; see Chapter 669) and combinations with other topical agents such as corticosteroids are, in general, inadvisable. Whenever possible, the etiologic agent should be identified and treated specifically. Antibiotics in wide use as systemic preparations should be avoided because of the risk of bacterial resistance. The sensitizing potential of certain topical antibiotics, such as neomycin and nitrofurazone, should be kept in mind and avoided when possible. Mupirocin, fusidic acid, and retapamulin are the most effective topical agents currently available and are as effective as oral erythromycin in treatment of mild to moderate impetigo. Polysporin and bacitracin are not as effective.

TOPICAL CORTICOSTEROIDS

Topical corticosteroids are potent antiinflammatory agents and effective antipruritic agents. Successful therapeutic results are achieved in a wide variety of skin conditions. Corticosteroids can be divided into 7 different categories on the basis of strength (Table 646-1), but for practical purposes, 4 categories can be used: low, moderate, high, and super. Low-potency preparations include hydrocortisone, desonide, and hydrocortisone butyrate. Medium-potency compounds include amcinonide, betamethasone, flurandrenolide, fluocinolone, mometasone furoate, and triamcinolone. High-potency topical steroids include fluocinonide and halcinonide. Betamethasone dipropionate and clobetasol propionate are superpotent preparations and should be prescribed with care. Some of these compounds are formulated in several strengths according to clinical efficacy and degree of vasoconstriction. Physicians using topical steroids should become familiar with preparations within each class.

All corticosteroids can be obtained in various vehicles, including creams, ointments, solutions, gels, and aerosols. Some are available in a foam vehicle. Absorption is enhanced by an ointment or gel vehicle, but the vehicle should be selected on the basis of the type of disorder and the site of involvement. Frequency of application should be determined by the potency of the preparation, the location on the body, and the severity of the eruption. Applying a thin film 2 times daily usually suffices. Adverse local effects include cutaneous atrophy, striae, telangiectasia, acneiform eruptions, purpura, hypopigmentation, and increased hair growth. Systemic adverse effects of high-potency and superpotent topical steroids occur with long-term use and include poor growth, cataracts, and suppression of adrenal function.

Table 646-1 Potency of Topical Glucocorticosteroids

CLASS 1—SUPERPOTENT
Betamethasone dipropionate, 0.05% gel, ointment
Clobetasol propionate cream, ointment, 0.05%
Halobetasol propionate cream, ointment, 0.05%
CLASS 2—POTENT
Betamethasone dipropionate cream 0.05%
Desoximetasone cream, ointment, gel 0.05% and 0.25%
Fluocinonide cream, ointment, gel, 0.05%
CLASS 3—UPPER MID-STRENGTH
Betamethasone dipropionate cream, 0.05%
Betamethasone valerate ointment, 0.1%
Fluticasone propionate ointment, 0.005%
Mometasone furoate ointment, 0.1%
Triamcinolone acetonide cream, 0.5%
CLASS 4—MID-STRENGTH
Desoximetasone cream, 0.05%
Fluocinolone acetonide ointment, 0.025%
Triamcinolone acetonide ointment, 0.1%
CLASS 5—LOWER MID-STRENGTH
Betamethasone valerate cream/lotion, 0.1%
Fluocinolone acetonide cream, 0.025%
Fluticasone propionate cream, 0.05%
Triamcinolone acetonide cream/lotion, 0.1%
CLASS 6—MILD STRENGTH
Desonide cream, 0.05%
CLASS 7—LEAST POTENT
Topicals with hydrocortisone, dexamethasone, flumethasone, methylprednisolone, and prednisolone

From Weston WL, Lane AT, Morelli JG: Color textbook of pediatric dermatology, *ed 4, St. Louis, 2007, Mosby, p. 418.*

The relative skin thickness should be considered in regard to the selection of class of steroid (see Table 646-1). Thin skin such as the eyelids, face, groin, and genitalia will absorb a substantial amount of medication compared to the thickest skin on the palms and soles. One adult fingertip's worth of medication is enough to cover an area the size of an adult palm and is approximately half a gram of medication. Knowing the area being treated and which medication class to prescribe can decrease potential for side effects.

In selected circumstances, corticosteroids may be administered by intralesional injection (acne cysts, keloids, psoriatic plaques, alopecia areata, persistent insect bite reactions). Only experienced physicians should use this method of administration.

TOPICAL NONSTEROIDAL ANTIINFLAMMATORY AGENTS

Calcineurin-inhibiting antiinflammatory agents that inhibit T-cell activation may be used instead of topical steroids for the treatment of atopic dermatitis and other inflammatory conditions. These agents are pimecrolimus and tacrolimus. They do not have the adverse local effects seen with topical steroid. Stinging with application is the most common complaint and may be lessened by mixing the medication with an ointment such as petrolatum jelly for the initial applications. These agents are only as strong as medium-potency topical steroids. They should be used with caution owing to evidence from animal experiments and case reports of an increased risk of lymphoma.

SUNSCREENS

Sunscreens are of 2 general types: (1) those, such as zinc oxide and titanium dioxide, that absorb all wavelengths of the UV and visible spectrums; and (2) a heterogeneous group of chemicals that selectively absorb energy of various wavelengths within the UV spectrum. In addition to the spectrum of light that is blocked, other factors to be considered include cosmetic acceptance, sensitizing potential, retention on skin while swimming or sweating, required frequency of application, and cost. Sunscreen ingredients include para-aminobenzoic acid (PABA) with ethanol, PABA esters, cinnamates, and benzophenone. These block transmission of the majority of solar UVB and some UVA wavelengths. Avobenzone and ecamsule are more effective in blocking UVA. Antioxidants may also be found in some sunscreens. Lip protectants that absorb in the UVB range are also available. Sunscreens are designated by sun protection factor (SPF). The SPF is defined as the amount of time to develop a mild sunburn with the sunscreen compared with the amount of time without the sunscreen. A minimum SPF factor of 15 is required for most fair-skinned individuals to prevent sunburn; however, an SPF of 30 should be recommended most often. The higher the SPF, the better the protection is against UVB rays. Sunscreens do not include any measurement of the efficacy in blocking UVA. The efficacy of these agents depends on careful attention to instructions for use. Chemical sunscreens should be applied at least 30 min before sun exposure to permit penetration into the epidermis, again on arrival at the destination, and every subsequent hour when exposed to direct sunlight. Most patients with photosensitivity eruptions require protection by agents that absorb both UVB and UVA wavelengths (see Chapter 656).

Although sunscreens do confer photoprotection and may decrease the development of nevi, protection is incomplete against all harmful UV light. Midday (10 AM to 4 PM) sun avoidance is the primary method of photoprotection. Clothing, hats, and staying in the shade offer additional sun protection.

LASER THERAPY

The vascular-specific pulsed dye laser therapy is used mainly for the treatment of capillary malformations (port-wine stains). Spider telangiectasia, small facial pyogenic granulomas, superficial and ulcerated hemangioma, and warts may also be treated. Vascular-specific pulsed dye lasers produce light that is readily absorbed by oxyhemoglobin, producing selective photothermolysis of vascular lesions.

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Chapter 647

Diseases of the Neonate

Kari L. Martin

Minor evanescent lesions of newborn infants, particularly when florid, may cause undue concern. Most of the entities are relatively common, benign, and transient and do not require therapy.

SEBACEOUS HYPERPLASIA

Minute, profuse, yellow-white papules are frequently found on the forehead, nose, upper lip, and cheeks of a term infant; they represent hyperplastic sebaceous glands (Fig. 647-1). These tiny papules diminish gradually in size and disappear entirely within the 1st few wk of life.

MILIA

Milia are superficial epidermal inclusion cysts that contain laminated keratinized material. The lesion is a firm cyst, 1-2 mm in diameter, and pearly, opalescent white. Milia may occur at any age but in neonates are most frequently scattered over the face and gingivae and on the midline of the palate, where they are called **Epstein pearls**. Milia exfoliate spontaneously in most infants and may be ignored; those that appear in scars or sites of trauma in older children may be gently unroofed and the contents extracted with a fine-gauge needle.

SUCKING BLISTERS

Solitary or scattered superficial bullae present at birth on the upper limbs of infants at birth are presumably induced by vigorous sucking on the affected part in utero. Common sites are the radial aspect of the forearm, thumb, and index finger. These bullae resolve rapidly without sequelae and should be distinguished from sucking pads (calluses), which are found on the lips in the 1st few mo and are a result of combined intracellular edema and hyperkeratosis. The diagnosis can be confirmed by observing the neonate sucking the affected area.

CUTIS MARMORATA

When a newborn infant is exposed to low environmental temperatures, an evanescent, lacy, reticulated red and/or blue cutaneous vascular

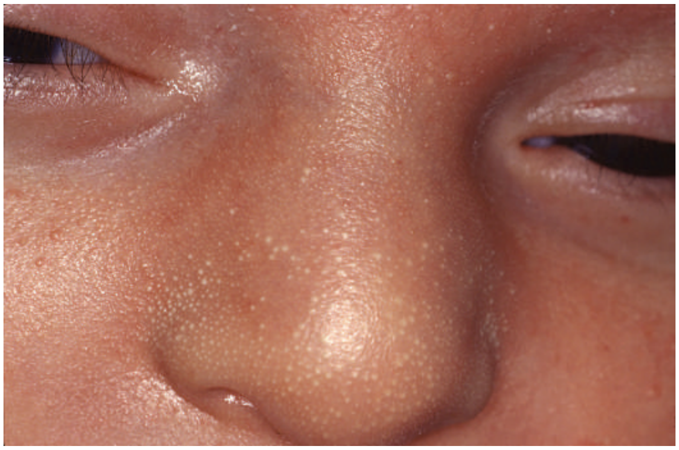

Figure 647-1 Sebaceous hyperplasia. Minute white-yellow papules on the nose of a newborn.

Figure 647-2 Newborn girl with reticulate erythema/livedo on legs, right arm, and cheeks. *(From Pleimes M, Gottler S, Weibel L: Characteristic congenital reticular erythema: cutis marmorata telangiectatica congenital.* J Pediatr *163:604, 2013, Fig. 1.)*

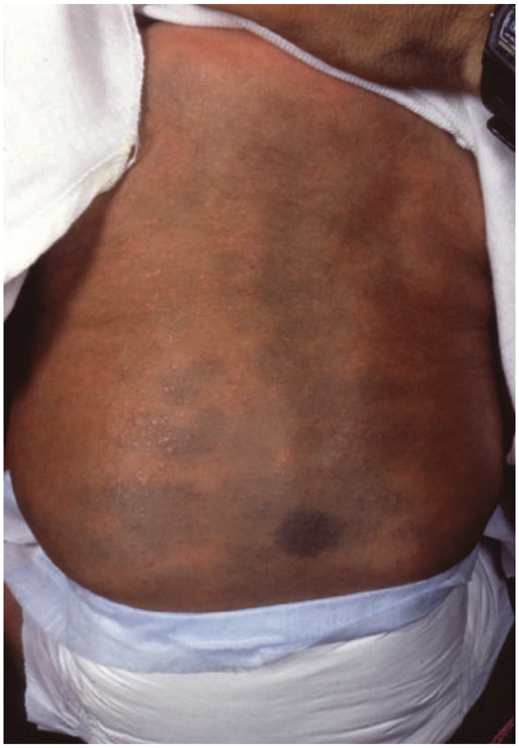

Figure 647-3 Extensive Mongolian spot on the back of a newborn. *(Courtesy of Fitzsimons Army Medical Center teaching file.)*

pattern appears over most of the body surface. This vascular change represents an accentuated physiologic vasomotor response that disappears with increasing age, although it is sometimes discernible even in older children. **Cutis marmorata telangiectatica congenita** is clinically similar, but the lesions are more intense, may be segmental, are persistent, and may be associated with loss of dermal tissue, epidermal atrophy, and ulceration (Fig. 647-2). The lower extremities are usually affected with limb atrophy noted on the affected side. Gradual fading of the livid erythema occurs over 3-5 yr, but limb asymmetry is permanent.

HARLEQUIN COLOR CHANGE

A rare but dramatic vascular event, harlequin color change occurs in the immediate newborn period and is most common in low-birthweight infants. It probably reflects an imbalance in the autonomic vascular regulatory mechanism. When the infant is placed on 1 side, the body is bisected longitudinally into a pale upper half and a deep red dependent half. The color change lasts only for a few minutes and occasionally affects only a portion of the trunk or face. Changing the infant's position may reverse the pattern. Muscular activity causes generalized flushing and obliterates the color differential. Repeated episodes may occur but do not indicate permanent autonomic imbalance.

NEVUS SIMPLEX (SALMON PATCH)

Nevus simplex is a small, pale pink, ill-defined, vascular macule that occurs most commonly on the glabella, eyelids, upper lip, and nuchal area of 30-40% of normal newborn infants. These lesions, which represent localized **vascular ectasia,** persist for several months and may become more visible during crying or changes in environmental temperature. Most lesions on the face eventually fade and disappear completely, although lesions occupying the entire central forehead often do not. Those on the posterior neck and occipital areas usually persist. The facial lesion should not be confused with a port-wine stain, which is a permanent lesion and may be associated with Sturge-Weber syndrome. Nevus simplex is usually symmetric, with lesions on both eyelids or on both sides of midline. Port-wine stains are often larger and unilateral, and they usually end along the midline (see Chapter 650).

DERMAL MELANOCYTOSIS (MONGOLIAN SPOTS)

Dermal melanocytosis, which appears as blue or slate-gray macular lesions, has variably defined margins. It occurs most commonly in the presacral area but may be found over the posterior thighs, legs, back, and shoulders (Fig. 647-3). The spots may be solitary or numerous and often involve large areas. The incidence of these lesions varies widely across ethnicities, being most common in African-American, Asian, and Hispanic infants (25-80% depending on the study) and less common in white infants (around 6%). The peculiar hue of these macules is a result of the dermal location of melanin-containing melanocytes (mid-dermal melanocytosis) that are presumably arrested in their migration from neural crest to epidermis. They usually fade during the 1st few yr of life as a result of darkening of the overlying skin. Malignant degeneration does not occur. The characteristic appearance and congenital onset distinguish these spots from the bruises of child abuse. Rarely Mongolian spots are associated with Hurler syndrome or GM_1 gangliosidosis type 1.

ERYTHEMA TOXICUM

A benign, self-limited, evanescent eruption, erythema toxicum occurs in approximately 50% of full-term infants; preterm infants are affected less commonly. The lesions are firm, yellow-white, 1-2 mm papules or pustules with a surrounding erythematous flare (Fig. 647-4). At times, splotchy erythema is the only manifestation. Lesions may be sparse or numerous and either clustered in several sites or widely dispersed over much of the body surface. The palms and soles are usually spared. Peak incidence occurs on the 2nd day of life, but new lesions may erupt during the 1st few days as the rash waxes and wanes. Onset may occasionally be delayed for a few days to weeks in premature infants. The pustules form below the stratum corneum or deeper in the epidermis and represent collections of eosinophils that also accumulate around the upper portion of the pilosebaceous follicle. The **eosinophils** can be demonstrated in Wright-stained smears of the intralesional contents. Cultures are sterile.

The cause of erythema toxicum is unknown. The lesions can mimic pyoderma, candidiasis, herpes simplex, transient neonatal pustular melanosis, and miliaria but can be differentiated by the characteristic infiltrate of eosinophils and the absence of organisms on a stained smear. The course is brief, and no therapy is required. Incontinentia pigmenti and eosinophilic pustular folliculitis also have eosinophilic

Figure 647-4 Erythema toxicum on the trunk of a newborn infant.

Figure 647-5 Transient neonatal pustular melanosis. Multiple papules present at birth on the arm of an infant. *(From Weston WL, Lane AT, Morelli JG, editors:* Color textbook of pediatric dermatology, *ed 3, Philadelphia, 2002, Mosby, p. 331.)*

infiltration but can be distinguished by their distribution, histologic type, and chronicity.

TRANSIENT NEONATAL PUSTULAR MELANOSIS

Pustular melanosis, which is more common among African-American than among white infants, is a transient, benign, self-limited dermatosis of unknown etiology that is characterized by 3 types of lesions: (1) evanescent superficial pustules, (2) ruptured pustules with a collarette of fine scale, at times with a central hyperpigmented macule, and (3) hyperpigmented macules (Fig. 647-5). Lesions are present at birth, and 1 or all types of lesions may be found in a profuse or sparse distribution. Pustules represent the early phase of the disorder, and macules, the late phase. The pustular phase rarely lasts more than 2-3 days; hyperpigmented macules may persist for as long as 3 mo. Sites of predilection are the anterior neck, forehead, and lower back, although the scalp, trunk, limbs, palms, and soles may be affected.

The active phase shows an intracorneal or subcorneal pustule filled with **polymorphonuclear leukocytes,** debris, and an occasional eosinophil. The macules are characterized only by increased melanization of epidermal cells. Cultures and smears can be used to distinguish these pustules from those of pyoderma and erythema toxicum, because the lesions of pustular melanosis do not contain bacteria or dense aggregates of eosinophils. No therapy is required.

INFANTILE ACROPUSTULOSIS

Onset of infantile acropustulosis generally occurs at 2-10 mo of age; lesions are occasionally noted at birth. Darkly pigmented males have a predisposition, but infants of both sexes and all races may be affected. The cause is unknown.

The lesions are initially discrete erythematous papules that become vesiculopustular within 24 hr and subsequently crust before healing. They are intensely pruritic. Preferred sites are the palms of the hands and the soles and sides of the feet, where the lesions may be extensive. A less dense eruption may be found on the dorsum of the hands and feet, ankles, and wrists. Pustules occasionally occur elsewhere on the body. Each episode lasts 7-14 days, during which time pustules continue to appear in crops. After a 2-4 wk remission, a new outbreak follows. This cyclic pattern continues for approximately 2 yr; permanent resolution is often preceded by longer intervals of remission between periods of activity. Infants with acropustulosis are otherwise well.

Wright-stained smears of intralesional contents show abundant neutrophils or, occasionally, a predominance of eosinophils. Histologically, well-circumscribed, subcorneal, neutrophilic pustules, with or without eosinophils, are noted.

The **differential diagnosis** in neonates includes transient neonatal pustular melanosis, erythema toxicum, milia, cutaneous candidiasis, and staphylococcal pustulosis. In older infants and toddlers, additional diagnostic considerations include scabies, dyshidrotic eczema, pustular psoriasis, subcorneal pustular dermatosis, and hand-foot-and-mouth disease. A therapeutic trial of a scabicide is warranted in equivocal cases.

Therapy is directed at minimizing discomfort for infants. Topical corticosteroid preparations and/or oral antihistamines decrease the severity of the pruritus and an infant's irritability. Dapsone (2 mg/kg/day taken orally twice daily) is effective but has potentially serious side effects—notably, hemolytic anemia and methemoglobinemia—and should be used with caution.

EOSINOPHILIC PUSTULAR FOLLICULITIS

Eosinophilic pustular folliculitis is defined as recurrent crops of pruritic, coalescing, follicular papulopustules on the face, trunk, and extremities. Fifty percent of patients have peripheral eosinophilia with eosinophil counts exceeding 5%, and approximately 30% have leukocytosis (>10,000 leukocytes/mm^3).

Infants account for <10% of all cases of eosinophilic pustular folliculitis. The clinical and histologic appearances of this disorder in infants closely resemble those in immunocompetent adults, with minor exceptions. In infants, the lesions are most prominent on the scalp, although they also occur on the trunk and extremities and occasionally are found on the palms and soles. The classic annular and polycyclic appearance with centrifugal enlargement is not seen in infants. Adults have an eosinophilic infiltrate that invades sebaceous glands and the outer root sheath of hair follicles, often leading to spongiosis in the outer root sheath. The eosinophilic infiltrate in most infants, however, is perifollicular, without spongiosis in the outer root sheath. Because of the slight differences between clinical findings and course in immunocompetent adults, immunocompromised adults and those in infants, it has been proposed that eosinophilic pustular folliculitis be **subclassified** into classic, HIV-related, and infantile forms. The **differential diagnosis** includes erythema toxicum neonatorum, infantile acropustulosis, localized pustular psoriasis, pustular folliculitis, and transient neonatal pustular melanosis.

High-potency or superpotent topical corticosteroids are the most effective treatment (see Table 646-1 in Chapter 646).

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Chapter 648

Cutaneous Defects

Kari L. Martin

SKIN DIMPLES

Cutaneous depressions over bony prominences and in the acral area, at times associated with pits and creases, may occur in normal children and in association with dysmorphologic syndromes. Skin dimples may develop in utero as a result of interposition of tissue between a sharp bony point and the uterine wall, which leads to decreased subcutaneous tissue formation.

Dimples may also be present overlying an area of **bone hypoplasia**. Bilateral acromial skin dimples are usually an isolated finding, but they are also seen in association with deletion of the long arm of chromosome 18. Dimples tend to occur over the patella in congenital rubella, over the lateral aspects of the knees and elbows in prune-belly syndrome, on the pretibial surface in campomelic dwarfs, and in the shape of an H on the chin in whistling-face syndrome.

Sacral dimples are common and usually are isolated findings. They may be seen in multiple syndromes or in association with spina bifida occulta and diastomyelia. Association with a mass or other cutaneous stigma (hair, aplasia cutis, lipoma, hemangioma) should increase concern for underlying **spinal dysraphism** (see Chapter 591). Ultrasonography during the 1st 3 mo of life, before ossification of the posterior elements of the lower spine, may provide a cost-effective, noninvasive method of assessing any associated lumbosacral spine abnormalities in infants with an isolated sacral dimple. *Nonetheless, MRI of the spine is indicated if there is a strong suspicion of a spinal dysraphism.*

REDUNDANT SKIN

Loose folds of skin must be differentiated from a congenital defect of elastic tissue or collagen such as cutis laxa, Ehlers-Danlos syndrome, or pseudoxanthoma elasticum. Redundant skin over the posterior part of the neck is common in the Turner, Noonan, Down, and Klippel-Feil syndromes and monosomy 1p36; more generalized folds of skin occur in infants with trisomy 18 and short-limbed dwarfism.

AMNIOTIC CONSTRICTION BANDS

Partial or complete constriction bands that produce defects in extremities and digits are found in 1 in 10,000-45,000 otherwise normal infants. Constrictive tissue bands are caused by primary amniotic rupture, with subsequent entanglement of fetal parts, particularly limbs, in shriveled fibrotic amniotic strands. This event is probably sporadic, with negligible risk of recurrence. Formation of constrictive tissue bands is associated with abdominal trauma, amniocentesis, and hereditary defects of collagen such as Ehlers-Danlos syndrome and osteogenesis imperfecta.

Adhesive bands involve the craniofacial area and are associated with severe defects such as encephalocele and facial clefts. Adhesive bands result from broad fusion between disrupted fetal tissue and an intact amniotic membrane. The craniofacial defects appear not to be caused by constrictive amniotic bands but to result from a vascular disruption sequence with or without cephaloamniotic adhesion (see Chapter 108).

The **limb–body wall complex** involves vascular disruption early in development, affecting several embryonic structures; it includes at least 2 of the following 3 characteristics: exencephaly or encephalocele with facial clefts, thoracoschisis and/or abdominoschisis, and limb defects.

PREAURICULAR SINUSES AND PITS

Pits and sinus tracts anterior to the pinna may be a result of imperfect fusion of the tubercles of the 1st and 2nd branchial arches. These anomalies may be unilateral or bilateral, may be familial, are more common among females and African-Americans, and at times are associated with other anomalies of the ears and face. Preauricular pits are present in **branchiootorenal dysplasia 1 syndrome** (*EYA-1* gene), an autosomal dominant disorder that consists of external ear malformations, branchial fistulas, hearing loss, and renal anomalies. When the tracts become chronically infected, retention cysts may form and drain intermittently; such lesions may require excision.

Figure 648-1 Accessory tragus on cheek along jaw line.

ACCESSORY TRAGI

An accessory tragus typically appears as a single pedunculated, flesh-colored papule in the preauricular region anterior to the tragus. Less commonly, accessory tragi are multiple or bilateral, and may be located in the preauricular area, on the cheek along the line of the mandible (Fig. 648-1), or on the lateral aspect of the neck anterior to the sternocleidomastoid muscle. In contrast to the rest of the pinna, which develops from the 2nd branchial arch, the tragus and accessory tragi derive from the 1st branchial arch. Accessory tragi may occur as isolated defects or in chromosomal 1st branchial arch syndromes that include anomalies of the ears and face, such as cleft lip, cleft palate, and mandibular hypoplasia. An accessory tragus is consistently found in **oculoauriculovertebral syndrome** (**Goldenhar syndrome**). Surgical excision is appropriate.

BRANCHIAL CLEFT AND THYROGLOSSAL CYSTS AND SINUSES

Cysts and sinuses in the neck may be formed along the course of the 1st, 2nd, 3rd, or 4th branchial clefts as a result of improper closure during embryonic life. Second branchial cleft cysts are the most common. The lesions may be unilateral or bilateral (2-3%) and may open onto the cutaneous surface or drain into the pharynx. Secondary infection is an indication for systemic antibiotic therapy. These anomalies may be inherited as autosomal dominant traits.

Thyroglossal cysts and fistulas are similar defects located in or near the midline of the neck; they may extend to the base of the tongue. A pathognomonic sign is vertical motion of the mass with swallowing and tongue protrusion. In nearly 50% of affected children, the cyst or fistula manifests as an infected midline upper neck mass. Cysts in the tongue base may be differentiated from an undescended lingual thyroid by radionuclide scanning. Unlike branchial cysts, a thyroglossal duct cyst often appears after an upper respiratory infection (see Chapter 563).

SUPERNUMERARY NIPPLES

Solitary or multiple accessory nipples may occur in a unilateral or bilateral distribution along a line from the anterior axillary fold to the inguinal area. They are more common among African-American (3.5%) than white (0.6%) children. Accessory nipples may or may not

have areolae and may be mistaken for congenital nevi. They may be excised for cosmetic reasons. Renal or urinary tract anomalies and hematologic abnormalities may rarely occur in children with this finding (see Chapter 551).

APLASIA CUTIS CONGENITA (CONGENITAL ABSENCE OF SKIN)

Developmental absence of skin is usually noted on the scalp as multiple or solitary (70%), noninflammatory, well-demarcated, oval or circular 1-2 cm ulcers (Table 648-1). The appearance of lesions varies, depending on when they occurred during intrauterine development. Those that form early in gestation may heal before delivery and appear as atrophic, fibrotic scars with associated alopecia, whereas more recent defects may manifest as ulcerations. Most occur at the vertex of the scalp just lateral to the midline, but similar defects may also occur on the face, trunk, and limbs, where they are often symmetric and usually associated with an intrauterine fetal demise of a twin (**fetus papyraceus**). The depth and size of the ulcer varies. Only the epidermis and upper dermis may be involved, resulting in minimal scarring or hair loss, or less often the defect may extend to the deep dermis, to the subcutaneous tissue, and, rarely, to the periosteum, skull, and dura. Lesions may be surrounded by a collar of hair (Fig. 648-2).

Diagnosis is made on the basis of physical findings indicative of in utero disruption of skin development. Lesions are sometimes mistakenly attributed to scalp electrodes or obstetric trauma. Most are sporadic, but autosomal dominant and recessive cases occur as well; some are due to mutations in *BMS1*, a ribosomal guanosine triphosphatase.

Table 648-1 Freiden's Classification of Aplasia Cutis Congenita

GROUP	DEFINITION	INHERITANCE
1	Isolated scalp involvement; may be associated with single defects	AD
2	Scalp ACC with limb reduction defects (Adams-Oliver syndrome); may be associated with encephalocele	AD
3	Scalp ACC with epidermal nevus	Sporadic
4	ACC overlying occult spinal dysraphism, spina bifida, or meningoencephalocele	Sporadic
5	ACC with placental infarcts, and/or fetus papyraceus	Sporadic
6	ACC with epidermolysis bullosa	AD or AR
7	ACC localized to extremities without blistering; usually affecting pretibial areas and dorsum of hands and feet	AD or AR
8	ACC caused by teratogens (e.g., varicella, herpes, methimazole)	Sporadic
9	ACC associated with malformation syndromes (e.g., trisomy 13, deletion 4p–, deletion Xp22.1, ectodermal dysplasia, Johanson-Blizzard syndrome, Adams-Oliver syndrome)	Variable

ACC, Aplasia cutis congenital; AD, autosomal dominant; AR, autosomal recessive.

Modified from Frieden IJ: Aplasia cutis congenital: a clinical review and proposal for classification. J Am Acad Dermatol *14:646–660, 1986.*

Although most individuals with aplasia cutis congenita have no other abnormalities, these lesions may be associated with isolated physical anomalies or with malformation syndromes, including Opitz, Adams-Oliver, oculocerebrocutaneous, Johanson-Blizzard, and 4p(–), X-p22 microdeletion syndromes, trisomy 13-15, and chromosome 16-18 defects (see Table 648-1). Aplasia cutis congenita may also be found in association with an overt or underlying embryologic malformation, such as meningomyelocele, gastroschisis, omphalocele, or spinal dysraphism. Aplasia cutis congenita in association with fetus papyraceus is apparently caused by ischemic or thrombotic events in the placenta and fetus. Blistering or skin fragility and/or absence or deformity of nails in association with aplasia cutis congenita is a well-recognized manifestation of **epidermolysis bullosa.**

Major complications are rare and more often associated with large, stellate lesions of the midline parietal scalp. Hemorrhage, secondary local infection, and meningitis have been reported. If the defect is small, recovery is uneventful, with gradual epithelialization and formation of a hairless atrophic scar over a period of several weeks. Small bony defects usually close spontaneously in the 1st yr of life. Large or numerous scalp defects may require repair, but care must be taken as abnormal underlying venous structures have complicated surgical repair. Truncal and limb defects, despite being large, usually epithelialize and form atrophic scars, which can later be revised.

FOCAL FACIAL DERMAL DYSPLASIAS

The focal facial dermal dysplasias (FFDDs) are a rare group of conditions sharing bitemporal or preauricular lesions resembling scars or aplasia cutis congenita. FFDD1 (Brauer syndrome) is inherited in an autosomal dominant fashion and typically mild associated facial features. FFDD2 (Brauer-Setleis syndrome) and FFDD3 (Setleis syndrome) are associated with thin, puckered periorbital skin, distichiasis and/or absent eyelashes, upslating palpebral fissures, flat nasal bridge, large lips and redundant facial skin. FFDD2 is inherited in an autosomal dominant fashion whereas FFDD3 is autosomal recessive and caused by mutations in *TWIST2*. FFDD4 has no other related skin findings; it is inherited both in autosomal dominant and recessive manners and is caused by mutations in *CYP26C1*.

FOCAL DERMAL HYPOPLASIA (GOLTZ SYNDROME)

A rare congenital mesoectodermal and ectodermal disorder, focal dermal hypoplasia is characterized by dysplasia of connective tissue in the skin and skeleton. This disorder is an X-linked dominant disorder caused by mutations in the *PORCN* gene. It manifests as numerous soft tan papillomas. Other cutaneous findings include linear atrophic

Figure 648-2 Solitary scalp vertex lesion of aplasia cutis congenita with hair collar.

Figure 648-3 Reticulated dyspigmentation on neck of patient with dyskeratosis congenita.

lesions; reticulated hypopigmentation and hyperpigmentation; telangiectasias; congenital absence of skin; angiofibromas presenting as verrucous excrescences; and papillomas of the lips, tongue, circumoral region, vulva, anus, and the inguinal, axillary, and periumbilical areas. Partial alopecia, sweating disorders, and dystrophic nails are additional, less common ectodermal anomalies. The most frequent skeletal defects are syndactyly, clinodactyly, polydactyly, and scoliosis. **Osteopathia striata** are fine parallel vertical stripes noted on radiographs in the metaphyses of long bones of patients with this disorder; these are highly characteristic of focal dermal hypoplasia but are not pathognomonic. Many ocular abnormalities, the most common of which are colobomas, strabismus, nystagmus, and microphthalmia, are also characteristic. Small stature, dental defects, soft tissue anomalies, and peculiar dermatoglyphic patterns are also common. Cognitive impairment occurs occasionally.

DYSKERATOSIS CONGENITA (ZINSSER-ENGMAN-COLE SYNDROME)

Dyskeratosis congenita, a rare familial syndrome, consists classically of the triad of reticulated hyperpigmentation of the skin (Fig. 648-3), dystrophic nails, and mucous membrane leukoplakia in association with immunologic and hematologic abnormalities. Patients with dyskeratosis congenita also show signs of premature aging and increased occurrence of cancer, especially squamous cell carcinoma. Dyskeratosis congenita may be X-linked recessive (*DKC-1* gene), autosomal dominant (*hTERC* and *TINF2* genes), or autosomal recessive (*NOLA3* gene). Onset occurs in childhood, most commonly as **nail dystrophy.** The nails become atrophic and ridged longitudinally with progression to pterygia and complete nail loss. Skin changes usually appear after onset of nail changes and consist of reticulated gray-brown pigmentation, atrophy, and telangiectasia, especially on the neck, face, and chest. Hyperhidrosis and hyperkeratosis of the palms and soles, sparse scalp hair, and easy blistering of the hands and feet are also characteristic. Blepharitis, ectropion, and excessive tearing because of atresia of the lacrimal ducts are occasional manifestations. Oral leukokeratosis may give rise to squamous cell carcinoma. Other mucous membranes, including conjunctival, urethral, and genital, may be involved. Infection, malignancy, pulmonary fibrosis and bone marrow failure are common, and death before age 40 yr is typical.

CUTIS VERTICIS GYRATA

Cutis verticis gyrata, an unusual alteration of the scalp that is more common in males, may be present from birth or may develop during adolescence. The scalp is characterized by convoluted elevated folds, 1-2 cm in thickness, usually in the fronto-occipital axis. Unlike the lax skin of other disorders, the convolutions cannot generally be flattened by traction. Primary cutis gyrata may be associated with intellectual disability, retinitis pigmentosa, sensorineural deafness, and thyroid aplasia. Secondary cutis gyrata may be due to chronic inflammatory diseases, tumors, nevi, and acromegaly.

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Chapter 649

Ectodermal Dysplasias

Kari L. Martin

Ectodermal dysplasia (ED) is a heterogeneous group of disorders characterized by a constellation of findings involving defects of 2 or more of the following: teeth, skin, and appendageal structures including hair, nails, and eccrine and sebaceous glands. Although more than 150 EDs have been described, the majority are rare.

HYPOHIDROTIC ECTODERMAL DYSPLASIA

The syndrome known as hypohidrotic ectodermal dysplasia (HED) manifests as a triad of defects: partial or complete absence of sweat glands, anomalous dentition, and hypotrichosis. There are 4 recognized types of HED (Table 649-1); HED-1 (X-linked recessive) is most common.

In HED, affected patients are unable to sweat and may experience episodes of high fever in warm environments, which may be mistakenly considered to be fevers of **unknown origin.** This error is particularly common in infancy, when the facial changes are not easily appreciated. Diagnosis at this time may be made using the starch-iodine test or palmar or scalp biopsy. Scalp biopsy is the most sensitive and is 100% specific. The typical facies are characterized by frontal bossing; malar hypoplasia; a flattened nasal bridge; recessed columella; thick, everted lips; wrinkled, hyperpigmented periorbital skin; and prominent, low-set ears (Fig. 649-1). The skin over the entire body is dry, finely wrinkled, and hypopigmented, often with a prominent venous pattern. Extensive peeling of the skin is a clinical clue to diagnosis in the newborn period. The paucity of sebaceous glands may account for the dry skin. The scalp hair is sparse, fine, and lightly pigmented, and eyebrows and lashes are sparse or absent. Other body hair is also sparse or absent. Sexual hair growth is normal. Anodontia or hypodontia with widely spaced, conical teeth is a consistent feature (Fig. 649-1). Otolaryngic and ophthalmologic abnormalities secondary to decreased saliva and tear production are seen. The incidence of atopic diseases in children with HED is high. Gastroesophageal reflux is common and may play a role in failure to thrive, which is seen in 20% of cases. Sexual development is usually normal. Historically, the infant mortality rate has been 30%. Carrier females of X-linked HED have no or variable clinical manifestations.

Hypohidrotic ED with immune deficiencies causes similar findings in sweating and hair and nail development, in association with a **dysgammaglobulinemia.** Significant mortality is seen from recurrent infections.

Treatment of children with HED includes protecting them from exposure to high ambient temperatures. Early dental evaluation is necessary so that prostheses can be provided for cosmetic reasons and for adequate nutrition. The use of artificial tears prevents damage to the cornea in patients with defective lacrimation. Alopecia may necessitate the wearing of a wig to improve appearance.

Figure 649-1 Hypohidrotic ectodermal dysplasia is characterized by pointed ears, fine hair, periorbital hyperpigmentation, midfacial hypoplasia, and pegged teeth. *(Courtesy of the Fitzsimons Army Medical Center teaching file.)*

Table 649-1 Four Recognized Types of Anhidrotic Ectodermal Dysplasia

TYPE	INHERITANCE	GENE DEFECT
ED-1	X-linked recessive	Ectodysplasin A *(EDA)*
ED-2	Autosomal recessive	Ectodysplasin A anhidrotic receptor *(EDAR)* EDAR-associated death gene *(EDARADD)*
ED-3	Autosomal dominant	*EDAR* *EDARADD*
ED-anhidrotic with immune deficiency	X-linked recessive Autosomal dominant	*IκK-γ (NEMO)* *NFκB-IA*

HIDROTIC ECTODERMAL DYSPLASIA (CLOUSTON SYNDROME)

The salient features of the autosomal dominant disorder hidrotic ED are dystrophic, hypoplastic, or absent nails; sparse hair; and hyperkeratosis of the palms and soles. Conjunctivitis and blepharitis are common. The dentition and sweating are always normal. Absence of eyebrows and eyelashes and hyperpigmentation over the knees, elbows, and knuckles have been noted in some affected individuals. Mutations in the *GJB6* gene encoding the gap junction protein connexin 30 are responsible for this disorder. A similar disorder associated with deafness has been described with mutations in the *GJB2* gene encoding the connexin 26 protein.

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Chapter 650
Vascular Disorders

Kari L. Martin

Nearly all vascular lesions of childhood may be divided into vascular malformations and vascular tumors (Table 650-1). Vascular malformations are developmental errors in blood vessel formation. Malformations do not regress but slowly enlarge. They should be named after the predominant vessel(s) forming the lesion. Genetic disorders may involve arterial, capillary, lymph, or venous malformations. Vascular tumors exhibit endothelial cell hyperplasia and proliferation.

VASCULAR MALFORMATIONS

Capillary Malformation (Port-Wine Stain)

Capillary malformations (CMs) are present at birth. These vascular malformations consist of mature dilated dermal capillaries. The lesions are macular, sharply circumscribed, pink to purple, and tremendously varied in size (Fig. 650-1). The head and neck region is the most common site of predilection; most lesions are unilateral. The mucous

Table 650-1 International Society for the Study of Vascular Anomalies (ISSVA) Classification System

VASCULAR MALFORMATION	VASCULAR TUMOR
Slow-flow malformations	Infantile hemangioma
Capillary malformation	Congenital hemangioma
Venous malformation	Rapidly involuting congenital hemangioma
Lymphatic malformation	Noninvoluting congenital hemangioma
Fast-flow malformations	Kaposiform hemangioendothelioma
Arterial malformation	Tufted angioma
Arteriovenous malformation	Spindle cell hemangioendothelioma
Arteriovenous fistula	Epithelioid hemangioendothelioma
Combined vascular malformations	Other rare hemangioendotheliomas
	Angiosarcoma
	Acquired vascular tumors: pyogenic granuloma

Figure 650-1 **Capillary malformation.** Pink macule on the cheek of an infant.

membranes can be involved. As a child matures into adulthood, the CM may become darker in color and pebbly in consistency; it may occasionally develop elevated areas that bleed spontaneously.

True CM should be distinguished from **nevus simplex**, which, in contrast, is a relatively transient lesion often located in the midline (see Chapter 647). When a CM is lateral and localized to the forehead, and upper eyelid the diagnosis of **Sturge-Weber syndrome** (glaucoma, leptomeningeal venous angioma, seizures, hemiparesis contralateral to the facial lesion, intracranial calcification) must be considered (see Chapter 596.3). Early screening for glaucoma is important to prevent additional damage to the eye. CMs also occur as a component of Klippel-Trenaunay syndrome and with moderate frequency in other syndromes, including Cobb (spinal arteriovenous malformation, port-wine stain), Proteus, Beckwith-Wiedemann, and Bonnet-Dechaume-Blanc syndromes. In the absence of associated anomalies, morbidity from these lesions may include a poor self-image, hypertrophy of underlying structures, and traumatic bleeding. In contrast to unilateral lesions associated with Sturge-Weber syndrome, medial *frontofacial CMs* are bilateral and involve the forehead, glabella, upper eyelids, nose, philtrum, and upper lip. These lesions may be familial, complete (involving all 7 areas), or incomplete, and are associated with other CMs on the occiput, neck or lumbosacral areas. Atypical cases are associated with Beckwith-Wiedemann and Rubinstein-Taybi syndromes.

The most effective **treatment** for CM is with the pulsed-dye laser. This therapy is targeted to hemoglobin within the lesion and avoids thermal injury to the surrounding normal tissue. After such treatment, the texture and pigmentation of the skin are generally normal without scarring. Therapy can begin in infancy, when the surface area of involvement is smaller. There may be advantages to treating within the 1st yr of life. Although this approach is quite effective, redarkening of the stain may occur 10 yr after therapy. Masking cosmetics may also be used.

Angiokeratoma Circumscriptum

Several forms of angiokeratoma have been described. Angiokeratomas are characterized by ectasia of superficial lymphatic vessels and capillaries with hyperkeratosis of the overlying epidermis. Angiokeratoma circumscriptum is a rare disorder consisting of a solitary lesion or multiple lesions that manifest as a plaque or plaques of blue-red crusted papules or nodules. The limbs are the sites of predilection. If therapy is desired, surgical excision is the treatment of choice.

Venous Malformation

Venous malformations include vein-only malformations and combination malformations. Malformations consisting of veins only run the gamut from nodules containing a mass of venules (Fig. 650-2) to diffuse large vein abnormalities that may consist of either a superficial component resembling varicose veins, deeper venous malformations, or both. Most venous malformations are sporadic, although inherited forms exist as well. Inherited forms and up to 40% of sporadic venous malformations are caused by *TIE2* mutations. Treatment is reserved for painful or symptomatic lesions. Surgical excision is best for small or superficial nodular lesions and sclerotherapy or laser ablation is used for larger, diffuse lesions. Localized intravascular coagulopathy can be problematic in these lesions because of the chronic slow flow. This leads to both painful thrombotic episodes and the risk of progression to systemic disseminated intravascular coagulopathy.

Cutis Marmorata Telangiectatica Congenita

Cutis marmorata telangiectatica congenital is a benign vascular anomaly that represents dilation of superficial capillaries and veins and is apparent at birth. Involved areas of skin have a reticulated red or purple hue that resembles physiologic cutis marmorata but is more pronounced and relatively unvarying (Fig. 650-3). The lesions may be restricted to a single limb and a portion of the trunk or may be more widespread. The lesions become more pronounced during changes in environmental temperature, physical activity, or crying. In some cases, the underlying subcutaneous tissue is atrophic, and ulceration may occur within the reticulated bands. Rarely, defective growth of bone and other congenital abnormalities may be present. No specific therapy is indicated. Mild vascular-only cases may show gradual improvement. Cutis marmorata telangiectatica congenita may be associated with CM, Adams-Oliver syndrome, patent ductus arteriosus, and a variety of other anomalies. It must be differentiated from reticulate CM and physiologic cutis marmorata.

Blue Rubber Bleb Nevus Syndrome

Blue rubber bleb nevus is a rare syndrome consisting of numerous venous malformations of the skin, mucous membranes, and gastrointestinal tract. Typical lesions are blue-purple and rubbery in consistency; they vary in size from a few millimeters to a few centimeters in diameter. They are sometimes painful or tender. The nodules occasionally are present at birth but usually are progressive during childhood. New lesions may continue to develop throughout life. Large disfiguring and irregular blue marks may also occur. The lesions, which can rarely be located in the liver, spleen, and central nervous system in addition to the skin and gastrointestinal tract, do not involute spontaneously. Recurrent gastrointestinal hemorrhage due to lesions in the gastrointestinal tract may lead to severe anemia. Palliation can be achieved by excision of involved bowel.

KLIPPEL-TRENAUNAY AND PARKES-WEBER SYNDROMES

Klippel-Trenaunay syndrome is a term historically used to describe complex, mixed vascular malformation with overgrowth of bone and

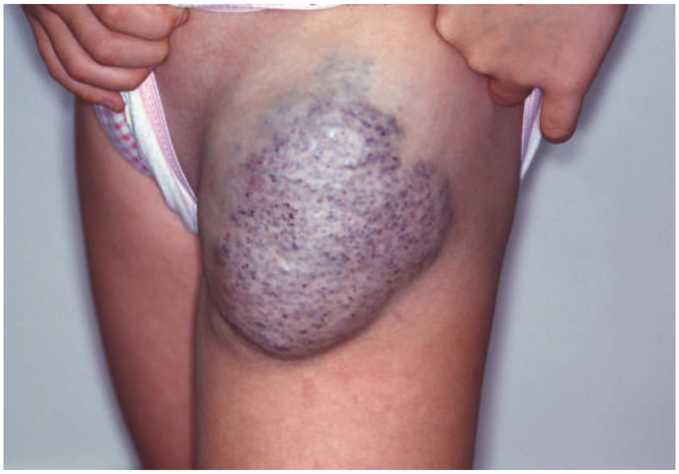

Figure 650-2 Nodular venous malformation on the leg of an adolescent.

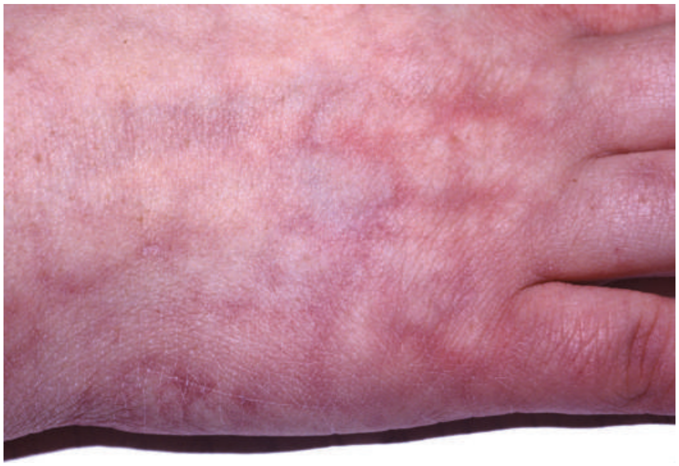

Figure 650-3 Mottled pattern of cutis marmorata telangiectatica congenita on the right hand.

Figure 650-4 Overgrowth of the right arm and hand in and adolescent with Klippel-Trenaunay syndrome.

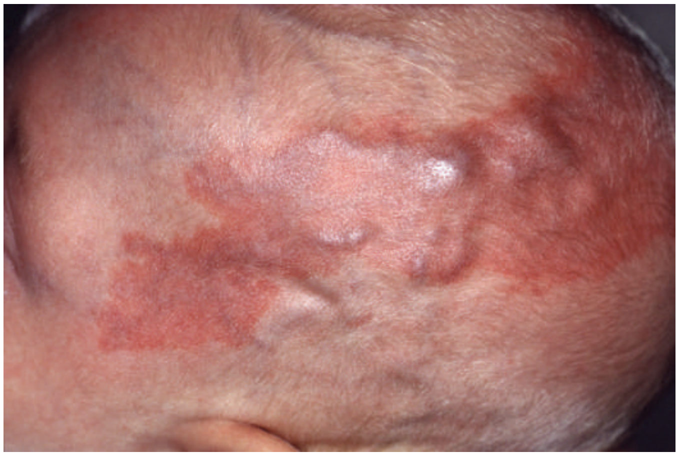

Figure 650-5 Arteriovenous malformation in conjunction with a port-wine stain of the scalp of a newborn.

soft tissue (Fig. 650-4). The anomaly is present at birth and usually involves a lower limb but may involve more than 1 limb, as well as portions of the trunk or face. Enlargement of the soft tissues may be gradual and may involve the entire extremity, a portion of it, or selected digits. The vascular lesion most often is a capillary malformation, generally localized to the hypertrophied area. The deep venous system may be absent or hypoplastic. Venous blebs and/or vesicular lymphatic lesions may be present on the malformation's surface. Thick-walled venous varicosities typically become apparent ipsilateral to the vascular malformation after the child begins to ambulate. If there is an associated arteriovenous malformation (AVM), the disorder is called Parkes-Weber syndrome.

These disorders can be confused with **Maffucci syndrome** or, if the surface vascular lesion is minimal, with **Milroy disease**. Pain, limb swelling, and cellulitis may occur. Thrombophlebitis, dislocations of joints, hematuria secondary to angiomatous involvement of the urinary tract, rectal bleeding from lesions of the gastrointestinal tract, pulmonary lesions, and malformations of the lymphatic vessels are infrequent complications. MRI may delineate the extent of the anomaly, but surgical correction or palliation is often difficult. Sclerotherapy or endovenous laser ablation may be of benefit when a venous component is the dominant vessel in the malformation. The indications for radiologic studies of viscera and bones are best determined by clinical evaluation. Supportive care includes compression bandages for varicosities; surgical treatment may help carefully selected patients. Leg-length differences should be treated with orthotic devices to prevent the development of spinal deformities. Corrective bone surgery may eventually be needed to treat significant leg-length discrepancy.

ARTERIOVENOUS MALFORMATION

AVMs are direct connections of artery to vein that bypass the capillary bed (Fig. 650-5). AVMs of the skin are very rare. Skin changes are often noted at birth, but they tend to be very subtle presenting as a red-pink patch. Over time the lesions deepen in color and often result in thickening of the skin and surrounding tissue. They are diagnosed from their obvious arterial palpation. Some AVMs are progressive and can lead to significant morbidity and even mortality, so early diagnosis and evaluation by an experienced multidisciplinary team is essential.

LYMPHATIC MALFORMATIONS

See Chapter 489.

PHAKOMATOSIS PIGMENTOVASCULARIS

Phakomatosis pigmentovascularis is a rare disorder characterized by the association of a capillary malformation and melanocytic lesions. Typically, the capillary malformation is extensive, and associated pigmentary lesions may include dermal melanocytosis (mongolian spots), café-au-lait macules, or a nevus spilus (speckled nevus). Nonpigmented skin lesions that may occur in this setting include nevus anemicus and epidermal nevi. Systemic anomalies are seen in rare cases.

NEVUS ANEMICUS

Although present at birth, nevus anemicus may not be detectable until early childhood. The nevus consists of solitary or numerous, sharply delineated pale macules or patches that are most often on the trunk but may also occur on the neck or limbs. These nevi may simulate plaques of vitiligo, leukoderma, or nevoid pigmentary defects, but they can be readily distinguished because of their response to firm stroking. Stroking evokes an erythematous line and flare in normal surrounding skin, but the skin of a nevus anemicus does not redden. They can also be diagnosed by diascopy, in which pressure of the skin with a glass slide will obscure the borders of a nevus anemicus. Although the cutaneous vasculature appears normal histologically, the blood vessels within the nevus do not respond to injection of vasodilators. It has been postulated that the persistent pallor may represent a sustained localized adrenergic vasoconstriction.

VASCULAR TUMORS

Vascular tumors include infantile hemangiomas, tufted angiomas, kaposiform hemangioendotheliomas, rapidly involuting congenital hemangiomas, and noninvoluting congenital hemangiomas.

Infantile Hemangioma

Infantile hemangiomas (IHs) are proliferative, benign vascular tumors of vascular endothelium that may be present at birth or, more commonly, may become apparent in the 1st 2 wk of life, predictably enlarge, and then spontaneously involute. IHs are the most common tumor of infancy, occurring in 5% of newborns. Risk factors include prematurity, low birthweight, female sex, and white race. IHs should be classified as superficial, deep, or mixed. The terms *strawberry* and *cavernous* should not be used to describe hemangiomas. The immunohistochemical marker GLUT-1 is specifically expressed in an IH, which helps distinguish it histologically from other vascular anomalies. Superficial IHs are bright red, protuberant, compressible, sharply demarcated lesions that may occur on any area of the body (Figs. 650-6 and 650-7). Although sometimes present at birth, they more often appear in the 1st 2 mo of life and are heralded by an erythematous or blue mark or an area of pallor, which subsequently develops a fine telangiectatic pattern before the growth phase. The presenting sign may occasionally be an ulceration of the perineum or lip. Favored sites are the face, scalp, back, and anterior chest; lesions may be solitary or multiple. Patterns of facial involvement include frontotemporal, maxillary, mandibular, and frontonasal regions. IHs that are more deeply situated are more diffuse and are less defined than superficial IHs. The lesions are cystic, firm, or compressible, and the overlying skin may appear normal in color or may have a bluish hue (Fig. 650-8).

Figure 650-6 Superficial hemangioma on the right knee.

Figure 650-7 Large hemangioma with central crusted ulcer.

Figure 650-8 Deep hemangioma of the chest.

Most IHs are mixed, having both superficial and deep components. IHs undergo a phase of rapid expansion, followed by a stationary period and finally by spontaneous involution. Regression may be anticipated when the lesion develops pale gray areas centrally. The course of a particular lesion is unpredictable, but approximately 60% of these lesions reach maximal involution by 5 yr of age, and 90-95% by 9 yr. Spontaneous involution cannot be correlated with size or site of involvement, but lip lesions seem to persist most often. Complications include impairment of a vital function, ulceration, secondary infection, and permanent disfigurement (Table 650-2). The location of a lesion may interfere with a vital function (e.g., on eyelid interfering with vision, on urethra with urination, on airway with respiration). IHs in a "beard" distribution may be associated with upper airway or subglottic involvement. Stridor should suggest a tracheobronchial lesion. Large visceral IHs may be complicated by coexistent hypothyroidism because of type 3 iodothyronine deiodinase, and symptoms may be difficult to detect in this age group. Table 650-3 lists other concerning features.

Table 650-2 Complications of Hemangioma and Their Treatment

CLINICAL FINDING	RECOMMENDED TREATMENT
Severe ulceration/ maceration	Encourage twice-daily cleansing regimen Dilute sodium bicarbonate soaks ± Flashlamp pulsed-dye laser ± Oral corticosteroids or propranolol ± Culture-directed systemic antibiotics for infection
Bleeding (not KMP)	Gelfoam or Surgifoam or propranolol Compression therapy ± embolization
Hemangioma with ophthalmologic sequelae	Patching therapy as directed by ophthalmologist Intralesional vs oral corticosteroids vs propranolol
Subglottic hemangioma	Oral corticosteroids, propranolol, ± potassium titanyl phosphate (KtP) laser Tracheotomy if required
KMP	Corticosteroids, aminocaproic acid, vincristine, interferon-α ± embolization
High-flow hepatic hemangioma	Corticosteroids or interferon ± embolization

KMP, Kasabach-Merritt phenomenon.
From Blei F: Vascular anomalies: From bedside to bench and back again. Curr Probl Pediatr Adolesc Health 32:72–93, 2002.

In the usual patient with an IH who has no serious complications or extensive growth resulting in tissue destruction and severe disfigurement, treatment consists of expectant observation. Because almost all lesions regress spontaneously, therapy is rarely indicated. Parents require repeated reassurance and support. After spontaneous involution, many patients are left with small cosmetic defects, such as telangiectasia, hypopigmentation, fibrofatty deposits, and scars if the lesion has ulcerated. Residual telangiectasias may be treated with pulsed-dye laser therapy. Other defects can be treated or minimized by judicious surgical repair if desired.

In the rare case in which intervention is required, topical timolol solution (0.5% gel; maximum dose 0.5 mg/day) is effective, especially in small, superficial, nonulcerating and nonmucosal IH. At this time, topical timolol treatment appears a very safe alternative to observation alone for a superficial IH. Timolol solution may also be used with caution in the treatment of an ulcerated IH, with or without occlusion.

In a disfiguring, life- or vision-threatening, or ulcerated IH that is not responding to other treatment, oral propranolol is the first-line treatment in most cases. IHs typically respond with growth arrest and often early signs of involution within a couple weeks of treatment initiation. Dosing varies ranging from 1-3 mg/kg/day. Some recommend inpatient initiation of propranolol for infants younger than 8 wk gestational age or those with comorbid conditions. The dose is initiated at 1 mg/kg/day divided into 3 doses with heart rate and blood pressure monitoring at 1 and 2 hr after each dose. If that dose is tolerated, the dose is increased to 2 mg/kg/day tid. The outpatient initiation assumes

Table 650-3 Clinical "Red Flags" Associated with Hemangiomas

CLINICAL FINDING	RECOMMENDED EVALUATION
Facial hemangioma involving significant area of face	Evaluate for PHACES (posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities): MRI for orbital hemangioma ± posterior fossa malformation Cardiac, ophthalmologic evaluation Evaluate for midline abnormality: supraumbilical raphe, sternal atresia, cleft palate, thyroid abnormality
Cutaneous hemangiomas in beard distribution	Evaluate for airway hemangioma, especially if manifesting with stridor
Periocular hemangioma	MRI of orbit Ophthalmologic evaluation
Paraspinal midline vascular lesion	Ultrasonography or MRI to evaluate for occult spinal dysraphism
Hemangiomatosis (multiple small cutaneous hemangiomas)	Evaluate for parenchymal hemangiomas, especially hepatic/central nervous system Guaiac stool test
Large hemangioma, especially hepatic	Ultrasonography with Doppler flow study MRI Thyroid function studies
Thrill and/or bruit associated with hemangioma	Consider cardiac evaluation and echocardiography to rule out diastolic reversal of flow in aorta MRI to evaluate extent and flow characteristics
Head tilting	Evaluate appropriately for specific site of lesion, and consider physical therapy evaluation
Delayed milestones	Consider side effect of corticosteroids (myopathy, weight-related) Consider side effect of interferon (especially spastic diplegia)
LUMBAR syndrome	MRI of spine, kidneys

LUMBAR, lower body infantile hemangiomas and other skin defects, urogenital anomalies and ulceration, myelopathy, boney deformities, anorectal malformations and arterial anomalies, renal anomalies.

From Blei F: Vascular anomalies: from bedside to bench and back again. Curr Probl Pediatr Adolesc Health *32:67–102, 2002.*

good social support and access to the hospital. The initial dose and monitoring is similar to the inpatient plan; if the dose is tolerated for 3-7 days, the dose is increased to 1.5 mg/kg/day tid. If the latter dose is tolerated after 3-7 days, the dose is increased to 2 mg/kg/day tid. *In all situations, propranolol must be given a minimum of 6 hr after the last dose.* Risks of propranolol treatment include hypoglycemia, bradycardia, hypotension, gastroesophageal reflux disease or worsening of existing disease, hyperkalemia, and bronchospasm/wheezing. Nonetheless, reports of side effects of propranolol used for IH treatment are rare. Increased propranolol levels occur with inhibitors of CYP2D6 (cimetidine, amiodarone, fluoxetine, quinidine, ritonavir) and CPY1A2 (cimetidine, ciprofloxacin, isoniazid, ritonavir, theophylline); decreased blood levels occur with inducers of hepatic drug metabolism (rifampin, phenytoin, phenobarbital).

In patients unable to tolerate propranolol, or if the IH has not responded after a couple of weeks of treatment, systemic oral corticosteroids may be used. Termination of growth and sometimes regression may be evident after 2-4 wk of therapy. When a response is obtained, the dose should be decreased gradually, though most patients will require treatment until about 1 year of age.

Figure 650-9 Disseminated cutaneous (and liver) neonatal hemangiomatosis. *(From Eichenfield LF, Frieden IJ, Esterly NB:* Textbook of neonatal dermatology, *ed 2, Philadelphia, 2008, WB Saunders, p. 359.)*

Intralesional corticosteroid injection in the hands of an experienced physician can also induce rapid involution of a localized IH, but has risks of ulceration, tissue atrophy, and blindness if used near the orbit. Vincristine is used by some oncologists to treat significant IH. Interferon-α therapy may also be effective, but spastic diplegia is seen in 10% of cases. Use of these therapies has become less necessary since the introduction of propranolol.

In patients with large segmental IH of the face, PHACE syndrome should be considered. **PHACE stands for p**osterior fossa brain defects such as Dandy-Walker malformation or cerebellar hypoplasia, large segmental facial infantile **h**emangioma, **a**rterial cerebrovascular abnormalities such as aneurysms and stroke, **c**oarctation of the aorta, **e**ye abnormalities. **S**ternal raphe defects such as pits, scars, or **s**upraumbilical raphe are infrequently observed. Evaluation of children at risk for PHACE is important both to detect any underlying abnormalities and also before starting systemic therapy, which may be indicated given the size and location of the IH typically associated with this syndrome. PHACE children with cervical and intracranial arterial abnormalities are at increased risk of cerebrovascular accidents and specialized care by an experienced multidisciplinary team is essential.

Multifocal Infantile Hemangioma

Diffuse neonatal hemangiomatosis (or benign neonatal hemangiomatosis) is a historical term to describe a condition in which numerous or multifocal vascular lesions are widely distributed (Fig. 650-9). In the past, several distinct diagnoses have been lumped together under this clinical phenotype with mortality cited as high as 60-80%. Upon further analysis, this group of disorders has been found to comprise several distinct entities which are important to distinguish from one another given their varying prognoses and management strategies. Multifocal IHs may occur in the skin as well as visceral organs, but remain GLUT-1–positive when biopsied, have a relatively good prognosis with low morbidity, and respond to systemic propranolol just as solitary cutaneous IH. **Multifocal lymphangioendotheliomatosis** (also known as cutaneovisceral angiomatosis) also presents with many vascular tumors in the skin and visceral organs, but is GLUT-1–negative and complicated by severe thrombocytopenia and gastrointestinal bleeding with high mortality. Therefore accurate diagnosis in patients who present with multifocal vascular tumors is critical so early, appropriate management may be initiated.

Kaposiform Hemangioendothelioma

Kaposiform hemangioendothelioma (KHE) is a rare and potentially life-threatening vascular tumor. Initial cases described IHs with purpura and coagulopathy, but these are now known to have been KHE. KHE classically present as a red to purple firm plaque on the lateral neck, axilla, trunk or extremities. Visceral tumors occur as well. Lesions may occasionally get smaller over time but rarely resolve completely. **Tufted angioma,** once thought to be a separate tumor on the same clinical spectrum as KHE, is considered under the umbrella term of KHE (Fig. 650-10). The main complication of these tumors is the development of Kasabach-Merritt phenomenon (KMP), which may be fatal; therefore, early diagnosis and treatment is important. Retroperitoneal or intrathoracic lesions in the absence of cutaneous lesions are uncommon but are often associated with KMP.

Kasabach-Merritt Phenomenon

KMP is a life-threatening combination of a rapidly enlarging KHE, thrombocytopenia, microangiopathic hemolytic anemia, and an acute or chronic consumption coagulopathy. The clinical manifestations are usually evident during early infancy. The vascular lesion is usually cutaneous and is only rarely located in viscera. The associated thrombocytopenia may lead to precipitous hemorrhage accompanied by ecchymoses, petechiae, and a rapid increase in the size of the vascular lesion. Severe anemia from hemorrhage or microangiopathic hemolysis may ensue. The platelet count is depressed, but the bone marrow contains increased numbers of normal or immature megakaryocytes. The thrombocytopenia has been attributed to sequestration or increased destruction of platelets within the lesion. Hypofibrinogenemia and decreased levels of consumable clotting factors are relatively common (see Chapter 484.6).

Treatment includes surgical excision of small lesions, although this is often difficult because of coagulopathy. Additional pharmacologic treatments include systemic steroids with or without vincristine as first-line therapy in most cases. Antiplatelet, antifibrinolytic, and other chemotherapeutic agents have been used with mixed results. Ongoing studies of sirolimus use in KHE patients are underway; initial case reports have been promising. The mortality rate overall once patients have KMP is significant.

Pyogenic Granuloma (Lobular Capillary Hemangioma)

A pyogenic granuloma (PG) is a small red, glistening, sessile, or pedunculated papule that often has a discernible epithelial collarette (Fig. 650-11). The surface may be weeping and crusted or completely epithelialized. PGs initially grow rapidly, may ulcerate, and bleed easily when traumatized because they consist of exuberant granulation tissue. They are relatively common in children, particularly on the face, arms, and hands. Such a lesion located on a finger or hand may appear as a subcutaneous nodule. PGs may arise at sites of injury, but a history of trauma often cannot be elicited.

Figure 650-10 Nodular tufted angioma on the left thigh.

PGs are benign but a nuisance because they bleed easily with trauma and may recur if incompletely removed. Numerous satellite papules have developed after surgical excision of PGs from the back, particularly in the interscapular region. Small lesions may regress after cauterization with silver nitrate; larger lesions require excision and electrodesiccation of the base of the granuloma. Small (<5 mm) lesions may be treated successfully with pulsed-dye laser therapy.

Angiokeratoma of Mibelli

Angiokeratoma of Mibelli is characterized by 1-8 mm red, purple, or black scaly, verrucous, occasionally crusted papules and nodules that appear on the dorsum of the fingers and toes and on the knees and the elbows. Less commonly, palms, soles, and ears may be affected. In many patients, onset has followed frostbite or chilblains. These nodules bleed freely after injury and may involute in response to trauma. They may be effectively eradicated by cryotherapy, electrofulguration, excision, or laser ablation.

Spider Angioma

A vascular spider (nevus araneus) consists of a central feeder artery with many dilated radiating vessels and a surrounding erythematous flush, varying from a few millimeters to several centimeters in diameter (Fig. 650-12). Pressure over the central vessel causes blanching; pulsations visible in larger nevi are evidence for the arterial source of the lesion. Spider angiomas are associated with conditions in which there are increased levels of circulating estrogens, such as cirrhosis and pregnancy, but they also occur in up to 15% of normal preschool-age children and 45% of school-age children. Sites of predilection in children are the dorsum of the hand, forearm, nose, infraocular region,

Figure 650-11 Pyogenic granuloma on the left cheek.

Figure 650-12 Spider telangiectasia with visible central arteriole component.

lips, and ears. Lesions often regress spontaneously after puberty. If removal is desired, pulsed dye laser therapy is the mode of choice; resolution is achieved in 90% of cases with a single treatment.

Maffucci Syndrome

The association of spindle cell hemangiomas with **nodular enchondromas** in the metaphyseal or diaphyseal cartilaginous portion of long bones is known as Maffucci syndrome. Maffucci syndrome is caused by somatic mosaic mutations in the *IDH1* and *IDH2* genes. Vascular lesions are typically soft, compressible, asymptomatic blue to purple subcutaneous masses that grow in proportion to a child's growth and stabilize by adulthood. Mucous membranes or viscera may also be involved. Onset occurs during childhood. Bone lesions may produce limb deformities and pathologic fractures. Malignant transformation of enchondromas (chondrosarcoma, angiosarcoma) or primary malignancies (ovarian, fibrosarcoma, glioma, pancreatic) may be a complication (see Chapter 501).

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Hereditary hemorrhagic telangiectasia (HHT), which is inherited as an autosomal dominant trait, occurs in 2 types. The gene in HHT-1 encodes endoglin (*ENG*), a membrane glycoprotein on endothelial cells that binds transforming growth factor-β. HHT-2 is caused by mutations in the *ACVRL1* gene (activin A receptor type 2-like kinase 1) and is associated with increased risk for hepatic involvement and pulmonary hypertension. Affected children may experience recurrent epistaxis before detection of the characteristic skin and mucous membrane lesions. The mucocutaneous lesions, which usually develop at puberty, are 1-4 mm, sharply demarcated red to purple macules, papules, or spider-like projections, each composed of a tightly woven mat of tortuous telangiectatic vessels (Fig. 650-13). The nasal mucosa, lips, and tongue are usually involved; less commonly, cutaneous lesions occur on the face, ears, palms, and nail beds. Vascular ectasias may also arise in the conjunctivae, larynx, pharynx, gastrointestinal tract, bladder, vagina, bronchi, brain, and liver.

Figure 650-13 Hereditary hemorrhagic telangiectasia. Telangiectases are found on the lips, oral mucosa, nasal mucosa, skin, and conjunctiva. Epistaxis is the most common manifestation of the disease. Blood transfusions may be required. *(From Habif TP:* Clinical dermatology: a color guide to diagnosis and therapy, *ed 4, Philadelphia, 2004, Mosby, Fig. 23-22, p. 831.)*

Massive hemorrhage is the most serious complication of HHT and may result in severe anemia. Bleeding may occur from the nose, mouth, gastrointestinal tract, genitourinary tract, or lungs; epistaxis is often the only complaint occurring in 80% of patients. Approximately 15-20% of patients with AVMs in the lungs present with stroke due to embolic abscesses (Fig. 650-14). Persons with HHT have normal levels of clotting factors and an intact clotting mechanism. In the absence of serious complications, the life span of a person with HHT is normal. Local lesions may be ablated temporarily with chemical cautery or electrocoagulation. More drastic surgical measures may be required for lesions in critical sites, such as the lung or gastrointestinal tract. Bevacizumab, an antivascular endothelial growth factor agent, has been effective in treating affected patients with HHT, who have high cardiac output secondary to hepatic AVMs.

Ataxia-Telangiectasia

See Chapter 597.1.

Ataxia-telangiectasia is transmitted as an autosomal recessive trait because of a mutation in the *ATM* gene. The characteristic telangiectasias develop at approximately 3 yr of age, first on the bulbar conjunctivae and later on the nasal bridge, malar areas, external ears, hard palate, upper anterior chest, and antecubital and popliteal fossae. Additional cutaneous stigmata include café-au-lait spots, premature graying of the hair, and sclerodermatous changes. Progressive cerebellar ataxia, neurologic deterioration, sinopulmonary infections, and malignancies are also seen.

Angiokeratoma Corporis Diffusum (Fabry Disease)

See Chapter 86.4.

An inborn error of glycolipid metabolism (α-galactosidase), angiokeratoma corporis diffusum is an X-linked recessive disorder that is fully penetrant in males and is of variable penetrance in carrier females. Angiokeratomas appear before puberty and occur in profusion over the genitalia, hips, buttocks, and thighs and in the umbilical and inguinal regions. They consist of 0.1-3.0 mm red to blue-black papules that may have a hyperkeratotic surface. Telangiectasias are seen in the mucosa and conjunctiva. On light microscopy, these angiokeratomas appear as blood-filled, dilated, endothelium-lined vascular spaces. Granular lipid deposits are demonstrable in dermal macrophages, fibrocytes, and endothelial cells.

Additional clinical manifestations include recurrent episodes of fever and agonizing pain, cyanosis and flushing of the acral limb areas, paresthesias of the hands and feet, corneal opacities detectable on slit-lamp examination, and hypohidrosis. Renal involvement and cardiac involvement are the usual causes of death. The biochemical defect is a deficiency of the lysosomal enzyme α-galactosidase, with accumulation of ceramide trihexoside in tissues, particularly vascular endothelium, and excretion in urine (see Chapter 86.4 for therapy). Similar cutaneous lesions have also been described in another lysosomal enzyme disorder, α-L-fucosidase deficiency, and in sialidosis, a storage disease with neuraminidase deficiency.

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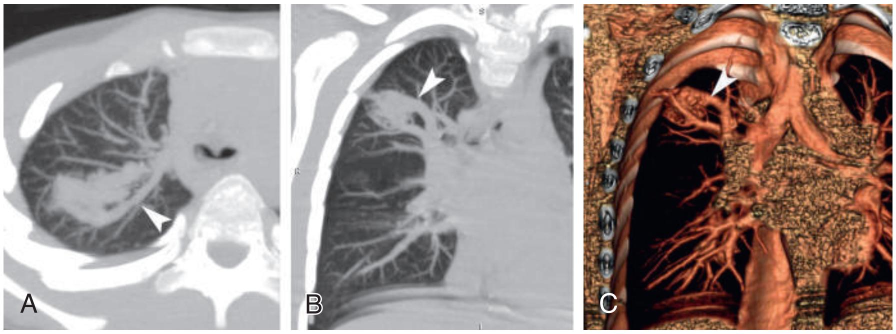

Figure 650-14 Chest multislice spiral CT in patient 2 showing a large pulmonary arteriovenous malformation in the posterior segment of right upper lobe *(arrowhead).* **A,** Axial maximum intensity projection image. **B,** Coronal maximum intensity projection image. **C,** Three-dimensional volume rendering. *(From Giordano P, Lenato GM, Suppressa P, et al: Hereditary hemorrhagic telangiectasia: arteriovenous malformations in children.* J Pediatr *163:179–186, 2013, Fig. 1, p. 182.)*

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Chapter 651

Cutaneous Nevi

Kari L. Martin

Nevus skin lesions are characterized histopathologically by collections of well-differentiated cell types normally found in the skin. Vascular nevi are described in Chapter 650. Melanocytic nevi are subdivided into 2 broad categories: those that appear after birth (acquired nevi) and those that are present at birth (congenital nevi).

ACQUIRED MELANOCYTIC NEVUS

Melanocytic nevus is a benign cluster of melanocytic nevus cells that arises as a result of alteration and proliferation of melanocytes at the epidermal–dermal junction.

Epidemiology

The number of acquired melanocytic nevi increases gradually during childhood and more slowly in early adulthood. The number reaches a plateau in the 3rd or 4th decade and then slowly decreases thereafter. The mean number of melanocytic nevi in an adult varies depending on genetics, skin color, and sun exposure. The greater the number of nevi present, the greater is the risk for development of **melanoma,** though the majority of melanomas arise de novo. Sun exposure during childhood, particularly intermittent, intense exposure of an individual with light skin, and a propensity to burn and freckle rather than tan are important determinants of the number of melanocytic nevi that develop. Red-haired children, despite their light skin and propensity to freckle and sunburn, have fewer nevi than other children. Increased numbers of nevi are also associated with immunosuppression and administration of chemotherapy.

Clinical Manifestations

Nevocellular nevi have a well-defined life history and are classified as **junctional, compound,** or **dermal** in accordance with the location of the nevus cells in the skin. In childhood, >90% of nevi are junctional; melanocyte proliferation occurs at the junction of the epidermis and dermis to form nests of cells. Junctional nevi appear anywhere on the body in various shades of brown; they are relatively small, discrete, flat, and variable in shape. The melanized nevus cells are cuboidal or epithelioid in configuration and occur in nests on the epidermal side of the basement membrane. Although some nevi, particularly those on the palms, soles, and genitalia, remain junctional throughout life, most become compound as melanocytes migrate into the papillary dermis to form nests at both the epidermal–dermal junction and within the dermis. If the junctional melanocytes stop proliferating, nests of melanocytes remain only within the dermis, forming an intradermal nevus. With maturation, compound and intradermal nevi may become raised, dome-shaped, verrucous, or pedunculated. Slightly elevated lesions are usually compound. Distinctly elevated lesions are usually intradermal. With age, the dermal melanocytic nests regress and the nevi gradually disappear.

Prognosis and Treatment

Acquired pigmented nevi are benign, but a very small percentage undergo malignant transformation. Suspicious changes are indications for excision and histopathologic evaluation; they include rapid increase in size; development of satellite lesions; variegation of color, particularly with shades of red, brown, gray, black, and blue; pigmentary incontinence; notching or irregularity of the borders; changes in texture such as scaling, erosion, ulceration, and induration; and regional lymphadenopathy. Most of these changes are from irritation, infection, or maturation; darkening and gradual increase in size and elevation normally occur during adolescence and should not be cause for concern. Two common benign changes are clonal nevi (fried-egg moles) and eclipse nevi. A clonal nevus is light brown with a dark raised center representing a clonal change of a subset of nevus cells within the lesion. Eclipse nevi are flat and light brown with dark brown rims. They are seen primarily in the scalp (Fig. 651-1). Consideration should be given to the presence of risk factors for development of melanoma and the patient's parents' wishes about removal of the nevus. If doubt remains about the benign nature of a nevus, excision is a safe and simple outpatient procedure that may be justified to allay anxiety.

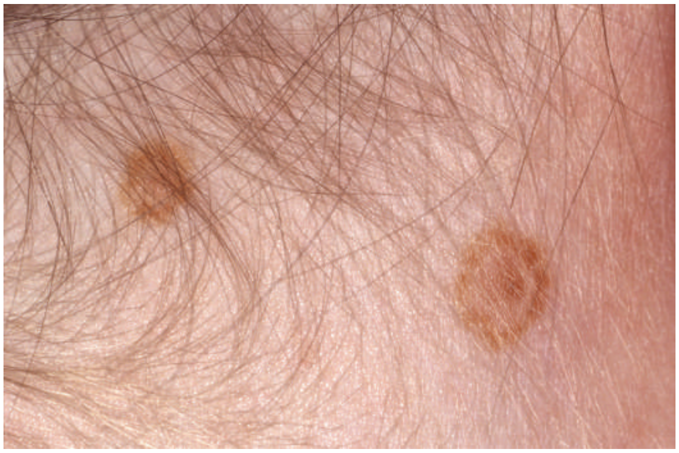

Figure 651-1 Eclipse nevi (rim moles) in the scalp.

ATYPICAL MELANOCYTIC NEVUS

Atypical melanocytic nevi occur both in an **autosomal dominant familial melanoma-prone** setting (familial mole–melanoma syndrome, dysplastic nevus syndrome, BK mole syndrome) and as a sporadic event. Only 2% of all pediatric melanomas occur in individuals with this familial syndrome; melanoma develops before age 20 yr in 10% of individuals with the syndrome. Malignant melanoma has been reported in children with the dysplastic nevus syndrome as young as 10 yr. Risk for development of melanoma is essentially 100% in individuals with dysplastic nevus syndrome who have 2 family members who have had melanomas. The term *atypical mole syndrome* describes lesions in those individuals without an autosomal dominant familial history of melanoma but with more than 50 nevi, some of which are atypical. The lifetime risk of melanoma associated with dysplastic nevi in this context is estimated to be 5-10%.

Atypical nevi tend to be large (5-15 mm) and round to oval. They have irregular margins and variegated color, and portions of them are elevated. These nevi are most common on the posterior trunk, suggesting that intermittent, intense sun exposure has a role in their genesis. They may also occur in sun-protected areas such as the breasts, buttocks, and scalp. Atypical nevi do not usually develop until puberty, although scalp lesions may be present earlier. Atypical nevi demonstrate disordered proliferation of atypical intraepidermal melanocytes, lymphocytic infiltration, fibroplasia, and angiogenesis. It may be helpful to obtain histopathologic documentation of dysplastic change by biopsy to identify these individuals. It is prudent to excise borderline atypical nevi in immunocompromised children or in those treated with irradiation or chemotherapeutic agents. Although chemotherapy is associated with the development of a greater number of melanocytic nevi, it has not been directly linked to increased risk for development of melanoma. The threshold for removal of clinically atypical nevi is also lower at sites that are difficult to observe, such as the scalp. Children with atypical nevi should undergo a complete skin examination every 6-12 mo. In these children, photographic mole mapping serves as a useful adjunct in following nevus change. Parents must be counseled about the importance of sun protection and avoidance and should be instructed to look for early signs of melanoma on a regular basis, approximately every 3-4 mo.

CONGENITAL MELANOCYTIC NEVUS

Congenital melanocytic nevi are present in ≈1% of newborn infants. These nevi have been categorized by size: giant congenital nevi are >20 cm in diameter (adult size) or >5% of the body surface; small congenital nevi are <1.5 cm in diameter, and intermediate nevi are in between these dimensions. Congenital nevi are characterized by the presence of nevus cells in the lower reticular dermis; between collagen bundles; surrounding cutaneous appendages, nerves, and vessels in the lower dermis; and occasionally extending to the subcuticular fat. They often harbor *NRAS* mutations, but not *BRAF* mutations typically seen in regular melanocytic nevi. Identification is often uncertain, however, because they may have the histologic features of ordinary junctional, compound, or intradermal nevi. Some nevi that were not present at birth display histopathologic features of congenital nevi; these should not be considered congenital. Furthermore, congenital nevi may be difficult to distinguish clinically from other types of pigmented lesions, adding to the difficulty that parents may have in identifying nevi that were present at birth. The clinical differential diagnosis includes dermal melanocytosis, café-au-lait macules, and smooth muscle hamartoma.

Sites of predilection for small congenital nevi are the lower trunk, upper back, shoulders, chest, and proximal limbs. The lesions may be flat, elevated, verrucous, or nodular and may be various shades of brown, blue, or black. Given the difficulty in identifying small congenital nevi with certainty, data regarding their malignant potential are controversial and likely overstated. The true incidence of melanoma in congenital nevi, especially small and medium-sized lesions, is unknown. Removal of all small congenital nevi is not warranted because the development of melanoma in a small congenital nevus is an exceedingly rare event before puberty. A number of factors must be weighed in the decision about whether or not to remove a nevus, including its location, the ability to monitor it clinically, the potential for scarring, the presence of other risk factors for melanoma, and the presence of atypical clinical features.

Giant congenital pigmented nevi (<1 in 20,000 births) occur most commonly on the posterior trunk (Fig. 651-2) but may also appear on the head or extremities. These nevi are of special significance because of their association with leptomeningeal melanocytosis (neurocutaneous melanocytosis) and their predisposition for development of malignant melanoma. Leptomeningeal involvement occurs most often when the nevus is located on the head or midline on the trunk, particularly when associated with multiple "satellite" melanocytic nevi (>20 lesions). Nevus cells within the leptomeninges and brain parenchyma may cause increased intracranial pressure, hydrocephalus, seizures, intellectual disability, and motor deficits and may result in melanoma. Malignancy can be identified by careful cytologic examination of the cerebrospinal fluid for melanin-containing cells. MRI demonstrates asymptomatic leptomeningeal melanosis in ≈30% of individuals with giant congenital nevus of the type described above. The overall incidence of malignant melanoma arising in a giant congenital nevus has been estimated to be ≈5-10% but is more likely to be approximately 1-2%. The median age at diagnosis of the melanomas that arise within a giant congenital nevus is 7 yr. The mortality rate approaches 100%. The risk of melanoma is greater in patients in whom the predicted adult size of the nevus is >40 cm, lesions on trunk, and presence of satellite lesions. Management of giant congenital nevi remains controversial and should involve the parents, pediatrician, dermatologist, and plastic surgeon. If the nevus lies over the head or spine, MRI may allow detection of **neural melanosis,** the presence of which makes gross removal of a nevus from the skin a futile effort. In the absence of neural melanosis, early excision and repair aided by tissue expanders or grafting may reduce the burden of nevus cells and thus the potential for development of melanoma, but at the cost of many potentially disfiguring operations. Nevus cells deep within subcutaneous tissues may evade excision. Random biopsies of the nevus are not helpful, but biopsy of newly expanding nodules is indicated. Follow-up every 6 mo for 5 yr and every 12 mo thereafter is recommended. Serial photographs of the nevus may aid in detecting changes.

Figure 651-2 "Bathing suit" large congenital melanocytic nevus.

MELANOMA

Malignant melanoma accounts for 1-3% of all pediatric malignancies, and approximately 2% of all melanomas occur before age 20 yr. The incidence of melanoma continues to increase. Melanoma is 7 times more frequent in the 2nd decade of life than in the 1st decade of life. Melanoma develops primarily in white individuals, on the head and trunk in males, and on the extremities in females. Risk factors for development of melanoma include the presence of the familial atypical mole–melanoma syndrome or xeroderma pigmentosum; an increased number of acquired melanocytic nevi, or atypical nevi; fair complexion; excessive sun exposure, especially intermittent exposure to intense sunlight; a personal or family (1st-degree relative) history of a previous melanoma, giant congenital nevus, and immunosuppression. In previously well children, UV radiation is responsible for most melanomas. Fewer than 5% of childhood melanomas develop within giant congenital nevi or in individuals with the familial atypical mole–melanoma syndrome. Approximately 40-50% of the time, melanoma develops at a site where there was no apparent nevus. The mortality rate from melanoma is related primarily to tumor thickness and the level of invasion into the skin. The overall mortality rate reaches ≈40%, regardless of whether the tumor arises in a child or adult.

Given the lack of effective therapy for melanoma, prevention and early detection are the most effective measures. Emphasis should be given to avoidance of intense midday sun exposure between 10 AM and 3 PM; wearing of protective clothing such as a hat, long sleeves, and pants; and use of sunscreen. Early detection includes frequent clinical and photographic examinations of patients at risk (dysplastic nevus syndrome) and prompt response to rapid changes in nevi (size, shape, color, inflammation, bleeding or crusting, and sensation). The **ABCD rule** (asymmetry, border irregularities, color variability, diameter >6 mm), which is a useful screening tool for adults, may not be as effective for children.

HALO NEVUS

Halo nevi occur primarily in children and young adults, most commonly on the back (Fig. 651-3). Development of the lesion may coincide with puberty or pregnancy. Several pigmented nevi frequently develop halos simultaneously. Subsequent disappearance of the central nevus over several months is the usual outcome, and the depigmented area usually repigments. Excision and histopathologic examination of the lesion is indicated only when the nature of the central lesion is in question. An acquired melanocytic nevus occasionally develops a peripheral zone of depigmentation over a period of days to weeks. There is a dense inflammatory infiltrate of lymphocytes and histiocytes in addition to the nevus cells. The pale halo reflects disappearance of the melanocytes. This phenomenon is associated with congenital nevi,

Figure 651-3 Well-developed halo nevus.

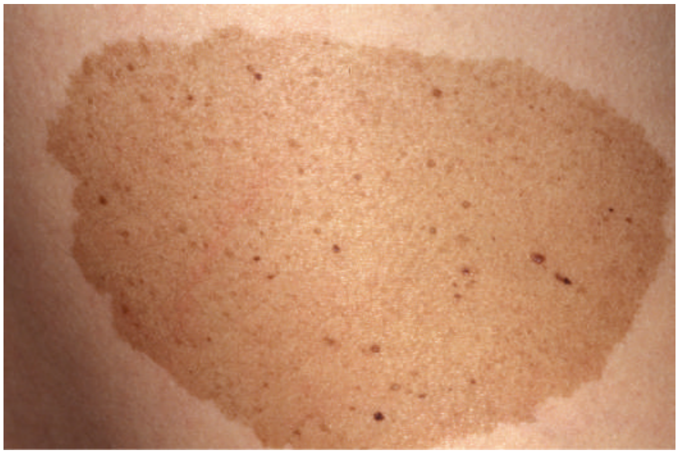

Figure 651-5 Nevus spilus.

Figure 651-4 Dome-shaped red Spitz nevus.

blue nevi, Spitz nevi, dysplastic nevi, neurofibromas, and primary and secondary malignant melanoma, and occasionally with poliosis, Vogt-Koyanagi-Harada syndrome, and pernicious anemia. Patients with vitiligo have an increased incidence of halo nevi. Individuals with halo nevi have circulating antibodies against the cytoplasm of melanocytes and nevus cells.

SPITZ NEVUS (SPINDLE AND EPITHELIOID CELL NEVUS)

Spitz nevus manifests most commonly in the 1st 2 decades of life as a pink to red, smooth, dome-shaped, firm, hairless papule on the face, shoulder, or upper limb (Fig. 651-4). Most are <1 cm in diameter, but they can achieve a size of 3 cm. Rarely, they occur as numerous grouped lesions. Visually similar lesions include pyogenic granuloma, hemangioma, nevocellular nevus, juvenile xanthogranuloma, and basal cell carcinoma, but these entities are histologically distinguishable. Spitz nevus may be difficult to distinguish histopathologically from malignant melanoma because nuclear atypia is a common feature, particularly after local recurrence of the nevus. Difficulty arises in the fact that many other clinical types of melanocytic nevi have a similar histologic appearance. Local recurrence after excision may occur up to 5% of the time. If a nevus arouses clinical suspicion that it may be a melanoma, an excisional biopsy of the entire lesion is recommended. If the margins of excision of a Spitz nevus are positive, reexcision of the site is prudent to avoid difficulties in histopathologic interpretation of the lesion in the future.

ZOSTERIFORM LENTIGINOUS NEVUS (AGMINATED LENTIGINES)

Zosteriform lentiginous nevus is a unilateral, linear, band-like collection of numerous 2-10 mm brown or black macules on the face, trunk, or limbs. The nevus may be present at birth or may develop during childhood. There are higher numbers of melanocytes in elongated rete ridges of the epidermis.

NEVUS SPILUS (SPECKLED LENTIGINOUS NEVUS)

Nevus spilus is a flat brown patch within which are darker flat or raised brown melanocytic elements (Fig. 651-5). It varies considerably in size and can occur anywhere on the body. The color of the macular component may vary from light to dark brown, and the number of darker lesions may be low or high. Nevus spilus is rare at birth and is commonly acquired in late infancy or early childhood. Dark elements within the nevus are usually present initially and tend to increase in number gradually over time. The darker macules represent nevus cells in a junctional or dermal location; the patch has increased numbers of melanocytes in a lentiginous epidermal pattern. The malignant potential of these nevi is uncertain; nevus spilus is found more commonly in individuals with melanoma than in matched control subjects. The nevi need not be excised, unless atypical features or recent clinical changes are noted.

NEVUS OF OTA AND NEVUS OF ITO

Nevus of Ota is more common among females and Asian, and African-American patients. This nevus consists of a permanent patch composed of partially confluent blue, black, and brown macules. Enlargement and darkening may occur with time. Occasionally, some areas of the nevus are raised. The macular nevi resemble the more common dermal melanocytosis of the lower back and buttocks in color and occur unilaterally in the areas supplied by the 1st and 2nd divisions of the trigeminal nerve. Nevus of Ota differs from a more common dermal melanocytosis patch, not only by its distribution but also by having a speckled rather than a uniform appearance. Both are forms of mid-dermal melanocytosis. Nevus of Ota also has a greater concentration of elongated, dendritic dermal melanocytes located in the upper rather than the lower portion of the dermis. This nevus is sometimes present at birth; in other cases, it may arise during the 1st or 2nd decade of life. Patchy involvement of the conjunctiva, hard palate, pharynx, nasal mucosa, buccal mucosa, or tympanic membrane occurs in some patients. Malignant change is exceedingly rare. Laser therapy may effectively decrease the pigmentation but can be unpredictable.

Nevus of Ito is localized to the supraclavicular, scapular, and deltoid regions. This nevus tends to be more diffuse in its distribution and less mottled than nevus of Ota. It is also a form of mid-dermal

melanocytosis. The only available treatments are masking with cosmetics and laser therapy.

BLUE NEVI

The common blue nevus is a solitary, asymptomatic, smooth, dome-shaped, blue to blue-gray papule <10 mm in diameter on the dorsal aspect of the hands and feet. Rarely, common blue nevi form large plaques. Blue nevus is nearly always acquired, often during childhood and more commonly in females. Microscopically, it is characterized by groups of intensely pigmented spindle-shaped melanocytes in the dermis. This nevus is benign.

The cellular blue nevus is typically 1-3 cm in diameter and occurs most frequently on the buttocks and in the sacrococcygeal area. In addition to collections of deeply pigmented dermal dendritic melanocytes, cellular islands composed of large spindle-shaped cells are noted in the dermis and may extend into the subcutaneous fat. A histologic continuum may be seen from blue nevi to cellular blue nevi. A combined nevus is the association of a blue nevus with an overlying melanocytic nevus.

The blue-gray that is characteristic of these nevi is an optical effect caused by dermal melanin. Longer wavelengths of visible light penetrate to the deep dermis and are absorbed there by melanin; shorter-wavelength blue light cannot penetrate deeply but instead is reflected back to the observer.

NEVUS DEPIGMENTOSUS (ACHROMIC NEVUS)

Nevi depigmentosi are usually present at birth; they are localized macular hypopigmented patches or streaks, often with bizarre, irregular borders (Fig. 651-6). They can resemble hypomelanosis of Ito clinically, except that they are more localized and often unilateral. Small lesions may also resemble the ash leaf macules of tuberous sclerosis. Nevi depigmentosi appear to represent a focal defect in transfer of melanosomes to keratinocytes.

Figure 651-6 Large nevus depigmentosus of the abdomen.

EPIDERMAL NEVI

Epidermal nevi may be visible at birth or may develop in the 1st few mo or yr of life. They affect both sexes equally and usually occur sporadically. Epidermal nevi are hamartomatous lesions characterized by hyperplasia of the epidermis and/or adnexal structures in a focal area of the skin.

Epidermal nevi are classified into a number of variants, depending on the morphology and extent of the individual nevus and the predominant epidermal structure. An epidermal nevus may appear initially as a discolored, slightly scaly patch that, with maturation, becomes more linear, thickened, verrucous, and hyperpigmented. *Systematized* refers to a diffuse or extensive distribution of lesions, and *ichthyosis hystrix* indicates that the distribution is extensive and bilateral (Fig. 651-7). Morphologic types include pigmented papillomas, often in a linear distribution; unilateral hyperkeratotic streaks involving a limb and perhaps a portion of the trunk; velvety hyperpigmented plaques; and whorled or marbled hyperkeratotic lesions in localized plaques or over extensive areas of the body along Blaschko lines. An inflammatory linear verrucous variant is markedly pruritic and tends to become erythematous, scaling, and crusted. Many harbor *RAS* mutations.

The histologic pattern evolves as an epidermal nevus matures, but epidermal hyperplasia of some degree is apparent in all stages of development. One or another dermal appendage may predominate in a particular lesion. These nevi must be distinguished from lichen striatus, lymphangioma circumscriptum, shagreen patch of tuberous sclerosis, congenital hairy nevi, linear porokeratosis, linear lichen planus, linear psoriasis, the verrucous stage of incontinentia pigmenti, and nevus sebaceus (Jadassohn). Keratolytic agents such as retinoic acid and salicylic acid may be moderately effective in reducing scaling and controlling pruritus, but definitive treatment requires full-thickness excision; recurrence is usual if more superficial removal is attempted. Alternatively, the nevus may be left intact. Epidermal nevi are occasionally associated with other abnormalities of the skin and soft tissues, eyes, and nervous, cardiovascular, musculoskeletal, and urogenital systems. In these instances, the disorder is referred to as epidermal nevus syndrome. This syndrome, however, is not a distinct clinical entity. The well-established syndromes that involve a type of epidermal nevus and distinct birth defects include the **proteus** and **CHILD** (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndromes.

Nevus Sebaceus (Jadassohn)

A relatively small, sharply demarcated, oval or linear, elevated yellow-orange plaque that is usually devoid of hair, nevus sebaceus occurs on the head and neck of infants (Fig. 651-8). Although the lesion is characterized histopathologically by an abundance of sebaceous glands, all

Figure 651-7 Epidermal nevus (ichthyosis hystrix type).

Figure 651-8 Orange-yellow nevus sebaceus of the scalp.

Figure 651-10 Large smooth muscle hamartoma of the buttock.

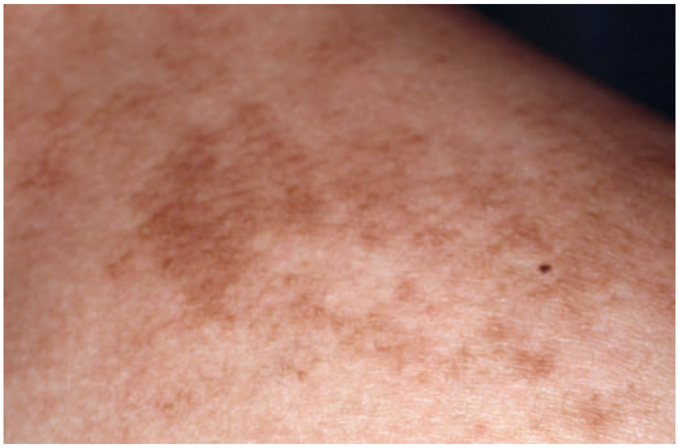

Figure 651-9 Becker nevus on the shoulder of an adolescent male.

elements of the skin are represented. It is frequently flat and inconspicuous in early childhood. With maturity, usually during adolescence, the lesions become verrucous and studded with large rubbery nodules. The changing clinical appearance reflects the histologic pattern, which is characterized by a variable degree of hyperkeratosis, hyperplasia of the epidermis, malformed hair follicles, and often a profusion of sebaceous glands and the presence of ectopic apocrine glands. Sebaceous nevi are caused by somatic mosaic mutations in *HRAS* and *KRAS.* The disruption of these oncogenes helps explain the 14% incidence of these lesions developing tumors throughout a patient's lifetime. Most tumors are benign (trichoblastomas, syringocystadenoma papilliferum, trichilemmomas), but basal cell carcinoma can occur as well. The *treatment of choice* is total excision before adolescence. Sebaceous nevi associated with central nervous system, skeletal, and ocular defects represent a variant of the epidermal nevus syndrome.

Becker Nevus (Becker Melanosis)

Becker nevus develops predominantly in males, during childhood or adolescence, initially as a hyperpigmented patch. The lesion commonly develops hypertrichosis, limited to the area of hyperpigmentation, and evolves into a unilateral, slightly thickened, irregular, hyperpigmented plaque. The most common sites are the upper torso and upper arm (Fig. 651-9). The nevus shows an increased number of basal melanocytes and variable epidermal hyperplasia. Becker melanosis is commonly associated with a smooth muscle hamartoma, which may appear as slight perifollicular papular elevations or slight induration. Stroking of such a lesion may induce smooth muscle contraction and make the hairs stand up (pseudo-Darier sign). The nevus is benign, has no risk for malignant change, and is rarely associated with other anomalies.

NEVUS COMEDONICUS

An uncommon organoid nevus of epithelial origin, nevus comedonicus consists of linear plaques of plugged follicles that simulate comedones; they may be present at birth or may appear during childhood. The horny plugs represent keratinous debris within dilated, malformed pilosebaceous follicles. The lesions are most often unilateral and may develop at any site. Rarely, they are associated with other congenital malformations, including skeletal defects, cerebral anomalies, and cataracts. Although these lesions are often asymptomatic, some affected individuals experience recurrent inflammation, resulting in cyst formation, fistulas, and scarring. There is no effective treatment except full-thickness excision; palliation of larger lesions may be achieved by regular applications of a retinoic acid preparation.

CONNECTIVE TISSUE NEVUS

Connective tissue nevus is a hamartoma of collagen, elastin, and/or glycosaminoglycans of the dermal extracellular matrix. It may occur as a solitary defect or as a manifestation of an associated disorder. These nevi may occur at any site but are most common on the back, buttocks, arms, and thighs. They are skin-colored, ivory, or yellow plaques, 2-15 cm in diameter, composed of many tiny papules or grouped nodules that are frequently difficult to appreciate visually because of the subtle color changes. The plaques have a rubbery or cobblestone consistency on palpation. Biopsy findings are variable and include increased amounts and/or degeneration or fragmentation of dermal collagen, elastic tissue, or ground substance. Similar lesions occurring with tuberous sclerosis are called shagreen patches; however, shagreen patches consist only of excessive amounts of collagen. The association of many small papular connective tissue nevi with osteopoikilosis is called dermatofibrosis lenticularis disseminata **(Buschke-Ollendorf syndrome).**

SMOOTH MUSCLE HAMARTOMA

Smooth muscle hamartoma is a developmental anomaly resulting from hyperplasia of the smooth muscle (arrector pili) associated with hair follicles. It is usually evident at birth or shortly thereafter as a flesh-colored or lightly pigmented plaque with overlying hypertrichosis on the trunk or limbs (Fig. 651-10). Transient elevation or a rippling movement of the lesion, caused by contraction of the muscle bundles, can sometimes be elicited by stroking of the surface (pseudo-Darier sign). Smooth muscle hamartoma can be mistaken for congenital pigmented nevus, but the distinction is important because the former has no risk for malignant melanoma and need not be removed.

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Chapter 652

Hyperpigmented Lesions

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DISORDERS OF PIGMENT

Normal pigmentation requires migration of melanoblasts from the neural crest to the dermal–epidermal junction, enzymatic processes to form pigment, structural components to contain the pigment (melanosomes), and transfer of pigment to the surrounding keratinocytes. Increased skin color may be generalized or localized and may result from various defects in any of these requirements. Some of these aberrations are a manifestation of systemic disease, others represent generalized or focal developmental or genetic defects, and still others may be nonspecific and the result of cutaneous inflammation.

EPHELIDES (FRECKLES)

Ephelides are light or dark brown, round, oval or irregularly shaped, well-demarcated, macules usually <3 mm in diameter that occur in sun-exposed areas such as the face, upper back, arms, and hands. They are induced by exposure to sun, particularly during the summer, and may fade or disappear during the winter. They are a result of increased sun-induced melanogenesis and melanosome transport from melanocytes to keratinocytes, and not increased number of melanocytes. They are more common in redheads and fair-haired individuals and first appear in the preschool years. Histologically, they are marked by increased melanin pigment in epidermal basal cells, which have more numerous and larger dendritic processes than the melanocytes of the surrounding paler skin. The lack of melanocytic proliferation or elongation of epidermal rete ridges distinguishes them from lentigines. Freckles have been identified as a marker for increased risk for UV-induced neoplasia and hence melanoma, independent of melanocytic nevi.

LENTIGINES

Lentigines, often mistaken for freckles or junctional nevi, are small (<3 cm), round, dark brown macules that can appear anywhere on the body with an early age of onset. They are more common in darkly pigmented than in lightly pigmented individuals. They are unrelated to sun exposure and remain permanently. Histologically, they have elongated, club-shaped, epidermal rete ridges with increased numbers of melanocytes and dense epidermal deposits of melanin. No nests of melanocytes are found. The lesions are benign and, when few, may be viewed as a normal occurrence and are seen most commonly on the lower lip.

Eruptive/generalized lentiginosis (lentiginosis profusa) involves innumerable small, pigmented macules that are present at birth or appear during childhood. There are no associated abnormalities, and mucous membranes are spared. **Carney complex** is an autosomal dominant syndrome characterized by multiple lentigines and multiple neoplasias, including: myxomas of the skin, heart (atrial) and breast; psammomatous melanotic schwannomas; epithelioid blue nevi of skin and mucosae; growth hormone-producing pituitary adenomas; and testicular Sertoli cell tumors. Components of the Carney complex have been described previously as the NAME (nevi, atrial myxoma, myxoid neurofibroma, ephelides) and LAMB (lentigines, atrial myxoma, mucocutaneous myxoma, blue nevi) syndromes. It is inherited in an autosomal dominant pattern and caused by an inactivating mutation of the *PRKAR1* gene.

The **multiple lentigines syndrome** (formerly LEOPARD) is an autosomal dominant entity consisting of a generalized, symmetric distribution of *l*entigines (Fig. 652-1) in association with *e*lectrocardiogram *a*bnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals (cryptorchidism, hypogonadism, hypospadias), growth *r*etardation, and sensorineural *d*eafness (type 1, *PTPN11* gene; type 2, *RAF1* gene). Other features include hypertrophic obstructive cardiomyopathy and pectus excavatum or carinatum.

Figure 652-1 Multiple lentigines in LEOPARD (*l*entigines in association with electrocardiogram *a*bnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals [cryptorchidism, hypogonadism, hypospadias], growth *r*etardation, and sensorineural *d*eafness) syndrome.

The **Peutz-Jeghers syndrome** is characterized by melanotic macules on the lips and mucous membranes and by gastrointestinal (GI) polyposis. It is inherited as an autosomal dominant trait (*STK11* gene). Onset is noted in infancy and early childhood when pigmented macules appear on the lips and buccal mucosa. The macules are usually a few millimeters in size but may be as large as 1-2 cm. Macules also appear occasionally on the palate, gums, tongue, and vaginal mucosa. Cutaneous lesions may develop on the nose, hands, and feet; around the mouth, eyes, and umbilicus; and as longitudinal bands or diffuse hyperpigmentation of the nails. Pigmented macules often fade from the lips and skin during puberty and adulthood but generally do not disappear from mucosal surfaces. Buccal mucosal macules are the most constant feature of the disorder; in some families, occasional members may be affected only with the pigmentary changes. Indistinguishable pigmentary changes beginning in adult life, without intestinal involvement, also occur sporadically in individuals.

Polyposis usually involves the jejunum and ileum but may also occur in the stomach, duodenum, colon, and rectum (see Chapter 345). Episodic abdominal pain, diarrhea, melena, and intussusception are frequent complications. Patients have a significantly increased risk of GI tract and non–GI tract tumors at a young age. GI cancer has been reported in ≈2-3% of patients; the lifetime relative risk for GI malignancy is 13. The relative risk of non–GI tract malignancies, including ovarian, cervical, and testicular tumors, is 9. Peutz-Jeghers syndrome must be differentiated from other syndromes associated with multiple lentigines (Laugier-Hunziker syndrome), from ordinary freckling, from Gardner syndrome, and from Cronkhite-Canada syndrome, a disorder characterized by GI polyposis, alopecia, onychodystrophy, and diffuse pigmentation of the palms, volar aspects of the fingers, and dorsal hands. Treatment of Peutz-Jeghers melanotic macules is not required or indicated, but multiple different lasers have been successful for cosmesis, in some cases.

CAFÉ-AU-LAIT SPOTS

Café-au-lait spots are uniformly hyperpigmented, sharply demarcated macular lesions, the hues of which vary with the normal degree of pigmentation of the individual: They are tan or light brown in white individuals and may be dark brown in black children (Figs. 652-2 and 652-3). Café-au-lait spots vary tremendously in size and may be large, covering a significant portion of the trunk or limb. Generally the borders are smooth, but some have exceedingly irregular borders. The lesions are characterized by increased numbers of melanocytes and

Figure 652-2 Multiple café-au-lait macules on a child with neurofibromatosis type 1. *(From Eichenfield LF, Frieden IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 372.)*

melanin in the epidermis but lack the clubbed rete ridges that typify lentigines. One to 3 café-au-lait spots are common in normal children; ≈10% of normal children have café-au-lait macules. The spots may be present at birth or may develop during childhood.

Large, often asymmetric café-au-lait spots with irregular borders are characteristic of patients with Albright **(McCune-Albright)** syndrome (*GNAS1* gene; see Chapter 562.6). This disorder includes polyostotic fibrous dysplasia of bone, leading to pathologic fractures; precocious puberty; and numerous hyperfunctional endocrinopathies. The macular hyperpigmentation may be present at birth or may develop late in childhood (see Fig. 652-3). Cutaneous pigmentation is typically most extensive on the side showing the most severe bone involvement.

Neurofibromatosis Type 1 (von Recklinghausen Disease)

The café-au-lait spot (macule) is the most familiar cutaneous hallmark of the autosomal dominant neurocutaneous syndrome known as neurofibromatosis type 1 (*NF-1*, neurofibromin gene; see Fig. 652-2 and Chapter 596.1). Included in the criteria for this diagnosis is the presence of 5 or more café-au-lait spots >5 mm in diameter in prepubertal patients or 6 or more café-au-lait spots >15 mm in diameter in postpubertal patients. Multiple café-au-lait macules commonly produce a freckled appearance of non–sun-exposed areas such as the axillae (Crowe sign), the inguinal and inframammary regions, and under the chin. Café-au-lait macules can also be seen in segmental NF-1 which results from somatic mosaicism arising from postzygotic mutations in the *NF-1* gene such that the clinical manifestations of NF-1 are present only in a localized body segment. Another variant of NF-1 is hereditary spinal neurofibromatosis, which is a rare disorder that generally presents with multiple café-au-lait macules and multiple, symmetric spinal root neurofibromas but other stigmata of NF-1 are typically absent. The lesions also occur with certain other disorders, including other types of neurofibromatosis, but in these disorders the café-au-lait spots are not a major feature of the disorder (Table 652-1).

Table 652-1 Other Syndromes Associated with Café-Au-Lait Macules

STRENGTH OF ASSOCIATION	SYNDROME	CLINICAL FEATURES	GENE OR LOCUS
Strong	Neurofibromatosis type 2	Acoustic neuromas, schwannomas, neurofibromas, meningiomas, juvenile posterior subcapsular lenticular opacity; café-au-lait seen but not a criterion for diagnosis	*NF-2*
	Multiple familial café-au-lait	Multiple café-au-lait without other stigmata of NF-1	?
	Legius (NF-1–like) syndrome	Multiple café-au-lait and skinfold freckling without other stigmata of NF-1	*SPRED1*
	McCune-Albright syndrome	Segmental café-au-lait, precocious puberty, other endocrinopathies, polyostotic fibrous dysplasia	*GNAS1*
	Constitutional mismatch repair deficiency syndrome	Multiple café-au-lait, adenomatous colonic polyps, multiple malignancies, including colonic adenocarcinoma, glioblastoma, medulloblastoma, and lymphoma	*MLH1, MSH2, MSH6, PMS2*
	Ring chromosome syndromes	Multiple café-au-lait, microcephaly, mental retardation, short stature, skeletal anomalies	Chromosomes 7, 11, 12, 15, 17
	LEOPARD/multiple lentigines syndrome	Café-au-lait, café-noir, lentigines, cardiac conduction defects, ocular hypertelorism, pulmonary stenosis, genitourinary anomalies, growth retardation, hearing loss	*PTPN11*
	Cowden syndrome (multiple hamartoma syndrome)	Facial trichilemmomas, cobblestoning of the oral mucosa, predisposition to soft tissue tumors (lipomas, neuromas), gastrointestinal polyps, fibrocystic breast disease and breast carcinoma, thyroid adenoma, and thyroid cancer	*PTEN*

Continued

Table 652-1 Syndromes Associated with Café-Au-Lait Macules—cont'd

STRENGTH OF ASSOCIATION	SYNDROME	CLINICAL FEATURES	GENE OR LOCUS
	Bannayan-Riley-Ruvalcaba syndrome	Facial trichilemmomas, oral papillomas, pigmented genital macules, gastrointestinal polyps, macrocephaly, vascular anomalies, mental retardation	*PTEN*
Weak	Ataxia-telangiectasia	Cerebellar ataxia, cutaneous and ocular telangiectasias, immunodeficiency, hypogonadism, predisposition to lymphoreticular malignancy	*ATM*
	Bloom syndrome	Photosensitivity, immunodeficiency, chronic lung disease, cryptorchidism, syndactyly, short stature, susceptibility to malignancy	*RECQL3*
	Fanconi anemia	Bone marrow failure, multiple congenital anomalies, predisposition to malignancy, mental retardation, microcephaly	*FANCA, FANCB* (putative), *FANCC, FANCD* locus on chromosome 3, *FANCE* locus on chromosome 6, *FANCF, FANCG, FANCH* (putative)
	Russell-Silver syndrome	Short stature, craniofacial and body asymmetry, low birthweight, microcephaly, triangular facies, fifth finger clinodactyly, congenital cardiac defects	?
	Tuberous sclerosis	Facial angiofibromas, cutaneous collagenomas, seizures, mental retardation, hypomelanotic macules, periungual fibromas, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, pulmonary lymphangiomyomatosis renal angiomyolipoma, retinal hamartomas	*TSC1, TSC2*
	Turner syndrome	Short stature, lymphedema, congenital heart disease, valgus deformity	X-chromosomal anomalies (XO karyotype or Xp deletion)
	Noonan syndrome	Facial dysmorphism, pulmonary valve stenosis, webbed neck, pectus excavatum, mental retardation, short stature, cryptorchidism, hematologic malignancies	*PTPN11, SOS1, RAF1, KRAS*
	Multiple mucosal neuroma (MEN) syndrome 1	Parathyroid adenoma, pituitary adenoma, pancreatic islet adenoma, lipoma, gingival papules, facial angiofibromas, collagenomas	*MENIN*
	MEN syndrome 2B	Mucosal neuromas, pheochromocytoma, medullary thyroid carcinoma, parathyroid adenoma, marfanoid habitus	*RET*
	Johanson-Blizzard syndrome	Short stature, failure to thrive, microcephaly, sensorineural hearing loss, dental anomalies, congenital heart disease, exocrine pancreatic insufficiency, imperforate anus, genitourinary anomalies, mental retardation, hypothyroidism	*UBR1*
	Microcephalic osteodysplastic primordial dwarfism, type II	Short stature, microcephaly, intrauterine growth retardation, dysmorphic facies, skeletal anomalies, developmental delay, premature puberty	*PCNT2*
	Nijmegen breakage syndrome	Short stature, growth retardation, microcephaly, cleft lip/palate, dysmorphic facies, bronchiectasis, sinusitis, dysgammaglobulinemia with recurrent urinary tract and gastrointestinal infections, mental retardation, spontaneous chromosomal instability, predisposition to malignancy	*NBS1*
	Rubinstein-Taybi syndrome	Short stature, microcephaly, dysmorphic facies, congenital cardiac disease, sternal anomalies, skeletal anomalies, mental retardation	*CREBBP, EP300*
	Kabuki syndrome	Postnatal growth retardation, microcephaly, dysmorphic facies, congenital cardiac defects, malabsorption, anal stenosis, genitourinary anomalies, congenital hip dysplasia, hirsutism, mental retardation	?

From Shah KN: The diagnostic and clinical significance of café-au-lait macules. Pediatr Clin North Am *57(5):1131–1153, 2010, Table 2.*

Figure 652-3 Multiple patterned café-au-lait spots in a child with McCune-Albright syndrome. *(From Eichenfield LF, Frieden IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 373.)*

INCONTINENTIA PIGMENTI (BLOCH-SULZBERGER DISEASE)

See Chapter 596.7.

POSTINFLAMMATORY PIGMENTARY CHANGES

Either hyperpigmentation or hypopigmentation can occur as a result of cutaneous inflammation. Alteration in pigmentation usually follows a severe inflammatory reaction but may result from mild dermatitis. Dark-skinned children are more likely to show these changes than fair-skinned ones. Although altered pigmentation may persist for weeks to months, patients can be reassured that these lesions are usually temporary.

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Chapter 653

Hypopigmented Lesions

Sheila S. Galbraith

ALBINISM

Several types of congenital oculocutaneous albinism (OCA) consist of partial or complete failure of melanin production in the skin, hair, and eyes despite the presence of normal number, structure, and distribution of melanocytes. They may be divided into 2 major classes: those with abnormal protein function involved in the formation and transfer of melanin, and those with defects in melanosomes (Table 653-1).

Table 653-1 Genes Associated with Hypopigmentation

DISORDER	GENE DEFECT
OCULOCUTANEOUS ALBINISM	
OCA1	Tyrosinase
OCA2	P protein
OCA3	*TRP-1*
OCA4	*MATP*
HERMANSKY-PUDLAK	
Type 1	HPS-1 Mouse (pale ear)
Type 2	HPS-2 b3A subunit of AP3
Type 3	HPS-3 Mouse (cocoa)
Type 4	HPS-4 Mouse (light ear)
Type 5	HPS-5 KIAA107
Type 6	HPS-6 Mouse (ruby eye)
Type 7	HPS-7 DTNBP1
Type 8	HPS-8 Bloc153
CHÉDIAK-HIGASHI	*CHS1/LYST*
PIEBALDISM	C-KIT receptor Heterozygous SLUG
WAARDENBURG	
Type 1	Heterozygous PAX-3
Type 2a	*MITF*
Type 2b	Chromosome 1p
Type 2c	Chromosome 8p23
Type 2d	*SNAIL*
Type 2e	*SOX10*
Type 3	Homozygous PAX-3
Type 4	*SOX10* Endothelin 3 Endothelin B receptor

Tyrosinase is the copper-containing enzyme that catalyzes at multiple steps in melanin biosynthesis (see Chapter 85.2). Tyrosinase-positive variants are characterized by darkening of the hair bulb on incubation with tyrosine.

Oculocutaneous albinism type 1 (OCA1) is characterized by great reduction in or absence of tyrosinase activity. OCA1A, the most severe form, is characterized by a lack of visible pigment in hair, skin, and eyes (Fig. 653-1). This manifests as photophobia, nystagmus, defective visual acuity, white hair, and white skin. The irises are blue-gray in oblique light and prominent pink in reflected light. OCA1B, or yellow mutant albinism, manifests at birth as white hair, pink skin, and gray eyes. This type is particularly prevalent in Amish communities. Progressively the hair becomes yellow-red, the skin tans lightly on exposure to the sun, and the irises may accumulate some brown pigment, with a resultant improvement in visual acuity. Photophobia and nystagmus are present but mild. OCATS is a temperature-sensitive type of albinism. The abnormal tyrosinase has decreased activity at 35-37°C (95-98.6°F). Therefore, cooler regions of the body such as the limbs and head pigment to some degree, whereas other areas remain depigmented.

OCA2 ranges from nearly normal to closely resembling type 1 albinism. This is the most common form of albinism seen worldwide. Little or no melanin is present at birth, but pigment, particularly red-yellow pigment, may accumulate during childhood to produce straw-colored or light brown skin in white individuals. Pigmented nevi may develop. Progressive improvement in visual acuity and nystagmus occurs with aging. Black individuals may have yellow-brown skin, dark-brown freckles in sun-exposed areas, and brown coloration of the irises. **Brown OCA** is an allelic variant of OCA2. Prader-Willi and Angelman syndromes, which include hypopigmentation, have deletions that include the gene involved in OCA2.

OCA3 (rufous albinism) is seen predominantly in patients of African descent. It is characterized by red hair, reddish brown skin, pigmented nevi, freckles, reddish brown to brown eyes, nystagmus, photophobia, and decreased visual acuity.

Figure 653-1 White hair and skin in oculocutaneous albinism type 1 (OCA1).

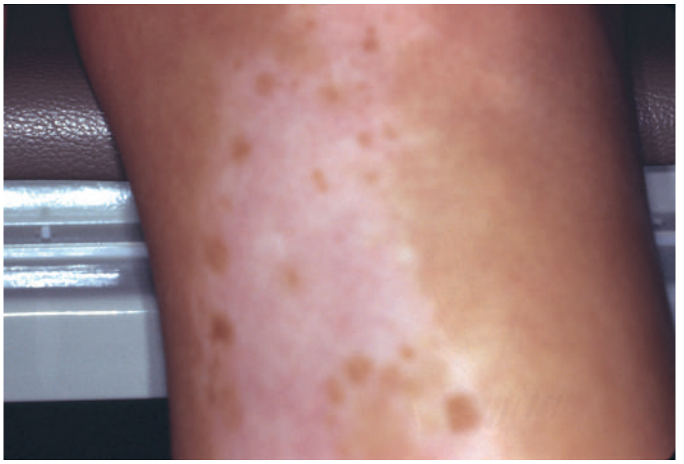

Figure 653-2 Depigmented macule with islands of hyperpigmentation in piebaldism.

OCA4 is a rare OCA with clinical findings similar to those in OCA2.

The **Cross-McKusick-Breen syndrome** consists of tyrosinase-positive albinism with ocular abnormalities, cognitive impairment, spasticity, and athetosis. The genetic defect is unidentified.

Because of the absence of normal protection by adequate amounts of epidermal melanin, persons with albinism are predisposed to development of actinic keratoses and cutaneous carcinoma secondary to skin damage by ultraviolet light. Protective clothing and a broad-spectrum sunscreen (see Chapter 656) should be worn during exposure to sunlight.

Oculocutaneous Albinism with Melanosomal Abnormalities

See Table 653-1.

Hermansky-Pudlak syndrome is a collection of autosomal recessive genetic disorders characterized by OCA, ceroid accumulation in lysosomes, and prolonged bleeding time. In mice, 16 distinct genetic loci that produce coat color mutant phenotypes associated with platelet deficiencies are recognized; eight have been identified in humans.

Chédiak-Higashi syndrome (see Chapter 130) is another genetic abnormality associated with dysfunction of lysosome-related organelles. Patients with Chédiak-Higashi syndrome have hypopigmentation of the skin, eyes, and hair; prolonged bleeding times and easy bruising; recurrent infections; abnormal natural killer cell function; and peripheral neuropathy. Chédiak-Higashi syndrome is caused by mutations in the *CHS1/LYST* gene, which is a lysosomal trafficking regulatory gene.

MELANOBLAST MIGRATION ABNORMALITIES

See Table 653-1.

Piebaldism

A congenital autosomal dominant disorder, piebaldism is characterized by sharply demarcated amelanotic patches that occur most frequently on the forehead, anterior scalp (producing a white forelock), ventral trunk, elbows, and knees. Islands of normal or darker-than-normal pigmentation may be present within the amelanotic areas (Fig. 653-2). The plaques are a result of a permanent localized absence of melanocytes as a result of a defect in the *KIT* protooncogene, which encodes the cell surface receptor transmembrane tyrosine kinase. The pattern of depigmentation arises from defective melanoblast migration from the neural crest during development. The reason that piebaldism is a localized and not a generalized process remains unknown. Piebaldism must be differentiated from vitiligo, which may be progressive and is not usually congenital, nevus depigmentosus, and Waardenburg syndrome.

Waardenburg Syndrome

Waardenburg syndrome also manifests at birth as localized areas of depigmented skin and hair. There are 4 types of Waardenburg syndrome. The hallmark of Waardenburg type 1 is the white forelock, which is seen in 20-60% of patients. Only 15% of patients have areas of depigmented skin. Deafness occurs in 9-37%, heterochromia irides in 20%, and unibrow (synophrys) in 17-69% of those affected. Dystopia canthorum (i.e., telecanthus) is seen in all patients with Waardenburg type 1. Waardenburg type 2 is similar to type 1, except that patients with type 2 lack dystopia canthorum, but they also have a higher incidence of deafness. Waardenburg type 3 is similar to Waardenburg type 1, except that patients also have limb abnormalities. It is also called the Klein-Waardenburg syndrome. Waardenburg type 4 is also called the Shah-Waardenburg syndrome. Patients with this type all have Hirschsprung disease. Dystopia canthorum is seldom seen in these patients.

Tuberous Sclerosis Complex (*TSC1, TSC2* Genes)

See Chapter 596.2 for a discussion of this complex.

Hypomelanosis of Ito

Hypomelanosis of Ito is a rare congenital skin disorder affecting children of both sexes that can have associated defects in several organ systems. There is no evidence for genetic transmission; chromosomal mosaicism and chromosomal translocations have been reported. Hypomelanosis of Ito is currently a descriptive rather than definitive diagnosis. Blaschkoid or mosaic hypomelanosis is a better descriptive term.

The skin lesions of hypomelanosis of Ito are generally present at birth but may be acquired in the 1st 2 yr of life. The lesions are similar to a negative image of those present in incontinentia pigmenti, consisting of bizarre, patterned, hypopigmented macules arranged over the body surface in sharply demarcated whorls, streaks, and patches that follow the lines of Blaschko (Fig. 653-3). The palms, soles, and mucous

Figure 653-3 Marbled hypopigmented streaks on the abdomen in hypomelanosis of Ito.

Figure 653-4 Sharply demarcated, symmetric, depigmented areas of vitiligo.

membranes are spared. The hypopigmentation remains unchanged throughout childhood but fades during adulthood. The degree of depigmentation varies from hypopigmented to achromic. Neither inflammatory nor vesicular lesions precede the development of the pigmentary changes as in incontinentia pigmenti. The hypopigmented areas demonstrate fewer and smaller melanocytes and a decreased number of melanin granules in the basal cell layer than normal. Inflammatory cells and pigment incontinence are lacking.

The majority of patients with mosaic hypomelanosis have no associated abnormalities, but involvement of other organs systems can rarely occur. The most commonly associated abnormalities involve the nervous system, including intellectual disability (70%), seizures (40%), microcephaly (25%), and muscular hypotonia (15%). The musculoskeletal system is the second most frequently involved system, affected by scoliosis and thoracic and limb deformities. Minor ophthalmologic defects (strabismus, nystagmus) are present in 25% of patients, and 10% have cardiac defects. These frequencies are likely to be overestimated because patients with isolated skin disease often do not seek further evaluation. The differential diagnosis includes systematized nevus depigmentosus, which is a stable leukoderma not associated with systemic manifestations. Differentiation from incontinentia pigmenti, particularly the hypopigmented fourth stage, is critical for genetic counseling because incontinentia pigmenti, unlike hypomelanosis of Ito, is inherited.

Vitiligo

Epidemiology and Etiology

Vitiligo is macular depigmentation associated with the destruction of melanocytes. The disorder represents a clinical end-point resulting from a complex interaction of environmental, genetic, and immunologic factors. Autoimmune, genetic, autocytotoxic, and neural theories have been postulated. The prevalence is 0.5% of most populations.

There is definitely an **autoimmune** component to vitiligo. Eighty percent of patients with active disease have an antibody to a surface antigen on pigmented melanocytes. These antibodies appear to be cytotoxic for melanocytes. There is also a correlation between disease activity and the titer of serum antimelanocyte antibody. Melanocyte-specific CD8+ T lymphocytes are also involved in the pathogenesis of vitiligo. These antibodies and T cells recognize a variety of melanocyte enzymatic and structural proteins.

The genetic epidemiology of vitiligo is part of a broader genetically determined autoimmune and autoinflammatory diathesis. Fifteen to 20% of patients with generalized vitiligo have 1 or more affected 1st-degree relatives. In these families the genetic pattern is suggestive of polygenic, multifactorial inheritance. In the other patients, the disease occurs sporadically.

Many authorities believe that the cause of melanocyte destruction in vitiligo is an endogenous cellular abnormality. It has been suggested that melanocytes are destroyed because of the accumulation of a toxic melanin synthesis intermediate and/or lack of protection from hydrogen peroxide and other oxygen radicals. There is in vitro evidence that some of these metabolites may be lethal to melanocytes. Others believe that neurochemical factors damage melanocytes and cause depigmentation. This possibility would explain the pattern of involvement in segmental vitiligo that runs roughly along the course of a dermatome.

Table 653-2 Typical Features of Segmental and Nonsegmental Vitiligo

SEGMENTAL VITILIGO	NONSEGMENTAL VITILIGO
Often begins in childhood	Can begin in childhood, but later onset is more common
Has rapid onset and stabilizes	Is progressive, with flare-ups
Involves hair compartment soon after onset	Involves hair compartment in later stages
Is usually not accompanied by other autoimmune diseases	Is often associated with personal or family history of autoimmunity
Often occurs in the face	Commonly occurs at sites sensitive to pressure and friction and prone to trauma
Is usually responsive to autologous grafting, with stable repigmentation	Frequently relapses in situ after autologous grafting
Can be difficult to distinguish from nevus depigmentosus, especially in cases with early onset	

From Taïeb A, Picardo M: Vitiligo, N Engl J Med *360:160–168, 2009.*

Clinical Manifestations

There are 2 subtypes of vitiligo, generalized (nonsegmental) and segmental, which probably are distinctly different diseases (Table 653-2). Generalized vitiligo (85-90% of cases) may be divided into widespread (type A) and localized (type B). Approximately 50% of all patients with vitiligo have onset before 18 yr of age, and 25% demonstrate depigmentation before age 8 yr. Most children have the generalized form, but the segmental type is more common among children than among adults. Patients with the generalized form usually present with a remarkably symmetric pattern of white macules and patches (Fig. 653-4); the margins may be somewhat hyperpigmented. The

patches tend to be acral and/or periorificial. Occasionally, almost the entire skin surface becomes depigmented.

There are several varieties of localized vitiligo. A form of localized vitiligo is the halo nevus phenomenon, whereby benign moles develop depigmented rings at the periphery. Premature graying of scalp hair (canities) has also been considered a form of localized vitiligo. In segmental vitiligo, depigmented areas are limited to a quasidermatomal distribution. This type of vitiligo has a rapid onset and progression in a localized area without the development of depigmentation in other areas.

A number of **autoimmune diseases** occur in patients with vitiligo, including Addison disease, Hashimoto thyroiditis, pernicious anemia, diabetes mellitus, hypoparathyroidism, and polyglandular autoimmune syndrome with selective immunoglobulin A deficiency. In addition, other diseases with possible immune defects, such as alopecia areata and morphea, have been seen in patients with vitiligo.

Vogt-Koyanagi-Harada syndrome is vitiligo associated with uveitis, dysacusia, meningoencephalitis, and depigmentation of the skin, scalp hair, eyebrows, and eyelashes. In the **Alezzandrini syndrome**, vitiligo is associated with tapetoretinal degeneration and deafness.

Light microscopic examination of early lesions shows mild inflammatory change. Over time, degenerative changes occur in melanocytes, leading to their complete disappearance.

The differential diagnosis of vitiligo includes other causes of widespread acquired leukoderma. The two most common problem diagnoses are tinea versicolor and postinflammatory hypopigmentation.

Treatment

Localized areas of vitiligo may respond to potent topical steroid, topical tacrolimus, or topical pimecrolimus. In patients with more extensive involvement, narrow-band ultraviolet light B (UVB) [UVB311] is the treatment of choice. In all forms of vitiligo, response to therapy is slow, taking many months to years. For those not interested in treatment, cover-up cosmetics may be used. All areas of vitiligo are susceptible to sun damage, and care should be taken to minimize sun exposure of affected areas. Spontaneous remission may be seen in a small percentage of cases.

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Chapter 654

Vesiculobullous Disorders

Joel C. Joyce

Many diseases are characterized by vesiculobullous lesions; they vary considerably in cause, age of onset, and pattern. The morphology and distribution of the blister often provides a visual clue to the location of the lesion within the skin. Blisters localized to the **epidermal layers** are thin-walled, relatively flaccid, and easily ruptured. **Subepidermal blisters** are tense, thick-walled, and more durable. Biopsies of blisters can be diagnostic because the level of cleavage within the skin and associated findings, such as the nature of the inflammatory infiltrate, are characteristic for a particular disorder. Other diagnostic procedures, such as immunofluorescence and electron microscopy, can often help distinguish vesiculobullous disorders that have nearly identical histopathologic findings (Table 654-1).

Table 654-1 Sites of Blister Formation and Diagnostic Studies for the Vesiculobullous Disorders

DISORDER	BLISTER CLEAVAGE SITE	DIAGNOSTIC STUDIES
Acrodermatitis enteropathica	IE	Zn level
Bullous impetigo	GL	Smear, culture
Bullous pemphigoid	SE (junctional)	Direct and indirect immunofluorescence studies
Candidosis	SC	KOH preparation, culture
Dermatitis herpetiformis	SE	Direct immunofluorescence studies
Dermatophytosis	IE	KOH preparation, culture
Dyshidrotic eczema	IE	Routine histopathology
EB—simplex	IE	Electron microscopy; immunofluorescence mapping
EB of the hands and feet	IE	Electron microscopy; immunofluorescence mapping
Junctional EB (lethalis)	SE (junctional)	Electron microscopy; immunofluorescence mapping
Recessive dystrophic EB	SE	Electron microscopy; immunofluorescence mapping
Dominant dystrophic EB	SE	Electron microscopy; immunofluorescence mapping
Epidermolytic hyperkeratosis	IE	Routine histopathology
Erythema multiforme	SE	Routine histopathology
Erythema toxicum	SC, IE	Smear for eosinophils
Incontinentia pigmenti	IE	Smear for eosinophils Routine histopathology
Insect bites	IE	Routine histopathology
Kindler syndrome	IE, SE	Electron microscopy; immunostaining
Linear immunoglobulin A dermatosis	SE	Direct immunofluorescence studies

Table 654-1 Sites of Blister Formation and Diagnostic Studies for the Vesiculobullous Disorders—cont'd

DISORDER	BLISTER CLEAVAGE SITE	DIAGNOSTIC STUDIES
Mastocytosis	SE	Routine histopathology
Miliaria crystallina	IC	Routine histopathology
Neonatal pustular melanosis	SC, IE	Smear for cells
Pemphigus foliaceus	GL	Direct and indirect immunofluorescence studies Tzanck smear
Pemphigus vulgaris	Suprabasal	Direct and indirect immunofluorescence studies Tzanck smear
Scabies	IE	Scraping
Staphylococcal scalded skin syndrome	GL	Routine histopathology
Toxic epidermal necrolysis	SE	Routine histopathology
Viral blisters	IE	Tzanck smear for herpesvirus infections Direct immunofluorescence for herpes simplex virus and varicella-zoster virus Culture Routine histopathology

EB, epidermolysis bullosa; GL, granular layer; IC, intracorneal; IE, intraepidermal; KOH, potassium hydroxide; SC, subcorneal; SE, subepidermal.

654.1 Erythema Multiforme

Joel C. Joyce

ETIOLOGY

Among the numerous factors implicated in the etiology of erythema multiforme (EM), infection with herpes simplex virus (HSV) is the most common. Infection with *Mycoplasma pneumoniae* is implicated, particularly in children and young adults, but differentiation from Stevens-Johnson syndrome and the so-called *M. pneumoniae*-associated mucositis (see below) can be confusing. HSV labialis and, less commonly, HSV genitalis are implicated in 60-70% of episodes of EM and are believed to trigger nearly all episodes of recurrent EM, frequently in association with sun exposure. HSV antigens and DNA are present in skin lesions of EM but are absent in nonlesional skin. The presence of the human leukocyte antigens A33, B62, B35, DQw3 (DQB1*0301 split), and DR53 is associated with an increased risk of HSV-induced EM, particularly the recurrent form. Most patients experience a single self-limited episode of EM. Lesions of HSV-induced recurrent EM typically develop 10-14 days after onset of recurrent HSV eruptions, have a similar appearance from episode to episode, but may vary in frequency and duration in a given patient. Not all episodes of recurrent HSV evolve into EM in susceptible patients.

Drug-related EM is less common (<10% of patients) and may be associated with nonsteroidal antiinflammatory agents, including acetaminophen, sulfonamides, and other antibiotics. The differential diagnosis in drug-related EM should include toxic epidermal necrolysis and drug hypersensitivity syndrome.

CLINICAL MANIFESTATIONS

EM has numerous morphologic manifestations on the skin, varying from erythematous macules, papules, vesicles, bullae, or urticaria-appearing plaques to patches of confluent erythema. The eruption appears most commonly in patients between the ages of 10 and 40 yr (with highest incidence in males in the 2nd decade) and usually is asymptomatic, although a burning sensation or pruritus may be present. The diagnosis of EM is established by finding the classic lesion: doughnut-shaped, target-like (iris or bull's-eye) papules with an erythematous outer border, an inner pale ring, and a dusky purple to necrotic center (which sometimes blisters and erodes; Figs. 654-1 and 654-2).

Figure 654-1 Early fixed papules with a central dusky zone on the dorsum of the hand of a child with erythema multiforme caused by herpes simplex virus. *(From Weston WL, Lane AT, Morelli J:* Color textbook of pediatric dermatology, *ed 3, St. Louis, 2002, Mosby, p. 156.)*

EM is characterized by an abrupt, symmetric cutaneous eruption, most commonly on the extensor upper extremities; lesions are relatively sparse on the face, trunk, and legs. Lesions can be seen on the palms and soles. The eruption often appears initially as red macules or urticarial plaques that expand centrifugally to form lesions up to 2 cm in diameter with a dusky to necrotic center. Lesions of a particular episode typically appear within 72 hr and remain fixed in place (average duration: 7 days). Oral lesions may occur with a predilection for the vermilion border of the lips and the buccal mucosa, but other mucosal surfaces are spared. EM may manifest initially as urticarial-like lesions, but in distinction to urticaria, a given lesion of EM does not fade within 24 hr. Prodromal symptoms are generally absent. Prognosis is favorable with limited long-term morbidity. Lesions typically resolve without sequelae in approximately 2 wk, but in darker pigmented individuals, pigmentary alterations at the site of lesions can be longstanding. Progression to Stevens-Johnson syndrome does not occur. Many authors distinguish between EM minor (mainly cutaneous typical or atypical targetoid lesions affecting less than 10% body surface area plus no or limited mucosal involvement, often limited to 1 site,

Figure 654-2 "Target" or "iris" lesions with characteristic central dusky zone on palms of a child with erythema multiforme caused by herpes simplex virus. *(From Weston WL, Lane AT, Morelli J: Color* textbook of pediatric dermatology, *ed 3, St. Louis, 2002, Mosby, p. 156.)*

such as the mouth) from EM major (same cutaneous involvement pattern as EM minor plus 2 or more mucosal sites with more-severe oral involvement). EM major and Stevens-Johnson syndrome are accepted to be separate entities.

Pathogenesis

The pathogenesis of EM is unclear, but it may be a host-specific, cell-mediated immune response to an antigenic stimulus, resulting in damage to keratinocytes. HSV *Pol1* gene expressed in HSV-induced recurrent EM lesions upregulates/activates the transcription factor SP1 and inflammatory cytokines. These cytokines, released by activated mononuclear cells and keratinocytes, may contribute to epidermal cell death and constitutional symptoms.

Pathology

Microscopic findings in EM are variable but may aid in diagnosis. Early lesions typically show slight intercellular edema, rare dyskeratotic keratinocytes, and basal vacuolation in the epidermis and a perivascular lymphohistiocytic infiltrate with edema in the upper dermis. More mature lesions show an accentuation of these characteristics and the development of lymphocytic exocytosis and an intense, perivascular, and interstitial mononuclear infiltrate in the upper third of the dermis. In severe cases, the entire epidermis becomes necrotic.

Differential Diagnosis

The **differential diagnosis** of EM also includes bullous pemphigoid, pemphigus, linear immunoglobulin (Ig) A dermatosis, graft-versus-host disease, fixed-drug eruption, bullous-drug eruption, urticaria, viral infections such as HSV, reactive arthritis syndromes, Kawasaki disease, Sweet syndrome, Behçet disease, allergic vasculitis, erythema annulare centrifugum, polymorphous-drug eruption, and periarteritis nodosa. EM that primarily involves the oral mucosa may be confused with Stevens-Johnson syndrome, bullous pemphigoid, pemphigus vulgaris, vesiculobullous or erosive lichen planus, Behçet syndrome, recurrent aphthous stomatitis, and primary herpetic gingivostomatitis. Serum sickness–like reaction to cefaclor (or other antibiotics) may also manifest as EM-like lesions; the lesions may develop a dusky to purple center, but in most cases, the eruption of cefaclor-induced serum sickness–like reaction is pruritic, transient, and migratory and is probably urticarial rather than true EM.

Treatment

Treatment of EM is supportive. Topical emollients, systemic antihistamines, and nonsteroidal antiinflammatory agents do not alter the course of the disease but may provide symptomatic relief. For individuals with severe mucosal disease, opioids can be used to control pain and diligent oral hygiene is essential. No controlled, prospective studies support the use of corticosteroids in the management of EM. Prophylactic oral acyclovir given for 6 mo may be effective in controlling *recurrent episodes of HSV-associated EM*. On discontinuation of acyclovir, both HSV and EM may recur, although episodes may be less frequent and milder. For recurrent cases not responsive to antiviral therapy, steroid-sparing agents used to decrease frequency of recurrence include azathioprine, mycophenolate mofetil, and dapsone. Appropriate laboratory monitoring is recommended.

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654.2 Stevens-Johnson Syndrome

Joel C. Joyce

ETIOLOGY

Drugs, particularly sulfonamides, nonsteroidal antiinflammatory agents, antibiotics, and anticonvulsants, are the most common precipitants of Stevens-Johnson syndrome and toxic epidermal necrolysis. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN; see below) exist along a spectrum: SJS is defined as affected body surface area <10%, SJS-TEN overlap syndrome is affected body surface area between 10% and 30%, and TEN is affected body surface area >30%. **TEN** is the most-severe disorder in the clinical spectrum of the disease, involving considerable constitutional toxicity and extensive necrolysis of the mucous membranes and >30% of the body surface area. Human leukocyte antigen (HLA)-B*1502 and HLA-B*5801 are implicated in the development of these 2 disorders in Han Chinese patients receiving carbamazepine and in Japanese patients receiving allopurinol, respectively.

Infections, particularly in children, also are associated with SJS, although current thinking defines most cases of classic SJS as secondary to medications. Terms such as "***M. pneumoniae*-associated mucositis**" or "**atypical SJS**" have caused difficulty with diagnosis and classification. Individuals, typically children or young adults, often with upper respiratory symptoms from *M. pneumoniae* infection, suffer from variable degrees of mucosal ulceration and erosion (typically mouth but including other mucosae) but lack other cutaneous involvement (unlike traditional SJS-TEN) and are found to have evidence of infection with *M. pneumoniae*, typically by polymerase chain reaction evaluation. In addition to supportive treatment below, affected individuals benefit from antimicrobial treatment for *M. pneumoniae*. Morbidity is typically less severe than for SJS-TEN spectrum disease.

Clinical Manifestations

Cutaneous lesions in SJS generally consist initially of erythematous macules that rapidly and variably develop central necrosis to form vesicles, bullae, and areas of denudation on the face, trunk, and extremities. The skin lesions are typically more widespread than in EM and are accompanied by involvement of **2 or more mucosal surfaces,** namely the eyes, oral cavity, upper airway or esophagus, gastrointestinal tract, or anogenital mucosa (Fig. 654-3). A burning sensation, edema, and erythema of the lips and buccal mucosa are often the presenting signs, followed by development of bullae, ulceration, and hemorrhagic crusting. Lesions may be preceded by a flu-like upper respiratory illness. Pain from mucosal ulceration is often severe, but skin tenderness is minimal to absent in SJS, in contrast to pain in TEN. Corneal ulceration, anterior uveitis, panophthalmitis, bronchitis, pneumonitis, myocarditis, hepatitis, enterocolitis, polyarthritis, hematuria, and acute tubular necrosis leading to renal failure may occur. Disseminated cutaneous bullae and erosions may result in increased insensible fluid loss and a high risk of bacterial superinfection and sepsis. New lesions occur in crops, and complete healing may take 4-6 wk; ocular scarring, visual impairment, and strictures of the

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Figure 654-3 Bullae are present on the conjunctivae **(A)** and in the mouth **(B)** with Stevens-Johnson syndrome. **C,** Sloughing, ulceration, and necrosis in the oral cavity interfere with eating. Genital lesions cause dysuria and interfere with voiding. *(From Habif TP, editor:* Clinical dermatology, *ed 4, Philadelphia, 2004, Mosby, p. 631.)*

esophagus, bronchi, vagina, urethra, or anus may remain. Nonspecific laboratory abnormalities in SJS include leukocytosis, elevated erythrocyte sedimentation rate, and, occasionally, increased liver transaminase levels and decreased serum albumin values.

Pathogenesis

Pathogenesis is related to drug-specific CD8+ cytotoxic T cells, with perforin/granzyme B and granulysin triggering keratinocyte apoptosis. This process is followed by expanded enactment of apoptosis involving the interaction of soluble Fas ligand with Fas receptor. Recently, consideration has been given to the role that macrophages/monocytes play in development of SJS/TEN via tumor necrosis factor-α, tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), and tumor necrosis factor–inducer of apoptosis weak (TWEAK) signaling pathways. It is likely that many affected individuals have yet unrecognized underlying genetic predispositions.

Differential Diagnosis

The differential diagnosis of SJS includes TEN, urticaria, *M. pneumoniae*–associated mucositis, DRESS (drug rash [or reaction] with eosinophilia and systemic symptoms) syndrome (see Chapter 645.2) and other drug eruptions and viral exanthems, including Kawasaki disease. SJS has rarely been reported in patients with systemic lupus erythematosus.

Treatment

Management of SJS is supportive and symptomatic. Potentially offending drugs must be discontinued as soon as possible. Ophthalmologic consultation is mandatory because ocular sequelae such as corneal scarring can lead to vision loss. Application of cryopreserved amniotic membrane to the ocular surface during the acute phase of the disease limits the destructive and long-term sequelae. Early topical steroid treatment may also reduce ocular sequelae. Oral lesions should be managed with mouthwashes and glycerin swabs. Vaginal lesions should be observed closely and treated to prevent vaginal stricture or fusion. Topical anesthetics (diphenhydramine, dyclonine, viscous lidocaine) may provide relief from pain, particularly when applied before eating. Denuded skin lesions can be cleansed with saline or Burrow solution compresses. Antibiotic therapy is appropriate for documented secondary bacterial infection. Treatment may require admission to an intensive care unit; IV fluids; nutritional support; sheepskin or air–fluid bedding; daily saline or Burrow solution compresses; paraffin gauze or colloidal gel (Hydrogel) dressing of denuded areas; saline compresses on the eyelids, lips, or nose; analgesics; and urinary catheterization (when needed). A daily examination for infection and ocular lesions, which constitute the major cause of long-term morbidity, is essential. Systemic antibiotics are indicated for documented urinary or cutaneous infections and for suspected bacteremia (*Staphylococcus aureus* or *Pseudomonas aeruginosa*) because infection is the leading cause of death. Prophylactic systemic antibiotics are not necessary. Although corticosteroids are sometimes advocated in early, severe cases of SJS, no prospective double-blind studies evaluating their efficacy have been reported. Most authorities discourage their use because of reports of increased morbidity and mortality (sepsis) with their administration, although definitive trials in children are lacking. IV immunoglobulin (IVIG; 1.5-2.0 g/kg/day × 3 days) should be considered in early disease. Total dose greater than 2 g/kg has shown improved but not statistically significant outcomes in children compared to adults. Other immunosuppressive treatment regimens have not demonstrated clear benefit or repeated success in multiple controlled studies.

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654.3 Toxic Epidermal Necrolysis

Joel C. Joyce

EPIDEMIOLOGY AND ETIOLOGY

The pathogenesis of TEN is not proved but may involve a hypersensitivity phenomenon that results in damage primarily to the basal cell layer of the epidermis. Epidermal damage appears to result from keratinocyte apoptosis (see Chapter 654.2). This condition is triggered by many of the same factors that are thought to be responsible for SJS, principally drugs such as the sulfonamides, amoxicillin, phenobarbital, hydantoin, and allopurinol. TEN is defined by (1) widespread blister formation and morbilliform or confluent erythema, associated with skin tenderness; (2) absence of target lesions; (3) sudden onset and generalization within 24-48 hr; (4) histologic findings of full-thickness epidermal necrosis and a minimal-to-absent dermal infiltrate. These criteria categorize TEN as a separate entity from EM.

CLINICAL MANIFESTATIONS

The prodrome consists of fever, malaise, localized skin tenderness, and diffuse erythema. Inflammation of the eyelids, conjunctivae, mouth, and genitals may precede skin lesions. Flaccid bullae may develop,

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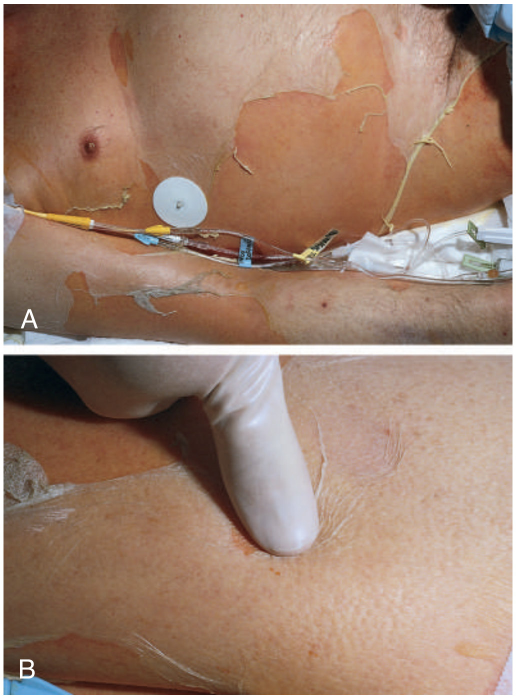

Figure 654-4 **A,** Large sheets of full-thickness epidermis are shed. **B,** Toxic epidermal necrolysis begins with diffuse, hot erythema. In hours the skin becomes painful, and with slight thumb pressure, the skin wrinkles, slides laterally, and separates from the dermis (Nikolsky sign). *(From Habif TP, editor:* Clinical dermatology*, ed 4, Philadelphia, 2004, Mosby, p. 633.)*

although this is not a prominent feature. Characteristically, full-thickness epidermis is lost in large sheets (Fig. 654-4). The **Nikolsky sign** (denudation of the skin with gentle tangential pressure) is present but only in the areas of erythema (Fig. 654-4). Healing takes place over 14 or more days. Scarring, particularly of the eyes, may result in corneal opacity. The course may be relentlessly progressive, complicated by severe dehydration, electrolyte imbalance, shock, and secondary localized infection and septicemia. Loss of nails and hair may also occur. Long-term morbidity includes alterations in skin pigmentation, eye problems (lack of tears, conjunctival scarring, loss of lashes), and strictures of mucosal surfaces. The **differential diagnosis** includes staphylococcal scalded skin syndrome, in which the blister cleavage plane is intraepidermal; graft-versus-host disease; chemical burns; drug eruptions; toxic shock syndrome; and pemphigus. The use of skin histopathology to differentiate SJS-TEN from other similar blistering disorders can be difficult, but early full-thickness epidermal necrosis tends to portend a worse clinical prognosis.

Anticonvulsant hypersensitivity syndrome (DRESS syndrome; see Chapter 645.2) is a multisystem reaction that appears approximately 3 wk to 3 mo after the start of therapy with the offending agent. The skin eruption is red-pink morbilliform eruption often associated with facial swelling, lymphadenopathy, fever, hepatic, renal and pulmonary disease, eosinophilia, atypical lymphocytosis, and leukocytosis.

TREATMENT

Appreciation of the specific etiologic factor is crucial. As most cases are drug-induced, cessation of the offending agent is critical as soon as possible. Management is similar to that for severe burns and may be best accomplished in a burn unit (see Chapter 75). It may include strict reverse isolation, meticulous fluid and electrolyte therapy, use of an air–fluid bed, and daily cultures. Systemic antibiotic therapy is indicated when secondary infection is evident or suspected. Skin care consists of cleansing with isotonic saline or Burrow solution. Biologic or colloid gel (Hydrogel) dressings alleviate pain and reduce fluid loss. Narcotics are often required for pain relief. Mouth and eye care, as for EM major and SJS, may be necessary. Because of an immune mechanism, systemic glucocorticosteroids and IVIG have been used with apparent success. Nonetheless, this treatment remains controversial although trends toward decreased morbidity and mortality in children receiving high-dose IVIG have been demonstrated (see Chapter 654.2).

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654.4 Mechanobullous Disorders

Joel C. Joyce

EPIDERMOLYSIS BULLOSA

Diseases categorized under the general term epidermolysis bullosa (EB) are a heterogeneous group of congenital, genetic blistering disorders. They differ in severity and prognosis, clinical and histologic features, and inheritance patterns but are all characterized by induction of blisters by trauma and exacerbation of blistering in warm weather. The disorders can be categorized under 3 major headings with multiple subgroupings: epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), and dystrophic epidermolysis bullosa (DEB) (Table 654-2). **Kindler syndrome**, which includes poikiloderma and photosensitivity as well as easy blistering, is also considered a separate form of EB. Epidermolysis bullosa acquisita is an autoimmune disorder producing antibodies to the α chain of type VII collagen. Affected mothers may pass the autoantibody to the fetus resulting in similar but transient lesions in the newborn.

EPIDERMOLYSIS BULLOSA SIMPLEX

EBS is a nonscarring, autosomal dominant disorder. The defect in most common types of EBS is in keratin 5 or 14, which makes up intermediate filaments of the basal keratinocytes. The intraepidermal bullae result from cytolysis of the basal cells. There are multiple other rare variants with defects that also result in intraepidermal blistering.

In **EBS–generalized other (formerly Koebner)**, blisters are usually present at birth or during the neonatal period. Sites of predilection are the hands, feet, elbows, knees, legs, and scalp. Intraoral lesions are minimal, nails rarely become dystrophic and usually regrow even when they are shed, and dentition is normal. Bullae heal with minimal to no scar or milia formation. Secondary infection is the primary complication. The propensity to blister decreases with age, and the long-term prognosis is good. Blisters should be drained by puncturing, but the blister top should be left intact to protect the underlying skin. Erosions may be covered with a semipermeable dressing.

EBS–localized (**formerly Weber-Cockayne**) predominantly affects the hands and feet and often manifests when a child begins to walk; onset may be delayed until puberty or early adulthood, when heavy shoes are worn or the feet are subjected to increased trauma. Bullae are usually restricted to the hands and feet (Fig. 654-5); rarely, they occur elsewhere, such as the dorsal aspect of the arms and the shins. The disorder ranges from mildly incapacitating to crippling at times of severe exacerbations.

EBS–Dowling-Meara (herpetiformis) is characterized by grouped blisters resembling those of herpes simplex (Fig. 654-6). During infancy, blistering may be severe and extensive, may involve mucous membranes, and may result in shedding of nails, formation of milia, and mild pigmentary changes, without scarring. After the 1st few mo of life, warm temperatures do not appear to exacerbate blistering. Hyperkeratosis and hyperhidrosis of the palms and soles may develop, but generally, the condition improves with age.

JUNCTIONAL EPIDERMOLYSIS BULLOSA

JEB–Herlitz is an autosomal recessive condition that is life-threatening. Blisters appear at birth or develop during the neonatal period, particularly on the perioral area, scalp, legs, diaper area, and thorax. Nails eventually become dystrophic and then often permanently lost.

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Table 654-2 Clinical Presentation and Diagnosis of Selected Epidermolysis Bullosa Subtypes in the Neonatal Period

EB SUBTYPE (USUAL INHERITANCE)	CLINICAL FEATURES		DIAGNOSIS
	Cutaneous	Extracutaneous	
EB simplex–generalized (AD)	Mild to moderate blistering, often generalized Rare scarring, milia	Occasional mucosal blistering	EM: Intrabasal layer split IF: BPAG1 (BP230), BP-180 (BPAG2, collagen XVII), $\alpha_6\beta_4$ integrin, laminin 1, laminin 332, type IV collagen, type VII collagen (EBA antigen) at base of blister
EB simplex–localized (AD)	Mild blistering, often localized, sometimes in 1st 24 mo, but often not until later infancy or childhood Rare scarring, milia	Rare mucosal involvement	EM: Intrastratum basale split IF: Same as for EB simplex—generalized
EB simplex–Dowling-Meara (AD)	Moderate to severe blistering, which starts generalized, then is grouped (herpetiform); milia; nail dystrophy, shedding	Mild mucosal blistering	EM: Intrastratum basale split; clumped keratin filaments IF: Same as for EB simplex—generalized
Junctional EB–non-Herlitz (AR)	Moderate blistering; atrophic scars; nail dystrophy	Mild mucosal blistering; enamel hypoplasia	EM: Intralamina lucida cleavage; variable reduction in hemidesmosomes IF: Absence of staining with 19-DEJ-1 (uncein); variable staining with GB3 and other laminin 332 antibodies, including 46 and K140; BPAG1 (BP230) BP180 (BPAG2, type XVII collagen), $\alpha_6\beta_4$ integrin in blister roof; laminin 1, type IV collagen, type VII collagen (EBA antigen) at base of blister
Junctional EB–Herlitz (AR)	Severe generalized blistering that heals poorly; granulation tissue; scarring; nail dystrophy	Severe mucosal blistering; GI involvement common; laryngeal involvement with airway obstruction; urologic involvement	EM: Cleavage intralamina lucida; markedly reduced or no hemidesmosomes; absence of sub-basal dense plates IF: Absence of staining with 19-DEJ-1 (uncein) and GB3 (laminin 332) and of staining with other laminin 332 antibodies, including 46 and K140; BPAG1 (BP230) and BP180 (BPAG2, type XVII collagen) in blister roof; laminin-1, type IV collagen, and type VII collagen at base of blister
Junctional EB–pyloric atresia (AR)	Severe blistering	Polyhydramnios; pyloric atresia; urologic involvement: uretovesicular obstruction, hydronephrosis	EM: Cleavage intralamina lucida and intraplasma membrane; small hemidesmosomes IF: BPAG1 (BP230) and BP180 (BPAG2, type XVII collagen) in blister roof; laminin-1, type IV collagen, and type VII collagen at base of blister; Absence of 19-DEJ-1(uncein), $\alpha_6\beta_4$ integrin absent or reduced
Dominant dystrophic EB (AD)	Mild to moderate blistering (but may be more severe in newborn period) Milia, scarring Nail dystrophy	Mild mucosal blistering	EM: Cleavage sublamina densa; variable reduction in anchoring fibrils IF: BPAG1 (BP230), BPAG2 (BP180, type XVII collagen), $\alpha_6\beta_4$ integrin, laminin 1, type IV collagen at top of blister Staining for type VII collagen (EBA antigen) is normal, variable, or absent
Recessive dystrophic EB–Hallopeau-Siemens (AR)	Severe blistering Milia, scarring	Severe mucosal blistering; GI involvement common; urologic involvement	EM: Cleavage sublamina densa; absence of anchoring fibrils IF: BPAG1 (BP230), BP-180 (BPAG2, type XVII collagen), $\alpha_6\beta_4$ integrin, laminin 1, type IV collagen at top of blister Variability or absence of staining for type VII collagen (EBA antigen)

AD, autosomal dominant; AR, autosomal recessive; EB, epidermolysis bullosa; EBA, epidermolysis bullosa acquisita; EM, electron microscopy; GI, gastrointestinal; IF, immunohistochemical and immunofluorescence antigen mapping findings.

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Figure 654-5 Bullae of the feet in epidermolysis bullosa simplex–localized (Weber-Cockayne).

Figure 654-7 Nonhealing granulation tissue in junctional epidermolysis bullosa.

Figure 654-6 Grouped vesicle on an erythematous base in epidermolysis bullosa simplex–Dowling-Meara.

Figure 654-8 Scarring with milia formation over the knee in dominant dystrophic epidermolysis bullosa.

Mucous membrane involvement may be severe, and ulceration of the respiratory, gastrointestinal, and genitourinary epithelium has been documented in many affected children, although less frequently than in severe recessive dystrophic epidermolysis bullosa. Healing is delayed, and vegetating granulomas may persist for a long time. Large, moist, erosive plaques (Fig. 654-7) may provide a portal of entry for bacteria, and septicemia is a frequent cause of death. Mild atrophy may be seen in areas of recurrent blistering. Defective dentition with early loss of teeth as a result of rampant caries is characteristic. Growth retardation and recalcitrant anemia are almost invariable. In addition to infection, cachexia and circulatory failure are common causes of death. Most patients die within the 1st 3 yr of life.

JEB–non-Herlitz is a heterogeneous group of disorders. Blistering may be severe in the neonatal period, making differentiation from the Herlitz type difficult. All conditions associated with the Herlitz type may be seen but are usually milder. **JEB–non-Herlitz generalized (formerly generalized atrophic benign EB)** is included as a variant of non-Herlitz JEB. Another variant of non-Herlitz JEB is associated with **pyloric atresia**.

In all types of JEB, a subepidermal blister is found on light microscopic examination, and electron microscopy demonstrates a cleavage plane in the lamina lucida, between the plasma membranes of the basal cells and the basal lamina. Absence or a great reduction of hemidesmosomes is seen on electron micrographs in **JEB–Herlitz** and some cases of **JEB–non-Herlitz**. The defect is in laminin 332 (formerly laminin 5 or epiligrin), a glycoprotein associated with anchoring filaments beneath the hemidesmosomes. In JEB–non-Herlitz, defects have also been described in other hemidesmosomal components, such as type XVII collagen (BP180). In **JEB–pyloric atresia**, the defect is in the $\alpha_6\beta_4$ integrin.

Treatment for JEB is supportive. The diet should provide adequate calories and supplemental iron. Infections should be treated promptly. Transfusions of packed red blood cells may be required if the patient shows no response to iron and erythropoietin therapy. Strict adherence to wound care regimens is essential. Tissue-engineered skin grafts (artificial skin derived from human keratinocytes and fibroblasts) may be beneficial.

DYSTROPHIC EPIDERMOLYSIS BULLOSA

All forms of DEB result from mutations in collagen VII, a major component of anchoring fibrils that tether the basement membrane and overlying epidermis to its dermal foundation. The blister is subepidermal in all types of DEB. The type and location of the mutation dictate the severity of the phenotype.

Dominant DEB is the most common type of DEB. The spectrum of dominant DEB is varied. Blisters may be manifest at birth and are often limited and characteristically form over acral bony prominences. The lesions heal promptly, with the formation of soft, wrinkled scars, milia, and alterations in pigmentation (Fig. 654-8). Abnormal nails and nail loss are common. In many cases, the blistering process is mild, causing little restriction of activity and not impairing growth and development. Mucous membrane involvement tends to be minimal.

Figure 654-9 Severe scarring of the hands and knees in recessive dystrophic epidermolysis bullosa.

Figure 654-10 Mitten-hand deformity of recessive dystrophic epidermolysis bullosa.

Recessive DEB–severe generalized (formerly recessive DEB–Hallopeau-Siemens) is the most incapacitating form of EB, although the clinical spectrum is wide. Some patients have blisters, scarring, and milia formation primarily on the hands, feet, elbows, and knees (Fig. 654-9). Others have extensive erosions and blister formation at birth that seriously impede their care and feeding. Mucous membrane lesions are common and may cause severe nutritional deprivation, even in older children, whose growth may be retarded. During childhood, esophageal erosions and strictures, scarring of the buccal mucosa, flexion contractures of joints secondary to scarring of the integument, development of cutaneous squamous cell carcinomas, and the development of digital fusion may significantly limit the quality of life (Fig. 654-10). Squamous cell carcinomas and infection are major causes of morbidity and mortality.

Although the skin becomes less sensitive to trauma with aging in patients with recessive DEB, the progressive and permanent deformities complicate management, and the overall prognosis is poor. Foods that traumatize the buccal or esophageal mucosa should be avoided. If esophageal scarring develops, a semiliquid diet and esophageal dilatations may be required. Stricture excision or colonic interposition may be needed to relieve esophageal obstruction. In infants, severe oropharyngeal involvement may necessitate the use of special feeding devices such as a gastrostomy tube. Iron therapy for anemia, intermittent antibiotic therapy for secondary infections, and periodic surgery for release of digits may reduce morbidity. Newer generation wound care dressings, including non-stick dressings made from silicone, are a mainstay of treatment and the daily maintenance of the skin barrier to reduce new skin trauma and promote healing. Tissue-engineered skin grafts containing keratinocytes and fibroblasts are of some benefit. Transdermal gene therapy with allogeneic fibroblasts and the delivery of functional collagens is being pursued. Allogeneic bone marrow transplantation may also be beneficial as may the induction of pluripotent stem cells.

KINDLER SYNDROME

Kindler syndrome, often considered a distant subtype of EB, contains features of both EB such as congenital blistering, and features of the congenital poikilodermas, such as Rothmund-Thomson syndrome and Bloom syndrome (see Chapter 656), which include photosensitivity, congenital poikiloderma, and progressive cutaneous atrophy. Blisters tend to appear on acral sites in infancy or early childhood and are provoked by trauma. Photosensitivity can appear as increased susceptibility to sunburn. Both blistering and photosensitivity can improve greatly with advancing age, but poikilodermatous changes can be progressive. Sclerodermoid-like changes and nail abnormalities of the hands and feet as well as dental abnormalities have been reported.

Kindler syndrome is an autosomal recessive disorder caused by mutations in *KIND1* (also known as *FERMT1*), which encodes kindlin-1, a protein thought to regulate interactions between the extracellular matrix and actin filaments. Blister formation has been shown to occur within the epidermis, within the basement membrane zone, and below the basement membrane. As Kindler syndrome is often confused with EB, at least initially, it can be confirmed by electron microscopy, immunostaining for anti-kindlin-1 antibodies within the skin, or by mutation analysis of the *KIND1* gene.

Treatment is similar to that for EB above, with efforts to reduce trauma to the skin, meticulous wound care, and treatment of skin infections. In addition, sun avoidance measures are beneficial as they can slow the rate of the development of poikiloderma.

Bibliography is available at Expert Consult.

654.5 Pemphigus

Joel C. Joyce

PEMPHIGUS VULGARIS

Etiology/Pathogenesis

Pemphigus vulgaris (PV) is a rare autoimmune blistering disorder caused by circulating antibodies to desmoglein III that result in suprabasal cleaving with consequent blister formation. Desmoglein III is a 30-kDa glycoprotein that is complexed with plakoglobin, a plaque protein of desmosomes. The desmogleins are a subfamily of the cadherin family of cell adhesion molecules.

Clinical Manifestations

PV usually first appears as painful oral ulcers, which may be the only evidence of the disease for weeks or months. Subsequently, large, flaccid bullae emerge on nonerythematous skin, most commonly on the face, trunk, pressure points, groin, and axillae. The **Nikolsky sign**

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is present. The lesions rupture and enlarge peripherally, producing painful, raw, denuded areas that have little tendency to heal. When healing occurs, it is without scarring, but hyperpigmentation is common. Malodorous, verrucous, and granulomatous lesions may develop at sites of ruptured bullae, particularly in the skinfolds; as this pattern becomes more pronounced, the condition may be more properly referred to as *pemphigus vegetans*. Because the course may rapidly lead to debility, malnutrition, and death, prompt diagnosis is essential. **Neonatal PV** develops in utero as a result of placental transfer of maternal antidesmoglein antibodies from women who have active PV, although it may occur when the mother is in remission. High antepartum maternal titers of PV antibodies and increased maternal disease activity correlate with a poor fetal outcome, including demise.

Pathology

Biopsy of a fresh small blister reveals a suprabasal (intraepidermal) blister containing loose, acantholytic epidermal cells that have lost their intercellular bridges and thus their contact with one another. Immunofluorescence staining with an IgG antibody produces a characteristic pattern ("chicken wire") on direct immunofluorescence preparations of both involved and uninvolved skin of essentially all patients. Serum IgG antibody titers to desmoglein correlate with the clinical course in many patients; thus, serial determinations may have predictive value.

Differential Diagnosis

PV must be differentiated from EM, bullous pemphigoid, SJS, and TEN.

Treatment

The disease is best treated initially with systemic methylprednisolone 1-2 mg/kg/day. Azathioprine, cyclophosphamide, and methotrexate therapy all have been useful in maintenance regimens. IVIG given in cycles may be beneficial to patients whose disease does not respond to steroids. Rituximab with IVIG replacement has been effective in the management of severe pemphigus. Excellent control of the disease may be obtained, but relapse is common. It has been successfully used in children.

PEMPHIGUS FOLIACEUS

Etiology/Pathogenesis

Pemphigus foliaceus is caused by circulating antibodies to a 50-kDa portion of the 160-kDa desmosomal glycoprotein desmoglein I, which result in subcorneal cleavage leading to superficial erosions. This extremely rare disorder is characterized by subcorneal blistering; the site of cleavage is high in the epidermis rather than suprabasal as in PV.

Clinical Manifestations

The superficial blisters rupture quickly, leaving erosions surrounded by erythema that heal with crusting and scaling (Fig. 654-11). The **Nikolsky sign** is present. Focal lesions are usually localized to the scalp, face, neck, and upper trunk. Mucous membrane lesions are minimal or absent. Pruritus, pain, and a burning sensation are frequent complaints. The clinical course varies but is generally more benign than that of PV. **Fogo selvagem (endemic pemphigus foliaceus),** which is endemic in certain areas of Brazil, is identical clinically, histopathologically, and immunologically to pemphigus foliaceus. Recently, it was shown that anti–desmoglein-1 antibodies in individuals with fogo selvagem crossreact with sand fly (*Lutzomyia* sp.) salivary proteins, suggesting an environmental trigger for this autoimmune disease.

Pathology

An intraepidermal acantholytic bulla high in the epidermis is diagnostic. It is imperative to select an early lesion for biopsy. Immunofluorescent staining with an IgG antibody reveals a characteristic intercellular staining pattern similar to that of PV but higher in the epidermis.

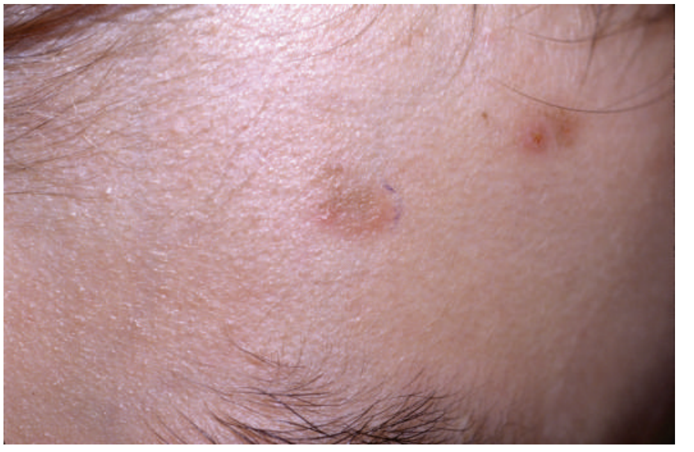

Figure 654-11 Superficial erosions in pemphigus foliaceus.

Differential Diagnosis

When generalized, the eruption may resemble exfoliative dermatitis or any of the chronic blistering disorders; localized erythematous plaques simulate seborrheic dermatitis, psoriasis, impetigo, eczema, and systemic lupus erythematosus.

For localized disease, superpotent topical corticosteroids used twice a day may be all that is needed for control until remission. For more generalized disease, long-term remission is usual after suppression of the disease by systemic methylprednisolone (1 mg/kg/day) therapy. Dapsone (25-100 mg/day) also may be used.

BULLOUS PEMPHIGOID

Etiology/Pathogenesis

Bullous pemphigoid (BP) is caused by circulating antigens to either the 180-kDa or 230-kDa BP antigen that result in a subepidermal blister. The 230-kDa protein (BP230) is part of the hemidesmosome, whereas the 180-kDa protein (BP180, now known as type XVII collagen) localizes to both the hemidesmosome and the upper lamina lucida and is a transmembrane collagenous protein.

Clinical Manifestations

The blisters of BP typically arise in crops on a normal, erythematous, eczematous, or urticarial base. Bullae appear predominantly on the flexural aspects of the extremities, in the axillae, and on the groin and central abdomen. Infants have involvement of the palms, soles, and face more frequently than older children. Individual lesions vary greatly in size, are tense, and are filled with serous fluid that may become hemorrhagic or turbid. Oral lesions occur less frequently and are less severe than in PV. Pruritus, a burning sensation, and subcutaneous edema may accompany the eruption, but constitutional symptoms are not prominent.

Pathology

Biopsy material should be taken from an early bulla arising on an erythematous base. A subepidermal bulla and a dermal inflammatory infiltrate, predominantly of eosinophils, can be identified histopathologically. In sections of a blister or perilesional skin, a band of Ig (usually IgG) and C3 can be demonstrated in the basement membrane zone by direct immunofluorescence. Indirect immunofluorescence studies of serum have positive results in ≈70% of cases for IgG antibodies to the basement membrane zone; the titers, however, do not correlate well with the clinical course.

Diagnosis and Differential Diagnoses

BP rarely occurs in children but must be considered in the differential diagnosis of any chronic blistering disorder. The **differential diagnosis** includes bullous EM, pemphigus, linear IgA dermatosis, bullous drug eruption, dermatitis herpetiformis, herpes simplex infection,

and bullous impetigo, which can be differentiated by histologic examination, immunofluorescence studies, and cultures. The large, tense bullae of BP can generally be distinguished from the smaller, flaccid bullae of PV.

Treatment

Localized bullous pemphigoid can be successfully suppressed with superpotent topical corticosteroids twice a day. Generalized disease usually requires systemic methylprednisolone (1 mg/kg/day) therapy. Rarely are other immunosuppressive treatments necessary, such as azathioprine or mycophenolate mofetil. Refractory cases have been treated with rituximab, but the condition usually remits within a year in most children.

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654.6 Dermatitis Herpetiformis

Joel C. Joyce

ETIOLOGY/PATHOGENESIS

In dermatitis herpetiformis (DH), IgA antibodies are directed at epidermal transglutaminase (transglutaminase 3). **Gluten-sensitive enteropathy (celiac disease)** is found in all patients with DH, although the majority are asymptomatic or have minimal gastrointestinal symptoms (see Chapter 338.2). The severity of the skin disease and the responsiveness to gluten restriction do not correlate with the severity of the intestinal inflammation. An antibody to smooth muscle endomysium is found in 70-90% of patients with DH. Ninety percent of patients with the disease express HLA-DQ2. HLA-DQ2–negative patients with DH usually express HLA-DQ8.

CLINICAL MANIFESTATIONS

DH is characterized by symmetric, grouped, small, tense, erythematous, stinging, intensely pruritic papules and vesicles. The eruption is pleomorphic, including erythematous, urticarial, papular, vesicular, and bullous lesions. Sites of predilection are the knees, elbows, shoulders, buttocks, forehead, and scalp; mucous membranes are usually spared. Hemorrhagic lesions may develop on the palms and soles. When pruritus is severe, excoriations may be the only visible sign (Fig. 654-12).

PATHOLOGY

Subepidermal blisters composed predominantly of neutrophils are found in dermal papillae. The presence of granular IgA on direct immunofluorescence in the dermal papillary tips is diagnostic.

Figure 654-12 Multiple excoriations around the elbows in dermatitis herpetiformis.

DIFFERENTIAL DIAGNOSIS

DH may mimic other chronic blistering diseases and may also resemble scabies, papular urticaria, insect bites, contact dermatitis, and papular eczema.

TREATMENT

Patients with DH show response within weeks to months to a gluten-free diet. Oral administration of dapsone (0.5-2.0 mg/kg/day divided qd or bid) provides immediate relief from the intense pruritus but must be used with caution because of possible serious side effects (methemoglobinemia, hemolysis, and hypersensitivity syndrome [sulfone syndrome]). Dapsone alone may not relieve the intestinal inflammation of celiac disease. Local antipruritic measures may also be useful. Jejunal biopsy is indicated to diagnose gluten-sensitive enteropathy, because cutaneous manifestations may precede malabsorption. The disease is chronic and either a gluten-free diet or dapsone must be continued indefinitely to prevent relapse.

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654.7 Linear Immunoglobulin A Dermatosis (Chronic Bullous Dermatosis of Childhood)

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ETIOLOGY/PATHOGENESIS

Linear IgA dermatosis is a heterogeneous autoimmune disorder with antibodies targeting multiple antigens. It is caused by circulating IgA antibodies, most commonly to LABD97 and LAD-1, which are degradation proteins of BP180 (type XVII collagen). Linear IgA dermatosis may also be seen as a drug eruption. Most cases of drug-induced linear IgA dermatosis are related to vancomycin, although anticonvulsants, ampicillin, cyclosporine, and captopril are implicated.

CLINICAL MANIFESTATIONS

This rare dermatosis is most common in the 1st decade of life, with a peak incidence during the preschool years. The eruption consists of many large symmetrically located, tense bullae filled with clear or hemorrhagic fluid. The bullae are often clustered together and develop on a normal or erythematous, urticarial base. Areas of predilection are the genitals and buttocks (Fig. 654-13), the perioral region, and the scalp. Sausage-shaped bullae may be arranged in an annular or rosette-like fashion around a central crust (Fig. 654-14). Erythematous plaques with gyrate margins bordered by intact bullae may develop over larger areas. Pruritus may be absent or very intense, and systemic signs or symptoms are absent.

PATHOLOGY

The subepidermal bullae are infiltrated with a mixture of inflammatory cells. Neutrophilic abscesses may be noted in the dermal papillary tips, indistinguishable from those of DH. The infiltrate may also be largely eosinophilic, resembling that in BP. Therefore, direct immunofluorescence studies are required for a definitive diagnosis of linear IgA dermatosis; perilesional skin demonstrates linear deposition of IgA and sometimes IgG and C3 at the dermal–epidermal junction. Immunoelectron microscopy has localized the immunoreactants to the sublamina densa, although a combined sublamina densa and lamina lucida pattern has also been seen.

DIFFERENTIAL DIAGNOSIS

The eruption can be distinguished by histopathologic and immunofluorescence studies from pemphigus, BP, DH, and EM. Gram stain and culture preclude the diagnosis of bullous impetigo.

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Figure 654-13 Erosion on an erythematous base after loss of blister roof in linear IgA dermatosis.

Figure 654-14 Rosette-like blisters around a central crust typical of linear IgA dermatosis (chronic bullous dermatosis of childhood).

TREATMENT

Many cases of linear IgA dermatosis respond favorably to oral dapsone (see treatment of DH) or sulfapyridine. Other antibiotics, including erythromycin and dicloxacillin have been used, but the response is often transient. Children who show no response to dapsone may benefit from oral therapy with methylprednisolone (1 mg/kg/day) or a combination of these drugs. The usual course is 2-4 yr, although some children have persistent or recurrent disease; there are typically no long-term sequelae. IgA nephropathy is a rare complication.

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Chapter 655
Eczematous Disorders
Brianne Z. Dickey and Yvonne E. Chiu

Eczematous skin disorders are a broad group of cutaneous eruptions characterized by erythema, edema, and pruritus. Acute eczematous lesions demonstrate erythema, weeping, oozing, and the formation of microvesicles within the epidermis. Chronic lesions are generally thickened, dry, and scaly, with coarse skin markings (lichenification) and altered pigmentation. Many types of eczema occur in children; the most common is **atopic dermatitis** (see Chapter 145), although seborrheic dermatitis, allergic and irritant contact dermatitis, nummular eczema, and acute palmoplantar eczema (dyshidrosis) are also relatively common in childhood.

Once the diagnosis of eczema has been established, it is important to classify the eruption more specifically for proper management. Pertinent historical data often provide the clue. In some instances, the subsequent course and character of the eruption permit classification. Histologic changes are relatively nonspecific, but all types of eczematous dermatitis are characterized by intraepidermal edema known as spongiosis.

655.1 Contact Dermatitis
Brianne Z. Dickey and Yvonne E. Chiu

The form of eczema known as contact dermatitis can be subdivided into irritant dermatitis, in which nonspecific injury to the skin causes immediate inflammation, and allergic contact dermatitis, resulting from a delayed hypersensitivity reaction. Irritant dermatitis is more frequent in children, particularly during the early years of life. Allergic reactions increase in frequency upon maturation of the immune system.

IRRITANT CONTACT DERMATITIS
Irritant contact dermatitis can result from prolonged or repetitive contact with physical, chemical, or mechanical irritants, including saliva, urine, feces, fragrance, detergents, dyes, henna, plants, caterpillars, abrasive materials, and chafing.

Irritant contact dermatitis may be difficult to distinguish from atopic dermatitis or allergic contact dermatitis. A detailed history and consideration of the sites of involvement, the age of the child, and contactants usually provide clues to the etiologic agent. The propensity for development of irritant dermatitis varies considerably among children; some may respond to minimal injury, making it difficult to identify the offending agent through history. Children with atopic dermatitis are more prone to irritant contact dermatitis as an exacerbating factor. Irritant contact dermatitis usually clears after removal of the stimulus and temporary treatment with a topical corticosteroid preparation (see Chapter 646). Education of patients and parents about the causes of contact dermatitis is crucial to successful therapy.

Dry skin dermatitis results from repetitive wet-to-dry behaviors such as lip-licking (Fig. 655-1), thumb-sucking, frequent hand washing, or excessive sweating. Involved skin is erythematous and fissured, localized to the area of exposure. Treatment of dry skin dermatitis begins with eliminating the offending wet-to-dry behavior. Moisturizer cream applied twice daily decreases transepidermal water loss and replenishes skin lipids to improve hydration. A topical steroid is usually necessary to treat the inflammation.

Juvenile plantar dermatosis occurs mainly in prepubertal children with hyperhidrosis who wear occlusive synthetic footwear. Weight-bearing surfaces of the foot may be pruritic or painful and

Figure 655-1 Perioral irritant contact dermatitis from lip licking.

Figure 655-2 Red, scaly juvenile plantar dermatosis.

develop a fissured or glazed appearance (Fig. 655-2). Immediate application of a thick emollient when socks and shoes are removed or immediately after swimming usually minimizes juvenile plantar dermatosis. Severe inflammatory cases may require short-term (1-2 wk) application of a medium- to high-potency topical steroid.

DIAPER DERMATITIS

Diaper dermatitis refers to any rash in the diaper region; the most common of these is irritant diaper dermatitis. Elevated pH in the diaper area and synergistic activity of urinary and fecal enzymes lead to inflammation, which disrupts the normal skin barrier and increases susceptibility to other irritants and organisms. Additional factors are occlusion, friction, and use of diaper wipes and topical preparations. Loose or frequent stooling predisposes an infant to diaper dermatitis. Diaper dermatitis presents with erythema and scaling, often with papulovesicular or bullous lesions, fissures, and erosions in a patchy or confluent pattern (Fig. 655-3). The genitocrural folds are often spared because concave areas are relatively protected. Chronic hypertrophic, flat-topped papules and infiltrative nodules may occur. **Candidal infection** typically represents a secondary process. It is characterized by "beefy" red-pink, tender skin that has numerous 1-2 mm pustules and satellite papules and involves both concave and convex areas. Discomfort may be marked because of intense inflammation. Allergic contact dermatitis, seborrheic dermatitis, psoriasis, candidiasis, atopic dermatitis, child abuse, and rare disorders such as Langerhans cell histiocytosis, nutritional deficiencies, and acrodermatitis enteropathica should be considered when the eruption is persistent or is recalcitrant to simple therapeutic measures.

Figure 655-3 Severe, erosive diaper dermatitis.

Diaper dermatitis often responds to simple measures; some infants are predisposed to diaper dermatitis, and management may be difficult. The damaging effects of overhydration of the skin and prolonged contact with feces and urine can be obviated by frequent changing of the diapers and periods of "rest" free of diaper use. Cleansing of affected skin is best accomplished with a soft cloth and lukewarm water, patted dry. Overwashing should be avoided because it leads to chapping and a worsening of the dermatitis. Disposable diapers containing a superabsorbent material may help maintain a relatively dry environment. First-line therapy for diaper dermatitis is application of a protective barrier agent (ointment or paste) containing petroleum or zinc oxide at every diaper change. Topical sucralfate is an effective barrier with some antibacterial activity, useful for recalcitrant cases. Low-potency nonhalogenated topical corticosteroids, such as 2.5% hydrocortisone, may be used for short time periods (3-5 days). Treatment with a topical anticandidal agent is indicated for secondary candidal infection. Topical preparations containing triamcinolone-nystatin and betamethasone dipropionate–clotrimazole are generally inappropriate for diaper dermatitis in infants because of the higher potency of the corticosteroid component. If using multiple topical agents, the protective barrier should be applied last. When diaper dermatitis does not respond to typical prevention and treatment strategies, non–diaper-associated causes must be considered.

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis is common in childhood and should be considered in any child with recalcitrant eczema. This is a T-cell–mediated hypersensitivity reaction that is provoked by application of an antigen to the skin surface. The antigen penetrates the skin, where it is conjugated with a cutaneous protein, and the hapten–protein complex is transported to the regional lymph nodes by antigen-presenting Langerhans cells. A primary immunologic response occurs locally in the nodes and becomes generalized, presumably because of dissemination of sensitized T cells. Sensitization requires several days and, when followed by a fresh antigenic challenge, manifests as allergic contact dermatitis. Generalized distribution may also occur if enough antigen finds its way into the circulation, such as by consumption. Once sensitization has occurred, each new antigenic challenge may provoke an inflammatory reaction within 8-12 hr; sensitization to a particular antigen usually persists for many years.

Acute allergic contact dermatitis is an erythematous, intensely pruritic, eczematous dermatitis. Acute cases may be edematous and vesiculobullous. The chronic condition has the features of long-standing eczema: lichenification, scaling, fissuring, and pigmentary change. The distribution of the eruption often provides a clue to the diagnosis. Airborne sensitizers usually affect exposed areas, such as the face and arms. Jewelry, topical agents, shoes, clothing, henna tattoo dyes, plants, and even toilet seats cause dermatitis at points of contact.

Rhus dermatitis (poison ivy, poison sumac, poison oak), a response to the plant allergen urushiol, is the most common allergic contact dermatitis. It is often vesiculobullous and may be distinguished by linear streaks of vesicles where the plant leaves have brushed against the skin (Fig. 655-4). Fluid from ruptured cutaneous vesicles does not spread the eruption; antigen retained on skin, clothing, or under fingernails initiates new plaques of dermatitis if not removed by washing with soap and water. Antigen may also be carried by animals on their fur. "Black spot" poison ivy dermatitis is a rare variant that results from oxidation of concentrated urushiol left on the skin and manifests as small discrete black lacquer–like glossy papules with surrounding erythema and edema. Sensitization to 1 plant produces crossreactions with the others. Spontaneous resolution occurs in 1-3 wk, with the most common complication being secondary bacterial infection with normal skin flora. Exposure avoidance and thorough washing after exposure are the mainstays for prevention. Barrier creams or organoclay compounds such as bentoquatam may be effective if applied prior to expected exposure.

Nickel dermatitis develops from contact with jewelry, metal closures on clothing, or even cell phones. Metal closures on pants frequently cause periumbilical dermatitis (Fig. 655-5). Some children are exquisitely sensitive to nickel, with even the trace amounts found in gold jewelry provoking eruptions. The most frequently involved sites from jewelry are the earlobes from nickel-containing earrings. Early ear piercing increases risk of sensitization, and it is recommended to delay piercing until after 10 yr of age. Patch testing for nickel sensitivity is unreliable in infants and toddlers and should only be performed if there is high clinical suspicion.

Shoe dermatitis typically affects the dorsum or soles of the feet and toes, sparing the interdigital spaces; it is usually symmetric. Other forms of allergic contact dermatitis, in contrast to irritant dermatitis, rarely involve the palms and soles. Common allergens are the antioxidants and accelerators in shoe rubber, adhesives, and the chromium salts in tanned leather or shoe dyes. Excessive sweating often leaches these substances from their source.

Apparel contains a number of sensitizers, including dyes, dye fixative, fabric finishes, fibers, resins, and cleaning solutions. Dye may be poorly fixed to clothing and so may be leached out with sweating, as can partially cured formaldehyde resins. The elastic in garments is a frequent cause of clothing dermatitis, and contact allergy to the ink "tag" of tagless baby clothing has been reported. Exposure to other items with fabric, such as infant car seats, may induce reactions similar to clothing.

Topical medications and cosmetics may be unsuspected as allergens, particularly if a medication is being used for a preexisting dermatitis. The most common offenders are neomycin, topical antihistamines, topical anesthetics, fragrances, topical corticosteroids, oxybenzone and octocrylene in chemical sunscreens, preservatives, dye in temporary tattoos, and ethylenediamine, a stabilizer present in many medications. All types of cosmetics can cause facial dermatitis; involvement of the eyelids is characteristic for nail polish sensitivity.

Neomycin sulfate is present in many nonprescription topical antibiotic preparations, and thus children are frequently exposed at an early age. It is one of the most common causes of allergic contact dermatitis, and use of combination products of neomycin with other antibiotics, antifungals, or corticosteroids may induce co-reactivity with these chemically-unrelated substances.

Diagnosis of allergic contact dermatitis is usually based on history; however, patch testing may be helpful, especially in older children. Identification and avoidance of the offending agent is the mainstay of

Figure 655-4 Linear lesions in poison ivy.

Figure 655-5 Chronic periumbilical nickel dermatitis.

managing allergic contact dermatitis. First-line treatment for acute eruption is with midpotency topical corticosteroid ointment for 2-3 wk, as well as symptom management with wet dressings and sedating antihistamines to allow for sleep. Systemic corticosteroids are used when >10% of skin is involved (0.5-1.0 mg/kg prednisone for 7-10 days, followed by a 7-10 day taper). More chronic allergic contact dermatitis is treated with low- to midpotency topical corticosteroids. Desensitization therapy is rarely indicated. Differential diagnosis of allergic contact dermatitis includes herpes simplex virus, impetigo, cellulitis, atopic dermatitis, irritant contact dermatitis, and dermatophytoses.

Bibliography is available at Expert Consult.

655.2 Nummular Eczema

Brianne Z. Dickey and Yvonne E. Chiu

Nummular eczema is characterized by coin-shaped, severely pruritic, eczematous plaques, commonly involving the extensor surfaces of the extremities (Fig. 655-6), buttocks, and shoulders with facial sparing. The plaques are relatively discrete, boggy, vesicular, slightly scaly, and exudative; when chronic, they often become thickened and lichenified, and may develop central clearing. The etiology remains unclear, although nummular eczema possibly represents an atypical morphology of atopic dermatitis. Flares are generally sporadic but may be precipitated by xerosis, irritants, allergens, or occult staphylococcal infection. Most frequently, these lesions are mistaken for tinea corporis, but plaques of nummular eczema are distinguished by the lack of a raised, sharply circumscribed border, the lack of fungal organisms on a potassium hydroxide (KOH) preparation, and frequent weeping or bleeding when scraped. First-line treatment is with emollients, wet dressings, and potent topical corticosteroids. Steroid-impregnated tapes may simultaneously treat and provide barrier protection to these circumscribed eczematous plaques. An oral antihistamine may be helpful, particularly a sedating antihistamine at night. Antibiotics are indicated for secondary infection.

Bibliography is available at Expert Consult.

655.3 Pityriasis Alba

Brianne Z. Dickey and Yvonne E. Chiu

Pityriasis alba occurs mainly in children and causes lesions that are hypopigmented, ill-defined, round or oval patches (Fig. 655-7). They may be mildly erythematous and finely scaly. Lesions occur on the face, neck, upper trunk, and proximal portions of the arms, and are most pronounced on darker skin tones or after tanning of surrounding skin. Itching is minimal or absent. The cause is unknown, but the eruption appears to be exacerbated by dryness and is often regarded as a mild form of eczema. Pityriasis alba is frequently misdiagnosed as vitiligo, tinea versicolor, or tinea corporis. The lesions wax and wane but eventually disappear, and normal pigmentation often takes months to return. Application of a lubricant or emollient may ameliorate the condition. If pruritus is troublesome, a low-potency topical steroid or calcineurin inhibitor may be used.

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655.4 Lichen Simplex Chronicus

Brianne Z. Dickey and Yvonne E. Chiu

Lichen simplex chronicus is a secondary skin disorder resulting from excessive scratching. It is characterized by a chronic pruritic, eczematous, circumscribed plaque that is usually lichenified and hyperpigmented (Fig. 655-8). All affected areas must be accessible to scratching, with the most common sites being the posterior neck, genitalia, wrists, ankles, and dorsal feet. Although the initiating event may be a transient lesion such as an insect bite, trauma from rubbing and scratching accounts for persistence of the plaque. Pruritus must be controlled to

Figure 655-7 Patchy hypopigmented lesions with diffuse borders characteristic of pityriasis alba.

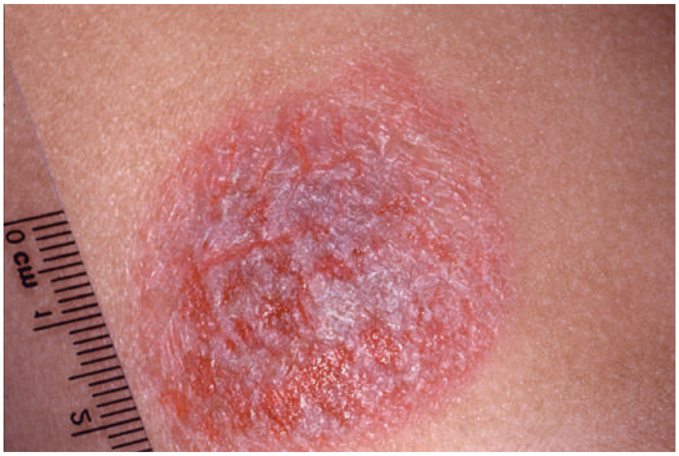

Figure 655-6 Discrete, boggy plaque of nummular dermatitis.

Figure 655-8 Thickened plaque of lichen simplex chronicus.

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permit healing, thus a covering to prevent scratching may be necessary. A high potency topical corticosteroid under occlusion is often helpful. Second-line therapy includes adding 6% salicylic acid gel to the topical corticosteroid preparation.

655.5 Acute Palmoplantar Eczema (Dyshidrotic Eczema, Dyshidrosis, Pompholyx)

Brianne Z. Dickey and Yvonne E. Chiu

A recurrent, sometimes seasonal, blistering disorder of the hands and feet, acute palmoplantar eczema occurs in all age groups but is uncommon in infancy. The pathogenesis is unknown, although possible predisposing factors include a history of atopy, exposure to contact allergens or irritants, or IV immunoglobulin therapy. The disease is characterized by recurrent crops of small, deep-seated "tapioca-like" vesicles, which are intensely pruritic and may coalesce into tense bullae (Fig. 655-9). Sites of predilection are the palms, soles, and lateral aspects of the fingers and toes. Primary lesions are noninflammatory and are filled with clear fluid, which, unlike sweat, has a physiologic pH and contains protein. Maceration and secondary infection are frequent because of scratching. The chronic phase is characterized by thickened, fissured plaques that may cause considerable discomfort, as well as dystrophic nails. Hyperhidrosis is common in many patients, but the association may be fortuitous. The diagnosis is made clinically. The disorder may be confused with allergic contact dermatitis, which usually affects the dorsal rather than the volar surfaces, and with dermatophytosis, which can be distinguished by a KOH preparation of the roof of a vesicle and by appropriate cultures.

Acute palmoplantar eczema responds to wet dressings, liberal emollient use, and potent topical corticosteroid ointment applied twice daily for 2-4 wk. Weeping skin benefits from twice daily soaking in an astringent solution, such as aluminum subacetate. Second-line treatment is topical tacrolimus 0.1% ointment. Severe disease may require oral corticosteroids with 2 wk taper, or even psoralen UVA therapy. Control of the chronic stage is difficult; lubricants containing mild keratolytic agents in conjunction with a potent topical fluorinated corticosteroid preparation may be indicated. Secondary bacterial infection should be treated systemically with an appropriate antibiotic. Patients should be told to expect recurrence and should protect their hands and feet from the damaging effects of excessive sweating, chemicals, harsh soaps, and adverse weather. Unfortunately, it is impossible to prevent recurrence or to predict its frequency.

Figure 655-9 Vesicular palmar lesions of dyshidrotic eczema with large bullae.

655.6 Seborrheic Dermatitis

Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY

Seborrheic dermatitis is a chronic inflammatory disease most common in infancy and adolescence that parallels the distribution, size, and activity of the sebaceous glands. The cause is unknown, as is the role of the sebaceous glands in the disease. *Malassezia furfur* is implicated as a causative agent, although it remains unclear whether dermatitis results from the action of the fungus, its byproducts, or an exaggerated response of the host. In adolescence, seborrheic dermatitis typically occurs after puberty, indicating a possible role for sex hormones.

It is also unknown whether infantile seborrheic dermatitis and adolescent seborrheic dermatitis are the same or different entities. There is no evidence that children with infantile seborrheic dermatitis will experience seborrheic dermatitis as adolescents.

CLINICAL MANIFESTATIONS

The disorder may begin in the 1st mo of life and typically self-resolves by 1 yr. Diffuse or focal scaling and crusting of the scalp, sometimes called cradle cap (Fig. 655-10), may be the initial and at times the only manifestation. A greasy, scaly, erythematous papular dermatitis, which is usually nonpruritic in infants, may involve the face, neck, retroauricular areas, axillae, umbilicus, and diaper area. The dermatitis may be patchy and focal or may spread to involve almost the entire body (Fig. 655-11). Postinflammatory pigmentary changes are common, particularly in black infants. When the scaling becomes pronounced, the condition may resemble psoriasis and, at times, can be distinguished only with difficulty. The possibility of coexistent atopic dermatitis must be considered when there is an acute weeping dermatitis with pruritus, and the two are often clinically inseparable at an early age. An intractable seborrhea-like dermatitis with chronic diarrhea and failure to thrive may reflect systemic dysfunction of the immune system. A chronic seborrhea-like pattern, which responds poorly to treatment, may also result from cutaneous histiocytic infiltrates in infants with Langerhans cell histiocytosis. Seborrheic dermatitis is a common cutaneous manifestation of AIDS in young adults and is characterized by thick, greasy scales on the scalp and large hyperkeratotic erythematous plaques on the face, chest, and genitals.

During adolescence, seborrheic dermatitis is more localized and may be confined to the scalp and intertriginous areas. Also noted may be marginal blepharitis and involvement of the external auditory canal. Scalp changes vary from diffuse, brawny scaling to focal areas of

Figure 655-10 Cradle cap in an infant.

Figure 655-11 Widespread seborrheic dermatitis.

thick, oily, yellow crusts with underlying erythema. Loss of hair is common, and pruritus may be absent to marked. When the dermatitis is severe, erythema and scaling occur at the frontal hairline, the medial aspects of the eyebrows, and in the nasolabial and retroauricular folds. Red, scaly plaques may appear in the axillae, inguinal region, gluteal cleft, and umbilicus. On the extremities, seborrheic plaques may be more eczematous and less erythematous and demarcated. Unlike infantile seborrheic dermatitis, adolescent seborrheic dermatitis generally does not self-resolve and has a chronic relapsing course.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of seborrheic dermatitis includes psoriasis, atopic dermatitis, dermatophytosis, histiocytic disorders, and candidiasis. Secondary bacterial infections and superimposed candidiasis are common.

TREATMENT

Initial management for infantile seborrheic dermatitis is generally conservative given the self-limited nature of this condition. Emollients, baby oil, gentle shampooing with nonmedicated baby shampoo, and gentle use of a soft brush to remove scales are usually effective measures. Persistent lesions may be treated with low-potency topical corticosteroids if inflamed (applied once daily for 1 wk) and a topical antifungal (e.g., ketoconazole 2% cream twice daily). Antifungal shampoos such as ketoconazole 2% shampoo should be used cautiously as they are not tear-free.

First-line therapy for children and adolescents with scalp seborrheic dermatitis is antifungal shampoo used several times weekly to daily (selenium sulfide, ketoconazole, ciclopirox, zinc pyrithione, salicylic acid, or tar). Midpotency topical corticosteroids such as fluocinolone 0.01% shampoo may also be used for inflamed lesions, applied once daily for 2-4 wk. Nonscalp lesions are treated with topical corticosteroid cream (low-potency for facial lesions, midpotency elsewhere), as well as topical antifungals such as ketoconazole 2% cream or ketoconazole 2% shampoo used as a body wash. Second-line therapy for seborrheic dermatitis includes topical calcineurin inhibitors and keratolytic agents such as urea. Severe adult cases improve with oral antifungal agents; however, pediatric studies are lacking. Once acute disease is controlled, antifungal shampoo used on a weekly basis is effective maintenance to reduce risk of relapse.

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Chapter 656

Photosensitivity

Brianne Z. Dickey and Yvonne E. Chiu

Photosensitivity denotes a qualitatively or quantitatively abnormal cutaneous reaction to sunlight or artificial light because of UV radiation. The UV light spectrum contains UVA (320-400 nm wavelength), UVB (290-320 nm wavelength), and UVC (100-290 nm wavelength) subtypes. Transmitted radiation <300 nm is largely absorbed in the epidermis, whereas that >300 nm is mostly transmitted to the dermis after variable epidermal melanin absorption. Children vary in susceptibility to UV radiation, depending on their skin type (i.e., its amount of pigment; Table 656-1).

ACUTE SUNBURN REACTION

The most common photosensitive reaction seen in children is acute sunburn. Sunburn is caused mainly by UVB radiation. Sunlight contains many times more UVA than UVB radiation, but UVA must be encountered in much larger quantities than UVB radiation to produce sunburn. Immediate pigment darkening is caused by UVA radiation–induced photooxidative darkening of existing melanin and its transfer from melanocytes to keratinocytes. This effect generally lasts for a few hours and is not photoprotective. UVB-induced effects appear 6-12 hr after initial exposure and reach a peak in 24 hr. Effects include redness, tenderness, edema, and blistering (Fig. 656-1). Severe sunburn induces systemic symptoms of fever, nausea, and headache. Reactive oxidation species generated by UVB induce keratinocyte

Table 656-1 Sun-Reactive Skin Types

FITZPATRICK SKIN TYPE	SUNBURN, TANNING HISTORY
I	Always burns easily, no tanning
II	Usually burns, minimal tanning
III	Sometimes burns, gradual light brown tan
IV	Minimal to no burning, always tans
V	Rarely burns, tans profusely dark brown
VI	Never burns, pigmented black

Figure 656-1 **Sunburn.** Well-demarcated, severe erythema.

membrane damage and are involved in the pathogenesis of sunburn. A portion of the vasodilation seen in UVB-induced erythema is mediated by prostaglandins E_2, E_3, and F_{2A}. Other inflammatory cytokines induced by UVB include interleukins 1, 6, and 8, and tumor necrosis factor-α. Acute sunburn is a self-limited condition that resolves within 1 wk with desquamation and without scarring. Delayed melanogenesis as a result of UVB radiation begins in 2-3 days and lasts several days to a few weeks. Manufacture of new melanin in melanocytes, transfer of melanin from melanocytes to keratinocytes, increase in size and arborization of melanocytes, and activation of quiescent melanocytes produce delayed melanogenesis. This effect reduces skin sensitivity to development of UV-induced erythema. The amount of protection afforded depends on the skin type of the patient. Additional effects and possible complications of sun exposure include increased thickness of the stratum corneum, recurrence or exacerbation of herpes simplex labialis, lupus erythematosus, and many other conditions (Table 656-2).

Acute sunburn should be managed conservatively with cool compresses, aloe vera products, and calamine lotion. Oral analgesics such as ibuprofen and acetaminophen may decrease pain. Topical corticosteroids are only helpful in the acute phase and generally should not be used to treat sunburn once peak erythema has been reached. Topical anesthetics are relatively ineffective and potentially hazardous because of their propensity to cause contact dermatitis. A bland emollient is effective in the desquamative phase.

The long-term sequelae of chronic and intense sun exposure are not often seen in children, but most individuals receive >50% of their lifetime UV dose by age 20 yr; therefore, pediatricians have a pivotal role in educating patients and their parents about the harmful effects, potential malignancy risks, and irreversible skin damage that result from prolonged exposure to the sun and tanning lights. Premature aging, senile elastosis, actinic keratoses, squamous and basal cell carcinomas, and melanomas all occur with greater frequency in sun-damaged skin. In particular, blistering sunburns in childhood and adolescence significantly increase the risk for development of malignant melanoma.

Sun protection is best achieved by sun avoidance, which includes minimizing time in the midday sun (10 AM to 3 PM), staying in the shade, and wearing protective clothing including wide-brimmed hats. Protection is enhanced by a wide variety of sunscreen agents. Physical sunscreens (zinc oxide, titanium dioxide) block UV light, whereas chemical sunscreens (para-aminobenzoic acid [PABA], PABA esters, salicylates, benzophenones, avobenzone, cinnamates, ecamsule) absorb damaging radiation. Most chemical sunscreens are effective for only UVB wavelengths but benzophenones and avobenzone provide protection in both the UVA and UVB ranges; ecamsule is a UVA sunscreen. Stabilizers such as octocrylene and diethyl 2,6-naphthalate increase the time of function of the chemical sunscreens. “Broad-spectrum” sunscreens are combination products that absorb both UVA and UVB, and families should be advised to use products labeled as “broad spectrum” with a sun protective factor (SPF) of at least 30, reapply liberally at least every 2 hr while outdoors, and reapply after swimming. Infants younger than 6 mo of age should not be exposed to direct sunlight but may have SPF 15 physical sunscreens applied to small areas of skin if sunlight avoidance is not possible. SPF is defined as the minimal dose of sunlight required to produce cutaneous erythema after application of a sunscreen, divided by the dose required with no use of sunscreen. SPF applies only to UVB protection; there is no associated rating for UVA protection in the United States aside from the “broad spectrum” designation.

Table 656-2 Cutaneous Reactions to Sunlight

SUNBURN

Photoallergic drug eruptions:
- Systemic drugs include tetracyclines, psoralens, chlorothiazides, sulfonamides, barbiturates, griseofulvin, thiazides, quinidine, phenothiazines
- Topical agents include coal tar derivatives, psoralens, halogenated salicylanilides (soaps), perfume oils (e.g., oil of bergamot), sunscreens (e.g., para-aminobenzoic acid [PABA], cinnamates, benzophenones)

Phototoxic drug eruptions:
- Systemic agents include nalidixic acid, furosemide, nonsteroidal antiinflammatory agents (naproxen, piroxicam), and high doses of agents causing photoallergic eruptions
- Topical agents include 5-fluorouracial, furocoumarins (e.g., lime, lemon, carrot, celery, dill, parsnip, parsley), and high doses of agents causing photoallergic eruptions

Genetic disorders with photosensitivity:
- Xeroderma pigmentosum
- Bloom syndrome
- Cockayne syndrome
- Rothmund-Thomson syndrome
- Trichothiodystrophy
- Smith-Lemli-Opitz syndrome
- Kindler syndrome

Inborn errors of metabolism:
- Porphyrias, protoporphyria
- Hartnup disease and pellagra

Infectious diseases associated with photosensitivity:
- Recurrent herpes simplex infection
- Viral exanthems (accentuated photodistribution; e.g., varicella)

Skin disease exacerbated or precipitated by light:
- Lichen planus
- Darier disease
- Lupus erythematosus including neonatal
- Dermatomyositis
- Psoriasis
- Erythema multiforme
- Atopic dermatitis
- Hailey-Hailey disease

Deficient protection because of a lack of pigment:
- Vitiligo
- Oculocutaneous albinism
- Phenylketonuria
- Chédiak-Higashi syndrome
- Hermansky-Pudlak syndrome
- Waardenburg syndrome
- Piebaldism

PHOTOSENSITIVE REACTIONS

Photosensitizers in combination with a particular wavelength of light (typically UVA) cause dermatitis that can be classified as phototoxic or photoallergic reactions. Contact of the skin with the photosensitizer may occur externally, internally by enteral or parenteral administration, or through host synthesis of photosensitizers in response to an administered drug.

Photoallergic reactions occur in only a small percentage of persons exposed to photosensitizers and light and require a time interval for sensitization to take place. Thereafter, dermatitis appears within 24 hr of reexposure to the photosensitizer and light. Photoallergic dermatitis is a T-cell–mediated delayed hypersensitivity reaction in which the drug, acting as a hapten, may combine with a skin protein to form the antigenic substance. Photoallergic reactions vary in morphology and may occur on partially covered and on light-exposed skin. Table 656-2 lists some of the important classes of drugs and chemicals responsible for photosensitivity reactions. The most common photoallergens are chemicals present in sunscreens.

Phototoxic reactions occur in all individuals who accumulate adequate amounts of a photosensitizing drug or chemical within the skin. UV radiation excites the agent to a state capable of causing cell or tissue damage through reactive oxygen species formation. Prior sensitization is not required. Dermatitis develops within hours after exposure to radiation in the range of 285-450 nm. The eruption is confined to light-exposed areas and often resembles exaggerated sunburn, but it may be urticarial or bullous. It results in postinflammatory hyperpigmentation. All the drugs that cause photoallergic reactions may also cause a phototoxic dermatitis if given in sufficiently high doses. Several

additional drugs and contactants cause phototoxic reactions (see Table 656-2). Differentiating contact phototoxicity from contact dermatitis caused by poison ivy or poison oak may be difficult, but itching is prominent in contact dermatitis while burning is more prominent in photodermatitis. Postinflammatory hyperpigmentation develops rapidly and can be the presenting sign. Contact with furoucoumarin-containing plants causes a disorder called **phytophotodermatitis**. The most common phytophotodermatitis seen in children is caused by lime juice, which presents as hyperpigmentation in streaky patterns on sun-exposed skin consistent with dripping juice or handprints.

Diagnosis of photosensitive reactions caused by drugs or chemicals relies on a high index of suspicion, an appreciation of the distribution pattern of the eruption, and a history of application or ingestion of a known photosensitizing agent. Phototesting and photopatch testing are also helpful when available. First-line treatment for both photoallergy and phototoxicity consists of discontinuation of the offending agent and good sun protection practices, including avoidance of sun exposure. Photoallergic reactions are treated similarly to contact dermatitis, with a topical corticosteroid to alleviate pruritus when necessary. Severe reactions may necessitate a 2-3 wk course of systemic corticosteroid therapy. Phototoxic reactions are treated similarly to sunburn, with comfort measures such as cool compresses, emollients, and oral analgesics.

PORPHYRIAS

See Chapter 91.

Porphyrias are acquired or inborn disorders due to abnormalities of specific enzyme mutations in the heme biosynthetic pathway. Some have childhood photosensitivity as a consistent feature. The pathogenesis of photosensitivity in porphyria relates to deposition of excess porphyrins in the skin; UV radiation excites these molecules, causing cell and tissue damage via generation of reactive oxygen species. Signs and symptoms may be negligible during the winter, when sun exposure is minimal.

Congenital erythropoietic porphyria (Günther disease) is a rare autosomal recessive disorder affecting the enzyme uroporphyrinogen III synthase. It may cause hydrops fetalis, but more typically manifests in the 1st few mo of life as hemolytic anemia and exquisite sensitivity to light, which may induce repeated severe bullous eruptions that result in mutilating scars (Fig. 656-2). **Hyperpigmentation,** hyperkeratosis, vesiculation, and fragility of skin as well as various nail changes develop in light-exposed areas. Light therapy for an affected neonate presenting with jaundice may inadvertently induce skin manifestations. **Hirsutism** in areas of mild involvement, scarring **alopecia** in severely affected areas, pink to red urine, brown teeth (erythrodontia), splenomegaly, and corneal ulceration are additional characteristic manifestations. Laboratory findings include uroporphyrin I and coproporphyrin I in urine, plasma, and erythrocytes, and coproporphyrin I in feces. Teeth and urine from affected patients fluoresce reddish pink under a Wood lamp as a result of the presence of porphyrins. Skin findings for **hepatoerythropoietic porphyria** closely resemble those seen in congenital erythropoietic porphyria; this extremely rare disorder presents in early childhood and is discussed in greater depth in Chapter 91.

Erythropoietic protoporphyria may be autosomal dominant, autosomal recessive, or X-linked and most commonly involves the enzyme ferrochelatase (FECH). Symptoms develop in early childhood and manifest as intense pain, tingling, or pruritus within 30 minutes of sun exposure, followed by erythema, edema, urticaria, or mild systemic symptoms; these acute manifestations resolve completely within days. The absence of blistering distinguishes erythropoietic protoporphyria from the other cutaneous porphyrias. Nail changes consist of opacification of the nail plate, onycholysis, pain, and tenderness. Recurrent sun exposure produces a subtle chronic eczematous dermatitis with thickened, lichenified skin, especially over the finger joints (Fig. 656-3*A*), as well as mild facial scarring (Fig. 656-3*B*). Pigmentation, hypertrichosis, skin fragility, and mutilation are not seen. Gallstones develop frequently; however, severe liver disease occurs in <5% of patients. Protoporphyrin is detected in plasma, erythrocytes, and feces.

The wavelengths of light mainly responsible for eliciting cutaneous reactions in porphyria are in the region of 400 nm (UVA light). Window glass, including that in automobiles, transmits wavelengths >320 nm and is not protective, and fluorescent indoor lights may be pathogenic. Patients must avoid direct sunlight, wear protective clothing, and use a sunscreen agent that effectively blocks UVA light. Oral beta-carotene also provides some photoprotective benefit. Cutaneous porphyria symptoms are typically constant throughout life, and secondary bacterial infections commonly complicate disease course. Cutaneous porphyrias do not appear to increase risk for skin malignancies. Diagnostic and treatment recommendations for **congenital erythropoietic porphyria** and **erythropoietic protoporphyria** are outlined in Chapter 91.

Figure 656-2 Crusted ulcerations in an infant with congenital erythropoietic porphyria.

Figure 656-3 Erythropoietic protoporphyria. **A,** Erythematous thickening over the metacarpal phalangeal joints. **B,** Linear crusts and scarring.

COLLOID MILIUM

Colloid milium is a rare, asymptomatic disorder that occurs on the face (nose, upper lip, upper cheeks) and may extend to the dorsum of the hands and the neck as a profuse eruption of tiny, ivory to yellow, firm, grouped papules. Lesions appear before puberty on otherwise normal skin, unlike the adult variant that develops on sun-damaged skin. Onset may follow an acute sunburn or long-term sun exposure. Most cases reach maximal severity within 3 yr and remain unchanged thereafter, although the condition may remit spontaneously after puberty. Treatment is usually not necessary.

HYDROA VACCINIFORME

Hydroa vacciniforme is a vesiculobullous disorder with unclear etiology, although chronic or latent Epstein-Barr virus infections or lymphoproliferative disorders have been implicated. It begins in early childhood and may remit at puberty, with peak incidence in the spring and summer. Erythematous, pruritic macules develop symmetrically within hours of sun exposure over the ears, nose, lips, cheeks, and dorsal surfaces of the hands and forearms. Lesions progress to stinging tender papules and hemorrhagic vesicles and bullae, resembling chickenpox. They become umbilicated, ulcerated, and crusted, eventually healing with pitted scars and telangiectasias. Associated features are rare but include fever, malaise, hypersensitivity to mosquito bites, conjunctivitis, and other ocular symptoms. This eruption should be distinguished from erythropoietic protoporphyria, which rarely shows vesicles. Typical lesions have been reproduced with repeated doses of UVA or UVB light. First-line treatment includes sun avoidance, broad-spectrum sunscreens, and other sun-protective habits. Other potential therapies include mid-potency topical corticosteroids for inflamed lesions, low-dose courses of narrow-band UVB (NB-UVB) therapy, beta-carotene, hydroxychloroquine, or antiviral agents such as acyclovir.

SOLAR URTICARIA

Solar urticaria is a rare disorder induced by UV or visible irradiation. The disorder is mediated by immunoglobulin E antibodies to either an abnormal photoallergen present only in affected patients (type I) or a normal photoallergen ordinarily present in skin (type II), leading to mast cell degranulation and histamine release. Classic urticarial lesions consisting of erythematous pruritic wheals develop on sun-exposed skin (Fig. 656-4) within 5-10 minutes of sun exposure and fade within 24 hr. Severe reactions involving large areas of skin may lead to systemic symptoms or anaphylaxis. Diagnosis is achieved by history alone or with phototesting. First-line treatment is an oral H_1 antihistamine, plus sun avoidance and protection. Second-line therapy possibilities include oral or topical corticosteroids, photodesensitization using NB-UVB, omalizumab, or intravenous immunoglobulin.

POLYMORPHOUS LIGHT ERUPTION

Polymorphous light eruption (PMLE) is a common photosensitivity reaction that develops most commonly in females. The first eruption typically appears in the spring after the first episode of prolonged sun exposure of the season. Onset of the eruption is delayed by hours to days after sun exposure and lasts for days to sometimes weeks. PMLE usually resolves with increased sun exposure throughout the spring and summer. Areas of involvement tend to be symmetric and are characteristic for a given patient, including some but not all of the exposed or lightly covered skin on the face, neck, upper chest, and distal extremities. Lesions have various morphologies but most commonly are pruritic, 2-5 mm, grouped, erythematous papules or papulovesicles or >5 cm, edematous plaques; lesions are nonscarring. A PMLE variant known as **juvenile spring eruption** characteristically occurs on affected boys' ears each spring, while **pinpoint papular PMLE** is a variant characterized by pinpoint-sized lesions occurring in darker-skinned individuals. Most PMLE cases involve sensitivity to UVA radiation, although some are UVB induced. PMLE most likely results from a delayed-type hypersensitivity reaction to a photo-induced antigen within the skin, with individuals having a genetic predisposition. Provocative phototesting, as well as skin biopsy (showing epidermal spongiosis and superficial and deep lymphocytic infiltrate), aid in diagnosis. Treatment is aimed at prevention with sun avoidance, protective clothing, and broad-spectrum sunscreens. Topical corticosteroids (low-potency for facial lesions, high-potency for lesions elsewhere) can be used for mild eruptions. Second-line approaches include prophylactic NB-UVB phototherapy or hydroxychloroqine in early spring and short course systemic glucocorticoids for severe flares.

ACTINIC PRURIGO

Actinic prurigo, often classified as a variant of PMLE, is a chronic familial photodermatitis inherited as an autosomal dominant trait seen most commonly in Native Americans of North and South America. Human leukocyte antigen (HLA) DRB1*0407 (60-70%) and HLA DRB1*0401 (20%) are strongly associated with actinic prurigo. Most patients are female and are sensitive to UVA radiation. The first episode generally occurs in early childhood, several hr to 2 days after intense sun exposure. The papulonodular lesions are intensely pruritic, erythematous, and crusted. Areas of predilection include the face (Fig. 656-5), lower lip, distal extremities, and, in severe cases, buttocks. Facial lesions may heal with minute pitted or linear scarring. Lesions often become chronic, without periods of total clearing, merging into

Figure 656-4 Urticaria after 5 minutes of exposure to artificial ultraviolet A radiation.

Figure 656-5 Erythematous, excoriated papules in actinic prurigo.

eczematous plaques that become lichenified and occasionally secondarily infected. Associated features that distinguish this disorder from other photoeruptions and atopic dermatitis include cheilitis, conjunctivitis, and traumatic alopecia of the outer half of the eyebrows. Actinic prurigo is a chronic condition that generally persists into adult life, although it may improve spontaneously in the late teenage years. Sun avoidance, protective clothing, and broad-spectrum sunscreens may be helpful in preventing the eruption. Mid- to high-potency topical corticosteroids and antihistamines palliate the pruritus and inflammation. Severe acute eruptions may require oral glucocorticoids. Treatment with NB-UVB beginning in springtime has shown improved tolerance of sunlight during summer months; however, it may induce symptoms in some patients. Thalidomide 50-100 mg/day is very effective, but its use is limited by toxicity, especially severe birth defects when taken by pregnant females.

COCKAYNE SYNDROME

Cockayne syndrome is a rare autosomal recessive disorder. Onset occurs at 1 year of age and is characterized by facial erythema in a butterfly distribution after sun exposure. Later characteristics include loss of adipose tissue and development of thin, atrophic, hyperpigmented skin, particularly over the face. Associated features include dwarfism; microcephaly; mental retardation; progressive dementia; distinct facies (aged look, pinched nose, sunken eyes, large protuberant ears); long limbs; disproportionately large hands and feet; cool and cyanotic extremities; carious teeth; unsteady gait with tremor; limitation of joint mobility; progressive deafness; cataracts; retinal degeneration; optic atrophy; decreased sweating and tearing; and premature graying of the hair. Complications include diabetes and hepatic or renal impairment. Diffuse extensive demyelination of the peripheral and central nervous systems ensues, and patients generally die of atheromatous vascular disease or infections (especially pneumonia) before the 3rd decade. There are 2 types of Cockayne syndrome. Type I (*CSA* gene) is less severe than type II (*CSB* gene). Patients may have xeroderma pigmentosum–Cockayne syndrome overlap, which is phenotypically more like Cockayne syndrome. Photosensitivity in Cockayne syndrome is a result of deficient nucleotide excision repair of UV-induced damage, specifically within actively transcribing regions of DNA (transcription-coupled DNA repair). The etiology of neurologic and other associated features remains unclear; however, evidence points toward a mitochondriopathy. The syndrome is distinguished from progeria (see Chapter 90) by the presence of photosensitivity and ocular abnormalities and from xeroderma pigmentosum by the fact that patients with Cockayne syndrome do not develop skin cancers. Diagnosis is accomplished by genetic testing and performing various tests on cultured fibroblasts. The mainstay of treatment for the photosensitivity of Cockayne syndrome is strict sunlight avoidance and protective measures.

XERODERMA PIGMENTOSUM

Xeroderma pigmentosum is a rare autosomal recessive disorder that results from a defect in nucleotide excision repair. Eight genetic groups have been recognized on the basis of each group's separate defect in ability to repair (xeroderma pigmentosum A through G) or replicate (xeroderma pigmentosum V [variant]) damaged DNA. The wavelength of light that induces the DNA damage ranges from 280-340 nm. Skin changes are first noted during infancy or early childhood in sun-exposed areas though lesions may occur at other sites, including the scalp. The skin lesions consist of erythema, scaling, bullae, crusting, ephelides (freckles), telangiectasia, keratoses (Fig. 656-6), basal and squamous cell carcinomas, and malignant melanomas. Interestingly, although most patients experience exaggerated acute sunburn reactions following minimal UV exposure, up to half of affected patients do not and instead develop progressive freckling. This difference in presentation depends on genetic subtype. Ocular manifestations include photophobia, lacrimation, blepharitis, symblepharon, keratitis, corneal opacities, tumors of the lids, and possible

Figure 656-6 Dyspigmentation and actinic keratoses in child with xeroderma pigmentosum.

Figure 656-7 Poikiloderma on the arm of an infant with Rothmund-Thomson syndrome.

eventual blindness. Neurologic abnormalities such as cognitive deterioration and sensorineural deafness develop in approximately 20% of patients.

This disease is a serious mutilating disorder, and the life span of an affected patient is often brief. Affected families should have genetic counseling. Xeroderma pigmentosum is detectable in cells cultured from amniotic fluid or DNA analysis of chorionic villous samples. Cultured skin fibroblast tests and genetic testing after birth also confirm diagnosis. Affected children should be totally protected from sun exposure; protective clothing, sunglasses, and opaque broad-spectrum sunscreens should be used even for mildly affected children. Light from unshielded fluorescent bulbs and sunlight passing through glass windows (including vehicle windows) are also harmful, thus applied window films are recommended. Early detection and removal of malignancies is mandatory, and oral isotretinoin may be used to prevent nonmelanoma skin cancers. There is crossover between several subtypes of xeroderma pigmentosum and both Cockayne syndrome and trichothiodystrophy.

ROTHMUND-THOMSON SYNDROME

Rothmund-Thomson syndrome is also known as poikiloderma congenitale because of the striking skin changes (Fig. 656-7). It is inherited as an autosomal recessive trait. Mutations in the *RECQL4* gene, which encodes a DNA helicase involved in repair and replication of DNA and

telomeres, are found in approximately 65% of patients. The other mutations causing Rothmund-Thomson syndrome are unknown. Skin changes are noted as early as 3 mo of age and begin on the face. Plaques of erythema and edema appear in a butterfly distribution, as well as on the forehead, ears, neck, dorsal portions of the hands, extensor surfaces of the arms, and buttocks. These are replaced gradually by poikiloderma (reticulated, atrophic, hyperpigmented and hypopigmented telangiectatic patches or plaques). Palmoplantar hyperkeratosis develops in one-third of patients. Light sensitivity is present in many cases, and exposure to the sun may provoke formation of bullae. Areas of involvement, however, are not strictly photodistributed. Short stature; small hands and feet; sparse eyebrows, eyelashes, and pubic and axillary hair, and sparse, fine, prematurely gray scalp hair or alopecia; dystrophic nails; various tooth and skeletal abnormalities; and hypogenitalism are common. Cataracts may also occur at an early age. Most patients have normal mental development. Keratoses and later squamous cell carcinomas may develop on exposed skin. The most worrisome association is that with osteosarcoma, which occurs only in those patients with Rothmund-Thomson syndrome and *RECQL4* mutations. Genetic testing aids diagnosis. Management of dermatologic findings begins with sun avoidance and protection behaviors, and telangiectatic lesions have been shown to respond to pulsed dye laser therapy. In the absence of malignancy, life expectancy is normal.

BLOOM SYNDROME

Bloom syndrome is inherited in an autosomal recessive manner, most commonly in the Ashkenazi Jewish population. It is caused by a mutation in the *BLM/RECQL3* gene, encoding a DNA helicase. Patients are sensitive to UV radiation, with increased rates of chromosomal breaks and sister chromatid exchanges. Erythema and telangiectasia develop during infancy in a butterfly distribution on the face after exposure to sunlight. A bullous eruption on the lips and telangiectatic erythema on the hands and forearms may develop. Café-au-lait spots and hypopigmented macules may be present. Intrauterine growth deficiency developing into short stature and a distinctive facies consisting of a prominent nose and ears and a small, narrow face are generally found. Intellect is average to low average. Immunodeficiency is seen in all patients, manifesting as recurrent ear and pulmonary infections. Gastrointestinal malabsorption, gastroesophageal reflux, and hypogonadism are common. Affected children have an unusual tendency to develop both solid tumors (especially of the skin) and lymphoreticular malignancies, which often result in death during childhood or early adulthood. Sister chromatid exchange analysis is generally performed to confirm diagnosis. The only effective measures to reduce skin disease are sun protection and avoidance.

HARTNUP DISEASE

See Chapter 85.5.

Hartnup disease is a rare inborn error of metabolism with autosomal recessive inheritance. Neutral amino acids, including tryptophan, are not transported across the brush border epithelium of the intestine and kidneys due to mutation of the SLC6A19 gene encoding the transporter. This results in deficiency of nicotinamide synthesis and causes a photo-induced **pellagra-like syndrome.** The urine contains increased amounts of monoamine monocarboxylic amino acids, distinguishing Hartnup disease from dietary pellagra. Cutaneous signs, which precede neurologic manifestations, initially develop during the early months of life. An eczematous, occasionally vesiculobullous, eruption occurs on the face and extremities in a glove-and-stocking photodistribution. Hyperpigmentation and hyperkeratosis may supervene and are intensified by further exposure to sunlight. Episodic flares may be precipitated by febrile illness, sun exposure, emotional stress, and poor nutrition. In most cases, mental development is normal, but some patients display emotional instability and episodic cerebellar ataxia. Neurologic symptoms are fully reversible. Administration of nicotinamide and protection from sunlight results in improvement of both cutaneous and neurologic manifestations.

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Chapter 657
Diseases of the Epidermis

657.1 Psoriasis

Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

Psoriasis is an inflammatory autoimmune-related disease characterized by inflammation and keratinocyte proliferation. Within the dermis, dendritic cells are activated by self-antigens and release cytokines such as interferon-γ, tumor necrosis factor, and interleukin (IL)-12, IL-17, IL-22, and IL-23, which recruit T cells. Once activated, the T cells release cytokines that induce proliferation and abnormal differentiation of epidermal keratinocytes; in turn, more cytokines are produced to perpetuate the cycle. Psoriasis has a complex multifactorial genetic basis. The major psoriasis-susceptibility gene *(PSORS1)* is human leukocyte antigen (HLA)-CW*0602, encoding a class I major histocompatibility complex protein involved in recognition of self-antigens. Numerous other psoriasis susceptibility genes have been identified.

Factors contributing to disease onset/flares in some patients include bacterial and viral infections, trauma, physical or emotional stress, tobacco use/secondhand exposure, and certain medications. There is an association between psoriasis and childhood obesity worldwide.

CLINICAL MANIFESTATIONS

This common, chronic skin disorder is first evident within the 1st 2 decades of life for approximately 30% of affected individuals. **Plaque psoriasis**, the most common (>80%) subtype, is characterized by erythematous papules that coalesce to form plaques with sharply demarcated, irregular borders. If they are unaltered by treatment, a thick silvery or yellow-white scale (resembling mica) develops (Fig. 657-1*A*). Removal of the scale may result in pinpoint bleeding (**Auspitz sign**). The **Koebner phenomenon,** in which new lesions appear at sites of trauma, is a valuable diagnostic feature. Lesions may occur anywhere, but preferred sites are the scalp, knees, elbows, umbilicus, superior intergluteal fold, genitals, and ear canal. Nail involvement, a valuable diagnostic sign, is characterized by pitting of the nail plate, detachment of the plate (onycholysis), yellowish-brown subungual discoloration, and accumulation of subungual debris (Fig. 657-1*B*). Plaques are generally asymptomatic; however, pruritus is more common in children than adults.

Guttate psoriasis, a variant that occurs predominantly in children, is characterized by an acute eruption of many oval or round papules smaller than 1.5 cm that are morphologically identical to the larger plaques of psoriasis (see Fig. 657-1*C*). Sites of predilection are the trunk, face, and proximal portions of the limbs. The onset usually follows a **streptococcal** infection such as pharyngitis; thus, throat culture and serologic titers should be obtained. Guttate psoriasis has also been observed after perianal streptococcal infection, viral infections, sunburn, and withdrawal of systemic corticosteroid therapy or tumor necrosis factor (TNF)-α inhibitors. Clinical course ranges from spontaneous resolution to chronic disease.

Pustular psoriasis is a multisystem autoinflammatory disease characterized by recurrent episodes with the sudden onset of fever, malaise, extracutaneous organ involvement, and a diffuse erythematous-pustular exanthema. It may be associated with plaque psoriasis in some patients; unregulated cytokine production as a result of mutations in the IL-36Ra gene is implicated.

Psoriasis is rare in infants but may be severe and recalcitrant and may pose a diagnostic problem. Psoriatic diaper rash is a common presentation in children younger than 2 yr old. Other rare forms

Figure 657-1 **A,** Chronic psoriatic plaques. **B,** Psoriatic nail dystrophy. **C,** Guttate psoriasis in widespread distribution over the trunk.

include psoriatic erythroderma, localized or generalized pustular psoriasis, linear psoriasis, palmoplantar psoriasis, and inverse psoriasis (occurring in intertriginous areas).

DIFFERENTIAL DIAGNOSIS

Psoriasis is a clinical diagnosis. The differential diagnosis of plaque-type psoriasis includes nummular dermatitis, tinea corporis, seborrheic dermatitis, postinfectious arthritis syndromes, and pityriasis rubra pilaris. Scalp lesions may be confused with seborrheic dermatitis, atopic dermatitis, or tinea capitis. Diaper area psoriasis may mimic seborrheic dermatitis, eczematous diaper dermatitis, perianal streptococcal disease, or candidiasis. Guttate psoriasis can be confused with viral exanthems, secondary syphilis, pityriasis rosea, and pityriasis lichenoides chronica (PLC). Nail psoriasis must be differentiated from onychomycosis, lichen planus, and other causes of onychodystrophy.

PATHOLOGY

When the diagnosis is in doubt, histopathologic examination of an untreated lesion can be helpful. Characteristic changes of psoriasis include parakeratosis, acanthosis, elongated rete ridges, neutrophilic infiltrate in the epidermis sometimes forming microabscesses, dilated dermal blood vessels, and lymphocytic infiltrate in the dermis.

TREATMENT

The therapeutic approach varies with the age of the child, type of psoriasis, sites of involvement, and extent of the disease. Physical and chemical trauma to the skin should be avoided as much as possible to prevent Koebner response lesions. The treatment of psoriasis should be viewed as a 4-tier process.

The **first tier** is **topical therapy.** The first-line topical agents for lesions on the body are emollients, vitamin D analogs (calcipotriene or calcitriol, although calcitriol is less irritating for children), and mid- to high-potency corticosteroids (see Chapter 646). A proprietary formulation containing both calcipotriene and betamethasone dipropionate (a high-potency topical corticosteroid) exists in ointment and solution forms. The preparation that is least potent but effective should be applied twice a day. Second-line topical options for lesions on the body include retinoids (tazarotene), tar preparations, anthralin, and keratolytics (salicylic acid or urea). Facial or intertriginous lesions may be treated with low-potency topical corticosteroids, and/or topical vitamin D analogs or calcineurin inhibitors as corticosteroid-sparing agents. For scalp lesions, applications of a phenol and saline solution (e.g., Baker Cummins P & S liquid) followed by a tar shampoo are effective in the removal of scales. A high- to superpotency corticosteroid in a foam, solution, or lotion base may be applied when the scaling is diminished. Nail lesions are difficult to treat topically; the first-line approach is a high-potency topical corticosteroid to the proximal nail fold.

The **second tier** of therapy is **phototherapy.** Narrow-band UVB (311 nm; NB-UVB) irradiation is the primary form of UVB therapy used in childhood. If available, phototherapy should be used alone or with tar ("Goeckerman treatment") for older children with extensive disease in whom topical therapy alone has failed. Excimer (308 nm) laser UVB irradiation may be used for localized treatment-resistant plaques. Exposure to natural sunlight is often effective for less-severe psoriasis.

The **third tier** is **systemic therapy, required rarely for** children with severe and generalized psoriasis. Methotrexate (0.2-0.7 mg/kg/wk) is the first-line systemic agent for children; other options include oral

retinoids (0.5-1.0 mg/kg/day) and cyclosporine (3-5 mg/kg/day). Oral retinoids may be cautiously combined with phototherapy, although doses may need to be decreased because of the photosensitizing effects of the medication.

The **fourth tier** of therapy is the **biologic response modifiers**, including the TNF-α inhibitors etanercept, infliximab, and adalimumab, and the T-cell function inhibitor alefacept. Ustekinumab is a human monoclonal antibody that prevents interactions between IL-12 and IL-23 and their cell-surface receptors. Anti–IL-17 and anti–IL-17 receptor agents also demonstrate some efficacy. Adult studies with all of these agents show efficacy in treating moderate to severe chronic psoriasis and psoriatic arthritis, although experience in children is limited. Novel small molecules that inhibit the inflammatory response are being tested; these include A3 adenosine receptor agonists, Janus kinase inhibitors, and phosphodiesterase 4 inhibitors.

PROGNOSIS

Prognosis is best for children with limited disease. Psoriasis is a lifelong disease characterized by remissions and exacerbations. Arthritis or various eye diseases may be extracutaneous complications. Metabolic and cardiovascular disorders also occur with increased frequency in patients with psoriasis. For example, increasing degree of obesity and the associated metabolic syndrome (hyperglycemia, hyperlipidemia, hypertension) correlates with psoriasis severity. Patients with psoriasis also have increased rates of stroke, myocardial infarction, and other vascular diseases later in adult life. A proposed mechanism involves the systemic proinflammatory state induced by both psoriasis and these associated conditions, although the direction of causality remains unclear.

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657.2 Pityriasis Lichenoides

Brianne Z. Dickey and Yvonne E. Chiu

Pityriasis lichenoides encompasses a disease spectrum ranging from pityriasis lichenoides chronica (PLC) to pityriasis lichenoides et varioliformis acuta (PLEVA; Mucha-Habermann disease). The designation of pityriasis lichenoides as acute or chronic refers to the morphologic appearance of the lesions rather than to the duration of the disease. No correlation is found between the type of lesion at the onset of the eruption and the duration of the disease. Many patients have both acute and chronic lesions simultaneously, and transition of lesions from 1 form into another occurs occasionally. Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) is a rare subtype of PLEVA that is more severe and potentially life-threatening.

ETIOLOGY/PATHOGENESIS

Two main theories exist for the etiology of pityriasis lichenoides. The first is that it arises in a genetically susceptible individual as a hypersensitivity reaction to an infection. The second is that it represents a monoclonal T-cell lymphocytic proliferation on the pathway to cutaneous T-cell dyscrasia.

CLINICAL MANIFESTATIONS

Pityriasis lichenoides most commonly manifests in the 2nd and 3rd decades of life; 30% of cases manifest before age 20 yr. The overall eruption persists for months to years with a tendency to eventually remit.

PLC manifests gradually as generalized, multiple, 3-5 mm, brown-red papules that are covered by a fine grayish scale (Fig. 657-2). Lesions may be asymptomatic or may cause minimal pruritus and occasionally become vesicular, hemorrhagic, crusted, or superinfected. Individual papules become flat and brownish in 2-6 wk, ultimately leaving a hyperpigmented or hypopigmented macule. Scarring is unusual. Various stages of lesions are present most commonly on the trunk and extremities and generally spare the face, palmoplantar surfaces, scalp, and mucous membranes.

Figure 657-2 Widespread plaques with fine scale in pityriasis lichenoides chronica.

Figure 657-3 Necrotic lesion with erythematous halo in pityriasis lichenoides et varioliformis acuta.

PLEVA manifests as an abrupt eruption of numerous papules that have a vesiculopustular and then a purpuric center, are covered by a dark adherent hemorrhagic or necrotic crust, and are surrounded by an erythematous halo (Fig. 657-3). Constitutional symptoms, such as fever, malaise, headache, and arthralgias, may be present for 2-3 days after the initial outbreak. Lesions are distributed diffusely on the trunk and extremities, as in PLC. Individual lesions heal within a few weeks, sometimes leaving a varioliform scar, and successive crops of papules produce the characteristic polymorphous appearance of the eruption, with lesions in various stages of evolution.

FUMHD manifests as fever and ulceronecrotic nodules up to a few centimeters in diameter, which are most common on the anterior trunk and flexor surfaces of the proximal upper extremities. Hemorrhagic bullae, mucosal ulcers, arthritis, cardiomyopathy, vasculitis, abdominal complaints, and superinfection of cutaneous lesions with *Staphylococcus aureus* may also develop. The ulceronecrotic lesions heal with hypopigmented scarring in a few weeks.

PATHOLOGY

PLC histologically shows a parakeratotic, thickened corneal layer; epidermal spongiosis; a superficial perivascular infiltrate of macrophages and predominantly CD8 lymphocytes that may extend into the epidermis; and small numbers of extravasated erythrocytes in the papillary dermis.

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The histopathologic changes of PLEVA and FUMHD reflect their more-severe nature. Intercellular and intracellular edema in the epidermis may lead to degeneration of keratinocytes. A dense perivascular mononuclear cell infiltrate, endothelial cell swelling, and extravasation of erythrocytes into the epidermis and dermis are additional characteristic features.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pityriasis lichenoides includes guttate psoriasis, pityriasis rosea, drug eruptions, secondary syphilis, viral exanthems, lymphomatoid papulosis, and lichen planus. The chronicity of pityriasis lichenoides helps preclude pityriasis rosea, viral exanthems, and some drug eruptions. A skin biopsy helps distinguish pityriasis lichenoides from other entities in the differential diagnosis.

TREATMENT

In general, pityriasis lichenoides should be considered a benign condition that does not alter the health of the child. A lubricant to remove excessive scaling may be all that is necessary if the patient is asymptomatic. If treatment is required, first-line agents are oral anti-inflammatory antibiotics such as erythromycin (30-50 mg/kg/day for 2-3 mo). Topical corticosteroids (mid-potency, applied twice daily) and topical calcineurin inhibitors may help the pruritus and inflammation, but do not alter the course of the disease. Phototherapy (NB-UVB) is the second-line treatment option. Methotrexate should be reserved for severely symptomatic cases. The rare FUMHD usually requires inpatient treatment; initially, systemic corticosteroids, methotrexate, intravenous immunoglobulin, or cyclosporine may be necessary, with eventual transition to another form of treatment, as mentioned above, once the disease improves and stabilizes.

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657.3 Keratosis Pilaris

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Keratosis pilaris is a common papular eruption resulting from keratin plugging of hair follicles. It displays an autosomal dominant transmission with variable penetrance. Typical areas of involvement include the upper extensor surfaces of the arms and thighs, cheeks, and buttocks. The lesions may resemble gooseflesh; they are noninflammatory, scaly, follicular papules that do not coalesce. They are generally asymptomatic but may be pruritic. Irritation of the follicular plugs occasionally causes erythema surrounding the keratotic papules (Fig. 657-4). A subset of patients have keratosis pilaris associated with facial telangiectasia and ulerythema ophryogenes, a rare cutaneous disorder characterized by inflammatory keratotic facial papules that may result in scars, atrophy, and alopecia. Because the lesions of keratosis pilaris are associated with and accentuated by dry skin, they are often more prominent during the winter. Keratosis pilaris is more frequent in patients with atopic dermatitis and is most common during childhood and early adulthood, tending to subside in the 3rd decade of life. Treatment of keratosis pilaris is optional. Measures to decrease pruritus include moisturization with a bland emollient. Regular applications of a 10-40% urea cream or an α-hydroxy acid preparation such as 12% lactic acid cream or lotion can improve the appearance of keratosis pilaris but may further contribute to pruritus and irritation. Therapy may improve the condition but does not cure it.

Figure 657-4 Keratotic follicular plugs with surrounding erythema in keratosis pilaris.

657.4 Lichen Spinulosus

Brianne Z. Dickey and Yvonne E. Chiu

Lichen spinulosus is an uncommon disorder that occurs principally in children and more frequently in boys. The cause is unknown. The lesions consist of sharply circumscribed irregular plaques of spiny, keratotic, follicular plugs. Plaques may occur anywhere on the body and are often distributed symmetrically on the trunk, elbows, knees, and extensor surfaces of the limbs. Although sometimes erythematous or pruritic, the lesions are usually skin colored and asymptomatic.

Treatment is usually unnecessary. For patients who regard the eruption as a cosmetic defect, urea-containing lubricants (10-40%) are often effective in flattening the projections. The plaques usually disappear spontaneously after several months or years.

657.5 Pityriasis Rosea

Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

The cause of pityriasis rosea is unknown; a viral agent is suspected, and there is debate over the role of human herpesviruses 6, 7, and 8 in this condition. Supporting evidence for an infectious etiology is the tendency for it to occur in case clusters, although the rash itself is not contagious.

CLINICAL MANIFESTATIONS

This benign, common eruption occurs most frequently in children and young adults. Although a prodrome of fever, malaise, arthralgia, and pharyngitis may precede the eruption, children rarely complain of such symptoms. A **herald patch** classically precedes the generalized eruption and may occur anywhere on the body. Herald patches are generally larger than other lesions and vary from 1-10 cm in diameter; they are annular in configuration and have a raised border with fine, adherent scales. Approximately 5-10 days after the appearance of the herald patch, a widespread, symmetric eruption involving mainly the trunk and proximal limbs becomes evident (Fig. 657-5). In the inverse form of pityriasis rosea, the face, scalp, and distal limbs may be preferentially involved. Lesions may appear in crops for several days. Typical lesions are oval or round, <1 cm in diameter, slightly raised, and pink to brown. The developed lesion is covered by a fine scale, which gives the skin a crinkly appearance. Some lesions clear centrally and produce a collarette of scale that is attached only at the periphery. Papular (more common in black children), vesicular, urticarial, hemorrhagic, large annular, and mucosal lesions are unusual variants. The long axis of each lesion is usually aligned with the cutaneous cleavage lines, a feature that creates the so-called **Christmas tree pattern** on the back. Conformation to skin lines is often more discernible in the anterior and posterior axillary folds and supraclavicular areas. The lesions most commonly are asymptomatic but may be mildly to severely pruritic.

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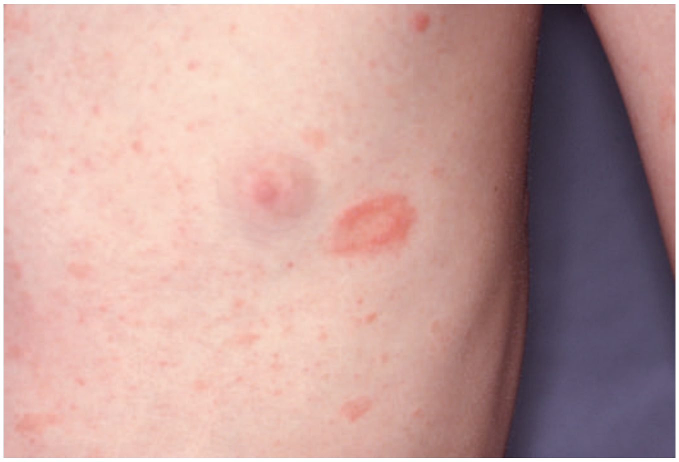

Figure 657-5 Herald patch and surrounding pityriasis rosea.

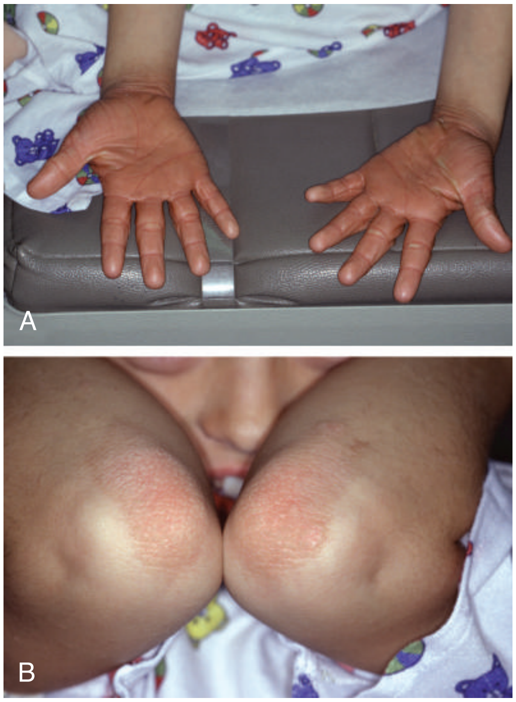

Figure 657-6 Pityriasis rubra pilaris. **A,** Orange palmar hyperkeratosis. **B,** Elbow lesions.

Duration of the eruption varies from 2-12 wk, with self-resolution. After the eruption has resolved, postinflammatory hypopigmentation or hyperpigmentation may be pronounced, particularly in dark-skinned patients. These changes disappear in subsequent weeks to months.

DIFFERENTIAL DIAGNOSIS

The herald patch may be mistaken for tinea corporis, a pitfall that can be avoided if microscopic evaluation of a potassium hydroxide preparation of scrapings of the lesion is performed. The generalized eruption resembles a number of other diseases; secondary syphilis is the most important. Drug eruptions, viral exanthems, guttate psoriasis, PLC, and nummular dermatitis can also be confused with pityriasis rosea.

TREATMENT

Therapy is unnecessary for asymptomatic patients with pityriasis rosea. If scaling is prominent, a bland emollient may suffice. Pruritus may be suppressed by a lubricating lotion containing menthol and camphor or by an oral antihistamine for sedation, particularly at night, when itching may be troublesome. Occasionally, a mid-potency topical corticosteroid preparation may be necessary to alleviate pruritus. Exposure to natural sunlight and NB-UVB phototherapy may reduce disease duration and severity.

Bibliography is available at Expert Consult.

657.6 Pityriasis Rubra Pilaris

Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

The cause of pityriasis rubra pilaris is unknown. Although genetic forms with autosomal dominant or recessive transmission may account for some cases in childhood, most cases are sporadic. Some studies have indicated a role for TNF-α in disease development, while other hypotheses for causal factors include abnormal vitamin A metabolism, trauma, infections, immunosuppression, and UV light exposure.

CLINICAL MANIFESTATIONS

This rare inflammatory dermatosis is known for its variability in clinical presentation and course of disease. It often has an insidious onset with diffuse scaling and erythema of the scalp, which is indistinguishable from the findings in seborrheic dermatitis, and with thick hyperkeratosis of the palms and soles (Fig. 657-6*A*). Lesions over the elbows and knees are also common (Fig. 657-6*B*), and generalized erythroderma develops in some patients. The characteristic primary lesion is a firm, dome-shaped, tiny, acuminate, pink to red papule, which has a central keratotic plug pierced by a vellus hair. Masses of these papules coalesce to form large, erythematous, sharply demarcated orange-pink plaques with overlying scale, within which islands of normal skin can be distinguished. Typical papules on the dorsum of the proximal phalanges are readily palpated. Gray plaques or papules resembling lichen planus may be found in the oral cavity. Dystrophic changes in the nails may occur and mimic those of psoriasis. Lesions are commonly pruritic. In childhood, the prognosis for eventual resolution is relatively good.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes ichthyosis, seborrheic dermatitis, keratoderma of the palms and soles, and psoriasis.

HISTOLOGY

Skin biopsy revealing follicular plugging, epidermal acanthosis, perivascular infiltrate, checkerboard pattern of orthokeratosis and parakeratosis, and an intact granular layer may differentiate this condition from psoriasis and seborrheic dermatitis.

TREATMENT

The numerous therapeutic regimens recommended are difficult to evaluate because pityriasis rubra pilaris has a capricious course with exacerbations and remissions. Moisturization alone is useful in mild cases. Topical agents, such as mid- to high-potency corticosteroids, keratolytics (urea, salicylic acid), vitamin D analogs (calcipotriene), retinoids (tazarotene, tretinoin), and tar, are used in combination with systemic agents for widespread disease and as monotherapy for localized disease. When further treatment is necessary, oral retinoids (isotretinoin 1 mg/kg/day or acitretin 0.5 mg/kg/day) are used as first-line agents, while methotrexate is used as a second-line agent. Third-line treatment options include biologic TNF-α inhibitors, cyclosporine, azathioprine, and NB-UVB phototherapy.

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657.7 Darier Disease (Keratosis Follicularis)

Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

A rare genetic disorder, Darier disease is inherited as an autosomal dominant trait and is caused by mutations in the *ATP2A2* gene. This gene encodes a cellular calcium pump, and dysfunction results in loss of adhesion between epidermal cells and abnormal keratinization.

CLINICAL MANIFESTATIONS

Onset usually occurs in late childhood. Typical lesions are small, firm, skin-colored, warty papules that are not always follicular in location. The lesions eventually acquire yellow, malodorous, greasy crusts and coalesce to form large, gray-brown, vegetative plaques (Fig. 657-7). The scalp, face, neck, shoulders, chest, back, axillae, limb flexures, and groin are symmetrically involved. Papules, fissures, crusts, and ulcers may appear on the mucous membranes of the lips, tongue, buccal mucosa, pharynx, larynx, and vulva. Hyperkeratosis of the palms and soles and nail dystrophy with subungual hyperkeratosis and longitudinal red and white banding are variable features. Severe pruritus, secondary infection, offensive odor, and pain may occur. Several exacerbating triggers have been identified: sweating, UV light exposure, heat, friction, and infections. Thus, Darier disease has a chronic relapsing course that usually worsens in summertime.

HISTOLOGY

Histologic changes seen in Darier disease are diagnostic. Hyperkeratosis with keratin plugging, intraepidermal separation (acantholysis) with formation of suprabasal clefts, and dyskeratotic epidermal cells are characteristic features.

DIFFERENTIAL DIAGNOSIS

Darier disease is most likely to be confused with seborrheic dermatitis, flat warts, or Hailey-Hailey disease.

TREATMENT

Treatment is nonspecific and begins with emollients and avoidance of triggers. First-line treatment for mild/localized disease is low- to mid-potency corticosteroids; second-line is topical retinoids. Further treatment options include topical keratolytic agents (urea, lactic acid), antiseptic washes (triclosan, chlorhexidine gluconate, or bleach), or calcineurin inhibitors. More severe/generalized disease is treated with oral isotretinoin or acitretin (0.5-1.0 mg/kg/day for 3-4 mo). Secondary infections must be treated appropriately.

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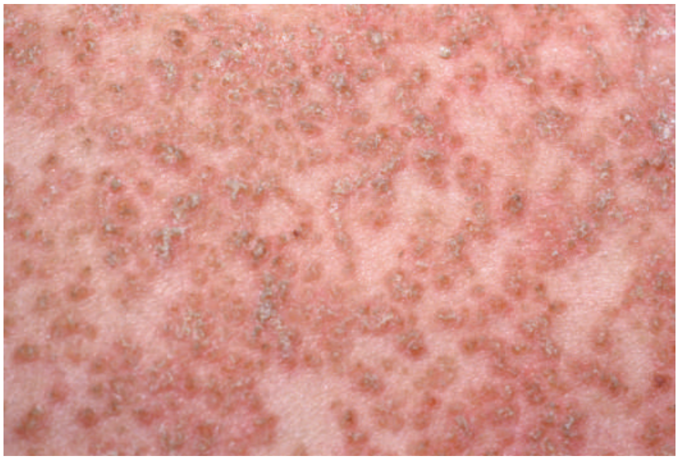

Figure 657-7 Papules coalescing into large plaque on the back of a patient with Darier disease.

657.8 Lichen Nitidus

Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

The etiology of lichen nitidus is unknown.

CLINICAL MANIFESTATIONS

This chronic, benign, papular eruption is characterized by minute (1-2 mm), flat-topped, shiny, firm papules of uniform size. The papules are most often skin-colored but may be pink or red. In black individuals, they are usually hypopigmented (Fig. 657-8). Sites of predilection are the genitals, abdomen, chest, forearms, wrists, and inner aspects of the thighs. The lesions may be sparse or numerous and may form large plaques; careful examination usually discloses linear papules in a line of scratch (Koebner phenomenon), a valuable clue to the diagnosis because it occurs in only a few diseases. Lichen nitidus occurs in all age groups. The cause is unknown. Patients with lichen nitidus are usually asymptomatic and constitutionally well, although pruritus may be severe. The lesions may be confused with those of lichen planus, and lichen nitidus can rarely occur concurrently with lichen planus.

DIFFERENTIAL DIAGNOSIS

Widespread keratosis pilaris can also be confused with lichen nitidus, but the follicular localization of the papules and the absence of Koebner phenomenon in the former distinguish them. Verruca plana (flat warts), if small and uniform in size, may occasionally resemble lichen nitidus.

HISTOLOGY

Although the diagnosis can be made clinically, a biopsy is occasionally indicated. The lichen nitidus papule consists of sharply circumscribed nests of lymphocytes and histiocytes in the upper dermis enclosed by claw-like epidermal rete ridges.

TREATMENT

The course of lichen nitidus spans months to years, but the lesions eventually involute completely. No treatment is necessary, but mid- to high-potency topical steroids may be used for pruritus.

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Figure 657-8 Slightly hypopigmented, uniform papules of lichen nitidus.

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657.9 Lichen Striatus

Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

Lichen striatus is hypothesized to be caused by a combination of genetic predisposition present in a mosaic manner (following the lines of Blaschko) and an infectious trigger.

CLINICAL MANIFESTATIONS

A benign, self-limited eruption, lichen striatus consists of a continuous or discontinuous linear band of papules in a Blaschkoid distribution. The primary lesion is a flat-topped, hypopigmented or pink papule covered with fine scale. Aggregates of these papules form multiple bands or plaques. The papules are gradually replaced by hypopigmented macules, which may be the presenting lesion in some cases. The eruption evolves over a period of days or weeks in an otherwise healthy child, remains stationary for weeks to months, and finally remits without sequelae usually within 2 yr. Symptoms are usually absent, although some children complain of itching. Nail dystrophy may occur when the eruption involves the proximal nail fold and matrix (Fig. 657-9).

DIFFERENTIAL DIAGNOSIS

Lichen striatus is occasionally confused with other disorders. The initial plaque may resemble papular eczema or lichen nitidus until the linear configuration becomes apparent. Linear lichen planus and linear psoriasis are usually associated with typical individual lesions elsewhere on the body. Linear epidermal nevi are permanent lesions that often become more hyperkeratotic and hyperpigmented than those of lichen striatus.

TREATMENT

Treatment is not necessary and generally not very effective. A low-potency topical corticosteroid preparation can be used when pruritus is a problem in a patient with lichen striatus.

Bibliography is available at Expert Consult.

657.10 Lichen Planus

Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

Lichen planus is the result of an attack on the skin by cytotoxic T cells. The cause is unknown, but granzyme B, perforin, and granulysin are markedly increased in skin involved with lichen planus. A genetic predisposition may exist, and other proposed triggers include metal exposure, certain medications, liver disease, vaccinations (especially hepatitis B vaccination), and infections (especially hepatitis C virus).

CLINICAL MANIFESTATIONS

This is a rare disorder in young children and uncommon in older ones. It is more often seen in children from the Indian subcontinent and of African-American background. The classic form of lichen planus is the most common subtype in children, often exhibiting an acute eruptive onset. The lesions erupt in an explosive fashion, much like a viral exanthem, and spread to involve most of the body surface. The primary lesion is a violaceous, sharply demarcated, polygonal papule with fine white lines (Wickham's striae) or scale on the surface. Papules may coalesce to form large plaques (Fig. 657-10). The papules are intensely pruritic, and additional papules are often induced by scratching (Koebner phenomenon) so that lines of them are detected. Sites of predilection are the flexor surfaces of the wrists, the forearms, the inner aspects of the thighs, and the ankles.

Hypertrophic, linear, bullous, atrophic, annular, follicular, erosive, ulcerative, and actinic forms of lichen planus may also occur in children. Characteristic lesions of mucous membranes consist of pinhead-size white papules that coalesce to form reticulated and lacy patterns on the buccal mucosa. Erosive ulcers are also common in the oral mucosa, and may also involve the gastrointestinal tract. Nail involvement causes nail dystrophy. The disorder may persist for months to years, but the acute eruptive form is most likely to involute permanently. Self-resolution eventually occurs. Intense hyperpigmentation frequently persists for a long time after the resolution of lesions.

HISTOLOGY

The histopathologic findings in lichen planus are specific, consisting of hyperkeratosis, irregular acanthosis, wedge-shaped hypergranulosis, apoptotic keratinocytes in the lower epidermis and upper dermis, and basal cell degeneration with a bandlike lymphocytic infiltrate at the epidermal-dermal junction. Pigment incontinence is frequently seen. Biopsy is indicated if the diagnosis is unclear.

TREATMENT

Treatment is directed at alleviation of the intense pruritus and amelioration of the skin lesions. First-line treatment with a high-potency topical corticosteroid applied twice daily is effective for localized disease on the trunk or extremities; lesions on the face and genitals may be treated with low- to mid-potency corticosteroids. Alternatives to topical steroids include topical calcineurin inhibitors or vitamin D analogs. Thick lesions may require intralesional corticosteroid injection. Oral antihistamines (hydroxyzine) are often added for the

Figure 657-9 Lichen striatus with nail dystrophy.

Figure 657-10 Flat-topped, purple polygonal papules of lichen planus.

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pruritus. A short course of systemic glucocorticoids or phototherapy (NB-UVB) are used as second-line approaches for rare cases of widespread, intractable lesions. Other medications with efficacy include oral retinoids (acitretin), dapsone, metronidazole, griseofulvin, and methotrexate.

Bibliography is available at Expert Consult.

657.11 Porokeratosis

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ETIOLOGY/PATHOGENESIS

Porokeratosis is a disorder of epidermal keratinization. The etiology is unknown except for the disseminated actinic form, which is secondary to chronic sun exposure. Genetic susceptibility, with autosomal dominant transmission, and immunosuppression may also be involved.

CLINICAL MANIFESTATIONS

Porokeratosis is a rare, chronic, progressive disease of keratinization. The prototypical lesion is an atrophic papule or plaque with a surrounding ridge of hyperkeratosis, called cornoid lamella. Several forms have been delineated: solitary plaques, linear porokeratosis, hyperkeratotic lesions of the palms and soles, disseminated eruptive lesions, and superficial actinic porokeratosis. **Classic porokeratosis of Mibelli** begins in childhood and is more common in males. Sites of predilection are the limbs, face, genitals, mucous membranes, palms, and soles. The primary lesion is a small, keratotic papule that slowly enlarges peripherally so that the center becomes depressed, with the edge forming an elevated wall or collar (Fig. 657-11). The configuration of the plaque may be round, oval, or gyrate. The elevated border is split by a thin groove from which minute cornified projections protrude. The central atrophic area is yellow, gray, or tan, and sclerotic, smooth, and dry, whereas the hyperkeratotic border is a darker gray, brown, or black. **Linear porokeratosis** is also more common in childhood and typically follows the lines of Blaschko. The disease is slowly progressive but relatively asymptomatic; some patients experience pruritus or pain. Malignant degeneration to **squamous cell carcinoma** has been reported in long-standing cases.

HISTOLOGY

A skin biopsy is usually unnecessary, but will disclose the characteristic cornoid lamella (plug of stratum corneum cells with retained nuclei), which is responsible for the invariable linear ridge of the lesion. The granular layer is absent beneath the cornoid lamella.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of porokeratosis includes warts, epidermal nevi, lichen planus, granuloma annulare, tinea corporis, nummular eczema, pityriasis rosea, and elastosis perforans serpiginosa.

TREATMENT

No treatment is uniformly successful, thus therapeutic decisions depend largely on lesion size, location, symptoms, and patient preference. Most lesions are asymptomatic and do not require any intervention; however, when treatment is necessary options include pharmacologic management (topical retinoids, topical 5-fluorouracil, topical imiquimod, or oral retinoids [severe cases only]), destructive therapy (liquid nitrogen cryotherapy, electrodessication and curettage, or various lasers), and surgical removal. In general, the less-invasive topical agents should be attempted first. Good sunlight protection should also be encouraged to decrease risk of malignant transformation.

Bibliography is available at Expert Consult.

657.12 Gianotti-Crosti Syndrome (Papular Acrodermatitis)

Brianne Z. Dickey and Yvonne E. Chiu

ETIOLOGY/PATHOGENESIS

The pathogenesis of Gianotti-Crosti syndrome, also known as papular acrodermatitis, is unclear, but an immunologic reaction to viral infections and immunizations has been postulated. Historically, the most common associations are with Epstein-Barr virus, hepatitis B virus (primarily in countries without routine childhood vaccination programs), coxsackievirus A16, and parainfluenza virus, as well as with many childhood immunizations.

CLINICAL MANIFESTATIONS

This distinctive eruption is benign and predominantly occurs in children younger than 5 yr old about 1 wk after a viral illness. Cases are usually sporadic, but epidemics have been recorded. Skin lesions are monomorphic, firm, dusky or coppery red papules ranging in size from 1-10 mm (Fig. 657-12), although there is considerable variation in lesion appearance between patients. The papules often have the appearance of vesicles; when opened, however, no fluid is obtained. The papules sometimes become hemorrhagic. Lines of papules (**Koebner phenomenon**) may be noted on the extremities following minor local

Figure 657-11 Large plaque of porokeratosis of Mibelli with raised border and depressed center.

Figure 657-12 Numerous, flat-topped, red papules in Gianotti-Crosti syndrome.

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trauma. The papules occur in crops and may become profuse and coalesce into plaques, forming a symmetric eruption on the face, ears, buttocks, and limbs, including the palms and soles. The trunk is relatively spared, as are the scalp and mucous membranes. The eruption is occasionally associated with malaise and low-grade fever but few other constitutional symptoms. Generalized lymphadenopathy and hepatomegaly (in patients with hepatitis B viremia) constitute the only other abnormal physical findings; jaundice is classically absent despite hepatic enzyme elevation. The eruption resolves spontaneously but may take up to 2 mo. Some residual pigment change may occur but not scarring.

HISTOLOGY

Skin biopsy in Gianotti-Crosti syndrome is not specific, being characterized by a dermal perivascular mononuclear cell infiltrate, capillary endothelial swelling, and epidermal spongiosis and parakeratosis.

DIFFERENTIAL DIAGNOSIS

Gianotti-Crosti syndrome can be confused with other viral exanthems, erythema infectiosum, lichen planus, erythema multiforme, and Henoch-Schönlein purpura.

TREATMENT

The lesions are typically asymptomatic and resolve spontaneously, thus requiring no treatment. If present, pruritus may be relieved by emollients or calamine lotion. Mid-potency topical steroids may relieve pruritus but do not alter disease course. Sedating antihistamines at bedtime are also helpful.

Bibliography is available at Expert Consult.

657.13 Acanthosis Nigricans

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See also Chapter 47.

ETIOLOGY/PATHOGENESIS

The skin lesions of acanthosis nigricans may be genetic due to mutations in the fibroblast growth factor receptor gene, or acquired as a manifestation of insulin resistance. In familial cases, acanthosis nigricans is inherited as an autosomal dominant trait and develops in infancy. Insulin resistance with compensatory hyperinsulinism may lead to insulin binding to and activation of insulin-like growth factor receptors, promoting epidermal growth. Common causes of insulin resistance in children are obesity and diabetes mellitus, with acanthosis nigricans seen in >60% of children with a body mass index >98%. In the paraneoplastic form (rare in children), tumor-secreted growth factors induce acanthosis nigricans.

CLINICAL MANIFESTATIONS

Acanthosis nigricans is characterized by symmetric, hyperpigmented, velvety, hyperkeratotic plaques with exaggerated skin lines in intertriginous areas. The most common locations are the posterior neck and axillae (Fig. 657-13), but it is also seen in the inframammary areas, groin, inner thighs, and anogenital region. Prior to plaque development, patients notice a “dirty” appearance of affected skin that does not wash clean. Skin lesions remain asymptomatic unless maceration or secondary infection occurs. Acanthosis nigricans is found more commonly in African-American, Hispanic, and Native American children. The clinical severity and histopathologic features of acanthosis nigricans correlate positively with the degree of hyperinsulinism and with the degree of obesity.

HISTOLOGY

The histologic changes are those of papillomatosis and hyperkeratosis rather than acanthosis or excessive pigment formation. A mild dermal inflammatory infiltrate may be present.

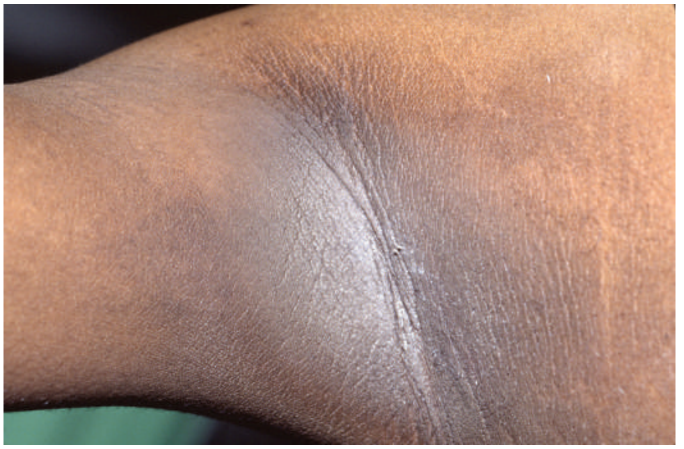

Figure 657-13 Velvety hyperpigmentation of the axilla in acanthosis nigricans.

TREATMENT

Treatment is aimed at palliation of the underlying disorder. Acanthosis nigricans in the obese child is associated with risk factors for glucose homeostasis abnormalities, and counseling families on its causes and consequences may motivate them to make healthy lifestyle changes that can decrease the risk for development of cardiac disease and diabetes mellitus. In children with obesity-related acanthosis nigricans, weight loss should be the primary goal. Appearance of skin lesions responds poorly to local medical management; some patients benefit from topical keratolytic agents (40% urea cream or 12% ammonium lactate cream) and agents that inhibit keratinocyte proliferation (topical vitamin D analogs).

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Chapter 658

Disorders of Keratinization

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DISORDERS OF CORNIFICATION

Mendelian disorders of cornification (**ichthyoses**) are a primary group of inherited conditions characterized clinically by patterns of scaling and histopathologically by hyperkeratosis. They are usually distinguishable on the basis of inheritance patterns, clinical features, associated defects, and histopathologic changes (Table 658-1). Much work is currently underway to better categorize the genotype-phenotype correlation of these diseases.

COLLODION BABY

Collodion baby is not a single entity but a newborn phenotype that is most often seen in babies who will eventually demonstrate **lamellar ichthyosis** or congenital **ichthyosiform erythroderma**. Less commonly, collodion babies evolve into babies with other forms of ichthyosis or Gaucher disease. A small subset become otherwise healthy babies without chronic skin disease.

Table 658-1 Disorders of Cornification That Usually Manifest in the First Weeks of Life

DISORDER	INHERITANCE	CLINICAL FEATURES	MUTATION	VISUAL METHOD OF DIAGNOSIS
Harlequin ichthyosis	AR	Thick, armor-like scale with fissuring	*ABCA12*	Clinical
Collodion baby	Usually AR	Shiny collodion membrane	Various	Clinical
Recessive X-linked ichthyosis	Recessive X-linked	Collodion membrane May have genital anomalies	Steroid sulfatase	Plasma cholesterol sulfate
Lamellar ichthyosis	Usually AR	Collodion membrane	Transglutaminase I *ABCA12* *CYP4F22*	Clinical
Congenital ichthyosiform erythroderma	AR	Collodion membrane	Transglutaminase 1 *ALOX12B* *ALOXE3*	Clinical
Epidermolytic ichthyosis	AD	Scaling and blistering	Keratins 1, 10, 2e	Clinical and histologic
Ichthyosis hystrix	AD	Plaques of hyperkeratosis	Keratin 1, *GJB2*	Clinical
Familial peeling skin	AR	Superficial peeling	Unknown	Clinical and histologic
Sjögren-Larsson syndrome	AR	Variable skin thickening Mental, developmental retardation Spastic diplegia Seizures "Glistening dots"	*FAD*	Clinical and fibroblast cultures for FAD
Neutral lipid storage disease	AR	Collodion membrane or ichthyosiform erythroderma	*CGI58*	Blood smear for vacuolated polymorphonuclear leukocytes
Netherton syndrome	AR	Ichthyosiform erythroderma Scant hair, often failure to thrive	*SPINK 5* Unknown	Clinical; hair exam later in infancy Clinical and hair microscopy; hair sulfur content
Trichothiodystrophy	AR	Collodion membrane Broken hair	*XPB* *XPD*	
KID (keratitis with ichthyosis and deafness) syndrome	May be AD, AR	Erythrokeratodermatous or thick, leathery skin with stippled papules	*GJB2*	Clinical; auditory evoked potentials
CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndrome	X-linked dominant	Alopecia Unilateral waxy yellow, scaling Hemidysplasia Limb defects	*NSDHL*	Clinical
Conradi-Hünermann syndrome	X-linked dominant	Thick, psoriasiform scale over erythroderma, patterned along Blaschko lines Proximal limb shortening	*ARSE*	Clinical
Ichthyosis follicularis	Usually X-linked recessive	Prominent follicular hyperkeratoses Alopecia Photophobia	*MBTPS2*	Clinical
CHIME (colobomas of the eyes, heart defects, ichthyosiform dermatosis, mental retardation, and ear abnormalities) syndrome	AR	Ichthyotic erythematous plaques Cardiac defects; typical facies Retinal colobomas	Unknown	Clinical
Gaucher disease	AR	Collodion membrane Hepatosplenomegaly	β-Glucocerebrosidase	Clinical; fibroblast cultures

AD, autosomal dominant; AR, autosomal recessive.; FAD, fatty aldehyde.
From Eichenfield LF, Frieden IJ, Esterly NB: Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 277.*

Collodion babies are covered at birth by a thick, taut membrane resembling oiled parchment or collodion (Fig. 658-1), which is subsequently shed. Affected neonates have ectropion, flattening of the ears and nose, and fixation of the lips in an O-shaped configuration. Hair may be absent or may perforate the abnormal covering. The membrane cracks with initial respiratory efforts and, shortly after birth, begins to desquamate in large sheets. A high-humidity environment and application of nonocclusive lubricants facilitates shedding of the membrane. Complete shedding may take several weeks, and a new membrane may occasionally form in localized areas.

Neonatal morbidity and mortality may be due to cutaneous infection, aspiration pneumonia (squamous material), hypothermia, or hypernatremic dehydration from excessive transcutaneous fluid losses as a result of increased skin permeability. The outcome is uncertain,

Figure 658-1 Typical appearance of a collodion baby.

Figure 658-2 Scale over the shin in ichthyosis vulgaris.

and accurate prognosis depends on identification of the underlying ichthyosis.

COMMON ICHTHYOSES

Ichthyosis Vulgaris

Etiology/Pathogenesis

Autosomal dominant or recessive mutations in the filaggrin gene cause ichthyosis vulgaris (IV). Filaggrin is a filament-aggregating protein that assembles the keratin filament cytoskeleton, causing collapse of the granular cells into classic flattened squamous cell shape. Mutations in filaggrin lead to absence or marked reductions in keratohyalin granules.

Clinical Manifestations

IV is the **most common** of the disorders of keratinization, with an incidence of 1/250 live births. Onset generally occurs in the 1st yr of life. In most cases, it is trivial, consisting only of slight roughening of the skin surface. Scaling is most prominent on the extensor aspects of the extremities, particularly the legs (Fig. 658-2). Flexural surfaces are spared, and the abdomen, neck, and face are relatively uninvolved. **Keratosis pilaris**, particularly on the upper arms and thighs, accentuated markings, and hyperkeratosis on the palms and soles, and atopy are relatively common. Scaling is most pronounced during the winter mo and may abate completely during warm weather. There is no accompanying disorder of hair, teeth, mucosal surfaces, or other organ systems.

Figure 658-3 Sparing of the antecubital fossa in X-linked ichthyosis.

Treatment

Scaling may be diminished by daily applications of an emollient or a lubricant containing urea (10-40%), salicylic acid, or an α-hydroxy acid such as lactic acid (5-12%).

X-Linked Ichthyosis

Etiology/Pathogenesis

X-linked ichthyosis (XLI) involves a deficiency of steroid sulfatase, which hydrolyzes cholesterol sulfate and other sulfated steroids to cholesterol. Cholesterol sulfate accumulates in the stratum corneum and plasma. In the epidermis this accumulation causes malformation of intercellular lipid layers, leading to barrier defects and delay of corneodesmosome degradation, resulting in corneocyte retention.

Clinical Manifestations

Skin peeling may be present at birth but typically begins at 3-6 mo of life. Scaling is most pronounced on the sides of the neck, lower face, preauricular areas, anterior trunk, and the limbs, particularly the legs. The elbow (Fig. 658-3) and knee flexures are generally spared but may be mildly involved. The palms and soles may be slightly thickened but are also usually spared. The condition gradually worsens in severity and extent. Keratosis pilaris is not present, and there is no increased incidence of atopy. Deep corneal opacities that do not interfere with vision develop in late childhood or adolescence and are a useful marker for the disease because they may also be present in carrier females. Some patients have larger deletions on the X chromosome that encompass neighboring genes, generating *contiguous gene deletion syndromes*. These include **Kallmann syndrome** (*KAL1* gene), which consists of hypogonadotrophic hypogonadism and anosmia, **X-linked chondroplasia punctata** (*ARSE* gene), **short stature,** and **ocular albinism**. The rate of testicular cancer may be increased in patients with coexistent Kallmann syndrome. There is also an increased risk of attention deficit hyperactivity disorder and autism owing to a contiguous gene defect in neuroligin 4.

Reduced steroid sulfatase enzyme activity can be detected in fibroblasts, keratinocytes, and leukocytes and, prenatally, in amniocytes or chorionic villus cells. In affected families, an affected male can be detected by restriction enzyme analysis of cultured chorionic villus cell DNA or amniocytes or by in situ hybridization, which identifies steroid sulfatase gene deletions prenatally in chorionic villus cells. A placental steroid sulfatase deficiency in carrier mothers may result in low urinary and serum estriol values, prolonged labor, and insensitivity of the uterus to oxytocin and prostaglandins.

Treatment

Daily application of emollients and a urea-containing lubricant (10-40%) is usually effective. Glycolic or lactic acid (5-12%) in an

emollient base and propylene glycol (40-60%) in water with occlusion overnight are alternative forms of therapy.

AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSES (ARCI)

Harlequin Ichthyosis

Etiology/Pathogenesis

Harlequin ichthyosis (HI) is caused by mutations in the *ABCA12* gene. Mutation in the gene leads to defective lipid transport and *ABCA12* activity is required for the generation of long-chain ceramides that are essential for the development of the normal skin barrier.

Clinical Manifestations

At birth, markedly thickened, ridged, and cracked skin forms horny plates over the entire body, disfiguring the facial features and constricting the digits. Severe ectropion and chemosis obscure the orbits, the nose and ears are flattened, and the lips are everted and gaping. Nails and hair may be absent. Joint mobility is restricted, and the hands and feet appear fixed and ischemic. Affected neonates have respiratory difficulty, suck poorly, and are subject to severe cutaneous infection. HI used to be uniformly fatal in the neonatal period, but with the use of oral retinoids, more patients survive (~80%) beyond infancy and have severe ichthyosis usually resembling lamellar ichthyosis or nonbullous congenital ichthyosiform erythroderma as adolescents and adults. Those with a compound heterozygous genotype have a better prognosis.

Treatment

Initial treatment includes high fluid intake to avoid dehydration from transepidermal water loss and use of a humidified heated incubator, emulsifying ointments, careful attention to hygiene, and oral retinoids (1 mg/kg/day). Prenatal diagnosis has been accomplished by fetoscopy, fetal skin biopsy, and microscopic examination of cells from amniotic fluid.

Lamellar Ichthyosis and Congenital Ichthyosiform Erythroderma (Nonbullous Congenital Ichthyosiform Erythroderma)

Lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE; nonbullous congenital ichthyosiform erythroderma; non-HI ARCI) are the most common types of autosomal recessively inherited ichthyosis. Both forms are present at or shortly after birth. Most infants with these forms of ichthyosis present with erythroderma and scaling; but among collodion babies, most turn out to have one of these ichthyosis variants.

Etiology/Pathogenesis

Six genes have been identified that cause non-HI ARCI: *TGM* (the gene encoding transglutaminase), *ABCA12*, *NIPAL4* (also known as *ICHTHYIN*), *CYP4F22*, and the lipoxygenase genes *ALOX12B* and *ALOXE3*. Transglutaminase mutations lead to abnormalities in the cornified envelope, whereas defects in *ABCA12* cause abnormal lipid transport and those in *CYP4F22* produce abnormal lamellar granules. The lipoxygenases are likely to play a role in epidermal barrier formation by affecting lipid metabolism.

Clinical Manifestations

After shedding of the collodion membrane, if present, lamellar ichthyosis evolves into large, quadrilateral, dark scales that are free at the edges and adherent at the center. Scaling is often pronounced and involves the entire body surface, including flexural surfaces (Fig. 658-4). The face is often markedly involved, including ectropion and small, crumpled ears. The palms and soles are generally hyperkeratotic. The hair may be sparse and fine, but the teeth and mucosal surfaces are normal. Unlike in congenital ichthyosiform erythroderma, there is little erythema.

In congenital ichthyosiform erythroderma**,** erythroderma tends to be persistent, and scales, although they are generalized, are finer and whiter than in lamellar ichthyosis (Fig. 658-5). Hyperkeratosis is

Figure 658-4 Generalized scaling of lamellar ichthyosis.

Figure 658-5 Prominent erythema and scale in congenital ichthyosiform erythroderma.

particularly noticeable around the knees, elbows, and ankles. Palms and soles are uniformly hyperkeratotic. Patients have sparse hair, cicatricial alopecia, and nail dystrophy. Neither form includes blistering.

Treatment

Pruritus may be severe and responds minimally to antipruritic therapy. The unattractive appearance of the child and the bad odor from bacterial colonization of macerated scales may create serious psychologic problems. A high-humidity environment in winter and air conditioning in summer reduce discomfort. Generous and frequent applications of emollients and keratolytic agents such as lactic or glycolic acid (5-12%), urea (10-40%), tazarotene (0.1% gel), and retinoic acid (0.1% cream) may lessen the scaling to some extent, although these agents produce stinging if applied to fissured skin. Oral retinoids (1 mg/kg/day) have a beneficial effect in these conditions but do not alter the underlying defect and, therefore, must be administered indefinitely. The long-term risks of these compounds (teratogenic effects and toxicity to bone) may limit their usefulness. Ectropion requires ophthalmologic care and, at times, plastic surgical procedures.

KERATINOPATHIC ICHTHYOSES

Epidermolytic Ichthyosis (Bullous Congenital Ichthyosiform Erythroderma; Epidermolytic Hyperkeratosis)

Etiology/Pathogenesis

Epidermolytic ichthyosis (EI) is an autosomal dominant trait that has been shown to be due to defects in either keratin 1 or keratin 10. These

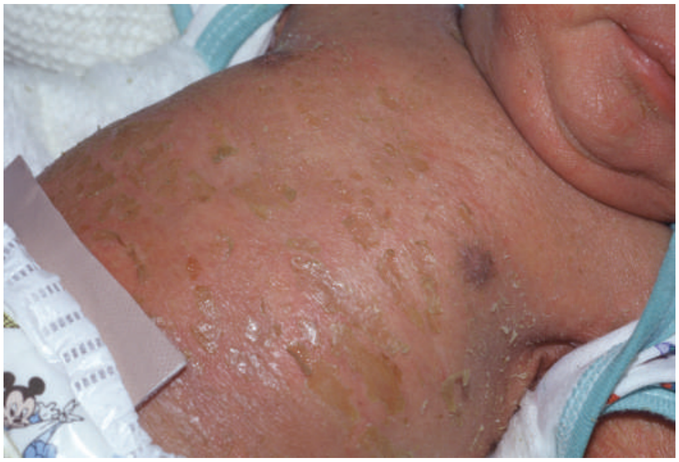

Figure 658-6 Superficial erosions and hyperkeratosis in epidermolytic hyperkeratosis.

keratins are required to form the keratin-intermediate filaments in cells of the suprabasilar layers of the epidermis.

Clinical Manifestations

The clinical manifestations are initially characterized by the onset at birth of widespread blisters and erosions on a background of generalized erythroderma (Fig. 658-6). Recurrent blistering may be widespread in neonates and may cause diagnostic confusion with other blistering disorders. With time, the blister formation ceases, erythema decreases, and generalized hyperkeratosis develops. The scales are small, hard, and verrucous. Distinctive, parallel hyperkeratotic ridges develop over the joint flexures, including the axillary, popliteal, and antecubital fossae, and on the neck and hips. **Palmoplantar keratoderma** is associated with keratin 1 defects. The hair, nails, mucosa, and sweat glands are normal. Malodorous secondary bacterial infection is common and requires appropriate antibiotic therapy.

Histopathology

The histopathology is diagnostic of EI, consisting of hyperkeratosis, degeneration of the epidermal granular layer with an increased number of keratohyalin granules, clear spaces around nuclei, and indistinct cellular boundaries of cells in the upper epidermis. On electron microscopic examination, keratin-intermediate filaments are clumped, and many desmosomes are attached to only one keratinocyte instead of connecting neighboring keratinocytes. Localized forms of the disease may resemble epidermal nevi or keratoderma of the palms and soles but share the distinctive histopathologic changes of EI.

Treatment

Treatment of EI is difficult. Morbidity is increased in the neonatal period as a result of prematurity, sepsis, and fluid and electrolyte imbalance. Bacterial colonization of macerated scales produces a distinctive bad odor that can be controlled somewhat by use of an antibacterial cleanser. Intermittent oral antibiotics are generally necessary. Keratolytic agents are often poorly tolerated. Oral retinoids (1 mg/kg/day) may produce significant improvement. Prenatal diagnosis for affected families is possible by examination of DNA extracts from chorionic villus cells or amniocytes, provided that the specific mutation in the affected parent is known.

OTHER NONSYNDROMIC ICHTHYOSES

Erythrokeratoderma Variabilis

Etiology/Pathogenesis

An autosomal dominant disorder, erythrokeratoderma variabilis (EKV) is caused by mutations in connexins 31 and 30.3. Connexins are proteins that form gap junctions between cells that allow for transport and signaling between neighboring epidermal cells.

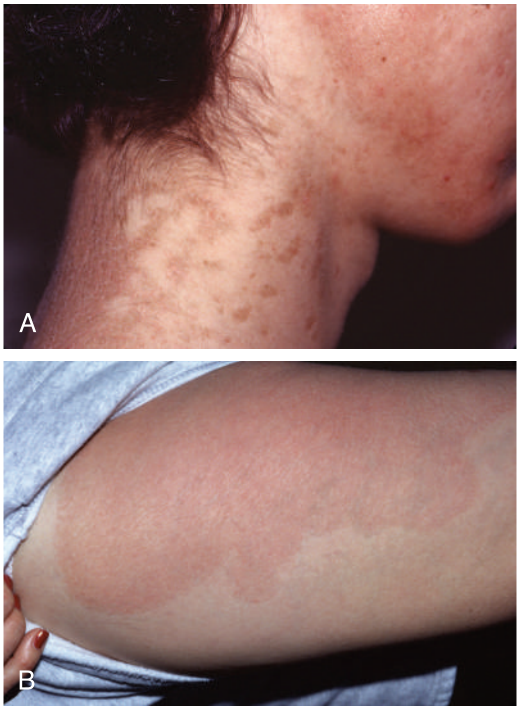

Figure 658-7 Erythrokeratoderma variabilis. **A,** Fixed, hyperkeratotic plaques, **B,** Migratory, erythematous lesion.

Clinical Manifestations

EKV usually manifests in the early mo of life, progresses in childhood, and stabilizes in adolescence. It is characterized by two distinctive manifestations: sharply demarcated, hyperkeratotic plaques (Fig. 658-7*A*) and transient figurate erythema (Fig. 658-7*B*). The distribution is generalized but sparse; sites of predilection are the face, buttocks, axillae, and extensor surfaces of the limbs. The palms and soles may be thickened, but hair, teeth, and nails are normal.

Treatment

There are case reports that topical tazarotene gel 0.1% and oral retinoids (1 mg/kg/day) are effective for treatment of EKV.

Symmetric Progressive Erythrokeratoderma

Etiology/Pathogenesis

Symmetric progressive erythrokeratoderma is an autosomal dominant disorder caused by mutations in the gene encoding loricrin. Loricrin is a major component of the epidermal cornified cell envelope.

Clinical Manifestations

The disorder manifests in childhood as large, fixed, geographic and symmetric, fine, scaling, hyperkeratotic, erythematous plaques primarily on the extremities, buttocks, face, ankles, and wrists. The primary feature distinguishing this disorder from EKV is the lack of variable erythema seen in the latter condition.

Treatment

Symmetric progressive erythrokeratoderma is a very rare disorder, but reports of response to topical and oral retinoids (1 mg/kg/day) exist.

SYNDROMIC ICHTHYOSES

Sjögren-Larsson Syndrome

Etiology/Pathogenesis

The autosomal recessive inborn error of metabolism known as Sjögren-Larsson syndrome is an abnormality of fatty alcohol oxidation that results from a deficiency of fatty aldehyde dehydrogenase (*FALDH3A2*), a component of the fatty alcohol–nicotinamide adenine dinucleotide oxidoreductase enzyme complex.

Clinical Manifestations

The clinical picture of Sjögren-Larsson syndrome consists of ichthyosis, cognitive impairment, and spasticity. The ichthyosis is generalized but is accentuated on the flexures and the lower abdomen and consists of erythroderma, fine scaling, larger platelike scales, and dark hyperkeratosis. The degree of scale varies markedly from patient to patient. Most individuals have **palmoplantar hyperkeratosis**. The skin changes may be identical to the other forms of ichthyosis, and diagnosis is often delayed until the onset of neurologic symptoms. Pruritus is severe and hypohidrosis is common. Glistening dots in the foveal area are a cardinal ophthalmologic sign. About half the patients have primary retinal degeneration. Motor and speech developmental delays are usually noted before 1 yr of age, and spastic diplegia or tetraplegia, epilepsy, and intellectual disability generally become evident in the 1st 3 yr of life. Some patients may walk with the aid of braces, but most are confined to wheelchairs. This deficiency can be demonstrated in cultured skin fibroblasts of affected patients and carriers and, prenatally, in cultured chorionic villus cells and amniocytes from affected fetuses. Elevation of urinary leukotriene B4 (LTB4) may provide an easier approach to diagnosis.

Treatment

Treatment is similar to that for the other forms of ichthyosis; 5-lipoxygenase inhibitors have been used to decrease pruritus.

Netherton Syndrome

Etiology/Pathogenesis

A rare autosomal recessive disorder, Netherton syndrome is caused by mutations in the *SPINK 5* gene, which encodes a serine protease inhibitor (*LEKT1*).

Clinical Manifestations

Netherton syndrome is characterized by ichthyosis (usually ichthyosis linearis circumflexa but occasionally the lamellar or congenital types of ichthyosiform erythroderma), trichorrhexis invaginata and other hair shaft anomalies, and atopic diathesis. The disorder manifests at birth or in the 1st few mo of life as generalized erythema and scaling. The trunk and limbs have diffuse erythema and superimposed migratory, polycyclic, and serpiginous hyperkeratotic lesions (Fig. 658-8), some with a distinctive double-edged margin of scale. Lichenification or hyperkeratosis tends to persist in the antecubital and popliteal fossae. The face and scalp may remain erythematous and scaling. Many hair shaft deformities, most notably, trichorrhexis invaginata, have been described in most patients with Netherton syndrome.

The ichthyosis is present in the 1st 10 days of life and may be especially marked around the eyes, mouth, and perineal area. The erythroderma is often intensified after infection. Infants may suffer from failure to thrive, recurrent bacterial and candidal infections, elevated serum immunoglobulin IgE values, and marked hypernatremic dehydration. The most frequent allergic manifestations are urticaria, angioedema, atopic dermatitis, and asthma. Scalp hair is sparse and short and fractures easily (Fig. 658-9); eyebrows, eyelashes, and body hair are also abnormal. The characteristic hair abnormality can be identified with light microscopy; in the newborn, it may best be identified in eyebrow hair.

Treatment

Owing to the inflammatory nature of the skin disease, oral antihistamines and topical steroids, as used in the treatment of atopic dermatitis, are helpful for Netherton syndrome.

Refsum Syndrome

See Chapters 86.2 and 613.5.

Etiology/Pathogenesis

There are 2 types of Refsum syndrome. The classic form is autosomal recessive and caused by mutations in the *PAHX* gene that result in an increase in phytanic acid. The infantile forms of Refsum syndrome are also autosomal recessive and caused by mutations in the *PEX1*, *PEX2*, or *PEX26* genes. These are peroxisomal abnormalities that lead to an increase in very long chain fatty acids, di- and tri-hydroxycholestanoic acid, and pipecolic acid as well as phytanic acid.

Clinical Manifestations

Refsum syndrome is a multisystem disorder that becomes symptomatic in the 2nd or 3rd decade of life. The ichthyosis may be generalized, is relatively mild, and resembles ichthyosis vulgaris. The ichthyosis may also be localized to the palms and soles. Chronic polyneuritis with progressive paralysis and ataxia, retinitis pigmentosa, anosmia, deafness, bony abnormalities, and electrocardiographic changes are the most characteristic features. The condition is diagnosed through lipid analysis of the blood or skin, which shows elevated phytanic acid values.

The infantile form begins, as suggested by the name, early in life, and in addition to the changes seen in the classic form, affected patients have hepatomegaly, abnormal bile acid profiles, developmental delay, and cognitive impairment.

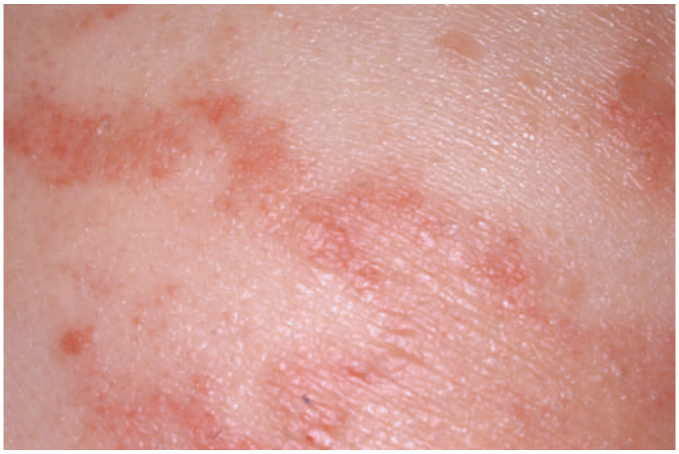

Figure 658-8 Serpiginous, erythematous, hyperkeratotic lesions of ichthyosis linearis circumflexa.

Figure 658-9 Very short scalp hair and thick scale in Netherton syndrome.

Treatment

Phytanic acid is exclusively derived from dietary chlorophyll. Lifelong dietary avoidance of phytanic acid–containing produces clinical improvement in classic Refsum syndrome.

Chondrodysplasia Punctata

See Chapter 86.2.

Etiology/Pathogenesis

Chondrodysplasia punctata (CPD) is a clinically and genetically heterogeneous condition. X-linked dominant CPD, also known as **Conradi-Hünermann syndrome**, is the best-characterized form. There is also an X-linked recessive form caused by mutation in the *ARSE* gene. Rhizomelic chondrodysplasia punctata type 1 is an autosomal recessive disorder caused by mutations in the *PEX7* gene, which encodes the peroxisomal type 2 targeting signal (*PTS2*) receptor. CPD can also be caused by maternal vitamin K deficiency or warfarin teratogenicity.

Clinical Manifestations

These heterogeneous disorders are marked by ichthyosis and bone changes. Nearly all patients with the X-linked dominant form and approximately 25% of those with the recessive type have cutaneous lesions, ranging from severe, generalized erythema and scaling to mild hyperkeratosis. **Rhizomelic chondrodysplasia punctata** is associated with cataracts, hypertelorism, optic nerve atrophy, disproportionate shortening of the proximal extremities, psychomotor retardation, failure to thrive, and spasticity; most affected patients die in infancy. Patients with the X-linked dominant form have asymmetric, variable shortening of the limbs and a distinctive ichthyosiform eruption at birth. Thick, yellow, tightly adherent, keratinized plaques are distributed in a whorled pattern over the entire body. The eruption typically resolves in infancy and may be superseded by a follicular atrophoderma and patchy alopecia.

Additional features in all variants include cataracts and abnormal facies with saddle nose and frontal bossing. The pathognomonic defect, termed **chondrodysplasia punctata**, is stippled epiphyses in the cartilaginous skeleton. This defect, which is seen in various settings and inherited disorders, often in association with peroxisomal deficiency and disturbance of cholesterol biosynthesis, disappears by 3-4 yr of age.

OTHER SYNDROMES WITH ICHTHYOSIS

A number of other rare syndromes with ichthyosis as a consistent feature include the following: keratitis with ichthyosis and deafness (**KID syndrome**, connexin 26 gene), ichthyosis with defective hair having a banded pattern under polarized light and a low sulfur content (**trichothiodystrophy**), multiple sulfatase deficiency, neutral lipid storage disease with ichthyosis (**Chanarin-Dorfman syndrome;** *CGI58* gene), and **CHILD syndrome** (Fig. 658-10; congenital hemidysplasia with ichthyosiform erythroderma and limb defects; *NSDHL* gene).

Figure 658-10 Limb dysplasia and ichthyosiform eruption in CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndrome.

Palmoplantar Keratodermas

Excessive hyperkeratosis of the palms and soles may occur as a manifestation of a focal or generalized congenital hereditary skin disorder or may result from such chronic skin diseases as psoriasis, eczema, pityriasis rubra pilaris, lupus erythematosus, or postinfectious arthritis syndrome.

Diffuse Hyperkeratosis of Palms and Soles (Unna-Thost, Vorner)

Unna-Thost and Vorner type palmoplantar keratodermas (PPKs), although clinically inseparable, were thought to be separate entities. They were separated histologically by the presence (Vorner) or absence (Unna-Thost) of epidermolytic hyperkeratosis. They represent the clinical spectrum of the same disease caused by mutations in keratin (*KRT1* and *KRT9* genes). This autosomal dominant disorder manifests in the 1st few mo of life as erythema that gradually progresses to sharply demarcated, hyperkeratotic, scaling plaques over the palms (Fig. 658-11) and soles. The margins of the plaques often remain red; plaques may extend along the lateral aspects of the hands and feet and onto the volar wrists and the heels. Hyperhidrosis is usually present, but hair, teeth, and nails are usually normal. Striate (*DSG1*, *DSP*, *KRT1* genes) and punctate forms of palmar and plantar hyperkeratosis represent distinct entities.

Figure 658-11 Palmar keratoderma with epidermolytic changes seen on biopsy.

Mal De Meleda (*SLURP-1* Gene)

A rare, progressive autosomal recessive condition, mal de Meleda is characterized by erythema and thick scales on the palms, fingers, soles, and flexor aspects of the wrists, knees, and elbows. Hyperhidrosis, nail thickening or koilonychia, and eczema may also occur.

Vohwinkel Palmoplantar Keratoderma (Mutilating Keratoderma)

Vohwinkel PPK is a progressive autosomal dominant disease consisting of honeycombed hyperkeratosis of palms and soles, sparing the arches; starfish-like and linear keratoses on the dorsum of the hands, fingers, feet, and knees; and ainhum-like constriction of the digits that sometimes leads to autoamputation. Varying degrees of alopecia may be seen. Two forms have been identified. Vohwinkel PPK with ichthyosis is caused by mutations in the loricrin gene, and Vohwinkel PPK with deafness by mutations in connexin 26.

Papillon-Lefèvre Syndrome (Cathepsin C Gene)

An autosomal recessive erythematous hyperkeratosis of the palms and soles, Papillon-Lefèvre syndrome sometimes extends to the dorsal

hands and feet, elbows, and knees later in childhood. The PPK may be either diffuse, striate, or punctuate. This syndrome is characterized by periodontal inflammation, leading to loss of teeth by age 4-5 yr if untreated.

Other Syndromes

Keratoderma of palms and soles also occurs as a feature of some forms of ichthyosis and ectodermal dysplasia. **Richner-Hanhart syndrome** is an autosomal recessive focal palmoplantar keratoderma with corneal ulcers, progressive mental impairment, and a deficiency of tyrosine aminotransferase, which leads to tyrosinemia. **Pachyonychia congenita** is transmitted as an autosomal dominant trait with variable expressivity. The classic type I form **(Jadassohn-Lewandowski syndrome)** is due to mutations in the gene for keratin 16. Major features of the syndrome are onychogryposis; palmoplantar keratoderma; follicular hyperkeratosis, especially of the elbows and knees; and oral leukokeratosis. The nail dystrophy is the most striking feature and may be present at birth or develop early in life. The nails are thickened and tubular, projecting upward at the free edge to form a conical roof over a mass of subungual keratotic debris. Repeated paronychial inflammation may result in shedding of the nails. The feature seen most consistently among patients with this condition is keratoderma of the palms and soles. Additional associated features include hyperhidrosis of the palms and soles, and bullae and erosions on the palms and soles. Some patients have shown a selective cell-mediated defect in recognition and processing of *Candida*. Surgical removal of the nails and excision of the nail matrix have been helpful in some patients.

Treatment

Treatment for PPK is the same no matter what its cause. In mild cases, emollient therapy may suffice. Keratolytic agents such as salicylic acid, lactic acid, and urea creams may be required. Oral retinoids are the treatment of choice for severe cases unresponsive to topical therapy.

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Chapter 659
Diseases of the Dermis

Sheila S. Galbraith

KELOID

Etiology and Pathogenesis

Keloids are usually induced by trauma and commonly follow ear piercing, burns, scalds, and surgical procedures. The resulting keloid is larger than the initial area of trauma to the skin. Certain individuals are predisposed to keloid formation; a familial tendency (recessive or dominant inheritance) or the presence of foreign material in the wound may have a pathogenic role. *Keloids are a rare feature of Ehlers-Danlos syndrome, Rubinstein-Taybi syndrome*, and pachydermoperiostosis. Keloids result from an abnormal fibrous wound healing response in which tissue repair and regeneration–regulation control mechanisms are lost. Collagen production is 20 times that seen in normal scars and the type I : type III collagen ratio is abnormally high. In keloids, tissue values of tumor growth factor-β and platelet-derived growth factor are elevated; fibroblasts are more sensitive to their effects, and their degradation rate is decreased.

Figure 659-1 Keloid of earlobe after piercing.

Clinical Manifestations

A *keloid* is a sharply demarcated, benign, dense growth of connective tissue that forms in the dermis after trauma. The lesions are firm, raised, pink to hyperpigmented, and rubbery; they may be tender or pruritic. Sites of predilection are the face, earlobes (Fig. 659-1), neck, shoulders, upper trunk, sternum, and lower legs. In both keloids and hypertrophic scars, new collagen forms over a much longer period than in wounds that heal normally.

Histology

A keloid consists of whorled and interlaced hyalinized collagen fibers.

Differential Diagnosis

Keloids should be differentiated from *hypertrophic scars*, which remain confined to the site of injury and gradually involute over time.

Treatment

Young keloids may diminish in size if injected intralesionally at 4 wk intervals with triamcinolone suspension (10-40 mg/mL). At times, a more concentrated suspension is required. Large or old keloids may require surgical excision followed by intralesional injections of corticosteroid. The risk of recurrence at the same site argues against surgical excision alone, although earlobe keloids respond well to surgical excision, pressure dressings, and intralesional steroids. Placement of topical silicone gel sheeting over the keloid for several hours per day for several weeks may help in some patients.

STRIAE CUTIS DISTENSAE (STRETCH MARKS)

Etiology and Pathogenesis

Striae formation is common in adolescence. The most frequent causes are rapid growth, pregnancy, obesity, Cushing disease, and prolonged corticosteroid therapy. The pathogenesis is unknown, but the occurrence of alterations in elastic fibers is thought to be the primary process.

Clinical Manifestations

These thinned, depressed, erythematous bands of atrophic skin eventually become silvery, opalescent, and smooth. They occur most frequently in areas that have been subject to distention, such as the lower back (Fig. 659-2), buttocks, thighs, breasts, abdomen, and shoulders.

Differential Diagnosis

Striae distensae resemble atrophic scars.

Treatment

Controlled trials of treatments for striae are lacking; however, striae tend to spontaneously become less conspicuous as the color fades with time.

Figure 659-2 Striae on the back of an adolescent.

Figure 659-3 Annular lesion with a raised papular border and depressed center, characteristic of granuloma annulare.

CORTICOSTEROID-INDUCED ATROPHY

Etiology and Pathogenesis

Both topical and systemic corticosteroid treatment can result in cutaneous atrophy. This is particularly common when a potent or superpotent topical corticosteroid is applied under occlusion or to an intertriginous area for a prolonged period. Keratinocyte growth is decreased, but epidermal maturation is accelerated, resulting in a thinning of the epidermis and stratum corneum. Fibroblast growth and function are also decreased, leading to the dermal changes. The mechanism involves inhibition of synthesis of collagen type I, noncollagenous proteins, and total protein content of the skin, along with progressive reduction of dermal proteoglycans and glycosaminoglycans.

Clinical Manifestations

Affected skin is thin, fragile, smooth, and semitransparent, with telangiectasias, prominent veins, and loss of normal skin markings.

Histology

Histopathologically, one sees thinning of the epidermis. Spaces between dermal collagen and elastic fibers are small, producing a more compact but thin dermis.

Treatment

Optimal treatment is prevention by proper use of topical steroids to avoid side effects.

GRANULOMA ANNULARE

Etiology and Pathogenesis

The cause of granuloma annulare is unknown. Some cases of granuloma annulare, particularly the generalized form, may be associated with diabetes mellitus or with anterior uveitis. However, most cases are seen in healthy children.

Clinical Manifestations

This common dermatosis occurs predominantly in children and young adults. Affected children are usually healthy. Typical lesions begin as firm, smooth, erythematous papules. They gradually enlarge to form annular plaques with a papular border and a normal, slightly atrophic or discolored central area up to several centimeters in size. Lesions may occur anywhere on the body, but mucous membranes are spared. Favored sites include the dorsum of the hands (Fig. 659-3) and feet. The disseminated papular form is rare in children. Subcutaneous granuloma annulare tends to develop on the scalp and limbs, particularly in the pretibial area. These lesions are firm, usually nontender, skin-colored nodules. Perforating granuloma annulare is characterized by the development of a yellowish center in some of the superficial papular lesions as a result of transepidermal elimination of altered collagen.

Differential Diagnosis

Annular lesions are often mistaken for tinea corporis because of the elevated advancing border. They differ in that they are not scaly. Papular lesions, another variant, may simulate rheumatoid nodules, particularly when grouped on the fingers and elbows.

Histology

The lesion of granuloma annulare consists of a granuloma with a central area of necrotic collagen; mucin deposition; and a peripheral palisading infiltrate of lymphocytes, histiocytes, and foreign body giant cells. The pattern resembles that of necrobiosis lipoidica and rheumatoid nodule, but subtle histologic differences usually permit differentiation.

Treatment

The eruption persists for months to years, but spontaneous resolution without residual change is usual; 50% of lesions clear within 2 yr. Application of a potent or superpotent topical corticosteroid preparation or intralesional injections (5-10 mg/mL) of corticosteroid may hasten involution, but nonintervention is usual.

NECROBIOSIS LIPOIDICA

Etiology and Pathogenesis

The cause of necrobiosis lipoidica is unknown, but 50-75% of patients have **diabetes mellitus**; necrobiosis lipoidica occurs in 0.3% of all diabetic patients.

Clinical Manifestations

This disorder manifests as erythematous papules that evolve into irregularly shaped, sharply demarcated, yellow, sclerotic plaques with central telangiectasia and a violaceous border. Scaling, crusting, and ulceration are frequent. Lesions develop most commonly on the shins (Fig. 659-4). Slow extension of a given lesion over the years is usual, but long periods of quiescence or complete healing with scarring may occur.

Histology

Poorly defined areas of necrobiotic collagen are seen throughout, but primarily low in the dermis, associated with mucin deposition. Surrounding the necrobiotic, disordered areas of collagen is a palisading lymphohistiocytic granulomatous infiltrate. Some lesions are more characteristically granulomatous, with limited necrobiosis of collagen.

Differential Diagnosis

Necrobiosis lipoidica must be differentiated clinically from xanthomas, morphea, granuloma annulare, erythema nodosum, and pretibial myxedema.

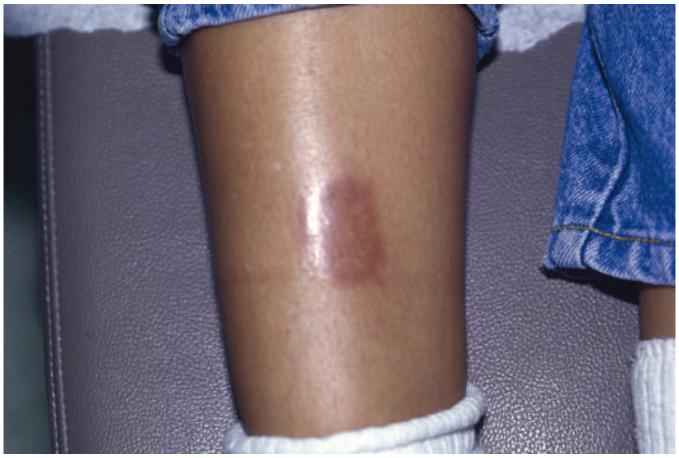

Figure 659-4 Yellow sclerotic plaque of necrobiosis lipoidica on the shin.

Figure 659-5 Ivory-colored perivaginal plaque with hemorrhage.

Treatment

The lesions persist despite good control of the diabetes but may improve minimally after applications of high-potency topical steroids or local injection of a corticosteroid. Pentoxifylline has also been used.

LICHEN SCLEROSUS

Etiology and Pathogenesis

The cause of lichen sclerosis is unknown. Several studies have identified the presence of autoantibodies to the glycoprotein extracellular matrix protein 1 (ECM-1). The exact role of these antibodies are currently under investigation, however.

Clinical Manifestations

Lichen sclerosus manifests initially as shiny, indurated, ivory-colored papules, often with a violaceous halo. The surface shows prominent dilated pilosebaceous or sweat duct orifices that often contain yellow or brown plugs. The papules coalesce to form irregular plaques of variable size, which may develop hemorrhagic bullae in their margins. In the later stages, atrophy results in a depressed plaque with a wrinkled surface. This disorder occurs more commonly in girls than in boys. Sites of predilection in girls are the vulvar (Fig. 659-5), perianal, and perineal skin. Extensive involvement may produce a sclerotic, atrophic plaque of hourglass configuration; shrinkage of the labia and stenosis of the introitus may result. Vaginal discharge precedes vulvar lesions in approximately 20% of patients. In boys, the prepuce and glans penis are often involved, usually in association with phimosis; most boys with the disorder were not circumcised early in life. Sites elsewhere on the body that are most commonly involved include the upper trunk, the neck, the axillae, the flexor surfaces of wrists, and the areas around the umbilicus and the eyes. Pruritus may be severe.

Figure 659-6 Erythematous, hyperpigmented plaque of early morphea.

Differential Diagnosis

In children, lichen sclerosus is most frequently confused with focal morphea (see Chapter 160), with which it may coexist. In the genital area, it may be mistakenly attributed to sexual abuse.

Histology

Biopsy is diagnostic, revealing hyperkeratosis with follicular plugging, hydropic degeneration of basal cells, a bandlike dermal lymphocytic infiltrate, homogenized collagen, and thinned elastic fibers in the upper dermis.

Treatment

Vulvar lichen sclerosus in childhood usually improves with puberty but does not always resolve completely, and symptoms can recur throughout life. Long-term observation for the development of squamous cell carcinoma is necessary. Superpotent topical corticosteroids provide relief from pruritus and produce clearing of lesions, including those in the genital area. Topical tacrolimus and pimecrolimus have also been used. It is not known how response to treatment affects long-term cancer risk.

MORPHEA

Etiology and Pathogenesis

Morphea is a sclerosing condition of the dermis and subcutaneous tissue of unknown etiology.

Clinical Manifestations

Morphea is characterized by solitary, multiple, or linear circumscribed areas of erythema that evolve into indurated, sclerotic, atrophic plaques (Fig. 659-6), later healing, or "burning out" with pigment change. It is seen more commonly in females. The most common types of morphea are plaque and linear. Morphea can affect any area of skin. When confined to the frontal scalp, forehead, and midface in a linear band, it is referred to as **en coup de sabre**. When located on one side of the face, it is called **progressive hemifacial atrophy**. These forms of morphea carry a poorer prognosis because of the associated underlying central nervous system involvement or musculoskeletal atrophy that can be cosmetically disfiguring. Linear morphea over a joint may lead to restriction of mobility (Fig. 659-7). Pansclerotic morphea is a rare, severe, disabling variant.

Differential Diagnosis

The differential diagnosis of morphea includes granuloma annulare, necrobiosis lipoidica, lichen sclerosis, and late-stage Lyme disease (acrodermatitis chronica atrophicans).

Figure 659-7 Linear morphea with involvement over the ankle.

Histology

Thickening or sclerosis of the dermis with collagen degeneration is seen in morphea.

Treatment

Morphea tends to persist, with gradual outward expansion on the skin for 3-5 yr until spontaneous cessation of the inflammatory phase occurs. Topical calcipotriene alone or in combination with high- to superpotency topical steroids or topical tacrolimus have been used for less-severe disease. For the various forms of linear morphea and for severe plaque morphea, ultraviolet A-1 (UVA-1) phototherapy, or methotrexate with or without pulsed intravenous or oral glucocorticosteroids may halt progression and help shorten the disease course. There are no good comparison studies to suggest which therapy is optimal. Physical therapy is needed in linear morphea over a joint to maintain mobility. Significant postinflammatory pigment alteration may persist for years.

SCLEREDEMA (SCLEREDEMA ADULTORUM, SCLEREDEMA OF BUSCHKE)

Etiology and Pathogenesis

The cause of scleredema is unknown. There are 3 types. Type 1 (55% of cases) is preceded by a febrile illness, often related to an upper or lower respiratory infection (streptococcal most commonly). Type 2 (25%) is associated with paraproteinemias, including multiple myeloma. Type 3 (20%) is seen in diabetes mellitus.

Clinical Manifestations

Fifty percent of patients with scleredema are younger than 20 yr old and almost always have type 1. Onset of type 1 is sudden, with brawny edema of the face and neck that spreads rapidly to involve the thorax and arms in a sweater distribution; the abdomen and legs are usually spared. The face acquires a waxy, mask-like appearance. The involved areas feel indurated and woody, are nonpitting, and are not sharply demarcated from normal skin. The overlying skin is normal in color and is not atrophic.

Onset in patients with type 2 and type 3 scleredema may occur insidiously. Systemic involvement, which is uncommon and usually associated with types 2 and 3, is marked by thickening of the tongue; dysarthria; dysphagia; restriction of eye and joint movements; and pleural, pericardial, and peritoneal effusions. Electrocardiographic changes may also be observed. Laboratory data are not helpful.

Differential Diagnosis

Scleredema must be differentiated from scleroderma (see Chapter 160), morphea, myxedema, trichinosis, dermatomyositis, sclerema neonatorum, and subcutaneous fat necrosis.

Histology

Skin biopsy demonstrates an increase in dermal thickness as a result of swelling and homogenization of the collagen bundles, which are separated by large interfibrous spaces. Special stains can identify increased amounts of mucopolysaccharides in the dermis of patients with scleredema.

Treatment

In type 1 scleredema, the active phase of the disease persists for 2-8 wk; spontaneous and complete resolution usually occurs in 6 mo to 2 yr. Recurrent attacks are unusual. In type 2 and 3, disease is slowly progressive. There is no specific therapy.

LIPOID PROTEINOSIS (URBACH-WIETHE DISEASE, HYALINOSIS CUTIS ET MUCOSAE)

Etiology and Pathogenesis

Lipoid proteinosis, an autosomal recessive disorder, is caused by mutations in the *ECM-1* gene, which encodes the ECM-1 protein. ECM-1 has a functional role in the structural organization of the dermis by binding to perlecan, matrix metalloproteinase 9, and fibulin. Pathogenesis involves infiltration of hyaline material into the skin, oral cavity, larynx, and internal organs.

Clinical Manifestations

Lipoid proteinosis may be noted initially in early infancy as hoarseness. Skin lesions appear during childhood and consist of yellowish papules and nodules that may coalesce to form plaques. The classic sign is beaded papules on the eyelids. Lesions also occur on the face, forearms, neck, genitals, dorsum of the fingers, and scalp, where they result in patchy alopecia. Similar deposits are found on the lips, undersurface of the tongue, fauces, uvula, epiglottis, and vocal cords. The tongue becomes enlarged and feels firm on palpation. The patient may be unable to protrude the tongue. Pock-like atrophic scars may develop on the face. Hypertrophic, hyperkeratotic nodules occur at sites of friction, such as the elbows and knees; the palms may be diffusely thickened. The disease progresses until early adult life, but the prognosis is good. Symmetric ossification lateral to the sella turcica in the medial temporal region, identifiable roentgenographically, is pathognomonic but is not always present. Involvement of the larynx can lead to respiratory compromise, particularly in infancy, necessitating tracheostomy. Associated anomalies include dental abnormalities, epilepsy, and recurrent parotitis as a result of infiltrates in the Stensen duct. Virtually any organ can be involved.

Histology

The distinctive histologic pattern in lipoid proteinosis includes dilation of dermal blood vessels and infiltration of homogeneous eosinophilic extracellular hyaline material along capillary walls and around sweat glands. Hyaline material in homogeneous bundles, diffusely arranged in the upper dermis, produces a thickened dermis. The infiltrates appear to contain both lipid and mucopolysaccharide substances.

Treatment

There is no specific treatment for lipoid proteinosis.

MACULAR ATROPHY (ANETODERMA)

Etiology and Pathogenesis

Anetoderma is characterized by circumscribed areas of slack skin associated with loss of dermal substance. This disorder may have no associated underlying disease (primary macular atrophy) or may develop after an inflammatory skin condition. Secondary macular atrophy may be a result of direct destruction of dermal elastin or elastolysis on an immunologic basis, especially the presence of antiphospholipid antibodies, which are related to autoimmune disorders. The elastolysis may then be a result of release of elastase from inflammatory cells.

Clinical Manifestations

Lesions vary from 0.5-1.0 cm in diameter and, if inflammatory, may initially be erythematous. They subsequently become thin, wrinkled,

and blue-white or hypopigmented. The lesions often protrude as small outpouchings that, on palpation, may be readily indented into the subcutaneous tissue because of the dermal atrophy. Sites of predilection include the trunk, thighs, upper arms, and, less commonly, the neck and face. Lesions remain unchanged for life; new lesions often continue to develop for years.

Histology
All types of macular atrophy show focal loss of elastic tissue on histopathologic examination, a change that may not be recognized unless special stains are used.

Differential Diagnosis
Lesions of anetoderma occasionally resemble morphea, lichen sclerosus, focal dermal hypoplasia, atrophic scars, or end-stage lesions of chronic bullous dermatoses.

Treatment
There is no effective therapy for macular atrophy.

CUTIS LAXA (DERMATOMEGALY, GENERALIZED ELASTOLYSIS)
Etiology and Pathogenesis
Cutis laxa is a heterogenous group of disorders related to abnormalities in elastic tissue. It may be autosomal recessive (type I: *fibulin* 5 and *fibulin* 4 genes; type II: *ATP6V0A2* gene), autosomal dominant (*elastin* and *fibulin* 5 genes), X-linked (*Cu^{2+}-transporting adenosine triphosphatase, α-polypeptide*), or acquired. Acquired cutis laxa has developed after a febrile illness, inflammatory skin diseases such as lupus erythematosus or erythema multiforme, amyloidosis, urticaria, angioedema, and hypersensitivity reactions to penicillin, and in infants born to women who were taking penicillamine.

Clinical Manifestations
There may be widespread folds of lax skin, or changes may be mild and limited in extent, resembling anetoderma. Patients with severe cutis laxa have characteristic facial features, including an aged appearance with sagging jowls (bloodhound appearance; Fig. 659-8), a hooked nose with everted nostrils, a short columella, a long upper lip, and everted lower eyelids. The skin is also lax elsewhere on the body and may resemble an ill-fitting suit. Hyperelasticity and hypermobility of the joints are not present as they are in the Ehlers-Danlos syndrome. Many infants have a hoarse cry, probably as a result of laxity of the vocal cords. Tensile strength of the skin is normal.

The dominant form of cutis laxa may develop at any age and is generally benign. When it manifests in infancy, it may be associated with intrauterine growth restriction, ligamentous laxity, and delayed closure of the fontanels. Pulmonary emphysema and mild cardiovascular manifestations may also occur. Patients with the more *common recessive* form of the disease are susceptible to severe complications, such as multiple hernias, rectal prolapse, diaphragmatic atony, diverticula of the gastrointestinal and genitourinary tracts, cor pulmonale, emphysema, pneumothoraces, peripheral pulmonary artery stenosis, and aortic dilation. Characteristic facial features include downward-slanting palpebral fissures, a broad, flat nose, and large ears. Skeletal anomalies, dental caries, growth retardation, and developmental delay also occur. Such patients often have a shortened life span.

Cutis laxa–like skin changes may also be seen in association with multiple other syndromes, including De Barsy syndrome, Lenz-Majewski syndrome, hyperostotic dwarfism, SCARF (**s**keletal abnormalities, **c**utis laxa craniostenosis, **a**mbiguous genitalia, **r**etardation, **f**acial abnormalities) syndrome, wrinkling skin syndrome, and Costello syndrome.

Histology
Histologically, elastic tissue is reduced throughout the dermis, with fragmentation, distention, and clumping of the elastic fibers.

Treatment
Treatment for cutis laxa is supportive.

EHLERS-DANLOS SYNDROME
Ehlers-Danlos syndrome (EDS) is a group of genetically heterogeneous connective tissue disorders. Affected children appear normal at birth, but skin hyperelasticity, fragility of the skin and blood vessels, delayed wound healing, and joint hypermobility (Fig. 659-9) develop. The essential defect is a quantitative deficiency of fibrillar collagen. Additional features include autonomic dysfunction (hypermobility types) characterized by recurrent or chronic musculoskeletal pain, orthostatic intolerance, sudomotor dysfunction, and gastrointestinal disturbances (gastroparesis, diarrhea, constipation). Dysautonomic features may be exacerbated by vasoactive medications. In addition, patients with EDS have an increased incidence of Chiari type 1 malformations, perhaps due to hypermobility of the occipitoatlantal and atlantoaxial joints or poor connective tissue support. Basilar impression symptoms from herniation may contribute to the morbidity of EDS. In patients with a Chiari type 1 malformation there may also be a spinal cord syrinx distal to the malformation. Pulmonary complications may include pneumothorax, hemoptysis, bullous lung disease, and tracheomegaly.

Classification
EDS has been reclassified into 6 clinical recognized forms and 1 unclassified group (Table 659-1).

Figure 659-8 Pendulous folds of skin of an infant with cutis laxa.

Figure 659-9 Joint hyperextensibility in classic Ehlers-Danlos syndrome.

Table 659-1 Ehlers-Danlos Syndrome

TYPE	FORMER NAME	CLINICAL FEATURES*	INHERITANCE	OMIM†	MOLECULAR DEFECT
Classic	EDS I and II	Joint hypermobility; skin hyperextensibility; atrophic scars; smooth, velvety skin; subcutaneous spheroids	AD	130000 130010	Structure of type V collagen because of mutations in *COL5A1, COL5A2*
Hypermobility	EDS III	Joint hypermobility; some skin hyperextensibility, with or without smooth, velvety texture	AD AR	130020 225320	? Tenascin-X *(TNX)*
Vascular	EDS IV	Thin skin; easy bruising; pinched nose; acrogeria; rupture of large-caliber and medium-caliber arteries, uterus, and large bowel	AD	130050 (225350) (225360)	Deficient type III collagen *(COL3A1)*
Kyphoscoliotic	EDS VI	Joint hypermobility; congenital, progressive rupture; scoliosis; scleral fragility with globe rupture; tissue fragility, aortic dilation, MVP	AR	225400	Deficiency of lysyl hydroxylase
Arthrochalasis	EDS VII A	Joint hypermobility, severe, with subluxations, congenital hip dislocation; skin hyperextensibility; tissue fragility	AD	130060	No cleavage of amino terminus of type I procollagen because of mutations in *COL1A1* or *COL1A2*
Dermatosparaxis	EDS VII C	Severe skin fragility; decreased skin elasticity, easy bruising; hernias; premature rupture of fetal membranes	AR	225410	No cleavage of amino terminus of type I procollagen because of deficiency of peptidase
Unclassified types	EDS V	Classic features	XL	305200	?
	EDS VIII	Classic features and periodontal disease	AD	130080	?
	EDS X	Mild classic features, MVP	?	225310	?
	EDS XI	Joint instability	AD	147900	?
	EDS IX	Classic features; occipital horns	XL	309400	Allelic to Menkes syndrome
	EDS, progeroid form	Classic features and premature aging	AR	130700	Deficiency of galactosyltransferase I

*Listed in order of diagnostic importance.
†Entries in Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). Available at: http://omim.org/
AD, autosomal dominant; AR, autosomal recessive; EDS, Ehlers-Danlos syndrome; MVP, mitral valve prolapse; XL, X-linked.
From Pyeritz RD: Inherited diseases of connective tissue. In Goldman L, Schafer AI, editors: Goldman's Cecil medicine, *ed 24, Philadelphia, 2012, Elsevier, Table 268-2.*

Classic (*COL5A1, COL5A2, COL1A1* Genes; Previously EDS Type I—Gravis, EDS Type II—MITIS)

This autosomal dominant disorder is characterized by premature birth caused by rupture of membranes, skin hyperelasticity and fragility, easy bruising, generalized and severe joint hypermobility, scoliosis, and mitral valve prolapse. Insignificant lacerations may form gaping wounds that leave broad, atrophic, papyraceous scars. Additional cutaneous manifestations include molluscoid pseudotumors over pressure points from accumulations of connective tissue and piezogenic papules (fat herniation into the dermis) (Fig. 659-10). Life expectancy is not reduced.

Figure 659-10 Piezogenic papules on the medial aspects of the heels in a 41-year-old patient with Ehlers-Danlos syndrome *(top)* and his 2-year-old daughter *(bottom)*. *(From Poppe H, Hamm H: Piezogenic papules in Ehlers-Danlos syndrome.* J Pediatr *163:1788, 2013.)*

Hypermobile (*COL3A1* Gene; Previously EDS Type III)

This disorder has autosomal dominant inheritance and manifests as generalized severe joint hypermobility and minimal skin manifestations. Musculoskeletal pain is common, and osteoarthritis may develop prematurely.

Vascular (*COL3A1* Gene; Previously EDS Type IV—Arterial Ecchymotic)

This autosomal dominant disorder shows the most pronounced dermal thinning of all. Consequently, the underlying venous network is prominent. The skin has minimal hyperextensibility, and the joints are not hypermobile, except perhaps during childhood. Premature birth, extensive ecchymoses from trauma, a high incidence of keloids, rupture of the bowel (especially the colon), uterine rupture during pregnancy,

rupture of the great vessels, dissecting aortic aneurysm, and stroke all contribute to the increased morbidity and shortened life span. Patients should be advised to avoid becoming pregnant, avoid activities that raise intracranial pressure as a result of a Valsalva maneuver, such as trumpet playing, and minimize trauma to the skin. Celiprolol, a β_1 antagonist and a β_2 agonist (vasodilates), may reduce vascular events.

Kyphoscoliosis (Lysyl Hydroxylase [*PLOD* Gene] Deficiency; Previously EDS Type VI)

Patients with this autosomal recessive type have joint hyperextensibility, hypotonia, kyphoscoliosis, fragile cornea, keratoconus, skin hyperelasticity, and fragile bones. Prenatal diagnosis is available through measurement of lysyl hydroxylase activity in amniocytes. The diagnosis can also be confirmed by detection of decreased lysyl hydroxylase activity in cultured dermal fibroblasts.

Arthrochalasia (*COLA1A* Gene, Type A; *COL1A2* Gene, Type B; Previously EDS Types VIIA and B—Arthrochalasis Multiplex Congenita)

The A type is an autosomal dominant disorder characterized by short stature, marked joint hyperextensibility and dislocation, and moderate hyperelasticity and bruisability of skin. The B type is autosomal dominant and is characterized by skin hyperelasticity and marked joint hypermobility.

Dermatosparaxis (Type 1 Collagen *N*-Peptidase; Previously EDS Type VIIC)

This autosomal recessive condition that includes premature rupture of membranes; delayed closure of fontanels; skin fragility and laxity; easy bruisability; growth retardation; short limbs; umbilical hernia; and characteristic facies with micrognathia, jowls, and prominent, puffy eyelids.

Differential Diagnosis

EDS has been confused with cutis laxa, but the features of the 2 disorders differ considerably. The skin of patients with cutis laxa hangs in redundant folds, whereas the skin of those with EDS is hyperextensible and snaps back into place when stretched. Because of the marked skin fragility in EDS, minor trauma results in ecchymoses, bleeding, and poor healing with atrophic cigarette-paper scars, which are most prominent on the forehead and lower legs and over pressure points. Surgical procedures are fraught with risk; dehiscence of wounds is common.

Joint hypermobility is seen in other connective tissue disorders (Fig. 659-11). Joint hypermobility is scored with the 9 point Beighton score (Table 659-2) and can be assessed by history (Table 659-3).

Figure 659-12 provides an initial approach to the diagnosis of EDS.

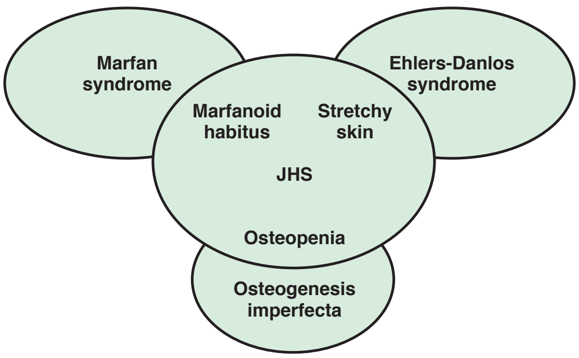

Figure 659-11 **A Venn diagram illustrating the overlap features between the 4 major heritable disorders of connective tissue.** Joint hypermobility syndrome (JHS) maintains a central position sharing key features with Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome, and is seen as a benign forme fruste of all 3 heritable disorders of connective tissue "rolled into one." *(From Hakim A, Grahame R: Joint hypermobility.* Best Pract Res Clin Rheumatol *17:989–1004, 2003, Fig. 1.)*

Table 659-2 The Nine-Point Beighton Hypermobility Score

The ability to:	RIGHT	LEFT
1. Passively dorsiflex the fifth metacarpophalangeal joint to ≥90°	1	1
2. Oppose the thumb to the volar aspect of the ipsilateral forearm	1	1
3. Hyperextend the elbow to ≥10°	1	1
4. Hyperextend the knee to ≥10°	1	1
5. Place hands flat on the floor without bending the knees	1	
	Total 9	

One point may be gained for each side for maneuvers 1-4 so the hypermobility score will have a maximum of 9 points if all are positive.

From Hakim A, Grahame R: Joint hypermobility. Best Pract Res Clin Rheumatol *17:989–1004, 2003, Table 1.*

Table 659-3 A Five-Part Questionnaire for Identifying Hypermobility

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child did you amuse your friends by contorting your body into strange shapes *or* could you do the splits?
4. As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself double-jointed?

Answer in the affirmative to 2 or more questions suggests hypermobility with sensitivity 80-85% and specificity 80-90%

From Hakim A, Grahame R: Joint hypermobility. Best Pract Res Clin Rheumatol *17:989–1004, 2003, Table 3.*

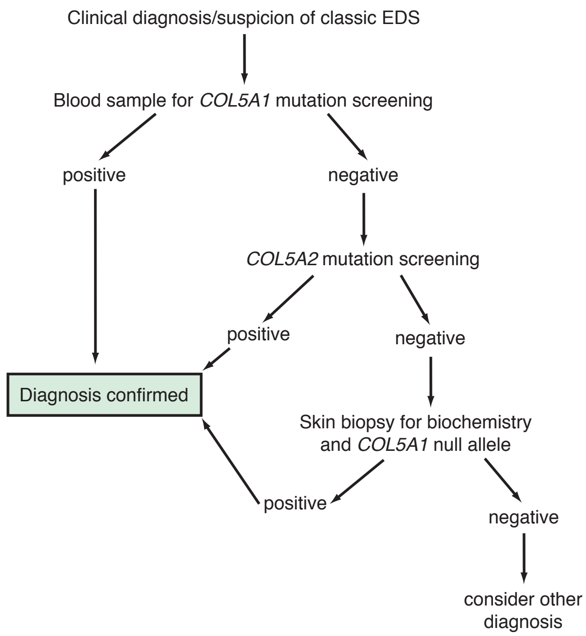

Figure 659-12 **Diagnostic flow chart for Ehlers-Danlos syndrome, classic type.** *(From De Paepe A, Malfait F: The Ehlers-Danlos syndrome, a disorder with many faces.* Clin Genet *82:1–11, 2012, Fig. 3.)*

PSEUDOXANTHOMA ELASTICUM

Etiology and Pathogenesis

Pseudoxanthoma elasticum (PXE) is a primary disorder of elastic tissue. The overwhelming majority of cases are caused by mutations in the *ABCC6* gene. The primary abnormality seen in PXE is an accumulation of mineralized tissue in the skin, Bruch membrane in the retina, and vessel walls. Although other forms of PXE have been postulated, their existence is now debated.

Clinical Manifestations

Onset of skin manifestations often occurs during childhood, but the changes produced by early lesions are subtle and may not be recognized. The characteristic **pebbly, "plucked chicken skin" cutaneous lesions** are 1-2 mm, asymptomatic, yellow papules that are arranged in a linear or reticulated pattern or in confluent plaques. Preferred sites are the flexural neck (Fig. 659-13), axillary and inguinal folds, umbilicus, thighs, and antecubital and popliteal fossae. As the lesions become more pronounced, the skin acquires a velvety texture and droops in lax, inelastic folds. The face is usually spared. Mucous membrane lesions may involve the lips, buccal cavity, rectum, and vagina. There is involvement of the connective tissue of the media, and intima of blood vessels, Bruch membrane of the eye, and endocardium or pericardium may result in visual disturbances, angioid streaks in Bruch membrane, intermittent claudication, cerebral and coronary occlusion, hypertension, and hemorrhage from the gastrointestinal tract, uterus, or mucosal surfaces. Women with PXE have an increased risk of miscarriage in the 1st trimester. Arterial involvement generally manifests in adulthood, but claudication and angina have occurred in early childhood.

Pathology

Histopathologic examination shows fragmented, swollen, and clumped elastic fibers in the middle and lower third of the dermis. The fibers stain positively for calcium. Collagen in the vicinity of the altered elastic fibers is reduced in amount and is split into small fibers. Aberrant calcification of the elastic fibers of the internal elastic lamina of arteries in PXE leads to narrowing of vessel lumina.

Treatment

There is no effective treatment for PXE, although laser therapy may help prevent retinal hemorrhage. The use of oral phosphate binders has shown promise in decreasing calcification of elastic fibers.

ELASTOSIS PERFORANS SERPIGINOSA

Etiology and Pathogenesis

Elastosis perforans serpiginosa (EPS) is characterized by the extrusion of altered elastic fibers through the epidermis. The primary abnormality is probably in the dermal elastin, which provokes a cellular response that ultimately leads to extrusion of the abnormal elastic tissue.

Clinical Manifestations

This is an unusual skin disorder in which 1-3 mm, firm, skin-colored, keratotic papules tend to cluster in arcuate and annular patterns on the posterolateral neck and limbs (Fig. 659-14) and occasionally on the face and trunk. Onset usually occurs in childhood or adolescence. A papule consists of a circumscribed area of epidermal hyperplasia that communicates with the underlying dermis by a narrow channel. There is a great increase in the amount and size of elastic fibers in the upper dermis, particularly in the dermal papillae. Approximately 30% occur in association with osteogenesis imperfecta, Marfan syndrome, PXE, EDS, Rothmund-Thomson syndrome, scleroderma, acrogeria, and Down syndrome. EPS has also occurred in association with penicillamine therapy.

Histology

Histopathology reveals a hyperplastic epidermis with extrusion of abnormal elastic fibers and a lymphocytic superficial infiltrate.

Differential Diagnosis

Differential diagnosis of EPS includes tinea corporis, perforating granuloma annulare, reactive perforating collagenosis, lichen planus, creeping eruption, and porokeratosis of Mibelli.

Treatment

Treatment of EPS is ineffective; however, the lesions are asymptomatic and may disappear spontaneously.

REACTIVE PERFORATING COLLAGENOSIS

Etiology and Pathogenesis

The primary process in reactive perforating collagenosis represents transepidermal elimination of altered collagen. A familial autosomal recessive form has been described.

Clinical Manifestations

Reactive perforating collagenosis usually manifests in early childhood as small papules on the dorsal areas of the hands and forearms, elbows, knees, and, sometimes, face and trunk. Over a period of several weeks, the papules enlarge to 5-10 mm, become umbilicated, and develop keratotic plugs in their centers (Fig. 659-15). Individual lesions resolve spontaneously in 2-4 mo, leaving hypopigmented macules or scars. Lesions may recur in crops; may undergo a linear Koebner phenomenon; and may form in response to cold temperatures or superficial trauma such as abrasions, insect bites, and acne lesions.

Figure 659-13 Confluent plaque of pebbly skin in pseudoxanthoma elasticum.

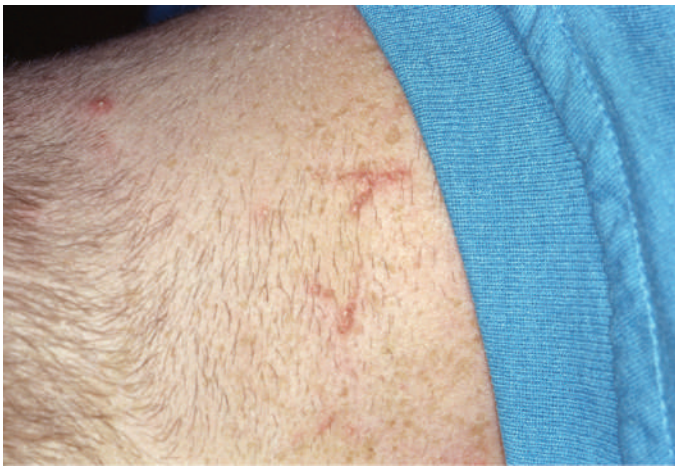

Figure 659-14 Arcuate keratotic papule of elastosis perforans serpiginosa.

Figure 659-15 Hyperkeratotic papules in reactive perforating collagenosis.

Figure 659-16 Ivory-colored papules on the upper back in Hunter syndrome.

Histology

Collagen in the papillary dermis is engulfed within a cup-shaped perforation in the epidermis. The central crater contains pyknotic inflammatory cells and keratinous debris.

Differential Diagnosis

EPS and Kyrle disease may mimic reactive perforating collagenosis.

Treatment

Reactive perforating collagenosis resolves spontaneously in 6-8 wk. Topical retinoic acid enhances the resolution.

XANTHOMAS

See Chapter 86.

FABRY DISEASE

See Chapter 86.

MUCOPOLYSACCHARIDOSES

See Chapter 88.

In several of the mucopolysaccharidoses, thick, rough, inelastic skin, particularly on the extremities, and generalized hirsutism are characteristic but nonspecific features. Telangiectasias on the face, forearms, trunk, and legs have been observed in Scheie and Morquio syndromes. In some patients with Hunter syndrome, ivory-colored, distinctive firm papulonodules with a corrugated surface texture are grouped into symmetric plaques on the upper trunk (Fig. 659-16), arms, and thighs. Onset of these unusual lesions occurs in the 1st decade of life, and spontaneous disappearance has been noted.

MASTOCYTOSIS

Etiology and Pathogenesis

Mastocytosis encompasses a spectrum of disorders that range from solitary cutaneous nodules to diffuse infiltration of skin associated with involvement of other organs (Table 659-4). All of the disorders are characterized by aggregates of mast cells in the dermis. There are 4 types of mastocytoses: solitary mastocytoma, urticaria pigmentosa (2 forms), diffuse cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans. The 2 forms of urticaria pigmentosa are the childhood variant, which resolves without sequelae, and the form that may start in either childhood or adult life and is associated with a mutation (most commonly the *D816V* mutation) in the stem cell factor gene. Stem cell factor (mast cell growth factor), which can be secreted by keratinocytes, stimulates the proliferation of mast cells and increases the production of melanin by melanocytes. The local and systemic manifestations of the disease are at least partly a result of the release of histamine and heparin from mast cell granules; although heparin is present in significant amounts in mast cells, coagulation disturbances occur only rarely. The vasodilator prostaglandin D_2 or its metabolite appears to exacerbate the flushing response. Serum tryptase values can be elevated.

Table 659-4 Mastocytosis Classification
Cutaneous mastocytosis:
1. Urticaria pigmentosa:
(a) Classic infantile type; (b) Chronic with stem cell factor mutations
2. Diffuse cutaneous mastocytosis
3. Mastocytoma of the skin
4. Telangiectasia macularis eruptive perstans
Systemic mastocytosis (without an associated hematologic non–mast cell disorder or leukemic mast cell disease):
1. Systemic indolent mastocytosis
2. Systemic smoldering mastocytosis
Systemic mastocytosis with an associated hematologic non–mast cell disorder:
1. Myeloproliferative syndrome
2. Myelodysplastic syndrome
3. Acute myeloid leukemia
4. Non-Hodgkin lymphoma
Systemic aggressive mastocytosis
Mast cell leukemia
Mast cell sarcoma
Extracutaneous mastocytoma

Adapted from Valent PHH, Li CY, Longley BJ, et al. World Health Organization classification of tumours, pathology and genetics of tumours of the haematopoietic and lymphoid tissues, *Lyon, France, 2001, IARC Press; and Carter MC, Metcalfe DD: Paediatric mastocytosis,* Arch Dis Child *86:315–319, 2002, Table 3.*

Clinical Manifestations

Solitary mastocytomas are usually 1-5 cm in diameter. Lesions may be present at birth or may arise in early infancy at any site. The lesions may manifest as recurrent, evanescent wheals or bullae; in time, an infiltrated, pink, yellow, or tan, rubbery plaque develops at the site of whealing or blistering (Fig. 659-17). The surface acquires a pebbly, orange peel–like texture, and hyperpigmentation may become prominent. Stroking or trauma to the nodule may lead to urtication (Darier sign) as a result of local histamine release; rarely, systemic signs of histamine release become apparent.

Figure 659-17 Solitary mastocytoma that is partially blistered.

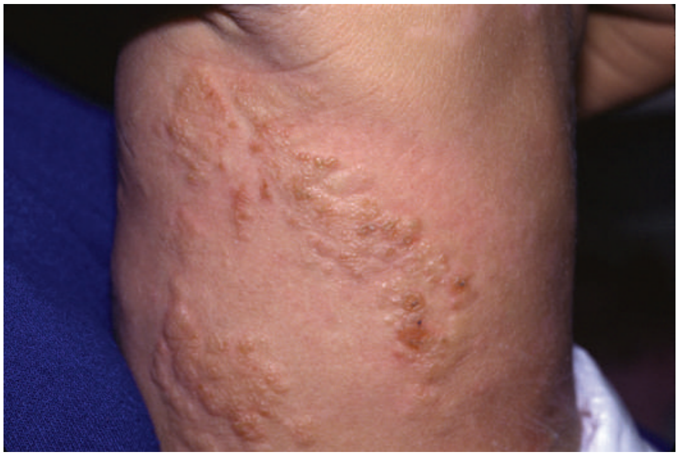

Figure 659-19 Severe blistering in diffuse cutaneous mastocytosis.

Figure 659-18 Hyperpigmented papular lesions of urticaria pigmentosa.

Urticaria pigmentosa is the most common form of mastocytosis. In the first type of urticaria pigmentosa, the classic infantile type, lesions may be present at birth but more often erupt in crops in the 1st several mo to 2 yr of age. New lesions seldom arise after age 3-4 yr. In some cases, early bullous or urticarial lesions fade, only to recur at the same site, ultimately becoming fixed and hyperpigmented. In others, the initial lesions are hyperpigmented. Vesiculation usually abates by 2 yr of age. Individual lesions range in size from a few millimeters to several centimeters and may be macular, papular, or nodular. They range in color from yellow-tan to chocolate brown and often have ill-defined borders (Fig. 659-18). Larger nodular lesions, like solitary mastocytomas, may have a characteristic orange peel texture. Lesions of urticaria pigmentosa may be sparse or numerous and are often symmetrically distributed. Palms, soles, and face are sometimes spared, as are the mucous membranes. The rapid appearance of erythema and whealing in response to vigorous stroking of a lesion can usually be elicited; dermographism of intervening normal skin is also common. Affected children can have intense pruritus. Systemic signs of histamine release, such as hypotension, syncope, headache, episodic flushing, tachycardia, wheezing, colic, and diarrhea, are uncommon and occur most frequently in the more severe types of mastocytosis. Flushing is by far the most common symptom seen.

The second type of urticaria pigmentosa may begin in infancy but typically develops in adulthood. This type does not resolve, and new lesions continue to develop throughout life. It is associated with mutations in the stem cell factor gene. Patients with this type of mastocytosis are the population in whom systemic involvement may develop.

Systemic mastocytosis is marked by an abnormal increase in the number of mast cells in other than cutaneous tissues. It occurs in approximately 5-10% of patients with mutant stem cell factor–related mastocytosis and is uncommon in children. Bone lesions may be silent but are detectable radiologically as osteoporotic or osteosclerotic areas, principally in the axial skeleton. Gastrointestinal tract involvement may produce complaints of abdominal pain, nausea, vomiting, diarrhea, steatorrhea, and bloating. Mucosal infiltrates may be detectable by barium studies or by small bowel biopsy. Peptic ulcers also occur. Hepatosplenomegaly as a result of mast cell infiltrates and fibrosis has been described, as has mast cell proliferation in lymph nodes, kidneys, periadrenal fat, and bone marrow. Abnormalities in the peripheral blood, such as anemia, leukocytosis, and eosinophilia, are noted in approximately 30% of patients. Mast cell leukemia may occur.

Diffuse cutaneous mastocytosis is characterized by diffuse involvement of the skin rather than discrete hyperpigmented lesions. Affected patients are usually normal at birth and demonstrate features of the disorder after the 1st few mo of life. Rarely, the condition may present with intense generalized pruritus in the absence of visible skin changes. The skin usually appears thickened and pink to yellow and may have a doughy feel and a texture resembling an orange peel. Surface changes are accentuated in flexural areas. Recurrent bullae (Fig. 659-19), intractable pruritus, and flushing attacks are common, as is systemic involvement.

Telangiectasia macularis eruptiva perstans is another variant that consists of telangiectatic hyperpigmented macules that are usually localized to the trunk. These lesions do not urticate when stroked. This form of the disease is seen primarily in adolescents and adults.

Differential Diagnosis

The differential diagnosis of solitary mastocytomas includes recurrent bullous impetigo, herpes simplex, congenital melanocytic nevi, and juvenile xanthogranuloma.

Urticaria pigmentosa can be confused with drug eruptions, postinflammatory pigmentary change, juvenile xanthogranuloma, pigmented nevi, ephelides, xanthomas, chronic urticaria, insect bites, and bullous impetigo. Diffuse cutaneous mastocytoma may be confused with epidermolytic hyperkeratosis.

Telangiectasia macularis eruptiva perstans must be differentiated from other causes of telangiectasia.

Table 659-5	Pharmacologic Agents and Physical Stimuli That May Exacerbate Mast Cell Mediator Release in Patients with Mastocytosis
IMMUNOLOGIC STIMULI Venoms (immunoglobulin E–mediated bee venom) Complement-derived anaphylatoxins Biologic peptides (substance P, somatostatin) Polymers (dextran)	
NONIMMUNOLOGIC STIMULI Physical stimuli (heat, cold, rubbing, trauma, sunlight) Drugs Acetylsalicylic acid and related nonsteroidal analgesics* Thiamine Ketorolac tromethamine Alcohol Vancomycin Dextromethorphan Narcotics (codeine, morphine)* Radiographic dyes (iodine containing)	
EMOTIONAL ISSUES Anxiety Sleep deprivation Stress	

*Appears to be a problem in <10% of patients.

From Carter MC, Metcalfe DD: Paediatric mastocytosis, Arch Dis Child *86:315–319, 2002, Table 4.*

Prognosis

Spontaneous involution occurs in all patients with solitary mastocytomas and classic infantile urticaria pigmentosa. The incidence of systemic manifestations in these patients is very low. The continued development of lesions past the age of 4 yr implies likely chronic disease with stem cell factor gene mutation and a higher risk for systemic involvement.

Treatment

Solitary mastocytomas usually do not require treatment. Lesions that blister may be treated with topical steroids following each blistering episode.

In urticaria pigmentosa, flushing can be precipitated by excessively hot baths, vigorous rubbing of the skin, and certain drugs, such as codeine, aspirin, morphine, atropine, ketorolac, alcohol, tubocurarine, iodine-containing radiographic dyes, and polymyxin B (Table 659-5). Avoidance of these triggering factors is advisable; it is notable that general anesthesia may be safely performed with appropriate precautions.

For patients who are symptomatic, oral antihistamines may be palliative. H_1 receptor antagonists (hydroxyzine) are the initial drugs of choice for systemic signs of histamine release. If H_1 antagonists are unsuccessful, H_2 receptor antagonists may be helpful in controlling pruritus or gastric hypersecretion. Topical steroids are of benefit in controlling skin urtication and blistering. Oral mast cell–stabilizing agents, such as cromolyn sodium or ketotifen, may also be effective for diarrhea or abdominal cramping and some systemic symptoms such as headache or muscle pain.

For patients with diffuse cutaneous mastocytosis, the treatment is the same as for urticaria pigmentosa, although in early life. Phototherapy with narrow-band UV (UVB or UVA-1) or psoralen with UVA treatment may be required to control symptoms.

Lesions of telangiectasia macularis eruptiva perstans may be cautiously treated with vascular pulsed-dye lasers.

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Chapter 660

Diseases of Subcutaneous Tissue

JiaDe Yu and Beth A. Drolet

Diseases involving the subcutis are usually characterized by necrosis and/or inflammation; they may occur either as a primary event or as a secondary response to various stimuli or disease processes. The principal diagnostic criteria relate to the appearance and distribution of the lesions, associated symptoms, results of laboratory studies, histopathology, and natural history and exogenous provocative factors of these conditions.

CORTICOSTEROID-INDUCED ATROPHY

Intradermal or subcutaneous injection of a corticosteroid can produce deep atrophy accompanied by surface pigmentary changes and telangiectasia (Fig. 660-1). These changes occur approximately 2-8 wks after injection and may last for months.

660.1 Panniculitis and Erythema Nodosum

JiaDe Yu

Inflammation of fibrofatty subcutaneous tissue may primarily involve the fat lobule or, alternatively, the fibrous septum that compartmentalizes the fatty lobules. Lobular panniculitis that spares the subcutaneous vasculature includes poststeroid panniculitis, lupus erythematosus profundus, pancreatic panniculitis, α_1-antitrypsin deficiency, subcutaneous fat necrosis of the newborn, sclerema neonatorum, cold panniculitis, subcutaneous sarcoidosis, and factitial panniculitis. Lobar panniculitis with vasculitis occurs in erythema induratum and, occasionally, as a feature of Crohn disease (see Chapter 336.2). Inflammation predominantly within the septum, sparing the vasculature, may be seen in erythema nodosum (Table 660-1 and Fig. 660-2), necrobiosis lipoidica, progressive systemic sclerosis (see Chapter 160), and subcutaneous granuloma annulare (see Chapter 659). Septal panniculitis that includes inflammation of the vessels is found primarily in leukocytoclastic vasculitis and polyarteritis nodosa (see Chapter 167).

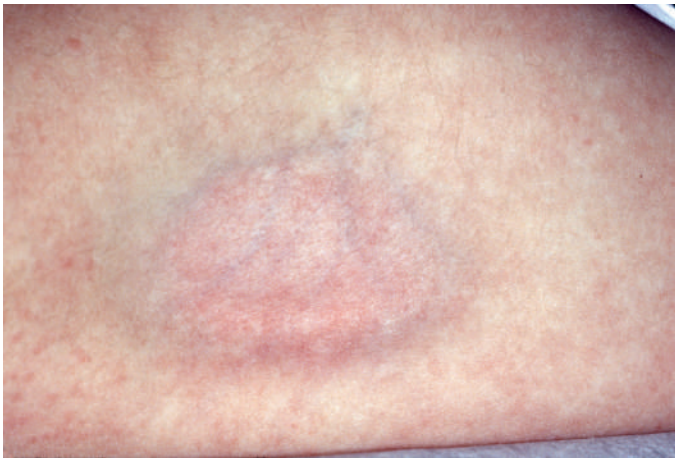

Figure 660-1 Localized fat atrophy with overlying erythema after steroid injection.

ERYTHEMA NODOSUM

Etiology and Pathogenesis

The etiology is unknown in 30-50% of pediatric cases of erythema nodosum; Table 660-1 lists other etiologies. Most common etiologies in children include: group A streptococcal infection, *Yersinia enterocolitica* gastroenteritis, medications (cephalosporins, penicillins, macrolides), and inflammatory disorders (inflammatory bowel disease); sarcoidosis should be considered in young adults.

Clinical Manifestations

Erythema nodosum is a nodular, erythematous hypersensitivity reaction that typically appears with multiple lesions on the anterior surfaces of the arms and legs in the pretibial area (more common) and less often in other cutaneous areas containing subcutaneous fat. The lesions vary in size from 1-6 cm, are symmetric, and are oval with the longer axis parallel to the extremity. They initially appear bright or dull red but progress to a brown or purple; they are painful and usually do not ulcerate (see Fig. 660-2). Initial lesions may resolve in 1-2 wk, but new lesions may continue to appear for 2-6 wk. Repeat episodes may occur weeks to months later. Prior to or immediately at the onset of lesions, there may be systemic manifestations that include fever, malaise, arthralgias (50-90%) and rheumatoid factor negative arthritis.

Table 660-1 Etiology of Erythema Nodosum
VIRUSES Epstein-Barr, hepatitis B, mumps
FUNGI Coccidioidomycosis, histoplasmosis, blastomycosis, sporotrichosis
BACTERIA AND OTHER INFECTIOUS AGENTS Group A streptococcus,* tuberculosis,* *Yersinia*, cat-scratch disease, leprosy, leptospirosis, tularemia, mycoplasma, Whipple disease, lymphogranuloma venereum, psittacosis, brucellosis
OTHER Sarcoidosis, inflammatory bowel disease,* estrogen-containing oral contraceptives,* systemic lupus erythematosus, Behçet syndrome, severe acne, Hodgkin disease, lymphoma, sulfonamides, bromides, Sweet syndrome, pregnancy, idiopathic*

*Common.

Figure 660-2 Tender red nodules with indistinct borders in a teenage girl with erythema nodosum. *(From Weston AL, Lane AT, Morelli JG: Color textbook of pediatric dermatology, ed 3, St. Louis, 2002, Mosby, p. 212.)*

Histology

A septal panniculitis with thickening of the septa with inflammatory cells infiltrate comprised of neutrophils acutely. Monocytes and histiocytes predominate in chronic erythema nodosum.

Treatment

Treatment includes that of the underlying disease as well as symptomatic relief with nonsteroidal antiinflammatory agents. Salicylates, supersaturated solution of potassium iodide (oral), colchicine, intralesional injections of steroids and, in severe, persistent, or recurrent lesions, oral steroids have been employed. The idiopathic form is a self-limited disorder. Protracted or recurrent cases may warrant further workup including antistreptolysin O/deoxyribonuclease B, complete blood count, throat culture, purified protein derivative, QuantiFERON-TB gold assay, chest radiograph, erythrocyte sedimentation rate, and C-reactive protein.

POST-STEROID PANNICULITIS

Etiology and Pathogenesis

The mechanism of the inflammatory reaction in the fat in poststeroid panniculitis is unknown.

Clinical Manifestations

Majority of the cases of post-steroid panniculitis have been reported in children. The disorder occurs in children who have received high-dose corticosteroids. In 1-2 wk after discontinuation of the drug, multiple subcutaneous nodules usually appear on the cheeks, although other areas may be involved. Nodules range in size from 0.5-4.0 cm, are erythematous or skin colored, and may be pruritic or painful.

Histology

A lobular panniculitis with a mixed infiltrate of lymphocytes, histiocytes, and neutrophils is seen. Scattered swollen adipocytes with eosinophilic, needle-shaped crystals are also seen. The epidermis, dermis, and fibrous septa of the fat are normal. Vasculitis is not seen.

Treatment

Treatment of poststeroid panniculitis is unnecessary because the lesions remit spontaneously over a period of months without scarring.

LUPUS ERYTHEMATOSUS PROFUNDUS (LUPUS ERYTHEMATOSUS PANNICULITIS)

Etiology and Pathogenesis

It is unknown what separates those patients in whom lupus erythematosus profundus develops from other patients with systemic lupus erythematosus. This variant of chronic cutaneous lupus erythematosus is rare in childhood. Recent studies show only 2-5% of patients with lupus erythematosus profundus have associated systemic lupus erythematosus. Mean age of onset in reported pediatric cases is 9.8 yr.

Clinical Manifestations

Lupus erythematosus profundus manifests as 1 to several firm, tender, well-defined, purple plaques or nodules 1-3 cm in diameter. Majority of pediatric cases involve the face and proximal upper extremities. This condition may occur in patients with systemic or discoid lupus erythematosus and may precede or follow the development of other cutaneous lesions. The overlying skin is usually normal but may be erythematous, atrophic, poikilodermatous, or hyperkeratotic (Fig. 660-3). On healing, a shallow depression generally remains or, rarely, soft pink areas of anetoderma result.

Figure 660-3 Deep nodule of lupus profundus with overlying hyperkeratotic lesion of discoid lupus erythematosus.

Histology
The histopathologic changes in lupus erythematosus profundus are distinctive and may allow the clinician to make the diagnosis in the absence of other cutaneous lesions of lupus erythematosus. The panniculitis is characterized by a mostly nodular dense infiltrate of lymphocytes and plasma cells. Necrosis of the fat lobule is characteristic. A dense perivascular and periappendiceal lymphocytic infiltrate is seen in the dermis. Lichenoid changes may be identified at the epidermal–dermal junction. Histopathologic differentiation from subcutaneous panniculitis–like T-cell lymphoma may be difficult. Results of lupus band and antinuclear antibody tests are usually positive.

Treatment
Nodules tend to be persistent and frequently ulcerate. Long-term follow-up for possible systemic involvement is warranted. There is no consensus on the utility of laboratory testing. antinuclear antibody is positive in only a small subset of patients. Few case reports show slight neutropenia, leukopenia, and mildly elevated liver function tests. Hydroxychloroquine (2-5 mg/kg/day) is the **treatment of choice** for lupus erythematosus profundus. Intralesional corticosteroids may worsen the residual lipoatrophy. Immunosuppressive agents are indicated only for treatment of other severe manifestations of systemic lupus erythematosus. Avoidance of sun exposure and trauma is also important.

α_1-ANTITRYPSIN DEFICIENCY
Etiology and Pathogenesis
Individuals with α_1-antitrypsin deficiency have severe homozygous deficiency or, rarely, a partial deficiency of the protease inhibitor α_1-antitrypsin, which inhibits trypsin activity and the activity of elastase, serine proteases, collagenase, factor VIII, and kallikrein (see Chapter 393). Panniculitis occurs with severe α_1-antitrypsin deficiency or the Z subtype.

Clinical Manifestations
Cellulitis-like areas or tender, red nodules occur on the trunk or proximal extremities (see Chapter 393). Nodules tend to ulcerate spontaneously and discharge an oily yellow fluid. Panniculitis may be associated with other manifestations of the disease, such as panacinar emphysema, noninfectious hepatitis, cirrhosis, persistent cutaneous vasculitis, cold contact urticaria, and acquired angioedema. Diagnosis can be substantiated by a decreased level of serum α_1-antitrypsin activity.

Histology
Extensive septal and lobular neutrophilic infiltrate with necrosis of the fat is observed.

Treatment
Treatment of the panniculitis in with α_1-antitrypsin deficiency is part of the overall treatment of the disease (see Chapter 393).

PANCREATIC PANNICULITIS
Etiology and Pathogenesis
Pathogenesis of pancreatic panniculitis appears to be multifactorial, involving liberation of the lipolytic enzymes lipase, trypsin, and amylase into the circulation, causing adipocyte membrane damage and intracellular lipolysis. There is no correlation, however, between the occurrence of panniculitis and the serum concentration of pancreatic enzymes.

Clinical Manifestations
Pancreatic panniculitis manifests most commonly on the pretibial regions, thighs, or buttocks as tender, erythematous nodules that may be fluctuant and occasionally discharge an oily yellowish substance. It appears most often in males with alcoholism but may also occur in patients with pancreatitis as a result of cholelithiasis or abdominal trauma, with rupture of a pancreatic pseudocyst, with pancreatic ductal adenocarcinoma, or with pancreatic acinar cell carcinoma. Associated features may include polyarthritis (pancreatitis-panniculitis-polyarthritis syndrome). In almost 65% of patients, abdominal signs are absent or mild, making the diagnosis difficult.

Histology
Microscopic changes consist of multiple foci of fat necrosis that contain ghost cells with thick, shadowy walls and no nuclei. A polymorphous inflammatory infiltrate surrounds the areas of fat necrosis.

Treatment
The primary pancreatic disorder must be treated. The arthritis may be chronic and responds poorly to treatment with nonsteroidal antiinflammatory drugs and oral corticosteroids.

SUBCUTANEOUS FAT NECROSIS
Etiology and Pathogenesis
The cause of subcutaneous fat necrosis (SCFN) is unknown. The disease in infants may be a result of ischemic injury from various perinatal complications, such as maternal preeclampsia, birth trauma, asphyxia, and prolonged hypothermia. Whole-body cooling for neonatal encephalopathy is increasingly associated with SCFN. Susceptibility is attributed to differences in composition between the subcutaneous tissue of young infants and that of older infants, children, and adults. Neonatal fat solidifies at a relatively high temperature because of its relatively greater concentration of high-melting-point saturated fatty acids, such as palmitic and stearic acids.

Clinical Manifestations
This inflammatory disorder of adipose tissue occurs primarily in the 1st 4 wk of life in full-term or postterm infants. Typical lesions are asymptomatic, indurated, erythematous to violaceous, sharply demarcated plaques or nodules on the cheeks, buttocks, back, thighs, or upper arms (Fig. 660-4). Lesions may be focal or extensive and are generally asymptomatic, although they may be tender during the acute phase. Uncomplicated lesions involute spontaneously within weeks to months, usually without scarring or atrophy. Calcium deposition may occasionally occur within areas of fat necrosis, which may sometimes result in rupture and drainage of liquid material. These areas may heal with atrophy. A rare but potentially life-threatening complication is **hypercalcemia**. It manifests at 1-6 mo of age (in a review of 20 cases, average age at onset was 6.7 wk) as lethargy, poor feeding, vomiting, failure to thrive, irritability, seizures, shortening of the QT interval on electrocardiography, or renal failure. The origin of the hypercalcemia is unknown, but an accepted hypothesis is that the macrophages present produce 1,25-dihydroxyvitamin D_3 which, in turn, increases calcium uptake. Infants with SCFN should be followed for several months to monitor for delayed hypercalcemia.

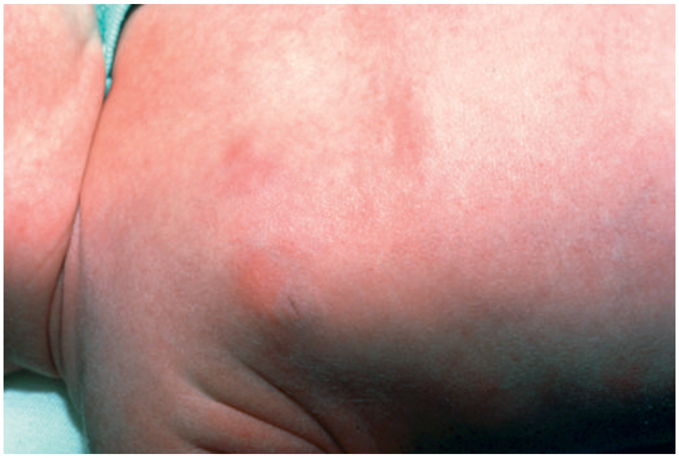

Figure 660-4 Red-purple nodular infiltration of the skin of the chest caused by subcutaneous fat necrosis.

Histology
Histopathologic changes in SCFN are diagnostic, consisting of: necrosis of fat; a granulomatous cellular infiltrate composed of lymphocytes, histiocytes, multinucleated giant cells, and fibroblasts; and radially arranged clefts of crystalline triglyceride within fat cells and multinucleated giant cells. Calcium deposits are commonly found in areas of fat necrosis.

Differential Diagnosis
SCFN can be confused with sclerema neonatorum, panniculitis, cellulitis, and hematoma.

Treatment
Because the lesions are self-limited, therapy is not required for uncomplicated cases of SCFN. Needle aspiration of fluctuant lesions may prevent rupture and subsequent scarring but is rarely needed. Treatment of hypercalcemia is aimed at enhancing renal calcium excretion with hydration and furosemide (1-2 mg/kg/dose) and at limiting dietary calcium and vitamin D intake. Reduction of intestinal calcium absorption and alteration of vitamin D metabolism may be accomplished by administration of corticosteroids (0.5-1.0 mg/kg/day). Pamidronate (0.25-0.5 mg/kg/day) has been used in severe cases.

SCLEREMA NEONATORUM
Etiology and Pathogenesis
Although the cause remains unknown, 4 theories of pathogenesis for sclerema neonatorum have been proposed. It is theorized that sclerema neonatorum results from hardening of the subcutaneous fat because of a decrease in body temperature as a consequence of circulatory shock; a defect in lipolytic enzymes or in lipid transport; association with an underlying severe disease; or a special form of edema affecting the connective tissue that supports the adipocytes.

Clinical Manifestations
This uncommon disorder of adipose tissue manifests abruptly in preterm, gravely ill infants as diffuse, yellowish white woody induration of the skin. It begins on the legs and buttocks then quickly progresses to other areas, sparing palms and soles. Affected skin becomes stony in consistency, cold, and nonpitting. The face assumes a masklike expression, and joint mobility may be compromised because of inflexibility of the skin.

Histology
Histopathologic changes in sclerema neonatorum consist of increases in the size of fat cells and in the width of the fibrous connective tissue septa. In contrast to SCFN, with which this disorder is most apt to be confused, fat necrosis, inflammation, giant cells, and calcium crystals are generally absent.

Treatment
Sclerema neonatorum is almost always associated with serious illness, such as sepsis, congenital heart disease, multiple congenital anomalies, or hypothermia. The appearance of sclerema in a sick infant should be regarded as an ominous prognostic sign. The outcome depends on the response of the underlying disorder to treatment.

COLD PANNICULITIS
Etiology and Pathogenesis
The pathogenic mechanism of cold panniculitis may be similar to that of SCFN, involving a greater propensity of fat to solidify in infants than in older children and adults as a result of the higher percentage of saturated fatty acids in the subcutaneous fat of infants. Lesions occur in infants after prolonged cold exposure, especially on the cheeks, or after prolonged application of a cold object such as an ice cube, ice bag, or fruit ice pop to any area of the skin.

Clinical Manifestations
Ill-defined, erythematous to bluish, indurated plaques or nodules arise within hours to a couple days of exposure on exposed surfaces (face, arms, legs), persist for 2-3 wk, and heal without residua.

Histology
Histopathologic examination reveals an infiltrate of lymphoid and histiocytic cells around blood vessels at the dermal–subdermal junction and in the fat lobules; by the 3rd day, some of the fat cells in the subcutis may have ruptured and coalesced into cystic structures.

Differential Diagnosis
Cold panniculitis may be confused with facial cellulitis caused by *Haemophilus influenzae* type b. Unlike in buccal cellulitis, the area may be cold to the touch, and the patient is afebrile and appears well.

Treatment
Treatment is unnecessary because cold panniculitis spontaneously resolves. Recurrence of the lesions is common, emphasizing the importance of parental education in treating affected patients.

CHILBLAINS (PERNIO)
Etiology and Pathogenesis
Vasospasm of arterioles from damp cold exposure with resultant hypoxemia and localized perivascular mononuclear inflammation appears to be responsible for chilblains. The disease is associated with cryoglobulins, lupus erythematosus with antiphospholipid antibodies, anorexia nervosa, and thin body habitus.

Clinical Manifestations
The condition is characterized by localized symmetric erythematous to purplish edematous plaques and nodules in areas exposed to cold, typically acral areas (distal hands and feet, ears, face; see Chapter 76). Lesions develop 12-24 hr after cold exposure and may be associated with itching, burning, or pain. Blister formation and ulceration are rare.

Histology
Histopathologic examination reveals marked dermal edema and a perivascular and periappendiceal, predominantly T-cell lymphocytic infiltrate in the papillary and reticular dermis.

Differential Diagnosis
Raynaud phenomenon is more acute in nature than chilblains, with characteristic color changes and no chronic lesions. Frostbite due to extreme cold exposure is painful and involves freezing of the tissue with resultant tissue necrosis.

Treatment
Most cases of chilblains resolve spontaneously but can last 2-3 wk. Prevention is the treatment of choice. Nifedipine (0.25-0.5 mg/kg tid,

maximum 10 mg/dose) may be used in severe cases. Unusual or persistent cases of perniosis in children may warrant further work-up including antinuclear antibody titer, cryoglobulins, complete blood count, and cold agglutinins.

FACTITIAL PANNICULITIS

Etiology and Pathogenesis

Factitial panniculitis results from subcutaneous injection by the patient or a proxy of a foreign substance, the most common types of which are organic materials, such as milk and feces; drugs, such as the opiates and pentazocine; oily materials, such as mineral oil and paraffin; and the synthetic polymer povidone.

Clinical Manifestations

Indurated plaques, ulcers, or nodules that liquefy and drain may be noted clinically in factitial panniculitis.

Histology

The histopathology is variable, depending on the injected substance, but may include the presence of birefringent crystals, oil cysts surrounded by fibrosis and inflammation, and an acute inflammatory reaction with fat necrosis. Vessels are characteristically spared.

Treatment

Treatment of factitial panniculitis must address the primary reason the patient is performing the self-destructive act. Munchausen syndrome by proxy should be considered in young children.

Bibliography is available at Expert Consult.

660.2 Lipodystrophy

JiaDe Yu

Several rare conditions are associated with loss of fatty tissue in a partial or generalized distribution and can be familial or acquired. Loss of adipose at certain sites is often accompanied by fat redistribution and consequent hypertrophy of adipose at other sites. Extent of fatty tissue loss or expansion correlates with the degree of clinical and metabolic abnormalities.

PARTIAL LIPODYSTROPHY

Partial lipodystrophy may be familial or acquired. Loss of adipose tissue is not preceded by an inflammatory phase, and histopathologic examination reveals only absence of subcutaneous fat.

There are 5 forms of familial partial lipodystrophy (FPLD):

- **Type I (FPLD1–Kobberling)** is characterized by loss of adipose tissue confined to the extremities and gluteal region. Fat distribution of the face, neck, and trunk may be normal or increased. Hyperlipidemia, insulin-resistant diabetes mellitus, and eruptive xanthomas may be seen. The gene is unknown, but only females are affected.
- **Type 2 (FPLD2–Dunnigan)** is the most common form of FPLD and caused by mutations in the *laminin A/C* gene leading to premature death of adipocytes. Fat distribution is normal in childhood, but atrophy commences with puberty. Lipodystrophy is seen in the trunk, gluteal region, and extremities. Adipose tissue accumulates in the face and neck and may also be seen in the axillae, back, labia majora, and infraabdominal region. Insulin-resistant diabetes mellitus and hypertriglyceridemia develop, but high-density lipoprotein and cholesterol levels are low. Both males and females are affected, but the diagnosis may be more difficult in males owing to body habitus.
- **Type 3 (FPLD3)** is caused by mutations in the peroxisome proliferation–activated receptor γ *(PPARG)* gene inhibiting adipocyte differentiation. Lipodystrophy is seen in the distal limbs and gluteal region. Insulin-resistant diabetes mellitus, primary amenorrhea, acanthosis nigricans, hypertension, and fatty infiltration of the liver are present.
- **Type 4 (FPLD4)** and **Type 5 (FPLD5)** are caused by mutations in *AKT2* and *Perilipin-1 (PLIN1)*, respectively. Both types are also characterized by loss of subcutaneous fat primarily from the extremities.

Acquired partial lipodystrophy (Barraquer-Simons syndrome) is caused by mutations in the *LMNB2* gene. Females are more commonly affected. Fat loss begins in childhood or adolescence and progresses in a cephalotruncal direction, beginning on the face and sparing the lower extremities. Excess fat deposition is seen in the hips and legs, especially in females. Low levels of complement C3 are almost universally seen because of the presence of C3 nephritic factor that stabilizes C3 convertase, allowing for unopposed activation of the alternate complement pathway leading to decreased level of C3. Membranous proliferative glomerulonephritis and other autoimmune diseases may develop. Insulin-resistant diabetes mellitus is rare.

GENERALIZED LIPODYSTROPHY

Generalized lipodystrophy may also be congenital or acquired.

Congenital generalized lipodystrophy is seen in 4 forms:

- **Type 1 (Berardinelli-Seip congenital lipodystrophy type 1 [BSCL1])** is an autosomal recessive disorder caused by mutations in the 1-acylglycerol-3-phosphate-*O*-acyltransferase *(AGPAT2)* gene.
- **Type 2 (Berardinelli-Seip congenital lipodystrophy type 2 [BSCL2])** is also autosomal recessive and caused by mutations in the seipin gene.
- **Type 3 *(CAV1)*** is autosomal recessive and caused by mutations in the caveolin 1 gene.
- **Type 4 (*PTRF*)** is autosomal recessive and caused by mutations in the polymerase I and transcript release factor gene. In addition to the classic phenotype of congenital generalized lipodystrophy, these patients also have muscular dystrophy and cardiac conduction abnormalities (QT prolongation).

Marked lipodystrophy occurs at birth or in early infancy with prominent muscularity. Diabetes mellitus, hypertriglyceridemia, hepatic steatosis, acanthosis nigricans, and muscular hypertrophy occur. Congenital generalized lipodystrophy type 1 and type 2 are the most common, with the latter having a more severe phenotype characterized by extensive fat loss, cardiomyopathy, intellectual impairment, and premature death in ≈15% of cases.

Acquired generalized lipodystrophy is more common in females. The most common associated disorder is juvenile dermatomyositis (78%). Panniculitis preceding the loss of fat is seen in 17% of affected individuals. More than half of the children may have other complications, including acanthosis nigricans, hyperpigmentation, hepatomegaly, hypertension, protuberant abdomen, and hyperlipidemia.

Localized lipoatrophy can be idiopathic or secondary to subcutaneous medication injections, pressure, and panniculitis. Unlike generalized or partial lipodystrophy, localized lipoatrophy involve a small part of the body and have no accompanying metabolic derangements. Idiopathic localized lipoatrophy manifests as annular atrophy at the ankles; a bandlike semicircular depression 2-4 cm in diameter on the thighs, abdomen, and/or upper groin or as a centrifugally spreading, depressed, bluish plaque with an erythematous margin. **Insulin lipoatrophy** usually occur approximately 6 mo to 2 yr after initiation of relatively high doses of insulin. A dimple or well-circumscribed depression at or surrounding the site of injection is typically seen. Biopsy reveals a marked decrease or absence of subcutaneous tissue, without inflammation or fibrosis. In some patients, hypertrophy occurs clinically. In these cases, the mid-dermal collagen is replaced by hypertrophic fat cells on histopathologic sections. A recent study shows that adipocytes chronically exposed to high insulin concentrations become insulin-resistant, leading to lipolysis and atrophy. Lesions may also be prevented by frequent alteration of injection sites.

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Chapter 661

Disorders of the Sweat Glands

Kari L. Martin

Eccrine glands are found over nearly the entire skin surface and provide the primary means, through evaporation of the water in sweat, of cooling the body. These glands have no anatomic relationship to hair follicles and secrete a relatively large amount of odorless aqueous sweat. In contrast, apocrine sweat glands are limited in distribution to the axillae, anogenital skin, mammary glands, ceruminous glands of the ear, Moll glands in the eyelid, and selected areas of the face and scalp. Each apocrine gland duct enters the pilosebaceous follicle at the level of the infundibulum and secretes a small amount of a complex, viscous fluid that, on alteration by microorganisms, produces a distinctive body odor. Some disorders of these 2 types of sweat glands are similar pathogenetically, whereas others are unique to a given gland.

ANHIDROSIS

Neuropathic anhidrosis results from a disturbance in the neural pathway from the control center in the brain to the peripheral efferent nerve fibers that activate sweating. Disorders in this category, which are characterized by generalized anhidrosis, include tumors of the hypothalamus and damage to the floor of the third ventricle. Pontine or medullary lesions may produce anhidrosis of the ipsilateral face or neck and ipsilateral or contralateral anhidrosis of the rest of the body. Peripheral or segmental neuropathies, caused by leprosy, amyloidosis, diabetes mellitus, alcoholic neuritis, or syringomyelia, may be associated with anhidrosis of the innervated skin. Various autonomic disorders are also associated with altered eccrine sweat gland function.

At the level of the sweat gland, anticholinergics (drugs such as atropine and scopolamine) may paralyze the sweat glands. Acute intoxication with barbiturates or diazepam has produced necrosis of sweat glands, resulting in anhidrosis with or without erythema and bullae. Eccrine glands are largely absent throughout the skin or are present in a localized area among patients with **hypohidrotic ectodermal dysplasia** or **localized congenital absence of sweat glands,** respectively. Infiltrative or destructive disorders that may produce atrophy of sweat glands by pressure or scarring include scleroderma, acrodermatitis chronica atrophicans, radiodermatitis, burns, Sjögren syndrome, multiple myeloma, and lymphoma. Obstruction of sweat glands may occur in miliaria and in a number of inflammatory and hyperkeratotic disorders, such as the ichthyoses, psoriasis, lichen planus, pemphigus, porokeratosis, atopic dermatitis, and seborrheic dermatitis. Occlusion of the sweat pore may also occur with the topical agents aluminum and zirconium salts, formaldehyde, or glutaraldehyde.

Diverse disorders that are associated with anhidrosis by unknown mechanisms include dehydration; toxic overdose with lead, arsenic, thallium, fluorine, or morphine; uremia; cirrhosis; endocrine disorders such as Addison disease, diabetes mellitus, diabetes insipidus, and hyperthyroidism; and inherited conditions such as autonomic neuropathies, Fabry disease, Franceschetti-Jadassohn syndrome, which combines features of incontinentia pigmenti and hypohidrotic ectodermal dysplasia, congenital insensitivity to pain with anhidrosis syndrome, and familial anhidrosis with neurolabyrinthitis.

Anhidrosis may be complete, but in many cases, what appears clinically to be anhidrosis is actually **hypohidrosis** caused by anhidrosis of many, but not all, eccrine glands. Compensatory, localized hyperhidrosis of the remaining functional sweat glands may occur, particularly in diabetes mellitus and miliaria. The primary complication of anhidrosis is **hyperthermia,** seen primarily in anhidrotic ectodermal dysplasia or in otherwise normal preterm or full-term neonates who have immature eccrine glands.

HYPERHIDROSIS

Etiology and Pathogenesis

Hyperhidrosis is excessive sweating beyond what is physiologically necessary for temperature control and occurs in 3% of the population with about half having axillary hyperhidrosis. The numerous disorders that may be associated with increased production of eccrine sweat may also be classified into those with neural mechanisms involving an abnormality in the pathway from the neural regulatory centers to the sweat gland and those that are nonneurally mediated and occur by direct effects on the sweat glands (Table 661-1).

Clinical Manifestations

The average age at onset of hyperhidrosis is 14-25 yr. The excess sweating may be continuous or may occur in response to emotional stimuli. In severe cases, sweat may be seen to drip constantly from the hands.

Treatment

Excessive sweating of the palms and soles (volar hyperhidrosis) and axillary sweating may respond to 20% aluminum chloride in anhydrous ethanol applied under occlusion for several hours, iontophoresis, injection with botulinum toxin, therapy with oral anticholinergics, or in severe, refractory cases, cervicothoracic or lumbar sympathectomy. Reports of successful treatment of hyperhidrosis with microwave technology are available, but studies are faulted with small sample size and lack of controls.

Table 661-1 Causes of Hyperhidrosis

CORTICAL	Cardiovascular:
Emotional	Heart failure
Familial dysautonomia	Shock
Congenital ichthyosiform erythroderma	Vasomotor
Epidermolysis bullosa	Cold injury
Nail-patella syndrome	Raynaud phenomenon
Jadassohn-Lewandowsky syndrome	Rheumatoid arthritis
Pachyonychia congenita	Neurologic:
Palmoplantar keratoderma	Abscess
Stroke	Familial dysautonomia
HYPOTHALAMIC	Postencephalitic
Drugs:	Tumor
Alcohol	Miscellaneous:
Antipyretics	Chédiak-Higashi syndrome
Cocaine	Compensatory
Emetics	Lymphoma
Insulin	Phenylketonuria
Opiates (including withdrawal)	Vitiligo
Ciprofloxacin	MEDULLARY
Exercise	Physiologic gustatory sweating
Infection:	Encephalitis
Defervescence	Granulosis rubra nasi
Chronic illness	Syringomyelia
Metabolic:	Thoracic sympathetic trunk injury
Carcinoid syndrome	SPINAL
Debility	Cord transection
Diabetes mellitus	Syringomyelia
Hyperpituitarism	CHANGES IN BLOOD FLOW
Hyperthyroidism	Maffucci syndrome
Hypoglycemia	Arteriovenous fistula
Obesity	Klippel-Trenaunay syndrome
Pheochromocytoma	Glomus tumor
Porphyria	Blue rubber-bleb nevus syndrome
Pregnancy	
Rickets	
Infantile scurvy	

MILIARIA

Etiology and Pathogenesis

Miliaria results from retention of sweat in occluded eccrine sweat ducts. The keratinous plug does not form until the later stages of the disease and therefore does not appear to be the primary cause of the sweat duct obstruction. The initial obstruction is postulated to be caused by swelling of the ductal epidermal cells, perhaps from imbibition of water. Retrograde pressure may result in rupture of the duct and leakage of sweat into the epidermis and/or the dermis. The eruption is most often induced by hot, humid weather, but it may also be caused by high fever. Infants who are dressed too warmly may demonstrate this eruption indoors, even during the winter.

Clinical Manifestations

In **miliaria crystallina,** asymptomatic, noninflammatory, pinpoint, clear vesicles may suddenly erupt in profusion over large areas of the body surface, leaving brawny desquamation on healing (Fig. 661-1). This type of miliaria occurs most frequently in newborn infants because of the relative immaturity and delayed patency of the sweat duct and the tendency for infants to be nursed in relatively warm, humid conditions. It may also occur in older patients with hyperpyrexia.

Miliaria rubra is a less superficial eruption characterized by erythematous, minute papulovesicles that may impart a prickling sensation. The lesions are usually localized to sites of occlusion or to flexural areas, such as the neck, groin, and axillae, where friction may have a role in their pathogenesis. Involved skin may become macerated and eroded. Lesions of miliaria rubra, however, are extrafollicular.

Repeated attacks of miliaria rubra may lead to **miliaria profunda,** which is caused by rupture of the sweat duct deeper in the skin, at the level of the dermal–epidermal junction. Severe, extensive miliaria rubra or miliaria profunda may result in disturbance of heat regulation. Lesions of miliaria rubra may become infected, particularly in malnourished or debilitated infants, leading to development of **periporitis staphylogenes,** which involves extension of the process from the sweat duct into the sweat gland.

Histology

Histologically, miliaria crystallina reveals an intracorneal or subcorneal vesicle in communication with the sweat duct, whereas in miliaria rubra, one sees focal areas of spongiosis and spongiotic vesicle formation in close proximity to sweat ducts that generally contain a keratinous plug.

Differential Diagnosis

The clarity of the fluid, superficiality of the vesicles, and absence of inflammation permit differentiation of miliaria crystalline from other blistering disorders. Miliaria rubra may be confused with or superimposed on other diaper area eruptions, including candidosis and folliculitis.

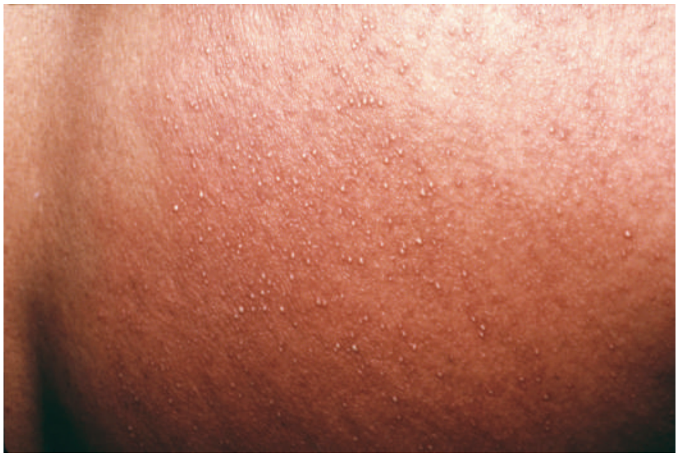

Figure 661-1 Superficial clear vesicles of miliaria crystallina.

Treatment

All forms of miliaria respond dramatically to cooling of the patient by regulation of environmental temperatures and by removal of excessive clothing; administration of antipyretics is also beneficial to patients with fever. Topical agents are usually ineffective and may exacerbate the eruption.

BROMHIDROSIS

The excessive odor that characterizes bromhidrosis may result from alteration of either apocrine or eccrine sweat. Apocrine bromhidrosis develops after puberty as a result of the formation of short-chain fatty acids and ammonia by the action of anaerobic diphtheroids on axillary apocrine sweat. Eccrine bromhidrosis is caused by microbiologic degradation of stratum corneum that has become softened by excessive eccrine sweat. The soles of the feet and the intertriginous areas are the primary affected sites. Hyperhidrosis, warm weather, obesity, intertrigo, and diabetes mellitus are predisposing factors. **Treatments** that may be helpful include cleansing with germicidal soaps, topical clindamycin or erythromycin, or topical application of aluminum or zirconium. Treatment of any associated hyperhidrosis is mandatory.

HIDRADENITIS SUPPURATIVA

Etiology and Pathogenesis

Hidradenitis suppurativa is a disease of the apocrine gland–bearing areas of the skin. Pathogenesis of hidradenitis suppurativa is controversial. It is believed that it is a primary inflammatory disorder of the hair follicle and not solely an alteration of apocrine glands. It is considered a part of the follicular occlusion tetrad, along with acne conglobata, dissecting cellulites of the scalp, and pilonidal sinus. The natural history of the disease involves progressive dilation below the follicular obstruction, leading to rupture of the duct, inflammation, sinus tract formation, and destructive scarring.

Clinical Manifestations

Hidradenitis suppurativa is a chronic, inflammatory, suppurative disorder of the follicular units in the axillae, the anogenital area, and, occasionally, the scalp, posterior aspect of the ears, female breasts, and periumbilical area. Onset of clinical manifestations is sometimes preceded by pruritus or discomfort and usually occurs during puberty or early adulthood. Solitary or multiple painful erythematous nodules, deep abscesses, and contracted scars are sharply confined to areas of skin containing apocrine glands. When the disease is severe and chronic, sinus tracts, ulcers, and thick, linear fibrotic bands develop. Hidradenitis suppurativa tends to persist for many years, punctuated by relapses and partial remissions. Complications include cellulitis, ulceration, and burrowing abscesses that may perforate adjacent structures, forming fistulas to the urethra, bladder, rectum, or peritoneum. Episodic inflammatory arthritis develops in some patients.

Histology

Early lesions are characterized by a keratinous plug in the apocrine duct or hair follicle orifice and by cystic distention of the follicle. The process generally but not necessarily extends into the apocrine gland. Later changes include inflammation within and around apocrine glands. Scarring may obliterate skin appendages.

Differential Diagnosis

Early lesions of hidradenitis suppurativa are often mistaken for infected epidermal cysts, furuncles, scrofuloderma, actinomycosis, cat-scratch disease, granuloma inguinale, or lymphogranuloma venereum. Sharp localization to areas of the body that bear apocrine glands, however, should suggest hidradenitis. When involvement is limited to the anogenital region, the condition may be difficult to distinguish from Crohn disease.

Treatment

Conservative management includes cessation of smoking, weight loss, and avoidance of irritation of the affected area. Warm compresses and topical antiseptic or antibacterial soaps may also be helpful. For mild,

early disease, topical clindamycin 1% may be helpful. For more-severe disease, therapy may be initiated with doxycycline (100 mg bid) or minocycline (100 mg bid). Some patients require intermittent or long-term antibiotic treatment. Combination therapy with clindamycin and rifampin is helpful in some patients. Oral retinoids (1 mg/kg/day) for 5-6 mo may also be effective. Oral contraceptive agents, which contain a high estrogen : progesterone ratio and low androgenicity of the progesterone, are another alternative. Laser hair ablation has proven helpful in some studies as well. Systemic immunosuppressants (infliximab, adalimumab, cyclosporine) and medications targeted at glucose metabolism and the metabolic syndrome (metformin) have been helpful. Surgical measures may be required for control or cure, especially in localized, recalcitrant cases.

FOX-FORDYCE DISEASE

Etiology and Pathogenesis

The cause of Fox-Fordyce disease is unknown.

Clinical Manifestations

This disease is most common in females and manifests during puberty to the 3rd decade of life as pruritus in the axillae. Pruritus is exacerbated by emotional stress and stimuli that induce apocrine sweating. Dome-shaped, skin-colored to slightly hyperpigmented, follicular papules develop in the pruritic areas.

Histology

Histopathologically, one sees keratinous plugging of the distal apocrine duct, rupture of the intraepidermal portion of the apocrine duct, periductal microvesicle formation, and periductal acanthosis.

Treatment

Fox-Fordyce disease is difficult to treat. Oral contraceptive pills and topical corticosteroids or retinoic acid may help some patients.

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Table 662-1	Causes of and Conditions Associated with Hypertrichosis

INTRINSIC FACTORS
Racial and familial forms such as hairy ears, hairy elbows, intraphalangeal hair, or generalized hirsutism

EXTRINSIC FACTORS
Local trauma
Malnutrition
Anorexia nervosa
Long-standing inflammatory dermatoses
Drugs: Diazoxide, phenytoin, corticosteroids, Cortisporin, cyclosporine, androgens, anabolic agents, hexachlorobenzene, minoxidil, psoralens, penicillamine, streptomycin

HAMARTOMAS OR NEVI
Congenital pigmented nevocytic nevus, hair follicle nevus, Becker nevus, congenital smooth muscle hamartoma, fawn-tail nevus associated with diastematomyelia

ENDOCRINE DISORDERS
Virilizing ovarian tumors, Cushing syndrome, acromegaly, hyperthyroidism, hypothyroidism, congenital adrenal hyperplasia, adrenal tumors, gonadal dysgenesis, male pseudohermaphroditism, non–endocrine hormone–secreting tumors, polycystic ovary syndrome

CONGENITAL AND GENETIC DISORDERS
Hypertrichosis lanuginosa, mucopolysaccharidosis, leprechaunism, congenital generalized lipodystrophy, de Lange syndrome, trisomy 18, Rubinstein-Taybi syndrome, Bloom syndrome, congenital hemihypertrophy, gingival fibromatosis with hypertrichosis, Winchester syndrome, lipoatrophic diabetes (Lawrence-Seip syndrome), fetal hydantoin syndrome, fetal alcohol syndrome, congenital erythropoietic or variegate porphyria (sun-exposed areas), porphyria cutanea tarda (sun-exposed areas), Cowden syndrome, Seckel syndrome, Gorlin syndrome, partial trisomy 3q, Ambras syndrome

Chapter 662
Disorders of Hair

Kari L. Martin

Disorders of hair in infants and children may be a result of intrinsic disturbances of hair growth, underlying biochemical or metabolic defects, inflammatory dermatoses, or structural anomalies of the hair shaft. Excessive and abnormal hair growth is referred to as hypertrichosis or hirsutism. **Hypertrichosis** is excessive hair growth at inappropriate locations; hirsutism is an androgen-dependent male pattern of hair growth in women. **Hypotrichosis** is deficient hair growth. Hair loss, partial or complete, is called *alopecia*. Alopecia may be classified as nonscarring or scarring; the latter type is rare in children and, if present, is most often caused by prolonged or untreated inflammatory conditions, such as pyoderma and tinea capitis.

HYPERTRICHOSIS

Hypertrichosis is rare in children and may be localized or generalized and permanent or transient. Table 662-1 lists some of the many causes of hypertrichosis.

HYPOTRICHOSIS AND ALOPECIA

Table 662-2 lists some of the disorders associated with hypotrichosis and alopecia. True alopecia is rarely congenital; it is more often related

Table 662-2	Disorders Associated with Alopecia and Hypotrichosis

Congenital total alopecia: Atrichia with papules, Moynahan alopecia syndrome
Congenital localized alopecia: Aplasia cutis, triangular alopecia, sebaceous nevus
Hereditary hypotrichosis: Marie-Unna syndrome, hypotrichosis with juvenile macular dystrophy, hypotrichosis–Mari type, ichthyosis with hypotrichosis, cartilage-hair hypoplasia, Hallermann-Streiff syndrome, trichorhinophalangeal syndrome, ectodermal dysplasia "pure" hair and nail and other ectodermal dysplasias
Diffuse alopecia of endocrine origin: Hypopituitarism, hypothyroidism, hypoparathyroidism, hyperthyroidism
Alopecia of nutritional origin: Marasmus, kwashiorkor, iron deficiency, zinc deficiency (acrodermatitis enteropathica), gluten-sensitive enteropathy, essential fatty acid deficiency, biotinidase deficiency
Disturbances of the hair cycle: Telogen effluvium
Toxic alopecia: Anagen effluvium
Autoimmune alopecia: Alopecia areata
Traumatic alopecia: Traction alopecia, trichotillomania
Cicatricial alopecia: Lupus erythematosus, lichen planopilaris, pseudopelade, morphea (en coup de saber) dermatomyositis, infection (kerion, favus, tuberculosis, syphilis, folliculitis, leishmaniasis, herpes zoster, varicella), acne keloidalis, follicular mucinosis, sarcoidosis
Hair shaft abnormalities: Monilethrix, pili annulati, pili torti, trichorrhexis invaginata, trichorrhexis nodosa, woolly hair syndrome, Menkes disease, trichothiodystrophy, trichodento-osseous syndrome, uncombable hair syndrome (spun-glass hair, pili trianguli et canaliculi)

Table 662-3 Helpful Historical Clues in Diagnosis of Hair Disorders

HISTORICAL CONSIDERATIONS	TELOGEN EFFLUVIUM	TRICHOTILLOMANIA	TINEA CAPITIS	ALOPECIA AREATA
Are the spots itchy?	Negative	Negative	Positive	Usually negative
Do the spots come and go?	Negative	Sometimes positive	Negative	Sometimes positive
Is the hair falling out in clumps?	Positive	Negative	Negative	Usually negative
Are there any anxiety disorders or obsessive–compulsive tendencies?	Negative	Positive	Negative	Negative

From Lio PA: What's missing from this picture? An approach to alopecia in children, Arch Dis Child Educ Pract Ed *92:193–198, 2007.*

Table 662-4 Helpful Physical Examination Clues in Diagnosis of Hair Disorders

PHYSICAL FINDINGS	TELOGEN EFFLUVIUM	TRICHOTILLOMANIA	TINEA CAPITIS	ALOPECIA AREATA
Scarring?	Negative	Negative	Usually negative	Negative
Exclamation-point hairs?	Negative	Negative	Negative	Positive
Irregular pattern with mixed length and stubbly hairs?	Negative	Positive	Negative	Negative
Scaling, pustules or kerion?	Negative	Negative	Positive	Negative
Positive hair-pull test result?	Positive	Negative	Negative	Usually negative
Nail pitting or grooves?	Negative	Negative	Negative	Positive

From Lio PA: What's missing from this picture? An approach to alopecia in children, Arch Dis Child Educ Pract Ed *92:193–198, 2007.*

to an inflammatory dermatosis, mechanical factors, drug ingestion, infection, endocrinopathy, nutritional disturbance, or disturbance of the hair cycle. Any inflammatory condition of the scalp, such as atopic dermatitis or seborrheic dermatitis, if severe enough, may result in partial alopecia; hair growth returns to normal if the underlying condition is treated successfully, unless the hair follicle has been permanently damaged.

Hair loss in childhood should be divided into the following 4 categories: congenital diffuse, congenital localized, acquired diffuse, and acquired localized.

Acquired localized hair loss is the most common type of hair loss seen in childhood. Three conditions—traumatic alopecia, alopecia areata, tinea capitis—are predominantly seen (Tables 662-3 and 662-4).

Figure 662-1 Traction alopecia.

TRAUMATIC ALOPECIA (TRACTION ALOPECIA, HAIR PULLING, TRICHOTILLOMANIA)

Traction Alopecia

Traction alopecia is common and is seen in almost 20% of African-American schoolgirls. It is caused by trauma to hair follicles from tight braids or ponytails, headbands, rubber bands, curlers, or rollers (Fig. 662-1). There is a greater risk of traction alopecia if hair trauma is combined with chemically relaxed hair. Broken hairs and inflammatory follicular papules in circumscribed patches at the scalp margins are characteristic and may be subtended by regional lymphadenopathy. Children and parents must be encouraged to avoid devices that cause trauma to the hair and, if necessary, to alter the hairstyle. Otherwise, scarring of hair follicles may occur.

Hair Pulling

Hair pulling in childhood is usually an acute reactional process related to emotional stress or a habit (especially in young children). It may also be seen in trichotillomania (obsessive–compulsive disorder) and as part of more severe psychiatric disorders usually in adolescents.

Trichotillomania

Etiology and Pathogenesis. The diagnostic criteria for trichotillomania include visible hair loss attributable to pulling; mounting tension preceding hair pulling; gratification or release of tension after hair pulling; and absence of hair pulling attributable to hallucinations, delusions, or an inflammatory skin condition.

Clinical Manifestations. Compulsive pulling, twisting, and breaking of hair produces irregular areas of incomplete hair loss, most often on the crown and in the occipital and parietal areas of the scalp. Occasionally, eyebrows, eyelashes, and body hair are traumatized. Some plaques of alopecia may have a linear outline. The hairs remaining within the areas of loss are of various lengths (Fig. 662-2) and are typically blunt-tipped because of breakage. The scalp usually appears normal, although hemorrhage, crusting (Fig. 662-3), and chronic folliculitis may also occur. Trichophagy, resulting in **trichobezoars,** may complicate this disorder.

Differential Diagnosis. Acute reactional hair pulling, tinea capitis, and alopecia areata must be considered in the differential diagnosis of trichotillomania (see Tables 662-3 and 662-4).

Histology. Histologic changes include coexistent normal and damaged follicles, perifollicular hemorrhage, atrophy of some follicles, and catagen transformation of hair. In late stages, perifollicular fibrosis may occur. Long-term repeated trauma may result in irreversible damage and permanent alopecia.

Figure 662-2 Hair pulling. Hairs are broken off at various lengths.

Figure 662-4 Circular patch of alopecia areata with normal-appearing scalp.

Figure 662-3 Hemorrhage and crusting secondary to hair pulling.

Figure 662-5 Alopecia totalis: total loss of scalp hair.

Treatment. Trichotillomania is closely related to obsessive-compulsive disorder and may be an expression of it for some children. When trichotillomania occur secondary to **obsessive–compulsive disorder**, clomipramine 50-150 mg/day or fluoxetine 40-80 mg/day may be helpful, particularly when combined with behavioral interventions (see Chapter 24). *N*-Acetylcysteine may also be helpful.

ALOPECIA AREATA

Etiology and Pathogenesis

Alopecia areata is a T-cell driven autoimmune disorder producing nonscarring alopecia. The cause is unknown. It is hypothesized that in genetically susceptible individuals, loss of immune privilege of the hair follicle allows for T-cell inflammation against anagen hairs, follicles, leading to stoppage of hair growth.

Clinical Manifestations

Alopecia areata is characterized by rapid and complete loss of hair in round or oval patches on the scalp (Fig. 662-4) and on other body sites. In alopecia totalis, all the scalp hair is lost (Fig. 662-5); alopecia universalis involves all body and scalp hair. The lifetime incidence of alopecia areata is 0.1-0.2% of the population. More than half of affected patients are younger than 20 yr.

The skin within the plaques of hair loss appears normal. Alopecia areata is associated with atopy and with nail changes such as pits (Fig. 662-6), longitudinal striations, and leukonychia. **Autoimmune diseases** such as Hashimoto thyroiditis, Addison disease, pernicious anemia, ulcerative colitis, myasthenia gravis, collagen vascular diseases,

Figure 662-6 Multiple nail pits in alopecia areata.

and vitiligo may also be seen. An increased incidence of alopecia areata has been reported in patients with Down syndrome (5-10%).

Differential Diagnosis

Tinea capitis, seborrheic dermatitis, trichotillomania, traumatic alopecia, and lupus erythematosus should be considered in the differential diagnosis of alopecia areata (see Tables 662-3 and 662-4).

Histology

A perifollicular infiltrate of inflammatory round cells is found in biopsy specimens from active areas of alopecia areata.

Treatment

The course is unpredictable, but spontaneous resolution in 6-12 mo is usual, particularly when relatively small, stable patches of alopecia are present. Recurrences are common. Onset at a young age, extensive or prolonged hair loss, and numerous episodes are usually poor prognostic signs. Alopecia universalis, alopecia totalis, and alopecia ophiasis (Fig. 662-7)—a type of alopecia areata in which hair loss is circumferential—are also less likely to resolve. Therapy is difficult to evaluate because the course is erratic and unpredictable. The use of high- or superpotency topical corticosteroids is effective in some patients. Intradermal injections of steroid (triamcinolone 5 mg/mL) every 4-6 wk may also stimulate hair growth locally, but this mode of treatment is impractical in young children or in patients with extensive hair loss. Systemic corticosteroid therapy (prednisone 1 mg/kg/day) is associated with good results; the permanence of cure is questionable, however, and the side effects of chronic oral corticosteroids are a serious deterrent. Some patients may maintain hair growth by switching to a more appropriate long-term immunosuppressant such as methotrexate. Additional therapies that are sometimes effective include short-contact anthralin, topical minoxidil, and contact sensitization with squaric acid dibutylester or diphencyprone. In general, parents and patients can be reassured that spontaneous remission of alopecia areata usually occurs. New hair growth may initially be of finer caliber and lighter color, but replacement by normal terminal hair can be expected.

ACQUIRED DIFFUSE HAIR LOSS

Telogen Effluvium

Telogen effluvium manifests as sudden loss of large amounts of hair, often with brushing, combing, and washing of hair. Diffuse loss of scalp hair occurs from premature conversion of growing, or anagen, hairs, which normally constitute 80-90% of hairs, to resting, or telogen, hairs. Hair loss is noted 6 wk to 3 mo after the precipitating cause, which may include childbirth; a febrile episode; surgery; acute blood loss, including blood donation; sudden severe weight loss; discontinuation of high-dose corticosteroids or oral contraceptives; and psychiatric stress. Telogen effluvium also accounts for the loss of hair by infants in the 1st few mo of life; friction from bed sheets, particularly in infants with pruritic, atopic skin, may exacerbate the problem. There is no inflammatory reaction; the hair follicles remain intact, and telogen bulbs can be demonstrated microscopically on shed hairs. Because >50% of the scalp hair is rarely involved, alopecia is usually not severe. Parents should be reassured that normal hair growth will return within approximately 3-6 mo.

Figure 662-7 Ophiasis pattern of alopecia areata.

Toxic Alopecia (Anagen Effluvium)

Anagen effluvium is an acute, severe, diffuse inhibition of growth of anagen follicles, resulting in loss of >80-90% of scalp hair. Hairs become dystrophic, and the hair shaft breaks at the narrowed segment. Loss is diffuse, rapid (1-3 wk after treatment), and temporary, as regrowth occurs after the offending agent is discontinued. Causes of anagen effluvium include radiation; cancer chemotherapeutic agents such as antimetabolites, alkylating agents, and mitotic inhibitors; thallium; thiouracil; heparin; the coumarins; boric acid; and hypervitaminosis A.

CONGENITAL DIFFUSE HAIR LOSS

Congenital diffuse hair loss is defined as congenitally thin hair diffusely related to either hypoplasia of hair follicles or to structural defects in hair shafts.

Structural Defects of Hair

Structural defects of the hair shaft may be congenital, reflect known biochemical aberrations, or relate to damaging grooming practices. All the defects can be demonstrated by microscopic examination of affected hairs, particularly with scanning and transmission electron microscopy, though many can even be seen by simple trichogram done in the office.

Trichorrhexis Nodosa

Congenital trichorrhexis nodosa is an autosomal dominant condition. The hair is dry, brittle, and lusterless, with irregularly spaced grayish white nodes on the hair shaft. Microscopically, the nodes have the appearance of two interlocking brushes (Fig. 662-8*A*). The defect results from a fracture of the hair shaft at the nodal points caused by disruption of the cells in the hair cortex. Trichorrhexis nodosa has also been observed in some infants with Menkes syndrome, trichothiodystrophy, citrullinemia, and argininosuccinic aciduria.

Acquired Trichorrhexis Nodosa

Acquired trichorrhexis nodosa, the most common cause of hair breakage, occurs in 2 forms. Proximal defects are found most frequently in African-American children, whose complaint is not of alopecia but of failure of the hair to grow. The hair is short, and longitudinal splits, knots, and whitish nodules can be demonstrated in hair mounts. Easy breakage is demonstrated by gentle traction on the hair shafts. A history of other affected family members may be obtained. The problem may be caused by a combination of genetic predisposition and the cumulative mechanical trauma of rough combing and brushing, hair-straightening procedures, and "permanents." Patients must be cautioned to avoid damaging grooming techniques. A soft, natural-bristle brush and a wide-toothed comb should be used. The condition is self-limited, with resolution in 2-4 yr, if patients avoid damaging practices. Distal trichorrhexis nodosa is seen more frequently in white and Asian children. The distal portion of the hair shaft is thinned, ragged, and faded; white specks, sometimes mistaken for nits, may be noted along the shaft. Hair mounts reveal the paintbrush defect and the sites of excessive fragility and breakage. Localized areas of the moustache or beard may also be affected. Avoidance of traumatic grooming, regular trimming of affected ends, and the use of cream rinses to lessen tangling ameliorate this condition.

Pili Torti

Patients with pili torti present with spangled, brittle, coarse hair of different lengths over the entire scalp. There is a structural defect in which the hair shaft is grooved and flattened at irregular intervals and is twisted on its axis to various degrees. Minor twists that occur in normal hair should not be misconstrued as pili torti. Curvature of the hair follicle apparently leads to the flattening and rotation of the hair shaft. The genetic defect in isolated pili torti is unknown, and both autosomal dominant and recessive forms have been described. **Syndromes** in which the hair shaft abnormalities of pili torti are seen in association with other cutaneous and systemic abnormalities include Menkes kinky hair syndrome, Björnstad syndrome (pili torti with deafness; *BCS1L* gene), and multiple ectodermal dysplasia syndromes.

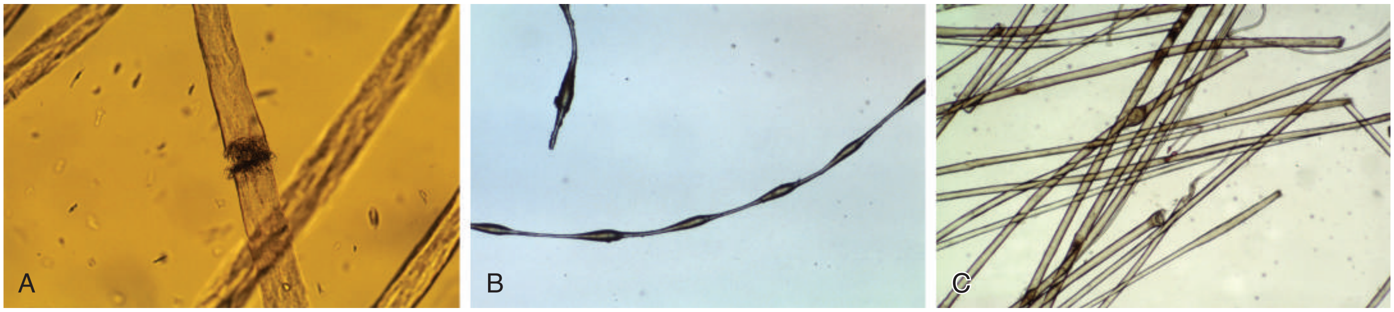

Figure 662-8 **A,** Microscopic hair fracture in trichorrhexis nodosa. **B,** Beading of hair in monilethrix. **C,** Cup-like abnormality of hair in Netherton syndrome.

Menkes Kinky Hair Syndrome (Trichopoliodystrophy)

Males with Menkes kinky hair syndrome, an X-linked recessive trait, are born to an unaffected mother after a normal pregnancy. Neonatal problems include hypothermia, hypotonia, poor feeding, seizures, and failure to thrive. Hair is normal to sparse at birth but is replaced by short, fine, brittle, light-colored hair that may have features of trichorrhexis nodosa, pili torti, or monilethrix. The skin is hypopigmented and thin, cheeks typically appear plump, and the nasal bridge is depressed. Progressive psychomotor retardation is noted in early infancy. Mutations in the *ATP7A* gene, encoding a copper-transporting adenosine triphosphatase protein, cause Menkes kinky hair syndrome. It is a result of maldistribution of the copper in the body. Copper uptake across the brush-border of the small intestine is increased, but copper transport from these cells into the plasma is defective, resulting in low total body copper stores. Parenteral administration of copper-histidine is helpful if begun in the 1st 2 mo of life.

Monilethrix

The hair shaft defect known as monilethrix is inherited as an autosomal dominant trait with variable age of onset, severity, and course. Mutations in the hair keratins HB1, HB3, and HB6 have been identified in autosomal dominant cases, and mutations in desmoglein 4 are found in autosomal recessive cases. The hair appears dry, lusterless, and brittle, and it fractures spontaneously or with mild trauma. Eyebrows, lashes, body and pubic hair, and scalp hair may be affected. Monilethrix may be present at birth, but the hair is usually normal at birth and is replaced in the 1st few mo of life by abnormal hairs; the condition is sometimes first apparent in childhood. Follicular papules may appear on the nape of the neck and the occiput and, occasionally, over the entire scalp. Short, fragile beaded hairs that emerge from the horny follicular plugs give a distinctive appearance. Keratosis pilaris and koilonychia of fingernails and toenails may also be present. Microscopically, a distinctive, regular beading pattern of the hair shaft is evident, characterized by elliptic nodes that are separated by narrower internodes (see Fig. 662-8*B*). Not all hairs have nodes, and both normal and beaded hairs may break. Patients should be advised to handle the hair gently to minimize breakage. Treatment is generally ineffective.

Trichothiodystrophy

Hair in trichothiodystrophy is sparse, short, brittle, and uneven; the scalp hair, eyebrows, or eyelashes may be affected. Microscopically, the hair is flattened, folded, and variable in diameter; has longitudinal grooving; and has nodal swellings that resemble those seen in trichorrhexis nodosa. Under a polarizing microscope, distinctive alternating dark and light bands are seen. The abnormal hair has a cystine content that is <50% of normal because of a major reduction in and altered composition of constituent high-sulfur matrix proteins. Trichothiodystrophy may occur as an isolated finding or in association with various syndrome complexes that include intellectual impairment, short stature, ichthyosis, nail dystrophy, dental caries, cataracts, decreased fertility, neurologic abnormalities, bony abnormalities, and immunodeficiency (*TTDN1* gene). Some patients are photosensitive and have impairment of DNA repair mechanisms, similar to that seen in groups B and D xeroderma pigmentosum; the incidence of skin cancers, however, is not increased. Patients with trichothiodystrophy tend to resemble one another, with a receding chin, protruding ears, raspy voice, and sociable, outgoing personality. Trichoschisis, a fracture perpendicular to the hair shaft, is characteristic of the many syndromes that are associated with trichothiodystrophy. Perpendicular breakage of the hair shaft has also been described in association with other hair abnormalities, particularly monilethrix.

Trichorrhexis Invaginata (Bamboo Hair)

Short, sparse, fragile hair without apparent growth is characteristic of trichorrhexis invaginata, which is found primarily in association with Netherton syndrome (see Chapter 658). It has also been reported in other ichthyosiform dermatoses. The distal portion of the hair is invaginated into the cup-like proximal portion, forming a fragile nodal swelling (see Fig. 662-8*C*).

Pili Annulati

Alternate light and dark bands of the hair shaft characterize pili annulati. When viewed under the light microscope, the region of the hair shaft that appeared bright in reflected light instead appears dark in the transmitted light as a result of focal aggregates of abnormal air-filled cavities within the shaft. The hair is not fragile. The defect may be autosomal dominant or sporadic in inheritance. Pseudopili annulati is a variant of normal blond hair; an optical effect caused by the refraction and reflection of light from the partially twisted and flattened shaft creates the impression of banding.

Woolly Hair Disease

Woolly hair diseases manifest at birth as peculiarly tight, curly, abnormal hair in a non-black person. Autosomal dominant and recessive (*PKRY5* gene) types have been described. Woolly hair nevus, a sporadic form, involves only a circumscribed portion of the scalp hair. The affected hair is fine, tightly curled, and light colored, and it grows poorly. Microscopically, an affected hair is oval and shows twisting of 180 degrees on its axis.

Uncombable Hair Syndrome (Spun-Glass Hair)

The hair of patients with uncombable hair syndrome appears disorderly, is often silvery blond (Fig. 662-9), and may break because of repeated, futile efforts to control it. The condition is probably autosomal dominant in inheritance. Eyebrows and eyelashes are normal. A longitudinal depression along the hair shaft is a constant feature, and most hair follicles and shafts are triangular (pili trianguli et canaliculi). The shape of the hair varies along its length, however, preventing the hairs from lying flat.

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Figure 662-9 Disorderly, silvery blond hair in uncombable hair syndrome.

Chapter **663**

Disorders of the Nails

Kari L. Martin

Nail abnormalities in children may be manifestations of generalized skin disease, skin disease localized to the periungual region, systemic disease, drugs, trauma, or localized bacterial and fungal infections (Table 663-1). Nail anomalies are also common in certain congenital disorders (Table 663-2).

ABNORMALITIES IN NAIL SHAPE OR SIZE

Anonychia is absence of the nail plate, usually a result of a congenital disorder or trauma. It may be an isolated finding or may be associated with malformations of the digits. **Koilonychia** is flattening and concavity of the nail plate with loss of normal contour, producing a spoon-shaped nail (Fig. 663-1). Koilonychia occurs as an autosomal dominant trait or in association with iron-deficiency anemia, Plummer-Vinson syndrome, or hemochromatosis. The nail plate is relatively thin for the 1st yr or 2 of life and, consequently, may be spoon-shaped in otherwise normal children.

Congenital nail dysplasia, an autosomal dominant disorder, manifests at birth as longitudinal streaks and thinning of the nail plate. There is platyonychia and koilonychia, which may overgrow the lateral folds and involve all nails of the toes and fingers.

Nail–patella syndrome is an autosomal dominant disorder in which the nails are 30-50% of their normal size and often have triangular or pyramidal lunulae. The thumbnails are always involved, although in some cases only the ulnar half of the nail may be affected or may be missing. The nails from the index finger to the little finger are progressively less damaged. The patella is also smaller than usual, and this anomaly may lead to knee instability. Bony spines arising from the posterior aspect of the iliac bones, overextension of joints, skin laxity, and renal anomalies may also be present. Nail–patella syndrome is caused by mutations in the transcription factor *LMX1B* gene.

For a discussion of **pachyonychia congenita**, see Chapter 658.

Habit tic deformity consists of a depression down the center of the nail with numerous horizontal ridges extending across the nail from it. One or both thumbs are usually involved as a result of chronic rubbing and picking at the nail with an adjacent finger.

Table 663-1 White Nail or Nail Bed Changes

DISEASE	CLINICAL APPEARANCE
Anemia	Diffuse white
Arsenic	Mees lines: transverse white lines
Cirrhosis	Terry nails: most of nail, zone of pink at distal end (see Fig. 663-3)
Congenital leukonychia (autosomal dominant; variety of patterns)	Syndrome of leukonychia, knuckle pads, deafness; isolated finding; partial white
Darier disease	Longitudinal white streaks
Half-and-half nail	Proximal white, distal pink azotemia
High fevers (some diseases)	Transverse white lines
Hypoalbuminemia	Muehrcke lines: stationary paired transverse bands
Hypocalcemia	Variable white
Malnutrition	Diffuse white
Pellagra	Diffuse milky white
Punctate leukonychia	Common white spots
Tinea and yeast	Variable patterns
Thallium toxicity (rat poison)	Variable white
Trauma	Repeated manicure: transverse striations
Zinc deficiency	Diffuse white

From Habif TP, editor: Clinical dermatology, *ed 4, Philadelphia, 2004, Mosby, p. 887.*

Table 663-2 Congenital Diseases with Nail Defects

Large nails	Pachyonychia congenita, Rubinstein-Taybi syndrome, hemihypertrophy
Smallness or absence of nails	Ectodermal dysplasias, nail-patella, dyskeratosis congenita, focal dermal hypoplasia, cartilage-hair hypoplasia, Ellis–van Creveld, Larsen, epidermolysis bullosa, incontinentia pigmenti, Rothmund-Thomson, Turner, popliteal web, trisomy 13, trisomy 18, Apert, Gorlin-Pindborg, long arm 21 deletion, otopalatodigital, fetal alcohol, fetal hydantoin, elfin facies, anonychia, acrodermatitis enteropathica
Other	Congenital malalignment of the great toenails, familial dystrophic shedding of the nails

Clubbing of the nails (hippocratic nails) is characterized by swelling of each distal digit, an increase in the angle between the nail plate and the proximal nail fold (Lovibond angle) to >180 degrees, and a spongy feeling when one pushes down and away from the interphalangeal joint, because of an increase in fibrovascular tissue between the matrix and the phalanx (Fig. 663-2). The pathogenesis is not known. Nail clubbing is seen in association with diseases of numerous organ systems, including pulmonary, cardiovascular (cyanotic heart disease), gastrointestinal (celiac disease, inflammatory bowel disease), and hepatic (chronic hepatitis) systems, as well as in healthy individuals as an idiopathic or familial finding.

CHANGES IN NAIL COLOR

Leukonychia is a white opacity of the nail plate that may involve the entire plate or may be punctate or striate (see Table 663-1). The nail

Figure 663-1 Spoon nails (koilonychia). Most cases are a variant of normal. *(From Habif TP, editor:* Clinical dermatology, *ed 4, Philadelphia, 2004, Mosby, p. 885.)*

Figure 663-2 Finger clubbing. The distal phalanges are enlarged to a rounded bulbous shape. The nail enlarges and becomes curved, hard, and thickened. *(From Habif TP, editor:* Clinical dermatology, *ed 4, Philadelphia, 2004, Mosby, p. 885.)*

Figure 663-3 Terry nails. The nail bed is white with only a narrow zone of pink at the distal end. *(From Habif TP, editor:* Clinical dermatology, *ed 4, Philadelphia, 2004, Mosby, p. 885.)*

Figure 663-4 Green/black discoloration at the edge of the nails secondary to *Pseudomonas* infection.

plate itself remains smooth and undamaged. Leukonychia can be traumatic or associated with infections such as leprosy and tuberculosis, dermatoses such as lichen planus and Darier disease, malignancies such as Hodgkin disease, anemia, and arsenic poisoning (Mees lines). Leukonychia of all nail surfaces is an uncommon hereditary autosomal dominant trait that may be associated with congenital epidermal cysts and renal calculi. Paired parallel white bands that do not change position with growth of the nail and thus reflect a change in the nail bed are associated with hypoalbuminemia and are called Muehrcke lines. When the proximal portion of the nail is white and the distal 20-50% of the nail is red, pink, or brown, the condition is called half-and-half nails or Lindsay nails; this is seen most commonly in patients with renal disease but may occur as a normal variant. White nails of **cirrhosis,** or Terry nails (Fig. 663-3), are characterized by a white ground-glass appearance of the entire or the proximal end of the nail and a normal pink distal 1-2 mm of the nail; this finding is associated with hypoalbuminemia.

Black pigmentation of an entire nail plate or linear bands of pigmentation (melanonychia striata) is common in African-American (90%) and Asian (10-20%) individuals, but is unusual in white individuals (<1%). Most often, the pigment is melanin, which is produced by melanocytes of a junctional nevus in the nail matrix and nail bed and is of no consequence. Extension or alteration in the pigment should be evaluated by biopsy because of the possibility of malignant change.

Bluish black to greenish nails may be caused by *Pseudomonas* infection (Fig. 663-4), particularly in association with onycholysis or chronic paronychia. The coloration is caused by subungual debris and pyocyanin pigment from the bacterial organisms.

Yellow nail syndrome manifests as thickened, excessively curved, slow-growing yellow nails without lunulae. All nails are affected in most cases. Associated systemic diseases include bronchiectasis, recurrent bronchitis, chylothorax, and focal edema of the limbs and face. Deficient lymphatic drainage, caused by hypoplastic lymphatic vessels, is believed to lead to the manifestations of this syndrome.

Splinter hemorrhages most often result from minor trauma but may also be associated with subacute bacterial endocarditis, vasculitis, Langerhans cell histiocytosis, severe rheumatoid arthritis, peptic ulcer disease, hypertension, chronic glomerulonephritis, cirrhosis, scurvy, trichinosis, malignant neoplasms, and psoriasis.

NAIL SEPARATION

Onycholysis indicates separation of the nail plate from the distal nail bed. Common causes are trauma, long-term exposure to moisture, hyperhidrosis, cosmetics, psoriasis, fungal infection (distal onycholysis), atopic or contact dermatitis, porphyria, drugs (bleomycin, vincristine, retinoid agents, indomethacin, chlorpromazine [Thorazine]), and drug-induced phototoxicity from tetracyclines (Fig. 663-5) or chloramphenicol.

Beau lines are transverse grooves in the nail plate (Fig. 663-6) that represent a temporary disruption of formation of the nail plate. The

Figure 663-5 Distal onycholysis secondary to oral tetracycline usage and ultraviolet light exposure.

Figure 663-6 Beau lines. Longitudinal disruption of nail.

lines first appear a few weeks after the event that caused the disruption in nail growth. A single transverse ridge appears at the proximal nail fold in most 4-6 wk old infants and works its way distally as the nail grows; this line may reflect metabolic changes after delivery. At other ages, Beau lines are usually indicative of periodic trauma or episodic shutdown of the nail matrix secondary to a systemic disease such as hand-foot-and-mouth disease, measles, mumps, pneumonia, or zinc deficiency. **Onychomadesis** is an exaggeration of Beau lines leading to proximal separation of the nail bed (Fig. 663-7).

NAIL CHANGES ASSOCIATED WITH SKIN DISEASE

Nail changes may be particularly associated with various other diseases. Nail changes of **psoriasis** most characteristically include pitting, onycholysis, yellow-brown discoloration, and thickening. Nail changes in lichen planus include violaceous papules in the proximal nail fold and nail bed, leukonychia, longitudinal ridging, thinning of the entire nail plate, and pterygium formation, which is abnormal adherence of the cuticle to the nail plate or, if the plate is destroyed focally, to the nail bed. Postinfectious reactive arthritis syndromes may include painless erythematous induration of the base of the nail fold; subungual parakeratotic scaling; and thickening, opacification, or ridging of the nail plate. Dermatitis that involves the nail folds may produce dystrophy, roughening, and coarse pitting of the nails. Nail changes are more common in atopic dermatitis than in other forms of dermatitis that affect the hands. Darier disease is characterized by red or white streaks that extend longitudinally and cross the lunula. Where the streak meets the distal end of the nail, a V-shaped notch may be present. Total

Figure 663-7 Onychomadesis. Proximal nail bed separation.

Figure 663-8 Dystrophy of all nails in trachyonychia.

leukonychia may also occur. Transverse rows of fine pits are characteristic of alopecia areata. In severe cases, the entire nail surface may be rough. Patients with acrodermatitis enteropathica may have transverse grooves (Beau lines) and nail dystrophy as a result of periungual dermatitis.

TRACHYONYCHIA (20-NAIL DYSTROPHY)

Trachyonychia is characterized by longitudinal ridging, pitting, fragility, thinning, distal notching, and opalescent discoloration of all the nails (Fig. 663-8). Patients have no associated skin or systemic diseases and no other ectodermal defects. Its occasional association with alopecia areata has led some authorities to suggest that trachyonychia may reflect an abnormal immunologic response to the nail matrix, whereas histopathologic studies have suggested that it may be a manifestation of lichen planus, psoriasis, or spongiotic (eczematous) inflammation of the nail matrix. The disorder must be differentiated from fungal infections, psoriasis, nail changes of alopecia areata, and nail dystrophy secondary to eczema. Eczema and fungal infections rarely produce changes in all the nails simultaneously. The disorder is self-limited and eventually remits by adulthood.

NAIL INFECTION

Fungal infection (onychomycosis)of the nails has been classified into 4 types. *White superficial onychomycosis* manifests as diffuse or speckled white discoloration of the surface of the toenails. It is caused primarily by *Trichophyton mentagrophytes,* which invades the nail plate. The organism may be scraped off the nail plate with a blade, but **treatment** is best accomplished by the addition of a topical azole antifungal agent. *Distal subungual onychomycosis* involves foci of onycholysis under the distal nail plate or along the lateral nail groove, followed by development of hyperkeratosis and yellow-brown discoloration. The process extends proximally, resulting in nail plate thickening,

Figure 663-9 Discoloration, hyperkeratosis, and crumbling of nail secondary to dermatophyte infection.

Figure 663-10 Acute paronychia secondary to *Staphylococcus aureus*.

crumbling (Fig. 663-9), and separation from the nail bed. *Trichophyton rubrum* and, occasionally, *T. mentagrophytes* infect the toenails; fingernail disease is almost exclusively caused by *T. rubrum,* which may be associated with superficial scaling of the plantar surface of the feet and often of one hand. The dermatophytes are found most readily at the most proximal area of the nail bed or adjacent ventral portion of the involved nail plates. **Topical therapies** such as ciclopirox 8% lacquer or amorolfine 5% lacquer, may be effective for solitary nail infection. Topical efinaconazole 10% may also be effective; laser treatment is an expensive but safe alternative to oral therapy. Because of its long half-life in the nail, oral itraconazole may be effective when given as pulse therapy (1 wk of each month for 3-4 mo). Dosage is weight dependent. Oral daily terbinafine is also quite effective. Either agent is superior to griseofulvin, fluconazole, or ketoconazole. The risks, the most concerning of which is hepatic toxicity, and costs of oral therapy are minimized with the use of pulsed dosing.

Proximal white subungual onychomycosis occurs when the organism, generally *T. rubrum,* enters the nail through the proximal nail fold, producing yellow-white portions of the undersurface of the nail plate. The surface of the nail is unaffected. This occurs almost exclusively in immunocompromised patients and is a well-recognized manifestation of AIDS. Treatment includes oral terbinafine or itraconazole.

Candidal onychomycosis involves the entire nail plate in patients with chronic mucocutaneous candidiasis. It is also commonly seen in patients with AIDS. The organism, generally *Candida albicans,* enters distally or along the lateral nail folds, rapidly involves the entire thickness of the nail plate, and produces thickening, crumbling, and deformity of the plate. Topical azole antifungal agents may be sufficient for treatment of candidal onychomycosis in an immunocompetent host, but oral antifungal agents are necessary for treatment of patients with immune deficiencies. Table 663-3 outlines the differential diagnosis of onychomycosis.

PARONYCHIAL INFLAMMATION

Paronychial inflammation may be acute or chronic and generally involves 1 or 2 nail folds on the fingers. **Acute paronychia** manifests as erythema, warmth, edema, and tenderness of the proximal nail fold, most commonly as a result of pathogenic staphylococci, streptococci, or candidal (Fig. 663-10). Warm soaks and oral agents are generally effective; incision and drainage may be occasionally necessary. Development of chronic paronychia follows prolonged immersion in water (Fig. 663-11), such as occurs in finger or thumb sucking, exposure to irritating solutions, nail fold trauma, or diseases, including Raynaud phenomenon, collagen vascular diseases, and diabetes. Swelling of the proximal nail fold is followed by separation of the nail fold from the underlying nail plate and suppuration. Foreign material, embedded in the dermis of the nail fold, becomes a nidus for inflammation and infection with *Candida* species and mixed bacterial flora. A combination of attention to predisposing factors, meticulous drying of the hands, and long-term topical antifungal agents and topical potent corticosteroids may be required for successful treatment of chronic paronychia.

Table 663-3	Differential Diagnosis of Onychomycosis
Psoriasis • As in onychomycosis: onycholysis, subungual hyperkeratosis, splinter hemorrhages, leuconychia, dystrophy • Pitting • Oil drop sign (a translucent yellow-red discoloration seen in the nail bed) • Other cutaneous features of psoriasis, family history of psoriasis Lichen planus • Cutaneous disease at other sites • Thin nail plate and ridging • Dorsal pterygium—scarring at proximal aspect of nail Trauma • Nail plate can appear abnormal • Nail bed should be normal • Distal onycholysis with repeated trauma • Single nail affected, shape of nail changed, homogenous alteration of nail color Eczema • Irregular buckled nails with ridging • Cutaneous signs of eczema Yellow nail syndrome • Nail plate is discolored green-yellow • Nails are hard with elevated longitudinal curvature • Nails may be shed, painful • Associations with bronchiectasis, lymphoedema, and chronic sinusitis Lamellar onychoschizia (lamellar splitting) • History of repeated soaking in water • Usually distal portion of nail Periungual squamous cell carcinoma/Bowens disease • Single nail, warty changes of nail fold, ooze from edge of nail Malignant melanoma • Black discoloration of nail plate or nail bed • Pigment can extend onto nail fold • Can get associated bleeding Myxoid (mucous) cyst • Cyst at base of nail, groove in nail extending length of nail Alopecia areata • Pits, longitudinal ridging, brittleness • Hair loss	

From Eisman S, Sinclair R: Fungal nail infection: diagnosis and management. BMJ 348:g1800, 2014.

Ingrown nail occurs when the lateral edge of the nail, including spicules that have separated from the nail plate, penetrates the soft

Figure 663-11 Chronic paronychia with erythema and lateral nail fold separation.

tissue of the lateral nail fold. Erythema, edema, and pain, most often involving the lateral great toes, are noted acutely; recurrent episodes may lead to formation of granulation tissue. Predisposing factors include (1) congenital malalignment (especially of the great toes); (2) compression of the side of the toe from poorly fitting shoes, particularly if the great toes are abnormally long and the lateral nail folds are prominent; and (3) improper cutting of the nail in a curvilinear manner rather than straight across. **Management** includes proper fitting of shoes; allowing the nail to grow out beyond the free edge before cutting it straight across; warm water soaks; oral antibiotics if cellulitis affects the lateral nail fold; and, in severe, recurrent cases, application of silver nitrate to granulation tissue, nail avulsion, or excision of the lateral aspect of the nail followed by matricectomy.

PARONYCHIAL TUMORS

Tumors in the paronychial area include pyogenic granulomas, mucous cysts, subungual exostoses, and junctional nevi. Periungual fibromas that appear in late childhood should suggest a diagnosis of tuberous sclerosis.

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Chapter 664

Disorders of the Mucous Membranes

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The mucous membranes may be involved in developmental disorders, genodermatoses, infections, acute and chronic skin diseases, or benign and malignant tumors.

ANGULAR CHEILITIS

Angular cheilitis (perlèche) is characterized by inflammation and fissuring at the corners of the mouth, often with associated erosion, maceration, and crusting (Fig. 664-1). Chapping or moisture collection at the angles of the mouth predispose children to developing angular cheilitis. Children who are chronic lip lickers or who have excessive salivation or drooling related to neurologic deficits, orthodontic appliances, or mouth breathing are at increased risk. Atopic dermatitis or contact dermatitis related to toothpaste, chewing gum, mouthwash, or cosmetics are also common causes. Nutritional deficiencies are a less-frequent etiology. Protection can be provided by frequent application of a bland ointment such as petrolatum. Candidosis should be treated with an appropriate antifungal agent, and contact dermatitis of the perioral skin should be treated with a low-potency topical corticosteroid ointment preparation and frequent use of petrolatum or a similar emollient. Correction of the underlying predisposing factors (if possible) will prevent recurrence.

Figure 664-1 Angular cheilitis.

Figure 664-2 Aphthous ulceration on lower lip.

APHTHOUS STOMATITIS (CANKER SORES)

Aphthous stomatitis consists of solitary or multiple painful ulcerations occur on the labial (Fig. 664-2), buccal, lingual, sublingual, palatal, or gingival mucosa (see Chapter 315). Lesions may manifest initially as erythematous, indurated papules that erode rapidly to form sharply circumscribed, necrotic ulcers with a gray fibrinous exudate and an erythematous halo. Minor aphthous ulcers are 2-10 mm in diameter and heal spontaneously in 7-10 days. Major aphthous ulcers are >10 mm in diameter, take from 10-30 days to heal, and may heal with scarring. A third type of aphthous ulceration is herpetiform in appearance, manifesting as a few to numerous grouped 1-2 mm lesions which tend to coalesce into plaques and heal over 7-10 days. Approximately 30% of patients with recurrent lesions have a family history of the disorder (see Chapter 315 for the differential diagnosis).

The etiology of aphthous stomatitis is multifactorial; the condition probably represents an oral manifestation of a number of conditions. Altered local regulation of the cell-mediated immune system, after activation and accumulation of cytotoxic T cells, may contribute to the

localized mucosal breakdown. It is a common misconception that aphthous stomatitis is a manifestation of herpes simplex virus infection. Recurrent herpes infections remain localized to the lips and rarely cross the mucocutaneous junction; involvement of the oral mucosa occurs only in primary infections.

Treatment of aphthous stomatitis is palliative. The majority of mild cases do not require therapy. Relief of pain, particularly before eating, may be achieved with the use of a topical anesthetic such as viscous lidocaine or an oral rinse with a combined solution of elixir of diphenhydramine, viscous lidocaine, and an oral antacid. Caution must be taken to avoid hot food and drink after topical anesthetic use. A superpotent topical corticosteroid in a mucosa-adhering agent may help reduce inflammation, and topical tetracycline mouthwash may also hasten healing. In severe, debilitating cases, systemic therapy with corticosteroids, colchicine, dapsone, or thalidomide may be helpful.

FORDYCE SPOTS

Fordyce spots (Fordyce granules) are asymptomatic, 1-3 mm, yellow-white macules and papules on the vermilion lips and buccal mucosa. They are a common clinical finding and represent a normal anatomic variant of sebaceous glands. They can present in either sex from infancy to adulthood and may become more prominent during puberty due to the influence of androgens. No therapy is required.

EPSTEIN PEARLS (GINGIVAL CYSTS OF THE NEWBORN)

Epstein pearls are white, keratin-containing cysts on the palatal or alveolar mucosa of approximately 80% of neonates. They are epidermal inclusion cysts that form when the soft and hard palates fuse and are analogous to facial milia. They cause no symptoms and are generally shed within a few weeks; no therapy is necessary.

MUCOCELE

Mucus retention cysts are painless, fluctuant, tense, 2-10 mm, bluish papules on the lips (Fig. 664-3), tongue, palate, or buccal mucosa. Traumatic severance of the duct of a minor salivary gland leads to submucosal retention of mucus secretion. Lesions on the floor of the mouth are known as ranulas when the sublingual or submandibular salivary gland ducts are involved. Fluctuations in size are typical, and the lesions may disappear temporarily after traumatic rupture. Recurrence is prevented by surgical excision of the mucus deposit and associated salivary gland(s).

FISSURED TONGUE

Fissured tongue (scrotal tongue, or lingua plicata) is a common benign developmental anomaly of the tongue. The dorsal tongue has many folds with deep grooves and a pebbled appearance. Fissured tongue can be seen in individuals with Melkersson-Rosenthal syndrome and Down syndrome, and it is often seen in association with geographic tongue. Food particles and debris may become trapped in the fissures, resulting in irritation, inflammation, and halitosis. Careful cleansing with a mouth rinse and soft-bristled toothbrush is recommended.

GEOGRAPHIC TONGUE (BENIGN MIGRATORY GLOSSITIS)

Geographic tongue consists of single or multiple sharply demarcated, irregular, smooth red patches surrounded by an elevated yellowish-white serpiginous border on the dorsum of the tongue. Onset is rapid, and the pattern may change over hours to days. The smooth patches correspond to atrophic filiform papillae, and the elevated margins represent hypertrophic papillae (Fig. 664-4). The etiology of this condition remains unclear. Lesions are typically asymptomatic, but some patients may experience a burning sensation or sensitivity to spicy, hot, or cold foods. No therapy other than reassurance is necessary.

BLACK HAIRY TONGUE

Black hairy tongue is a dark coating on the dorsum of the tongue caused by hyperplasia and elongation of the filiform papillae; overgrowth of chromogenic bacteria and fungi and entrapped pigmented residues that adsorb to microbial plaque and desquamating keratin may contribute to the dark coloration. Changes often begin posteriorly and extend anteriorly on the dorsum of the tongue. The condition is most common in adults but may also manifest during adolescence. Poor oral hygiene, lack of oral feeding, treatment with systemic antibiotics such as tetracycline (which promote the growth of *Candida* spp.), and smoking are predisposing factors. Improved oral hygiene and brushing with a soft-bristled toothbrush may be all that is necessary for treatment.

ORAL HAIRY LEUKOPLAKIA

Oral hair leukoplakia occurs in approximately 25% of patients with AIDS but is rare in the pediatric population. It manifests as corrugated and shaggy white plaques on the lateral margins of the tongue which cannot be removed by rubbing. The lesions occasionally may spread to the ventral tongue surface, floor of the mouth, tonsillar pillars, and pharynx. The condition is caused by Epstein-Barr virus, which is present in the upper layer of the affected epithelium. The plaques have no malignant potential. The disorder occurs predominantly in HIV-infected patients but may also be found in individuals who are immunosuppressed for other reasons, such as organ transplantation, leukemia, chemotherapy, and long-term use of inhaled steroids. The condition is generally asymptomatic and does not require therapy.

ACUTE NECROTIZING ULCERATIVE GINGIVITIS (VINCENT STOMATITIS, FUSOSPIROCHETAL GINGIVITIS, TRENCH MOUTH)

Acute necrotizing ulcerative gingivitis manifests as painful punched-out ulceration, necrosis, and bleeding of the interdental papillae. A

Figure 664-3 Mucocele on lower lip.

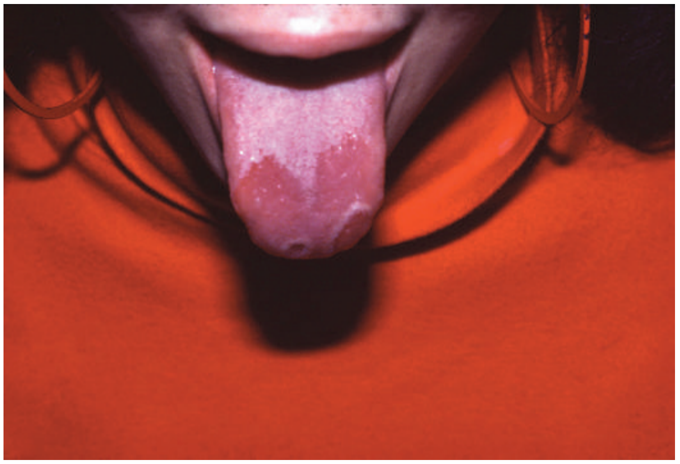

Figure 664-4 Geographic tongue.

grayish white pseudomembrane may cover the ulcerations. Lesions may spread to involve the buccal mucosa, lips, tongue, tonsils, and pharynx and may be associated with dental pain, a bad taste, low-grade fever, and lymphadenopathy. It occurs most commonly in the 2nd or 3rd decade, particularly in the context of poor dental hygiene, poor nutrition, smoking, and stress.

NOMA

Noma is a severe form of fusospirillary gangrenous stomatitis that occurs primarily in malnourished, impoverished children 2-5 yr of age who have had a preceding illness such as measles, scarlet fever, tuberculosis, malignancy, or immunodeficiency. The disease is most prevalent in Africa, but also occurs in Asia and Latin America. Sporadic cases associated with immunodeficiency have been reported in developed countries. It manifests as a painful, red, indurated papule on the alveolar margin, followed by ulceration and mutilating gangrenous destruction of tissue in the oronasal region. The process may also involve the scalp, neck, shoulders, perineum, and vulva. Noma neonatorum manifests in the 1st mo of life as gangrenous lesions of the lips, nose, mouth, and anal regions. Affected infants are usually small for gestational age, malnourished, premature, and frequently ill (particularly with *Pseudomonas aeruginosa* sepsis). Care consists of nutritional support, conservative debridement of necrotic soft tissues, empirical broad-spectrum antibiotics such as penicillin and metronidazole, and, in the case of noma neonatorum, antipseudomonal antibiotics (see Chapter 46).

COWDEN SYNDROME (MULTIPLE HAMARTOMA SYNDROME)

Cowden syndrome is an autosomal dominant condition caused by loss-of-function mutations in the *PTEN* tumor-suppressor gene. Mucocutaneous lesions typically appear in the 2nd or 3rd decade. Oral papillomas are 1-3 mm smooth, pink or whitish papules on the palatal, gingival, buccal, and labial mucosae and may coalesce into a cobblestone appearance. Numerous flesh-colored papules also develop on the face, particularly around the mouth, nose, and ears. These papules are most commonly trichilemmomas, a benign neoplasm of the hair follicle. Associated findings may include acral keratoses, thyroid adenoma, goiter, gastrointestinal polyps, fibrocystic breast nodules, and carcinoma of the breast or thyroid.

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Chapter 665

Cutaneous Bacterial Infections

665.1 Impetigo

Anna M. Juern and Beth A. Drolet

ETIOLOGY/PATHOGENESIS

Impetigo is the most common skin infection in children throughout the world. There are 2 classic forms of impetigo: nonbullous and bullous.

Staphylococcus aureus is the predominant organism of nonbullous impetigo in the United States; group A β-hemolytic streptococci (GABHS) are implicated in the development of some lesions. The staphylococcal types that cause nonbullous impetigo are variable but are not generally from phage group 2, the group that is associated with scalded skin and toxic shock syndromes. Staphylococci generally spread from the nose to normal skin and then infect the skin. In contrast, the skin becomes colonized with GABHS an average of 10 days before development of impetigo. The skin serves as the source for acquisition of GABHS and the probable primary source for spread of impetigo. Lesions of nonbullous impetigo that grow staphylococci in culture cannot be distinguished clinically from those that grow pure cultures of GABHS.

Bullous impetigo is always caused by *S. aureus* strains that produce exfoliative toxins. The staphylococcal exfoliative toxins (ETA, ETB, ETD) blister the superficial epidermis by hydrolyzing human desmoglein 1, resulting in a subcorneal vesicle. This is also the target antigen of the autoantibodies in pemphigus foliaceus (see Chapters 181 and 183).

CLINICAL MANIFESTATIONS

Nonbullous Impetigo

Nonbullous impetigo accounts for more than 70% of cases. Lesions typically begin on the skin of the face or on extremities that have been traumatized. The most common lesions that precede nonbullous impetigo are insect bites, abrasions, lacerations, chickenpox, scabies pediculosis, and burns. A tiny vesicle or pustule forms initially and rapidly develops into a honey-colored crusted plaque that is generally <2 cm in diameter (Fig. 665-1). The infection may be spread to other parts of the body by the fingers, clothing, and towels. Lesions are associated with little to no pain or surrounding erythema, and constitutional symptoms are generally absent. Pruritus occurs occasionally, regional adenopathy is found in up to 90% of cases, and leukocytosis is present in approximately 50%.

Bullous Impetigo

Bullous impetigo is mainly an infection of infants and young children. Flaccid, transparent bullae develop most commonly on skin of the face, buttocks, trunk, perineum, and extremities. **Neonatal bullous impetigo** can begin in the diaper area. Rupture of a bulla occurs easily, leaving a narrow rim of scale at the edge of shallow, moist erosion. Surrounding erythema and regional adenopathy are generally absent. Unlike those of nonbullous impetigo, lesions of bullous impetigo are a manifestation of localized staphylococcal scalded skin syndrome and develop on intact skin.

Differential Diagnosis

The differential diagnosis of **nonbullous impetigo** includes viruses (herpes simplex, varicella-zoster), fungi (tinea corporis, kerion),

Figure 665-1 Multiple crusted and oozing lesions of impetigo.

arthropod bites, and parasitic infestations (scabies, pediculosis capitis), all of which may become impetiginized.

The differential diagnosis of **bullous impetigo** in neonates includes epidermolysis bullosa, bullous mastocytosis, herpetic infection, and early scalded skin syndrome. In older children, allergic contact dermatitis, burns, erythema multiforme, linear immunoglobulin A dermatosis, pemphigus, and bullous pemphigoid must be considered, particularly if the lesions do not respond to therapy.

COMPLICATIONS

Potential but very rare complications of either nonbullous or bullous impetigo include osteomyelitis, septic arthritis, pneumonia, and septicemia. Positive blood culture results are very rare in otherwise healthy children with localized lesions. Cellulitis has been reported in up to 10% of patients with nonbullous impetigo and rarely follows the bullous form. Lymphangitis, suppurative lymphadenitis, guttate psoriasis, and scarlet fever occasionally follow streptococcal disease. There is no correlation between number of lesions and clinical involvement of the lymphatics or development of cellulitis in association with streptococcal impetigo.

Infection with nephritogenic strains of GABHS may result in **acute poststreptococcal glomerulonephritis** (see Chapter 511.1). The clinical character of impetigo lesions is not predictive of the development of poststreptococcal glomerulonephritis. The most commonly affected age group is children 3-7 yr of age. The latent period from onset of impetigo to development of poststreptococcal glomerulonephritis averages 18-21 days, which is longer than the 10-day latency period after pharyngitis. Poststreptococcal glomerulonephritis occurs epidemically after either pharyngeal or skin infection. Impetigo-associated epidemics have been caused by M groups 2, 49, 53, 55, 56, 57, and 60. Strains of GABHS that are associated with endemic impetigo in the United States have little or no nephritogenic potential. Acute rheumatic fever does not occur as a result of impetigo.

TREATMENT

The decision on how to treat impetigo depends on the number of lesions and their locations. Topical therapy with mupirocin 2%, and retapamulin 1% 2-3 times a day for 10-14 days is acceptable for localized disease caused by *S. aureus.*

Systemic therapy with oral antibiotics should be prescribed for patients with streptococcal or widespread involvement of staphylococcal infections; when lesions are near the mouth, where topical medication may be licked off; or in cases with evidence of deep involvement, including cellulitis, furunculosis, abscess formation, or suppurative lymphadenitis. Cephalexin, 25-50 mg/kg/day in 3-4 divided doses for 7-10 days, is an excellent choice for initial therapy. No evidence suggests that a 10-day course of therapy is superior to a 7-day course. The emergence of methicillin-resistant *S. aureus* (MRSA) dictates that if a satisfactory clinical response is not achieved within 7 days, a culture should be performed and an appropriate antibiotic based on drug sensitivity should be given for an additional 7 days. If MRSA is suspected, clindamycin, doxycycline or sulfamethoxazole-trimethoprim is indicated.

Bibliography is available at Expert Consult.

665.2 Subcutaneous Tissue Infections

Anna M. Juern and Beth A. Drolet

The principal determinations for soft-tissue infections is whether it is *nonnecrotizing* or *necrotizing,* as well as *purulent* or *nonpurulent* (see Fig. 665-1). The former responds to antibiotic therapy alone, whereas the latter requires prompt surgical removal of all devitalized tissue in addition to antimicrobial therapy. Necrotizing soft-tissue infections are life-threatening conditions that are characterized by rapidly advancing local tissue destruction and systemic toxicity. Tissue necrosis distinguishes them from cellulitis. In cellulitis, an inflammatory infectious process involves subcutaneous tissue but does not destroy it. Necrotizing soft-tissue infections characteristically manifest with a paucity of early cutaneous signs relative to the rapidity and degree of destruction of the subcutaneous tissues.

CELLULITIS

Etiology

Cellulitis is characterized by infection and inflammation of loose connective tissue, with limited involvement of the dermis and relative sparing of the epidermis. A break in the skin from previous trauma, surgery, or an underlying skin lesion predisposes to cellulitis. Cellulitis is also more common in individuals with lymphatic stasis, diabetes mellitus, or immunosuppression.

Streptococcus pyogenes (group A streptococcus) and *S. aureus* are the most common etiologic agents. In patients who are immunocompromised or have diabetes mellitus, a number of other bacterial or fungal agents may be involved, notably *Pseudomonas aeruginosa; Aeromonas hydrophila* and, occasionally, other Enterobacteriaceae; *Legionella* spp.; the Mucorales, particularly *Rhizopus* spp., *Mucor* spp., and *Absidia* spp.; and *Cryptococcus neoformans.* Children with relapsed nephrotic syndrome may experience cellulitis caused by *Escherichia coli.* In children age 3 mo to 5 yr, *Haemophilus influenzae* type b was once an important cause of facial cellulitis, but its incidence has declined significantly since the institution of immunization against this organism.

Clinical Manifestations

Cellulitis manifests clinically as an area of edema, warmth, erythema, and tenderness. The lateral margins tend to be indistinct because the process is deep in the skin, primarily involving the subcutaneous tissues in addition to the dermis. Application of pressure may produce pitting. Although distinction cannot be made with certainty in any particular patient, cellulitis due to *S. aureus* tends to be more localized and may suppurate, whereas infections caused by *S. pyogenes* (group A streptococci) tend to spread more rapidly and may be associated with lymphangitis. Regional adenopathy and constitutional signs and symptoms such as fever, chills, and malaise are common. Complications of cellulitis are uncommon but include subcutaneous abscess, bacteremia, osteomyelitis, septic arthritis, thrombophlebitis, endocarditis, and necrotizing fasciitis. Lymphangitis or glomerulonephritis can also follow infection with *S. pyogenes.*

Diagnosis

Aspirates from the site of inflammation, skin biopsy, and blood cultures allow identification of the causal organism in approximately 25% of cases of cellulitis. Blood cultures are usually negative in immunocompetent patients with mild to moderate infection. Yield of the causative organism is approximately 30% when the site of origin of the cellulitis is apparent, such as an abrasion or ulcer. An aspirate taken from the point of maximum inflammation yields the causal organism more often than a leading-edge aspirate. Lack of success in isolating an organism stems primarily from the low number of organisms present within the lesion. *Ultrasonography is used if an associated subcutaneous abscess is suspected.*

The differential diagnosis should include an exuberant immune-allergic reaction to insect bites particularly mosquito bites (Skeeter syndromes) (see Chapter 146). The skeeter syndrome is characterized by swelling disproportionate to erythremia; there is pruritus but usually no tenderness. In addition, cold panniculitis may appear as an erythematous but usually nontender swelling after exposure to cold, such as sledding or eating a cold Popsicle (see Chapter 660.1).

Treatment

Empirical therapy for cellulitis should be directed by the history of the illness, the location and severity of the cellulitis, and the age and immune status of the patient (Fig. 665-2). Cellulitis in a neonate should prompt a full sepsis evaluation, followed by initiation of empirical intravenous therapy with a β-lactamase–stable antistaphylococcal antibiotic such as methicillin or vancomycin and an aminoglycoside such as gentamicin or a cephalosporin such as cefotaxime. Treatment of

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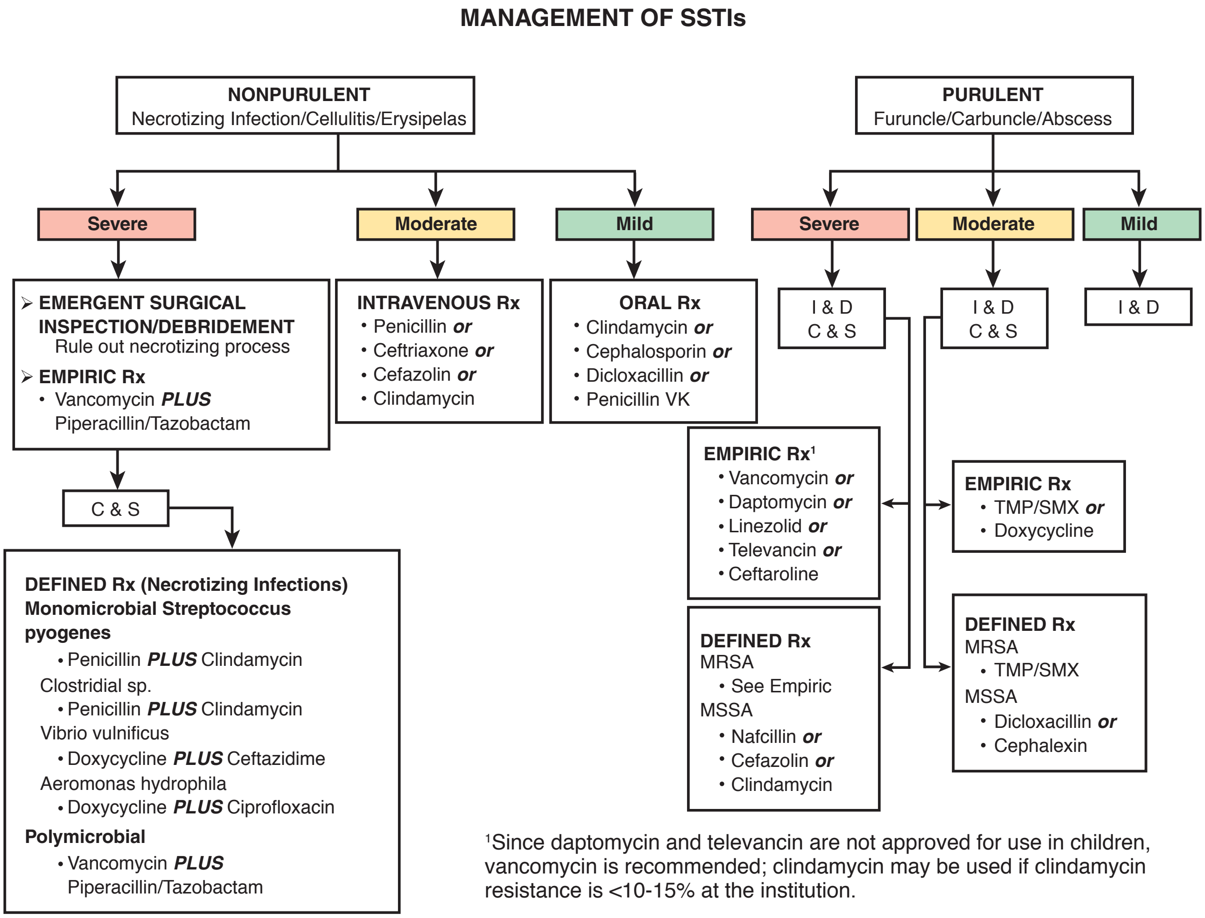

Figure 665-2 Purulent skin and soft-tissue infections (SSTIs)—*Mild infection:* For purulent SSTI, incision and drainage is indicated. *Moderate infection:* Patients with purulent infection with systemic signs of infection. *Severe infection:* Patients who have failed incision and drainage plus oral antibiotics or those with systemic signs of infection such as temperature >38°C (100.4°F), tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >24 breaths/min) or abnormal white blood cell count (<12,000 or <400 cells/µL), or immunocompromised patients. **Nonpurulent SSTIs**—*Mild infection:* Typical cellulitis/erysipelas with no focus of purulence. *Moderate infection:* Typical cellulitis/erysipelas with systemic signs of infection. *Severe infection:* Patients who have failed oral antibiotic treatment or those with systemic signs of infection (as defined above under purulent infection), or those who are immunocompromised, or those with clinical signs of deeper infection such as bullae, skin sloughing, hypotension, or evidence of organ dysfunction. Three newer agents, oritavancin, tedizolid, and dalbavancin, are also effective agents in SSTIs, including those caused by methicillin-resistant *Staphylococcus aureus. C & S,* culture and sensitivity; *I & D,* incision and drainage; *MRSA,* methicillin-resistant *Staphylococcus aureus; MSSA,* methicillin-susceptible *Staphylococcus aureus; Rx,* treatment; *TMP/SMX,* trimethoprim-sulfamethoxazole. *(Modified from Stevens DL, Bisno AL, Chambers HF, et al: Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America.* Clin Infect Dis *59:147–159, 2014, Fig. 1.)*

cellulitis in an infant or child younger than about 5 yr of age should provide coverage for *S. pyogenes* and *S. aureus* as well as *H. influenzae* type b and *Streptococcus pneumoniae.* The evaluation should include a blood culture, and if the infant is younger than 1 yr of age, if signs of systemic toxicity are present, or if an adequate examination cannot be carried out, a lumbar puncture should also be performed. In most cases of cellulitis on an extremity, regardless of age, *S. aureus* and *S. pyogenes* are the cause and bacteremia is highly unlikely in an otherwise well-appearing child. Blood cultures should be performed if sepsis is suspected.

If fever, lymphadenopathy, and other constitutional signs are absent (white blood cell count <15,000), treatment of cellulitis on an extremity may be initiated orally on an outpatient basis with a penicillinase-resistant penicillin such as dicloxacillin or cloxacillin or a first-generation cephalosporin such as cephalexin or, if MRSA is suspected, with clindamycin. If improvement is not noted or the disease progresses significantly in the 1st 24-48 hr of therapy, parenteral therapy is necessary. If fever, lymphadenopathy, or constitutional signs are present, parenteral therapy should be initiated. Oxacillin or nafcillin is effective in most cases, although if systemic toxicity is significant, consideration should be given to the addition of clindamycin or vancomycin. Three new agents for skin and skin structure infections have been approved by the FDA in adults. Dalbavancin (intravenous given once weekly; active against MRSA; *S. pyogenes*, and vancomycin-resistant enterococcus and *S. aureus*), tedizolid (oral or IV given bid, active against MRSA, *S. pyogenes*, coagulase-negative *Staphylococcus*), and oritavancin (IV; active against MRSA, *S. pyogenes*). Once the erythema, warmth, edema, and fever have decreased significantly, a 10-day course of treatment may be completed on an outpatient basis. Immobilization and elevation of an affected limb, particularly early in the course of therapy, may help reduce swelling and pain. *If present, a subcutaneous abscess should be drained.*

NECROTIZING FASCIITIS

Etiology

Necrotizing fasciitis is a subcutaneous tissue infection that involves the deep layer of superficial fascia but may spare adjacent epidermis, deep fascia, and muscle.

Relatively few organisms possess sufficient virulence to cause necrotizing fasciitis when acting alone. The majority (55-75%) of cases of necrotizing fasciitis are polymicrobial in nature (synergistic necrotizing fasciitis), with an average of 4 different organisms isolated. The

organisms most commonly isolated in polymicrobial necrotizing fasciitis are *S. aureus*, streptococcal species, *Klebsiella* species, *E. coli,* and anaerobic bacteria.

The rest of the cases and the most fulminant infections, associated with toxic shock syndrome and a high case fatality rate, are usually caused by *S. pyogenes* (group A streptococcus) (see Chapter 183). Streptococcal necrotizing fasciitis may occur in the absence of toxic shock–like syndrome and is potentially fatal and associated with substantial morbidity. Necrotizing fasciitis can occasionally be caused by *S. aureus; Clostridium perfringens; Clostridium septicum; P. aeruginosa; Vibrio* spp., particularly *Vibrio vulnificus;* and fungi of the order Mucorales, particularly *Rhizopus* spp., *Mucor* spp., and *Absidia* spp. Necrotizing fasciitis has also been reported, on rare occasions, to result from non–group A streptococci such as group B, C, F, or G streptococci, *S. pneumoniae,* or *H. influenzae* type b.

Infections caused by any 1 organism or combination of organisms cannot be distinguished clinically from one another, although development of **crepitans** signals the presence of *Clostridium* spp. or Gram-negative bacilli such as *E. coli, Klebsiella, Proteus,* or *Aeromonas.*

Clinical Manifestations

Necrotizing fasciitis may occur anywhere on the body. Polymicrobial infections tend to occur on perineal and trunk areas. The incidence of necrotizing fasciitis is highest in hosts with systemic or local tissue immunocompromise, such as those with diabetes mellitus, neoplasia, or peripheral vascular disease as well as those who have recently undergone surgery, who abuse intravenous drugs, or who are undergoing immunosuppressive treatment, particularly with corticosteroids. The infection can also occur in healthy individuals after minor puncture wounds, abrasions, or lacerations; blunt trauma; surgical procedures, particularly of the abdomen, gastrointestinal or genitourinary tracts, or the perineum; or hypodermic needle injection.

There has been a resurgence of fulminant necrotizing soft-tissue infections caused by *S. pyogenes,* which may occur in previously healthy individuals. Streptococcal necrotizing fasciitis is classically located on an extremity. There may be a history of recent trauma to or operation in the area. Necrotizing fasciitis due to *S. pyogenes* may also occur after superinfection of varicella lesions. Children with this disease have tended to display onset, recrudescence, or persistence of high fever and signs of toxicity after the 3rd or 4th day of varicella. Common predisposing conditions in neonates are omphalitis and balanitis after circumcision.

Necrotizing fasciitis begins with acute onset of local, and at times tense, edema, erythema, tenderness, and heat. Fever is usually present, and pain, tenderness, and constitutional signs are disproportionate to cutaneous signs, especially with involvement of fascia and muscle. Lymphangitis and lymphadenitis may or may not be present. The infection advances along the superficial fascial plane, and initially there are few cutaneous signs to herald the serious nature and extent of the subcutaneous tissue necrosis that is occurring. Skin changes may appear over 24-48 hr as nutrient vessels are thrombosed and cutaneous ischemia develops. Early clinical findings include ill-defined cutaneous erythema and edema that extends beyond the area of erythema. Additional signs include formation of bullae filled initially with straw-colored and later bluish to hemorrhagic fluid, and darkening of affected tissues from red to purple to blue. Skin anesthesia and, finally, frank tissue gangrene and slough develop owing to the ischemia and necrosis. Vesiculation or bulla formation, ecchymoses, crepitus, anesthesia, and necrosis are ominous signs indicative of advanced disease. Children with varicella lesions may initially show no cutaneous signs of superinfection with invasive *S. pyogenes,* such as erythema or swelling. Significant systemic toxicity may accompany necrotizing fasciitis, including shock, organ failure, and death. Advance of the infection in this setting can be rapid, progressing to death within hours. Patients with involvement of the superficial or deep fascia and muscle tend to be more acutely and systemically ill and have more rapidly advancing disease than those with infection confined solely to subcutaneous tissues above the fascia. In an extremity, a **compartment syndrome** may develop, manifesting as tight edema, pain on motion, and loss of distal sensation and pulses; this is a surgical emergency.

Diagnosis

Definitive diagnosis of necrotizing fasciitis is made by surgical exploration, which should be undertaken as soon as the diagnosis is suspected. Necrotic fascia and subcutaneous tissue are gray and offer little resistance to blunt probing. Although CT and MRI aids in delineating the extent and tissue planes of involvement, this procedure should not delay surgical intervention. Frozen-section incisional biopsy specimens obtained early in the course of the infection can aid management by decreasing the time to diagnosis and helping establish margins of involvement. Gram staining of tissue can be particularly useful if chains of Gram-positive cocci, indicative of infection with *S. pyogenes,* are seen.

Treatment

Early supportive care, surgical debridement, and parenteral antibiotic administration are mandatory for necrotizing fasciitis. All devitalized tissue should be removed to freely bleeding edges, and repeat exploration is generally indicated within 24-36 hr to confirm that no necrotic tissue remains. This procedure may need to be repeated on several occasions until devitalized tissue has ceased to form. Meticulous daily wound care is also paramount.

Parenteral antibiotic therapy should be initiated as soon as possible with broad-spectrum agents against all potential pathogens. Initial empirical therapy should be instituted with vancomycin, linezolid, daptomycin, or quinupristin to cover Gram-positive and piperacillin-tazobactam to cover Gram-negative organisms. An alternative is to add ceftriaxone with metronidazole to cover mixed aerobic–anaerobic organisms. Therapy should then be based on sensitivity of isolated organisms. Penicillin with clindamycin is indicated for documented group A streptococcal necrotizing fasciitis. Some centers employ hyperbaric oxygen therapy, although it should not delay resuscitation or surgical debridement.

Prognosis

The combined case fatality rate among children and adults with necrotizing fasciitis and syndrome due to polymicrobial infection or *S. pyogenes* has been as high as 60%. Death is less common in children, however, and in cases not complicated by toxic shock–like syndrome.

Bibliography is available at Expert Consult.

665.3 Staphylococcal Scalded Skin Syndrome (Ritter Disease)

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ETIOLOGY AND PATHOGENESIS

Staphylococcal scalded skin syndrome is caused predominantly by phage group 2 staphylococci, particularly strains 71 and 55, which are present at localized sites of infection. Foci of infection include the nasopharynx and, less commonly, the umbilicus, urinary tract, a superficial abrasion, conjunctivae, and blood. The clinical manifestations of staphylococcal scalded skin syndrome are mediated by hematogenous spread, in the absence of specific antitoxin antibody of staphylococcal epidermolytic or exfoliative toxins A or B. The toxins have reproduced the disease in both animal models and human volunteers. Decreased renal clearance of the toxins may account for the fact that the disease is most common in infants and young children, as well as lack of protection from antitoxin antibodies. Epidermolytic toxin A is heat stable and is encoded by bacterial chromosomal genes. Epidermolytic toxin B is heat labile and is encoded on a 37.5-kb plasmid. The site of blister cleavage is subcorneal. The epidermolytic toxins produce the split by binding to and cleaving desmoglein 1. Intact bullae are consistently

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Figure 665-3 Nikolsky sign. With slight thumb pressure the skin wrinkles, slides laterally, and separates from the dermis. *(From Habif TP, editor:* Clinical dermatology*, ed 4, Philadelphia, 2004, Mosby.)*

sterile, unlike those of bullous impetigo, but culture specimens should be obtained from all suspected sites of localized infection and from the blood to identify the source for elaboration of the epidermolytic toxins.

CLINICAL MANIFESTATIONS

Staphylococcal scalded skin syndrome, which occurs predominantly in infants and children younger than 5 yr of age, includes a range of disease from localized bullous impetigo to generalized cutaneous involvement with systemic illness. Onset of the rash may be preceded by malaise, fever, irritability, and exquisite tenderness of the skin. **Scarlatiniform erythema** develops diffusely and is accentuated in flexural and periorificial areas. The conjunctivae are inflamed and occasionally become purulent. The brightly erythematous skin may rapidly acquire a wrinkled appearance, and in severe cases, sterile, flaccid blisters and erosions develop diffusely. Circumoral erythema is characteristically prominent, as is radial crusting and fissuring around the eyes, mouth, and nose. At this stage, areas of epidermis may separate in response to gentle shear force (Nikolsky sign; Fig. 665-3). As large sheets of epidermis peel away, moist, glistening, denuded areas become apparent, initially in the flexures and subsequently over much of the body surface (Fig. 665-4). This development may lead to secondary cutaneous infection, sepsis, and fluid and electrolyte disturbances. The desquamative phase begins after 2-5 days of cutaneous erythema; healing occurs without scarring in 10-14 days. Patients may have pharyngitis, conjunctivitis, and superficial erosions of the lips, but intraoral mucosal surfaces are spared. Although some patients appear ill, many are reasonably comfortable except for the marked skin tenderness.

DIFFERENTIAL DIAGNOSIS

A presumed **abortive** form of the disease manifests as diffuse, scarlatiniform, tender erythroderma that is accentuated in the flexural areas but does not progress to blister formation. In patients with this form, Nikolsky sign may be absent. Although the exanthem is similar to that of streptococcal scarlet fever, strawberry tongue and palatal petechiae are absent. Staphylococcal scalded skin syndrome may be mistaken for a number of other blistering and exfoliating disorders, including bullous impetigo, epidermolysis bullosa, epidermolytic hyperkeratosis, pemphigus, drug eruption, erythema multiforme, and drug-induced toxic epidermal necrolysis. Toxic epidermal necrolysis can often be distinguished by a history of drug ingestion, the presence of Nikolsky sign only at sites of erythema, absence of perioral crusting, full-thickness epidermal necrosis, and a blister cleavage plane in the lowermost epidermis.

HISTOLOGY

A subcorneal, granular layer split can be identified on skin biopsy. Absence of an inflammatory infiltrate is characteristic. Histology is identical to that seen in pemphigus foliaceus and subcorneal pustular dermatosis.

Figure 665-4 Infant with staphylococcal scalded skin syndrome.

TREATMENT

Systemic therapy, given either orally in cases of localized involvement or parenterally with a semisynthetic penicillinase-resistant penicillin or vancomycin if MRSA is considered, should be prescribed. Clindamycin should be added to inhibit bacterial protein (toxin) synthesis. The skin should be gently moistened and cleansed. Application of an emollient provides lubrication and decreases discomfort. Topical antibiotics are unnecessary. In neonates, or in infants or children with severe infection, hospitalization is mandatory, with attention to fluid and electrolyte management, infection control measures, pain management, and meticulous wound care with contact isolation. In particularly severe disease, care in an intensive care or burn unit is required. Recovery is usually rapid, but complications such as excessive fluid loss, electrolyte imbalance, faulty temperature regulation, pneumonia, septicemia, and cellulitis may cause increased morbidity.

Bibliography is available at Expert Consult.

665.4 Ecthyma

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See also Chapters 181, 183, 205.

Ecthyma resembles nonbullous impetigo in onset and appearance but gradually evolves into a deeper, more chronic infection. The initial lesion is a vesicle or vesicular pustule with an erythematous base that erodes through the epidermis into the dermis to form an ulcer with elevated margins. The ulcer becomes obscured by a dry, heaped-up, tightly adherent crust (Fig. 665-5) that contributes to the persistence of the infection and scar formation. Lesions may be spread by autoinoculation, may be as large as 4 cm, and occur most frequently on the

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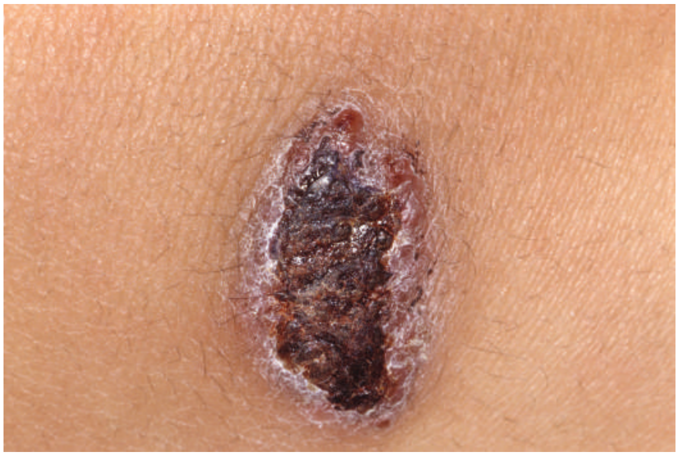

Figure 665-5 Dry, tightly adherent crust in ecthyma.

Figure 665-6 Large vegetating lesion of pyoderma vegetans.

legs. Predisposing factors include the presence of pruritic lesions, such as insect bites, scabies, or pediculosis, that are subject to frequent scratching; poor hygiene; and malnutrition. Complications include lymphangitis, cellulitis, and, rarely, poststreptococcal glomerulonephritis. The causative agent is usually GABHS; *S. aureus* is also cultured from most lesions but is probably a secondary pathogen. Crusts should be softened with warm compresses and removed. Systemic antibiotic therapy, as for impetigo, is indicated; almost all lesions are responsive to treatment with penicillin.

Ecthyma gangrenosa is a necrotic ulcer covered with a gray-black eschar. It is usually a sign of *P. aeruginosa* sepsis and usually occurs in immunosuppressed patients. Neutropenia is a risk factor for ecthyma gangrenosum. Ecthyma gangrenosum occurs in up to 6% of patients with systemic *P. aeruginosa* infection but can also occur as a primary cutaneous infection by inoculation. The lesion begins as a red or purpuric macule that vesiculates and then ulcerates. There is a surrounding rim of pink to violaceous skin. The punched-out ulcer develops raised edges with a dense, black, depressed, crusted center. Lesions may be single or multiple. Patients with bacteremia commonly have lesions in apocrine areas. Clinically similar lesions may also develop as a result of infection with other agents, such as *S. aureus, A. hydrophila, Enterobacter* spp., *Proteus* spp., *Burkholderia cepacia, Serratia marcescens, Aspergillus* spp., Mucorales, *E. coli,* and *Candida* spp. There is bacterial invasion of the adventitia and media of dermal veins but not arteries. The intima and lumina are spared. Blood and skin biopsy specimens for culture should be obtained, and empirical broad-spectrum, systemic therapy that includes coverage for *Pseudomonas* (i.e., aminoglycoside and an antipseudomonal penicillin) should be initiated as soon as possible.

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665.5 Other Cutaneous Bacterial Infections

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BLASTOMYCOSIS-LIKE PYODERMA (PYODERMA VEGETANS)

Blastomycosis-like pyoderma is an exuberant cutaneous reaction to bacterial infection that occurs primarily in children who are malnourished and immunosuppressed. The organisms most commonly isolated from lesions are *S. aureus* and group A streptococcus, but several other organisms have been associated with these lesions, including *P. aeruginosa, Proteus mirabilis,* diphtheroids, *Bacillus* spp., and *C. perfringens.* Crusted, hyperplastic plaques on the extremities are characteristic, sometimes forming from the coalescence of many pinpoint, purulent, crusted abscesses (Fig. 665-6). Ulceration and sinus tract formation

Figure 665-7 Cutaneous blastomycosis. Verrucous, crusted, erythematous plaque on the chin in a 15 yr old boy with respiratory symptoms and bone pain. *(From Paller AS, Mancini AJ, editors:* Hurwitz clinical pediatric dermatology, *ed 3, Philadelphia, 2006, Elsevier, Fig. 14-13.)*

may develop, and additional lesions may appear at sites distant from the site of inoculation. Regional lymphadenopathy is common, but fever is not. Histopathologic examination reveals pseudoepitheliomatous hyperplasia and abscesses composed of neutrophils and/or eosinophils. Giant cells are usually lacking. The **differential diagnosis** includes deep fungal infection, particularly blastomycosis (Fig. 665-7) and tuberculous and atypical mycobacterial infection. Underlying immunodeficiency should be ruled out, and the selection of antibiotics should be guided by susceptibility testing because the response to antibiotics is often poor.

BLISTERING DISTAL DACTYLITIS

Blistering distal dactylitis is a superficial blistering infection of the volar fat pad on the distal portion of the finger or thumb (Fig. 665-8). More than 1 finger may be involved, as may the volar surfaces of the proximal phalanges, palms, and toes. Blisters are filled with a watery purulent fluid that contains polymorphonuclear leukocytes and, usually, chains of Gram-positive cocci. Patients commonly have no preceding history of trauma, and systemic symptoms are generally absent. Poststreptococcal glomerulonephritis has not occurred after blistering distal dactylitis. The infection is caused most commonly by group A streptococcus but has also occurred as a result of infection with *S. aureus.* If left untreated, blisters may continue to enlarge and

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Figure 665-8 **Blistering dactylitis.** Edema and a tense bulla on the thumb of this 7 yr old girl. Culture of the blister fluid yielded *Staphylococcus aureus* rather than the more commonly seen group A β-hemolytic streptococcus (GABHS). *(From Paller AS, Mancini AJ, editors:* Hurwitz clinical pediatric dermatology, *ed 3, Philadelphia, 2006, Elsevier, Fig. 14-14.)*

Figure 665-9 **Perianal streptococcal dermatitis.** Bright red erythema with a moist, tender surface. *(From Paller AS, Mancini AJ, editors:* Hurwitz clinical pediatric dermatology, *ed 3, Philadelphia, 2006, Elsevier, Fig. 17-38.)*

extend to the paronychial area. The infection responds to incision and drainage and a 10-day course of systemic cephalosporin therapy.

PERIANAL INFECTIOUS DERMATITIS

Perianal infectious dermatitis presents most commonly in boys (70% of cases) between the ages of 6 mo and 10 yr as perianal dermatitis (90% of cases) and pruritus (80% of cases; Fig. 665-9). The incidence of perianal infectious dermatitis is not known precisely but ranges from 1 in 2,000 to 1 in 218 patient visits. The rash is superficial, erythematous, well marginated, nonindurated, and confluent from the anus outward. Acutely (<6 wk), the rash tends to be bright red, moist, and tender to touch. At this stage, a white pseudomembrane may be present. As the rash becomes more chronic, the perianal eruption may consist of painful fissures, a dried mucoid discharge, or psoriasiform plaques with yellow peripheral crust. In girls, the perianal rash may be associated with vulvovaginitis. In boys, the penis may be involved. Approximately 50% of patients have rectal pain, most commonly described as burning inside the anus during defecation, and 33% have blood-streaked stools. Fecal retention is a frequent behavioral response to the infection. Patients also have presented with guttate psoriasis. Although local induration or edema may occur, constitutional symptoms such as fever, headache, and malaise are absent, suggesting that subcutaneous involvement, as in cellulitis, is absent. Familial spread of perianal infectious dermatitis is common, particularly when family members bathe together or use the same water.

Perianal infectious dermatitis is usually caused by GABHS, but it may also be caused by *S. aureus.* The index case and family members should undergo culture; follow-up cultures to document bacteriologic cure after a course of treatment are recommended.

The **differential diagnosis** of perianal infectious dermatitis includes psoriasis, seborrheic dermatitis, candidiasis, pinworm infestation, sexual abuse, and inflammatory bowel disease.

For GABHS perianal infectious dermatitis, treatment with a 7-day course of cefuroxime (20 mg/kg/day in 2 divided doses) is superior to treatment with penicillin. Concomitant topical mupirocin ointment 2-3 times a day also may be used. If *S. aureus* is cultured, treatment should be based on sensitivities.

ERYSIPELAS

See Chapter 183.

Figure 665-10 **Folliculitis.** Multiple follicular pustules.

FOLLICULITIS

Folliculitis, or superficial infection of the hair follicle, is most often caused by *S. aureus* (Bockhart impetigo). The lesions are typically small, discrete, dome-shaped pustules with an erythematous base, located at the ostium of the pilosebaceous canals (Fig. 665-10). Hair growth is unimpaired, and the lesions heal without scarring. Favored sites include the scalp, buttocks, and extremities. Poor hygiene, maceration, drainage from wounds and abscesses, and shaving of the legs can be provocative factors. Folliculitis can also occur as a result of tar therapy or occlusive wraps. The moist environment encourages bacterial proliferation. In HIV-infected patients, *S. aureus* may produce confluent erythematous patches with satellite pustules in intertriginous areas and violaceous plaques composed of superficial follicular pustules in the scalp, axillae, or groin. The **differential diagnosis** include *Candida,* which may cause satellite follicular papules and pustules surrounding erythematous patches of intertrigo, and *Malassezia furfur,* which produces 2-3 mm, pruritic, erythematous, perifollicular papules and pustules on the back, chest, and extremities, particularly in patients who have diabetes mellitus or are taking corticosteroids or antibiotics.

Diagnosis is made by examining potassium hydroxide–treated scrapings from lesions. Detection of *Malassezia* may require a skin biopsy, demonstrating clusters of yeast and short, branching hyphae ("macaroni and meatballs") in widened follicular ostia mixed with keratinous debris.

Topical antibiotic therapy (e.g., clindamycin 1% lotion or solution twice a day) is usually all that is needed for mild cases, but more severe cases may require use of a systemic antibiotic such as dicloxacillin or cephalexin. Bacterial culture should be performed in treatment-resistant cases. In chronic recurrent folliculitis, daily application of a benzoyl peroxide 5% gel or wash may facilitate resolution.

Folliculitis barbae (sycosis barbae) is a deeper, more severe recurrent inflammatory form of folliculitis caused by *S. aureus* that involves the entire depth of the follicle. Erythematous follicular papules and pustules develop on the chin, upper lip, and angle of the jaw, primarily in young black males. Papules may coalesce into plaques, and healing may occur with scarring. Affected individuals are frequently found to be *S. aureus* carriers. **Treatment** with warm saline compresses and topical antibiotics such as mupirocin generally clears the infection. More extensive, recalcitrant cases may require therapy with β-lactamase–resistant systemic antibiotics for several weeks, and elimination of *S. aureus* from sites of carriage.

Pseudomonal folliculitis (hot tub folliculitis) is attributable to *P. aeruginosa,* predominantly serotype O-11. It occurs after exposure to poorly chlorinated hot tubs/whirlpools and swimming pools, as well as to a contaminated water slide, or loofah sponge. The lesions are pruritic papules and pustules or deeply erythematous to violaceous nodules that develop 8-48 hr after exposure and are most dense in areas covered by a bathing suit (Fig. 665-11). Patients occasionally experience fever, malaise, and lymphadenopathy. The organism is readily cultured from pus. The eruption usually resolves spontaneously in 1-2 wk, often leaving postinflammatory hyperpigmentation. Consideration should be given to use of systemic antibiotics (ciprofloxacin) in adolescent patients with constitutional symptoms. Immunocompromised children are susceptible to complications of *Pseudomonas* folliculitis (cellulitis) and should avoid hot tubs.

FURUNCLES AND ABSCESSES

Etiology

The causative agent in furuncles ("boils") and carbuncles is usually *S. aureus,* which penetrates abraded perifollicular skin. Conditions predisposing to furuncle formation include obesity, hyperhidrosis, maceration, friction, and preexisting dermatitis. Furunculosis is also more common in individuals with low serum iron levels, diabetes, malnutrition, HIV infection, or other immunodeficiency states. Recurrent furunculosis is frequently associated with carriage of *S. aureus* in the nares, axillae, or perineum or close contact with someone such as a family member who is a carrier. Other bacteria or fungi may occasionally cause furuncles or carbuncles.

Community-acquired MRSA abscesses can also complicate folliculitis. Community-acquired MRSA infections commonly affect children and young adults, especially athletes where spread of the infection is enhanced by skin-to-skin contact. Infection can also be spread by crowding conditions, shared personal hygiene items, and a compromised skin barrier. They may occur in any location, however, they are most common on the lower abdomen, buttocks, and legs. Abscesses which are a common manifestation of community-acquired MRSA should be incised and drained. If oral antibiotics are needed, those with coverage against MRSA are recommended and commonly include oral trimethoprim-sulfamethoxazole (8-12 mg trimethoprim/kg/day in divided doses every 12 hr) or clindamycin (10-20 mg/kg/day in divided doses 3 times daily). To reduce colonization and hence reinfection, bleach baths for patients, and mupirocin intranasally in patients and in family members has been recommended.

Clinical Manifestations

This follicular lesion may originate from a preceding folliculitis or may arise initially as a deep-seated, tender, erythematous, perifollicular nodule. Although lesions are initially indurated, central necrosis and suppuration follow, leading to rupture and discharge of a central core of necrotic tissue and destruction of the follicle (Fig. 665-12). Healing occurs with scar formation. Sites of predilection are the hair-bearing areas on the face, neck, axillae, buttocks, and groin. Pain may be intense if the lesion is situated in an area where the skin is relatively fixed, such as in the external auditory canal or over the nasal cartilages. Patients with furuncles usually have no constitutional symptoms; bacteremia may occasionally ensue. Rarely, lesions on the upper lip or cheek may lead to cavernous sinus thrombosis. Infection of a group of contiguous follicles, with multiple drainage points, accompanied by inflammatory changes in surrounding connective tissue is a **carbuncle**. Carbuncles may be accompanied by fever, leukocytosis, and bacteremia.

Treatment

Treatment for furuncle and carbuncle includes regular bathing with antimicrobial soaps (chlorhexidine) and wearing of loose-fitting clothing to minimize predisposing factors for furuncle formation. Frequent application of a hot, moist compress may facilitate drainage of lesions. Large lesions may be drained by a small incision. Carbuncles and large or numerous furuncles should be treated with systemic antibiotics chosen on the basis of culture and sensitivity testing results.

PITTED KERATOLYSIS

Pitted keratolysis occurs most frequently in humid tropical and subtropical climates, particularly in individuals whose feet are moist for prolonged periods, for example, as a result of hyperhidrosis, prolonged wearing of boots, or immersion in water. It occurs most commonly in young males from early adolescence to the late 20s. The lesions consist

Figure 665-11 Papules and pustules in hot tub folliculitis.

Figure 665-12 Rupture and discharge of pus in a furuncle.

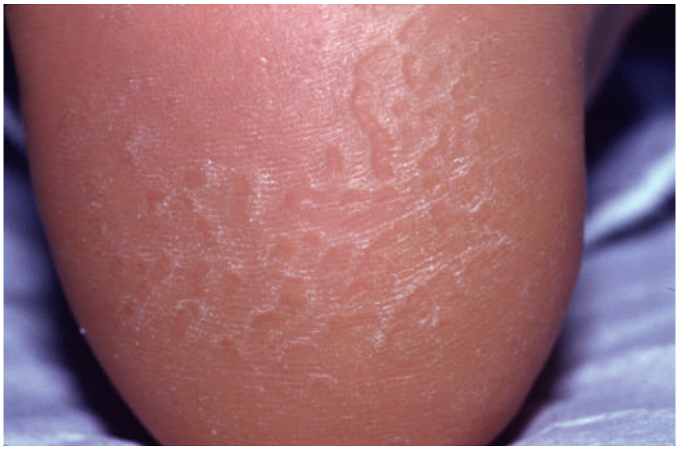

Figure 665-13 Superficial erosions of the horny layer in pitted keratolysis.

of 1-7 mm, irregularly shaped, superficial erosions of the horny layer on the soles, particularly at weight-bearing sites (Fig. 665-13). Brownish discoloration of involved areas may be apparent. A rare variant manifests as thinned, erythematous to violaceous plaques in addition to the typical pitted lesions. The condition is frequently malodorous, and is painful in approximately 50% of cases. The most likely etiologic agent is *Corynebacterium (Kytococcus) sedentarius.* Treatment of hyperhidrosis is mandatory with prescription-strength aluminum chloride products or 40% formaldehyde in petrolatum ointment. Avoidance of moisture and maceration produces slow, spontaneous resolution of the infection. Topical or systemic erythromycin and topical imidazole creams are standard therapy.

ERYTHRASMA

Erythrasma is a benign chronic superficial infection caused by *Corynebacterium minutissimum.* Predisposing factors include heat, humidity, obesity, skin maceration, diabetes mellitus, and poor hygiene. Approximately 20% of affected patients have involvement of the toe webs. Other frequently affected sites are moist, intertriginous areas such as the groin and axillae. The inframammary and perianal regions are occasionally involved. Sharply demarcated, irregularly bordered, slightly scaly, brownish red patches are characteristic of the disease. Mild pruritus is the only constant symptom. *C. minutissimum* is a complex of related organisms that produce porphyrins that fluoresce brilliant coral red under ultraviolet light. The diagnosis is readily made, and erythrasma is differentiated from dermatophyte infection and from tinea versicolor on Wood lamp examination. Bathing within 20 hr of Wood lamp examination, however, may remove the water-soluble porphyrins. Staining of skin scrapings with methylene blue or Gram stain reveals the pleomorphic, filamentous coccobacillary forms.

Effective **treatment** can be achieved with topical erythromycin, clindamycin, miconazole, or a 10-14 day course of oral erythromycin or an oral tetracycline.

ERYSIPELOID

A rare cutaneous infection, erysipeloid is caused by inoculation of *Erysipelothrix rhusiopathiae* from handling contaminated animals, birds, fish, or their products. The localized cutaneous form is most common, characterized by well-demarcated diamond-shaped erythematous to violaceous patches at sites of inoculation. Local symptoms are generally not severe, constitutional symptoms are rare, and the lesions resolve spontaneously after weeks but can recur at the same site or develop elsewhere weeks to months later. The diffuse cutaneous form manifests as lesions at several areas of the body in addition to the site of inoculation. It is also self-limited. The systemic form, caused by hematogenous spread, is accompanied by constitutional symptoms and may include endocarditis, septic arthritis, cerebral infarct and abscess, meningitis, and pulmonary effusion. Diagnosis is confirmed by skin biopsy, which reveals the Gram-positive organisms, and culture. The **treatment** of choice is parenteral penicillin or erythromycin.

TUBERCULOSIS OF THE SKIN

See Chapters 215 and 217.

Cutaneous tuberculosis infection occurs worldwide, particularly in association with HIV infection, malnutrition, and poor sanitary conditions. Primary cutaneous tuberculosis is rare in the United States. All forms of cutaneous disease are caused by *Mycobacterium tuberculosis, Mycobacterium bovis,* and occasionally by the bacillus Calmette-Guérin (BCG), an attenuated vaccine form of *M. bovis.* The manifestations caused by a given organism are indistinguishable from one another. After invasion of the skin, mycobacteria either multiply intracellularly within macrophages, leading to progressive disease, or are controlled by the host immune reaction.

Primary cutaneous tuberculosis (tuberculous chancre) results when *M. tuberculosis* or *M. bovis* gains access to the skin or mucous membranes through trauma in a previously uninfected individual without immunity to the organism. Sites of predilection are the face, lower extremities, and genitals. The initial lesion develops 2-4 wk after introduction of the organism into the damaged tissue. A red-brown papule gradually enlarges to form a shallow, firm, sharply demarcated ulcer. Satellite abscesses may be present. Some lesions acquire a crust resembling impetigo, and others become heaped up and verrucous at the margins. The primary lesion can also manifest as a painless ulcer on the conjunctiva, gingiva, or palate and occasionally as a painless acute paronychia. Painless regional adenopathy may appear several weeks after the development of the primary lesion and may be accompanied by lymphangitis, lymphadenitis, or perforation of the skin surface, forming **scrofuloderma**. Untreated lesions heal with scarring within 12 mo but may reactivate, may form lupus vulgaris, or, rarely, may progress to the acute miliary form. Therefore, antituberculous therapy is indicated (see Chapter 215).

M. tuberculosis or *M. bovis* can be cultured from the skin lesion and local lymph nodes, but acid-fast staining of histologic sections, particularly of a well-controlled infection, often does not reveal the organism. The **differential diagnosis** is broad, including a syphilitic chancre; deep fungal or atypical mycobacterial infection; leprosy; tularemia; cat-scratch disease; sporotrichosis; nocardiosis; leishmaniasis; reaction to foreign substances such as zirconium, beryllium, silk or nylon sutures, talc, and starch; papular acne rosacea; and lupus miliaris disseminatus faciei.

Scrofuloderma results from enlargement, cold abscess formation, and breakdown of a lymph node, most frequently in a cervical chain, with extension to the overlying skin from underlying foci of tuberculous infection. Linear or serpiginous ulcers and dissecting fistulas and subcutaneous tracts studded with soft nodules may develop. Spontaneous healing may take years, eventuating in cordlike keloid scars. Lupus vulgaris may also develop. Lesions may also originate from an underlying infected joint, tendon, bone, or epididymis. The **differential diagnosis** includes syphilitic gumma, deep fungal infections, actinomycosis, and hidradenitis suppurativa. The course is indolent, and constitutional symptoms are typically absent. Antituberculous therapy is indicated (see Chapter 215).

Direct cutaneous inoculation of the tubercle bacillus into a previously infected individual with a moderate to high degree of immunity initially produces a small papule with surrounding inflammation. **Tuberculosis verrucosa cutis** (warty tuberculosis) forms when the papule becomes hyperkeratotic and warty, and several adjacent papules coalesce or a single papule expands peripherally to form a brownish red to violaceous, exudative, crusted verrucous plaque. Irregular extension of the margins of the plaque produces a serpiginous border. Children have the lesions most commonly on the lower extremities after trauma and contact with infected material such as sputum or soil. Regional lymph nodes are involved only rarely. Spontaneous healing with atrophic scarring takes place over months to years. Healing is also gradual with antituberculous therapy.

Lupus vulgaris is a rare, chronic, progressive form of cutaneous tuberculosis that develops in individuals with a moderate to high

degree of tuberculin sensitivity induced by previous infection. The incidence is greater in cool, moist climates, particularly in females. Lupus vulgaris develops as a result of direct extension from underlying joints or lymph nodes; through lymphatic or hematogenous spread; or, rarely, by cutaneous inoculation with BCG vaccine. It most commonly follows cervical adenitis or pulmonary tuberculosis. Approximately 33% of cases are preceded by scrofuloderma, and 90% of cases manifest on the head and neck, most commonly on the nose or cheek. Involvement of the trunk is uncommon. A typical solitary lesion consists of a soft, brownish red papule that has an apple-jelly color when examined by diascopy. Peripheral expansion of the papule or, occasionally, the coalescence of several papules forms an irregular lesion of variable size and form. One or several lesions may develop, including nodules or plaques that are flat and serpiginous, hypertrophic and verrucous, or edematous in appearance. Spontaneous healing occurs centrally, and lesions characteristically reappear within the area of atrophy. Chronicity is characteristic, and persistence and progression of plaques over many years is common. Lymphadenitis is present in 40% of those with lupus vulgaris, and 10-20% has infection of the lungs, bones, or joints. Extensive deformities may be caused by vegetative masses and ulceration involving the nasal, buccal, or conjunctival mucosa; the palate; the gingiva; or the oropharynx. Squamous cell carcinoma, with a relatively high metastatic potential, may develop, usually after several years of the disease. After a temporary impairment in immunity, particularly after measles infection (lupus exanthematicus), multiple lesions may form at distant sites as a result of hematogenous spread from a latent focus of infection. The histopathology reveals a tuberculoid granuloma without caseation; organisms are extremely difficult to demonstrate. The **differential diagnosis** includes sarcoidosis, atypical mycobacterial infection, blastomycosis, chromoblastomycosis, actinomycosis, leishmaniasis, tertiary syphilis, leprosy, hypertrophic lichen planus, psoriasis, lupus erythematosus, lymphocytoma, and Bowen disease. Small lesions can be excised. Antituberculous drug therapy usually halts further spread and induces involution.

Orificial tuberculosis (tuberculosis cutis orificialis) appears on the mucous membranes and periorificial skin after autoinoculation of mycobacteria from sites of progressive infection. It is a sign of advanced internal disease and carries a poor prognosis and occurs in s sensitized host with impaired cellular immunity. Lesions appear as painful, yellowish or red nodules that form punched-out ulcers with inflammation and edema of the surrounding mucosa. **Treatment** consists of identification of the source of infection and initiation of antituberculous therapy.

Miliary tuberculosis (hematogenous primary tuberculosis) rarely manifests cutaneously and occurs most commonly in infants and in individuals who are immunosuppressed after chemotherapy or infection with measles or HIV. The eruption consists of crops of symmetrically distributed, minute, erythematous to purpuric macules, papules, or vesicles. The lesions may ulcerate, drain, crust, and form sinus tracts or may form subcutaneous gummas, especially in malnourished children with impaired immunity. Constitutional signs and symptoms are common, and a leukemoid reaction or aplastic anemia may develop. Tubercle bacilli are readily identified in an active lesion. A fulminant course should be anticipated, and aggressive antituberculous therapy is indicated.

Single or multiple metastatic tuberculous abscesses (**tuberculous gummas**) may develop on the extremities and trunk by hematogenous spread from a primary focus of infection during a period of decreased immunity, particularly in malnourished and immunosuppressed children. The fluctuant, nontender, erythematous subcutaneous nodules may ulcerate and form fistulas.

Vaccination with BCG characteristically produces a papule approximately 2 wk after vaccination. The papule expands in size, typically ulcerates within 2-4 mo, and heals slowly with scarring. In 1-2 per million vaccinations, a complication caused specifically by the BCG organism occurs, including regional lymphadenitis, lupus vulgaris, scrofuloderma, and subcutaneous abscess formation.

Tuberculids are skin reactions that exhibit tuberculoid features histologically but do not contain detectable mycobacteria. The lesions appear in a host who usually has moderate to strong tuberculin reactivity, has a history of previous tuberculosis of other organs, and usually shows a therapeutic response to antituberculous therapy. The cause of tuberculids is poorly understood. Most affected patients are in good health with no clear focus of disease at the time of the eruption. The most commonly observed tuberculid is the papulonecrotic tuberculid. Recurrent crops of symmetrically distributed, asymptomatic, firm, sterile, dusky-red papules appear on the extensor aspects of the limbs, the dorsum of the hands and feet, and the buttocks. The papules may undergo central ulceration and eventually heal, leaving sharply delineated, circular, depressed scars. The duration of the eruption is variable, but it usually disappears promptly after treatment of the primary infection. Lichen scrofulosorum, another form of tuberculid, is characterized by asymptomatic, grouped, pinhead-sized, often follicular pink or red papules that form discoid plaques, mainly on the trunk. Healing occurs without scarring.

Atypical mycobacterial infection may cause cutaneous lesions in children. *Mycobacterium marinum* is found in saltwater, freshwater, and diseased fish. In the United States, it is most commonly acquired from tropical fish tanks and swimming pools. Traumatic abrasion of the skin serves as a portal of entry for the organism. Approximately 3 wk after inoculation, a single reddish papule develops and enlarges slowly to form a violaceous nodule or, occasionally, a warty plaque (Fig. 665-14). The lesion occasionally breaks down to form a crusted ulcer or a suppurating abscess. Sporotrichoid erythematous nodules along lymphatics may also suppurate and drain. Lesions are most common on the elbows, knees, and feet of swimmers, and on the hands and fingers in persons with aquarium-acquired infection. Systemic signs and symptoms are absent. Regional lymph nodes occasionally become slightly enlarged but do not break down. Rarely, the infection becomes disseminated, particularly in an immunosuppressed host. A biopsy specimen of a fully developed lesion demonstrates a granulomatous infiltrate with tuberculoid architecture. Treatment options include tetracycline, doxycycline, minocycline, clarithromycin, and rifampin plus ethambutol. Application of heat to the affected site may be a useful adjunctive therapy (see Chapter 217).

Mycobacterium kansasii primarily causes pulmonary disease; skin disease is rare, often occurring in an immunocompromised host. Most commonly, sporotrichoid nodules develop after inoculation of traumatized skin. Lesions may develop into ulcerated, crusted, or verrucous plaques. The organism is relatively sensitive to antituberculous medications, which should be chosen on the basis of susceptibility testing.

Mycobacterium scrofulaceum causes cervical lymphadenitis (scrofuloderma) in young children, typically in the submandibular region. Nodes enlarge over several weeks, ulcerate, and drain. The local reaction is nontender and circumscribed, constitutional symptoms are absent, and there generally is no evidence of lung or other organ involvement. Other atypical mycobacteria may cause a similar

Figure 665-14 Violaceous, warty plaque of *Mycobacterium marinum* infection.

presentation, including *Mycobacterium avium* complex, *Mycobacterium kansasii,* and *Mycobacterium fortuitum.* **Treatment** is accomplished by excision and administration of antituberculous drugs (see Chapter 217).

Mycobacterium ulcerans (Buruli ulcer) causes a painless subcutaneous nodule after inoculation of abraded skin. Most infections occur in children in tropical rain forests. The nodule usually ulcerates, develops undermined edges, and may spread over large areas, most commonly on an extremity. Local necrosis of subcutaneous fat, producing a septal panniculitis, is characteristic. Ulcers persist for months to years before healing spontaneously with scarring and sometimes with lymphedema. Constitutional symptoms and lymphadenopathy are absent. Diagnosis is made by culturing the organism at 32-33°C (89.6-91.4°F). **Treatment of choice** is early excision of the lesion. Local heat therapy and oral chemotherapy may benefit some patients.

M. avium complex, composed of more than 20 subtypes, most commonly causes chronic pulmonary infection. Cervical lymphadenitis and osteomyelitis occur occasionally, and papules or purulent leg ulcers occur rarely by primary inoculation. Skin lesions may be an early sign of disseminated infection. The lesions may take various forms, including erythematous papules, pustules, nodules, abscesses, ulcers, panniculitis, and sporotrichoid spread along lymphatics. For treatment, see Chapter 217.

M. fortuitum complex causes disease in an immunocompetent host principally by primary cutaneous inoculation after traumatic injury, injection, or surgery. A nodule, abscess, or cellulitis develops 4-6 wk after inoculation. In an immunocompromised host, numerous subcutaneous nodules may form, break down, and drain. **Treatment** is based on identification and susceptibility testing of the organism.

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Chapter 666
Cutaneous Fungal Infections

Anna M. Juern and Beth A. Drolet

TINEA VERSICOLOR

A common, innocuous, chronic fungal infection of the stratum corneum, tinea versicolor is caused by the dimorphic yeast *Malassezia globosa*. The synonyms *Pityrosporum ovale* and *Pityrosporum orbiculare* were used previously to identify the causal organism.

Etiology

M. globosa is part of the indigenous flora, predominantly in the yeast form, and is found particularly in areas of skin that are rich in sebum production, and is part of normal skin flora. Proliferation of filamentous forms occurs in the disease state. Predisposing factors include a warm, humid environment, excessive sweating, occlusion, high plasma cortisol levels, immunosuppression, malnourishment, and genetically determined susceptibility. The disease is most prevalent in adolescents and young adults.

Clinical Manifestations

The lesions of tinea versicolor vary widely in color. In white individuals, they are typically reddish brown, whereas in black individuals they may be either hypopigmented or hyperpigmented. The characteristic macules are covered with a fine scale. They often begin in a perifollicular location, enlarge, and merge to form confluent patches, most commonly on the neck, upper chest, back, and upper arms (Fig. 666-1). Facial lesions are common in adolescents; lesions occasionally appear on the forearms, dorsum of the hands, and pubis. There may be little or no pruritus. Involved areas do not tan after sun exposure. A papulopustular perifollicular variant of the disorder may occur on the back, chest, and sometimes the extremities.

Figure 666-1 Hyperpigmented, sharply demarcated macules of varying sizes on the upper trunk characteristic of tinea versicolor.

Differential Diagnosis

Examination with a Wood lamp discloses a yellowish gold fluorescence. A potassium hydroxide (KOH) preparation of scrapings is diagnostic, demonstrating groups of thick-walled spores and myriad short, thick, angular hyphae resembling macaroni/spaghetti and meatballs. Skin biopsy, including culture and special stains for fungi (periodic acid–Schiff), are often necessary to make the diagnosis in cases of primarily follicular involvement. Microscopically, organisms and keratinous debris can be seen within dilated follicular ostia.

Tinea versicolor must be distinguished from dermatophyte infections, seborrheic dermatitis, pityriasis alba, and secondary syphilis. Tinea versicolor may mimic nonscaling pigmentary disorders, such as postinflammatory pigmentary change, if a patient has removed the scales by scrubbing. *M. globosa* folliculitis must be distinguished from the other forms of folliculitis.

Treatment

Many therapeutic agents can be used to treat this disease successfully. The causative agent, a normal human saprophyte, is not eradicated from the skin, however, and the disorder recurs in predisposed individuals. Appropriate topical therapy may include 1 of the following: selenium 2% shampoo applied for 10 minutes before rinsing for 2 wk; ketoconazole 2% shampoo 3 times a wk for a month or a single application daily for 3 days; and terbinafine spray once to twice daily for 1-2 wk. Antifungal creams are available and can be used; however, these can be impractical to apply given the large surface of skin involved. Oral therapy may be more convenient and may be achieved successfully with ketoconazole or fluconazole, 400 mg, repeated in 1 wk, or itraconazole, 200 mg/24 hr for 5-7 days. Recurrent episodes continue to respond promptly to these agents. Oral therapy is particularly helpful in those with severe disease or recurrent disease, or in those where topical therapies have failed. Maintenance therapy with selenium sulfide shampoo or ketoconazole 2% shampoo once a week may be used.

DERMATOPHYTOSES

Dermatophytoses are caused by a group of closely related filamentous fungi with a propensity for invading the stratum corneum, hair, and nails. The 3 principal genera responsible for infections are *Trichophyton, Microsporum,* and *Epidermophyton.*

Etiology

Trichophyton spp. cause lesions of all keratinized tissue, including skin, nails, and hair. *Trichophyton rubrum* is the most common dermatophyte pathogen. *Microsporum* spp. principally invade the hair, and the *Epidermophyton* spp. invade the intertriginous skin. Dermatophyte infections are designated by the word **tinea** followed by the Latin word for the anatomic site of involvement. The dermatophytes are also classified according to source and natural habitat. Fungi acquired from the soil are called *geophilic*. They infect humans sporadically, inciting an inflammatory reaction. Dermatophytes that are acquired from animals are *zoophilic*. Transmission may be through direct contact or indirectly by infected animal hair or clothing. Infected animals are frequently asymptomatic. Dermatophytes acquired from humans are referred to as *anthropophilic*. These infestations range from chronic low-grade to acute inflammatory disease. *Epidermophyton* infections are transmitted only by humans, but various species of *Trichophyton* and *Microsporum* can be acquired from both human and nonhuman sources.

Epidemiology

Host defense has an important influence on the severity of the infection. Disease tends to be more severe in individuals with diabetes mellitus, lymphoid malignancies, immunosuppression, and states with high plasma cortisol levels, such as Cushing syndrome. Some dermatophytes, most notably the zoophilic species, tend to elicit more severe, suppurative inflammation in humans. Some degree of resistance to reinfection is acquired by most infected persons and may be associated with a delayed hypersensitivity response. No relationship has been demonstrated, however, between antibody levels and resistance to infection. The frequency and severity of infection are also affected by the geographic locale, the genetic susceptibility of the host, and the virulence of the strain of dermatophyte. Additional local factors that predispose to infection include trauma to the skin, hydration of the skin with maceration, occlusion, and elevated temperature.

Occasionally, a secondary skin eruption, referred to as a dermatophytid or "id" reaction, appears in sensitized individuals and has been attributed to circulating fungal antigens derived from the primary infection. The eruption is characterized by grouped papules (Fig. 666-2) and vesicles and, occasionally, by sterile pustules. Symmetric urticarial lesions and a more generalized maculopapular eruption also can occur. Id reactions are most often associated with tinea pedis but also occur with tinea capitis.

Tinea Capitis

Clinical Manifestations

Tinea capitis is a dermatophyte infection of the scalp most often caused by *Trichophyton tonsurans,* occasionally by *Microsporum canis*, and, much less commonly, by other *Microsporum* and *Trichophyton* spp. It is particularly common in black children age 4-14 yr. In *Microsporum* and some *Trichophyton* infections, the spores are distributed in a sheath-like fashion around the hair shaft (**ectothrix** infection), whereas *T. tonsurans* produces an infection within the hair shaft (endothrix). **Endothrix** infections may continue past the anagen phase of hair growth into telogen and are more chronic than infections with ectothrix organisms that persist only during the anagen phase. *T. tonsurans* is an anthropophilic species acquired most often by contact with infected hairs and epithelial cells that are on such surfaces as theater seats, hats, and combs. Dermatophyte spores may also be airborne within the immediate environment, and high carriage rates have been demonstrated in noninfected schoolmates and household members. *M. canis* is a zoophilic species that is acquired from cats and dogs.

The clinical presentation of tinea capitis varies with the infecting organism. Endothrix infections such as those caused by *T. tonsurans* create a pattern known as "black-dot ringworm," characterized initially by many small circular patches of alopecia in which hairs are broken off close to the hair follicle (Fig. 666-3). Another clinical variant manifests as diffuse scaling, with minimal hair loss secondary. It strongly resembles seborrheic dermatitis, psoriasis, or atopic dermatitis (Fig. 666-4). *T. tonsurans* may also produce a chronic and more diffuse alopecia. Lymphadenopathy is common (Fig. 666-5). A severe inflammatory response produces elevated, boggy granulomatous masses (**kerions**), which are often studded with pustules (Fig. 666-6*A*). Fever, pain, and regional adenopathy are common, and permanent scarring and alopecia may result (Fig. 666-6B). The zoophilic organism *M. canis* or the geophilic organism *Microsporum gypseum* also may cause kerion formation. The pattern produced by *Microsporum audouinii*, the most

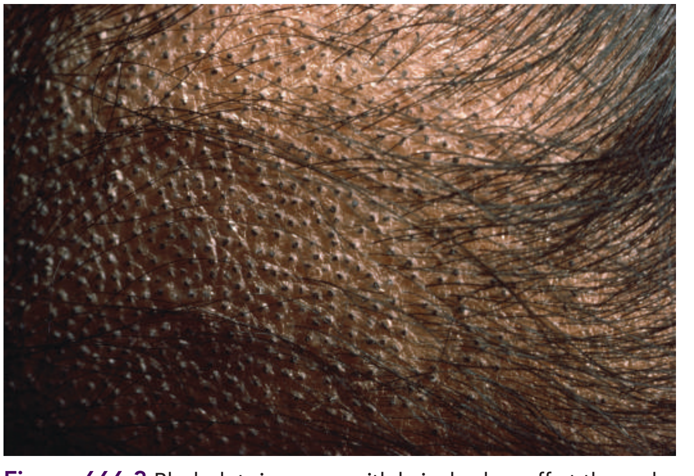

Figure 666-3 Black-dot ringworm with hairs broken off at the scalp.

Figure 666-2 Id reaction. Papular eruption of the face associated with severe tinea infection of the hand.

Figure 666-4 Tinea capitis mimicking seborrheic dermatitis.

Figure 666-5 Lymphadenopathy associated with tinea capitis.

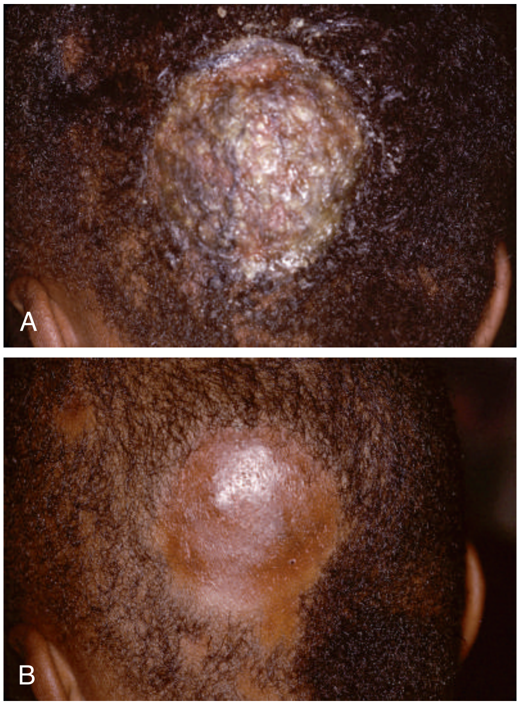

Figure 666-6 **A,** Kerion. Boggy granulomatous mass of the scalp. **B,** Scarring after kerion.

common cause of tinea capitis in the 1940s and 1950s, is characterized initially by a small papule at the base of a hair follicle. The infection spreads peripherally, forming an erythematous and scaly circular plaque (**ringworm**) within which the infected hairs become brittle and broken. Numerous confluent patches of alopecia develop, and patients may complain of severe pruritus. *M. audouinii* infection is no longer common in the United States. **Favus** is a chronic form of tinea capitis that is rare in the United States and is caused by the fungus *Trichophyton schoenleinii.* Favus starts as yellowish red papules at the opening of hair follicles. The papules expand and coalesce to form cup-shaped, yellowish, crusted patches that fluoresce dull green under a Wood lamp.

Differential Diagnosis

Tinea capitis can be confused with seborrheic dermatitis, psoriasis, alopecia areata, trichotillomania, and certain dystrophic hair disorders. When inflammation is pronounced, as in kerion, primary or secondary bacterial infection must also be considered. In adolescents, the patchy, moth-eaten type of alopecia associated with secondary syphilis may resemble tinea capitis. If scarring occurs, discoid lupus erythematosus and lichen planopilaris must also be considered in the differential diagnosis.

The important diagnostic procedures for the various dermatophyte diseases include examination of infected hairs with a Wood lamp, microscopic examination of KOH preparations of infected material, and identification of the etiologic agent by culture. Hairs infected with common *Microsporum* spp. fluoresce a bright blue-green. Most *Trichophyton*-infected hairs do not fluoresce.

Microscopic examination of a KOH preparation of infected hair from the active border of a lesion discloses tiny spores surrounding the hair shaft in *Microsporum* infections and chains of spores within the hair shaft in *T. tonsurans* infections. Fungal elements are not usually seen in scales. A specific etiologic diagnosis of tinea capitis may be obtained by planting broken off infected hairs on Sabouraud medium with reagents to inhibit growth of other organisms. Such identification may require 2 wk or more.

Treatment

Oral administration of griseofulvin microcrystalline (20-25 mg/kg/24 hr, or 10-15 mg/kg per day if the ultramicrosize form is used) is the recommended treatment for all forms of tinea capitis. Absorption of griseofulvin is enhanced by ingestion of a fatty meal and should be recommended for the patient. It may be necessary for 8-12 wk and should be terminated only after fungal culture results are negative. Treatment for 1 mo after a negative culture result minimizes the risk of recurrence. Adverse reactions to griseofulvin are rare but include nausea, vomiting, headache, blood dyscrasias, phototoxicity, and hepatotoxicity. Terbinafine is also effective at a dosage of 3-6 mg/kg/24 hr for 4-6 wk or possibly in pulse therapy, although it has limited activity against *M. canis.* The oral granules formulation of terbinafine is approved by the FDA for tinea capitis in children 4 yr of age and older. Oral itraconazole is useful in instances of griseofulvin resistance, intolerance, or allergy. Itraconazole is given for 4-6 wk at a dosage of 3-5 mg/kg/24 hr with food. Capsules are preferable to the syrup, which may cause diarrhea. Itraconazole is not approved by the FDA for treatment of dermatophyte infections in the pediatric population. Topical therapy alone is ineffective, but it may be an important adjunct because it may decrease the shedding of spores, and should be recommended in all patients. Asymptomatic dermatophyte carriage in family members is common. Because 1 in 3 families have at least 1 member who is a carrier, treatment of both patient and potential carriers with a sporicidal shampoo may hasten clinical resolution. Vigorous shampooing with a 2.5% selenium sulfide, zinc pyrithione, or ketoconazole shampoo is helpful. It is not necessary to shave the scalp.

Tinea Corporis

Clinical Manifestations

Tinea corporis, defined as infection of the glabrous skin, excluding the palms, soles, and groin, can be caused by most of the dermatophyte species, although *T. rubrum* and *Trichophyton mentagrophytes* are the most prevalent etiologic organisms. In children, infections with *M. canis* are also common. Tinea corporis can be acquired by direct contact with infected persons or by contact with infected scales or hairs deposited on environmental surfaces. *M. canis* infections are usually acquired from infected pets.

The most typical clinical lesion begins as a dry, mildly erythematous, elevated, scaly papule or plaque that spreads centrifugally and clears centrally to form the characteristic annular lesion responsible for the designation ringworm (Fig. 666-7). At times, plaques with advancing borders may spread over large areas. Grouped pustules are another variant. Most lesions clear spontaneously within several months, but some may become chronic. Central clearing does not always occur (Fig. 666-8), and differences in host response may result in wide variability in the clinical appearance—for example, granulomatous lesions called **Majocchi granuloma,** which are caused by penetration of organisms along the hair follicle to the level of the dermis, produce a fungal folliculitis and perifolliculitis (Fig. 666-9), and the kerion-like lesions referred to as tinea profunda. Majocchi granuloma is more

Figure 666-7 Annular plaque of tinea corporis with central clearing.

Figure 666-8 Minimal central clearing with tinea corporis.

Figure 666-9 Follicular papule and pustule in Majocchi granuloma after use of a superpotent topical steroid.

common after inappropriate treatment with topical corticosteroids, especially the superpotent class.

Differential Diagnosis

Many skin lesions, both infectious and noninfectious, must be differentiated from the lesions of tinea corporis. Those most frequently confused are granuloma annulare, nummular eczema, pityriasis rosea, psoriasis, seborrheic dermatitis, erythema chronicum migrans, and tinea versicolor. Microscopic examination of KOH wet mount preparations and cultures should always be performed when fungal infection is considered. Tinea corporis usually does not fluoresce with a Wood lamp.

Treatment

Tinea corporis usually responds to treatment with one of the topical antifungal agents (e.g., imidazoles, terbinafine, naftifine) twice daily for 2-4 wk. In unusually severe or extensive disease, a course of therapy with oral griseofulvin microcrystalline may be required for 4 wk. Itraconazole has produced excellent results in many cases with a 1-2 wk course of oral therapy. Combination topical corticosteroid/antifungal preparations should not be used as it may result in worsening or persistent infection.

Tinea Cruris

Clinical Manifestations

Tinea cruris, or infection of the groin, occurs most often in adolescent males and is usually caused by the anthropophilic species *Epidermophyton floccosum* or *T. rubrum,* but occasionally by the zoophilic species *T. mentagrophytes.*

The initial clinical lesion is a small, raised, scaly, erythematous patch on the inner aspect of the thigh. This spreads peripherally, often developing numerous tiny vesicles at the advancing margin. It eventually forms bilateral, irregular, sharply bordered patches with hyperpigmented scaly centers. In some cases, particularly in infections with *T. mentagrophytes,* the inflammatory reaction is more intense and the infection may spread beyond the crural region. The scrotum and labia are usually not involved in the infection, an important distinction from candidosis. Pruritus may be severe initially but abates as the inflammatory reaction subsides. Bacterial superinfection may alter the clinical appearance, and erythrasma or candidosis may coexist. Tinea cruris is more prevalent in obese persons and in persons who perspire excessively and wear tight-fitting clothing.

Differential Diagnosis

The diagnosis of tinea cruris is confirmed by culture and by demonstration of septate hyphae on a KOH preparation of epidermal scrapings. The disorder must be differentiated from intertrigo, allergic contact dermatitis, candidosis, and erythrasma. Bacterial superinfection must be precluded when there is a severe inflammatory reaction.

Treatment

Patients should be advised to wear loose cotton underwear. **Topical treatment** with an imidazole twice a day for 3-4 wk is recommended for severe infection, especially because these agents are effective in mixed candidal-dermatophytic infections.

Tinea Pedis

Clinical Manifestations

Tinea pedis (athlete's foot), infection of the toe webs and soles of the feet, is uncommon in young children but occurs with some frequency in preadolescent and adolescent males. The usual etiologic agents are *T. rubrum, T. mentagrophytes,* and *E. floccosum.*

Most commonly, the lateral toe webs (3rd to 4th and 4th to 5th interdigital spaces) and the subdigital crevice are fissured, with maceration and peeling of the surrounding skin (Fig. 666-10). Severe tenderness, itching, and a persistent foul odor are characteristic. These lesions may become chronic. This type of infection may involve overgrowth by bacterial flora, including *Kytococcus sedentarius, Brevibacterium epidermidis,* and Gram-negative organisms. Less commonly, a chronic diffuse hyperkeratosis of the sole of the foot occurs with only mild erythema (Fig. 666-11). In many cases, 2 feet and 1 hand are involved. This type of infection is more refractory to treatment and tends to recur. An inflammatory vesicular type of reaction may occur with *T. mentagrophytes* infection. This type is most common in young children. The lesions involve any area of the foot, including the dorsal surface, and are usually circumscribed. The initial papules progress to

Figure 666-10 Interdigital tinea pedis.

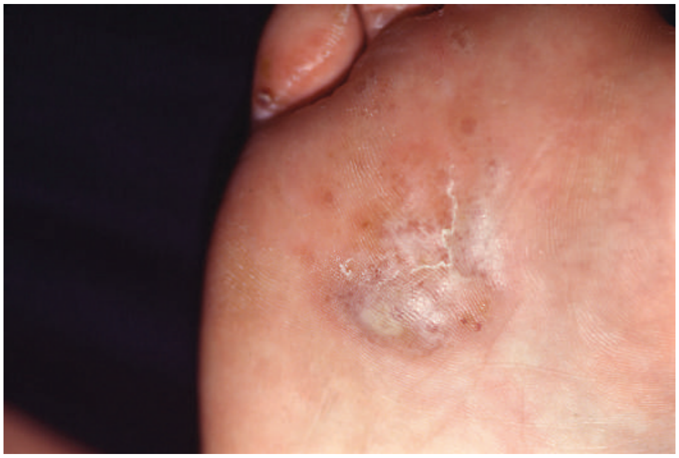

Figure 666-12 Vesicobullous tinea pedis.

Figure 666-11 Diffuse, minimally erythematous tinea pedis.

Figure 666-13 Hyperkeratotic nail in onychomycosis.

vesicles and bullae that may become pustular (Fig. 666-12). A number of factors, such as occlusive footwear and warm, humid weather, predispose to infection. Tinea pedis may be transmitted in shower facilities and swimming pool areas.

Differential Diagnosis

Tinea pedis must be differentiated from simple maceration and peeling of the interdigital spaces, which is common in children. Infection with *Candida albicans* and various bacterial organisms (erythrasma) may cause confusion or may coexist with primary tinea pedis. Contact dermatitis, vesicular foot dermatitis, atopic dermatitis, and juvenile plantar dermatitis also simulate tinea pedis. Fungal mycelia can be seen on microscopic examination of a KOH preparation or by culture.

Treatment

Treatment for mild infections includes simple measures such as avoidance of occlusive footwear, careful drying between the toes after bathing, and the use of an absorbent antifungal powder such as zinc undecylenate. Topical therapy with an imidazole is curative in most cases. Each of these agents is also effective against candidal infection. Several weeks of therapy may be necessary, and low-grade, chronic infections, particularly those caused by *T. rubrum*, may be refractory. In refractory cases, oral griseofulvin therapy may effect a cure, but recurrences are common.

Tinea Unguium

Clinical Manifestations

Tinea unguium (onychomycosis) is a dermatophyte infection of the nail plate. It occurs most often in patients with tinea pedis, but it may occur as a primary infection. It can be caused by a number of dermatophytes, of which *T. rubrum* and *T. mentagrophytes* are the most common.

The most superficial form of tinea unguium (i.e., white superficial onychomycosis) is caused by *T. mentagrophytes.* It manifests as irregular single or numerous white patches on the surface of the nail unassociated with paronychial inflammation or deep infection. *T. rubrum* generally causes a more invasive, subungual infection that is initiated at the lateral distal margins of the nail and is often preceded by mild paronychia. The middle and ventral layers of the nail plate, and perhaps the nail bed, are the sites of infection. The nail initially develops a yellowish discoloration and slowly becomes thickened, brittle, and loosened from the nail bed (Fig. 666-13). In advanced infection, the nail may turn dark brown to black and may crack or break off.

Differential Diagnosis

Tinea unguium must be differentiated from various dystrophic nail disorders. Changes as a result of trauma, psoriasis, lichen planus, eczema, and trachyonychia can all be confused with tinea unguium. Nails infected with *C. albicans* have several distinguishing features; most prominently, a pronounced paronychial swelling. Thin shavings taken from the infected nail, preferably from the deeper areas, should be examined microscopically with KOH and cultured. Repeated attempts may be required to demonstrate the fungus. Histologic evaluation of nail clippings with special stains for dermatophytes can be diagnostic.

The long half-life of itraconazole in the nail has led to promising trials of intermittent short courses of therapy (double the normal dose for 1 wk of each mo for 3-4 mo). Oral terbinafine is also used for the

treatment of onychomycosis. Terbinafine once daily for 12 wk is more effective than itraconazole pulse therapy. Griseofulvin and application of topical fungistatic agents to the nail bed are often ineffective and are not recommended.

Tinea Nigra Palmaris

Tinea nigra palmaris is a rare but distinctive superficial fungal infection that occurs principally in children and adolescents. It is caused by the dimorphic fungus *Phaeoannellomyces werneckii,* which imparts a gray-black color to the affected palm. The characteristic lesion is a well-defined hyperpigmented macule. Scaling and erythema are rare, and the lesions are asymptomatic. Tinea nigra is often mistaken for a junctional nevus, melanoma, or staining of the skin by contactants. Treatment is with an imidazole antifungal. *Keratolytic agents, such as salicylic acid, once to twice daily* can also be used.

CANDIDAL INFECTIONS (CANDIDOSIS, CANDIDIASIS, AND MONILIASIS)

See Chapter 234.

The dimorphic yeasts of the genus *Candida* are ubiquitous in the environment, but *C. albicans* usually causes candidosis in children. This yeast is not part of the indigenous skin flora, but it is a frequent transient on skin and may colonize the human alimentary tract and the vagina as a saprophytic organism. Certain environmental conditions, notably elevated temperature and humidity, are associated with an increased frequency of isolation of *C. albicans* from the skin. Many bacterial species inhibit the growth of *C. albicans,* and alteration of normal flora by the use of antibiotics may promote overgrowth of the yeast.

Chronic mucocutaneous candidiasis is associated with a diverse group of primary immunodeficiency diseases (Table 666-1). Chronic

Table 666-1 Primary Immunodeficiencies Underlying Fungal Infections

DISEASE	ASSOCIATED INFECTIONS	IMMUNOLOGIC PHENOTYPE	GENE, TRANSMISSION
CMC			
SCID	Bacteria, viruses, fungi, mycobacteria	No T cells, with or without B and/or NK cell lymphopenia	>30 genes: *IL2RG,* X-linked; *JAK3,* autosomal recessive; RAG1, autosomal recessive; *RAG2,* autosomal recessive; *ARTEMIS,* autosomal recessive; *ADA,* autosomal recessive; *CD3,* autosomal recessive, etc.
CID		T-cell defect	
CD25 deficiency	Viruses and bacteria		*IL2RA,* autosomal recessive
NEMO or iκBγ deficiency	Pyogenic bacteria, mycobacteria, viruses		*NEMO* or *IKBG* X-linked
IκBα GOF mutation			*IKBA,* autosomal dominant
DOCK8 deficiency	Viruses, bacteria and fungi		*DOCK8,* autosomal recessive
TCR-α deficiency	Viruses and bacteria		*TCRA,* autosomal recessive
CRACM1 deficiency	Viruses, mycobacteria, bacteria and fungi		*CRACM1,* autosomal recessive
MST1/STK4 deficiency	Viruses and bacteria		*MST1/STK4,* autosomal recessive
MHC class II deficiency	Viruses, bacteria and fungi		*CIITA, RFXANK, RFXC, RFXAP,* all autosomal recessive
Idiopathic CD4 lymphopenia	*Pneumocystis, Cryptococcus,* virus	CD4 T cells <300 cells/mm^3	*UNC119,* autosomal dominant, *MAGT1* X-linked, *RAG1,* autosomal recessive
SYNDROMIC CMC			
Interleukin-12Rβ1 and interleukin-12p40 deficiencies	*Mycobacteria, Salmonella*	Deficit of interleukin-17–producing T cells	*IL12RB1,* autosomal recessive, *IL12B,* autosomal recessive
STAT3 deficiency (autosomal dominant-HIES)	*Staphylococcus aureus, Aspergillus*	Hyperimmunoglobulin E, deficit of interleukin-17–producing T cells	*STAT3,* autosomal dominant
APECED/APS-1	No	Neutralizing anti–interleukin-17A, anti–interleukin-17F, and/or anti–interleukin-22 autoantibodies	*AIRE,* autosomal recessive
CARD9 deficiency	Dermatophytes, *Candida,* brain abscess	Deficit of interleukin-17–producing T cells	*CARD9,* autosomal recessive
CMCD			
Complete interleukin-17RA deficiency	*S. aureus*	No interleukin-17 response	*IL17RA,* autosomal recessive
Partial interleukin-17F deficiency	*S. aureus*	Impaired interleukin-17F, interleukin-17A/F function	*IL17F,* autosomal dominant
STAT1 GOF mutations	Bacteria, viruses, fungi, mycobacteria	Low interleukin-17–producing T cells	*STAT1,* autosomal dominant

AIRE, autoimmune regulator; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APS-1, autoimmune polyendocrinopathy syndrome type 1; CARD9, caspase recruitment domain-containing protein 9; CID, combined immunodeficiency; CMC, chronic mucocutaneous candidiasis; CMCD, chronic mucocutaneous candidiasis disease; CRACM1, calcium release-activated calcium modulator 1; GOF, gain-of-function; HIES, hyperimmunoglobulin E syndrome; IκBα, inhibitor of nuclear factor of kappa light polypeptide gene enhancer in B-cells, alpha; iκBγ, inhibitor of nuclear factor of kappa light polypeptide gene enhancer in B-cells, gamma; MHC, major histocompatibility complex; MST1, macrophage stimulating 1; NEMO, nuclear factor κB essential modulator; NK, natural killer; SCID, severe combined immunodeficiency; STAT, signal transducer and activator of transcription; STK4, serine/threonine protein kinase 4; TCR, T-cell receptor.

From Lanternier F, Cypowyj S, Picard, C, et al: Primary immunodeficiencies underlying fungal infections. Curr Opin Pediatr *25:736–747, 2013.*

mucocutaneous candidiasis is characterized by chronic or recurrent *Candida* infections of the oral cavity, esophagus, genitals, nails, and skin. Chronic mucocutaneous candidiasis may also be seen as an acquired infection in patients with HIV infection, and during immunosuppressive treatments.

Oral Candidosis (Thrush)

See Chapter 234.

Vaginal Candidosis

See Chapters 120 and 234.

C. albicans is an inhabitant of the vagina in 5-10% of women, and vaginal candidosis is not uncommon in adolescent girls. A number of factors can predispose to this infection, including antibiotic therapy, corticosteroid therapy, diabetes mellitus, pregnancy, and the use of oral contraceptives. The infection manifests as cheesy white plaques on an erythematous vaginal mucosa and a thick white-yellow discharge. The disease may be relatively mild or may produce pronounced inflammation and scaling of the external genitals and surrounding skin with progression to vesiculation and ulceration. Patients often complain of severe itching and burning in the vaginal area. Before treatment is initiated, the diagnosis should be confirmed by microscopic examination and/or culture. The infection may be eradicated by insertion of nystatin or imidazole vaginal tablets, suppositories, creams, or foam. If these products are ineffective, the addition of one dose of fluconazole (150 mg) is effective.

Congenital Cutaneous Candidosis

See Chapter 234.

Candidal Diaper Dermatitis

Candidal diaper dermatitis is a ubiquitous problem in infants and, although relatively benign, is often frustrating because of its tendency to recur. Predisposed infants usually carry *C. albicans* in their intestinal tracts, and the warm, moist, occluded skin of the diaper area provides an optimal environment for its growth. A seborrheic, atopic, or primary irritant contact dermatitis usually provides a portal of entry for the yeast.

The primary clinical manifestation consists of an intensely erythematous, confluent plaque with a scalloped border and a sharply demarcated edge. It is formed by the confluence of numerous papules and vesicular pustules. Satellite pustules, those that stud the contiguous skin, are a hallmark of localized candidal infections. The perianal skin, inguinal folds, perineum, and lower abdomen are usually involved (Fig. 666-14). In males, the entire scrotum and penis may be involved, with an erosive balanitis of the perimeatal skin. In females, the lesions may be found on the vaginal mucosa and labia. In some infants, the process is generalized, with erythematous lesions distant from the diaper area. In some cases, the generalized process may represent a fungal id (hypersensitivity) reaction.

The **differential diagnosis** of candidal diaper dermatitis includes other eruptions of the diaper area that may coexist with candidal infection. For this reason, it is important to establish a diagnosis by means of KOH preparation or culture.

Treatment consists of applications of an imidazole cream 2 times daily. The combination of a corticosteroid and an antifungal agent may be justified if inflammation is severe but may confuse the situation if the diagnosis is not firmly established. Corticosteroid should not be continued for more than a few days. Protection of the diaper area by an application of thick zinc oxide paste overlying the anticandidal preparation may be helpful. The paste is more easily removed with mineral oil than with soap and water. Fungal id reactions gradually abate with successful treatment of the diaper dermatitis or may be treated with a mild corticosteroid preparation. When recurrences of diaper candidosis are frequent, it may be helpful to prescribe a course of oral anticandidal therapy to decrease the yeast population in the gastrointestinal tract. Some infants seem to be receptive hosts for *C. albicans* and may reacquire the organism from a colonized adult.

Intertriginous Candidosis

Intertriginous candidosis occurs most often in the axillae and groin, on the neck (Fig. 666-15) under the breasts, under pendulous abdominal fat folds, in the umbilicus, and in the gluteal cleft. Typical lesions are large, confluent areas of moist, denuded, erythematous skin with an irregular, macerated, scaly border. Satellite lesions are characteristic and consist of small vesicles or pustules on an erythematous base. With time, intertriginous candidal lesions may become lichenified, dry, scaly plaques. The lesions develop on skin subjected to irritation and maceration. Candidal superinfection is more likely to occur under conditions that lead to excessive perspiration, especially in obese children and in children with underlying disorders, such as diabetes mellitus. A similar condition, interdigital candidosis, commonly occurs in individuals whose hands are constantly immersed in water. Fissures occur between the fingers and have red denuded centers, with an overhanging white epithelial fringe. Similar lesions between the toes may be secondary to occlusive footwear. Treatment is the same as for other candidal infections.

Perianal Candidosis

Perianal dermatitis develops at sites of skin irritation as a result of occlusion, constant moisture, poor hygiene, anal fissures, and pruritus from pinworm infestation. It may become superinfected with *C. albicans,* especially in children who are receiving oral antibiotic or corticosteroid medication. The involved skin becomes erythematous, macerated, and excoriated, and the lesions are identical to those of candidal intertrigo or candidal diaper rash. Application of a topical

Figure 666-14 Erythematous confluent plaque caused by candidal infection.

Figure 666-15 Intertriginous candidosis of the neck.

antifungal agent in conjunction with improved hygiene is usually effective. Underlying disorders such as pinworm infection must also be treated (see Chapter 293).

Candidal Paronychia and Onychia

See Chapter 663.

Candidal Granuloma

Candidal granuloma is a rare response to an invasive candidal infection of skin. The lesions appear as crusted, verrucous plaques and hornlike projections on the scalp, face, and distal limbs. Affected patients may have single or numerous defects in immune mechanisms, and the granulomas are often refractory to topical therapy. A systemic anticandidal agent may be required for palliation or eradication of the infection.

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Figure 667-1 Verrucous papules on the back of the hand.

Chapter 667
Cutaneous Viral Infections

Anna M. Juern and Beth A. Drolet

WART (VERRUCA)

Etiology

Human papillomaviruses (HPVs) cause a spectrum of disease from warts (verrucae vulgaris) to squamous cell carcinoma of the skin and mucous membranes, including the larynx (see Chapter 390.2). The HPVs are classified by genus, species, and type. More than 200 types are known, and the entire genomes of approximately 100 are completely sequenced. The incidence of all types of warts is highest in children and adolescents. HPV is spread by direct contact and autoinoculation; transmission within families and by fomites occurs. The clinical manifestations of infection develop 1 mo or longer after inoculation and depend on the HPV type, the size of the inoculum, the immune status of the host, and the anatomic site.

Clinical Manifestations

Cutaneous warts develop in 5-10% of children. **Common warts** (verruca vulgaris), caused most commonly by HPV types 2 and 4, occur most frequently on the fingers, dorsum of the hands (Fig. 667-1), paronychial areas, face, knees, and elbows. They are well-circumscribed papules with an irregular, roughened, keratotic surface. When the surface is pared away, many black dots representing thrombosed dermal capillary loops are often visible. **Periungual warts** are often painful and may spread beneath the nail plate, separating it from the nail bed (Fig. 667-2). **Plantar warts (verruca plantaris),** although similar to the common wart, are caused by HPV type 1 and are usually flush with the surface of the sole because of the constant pressure from weight bearing. When plantar warts become hyperkeratotic (Fig. 667-3), they may be painful. Similar lesions (palmar–verruca palmaris) can also occur on the palms. They are sharply demarcated, often with a ring of thick callus. The surface keratotic material must sometimes be removed before the boundaries of the wart can be appreciated. Several contiguous warts (HPV type 4) may fuse to form a large plaque, the so-called mosaic wart. Flat warts (verruca plana), caused by HPV types 3 and 10, are slightly elevated, minimally hyperkeratotic papules that usually remain <3 mm in diameter and vary in color from pink to brown. They may occur in profusion on the face, arms, dorsum of the hands, and knees. The distribution of several lesions along a line of cutaneous trauma is a helpful diagnostic feature (Fig. 667-4). Lesions may be disseminated in the beard area and on the legs by shaving and from the hairline onto the scalp by combing the hair. **Epidermodysplasia verruciformis** (*EVER1, EVER2* genes), caused primarily by HPV types 5 and 8 (β-papillomaviruses, species 1), manifests as many diffuse verrucous papules. Wart types 9, 12, 14, 15, 17, 25, 36, 38, 47,

Figure 667-2 Periungual wart with disruption of nail growth.

Figure 667-3 Hyperkeratotic plantar wart.

Figure 667-4 Multiple flat warts on the face with lesions in line of trauma.

Figure 667-5 Condylomata acuminata in the perianal area of a toddler.

and 50 may also be involved. Inheritance is thought to be primarily autosomal recessive, but an X-linked recessive form also has been postulated. Warts progress to **squamous cell carcinoma** in 10% of patients with epidermodysplasia verruciformis.

Genital HPV infection occurs in sexually active adolescents, most commonly as a result of infection with HPV types 6 and 11. **Condylomata acuminata** (mucous membrane warts) are moist, fleshy, papillomatous lesions that occur on the perianal mucosa (Fig. 667-5), labia, vaginal introitus, and perineal raphe, and on the shaft, corona, and glans penis. Occasionally, they obstruct the urethral meatus or the vaginal introitus. Because they are located in intertriginous areas, they may become moist and friable. When untreated, condylomata proliferate and become confluent, at times forming large cauliflower-like masses. Lesions can also occur on the lips, gingivae, tongue, and conjunctivae. Genital warts in children may occur after inoculation during birth through an infected birth canal, as a consequence of sexual abuse, or from incidental spread from cutaneous warts. A significant proportion of genital warts in children contain HPV types that are usually isolated from cutaneous warts. HPV infection of the cervix is a major risk factor for development of carcinoma, particularly if the infection is caused by HPV type 16, 18, 31, 33, 35, 39, 45, 52, 59, 67, 68, or 70. Immunization against types 6, 11, 16, and 18 is now available. Laryngeal (respiratory) papillomas contain the same HPV types as in anogenital papillomas. Transmission is believed to occur from mothers with genital HPV infection to neonates who aspirate infectious virus during birth and may develop laryngeal papillomatosis.

Histology

The various types of warts share the basic changes of hyperplasia of the epidermal cells and vacuolation of the spinous keratinocytes, which may contain basophilic intranuclear inclusions (viral particles). Warts are confined to the epidermis and do not have "roots." Individuals with impaired cell-mediated immunity are particularly susceptible to HPV infection. Antibodies occur in response to infection but appear to have little protective effect.

Differential Diagnosis

Common warts are most often confused with molluscum contagiosum. Plantar and palmar warts may be difficult to distinguish from punctate keratoses, corns, and calluses. In contrast to calluses, warts obliterate normal skin markings. Juvenile flat warts mimic lichen planus, lichen nitidus, angiofibromas, syringomas, milia, and acne. Condylomata acuminata may resemble condylomata lata of secondary syphilis.

Treatment

Various therapeutic measures are effective in the treatment of warts. More than 65% of warts disappear spontaneously within 2 yr. Warts are epidermal lesions and do not produce scarring unless they are managed surgically or treated in an overly aggressive fashion. Hyperkeratotic lesions (common, plantar, and palmar warts) are more responsive to therapy if the excess keratotic debris is gently pared with a scalpel until thrombosed capillaries are apparent; further paring induces bleeding. Treatment is most successful when performed regularly and frequently (every 2-4 wk).

Common warts can be destroyed by applications of liquid nitrogen or by pulsed dye laser. Daily application of salicylic acid in flexible collodion or as a stick is a slow but painless method of removal that is effective in some patients. Plantar and palmar warts may be treated with 40% salicylic acid plasters. These should be applied for 5 days at a time with a 2-day rest period between applications. Following removal of the plaster and prolonged soaking in hot water, keratotic debris can be removed with an emery board or pumice stone. Condylomata respond best to weekly applications of 25% podophyllin in tincture of benzoin. The medication should be left on the warts for 4-6 hr and then removed by bathing. Keratinized warts near the genitalia (buttocks) do not respond to podophyllin. Imiquimod (5% cream) applied 3 times weekly is also beneficial. Imiquimod is indicated for genital warts but has also been used successfully to treat warts in other locations. For nongenital warts, imiquimod should be applied daily. Cimetidine 30-40 mg/kg/day has been used in children with multiple warts unresponsive to other treatments. Immunotherapy with intralesional candida or trichophyton antigen may also be employed especially when lesions are numerous or resistant to other tried therapies. Immunotherapy is performed in clinic and multiple treatments every month (at least 3-4) are usually required. With all types of therapy, care should be taken to protect the surrounding normal skin from irritation.

MOLLUSCUM CONTAGIOSUM

Etiology

The poxvirus that causes molluscum contagiosum is a large double-stranded DNA virus that replicates in the cytoplasm of host epithelial cells. The 3 types cannot be differentiated on the basis of clinical appearance, location of lesions, or a patient's age or sex. Type 1 virus causes most infections. The disease is acquired by direct contact with an infected person or from fomites and is spread by autoinoculation. Children age 2-6 yr who are otherwise well and individuals who are immunosuppressed are affected most commonly. The incubation period is estimated to be 2 wk or longer.

Clinical Manifestations

Discrete, pearly, skin-colored, smooth, dome-shaped, papules vary in size from 1-5 mm. They typically have a central umbilication from which a plug of cheesy material can be expressed. The papules may occur anywhere on the body, but the face, eyelids, neck, axillae, and thighs are sites of predilection (Fig. 667-6). They may be found in

Figure 667-6 Grouped molluscum.

Figure 667-7 Molluscum with surrounding dermatitis.

clusters on the genitals or in the groin of adolescents and may be associated with other venereal diseases in sexually active individuals. Lesions commonly involve the genital area in children but are not acquired by sexual transmission in most cases. Mild surrounding erythema or an eczematous dermatitis may accompany the papules (Fig. 667-7). Lesions on patients with AIDS tend to be large and numerous, particularly on the face. Exuberant lesions may also be found in children with leukemia and other immunodeficiencies. Children with atopic dermatitis are susceptible to widespread involvement in areas of dermatitis. A pustular eruption at the site of individual molluscum lesions is seen (Fig. 667-8). It is not a secondary bacterial infection, but an immunologic reaction to the molluscum virus and it should not be treated with antibiotics. Atrophic scars are often seen after this type of reaction.

Differential Diagnosis

Differential diagnosis of molluscum contagiosum includes trichoepithelioma, basal cell carcinoma, ectopic sebaceous glands, syringoma, hidrocystoma, keratoacanthoma, and warty dyskeratoma. In individuals with AIDS, cryptococcosis may be indistinguishable clinically from molluscum contagiosum. Rarely, coccidioidomycosis, histoplasmosis, or *Penicillium marneffei* infection masquerades as molluscum-like lesions in an immunocompromised host.

Histology

The epidermis is hyperplastic and hypertrophied, extending into the underlying dermis and projecting above the skin surface. The central plug of material, which is composed of virus-laden cells, may be shelled out from a lesion and examined under the microscope. The rounded, cup-shaped mass of homogeneous cells, often with identifiable lobules,

Figure 667-8 Inflamed molluscum. Crusted papule at site of previous molluscum.

is diagnostic. Specific antibody against molluscum contagiosum virus is detectable in most infected individuals but is of uncertain immunologic significance. Cell-mediated immunity is thought to be important in host defense.

Treatment

Molluscum contagiosum is a self-limited disease. The average attack lasts 6-9 mo. However, lesions can persist for years, can spread to distant sites, and may be transmitted to others. Affected patients should be advised to avoid shared baths and towels until the infection is clear. Infection may spread rapidly and produce hundreds of lesions in children with atopic dermatitis or immunodeficiency. Immunotherapy with either candida or trichophyton antigen, is now the most commonly used therapy. This is repeated every 4 wk until resolution. If lesions are limited in number, then depending on the age of the patient, individual lesions can be treated with liquid nitrogen cryotherapy. For younger children, cantharidin may be applied to the lesions and covered with adhesive bandages to prevent unwanted spread of the blistering agent. A blister forms at the site of application, and the molluscum is removed with the blister. Cantharidin should not be used on the face. Cantharidin however, is now very limited or completely unavailable in the United States. Facial molluscum is more cosmetically upsetting to children and parents; imiquimod applied topically is beneficial if not excessively irritating. Molluscum is an epidermal disease and should not be overtreated such that scarring results.

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Chapter 668
Arthropod Bites and Infestations

668.1 Arthropod Bites

Anna M. Juern and Beth A. Drolet

Arthropod bites are a common affliction of children and occasionally pose a problem in diagnosis. A patient may be unaware of the source of the lesions or may deny being bitten, making interpretation of the

eruption difficult. In these cases, knowledge of the habits, life cycle, and clinical signs of the more common arthropod pests of humans may help lead to a correct diagnosis (Table 668-1).

CLINICAL MANIFESTATIONS

The type of reaction that occurs after an arthropod bite depends on the species of insect and the age group and reactivity of the human host. Arthropods may cause injury to a host by various mechanisms, including mechanical trauma, such as the lacerating bite of a tsetse fly; invasion of host tissues, as in myiasis; contact dermatitis, as seen with repeated exposure to cockroach antigens; granulomatous reaction to retained mouthparts; transmission of systemic disease; injection of irritant cytotoxic or pharmacologically active substances, such as hyaluronidase, proteases, peptidases, and phospholipases in sting venom; and induction of anaphylaxis. Most reactions to arthropod bites depend on antibody formation to antigenic substances in saliva or venom. The type of reaction is determined primarily by the degree of previous exposure to the same or a related species of arthropod. When someone is bitten for the first time, no reaction develops. An immediate petechial reaction is occasionally seen. After repeated bites, sensitivity develops, producing a pruritic papule (Fig. 668-1) approximately 24 hr after the bite. This is the most common reaction seen in young children. With prolonged, repeated exposure, a wheal develops within minutes after a bite, followed 24 hr later by papule, vesicle, or bullae formation. By adolescence or adulthood, only a wheal may form, unaccompanied by the delayed papular reaction. Thus, adults in the same household as affected children may be unaffected. Ultimately, as a person becomes insensitive to the bite, no reaction occurs at all. This stage of nonreactivity is maintained only as long as the individual continues to be bitten regularly. Individuals in whom papular urticaria develops are in the transitional phase between development of primarily a delayed papular reaction and development of an immediate urticarial reaction.

Arthropod bites may occur as solitary, numerous, or profuse lesions, depending on the feeding habits of the perpetrator. Fleas tend to sample their host several times within a small localized area, whereas mosquitoes tend to attack a host as more randomly scattered sites. Delayed hypersensitivity reactions to insect bites, the predominant lesions in the young and uninitiated, are characterized by firm, persistent papules that may become hyperpigmented and are often excoriated and crusted. Pruritus may be mild or severe, transient or persistent. A central punctum is usually visible but may disappear as the lesion ages or is scratched. The immediate hypersensitivity reaction is characterized by an evanescent, erythematous wheal. If edema is marked, a tiny vesicle may surmount the wheal. Certain beetles produce bullous lesions through the action of cantharidin, and various insects, including beetles and spiders, may cause hemorrhagic nodules and ulcers. Bites on the lower extremities are more likely to be severe or persistent or to become bullous than those located elsewhere. Complications of arthropod bites include development of impetigo, folliculitis, cellulitis, lymphangitis, and severe anaphylactic hypersensitivity reactions, particularly after the bite of certain hymenopterans. The histopathologic changes are variable, depending on the arthropod, the age of the lesion, and the reactivity of the host. Acute urticarial lesions tend to show central vesiculation in which eosinophils are numerous. Papules most commonly show dermal edema and a mixed superficial and deep

Figure 668-1 Pruritic papules after bedbug bites.

Table 668-1 Bed Bugs vs Other Arthropod Bites: Main Clinical and Epidemiologic Features*

ARTHROPOD	CLINICAL FEATURES ON EXAMINATION	LOCATION	TIMING OF PRURITUS	CONTEXT
Bed bugs	3-4 Bites in a line or curve	Uncovered areas	Morning	Travelling
Fleas	3-4 Bites in a line or curve	Legs and buttocks	Daytime	Pet owners or rural living
Mosquitoes	Nonspecific urticarial papules	Potentially anywhere	*Anopheles* spp. night; *Culex* spp. night; *Aedes* spp. day	Worldwide distribution
Head lice	Live lice on the head associated with itchy, scratched lesions	Scalp, ears, and neck	Any	Children, parents, or contact with children
Body lice	Excoriated papules and hyperpigmentation; live lice inside clothes	Back	Any	Homeless people, developing countries
Sarcoptes scabiei mites (scabies)	Vesicles, burrows, nodules, and nonspecific secondary lesions	Interdigital spaces, forearms, breasts, genitalia	Night	Sexually transmitted, households or institutions
Ticks	Erythema migrans or ulcer	Potentially anywhere	Asymptomatic	Pet owners or hikers
Pyemotes X ventricosus	Comet sign, a linear erythematous macular tract	Under clothes	Any time when inside habitat	People exposed to woodworm contaminated furniture (*Pediculoides ventricosus* is a woodworm parasite)
Spiders	Necrosis (uncommon)	Face and arms	Immediate pain, no itching	Rural living

*It is difficult to diagnose a bite. Diagnosis relies on an array of arguments, none of which is specific by itself; it is the association of elements that is suggestive. Any arthropod bite can be totally asymptomatic.

From Bernardeschi C, Le Cleach L, Delaunay P, Chosidow O: Bed bug infestation. BMJ *346:f138, 2013.*

Figure 668-2 Red-brown papules in papular urticaria.

perivascular inflammatory infiltrate, often including a number of eosinophils. At times, however, the dermal cellular infiltrate is so dense that a lymphoma is suspected. Many young children demonstrate extensive dermal but nonerythematous, nontender edema and which responds to oral antihistamines in response to mosquito bites ("skeeter" syndrome), and must be distinguished from cellulitis, which tends to be painful, tender, and red. Retained mouthparts may stimulate a foreign body type of granulomatous reaction.

Papular urticaria occurs principally in the 1st decade of life. It may occur at any time of the year. The most common culprits are species of fleas, mites, bedbugs, gnats, mosquitoes, chiggers, and animal lice. Individuals with papular urticaria have predominantly transitional lesions in various stages of evolution between delayed-onset papules and immediate-onset wheals. The most characteristic lesion is an edematous, red-brown papule (Fig. 668-2). An individual lesion frequently starts as a wheal that, in turn, is replaced by a papule. A given bite may incite an id reaction at distant sites of quiescent bites in the form of erythematous macules, papules, or urticarial plaques. After a season or two, the reaction progresses from a transitional to a primarily immediate hypersensitivity urticarial reaction.

One of the most commonly encountered arthropod bites is that resulting from human, cat, or dog fleas (family *Pulicidae*). Eggs, which are generally laid in dusty areas and cracks between floorboards, give rise to larvae that then form cocoons. The cocoon stage can persist for up to 1 yr, and the flea emerges in response to vibrations from footsteps, accounting for the assaults that frequently befall the new owners of a recently reopened dwelling. Adult dog fleas can live without a blood meal for approximately 60 days. Attacks from fleas are more likely to occur when the fleas do not have access to their usual host; cat or dog fleas are more voracious and problematic when one visits an area frequented by the pet than when the pet is encountered directly. Flea bites tend to be grouped in lines or irregular clusters on the lower extremities. Fleas are often not seen on the body of a pet. Diagnosis of flea bites is aided by examination of debris from the animal's bedding material. The debris is collected by shaking the bedding into a plastic bag and examining the contents for fleas or their eggs, larvae, or feces.

TREATMENT

Treatment is directed at alleviation of pruritus by oral antihistamines and cool compresses. Potent topical corticosteroids are helpful. Topical antihistamines are potent immunologic sensitizers and have no role in the treatment of insect bite reactions. A short course of systemic steroids may be helpful if many severe reactions occur, particularly around the eyes. Insect repellents containing *N,N*-diethyl-3-methylbenzamide (DEET) may afford moderate protection against mosquitoes, fleas, flies, chiggers, and ticks, but are relatively ineffective against wasps, bees, and hornets. DEET must be applied to exposed skin and clothing to be effective. The most effective protection against mosquitoes, the human body louse, and other blood-feeding arthropods is use of DEET and permethrin-impregnated clothing. These measures are not effective, however, against the phlebotomine sand fly, which transmits leishmaniasis. Because of the potential for toxicity, the lowest effective DEET dose should be selected. Additional insect repellents include picaridin (flies, mosquitoes, chiggers, ticks), IR3535 (mosquitoes), oil of lemon, eucalyptus (mosquitoes), and citronella (mosquitoes). Table 668-2 lists methods to eliminate bed bugs.

An effort should be made to identify and eradicate the etiologic agent. Pets should be carefully inspected. Crawl spaces, eaves, and other sites of the house or outbuildings frequented by animals and birds should be decontaminated, and baseboard crevices, mattresses, rugs, furniture, and animal sleeping quarters should be decontaminated. Agents that are effective for ridding the home of fleas include lindane, pyrethroids, and organic thiocyanates. Flea-infested pets may be treated with powders containing rotenone, pyrethroids, Malathion, or methoxychlor. Lufenuron, an agent that prevents fleas from reproducing, is effective for animals in oral and injectable formulations. Fipronil is effective as a topical agent for the prevention of flea infestation.

Table 668-2 Patient Education to Eliminate Bed Bugs
Detection
• Look for brown insects no bigger than apple seeds on the mattress, sofa, and curtains and in darker places in the room (especially cracks in the walls, crevices in box springs, and furniture)
• Look for black spots on the mattress or blood traces on the sheets
Elimination
• Contact a pest management company
• Wash clothes at 60°C (140°F) or freeze delicate clothing, vacuum, and clean your home before the pest manager visits
• Collaborate with professionals who are used to dealing with bed bug infestation to increase eradication efficacy
Prevention
• Carefully examine secondhand furniture to assure the absence of bed bugs before purchase so as not to contaminate your home
• When sleeping in a hotel, even an upmarket establishment, lift mattresses to look for bed bugs or black spots
• Do not leave luggage in dark places, near furniture, or close to your bed. Before going to bed, close suitcases and put them in the bathroom—in the bathtub or shower stall

From Bernardeschi C, Le Cleach L, Delaunay P, Chosidow O: Bed bug infestation. BMJ *346:f138, 2013.*

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668.2 Scabies

Anna M. Juern and Beth A. Drolet

Scabies is caused by burrowing and release of toxic or antigenic substances by the female mite *Sarcoptes scabiei* var. *hominis*. The most important factor that determines spread of scabies is the extent and duration of physical contact with an affected individual. The children and sexual partner of an affected individual are most at risk. Scabies is transmitted only rarely by fomites because the isolated mite dies within 2-3 days.

ETIOLOGY AND PATHOGENESIS

An adult female mite measures approximately 0.4 mm in length, has 4 sets of legs, and has a hemispheric body marked by transverse corrugations, brown spines, and bristles on the dorsal surface. A male mite is approximately half her size and is similar in configuration. After impregnation on the skin surface, a gravid female exudes a keratolytic substance and burrows into the stratum corneum, often forming a shallow well within 30 min. She gradually extends this tract by

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0.5-5.0 mm/24 hr along the boundary with the stratum granulosum. She deposits 10-25 oval eggs and numerous brown fecal pellets (scybala) daily. When egg laying is completed, in 4-5 wk, she dies within the burrow. The eggs hatch in 3-5 days, releasing larvae that move to the skin surface to molt into nymphs. Maturity is achieved in approximately 2-3 wk. Mating occurs, and the gravid female invades the skin to complete the life cycle.

CLINICAL MANIFESTATIONS

In an immunocompetent host, scabies is frequently heralded by intense pruritus, particularly at night. The first sign of the infestation often consists of 1-2 mm red papules, some of which are excoriated, crusted, or scaling. Threadlike burrows are the classic lesion of scabies (Fig. 668-3) but may not be seen in infants. In infants, bullae and pustules are relatively common. The eruption may also include wheals, papules, vesicles, and a superimposed eczematous dermatitis (Fig. 668-4). The palms, soles, and scalp are often affected. In older children and adolescents, the clinical pattern is similar to that in adults, in whom preferred sites are the interdigital spaces, wrist flexors, anterior axillary folds, ankles, buttocks, umbilicus and belt line, groin, genitals in men, and areolas in women. The head, neck, palms, and soles are generally spared. Infants will often have a diffuse eczematous eruption that will involve the scalp, neck, and face. Red-brown nodules, most often located in covered areas such as the axillae, groin, and genitals, predominate in the less common variant called nodular scabies. Additional clues include facial sparing, affected family members, poor response to topical antibiotics, and transient response to topical steroids. Untreated, scabies may lead to eczematous dermatitis, impetigo, ecthyma, folliculitis, furunculosis, cellulitis, lymphangitis, and id reaction. Glomerulonephritis has developed in children from streptococcal impetiginization of scabies lesions. In some tropical areas, scabies is the predominant underlying cause of pyoderma. A latent period of approximately 1 mo follows an initial infestation. Thus, itching may be absent and lesions may be relatively inapparent in contacts who are asymptomatic carriers. On reinfestation, however, reactions to mite antigens are noted within hours.

Figure 668-3 Classic scabies burrow.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of scabies can often be made clinically but is confirmed by microscopic identification of mites (Fig. 668-5*A*), ova, and scybala (Fig. 668-5*B*) in epithelial debris. Scrapings most often test positive when obtained from burrows or fresh papules. A reliable method is application of a drop of mineral oil on the selected lesion, scraping of it with a No. 15 blade, and transferring the oil and scrapings to a glass slide.

The differential diagnosis depends on the types of lesions present. Burrows are virtually pathognomonic for human scabies. Papulovesicular lesions are confused with papular urticaria, canine scabies, chickenpox, viral exanthems, drug eruptions, dermatitis herpetiformis, and folliculitis. Eczematous lesions may mimic atopic dermatitis and seborrheic dermatitis, and the less common bullous disorders of childhood may be suspected in infants with predominantly bullous lesions. Nodular scabies is frequently misdiagnosed as urticaria pigmentosa and Langerhans cell histiocytosis. The histopathologic appearance of nodular scabies, consisting of a deep, dense, perivascular infiltrate of lymphocytes, histiocytes, plasma cells, and atypical mononuclear cells, may mimic malignant lymphoid neoplasms.

Figure 668-4 A, Diffuse scabies on an infant. The face is clear. The lesions are most numerous around the axillae, chest, and abdomen. **B,** Scabies. Infestation of the palms and soles is common in infants. The vesicular lesions have all ruptured. *(From Habif TP, editor:* Clinical dermatology*, ed 4, Philadelphia, 2004, Mosby, Figs. 15-8 and 15-9.)*

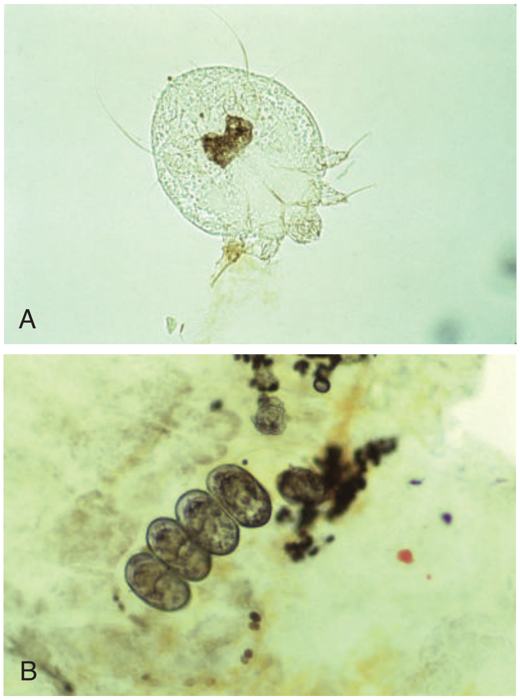

Figure 668-5 **A,** Human scabies mite obtained from scraping. **B,** Scabies ova and scybala.

TREATMENT

The treatment of choice for scabies is permethrin 5% cream (Elimite) applied to the entire body from the neck down, with particular attention to intensely involved areas, which is also standard therapy. Scabies is frequently found above the neck in infants (younger than 2 yr old), necessitating treatment of the scalp. The medication is left on the skin for 8-12 hr and should be reapplied in 1 wk for another 8-12 hr period. Additional therapies may include lindane 1% lotion or cream, sulfur ointment 5-10%, and crotamiton 10% lotion or cream. For severe infestations and in immunocompromised patients oral ivermectin 200 µg/kg per dose given orally for 2 doses, 2 wk apart can be used (off-label use). Single dose ivermectin (200 µg/kg) has also been effective in immunocompetent patients with improvement (cure) noted in 60% at 2 wk and 89% at 4 wk after treatment.

Transmission of mites is unlikely more than 24 hr after treatment. Pruritus, which is a result of hypersensitivity to mite antigens, may persist for a number of days to weeks, and may be alleviated by a topical corticosteroid preparation. If pruritus persists for >2 wk after treatment and new lesions are occurring, the patient should be reexamined for mites. Nodules are extremely resistant to treatment and may take several months to resolve. The entire family should be treated, as should caretakers of the infested child. Clothing, bed linens, and towels should be washed in hot water and dried using high heat. Clothing or other items (e.g., stuffed animals) that cannot be washed may be dry cleaned or stored in bags for 3 days to 1 wk, as the mite will die when separated from the human host.

NORWEGIAN SCABIES

The Norwegian variant of human scabies is highly contagious and occurs mainly in individuals who are cognitively and physically debilitated, particularly those who are institutionalized and those with Down syndrome; in patients with poor cutaneous sensation (leprosy, spina bifida); in patients who have severe systemic illness (leukemia, diabetes); and in immunosuppressed patients (HIV infection). Affected individuals are infested by myriad mites that inhabit the crusts and exfoliating scales of the skin and scalp. The nails may become thickened and dystrophic. The subungual debris is densely populated by mites. The infestation is often accompanied by generalized lymphadenopathy and eosinophilia. There is massive orthokeratosis and parakeratosis with numerous interspersed mites, psoriasiform epidermal hyperplasia, foci of spongiosis, and neutrophilic abscesses. Norwegian scabies is thought to represent a deficient host immune response to the organism. Management is difficult, requiring scrupulous isolation measures, removal of the thick scales, and repeated but careful applications of permethrin 5% cream. Ivermectin (200-250 µg/kg) has been used successfully as single-dose therapy in refractory cases, particularly in HIV-infected patients. A second dose may be needed a week later. The FDA has not approved this agent for treatment of scabies.

CANINE SCABIES

Canine scabies is caused by *S. scabiei* var. *canis,* the dog mite that is associated with mange. The eruption in humans, which is most frequently acquired by cuddling an infested puppy, consists of tiny papules, vesicles, wheals, and excoriated eczematous plaques. Burrows are not present because the mite infrequently inhabits human stratum corneum. The rash is pruritic and has a predilection for the arms, chest, and abdomen, the usual sites of contact with dogs. Onset is sudden and usually follows exposure by 1-10 days, possibly resulting from development of a hypersensitivity reaction to mite antigens. Recovery of mites or ova from scrapings of human skin is rare. The disease is self-limited because humans are not a suitable host. Bathing and changing clothes are generally sufficient. Removal or treatment of the infested animal is necessary. Symptomatic therapy for itching is helpful. In rare cases in which mites are demonstrated in scrapings from an affected child, they can be eradicated by the same measures applicable to human scabies.

OTHER TYPES OF SCABIES

Other mites that occasionally bite humans include the chigger or harvest mite *(Eutrombicula alfreddugesi),* which prefers to live on grass, shrubs, vines, and stems of grain. Larvae have hooked mouthparts, which allow the chigger to attach to the skin, but not to burrow, to obtain a blood meal, most commonly on the lower legs. Avian mites may affect those who come into close contact with chickens or pet gerbils. Humans may occasionally be assaulted by avian mites that have infested a nest outside a window, an attic, heating vents, or an air conditioner. The dermatitis is variable, including grouped papules, wheals, and vesicular lesions on the wrists, neck, breasts, umbilicus, and anterior axillary folds. A prolonged investigation is often undertaken before the cause and source of the dermatitis are discovered.

Bibliography is available at Expert Consult.

668.3 Pediculosis

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Three types of lice are obligate parasites of the human host: body or clothing lice *(Pediculus humanus corporis),* head lice *(Pediculus humanus capitis),* and pubic or crab lice *(Phthirus pubis).* Only the body louse serves as a vector of human disease (typhus, trench fever, relapsing fever). Body and head lice have similar physical characteristics. They are approximately 2-4 mm in length. Pubic lice are only 1-2 mm in length and are greater in width than length, giving them a crab-like appearance. Female lice live for approximately 1 mo and deposit 3-10 eggs daily on the human host. Body lice, however, generally lay eggs in or near the seams of clothing. The ova or nits are glued to hairs or fibers of clothing but not directly on the body. Ova hatch in 1-2 wk and require another week to mature. Once the eggs hatch, the nits remain attached to the hair as empty sacs of chitin. Freshly hatched larvae die unless a meal is obtained within 24 hr and every few days thereafter. Both nymphs and adult lice feed on human blood, injecting their salivary juices into the host and depositing their fecal matter on the skin. Symptoms of infestation do not appear immediately but develop as an individual becomes sensitized. The hallmark of all types of pediculosis is pruritus.

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Pediculosis corporis is rare in children except under conditions of poor hygiene, especially in colder climates when the opportunity to change clothes on a regular basis is lacking. The parasite is transmitted mainly on contaminated clothing or bedding. The primary lesion is a small, intensely pruritic, red macule or papule with a central hemorrhagic punctum, located on the shoulders, trunk, or buttocks. Additional lesions include excoriations, wheals, and eczematous, secondarily infected plaques. Massive infestation may be associated with constitutional symptoms of fever, malaise, and headache. Chronic infestation may lead to "vagabond's skin," which manifests as lichenified, scaling, hyperpigmented plaques, most commonly on the trunk. Lice are found on the skin only transiently when they are feeding. At other times, they inhabit the seams of clothing. Nits are attached firmly to fibers in the cloth and may remain viable for up to 1 mo. Nits hatch when they encounter warmth from the host's body when the clothes are worn again. Therapy consists of improved hygiene and hot water laundering of all infested clothing and bedding. A uniform temperature of 65°C (149°F), wet or dry, for 15-30 min kills all eggs and lice. Alternatively, eggs hatch and nymphs starve if clothing is stored for 2 wk at 23.9-29.4°C (75-85°F).

Pediculosis capitis is an intensely pruritic infestation of lice in the scalp hair. It is the most common form of lice to affect children, in particular those between the ages of 3 and 12 yr. Fomites and head-to-head contact are important modes of transmission. In summer months in many areas of the United States and in the tropics at all times of the year, shared combs, brushes, or towels have a more important role in louse transmission. Translucent 0.5 mm eggs are laid near the proximal portion of the hair shaft and become adherent to 1 side of the shaft (Fig. 668-6). A nit cannot be moved along or knocked off the hair shaft with the fingers. Secondary pyoderma, after trauma from scratching, may result in matting together of the hair and cervical and occipital lymphadenopathy. Hair loss does not result from pediculosis but may accompany the secondary pyoderma. Head lice are a major cause of numerous pyodermas of the scalp, particularly in tropical environments. Lice are not always visible, but nits are detectable on the hairs, most commonly in the occipital region and above the ears, rarely on beard or pubic hair. Dermatitis may also be noted on the neck and pinnae. An id reaction, consisting of erythematous patches and plaques, may develop, particularly on the trunk. Head lice rarely infest African-Americans and this is possibly related to the diameter, shape or twisted nature of their hair shafts (which makes grasping of the shaft more difficult for the louse).

Figure 668-6 Intact nits on human hairs.

Because of resistance of head lice to pyrethroids, malathion 0.5% in isopropanol is the treatment of choice for head lice and should be applied to dry hair until hair and scalp are wet, and left on for 12 hr. A second application 7-9 days after initial treatment may be necessary. This product is flammable, so care should be taken to avoid open flames. Malathion, like lindane shampoo, is not indicated for use in neonates and infants. Additional approved therapies include spinosad (if >4 yr old), benzyl alcohol lotion (if >6 mo), and ivermectin for difficult-to-treat head lice (Table 668-3). All household members should be treated at the same time. Nits can be removed with a fine-toothed comb after application of a damp towel to the scalp for 30 min. Clothing and bed linens should be laundered in very hot water or dry-cleaned; brushes and combs should be discarded or coated with a pediculicide for 15 min and then thoroughly cleaned in boiling water. Children may return to school after the initial treatment.

Pediculosis pubis is transmitted by skin-to-skin or sexual contact with an infested individual; the chance of acquiring the lice with 1 sexual exposure is 95%. The infestation is usually encountered in adolescents, although small children may occasionally acquire pubic lice on the eyelashes. Patients experience moderate to severe pruritus and may develop a secondary pyoderma from scratching. Excoriations tend to be shallower, and the incidence of secondary infection is lower than in pediculosis corporis. Maculae ceruleae are steel-gray spots, usually <1 cm in diameter, which may appear in the pubic area and on the chest, abdomen, and thighs. Oval translucent nits, which are firmly attached to the hair shafts, may be visible to the naked eye or may be readily identified by a hand lens or by microscopic examination (see Fig. 668-6). Grittiness, as a result of adherent nits, may sometimes be detected when the fingers are run through infested hair. Adult lice are difficult to detect than head or body lice because of their lower level of activity and smaller, translucent bodies. Because pubic lice occasionally may wander or may be transferred to other sites on fomites, terminal hair on the trunk, thighs, axillary region, beard area, and eyelashes should be examined for nits. The coexistence of other venereal diseases should be considered. Treatment with a 10-min application of a pyrethrin preparation is usually effective. Retreatment may be required in 7-10 days. The shampoo form of lindane, which requires a 10 min application time, is an alternative choice, but lindane cream and lotion are no longer recommended for treatment of pubic lice. Infestation of eyelashes is eradicated by petrolatum applied 3-5 times per 24 hr for 8-10 days. Clothing, towels, and bed linens may be contaminated with nit-bearing hairs and should be thoroughly laundered or dry-cleaned.

Bibliography is available at Expert Consult.

668.4 Seabather's Eruption

Anna M. Juern and Beth A. Drolet

Seabather's eruption is a severely pruritic dermatosis of inflammatory papules that develops within ≈12 hr of bathing in saltwater, primarily on body sites that were covered by a bathing suit. The eruption has been described primarily in connection with bathing in the waters of Florida and the Caribbean. Lesions, which may include pustules, vesicles, and urticarial plaques, are more numerous in individuals who keep their bathing suits on for an extended period after leaving the water. The eruption may be accompanied by systemic symptoms of fatigue, malaise, fever, chills, nausea, and headache; in 1 large series, ≈40% of children younger than 16 yr of age had fever. Duration of the pruritus and skin eruption is 1-2 wk. Lesions consist of a superficial and deep perivascular and interstitial infiltrate of lymphocytes, eosinophils, and neutrophils. The eruption appears to be due to an allergic hypersensitivity reaction to venom from larvae of the thimble jellyfish *(Linuche unguiculata)*. Treatment is largely symptomatic. Potent topical corticosteroids have been shown to provide relief to some patients.

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Table 668-3 Drugs for Head Lice

DRUG	RESISTANCE	FDA-APPROVED LOWER AGE OR WEIGHT LIMIT	DOSAGE AND ADMINISTRATION	COST[a]/SIZE
Ivermectin 0.5% lotion–Sklice (Sanofi Pasteur)	No[b]	6 months	Apply to dry hair and scalp for 10 min, then rinse	$257.88/4 oz
Ivermectin tablets[c]–Stromectol (Merck)	No	15 kg	200-400 μg/kg PO once; repeat 7-10 days later	9.97[d]
Spinosad 0.9% suspension–Natroba (ParaPro)	No[b]	4 yr	Apply to dry hair for 10 min, then rinse; repeat 7 days later if necessary	219.00/4 oz
Benzyl alcohol 5% lotion–Ulesfia (Shionogi)	No	6 months	Apply to dry hair for 10 min, then rinse; repeat 7 days later	52.62/8 oz
Pyrethrins with piperonyl butoxide shampoo[e,f]–Generic Rid (Bayer)	Yes	2 yr	Apply to dry hair for 10 min, then shampoo; repeat 7-10 days later	12.49/8 oz 19.99/8 oz[g]
Permethrin 1% creme rinse[e]–Generic Nix (Insight)	Yes	2 months	Apply to shampooed, towel-dried hair for 10 min, then rinse; repeat 7 days later	18.49/4 oz 19.99/4 oz[g]
Malathion 0.5% lotion– Generic Ovide (Taro)	Not in U.S.	6 yr	Apply to dry hair for 8-12 hr,[h] then shampoo; repeat 7-9 days later if necessary	152.67/2 oz 160.46/2 oz

[a]Wholesale acquisition cost (WAC). Source: PricePointRx. Reprinted with permission by FDB, Inc. All rights reserved. Copyright 2012. www.firstdatabank.com/support/drug-pricing-policy.aspx. Actual retail prices may be higher. Amount needed may vary.
[b]Product new to market: currently no reports of resistance.
[c]Not FDA-approved for treatment of head lice. Stromectol is available in 3 mg tablets.
[d]Cost of 1 dose for a 30 kg child at the lowest dosage.
[e]Available without a prescription.
[f]Products that contain benzyl alcohol as their vehicle may be more effective.
[g]Cost according to drugstore.com.
[h]One or two 20 min applications have also been effective (Meinking TL, Vicaria M, Eyerdam DH,, et al: Efficacy of a reduced application time of Ovide lotion (0.5% malathion) compared to Nix creme rinse (1% permethrin) for the treatment of head lice, Pediatr Dermatol 21:670–674, 2004.)

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Chapter 669
Acne
Sheila S. Galbraith

ACNE VULGARIS

Acne, particularly the comedonal form, occurs in 80% of adolescents.

Pathogenesis

Lesions of acne vulgaris develop in sebaceous follicles, which consist of large, multilobular sebaceous glands that drain their products into the follicular canals. The initial lesion of acne is a microcomedone, which progresses to a comedone. A comedone is a dilated epithelium-lined follicular sac filled with lamellated keratinous material, lipid, and bacteria. An open comedone, known as a **blackhead,** has a patulous pilosebaceous orifice that permits visualization of the plug. An open comedone becomes inflammatory less commonly than does a closed comedone or whitehead, which has only a pinpoint opening. An inflammatory papule or nodule develops from a comedone that has ruptured and extruded its follicular contents into the subadjacent dermis, inducing a neutrophilic inflammatory response. If the inflammatory reaction is close to the surface, a papule or pustule develops. If the inflammatory infiltrate develops deeper in the dermis, a nodule forms. Suppuration and an occasional giant cell reaction to the keratin and hair are the cause of nodulocystic lesions. These are not true cysts but liquefied masses of inflammatory debris.

The primary pathogenetic alterations in acne are (1) abnormal keratinization of the follicular epithelium, resulting in impaction of keratinized cells within the follicular lumen; (2) increased sebaceous gland production of sebum; (3) proliferation of *Propionibacterium acnes* within the follicle; and (4) inflammation. Comedonal acne (Fig. 669-1), particularly of the central face, is frequently the first sign of pubertal maturation. At puberty, the sebaceus gland enlarges and sebum production increases in response to the increased activities of androgens of primarily adrenal origin. Most patients with acne do not have endocrine abnormalities. Hyperresponsiveness of the sebocyte to androgens is likely involved in determining the severity of acne in a given individual. Sebocytes and follicular keratinocytes contain 5α-reductase and 3β- and 17β-hydroxyl-steroid dehydrogenase, which are capable of metabolizing androgens. A significant number of women with acne (25-50%), particularly those with

Figure 669-1 Primarily comedonal acne in a 7 yr old girl.

relatively mild papulopustular acne, note that their acne flares about 1 wk before menstruation.

Freshly formed sebum consists of a mixture of triglycerides, wax esters, squalene, and sterol esters. Normal follicular bacteria produce lipases that hydrolyze sebum triglycerides to free fatty acids. Those of medium-chain length (C8-C14) may be provocative factors in initiating an inflammatory reaction. Sebum also provides a favorable substrate for proliferation of bacteria. *P. acnes* appears to be largely responsible for the formation of free fatty acids. Skin surface *P. acnes* counts do not correlate with the severity of acne. There is a correlation between reduction of *P. acnes* count and improvement in acne vulgaris. It is probable that bacterial proteases, hyaluronidases, and hydrolytic enzymes produce biologically active extracellular materials that increase the permeability of the follicular epithelium. Chemotactic factors released by the intrafollicular bacteria attract neutrophils and monocytes. Lysosomal enzymes from the neutrophils, released in the process of phagocytizing the bacteria, further disrupt the integrity of the follicular wall and intensify the inflammatory reaction.

Clinical Manifestations

Acne vulgaris is characterized by 4 basic types of lesions: open and closed comedones, papules, pustules (Fig. 669-2), and nodulocystic lesions (Fig. 669-3 and Table 669-1). One or more types of lesions may predominate. In its mildest form, which is often seen early in adolescence, lesions are limited to comedones on the central area of the face. Lesions may also involve the chest, upper back, and deltoid areas. A predominance of lesions on the forehead, particularly closed comedones, is often attributable to prolonged use of greasy hair preparations (pomade acne) (Fig. 669-4). Marked involvement on the trunk is most often seen in males. Lesions often heal with temporary postinflammatory erythema and hyperpigmentation. Pitted, atrophic, or hypertrophic scars may be interspersed, depending on the severity, depth, and chronicity of the process. Diagnosis of acne is rarely difficult, although flat warts, folliculitis, and other types of acne (drug induced: glucocorticoid agents, anabolic steroids, gold, dactinomycin, isoniazid, lithium, phenytoin, progestins) may be confused with acne vulgaris. The differential diagnosis includes sarcoidosis, angiofibromas, keratosis pilaris, chloracne, rosacea, and fibrofolliculomas.

Treatment

No evidence shows that early treatment, with the exception of isotretinoin, alters the course of acne. Acne can be controlled and severe scarring prevented by judicious maintenance therapy that is continued until the disease process has abated spontaneously. Therapy must be individualized and aimed at preventing microcomedone formation through reduction of follicular hyperkeratosis, sebum production, the *P. acnes* population in follicular orifices, and free fatty acid production. Initial control takes at least 6-8 wk, depending on the severity of the acne (Table 669-2 and Fig. 669-5). It is also important to address the potentially severe emotional impact of acne on adolescents.

Figure 669-2 Inflammatory papules and pustules.

Table 669-1 Classification of Acne

SEVERITY	DESCRIPTION
Mild	Comedones (noninflammatory lesions) are the main lesions. Papules and pustules may be present but are small and few in number (generally <10).
Moderate	Moderate numbers of papules and pustules (10-40) and comedones (10-40) are present. Mild disease of the trunk may also be present.
Moderately severe	Numerous papules and pustules are present (40-100), usually with many comedones (40-100) and occasional larger, deeper nodular inflamed lesions (up to 5). Widespread affected areas usually involve the face, chest, and back.
Severe	Nodulocystic acne and acne conglobata, with many large, painful nodular or pustular lesions, are present, along with many smaller papules, pustules, and comedones.

From James WD: Clinical practice: acne, N Engl J Med *352:1463–1472, 2005.*

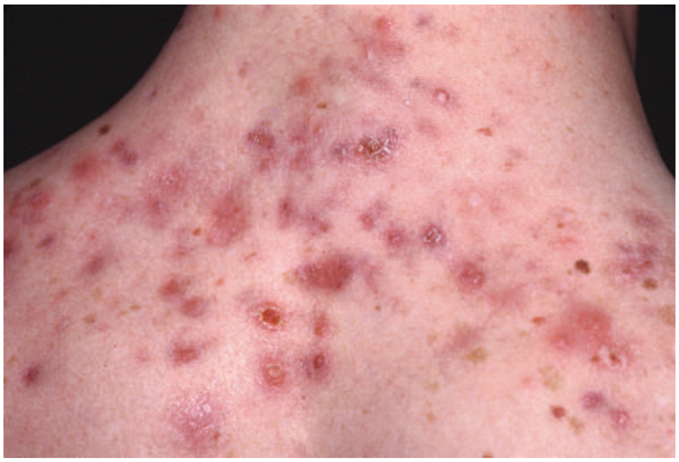

Figure 669-3 Severe nodulocystic acne.

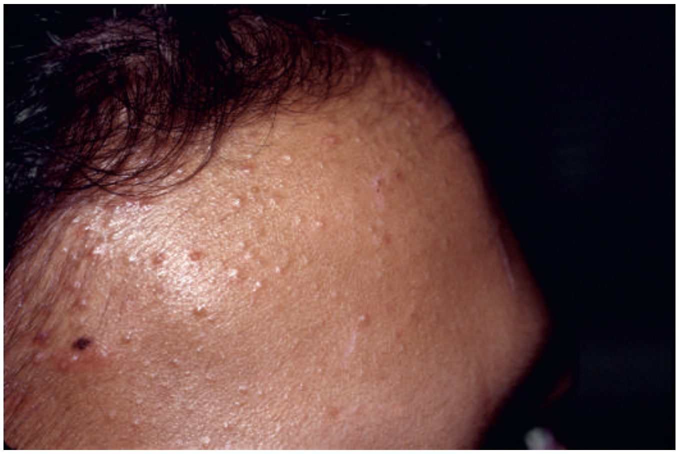

Figure 669-4 Pomade acne along the hairline.

The pediatrician must be aware of the frequently poor correlation between acne severity and psychosocial impact, particularly in adolescents. As adolescents become preoccupied with their appearance, offering treatment even to the youngster whose acne is mild may enhance self-image.

Diet

Little evidence shows that ingestion of particular foods can trigger acne flares. When a patient is convinced that certain dietary items exacerbate acne, it is prudent for the patient to omit those foods.

Climate

Climate appears to influence acne, in that improvement frequently occurs in summer and flares are more common in winter. Remission in summer may relate, in part, to the relative absence of stress. Emotional tension and fatigue seem to exacerbate acne in many individuals; the mechanism is unclear but has been proposed to relate to an increased adrenocortical response.

Table 669-2 Typical Treatment Regimens for Acne
COMEDONAL ACNE Topical retinoid *or* Azelaic acid *or* Salicylic acid
MILD PAPULOPUSTULAR ACNE Topical retinoid *plus* Benzoyl peroxide *or* Benzoyl peroxide/topical antibiotic *or* Benzoyl peroxide/oral antibiotic
SEVERE PAPULOPUSTULAR OR NODULAR ACNE Topical retinoid *plus* Benzoyl peroxide and oral antibiotic *or* Isotretinoin 1 mg/kg/day

Cleansing

Cleansing with soap and water removes surface lipid and renders the skin less oily in appearance, but no evidence shows that surface lipid has a role in generating acne lesions. Only superficial drying and peeling are achieved by cleansing, and almost any mild soap or astringent is adequate. Repetitive cleansing can be harmful because it irritates and chaps the skin. Cleansing agents that contain abrasives and keratolytic agents, such as sulfur, resorcinol, and salicylic acid, may temporarily remove sebum from the skin surface. They exert a mild drying and peeling effect and suppress lesions to a limited degree. They do not prevent microcomedones from forming. No evidence shows that preparations containing alcohol or hexachlorophene decrease acne because surface bacteria are not involved in the pathogenesis. Greasy cosmetic and hair preparations must be discontinued because they exacerbate preexisting acne and cause further plugging of follicular pores. Manipulation and squeezing of facial lesions only ruptures intact lesions and provokes a localized inflammatory reaction.

Topical Therapy

All topical preparations must be used for 6-8 wk before their effectiveness can be assessed. Retinoids may be used alone for mild acne, but combination therapy is frequently more effective. A popular and effective combination is use of benzoyl peroxide gel in the morning and a retinoid at night.

Retinoids. A topical retinoid should be the **primary treatment** for acne vulgaris. Topical retinoids have multiple actions, including inhibition of the formation and number of microcomedones, reduction of mature comedones, reduction of inflammatory lesions, and production of normal desquamation of the follicular epithelium. Retinoids should be applied daily to all the affected areas. The main side effects of retinoids are irritation and dryness. Not all patients initially

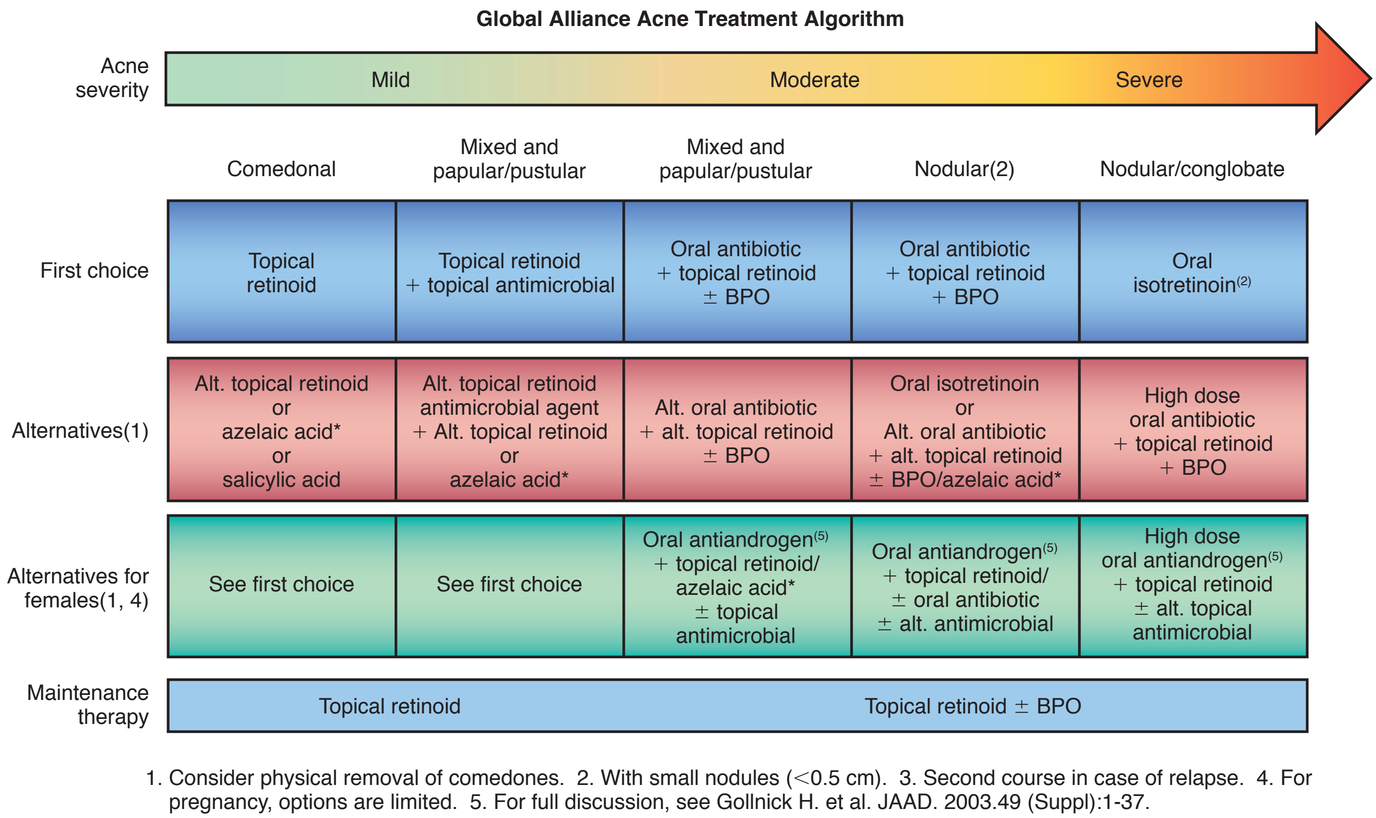

Figure 669-5 Acne treatment algorithm. BPO, benzoyl peroxide. *(From Thiboutot D, Gollnick H; Global Alliance to Improve Acne, et al: New insights into the management of acne: an update from the global alliance to improve outcomes in acne,* J Am Acad Dermatol *60:S1–S50, 2009.)*

tolerate daily use of a retinoid. It is prudent to begin therapy every other or every 3rd day and slowly increase the frequency of application as tolerated. Tretinoin, adapalene, and tazarotene (Table 669-3) are the available retinoids. They vary in strength and efficacy, although adapalene tends to be less irritating and tazarotene is more irritating but may be more effective.

Benzoyl Peroxide. Benzoyl peroxide is primarily an antimicrobial agent. It has an advantage over topical antibiotics in that it does not enhance antimicrobial resistance. It is available in multiple formulations and concentrations. The gel formulations are preferred, owing to better stability and more consistent release of the active ingredient. Washes and cleansers are useful for covering large surface areas such as the chest and back. As with retinoids, the main side effects are irritation and drying. Benzoyl peroxide can also bleach clothing.

Topical Antibiotics. Topical antibiotics are indicated for the treatment of inflammatory acne. Clindamycin is the most commonly used. It is not as effective as oral antibiotics. It should not be used as monotherapy because it does not inhibit microcomedone formation and it has the potential to induce antimicrobial resistance. Irritation and dryness are generally less than with retinoids or benzoyl peroxide. Topical antibiotics are best used as combination products. The most common is benzoyl peroxide/clindamycin. A combination tretinoin/clindamycin product may also be used.

Table 669-3 Medications for the Treatment of Acne

DRUG	DOSE	SIDE EFFECT(S)	OTHER CONSIDERATIONS
TOPICAL AGENTS			
Retinoids			
Tretinoin	Applied once nightly; strengths of 0.025-0.1% available**	Irritation (redness and scaling)	Generics available
Adapalene	Applied once daily, at night or in the morning; 0.01% and 0.3%**	Minimal irritation	0.1% generic available
Tazarotene*	Applied once nightly; 0.05% and 0.1%**	Irritation	Limited data suggest tazarotene more effective than alternatives
Antimicrobials			
Benzoyl peroxide, alone or with zinc, 2.5-10%	Applied once or twice daily	Benzoyl peroxide can bleach clothing and bedding	Available over the counter; 2.5-5% concentrations as effective as and less drying than 10% concentration
Clindamycin, erythromycin†	Applied once or twice daily	Propensity to resistance	Most effective for inflammatory lesions (rather than comedones); resistance a concern when used alone
Combination benzoyl peroxide and clindamycin or erythromycin Combination tretinoin and clindamycin	Applied once or twice daily		Combination more effective than topical antibiotics alone; limits development of resistance; use of individual products in combination less expensive and appears similarly effective
Other Topical Agents			
Azelaic acid, sodium sulfacetamide-sulfur, salicylic acid†	Applied once or twice daily	Well tolerated	Good adjunctive or alternative treatments
ORAL ANTIBIOTICS‡			
Tetracycline§	250-500 mg once or twice daily	Gastrointestinal upset, pseudomotor cerebri	Inexpensive; dosing limited by need to take on empty stomach
Doxycycline§	50-100 mg once or twice daily	Phototoxicity, pseudomotor cerebri, pill esophagitis, gastrointestinal upset	20 mg dose antiinflammatory only; limited data on efficacy
Minocycline§	50-100 mg once or twice daily	Hyperpigmentation of teeth, oral mucosa, and skin; lupus-like reactions with long-term treatment, pseudomotor cerebri, DRESS	
Trimethoprim-sulfamethoxazole	One dose (160 mg trimethoprim, 800 mg sulfamethoxazole) twice daily	Toxic epidermal necrolysis and allergic eruptions	Trimethoprim may be used alone in 300 mg dose twice daily; limited data available
Erythromycin†	250-500 mg twice daily	Gastrointestinal upset	Resistance problematic; consensus is that efficacy is limited
HORMONAL AGENTS¶			
Spironolactone§	50-200 mg in divided doses	Menstrual irregularities, breast tenderness	Higher doses more effective but cause more side effects; best given in combination with oral contraceptives
Estrogen-containing oral contraceptives	Daily	Potential side effects include thromboembolism	

Continued

Table 669-3 Medications for the Treatment of Acne—cont'd

DRUG	DOSE	SIDE EFFECT(S)	OTHER CONSIDERATIONS
ORAL RETINOID			
Isotretinoin[‖] (Accutane)	0.5-1.0 mg/kg/day in divided doses	Birth defects; adherence to pregnancy prevention program outlined by drug manufacturer, including 2 initial negative pregnancy tests, is essential; hypertriglyceridemia, elevated results on liver function tests, abnormal night vision, benign intracranial hypertension, dryness of the lips, ocular, nasal, and oral mucosa and skin, secondary staphylococcal infections, arthralgias, and mood disturbances are possible common or important side effects; laboratory testing of lipid profiles and liver function tests monthly should be performed monthly until dose is stabilized	Relapse rate higher if patient is younger than age 16 yr at initial treatment, if acne is of high severity and involves the trunk, or if drug is used in adult women
Absorica (isotretinoin agent)	0.5-1 mg/kg/day bid	Same as Accutane	Same as Accutane

*Tazarotene is in pregnancy category X: contraindicated in pregnancy.
[†]Clindamycin, erythromycin, and azelaic acid are in pregnancy category B: no evidence of risk in humans.
[‡]Oral antibiotics are indicated for moderate to severe disease; for the treatment of acne on the chest, back, or shoulders; and in patients with inflammatory disease in whom topical combinations have failed or are not tolerated.
[§]This drug is in pregnancy category D: positive evidence of risk in humans.
[¶]Hormonal agents are for use in women only.
[‖]Isotretinoin is in pregnancy category X: contraindicated in pregnancy. It should be used only in patients with severe acne that does not clear with combined oral and topical therapy.
**As cream or gel.
DRESS, drug rash with eosinophilia and systemic symptoms.
Modified from James WD: Clinical practice: acne, N Engl J Med *352:1463–1472, 2005.*

Azelaic Acid. Azelaic acid (20% cream) has mild antimicrobial and keratolytic properties. It can also help expedite resolution of postinflammatory hyperpigmentation.

Systemic Therapy

Antibiotics, especially tetracycline and its derivatives (see Table 669-3), are indicated for treatment of patients whose acne has not responded to topical medications, who have moderate to severe inflammatory papulopustular and nodulocystic acne, and who have a propensity for scarring. Tetracycline and its derivatives act by reducing the growth and metabolism of *P. acnes.* They also have antiinflammatory properties. For most adolescent patients, therapy may be initiated twice daily, for at least 6-8 wk, followed by a gradual decrease to the minimal effective dose. The drugs should always be administered in combination with a topical retinoid and topical benzoyl peroxide, but not topical antibiotics. Tetracycline absorption is inhibited by food, milk, iron supplements,, and calcium-magnesium salts. It should be taken on an empty stomach 1 hr before or 2 hr after meals. Minocycline and doxycycline may be taken with food. Side effects of tetracycline and derivatives are rare. Side effects of tetracycline include vaginal candidosis, particularly in those who take tetracycline concurrently with oral contraceptives; gastrointestinal irritation; phototoxic reactions, including onycholysis and brown discoloration of nails; esophageal ulceration; inhibition of fetal skeletal growth; and staining of growing teeth, precluding its use during pregnancy and in those younger than age 8 yr. Doxycycline is the most photosensitizing of the tetracycline derivatives and is also more likely to cause pill esophagitis. Rarely, minocycline causes dizziness, intracranial hypertension, bluish discoloration of the skin and mucous membranes, hepatitis, a lupus-like syndrome, and drug reaction with eosinophilia and systemic symptoms. A possible complication of prolonged systemic antibiotic use is proliferation of Gram-negative organisms, particularly *Enterobacter, Klebsiella, Escherichia coli,* and *Pseudomonas aeruginosa,* producing severe, refractory folliculitis.

Women who have acne and hormonal abnormalities, whose acne is unresponsive to antibiotic therapy, or who are not candidates for isotretinoin therapy should be considered for a trial of hormonal therapy. Combined oral contraceptive pills are the primary form of hormonal therapy. Spironolactone has also shown effectiveness.

Isotretinoin (13-*cis*-retinoic acid; Accutane) is indicated for severe nodulocystic acne and moderate to severe acne that has not responded to conventional therapy. The recommended dosage is 0.5-1.0 mg/kg/day. A standard course in the United States lasts 16-20 wk. At the end of 1 course of isotretinoin, 70-80% of patients are cured, 10-20% need conventional topical and/or oral medications to maintain adequate control, and 10-20% have relapses and need an additional course of isotretinoin. Dosages <0.5 mg/kg/day, or a cumulative dose of <120 mg/kg, are associated with a significantly higher rate of treatment failure and relapse. If the disease process is not in remission 2 mo after the first course of isotretinoin, a second course should be considered. Isotretinoin reduces size and secretion of sebaceous glands, normalizes follicular keratinization, prevents new microcomedone formation, decreases the population of *P. acnes,* and exerts an antiinflammatory effect.

Isotretinoin use has many side effects. It is highly **teratogenic** and is **absolutely contraindicated** in pregnancy. Pregnancy should be avoided for 6 wk after discontinuation of therapy. Two forms of birth control are required, as are monthly pregnancy tests. *Concerns over cases of pregnancy despite warnings have prompted a manufacturer registration program, iPLEDGE (www.ipledgeprogram.com), which requires physician enrollment and careful patient pregnancy screening to prescribe isotretinoin.* Many patients also experience cheilitis, xerosis, periodic epistaxis, and blepharoconjunctivitis. Increased serum triglyceride and cholesterol levels are also common. It is important to rule out

Icepick (V)	Rolling (U)	Boxcar (M)	Keloids	Hypertrophic
Punch excision (deep bases) Elevation and grafting Laser resurfacing/ dermabrasion (many scars close together) Spot TCA peel	**Combined therapy** Micrograft and subcision + ± filler Resurfacing microdermabrasion Deep-spot TCA peel	**Shallow** ≤3 mm diameter-laser skin resurfacing >3 mm diameter-laser skin resurfacing ± punch elevation **Deep** ≤3 mm diameter-punch excision >3 mm diameter-punch excision or punch elevation Fractional thermolysis (deep or shallow) Dermabrasion CO_2 laser resurfacing	Intralesional corticosteroids Intralesional 5-FU Intralesional bleomycin Compression Imiquimod after intralesional excision Cryotherapy Pulsed-dye laser Excision + electrotherapy	Intralesional steroids Intralesional 5-FU Vascular laser Intralesional bleomycin Compression Imiquimod after intralesional excision
Adjunctive treatment: Topical retinoids 2 weeks prior to and following treatment, sunscreens, moisturizers				

Non-ablative lasers for mild disease; ablative and fractional lasers for moderate scarring

Figure 669-6 Treatment options for acne scars. CO_2, carbon dioxide; FU, fluorouracil; TCA, trichloroacetic acid. *(From Thiboutot D, Gollnick H; Global Alliance to Improve Acne, et al: New insights into the management of acne: an update from the global alliance to improve outcomes in acne,* J Am Acad Dermatol *60:S1–S50, 2009.)*

preexisting liver disease and hyperlipidemia before initiating therapy and to recheck laboratory values 4 wk after commencement of therapy. Less common but significant side effects include arthralgias, myalgias, temporary thinning of the hair, paronychia, increased susceptibility to sunburn, formation of pyogenic granulomas, and colonization of the skin with *Staphylococcus aureus,* leading to impetigo, secondarily infected dermatitis, and scalp folliculitis. Rarely, hyperostotic lesions of the spine develop after more than 1 course of isotretinoin. Concomitant use of tetracycline and isotretinoin is contraindicated because either drug, but particularly when they are used together, can cause benign intracranial hypertension. Although no cause-and-effect relationship has been established, drug-induced mood changes and depression and/or suicide have mandated close attention to psychiatric well-being before and during isotretinoin prescription.

Surgical Therapy

Intralesional injection of low-dose (3-5 mg/mL) mid-potency glucocorticoids (e.g., triamcinolone) with a 30-gauge needle on a tuberculin syringe may hasten the healing of individual, painful nodulocystic lesions. Dermabrasion or laser peel to minimize scarring should be considered only after the active process is quiescent. Figure 669-6 describes the management of scarring.

The role of pulsed-dye laser in the treatment of inflammatory acne is controversial and inconclusive.

DRUG-INDUCED ACNE

Pubertal and postpubertal patients who are receiving systemic corticosteroid therapy are predisposed to steroid-induced acne. This monomorphous folliculitis occurs primarily on the face, neck, chest (Fig. 669-7), shoulders, upper back, arms, and, rarely, on the scalp. Onset follows the initiation of steroid therapy by approximately 2 wk. The lesions are small, erythematous papules or pustules that may erupt in profusion and are all in the same stage of development. Comedones may occur subsequently, but nodulocystic lesions and scarring are rare. Pruritus is occasional. Although steroid acne is relatively refractory if the medication is continued, the eruption may respond to use of tretinoin and a benzoyl peroxide gel.

Figure 669-7 Monomorphous papular eruption of steroid acne.

Other **drugs** that can induce **acneiform lesions** in susceptible individuals include isoniazid, phenytoin, phenobarbital, trimethadione, lithium carbonate, androgens (anabolic steroids), and vitamin B_{12}.

HALOGEN ACNE

Administration of medications containing iodides or bromides or, rarely, ingestion of massive amounts of vitamin–mineral preparations or iodine-containing "health foods" such as kelp may induce halogen acne. The lesions are often very inflammatory. Discontinuation of the provocative agent and appropriate topical preparations usually achieve reasonable therapeutic results.

CHLORACNE

Chloracne is a result of external contact with, inhalation of, or ingestion of halogenated aromatic hydrocarbons, including polyhalogenated biphenyls, polyhalogenated naphthalenes, and dioxins. Lesions are primarily comedonal. Inflammatory lesions are infrequent but may include papules, pustules, nodules, and cysts. Healing occurs with atrophic or hypertrophic scarring. The face, postauricular regions, neck, axillae, genitals, and chest are most commonly involved. The nose is often spared. In cases of severe exposure, associated findings may include hepatitis, production of porphyrins, bulla formation on sun-exposed skin, hyperpigmentation, hypertrichosis, and palmar and plantar hyperhidrosis. Topical or oral retinoids may be effective; benzoyl peroxide and antibiotics are generally ineffective.

NEONATAL ACNE

Approximately 20% of normal neonates demonstrate acne in the 1st mo of life. Small inflammatory papules and pustules predominate on the cheeks and forehead (Fig. 669-8); comedones are absent. The cause of neonatal acne is unknown but it has been theorized that it may be an inflammatory reaction to *Pityrosporum* species rather than true acne; therefore, the term neonatal cephalic pustulosis has been proposed. Other theories include placental transfer of maternal androgens, hyperactive neonatal adrenal glands, and a hypersensitive neonatal end-organ response to androgenic hormones. The eruption involutes spontaneously over a few months. **Treatment** is usually unnecessary. If desired, the lesions can be treated effectively with topical antifungals, and/or benzoyl peroxide.

INFANTILE ACNE

Infantile acne usually manifests between 3 mo and 2 yr of age, more commonly in boys than in girls. Acne lesions are more numerous, pleomorphic, severe, and persistent than in neonatal acne (Fig. 669-9). Open and closed comedones predominate on the face. Papules and pustules occur frequently, but only occasionally do nodulocystic lesions develop. Pitted scarring is seen in 10-15%. The course may be relatively brief, or the lesions may persist for many months or years, although the eruption generally resolves by age 4 yr. Use of topical benzoyl peroxide gel and tretinoin usually clears the eruption within a few weeks. Oral erythromycin is occasionally necessary. A child with refractory acne warrants a search for an abnormal source of androgens, such as a virilizing tumor or congenital adrenal hyperplasia.

TROPICAL ACNE

A severe form of acne occurs in tropical climates and is believed to be caused by the intense heat and humidity. Hydration of the pilosebaceous duct pore may accentuate blockage of the duct. Affected individuals tend to have an antecedent history of adolescent acne that is quiescent at the time of the eruption. Lesions occur mainly on the entire back, chest, buttocks, and thighs, with a predominance of suppurating papules and nodules. Secondary infection with *S. aureus* may be a complication. The eruption is refractory to acne therapy if the environmental factors are not eliminated.

ACNE CONGLOBATA

Acne conglobata is a chronic progressive inflammatory disease that occurs mainly in men, and more commonly in white than in black individuals, but it may begin during adolescence. Patients usually have a history of preexisting acne vulgaris. The principal lesion is the nodule, although there is often a mixture of comedones with multiple pores, papules, pustules, nodules, cysts, abscesses, and subcutaneous dissection with formation of multichanneled sinus tracts. Severe scarring is characteristic. The face is relatively spared, but in addition to the back and chest, the buttocks, abdomen, arms, and thighs may be involved. Constitutional symptoms and anemia may accompany the inflammatory process. Coagulase-positive staphylococci and β-hemolytic streptococci are frequently cultured from lesions but do not appear to be primarily involved in the pathogenesis. Acne conglobata occasionally occurs in association with hidradenitis suppurativa and dissecting cellulitis of the scalp (as the follicular occlusion triad) and may be complicated by erosive arthritis and ankylosing spondyloarthritis. Endocrinologic studies are not revealing. Routine acne therapy is generally ineffective. Systemic therapy with a corticosteroid may be required to suppress the intense inflammatory activity. Isotretinoin is the most effective form of therapy for some patients but may produce a flare after its initiation.

ACNE FULMINANS (ACUTE FEBRILE ULCERATIVE ACNE)

Acne fulminans is characterized by abrupt onset of extensive inflammatory, tender ulcerative acneiform lesions on the back and chest of male teenagers. The distinctive feature is the tendency for large nodules to form exudative, necrotic, ulcerated, crusted plaques. Lesions often spare the face and heal with scarring. A preceding history of mild papulopustular or nodular acne is noted in most patients. Constitutional symptoms and signs are common, including fever, debilitation, arthralgias, myalgias, weight loss, and leukocytosis. Blood cultures are sterile. Lesions of **erythema nodosum** sometimes develop on the shins. **Osteolytic bone** lesions may develop in the clavicle, sternum, and epiphyseal growth plates; affected bones appear normal or have slight sclerosis or thickening on healing. Salicylates may be helpful for the myalgias, arthralgias, and fever. Corticosteroids (1 mg/kg of

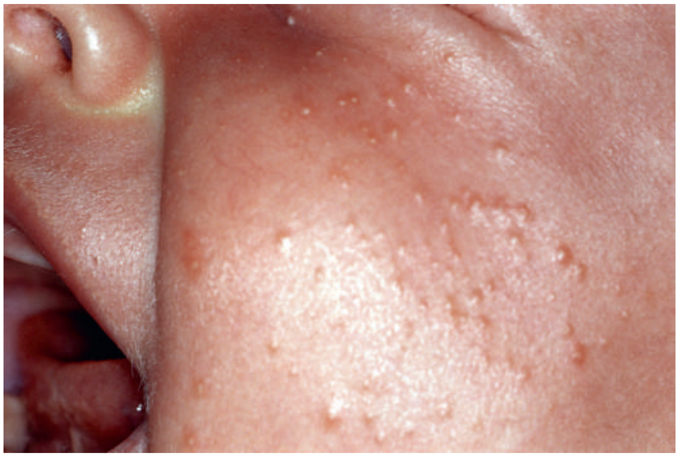

Figure 669-8 Comedonal acne in a neonate.

Figure 669-9 Inflammatory infantile acne.

prednisone) are started first. Then 1 wk later, isotretinoin (0.5-1.0 mg/kg) is added. Dapsone may be effective if isotretinoin cannot be used. The corticosteroid dosage is tapered over approximately 6 wk. Antibiotics are not indicated unless there is evidence of secondary infection. Compared with acne conglobata, acne fulminans occurs in younger patients, is more explosive in onset, more commonly has associated constitutional symptoms and ulcerated crusted lesions, and less commonly has multiheaded comedones or involves the face.

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Chapter 670
Tumors of the Skin
Kari L. Martin

See also Chapters 506.2 and 596.

EPIDERMAL INCLUSION CYST (EPIDERMOID CYST)

Epidermoid cysts are the nodules most commonly seen in children. Such a cyst is a sharply circumscribed, dome-shaped, firm, freely movable, skin-colored nodule (Fig. 670-1) often with a central dimple or punctum that is a plugged, dilated pore of a pilosebaceous follicle. Epidermoid cysts form most frequently on the face, neck, chest, or upper back and may periodically become inflamed and infected secondarily, particularly in association with acne vulgaris. The cyst wall may also rupture and induce an inflammatory reaction in the dermis. The wall of the cyst is derived from the follicular infundibulum. A mass of layered keratinized material that may have a cheesy consistency fills the cavity. Epidermoid cysts may arise from occlusion of pilosebaceous follicles, from implantation of epidermal cells into the dermis as a result of an injury that penetrates the epidermis, and from rests of epidermal cells. Multiple epidermoid cysts may be present in Gardner syndrome and the nevoid basal cell carcinoma syndrome. Excision of the cysts with removal of the entire sac and its contents is indicated, particularly if the cyst becomes recurrently infected. A fluctuant, infected cyst should be treated with antibiotics or intralesional corticosteroids. After the inflammation subsides, the cyst should be removed.

MILIUM

Milium is a 1-2 mm, firm, pearly white or yellowish, subepidermal keratin cyst. Milia in newborns is discussed in Chapter 647. Secondary milia occur in association with subepidermal blistering diseases, after dermabrasion or other injury to the skin. They are retention cysts caused by hyperproliferation of injured epithelium and are indistinguishable histopathologically from primary milia. Those that develop after blistering usually arise from the eccrine sweat duct, but they may develop from the hair follicle, sebaceous duct, or epidermis. A milium body differs from an epidermoid cyst only in its small size and superficial location.

FIBROFOLLICULOMAS

These lesions usually appear in late adolescents or in young adults and are characterized by multiple dome-shaped clear-white papules appearing on the nose, cheeks, and neck, and at times the trunk or ears (Fig. 670-2). They are associated with the familial cancer syndrome of Birt-Hogg-Dubé, an autosomal dominant disorder that results from a mutation in the folliculin *(FLCN)* gene. Associated features include pulmonary cysts, pneumothorax, renal cell carcinoma, and other benign or malignant tumors.

PILAR CYST (TRICHILEMMAL CYST)

Pilar cyst may be clinically indistinguishable from an epidermoid cyst. It manifests as a smooth, firm, mobile nodule, predominantly on the scalp (Fig. 670-3). Pilar cysts occasionally develop on the face, neck, or trunk. A cyst may become inflamed and may occasionally suppurate and ulcerate. The cyst wall is composed of epithelial cells with indistinct intercellular bridges. The peripheral cell layer of the wall shows a palisade arrangement, which is not seen in an epidermoid cyst. No granular layer is present. The cyst cavity contains homogeneous eosinophilic keratinous material, and foci of calcification are seen in 25% of cases. The propensity for development of pilar cysts may be inherited in an autosomal dominant manner. More than one cyst generally develops in a patient. Numerous pilar and epidermoid cysts, desmoid tumors, fibromas, lipomas, or osteomas may be associated with colonic polyposis or adenocarcinoma in Gardner syndrome. Pilar cysts shell out easily from the dermis.

PILOMATRICOMA

The second most common nodule seen in children, pilomatricoma is a benign tumor that manifests as a 3-30 mm, firm, solitary, deep dermal or subcutaneous tumor on the head, neck, or upper extremities. The overlying epidermis is usually normal. The tumor may occasionally be located more superficially, however, tinting the overlying skin

Figure 670-1 Flesh-colored cyst on the forehead.

Figure 670-2 Multiple, dome-shaped, whitish papules on the nose and cheeks in a 31 yr old carrier of an *FLCN* mutation. *(From Menko FH, van Steensel MAM, Giraud S, et al: Birt-Hogg-Dubé syndrome: diagnosis and management.* Lancet *10:1199–1206, 2009, Fig. 1.)*

blue-red (Fig. 670-4). Multiple pilomatricomas are seen in myotonic dystrophy, Gardner syndrome, Rubinstein-Taybi syndrome, and Turner syndrome. In general, however, pilomatricomas are not hereditary. Histopathologically, irregularly shaped islands of epithelial cells are embedded in a cellular stroma. Calcium deposits are found in 75% of tumors. Pilomatricomas are caused by mutations in β-catenin.

TRICHOEPITHELIOMA

A 2-8 mm, smooth, round, firm, skin-colored papule, trichoepithelioma is derived from an immature hair follicle. Trichoepitheliomas generally occur singly on the face in childhood or early adulthood. Multiple trichoepitheliomas are inherited autosomal dominantly (type 1: *CYLD* gene; type 2: 9p21 gene currently unidentified), appear in childhood or at puberty, and gradually increase in number on the nasofacial folds, nose, forehead, and upper lip and, occasionally, on the scalp, neck, and upper trunk. Microscopically, these benign tumors are characterized by horn cysts composed of a fully keratinized center surrounded by basophilic cells in an adenoid network. Topical imiquimod therapy may be beneficial. Surgical excision is the only other therapy.

ERUPTIVE VELLUS HAIR CYSTS

Eruptive vellus hair cysts are 1-3 mm, asymptomatic, soft, skin-colored follicular papules on the central chest (Fig. 670-5). They may become crusted or umbilicated. Abnormal vellus hair follicles become occluded at the level of the infundibulum, resulting in retention of hairs within an epithelium-lined cystic dilation of the proximal part of the follicle. Most cases are chronic, but spontaneous regression has been reported.

Figure 670-3 Pilar cyst of the anterior scalp.

Figure 670-4 Pilomatricoma. Firm tumor with overlying bluish discoloration of the skin.

STEATOCYSTOMA MULTIPLEX

An autosomal dominant (*KRT17* gene) condition, steatocystoma multiplex usually manifests in adolescence or early adulthood as numerous soft to firm cystic nodules that are adherent to the underlying skin and are 3 mm to 3 cm in diameter. When punctured, the cysts may drain oily or cheesy material. Sites of predilection include the sternal region, axillae, arms, and scrotal skin. The multiply folded cyst wall is lined on the luminal side with a thick, homogeneous, eosinophilic horny layer and lacks a granular layer. Flattened sebaceous gland lobules are often visible in the cyst wall, and lanugo hairs may be present in the cystic cavity.

SYRINGOMA

The benign tumors known as syringomas are soft, small, skin-colored or yellowish brown papules that develop on the face, particularly in the periorbital regions (Fig. 670-6). Other sites of predilection include the axillae and umbilical and pubic areas. They often develop during puberty and are more frequent in females. Eruptive syringomas develop in crops over the anterior trunk during childhood or adolescence. A

Figure 670-5 Eruptive vellus hair cysts. Multiple papules on the chest.

Figure 670-6 Syringomas. Multiple yellow papules near the eye.

syringoma is derived from an intraepidermal sweat gland duct. Syringomas are of cosmetic significance only. Sparse lesions may be excised, but they are often too numerous to remove.

INFANTILE DIGITAL FIBROMA

Infantile digital fibroma is a smooth, firm, erythematous or skin-colored nodule on the dorsal or lateral surface of a distal phalanx of a finger or toe. More than 80% of tumors occur in infancy. They may be present at birth. Lesions may be solitary or multiple and may manifest as "kissing" tumors on opposing digits. They are usually asymptomatic, but flexion deformity of the digits may occur. Clinically, the lesion resembles a fibroma, leiomyoma, angiofibroma, acquired digital fibrokeratoma, accessory digit, or mucous cyst. The diagnosis is confirmed by the finding of numerous spindle-shaped fibroblasts that contain small, round, dense, eosinophilic cytoplasmic inclusion bodies composed of collections of actin microfilaments. Local recurrence after simple excision of this tumor has been reported in 75% of patients. Because the tumor does not metastasize and may regress spontaneously in 2-3 yr, a course of expectant observation is advised. If functional impairment or flexion deformity of the digit becomes apparent, prompt full excision of the tumor is indicated.

DERMATOFIBROMA (HISTIOCYTOMA)

A benign dermal tumor, dermatofibroma may be pedunculated, nodular (Fig. 670-7), or flat and is usually well circumscribed and firm but occasionally feels soft on palpation. The overlying skin is usually hyperpigmented, may be shiny or keratotic, and dimples when the tumor is pinched. Dermatofibromas range in size from 0.5-10.0 mm, arise most frequently on the limbs, and are usually asymptomatic but may occasionally be pruritic. They are composed of fibroblasts, young and mature collagen, capillaries, and histiocytes in varying proportions, forming a nodule in the dermis that has poorly defined edges. The cause of these tumors is unknown, but trauma such as an insect bite or folliculitis appears to induce reactive fibroplasia. The differential diagnosis includes epidermal inclusion cyst, juvenile xanthogranuloma, hypertrophic scar, and neurofibroma. Dermatofibromas may be excised or left intact, according to the patient's preference. They usually persist indefinitely.

JUVENILE XANTHOGRANULOMA

A firm, dome-shaped, yellow, pink, or orange papule or nodule (Fig. 670-8), juvenile xanthogranuloma varies from 5 mm to approximately 4 cm in diameter. The average age at onset is 2 yr. These nodules are 10 times more common in white than in African-American individuals. Sites of predilection are the scalp, face, and upper trunk, where they may erupt in profusion or remain as solitary lesions. Nodular lesions may appear on the oral mucosa. Mature lesions are characterized histopathologically by a dermal infiltrate of lipid-laden histiocytes, admixed inflammatory cells, and Touton giant cells. The lesions may clinically resemble papulonodular urticaria pigmentosa, dermatofibromas, or xanthomas of hyperlipoproteinemia, but can be distinguished from these entities histopathologically.

Affected infants are nearly always otherwise normal, and blood lipid values are not elevated. Café-au-lait macules are found on 20% of patients with juvenile xanthogranuloma. Xanthogranulomatous infiltrates occur occasionally in ocular tissues. This process may result in glaucoma, hyphema, uveitis, heterochromia iridis, iritis, or sudden proptosis. Age less than 2 yr, multiple lesions, and periocular location may heighten concerns for intraocular involvement. There appears to be an association among juvenile xanthogranuloma, neurofibromatosis, and childhood leukemia, most frequently juvenile chronic myelogenous leukemia. There is no need to remove the benign lesions of juvenile xanthogranuloma because most of them regress spontaneously in the 1st few yr. Residual pigmentation and atrophy may result.

LIPOMA

A benign collection of fatty tissue, lipoma appears on the trunk, neck, or proximal portions of the limbs. Lipomas are soft, compressible, lobulated, subcutaneous masses. Multiple lesions may occur occasionally, as in Gardner syndrome. Atrophy, calcification, liquefaction, or xanthomatous change may sometimes complicate their course. A lipoma is composed of normal fat cells surrounded by a thin connective tissue capsule. Lipomas represent a cosmetic defect and may be surgically excised. Multiple lipomas, identical to those that occur singly, are inherited in an autosomal dominant fashion and often appear by the 3rd decade in patients with familial multiple lipomatosis. Lipomas may appear intraabdominally, intramuscularly, and subcutaneously. Congenital lipomatosis manifests in the 1st few mo of life as large subcutaneous fatty masses on the chest, with extension into skeletal muscle. Congenital lipomatosis can also be a manifestation of Proteus syndrome (overgrowth/hyperplasia skin, connective tissue, mutation in *AKT1*). Angiolipomas usually manifest as numerous painful subcutaneous nodules on the arms and trunk.

CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal-spinal anomalies) is usually a sporadic disorder with an asymmetric truncal lipomatous mass present at birth. Additional features include macrodactyly, vascular malformations (low flow), linear epidermal nevus and renal anomalies. The differential diagnosis includes Proteus, Klippel-Trenaunay, and Bannayan-Riley-Ruvalcaba syndrome.

BASAL CELL CARCINOMA

Basal cell carcinoma is very rare in children in the absence of a predisposing condition, such as nevoid basal cell carcinoma syndrome, xeroderma pigmentosum, nevus sebaceus of Jadassohn, arsenic intake, or exposure to irradiation. The lesions are smooth, pearly, pink, telangiectatic papules that enlarge slowly and may bleed or ulcerate. Sites of predilection are the face, scalp, and upper back. The differential

Figure 670-7 Dermatofibroma. Red-brown nodular variant.

Figure 670-8 Juvenile xanthogranuloma. Solitary orange papule.

diagnosis includes pyogenic granuloma, nevocellular nevus, epidermal inclusion cyst, closed comedo, dermatofibroma, and adnexal tumor. Depending on the site of occurrence and associated disease of the host, electrodesiccation and curettage or simple excision of basal cell epithelioma is usually curative. When the tumor is recurrent, >2 cm in diameter, located on problematic anatomic areas such as the midface or ears, or is an aggressive histopathologic type, Mohs microscopically controlled surgery may be the most appropriate treatment.

NEVOID BASAL CELL CARCINOMA SYNDROME (BASAL CELL NEVUS SYNDROME, GORLIN SYNDROME)

The autosomal dominant entity known as nevoid basal cell carcinoma syndrome is caused by mutations in the *PTCH1* and *PTCH2* ("patched") genes. These tumor-suppressor genes, part of the hedgehog signaling pathway, are important in determining embryonic patterning and cell fate in a number of structures in the developing embryo. Mutations in human patched genes produce dysregulation of several genes involved in organogenesis and carcinogenesis. Consequently, the syndrome includes a wide spectrum of defects involving the skin, eyes, central nervous and endocrine systems, and bones. The predominant features are early-onset basal cell carcinomas and mandibular cysts. Approximately 20% of those in whom a basal cell carcinoma develops before age 19 yr have this syndrome. Basal cell carcinomas appear between puberty and age 35 yr, erupting in crops of tumors that vary in size, color, and number, and may be difficult to distinguish from other types of skin lesions. Sites of predilection are the periorbital skin, nose, malar areas, and upper lip, but the lesions can develop on the trunk and limbs and are not restricted to sun-exposed areas. Ulceration, bleeding, crusting, and local invasion can occur. Small milia, epidermal cysts, pigmented lesions, hirsutism, and palmar and plantar pits are additional cutaneous findings.

The facies of patients with this syndrome are characterized by temporoparietal bossing, prominent supraorbital ridges, a broad nasal root, ocular hypertelorism or dystopia canthorum, and prognathism. Keratinized cysts (odontogenic keratocysts) in the maxilla and mandible occur in most patients. They range in size from a few millimeters to several centimeters, may result in maldevelopment of the teeth, and cause pain, swelling of the jaw, facial deformity, bone erosion, pathologic fractures, and suppurating sinus tracts. Osseous defects such as anomalous rib development, spina bifida, kyphoscoliosis, and brachymetacarpalism occur in 60% of patients, and ocular abnormalities including cataracts, glaucoma, coloboma, strabismus, and blindness occur in approximately 25%. Some males have hypogonadism, and the testes are absent or undescended. Kidney malformations have also been reported. Neurologic manifestations include calcification of the falx, seizures, mental retardation, partial agenesis of the corpus callosum, hydrocephalus, and nerve deafness. The incidence of medulloblastoma, ameloblastoma of the oral cavity, fibrosarcoma of the jaw, teratoma, cystadenoma, cardiac fibroma, ovarian fibroma, and fetal onset rhabdomyoma is higher in patients with nevoid basal cell carcinoma syndrome.

Treatment of these patients requires the participation of various specialists according to individual clinical problems. Basal cell carcinomas should not be treated with irradiation. Most of the basal cell carcinomas have a clinically benign course, and it is often impossible to remove them all. Those with an aggressive growth pattern and those on the central areas of the face, however, should be removed promptly. Treatment options include surgery, Mohs micrographic surgery, laser ablation, cryotherapy, photodynamic therapy, topical 5% imiquimod and oral retinoids (0.5-1.0 mg/kg/day). Vismodegib, which inhibits smoothened protein in the hedgehog pathway, is a targeted therapy available for unresectable basal cell carcinomas. Genetic counseling is also indicated.

MUCOSAL NEUROMA SYNDROME (MULTIPLE ENDOCRINE NEOPLASIA TYPE IIB)

Mucosal neuroma syndrome, an autosomal dominant trait, is characterized by an asthenic or marfanoid habitus with scoliosis, pectus excavatum, pes cavus, and muscular hypotonia. The syndrome is caused by mutations in the tyrosine kinase domain of the *RET* gene. Patients have thick, patulous lips and soft-tissue prognathism simulating acromegaly. Multiple mucosal neuromas or neurofibromas appear as pink, pedunculated or sessile nodules on the anterior third of the tongue, at the commissures of the lips, and on the buccal mucosa and palpebral conjunctiva. Various ophthalmologic defects and intestinal ganglioneuromatosis with recurrent diarrhea are additional common findings. There is a high incidence of medullary thyroid carcinoma in association with high calcitonin levels, pheochromocytoma, and hyperparathyroidism in patients with this syndrome. Periodic screening tests for the associated malignant tumors are mandatory.

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Chapter 671

Nutritional Dermatoses

Joel C. Joyce

ACRODERMATITIS ENTEROPATHICA

Acrodermatitis enteropathica is a rare autosomal recessive disorder caused by an inability to absorb sufficient zinc from the diet. The genetic defect is in the intestinal zinc-specific transporter gene *SLC39A4*. Initial signs and symptoms usually occur in the 1st few mo of life, often after weaning from breast milk to cow's milk. The cutaneous eruption consists of vesiculobullous, eczematous, dry, scaly, or psoriasiform skin lesions symmetrically distributed in the perioral, acral, and perineal areas (Fig. 671-1) and on the cheeks, knees, and elbows (Fig. 671-2). The hair often has a peculiar, reddish tint, and alopecia of some degree is characteristic. Ocular manifestations include photophobia, conjunctivitis, blepharitis, and corneal dystrophy detectable by slit-lamp examination. Associated manifestations include chronic diarrhea, stomatitis, glossitis, paronychia, nail dystrophy, growth retardation, irritability, delayed wound healing, intercurrent bacterial infections, and superinfection with *Candida albicans*. Lymphocyte function and free radical scavenging are impaired. Without treatment, the course is chronic and intermittent but often relentlessly progressive. When the disease is less severe, only growth retardation and delayed development may be apparent.

The **diagnosis** is established by the constellation of clinical findings and detection of a low plasma zinc concentration. A serum zinc level less than 50 µg/dL is suggestive, but not diagnostic, of acrodermatitis enteropathica. Levels of alkaline phosphatase, a zinc-dependent enzyme, may also be decreased. Histopathologic changes in the skin are nonspecific and include parakeratosis and pallor of the upper epidermis. The variety of manifestations of the syndrome may be because zinc has a role in numerous metabolic pathways, including those of copper, protein, essential fatty acids, and prostaglandins, and that zinc is incorporated into many zinc metalloenzymes.

Oral **therapy** with zinc compounds is the treatment of choice. Replacement for individuals with inherited acrodermatitis enteropathica is with 3 mg/kg/24 hr of elemental zinc found in zinc sulfate, gluconate, or acetate (i.e., 220 mg of zinc sulfate contains 50 mg of elemental zinc). Zinc gluconate carries less risk of gastrointestinal distress. Plasma zinc levels should be monitored every 3-6 mo, however, to individualize the dosage. Zinc therapy rapidly abolishes the manifestations of the disease. A syndrome resembling acrodermatitis enteropathica has been observed in patients with secondary zinc deficiency resulting from long-term total parenteral nutrition without

Figure 671-1 **A,** Periorificial eruption. **B,** Diaper rash. The skin findings are typical of zinc deficiency, in this case caused by low levels of zinc in breast milk. *(From Eichenfield LF, Frieden IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, Fig. 14-14.)*

supplemental zinc or to chronic malabsorption syndromes. A rash similar to that of acrodermatitis enteropathica has also been reported in infants fed breast milk that is low in zinc and in those with maple syrup urine disease, organic aciduria, methylmalonic acidemia, biotinidase deficiency, essential fatty acid deficiency, severe protein malnutrition (kwashiorkor), and cystic fibrosis. For those individuals with acquired zinc deficiency, oral replacement with 0.5-1.0 mg/kg/24 hr of elemental zinc should be undertaken and the cause of underlying malnutrition should be addressed.

ESSENTIAL FATTY ACID DEFICIENCY

Essential fatty acid deficiency causes a generalized, scaly dermatitis composed of thickened, erythematous, desquamating plaques. Individuals may also show failure-to-thrive, growth retardation, alopecia, thrombocytopenia, and poor wound healing. The eruption has been induced experimentally in animals fed a fat-free diet and has been observed in patients with chronic severe malabsorption, such as in short-gut syndrome, and in those sustained on a fat-free diet or fat-free parenteral alimentation. Linoleic acid (18 : 2 n-6) and arachidonic acid (20 : 4 n-6) are deficient, and an abnormal metabolite, 5,8,11-eicosatrienoic acid (20 : 3 n-9), is present in the plasma. Alterations in the triene : tetraene ratio are diagnostic (arachidonic acid : eicosatrienoic acid ratio greater than 0.4 or linoleic acid : arachidonic acid ratio greater than 2.3). The horny layer of the skin contains microscopic cracks, the barrier function of the skin is disturbed, and transepidermal water loss is increased. Topical application of linoleic acid, which is present in sunflower seed and safflower oils, may ameliorate the clinical and biochemical skin manifestations. Oral and/or parenteral therapy can also be considered. Appropriate nutrition should be provided.

KWASHIORKOR

Severe protein and essential amino acid deprivation in association with adequate caloric intake can lead to kwashiorkor, particularly at the time of weaning to a diet that consists primarily of corn, rice (or rice milk), or beans (see Chapter 46). Children can be fed such a restricted diet for cultural reasons or because of misdiagnosis on the part of the child's parents or healthcare providers of perceived food allergies. Diffuse fine reddish brown scaling (enamel/flaky paint sign) is the classic cutaneous finding. In severe cases, erosions and linear fissures

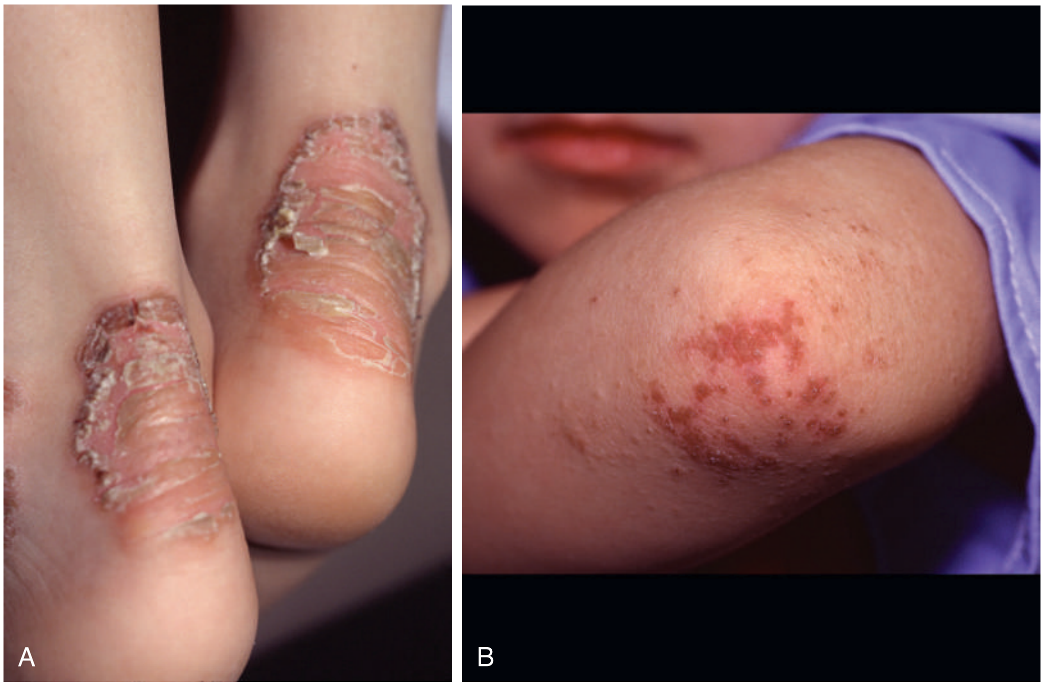

Figure 671-2 **A,** Psoriasiform lesion of zinc deficiency dermatitis on the ankles. **B,** Similar lesions on the elbows.

Figure 671-3 Erosions and scaling in kwashiorkor.

develop (Fig. 671-3). Nails are thin and soft, and hair is sparse, thin, and depigmented, sometimes displaying a "flag sign" consisting of alternating light and dark bands that reflect alternating periods of adequate and inadequate nutrition. The cutaneous manifestations may closely resemble those of acrodermatitis enteropathica, however; edema of the extremities and face ("moon facies") and a protuberant abdomen ("pot belly") are key features uniformly observed in kwashiorkor. The serum zinc level is often deficient, and in some cases, skin lesions of kwashiorkor heal more rapidly when zinc is applied topically.

CYSTIC FIBROSIS

See Chapter 403.

Protein-calorie malnutrition develops in 5-10% of patients with cystic fibrosis. Rash in infants with cystic fibrosis and malnutrition is rare but may appear by age 6 mo. The initial eruption consists of scaling, erythematous papules and progresses in 1-3 mo to extensive desquamating plaques. The rash is accentuated around the mouth and perineum and on the extremities (lower > upper). Alopecia may be present, but mucous membranes and nails are uninvolved.

PELLAGRA

See Chapter 49.

Pellagra manifests as edema, erythema, and burning of sun-exposed skin on the face, neck, and dorsal aspects of the hands, forearms, and feet. Lesions of pellagra may also be provoked by burns, pressure, friction, and inflammation. The eruption on the face frequently follows a butterfly distribution, and the dermatitis encircling the neck has been termed "Casal's necklace." Blisters and scales develop, and the skin increasingly becomes dry, rough, thickened, cracked, and hyperpigmented. Skin infections may be unusually severe. Pellagra develops in patients with insufficient dietary intake or malabsorption of niacin and/or tryptophan. Administration of isoniazid, 6-mercaptopurine, or 5-fluorouracil may also produce pellagra. Hartnup disease (see Chapter 85), caused by a mutation in *SLC6A19* that encodes a neutral amino acid transporter, is a rare autosomal recessive disorder that presents in infancy with a "pellagra-like syndrome" as a result of decreased absorption of tryptophan. Nicotinamide supplementation and sun avoidance are the mainstays of therapy in pellagra.

SCURVY (VITAMIN C OR ASCORBIC ACID DEFICIENCY)

See Chapter 50.

Scurvy manifests initially as follicular hyperkeratosis, coiling of the hair on the upper arms, back, buttocks, and lower extremities. Other features are perifollicular erythema and hemorrhage, particularly on the legs and advancing to involve large areas of hemorrhage; swollen, erythematous gums; stomatitis; and subperiosteal hematomas. In children, the most common risk factors are behavioral or psychiatric disease that results in poor nutrition. The best method of confirmation of a clinical diagnosis of scurvy is a trial of vitamin C supplementation.

VITAMIN A DEFICIENCY

See Chapter 48.1.

Vitamin A deficiency manifests initially as impairment of visual adaptation to the dark. Cutaneous changes include xerosis and hyperkeratosis and hyperplasia of the epidermis, particularly the lining of hair follicles and sebaceous glands. In severe cases, desquamation may be prominent.

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Bone and Joint Disorders

PART XXXII

Section 1

Orthopedic Problems

Chapter 672
Growth and Development

Keith D. Baldwin, Lawrence Wells, and John P. Dormans

Statistically, normal is defined as 95% of a population that falls within 2 SD of the mean from any given measurement. Statistically normal should not be confused with ideal in any given person or parent's mind. Table 672-1 lists terms used to describe some common deviations from normal. Congenital anomalies can be categorized into production problems and packaging problems. Production problems include abnormalities caused by malformation, dysplasia, or disruption that will not spontaneously resolve (see Chapter 108). Packaging problems include deformations caused by mechanical causes including in utero positioning and molding, and they usually resolve with time.

IN UTERO POSITIONING

In utero positioning produces temporary joint and muscle contractures and affects the torsional alignment of the long bones, particularly those of the lower extremities. Normal full-term newborns can have up to 20-30 degree hip and knee flexion contractures. These contractures tend to resolve by 4-6 mo of age. The newborn hip externally rotates in extension up to 80-90 degrees and has limited internal rotation to approximately 0-10 degrees. The lower leg often has inward rotation (internal tibial torsion). The face may also be distorted; the spine and upper extremities are less affected by the in utero position. The effects of in utero positioning, therefore, are physiologic in origin and resolve by 3-4 mo of age.

Table 672-1 Terminologies for Deviations

TERMINOLOGY	DESCRIPTION
Congenital	Anomaly that is apparent at birth
Deformation	A normally formed structure that is pushed out of shape by mechanical forces
Deformity	A body part altered in shape from normal, outside the normal range
Developmental	A deviation that occurs over time; one that might not be present or apparent at birth
Disruption	A structure undergoing normal development that stops developing or is destroyed or removed
Dysplasia	A tissue that is abnormal or wrongly constructed
Malformation	A structure that is wrongly built; failure of embryologic development or differentiation resulting in abnormal or missing structures

GROWTH AND DEVELOPMENT

Consideration of growth and development helps to formulate treatment strategies designed to preserve or restore normal growth potential. Growth is subject to many variables including genetics, nutrition, general health, endocrine status, mechanical forces, and physiologic age. Growth also varies between 2 anatomic regions and even between 2 bones of the same region.

Bone formation or ossification occurs in 2 different ways. In **endochondral ossification**, mesenchymal cells undergo chondrogenesis to form cartilage that matures to become bone. Most bones in the axial and appendicular skeleton are formed in this manner. In **intramembranous ossification**, osteoblasts are formed by direct differentiation of mesenchymal cells into bone. Flat bones of the skull and clavicle are examples of this pattern of bone formation.

CENTERS OF OSSIFICATION

At the beginning of the fetal period the chondrocytes in the midshaft of the long bones form the **primary** centers of growth from which the bone eventually lengthens. **Secondary** centers of ossification appear in the chondroepiphysis and mostly appear postnatally. They direct the formation of bone throughout growth, particularly joint development. The ossification centers that are typically present at birth are the distal femur, proximal tibia, calcaneus, and talus.

Anatomic Locations: Descriptive Terms

Typical **long bones are divided into** the physis, epiphysis, metaphysis, diaphysis, and perichondrial ring (Fig. 672-1). The physis is the growth plate located at the end of bone. The epiphysis is typically a secondary ossification center that contributes to joint development. The metaphysis is the bone adjacent to the physis on the side away from the joint. The diaphysis is the central part or shaft of long bones. The perichondrial ring contributes to appositional growth.

The articular cartilage also contributes to the growth of the epiphysis. The perichondrial ring, which surrounds the physes, and the perichondrium around the epiphyses and periosteum, which surrounds the metaphysis and diaphyseal regions of the bone, contribute to appositional or circumferential growth. Bones without physes (pelvis, scapulae, carpals, tarsals) grow by appositional bone growth from their surrounding perichondrium and periosteum. Other bones (metacarpals, metatarsals, phalanges, spine) grow by a combination of appositional and endochondral ossification.

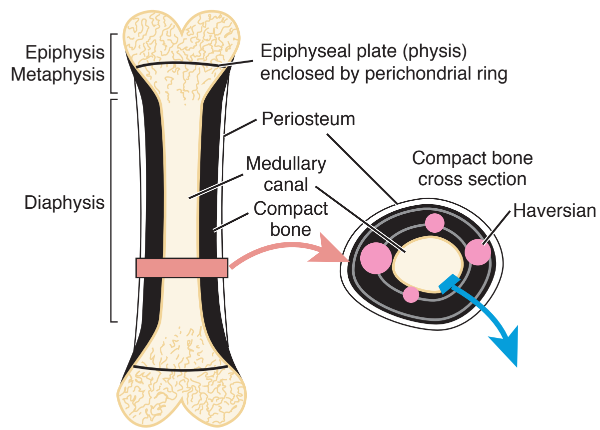

Figure 672-1 Diagram showing typical long bone divisions.

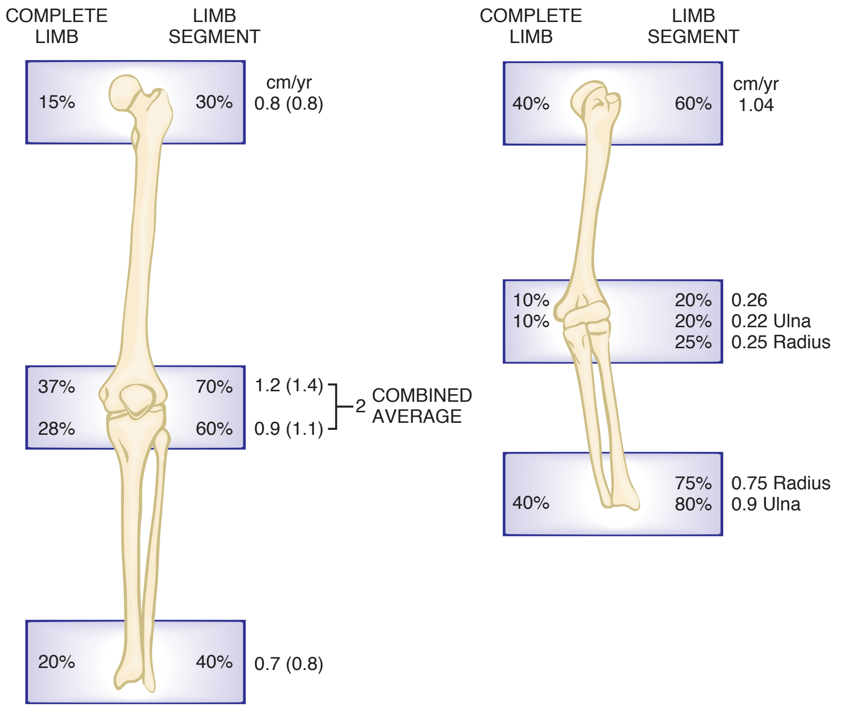

Figure 672-2 The contribution (%) of each physis to the overall length of the extremities. *(From Morrissy R, Weinstein S, editors:* Lovell and Winter's pediatric orthopedics, *ed 5, Philadelphia, 2001, Lippincott Williams & Wilkins.)*

Table 672-2	Skeletal Growth Considerations

- Abnormal stature can be assessed as "proportionate" or "disproportionate" based on comparing the ratio of sitting height with subischial height (lower limbs).
- Normally the arm span is almost equal to standing height.
- The head is disproportionately large at birth and ratio of head height to total height is approximately 1:4 at birth, which changes to 1:7.5 at skeletal maturity.
- Lower extremities account for approximately 15% of height at birth and 30% at skeletal maturity.
- The rate of height and growth increase is not constant and varies with growth spurts.
- By age 5 yr, birth height usually doubles and the child is approximately 60% of adult height. The child is approximately 80% of final height at 9 yr. During puberty, the standing height increases by approximately 1 cm/mo.
- Bone age is more important than chronologic age in determining future growth potential.

Important Growth and Developmental Milestones

Table 672-2 summarizes some important musculoskeletal growth considerations.

Growth Patterns in Upper and Lower Extremities

The upper extremity grows longitudinally, primarily from physes of the proximal humeral physis and the distal radial and ulnar physes. In the lower extremity, most of the longitudinal growth occurs around the knee, in the distal femoral and the proximal tibial physes (Fig. 672-2).

In the hip joint, the acetabulum forms with the convergence of 3 primary ossification centers: ischium, ilium, and pubis.

GAIT/FUNCTIONAL MATURATION

Functional mobility develops in infants in a predictable fashion (Table 672-3). Failure to achieve functional milestones is an indication for referral to a neurologist to determine if a central nervous system problem exists. Central nervous system maturation contributes significantly to the development of gait. In early ambulation (at 8-15 mo), the child usually has a wide-based gait with hyperflexion of hips and knees, and initial contact with the heel. By the age of 2 yr, the wide gait diminishes, reciprocal arm swing begins, and there is increased stride length and velocity. Adult fluid gait patterns usually start developing by 3 yr and mature to an adult-like pattern by age 7 yr.

Table 672-3 Functional Milestones

MILESTONE	ACHIEVED BY
Head control	3-6 months
Sitting	6-9 months
Crawling	8 months
Pulling to stand	8-12 months
Ambulating	12-18 months

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Chapter 673

Evaluation of the Child

Keith D. Baldwin, Lawrence Wells, and John P. Dormans

A detailed history and thorough physical examination are critical to the evaluation of a child with an orthopedic problem. The child's family and acquaintances are important sources of information, especially in younger children and infants. Appropriate radiographic imaging and, occasionally, laboratory testing may be necessary to support the clinical diagnosis.

HISTORY

A comprehensive history should include details about the prenatal, perinatal, and postnatal periods. Prenatal history should include maternal health issues: smoking, prenatal vitamins, illicit use of drugs or narcotics, alcohol consumption, diabetes, rubella, and sexually transmitted infections. The child's prenatal and perinatal history should include information about the length of pregnancy, length of labor, type of labor (induced or spontaneous), presentation of fetus, evidence of any fetal distress at delivery, requirements of oxygen following the delivery, birth length and weight, Apgar score, muscle tone at birth, feeding history, and period of hospitalization. In older infants and young children, evaluation of developmental milestones for posture, locomotion, dexterity, social activities, and speech are important. Specific orthopedic questions should focus on joint, muscular, appendicular, or axial skeleton complaints. Information regarding pain or other symptoms in any of these areas should be appropriately elicited (Table 673-1). The family history can give clues to heritable disorders. It also can forecast expectations of the child's future development and allow appropriate interventions as necessary.

PHYSICAL EXAMINATION

The orthopedic physical examination includes a thorough examination of the musculoskeletal system along with a comprehensive neurologic examination. The musculoskeletal examination includes inspection, palpation, and evaluation of motion, stability, and gait. A basic neurologic examination includes sensory examination, motor function, and reflexes. The orthopedic physical examination requires basic knowledge of anatomy of joint range of motion, alignment, and stability. Many common musculoskeletal disorders can be diagnosed by the history and physical examination alone. One screening tool that has been useful in adults has now been adapted and evaluated for use in children, the pediatric gait, arms, legs, spine (pGALS) test, the components of which are listed in Figure 673-1.

Inspection

Initial examination of the child begins with inspection. The clinician should use the guidelines listed in Table 673-2 during inspection.

Palpation

Palpation of the involved region should include assessment of local temperature and tenderness; assessment for a swelling or mass, spasticity or contracture, and bone or joint deformity; and evaluation of anatomic axis of limb and of limb lengths.

Contractures are a loss of mobility of a joint from congenital or acquired causes and are caused by periarticular soft-tissue fibrosis or involvement of muscles crossing the joint. Congenital contractures are common in **arthrogryposis** (see Chapter 682). Spasticity is an abnormal increase in tone associated with hyperreflexia and is common in cerebral palsy.

Deformity of the bone or joint is an abnormal fixed shape or position from congenital or acquired causes. It is important to assess the type of deformity, its location, and degree of deformity upon clinical examination. It is also important to assess whether the deformity is fixed or can be passively or actively corrected and whether there is any associated muscle spasm, local tenderness, or pain on motion. Classification of the deformity depends on the plane of deformity: **varus** (away from midline) or **valgus** (apex toward midline), or **recurvatum** (backward curvature) or **flexion** deformity (sagittal plane). In the axial skeleton, especially the spine, deformity can be defined as scoliosis, kyphosis, hyperlordosis, and kyphoscoliosis.

Range of Motion

Active and passive joint motion should be assessed, recorded, and compared to the opposite side. Objective evaluation should be done with a goniometer and recorded.

Vocabulary for direction of joint motion is as follows:

Abduction: Away from the midline
Adduction: Toward the midline
Flexion: Movement of bending from the starting position
Extension: Movement from bending to the starting position
Supination: Rotating the forearm to face the palm upward
Pronation: Rotating the forearm to face the palm downward
Inversion: Turning the hindfoot inward
Eversion: Turning the hindfoot outward
Plantarflexion: Pointing the toes away from the body (toward the floor)
Dorsiflexion: Pointing the toes toward the body (toward the ceiling)
Internal rotation: Turning inward toward the axis of the body
External rotation: Turning outward away from the axis of the body

Table 673-1 Characterization of Pain and Presenting Symptom

Location: Whether pain is localized to a particular segment or involves a larger area
Intensity: Usually on a pain scale of 1-10
Quality: Tumor pain is often unrelenting, progressive, and often present during the night. Pain at night particularly suggests osteoid osteoma. Pain in inflammation and infection is usually continuous
Onset: Was it acute and related to specific trauma or was it insidious? Acute pain and history of trauma are more commonly associated with fractures.
Duration: Whether transient, only lasting for minutes, or lasting for hours or days. Pain lasting for longer than 3-4 wk suggests a serious underlying problem.
Progress: Whether static, increasing, or decreasing
Radiation: Pain radiating to upper or lower extremities or complaints of numbness, tingling, or weakness require appropriate work-up.
Aggravating factors: Relationship to any activities such as swimming or diving or any particular position
Alleviating factors: Is the pain relieved by rest, heat, and/or medication? Conditions such as spondylolysis, Scheuermann disease, inflammatory spondyloarthropathy, muscle pulls, or overuse are improved by bed rest.
Gait and posture: Disturbances associated with pain

Table 673-2 Guidelines During Inspection of a Child with Musculoskeletal Problem

- The patient should be *comfortable with adequate exposure and well-lit surroundings* (lest some important physical finding be missed). Infants or young children may be examined on their parent's lap so that they feel more secure and are more likely to be cooperative.
- It is important to inspect how the patient moves about in the room before and during the examination, as well as during various maneuvers. *Balance, posture, and gait pattern* should also be checked.
- *General examination* findings should include inspection for skin rashes, café-au-lait spots, hairy patches, dimples, cysts, tuft of hair, or evidence of spinal midline defects that can indicate serious underlying problems that need review.
- *General body habitus,* including signs of cachexia, pallor, and nutritional deficiencies, should be noted.
- Note any obvious spinal asymmetry, axial or appendicular deformities, trunk decompensation, and evidence of muscle spasm or contractures. The *forward bending test* is valuable in assessing asymmetry and movement of the spine.
- It is essential to perform and document a *thorough neurologic examination.* Motor, sensory, and reflex testing should be performed and recorded.
- Any *discrepancies in limb lengths*, as well as *muscle atrophy*, should be recorded.
- The range of motion of all joints, their stability, and any evidence of hyperlaxity, peripheral pulsations, and lymphadenopathy should also be noted in all cases.

Gait

A "Walk on your tip-toes."* Observe the child walking

B "Walk on your heels."* Observe the child walking

Arms

C "Put your hands out in front of you."

D "Turn your hands over and make a fist. Pinch your index finger and thumb together."

E "Touch the tips of your fingers with your thumb."

F Squeeze metacarpophalangeal joints

G "Put your hands together."*

H "Put your hands back to back."*

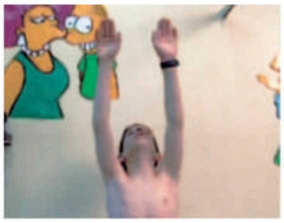

I "Reach up and touch the sky.* Look at the ceiling."

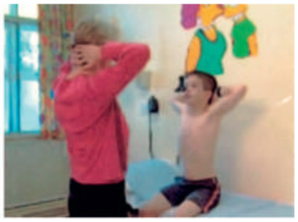

J "Put your hands behind your neck."

Legs

K Feel for effusion at the knee

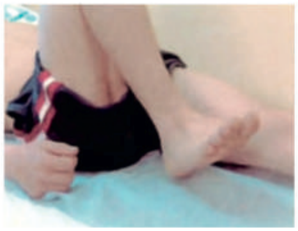

L "Bend and the straighten your knee." (active movement of knees and examiner feels for crepitus)

M Passive flexion (90 degrees) with internal rotation of hip

Spine

N "Open your mouth and put 3 of your (child's own) fingers in your mouth."*

O Lateral flexion of cervical spine: "Try and touch your shoulder with your ear."

P Observe spine from behind

Q "Can you bend and touch your toes?" Observe curve of spine from side and behind

Figure 673-1 The components of pediatric gait, arms, legs, spine (pGALS) screen, with illustration of movement. Screening questions: (1) Do you have any pain or stiffness in your joints, muscles, or back? (2) Do you have any difficulty getting yourself dressed without any help? (3) Do you have any difficulty going up and down stairs? *Additions and amendments to the original adult gait, arms, legs, spine screen. *(From Foster HE, Kay LJ, Friswell M, et al: Musculoskeletal screening examination [pGALS] for school-age children based on the adult GALS screen,* Arthritis Rheum *55:709–716, 2006.)*

Gait Assessment

Children typically begin walking between 8 and 16 mo of age. Early ambulation is characterized by short stride length, a fast cadence, and slow velocity with a wide-based stance. Gait cycle is a single sequence of functions that starts with heel strike, toe off, swing, and heel strike. The 4 events describe 1 gait cycle and include 2 phases: stance and swing. The stance phase is the period during which the foot is in contact with the ground. The swing phase is the portion of the gait cycle during which a limb is being advanced forward without ground contact (see Chapter 672). Normal gait is a symmetric and smooth process. Deviation from the norm indicates potential abnormality and should trigger investigation.

Neurologic maturation is necessary for the development of gait and the normal progression of developmental milestones. A child's gait changes with neurologic maturation. Infants normally walk with greater hip and knee flexion, flexed arms, and a wider base of gait than older children. As the neurologic system continues to develop in the cephalocaudal direction, the efficiency and smoothness of gait increase. The gait characteristics of a 7 yr old child are similar to those of an adult. When the neurologic system is abnormal (cerebral palsy), gait can be disturbed, exhibiting pathologic reflexes and abnormal movements.

Deviations from normal gait occur in a variety of orthopedic conditions. Disorders that result in muscle weakness (e.g., spina bifida, muscular dystrophy), spasticity (e.g., cerebral palsy), or contractures (e.g., arthrogryposis) lead to abnormalities in gait. Other causes of gait disturbances include limp, pain, torsional variations (in-toeing and out-toeing), toe walking, joint abnormalities, and leg-length discrepancy (Table 673-3).

LIMPING

A thorough history and clinical examination are the first steps toward early identification of the underlying problem causing a limp. Limping can be considered as either **painful (antalgic)** or painless, with the differential diagnosis ranging from benign to serious causes (septic hip, tumor). In a painful gait, the stance phase is shortened as the child decreases the time spent on the painful extremity. In a painless gait, which indicates underlying proximal muscle weakness or hip instability, the stance phase is equal between the involved and uninvolved sides, but the child leans or shifts the center of gravity over the involved extremity for balance. A bilateral disorder produces a waddling gait. Trendelenburg gait is produced by weak abnormal hip abductors. In single leg stance, a Trendelenburg sign can often be elicited when abductors are weak.

Disorders most commonly responsible for an abnormal gait generally vary based on the age of the patient. The differential diagnosis of limping varies based on age group (Table 673-4) or mechanism (Table 673-5). Neurologic disorders, especially spinal cord or peripheral nerve disorders, can also produce limping and difficult walking. Antalgic gait is predominantly a result of trauma, infection, or pathologic fracture. Trendelenburg gait is generally caused by congenital, developmental, or muscular disorders. In some cases, limping also may be caused by nonskeletal causes such as testicular torsion, inguinal hernia, and appendicitis.

BACK PAIN

Children frequently have a specific skeletal pathology as the cause of back pain. The most common causes of back pain in children are trauma, spondylolysis, spondylolisthesis, and infection (see Table 679-2). Tumor and tumor-like lesions that cause back pain in children are likely to be missed unless a thorough clinical assessment and adequate work-up are performed when required. Nonorthopedic causes of back pain include urinary tract infections, nephrolithiasis, and pneumonia.

NEUROLOGIC EVALUATION

A careful neurologic evaluation is a part of every pediatric musculoskeletal examination (see Chapter 590). The assessment should include evaluation of developmental milestones, muscle strength, sensory assessment, muscle tone, and deep tendon reflexes. The neurologic evaluation should also assess the spine and identify any deformity, such as scoliosis and kyphosis, or abnormal spinal mobility. The hips and feet should also be examined specifically, along with torsional abnormalities of the lower extremity, which are vastly more common in the neurologically involved population. Specific peripheral nerve examinations may be necessary.

As the nervous system matures, the developing cerebral cortex normally inhibits rudimentary reflexes that are often present at birth (see Chapter 590). Therefore, persistence of these reflexes can indicate neurologic abnormality. The most commonly performed deep tendon reflex tests include biceps, triceps, quadriceps, and gastrocnemius and soleus tendons. Upper motor neuron signs should also be noted. The

Table 673-3 Causes of Abnormal Gait

Limp
Pain
Torsional variations
Toe walking
Joint abnormalities
Leg-length discrepancy
Neuromuscular disorders

Table 673-4 Common Causes of Limping According to Age

ANTALGIC	TRENDELENBURG	LEG-LENGTH DISCREPANCY
TODDLER (1-3 YR)		
Infection	Hip dislocation (DDH)	–
Septic arthritis	Neuromuscular disease	
Hip	Cerebral palsy	
Knee	Poliomyelitis	
Osteomyelitis		
Diskitis		
Occult trauma		
Toddler's fracture		
Neoplasia		
CHILD (4-10 YR)		
Infection	Hip dislocation (DDH)	+
Septic arthritis	Neuromuscular disease	
Hip	Cerebral palsy	
Knee	Poliomyelitis	
Osteomyelitis		
Diskitis		
Transient synovitis, hip		
LCPD		
Tarsal coalition		
Rheumatologic disorder		
JRA		
Trauma		
Neoplasia		
ADOLESCENT (11+ YR)		
SCFE		+
Rheumatologic disorder		
JRA		
Trauma: fracture, overuse		
Tarsal coalition		
Neoplasia		

–, Absent; +, present; DDH, developmental dysplasia of the hip; JRA, juvenile rheumatoid arthritis; LCPD, Legg-Calvé-Perthes disease; SCFE, slipped capital femoral epiphysis.

From Thompson GH: Gait disturbances. In Kliegman RM, editor: Practical strategies of pediatric diagnosis and therapy, *Philadelphia, 1996, WB Saunders, pp. 757–778.*

Table 673-5 Differential Diagnosis of Limping

ANTALGIC GAIT *Congenital* Tarsal coalition *Acquired* Legg-Calvé-Perthes disease Slipped capital femoral epiphysis *Trauma* Sprains, strains, contusions Fractures Occult Toddler's fracture Abuse *Neoplasia* Benign • Unicameral bone cyst • Osteoid osteoma Malignant • Osteogenic sarcoma • Ewing sarcoma • Leukemia • Neuroblastoma • Spinal cord tumors *Infectious* Septic arthritis Reactive arthritis Osteomyelitis • Acute • Subacute Diskitis *Rheumatologic* Juvenile rheumatoid arthritis Hip monoarticular synovitis (toxic transient synovitis)
TRENDELENBURG *Developmental* Developmental dysplasia of the hip Leg-length discrepancy *Neuromuscular* Cerebral palsy Poliomyelitis

From Thompson GH: Gait disturbances. In Kliegman RM, editor: Practical strategies of pediatric diagnosis and therapy, *Philadelphia, 1996, WB Saunders, pp. 757–778.*

Table 673-6 Ashworth Scale of Spasticity

0	No increase in muscle tone
1	Slight increase in muscle tone, usually a catch or minimal resistance at end range of motion
2	Moderate tone throughout range of motion
3	Considerable increase in tone; passive range of motion difficult
4	Rigid in flexion or extension

Table 673-7 Clinical Scale of Upper-Extremity Motor Control

GRADE	DEFINITION
Grade 1	Hypotonic, no volitional motion
Grade 2	Hypertonic, no volitional motion
Grade 3	Mass flexion or extension in response to a stimulus
Grade 4	Patient can initiate movement but results in mass flexion or extension
Grade 5	Slow volitional movement; stress or rapid movement results in mass action
Grade 6	Volitional control of specific joints/muscles

Ashworth scale is often used to grade spasticity (Table 673-6). Upper-extremity motor control is often graded, and these grades are useful both diagnostically and prognostically. Passive range of motion should be assessed to determine contractures (Table 673-7). Localized or diffuse weakness must be determined and documented. A thorough assessment and grading of muscle strength is mandatory in all cases of neuromuscular disorders.

RADIOGRAPHIC ASSESSMENT

Plain radiographs are the first step in evaluation of most musculoskeletal disorders. Advanced imaging includes special procedures such as nuclear bone scans, ultrasonography, MRI, CT, and positron emission tomography.

Plain Radiographs

Routine radiographs are the first step and consist of anteroposterior and lateral views of the involved area with 1 joint above and below. Comparison views of the opposite side, if uninvolved, may be helpful in difficult situations but are not always necessary. It is important for the clinician to be aware of normal radiographic variants of the immature skeleton. Several synchondroses may be mistaken for fractures. A patient with "normal" plain radiographic appearance but having persistent pain or symptoms might need to be evaluated further with additional imaging studies.

Nuclear Medicine Imaging

A bone scan displays physiologic information rather than pure anatomy and relies on the emission of energy from the nucleotide injected into the patient. Indications include early septic arthritis, osteomyelitis, avascular necrosis, tumors (osteoid osteoma), metastatic lesions, occult and stress fractures, and cases of child abuse.

Total-body radionuclide scan (technetium-99) is useful to identify bony lesions, inflammatory tumors, and stress fractures. Tumor vascularity can also be inferred from the flow phase and the blood pool images. Gallium or indium scans have high sensitivity for local infections. Thallium-201 chloride scintiscans have >90% sensitivity and between 80% and 90% accuracy in detecting malignant bone or soft-tissue tumors.

Ultrasonography

Ultrasonography is useful to evaluate suspected fluid-filled lesions such as popliteal cyst and hip joint effusions. Major indications for ultrasonography are fetal studies of the extremities and spine, including detection of congenital anomalies like spondylocostal dysostosis, fractures suggesting osteogenesis imperfecta, developmental dysplasia of the hip, joint effusions, occult *neonatal* spinal dysraphism, foreign bodies in soft tissues, and popliteal cysts of the knee.

Magnetic Resonance Imaging

MRI is the **imaging modality of choice** for defining the exact anatomic extent of most musculoskeletal lesions (particularly if the structure is soft tissue). MRI avoids ionizing radiation and doing does not produce any known harmful effects. It produces excellent anatomic images of the musculoskeletal system, including the soft tissue, bone marrow cavity, spinal cord, and brain. It is especially useful for defining the extent of soft-tissue lesions, infections, and injuries. Tissue planes are well delineated, allowing more accurate assessment tumor invasion into adjacent structures. Cartilage structures can be visualized (articular cartilage of the knee can be distinguished from the fibrocartilage of the meniscus). MRI is also helpful in visualizing unossified joints in the pediatric population including the shoulders, elbows, and hips of young infants.

Magnetic Resonance Angiography

Magnetic resonance angiography has largely replaced routine angiography in the preoperative assessment of vascular lesions and bone tumors. Magnetic resonance angiography provides good visualization of peripheral vascular branches and tumor neovascularity in patients with primary bone tumors.

Computed Tomography

CT has enhanced the evaluation of multiple musculoskeletal disorders. Coronal, sagittal, and axial imaging is possible with CT including 3-dimensional reconstructions that can be beneficial in evaluating complex lesions of the axial and appendicular skeleton. It allows visualization of the detailed bone anatomy and the relationship of bones to contiguous structures. CT is useful to readily evaluate tarsal coalition, accessory navicular bone, infection, growth plate arrest, osteoid osteoma, pseudoarthrosis, bone and soft tissue tumors, spondylolysis, and spondylolisthesis. CT is superior to MRI for assessing bone involvement and cortical destruction (even subtle changes), including calcification or ossification and fracture (particularly if displacement of an articular fracture is suspected.

LABORATORY STUDIES

Laboratory tests are occasionally necessary in the evaluation of a child with musculoskeletal disorder. These may include a complete blood cell count; erythrocyte sedimentation rate; C-reactive protein assay; Lyme titers; and blood, wound, joint, periosteum, or bone cultures for infectious conditions such as septic arthritis or osteomyelitis. Rheumatoid factor, antinuclear antibodies, and human leukocyte antigen B27 may be necessary for children with suspected rheumatologic disorders. Creatine kinase, aldolase, aspartate aminotransferase, and dystrophin testing are indicated in children with suspected disorders of striated muscle such as Duchenne muscular dystrophy.

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Chapter 674
The Foot and Toes
Jennifer J. Winell and Richard S. Davidson

Abnormalities affecting the osseous and articular structures of the foot may be congenital, developmental, neuromuscular, inflammatory, or acquired. Problems with the foot and/or toes may be associated with a host of connective tissue diseases and syndromes; overuse syndromes are commonly observed in young athletes. Symptoms may include pain and abnormal shoe wear; cosmetic concerns are common. The foot may be divided into the **forefoot** (toes and metatarsals), the **midfoot** (cuneiforms, navicular, cuboid), and the **hindfoot** (talus and calcaneus). While the tibiotalar joint (ankle) provides plantarflexion and dorsiflexion, the subtalar joint (between the talus and calcaneus) is oriented obliquely, providing inversion and eversion. Inversion represents a combination of plantarflexion and varus, while eversion involves dorsiflexion and valgus. The subtalar joint is especially important for walking on uneven surfaces. Inversion of the transverse tarsal (Chopart) joint locks the midfoot to provide a stable base on which to perform toe off during the gait cycle. Eversion of the transverse tarsal joint unlocks the **hindfoot** to provide accommodation during heel strike of the of the gait cycle. The talonavicular and calcaneocuboid joints connect the midfoot with the hindfoot.

674.1 Metatarsus Adductus
Jennifer J. Winell and Richard S. Davidson

Metatarsus adductus involves adduction of the forefoot relative to the hindfoot. When the forefoot is supinated and adducted, the deformity is termed *metatarsus varus* (Fig. 674-1). The disorder is common in newborns, most frequently caused by intrauterine molding; the deformity is bilateral in 50% of cases. As with other intrauterine positional foot deformities, a careful hip and neck examination should always be performed to look for other abnormalities associated with intrauterine positioning.

CLINICAL MANIFESTATIONS
The forefoot is adducted (occasionally supinated), whereas the midfoot and hindfoot are normal. The lateral border of the foot is convex, and the base of the 5th metatarsal appears prominent. Range of motion at the ankle and subtalar joints is normal. Both the magnitude and the degree of flexibility should be documented. When the foot is viewed from the plantar surface, a line through the midpoint of (and parallel to) the heel should normally extend through the 2nd toe. Flexibility is assessed by stabilizing the hindfoot and midfoot in a neutral position with 1 hand and applying pressure over the 1st metatarsal head with the other. Correction with little pressure is indicative of a more flexible deformity. In the walking child with an uncorrected metatarsus adductus deformity, an in-toe gait and abnormal shoe wear may occur. A subset of patients will also have a dynamic adduction deformity of the great toe (hallux varus), which is often most noticeable during ambulation. This usually improves spontaneously and does not require treatment.

RADIOGRAPHIC EVALUATION
Radiographs are not performed routinely in infants. Older children with residual deformity should have anteroposterior (AP) and lateral weight-bearing or simulated weight-bearing radiographs. The AP radiographs demonstrate adduction of the metatarsals at the tarsometatarsal articulation and an increased intermetatarsal angle between the 1st and 2nd metatarsals.

TREATMENT
The treatment of metatarsus adductus is based on the rigidity of the deformity; most children respond to nonoperative treatment. Deformities that are flexible and overcorrect into abduction with passive manipulation may be observed. Those feet that correct just to a neutral position may benefit from stretching exercises which can be demonstrated to the parents in the office. In a walking child, the parents can try reversing the shoes as well. If this is not effective, reverse-last shoes to maintain the abducted position of foot can be prescribed. These are worn full time (22 hr/day), and the condition is reevaluated in 4-6 wk.

Figure 674-1 Clinical picture of metatarsus adductus with a normal foot on opposite side.

If improvement occurs, treatment can be continued. If there is no improvement, serial plaster casts should be considered. When stretching a foot with metatarsus adductus, care should be taken to maintain the hindfoot in neutral to slight varus alignment to avoid creating hindfoot valgus. Feet that cannot be corrected to a neutral position may benefit from serial casting; the best results are obtained when treatment is started before 8 mo of age. In addition to stretching the soft tissues, the goal is to alter physeal growth and stimulate remodeling, resulting in permanent correction. Once flexibility and alignment are restored, orthoses or corrective shoes are generally recommended for an additional period. A dynamic hallux varus usually improves spontaneously, and no active treatment is required.

Surgical treatment may be considered in the small subset of patients with symptomatic residual deformities that have not responded to previous treatment. Surgery is generally delayed until children are 4-6 yr of age. Cosmesis is often a concern, and pain and/or the inability to wear certain types of shoes may occasionally lead patients to consider surgery. Options for surgical treatment include either soft-tissue releases or osteotomies. An osteotomy (midfoot or multiple metatarsals) is most likely to result in permanent restoration of alignment.

Bibliography is available at Expert Consult.

674.2 Calcaneovalgus Feet

Jennifer J. Winell and Richard S. Davidson

A common finding in the newborn, the calcaneovalgus foot is secondary to in utero positioning. Excessive dorsiflexion and eversion are observed in the hindfoot, and the forefoot may be abducted. There may be an associated external tibial torsion (see Chapter 675).

CLINICAL MANIFESTATIONS

The infant typically presents with the foot dorsiflexed and everted, and occasionally the dorsum of the foot or toes, will be in contact with the anterolateral surface of the lower leg (Fig. 674-2). Dimpling may be indicative of reduced subcutaneous fat at the dorsolateral ankle. Plantarflexion and inversion are often restricted. As with other intrauterine positional deformities, a careful hip examination should be performed; if there is any concern, hip ultrasonography should be considered. When comparing risk for developmental hip dysplasia (DDH) with other congenital foot deformities, congenital calcaneovalgus has the highest association with 19.4% of patients having coexisting DDH. The calcaneovalgus foot may be confused with a congenital vertical talus and may rarely be associated with a posteromedial bow of the tibia. A calcaneovalgus deformity may also be seen in older patients, typically those with a neuromuscular imbalance involving weakness or paralysis of the gastrocsoleus muscle (polio, myelomeningocele).

RADIOGRAPHIC EVALUATION

Radiographs are usually not required but should be ordered if the deformity fails to correct spontaneously or with early treatment. AP and lateral radiographs along with a lateral radiograph of the foot in maximal plantarflexion may help distinguish calcaneovalgus from a congenital vertical talus or congenital oblique talus. Evaluation of the position of the talus in relation to the navicular in both the lateral and maximally plantarflexed lateral view confirm congenital vertical or oblique talus. If a posteromedial bow of the tibia is suspected, AP and lateral radiographs of the tibia and fibula are necessary. In posteromedial bowing of the tibia, the deformity is located in the tibia with the apex of deformity positioned posterior and medial. All three conditions may be confused clinically with calcaneovalgus feet.

TREATMENT

Mild cases of calcaneovalgus foot, in which full passive range of motion is present at birth, require no active treatment. These usually resolve within the 1st few wk of life. A gentle stretching program, focusing on plantarflexion and inversion, is recommended for cases with some restriction in motion. For cases with a greater restriction in mobility, serial casts may be considered to restore motion and alignment. Casting is rarely required in the treatment of calcaneovalgus feet. The management for those cases associated with a posteromedial bow of the tibia is similar.

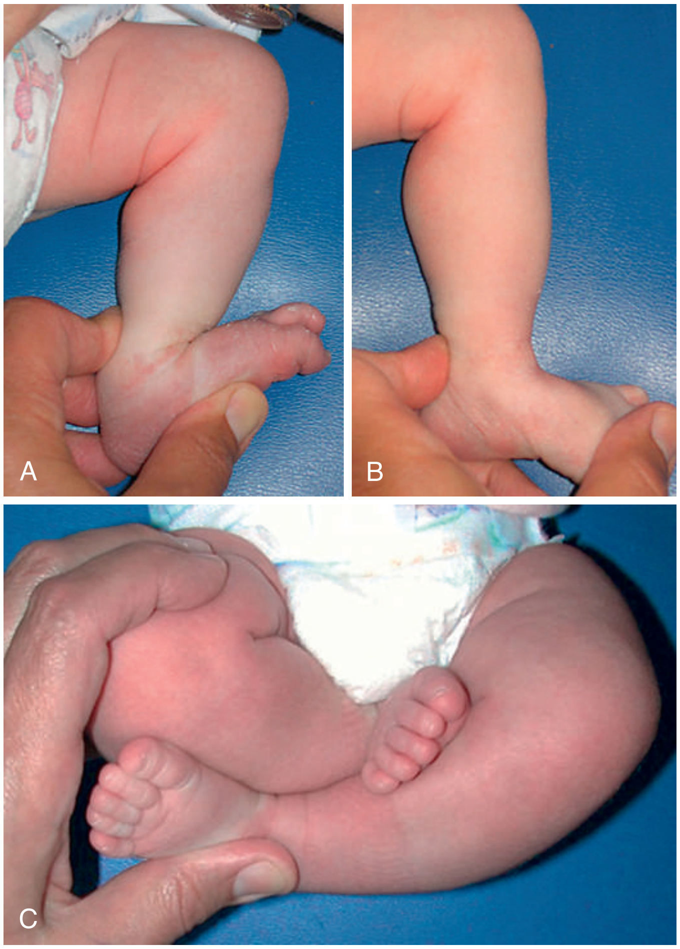

Figure 674-2 Clinical picture of calcaneovalgus foot **(A)** that is passively correctable **(B)** because of intrauterine positioning **(C)**.

Bibliography is available at Expert Consult.

674.3 Talipes Equinovarus (Clubfoot)

Jennifer J. Winell and Richard S. Davidson

Clubfoot or congenital talipes equinovarus (CTEV) is the term used to describe a deformity involving malalignment of the calcaneotalar-navicular complex. Components of this deformity may be best understood using the mnemonic **CAVE** (cavus, adductus, varus, equinus). Although this is predominantly a hindfoot deformity, there are plantarflexion (cavus) of the first ray and adduction of the forefoot/midfoot on the hindfoot. The hindfoot is in varus and equinus. The clubfoot deformity may be positional, congenital, associated with a variety of underlying diagnoses (neuromuscular or syndromic) or a focal dysplasia of musculoskeletal tissue distal to the knee.

The **positional (or postural) clubfoot** is a normal foot that has been held in a deformed position in utero and is found to be flexible on examination in the newborn nursery. The **congenital clubfoot** can either be idiopathic or syndromic. There is a spectrum of severity, but clubfoot associated with neuromuscular diagnoses or syndromes is

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typically rigid and more difficult to treat. Clubfoot is also extremely common in patients with myelodysplasia, arthrogryposis, and other chromosomal syndromes such as trisomy 18 and chromosome 22q11 deletion syndrome (see Chapter 81).

Congenital clubfoot is seen in approximately 1 in 1,000 births and most likely results from a complex multifactorial polygenic inheritance. The risk is approximately 1 in 4 when both a parent and 1 sibling have clubfeet. It occurs more commonly in males (2 : 1) and is bilateral in 50% of cases. The pathoanatomy involves both abnormal tarsal morphology (plantar and medial deviation of the head and neck of the talus) and abnormal relationships between the tarsal bones in all 3 planes, as well as associated contracture of the soft tissues on the plantar and medial aspects of the foot.

CLINICAL MANIFESTATIONS

A complete physical examination should be performed to rule out coexisting musculoskeletal and neuromuscular problems. The spine should be inspected for signs of occult dysraphism. Examination of the infant clubfoot demonstrates forefoot cavus and adductus and hindfoot varus and equinus (Fig. 674-3). The degree of flexibility varies, and all patients will exhibit calf atrophy. Internal tibial torsion, foot length shortening and leg-length discrepancy (shortening of the ipsilateral extremity) will be observed in a subset of cases. Although classically not associated with DDH (see Chapter 678), there is a higher association of CTEV and DDH than in the general population.

RADIOGRAPHIC EVALUATION

Anteroposterior and lateral radiographs are not recommended for idiopathic clubfoot. For arthrogrypotic or syndromic feet, x-rays may be helpful but must be performed, with the foot held in the maximally corrected position. Multiple radiographic measurements can be made to describe malalignment between the tarsal bones. The navicular bone does not ossify until 3-6 yr of age, so the focus of radiographic interpretation is the relationships between segments of the foot, forefoot to hindfoot. A common radiographic finding is "parallelism" between lines drawn through the axis of the talus and the calcaneus on the lateral radiograph, indicating hindfoot varus. X-ray may be particularly useful for older children with persistent or recurrent deformities that are difficult to assess.

TREATMENT

Nonoperative treatment is initiated in all infants and should be started as soon as possible following birth. Techniques have included taping and strapping, manipulation and serial casting, and functional treatment. Historically, a significant percentage of patients treated by manipulation and casting required a surgical release, which was usually performed between 3 and 12 mo of age. Although many feet remain well aligned after surgical releases, a significant percentage of patients have required additional surgery for recurrent or residual deformities. Stiffness remains a concern at long-term follow-up. While pain is uncommon in childhood and adolescence, symptoms may appear during adulthood. These concerns have led to considerable interest in less-invasive methods for treating the deformity. The Ponseti method of clubfoot treatment, which has now become the standard of initial treatment, involves a specific technique for manipulation and serial casting and may be best described as minimally invasive rather than nonoperative. The order of correction follows the mnemonic **CAVE**. Weekly cast changes are performed; 5-10 casts are typically required. The most difficult deformity to correct is the hindfoot equinus, and approximately 90% of patients will require a percutaneous tenotomy of the heel cord as an outpatient. Following the tenotomy, a long leg cast with the foot in maximal abduction (up to 70 degrees) and dorsiflexion is worn for 3-4 wk; the patient then begins a bracing program. An abduction brace is worn full time for 3 mo and then at nighttime for 3-5 yr. A small subset of patients (up to 20%) with recurrent, dynamic supination deformity will require transfer of the tibialis anterior tendon to the middle cuneiform for recurrence. Although most patients require some form of surgery, the procedures are minimal in comparison with extensive surgical release, which requires lengthening and/or release of muscles and tendons about the ankle and capsulotomy of the major joints to reposition the foot. The results of the Ponseti method are excellent at up to 40 yr of follow-up. Despite casting, children do not have much dysfunction or delay in achieving normal motor milestones. Compliance with the splinting program is essential; recurrence is common if the brace is not worn as recommended. Functional treatment, or the "French method," involves daily manipulations (supervised by a physical therapist) and splinting with elastic tape, as well as continuous passive motion (machine required) while the baby sleeps. While results are promising, it is usually performed in the

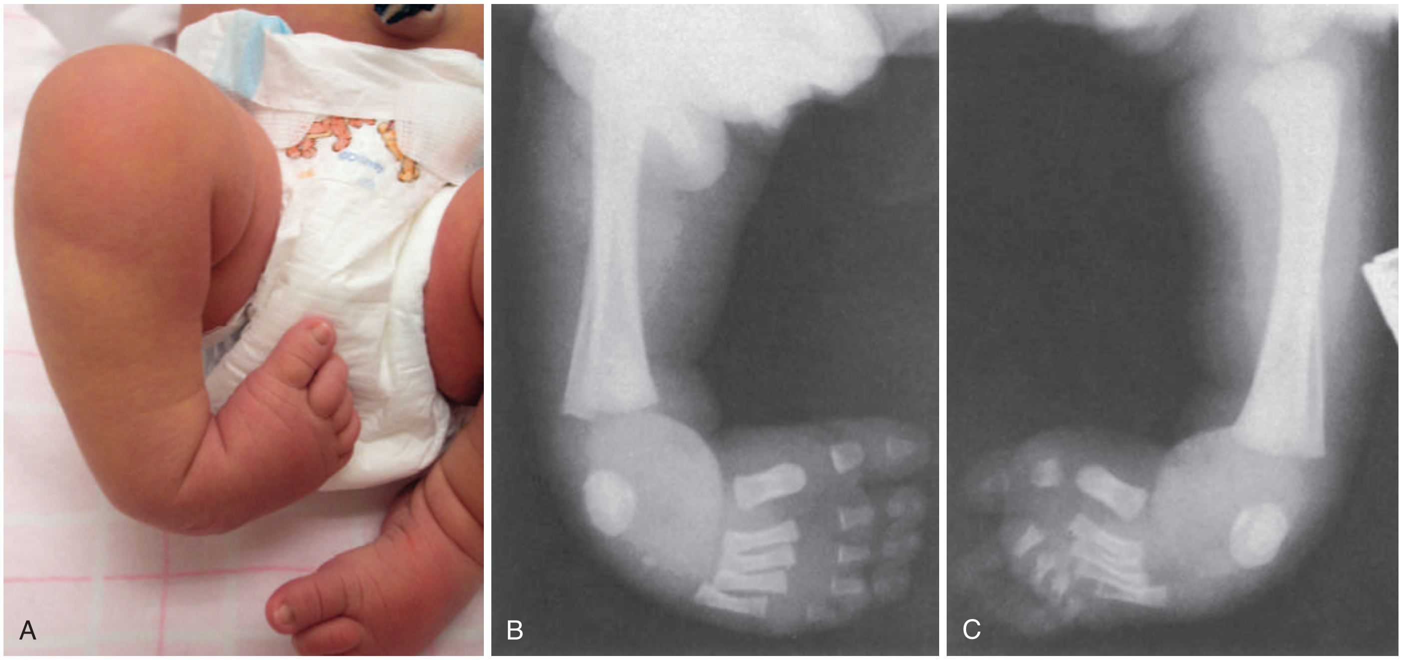

Figure 674-3 Talipes equinovarus in a newborn. **A,** Clinical appearance of an untreated clubfoot. **B** and **C,** Initial radiographic appearance of bilateral untreated clubfeet. *(From Herring JA:* Tachdjian's pediatric orthopaedics, *ed 5, Philadelphia, 2014, WB Saunders, Fig. 23-42, p. 791.)*

inpatient setting as the method is labor intensive. Implementation on an outpatient basis may be challenging, although just as successful. It remains unclear whether the technique will gain popularity in the United States. These minimally invasive methods are most successful when treatment is begun at birth or during the 1st few mo of life and with good compliance with postmanipulation bracing. As there are varying degrees of severity for idiopathic CTEV, grading systems have been proposed based on rigidity and magnitude of deformity.

Aggressive surgical realignment has a definite role in the management of clubfeet, especially in the minority of congenital clubfeet that have failed nonoperative or minimally invasive methods, and for the rigid neuromuscular and syndromic clubfeet. In such cases, nonoperative methods such as the Ponseti technique may potentially be of value in decreasing the magnitude of surgery required. Common surgical approaches include a release of the involved joints (realignment of the tarsal bones), a lengthening of the shortened posteromedial musculotendinous units, and usually pinning of the foot in the corrected position. The “a la carte” method allows the surgeon to apply the principles to be tailored to the unique characteristics of each deformity. For older children with untreated clubfeet or those in whom a recurrence or residual deformity is observed, bony procedures (osteotomies) may be required in addition to soft-tissue surgery. Triple arthrodesis is reserved as salvage for painful, deformed feet in adolescents and adults.

Bibliography is available at Expert Consult.

674.4 Congenital Vertical Talus

Jennifer J. Winell and Richard S. Davidson

Congenital vertical talus is an uncommon foot deformity in which the midfoot is dorsally dislocated on the hindfoot and the ankle is in fixed equinus. There is nearly an even split between idiopathic cases and cases with an underlying neuromuscular condition or a syndrome. Neurologic causes include myelodysplasia, tethered cord, and sacral agenesis. Other associated conditions include arthrogryposis, Larsen syndrome, multiple pterygium syndrome, and chromosomal abnormalities (trisomy 13-15, 19: see Chapter 81). Depending on the age at diagnosis, the differential diagnosis may include a calcaneovalgus foot, oblique talus (talonavicular joint reduces passively), flexible flatfoot with a tight Achilles tendon, and tarsal coalition. Genetic studies are ongoing regarding abnormal muscle morphology on biopsy.

CLINICAL MANIFESTATIONS

Congenital vertical talus has also been described as a **rocker-bottom foot** (Fig. 674-4) or a Persian slipper foot. The plantar surface of the foot is convex, and the talar head is prominent along the medial border of the midfoot. The fore part of the foot is dorsiflexed (dorsally dislocated on the hindfoot) and abducted relative to the hindfoot, and the hindfoot is in equinus and valgus. There is an associated contracture of the anterolateral (tibialis anterior, toe extensors) and the posterior (Achilles tendon, peroneals) soft tissues. The deformity is typically rigid. A thorough physical examination is required to identify any coexisting neurologic and/or musculoskeletal abnormalities.

RADIOGRAPHIC EVALUATION

AP, lateral, and maximal plantarflexion and dorsiflexion lateral radiographs should be obtained when the diagnosis is suspected. The plantarflexion view helps to determine whether the dorsal subluxation or dislocation of the midfoot on the hindfoot can be reduced passively. The dorsiflexion lateral view confirms the equinus contracture of the ankle. Although the navicular does not ossify until 3-6 yr of age, the relationship between the talus and the 1st metatarsal may be evaluated.

TREATMENT

The initial management consists of serial manipulation and casting, which is started shortly after birth. A “reverse” Ponseti method of casting is particularly useful in stretching out the dorsiflexion and valgus deformities. Open reduction and pin fixation can then stabilize the midfoot allowing simultaneous heel cord tenotomy and dorsiflexion with casting to correct the ankle equinus.

In recalcitrant cases the competing deformities of the midfoot and the hindfoot make conservative treatment difficult. Initially, an attempt is made to reduce the dorsal dislocation of the forefoot/midfoot on the hindfoot. Once this has been achieved, attention can be directed toward stretching the hindfoot contracture. These deformities are typically rigid, and surgical intervention is required in the majority of cases. In such cases, casting helps to stretch out the contracted soft tissues. Surgery is generally performed between 6 and 12 mo of age; a soft-tissue release is performed as a 1 or 2 stage procedure. One component involves release/lengthening of the contracted anterior soft tissues in concert with an open reduction of the talonavicular joint, while the other involves a posterior release with lengthening of the contracted musculotendinous units. Fixation with Kirschner wires is commonly performed to maintain alignment. Postoperatively, casting is employed for a variable period of time; patients often require the use of an orthosis for extended periods, depending on the underlying diagnosis. Salvage options for recurrent or residual deformities in older children include a subtalar or triple arthrodesis.

Bibliography is available at Expert Consult.

674.5 Hypermobile Pes Planus (Flexible Flatfeet)

Jennifer J. Winell and Richard S. Davidson

Flatfoot is a common diagnosis; it has been estimated that up to 23% of the public may be affected, depending on the diagnostic criteria. Three types of flatfeet may be identified: a flexible flatfoot, a flexible flatfoot with a tendo-Achilles contracture, and a rigid flatfoot. Flatfoot describes a change in foot shape, and there are several abnormalities in alignment between the tarsal bones. There is eversion of the subtalar complex. The hindfoot is aligned in valgus. There is midfoot sag at the naviculocuneiform and/or the talonavicular joints. The forefoot is abducted relative to the hindfoot, and the head of the talus is uncovered and prominent along the plantar and medial border of the midfoot/hindfoot. Although hypermobile or flexible pes planus represents a common source of concern for parents, these children are rarely symptomatic. Flatfeet are common in neonates and toddlers and are associated with physiologic ligamentous laxity. Improvement may be seen when the longitudinal arch develops between 5 and 10 yr of age. Flatfoot is less common in societies where shoes are not worn during infancy and childhood. In general, comfortable flexible-soled shoes are recommended for children. Flexible flatfeet persisting into adolescence and adulthood are usually associated with **familial ligamentous laxity** and can often be identified in other family members.

CLINICAL MANIFESTATIONS

Patients typically have a normal longitudinal arch when examined in a non–weightbearing position or standing on the toes, but the arch disappears when standing flat. The hindfoot collapses into valgus, and the midfoot sag becomes evident. Generalized ligamentous laxity is commonly observed. Range of motion should be assessed at both the subtalar and the ankle joints and will be normal in patients with a flexible flatfoot. When assessing range of motion at the ankle, the foot should always be inverted while testing dorsiflexion. If the foot is neutral or everted, spurious dorsiflexion may occur through the midfoot, masking a tendo-Achilles contracture. If subtalar motion is restricted, then the flatfoot is not hypermobile/flexible, and other diagnoses, such as tarsal coalition and juvenile rheumatoid arthritis, must be considered. On occasion, there may be tenderness and/or callus formation under the talar head medially. The shoes should be assessed as well and may have evidence of excessive wear along the medial border.

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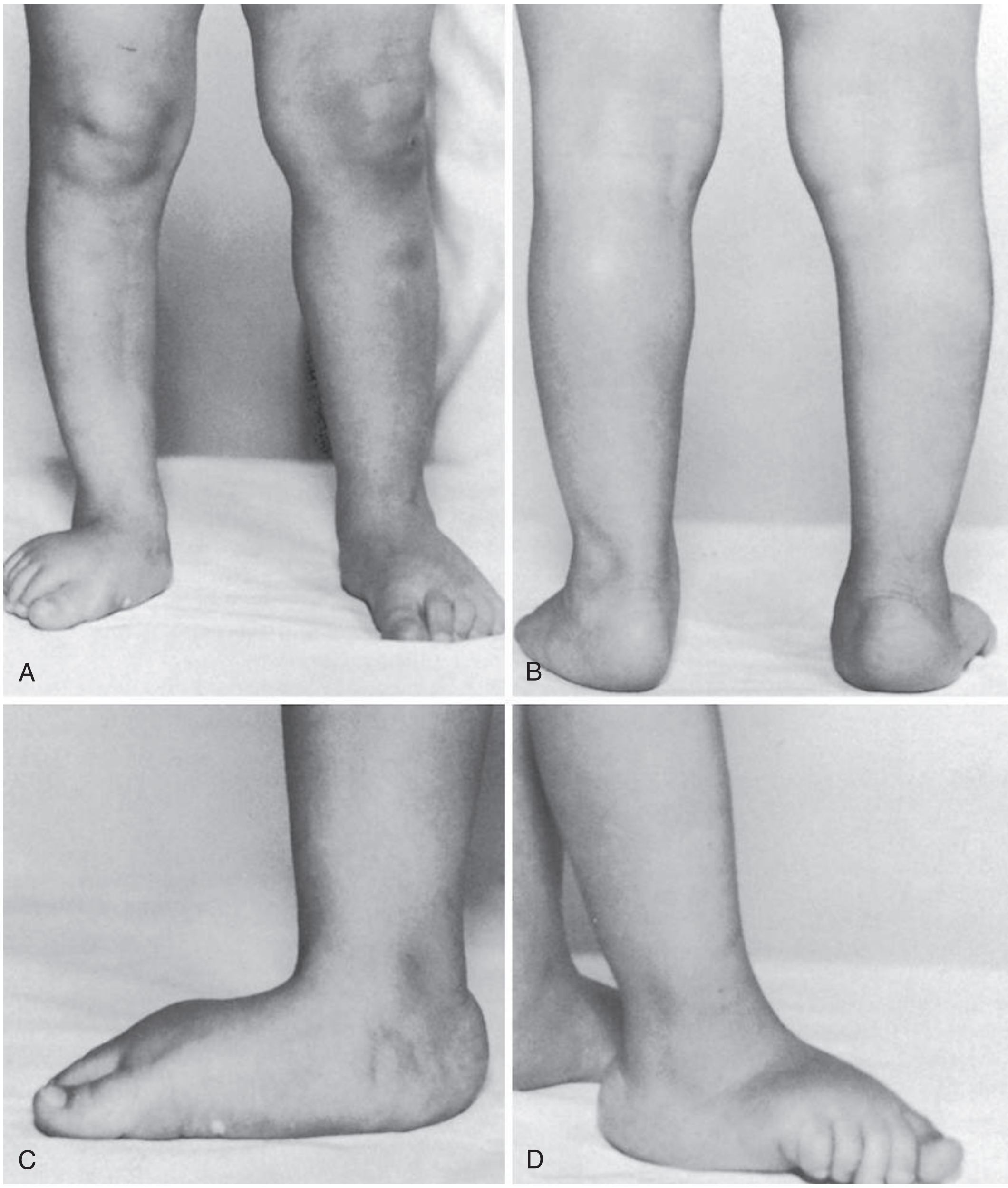

Figure 674-4 **Congenital vertical talus. A,** Pronation of the forefoot. **B,** Valgus of the heel. **C,** Absence of an arch, the rocker bottom deformity. **D,** Elevation of the lateral toes and tight peroneal tendons. *(From Herring JA:* Tachdjian's pediatric orthopaedics, *ed 5, Philadelphia, 2014, WB Saunders, Fig. 23-67, p. 821)*

RADIOGRAPHIC EVALUATION

Routine radiographs of asymptomatic flexible flatfeet are usually not indicated. If obtained for diagnostic reasons, weightbearing radiographs (AP and lateral) are required to assess the deformity. On the AP radiograph, there is widening of the angle between the longitudinal axis of the talus and the calcaneus, indicating excessive heel valgus. The lateral view shows distortion of the normal straight-line relationship between the long axis of the talus and the 1st metatarsal with sag either of the talonavicular or naviculocuneiform joint, resulting in flattening of the normal medial longitudinal arch (Fig. 674-5).

Figure 674-5 Lateral weightbearing radiograph demonstrating features of flatfoot.

TREATMENT

Although the natural history of the flexible flatfoot remains unknown, there is little evidence to suggest that this condition results in long-term problems or disability. As such, treatment is reserved for the small

subset of patients who develop symptoms. Patients may complain of hindfoot pain, abnormal shoe wear or fatigue after long walking. These patients may benefit from an nonprescription orthosis, such as a medial arch support. Severe cases, often associated with an underlying connective tissue disorder such as Ehlers-Danlos syndrome (see Chapter 659) or Down syndrome (see Chapter 81), may benefit from a custom orthosis such as the UCBL (University of California Biomechanics Laboratory) orthosis to better control the hindfoot and prevent collapse of the arch. Although an orthosis may relieve symptoms, there is no evidence to suggest any permanent change in the shape of the foot or alignment of the tarsal bones. Patients with a flexible flatfoot and a tight tendo-Achilles should be treated with stretching exercises. Many times patients are referred to physical therapy to ensure that the patients are stretching appropriately. On occasion, the muscle will need to be lengthened surgically. For the few patients with persistent pain, surgical treatment can be considered. There has been considerable interest in a lateral column lengthening, which addresses all components of the deformity. The procedure involves an osteotomy of the calcaneus, with placement of a trapezoidal bone graft. A lengthening of the tendo-Achilles is required, often with a plantarflexion osteotomy of the medial cuneiform. This procedure preserves the mobility of the hindfoot joints, in contrast to a subtalar or triple arthrodesis. While a hindfoot arthrodesis may correct the deformity adequately, the stress transfer to neighboring joints may result in late-onset, painful degenerative changes.

Bibliography is available at Expert Consult.

674.6 Tarsal Coalition

Jennifer J. Winell and Richard S. Davidson

Tarsal coalition, also known as **peroneal spastic flatfoot**, is characterized by a painful, rigid flatfoot deformity and peroneal (lateral calf) muscle spasm but without true spasticity. It represents a congenital fusion or failure of segmentation between 2 or more tarsal bones. Any condition that alters the normal gliding and rotatory motion of the subtalar joint may produce the clinical appearance of a tarsal coalition. Thus, congenital malformations, arthritis or inflammatory disorders, infection, neoplasms, and trauma can be possible causes.

The most common tarsal coalitions occur at the medial talocalcaneal (subtalar) facet and between the calcaneus and navicular (calcaneonavicular). Coalitions can be fibrous, cartilaginous, or osseous. Tarsal coalition occurs in approximately 1% of the general population and appears to be inherited as an autosomal dominant trait with nearly full penetrance. Approximately 60% of calcaneonavicular and 50% of the medial facet talocalcaneal coalitions are bilateral.

CLINICAL MANIFESTATIONS

Approximately 25% of patients will become symptomatic, typically during the 2nd decade of life. Although the flatfoot and a decrease in subtalar motion may have been present since early childhood, the onset of symptoms may correlate with the additional restriction in motion that occurs as a cartilaginous bar ossifies. Recurrent “ankle sprains” often accompany the presenting symptoms. The timing of ossification varies between the talonavicular (3-5 yr of age), the calcaneonavicular (8-12 yr of age), and the talocalcaneal (12-16 yr of age) coalitions. Hindfoot pain is commonly observed, especially in the region of the sinus tarsi and also under the head of the talus. Symptoms are activity related and are often increased with running or prolonged walking, especially on uneven surfaces. There may be tenderness over the site of the coalition and/or pain with testing of subtalar motion. The clinical appearance of a flatfoot is seen in both the weightbearing and non–weightbearing positions. There is a restriction in subtalar motion.

RADIOGRAPHIC EVALUATION

AP and lateral weightbearing radiographs and an oblique radiograph of the foot should be obtained (Table 674-1). A calcaneonavicular coalition is seen best on the oblique radiograph (Fig. 674-6). On the lateral radiograph, there may be elongation of the anterior process of the calcaneus, known as the “anteater sign.” A talocalcaneal coalition may be seen on a Harris (axial) view of the heel. On the lateral radiograph, there may be narrowing of the posterior facet of the subtalar joint, or a C-shaped line along the medial outline of the talar dome and the inferior outline of the sustentaculum tali (“C sign”). This “C sign” is made up of the sustentaculum talus of the calcaneus in continuity with the coalition. Beaking of the anterior aspect of the talus on the lateral view is seen with some frequency, and results from an alteration in the distribution of stress. This finding does not imply the presence of degenerative arthritis. Irregularity in the subchondral bony surfaces may be seen in patients with a cartilaginous coalition, in contrast to a well-formed bony bridge in those with an osseous coalition. A fibrous coalition may require additional imaging studies to diagnose. While plain films may be diagnostic, a CT scan is the *imaging modality of choice* when a coalition is suspected (Fig. 674-7). In addition to securing the diagnosis, this study helps to define the degree of joint involvement in patients with a talocalcaneal coalition. Although uncommon, more than one tarsal coalition may be observed in the same patient. Only in young children, MRI may be more effective in identifying either the coalition or a differential diagnosis for the foot pain. MRI offers less radiation exposure but requires more time and may necessitate sedation.

TREATMENT

The treatment of symptomatic tarsal coalitions varies according to the type and extent of coalition, the age of the patient, and the presence and magnitude of symptoms. Treatment is required only for symptomatic coalitions, and the initial management consists of activity

Table 674-1	Radiographic Secondary Signs Associated with Tarsal Conditions
Talar breaking Posterior subtalar facet narrowing Rounding and flattening of the lateral talar process Hypoplasia of the talus, shortening of the talar neck Anterior nose sign Ball-and-socket ankle joint Continuous C-sign Flatfoot deformity Altered navicular morphology (wide or laterally tapering) Dysmorphic sustentaculum tali (enlarged and ovoid on lateral radiograph)	

From Slovis TL, editor: Caffey’s pediatric diagnostic imaging, *ed 11, vol 2, Philadelphia, 2008, Mosby, p. 2604.*

Figure 674-6 Oblique radiograph of the foot demonstrating a calcaneonavicular tarsal coalition.

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Figure 674-7 CT scan of the talocalcaneal complex demonstrating a talocalcaneal (subtalar).

restriction and nonsteroidal antiinflammatory medications, with or without a shoe insert. Immobilization in a short leg walking cast for 4-6 wk may be required in patients with more pronounced symptoms. For patients with chronic pain despite an adequate trial of nonoperative therapy, surgical treatment should be considered, and options include resection of the coalition, osteotomy, or arthrodesis. For the calcaneonavicular coalition, resection and interposition of the extensor digitorum brevis muscle have been successful. Often, concomitant hindfoot valgus and contracture of the gastrocnemius-soleus is present. In these patients, more reliable pain relief can be obtained with resection of the coalition, correction of the hindfoot valgus by calcaneal lengthening osteotomy with bank bone graft and lengthening of the gastrocnemius-soleus. For those with extensive involvement of the joint and/or degenerative changes, a triple arthrodesis may be the best option; however, this is rarely needed in adolescents.

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674.7 Cavus Feet

Jennifer J. Winell and Richard S. Davidson

Cavus is a deformity involving plantarflexion of the forefoot or midfoot on the hindfoot and may involve the entire forepart of the foot or just the medial column. The result is an elevation of the medial longitudinal arch (Fig. 674-8). A deformity of the hindfoot will often develop to compensate for the primary forefoot abnormality. While familial cavus may occur, the majority of patients with this deformity will have an underlying neuromuscular etiology. The initial goal is to rule out (and treat) any underlying causes. These diagnoses may relate to abnormalities of the spinal cord (occult dysraphism, tethered cord, polio, myelodysplasia, etc.) and peripheral nerves (hereditary motor and sensory neuropathies [see Chapter 613] such as Charcot-Marie-Tooth [CMT] disease, Dejerine-Sottas disease, or Refsum disease). Although a unilateral cavus foot is most likely to result from an occult intraspinal anomaly, bilateral involvement usually suggests an underlying nerve or muscle disease. Cavus is commonly observed in association with a hindfoot deformity. Two-thirds of CMT patients have pes cavovarus, while 80% of pes cavovarus is most commonly seen in patients with the hereditary motor and sensory neuropathies (CMT), with 80% of CMT patients having pes cavovarus and 65% of patients with cavovarus having CMT. In patients with hereditary motor and sensory neuropathies, progressive weakness and muscle imbalance result in plantarflexion of the 1st ray/medial column. To obtain a plantigrade foot, the hindfoot must roll into varus. With equinocavus, the hindfoot is in equinus, whereas in calcaneocavus (usually seen in polio or myelodysplasia), the hindfoot is in calcaneus (excessive dorsiflexion).

Figure 674-8 Clinical picture demonstrating pes cavus.

TREATMENT

Any underlying diagnosis must be identified as this knowledge also helps to address the specific disorder and formulate the proper management strategy. With mild deformities, stretching through physical therapy or serial casting of the plantar fascia and contracted muscles with exercises to strengthen weakened muscles may help to delay progression. An ankle–foot orthosis may be necessary to stabilize the foot and improve ambulation. Surgical treatment is indicated for progressive or symptomatic deformities that have failed to respond to nonoperative measures or in the foot that is no longer braceable. The specific procedures recommended depend on the degree of deformity and the underlying diagnosis. In the case of a progressive neuromuscular condition, recurrence of deformity is commonly observed, and additional procedures may be required to maintain a plantigrade foot. Families should be counseled in detail regarding the disease process and the expected gains from the surgery. The goal of surgery is to restore motion and alignment and to improve muscle balance. For milder deformities, a soft-tissue release of the plantar fascia, often combined with a tendon transfer, may suffice. For patients with a fixed bony deformity of the forefoot, midfoot and/or the hindfoot, 1 or more osteotomies may be required for realignment. A triple arthrodesis (calcaneocuboid, talonavicular, and subtalar) may be required for severe feet (or recurrent deformities) in older patients. Long-term bracing is usually helpful in preventing recurrence.

Bibliography is available at Expert Consult.

674.8 Osteochondroses/Apophysitis

Jennifer J. Winell and Richard S. Davidson

Osteochondroses are idiopathic avascular necrosis of bones which may involve tarsal bones as well. Although rare, they may be observed in the tarsal navicular **(Köhler disease)** or the 2nd or 3rd metatarsal head **(Freiberg infraction)** (Fig. 674-9). These are generally self-limited conditions that commonly result in activity-related pain, which can at times be disabling. The treatment is based on the degree of symptoms and commonly includes restriction of activity. The diagnosis is often made by history and physical exam in conjunction with concordant radiographic findings. The navicular is particularly sensitive

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Figure 674-9 Radiographs of Köhler disease **(A)** and Freiberg infraction **(B)**.

as it is the last tarsal bone to ossify which may lead to compression from adjacent ossified bones. For patients with Köhler disease, nonsurgical treatment with a short leg cast for 6-8 wk may provide significant relief. Patients with Freiberg infraction may benefit from a period of casting and/or shoe modifications such as a rocker-bottom sole, a stiff-soled shoe, or a metatarsal bar. Degenerative changes and collapse of the metatarsal head will occasionally occur following the gradual healing process, and surgical intervention is required in a small subset of cases. Procedures have included joint debridement, bone grafting, redirectional osteotomy, subtotal or complete excision of the metatarsal head, and joint replacement.

Apophysitis represents inflammation at the tendinous insertion of a muscle from repetitive tensile loading and is most commonly observed during periods of rapid growth. These stresses result in microfractures at the fibrocartilaginous insertion site, associated with inflammation. Calcaneal apophysitis **(Sever disease)** is the most common cause of heel pain in children; treatment includes activity modification, nonsteroidal antiinflammatory medications, heel cord stretching exercises, and heel cushions or arch supports. **Iselin disease** represents an apophysitis at the 5th metatarsal base where the peroneus brevis attaches and is less common. Even though the mandate for imaging heel pain in all children remains controversial, radiographs should be considered when the symptoms are unilateral or with a failure to respond to treatment. A period of rest (6-8 wk) and avoidance of sports will often resolve symptoms, although recurrence is common until maturity when the apophyses close.

Bibliography is available at Expert Consult.

674.9 Puncture Wounds of the Foot

Jennifer J. Winell and Richard S. Davidson

Most puncture wound injuries to the foot may be adequately managed in the emergency department. **Treatment** involves a thorough irrigation and a tetanus booster, if appropriate; many clinicians will recommend antibiotics. Using this approach, the majority will heal without a complication. A subset of cases may develop cellulitis, most often caused by *Staphylococcus aureus*, and require intravenous antibiotics with or without surgical drainage. Persistent signs of infection should be investigated more thoroughly. Deep infection is uncommon and may be associated with septic arthritis or osteomyelitis. The most common organisms are *S. aureus* and *Pseudomonas aeruginosa*; the treatment involves a thorough surgical debridement followed by a short course (10-14 days) of systemic antibiotics. Although plain radiographs will demonstrate any metallic fragments or other radiopaque foreign bodies, ultrasonography (or advanced imaging such as CT or MRI) may be necessary to identify radiolucent objects such as glass, plastic, or wood. Routine exploration and removal of foreign bodies is not required, but may be necessary when symptoms are present, with recurrences, or when an infection is suspected. Pain and/or gait disturbance is more likely with superficial objects under the plantar surface of the foot.

A special situation occurs when a puncture wound from a nail comes through a rubber sneaker or running shoe. This situation presents a high risk of a *Pseudomonas* infection, and consideration should be given to a thorough irrigation and debridement under general anesthesia followed by systemic antibiotics for 10-14 days. Foreign-body entrapment of rubber may also occur.

Bibliography is available at Expert Consult.

674.10 Toe Deformities

Jennifer J. Winell and Richard S. Davidson

JUVENILE HALLUX VALGUS (BUNION)

Juvenile hallux valgus is most common in females (~10-fold), and while a family history is uncommon, it is typically associated with familial ligamentous laxity. The etiology is multifactorial, and important factors include genetic factors, ligamentous laxity, pes planus, wearing shoes with a narrow toe box, and occasionally spasticity (cerebral palsy).

Clinical Manifestations

There is prominence of the 1st metatarsophalangeal (MTP) joint and often erythema and callus from chronic irritation. The great toe is in valgus and is usually pronated, and there is splaying of the forefoot. Pes planus, with or without an associated heel cord contracture, is also observed commonly. Although cosmesis is perhaps the most common concern, patients may have pain in the region of the 1st MTP joint and/or difficulty with shoe wear.

Radiographic Evaluation

Weightbearing AP and lateral radiographs of the feet are obtained. On the AP view, common measurements include the angular relationships between the 1st and 2nd metatarsals (intermetatarsal angle, <10 degrees is normal) and between the 1st metatarsal and the proximal phalanx (hallux valgus angle, <25 degrees is normal). The orientation of the 1st metatarsal–medial cuneiform joint is also documented. On the lateral radiograph, the angular relationship between the talus and the 1st metatarsal helps to identify a midfoot break associated with pes planus. Radiographs are more helpful in surgical planning than in establishing the diagnosis.

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Treatment

Conservative management of adolescent bunions consists primarily of shoe modifications. It is important that footwear accommodate the width of the forefoot. Patients should avoid wearing shoes with a narrow toe box and/or a high heel. Shoe modifications, such as a soft upper, bunion last, or heel cup, may also be recommended. In the presence of a pes planus, an orthotic to restore the medial longitudinal arch may be beneficial. If a tendo-Achilles contracture is present, stretching exercises are recommended. The value of night splinting remains to be determined. Surgical treatment is reserved for those patients with persistent and disabling pain who have failed a course of nonoperative therapy. Surgery is not advised purely for cosmesis. Surgery is usually delayed until skeletal maturity to decrease the risk of recurrence or overcorrection. Radiographs are essential in preoperative planning to assess both the magnitude of deformity (hallux valgus angle, intermetatarsal angle, distal metatarsal articular angle) and associated features such as obliquity of the 1st metatarsal–medial cuneiform joint. Surgical treatment often involves a soft-tissue release and or rebalancing procedure at the 1st MTP joint, and a single or double osteotomy of the 1st metatarsal to decrease foot width and realign the joints along the medial column of the forefoot. An arthrodesis of the 1st MTP joint may be indicated in patients with spasticity to prevent recurrence.

CURLY TOES

A curly toe is caused by contracture of the flexor digitorum longus, and there is flexion at the MTP and the interphalangeal (IP) joints associated with medial deviation of the toe. The toe usually lies underneath its neighbor, and the 4th and 5th toes are most commonly involved. The deformity rarely causes symptoms, and active treatment (stretching, splinting, or taping) is not required. Most cases improve over time, and a subset will resolve completely. For the rare case in which there is chronic pain or skin irritation, release of the flexor digitorum longus muscle at the distal IP joint may be considered when the child is older.

OVERLAPPING FIFTH TOE

Congenital digitus minimus varus, or varus 5th toe, involves dorsiflexion and adduction of the 5th toe. The 5th toe typically overlaps the 4th. There is also a rotatory deformity of the toe, and the nail tends to point outward. The deformity is usually bilateral and may have a genetic basis. Symptoms are frequent and involve pain over the dorsum of the toe from shoe wear. Nonoperative treatment has not been successful. For symptomatic patients, several different options for reconstruction have been described. Common features include releasing the contracted extensor tendon and the MTP joint capsule (dorsal, dorsomedial, or complete). A partial removal of the proximal phalanx and creation of a syndactyly between the 4th and 5th toes has been performed in conjunction with the release as well.

POLYDACTYLY

Polydactyly is the most common congenital toe deformity and is seen in approximately 2 in 1,000 births and is bilateral in 50% of cases. Polydactyly may be preaxial (great toe) or postaxial (5th toe), and occasionally one of the central toes is duplicated. Associated anomalies are found in approximately 10% of the preaxial and 20% of postaxial polydactyly. One-third of patients will also have polydactyly of the hand. Conditions that may be associated with polydactyly include Ellis-Van Creveld (chondroectodermal dysplasia), longitudinal deficiency of the tibia, and Down syndrome. The extra digit may be either rudimentary or well formed, and plain radiographs of the foot help to define the anatomy and evaluate any coexisting bony anomalies. Treatment is indicated for cosmesis and to allow for fitting with standard shoes. This involves surgical removal of the extra digit, and the procedure is generally performed between 9 and 12 mo of age. Rudimentary digits may be surgically excised earlier, but should not be "tied off."

SYNDACTYLY

Syndactyly involves webbing of the toes, which may be incomplete or complete (extends to the tip of the toes), and the toenails may be confluent. There is often a positive family history, and the 3rd and 4th toes are involved most commonly. Symptoms are extremely rare, and cosmetic concerns are infrequent. Treatment is only required for a subset of cases in which there is an associated polydactyly (Fig. 674-10). In such cases, the border digit is excised, and the extra skin facilitates coverage of the wound. If the syndactyly does not involve the extra toe, then it can be observed. A complex syndactyly may be seen in patients with Apert syndrome.

Figure 674-10 Clinical picture of polysyndactyly involving the great toe.

HAMMER TOE

A hammer toe involves flexion at the proximal IP (PIP) joint with or without the distal IP (DIP) joint, and the MTP joint may be hyperextended. This deformity may be distinguished from a curly toe by the absence of rotation. The 2nd toe is most commonly involved, and a painful callus may develop over the dorsum of the toe where it rubs on the shoe. Nonoperative therapy is rarely successful, and surgery is recommended for symptomatic cases. A release of the flexor tendons will suffice in the majority of cases. Some authors recommend a transfer of the flexor tendon to the extensor tendon. For severe cases with significant rigidity, especially in older patients, a partial or complete resection of the proximal phalanx and a PIP fusion may be required.

MALLET TOE

Mallet toe involves a flexion contracture at the DIP joint and results from congenital shortening of the flexor digitorum longus tendon. Patients may develop a painful callus on the plantar surface of the tuft. As nonoperative therapy is usually unsuccessful, surgery is required for patients with chronic symptoms. For flexible deformities in younger children, release of the flexor digitorum longus tendon is recommended. For stiffer deformities in older patients, resection of the head of the middle phalanx, or arthrodesis of the DIP joint, may be considered.

CLAW TOE

A claw toe deformity involves hyperextension at the MTP joint and flexion at both the PIP and DIP joints, often associated with dorsal subluxation of the MTP joint. The majority are associated with an underlying neurologic disorder such as CMT disease. The etiology is usually muscle imbalance, and the extensor tendons are recruited to substitute for weakening of the tibialis anterior muscle. If treatment is elected, then surgery is required. Transfer of the extensor digitorum (or hallucis) tendon to the metatarsal neck is commonly performed along with a dorsal capsulotomy of the MTP joint and fusion of the fusion of the PIP joint (IP joint of the great toe).

ANNULAR BANDS

Bands of amniotic tissue associated with amniotic disruption syndrome (early amniotic rupture sequence, congenital constriction band syndrome, annular band syndrome) may become entwined along the

Figure 674-11 Constriction band syndrome with congenital amputation.

Figure 674-12 Constriction band syndrome with foot involvement.

extremities, resulting in a spectrum of problems from in utero amputation (Fig. 674-11) to a constriction ring along a digit (Fig. 674-12) (see Chapter 108). These rings, if deep enough, may result in impairment of arterial or venous blood flow. Even though concerns regarding tissue viability are less common, swelling from impairment in venous return is often a great problem. The treatment of annular bands usually involves observation; however, circumferential release of the band may be required emergently if arterial inflow is obstructed or electively to relieve venous congestion.

MACRODACTYLY

Macrodactyly represents an enlargement of the toes and may occur as an isolated problem or in association with a variety of other conditions such as Proteus syndrome (Fig. 674-13), neurofibromatosis, tuberous sclerosis, and Klippel-Trenaunay-Weber syndrome. This condition results from a deregulation of growth, and there is hyperplasia of one or more of the underlying tissues (osseous, nervous, lymphatic, vascular, fibrofatty). Macrodactyly of the toes may be seen in isolation (localized gigantism) or with enlargement of the entire foot. In addition to cosmetic concerns, patients may have difficulty wearing standard shoes. The treatment is observation, if possible. This is a difficult condition to treat surgically, and complications are frequent. For involvement of a single toe, the best option may be a resection of the ray (including the metatarsal). For greater degrees of involvement, debulking of the various tissues is required. Often, a growth arrest of the underlying osseous structures is performed. Stiffness and wound problems are common. The rate of recurrence is high, and more than one

Figure 674-13 Macrodactyly of the great toe in a case of Proteus syndrome.

debulking may be required. Patients may elect to have an amputation if the process cannot be controlled by less extensive procedures.

SUBUNGUAL EXOSTOSIS

A subungual exostosis is a mass of normal bone tissue that projects out from the dorsal and medial surface of a toe, under the nail. The etiology is unknown but may relate to minor, repetitive trauma. The great toe is involved most often. Patients present with discomfort, and the toenail may be elevated. The lesion may be demonstrated on plain radiographs, and histologically involves normal bone with a fibrocartilaginous cap. The treatment for symptomatic lesions is excision, and the recurrence rate is in the range of 10%.

INGROWN TOENAIL

Ingrown toenails are relatively common in infants and young children and usually involve the medial or lateral border of the great toe. Symptoms include chronic irritation and discomfort, and recurrent infection is seen in some cases. Parents should be instructed when cutting toe nails to cut straight across the distal aspect of the nail, rather than curve inwards at the nail edges. If conservative measures including shoe modifications, warm soaks, and appropriate nail trimming fail to control the symptoms, then surgical removal of a portion of the nail should be considered.

Bibliography is available at Expert Consult.

674.11 Painful Foot

Jennifer J. Winell and Richard S. Davidson

Table 674-2 shows a differential diagnosis for foot pain in different age ranges. In addition to the history and physical examination, plain

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Table 674-2	Differential Diagnosis of Foot Pain By Age	
0-6 YR	**6-12 YR**	**12-20 YR**
Poorly fitting shoes	Poorly fitting shoes	Poorly fitting shoes
Foreign body	Sever disease	Stress fracture
Fracture	Enthesopathy (JIA)	Foreign body
Osteomyelitis	Foreign body	Ingrown toenail
Leukemia	Accessory navicular	Metatarsalgia
Puncture wound	Tarsal coalition	Plantar fasciitis
Drawing of blood	Ewing sarcoma	Osteochondroses (avascular necrosis)
Dactylitis	Hypermobile flatfoot	Freiberg
JIA	Trauma (sprains, fractures) Puncture wound	Köhler Achilles tendinitis Trauma (sprains) Plantar warts Tarsal coalition

JIA, juvenile idiopathic arthritis.

radiographs are most helpful in establishing the diagnosis. Occasionally, more sophisticated imaging modalities such as CT or MRI will be required.

674.12 Shoes

Jennifer J. Winell and Richard S. Davidson

In toddlers and children, a well-fitting shoe with a **flexible** sole is recommended. This recommendation is in part based on studies suggesting that the development of the longitudinal arch seems to be best in societies where shoes are not worn and flatfeet are more common in shod children. Well-cushioned, shock-absorbing shoes are helpful in the child and adolescent athlete to decrease the chances of developing an overuse injury. Otherwise, shoe modifications are generally reserved for abnormalities in either alignment between segments of the foot or symptoms from an underlying condition (such as a limb-length discrepancy). Numerous modifications are available.

As a rule, shoes protect the foot from abnormal temperature as well as rough surfaces and sharp objects but have not been shown to help the normal foot develop. Poorly fitting shoes may create problems.

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Chapter 675

Torsional and Angular Deformities

675.1 Normal Limb Development

Keith D. Baldwin and Lawrence Wells

Pediatricians must understand normal limb development so as to recognize pathologic conditions during routine and targeted exams. During the 7th wk of intrauterine life, the lower limb rotates medially to bring the great toe toward the midline. The hip joint forms by the 11th wk; the proximal femur and acetabulum continue to develop until physeal closure in adolescence. At birth, the femoral neck is rotated forward approximately 40 degrees. This forward rotation is referred to as anteversion (the angle between the axis of the femoral neck and the transcondylar axis). The increased anteversion increases the internal rotation of the hip. Femoral anteversion decreases to 15-20 degrees by 8-10 yr of age. Conditions such as cerebral palsy that involve spasticity of the lower extremities can result in the persistence of fetal anteversion, which results in torsional abnormalities of the lower limb and gait disturbances. The second source of limb rotation is found in the tibia. Infants can have 30 degrees of medial rotation of the tibia, and by maturity the rotation is between 5 degrees of medial rotation and 15 degrees of lateral rotation (Fig. 675-1). Excessive medial rotation of tibia is referred to as **medial tibial torsion**. This is very common, and although very concerning to parents, very rarely requires treatment. Observation is indicated for most cases of medial tibial torsion. The tibial torsion is the angular difference between the axis of the knee and the transmalleolar axis. The medial or lateral rotation beyond ±2 SDs from the mean is considered abnormal rotation. The third source of rotational (axial) abnormalities of the lower extremity comes from the foot. Metatarsus adductus can cause the toes to point inward, and can be assessed by assessing if the medial border of the foot is straight.

Torsional deformity may be simple, involving a single segment, or complex, involving multiple segments. Complex deformities may be additive (internal tibial torsion and internal femoral torsion are additive) or compensatory (external tibial torsion and internal femoral torsion are compensatory).

The normal tibiofemoral angle at birth is 10-15 degrees of physiologic varus. The alignment changes to 0 degrees by 18 mo, and physiologic valgus up to 12 degrees is reached in between 3 and 4 yr of age. The normal valgus of 7 degrees is achieved by 5-8 yr of age (Fig. 675-2). Persistence of varus beyond 2 yr of age may be pathologic and is seen in conditions such as Blount disease. Overall, 95% of developmental physiologic genu varum and genu valgum cases resolve with growth. Persistent genu valgum or valgus into adolescence is considered pathologic and deserves further evaluation.

Bibliography is available at Expert Consult.

675.2 Evaluation

Keith D. Baldwin and Lawrence Wells

In evaluation of concerns relating to the limb, the pediatrician should obtain a history of the onset, progression, functional limitations, previous treatment, evidence of neuromuscular disorder, and any significant family history.

The examination should assess the exact torsional profile and include (1) foot progression angle, (2) femoral anteversion, (3) tibial version with thigh–foot angle, and (4) assessment of foot adduction and abduction.

FOOT PROGRESSION ANGLE

Limb position during gait is expressed as the foot progression angle and represents the angular difference between the axis of the foot with the direction in which the child is walking. Its value is usually estimated by asking the child to walk in the clinic hallway (Fig. 675-3). Inward rotation of the foot is assigned a negative value, and outward rotation is designated with positive value. The normal foot progression angle in children and adolescents is 10 degrees (range: −3 to 20 degrees). The foot progression angle serves only to define whether there is an in-toeing or out-toeing gait.

FEMORAL ANTEVERSION

Measuring the hip rotation with the child in prone position, the hip in neutral flexion or extension, thighs together, and the knees flexed 90

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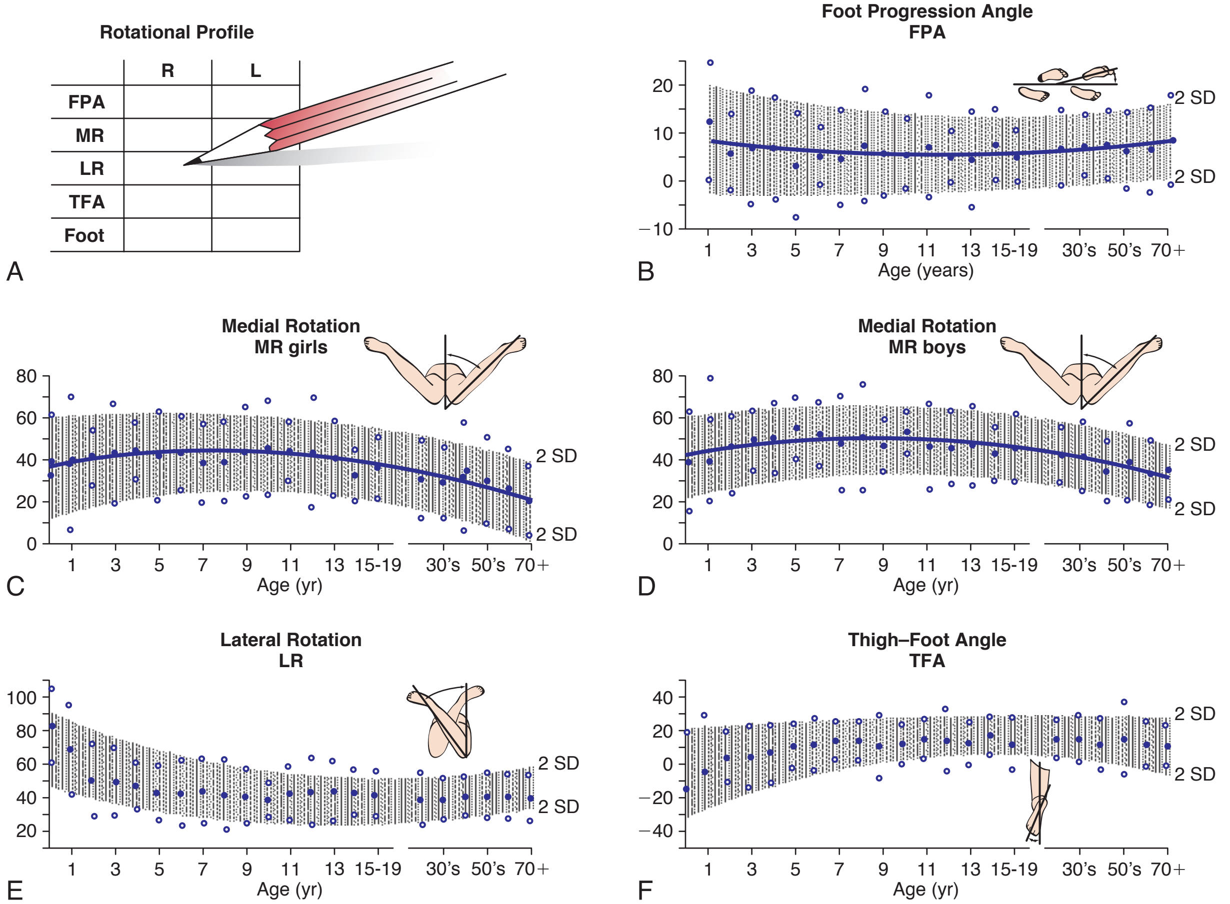

Figure 675-1 **A-F,** The rotational profile from birth to maturity is depicted graphically. All graphs include 2 SD from the mean for the foot progression angle *(FPA)* for femoral medial rotation *(MR)* and lateral rotation *(LR)* (for boys and girls), and the thigh–foot angle *(TFA)*. *(From Morrissey RT, Weinstein SL, editors:* Lovell and Winter's pediatric orthopaedics, *ed 3, Philadelphia, 1990, Lippincott Williams & Wilkins.)*

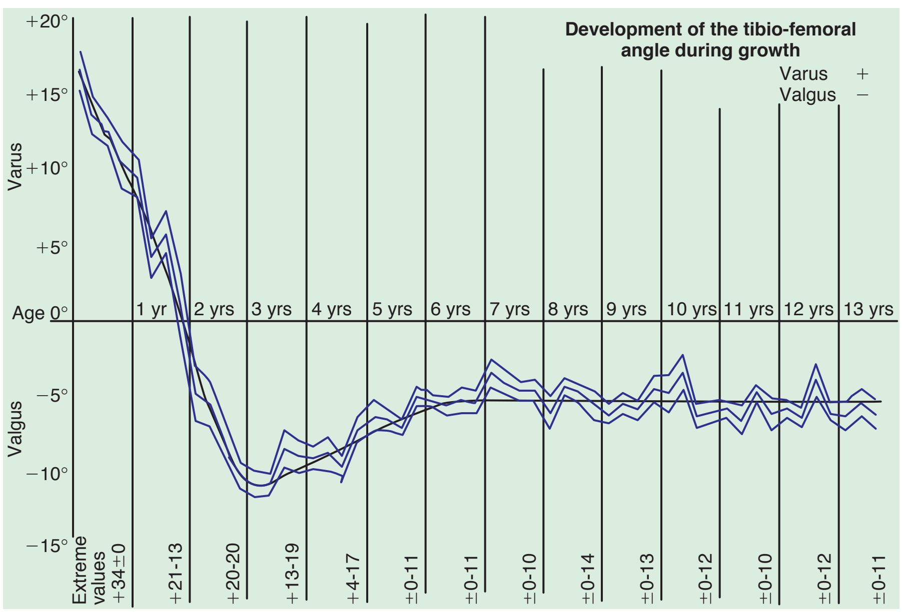

Figure 675-2 The normal coronal alignment of the knee plotted for age. *(From Salenius P, Vanka E: The development of the tibiofemoral angle in children.* J Bone Joint Surg Am *57:259–261, 1975.)*

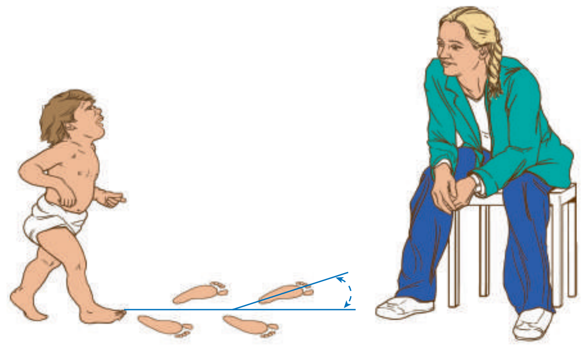

Figure 675-3 **Foot progression angle.** The long axis of the foot is compared with the direction in which the child is walking. If the long axis of the foot is directed outward, the angle is positive. If the foot is directed inward, the angle is negative and indicates in-toeing. *(From Thompson GH: Gait disturbances. In Kliegman RM, editor:* Practical strategies in pediatric diagnosis and therapy*. Philadelphia, 2004, WB Saunders.)*

Figure 675-4 Anteversion measured by medial rotation of hip **(A)** and lateral rotation of hip **(B)**.

degrees indirectly assesses the anteversion (Fig. 675-4). Both hips are assessed at the same time. As the lower leg is rotated ipsilaterally, this produces internal rotation of the hip, whereas contralateral rotation produces external rotation. Excessive anteversion increases internal rotation, and, retroversion increases the external rotation. The amount of anteversion can be roughly estimated by palpating the greater trochanter of the hip while internally rotating the limb. The point of maximal prominence of the greater trochanter corresponds to femoral anteversion.

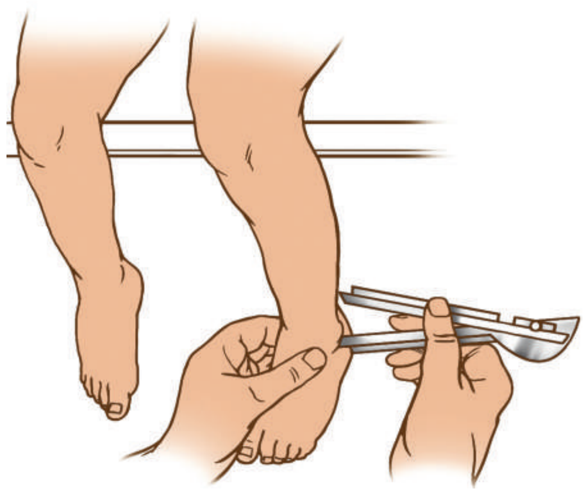

Figure 675-5 The transmalleolar angle is measured with the patient sitting at the edge of the table and the distal femoral condyles aligned with the side of the table. The angle between a line through the medial and lateral malleoli and edge of the table should be approximately 30 degrees external. *(From Bleck EE:* Orthopaedic management in cerebral palsy*, London, 1987, MacKeith Press, p. 55.)*

Figure 675-6 Thigh–foot angle.

TIBIAL ROTATION

Tibial rotation is measured using the transmalleolar angle. The transmalleolar angle is the angle between the longitudinal axis of the thigh with a line perpendicular to the axis of the medial and lateral malleolus (Fig. 675-5). In the absence of foot deformity, the thigh–foot angle is preferred (Fig. 675-6). It is measured with the child lying prone. The angle is formed between the longitudinal axis of the thigh and the longitudinal axis of the foot. It measures the tibial and hindfoot rotational status. Inward rotation is assigned a negative value, and outward rotation is designated a positive value. Inward rotation indicates internal tibial torsion, whereas outward rotation represents external tibial torsion. Infants have a mean angle of −5 degrees (range: −35 to 40 degrees) as a consequence of normal in utero position. In mid-childhood through adult life, the mean thigh–foot angle is 10 degrees (range: −5 to 30 degrees).

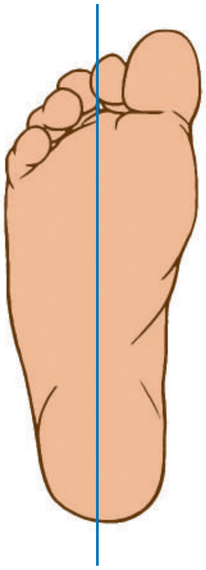

Figure 675-7 Schematic demonstration of heel bisector line.

FOOT SHAPE AND POSITION

The foot is observed for any deformities in prone and standing position. The heel bisector line (HBL) is used to evaluate the foot adduction and abduction deformities. The HBL is a line that divides the heel in 2 equal halves along the longitudinal axis (Fig. 675-7). It normally extends to the 2nd toe. When the HBL points medial to the 2nd toe, the forefoot is abducted, and when the HBL is lateral to the 2nd toe, the forefoot is adducted. Other lower-extremity problems, such as heel varus or valgus, can also make assessment of axial plane issues more difficult.

It is also important to screen every affected child for associated hip dysplasia and neuromuscular problems (cerebral palsy).

Bibliography is available at Expert Consult.

675.3 Torsional Deformities

Keith D. Baldwin and Lawrence Wells

INTERNAL FEMORAL TORSION

In-toeing gait most commonly results from excessive femoral anteversion. It occurs more commonly in girls than boys (2 : 1) in children 3-6 yr of age. The etiology of femoral torsion is controversial. Some believe that it is congenital and a result of persistent infantile femoral anteversion, whereas others believe it is acquired secondary to abnormal sitting habits. Some children are in habit of sitting in a W position or sleeping prone. On examination, most children with this condition have **generalized ligamentous laxity**. Gait examination reveals that entire leg is inwardly rotated. Internal hip rotation is increased beyond 70 degrees, and consequently the external rotation is restricted to 10-20 degrees. The patellas are pointing inward when the foot is straight, and compensatory external rotation of the tibia is demonstrated. The amount of anteversion can be roughly estimated by palpating the greater trochanter of the hip while internally rotating the limb. The point of maximal prominence of the greater trochanter corresponds to femoral anteversion.

Diagnosis is made clinically on examination; CT can provide objective measurements but is rarely indicated. The treatment is predominantly observation and correction of abnormal sitting habits. The torsion usually corrects with growth by 8-10 yr of age. Persistent deformity, unacceptable cosmesis, functional impairment, anteversion >45 degrees, and no external rotation beyond neutral are some of the indications for operative intervention. Surgery involves derotation osteotomy of the femur but is rarely performed or necessary.

INTERNAL TIBIAL TORSION

Medial (internal) tibial torsion manifests with **in-toeing gait** and is commonly associated with congenital metatarsus varus, genu valgum, or femoral anteversion. This condition is usually seen during the 2nd yr of life. Normally at birth, the medial malleolus lies behind the lateral malleolus, but by adulthood, it is reversed, with the tibia in 15 degrees of external rotation. The treatment is essentially observation and reassurance, because spontaneous resolution with normal growth and development can be anticipated. Significant improvement usually does not occur until the child begins to pull to stand and walk independently. Thereafter, correction can be seen as early as 4 yr of age and in some children by 8-10 yr of age. Persistent deformity with functional impairment is treated with supramalleolar osteotomy, which is rarely necessary.

EXTERNAL FEMORAL TORSION

External femoral torsion can follow a **slipped capital femoral epiphysis**; there is a low threshold to perform radiographs of the hips in children older than 10 yr of age. Femoral retrotorsion, when of idiopathic origin, is usually bilateral. The disorder is associated with an **out-toeing gait** and increased incidence of degenerative arthritis. The clinical examination of external femoral torsion shows excessive hip external rotation and limitation of internal rotation. The hip will externally rotate up to 70-90 degrees, whereas internal rotation is only 0-20 degrees. If slipped capital femoral epiphysis is detected, it is treated surgically. Occasionally, persistent femoral retroversion after slipped capital femoral epiphysis can produce functional impairment such as a severe out-toeing gait and difficulty opposing one's knees in the sitting position. The latter can be disabling to adolescent girls. Should this occur, a Southwick osteotomy or surgical realignment might be necessary.

EXTERNAL TIBIAL TORSION

Lateral tibial torsion is less common than medial rotation and is often associated with a **calcaneovalgus foot**. It can be compensatory to persistent femoral anteversion and idiopathic or secondary to a tight iliotibial band. The natural growth rotates the tibia externally, and hence external tibial torsion can become worse with time. Clinically, the patella faces outward when the foot is straight. The thigh–foot angle and the transmalleolar angle are increased. There may be associated patellofemoral instability with knee pain. Though some correction can occur with growth, extremely symptomatic children need supramalleolar osteotomy, which is usually done by 10-12 yr of age.

METATARSUS ADDUCTUS

Metatarsus adductus (see Chapter 674.1) manifests with forefoot adduction and inversion of all metatarsals. Ten percent to 15% are associated with hip dysplasia. The prognosis is good, because the majority get better with nonoperative intervention. The feet, which are flexible and correctable up to neutral, are treated with stretching exercises. Those that are not completely correctable are treated with serial casting. Rigid deformities, which are not correctable by stretching, are treated with medial capsulotomy of the 1st metatarsal cuneiform joint and soft-tissue release by 2 yr of age. Osteotomies of the base of the metatarsal may be performed after 6 yr of age.

Bibliography is available at Expert Consult.

675.4 Coronal Plane Deformities

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Genu varum and genu valgum are common pediatric deformities of the knee. Figure 675-2 presents the age-appropriate normal values for

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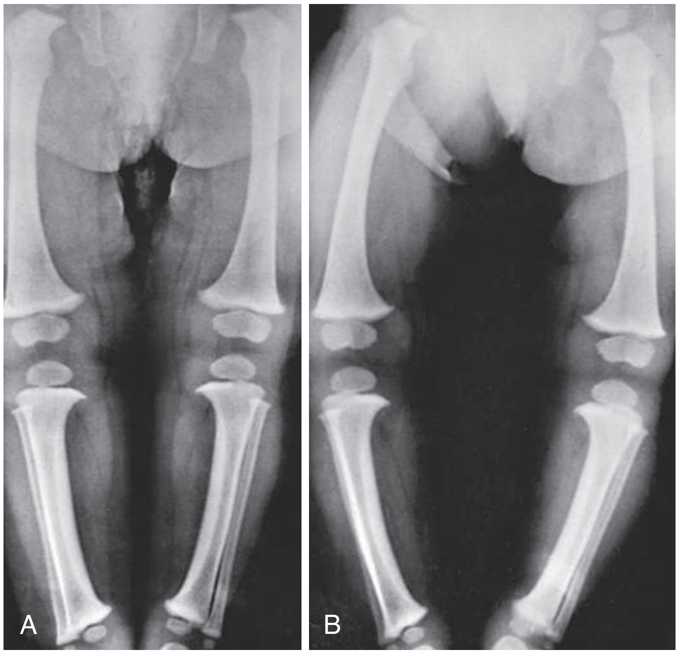

Figure 675-8 **A,** In recumbent position, tibia and femora are bowed but the legs do not appear bowed. **B,** In erect position during weight bearing and with ankles in apposition, the legs are bowed. *(From Slovis TL, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby.)*

knee angle. Tibial bowing is common during the 1st yr, bowlegs are common during the 2nd yr, and knock-knees are most prominent between 3 and 4 yr of age.

GENU VARUM

Physiologic bowleg is a common torsional combination that is secondary to normal in utero positioning (Fig. 675-8). Spontaneous resolution with normal growth and development can be anticipated. Persistence of varus beyond 2 yr of age may be pathologic. The different causes are metabolic bone disease (vitamin D deficiency, rickets, hypophosphatasia), asymmetric growth arrest (trauma, infection, tumor, Blount), bone dysplasia (dwarfism, metaphyseal dysplasia), and congenital and neuromuscular disorders (Table 675-1). It is prudent to differentiate physiologic bowing from Blount disease (Table 675-2). Physiologic bowing should also be differentiated from rickets and skeletal dysplasia. Rickets has classic bone changes with trumpeting widening and fraying of the metaphysis and widening of the physis (see Chapter 51).

Table 675-1 Classification of Genu Varum (Bowlegs)
PHYSIOLOGIC
ASYMMETRIC GROWTH Tibia vara (Blount disease) • Infantile • Juvenile • Adolescent Focal fibrocartilaginous dysplasia Physeal injury Trauma Infection Tumor
METABOLIC DISORDERS Vitamin D deficiency (nutritional rickets) Vitamin D–resistant rickets Hypophosphatasia
SKELETAL DYSPLASIA Metaphyseal dysplasia Achondroplasia Enchondromatosis

Modified from Thompson GH: Angular deformities of the lower extremities. In Chapman MW (ed): Operative orthopedics, *ed 2, Philadelphia, 1993, JB Lippincott, Tab 222-1, p. 3132.*

Table 675-2 Differentiation of Leg Bowing

PHYSIOLOGIC BOWING	BLOUNT DISEASE
Gentle and symmetric deformity	Asymmetric, abrupt, and sharp angulation
Metaphyseal–diaphyseal angle <11 degrees	Metaphyseal–diaphyseal angle >11 degrees
Normal appearance of the proximal tibial growth plate	Medial sloping of the epiphysis Widening of the physis Fragmentation of the metaphysis
No significant lateral thrust	Significant lateral thrust

TIBIA VARA

Idiopathic tibia vara, or **Blount disease**, is a developmental deformity resulting from abnormal endochondral ossification of the medial aspect of the proximal tibial physis leading to varus angulation and medial rotation of the tibia (Fig. 675-9). The incidence is greater in African-Americans and in toddlers who are overweight, have an affected family member, or started walking early in life. It has been classified into 3 types, depending on the age at onset: infantile (1-3 yr of age), juvenile (4-10 yr of age), and adolescent (11 yr or older). The juvenile and adolescent forms are commonly combined as late-onset tibia vara. The exact cause of tibia vara remains unknown, although it is thought to involve abnormal growth resultant from excessive weight.

The infantile form of tibia vara is the most common; its characteristics include predominance in black females, approximately 80% bilateral involvement, a prominent medial metaphyseal beak, internal tibial torsion, and leg-length discrepancy (LLD). The characteristics of the juvenile and adolescent forms (late onset) include predominance in black males, normal or greater than normal height, approximately 50% bilateral involvement, slowly progressive genu varum deformity, pain rather than deformity as the primary initial complaint, no palpable proximal medial metaphyseal beak, minimal internal tibial torsion, mild medial collateral ligament laxity, and mild lower extremity length discrepancy. The infantile group has the greatest potential for progression.

An anteroposterior standing radiograph of both lower extremities with patellas facing forward and a lateral radiograph of the involved extremity should be obtained (Fig. 675-10). Weightbearing radiographs are preferred and allow maximal presentation of the clinical deformity. The metaphyseal–diaphyseal angle can be measured and is useful in distinguishing between physiologic genu varum and early tibia vara (Fig. 675-11). Langenskiöld has 6 stages on radiographs (Fig. 675-12). The differentiation is based on fragmentation of the epiphysis, beaking of the medial tibial epiphysis, depression of the medial tibial plateau, and formation of a bony bar. Occasionally, CT with 3-dimensional reconstructions, or MRI, may be necessary to assess the meniscus, the articular surface of the proximal tibia including the posteromedial slope, or the integrity of the proximal tibial physis.

Management is based on the stage of the disease, the age of the child, and nature of presentation (primary or recurrent deformity). In children younger than 3 yr and Langenskiöld stage <3, bracing is effective and can prevent progression in 50% of these children. A maximal trial of 1 yr of orthotic management is recommended. If complete correction is not obtained after 1 yr or if progression occurs during this

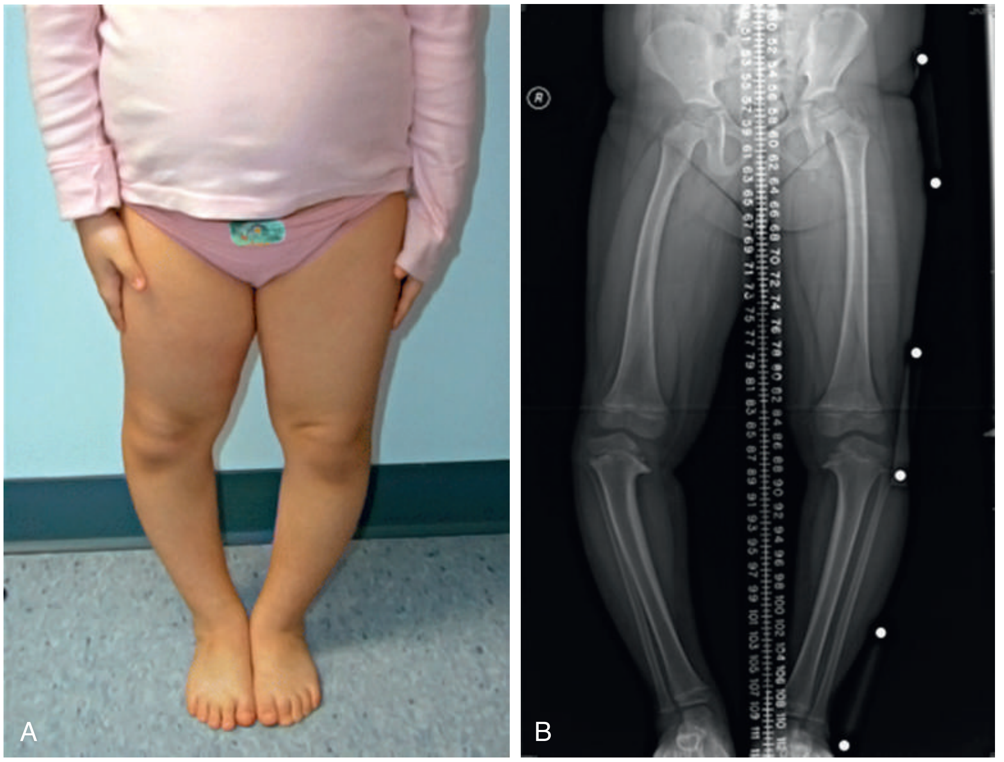

Figure 675-9 Clinical photograph **(A)** and standing anteroposterior radiograph **(B)** of a 5 yr old girl with bilateral early-onset Blount disease. *(From Sabharwal S: Blount disease,* J Bone Joint Surg Am *91:1758–1776, 2009.)*

Figure 675-10 Anteroposterior radiograph of both knees in Blount disease.

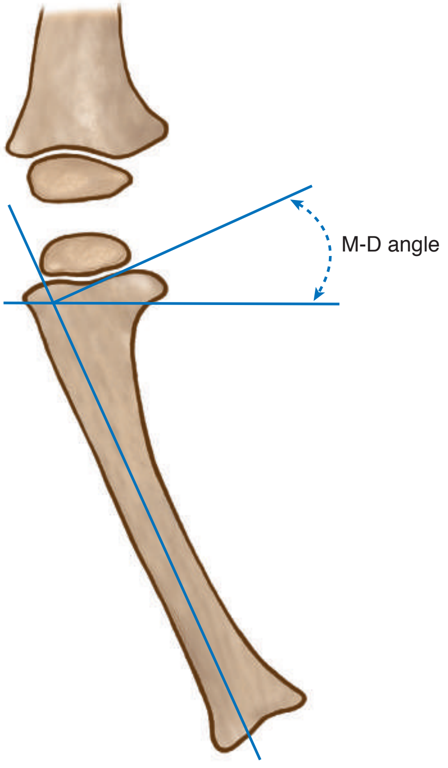

Figure 675-11 **Metaphyseal–diaphyseal (M-D) angle.** Draw a line on the radiograph through the proximal tibial physis. Draw another line along the lateral tibial cortex. Last, draw a line perpendicular to the shaft line as demonstrated in the diagram. *(From Morrissey RT, Weinstein SL, editors:* Lovell and Winter's pediatric orthopaedics, *ed 3, Philadelphia, 1990, Lippincott Williams & Wilkins.)*

Figure 675-12 Depiction of the stages of infantile Blount disease. *(From Langeskiöld A: Tibia vara (osteochondrosis deformans tibiae): a survey of 23 cases, Acta Chir Scand 103:1, 1952.)*

time, a corrective osteotomy may be indicated. Surgical treatment is also indicated in children >4 yr of age, those at Langenskiöld stage >3, and those with severe deformities. A proximal tibial valgus osteotomy and associated fibular diaphyseal osteotomy are usually the procedures of choice. In late-onset tibia vara, correction is also necessary to restore the mechanical axis of the knee. Hemiplateau elevation with correction of posteromedial slope has also been established as a treatment modality in relapsed cases.

GENU VALGUM (KNOCK-KNEES)

The normal valgus is achieved by 4 yr of age. Variation up to 15 degrees of valgus is possible until 6 yr of age, and thus physiologic valgus has a good chance of correction until this age. The intermalleolar distance with the knees approximated is normally <2 cm, and in a severe valgus deformity it could measure >10 cm. Pathologic conditions leading to valgus are metabolic bone disease (rickets, renal osteodystrophy), skeletal dysplasia, posttraumatic physeal arrest, tumors, and infection. The increased valgus at the knee causes lateral deviation of the mechanical axis with stretching of the medial aspect of the knee leading to knee pain. Deformities >15 degrees and occurring after 6 yr of age are unlikely to correct with growth and require surgical management. In the skeletally immature, medial tibial epiphyseal hemiepiphysiodesis or stapling (guided growth) is attempted for correction. In the skeletally mature, osteotomy is necessary at the center of rotation of angulation and is usually situated in the distal femur. Long-length anteroposterior radiographs of the leg in a weight-bearing stance are necessary for preoperative planning.

Bibliography is available at Expert Consult.

675.5 Congenital Angular Deformities of the Tibia and Fibula

Keith D. Baldwin and Lawrence Wells

POSTEROMEDIAL TIBIAL BOWING

Congenital posteromedial bowing is typically associated with a calcaneovalgus foot and rarely with secondary valgus of the tibia. The exact cause is unknown. Early operative intervention is not indicated because this bowing generally corrects with growth. However, despite the correction of angulation, there is residual shortening in the tibia and fibula. The mean growth inhibition is 12-13% (range: 5-27%). The mean LLD at maturity is 4 cm (range: 3-7 cm). The diagnosis of bowing is confirmed on radiographs, which show the posteromedial angulation without any other osseous abnormalities. The calcaneovalgus deformity of the foot improves with stretching or modified shoe wear and occasionally ankle-foot orthosis. Predicted LLD <4 cm is managed with age-appropriate epiphysiodesis of the normal leg. LLD >4 cm is managed with combination of contralateral epiphysiodesis and ipsilateral lengthening. A corrective osteotomy for distal valgus may be required and can be done in the same setting while correcting LLD.

ANTEROMEDIAL TIBIAL BOWING (POSTAXIAL HEMIMELIA)

Fibular hemimelia is the most common cause of anteromedial bowing of the tibia. The fibular deficiency can occur with complete absence of fibula or a partial development both proximally and distally. It is associated with deformities of femur, knee, tibia, ankle, and foot. The femur is short and has lateral condylar hypoplasia, causing patellar instability and genu valgum deformity. The tibia has anteromedial bowing with reduced growth potential. The keys for management are the ankle stability and foot deformities. The ankle resembles a ball-and-socket joint with lateral instability. The foot deformities are characterized by the absence of lateral digits, equinocavovarus foot, and tarsal coalition.

Various surgical options have been described, and the treatment is tailored to the patient's needs and parents' acceptance. A severely deformed foot could be best managed with Syme or Boyd amputation, with prosthesis as early as 1 yr of age. In the salvageable foot, LLD can be treated with contralateral leg epiphysiodesis or ipsilateral limb lengthening.

ANTEROLATERAL TIBIAL BOWING

Anterolateral tibial bowing is associated with congenital pseudarthrosis of tibia. Fifty percent of the patients have neurofibromatosis, but only 10% of the neurofibromatosis patients have this lesion. The pseudarthrosis or site of nonunion is typically situated at the middle third and distal third of the tibia. Boyd has classified it in increasing severity depending on the presence of cystic and dysplastic changes. The treatment for this condition has been very frustrating, with poor results. Bracing has been recommended to prevent fracture early in the course; however, it has not been successful. Numerous surgical interventions have been attempted to achieve union, such as single- and dual-onlay grafting with rigid internal fixation, intramedullary pinning with or without bone grafting, and an Ilizarov device. With the advent of microsurgery, live fibular grafts have been used with varying results. Because of the poor chances of successful union and considerable LLD, a below-knee amputation with early rehabilitation may be preferred. It is important not to attempt any osteotomy for correction of the tibial bowing.

TIBIAL LONGITUDINAL DEFICIENCY

Tibial longitudinal deficiency follows an autosomal dominant inheritance pattern and has been divided into four types depending on the deficient part of the tibia. The other associated anomalies are foot deformities, hip dysplasia, and symphalangism of the hand. The treatment revolves around presence of proximal tibial anlage and a functional quadriceps mechanism. In type Ia deformity, the proximal tibial anlage is absent and knee disarticulation with prosthesis is recommended. In types Ib and II, the tibial anlage is present and the management consists of an early Syme amputation, followed later by synostosis of the fibula with the tibia, and a below-knee prosthesis. Type III is rare and the principal management is with Syme amputation and a prosthesis. Type IV deformity is associated with ankle diastasis, which requires stabilization of the ankle and correction of LLD at a later stage.

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Chapter 676

Leg-Length Discrepancy

Richard S. Davidson

A discrepancy in the leg lengths may result from a variety of congenital or acquired conditions (Table 676-1). Although up to 25% of the American public may have a difference of more than 1 cm, only a small percentage have more than a 2 cm difference. The main consequence is gait asymmetry. An increase in vertical pelvic motion is observed, and more energy must be expended during ambulation. Although a small compensatory lumbar curvature may develop, there is little evidence to suggest that leg-length discrepancy results in back pain, structural scoliosis, or degenerative arthritis. The goal of treatment is to have a discrepancy of <2-2.5 cm at skeletal maturity, and a variety of treatment methods are available to achieve this objective. Knowledge of the underlying etiology, coupled with regular follow-up to assess limb growth and skeletal maturity, allows the treating physician to project the discrepancy at skeletal maturity and to plan treatment. A subset of patients will have coexisting abnormalities in the viscera or musculoskeletal system, which must be identified and treated as well.

DIAGNOSIS AND CLINICAL FINDINGS

Gait asymmetry is the most frequent complaint. The long leg is often kept flexed in stance to level the pelvis. The diagnosis is made on physical examination, and specialized radiographs help to quantify the existing discrepancy and predict what the discrepancy will be at maturity The discrepancy may be caused by hypoplasia, hyperplasia, or angular deformity (structural discrepancy), by soft-tissue contracture at the hips, knees, or ankles (apparent or functional shortening), or by a combination of these conditions. Other contributing factors include joint subluxation or dislocation (hip), a decrease in the height of the foot (congenital or neuromuscular) or structural disorders of the pelvis. A careful physical examination is required to identify all factors contributing to the discrepancy. Muscle contracture about the hip will also create the appearance of leg-length inequality. For example, to bear weight on an abducted hip, the patient must hike up the contralateral hip and pelvis, making the contralateral leg appear short.

There are several clinical methods for measuring limb length. Our preference is to perform a standing examination, in which blocks of various sizes are placed under the short leg until the pelvis is leveled (Fig. 676-1). An alternate method is to measure the length of each leg with the patient supine by the Galiazzi and Alis tests. The traditional method of using a tape measure is very inaccurate because of, for example, the line of measurement used, muscle atrophy, and moving patients. The range of motion at the hip, knee, and ankle must be also assessed to identify any causes of apparent discrepancy. A 10 degree fixed abduction (or adduction) contracture of the hip will create an apparent leg-length discrepancy of 2-3 cm. Similarly, a flexion contracture of the hip and/or knee will create apparent shortening of the extremity, while an equinus contracture at the ankle will create apparent lengthening of the extremity. A rigid lumbar scoliosis (suprapelvic contracture) will create pelvic obliquity and an associated limb length inequality. Once a discrepancy is quantified, it must be followed at regular intervals until maturity. Assessments at 6-12 mo intervals are most common.

Table 676-1 Causes of Leg-Length Discrepancy
CONGENITAL CAUSES
Defects in Growth
Proximal femoral focal deficiency
Congenital pseudarthrosis of the tibia
Fibular hemimelia (see Fig. 676-8)
Bone Tumors/Disease
Skeletal dysplasia
Multiple hereditary exostoses
Neurofibromatosis
Enchondromatosis (Ollier disease)
Osteogenesis imperfecta
Vascular
Klippel-Trenaunay-Weber syndrome
Russell-Silver syndrome
Miscellaneous
Congenital coxa vara
Proteus syndrome
ACQUIRED CAUSES
Trauma
Overriding fractures
Epiphyseal fractures with growth plate damage
Developmental
Developmental dysplasia of the hip
Neoplastic
Malignant tumors
Tumors across epiphysis
Neurologic
Myelodysplasia
Cerebral palsy
Infections/Inflammatory
Septic arthritis of hip
Osteomyelitis
Rheumatoid arthritis
Miscellaneous
Acquired coxa vara
Fixed pelvic obliquity in scoliosis

RADIOGRAPHIC EVALUATION

The radiologic evaluation complements the clinical examination; both are typically employed when making treatment decisions. Five

Figure 676-1 Examination with blocks under short leg until the pelvis is squared.

different techniques are available. The ***teleoroentgenogram*** is a single radiographic exposure of both lower extremities (standing) and requires a long cassette. A ruler is placed on the film, and direct measurements are made, factoring in a 6% magnification error. One advantage is that angular deformities may be assessed. Its primary indication is for young children. Unfortunately, as only one exposure is used for the leg and as the ankle is less dense than the hip, it may be difficult to "see" the whole leg. Additionally, because the x-ray source is at the knee projecting up to the hip and down to the ankle, this method projects the hip and ankle along the ruler making the leg appear longer than it really is, particularly in obese patients. The ***orthoroentgenogram*** consists of 3 separate exposures of the hips, knees, and ankles on a long cassette. The patient is supine, and a ruler is placed on the cassette for measurement of bone length. However, the patient must lie still for the 3 exposures, which is often difficult to achieve in younger children. Because the x-ray beam is pointed at the hip, knee, and ankle in each of the 3 exposures, the length measurement is accurate and each of the 3 joints can be exposed properly. The x-rays expose from the top of the pelvis to the mid femur, from the mid femur to the mid tibia, and from the mid tibia to below the foot for each of the 3 exposures, respectively, permitting angular deformity assessment in the frontal plane only. The ***scanogram*** also consists of separate exposures of the hips, knees, and ankles on a cassette with a radiographic ruler; a chest sized film cassette is used (Fig. 676-2). There is no magnification error; patients must remain still for the 3 exposures, and angular deformities cannot be assessed. While ***CT*** is an accurate technique, the assessment is time-consuming, and the technique is not available in most centers. Additionally a radiologist must normalize the axis of the leg to the screen to accurately measure the limbs. Another technique, called ***EOS***, employs a 3D, low-dose ($\frac{1}{7}$ to $\frac{1}{10}$ the radiation) scanner but requires a sophisticated radiologist to correctly align the limbs for computer measurement. Regardless of the technique it is critical that the patellae be pointed forward, that measurements be made in the plane of the limb, and that the same method be used in sequential measurements to be compared.

In the presence of flexion or extension deformities, each bone should be x-rayed individually with a ruler where the x-ray beam is perpendicular to the bone and the ruler parallel to the bone.

In addition to quantifying the discrepancy, it is essential to determine skeletal age (bone age). An anteroposterior radiograph of the hand and wrist is usually obtained at each visit and compared with the standards in the Greulich and Pyle Atlas to estimate skeletal age. While more accurate techniques are available, most are time-consuming and impractical for routine clinical application. The range of variability using the atlas is approximately 9 mo, so the method is most accurate when multiple data points have been collected.

Figure 676-2 Scanogram to demonstrate exact leg-length discrepancy.

TREATMENT

Options for treatment include observation, a shoe lift or custom orthosis, a limb-shortening procedure (acute shortening and internal fixation vs gradual shortening by growth arrest or guided growth), a limb-lengthening procedure (with internal or external fixation), or a combination of these. Deformity correction is often accomplished simultaneously. In the congenital deficiencies (femur, tibia, fibula) in which the predicted limb-length inequality will require more than 3 lengthening operations (more than 20 cm), an early foot amputation may be the best option to achieve an optimal functional outcome. In addition to the magnitude of discrepancy predicted at skeletal maturity, both the anticipated adult height of the patient (estimated from family members) and the desires of the patient and the patient's family are important considerations.

Discrepancies of up to 2.5 cm may be treated by observation or a shoe lift. Up to 1 cm may be placed within the shoe, and up to 5 cm may be placed on the outside of the shoe. Complete correction of inequality is not required, and the height of the lift should be adjusted based on the patient's gait and comfort. An orthotic may be used as a temporizing measure prior to definitive treatment. For extended discrepancies, "foot in foot" prostheses are a reasonable alternative until limb length can be accomplished or for patients who cannot or do not wish to undergo surgical correction.

For patients with a discrepancy between 2 and 5 cm, an **epiphysiodesis** is offered in skeletally immature patients, and an acute shortening may be performed in a skeletally mature patient. Epiphysiodesis refers to a temporary or permanent cessation of growth at 1 or more physes. A permanent growth arrest is most commonly performed as long as sufficient data are available with which to accurately predict when to perform the procedure. Approximately 65% of the growth of the lower extremity comes from the distal femur (37%, 9 mm/yr) and proximal tibia (28%, 6 mm/yr). Males typically grow until 16 yr of age, whereas females grow until 14 yr of age. As such, performing an epiphysiodesis of both the distal femur and the proximal tibia in a patient with 3 yr of growth remaining should achieve approximately 4.5 cm of correction. Techniques used to determine the timing of epiphysiodesis are the Menelaus method ("rule of thumb"), the Green and Anderson method, the Moseley straight-line graph, and the multiplier method (Figs. 676-3, 676-4, and 676-5). The most common surgical technique is the percutaneous epiphysiodesis, in which the physis is ablated with a drill and curette under image intensification. This is an outpatient procedure with few complications. Insertion of plates and screws or just screws across the physis is an alternative but usually requires a second operation to remove the hardware. For patients for whom sufficient data are unavailable or those for whom the underlying diagnosis is associated with an unpredictable pattern of growth, then a reversible technique, such as staples, plates, and/or screws, may be considered. Once equalization has been achieved, the hardware can be removed, allowing growth to resume. When the patient is skeletally mature or if it is deemed appropriate to wait until maturity before treatment, acute shortening may be the best option. Acute shortening is typically performed at the femur (several techniques have been described), given the increased risk of complications (compartment syndrome, neurovascular problems) associated with shortening of the tibia and fibula.

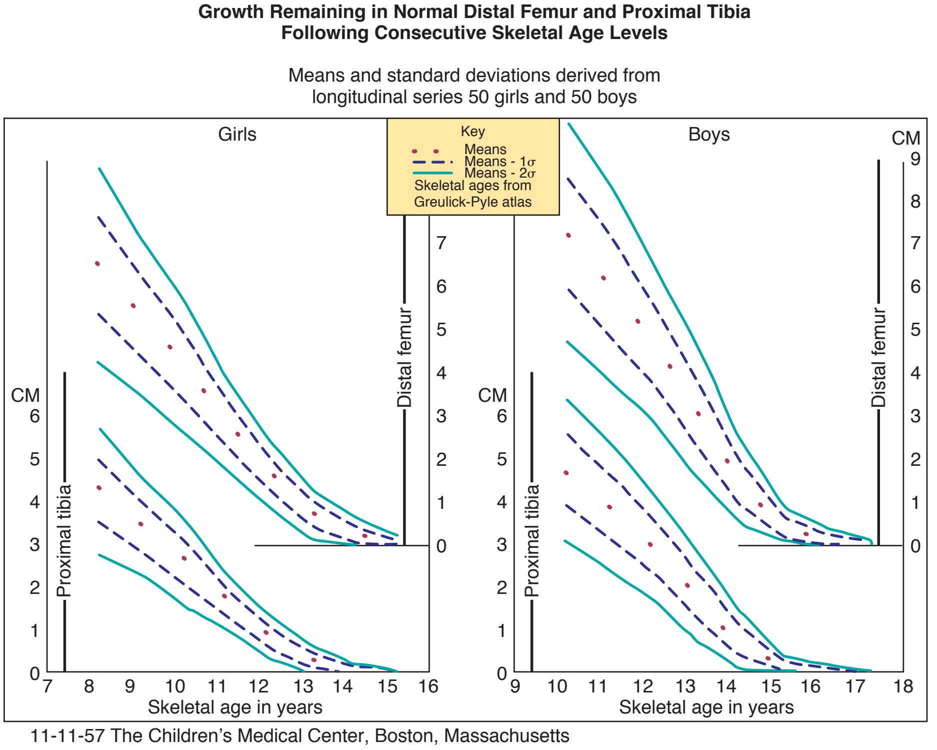

Figure 676-3 **Growth remaining charts for girls and boys.** The growth remaining charts for girls and boys are different. Actual correction is based on growth of the short limb. To use the chart correctly, the discrepancy at maturity and the percentage of growth retardation of the short limb should be calculated. *(Redrawn from Anderson M, Green WT, Messner MB: Growth and predictions of growth in lower extremities.* J Bone Joint Surg Am *45:1–4, 1963.)*

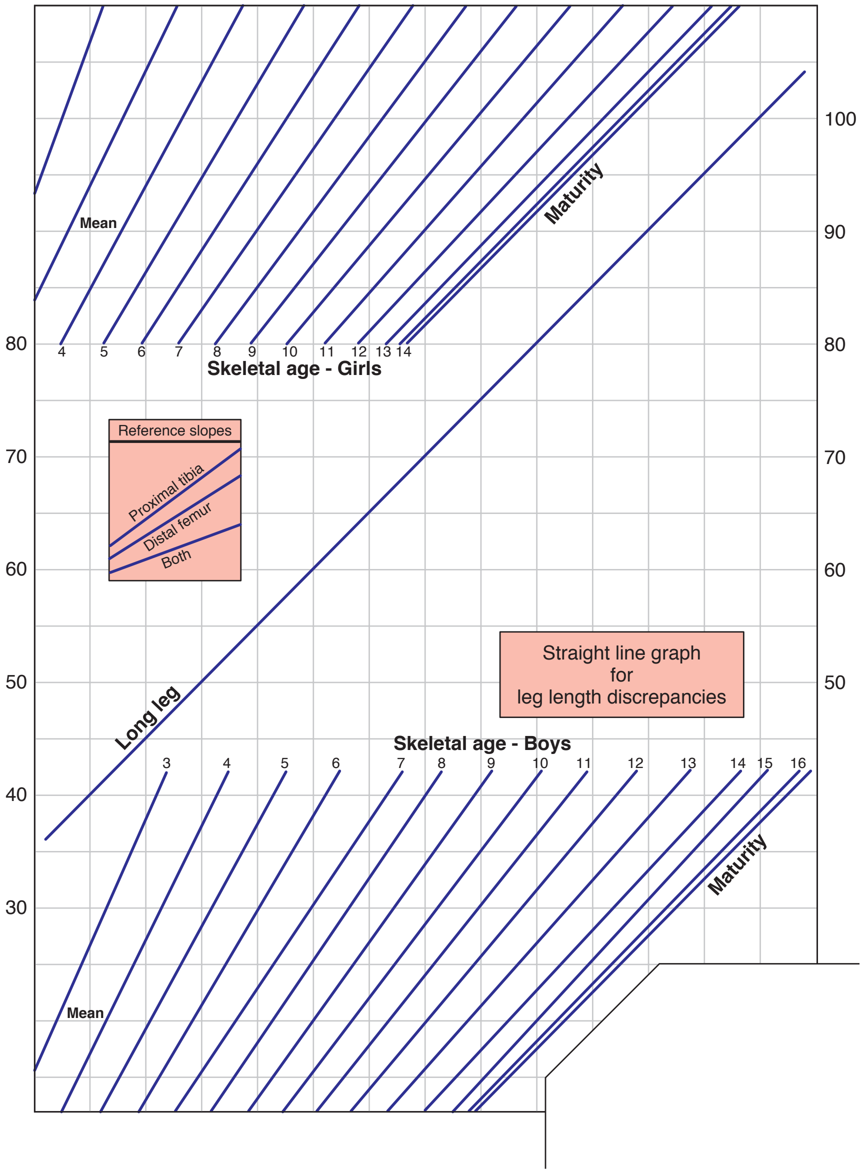

Figure 676-4 **The Moseley straight-line graph for the assessment of leg-length inequalities.** This allows simultaneous correlation of the normal leg, short leg, and bone age of the child. It will accurately predict lengths of each extremity at skeletal maturity. The reference slopes are used as a guide in determining when appropriate treatment should be performed. *(From Moseley CF: A straight-line graph for leg-length discrepancies.* J Bone Joint Surg Am *59:174–179, 1977.)*

Multiplier for Boys and Girls (Paley et al, 1999)

Boys Age	Boys Multiplier	Girls Age	Girls Multiplier
0	5.08	0	4.63
0.4	4.01	0.3	4.01
1	3.24	1	2.97
1.3	2.99	2	2.39
2	2.59	3	2.05
3	2.23	3.3	2.00
4	2.00	4	1.83
5	1.83	5	1.66
6	1.68	6	1.53
7	1.57	7	1.43
8	1.47	8	1.33
9	1.38	9	1.26
10	1.31	10	1.19
11	1.24	11	1.13
12	1.18	12	1.07
13	1.12	13	1.03
14	1.07	14	1.00
15	1.03	15	1.00
16	1.01	16	1.00
17	1.00		
18	1.00		

LLD Prediction Formulas

Prenatal LLD (congenital)
$\Delta_m = \Delta \times M$

Postnatal LLD (developmental)
$\Delta_m = \Delta + I \times G$

Inhibition $\approx I = 1 - \frac{S - S'}{L - L'}$

Growth remaining $= G = L(M - 1)$

Δ_m = LLD at maturity

Δ = Current LLD

L & S = Current length of long and short leg

L' & S' = Length of long and short leg at any other date since LLD began

Figure 676-5 Paley multiplier. This is a simple method of determining the leg-length discrepancy (LLD) at maturation. This is applicable for shortening conditions in which growth retardation is consistent. *(From Paley D, Bhave A, Herzenberg JE, Bowen JR: Multiplier methods for predicting limb-length discrepancy.* J Bone Joint Surg Am *82;1432–1446, 2000.)*

Figure 676-6 Ilizarov device demonstrating bone lengthening by distraction osteogenesis.

For discrepancies >5 cm, lengthening of the short limb is the procedure of choice. An exception would be a discrepancy secondary to overgrowth of 1 limb, in which limb shortening would be preferred so as to preserve body proportions, for which acute or gradual shortening of the abnormal limb is preferred. Patients with anticipated discrepancies greater than 8-10 cm often require 1 or more limb-lengthening procedures (several years apart) with or without an epiphysiodesis. The most common technique used for limb lengthening involves placement of an external fixator, either a ring fixator such as the Ilizarov device or a monolateral device (Fig. 676-6). The bone is cut at the metaphyseal–diaphyseal junction, and lengthening is achieved gradually through distraction at the corticotomy. The usual rate of lengthening is 1 mm/day, and it takes approximately 1 mo wearing the fixator for each centimeter of length gained with a minimum of 3 mo in the fixator. Additional time in the fixation may be required for pathologic bone or for metabolic diseases affecting bone formation. A maximum of 15-25% of the original length of the bone may be gained at each session. An advantage of the circular fixator or multiaxial external fixators is the ability to correct coexisting angular deformities at the same time. Technologic advances have allowed the development of intramedullary lengthening and compression rods driven by external magnets. These may provide improvements in patient satisfaction and reduced complications.

Complications include pin tract infection (most common), wound infection, hypertension, joint subluxation, muscle contracture, premature consolidation, delayed union, implant-related problems, and fractures after implant removal. Finally, early amputation and prosthetic fitting may provide the best long-term function in patients with projected discrepancies in excess of 18-20 cm, especially when there are coexisting deformities or deficiencies of the ipsilateral foot (Figs. 676-7 and 676-8). The alternative would be multiple reconstructive procedures throughout childhood and adolescence. The impact of multiple procedures on the child's psychosocial development must also be kept in mind when formulating the treatment plan in these complex cases.

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Figure 676-7 Extension prosthesis leg-length discrepancy **(A)** and compensated with extension prosthesis **(B).**

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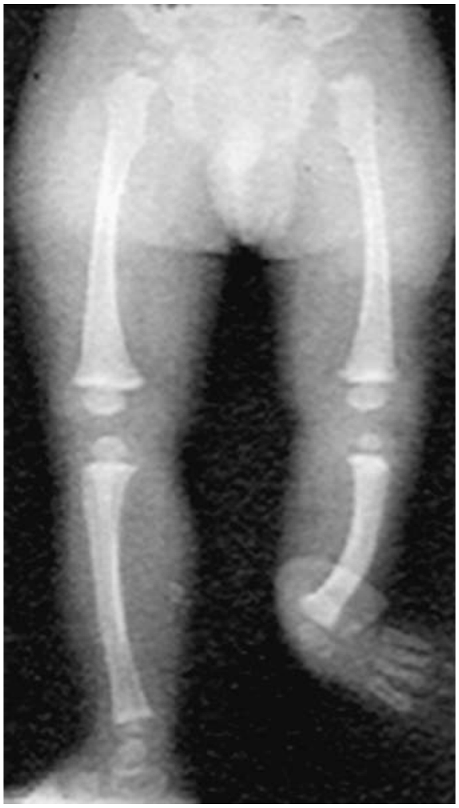

Figure 676-8 Anteroposterior radiograph of fibular hemimelia with leg-length discrepancy.

Chapter 677
The Knee

Eric J. Sarkissian and J. Todd R. Lawrence

NORMAL DEVELOPMENT OF THE KNEE

The knee, a major synovial joint, forms between the 3rd and 4th mo of fetal development, with secondary ossification centers forming between the 6th and 9th fetal mo at the distal femur and between the 8th fetal mo and the 1st postnatal mo at the proximal tibia. The patellar ossification center appears between the ages of 2 and 4 yr in girls and 3 and 5 yr in boys.

ANATOMY AND RANGE OF MOTION

The knee is the largest joint in the body and acts primarily as a modified hinge. The distal femur is cam shaped with the medial and lateral femoral condyles having slightly different shapes. This allows for a posterior gliding motion of the femur on the tibial plateau to occur during knee flexion. This also permits about 8-12 degrees of rotation through the flexion and extension arc. The normal range of motion of the knee is from neutral (or fully straight) to 140 degrees of flexion. Increased ligament laxity including hyperextension of up to 10-15 degrees can be normal in many children. Most activities can be performed in the flexion arc of 0-70 degrees.

The knee consists of three articulations: *patellofemoral*, *tibiofemoral*, and *tibiofibular*. The anterior and posterior cruciate ligaments as well as medial and lateral collateral ligaments stabilize the knee during movement. The medial and lateral menisci provide support under compressive forces, helping to redistribute the forces from the more rounded distal femur to the more flat proximal tibia. The medial patellofemoral ligament is the primary static soft-tissue restraint against lateral patellar displacement. There are also several bursae located about the knee to cushion and reduce friction on tendons acting across the knee joint.

677.1 Discoid Lateral Meniscus

Eric J. Sarkissian and J. Todd R. Lawrence

Discoid lateral meniscus (DLM) is a congenital anatomic variation of the lateral meniscus that may be asymptomatic or cause the classic *snapping knee syndrome*. Because of asymptomatic cases, the true incidence is difficult to determine, but it is estimated to occur in 3-5% of children and adolescents. Up to 25% of DLM cases may be bilateral. Previously thought to result from a failure of an embryologic sequence of degeneration at the center of the meniscus, discoid menisci have been subsequently shown to not be the developmental precursors for normal menisci.

Anatomically, the normal meniscus (Fig. 677-1*A*) is attached around its periphery and at the tips of the C anteriorly and posteriorly onto the tibia. During knee motion, the meniscus translates anteriorly and posteriorly to match the slight rollback of the lateral femoral condyle on the tibia with knee flexion. However, with a DLM, the meniscal tissue trapped between the articular surfaces is pushed anteriorly as the knee flexes. These abnormal forces, over time, result in tears in the meniscal tissue or in the posterior attachments, creating excessive meniscal displacement anteriorly during knee flexion. This produces a pop when flexing, usually at about 90-120 degrees of knee flexion as the meniscus is extruded anteriorly, and a loud click or clunk when extending the knee, usually in the last 30 degrees of extension, as the meniscus reduces back between the joint surfaces.

There are 3 types of DLM, according to the widely used **Watanabe classification**. Type I, or **complete, most commonly produces symptoms and** is characterized by a thickened lateral meniscus with complete coverage of the tibial surface (see Fig. 677-1*B*). Meniscus tissue is always between the joint surfaces. **Type II,** or incomplete, is of variable size and covers a lower percentage of the tibial surface (see Fig. 677-1*C*) compared to the complete type. Although they can become stretched or torn over time, both the complete and the incomplete types are thought to develop with normal peripheral attachments. Type III, or the Wrisberg ligament type, is a lateral meniscus with no peripheral attachments posteriorly. Instead it is stabilized posteriorly by a prominent meniscofemoral ligament, or ligament of Wrisberg, that secures the posterior horn of the lateral meniscus to the lateral surface of the medial femoral condyle (see Fig. 677-1*D*). As a result, the Wrisberg ligament type DLM is extremely mobile. Although its shape is not necessarily discoid, the hypermobility of the posterior portion of the meniscus allows it to be extruded anteriorly with flexion and for it to pop back in place with extension, as is characteristic of the other DLM variants.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The complete and incomplete types of DLM can be asymptomatic, especially if they have stable peripheral attachments. A symptomatic DLM in early childhood is usually caused by a meniscal tear or absent peripheral attachments allowing for the anterior extrusion during flexion and reduction with extension, producing the classical **snapping knee**. These patients can present as early as 2 yr of age, but more commonly present after approximately 6 yr of age; most patients present with symptoms during their teenage years. As these patients gain weight with their adolescent growth spurt, they place increasing static and dynamic loads on the tissue, often with high-level sports. Degeneration in the central portion of the DLM with direct weight bearing makes the meniscus highly susceptible to injury and tears, producing lateral pain and swelling in the knee. Often, the classic popping is not appreciated in these patients.

Younger children usually present with no history of trauma or acute inciting event and with a complaint of popping in the knee with

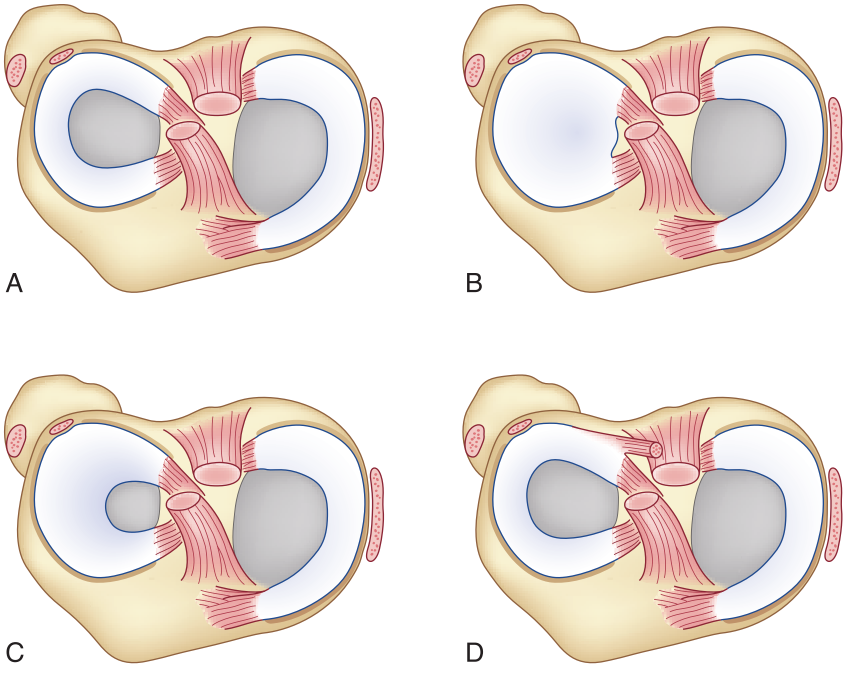

Figure 677-1 The anatomy of the normal meniscus and discoid variants. **A,** The lateral meniscus normally has a C shape with circumferential and root attachments. **B,** A type I, or complete, discoid lateral meniscus covers the entire tibial plateau and has normal attachments. **C,** A type II, or incomplete, discoid lateral meniscus partially covers the tibial plateau and also has normal attachments. **D,** A type III, or Wrisberg ligament type, appears similar in shape to a normal lateral meniscus but lacks sufficient attachments posteriorly resulting in a hypermobile meniscus. The ligament of Wrisberg secures the posterior horn of the meniscus to the lateral aspect of the medial femoral condyle.

occasional swelling. Older children and adolescents often can recall an inciting event and will sometimes report the mechanical popping, but more often note the lateral joint line pain and knee swelling. Physical examination might show a mild effusion and tenderness over the lateral joint line. With knee flexion, a pop with a slight protuberance along the lateral joint line anteriorly can sometimes be appreciated as the meniscus is extruded anteriorly. As the knee is brought back into extension at approximately 20-30 degrees short of full extension, the meniscus can be felt to snap back into the joint and the protuberance at the lateral joint line disappears.

A high index of suspicion is necessary based on history and clinical exam findings. Standard anteroposterior, lateral, merchant (patellar), and 45 degrees flexed posteroanterior (tunnel) views should be obtained if this diagnosis is considered. Radiography of the knee may show widening of the lateral aspect of the knee joint, flattening of the lateral femoral condyle resulting in a squared-off appearance, and cupping of the lateral aspect of the tibial plateau. Because these findings are very nonspecific, with any history or physical examination findings suggestive of a DLM, evaluation with MRI provides a definitive diagnosis.

TREATMENT

Patients with asymptomatic or incidentally found DLM without evidence of a tear or meniscal instability are treated nonoperatively with observation. They should be educated on symptoms to watch out for, but no activity restrictions are often necessary. If knee pain or mechanical symptoms limit activity or a meniscal tear develops, consideration is given for surgical intervention. **Partial meniscectomy**, referred to as **saucerization,** is often performed to reshape the meniscus arthroscopically with the goal of obtaining an anatomically normal-appearing meniscus (Fig. 677-2). Tears remaining in what would be the normal rim of meniscal tissue are either repaired or excised. Meniscal instability is also addressed with repairs as appropriate. If tears extend all the way to the periphery of the meniscus, sometimes a **total meniscectomy**, or complete excision of the meniscus, may be necessary. Because this leaves the joint surfaces unprotected and can lead to early osteoarthritis, addressing DLM tears as soon as they develop and before they extend to the periphery is preferred.

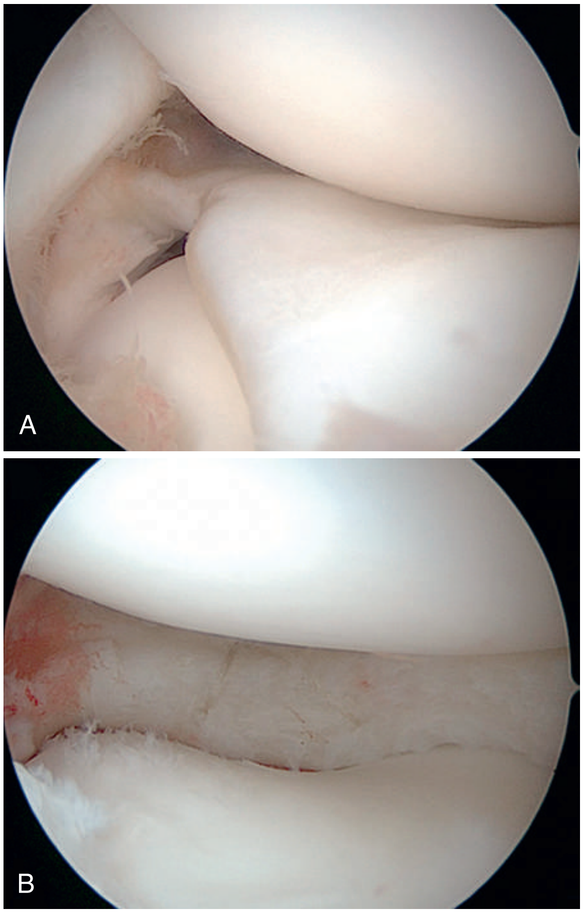

Figure 677-2 Surgical treatment of discoid lateral meniscus. Arthroscopic images of a complete discoid lateral meniscus before **(A)** and after **(B)** partial meniscectomy.

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677.2 Popliteal Cysts (Baker Cysts)

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Popliteal cysts, or **Baker cysts,** are cystic masses filled with gelatinous material that develop in the popliteal fossa, the shallow depression located at the posterior part of the knee. They are considered rare in children. They most commonly occur in the region of the medial head of the gastrocnemius and semimembranosus. They occur as an isolated fluid-filled bursa or via herniation through the posterior joint capsule of the knee into this same location. Histologically, the cysts are classified as fibrous, synovial, inflammatory, or transitional. Typically, popliteal cysts resolve spontaneously, although the process may take several years.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Patients commonly present with a mass behind the knee that may be fairly large when first noted. There are usually no symptoms of internal derangement of the knee. Physical examination reveals a firm mass in the popliteal fossa, often medially located and distal to the popliteal crease. The mass is usually most prominent when the knee is extended. Transillumination of the cyst on physical examination is a simple diagnostic test. Knee radiographs are normal and should be obtained to identify other lesions, such as osteochondromas, osteochondritis dissecans, and malignancies. The diagnosis may be confirmed by ultrasonography, MRI, or aspiration. Ultrasound differentiates a solid mass from a cystic lesion. In the presence of a knee effusion, consideration should be given to an MRI to evaluate for knee intraarticular pathology that may be causing the swelling, such as a meniscal tear or a DLM. These children should also be assessed for *other pathology* that may cause recurrent or intermittent knee effusions, including Lyme disease, juvenile idiopathic arthritis, or other autoimmune processes. The presence of a solid mass detected on ultrasound or MRI warrants additional diagnostic testing and referral for biopsy consideration.

TREATMENT

In most cases, popliteal cysts are observed because they often resolve spontaneously. Rest and leg elevation are beneficial to promote drainage of fluid accumulating within the cyst. If necessary, aspiration can reduce the size of the cyst and a corticosteroid injection can reduce inflammation. Cysts will often recur after aspiration. Surgical excision of a popliteal cyst is indicated only when symptoms are debilitating and have not resolved after several months.

Bibliography is available at Expert Consult.

677.3 Osteochondritis Dissecans

Eric J. Sarkissian and J. Todd R. Lawrence

Osteochondritis dissecans (OCD) is a localized pathologic process of the subchondral bone that secondarily affects the overlying articular cartilage and can progress to cartilage separation and fragmentation. The precise cause for OCD remains unclear, although repetitive microtrauma appears to be the leading candidate. Roles for genetics and ischemia have also been implicated in the etiology. The disorder is being seen with rising frequency in children and adolescents, likely in large part, as a consequence of increased sports participation in young athletes. In the knee, OCD most commonly affects the lateral aspect of the medial femoral condyle. The lateral femoral condyle and patella may also be affected, as well as joints other than the knee, such as the elbow or ankle. Characteristic pathology of the lesion includes an area of avascular necrosis in the subchondral bone, the segment of bone just below the joint surface, and varying degrees of ischemia and fibrosis of the overlying hyaline cartilage. Failure of both the bone and the cartilage surface to heal completely is associated with an increased risk for developing premature osteoarthritis.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The most common presenting complaint is a vague or **deep knee pain** that may localize along the medial or lateral joint line. If the osteochondral fragment becomes unstable, the patient may also develop **mechanical symptoms**, such as catching or locking. Physical exam findings include effusion, tenderness to palpation over the femoral condyles, quadriceps atrophy, and diminished range of motion.

Because most OCD lesions are located more on the posterior aspect of the femoral condyle, a posteroanterior radiograph with a 45 degree flexed knee (tunnel view) is often required to evaluate for the presence of an OCD. Many of these patients also have some degree of patellar-related pain, necessitating merchant (patellar) view plain films. Thus, standard radiographic evaluation of nontraumatic adolescent knee pain should routinely include anteroposterior, lateral, tunnel, and merchant radiographs of the knee. An early lesion may appear as a small radiolucency at the articular surface. A more advanced lesion may have a well-demarcated segment of subchondral bone with a lucent line demonstrating separation from the condyle. In children younger than age 10 yr, irregularities in the ossification center of the developing epiphysis may be difficult to distinguish from an OCD lesion.

MRI is useful for determining the size of the OCD, integrity of the articular cartilage, and presence of loose bodies. Fluid observed between the fragment and subchondral bone suggests an unstable lesion and high risk for detachment. Any linear signal through the articular cartilage or displacement of the fragment indicates a potentially unstable lesion as well. For an unstable-appearing OCD, either based on the patients' symptoms and signs, or the imaging, arthroscopy should be performed to evaluate the status of the lesion.

TREATMENT

Treatment for juvenile OCD includes nonoperative and surgical management, with treatment decisions being based on many factors, including the growth status and skeletal maturity of the patient, the presence of symptoms, the lesion size, and whether the lesion appears intact and stable or if there is any suggestion of instability. Skeletal immaturity (i.e., younger age), smaller lesion size, and the absence of mechanical symptoms or pain have been associated with a higher likelihood of OCD healing with nonoperative treatment. Unstable lesions will not usually heal with conservative treatment.

Thus, young patients with stable lesions, as evidenced by an intact articular surface on imaging (Fig. 677-3*A*), are deemed to have an acceptable probability of healing and are often initially managed conservatively with a period of non–weightbearing and immobilization, followed by a period of strict activity restriction and physical therapy for 3-6 mo. OCD healing is followed with radiographs, usually at approximately 3 mo intervals, until lesion healing has been noted. If healing has not been radiographically confirmed in 3-6 mo, surgical intervention is often considered. Because of the low rate of healing in skeletally mature patients, even intact lesions are not usually managed conservatively in this patient population, but recommended for surgery.

Although nonsurgical treatment can be successful in intact lesions, surgical treatment of intact lesions is often more successful and induces healing at a faster rate. Consequently, patients often choose to pursue early surgical intervention. For stable and intact lesions, surgical management involves arthroscopic evaluation of the joint followed by either a transarticular or retroarticular drilling to stimulate bony healing by creating channels in the subchondral bone that allow revascularization to occur. Both techniques are comparably effective in producing short-term patient-oriented outcomes and radiographic healing.

More advanced lesions with edema beneath the fragment, subchondral cyst formation, and partial (see Fig. 677-3*B*) or complete (see Fig. 677-3*C*) fragment detachment on arthroscopy are potentially salvageable. Treatment involves drilling or fixation with possible bone grafting. OCD lesions may progress to become unstable and dislodge into the joint space (see Fig. 677-3*D*). Removal of the loose body in addition to cartilage repair and restoration are typically performed for such unsalvageable lesions. In the postoperative period, patients undergo

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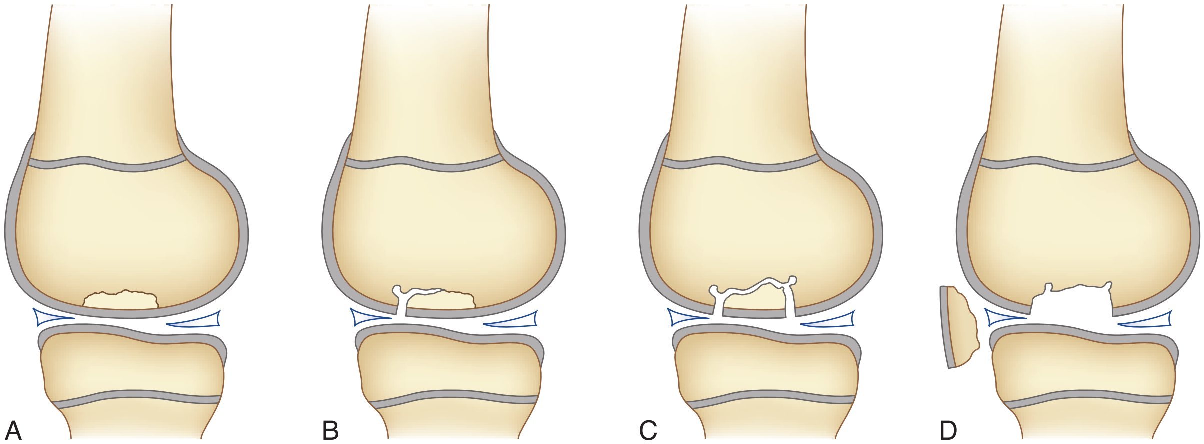

Figure 677-3 The spectrum of osteochondritis dissecans (OCD) pathology of the knee. **A,** A stable and intact lesion without breach of the overlying articular cartilage. **B,** An OCD with fluid beneath the fragment, subchondral cyst formation, and partial fragment detachment. **C,** An unstable but located lesion with fluid beneath the fragment, multiple subchondral cysts, and complete fragment detachment. **D,** A dislodged OCD lesion resulting in a loose body within the knee joint space.

physical therapy to regain strength and range of motion, with a gradual return to baseline activity levels. Treating OCD early and effectively often prevents recurrent symptoms in adulthood and reduces risk for early-onset osteoarthritis.

Bibliography is available at Expert Consult.

677.4 Osgood-Schlatter Disease and Sinding-Larsen-Johansson Syndrome

Eric J. Sarkissian and J. Todd R. Lawrence

In skeletally immature patients, the tibial tubercle is an extension of the proximal tibial epiphysis. As the femur rapidly grows in length, patients often develop tight musculature, particularly of the quadriceps, across the knee joint. These patients also develop movement patterns that preferentially place stress at the knees during activities instead of distributing that stress across other joints in the lower extremity. The repetitive tensile microtrauma sustained during sports or other athletic activities then creates traction injuries at the weak points in the extensor mechanism at the knee, as the stress exceeds the developing skeleton's ability to repair the damage.

Sinding-Larsen-Johansson syndrome is an insertional periostitis at the inferior pole of the patella. **Osgood-Schlatter (OS) disease** is an irritation of the patellar tendon at its insertion into the tibial tubercle or a traction apophysitis of the tibial tubercle growth plate. These conditions typically present during periods of relative accelerated growth. Sinding-Larsen-Johansson syndrome tends to occur in a slightly younger patient population, whereas OS disease presents in slightly older patients with most symptomatic between the ages of 10 and 15 yr. These conditions are most common in very physically active boys. However, as the number and intensity of female athletics has increased, the incidence in females seems to be on the rise.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Anterior knee pain, very specifically localized to the inferior pole of the patella (Sinding-Larsen-Johansson syndrome) or over the tibial tubercle (OS disease) is the most common patient complaint. Swelling, as well as an eventual firm and fixed increased prominence at the tibial tubercle, may occur with OS disease and may also be part of the initial complaint (Fig. 677-4). There is typically no acute traumatic inciting event. The pain is aggravated by sports activities, but may often persist with daily activities and even at rest. Physical examination reveals point tenderness over the tibial tubercle and the distal portion of the patellar tendon (OS disease). Diagnosis is usually made clinically, but radiographs may reveal fragmentation of the tibial tubercle and soft tissue swelling (Fig. 677-5).

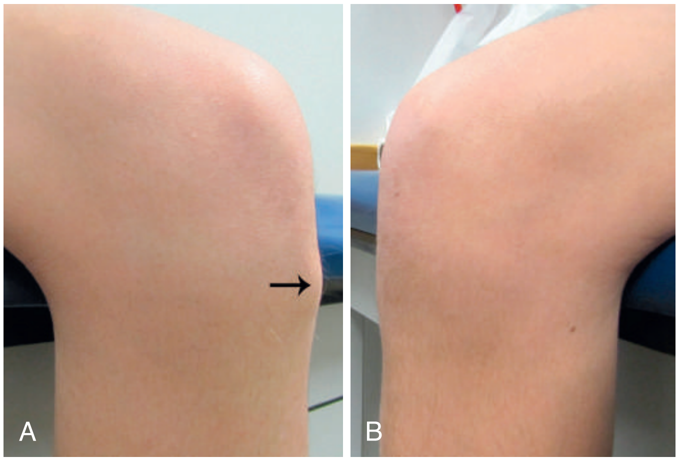

Figure 677-4 Clinical manifestations of Osgood-Schlatter disease. The increased prominence of the tibial tubercle, indicated by the *arrow*, **(A)** from traction apophysitis in a 15 yr old boy's knee is contrasted with the normal appearance of the tibial tubercle **(B)** in his contralateral, unaffected knee.

TREATMENT

In most patients, Sinding-Larsen-Johansson syndrome and OS disease are self-limited processes and resolve with rest. Patients are treated with an escalating treatment regime until they are pain free with activity. If they are pain free with normal daily activities, they may maintain this level of activity for 2 additional wk. In more-severe cases, a knee immobilizer or even crutches with restricted weightbearing are required to get the patient comfortable. Patients are usually advised to maintain a level of activity for 1-2 wk before attempting to advance. Sports and other dynamic activities are restricted until the patient has been pain free to palpation for at least 2 wk. During this rest period, addressing some of the contributing factors, such as muscular tightness, can help prevent recurrence with activity resumption. A self-directed stretching regime concentrating on the quadriceps and hamstrings may be provided. Some patients and resistant cases may benefit from formal instruction in these exercises with a physical therapist.

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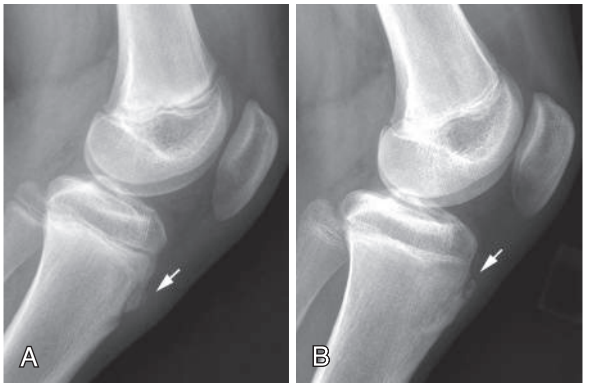

Figure 677-5 Radiographic findings of Osgood-Schlatter disease. **A,** Lateral radiograph of the knee of a 13 yr old male demonstrates a sliver of new bone formation *(arrow)* at the tibial tubercle. **B,** Lateral radiograph of the same child at 15 yr of age demonstrates characteristic fragmentation *(arrow)* of the tibial tubercle.

Reassurance is important, because some patients and parents fear that the swollen tubercle may be a sign of malignancy. Patients and family members should be advised, however, that the tibial tubercle swelling will not likely resolve. Hyperosmolar dextrose local injections may improve outcomes in patients with recalcitrant disease. Removal of ossicles from the tubercle is rarely necessary in pediatric patients but may be required with persistent disabling symptoms in young adults. Complications are rare and include early closure of the tibial tubercle with recurvatum, or hyperextension, deformity, and rarely, patellar tendon rupture or avulsion fracture of the tibial tubercle. Although rare, these complications can have significant long-term consequences and should thus prompt counseling to avoid playing through the pain.

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677.5 Patellofemoral Pain Syndrome

Eric J. Sarkissian and J. Todd R. Lawrence

Also known as anterior knee pain syndrome, patellofemoral pain syndrome (PFPS) is one of the most common causes of knee pain, particularly in adolescent girls. Previously, PFPS was thought to arise from a deranged patellar articular surface, hence, the former term chondromalacia patella. Increasing evidence shows that anterior knee pain is frequently present even with normal articular cartilage of the patella, resulting in more appropriate labeling of the condition. The precise etiology of the knee pain remains unknown and is likely multifactorial.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Pain beneath or near the patella is the most common symptom. Classically, walking up and down stairs, which puts the patella under high compressive loads, aggravates the pain. Squatting, running, and other vigorous physical activities also exacerbate the anterior knee pain. Sitting in a flexed knee position for an extended period of time, the so-called theater sign, is another common complaint. There is usually no history of antecedent trauma, although falling onto a flexed knee is sometimes noted. Buckling or a sense of the knee *giving way* can occur, but there is rarely any true knee instability. Swelling is not common and if present should prompt further investigation. Pain is often relieved through knee extension.

Physical exam reveals isolated tenderness with palpation about the medial or lateral aspects of the patella. With the knee extended and the quadriceps relaxed, placing pressure on the patella and translating it distally into the top of the trochlear groove, the so-called **grind test**, often also causes pain. Reproduction of the patient's pain with these maneuvers is an important component of the exam. Active and passive range of motion of the knee, alignment of the lower extremity, knee ligamentous stability, patellar tracking, and gait should be evaluated to identify any obvious causes of malalignment or an unstable patella. These patients often have tight quadriceps, hamstrings, and heel cords, as well as weak hip musculature and poor overall balance. A single leg squat can often highlight the hip weakness and balance and alignment issues that contribute to this condition. Routine radiographs of the knee, including anteroposterior, lateral, tunnel (posteroanterior with 45 degrees flexed knee), and merchant (patellar) views, are usually normal, but are helpful in eliminating other etiologies. Radiographs of the hip should be considered in suspected cases to rule out hip pathology, such as a slipped capital femoral epiphysis, that can manifest as ill-defined knee pain in adolescents as well. An MRI is not routinely required for evaluation but should be considered in any patient with a history of mechanical symptoms or an effusion.

TREATMENT

Several methods of nonoperative treatment are utilized to address PFPS. The mainstay of treatment is continued physiotherapy, involving overall lower-extremity stretching and strengthening, including short-arc quadriceps strengthening, hip and core strengthening, and exercises designed to address balance and overall body positioning during dynamic activities. No one particular regime seems to demonstrate results superior to the others. Home exercise programs can be effective for the properly disciplined and motivated patient, but formal physical therapy should be considered in resistant cases or in patients who may not have the motivation or wherewithal to adhere to a self-directed program. Orthoses, including patellar taping, knee sleeves, customized knee braces, or even shoe inserts are often used in conjunction with physical therapy. However, evidence for long-term benefit from orthotic use is unclear. Treatment with Botulinum toxin injections, nonsteroidal antiinflammatory medications, or therapeutic ultrasound is not substantiated. Most cases of PFPS resolve spontaneously over a period of years. Arthroscopic evaluation of the knee and patellofemoral joint is rarely necessary.

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677.6 Patellofemoral Instability

Eric J. Sarkissian and J. Todd R. Lawrence

Patellofemoral joint stability depends on a balance of the static restraints and the dynamic forces acting on the patella. These include the restraining ligaments and the articular anatomy of the patellofemoral groove that serve to balance the dynamic forces of the quadriceps mechanism and overall limb positioning. During knee flexion, the pull of the quadriceps mechanism tends to place an overall lateral displacing force at the patella. The **Q angle** refers to the deviation between the angle of the patellar tendon and the line of the quadriceps. Wider hips and valgus (knock-kneed) positioning increase the Q angle and thus the lateral force applied at the patella. In extension, the static restraints, including the medial restraining ligaments, primarily the medial patellofemoral ligament, are responsible for guiding the patella into the trochlear grove in the distal femur. The pull of the vastus medialis obliquus is the only dynamic restraint. Once in the trochlea, the bony congruity becomes the primary restraint to the net lateral muscular forces.

Factors that contribute to patellofemoral instability are multifactorial and include vastus medialis insufficiency, ligamentous laxity, shallow sulcus, condylar hypoplasia, patella alta (high riding patella), or malalignment that effectively increases the Q angle, such as genu valgum, internal femoral torsion, or external tibial torsion.

Acute patellofemoral dislocation is the most common acute knee disorder in children and adolescents and often occurs after a sudden valgus strain during a sporting activity but may be the result of direct

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trauma. **Recurrent patellofemoral subluxation** is more than 1 episode of patellar subluxation without frank dislocation. Lateral malalignment of the quadriceps mechanism is the most common etiologic factor. **Habitual dislocation of the patella** describes patellar dislocation occurring during every knee flexion. A dysplastic knee with contracture of the lateral portion of the quadriceps mechanism is often associated. Several syndromes are associated with patellar instability, including Down syndrome (see Chapter 81), Turner syndrome (see Chapter 81), Kabuki syndrome, and Rubinstein-Taybi syndrome.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

With an acute patellar dislocation, patients will recall the acute event and the sensation that their knee cap was out of place. Straightening the knee is all that is usually required to reduce the patella, but sometimes this requires medical attention. Swelling is usually almost immediate following the injury and appreciable on examination with an effusion. The patella may appear laterally displaced when the knee is fully extended or higher than normal with the knee slightly flexed. Pain along the medial knee from the medial patella to the medial epicondyle of the femur is common. Lateral patellar translocation with the knee slightly flexed should be tested with the **patellar apprehension test**. In the acute setting there will be increased translation and pain as well as a feeling of insecurity. Patellar tracking is also an important component to the exam but may not be possible due to pain in the acute setting. The **J sign** refers to the inverted J-path the patella takes, beginning in a laterally subluxated position and then suddenly shifting medially to engage the femoral groove with early knee flexion. The torsional profile of the patient is also important to assess to rule out possible rotational abnormalities of the femur or tibia.

Radiographs of a patient with patellar instability should include anteroposterior, lateral, and merchant views (obtained with the knee bent 45 degrees, with the beam of the x-ray through the knee from head to toe) of the patella. Radiographs should also be carefully examined for occult fractures. In the presence of a significant knee effusion, mechanical symptoms, acute traumatic patellar dislocation, or uncertainty in the diagnosis, further investigation may warrant an MRI to evaluate for loose bodies or cartilage damage. MRI will illustrate bone bruise patterns typical of patellar dislocation at the medial patellar facet and at the lateral femoral condyle. A tear in the medial patellofemoral ligament may also be seen, especially in cases of an acute patellofemoral dislocation.

TREATMENT

Nonoperative management is initially recommended for acute patellar dislocation and recurrent patellar subluxation, unless an osteochondral fracture or additional intra-articular pathology is seen on imaging studies. Although early physical therapy has also been shown to be successful, a brief 4-6 wk period of immobilization in full extension may help with healing of the medial knee restraints following an initial traumatic dislocation. After this, transition to a patellar stabilizing brace usually improves symptoms. Successful treatment is usually achieved with formal physical therapy aimed at improving extensor muscle tone, particularly the vastus medialis obliquus, activity-related body positioning, and hip and core muscle strengthening. The reported redislocation rate following an initial traumatic patellar dislocation ranges from 15-44%.

Failure to improve after nonoperative treatment and persistent episodes of patellar subluxation or dislocation are indications for surgical intervention to address patellofemoral instability. Patients with loose bodies, osteochondral fractures, or chondral damage are surgical candidates for early intervention. Many different types of surgical procedures exist to prevent lateral excursion of the patella from occurring. These include proximal realignment of the patella, distal realignment of the patellar tendon insertion, lateral release, medial patellofemoral ligament reconstruction, or guided growth techniques. The surgical approach that is selected should be individualized for each patient depending on the pathoanatomy contributing to the recurrent subluxations or dislocations.

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677.7 Anterior Cruciate Ligament Rupture

Eric J. Sarkissian and J. Todd R. Lawrence

Pediatric anterior cruciate ligament (ACL) reconstruction has become more prevalent as ACL tears in skeletally immature patients have greatly increased in recent years. Increased sports participation, increased intensity of training and competition, participation on multiple teams, heightened awareness, and improved methods for diagnosis are all cited as contributing factors to the growing awareness of ACL injuries in children and adolescents.

Females are also known to have a greater risk for ACL injury than males. The gender-specific discrepancy appears to be caused mostly by insufficient neuromuscular activation patterns in females, resulting in increased **genu valgum**, or knock-knee, biased landing and, therefore, a heightened tendency toward landing or stopping in an injury prone position. Various pediatric ACL injury prevention programs show benefit in not only reducing the rate of injuries but also in increasing athletic strength and performance.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The majority of ACL tears occurs as a result of a noncontact injury. Patients may report a pop associated with the acute onset of knee pain. Later they develop swelling, limited range of motion, and sometimes a sensation of instability. After the initial injury, patients may have surprisingly little pain. On physical exam, the anterior drawer sign or Lachman test may indicate increased anterior tibial translation. The Lachman examination is performed by applying an anteriorly directed force to the proximal tibia with the femur stabilized and the knee flexed 20-30 degrees. The amount of translation and the end point are assessed, with increased translation and an indistinct end point indicating a positive test. A pivot shift test can also be performed to confirm the diagnosis but is rarely successful in the conscious patient. It is conducted by gently bending the knee while just supporting the lower leg. A gentle valgus stress and slight internal rotation can enhance the shift.

Radiographs of the knee are performed, including anteroposterior, lateral, tunnel (posteroanterior with 45 degrees flexed knee), and merchant (patellar) views, to assess for other potential injuries common in pediatric and adolescent patients, such as tibial spine avulsion fractures or OCD. In traumatic injuries, internal and external oblique radiographs can also be helpful. Ultimately, knee MRI can confirm the presence of an intrasubstance ACL tear, as well as meniscal or chondral pathology. Arthroscopic evaluation is the gold standard for diagnosis and treatment.

TREATMENT

The management of ACL injury in this patient population can be challenging and the severity of the ACL tear is important to differentiate. Incomplete ACL tears may be treated nonoperatively and the patient and family's understanding and willingness to adhere to a protocol of bracing and activity restriction are important factors in optimizing outcomes. For complete tears of the ACL, because of the risk of ongoing knee damage if stabilization of the knee is delayed, surgical reconstruction is now recommended for patients who are physically, mentally, and emotionally capable after a thorough discussion with the patient and family about the risks and benefits. All-epiphyseal, partial transphyseal, or traditional transphyseal reconstruction techniques are used based upon the skeletal maturity of the patient to minimize the risk for growth disturbance across the distal femoral and proximal tibial physes.

Depending on the technique used for reconstruction and any associated meniscal pathology addressed, weight bearing is restricted and a brace is used for the 1st 4-6 wk postoperatively. Physical therapy is used postoperatively and continued until strength and functional testing are equal to the contralateral, unaffected limb. Routine follow-up visits and radiographs are conducted to monitor progress and signs of growth disturbance. Patients return to sports typically at a minimum of 9 mo postoperatively and are followed on a yearly basis thereafter until skeletal maturity.

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Chapter 678

The Hip

Wudbhav N. Sankar, B. David Horn, Lawrence Wells, and John P. Dormans

Anatomically, the hip joint is a ball-and-socket articulation between the femoral head and acetabulum.

The hip joint is a pivotal joint of the lower extremity, and its functional demands require both stability and flexibility.

GROWTH AND DEVELOPMENT

The hip joint begins to develop at about the 7th wk of gestation, when a cleft appears in the mesenchyme of the primitive limb bud. These precartilaginous cells differentiate into a fully formed cartilaginous **femoral head** and **acetabulum** by the 11th wk of gestation (see Chapter 8). At birth, the neonatal acetabulum is completely composed of cartilage, with a thin rim of fibrocartilage called the **labrum**.

The very cellular hyaline cartilage of the acetabulum is continuous with the triradiate cartilages, which divide and interconnect the 3 osseous components of the pelvis (the **ilium**, **ischium**, and **pubis**). The concave shape of the hip joint is determined by the presence of a spherical femoral head.

Several factors determine acetabular depth, including interstitial growth within the acetabular cartilage, appositional growth under the perichondrium, and growth of adjacent bones (the ilium, ischium, and pubis). In the neonate, the entire proximal femur is a cartilaginous structure, which includes the femoral head and the greater and lesser trochanters. The 3 main growth areas are the physeal plate, the growth plate of the greater trochanter, and the femoral neck isthmus. Between the 4th and 7th mo of life, the proximal femoral ossification center (in the center of the femoral head) appears. This ossification center continues to enlarge, along with its cartilaginous anlage, until adult life, when only a thin layer of articular cartilage remains. During this period of growth, the thickness of the cartilage surrounding this bony nucleus gradually decreases, as does the thickness of the acetabular cartilage. The growth of the proximal femur is affected by muscle pull, the forces transmitted across the hip joint with weight bearing, normal joint nutrition, circulation, and muscle tone. Alterations in these factors can cause profound changes in the development of the proximal femur.

VASCULAR SUPPLY

The blood supply to the capital femoral epiphysis is complex and changes with growth of the proximal femur. The proximal femur receives its arterial supply from intraosseous (primarily the medial femoral circumflex artery) and extraosseous vessels (Fig. 678-1). The **retinacular vessels** (extraosseous) lie on the surface of the femoral neck but are intracapsular because they enter the epiphysis from the periphery. This makes the blood supply vulnerable to damage from septic arthritis, trauma, thrombosis, and other vascular insults. Interruption of this tenuous blood supply can lead to avascular necrosis of the femoral head and permanent deformity of the hip.

678.1 Developmental Dysplasia of the Hip

Wudbhav N. Sankar, B. David Horn, Lawrence Wells, and John P. Dormans

Developmental dysplasia of the hip (DDH) refers to a spectrum of pathology in the development of the immature hip joint. Formerly called *congenital dislocation of the hip*, DDH more accurately describes the variable presentation of the disorder, encompassing mild dysplasias as well as frank dislocations.

CLASSIFICATION

Acetabular **dysplasia** refers to abnormal morphology and development of the acetabulum. Hip **subluxation** is defined as partial contact between the femoral head and acetabulum. Hip **dislocation** refers to a hip with no contact between the articulating surfaces of the hip. DDH is classified into 2 major groups**:** **typical** and **teratologic**. Typical DDH occurs in otherwise normal patients or those without defined syndromes or genetic conditions. Teratologic hip dislocations usually have identifiable causes, such as arthrogryposis or a genetic syndrome, and occur before birth.

ETIOLOGY AND RISK FACTORS

Although the etiology remains unknown, the final common pathway in the development of DDH is increased laxity of the joint, which fails to maintain a stable femoroacetabular articulation. This increased laxity is probably the result of a combination of hormonal, mechanical, and genetic factors. A positive family history for DDH is found in 12-33% of affected patients. DDH is more common among female patients (80%), which is thought to be because of the greater susceptibility of female fetuses to maternal hormones such as relaxin, which increases ligamentous laxity. Although only 2-3% of all babies are born

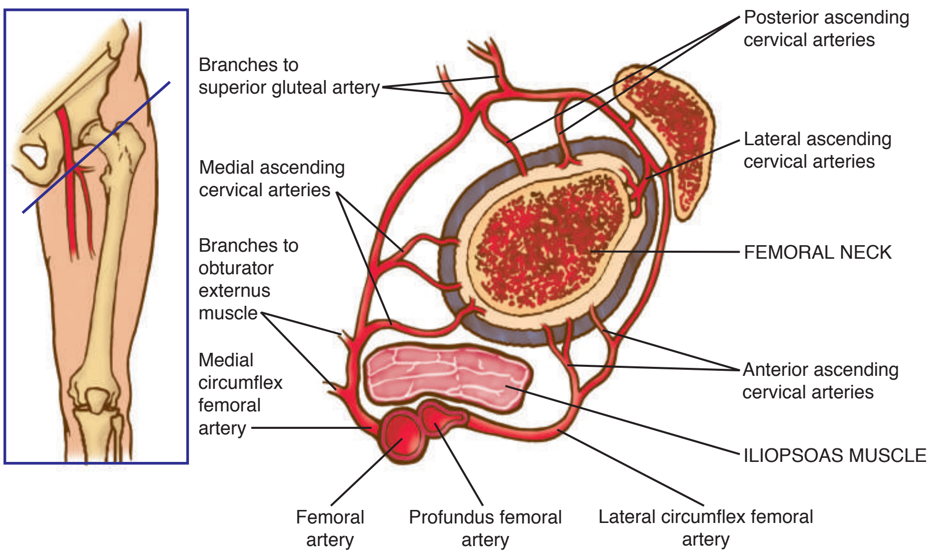

Figure 678-1 Diagram of vascular anatomy of the proximal femur.

in breech presentation, the incidence of DDH in these patients is 16-25%.

Any condition that leads to a tighter intrauterine space and, consequently, less room for normal fetal motion may be associated with DDH. These conditions include oligohydramnios, large birth weight, and 1st pregnancy. The high rate of association of DDH with other *intrauterine molding abnormalities*, such as torticollis and metatarsus adductus, supports the theory that the *crowding phenomenon* has a role in the pathogenesis. The left hip is the most commonly affected hip; in the most common fetal position, this is the hip that is usually forced into adduction by the mother's sacrum.

EPIDEMIOLOGY

Although most newborn screening studies suggest that some degree of hip instability can be detected in 1 in 100 to 1 in 250 babies, actual dislocated or dislocatable hips are much less common, being found in 1-1.5 of 1,000 live births.

There is marked geographic and racial variation in the incidence of DDH. The reported incidence based on geography ranges from 1.7 in 1,000 babies in Sweden to 75 in 1,000 in Yugoslavia to 188.5 in 1,000 in a district in Manitoba, Canada. The incidence of DDH in Chinese and African newborns is almost 0%, whereas it is 1% for hip dysplasia and 0.1% for hip dislocation in white newborns. These differences may be the result of environmental factors, such as child-rearing practices, rather than to genetic predisposition. African and Asian caregivers have traditionally carried babies against their bodies in a shawl so that a child's hips are flexed, abducted, and free to move. This keeps the hips in the optimal position for stability and for dynamic molding of the developing acetabulum by the cartilaginous femoral head. Children in Native American and Eastern European cultures, which have a relatively high incidence of DDH, have historically been swaddled in confining clothes that bring their hips into extension. This position increases the tension of the psoas muscle-tendon unit and might predispose the hips to displace and eventually dislocate laterally and superiorly.

PATHOANATOMY

In DDH, several secondary anatomic changes can develop that can prevent reduction. Both the fatty tissue in the depths of the socket, known as the **pulvinar,** and the ligamentum teres can hypertrophy, blocking reduction of the femoral head. The transverse acetabular ligament usually thickens as well, which effectively narrows the opening of the acetabulum. In addition, the shortened iliopsoas tendon becomes taut across the front of the hip, creating an hourglass shape to the hip capsule, which limits access to the acetabulum. Over time, the dislocated femoral head places pressure on the acetabular rim and labrum, causing the labrum to infold and become thick.

The shape of a normal femoral head and acetabulum depends on a concentric reduction between the two. The more time that a hip spends dislocated, the more likely that the acetabulum will develop abnormally. Without a femoral head to provide a template, the acetabulum will become progressively shallow, with an oblique acetabular roof and a thickened medial wall.

CLINICAL FINDINGS

The Neonate

DDH in the neonate is asymptomatic and must be screened for by specific maneuvers. Physical examination must be carried out with the infant unclothed and placed supine in a warm, comfortable setting on a flat examination table.

The **Barlow** provocative maneuver assesses the potential for dislocation of a nondisplaced hip. The examiner adducts the flexed hip and gently pushes the thigh posteriorly in an effort to dislocate the femoral head (Fig. 678-2). In a positive test, the hip is felt to slide out of the acetabulum. As the examiner relaxes the proximal push, the hip can be felt to slip back into the acetabulum.

The **Ortolani** test is the reverse of Barlow test: The examiner attempts to reduce a dislocated hip (Fig. 678-3). The examiner grasps the child's thigh between the thumb and index finger and, with the 4th and 5th

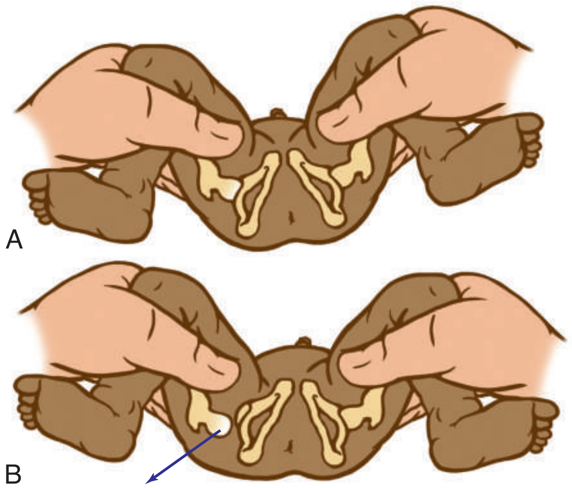

Figure 678-2 The Barlow provocative test is performed with the patient's knees and hips flexed. **A,** Holding the patient's limbs gently, with the thigh in adduction, the examiner applies a posteriorly directed force. **B,** This test is positive in a dislocatable hip.

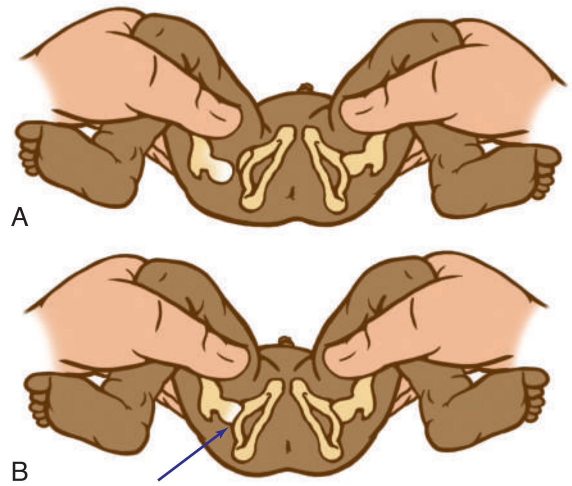

Figure 678-3 The Ortolani maneuver is the sign of the ball of the femoral head moving in and out of the acetabulum. **A,** The examiner holds the patient's thigh and gently abducts the hip while lifting the greater trochanter with 2 fingers. **B,** When the test is positive, the dislocated femoral head falls back into the acetabulum with a palpable clunk as the hip is abducted.

fingers, lifts the greater trochanter while simultaneously abducting the hip. When the test is positive, the femoral head will slip into the socket with a delicate clunk that is palpable but usually not audible. It should be a gentle, nonforced maneuver.

A **hip click** is the high-pitched sensation (or sound) felt at the very end of abduction during testing for DDH with Barlow and Ortolani maneuvers. Classically, a hip click is differentiated from a **hip clunk**, which is felt as the hip goes in and out of joint. Hip clicks usually originate in the ligamentum teres or occasionally in the fascia lata or psoas tendon and do not indicate a significant hip abnormality.

The Infant

As the baby enters the 2nd and 3rd mo of life, the soft tissues begin to tighten and the Ortolani and Barlow tests are no longer reliable. In this age group, the examiner must look for other specific physical findings, including limited hip abduction, apparent shortening of the thigh, proximal location of the greater trochanter, asymmetry of the gluteal

Figure 678-4 Asymmetry of thigh folds in a child with developmental dysplasia of the hip.

Figure 678-5 Positive Galeazzi sign noted in a case of untreated developmental dysplasia of the hip.

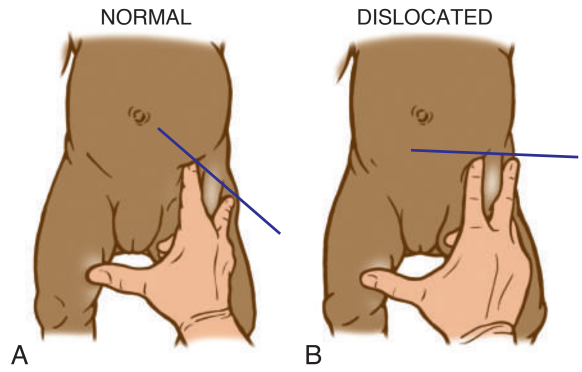

Figure 678-6 Klisic test. **A,** In a normal hip, an imaginary line drawn down through the tip of an index finger placed on the patient's iliac crest and the tip of the long finger placed on the patient's greater trochanter should point to the umbilicus. **B,** In a dislocated hip, this line drawn through the 2 fingertips runs below the umbilicus because the greater trochanter is abnormally high.

or thigh folds (Fig. 678-4), and positioning of the hip. Limitation of abduction is the most reliable sign of a dislocated hip in this age group.

Shortening of the thigh, the **Galeazzi sign,** is best appreciated by placing both hips in 90 degrees of flexion and comparing the height of the knees, looking for asymmetry (Fig. 678-5). Asymmetry of thigh and gluteal skin folds may be present in 10% of normal infants but suggests DDH. Another helpful test is the **Klisic test,** in which the examiner places the 3rd finger over the greater trochanter and the index finger of the same hand on the anterior superior iliac spine. In a normal hip, an imaginary line drawn between the 2 fingers points to the umbilicus. In the dislocated hip, the trochanter is elevated, and the line projects halfway between the umbilicus and the pubis (Fig. 678-6).

The Walking Child

The walking child often presents to the physician after the family has noticed a limp, a waddling gait, or a leg-length discrepancy. The affected side appears shorter than the normal extremity, and the child toe-walks on the affected side. The Trendelenburg sign is positive in these children, and an abductor lurch is usually observed when the child walks. As in the younger child, there is limited hip abduction on the affected side and the knees are at different levels when the hips are flexed (the Galeazzi sign). Excessive lordosis, which develops secondary to altered hip mechanics, is common and is often the presenting complaint.

DIAGNOSTIC TESTING

Ultrasonography

Because it is superior to radiographs for evaluating cartilaginous structures, ultrasonography is the diagnostic modality of choice for DDH before the appearance of the femoral head ossific nucleus (4-6 mo). During the early newborn period (0-4 wk), however, physical examination is preferred over ultrasonography because there is a high incidence of false-positive sonograms in this age group. In addition to elucidating the static relationship of the femur to the acetabulum, ultrasonography provides dynamic information about the stability of the hip joint. The ultrasound examination can be used to monitor acetabular development, particularly of infants in Pavlik harness treatment; this method can minimize the number of radiographs taken and might allow the clinician to detect failure of treatment earlier.

In the Graf technique, the transducer is placed over the greater trochanter, which allows visualization of the ilium, the bony acetabulum, the labrum, and the femoral epiphysis (Fig. 678-7). The angle formed by the line of the ilium and a line tangential to the boney roof of the acetabulum is termed the **α angle** and represents the depth of the acetabulum. Values >60 degrees are considered normal, and those <60 degrees imply acetabular dysplasia. The **β angle** is formed by a line drawn tangential to the labrum and the line of the ilium; this represents the cartilaginous roof of the acetabulum. A normal β angle is <55 degrees; as the femoral head subluxates, the β angle increases. Another useful test is to evaluate the position of the center of the head compared to the vertical line of the ilium. If the line of the ilium falls lateral to the center of the head, the epiphysis is considered reduced. If the line falls medial to the center of the head, the epiphysis is uncovered and is either subluxated or dislocated.

Screening for DDH with ultrasound remains controversial. Although routinely performed in Europe, meta-analyses indicate that data are insufficient to give clear recommendations. In the United States, the current recommendations are that every newborn undergo a clinical examination for hip instability. Children who have findings suspicious for DDH should be followed up with ultrasound. Most authors agree that infants with *risk factors* for DDH (breech position, family history, torticollis) should be screened with ultrasound regardless of the clinical findings.

Radiography

Radiographs are recommended for an infant once the proximal femoral epiphysis ossifies, usually by 4-6 mo. In infants of this age, radiographs have proved to be more effective, less costly, and less operator dependent than an ultrasound examination. An anteroposterior (AP) view of the pelvis can be interpreted with the aid of several classic lines drawn on it (Fig. 678-8).

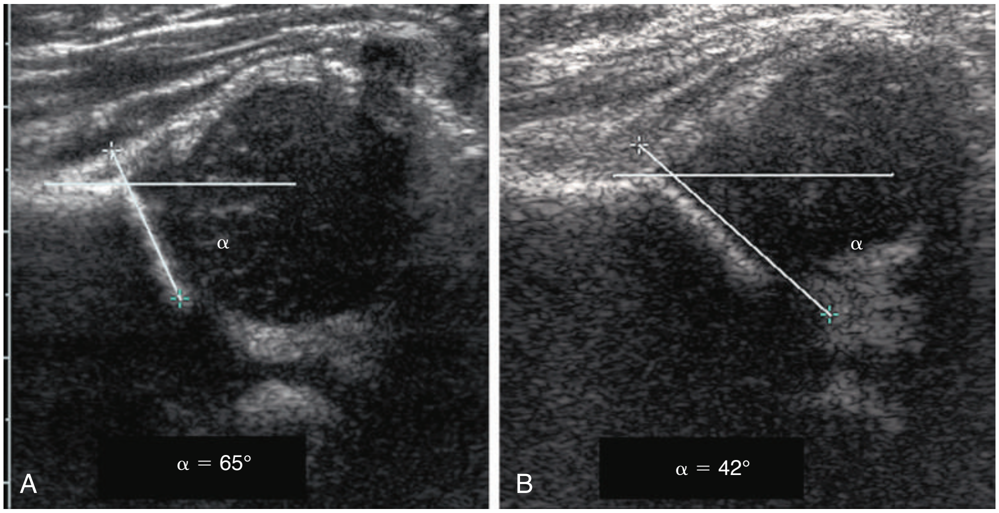

Figure 678-7 **A,** Normal ultrasonographic image of the hip in an infant. The α angle is >60 degrees. Note that a line drawn tangential to the ilium falls lateral to the center of the femoral head. **B,** In this child with developmental dysplasia of the hip, the left hip demonstrates an α angle of 42 degrees, and a line drawn tangential to the ilium shows that <50% of the femoral head is contained within the acetabulum.

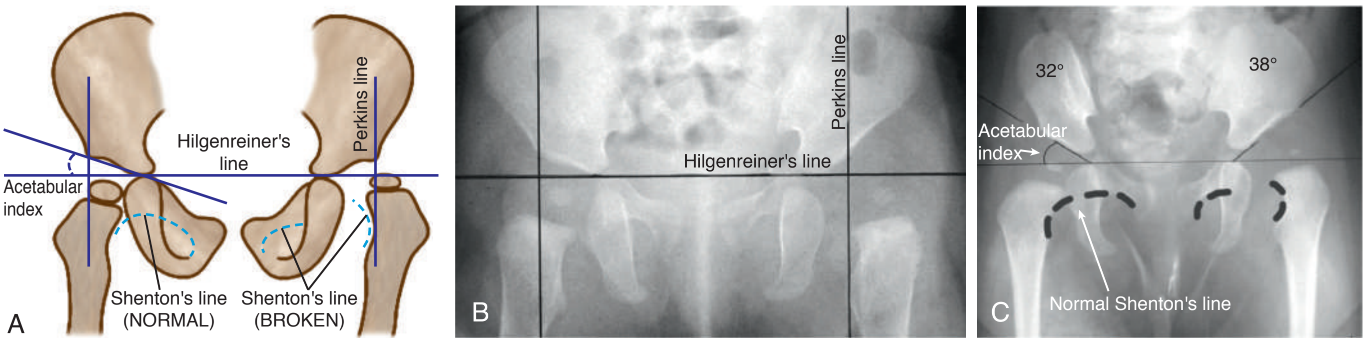

Figure 678-8 **A-C,** Radiographic measurements are useful in evaluating developmental dysplasia of the hip. Hilgenreiner's line is drawn through the triradiate cartilages. Perkins line is drawn perpendicular to Hilgenreiner's line at the lateral edge of the acetabulum. The ossific nucleus of the femoral head should be located in the medial lower quadrant of the intersection of these 2 lines. Shenton's line curves along the femoral metaphysis and connects smoothly to the inner margin of the pubis. In a child with hip subluxation or dislocation, this line consists of 2 separate arcs and is described as broken. The acetabular index is the angle between a line drawn along the margin of the acetabulum and Hilgenreiner's line; in normal newborns, it averages 27.5 degrees and decreases with age.

Hilgenreiner's **line** is a horizontal line drawn through the top of both triradiate cartilages (the clear area in the depth of the acetabulum). **Perkins line** is a vertical line through the most lateral ossified margin of the roof of the acetabulum, drawn perpendicular to Hilgenreiner's line. The ossific nucleus of the femoral head should be located in the medial lower quadrant of the intersection of these 2 lines. **Shenton's line** is a curved line drawn from the medial aspect of the femoral neck to the lower border of the superior pubic ramus. In a child with normal hips, this line is a continuous contour. In a child with hip subluxation or dislocation, this line consists of 2 separate arcs and is described as "broken."

The **acetabular index** is the angle formed between Hilgenreiner's line and a line drawn from the depth of the acetabular socket to the most lateral ossified margin of the roof of the acetabulum. This angle measures the development of the osseous roof of the acetabulum. In the newborn, the acetabular index can be up to 40 degrees; by 4 mo in the normal infant, it should be no more than 30 degrees. In the older child, the **center-edge angle** is a useful measure of femoral head coverage. This angle is formed at the juncture of the Perkins line and a line connecting the lateral margin of the acetabulum to the center of the femoral head. In children 6-13 yr old, an angle >19 degrees is normal, whereas in children 14 yr and older, an angle >25 degrees is considered normal.

TREATMENT

The goals in the management of DDH are to obtain and maintain a concentric reduction of the femoral head within the acetabulum in order to provide the optimal environment for the normal development of both the femoral head and acetabulum. The later the diagnosis of DDH is made, the more difficult it is to achieve these goals, the less potential there is for acetabular and proximal femoral remodeling, and the more complex the required treatments.

Newborns and Infants Younger Than 6 Months

Newborns hips that are Barlow-positive (reduced but dislocatable) or Ortolani-positive (dislocated but reducible) should generally be treated with a Pavlik harness as soon as the diagnosis is made. The management of newborns with dysplasia who are younger than 4 wk of age is less clear. A significant proportion of these hips normalize within 3-4 wk; consequently, many physicians prefer to reexamine these newborns after a few weeks before making treatment decisions. A study of 128 newborns with mildly dysplastic hips based on the results of an ultrasound (alpha angles between 43 and 50 degrees) who were randomly assigned to receive immediate abduction splinting or active sonographic surveillance from birth with Frejka splinting provided if treatment was subsequently needed revealed no difference in radiologic findings at 6 yr of age.

Figure 678-9 Photograph of a Pavlik harness.

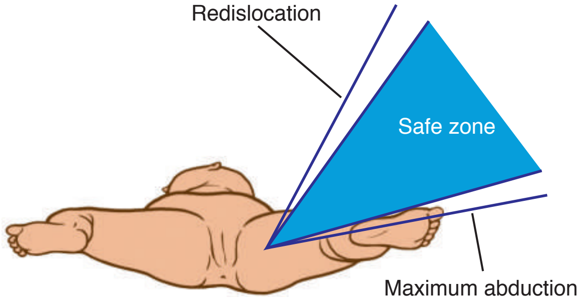

Figure 678-10 Diagram of the safe zone of Ramsey.

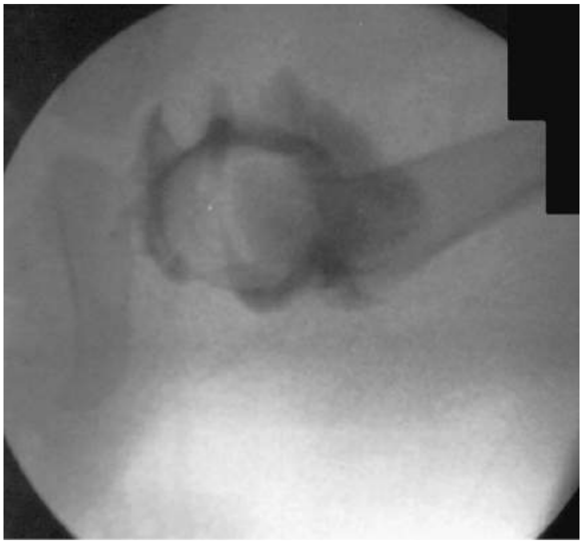

Figure 678-11 Arthrogram of a reduced hip for evaluating the stability of reduction.

Triple diapers or abduction diapers have no place in the treatment of DDH in the newborn; they are usually ineffective and give the family a false sense of security. *Acetabular dysplasia, subluxation, or dislocation can all be readily managed with the Pavlik harness.* Although other braces are available (von Rosen splint, Frejka pillow), the Pavlik harness remains the most commonly used device worldwide (Fig. 678-9). By maintaining the Ortolani-positive hip in a Pavlik harness on a full-time basis for 6 wk, hip instability resolves in 95% of cases. After 6 mo of age, the failure rate for the Pavlik harness is >50% because it is difficult to maintain the increasingly active and crawling child in the harness. Frequent examinations and readjustments are necessary to ensure that the harness is fitting correctly. The anterior straps of the harness should be set to maintain the hips in flexion (usually ~90-100 degrees); excessive flexion is discouraged because of the risk of femoral nerve palsy. The posterior straps are designed to encourage abduction. These are generally set to allow adduction just to neutral, as forced abduction by the harness can lead to avascular necrosis of the femoral epiphysis.

If follow-up examinations and ultrasounds do not demonstrate concentric reduction of the hip after 3-4 wk of Pavlik harness treatment, the harness should be abandoned. Continued use of the harness beyond this period in a persistently dislocated hip can cause *Pavlik harness disease*, or wearing away of the posterior aspect of the acetabulum, which can make the ultimate reduction less stable.

Children 6 Months to 2 Years of Age

The principal goals in the treatment of late-diagnosed dysplasia are to obtain and maintain reduction of the hip without damaging the femoral head. **Closed reductions** are performed in the operating room under general anesthesia. The hip is moved to determine the range of motion in which it remains reduced. This is compared to the maximal range of motion to construct a "safe zone" (Fig. 678-10). An arthrogram obtained at the time of reduction is very helpful for evaluating the depth and stability of the reduction (Fig. 678-11). The reduction is maintained in a well-molded spica cast, with the "human position" of moderate flexion and abduction being the preferred position. After the procedure, single-cut CT or MRI may be used to confirm the reduction. Twelve weeks after closed reduction, the plaster cast is removed; an abduction orthosis is often used at this point to encourage further remodeling of the acetabulum. Failure to obtain a stable hip with a closed reduction indicates the need for an **open reduction**. In patients younger than 2 yr of age, a secondary acetabular or femoral procedure is rarely required. The potential for acetabular development after closed or open reduction is excellent and continues for 4-8 yr after the procedure.

Children Older Than 2 Years

Children 2-6 yr of age with a hip dislocation usually require an open reduction. In this age group, a concomitant femoral shortening osteotomy is often performed to reduce the pressure on the proximal femur and minimize the risk of osteonecrosis. Because the potential for acetabular development is markedly diminished in these older children, a pelvic osteotomy is usually performed in conjunction with the open reduction. Postoperatively, patients are immobilized in a spica cast for 6-12 wk.

COMPLICATIONS

The most important complication of DDH is **avascular necrosis** of the femoral epiphysis. Reduction of the femoral head under pressure or in extreme abduction can result in occlusion of the epiphyseal vessels and produce either partial or total infarction of the epiphysis. Revascularization soon follows, but if the physis is severely damaged, abnormal growth and development can occur. The hip is most vulnerable to this complication before 4-6 mo, when the ossific nucleus appears. Management, as previously outlined, is designed to minimize this complication. With appropriate treatment, the incidence of avascular necrosis for DDH is reduced to 5-15%. Other complications in DDH include redislocation, residual subluxation, acetabular dysplasia, and postoperative complications, including wound infections.

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678.2 Transient Monoarticular Synovitis (Toxic Synovitis)

Wudbhav N. Sankar, B. David Horn, Lawrence Wells, and John P. Dormans

Transient synovitis (toxic synovitis) is a reactive arthritis and is one of the most common causes of hip pain in young children.

ETIOLOGY

The cause of transient synovitis remains unknown. It has been variously described as a nonspecific inflammatory condition or as a postviral immunologic synovitis because it tends to follow recent viral illnesses.

CLINICAL MANIFESTATIONS

Although transient synovitis can occur in all age groups, it is most prevalent in children between 3 and 8 yr of age, with a mean onset at age 6 yr. Approximately 70% of all affected children have had a nonspecific upper respiratory tract infection 7-14 days before the onset of symptoms. Symptoms often develop acutely and usually consist of pain in the groin, anterior thigh, or knee, which may be referred from the hip. These children are usually able to bear weight on the affected limb and typically walk with a painful, limping gait. The hip is not held flexed, abducted, or laterally rotated unless a significant effusion is present. They are often afebrile or have a low-grade fever <38°C (100.4°F).

DIAGNOSIS

Transient synovitis is a clinical diagnosis, but laboratory and radiographic tests can be useful to rule out other more serious conditions. In transient synovitis, infection labs (erythrocyte sedimentation rate, serum C-reactive protein, and white blood cell counts) are relatively normal, but on occasion a mild elevation in the erythrocyte sedimentation rate is observed. AP and Lauenstein (frogleg) lateral radiographs of the pelvis may be acquired and are also usually found to be normal. Ultrasonography of the hip is preferred to x-rays and often demonstrates a joint effusion.

The most important condition to exclude before confirming a diagnosis of toxic synovitis is septic arthritis. Children with septic arthritis usually appear more systemically ill than those with transient synovitis. The pain associated with septic arthritis is more severe, and children often refuse to walk or move their hip at all. High fever, refusal to walk, and elevations of the erythrocyte sedimentation rate, serum C-reactive protein, and white blood cell count all point toward a diagnosis of septic arthritis. If the clinical scenario is suspicious for septic arthritis, an ultrasound-guided aspiration of the hip joint should be performed to make the definitive diagnosis (see Chapter 685). An exception to these criteria is hip septic arthritis due to *Kingella kingae*, which may have minimal inflammation and low grade or no fever (see Chapter 685). MRI may be needed to detect an associated osteomyelitis.

TREATMENT

The treatment of transient monoarticular synovitis of the hip is symptomatic. Recommended therapies include activity limitation and relief of weight bearing until the pain subsides. Antiinflammatory agents and analgesics can shorten the duration of pain. Most children recover completely within 3-6 wk.

Bibliography is available at Expert Consult.

678.3 Legg-Calvé-Perthes Disease

Wudbhav N. Sankar, B. David Horn, Lawrence Wells, and John P. Dormans

Legg-Calvé-Perthes disease (LCPD) is a hip disorder of unknown etiology that results from temporary interruption of the blood supply to the proximal femoral epiphysis, leading to osteonecrosis and femoral head deformity.

ETIOLOGY

Although the underlying etiology remains obscure, most authors agree that the final common pathway in the development of LCPD is disruption of the vascular supply to the femoral epiphysis, which results in ischemia and osteonecrosis. Infection, trauma, and transient synovitis have all been proposed as causative factors but are unsubstantiated. Factors leading to thrombophilia, an increased tendency to develop thrombosis and hypofibrinolysis, and a reduced ability to lyse thrombi have been identified. Factor V Leiden mutation, deficiency of proteins C and S, lupus anticoagulant, anticardiolipin antibodies, antitrypsin, and plasminogen activator might play a role in the abnormal clotting mechanism. These abnormalities in the clotting cascade are thought to increase blood viscosity and the risk for venous thrombosis. Poor venous outflow leads to increased intraosseous pressure, which, in turn, impedes arterial inflow, causing ischemia and cell death.

EPIDEMIOLOGY

The incidence of LCPD in the United States is 1 in 1,200 children with boys 4-5 times more likely to be affected than girls. The peak incidence of the disease is between the ages of 4 and 8 yr. Bilateral involvement is seen in approximately 10% of the patients, but the hips are usually in different stages of collapse. East Asians have the lowest incidence of the disease and whites the highest.

PATHOGENESIS

Early pathologic changes in the femoral head are the result of ischemia and necrosis; subsequent changes result from the repair process. The disease course may have 4 stages, although variations have been described. The **initial** stage of the disease, which often lasts 6 mo, is characterized by synovitis, joint irritability, and early necrosis of the femoral head. Revascularization then leads to osteoclastic-mediated resorption of the necrotic segment. The necrotic bone is replaced by fibrovascular tissue rather than new bone, which compromises the structural integrity of the femoral epiphysis. The second stage is the **fragmentation** stage, which typically lasts 8 mo. During this stage, the femoral epiphysis begins to collapse, usually laterally, and begins to extrude from the acetabulum. The **healing** stage, which lasts approximately 4 yr, begins with new bone formation in the subchondral region. Reossification begins centrally and expands in all directions. The degree of femoral head deformity depends on the severity of collapse and the amount of remodeling that occurs. The final stage is the **residual** stage, which begins after the entire head has reossified. A mild amount of remodeling of the femoral head still occurs until the child reaches skeletal maturity. LCPD often damages the proximal femoral physis leading to a short neck (coxa breva) and trochanteric overgrowth.

CLINICAL MANIFESTATIONS

The most common presenting symptom is a limp of varying duration. Pain, if present, is usually activity related and may be localized in the groin or referred to the anteromedial thigh or knee region. *Failure to recognize that thigh or knee pain in a child may be secondary to hip pathology can cause further delay in the diagnosis.* Less commonly, the onset of the disease may be much more acute and may be associated with a failure to ambulate.

Antalgic gait (a limp characterized by a shortening of gait phase on the injured side to alleviate weight-bearing pain) may be particularly prominent after strenuous activity at the end of the day. Hip motion, primarily internal rotation and abduction, is limited. Early in the course of the disease, the limited abduction is secondary to synovitis and muscle spasm in the adductor group; however, with time and the subsequent deformities that can develop, the limitation of abduction can become permanent. A mild hip flexion contracture of 10-20 degrees may be present. Atrophy of the muscles of the thigh, calf, or buttock from disuse secondary to pain may be evident. An apparent leg-length inequality may be caused by an adduction contracture or true shortening on the involved side from femoral head collapse.

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DIAGNOSIS

Routine plain radiographs are the primary diagnostic tool for LCPD. AP and Lauenstein (frogleg) lateral views are used to diagnose, stage, provide prognosis for, and follow the course of the disease (Fig. 678-12). It is important when evaluating disease progression that all radiographs be viewed sequentially and compared with previous radiographs to assess the stage of the disease and to determine the true extent of epiphyseal involvement.

In the initial stage of LCPD, the radiographic changes include a decreased size of the ossification center, lateralization of the femoral head with widening of the medial joint space, a subchondral fracture, and physeal irregularity. In the fragmentation stage, the epiphysis appears fragmented, and there are scattered areas of increased radiolucency and radiodensity. During the reossification stage, the bone density returns to normal by new (woven) bone formation. The residual stage is marked by the reossification of the femoral head, gradual remodeling of head shape until skeletal maturity, and remodeling of the acetabulum.

In addition to these radiographic changes, several classic radiographic signs have been reported that describe a "head at risk" for severe deformity. Lateral extrusion of the epiphysis, a horizontal physis, calcification lateral to the epiphysis, subluxation of the hip, and a radiolucent horizontal V in the lateral aspect of the physis (Gage's sign) are all associated with a poor prognosis.

In the absence of changes on plain radiographs, particularly in the early stages of the disease, MRI is useful to diagnose early infarction and determine the degree of impaired perfusion. During the remodeling or residual stages, MRI is extremely helpful to define the abnormal anatomy and determine the extent of intra-articular injury. Arthrography can be useful to dynamically assess the shape of the femoral head, demonstrate whether a hip can be contained, and diagnose hinge abduction. Table 678-1 outlines the differential diagnosis.

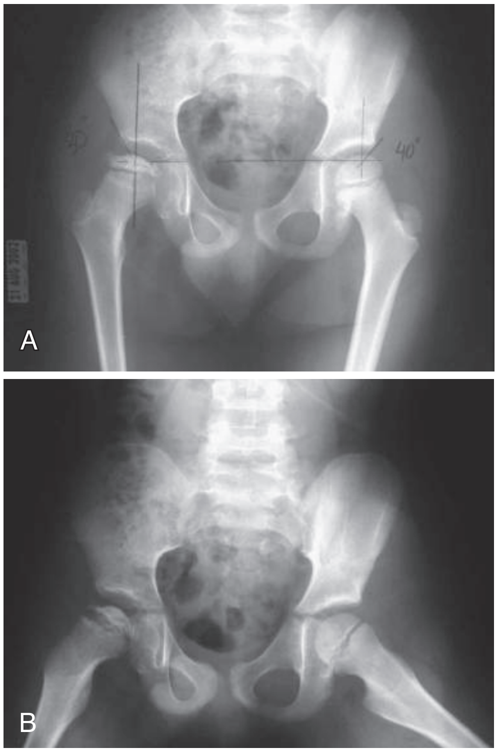

Figure 678-12 **A,** Anteroposterior radiograph of the pelvis shows epiphyseal fragmentation in the right hip, characteristic of the fragmentation phase of Legg-Calvé-Perthes disease. **B,** The frogleg lateral view demonstrates subchondral fracture, increased density of the femoral head, and some collapse.

CLASSIFICATION

Catterall proposed a 4-group classification based on the amount of femoral epiphysis involvement and a set of radiographic "head at-risk" signs. Group I hips have anterior femoral head involvement of 25%, no sequestrum (an island of dead bone within the epiphysis), and no metaphyseal abnormalities. Group II hips have up to 50% involvement and a clear demarcation between involved and uninvolved segments. Metaphyseal cysts may be present. Group III hips display up to 75% involvement and a large sequestrum. In group IV, the entire femoral head is involved. Use of the Catterall classification system has been limited because of a high degree of interobserver variability.

The **Herring lateral pillar classification** is the most widely used radiographic classification system for determining treatment and prognosis during the active stage of the disease (Fig. 678-13). Unlike the Catterall system, the Herring classification has a high degree of interobserver reliability. Classification is based on several radiographs taken during the early fragmentation stage. The lateral pillar classification system for LCPD evaluates the shape of the femoral head epiphysis on AP radiograph of the hip. The head is divided into 3 sections or pillars. The lateral pillar occupies the lateral 15-30% of the head width, the central pillar is approximately 50% of the head width, and the medial pillar is 20-35% of the head width. The degree of involvement of the lateral pillar can be subdivided into 3 groups. In group A, the lateral pillar is radiographically normal. In group B, the lateral pillar has some lucency but >50% of the lateral pillar height is maintained. In group C, the lateral pillar is more lucent than in group B and <50% of the pillar height remains. Herring has added a B/C border group to the

Table 678-1 Differential Diagnosis of Legg-Calvé-Perthes Disease
OTHER CAUSES OF AVASCULAR NECROSIS
Sickle cell disease
Other hemoglobinopathies (e.g., thalassemia)
Chronic myelogenous leukemia
Steroid medication
Sequela of traumatic hip dislocation
Treatment of developmental dysplasia of the hip
Septic arthritis
EPIPHYSEAL DYSPLASIAS
Multiple epiphyseal dysplasia
Spondyloepiphyseal dysplasia
Mucopolysaccharidoses
Hypothyroidism
OTHER SYNDROMES
Osteochondromatosis
Metachondromatosis
Schwartz-Jampel syndrome
Trichorhinophalangeal syndrome
Maroteaux-Lamy syndrome
Martsolf syndrome

(From Kim HKW, Herring JA: Legg-Calvé-Perthes Disease. In Herring JA, editor: Tachdjian's pediatric orthopaedics, *ed 5. Philadelphia, 2014, WB Saunders, Box 17-6, p. 613.)*

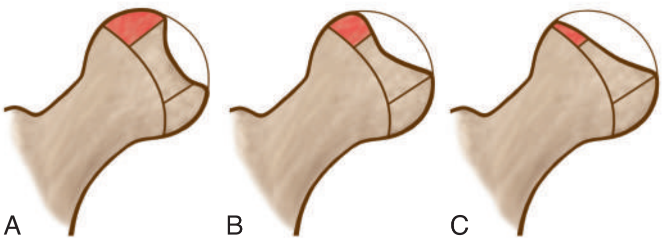

Figure 678-13 Lateral pillar classification for Legg-Calvé-Perthes disease. **A,** There is no involvement of the lateral pillar. **B,** More than 50% of the lateral pillar height is maintained. **C,** Less than 50% of the lateral pillar height is maintained.

classification system to describe patients with approximately 50% collapse of the lateral pillar.

NATURAL HISTORY AND PROGNOSIS

Children who develop signs and symptoms of LCPD before the age of 6 yr tend to recover with fewer residual problems. Patients older than 9 yr of age at presentation usually have a poor prognosis. The reason for this difference is that the remodeling potential of the femoral head is higher in younger children. Greater extent of femoral head involvement and duration of the disease process are additional factors associated with a poor prognosis. Hips classified as Catterall groups III and IV and lateral pillar group C generally have a poor prognosis.

TREATMENT

The goal of treatment in LCPD is preservation of a spherical, well-covered femoral head and maintenance of hip range of motion that is close to normal. Although the treatment of LCPD remains controversial, most authors agree that the general approach to these patients should be guided by the principle of containment. This principle is predicated on the fact that while the femoral head is fragmenting, and therefore in a softened condition, it is best to contain it entirely within the acetabulum; by doing so, the acetabulum acts as a mold for the regenerating femoral head. Conversely, failure to contain the head permits it to deform, with resulting extrusion and impingement on the lateral edge of the acetabulum. To be successful, containment must be instituted early while the femoral head is still moldable; once the head has healed, repositioning the femoral epiphysis will not aid remodeling and can, in fact, worsen symptoms.

Initial options to manage symptoms include activity limitation, protected weightbearing, and nonsteroidal antiinflammatory medications. "Nonoperative" containment can be achieved by using a Petrie cast to restore abduction and to direct the femoral head deeper into the acetabulum. Petrie casts are 2 long-leg casts that are connected by a bar and can be helpful to keep the hips in abduction and internal rotation (the best position for containment). Casting is generally done in conjunction with an arthrogram to confirm containment and a tenotomy of the adductor tendons. After 6 wk, patients can be transitioned into an abduction orthosis with limited weightbearing. Several older studies did not support the efficacy of casting and long-term bracing as a means of containment, but a subsequent large series reported excellent results with this form of treatment.

Surgical containment may be approached from the femoral side, the acetabular side, or both sides of the hip joint. A varus osteotomy of the proximal femur is the most common procedure. Pelvic osteotomies in LCPD are divided into 3 categories: acetabular rotational osteotomies, shelf procedures, and medial displacement or Chiari osteotomies. Any of these procedures can be combined with a proximal femoral varus osteotomy when severe deformity of the femoral head cannot be contained by a pelvic osteotomy alone.

After healing of the epiphysis, surgical treatment shifts from containment to managing the residual deformity. Patients with hinge abduction or joint incongruity might benefit from a valgus-producing proximal femoral osteotomy. Coxa breva and overgrowth of the greater trochanter can be managed by performing an advancement of the trochanter. This helps restore the length–tension relationship of the abductor mechanism and can alleviate abductor fatigue. Patients with femoroacetabular impingement from irregularity of the femoral head can often be helped with an osteoplasty or cheilectomy of the offending prominence.

Bibliography is available at Expert Consult.

678.4 Slipped Capital Femoral Epiphysis

Wudbhav N. Sankar, B. David Horn, Lawrence Wells, and John P. Dormans

Slipped capital femoral epiphysis (SCFE) is a hip disorder that affects adolescents, most often between 10 and 16 yr of age, and involves failure of the physis and displacement of the femoral head relative to the neck.

CLASSIFICATION

SCFEs may be classified temporally, according to onset of symptoms (acute, chronic, acute-on-chronic); functionally, according to patient's ability to bear weight (stable or unstable); or morphologically, as the extent of displacement of the femoral epiphysis relative to the neck (mild, moderate, or severe), as estimated by measurement on radiographic or CT images.

An **acute** SCFE is characterized as one occurring in a patient who has prodromal symptoms for ≤3 wk and should be distinguished from a purely traumatic separation of the epiphysis in a previously normal hip (a true Salter-Harris type I fracture; see Chapter 683). The patient with an acute slip usually has some prodromal pain in the groin, thigh, or knee, and usually reports a relatively minor injury (a twist or fall) that is not sufficiently violent to produce an acute fracture of this severity.

Chronic SCFE is the most common form of presentation. Typically, an adolescent presents with a few-month history of vague groin, thigh, or knee pain and a limp. Radiographs show a variable amount of posterior and inferior migration of the femoral epiphysis and remodeling of the femoral neck in the same direction.

Children with **acute-on-chronic** SCFE can have features of both acute and chronic conditions. Prodromal symptoms have been present for >3 wk with a sudden exacerbation of pain. Radiographs demonstrate femoral neck remodeling and further displacement of the capital epiphysis beyond the remodeled point of the femoral neck.

The stability classification separates patients based on their ability to ambulate and is more useful in predicting prognosis and establishing a treatment plan. The SCFE is considered **stable** when the child is able to walk with or without crutches. A child with an **unstable** SCFE is unable to walk with or without walking aids. Patients with unstable SCFE have a much higher prevalence of osteonecrosis (up to 50%) compared to those with stable SCFE (nearly 0%). This is most likely because of the vascular injury caused at the time of initial displacement.

SCFE may also be categorized by the degree of displacement of the epiphysis on the femoral neck. The head-shaft angle difference is <30 degrees in mild slips, between 30 and 60 degrees in moderate slips, and >60 degrees in severe slips, compared to the normal contralateral side.

ETIOLOGY AND PATHOGENESIS

SCFEs are most likely caused by a combination of mechanical and endocrine factors. The plane of cleavage in most SCFEs occurs through the hypertrophic zone of the physis. During normal puberty, the physis becomes more vertically oriented, which converts mechanical forces from compression to shear. In addition, the hypertrophic zone becomes elongated in pubertal adolescents due to high levels of circulating hormones. This widening of the physis decreases the threshold for mechanical failure. Normal ossification depends on a number of different factors, including thyroid hormone, vitamin D, and calcium. Consequently, it is not surprising that SCFEs occur with increased incidence in children with medical disorders such as hypothyroidism, hypopituitarism, and renal osteodystrophy. Obesity, one of the largest risk factors for SCFE, affects both the mechanical load on the physis and the level of circulating hormones. The combination of mechanical and endocrine factors results in gradual failure of the physis, which allows posterior and inferior displacement of the head in relation to the femoral neck.

EPIDEMIOLOGY

The annual incidence of SCFE is 2 per 100,000 in the general population. Incidence has ranged from 0.2 per 100,000 in eastern Japan to 10.08 per 100,000 in the northeastern United States. The African-American and Polynesian populations are reported to have an increased incidence of SCFE. Obesity is the most closely associated risk factor in the development of SCFE; approximately 65% of the patients are >90th percentile in weight-for-age profiles. There is a predilection for boys to

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Figure 678-14 Progressive external rotation noted with flexion: the knee-axilla sign.

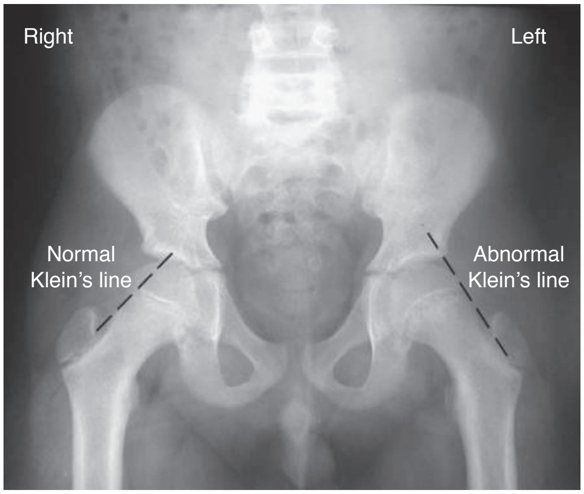

Figure 678-15 Illustration of Klein's line.

be affected more often than girls and for the left hip to be affected more often than the right. Bilateral involvement has been reported in as many as 60% of cases, nearly half of which may be present at the time of initial presentation.

CLINICAL MANIFESTATIONS

The classic patient presenting with a SCFE is an obese, African-American boy between the ages of 11 and 16 yr. Girls present earlier, usually between 10 and 14 yr of age. Patients with chronic and stable SCFEs tend to present after weeks to months of symptoms. Patients usually limp to some degree and have an externally rotated lower extremity. Physical examination of the affected hip reveals a restriction of internal rotation, abduction, and flexion. Commonly, the examiner notes that as the affected hip is flexed, the thigh tends to rotate progressively into more external rotation with increased flexion (Fig. 678-14). Most patients complain of groin symptoms, but isolated thigh pain or knee pain is a common presentation from referred pain along the course of the obturator nerve. Missed or delayed diagnosis often occurs in children who present with knee pain and do not receive appropriate imaging of the hip. Patients with unstable SCFEs usually present in an urgent fashion. Children typically refuse to allow any range of motion of the hip; much like a hip fracture, the extremity is shortened, abducted, and externally rotated.

DIAGNOSTIC STUDIES

AP and frogleg lateral radiographic views of both hips are usually the only imaging studies needed to make the diagnosis. Because approximately 25% of patients have a contralateral slip on initial presentation, it is critical that both hips be carefully evaluated by the treating physician. Radiographic findings include widening and irregularity of the physis, a decrease in epiphyseal height in the center of the acetabulum, a crescent-shaped area of increased density in the proximal portion of the femoral neck, and the "blanch sign of Steel" corresponding to the double density created from the anteriorly displaced femoral neck overlying the femoral head. In an unaffected patient, Klein's line, a straight line drawn along the superior cortex of the femoral neck on the AP radiograph, should intersect some portion of the lateral capital femoral epiphysis. With progressive displacement of the epiphysis, Klein's line no longer intersects the epiphysis (Fig. 678-15). Although some of these radiographic findings can be subtle, most diagnoses can be readily made on the frogleg lateral view, which reveals the characteristic posterior and inferior displacement of the epiphysis in relation to the femoral neck (Fig. 678-16).

TREATMENT

Once the diagnosis is made, the patient should be admitted to the hospital immediately and placed on bed rest. Allowing the child to go home without definitive treatment increases the risk that a stable SCFE will become an unstable SCFE and that further displacement will occur. Children with atypical presentations (younger than 10 yr of age, thin body habitus) should have screening labs sent to rule out an underlying endocrinopathy.

The goal of treatment is to prevent further progression of the slip and to stabilize (i.e., close) the physis. Although various forms of treatment have been used in the past, including spica casting, the current gold standard for the treatment of SCFE is in situ pinning with a single, large screw (Fig. 678-17). The term *in situ* implies that no attempt is made to reduce the displacement between the epiphysis and femoral neck because doing so increases the risk of osteonecrosis. Screws are typically placed percutaneously under fluoroscopic guidance. Postoperatively, most patients are allowed partial weightbearing with crutches for 4-6 wk, followed by a gradual return to normal activities. Patients should be monitored with serial radiographs to be sure that the physis is closing and that the slip is stable. After healing from the initial stabilization, patients with severe residual deformity may be candidates for proximal femoral osteotomy to correct the deformity, reduce impingement, and improve range of motion.

Because 20-40% of children will develop a contralateral SCFE at some point, many orthopedists advocate prophylactic pin fixation of the contralateral (normal) side in patients with a unilateral SCFE. The benefits of preventing a possible slip must be balanced with the risks of performing a potentially unnecessary surgery. Several recent studies have attempted to analyze decision models for prophylactic pinning, but controversy remains regarding the optimal course of treatment.

COMPLICATIONS

Osteonecrosis and chondrolysis are the 2 most serious complications of SCFE. Osteonecrosis, or avascular necrosis, usually occurs as a result of injury to the retinacular vessels. This can be caused by an initial force of injury, particularly in unstable slips, forced manipulation of an acute or unstable SCFE, compression from intracapsular hematoma, or as a direct injury during surgery. Partial forms of osteonecrosis can also appear following internal fixation; this can be caused by a disruption of the intraepiphyseal blood vessels. Chondrolysis, on the other

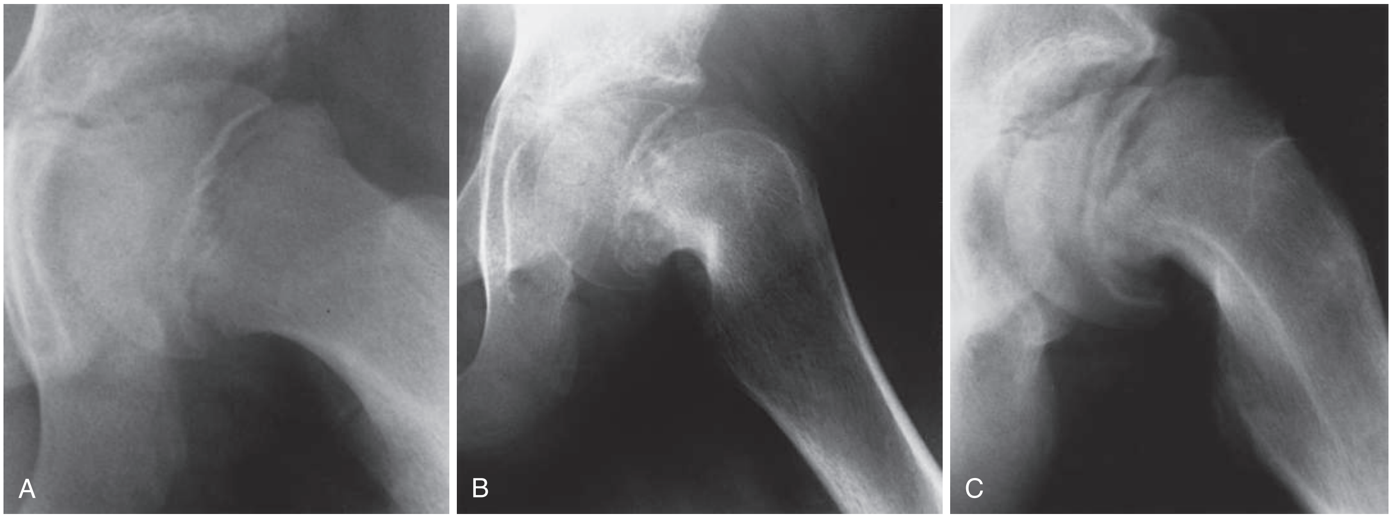

Figure 678-16 **Radiographic appearance of slipped capital femoral epiphysis (SCFE) on presentation. A,** Appearance of acute SCFE on a frogleg lateral view. The displacement of the epiphysis is suggestive of a Salter-Harris type I fracture of the upper femoral physis. There are no secondary adaptive changes noted in the femoral neck. **B,** Frogleg lateral radiographs in a patient with many months of thigh discomfort and a chronic slipped epiphysis. Adaptive changes in the femoral neck predominate, and the epiphysis is centered on the adapted femoral neck. **C,** Frogleg lateral radiographs of a patient with acute-on-chronic SCFE. The patient had several months of vague thigh pain, with sudden, severe exacerbation of that pain. The acute displacement of the epiphysis is evident. Unlike in acute SCFE (see **A**), secondary adaptive remodeling changes are also present in the femoral neck, beyond which the epiphysis has acutely displaced. *(From Herring JA: Slipped capital femoral epiphysis. In Herring JA, editor:* Tachdjian's pediatric orthopaedics*, ed 5, Philadelphia, 2014, WB Saunders, Fig. 18-1, p. 632.)*

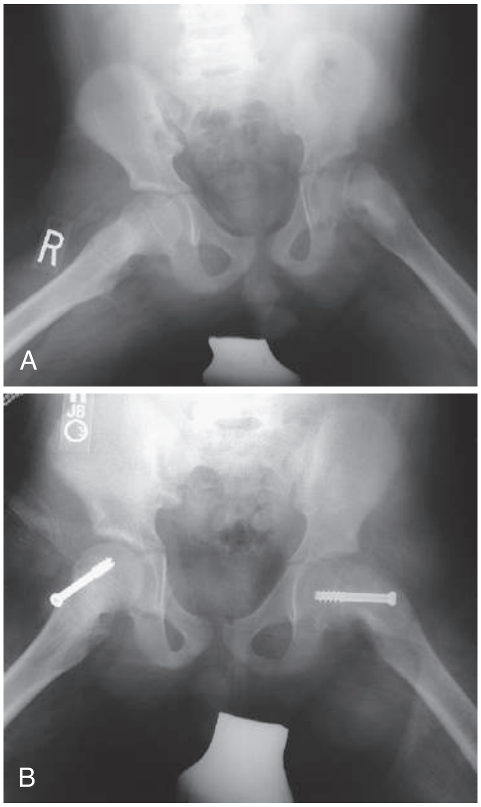

Figure 678-17 Preoperative **(A)** and postoperative **(B)** radiographs demonstrating the in situ pinning in a case of slipped capital femoral epiphysis.

hand, is an acute dissolution of articular cartilage in the hip. There are no clear causes of this complication, but it is believed to be associated with more-severe slips, to occur more commonly among African-Americans and girls, and to be associated with pins or screws protruding out of the femoral head.

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Chapter 679

The Spine

R. Justin Mistovich and David A. Spiegel

Abnormalities of the spine can result from a variety of causes including congenital, developmental, and traumatic. In addition to spinal deformities, back pain has become increasingly prevalent in childhood and adolescence, and a thoughtful diagnostic evaluation is required to establish the diagnosis while minimizing the overutilization of healthcare resources. The most common deformities are scoliosis and kyphosis. An early diagnosis is important, as a subset of patients may be candidates for "preventive" strategies such as bracing. Early intervention may potentially reduce the number requiring surgery, or at least reduce the magnitude or risks if surgical treatment is required.

Scoliosis may be from congenital bony deformities, may be idiopathic, including infantile, juvenile, or adolescent idiopathic scoliosis, or may be associated with a variety of underlying conditions, including neuromuscular diseases, connective tissue diseases, and genetic

Table 679-1 Classification of Spinal Deformities

SCOLIOSIS	*Myopathies*
Idiopathic	Duchenne muscular dystrophy
Infantile	Arthrogryposis
Juvenile	Other muscular dystrophies
Adolescent	*Syndromes*
Congenital	Neurofibromatosis
Failure of formation	Marfan syndrome
Wedge vertebrae	*Compensatory*
Hemivertebrae	Leg-length discrepancy
Failure of segmentation	KYPHOSIS
Unilateral bar	Postural kyphosis (flexible)
Block vertebra	Scheuermann disease
Mixed	Congenital kyphosis
Neuromuscular	Failure of formation
Neuropathic diseases	Failure of segmentation
Upper motor neuron	Mixed
Cerebral palsy	
Spinocerebellar degeneration (Friedreich ataxia, Charcot-Marie-Tooth disease)	
Syringomyelia	
Spinal cord tumor	
Spinal cord trauma	
Lower motor neuron	
Poliomyelitis	
Spinal muscular atrophy	

Adapted from the Terminology Committee, Scoliosis Research Society: A glossary of scoliosis terms. Spine (Phila Pa 1976) *1:57, 1976.*

syndromes (Table 679-1). The pediatrician is often the first to diagnose these conditions. A familiarity with the physical examination, as well as the natural history and treatment options, will help the pediatrician to not only establish an early diagnosis but also to provide basic counseling for the patient and family regarding the diagnosis, general prognosis, and whether any referral and/or further workup might be indicated.

While parents and families are primarily concerned about the resulting cosmetic abnormalities, the physician diagnosing a patient with a spine deformity must carefully consider both the potential for underlying causes requiring treatment and the patient's long-term prognosis. If a certain curve magnitude is crossed in a patient with adolescent idiopathic scoliosis, the curve will be likely to continue to progress in adulthood and may require surgical treatment. Progressive curvatures in the neuromuscular population may result in respiratory insufficiency in addition to a loss of sitting balance. Additionally, while the majority of patients with excessive thoracic kyphosis have benign flexible curves and require no active treatment, a subset will have a progressive or rigid deformity which may require treatment. Parents and the patient must have an understanding of the deformity, how it may progress, and potential complications associated with the diagnosis. Table 679-1 presents a classification of common spinal abnormalities.

NORMAL SPINAL CURVATURES

The spine has curvatures that are anatomically normal in the lateral (sagittal) plane. Cervical lordosis (convex anteriorly), thoracic kyphosis (convex posteriorly), and lumbar lordosis regions are biomechanically advantageous as they maintain relationships of the body relative to the forces of gravity, which is important for balance. These curvatures also help to conserve energy by minimizing the amount of muscular activity required to maintain an upright posture.

Abnormalities affecting these normal curvatures, termed *sagittal plane imbalances*, can be measured on a sagittal spine radiograph. A vertical line, or *plumb line*, drawn from the center of the 7th cervical vertebra should normally fall through the posterosuperior corner of the sacrum. Disorders affecting sagittal alignment include thoracic hyperkyphosis and lumbar hyperlordosis. Although scoliosis is a 3-dimensional deformity, it is most commonly described as a lateral curvature of the spine in the frontal (coronal) plane.

679.1 Idiopathic Scoliosis

R. Justin Mistovich and David A. Spiegel

DEFINITION

The word *scoliosis* takes its origin from the Greek word *skolios*, meaning bent or curved. Medically recognized for centuries, Hippocrates described scoliosis in his treatise *On Articulations*. Scoliosis is a complex 3-dimensional spinal deformity that is defined in the coronal plane as a curve of at least 10 degrees, measured by the Cobb method, on a **posteroanterior (PA)** radiograph of the spine. The deformity also includes rotation of the vertebrae and also malalignment in the sagittal plane, such as a segmental apical lordosis in thoracic curves.

ETIOLOGY

The etiology of idiopathic scoliosis remains unknown; it is likely that the cause is multifactorial with genetic, hormonal, cellular, anatomic, and functional contributions.

A genetic link has been proposed with sex-linked dominant, autosomal dominant and polygenetic inheritance patterns all suggested. Genetic involvement has been substantiated in studies of twins, demonstrating a 73% concordance rate for **adolescent idiopathic scoliosis (AIS)** in monozygotic twins compared to a 36% concordance rate in dizygotic twins.

AIS is 2-10 times more common in females than males. Investigators have attempted to explain this difference as a genetic effect: It has been hypothesized that males are not as susceptible to the involved genes as females. Therefore, affected males must inherit a larger number of susceptibility genes to have a scoliosis phenotype. Males would pass more susceptibility genes onto their children and would therefore have more affected children. This polygenetic prediction is known as the Carter effect; fathers with AIS *transmit* the disease to 80% of their children, but mothers with AIS *transmit* the disease to only 56% of their children.

Certain polymorphisms in the estrogen receptor gene are linked to an increased curve progression and higher risk of requiring operative treatment. Genetic analysis may also be able to determine curve progression, although data concerning the effectiveness and validity of this are limited.

Endocrine factors may have a possible role in the disease pathology. Lower plasma melatonin levels have been noted in patients with progressive curvatures. Abnormal levels of growth hormone and insulin-like growth factor-1 have also been discovered. Leptin, the hormone responsible for satiety, is found at lower levels in patients with AIS.

Cellular structures may be involved in the disease process. Calmodulin, a regulator of the contractile properties of muscle, occurs at increased levels in the platelets of patients with progressive AIS.

MRI studies of the brain in patients with AIS have found that the cerebellum of affected patients is hypertrophied in areas involving the somatosensory tracts, motor control, and response to visual stimulation. These areas of hypertrophy may be a compensation for impaired balance resulting from malalignment of the spine. Other studies have noted a decrease in regional brain volumes and white matter in the corpus callosum and internal capsule between patients affected with AIS and normal adolescents. Girls with AIS have also been noted to have a larger foramen magnum. The importance of these imaging findings remains unclear.

Functional evaluations of patients with AIS have noted abnormalities in proprioception, postural balance, somatosensory function, somatosensory evoked potentials and electromyography. Patients with AIS have differences in vestibular-evoked myogenic potentials, suggesting that otolith system dysfunction may play a role in the disease. Approximately one-third of girls with AIS have osteopenia on dual-energy x-ray absorptiometry studies, and of these, 80% will have lifelong osteopenia. Osteopenia is linked to an increased risk of curve

progression. It is nonetheless difficult to determine which findings are primary or causative, and which are secondary to the disease.

EPIDEMIOLOGY

The overall prevalence of idiopathic scoliosis in skeletally immature patients ranges from 1-3% of the population. Most curves are mild and do not require treatment, with only 0.5% greater than 20 degrees and 0.3% exceeding 30 degrees. While curves of ≤10 degrees occur equally in males and females, those requiring an intervention occur in a 7 : 1 female : male ratio.

CLASSIFICATION OF IDIOPATHIC SCOLIOSIS

Idiopathic scoliosis is classified according to the age at onset. **Infantile scoliosis** is rare, comprising 0.5-4% of all cases of idiopathic scoliosis. It describes patients with spinal curves noted from birth to 3 yr of age. Juvenile scoliosis accounts for 8-16% of cases of idiopathic scoliosis and affects children age 3-10 yr. AIS affects patients 11 yr of age and older, and comprises 70-80% of all cases of idiopathic scoliosis.

CLINICAL PRESENTATION OF IDIOPATHIC SCOLIOSIS

When evaluating a patient with a structural spinal curvature, a thorough history and physical examination are required because idiopathic scoliosis is a diagnosis of exclusion. All other potential causes, including congenital bone malformations, neuromuscular and connective tissue diseases, and tumors, must carefully be excluded.

Patients often present after a positive screening by their primary care physician, through a school screening program, or because they (or their family or friends) have noticed a cosmetic deformity. It should be noted that school screening programs have become controversial, as some authors claim that the programs do not change the outcomes of patients requiring intervention, result in unnecessary physician visits and radiographs, and are not cost-effective. The British Orthopaedic Association and the U.S. Preventive Services Task Force have both issued statements recommending against routine screening for the above reasons. However, citing the need for early identification of scoliosis to reduce the risk of operative complications common to correction of large, neglected curves, the Scoliosis Research Society, an international organization of spine surgeons, still advocates for school screening.

Back pain is not commonly a primary presenting complaint of patients with scoliosis, although when questioned, one-third of adolescents with idiopathic scoliosis will endorse some degree of back discomfort at some point in time. To keep this finding in perspective, approximately 35% of healthy adolescents complain of episodes of low back pain and discomfort. However, if a patient presents with the complaint of significant back pain associated with a curvature, the physician must perform a careful physical exam, check spinal radiographs, and evaluate for other causes of pain, including spondylosis, spondylolisthesis, tethered cords or a syrinx, herniated discs, or tumors such as osteoid osteoma or spinal cord tumor (see Chapter 679.5 below).

PHYSICAL EXAMINATION OF IDIOPATHIC SCOLIOSIS

Evaluate the patient in the standing position, from both the front and the side, to identify any asymmetry in the chest wall, trunk, and/or shoulders.

Begin the examination focusing on the back. The earliest abnormality noted on physical exam in patients with scoliosis is asymmetry of the posterior chest wall on forward bending. This test, called the Adams forward-bending test (Fig. 679-1) is performed by placing a scoliometer at the apex of the deformity with the patient bending 45 degrees forward. An inclination measuring 7 degrees or more has been suggested as the cut off for orthopaedic referral. Scoliosis is a 3-dimensional deformity. Patients develop a posterior rib hump on the convex side of the spinal curve as a result of the rotational component of the deformity. The anterior chest wall may be prominent on the concavity of the curve as a result of outward rib rotation. Other

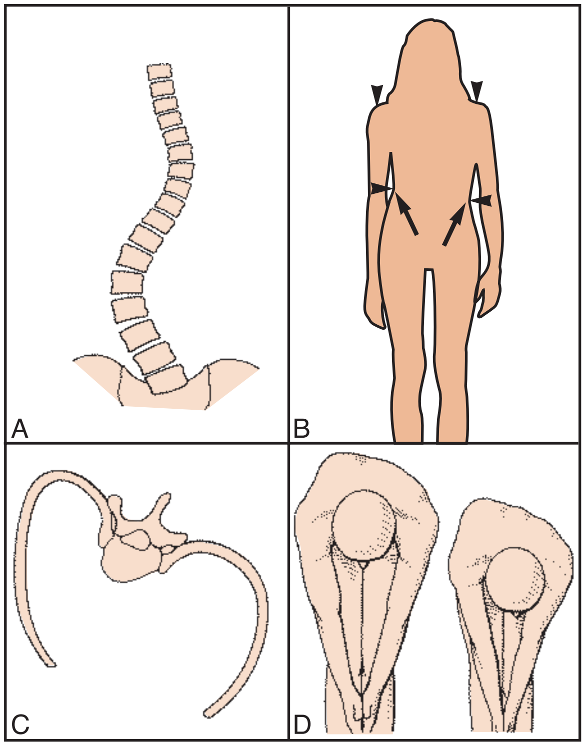

Figure 679-1 Structural changes in idiopathic scoliosis. **A,** As curvature increases, alterations in body configuration develop in both the primary and compensatory curve regions. **B,** Asymmetry of shoulder height, waistline, and elbow-to-flank distance are common findings. **C,** Vertebral rotation and associated posterior displacement of the ribs on the convex side of the curve are responsible for the characteristic deformity of the chest wall in scoliosis patients. **D,** In the school screening examination for scoliosis, the patient bends forward at the waist. Rib asymmetry of even a small degree is obvious. *(From Scoles PV: Spinal deformity in childhood and adolescence. In Behrman RE, Vaughn VC III, editors:* Nelson textbook of pediatrics, update 5, *Philadelphia, 1989, WB Saunders.)*

associated findings may include elevation of the shoulder, a lateral shift of the trunk, or an apparent leg-length discrepancy. A lumbar curve may also compensate for a primary limb-length discrepancy, with the apex toward the shorter leg.

Next, examine the patient from the side to evaluate the degree of kyphosis and lordosis. The upper thoracic spine normally has a smooth, gently rounded kyphotic curve with an apex in the midthoracic region. The cervical spine and lower lumbar spine have concave, or lordotic curves. The magnitude of these sagittal contours varies both with age and among individuals of the same age. Children have less cervical lordosis and more lumbar lordosis than do adults or adolescents. When examining a patient with idiopathic scoliosis, a common finding is a loss of the normal thoracic kyphosis, resulting in what is called a relative thoracic lordosis. A common benign finding in normal adolescent thoracic spines is a flexible roundback, or postural kyphosis. This can be corrected voluntarily when the patient extends his or her spine. This is different from sharp, abrupt, or accentuated forward angulation in the thoracic or thoracolumbar region, which is indicative of a pathologic kyphotic deformity.

The final exam component is a careful neurologic examination, as scoliosis may be associated with an underlying neurologic diagnosis. Check superficial abdominal reflexes, extremity reflexes, muscle strength, and examine for clonus. A high suspicion is necessary in patients with infantile and juvenile idiopathic scoliosis because 20% have an associated intraspinal abnormality such as a tethered spinal cord or syringomyelia. The index of suspicion for neurologic involvement is further raised in the presence of back pain or neurologic symptoms, café-au-lait spots, a sacral dimple, midline cutaneous

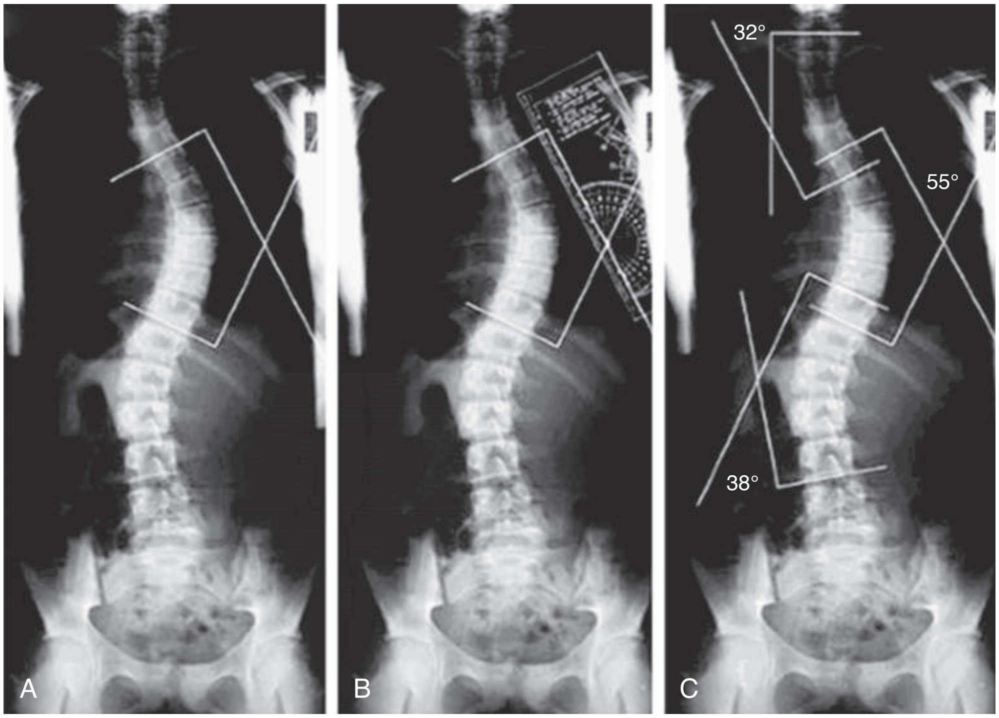

Figure 679-2 **A-C,** Cobb angles measurements. *(From Morrissy, RT, Weinstein, SL:* Lovell & Winter's pediatric orthopaedics, *ed 6, Philadelphia, 2006, Lippincott Williams & Wilkins.)*

abnormalities such as a hair patch or skin tag, or a unilateral foot deformity.

RADIOGRAPHIC EVALUATION OF IDIOPATHIC SCOLIOSIS

Standing, high-quality, PA and lateral radiographs of the entire spine are recommended at the initial evaluation for patients with clinical findings suggestive of a spinal deformity. On the PA radiograph, the degree of curvature is determined by the Cobb method, in which the angle between the superior and inferior vertebrae tilted into the curve is measured (Fig. 679-2). A line is drawn across the superior end plate of each end vertebra, and the angle between perpendicular lines drawn from each of these is measured.

Spinal MRI is indicated when there is suspicion of an underlying cause for the scoliosis, such as spinal cord abnormality based on age (infantile or juvenile curves), abnormal findings on the history and physical examination, and atypical radiographic features. Atypical radiographic findings may include certain curve patterns such as a left thoracic curve, double thoracic curves, or high thoracic curves. Other radiographic abnormalities include widening of the spinal canal and erosive or dysplastic changes in the vertebral body or ribs. On the lateral radiograph, an increase in thoracic kyphosis or an absence of segmental lordosis may be suggestive of an underlying neurologic abnormality.

NATURAL HISTORY OF IDIOPATHIC SCOLIOSIS

The decision to treat the patient is based on the natural history of idiopathic scoliosis. Uniquely, infantile idiopathic scoliosis may spontaneously resolve in 20-90% of cases. Patients with infantile scoliosis who have developmental delay, curves presenting after 1 yr of age, and larger magnitude curves are more likely to progress. A radiographic parameter called the *Mehta angle* can also be used to predict curve progression. This measurement examines the vertebra at the apex of the thoracic curve. It measures the angle formed by a line perpendicular from the vertebral end plate and a line down the center of the rib. The measurement is calculated on the convex and concave side, and the final *rib vertebral angle difference* is calculated by subtracting the convex side from the concave side. A curve with an rib vertebral angle difference <20 degrees will resolve in approximately 80% of cases, whereas a curve with an rib vertebral angle difference >20 degrees will progress in more than 80% of cases. Curves that resolve typically do so before 2 yr of age.

Several factors affect the rate of curve progression in patients with AIS. Curves are more likely to progress in patients with significant growth remaining and skeletal immaturity, meaning that the growth plates, or physes, remain open allowing for continued skeletal growth. Findings associated with significant growth remaining are younger age, premenarchal status, Tanner stage I or II, and Risser sign (a radiographic measurement of ossification of the iliac crest) of 0 or 1. Other factors affecting progression are the curve magnitude, pattern, and patient gender. There is a relationship between curve progression and 3-dimensional spinal measurements of vertebral wedging, axial rotation, and torsion, possibly allowing for better prognostication of curves at risk. In general, female patients are more likely than males to have curves that progress. Younger, premenarchal girls with curves between 20 degrees and 30 degrees have a significantly higher risk of progression than do girls 2 yr after menarche with similar curves, demonstrating the significance of age on progression. The older group is unlikely to have any progression at all while premenarchal girls with the same curve are likely to progress. Thoracic curves <30 degrees rarely progress after skeletal maturity, whereas those >45-50 degrees may progress approximately 1 degree per year through life.

Functionally, there are not many significant, clinically detrimental effects of smaller curves. Idiopathic thoracic curvatures greater than 60-70 degrees may be associated with abnormalities on pulmonary function testing, and curves of higher magnitude may cause clinically significant cardiopulmonary impairment and even cor pulmonale in severe curves. Long-term studies demonstrate that a degree of chronic back pain may be a problem for patients with scoliosis, although there is no definitive connection between pain and the curve magnitude or location. Furthermore, nearly 70% of patients with pain reported low or moderate severity of symptoms, stating that the pain does not interfere with normal activities.

TREATMENT OF IDIOPATHIC SCOLIOSIS

Brace treatment may prevent curve progression in a significant number of patients with AIS and is most successful when an early diagnosis is established. The success rate depends upon the amount of growth remaining; patients with infantile or juvenile scoliosis are much more likely to require a surgical procedure than those with AIS. Adherence with the recommended protocol for wearing the brace will influence the outcome. Although various schedules for brace wear have been reported, from 12-23 hr daily, the brace is generally worn for 16 or more hours per day, maximizing wear when the patient is upright. Adherence can be a challenge in the adolescent population. Braces are offered for treatment of skeletally immature patients with curves >30 degrees at the first visit, or in patients who are being followed and have developed progression of their curvature beyond 25 degrees. Bracing is ineffective in curvatures >45 degrees. The brace is worn until cessation of growth in males, but in females some authors will consider weaning from the brace when the patient is more than 1.5 yr postmenarchal, is a Risser 4 or greater and/or has grown less than 1 cm over the previous 6 mo.

Surgical treatment involves spinal arthrodesis or fusion and is usually recommended for skeletally immature patients with progressive curves >45 degrees and skeletally mature patients with curves >50 degrees. The goals of surgery are to arrest progression of the deformity, to improve cosmesis, and to achieve a balanced spine, all while minimizing the number of vertebral segments that are stabilized.

Implants, including pedicle screws, sublaminar wires, and hooks, are attached to 2 longitudinal rods (Fig. 679-3). These are used to apply mechanical forces to the spine, correcting the deformity in both the frontal and lateral planes. The spine is decorticated and bone graft is placed for the fusion portion of the procedure. Correction also maintains normal frontal and sagittal spinal balance. The strength of the spinal implants maintains correction without requiring a postoperative brace in the majority of cases.

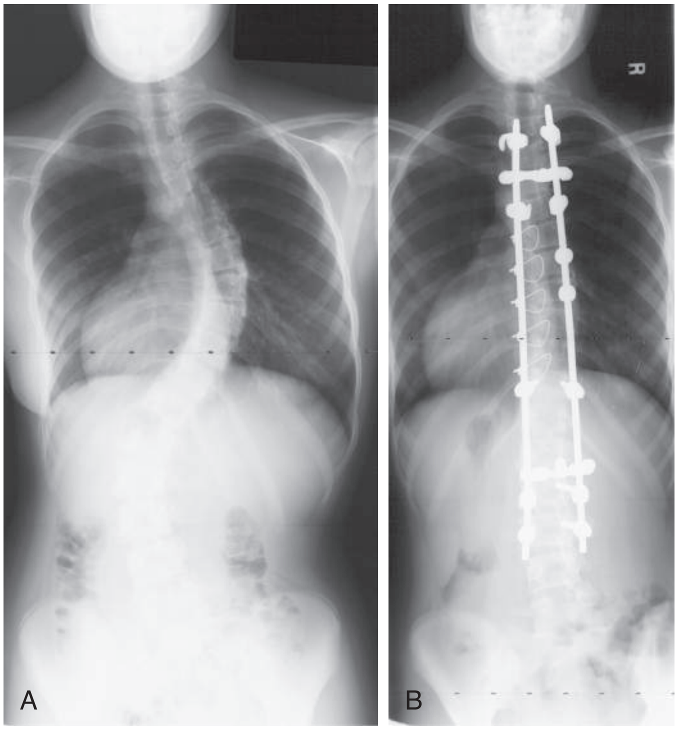

Figure 679-3 **A,** Preoperative standing posteroanterior radiograph of a 14 yr old girl who was skeletally immature and developed a 68 degree right thoracic and a 53 degree left lumbar scoliosis. Her trunk was shifted to the right, and the left shoulder was slightly depressed. **B,** Based upon the risk of future progression, she was treated by an instrumented posterior spinal fusion from T3 to L3 with correction of the right thoracic curve to 20 degrees and the left lumbar curve to 10 degrees. Coronal spinal balance was restored, and shoulder height was maintained.

Most procedures are performed posteriorly using pedicle screw fixation, which affords excellent correction, especially of the rotational component of the deformity. Posterior osteotomies are often added to enhance flexibility and improve the degree of correction in stiffer curves. Anterior spinal releases requiring a thoracotomy are performed infrequently. Open anterior thoracic and thoracolumbar procedures violate the chest wall and often the diaphragm, and pulmonary function may take up to 2 yr to return to normal values. Even though thoracoscopic techniques can be utilized to perform anterior spinal release with or without instrumentation and fusion, their use is limited. Patients with conditions such as neurofibromatosis (see Chapter 596.1) and myelomeningocele (see Chapter 591.4) have a higher likelihood of achieving a non-union of their fusion, and an anterior fusion is considered in addition to the posterior fusion in these groups. Younger patients, in whom the triradiate cartilage remain open, are at risk for crankshaft, or progressive deformity/loss of correction as a consequence of continued anterior spinal growth, after a posterior fusion. Traditionally, these patients were treated by simultaneous anterior fusion to remove the growth potential; however, the rigidity of constructs with pedicle screws negates the need for this additional surgery. For idiopathic thoracolumbar and lumbar curves, an anterior fusion with instrumentation can be considered, although the posterior approach with osteotomies and pedicle screw fixation is being used more frequently to avoid the need for anterior surgery. Posterior spinal fusion has been associated with accelerated degeneration of the unfused levels. In many, this remains asymptomatic, but the long-term effects remain unknown.

Several emerging techniques are being evaluated in the management of idiopathic scoliosis. These include new approaches to the spine, attempts to preserve remaining growth in younger patients, and even specialized treatments to save the lives of young patients with curves so significant that they result in mortality secondary to inadequate pulmonary volume. There are techniques to correct curves without limiting future growth and even to modulate spinal growth and prevent future fusion surgeries. The FDA-approved **VEPTR (vertical expandable prosthetic titanium rib)** helps young children with thoracic insufficiency syndrome caused by severe spinal curves with restrictive lung disease, often associated with a high mortality rate (see Chapter 679.2 below). The chest wall device can enlarge the thorax and correct scoliosis without adverse effect to somatic growth, likely triggering lung growth. After implantation, it is lengthened twice a year by minor surgery. Long-term survival rates are favorable for these extremely severe scoliosis patients treated by VEPTR. The device obtains and maintains correction without fusing the spine, which allows for alveolar development and maximizes trunk height prior to definitive spinal fusion.

Growing rods have also been used in young children with scoliosis. These devices have fixation points placed at the proximal and distal ends of the deformity, with expandable rods placed subcutaneously, spanning the length of the deformity. Similar to the VEPTR, growing rods require additional minor operations to lengthen the rods twice a year until skeletal maturity or definitive spinal fusion.

Intervertebral stapling is an experimental technique that attempts to dynamically modify spinal growth in immature individuals with smaller curves. Staples are placed through either an open or thoracoscopic approach across the intervertebral disk space (growth zone) on the convex side of the curve. This technique holds the spine in a corrected position and limits growth on the convex side, preventing further curvature, and achieving correction through concave growth. It remains to be seen whether this technique will play a role in the management of patients with idiopathic scoliosis.

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679.2 Congenital Scoliosis

R. Justin Mistovich and David A. Spiegel

DEFINITION

Congenital scoliosis is a spinal deformity that results from abnormal development of the bony spinal column. Asymmetric spinal growth as a result of 1 or more vertebral anomalies leads to spinal curvature. The malformation(s) is (are) present at birth but may not become clinically apparent until a later time as growth progresses.

ETIOLOGY

Although the underlying cause of congenital scoliosis remains unknown, embryologic development of the spine begins at the 5th wk of gestation. An insult to the normal developmental process occurs, resulting in abnormal growth of 1 or more vertebrae.

ASSOCIATED CONDITIONS

The developmental insult is typically not limited to the spine alone: it is extremely common for children with congenital scoliosis to have associated malformations in other organ systems, which must be ruled out. Nearly 60% of patients with congenital scoliosis have other developmental malformations.

Genitourinary abnormalities are identified in 20-40% of children with congenital scoliosis and include unilateral renal agenesis, ureteral duplication, horseshoe kidney, and genital anomalies. Approximately 2% of these patients have a silent obstructive uropathy that may be life-threatening. Renal ultrasonography should be performed early on in all children with congenital scoliosis, and other studies such as CT or MRI may also be required.

Cardiac anomalies are identified in 10-25% of patients. A careful cardiac examination should be performed. Some clinicians recommend routine echocardiography.

Intraspinal anomalies are identified in approximately 15-40% of patients. Spinal dysraphism is the general term applied to such lesions (see Chapters 591 and 606). Examples include diastematomyelia, split-cord malformations, intraspinal lipomas, arachnoid cysts, teratomas, dermoid sinuses, fibrous bands, and tight filum terminale. Cutaneous findings that may be seen in patients with closed spinal dysraphism include hair patches, skin tags or dimples, sinuses, and hemangiomas. Infants with these cutaneous abnormalities overlying the spine may benefit from ultrasonography to rule out an occult spinal dysraphic condition. MRI is indicated in infants, but in the past was delayed in older patients until a clinical indication is present, such as tethering of the spinal cord, which may present as back or leg pain, calf atrophy, progressive unilateral foot deformity (especially cavovarus), and problems with bowel or bladder function.

CLASSIFICATION OF CONGENITAL SCOLIOSIS

Congenital scoliosis is classified by the type of developmental abnormality: either a failure of formation or a failure of segmentation. The deformities are then further described by the anatomic features of the affected vertebra. Failures of formation result in wedge vertebrae or hemivertebrae. Failures of segmentation result in unilateral bars vertebrae, or block vertebrae. Lastly, some instances of congenital scoliosis result from a combination of both failure of formation and failure of segmentation (Fig. 679-4). One or more bony anomalies may occur in isolation or in combination.

NATURAL HISTORY OF CONGENITAL SCOLIOSIS

The risk of progression depends on the growth potential of each anomaly, which may vary considerably. Close radiographic follow-up is required. Progression of these curves is most pronounced during periods of rapid growth associated with the 1st 2-3 yr of life and during the adolescent growth spurt.

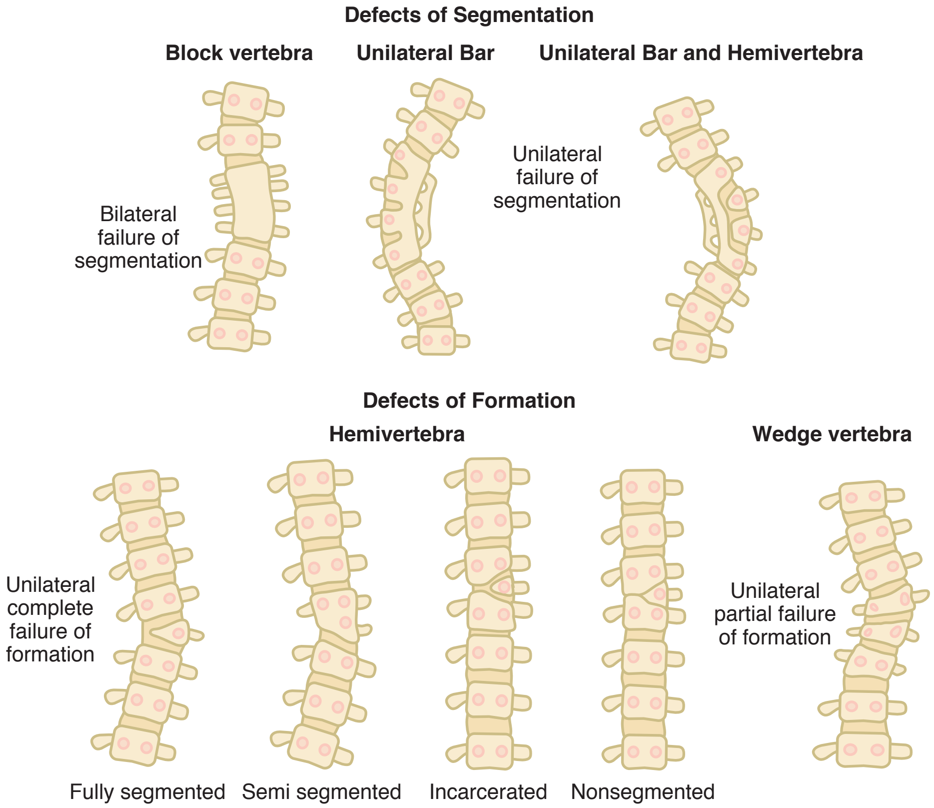

Figure 679-4 The defects of segmentation and formation that can occur during spinal development. *(From McMaster MJ: Congenital scoliosis. In Weinstein SL, editor:* The pediatric spine: principles and practice*, ed 2, Philadelphia, 2001, Lippincott Williams & Wilkins, p. 163.)*

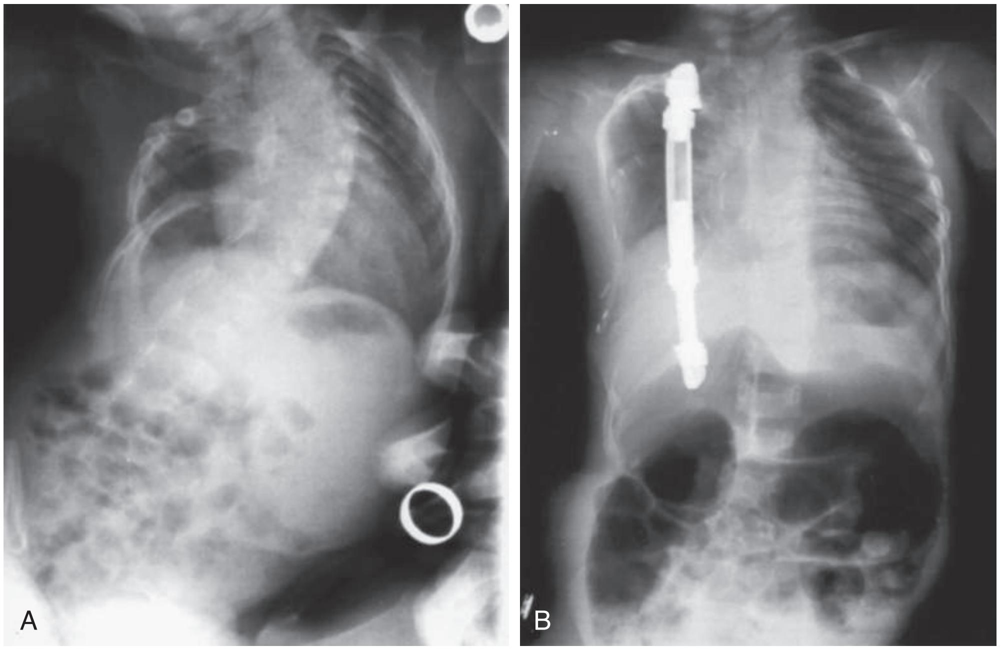

Figure 679-5 **A,** Anteroposterior preoperative radiograph of a 7 mo old boy with congenital scoliosis and fused ribs. A 3-dimensional reconstruction of a CT scan of the chest of this infant estimated his lung volume to be 173.2 mL^3. **B,** Anteroposterior radiograph after implantation of a vertically expandable prosthetic titanium rib and several expansions over 33 mo. The lung volume now measures 330.3 mL^3, an increase of 90.7%. *(From Gollogly S, Smith JT, Campbell RM: Determining lung volume with three-dimensional reconstructions of CT scan data: a pilot study to evaluate the effects of expansion thoracoplasty on children with severe spinal deformities.* J Pediatr Orthop *23:323–328, 2004.)*

The anatomic characteristics of the malformed vertebra play a significant role in the progression of deformity. The most severe form of congenital scoliosis is a unilateral unsegmented bar with a contralateral hemivertebra. In this anomaly, the spine is fused the side of the unsegmented bar but also has a growth center on the other side at the location of the hemivertebra at the same level. This combination of deformities in the bony spine results in a rapidly progressive curve. As a result, all affected patients usually require surgical stabilization. A unilateral unsegmented bar is also associated with significant progression and in most cases will require surgical intervention. An isolated hemivertebra must be followed closely, and many, but not all, of these will be associated with a progressive deformity that requires surgical intervention. In contrast, an isolated block vertebra has little growth potential and rarely requires treatment.

TREATMENT OF CONGENITAL SCOLIOSIS

Early diagnosis and prompt treatment of progressive curves are essential. Bracing is not indicated for most congenital curves because of their structural nature, except in rare cases to treat additional curves not associated with the congenital abnormality. The treatment of progressive curves is spinal fusion, or *arthrodesis*. Once a bony abnormality is identified that is likely to progress, surgery is performed before progression occurs, preventing development or further inevitable progression of spinal deformity. If the deformity has already developed, surgical correction is difficult to achieve and the risk of neurologic complications is high.

Both anterior and posterior spinal fusion is often required. Other procedures that are employed in selected patients include an isolated posterior spinal fusion. A convex hemiepiphysiodesis can be performed with certain deformities, fusing only 1 side of the spine to allow some correction of the deformity by permitting growth on the noninvolved side of the curve. Complete excision of a hemivertebra, along with fusion of a short segment of the spine, can be performed via a posterior approach and may result in better correction and spinal balance in selected cases.

It should be noted that surgery in these young, syndromic patients is not without risk. One recent study found a complication rate of nearly 85% and a mortality rate of >15% in patients who underwent operative treatment for all types of early onset scoliosis, including those with congenital scoliosis as well as other associated syndromes producing early onset scoliosis.

THORACIC INSUFFICIENCY SYNDROME

When multiple levels of the thoracic spine are involved in the presence of fused ribs, a progressive 3-dimensional deformity of the chest wall may impair lung development and function. This development is termed **thoracic insufficiency syndrome**. As a result of thoracic insufficiency syndrome, the chest wall cannot support normal respiration resulting in decreased life expectancy.

Thoracic insufficiency syndrome may be seen in patients with several recognized conditions such as Jarcho-Levin syndrome (spondylocostal or spondylothoracic dysplasia; see Chapter 108) and Jeune syndrome (asphyxiating thoracic dystrophy; see Chapter 417.3), as well as patients with severe spinal deformities. These difficult cases are being treated with a technique called *expansion thoracoplasty*, in which the thoracic cage is gradually expanded over time by progressive lengthening of the chest wall on the concavity of the spinal deformity (or in some cases on both sides of the spine). The procedure involves an opening wedge thoracostomy, followed by placement of a vertical expandable titanium prosthetic rib. The implant is then lengthened at regular intervals (Fig. 679-5). The primary goal is to gradually correct the chest wall deformity to improve pulmonary function, and a secondary goal is correction of an associated spinal deformity. This technique is currently not approved by the FDA for the treatment of scoliosis in the absence of a thoracic insufficiency, and further study will help to refine and possible expand the indications for this new technique.

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679.3 Neuromuscular Scoliosis, Genetic Syndromes, and Compensatory Scoliosis

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NEUROMUSCULAR SCOLIOSIS

Scoliosis is frequently identified in children with neuromuscular diseases such as cerebral palsy, muscular dystrophies and other myopathies, spinal muscular atrophy, Friedreich ataxia, myelomeningocele, polio, and arthrogryposis. Children with spinal cord injuries are also at high risk for a progressive curvature. The etiology and natural history of these patients differ from idiopathic and congenital scoliosis. Most cases result from weakness and/or imbalance of the trunk musculature. Spasticity may also contribute to spinal curvatures. In some cases, such as myelomeningocele, coexisting congenital vertebral anomalies may be present, further contributing to curve development.

As might be expected, neuromuscular scoliosis is most common in patients with higher degrees of neurologic impairment, usually those who are nonambulatory and may not have adequate control of their trunk. It is diagnosed in more than 70% of nonambulatory patients with cerebral palsy (see Chapter 598.1), and in more than 90% of patients with Duchenne muscular dystrophy (see Chapter 609.1).

The diagnosis is suspected on physical examination. In nonambulators, the most common curve pattern is a C-shaped thoracolumbar or lumbar curve (Fig. 679-6). This curve is typically associated with pelvic obliquity. In contrast, ambulatory patients with diagnoses such as Friedreich ataxia may have curve patterns more similar to idiopathic scoliosis.

In ambulatory patients, the examination is similar to the previously described physical examination for idiopathic scoliosis. In nonambulators, the back is inspected with the patient sitting upright. Any asymmetry should be noted. These patients often need manual support to maintain an upright position. If any progressive asymmetry is observed, then sitting PA and lateral radiographs are obtained. Because prophylactic treatment cannot alter the natural history of the disease, it is appropriate to establish the diagnosis clinically and obtain radiographs if the curve is noted to progress.

The clinical course of patients with neuromuscular scoliosis depends on the severity of neuromuscular involvement as well as the nature of the underlying disease process. Progressive diseases are often associated with progressive curvatures. The consequences of a progressive scoliosis in the neuromuscular population involve both function, especially sitting and standing balance, as well ease of hygiene and personal care. Pulmonary dysfunction may be expected with the gradual deformation of the rib cage and vertebra–pelvic axis, as well as collapse of the spine with the pelvis impinging on the rib cage. Diaphragmatic function is impaired, and changes in chest volume and chest wall architecture will undoubtedly exacerbate the pulmonary dysfunction owing to underlying muscle weakness. Pulmonary function may be difficult to document in some patient populations, especially those with severe cerebral palsy. Additionally, patients who initially were marginal ambulators may lose the ability to walk altogether as their scoliosis advances. Curves associated with pelvic obliquity result in asymmetric seating pressures, which may limit sitting endurance and may rarely cause skin breakdown and decubitus ulcers. Patients may also experience pain from impingement of the rib cage on the iliac crest.

Figure 679-6 Imaging shows a long C-shaped curve with convexity to the left side and significant pelvic obliquity, a curve pattern often seen in patients with neuromuscular scoliosis. *(From Pruthi S: Scoliosis. In Coley BD, editor:* Caffey's pediatric diagnostic imaging, *ed 12, Philadelphia, 2013, WB Saunders, eFig. 135-10B.)*

The treatment of neuromuscular scoliosis depends on the age of the patient, the underlying diagnosis, and the magnitude of the deformity. The goal is to achieve or maintain a straight spine over a level pelvis, especially in patients who are wheelchair bound, and to intervene early before curve magnitude and rigidity become severe. In contrast to idiopathic and congenital scoliosis, neuromuscular curves often continue to progress after skeletal maturity. In general, curves of greater than 40-50 degrees will continue to worsen over time. Brace treatment does not affect the natural history of neuromuscular scoliosis, and standard braces used for idiopathic scoliosis are poorly tolerated in neuromuscular patients. A soft spinal orthosis may improve sitting balance and ease of care, although it does not prevent progression of the curvature.

In general, a spinal arthrodesis is offered to patients with progressive curvatures >40-50 degrees. The indications will differ somewhat based on the underlying diagnosis. For example, patients with Duchenne muscular dystrophy are offered surgery when their curves progress beyond 20-30 degrees, thereby having surgery before the anticipated decline in pulmonary or cardiac function preclude their ability to tolerate it. Ambulatory patients with curvatures similar to those seen in idiopathic scoliosis are managed by similar principles. Patients who are nonambulatory with pelvic obliquity are usually managed by a spinal fusion extending from the upper thoracic spine to the pelvis, similar to that described in the idiopathic scoliosis section. A brace is not required following this procedure. Treatment decisions must be individualized in those nonambulatory patients with spastic quadriplegia, and are based on loss of function, the potential to improve hygiene or personal care, and the desires of the family and/or caregivers.

Although complications are relatively frequent in comparison with patients with nonneuromuscular curves, the available literature suggests that most patients benefit in terms of function and ease of care. To better identify patients at risk of complications, a recent study found that nonambulatory patients and those with curves 60 degrees or greater had a significantly increased risk of postoperative major complications, including ileus, pneumonia, infection, and wound problems. Because of the risks involved and potential for complications, this surgery should ideally be performed at centers with significant experience.

SYNDROMES AND GENETIC DISORDERS

Representative examples of this diverse group of diagnoses include neurofibromatosis, osteogenesis imperfecta, connective tissue diseases including Marfan syndrome (see Chapter 702), Ehlers-Danlos syndrome (see Chapter 659), and Prader-Willi syndrome (see Chapter 81), among many others. Patients with these diagnoses should have their spine examined routinely during visits to their primary care physician. Similar to other types of scoliosis, the follow-up and treatment are based on the age of the patient, the degree of deformity, whether progression has been documented, and the underlying diagnosis.

COMPENSATORY SCOLIOSIS

Leg-length inequality is a common clinical diagnosis and is usually associated with a small compensatory lumbar curvature (see Chapter

676). This is one cause of false-positive screening examinations. Patients with leg-length inequality may have the pelvis become tilted toward the shorter limb and subsequently develop an associated lumbar curve. The apex of the curve points toward the short leg. There is little evidence to suggest that a small compensatory lumbar curve places the patient at risk of progression or back pain. However, children with leg-length inequality may also have idiopathic or congenital scoliosis. A standing radiograph may be obtained with a block under the foot on the short side, which corrects the leg-length discrepancy and levels the pelvis. If the curvature disappears when the limb-length discrepancy is corrected, then a diagnosis of a compensatory curve is made. An alternative is a PA radiograph with the patient seated.

In neuromuscular disorders such as polio or cerebral palsy, an adduction or abduction contracture of the hip, described as a fixed infrapelvic contracture, may have an associated compensatory lumbar scoliosis to maintain standing balance. For patients who ambulate, a 10-degree fixed contracture will result in up to 3 cm apparent leg-length discrepancy.

Bibliography is available at Expert Consult.

679.4 Kyphosis (Round-Back)

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The normal thoracic spine has 20-50 degrees of kyphosis as measured from T3 to T12. This is measured using the Cobb method on a standing lateral radiograph of the thoracolumbar spine. A thoracic kyphosis in excess of the normal range of values is termed *hyperkyphosis*. These patients may present with cosmetic concerns, back pain, or both. A flexible or postural kyphosis may be overcorrected voluntarily or with postural adjustment, whereas a rigid kyphosis cannot be corrected passively. Causes of rigid kyphosis include Scheuermann disease and congenital kyphosis, among others. Table 679-2 lists conditions associated with hyperkyphosis.

The evaluation and treatment depends on the underlying diagnosis, the degree of deformity and its flexibility, whether the deformity is progressive, and whether any symptoms are present.

FLEXIBLE KYPHOSIS (POSTURAL KYPHOSIS)

Postural kyphosis is a common cosmetic concern and is most often recognized by family and friends. Adolescents with postural kyphosis can correct the curvature voluntarily. A standing lateral radiograph will show an increase in kyphosis but no pathologic changes of the involved vertebrae. There is no evidence to suggest that postural kyphosis progresses to a structural deformity. Although mild aching discomfort is sometimes reported, there is no evidence that the conditions leads to long-term symptoms or alterations in function or quality of life. The mainstay of treatment is reassurance. Physical therapy can be considered for muscular discomfort, although there are no data to suggest that a permanent alteration in alignment can be maintained.

Table 679-2 Conditions Associated with Hyperkyphosis
• Trauma causing spinal fractures
• Spinal infections resulting from bacterial, tuberculosis, and fungal diseases
• Metabolic diseases such as osteogenesis imperfecta or osteoporosis
• Iatrogenic (laminectomy, spinal irradiation)
• Neuromuscular diseases
• Neoplasms
• Congenital/developmental
• Disorders of collagen such as Marfan syndrome
• Dysplasias such as neurofibromatosis, achondroplasia, and mucopolysaccharidoses

Neither bracing nor surgery plays a role in the management of this condition.

STRUCTURAL KYPHOSIS

Scheuermann Disease

Scheuermann disease is the most common form of structural hyperkyphosis and is defined by wedging of greater than 5 degrees of 3 or more consecutive vertebral bodies at the apex of the deformity on a lateral radiograph. In addition, the apex of the thoracic kyphosis is lower than expected. Other radiographic findings include irregularities of the vertebral end plates and Schmorl nodes, which are herniations of the vertebral disc into the surface of the vertebral body. The etiology remains unknown but most likely involves the influence of mechanical forces in a genetically susceptible individual. Histologic specimens taken from patients with Scheuermann disease show a disordered pattern of endochondral ossification. However, it remains unclear whether these findings are the primary result of a genetic or metabolic pathologic process, or simply the secondary result of mechanical overload. The reported incidence varies from 0.4-10%, affecting boys 3 times more frequently than girls.

Physical Exam and Clinical Manifestations

Examine the patient from the side. There is a hyperkyphosis of the thoracic spine typically associated with a sharp contour. The apex of the deformity will often be in the lower thoracic spine. Patients are unable to correct the deformity voluntarily. Pain is a relatively common complaint. It is typically mild and near the apex of the kyphosis. The symptoms are intermittent, rarely severe, and occasionally limit certain activities. Neurologic symptoms are uncommon.

Radiographic Evaluation

The standard imaging protocol includes standing PA and lateral radiographs (Fig. 679-7). A specific, standardized technique in which the

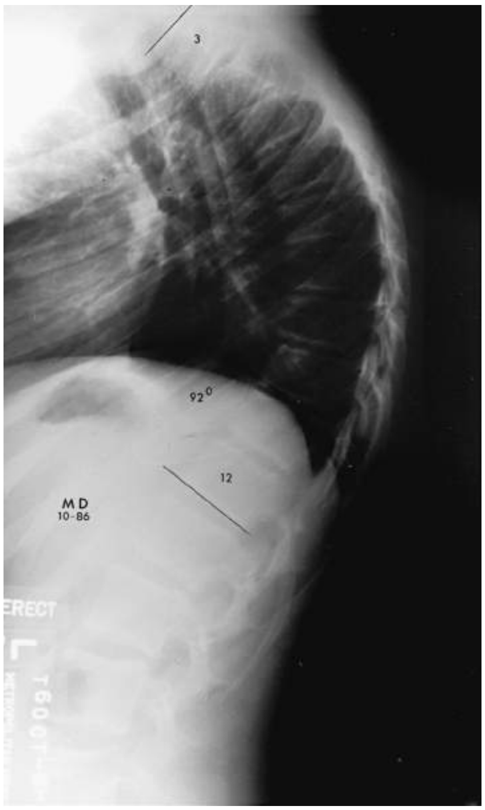

Figure 679-7 Standing lateral radiograph of a 14 yr old boy with severe Scheuermann kyphosis. This measures 92 degrees between T3 and T12. Note the wedging of the vertebrae at T6, T7, T8, and T9. The normal thoracic kyphosis is ≤40 degrees.

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arms are folded across the chest is recommended for the lateral view. In addition to the diagnostic findings noted above, a mild scoliosis is commonly seen. Less frequently, a spondylolisthesis may be identified on the lateral radiograph.

Natural History

Treatment depends on the age of the patient, the degree of deformity, and whether any symptoms are present. As adolescents, patients with Scheuermann kyphosis may have more complaints of back pain compared to other adolescents, but this often improves after skeletal maturity. With regard to back pain, several studies have found no difference between Scheuermann patients and controls, whereas others have noted an increased incidence of constant back pain. Patients' self-esteem, participation in activities of daily living and recreational activities, and level of education are not different than in the general population. Kyphotic deformities greater than 90 degrees are more likely to be aesthetically unacceptable, symptomatic, and progressive. Deformities in excess of 100 degrees may be associated with restrictive pulmonary dysfunction.

Treatment

Because there are few absolute guidelines for treatment, treatment decisions must be individualized. Skeletally immature patients with mild deformity may benefit from a hyperextension exercise program, but the effects of this strategy on pain relief and spinal alignment, or the natural history, remain unknown. Patients with more than 1 yr of growth remaining and a kyphosis of greater than 55-60 degrees may benefit from a bracing program. A Milwaukee brace, which extends up to the neck, is recommended for curves with an apex above T7, while curves with a lower apex often may be treated by a thoracolumbar orthosis. The brace should be worn for up to 23 hr daily. Consideration also may be given to a serial casting or stretching program to gain flexibility prior to instituting the brace program. The goal of the brace is to prevent progression. A permanent improvement in alignment is seen less frequently. Skeletally mature patients with little or no pain and acceptable cosmesis are not treated. A spinal fusion may be considered in the rare patient with progressive deformity >70-80 degrees who is dissatisfied with his or her cosmetic appearance or who has persistent back pain despite nonoperative measures. An instrumented posterior spinal fusion from the upper thoracic to the mid lumbar spine is commonly performed, with spinal osteotomies to promote shortening of the spine when correcting with compressive forces. Some surgeons have recommended an anterior spinal release (discectomies and fusion) in addition to the posterior spinal fusion; however, this procedure is performed less frequently because of the increased neurologic risks of this combined procedure as the spine is lengthened during the correction.

CONGENITAL KYPHOSIS

Congenital kyphosis results from congenital anomalies of the vertebrae. In an anterior failure of formation (type I), a portion of the vertebral body fails to form. A kyphosis is typically identified after birth, and there is a high risk of progression and neurologic dysfunction. Spinal cord dysfunction commonly results from compression at the apex of the deformity. The second type of congenital kyphosis involves an anterior failure of segmentation, in which 2 vertebrae are fused (type II). The posterior elements of the spine continue to grow but the anterior spine does not, resulting in a variably progressive kyphosis and a much lower risk of neurologic dysfunction. Patients must be followed closely, and treatment is required in a significant number of cases. Similar to congenital scoliosis, abnormalities of other organ systems should be ruled out.

The treatment depends on the type of malformation, the degree of deformity, and whether neurologic symptoms are present. Bracing is ineffective, and surgical treatment is the only option for progressive curves. Because the natural history is so poor for type I deformities, spinal fusion is usually performed shortly after the diagnosis is made. The surgical goals are to prevent or treat kyphotic deformities, avoid neurologic deterioration, while maximizing spinal growth to the extent possible. This usually involves some form of spinal fusion, which may include anterior and/or posterior components, with or without resection of the vertebral remnant, and spinal instrumentation. Ideally, only a short segment of the spine will be fused to try and maximize trunk height. Deformities caused by anterior failure of segmentation also require spinal stabilization in some cases, but progression is typically slower, and patients are often followed over years to determine whether surgical stabilization will be required.

Bibliography is available at Expert Consult.

679.5 Back Pain in Children

R. Justin Mistovich and David A. Spiegel

With a lifetime prevalence of >70%, only the common cold affects individuals more frequently than back pain. Back pain is a frequent complaint in the pediatric and adolescent patient, affecting approximately 35% of adolescents. Back pain may be a physical manifestation of psychosocial factors in adolescents, similar to adults. Traditionally, the pediatric patient presenting with back pain warranted an aggressive clinical evaluation as the probability of establishing a specific diagnosis was high. Recent literature suggests that the incidence of both pediatric and adolescent back pain is increasing, while the proportion of patients having a diagnosable pathology is decreasing. In fact, a recent large cohort found no diagnosable pathology in 76% of patients. These trends add further complexity to determining the proper approach to diagnosis and treatment. The differential diagnosis is extensive (Table 679-3). Given the potential for serious pathology, a complete history and careful physical exam must be performed on all patients presenting with back pain, with appropriate diagnostic follow-up of concerning findings.

CLINICAL EVALUATION

A full, careful history is very important. Identify the location, character, and duration of symptoms. Any history of acute trauma or repetitive physical activities should be sought. Identify patients with at-risk athletic pursuits, including football lineman and gymnasts, who have a high incidence of spondylolysis (see Chapter 679.6). Symptoms consistent with a neoplastic or infectious etiology include pain that is constant or unrelenting, not relieved by rest, and wakes the patient from sleep. Fevers, chills, or constitutional symptoms of weight loss or malaise are additional red flags for infectious or neoplastic processes.

Symptoms of neurologic dysfunction must also be uncovered. Patients should be questioned about the presence of any radicular symptoms, gait disturbance, muscle weakness, alterations in sensation, and changes in bowel or bladder function.

The physical examination includes a complete musculoskeletal and neurologic assessment. The patient should be adequately undressed for the clinical exam. Inspect the patient from the back and the side, identifying any changes in alignment in the frontal or sagittal plane. Assess range of motion in flexion, extension, and lateral bending. Pain with extension suggests pathology within the posterior elements of the spine such as spondylolysis. Forward flexion will exacerbate pain linked to abnormalities of the anterior column of the spine (vertebral body or disc), such as a herniated disc or discitis. Younger children may be asked to pick up an object off the floor to assess spinal flexion.

Palpation will reveal any areas of point tenderness over the posterior elements or the muscles and identify muscle spasm.

As spinal pain may be referred, an abdominal examination should be performed, and a gynecologic evaluation should also be considered. Pathology at the sacroiliac joint may also mimic low back pain. This joint should be stressed by compression of the iliac wings or by external rotation at the hip (Faber test).

A careful neurologic examination should be performed, including manual muscle testing, sensation, proprioception, and reflexes. Examine for myelopathy by performing the Babinski test, assessing for hyperreflexia, and checking for sustained, or greater than 3 beats, of

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Table 679-3 Differential Diagnosis of Back Pain

INFLAMMATORY/INFECTIOUS
Diskitis
Vertebral osteomyelitis (pyogenic, tuberculous)
Spinal epidural abscess
Pyelonephritis
Pancreatitis
Psoas abscess
RHEUMATOLOGIC
Pauciarticular juvenile idiopathic arthritis
Reiter syndrome
Ankylosing spondylitis
Psoriatic arthritis
DEVELOPMENTAL
Spondylolysis
Spondylolisthesis
Scheuermann disease
Scoliosis
TRAUMATIC (ACUTE VERSUS REPETITIVE)
Hip–pelvic anomalies
Herniated disk
Overuse syndromes
Vertebral stress fractures
Upper cervical spine instability
NEOPLASTIC
Vertebral tumors
Benign
Eosinophilic granuloma
Aneurysmal bone cyst
Osteoid osteoma
Osteoblastoma
Malignant
Osteogenic sarcoma
Leukemia
Lymphoma
Metastatic tumor
Spinal cord, ganglia, and nerve roots
Intramedullary spinal cord tumor
Sympathetic chain
Ganglioneuroma
Ganglioneuroblastoma
Neuroblastoma
OTHER
Intraabdominal or pelvic pathology
Following lumbar puncture
Conversion reaction
Juvenile osteoporosis

clonus. The superficial abdominal reflex should be tested by gently stroking the skin on each of the four quadrants surrounding the umbilicus. Normally, the umbilicus will move toward the area stimulated. A normal examination includes symmetry in the response on both sides of the midline, even if the reflex cannot be elicited on either side. An abnormal test suggests the presence of a subtle abnormality of spinal cord function, most commonly syringomyelia. Perform a straight-leg raise test to check for nerve root tension caused by a herniated disk, slipped vertebral apophysis, or other pathology. This examination should reproduce any neurologic symptoms distal to the knee.

MEDICAL DECISION MAKING

A detailed history and physical exam are the most important components of the initial evaluation, and should focus on identifying *red flags* and differentiating between mechanical and nonmechanical back pain. Findings consistent with a nonmechanical etiology, warrant a more aggressive evaluation and/or prompt referral (Table 679-4).

Patients with mechanical back pain and symptoms that are activity-related and improve with rest are typically treated by rest or activity restrictions and nonnarcotic analgesics. Physical therapy for core strengthening can be considered. The patient is asked to return for a follow-up appointment after 4-6 wks. Plain radiographs are commonly obtained at the discretion of individual practitioners, although, if no red flags are present, consider delaying radiographs until the follow-up appointment because of the cumulative adverse effects of radiation exposure. Patients presenting with concerning findings or those who have not improved after 6 wk of conservative care are subject to further investigation.

Table 679-4 Findings Consistent with a Nonmechanical Etiology Warranting Further Evaluation

- History of trauma
- Pain that wakes the patient from sleep
- Constant pain unrelieved by rest
- Constitutional or systemic symptoms of fevers, chills, malaise, weight loss
- Any neurologic dysfunction including weakness, numbness, radicular pain, gait changes, or bowel and bladder changes
- Abnormalities in spinal alignment
- Bony tenderness to palpation or vertebral step-offs
- Significant pain with provocative tests (spinal flexion or extension)
- Positive straight-leg raise test for neurologic symptoms below the knee
- Abnormal neurologic exam

RADIOGRAPHIC AND LABORATORY EVALUATION

When further workup is indicated, posteroanterior and lateral radiographs of the involved region of the spine are the initial images of choice. Some clinicians will also utilize oblique radiographs of the lumber spine when spondylolysis is in the differential diagnosis. If plain radiographs are normal, advanced imaging modalities are considered including a 3-phase technetium bone scan, a bone scan with single-photon emission CT if spondylolysis is suspected, CT for viewing osseous detail, and MRI for viewing soft tissue and intraspinal detail. There are advantages and disadvantages with each, and no evidenced-based guidelines are available for the work-up or back pain in the pediatric population.

When systemic signs or constitutional symptoms are present, a complete blood cell count with differential, erythrocyte sedimentation rate, and C-reactive protein should be ordered. In certain cases, laboratory tests to evaluate for inflammatory diseases, such as juvenile idiopathic arthritis, seronegative spondyloarthropathies, and ankylosing spondylitis, are indicated.

Bibliography is available at Expert Consult.

679.6 Spondylolysis and Spondylolisthesis

R. Justin Mistovich and David A. Spiegel

Spondylolysis represents a defect in the pars interarticularis, the segment of bone connecting the superior and inferior articular facets in the vertebra. It is thought to result from repetitive hyperextension stresses, in which compressive forces are transmitted from the inferior articular facet of the superior vertebra to the pars interarticularis of the inferior vertebra. A stress fracture, unilateral or bilateral, may progress to a spondylolysis. In many cases, this stress fracture does not heal, resulting in a pseudarthrosis or false joint, and thereby allowing motion through this bony area where motion should not normally exist.

Spondylolysis is common in athletes who engage in repetitive spinal hyperextension, especially gymnasts, football interior lineman, weight lifters, and wrestlers. Approximately 4-8% of the entire pediatric population is affected, making it the most common cause of back pain in

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adolescents when a diagnosis can be established. Patients with excessive lordosis in the lumbar spine may be predisposed to developing a spondylolysis, and a genetic component has also been suggested. The lesion is most common at L5, but it may be identified at upper lumbar levels as well.

Spondylolisthesis represents a forward slippage of 1 vertebra on another and is also identified in approximately 4-5% of the population. There are multiple causes of spondylolisthesis, including dysplastic/congenital, isthmic (from a pars stress fracture), traumatic, and neoplastic. In children and adolescents, the most common types are dysplastic and isthmic. Between 5% and 15% of patients with spondylolysis will develop *spondylolisthesis*.

Spondylolisthesis is assessed on a standing lateral radiograph of the lumbosacral junction according to (1) percentage of forward translation of 1 vertebra on the other, (2) rotation of the involved vertebrae in the sagittal plane (slip angle), and (3) relative position of the sacrum during upright posture. For example, a grade 1 slip of L5 on S1 has less than 25% of the width of the vertebral body of L5 translated anteriorly on S1. Similarly, grade 2 is 25-50%, grade 3 is 50-75%, grade 4 is 75-100%. *Spondyloptosis*, or grade 5, describes a complete displacement of 1 vertebral body on the level below. The slip angle, which demonstrates the degree to which the superior vertebra is flexed forward relative to the underlying vertebra, and the verticality of the sacrum, both have a significant effect on sagittal balance or relationship of the sagittal weightbearing axis to the body segments. Abnormalities in sagittal spinal balance may be associated with compensatory flexion of the knees during ambulation, hamstring spasm and/or contracture, and back pain.

CLINICAL MANIFESTATIONS

Spondylolysis may occasionally be asymptomatic and diagnosed incidentally on imaging obtained for other reasons. Usually though, it presents with mechanical low back pain that may radiate to the buttocks, with or without spasm of the hamstring muscles. Neurologic symptoms are rare in patients with spondylolysis. However, patients with spondylolisthesis may experience neurologic symptoms from compression of the nerve roots causing radiculopathy or even the surgical emergency of cauda equina in which bowel and bladder function is affected.

PHYSICAL EXAM

Patients with spondylolysis often have discomfort with spinal extension or hyperextension. Provocative testing may include keeping the spine extended for 10-20 seconds to see if back pain can be reproduced. There may be discomfort with palpation of the spinous process of the involved vertebra. Patients with higher grades of spondylolisthesis demonstrate loss of lumbar lordosis, flattening of the buttocks on visual inspection, and a vertical sacrum caused by posterior rotation of the pelvis. A step off may be palpated between the spinous processes of the involved vertebrae. Hamstring contracture is testing by measuring the popliteal angle. The hip is flexed to 90 degrees while fully extending the contralateral hip to level the pelvis. The knee is then passively extended, and the popliteal angle represents the angle between the thigh (vertical) and the lower leg axis. The involved spinous processes may be tender to palpation. A careful, complete neurologic examination is essential.

RADIOGRAPHIC EVALUATION

The initial evaluation of the lumbar region should include high-quality anteroposterior and lateral radiographs. Some authors also prefer to obtain oblique radiographs, which demonstrate the classic "Scotty dog" finding. One study suggests that a series of 4 views may not offer greater diagnostic accuracy than 2 views. Standing PA and lateral radiographs are obtained if findings suggestive of scoliosis or hyperkyphosis are also present (Figs. 679-8 and 679-9). In patients with normal plain films, a bone scan with single-photon emission CT may help to diagnose a spondylolysis during the earliest stage of a stress reaction, prior to the formation of a stress fracture or an established pseudarthrosis. A CT scan with thin cuts may provide additional information to establish the presence of a pars defect. MRI is indicated in the presence of signs or symptoms of cauda equina or nerve root involvement.

TREATMENT

The asymptomatic patient with spondylolysis requires no treatment. Patients with pain are treated initially by activity modification, physical therapy for core strengthening, and nonnarcotic analgesics. The use of a lumbosacral orthosis, which immobilizes the spine in slight flexion to decompress the posterior elements, may lead to a faster resolution of symptoms. This orthosis is typically worn for 3-4 mo. Participation

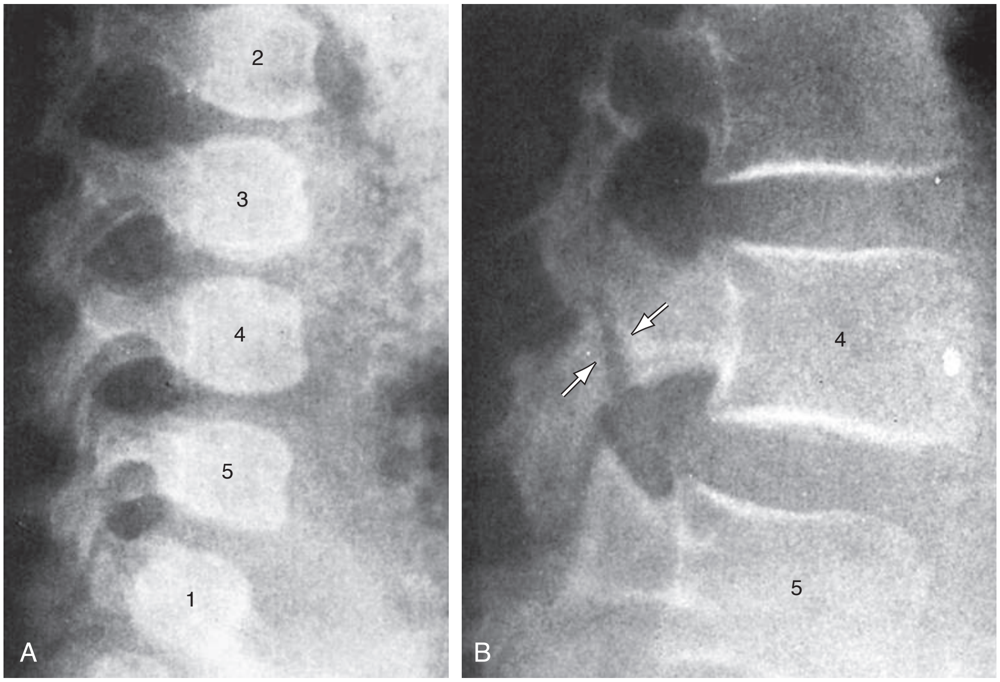

Figure 679-8 A, Normal spine at 9 mo of age. **B,** Spondylolysis in the L4 vertebra at 10 yr of age. *(From Silverman FN, Kuhn JP:* Essentials of Caffey's pediatric x-ray diagnosis, *Chicago, 1990, Year Book Medical Publishers, p. 94.)*

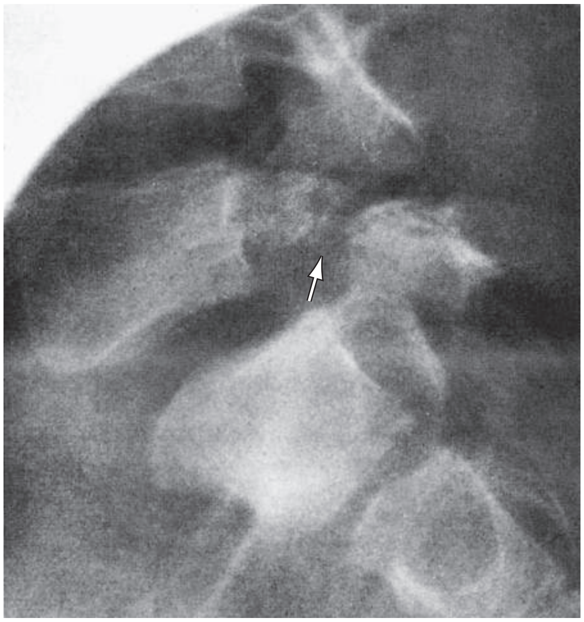

Figure 679-9 Defect in the pars interarticularis *(arrow)* of the neural arch of L5 (spondylolysis) that has permitted the body of L5 to slip forward (spondylolisthesis) on the body of S1. *(From Silverman FN, Kuhn JP:* Essentials of Caffey's pediatric x-ray diagnosis, *Chicago, 1990, Year Book Medical Publishers, p. 95.)*

in sports or other activities that exacerbate pain should be restricted until the symptoms have resolved.

Most patients experience resolution of their symptoms even though the spondylolysis heals in only a small number of patients. Surgery is offered for chronic, refractory back pain when conservative measures have failed. For those with spondylolysis at L5, a posterior spinal fusion from L5 to S1 is indicated as the mobility at this joint is limited relative to that observed at higher levels in the spine. For the infrequent cases in which the defect is at higher levels in the lumbar spine, techniques for repairing the pseudarthrosis without fusion are considered.

Recommendations for the management of spondylolisthesis depend on the age of the patient, the presence of pain or neurologic symptoms, and the degree of deformity. For low-grade lesions with a slip <50%, the management is similar to that for spondylolysis. As progressive slippage may occur in a subset of skeletally immature patients, patients must be followed through skeletal maturity. Guidelines for the timing of follow-up, and whether or not to obtain routine radiographs at each follow-up, differ between individuals and institutions. The authors typically follow asymptomatic patients yearly with a standing lateral of the lumbosacral junction.

For low-grade slips (<50% translation) with persistent symptoms despite nonoperative measures, an in situ posterior spinal arthrodesis is suggested. Surgery is also offered to skeletally immature patients with a high-grade slip (>50% translation) based on the likelihood of slip progression. The surgical approach for these high-grade slips varies between surgeons and institutions. The main principle is to stabilize the unstable segment of the spine and avoid neurologic complications. The typical components of these complex procedures include (1) posterior decompression of the L5 and S1 nerve roots (laminectomy and takedown of pseudarthrosis), (2) instrumented posterior spinal fusion from L5-S1, (3) discectomy at L5-S1 with placement of anterior column support (transforaminal cage or fibular allograft from sacrum to L5), and (4) reduction of the slippage by positioning the hips in extension or by an "instrumented reduction" utilizing the spinal implants. The risk of neurologic complications is higher when an instrumented reduction is attempted.

Bibliography is available at Expert Consult.

679.7 Spine Infection

R. Justin Mistovich and David A. Spiegel

Spondylitis, meaning inflammation of the vertebrae, is most commonly caused by infectious or autoimmune processes. Both *diskitis* and *vertebral osteomyelitis* are causes within the spectrum of **infectious spondylitis**. Most causes of infectious spondylitis result from hematogenous seeding of osteoarticular structures. Diskitis involves bacterial infection of the disc space and is generally seen in children younger than 5 yr of age. In contrast, vertebral osteomyelitis most often occurs in older children and adolescents and involves the vertebral body. Differences in anatomic location of the infectious focus relate to the vascular development of the spine. Patients in the younger age range have vascular channels between the vertebral end plate and the disc space, explaining the prevalence of discitis. In older children these channels have closed, and the infection remains in the vertebra causing osteomyelitis.

Staphylococcus aureus (see Chapter 181) is the most common organism causing spine infections. Other, less-common organisms include *Kingella kingae*, group A streptococcus, *Bartonella henselae*, *Salmonella*, and *Escherichia coli*. Blood cultures have a sensitivity of only 30%. Percutaneous or open biopsy of the disc space is positive only 50-85% of the time. The differential diagnosis must include tuberculosis of the spine.

CLINICAL MANIFESTATIONS

A high index of suspicion is required to establish the diagnosis of infectious spondylitis. Patients may experience back pain, abdominal pain, fever, or malaise. Fever is less common and may be present in only 30% of patients. Toddlers may develop a limp, or refuse to walk or sit. In an effort to reduce the pain associated with spinal motion, the child will hold the spine in a rigid position. There may also be paraspinal muscle spasm. Local point tenderness over the affected spinous process is common. There may be a list or leaning of the trunk when the patient is viewed from the front or back, and from the side there may be a loss of lumbar lordosis. Neurologic manifestations are rare and if present suggest that an epidural abscess may be present. The L3-4 or L4-5 spaces are most commonly affected in diskitis.

Spine flexion compresses the anterior elements of the spine and will elicit an increase in pain. Asking a child to pick up an object from the ground is a simple way to elicit this provocative test.

Although the white blood count may remain normal, the erythrocyte sedimentation rate is elevated in 80% of cases, and the C-reactive protein is also elevated.

RADIOGRAPHIC EVALUATION

The earliest radiographic finding is loss of lumbar lordosis. The characteristic features on plain radiographs are disc space narrowing, or loss of disc height, and irregularity of the adjacent vertebral end plates. However, these findings do not develop until 2-3 wk after the onset of symptoms. The diagnosis may be established earlier using either a technetium bone scan or MRI, although MRI is the most sensitive and specific imaging to diagnose osteomyelitis and to identify abscesses and/or neural compression (Fig. 679-10).

TREATMENT

Once the diagnosis is suspected clinically, the treatment involves symptomatic care and empiric antistaphylococcal antibiotics. Blood cultures should be obtained **prior** to the administration of antibiotics. The antibiotic agent may be modified if blood cultures are positive. Symptomatic care includes rest and analgesics, and a spinal orthosis may also be considered. The typical antibiotic course is from 4-6 wk; conversion from intravenous to oral agents may be acceptable after several days of improvement of the clinical course. A CT-guided needle biopsy of the disk space is usually reserved for patients who do not respond to empiric antibiotics. Surgical treatment is rarely required, and indications include establishing the diagnosis in patients who fail to respond

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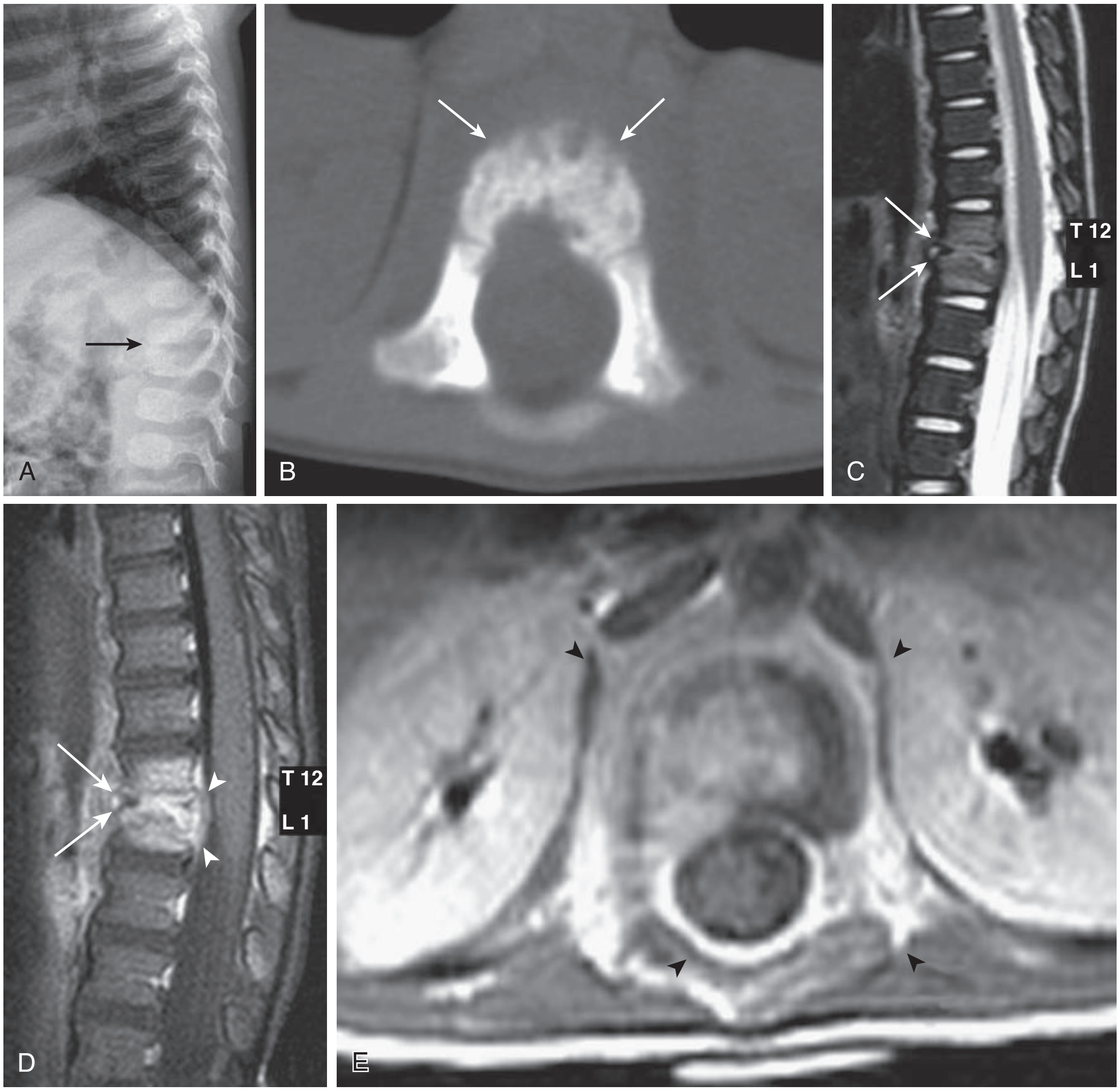

Figure 679-10 **A 15 mo old girl with abnormal gait and concern for an intraspinal mass had discitis/osteomyelitis.** Lateral spine radiographs demonstrate narrowing of the T12-L1 intervertebral disc space (*arrow* in **A**). An axial bone window from a noncontrast CT scan of the spine demonstrates irregularity to the vertebral end plates (*arrows* in **B**). A sagittal T2-weighted image **(C),** a sagittal fat-saturated T1-weighted postcontrast image **(D),** and an axial T1-weighted postcontrast image **(E)** of the thoracolumbar junction demonstrate loss of height of the T12-L1 intervertebral disc space with adjacent T2 prolongation of the adjacent endplates (*arrows* in **C**), with corresponding abnormal enhancement in the same regions (*arrows* in **D**), and surrounding mass-like soft-tissue enhancement (*arrowheads* in **E**). Note the thickening/elevation and enhancement of the posterior longitudinal ligament (*arrowheads* in **D**). *(From Pollock AN, Henesch SM: Infections of the spine and spinal cord. In Cooley BD, editor:* Caffey's pediatric diagnostic imaging, *ed 12, Philadelphia, 2013, WB Saunders, Fig. 44-6, p. 465.)*

to empiric antibiotics, and in those in whom an abscess and/or neurologic involvement are identified.

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679.8 Intervertebral Disc Herniation/ Slipped Vertebral Apophysis

R. Justin Mistovich and David A. Spiegel

Intervertebral disc herniation is the result of a tear in the outer layer of the vertebral disc, called the *annulus fibrosus*, which then allows for protrusion of the inner *nucleus pulposus*. At times, a free fragment of disc can rupture and compress the nerve roots or spinal cord. Bulging of the annulus without rupture may also be observed, resulting in back pain and occasionally radicular symptoms. Symptoms are from either direct mechanical compression and/or a local inflammatory response.

Slipped vertebral apophysis, also called a posterior ring apophysis separation, is caused by an injury and is only found in the skeletally immature. A small fragment of osseous or osteocartilagenous material from the posterior corner of the vertebral body apophysis avulses and may cause direct mechanical compression to the spinal cords and/or nerve roots, similar to a disc herniation. Both disc herniations and ring apophysis separations can cause back pain, radicular symptoms (nerve root compression or irritation), and/or spinal cord compression.

ETIOLOGY

The etiology remains unknown, but predisposing activities for both of these conditions include heavy lifting, repetitive axial loading activities, and occasionally traumatic injury such as a fall. Approximately 30-60% of patients with symptomatic herniated discs have a history of

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a trauma or sports-related injury. Other associations include preexisting disc degeneration, congenital malformation, and genetic or environmental factors. There is also a potential association between disc degeneration and the herpes virus, adding the possibility of an infectious etiology.

CLINICAL MANIFESTATIONS

Symptoms of intervertebral disc herniation or slipped vertebral apophysis in adolescents are similar to adult herniated disc symptoms. The major complaint is back pain, present in nearly 90% of patients. More than 30% of patients complain of radicular symptoms, or radiating sciatic-type pain into the legs. The back pain is often made worse by coughing, a Valsalva maneuver, or sitting. Pain may be relieved by standing or back extension. Inquire about weight loss, fever, or other constitutional symptoms to rule out an infectious or neoplastic etiology.

On physical examination, both paraspinal muscle spasm and a generalized spinal stiffness are common. Patients may lean toward the unaffected side to increase the size of the affected neural foramen thereby partially relieving symptoms. This results in a *reactive scoliosis*, not a true spinal curve, which improves with symptom resolution. Although overt signs of neurologic involvement are absent in most patients, a positive straight-leg raise test, causing radicular pain to shoot down the affected leg, is usually present. Pain is also worsened by spinal flexion.

It is critical perform a full neurologic evaluation. Evaluate sensation to light touch, pinprick, and proprioception. Check muscle strength and reflexes. It is critical to evaluate for perineal numbness, or *saddle anesthesia*. This finding, combined with changes in bowel or bladder function, which is also critical to specifically discern in the history, is indicative of cauda equina syndrome, a surgical emergency in which the nerve roots at the caudal end of the spinal cord are compressed or damaged.

RADIOGRAPHIC EVALUATION

Radiographs often show loss of lumbar lordosis, which is a result of muscle spasm, and sometimes a mild lumbar scoliosis. Other radiographic findings include degenerative changes and a loss of intervertebral disc height. MRI is the best study to establish the diagnosis of a disc herniation. CT is especially helpful to visualize a partially ossified fragment associated with a slipped apophysis.

TREATMENT

The initial treatment is nonoperative in the vast majority of patients—even if symptoms or findings of radiculopathy are observed. Treatment focuses on rest, activity modification, nonsteroidal antiinflammatory drugs, and physical therapy. An orthosis may provide additional symptomatic relief. Complete bed rest is not recommended. **Epidural steroid injection** may be discussed with patients after approximately 6 wk of treatment if symptoms persist; evidence suggests faster short-term pain relief but no difference in long-term outcome. However, if patients elect to undergo an epidural steroid injection, they should only have a single injection, even if the first did not provide any relief. Multiple injections are no more likely to provide relief than a single injection, and multiple injections expose patients to additional risks of infection, scarring, and neural injury. If a patient experiences substantial relief from an epidural steroid injection and has a later recurrence of symptoms, consideration may be given for a repeat injection after performing a complete physical exam and ruling out any new pathology.

Surgical treatment should be considered when nonoperative measures have failed or when a profound neurologic deficit such as cauda equina syndrome is present or evolving. Unfortunately, children and adolescents respond less favorably to nonoperative therapy compared with adults, and a significant percentage will require surgical intervention. Although patients with disc herniation may improve with reduction in the local inflammatory response around the nerve root, and also as the disc material loses water volume and shrinks, which eliminates mechanical compression, patients with symptomatic ring apophyseal separations have a bony fragment causing their symptoms and are much less likely to improve spontaneously.

The surgical technique involves removing a small area of the lamina via a posterior approach, called a **laminotomy**, which allows exposure of the neural elements and underlying disc. Any loose fragments are removed. A bulging disc may also be opened surgically to decompress the area compressing the neural elements, although a complete discectomy is inadvisable. The surgical approach is similar in the case of a slipped vertebral apophysis, in which fragments of bone and cartilage must also be removed. This often requires a bilateral laminotomy to completely address the pathology.

The initial results are excellent in the majority of patients. Up to one-third of patients may have recurrent herniations and resultant symptoms of back or leg pain with longer-term follow-up. These recurrences are initially treated nonoperatively. A spinal fusion may be required when there is instability, for example, a spondylolisthesis.

Bibliography is available at Expert Consult.

679.9 Tumors

R. Justin Mistovich and David A. Spiegel

Back pain may be the most common presenting complaint in children who have a tumor involving the vertebral column or the spinal cord. Other associated symptoms may include weakness of the lower extremities, scoliosis, and loss of sphincter control. The majority of tumors are benign (see Chapter 501), including osteoid osteoma, osteoblastoma, aneurysmal bone cyst, and eosinophilic granuloma. Malignant tumors involving the vertebral column may be osseous, such as osteosarcoma or Ewing sarcoma. The may involve the spinal cord and sympathetic or parasympathetic nerves, in cases of ganglioneuroma, ganglioneuroblastoma, neuroblastoma. Tumors from other primary sites can also metastasize to the spine.

In addition to high-quality plain radiographs, useful imaging modalities include bone scans, which help with localization and identification of other lesions; MRI, which is helpful to identify soft-tissue extension and neurologic compression; and CT, which provides excellent bony detail.

A biopsy is usually required to establish the diagnosis. Treatment of tumors of the spinal column may require a multidisciplinary approach. These cases should ideally be managed in centers with experience in the care patients with these lesions.

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Chapter 680 The Neck

680.1 Torticollis

Patrick O'Toole and David A. Spiegel

Torticollis, literally meaning *twisted neck*, is not a diagnosis but rather a manifestation of a variety of underlying conditions (Table 680-1). Alternative names associated with this condition include *wry-neck* and *cock-robin* deformity.

CONGENITAL MUSCULAR TORTICOLLIS

Typically diagnosed during infancy, **congenital muscular torticollis (CMT)** is contracture of the sternocleidomastoid muscle, which results in tilting of the head and neck toward the side of the contracted muscle with rotation to the contralateral side. In the majority of cases (75%)

Table 680-1	Differential Diagnosis of Torticollis
CONGENITAL Muscular torticollis Positional deformation Vertebral anomalies (failure segmentation, formation or both) Unilateral atlantooccipital fusion Klippel-Feil syndrome Unilateral absence of sternocleidomastoid Pterygium colli	
TRAUMA Muscular injury (cervical muscles) Atlantooccipital subluxation Atlantoaxial subluxation C2-3 subluxation Rotary subluxation Fractures (C1, others)	
INFLAMMATION Cervical lymphadenitis Retropharyngeal abscess Cervical vertebral osteomyelitis or diskitis Juvenile idiopathic arthritis Grisel syndrome (nontraumatic rotary subluxation of the atlantoaxial joint caused by inflammation) Upper lobe pneumonia	
NEUROLOGIC Visual disturbances (nystagmus, superior oblique or lateral rectus paresis) Dystonic oculogyric drug reactions (phenothiazines, haloperidol, metoclopramide) Cervical cord tumor Posterior fossa brain tumor Acoustic neuroma Syringomyelia Wilson disease Dystonia musculorum deformans	
OTHER Acute cervical disk calcification Sandifer syndrome (gastroesophageal reflux, hiatal hernia) Benign paroxysmal torticollis Bone tumors (eosinophilic granuloma, osteoid osteoma) Soft-tissue tumor Psychogenic	

the right-hand sided sternocleidomastoid muscle is involved, causing the patient's face and chin to point to the left side.

CMT is thought to be the result of an intrauterine deformation and is more common in first pregnancies and in those with uterine compression syndrome or decreased amniotic fluid volume. CMT may be associated with the presence of a palpable mass (fibrous tissue) within the substance of the sternocleidomastoid muscle in approximately 50% of cases. The mass disappears during infancy and is replaced by a fibrous band. Information from muscle biopsies and magnetic resonance imaging has led to the suggestion that muscle injury from compression and/or stretch may create localized ischemia resulting in fibrosis and subsequent contracture: an intramuscular compartment syndrome. The condition may rarely be caused by hereditary muscle aplasia. Associated findings in CMT include plagiocephaly, facial asymmetry, and positional musculoskeletal deformities such as metatarsus adductus (15%) and calcaneovalgus feet. Hip dysplasia may be identified in 8-20% of CMT cases.

Although standards for screening in patients with a normal hip examination have not been established, as many as 15% of patients with CMT have developmental dysplasia of the hip based on screening ultrasound, some of whom required treatment. Consideration should be given to obtaining either an ultrasound scan (4 wks of age) or a plain radiograph of the hips (4-6 mo of age).

A muscle-stretching program should be successful in more than 90% of patients with CMT, especially when treatment is started within the 1st 3 mo of life. Although firm guidelines for imaging the cervical spine have not been established, consideration may be given to obtaining anteroposterior and lateral radiographs of the cervical spine when the typical clinical features associated with CMT are absent or if the deformity does not respond to treatment, as torticollis in infants may be a result of congenital vertebral anomalies. Surgical release of the sternocleidomastoid is considered in patients with persistent deformity despite nonoperative treatment. The muscle may be released at its insertion on the clavicle (unipolar release) or off both its origin and insertion (bipolar release). There is no agreement as to the most appropriate time for the surgical release, but surgical treatment is typically delayed until after 18 mo of age, and some even suggest waiting until the child is approaching school age. Although range of motion can be improved following surgical release even during the teenage years, remodeling of facial asymmetry and plagiocephaly may be less predictable in patients older than infancy. Surgical management results in adequate function and acceptable cosmesis in more than 90% of patients. However with early diagnosis and medical treatment, surgery should only be required in a minority of cases.

OTHER CAUSES OF TORTICOLLIS

The evaluation of torticollis becomes more complex when the typical findings associated with CMT are absent, the usual clinical response is not observed, or when the torticollis presents at a later age. In addition to a careful history and physical examination, consultation with an ophthalmologist and/or neurologist may be helpful. Plain radiographs should be obtained, and an MRI scan of the brain and cervical spine will be required in a subset of cases.

The differential diagnosis is extensive (see Table 680-1). **Neurogenic torticollis** is uncommon and results from tumors of the posterior fossa or brainstem, syringomyelia (see Chapter 606.3), and Arnold-Chiari malformation (see Chapter 591.11). In addition to the neurologic examination, MRI of the brain and cervical spine is required to establish the diagnosis. **Paroxysmal torticollis of infancy** is also uncommon and may be a result of vestibular dysfunction. Episodes may last from minutes to days, and the side of the deformity may alternate. The condition is self-limiting, and no specific treatment is required other than ruling out other treatable causes.

Torticollis may also be seen in association with discitis or vertebral osteomyelitis, juvenile idiopathic arthritis, cervical disc calcification, visual problems such as congenital nystagmus or paresis of the superior oblique or lateral rectus muscles, benign or malignant bone tumors, and in patients with cerebral palsy and chronic gastroesophageal reflux (Sandifer syndrome).

Atlantoaxial rotatory displacement represents a spectrum of rotational malalignment from subluxation to frank dislocation between the atlas (C1) and the axis (C2), and may best be described as a pathologic stickiness in the arc of joint motion. In some cases there is fixed malalignment between C1 and C2 (atlantoaxial rotary fixation) that results in a 50% loss of cervical rotation. The malalignment is often reducible initially but may become irreducible and fixed after weeks to months. As such, prompt diagnosis and treatment are essential. Atlantoaxial rotatory displacement may be diagnosed after infection or inflammation of the tissues of the upper airway, neck, and/or pharynx (**Grisel syndrome**), following traumatic injuries (usually minor), and as a complication of surgical procedures in the oropharynx, ear, or nose. The diagnosis is established using a dynamic rotational computerized tomography scan, in which axial images are obtained through the upper cervical spine with the head rotated maximally toward both the right and the left. If the patient is seen within a few days of the onset of symptoms, then a trial of analgesics and a soft collar may be attempted. Patients with symptoms for more than a week are often admitted to the hospital for analgesia, muscle relaxants, and a period of cervical traction. If this fails to reduce the displacement, then halo traction may be attempted. If the joint can be reduced, patients are typically immobilized for at least 6 wk in a halo vest. Patients with a fixed deformity may require a posterior atlantoaxial fusion to stabilize

the articulation. Most children with Grisel syndrome improve with supportive care (nonsteroidal antiinflammatory drugs, muscle relaxants) and treatment of their head and neck infections.

Bibliography is available at Expert Consult.

680.2 Klippel-Feil Syndrome

Patrick O'Toole and David A. Spiegel

Klippel-Feil syndrome (KFS) includes the classic triad of a low posterior hairline, short neck, and decreased cervical range of motion. These clinical findings are present in <50% of patients with KFS. Patients have a congenital fusion (failure of segmentation) of 1 or more cervical motion segments at the craniocervical junction or in the subaxial spine and often have associated congenital anomalies of the cervical spine and other organ systems (Fig. 680-1). Clinical problems are more common in adults and include pain and/or neurologic symptoms, from spinal instability and/or stenosis. The incidence has been estimated at 1:40,000-42,000 births; not every patient with the condition is diagnosed.

ETIOLOGY AND CLASSIFICATION

The etiology is felt to be sporadic when KFS is seen in isolation, but several candidate genes have been proposed in patients with associated anomalies. Additional findings in the cervical spine include occipitocervical synostosis, odontoid abnormalities, and basilar impression (proximal migration of the C2 vertebra). Other associations include **Sprengel's deformity** (congenital elevation of the scapula), congenital scoliosis, genitourinary anomalies (25-35%), sensorineural hearing loss (5%), and congenital heart disease (5-10%). Renal abnormalities include double collecting systems, renal aplasia, and horseshoe kidney. The cervical spine anomalies seen in patients with KFS may also be seen with Goldenhar syndrome, Mohr syndrome, VACTERL (vertebral defects, imperforate anus, congenital heart disease, tracheoesophageal fistula, renal and limb defects) syndrome, and fetal alcohol syndrome.

Traditionally, the classification of KFS has been based on the anatomic distribution of the cervical fusions and the kinematics of the cervical spine in flexion and extension. As more information regarding the genetics of this condition has become available, the classification system has incorporated these changes. KF 1 involves a fusion at C1 with or without a more caudal fusion level (autosomal recessive) and is associated with severe anomalies. KF 2 has a fusion of C2 and C3 with or without a more caudal fusion (autosomal dominant with 100% penetrance). KF 3 is an isolated fusion caudal to C1 and C2/3 (autosomal dominant or recessive). KF 4 (X-linked dominant) is synonymous with **Wildervanck syndrome**, which involves congenital cervical synostosis associated with hearing loss and the **Duane anomaly** (congenital rare type of strabismus).

CLINICAL PRESENTATION

KFS is present at birth but does not usually become clinically apparent until the 2nd or 3rd decades, when patients present with pain, loss of motion, and/or neurologic symptoms. Given that the same physiologic stresses are applied to a smaller number of mobile spinal segments, patients are at risk for the development of hypermobility and often instability, especially at motion segments adjacent to the fused vertebrae. Weakness or clumsiness may be the presenting symptoms. A complete history is essential, including a detailed family and birth history and review of systems.

PHYSICAL EXAMINATION

A comprehensive musculoskeletal and neurologic examination is required, given associated anomalies in the musculoskeletal and visceral systems. Scoliosis is present in more than 50% of patients with KFS, and congenital anomalies may be identified in other regions of the spine as well. The neurologic exam focuses on identifying any signs of radiculopathy or myelopathy. Spinal cord compression (myelopathy) may result from stenosis or instability, and may result in upper motor neuron signs such as hyperreflexia, Babinski's sign, and sustained clonus, with more than 3 beats considered pathologic. Nerve root compression (radiculopathy) may be from stenosis and is identified by weakness or decreased sensation in the muscles or dermatomes served by a particular nerve root, respectively.

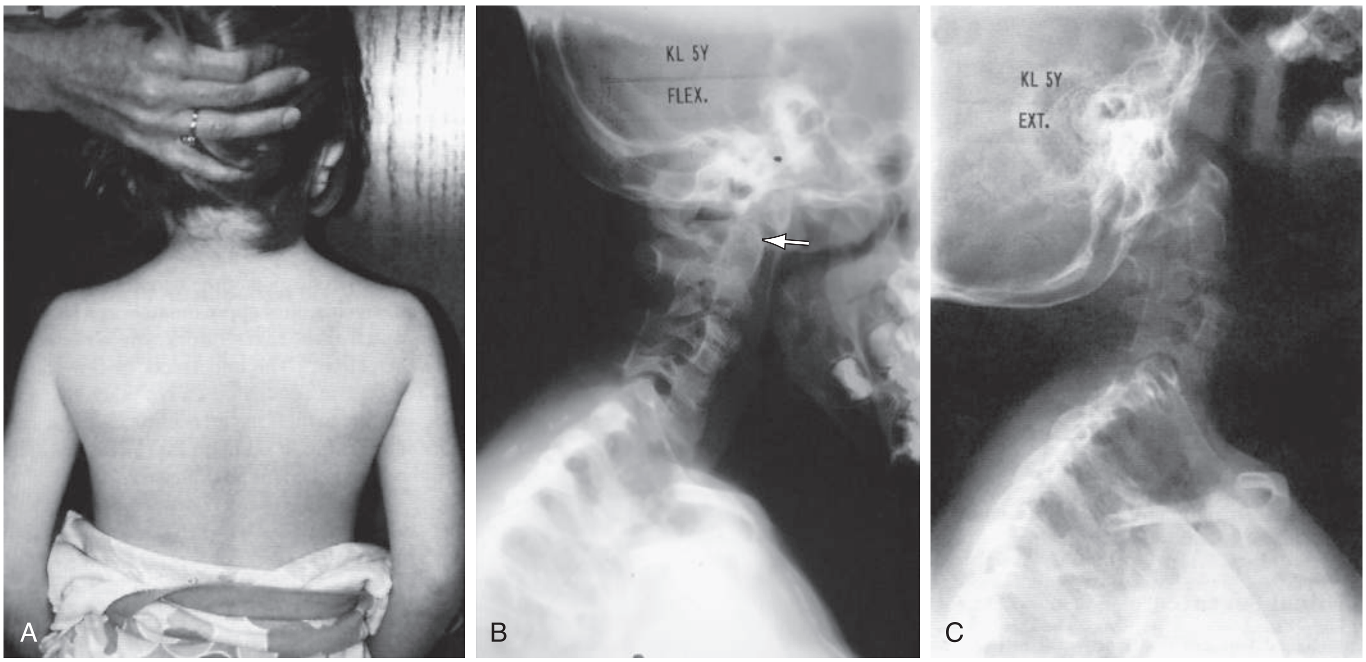

Figure 680-1 Clinical picture of a 5 yr old with Klippel-Feil syndrome. **A,** Note short neck and low hairline. **B** and **C,** Radiographs of the cervical spine (**B,** flexion; **C,** extension) demonstrate congenital fusion and evidence of spinal instability *(arrow)*. *(From Drummond DS: Pediatric cervical instability. In Weisel SE, Boden SD, Wisnecki RI, editors:* Seminars in spine surgery, *Philadelphia, 1996, WB Saunders, pp. 292–309.)*

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RADIOGRAPHIC INVESTIGATION

Initial radiologic evaluation should include an anteroposterior, lateral, and oblique view of the cervical spine. The characteristic finding is a congenital fusion of 2 or more vertebrae (failure of segmentation); however, multiple vertebrae may be involved. Because congenital anomalies may exist in more than 1 region of the spine, radiographs of the thoracic and lumbosacral spine should be routinely obtained. Flexion–extension lateral views of the cervical spine may help to identify segments with excessive motion. Referral to an orthopedist is appropriate if the diagnosis is established. Patients with this condition usually undergo CT and MRI of the spine to accurately characterize the bony anomalies and also identify any coexisting neural pathology. A renal ultrasound is routinely obtained, and additional tests may be indicated.

TREATMENT

The 3 patterns commonly associated with instability include (1) C2/C3 fusion with occipitocervical synostosis, (2) extensive fusion over multiple levels with an abnormal occipitocervical junction, and (3) 2 fused segments separated by an open joint space. Pain may often be controlled by activity restriction, intermittent immobilization, or other nonoperative modalities. Patients who are chronically symptomatic and/or have instability with positive neurologic symptoms and/or findings, or are felt to be at increased risk for neurologic deterioration, are candidates for surgical treatment. Operative interventions include decompression of a nerve root(s) or the spinal cord, and/or spinal fusion to address spinal instability.

Bibliography is available at Expert Consult.

680.3 Cervical Anomalies and Instabilities

Patrick O'Toole and David A. Spiegel

One or more anomalies of the craniovertebral junction and/or lower cervical spine may be seen in isolation or in association with other conditions, including genetic syndromes, skeletal dysplasias, connective tissue disorders, and metabolic disorders. These anomalies may be congenital, resulting from a mutation in the homeobox genes, or developmental. Even though most anomalies remain asymptomatic and undiagnosed, a subset will place the patient at risk of neurologic injury as a result of instability or spinal canal stenosis. The most frequently encountered causes of cervical spine instability in children can be categorized etiologically (Table 680-2). Patients with conditions that have known associations involving the cervical spine should have a complete evaluation, including history, physical examination, and initial radiographic examination.

Patients may complain of neck pain and/or neurologic symptoms. Radicular symptoms include pain, weakness, and numbness within the distribution of a nerve root; myelopathic symptoms may include generalized weakness, gait disturbance, increased fatigue with ambulation, upper-extremity clumsiness, and abnormalities in bowel or bladder function. Physical findings may include a restriction in cervical mobility, cervical tenderness and/or spasm, and neurologic abnormalities.

The upper cervical spine has limited flexion and extension, with roughly 50% of cervical rotation occurring at the atlantoaxial (C1-2) joint. The main constraints to motion in the upper cervical spine are soft tissue (ligaments and joint capsules) rather than osseous, and excessive motion or instability may put neural tissues at risk, and result in compressive injury to the brainstem or spinal cord. Anomalies at the craniovertebral junction include congenital fusion of the occiput to C1 (occipitalization of the atlas), basilar impression and invagination (proximal migration of the C2 vertebra as the result of softening of the bones and with normal bones respectively), and accessory vertebrae. Aplasia or hypoplasia of the atlas or the axis may result in atlantoaxial instability.

Table 680-2 Causes of Pediatric Cervical Instability

CAUSES	SUBTYPES
Congenital	Cranio-occipital defects (occipital vertebrae, basilar impression, occipital dysplasias, condylar hypoplasia, occipitalized atlas) Atlantoaxial defects (aplasia of atlas arch, aplasia of odontoid process) Subaxial anomalies (failure of segmentation and/or fusion, spina bifida, spondylolisthesis) Syndromic disorders (i.e., Down syndrome, Klippel-Feil syndrome, 22q11.2 deletion syndrome, Larsen syndrome, Marfan syndrome, Ehlers-Danlos syndrome)
Acquired	Trauma Infection (pyogenic/granulomatous) Tumor (including neurofibromatosis) Inflammatory conditions (i.e., juvenile idiopathic arthritis) Osteochondrodysplasias (i.e., achondroplasia, diastrophic dysplasia, metatropic dysplasia, spondyloepiphyseal dysplasia) Storage disorders (i.e., mucopolysaccharidoses) Metabolic disorders (rickets) Miscellaneous (including osteogenesis imperfecta, postsurgery)

OS ODONTOIDEUM

Os odontoideum is the most common anomaly of the odontoid peg (dens) and radiographically appears as an oval-shaped, well-corticated, bony ossicle that is positioned cephalad to the body of the axis. There is a discontinuity in the midportion of the dens, and the upper portion of the dens moves with the ring of C1, narrowing the space available for the spinal cord and placing the spinal cord at risk for injury. The body of the dens is mesenchymal in origin and originates from the 1st cervical vertebra, subsequent separation allows it to then fuse with the C2 vertebra. It is formed by 2 separate ossification centers, 1 on either side of the midline, which fuse and are visible at birth. Three etiologies have been proposed: (1) that the os odontoideum represents a fracture nonunion of the odontoid peg; (2) that the os odontoideum represents damage to the epiphyseal plate that has occurred in the 1st yr of life; and (3) that the os odontoideum represents a congenital malformation of the dens itself. The most widely accepted etiology is that a fracture of the dens occurs and subsequently develops a nonunion.

The symptoms and physical findings vary with the location of compression or impingement. In a large series, the average age at presentation was 18.9 yr. The most common presenting symptom was neck pain followed by upper- and lower-limb paresthesia, while torticollis, neck stiffness, gait disturbance, and headaches were uncommon symptoms at presentation. Neurologic examination may reveal a combination of both upper and lower motor neuron signs. Some patients are completely asymptomatic with the anomaly noted incidentally on a lateral cervical spine radiograph.

The radiographic evaluation begins with anteroposterior, lateral, and open mouth (odontoid) views, which may be supplemented by flexion and extension lateral radiographs. CT provides the best bony detail and is useful in defining each anomaly. MRI, including dynamic images in flexion and extension, is best for evaluating neurologic impingement. Symptomatic treatment may be helpful; however, patients with cervical instability and/or neurologic impingement require surgical decompression with or without stabilization.

DOWN SYNDROME

Ligamentous hyperlaxity is a characteristic feature of Down syndrome and may result in hypermobility or instability at the occipitoatlantal or the atlantoaxial joints in 10-30% of patients (see Chapter 81). These patients may also have coexisting congenital or developmental

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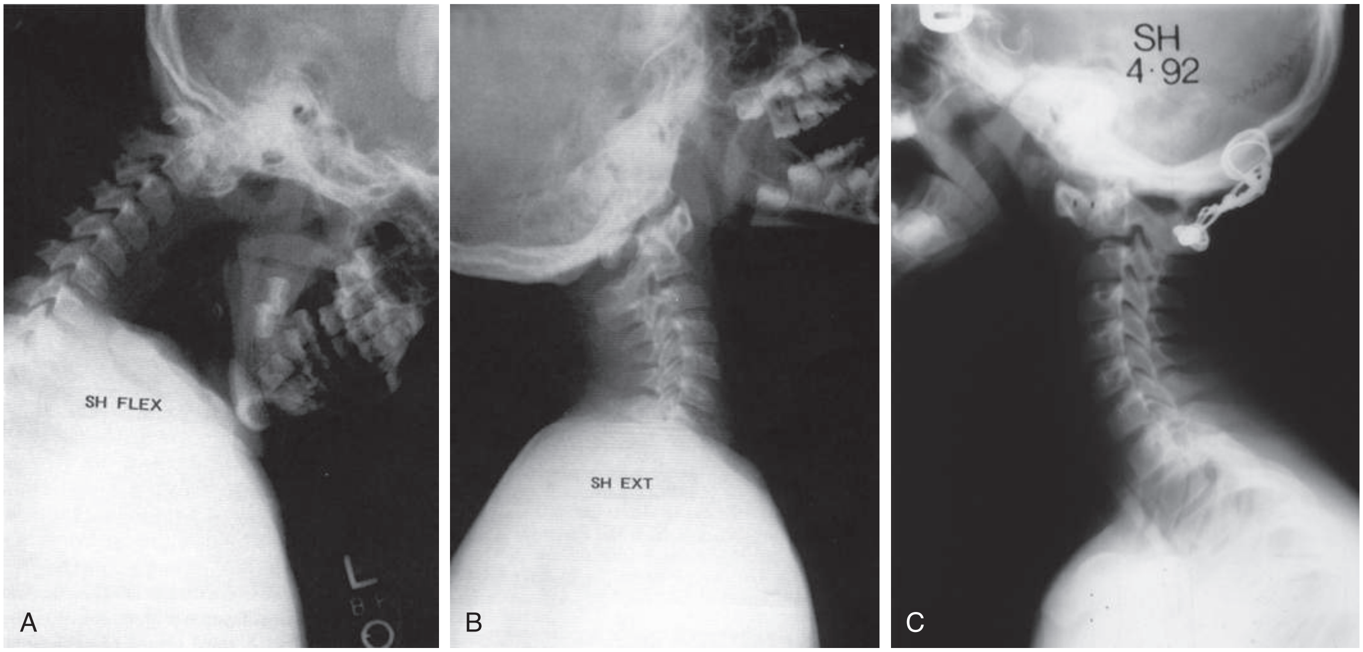

Figure 680-2 Flexion **(A)** and extension **(B)** radiographs of a case of Down syndrome demonstrating atlantooccipital hypermobility and subluxation. **C,** Instability and symptoms were relieved by an occipitoaxial arthrodesis.

anomalies of the cervical spine such as occipitalization of the atlas, atlantal arch hypoplasia, basilar invagination, and os odontoideum.

Even though the natural history of this spectrum of pathology remains unknown, a subset of patients may develop or be at significant risk of developing neurologic dysfunction. The clinical diagnosis of neurologic dysfunction may be challenging, and subtle findings, such as decreased exercise tolerance and gait abnormalities, including increased tripping or falling, may be the earliest signs of myelopathy. In addition to a neurologic examination, focusing on the presence of long tract signs, imaging studies (plain films, MRI) are required to evaluate patients suspected of having neurologic involvement.

All patients require screening by history and physical examination (at regular intervals) and at least a single series of cervical spinal radiographs, including a lateral view in flexion and extension. Plain radiographs are the preliminary imaging modality used to evaluate for hypermobility or instability. The atlantodens interval (ADI) is used to evaluate the relationship between C1 and C2 (atlantoaxial joint) and is measured as the space between the dens and the anterior ring of C1 (ADI) on lateral radiographs in neutral, flexion, and extension (Fig. 680-2). Although the ADI should be 3 mm or less in the population without Down syndrome, a normal ADI in children with Down syndrome is <4.5 mm. Hypermobility is diagnosed as an ADI between 4.5 and 10 mm, while an ADI >10 mm represents instability and carries a significant risk of neurologic injury. MRI is indicated to detect neurologic involvement in patients with radiographic instability. Recommendations for surveillance of the cervical spine in children with Down syndrome remain varied. Routine clinical evaluations, including a neurologic examination, should be performed; the indications for repeating imaging studies in the absence of clinical symptoms or findings have not been defined. Surveillance helps to define the most appropriate level of physical activity and to identify the small subset of those with either progressive hyperlaxity or instability. Although the specific recommendations vary between states, both clinical and radiographic screenings are also required prior to participation in the Special Olympics. Patients with normal radiographs who are also neurologically normal may be allowed to participate in full activity. Those who are diagnosed with hypermobility may be restricted from contact sports and other high-risk activities that increase the risk of trauma to the cervical spine. Patients with C1-C2 instability with or without neurologic findings are candidates for an atlantoaxial fusion. The risks of a major complication are extremely high for a posterior cervical fusion in this population and include death, neurologic deterioration, and pseudarthrosis with or without graft resorption.

Although hypermobility at the occipitoatlantal joint is present in >50% of children with Down syndrome, most patients do not develop instability or neurologic symptoms. The relationships at this articulation are difficult to measure reliably on plain radiographs and an MRI in flexion and extension is required to evaluate any questionable radiographic findings, especially in the presence of symptoms. Involvement of the subaxial spine is less common and is typically encountered in the adult population of patients with Down syndrome, where degenerative changes and/or instability may result in pain, radiculopathy, and/or myelopathy.

22q11.2 DELETION SYNDROME

The chromosome abnormality deletion of 22q11.2 is a common genetic syndrome, with an overall prevalence of 1 in 5,950 births, and encompasses a wide spectrum of abnormalities. There are characteristic facial features, cleft palate, and cardiac anomalies. Cervical spine anomalies are also common phenotypic features of this syndrome.

At least 1 developmental variation of the occiput or cervical spine is noted in all patients. The occipital variations observed include platybasia (abnormal flattening of the base of the skull) and basilar impression. Variations in anatomy of C1 include dysmorphic shape, an open posterior arch, and occipitalization; axis variations include a dysmorphic dens and "C2 swoosh" (upswept lamina and posterior elements). A range of cervical vertebral fusions is noted in these patients, the most common being at the C2-3 level. Increased segmental motion in the cervical spine is noted in more than half of these patients, and more than a third of patients have increased segmental motion at more than 1 level. With frequent occurrence of upper cervical spine variations in the 22q11.2 deletion syndrome (Fig. 680-3), advanced imaging of the upper cervical spine and regular follow-up of patients to clarify their clinical course is recommended.

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Figure 680-3 Radiographs of the cervical spine in a child with 22q11.2 deletion syndrome showing evidence of platybasia, occipitocervical, and atlantoaxial instability. **A,** Neutral radiograph. **B,** Flexion. **C,** Extension. *(From Drummond DS: Pediatric cervical instability. In Weisel SE, Boden SD, Wisnecki RI, editors:* Seminars in spine surgery, *Philadelphia, 1996, WB Saunders, pp. 292–309.)*

Chapter 681

The Upper Limb

Robert B. Carrigan

SHOULDER

The shoulder is a ball-and-socket joint. Although similar to the hip, the shoulder has a greater range of motion because of the size of the humeral head relative to the glenoid, as well as to the presence of scapulothoracic motion. The shoulder positions the hand along the surface of a theoretical sphere in space, with its center at the glenohumeral joint.

Brachial Plexus Birth Palsy

(See also Chapter 99.7.)

Injuries to the brachial plexus can occur in the peripartum time, usually as a result of a stretching mechanism. This palsy is often associated with large fetal size and shoulder dystocia. The incidence is 1-3 per 1,000 live births. The injury can range in severity from neurapraxia, to complete rupture of the nerve roots or avulsion of the nerve root from the spinal cord. More often, the upper roots (C5 and C6) of the brachial plexus are affected, rather than a complete brachial plexus palsy itself (C5-T1). Rarely, in isolation, is a lower plexus injury (C8 and T1) observed. The clinical appearance of a C5-C6 brachial plexus birth palsy (Erb-Duchenne palsy) is the waiter's tip position. The arm is held in a position of shoulder adduction and internal rotation, elbow extension, and wrist flexion.

Treatment

Occupational therapy should be instituted quickly after brachial plexus injury to maintain passive range of motion of the limb and encourage use of the arm. If the biceps muscle does not demonstrate evidence of recovery by 3 mo of age, or shows persistent weakness at 5 mo of age, a more severe nerve injury may be suspected. MRI and electrodiagnostic testing are not consistently reliable for delineation of nerve injury in this setting. Surgical exploration and nerve grafting of the brachial plexus are then indicated.

After complete or incomplete neurologic recovery shoulder dysplasia and dislocation (analogous to developmental dysplasia of the hip) can occur. This occurs as a result of muscle imbalances in the shoulder. In the typical Erb palsy a child may have a persistent internal rotation contracture of the shoulder as a result of the imbalance of the weak abductors and external rotators and stronger adductors and internal rotators. Infants and older children may require arthroscopic or open reduction of shoulder contractures. Older children with residual weakness in shoulder abduction and external rotation can benefit from muscle transfers. Osteotomies are reserved for children with severely deformed glenohumeral joints and functional impairment from persistent shoulder internal rotation contracture (Fig. 681-1).

Sprengel's Deformity

Sprengel's deformity, or congenital elevation of the scapula, is a disorder of development that involves a high scapula and limited scapulothoracic motion. The scapula originates in early embryogenesis at a level posterior to the 4th cervical vertebra, but it descends during development to below the 7th cervical vertebra. Failure of this descent, either unilateral or bilateral, is Sprengel's deformity. The severity of the deformity depends on the location of the scapula and associated anomalies. The scapula in mild cases is simply rotated, with a palpable or visible bump corresponding to the superomedial corner of the scapula in the region of the trapezius muscle. Function is generally good. In moderate cases, the scapula is higher on the neck and connected to the spine with an abnormal omovertebral ligament or even bone. Shoulder motion, particularly abduction, is limited. In severe cases, the scapula is small and positioned on the posterior neck, and the neck may be webbed. The majority of patients have associated anomalies of the musculoskeletal system, especially in the spine, making spinal evaluation important.

Treatment

In mild cases, treatment is generally unnecessary, although a prominent and unsightly superomedial corner of the scapula can be excised. In more severe cases, surgical repositioning of the scapula with rebalancing of parascapular muscles can significantly improve both function and appearance.

ELBOW

The elbow is the most congruent joint in the body. The stability of the elbow is imparted via this bony congruity as well as through the medial and radial collateral ligaments. Where the shoulder positions the hand along the surface of a theoretical sphere, the elbow positions the hand within that sphere. The elbow allows extension and flexion through the ulnohumeral articulation and pronation and supination through the radiocapitellar articulation.

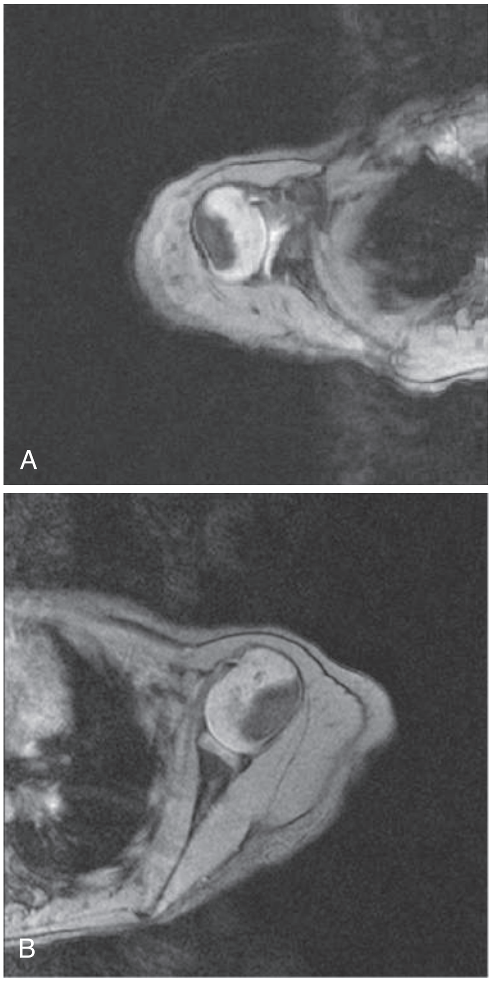

Figure 681-1 **A,** Shoulder MRI demonstrating glenohumeral dysplasia following brachial plexus birth palsy. **B,** Comparison MRI of uninvolved contralateral shoulder.

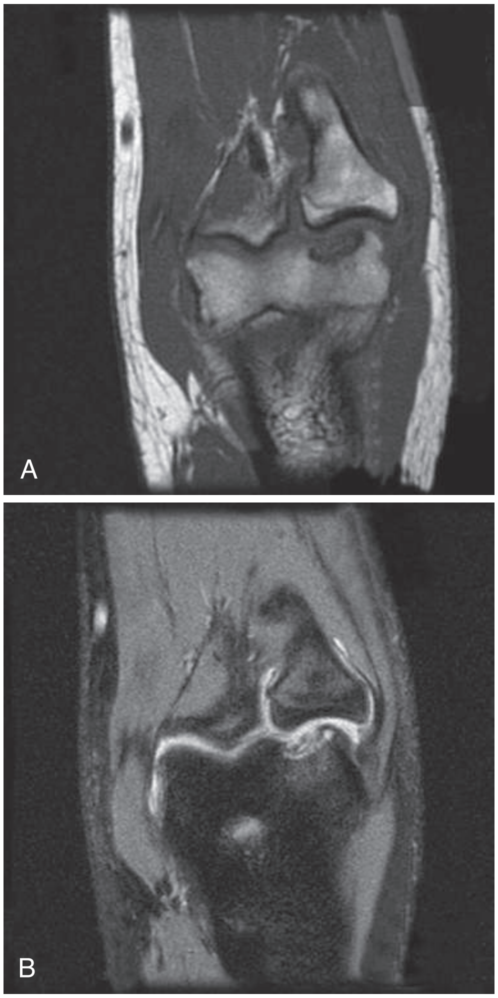

Figure 681-2 T1 **(A)** and T2 **(B)** coronal MRI images of the elbow depicting Panner disease of the elbow.

Panner Disease

Panner disease is a disruption of the blood flow to the articular cartilage and subchondral bone to the capitellum (Fig. 681-2). It typically occurs in boys between the ages of 5 and 13 yr. Presenting symptoms include lateral elbow pain, loss of motion, and, in advanced cases, mechanical symptoms of the elbow (loose bodies).

The mechanism of injury can be impaction or overloading of the joint, as seen with sports such as gymnastics and baseball. It can also be idiopathic. Radiographs of the elbow may be normal, but they may also show a small lucency within the subchondral bone of the capitellum. MRI is the study of choice to evaluate a suspected capitellar lesion. MRI can demonstrate the extent of the involvement in the subchondral bone as well as the integrity of the cartilage of the articular surface.

Treatment

Treatment is typically conservative. Rest, activity modification, and patient education are initial treatment options. In cases where the articular cartilage fragments and loose bodies form, arthroscopy of the elbow is warranted to remove the loose bodies. When the cartilage defect in the capitellum is large and symptomatic, procedures for restoration of the articular cartilage may be considered. These procedures include drilling of the subchondral bone (microfracture) to promote scar cartilage and osteochondral autograft transplantation.

Radial Longitudinal Deficiency

Radial longitudinal deficiency of the forearm comprises a spectrum of conditions and diseases that have resulted in hypoplasia or absence of the radius (Table 681-1). This process was formerly referred to as *radial club hand,* but the name has been changed to *radial longitudinal deficiency,* which better characterizes the condition. Clinical characteristics consist of a small, shortened limb with the hand and wrist in excessive radial deviation. Partial or complete absence of the radial structures of the forearm and hand are observed (Fig. 681-3).

Radial longitudinal deficiency can range in severity from mild to severe and has been classified into 4 types (Table 681-2). Radial longitudinal deficiency can be associated with other syndromes such as Holt-Oram and Fanconi anemia (see Table 681-1).

Treatment

The goals for the treatment of radial longitudinal deficiency include centralizing the hand and wrist on the forearm, balancing the wrist, and maintaining appropriate thumb and digital motion. Shortly after birth, parents are encouraged to passively stretch the wrist and hand to elongate the contracted radial soft tissues. Serial casting and splinting are ineffective at this time, because of the small size of the arm.

Surgery for correction of the wrist deformity remains controversial. Historically, for children with good elbow motion, centralization of the wrist on the forearm was performed. However recurrence of the deformity was often observed. For this reason some surgeons have elected to abandon this procedure.

When considering a centralization procedure, the preoperative plan begins with careful examination of the patient; considerations in regard to thumb and elbow function must be made before surgery. The surgery typically occurs when the child is 1 yr of age. Correction of the

Table 681-1 Syndromic Association with Radial Day Deficiency

SYSTEM	CONDITION
Cardiac	Holt-Oram syndrome VACTERL association Ventriculoradial dysplasia
Chromosomal	Trisomies 13, 17, and 18 Deletions 4q and 14q
Craniofacial	Acrorenal–ocular syndrome Craniosynostosis–radial aplasia (Baller-Gerold syndrome) Cleft lip/palate Oculoauriculovertebral dysplasia (Goldenhar syndrome) Orofacial–digital syndrome (Juberg-Hayward syndrome) Roberts SC phocomelia syndrome Treacher Collins syndrome Eye–radial dysplasia (Duane syndrome) Möbius syndrome Hemifacial microsomia
Cutaneous	Rothmund-Thompson syndrome (cutaneous poikiloderma)
Developmental delay	de Lange syndrome
Hematologic	Thrombocytopenia–absent radius syndrome Fanconi anemia Anemia–triphalangeal thumb (Aase-Smith syndrome)
Renal	Renal–radial ray aplasia (Sofer syndrome)
Skeletal	Cervical rib–radial ray defect (Funston syndrome) Costovertebral dysplasia–humeroradial synostosis (Keutel syndrome) Klippel-Feil syndrome VACTERL association
Teratogenic	
Other	IVIC (Instituto Venezolano de Investigaciones Científicas) syndrome

VACTERL, Vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophageal fistula and/or esophageal atresia, renal agenesis and dysplasia, and limb defects.

Adapted from Gupta A, Kay SPJ, Scheker LR, editors: The growing hand: diagnosis and management of the upper extremity in children, *St Louis, 2000, Mosby, p 147.*

Table 681-2 Classification of Radial Longitudinal Deficiency

TYPE	CHARACTERISTICS
I	Short radius Minor radial deviation of the hand
II	Hypoplastic radius with abnormal growth at proximal and distal ends Moderate radial deviation of the hand
III	Partial absence of the radius Severe radial deviation of the hand
IV	Complete absence of the radius The most common type

Adapted from Bayne LG, Klug MS: Long-term review of the surgical treatment of radial deficiencies, J Hand Surg Am *12(2):169–179, 1987.*

radial deviation as well as centralization of the wrist can be accomplished with a variety of different surgical techniques. These techniques include open release, capsular reefing, and tendon rebalancing. External fixation techniques have also been described.

Nursemaid Elbow

Nursemaid elbow is a subluxation of a ligament rather than a subluxation or dislocation of the radial head. The proximal end of the radius, or radial head, is anchored to the proximal ulna by the annular ligament, which wraps like a leash from the ulna, around the radial head, and back to the ulna. If the radius is pulled distally, the annular ligament can slip proximally off the radial head and into the joint between the radial head and the humerus (Fig. 681-4). The injury is typically produced when a longitudinal traction force is applied to the arm, such as when a falling child is caught by the hand, or when a child is pulled by the hand. The injury usually occurs in toddlers and rarely occurs in children older than 5 yr of age. Subluxation of the annular ligament produces immediate pain and limitation of supination. Flexion and extension of the elbow are not limited, and swelling is generally absent. The diagnosis is made by history and physical examination, as radiographs are typically normal.

Treatment

The annular ligament is reduced by rotating the forearm into supination while holding pressure over the radial head. A palpable click or clunk can be felt. The child recovers active supination immediately and usually has immediate relief of discomfort. Immobilization is not required, but recurrent annular ligament subluxations can occur, and the parents should avoid activities that apply traction to the elbows. Parents can learn reduction maneuvers for recurrent episodes to avoid trips to the emergency department or pediatrician's office. Recurrent subluxation beyond 5 yr of age is rare. Irreducible subluxations tend to resolve spontaneously, with gradual resolution of symptoms over days to weeks; surgery is rarely indicated.

WRIST

The wrist is composed of the 2 forearm bones as well as the 8 carpal bones. The wrist allows flexion, extension, and radial and ulnar deviation through the radiocarpal and midcarpal articulations. Pronation and supination occur, at the wrist, through the distal radial ulnar joint. The wrist is a complex joint with numerous ligamentous and soft-tissue attachments. It has complex kinematics that allows for its generous range of motion, but when these kinematics are altered, significant dysfunction can occur.

Madelung Deformity

Madelung deformity is a deformity of the wrist that is characterized as radial and palmar angulations of the distal aspect of the radius (Fig. 681-5). Growth arrest of the palmar and ulnar aspect of the distal radial physis is the underlying cause of this deformity. Bony physeal lesions and an abnormal radiolunate ligament (Vicker's ligament) have been implicated. The deformity can be bilateral and affects girls more than boys.

Treatment

Treatment of Madelung's deformity is typically observation. Mild deformities can be observed until skeletal maturity. Moderate to severe deformities that either are painful or limit function may be candidates for surgical intervention. Surgical treatment for Madelung's deformity is often motivated by appearance. Patients and their families may be concerned about the palmar angulation of the wrist as well as the resulting prominent distal ulna.

There are a multitude of surgical options for treating Madelung's deformity. For the skeletally immature patient, resection of the tethering soft tissue (Vicker's ligament) and physiolysis (fat grafting of any bony lesion seen within the physis) is often the first option. When Madelung's deformity is encountered in skeletally mature patients, an osteotomy may be considered. Dorsal closing wedge, dome, and ulnar

Figure 681-3 Spectrum of phenotypes of radial dysplasia. **A,** Type 1 radius with a hypoplastic thumb. **B,** Type IV radius with an absent thumb. **C,** Radiograph of a type IV radius. **D** and **E**, Phocomelic radial deficiency. *(From Ho C: Disorders of the upper extremity. In Herring JA, editor:* Tachdjian's pediatric orthopaedics*, ed 5, Philadelphia, 2014, WB Saunders, Fig. 15-72, p. 391.)*

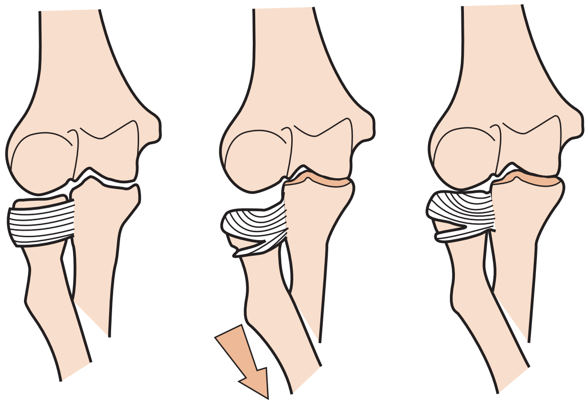

Figure 681-4 The pathology of nursemaid, or pulled, elbow. The annular ligament is partially torn when the arm is pulled. The radial head moves distally, and when traction is discontinued, the ligament is carried into the joint. *(From Rang M:* Children's fractures*, ed 2, Philadelphia, 1983, JB Lippincott, p. 193.)*

Figure 681-5 Radiograph of an adolescent with Madelung's deformity.

shortening osteotomies may be used alone or in combination to achieve the desired result.

Long-term considerations of Madelung's deformity concern the incongruity of the distal radial ulnar joint and resulting premature distal radial ulnar joint arthritis.

Ganglion

As a synovial joint, the wrist articulation is lubricated with synovial fluid, which is produced by the synovial lining of the joint and maintained within the joint by the joint capsule. A defect in the capsule can allow fluid to leak from the joint into the soft tissues, resulting in a ganglion. The term *cyst* is a misnomer, because this extraarticular collection of fluid does not have its own true lining. The defect in the capsule can occur as a traumatic event, although trauma is rarely a feature of the presenting history. The fluid usually exits the joint in the interval between the scaphoid and lunate, resulting in a ganglion located at the dorsoradial aspect of the wrist. Ganglia can occur at other locations, such as the volar aspect of the wrist, or in the palm as a result of leakage of fluid from the flexor tendon sheaths. Pain is not commonly associated with ganglia in children, and when it is, it is unclear whether the cyst is the cause of the pain. The diagnosis is usually evident on physical examination, especially if the lesion transilluminates. Extensor tenosynovitis and anomalous muscles can mimic ganglion cysts, but radiography or MRI is not routinely required. Ultrasonography is an effective, noninvasive tool to support the diagnosis and reassure the patient and family.

Treatment

Regarding the treatment of ganglia in children, consider the vowels AEIOU.

Aspiration: Simple aspiration of the fluid has a high recurrence rate and is painful for children given the large-bore needle required to aspirate the gelatinous fluid. However, in older children who would like try and decompress the cyst before considering surgery, this may be reasonable.

Excision: Surgical excision, including excision of the stalk connecting the ganglion to its joint of origin, has a high success rate, although the ganglion can recur.

Injection: Aspiration of the cyst and a simultaneous injection of a corticosteroid have been shown to be effective in treating recurrence in children.

Observation: Up to 80% of ganglia in children younger than 10 yr of age resolve spontaneously within 1 yr of being noticed. If the ganglion is painful or bothersome and the child is older than 10 yr of age, treatment may be warranted.

Ultrasound: For children's parents who are concerned about the mass and want a radiographic study to confirm the diagnosis, ultrasound is a noninvasive test to confirm the diagnosis.

HAND

The hand and fingers allow complex and fine manipulations. An intricate balance among extrinsic flexors, extensors, and intrinsic muscles allow these complex motions to occur. Congenital anomalies of the hand and upper extremity rank just behind cardiac anomalies in incidence, and like cardiac anomalies, if they are not properly identified and remedied, they can have long-term consequences.

Camptodactyly

Camptodactyly is a nontraumatic flexion contracture of the proximal interphalangeal joint that is often progressive. The small and ring fingers are most often affected. Bilateralism is observed two-thirds of the time. The etiology of camptodactyly is varied. Several different hypotheses have been offered as to the cause of this condition. Camptodactyly can be divided into 3 different types (Table 681-3).

Treatment

Nonsurgical treatment is the primary treatment of camptodactyly. Mild contractures of <30 degrees are usually well tolerated and do not need treatment. Serial casting and static and dynamic splinting are the treatments of choice for preventing progression of contractures. This should be performed until the child is skeletally mature.

Surgical treatment is limited to the treatment of severe contractures. At the time of surgery, all contracted and anomalous structures are released. Results of contracture release for camptodactyly are mixed; often a loss of flexion results from an attempt to improve extension.

Clinodactyly

Angular deformity of the digit in the coronal plane, distal to the metacarpophalangeal joint is clinodactyly. The most commonly observed finding is a mild radial deviation of the small finger at the level of the distal interphalangeal joint. This is often because of a triangular or trapezoidal middle phalanx. In some cases, a disruption of the physis at the middle phalanx produces a longitudinal epiphysial bracket. This

Table 681-3 Classification of Camptodactyly

TYPE	CHARACTERISTICS
I	Congenital, no sex bias, small finger only
II	Acquired between ages 7 and 11 yr, typically progressive
III	Severe, significant contracture, bilateral, and associated with other musculoskeletal syndromes

Adapted from Kozin SH: Pediatric hand surgery. In Beredjiklian PK, Bozentka DJ, editors: Review of hand surgery, *Philadelphia, 2004, WB Saunders, pp. 223–245.*

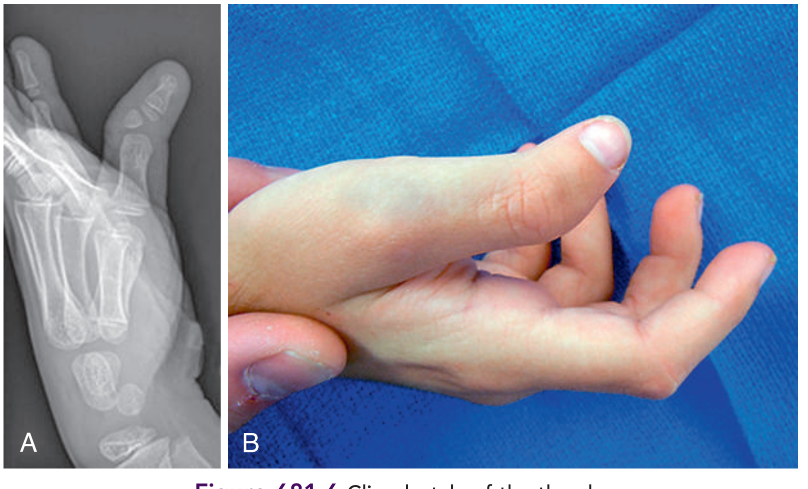

Figure 681-6 Clinodactyly of the thumb.

bracket is thought to be the underlying cause for the formation the "delta phalanx" that is often observed in clinodactyly. Clinodactyly has been observed in other fingers, including the thumb (Fig. 681-6) and ring finger.

Treatment

Often the treatment for clinodactyly is observation and not surgery. For severe deformities and for those affecting the thumb, surgery may be indicated. Surgery is technically demanding. Bracket resections, corrective osteotomies, and growth plate ablations are the most common procedures performed to correct the observed angular deformities. Results are good and recurrences are few when an appropriate procedure is performed.

Polydactyly

Polydactyly or duplication of a digit can occur either as a preaxial deformity (involving the thumb) or as a postaxial deformity (involving the small finger) (Table 681-4; Fig. 681-7). Each has an inherited and genetic component. Duplication of the thumb occurs more often in whites and Asians and is often unilateral, whereas duplication of the small finger occurs more frequently in African-Americans and may be bilateral. Transmission is typically in an autosomal dominant pattern and has been linked to defects in genes localized to chromosome 2.

Duplication of the thumb is subdivided on the basis of the degree of duplication. Table 681-5 lists the 7 types. Small finger duplication has been further subdivided into 2 types. Type A is a well-formed digit. Type B is a small, often underdeveloped supernumerary digit.

Treatment

Thumb and small finger duplication is typically treated with ablation of the supernumerary digit. Treatment options vary based on the

Table 681-4	Syndromes Associated with Polydactyly
Carpenter syndrome	
Ellis-van Creveld syndrome	
Meckel-Gruber syndrome	
Polysyndactyly	
Trisomy 13	
Orofaciodigital syndrome	
Rubinstein-Taybi syndrome	

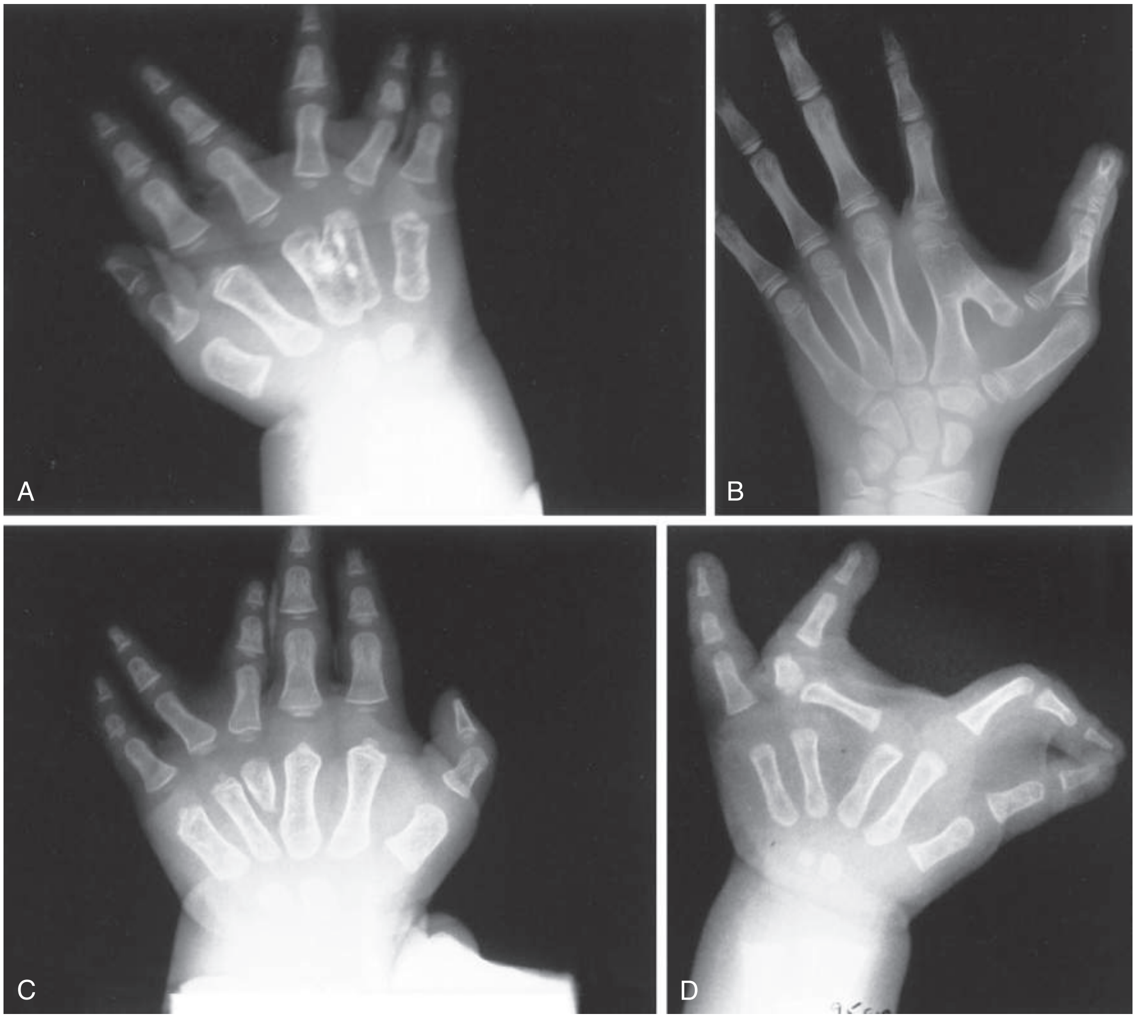

Figure 681-7 Several types of central polydactyly are recognized. Type I central polydactyly is characterized by no skeletal attachment of a soft-tissue mass. (No illustration of this unusual type is provided.) **A,** Type IIA central polydactyly: duplication on a common metacarpal or phalanx without syndactyly. **B,** Type IIB central polydactyly: duplication on a common metacarpal or phalanx with syndactyly to adjacent digits, which is often manifested as an extra digit hidden within a syndactyly. **C,** Type III central polydactyly. A complete duplication, including the metacarpal, is a rare anomaly. **D,** Relationship of central polydactyly and cleft hand. *(From From Ho C: Disorders of the upper extremity. In Herring JA, editor:* Tachdjian's pediatric orthopaedics*, ed 5, Philadelphia, 2014, WB Saunders, Fig. 15-99, p. 416.)*

degree of involvement. Less-well-formed digits can be treated with suture ligation. Well-formed digits require reconstructive procedures that preserve important structures such as the collateral ligaments and nail folds (Fig. 681-8).

Thumb Hypoplasia

Hypoplasia of the thumb is a challenging condition for both the patient and the doctor. The thumb represents approximately 40% of hand function. A less-than-optimal thumb can severely limit a patient's function as the patient grows and develops. Hypoplasia of the thumb can range from being mild with slight shortening and underdeveloped musculature to complete absence of the thumb (Fig. 681-9). Radiographs are useful to help determine osseous abnormalities. The most important finding on physical exam is the presence or absence of a stable carpometacarpal joint. This finding helps guide surgical treatment.

Treatment

If the thumb has a stable carpometacarpal joint, reconstruction is advised. Key elements of thumb reconstruction include rebuilding the ulnar collateral ligament of the metacarpophalangeal joint, tendon transfers to aid thumb abduction, and procedures to deepen the web space.

If a stable carpometacarpal joint is not present or the thumb is completely absent, **pollicization** (surgical construction of a thumb from a finger) is the definitive treatment. Pollicization is a complex procedure rotating the index finger along its neurovascular pedicle to form a thumb. This procedure is typically performed at around 1 yr of age and may be followed by subsequent procedures to deepen the web space or augment abduction (Fig. 681-10).

Syndactyly

Failure of the individual digits to separate during development produces syndactyly. Syndactyly is one of the more common anomalies observed in the upper limb (Table 681-6). It is seen in 0.5 of 1,000 live births. Syndactyly can be classified as simple (skin attachments only), complicated (bone and tendon attachments), complete (fusion to the tips, including the nail), or incomplete (simple webbing).

Treatment

Division of the conjoined digits should be considered before the 2nd yr of life. Border digits should be divided earlier (3-6 mo) because of concern for tethered growth of digits of unequal length. Digits of similar size, such as the ring and middle, may wait until the child is older to consider separation. Reconstruction of the web space and nail folds as well as appropriate skin-grafting techniques must be used to ensure the best possible functional and cosmetic result (Fig. 681-11).

Fingertip Injuries

Young children are fascinated with doorjambs or car doors and other tight spaces, making crush injuries to the fingertips quite common.

Table 681-5 Wassel Classification of Thumb Duplication

TYPE	CHARACTERISTICS
I	Bifid distal phalanx
II	Duplicate distal phalanx
III	Bifid proximal phalanx
IV	Duplicate proximal phalanx
V	Bifid metacarpal
VI	Duplicate metacarpal
VII	Triphalangeal component

Adapted from Wassel, HD: The results of surgery for polydactyly of the thumb. A review, Clin Orthop 125:175–193, 1969.

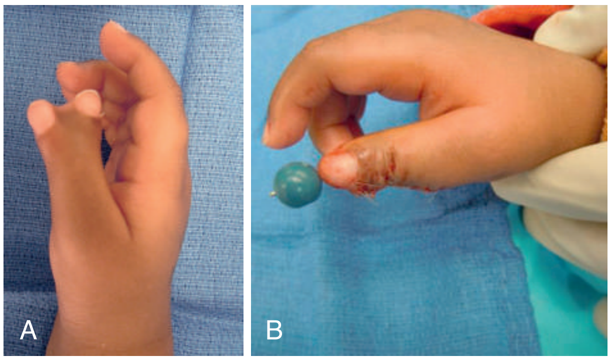

Figure 681-8 Pre- **(A)** and postoperative **(B)** pictures of a Wassel II thumb duplication.

Figure 681-9 Congenital absence of the thumb.

Figure 681-10 Postsurgical image after pollicization.

Injury can range from a simple subungual hematoma to complete amputation of part or the entire fingertip. Radiographs are important to rule out fractures. Physeal fractures associated with nail bed injuries are **open fractures** with a high risk of osteomyelitis, growth arrest, and deformity if not treated promptly with formal surgical debridement and reduction. Tuft fractures involving the very distal portion of the distal phalanx are common and require little specific treatment other than that for the soft-tissue injury.

The treatment of the soft-tissue injury depends on the type of injury. For suture repairs, only absorbable sutures should be used, because suture removal from a young child's fingertip can require sedation or general anesthesia. If a subungual hematoma exists but the nail is normal and no displaced fracture exists, the nail need not be removed for nail bed repair. If the nail is torn or avulsed, the nail should be removed, the nail bed and skin should be repaired with absorbable sutures, and the nail (or a piece of foil if the nail is absent) should be replaced under the eponychial fold to prevent scar adhesion of the eponychial fold to the nail bed that can prevent nail regrowth.

Table 681-6	Syndromes Associated with Syndactyly
Apert syndrome	Trisomy 21
Carpenter syndrome	Fetal hydantoin syndrome
de Lange syndrome	Laurence-Moon-Biedl syndrome
Holt-Oram syndrome	Fanconi pancytopenia
Orofaciodigital syndrome	Trisomy 13
Polysyndactyly	Trisomy 18

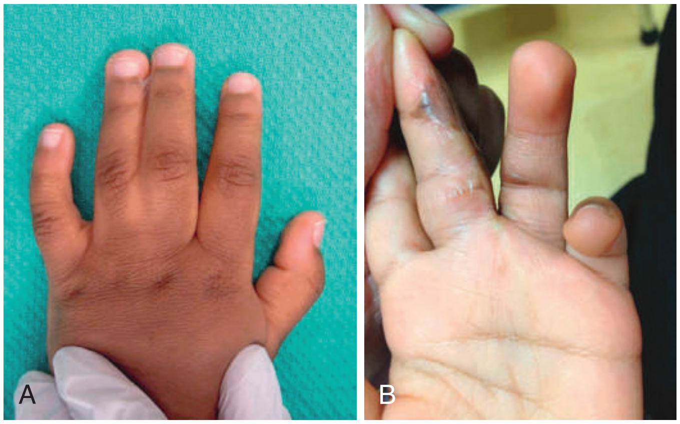

Figure 681-11 Pre- and postoperative pictures of a simple incomplete syndactyly.

If the fingertip is completely amputated, treatment depends on the level of amputation and the age of the child. Distal amputations of skin and fat in children younger than 2 yr of age can be replaced as a composite graft with a reasonable chance of surviving. Similar amputations in older children can heal without replacing the skin as long as no bone is exposed and the amputated area is small. A variety of coverage procedures exist for amputations through the mid-portion of the nail. Amputations at or proximal to the proximal edge of the fingernail should be referred emergently to a replant center for consideration for microvascular replantation. When referring, all amputated parts should be saved, wrapped in saline-soaked gauze, placed in a watertight bag, and then placed in ice water. Ice should never directly contact the part, because it can cause severe osmotic and thermal injury.

Trigger Thumb and Fingers

The flexor tendons for the thumb and fingers pass through fibrous tunnels made up of a series of pulleys on the volar surface of the digits. These tunnels, for reasons that are not well understood, can become tight at the most proximal or first annular pulley. Swelling of the underlying tendon occurs, and the tendon no longer glides under the pulley. In children, the most common digit involved is the thumb. It has classically been thought to be a congenital problem, but prospective screening studies of large numbers of neonates have failed to find a single case in a newborn child. The incidence of trigger thumb is approximately 3 per 1,000 children at 1 yr of age. Trauma is rarely a feature of the history, and the condition is often painless. Overall function is rarely impaired. A trigger thumb typically manifests with the inability to fully extend the thumb interphalangeal joint. A palpable nodule can be felt in the flexor pollicis longus tendon at the base of the thumb metacarpal phalangeal joint volarly. Other conditions can mimic trigger thumb, including the thumb-in-palm deformity of cerebral palsy. Similar findings in the fingers (index through small) are much less common and may be associated with inflammatory conditions such as juvenile rheumatoid arthritis (Fig. 681-12).

Treatment

Trigger thumbs spontaneously resolve in up to 30% of children in whom they are diagnosed before 1 yr of age. Spontaneous resolution beyond that age is not common. Corticosteroid injections are effective in adults but are not effective in children and risk injury to the nearby digital nerves. Surgical release of the first annular pulley is curative and is generally performed between 1 and 3 yr of age. Treatment of trigger fingers other than the thumb in children involves evaluation and treatment of any underlying inflammatory process and in some cases surgical decompression of the flexor sheath and possible flexor tendon partial excision.

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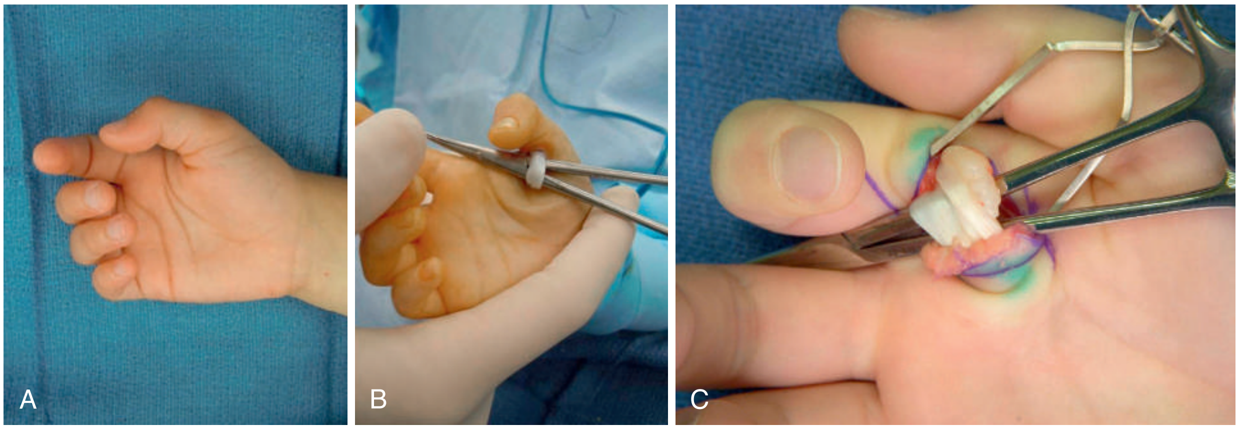

Figure 681-12 **A,** Clinical picture of trigger thumb in a 2 yr old. Note flexed posture of the interphalangeal joint. **B,** Intraoperative picture of flexor tendon following release of A1 pulley. **C,** Intraoperative picture of benign growth along flexor tendon causing triggering in an index finger.

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Chapter 682

Arthrogryposis

Helen M. Horstmann, Christine M. Conroy, and Richard S. Davidson

Arthrogryposis multiplex congenita refers to a heterogeneous group of muscular, neurologic, and connective tissue anomalies that present with 2 or more joint contractures at birth as well as muscle weakness. It is associated with abnormal contraction of muscle fibers, causing reduced mobility with a decreased active and passive arc of motion. Arthrogryposis is not a specific diagnosis but a descriptive term with various etiologies and complex clinical features, including multiple congenital contractures of various limb joints. It is associated with 200-300 different disorders encompassing malformations, malfunction, and neurologic deficiencies.

Approximately 1% of all births show some form of contractures of the joints ranging from unilateral clubfoot to pervasive, crippling contractures due to amyoplasia. Overall incidents of arthrogryposis have been reported to be 1 in 5,000-10,000 live births with equal gender ratios.

Although children with arthrogryposis have many other problems, such as micrognathia, nutrition issues, and sucking issues, here we focus on the orthopedic problems frequently seen in this group of children. In the absence of central nervous system lesions, many children have normal intelligence.

ETIOLOGY

In humans, both the intrinsic and extrinsic causes of arthrogryposis are categorized into 6 groups (Fig. 682-1), including a multitude of disorders (Table 682-1).

Neurologic Abnormalities

As one of the most common causes of arthrogryposis, neurologic abnormalities are present in 70-80% of cases. Patchy damage to the anterior horn cells of the spinal cord can lead to characteristic limb posturing of arthrogryposis. Neurologic disorders, such as spinal muscular atrophy and anterior horn disease, including Werdnig-Hoffmann disease, are associated with arthrogryposis; however, the type of anterior horn cell involvement is usually not from spinal muscular atrophy syndrome (Werdnig-Hoffman disease). Other, less-common neurologic disorders include neonatal myasthenia and myotonic dystrophy.

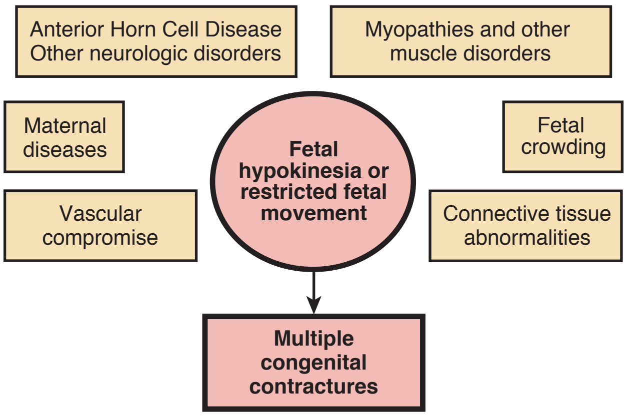

Figure 682-1 Etiology of arthrogryposis. *(Modified from Hall JG: Arthrogryposis multiplex congenital: Etiology, genetics, classification, diagnostic approach, and general aspects.* J Pediatr Orthop B *6:159–166, 1996.)*

Table 682-1 Associated Etiologies of Arthrogryposis

ARTHROGRYPOSIS CAUSED BY NERVOUS SYSTEM DISORDERS • Focal anterior horn cell deficiency • Generalized anterior horn cell deficiency • Structural brain disorder/damage • Uncertain location (Spastic conditions are excluded)
DISTAL ARTHROGRYPOSIS SYNDROMES • Type I dominant distal • Type IIa dominant distal (Gordon syndrome) • Type IIe distal • Digitotalar dysmorphism • Trismus pseudocamptodactyly • Distal distribution, type not specified
PTERYGIUM SYNDROMES • Multiple pterygium syndrome • Lethal multiple pterygium syndrome • Popliteal pterygium syndrome • Ptosis, scoliosis, pterygia • Antecubital webbing syndrome (Liebenberg)
MYOPATHIES • Emery-Dreifuss muscular dystrophy • Hypotonia, myopathy, mild contractures
ABNORMALITIES OF JOINTS AND CONTIGUOUS TISSUE • Congenital contractural arachnodactyly • Freeman-Sheldon syndrome • Laxity or hypertonicity with intrauterine dislocation and contractures • Larsen syndrome • Spondyloepimetaphyseal dysplasia with joint laxity • Trisomy 18, extended breech position with bilateral hip dislocation • Siblings with bifid humeri, hypertelorism, and hip and knee joint dislocations
SKELETAL DISORDERS • Diastrophic dysplasia • Parastremmatic dysplasia • Kniest dysplasia • Metatropic dysplasia • Campomelic dysplasia • Schwartz syndrome • Fetal alcohol syndrome with synostoses • Osteogenesis imperfecta with bowing/contractures
INTRAUTERINE/MATERNAL FACTORS • Fetal alcohol syndrome with contractures • Infections • Untreated maternal systemic lupus erythematosus • Intrauterine fetal constraint • Deformity (pressure) • Amniotic fluid leakage • Multiple pregnancies • Intrauterine tumors • Disruption (bands)
MISCELLANEOUS • Pseudotrisomy 18 with contractures • Roberts pseudothalidomide syndrome • Deafness with distal contractures • VACTERL association • Multiple abnormalities and contractures not otherwise specified • ARC
SINGLE JOINT • Campomelia • Symphalangism • "Trigger" finger

ARC, arthrogryposis, renal tubular acidosis, cholestasis; VACTERL, vertebral defects, imperforate anus, congenital heart disease, tracheoesophageal fistula, renal and limb defects.

Modified from Mennen U, Van Heest A, Ezaki MB, et al: Arthrogryposis multiplex congenita. J Hand Surg Br *30:5:468–474, 2005. Copyright 2005 The British Society for Surgery of the Hand.*

Muscular Abnormalities

These rare abnormalities affect the function and structure of the muscles. Some muscular diseases associated with arthrogryposis are muscular dystrophies, congenital muscular dystrophies (central core, nemaline, centronuclear), intrauterine myositis and mitochondrial diseases.

Limited Intrauterine Spacing

With a less than 0.1% occurrence rate, uterine constraint is rarely the primary cause of arthrogryposis. Maternal uterine anomalies will occasionally increase contractures of fetal limbs with arthrogryposis already existing. Other known causes are lack of amniotic fluid within the uterus and tumors, such as fibroids that can impinge on uterine space, preventing movement.

Connective Tissue Abnormalities

When the tendons, bones, joints, and joint lining develop atypically, decrease in fetal movement causes congenital contractures. Diseases such as diastrophic dysplasia and metatropic dwarfism result from connective tissue not developing properly. These are specific diagnoses resulting in limited joint motion and not true distal arthrogryposis. Other cases show that individuals who lack normal joint movement have distal joint involvement because the connective tissue develops normally but does not attach to the proper location around a joint bone or joint.

Maternal Diseases

Maternal diseases, such as multiple sclerosis, diabetes mellitus, myasthenia gravis, maternal hyperthermia, infection, drugs, and trauma, are associated with an increased incidence of arthrogryposis. In approximately 10% of neonates born to mothers with myasthenia gravis, maternal antibodies enter the fetal circulation through the placenta, causing transient myasthenia gravis; this inhibits fetal acetylcholine receptors, which leads to damaged fetal muscles.

Intrauterine Vascular Compromise

Inadequate vascular supply to the fetus causes fetal hypoxia resulting in anterior horn cell death, which decreases neurologic and myopathic function, resulting in fetal akinesia and secondary joint contractures. Multiple congenital contractures have been reported in individuals after bleeding throughout pregnancy or after a failed attempt at terminating the pregnancy.

CLASSIFICATION

Arthrogryposis multiplex congenita is divided into subgroups with different signs, symptoms, and causes as a practical way to make a differential diagnosis. Disorders involving primarily limbs such as **amyoplasia** and **distal arthrogryposis** are the most common subgroups (Table 682-2). Disorders involving limbs *and* other body parts typically represent a form of *multiple pterygium,* which is characterized by a web-like membrane that forms across joints affecting a child's ability to extend and causing fixed flexion. Disorders with limb involvement and abnormal neurologic function are caused by atypical central nervous system, peripheral nervous system, and damaged or absent anterior horn cells.

Amyoplasia, also known as *classic arthrogryposis,* is a sporadic symmetric disorder that causes fibrotic replacement of the muscles. Symptoms include internally rotated and adducted shoulders, extended elbows, pronated forearms, flexed fingers and wrists, dislocated hips, feet with severe equinovarus contractures, and extended knees. Involved muscles are hypoplastic and fibrotic. Often patients have midfacial hemangioma. Intelligence is usually normal (Figs. 682-2 and 682-3).

Distal arthrogryposis is an autosomal dominant disorder that primarily affects the distal joints of the limbs. Characteristics of the upper limbs are medially overlapping fingers, clenched fists, ulnar deviation of fingers, camptodactyly, and hypoplasia. Lower limbs show talipes equinovarus, calcaneovalgus, vertical talus, or metatarsus varus (Fig. 682-4).

Ten different types of distal arthrogryposis have been categorized based on specific traits they share with each other.

MANAGEMENT OF ORTHOPEDIC PROBLEMS OF ARTHROGRYPOSIS

When a child is born with arthrogryposis, the many stiff or dislocated joints pose issues of timing and best practices of management.

Table 682-2 Current Labels and OMIM Numbers for the Distal Arthrogryposis Syndromes

SYNDROME	OMIM NUMBER
Distal arthrogryposis type 1	108120
Distal arthrogryposis type 2A (Freeman-Sheldon syndrome)	193700
Distal arthrogryposis type 2B (Sheldon-Hall syndrome)	601680
Distal arthrogryposis type 3 (Gordon syndrome)	114300
Distal arthrogryposis type 4 (scoliosis)	609128
Distal arthrogryposis type 5 (ophthalmoplegia, ptosis)	108145
Distal arthrogryposis type 6 (sensorineural hearing loss)	108200
Distal arthrogryposis type 7 (trismus-pseudocamptodactyly)	158300
Distal arthrogryposis type 8 (autosomal dominant multiple pterygium syndrome)	178110
Distal arthrogryposis type 9 (congenital contractural arachnodactyly)	121050
Distal arthrogryposis type 10 (congenital plantar contractures)	187370

From Bamshad M, Van Heest AE, Pleasure D: Arthrogryposis: a review and update. J Bone Joint Surg Am *91 Suppl 4:40–46, 2009, Table 1, p. 43.*

Figure 682-2 Infant with stiff elbows, wrists, fingers, dislocated left hip, valgus stiff knees, and clubfeet.

Figure 682-3 Infant with stiff elbows, wrists, fingers, dislocated left hip, clubfeet, and micrognathia.

Figure 682-4 Infant with club feet, stiff knees, dislocated hips, stiff fingers, and facial hemangioma.

Figure 682-5 Child with stiff elbows, wrists, knees, and clubfeet.

Figure 682-6 Infant with splints to extend metatarsophalangeal joints, wrists, and knees.

Typically a child can have stiff elbows, dislocated hips, dislocated, hyperextended or contracted knees, and clubfeet (Fig. 682-5). The stiffness and deformity need to be aggressively addressed through a combination of modalities. A team of clinicians including therapists for the upper and lower extremities, orthotists, and orthopedic surgeons will be involved.

Initially, passive range-of-motion exercises and judicious splinting directed and assisted by physical and occupational therapy will help to address the various deformities. Splinting and casting can be augmented by a taping program which can be taught to the family so that the taping can be redone frequently to take advantage of improved range of motion. The ingenuity of the therapists and/or orthotist to create the right splints and braces using appropriate thermoplastics, neoprene, Velcro, and other materials can be simple yet effective (Fig. 682-6).

The therapeutic and orthopedic goal for the child with arthrogrypotic limb deformities is to achieve maximal joint motion and to optimize joint position for function. In the lower extremities, the foot needs to be plantigrade. The knees need to have optimal motion for sitting and standing. Hips need to be stabilized especially if the child has walking potential. In the upper extremities, the goals should

Figure 682-7 Clubfeet in infant with arthrogryposis.

include positioning of 1 arm for feeding and the other for toileting in cases where there is extreme stiffness. Two-handed activities require some symmetry, which can be a challenging goal with extreme contractures and limited muscle strength.

Although scoliosis is common, it usually does not become a problem until adolescence.

FOOT PROBLEMS

Clubfoot deformities are the most commonly seen deformities with arthrogryposis (Fig. 682-7). A clubfoot has components of hindfoot equinus, midfoot varus, and forefoot adduction. Feet in arthrogryposis tend to be resistant to improvement but the traditional methods of treatment are nevertheless employed. Casting is begun shortly after birth in a method known as the Ponseti method. Casts are changed weekly until a plateau is reached and heel cord lengthening is needed. Other deformities such as vertical talus are also seen and are addressed in a similar approach although with appropriately differing techniques.

Persistent stiffness often leads to more comprehensive soft tissue releases. This is typically done around age 6-12 mo and is followed by 3 mo of further casting and additional bracing as needed, especially as the foot is growing. When deformities are not corrected in early childhood, additional bony surgery may be needed later. Some of the approaches to this involve bony wedge osteotomies, lateral column lengthening, bone decancellation or talectomy. Ilizarov ring or multiaxial monolateral external fixation with or without osteotomies are used in late correction of residual deformities.

Children with significant deformities are often in ankle foot orthoses through much of their lives to avoid deformity recurrence and to augment the standing base due to weak leg muscles. A plantigrade, pain free, stable foot is the goal of foot management. Foot stiffness is anticipated and unavoidable in arthrogryposis involving the foot.

KNEE PROBLEMS

Knee issues, including knee extension or flexion, subluxation, and stiffness, respond well to therapy and splinting. Knee flexion is more common in arthrogryposis. Infrequently it can structurally be complex and associated with skin webbing known as pterygiums. Pterygiums are resistant to nonsurgical intervention and require plastic Z lengthenings. In the case of a flexion contracture, the quadriceps musculature is often deficient and weak. Sometimes the casting and splinting of the knee contractures is insufficient. Hamstring lengthenings with additional posterior knee capsular releases are often needed.

In the case of knee hyperextension, the quadriceps are sometimes fibrotic and weak in spite of seeming to overpower the hamstrings. Casting and splinting should begin shortly after birth, which can be done in conjunction with clubfoot casting following the principles of Ponseti. If splinting and therapy fail, lengthening of the quadriceps can be achieved through release of the lateral medial quadriceps, with proximal detachment of the rectus femoris, lengthening of the quadriceps either percutaneously or through a mini open procedure which may minimize scarring.

Long-standing stiffness may lead to joint surface flattening permanently reducing the arc of motion. Repositioning the arc of motion may improve sitting or standing, a choice to be made by the patient, family and physician. Follow up bracing can help to compensate for weak, fibrotic muscles of the legs.

HIP PROBLEMS

Teratologic hip dislocations are common within the spectrum of arthrogryposis and usually require open reduction of the hip. Hips in a child with less upper-extremity involvement and more supple hips that are not pathologically stiff *may* respond to early treatment with a Pavlik harness. Knee hyperextension can often be treated with physical therapy and serial casting. Careful observation of the hip during knee flexion as tightening of the quadriceps and hip flexors can push the hip into posterior dislocation. Once some knee flexion has been achieved, the Pavlik harness can be useful in further flexing the knee and maintaining hip stability in the infant. Most often the hips are stiff and not reducible closed. For these, open reduction with pelvic reconstruction and femoral osteotomy are commonly required, typically at 1 yr of age. There is some controversy about reducing bilateral hip dislocations as a high failure rate can result in asymmetry of the pelvis, pain, leg length inequality, and stiffness. If a child has little ambulation potential, he may do as well retaining the bilateral hip dislocations and positioning the hips for sitting. Management judgment should be made in conjunction with the family guided by a pediatric hip surgeon.

Ambulation

As would be expected walking is more difficult for children with arthrogryposis due to the muscle weakness and limited joint motion. Children with arthrogryposis who walk have lower activity levels and take fewer steps than their peers. Not surprisingly muscle fatigue and pain on exertion was noted in a study that included adults with distal arthrogryposis.

UPPER-EXTREMITY PROBLEMS

If splinting and a movement exercise program do not result in optimally functional upper extremities, surgical management may improve use of the arms of the child with arthrogryposis. A typical child with arthrogrypotic involvement of the upper extremities has internally rotated arms, extended elbows, flexed wrists, and thumb in palm or clasp thumb deformities (see Figs. 682-2 and 682-3).

Treatment is geared toward optimizing use of the arms and hands particularly for critical activities of daily living, such as feeding and toileting. Therapy to improve motion of the joints is started immediately after birth. Pediatric hand therapists are the optimal leaders of the mobility treatment program. Therapy is augmented by use of splints so that less-extensive surgery will be required. The elbow is the critical length adjuster of the arm, allowing the arm to reach out as is necessary for toileting or to approach the mouth for feeding. If necessary, lack of these motions can be compensated by modified silverware and other adaptive equipment, including arm extenders for grabbing.

Surgery of the Upper Extremity

Surgical correction of arthrogrypotic upper extremity contractures should be started after 1-3 mo and completed by age 12 mo so that the child can optimize his or her motor development. This allows for improved results optimizing the joint growth remodeling plasticity. One-stage procedures yield the best results. Delays in surgery result in more problems of intraarticular adhesions as well as fixed joint incongruity.

Shoulder

Because of the rotational capacity of the shoulder derotation osteotomy of the humerus is only occasionally needed. This is usually done in later childhood.

Elbow

A stiff elbow that does not respond to therapy requires surgical intervention starting with soft tissue and capsular release. Capsulotomy of the posterior elbow combined with a V-Y or Z reconstructive lengthening of the triceps allows improved elbow flexion. The triceps may need to be lengthened. Muscle transfer to the forearm can permit active elbow flexion. Each child needs individual assessment as to available flexor source. Most commonly available is the triceps. An elbow with some flexion is extremely important for arm function. Use of the triceps can create elbow flexion overpowering and contracture.

Wrist

Wrist flexion deformity is improved with soft-tissue balancing as well as partial carpectomies. The carpectomies need to be trapezoidal with more removed from the dorsum and the radial side to balance the wrist flexion contracture as well as the tendency for ulnar deviation. Thumb adduction may require an adductor release with an opponensplasty. Tendon transfers such as transfer of the extensor indicis pollicis to the extensor pollicis longus is helpful for improved function of the thumb in clasp thumb deformity.

Finger stiffness and wrist contractures often respond to therapy and bracing without need for surgery.

Scoliosis

Scoliosis is frequent in arthrogrypotic children, although the reported incidence of between 28% and 66% is probably skewed upward in reports as they reflect the experience of scoliosis surgeons. Scoliosis can be congenital or paralytic. The scoliosis is often accompanied by hip contractures associated with hip dislocation and compensatory lumbar lordosis. Curves <30 degrees can be treated initially with bracing in a thoracolumbar spinal orthosis (TLSO brace). After 40 degrees, spinal fusion is warranted.

Surgical Staging

At Children's Hospital of Philadelphia, surgical treatment of the lower limbs usually begins distally and works proximally. The feet are corrected around 6 mo of age, the knees around 8 mo of age, and the hips around 12 mo of age as pelvic osteotomy is often needed to stabilize the hips properly.

The upper extremities are corrected during infancy when the child is seen early. Hand, physical, and occupational therapy are a critical part of the team to optimize function and function prior to and after surgery. Further surgery as a child may be needed to tweak and optimize functional use of the upper and lower extremities.

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Chapter 683
Common Fractures

Keith D. Baldwin, Lawrence Wells, and John P. Dormans

Trauma is a leading cause of death and disability in children older than 1 yr of age (see Chapter 5.1). Several factors make fractures of the immature skeleton different from those involving the mature skeleton. The anatomy, biomechanics, and physiology of the pediatric skeletal system are different from those of adults. This results in different fracture patterns (Fig. 683-1), diagnostic challenges, and management techniques specific to children to preserve growth and function.

Epiphyseal lines, rarefaction, dense growth lines, congenital fractures, and pseudofractures appear on radiographs, which could confuse the interpretation of a fracture. Although most fractures in children heal well with indifferent treatment, some fractures terminate disastrously if handled with inexpertise. The differences in the pediatric skeletal system predispose children to injuries different from those of adults. The important differences are the presence of periosseous cartilage, physes, and a thicker, stronger, more osteogenic periosteum that produces new bone, called *callus*, more rapidly and in greater amounts. The pediatric bone has low density and more porosity. The low density is from lower mineral content and the increased porosity is the result of an increased number of haversian canals and vascular channels. These differences result in a comparatively lower modulus of elasticity and lower bending strength. The bone in children can fail either in tension or in compression; because the fracture lines do not propagate as in adults, there is less chance of comminuted fractures. Hence, pediatric bone can crush, splinter, and break incompletely, as opposed to adult bone which generally breaks like glass and may comminute.

A common teaching is that joint injuries, dislocation, and ligament disruptions are infrequent in children. Although this is generally true, MRI studies show that ligament damage in ankle injuries may not be as unusual as once thought. Damage to a contiguous physis is more likely. Interdigitating mammillary bodies and the perichondrial ring enhance the strength of the physes. Biomechanically, the physes are not as strong as the ligaments or metaphyseal bone. The physis is most resistant to traction and least resistant to torsional forces. The periosteum is loosely attached to the shaft of bone and adheres densely to the physeal periphery. The periosteum is usually injured in all fractures, but it is less likely to have complete circumferential rupture, because of its loose attachment to the shaft. This intact hinge or sleeve of periosteum lessens the extent of fracture displacement and assists in reduction and maintenance of reduction. The thick periosteum can also act as an impediment to closed reduction, particularly if the fracture has penetrated the periosteum, or in reduction of displaced growth plate.

683.1 Unique Characteristics of Pediatric Fractures

Keith D. Baldwin, Lawrence Wells, and John P. Dormans

FRACTURE REMODELING

Remodeling is the third and final phase in biology of fracture healing, preceded by the inflammatory and reparative phases. This occurs from a combination of appositional bone deposition on the concavity of deformity, resorption on the convexity, and asymmetric physeal growth. Thus, reduction accuracy is somewhat less important than it is in adults (Fig. 683-2). The 3 major factors that have a bearing on the potential for angular correction are skeletal age, distance to the joint, and orientation to the joint axis. The rotational deformity and angular deformity not in the axis of the joint motion are less likely to remodel. Remodeling is best when the fracture occurs close to the physis, the child has more growth remaining, has less deformity to remodel, and is adjacent to a rapidly growing physis (i.e., the proximal humerus). Remodeling typically occurs over the next several months following injury throughout skeletal maturity. Skeletal maturity is reached in girls between 13 and 15 yr of age, and in boys between 14 and 17 yr of age.

OVERGROWTH

Physeal stimulation from the hyperemia associated with fracture healing causes overgrowth. It is usually prominent in long bones such as the femur. The growth acceleration is usually present for 6 mo to 1 yr following the injury. Femoral fractures in children younger than 10 yr of age often overgrow by 1-3 cm. If external fixation or casting is employed, bayonet apposition of bone may be preferred to

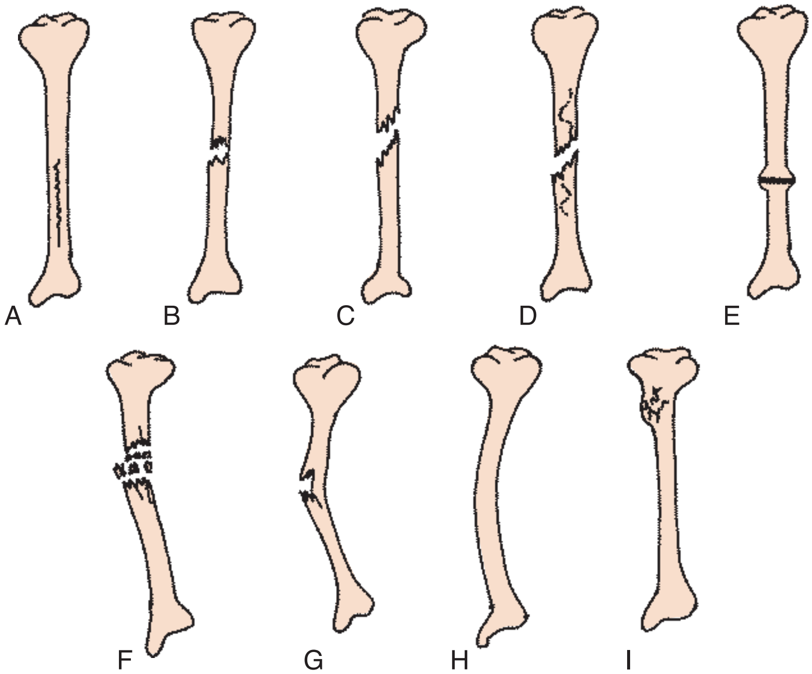

Figure 683-1 Illustration of fracture patterns. **A,** Longitudinal fracture line parallel to bony axis. **B,** Transverse fracture line perpendicular to bony axis. **C,** Oblique fracture line at angle to bony axis. **D,** Spiral fracture line runs a curvilinear course to the bony axis. **E,** Impacted fractured bone ends compressed together. **F,** Comminuted fragmentation of bone into 3 or more parts. **G,** Greenstick bending of bone with incomplete fracture of convex side. **H,** Bowing bone plastic deformation. **I,** Torus buckling fracture. *(From White N, Sty R: Radiological evaluation and classification of pediatric fractures,* Clin Pediatr Emerg Med *3:94–105, 2002.)*

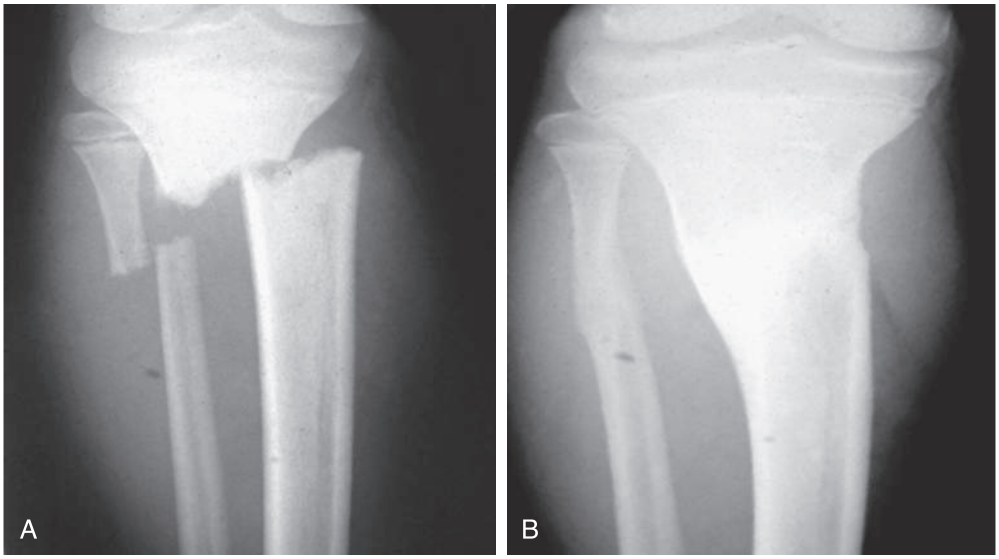

Figure 683-2 Remodeling in children is often extensive, as in this proximal tibial fracture **(A)** and as seen 1 yr later **(B).** *(From Dormans JP:* Pediatric orthopedics: introduction to trauma, *Philadelphia, 2005, Mosby, p. 38.)*

compensate for the expected overgrowth. This overgrowth phenomenon will result in equal or near equal limb lengths at the conclusion of fracture remodeling if the fracture shortens less than 2 cm. After 10 yr of age, overgrowth is less of a problem and anatomic alignment is recommended. In physeal injuries, growth stimulation is associated with use of implants or fixation hardware that can cause chronic stimulus for longitudinal growth.

PROGRESSIVE DEFORMITY

Injuries to the physes can be complicated by progressive deformities with growth. The most common cause is complete or partial closure of the growth plate. This can be common in fractures of the distal ulna, distal femur, and proximal tibia. An MRI can be helpful to diagnose percent of physeal closure after such an injury. Harris growth arrest lines may be observed in the setting of asymmetric growth and will point toward the area of growth arrest (Fig. 683-3). As a consequence, angular deformity, shortening, or both, can occur. The partial arrest may be peripheral, central, or combined. The magnitude of deformity depends on the physis involved and the amount of growth remaining.

RAPID HEALING

Children's fractures heal more quickly than adults as a result of children's growth potential and thicker, more active periosteum. As

Figure 683-3 **A,** Harris growth arrest lines on either side of the femur pointing centrally in the femur indicating a central growth arrest. **B,** Corresponding MRI image showing central growth arrest. *(**A** courtesy of Keith D. Baldwin, MD, MPH, Children's Hospital of Philadelphia.)*

children approach adolescence and maturity, the rate of healing slows and becomes similar to that of an adult.

Bibliography is available at Expert Consult.

683.2 Pediatric Fracture Patterns

Keith D. Baldwin, Lawrence Wells, and John P. Dormans

The different pediatric fracture patterns are the reflection of a child's characteristic skeletal system. The majority of pediatric fractures can be managed by closed methods and heal well.

PLASTIC DEFORMATION

Plastic deformation is unique to children. It is most commonly seen in the ulna and occasionally the fibula. The fracture results from a force that produces microscopic failure on the tensile side of bone and does not propagate to the concave side (Fig. 683-4). The concave side of bone also shows evidence of microscopic failure in compression. The bone is angulated beyond its elastic limit, but the energy is insufficient to produce a fracture. Thus, no fracture line is visible radiographically (Fig. 683-5). The plastic deformation is permanent, and a bend in the ulna of <20 degrees in a 4 yr old child is expected to correct with growth.

BUCKLE OR TORUS FRACTURE

A compression failure of bone usually occurs at the junction of the metaphysis and diaphysis, especially in the distal radius (Fig. 683-6). This injury is referred to as a *torus fracture* because of its similarity to the raised band around the base of a classic Greek column. They are inherently stable and heal in 3-4 wk with simple immobilization.

GREENSTICK FRACTURE

These fractures occur when the bone is bent, and there is failure on the tensile (convex) side of the bone. The fracture line does not propagate to the concave side of the bone (Fig. 683-7). The concave side shows evidence of microscopic failure with plastic deformation. It is necessary to break the bone on the concave side because the plastic deformation recoils it back to the deformed position.

COMPLETE FRACTURES

Fractures that propagate completely through the bone are called *complete fractures*. These fractures may be classified as spiral, transverse, or oblique, depending on the direction of the fracture lines. A rotational force usually creates the spiral fractures, and reduction is easy because of the presence of an intact periosteal hinge. Oblique fractures are in the diaphysis at 30 degrees to the axis of the bone and are inherently unstable. The transverse fractures occur following a 3-point

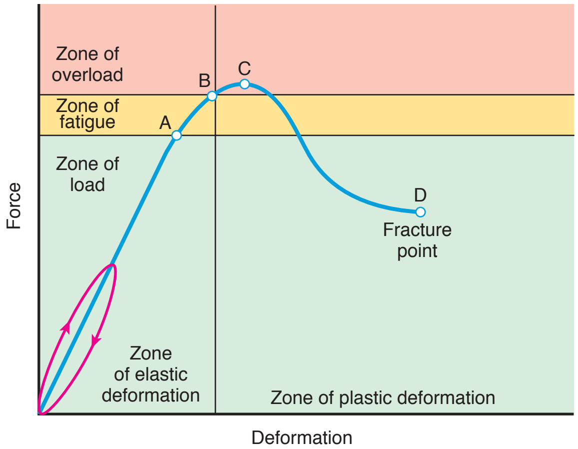

Figure 683-4 Graphic relation of bony deformation (bowing) and force (longitudinal compression) showing that the limit of an elastic response is not a fracture but plastic deformation. If the force continues, a fracture results. **A,** Reversible bowing with stress; **B,** microfractures occur; **C,** point of maximal strength; between **C** and **D,** bowing fractures; **D,** linear fracture occurs. *(Modified from Borden S IV: Roentgen recognition of acute plastic bowing of the forearm in children,* Am J Roentgenol Radium Ther Nucl Med *125:524–530, 1975.)*

Figure 683-5 Plastic deformation is a microfailure in tension without a visible fracture line. *(Courtesy of Dr. John Flynn, Children's Hospital, Philadelphia.)*

bending force and are easily reduced by using the intact periosteum from the concave side.

EPIPHYSEAL FRACTURES

The injuries to the epiphysis involve the growth plate. There is always a potential for deformity to occur, and hence long-term observation is

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necessary. The distal radial physis is the most commonly injured physis. Salter and Harris (SH) classified epiphyseal injuries into 5 groups (Table 683-1 and Fig. 683-8). This classification helps to predict the outcome of the injury and offers guidelines in formulating treatment. SH types I and II fractures usually can be managed by closed reduction techniques and do not require perfect alignment, because they tend to remodel with growth. SH type II fractures of the distal femoral epiphysis need anatomic reduction. The SH type III and IV epiphyseal fractures involve the articular surface and require anatomic alignment (<2 mm displacement) to prevent any step off and realign the growth cells of the physis. SH type V fractures are usually not diagnosed initially. They manifest in the future with growth disturbance. Other injuries to the epiphysis are avulsion injuries of the tibial spine and muscle attachments to the pelvis. Osteochondral fractures are also defined as physeal injuries that do not involve the growth plate.

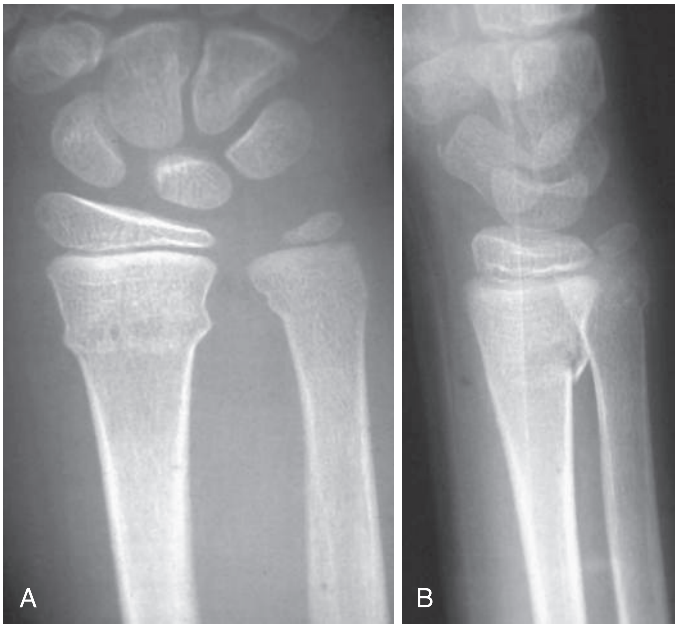

Figure 683-6 Buckle fracture is a partial failure in compression: anteroposterior **(A)** and lateral **(B)** radiographs of the distal radius. *(From Dormans JP: Pediatric orthopedics: introduction to trauma, Philadelphia, 2005, Mosby, p. 37.)*

Figure 683-7 This displaced distal radius fracture has an ulna fracture that is a greenstick (complete failure on the tensile side with microscopic failure on the compression side).

CHILD ABUSE

(See also Chapter 40.)

Fractures are the second most common manifestation of child abuse after skin injury (bruises, burns/abrasions). The orthopedic surgeon sees 30-50% of physically abused children. Child abuse should be expected in nonambulatory children with lower-extremity long-bone fractures. No fracture pattern or types are pathognomonic for child abuse; any type of fracture can result from nonaccidental trauma. The fractures that suggest nonaccidental injury include femur fractures in nonambulatory children (younger than age18 months), distal femoral metaphyseal corner fractures, posterior rib fractures, scapular spinous process fractures, and proximal humeral fractures. Fractures that were unwitnessed or carry a suspicious or changing story also warrant investigation. A full skeletal survey (as opposed to a "babygram") is essential in every suspected case of child abuse, because it can demonstrate other fractures in different stages of healing. Radiographically, some systemic diseases mimic signs of child abuse, such as osteogenesis imperfecta, osteomyelitis, Caffey disease, and fatigue fractures. Many hospitals have a multidisciplinary team to evaluate and treat patients who are victims of child abuse, these teams are critical to engage early and preferably in the emergency room setting, as difficulty arises managing these emotionally charged issues in a clinic setting. Dedicated teams are most well equipped to identify and manage these issues. It is mandatory to report these cases to social welfare agencies.

Bibliography is available at Expert Consult.

Table 683-1 Salter-Harris Classification

SALTER-HARRIS TYPE	CHARACTERISTICS
I	Separation through the physis, usually through the zones of hypertrophic and degenerating cartilage cell columns
II	Fracture through a portion of the physis but extending through the metaphyses
III	Fracture through a portion of the physis extending through the epiphysis and into the joint
IV	Fracture across the metaphysis, physis, and epiphysis
V	Crush injury to the physis

Figure 683-8 Salter-Harris classification of physeal fractures, types I-V.

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683.3 Upper Extremity Fractures

Keith D. Baldwin, Lawrence Wells, and John P. Dormans

PHALANGEAL FRACTURES

The different phalangeal fracture patterns in children include physeal, diaphyseal, and tuft fractures. The mechanism of injury is a direct blow to the finger or a finger trapped in a door (see Chapter 681). Crush injuries of the distal phalanx manifest with severe comminution of the underlying bone (tuft fracture), disruption of the nail bed, and significant soft-tissue injury. These injuries are best managed with antibiotics, tetanus prophylaxis, and irrigation. A mallet finger deformity is the inability to extend the distal portion of the digit and is caused by a hyperextension injury. It represents an avulsion fracture of the physis of the distal phalanx. The treatment is splinting the digit in extension for 3-4 wk. The physeal injuries of the proximal and middle phalanx are similarly treated with splint immobilization. Diaphyseal fractures may be oblique, spiral, or transverse in fracture geometry. They are assessed for angular and rotational deformity with the finger in flexion. The patient should be asked to make a fist. All fingers should point toward the scaphoid. If they do not, a malrotation is suspected, even in the presence of x-rays which appear minimally displaced. Any malrotation or angular deformity requires correction for optimal functioning of the hand. These deformities are corrected with closed reduction, and if unstable, they need stabilization.

FOREARM FRACTURES

Fractures of the wrist and forearm are very common fractures in children, accounting for nearly half of all fractures seen in the skeletally immature. The most common mechanism of injury is a fall on the outstretched hand. Eighty percent of forearm fractures involve the distal radius and ulna, 15% involve the middle third, and the rest are rare fractures of the proximal third of the radius or ulnar shaft. The majority of forearm fractures are torus or greenstick fractures. The torus fracture is an impacted fracture, and there is minimal soft-tissue swelling or hemorrhage. They are best treated in a short arm (below the elbow) cast and usually heal within 3-4 wk. Wrist buckle fractures have also been successfully treated with a removable splint. Impacted greenstick fractures of the forearm tend to be intrinsically stable (no cortical disruption) and may be managed with a soft bandage rather than casting.

Diaphyseal fractures can be more difficult to treat because the limits of acceptable reduction are much more stringent than for distal radial fractures. A significant malunion of a forearm diaphyseal fracture can lead to a permanent loss of pronation and supination, leading to functional difficulties. This is particularly true with malrotation of the fragments. Diaphyseal fractures are vulnerable to rotational malalignment due to insertion of the pronator muscle groups and the supinator groups. This malalignment is particularly hard to assess because the deformity is in the axial plane and is evaluated with anteroposterior (AP) and lateral radiographs (Fig. 683-9). The physical examination focuses on soft-tissue injuries and ruling out any neurovascular involvement. The AP and lateral radiographs of the forearm and wrist confirm the diagnosis. Displaced and angulated fractures require manipulative closed reduction under general anesthesia or conscious sedation. They are immobilized in an above-elbow cast for at least 6 wk. Both bone fractures in older children and adolescents (<10 yr of age) must be followed carefully as they are vulnerable to loss of reduction. Loss of reduction and unstable fractures require open reduction and internal fixation. Fixation may be with intramedullary nails or plate fixation, which yield equivalent results.

Figure 683-9 **A rotationally malaligned forearm fracture that initially had good alignment but lost reduction in the cast.** Note that the radial styloid is visible, but the biceps tuberosity is not. The 2 should normally be 180 degrees from one another. These landmarks are sometimes hard to appreciate in children but were visible on other views in this child.

DISTAL HUMERAL FRACTURES

Fractures around the elbow receive more attention because more aggressive management is needed to achieve a good result. Many injuries are intraarticular, involve the physeal cartilage, and can result in rare malunion or nonunion. As the distal humerus develops from a series of ossification centers, these ossification centers can be mistaken for fractures by inexperienced eyes. Careful radiographic evaluation is an essential part of diagnosing and managing distal humeral injuries. Observation of soft-tissue swelling and tenderness is critical to pick up subtle injuries. Common fractures include separation of the distal humeral epiphysis (transcondylar fracture), supracondylar fractures of the distal humerus, and epiphyseal fractures of the lateral condyle or medial epicondyle. The mechanism of injury is a fall on an outstretched arm. The physical examination includes noting the location and extent of soft-tissue swelling, ruling out any neurovascular injury, specifically anterior interosseous nerve involvement or evidence of compartment syndrome. A transcondylar fracture in neonates should raise suspicion of child abuse. AP and lateral radiographs of the involved extremity are necessary for the diagnosis. If the fracture is not visible, but there is an altered relationship between the humerus and the radius and ulna or the presence of a posterior fat pad sign, a transcondylar fracture or an occult fracture should be suspected. Imaging studies such as oblique radiographs, CT, MRI, and ultrasonography may be required for further confirmation. Displaced supracondylar fractures may be associated with concomitant neurovascular injury (Fig. 683-10) or, rarely, a compartment syndrome. Neurologic injury may also appear in the postoperative period. Careful neurologic examination of the hand before and after are needed to document and treat nerve injury. Preoperative nerve injury requires immediate attention and treatment of the fracture.

In general, distal humeral fractures need good restoration of anatomic alignment. This is necessary to prevent deformity and to allow for normal growth and development. Closed reduction alone, or in

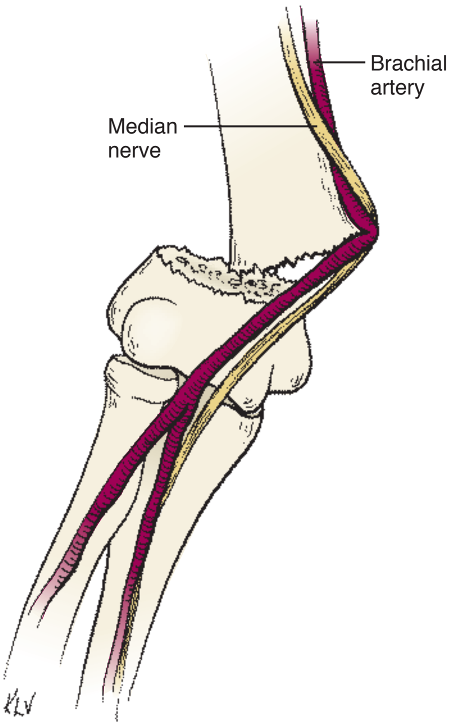

Figure 683-10 **Posterolaterally displaced type III (extension-type) supracondylar humeral fracture.** The proximal fragment displaces anteromedially. Thus placing the brachial artery and median nerve at risk. *(From Herring JA, Ho C: Upper extremity injuries. In Herring JA, editor:* Tachdjian's pediatric orthopaedics, *ed 5, Philadelphia, 2014, WB Saunders, Fig. 33-36, p. 1268.)*

association with percutaneous fixation, is the preferred method. Open reduction is indicated for fractures that cannot be reduced by closed methods, fractures with vascular compromise following closed reduction, open fractures, or interarticular fractures, particularly in older children. Inadequate reductions can lead to loss of motion, cubitus varus, cubitus valgus, and rare nonunion or elbow instability. Elbow stiffness is not as common as in adult fractures, but may occur with fractures which are severe or intra-articular.

PROXIMAL HUMERUS FRACTURES

Fractures of the proximal humerus account for <5% of fractures in children. They usually result from a fall onto an outstretched arm. The fracture pattern tends to vary with the age group. Children younger than 5 yr of age have an SH I injury, those 5-10 yr of age have metaphyseal fractures, and children older than 11 yr of age have SH II injury. Examination includes a thorough neurologic evaluation, especially of the axillary nerve. The diagnosis is made on AP radiographs of the shoulder. An axillary view is obtained to rule out any dislocation. Many children are too uncomfortable to tolerate this view. In this case, a Velpeau axillary can be obtained while the arm remains in a sling. SH I injuries do not require reduction because they have excellent remodeling capacity, and simple immobilization in a sling for 2-3 wk is sufficient. The proximal humerus contributes 80% of the growth to the humerus. The metaphyseal fractures usually do not need reduction unless the angulation is >50 degrees. A closed reduction with sling immobilization adequately treats this fracture. SH II fractures with <30 degrees of angulation and <50% displacement are managed in a sling. Displaced fractures are treated with closed reduction and further stabilization if unstable. Occasionally, open reduction is required because of button-holing of the fracture spike through the deltoid or interposition of the tendon of biceps. The majority of longitudinal growth of the limb comes from the proximal humeral physis. Additionally, the glenohumeral joint is capable of a large amount of motion. As such this area is extremely tolerant to deformity. Indications for open reduction are rare. However, as adolescents approach adulthood, these fractures will remodel less.

CLAVICULAR FRACTURES

Neonatal fractures occur as a result of direct trauma during birth, most often through a narrow pelvis or following shoulder dystocia. They can be missed initially and can appear with pseudoparalysis. Childhood fractures are usually the result of a fall on the affected shoulder or direct trauma to the clavicle. The most common site for fracture is the junction of the middle and lateral 3rd clavicle. Tenderness over the clavicle will make the diagnosis. A thorough neurovascular examination is important to diagnose any associated **brachial plexus injury.** Biceps function is important to assess as it is a prognostic indicator for future function.

An AP radiograph of the clavicle demonstrates the fracture and can show overlap of the fragments. Physeal injuries occur through the medial or lateral growth plate and are sometimes difficult to differentiate from dislocations of the acromioclavicular or sternoclavicular joint. Further imaging such as a CT scan may be necessary to further define the injury. Posterior medial clavicular physeal injuries are particularly problematic due to their proximity to the great vessels and the trachea. Closed vs open reduction with a cardiac/thoracic team on standby is necessary. This can be delayed if there is no sign of vascular or respiratory compromise.

The treatment of most clavicle fractures consists of an application of a figure-of-eight clavicle strap or a simple sling. A figure-of-eight strap will extend the shoulders and minimize the amount of overlap of the fracture fragments. Evidence exists for adults — that fractures that are shortened or displaced result in strength loss of the shoulder without anatomic reduction and fixation. Many centers are extending that indication to older adolescents, though the data are currently not as strong as for adults. If a fracture is tenting the skin, or open or resulting in neurovascular compromise, surgery is indicated. The physeal fractures are treated with simple sling immobilization without any reduction attempt. Often, anatomic alignment is not achieved, nor is it necessary. The fractures heal rapidly usually in 3-6 wk. A palpable mass of callus is usually visible in thin children. This remodels satisfactorily in 6-12 mo. Complete restoration of shoulder motion and function is uniformly achieved.

Bibliography is available at Expert Consult.

683.4 Fractures of Lower Extremity

Keith D. Baldwin, Lawrence Wells, and John P. Dormans

HIP FRACTURE

Hip fractures in children account for <1% of all children's fractures. These injuries result from high-energy trauma and are often associated with injury to the chest, head, or abdomen. Treatment of hip fractures in children entails a complication rate of up to 60%, an overall avascular necrosis rate of 50%, and a malunion rate of up to 30%. The unique blood supply to the femoral head accounts for the high rate of avascular necrosis. Fractures are classified by the Delbet classification as transphyseal separations, transcervical fractures, cervicotrochanteric fractures, and intertrochanteric fractures. The management principle includes urgent anatomic reduction (either open or closed), stable internal fixation (avoiding the physis if possible), and spica casting. Urgent management has been associated with a lower rate of avascular necrosis and superior overall outcomes. Capsular decompression also has been advocated as decreasing overall pressure on the epiphyseal vessels, and has been demonstrated experimentally. The clinical results have been mixed.

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Figure 683-11 A spiral fracture of the tibia in a 3 yr old (toddler fracture). The mechanism was a twisting fall.

TODDLER FRACTURE

Toddler fractures occur in young ambulatory children. The age range for this fracture is typically from around 1-4 yr (Fig. 683-11). The injury often occurs after a seemingly harmless twist or fall and is often unwitnessed. The children in this age group are usually unable to articulate the mechanism of injury clearly or to describe the area of injury well. The radiographs may show no fracture; the diagnosis is made by physical examination. The classic symptom is refusal to bear weight, which can manifest as pulling up the affected extremity or florid display of protest. The AP and lateral views of the tibia–fibula might show a nondisplaced spiral fracture of the distal tibial metaphysis. An oblique view is often helpful because the fracture line may be visible in only 1 of the 3 views. Inflammatory markers may be ordered to rule out infectious processes if the diagnosis is in doubt. Bone scans were employed in the past but impart a large amount of radiation to the child. The fracture is treated with an above-knee cast for approximately 3 wk.

PROXIMAL TIBIA FRACTURES

Proximal tibia fractures can be physeal injuries, metaphyseal injuries, or avulsion injuries of the tibial spine or tubercle. Physeal injuries can be either isolated or as part of tibial tubercle fracture. If the distal segment is displaced posteriorly the trifurcation of the popliteal vessels may be involved. Careful neurovascular examination is warranted both pre- and postreduction. Anatomic reduction and pin fixation is preferred with unstable fractures or displaced Salter-Harris III or IV fractures.

Proximal tibial metaphyseal fractures, or the so-called cozen fracture, are most common in the 3-6 yr old age group. They result in a late valgus deformity even if anatomically reduced. This deformity remodels within 1-2 yr but can cause great distress to parents and treating clinicians.

Tibial eminence fractures are fractures of the bony prominence that is the attachment of the anterior cruciate ligament. The mechanism of injury is similar to that of an anterior cruciate ligament tear in an adult. Displaced fractures require surgical reduction and fixation. This may be done either open or arthroscopically.

Tibial tubercle fractures are common in patients with Osgood-Schlatter syndrome. Care must be taken to observe for compartment syndrome as the injury is associated with injury of the recurrent anterior tibial artery. The injury may be treated non operatively if the fracture is displaced <2 mm and the patient has no extensor lag (rare). Open reduction and internal fixation is preferred otherwise.

Table 683-2 Femoral Shaft Fracture: Treatment Options by Age

TREATMENT OPTIONS	0-2 YR	3-5 YR	6-10 YR	>11 YR
Spica cast	x	x		
Traction and spica cast		x	x	x
Intramedullary rod		x	x	x
External fixator		x*	x*	x*
Screw or plate		x	x	x

*Open fracture.

Modified from Wells L: Trauma related to the lower extremity. In Dormans JP, editor: Pediatric orthopaedics: core knowledge in orthopaedics, *Philadelphia, 2005, Mosby, p. 93.*

TIBIA AND FIBULA SHAFT FRACTURES

The tibia is the most commonly fractured bone of the lower limb in children. This fracture generally results from a direct injury. Most tibial fractures are associated with a fibular fracture, and the mean age of presentation is 8 yr. The child has pain, swelling, and deformity of the affected leg and is unable to bear weight. Distal neurovascular examination is important in assessment. The AP and lateral radiographs should include the knee and ankle. Closed reduction and immobilization are the standard method of treatment. Most fractures heal well, and children usually have excellent results. Open fractures need to undergo irrigation and debridement, and antibiotic treatment. The tibia is a subcutaneous bone. Severe soft-tissue loss may necessitate plastic surgery consultation. Definitive external fixation vs internal fixation and simultaneous soft-tissue coverage are alternate treatment strategies to minimize infection. Tibia fractures are associated with compartment syndrome. Vigilance is necessary to avoid disastrous outcomes in the setting of missed compartment syndrome. Emergent fasciotomy is indicated as soon as compartment syndrome is diagnosed. Several return trips to the operating room are often necessary to close, vs cover, the fasciotomy wounds.

FEMORAL SHAFT FRACTURES

Fractures of the femur in children are common. All age groups, from early childhood to adolescence, can be affected. The mechanism of injury varies from low-energy twisting type injuries to high-velocity injuries in vehicular accidents. Femur fractures in children younger than age 2 yr should raise the concern for child abuse. A thorough physical examination is necessary to rule out other injuries and assess the neurovascular status. In the case of high-energy trauma, any signs of hemodynamic instability should prompt the examiner to look for other sources of bleeding. AP and lateral radiographs of the femur demonstrate the fracture. An AP radiograph of the pelvis is obtained to rule out any associated pelvic fracture. Treatment of shaft fractures varies with the age group, as described in Table 683-2.

TRIPLANE AND TILLAUX FRACTURES

Triplane and Tillaux fracture patterns occur at the end of the growth period and are based on relative strength of the bone–physis junction and asymmetric closure of the tibial physis. The triplane fractures are so named because the injury has coronal, sagittal, and transverse components (Fig. 683-12). The Tillaux fracture is an avulsion fracture of the anterolateral aspect of the distal tibial epiphysis. Radiographs and further imaging with CT and 3-dimensional reconstructions are necessary to analyze the fracture geometry. The triplane fracture involves the articular surface and hence anatomic reduction is necessary. The reduction is further stabilized with internal fixation. The Tillaux fracture is treated by closed reduction. Open reduction is recommended if a residual intraarticular step-off persists.

METATARSAL FRACTURES

Metatarsal fractures are common in children. They usually result from direct trauma to the dorsum of the foot. High-energy trauma or

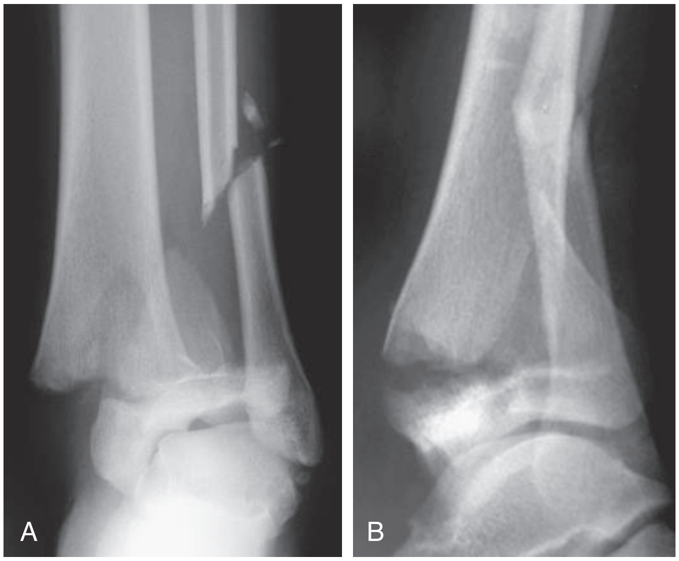

Figure 683-12 The triplane fracture is a transitional fracture: anteroposterior **(A)** and lateral **(B)** radiographs. *(From Dormans JP:* Pediatric orthopedics: introduction to trauma, *Philadelphia, 2005, Mosby, p. 38.)*

multiple fractures of the metatarsal base are associated with significant swelling. A high index for compartment syndrome of the foot must be maintained and compartment pressures must be measured if indicated. Diagnosis is obtained by AP, lateral, and oblique radiographs of the foot. Most metatarsal fractures can be treated by closed methods in a below-knee cast. Weight bearing is allowed as tolerated. Displaced fractures can require closed or open reduction with internal fixation. Percutaneous, smooth Kirschner wires generally provide sufficient internal fixation for these injuries. If the compartment pressure is increased, complete release of all compartments in the foot is necessary.

TOE PHALANGEAL FRACTURES

Fractures of the lesser toes are common and are usually secondary to direct blows. They commonly occur when the child is barefoot. The toes are swollen, ecchymotic, and tender. There may be a mild deformity. Diagnosis is made radiographically. Bleeding suggests the possibility of an open fracture. The lesser toes usually do not require closed reduction unless significantly displaced. If necessary, reduction can usually be accomplished with longitudinal traction on the toe. Casting is not usually necessary. Buddy taping of the fractured toe to an adjacent stable toe usually provides satisfactory alignment and relief of symptoms. Crutches and heel walking may be beneficial for several days until the soft-tissue swelling and the discomfort decrease.

Bibliography is available at Expert Consult.

683.5 Operative Treatment

Keith D. Baldwin, Lawrence Wells, and John P. Dormans

Surgery is required for 4-5% of pediatric fractures. The common indications for operative treatment in children and adolescents include displaced physeal fractures, displaced intraarticular fractures, unstable fractures, multiple injuries, open fractures, failure to achieve adequate reduction in older children, failure to maintain an adequate reduction, and certain pathologic fractures.

The aim of operative intervention is to obtain anatomic alignment and relative stability. Rigid fixation is not necessary as it is in adults for early mobilization. The relatively stable construct can be supplemented with external immobilization. SH types III and IV injuries require anatomic alignment, and if they are unstable, internal fixation is used (smooth Kirschner wires, preferably avoiding the course across the growth plate). Multiple closed reductions of an epiphyseal fracture are contraindicated because they can cause permanent damage to the germinal cells of the physis.

Table 683-3	Common Indications for External Fixation in Pediatric Fractures
Grades II and III open fractures Fractures associated with severe burns Fractures with soft-tissue loss requiring free flaps or skin grafts Fractures requiring distractions such as those with significant bone loss Unstable pelvic fractures Fractures in children with associated head injuries and spasticity Fractures associated with vascular or nerve repairs or reconstruction	

SURGICAL TECHNIQUES

It is important to take great care with soft tissues and skin. The other indications for open reduction and internal fixation are unstable fractures of the spine, ipsilateral fractures of the femur, neurovascular injuries requiring repair, and, occasionally, open fractures of the femur and tibia. Closed reduction and minimally invasive fixation are specifically used for supracondylar fractures of the distal humerus, phalangeal fractures. Failure to obtain anatomic alignment by closed means is an indication for an open reduction. Percutaneous techniques such as intramedullary fixation and minimally invasive plate osteosynthesis are increasingly popular as well.

As children become older and more similar to adults, techniques become more similar to adult techniques. The classic example of this is the femoral shaft fracture. Newborns may be treated with a soft dressing or Pavlik harness; young children may have a spica cast; older children will often be treated with flexible nails. Adolescents will frequently be treated with rigid intramedullary fixation similar to their adult counterparts.

Table 683-3 summarizes the main indications for external fixation. The advantages of external fixation include rigid immobilization of the fractures, access to open wounds for continued management, and easier patient mobilization for treatment of other injuries and transportation for diagnostic and therapeutic procedures. The majority of complications with external fixation are pin tract infections, chronic osteomyelitis, and refractures after pin removal.

Bibliography is available at Expert Consult.

683.6 Complications of Fractures in Children

Keith D. Baldwin, Lawrence Wells, and John P. Dormans

Complications of fractures in children can be as the result of the injury itself, of treatment, or of late effects of the injury on growth and development of the limb.

The fracture itself may cause growth arrest; this is most common in the proximal tibia, distal femur, and distal ulna. Fractures about the hip may cause avascular necrosis or premature physeal closure. Unacceptable alignment may cause loss of motion or limb malalignment. Fracture healing may cause cosmetically unappealing bumps or curves in the limb. Injuries to the limbs may cause neurovascular compromise or compartment syndrome. Nonunions are rare in children.

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Treatment may complicate fractures. Cast immobilization can result in cast ulcers, either from inadequate padding of bony prominences or from patients placing objects in the cast. Casts that are too tight can cause neurovascular compromise. Patients can get cast saw burns from using cast saws that are too dull to remove the cast. Improperly placed casts can promote fracture displacement. Improper follow-up of fractures can result in malunited fractures. Surgical treatment can be complicated by blood loss, neurovascular compromise, iatrogenic physeal damage and hardware complications such as infection or hardware failure.

Late effects of trauma can be from partial or complete closure of the physis. This can lead to limb angular deformity or shortening. Angular deformities can be treated by hemiepiphysiodesis or osteotomy. Reflex sympathetic dystrophy is another poorly understood late effect of trauma but can be debilitating. Physical and occupational therapists are very helpful in managing this condition. Some evidence exists that vitamin C may be useful in the acute setting of high-risk injuries to prevent this complication.

Chapter **684**

Osteomyelitis

Sheldon L. Kaplan

Bone infections in children are relatively common. Early recognition of osteomyelitis in young patients is of critical importance; prompt institution of appropriate medical and surgical therapy before extensive infection develops will minimize permanent damage. The risk is greatest if the physis (the growth plate of bone) is damaged.

ETIOLOGY

Bacteria are the most common pathogens in acute skeletal infections. *Staphylococcus aureus* (see Chapter 181.1) is the most common infecting organism in osteomyelitis among all age groups, including newborns. Community-acquired methicillin-resistant *S. aureus* (CA-MRSA) isolates account for more than 50% of *S. aureus* isolates recovered from children with osteomyelitis in some reports. The USA300 clone of *S. aureus* is the most common among CA-MRSA isolates in the United States and is more likely to cause venous thrombosis in children with acute osteomyelitis than other *S. aureus* clones or other bacteria for reasons that are not known.

Group B streptococcus (see Chapter 184) and Gram-negative enteric bacilli (*Escherichia coli,* see Chapter 200) are also prominent pathogens in neonates; group A streptococcus (see Chapter 183) constitutes <10% of all cases. After 6 yr of age, most cases of osteomyelitis are caused by *S. aureus,* streptococcus, or *Pseudomonas aeruginosa* (see Chapter 205). Cases of *Pseudomonas* infection are related almost exclusively to puncture wounds of the foot, with direct inoculation of *P. aeruginosa* from the foam padding of the shoe into bone or cartilage, which develops as osteochondritis. *Salmonella* species (see Chapter 198) and *S. aureus* are the 2 most common causes of osteomyelitis in children with sickle cell anemia (see Chapter 462.1). *Streptococcus pneumoniae* (see Chapter 182) most commonly causes osteomyelitis in children younger than 24 mo of age and in children with sickle cell anemia, but its frequency has declined because of pneumococcal conjugate vaccines. *Bartonella henselae* (see Chapter 209.2) can cause osteomyelitis of any bone, but especially in pelvic and vertebral bones.

Kingella kingae (see Chapter 193) may be the second most common cause of osteomyelitis in children younger than 5 yr of age in some parts of the world. The organism is increasingly recognized as a cause of osteomyelitis, spondylodiskitis, and septic arthritis, especially when polymerase chain reaction testing is employed. Nearly 90% of identified *K. kingae* infections have been in young children.

Infection with atypical mycobacteria (see Chapter 217), *S. aureus,* or *Pseudomonas* can occur after penetrating injuries. These organisms as well as coagulase-negative staphylococci or Gram-negative enteric bacteria may cause bone infection related to implanted materials such as spinal instrumentation or any orthopedic hardware. Fungal infections usually occur as part of multisystem disseminated disease; *Candida* (see Chapter 234) osteomyelitis sometimes complicates fungemia in neonates with or without indwelling vascular catheters.

A microbial etiology is confirmed in approximately 60% of cases of osteomyelitis. Blood cultures are positive in approximately 50% of patients. Prior antibiotic therapy and the inhibitory effect of pus on microbial growth might explain the low bacterial yield.

EPIDEMIOLOGY

The median age of children with musculoskeletal infections is approximately 6 yr. Bone infections are more common in boys than girls; the behavior of boys might predispose them to traumatic events. Except for the increased incidence of skeletal infection in patients with sickle cell disease, there is no predilection for osteomyelitis based on race.

The majority of osteomyelitis cases in previously healthy children are hematogenous. Minor closed trauma is a common preceding event in cases of osteomyelitis, occurring in approximately 30% of patients. Infection of bones can also follow penetrating injuries or open fractures. Bone infection following orthopedic surgery is unusually associated with an implanted surgical device. Impaired host defenses also increase the risk of skeletal infection. Table 684-1 lists other risk factors.

PATHOGENESIS

The unique anatomy and circulation of the ends of long bones result in the predilection for localization of bloodborne bacteria. In the metaphysis, nutrient arteries branch into nonanastomosing capillaries

Table 684-1 Microorganisms Isolated from Patients with Osteomyelitis and Their Clinical Associations

MOST COMMON CLINICAL ASSOCIATION	MICROORGANISM
Frequent microorganism in any type of osteomyelitis	*Staphylococcus aureus* (susceptible or resistant to methicillin)
Foreign body–associated infection	Coagulase-negative staphylococci, other skin flora, atypical mycobacteria, fungi
Common in nosocomial infections	*Enterobacteriaceae, Pseudomonas aeruginosa, Candida* spp.
Decubitus ulcer	*S. aureus*, streptococci, Gram-negative enterics, and/or anaerobic bacteria; polymicrobial infections are common
Sickle cell disease	*Salmonella* spp., *S. aureus*, or *Streptococcus pneumoniae*
Exposure to kittens	*Bartonella henselae*
Human or animal bites	*Pasteurella multocida* or *Eikenella corrodens*
Immunocompromised patients	*Aspergillus* spp., *Candida albicans,* or *Mycobacteria* spp.
Populations in which tuberculosis is prevalent	*Mycobacterium tuberculosis*
Populations in which these pathogens are endemic	*Brucella* spp., *Coxiella burnetii*, fungi found in specific geographic areas (coccidioidomycosis, blastomycosis, histoplasmosis)

Modified From Lew DP, Waldvogel FA: Osteomyelitis, Lancet *364:369–379, 2004.*

under the physis, which make a sharp loop before entering venous sinusoids draining into the marrow. Blood flow in this area is thought to be "sluggish," predisposing to bacterial invasion. Once a bacterial focus is established, phagocytes migrate to the site and produce an inflammatory exudate (metaphyseal abscess). The generation of proteolytic enzymes, toxic oxygen radicals, and cytokines results in decreased oxygen tension, decreased pH, osteolysis, and tissue destruction. As the inflammatory exudate progresses, pressure increases spread through the porous metaphyseal space via the haversian system and Volkmann canals into the subperiosteal space. Purulence beneath the periosteum may lift the periosteal membrane of the bony surface, further impairing blood supply to the cortex and metaphysis.

In newborns and young infants, transphyseal blood vessels connect the metaphysis and epiphysis, so it is common for pus from the metaphysis to enter the joint space. This extension through the physis has the potential to result in abnormal growth and bone or joint deformity. During the latter part of the 1st yr of life, the physis forms, obliterating the transphyseal blood vessels. Joint involvement, once the physis forms, can occur in joints where the metaphysis is intra-articular (hip, ankle, shoulder, and elbow), and subperiosteal pus ruptures into the joint space.

In later childhood, the periosteum becomes more adherent, favoring pus to decompress through the periosteum. Once the growth plate closes in late adolescence, hematogenous osteomyelitis more often begins in the diaphysis and can spread to the entire intramedullary canal. Septic arthritis contiguous with a site of osteomyelitis is also seen in older children with *S. aureus* osteomyelitis, which may be related to simultaneous hematogenous inoculation of bone and joint space.

CLINICAL MANIFESTATIONS

The earliest signs and symptoms of osteomyelitis, often subtle and nonspecific, are generally highly dependent on the age of the patient. Neonates might exhibit **pseudoparalysis** or pain with movement of the affected extremity (e.g., diaper changes). Half of neonates do not have fever and might not appear ill. Older infants and children are more likely to have pain, fever, and localizing signs such as edema, erythema, and warmth. With involvement of the lower extremities, limp or refusal to walk is seen in approximately half of patients.

Focal tenderness over a long bone can be an important finding. Local swelling and redness with osteomyelitis can mean that the infection has spread out of the metaphysis into the subperiosteal space, representing a secondary soft-tissue inflammatory response. Pelvic osteomyelitis can manifest with subtle findings such as hip, thigh, or abdominal pain. Back pain with or without tenderness to palpation overlying the vertebral processes is noted in vertebral osteomyelitis.

Long bones are principally involved in osteomyelitis (Table 684-2); the femur and tibia are equally affected and together constitute almost half of all cases. The bones of the upper extremities account for 25% of all cases. Flat bones are less commonly affected.

Usually only a single site of bone or joint is involved, although multiple sites of osteomyelitis may be noted in up to 20% of children with *S. aureus* infections. In neonates, 2 or more bones are involved in almost half of the cases. Children with subacute symptoms and focal findings in the metaphyseal area (usually of tibia) might have a **Brodie abscess,** with radiographic lucency and surrounding reactive bone. Typically the contents of Brodie abscesses are sterile (Fig. 684-1).

Table 684-2 Sites of Osteomyelitis in Children

BONE	PERCENT (%)	BONE	PERCENT (%)
Femur	23-28	Carpal bone	<1
Tibia	20-26	Rib	<1
Humerus	8-13	Metacarpal	<1
Radius	5-6	Cuboid	<1
Phalanx	2-4	Cuneiform	<1
Pelvis	5-9	Pyriform aperture	<1
Calcaneus	4-6	Olecranon	<1
Ulna	5-6	Maxilla	<1
Metatarsal	~2	Mandible	<1
Vertebrae	2-4	Scapula	<1
Sacrum	~2	Sternum	<1
Clavicle	1-2	Foot	1
Skull	~1		

Modified from Gafur OA, Copley LA, Hollmig ST, et al: The impact of the current epidemiology of pediatric musculoskeletal infection on evaluation and treatment guidelines, J Pediatr Orthop *28(7):777–785, 2008.*

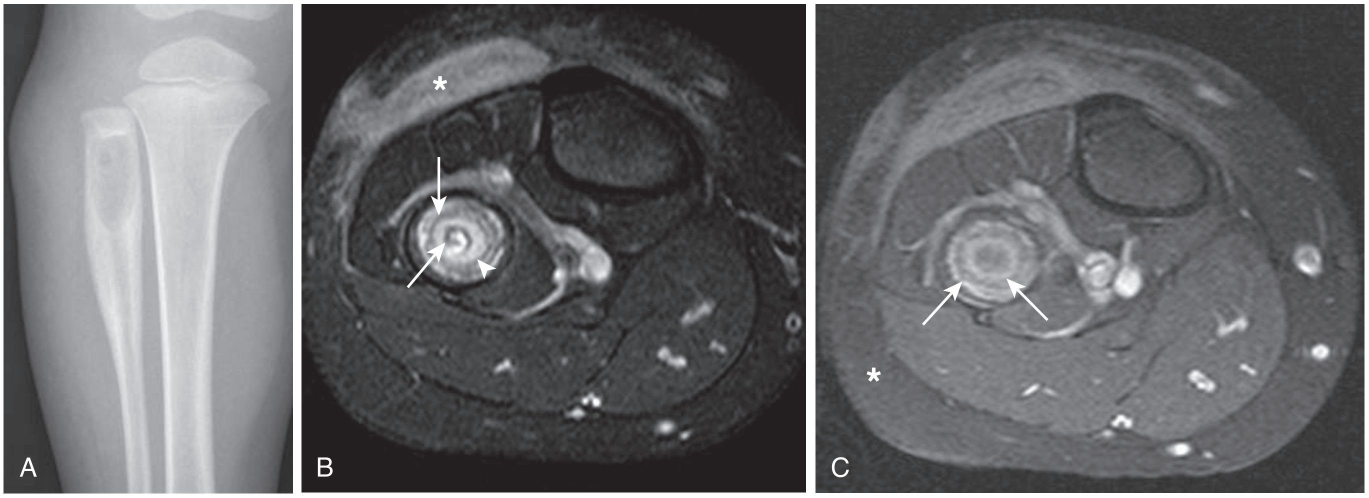

Figure 684-1 A, Radiograph demonstrates a lytic lesion in the proximal fibula with laminated thick periostitis. T2-weighted fat-saturated axial **(B)** and T1-weighted fat-saturated postgadolinium axial **(C)** magnetic resonance images demonstrate a Brodie abscess with sclerotic outer rim *(asterisk)* and inner granulation tissue with enhancement *(arrowhead).* Note the nonenhancing central abscess, which contains a small sequestrum *(arrows)* that is only seen on the T2-weighted fat-saturated sequence. *(From Kan JH, Azouz EM: Musculoskeletal infections. In Coley BD, editor:* Caffey's pediatric diagnostic imaging, *ed 12, Philadelphia, 2013, WB Saunders,* Fig. 138-15, *p. 1477.)*

Some patients with an adjacent deep venous thrombosis develop septic pulmonary emboli and are more acutely ill than those with a more insidious onset.

DIAGNOSIS

The diagnosis of osteomyelitis is clinical; **blood cultures should be performed in all suspected cases.** Depending on the results of imaging studies (see later) aspiration or biopsy of bone or subperiosteal abscess for Gram stain, culture, and possibly bone histology provides the optimal specimen for culture to confirm the diagnosis. These specimens are often obtained by the interventional radiologist or at the time of surgical drainage by the orthopedic surgeon. Direct inoculation of clinical specimens into aerobic blood culture bottles can improve the recovery of *K. kingae,* particularly if held for 1 wk. Polymerase chain reaction appears to be the most sensitive technique to detect *K. kingae*, even up to 6 days after antibiotics are initiated.

There are no specific laboratory tests for osteomyelitis. The white blood cell count and differential, erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) are generally elevated in children with bone infections but are nonspecific and not helpful in distinguishing between skeletal infection and other inflammatory processes. The leukocyte count and ESR may be normal during the 1st few days of infection, and normal test results do not preclude the diagnosis of skeletal infection. However, most children with acute hematogenous osteomyelitis have elevations in the ESR and/or CRP. Monitoring elevated ESR and CRP may be of value in assessing response to therapy or identifying complications.

RADIOGRAPHIC EVALUATION

Radiographic studies play a crucial role in the evaluation of osteomyelitis. Conventional radiographs, MRI, ultrasonography, CT, and radionuclide studies can all contribute to establishing the diagnosis. Plain radiographs are often used for initial evaluation to exclude other causes such as trauma and foreign bodies. The sequence of radionuclide studies or MRI is often determined by age, site, and clinical presentation.

Plain Radiographs

Within 72 hr of onset of symptoms of osteomyelitis, plain radiographs of the involved site using soft-tissue technique and compared to the opposite extremity, if necessary, can show displacement of the deep muscle planes from the adjacent metaphysis caused by deep-tissue edema. Lytic bone changes are not visible on radiographs until 30-50% of the bony matrix is destroyed. Tubular long bones do not show lytic changes for 7-14 days after onset of infection. Infection in flat and irregular bones can take longer to appear.

Computed Tomography and Magnetic Resonance Imaging

CT can demonstrate osseous and soft-tissue abnormalities and is ideal for detecting gas in soft tissues. In selected children who cannot remain still or tolerate sedation, CT is a valuable imaging modality. **MRI is more sensitive than CT or radionuclide imaging in acute osteomyelitis and is the best radiographic imaging technique for identifying abscesses and for differentiating between bone and soft-tissue infection.** MRI provides precise anatomic detail of subperiosteal pus and accumulation of purulent debris in the bone marrow and metaphyses for possible surgical intervention. In acute osteomyelitis, purulent debris and edema appear dark, with decreased signal intensity on T1-weighted images, with fat appearing bright (Figs. 684-2 and 684-3). The opposite is seen in T2-weighted images. The signal from fat can be diminished with fat-suppression techniques to enhance visualization. Gadolinium administration can also enhance MRI. Cellulitis and sinus tracts appear as areas of high signal intensity on T2-weighted images. Short tau inversion recovery MRI is a rapid imaging modality for osteomyelitis (Fig. 684-4). MRI can also demonstrate a contiguous or isolated septic arthritis, pyomyositis, or venous thrombosis.

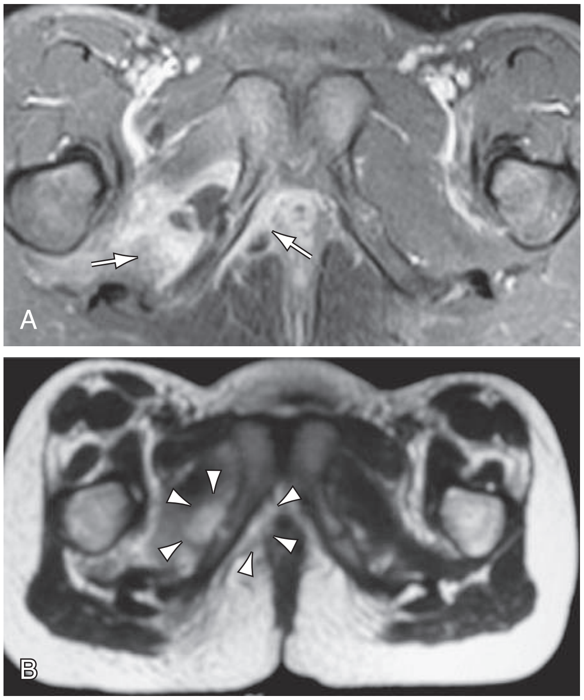

Figure 684-2 **MRI of an 8 yr old girl with acute pelvic hematogenous osteomyelitis. A,** Axial T1-weighted contrast-enhanced MRI with fat saturation reveals a nonenhancing fluid collection adjacent to the inflamed pubic synchondrosis. **B,** The fluid collection appears hyperintense on the corresponding T2-weighted image *(arrowheads).* In addition, a contrast enhancement within the adjacent internal obturator muscle is seen *(arrow),* indicating pelvic acute pelvic hematogenous osteomyelitis with complicating adjacent abscess formation and soft-tissue inflammation. *(From Weber-Chrysochoou C, Corti N, Goetschel P, et al: Pelvic osteomyelitis: a diagnostic challenge in children,* J Pediatr Surg *42:553–557, 2007.)*

Radionuclide Studies

Radionuclide imaging can be valuable in suspected bone infections, especially early in the course of infection and/or if multiple foci are suspected or an unusual site is suspected, as in the pelvis. Technetium-99 methylene diphosphonate (^{99m}Tc), which accumulates in areas of increased bone turnover, is the preferred agent for radionuclide bone imaging (3-phase bone scan). Osteomyelitis causes increased vascularity, inflammation, and increased osteoblastic activity, resulting in an increased concentration of ^{99m}Tc. Any areas of increased blood flow or inflammation can cause increased uptake of ^{99m}Tc in the 1st and 2nd phases, but osteomyelitis causes increased uptake of ^{99m}Tc in the 3rd phase (4-6 hr). Three-phase imaging with ^{99m}Tc has excellent sensitivity (84-100%) and specificity (70-96%) in hematogenous osteomyelitis and can detect osteomyelitis within 24-48 hr after onset of symptoms. The sensitivity in neonates is much lower, because of poor bone mineralization. Advantages include infrequent need for sedation, lower cost, and the ability to image the entire skeleton for detection of multiple foci.

DIFFERENTIAL DIAGNOSIS

Distinguishing osteomyelitis from cellulitis or trauma (accidental or abuse) is the most common clinical circumstance. Myositis or pyomyositis can also appear similar to osteomyelitis with fever, warm and swollen extremities, and limping; tenderness to palpation of the affected soft-tissue area is generally more diffuse than noted in acute osteomyelitis. Nevertheless, distinguishing myositis and pyomyositis from osteomyelitis clinically may be difficult. Myositis and pyomyositis may be isolated but are often found adjacent to an osteomyelitis on MRI. Pyomyositis is most often caused by *S. aureus* followed by group A streptococcus. The pelvic muscles are a common site of pyomyositis

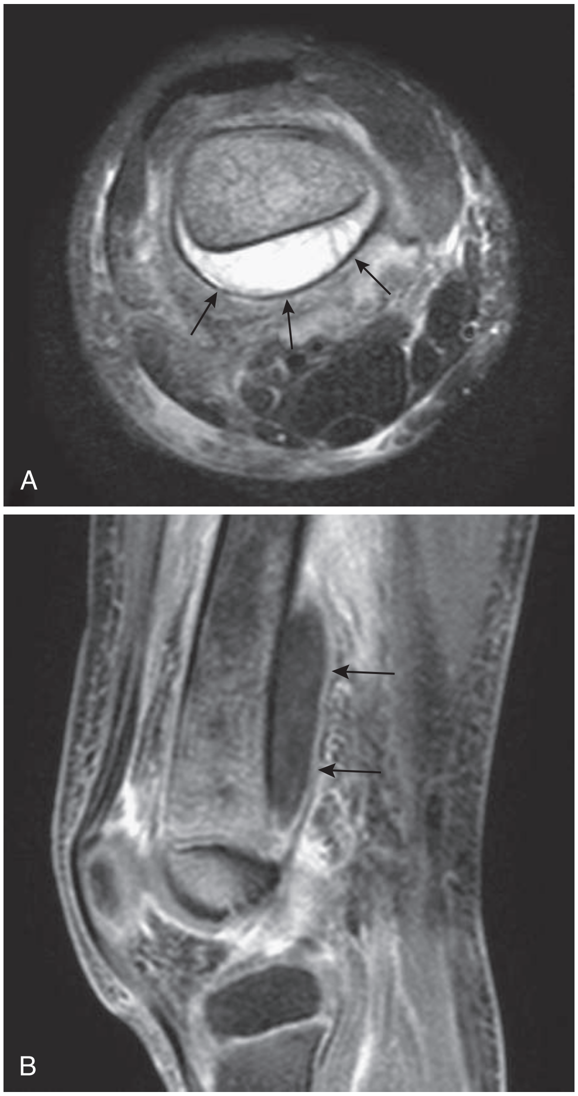

Figure 684-3 Acute osteomyelitis of the distal femur in a 5 yr old boy. **A,** T2-weighted fat-saturated axial MRI shows a large subperiosteal abscess *(arrows)* at the posterior aspect of the femur. Increased signal is seen within the bone, and there is adjacent soft-tissue edema. **B,** T1-weighted fat-saturated postgadolinium sagittal MRI shows the longitudinal extent of the subperiosteal abscess with enhancing wall *(arrows). (From Kan JH, Azouz EM: Musculoskeletal infections. In Coley BD, editor:* Caffey's pediatric diagnostic imaging, *ed 12, Philadelphia, 2013, WB Saunders,* Fig. 138-13, *p. 1476.)*

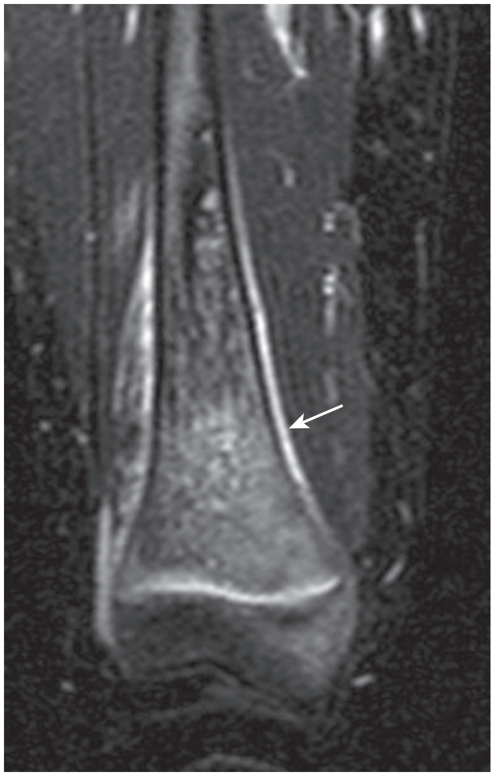

Figure 684-4 Short tau inversion (STIR) recovery coronal magnetic resonance image demonstrates a salt-and-pepper appearance to marrow edema and periosteal reaction *(arrow). (From Kan JH, Azouz EM: Musculoskeletal infections. In Coley BD, editor:* Caffey's pediatric diagnostic imaging, *ed 12, Philadelphia, 2013, WB Saunders,* Fig. 138-14, *p. 1477.)*

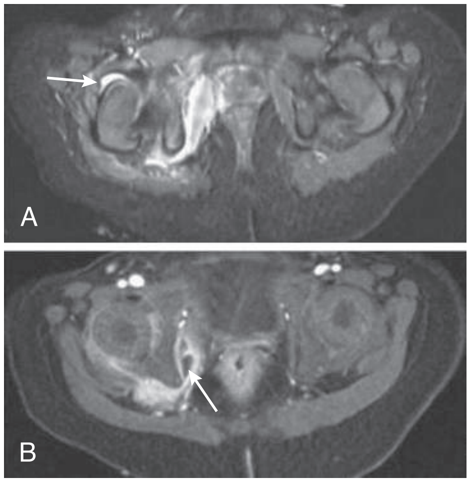

Figure 684-5 **A,** Axial short tau inversion recovery (STIR) MR demonstrates high signal in the left internal obturator muscle. **B,** Postcontrast fast multiplanar spoiled gradient recalled MR demonstrates a small abscess *(arrow).* This child had *Staphylococcus aureus* pyomyositis and responded to intravenous antibiotic treatment. *(From Karmazyn B, Loder RT, Kleiman MB, et al: The role of pelvic magnetic resonance in evaluating nonhip sources of infection in children with acute nontraumatic hip pain.* J Pediatr Orthop *27:158–164, 2007, Fig. 1, p. 160.)*

and can mimic a pelvic osteomyelitis. MRI is the definitive study to identify and localize pelvic pyomyositis (Fig. 684-5). An iliopsoas abscess can manifest with thigh pain, limp, and fever and must be considered in the differential diagnosis of osteomyelitis. The iliopsoas abscess may be primary (hematogenous: *S. aureus*) or secondary to infection in adjacent bone (*S. aureus*), kidney (*E. coli*) or intestine (*E. coli*, *Bacteroides* spp.). *Mycobacterium tuberculosis* has been reported in patients with HIV infection. Any child with negative bone imaging and a negative hip aspiration, who presents with fever, limp, and elevated inflammatory marks should be evaluated for pyomyositis.

Appendicitis, urinary tract infection, and gynecologic disease are among the conditions in the differential diagnosis of pelvic osteomyelitis. Children with leukemia commonly have bone pain or joint pain as an early symptom. Neuroblastoma with bone involvement may be mistaken for osteomyelitis. Primary bone tumors need to be considered, but fever and other signs of illness are generally absent except in Ewing sarcoma. In patients with sickle cell disease, distinguishing bone infection from infarction may be challenging.

Chronic recurrent multifocal osteomyelitis (CRMO) is a nonpyrogenic, sterile inflammatory bone disease that is considered an autoinflammatory disorder (see Chapter 163). It is also associated with a family history of autoimmune disease; the affected patient may also

Figure 684-6 MRI in a patient with chronic recurrent multifocal osteomyelitis. **A,** Whole-body image showing multiple foci of osteomyelitis, some of which are distributed symmetrically. **B,** Image of the ankle showing inflammatory metaphyseal and epiphyseal lesions. **C,** Image of the left femur showing involvement of the diaphysis with a soft-tissue reaction. *(From Wipff J, Adamsbaum C, Kahan A, Job-Deslandre C: Chronic recurrent multifocal osteomyelitis.* Joint Bone Spine *78:555–560, 2011, Fig. 3, p. 557.)*

have other inflammatory diseases such as Crohn disease, Sweet syndrome, psoriasis, and palmer plantar pustulosis. CRMO in children has many similarities with synovitis, acne, pustulosis, hyperostosis, and osteitis seen in adults. In addition, CRMO has similarities to Majeed syndrome, an autosomal recessive disorder with a microcytic dyserythropoietic anemia and with a deficiency of interleukin-1 receptor antagonist, an autosomal recessive autoinflammatory disease.

In contrast to infectious osteomyelitis, CRMO is multifocal, recurrent, and may involve bones not typical of osteomyelitis (spine, pelvis, clavicle, mandible, calcaneus). Plain radiographs reveal osteolytic lesions or sclerosis; whole-body short tau inversion recovery MRI imaging is the diagnostic study of choice (Fig. 684-6), followed by bone scan.

Pain in CRMO is usually insidious, noted at night; fever is not always present. The mean age of onset is 10 yr. The ESR and CRP may be elevated but are not as high as in bacterial osteomyelitis. Pain usually responds to nonsteroidal antiinflammatory drug agents or, in more severe cases, a short course of prednisone.

TREATMENT

Optimal treatment of skeletal infections requires collaborative efforts of pediatricians, orthopedic surgeons, and radiologists. Obtaining material for culture (blood, periosteal abscess, bone) **before** antibiotics are given is essential. Because most patients with osteomyelitis have an indolent, non–life-threatening condition, optimally cultures should be obtained, even if there is a delay of a few hours in initiating antibiotics.

Antibiotic Therapy

The initial empirical antibiotic therapy is based on knowledge of likely bacterial pathogens at various ages, the results of the Gram stain of aspirated material, and additional considerations. In neonates, an antistaphylococcal penicillin, such as nafcillin or oxacillin (150-200 mg/kg/24 hr divided q6h IV), and a broad-spectrum cephalosporin, such as cefotaxime (150-225 mg/kg/24 hr divided q8h IV), provide coverage for the methicillin-susceptible *S. aureus,* group B streptococcus, and Gram-negative bacilli. If methicillin-resistant *Staphylococcus* is suspected, vancomycin is substituted for nafcillin. If the neonate is a small premature infant or has a central vascular catheter, the possibility of nosocomial bacteria (Gram-negative enteric, *Pseudomonas,* or *S. aureus*) or fungi *(Candida)* should be considered. In older infants and children, the principal pathogens are *S. aureus* and streptococcus.

A major factor influencing the selection of empirical therapy is the rate of methicillin resistance among community *S. aureus* isolates. **If methicillin-resistant *S. aureus* (MRSA) accounts for ≥10% of community *S. aureus* isolates, including an antibiotic effective against CA-MRSA in the initial empirical antibiotic regimen is suggested.** Vancomycin (60 mg/kg/24 hr divided q6h IV) is the gold standard agent for treating invasive MRSA infections, especially when the child is critically ill. Clindamycin (40 mg/kg/24 hr q8hr) is also recommended when the rate of clindamycin resistance is ≤10% among community *S. aureus* isolates, the child is not severely ill and bacteremia is not a concern or blood cultures are known to be negative. Cefazolin (100 mg/kg/24 hr divided q8h IV) or nafcillin (150-200 mg/kg/24 hr divided q6h) is the agent of choice for parenteral treatment of osteomyelitis caused by methicillin-susceptible *S. aureus*. Penicillin is first-line therapy for treating osteomyelitis caused by susceptible strains of *S. pneumoniae* as well as all group A streptococci. Cefotaxime or ceftriaxone is recommended for pneumococcal isolates with resistance to penicillin and for most *Salmonella* spp.

Special situations dictate deviations from the usual empirical antibiotic selection. In patients with sickle cell disease with osteomyelitis, Gram-negative enteric bacteria *(Salmonella)* are common pathogens as well as *S. aureus,* so a broad-spectrum cephalosporin such as cefotaxime (150-225 mg/kg/24 hr divided q8h) is used in addition to vancomycin or clindamycin. Clindamycin (40 mg/kg/24 hr divided q6h IV) is a useful alternative drug for patients allergic to β-lactam drugs. In addition to good antistaphylococcal activity, clindamycin has broad activity against anaerobes and is useful for treating infections secondary to penetrating injuries or compound fractures. For immunocompromised patients, combination therapy is usually initiated, such as with vancomycin and ceftazidime, or with piperacillin-tazobactam and an aminoglycoside. *K. kingae* usually responds to β-lactam antibiotics, including cefotaxime. Although the efficacy of treating osteomyelitis

caused by *B. henselae* is uncertain, azithromycin plus rifampin may be considered.

When the pathogen is identified and antibiotic susceptibilities are determined, appropriate adjustments in antibiotics are made as necessary. If a pathogen is not identified and a patient's condition is improving, therapy is continued with the initially selected antibiotic. This selection is more complicated currently owing to the presence of MRSA isolates in the community. If a pathogen is not identified and a patient's condition is not improving, reaspiration or biopsy and the possibility of a noninfectious condition should be considered.

Duration of antibiotic therapy is individualized depending on the organism isolated and clinical course. For most infections including those caused by *S. aureus*, the minimal duration of antibiotics is 21-28 days, provided that the patient shows prompt resolution of signs and symptoms (within 5-7 days) and the CRP and ESR have normalized; a total of 4-6 wk of therapy may be required. For group A streptococcus, *S. pneumoniae,* or *Haemophilus influenzae* type b, treatment duration maybe shorter. A total of 7-10 postoperative days of treatment is adequate for *Pseudomonas* osteochondritis when thorough curettage of infected tissue has been performed. Immunocompromised patients generally require prolonged courses of therapy, as do patients with mycobacterial or fungal infection.

Changing antibiotics from the intravenous route to oral administration when a patient's condition clearly has improved and the child is afebrile for ≥48-72 hr may be considered. For the oral antibiotic regimen with β-lactam drugs for susceptible staphylococcal or streptococcal infection, cephalexin (80-100 mg/kg/24 hr q8h) or oral clindamycin (30-40 mg/kg/24 hr q8h) can be used to complete therapy for children with clindamycin-susceptible CA-MRSA or for patients who are seriously allergic or cannot tolerate β-lactam antibiotics. The oral regimen decreases the risk of complications related to prolonged intravenous therapy, is more comfortable for patients, and permits treatment outside the hospital if adherence to treatment can be ensured. Outpatient intravenous antibiotic therapy via a central venous catheter can be used for completing therapy at home, as an alternative; however, catheter-related complications, including infection or mechanical problems, can lead to readmission or emergency department visits.

In children with venous thrombosis complicating osteomyelitis, anticoagulants generally are administered under the supervision of a hematologist until the thrombus has resolved.

Surgical Therapy

When frank pus is obtained from subperiosteal or metaphyseal aspiration or is suspected based on MRI findings, a surgical drainage procedure is usually indicated. Surgical intervention is also often indicated after a penetrating injury and when a retained foreign body is possible. In selected cases, catheter drainage performed by an interventional radiologist is adequate.

Treatment of chronic osteomyelitis consists of surgical removal of sinus tracts and sequestrum, if present. Antibiotic therapy is continued for several months or longer until clinical and radiographic findings suggest that healing has occurred. Monitoring the CRP or ESR is not helpful in most cases of chronic osteomyelitis.

Physical Therapy

The major role of physical medicine is a preventive one. If a child is allowed to lie in bed with an extremity in flexion, limitation of extension can develop within a few days. The affected extremity should be kept in extension with sandbags, splints, or, if necessary, a temporary cast. Casts are also indicated when there is a potential for pathologic fracture. After 2-3 days, when pain is easing, passive range of motion exercises are started and continued until the child resumes normal activity. In neglected cases with flexion contractures, prolonged physical therapy is required.

PROGNOSIS

When pus is drained and appropriate antibiotic therapy is given, the improvement in signs and symptoms is rapid. Failure to improve or worsening by 72 hr requires review of the appropriateness of the antibiotic therapy, the need for surgical intervention, or the correctness of the diagnosis. Acute-phase reactants may be useful as monitors. The serum CRP typically normalizes within 7 days after start of treatment, whereas the ESR typically rises for 5-7 days, and then falls slowly, dropping sharply after 10-14 days. Failure of either of these acute-phase reactants to follow the usual course should raise concerns about the adequacy of therapy. Recurrence of disease and development of chronic infection after treatment occur in <10% of patients.

Because children are in a dynamic state of growth, sequelae of skeletal infections might not become apparent for months or years; therefore, long-term follow-up is necessary with close attention to range of motion of joints and bone length. Although firm data about the impact of delayed treatment on outcome are not available, it appears that initiation of medical and surgical therapy within 1 wk of onset of symptoms provides a better prognosis than delayed treatment.

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Chapter 685
Septic Arthritis

Sheldon L. Kaplan

Without early recognition and prompt institution of appropriate medical and surgical therapy, septic arthritis in infants and children has the potential to damage to the synovium, adjacent cartilage, and bone, and cause permanent disability.

ETIOLOGY

Historically, *Haemophilus influenzae* type b (see Chapter 194) accounted for more than half of all cases of bacterial arthritis in infants and young children. Since the development of the conjugate vaccine, it is now a rare cause; *Staphylococcus aureus* (see Chapter 181.1) is now the most common infection in all age groups. Methicillin-resistant *S. aureus* accounts for a high proportion (>25%) of community *S. aureus* isolates in many areas of the United States and throughout the world. Group A streptococcus (see Chapter 183) and *Streptococcus pneumoniae* (pneumococcus; see Chapter 182) historically cause 10-20%; *S. pneumoniae* is most likely in the 1st 2 yr of life, but its frequency has declined since the introduction of the pneumococcal conjugate vaccines. *Kingella kingae* is recognized as a relatively common etiology with improved culture and polymerase chain reaction methods in children younger than 5 yr old (see Chapters 193 and 684). In sexually active adolescents, gonococcus (see Chapter 192) is a common cause of septic arthritis and tenosynovitis, usually of small joints or as a monoarticular infection of a large joint (knee). *Neisseria meningitidis* (see Chapter 191) can cause either a septic arthritis that occurs in the 1st few days of illness or a reactive arthritis that is typically seen several days after antibiotics have been initiated. Group B streptococcus (see Chapter 184) is an important cause of septic arthritis in neonates.

Fungal infections usually occur as part of multisystem disseminated disease; *Candida* arthritis can complicate systemic infection in neonates with or without indwelling vascular catheters. Primary viral infections of joints are rare, but arthritis accompanies many viral (parvovirus, mumps, rubella live vaccines) syndromes, suggesting an immune-mediated pathogenesis.

A microbial etiology is confirmed in approximately 65% of cases of septic arthritis. Prior antibiotic therapy and the inhibitory effect of synovial fluid on microbial growth might explain the low bacterial yield. Additionally, some cases treated as bacterial arthritis are actually postinfectious (gastrointestinal or genitourinary) reactive arthritis (see Chapter 157) rather than primary infection. Lyme disease produces an arthritis more like a rheumatologic disorder and not typically suppurative.

EPIDEMIOLOGY

Septic arthritis is more common in young children. Half of all cases occur by 2 yr of age and three-fourths of all cases occur by 5 yr of age. Adolescents and neonates are at risk of gonococcal septic arthritis.

The majority of infections in otherwise healthy children are of hematogenous origin. Infection of joints can follow penetrating injuries or procedures such as trauma, arthroscopy, prosthetic joint surgery, intraarticular steroid injection, and orthopedic surgery, although this is uncommon. Immunocompromised patients and those with rheumatologic joint disease are also at increased risk of joint infection.

PATHOGENESIS

Septic arthritis primarily occurs as a result of hematogenous seeding of the synovial space. Less often, organisms enter the joint space by direct inoculation or extension from a contiguous focus. The synovial membrane has a rich vascular supply and lacks a basement membrane, providing an ideal environment for hematogenous seeding. The presence of bacterial products (endotoxin or other toxins) within the joint space stimulates cytokine production (tumor necrosis factor-α, interleukin-1) within the joint, triggering an inflammatory cascade. The cytokines stimulate chemotaxis of neutrophils into the joint space, where proteolytic enzymes and elastases are released by neutrophils, damaging the cartilage. Proteolytic enzymes released from the synovial cells and chondrocytes also contribute to destruction of cartilage and synovium. Bacterial hyaluronidase breaks down the hyaluronic acid in the synovial fluid, making the fluid less viscous and diminishing its ability to lubricate and protect the joint cartilage. Damage to the cartilage can occur through increased friction, especially for weight-bearing joints. The increased pressure within the joint space from accumulation of purulent material can compromise the vascular supply and induce pressure necrosis of the cartilage. Synovial and cartilage destruction results from a combination of proteolytic enzymes and mechanical factors.

CLINICAL MANIFESTATIONS

Most septic arthritides are monoarticular. The signs and symptoms of septic arthritis depend on the age of the patient. Early signs and symptoms may be subtle, particularly in neonates. Septic arthritis in neonates and young infants is often associated with adjacent osteomyelitis caused by transphyseal spread of infection, although osteomyelitis contiguous with an infected joint can be seen at any age (see Chapter 684).

Older infants and children might have fever and pain, with localizing signs such as swelling, erythema, and warmth of the affected joint. With involvement of joints of the pelvis and lower extremities, limp or refusal to walk is often seen.

Erythema and edema of the skin and soft tissue overlying the site of infection are seen earlier in septic arthritis than in osteomyelitis, because the bulging infected synovium is usually more superficial, whereas the metaphysis is located more deeply. Septic arthritis of the hip is an exception because of the deep location of the hip joint.

Joints of the lower extremity constitute 75% of all cases of septic arthritis (Table 685-1). The elbow, wrist, and shoulder joints are involved in approximately 25% of cases, and small joints are uncommonly infected. Suppurative infections of the hip, shoulder, elbow, and ankle in older infants and children may be associated with an adjacent osteomyelitis of the proximal femur, proximal humerus, proximal radius, and distal tibia because the metaphysis extends intraarticularly.

Table 685-1 Anatomic Distribution of Septic Arthritis

BONE	PERCENT (%)	BONE	PERCENT (%)
Knee	~40	Interphalangeal	<1
Hip	22-40	Metatarsal	<1
Ankle	4-13	Sacroiliac	<1
Elbow	8-12	Acromioclavicular	<1
Wrist	1-4	Metacarpal	<1
Shoulder	~3	Toe	~1

Modified from Gafur OA, Copley LA, Hollmig ST, et al: The impact of the current epidemiology of pediatric musculoskeletal infection on evaluation and treatment guidelines, J Pediatr Orthop *28:777–785, 2008.*

DIAGNOSIS

Blood cultures should be performed in all cases of suspected septic arthritis. Aspiration of the joint fluid for Gram stain and culture when the history and physical findings indicate septic arthritis remains the definitive diagnostic technique and provides the optimal specimen for culture to confirm the diagnosis. Most large joint spaces are easy to aspirate, but the hip can pose technical problems; ultrasound guidance facilitates aspiration. Aspiration of joint pus provides the best specimen for bacteriologic culture of infection. If gonococcus is suspected, cervical, anal, and throat cultures should also be obtained. In addition to prompt inoculation onto solid media, inoculation of the specimen in blood culture bottles can increase recovery of *K. kingae.* Polymerase chain reaction appears to be the most sensitive method for detecting *K. kingae* in joint fluid.

Synovial fluid analysis for cell count, differential, protein, and glucose has limited usefulness because noninfectious inflammatory diseases, such as rheumatic fever (see Chapter 183.1) and rheumatoid arthritis (see Chapter 155), can also cause exuberant reaction with increased cells and protein and decreased glucose. Nevertheless, cell counts >50,000-100,000 cells/mm^3 generally indicate an infectious process. Synovial fluid characteristics of septic arthritis can suggest infection but are not sufficiently specific to exclude infection. When the joint aspiration is negative, pyomyositis, especially of pelvic muscles, must be excluded by MRI (see Chapter 684).

The white blood cell count and differential, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are generally elevated in children with joint infections but are nonspecific and might not be helpful in distinguishing between infection and other inflammatory processes. The leukocyte count and ESR may be normal during the 1st few days of infection, and normal test results do not preclude the diagnosis of septic arthritis. Monitoring elevated ESR and CRP may be of value in assessing response to therapy or identifying complications. In one study of *S. aureus* septic arthritis, risk features for a site of osteomyelitis contiguous with septic arthritis included a CRP >10 mg/dL at the time of admission, positive blood cultures or more than 2 days of fever following admission.

Radiographic Evaluation

Radiographic studies play a crucial role in evaluating septic arthritis. Conventional radiographs, ultrasonography, CT, MRI, and radionuclide studies can all contribute to establishing the diagnosis (Fig. 685-1).

Plain Radiographs

Plain films of septic arthritis can show widening of the joint capsule, soft-tissue edema, and obliteration of normal fat lines. Plain films of the hip can show medial displacement of the obturator muscle into the pelvis (the obturator sign), lateral displacement or obliteration of the gluteal fat lines, and elevation of Shenton's line with a widened arc.

Ultrasonography

Ultrasonography is particularly helpful in detecting joint effusion and fluid collection in the soft-tissue and subperiosteal regions. Ultrasonography is highly sensitive in detecting joint effusion, particularly for the hip joint, where plain radiographs are normal in more than 50% of cases of septic arthritis of the hip. Ultrasonography can serve as an aid in performing hip aspiration.

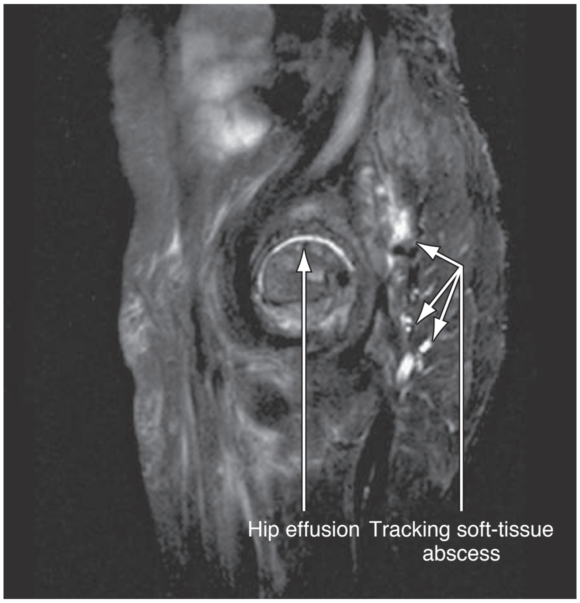

Figure 685-1 MRI of staphylococcal septic arthritis of left hip, with fluid collections between planes of gluteal muscles. *Arrows* indicate fluid collection. *(From Matthews CJ, Weston VC, Jones A, et al: Bacterial septic arthritis in adults,* Lancet *375:846–854, 2010.)*

Magnetic Resonance Imaging and Computed Tomography

MRI and CT may be useful in confirming the presence of joint fluid in patients with suspected osteoarthritis infections. MRI may be useful in excluding adjacent osteomyelitis.

Radionuclide Imaging

Radionuclide imaging compared to radiographs is more sensitive in providing supportive evidence of the diagnosis of septic arthritis; a scan may be positive within 2 days of the onset of symptoms. Three-phase imaging with technetium-99 methylene diphosphonate shows symmetric uptake on both sides of the joint, limited to the bony structures adjacent to the joint. Radionuclide imaging is also useful for evaluating the sacroiliac joint.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of septic arthritis depends on the joint or joints involved and the age of the patient. For the hip, toxic synovitis, pyomyositis, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, psoas abscess, and proximal femoral, pelvic, or vertebral osteomyelitis as well as diskitis should be considered. For the knee, distal femoral or proximal tibial osteomyelitis, pauciarticular rheumatoid arthritis, and referred pain from the hip should be considered. Knee or thigh pain may be referred from the hip. Other conditions such as trauma, cellulitis, pyomyositis, sickle cell disease, hemophilia, and Henoch-Schönlein purpura can mimic purulent arthritis. When several joints are involved, serum sickness, collagen vascular disease, rheumatic fever, and Henoch-Schönlein purpura should be considered. Arthritis is one of the extraintestinal manifestations of inflammatory bowel disease. Reactive arthritis following a variety of bacterial (gastrointestinal or genital) and parasitic infections, streptococcal pharyngitis, or viral hepatitis can resemble acute septic arthritis (see Chapter 157).

TREATMENT

Optimal treatment of septic arthritis requires cooperation of pediatricians, orthopedic surgeons, and radiologists to benefit the patient.

Antibiotic Therapy

The initial empirical antibiotic therapy is based on knowledge of likely bacterial pathogens at various ages, the results of the Gram stain of aspirated material, and additional considerations. In neonates, an antistaphylococcal penicillin, such as nafcillin or oxacillin (150-200 mg/kg/24 hr divided q6h IV), and a broad-spectrum cephalosporin, such as cefotaxime (150-225 mg/kg/24 hr divided q8h IV), provide coverage for the *S. aureus,* group B streptococcus, and Gram-negative bacilli. If methicillin-resistant *S. aureus* (MRSA) is a concern, vancomycin is selected in stead of nafcillin or oxacillin. If the neonate is a small premature infant or has a central vascular catheter, the possibility of nosocomial bacteria (*S. aureus*, Gram-negative enterics, or *Pseudomonas aeruginosa*) or fungi *(Candida)* should be considered.

In older infants and children with septic arthritis, empirical therapy to cover for *S. aureus*, streptococci, and *K. kingae* includes cefazolin (100-150 mg/kg/24 hr divided q8h) or nafcillin (150-200 mg/kg/24 hr divided q6h).

In areas where methicillin resistance is noted in ≥10% of community-acquired methicillin-resistant *S. aureus* strains (CA-MRSA), including an antibiotic that is effective against CA-MRSA isolates is suggested. Clindamycin (40 mg/kg divided q8h) and vancomycin (15 mg/kg q6 IV) are alternatives when treating CA-MRSA infections. For immunocompromised patients, combination therapy is usually initiated, such as with vancomycin and ceftazidime or with extended-spectrum penicillins and β-lactamase inhibitors with an aminoglycoside. Adjunct therapy with dexamethasone for 4 days with antibiotic therapy appeared to benefit children with septic arthritis in one study but has not been studied in children with CA-MRSA septic arthritis.

When the pathogen is identified, appropriate changes in antibiotics are made, if necessary. If a pathogen is not identified and a patient's condition is improving, therapy is continued with the antibiotic selected initially. If a pathogen is not identified and a patient's condition is not improving, reaspiration or the possibility of a noninfectious condition should be considered.

Duration of antibiotic therapy is individualized depending on the organism isolated and the clinical course. Ten to 14 days is usually adequate for streptococci, *S. pneumoniae*, and *K. kingae;* longer therapy may be needed for *S. aureus* and Gram-negative infections. Normalization of ESR and CRP in addition to a normal examination supports discontinuing antibiotic therapy. In selected patients, obtaining a plain radiograph of the joint before completing therapy can provide evidence (typically periosteal new bone) of a previously unappreciated contiguous site of osteomyelitis that would likely prolong antibiotic treatment. Oral antibiotics can be used to complete therapy once the patient is afebrile for 48-72 hr and is clearly improving.

Surgical Therapy

Infection of the hip is generally considered a surgical emergency because of the vulnerability of the blood supply to the head of the femur. For joints other than the hip, daily aspirations of synovial fluid may be required. Generally, 1 or 2 subsequent aspirations suffice. If fluid continues to accumulate after 4-5 days, arthrotomy or video-assisted arthroscopy is needed. At the time of surgery, the joint is flushed with sterile saline solution. Antibiotics are not instilled because they are irritating to synovial tissue, and adequate amounts of antibiotic are achieved in joint fluid with systemic administration.

PROGNOSIS

When pus is drained and appropriate antibiotic therapy is given, the improvement in signs and symptoms is rapid. Failure to improve or worsening by 72 hr requires review of the appropriateness of the antibiotic therapy, the need for surgical intervention, and the correctness of the diagnosis. Acute-phase reactants may be useful as monitors. Failure of either of these acute-phase reactants to follow the usual course should raise concerns about the adequacy of therapy. Recurrence of disease and development of chronic infection after treatment occur in <10% of patients.

Because children are in a dynamic state of growth, sequelae of skeletal infections might not become apparent for months or years; therefore, long-term follow-up is necessary, with close attention to range of motion of joints and bone length. Although firm data about the impact of delayed treatment on outcome are not available, it appears that initiation of medical and surgical therapy within 1 wk of onset of symptoms provides a better prognosis than delayed treatment.

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Section 2

Sports Medicine

Chapter 686

Epidemiology and Prevention of Injuries

Gregory L. Landry

The Centers for Disease Control and Prevention recommend moderate to vigorous physical activity on a regular basis for all adolescents. Physical activity has favorable effects on hypertension, obesity, and serum lipid levels in youths and is associated with lower rates of cardiovascular disease, type 2 diabetes mellitus, osteoporosis, and colon and breast cancer among adults.

Pediatricians should promote physical activity to their patients, especially those with lower rates of physical activity and sports participation, including children with special healthcare needs (see Chapter 717) and those from lower socioeconomic groups. Physicians also have the responsibility of providing medical clearance for participation in physical activity and sports and for diagnosis and rehabilitation of injuries.

Approximately 30 million children and adolescents participate in organized sports in the United States. Approximately 3 million injuries occur annually if injury is defined as time lost from the sport. Deaths in sports are rare, with the majority of nontraumatic deaths caused by cardiac diseases (see Chapter 436). Nonetheless, approximately 30% of life-threatening injuries in children presenting to an emergency room are sports related. Overall, injury rates and injury severity in sports increase with age and pubertal development, related to the greater speed, strength, and intensity of competition.

Identifying mechanisms of injury and establishing and enforcing rules that reduce the likelihood of that mechanism of injury, including penalizing dangerous play, have reduced catastrophic injury rates. Injury rates also have been reduced by removing environmental hazards, such as trampolines in gymnastics and stationary (vs breakaway) bases in softball, and by modifying heat injury rates in soccer tournaments by adding water breaks and reducing the playing time. Wearing equipment such as mouth guards can reduce dental injuries. A common reason for reinjury is lack of rehabilitation of old injuries; appropriate rehabilitation reduces injury rates. Preseason training for high school athletes, with an emphasis on speed, agility, jump training, and flexibility, is associated with lower injury rates in soccer and fewer serious knee injuries in female athletes. Traditional stretching maneuvers or massage have not been demonstrated to reduce the risk of injury or muscle soreness, but ankle taping is helpful particularly to prevent reinjury of the ankle. One setting for implementing some of these prevention strategies and for detecting unrehabilitated injuries and medical problems that could affect participation in sports is the preparticipation sports examination.

Table 686-1	Objectives of the Preparticipation Sports Examination

- Determination of the general health of the athlete
- Disclosure of defects that may limit participation
- Detection of conditions that may predispose the athlete to injury
- Determination of optimal level of performance
- Classification of the athlete according to individual qualifications
- Fulfillment of legal and insurance requirements for organized athletic programs
- Evaluation of size and level of maturation of younger athletes
- Improvement of fitness and performance
- Provision of opportunities for students to compete who have either physiologic or pathologic health conditions that may preclude blanket approval
- Provision of the opportunity to counsel youths and answer health and personal questions
- Entry of the athlete into the local sports medicine system establishing a doctor-patient relationship that continues

From Sanders B, Blackburn TA, Boucher B: Preparticipation screening-the sports physical therapy perspective. Int J Sports Phys Ther *8(2):180–193, 2013, Table 1.*

PREPARTICIPATION SPORTS EXAMINATION

The preparticipation sports examination (PSE) is performed with a directed history and a directed physical examination, including a screening musculoskeletal examination. It identifies possible problems in 1-8% of athletes and excludes fewer than 1% from participation. The PSE is not a substitute for the recommended comprehensive annual evaluation, which looks at behaviors that are potentially harmful to teens, such as sexual activity, drug use, and violence, and assesses for depression and suicidal ideation and addresses broader issues of prevention. Table 686-1 identifies the purposes of the PSE. If possible, the PSE should be combined with the comprehensive annual health visit with emphasis on preventive healthcare (see Chapters 5 and 16).

State requirements for how often a youth needs a PSE differ, ranging from annually to entry to a new school level (middle school, high school, college). At a minimum, a focused, annual interim evaluation should be done on an otherwise healthy young athlete. The PSE is optimally performed 3-6 wk before the start of practice.

History and Physical Examination

The essential components of the PSE are the history and focused medical and musculoskeletal screening examinations. Identified problems require more investigation (Tables 686-2 and 686-3). In the absence of symptoms, no screening laboratory tests are required.

Seventy-five percent of significant findings are identified by the history; a standardized questionnaire given to the parent and athlete is important because the young athlete might not know or might forget important aspects of his or her history. The questionnaire should include questions about previous medical, surgical, cardiac, pulmonary, neurologic, dermatologic, visual, psychologic, musculoskeletal, and menstrual problems, as well as about heat illness, medications, allergies, immunizations, and diet. The most commonly identified problems are **unrehabilitated injuries.** An investigation of previous injuries, including diagnostic tests, treatment, and present functional status, is indicated.

Sudden death during sports can result from undetected cardiac disease such as hypertrophic or other cardiomyopathies (see Chapter 439), anomalous coronary vessels (see Chapter 432.2), or a ruptured aorta in Marfan syndrome (see Chapter 702). In many cases, the underlying heart disease is not suspected, and death is the first sign of heart disease (see Chapter 436). However, in approximately 25-50% of cases,

Text continued on p. 3335

Table 686-2 Preparticipation Sports Examination

COMPONENT OF THE PHYSICAL EXAMINATION	CONDITION TO BE DETECTED
Vital signs	Hypertension, cardiac disease, brady- or tachycardia
Height and weight	Obesity, eating disorders, malabsorption
Vision and pupil size	Legal blindness, absent eye, anisocoria, amblyopia
Lymph node	Infectious diseases, malignancy
Cardiac (performed standing and supine)	Heart murmur, prior surgery, dysrhythmia
Pulmonary	Recurrent and exercise-induced bronchospasm, chronic lung disease
Abdomen	Organomegaly, abdominal mass
Skin	Contagious diseases (impetigo, herpes, staphylococcal, streptococcal)
Genitourinary	Varicocele, undescended testes, tumor, hernia
Musculoskeletal	Acute and chronic injuries, physical anomalies (scoliosis)

Table 686-3 Medical Conditions and Sports Participation

CONDITION	MAY PARTICIPATE	EXPLANATION
Atlantoaxial instability (instability of the joint between cervical vertebrae 1 and 2)	Qualified yes	Athlete (particularly if the athlete has Down syndrome or juvenile rheumatoid arthritis with cervical involvement) needs evaluation to assess the risk of spinal cord injury during sports participation, especially when using a trampoline
Bleeding disorder	Qualified yes	Athlete needs evaluation
Diabetes mellitus	Yes	All sports can be played with proper attention and appropriate adjustments to diet (particularly carbohydrate intake), blood glucose concentrations, hydration, and insulin therapy Blood glucose concentrations should be monitored before exercise, every 30 min during continuous exercise, 15 min after completion of exercise, and at bedtime
Eating disorders	Qualified yes	Athlete with an eating disorder needs medical and psychiatric assessment before participation
Fever	No	Elevated core temperature can indicate a pathologic medical condition (infection or disease) that is often manifest by increased resting metabolism and heart rate. Accordingly, during the athlete's usual exercise regimen, fever can result in greater heat storage, decreased heat tolerance, increased risk of heat illness, increased cardiopulmonary effort, reduced maximal exercise capacity, and increased risk of hypotension because of altered vascular tone and dehydration. On rare occasions, fever accompanies myocarditis or other conditions that can make usual exercise dangerous
Heat illness, history of	Qualified yes	Because of the likelihood of recurrence, the athlete needs individual assessment to determine the presence of predisposing conditions and behavior and to develop a prevention strategy that includes sufficient acclimatization (to the environment and to exercise intensity and duration), conditioning, hydration, and salt intake, as well as other effective measures to improve heat tolerance and to reduce heat injury risk (e.g., protective equipment and uniform configurations)
HIV infection	Yes	Because of the apparent minimal risk to others, all sports may be played as athlete's state of health allows (especially if viral load is undetectable or very low) For all athletes, skin lesions should be covered properly, and athletic personnel should use universal precautions when handling blood or body fluids with visible blood Certain sports (such as wrestling and boxing) can create a situation that favors viral transmission (likely bleeding plus skin breaks); if viral load is detectable, then athletes should be advised to avoid such high-contact sports
Malignant neoplasm	Qualified yes	Athlete needs individual assessment
Musculoskeletal disorders	Qualified yes	Athlete needs individual assessment

Continued

Table 686-3 Medical Conditions and Sports Participation—cont'd

CONDITION	MAY PARTICIPATE	EXPLANATION
Myopathies	Qualified yes	Athlete needs individual assessment
Obesity	Yes	Because of the increased risk of heat illness and cardiovascular strain, obese athletes particularly need careful acclimatization (to the environment and to exercise intensity and duration), sufficient hydration, and potential activity and recovery modifications during competition and training.
Organ transplant recipient (and those taking immunosuppressive medications)	Qualified yes	Athlete needs individual assessment for contact, collision, and limited-contact sports In addition to potential risk of infections, some medications (e.g., prednisone) increase tendency for bruising
Skin infections, including herpes simplex, molluscum contagiosum, verrucae (warts), staphylococcal and streptococcal infections (furuncles [boils], carbuncles, impetigo, methicillin-resistant *Staphylococcus aureus* [cellulitis and/or abscesses]), scabies, and tinea	Qualified yes	During contagious periods, participation in gymnastics or cheerleading with mats, martial arts, wrestling, or other collision, contact, or limited-contact sports is not allowed
Spleen, enlarged	Qualified yes	If the spleen is acutely enlarged, then participation should be avoided because of risk of rupture If the spleen is chronically enlarged, then individual assessment is needed before collision, contact, or limited-contact sports are played
CARDIOVASCULAR		
Carditis (inflammation of the heart)	No	Carditis can result in sudden death with exertion
Hypertension (high blood pressure)	Qualified yes	Those with hypertension >5 mm Hg above the 99th percentile for age, sex, and height should avoid heavy weightlifting and power lifting, bodybuilding, and high-static component sports Those with sustained hypertension (>95th percentile for age, sex, and height) need evaluation The National High Blood Pressure Education Program Working Group report defined prehypertension and stage 1 and stage 2 hypertension in children and adolescents younger than 18 yr of age
Congenital heart disease (structural heart defects present at birth)	Qualified yes	Consultation with a cardiologist is recommended Those who have mild forms may participate fully in most cases; those who have moderate or severe forms or who have undergone surgery need evaluation The 36th Bethesda Conference defined mild, moderate, and severe disease for common cardiac lesions
Heart murmur	Qualified yes	If the murmur is innocent (does not indicate heart disease), full participation is permitted; otherwise, athlete needs evaluation (see structural heart disease, especially hypertrophic cardiomyopathy and mitral valve prolapse)
Dysrhythmia (Irregular Heart Rhythm)		
Long-QT syndrome	Qualified yes	Consultation with a cardiologist is advised. Those with symptoms (chest pain, syncope, near-syncope, dizziness, shortness of breath, or other symptoms of possible dysrhythmia) or evidence of mitral regurgitation on physical examination need evaluation; all others may participate fully
Malignant ventricular arrhythmias	Qualified yes	
Symptomatic Wolff-Parkinson-White syndrome	Qualified yes	
Advanced heart block	Qualified yes	
Family history of sudden death or previous sudden cardiac event	Qualified yes	
Implantation of a cardioverter-defibrillator	Qualified yes	
Structural or Acquired Heart Disease		
Hypertrophic cardiomyopathy	Qualified no	Consultation with a cardiologist is recommended. The 36th Bethesda Conference provided detailed recommendations. Most of these conditions carry a significant risk of sudden cardiac death associated with intense physical exercise. Hypertrophic cardiomyopathy requires thorough and repeated evaluations, because disease can change manifestations during later adolescence. Marfan syndrome with an aortic aneurysm also can cause sudden death during intense physical exercise. An athlete who has ever received chemotherapy with anthracyclines may be at increased risk for cardiac problems owing to the cardiotoxic effects of the medications, and resistance training in this population should be approached with caution; strength training that avoids isometric contractions may be permitted. Athlete needs evaluation
Coronary artery anomalies	Qualified no	
Arrhythmogenic right ventricular cardiomyopathy	Qualified no	
Acute rheumatic fever with carditis	Qualified no	
Ehlers-Danlos syndrome, vascular form	Qualified no	
Marfan syndrome	Qualified yes	
Mitral valve prolapse	Qualified yes	
Anthracycline use	Qualified yes	
Vasculitis, vascular disease	Qualified yes	
Kawasaki disease (coronary artery vasculitis)	Qualified yes	Consultation with a cardiologist is recommended. Athlete needs individual evaluation to assess risk on the basis of disease activity, pathologic changes, and medical regimen
Pulmonary hypertension	Qualified yes	

Table 686-3 Medical Conditions and Sports Participation—cont'd

CONDITION	MAY PARTICIPATE	EXPLANATION
EYES		
Functionally 1-eyed athlete	Qualified yes	A functionally 1-eyed athlete is defined as having best-corrected visual acuity worse than 20/40 in the poorer-seeing eye. Such an athlete would suffer significant disability if the better eye were seriously injured, as would an athlete with loss of an eye. Specifically, boxing and full-contact martial arts are not recommended for functionally 1-eyed athletes, because eye protection is impractical and/or not permitted. Some athletes who previously underwent intraocular eye surgery or had a serious eye injury may have increased risk of injury because of weakened eye tissue. Availability of eye guards approved by the American Society for Testing and Materials and other protective equipment might allow participation in most sports, but this must be judged on an individual basis
Loss of an eye	Qualified yes	
Detached retina or family history of retinal detachment at young age	Qualified yes	
High myopia	Qualified yes	
Connective tissue disorder, such as Marfan or Stickler syndrome	Qualified yes	
Previous intraocular eye surgery or serious eye injury	Qualified yes	
Conjunctivitis, infectious	Qualified no	Athlete with active infectious conjunctivitis should be excluded from swimming
GASTROINTESTINAL		
Malabsorption syndromes (celiac disease or cystic fibrosis)	Qualified yes	Athlete needs individual assessment for general malnutrition or specific deficits resulting in coagulation or other defects; with appropriate treatment, these deficits can be treated adequately to permit normal activities
Short-bowel syndrome or other disorders requiring specialized nutritional support, including parenteral or enteral nutrition	Qualified yes	Athlete needs individual assessment for collision, contact, or limited-contact sports Central or peripheral indwelling venous catheter might require special considerations for activities and emergency preparedness for unexpected trauma to the device(s)
Hepatitis, infectious (primarily hepatitis C)	Yes	All athletes should receive hepatitis B vaccination before participation. Because of the apparent minimal risk to others, all sports may be played as the athlete's state of health allows For all athletes, skin lesions should be covered properly, and athletic personnel should use universal precautions when handling blood or body fluids with visible blood
Liver, enlarged	Qualified yes	If the liver is acutely enlarged, participation should be avoided because of risk of rupture If the liver is chronically enlarged, individual assessment is needed before collision, contact, or limited-contact sports are played Patients with chronic liver disease can have changes in liver function that affect stamina, mental status, coagulation, or nutritional status
Diarrhea, infectious	Qualified no	Unless symptoms are mild and athlete is fully hydrated, no participation is permitted, because diarrhea can increase risk of dehydration and heat illness (see fever)
GENITOURINARY		
Kidney, absence of one	Qualified yes	Athlete needs individual assessment for contact, collision, and limited-contact sports Protective equipment can reduce risk of injury to the remaining kidney sufficiently to allow participation in most sports, providing such equipment remains in place during the activity
Ovary, absence of one	Yes	Risk of severe injury to remaining ovary is minimal
Pregnancy and postpartum period	Qualified yes	Athlete needs individual assessment As pregnancy progresses, modifications to usual exercise routines become necessary; activities with high risk of falling or abdominal trauma should be avoided Scuba diving and activities posing risk of altitude sickness should also be avoided during pregnancy After the birth, physiologic and morphologic changes of pregnancy take 4-6 wk to return to baseline
Testicle, undescended or absence of 1	Yes	Certain sports require a protective cup
NEUROLOGIC		
Cerebral palsy	Qualified yes	Athlete needs evaluation to assess functional capacity to perform sports-specific activity
History of serious head or spine trauma or abnormality, including craniotomy, epidural bleeding, subdural hematoma, intracerebral hemorrhage, second-impact syndrome, vascular malformation, and neck fracture	Qualified yes	Athlete needs individual assessment for collision, contact, or limited-contact sports
History of simple concussion (mild traumatic brain injury), multiple simple concussions, and/or complex concussion	Qualified yes	Athlete needs individual assessment Research supports a conservative approach to concussion management, including no athletic participation while symptomatic or when deficits in judgment or cognition are detected, followed by graduated return to full activity
Recurrent headaches	Yes	Athlete needs individual assessment
Seizure disorder, well controlled	Yes	Risk of seizure during participation is minimal

Continued

Table 686-3 Medical Conditions and Sports Participation—cont'd

CONDITION	MAY PARTICIPATE	EXPLANATION
Seizure disorder, poorly controlled	Qualified yes	Athlete needs individual assessment for collision, contact, or limited-contact sports The following noncontact sports should be avoided: archery, riflery, swimming, weightlifting, power lifting, strength training, and sports involving heights; in these sports, a seizure during activity can pose a risk to self or others
Recurrent plexopathy (burner or stinger) and cervical cord neurapraxia with persistent defects	Qualified yes	Athlete needs individual assessment for collision, contact, or limited-contact sports; regaining normal strength is an important benchmark for return to play
RESPIRATORY		
Pulmonary compromise, including cystic fibrosis	Qualified yes	Athlete needs individual assessment but, generally, all sports may be played if oxygenation remains satisfactory during graded exercise test Athletes with cystic fibrosis need acclimatization and good hydration to reduce risk of heat illness
Asthma	Yes	With proper medication and education, only athletes with severe asthma need to modify their participation For those using inhalers, recommend having a written action plan and using a peak flowmeter daily Athletes with asthma might encounter risks when scuba diving
Acute upper respiratory infection	Qualified yes	Upper respiratory obstruction can affect pulmonary function Athlete needs individual assessment for all except mild disease (see fever)
RHEUMATOLOGIC		
Juvenile rheumatoid arthritis	Qualified yes	Athletes with systemic or polyarticular juvenile rheumatoid arthritis and history of cervical spine involvement need radiographs of C1 and C2 to assess risk of spinal cord injury Athletes with systemic or HLA-B27–associated arthritis require cardiovascular assessment for possible cardiac complications during exercise For those with micrognathia (open bite and exposed teeth), mouth guards are helpful If uveitis is present, risk of eye damage from trauma is increased; ophthalmologic assessment is recommended In visually impaired athletes, guidelines for functionally 1-eyed athletes should be followed
Juvenile dermatomyositis, idiopathic myositis Systemic lupus erythematosus Raynaud phenomenon	Qualified yes Qualified yes Qualified yes	Athlete with juvenile dermatomyositis or systemic lupus erythematosus with cardiac involvement requires cardiology assessment before participation. Athletes receiving systemic corticosteroid therapy are at higher risk for osteoporotic fractures and avascular necrosis, which should be assessed before clearance; those receiving immunosuppressive medications are at higher risk for serious infection. Sports activities should be avoided when myositis is active. Rhabdomyolysis during intensive exercise can cause renal injury in athletes with idiopathic myositis and other myopathies. Because of photosensitivity with juvenile dermatomyositis and systemic lupus erythematosus, sun protection is necessary during outdoor activities. With Raynaud phenomenon, exposure to the cold presents risk to hands and feet
SICKLE CELL		
Sickle cell disease	Qualified yes	Athlete needs individual assessment In general, if illness status permits, all sports may be played; however, any sport or activity that entails overexertion, overheating, dehydration, or chilling should be avoided Participation at high altitude, especially when not acclimatized, also poses risk of sickle cell crisis
Sickle cell trait	Yes	Athletes with sickle cell trait generally do not have increased risk of sudden death or other medical problems during athletic participation under normal environmental conditions; however, when high exertional activity is performed under extreme conditions of heat and humidity or increased altitude, such catastrophic complications have occurred rarely Athletes with sickle cell trait, like all athletes, should be progressively acclimatized to the environment and to the intensity and duration of activities and should be sufficiently hydrated to reduce the risk of exertional heat illness and/or rhabdomyolysis According to National Institutes of Health management guidelines, sickle cell trait is not a contraindication to participation in competitive athletics, and there is no requirement for screening before participation More research is needed to fully assess potential risks and benefits of screening athletes for sickle cell trait

This table is intended for use by medical and nonmedical personnel. "Needs evaluation" means that a physician with appropriate knowledge and experience should assess the safety of a given sport for an athlete with the listed medical condition. Unless otherwise noted, this need for special consideration is because of variability in the severity of the disease, the risk of injury for the specific sports, or both.

From Rice SG; the Council on Sports Medicine and Fitness, American Academy of Pediatrics: Medical conditions affecting sports participation, Pediatrics *121:841–848, 2008.*

Increasing dynamic component →

Increasing static component ↑	A. Low (<40% Max O_2)	B. Moderate (40-70% Max O_2)	C. High (>70% Max O_2)
III. High (>50% MVC)	**IIIA (Moderate)** Bobsledding/luge[a, b] Field events (throwing) Gymnastics[a, b] Martial arts[a] Sailing Sport climbing Water skiing[a, b] Weight lifting[a, b] Wind surfing[a, b]	**IIIB (High moderate)** Body building[a, b] Downhill skiing[a, b] Skateboarding[a, b] Snowboarding[a, b] Wrestling[a]	**IIIC (High)** Boxing[a, c] Canoeing/kayaking Cycling[a, b] Decathlon Rowing Speed skating[a, b] Triathlon[a, b]
II. Moderate (20-50% MVC)	**IIA (Low moderate)** Archery Auto racing[a, b] Diving[a, b] Equestrian[a, b] Motorcycling[a, b]	**IIB (Moderate)** American football[a] Field events (jumping) Figure skating[a] Rodeoing[a, b] Rugby[a] Running (sprint) Surfing[a, b] Synchronized swimming[b]	**IIC (High moderate)** Basketball[a] Ice hockey[a] Cross-country skiing (skating technique) Lacrosse[a] Running (middle distance) Swimming Team handball
I. Low (<20% MVC)	**IA (Low)** Billiards Bowling Cricket[d] Curling Golf Riflery	**IB (Low moderate)** Baseball/softball[a] Fencing Table tennis Volleyball	**IC (Moderate)** Badminton Cross-country skiing (classic technique) Field hockey[a] Orienteering Race walking Racquetball/squash Running (long distance) Soccer[a] Tennis

Figure 686-1 **Classification of sports according to cardiovascular demands (based on combined static and dynamic components).** This classification is based on peak static and dynamic components achieved during competition. The higher values may be reached during training. The increasing dynamic component is defined in terms of the estimated percentage of maximal oxygen uptake (Max O_2) achieved and results in increasing cardiac output. The increasing static component is related to the estimated percentage of maximal voluntary contraction (MVC) reached and results in increasing blood pressure load. Activities with the lowest total cardiovascular demands (cardiac output and blood pressure) are shown in box IA, and those with the highest demands are shown in box IIIC. Boxes IIA and IB depict activities with low to moderate total cardiovascular demands; boxes IIIA, IIB, and IC depict activities with moderate total cardiovascular demands; and boxes IIIB and IIC depict high-moderate total cardiovascular demands. These categories progress diagonally across the graph from lower left to upper right. [a]Danger of bodily collision. [b]Increased risk if syncope occurs. [c]Participation is not recommended by the American Academy of Pediatrics. [d]The American Academy of Pediatrics classifies cricket in the IB box (low static component and moderate dynamic component). *(From Mitchell JH, Haskell W, Snell P, et al: 36th Bethesda conference. Task force 8: classification of sports.* J Am Coll Cardiol *45:1364–1367, 2005.)*

in retrospect there were preceding symptoms of dizziness, chest pain, syncope, palpitations, shortness of breath, and/or a family history of early, unexpected death. Chest radiographs, electrocardiograms, and echocardiograms are not recommended as routine screening tests. If there is a **suspicion** of heart disease, such as a history of syncope, presyncope, palpitations, or excessive dyspnea with exercise, or a family history of a condition such as hypertrophic cardiomyopathy or prolonged QT or Marfan syndrome, the evaluation should be complete and include a 12-lead electrocardiogram, an echocardiogram, Holter or event-capture monitoring, and a stress test with electrocardiographic monitoring. Recommendations for participation with identified cardiac disease should be made in consultation with a cardiologist.

Disqualification and limitations for sports participation among various medical conditions are available from the American Academy of Pediatrics (see Table 686-3). Sports may also be classified by intensity (Fig. 686-1) and contact (Table 686-4). Athletes may seek to participate in sports against medical advice and have done so successfully for professional sports. Section 504(a) of the Rehabilitation Act of 1973 prohibits discrimination against disabled athletes if they have the capabilities or skills required to play a competitive sport. This was reinforced through the Americans with Disabilities Act of 1990. An amateur athlete has no absolute right to decide whether to participate in competitive sports. Participation in competitive sports is considered a privilege, not a right. *Knapp v Northwestern University* established that "difficult medical decisions involving complex medical problems can be made by responsible physicians exercising prudent judgment (which will be necessarily conservative when definitive scientific evidence is lacking or conflicting) and relying on the recommendations of specialist consultants or guidelines established by a panel of experts."

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Table 686-4 Classification of Sports by Contact

Contact or Collision	Limited Contact	Noncontact
Basketball	Baseball	Archery
Boxing*	Bicycling	Badminton
Diving	Cheerleading	Body building
Field hockey	Canoeing or kayaking (white water)	Bowling
Football, tackle	Fencing	Canoeing or kayaking (flat water)
Ice hockey†	Field events	Crew or rowing
Lacrosse	• High jump	Curling
Martial arts	• Pole vault	Dancing
Rodeo	Floor hockey	• Ballet
Rugby	Football, flag	• Modern
Ski jumping	Gymnastics	• Jazz
Soccer	Handball	Field events
Team handball	Horseback riding	• Discus
Water polo	Racquetball	• Javelin
Wrestling	Skating	• Shot put
Skateboarding	• Ice	Golf
Snowboarding	• Inline	Orienteering‡
Softball	• Roller	Power lifting
Squash	Skiing	Race walking
Ultimate Frisbee	• Cross-country	Riflery
Volleyball	• Downhill	Rope jumping
Windsurfing or surfing	• Water	Running
		Sailing
		Scuba diving
		Swimming
		Table tennis
		Tennis
		Track
		Weight lifting

*Participation not recommended by the American Academy of Pediatrics.

†The American Academy of Pediatrics recommends limiting the amount of body checking allowed for hockey players ≤15 yr to reduce injuries.

‡A race (contest) in which competitors use a map and compass to find their way through unfamiliar territory.

From the American Academy of Pediatrics, Committee on Sports Medicine and Fitness: Medical conditions affecting sports participation, Pediatrics *107:1205, 2001.*

Chapter 687

Management of Musculoskeletal Injury

Kevin P. Murphy and Aaron M. Karlin

MECHANISM OF INJURY

Acute Injuries

Sprains, strains, and contusions account for the majority of musculoskeletal injuries. A **sprain** is an injury to a ligament or joint capsule. Most sprains are grades I-III. A *grade I* sprain is defined as mild damage to a ligament or ligaments without instability of the affected joint. A *grade II* sprain is considered a partial tear to the ligament, stretched to the point that it becomes loose. *Grade III is a complete tear of the ligament with instability to the affected joint.* A **strain** is an injury to a muscle or tendon and these, too, are graded I-III. *Grade I* muscle strains involve disruption of only a few muscle fibers, pain is mild to moderate and range of motion and strength are at or near normal. *Grade II* strains represent a more significant partial tear of the muscle and frequently involve loss of range of motion and strength. *Grade III* strains are defined as complete rupture of the musculotendinous unit. A **contusion** is a crush injury to any soft tissue. The history of the injury is especially helpful in assessing musculoskeletal trauma. More severe injuries, indicating internal derangement, can have acute signs and symptoms such as immediate swelling, deformity, numbness or "give-way" weakness, a loud painful pop, mechanical locking of the joint, or instability.

Overuse Injuries

Overuse injuries are caused by repetitive microtrauma that exceeds the body's rate of repair. This occurs in muscles, tendons, bone, bursae, cartilage, and nerves. Overuse injuries occur in all sports but more commonly in sports emphasizing repetitive motion (swimming, running, tennis, and gymnastics). Factors can be categorized into extrinsic (training errors, poor equipment or workout surface) and intrinsic (athlete's anatomy or medical conditions). Training error is the most commonly identified factor. At the beginning of the workout program, athletes might violate the 10% rule: Do not increase the duration or intensity of workouts more than 10% per week. Intrinsic factors include abnormal biomechanics (leg-length discrepancy, pes planus, pes cavus, tarsal coalition, valgus heel, external tibial torsion, and femoral anteversion), muscle imbalance, inflexibility, and medical conditions (deconditioning, nutritional deficits, amenorrhea, and obesity). The athlete should be asked about the specifics of training. Runners should be asked about their shoes, orthotics, running surface, weekly mileage or time spent running per week, speed or hill workouts, and previous injuries and rehabilitation. When causative factors are identified, they can be eliminated or modified so that after rehabilitation the athlete does not return to the same regimen and suffer reinjury.

For athletes engaged in excessive training that causes an overuse injury (e.g., multiple-sport school athletes), curtailing all exercise may not be necessary. Treatment is a reduction of training load (relative rest) combined with a rehabilitation program designed to return athletes to their sport as soon as possible while minimizing exposure to reinjury. Early identification of an overuse injury requires less alteration of the workout regimen.

The goals of treatment are to control pain and spasm to rehabilitate flexibility, strength, endurance, and proprioceptive deficits (Table 687-1). In many overuse injuries, the role of inflammation in the process is minimal. For most injuries to tendons, the term *tendinitis* is obsolete because there is little or no inflammation on histopathology of tendons. Instead, there is evidence of microscopic trauma to the tissue. Most of these entities are now more appropriately called **tendinosis** and, when the tendon tissue is scarred and very abnormal, **tendinopathy**. With tendinosis, there is less of a role for antiinflammatory medication in the treatment, except as an analgesic.

INITIAL EVALUATION OF THE INJURED EXTREMITY

Initially, the examiner should determine the quality of the peripheral pulses and capillary refill rate as well as the gross motor and sensory function to assess for neurovascular injury. The first priorities are to maintain vascular and skeletal stability.

Criteria for immediate attention and rapid orthopedic consultation include vascular compromise, nerve compromise, and open fracture. The exposed wound should be covered with sterile saline-soaked gauze, and the injured limb should be padded and splinted. Pressure should

Table 687-1 Staging of Overuse Injuries

GRADE	GRADING SYMPTOMS	TREATMENT
I	Pain only after activity Does not interfere with performance or intensity Generalized tenderness Disappears before next session	Modification of activity, consider cross-training, home rehabilitation program
II	Minimal pain with activity Does not interfere with performance More localized tenderness	Modification of activity, cross-training, home rehabilitation program
III	Pain interferes with activity and performance Definite area of tenderness Usually disappears between sessions	Significant modification of activity, strongly encourage cross-training, home rehabilitation program, and outpatient physical therapy
IV	Pain with activities of daily living Pain does not disappear between sessions Marked interference with performance and training intensity	Discontinue activity temporarily, cross-training only, oral analgesic, home rehabilitation program, and intensive outpatient physical therapy
V	Pain interferes with activities of daily living Signs of tissue injury (e.g., edema) Chronic or recurrent symptoms	Prolonged discontinuation of activity, cross-training only, oral analgesic, home rehabilitation program, and intensive outpatient physical therapy

be applied to any site of bleeding. Additional criteria include deep laceration over a joint, unreducible dislocation, grade III (complete) tear of a muscle–tendon unit, and displaced, significantly angulated fractures (depends on the bone involved, the degree of displacement and angulation, and neurovascular status of the extremity).

TRANSITION FROM IMMEDIATE MANAGEMENT TO RETURN TO PLAY

Rehabilitation of a musculoskeletal injury should begin on the day of the injury.

Phase 1

Limit further injury, control swelling and pain, and minimize strength and flexibility losses. **PRICE** principles (**P**rotection, **R**est, **I**ce, **C**ompression, and **E**levation) need to be applied. Crutches, air stirrups for ankle sprains, slings for arm injuries and elastic wraps (4-8 inches) for compression are a helpful inventory of office supplies. Ice can be placed directly over the injury as tolerated for 20 min continuously 3-4 times per day until the swelling resolves. Compression limits further bleeding and swelling but should not be so tight that it limits perfusion. Elevation of the extremity promotes venous return and limits swelling. A nonsteroidal antiinflammatory drug or acetaminophen is indicated for analgesia.

Pain-free isometric strengthening and range of motion should be initiated as soon as possible. Pain inhibits full muscle contraction; deconditioning results if the pain and resultant nonuse persist for days to weeks, thus delaying recovery. Education about the nature of the injury and the specifics of rehabilitation exercises, including handouts with written instructions and drawings demonstrating the exercises, are helpful.

Phase 2

Improve strength and range of motion (i.e., flexibility) while allowing the injured structures to heal. Protective devices are removed when the patient's strength and flexibility improve and activities of daily living are pain free. Flexibility can then be improved by a program of specific stretches, held for 15-30 sec for 3-5 repetitions, once or twice daily. A physical therapist or athletic trainer is invaluable in guiding the athlete through this process. Protective devices might need to be used for months during sports participation. Swimming, water jogging, and stationary cycling are good aerobic exercises that can allow the injured extremity to get relative rest or be used pain free while maintaining cardiovascular fitness.

Phase 3

Achieve near-normal strength and flexibility of the injured structures and further improve or maintain cardiovascular fitness. Strength and endurance are improved under controlled conditions using elastic bands and eventually exercise equipment followed by free weights. Sensory proprioceptive training allows the athlete to redevelop the kinesthetic sense critical to joint function and stability.

Phase 4

Return to exercise or competition without restriction. When the athlete has reached nearly normal flexibility, strength, proprioception, and endurance, the athlete can start sports-specific exercises. The athlete will make the transition from the rehabilitation program to functional rehabilitation appropriate for the sport. Substituting sports participation for rehabilitation is inappropriate; rather, there should be progressive stepwise functional return to a full activity or play program. For instance, a basketball player recovering from an ankle injury might begin a walk-run-sprint-cut program before returning to competition. At any point in this progression, if pain is experienced, the athlete needs to stop, apply ice, avoid running for 1-2 days, continue to do ankle exercises, and then resume running at a lower intensity and progress accordingly.

Relative Rest and Return-to-Play Guidelines

Relative rest means that the athlete can do whatever the athlete wants as long as the injured structures do not hurt during or within 24 hr of the activity. Exercising beyond the pain threshold delays recovery.

DIFFERENTIAL DIAGNOSES OF MUSCULOSKELETAL PAIN

Traumatic, rheumatologic, infectious, hematologic, psychologic, congenital, and oncologic processes can cause the presenting complaint of musculoskeletal pain. Symptoms such as fatigue, weight loss, rash, multiple joint complaints, fever, chronic or recent illness, and persistent pain despite conservative care suggests a diagnosis other than sports-related trauma. The possibility of child abuse as an etiology is not to be overlooked permeating all socioeconomic strata. Incongruity between the patient's history and physical examination findings should lead to further evaluation. A negative review of systems with an injury history consistent with the physical findings suggests a sports-related etiology.

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687.1 Growth Plate Injuries

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Approximately 20% of pediatric sports injuries seen in the emergency department are fractures, and 25% of those fractures involve an epiphyseal growth plate or physis (see Chapter 683). Growth in long bones occurs in 3 areas and is susceptible to injury. Immature bone can be acutely injured at the **physis** (Salter-Harris fractures, see Chapter 683.2), the **articular surface** (osteochondritis dissecans), or the **apophysis** (avulsion fractures). Boys suffer about twice as many physeal fractures as girls; the peak incidence of fracture is during peak height velocity (girls: age 12 ± 2.5 yr; boys: age 14 ± 2 yr). The physis is a pressure growth plate and is responsible for longitudinal growth in bone. The apophysis is a bony outgrowth at the attachment of a tendon and is a traction physis. The epiphysis is the end of a long bone, distal or proximal to the long bone, and contains articular cartilage at the joint.

Physeal injuries of the distal radius occur most often in the growing child or adolescent resulting from excessive force applied to the upper extremity. Injuries of this nature can be seen in athletes including those participating in gymnastics, cheerleading, ice skating, hockey and weight lifting. Mechanisms of injury include falls onto an outstretched hand or repetitive dorsiflexion and axial loading through the distal radius (see Chapter 693). Chronic wrist pain can be seen in up to 79% of young gymnasts, particularly female gymnasts between the ages of 12 and 14 yr. With repetitive axial loading temporary metaphyseal ischemia may be induced preventing cartilage calcification and causing the physis to widen. With widening of the distal radial physis, microfractures can develop. Clinical features involve radial wrist pain particularly dorsal with passive and active hyperextension activities relieved with suspension of the offending activity. Tenderness or focal pain around the circumference of the distal radius is often noted. Differential diagnosis includes metacarpal fractures, scaphoid fracture and in the older child, De Quervain tenosynovitis. Juvenile idiopathic arthritis always needs to be considered in a child with a painful swollen wrist not to exclude malignancy or an infectious process. X-rays of the wrist can be helpful particularly when compared to the contralateral extremity. Radiographs can show physeal widening with cystic changes involving the metaphyseal segment, beaking of the distal epiphysis and in later stages, positive ulnar variance. Bone scan may be helpful for stress fractures followed by MRI if subsequently needed. PRICE principles are followed with nonnarcotic pain management. Salter-Harris fractures types I and II can be treated with closed reduction and immobilization. Ulnar shortening osteotomy may be necessary in the athlete with significant ulnar positive variance. Physeal injuries at the knee (distal femur, proximal tibia) are rare. Growth disturbance following a growth plate injury is a function of location and the part of the physis fractured. These factors influence the probability a physeal bar will form, resulting in growth arrest. The areas making the largest contribution to longitudinal growth in the upper extremities are the proximal humerus and distal radius and ulna; in the lower extremities, they are the distal femur and the proximal tibia and fibula. Injuries to these areas are more likely to cause growth disturbance compared with physeal injuries at the other end of these long bones. The type of the physis fracture relative to risk of growth disturbance is described by the Salter-Harris classification system (see Table 683-1). A grade I injury is least likely to result in growth disturbance, and grade V is the most likely fracture to result in growth disturbance.

Osteochondritis dissecans (OCD) affects the subchondral bone and overlying articular surface (see Chapter 683). With avascular necrosis of subchondral bone, the articular surface can flatten, soften, or break off in fragments. The etiology is unknown but may be related to repetitive stress injury in some patients. The condition most commonly affects the knee (lateral aspect of the medial femoral condyle in 70% of patients and lateral femoral condyle in 20%) with the patella in 10%. Other joints where OCD lesions are also seen are the ankle (talus), elbow (usually involving the capitellum), and radial head. OCD classically affects athletes in their 2nd decade. The most common presentation is poorly localized vague knee pain. There is rarely a history of recent acute trauma. Some OCD lesions are asymptomatic (diagnosed on "routine" radiographs), whereas others are manifested as joint effusion, pain, decreased range of motion, and mechanical symptoms (locking, popping, catching). Activity usually worsens the pain.

Figure 687-1 Osteochondritis dissecans in the elbow. *(From Anderson SJ: Sports injuries.* Curr Probl Pediatr Adolesc Health *35:105–176, 2005.)*

Physical examination might show no specific findings. Sometimes tenderness over the involved condyle can be elicited by deep palpation with the knee flexed. Diagnosis is usually made with plain radiographs (Fig. 687-1). A tunnel view radiograph can be obtained to better view the posterior two-thirds of the femoral condyle. Treatment of OCD remains controversial. Intact lesions can often be treated symptomatically with or without activity modification or immobilization. Free fragments often require surgical removal. Drilling techniques can be utilized and are helpful in stimulating new bone formation, healing, and return of mobile bodies to their original donor sites. Long-term sequelae can be seen in up to 25% with atypical lesions, older age, effusion, and lesions of large size.

Avulsion fractures occur when a forceful muscle contraction dislodges the apophysis from the bone. They occur most commonly around the hip (Fig. 687-2) and are treated nonsurgically. Acute fractures to other apophyses (knee and elbow) require urgent orthopedic consultation. Chronically increased traction at the muscle–apophysis attachment can lead to repetitive microtrauma and pain at the apophysis. The most common areas affected are the knee (Osgood-Schlatter and Sinding-Larsen-Johansson disease), the ankle (Sever disease) (Fig. 687-3), and the medial epicondyle (Little League elbow). Traction apophysitis of the knee and ankle can potentially be treated in a primary care setting. The main goal of treatment is to minimize the intensity and incidence of pain and disability. Exercises that increase the strength, flexibility, and endurance of the muscles attached at the

Figure 687-2 Anterior inferior iliac spine avulsion. *(From Anderson SJ: Lower extremity injuries in youth sports.* Pediatr Clin North Am *49:62–641, 2003.)*

Figure 687-3 Calcaneal apophysitis (Sever disease). *(From Anderson SJ: Sports injuries.* Curr Probl Pediatr Adolesc Health *35:105–176, 2005.)*

apophysis, using the relative rest principle, are appropriate. Symptoms can last for 12-24 mo if untreated. As growth slows, symptoms abate.

Bibliography is available at Expert Consult.

687.2 Shoulder Injuries

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Shoulder pain associated with radiating symptoms down the arm should raise the possibility of a neck injury. *Neck pain and tenderness or limitation of cervical range of motion requires that the cervical spine be immobilized and that the athlete be transferred for further evaluation.* If there is no neck pain or tenderness or limitation of motion of the cervical spine, then the shoulder is likely the site of the primary injury.

CLAVICLE FRACTURES

Clavicle fracture is one of the most common shoulder injuries. Injury is usually sustained by a fall on the lateral shoulder, on an outstretched hand, or by direct blow. Approximately 80% of fractures occur in the middle third of the clavicle. With younger children, plastic bowing of the clavicle may be present instead of an overt fracture and should be treated in the same fashion. Treatment is conservative and includes the use of an arm sling for comfort and protection. Healing time is shorter in comparison to adults, generally 4-6 wk. And additional 2-3 wk period of protection from contact/collision activities is recommended after clinical and radiographic healing is achieved to prevent reinjury. If nondisplaced, most medial and lateral clavicular fractures can be managed similar to middle 3rd clavicular fractures. Displaced lateral and medial third fractures require orthopedic consultation because of a higher incidence of acromioclavicular osteoarthritis (lateral) and physeal involvement (medial). Distal clavicular osteolysis is likely an overuse injury associated with slow dissolution and resorption of bone. The cause of injury is unclear, appearing most consistent with a stress reaction or fracture at the site of considerable force. This lesion is commonly seen in weightlifting athletes and can be seen in the older children. Nonoperative treatment including activity limitations, ice, nonsteroidal antiinflammatory agents and cortisone injections can be helpful. Gripping the bar at a greater distance for the weightlifter may be helpful. For those not willing to modify weightlifting activity or with persistent symptoms despite conservative care, surgery can be very successful and involves removal of the distal clavicle (approximately 1 cm) with no loss of strength and full return to activity anticipated.

ACROMIOCLAVICULAR SEPARATION

An acromioclavicular (AC) separation most commonly occurs when an athlete sustains a direct blow to the acromion with the humerus in an adducted position, forcing the acromion inferiorly and medially. Force is directed toward the AC and coracoclavicular ligaments because of the inherent stability of the sternoclavicular joint. Patients have point tenderness at the AC joint, pain with lifting their arms above the level of their shoulder, and may have an apparent step-off between the distal clavicle and the acromion (Fig. 687-4).

Type I AC injuries involve isolated sprain of the AC ligament with the periosteal sleeve intact. There is no visible deformity and radiographs are normal. Pain is elicited with adduction of the humerus across the chest. **Type II** injuries involve the AC ligament and coracoclavicular ligament, as well as partial disruption of the periosteal sleeve. Radiographs may show slight widening of the AC joint though the distance between the clavicle and the coracoid process is unchanged in comparison to the uninjured shoulder. Treatment of type I and type II AC injuries is conservative and nonoperative and consists of ice, nonsteroidal antiinflammatories and a sling for immobilization and pain control acutely. Shoulder range of motion exercises and strengthening of the rotator cuff, deltoid and trapezius musculature are incorporated early in the course once pain free range improves to prevent residual joint stiffness. A short course of physical therapy may be helpful if range of motion limitations are present 2-4 wk out from

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Figure 687-4 Palpitation of acromioclavicular joint. *(From Anderson SJ: Sports injuries,* Curr Probl Pediatr Adolesc Health *35:105–176, 2005.)*

injury. Consideration for return to play is made when the patient no longer has focal AC joint tenderness, exhibits full painless range of motion, has strength sufficient to be functionally protected from a collision or fall, and can perform maneuvers required within their sport. Typically, return to play from a type I AC injury is 1-2 wk, and 2-4 wk for type II.

Type III injury is more severe involving further tearing of the AC and coracoclavicular ligaments and disruption of the periosteal tube with instability of the distal clavicle because of deltotrapezial fascial detachment. Radiographs will commonly show superior displacement of the distal clavicle from the coracoid of 25-100%. Treatment of type III AC injuries is controversial, although many can be treated nonoperatively similar to that described for types I and II AC injuries if there is no damage to the overlying skin or neurovascular compromise to the injured limb. The patient should be counseled regarding this injury, likely resulting in a noticeable defect, to ascertain whether this is acceptable. Surgery for type III AC injuries are uncommon and primarily for cosmetic reasons. **Types IV, V, and VI** AC injuries have progressive worsening of ligamentous and fascial disruption with varied locations of the clavicular displacement. These injuries should be referred to an orthopedist for consultation and operative repair.

ANTERIOR DISLOCATION

The most common mechanism of injury is making contact with another player with the shoulder abducted to 90 degrees and forcefully rotated externally. A common example of the latter is a football player tackling another player only with the arm. Patients complain of severe pain and that their shoulder "popped out of place" or "shifted." Patients with an unreduced anterior dislocation have a hollow region inferior to the acromion and a bulge in the anterior portion of the shoulder caused by anterior displacement of the humeral head. Abnormal sensation of the lateral deltoid region (axillary nerve) and the extensor surface of the proximal forearm (musculocutaneous nerve) should be noted.

Reduction of a dislocated shoulder should be made expediently assuming no presence of crepitans (concerning for fracture). Numerous safe methods for closed reduction have been described, including the traction–counter traction technique, the Stimson maneuver, and the abduction maneuver. Postreduction radiographs are helpful and may show evidence of a posterior lateral humeral head impaction fracture (Hill-Sachs lesion). Injuries to the surrounding soft tissues, including the anterior capsule and labrum, are best evaluated by MRI, often with an accompanying arthrogram of the glenohumeral joint. Once reduced, initial treatment of a dislocation includes placing the patient into an arm sling for comfort and protection. The duration of immobilization is controversial and may last anywhere from a few days to 4-6 wk. The most significant risk after an acute traumatic dislocation is recurrence. Most sports medicine practitioners encourage early range of motion and strengthening exercises as tolerated. Rehabilitation focuses upon progressive strengthening of the rotator cuff, deltoid, and periscapular muscles at increasing degrees of abduction and external rotation. Strengthening of the rotator cuff muscles is extremely important as they are the dynamic stabilizers of the glenohumeral joint, integral in preventing future dislocation. Plyometric exercises may also be incorporated near the end of rehabilitation to improve proprioceptive function in preparation for return to athletics. Patients can return to play when strength, flexibility, and proprioception are equal to the uninjured shoulder to the extent that they are able to protect the shoulder and perform sports specific activities without pain. Surgery is to be considered in cases of multiple recurrent dislocations or in those individuals that fail to heal adequately after prolonged rehabilitation. Additionally, early operative repair should be considered for athletes participating in contact or collision spots that inherently have higher recurrence rates.

ROTATOR CUFF INJURY

The rotator cuff muscles comprise the supraspinatus, infraspinatus, teres minor, and subscapularis. The function of these muscles is to rotate the humerus and stabilize the humeral head against the glenoid. The supraspinatus is most commonly injured, an acute strain caused by trauma or chronic tendinosis from overuse. Specifically, rotator cuff tendinosis commonly presents with complaint of pain with overhead arc of motion, such as with throwing, lifting, or reaching for objects above one's head. Pain is often poorly localized about the shoulder, although may be referred to the deltoid. Onset of pain is often insidious and commonly associated with increased frequency or duration of overhead throwing or lifting activities. Pain is exacerbated with these or other activities but is often present at rest; nighttime pain in more severe cases. On exam, manual muscle testing of the cuff muscles often produces pain and in some cases weakness in comparison to the uninjured shoulder. Supraspinatus tendinosis produces pain with active abduction against resistance in which the patient abducts the arm to 90 degrees, forward flexes to 30 degrees anterior to the parasagittal plane, and internally rotates the humerus.

Treatment of rotator cuff tendinosis includes relative rest from athletics or activities causing pain, ice, analgesia or nonsteroidal antiinflammatory use. Strengthening of the rotator cuff and scapular stabilizer musculature, modifications of technique, and core strengthening are important components of rehabilitation often supervised by a physical therapist. In the young athlete, rotator cuff pain is most commonly a result of glenohumeral instability and not rotator cuff impingement syndrome, more commonly seen in adults and caused by impingement of the rotator cuff by the bony structures superior to it. As a result, treatment focusing on stretching alone can make symptoms worse. Return to play often includes gradual increases in load placed upon the rotator cuff as the patient resumes their prior activities such as an interval throwing program in baseball.

Glenoid labrum tears may present in similar insidious fashion to rotator cuff tendinosis or be associated with an acute traumatic dislocation. This is frequently manifested with pain in the glenohumeral joint

and may be associated with a sensation of clicking or catching in the shoulder. This can frequently be reproduced on exam. One of the most common lesions is a superior labrum anterior and posterior lesion. Throwing athletes are at particular risk. Mechanism of injury is thought to be related to a traction injury along the long head of the biceps at its attachment at the superior glenoid labrum occurring during a throwing cycle. Radiographs are usually normal. MRI with arthrogram is the best study to identify glenoid labrum pathology.

Proximal humeral stress fracture (epiphysiolysis) is an uncommon cause of proximal shoulder pain and is suspected when shoulder pain does not respond to routine measures. Gradual onset of deep shoulder pain occurs in a young (open epiphyseal plates) athlete involved in repetitive overhead motion, such as in baseball, tennis, or swimming, but with no history of trauma. Tenderness is noted over the proximal humerus; the diagnosis is confirmed by detecting a widened epiphyseal plate on plain radiographs, increased uptake on nuclear scan, or edema of the physis on MRI. Treatment is total rest from throwing for 6-8 wk.

Non–sports-related conditions that need to be considered in the child with a painful shoulder include the Sprengel deformity. This deformity involves the scapula, which fails to descend from its cervical region overlying the 1st through 5th ribs. Children often present with a shortened neckline and lack of normal scapular thoracic motion. Malpositioning of a glenoid can cause limited forward flexion and abduction of the shoulder. An omovertebral bar is present in up to 50% of cases. This bar connects the superior medial angle of the scapula and the cervical spine and consists of fibrous cartilaginous tissue or bone. Other regional abnormalities can include scoliosis with a prominent scapula on the convex side, rib anomalies, and Klippel-Feil syndrome. Winging of the scapula always raises the question of muscular dystrophy, particularly scapular thoracic. Family histories can be most helpful. Primary bone tumors (see Chapter 501) common to the upper extremities include Ewing sarcoma of the scapula and osteogenic sarcoma of the proximal humerus, in addition to osteoblastomas and chondroblastomas common to the diaphysis and epiphysis of long bones. The most common presenting manifestations of osteosarcoma are pain, upper limb dysfunction, and swelling. Similar presentations can be seen in Ewing sarcoma, along with weight loss and fever. Symptoms not responding to conservative treatment require further investigation and specialty consultation.

Bibliography is available at Expert Consult.

687.3 Elbow Injuries

Kevin P. Murphy and Aaron M. Karlin

ACUTE INJURIES

The most commonly dislocated joint in childhood is the elbow. Radial head subluxation, or "nurse maid's elbow," comprises the majority of these and is discussed in more depth in Chapter 681. Posterior dislocation is the next most common type of elbow dislocation, with its mechanism being that of falling backward onto an outstretched arm with the elbow in extension. The dislocation may be complete or incomplete, termed "perched," with the trochlea subluxed upon the top of the coronoid process. The ulnar collateral ligament is commonly disrupted along with other components of the soft-tissue capsule about the elbow. Fractures of the olecranon (greater than 80%) or medial epicondyle may be present as well. An obvious deformity is visualized with the olecranon process displaced prominently behind the distal humerus. Careful examination of the distal radius and ulnar pulses to assess vascular integrity of the distal upper arm is important because of the potential for injury to the brachial artery. Sensation to the distal extremity should also be assessed because of possible injury to the radial, median, and ulnar nerves. Reduction should be performed as soon as possible before significant swelling and muscle spasm potentially complicate the procedure. Longitudinal traction is applied to the forearm with gentle upward pressure on the distal humerus so that the coronoid process clears the trochlea. If reduction is unable to be performed, the arm should be placed in a padded splint and sling and the patient transported to an emergency facility.

Figure 687-5 Deflection of the coronoid fat pad with a joint effusion (fat pad sign) showing evidence of a fracture. *(From Gomez JE: Upper extremity injuries in youth sports.* Pediatr Clin North Am *49:593–626, 2002.)*

Supracondylar humeral fractures can result from the same mechanism of injury as elbow dislocations and can be difficult to distinguish from a posterior dislocation because of significant swelling about the elbow joint. These, too, can be complicated by concomitant injury to the brachial artery and to a lesser extent the median, radial, and ulnar nerves. The injury typically occurs in the 1st decade of life, which is associated with peak hyperlaxity of the elbow joint in children between the ages of 5 and 8 yr. An acute compartment syndrome can develop after these fractures, which is associated with a fat pad sign (Fig. 687-5). These fractures should be referred for orthopedic consultation and are discussed in more depth in Chapter 683.

Direct trauma to the elbow can cause bleeding and inflammation in the olecranon bursa resulting in *olecranon bursitis*. Aspiration is rarely required and this injury can be managed with ice, compressive dressing and analgesia (RICE principles). An overlying elbow pad provides comfort during activity and prevention of reinjury.

Chronic Injuries

Overuse injuries occur primarily in throwing sports and sports that require repetitive wrist flexion or extension or demand weightbearing on hands (gymnastics). "Little League elbow" is a broad term for several different elbow problems.

Throwing overhand creates valgus stress to the elbow with medial opening of the joint and lateral compressive forces.

Medial elbow pain is a common complaint of young throwers, resulting from repetitive valgus overload of the wrist flexor-pronator muscle groups and their attachment on the medial apophysis. In preadolescents who still have maturing secondary ossification centers,

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traction apophysitis of the medial epicondyle is likely. Patients have tenderness along the medial epicondyle; pain is exacerbated by valgus stress or resisted wrist flexion and pronation. Wrist pain may be present in more severe cases. Radiographs may show widening of the growth plate at the medial apophysis in comparison to the uninjured elbow. Treatment includes no throwing for 4-6 wk, pain-free strengthening, and stretching of the flexor–pronator group followed by a 1-2 wk progressive functional throwing program with careful rehabilitation. Incorporation of core strengthening and scapular stabilizing exercise, as well as addressing proper throwing mechanics (to reduce the load upon the medial elbow), are important components of rehabilitation. This problem has to be treated with rest because of the risk of nonunion of the apophysis and chronic pain. If pain occurs acutely, *avulsion fracture of the medial epicondyle* must be considered. Radiographs should be taken in any thrower with acute elbow pain (Fig. 687-6). If the medial epicondyle is avulsed, orthopedic consultation is indicated.

In older adolescents and young adults with a fused apophysis, the vulnerable structure is the *ulnar collateral ligament* (UCL). UCL sprains/tears are common in sports requiring high-velocity throwing or overhead activities. Medial elbow pain primarily worse during the acceleration phase of throwing is common. A sensation of elbow "opening" during throwing is also frequently described. On exam focal tenderness to palpation over the UCL is present. Additionally laxity may be appreciated with valgus stress of the elbow when flexed to 30 and/or 90 degrees. Radiographs are generally unremarkable. MRI with arthrography or ultrasonography is often necessary to assess the integrity of the UCL. Partial tears can be treated with a period of time off from throwing (2-4 wk) followed by careful progressive rehabilitation as discussed above for medial elbow pain. If there is a complete tear, surgical repair is indicated if the athlete desires to continue a pitching career.

Medial epicondylitis (golfer's elbow) is another common cause of medial elbow pain in the individual with fused apophysis. It is commonly caused by overuse of the flexor pronator muscle groups at their origin at the medial humeral epicondyle. This occurs frequently in athletics or activities with repetitive wrist flexion. Tenderness is noted over the medical epicondyle and exacerbated by passive wrist extension or resisted wrist flexion. Treatment includes rest from the inciting activity, ice, stretching and strengthening of the wrist flexors, forearm straps, counterforce bracing, and analgesia. Ulnar nerve dysfunction can be a complication of valgus overload and can occur with any of the diagnoses previously discussed. Persisting paresthesia or motor weakness in the ulnar nerve distribution should be evaluated with electromyography and nerve conduction studies.

Lateral elbow pain can be caused by compression during the throwing motion at the radiocapitellar joint. *Panner disease* is osteochondrosis of the capitellum that occurs between ages 7 and 12 yr (Fig. 687-7). *OCD* of the capitellum occurs at age 13-16 yr (see Fig. 687-1). These 2 entities might represent a continuum of the same disease. Although patients with both conditions present with insidious onset of lateral elbow pain exacerbated by throwing, patients with OCD have mechanical symptoms (popping, locking) and, more commonly, decreased range of motion. Patients with Panner disease have no mechanical symptoms and often have normal range of motion. The prognosis of Panner disease is excellent, and treatments consist of relative rest (no throwing), brief immobilization, and repeat radiographs in 6-12 wk to assess bone remodeling. In OCD, radiographs show a more focal lesion in the capitellum with eventual flattening and potentially fragmentation. MRI scan can be very helpful in the diagnosis early on and with subsequent staging. A diagnosis of OCD requires orthopedic consultation with treatment dependent upon the severity of the lesion and fragmentation.

Lateral epicondylitis (tennis elbow), the most common overuse elbow injury in adults, is relatively uncommon in children and

Figure 687-6 Medial epicondylitis. *(From Anderson SJ: Sports injuries.* Curr Probl Pediatr Adolesc Health *35:105–176, 2005.)*

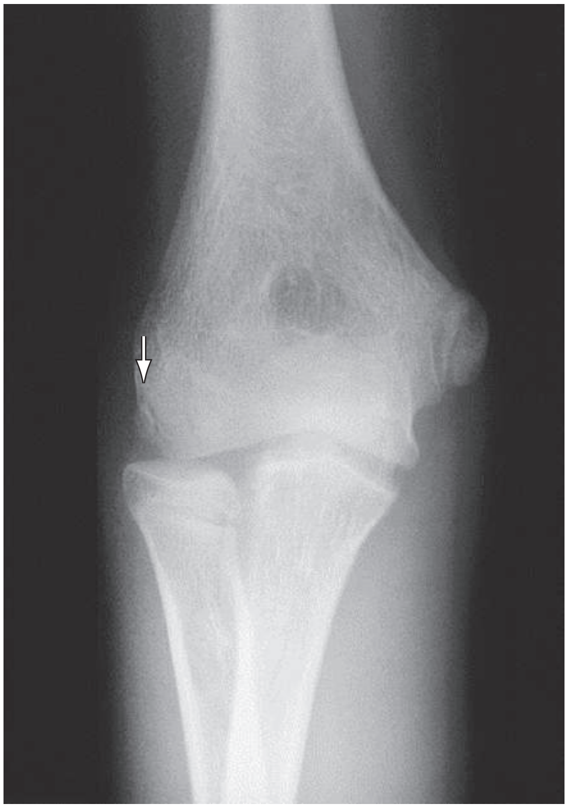

Figure 687-7 Panner disease. Note fragmentation of the humeral capitellum and flattening of the articular surface *(arrow). (Courtesy of Dr. Ralph J. Curtis. From Gomez JE: Upper extremity injuries in youth sports.* Pediatr Clin North Am *49:593–626, 2002.)*

adolescents. It is a tendinosis of the extensor muscle origin at the lateral humeral epicondyle commonly found in individuals performing activities requiring repetitive or prolonged grip. Tenderness is localized over the upper lateral epicondyle and is worsened with passive wrist flexion or resisted wrist extension. Treatment includes relative rest, analgesia, and specific stretching and strengthening exercises for the elbow and forearm. Improper equipment (i.e., wrong grip size or overstrung racket) and poor technique can contribute to onset of symptoms. Return to play should be gradual and progressive to prevent reinjury.

Elbow injuries can be minimized but not necessarily prevented by preseason stretching and strengthening exercises. The importance of core strengthening and scapular stabilization with respect to preventing elbow and shoulder injuries in the throwing athlete cannot be overstated. The most important consideration for preventing elbow injuries in throwers is limitation of the number of pitches and advising players, coaches, and athletes that they should stop immediately when they experience elbow pain. If it persists, they need medical evaluation. It has been recommended that a young pitcher have age specific limits on pitch counts including number of pitches thrown per game and per week, as well as maintaining appropriate days off between games pitched. A good rule of thumb is the maximal number of pitches per game should be approximately 6 times the pitcher's age in years.

Other less-common problems that cause elbow pain are ulnar neuropathy/subluxation, tricipital or bicipital tendonitis (distal), olecranon apophysitis, and loose bodies. Non–sports-related injuries that need to be considered in the child with a painful elbow include congenital conditions, such as radial dysplasia, including radial ulnar synostosis and mild persistent brachial plexus palsy. The elbow is not an uncommon site for inflammatory arthritides, including juvenile idiopathic arthritis, sepsis, hemophilia, and sickle cell disease. Neoplasia to consider includes osteoblastomas and chondroblastomas, common in the diaphysis and epiphysis of longer bones, in addition to osteosarcoma. As always, in the child with persistent symptoms who is not responding to conservative care, further diagnostic work up is always indicated.

Bibliography is available at Expert Consult.

687.4 Low Back Injuries

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SPONDYLOLYSIS, SPONDYLOLISTHESIS, AND FACET SYNDROME

Spondylolysis

Spondylolysis, a common cause of back pain in athletes, is a stress fracture of the pars interarticularis (see Chapter 679.6). It can occur at any vertebral level but is most likely at L4 or L5. Complete spondylolysis has never been found in the newborn. Its occurrence increases between the ages of 5.5 and 6.5 yr to a rate of 5%, close to the frequency of 5.8% in the white population. Prevalence in adolescent athletes evaluated for low back pain is 13-47%. Besides acute hyperextension that causes an acute fracture, the mechanism of injury is either a congenital defect or hypoplastic pars, which is exacerbated by lumbar extension loading, or a stress fracture caused by repetitive extension loading. Ballet, weightlifting, gymnastics, and football are examples of sports in which repetitive extension loading of the lumbar spine occurs; it occurs in any activity in which there is repetitive extension loading, including swimming.

Patients often present with pain of insidious onset. However, there may be a precipitating injury such as a fall or single episode of hyperextension. The pain is worse with extension, can radiate to the buttocks, and can eventually affect activities of daily living. Rest or supine positioning usually alleviates the pain.

On examination, the pain is reproduced with lumbar extension while standing, especially when standing on 1 leg (single-leg hyperextension test). Limited forward spinal flexion and tight hamstrings may be seen. Neurologic examination should be normal. There is well-localized tenderness to deep palpation just lateral to the spinous process on the affected side and is usually at L4 or L5.

The diagnosis is confirmed by finding a pars defect on an oblique lumbar spine radiograph. The defect is rarely seen on anteroposterior (AP) and lateral views. Bone single-photon emission CT is needed to confirm diagnosis if radiographs are normal. A plain CT scan can help to identify the degree of bony involvement and is sometimes used to assess healing.

Treatment includes pain relief and activity restriction. Rehabilitation consisting of trunk strengthening, hip flexor stretching, and hamstring stretching is important in most cases. A thoracic lumbar sacral orthotic on a temporary basis may be helpful for the spondylolytic stress fracture resistant to healing by alternative conservative means.

Spondylolisthesis and Facet Syndrome

Spondylolysis, spondylolisthesis, and facet syndrome are injuries posterior to vertebral elements. *Spondylolisthesis* occurs when bilateral pars defects exist and forward displacement or slippage of a vertebra occurs on the vertebra inferior to it (see Chapter 679.6). *Facet syndrome* has a similar history and physical examination findings as spondylolysis. It is caused by instability or injury to the facet joint, posterior to the pars interarticularis and at the interface of the inferior and superior articulating processes. Facet syndrome can be established by identifying facet abnormalities on CT or by exclusion, requiring a nondiagnostic radiograph and nuclear scan to rule out spondylolysis.

Treatment of posterior element injuries is conservative, directed at reducing the extension-loading activity, often for 2-3 mo. Body mechanics, posture principals, core strengthening, and lumbar pelvic stabilization routines can be very helpful in the functional recovery of the motivated athlete. Walking, swimming and cycling can be appropriate exercises also during the rehabilitation phase. Rarely spinal segmental fusion can be indicated in the athlete with spondylolisthesis and persistent symptomatic segmental instability despite further conservative care.

LUMBAR DISK HERNIATION, STRAIN, AND CONTUSION

Intervertebral disc injury in children and the young athlete is uncommon. In contrast to the selective motor and sensory deficits often observed in adults with disc herniation, athletes younger than 20 yr of age have pain or tenderness less commonly identified over the course of the sciatic nerve. Physical examination findings may be minimal but usually include pain with forward flexion and lateral bending. It is unusual to have a positive straight leg test or any neurologic deficit in the young athlete with an injured disc. There may be tenderness of the vertebral spinous process at the level of the disc. A general aching sensation in the lower back or upper buttocks may be present. MRI usually confirms a clinical diagnosis. Assuming the herniation is not large and the pain is not intractable, the treatment of choice is conservative with analgesia and physical therapy. Surgery is rarely necessary.

Acute lumbar strain or contusion can be seen in the younger athlete and is usually associated with precipitating activity often outside of the normal routine. Physical examination reveals tenderness in the paraspinal and lateral soft tissues often associated with recreating the mechanisms of injury. Thoracic and lumbar strain in the school-age child is associated with obesity, deconditioning, positive family history, and poorly supervised and equipped recreational activity. Up to 20% of youth have experienced back pain at some point in their life (younger than age 15 yr). The school-age backpack is rapidly becoming the most common cause of back pain of a benign nature in children. Up to 74% of school backpackers experience pain. Back pain is more common with the heavy backpack (greater than 10-20% of body weight), female gender, large body mass index, and single shoulder strap.

Treatment is conservative including analgesia, myofascial release, massage, and physical therapy, as tolerated. The natural history of acute

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back strain in adults is that 50% are better in 1 wk, 80% in 1 mo, and 90% in 2 mo, regardless of therapy. The course of back pain in young athletes is likely similar given the elimination of obvious precipitating influence and/or activities, as discussed above.

SACROILIITIS

Sacroiliitis manifests as pain over the sacroiliac joints; it is usually chronic but occasionally associated with a history of trauma. Patients have a positive result with the **Patrick test,** which includes resting the foot of the affected side on the opposite knee (hip flexed 90 degrees), stabilizing the opposite iliac crest, and externally rotating the hip on the affected side (pushing the knee down and lateral). Symptomatic improvement with knee-to-chest maneuvers and subsequent posterior pelvic tilt may be present. A radiograph of the sacroiliac joints is indicated, and if results are positive, exploration for a rheumatologic disease (ankylosing spondylitis [see Chapter 156], juvenile rheumatoid arthritis [see Chapter 155], ulcerative colitis [see Chapter 336]) is warranted.

Treatment is with relative rest, nonsteroidal antiinflammatory drugs, and physical therapy. Ankylosing spondylitis is more likely if the onset of lower back pain is before age 40 yr, if there is morning stiffness that is associated with improvement with activity, and if the pain has a gradual onset and has lasted longer than 3 mo.

OTHER CAUSES

Non–sports-related causes of low back pain are numerous and include infection (osteomyelitis, diskitis) and neoplasia. These should be considered in patients with fever, weight loss, other constitutional signs, or lack of response to initial therapy. Osteomyelitis of the lower back or pelvis is often, but not always, associated with fever. Scheuermann disease needs to be considered more common in males and younger adolescents, and needs to be distinguished from symptomatic postural roundback and congenital decompensating kyphosis. Atypical Scheuermann disease or thoracolumbar apophysitis can progress and become the pediatric equivalent of an adult compression fracture. Benign tumors of the spine include osteoid osteoma with intense focal nighttime pain, not activity related and almost always relieved by aspirin or nonsteroidal antiinflammatory agents. Osteoblastoma, eosinophilic granuloma, aneurismal bone cyst, and fibrous dysplasia are additional benign tumors not to be excluded. Malignant spinal tumors include the Ewing sarcoma (onion skin appearance) and osteogenic sarcoma (sunburst pattern) both associated with the Codman triangle. Metastatic tumors of the spine include neuroblastoma, spinal cord tumors, leukemia, and lymphoma. Wilms tumor can also metastasize to the spine and be associated with hemihypertrophy. Referred pain to the spine always needs to be considered. Conditions that can refer pain include pyelonephritis, renal osteodystrophy, pneumonia, endocarditis, cholecystitis, nephrolithiasis, pancreatitis, megacolon, constipation/ileus, hiatal hernia/reflux, pelvic inflammatory disease, and sickle cell crisis. Pregnancy is always a consideration in the age-appropriate female. Psychogenic pain and fibromyalgia can be seen in children. Child abuse can present in the spine with soft-tissue injuries more common than fractures. Posterior rib and spinous process fractures can be seen in up to 30% of abused children. Skeletal survey can be helpful with multiple injuries in multiple stages of healing.

Bibliography is available at Expert Consult.

687.5 Hip and Pelvis Injuries

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Hip and pelvis injuries represent a small percentage of sports injuries, but they are potentially severe and require prompt diagnosis. Hip pathology can manifest as knee pain and normal findings on knee examination.

In children, *transient synovitis* is the most common cause. It usually manifests with acute onset of a limp, with the child refusing to use the affected leg and having painful range of motion on examination. There may be a history of minor trauma. This is a self-limiting condition that usually resolves in 48-72 hr.

Legg-Calvé-Perthes disease (avascular necrosis of the femoral head) also manifests in childhood with insidious onset of limp and hip pain (see Chapter 678.3).

Until the skeleton matures (Table 687-2), younger athletes are susceptible to apophyseal injuries (e.g., the anterior superior iliac spine). *Apophysitis* develops from overuse or from direct trauma. *Avulsion fractures* occur in adolescents playing sports requiring sudden, explosive bursts of speed (see Fig. 687-2). Large muscles contract and create force greater than the strength of the attachment of the muscle to the apophysis. Biomechanical susceptibility of the pelvis allows separation to occur in the cartilaginous region between the apophysis and the adjoining bone. The most common sites of avulsion fractures are the anterior superior iliac spine (sartorius and tensor fasciae lata), anterior inferior iliac spine (rectus femoris), lesser femoral trochanter (iliopsoas), ischial tuberosity (hamstrings), and the iliac crest (abdominal muscles). Symptoms include localized pain and swelling, with decreased strength and range of motion. Bilateral radiographs are important in order to allow for comparison to assess for displacement, if any, of the fracture fragment. Significant displacement or presence of a large fragment may require orthopedic consultation. Initial **treatment** includes ice, analgesics, rest, and pain-free range-of-motion exercises. Crutches are usually needed for ambulation. Surgery is usually not indicated because most of these fractures—even large or displaced ones—heal well. Direct contact to the bone around the hip and pelvis causes exquisitely tender subperiosteal hematomas called

Table 687-2 Age of Appearance and Fusion of Apophyses in Hip and Pelvis

APOPHYSIS	APPEARANCE (YR)	FUSION (YR)	RELATED MUSCLE GROUP(S)
AIIS	13-15	16-18	Quadriceps
ASIS	13-15	21-25	Sartorius
Lesser trochanter	11-12	16-17	Iliopsoas
Greater trochanter	2-3	16-17	Gluteal
Ischial tuberosity	13-15	20-25	Hamstrings
Iliac crest	13-15	21-25	Abdominal obliques Latissimus dorsi

AIIS, anterior inferior iliac spine; ASIS, anterior superior iliac spine.

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hip pointers. These injuries are more commonly seen around the anterior superior iliac spine and the iliac crest. Limited active range of motion can be identified about the hip brought on by contracture of locally attached musculature such as hip flexors and hip abductors. Symptomatic care includes rest, ice, analgesia, and protection from reinjury.

Slipped capital femoral epiphysis usually occurs in the 11-15 yr age range during the time of rapid linear bone growth (see Chapter 678.4).

A *femoral neck stress fracture* can manifest as vague progressive hip pain in an endurance athlete. Girls with the female athlete triad are especially at risk. This diagnosis should always be kept in mind in the running athlete with vague anterior thigh pain. On examination, there may be pain with passive stretch of the hip flexors and pain with hip rotation. If radiographs do not demonstrate a periosteal reaction consistent with a stress fracture, a bone scan or MRI may be required. Orthopedic consultation is necessary in femoral neck stress fractures because of their predisposition to nonunion and displacement with minor trauma or continued weight bearing. These fractures carry increased risk of avascular necrosis of the femoral head.

Osteitis pubis is an inflammation at the pubic symphysis that may be caused by excessive side-to-side rocking of the pelvis. It can be seen in an athlete in any running sport and is more common in sports requiring more use of the adductor muscles such as ice hockey, soccer, and inline skating. Athletes typically present with vague groin pain that may be unilateral or bilateral. On physical examination, there is tenderness over the symphysis and sometimes over the proximal adductors. Adduction strength testing causes discomfort. Radiographic evidence (irregularity, sclerosis, widening of the pubic symphysis with osteolysis) might not be present until symptoms are present for 6-8 wk; a bone scan and MRI are more sensitive to early changes. Relative rest for 6-12 wk may be required. Some patients require corticosteroid injection as adjunctive therapy.

Acetabular labrum tears can occur in the hip, similar to glenoid labrum tears in the shoulder. Athletes might have a history of trauma and complain of sharp anterior hip pain associated with a clicking or catching sensation. Clinical diagnosis is difficult; magnetic resonance arthrography is useful for diagnosis.

Snapping hip syndrome is caused by the iliopsoas musculotendinous unit riding over the pectineal eminence of the pelvis, anterior hip capsule or the iliotibial band over the greater trochanter. Lack of flexibility in these muscles results in snapping, as the musculotendinous unit slides over the associated bony prominences. It is commonly seen in ballet dancers and runners; it can occur as an acute or overuse injury (more common). Athletes present with either a painful or painless click or snap in the hip, usually located lateral or anterior and deep in the joint. Examination often reproduces the symptoms. Radiographs are not usually needed in the work-up. Core weakness may be present leading to excessive movement about the hip girdle contributing to increased sliding of the tight muscle over the boney prominence. **Treatment** involves an analgesia, relative rest, biomechanical assessment, core flexibility, with stretching and strengthening of the involved soft tissue. The athlete may return to activity as tolerated. Common soft-tissue injuries around the hip and pelvis include strain and tendinosis of the hip flexors (groin) and hamstrings in addition to quadriceps contusions and greater trochanteric bursitis. Sportsman hernia also needs to be considered in the athlete with insidious onset exertional groin pain, worsening with Valsalva. Pain may radiate into the anterior thigh, inguinal region, rectum, perineum and/or scrotum. Tenderness to deep palpation may or may not be present. Resisted hip flexion and/or half sit ups may be provocative. MRI, CT scan, and bone scan can be helpful in ruling out other diagnoses, but usually are negative with respect to sports hernia pathology. Patients who continue with symptoms despite conservative care may be surgical candidates. Surgical repair can be 95% successful if anatomical lesions are identified. As with any child or adolescent presenting with a painful hip or pelvis, non–sports-related conditions need to be considered. Differential diagnoses may also include the epiphyseal dysplasias, recurrent or undiagnosed congenital or developmental hip dysplasia, additional causes of avascular necrosis including sickle cell anemia, Gaucher disease, rheumatoid arthritis, and other collagen disorders including steroid therapy. Traumatic hip dislocations are relatively rare in children but not to be overlooked. Leg-length discrepancies can be symptomatic at the hip in an otherwise able bodied child. Common tumors in lower extremities include osteosarcoma along with osteoblastoma, aneurismal bone cysts, and fibrous dysplasia (more common in the pelvis). Metastatic tumors to the lower extremities include neuroblastoma and lymphomas of various types, not to exclude leukemic infiltration with joint arthralgia. Child abuse always needs to be considered in a young patient with musculoskeletal pain no matter what the socioeconomic status.

Bibliography is available at Expert Consult.

687.6 Knee Injuries

Kevin P. Murphy and Aaron M. Karlin

Knee pain is common among adolescents. Acute knee injuries that cause immediate disability are likely to be due to fracture, patellar dislocation, anterior cruciate ligament (ACL) injury, or meniscal tear. The mechanism of injury is usually a weightbearing event. If the knee swells more immediately (within several hours of injury), the swelling is likely caused by a hemarthrosis and more severe injury. The injury most likely to occur with a hemarthrosis is an **ACL** injury. This injury (rare in children younger than 12 yr) is usually caused from being hit directly, landing off-balance from a jump, quickly changing direction while running, or hyperextension. Instability is often present but may be hard to detect in the presence of significant swelling. Girls are more than twice as likely as boys to disrupt their ACL, with a soccer injury a common scenario. Often, these injuries are associated with an avulsion injury of the anterior tibial spine. The majority of athletes with significant ACL injury need orthopedic consultation with consideration of ACL reconstruction. Chronic ACL insufficiency may increase the risk of meniscal injury and further joint dysfunction. Additional physeal-sparing reconstructions with minimal risk of growth arrest or angular deformity have been reported with success in children younger than 12 yr and adolescents.

Posterior cruciate ligament injury occurs from a direct blow to the region of the proximal tibia, such as might occur with a dashboard injury or a fall to the knees in volleyball. Posterior cruciate ligament injuries are rare and are usually treated nonsurgically.

Medial collateral ligament injuries result from a valgus blow to the outside of the knee. Isolated *lateral collateral ligament* injuries are uncommon and result from significant varus knee stress. Because they are extraarticular, lateral collateral ligament injuries should not produce much of a knee effusion and are generally less disabling. Isolated medial and lateral collateral injuries are generally managed nonsurgically with conservative care and appropriate rehabilitation.

Meniscal tears generally occur by the same mechanisms as ACL injuries. They are often associated with less hemarthrosis, significant joint line pain, and increased pain with full knee flexion. MRI scan will often yield the diagnosis; conservative care, including **PRICE** principles, is therapeutic for smaller injuries. Orthopedic consultation is indicated for larger tears not healing with conservative care and causing significant dysfunction inhibiting quality of life. An isolated meniscal tear in a child younger than age 10 yr is unusual, with surgery, again, only if conservative measures fail. The choice is often repair of the meniscus rather than surgical resection because of the increased potential in children for cartilaginous healing. Physeal injuries tend to predominate in younger patients, whereas the more skeletally mature adolescents tend to sustain medial collateral ligament injuries. Discoid meniscus (anatomical variant covering lateral tibial plateau) always needs to be considered, particularly in children younger than age 12 yr.

Patellar dislocation occurs most often as a noncontact injury when the quadriceps muscles forcefully contract to extend the knee while the lower leg is externally rotated. Patellar dislocation is the second most

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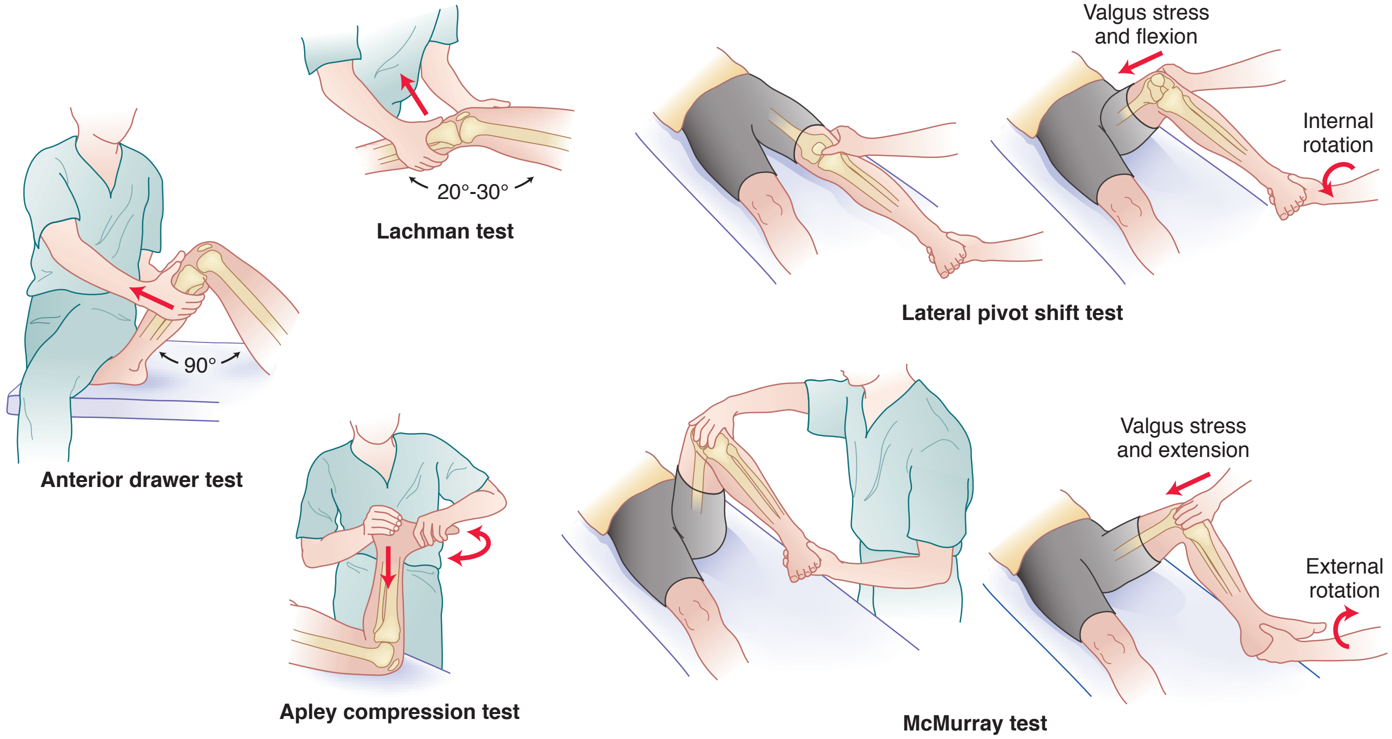

Figure 687-8 **Examination maneuvers include the Lachman, anterior drawer, lateral pivot shift, Apley compression, and McMurray tests (the right knee is shown).** The Lachman test, performed to detect anterior cruciate ligament (ACL) injuries, is conducted with the patient supine and the knee flexed 20-30 degrees. The anterior drawer test detects ACL injuries and is performed with the patient supine and the knee in 90 degrees of flexion. The lateral pivot shift test is performed with the patient supine, the hip flexed 45 degrees, and the knee in full extension. Internal rotation is applied to the tibia while the knee is flexed to 40 degrees under a valgus stress (pushing the outside of the knee medially). The Apley compression test, used to assess meniscal integrity, is performed with the patient prone and the examiner's knee over the patient's posterior thigh. The tibia is externally rotated while a downward compressive force is applied over the tibia. The McMurray test, used to assess meniscal integrity, is performed with the patient supine and the examiner standing on the side of the affected knee.

common cause of hemarthrosis. The patella is almost always dislocated laterally, and this motion tears the medial patellar retinaculum, causing bleeding in the joint. Recurrent episodes of patellar instability are associated with less swelling. Patellar dislocations are often associated with genu valgum, external tibial torsion, and general ligamentum hyperlaxity. Exercises to strengthen the quadriceps, particularly the vastus medialis, and the use of patella-tracking braces may be helpful. Recurrent instability can require surgical intervention. Surgical stabilization of the medial patellar tissues and lateral retinacular release can be helpful in more difficult cases.

INITIAL TREATMENT OF ACUTE KNEE INJURIES

The physician should inspect for an effusion and obvious deformities; if any deformity is present, the physician should assess neurovascular status and transfer the patient for emergency care as indicated. If no gross deformities are present and neurovascular integrity is intact, initial maneuvers include full passive extension and gentle valgus and varus stress to the knee while in extension. Comparison to the noninjured knee is always helpful for assessing degrees of laxity and range of motion. The patient's ability to contract the quadriceps should be noted. Pain occurring with quadriceps contraction or inability to contract the quadriceps muscle implies an injury to the extensor mechanism. Tenderness over the medial patella, medial retinaculum, or above the adductor tubercle is associated with a patellar dislocation (usually lateral). Point tenderness is consistent with fracture or injury to the underlying structure. Meniscal tears usually manifest as tenderness along the joint line, accentuated with flexion of the knee often beyond 90 degrees. Pain or limitation in either flexion or extension while rotating the tibia implies a meniscal injury. Ligament injury is manifested as pain or laxity with the appropriate maneuver (Fig. 687-8).

If a patient cannot weight-bear pain free or has clinical signs of instability, significant swelling or other major concern, the knee should be immobilized, crutches provided, and plain radiographs obtained. If the patella is dislocated, reduction may be achieved with gentle active assistive knee extension Straight-leg immobilizers offer no structural support and are only used for comfort and reminding the patient to be careful with any weight-bearing. A derotational hinge brace may be indicated for stabilization such as an injury when both ACL and medial collateral ligament have been traumatized. The leg should be elevated and an elastic wrap can be applied for compression (PRICE principles).

CHRONIC INJURIES

Patellofemoral Stress Syndrome

Patellofemoral stress syndrome (PFSS) is the most common cause of anterior knee pain. PFSS is also known as *patellofemoral pain syndrome* or *patellofemoral dysfunction* (see Chapter 677.5). It is a diagnosis of exclusion used to describe anterior knee pain that has no other identifiable pathology. Chondromalacia may be seen in association with softening of the articular cartilage underneath the patellar surface. Pain is usually difficult to localize. Patients indicate a diffuse area over the anterior knee as the source, or they might feel as if the pain is coming from behind the patella. Bilateral pain is common, and pain is often worse going up stairs, after sitting for prolonged periods, or after squatting or running. There should be a negative history for significant swelling, which would indicate a more serious injury. History of change

in activity is common, such as altered training surface or terrain, increased training regimen, or performance of new tasks.

Examination should include evaluation of stance and gait for lower limb alignment, musculature, and midfoot hyperpronation. Flexibility of the hamstrings, iliotibial band (ITB), and gastrocnemius should be assessed, because stress is increased across the patellofemoral joint when these structures are tight. Hip range of motion should be assessed to rule out hip pathology. Medial patellar tenderness or pain with compression of the patellofemoral joint confirms the diagnosis in the absence of a significant effusion and other positive findings. PFSS is a clinical diagnosis usually managed without imaging.

Treatment focuses on assessing and improving flexibility, strength, and gait abnormalities. In the presence of midfoot hyperpronation (ankle valgus), new shoes or use of arch supports can improve patellofemoral mechanics and improve pain. Ice and an analgesic can be used to help control pain. Reduced overall activity or training is important initially in rehabilitation along with limiting knee flexion no greater than 60 degrees as possible. Short arc quadriceps strengthening exercises can be helpful (active knee extension with or without resistance between 0 and 30 degrees of knee flexion). Therapeutic taping techniques to help improve patella tracking within the trochlear groove can be helpful with the assistance of a sports physical therapist.

Osgood-Schlatter Disease

Osgood-Schlatter disease is a traction apophysitis occurring at the insertion of the patellar tendon on the tibial tuberosity (see Chapter 677.4). Because it is also related to overuse of the extensor mechanism, Osgood-Schlatter disease is **treated** like PFSS. A protective pad to protect the tibial tubercle from direct trauma can be used. Therapeutic taping of the tibial tubercle may provide comfort, along with well-fitted knee sleeves and/or straps. Nonsteroidal antiinflammatory drugs are often prescribed as well. Pain-free strengthening of weightbearing soft tissues using more closed-kinetic chain techniques may be best. PRICE principles apply. Make certain that patients and parents are aware that resolution is usually slow, often requiring 12-18 mo. Complications are rare and can include growth arrest with recurvatum deformity and rupture or avulsion of the patellar tendon/tibial tubercle.

Other Chronic Injuries

Sinding-Larsen-Johansson disease is a traction apophysitis occurring at the inferior pole of the patella. It occurs most often in volleyball and basketball athletes. **Treatment** is similar to that of PFSS and Osgood-Schlatter disease.

Patellar tendinosis (jumper's knee) is caused by repetitive microtrauma of the patellar tendon, usually at the inferior pole of the patella. In approximately 10% of the cases, the quadriceps tendon above the patella is affected. It is associated with jumping sports but occurs in runners as well. **Treatment** is similar to that for PFSS. Relative rest is more important in patellar tendinosis because chronic pain can be associated with irreversible changes in the tendon.

ITB friction syndrome is the most common cause of chronic lateral knee pain. Generally it is not associated with swelling or instability. It is from friction of the ITB along the lateral knee, resulting in bursitis. Tenderness is elicited along the ITB as it courses over the lateral femoral condyle or at its insertion at the Gerdy tubercle, along the lateral tibial plateau. Tightness of the ITB is also noted using the Ober test. To perform an Ober test, the athlete lies on one side and the superior hip is extended with the knee flexed. The examiner holds the ankle in midair, and if the knee moves inferiorly, it implies a flexible ITB and a negative Ober test. If the knee and leg stay in midair, the ITB is tight and the Ober test is positive. **Treatment** principles follow those for PFSS, except emphasis is on improving flexibility of the ITB.

Other soft-tissue injuries not to be excluded include prepatellar and pes anserine bursitis, plical syndromes, and Hoffa syndrome. The pes anserine bursa lies just under the conjoined tendon of the sartorius, gracilis, and semitendinosus muscles as it attaches medially to the proximal tibia. In Hoffa syndrome, the fat pad beneath the patella and posterior to the patella ligament becomes pinched with anterior pain on knee extension. These conditions are generally more common in adolescents, those with genu recurvatum, and long distance runners. Non–sports-related conditions, again, always need to be considered in the context of any child with a painful knee, particularly in a child younger than age 12 yr. These include conditions such as OCD (see Chapter 677.3), which is most common on the lateral aspect of the medial femoral condyle. Inflammatory and infectious arthritis, Baker's cyst (see Chapter 677.2), and hip pain referred to the knee are additional considerations. Tumors more common to the knee joint include osteogenic sarcoma (distal femoral and proximal tibial), histiocytosis X in the diaphysis, and eosinophilic granuloma in the epiphysis of long bones. Metastatic tumors to the lower extremities include neuroblastoma and lymphomas of various types. As with any apparent musculoskeletal injury in a child not responding to conservative care, more in-depth diagnostic pursuit for alternative pathology is mandatory.

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687.7 Lower Leg Pain: Shin Splints, Stress Fractures, and Chronic Compartment Syndrome

Kevin P. Murphy and Aaron M. Karlin

Stress injury to the bones of the lower leg occurs on a continuum from mild injury (shin splints) to stress fracture. All occur by an overuse mechanism.

Shin splints, also known as medial tibial stress syndrome, manifests with pain along the medial tibia or both tibiae and is the most common overuse injury of the lower leg. The pain initially appears toward the end of exercise, and if exercise continues without rehabilitation, the pain worsens and occurs earlier in the exercise period. There is diffuse tenderness over the lower third to half of the distal medial tibia. Any focal tenderness or tenderness of the proximal tibia is suspicious for a stress fracture. A stress fracture tends to be painful during the entire workout. Shin splints can usually be distinguished from a **tibial stress fracture** in which the tenderness is more focal (2-5 cm) and more severe. Shin splints and stress fracture represent a continuum of stress injury to the tibia and are thought to be related to traction of the soleus on the tibia. Eccentric contraction of the medial aspect of the soleus is required to control pronation from initial contact to mid-stance with running. This contraction increases the stress of the fascial origin of the soleus possibly through Sharpey's fibers causing disruption to the tibial periosteum and fibrocartilaginous attachments.

The diagnosis can be made by history and physical examination. Findings on plain radiographs of the tibia are normal with shin splints and in tibial stress fractures within the 1st 2 wk of the injury. Afterward, the radiographs can demonstrate periosteal reaction if a stress fracture is present. Sensitivity of plain radiographs may be increased by obtaining 4 views of the tibia: AP, lateral, and both oblique views. A bone scan is the most sensitive test to diagnose stress fractures; it demonstrates discrete tracer uptake at the site(s) of the stress fracture. Increased uptake may be noted in the presence of shin splints, but in a fusiform pattern along the periosteal surface. If results of the bone scan are normal, the diagnosis is likely to be shin splints or chronic compartment syndrome. MRI has replaced bone scan as the most sensitive tool for diagnosing stress fractures in long bones in many medical centers.

The treatment of shin splints and tibial stress fractures is similar, involving relative rest, correcting training errors and addressing quartile muscle imbalances and abnormal mechanical alignment. Orthotics and/or new shoes may be useful in patients who hyperpronate. Fitness can be maintained with non-weightbearing activities, such as swimming, cycling, and water jogging. With shin splints, after

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7-10 days, patients can usually start on the walk–jog program. If pain worsens, 2-3 pain-free days are required before resuming the walk–jog program. Ice should be used daily and an analgesic should be used for pain control. Stretching the plantar flexors, hamstrings and strengthening the ankle dorsiflexors may be useful. Therapeutic taping and wrapping techniques to support the soft-tissue attachments have been useful in some when directed by a skilled sports therapist. Being pain free for 7-10 days is recommended before exercises are commenced. Individuals with pain at rest and not responsive to treatment require continued suspicion for stress fracture.

Chronic compartment syndrome occurs in an athlete in a running sport, usually during a period of heavy training. It is caused by muscle hypertrophy and increased intracompartmental pressure with exercise. There is typically a pain-free period of about 10 min at the beginning of a workout before onset of constant throbbing pain that is difficult to localize. It lasts for minutes to hours after exercise and is relieved by ice and elevation. In a classic case, there is numbness of the foot associated with high pressure within the corresponding muscle compartment. The most common compartment affected is the anterolateral compartment with compression of the fibular nerve followed by the deep posterior compartment. The physical examination in the office is often normal but weakness of the extensor hallucis longus (anterolateral compartment) and decreased sensation between the 1st and 2nd toe may be present. X-rays, bone scan, and MRI are negative and are used to rule out other conditions. Compartment pressure measurements are the test of choice. Treatment involves reduction of activity, antiinflammatory medication, orthotics (hyperpronation), heel cord stretching, light strengthening of distal musculature, optimal footwear, and crosstraining (swimming, cycling and water jogging). Cryotherapy and superficial heat can be of help in addition. Persistent systems, despite conservative care, require fasciotomy (successful in up to 90% of cases).

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687.8 Ankle Injuries

Kevin P. Murphy and Aaron M. Karlin

Ankle injuries are the most common acute athletic injury. Approximately 85% of ankle injuries are sprains, and 85% of those are inversion injuries (foot planted with the lateral fibula moving toward the ground), 5% are eversion injuries (foot planted with the medial malleolus moving toward the ground), and 10% are combined.

EXAMINATION AND INJURY GRADING SCALE

In obvious cases of fracture or dislocation, evaluating neurovascular status with as little movement as possible is the priority. If no deformity is obvious, the next step is inspection for edema, ecchymosis, and anatomic variants. Key sites to palpate for tenderness are the entire length of the fibula; the medial and lateral malleoli; the base of the 5th metatarsal; the anterior, medial, and lateral joint lines; and the navicular and the Achilles tendon complex. Assessment of active range of motion (patient alone) in dorsiflexion, plantar flexion, inversion, and eversion along with gentle resisted range of motion can be helpful.

Provocative testing attempts to evaluate the integrity of the ligaments. In a patient with a markedly swollen, painful ankle, provocative testing is difficult because of muscle spasm and involuntary guarding. It is more useful on the field before much bleeding and edema have occurred. The anterior drawer test assesses for anterior translation of the talus and competence of the anterior talofibular ligament. The inversion stress test examines the competence of the anterior talofibular and calcaneofibular ligaments (Fig. 687-9). In the acute setting, the integrity of the tibiofibular ligaments and syndesmosis is examined by the syndesmosis squeeze test. Pain with squeezing the lower leg implies injury to the interosseous membrane and syndesmosis between the tibia and fibula, making a high ankle sprain or more severe injury suspicious. Athletes with this injury cannot bear any weight and also have severe pain with external rotation of the foot. Occasionally, the peroneal tendon dislocates from the fibular groove simultaneously with an ankle sprain. To assess for peroneal tendon instability, the examiner applies pressure from behind the peroneal tendon with resisting eversion and plantar flexion, and the tendon pops anteriorly. If either a significant syndesmotic injury or an acute peroneal dislocation is suspected, orthopedic consultation should be sought.

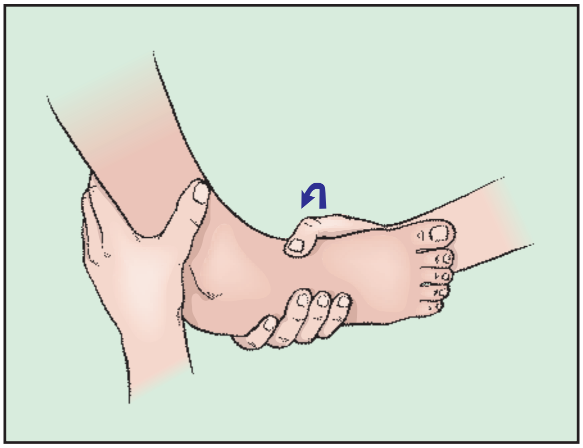

Figure 687-9 Inversion stress tilt test for ankle instability. *(From Hergenroeder AC: Diagnosis and treatment of ankle sprains. A review, Am J Dis Child 144:809–814, 1990.)*

RADIOGRAPHS

AP, lateral, and mortise views of the ankle are obtained when patients have pain in the area of the malleoli, are unable to bear weight, or have focal bone tenderness over the distal tibia or fibula. The Ottawa ankle rules help define who requires radiographs (Fig. 687-10). A foot series (AP, lateral, and oblique views) should be obtained when patients have pain in the area of the midfoot or bone tenderness over the navicular or 5th metatarsal. It is important to differentiate an avulsion fracture of the proximal 5th metatarsal (Dancer's fracture) from the Jones fracture of the proximal 5th metatarsal (a lucency about 2 cm from the proximal end). The former is treated more like an ankle sprain; the latter fracture has an increased risk of nonunion and requires orthopedic consultation. Injury to the deltoid ligament in the medial ankle (more rare) should raise the question of proximal fibular fracture. In this circumstance more proximal tibial imaging may be necessary. The *talar dome fracture* is manifested as an ankle sprain that does not improve. Radiographs on initial presentation can have subtle abnormalities. Any suspicion on the initial radiographs of a talar dome fracture warrants orthopedic consultation and further imaging. In the early adolescent, always look carefully at the tibial epiphysis. Nondisplaced Salter III fractures can be subtle and need to be recognized early and referred to an orthopedic surgeon promptly.

INITIAL TREATMENT OF ANKLE SPRAINS

Ankle sprains need to be **treated** with **PRICE**. This should be followed for the 1st 48-72 hr after the injury to minimize bleeding and edema. For an ankle injury, this might consist of crutches and an elastic wrap, although other compression devices such as an air stirrup splint work quite well. This allows early weightbearing with protection and can be removed for rehabilitation. It is important to start a rehabilitation program as soon as possible.

Rehabilitation

Rehabilitation should begin the day of injury; for patients who have pain with movement, isometric strengthening can be started. Early phase intervention includes restoration of functional range of motion, strengthening with emphasis on peroneal musculature and early sensory proprioceptive training. Later intervention includes

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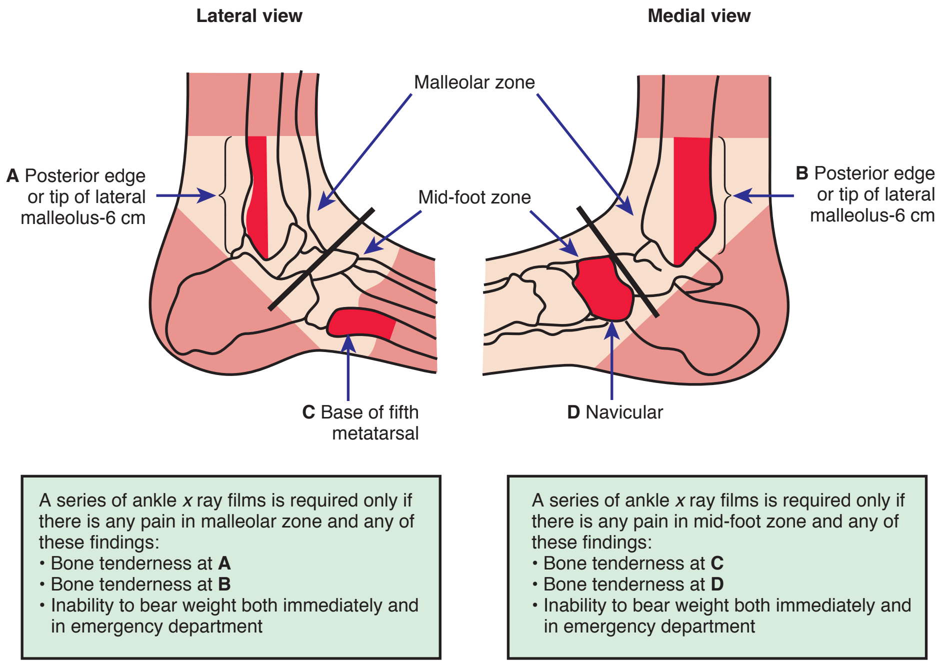

Figure 687-10 Ottawa ankle rules. *(From Bachmann LM, Kolb E, Koller MT, et al: Accuracy of Ottawa ankle rules to exclude fractures of the ankle and mid-foot; systematic review,* BMJ *326:417–419, 2003.)*

higher-level balance activities, advanced proprioception exercises, and endurance training. When determining when an athlete is ready for running, there must be full range of motion and nearly full strength compared to the uninjured side. While standing on the uninjured side only, the athlete is instructed to hop 8-10 times, if possible. When this can be achieved without pain on the injured side, the athlete can begin to run, starting out with jogging and gradually progressing in speed, and finally to sprints. The athlete must stop if there is significant pain or limp. Finally, before returning to sport, the athlete must be able to sprint and change directions off the injured ankle comfortably. Performing some sport-related tasks is also helpful in determining readiness for return to play.

Recurrent ankle injuries are more likely in patients who have not undergone complete rehabilitation. Ankle sprains are less likely in players wearing high-top shoes. Proper taping of the ankle with adhesive tape can provide functional support but loosens with use and is often unavailable. Lace-up ankle supports are felt to be more useful for preventing recurrences by many. They are more supportive than tape and can be tightened repeatedly during the course of a practice or a game. Most sports physicians recommend their use indefinitely to help prevent further sprains. Surgery is a consideration for chronic mechanical instability with lateral complex ligamentous laxity in the failure of more conservative care. Salter-Harris grade I distal fibular fractures need careful consideration, particularly in the child younger than 12 yr old. The physeal plates are generally the weakest link in the musculoskeletal chain and tend to slide or pull apart before the surrounding soft tissue and/or ligaments tear in this younger population. Toddler's fracture also needs to be considered especially in those younger than age 8 yr. The proposed mechanism involves sheer stress with lack of displacement because of the periosteum that is relatively strong compared to the elastic bone in younger children. Additional radiographs may be inconspicuous (a faint spiral oblique line) or even normal. After 1 or 2 wk callous develops. The condition can be mistaken for osteomyelitis, transient synovitis, and/or even child abuse. Toddler's fracture usually occurs in the lower third of the tibia, whereas nonaccidental injury typically affects the upper two-thirds or midshaft of the tibia. Other, more rare conditions that cannot be excluded include os fibulare, a congenital unfused secondary ossification center of the distal fibula. This can be seen in younger patients with recurrent ankle sprains, particularly as their body weight and activity increase during the early academic years. Tarsal coalitions can be seen also in the presence of ankle sprains in younger children the most common being talocalcaneal and calcaneal navicular. More common muscular strains and/or tendinosis remains more prevalent in the older child and adolescent including peroneal, posterior tibialis, and gastrocnemius/Achilles types. Tarsal tunnel syndrome is also more prevalent in the adolescent/younger adult and can be associated with medial ankle pain with burning or tingling into the sole of the foot.

Bibliography is available at Expert Consult.

687.9 Foot Injuries

Kevin P. Murphy and Aaron M. Karlin

Metatarsal stress fractures can occur in any running athlete. The history is insidious pain with activity that is getting worse. Examination reveals point tenderness over the midshaft of the metatarsal, most commonly the 2nd or 3rd metatarsal. Radiographs might not show the periosteal reaction before pain has been present for 2 wk or more. **Treatment** is relative rest for 6-8 wk. Shoes with good arch supports reduce stress to the metatarsals.

Vague dorsal foot pain in an athlete in a running sport can represent a **navicular stress fracture.** Unlike other stress fractures, it might not localize well on examination. If there is any tenderness around the navicular, a stress fracture should be suspected. This stress fracture can take many weeks to show up on plain radiographs, so a bone scan or MRI should be obtained to make the diagnosis. Because this fracture is at high risk of nonunion, immobilization and non-weightbearing for 8 wk is the usual **treatment.** A CT scan should be obtained to document full healing after the period of immobilization.

Sever disease (calcaneal apophysitis) occurs at the insertion of the Achilles tendon on the calcaneus and manifests as activity-related pain (see Fig. 687-3). It is more common in boys (2:1), is often bilateral, and usually occurs between ages 8 and 13 yr. Tenderness is elicited at the insertion of the Achilles tendon into the calcaneus, especially with squeezing the heel (positive squeeze test). Sever disease is associated with tight Achilles tendons and midfoot hyperpronation that puts more stress on the plantar flexors of the foot. **Treatment** includes relative rest, ice, massage, stretching, and strengthening the Achilles tendon. Correcting the midfoot hyperpronation with orthotics, arch supports, or better shoes is important in most athletes with Sever disease. If the foot is neutral or there is mild hyperpronation, in-heel

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lifts can be helpful to unload the Achilles tendon and its insertion. With optimal management, symptoms improve in 4-8 wk. Generally, if there is no limp during the athletic activity, young athletes with Sever disease should be allowed to play.

Plantar fasciitis is an overuse injury resulting in degeneration of the plantar aponeurosis. Rare in prepubertal children, this diagnosis is more likely in an adolescent or young adult. Athletes report heel pain with activity that is worse with first steps of the day or after several hours of non-weightbearing. Tenderness is elicited on the medial calcaneal tuberosity. Relative rest from weightbearing activity is helpful. Athletes get plantar fasciitis when shoes are worn with inadequate arch supports. New shoes or use of semirigid arch supports often lessen the pain. Stretching the calves and plantar fascia helps, assisted at times with therapeutic ultrasound treatment. Some patients benefit from night splints even though they can make sleep difficult. As long as there is no limping with athletic activity, the athlete may continue participation. Complete recovery is usually seen at 6 mo. Corticosteroid and extracorporeal shock-wave therapy are reserved for severe, chronic cases.

Calcaneal stress fracture is seen in the older adolescent or young adult involved in a running sport. There is heel pain with any weightbearing activity. The physical examination reveals pain with squeezing the calcaneus. Sclerosis can show up on the AP and lateral radiographs after 2-3 wk of pain. A bone scan or MRI needs to be performed to clinch the diagnosis in some cases. The calcaneus is an uncommon location for a stress fracture; it is associated with osteopenia (amenorrheic girls). **Treatment** is rest from running and other weight-bearing activity for at least 8 wk. Immobilization is rarely necessary.

Flatfeet or pes planus may be flexible or rigid. Flexible pes planus is usually asymptomatic, at least in the early years and is the most common type found in children. Scaphoid pads or medial inserts may be helpful to create plantigrade weightbearing posture. Untreated sports progression may occur with compensatory hallux valgus, planovalgus, and secondary bunion and toe deformities. With progression pain may develop, along with shortening in the peroneal musculature. Rigid pes planus is a congenital deformity associated with other anomalies in 50% of cases. It is caused by failure of the tarsal bones to separate leaving a bony cartilaginous or fibrous bridge or coalition between 2 or more tarsal bones. Talocalcaneal coalitions are more symptomatic between 8 and 12 yr of age, whereas calcaneal navicular coalitions are more symptomatic between 12 and 16 yr of age. Symptoms are insidious with occasional acute arch, ankle, and midfoot pain, at times brought on with sports-related activities. The hindfoot often does not align in its normal varus position on tiptoe maneuvers. Patients are predisposed to ankle sprains secondary to limited subtalar motion and stress to the subtalar and transverse tarsal joints frequently causes pain. CT scans are diagnostic and initial treatment is conservative with short leg casting and/or molded orthoses and rest. In the case of failure of conservative care, surgical intervention is usually necessary. Rigid cavus feet can also be associated with metatarsalgia, clawing, and intrinsic muscle atrophy, all possible in the young athlete. With a cavus foot, underlying neurologic conditions, such a Charcot-Marie-Tooth disease, spinal dysraphism, Friedrich ataxia, or other spinal tumor, need be considered. Custom-molded orthotics may be helpful. Family history can be critical. Coleman block test can help determine hindfoot flexibility and more rigid vs flexible pes planus. Plantar fascial surgical release is standard for all cavus foot procedures. Accessory navicular bones and sesamoiditis need to be considered in all symptomatic feet, especially those with rigid components. These conditions are more common in the adolescent or younger adult and can be exacerbated with sporting activities.

Other conditions not to be excluded include Lisfranc sprain and/or dislocation, more common in football linemen or other athletes requiring heavy loading on the mid and forefoot joints and gymnasts using the balance beam. Lisfranc joint is the tarsal metatarsal articulation of the 3 cuneiform bones and the cuboid with the 5 proximal metatarsals. Turf toe can be seen, particularly in the older child and/or adolescent running on artificial or synthetic surfaces. It usually involves hyperextension through the 1st metatarsal phalangeal joint, spraining the ligaments surrounding the joint often in a football and/or soccer activity.

Iselin apophysitis is an apophysitis that occurs at the tuberosity of the fifth metatarsal. The apophysis at this site appears between the ages of 9 and 14 yr and is located within the insertion of the peroneus brevis tendon. This condition can be a predisposing factor to the Dancer's fracture (see Chapter 687.8). Osteochondroses (see Chapter 674.08) of the foot to always consider include Freiberg disease, which involves collapse of the articular service and subchondral bone, usually of the 2nd metatarsal. Kohler disease involves irregular ossification of the tarsal navicular joint with localized pain and increased density. Freiberg disease is more common in girls between the ages of 12 and 15 yr, whereas Kohler disease occurs in younger individuals, age 2-9 yr, and is frequently reversible with conservative care including orthoses and casting.

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Chapter 688

Sports-Related Traumatic Brain Injury (Concussion)

Christopher W. Liebig and Joseph A. Congeni

Concussion is defined as a traumatically induced transient disturbance of brain function that involves a complex pathophysiologic process. Concussion may be caused either by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head, whether these are linear or rotational forces. Concussion is a subset of mild traumatic brain injury; it is important to communicate this fact to families and patients as the word "concussion" unintentionally and incorrectly has been found to communicate to some families that a brain injury has not occurred, resulting in less-than-adequate follow-up.

EPIDEMIOLOGY

At least 1.6-3.8 million concussions occur in the United States each year during competitive sports and other recreational activities. This number is likely to represent only a fraction of the true incidence as there is underreporting of symptoms by athletes from direct withholding of information to continue participation and poor understanding of their symptoms. From 1997 to 2007, visits to emergency departments for sports concussion doubled in the 8-13 yr old group; in 14-19 yr olds, the incidence has increased by more than 200%. Activities include football, bicycling, hockey, lacrosse, soccer, field hockey, basketball, and playground injuries.

PATHOPHYSIOLOGY

The pathophysiologic process following a concussion is best described as an "energy crisis" following a neurometabolic cascade. In animal models, these ionic and metabolic events, along with microscopic axonal injury, results in a desperation use of glucose to begin the healing process. The increased energy demand is met with a decreased cerebral blood flow, resulting in less available energy for other brain processes and a true mismatch of energy supply and demand.

ASSESSMENT OF THE INJURED PLAYER

The most current assessment tools are the Sport Concussion Assessment Tool (SCAT3) and the Child-SCAT3 for children ages 5-12, available at: http://bjsm.bmj.com/content/47/5/259.citation; http://bjsm.bmj.com/content/47/5/263.citation

These tests include the Glasgow coma scale, presence and duration of loss of consciousness, memory of the activity ("Who scored last?" "What team did you play last week?"), general memory/orientation (date, day of week, season), short-term memory (list 3 words and have patient repeat), concentration (give digits: 5-8-3, and have patient repeat backwards or do serial 7s), balance testing (double, single, tandem leg stances), finger to nose coordination, and cognitive testing (repeat list of words).

The signs and symptoms of concussion fall into 4 categories: physical, cognitive, emotional, and sleep (Table 688-1), with the most common symptom reported being headache. Transient loss of consciousness occurs in less than 10% of concussions and does not correlated with severity of injury. Assessment can be challenging as several or only 1 of the symptoms listed are identified. Furthermore, patients with preexisting mental health disorders such as depression or attention-deficit/hyperactivity disorder may experience exacerbations in their symptoms, making them more difficult to control.

Table 688-1 Postconcussion Symptom Scale

Symptom							
Headache	0	1	2	3	4	5	6
Nausea	0	1	2	3	4	5	6
Vomiting	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Fatigue	0	1	2	3	4	5	6
Trouble falling to sleep	0	1	2	3	4	5	6
Excessive sleep	0	1	2	3	4	5	6
Loss of sleep	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
Light sensitivity	0	1	2	3	4	5	6
Noise sensitivity	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervousness	0	1	2	3	4	5	6
More emotional	0	1	2	3	4	5	6
Numbness	0	1	2	3	4	5	6
Feeling "slow"	0	1	2	3	4	5	6
Feeling "foggy"	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
Visual problems	0	1	2	3	4	5	6

Scale: 0, no symptoms; 3, moderate; 6, severe.

Use of the postconcussion symptom scale: The athlete should complete the form, on the athlete's own, by circling a subjective value for each symptom. This form can be used with each encounter to track progress toward symptom resolution. Many athletes may have some of these reported symptoms at a baseline, such as concentration difficulties in the patient with attention-deficit disorder or sadness in an athlete with underlying depression. This must be taken into consideration when interpreting the score. Athletes do not need a total score of 0 to return to play if they had symptoms before their concussion. This scale has not been validated to determine concussion severity.

From Halstead ME, Walter KD, Council on Sports Medicine and Fitness. Sport-related concussion in children and adolescents. Pediatrics *126(3):597–615, 2010.*

A gold-standard assessment of suspected concussion has been difficult to ascertain throughout the years. Particularly difficult is the sideline evaluation where simply recognizing the injury can be most challenging for medical personnel. Initial sideline evaluation should include cervical spine stabilization, 4-limb neurologic testing, and evaluation of ABCs (airway, breathing, circulation). Secondly, discussion of the athlete's symptoms with an accepted sideline assessment tool (SCAT3 or Child-SCAT3) with balance testing should be completed because sensory coordination and vestibular systems are also affected by concussion. When available, preinjury baseline performance can be compared to the individual's postinjury test. Given the variability in concussion presentation, medical personnel are encouraged to err on the side of safety by adapting the phrase *when in doubt, sit them out*. If concussion is suspected, an athlete must be removed from participation and forbidden to return on the day of injury.

Evaluation with neuropsychologic testing provides another objective measurement of brain function. Computerized neurocognitive tests can be most useful to those familiar with the test and when athletes were able to perform baseline testing.

Concussion lacks structural changes with conventional imaging studies (MRI and CT) limiting their usefulness in evaluation. Neuroimaging should be used if suspicion of intracerebral lesion exists. Advances in functional neuroimaging have shown positive findings but require further research before clinical utilization and recommendation. Imaging may be indicated for possible related neck injury (see Chapter 689). CT imaging may be indicated for prolonged loss of consciousness, persistent altered mental status, focal neurologic deficits, suspicion of a skull fracture, or signs of clinical deterioration.

MANAGEMENT AND TREATMENT

Initial Phase

Management of a concussion also continues to evolve and is primarily based on symptom control while protecting the athlete from activities that may slow recovery. Initiating a management plan consisting of complete physical and cognitive rest is paramount. Symptoms may be followed with a postconcussion symptom scale (see Table 688-1), where symptoms are more likely to be reported. Concussed patients will often complain of increased symptoms with cognitive activities such as reading, video games, music, and even texting. They often have difficulty attending school, focusing on schoolwork, and trying to keep up with assignments. Taking standardized tests while recovering from a concussion is discouraged as lower-than-expected scores may occur. Cognitive rest may include shortened school days, reduced workload, or even temporary leave of absence with gradual return to school. Controlling symptoms can be difficult as there is no evidence-based pharmacologic treatment to offer a concussed athlete. However, medication is considered in those with prolonged recovery and specific symptoms. Vestibular therapy consisting of balance and oculomotor exercises has shown results in combating dizziness and vertigo. The duration of rest has been controversial, but one randomized controlled trial suggested that rest for 1-2 days when compared to 5 days resulted in **fewer** daily postconcussive symptoms and **faster** recovery.

Returning to Sport

No athlete should return to sport until clinically and completely asymptomatic at rest and without medication use. Each athlete's return should be individually based as recovery occurs at different rates with the majority of youth fully recovered by 1-3 wk; some may require 1-2 mo, particularly those who have had repeated concussions. Younger athletes may take longer to recover to neurocognitive and symptom baseline than older athletes. A return to play protocol provides a structured guideline that athletes progress through gradually, provided that the athlete remains asymptomatic for 24 hr at each step (Table 688-2). If no symptoms return, the athlete should wait 5 full days to complete and return to play. If symptoms have occurred, the athlete is required to rest until asymptomatic for 24 hr and resume at the previous asymptomatic step. It is important to consider individual factors at this juncture that are suspected to prolong recovery or increase patient

Table 688-2 Graduated Return to Play Protocol

REHABILITATION STAGE	FUNCTIONAL EXERCISE AT EACH STAGE OF REHABILITATION	OBJECTIVE OF EACH STAGE
1. No activity	Symptom limited physical and cognitive rest	Recovery
2. Light aerobic exercise	Walking, swimming or stationary cycling keeping intensity <70% maximum permitted heart rate No resistance training	Increase heart rate
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No head impact activities	Add movement
4. Noncontact training drills	Progression to more complex training drills, e.g., passing drills in football and ice hockey May start progressive resistance training	Exercise, coordination and cognitive load
5. Full-contact practice	Following medical clearance participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6. Return to play	Normal game play	

From McCrory P, Meeuwise WH, Aubry M, et al. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. Br J Sports Med *47:250–258, 2013.*

susceptibility. Females may be at greater risk for concussion, increased severity, and longer duration of recovery.

After sustaining a concussion, a child is 2-6–fold more likely to sustain another concussion. This risk is heightened while recovering from an initial injury with a rare, yet catastrophic injury known as **second-impact syndrome**. In this injury, seen more frequently in child athletes, a mild impact may result in brain swelling and death. Previous and repeat concussions may be associated with slower recovery with more cognitive, emotional, physical, and sleep symptoms than those who have experienced 1 or no concussions.

Those with multiple concussions may experience a cumulative effect resulting in difficulty in attention and concentration. Prolonged concussive symptoms or postconcussion syndrome is another complication that is most simply noted as symptoms of concussion that persist beyond an expected time frame. Causes and correlations have yet to be determined, making this diagnosis difficult to establish.

PREVENTION

Despite ongoing research and technologic advances, personal protective equipment has not decreased the severity or reduced the incidence of concussion in team sports. Therefore, educating athletes, coaches, officials, and parents to adhere to rule changes should be emphasized. Concussion-related legislations may prove to be the most effective methods in managing and preventing concussion.

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when a force is applied to the top of the head in this flexed position transmitting force through the spine.

SOFT-TISSUE INJURY

The most frequent injury resulting from trauma to the head and neck involves the muscles, tendons, and ligamentous structures. Even though strains, sprains, and contusions are common, proper examination and evaluation is required to rule out more serious injuries. Even without bony abnormalities, the cervical spine may become unstable secondary to soft-tissue injury.

Spinal laxity results when most restraining ligaments are injured. When compared to adjacent vertebra, laxity should horizontally be less than 3.5 mm, and angular displacement less than 11 degrees on plain flexion/extension films. However, younger athletes have more baseline laxity making the criteria less applicable and muscle spasm can acutely mask instability. If subluxation is remotely suspected, a hard cervical collar should be placed and imaging obtained again at 2-4 wk when inflammation and spasm have subsided.

Disk injuries are rare in pediatric patients. Rupture or herniation must be considered in any cervical pain differential (see Chapter 679.8).

SPEAR TACKLER'S SPINE

This clinical entity is characterized by progressive spinal changes secondary to incorrect tackling form. Findings on plain x-ray consist of (1) narrowing of cervical spinal canal, (2) loss or reversal of normal cervical lordosis, and (3) preexisting minor posttraumatic x-ray evidence of bony or ligamentous injury. Although rule changes in collision and contact sports have limited the practice of making contact with a "head-down" neck position, this condition still persists.

Many experts argue that this condition disqualifies athletes from return to play. Others argue that if physical therapy and rehabilitation are able to correct the curvature and improper technique is corrected, then athletes are not at a high risk of reinjury and could return. Data are lacking and more research required for a definitive answer.

CERVICAL FRACTURES

All significant neck injuries should be treated seriously until cleared with appropriate examination and imaging. Although many cervical fractures are stable, improper management or inadequate evaluation could end with catastrophic results. **Until properly evaluated, the patient should be immobilized and treated as if the patient has an unstable cervical fracture.**

STINGERS (BURNERS)

Stingers are unilateral peripheral nerve injuries occurring somewhere between the cervical nerve root and the brachial plexus. Three

Chapter 689

Cervical Spinal Injuries

Joseph A. Congeni and John H. Lockhart

Sports participation has surpassed motor vehicle crashes as the number 1 cause of cervical spine injuries in youth older than 9 yr of age. American football, hockey, and wrestling have the highest incidence in the United States; internationally, rugby is nearly as high.

The normal cervical spine has a lordotic curve, allowing it to absorb shock and dissipate force. When the neck is flexed forward, the spine straightens, losing this shock-absorbing property. Axial loading is

proposed mechanisms are traction or tensile stretch injury, compressive injury, and direct trauma. Typical presentation is a transient episode of unilateral pain, with or without paresthesia, in an upper extremity. Symptoms of C5 and C6 roots and upper trunk are most common. Careful examination for weakness should be performed, especially shoulder abduction, external rotation, and elbow flexion. Cervical spine should have pain-free full range of motion and have no tenderness to palpation. Spurling's Compression test, a head-tilting maneuver that when positive differentiates cervical radiculopathy from other causes of upper-extremity pain, may or may not be positive. The test is only 30% sensitive, but specificity is 93%.

Return to play may be considered the same day if the exam is reassuring. This requires complete resolution of symptoms, full range of motion, and normal strength. Multiple stingers, bilateral symptoms, or symptoms persisting for longer than 1 hr should prompt further evaluation before resumption of any physical activities.

TRANSIENT QUADRIPARESIS

Transient quadriparesis (TQ) is a temporary neurologic episode encompassing sensory symptoms with or without motor changes. TQ is also known as *cervical cord neurapraxia*, *burning hands syndrome*, *commotio spinalis*, and *spinal cord concussion*. TQ can be divided into 3 types: plegia (complete loss of motor function), paresis (motor weakness), and paresthesia (sensory symptoms only). There is also a 3-part grading system: grade 1 symptoms last <15 min, grade 2 symptoms last 15 min to 24 hr, and grade 3 symptoms persist beyond 24 hr. TQ must be differentiated from just a stinger and the player should be removed from activity and spinal cord injury considered.

Mechanisms of injury include hyperextension, hyperflexion, and axial loading. Anatomically, when the neck is hyperflexed or hyperextended, the spinal canal is narrowed by up to 30%, increasing the likelihood of cord injury.

Burning hands syndrome is the most common presentation. The athlete has intense paresthesias in both upper extremities. This is suggestive of a central cord syndrome and includes burning, tingling, and loss of sensation. Treat athletes with full cervical precautions to prevent injury progression.

Evaluation should start with plain flexion and extension films if stable. CT can be utilized if cervical fracture is suspected. MRI should then be used to evaluate for intrinsic spinal cord abnormalities or ongoing cord or root compression. Spinal stenosis is discussed below.

Return to play for TQ is heavily debated and lacks data to support it. Conservatively, some argue that 1 episode is a contraindication to return to contact sports, whereas others agree with utilizing the Return to Play Table (Table 689-1) for absolute and relative contraindications for return. If allowed to return to play and second episode of TQ occurs, the complete work-up needs repeating.

CONGENITAL SPINAL STENOSIS

Developmental narrowing of the cervical spinal canal predisposes an athlete to higher risk of spinal cord injury. This condition can be found incidentally while working up other conditions. The Torg Ratio, the ratio of vertebral body width to canal width on plain lateral film (cutoff for normal is 0.7 or 0.8, depending on clinical setting), is being evaluated for utility as a diagnostic test. Alternatively, a canal width measuring <13 mm between C3 and C7 can be used to define stenosis, with "normal" being >15 mm.

Functional stenosis can be seen with dynamic MRI in flexion and extension to see if the canal space decreases with movement. The positioning of the canal in flexion or extension causes narrowing from positioning of the vertebra and ligament, respectively. The measured diameter may be irrelevant if disc protrusion or ligament hypertrophy causes compression. This narrow "reserve space" around the spinal cord puts the athlete at greater risk for injury as compared to the same force on a normal spine.

SPINAL CORD INJURY

Spinal cord injury is the most dreaded complication of cervical trauma and is categorized into 4 entities. Hemorrhage and transection are

Table 689-1 Return to Play (RTP) Table

NO CONTRAINDICATION TO RTP	
Healed fractures including:	Healed C1 or C2 fracture with normal cervical spine range of motion (ROM) Healed subaxial fracture without sagittal plane deformity Asymptomatic clay-shoveler's (C7) spinous process avulsion fracture
Congenital conditions	Klippel-Feil (single-level anomaly not C0/C1 articulation) Spina bifida occulta
Degenerative/ postsurgical conditions	Cervical disc disease (no change in baseline neurologic status) Single-level anterior cervical fusion (ACF) with/without instrumentation Single- or multiple-level posterior cervical laminotomy
Recurrent stingers	Less than 3 episodes lasting <24 hr Must have full cervical range of motion No persisting neurologic deficit
Transient quadriparesis	Single episode Full cervical range of motion Normal neurologic exam No radiologic instability Normal spinal reserve (as evidenced on MRI)
RELATIVE CONTRAINDICATION TO RTP	
Stingers/Burners	Prolonged symptomatic burner/stinger Three or more stingers
Transient quadriparesis	Transient quadriparesis lasting >24 hr More than 1 episode with symptoms of any duration
Postsurgical	Healed 2-level ACF Posterior cervical fusion (PCF) with/ without instrumentation
ABSOLUTE CONTRAINDICATION TO RTP	
Transient quadriparesis and any 1 or more of:	Cervical myelopathy Continued neck discomfort Reduced ROM Neurologic deficit from baseline after injury
Surgical procedures	C1 + C2 fusion Cervical laminectomy Three-level ACF or PCF
Soft-tissue injuries	Asymptomatic ligamentous laxity (>11 degrees of kyphotic deformity) C1 + C2 hypermobility with anterior dens >3.5 mm (adult), >4 mm (child), i.e., Down syndrome (see Chapter 680) Symptomatic cervical disc herniation
Other conditions including:	Spear tackler's spine Multilevel Klippel-Feil anomaly (see Chapter 680) Healed subaxial fracture with sagittal kyphosis coronal plane abnormality, or cord encroachment Ankylosing spondylitis Rheumatoid arthritis with spinal abnormalities Spinal cord abnormality (cord edema, compression, etc.) Arnold-Chiari syndrome Basilar invagination Occipital-C1 assimilation (occipitalization or connection) Spinal stenosis (canal width <13 mm between C3 and C7)

Adapted from Cantu R, Li YM, Abdulhamid M, Chin LS: Return to play after cervical spine injury in sports. Curr Sports Med Rep *12:14–17, 2013.*

Figure 689-1 A magnetic resonance image (sagittal) demonstrating spinal cord contusion (edema in central portion of spinal cord). *(From Krabak BJ, Kanarek SL: Cervical spine pain in the competitive athlete.* Phys Med Rehabil Clin N Am *22:459–471, 2011, Fig. 2.)*

considered irreversible and associated with complete cord injury, whereas contusion and edema (Fig. 689-1) are considered to have more potential for recovery. Steroids and hypothermia are 2 proposed treatments to prevent secondary injury. These severe injuries should be managed by providers with expertise in this area.

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Chapter 690

Heat Injuries

Gregory L. Landry

Heat illness is the third leading cause of death in U.S. high school athletes. It is a continuum of clinical signs and symptoms that can be mild (heat stress) to fatal (heatstroke) (see Chapter 70). Children are more vulnerable to heat illness than adults because they have greater ratio of surface area to body mass and produce greater heat per kilogram of body weight during activity. The sweat rate is lower in children and the temperature at which sweating occurs is higher. Children can take longer to acclimatize to warmer, more humid environments (typically 8-12 near-consecutive days of 30-45 min exposures). Children also have a blunted thirst response compared to adults and might not consume enough fluid during exercise to prevent dehydration.

Three categories for heat illness are generally used: **heat cramps, heat exhaustion,** and **heat stroke** (Table 690-1). However, symptoms of heat illness overlap and advance as the core temperature rises. **Heat cramps** are the most common heat injury and usually occur in mild dehydration and/or salt depletion, usually affecting the calf and hamstring muscles. They tend to occur later in activity, as muscle fatigue is reached and water loss and sodium loss worsen. They respond to oral rehydration with electrolyte solution and with gentle stretching. The athlete can return to play when ability to perform is not impaired. **Heat syncope** is fainting after prolonged exercise attributed to poor vasomotor tone and depleted intravascular volume, and it responds to fluids, cooling, and supine positioning. **Heat edema** is mild edema of the hands and feet during initial exposure to heat; it resolves with acclimatization. **Heat tetany** is carpopedal tingling or spasms caused by heat-related hyperventilation. It responds to moving to a cooler environment and decreasing respiratory rate (or rebreathing by breathing into a bag).

Table 690-1	Spectrum of Heat Illness
Heat cramps and dehydration: Cautious return to play Muscle cramps Thirst Fatigue Light-headedness Sweating Flushed face **Heat Exhaustion:** Remove from play Dizziness Rapid pulse Headaches Nausea Vomiting Loss of coordination Profuse sweating Core temperature less than 40°C (104°F) **Heat Stroke:** Medical emergency, call 911 Core temperature of 40°C (104°F) or higher Hot dry skin Multiple system failure Delirium Convulsions Abnormal vital signs	

(From Merkel DL, Molony JT Jr. Medical sports injuries in the youth athlete: emergency management. Int J Sports Phys Ther *7:242–251, 2012, Table 4.)*

Heat exhaustion is a moderate illness with core temperature 37.7-39.4°C (100-103°F). Performance is obviously affected, but central nervous system dysfunction is mild, if present. It is manifested as headache, nausea, vomiting, dizziness, orthostasis, weakness, piloerection, and possibly syncope. **Treatment** includes moving to a cool environment, cooling the body with fans, removing excess clothing, and placing ice over the groin and axillae. If a patient is not able to tolerate oral rehydration, IV fluids are indicated. Patients should be monitored, including rectal temperature, for signs of heat stroke. If rapid improvement is not achieved, transport to an emergency facility is recommended.

Heat stroke is a severe illness manifested by central nervous system disturbances and potential tissue damage. It is a medical emergency; *the mortality rate is 50%*. Sports-related heat stroke is characterized by profuse sweating and is related to intense exertion, whereas "classic" heatstroke with dry, hot skin is of slower onset (days) in elderly or chronically ill persons. Rectal temperature is usually >40°C (104°F). Significant damage to the heart, brain, liver, kidneys, and muscle occurs, with possible fatal consequences if untreated. **Treatment** is immediate whole-body cooling via cold water immersion. Airway, breathing, circulation, core temperature, and central nervous system status should be monitored constantly. Rapid cooling should be ceased when core temperature is approximately 38.3-38.9°C (101-102°F). IV fluid at a rate of 800 mL/m^2 in the 1st hr with normal saline or lactated Ringer solution improves intravascular volume and the body's ability to dissipate heat. Immediate transport to an emergency facility is necessary. Physician clearance is required before return to exercise.

Dehydration is common to all heat illness; consequently, measures to prevent dehydration can also prevent heat illness. Thirst is not an adequate indicator of hydration status because it is initiated at 2-3% dehydration. Athletes are advised to be well hydrated before exercise and should drink every 20 min during exercise (5 oz for those

Heat index °F (°C)													
	Relative humidity (%)												
Temperature °F (°C)	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**
110 (47)	136 (58)												
108 (43)	130 (54)	137 (58)											
106 (41)	124 (51)	130 (54)	137 (58)										
104 (40)	119 (48)	124 (51)	131 (55)	137 (58)									
102 (39)	114 (46)	119 (48)	124 (51)	130 (54)	137 (58)								
100 (38)	109 (43)	114 (46)	118 (48)	124 (51)	129 (54)	136 (58)							
98 (37)	105 (41)	109 (43)	113 (45)	117 (47)	123 (51)	128 (53)	134 (57)						
96 (36)	101 (38)	104 (40)	108 (42)	112 (44)	116 (47)	121 (49)	126 (52)	132 (56)					
94 (34)	97 (36)	100 (38)	103 (39)	106 (41)	110 (43)	114 (46)	119 (48)	124 (51)	129 (54)	135 (57)			
92 (33)	94 (34)	96 (36)	99 (37)	101 (38)	105 (41)	108 (42)	112 (44)	116 (47)	121 (49)	126 (52)	131 (55)		
90 (32)	91 (33)	93 (34)	95 (35)	97 (36)	100 (38)	103 (39)	106 (41)	109 (43)	113 (45)	117 (47)	122 (50)	127 (53)	132 (56)
88 (31)	88 (31)	89 (32)	91 (33)	93 (34)	95 (35)	98 (37)	100 (38)	103 (39)	106 (41)	110 (43)	113 (45)	117 (47)	121 (49)
86 (30)	85 (29)	87 (31)	88 (31)	89 (32)	91 (33)	93 (34)	95 (35)	97 (36)	100 (38)	102 (39)	105 (41)	108 (42)	112 (44)
84 (29)	83 (28)	84 (29)	85 (29)	86 (30)	88 (31)	89 (32)	90 (32)	92 (33)	94 (34)	96 (36)	98 (37)	100 (38)	103 (39)
82 (28)	81 (27)	82 (28)	83 (28)	84 (29)	84 (29)	85 (29)	86 (30)	88 (31)	89 (32)	90 (32)	91 (33)	93 (34)	95 (35)
80 (27)	80 (27)	80 (27)	81 (27)	81 (27)	82 (28)	82 (28)	83 (28)	84 (29)	84 (29)	85 (29)	86 (30)	86 (30)	87 (31)

Category	Heat index	Possible heat disorders for people in high risk groups
Extreme danger	130°F or higher (54°C or higher)	Heat stroke or sunstroke likely.
Danger	105 - 129°F (41 - 54°C)	Sunstroke, muscle cramps, and/or heat exhaustion likely. Heatstroke possible with prolonged exposure and/ or physical activity.
Extreme caution	90 - 105°F (32 - 41°C)	Sunstroke, muscle cramps, and/or heat exhaustion possible with prolonged exposure and/ or physical activity.
Caution	80 - 90°F (27 - 32°C)	Fatigue possible with prolonged exposure and/or physical activity.

Heat index reference chart provided by the National Weather Service, Tulsa, Oklahoma.
Note: Exposure to full sunshine can increase Heat Index values by up to 15°F

Figure 690-1 Heat stroke index. *(From Jardine DS: Heat illness and heat stroke,* Pediatr Rev *28:249–258, 2007.)*

weighing 40 kg, 9 oz for 60 kg, and 10-12 oz for those >60 kg). Free access to cold water should be advocated to coaches. During a football practice, scheduled breaks every 20-30 min with helmets off to get out of the heat can decrease the cumulative amount of heat exposure. Practices and competition should be scheduled in the early morning or late afternoon to avoid the hottest part of the day. Guidelines have been published about modifying activity related to temperature and humidity (Fig. 690-1). Proper clothing such as shorts and T-shirts without helmets can improve heat dissipation. Prepractice and post-practice weight can be helpful in determining the amount of fluid necessary to replace (8 oz for each pound of weight loss).

Water is adequate for most persons who exercise <1 hr, although there is evidence that children drink more water when it is flavored. Fluids with electrolyte and carbohydrate are more important for persons who exercise for longer than 1 hr. Salt pills should not be used by most people because of the risk of their causing hypernatremia and delayed gastric emptying. They may be useful in a person with a high sweat rate or recurrent heat cramps. Prolonged exercise (marathon running) with only water replacement places the athlete at risk of hyponatremia.

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Chapter **691**

Female Athletes: Menstrual Problems and the Risk of Osteopenia

Gregory L. Landry

Physical training in young women can adversely affect reproductive function and bone mineral status especially when combined with calorie restriction (see Chapters 28 and 116).

The majority of bone mass is acquired by the end of the 2nd decade (see Chapter 707). Approximately 60-70% of adult bone mass is genetically determined, and the remaining is influenced by 3 controllable factors: exercise, calcium intake, and sex steroids, primarily estrogen. Exercise promotes bone mineralization in the majority of young women and is to be encouraged. In girls with eating disorders and those who exercise to the point of excessive weight loss with amenorrhea or oligomenorrhea, exercise can be detrimental to bone mineral acquisition, resulting in reduced bone mineral content, or **osteopenia**.

Specifically, bone mineralization is negatively affected by amenorrhea (absence of menstruation for ≥3 consecutive months). This may be influenced by abnormal eating patterns, or "disordered eating." When occurring together, disordered eating, amenorrhea, and osteoporosis form the **female athlete triad**. At health supervision visits and the preparticipation physical examination, special attention should be given to screening for any features of the triad.

Menstrual abnormalities (including **amenorrhea**) results from suppression of the spontaneous hypothalamic pulsatile secretion of gonadotropin-releasing hormone (see Chapter 116.1). It is believed that the amenorrhea results from reduced energy availability, defined as energy intake minus expenditure. Energy availability below a threshold of 30 kcal/kg/day lean body mass is thought to result in menstrual disturbances. Negative energy balance also appears to lower levels of leptin, which affects both nutritional state and the reproductive system. Other causes to be ruled out are pregnancy (see Chapter 118), pituitary tumors, thyroid abnormalities, polycystic ovary syndrome (see Chapter 552), anabolic–androgenic steroid use (see Chapters 114 and 692), and other medication side effects.

The low estrogen state of amenorrhea predisposes the female athlete to osteopenia and puts her at risk for stress fractures, especially of the spine and lower extremity. If left unchecked, bone loss is partially irreversible despite resumed menses, estrogen replacement, or calcium supplements. Routine bone mineral density screening is not recommended but can help guide treatment and return to activity in severe cases.

Normal ovulation and menses can be recovered in athletes with amenorrhea. This usually involves decreasing exercise amount and/or increasing caloric intake. However, many athletes are resistant to a decrease their training, and other methods, such as hormone supplementation, should be discussed. Nutritional counseling is important to help the athlete develop a plan for increasing calories. Calcium intake should be addressed, with the goal being at least 1,500 mg daily. If amenorrhea is present for ≥6 mo, hormone supplementation is recommended.

Three eating disorders can occur in the context of amenorrhea. Anorexia nervosa manifests as weight <85% of estimated ideal body weight with evidence of starvation manifesting as bradycardia, hypothermia, and orthostatic hypotension or orthostatic tachycardia. Bulimia nervosa manifests as recurrent episodes (at least once weekly) of binge eating with a sense of lack of control over eating during an episode with recurrent episodes of compensatory behaviors. A third category, "Unspecified Feeding and Eating Disorder," is a general description for disorders failing to meet the criteria for the 2 previous disorders. With the revised diagnostic criteria for bulimia and anorexia nervosa in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* it is anticipated that many young women who previously were diagnosed as "Unspecified Feeding and Eating Disorder" will receive a specific diagnosis of anorexia or bulimia. Signs of an eating disorder are weight loss, food restriction, depression, fatigue, and worsened athletic performance, and preoccupation with calories and weight. The athlete might avoid events surrounding food consumption or might hide and discard food. Signs and symptoms include fat depletion, muscle wasting, bradycardia worsened from baseline, orthostatic hypotension, constipation, cold intolerance, hypothermia, gastric motility problems, and, in some cases, lanugo (see Chapter 28). Electrolyte abnormalities can lead to cardiac dysrhythmias. Psychiatric problems (depression [see Chapter 26], anxiety [see Chapter 25], suicide risk [see Chapter 27]) are of higher incidence in this population.

For **treatment** of eating disorders, control of the symptoms is a central theme. The first step is confronting the athlete about the abnormal behavior and unhealthy weight. Generally, exercise is not recommended if the body weight is <85% of estimated ideal body weight, although there are exceptions, especially if the athlete is eumenorrheic. If the athlete is unable to gain weight with nutrition and medical counseling alone, then psychologic consultation is sought.

Most athletes will not initially admit a problem, and many are unaware of the serious physical consequences. A helpful technique in talking to these athletes is to sensitively point out performance issues. Education about decreased strength, endurance, and concentration can be a motivating factor for treatment. Often, the athlete's family needs to be involved, and the athlete should be encouraged to reveal necessary information to them. Psychology or psychiatry referral is important in the multidisciplinary approach to treatment of disordered eating. It is important for the physician to monitor the athlete's physical health while the mental health professional is caring for the mental aspects of the eating disorder.

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Chapter 692

Performance-Enhancing Aids

Gregory L. Landry

See also Chapter 114.

Ergogenic aids are substances used for performance enhancement, most of which are unregulated supplements (Table 692-1). The 1994 Dietary Supplement and Health Education Act limited the ability of the U.S. Food and Drug Administration to regulate any product labeled as a supplement. Many agents have significant side effects without proven ergogenic properties. In 2005, the American Academy of Pediatrics published a policy statement strongly condemning their use in children and adolescents. The 2004 Controlled Substance Act outlawed the purchase of steroidal supplements such as androstenediol, and androstenedione, with the exception of dehydroepiandrosterone (DHEA).

The prevalence of lifetime steroid use is highest among boys in the United States; among a large representative sample in 2010, 5.5% of

Table 692-1 Ergogenic Drugs				
ERGOGENIC DRUG	**CATEGORY**	**GOALS OF USE**	**ATHLETIC EFFECT**	**ADVERSE EFFECTS**
Anabolic–androgenic steroids	Controlled substance	Gain muscle mass, strength	Increase muscle mass, strength	Multiple organ systems: infertility, gynecomastia, female virilization, hypertension, atherosclerosis, physeal closure, aggression, depression
Androstenedione	Controlled substance	Increase testosterone to gain muscle mass, strength	No measurable effect	Increase estrogens in men; overlaps systemic risks with steroids
Dehydroepiandrosterone (DHEA)	Nutritional supplement	Increase testosterone to gain muscle mass, strength	No measurable effect	Increase estrogens in men; impurities in preparation
Growth hormone	Controlled substance	Increase muscle mass, strength, and definition	Decreases subcutaneous fat; no performance effect	Acromegaly effects: increased lipids, myopathy, glucose intolerance, physeal closure
Creatine	Nutritional supplement	Gain muscle mass, strength	Increase muscle strength gains; performance benefit in short, anaerobic tasks	Dehydration, muscle cramps, gastrointestinal distress, compromised renal function
Ephedra alkaloids	Possibly returning as nutritional supplement	Increase weight loss, delay fatigue	Increases metabolism; no clear performance benefit	Cerebral vascular accident, arrhythmia, myocardial infarction, seizure, psychosis, hypertension, death

From Calfee R, Fadale P: Popular ergogenic drugs and supplements in young athletes, Pediatrics *117:e577–e589, 2006.*

boys in middle school and 6.6% of those in high school report having used steroids for muscle-enhancement. The European School Survey Project on Alcohol and Other Drugs found that 1% of European youth reported any use of steroids. Steroids in oral, injectable, and skin cream form are taken in various patterns. *Cycling* is a term used to describe taking multiple doses of steroids for a period, ceasing, and then starting again. *Stacking* refers to the use of different types of steroids in both oral and injectable forms. *Pyramiding* involves slowly increasing the steroid dose to a peak amount and then gradually tapering down.

Anabolic–androgenic steroids have been used in supraphysiologic doses for their ability to increase muscle size and strength and decrease body fat. An evidence-base does support the increase in muscle mass and strength; the effects appear to be related to the myotrophic action at androgen receptors as well as competitive antagonism at catabolism-mediating corticosteroid receptors. However, they have significant endocrinologic side effects, such as decreased sperm count and testicular atrophy in men and menstrual irregularities and virilization in women. Hepatic problems include elevated aminotransaminases and γ-glutamyl transferase, cholestatic jaundice, peliosis hepatitis, and a variety of tumors, including hepatocellular carcinoma. There is evidence that anabolic–androgenic steroids might cause cardiovascular problems as well, including higher blood pressure, lower high-density lipoprotein, higher low-density lipoprotein, higher homocysteine, and decreased glucose tolerance. The psychologic effects include aggression, several personality disorders, and a variety of other psychologic problems (anxiety, paranoia, mania, depression, psychosis). Physical findings in males include gynecomastia, testicular shrinkage, jaundice, male pattern baldness, acne, and marked striae. Women can develop hirsutism, voice deepening, cliterol hypertrophy, male-pattern baldness, acne, and marked striae.

Testosterone precursors (also known as *prohormones*) include androstenedione and DHEA. Their use in the adolescent population has increased markedly in conjunction with reports of high-profile athletes' use. They are androgenic but have not been proved to be anabolic. If they are anabolic at all, they work by increasing the production of testosterone. They also increase production of estrogenic metabolites. The side effects are similar to those of anabolic–androgenic steroids and far outweigh any ergogenic benefit. Since January 2005, these substances cannot be sold without prescription.

Creatine is an amino acid mostly stored in skeletal muscle. Its key feature is ability to rephosphorylate adenosine diphosphate to adenosine triphosphate, therefore increasing muscle performance. Its use has increased, especially since other supplements have been withdrawn from the market. Thirty percent of high school football players have used creatine. There is evidence that creatine, as a source of increased energy, enhances strength and maximal exercise performance when used during training. There is no evidence that creatine affects hydration or temperature regulation. Concerns about nephritis in case reports have not been supported by controlled studies. However, there are few long-term studies evaluating creatine use.

Caffeine is an active ingredient in energy drinks and some endurance sport supplements. More of a problem as an energy drink when combined with alcohol, excessive caffeine ingestion may result in tachycardia, gastritis, nausea, vomiting, and central nervous system excitation. Overdoses may result in seizures, arrhythmias, and hypotension.

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Chapter 693

Specific Sports and Associated Injuries

Kevin P. Murphy and Aaron M. Karlin

GYMNASTICS

Typically, males and females begin gymnastics participation at 4-5 yr of age. The highest level of competition is in the mid-teens followed by retirement, often by 20 yr for females and mid-twenties for males. Lower-extremity injuries are more common in female gymnasts,

whereas upper body injuries occur with higher frequency in male gymnasts. Apparatus competed upon accounts for this discrepancy, such as the horizontal bar and ring exercises for male gymnasts, which place a great deal of stress upon the shoulders. In addition to mechanical or traumatic injuries, female gymnastics commonly have delayed menarche and are at risk for hypothalamic amenorrhea or oligomenorrhea, as well as low body weight for height related to disordered eating. Despite the presence of these 2 components of the *female athlete triad* (see Chapter 691), the third component, reduced bone density or osteoporosis, is not commonly seen. In fact, bone density tends to be high in most gymnasts, which is thought to be secondary to their performance involving repetitive high-impact activities. Nevertheless, stress fractures, in both the upper and lower extremities, are a significant problem. The short stature associated with male and female gymnasts is probably caused by selection bias and not the result of gymnastics training.

Both acute and chronic injuries are seen in gymnasts and commonly involve the ankles, wrists, and spine. The incidence of injury increases with the skill level and is greatest with the floor exercise. The amount of weightbearing through the upper extremities in gymnastics lends itself to the development of both traumatic and overuse injuries. At the wrist, this can manifest as Salter I stress fractures of the distal radial physis *(gymnast's wrist*), triangular fibrocartilage tears, scaphoid fractures, dorsal ganglions, and, most commonly, wrist sprains (see Chapter 683.2). Spine injuries are notable for a high incidence of spondylolysis (stress fracture of the pars interarticularis) and, in less frequent cases, spondylolisthesis, both related to repetitive extension loading of spine (see Chapter 679.6). Ligamentous laxity can predispose to elbow or shoulder dislocation and ankle sprains.

Treatment of many of these injuries includes relative rest from the inciting activity, immobilization, ice, and nonsteroidal antiinflammatory drugs. Imaging begins with radiographs but may include bone scan with single-photon emission computed tomography to evaluate spondylolysis, or MRI to rule out intraarticular tears, loose bodies, ligamentous instability, or physeal injury. A pediatrician should have a low threshold for referral to a sports medicine or orthopedic specialist in a child with a wrist injury not improving with rest.

SWIMMING

Injuries of the shoulder in competitive swimming are most common and generally a result of chronic, overuse. *Swimmer's shoulder* is a combination of subacromial bursitis and tendinosis of the rotator cuff and long-head of the biceps. Commonly, increased laxity of the shoulder capsule and weakness of the scapular stabilizers contribute over time leading to the insidious onset of shoulder pain (see Chapter 687.2). Freestyle, back, and butterfly strokes tend to exacerbate the pain. Pain may be provoked on exam by passively abducting the arm to 90 degrees, forward flexing to 30 degrees, and internally rotating the humerus with the elbow extended while having the patient actively abduct against resistance (*Empty Can* Test). The Hawkins impingement test involves the same position of the shoulder with the elbow flexed to 90 degrees and the examiner internally rotating the humerus. Pain and/or weakness indicates supraspinatus injury. Treatment includes relative rest, ice, and modification of stroke technique. The multi-axial instability of the glenohumeral joint common to swimmers is addressed with rehabilitation focusing upon strengthening of the rotator cuff and scapular stabilizer musculature. Prevention includes monitoring training load, proper technique and strengthening exercises.

Swimmer's ear, or otitis externa, presents with pain and often drainage from the external auditory canal. It is caused by bacterial, or less commonly, fungal infection of the external auditory canal due to chronic, excessive wetness (see Chapter 639).

BASEBALL

Throwing injuries of the elbow and shoulder (particularly among pitchers) are the most common baseball injuries (see Chapters 687.2 and 687.3). Monitoring the number of pitches thrown per game, no more than 6 times the young athlete's age in years and per week based upon the athlete's age, is important. Counseling athletes (and coaches) to stop all throwing activities if the player experiences elbow pain, with medical evaluation to be sought if there is no resolution with rest, is essential. Death or serious injury in baseball is rare and generally from direct contact by the ball, causing serious head injury or, in the case of chest wall impact, *commotio cordis*. Batting helmets need to be worn properly to try to prevent face and head injuries; modifications to the hardness of baseballs used with younger athletes is also helpful. Injures to catchers can involve traumatic brain injury with various levels of concussion from contact of the ball to the face mask. Catchers are more vulnerable to traumatic sprains of the interphalangeal and metacarpal phalangeal joints along with internal derangement and ligamentous sprain of the knees associated with the deep squatting posture.

DANCE

Dance is a highly demanding activity that may be associated with delayed menarche and disordered eating in females (see Chapter 691). Acute injuries commonly involve the lower extremities. Overuse injuries are likely, due to the repetitive nature of maneuvers incorporated into training and performance. Frequently, kinetic chain dysfunction contributes to injury and this should be considered when evaluating the dancer. Common mistakes in technique can cause injury, such as forcing excessive "turnout" (external rotation at the hip) in ballet can result in undue stress being placed upon the knees (see Chapter 687.6). An unrehabilitated ankle sprain may cause favoring of the affected leg leading to development of a stress fracture of the contralateral tibia. In contrast to injuries in most types of dance, injuries associated with breakdancing more frequently involve the spine and upper extremities than lower extremities. This likely relates to the significant amount of twisting of the torso and weight bearing through the hands inherent in this genre of dance.

Foot problems are not uncommon and include metatarsal stress fractures, subungual hematomas, sesamoiditis, plantar fasciitis, calluses, and bunions (see Chapter 687.9). A *Dancer's fracture* is an avulsion fracture of the distal shaft of the 5th metatarsal. This is treated with immobilization for 4-6 wk, although poor healing, a result of the tenuous blood supply in the area, may necessitate surgical fixation. Common ankle injuries include acute sprains, anterior and posterior impingement syndromes, and osteochondritis dissecans of the talus. Medial tibial stress syndrome ("shin splints") and tibial stress fractures are noted in the lower leg. Patellar malalignment/hypermobility can result in patellofemoral pain syndrome or, less frequently, patellar subluxation/dislocation. Medial snapping hip syndrome, caused by the iliopsoas tendon riding over the anterior hip capsule, and hip flexor (rectus femoris, iliopsoas) tendinosis are commonly noted in addition. Gluteal region pain with sciatica may be a result of *piriformis syndrome,* which occurs because of the repetitive external hip rotation required in ballet (see Chapter 687.5).

The proper timing of allowing a ballet dancer to go *en pointe* is a common question asked by dancers and parent alike. An average age to go en pointe is 12 yr. A functional test should be part of that decision: If the young dancer is able to perform a passé steadily away from the barre as well as being able to maintain an en pointe position without pain or instability the dancer is likely ready to begin dancing en pointe.

WRESTLING

Wrestlers have great fluctuations in weight to meet weight-matched competition standards. Such fluctuations are associated with fasting, dehydration, and then binging. Counseling to wrestlers and their parents regarding impaired performance resulting from these components of disordered eating, especially with respect to decreased speed and strength, is important in order to deter athletes from incorporating them into routine practice.

Wrestling holds apply a variety of torques or forces to the extremities and spine producing a number of common injuries. Takedown maneuvers and subsequent impact with the mat can produce concussions, neck strain/sprain, or spinal cord injury (see Chapter 689). *Stingers* and *burners*, also seen among football players, are caused by stretching or pinching of the brachial plexus (see Chapter 689). Pain at the shoulder

often radiates down the arm and is frequently associated with paresthesias and weakness; the latter most commonly involving the deltoid and other C5/C6 innervated muscles. Overall, the 2 most common sites of injury in wrestling are the shoulder and knee.

At the shoulder, subluxation is common. This generally occurs anteriorly with the shoulder forcibly abducted and extended. Patients are commonly aware of their shoulder slipping in and out (see Chapter 687.2).

Injuries to the hand are less common and typically include metacarpophalangeal and proximal interphalangeal joint sprains. Treatment consists of buddy taping and/or splinting.

Knee injuries (see Chapter 687.6) are also common and include prepatellar bursitis, medial and lateral collateral ligament sprains, and medial and lateral meniscus tears. Acute or recurrent traumatic impact to the mat can result in prepatellar bursitis. Swelling is noted over the patella with the patient experiencing limitations to range of motion primarily with knee flexion as a result. If the overlying skin is broken, septic bursitis must be considered. Distinguishing between a traumatic and infected bursitis may require aspiration of the bursa. Treatment of traumatic bursitis includes protective padding upon return to wrestling, ice, nonsteroidal antiinflammatory drugs (NSAIDs), and, on occasion, aspiration if flexion is markedly impaired. Recurrence after aspiration is not uncommon. Rarely, bursectomy is needed if there are several reoccurrences.

Dermatologic problems associated with wrestling include herpes simplex (see Chapter 252: *herpes gladiatorum*), impetigo (see Chapter 665.1), staphylococcal furunculosis or folliculitis, superficial fungal infections, and contact dermatitis. Herpes gladiatorum and impetigo are contraindications to wrestling until the lesions have resolved. Treatment of herpes gladiatorum with oral antiviral medications, such as Acyclovir, for both acute outbreaks and long-term suppression is recommended. Washing of the wrestling mats with appropriate antibacterial and antifungal solution is required after daily wrestling sessions to keep the mats disinfected and protect the spread of dermatologic contagion.

Auricular hematoma is caused by friction or direct trauma to the auricle (see Chapter 642). If allowed to remain without evacuation, irreversible deformity of the auricle often results, termed *cauliflower ear*. Properly fitted headgear is the best means of prevention.

FOOTBALL

Football is the sport with the highest number of injuries, with the greatest number of participants (especially at the high school level) and with a higher rate of injury. The majority of these injuries is relatively minor and compared to many other sports, the injuries are less severe, as evidenced by less number of days lost from injury. The most common football injuries include joint sprains, muscle strains, and contusions, with the lower extremities injured most frequently. Treated appropriately, these injuries generally result in minimal time away from football. An important exception to this, contusions to the arm or thigh muscles can result in the development of a large hematoma if not treated aggressively in the acute stage, resulting in prolonged time away from football. Without the presence of fracture, treatment includes ice and compression for the 1st few days to reduce the expansion of the hematoma. Pain-free stretching and strengthening exercises are then incorporated. Therapeutic ultrasound per physical therapy staff can be helpful in stretching deeper tissue and resolving persistent hematoma limiting further flexibility. Return to contact play is initiated when baseline range of motion and strength are achieved. Large hematomas and those allowed to persist are at risk for development of myositis ossificans.

Although the majority of catastrophic sports injuries in the United States have occurred in football, these injuries are rare. Catastrophic injury is defined as a fatal injury or a severe injury with or without permanent severe functional disability. Disabling injuries include cervical spine and cerebral injuries.

Head and neck injuries in football include concussion, neck sprain, and brachial plexopathy. The latter, also seen among wrestlers, is referred to as a *stinger* or *burner* and represents a brachial plexus neurapraxia (see Chapter 689). This is the most common nerve injury in football and is often the result of a traction or compression injury to the upper nerve roots of the brachial plexus caused by forceful lateral neck bending. This results in painful arm dysesthesias and deltoid muscle weakness. This is usually transient, resolving in minutes to days, with return to play upon return of full range of motion, comfort and strength.

Compared to other sports, brain injury (**concussions)** occurs with the highest rate in football, a result of the frequent exposure to contact during practices and games. The prevention, diagnosis, and management of this significant injury with potentially lifelong implications are discussed in full in Chapter 688**.**

Lumbar spine injury manifested as low back pain can indicate spondylolysis (see Chapter 679.6). Shoulder trauma can cause glenohumeral dislocation, the majority of which are anterior dislocations, acromioclavicular joint sprain, and fractures to the clavicle or humerus (see Chapter 687.8). Knee injuries (see Chapter 687.6) are common and include anterior cruciate ligament and, less frequently, posterior cruciate ligament tears along with medial collateral ligament sprains.

Ankle sprains occur frequently, and the risk of reinjury may be reduced by rehabilitation and the use of a lace-up ankle brace (see Chapter 687.6). Turf toe, a sprain to the 1st metatarsophalangeal joint, is caused by forceful dorsiflexion of the toe while wearing soft, lightweight, flexible shoes. Treatment of turf toe includes ice, NSAIDs, and orthotic to limit extension of the great toe, along with rest.

ICE HOCKEY

Ice hockey is classified as a collision sport and is associated with injuries caused by contact from the puck or stick as well as from other players, the ice, or the boards. These injuries commonly include contusions, lacerations, fractures, sprains, or concussions. The risk of injury is reduced by the use of proper equipment (helmets with facemasks) and enforcement of the rules regarding dangerous body contact (checking from behind, high sticking, and fighting).

Specific hockey injuries include ankle sprains (dorsiflexion, eversion, and external rotation in contrast to the usual inversion sprain in other sports), hip adductor strain, osteitis pubis, and various shoulder injuries from body contact. The latter include acromioclavicular joint sprain, glenohumeral dislocation, and clavicle fractures (see Chapter 687.2). The most serious injuries are to the head and neck (see Chapters 688 and 689).

BASKETBALL AND VOLLEYBALL

Common maneuvers of these 2 sports include jumping, pivoting, running and sudden stopping which increase the risk for knee and ankle injuries. Similarly, injury to the fingers may result from the passing, catching, and striking of the ball inherent in these sports.

Knee injuries include those caused by overuse, such as **traction apophysitis** (Osgood-Schlatter disease) and **patellar tendinosis** (*jumper's knee*) (see Chapter 687.6). As with other jumping sports, acute ligament sprains (medial collateral with or without anterior cruciate ligaments) can occur. Shoulder injuries in volleyball players are similar to other overhead athletes and include rotator cuff tendinosis and glenohumeral instability.

Ankle sprain is the most common injury and is usually caused by inversion with plantar flexion, placing the lateral ligaments at high tension. An avulsion fracture of the base of the 5th metatarsal at the insertion of the peroneus brevis tendon is another sequelae of inversion ankle injuries. In terms of overuse injuries at the ankle, Achilles tendinosis is common. Foot pain may be from calcaneal apophysitis (Sever disease), retrocalcaneal bursitis, posterior tibialis tendinosis, accessory tarsal navicular, plantar fasciitis, stress fracture of the tarsal navicular, Jones's stress fracture of the 5th metatarsal, sesamoiditis, blisters, subungual hematoma, and paronychia (see Chapters 687.8 and 687.9).

RUNNING

Running problems are typically caused by an overuse injury related to muscle imbalance; a minor skeletal deformity; repetitive overload

trauma; or poor flexibility, strength, endurance, or proprioception. With each step while running, the foot impact ranges from 3-8 times the athlete's body weight. Errors in training, including increasing the distance or intensity of workouts too rapidly, often result in injury to the runner. Minor variations (e.g., malalignment) in anatomy that do not cause problems at rest can predispose to injury at specific sites, such as overpronation, contributing to increased patellofemoral stress. Muscle fatigue, environmental temperature (see Chapter 690), and running surface (grass vs unyielding concrete) also contribute to injury. Prevention of injuries is possible by muscle-strengthening exercises, incorporating periods of rest into training plans, and the use of good-quality running shoes that match an athlete's foot type. Those who overpronate may benefit from a motion control shoe for maximal rearfoot and arch support. Those who mildly overpronate should utilize a stability shoe that combines extra support in the medial midsole with midsole cushion. Those who supinate should wear a neutral, cushioned shoe with increased shock absorption in the midsole and less arch support.

Stress fractures of all bones of the lower extremities can occur in runners (see Chapter 683.4). They have been documented at the femoral neck, inferior pubic rami, subtrochanteric area, proximal femoral shaft, proximal tibia, fibula, navicular, metatarsals, desmoids, and calcaneal apophysis. The most common are in the metatarsals, tibia, and fibula. The anterior proximal tibia, femoral neck, and tarsal navicular are most at risk for nonunion. Muscle strains most frequently affect the hamstrings, followed by the quadriceps, hip adductors, soleus, and gastronomies muscles. Tendinosis is most common in the Achilles tendon, followed by the posterior tibial, peroneal, iliopsoas, and proximal hamstrings. Achilles tendinosis characterized by tenderness and crepitance if acute and nodularity if chronic, initially might get better when running, and must be distinguished from retrocalcaneal bursitis. Treatment includes a period of rest from running (substitute cross-training), a heel lift, Achilles tendon stretching, and NSAIDs.

Knee pain in the runner is frequently anterior in location and commonly caused by patellofemoral stress syndrome (**runner's knee**), which results from excessive dynamic, usually lateral, motion of the patella in relationship to the femoral intracondylar groove (see Chapter 687.6). The athlete's body habitus (i.e., increased Q-angle, overpronation) and presence of core weakness may contribute to this overuse injury. Posterior knee pain can be caused by gastrocnemius strain, while posteromedial pain may be caused by proximal tibial stress fracture or semimembranosus/semitendinosus tendinosis. Lateral knee pain is commonly caused by **iliotibial band syndrome** and less so by popliteal tendinosis. Iliotibial band syndrome may combine both a component of bursitis and tendinosis owing to mechanical friction of the iliotibial band (an extension of the tensor fasciae latae) over the lateral femoral epicondyle. Treatment for knee pain in the runner includes relative rest from running, ice, and stretching of the quadriceps, hamstrings, and, in some cases, the iliotibial band. Strengthening exercises should include the quadriceps, hips, and core muscles. Foot orthotics may be indicated if there is no improvement with this treatment plan.

Shin splints, or medial tibial stress syndrome, is a descriptive term for pain located diffusely over the distal medial tibia and should be distinguished from tibia stress fracture and chronic compartment syndrome. Medial tibial stress syndrome often occurs in new runners with overpronation, or runners that have markedly increased their training duration in a short period of time. See Chapter 687.7 for prevention, diagnosis, and treatment.

Chronic compartment syndromes involve any of the muscle compartments with the most common being anterior. There is typically poorly localized throbbing pain that onsets 10-15 min into a run. Pain typically prevents further training limiting the risk of nerve injury. Physical exam is usually normal. Diagnosis is made by measurement of intracompartmental pressures at rest or during exercise.

Plantar fasciitis is an inflammation of the supporting structures of the longitudinal arch, due to repetitive cyclic loading with foot strike. Pain is typically worst with the first step out of bed in the morning and with running and is located on the medial aspect of the heel. Pes planus and overpronation are common in these patients. Treatment includes relative rest, ice, heel cord stretching, transverse friction massage, proper shoes, use of a posterior night splint, and corticosteroid injection. Therapeutic ultrasound by a trained physical therapist can be helpful in stretching the deep plantar fascia pre-friction massage in certain individuals. Calcaneal stress fracture should be considered, especially in the amenorrheic distance runner (see Chapter 691).

SOCCER

Injuries in soccer include any of the running injuries previously noted as well as abrasions, contusions, muscle strains, and ligament sprains (ankle, knee predominantly), partly from body-to-body contact, falls, running, and kicking. Hip problems include the *hip pointer* (iliac crest contusion), iliac crest apophysitis, and chronic groin pain (muscle strain, hernia, osteitis pubis). Femoral neck stress fractures, slipped femoral capital epiphysis, and avulsion fractures of the pelvis or femur should also be considered in the differential despite being uncommon (see Chapter 687.5). In general, most other upper- and lower-extremity injuries can occur in soccer.

Traumatic brain injury (see the discussion of concussions in Chapter 688) is common in soccer because of contact between players, player and goal post, and player and ground. The American Academy of Pediatrics recommends that youth soccer participants minimize heading the ball until more is known about the risks in young children. Proper heading technique is vital and should be taught in youth soccer. Additional points of play to consider include: On long kicks, the receiving player should trap the ball with the chest or leg, not strike it with the head; players should kick the ball about 5 ft in front of their teammates so that the latter have to come to the ball and trap with their legs; players avoid heading the ball backward toward the goal (with cervical extension); referees, as with all sports, have to keep the game under control and penalize dangerous play; and guidelines for returning to play after a concussion should be followed.

TENNIS

Tennis injuries occur twice as often in the lower extremity compared to the upper extremity with overall injury rates similar for boys and girls. Common areas of injury include the muscles, tendons, and ligaments of the ankle, thigh, elbow, shoulder, back, wrist, and abdomen. The risk of injury is increased by increased training duration and intensity; anatomic considerations (muscle imbalance, malalignment); poorly rehabilitated injuries with resultant deficits in flexibility and strength; and poor technique. Injuries can also be related to improper equipment, such as a racquet that is too big, or trying to learn techniques, such as hitting with top spin or with power before proper coordination and technique have been established.

Acute injuries include ankle sprains, abdominal or extremity muscle strains, and knee sprains. Overuse injuries involve both the upper and lower extremities as well as the back. Lower-extremity injuries are related to the frequent directional changes inherent in the sport, creating significant concentric and eccentric loads on the lower extremities. These include patellofemoral stress syndrome, proximal tibial stress fractures, traction apophysitis of the calcaneus (Sever disease), and tibial tubercle (Osgood-Schlatter disease) (see Chapters 687.6 and 687.7)

In the upper extremities, overuse injuries include stress fractures of the humerus, ulna, and metacarpals, as well as traction apophysitis at the medial humeral epicondyle. The marked and rapid load and directional change associated with serving in tennis contributes to injuries of the back.

Tennis elbow, or lateral epicondylitis, is from repetitive overload of the wrist extensor-supinator mechanism, especially the extensor carpi radialis brevis (see Chapter 687.3). Medial epicondylitis is caused by repetitive overload of the wrist flexor–pronator muscle groups. This can secondarily involve the ulnar collateral ligament at the elbow. In young athletes, medial epicondylar apophysitis may also be associated with ulnar nerve dysfunction in the presence of an avulsion injury.

Olecranon apophysitis is similar to Osgood-Schlatter disease and is marked by pain at the olecranon with elbow extension.

At the shoulder (see Chapter 687.2), rotator cuff tendinosis is caused by repetitive overuse and may be related to anteroposterior glenohumeral instability. Subluxation of the glenohumeral joint may also be present. Biceps tendinosis can present as anterior shoulder pain. Wrist problems include an enlarged dorsal ganglion cyst, radiocarpal joint capsular (impingement) synovitis, chronic degenerative tears of the triangular fibrocartilage complex, and acute fracture of the hook of the hamate.

Basic treatment includes relative rest, ice, NSAIDs, rehabilitation, learning proper mechanics, use of properly sized racquets, counterforce bracing (elbow, wrist), forearm straps, strengthening exercises, and gradual return to tennis. Corticosteroid injections in the wrist extensor–supinator muscle group for tennis elbow are not recommended as outcomes at 1 yr are poorer than those treated with rehabilitation.

SKIING AND SNOWBOARDING

Injuries are related to falls (concussions, contusions, lacerations), and ski-specific mechanisms. Overall injuries have declined, partly because of better equipment (boots, bindings, poles) and slope conditions. It is strongly advised that children, adolescents, and adults wear helmets for skiing and snowboarding. Wrist protectors are also recommended for snowboarders. Injury patterns differ between these two sports with lower extremity injuries more commonly associated with skiing. Upper-extremity injuries (often from falls onto an outstretched arm) are more common in snowboarding related to the fact that both of the snowboarder's feet are strapped onto the same board reducing torque at the knees. The upper extremities, not poles, are used for balance in snowboarding putting them at increased risk.

Skier's thumb, a sprain of the ulnar collateral ligament of the thumb, often results from a fall with the thumb in abduction and hyperextension. Complete tears with a 45 degree joint opening require surgical intervention. Smaller degrees of joint opening can be treated with immobilization in a thumb spica cast × 4 wk. Care should be taken to rule out a concomitant Salter-Harris III fracture, which would require open reduction and internal fixation if the epiphyseal fracture is displaced. In snowboarding, shoulder dislocation, acromioclavicular joint sprain, and fractures of the wrist or collarbone are common injuries.

Lower-extremity injuries include fractures (often spiral) of the tibia ("boot top") and sprains of the high ankle and anterior cruciate ligament, the latter may include tibial eminence fracture. Hemarthrosis is present in fractures and anterior cruciate ligament injuries. Treatment is described in Chapter 683.4.

CHEERLEADING

Cheerleading injuries are mostly related to the gymnastic component of the sport, primarily stunting, tumbling, and pyramids. Sprains and strains comprise the majority of these injuries followed by fractures and contusions. These injuries involve the upper and lower extremities nearly equally, with the ankle being the most commonly injured joint followed by the head, neck, knee, and lower back. The use of impact-absorbing surfaces for practices reduces the risk of serious injury from falls. Ankle sprains in cheerleading predominantly involve the lateral ligaments with the ankle injured when forced into excessive plantarflexion and inversion during landings.

Similar to gymnasts, the excessive amount of repetitive hyperextension, flexion, rotation, and axial loading of the spine associated with stunting and tumbling maneuvers results in significant stress being placed upon the lower back. Another common mechanism of injury involves the act of spotting or basing another cheerleader during partner or group stunts. This involves the lifting or throwing of a teammate above the level of one's head, followed by catching them upon their descent. Injuries with this activity include sprains and strains to the upper and lower back, contributed to by poor technique, requiring coaching to avoid excessive lordosis and encourage lifting with one's legs. Concussions (brain injury) are not uncommon in cheerleading, primarily due to falls while stunting or from a pyramid. This sometimes places the cheerleaders on the bottom of these formations at greater risk of injury than those held aloft or thrown. Prevention, diagnosis, and treatment of concussion are described in Chapter 688.

SKATEBOARDING

Injuries associated with skateboarding are predominantly acute including contusions, lacerations, sprains, and fractures, affecting the wrists, forearms, and to a lesser extent, ankles and head. Fractures involving the upper extremities are more common in younger skateboarders, often from a fall onto an outstretched arm (see Chapter 683.3). Lower-extremity fractures and head injuries predominate in the adolescent population, likely because of higher complexity of the often airborne maneuvers attempted. Loss of balance leading to a fall when failing to perform a particular maneuver is generally the primary cause of injury. These falls can occur at high velocities, with speeds up to 40 mph documented in the literature, placing the skateboarder at risk for serious injuries.

Traumatic brain injuries are not uncommon within this sport, the incidence increasing with age as well as more common in males than females. In older children and adolescents, the neglected use of helmets and increased speed of their skating contribute to this fact. The prevention, diagnosis, and treatment of traumatic brain injuries are discussed in Chapter 688.

In addition to helmet use, other safety measures recommended include wrist guards with elbow and knee pads. The building of skateboard parks has been a recent strategy to remove skateboarders from pedestrians, bicyclists, and traffic while also encouraging adult supervision.

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Section 3

The Skeletal Dysplasias

Chapter 694

General Considerations

William A. Horton and Jacqueline T. Hecht

The **skeletal dysplasias**, **bone dysplasias**, and **osteochondrodysplasias** are a genetically and clinically heterogeneous group of disorders of skeletal development and growth with an estimated prevalence of 1 in 4,000 births. They can be divided into the osteodysplasias typified by osteogenesis imperfecta (see Chapter 701) and the chondrodysplasias. The latter result from mutations of genes that are essential for skeletal development and growth. The clinical picture is dominated by skeletal abnormalities. The manifestations may be restricted to the skeleton, but in most cases nonskeletal tissues are also involved. The disorders range in severity from lethal in utero to such mild features as to go undetected.

The chondrodysplasias are distinguished from other forms of short stature by a disproportionality of skeletal manifestations. Figure 694-1 notes the importance of cartilage in bone formation. There are 2 basic categories: predominantly with short limbs and predominantly with short trunks. Efforts to define the extent of clinical heterogeneity resulted in the delineation of well over 100 distinct entities. Many of these disorders result from mutations of a relatively small group of genes, the *chondrodysplasia genes*. An International Working Group on

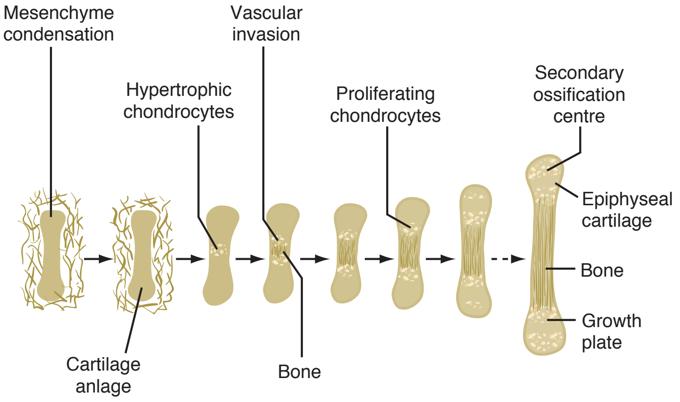

Figure 694-1 The importance of cartilage in bone formation. *(From Horton WA: Skeletal development: Insights from targeting the mouse genome,* Lancet *362:560, 2005.)*

Bone Dysplasias has named and classified these disorders into groups based on genetic cause if known or on similarities of clinical and radiographic manifestations, which often imply a common pathogenesis and a common genetic basis, if the cause is unknown (Table 694-1). The better-defined chondrodysplasia groups, such as the achondroplasia and type II collagenopathy groups, contain graded series of disorders that range from very severe to very mild. This may be true for other groups as more mutations are found and the full spectrum of clinical phenotypes associated with mutations of a given gene is defined. These disorders are clinical phenotypes distributed along spectra of phenotypic abnormality associated with mutations of particular genes. For mutations of some genes, such as *COL2A1,* the distribution is fairly continuous, with clinical phenotypes merging into one another across a broad range. There is much less clinical overlap for mutations of some other genes, such as *FGFR3,* in which the distribution is discontinuous. Because most clinicians and most reference materials refer to the disorders as distinct entities, this vernacular continues to be used.

Most chondrodysplasias require the analysis of information from the history, physical examination, skeletal radiographs, family history, and laboratory testing to make a diagnosis. The process involves recognizing complex patterns that are characteristic of the different disorders (Tables 694-2, 694-3, 694-4, and 694-5). Comprehensive descriptions of disorders and references are at the Online Mendelian Inheritance in Man (OMIM) Internet site (http://omim.org/about).

CLINICAL MANIFESTATIONS

Growth

The hallmark of the chondrodysplasias is disproportionate short stature. Although this refers to a disproportion between the limbs and the trunk, most disorders exhibit some shortening of both, and subtle degrees of disproportion may be difficult to appreciate, especially in premature, obese, or edematous infants. Disproportionate shortening of the limbs should be suspected if the upper limbs do not reach the mid pelvis in infancy or the upper thigh after infancy. Disproportionate shortening of the trunk is indicated by a short neck, small chest, and protuberant abdomen. Skeletal disproportion is usually accompanied by short stature (length and height below the 3rd percentile); these measurements are occasionally within the low-normal range early in the course of certain conditions.

There may also be disproportionate shortening of different segments of the limbs; the particular pattern can provide clues for specific diagnoses. Shortening is greatest in the proximal segments (upper arms and legs) in achondroplasia; this is termed **rhizomelic shortening.** Disproportionate shortening of the middle segments (forearms and lower legs) is called **mesomelic shortening; acromelic** shortening involves the hands and feet.

With some exceptions, there is a strong correlation between the age at onset and the clinical severity. Many of the lethal neonatal chondrodysplasias are evident during routine fetal ultrasound examinations performed at the end of the 1st trimester of gestation (see Table 694-4). Gestational standards exist for long-bone lengths; discrepancies are often detected between biparietal diameter of the skull and long-bone lengths. Many disorders become apparent around the time of birth; others manifest during the 1st yr of life. A number of disorders manifest in early childhood and a few in late childhood or later.

Non–Growth-Related Manifestations

Most patients also have problems unrelated to growth. Skeletal deformities, such as abnormal joint mobility, protuberances at and around joints, and angular deformities, are common and usually symmetric. Skeletal abnormalities can adversely affect nonskeletal tissues. Impaired growth at the base of the skull and of vertebral pedicles reduces the size of the spinal canal in achondroplasia and can contribute to spinal cord compression. Short ribs reduce thoracic volume, which can compromise breathing in patients with short trunk chondrodysplasias. Cleft palate (see Chapter 310) is common to many disorders, presumably reflecting defective palatal growth.

Manifestations may be unrelated to the skeleton; they reflect expression of mutant genes in nonskeletal tissues. Examples include retinal detachment in spondyloepiphyseal dysplasia congenita, sex reversal in camptomelic dysplasia, congenital heart malformations in Ellis-van Creveld syndrome, immunodeficiency in cartilage-hair hypoplasia, and renal dysfunction in asphyxiating thoracic dystrophy. These nonskeletal problems provide valuable clues to specific diagnoses and must be managed clinically (see Table 694-3).

Family and Reproductive History

A family history might identify relatives with the condition; a mendelian inheritance pattern may be elicited. Because the presentation can vary in some disorders, features that might be related to the disorder should be identified. Special attention should be given to mild degrees of short stature, disproportion, deformities, and other manifestations such as precocious osteoarthritis because they may be overlooked. Physical examination of relatives may be useful, as may the review of their photographs, radiographs, and medical and laboratory records.

A reproductive history might reveal previous stillbirths, fetal losses, and other abnormal pregnancy outcomes resulting from a skeletal dysplasia. Pregnancy complications, such as polyhydramnios or reduced fetal movement, are common in bone dysplasias, especially neonatal lethal variants.

Even though most of the skeletal dysplasias are genetic, it is common to have no family history of the disorder. New mutations are common for autosomal dominant disorders, especially lethal disorders in the perinatal period (thanatophoric dysplasia, osteogenesis imperfecta). Most cases of achondroplasia result from new mutations. Germ cell mosaicism, in which a parent has clones of mutant germ cells, has been observed in osteogenesis imperfecta and in other dominant disorders. A negative family history is usually seen in recessive disorders. Few of these conditions are caused by X-linked mutations. Prenatal diagnosis is available for disorders that have a genetic locus identified. Appropriateness of the testing depends on many factors, and genetic counseling is warranted for these families.

Radiographic Features

Radiographic evaluation for a chondrodysplasia should include plain films of the entire skeleton. Efforts should be made to identify which bones and which parts of bones (epiphyses, metaphyses, diaphyses) are most affected. If possible, films taken at different ages should be examined because the radiographic changes evolve with time. Films taken before puberty are generally more informative because pubertal closure of the epiphyses obliterates many of the signs needed for a radiographic diagnosis. Prenatal diagnosis may also be possible with fetal ultrasound.

DIAGNOSIS

If an infant or child is short with disproportionate features, a diagnosis is established by matching the observed clinical picture (defined

Table 694-1 Genetics of Skeletal Dysplasias

GENE LOCUS	CHROMOSOME LOCATION	PROTEIN	PROTEIN FUNCTION	CLINICAL PHENOTYPE	MIM	DISEASE MECHANISM	INHERIT
COL2A1	12q13.1-q13.3	Type II collagen α_1 chain	Cartilage matrix protein	Achondrogenesis II Hypochondrogenesis SED congenital Kniest dysplasia Late-onset SED Stickler dysplasia	200610 200610 183900 156550 108300	Dominant negative Dominant negative Dominant negative Dominant negative Dominant negative Haploinsufficiency	AD* AD* AD AD AD AD
ACG1	15q26.1	Aggrecan	Cartilage matrix protein	SED Kimberley SEMD Aggrecan type	608361 155760	Haploinsufficiency Dominant negative	AD AR
SEDL	Xp22.2-p22.1	Sedlin	Intracellular transporter	X-linked SED tarda	313400	Loss of function	XLR
COL11A1	1p21	Type XI collagen α_1 chain	Cartilage matrix protein	Stickler-like dysplasia	184840	Dominant negative	AD
COL11A2	6p21.3	Type XI collagen α_2 chain	Cartilage matrix protein	Stickler-like dysplasia	215150	Loss of function	AR
COMP	19p12-p13.1	Cartilage oligomeric matrix protein	Cartilage matrix protein	Pseudoachondroplasia MED	177170 600969	Dominant negative Dominant negative	AD AD
COL9A2	1p32.2-p33	Type IX collagen α_2 chain	Cartilage matrix protein	MED	600969	Dominant negative	AD
COL9A3	20q13.3	Type IX collagen α_3 chain	Cartilage matrix protein	MED	600969	Dominant negative	AD
MATN3	2p24-p23	Matrilin 3	Cartilage matrix protein	MED	600969	Dominant negative	AD
COL10A1	6q21-q22.3	Type X collagen α_1 chain	Hypertrophic cartilage matrix protein	Schmid metaphyseal chondrodysplasia	156500	Haploinsufficiency	AD
FGFR3	4p16.3	FGF receptor 3	Tyrosine kinase receptor for FGFs	Thanatophoric dysplasia I Thanatophoric dysplasia II Achondroplasia Hypochondroplasia	187600 187610 100800 146000	Gain of function Gain of function Gain of function Gain of function	AD* AD* AD AD
PTHR1	3p21-p22	PTHrP receptor	G protein-coupled receptor for PTH and PTHrP	Jansen metaphyseal chondrodysplasia	156400	Gain of function	AD
DTDST	5q32-q33	DTD sulfate transporter	Transmembrane sulfate transporter	Achondrogenesis 1B Atelosteogenesis II Diastrophic dysplasia	600972 256050 222600	Loss of function Loss of function Loss of function	AR* AR* AR
SOX9	17q24.3-q25.1	SRY box 9	Transcription factor	Campomelic dysplasia	114290	Haploinsufficiency	AD
RUNX2[†]	6p21	Runt-related transcription factor 2	Transcription factor	Cleidocranial dysplasia	119600	Haploinsufficiency	AD
LMX1B	9q34.1		Transcription factor	Nail-patella dysplasia	161200	Haploinsufficiency	AD
CTSK	1q21	Cathepsin K	Enzyme	Pyknodysostosis	265800	Loss of function	AR
RMPR	9p21-p12	Mitochondrial RNA-processing endoribonuclease	RNA-processing enzyme	CHH	250250	Loss of function	AR
DYNC2H1	11q13.5	Dynein, cytoplasmic 2, heavy chain 1	Cytoplasmic cilia-related protein	ATD SRPIII	208500 263510	Loss of function? Loss of function?	AR AR
TRPV4	12q24.1-12q24.2	Calcium-permeable TRP ion channel	Transmembrane channel protein	Brachyolmia SMDK Metatropic dysplasia	113500 1842522 156530	Gain of function Gain of function Gain of function	AD AD AD

*Usually lethal.

[†]Also called CBFA1.

AD, autosomal dominant; AR, autosomal recessive; ATD, Jeune asphyxiating thoracic dystrophy; CHH, cartilage-hair hypoplasia; DTD, diastrophic dysplasia; FGF, fibroblast growth factor; MED, multiple epiphyseal dysplasia; PTH, parathyroid hormone; PTHrP, parathyroid hormone–related protein; SED, spondyloepiphyseal dysplasia; SEMD, spondyloepimetaphyseal dysplasia; SMDK, spondylometaphyseal dysplasia Kozlowski type; SRPIII, short rib polydactyly syndrome type III; SRY, sex-determining region of the Y chromosome; TRPV4, transient receptor potential vanilloid family 4.

Table 694-2 Major Problems Associated with Skeletal Dysplasias

PROBLEM	EXAMPLE
Lethality*	Thanatophoric dysplasia
Associated anomalies†	Ellis-van Creveld syndrome
Short stature	Common to almost all
Cervical spine dislocations	Larsen syndrome
Severe limb bowing	Metaphyseal dysplasia, Schmid type
Spine curvatures	Metatropic dysplasia
Clubfeet	Diastrophic dysplasia
Fractures	Osteogenesis imperfecta
Pneumonias, aspirations	Camptomelic dysplasia
Spinal cord compression	Achondroplasia
Joint problems (hips, knees)	Most skeletal dysplasias
Hearing loss	Common (greatest with cleft palate)
Myopia/cataracts	Stickler syndrome
Immunodeficiency‡	Cartilage-hair hypoplasia, Schimke immunoosseous dysplasia
Poor body image	Variable, but common to all
Sex reversal	Camptomelic dysplasia

*Mostly a result of severely reduced size of thorax.
†See Table 694-3.
‡At least 4 additional disorders, all involving the metaphyses, can have immunodeficiency.

primarily from clinical, family, and gestational histories; physical examination; and radiographic evaluation) with clinical phenotypes of well-documented disorders. Pediatricians should be able to gather most of this information and, in consultation with a radiologist, diagnose the common chondrodysplasias. A number of reference texts and online databases provide information about the disorders and comprehensive lists of current references (http://www.ncbi.nlm.nih.gov/books/NBK1116/). For less-common disorders and for infants and children whose phenotypes do not closely match well-established clinical phenotypes, consultation with experts in the bone dysplasia field is warranted.

Molecular genetic testing for chondrodysplasias is very useful, especially for disorders in which recurrent mutations occur (typical achondroplasia has the same *FGFR3* mutation). Mutation testing for achondroplasia is available, although the diagnosis is usually made clinically. The greatest utility for testing may be for prenatal diagnosis for couples where both parents have typical (heterozygous) achondroplasia. Their children are at a 25% risk of the much more severe homozygous achondroplasia, which can be detected by mutation analysis. Preimplantation genetic testing can be used to identify double dominant mutations. Another example of testing is in disorders resulting from mutations of *DTDST*. These disorders are inherited in an autosomal recessive manner, and a limited number of mutant alleles have been found. If the mutations are identified in the patient, they should be detectable in the parents and potentially used for prenatal diagnosis. Mutational analysis is now commercially available for many of the skeletal dysplasias and is increasingly used to confirm clinical diagnosis and for future pregnancy planning.

Many of the chondrodysplasias have distinct histologic changes of the skeletal growth plate. Sometimes such tissues obtained at biopsy or discarded from a surgical procedure are helpful diagnostically. It is uncommon to make a diagnosis histologically if it was not already suspected on clinical or radiographic grounds.

Table 694-3 Associated Anomalies in Skeletal Dysplasias

ANOMALY	EXAMPLE
Heart defects	Ellis-van Creveld syndrome, Jeune syndrome
Polydactyly	Short rib polydactyly, Majewski type
Cleft palate	Diastrophic dysplasia
Ear cysts	Diastrophic dysplasia
Spinal cord compression	Achondroplasia
Encephalocele	Dyssegmental dysplasia
Hemivertebrae	Dyssegmental dysplasia
Micrognathia	Camptomelic dysplasia
Nail dysplasia	Ellis-van Creveld syndrome
Conical teeth, oligodontia	Ellis-van Creveld syndrome
Multiple oral frenula	Ellis-van Creveld syndrome
Dentinogenesis imperfecta	Osteogenesis imperfecta
Pretibial skin dimples	Camptomelic dysplasia
Cataracts, retinal detachment	Stickler syndrome
Intestinal atresia	Saldino-Noonan
Renal cysts	Saldino-Noonan
Camptodactyly	Diastrophic dysplasia
Craniosynostosis	Thanatophoric dysplasia
Ichthyosis	Chondrodystrophia punctata
Hitchhiker thumb	Diastrophic dysplasia
Sparse scalp hair	Cartilage-hair hypoplasia
Hypertelorism	Robinow syndrome
Hypoplastic nasal bridge	Acrodysostosis
Clavicular agenesis	Cleidocranial dysplasia
Genital hypoplasia	Robinow syndrome
Tail	Metatropic dysplasia
Omphalocele	Beemer-Langer syndrome
Blue sclera	Osteogenesis imperfecta

Table 694-4 Lethal Neonatal Dwarfism

USUALLY FATAL*
Achondrogenesis (different types)
Thanatophoric dysplasia
Short rib polydactyly (different types)
Homozygous achondroplasia
Camptomelic dysplasia
Dyssegmental dysplasia, Silverman-Handmaker type
Osteogenesis imperfecta, type II
Hypophosphatasia (congenital form)
Chondrodysplasia punctata (rhizomelic form)

OFTEN FATAL
Asphyxiating thoracic dystrophy (Jeune syndrome)

OCCASIONALLY FATAL
Ellis-van Creveld syndrome
Diastrophic dysplasia
Metatropic dwarfism
Kniest dysplasia

*A few prolonged survivors have been reported in most of these disorders.

Table 694-5	Usually Nonlethal Dwarfing Conditions Recognizable at Birth or Within 1st Few Mo of Life
MOST COMMON	
Achondroplasia	
Osteogenesis imperfecta (types I, III, IV)	
Spondyloepiphyseal dysplasia congenita	
Diastrophic dysplasia	
Ellis-van Creveld syndrome	
LESS COMMON	
Chondrodysplasia punctata (some forms)	
Kniest dysplasia	
Metatropic dysplasia	
Langer mesomelic dysplasia	

MOLECULAR GENETICS

A number of chondrodysplasia genes have been identified (see Table 694-1). They encode several categories of proteins, including cartilage matrix proteins, transmembrane receptors, ion transporters, and transcription factors. The number of identified gene loci is smaller than anticipated from the number of recognized clinical phenotypes. The majority of patients have disorders that map to fewer than 10 loci; mutations at 2 loci (*COL2A1* and *FGFR3*) account for more than half of all cases. There may be a limited number of genes whose function is critical to skeletal development, especially linear bone growth; mutations in these genes give rise to a wide range of chondrodysplasia clinical phenotypes. New genes harboring mutations that cause chondrodysplasias continue to be identified with advances in detection technology.

Mutations at the *COL2A1* and *FGFR3* loci illustrate different genetic characteristics. *COL2A1* mutations are distributed throughout the gene, with few instances of recurrence in unrelated persons. In contrast, *FGFR3* mutations are restricted to a few locations within the gene, and occurrence of new mutations at these sites in unrelated persons is the rule. There is a strong correlation between clinical phenotype and mutation site for *FGFR3,* but not *COL2A1,* mutations.

PATHOPHYSIOLOGY

Chondrodysplasia mutations act through different mechanisms. Most mutations involving cartilage matrix proteins cause disease when only 1 of the 2 copies (alleles) of the relevant gene is mutated. These mutations usually act through a dominant negative mechanism in which the protein products of the mutant allele interfere with the assembly and function of multimeric molecules that contain the protein products of both the normal and mutant alleles. The type II collagen molecule is a triple helix composed of 3 collagen chains, which are the products of the type II collagen gene *COL2A1.* When chains from both normal and mutant alleles are combined to form triple helices, most molecules contain at least 1 mutant chain. It is not known how many mutant chains are required to produce a dysfunctional molecule but, depending on the mutation, it theoretically could be as few as 1.

Mutations involving type X collagen differ from the model just described. They map to the region of the chain that is responsible for chain recognition; the chains must recognize each other before they can assemble into collagen molecules. Mutations are thought to disrupt this process. As a result, none of the mutant chains are incorporated into molecules. This mechanism is haploinsufficiency because the products of the mutant allele are functionally absent and the normal allele is insufficient for normal function. Mutations involving ion transport genes also act through a loss of function of the transporters. Mutations of transmembrane receptors studied to date appear to act through a gain of function; the mutant receptors initiate signals in a constitutive manner independent of their normal ligands.

Regardless of genetic mechanism, the mutations ultimately disrupt endochondral ossification, the biologic process responsible for the development and linear growth of the skeleton (see Fig. 694-1). Indeed, a wide range of morphologic abnormalities of the skeletal growth plate, the anatomic structure in which endochondral ossification occurs, have been described in the chondrodysplasias.

TREATMENT

The first step is to establish the correct diagnosis. This allows one to predict a prognosis and to anticipate the medical and surgical problems associated with a particular disorder. Establishing a diagnosis helps to distinguish between lethal disorders and nonlethal disorders in a premature or newborn infant (see Tables 694-4 and 694-5). A poor prognosis for long-term survival might argue against initiating extreme lifesaving measures for thanatophoric dysplasia or achondrogenesis types Ib or II, whereas such measures may be indicated for infants with spondyloepiphyseal dysplasia congenita or diastrophic dysplasia, which have a good prognosis if the infant survives the newborn period.

Because there is no definitive therapy to normalize bone growth in any of the disorders, management is directed at preventing and correcting skeletal deformities, treating nonskeletal complications, providing genetic counseling, and helping patients and families learn to cope. Each disorder has its own unique set of problems, and consequently management must be tailored to each disorder.

There are a number of problems common to many chondrodysplasias for which general recommendations can be made. Children with most chondrodysplasias should avoid contact sports and other activities that cause injury or stress to joints. Good dietary habits should be established in childhood to prevent or minimize obesity in adulthood. Dental care should be started early to minimize crowding and malalignment of teeth. Children and relatives should be given the opportunity to participate in support groups, such as the Little People of America (http://www.lpoaonline.org) and Human Growth Foundation (http://www.hgfound.org).

Two controversial approaches have been used to increase bone length. Surgical limb lengthening has been employed for a few disorders. Its greatest success has been in achondroplasia in which nonskeletal tissues tend to be redundant and easily stretched. The procedure is usually performed during adolescence. Pharmacologic doses of human growth hormone comparable to those used to treat Turner syndrome have also been tried in several disorders; the results have been equivocal. Animal studies suggest that C-type natriuretic peptide may promote linear bone growth in achondroplasia. Clinical trials are beginning to test the efficacy of this approach.

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Chapter 695

Disorders Involving Cartilage Matrix Proteins

William A. Horton and Jacqueline T. Hecht

Disorders of cartilage matrix proteins resulting in bone and joint disorders can be classified in 5 categories corresponding to the defective proteins: 3 collagens and the noncollagenous proteins COMP (cartilage oligomeric matrix protein), matrilin 3, and aggrecan. The clinical phenotypes and clinical severity differ between and within the groups, especially the **spondyloepiphyseal dysplasia (SED)** group.

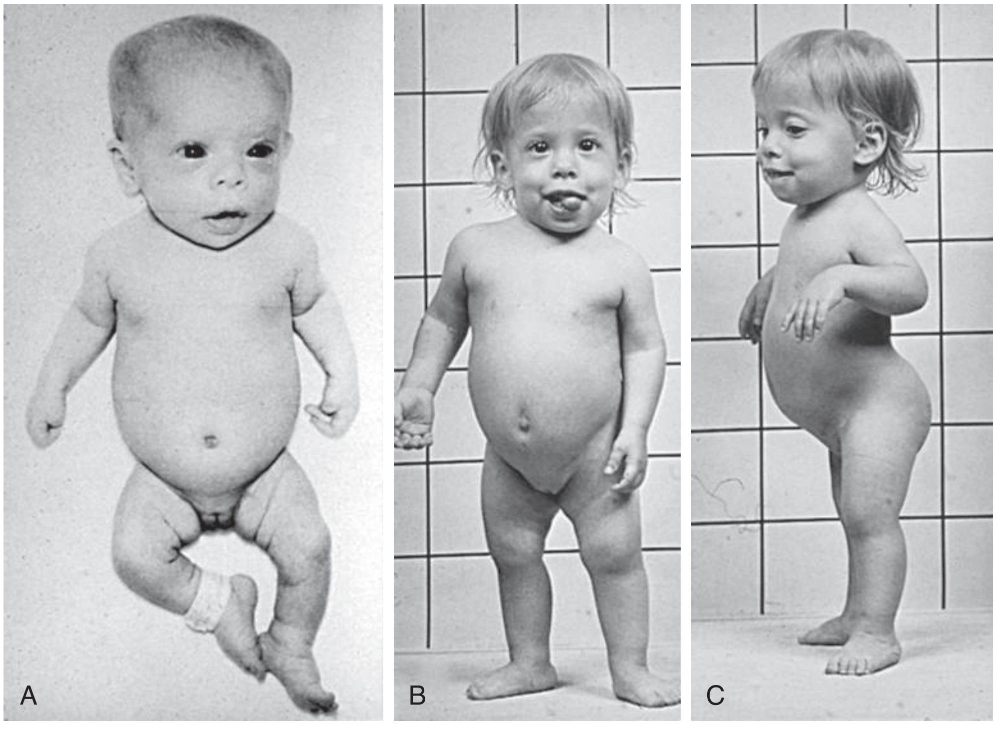

Figure 695-1 Spondyloepiphyseal dysplasia congenita is shown in infancy **(A)** and early childhood **(B, C).** Note the short extremities, relatively normal hands, flat facies, and exaggerated lordosis.

SPONDYLOEPIPHYSEAL DYSPLASIAS

The term *spondyloepiphyseal dysplasia* refers to a heterogeneous group of disorders characterized by shortening of the trunk and, to a lesser extent, the limbs. Severity ranges from achondrogenesis type II to the slightly less-severe hypochondrogenesis (although both types are lethal in the perinatal period) to SED congenita and its variants, including Kniest dysplasia (which is apparent at birth and is usually nonlethal), to late-onset SED (which might not be detected until adolescence or later). The radiographic hallmarks are abnormal development of the vertebral bodies and of epiphyses, the extent of which corresponds to the clinical severity. Most of the SEDs result from heterozygous mutations of *COL2A1;* they are autosomal dominant disorders. The mutations are dispersed throughout the gene; there is a poor correlation between the mutation's location and the resultant clinical phenotype. For familial cases, prenatal diagnosis is possible if the mutation is identified. Schimke immuno-osseous dysplasia may be an exception because it is an autosomal recessive disorder characterized by short stature, hyperpigmented macules, unusual facies, proteinuria and progressive renal failure, cerebral ischemia, and a T-cell defect with lymphopenia and recurrent infections.

Lethal Spondyloepiphyseal Dysplasias

Achondrogenesis type II (MIM 200610) is characterized by severe shortening of the neck and trunk and especially the limbs and by a large, soft head. Fetal hydrops and prematurity are common; infants are stillborn or die shortly after birth. Hypochondrogenesis (MIM 200610) refers to a clinical phenotype intermediate between achondrogenesis type II and SED congenita. It is typically lethal in the newborn period.

The severity of radiographic changes correlates with the clinical severity. Both conditions produce short, broad tubular bones with cupped metaphyses. The pelvic bones are hypoplastic, and the cranial bones are not well mineralized. The vertebral bodies are poorly ossified in the entire spine in achondrogenesis type II and in the cervical and sacral spine in hypochondrogenesis. The pedicles are ossified in both.

Spondyloepiphyseal Dysplasia Congenita

The phenotype of this group, SED congenita (MIM 183900), is apparent at birth. The head and face are usually normal, but a cleft palate is common. The neck is short and the chest is barrel shaped (Fig. 695-1). Kyphosis and exaggeration of the normal lumbar lordosis are common. The proximal segments of the limbs are shorter than the hands and feet, which often appear normal. Some infants have clubfoot or exhibit hypotonia.

Skeletal radiographs of the newborn reveal short tubular bones, delayed ossification of vertebral bodies, and proximal limb bone epiphyses (Fig. 695-2). Hypoplasia of the odontoid process, a short, square pelvis with a poorly ossified symphysis pubis, and mild irregularity of metaphyses are apparent.

Infants usually have normal developmental milestones; a waddling gait typically appears in early childhood. Childhood complications include respiratory compromise from spinal deformities and spinal cord compression because of cervicomedullary instability. The disproportion and shortening become progressively worse with age, and adult heights range from 95-128 cm. Myopia is typical; adults are predisposed to retinal detachment. Precocious osteoarthritis occurs in adulthood and requires surgical joint replacement.

KNIEST DYSPLASIA

The Kniest dysplasia variant of SED (MIM 156550) manifests at birth with a short trunk and limbs associated with a flat face, prominent eyes, enlarged joints, cleft palate, and clubfoot (Fig. 695-3). Radiographs show vertebral defects and short tubular bones with epiphyseal irregularities and metaphyseal enlargement that gives rise to a dumbbell appearance.

Motor development is often delayed because of the joint deformities, although intelligence is normal. Hearing loss and myopia commonly develop during childhood, and retinal detachment can occur as a late complication. Joint enlargement progresses during childhood and becomes painful; it is accompanied by flexion contractures and muscle atrophy, which may be incapacitating by adolescence.

Figure 695-2 Radiograph of spondyloepiphyseal dysplasia congenita pelvis demonstrating squared pelvis, hypoplastic capital femoral epiphyses, and femoral necks that are wide and short.

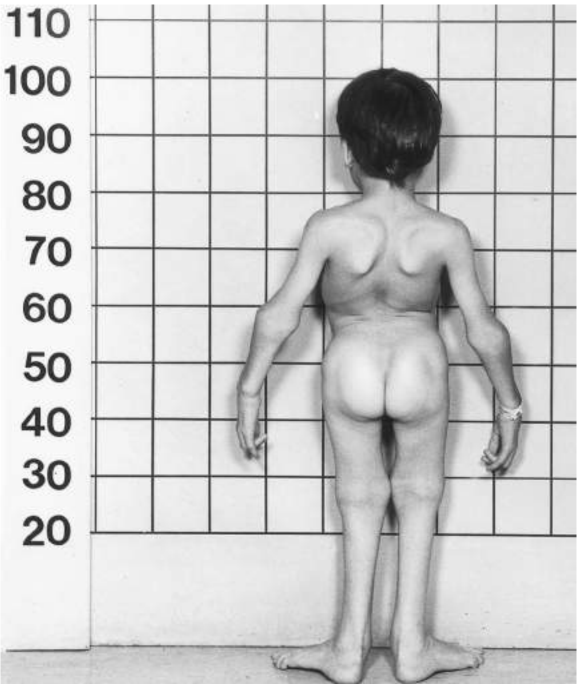

Figure 695-3 **Patient with Kniest dysplasia.** The trunk is short, and the epiphyses are broad. There is contracture of the fingers. *(From Traboulsi EI: Skeletal and connective tissue disorders with anterior segment manifestations. In Krachmer JH, Mannis MJ, Holland EJ, editors:* Cornea, *ed 3, Philadelphia, 2011, Elsevier, Fig. 60-9.)*

LATE-ONSET SPONDYLOEPIPHYSEAL DYSPLASIA

Late-onset SED is a mild to very mild clinical phenotype characterized by slightly short stature associated with mild epiphyseal and vertebral abnormalities on radiographs. It is typically detected during childhood or adolescence but can go unrecognized until adulthood when precocious osteoarthritis appears. This designation is nosologically distinct from SED tarda, which is clinically similar but results from mutation of the X-linked gene *SEDL.*

AGGRECAN-RELATED SPONDYLOEPIPHYSEAL DYSPLASIAS

Mutations of aggrecan have been detected in 2 SED-like conditions. SED-Kimberley (*MIM 608361*) is relatively mild, with short stature, stocky build, and early onset osteoarthritis of weightbearing joints. A more severe and generalized clinical phenotype with characteristic radiographic changes including widened metaphyses is observed in spondyloepimetaphyseal dysplasia–Aggrecan type (*MIM 612813*).

STICKLER SYNDROME/DYSPLASIA (HEREDITARY OSTEOARTHROOPHTHALMOPATHY)

Short stature is not a feature of Stickler dysplasia (MIM 184840). It resembles SED because of its joint and eye manifestations. Mutations of genes encoding type II (*COL2A1*), type XI (*COL11A1*, *COL11A2*), and type IX (*COL9A1*) collagens have been identified in Stickler-like disorders (MIM 184840, MIM 215150). Stickler dysplasia is often identified in the newborn because of cleft palate and micrognathia (Pierre Robin anomaly; see Chapter 311). Twenty-five percent of patients with Stickler syndrome have Pierre Robin anomaly; 30% of patients with Pierre Robin anomaly have Stickler syndrome. Infants typically have severe myopia and additional ophthalmologic complications, including choroidoretinal and vitreous degeneration; retinal detachment is common during childhood (Fig. 695-4). Sensorineural hearing loss can arise during adolescence, which is when symptoms of significant osteoarthritis can also begin. Special attention must be given to the eye complications even in childhood. Osteoarticular manifestations include joint hypermobility (especially hip), muscle hypotonia, metaphyseal–epiphyseal dysplasia; progressive osteoarthritis of spine and peripheral joints, which may require hip replacement surgery before age 30 yr and decreased bone density. Similar manifestations may be seen in other diseases with mutations in type II and XI collagen genes (Table 695-1).

Table 695-1	Other Genetic Diseases Associated with Mutations in Type II and Type XI Collagen Genes, with Clinical Presentations Similar to That of Stickler Syndrome
Phenotypes associated with COL2A1 *mutations*	
Achondrogenesis type 2	
Hypochondrogenesis	
Spondyloepiphyseal dysplasia congenita	
Spondyloepimetaphyseal dysplasia, Strudwick type	
Kniest dysplasia	
Dysplasia with altered vertebral contours	
Some of the juvenile joint diseases	
Phenotypes associated with COL11A1 *mutations*	
Marshall syndrome	
Phenotypes associated with COL11A2 *mutations*	
Otospondylometaphyseal dysplasia	
Weissenbach-Zweymuller syndrome	
Some cases of isolated sensorineural deafness	

From Couchouron T, Masson C: Early-onset progressive osteoarthritis with hereditary progressive ophthalmology or Stickler syndrome. Joint Bone Spine *78:45–49, 2011, Table 1, p. 48.*

Figure 695-4 Face and profile of the daughter with Stickler syndrome type I. Note the flat nasal bridge, the mild epicanthal folds and discrete micrognathia. Face and profile of the mother with Stickler syndrome type I. The mother shows at first sight no clear facial characteristics of Stickler syndrome. *(From Baijens LWJ, De Leenheer EMR, Weekamp HH, et al: Stickler syndrome type I and Stapes ankylosis.* Int J Pediatr Otorhinolaryngol *68:1573–1580, 2004, Fig. 2.)*

SCHMID METAPHYSEAL DYSPLASIA

Schmid metaphyseal dysplasia (MIM 156500) is one of several chondrodysplasias in which metaphyseal abnormalities dominate the radiographic features. It typically manifests in early childhood with mild short stature, bowing of the legs, and a waddling gait (Fig. 695-5). Joints, such as the wrist, may be enlarged. Radiographs show flaring and irregular mineralization of the metaphyses of tubular bones of the proximal limbs (Fig. 695-6). Coxa vara is usually present and can require surgical correction. Short stature becomes more evident with age and affects the lower extremities more than the upper extremities; the manifestations are limited to the skeleton.

Schmid metaphyseal chondrodysplasia is caused by heterozygous mutations of the gene encoding type X collagen; it is an autosomal dominant trait. The distribution of type X collagen is restricted to the region of growing bone in which cartilage is converted into bone. This might explain why radiographic changes are confined to the metaphyses.

PSEUDOACHONDROPLASIA AND MULTIPLE EPIPHYSEAL DYSPLASIA

Pseudoachondroplasia (MIM 177170) and multiple epiphyseal dysplasia (MED) (MIM 600969) are 2 distinct phenotypes that are grouped together because they result from mutations of the gene encoding COMP. The mutations are heterozygous in both; they are autosomal dominant traits. The clinical phenotypes are restricted to skeletal tissues.

Newborns with pseudoachondroplasia are average in size and appearance. Gait abnormalities and short stature mainly affect the limbs and become apparent in late infancy. The short stature becomes marked as the child grows and is associated with generalized joint laxity (Fig. 695-7). The hands are short, broad, and deviated in an ulnar direction; the forearms are bowed. Developmental milestones and intelligence are usually normal. Lumbar lordosis and deformities of the knee develop during childhood; the latter often requires surgical correction. Pain is common in weightbearing joints during childhood and adolescence, and osteoarthritis develops late in the 2nd decade of life. Adults range in height from 105-128 cm.

Skeletal radiographs show distinctive abnormalities of vertebral bodies and of both epiphyses and metaphyses of tubular bones (Fig. 695-8).

The MED phenotype has skeletal abnormalities that predominantly affect the epiphyses as noted on radiographs. Two classic forms are a severe Fairbank type and a mild Ribbing type. Because of overlap in clinical features and because COMP mutations are found in both types,

they may be considered clinical variants. This nomenclature is not generally used now.

The more severe clinical phenotype has its onset during childhood, with mild short-limbed short stature, pain in weightbearing joints, and a waddling gait. Radiographs show delayed and irregular ossification of epiphyses. In more mildly affected patients the disorder might not be recognized until adolescence or adulthood. Radiographic changes may be limited to the capital femoral epiphyses. In the latter case, mild MED must be distinguished from bilateral Legg-Calvé-Perthes disease (see Chapter 678.3). Precocious osteoarthritis of hips and knees is the major complication in adults with MED. Adult heights range from 136-151 cm.

There are families with clinical and radiographic manifestations of MED that are not caused by mutations of COMP. Some are linked to the gene encoding 1 of the type IX collagen chains. It has been suggested that COMP and type IX collagen interact functionally in cartilage matrix, thus explaining why mutations of different genes produce similar pictures. Mutations of the genes coding for another cartilage

Figure 695-5 **Female patient with metaphyseal dysplasia, type Schmid.** The facies are normal and stature is mildly reduced. Mild tibia vara is present.

Figure 695-6 Radiograph of lower extremities in Schmid metaphyseal dysplasia showing short tubular bones and metaphyseal flaring and irregularities, abnormal capital femoral epiphyses, and femoral necks. The epiphyses are normal. Coxa vara is present.

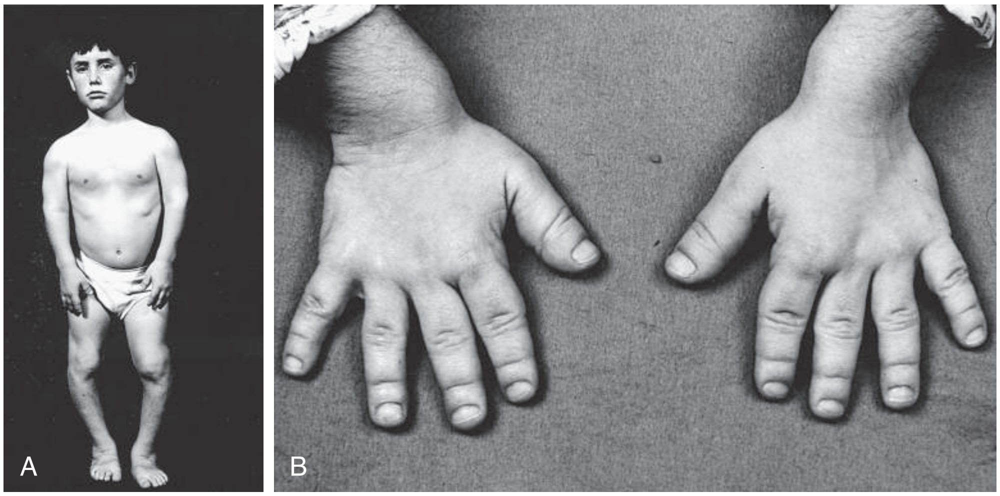

Figure 695-7 **A,** Pseudoachondroplasia in an adolescent boy. The facies and head circumference are normal. There is shortening of all extremities and bowing of the lower extremities. **B,** Photograph of hands, demonstrating short stubby fingers.

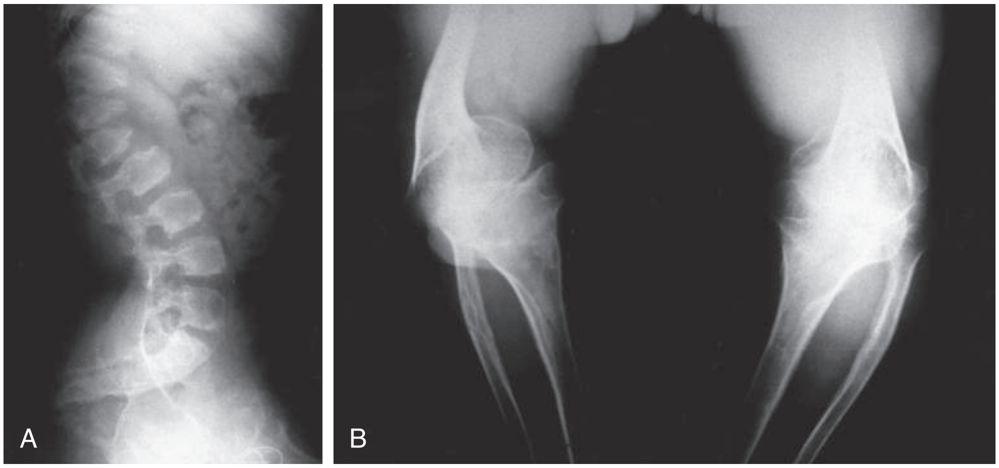

Figure 695-8 **A,** Lateral thoracolumbar spine radiograph of a patient with pseudoachondroplasia showing central protrusion (tonguing) of the anterior aspect of upper lumbar and lower thoracic vertebrae. Note reduced vertebral body heights (platyspondyly) and secondary lordosis. **B,** Lower-extremity radiograph of patient with pseudoachondroplasia showing large metaphyses, poorly formed epiphyses, and marked bowing of the long bones.

matrix protein, matrilin 3, and the diastrophic dysplasia sulfate transporter have also been found in patients with MED. For familial cases of pseudoachondroplasia and MED resulting from mutation in COMP, prenatal diagnosis is available.

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Chapter 696

Disorders Involving Transmembrane Receptors

William A. Horton and Jacqueline T. Hecht

Heterozygous mutations of genes encoding *FGFR3* (fibroblast growth factor receptor 3) and *PTHR* (parathyroid hormone receptor) result in disorders involving transmembrane receptors. The mutations cause the receptors to become activated in the absence of physiologic ligands, which accentuates normal receptor function of negatively regulating bone growth. The mutations act by gain of negative function. In the *FGFR3* mutation group, in which the clinical phenotypes range from severe to mild, the severity appears to correlate with the extent to which the receptor is activated. *PTHR* and especially *FGFR3* mutations tend to recur in unrelated individuals.

ACHONDROPLASIA GROUP

The achondroplasia group represents a substantial percentage of patients with chondrodysplasias and contains thanatophoric dysplasia (TD), the most common lethal chondrodysplasia, with a birth prevalence of 1 in 35,000 births; achondroplasia, the most common nonlethal chondrodysplasia, with a birth prevalence of 1 in 15,000 to 1 in 40,000 births; and hypochondroplasia. All 3 have mutations in a small number of locations in the *FGFR3* gene. There is a strong correlation between the mutation site and the clinical phenotype.

Thanatophoric Dysplasia

TD (MIM 187600, 187610) manifests before or at birth. In the former situation, ultrasonographic examination in midgestation or later reveals a large head and very short limbs; the pregnancy is often accompanied by polyhydramnios and premature delivery. Very short limbs, short neck, long narrow thorax, and large head with midfacial hypoplasia dominate the clinical phenotype at birth (Fig. 696-1). The cloverleaf skull deformity known as **kleeblattschädel** is sometimes found. Newborns have severe respiratory distress because of their small thorax. Although this distress can be treated by intense respiratory care, the long-term prognosis is poor.

Skeletal radiographs distinguish 2 slightly different forms called TD I and TD II. In the more common TD I, radiographs show large calvariae with a small cranial base, marked thinning and flattening of vertebral bodies visualized best on lateral view, very short ribs, severe hypoplasia of pelvic bones, and very short and bowed tubular bones

Figure 696-1 Identical twins with type I thanatophoric dysplasia. Disproportionately large head, bell-shaped chest, and micromelia. *(From Gilbert-Barness E, Kapur RP, Oligny LL, Siebert JR, editors:* Potter's pathology of the fetus, infant and child, *ed 2, Philadelphia, 2007, Elsevier,* Fig. 20-47.*)*

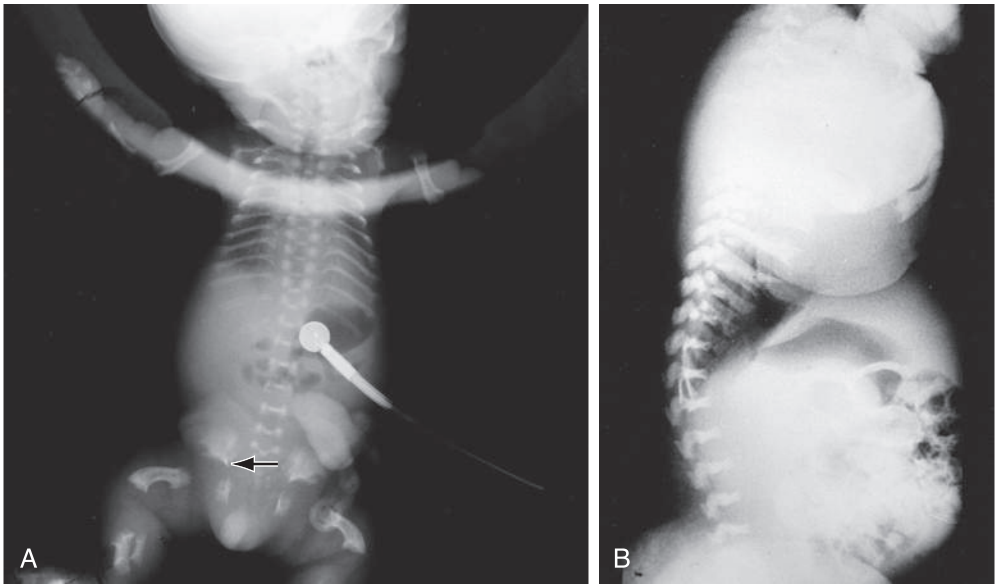

Figure 696-2 **A**, Neonatal radiograph of a child with thanatophoric dysplasia. Note medial acetabular spurs *(arrow)*, hypoplastic iliac bones, bowed femora with rounded protrusion of proximal femurs, hypoplastic thorax, and wafer-thin vertebral bodies. **B**, Lateral radiograph of the thoracolumbar spine in thanatophoric dysplasia, showing marked vertebral flattening and short ribs. Ossification defect of the central portion of the vertebral bodies is present.

with flared metaphyses (Fig. 696-2). The femurs are curved and shaped like a telephone receiver. TD II differs mainly in that there are longer and straighter femurs.

The TD II clinical phenotype is associated with mutations that map to codon 650 of *FGFR3*, causing the substitution of a glutamic acid for the lysine. This activates the tyrosine kinase activity of a receptor that transmits signals to intracellular pathways. Mutation of lysine 650 to methionine is associated with a clinical phenotype intermediate between TD and achondroplasia, referred to as **severe achondroplasia with developmental delay and acanthosis nigricans**. Mutations of the TD I phenotype mainly map to 2 regions in the extracellular domain of the receptor, where they substitute cysteine residues for other amino acids. Free cysteine residues are thought to form disulfide bonds promoting dimerization of receptor molecules, leading to activation and signal transmission.

TD I and TD II represent new mutations to normal parents. The recurrence risk is low. Because the mutated codons in TD are mutable for unknown reasons and because of the theoretical risk of germ cell mosaicism, parents are offered prenatal diagnosis for subsequent pregnancies.

Achondroplasia

Achondroplasia (MIM 100800) is the prototype chondrodysplasia. It typically manifests at birth with short limbs, a long narrow trunk, and a large head with midfacial hypoplasia and prominent forehead (Fig. 696-3). The limb shortening is greatest in the proximal segments, and the fingers often display a trident configuration. Most joints are hyperextensible, but extension is restricted at the elbow. A thoracolumbar gibbus is often found. Usually, birth length is slightly less than normal but occasionally plots within the low-normal range.

Diagnosis

Skeletal radiographs confirm the diagnosis (see Figs. 696-3 and 696-4). The calvarial bones are large, whereas the cranial base and facial bones are small. The vertebral pedicles are short throughout the spine as noted on a lateral radiograph. The interpedicular distance, which normally increases from the 1st to the 5th lumbar vertebra, decreases in achondroplasia. The iliac bones are short and round, and the acetabular roofs are flat. The tubular bones are short with mildly irregular and flared metaphyses. The fibula is disproportionately long compared with the tibia.

Clinical Manifestations

Infants usually exhibit delayed motor milestones, often not walking alone until 18-24 mo. This is because of hypotonia and mechanical difficulty balancing the large head on a normal-sized trunk and short extremities. Intelligence is normal unless central nervous system complications develop. As the child begins to walk, the gibbus usually gives way to an exaggerated lumbar lordosis.

Infants and children with achondroplasia progressively fall below normal standards for length and height. They can be plotted against standards established for achondroplasia. Adult heights typically are 118-145 cm for men and 112-136 cm for women. Surgical limb lengthening and human growth hormone treatment have been used to increase height; both are controversial. C-type natriuretic peptide may stimulate bone growth in achondroplasia based on studies in animal models. Clinical studies are in the initial phases of testing.

Virtually all infants and children with achondroplasia have large heads, although only a fraction have true hydrocephalus. Head circumference should be carefully monitored using standards developed for achondroplasia, as should neurologic function in general. The spinal canal is stenotic, and spinal cord compression can occur at the foramen magnum and in the lumbar spine. The former usually occurs in infants and small children; it may be associated with hypotonia, failure to thrive, quadriparesis, central and obstructive apnea, and sudden death. Surgical correction may be required for severe stenosis. Lumbar spinal stenosis usually does not occur until early adulthood. Symptoms include paresthesias, numbness, and claudication in the legs. Loss of bladder and bowel control may be late complications.

Bowing of the legs is common and might need to be corrected surgically. Other common problems include dental crowding, articulation difficulties, obesity, and frequent episodes of otitis media, which can contribute to hearing loss.

Genetics

All patients with typical achondroplasia have mutations at *FGFR3* codon 380. The mutation maps to the transmembrane domain of the receptor and is thought to stabilize receptor dimers that enhance receptor signals, the consequences of which inhibit linear bone growth. Achondroplasia behaves as an autosomal dominant trait; most cases arise from a new mutation to normal parents.

Because of the high frequency of achondroplasia among dwarfing conditions, it is relatively common for adults with achondroplasia to

Figure 696-3 Achondroplasia phenotype at different ages. **A,** Infant with achondroplasia with macrocephaly, frontal bossing, midface hypoplasia, small chest, rhizomelic shortening of all the limbs, redundant skin folds, and extreme joint laxity. Note the trident hand with short fingers and abducted hips. **B,** Typical radiographic findings from a child with achondroplasia. All of the tubular bones are short, but the fibula is relatively long compared to the tibia. There is protrusion of the epiphysis into the metaphysis of the distal femur, creating the chevron deformity, and to a lesser extent of the proximal tibia. The iliac bones are rounded, the acetabular roof is horizontal, and the sacrosciatic notches are small. **C,** A 3 yr old with achondroplasia with the typical features shown in **A.** Note that the redundant skin folds are no longer present and that joint laxity has improved. Rhizomelic shortening of the extremities is more pronounced and accompanied by tibial bowing. *(From Horton WA, Hall JG, Hecht JT: Achondroplasia,* Lancet *370:162–172, 2007.)*

Figure 696-4 Radiograph of infant with achondroplasia, demonstrating interpedicular narrowing of the 1st through 5th lumbar vertebrae, short round iliac bones, and flat acetabular roofs. The tubular bones are short and show mild irregularities of the metaphyses.

marry. Such couples have a 50% risk of transmitting their condition, heterozygous achondroplasia, to each offspring, as well as a 25% risk of **homozygous achondroplasia**. The latter condition exhibits intermediate severity between TD and heterozygous achondroplasia and is usually lethal in the newborn period. Prenatal diagnosis is available and has been used to diagnose homozygous achondroplasia. Preimplantation genetic testing can be used to identify double dominant mutations.

Hypochondroplasia

Hypochondroplasia (MIM 146000) resembles achondroplasia but is milder. Usually, it is not apparent until childhood, when mild short stature affecting the limbs becomes evident. Children have a stocky build and slight frontal bossing of the head. Learning disabilities may be more common in this condition. Radiographic changes are mild and consistent with the mild achondroplastic phenotype. Complications are rare; in some patients the condition is never diagnosed. Adult heights range from 116-146 cm. An *FGFR3* mutation at codon 540 has been found in many patients with hypochondroplasia. Genetic heterogeneity exists in hypochondroplasia; that is, *SHOX* mutations are associated with a very similar clinical phenotype. Recombinant growth hormone therapy may enhance growth and improve body disproportion.

JANSEN METAPHYSEAL DYSPLASIA

Jansen metaphyseal chondrodysplasia (MIM 156400) is a rare, dominantly inherited chondrodysplasia characterized by severe shortening of limbs associated with an unusual facial appearance. Sometimes it is accompanied by clubfoot and hypercalcemia. At birth, a diagnosis can be made from these clinical findings and radiographs that show short tubular bones with characteristic metaphyseal abnormalities that include flaring, irregular mineralization, fragmentation, and widening of the physeal space. The epiphyses are normal.

The joints become enlarged and limited in mobility with age. Flexion contractures develop at the knees and hips, producing a bent-over posture. Intelligence is normal, although there may be hearing loss.

Jansen metaphyseal chondrodysplasia is caused by activating mutations of *PTHR1*. This G-protein–coupled transmembrane receptor serves as a receptor for both parathyroid hormone and parathyroid hormone-related peptide. Signaling through this receptor serves as a brake on the terminal differentiation of cartilage cells at a critical step in bone growth. Because the mutations activate the receptor, they enhance the braking effect and thereby slow bone growth. Loss-of-function mutations of *PTHR1* are observed in Blomstrand chondrodysplasia, whose clinical features are the mirror image of Jansen metaphyseal chondrodysplasia.

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Chapter 697

Disorders Involving Ion Transporters

William A. Horton and Jacqueline T. Hecht

The disorders involving ion transporters result from the functional loss of the sulfate ion transporter called *diastrophic dysplasia sulfate transporter* (DTDST), which is also referred to as *SLC26A2* (solute carrier family 26, member 2). This protein transports sulfate ions into cells and is important for cartilage cells that add sulfate moieties to newly synthesized proteoglycans destined for cartilage extracellular matrix. Matrix proteoglycans are responsible for many of the properties of cartilage that allow it to serve as a template for skeletal development. The clinical manifestations result from defective sulfation of cartilage proteoglycans. In order of decreasing severity, the disorders include: achondrogenesis type 1B, atelosteogenesis type II, diastrophic dysplasia, and a rare recessive form of multiple epiphyseal dysplasia (MIM 226900).

A number of mutant alleles have been found for the *DTDST* gene; they variably disturb transporter function. The disorders are recessive traits requiring the presence of 2 mutant alleles. The phenotype is determined by the combination of mutant alleles; some alleles are present in more than one disorder.

DIASTROPHIC DYSPLASIA

Diastrophic dysplasia (MIM 22600) is a well-characterized disorder recognized at birth by the presence of very short extremities, clubfoot, and short hands, with proximal displacement of the thumb producing a hitchhiker appearance (Fig. 697-1). The hands are usually deviated in an ulnar direction. Bony fusion of the metacarpophalangeal joints (symphalangism) is common, as is restricted movement of many joints, including hips, knees, and elbows. The external ears often become inflamed soon after birth. The inflammation resolves spontaneously but leaves the ears fibrotic and contracted (cauliflower ear deformity). Many newborns have a cleft palate.

Radiographs reveal short and broad tubular bones with flared metaphyses and flat, irregular epiphyses (Fig. 697-2). The capital femoral epiphyses are hypoplastic, and the femoral heads are broad. The ulnas and fibulas are disproportionately short. Carpal centers may be developmentally advanced; the 1st metacarpal is typically ovoid, and the metatarsals are twisted medially. There may be vertebral abnormalities, including clefts of cervical vertebral lamina and narrowing of the interpedicular distances in the lumbar spine.

Complications are primarily orthopedic and tend to be severe and progressive. The clubfoot deformity in the newborn resists usual treatments, and multiple corrective surgeries are common. Scoliosis typically develops during early childhood. It often requires multiple surgical procedures to control, and it sometimes compromises respiratory function in older children. Despite the orthopedic problems, patients typically have a normal life span and reach adult heights in the 105-130 cm range, depending on the severity of scoliosis. Growth curves are available for diastrophic dysplasia.

Some patients are mildly affected and exhibit slight short stature and joint contractures, no clubfoot or cleft palate, and correspondingly mild radiographic changes. The mild phenotype tends to recur within families. The recurrence risk of this autosomal recessive condition is 25%. Ultrasonographic examination can be employed for prenatal diagnosis, but if *DTDST* mutations can be identified in the patients or parents, molecular genetic diagnosis is possible.

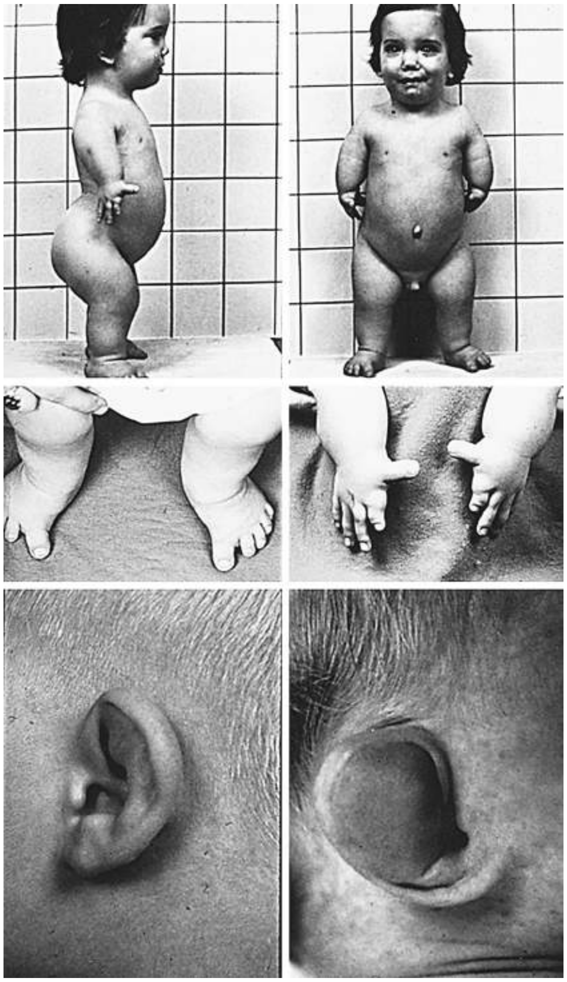

Figure 697-1 **Child with diastrophic dysplasia.** The extremities are dramatically shortened *(top).* Clubfoot is commonly observed *(middle left).* The fingers are short, especially the index finger; the thumb characteristically is proximally placed and has a hitchhiker appearance *(middle right).* The upper helix of the ears becomes swollen 3-4 wk postnatally *(lower left),* and this inflammation spontaneously resolves, leaving a cauliflower deformity of the pinnae *(lower right).*

Figure 697-2 **Radiograph of hands in diastrophic dysplasia.** The metacarpals and phalanges are irregular and short. The 1st metacarpal is ovoid.

ACHONDROGENESIS TYPE 1B AND ATELOSTEOGENESIS TYPE II

Achondrogenesis type 1B (MIM 600972) and atelosteogenesis type II (MIM 256050) are rare recessive lethal chondrodysplasias. The most serious is achondrogenesis type 1B, which demonstrates a severe lack

of skeletal development usually detected in utero or after a miscarriage. The limbs are extremely short, and the head is soft. Skeletal radiographs show poor to missing ossification of skull bones, vertebral bodies, fibulas, and ankle bones. The pelvis is hypoplastic, and the ribs are short. The femurs are short and exhibit a trapezoid shape with irregular metaphyses.

Infants with atelosteogenesis type II are stillborn or die soon after birth; prematurity is common. They exhibit very short limbs, especially the proximal segments. Clubfoot and dislocations of the elbows and knees may be detected. Hypoplasia of vertebral bodies, especially in the cervical and lumbar spine, is found on radiographs. The femora and humeri are hypoplastic and display a club-shaped appearance. The distal limb bones, including the ulna and fibula, are poorly ossified.

Both disorders carry a 25% recurrence risk and are potentially detectable in utero by mutation analysis if the mutant alleles are identified in the parents. Prenatal diagnosis is possible with fetal imaging and/or mutational testing, which is commercially available.

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Figure 698-1 A fetus of 21 weeks' gestation with campomelic dysplasia. Radiographic findings include a large skull with a small face; hypoplastic/absent scapular bodies; 11 ribs; poorly ossified thoracic pedicles; tall, narrow iliac wings; and short extremities with proportionately long, bowed femurs. *(From Dwek J, Lachman R: Skeletal dysplasias and selected chromosomal disorders. In Coley BD, editor:* Caffey's pediatric diagnostic imaging*, ed 12, Philadelphia, 2013, WB Saunders, Fig. 133-34.)*

Chapter 698

Disorders Involving Transcription Factors

William A. Horton and Jacqueline T. Hecht

There are 3 well-delineated disorders involving transcription factors that result in bone dysplasias. **Campomelic dysplasia** is historically considered a chondrodysplasia while **cleidocranial dysplasia** and **nail-patella syndrome**, have been regarded as dysostoses, or abnormalities of single bones. The mutant genes that encode these transcription factors, *SOX9, RUNX2 (CBFA1*), and *LMX1B*, respectively, are members of much larger gene families. *SOX9* is a member of the *SOX* family of genes related to the *SRY* (sex-determining region of the Y chromosome) gene; *RUNX2 (CBFA1*) belongs to the runt family of transcription factor genes, and *LMX1B* is one of the LIM homeodomain gene family. All 3 disorders are a result of haploinsufficiency of the respective gene products; the disorders are dominant traits. For familial cases of cleidocranial dysplasia and nail-patella syndrome, prenatal diagnosis is possible if the mutations are identified. Campomelic dysplasia results from new mutational events and has a low risk of recurrence in subsequent pregnancies.

CAMPOMELIC DYSPLASIA

Campomelic dysplasia (MIM 114290) is apparent at birth owing to bowing of long bones (especially in the lower legs), short bones, respiratory distress, and other anomalies that include defects of the cervical spine, central nervous system, heart, and kidneys. In some cases, femoral bowing is minimal (acampomelic campomelic dysplasia). Cases of sex reversal of XY males have been reported; 75% of those with a male karyotype have partial or complete sex reversal. Radiographs confirm the bowing and often show hypoplasia of the scapulae and pelvic bones (Fig. 698-1). Affected infants usually die of respiratory distress in the neonatal period. Complications in children and adolescents who survive include short stature with progressive kyphoscoliosis, hip dislocation, recurrent apnea and respiratory infections, and mild to moderate learning difficulties. Mutational testing is commercially available.

CLEIDOCRANIAL DYSPLASIA

Cleidocranial dysplasia (MIM 114290) is recognized in infants because of drooping shoulders, open fontanelles, prominent forehead, mild short stature, and dental abnormalities (Fig. 698-2). Radiographs reveal hypoplastic or absent clavicles, delayed ossification of the cranial bones with multiple ossification centers (wormian bones), and delayed ossification of pelvic bones. The course is usually uncomplicated except for dislocations, especially of the shoulders, and dental anomalies (numerous teeth) that require therapy.

NAIL-PATELLA SYNDROME

Dysplasia of the nails, absence or hypoplasia of the patella, abnormalities of the elbow, and spurs or "horns" extending from the iliac bones characterize the nail-patella syndrome (MIM 119600), which is also called *osteo-onychodysostosis.* Some patients have nephritis that resembles chronic glomerulonephritis. There is a wide spectrum of severity; some patients present in early childhood, whereas others are asymptomatic as adults.

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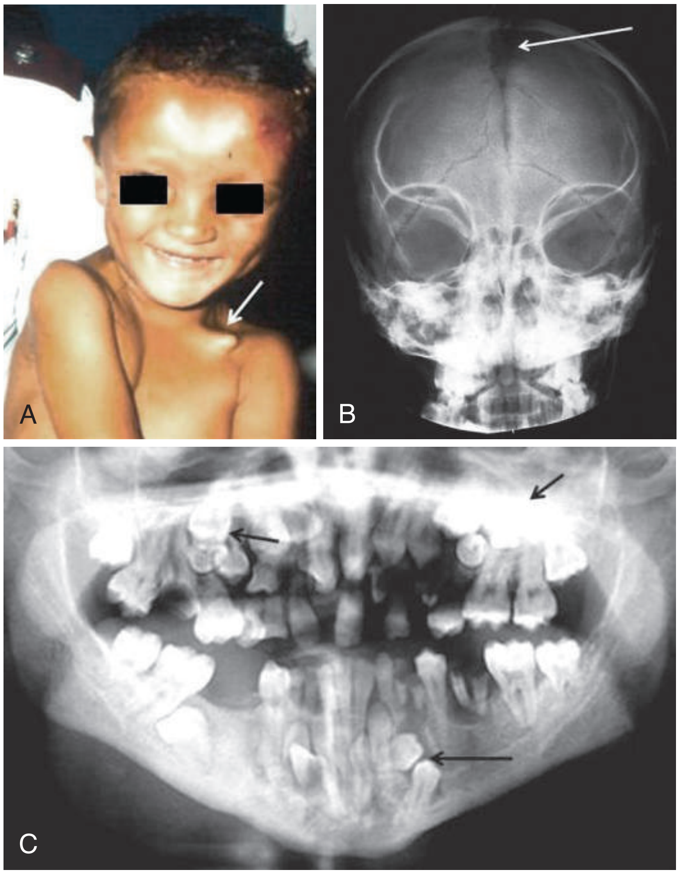

Figure 698-2 Features of cleidocranial dysplasia displayed. **A,** The forehead is bulky with a central depression, the eyes are widely spaced and the jaw is pointed. The clavicle is misshapen *(arrow)*. **B,** Note patency of the anterior fontanelle. **C,** Hyperdontia pantomogram of an affected male showing supernumerary teeth. *(From Roberts T, Stephen L, Beighton P. Cleidocranial dysplasia: a review of the dental, historical, and practical implications with an overview of the South African experience.* Oral Surg Oral Med Oral Pathol Oral Radiol *115(1):46–55, 2013, Figs. 1, 4, and 6.)*

Chapter 699

Disorders Involving Defective Bone Resorption

William A. Horton and Jacqueline T. Hecht

Osteopetrosis, which has many subtypes, and pyknodysostosis result from defective bone resorption. Overall, bone dysplasias displaying increased bone density are rare.

OSTEOPETROSIS

Two main forms of osteopetrosis have been delineated: a severe autosomal recessive form (MIM 259700) with an incidence of approximately 1 in 250,000 births and a mild autosomal dominant form (MIM 166600) with an incidence of approximately 1 in 20,000 births. Intrinsic disturbances of osteoclast function due to mutations in genes encoding osteoclast-specific subunits of the vacuolar proton pump (*TCIRG1*, *CLCN7*) are found in most patients with the recessive form. Mutations of *CLCN7* are observed in the dominant form of osteopetrosis. Both types of mutations lead to disturbances of acidification needed for normal osteoclast function. Rarely, patients lack bioactive RANKL (receptor activator of nuclear factor kappa B ligand), the master osteoclastogenic cytokine produced mainly by osteoblasts.

Figure 699-1 Lateral radiograph showing bone-in-bone appearance that is characteristic of osteopetrosis.

The severe form is usually detected in infancy or earlier because of macrocephaly, hepatosplenomegaly, deafness, blindness, and severe anemia. Radiographs reveal diffuse bone sclerosis and low serum calcium and phosphorus levels with elevated parathyroid hormone levels and normal vitamin D levels. may be detected. Later films show the characteristic bone-within-bone appearance (Fig. 699-1). With time, infants typically fail to thrive and show psychomotor delay and worsening of cranial neuropathies and anemia. Dental problems, osteomyelitis of the mandible, and pathologic fractures are common. Untreated, the most severely affected patients die during infancy; less severely affected patients rarely survive beyond the 2nd decade. Those who survive beyond infancy usually have learning disorders but might have normal intelligence despite hearing and vision loss.

Clinical Manifestations

Most of the manifestations are from failure to remodel growing bones. This leads to narrowing of cranial nerve foramina and encroachment on marrow spaces, which results in secondary complications, such as optic and facial nerve dysfunction, and anemia accompanied by compensatory extramedullary hematopoiesis in the liver and spleen. The unusually dense bones are weak, leading to increased risk of fractures.

The autosomal dominant form of osteopetrosis (Albers-Schönberg disease, osteopetrosis tarda, or marble bone disease) usually manifests during childhood or adolescence with fractures and mild anemia and, less often, as cranial nerve dysfunction, dental abnormalities, or osteomyelitis of the mandible. Skeletal radiographs reveal a generalized

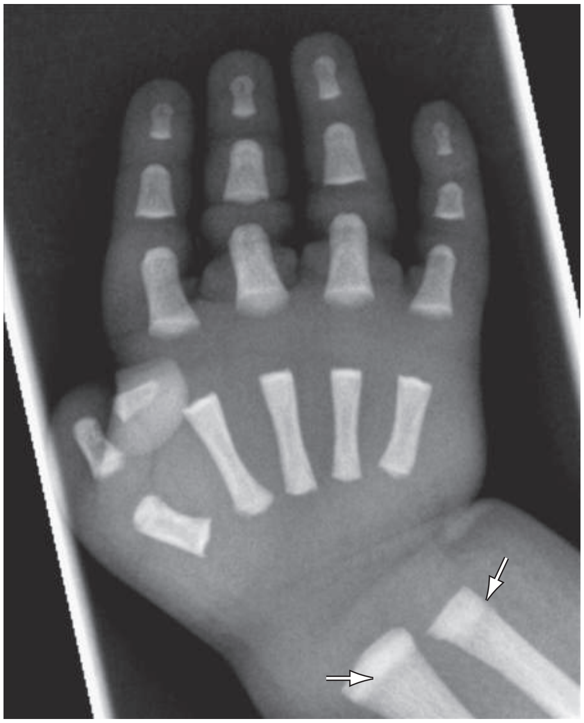

Figure 699-2 Right-hand radiograph of infant age 2 wk. Note metaphyseal lucent bands in the distal ulna and radius *(arrows)* and short tubular bones. *(From Stark Z, Savarirayan R: Osteopetrosis,* Orphanet J Rare Dis *4:5, 2009.)*

increase in bone density and clubbing of metaphyses. Alternating bands of lucent and dense bands produce a sandwich appearance to vertebral bodies. The radiographic changes are sometimes incidental findings in otherwise asymptomatic adolescents and adults.

Treatment

Most of the bone manifestations in severe osteopetrosis caused by intrinsic osteoclast defects can be prevented or reversed by hematopoietic stem cell transplantation, if carried out before development of irreversible secondary complications, such as visual impairment. RANKL replacement therapy may be useful in patients with RANKL deficiency. Calcitriol and interferon-γ have also been used with equivocal results. Symptomatic care, such as dental care, transfusions for anemia, and antibiotic treatment of infections, is important for patients who survive infancy.

PYKNODYSOSTOSIS

An autosomal recessive bone dysplasia, pyknodysostosis (MIM 265800) manifests in early childhood with short limbs, characteristic facies, an open anterior fontanel, a large skull with frontal and occipital bossing, and dental abnormalities. The hands and feet are short and broad, and the nails may be dysplastic. The sclerae may be blue. Minimal trauma often leads to fractures. Treatment is symptomatic and focused mainly on the management of dental problems and fractures. The prognosis is generally good, and patients typically reach heights of 130-150 cm.

Skeletal radiographs show a generalized increase in bone density. In contrast to many disorders in this group, the metaphyses are normal. Other changes include wide sutures and wormian bones in the skull, a small mandible, and hypoplasia of the distal phalanges (Fig. 699-2).

Several mutations have been found in the gene encoding cathepsin K, a cysteine protease that is highly expressed in osteoclasts. The mutations predict loss of enzyme function, suggesting that there is an inability of osteoclasts to degrade bone matrix and remodel bones.

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Chapter 700

Disorders for Which Defects Are Poorly Understood or Unknown

William A. Horton and Jacqueline T. Hecht

Despite great advances in our understanding of the genetic basis of disease in recent years, many chondrodysplasias, or chondrodysplasia clinical phenotypes, remain for which the genetic cause or basic mechanism is poorly understood or not known. Many illustrate features not found in other disorders and have historical significance in the evolution of chondrodysplasia nomenclature and classification.

ELLIS–VAN CREVELD SYNDROME

The Ellis-van Creveld syndrome (MIM 225500), also known as **chondroectodermal dysplasia**, is a skeletal and an ectodermal dysplasia. The skeletal dysplasia presents at birth with short limbs, especially the middle and distal segments, accompanied by postaxial polydactyly of the hands and sometimes of the feet (Fig. 700-1). Nail dysplasia and dental anomalies (including neonatal, absent, and premature loss of teeth and upper lip defects) constitute the ectodermal dysplasia. Common manifestations also include atrial septal defects and other congenital heart defects.

Skeletal radiographs reveal short tubular bones with clubbed ends, especially the proximal tibia and ulna (Fig. 700-2). Carpal bones display extra ossification centers and fusion; cone-shaped epiphyses are evident in the hands. A bony spur is often noted above the medial aspect of the acetabulum.

Ellis-van Creveld syndrome is an autosomal recessive trait that occurs most often in the Amish. Mutations have been identified in 1 of 2 genes, *EVC (EVC1*) or *EVC2*, which map in a head-to-head configuration to chromosome 4p. Mutations of *EVC2* are detected in the allelic condition Weyers acrofacial dysostosis. EVC and EVC2 proteins are thought to influence hedgehog signaling in cilia.

Approximately 30% of patients die of cardiac or respiratory problems during infancy. Life span is otherwise normal; adult heights range from 119-161 cm.

ASPHYXIATING THORACIC DYSTROPHY (see also Chapter 417.3)

Asphyxiating thoracic dystrophy (MIM 208500), or **Jeune syndrome**, is an autosomal recessive chondrodysplasia that resembles Ellis-van Creveld syndrome. Newborn infants present with a long, narrow thorax and respiratory insufficiency associated with pulmonary hypoplasia. Neonates often die. Other neonatal manifestations include slightly short limbs and postaxial polydactyly. This condition results from a disturbance of primary cilia, most often from mutations of the gene encoding cytoplasmic dynein 2 heavy chain 1 (*DYNC2H1*).

Skeletal radiographs show very short ribs with anterior expansion. Tubular limb bones are short with bulbous ends; cone-shaped epiphyses occur in hand bones. The iliac bones are short and square with a spur above the medial aspect of the acetabulum.

If infants survive the neonatal period, respiratory function usually improves as the rib cage grows. Surgery that produces lateral thoracic expansion improves rib growth and enhances chest wall dimensions. Progressive renal dysfunction often develops during childhood. Intestinal malabsorption and hepatic dysfunction have also been reported.

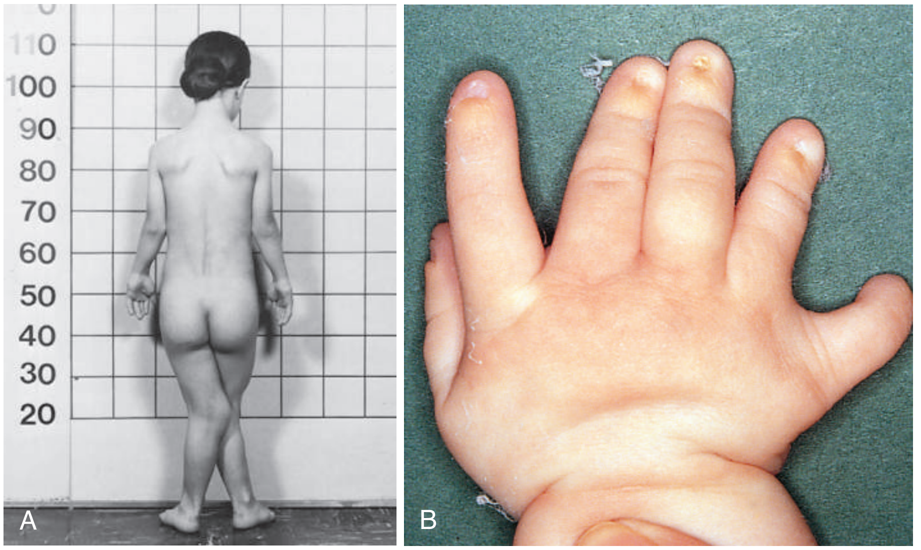

Figure 700-1 **A,** Ellis-van Creveld syndrome in a young woman. Note short stature, joint contractures at the elbows, and marked genu valgum. **B,** Multiple digits (polydactyly) in a different patient with Ellis-van Creveld syndrome. (*A from Zipes DP, Libby P, Bonow R, Braunwald E, editors:* Braunwald's heart disease: a textbook of cardiovascular medicine, *ed 7, Philadelphia, 2004, WB Saunders, Fig 70-6;* ***B*** *from Beerman LB, Kreutzer J, Allada V: Cardiology. In Zitelli BJ, McIntire SC, Nowalk AJ, editors:* Zitelli and Davis' atlas of pediatric physical diagnosis, *ed 6, Philadelphia, 2012, Elsevier, Fig 5-6.)*

Figure 700-2 Radiograph of lower extremities in Ellis-van Creveld syndrome. Tubular bones are short, and proximal fibula is short. Ossification is retarded in lateral tibia epiphyses, causing a knock-knee deformity.

Figure 700-3 Radiograph of lower extremities in cartilage-hair hypoplasia. The tubular bones are short and the metaphyses are flared and irregular. The fibula is disproportionately long compared with the tibia. The femoral necks are short.

SHORT-RIB POLYDACTYLY SYNDROMES

These conditions, which share the clinical features of constricted thoracic cage, short ribs, polydactyly, very short extremities, lethality during the newborn period and autosomal recessive inheritance, were originally grouped into 4 syndromes (SRP-I-IV). However, this classification is in flux as mutations that map to cilia-related genes *IFT80* and *DYNCH2H1* similar to those observed in Jeune syndrome have been detected in infants with SRP II and III. Mutations of two other cilia-related genes *NEK1* and *WDR34* have also been found in this group of disorders.

CARTILAGE-HAIR HYPOPLASIA

Cartilage-hair hypoplasia (CHH; MIM 250250) is also known as **metaphyseal chondrodysplasia–McKusick type**. It is recognized during the 2nd yr because of growth deficiency affecting the limbs, accompanied by flaring of the lower rib cage, a prominent sternum, and bowing of the legs. The hands and feet are short, and the fingers are very short with extreme ligamentous laxity. The hair is thin, sparse, and light colored, and nails are hypoplastic. The skin is hypopigmented.

Radiographs show short tubular bones with flared, irregularly mineralized, and cupped metaphyses (Fig. 700-3). The knees are more affected than are the hips, and the fibula is disproportionately longer

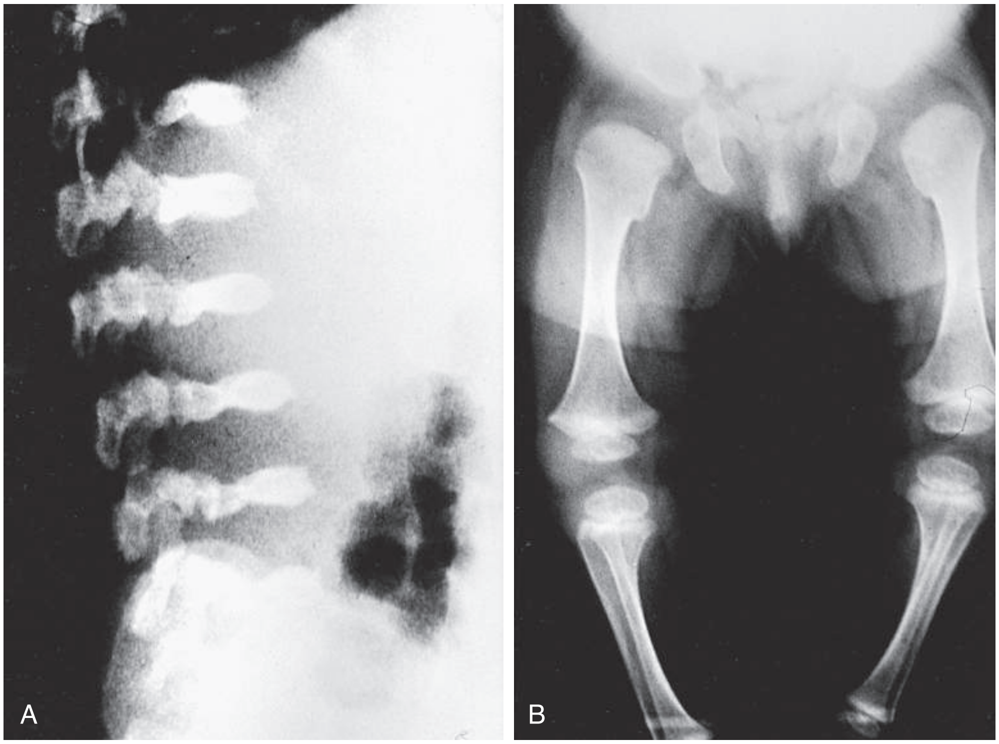

Figure 700-4 **A,** Radiograph of the lateral thoracolumbar spine in metatropic dysplasia showing severe platyspondyly. **B**, Radiograph of lower extremities in metatropic dysplasia showing short tubular bones with widened metaphyses. The femurs have a dumbbell appearance.

than the tibia. The metacarpals and phalanges are short and broad. Spinal radiographs reveal mild platyspondyly.

Nonskeletal manifestations associated with CHH include immunodeficiency (T-cell abnormalities, neutropenia, leukopenia, and susceptibility to chickenpox; children also may have complications from smallpox and polio vaccinations), malabsorption, celiac disease, and Hirschsprung disease. Adults are at risk for malignancy, especially non-Hodgkin lymphoma and skin tumors. Adults reach heights of 107-157 cm.

CHH shows autosomal recessive inheritance. Its highest prevalence is in the Amish and Finnish populations. It results from mutations of a gene coding for a large untranslated RNA component of an enzyme complex involved in processing mitochondrial RNA. Loss of this gene product interferes with processing of both messenger RNA and ribosomal RNA. Loss of ribosomal RNA processing correlates with the extent of bone dysplasia, whereas loss of messenger RNA processing correlates with degree of hair hypoplasia, immunodeficiency, and hematologic abnormality. Mutations of the RNA component of mitochondrial RNA processing are occasionally detected in patients with mild metaphyseal dysplasia lacking the extraskeletal features characteristic of CHH. Prenatal diagnosis is available if the mutation is identified either in the patient or parents.

METATROPIC DYSPLASIA

Metatropic dysplasia (MIM 156530) is an autosomal dominant disorder resulting from heterozygous mutations of *TRPV4* (transient receptor potential vanilloid family 4), which encodes a calcium-permeable cation channel. Newborn infants present with a long narrow trunk and short extremities. A tail-like appendage sometimes extends from the base of the spine. Odontoid hypoplasia is common and may be associated with cervical instability. Kyphoscoliosis appears in late infancy and progresses through childhood, often becoming severe enough to compromise cardiopulmonary function. The joints are large and become progressively restricted in mobility, except in the hands. Contractures often develop in the hips and knees during childhood. Although severely affected infants can die at a young age from respiratory failure, patients usually survive, although they can become disabled as adults from the progressive musculoskeletal deformities. Adult heights range from 110-120 cm.

Skeletal radiographs show characteristic changes dominated by severe platyspondyly and short tubular bones with expanded and deformed metaphyses that exhibit a dumbbell appearance (Fig. 700-4). The pelvic bones are hypoplastic and exhibit a halberd appearance because of a small sacrosciatic notch and a notch above the lateral margin of the acetabulum.

SPONDYLOMETAPHYSEAL DYSPLASIA, KOZLOWSKI TYPE

The Kozlowski type of spondylometaphyseal dysplasia (MIM 184252) is an autosomal dominant allelic disorder to metatropic dysplasia caused by *TRPV4* mutations. Mutations of *TRPV4* have also been identified in autosomal dominant brachyolmia, whose phenotype is dominated by progressive scoliosis and platyspondyly on x-rays.

The Kozlowski type of spondylometaphyseal dysplasia manifests in early childhood with mild short stature involving mostly the trunk and a waddling gait. The hands and feet may be short and stubby. Radiographs show flattening of vertebral bodies. The metaphyses of tubular bones are widened and irregularly mineralized, especially at the proximal femur. The pelvic bones manifest mild hypoplasia.

Scoliosis can develop during adolescence. The disorder is otherwise uncomplicated, and manifestations are limited to the skeleton. Adults reach heights of 130-150 cm.

DISORDERS INVOLVING FILAMINS

Mutations of genes encoding filamin A and filamin B proteins have been detected in diverse disorders of skeletal development: filamin A mutations in otopalatodigital syndromes type 1 and 2 frontometaphyseal dysplasia and Melnick-Needles syndrome (MIM 311300, 304120, 305620, 309350) and filamin B mutations in Larsen syndrome and perinatal lethal atelosteogenesis types I and III and Boomerang dysplasia (MIM 150250, 108720, 108721, 112310). Filamins functionally connect extracellular to intracellular structural proteins, thereby linking cells to their local microenvironment, which is essential for skeletal development and growth.

Table 700-1 Juvenile Osteochondroses

EPONYM	AFFECTED REGION	AGE AT PRESENTATION
Legg-Calvé-Perthes disease	Capital femoral epiphysis	3-12 yr
Osgood-Schlatter disease	Tibial tubercle	10-16 yr
Sever disease	Os calcaneus	6-10 yr
Freiberg disease	Head of second metatarsal	10-14 yr
Scheuermann disease	Vertebral bodies	Adolescence
Blount disease	Medial aspect of proximal tibial epiphysis	Infancy or adolescence
Osteochondritis dissecans	Subchondral regions of knee, hip, elbow, and ankle	Adolescence

JUVENILE OSTEOCHONDROSES

The juvenile osteochondroses are a heterogeneous group of disorders in which regional disturbances in bone growth cause noninflammatory arthropathies. Table 700-1 summarizes the juvenile osteochondroses. Some have localized pain and tenderness (Freiberg disease, Osgood-Schlatter disease [see Chapter 677.4], osteochondritis dissecans [see Chapter 677.3]), whereas others present with painless limitation of joint movement (Legg-Calvé-Perthes disease [see Chapter 678.3], Scheuermann disease [see Chapter 679.4]). Bone growth may be disrupted, leading to deformities. The diagnosis is usually confirmed radiographically, and treatment is symptomatic. The pathogenesis of these disorders is believed to involve ischemic necrosis of primary and secondary ossification centers. Although familial forms have been reported, these disorders usually occur sporadically.

CAFFEY DISEASE (INFANTILE CORTICAL HYPEROSTOSIS)

This is a rare disorder of unknown etiology characterized by cortical hyperostosis with inflammation of the contiguous fascia and muscle. It is often sporadic, but both autosomal dominant and autosomal recessive inheritance have been reported. In 3 unrelated families with autosomal dominant inheritance, a linkage to mutations of the *COL1A1* gene (codes for the α_1 chain of type I collagen) has been reported.

Prenatal and more often postnatal onset have been described. Prenatal onset may be mild (autosomal dominant) or severe (autosomal recessive). Severe prenatal disease is characterized by typical bone lesions, polyhydramnios, hydrops fetalis, severe respiratory distress, prematurity, and high mortality. Onset in infancy (younger than 6 mo; average: 10 wk) is most common; manifestations include the sudden onset of irritability, swelling of contiguous soft tissue that precedes the cortical thickening of the underlying bones, fever, and anorexia. The swelling is painful with a wood-like induration but with minimal warmth or redness; suppuration is absent. There are unpredictable remissions and relapses; an episode can last 2 wk to 3 mo. The most common bones involved include the mandible (75%) (Fig. 700-5), the clavicle, and the ulna. If swelling is not prominent or visible, the diagnosis might not be evident.

Laboratory features include elevated erythrocyte sedimentation rate and serum alkaline phosphatase as well as, in some patients, increased serum prostaglandin E levels. There may be thrombocytosis and anemia. The **radiographic features** include soft-tissue swelling and calcification and cortical hyperostosis (Fig. 700-6). All bones may be affected except the phalanges or vertebral bodies. The **differential diagnosis** includes other causes of hyperostosis such as chronic vitamin A intoxication, prolonged prostaglandin E infusion in children with ductal dependent congenital heart disease, primary bone tumors, and scurvy.

Complications are unusual but include pseudoparalysis with limb or scapula involvement, pleural effusions (rib), torticollis (clavicle), mandibular asymmetry, bone fusion (ribs or ulna and radius), and bone angulation deformities (common with severe prenatal onset).

Treatment includes indomethacin and prednisone (if there is a poor response to indomethacin).

Figure 700-5 Facies in infantile cortical hyperostosis. In almost all cases, the changes have appeared before the 5th mo of life. Unilateral swelling of the left cheek and left side of the jaw in an infant 12 wk of age. *(From Slovis TL:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby.)*

FIBRODYSPLASIA OSSIFICANS PROGRESSIVE

Fibrodysplasia ossificans progressive (FOP) (MIM 135100) is a rare and severely disabling disorder characterized by progressive extraskeletal bone formation in soft connective tissues including muscles, tendons, ligaments, fascia, and aponeuroses. With exception of deformity of the large toes, infants are normal at birth. Episodes of painful soft-tissue swelling with inflammation usually begin in early childhood initially involving the upper back and neck and later the entire trunk and extremities. Repeated episodes (flare-ups) slowly transform the soft tissues into bands or plates of bone that span joints and progressively limit movement and mobility. Episodes are often triggered by injury, intramuscular injections and viral infection. Most patients are wheelchair bound by their late teens. The average life span is approximately 40 yr, with death usually resulting from complications of thoracic insufficiency.

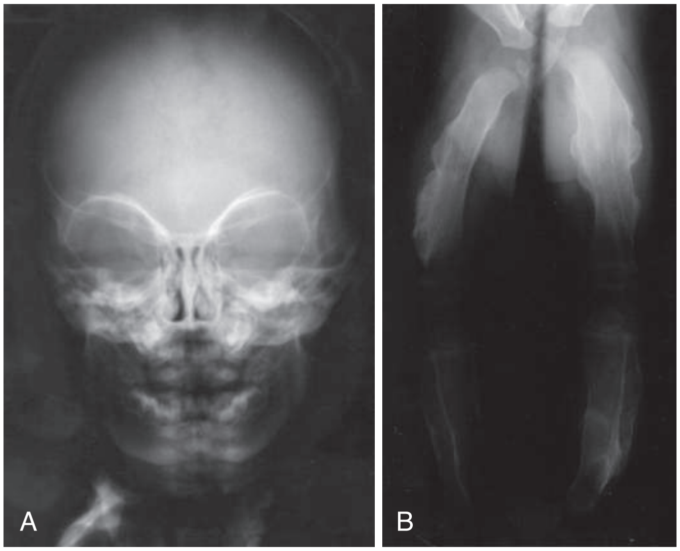

Figure 700-6 **A,** X-ray of a 5 mo old infant showing hyperostosis of the mandible. **B,** X-ray of a 5 mo old infant shoeing hyperostosis of both legs. *(From Kamoun-Goldrat A, le Merrer M: Infantile cortical hyperostosis (Caffey disease): a review.* J Oral Maxillofac Surg *66:2145–2150, 2008, Figs. 1 and 2.)*

FOP results from heterozygous activating mutations of the gene encoding the bone morphogenetic protein (BMP) type I receptor, activin A receptor type I (*ACVR1*). Patients with classic FOP have the same missense *ACVR1* mutation, which enhances BMP signaling, which, in turn, induces inflammation and aberrant endochondral ossification through mechanisms that are poorly understood. Environmental factors such as injury play an important role in triggering these events. *ACVR1* mutations usually occur sporadically, but autosomal dominant transmission has rarely been observed.

There is no definitive treatment for FOP. Supportive care includes avoidance of injury-prone physical activities, intramuscular injections including immunizations and overstretching of the jaw during dental procedures. Corticosteroids and other antiinflammatory agents reduce inflammation during flare-ups. Studies in FOP animal models suggest that BMP type I kinase inhibitors and retinoic acid receptor γ agonists, which block chondrogenesis, the initial step in endochondral ossification, may be useful therapies in the future.

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Chapter 701

Osteogenesis Imperfecta

Joan C. Marini

Osteoporosis is fragility of the skeletal system and a susceptibility to fractures of the long bones or vertebral compressions from mild or inconsequential trauma. **Osteogenesis imperfecta** (**OI**) (brittle bone disease), the most common genetic cause of osteoporosis, is a generalized disorder of connective tissue. The spectrum of OI is extremely broad, ranging from forms that are lethal in the perinatal period to a mild form in which the diagnosis may be equivocal in an adult.

ETIOLOGY

Structural or quantitative defects in type I collagen cause the full clinical spectrum of OI (types I-IV). Type I collagen is the primary component of the extracellular matrix of bone and skin. Between 10 and 15% of patients clinically indistinguishable from OI do not have a molecular defect in type I collagen (Table 701-1).These cases are caused by defects in genes whose protein products interact with type I collagen. One group of patients has overmodified collagen, with similar biochemical findings to those with collagen structural defects and severe or lethal OI bone dysplasia. These cases are caused by recessive null mutations in any of the 3 components of the collagen prolyl 3-hydroxylation complex, prolyl 3-hydroxylase 1 (coded by the *LEPRE1* gene on chromosome 1p34.1) or its associated protein, CRTAP, or cyclophilin B (CyPB, encoded by *PPIB*). A second set of cases without collagen defects have biochemically normal collagen. Defects in *IFITM5* and *SERPINF1* account for defects in mineralization in types V and VI OI, while mutations in *SERPINH1*, encoding the collagen chaperone HSP47, and *FKBP10*, encoding the peptidyl-prolyl *cis-trans* isomerase FKBP65, cause types X and XI OI, respectively. Rare mutations in *BMP1*, *TMEM38B* and *WNT1* also cause recessive OI; the genetic defect in some individuals is still unknown.

EPIDEMIOLOGY

The autosomal dominant forms of OI occur equally in all racial and ethnic groups, whereas recessive forms occur predominantly in ethnic groups with consanguineous marriages. The West African founder mutation for type VIII OI has a carrier frequency of 1 in 200-300 among African-Americans. The incidence of OI detectable in infancy is approximately 1 in 20,000. There is a similar incidence of the mild form OI type I.

PATHOLOGY

The collagen structural mutations cause OI bone to be globally abnormal. The bone matrix contains abnormal type I collagen fibrils and relatively increased levels of types III and V collagen. Several noncollagenous proteins of bone matrix are also reduced. Bone cells contribute to OI pathology, with abnormal osteoblast differentiation and increased numbers of active bone resorbing osteoclasts. The hydroxyapatite crystals deposited on this matrix are poorly aligned with the long axis of fibrils, and there is paradoxical hypermineralization of bone.

PATHOGENESIS

Type I collagen is a heterotrimer composed of 2 α1(I) chains and 1 α2(I) chain. The chains are synthesized as procollagen molecules with short globular extensions on both ends of the central helical domain. The helical domain is composed of uninterrupted repeats of the sequence Gly-X-Y, where Gly is glycine, X is often proline, and Y is often hydroxyproline. The presence of glycine at every third residue is crucial to helix formation because its small side chain can be accommodated in the interior of the helix. The chains are assembled into trimers at their carboxyl ends; helix formation then proceeds linearly in a carboxyl to amino direction. Concomitant with helix assembly and formation, helical proline and lysine residues are hydroxylated by prolyl 4-hydroxylase and lysyl hydroxylase and some hydroxylysine residues are glycosylated.

Collagen structural defects are predominantly of 2 types: 80% are point mutations causing substitutions of helical glycine residues or crucial residues in the C-propeptide by other amino acids, and 20% are single exon splicing defects. The clinically mild OI type I has a quantitative defect, with null mutations in 1 α1(I) allele leading to a reduced amount of normal collagen.

The glycine substitutions in the 2 α chains have distinct genotype–phenotype relationships. One-third of mutations in the α_1 chain are lethal, and those in α2(I) are predominantly nonlethal. Two lethal regions in α1(I) align with major ligand binding regions of the collagen helix. Lethal mutations in α2(I) occur in 8 regularly spaced clusters along the chain that align with binding regions for matrix proteoglycans in the collagen fibril.

Table 701-1 Osteogenesis Type, Gene Defects, and Phenotypes

OSTEOGENESIS IMPERFECTA TYPE	GENE DEFECT	PHENOTYPE
DOMINANT INHERITANCE		
Classical Sillence Types		
I	*COL1A1* null allele	Mild, nondeforming
II	*COL1A1* or *COL1A2*	Lethal perinatal
III	*COL1A1* or *COL1A2*	Progressively deforming
IV	*COL1A1* or *COL1A2*	Moderately deforming
COL1-Mutation Negative		
V	*IFITM5*	Distinct histology
RECESSIVE INHERITANCE		
Mineralization Defect		
VI	*SERPINF1*	Distinct histology
3-Hydroxylation Defects		
VII	*CRTAP*	Severe to lethal
VIII	*LEPRE1*	Severe to lethal
IX	*PPIB*	Moderate to lethal
Chaperone Defects		
X	*SERPINH1*	Severe
XI	*FKBP10*	Progressive deforming, Bruck syndrome 1
C-Propeptide Cleavage Defect		
XII	*BMP1*	Severe, high bone mass case
UNCLASSIFIED		
Zinc-finger transcription factor defect	*SP7*	Moderate
Cation channel defect	*TMEM38B*	Moderate to severe
WNT signaling pathway defect	*WNT1*	Moderate, progressively deforming

From Marini JC, Blissett AR: New genes in bone development: what's new in osteogenesis imperfecta. J Clin Endocrinol Metab *98:3095–3103, 2013, Table 1, p. 3096.*

Classical OI (Sillence types I-IV) is an autosomal dominant disorder, as is type V OI. Some familial recurrences of OI are caused by parental mosaicism for dominant collagen mutations. Recessive OI accounts for 5-7% of new OI in North America. Three recessive types are caused by null mutations in the genes coding for the components of the collagen prolyl 3-hydroxylation complex in the endoplasmic reticulum (*LEPRE1*, *CRTAP*, or *PPIB*). It is not yet clear whether absence of the complex itself or of the modification is the crucial feature of these types of recessive OI. Other recessive types are caused by null mutations in genes whose products are involved in collagen folding (*SERPINH1, FKBP10*), or mineralization (*SERPINF1*).

CLINICAL MANIFESTATIONS

Classical OI was described with the triad of fragile bones, blue sclerae, and early deafness, although most cases do not have all of these features. The Sillence classification divides OI into 4 types based on clinical and radiographic criteria. Types V and VI were later proposed based on histologic distinctions. Subsequent types VII-XII were based on identification of the molecular defect, followed by clinical description.

Osteogenesis Imperfecta Type I (Mild)

OI type I is sufficiently mild that it is often found in large pedigrees. Many type I families have blue sclerae, recurrent fractures in childhood, and presenile hearing loss (30-60%). Both types I and IV are divided into A and B subtypes, depending on the absence (A) or presence (B) of **dentinogenesis imperfecta**. Other possible connective tissue abnormalities include hyperextensible joints, easy bruising, thin skin, joint laxity, scoliosis, wormian bones, hernia, and mild short stature compared with family members. Fractures result from mild to moderate trauma but decrease after puberty.

Osteogenesis Imperfecta Type II (Perinatal Lethal)

Infants with OI type II may be stillborn or die in the 1st yr of life. Birthweight and length are small for gestational age. There is extreme fragility of the skeleton and other connective tissues. There are multiple intrauterine fractures of long bones, which have a crumpled appearance on radiographs. There are striking micromelia and bowing of extremities; the legs are held abducted at right angles to the body in the frogleg position. Multiple rib fractures create a beaded appearance, and the small thorax contributes to respiratory insufficiency. The skull is large for body size, with enlarged anterior and posterior fontanels. Sclerae are dark blue-gray. The cerebral cortex has multiple neuronal migration and other defects (agyria, gliosis, periventricular leukomalacia).

Osteogenesis Imperfecta Type III (Progressive Deforming)

OI type III is the most severe nonlethal form of OI and results in significant physical disability. Birthweight and length are often low normal. Fractures usually occur in utero. There is relative macrocephaly and triangular facies (Fig. 701-1). Postnatally, fractures occur from inconsequential trauma and heal with deformity. Disorganization of the bone matrix results in a "popcorn" appearance at the metaphyses (Fig. 701-2). The rib cage has flaring at the base, and pectal deformity is frequent. Virtually all type III patients have scoliosis and vertebral compression. Growth falls below the curve by the 1st yr; all type III patients have extreme short stature. Scleral hue ranges from white to blue. Dentinogenesis imperfecta, hearing loss, and kyphoscoliosis may be present or develop over time.

Osteogenesis Imperfecta Type IV (Moderately Severe)

Patients with OI type IV can present at birth with in utero fractures or bowing of lower long bones. They can also present with recurrent fractures after ambulation and have normal to moderate short stature. Most children have moderate bowing even with infrequent fractures. Children with OI type IV require orthopedic and rehabilitation intervention, but they are usually able to attain community ambulation skills. Fracture rates decrease after puberty. Radiographically, they are osteoporotic and have metaphyseal flaring and vertebral compressions. Patients with type IV have moderate short stature. Scleral hue may be blue or white.

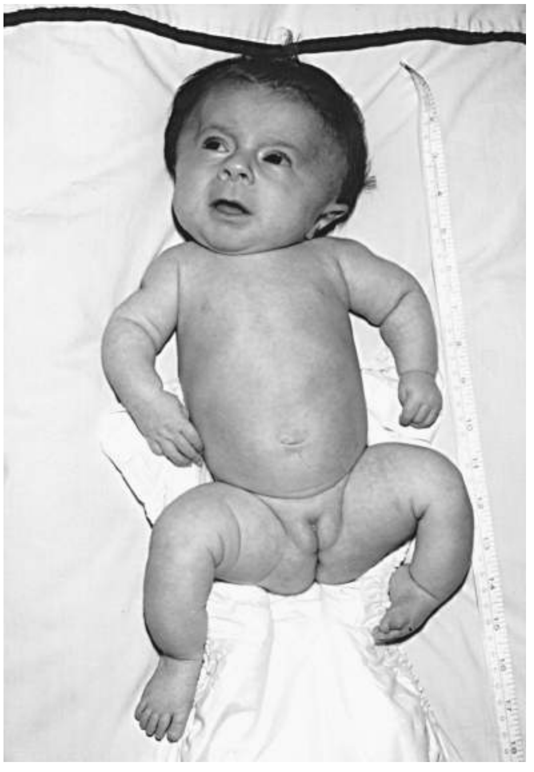

Figure 701-1 Infant with type III osteogenesis imperfecta displays shortened bowed extremities, thoracic deformity, and relative macrocephaly.

Osteogenesis Imperfecta Type V (Hyperplastic Callus) and Type VI Hyperosteoidosis (Mineralization Defect)

Types V and VI OI patients clinically have OI similar in skeletal severity to type IV, but they have distinct findings on bone histology. Type V patients also usually have some combination of hyperplastic callus, calcification of the interosseous membrane of the forearm, and/or a radiodense metaphyseal band. They constitute <5% of OI populations. All type V OI patients are heterozygous for the same mutation in *IFITM5*, which generates a novel start codon for the bone protein Bril. Ligamentous laxity may be present; blue sclera or dentinogenesis imperfect are not present. Patients with type VI OI have progressive deforming OI that does not manifest at birth. They have distinctive bone histology with broad osteoid seams and fish-scale lamellation under polarized light.

Osteogenesis Imperfecta Types VII, VIII, and IX (Autosomal Recessive)

Types VII and VIII patients overlap clinically with types II and III OI but have distinct features including white sclerae, rhizomelia, and small to normal head circumference. Surviving children have severe osteochondrodysplasia with extreme short stature and dual-energy x-ray absorptiometry L1-L2 z-score in the –6 to –7 range. Type IX OI is very rare (only 8 cases reported). The severity is quite broad, ranging from lethal to moderately severe. These children have white sclerae but do not have rhizomelia.

Osteogenesis Imperfecta Types X and XI (Autosomal Recessive)

Only 1 patient with type X OI has been reported; the child had severe OI with white sclerae and died of respiratory causes at age 3 yr. Type XI OI is a more prevalent recessive form with a moderate to severe skeletal phenotype, including white sclerae and normal teeth. Congenital contractures of large joints may occur with the same mutations that cause only skeletal fragility, even in sibships. At the opposite end of the spectrum, a deletion of a single tyrosine residue causes Kuskokwim syndrome, a congenital contracture disorder with very mild vertebral findings and osteopenia.

High Bone Mass Osteogenesis Imperfecta (Cleavage of the Procollagen C-Propeptide)

Autosomal dominant mutations in the C-propeptide cleavage site of procollagen or in the enzyme responsible for its cleavage cause bone fragility with normal or elevated dual-energy x-ray absorptiometry bone density z-scores. Individuals with dominant mutations have normal stature, white sclerae and teeth and mild to moderate OI. Null mutations in *BMP1* lead to a more severe skeletal phenotype with short stature, scoliosis and bone deformity, because *BMP1* has other substrates in addition to type I collagen.

Other Genes for Osteogenesis Imperfecta

A very small percentage of OI patients have bone dysplasia that cannot be accounted for by mutations in the genes described above.

LABORATORY FINDINGS

DNA sequencing is the first diagnostic laboratory test; several diagnostic labs offer panels to test for dominant and recessive OI. Mutation identification is useful to determine the type with certainty and to facilitate family screening and prenatal diagnosis. It is also possible to screen for type VI OI by determination of serum pigment epithelium-derived factor level, which is severely reduced in this type.

If dermal fibroblasts are obtained these can be useful for determining the level of transcripts of the candidate gene and also for collagen biochemical testing, which is positive in most cases of types I-IV and IX OI and all cases of VII/VIII OI. In OI type I, the reduced amount of type I collagen results in an increase in the ratio of type III to type I collagen on gel electrophoresis.

Severe OI can be detected prenatally by level II ultrasonography as early as 16 wk of gestation. OI and thanatophoric dysplasia may be confused. Fetal ultrasonography might not detect OI type IV and rarely detects OI type I. For recurrent cases, chorionic villus biopsy can be used for biochemical or molecular studies. Amniocytes produce false-positive biochemical studies but can be used for molecular studies in appropriate cases.

In the neonatal period, the normal to elevated alkaline phosphatase levels present in OI distinguish it from hypophosphatasia.

COMPLICATIONS

The morbidity and mortality of OI are cardiopulmonary. Recurrent pneumonias and declining pulmonary function occur in childhood, and cor pulmonale is seen in adults.

Neurologic complications include basilar invagination, brainstem compression, hydrocephalus, and syringohydromyelia. Most children with OI types III and IV have basilar invagination, but brainstem compression is uncommon. Basilar invagination is best detected with spiral CT of the craniocervical junction (Fig. 701-3).

TREATMENT

There is no cure for OI. For severe nonlethal OI, active physical rehabilitation in the early years allows children to attain a higher functional level than orthopedic management alone. Children with OI type I and some with type IV are spontaneous ambulators. Children with types III, IV, V, VI, and XI OI benefit from gait aids and a program of swimming and conditioning. Severely affected patients require a wheelchair for community mobility but can acquire transfer and self-care skills. Teens with OI can require psychologic support with body image issues. Growth hormone improves bone histology in growth-responsive children (usually types I and IV).

Orthopedic management of OI is aimed at fracture management and correction of deformity to enable function. Fractures should be promptly splinted or cast; OI fractures heal well, and cast removal should be aimed at minimizing immobilization osteoporosis. Correction of long bone deformity requires an osteotomy procedure and placement of an intramedullary rod.

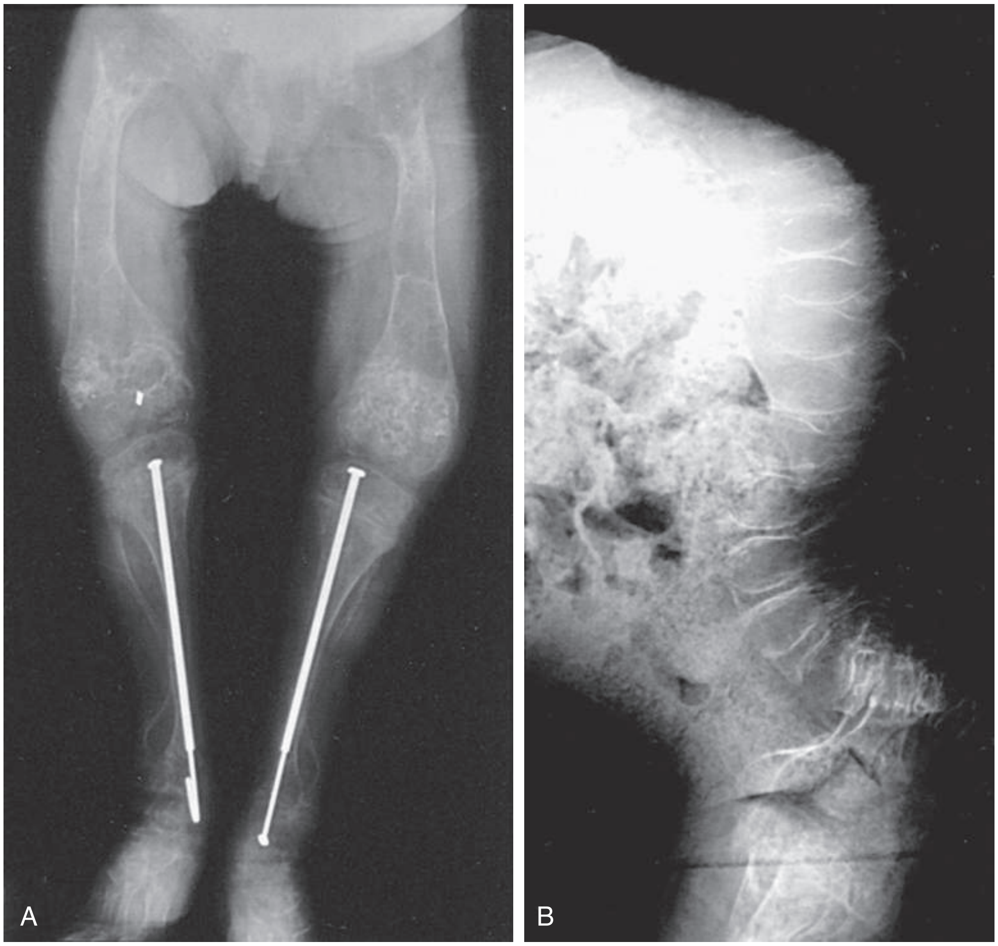

Figure 701-2 Typical features of type III osteogenesis imperfecta radiographs in a 6 yr old child. **A,** Lower long bones are osteoporotic, with metaphyseal flaring, "popcorn" formation at growth plates, and placement of intramedullary rods. **B,** Vertical bodies are compressed and osteoporotic.

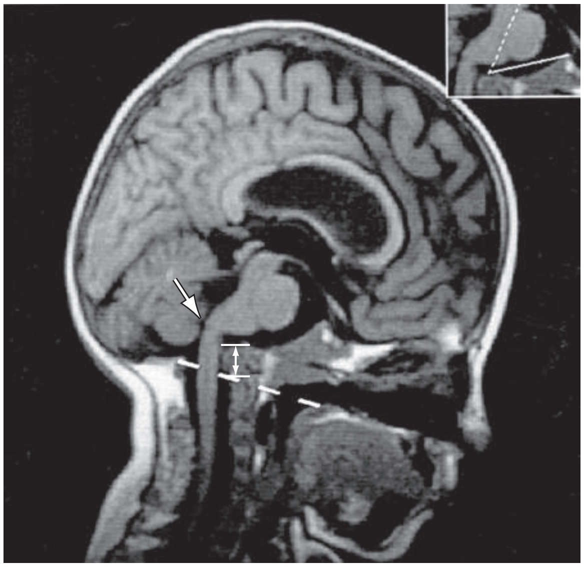

Figure 701-3 Typical feature of basilar invagination shown in the sagittal MRI of an asymptomatic child with type III osteogenesis imperfecta. There is invagination of the odontoid above the Chamberlain line, causing compression and kinking at the pontomedullary junction *(arrow)*.

A several-year course of treatment of children with OI with bisphosphonates (IV pamidronate or oral olpadronate or risedronate) confers some benefits. Bisphosphonates decrease bone resorption by osteoclasts; OI patients have increased bone volume that still contains the defective collagen. Bisphosphonates are more beneficial for vertebrae (trabecular bone) than long bones (cortical bone). Treatment for 1-2 yr results in increased L1-4 dual-energy x-ray absorptiometry and, more importantly, improved vertebral compressions and area, which can prevent or delay the scoliosis of OI. Relative risk of long bone fractures is modestly decreased. However, the material properties of long bones are weakened by prolonged treatment and nonunion after osteotomy is increased. There is no effect of bisphosphonates on mobility scores, muscle strength, or bone pain. Limiting treatment duration to 2-3 yr in mid-childhood can maximize benefits and minimize detriment to cortical material properties. Benefits appear to persist several years after the treatment interval. Side effects include abnormal long bone remodeling, increased incidence of fracture nonunion, and osteopetrotic-like brittleness to bone.

PROGNOSIS

OI is a chronic condition that limits both life span and functional level. Infants with OI type II usually die within months to a year of life. An occasional child with radiographic type II and extreme growth deficiency survives to the teen years. Persons with OI type III have a reduced life span with clusters of mortality from pulmonary causes in early childhood, the teen years, and the 40s. OI types I, IV, and V OI

are compatible with a full life span. The oldest reported individuals with type VIII are in their 3rd decade, and some with type XI are in their 4th decade. The long-term prognosis for most recessive types is still emerging, and many adults with OI have not had molecular testing.

Individuals with OI type III are usually wheelchair dependent. With aggressive rehabilitation, they can attain transfer skills and household ambulation. OI type IV children usually attain community ambulation skills either independently or with gait aids.

GENETIC COUNSELING

For autosomal dominant OI, the risk of an affected individual passing the gene to the individual's offspring is 50%. An affected child usually has about the same severity of OI as the parent; however, there is variability of expression, and the child's condition can be either more or less severe than that of the parent. The empirical recurrence risk to an apparently unaffected couple of having a second child with OI is 5-7%; this is the statistical chance that 1 parent has germline mosaicism. The collagen mutation in the mosaic parent is present in some germ cells and may be present in somatic tissues. If a parent is a mosaic carrier, the risk of recurrence may be as high as 50%.

For recessive OI, the recurrence risk is 25% per pregnancy. No known individual with severe nonlethal recessive OI has had a child.

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Chapter 702

Marfan Syndrome

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Marfan syndrome (MFS) is an inherited, systemic, connective tissue disorder caused by mutations in the gene encoding the *extracellular matrix* (ECM) protein fibrillin-1. It is primarily associated with skeletal, cardiovascular, and ocular pathology. The diagnosis is based on clinical findings, some of which are age dependent.

EPIDEMIOLOGY

The incidence is reported to be 1 in 10,000 live births and approximately one-fourth of cases are sporadic. The disorder shows autosomal dominant inheritance, with high penetrance, but variable expression; both interfamilial and intrafamilial clinical variation is common. There is no racial or gender preference.

PATHOGENESIS

MFS is associated with abnormal production, matrix deposition and/or stability of fibrillin-1, a 350-kDa ECM protein that is the major constituent of microfibrils, with prominent disruption of microfibrils and elastic fibers in diseased tissues. The ***fibrillin-1 (FBN1)*** locus resides on the long arm of chromosome 15 (15q21), and the gene is composed of 65 exons. Linkage analysis suggests an absence of locus heterogeneity and the involvement of *FBN1* has been demonstrated in >90% of cases, with more than 1,000 disease-causing mutations identified to date (the majority of which are missense point mutations and unique to a given family). With the exception of an early onset and severe presentations of the disease associated with some mutations in exons 26-27 and 31-32, no clear genotype–phenotype correlation has been identified. Given that there is considerable intrafamilial variability, genetic, epigenetic, environmental or other unidentified factors may influence expression of the disease.

MFS was traditionally considered to result from a structural deficiency of connective tissues. Reduced fibrillin-1 was thought to lead to a primary derangement of elastic fiber deposition, because both skin and aorta from affected patients show decreased elastin, along with elastic fiber fragmentation. In response to stress (such as hemodynamic forces in the proximal aorta), affected organs were thought to manifest this structural insufficiency with accelerated degeneration. Additional research identified a cytokine-regulatory role for fibrillin-1 that appears to have important implications for MFS. The *transforming growth factor beta (TGF-β)* family of cytokines influences a diverse repertoire of cellular processes, including cell proliferation, migration, differentiation, survival and synthetic activity. The *TGF-β* ligands (*TGF-*β_1, -β_2, or -β_3) are synthesized as inactive precursor complexes and sequestered by ECM proteins, including fibrillin-1. Mice heterozygous for a mutation in the fibrillin-1 gene, typical of those that cause MFS in humans, display many of the classic features of MFS including aortic root aneurysm, which associates with a tissue signature for increased TGF-β signaling, suggesting that failed ECM sequestration of latent TGF-β by fibrillin-1 leads to increased TGF-β activation and signaling. Furthermore, pharmacologic antagonism of TGF-β signaling ameliorates aortic aneurysm in mouse models of MFS, demonstrating that high TGF-β signaling is a cause rather than a consequence of disease progression.

Aberrant TGF-β signaling might also play a role in the wider spectrum of manifestations of MFS. Increased TGF-β signaling has been observed in other tissues in MFS mice, including the developing lung, mitral valve, and skeletal muscle. Treatment of these mice with agents that antagonize TGF-β attenuates or prevents pulmonary emphysema, myxomatous degeneration of the mitral valve, and skeletal muscle myopathy. The prominent role of TGF-β dysregulation in the pathogenesis of MFS was further validated by the discovery and characterization of another aortic aneurysm syndrome, **Loeys-Dietz syndrome**, in which patients have mutations in the TGF-β receptors and share many overlapping clinical features with MFS (see "Differential Diagnosis" below).

CLINICAL MANIFESTATIONS

MFS is a multisystem disorder, with cardinal manifestations in the skeletal, cardiovascular, and ocular systems.

Skeletal System

Overgrowth of the long bones (dolichostenomelia) is often the most obvious manifestation of MFS and may produce a reduced *upper segment: lower segment ratio* (US:LS) or an arm span to height ratio >1.05 times. Abnormal ratios are US:LS <1 for ages 0-5 yr, US:LS <0.95 for ages 6-7 yr, US:LS <0.9 for ages 8-9 yr, and <0.85 above age 10 yr. Anterior chest deformity is likely the result of excessive rib growth, pushing the sternum either outward (pectus carinatum) or inward (pectus excavatum). Abnormal curvatures of the spine (most commonly thoracolumbar scoliosis) may also partly result from increased vertebral growth. Other skeletal features include an inward bulging of the acetabulum into the pelvic cavity (protrusio acetabuli), flatfeet (pes planus), and joint hypermobility or joint contractures. Long and slender fingers in relation to the palm of the hand (arachnodactyly) is generally a subjective finding. The combination of arachnodactyly and hypermobile joints is examined by the Walker-Murdoch or wrist sign, which is positive if there is full overlap of the distal phalanges of the thumb and fifth finger when wrapped around the contralateral wrist (Fig. 702-1), and the Steinberg or thumb sign, which is present when the distal phalanx of the thumb fully extends beyond the ulnar border of the hand when folded across the palm (Fig. 702-1). Contracture of the fingers (camptodactyly) and elbows is commonly observed. A selection of craniofacial manifestations may be present including a long narrow skull (dolichocephaly), deep-set eyes (enophthalmos), recessed lower mandible (retrognathia) or small chin (micrognathia), flattening of the midface (malar hypoplasia), a high-arching palate, and downward-slanting palpebral fissures (Fig. 702-2).

Cardiovascular System

Within the heart, thickening of the atrioventricular valves is common and often associated with valvular prolapse. Variable degrees of regurgitation may be present. In children with early onset and severe MFS,

Figure 702-1 Note the joint laxity **(A),** Steinberg thumb sign **(B),** ability to join thumb and fifth finger around the wrist (Walker-Murdoch sign) **(C),** pes planus **(D),** and striae over hips and back **(E).** *(From Jones KL, Jones MC, del Campo M:* Smith's recognizable patterns of human malformation*, ed 7, Philadelphia, 2013, WB Saunders, Fig. 2, p. 616;* ***A-D*** *courtesy Dr. Lynne M. Bird, Rady Children's Hospital, San Diego, CA.)*

insufficiency of the mitral valve can lead to congestive heart failure, pulmonary hypertension and death in infancy; this manifestation is the leading cause of morbidity and mortality in young children with the disorder. Supraventricular arrhythmias and ventricular dysrhythmias may be seen in association with mitral valve dysfunction, and there is an increased prevalence of prolonged QT interval. Dilated cardiomyopathy occurs with increased prevalence in patients with MFS, most often attributed to volume overload imposed by valve regurgitation. Aortic valve dysfunction is generally a late occurrence and attributed to stretching of the aortic annulus by an expanding aortic root aneurysm.

Aortic aneurysm, dissection and rupture, principally at the level of the sinuses of Valsalva (aortic root), remains the most life-threatening manifestations of MFS, prompting lifelong monitoring by echocardiography or other imaging modalities. In severe cases, the aneurysm may be present in utero, but in mild examples, it may be absent or never exceed dimensions that require clinical intervention. Aortic dimensions must be interpreted in comparison to age-dependent nomograms. The most important risk factor for aortic dissection are the maximal aortic root size and a positive family history. The characteristic histologic findings from aortae of patients with MFS include cystic medial necrosis of the tunica media and disruption of elastic lamellae. Cystic medial necrosis describes the focal apoptosis and disappearance of vascular smooth muscle cells and elastic fibers from the of the tunica media of the aortic wall, and subsequent deposition of mucin-like material in the cystic space. These changes produce a thicker, less distensible and stiffer aorta, which is more prone to aortic dissection. Most patients experiencing acute aortic dissection present with classic symptoms including sudden-onset, severe, tearing chest pain, often radiate into the back. The dissection typically starts at the aortic root and may remain confined to the ascending aorta (type II) or continue into the descending aorta (type I). Acute-onset congestive heart failure may occur if aortic valve function is compromised and patients may suffer cerebrovascular injury depending on the involvement of the carotid arteries. Involvement of the coronary arteries may herald sudden cardiac death, secondary to myocardial infarction or rupture into the pericardial sac with subsequent pericardial tamponade. Chronic aortic dissection usually occurs more insidiously, often without chest pain. Dilation of the main pulmonary artery is common but does not typically cause any clinical sequelae. Enlargement of the

Figure 702-2 Marfan syndrome. Note the elongated facies, droopy lids, apparent dolichostenomelia, and mild scoliosis.

Table 702-1 Diagnostic Criteria for Marfan Syndrome

In the absence of a family history of MFS, a diagnosis can be established in 4 distinct scenarios:
1. Aortic root Z score >2 *and* ectopia Lentis*
2. Aortic root Z score >2 *and* a bona fide *FBN1* mutation
3. Aortic root Z score >2 *and* a systemic score >7*
4. Ectopia lentis *and* a bona fide *FBN1* mutation known to cause aortic disease

In the presence of a family history of MFS, a diagnosis can be established in the presence of:
1. Ectopia lentis
2. A systemic score >7*
3. Aortic root Z score >2 if older than 20 yr or >3 if younger than 20 yr*

In the absence of a family history of MFS, alternative diagnoses include:
1. Ectopia lentis ± systemic score *and FBN1* mutation not known to associate with aortic aneurysm or no *FBN1* mutation = ectopia lentis syndrome
2. Aortic root Z score <2 *and* a systemic score >5 (with at least 1 skeletal feature) without ectopia lentis = MASS (mitral valve prolapse, myopia, borderline and nonprogressive aortic enlargement, and nonspecific skin and skeletal findings) phenotype
3. Mitral valve prolapse *and* aortic root Z score <2 *and* a systemic score <5 without ectopia lentis = mitral valve prolapse syndrome

*Denotes caveat that features suggestive of an alternative diagnosis must be excluded and appropriate alternative molecular testing should be performed.

Table 702-2 Scoring of Systemic Features in Points

- Wrist *and* thumb sign = 3 (wrist *or* thumb sign = 1)
- Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)
- Hind foot deformity = 2 (plain pes planus = 1)
- Pneumothorax = 2
- Dural ectasia = 2
- Protrusio acetabuli = 2
- Reduced US : LS *and* increased arm : height *and* no severe scoliosis = 1
- Scoliosis or thoracolumbar kyphosis = 1
- Reduced elbow extension = 1
- Facial features (3/5) = 1 (dolichocephaly, enophthalmos, down-slanting palpebral fissures, midface hypoplasia, retrognathia)
- Skin striae = 1
- Myopia >3 diopters = 1
- Mitral valve prolapse (all types) = 1

Maximum total: 20 points; score ≥7 indicates systemic involvement.
US:LS, upper segment:lower segment ratio.

descending thoracic or abdominal aorta can also occur, although relatively rarely.

Ocular System

Dislocation of the ocular lens (ectopia lentis) occurs in approximately 60-70% of patients, although it is not unique to the disorder. Other ocular manifestations include early and severe myopia, flat cornea, increased axial length of the globe, hypoplastic iris, and ciliary muscle hypoplasia, causing decreased miosis. Patients are also predisposed to retinal detachment and early cataracts or glaucoma.

Other Systems

There is an increased incidence of pulmonary disease in MFS: progressive anterior chest deformity or thoracic scoliosis may contribute to a restrictive pattern of lung disease. A widening of the distal airspaces predisposes patients to spontaneous pneumothorax, which occurs in up to 15% of patients. Assessment of pulmonary volumes and function should account for long bone overgrowth affecting the lower extremities, which can lead to a reduction in the normalized forced vital capacity and total lung capacity. If normalized to thoracic size or sitting height, pulmonary function testing is often normal in patients with the disorder.

MFS patients typically have normal skin texture and elasticity. The most common skin finding is stretch marks—pinkish, scar-like lesions that later become white (striae atrophicae), which occur in about one-third of patients (see Fig. 702-1). These may occur in the absence of obesity, rapid gain in muscle mass, or pregnancy, and at sites not associated with increased skin distention (i.e., the anterior shoulder or lower back). Another common manifestation is congenital or acquired inguinal hernia. There is also an increased risk of surgical and recurrent hernias in the Marfan population.

Widening of the dural sac or root sleeves (dural ectasia) is present in 63-92% of MFS patients. Although dural ectasia can result in lumbar back pain, it is often asymptomatic and should be assessed by lumbosacral imaging with CT or MRI.

DIAGNOSIS

Given the complexity of the clinical examination in MFS and the relevant differential diagnoses, evaluation should be coordinated by a professional with extensive experience, such as a geneticist, cardiologist, or ophthalmologist. The diagnosis is based on a defined set of clinical criteria drawn up by an international panel of experts: revised Ghent nosology for the MFS (Table 702-1).

In the absence of a conclusive family history of MFS, the diagnosis can be established in 4 distinct scenarios:

1. The presence of either aortic root dilation when standardized to age and body size (an aortic root Z score ≥2) or aortic dissection combined with ectopia lentis allows for the unequivocal diagnosis of MFS, irrespective of the presence or absence of any systemic features (Table 702-2), except when these are indicative of an alternate diagnosis.

Table 702-3 Criteria for Causal *FBN1* Mutation

• Mutation previously shown to segregate in a Marfan family
• Any 1 of the following de novo mutations (with proven paternity and absence of disease in parents):
  • Nonsense mutation
  • Inframe and out of frame deletion/insertion
  • Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level
  • Missense mutation affecting/creating cysteine residues
  • Missense mutation affecting conserved residues of the EGF consensus sequence [(D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F) with m and n representing variable number of residues; D representing aspartic acid; N representing asparagine; E representing glutamic acid; Q representing glutamine; Y representing tyrosine; F representing phenylalanine; X representing any amino acid]
  • Other missense mutations: segregation in family if possible *and* absence in 400 ethnically matched control chromosomes; if no family history, absence in 400 ethnically matched control chromosomes
  • Linkage of haplotype for n ≥6 meioses to the *FBN1* locus

cDNA, complementary DNA; mRNA, messenger RNA;

From Loeys BL, Dietz HC, Braverman AC, et al: The revised Ghent nosology for the Marfan syndrome. J Med Genet *47:476–485, 2010.*

2. The presence of aortic root dilation (Z score ≥2) or aortic dissection and the identification of a bona fide *FBN1* mutation (Table 702-3) are sufficient to establish the diagnosis even if ectopia lentis is absent.
3. When aortic root dilation (an aortic root Z score ≥2) or aortic dissection is present, but ectopia lentis is absent and the *FBN1* status is either unknown or negative, the diagnosis may be confirmed by the presence of sufficient systemic findings (a systemic score ≥7 points; see Table 702-2). However, features suggestive of an alternate diagnosis must be excluded and the appropriate alternative molecular testing should be performed.
4. In the presence of ectopia lentis, but absence of aortic root dilation or aortic dissection, an *FBN1* mutation, which has previously been associated with aortic disease, is required before the diagnosis can be made. If the *FBN1* mutation is not unequivocally associated with cardiovascular disease in either a related or unrelated proband, the patient should be classified as *isolated ectopia lentis syndrome*.

Despite these diagnostic criteria, on occasion young (<20 yr) sporadic cases may not fit in 1 of the 4 proposed scenarios detailed above. If insufficient systemic features (systemic score <7) and/or borderline aortic root measurements (Z score <3) are present without documented evidence of a bona fide *FBN1* mutation, the term *nonspecific connective tissue disorder* is recommended. In those instances when a *FBN1* mutation is identified, the term *potential MFS* should be used instead.

In an individual with a positive family history of MFS (where a family member has been independently diagnosed using the above criteria), the diagnosis can be established in the presence of:

1. Ectopia lentis
2. A systemic score >7 points (see Table 702-1)
3. Aortic root dilation with Z score ≥2 in adults (≥20 yr old) or Z score ≥3 in individuals younger than 20 yr old

In the case of scenarios 2 and 3, features suggestive of an alternative diagnosis must again be excluded and appropriate alternative molecular testing should be performed.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of MFS includes disorders with aortic aneurysm (Loeys-Dietz syndrome, familial thoracic aortic aneurysm syndrome, Shprintzen-Goldberg syndrome); ectopia lentis (ectopia lentis syndrome, Weill-Marchesani syndrome, and homocystinuria [see Chapter 85.3]); or systemic manifestations of MFS (congenital contractural arachnodactyly and MASS phenotype) (Table 702-4).

Aortic Aneurysm Syndromes

An important differential diagnosis is **Loeys-Dietz syndrome (LDS)**, a systemic connective tissue disorder characterized by the triad of arterial tortuosity and aggressive aneurysm disease, hypertelorism, and bifid uvula or cleft palate, as well as many of the craniofacial and skeletal features found in MFS. The diagnosis may be classified into LDS type 1 or LDS type 2 depending on whether the mutant locus resides in the *TGFBR1* or the *TGFBR2* gene, which encode the type 1 or the type 2 TGF-β receptors respectively. Two new LDS variants have been described, LDS type 3 and LDS type 4, which are caused by heterozygous mutations in the genes encoding the TGF-β intracellular signaling molecule SMAD3 and the extracellular ligand TGF-β_2, respectively. These new subtypes are also characterized by widespread arterial tortuosity and aneurysm disease, aortic dissection, as well as typical craniofacial and skeletal abnormalities. Patients with *SMAD3* mutations also appear predisposed to early onset osteoarthritis and supraventricular arrhythmias. Distinguishing between MFS and the various LDS subtypes is important because aneurysms tend to dissect at younger ages and smaller dimensions in LDS patients, necessitating more aggressive management.

Like MFS, **familial thoracic aortic aneurysm** syndrome segregates as an autosomal dominant trait characterized aortic root aneurysm and dissection. Other systemic manifestations of MFS are typically absent and the disorder has reduced penetrance. Disease-causing heterozygous mutations have been identified in several genes with roles in the vascular smooth muscle contractile apparatus, including *MYH11*, *ACTA2*, and *MYLK*, which encode smooth muscle myosin heavy chain 11, vascular smooth muscle α-actin, and myosin light chain kinase. However, these genes only account for a fraction of cases of nonsyndromic familial thoracic aortic aneurysm. In most cases, the management principles that have been generated for MFS have proved effective for this form of familial aortic aneurysm.

Shprintzen-Goldberg syndrome is a systemic connective tissue disorder that includes virtually all the craniofacial, skeletal, skin and cardiovascular manifestations of MFS and LDS, with the additional findings of craniosynostosis, hydrocephalus, mental retardation and severe skeletal muscle hypotonia. The majority of cases are caused by heterozygous mutations in the *SKI* gene, which encodes an intracellular repressor of TGF-β signaling. Vascular involvement tends to be less prevalent and less severe when compared to MFS or LDS.

Ectopia Lentis Syndromes

Both **ectopia lentis syndrome** and **Weill-Marchesani syndrome** may also be caused by heterozygous mutations in *FBN1*. Compound heterozygous or homozygous mutations at a second locus, *ADAMTSL4,* have been shown to cause ectopia lentis associated with slightly younger age at diagnosis. Interestingly, the same *FBN1* mutation produces classical MFS, ectopia lentis, and ectopia lentis combined with skin, but not cardiovascular, manifestations of MFS, suggesting that these presentations are part of a spectrum of clinical features of the same disease.

Weill-Marchesani syndrome is a systemic connective tissue disorder characterized by skin, skeletal, and ocular abnormalities, including microspherophakia, ectopia lentis, and myopia. Features inconsistent with the diagnosis of MFS include short stature and brachydactyly. As well as *FBN1* mutations (type 2), the syndrome may be caused by homozygous or compound heterozygous mutations in *ADAMTS10* (type 1) or homozygous mutations in *LTBP2* (type 3).

Homocystinuria is a metabolic disorder caused by homozygous or compound heterozygous mutations in the gene encoding cystathionine β-synthase, which leads to increases in both homocysteine and methionine. The clinical features of untreated homocystinuria include ectopia lentis and skeletal abnormalities resembling MFS. However, in contrast to MFS, affected persons often suffer from developmental delay, a predisposition to thromboembolic events, and a high incidence of coronary artery disease.

Table 702-4 Differential Diagnosis of Marfan Syndrome

DIFFERENTIAL DIAGNOSIS	CARDIAC FEATURES	VASCULAR FEATURES	SYSTEMIC FEATURES
AORTIC ANEURYSM SYNDROMES			
Loeys-Dietz syndrome (MIM 609192)	Patent ductus arteriosus Atrial septal defect Bicuspid aortic valve	Aortic root aneurysm Arterial tortuosity Widespread aneurysms Vascular dissection at relatively young ages and small aortic dimensions	Hypertelorism Cleft palate Broad or bifid uvula Craniosynostosis Midface hypoplasia Blue sclerae Arachnodactyly Pectus deformity Scoliosis Joint hypermobility Pes planus Rarely Easy bruising Dystrophic scars Translucent skin Rarely developmental delay
Familial thoracic aortic aneurysm (MIM 132900)	Generally none Rare forms with patent ductus arteriosus	Aortic root aneurysm Ascending aortic aneurysm	Generally none Rarely livedo reticularis and iris flocculi
Shprintzen-Goldberg syndrome (MIM 182212)	None	Aortic root aneurysm	Hypertelorism Craniosynostosis Arched palate Arachnodactyly Pectus deformity Scoliosis Joint hypermobility Developmental delay
Bicuspid aortic valve with aortic aneurysm (MIM: 109730)	Bicuspid aortic valve	Aortic root aneurysm Ascending aortic aneurysm	
Ehlers-Danlos syndrome, type IV (MIM: 130050)	Mitral valve prolapse	Aneurysm and rupture of any medium to large muscular artery No predisposition for aortic root enlargement	Joint hypermobility Atrophic scars Translucent skin Easy bruising Hernias Rupture of hollow organs
ECTOPIA LENTIS SYNDROMES			
Familial ectopia lentis (MIM 129600)	None	None	Nonspecific skeletal features
Homocystinuria (MIM 236200)	Mitral valve prolapse	Intravascular thrombosis	Tall stature Ectopia lentis Long-bone overgrowth Developmental delay
SYNDROMES WITH SYSTEMIC MANIFESTATIONS OF MFS			
MASS phenotype (MIM 604308)	Mitral valve prolapse	Borderline or nonprogressive	Nonspecific skin and skeletal findings Myopia

Syndromes with Systemic Manifestations of Marfan Syndrome

Congenital contractural arachnodactyly is a connective tissue disorder caused by heterozygous mutations in the gene encoding fibrillin-2 (*FBN2*). There are a number of clinical features overlapping with MFS including dolichostenomelia, anterior chest deformity, scoliosis, joint contractures, and arachnodactyly, as well as some craniofacial malformations, including highly arched palate and retrognathia. In addition, both may suffer from severe cardiovascular abnormalities leading to premature death, but the specific cardiac anomalies are quite different; valvular insufficiency and aortic root dilation in MFS whereas congenital heart defects are more common in congenital contractural arachnodactyly. Patients with congenital contractural arachnodactyly also suffer from crumpled auricular helices (a hallmark of this condition).

Many patients referred for possible MFS are found to have evidence of a systemic connective tissue disorder, including long limbs, deformity of the thoracic cage, striae atrophicae, mitral valve prolapse, and borderline but nonprogressive dilation of the aortic root, but do not meet diagnostic criteria for MFS. This constellation of features is referred to by the acronym **MASS** phenotype (mitral valve prolapse, myopia, borderline and nonprogressive aortic enlargement, and nonspecific skin and skeletal findings). The MASS phenotype can segregate in large pedigrees and remain stable over time. The diagnosis is particularly challenging in the context of a young, sporadic patient in whom careful follow-up is needed to distinguish MASS phenotype from emerging MFS. Familial mitral valve prolapse syndrome can also be caused by mutations in the gene encoding fibrillin-1 and include subdiagnostic systemic manifestations.

LABORATORY FINDINGS

Laboratory studies should document a negative urinary cyanide nitroprusside test or specific amino acid studies to exclude cystathionine β-synthase deficiency (homocystinuria). Although it is estimated that most, if not all, people with classic MFS have an *FBN1* mutation, the large size of this gene and the extreme allelic heterogeneity in MFS have frustrated efficient molecular diagnosis. The yield of mutation screening varies based on technique and clinical presentation. It

remains unclear whether the "missing" mutations are simply atypical in character or location within *FBN1* or located in another gene. Other differential diagnoses, such as MASS phenotype, ectopia lentis, Weill-Marchesani syndrome, and Shprintzen-Goldberg syndrome, are associated with mutations in the *FBN1* gene. It is often difficult or impossible to predict the phenotype from the nature or location of a *FBN1* mutation in MFS. Hence, molecular genetic techniques can contribute to the diagnosis, but they do not substitute for comprehensive clinical evaluation and follow-up. The absence or presence of an *FBN1* mutation is not sufficient to exclude or establish the diagnosis, respectively.

MANAGEMENT

Management focuses on preventing complications and genetic counseling. Referral to a multidisciplinary center where a geneticist with experience in MFS works in concert with subspecialists to coordinate a rational approach to monitoring and treatment is advisable given the complex nature of some patient's disease. Yearly evaluations for cardiovascular disease, scoliosis, or ophthalmologic problems are imperative.

CURRENT THERAPIES

Most therapies currently available or under investigation aim to diminish cardiovascular complications, which can be categorized into activity restrictions, aortic surgery, endocarditis prophylaxis, and current pharmacologic approaches.

Activity Restrictions

Physical therapy can improve cardiovascular performance, neuromuscular tone, and psychosocial health, and so aerobic exertion in moderation is recommended. However, strenuous physical exertion, competitive or contact sports and particularly isometric activities, which invoke a Valsalva maneuver, such as weight lifting, should be avoided.

Aortic Surgery

Surgical outcome is more favorable if undertaken on an elective rather than an urgent or emergent basis (mortality of 1.5% vs 2.6% and 11.7%, respectively). Therefore, aortic surgery should be recommended for adult patients when their aortic root diameter approaches 50 mm, and early intervention considered for those with a rapid rate of enlargement (>5-10 mm per year) or a family history of early aortic dissection. There are no definitive criteria guiding the timing of surgery in children in whom dissection is extremely rare, irrespective of aortic size. This has prompted many centers to adopt the adult criterion of 50 mm, although early surgery may be undertaken in the presence of a rapid rate of growth (>10 mm per year) or the emergence of significant aortic regurgitation. Preserving the native aortic valve at the time of repair is desirable to avoid the need for lifelong anticoagulation. Replacement of the aortic root with a pulmonary root autograft (a Ross procedure) is not recommended as the neoaorta can undergo progressive enlargement and autograft failure once exposed to the systemic blood pressure. Mitral valve repair or replacement is advised for severe mitral valve regurgitation with associated symptoms or progressive left ventricular dilation or dysfunction.

Pregnancy

There is higher risk of aortic dissection during pregnancy in women with MFS. However, improved awareness and more recent analyses have indicated the risk is low in patients with an aortic root diameter <40 mm. Prophylactic aortic root replacement can minimize the risk of aortic dissection and death in women with MFS who wish to become pregnant.

Endocarditis Prophylaxis

The American Heart Association no longer recommends the use of antibiotic prophylaxis for persons with structural or valvular heart disease, but exceptions are made for select groups at the greatest risk for bad outcomes from infectious endocarditis. The Professional Advisory Board of the National Marfan Foundation believes that patients with MFS should continue to receive prophylaxis for bacterial endocarditis, in part because it remains unknown, but possible, that the myxomatous valves typical of MFS are a preferred substrate for bacterial infection.

Current Pharmacologic Approaches

β-Blockers have traditionally been considered the standard of care in MFS and multiple small observational studies suggest there is a protective effect on aortic root growth, with the dose typically titrated to achieve a resting heart rate <100 beats/min during submaximal exercise. Given the putative role of hemodynamic stress in aortic dilation and aortic dissection in MFS, these effects are attributed to the negative inotropic and chronotropic effects of β-blockade.

EMERGING THERAPEUTIC STRATEGIES

Angiotensin II Receptor Type 1 Blockers

There is extensive evidence linking angiotensin II signaling to TGF-β activation and signaling. In a mouse model of MFS, the **angiotensin II receptor type 1 blocker losartan** completely prevents pathologic aortic root growth and normalizes both aortic wall thickness and architecture. In support of its relevance to humans, a retrospective study assessing the effect of angiotensin II receptor type 1 blockers in a small cohort of pediatric patients with MFS who had severe aortic root enlargement despite previous alternate medical therapy, showed that angiotensin II receptor type 1 blockers significantly slowed the rate of aortic root and sinotubular junction dilation (both of which occur in MFS), whereas the distal ascending aorta (which does not normally become dilated in MFS) remained unaffected. Further evidence of a beneficial effect from losartan therapy is provided by 3 prospective clinical trials that demonstrated that losartan treatment alone or in combination with β-blockade slows the progression of aortic root dilation in patients with MFS. Nonetheless when compared to atenolol, losartan therapy in children and young adults with Marfan syndrome and aortic root dilation demonstrated equivalent rates of aortic root dilation during a 3-yr study.

PROGNOSIS

The major cause of mortality is aortic root dilation, dissection, and rupture, with the majority of fatal events occurring in the 3rd and 4th decade of life. A reevaluation of life expectancy in MFS suggests that early diagnosis and refined medical and surgical management has greatly improved the prognosis for patients with the condition. Nevertheless, MFS continues to be associated with significant morbidity and selected subgroups are refractory to therapy and continue to show early mortality. In a review of 54 patients diagnosed during infancy, 89% had serious cardiac pathology; cardiac disease was progressive despite standard care (22% died during childhood, 16% before age 1 yr). In the more classic form of MFS, it is estimated that more than 90% of individuals will have a cardiovascular event during their lifetime, placing both physical and mental stresses on patients and their families. Awareness of these issues and referral for support services can facilitate a positive perspective toward the condition.

GENETIC COUNSELING

The heritable nature of MFS makes recurrence risk (genetic) counseling mandatory. Fathers of these sporadic cases are, on average, 7-10 yr older than fathers in the general population. This paternal age effect suggests that these cases represent new dominant mutations with minimal recurrence risk to the future offspring of the normal parents. Owing to rare reports of gonadal mosaicism in a phenotypically normal parent, the recurrence risk for parents of a sporadic case can be reported as low, but not zero. Each child of an affected parent, however, has a 50% risk of inheriting the MFS mutation and thus being affected. Recurrence risk counseling is best accomplished by professionals with expertise in the issues surrounding the disorder.

Bibliography is available at Expert Consult.

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Section 4

Metabolic Bone Disease

Chapter 703

Bone Structure, Growth, and Hormonal Regulation

Russell W. Chesney

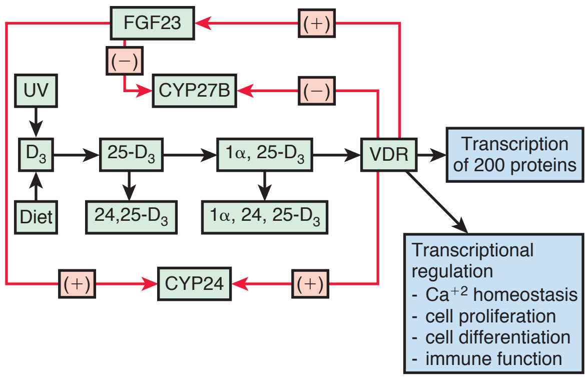

Figure 703-1 **Vitamin D metabolism.** Vitamin D can be synthesized in the skin under the influence of UV irradiation, or it can be absorbed from the diet. It is converted to 25(OH)D_3 (vitamin D_3) in the liver and then further converted by the kidney. The enzyme cytochrome P450 (CYP) 27B converts 25(OH)D_3 to 1α,25-$(OH)_2D_3$. 1,25$(OH)_2D_3$ binds to vitamin D receptor (VDR), which, after transport to the nucleus, acts to induce the transcription of more than 200 proteins. The functions of some of the proteins are indicated. VDR activation leads to productions of fibroblast growth factor 23 (FGF23). FGF23 induces phosphaturia (not shown), upregulates CYP 24, and downregulates CYP 27B.

See also Chapters 51 and 570.

Bone is a rigid organ but metabolically active in that it is constantly being formed **(modeling)** and reformed **(remodeling).** It is capable of rapid turnover, bearing weight, and withstanding the stresses of various physical activities. Bone is the major body reservoir for calcium, phosphorus, and magnesium. Other functions of bone include organ protection, structure, movement, and sound transmission. It is also an endocrine organ that produces fibroblast growth factor 23 (FGF23), which regulates renal phosphate handling. Disorders that affect this organ and the process of mineralization are designated **metabolic bone diseases.**

The human skeleton consists of a protein matrix, largely composed of a collagen-containing protein, osteoid, on which is deposited a crystalline mineral phase. Collagen-containing osteoid accounts for 90% of bone protein; other proteins, including osteocalcin, which contains γ-carboxyglutamic acid, are also present. Synthesis of osteocalcin depends on vitamin K and vitamin D; in states with high bone turnover, serum osteocalcin values are often elevated. Osteocalcin itself acts on insulin secretion and reduction of fat stores.

The microfibrillar matrix of osteoid permits deposition of highly organized calcium phosphate crystals, including hydroxyapatite $[C_{10}(PO_4)_6{\cdot}6H_2O]$ and octacalcium phosphate $[Ca_8(H_2PO_4)_6{\cdot}5H_2O]$, plus less-organized amorphous calcium phosphate, calcium carbonate, sodium, magnesium, and citrate. Hydroxyapatite is deep within bone matrix, whereas amorphous calcium phosphate coats the surface of newly formed or remodeled bone.

Because bone growth and turnover rates are high during childhood, many clinical and osseous features of metabolic bone diseases are more prominent in children than in adults.

The growth pattern of bones is an acceleration of bone growth (length) of the limbs during prepubescence, increased growth (length) of the trunk (spine) during early adolescence, and increased bone mineral deposition in late adolescence. The use of dual-energy x-ray absorptiometry or quantitative CT permits measurement of both mineral content and bone density in healthy subjects and in children with metabolic bone disease. Dual-energy x-ray absorptiometry scanning exposes the patient to less radiation than a chest radiograph.

Bone growth occurs in children by the process of calcification of the cartilage cells present at the ends of bone. In accord with the prevailing extracellular fluid calcium and phosphate concentrations, mineral is deposited in chondrocytes or cartilage cells set to undergo mineralization. The main function of the vitamin D–parathyroid hormone (PTH)–FGF23–endocrine axis is to maintain the extracellular fluid calcium and phosphate concentrations at appropriate levels to permit mineralization.

Other hormones also appear to regulate the growth and mineralization of cartilage, including growth hormone acting through insulin-like growth factors, thyroid hormones, insulin, leptin, ghrelin, and androgens and estrogens during the pubertal growth spurt. Supraphysiologic concentrations of glucocorticoids impair cartilage function and bone growth and augment bone resorption.

Rates of bone formation are coordinated with alterations in mineral metabolism in both the intestine and kidneys, where a number of hormones regulate the processes. Inadequate dietary intake or intestinal absorption of calcium causes a fall in serum levels of calcium and its ionized fraction. This serves as the signal for PTH synthesis and secretion, resulting in greater bone resorption (which raises the serum calcium level), enhanced distal tubular reabsorption of calcium, and promotes higher rates of renal synthesis of $1,25(OH]_2D$ or calcitriol, the most active metabolite of vitamin D (Fig. 703-1). Calcium homeostasis thus is controlled by the intestine because the availability of $1,25(OH)_2D$ ultimately determines the fraction of ingested calcium that is absorbed.

Phosphate homeostasis is regulated by the kidneys because intestinal phosphate absorption is nearly complete and renal excretion determines the serum level of phosphate. Excessive intestinal phosphate absorption causes a fall in serum levels of ionized calcium and a rise in PTH secretion, resulting in phosphaturia, thus lowering the serum phosphate level and permitting the calcium level to rise. Hypophosphatemia blocks PTH secretion and promotes renal 1,25-dihydroxyvitamin D $[1,25(OH]_2D]$ synthesis. This latter compound also promotes greater intestinal phosphate absorption. The important role of FGF23 in phosphate homeostasis is described below.

Vitamin D can be synthesized in the skin under the influence of UV irradiation, or it can be absorbed from the diet. It is converted to $25(OH)D_3$ (vitamin D_3) in the liver and then further converted by the kidney. An understanding of the metabolism of vitamin D is necessary to appreciate mineral homeostasis and metabolic bone disease and rickets. The skin contains 7-dehydrocholesterol, which is converted to vitamin D_3 $[25(OH)D_3]$ by UV radiation; other inactive vitamin D sterols are also produced (see Chapter 51). Vitamin D_3 is then transported in the bloodstream to the liver by a vitamin D–binding protein (DBP); DBP binds all forms of vitamin D. The plasma concentration of free or nonbound vitamin D is much lower than the level of DBP-bound vitamin D metabolites.

Vitamin D also can enter the metabolic pathway by ingestion of dietary vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol), both of which are absorbed from the intestine because of the action of bile salts. After absorption, ingested vitamin D is transported by chylomicrons to the liver, where, along with skin-derived vitamin D_3, it is converted to 25-hydroxyvitamin D [25(OH)D] by the action of a hepatic microsomal enzyme requiring oxygen, nicotinamide adenine dinucleotide phosphate, and magnesium to hydroxylate vitamin D at the 25th carbon atom. The 25(OH)D is next transported by DBP to the kidneys, where it undergoes further metabolism. 25(OH)D is the main circulating vitamin D metabolite in humans (Table 703-1). Because the synthesis of 25(OH)D is weakly regulated by feedback, its plasma level rises in summer and falls in winter. High vitamin D intake raises the plasma level of 25(OH)D to many times above normal, but the parent vitamin D compound itself is absorbed by adipose tissue.

In the kidneys, 25(OH)D undergoes further hydroxylation, depending on the prevailing serum concentration of calcium, phosphate, PTH and FGF23. If the calcium or phosphate level is reduced or the PTH level is elevated, the enzyme 25(OH)D-1-hydroxylase is activated and $1,25(OH)_2D$ is formed. The enzyme cytochrome P450 (CYP) 27B1 converts $25(OH)D_3$ to $1\alpha,25\text{-}(OH)_2D_3$. $1,25(OH)_2D_3$ binds to vitamin D receptor, which, after transport to the nucleus, acts to induce the transcription of 200-400 proteins and peptides. The functions of some of the proteins are known.

Another class of proteins important in the regulation of mineral balance and vitamin D synthesis are the phosphatonins. Among these are FGF23, sFRP-4 (secreted Frizzled-related protein 4), and MEPE (matrix extracellular phosphoglycoprotein). Overexpression of FGF23 results in hypophosphatemia, phosphaturia, reduced serum $1,25(OH)_2D$ values, and some forms of rickets. Disorders of phosphate balance, including hyper- and hypophosphatemia, can relate to loss or gain of function of these phosphatonins (see Fig. 703-1).

Vitamin D receptor activation by $1,25(OH)_2D$ leads to production of FGF23. FGF23 is produced by osteocytes and targets another organ, the kidney, to promote phosphaturia. FGF23 reduces expression/insertion of 2 sodium phosphate transporters into the renal proximal tubule, resulting in higher levels of urinary phosphate excretion. This bone-derived hormone also inhibits renal hydroxylase activity (CYP 27B1) and promotes 24-hydroxylase activity. Consequently, circulating $1,25(OH)_2D$ levels fall.

A gene termed *Klotho* codes for a single-pass transmembrane protein that is an aging suppressor in mice. Klotho protein also influences interaction of FGF23 with its receptor FGF23R. FGF23 is then able to inhibit the action of CYP27B1 and the sodium-dependent phosphate transporter in the kidney. The net result of Klotho FGF23 interaction is reduced $1,25(OH)_2D$ values and phosphaturia.

The active metabolite, $1,25(OH)_2D$, circulates at a level that is only 0.1% of the level of 25(OH)D (see Table 703-1) and acts on the intestine to increase the active transport of calcium and stimulate phosphate absorption. Because 1α-hydroxylase is a mitochondrial enzyme that is tightly feedback regulated, the synthesis of $1,25(OH)_2D$ declines after serum calcium or phosphate values return to normal. Excessive $1,25(OH)_2D$ is converted to an inactive metabolite. In the presence of normal or elevated serum calcium or phosphate concentrations, the renal 25(OH)D-24-hydroxylase is activated, producing 24,25-dihydroxyvitamin D [$24,25(OH)_2D$], which is a pathway for the removal of excess vitamin D; serum levels of $24,25(OH)_2D$ (1-5 ng/mL) increase after ingestion of large amounts of vitamin D (see Fig. 703-1), or in the presence of increased concentrations of FGF23. Although hypervitaminosis D and production of inactive metabolites can occur after oral dosing, extensive skin exposure to sunlight does not usually produce toxic levels of $25(OH)D_3$, suggesting natural regulation of the production of this metabolite in cutaneous tissue.

Serum $1,25(OH)_2D$ levels are higher in children than in adults, are not as subject to seasonal variability, and peak in the 1st yr of life and again during the adolescent growth spurt. These values must be interpreted in light of the prevailing serum calcium, phosphate, and PTH values, and with regard to the entire vitamin D metabolite profile.

Mineral deficiency prevents the normal process of bone mineral deposition. If mineral deficiency occurs at the growth plate, growth slows and bone age is retarded, a condition called *rickets.* Poor mineralization of trabecular bone resulting in a greater proportion of unmineralized osteoid is the condition of osteomalacia. Rickets is found only in growing children before fusion of the epiphyses, whereas osteomalacia is present at all ages. All patients with rickets have osteomalacia, but not all patients with osteomalacia have rickets. These conditions should not be confused with osteoporosis, a condition of equal loss of bone volume and mineral (see Chapter 707).

Rickets may be classified as calcium-deficient or phosphate-deficient rickets. Because both calcium and phosphate ions constitute bone mineral, the insufficiency of either type in the extracellular fluid that bathes the mineralizing surface of bone results in rickets and osteomalacia. The 2 types of rickets are distinguishable by their clinical manifestations (Table 703-2). Rickets can also occur in the face of mineral deficiency, despite adequate vitamin D stores. True dietary calcium deficiency rickets is found in some parts of Africa but rarely in North America or Europe. A form of phosphate-deficiency rickets can occur in infants given prolonged administration of phosphate-sequestering aluminum salts as a treatment for colic or gastroesophageal reflux. This results in the phosphate depletion syndrome.

Table 703-1 Vitamin D Metabolic Values in Plasma of Normal Healthy Subjects

METABOLITE	PLASMA VALUE
Vitamin D_2	1-2 ng/mL
Vitamin D_3	1-2 ng/mL
$25(OH)D_2$	4-10 ng/mL
$25(OH)D_3$	26-70 ng/mL
TOTAL 25(OH)D	30-80 ng/mL [The 2010 Institute of Medicine report states that a value of 25(OH)D above 20 ng/mL is the lower limit of normal.]
$24,25(OH)_2D$	1-4 ng/mL
$1,25(OH)_2D$	
Infancy	70-100 pg/mL
Childhood	30-50 pg/mL
Adolescence	40-80 pg/mL
Adulthood	20-35 pg/mL

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Table 703-2 Clinical Variants of Rickets and Related Conditions

TYPE	SERUM CALCIUM LEVEL	SERUM PHOSPHORUS LEVEL	ALKALINE PHOSPHATASE ACTIVITY	URINE CONCENTRATION OF AMINO ACIDS	GENETICS	GENE DEFECT KNOWN
CALCIUM DEFICIENCY WITH SECONDARY HYPERPARATHYROIDISM [DEFICIENCY OF VITAMIN D; LOW 25(OH)D AND NO STIMULATION OF HIGHER $1,25(OH)_2D$ VALUES]						
Lack of Vitamin D						
Lack of exposure to sunlight	N or L	L	E	E		
Dietary deficiency of vitamin D	N or L	L	E	E		
Congenital	N or L	L	E	E		
Other Deficiencies						
Malabsorption of vitamin D	N or L	L	E	E		
Liver diseases	N or L	L	E	E		
Anticonvulsant drug	N or L	L	E	E		
Renal osteodystrophy	N or L	E	E	V		
Vitamin D–dependent type I	L	N or L	E	E	AR	Y
PRIMARY PHOSPHATE DEFICIENCY (NO SECONDARY HYPERPARATHYROIDISM)						
Genetic Primary Hypophosphatemia	N	L	E	N	XI, AD, AR	Y
X-linked hypophosphatemic rickets					XL	Y
Autosomal dominant hypophosphatemic rickets					AD	Y
Autosomal recessive hypophosphatemic rickets					AR	Y
Fanconi Syndrome						
Cystinosis	N	L	E	E	AR	Y
Tyrosinosis	N	L	E	E	AR	Y
Lowe syndrome	N	L	E	E	XR	Y
Acquired	N	L	E	E		
Phosphate Deficiency or Malabsorption						
Parenteral hyperalimentation	N	L	E	N		
Low phosphate intake	N	L	E	N		
Other						
Renal tubular acidosis, type II proximal	N	L	E	N		Y
Tumor-induced osteomalacia	N	L	E	N		Y
END-ORGAN RESISTANCE TO $1,25(OH)_2D_3$						
Vitamin D-dependent type II (several variants)	L	L or N	E	E	AR	Y
RELATED CONDITIONS RESEMBLING RICKETS						
Hypophosphatasia	N	N	L	Phosphoethanolamine elevated	AR	Y
Metaphyseal Dysostosis						
Jansen type		N	E	N	AD	Y
Schmid type		N	E	N	AD	Y

AD, autosomal dominant; AR, autosomal recessive; E, elevated; L, low; N, normal; V, variable; XL, X-linked; Y, yes.

Chapter 704

Primary Chondrodystrophy (Metaphyseal Dysplasia)

Russell W. Chesney

Skeletal dysplasias are classified under 3 major categories: **osteodysplasias, chondrodysplasias,** and **dysostoses.** The osteodysplasias affect bone density and often lead to osteopenia. The chondrodysplasias are genetic disorders of cartilage and result in deficient linear growth. The dysostoses affect a single bone.

In primary chondrodystrophy, which is an autosomal dominant condition, bowing of the legs, short stature, and a waddling gait appear in the absence of abnormalities of serum levels of calcium and phosphate, alkaline phosphatase activity, or vitamin D metabolites. Metaphyseal chondrodysplasia **(Jansen type)** is very rare and is typified by cupped and ragged metaphyses, which develop mottled calcification at the distal ends of bone over time (Fig. 704-1). Hypercalcemia, with serum values of 13-15 mg/dL, can occur. The spine can also be deformed by the irregular growth of vertebrae. Three different mutations, resulting in ligand independent activation, have been identified in parathyroid hormone receptor type I as the molecular cause of this syndrome, as have some of the downstream target genes that can contribute to the pathogenesis of the disease. The **Schmid type** of metaphyseal chondrodysplasia is less severe, although the radiographic appearance of the knees and extreme bowing of the lower limbs resemble signs seen in patients with familial hypophosphatemia. It is associated with defects in collagen type X, alpha 1, and the hip abnormalities are more debilitating than in Jansen metaphyseal chondrodysplasia. Patients with both types of metaphyseal chondrodysplasia have lifelong short stature.

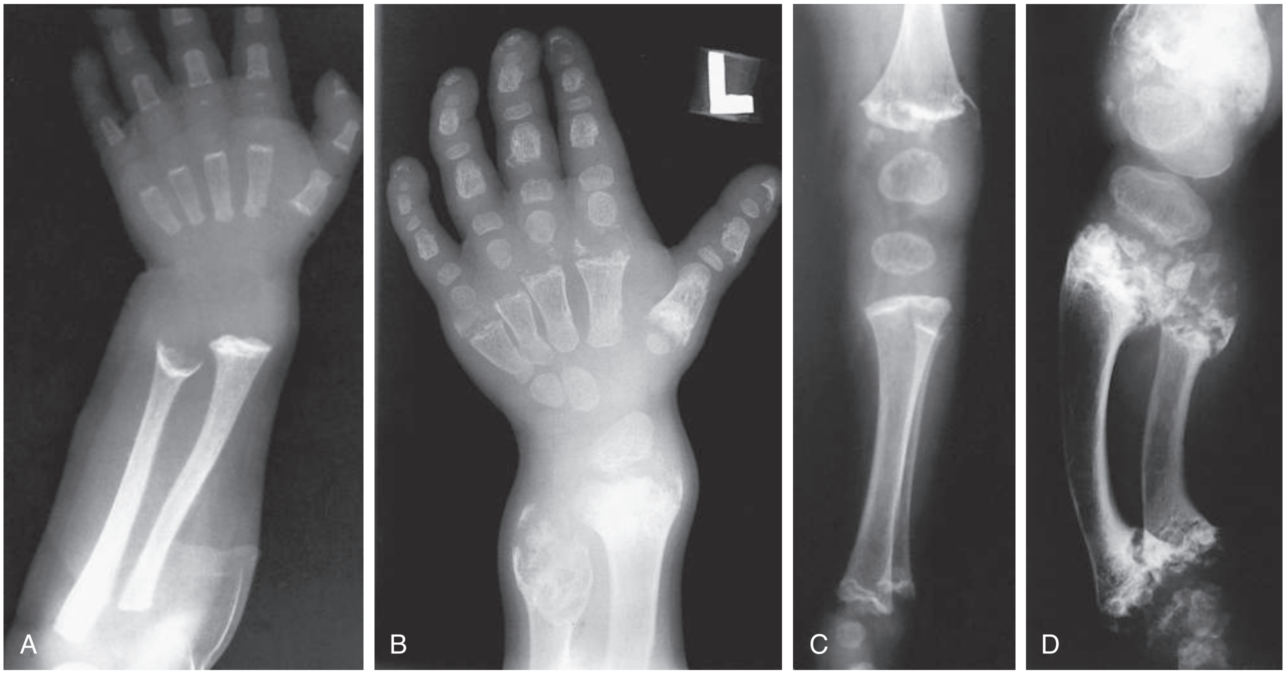

Figure 704-1 Radiographic findings in Jansen-type metaphyseal chondrodysplasia. **A,** At age 1 yr there is severe metaphyseal cupping and splaying at the wrists and also in the hand bones. **B,** At age 7 yr there is increasing metaphyseal change at the wrists with enlarged epiphysis; enlarged epiphyses with wide epiphyseal plates are also present in the hands. **C,** At age 1 yr there are severe metaphyseal irregularities at knees and ankles (femur, tibia, and fibula) and enlarged, rounded epiphyses. **D,** At age 7 yr there are severely fragmented, sclerotic metaphyses, wide epiphyseal plates, and enlarged epiphyses. Radiographic findings in Jansen-type metaphyseal chondrodysplasia. *(From Slovis TL, editor:* Caffey's pediatric diagnostic imaging*, ed 11, Philadelphia, 2008, Mosby.)*

Metaphyseal dysostosis, or **Pyle disease,** results from defects in endochondral bone formation and metaphyseal modeling. The long ends of bones are splayed, resulting in an "Erlenmeyer flask" defect. Short stature is not necessarily characteristic, and serum chemical levels are normal. Leonine features often develop if the facial bones are involved. Metaphyseal dysostosis may also be a clinical feature of Shwachman-Diamond syndrome, a rare autosomal recessive disorder characterized by neutropenia, pancreatic exocrine insufficiency, bone marrow dysfunction, and sometimes severe hematologic complications (see Chapter 448). Allogeneic bone marrow transplantation has been used as a therapeutic approach, with mixed results.

There are no other currently available forms of treatment known to be effective for the chondrodystrophies or dysostosis.

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Chapter 705

Hypophosphatasia

Russell W. Chesney

Hypophosphatasia, which radiographically resembles rickets, is defined by low serum alkaline phosphatase activity and mainly affects the skeleton and teeth. This inherited disorder (with both autosomal recessive and dominant forms) is an inborn error of metabolism in which activity of the tissue-nonspecific (liver, bone, kidney) alkaline phosphatase isoenzyme (TNSALP) is deficient, although activity of the intestinal and placental isoenzymes is normal. Single-point mutations of the gene prevent expression of the activity of this enzyme in vitro and indicate its necessity for normal skeletal mineralization. A large proportion of the more than 100 mutations of the gene identified to date are missense mutations, although splice-site mutations, small deletions, and frameshift mutations also have been found. The only phenotype associated with these mutations is hypophosphatasia. Some patients have a regulatory defect involving this enzyme rather than a mutation.

There is considerable heterogeneity in the severity of the disease and 6 forms of the condition are described. Some cases appear at birth, and diagnosis has even been made in utero by radiographic examination of a fetus. The disease can appear in a lethal neonatal or perinatal form **(congenital lethal hypophosphatasia),** a severe infantile form, or a milder form occurring in childhood or late adolescence **(hypophosphatasia tarda)** (Fig. 705-1). The lethal form is characterized by a moth-eaten appearance at the ends of the long bones, severe deficiency of ossification throughout the skeleton, and marked shortening of the long bones. Patients with mild disease can present with bowing of the legs and variable statural shortening. Hypercalcemia is common in the neonatal and infantile forms, and because calcium accumulation by mature chondrocytes does not occur, patients might appear to have rickets.

Unusual clinical manifestations include wormian bones in the calvariae; poor calcification of the frontal, parietal, and occipital bones; and premature loss of deciduous or permanent teeth, due to hypoplasia of dental cementum. Because of the hypercalcemia in the infantile form, nephrocalcinosis is also found.

In the childhood form, bone pain, frequent fractures, and milder skeletal deformities are evident, as well as premature tooth loss. The metaphyseal defect consists of irregular ossification, punched-out areas, and metaphyseal cupping.

There is an adult form, manifesting in middle age, which is characterized by recurrent metaphyseal stress fractures and femoral pseudofractures. The lethal and infantile forms are autosomal recessive. The milder forms can be either autosomal recessive or dominant.

In hypophosphatasia, large quantities of phosphoethanolamine are found in the urine because this compound cannot be degraded in the absence of TNSALP activity. Plasma inorganic pyrophosphate and pyridoxal-5-phosphate levels are also elevated for the same reason. Pyridoxal-5-phosphate levels tend to be lower than normal in most

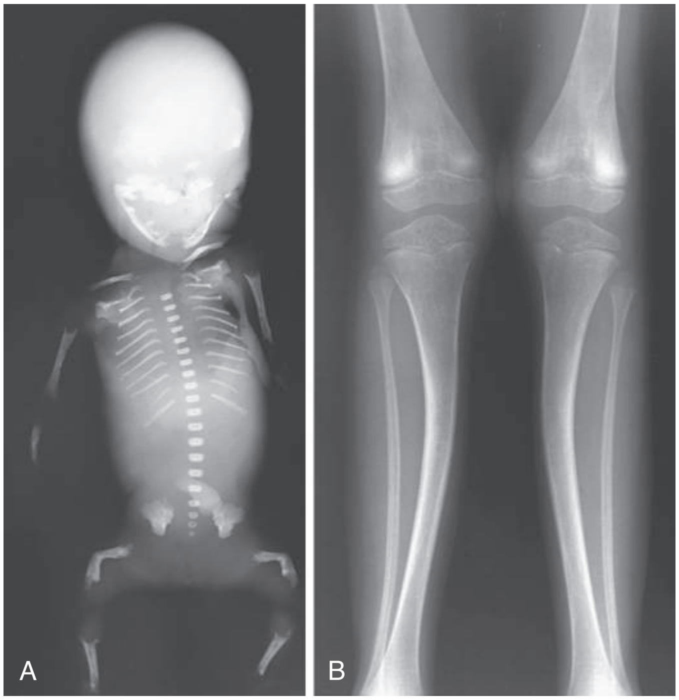

Figure 705-1 **A,** Fetus with congenital lethal hypophosphatasia showing thin wavy ribs, platyspondyly, missing cervical vertebrae, ossification, and bent femurs. **B,** A 7 yr old with hypophosphatasia tarda showing osteopenia, bent tibias, and punched-out metaphyseal lesions.

other bone diseases and hence can aid in the differential diagnosis of hypophosphatasia. Seizures in patients with the lethal and infantile forms of the disease may be related to impaired pyridoxine metabolism. Although no satisfactory therapy has been found, infusion of plasma rich in alkaline phosphatase activity has been helpful in healing bone in short-term studies. Enzyme replacement therapy with recombinant human TNSALP improves skeletal healing and mineral content, pulmonary status, and overall physical activity. Bone marrow transplantation has been successful using donors with normal TNSALP values. The clinical course of this condition often improves spontaneously as an affected child matures, although early death from renal failure or flail chest leading to pneumonia can occur in the severe infantile form of the disorder.

Rare patients presenting with identical clinical and radiographic patterns have normal serum alkaline phosphatase activity. Their disease has been labeled **pseudohypophosphatasia** and might represent the presence of a mutant alkaline phosphatase isoenzyme that reacts to artificial substrates in an alkaline environment (in a test tube) but not in vivo with natural substrates.

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Chapter 706
Hyperphosphatasia

Russell W. Chesney

Hyperphosphatasia is defined by excessive elevation of the bone isoenzyme of alkaline phosphatase in serum and significant growth failure. Osteoid proliferation in the subperiosteal portion of bone results in separation of the periosteum from the bone cortex. Bowing and thickening of the diaphyses are common, along with osteopenia (Fig. 706-1). The disease usually has its onset by 2-3 yr of age, when painful deformity developing in the extremities leads to abnormal gait and sometimes fractures. Other common findings include pectus carinatum, kyphoscoliosis, and rib fraying. The skull is large, and the cranium is thickened (widened diploë) and may be deformed. Skull involvement can lead to progressive and profound hearing loss. Radiographically, the bony texture is variable; dense areas (showing a teased cotton-wool appearance) are interspersed with radiolucent areas and general demineralization. Long bones appear cylindrical, lose metaphyseal modeling, and contain pseudocysts that show a dense, bony halo. There exist several clinical phenotypes.

Figure 706-1 Hyperphosphatasia showing bowing and thickening of the diaphyses and osteopenia. *(From Slovis TL, editor:* Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, Fig. 167-26, p. 2744.)*

In this autosomal recessive disorder, serum levels of both calcium and phosphate are normal, whereas urinary leucine amino acid peptidase activity and serum acid phosphatase levels are increased. This disorder is often called **juvenile Paget disease** because, as in adult-onset Paget disease, calcitonin can reduce the rapid bone turnover found in this disorder; in children, the disorder is more generalized and symmetric. This disorder is distinct from Paget disease because histology of bone reveals a lack of normal cortical bone remodeling and an absence of the classic mosaic pattern of lamellar bone found in the adult condition. Hence, the term *juvenile Paget disease* is inappropriate. A case has been reported in which intense intravenous bisphosphonate (ibandronate) therapy administered over a 3 yr period arrested progression of idiopathic hyperphosphatasia, preventing deformity and disability and improving hearing.

Transient hyperphosphatasia occurs between 2 mo and 2 yr of age, has no associated manifestations other than some mild gastrointestinal symptoms; it is usually detected during routine (screening) laboratory evaluation for some unrelated complaint. Liver and bone isoenzyme fractions are elevated; there are no other manifestations of hepatic or bone dysfunction. Serum alkaline phosphatase values as high as 3,000-6,000 IU/L may be encountered. The cause is unknown. Resolution usually occurs within 4-6 mo.

Familial hyperphosphatemia, an autosomal dominant trait, is another benign condition that is distinguished from the transient infantile form by persistent and asymptomatic elevations of serum alkaline phosphatase levels.

A more serious autosomal dominant variant, expansile skeletal hyperplasia, is characterized by early-onset deafness, premature loss of teeth, progressive hyperostotic widening of long bones causing painful phalanges in the hands, episodic hypercalcemia, and enhanced bone

remodeling. A defect in the gene that encodes receptor activation of nuclear factor γB is relevant. This gene appears to be necessary for osteogenesis, and the defect leads to increased activity of nuclear factor γB in the skeleton.

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Chapter 707
Osteoporosis

Russell W. Chesney

Osteoporosis, the most common bone disorder in adults, is relatively uncommon in children. This disorder is characterized by diminished bone volume and a marked increase in the prevalence of fractures. In contrast to osteomalacia, which shows undermineralization and normal bone volume, histologic sections of bone in all forms of osteoporosis reveal a normal degree of mineralization but a reduction in the volume of bone, especially trabecular bone (vertebral bone). There is a reduction in trabecular bone turnover as well. In osteoporosis, by definition, there is a reduced amount of bone tissue (termed *osteopenia*), which is associated with atraumatic (pathologic) fractures. Osteoporosis in children may be primary or secondary (Table 707-1). The primary osteoporoses can be divided into heritable disorders of connective tissue, including osteogenesis imperfect (see Chapter 701), Bruck syndrome, osteoporosis-pseudoglioma syndrome, Ehlers-Danlos syndrome (see Chapter 659), Marfan syndrome (see Chapter 702), homocystinuria, and idiopathic juvenile osteoporosis. Secondary forms of osteoporosis include various neuromuscular disorders, chronic illness, endocrine disorders, and drug-induced and inborn errors of metabolism, including lysinuric protein intolerance and Gaucher disease.

When no obvious primary or secondary cause can be detected, **idiopathic juvenile osteoporosis** should be considered, especially if the following clinical features are evident: onset before puberty, long-bone and lower back pain, vertebral fractures, long-bone and metatarsal fractures, a washed-out appearance of the spine and appendicular skeleton, and improvement after puberty. Trabecular bones such as the spine and metatarsals are particularly affected by atraumatic fractures.

In general, blood values of minerals, vitamin D metabolites, alkaline phosphatase, and parathyroid hormone are normal. Evaluation of bone mineral content and bone density by dual-energy x-ray absorptiometry or, less often, quantitative CT shows markedly reduced values. Several modes of therapy (including oral calcium supplements, calcitriol, bisphosphonates, and calcitonin) have been used with some success in individual conditions, but the effect of these treatments is difficult to gauge because spontaneous recovery occurs after the onset of puberty in more than 75% of cases.

Osteoporosis-pseudoglioma is an autosomal recessive disorder manifested by variable age at onset, low bone mass, fractures in childhood, and abnormal eye development; the defective gene has been

Table 707-1 Risks for Osteoporosis

ENDOCRINE DISORDERS	**CONNECTIVE TISSUE/BONE DISORDERS**
Female Hypogonadism	Juvenile osteoporosis
Turner syndrome	Osteogenesis imperfecta
Hypothalamic amenorrhea (athletic triad)	Ehlers-Danlos syndrome
Anorexia nervosa	Marfan syndrome
Premature and primary ovarian failure	Homocystinuria
Depot medroxyprogesterone acetate therapy	Fibrous dysplasia
Estrogen receptor α *(ESR1)* mutations	Previous or recurrent low impact fractures
Hyperprolactinemia	Early onset osteoporosis with *WNT1* mutations
Male Hypogonadism	X-linked osteoporosis with fractures with *PLS3* mutations
Primary gonadal failure (Klinefelter syndrome)	**DRUGS**
Secondary gonadal failure (idiopathic hypogonadotropic hypogonadism)	Alcohol
Delayed puberty	Heparin
Hyperthyroidism	Glucocorticosteroids
Hyperparathyroidism	Thyroxine
Hypercortisolism (therapeutic or Cushing disease)	Anticonvulsants
Growth hormone deficiency	Gonadotropin-releasing hormone agonists
Thyrotoxicosis	Cyclosporine
INFLAMMATORY DISORDERS	Chemotherapy
Dermatomyositis	Cigarettes
Chronic hepatitis	**MISCELLANEOUS DISORDERS**
Systemic lupus erythematosus	Immobilization (cerebral palsy, spinal muscular atrophy, Duchenne dystrophy)
GASTROINTESTINAL DISORDERS	Rheumatoid arthritis
Malabsorption syndromes (cystic fibrosis, celiac disease, biliary atresia)	Renal disease
True or perceived milk intolerance	Glycogen storage disease type 1
Inflammatory bowel disease	Chronic hepatitis
Chronic obstructive jaundice	Low calcium dietary intake
Primary biliary cirrhosis and other cirrhoses	Gaucher disease
Alactasia	Severe congenital neutropenia
Subtotal gastrectomy	
BONE MARROW DISORDERS	
Bone marrow transplant	
Lymphoma	
Leukemia	
Hemolytic anemias (sickle cell anemia, thalassemia)	
Systemic mastocytosis	

mapped to chromosome 11q12-13. The mutation is a loss of function in the gene for low-density lipoprotein receptor-related protein 5. Interestingly, gain-of-function mutations result in a gene product that increases bone density.

The life-cycle implications of either significant demineralization or osteoporosis in childhood need to be stressed. Events in childhood influence peak bone mass, and late adolescence is a period of rapid bone mineral accretion. Peak bone mass is achieved by 20-35 yr of age (depending on the bone measured), and the contribution during childhood is considerable. A number of measures influence bone mass: vitamin D (400-800 IU daily), calcium intake (≥1,200 mg/day in adolescents), and weightbearing exercise throughout childhood. Weightbearing exercise enhances bone formation and reduces bone resorption. Other factors that can prevent acquisition of peak bone mass include use of alcohol and tobacco. Excellent sources of dietary calcium include mainly dairy products but also bony fish, green vegetables, and calcium-supplemented drinks (e.g., orange juice). Yogurt and cheeses can be used in lactase-deficient children. Because it appears that adult-onset osteoporosis is the result of a number of genetic factors, thus forming a complex trait interaction, specific interventions during childhood to influence bone mass are not available.

The treatment of secondary osteoporosis is best achieved by treating the underlying disorder when feasible. Hypogonadism should be treated with hormone replacement therapy, especially in thin athletic women (see Chapter 691). Calcium intake should be increased to 1,500-2,000 mg/day. In glucocorticoid-induced osteoporosis, an emphasis on the lowest possible dose to prevent disease activity (inflammatory bowel disease) with alternate-day or topical therapy and the use of inhaled glucocorticoids in asthma is essential. Special diets for inborn errors of metabolism are also appropriate. Celiac disease may be overrepresented in adults with osteoporosis and should be screened for and treated appropriately (see Chapter 338.2). Treatment with bisphosphonates that inhibit bone resorption in certain secondary (glucocorticoid-induced) and adult-onset osteoporosis has been successful. Bisphosphonate therapy is also beneficial in osteogenesis imperfecta and cerebral palsy.

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Rehabilitation Medicine

PART XXXIII

Chapter 708

Principles of Rehabilitation Medicine

Dennis J. Matthews

Pediatric rehabilitative medicine is dedicated to improving the lives and daily function of children with acute and chronic disabilities and to maximizing their potential. It is based on an understanding of the importance of early intervention among those children identified as needing or potentially needing additional support; the development of simpler, culturally relevant surveillance systems that function well in all nations and within all populations within nations; and expanding intervention programs in the scope of services offered and reach of programs.

EPIDEMIOLOGY

The Centers for Disease Control estimates that the prevalence of developmental disabilities in the United States increased by 17% between 1997-1999 and 2006-2008 (Table 708-1). Over the past 3 decades, mortality rates have plummeted among children in lower- and middle-income nations (see Chapter 1). A least a portion of those who formerly would not have survived early childhood have disabilities; it is estimated that more than 200 million children from lower- and middle-income nations have developmental delays or disabilities.

APPROACH

Rehabilitation requires knowledge of the enabling/disabling process and the interrelationships of pathology, impairment, functional ability, and social participation, superimposed on normal development. Rehabilitation management of children with impairments requires the integration and identification of their functional capabilities and selection of the best rehabilitation intervention strategies. A well-designed rehabilitation program can reverse many disabling conditions and can help patients cope with deficits that cannot be reversed by medical care. *The goal of rehabilitation is to maximize an individual's function and participation in society*.

Pediatric rehabilitation medicine uses an interdisciplinary approach to address the prevention, diagnosis, treatment, and management of congenital and childhood-onset impairments, including related or secondary medical, physical, functional, cognitive, psychosocial, and vocational limitations or conditions, with an understanding of the life course of the disability. It requires identifying and managing common pediatric rehabilitation medical conditions and complications, including nutrition, bowel management, bladder management, gastroesophageal reflux, skin protection, pulmonary hygiene and protection, sensory impairments, sleep disorders, spasticity, swallowing dysfunction, and behavioral problems.

Therapeutic treatment includes (1) early intervention, (2) age-appropriate functional training, (3) programs of therapy, (4) play, (5) therapeutic exercise, (6) electrical stimulation and other modalities, (7) communication strategies, (8) oral motor interventions, (9) educational and vocational planning, (10) transitional planning, (11) adjustment to disability support, and (12) prevention strategies.

SCOPE OF PRACTICE

Rehabilitation management of common pediatric problems includes musculoskeletal disorders and trauma, cerebral palsy, spinal dysraphism and other congenital anomalies, spinal cord injury, traumatic and other acquired brain injuries (see Chapter 710), limb deficiency/amputation, neuromuscular disorders, peripheral nerve injuries, and spasticity management.

A significant deleterious effect of childhood disability is inactivity. This is defined as a reduced functional capacity of musculoskeletal and other body systems. It should be considered a distinct diagnosis from the original condition that has led to a curtailment of normal physical function. The main adverse effects are muscle atrophy and weakness, joint contracture, and immobilization osteoporosis.

PREVENTION OF MUSCLE WEAKNESS

Muscle weakness can be reduced by prescribing progressive resistance, stretching, and aerobic exercises. A minimum of once-a-day muscle contraction at 30-50% of maximal strength for 3-5 min, 3 times per wk for a single muscle group, may suffice to prevent muscle loss and weakness. For chronic disuse atrophy with weakness and stiffness, strengthening and stretching exercises may be required for many months, and even then, the child is unlikely to gain normal strength and range of motion.

Stretching to maintain optimal muscle resting length as well as viscoelastic properties is important for maintaining muscle function. Muscles that cross 2 joints, such as the hamstring, gastrocnemius, biceps, and long back extensor muscles, are particularly prone to stiffness. Once a contracture has developed, the treatment is active and passive range-of-motion exercises combined with a sustained terminal stretch on a daily basis. The daily stretching can prevent the loss of sarcomeres in series of immobilized muscles and maintain elongation properties of muscle fibers and surrounding connective tissue, maintaining range of motion.

Stretching techniques include ballistic, static, or passive and neuromuscular facilitation. Prevention of injury and treatment of specific joint injury, as well as the presence and effects of pain or muscle spasms, require modification. The intensity should be a mild degree of tightness without discomfort. Static stretches are held 15-60 sec. Passive and neuromuscular facilitation is a 6 sec contraction followed by 10-30 sec of assisted stretch. Stretching is generally more successful when used in combination with the application of deep heat (i.e., ultrasound). Sustained stretching lasting 2 hr can be obtained by splinting (orthotics, serial casting). In patients with spasticity, chemical denervation (botulinum toxin, phenol blocks) may improve positioning inside the cast or orthotic to improve the tolerance for wearing.

Dynamic splinting provides tension in the desired direction with the use of springs or elastic bands. This type of splinting is often used in the hand and arm because it allows a measure of function while providing stretching. To achieve optimal joint position, it is sometimes necessary to surgically lengthen the contracted tendon.

Maintenance of skeletal mass depends largely on mechanical loading applied to the bone by muscle pull and the force of gravity. Bone mass only increases with repeated loading and increase in muscle strength. Disuse osteoporosis can be prevented by regular use of isotonic exercises, weight bearing, and functional training. Passive loading and standing are of little benefit.

A variety of therapeutic exercise techniques have been developed to address central nervous system dysfunction. Most commonly used are neurodevelopmental techniques using reflex inhibitory patterns to inhibit increased tone along with advanced postural reactions to stimulate recovery. Other therapeutic programs include proprioceptive neuromuscular facilitation. There is no convincing evidence that any

Table 708-1	Specific Developmental Disabilities in U.S. Children Ages 3-17 Yr
DISABILITY	**PERCENT CHANGE BETWEEN 1997-1999 AND 2006-2008**
Any developmental disability	17.1%*
Attention-deficit/ hyperactivity disorder	33.0%*
Autism	289.5%*
Blind/unable to see at all	18.2%
Cerebral palsy	—
Moderate to profound hearing loss	–30.9%
Learning disability	5.5%
Intellectual disability	–1.5%
Seizures, past 12 mo	9.1%
Stuttered or stammered, past 12 mo	3.1%
Other developmental delay	24.7%*

*Statistically significant trend over 4 time periods: 1997-1999, 2000-2002, 2003-2005, and 2006-2008.

From Centers for Disease Control and Prevention, National Center for Health Statistics, NHIS, 1997-2008, https://iacc.hhs.gov/events/2011/slides_coleen_boyle_071911.pdf.

of these methods actually alter the natural history of recovery. These approaches to therapy seem to be most useful in enabling the child to develop compensatory techniques. Using these methods, patients improve performance in and gain independence with such tasks as making transfers, stretching, bed mobility, and safe ambulation.

OTHER ASSIST DEVICES

Rehabilitation often includes prescribing age-appropriate assistive devices and technology to assist environmental accessibility, including orthotics, prosthetics, wheelchairs, positioning, activities of daily living aids, interfaces and environmental controls, and augmentative communication devices. The goal of all assistive devices is to overcome the limitations and improve function and community participation.

Rehabilitation management of children with developmental or acquired disabilities is best accomplished through a medical home and team approach seeking to maximize the child's level of motor, intellectual, emotional, and social functioning.

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Chapter 709

Evaluation of the Child for Rehabilitative Services

Michael A. Alexander

CHILD CHARACTERISTICS

A rehabilitation evaluation starts with *determining physiologic impairments and strengths.* The strengths may turn out to be pivotal in how well the individual compensates for his or her actual impairments. Physiologic impairments are the biologic shortfalls, which limit the child. Many assessment tools are available and professional organizations have developed compendiums of such tools.

The assessment begins with **cognitive issues**. Where is the child in the developmental spectrum in language, social, and emotional abilities? How does the child function in the family, school, and community? Does the presence of an impairment act as an impediment to social acceptance? Poor impulse control, stuttering, or speaking loudly, perhaps because of hearing loss, will all distance a child from other children of the same age group.

Sensory issues need to be evaluated. Are vision, hearing, and other senses present and meeting the needs of the child? Impairment of the sense of touch and position sense may affect the child's extremity function, particularly in the area of fine motor activities. Deficiencies in these skills can also affect how others perceive the child.

For a child who has significant disabilities, the evaluation team needs to include educators, neuropsychologists, social workers, physical therapists, occupational therapists, speech therapists, augmentative communication and device technicians, and seating and adaptive equipment specialists, as well as the physician. The pediatric rehabilitation evaluation is a process that not only looks at the actual impairments but looks to see how they affect the functioning of the individual. Functional substitutions and adaptive equipment and strategies need to be applied by the team to minimize the overall impact of the child's impairments on the child's function, maturation, and separation from family and, ultimately, on the child's function as an adult.

Upper-extremity function is assessed to determine strength, range of motion, and agility. Obviously, weakness of both the arms and legs will result in a greater degree of dysfunction than weakness of only the arms or only the legs. Lower-extremity function affects movement in other environments as well.

For one child, a manual wheelchair may enhance mobility. But children with arm weakness may need electric wheelchairs, with their associated complications. Problems of accessibility, transport, and cost can become significant issues for the family. Fine motor and prehension (the highly complex motor and sensory tasks performed by the hand) tasks are closely assessed because some of these children may need to rely on their ability to interface with access joysticks and computers and strength in these areas may compensate for physical weaknesses.

Skeletal deformities, range-of-motion limitations, and contractures may affect gross motor function, balance, sitting, walking, and climbing. Scoliosis, kyphosis, and pelvic obliquity may limit sitting balance and tolerance, which can secondarily affect upper-extremity function and the amount of time a child is able to socialize.

FAMILY CHARACTERISTICS

The education, vocation, and mental well-being of the parents or caregivers have a dramatic impact on the child. We know that if a child with impairment is to reach maximum potential, a stable and loving family structure facilitates the child's outcome. Does the family have other stressors, such as illness, death, divorce, and legal problems? What are their health care resources?

THE PHYSICAL ENVIRONMENT

Environment assessment begins with the child's room and home. Access to and inside the home should be discussed. How is this child transported? If the child uses power mobility, does the chair travel with the child or does it need to reside at the school or home or elsewhere? How is the child mobile in environments in which the power chair is not available? Is the transport of the child the problem? What is the adequacy, cost, and reliability of the van that is being used by the family? How the child gets in and out of the wheelchair is a significant part of the evaluation. Does the child assist with this, or is the child totally and passively dependent on an adult to move the child from, for example, a toilet seat back to the wheelchair?

In the school, does the child have access to all of the building and can the child participate in all activities in the building, such as those in the art and music rooms, cafeteria, science lab, and stage? Does the

child participate in clubs, teams, and other activities outside of the home?

THE PREVIOUSLY HEALTHY CHILD

For children who have established themselves in the general community and functioned in their environment in a normal capacity but then acquire a significant impairment, it becomes incredibly important to understand what their world looked like before they were affected by this new set of problems. If the child is old enough to remember what life had been like, the loss of function can be devastating. Coping with “what could have been” coupled with what was lost will require the help of skilled psychosocial clinicians.

Chapter 710
Severe Traumatic Brain Injury
Linda E. Krach

Medical rehabilitation is an integral part of the process of assisting families and their children in transitioning from acute medical care after a severe traumatic brain injury (TBI) to reintegration into the community. Table 710-1 lists the quality of care indicators for inpatient pediatric TBI rehabilitation based on a review of evidence and the application of the RAND/UCLA modified Delphi Method.

ETIOLOGY
The cause of TBI varies by age. For young children, ages 0-4 yr, falls and nonaccidental trauma are the most common causes. The major cause of TBI among adolescents >14 yr is motor vehicle traffic. TBI is more common in males than females at all ages.

PATHOPHYSIOLOGY
Brain injury from trauma results from a combination of primary and secondary injury. The mechanism of injury can be different in children because of factors that differentiate them from adults; very young children have open sutures, so they can accommodate some increase in intracranial pressure by an increase in their head circumference or widening of the sutures. Compared with adults, children also have a larger head size compared to their neck musculature, higher brain water content, and less myelination, all of which are thought to contribute to greater brain distortion with resultant injury.

Table 710-1 Quality of Care Indicators for Pediatric Rehabilitation Care After Traumatic Brain Injury

- Dedicated pediatric specialty unit that has at least 1 inpatient with a TBI 90% of the time
- Physical accommodations for family to remain on-site 24 hr/day
- Age-appropriate therapeutic and adaptive equipment
- On-site classroom
- Medical director experienced in pediatric rehabilitation medicine
- Therapists with pediatric training/certification
- Pediatric clinical psychologist, at least 1 certified rehabilitation registered nurse
- 24 hr access to:
  - pharmacy
  - respiratory therapy
  - neurosurgery
  - neurology
  - radiology

ACUTE REHABILITATION
The acute rehabilitation course for children with severe TBI includes addressing multiple medical issues related to the injury in addition to the provision of rehabilitation services. One of these issues is the possibility of seizure activity. Although it is common practice to initiate prophylactic anticonvulsant therapy early after injury, it is appropriate to consider discontinuing this treatment if late seizures have not occurred. Among children, early seizures do not correlate with the later development of epilepsy. The severity of injury, the presence of severe edema, and a very young age at injury increase the likelihood of the later development of **posttraumatic seizures**.

Sleep disturbance is common after TBI and can have an effect on the individual's ability to function (Fig. 710-1). Various approaches, including sleep hygiene, sleep aids, strategic stimulants, cognitive behavioral therapy, strategic caffeine, and naps, can be tried for both the initiation and maintenance of sleep. Other chronotherapy techniques (coordinating the biologic rhythms of a child's body with his/her medical therapy) may be necessary to address sleep–wake cycle abnormalities.

Children with severe TBI may also experience **autonomic dysfunction** characterized by elevated temperature, heart rate, respiratory rate, and blood pressure, accompanied by diaphoresis and posturing. Autonomic dysfunction is a diagnosis of exclusion and is associated with poor outcome after acquired brain injury in children. Autonomic dysfunction develops in approximately 13% of children with acquired brain injury, 10% of those with TBI, and 31% of those with injury as a result of cardiac arrest. Autonomic dysfunction is associated with longer hospital lengths of stay and poorer outcomes.

Acute inpatient rehabilitation emphasizes functional goals and community reintegration. The child and family are integral members of the rehabilitation team. Community reintegration involves careful consultation and planning with the school system to facilitate the transition from hospital to school. In the United States, federal law requires that a physician document that a child had a TBI to qualify for special education services under this disability category. Rehabilitation team consultation with the school team is essential for optimal and expeditious transition back to the school setting. Participation in school is essential for peer interaction and a step toward normalization of the child's life. Schools can adapt to the child's needs rather than providing services in an isolating homebound manner.

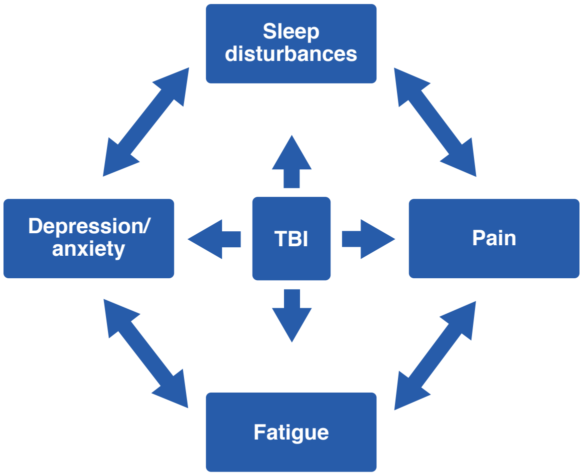

Figure 710-1 Relationship of sleep-related issues among patients recovering from traumatic brain injury. *(From Viola-Saltzman M, Watson NFL: Traumatic brain injury and sleep disorders.* Neurol Clin *30(4):1299–1312, 2012, Flowchart 2.)*

OUTCOMES ASSOCIATED WITH SEVERE TRAUMATIC BRAIN INJURY

The most disabling consequences of TBI are cognitive, particularly those associated with executive function.

In severe TBI, cognition is often the most affected area of functioning and outcomes are associated with preinjury adaptive functioning and family function. Attentional skills may remain impaired in children 10 yr after sustaining a TBI. Subsets of attention appear to be more impaired after TBI, particularly divided and sustained attention.

Other areas of long-term impairment of cognitive performance after pediatric TBI include overall intellectual performance, learning, metamemory, working memory, social competence, and a variety of behavioral concerns. Impairments have been noted in ability to perform self-care activities, communicate, and participate in community and social activities.

PEDIATRIC TRAUMATIC BRAIN INJURY AND PLASTICITY

In the past there has been an assumption that sustaining a TBI at a young age compared to more advanced age would allow for better outcomes because of plasticity. In fact, plasticity may actually be related to poorer outcomes in those injured at a very young age. The major task of childhood is development and learning; a significant TBI can impact the child's ability to learn. Likewise, children do not have overlearned material to fall back on as do adults. There is some evidence that the anticipated changes associated with brain maturation, including cortical thinning of specific regions, do not occur in children who have had TBI at a young age. There are potentially critical periods in development during which a child is more at risk for the effects of a brain injury. Because children are expected to develop cognitive skills over time, the full extent of the impairment from injury might not be recognized until a significant amount of time has elapsed following the injury. For example, if executive function were impaired, one wouldn't expect to see the manifestations of that until adolescence.

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Chapter 711

Spinal Cord Injury and Autonomic Crisis Management

David W. Pruitt and Mary A. McMahon

EVALUATION

The most accurate way to assess a patient who has sustained a **spinal cord injury (SCI)** is by performing a standardized physical examination as endorsed by the International Standards for Neurological and Functional Classification of Spinal Cord Injury (Fig. 711-1). These standards provide the basic definitions of the terms utilized by clinicians caring for patients with SCI. Caution is recommended in utilizing and trusting the anorectal examination portion of this examination in children and youth because of poor interrater reliability.

CLINICAL MANIFESTATIONS

Children with neurologic levels of injury at T6 or above are particularly at risk for interruption and decentralization of the autonomic nervous system. The most common manifestations include bradycardia, hypotension, temperature dysregulation, and, once spinal shock has resolved, **autonomic dysreflexia (AD).** Children and adolescents with cervical and upper level SCI have lower baseline blood pressure compared with the general population. Blood pressure elevations of 20-40 mm Hg above baseline may be considered a sign of AD. AD is a sustained sympathetic response in relation to a noxious stimulus *below* the level of injury. Symptoms resulting from AD typically include hypertension, bradycardia, headache, and flushing of skin above the level of injury. Noxious stimuli are most often localized to bladder or rectal distention, but may include a number of other causes (Table 711-1). Identification and treatment of the noxious stimulus is

Table 711-1 Potential Etiologies of Noxious Stimuli Causing Autonomic Dysreflexia

Urinary System • Bladder distention • Bladder or kidney stones • Blocked/kinked catheter • Detrusor sphincter dyssynergia • Urinary tract infection • Urologic instrumentation • Shock wave lithotripsy	Gastrointestinal System • Bowel distention • Bowel impaction • Gallstones • Appendicitis • Gastric ulcers • Gastritis • Gastrointestinal instrumentation • Hemorrhoids	Integumentary System • Constrictive clothing, shoes, or orthotics • Blisters • Burns, sunburn, or frostbite • Ingrown toenail • Insect bites • Pressure ulcers
Musculoskeletal System • Fractures • Heterotopic ossification • Functional electrical stimulation	Reproductive System–Male • Epididymitis • Scrotal compression (sitting on scrotum) • Sexual intercourse • Sexually transmitted infections	Reproductive System–Female • Menstruation • Pregnancy, especially labor and delivery • Vaginitis • Sexual intercourse • Sexually transmitted infections
Hematologic System • Deep vein thrombosis • Pulmonary embolus	Other Systemic Causes • Boosting (an episode of autonomic dysreflexia intentionally caused by an athlete with spinal cord injury in an attempt to enhance physical performance). • Excessive alcohol intake • Excessive caffeine or diuretic intake • Over-the-counter or prescribed stimulants • Substance abuse	

From Consortium for Spinal Cord Medicine: Acute management of autonomic dysreflexia: individuals with spinal cord injury presenting to health-care facilities, Washington, DC, 2001, Paralyzed Veterans of America, pp 10-11.

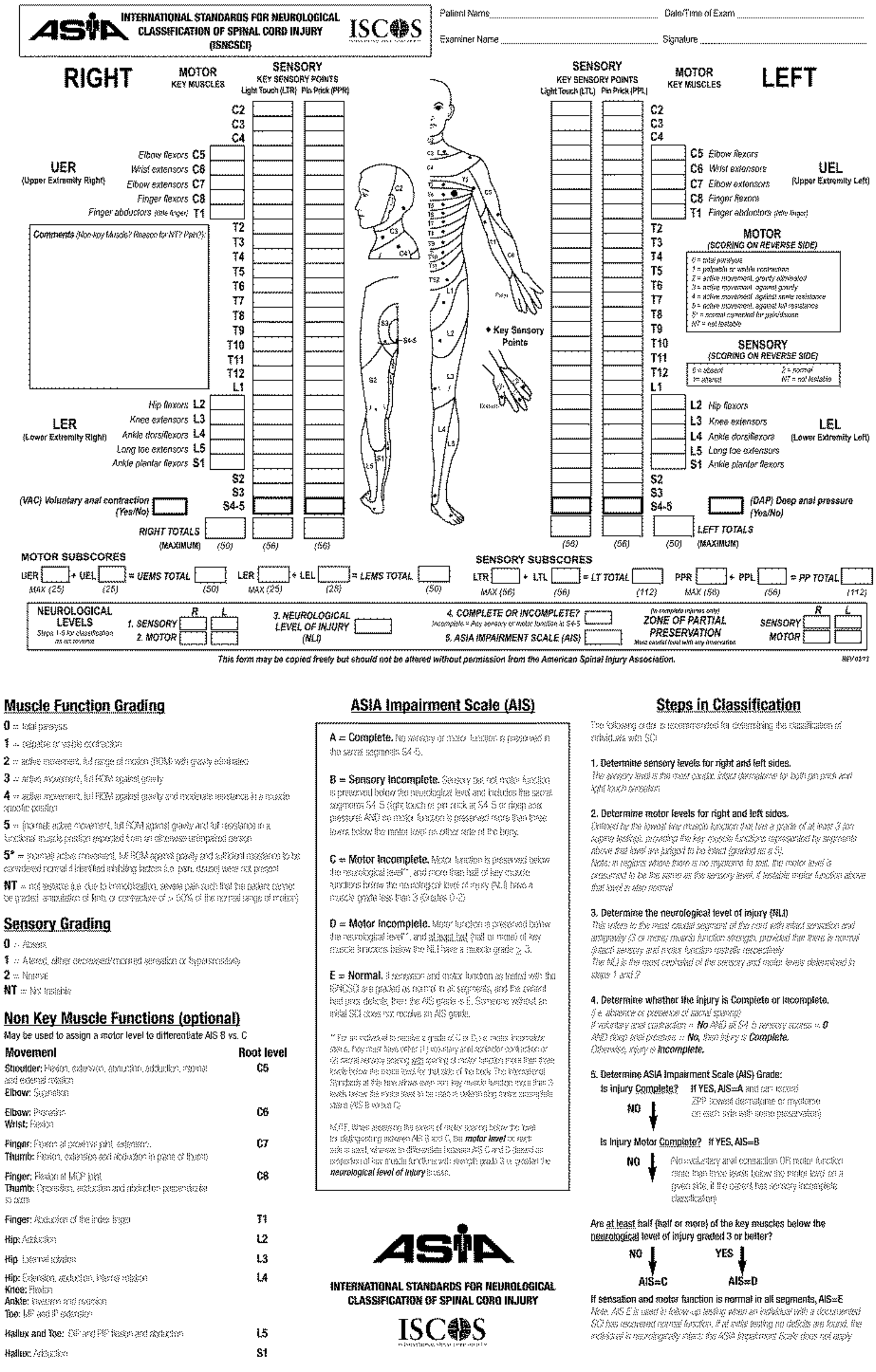

Figure 711-1 American Spinal Injury Association flow sheet. *(From American Spinal Injury Association/International Medical Society of Paraplegia. International standards for neurological and functional classification of spinal cord injury patients. Chicago, 2013, http://www.asia-spinalinjury.org/elearning/ISNCSCI.php.)*

typically associated with resolution of symptoms without the use of antihypertensive medication. If necessary, antihypertensive agents with a rapid onset and short duration, including nifedipine and nitropaste, are advocated (Fig. 711-2). Emergent management of AD is necessary owing to the risk of cerebrovascular accident and additional organ damage as a result of sustained hypertension.

Deep venous thrombosis and **pulmonary embolism** are common, potentially life-threatening conditions in patients with SCI. In children and youth, deep venous thromboses are more common in postpubertal children. Prophylactic treatment, including low-molecular-weight heparin and calf compression pumps, during acute rehabilitation is recommended. Late-occurring deep venous thrombosis most commonly occurs with increased immobilization related to illness or surgery and prophylactic measures should be considered during these situations as well.

Following SCI, the **bladder** can be **areflexic** or **hyperreflexic** and detrusor sphincter dyssynergia is possible. Clean intermittent catheterization is typically used 4-6 times/day to keep bladder volumes below capacity. Anticholinergic medications can improve bladder storage. Asymptomatic bacteriuria, without vesicoureteral reflux, is generally not treated.

Bowel continence requires optimal consistency through the use of diet and medications and planned evacuation, employing aids including gastrocolic reflex, digital stimulation, suppositories, and enemas. Individuals with SCI have increased risk for dysphagia, delayed gastric emptying, ileus, gastric ulceration, pancreatitis, and superior mesenteric artery syndrome.

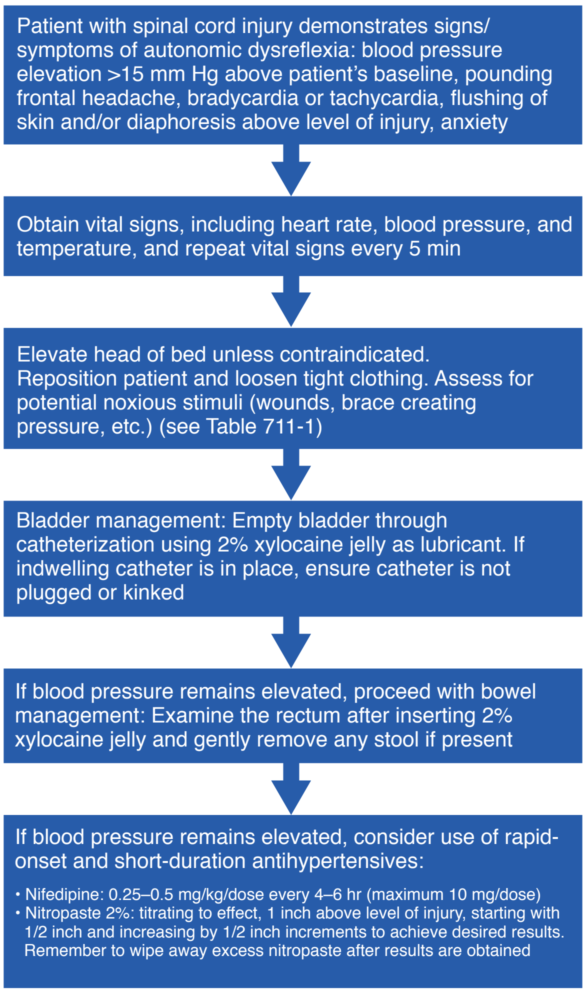

Figure 711-2 Algorithm for management of autonomic dysreflexia.

Frequent monitoring for **skin breakdown** and **pressure ulcers** is necessary both acutely as well as lifelong in individuals with SCI. Common locations include the occiput, elbows, sacrum, ischium, and heels. Devices such as halo vests and splints increase risk. Frequent inspection and repositioning are important means of minimizing risk.

Depending upon the level of the lesion, paralysis of the diaphragm or intercostal and abdominal muscles can result in restrictive ventilatory impairment and ineffective cough. Respiratory muscle training, abdominal binders, and noninvasive ventilation and airway clearance devices, such as the insufflator–exsufflator cough assist device, should be considered in select patients.

Immediately following SCI there is a period of **spinal shock** with low tone and absent reflexes. Eventually, signs of an upper motor neuron lesion will increase, including spasticity and involuntary muscle spasms. Symptoms typically increase with noxious stimulation and can interfere with sleep, comfort, positioning, and care. Management includes pharmacologic therapy, stretching, splinting, and positioning. Focal spasticity can be treated with chemodenervation using botulinum toxin or phenol. Intrathecal baclofen should be considered for severe generalized spasticity.

Increased bone resorption occurs as a result of immobilization. If excessive calcium is not adequately excreted by the kidneys, insidious onset of abdominal pain, nausea, vomiting, lethargy, polydipsia, and polyuria may occur. This **immobilization hypercalcemia** is managed with intravenous fluid hydration at 1.5-2 times the maintenance rate, as well as use of furosemide to hasten the renal excretion of calcium. Complications include nephrocalcinosis, urolithiasis, and renal failure.

Osteopenia begins immediately after an SCI occurs and plateaus 6-12 mo later. **Pathologic fractures** occur as a consequence of loss of bone mineral density. The most common sites of fracture include the supracondylar region of the femur and the proximal tibia; fracture is often associated with gait training, minor trauma, and range of motion. Treatment should include use of removable splints or casts that are well padded over bony prominences to prevent skin breakdown. Prevention through weight bearing and calcium and vitamin D supplementation is encouraged.

Development of spine deformity and scoliosis is prevalent in patients sustaining SCI prior to puberty and many of these individuals will require surgical correction. Because of the high incidence of scoliosis, radiographs of the thoracolumbar-sacral spine should be obtained every 6 mo prior to skeletal maturity and every 12 mo thereafter.

An SCI will impact the child's social-emotional development, so adjustment should be monitored closely. Positive coping strategies and strong social supports are associated with greater social participation. Education regarding sexual development and function with SCI injury should be provided.

PROGNOSIS

Prognosis for recovery of neurologic deficits resulting from SCI depends on the neurologic level of injury and level of completeness. Examination at least 72 hr after injury has been determined a better indicator of the prognosis than examinations done earlier. It is prudent for those determining and communicating the diagnosis to understand the particularities and limitations of the anorectal examinations, and thus completeness of injury, unique to children. Those individuals with incomplete injury tend to have increased likelihood of neurologic recovery. The neurologic level of injury can be assistive in determining the level of independence with functional activities (Table 711-2).

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Table 711-2 Projected Functional Outcomes at 1 Yr after Injury and/or Diagnosis According to Neurologic Level of Injury

	C1-C4	C5	C6	C7	C8-T1
Feeding	Dependent	Independent with adaptive equipment after set-up	Independent with or without adaptive equipment	Independent	Independent
Grooming	Dependent	Minimal assistance with equipment after set-up	Some assistance to independent with adaptive equipment	Independent with adaptive equipment	Independent
Upper-extremity dressing	Dependent	Requires assistance	Independent	Independent	Independent
Lower-extremity dressing	Dependent	Dependent	Requires assistance	Some assistance to independent with adaptive equipment	Usually independent
Bathing	Dependent	Dependent	Some assistance to independent with equipment	Some assistance to independent with equipment	Independent with equipment
Bed mobility	Dependent	Assistance	Assistance	Independent to some assistance	Independent
Weight shifts	Independent in power; dependent in manual wheelchair	Assistance unless in power wheelchair	Independent	Independent	Independent
Transfers	Dependent	Maximum assistance	Some assistance to independence on level surfaces	Independence with or without board for level surfaces	Independent
Wheelchair propulsion	Independent with power Dependent with manual	Independent in power; independent to some assistance in manual with adaptations on level surfaces	Independent–manual with coated rims on level surfaces	Independent–except curbs and uneven terrain	Independent
Driving	Unable	Independent with adaptations	Independent with adaptations	Car with hand controls or adapted van	Car with hand controls or adapted van
	T2-T9		**T10-L2**		**L3–L5**
Activities of daily living (grooming, feeding, dressing, bathing)	Independent		Independent		Independent
Bowel/bladder	Independent		Independent		Independent
Transfers	Independent		Independent		Independent
Ambulation	Standing in frame, tilt table, or standing wheelchair Exercise only		Household ambulation with orthosis		Community ambulation is possible

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Chapter 712

Spasticity

Joyce L. Oleszek and Loren T. Davidson

Spasticity is a component of the upper motor neuron syndrome characterized by velocity-dependent resistance to passive range of motion resulting in tonic stretch reflexes and accompanied by exaggerated tendon jerks. Spasticity management is determining what degree of spasticity may be tolerable and of functional benefit vs counterproductive and potentially injurious. When devising a treatment plan, both the positive and negative effects of spasticity on function must be considered; treatment should maximize function while minimizing sedation and adverse effects.

ORAL MEDICATIONS

Oral medications are often used as an early treatment for generalized spasticity (Table 712-1). Although efficacy of certain antispasmodics has been demonstrated, their use should be contingent upon functional benefit as adverse effects are quite common. Frequently used medications include baclofen, benzodiazepines (diazepam, clonazepam), dantrolene sodium, tizanidine, and clonidine.

GABAergic Medications

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter of the central nervous system. The 2 most relevant GABA receptors for the purposes of pharmacologic management of spasticity are $GABA_A$ and $GABA_B$. **Benzodiazepine medications** exert their effect through

Table 712-1 Dosing Guidelines, Pharmacologic Actions, and Adverse Event Profile of Commonly Prescribed Oral Antispasmodic Medications for Children

ORAL MEDICATION (DOSE/FREQ., AGE/ WEIGHT RANGE)	MODE OF ACTION	ADVERSE EVENTS/PRECAUTIONS
Baclofen (0.125-1 mg/kg/day) *Dosing guideline* *2-7 yr* 2.5-10 mg tid-qid (10-40 mg/day) *8-12 yr* 5-15 mg tid-qid (15-60 mg/day) *12-16 yr* 5-20 mg tid-qid (20-80 mg/day) *Note:* Caution advised with renal impairment, consider reducing dose.	Centrally acting, structural analog of γ-aminobutyric acid (GABA), binds to $GABA_B$ receptors of presynaptic excitatory interneurons (and postsynaptic primary afferents) causing presynaptic inhibition of monosynaptic/polysynaptic spinal reflexes. Rapid absorption, blood level peaks in 1 hr, half-life 5.5 hr. Renal (70-80% unchanged) and hepatic (15%) excretion.	Central nervous system (CNS) depression (sedation, drowsiness, fatigue), nausea, headache, dizziness, confusion, euphoria, hallucinations, hypotonia, ataxia, paresthesias. **Note: Abrupt withdrawal** may cause seizures, hallucinations, rebound muscle spasms, and hyperpyrexia.
Diazepam (0.12-0.8 mg/kg/day) *Dosing guideline* 6 mo-12 yr 0.12-0.8 mg/kg/day PO divided q6-8h >12 yr 2-10 mg PO bid-qid *Note:* Prescription of a *qhs* dose only or proportionately larger dose at bedtime may limit excessive daytime sedation.	Centrally acting; binds to $GABA_A$ receptors mediating presynaptic inhibition in brainstem reticular formation and spinal polysynaptic pathways. Rapid absorption; blood level peaks in 1 hr, with half-life of 30-60 hr. Metabolized in liver, producing pharmacologically active metabolites with long duration of action. Increased potential for adverse effects with low albumin levels as a result of being 98% protein bound.	CNS depression (sedation, impaired memory and attention), ataxia. Dependence/potential for substance abuse/overdose. Withdrawal syndrome (including anxiety, agitation, irritability, tremor, muscle twitching, nausea, insomnia, seizures, hyperpyrexia).
Dantrolene Sodium (3-12 mg/kg/day) *Dosing guideline (for children >5 yr old):* *6-8 mg/kg/day PO divided bid-qid* In children >5 yr old Start 0.5 mg/kg qd-bid for 7 days, then 0.5 mg/kg tid for 7 days, then 1 mg/kg tid for 7 days, then 2 mg/kg tid to a maximum of 12 mg/kg/day or 400 mg/day.	Peripheral action, blocking release of calcium from sarcoplasmic reticulum with uncoupling of nerve excitation and skeletal muscle contraction. Blood level peaks in 3-6 hr (active metabolite 4-8 hr), with half-life of approximately 15 hr. Metabolized largely in liver, with 15-25% of nonmetabolized drug excreted in urine.	Malaise, fatigue, nausea, vomiting, diarrhea, muscle weakness with high dose. *Note:* Hepatotoxicity (baseline liver function tests **must** be checked prior to starting dantrolene, tested weekly during dose titration, and regularly every 1-2 mo thereafter). Drug *should be discontinued* promptly if liver enzymes become elevated.
Tizanidine *Dosing guideline* In children <10 yr: Commence 1 mg orally at bedtime initially, increasing to 0.3-0.5 mg/kg in 4 divided doses. In children >10 yr: Commence 2 mg orally at bedtime initially, increased according to response, maximum 24 mg/day in 3-4 divided doses.	Centrally acting, α_2-adrenoceptor agonist activity at both spinal and supraspinal sites. Prevents release of excitatory amino acids, facilitating presynaptic inhibition. Good oral absorption, blood level peaks in 1-2 hr, with a half-life of 2.5 hr. Extensive first-pass hepatic metabolism with urinary excretion of inactive metabolites.	Dry mouth, drowsiness, tiredness, headache, dizziness, insomnia, anxiety, aggression, mood swings, visual hallucinations, risk of hypotension (although 10 times less antihypertensive potency than clonidine), nausea, vomiting, and constipation. Liver function tests should be monitored at baseline, 1, 3, and 6 mo. Then periodically.
Clonidine *Dosing guideline* 0.025-0.1 mg in 2-3 divided doses. *Note:* A retrospective chart review of literature about clonidine in children reported an average dosage based on weight was 0.02-0.03 mg/kg/day (0.4-0.5 mg/day), with a range of 0.0014-0.15 mg/kg/day.	Centrally acting, mixed α-adrenoceptor agonist with predominant α_2 activity causing membrane hyperpolarization at multiple sites in brain, brainstem, and dorsal horns of spinal cord. Inhibition of substance P may also contribute to tone reduction via an antinociceptive effect. Rapidly absorbed orally, blood level peaks in 1-1.5 hr, with a half-life of 6-20 hr.	Drowsiness, dry mouth, bradycardia, orthostatic hypotension. Abrupt cessation may result in rebound hypertension.

$GABA_A$ receptors by increasing the affinity of GABA for the $GABA_A$ receptor. This results in presynaptic inhibition and a net inhibitory effect at both spinal and supraspinal levels. Of the benzodiazepines, **diazepam** is the oldest and most commonly used medication to treat spasticity because of its long half-life and need for less-frequent administration. In children <2 yr of age, **clonazepam** is a good option because of the availability of a liquid formulation and dosing guidelines. The cognitive effects of benzodiazepines limit its use in persons with severe spasticity as dose escalation results in increased sedation. Furthermore, sedation and cognitive slowing limit the usefulness of benzodiazepines in persons with spasticity of cerebral origin as it may impede recovery in acquired brain injury and cognitive development in congenital developmental delay. The use of benzodiazepines may lead to physiologic dependence, and, thus, abrupt discontinuation should be avoided to prevent withdrawal.

Baclofen is a $GABA_B$ agonist and is a preferred agent in the treatment of spasticity of spinal origin. Baclofen exerts an inhibitory effect on both monosynaptic and polysynaptic spinal reflexes. Unfortunately, supraspinal receptor sites also exist, resulting in sedation, which is common to all GABAergic medications. In most instances, daytime dosing of oral baclofen is better tolerated than benzodiazepines with regard to sedation. Intrathecal administration of baclofen via a baclofen pump (see below) allows greater selectivity of spasticity reduction while minimizing adverse cognitive effects. Abrupt cessation of both oral and intrathecal baclofen therapy *must be avoided* as it may result in a life-threatening withdrawal response.

α_2-Adrenergic Agents

Clonidine and **tizanidine** are examples of centrally acting α_2-adrenergic agents that decrease spasticity and have an antinociceptive effect. Clonidine is the older of the 2 agents and is used more frequently as an antihypertensive agent. Clonidine exerts its effect on spasticity via both presynaptic inhibition of sensory afferents, as well as release of glutamate at the level of the spinal cord. Adverse effects of clonidine that limit its use as an antispasmodic include hypotension, bradycardia, sedation, cognitive impairment, and xerostomia.

Tizanidine is an α_2-noradrenergic agonist that is as effective as diazepam and baclofen in tone reduction. In comparison to clonidine, tizanidine has less-potent hemodynamic effects, which is desirable when it is used primarily for spasticity reduction. The half-life of tizanidine is approximately 2.5 hr, requiring frequent dosing to maintain a steady state. Adverse effects of tizanidine include hypotension, sedation, xerostomia, dizziness, hallucination, and hepatotoxicity.

Peripherally Acting Calcium Blockers

Dantrolene sodium works at the level of skeletal muscle to block calcium release from the sarcoplasmic reticulum. Despite its peripheral site of action, dantrolene may induce sedation, although to a lesser degree than other centrally acting agents. Dantrolene is effective at decreasing both clonus and spasticity but achieves this by weakening skeletal muscle in a nonselective fashion. The resultant generalized weakness seen with dantrolene use limits its utility in ambulatory patients. Dantrolene has a rare but significant adverse event of fatal hepatotoxicity in less than 1% of patients. Hepatotoxicity risk increases with increasing age, increasing dose, and female sex.

Pediatric dosing of spasticity medications is quite variable and needs to be tailored to the response of the child. The choice of medication is often based on personal experience and the impact of benefit vs potential adverse effects. See Table 712-1 for dosing guidelines.

SURGICAL MANAGEMENT

Surgical management of spasticity should be considered when spasticity causes significant functional impairments that are refractory to more conservative management. Combining treatment options such as injections and systemic medications can be very effective.

Botulinum toxin (BTX) intramuscular injections and **phenol/alcohol neurolysis** are used to treat focal areas of spasticity. These injections are most effective in children with hypertonia localized to specific muscles and those without significant contracture. BTX blocks signal transmission at the neuromuscular junction by preventing the release of acetylcholine from the presynaptic axon of the motor end plate. Treatment with BTX type A is most common but BTX type B is also used. The period of clinically useful relaxation is usually 12-16 wk and it is recommended that injections be spaced a minimum of 3 mo apart because of concern for neutralizing antibody formation. Adverse events related to BTX are rare and include injection-site pain and focal muscle weakness. The FDA requires black box labeling on BTX products cautioning that the effects of the BTX may spread from the area of injection to other areas of the body, causing symptoms similar to botulism. Coadministration of BTX and aminoglycosides or other agents interfering with neuromuscular transmission (curare-like nondepolarizing blockers, lincosamides, polymyxins, quinidine, magnesium sulfate, anticholinesterases, succinylcholine chloride) should be performed with caution as the effect of the toxin may be potentiated. BTX-A is an effective and generally safe treatment for spasticity of the upper and lower extremities; evidence regarding functional improvement is conflicting. Long-term use of BTX-A with repeated rounds of injections in children with cerebral palsy is safe and efficacious. BTX-A injections into the gastrocnemius can be combined with serial casting to help improve ankle range and gait.

Phenol perineural injections are typically performed in the large proximal muscles (biceps brachii, hip adductors, hamstrings) and duration of clinical effect may be longer than BTX, varying between 3 and 18 mo. Phenol injection of the anterior branch of the obturator nerve in children with cerebral palsy is safe and effective. The low cost of phenol is a significant advantage over BTX, but the need for electrical stimulation guidance and general anesthesia may offset any cost savings. Combining phenol injections with BTXs allows an increased number of affected muscles to be injected at the maximal recommended dose during one procedure. Phenol is safe in children, but transient sensory dysesthesias occur rarely.

Intrathecal baclofen (ITB) is highly effective in treating severe spasticity. ITB is delivered to the intrathecal space via a surgically implanted infusion pump and catheter. This method of delivery confers an advantage over enteral baclofen in that central nervous system depressive effects are minimized and dosages can be titrated to functional effect. A preoperative screening bolus dose of baclofen can be delivered via lumbar puncture and is used to evaluate responsiveness and impact on functional abilities. Goals of treatment, whether they are to improve function, comfort, and/or care, need to be firmly established. Cost and maintenance can be prohibitive for some families. Catheter tips are typically positioned at C5-T2 but can be placed intraventricularly for severe dystonia. ITB is effective in children with cerebral palsy; there may be a significant reduction in upper- and lower-extremity spasticity for up to 10 yr. Speech, communication, and saliva control can improve after ITB. The most frequent and serious adverse events related to device and implant procedures are catheter dislodgement from the intrathecal space, catheter break/cut, and implant site infection, including meningitis. Electromagnetic interference and MRI may cause transient operational changes to the pump and changes in flow rate. Although baclofen pumps do not prohibit MRI imaging, it is recommended that the pump be "interrogated" by a programmer after MRI as a precaution. ITB pumps need to be replaced every 5-7 yr for end of battery life. The pump comes in a 20 mL and 40 mL size, both of which measure 8.75 cm in diameter. The baclofen pump requires regular refills at 2-6 mo intervals depending on dose rate and pump size, and refills are readily performed in an outpatient clinic setting. **ITB withdrawal** is a medical emergency and needs to be identified early and managed aggressively. Sequelae can include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity that, in rare cases, can advance to rhabdomyolysis, multiple organ–system failure, and death. Prevention of abrupt discontinuation of ITB requires careful attention to programming and monitoring of the infusion system, refill scheduling, and pump alarms. Caregivers need to be educated about the early symptoms of baclofen withdrawal.

Selective dorsal rhizotomy (SDR) is a surgical procedure that has been widely used as a treatment for spasticity. The surgical technique

involves single-level or multilevel osteoplastic laminectomies exposing the L2-S1 nerve roots. Typically, 25-70% of dorsal rootlets are selectively cut with the aid of electrophysiologic monitoring. Children 3-8 yr of age with spastic diplegia, minimal upper-limb involvement, good selective motor skills and strength, and minimal contractures are the best candidates for SDR. The preoperative ability to rise from a squatted position with minimal support or a younger child's ability to crawl on hands and knees are positive predictors for a good outcome with SDR. Children must have the cognitive and social capacity for the requisite intensive postoperative therapy program. Long-term outcomes 5 and 20 yr after SDR in children show an improvement in spasticity, motor function, and gait pattern. SDR can reduce the need for orthopedic surgeries, with 35% of children avoiding surgery; this might be more likely if SDR is performed before the age of 5 yr. Long-term complications such as sensory dysfunction, bladder or bowel dysfunction, or back pain are infrequent. A concern with multilevel laminectomies is the potential increased risk of spinal deformities, but there is no clear evidence to support this.

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Chapter 713

Birth Brachial Plexus Palsy

Maureen R. Nelson

Birth brachial plexus palsy (BBPP) may cause significant arm weakness and subsequent functional deficits in children. The nerves to the arm are affected with variable degrees of weakness and sensory loss. Most children will have good recovery spontaneously, but functional deficits will remain in 20-30% of children with BBPP (see Chapter 99.7).

The mechanism for birth brachial plexus injury appears to be a lateral stretch of the plexus for the vast majority of cases. Anatomic variations in bones, blood vessels, and tendons lead to a very small number of cases. The incidence of BBPP is reported as 0.5-4.6 per 1,000 live births, with variability thought to be attributable to the type of obstetric care and the size of infants around the world.

Risk factors for birth brachial plexus injury include prior infants with BBPP, shoulder dystocia, birthweight greater than 4 kg, multiparous mothers, mothers with excessive weight gain, and diabetic mothers. Delivering twins or triplets, as well as cesarean sections, have been described as protective from BBPP.

Nerve injuries include neurapraxia, neurotmesis, and axonotmesis. *Neurapraxia* is the least severe of these types and is a reversible loss of nerve conduction. This type will recover. *Neurotmesis* is the most severe and is a total and complete disruption of the nerve; an *avulsion* describes a rupture of a preganglionic lesion, and a *rupture* describes the same event in a postganglionic lesion. *Axonotmesis* is the intermediate form and the most difficult to delineate. There is disruption of the epineurium with variable injury to the axons (Fig. 713-1). Nerves are made of groups of fascicles, which, in turn, are made of groups of axons. This type of lesion contributes greatly to the diagnostic dilemma and difficulty in prediction of recovery.

The brachial plexus consists of the anterior primary rami, or roots, from C5, C6, C7, C8, and T1 (Fig. 713-2). The trunks of the brachial plexus consist of C5-C6 forming the upper trunk, C7 forming the middle trunk, and C8-T1 forming the lower trunk; each trunk has anterior and posterior divisions. The posterior cord is formed from the posterior division of each trunk. The medial cord comes from the anterior division of the lower trunk. The lateral cord is formed from the anterior divisions of the upper and middle trunks. Evaluation of the roots, trunks, and cords from which the nerves arise helps determine the site of injury.

Erb palsy is generally described as the upper trunk or C 5-6 palsy. It is by far the most common injury seen in birth brachial plexus injury, present in three fourths of infants. It also demonstrates the greatest recovery rate at >80% with a functional arm. *Klumpke palsy,* C8-T1, is extremely rare in BBPP, likely not occurring except in the case of anatomic variation. If a baby presents with a C8-T1 deficit, the baby most likely originally had a complete C5-T1 BBPP and then had recovery of the upper portion of the plexus. This can happen because C4, C5, C6, and sometimes C7 are protected coming out from the spinal cord, held in a gutter along the transverse processes by connective tissue, whereas C8 and T1 are not. The sensory fibers are also relatively protected compared to the motor fibers because the sensory fibers run together until outside of the spinal cord into the dorsal root ganglion where their cell bodies lie. The motor fibers have the cell bodies within the spinal cord and so are not as cohesive in their path. Therefore the sensory fibers may be spared while motor fibers show clinical deficits. A C8-T1 deficit may also result from a spinal cord injury. Consequently, it is important to check for any other indications of spinal cord injury throughout the body. Consideration also must be given to the potential of an anatomic variation, such as an anomalous rib, that may actually cause a C8-T1 deficit alone.

Because various parts of the brachial plexus have different risks of injury, the clinical presentation can be quite variable, causing the diagnosis to be challenging. The phrenic nerve may also be involved with its innervation from C3, C4, and C5, with potential respiratory concerns.

Included in the differential diagnosis of an infant with an arm deficit is the possibility of a fracture of the humerus or clavicle, osteomyelitis, a tumor, or congenital varicella infection, all of which may lead to the limited ability to move the arm.

PHYSICAL EXAMINATION

The physical examination of the child begins with observation. Examination for sensation, particularly examining for sharp sensation, useful in its own right, will also frequently help with active motor evaluation in infants. Assessment of muscle stretch reflexes is important in that infants with a brachial plexus palsy will be areflexive or hyporeflexive in the involved arm. Evaluation of primitive reflexes, particularly the Moro reflex, is helpful as most of these infants will have C5-6 involvement and therefore the Moro may show shoulder abduction and elbow flexion on 1 side but not the involved side. Range-of-motion examination is critical. Deficits are commonly seen because of the imbalance of muscles that are active and those that are not. Shoulder adduction and internal rotation is a common position, as is elbow flexion, forearm pronation, and wrist and finger flexion. The size of the involved arm may also be smaller because of muscle atrophy and sometimes shorter length and smaller diameter of the bone. In children with very severe deficits, the arm may be cooler because of the sympathetic nervous system outflow at T1. **Torticollis** is commonly present and almost always with the face turned away from the involved arm.

Among older infants and children, compensatory movements of the arm may be noted. Common examples are use of trunk momentum to move (particularly to rotate) the proximal arm, hyperlordosis of the lumbar spine to position the arm more advantageously, use of the pectoralis muscle to flex the shoulder, and use of the knee to physically flex the elbow. Examination of the back for symmetry, along with the scapulae for winging, is also relevant. Having the older child manipulate buttons, snaps, or zippers, throw and catch a ball, and write, print, or color may be revealing.

LABORATORY EXAMINATION

Radiographic evaluation may be needed. Plain films can be viewed immediately if there is reason to consider clavicle or humerus fracture, infection, osteomyelitis, or tumor. Ultrasound shows the nerves and this is improving as technology advances. MRI and CT myelogram are used for evaluation of nerve roots and nerves.

Electrodiagnostic evaluation may also contribute to the diagnosis. Sensory nerve conduction studies are very useful in a child with severe

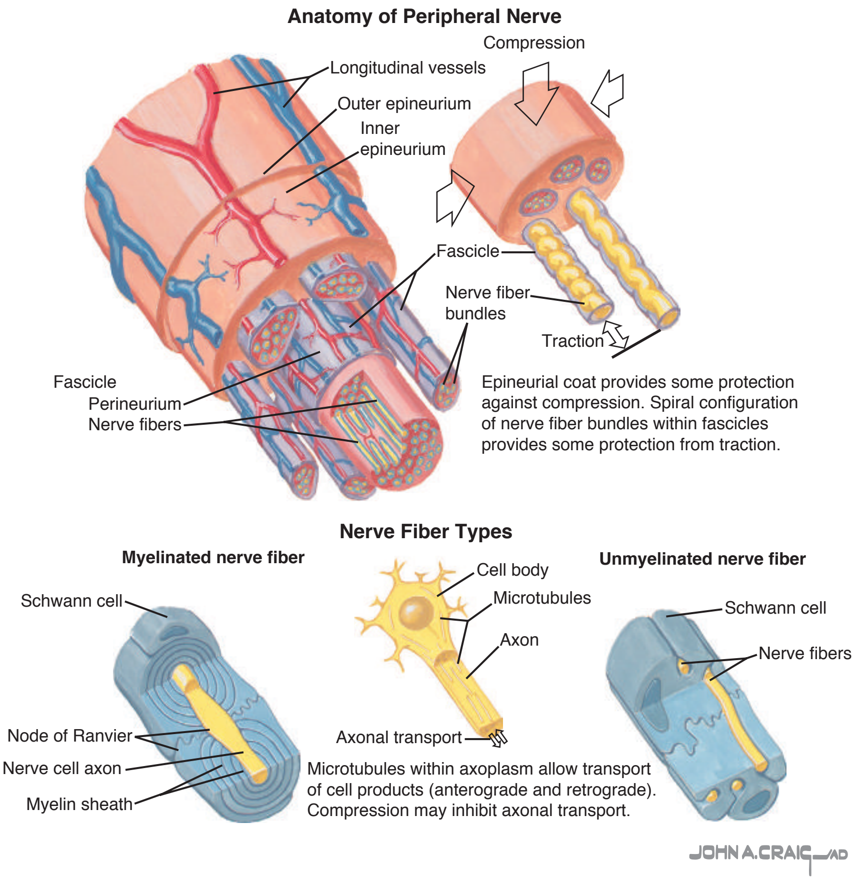

Figure 713-1 Anatomy of peripheral nerve. *(Netter illustration from www.netterimages.com. Elsevier, Inc. All rights reserved.)*

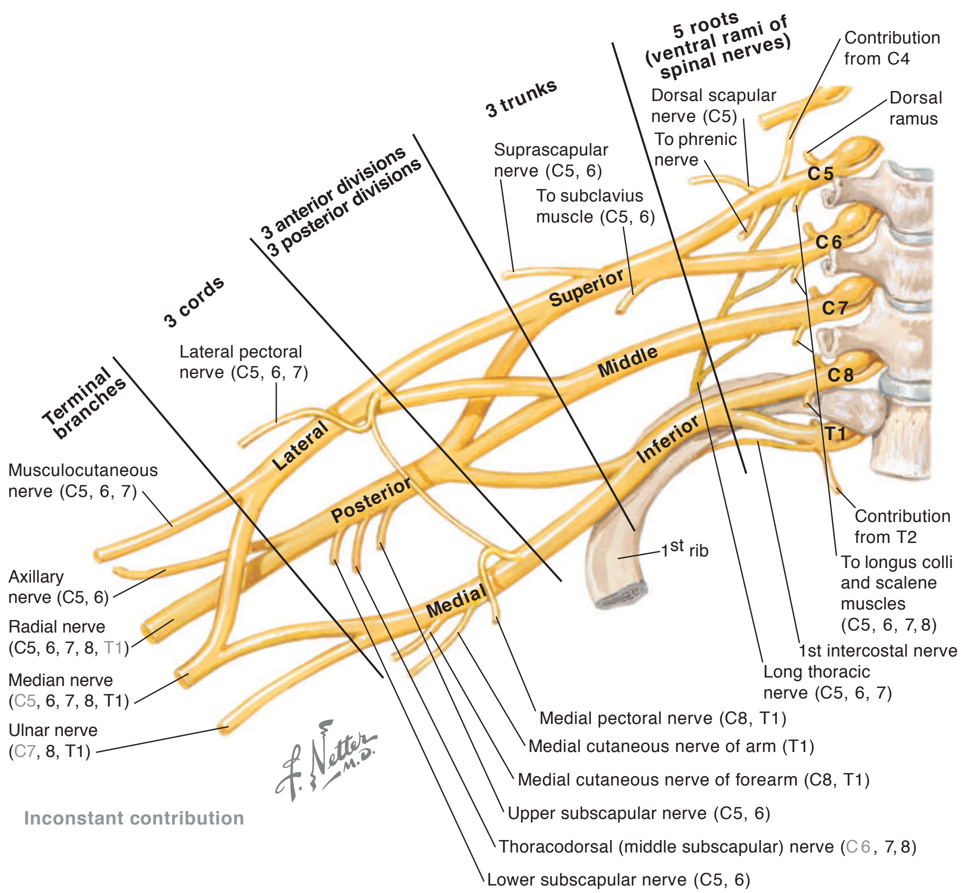

Figure 713-2 Schematic of the brachial plexus. *(Netter illustration from www.netterimages.com. Elsevier, Inc. All rights reserved.)*

injury who has insensate areas. Normal sensory response in areas where the child cannot feel indicates a *preganglionic neurotmesis* (avulsion). Motor nerve conduction studies are useful to check for continuity of nerve fibers to muscles that are weak or paralyzed. F waves are useful in evaluating proximally as these responses go from peripheral nerves to the spinal cord and back. **Somatosensory evoked potentials** are difficult to perform with infants because of motor artifact obliterating the responses with movement and are imprecise because of overlapping responses to peripheral stimulation. These are used intraoperatively as stimulation can be performed on the nerve roots themselves to determine proximal continuity. **Electromyography** can show activation in muscles with paralysis or severe weakness. It is important that these studies be performed by someone who is experienced in the examinations of infants and young children, both for the most precise evaluation and the most comfortable experience for the youngster. There are changes in nerve conduction velocities that occur with age, distances are nonclassic for traditional studies, and electrode placement is challenging because of the very small hands and limbs.

TREATMENT

Treatment begins on initial evaluation with instruction to the parents for positioning and early stretching exercises to begin at 10-14 days of age. They are also told of the critical task of maintaining infant awareness of the involved arm, initially by manually mimicking activities with the affected arm that the baby performs with the contralateral arm. The parents also are informed of the higher risk of BBPP for future infants, and so the families are encouraged to speak with the obstetrician about optimal management in future deliveries.

The baby will start with occupational or physical therapy at approximately 2 wk of age. The therapist will evaluate the baby as described above. The therapist will reiterate the importance of maximizing the awareness of the involved arm and will teach range-of-motion exercises. The therapist will often do splinting, commonly for wrist extension in a baby with wrist-drop, and possibly extending the fingers and abducting the thumb as well. Over time other splinting needs may be evident. There may be a supinator strap used during the therapeutic activities to turn the arm from a pronated position to supination. Therapeutic taping may be done for supination, wrist extension, or, most commonly, for shoulder positioning to minimize an adducted, internally rotated posture. The family is instructed in a home exercise program to be carried out on a daily basis, including stretching exercises, strengthening as a child is able, positioning, and use of splints.

After a few months of age the child may be able to tolerate electrical stimulation. Electrical stimulation to the muscles minimizes atrophy and promotes increased size, and therefore strength, of muscle fibers. Specific parameters for its use have not yet been determined but a 20-30 min twice-daily program is effective. Electrical stimulation to the nerves remains an area of contention, with some maintaining that it improves recovery while others stating that it impairs it. There are also proponents of the use of **constraint-induced movement training** to increase the active use of the involved hand. This is useful for a short-term increase in active use of the arm but less certain are long-term improvements.

Biofeedback has been used to attempt to retrain muscles in those with BBPP. Botulinum toxin injections are also used to help balance out muscles that are overpowering weak muscles to minimize contractures.

Functional assessments are not widely used in children with BBPP. Computer adaptive testing using selected items from large item banks relevant to the child's function may provide a meaningful evaluation tool. Hand function was evaluated with testing of children with upper-plexus involvement compared to their contralateral hand; 80% of the children had significantly greater-than-predicted decreased performance from the opposite hand. This indicated the hand function is impaired even in children who only have upper-plexus involvement.

Secondary problems can increase the negative impact of functional deficits in children with BBPP. Contractures from imbalance due to muscle weakness or paralysis, including shoulder adduction and internal rotation, elbow flexion, forearm pronation, and wrist and finger flexion, are all seen and interfere with function. A decrease in growth of the affected arm in length and atrophy of muscles are often seen. Lack of awareness of the arm, sometimes called *developmental disregard*, in children can have a significant impact on active use of the arm, with functional loss as a consequence. Pain is not usually seen in birth brachial plexus as opposed to injuries, which occur later in life. Scapular winging can be problematic both socially and clinically. The change in child development overall can be problematic. Toddlers with sensory loss sometimes chew on their fingers, causing injury.

Because the shoulder joint develops as the infant and toddler grows, deficits frequently develop. Shoulder deformity is a common musculoskeletal complication of BBPP. Muscular imbalance across the developing shoulder results in deformity of the skeletally immature glenohumeral joint. The weakness of shoulder external rotation, combined with strong internal rotation, leads to this difficulty. There can be progressive glenohumeral dysplasia, with increased glenoid retroversion, humeral head flattening, and posterior subluxation of the humeral head. The natural history of this deformity is progression if left untreated. This leads to further functional limitations even with a strong hand. Treatment aims to minimize this progression. Treatment options include botulinum toxin injections, arthroscopic surgeries, release of contracture, muscular tendinous lengthening (frequently a subscapularis slide), tendon transfers (commonly transfer of the latissimus dorsi to increase external rotation and abduction strength), and derotational humeral osteotomy.

Infants who do not show satisfactory improvement in muscle strength are candidates for surgical intervention. Classically the lack of elbow flexion to three fifths or greater strength merits referral for nerve surgery. The specific criteria and timing remain under debate. Those with a complete brachial plexus palsy with a flaccid arm and lack of sensation are under consideration for surgery between 2 and 4 mo of age, and those with upper-plexus involvement are considered between 3 and 6 mo of age. The surgical strategy for complete palsy is early microsurgery with the focus first on hand reinnervation. If the shoulder and elbow have continued deficits later, they will undergo secondary musculotendinous procedures.

Nerve transfers, nerve grafting, and neurolysis all are commonly performed. Intraoperative electrical nerve studies can help guide the procedure. The somatosensory evoked potentials and nerve conduction studies, both nerve-to-nerve and nerve-to-muscle, are commonly performed. These can assist in determining functional electrical continuity of nerve fibers. Nerve grafting is commonly performed using sural nerve fascicles, with several fascicles attached at each root level. For those with no intact nerve roots, intercostal nerve and other peripheral nerve transfers or grafts, or a cross C7 graft (from the contralateral plexus), may be performed.

Recovery of muscle function can occur with extremely varied nerve grafts and transfers providing innervation, showing the amazing adaptability of the body and its recuperative power. Postoperative improvement in hand and arm function has been shown to have a negative correlation with age at surgery, and therefore early intervention is recommended.

For older babies and children, muscle tendon and bony procedures are generally performed, sometimes combined with a peripheral nerve procedure. The Oberlin procedure, using a portion of the ulnar nerve to the musculocutaneous nerve, just as it enters the biceps, is a classic peripheral nerve procedure. The Steindler flexorplasty is sometimes used to obtain elbow flexion by moving the flexor and pronator muscles from the medial epicondyle to the more proximal humerus. A subscapularis release with latissimus dorsi transfer is commonly used for shoulder abduction and external rotation. Shoulder joint procedures are becoming more common. For those with very severe arm involvement, the gracilis is sometimes used by taking this muscle along with the nerve and vascular supply for transfer to the arm for elbow flexion and/or wrist extension. A derotational osteotomy of the humerus is an older procedure that is still performed for changing the position of the shoulder and arm.

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Chapter 714
Traumatic and Sports-Related Injuries of the Lower Extremity

See Chapters 687 and 693.

Chapter 715

Meningomyelocele (Spina Bifida)

Pamela Wilson and Janet Stewart

See also Chapter 591.

Meningomyelocele, or spina bifida, is a congenital neural tube defect that results in the malformation of the spine and spinal cord. It is the second most common disability in children and can range from spina bifida occulta (see Chapter 591.2) to anencephaly (see Chapter 591.6).

ETIOLOGY

See Chapter 591.1.

PREVENTION

See Chapter 591.1.

PRENATAL SCREENING

Prenatal screening is recommended for all pregnant women to detect neural tube defect. A simple blood test is done in the 2nd trimester to evaluate α-fetoprotein, human chorionic gonadotropin, estriol, and inhibin. If a neural tube defect is present, the α-fetoprotein is often elevated and further screening using high-resolution ultrasound is indicated. Ultrasound may reveal not only a spinal defect but also abnormal brain development, including the *lemon* and *banana signs*. The lemon sign is related to the shape of the head, whereas the banana sign is associated with hindbrain herniation of the cerebellum into the foramen magnum. The importance in early identification allows families to plan for delivery and consider fetal interventions, mainly prenatal closure of the defect. The Management of Meningomyelocele trial studied the safety and efficacy of prenatal spinal defect closure and the results suggest that prenatal closure may decrease the need for a shunt and lower the incidence of severe Arnold-Chiari malformations along with improved motor outcomes. However, study data show an increased incidence of preterm delivery and a risk for uterine dehiscence.

CLINICAL IMPLICATIONS

Spina bifida is often a multisystem problem that is most frequently associated with central nervous system abnormalities. The neurologic lesion is assessed by the actual anatomic level and then neurologic or functional level. Lesions associated with spina bifida are often grouped together as thoracic, upper lumbar (L1-2), midlumbar (L3), lower lumbar (L4-5), and sacral. Based on this information 1 can make inferences on the functional capabilities of the child and answer pertinent questions during the initial encounters (Table 715-1). The most basic question all families ask is: "Will my child walk?"

The first issue that must be dealt with after delivery is closure of the back defect. This is generally done the 1st day of life. Once the back is closed the child will be monitored to see if hydrocephalus develops. Hydrocephalus is very common in spina bifida and is related to hindbrain herniation. Hydrocephalus may develop most rapidly in the 1st postnatal mo; ventricular dilation may precede a change in head circumference or signs of increased intracranial pressure. The occurrence of hydrocephalus has been noted to be anywhere from 77-95% and does appear to have an association with level of lesion. Treatment is placement of a ventricular shunt or endoscopic third ventriculostomy. The risk for shunt revision in the 1st 2 yr is 30-50%, which decreases to 10% after 2 yr.

Hindbrain herniation or the **Chiari type II malformation** is seen in 80-90% of individuals with myelomeningocele. The classic manifestations include caudal displacement of the cerebellum, pons, and medulla and elongation of the fourth ventricle. This can impede cerebrospinal fluid flow and is involved in the development of hydrocephalus. The Chiari II malformation is symptomatic (from brainstem herniation/compression) in approximately 20% of children. Respiratory symptoms may be seen at birth or develop in the 1st few mo. These include stridor, vocal cord dysfunction, and central or obstructive apnea. Swallowing and feeding problems may require gastrostomy tube placement. If the child has a symptomatic Chiari II malformation, surgical

Table 715-1 Prognosticating in Myelomeningocele

MOTOR LEVEL SPINAL CORD SEGMENT	CRITICAL MOTOR FUNCTION PRESENT	MOBILITY: SCHOOL AGE	RANGE: ADULT	ACTIVITY: ADOLESCENT
T12	Totally paralyzed lower limbs	Standing brace, wheelchair	Wheelchair	Wheelchair, no ambulation
L1-2	Hip flexor muscles	Crutches, braces, wheelchair	Wheelchair, household ambulation	Wheelchair, nonfunctional ambulation
L3-4	Quadriceps muscles	Crutches, braces, household ambulation, wheelchair	Crutches, household ambulation, wheelchair	50% Wheelchair, household ambulation with crutches
L5	Medical hamstrings, anterior tibial muscles	Crutches, braces, community ambulation	Crutches, community ambulation	Community ambulation with crutches
S1	Lateral hamstring and peroneal muscles	Community ambulation	Community ambulation	Community ambulation 50% crutch or cane
S2-3	Mild loss of intrinsic foot muscles possible	Normal	Normal	Limited endurance because of late foot deformities

From Braddon RL, editor: Physical medicine & rehabilitation, *ed 4, Philadelphia, 2011, WB Saunders, Table 54-1, p. 1284.*

decompression is indicated. All children with spina bifida are at risk for **tethered cord syndrome**. After shunt malfunction, this is the second most common cause for neurologic decline. Clinical manifestations of tethered cord syndrome include any change in gait or bowel or bladder function, increasing scoliosis, back pain, or orthopedic changes. Surgical detethering procedures are indicated in those with neurologic decline but the success rate is variable.

The **orthopedic complications** of myelomeningocele are common and have predictable patterns. The spine deformities include scoliosis, lordosis, and kyphosis (see Chapter 679). The development of scoliosis has an association with the neurologic level. Children with thoracic level defects have an 80-100% risk, whereas those with a sacral level are at very low risk. Spine deformities tend to increase more rapidly during growth and puberty. Treatment of scoliosis includes both nonsurgical and surgical options. Braces, such as **thoracic-lumbar-sacral orthotics**, therapy, and proper seating options may be beneficial. Surgically implanted growing rods to support the developing spine have been used in younger children. Spine surgery should definitely be considered if the scoliotic spine curvature reaches 45 degrees; the child who is nearing skeletal maturity is a better candidate for spine surgery. Realistic expectations need to be discussed with the child and family. Correction of the spine may improve sitting, posture, and pelvic obliquity, but may have a negative impact on function and ambulation.

The **development of the hip** is also influenced by neurologic level (see Chapter 678). The risk for dislocation is highest in the L3 level followed by the L1-L2. Unilateral hip dislocations should be fixed surgically as they may result in pelvic obliquity and problems with sitting, whereas bilateral dislocations generally do not require interventions. Contractures of soft tissues are commonly seen in children with higher lesion levels. Hip flexors and knee flexors are commonly involved.

Abnormalities in the foot occur in approximately 90% of children and adolescents. The goal of treatment is to achieve a plantar grade foot for weight bearing and allow shoe wear. Clubfoot deformities are common in babies and treatment commonly includes serial casting and orthotics (see Chapter 674.3). The results are often suboptimal and surgery may be needed. In addition congenital vertical talus (rocker-bottom feet) are often encountered and need to be addressed (see Chapter 674.4).

Osteoporosis (see Chapter 707) begins to develop in childhood and is more severe in the higher-level injuries. Fractures of the lower extremities are most common in the femur followed by the tibia. Preventive treatment includes use of supplemental calcium and vitamin D. Those with documented fractures should undergo a diagnostic evaluation (see Table 707-1), including dual-energy x-ray absorptiometry. The use of bisphosphonates may be considered if the diagnostic evaluation does not reveal other underlying causes. The utility of early weight bearing has been advocated, but passive standing may have little impact on bone density.

Neurogenic bladder and bowel can be anticipated (see Chapters 543 and 606.1). The goals of treatment interventions are to protect kidney function and achieve social continence. The introduction of clean intermittent catheterization is the mainstay of management. It is not atypical for newborn babies to be started on a clean intermittent catheterization program. Urodynamics and renal ultrasounds are routinely used to monitor for hydronephrosis and track intravesicular pressures. Medications may be used to reduce bladder contractions and improve volume capacity. Surgical techniques are being used to improve continence, including bladder augmentation and the Mitrofanoff procedure (appendicovesicostomy). Symptomatic urinary tract infections should be treated with appropriate antibiotics. These children tend to have colonized bladders and should only be treated for symptoms and not the urinalysis or culture. A good bowel program is generally needed to achieve bowel continence. Nonsurgical interventions include adequate hydration, dietary manipulation, fiber regulation, and use of laxatives. Surgical interventions, such as the antegrade continence enema, have improved continence in many of these children and adolescents.

Latex allergies are fairly common in this population. The etiology may be multifactorial but increased exposure may play a role in development of severe reactions (see Chapter 149). Care providers need to be keenly aware of products that contain latex or that have a cross reactivity such as foods mixed with avocado, bananas or Kiwi fruit. **Radioallergosorbent testing** is used for identification of potential severe allergens.

Spina bifida is known to be associated with specific **neuropsychologic problems**. Various cerebral neuronal dysplasias may be present. The hallmark is a nonverbal learning disorder characterized by difficulties in math reasoning, visual spatial perception, and time concepts. In addition there are weaknesses in executive function, processing speed, and organizational skills. Children with spina bifida typically fall within the average IQ range although those with a higher lesion tend to cluster on the lower range. Hydrocephalus itself has an impact on cognition as noted by deficits in learning, memory, and executive function. Young children with spina bifida tend to do well early on as they have good verbal skills but as the academic demands increase school problems become more obvious. It is important to have appropriate neuropsychologic/educational testing done to identify difficulties each child or adolescent may encounter. Appropriate early intervention and support programs should be put in place and **individual education plans** or 504 plans developed (see Chapter 36). Structure in the home environment plays a key role in teaching self-care, dressing, and mobility skills. The importance of these early interventions cannot be underestimated as they will impact the quality of life and independence in adolescence and transition to an independent adulthood.

ADOLESCENCE AND TRANSITION INTO ADULTHOOD

Clinical care has increased the life span of individuals with spina bifida and the majority are living into adulthood. The physical problems in association with the learning disorders make the transition into independent living and competitive employment very difficult. The pediatrician in conjunction with specialty services plays a pivotal role in developing future planning. It is important to discuss early on strategies to encourage developmentally appropriate independence and self-help skills. Long-term financial arrangements, such as Special Needs Trusts, should be discussed. Transitioning primary and specialty care will need to be researched and introduced to the individual and family. Young adults may have depression and suicidal ideation.

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Chapter 716

Ambulation Assistance

Marisa Osorio and Susan Apkon

Assistive devices, such as orthoses, prostheses, walkers, crutches, and wheelchairs, are key components of the therapeutic prescription for children with physical disabilities. The type of device chosen depends on the underlying diagnosis, functional level of the child, prognosis for improvement, tone abnormalities, range of motion, strength, and the overall gait pattern. Physicians, licensed independent practitioners, and physical therapists perform the evaluation of a child requiring mobility assistance. The physician or licensed independent practitioner is ultimately responsible for writing the prescription for the assistive device.

ORTHOSES

An orthosis is a device that is applied to the surface of the body to maintain alignment or position, to prevent or assist movement of the body part, or to provide support. Orthoses can be static, indicating the brace is rigid and does not allow movement, or they can be dynamic,

allowing movement of the limb to occur. Orthoses are named for the body parts covered. For example, "AFO" stands for *ankle–foot orthosis*, a brace worn on the foot that extends from the toes to the midcalf position (Fig. 716-1). Orthoses are custom made by an orthotist and can be obtained either directly through the orthotist or through the child's physical therapist. The orthosis is replaced during periods of growth or changes in function. All braces must be prescribed by a physician or licensed independent practitioner.

The type of lower-extremity orthosis prescribed is based on evaluation of the child's gait, strength, tone, and range of motion. There are many types of braces that have specific functions to improve gait. Table 716-1 lists examples of these orthoses and their potential uses.

Solid and articulated AFOs are the most commonly prescribed braces. Solid AFOs are used for children with hypertonicity, as they help to biomechanically reduce tone and provide stability with standing. Solid-ankle AFOs are also used in children who are nonambulatory to maintain range of motion of the ankle.

Articulated (hinged) AFOs allow the child with active ankle dorsiflexion to achieve heel strike and a more typical-appearing gait pattern by allowing forward movement of the tibia. This design makes ambulating on uneven surfaces and using stairs easier because of the movement allowed at the ankle, while still supporting the foot position and medial-lateral stability of the ankle. Articulated AFOs should not be used in children with cerebral palsy, spina bifida, or other disorders if they have a crouched gait pattern because the braces do not prevent crouching and may, in fact, allow further crouching. With crouched gait the hips and knees are held in flexion and ankles in dorsiflexion throughout the gait cycle.

Figure 716-1 Hinged ankle-foot orthosis. *(Courtesy of Ultraflex Systems, Inc., Pottstown, PA.)*

PROSTHESES

A prosthesis is a device that replaces a missing body part, such as an arm or a leg. Lower-extremity prostheses are used to improve mobility, while upper-limb prostheses are not always needed to improve function as children can be quite independent with a single upper limb. Lower-limb prostheses are used in children with congenital amputations, limb deficiencies such as fibular longitudinal deficiency, and acquired amputations as a result of trauma or cancer.

There are multiple components to lower-limb prostheses, which include the socket and foot, but may also include a hip and knee joint depending on the level of amputation. A prosthetist works with the child and family to fabricate the prosthesis. A physician or licensed independent practitioner with experience in prostheses provides the prescription for this device.

The type of prosthesis and the age at which a child is fit for the device depends on the etiology of the amputation, healing after surgery, and weight-bearing restrictions. In very young children, use of a lower-extremity prosthesis follows developmental milestones, with the first prosthesis prescribed at the time the child is pulling to stand. Addition of joints to the prosthesis also occurs when developmentally appropriate, such as use of a knee joint around the age of 3 when the child is learning to use stairs.

Advances in technology are helping children who use prostheses achieve a fluid gait pattern that makes their prosthetic use virtually undetectable to the untrained eye. New components and designs allow amputees to lead active lifestyles, including running, swimming, biking, and mountain climbing.

ASSISTIVE DEVICES

The purpose of assistive devices is to provide a wider base of support to improve stability during ambulation. The least supportive device is a traditional single-point cane commonly used following an orthopedic injury. For most children with gait abnormalities secondary to neurologic disorders, this is not a functional option. More supportive gait aids, such as forearm or Lofstrand crutches, are appropriate in these children; however, use of these devices requires good coordination and strength. Children with cerebral palsy and spina bifida may benefit from these devices.

Walkers provide more support than crutches and canes; they do not require as much strength and coordination to operate. Children with cerebral palsy, for example, may use a reverse walker, which they pull behind them. This reverse configuration provides a wide base of support and stability, helps to maintain an erect posture, and allows the child to engage with the environment without the barrier of the walker in front of them. Having the walker behind them also reduces the risk for more serious injury after a forward fall.

Table 716-1 Orthotic Options

ORTHOSIS	FUNCTION	COMMENTS
Foot orthosis	Provides support of foot only	Not typically customized
Supramalleolar orthosis	Provides medial-lateral support	Appropriate for children with low tone such as in Down syndrome
Ankle–foot orthosis	Provides support at the ankle and reduces footdrop or plantarflexion tone	Commonly used for ambulatory and nonambulatory children
Ground reaction ankle–foot orthosis	Provides knee extension moment to reduce crouching	Appropriate for children with spina bifida who crouch when walking
Knee–ankle–foot orthosis	Provides support at the knee when there is quadriceps weakness	Less commonly used because of large size of brace

Figure 716-2 Gait trainer. *(Photo copyright 2013 by Rifton Equipment, http://www.rifton.com.)*

For children who require a significant amount of support, gait trainers are often used. These devices allow the child to work on leg movements while the trunk and pelvis are stabilized (Fig. 716-2).

WHEELCHAIRS

Wheelchairs should be considered as a means of mobility when ambulation is not possible or is difficult outside of the home setting. Children with spinal cord injuries, spina bifida, neuromuscular diseases, or cerebral palsy may benefit from the use of a wheelchair. The goal is to provide a wheelchair that will allow the child to move independently about the environment, including home, school, and the community. Children as young as age 2 yr can self-propel a manual wheelchair and drive a power wheelchair. The type of wheelchair will depend on the child's underlying diagnosis, cognitive abilities, vision, motor skills such as head and trunk control, ability to manually propel a wheelchair, strength and endurance, musculoskeletal deformities if present, and medical comorbidities. One must also consider future growth or anticipated changes in function over time as well as the family's ability to transport the chair. Unique to pediatric wheelchairs is the adjustability to accommodate growth. A typical wheelchair may last 3-5 yr with periodic adjustments to growth by a seating specialist. There are many components that can be added in order to provide more support in the wheelchair, including head rests, lateral trunk support, hip guides, antitippers that prevent the wheelchair from tipping backwards, and specialized tires. The seating system is considered a separate item from the wheelchair itself and should be properly fit for the child's current size and seating needs. Seats that are too large for the child can cause pressure ulcers, worsen scoliosis, and make it more difficult for the child to maneuver or propel.

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Chapter 717

Health and Wellness for Children with Disabilities

Margaret A. Turk

See also Chapter 42.

The number of children with developmental disabilities in the United States has increased by 17% in the past 20 yr, with nearly 3 million being of school age. Despite available medical support, many of these children and their families do not receive recommended childhood preventive care and anticipatory guidance, health education, discussions about appropriate activity and exercise, or an opportunity to engage in or learn about health promotion.

The expansion of the disability definition to include children with special healthcare needs, chronic conditions, and activity limitations from any cause (e.g., limitations in usual daily activities such as age-appropriate self-care, mobility, communication, and cognition) has made the health issues of the more traditional childhood disability types (e.g., cerebral palsy, intellectual disability, spina bifida, congenital musculoskeletal disorders) more difficult to identify. U.S. data identify developmental, emotional, and behavioral conditions as the leading conditions with activity or functional limitations, with physical health conditions comprising a smaller proportion of self-identified disabilities (although mobility and motor control issues may be noted among the aforementioned nonphysical conditions). Childhood cognitive, mental, and physical health problems contribute to continued economic and health problems into adulthood. Because these problems can respond to childhood and adolescent health promotion interventions, monitoring children with disabilities throughout their development is helpful in providing information and support to children and adolescents, their parents, and families to promote health over a lifetime.

HEALTH PROMOTION DEFINITIONS AND BACKGROUND FOR DISABILITY

The World Health Organization defines *health promotion* as “the process of enabling people to increase control over, and to improve, their health.” For people with disabilities, this concept is important because they are both underserved and have comparatively large health disparities. The World Health Organization further defines health promotion approaches as including more than health education, and consisting of community action, supportive and accessible environments, policy changes, health service modifications, and development of personal skills. Health and wellness programs also include traditional preventive management strategies, such as anticipatory guidance. There is ample evidence that engaging in specific areas of health promotion results in improvement, although the evidence for its influence on adult health is less robust.

Children with disabilities encounter many barriers to healthy behaviors (Table 717-1). Both broad and focused health promotion programs consider severity of condition, barriers and resources, and self-efficacy and resiliency, to achieve health-promoting behaviors. Children with disabilities may also require modeling or assistance to apply healthy behaviors to their particular disability or economic, social, and environmental circumstances.

Children and adults (and their families) often view health differently than those without disabilities. Disability may influence health and vice versa, but their perception of their own health and wellness does not equate with their level of disability. Children with congenital or

Table 717-1 Barriers and Facilitators for Children to Engage in Healthy Behaviors

BARRIERS	FACILITATORS
• Lack of knowledge and skills • Fear of injury or failure • Negative attitudes by parents, peers, healthcare providers • Poor parental healthy behaviors • Stress in the close family network • Personal choices • Fatigue • Lack of initiative • Limited function or capability • Inability to control behaviors • Inaccessible facilities or resources • Needing adult or aid assistance • Economic restrictions • Policies and procedures of facilities or programs	• Education or knowledge about healthy behaviors • Engaging child in discussions and decisions • Promotion of activities by rehabilitation and other healthcare professionals • Family support and participation • Involvement of friends and peers in activities • Desire to be active • Models or directions for participation with adaptations • Creative and knowledgeable professionals • Making activities a part of the routine—repetition and consistency promote ongoing activities • Accessible facilities and opportunities, with knowledgeable staff • Policies and resources promoting participation

acquired disabilities have a narrow view of healthy living, concentrating on nutrition and secondarily on physical activity, with little understanding of how they apply to their own condition. Experiences as a child with a disability often foreshadow adult behaviors, especially negative attitudes toward therapy, exercise, and activity. Beliefs of parents, families, and healthcare providers also influence the views of health by children with disabilities. Health promotion programs for these children must (1) understand and support the role and well-being of parents, (2) recognize that parents of children with more functional limitations may require more resources and support, (3) involve children with disabilities in design of programs and decisions about participation, and (4) address barriers to participation, perceived and real (see Table 717-1). Because many healthcare providers have a poor understanding of the needs of people with disabilities, engaging experienced rehabilitation health professionals in designing and promoting a health and wellness agenda is an important strategy.

An effective health and wellness program should involve multiple approaches and opportunities for success, including partnerships with families, school staff, and rehabilitation providers. Competency requires addressing any mismatch between the child's positive sense of health and well-being and that expected by the healthcare providers; limitations of an education-only model; engaging the child in discussions about the importance of healthy behaviors, ways to engage in healthy behaviors related to the child's disability and circumstances, and decisions about participation; and parent and family involvement coupled with sensitivity for the already overwhelming support a family provides for the child with a disability.

ANTICIPATORY GUIDANCE, COUNSELING, AND PREVENTIVE CARE

Preventive healthcare through health education, anticipatory guidance, and participation in screening and immunization schedules is the mainstay of pediatric public health programs (see Chapter 16). *Bright Futures,* developed by the American Academy of Pediatrics and their collaborators and supported by the Maternal and Child Health Bureau, Health Resources and Services Administration, provides a knowledge base for pediatric healthcare providers and the public about anticipatory guidance, health promotion, and prevention for children and adolescents; but it has few references to disability. Anticipatory guidance refers to general information related to growth/development and healthy practices. Counseling refers to advice given regarding specific conditions, which could include discussions of applications of general guidance to children with disabilities. For the general population, 25% of parents receive no information and <50% receive all recommended guidance. Although parents of children with special healthcare needs (the broad inclusive definition of disabilities) report similar or better receipt of general preventive information, it is not clear whether those with higher severity of functional limitations receive this guidance or counseling, and whether it is provided in the context of disability and other circumstances.

Children with special healthcare needs require typical prevention, as well as more specific counseling related to their disability. Some of this more specific counseling can be managed by specialty care providers, although children with special healthcare needs have difficulty obtaining appropriate specialty outpatient services. Additional barriers to care, especially with increasing age of the child, are the lack of accessible medical equipment and facilities. Although discussions of health risks with adolescents about smoking, drinking, and protected sexual activity should be undertaken, the discussions may require a different focus for adolescents with disabilities. Higher violence and abuse rates toward children with disabilities are reported for which providers must be vigilant.

The recommendation is to recognize the need for modifications to typical guidance, to be alert for any signs of violence, and to broaden counseling to include questions and discussions about conditions associated with the specific disabilities (e.g., epilepsy or cognitive impairments often seen with cerebral palsy, or neurogenic bladder and bowel in spinal cord dysfunction) or secondary conditions, such as pain, osteoporosis/fractures, or fatigue seen in many children and adolescents with disabilities. Although the patient-centered medical home may provide this inclusive support, it risks decreased access to the specialty physicians and healthcare providers who will provide much of this information.

PHYSICAL ACTIVITY AND EXERCISE

National health guidelines recommend at least 60 min of physical activity daily for children, and they suggest that specific advice from health professionals is needed for children with disabilities. Exercise and activity have shown to increase aerobic capacity, functional ability, and quality of life for children with many kinds of disabilities and chronic diseases (e.g., cerebral palsy, spinal cord dysfunction, cystic fibrosis, asthma, intellectual disabilities, diabetes). The vast majority of study participants noted benefits. And yet, most healthcare providers expect sedentary lifestyles for children and adolescents with disabilities, whatever their functional abilities. For children with disabilities, school physical education and recess programs can support activities at or greater than the recommendation, and school requirements can reinforce activity expectations. Despite this potential, most children with disabilities engage in very limited physical activity even in supported school environments. School and public playgrounds are not sufficiently accessible to support community physical activity.

Physical activity for children and adolescents improves fitness and quality of life for youth with developmental disabilities (Table 717-2). The described exercise and fitness programs require 2-3 mo of participation at least twice a week to achieve any changes, and many of the changes achieved are longer lasting than expected. These programs are not traditional therapy, and participation in therapy is not a substitute. The focused fitness and exercise programs cited here generally required the support and direction of rehabilitation professionals, although programs can be community based in nonmedical surroundings.

Table 717-2 Examples of Effective Exercise Programs for Children with Disabilities

PROGRAM	DESCRIPTION	OUTCOMES/COMMENTS
Center-based fitness program and home program*	Children with a variety of disabilities Group exercise: 2×/wk for 14 wk; warm-up, aerobics, strengthening, cool down Home program: 2×/wk for 12 wk using video exercises	Improved walking efficiency, strength, general function Group treatment more effective by measures and by satisfaction
Group aquatics aerobic exercise program[†]	Children with a variety of disabilities, >50% able to walk 2×/wk for 14 wk Recreation to achieve target heart rate; aquatic strengthening program	Improved walk/run, not strength to isometric testing Required adults monitoring to maintain target heart rates
Group training class[‡]	Children with cerebral palsy able to walk 2×/wk for 4 wk Warm-up, circuit training stations (treadmill, balance, stairs, closed-chain exercises)	Improved muscle strength, mobility, function except fine-motor test–maintained 8 wk later Therapists conducted and monitored
Strength training[§]	Children with cerebral palsy, including a majority able to walk with assistive devices 3×/wk for 6 wk Progressive strength training program, conducted in the home	Improved perceptions of strength, walking, stair management and improved psychologic benefits Clinicians to monitor, problem solve; some need for direct parental involvement
Walking–jogging program[‖]	Children with Down syndrome 3×/wk for 10 wk 30 min sessions, achieving 65-70% peak heart rate	Difficulty promoting increasing activity intensity Improved peak exercise time and grade, but not in aerobic capacity; improved walking capacity
Treadmill training program[¶]	Children with intellectual disabilities Daily for 2 mo Progressive treadmill use with goal of 20-30 min	Improved heart rate with and without activities Therapist developed and monitored, community staff implemented
Peer-guided exercise**	Adolescents with intellectual disabilities 2×/wk for 15 wk Typical adolescents and those with disabilities paired to support each other in 1 hr aerobic, weight-training, flexibility activities	Improved curl-ups, 6 min walk, and body mass index High attendance, less compliance with weight training

*Fragala-Pinkham MA, Haley SM, Rabin J, Kharasch VS. A fitness program for children with disabilities. Phys Ther 85(11):1182–1200, 2005.
[†]Fragala-Pinkham M, Haley SM, O'Neil ME. Group aquatic aerobic exercise for children with disabilities. Dev Med Child Neurol 50(11):822–827, 2008.
[‡]Blundell SW, Shepherd RB, Dean CM, Adams RD, Cahill BM. Functional strength training in cerebral palsy: a pilot study of a group circuit training class for children aged 4-8 years. Clin Rehabil 17(1):48–57, 2003.
[§]McBurney H, Taylor NF, Dodd KJ, Graham HK. A qualitative analysis of the benefits of strength training for young people with cerebral palsy. Dev Med Child Neurol 45(10):658–663, 2003.
[‖]Millar AL, Fernhall B, Burkett LN. Effects of aerobic training in adolescents with down syndrome. Med Sci Sports Exerc 25(2):270–274, 1993.
[¶]Lotan M, Isakov E, Kessel S, Merrick J. Physical fitness and functional ability of children with intellectual disability: effects of a short-term daily treadmill intervention. ScientificWorldJournal 4:449–457, 2004.
**Stanish HI, Temple VA. Efficacy of a peer-guided exercise programme for adolescents with intellectual disability. J Appl Res Intellect Disabil 25(4):319–328, 2012.

Recreation and organized sports are other areas where children and adolescents with disabilities can engage successfully, at times with modifications. Participation improves cardiopulmonary parameters, motor function, social competence, and general sense of well-being. Programs through Special Olympics International are an opportunity for children and adolescents to engage in supportive and monitored environments for sport and recreation.

NUTRITION AND OBESITY

Managing the combination of nutrition and physical activity is the key ingredient of weight control. Obesity is a significant problem affecting a large portion of the general population, including children with special needs. Estimates suggest that children with physical activity limitations were twice as likely as the general population to be overweight and youth with cognitive impairments are at increased risk. It is unclear if obesity is a cause for the activity limitations or is a result of the limited activity, which may be an important distinction in developing interventions. The concern with obesity contrasts with early life weight gain needs of many children with disabilities, and may pose important management confusion for parents and families with the change of focus to weight decrease. Confounding factors include (1) the propensity of some disabilities, usually those that are genetically mediated, to be associated with obesity; (2) standards of measurement may not be appropriate for certain diagnoses or disability types (e.g., expected body composition differences, short statures, contractures, or limb deficiencies or amputations); (3) obesity may be a side effect of medication and must be weighed against benefits (e.g., antidepressants, mood stabilizers, steroids); and (4) the social network of family, friends, schools, and healthcare providers may unwittingly influence healthy habits in a negative way, including use of food as reward for behavior management.

EMOTIONAL HEALTH AND LEISURE ACTIVITIES

Emotional health is often overlooked in children with disabilities, unless mental health or challenging behaviors are the cause for the disability. Youth and adolescents with disabilities appear to be at higher risk for feeling low, stressed, or anxious (especially those with higher levels of limitations), and those with mental health needs may have lower adaptive functioning, a family history of mental illness, or a diagnosis of autism spectrum disorder. Adolescents with physical disabilities participate in fewer social activities, have fewer close or intimate friends, and have few plans for ongoing education. There is a risk for continued isolation into adulthood. Medications may be considered, but effectiveness is not guaranteed and unwanted side effects may produce more health conditions. Counseling requires insurance support or discretionary funding.

Leisure and recreational activities provide social supports, additional stress-coping mechanisms, and ability to develop social skills and a stronger personal identity. Girls with disabilities tend to engage

Table 717-3 Targeting Healthy Behaviors for Children with Disabilities

HEALTH ACTIVITY TARGET	RELEVANCE TO CHILDREN WITH DISABILITIES
General prevention	• Recognize risks for less healthy behaviors and barriers and facilitators about behavior changes and participation • Cover typical topics for all children; counsel regarding disability or situation context • Specifically monitor for abuse and violence • Provide typical age-appropriate adolescent information about smoking, drinking, substance abuse, sexual contacts; refer if unable to provide • Monitor for disability-specific health conditions; may require referral
Physical activity	• Promote exercise and activity—should be an expectation for activity • Ensure that family and child/adolescent are knowledgeable about benefits and possible adaptation • Review need for possible dietary changes • Consider engaging rehabilitation professionals
Nutrition and obesity	• Recognize obesity can cause limitations, and can be the result of poor dietary habits and limited activity • Ensure that family and child/adolescent are knowledgeable about healthy nutrition • Consider referral to nutritionist or other professional to engage patient and family in modeling/direction or behavior suggestions • Review need for increased activity level with dietary changes
Emotional health	• Question for sense of anxiety/feeling low, stress management and ability to adapt, social activities • Consider medications and counseling based on expected effect, monitor effects/side effects; consider referral, making sure that insurance/payment coverage is available • Consider recreation and leisure activities to promote social support and ability to develop social skills
Recreation and leisure	• Question about social activities outside the home; promote importance for development of social skills, sense of self, support • Consider referral to community programs or rehabilitation professionals
Dental	• Discuss more than preventive dental care • Suggest behavior strategies if there are problems engaging in dental appointments and refer for this service as needed

in social or skill-based activities, and boys in physical activities, with decreasing participation with increasing age. Rehabilitation professionals can assist with problem-solving activities, such as using computerized technologies (e.g., Wii, Xbox), adaptation of equipment (e.g., modified upper-limb prosthesis to allow baseball glove use), and knowledge of adapted recreation programs in the area (e.g., horseback riding, winter/water sports) to increase participation.

DENTAL CARE

Dental care is a frequently unmet health care need for children with disabilities. The principal deficits are in receipt of further or specific dental care (not preventive services) and that condition severity and low income may be associated with unmet dental needs. Challenging behaviors often limit dental care, and the use of behavior management techniques and education programs have been effective in allowing both preventive and additional dental care.

ROLE OF HEALTHCARE PROVIDERS

Healthcare providers should have higher expectations for health and healthy behaviors for children with disabilities. Healthy behaviors do not come naturally to most people, including children with disabilities and their families, and there is a role for healthcare providers in providing a better understanding of health and behavior change concepts. Primary care and other healthcare providers should be mindful of discussing and promoting health and healthy behaviors with children and adolescents with disabilities and their families (Table 717-3).

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Environmental Health Hazards

PART XXXIV

Chapter 718
Biologic Effects of Radiation on Children

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BASIC PRINCIPLES

Radiation exposure occurs from both natural (50%) and manmade (50%) sources. Radon gas accounts for the majority (37%) of natural radiation. The contribution of medical radiation has dramatically increased to 50% in 2006 from 15% in the mid-1980s. CT is responsible for 24% of all radiation exposure and almost half of manmade radiation (Fig. 718-1). Medical radiation is concerning. Estimates of dose risks ranging from no risk to as much as 2% of all cancers in the United States may be attributable to radiation from CT studies. Studies implicate CT examinations in childhood with subsequent development of cancer. In addition, radiation doses from medical imaging can be poorly understood. Seventy-five percent of radiologists and emergency department physicians are reported to underestimate the radiation dose from CT. Some imaging procedures do not produce radiation (Table 718-1), and not all radiation-producing modalities expose a child to the same amount of radiation (Table 718-2).

Nuclear medicine and positron emission tomography examinations are described by the amount of radioactivity injected (millicuries or becquerels) or are converted to effective dose (milliSieverts). The units of absorbed dose, as defined by the International Commission of Radiation Units, are the **rad,** introduced in the 1960s, and the **Gray** (Gy), introduced in 1985. The metric used in denoting biologic response is the rem (older unit) and the Sievert (Sv) (Table 718-3). Equivalent dose and effective dose are measured in Sv and mSv. Not all radiation has the same effect on biologic tissue for a given dose. Beta rays are quite superficial; alpha particles and protons cause significantly more damage than gamma radiation (x-rays) for a given absorbed dose. Diagnostic imaging uses x-rays (gamma rays). Each dose has a modifier, for example, skin dose, whole-body dose, organ dose, or effective dose. **Effective dose** considers specific tissues and their radiosensitivity.

BIOLOGIC EFFECTS OF RADIATION

Biologic effects of radiation are divided into 2 types. **Tissue reactions** (previously **deterministic effects)** (determined by the dose) are characterized by a threshold dose and severity is directly related to the magnitude once the threshold is exceeded. For example, cataracts have traditionally been reported to occur with an acute exposure to >2.0 Gy or with long-term exposure to >5.0 Gy (Table 718-4), although publications indicate lower thresholds as well as debate about these thresholds. Tissue reactions never occur from the radiation organ doses generally used in single diagnostic examinations (<100 mGy), but invasive procedures (therapeutic and interventional) have on rare occasions led to these effects. **Stochastic** (random) **effects** are of concern because they can occur at any dose; that is, there is no threshold, with the probability of an effect increasing with rising dose. These effects can be caused by any radiation striking vulnerable tissue (most importantly DNA, but cytoplasm also may be at risk) and causing irreversible damage. These effects lead to the **linear no (dose) threshold** model, which states that radiation damage increases with rising dose in a linear fashion. This concept stresses that no level of radiation exposure can be considered to be absolutely safe.

Radiation can cause permanent cell injury, carcinogenesis, genetic mutations, or cell death. The biologic effects of radiation result primarily from damage to DNA directly (**direct effect**) through interaction of fast recoil electrons caused by the absorption of x-rays (one third of the damage) or secondarily by the formation of free radicals (**indirect effect**). Approximately 80% of the cell is water, so most of the energy deposited in a cell results in production of aqueous free radicals. The reactions are rapid (10^{-18} to 10^{-3} sec). A dose of 10 mGy results in approximately 10^3 ionizations per cell type. The biochemical and physiologic changes that follow take hours or days, whereas the induction of cancer may take a few years to decades.

The manifestations of DNA injury are variable. The cell containing the damaged DNA might die; cell death (apoptosis) is a mechanism for eliminating heavily damaged and potentially mutable cells. Damage to a base pair is the most prevalent and least significant effect. Breaks of a single strand of DNA usually have little biologic significance because each strand is repaired with use of the opposite strand as a template, but a mutation can result if misrepair occurs.

Breakage of both strands of DNA (the least-common event) is more problematic. The end result seems to depend on the proximity of the break in each strand. If widely separated, repairs occur as with a single-strand break. If the breaks in the 2 strands are opposite each other (or separated by only a few base pairs) repair is more difficult without a template. This type of break is the mechanism of radiation-induced cell death, chromosomal damage leading to mutations, and carcinogenesis.

When DNA damage occurs, aberrations are produced in chromosomes, resulting in an *unstable aberration* (usually lethal to dividing cells) or *stable aberration.* Stable aberrations can result in failure of chromosomes to reunite (leading to deletions) or in abnormal rearrangement of chromosomes, such as reciprocal translocation or aneuploidy. Although it is logical to think that these abnormalities in chromosomes lead to mutations that can activate oncogenes or protooncogenes or cause mutations in tumor-suppressor genes (see Chapter 492), few radiation-induced cancers show specific translocations such as would be associated with activation of specific oncogenes or known tumor-suppressor genes. An exception is the radiation induction of papillary thyroid carcinoma in children, which probably results from activation of the RET oncogene (see Chapter 506).

Radiation carcinogenesis seems to be a progressive multistep process composed of 3 independent stages: morphologic changes, cellular immortality, and tumorigenicity. Radiation exposure induces cellular genomic instability. This instability is transmitted to a cell's progeny, resulting in a continued elevation in the rate at which genetic changes arise in the subsequent generations of the irradiated cell (Fig. 718-2).

A longitudinal study of the lifetime risks of excess cancer mortality secondary to irradiation has been evaluated in *atomic bomb survivors*. More than 86,000 survivors have been followed for more than 65 yr since exposure. Individual radiation doses were estimated by considering the person's location in relation to distance from the epicenter and individual shielding situations. Most of the exposure was direct gamma irradiation, with some neutron exposure. Age at exposure and ethnic differences in cancer occurrence influence the sensitivity to radiation-induced cancers (Fig. 718-3). Compared with the middle-aged adult, children are 2-10 times more sensitive to radiation-induced carcinogenesis, and the youngest neonate is more sensitive than the older child. Because of the higher risks associated with breast and thyroid cancer, girls are more sensitive than boys. It must be understood that

cancer rates in this study are mortality figures. The incidence of cancer in this population is approximately 2 times greater than mortality incidence.

The doses used in *diagnostic radiology for multidetector CT* scans overlap with low-dose induced cancer in atomic bomb survivors (Fig. 718-4). Estimates for lifetime risk of cancer following head and abdominal CT scans in children vary widely, from as low as 1 : 500 to more than 1 : 10,000 (including the possibility that these doses do not incur a risk). Therefore, since stochastic effects are random but increase with rising dose, it is mandatory that we use the lowest dose necessary to get sufficiently diagnostic images. The advent of digital picture archiving communication systems utilizes postprocessing algorithms and can make all images diagnostic, even those with higher-than-necessary exposures. Since the elimination of film-based systems, where overexposures were evident as "dark" films, digital technology eliminates the imager's ability to know whether enough or too much radiation was given. It does not allow the imager to determine whether the patient received "as low as reasonably achievable" radiation dosing. It is for this reason that some radiation metric (and familiarity with this metric) should appear on each image.

Increased biologic vulnerability to radiation can be seen in the fetus exposed in utero through maternal radiation. In utero radiation exposure is associated with a 92% excess risk of dying from leukemia

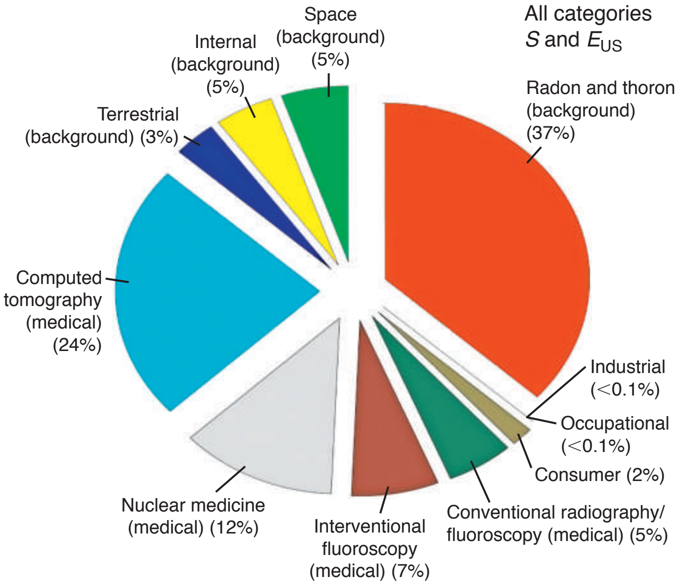

Figure 718-1 All exposure categories collective effective dose (percentage) 2006. *(From the National Council on Radiation Protection and Measurements. Ionizing Radiation Exposure of the Population of the United States (NCRP report 160), Bethesda, MD, National Council on Radiation Protection and Measurements http://pubs.rnsa.org/doi/full/10.1148/radiol.2532090494.)*

Table 718-1 Imaging Modalities

MODALITY	SOURCE
Plain film	Radiation (x-ray)
Angiography/fluoroscopy	Radiation (x-ray)
Ultrasound	Sound beams
Computed tomography	Radiation (x-ray)
Magnetic resonance imaging	Magnetic field; radiofrequency
Nuclear medicine (including positron emission tomography)	Radiation (injected isotope)

Table 718-2 Radiation Dose by Imaging Test*

EXAMINATION	DOSE	SITE MEASURED
Chest—2 views	0.1-0.2 mGy	Entrance (skin)
Abdominal—2 views	0.5-1.0 mGy	Entrance (skin)
Fluoroscopy		Entrance (skin)
Nonpulsed	3-5 mGy/min	
Pulsed	1-3 mGy/min	
Computed tomography†		
Head (2 yr old)	20-30 mGY	Middiameter of phantom of 16 cm
Abdomen (2 yr old)	2-3 mGY	Middiameter of phantom of 32 cm
Nuclear medicine‡ (technetium ^{99m}Tc mercaptoacetyltriglycine–renal)	120 mSv	Effective dose
Positron emission tomography‡ (brain fludeoxyglucose ^{18}F)	185 mSv	Effective dose, whole body

*Background radiation = 0.01 mSv/day or 3 mSv/yr.
†Scan explained as CT dose index (CTDI). First dose is with adult factors; second dose, shown in parentheses, is examination adjusted for children.
‡Expressed as effective dose. These are rough guidelines for dose given to a 5 yr old with normal renal function.
From Valentin J: Radiation dose to patients from radiopharmaceuticals. (Addendum 2 to ICRP Publication 53.) ICRP Publication 80. Approved by the Commission in September 1997. Ann ICRP *28:1, 1998.*

Table 718-3 Radiation Measurements

UNITS	RADIOACTIVITY	ABSORBED DOSE	DOSE EQUIVALENT	EXPOSURE
Common units	curie (Ci)	rad	rem	roentgen (R)
New units	Becquerel (Bq)	Gray (Gy)	Sievert (Sv)	coulombs/kg

CONVERSION EQUIVALENTS
1 millicurie (mCi) = 37 megabecquerels (MBq)*
100 rad = 1 Gy
1 rad = 1 cGy
100 rem = 1 Sv
1 rem = 10 mSv
Background radiation dose is approximately 1 millirad/day

*To convert mBq to mSv, use conversion table:
1 mrad = millirad = 1/1,000 of a rad.
rem = rad × radiation factor; weighting for gamma and x-ray, this factor is 1.
rem = rad × 1.

Table 718-4 Deterministic Dose Rates

INJURY	APPROXIMATE THRESHOLD
SKIN	
Transient erythema	200 rad (2 Gy)
Dry desquamation	1,000 rad (10 Gy)
Moist desquamation	1,500 rad (15 Gy)
Temporary epilation	200 rad (2 Gy)
Permanent epilation	700 rad (7 Gy)
EYES	
Cataracts (acute)	>200 rad (2.0 Gy)*

*Has been reported as occurring between 0.5 and 1.0 Gy.
Modified from Hall EJ: Radiobiology for the radiologist, *ed 5, Philadelphia, 2000, Lippincott Williams & Wilkins.*

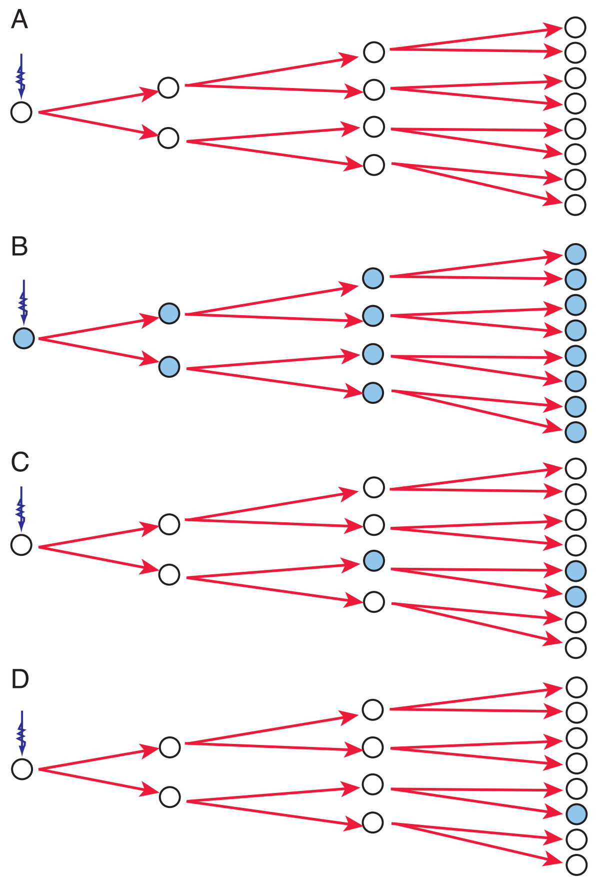

Figure 718-2 **Schematic of radiation-induced mutagenesis.** *Open circles* represent normal wild-type cells, whereas *solid blue circles* represent mutated cells. **A,** Most of the cells in an irradiated population retain the wild-type phenotype. **B,** Example of a cell directly mutated by radiation exposure; the mutation is transmitted to all of its progeny. **C** and **D** are examples of mutations arising as a result of radiation-induced genomic instability. The irradiated cell and its immediate progeny are wild type, but the frequency with which mutations arise among the more distant descendants of the irradiated cell is elevated. *(From Little JB: Ionizing radiation. In Kufe DW, Pollock RE, Weichselbaum RR, et al, editors:* Holland-Frei cancer medicine, *ed 3, Ontario, Canada, 2003, BC Decker.)*

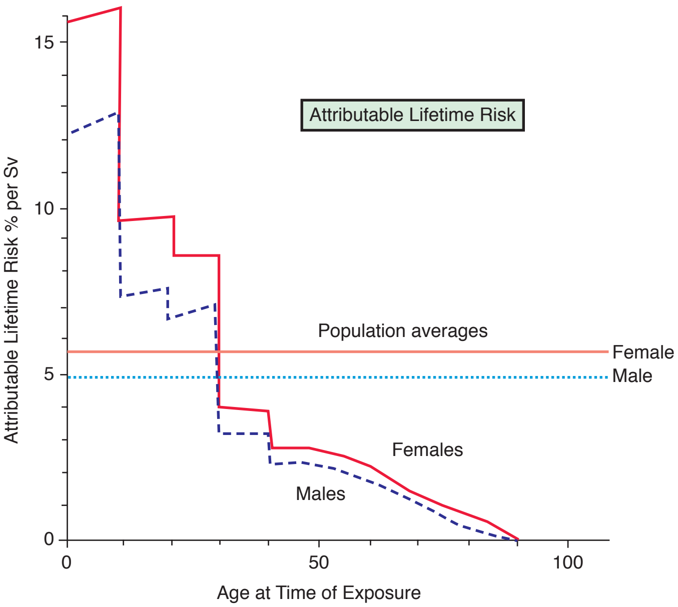

Figure 718-3 **Lifetime risk of excess cancer per Sievert (Sv) as a function of age at the time of exposure.** Data from the atomic bomb survivors. The average risk across all ages in a population is approximately 5% per Sievert, but the risk varies considerably with age: children are much more sensitive than adults. At early ages, girls are more sensitive than boys. *(From Hall EJ: Introduction to session I: Helical CT and cancer risk, Pediatr Radiol 32:225–227, 2002.)*

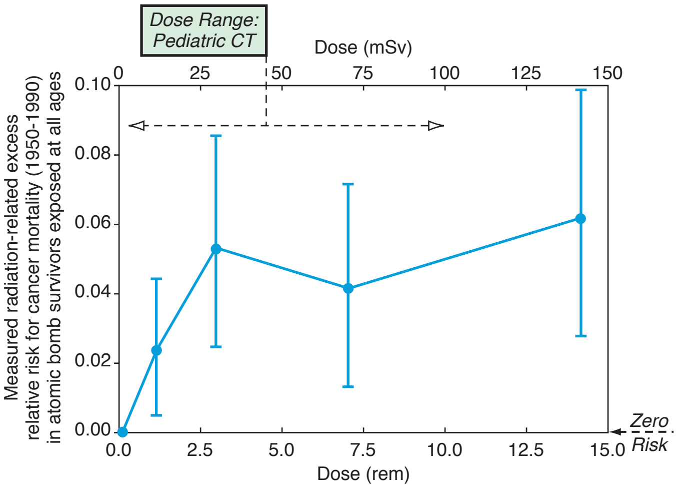

Figure 718-4 **Relevant dose range for pediatric CT: 6-100 mSv (0.006-0.1 Sv).** There is direct, statistically significant evidence for risk in the dose range from 0-0.1 Sv. *(From Brenner DJ: Estimating cancer risks from pediatric CT: going from the qualitative to the quantitative, Pediatr Radiol 32:228–231, 2002.)*

before age 10 yr and a 180% excess risk of dying from other malignant diseases. Even 40 yr later there is a 228% increased relative risk of cancer associated with radiation in utero.

The fetus and infant are most vulnerable to radiation-induced cancer because (1) they are growing rapidly, with many cells undergoing mitotic activity; (2) radiation-induced tumors (except leukemia) take a long time to develop and children have a longer lifetime; and (3) there is a greater time to have imaging studies, with accumulation of the risks related to doses.

Most childhood tumors occur sporadically, but 10-15% of cases have a strong familial association. Familial tumors have specific chromosomal deletions in common. In some of these tumors (retinoblastoma), the 2-hit hypothesis by Knudson is apparent (see Chapter 491). It is not coincidental that individuals with many of the congenital diseases are at risk for the development of tumors after irradiation.

Table 718-5 Inherited Human Syndromes Associated with Sensitivities to X-Rays

Ataxia-telangiectasia	Fanconi anemia
Basal cell nevoid syndrome	Gardner syndrome
Cockayne syndrome	Nijmegen breakage syndrome
Down syndrome	Usher syndrome

Modified from Slovis TL, Frush DP, Berdon WE, et al: Biologic effects of diagnostic radiation on children. In Slovis TL, editor: Caffey's pediatric diagnostic imaging, *ed 11, Philadelphia, 2008, Mosby, p. 5; and Hall EJ:* Radiobiology for the radiologist, *ed 6, Philadelphia, 2006, Lippincott Williams & Wilkins, p. 41.*

Table 718-5 lists diseases that are associated with sensitivity to radiation.

DECREASING UNNECESSARY DIAGNOSTIC RADIATION IN CHILDREN WHILE STILL OBTAINING DIAGNOSTIC IMAGES

Selecting the correct examination is the responsibility of the ordering physician and may involve consultation with the radiologist, preferably with pediatric expertise. Evidence-based medicine has shown little yield from an imaging work-up (including CT) of a child with a single nonfebrile seizure without other neurologic abnormalities. This is especially true if there is no antecedent history of abnormal behavior or of personality or developmental change. CT does not detect as many abnormalities as MRI, and CT involves ionizing radiation. MRI detects the subtle changes of congenital or acquired anomalies that may be responsible for seizures much more easily. Therefore, it is appropriate, **except** in an emergency situation, to obtain MRI within a reasonable time frame instead of performing 2 tests (CT followed by an MRI).

It has been estimated that perhaps up to 30% of imaging examinations, including CT examinations, are questionably indicated, and may be replaced by another, non–radiation-producing modality, or are performed without evidence-based indications.

Reducing Radiation from the CT Examination

The most common source of medical radiation is CT. We have progressed from a single-slice scanner to scanners that can obtain up to 320 slices in subsecond time. The images have excellent detail, including multiplanar and 3-dimensional reconstruction of the acquired data. It once took more than 30 min to obtain 10-12 images, but now hundreds to thousands of images are generated in seconds. When adult parameters for CT settings are used for children, the dosage for children is actually higher than the dosage for adults. This occurs because lower-energy x-rays that would have been absorbed in the near field in an adult pass into the entire child, irradiating all organs. When comparing dosages given to newborns and adults during CT scanning of the head, with the same parameters in both groups, the dosage given to newborns is 4 times that of the dosage given to adults. With abdominal imaging, the dosage is increased by 60%.

It is the role of the radiologist to tailor the examination to the pediatric patient. One can determine whether the examination is tailored to the pediatric patient by looking at the dose report or the parameters of tube current (milliamperage/second [mAs]) and peak kilovoltage (kVp). Scanning range should be limited to only the necessary area. Multiphase scanning should only be obtained when necessary. The radiologist has many ways to decrease parameters so that children receive diagnostic imaging without excessive radiation. In some instances, reducing the radiation dose by half, even in adults receiving CT, does not change the diagnostic efficacy of the study and the radiologist's ability to make the proper diagnosis.

RADIATION THERAPY—ACUTE AND LATE EFFECTS

Radiation therapy uses high doses to kill malignant cells. The sensitivity of normal cells is quite close to that of malignant cells, and to achieve significant cure rates, radiation oncologists must accept a given

Table 718-6 Late Effects of Radiation Therapy in Children Treated for Cancer

SYSTEM	LATE EFFECT	DOSE (Gy)
Musculoskeletal	Muscular hypoplasia	>20
	Scoliosis, kyphosis, lordosis	10-20
	Osteocartilaginous exostosis	?
Neuroendocrine (cranial or cranial spinal)	Impaired growth hormone	>18
	Adrenocorticotropic hormone deficiency	>40
	Thyrotropin-releasing deficiency	>40
	Precocious puberty (females mostly)	>20
	Gonadotropin deficiency	<40
Gonad failure	Ovarian failure	4-12
	Testicular failure	>3
Central nervous system dysfunction*	Structured changes	>18
	Cognitive changes	?
Other	Pulmonary fibrosis	
	Nephropathy	
	Liver failure	
	Arteritis	
	Eye impairment	
	Ear impairment	
	Bone marrow dysfunction	
	Cardiac impairment	

*With intrathecal chemotherapy (methotrexate).

Derived from Halperin EC, Constine LS, Tarbell NJ, et al, editors: Pediatric radiation oncology, *ed 3, Philadelphia, 1999, Lippincott Williams & Wilkins.*

percentage of serious complications (5-10%). Radiation causes tissue loss plus injury to the underlying vasculature. The vascular change may be progressive, leading to arteriocapillary fibrosis and irreparable injury, in turn leading to further tissue loss.

The acute effects of therapy (occurring less than 3 mo after therapy begins) are usually related to the area of the body being irradiated (except fatigue, which can begin during this time period). These acute effects include radiation-caused pneumonitis, dermatitis, mucositis and esophagitis, cerebral edema, and swelling of the organ irradiated. There may be changes in bowel movement patterns. Of these, one of the most severe acute reactions is pneumonitis. It can be manifest within 24 hr of irradiation when there is an exudation of proteinaceous material into the alveoli and intraalveolar edema. Most often, however, radiation pneumonitis begins 2-6 mo after the beginning of radiation with a clinical presentation of fever, cough, congestion, and pruritic pain. The late effects of therapy (beginning more than 3 mo after therapy) are numerous (Table 718-6). The most common are abnormalities of pulmonary function, hearing loss, endocrine/reproductive function, cardiac function, and neurocognitive loss.

Annually, childhood cancer affects 70-160 per million children between the ages of 0 and 14 yr. Because of earlier diagnosis and improved therapy, more than 79% of children who were diagnosed from 1995-2001 with cancer are long-term survivors. Approximately 1 in 570 young adults is a long-term survivor of cancer, and up to 25% have a complication related to their therapy. Second cancers account for 6-10% of all cancers in children or adults. Among children in the Childhood Cancer Survivor Study, there is a cumulative incidence of second neoplasms of 3.2% at 20 yr from original diagnosis. Primary malignancies with the highest cumulative incidence of a second neoplasm in the order of frequency are Hodgkin disease (7.6), soft tissue

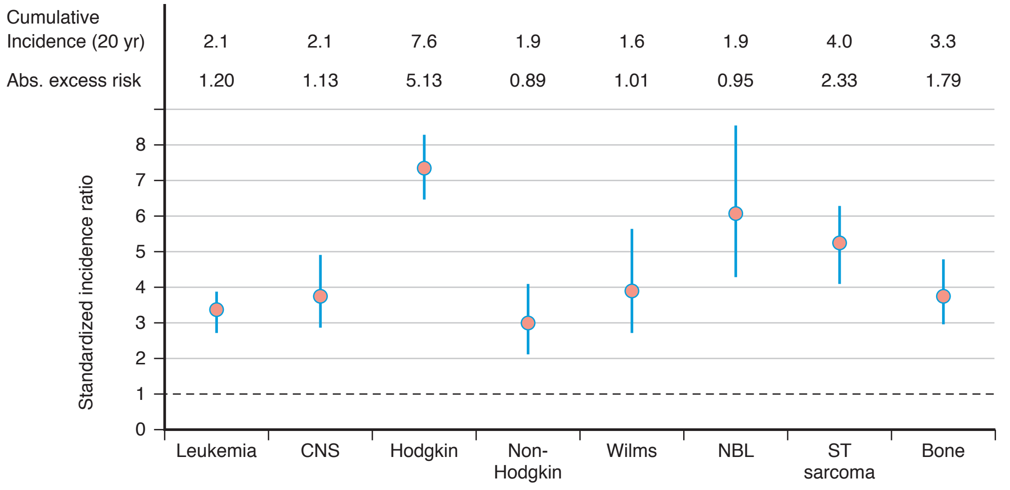

Figure 718-5 Second malignancies among the Childhood Cancer Survivor Study cohort. CNS, central nervous system; NBL, neuroblastoma; ST, soft tissue. *(From Robison LL: Treatment-associated subsequent neoplasms among long-term survivors of childhood cancer: the experience of the Childhood Cancer Survivor Study, Pediatr Radiol 39[Suppl 1]:S32–S37, 2009, Fig. 1.)*

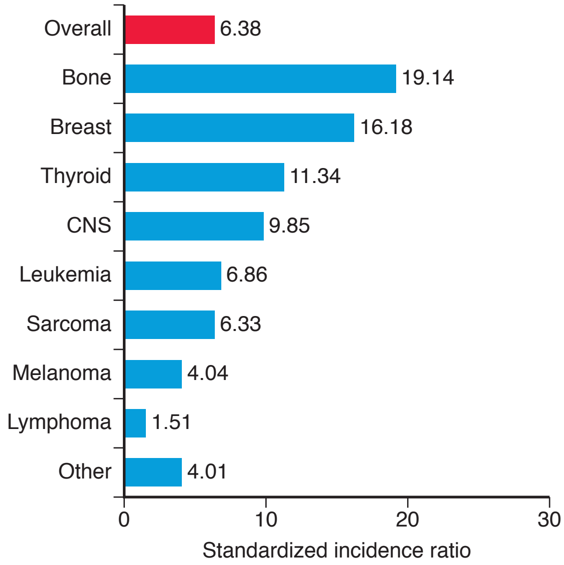

Figure 718-6 Standardized incidence ratio by type of second malignancy. CNS, central nervous system. *(Robison LL: Treatment-associated subsequent neoplasms among long-term survivors of childhood cancer: the experience of the Childhood Cancer Survivor Study, Pediatr Radiol 39[Suppl 1]:S32–S37, 2009, Fig. 2.)*

sarcoma (4.0), cancers of bone (3.3), leukemia (2.1), central nervous system (CNS) cancers (2.1), and non-Hodgkin disease lymphoma (1.9). This reflects an overall standard incidence rate of 6.38% (Fig. 718-5). The most prevalent second tumors are bone, breast, thyroid, and CNS lesions (Fig. 718-6). Table 718-7 relates second cancers to primary cancer and latency period. Almost 70% of the second neoplasms are in the field of the original irradiation. Radiation therapy increases the risk of second cancers in a dose-dependent manner for nongenetic neoplasms.

The exact complications depend on the location of the treatment field. In children, because of the location of many childhood tumors, the normal brain is commonly in the treatment field. Standard irradiation of the brain in children results in cortical atrophy in more than half of patients who receive 2,000-6,000 rads; 26% are left with white matter changes (leukoencephalopathy) and 8% with calcifications. The younger the child is at the time of irradiation, the greater is the atrophy. Some patients also demonstrate mineralizing microangiopathy. Radiation-induced changes of the brain are potentiated by methotrexate administered before, during, or after radiation therapy.

Cerebral necrosis is a serious complication of radiation-induced vascular disease. It usually is diagnosed 1-5 yr after irradiation but can occur up to a decade later. Brain necrosis may manifest as headache, increased intracranial pressure, seizures, sensory deficits, and psychotic changes.

Spinal cord irradiation may result in **radiation myelitis,** which may be either transient or permanent. Acute transient myelitis often appears 2-4 mo after irradiation. Patients with myelitis usually present with **Lhermitte sign,** a sensation of little electrical shocks in the arms and legs occurring with neck flexion or other movements that stretch the spinal cord. Reversal of transient myelopathy usually occurs between 8 and 40 wk and does not necessarily progress to delayed necrosis.

Delayed myelopathy occurs after a mean latent period of 20 mo but can occur earlier if the total dose or the dose per fraction is high. It usually manifests as discontinuous deterioration and is irreversible. In the cervical and thoracic regions, sensory dissociation develops, followed by spastic and then flaccid paresis. In the lumbar cord, flaccid paresis is dominant. The mortality for high thoracic and cervical lesions reaches 70%, death being due to pneumonia and urinary tract infections.

Central nervous system irradiation may also affect growth by compromising function of the pituitary-hypothalamic axis and leading to diminishing growth hormone production and release. Non–growth hormone trophins may also be affected by CNS irradiation, leading to gonadotrophin deficiency or precocious puberty. Central hypothyroidism can also develop. CNS irradiation also compromises bone mineral deposition both locally (in the radiation field) and systemically.

Irradiation also has other effects specific to children (see Table 718-6). Scoliosis and hypoplasia of bones may occur if fractionated treatment schemes exceed 4,000 rad. Fractionated doses higher than 2,500 rad can result in slipped capital femoral epiphyses. An increase in the incidence of benign osteochondromas also has been reported after childhood irradiation. Chest wall irradiation of girls (besides causing breast cancer) may impair breast development and/or cause fibrosis and atrophy of breast tissue.

WHOLE-BODY IRRADIATION

Uncontrolled Large- or Small-Scale Exposure to Radiation

Large-scale exposure to radiation can occur in an event of nuclear accidents, war, or terrorist attacks (see Chapters 39.2 and 723). Radiation as well as explosive and thermal injury need to be considered.

Table 718-7 Second Cancers and Their Relationship with Primary Cancers

SECOND CANCERS	PRIMARY CANCERS	LATENCY (MEDIAN IN Yr)	RISK FACTORS
Brain tumors	ALL; brain tumors; HD	9-10	Radiation; younger age
Myelodysplastic syndromes/acute myelogenous leukemia	ALL; HD; bone tumors	3-5	Topoisomerase II inhibitors; alkylating agents
Breast cancer	HD; bone tumors; soft-tissue sarcomas; ALL; brain tumors; Wilms tumors; NHL	15-20	Radiation; female gender
Thyroid cancer	ALL: HD; neuroblastoma; soft-tissue sarcomas; bone tumors; NH: L	13-15	Radiation; younger age; female gender
Bone tumors	Retinoblastoma (heritable); other bone tumors; Ewing sarcoma; soft-tissue sarcomas; ALL	9-10	Radiation; alkylating agents; removal of the spleen
Soft-tissue sarcomas	Retinoblastoma (heritable); soft-tissue sarcomas; HD; Wilms tumors; bone tumors; ALL	10-11	Radiation; younger age; anthracyclines

ALL, acute lymphocytic leukemia; HD, Hodgkin disease; NHL, non-Hodgkin lymphoma.
From Bhatia S, Sklar S: Second cancers in survivors of childhood cancer. Nat Rev Cancer *2:124–132, 2002.*

Table 718-8 Dose–Effect Relationships After Acute Whole-Body Irradiation from Gamma Rays or X-Rays

WHOLE-BODY ABSORBED DOSE, RAD (Gy)	FINDINGS
5 (0.05)	Asymptomatic
15 (0.15)	Asymptomatic (but chromosome aberrations may be present in cultured peripheral lymphocytes)
50 (0.5)	Asymptomatic (minor depression of white blood cell and platelet counts in a few persons)
100 (1.0)	Nausea and vomiting in approximately 10% of patients within 2 days of exposure
200 (2.0)	Nausea and vomiting in most persons exposed, with clear hematologic depression
400 (4.0)	Nausea, vomiting, and diarrhea within 48 hr; 50% mortality without medical treatment
600 (6.0)	100% mortality within 30 days from bone marrow failure without medical treatment
5,000 (50.0)	Cardiovascular collapse and central nervous system damage, with death in 24-72 hr

Table 718-9 Expected Outcome Based on Absolute Lymphocyte Count After Acute Penetrating Whole-Body Irradiation

MINIMAL LYMPHOCYTE COUNT WITHIN FIRST 48 HR AFTER EXPOSURE	PROGNOSIS
1,000-3,000 (normal range)	No significant injury
1,000-1,500	Significant but probably nonlethal injury, good prognosis
500-1,000	Severe injury, fair prognosis
100-500	Very severe injury, poor prognosis
<100	Lethal without compatible bone marrow donor

Clinical Manifestations

Table 718-8 presents dose–effect relationships for acute whole-body penetrating radiation. A large single exposure of penetrating radiation can result in **acute radiation syndrome.** The signs and symptoms of this syndrome result from damage to major organ systems that have different levels of radiation sensitivity, modulated by the rate at which the radiation exposure occurred. Delivery of 100 rads in 1 min would be symptomatic, but delivery of 1 rad/day for 100 days would not be symptomatic.

The **hematopoietic syndrome** results from acute whole-body doses above 200 rad. A prodromal phase consists of nausea and vomiting within the 1st 12 hr, with symptoms usually lasting up to 48 hr. A latent period of 2-3 wk, during which patients may feel quite well, follows. Although patients are asymptomatic, bone marrow impairment has occurred. The most obvious laboratory finding is lymphocyte depression (Table 718-9). Maximal bone marrow depression occurs approximately 30 days after exposure, when hemorrhage and infection can be major problems. If the bone marrow was not completely eradicated, a recovery phase then ensues. This radiation effect is similar to what occurs when whole-body irradiation (given as 1,200 rads in 2 treatments) is used to obliterate the bone marrow in children with leukemia before bone marrow transplantation.

The **gastrointestinal syndrome** occurs from acute whole-body doses above 800 rads. Prompt onset of nausea, vomiting, and diarrhea follows. There is a latent period of approximately 1 wk followed by recurrence of gastrointestinal symptoms, sepsis, and electrolyte imbalance, which may result in death.

At dose levels exceeding 3,000 rad, the **cardiovascular/CNS syndrome** predominates. Nausea, vomiting, prostration, hypotension, ataxia, and convulsions are almost immediate. Death usually occurs promptly.

Treatment

For the hematopoietic and gastrointestinal syndromes, treatment is supportive, involving transfusions, fluids, antibiotics, and antiviral agents.

Localized Irradiation

Clinical Manifestations

Because localized exposure involves a small amount of tissue, systemic manifestations may be less severe and patients may survive even if locally absorbed doses are very high. The hand is the most common

Table 718-10 Skin Changes After a Single, Acute, Localized Radiation Exposure

ABSORBED DOSE (Gy)	CHANGE
3-4	Epilation in 2-3 wk
10-15	Threshold for erythema; appears 18-20 days after exposure at lower doses; may appear within a few hours at higher doses
20	Moist desquamation, possible ulceration
25	Ulceration with slow healing
30-50	Blistering, necrosis at 3 wk
100	Blistering, necrosis at 1-2 wk

Data from Gusev I, Guskova AK, Mettler FA Jr, editors: Medical management of radiation accidents, *ed 2, Boca Raton, FL, 2001, CRC Press.*

site for accidental localized irradiation injuries, usually as a result of picking up or playing with lost radiation sources. The second most common accidental site is the thigh and buttocks, predominantly from placing unsuspected highly radioactive sources in the pockets.

Table 718-10 lists the skin changes that occur after a single acute, localized irradiation. As opposed to other forms of thermal burns, signs of irradiation appear a period of days *after* the exposure. Vascular insufficiency may appear months to years later and cause ulcerations or necrosis in formerly healed areas. The penetrability of the radiation is an important factor in the outcome of local radiation injury. Beta rays from heavy radiation fallout can cause superficial skin burns because they have low penetrability.

Some tissues that may receive localized radiation exposure are relatively radiosensitive. **Cataract formation** (see Chapter 628) may occur with single gamma ray exposures in the range of less than 1 Gy to several Gy. Such cataracts usually take from 2 mo to several years to develop. **Oligospermia** may take up to 2 mo to develop. Transient infertility in men may result from doses as low as 15 rad, and permanent sterility may occur in men at dose levels between 300 and 600 rad.

Treatment

Skin therapy is directed at prevention of infections. Treatment of localized injuries usually involves plastic surgery and grafting, if the radiation exposure was not very penetrating (see Chapter 75). The nature of the surgery depends on the dose at various depths in tissue and the location of the lesion. The full expression of radiation injury often is not apparent for 1-2 yr, owing to slow arteriolar narrowing that can cause delayed necrosis. After relatively penetrating radiation, amputation may be necessary because of obliterative changes in small vessels.

INTERNAL CONTAMINATION

Epidemiology

Accidents involving internal contamination are rare and are usually the result of misadministration in hospital settings or voluntary ingestion of unsuspected contaminated radioactive materials. Other possible causes of internal contamination of children include ingestion of breast milk from mothers who have had diagnostic nuclear medicine scans and radiation exposure when a parent or sibling receives a therapeutic dose of iodine-131.

Clinical Manifestations

The hazards from internal contamination depend on the nature of both the radionuclide (particularly in terms of its solubility in water, half-life, and radioactive emission) and the chemical compound.

Treatment

The most effective treatment requires knowledge of both the radionuclide and the chemical form. Treatment must be instituted quickly to be effective (Table 718-11). **Removal treatment** involves cleaning a contaminated wound and performing stomach lavage or administration of cathartics in the case of ingestion. Administration of alginate-containing antacids (e.g., Gaviscon) also usually helps in removal by decreasing absorption in the gastrointestinal tract. An example of **blocking therapy** is the administration of potassium iodine or other stable iodine-containing compounds to patients with known internal contamination with radioactive iodine. The stable iodine effectively blocks the thyroid, although its effectiveness decreases rapidly as time elapses after the contamination. The recommended dose of potassium iodine is 16 mg for neonates; 32 mg for children ages 3 yr or younger; and 65 mg for children ages 3-18 yr. Each dose protects for only 1 day. **Dilution therapy** is used in cases of tritium (radioactive hydrogen as water) contamination. Forcing fluids promotes excretion. Cases of internal contamination with transuranic elements (americium and plutonium) may require **chelation therapy** with calcium diethylene triamine pentaacetic acid.

Table 718-11 Specific Therapy for Internal Radiation Contamination

RADIONUCLIDE	THERAPEUTIC APPROACH
Tritium	Dilution (force fluids)
Iodine-125 or iodine-131	Blockage (saturated solution of potassium iodide or potassium iodide), mobilization (antithyroid drugs)
Cesium-134 or cesium-137	Reduction of gastrointestinal absorption (Prussian blue)
Strontium-89 or strontium-90	Reduction of absorption (aluminum phosphate gel antacids), blockage (strontium lactate), displacement (oral phosphate), mobilization (ammonium chloride or parathyroid extract)
Plutonium and other transuranic elements	Chelation with zinc or calcium diethylenetriamine pentaacetic acid (investigational agents)
Unknown	Reduction of absorption (emetics, lavage, charcoal, or laxatives) in cases of ingestion

From Mettler FA, Voelz GL: Major radiation exposure—what to expect and how to respond. N Engl J Med *346:1554, 2002.*

Prussian blue is a drug approved by the FDA for patients with internal contamination with cesium or thallium. It can speed fecal elimination of radioactive cesium from the body. It acts by intercepting the cesium coming into the gut from the bile. Prussian blue prevents the cesium from being absorbed again from the gut. Prussian blue can be given days after ingestion, unlike potassium iodine, which must be given initially in the 1st 12-24 hr after exposure.

EXTERNAL CONTAMINATION

The presence of external radioactive contamination on a patient's skin is not an immediate medical emergency. Management involves removing and controlling the spread of radioactive materials. If a patient has suspected surface contamination and no physical injuries, decontamination can be performed relatively easily. If substantial physical trauma or other life-threatening injuries are combined with external contamination, surface decontamination should proceed only after the patient has been stabilized physiologically. In many accident situations, essential medical care is delayed inappropriately by hospital emergency staff because of fear of radiation or spread of contamination in the hospital. After a radiation accident, triaging of patients is critical and is based on exposure and symptoms (Fig. 718-7).

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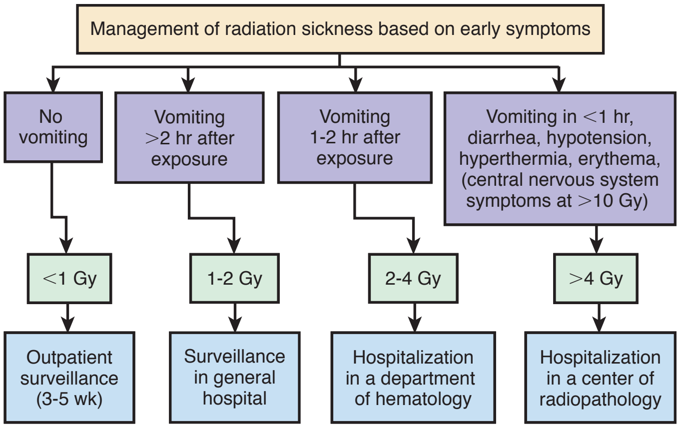

Figure 718-7 Management of radiation sickness at different levels of medical care, depending on the appearance of early symptoms and the estimated radiation dose to the whole body. *(From Turai I, Veress K, Günalp B, et al: Medical response to radiation incidents and radionuclear threats, BMJ 328:568–572, 2004.)*

Chapter 719
Chemical Pollutants

Philip J. Landrigan and Joel A. Forman

More than 85,000 new synthetic chemicals have been developed in the past 75 yr. Most did not previously exist in nature. These chemicals are used today in millions of products ranging from food packaging to clothing, building materials, motor fuels, cleaning products, cosmetics, medical products, toys, and baby bottles.

Synthetic chemicals are widely disseminated in the environment. The Toxic Release Inventory of the U.S. Environmental Protection Agency (EPA) reports that in 2011 more than 4 billion pounds of toxic chemicals were discharged to air, water, and land in the United States.

Human exposure to toxic synthetic chemicals is widespread. Children are especially likely to be exposed to the nearly 3,000 chemicals that are produced in amounts of 1 million pounds or more per yr. These are designated by the EPA as high-production-volume chemicals. Biomonitoring data on blood and urine levels of more than 200 high-production-volume chemicals are obtained annually by the Centers for Disease Control and Prevention in a sample of the U.S. population through the National Health and Nutrition Examination Survey. These data document that American children are exposed to a broad array of synthetic chemicals.

Toxic chemicals are being exported in ever-increasing quantities to the world's poorer countries as these countries pass through industrial development. Environmental safeguards in those countries are typically not as stringent as in the industrially developed nations, and the potential for serious exposure to children there is therefore high.

SYNTHETIC CHEMICALS AND HUMAN HEALTH

Some synthetic chemicals have greatly benefitted human health. Antibiotics have helped control the major communicable diseases. Chemical disinfectants have reduced deaths from dysentery. Chemotherapeutic agents have made possible the cure of many childhood cancers.

But new chemicals have also been responsible for tragic episodes of disease, death, and environmental degradation. Many of these episodes have resulted in severe injury to children. A recurrent pattern has been that new chemicals were brought to market with great enthusiasm, were presumed harmless, and underwent little or no premarket safety testing. Then yr or decades later, after they had come into wide use, established markets, and become widely disseminated in the environment, the chemicals were found to have harmful effects.

Historical examples of synthetic chemicals that were initially hailed as beneficial but later found to cause great harm include *thalidomide*, a mild sedative that proved very effective at suppressing "morning sickness" in the 1st trimester of pregnancy, but later was found to have caused an epidemic of phocomelia in infants exposed in utero; *tetraethyl lead*, which was added to gasoline in the United States from the early 1930s until 1980 and was responsible for widespread lead poisoning with subclinical neurotoxicity and reduction in IQ across 2 generations of U.S. children (see Chapter 721); the pesticide *dichlorodiphenyltrichloroethane (DDT)*, the environmental toxicity of which very nearly led to extinction of the osprey and the American bald eagle and that more recently was linked to increased risk for human breast cancer; the *polychlorinated biphenyls (PCBs)*, highly persistent pollutants of which production was banned in 1977 but which continue today to contaminate major lakes and rivers and which have been found also to be responsible for loss of IQ and disruption of behavior in U.S. children; *diethylstilbestrol (DES)*, which was administered to pregnant women to prevent miscarriage and later found to cause adenocarcinoma of the vagina in girls and young women who had been exposed in utero; and the ozone-destroying *chlorofluorocarbons*.

Other examples of synthetic chemicals that came into wide use with little assessment of their potential hazards include the *phthalates*, plasticizers widely used in plastics, cosmetics, and common household products, which are linked to increased risk for reproductive abnormalities in baby boys and to heightened risk of behavioral abnormalities that resemble attention-deficit/hyperactivity disorder (see Chapter 33); *polybrominated diphenyl ethers*, a class of chemicals widely used as flame retardants in carpets, furniture, and electronic equipment that are linked to persistent loss of intelligence and disruption of behavior; and *bisphenol A*, a plastics chemical that has been linked to neurodevelopmental disorders. These chemicals are all produced in volumes of millions of tons per yr, are widely disseminated in the environment, and are detectable in the bodies of nearly all Americans. Only now, decades after their introduction, are their possible hazards to children's health beginning to be assessed.

CHILDREN'S UNIQUE SUSCEPTIBILITY TO SYNTHETIC CHEMICALS

The health effects of synthetic chemicals are especially serious when exposure occurs in early life—during pregnancy, in infancy, or in early childhood. Children are uniquely vulnerable to chemical pollutants for several reasons:

1. Children have proportionally greater exposures to many environmental pollutants than adults. Because they drink more water, eat more food, and breathe more air per kilogram of body weight, children are more heavily exposed to pollutants in water, food, and air. Children's hand-to-mouth behavior and their play close to the ground further magnify their exposures.
2. Children's metabolic pathways, especially in the 1st few mo after birth, are immature. Although in some instances children are better able than adults to cope with environmental toxicants because they are unable to metabolize them to their active form, children are frequently less able to detoxify and excrete chemical pollutants.
3. Infants and children are growing and developing, and their complex, fast-moving, and highly choreographed developmental processes are uniquely sensitive to disruption by chemical pollutants. Exposures to even minute doses of toxic chemicals during windows of exquisite vulnerability in early development have been shown to cause a wide array of diseases in childhood and also to increase risk for chronic disease and disability lifelong (Table 719-1).
4. Because children have many future years of life, they have time for the development of multistage chronic diseases that may be triggered by early exposures.

Table 719-1 Effects of Selected Chemical Pollutants on Infants and Children

CHEMICAL POLLUTANT	EFFECT(S)
Air pollution	Asthma, other respiratory diseases, sudden infant death syndrome
Asbestos	Mesothelioma and lung cancer
Benzene, nitrosamine, vinyl chloride, ionizing radiation	Cancer
Diethylstilbestrol	Adenocarcinoma of the vagina after intrauterine exposure
Environmental tobacco smoke	Increased risk of sudden infant death syndrome and asthma
Ethyl alcohol	Fetal alcohol syndrome after intrauterine exposure
Lead	Neurobehavioral toxicity from low-dose exposure
Methyl mercury	Developmental neurotoxicity
Organophosphate insecticides	Developmental neurotoxicity
Polychlorinated biphenyls	Developmental neurotoxicity
Polybrominated diphenyl ethers	Developmental neurotoxicity
Phthalates	Developmental neurotoxicity and reproductive impairment
Thalidomide	Phocomelia after intrauterine exposure
Trichloroethylene	Elevated risk of leukemia after intrauterine exposure

The unique susceptibility of infants and children to toxic chemicals—susceptibility that is both quantitatively and qualitatively different from that of adults—is summarized in the phrase “children are not little adults.”

SAFETY TESTING OF SYNTHETIC CHEMICALS

A fundamental problem in environmental pediatrics is that only approximately 65% of high-production-volume chemicals have been tested for their potential hazards to human health, and fewer than 30% have been assessed for their pediatric or developmental toxicity. In the United States, chemicals are regulated under the 1976 Toxic Substances Control Act. Unfortunately, this law is obsolete, broken, and fails to protect children’s health against toxic synthetic chemicals.

At the time of its passage, the Toxic Substances Control Act was intended to be pioneering legislation that would require chemicals already in commerce to be tested for potential toxicity and that would also require premarket safety testing of all new chemicals. The Toxic Substances Control Act never fulfilled these noble intentions. A particularly egregious lapse was a decision by the Congress to “grandfather in” 62,000 chemicals already on the market without any toxicity testing. These chemicals were simply presumed to be safe and allowed to remain in commerce unless the EPA made a finding that they posed an “unreasonable risk.” Under the Toxic Substances Control Act, only 5 chemicals have been banned in the United States in the past 35 yr: PCBs, the ozone-destroying chlorofluorocarbons, dioxin, asbestos, and hexavalent chromium.

In consequence of the failure of current chemical safety legislation in the United States, chemicals are de facto presumed to be safe until they are proven beyond any shadow of doubt to cause harm. New chemicals are brought to the market with little or no safety testing. By contrast, the Registration, Evaluation, Authorization, and Restriction of Chemicals legislation, passed by the European Union in 2006, requires chemicals to be proven safe before they come to market and places the burden on industry to document chemical safety; there is no equivalent in the United States.

The EPA requires the manufacturers of 67 pesticide chemicals to determine whether these chemicals have the potential to disrupt the endocrine system. The results of this request for data led the EPA to develop a new Endocrine Disruptor Screening Program Comprehensive Management Plan that is analyzing the endocrine disrupting properties of chemical pesticides.

The United Nations Environment Programme (UNEP) is the agency within the United Nations that is responsible for the global management of chemicals. UNEP promotes chemical safety by providing information, policy advice, and technical guidance on toxic chemicals to developing and transitional countries. UNEP advocates for the establishment of international treaties to ban and control chemical substances. UNEP coordinates with other international organizations such as the Food and Agriculture Organization of the United Nations. UNEP has been centrally involved in partnership with the World Health Organization in coordinating the global effort to remove lead from gasoline in countries around the world.

SYNTHETIC CHEMICALS AND DISEASE IN CHILDREN

A large and growing body of evidence accumulated over the past 5 decades documents that chemical pollutants in the environment can cause disease and dysfunction in children. High-dose exposures can cause acute, clinically evident disease. Lower-dose exposures can cause subclinical injury—injury that is very real but detectable only through special testing—such as decreases in intelligence, shortening of attention span, and disruption of behavior. When exposure to a chemical pollutant is widespread, subclinical toxicity can reduce intelligence and cause other adverse effects across entire societies (Fig. 719-1).

CHEMICAL POLLUTANTS OF MAJOR CONCERN

Air Pollutants

The outdoor air pollutants of greatest concern are photochemical oxidants (especially ozone), oxides of nitrogen, fine particulates, sulfur oxides, and carbon monoxide. These pollutants result principally from the combustion of fossil fuels. Automotive emissions are the major source of air pollution worldwide, followed by stationary sources such as coal-fired power plants and other industrial sources.

Elevated values of air pollutants, especially fine particulates, ozone, and oxides of nitrogen, are associated with respiratory problems in children, including decreased pulmonary expiratory flow, wheezing, and exacerbations of asthma. Fine particulate air pollution, even at low levels, is associated with slight increases in cardiopulmonary mortality and with an increased death rate from sudden infant death syndrome (see Chapter 375). A prospective cohort study of air pollution and lung development in California found an association between pollution and reduced lung growth from ages 10-18 yr, which leads to clinically significant decreases in lung function that persist into adulthood. It is notable that these effects were seen at air toxic levels below the National Ambient Air Quality Standards set by the EPA under the Clean Air Act.

Indoor air also can be an important source of respiratory irritation, because many children spend 80-90% of their time indoors. Globally, indoor air pollution is largely caused by household use of solid fuel, such as wood, charcoal, or dung. According to the World Health Organization, globally more than 2 million children < age 5 yr die each year from acute respiratory infections of which 50% are attributable to the indoor burning of biomass fuels. Indoor air pollution has become especially important in the United States since the energy crises of the 1970s, which led to the construction of tighter, more energy-efficient homes. Second-hand cigarette smoke is an especially hazardous constituent of indoor air and a powerful asthma trigger. Allergens in indoor air can contribute to respiratory problems and include cockroach, mite, mold, and cat and dog allergens.

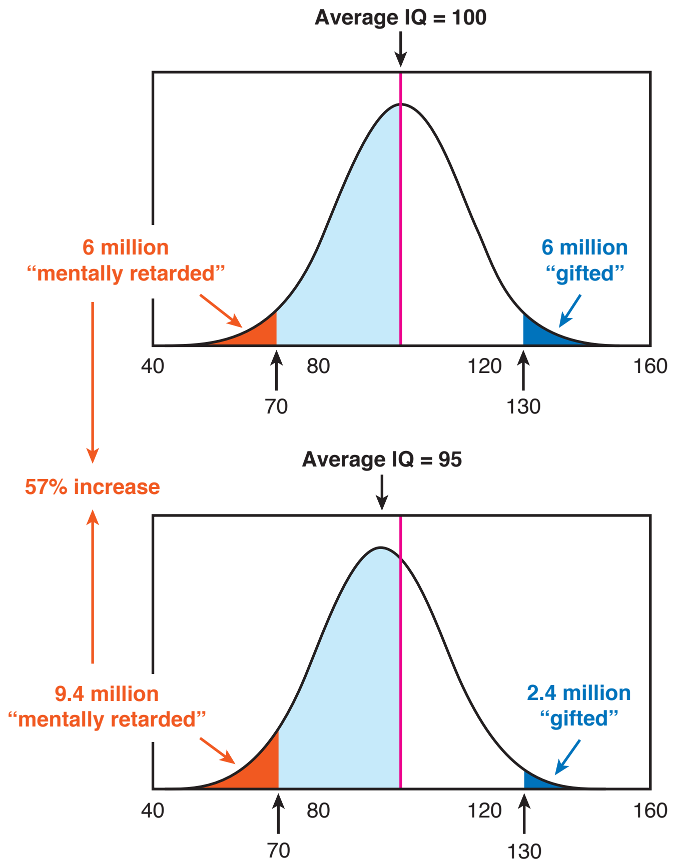

Figure 719-1 **Societal impact of subclinical neurotoxicity.** Widespread exposure to a neurotoxic chemical pollutant that reduces average IQ by 5 points can reduce the number of children in a society with truly superior intelligence (IQ scores above 130 points) by more than 50% and likewise cause a more than 50% increase in the number with IQ scores below 70, thus increasing the number of children who do poorly in school, require special education and other remedial programs, and cannot contribute fully to society when they become adults. Although subclinical effects may be small at the individual level, the aggregate effects at a population level can have far-reaching consequences. And until the toxicity is recognized, the damage can proceed unchecked for many years. *(From Schettler, T Stein J, Reich F, Valenti M.* In harm's way: toxic threats to child development. A report by Greater Boston Physicians for Social Responsibility, *2000, p 25. Available at: http://www.psr.org/chapters/boston/resources/in-harms-way.html.)*

Oil Spill Hazards

Through 2014, there have been at least 36 crude oil spills worldwide. Ten of these spills have occurred since 1980, the largest in 2010. Although specific composition and concentrations vary, crude oil contains many toxic chemicals that are of concern to human health, including metals (e.g., zinc, cadmium, and lead) (see Chapters 720 and 721), volatile organic compounds (including benzene, toluene, ethyl benzene, and styrene), and semivolatile organics (such as polycyclic aromatic compounds). Several of these compounds are classified as possible or potential carcinogens, endocrine disruptors, and neurotoxins. Chemical dispersants—mixtures of detergents and organic solvents—are often used to break up spilled oil and may also have potential adverse effects on health. Toxic effects may occur from exposure during contact with the skin, eyes, or respiratory tract or in a person's diet (e.g., drinking of contaminated water or eating of contaminated seafood).

Commonly reported symptoms from direct exposure to crude oil include eye redness and burning, rashes, sore throat, respiratory difficulty, and acute neurologic symptoms such as headache and nausea. Children with asthma may be particularly vulnerable to respiratory toxicity. The amount and duration of exposure along with individual genetic variability influence the degree of symptoms.

Most information on health effects of oil spills comes from studies of exposed adult workers; there are few studies of health effects, acute or long term, in children. Studies of workers exposed to spilled oil have noted elevated blood concentrations of heavy metals such as lead and cadmium, evidence of genotoxic effects, and endocrine disruption (as manifested by changes in prolactin and cortisol levels). Children and teens are at risk for exposure in a variety of settings, including recreational activities like swimming and boating as well as clean-up efforts. Children should not be allowed to play in or around areas where the water or beach contains oil or sludge. In light of teenagers' propensity to not adhere as well as adults to workplace safety regulations, teens should not be directly involved in spill clean-up efforts.

Lead

See Chapter 721.

Mercury

See Chapter 720.

Asbestos

Between 1947 and 1973, asbestos was sprayed as insulation on classroom walls and ceilings in approximately 10,000 schools in the United States. Subsequent deterioration of this asbestos has released asbestos fibers into the air. Asbestos is not a health hazard so long as it is intact, but once it becomes airborne, it can be inhaled by children to produce adverse health effects. Asbestos is a human carcinogen, and the 2 principal cancers caused by asbestos are lung cancer and mesothelioma. U.S. federal law requires that all schools be inspected periodically for asbestos and that the results be made public. Removal is required only when asbestos is visibly deteriorating or is within the reach of children. In most cases, placement of barriers (drywall walls or drop ceilings) provides appropriate protection.

Second-Hand Tobacco Smoke

Smoking during pregnancy poses a hazard to the fetus (see Chapter 96). Infants born to women who smoke are, on average, 10% smaller than infants born to nonsmoking women. Infants of parents who smoke have a higher risk of sudden infant death syndrome. Nicotine from tobacco smoke appears to be a developmental neurotoxin.

Second-hand smoke exposure is also a hazard to children. The United States has made substantial progress in reducing exposure to second-hand smoke over the last 15 yr and serum cotinine levels have declined by 70% in U.S. nonsmokers of all ages. Children <12 yr old continue to have mean cotinine levels twice those of adults, highlighting their unique vulnerability. Children exposed to second-hand tobacco smoke have increased frequency of lower respiratory illness, more middle-ear effusions, and more viral respiratory illnesses than unexposed children.

Pesticides

Pesticides are a diverse group of chemicals used to control insects, weeds, fungi, and rodents. Approximately 600 pesticides are registered with the EPA for use in the United States.

Diet is a major route of children's exposure to pesticides, because children are exposed to residues of multiple pesticides on fruit and vegetables, especially fruits and vegetables imported from countries where pesticide use is heavier than in the United States. Children also may be exposed in homes or schools, on lawns, and in gardens. They may be exposed to pesticide drift from agricultural areas that have been sprayed. Children employed in agriculture or living in migrant farm camps are at risk of direct exposure to many pesticides.

Children can be acutely overexposed to pesticides. High-dose exposure to both organophosphates and carbamate pesticides can cause acute neurotoxicity. Both of these classes of pesticides act through inhibition of acetylcholinesterase and are responsible for the largest number of acute poisoning cases. Symptoms include meiosis (although not in all cases), excess salivation, abdominal cramping, vomiting,

diarrhea, and muscle fasciculation. In severe cases, the child may experience loss of consciousness, cardiac arrhythmias, and death by respiratory arrest. The war gas sarin is an organophosphate. See Chapter 63 for treatment of poisoning from drugs, chemicals, and plants.

Pesticides can also cause a range of chronic toxic effects: polyneuropathy and central nervous system dysfunction (organophosphates); hormonal disruption and reproductive impairment (DDT, kepone, dibromochloropropane); cancer (aldrin, dieldrin, chlorophenoxy herbicides [2,4,5-T]); and pulmonary fibrosis (paraquat). Prenatal exposure to organophosphate pesticides at levels that produce no evident toxicity in pregnant women has been associated with neurodevelopmental disability in children, with reduction in IQ and disordered executive function.

Children's exposures to pesticides can be reduced by minimizing applications to lawns, gardens, schools, and playgrounds; adapting techniques of integrated pest management; and reducing pesticide applications to food crops. Consumption of organic produce dramatically reduces organophosphate pesticide exposure in school-age children. Exposure to herbicides may increase due to an EPA decision to expand their use in agriculture.

Polychlorinated Biphenyls, DDT, Dioxins, Brominated Flame Retardants, and Other Halogenated Hydrocarbons

Chlorinated hydrocarbons are used as insecticides (DDT), plastics (polyvinyl chloride), electrical insulators (PCBs), and solvents (trichloroethylene). Highly toxic dioxins and furans are formed during synthesis of chlorinated herbicides or as by-products of plastic combustion. All of these materials are widely dispersed in the environment. Brominated flame retardants are used in carpets, furniture, and computers. DDT, PCBs, and dioxins are highly persistent.

The embryo, fetus, and young child are at particularly high risk of injury from halogenated hydrocarbons. All of these compounds are lipid-soluble. They readily cross the placenta, and they accumulate in breast milk. Intrauterine exposure to PCBs and brominated flame retardants has been linked to persistent neurobehavioral dysfunction in children.

Fish from contaminated waters are a major source of children's exposure to PCBs. Children can be exposed in utero or through breast milk. To protect children and pregnant women in the United States against PCBs in fish, government agencies have issued advisories concerning fish consumption for certain lakes and rivers. Combustion of medical wastes containing polyvinyl chloride and the use of chlorine to bleach paper products are major preventable sources of environmental dioxin and should be discouraged. Older fluorescent light ballasts that were installed decades ago in schools in the United States are another source of PCB exposure. PCB-containing ballasts should be removed from schools as soon as possible to prevent environmental contamination. Removal must be performed by trained workers.

Endocrine Disruptors

A number of chemicals have been shown to adversely affect the endocrine systems of animals and humans, including DES, DDT, PCBs, and dioxins. Other chemicals, such as other pesticides and phthalates (plasticizers), are also suspected of possessing endocrine disruptor effects. Phthalates have been associated with obesity in animal experiments. Higher urinary levels of bisphenol A are associated with obesity-related outcomes, such as cardiovascular disease, in a cross-sectional analysis of National Health and Nutrition Examination Survey 2003-2004 data in adults. The many effects of endocrine disruptors on wildlife include eggshell thinning in birds, sterility in seals, feminization and cryptorchidism in panthers, and low hatching rates in alligators. In humans, endocrine disruption is implicated in the epidemiologic observations of a trend toward earlier thelarche and menarche in girls (see Chapter 14), the rising rates of testicular cancer and hypospadias, and diminishing sperm counts. The most clearly observed effects include adenocarcinoma of the vagina in women and cryptorchidism in men whose mothers took DES and shortening of the anogenital distance, a measure of in utero feminization, in baby boys whose mothers had elevated exposures to phthalates during pregnancy. The presence of elevated concentrations of plasma phthalate esters is associated with early thelarche in Puerto Rican girls. Some endocrine disruptors may also have adverse effects on brain development. Prenatal exposure to low-molecular-weight phthalates is associated with shortening of attention span in children 4-9 yr old.

Environmental Carcinogens

Children may be exposed to carcinogenic pollutants in utero or after birth. Children appear more sensitive than adults to certain chemical carcinogens and also to ionizing radiation (see Chapter 718). The potential for in utero carcinogenesis was first recognized with the discovery that clear cell adenocarcinoma of the vagina could develop in women after intrauterine exposure to DES.

Carcinogenesis also may be associated with exposures in the home and community. Children of asbestos workers and children who have grown up near asbestos plants have been found to have a higher incidence of mesothelioma than unexposed populations. Children who grow up on farms have elevated rates of leukemia; pesticides are suspected of playing an etiologic role. Intrauterine exposure to trichloroethylene via contaminated drinking water has been associated with an increased incidence of leukemia among girls living near an industrial facility and industrial waste site.

Routes of Exposure

Transplacental. Heavy metals such as lead and mercury, fat-soluble compounds such as PCBs and DDT, and endocrine disruptors such as phthalates readily cross the placenta. They may have serious and irreversible toxic effects on the developing nervous, endocrine, and reproductive organs, even at very low levels.

Water. Approximately 200 chemicals have been found in various amounts in water supplies. Lead is especially common. In some older neighborhoods, lead in water derives from lead pipes. More commonly, it is dissolved (leached) by soft, acidic water from lead-containing solder. The highest levels of lead occur in water that has been standing in pipes overnight. It is wise therefore to run water for 2-3 min each morning before making up infant formula. Solvents and components of gasoline such as methyl tertiary-butyl ether and benzene are commonly encountered in groundwater. Herbicides, like atrazine, are commonly found contaminants in drinking water in agricultural areas.

Air. Vehicular emissions are the major source of urban air pollution. Diesel exhaust is a human carcinogen. In rural areas, wood smoke can contribute to air pollution. Children living in the vicinity of smelters and chemical production plants can be exposed to toxic industrial emissions such as lead, benzene, and 1,3-butadiene.

Food. Many chemicals are intentionally added to food to improve appearance, taste, texture, or preservation, but many such chemicals have been poorly tested for potential toxicity. Residues of many pesticides are found in both raw and processed foods. Levels of pesticides are lower in organic produce than in conventionally grown fruits and vegetables. Children who consume organic produce have substantially lower urinary pesticide levels than children who eat conventional produce.

Work Clothes. Illnesses in children sometimes may be traced to contaminated dust from parents' work clothes; toxicity from lead, beryllium, dioxin, organophosphate pesticides, and asbestos has occurred. Such exposure (termed "fouling the nest") can be prevented by providing facilities at work for changing and showering.

Schools. Children may be exposed in schools, kindergartens, and nurseries to lead paint, molds, asbestos, environmental tobacco smoke, pesticides, and hazardous arts and crafts materials. Substantial opportunities for prevention exist in the school environment, and pediatricians are often consulted for advice.

Child Labor. Four to 5 million children and adolescents in the United States work for pay, and child labor is widespread around the world. Working children are at high risk of physical trauma and injury. They also may be exposed to a wide range of toxic chemicals, including

pesticides in agriculture and lawn work, asbestos in construction and building demolition, and benzene in pumping gasoline.

THE PHYSICIAN'S ROLE

Pediatricians have time and again played key roles in the initial recognition of diseases caused by toxic chemicals. Every pediatrician needs to be an "alert clinician" ever open to the possibility of discovering new diseases in children caused by exposures in the environment. In considering the origins of noninfectious disease, pediatricians should ask about the home environment, parental occupation, unusual exposures, and neighborhood factories. An environmental cause is particularly likely when several unusual cases of disease or constellations of findings occur together. Any adolescent with a traumatic injury may have been injured at work.

The history is the single most important instrument for obtaining information on environmental exposures. Information about current and past exposures (including questions about work and travel to or residence in developing countries) should be sought routinely on every new patient and on every patient with illness of unclear causation through a few brief screening questions. Changes in patterns of exposure or new exposures may be especially important. If suspicious information is elicited, more detailed follow-up should be pursued. Referral to a pediatric environmental health specialty unit may be indicated (http://aoec.org/PEHSU/index.html). Accurate diagnosis of an environmental cause of disease can lead to better care of sick children and prevention of disease in other children.

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Chapter 720

Heavy Metal Intoxication

Prashant V. Mahajan

Lead, mercury, arsenic, and cadmium, 4 of the World Health Organization's (WHO) "10 chemicals of greatest public health concern," are the heavy metals posing the greatest threats to humans. The most prevalent of these exposures is lead (see Chapter 721). This chapter discusses mercury and arsenic.

Heavy metal intoxication results in diverse multiorgan toxicity through widespread disruption of vital cellular functions. A meticulous history of environmental exposure may be necessary to correctly identify heavy metals as the source of the protean manifestations associated with such exposure. Arsenic exposure can occur from contaminated food or water; globally, more than 100 million people are estimated to be chronically exposed to drinking water containing high arsenic levels. Mercury exposure occurs primarily through food; fish is a major source of methyl mercury exposure.

ARSENIC

Epidemiology

Arsenic is a metalloid that exists in 4 forms: elemental arsenic, arsine gas, inorganic arsenic salts (pentavalent arsenate form or trivalent arsenite form), and organic arsenic compounds. Toxic manifestations are higher in the more soluble and higher-valence compounds. **Arsine gas** is the most toxic form of arsenic. Mass poisonings from exposure to arsenic have occurred throughout history, including one in 1998 in Wakayama, Japan, in which 70 people were poisoned. Children may be poisoned after exposure to inorganic arsenic found in pesticides, herbicides, dyes, homeopathic medicines, and certain contaminated folk remedies from China, India, and Southeast Asia (see Chapter 64). Soil deposits contaminate artesian well water. Groundwater contamination with arsenic is a common problem in developing countries and has been reported to be a common well contaminant in Alaska, Maine, North Carolina, and areas in western United States. Food products (e.g., rice, organic brown rice syrup, fruit juices) cooked in contaminated water may actually absorb arsenic, thus concentrating it in the food. The WHO has set 10 µg/L as the upper limit of safety. In many parts of Asia and South America, this limit is frequently exceeded. Arsenic concentrations in one quarter of the wells in Bangladesh exceed 50 µg/L and 35-77 million of the 125 million inhabitants of Bangladesh regularly consume arsenic-contaminated water. Occupational exposure may occur in industries involved in the manufacturing, mining, smelting, or refining of glass, pottery, electronic and semiconductor components, and lasers. Although arsenic is no longer produced in the United States, it is produced in many countries and is imported into the United States for industrial use. Organic arsenic compounds may be found in seafood, pesticides, and some veterinary pharmaceuticals. In contrast to mercury, the organic forms of arsenic found in seafood are nontoxic.

Pharmacokinetics

Elemental arsenic is insoluble in water and bodily fluids and, therefore, is insignificantly absorbed and nontoxic. Inhaled arsine gas is rapidly absorbed through the lungs. The inorganic arsenic salts are well absorbed through the gastrointestinal tract, lungs, and skin. The organic arsenic compounds are well absorbed through the gastrointestinal tract. After acute exposure, arsenic initially is bound to the protein portion of hemoglobin in the red blood cells (RBCs) and rapidly distributed to all tissues. Inorganic arsenic is methylated and is eliminated predominantly by the kidneys, with approximately 95% excreted in the urine and 5% excreted in the bile. Most of the arsenic is eliminated in the 1st few days, with the remainder slowly excreted over a period of several weeks. Arsenic concentrates in hair, nails, and skin. Measurement of the distance of **Mees lines** (transverse white striae on the nail) from the nail bed can provide an estimate of time of exposure (nails grow at the rate of 0.4 mm/day).

Pathophysiology

After exposure to arsine gas, absorbed arsine enters RBCs and is oxidized to arsenic dihydride and elemental arsenic. Complexing of these derivatives with red cell sulfhydryl groups results in cell membrane instability and massive hemolysis. The inorganic arsenic salts poison enzymatic processes vital to cellular metabolism. Trivalent arsenic binds to sulfhydryl groups, resulting in decreased production of adenosine triphosphate through the inhibition of enzyme systems such as the pyruvate dehydrogenase and α-ketoglutarate complexes. Pentavalent arsenic may be biotransformed to trivalent arsenic or substituted for phosphate in the glycolytic pathway, resulting in uncoupling of oxidative phosphorylation.

Clinical Manifestations

Arsine gas is colorless, odorless, nonirritating, and highly toxic. Inhalation causes no immediate symptoms. After a latent period of 2-24 hr, exposed individuals experience massive hemolysis, malaise, headache, weakness, dyspnea, nausea, vomiting, abdominal pain, hepatomegaly, pallor, jaundice, hemoglobinuria, and renal failure (Table 720-1). Acute ingestion of arsenic produces gastrointestinal toxicity within minutes to hours and is manifested as nausea, vomiting, abdominal pain, and diarrhea. Hemorrhagic gastroenteritis with extensive fluid loss and third spacing may result in hypovolemic shock. Cardiovascular toxicity includes QT interval prolongation, polymorphous ventricular tachycardia, congestive cardiomyopathy, pulmonary edema, and cardiogenic shock. Acute neurologic toxicity includes delirium, seizures, cerebral edema, encephalopathy, and coma. Lethal doses of arsenates are 5-50 mg/kg; lethal doses of arsenites are <5 mg/kg.

Late sequelae include hematuria, proteinuria, and acute tubular necrosis. A delayed sensorimotor peripheral neuropathy may appear days to weeks after acute exposure, secondary to axonal degeneration. Neuropathy manifests as painful dysesthesias followed by diminished vibratory, pain, touch, and temperature sensation; decreased deep tendon reflexes; and, in the most severe cases, an ascending paralysis with respiratory failure mimicking Guillain-Barré syndrome (see

Chapter 616). Adult survivors of infant arsenic poisoning experience higher mortality from disorders of the nervous system compared to adults without such exposure.

Subacute toxicity is characterized by prolonged fatigue, malaise, weight loss, headache, chronic encephalopathy, peripheral sensorimotor neuropathy, leukopenia, anemia, thrombocytopenia, chronic cough, and gastroenteritis. Mees lines in the nails become apparent 1-2 mo after exposure in approximately 5% of patients. Dermatologic findings include alopecia, oral ulceration, peripheral edema, a pruritic macular rash, and desquamation.

Chronic arsenic toxicity causes significant morbidity in children resulting in skin lesions, lung disease, and defect in intellectual function. **Chronic exposure** to low levels of arsenic is usually from environmental or occupational sources. Over the course of years, dermatologic lesions develop, including hyperpigmentation, hypopigmentation, hyperkeratoses (especially on the palms and soles), squamous and basal cell carcinomas, and **Bowen disease** (cutaneous squamous cell carcinoma in situ). Encephalopathy and peripheral neuropathy may be present. Hepatomegaly, hypersplenism, noncirrhotic portal fibrosis, and portal hypertension occur. **Blackfoot disease** is an obliterative arterial disease of the lower extremities associated with chronic arsenic exposure that has been described in Taiwan. Carcinogenicity of chronic arsenic exposure is reflected in increased rates of cancers of the skin, lung, liver, bladder, and kidney as well as of angiosarcomas. The effects of prenatal exposure to arsenic are uncertain but may include low birthweight.

Table 720-1 Effects of Arsenic on Organ Systems

ORGAN SYSTEM	EFFECTS OF ARSENIC
Gastrointestinal system	Submucosal vesicles, watery or bloody diarrhea, severe hematemesis
Cardiovascular system	Reduced myocardial contractility, prolonged QT intervals, tachyarrhythmias
	Vasodilation, hypotension
Kidneys	Hematuria, proteinuria, acute tubular necrosis
Nervous system	Toxic encephalopathy with seizures, cerebral edema, and coma
	Chronic exposure: peripheral painful sensorimotor neuropathy
Hematologic and lymphatic system	Anemia and thrombocytopenia; acute hemolysis with arsine gas
Liver	Fatty degeneration with central necrosis
Skin	Desquamation, alopecia, hyperkeratosis, nail changes
	Chronic exposure: hyperkeratosis, hyperpigmentation
Teratogenic	Neural tube defects in the fetus
Oncologic	Urologic cancer, other malignancies

Laboratory Findings

The diagnosis of arsenic intoxication is based on characteristic clinical findings, a history of exposure, and elevated urinary arsenic values, the last of which confirm the exposure. A spot urine arsenic level should be determined for symptomatic patients before chelation, although initially the result may be negative. Because urinary excretion of arsenic is intermittent, definitive diagnosis depends on a 24 hr urine collection. Concentrations greater than 50 μg/L in a 24 hr urine specimen are consistent with arsenic intoxication (Table 720-2). Urine specimens must be collected in metal-free containers. Ingestion of seafood containing nontoxic arsenobetaine and arsenocholine can cause elevations of urinary arsenic. Blood arsenic levels rarely are helpful because of their high variability and the rapid clearance of arsenic from the blood in acute poisonings. Elevated arsenic values in the hair or nails must be interpreted cautiously because of the possibility of external contamination. Abdominal radiographs may demonstrate ingested radiopaque arsenic.

Later in the course of illness, a complete blood cell count may show anemia, thrombocytopenia, and leukocytosis, followed by leukopenia, karyorrhexis, and basophilic stippling of RBCs. The serum concentrations of creatinine, bilirubin, and transaminases may be elevated; urinalysis may show proteinuria, pyuria, and hematuria; and examination of the cerebrospinal fluid may show protein elevations.

MERCURY

Epidemiology

Mercury exists in 3 forms: elemental mercury, inorganic mercury salts, and organic mercury (Table 720-3). **Elemental mercury** is present in thermometers, sphygmomanometers, barometers, batteries, and some latex paints produced before 1991. Workers in industries producing these products may expose their children to the toxin when mercury is brought home on contaminated clothing. Vacuuming of carpets contaminated with mercury and breaking of mercury fluorescent light bulbs may result in elemental mercury vapor exposure. Severe inhalation poisonings have resulted from attempts to separate gold from gold ore by heating mercury and forming a gold-mercury amalgam. Elemental mercury has been used in folk remedies by Asian and Mexican populations for chronic stomach pain, by Latin Americans and Caribbean natives in occult practices, and as a skin-lightening agent. Dental amalgams containing elemental mercury release trace amounts of mercury. An expert panel for the National Institutes of Health concluded that existing scientific evidence does not indicate that dental amalgams pose a health risk and should not be replaced merely to decrease mercury exposure. A 2009 WHO expert panel concluded that a global near-term ban on amalgam would be problematic for public and dental health. However, this committee recommended that alternatives to amalgam should be sought as part of a phase-out of the use of mercury-containing amalgams.

Inorganic mercury salts are found in pesticides, disinfectants, antiseptics, pigments, dry batteries, and explosives and as preservatives in some medicinal preparations. **Organic mercury** in the diet, especially fish containing methyl mercury, is a major source of mercury exposure among the general population. Industries that may produce mercury-containing effluents include chlorine and caustic soda production, mining and metallurgy, electroplating, chemical and textile manufacturing, paper and pharmaceutical manufacturing, and leather tanning. Mercury compounds in the environment are methylated to methyl

Table 720-2 Acceptable and Toxic Levels of Arsenic and Mercury

	ARSENIC	MERCURY
Molecular weight	74.9 Da	200.59 Da
Acceptable blood level	<5 μg/L (<0.665 nmol/L)	<10 μg/L (<50 nmol/L)
Acceptable urine level	<50 μg/L (<6.65 nmol/L) 24 hr urine sample	<20 μg/L (<100 nmol/L)
Intervene at blood level		>35 μg/L (>175 nmol/L)
Intervene at urine level	>100 μg/L (>13.3 nmol/L) 24 hr urine sample	>150 μg/L (>750 nmol/L)

Table 720-3 Differential Characteristics of Mercury Exposure

	ELEMENTAL	INORGANIC (SALT)	ORGANIC (ALKYL)
Primary route of exposure	Inhalation	Oral	Oral
Primary tissue distribution	CNS, kidney	Kidney	CNS, kidney, liver
Clearance	Renal, GI	Renal, GI	Methyl: GI Aryl: renal, GI
Clinical effects:			
CNS	Tremor	Tremor, erethism (irritability)	Paresthesias, ataxia, tremor, tunnel vision, dysarthria
Pulmonary	+++	—	—
Gastrointestinal	+	+++ (caustic)	+
Renal	+	+++ (acute tubular necrosis)	+
Acrodynia	+	++	—
Therapy	BAL, DMSA	BAL, DMSA	DMSA (early)

BAL, British antilewisite; CNS, central nervous system; DMSA, 2,3-dimercaptosuccinic acid; GI, gastrointestinal; +, mild; ++, moderate; +++, severe.

From Sue YJ: Mercury (heavy metals). In Nelson LS, Lewin NA, Howland MA, et al, editors: Goldfrank's toxicologic emergencies, *ed 9, New York, 2011, McGraw-Hill, Tab 96-4, p. 1330.*

mercury by soil and water microorganisms. Methyl mercury in the water rapidly accumulates in fish (swordfish, king mackerel, fresh tuna, tile fish, shark) and other aquatic organisms, which are in turn consumed by humans. To address concerns that maternal consumption of large quantities of fish during pregnancy may expose the fetus to concentrations of mercury with adverse consequences, the longitudinal Seychelles Child Development Study has been ongoing since the late 1980s. The first cohort of the study involved nearly 800 mother–child pairs, with subsequent cohorts enrolled. Despite a high maternal fish intake (mean of 12 fish meals per wk), follow-up of children at least through 9 yr of age has revealed no consistent adverse developmental effects. Well-known large outbreaks of methyl mercury intoxication include the incidents in Japan in the 1950s (**Minamata disease,** from consumption of contaminated seafood) and in Iraq in 1971 (from consumption of grain treated with a methyl mercury fungicide).

Thimerosal is a mercury-containing preservative used in some vaccines. Thimerosal contains 49.6% mercury by weight and is metabolized to ethyl mercury and thiosalicylate. During an ongoing review of biologic products in response to the U.S. Food and Drug Administration (FDA) Modernization Act of 1997, the FDA determined that infants who received thimerosal-containing vaccines at multiple visits might have been exposed to more mercury than recommended by federal guidelines. As a precautionary measure, the American Academy of Pediatrics, American Academy of Family Physicians, Advisory Committee on Immunization Practices, and U.S. Public Health Service issued a joint recommendation in 1999 that thimerosal be removed from vaccines as quickly as possible. *In the United States, thimerosal has been removed from all vaccines in the recommended childhood immunization schedule.* Infants and children who have received thimerosal-containing vaccines do not need to undergo blood, urine, or hair testing for mercury because the concentrations of mercury would be quite low and would not require treatment. The benefits and risks of vaccines containing thimerosal should be discussed with parents (as with all vaccines). The larger risks of not vaccinating children far outweigh any known risk of exposure to thimerosal-containing vaccines. Studies do *not* demonstrate a link between thimerosal-containing vaccines and autistic spectrum disorders (see Chapter 30.1), and no evidence supports a change in the standard of practice with regard to administration of thimerosal-containing vaccines in areas of the world where they are used. A rise in blood mercury levels following a single dose of hepatitis vaccine was seen in preterm infants, but the clinical significance is unknown.

Pharmacokinetics

Inhaled elemental mercury vapor is 80% absorbed by the lungs and is distributed rapidly to the central nervous system because of its high lipid solubility. The elemental mercury is oxidized by catalase to the mercuric ion, which is the reactive form that causes cellular toxicity. Elemental mercury liquid is poorly absorbed from the gastrointestinal tract, with less than 0.1% being absorbed. The half-life of elemental mercury in the tissues is approximately 60 days, most of the excretion occurring in the urine.

Inorganic mercury salts are approximately 10% absorbed from the gastrointestinal tract and cross the blood–brain barrier to a lesser extent than elemental mercury. Mercuric salts are more soluble than mercurous salts and, therefore, produce greater toxicity. Elimination occurs primarily in the urine, with a half-life of approximately 40 days.

Methyl mercury is the most avidly absorbed of the organic mercury compounds, with approximately 90% absorbed from the gastrointestinal tract. The lipophilic, short-chain alkyl structure of methyl mercury allows it to distribute rapidly across the blood–brain barrier and placenta. Methyl mercury is approximately 90% excreted in the bile, with the remainder being excreted in the urine. The half-life is 70 days.

Pathophysiology

After absorption, mercury is distributed to all tissues, particularly the central nervous system and kidneys. Mercury reacts with sulfhydryl, phosphoryl, carboxyl, and amide groups, resulting in disruption of enzymes, transport mechanisms, membranes, and structural proteins. Widespread cellular dysfunction or necrosis results in the multiorgan toxicity characteristic of mercury poisoning.

Clinical Manifestations

Five syndromes describe the clinical presentation of mercury poisoning. **Acute inhalation of elemental mercury vapor** results in rapid onset of cough, dyspnea, chest pain, fever, chills, headaches, and visual disturbances. Gastrointestinal findings include metallic taste, salivation, nausea, vomiting, and diarrhea. Depending on the severity of the exposure, the illness may be self-limited or may progress to necrotizing bronchiolitis, interstitial pneumonitis, pulmonary edema, and death from respiratory failure. Younger children are more susceptible to pulmonary toxicity. Survivors may demonstrate restrictive lung disease. Renal dysfunction and neurologic disturbances (ataxia, persistent weakness, emotional lability) may develop subacutely. Chronic exposure to volatilized elemental mercury in dental amalgams has not been found to be of any clinical significance.

Acute ingestion of inorganic mercury salts (typically secondary to ingestion of a button battery) can manifest in a few hours as corrosive gastroenteritis, signified by metallic taste, oropharyngeal burns, nausea, hematemesis, severe abdominal pain, hematochezia, acute tubular necrosis, cardiovascular collapse, and death.

Chronic inorganic mercury intoxication produces the **classic triad** consisting of tremor, neuropsychiatric disturbances, and

gingivostomatitis. The syndrome may result from long-term exposure to elemental mercury, inorganic mercury salts, or certain organic mercury compounds, all of which may be metabolized to mercuric ions. The tremor starts as a fine intention tremor of the fingers that is abolished during sleep but that may later involve the face and progress to choreoathetosis and spasmodic ballismus. Mixed sensorimotor neuropathy and visual disturbances may also be present. The neuropsychiatric disturbances include emotional lability, delirium, headaches, memory loss, insomnia, anorexia, and fatigue. Renal dysfunction ranges from asymptomatic proteinuria to nephrotic syndrome.

Acrodynia, or **pink disease,** is a rare idiosyncratic hypersensitivity reaction to mercury that occurs predominantly in children exposed to mercurous powders. The symptom complex includes generalized pain, paresthesias, and an acral (hands, feet) rash that may spread to involve the face. The rash typically is red-pink, papular, pruritic, and painful; it may progress to desquamation and ulceration. Morbilliform, vesicular, and hemorrhagic variants have been described. Other important features include anorexia, apathy, photophobia, and hypotonia, especially of the pectoral and pelvic girdles. Irritability, tremors, diaphoresis, insomnia, hypertension, and tachycardia may be present. Some cases initially were diagnosed as pheochromocytoma. The outcome is good after removal of the source of mercury exposure.

Methyl mercury intoxication (also known as **Minamata disease** after the widespread mercury poisoning that occurred at Minamata Bay in Japan in people who had ingested contaminated fish) manifests as delayed neurotoxicity that appears after a latent period of weeks to mo. It is characterized by ataxia; dysarthria; paresthesias; tremors; movement disorders; impairment of vision, hearing, smell, and taste; memory loss; progressive dementia; and death. Infants exposed in utero are the most severely affected, with low birthweight, microcephaly, profound developmental delay, cerebral palsy, deafness, blindness, and seizures. Although there is significant residual morbidity from methyl mercury neurotoxicity, observations on long-term follow-up of children exposed in Iraq reveal complete or partial resolution in most cases.

Laboratory Findings

The diagnosis of mercury intoxication is based on characteristic clinical findings, a history of exposure, and elevation of whole blood or urine mercury values, the last of which confirms the exposure. Thin-layer and gas chromatographic techniques can be used to distinguish organic from inorganic mercury. Blood should be collected in special tubes for trace elements from laboratories that are capable of performing those tests. Levels <10 μg/L in whole blood and <20 μg/L in a 24 hr urine specimen are considered normal (see Table 720-2). Although blood mercury levels may reflect acute exposure, they decrease as mercury redistributes into the tissues. Urine mercury levels are most useful for identifying long-term exposures, except in the case of methyl mercury, which undergoes minimal urinary excretion. Urinary mercury levels are used in monitoring efficacy of chelation therapy, whereas blood levels are used primarily in monitoring organic mercury poisonings. Hair analysis for mercury is not reliable because hair reflects both endogenous and exogenous mercury exposure (hair avidly binds mercury from the environment). Abdominal radiographs may demonstrate ingested radiopaque mercury.

Urinary markers of early nephrotoxicity include microalbuminuria, retinol-binding protein, β_2-microglobulin, and *N*-acetyl-β-D-glucosaminidase. Early neurotoxicity may be detected with neuropsychiatric testing and nerve conduction studies, whereas severe central nervous system toxicity is apparent on CT or MRI.

TREATMENT OF ARSENIC AND MERCURY INTOXICATION

The principles of management for arsenic and mercury intoxication include prompt removal from the source of poisoning, aggressive stabilization and supportive care, decontamination, and chelation therapy when appropriate. Once the diagnosis is suspected, the local poison control facility should be contacted, and care coordinated with physicians who are familiar with the management of heavy metal poisoning.

Supportive care for patients exposed to arsine gas requires close monitoring for signs of hemolysis, including evaluation of the peripheral blood smear and urinalysis. Transfusion of packed RBCs may be necessary, as may administration of intravenous fluids, sodium bicarbonate, and mannitol to prevent renal failure secondary to the deposition of hemoglobin in the kidneys. After inhalation of elemental mercury vapor, patients require careful monitoring of respiratory status, which may include pulse oximetry, arterial blood gas analysis, and chest radiography. Supportive care involves administration of supplemental oxygen and, in severe cases, intubation and mechanical ventilation.

Acute ingestion of inorganic arsenic and mercury salts results in hemorrhagic gastroenteritis, cardiovascular collapse, and multiorgan dysfunction. Fluid resuscitation, pressor agents, and transfusion of blood products may be required for management of cardiovascular instability. Severe respiratory distress, coma with loss of airway reflexes, intractable seizures, and respiratory paralysis are indications for intubation and mechanical ventilation. Renal function must be monitored carefully for signs of renal failure and the need for hemodialysis.

Gastrointestinal decontamination after ingestion of the inorganic arsenic and mercury salts has not been well studied. Because of the corrosive effects of these compounds, induced emesis is not recommended, and endoscopy may be considered before gastric lavage. Arsenic and mercury are not well adsorbed to activated charcoal, but its use may be helpful if coingestants are suspected. Whole-bowel irrigation is used to remove any radiopaque material remaining in the gastrointestinal tract.

Chelation for acute arsenic and mercury poisoning is most effective when administered as soon as possible after the exposure. Chelation should be continued until 24 hr urinary arsenic or mercury levels return to normal (<50 μg/L for arsenic and <20 μg/L for mercury), the patient is symptom-free, or the remaining toxic effects are believed to be irreversible. The efficacy of chelation in long-term exposures is reduced because heavy metal in the tissue compartment is relatively unexchangeable and some degree of irreversible toxicity has already occurred.

Dimercaprol, also known as *2,3-dimercaptopropanol* or *British antilewisite (BAL)*, is the chelator of choice for a patient who cannot tolerate oral therapy, as often is true for critically ill patients and after ingestion of the corrosive inorganic arsenic and mercury salts. BAL is available suspended in peanut oil and benzyl benzoate in 3 mL ampules at a concentration of 100 mg/mL for deep intramuscular (IM) injection. For **arsenic poisoning,** the recommended regimen of BAL is 2.5 mg/kg IM q6h for the 1st 2 days, 2.5 mg/kg IM q12h on the 3rd day, and then 2.5 mg/kg/day IM for 10 days. For severe arsenic poisoning, the dose of BAL is increased to 3 mg/kg IM q4h for 2 days, 3 mg/kg IM q6h on day 3, and then 3 mg/kg IM q12h for 10 days. The dose of BAL for **inorganic mercury poisoning** is 5 mg/kg IM on the 1st day, and then 2.5 mg/kg IM q12-24h for 10 days. The BAL–heavy metal complex is excreted in the urine and bile. A period of 5 days between courses of chelation is recommended. Adverse effects of BAL include pain at the injection site, hypertension, tachycardia, diaphoresis, nausea, vomiting, abdominal pain, a burning sensation in the oropharynx, and a feeling of constriction in the chest. BAL may cause hemolysis in glucose-6-phosphate dehydrogenase–deficient individuals. It is important to note that BAL is contraindicated for chelation of methyl mercury because BAL redistributes methyl mercury to the brain from other tissue sites, resulting in increased neurotoxicity.

D-Penicillamine is an orally administered chelator that can be considered for less-severe mercury poisoning or as an adjunct to BAL therapy in arsenic poisoning, but its use is largely restricted because of the potential for significant leukopenia, thrombocytopenia, and proteinuria. A newer investigational analog, *N*-acetyl-D,L-penicillamine, is used with variable success in mercury poisoning.

Oral chelating agents are used to replace the painful BAL injections when the patient is stable enough to tolerate oral therapy and prolonged chelation is necessary. **Succimer,** also known as *2,3-dimercaptosuccinic acid* (DMSA), is an orally administered water-soluble derivative of BAL. DMSA is available in 100 mg capsules. The

recommended regimen of DMSA is 10 mg/kg orally every 8 hr for 5 days. The DMSA–heavy metal complex is excreted in the urine and bile. A period of 2 wk between courses of chelation is recommended. Mild adverse effects include nausea, vomiting, diarrhea, loss of appetite, and transient elevations in liver enzyme levels. DMSA also may cause hemolysis in glucose-6-phosphate dehydrogenase–deficient patients. Patients with ingestion of elemental mercury require no follow-up unless there is an underlying disease that decreases the gastrointestinal transit time. Serial abdominal radiographs to document the progression of the metal are recommended. Acute inhalation of mercury fumes and ingestion of inorganic mercury require hospitalization to monitor the respiratory and gastrointestinal status, respectively. Therapeutic abortion may be considered in pregnant patients, because of the teratogenic effect of mercury.

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Chapter 721

Lead Poisoning

Morri Markowitz

Lead is a metal that exists in 4 isotopic forms. Clinically, it is purely a toxicant; no organism has an essential function that is lead dependent. Chemically, its low melting point and ability to form stable compounds have made it useful in the manufacture of hundreds of products; this commercial attractiveness has resulted in the processing of millions of tons of lead ore, leading to widespread dissemination of lead in the human environment.

The blood lead level (BLL) is the gold standard for determining health effects. However, the threshold level at which lead begins to cause biochemical, subclinical, or clinical disturbance remains to be determined. The Centers for Disease Control and Prevention (CDC), recognizing that a BLL of 10 µg/dL qualifies neither as a threshold of toxicity nor as a protective parameter of children with lead exposure, changed its standard. It no longer refers to a level of concern or toxicity but has designated 5 µg/dL as the *"reference value based on the 97.5th percentile of the population BLL in children aged 1-5 years to identify children living or staying for long periods in environments that expose them to lead hazards."* As a measure of the distribution of BLLs in young children, this number will change in a manner dependent on the epidemiology of BLLs rather than on identification of the starting point for toxicity.

Although stated as a reference value, it is likely that clinicians and departments of health will consider this a threshold for action. It is important to recognize that lead toxicity occurs at levels below 5 µg/dL; no safe level has been identified. In part, this reflects the accuracy limitations of available clinical laboratory methodologies.

PUBLIC HEALTH HISTORY

In the late 1970s, nearly all preschool-age children in the United States had BLLs above the current reference value of 5 µg/dL. Around that time government regulations were issued that resulted in the significant reduction of 3 main contributors to lead exposure by means of (1) the elimination of the use of tetraethyl lead as a gasoline additive, (2) the banning of lead-containing solder to seal cans of food and beverages, and (3) the application of a federal rule that limited the amount of lead allowed in paint intended for household use to less than 0.06% by weight (further reduced by the Consumer Product Safety Commission to 0.009% in 2008). Surveillance by many of the states in the United States and by national health surveys conducted by the CDC has shown that the prevalence of elevated BLLs has declined markedly. Approximately 535,000 young children currently have BLLs ≥5 µg/dL. Including all children <18 yr of age yields an estimated 705,000 with levels above the reference value (National Health and Nutritional Examination Surveys show that for 2007-2010, 0.95% of children < age 18 yr have BLL ≥5 µg/dL). Several subgroups remain at higher risk for lead poisoning. The mean BLL of non-Hispanic black children (1.8 µg/dL) is greater than that of either non-Hispanic white children (1.3 µg/dL) or Mexican American children (1.3 µg/dL); the mean BLL among poor children (1.6 µg/dL) is higher than among more well-to-do children (1.2 µg/dL). Another high-risk group that has been identified consists of recent immigrants from less-wealthy countries, including adoptees. Fortunately, children with levels high enough to be life-threatening (>100 µg/dL) are rarely seen in the United States.

As of 2014 only 6 countries continue to use leaded gasoline (Afghanistan, Algeria, Iraq, North Korea, Myanmar, and Yemen) and these are expected to phase out its use. In all countries examined, the end of this source of exposure was associated with a marked decrease in average BLLs at all ages. In Malta, after the import of red lead paint was banned and the use of lead-treated wood for fuel in bakeries was prohibited, mean BLLs of pregnant women and newborns decreased by 45%. After it was documented that children living in the neighborhood of a battery factory in Nicaragua had a mean BLL of 17.2 µg/dL whereas children in the control community had a mean BLL of 7.4 µg/dL, the factory was closed. Despite these advances, the World Health Organization estimates that nearly a quarter billion people have BLLs above 5 µg/dL; of those who are children, 90% live in developing countries, where, in some regions, BLLs may be 10-20–fold higher than in developed countries.

In 2010, the CDC and World Health Organization, after being alerted by Doctors Without Borders, identified numerous lead-contaminated villages in northern Nigeria. The grinding of ore to extract gold caused widespread leaded dust dissemination. It is likely that hundreds of children died as a consequence of this activity, and all remaining children in the villages assessed to date were lead poisoned, with 97% having a BLL ≥45 µg/dL.

SOURCES OF EXPOSURE

Lead poisoning may occur in utero, because lead readily crosses the placenta from maternal blood. The spectrum of toxicity is similar to that experienced by children after birth. The source of maternal blood lead content is either redistribution from endogenous stores (i.e., the mother's skeleton) or lead newly acquired from ongoing environmental exposure.

Several hundred products contain lead, including batteries, cable sheathing, cosmetics, mineral supplements, plastics, toys (Table 721-1),

Table 721-1 Sources of Lead
Paint chips
Dust
Soil
Parent's or older child's occupational exposure (auto repair, battery manufacturing or recycling, smelting, construction, mining, remodeling, plumbing, gun/bullet exposure, indoor firing ranges, painting)
Glazed ceramics
Herbal remedies (e.g., Ayurvedic medications)
Home remedies, including antiperspirants, deodorants (e.g., litargirio)
Jewelry (as toys or belonging to parents)
Stored battery casings (or living near a battery smelter)
Lead-based gasoline
Moonshine alcohol
Contaminated foods (e.g., Mexican candies; Ecuadorian chocolates, imported rice)
Indoor firing ranges
Imported spices (svanuri marili, saffron, kuzhambu)
Cosmetics (kohl, surma, kajal, tiro, lipstick)
Lead plumbing (water)
Imported foods in lead-containing cans
Imported toys
Home renovations
Antique toys or furniture

Table 721-2 Cases of Lead Encephalopathy Associated with Traditional Medicines by Type of Medication

TRADITIONAL MEDICAL SYSTEM	CASES OF LEAD ENCEPHALOPATHY N (%)	N (%) PEDIATRIC CASES WITHIN CAM SYSTEM OR MEDICATION
Ayurveda	5 (7)	1 (20)
Ghasard	1 (1)	1 (100)
Traditional Middle Eastern practices	66 (87)	66 (100)
Azarcón and greta	2 (3)	2 (100)
Traditional Chinese medicine	2 (3)	2 (100)
Total	76 (100)	72 (95)

CAM, complementary and alternative medicines.
From Karri SK, Saper RB, Kales SN: Lead encephalopathy due to traditional medicines, Curr Drug Saf *3:54–59, 2008.*

and traditional medicines (Table 721-2). Major sources of exposure vary among and within countries; the major source of exposure in the United States remains old lead-based paint. Approximately 38 million homes, mainly built before 1950, have lead-based paint (2000 estimate). As paint deteriorates, it chalks, flakes, and turns to dust. Improper rehabilitation work of painted surfaces (e.g., sanding) can result in dissemination of lead-containing dust throughout a home. The dust can coat all surfaces, including children's hands. All of these forms of lead can be ingested. If heat is used to strip paint, then lead vapor concentrations in the room can reach levels sufficient to cause lead poisoning via inhalation.

METABOLISM

The nonnutritive hand-to-mouth activity of young children is the most common pathway for lead to enter the body. In nearly all cases, lead is ingested as a component of solids or dissolved in liquids. Cutaneous contamination with inorganic lead compounds, such as those found in pigments, does not result in a substantial amount of absorption. Organic lead compounds, such as tetraethyl lead, may penetrate through skin, however. This is rarely encountered in the United States.

The percentage of lead absorbed from the gut depends on several factors: particle size, pH, other material in the gut, and nutritional status of essential elements. Large paint chips are difficult to digest and are mainly excreted; this is fortunate as a single chip may contain a lethal dose of lead. Fine dust can be dissolved more readily, especially in an acid medium. Lead eaten on an empty stomach is better absorbed than that taken with a meal. The presence of calcium and iron may decrease lead absorption by direct competition for binding sites; iron (and probably calcium) deficiency results in enhanced lead absorption, retention, and toxicity.

After absorption, lead is disseminated throughout the body. Most retained lead accumulates in bone, where it may reside for years. It circulates bound to erythrocytes; approximately 97% in blood is bound on or in the red blood cells. The plasma fraction is too small to be measured by conventional techniques employing atomic absorption spectroscopy or anodic stripping voltammetry; it is presumably the plasma portion that may enter cells and induce toxicity. Thus, clinical laboratories report the BLL, not the serum or plasma lead level. It is possible, but not yet sufficiently shown by testing, that some of the variance in the relationship between BLLs and outcome measures of toxicity is a result of the limitations of using BLLs to assess risk. Studies that examine plasma lead concentrations in relation to its toxicity are needed.

Lead has multiple effects in cells. It binds to enzymes, particularly those with available sulfhydryl groups, changing the contour and diminishing function. For example, the heme pathway, present in all cells, consists of 8 enzymes, 3 of which are susceptible to lead inhibitory effects. The accumulation of excess amounts of heme precursors also is toxic (see Chapter 91). The last enzyme in this pathway, ferrochelatase, enables protoporphyrin to chelate iron, thus forming heme. Heme is essential for multiple metabolic pathways and not merely as a component of hemoglobin. Erythrocyte protoporphyrin levels higher than 35 µg/dL are abnormal and are consistent with lead poisoning, iron deficiency, or recent inflammatory disease.

Erythrocyte protoporphyrin levels begin to rise several weeks after BLLs have reached 20 µg/dL in a susceptible portion of the population, and are elevated in nearly all children with BLLs higher than 50 µg/dL. A drop in erythrocyte protoporphyrin levels also lags behind a decline in BLLs by several weeks, because it depends on both cell turnover and cessation of further overproduction by marrow red blood cell precursors. Measurement of the erythrocyte protoporphyrin level is, therefore, a useful tool for monitoring more severe biochemical lead toxicity.

A second mechanism of lead toxicity works via its competition with calcium. Many calcium-binding proteins have a higher affinity for lead than for calcium. Lead bound to these proteins may alter function, resulting in abnormal intracellular and intercellular signaling. Neurotransmitter release is, in part, a calcium-dependent process that is adversely affected by lead.

Although these 2 mechanisms of toxicity may be reversible, a third mechanism prevents the development of the normal tertiary brain structure. In immature mammals the normal neuronal pruning process that results in elimination of multiple intercellular brain connections is inhibited by lead. Failure to construct the appropriate tertiary brain structure during infancy and childhood may result in a permanent abnormality. A longitudinal study of childhood lead poisoning that followed a cohort from birth and into their 20s performed MRI and functional MRI–phosphorus magnetic resonance spectroscopy assessments confirmed the association of early childhood lead exposure and subsequent decreased gray and white matter volume and neuronal function. The investigators concluded that early lead exposure in life causes a persistent reorganization of brain architecture and diminished function.

CLINICAL EFFECTS

The BLL is the best-studied measure of the lead burden in children. Although subclinical and clinical findings correlate with BLLs in populations, there is considerable interindividual variability in this relationship. Lead encephalopathy is more likely to be observed in children with BLLs higher than 100 µg/dL; however, 1 child with a BLL of 300 µg/dL may have no symptoms, whereas another with the same level may be comatose. Susceptibility may be associated with polymorphisms in genes coding for lead-binding proteins, such as Δ-aminolevulinic acid dehydratase, an enzyme in the heme pathway.

Several subclinical effects of lead have been demonstrated in cross-sectional epidemiologic studies. Hearing and height are inversely related to BLLs in children. As BLLs increased in the study population, more sound (at all frequencies) was needed to reach the hearing threshold. Children with higher BLLs are shorter than those with lower levels; for every 10 µg increase in the BLL, the children are 1 cm shorter. Chronic lead exposure also may delay puberty. However, these associations with rising BLLs do not reach a point that would bring an individual child to medical attention.

Several longitudinal studies have followed cohorts of children from birth for as long as 20 yr and examined the relationship between BLLs and cognitive test scores over time. In general, there is agreement that BLLs, expressed either as levels obtained at around 2 yr of age or as a measure that integrates multiple BLLs drawn from subjects over time, are inversely related to cognitive test scores. On average, for each 1 µg/dL elevation in BLL the cognitive score is approximately 0.25-0.50 points lower. Because the BLLs from early childhood are predictors of the cognitive test results performed years later, this finding implies that the effects of lead can be permanent. Concurrent testing of lead levels and cognition sometimes also shows an inverse association.

The effect of in utero lead exposure is less clear. Scores on the Bayley Scale of Mental Development were obtained repeatedly every 6 mo for the 1st 2 yr of life in a cohort of infants born to middle-class families. Results correlated inversely with cord BLLs, a measure of in utero exposure, but not with BLLs obtained concurrently at the time of developmental testing. After 2 yr of age, all other cognitive tests performed on the cohort over the next 10 yr correlated with the BLLs at age 2 yr but not with cord BLLs, indicating that the effects of prenatal lead exposure on brain function were superseded by early childhood events and later BLLs. Later studies, performed in cohorts of Mexican children monitored from the prenatal period, confirm the association between in utero lead exposure and later cognitive outcomes. No threshold for BLL was identified in these studies; maternal BLLs between 0 and 10 µg/dL, even as early as the 1st trimester, were associated with about a 6-point drop in cognitive test score results when the children were tested up to age 10 yr.

Behavior also is adversely affected by lead exposure. Hyperactivity is noted in young school-age children with histories of lead poisoning or with concurrent elevations in BLL. Older children with higher bone lead content are more likely to be aggressive and to have behaviors that are predictive of later juvenile delinquency. Multiple reports support the concept of long-term effects of early lead exposure. In 1 longitudinal study, the mothers of a cohort were enrolled during their pregnancies. BLLs were obtained early in pregnancy, at birth, and then multiple times in the offspring during the 1st 6 yr. The investigators report that the relative rate of arrests, especially for violent crimes, increased significantly in relationship to the presence of these BLLs early in life. For every 5 µg/dL increase in BLL the adjusted arrest rate was 1.40 for prenatal BLLs and 1.27 for 6 yr BLLs. Epidemiologic data support the findings in this observational study. In an analysis that combined 2 national data sets, total annual leaded gasoline use (U.S. Geological Survey) and total reported violent criminal acts (U.S. Department of Justice), the amount of leaded gasoline used yearly was found to be strongly associated with violent criminal behavior with a lag time of 23 yr; that is, early exposure was followed 2 decades later by violent behavior rising and falling in close tandem. A similar association was found, this time between urban air lead levels and later violent crime, with a similar best-fit model employing a lag of approximately 22 yr.

An intervention study, in which children with moderate lead poisoning and initial BLLs of 20-55 µg/dL were aggressively managed over 6 mo, addressed the issue of the effects of treatment on cognitive development. Components of treatment included education regarding sources of lead and its abatement, nutritional guidance, multiple home and clinic visits, and, for a subset, chelation therapy. Average BLLs declined and cognitive scores were inversely related to the change in BLLs. For every 1 µg/dL fall in BLLs, cognitive scores were 0.25 point higher. A randomized placebo-controlled treatment study of 2 yr old children with initial BLLs of 20-44 µg/dL that employed the chelating agent succimer administered over 6 mo found no difference in *mean* cognitive scores at age 4 yr. However, as in the earlier treatment study, regression analysis did find an inverse relation between *change* scores; that is, a change in BLLs was associated with a change in cognitive scores.

Whether the behavioral effects of lead are reversible is unclear. In one small, short-term study, 7 yr old hyperactive children with BLLs in the 20s were randomly allocated to receive a chelating agent (penicillamine), methylphenidate, or placebo. Teacher and parent ratings of behavior improved for the first 2 groups but not the placebo group. BLLs declined only in the chelated group. Lead-poisoned children age 2 yr old who were enrolled in a placebo-controlled trial of the chelating agent succimer showed no mean difference in behavior at 4 or 7 yr of age. However, mean BLLs were also not different in the 2 groups at those ages.

CLINICAL SYMPTOMS

Gastrointestinal Tract and Central Nervous System

Gastrointestinal symptoms of lead poisoning include anorexia, abdominal pain, vomiting, and constipation, often occurring and recurring over a period of weeks. Children with BLLs higher than 20 µg/dL are twice as likely to have gastrointestinal complaints as those with lower BLLs. **Central nervous system symptoms** are related to worsening cerebral edema and increased intracranial pressure. Headaches, change in mentation, lethargy, papilledema, seizures, and coma leading to death are rarely seen at levels lower than 100 µg/dL but have been reported in children with a BLL as low as 70 µg/dL. The last-reported death directly attributable to lead toxicity in the United States was in 2006 in a child with a BLL of 180 µg/dL. There is no clear cutoff BLL value for the appearance of hyperactivity, but it is more likely to be observed in children who have levels higher than 20 µg/dL.

Other organs also may be affected by lead toxicity, but symptoms usually are not apparent in children. At high levels (>100 µg/dL), **renal tubular dysfunction** is observed. Lead may induce a reversible Fanconi syndrome (see Chapter 529). In addition, at high BLLs, **red blood cell survival** is shortened, possibly contributing to a hemolytic anemia, although most cases of anemia in lead-poisoned children are a result of other factors, such as iron deficiency and hemoglobinopathies. Older patients may develop a peripheral neuropathy leading to wrist drop and footdrop.

DIAGNOSIS

Screening

It is estimated that 99% of lead-poisoned children are identified by screening procedures rather than through clinical recognition of lead-related symptoms. Until 1997 universal screening by blood lead testing of all children at ages 12 mo and 24 mo was the standard in the United States. Given the national decline in the prevalence of lead poisoning, the recommendations have been revised to target blood lead testing of high-risk populations. High risk is based on an evaluation of the likelihood of lead exposure. Departments of health are responsible for determining the local prevalence of lead poisoning, as well as the percentage of housing built before 1950, the period of peak leaded paint use. When this information is available, informed screening guidelines for practitioners can be issued. For instance, in the state of New York, where a large percentage of housing was built before 1950, the Department of Health mandates that all children be tested for lead poisoning via blood analyses. *In the absence of such data the practitioner should continue to test all children at both 12 mo and 24 mo.* In areas where the prevalence of lead poisoning and old housing is low, targeted screening may be performed on the basis of a risk assessment. Three questions form the basis of most published questionnaires (Table 721-3), and items that are pertinent to the locale or individual may be added. If there is a lead-based industry in the child's neighborhood, the child is a recent immigrant from a country that still permits use of leaded

Table 721-3	Minimum Personal Risk Questionnaire
1. Does the child live in or visit regularly a house that was built before 1950? (Include settings such as daycare, babysitter's or relative's home.)	
2. Does the child live in or regularly visit a house built before 1978 with recent (past 6 mo) or ongoing renovations or remodeling?	
3. Does the child have a sibling or playmate that has or did have lead poisoning?	

From Screening young children for lead poisoning: guidance for state and local public health officials, *Atlanta, 1997, Centers for Disease Control and Prevention.*

gasoline, or the child has pica or developmental delay, blood lead testing would be appropriate. All Medicaid-eligible children should be screened by blood lead testing. Unfortunately, answers on questionnaires are not more successful at identifying children with lead poisoning than is chance. Venous sampling is preferred to capillary sampling because the chances of false-positive and false-negative results are less with the former.

TREATMENT

Once lead is in bone, it is released slowly and is difficult to remove even with chelating agents. Because the cognitive/behavioral effects of lead may be irreversible, the main effort in treating lead poisoning is to **prevent** it from occurring and to **prevent** further ingestion by already-poisoned children. The main components in the effort to eliminate lead poisoning are universally applicable to all children (and adults) and are as follows: (1) identification and elimination of environmental sources of lead exposure, (2) behavioral modification to reduce nonnutritive hand-to-mouth activity, and (3) dietary counseling to ensure sufficient intake of the essential elements calcium and iron. For the small minority of children with more-severe lead poisoning, drug treatment is available that enhances lead excretion.

During health maintenance visits a limited risk assessment is warranted, which includes questions pertaining to the most common sources of lead exposure: the condition of old paint, secondary occupational exposure via an adult living in the home, and/or proximity to an industrial source of pollution. If such a source is identified, its elimination usually requires the assistance of public health and housing agencies as well as education for the parents. The family should move out of a lead-contaminated apartment until repairs are completed. During repairs, repeated washes of surfaces and the use of high-efficiency particle accumulator vacuum cleaners help reduce exposure to lead-containing dust. Careful selection of a contractor who is certified to perform lead abatement work is necessary. Sloppy work can cause dissemination of lead-containing dust and chips throughout a home or building and result in further elevation of a child's BLL. After the work is completed, dust wipe samples should be collected from floors and windowsills or wells to verify that the risk from lead has abated.

A single case of lead poisoning is often discovered in a household with multiple affected family members, including other young children, even in a household with a common source of exposure such as peeling lead-based paint. The mere presence of lead in an environment does not produce lead poisoning. Parental efforts at **reducing the hand-to-mouth activity** of the affected child are necessary to reduce the risk of lead ingestion. Handwashing effectively removes lead, but in a home with lead-containing dust, lead rapidly begins to reaccumulate on the child's hands after washing. Therefore, handwashing is best limited to the period immediately before nutritive hand-to-mouth activity occurs.

Because there is competition between lead and essential minerals, it is reasonable to promote a healthy diet that is sufficient in calcium and iron. The recommended daily intakes of these metals vary somewhat with age. In general, for children 1 yr of age and up a calcium intake of about 1 g/day is sufficient and convenient to remember (roughly the calcium content of a quart of milk [≈1,200 mg/qt] or calcium-fortified orange juice). Calcium absorption is vitamin D dependent; milk is fortified with vitamin D, but other nutritional sources of calcium often are not. A multivitamin containing vitamin D may be prescribed for children who do not drink sufficient milk or who have inadequate sunlight exposure. Iron requirements also vary with age, ranging from 6 mg/day for infants to 12 mg/day for adolescents. For children identified biochemically as being iron deficient, therapeutic iron at a daily dose of 5-6 mg/kg for 3 mo is appropriate. Iron absorption is enhanced when iron is ingested with ascorbic acid (citrus juices). Giving additional calcium or iron above the recommended daily intakes to mineral-sufficient children has not been shown to be of therapeutic benefit in the treatment of lead poisoning.

Drug treatment to remove lead is lifesaving for children with lead encephalopathy. In nonencephalopathic children, it prevents symptom progression and further toxicity. Guidelines for chelation are based on the BLL. *A child with a venous BLL of 45 µg/dL or higher should be treated.* Four drugs are available in the United States: 2,3-dimercaptosuccinic acid (DMSA [succimer]), $CaNa_2EDTA$ (versenate), British antilewisite (BAL [dimercaprol]), and penicillamine. DMSA and penicillamine can be given orally, whereas $CaNa_2EDTA$ and BAL can be administered only parenterally. The choice of agent is guided by the severity of the lead poisoning, the effectiveness of the drug, and the ease of administration (Table 721-4). Children with BLLs of 44-70 µg/dL may be treated with a single drug, preferably DMSA. Those with BLLs of 70 µg/dL or greater require 2-drug treatment: $CaNa_2EDTA$ in combination with either DMSA or BAL for those without evidence of encephalopathy, or $CaNa_2EDTA$ and BAL for those with encephalopathy. Published data on the combined treatment with $CaNa_2EDTA$ and DMSA for children with BLLs higher than 100 µg/dL are very limited. However, anecdotal information derived from the treatment of hundreds of severely lead poisoned children in northern Nigeria indicates that single-drug treatment with DMSA is lifesaving, although the degree of residual damage in survivors has not been reported.

Acute drug-related toxicities are minor and reversible. These include gastrointestinal distress, transient elevations in transaminases, active urinary sediment, and neutropenia. These types of events are least common for $CaNa_2EDTA$ and DMSA and more common for BAL and

Table 721-4 Chelation Therapy

NAME	SYNONYM	DOSE	TOXICITY
Succimer	Chemet, 2,3-dimercaptosuccinic acid (DMSA)	350 mg/m^2 body surface area/dose ***(not 10 mg/kg)*** q8h, PO for 5 days, then q12h for 14 days	Gastrointestinal distress, rashes; elevated LFTs, depressed white blood cell count
Edetate*	$CaNa_2EDTA$ (calcium disodium edetate), versenate	1,000-1,500 mg/m^2 body surface area/day; IV infusion—continuous or intermittent; IM divided q6h or q12h for 5 days	Proteinuria, pyuria, rising blood urea nitrogen/creatinine—all rare Hypercalcemia if too rapid an infusion Tissue inflammation if infusion infiltrates
British antilewisite (BAL)	Dimercaprol	300-500 mg/m^2 body surface area/day; **IM only** divided q4h for 3-5 days. Only for BLL ≥70 µg/dL	Gastrointestinal distress, altered mentation; elevated LFTs, hemolysis if glucose-6-phosphate dehydrogenase deficiency; no concomitant iron treatment
D-Pen	Penicillamine	10 mg/kg/day for 2 wk increasing to 25-40 mg/kg/day; oral, divided q12h. For 12-20 wk	Rashes, fever; blood dyscrasias, elevated LFTs, proteinuria Allergic cross reactivity with penicillin

*Always given as the calcium salt; never as the sodium salt without calcium.
BLL, blood lead level; IM, intramuscularly; IV, intravenously; LFT, liver function test; PO, by mouth.
From Markowitz ME: Lead poisoning, Pediatr Rev *21:327–335, 2000.*

penicillamine. All of the drugs are effective in reducing BLLs when given in sufficient doses and for the prescribed time. These drugs also may increase lead absorption from the gut and should be administered to children in lead-free environments. *Some authorities also recommend the administration of a cathartic immediately prior to or concomitant with the initiation of chelation to eliminate any lead already in the gut.*

None of these agents removes all lead from the body. Within days to weeks after completion of a course of therapy the BLL rises, even in the absence of new lead ingestion. The source of this rebound in the BLL is believed to be bone. Serial examinations of bone lead content have shown that chelation with $CaNa_2EDTA$ is associated with a decline in bone lead levels but that residual bone lead remains detectable even after multiple courses of treatment.

Repeat chelation is indicated if the BLL rebounds to 45 μg/dL or higher. Children with initial BLLs higher than 70 μg/dL are likely to require more than 1 course. A minimum of 3 days between courses is recommended to prevent treatment-related toxicities, especially in the kidney.

The indication for chelation therapy for children with BLLs <45 μg/dL is less clear. Although use of these drugs in children with BLLs from 20-44 μg/dL will result in transiently lowered BLLs, and in some cases reversal of lead-induced enzyme inhibition, few such children increase their excretion of lead significantly during chelation, raising the question of whether any long-term benefit is achieved. A study of 2 yr old children with BLLs of 20-44 μg/dL who were randomized to receive either DMSA or placebo found that the drop in BLLs was greater in the 1st 6 mo after enrollment in the DMSA-treated group, but the levels converged by 1 yr of follow-up. Mean cognitive test scores obtained at 4 and 7 yr of age were not statistically different between the groups. Chelation with DMSA (and $CaNa_2EDTA$) is not recommended for all children with BLLs <45 μg/dL. It remains to be demonstrated whether other chelating agents available in the United States or elsewhere are effective at either substantially reducing body stores (bone) of lead or at reversing the cognitive deficits attributable to lead at these BLLs.

With successful intervention (with or without chelation), BLLs decline, with the greatest fall in BLL occurring in the 1st 2 mo after therapy is initiated. Subsequently, the rate of change in BLL declines slowly so that by 6-12 mo after identification, the BLL of the average child with moderate lead poisoning (BLL >20 μg/dL) will be 50% lower. Children with more markedly elevated BLLs may take years to reach the CDC reference level, 5 μg/dL, even if all sources of lead exposure have been eliminated, behavior has been modified, and nutrition has been maximized. Early screening remains the best way of avoiding and therefore obviating the need for the treatment of lead poisoning.

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Chapter 722
Nonbacterial Food Poisoning

722.1 Mushroom Poisoning

Denise A. Salerno and Stephen C. Aronoff

Mushrooms are an ideal food. They are low in calories, fat free, and high in protein, making them a great source of nutrition. Unfortunately, some are highly toxic if ingested. Picking and consumption of wild mushrooms are increasingly popular in the United States. This rise in popularity has led to increased reports of severe and fatal mushroom poisonings.

The clinical syndromes produced by mushroom poisoning are divided according to the rapidity of onset of symptoms and the predominant system involved (Table 722-1). The symptoms are caused by the principal toxin present in the ingested mushrooms. The 8 major toxins produced by mushrooms are categorized as cyclopeptides, monomethylhydrazine, muscarine, hallucinogenic indoles, isoxazole, coprine (disulfiram-like reaction), orellanine, and gastrointestinal tract–specific irritants. The edible wild mushroom *Tricholoma equestre* is associated with delayed rhabdomyolysis, and *Clitocybe amoenolens* and *Clitocybe acromelalga* have been reported to cause erythromelalgia. The toxins responsible for these effects are unknown. An enzyme-linked immunosorbent assay immunoassay is available to detect amanitotoxin; additional rapid tests are becoming available to identify other specific toxins.

Symptoms after eating mushrooms may not be the direct effect of a toxin but may be an allergic reaction or a toxic effect of pesticides or other contaminants. In addition, all who ate the same mushroom may not become sick or if they do they may become sick at different intervals. Table 722-2 lists general principles of management.

GASTROINTESTINAL: DELAYED ONSET

Amanita Poisoning

Poisonings by species of *Amanita* and *Galerina* account for 95% of the fatalities from mushroom intoxication; the mortality rate for this group is 5-10%. Most species produce 2 classes of cyclopeptide toxins: (1) phallotoxins, which are heptapeptides believed to be responsible for the early symptoms of *Amanita* poisoning, and (2) amanitotoxin, an octapeptide that inhibits nuclear RNA polymerase II and subsequent production of messenger RNA leading to impaired protein synthesis and cell death. Cells with high turnover rates, such as those in the gastrointestinal mucosa, kidneys, and liver, are the most severely affected. Other suggested toxin effects are induction of apoptosis, glutathione depletion in the liver, and oxygen free radical formation. Acute yellow atrophy of the liver and necrosis of the proximal renal tubules are found in lethal cases.

The **clinical course** of poisoning with *Amanita* or *Galerina* species is biphasic. Nausea, vomiting, and severe abdominal pain ensue 6-24 hr after ingestion. Profuse watery diarrhea follows shortly thereafter and may last for 12-24 hr or longer. During this time, patients become severely dehydrated. From 24-48 hr after poisoning, jaundice, hypertransaminasemia (peaking at 72-96 hr), renal failure, and coma occur. Death occurs 4-7 days after the ingestion. A prothrombin time less than 10% of control is a poor prognostic factor.

Treatment

Treatment for *Amanita* poisoning is both supportive and specific. Fluid loss from severe diarrhea during the early course of the illness is profound, requiring aggressive correction of fluid loss, electrolytes, and acid–base disturbances. In the late phase of the disease, management of renal and hepatic failure is also necessary.

Specific therapy for *Amanita* poisoning is designed to remove the toxin rapidly and to block binding at its target site. Oral activated charcoal is recommended as part of the initial treatment for children with *Amanita* poisoning. Forced diuresis should be avoided, as this increases renal exposure. For significant ingestions, consider silibinin (5 mg/kg IV over 1 hr followed by a continuous intravenous infusion of 20 mg/kg/24 hr) for 3 days postingestion. If silibinin is not available, intravenous penicillin G (400,000 units/kg/24 hr) may be used. Silibinin and penicillin G inhibit binding of both toxins, interrupt enterohepatic recirculation of amanitotoxin, and protect the liver from further injury. Acetylcysteine has shown promise in some studies. Hemodialysis and hemoperfusion are also recommended as part of the initial treatment for intoxicated children. Orthotopic liver transplantation is recommended for children with severe hepatic failure.

Monomethylhydrazine Intoxication

Species of *Gyromitra* contain gyromitrin which decomposes in the stomach to form monomethylhydrazine (CH_3NHNH_2) and inhibits

Table 722-1 Summary of Common Mushroom-Associated Syndromes

SYNDROME	CLINICAL COURSE	TOXIN(S)	TYPICAL CAUSATIVE MUSHROOM(S)
Delayed gastroenteritis followed by hepatorenal syndrome	Stage 1: 24 hr after ingestion: onset of nausea, vomiting, profuse cholera-like diarrhea, abdominal pain, hematuria Stage 2: 12-48 hr after ingestion: apparent recovery; levels of hepatic enzymes are rising during this stage Stage 3: 24-72 hr after ingestion: progressive hepatic and renal failure, coagulopathy, cardiomyopathy, encephalopathy, convulsions, coma, death	Cyclopeptides, principally amatoxins	"Deadly *Amanitas*," *Galerina* species
Hyperactivity, delirium, coma	30 min to 2 hr after ingestion: delirium, hallucinations, and coma	Muscimol, ibotenic acid	*Amanita muscaria, Amanita pantherina*
Delayed gastroenteritis with central nervous system abnormalities	6-24 hr after ingestion: nausea, vomiting, diarrhea, abdominal pain, muscle cramps, delirium, convulsions, coma; hemolysis and methemoglobinemia may occur	Gyromitrin	*Gyromitra esculenta* ("false morel")
Cholinergic syndrome	30 min to 2 hr after ingestion: bradycardia, bronchorrhea, bronchospasm, salivation, perspiration, lacrimation, convulsions, coma	Muscarine	*Boletus* species, *Clitocybe* species, *Inocybe* species, *Amanita* species
Disulfiram-like reaction with ethanol	30 min after drinking ethanol (may occur up to 1 wk after eating coprine-containing mushrooms): flushing of skin of face and trunk, hypotension, tachycardia, chest pain, dyspnea, nausea, vomiting, extreme apprehension	Coprine	*Coprinus atramentarius*
Hallucinations	30 min to 3 hr after ingestion: hallucinations, euphoria, drowsiness, compulsive behavior, agitation	Psilocybin and psilocin	*Psilocybe* species
Delayed gastritis and renal failure	Abdominal pain, anorexia, vomiting starting over 30 hr after ingestion, followed by progressive renal failure 3-14 days later	Orelline, orellanine	*Cortinarius* species
Immune-mediated hemolytic anemia	Syncope, gastroenteritis, oliguria, hemoglobinuria, back pain, hemolysis	Immunoglobulin mediated	*Paxillus involutus*
General gastrointestinal irritants	30 min to 2 hr after ingestion: nausea, vomiting, abdominal cramping, diarrhea; may recover without treatment	Unidentified, probably multiple	*Chlorophyllum molybdites*, backyard mushrooms ("little brown mushrooms"), many others

From Brent J, Palmer RB: Mushrooms. In Shannon MW, Borron SW, Burns MJ, editors: Haddad and Winchester's clinical management of poisoning and drug overdose, *ed 4, Philadelphia, 2007, WB Saunders, Table 23-1.*

Table 722-2 General Management of Mushroom Ingestion

1. Determine history of ingestion: how many types of mushrooms ingested, what time, if anyone else ate them, and what symptoms are present.
2. Attempt to determine which of the possible syndromes (see Table 722-1) the patient may have. For example, gastrointestinal symptoms occurring more than 6 hr after ingestion strongly suggest cyclopeptide, gyromitrin, or *Cortinarius* poisoning.
3. Administer activated charcoal. If the patient has diarrhea, do not give a cathartic. If a cathartic is used, give it only with the first dose of activated charcoal. Use repeated doses of activated charcoal for suspected amatoxin poisonings.
4. If feasible and when indicated, send gastric aspirate or emesis, along with any remaining mushrooms, to a mycologist for identification.
5. Try to perform a preliminary identification of mushroom and spores. Start to develop a spore print as soon as possible.
6. Maintain supportive measures, including airway support, intravenous fluids, and vasopressors (if needed). Monitor volume status.
7. Avoid antispasmodics for gastrointestinal symptoms.
8. Anticipate the clinical course.

From Brent J, Palmer RB: Mushrooms. In Shannon MW, Borron SW, Burns MJ, editors: Haddad and Winchester's clinical management of poisoning and drug overdose, *ed 4, Philadelphia, 2007, WB Saunders, Box 23-1.*

central nervous system (CNS) enzymatic production of γ-aminobutyric acid. Monomethylhydrazine also oxidizes iron in hemoglobin, resulting in methemoglobinemia. Children with *Gyromitra* poisoning experience vomiting, diarrhea, hematochezia, and abdominal pain within 6-24 hr of ingestion of the toxin. CNS symptoms such as vertigo, diplopia, headache, ataxia, and seizures develop later in the clinical course. Hemolysis and methemoglobinemia (see Chapter 462.6) are rare but potential life-threatening complications of gyromitrin poisoning.

Treatment

Hypovolemia from gastrointestinal fluid losses and seizures require supportive intervention. Pyridoxal phosphate, the coenzyme that catalyzes the production of γ-aminobutyric acid, can reverse the effects of monomethylhydrazine when administered in high doses. **Pyridoxine hydrochloride (25 mg/kg infused over 30 min)** is given at a frequency that is dependent on clinical improvement. Diazepam is given for persistent seizures. Parenteral administration of methylene blue is indicated if the methemoglobin concentration exceeds 30%; severe methemoglobinemia may require dialysis. Blood transfusions may be required for significant hemolysis.

RENAL: DELAYED ONSET

Orellanine Poisoning

Species of *Cortinarius* contain the heat-stable toxin bipyridyl orellanine, which causes severe nonglomerular renal injury characterized by

interstitial fibrosis and acute tubular necrosis. Although the exact mechanism of injury is not fully understood, a metabolite of orellanine is thought to inhibit renal protein synthesis. *Cortinarius* poisoning is characterized by nausea, vomiting, and diarrhea that manifest 36-48 hr after ingestion. Although the initial symptoms may be trivial, more serious renal toxicity occurs in several days. Acute renal failure occurs in 30-50% of those affected, beginning with polyuria and progressing to renal failure (see Chapter 535).

Treatment

Treatment for orellanine poisoning is supportive. Early presentation, within 4-6 hr after ingestion, can be treated with activated charcoal and gastric lavage. Hemodialysis may be needed in patients suffering from renal failure. Most patients recover within 1 mo but chronic renal insufficiency develops in one third to one half of patients who subsequently require renal transplantation.

AUTONOMIC NERVOUS SYSTEM: RAPID ONSET

Muscarine Poisoning

Mushrooms of the genera *Inocybe* and, to a lesser degree, *Clitocybe* contain muscarine or muscarine-related compounds. These quaternary ammonium derivatives bind to postsynaptic receptors, producing an exaggerated cholinergic response.

The onset of symptoms is rapid (30 min to 2 hr after consumption) and intoxication is characterized by a hypercholinergic response: diaphoresis, excessive lacrimation, salivation, miosis, bradycardia, hypotension, urinary and fecal incontinence, and vomiting. Respiratory distress caused by bronchospasm and increased bronchopulmonary secretions is the most serious complication. The symptoms subside spontaneously within 6-24 hr.

Treatment

Atropine sulfate, the specific antidote, is administered intravenously (0.01 mg/kg; maximum: 2 mg). This is repeated until the pulmonary symptoms resolve or the patient becomes overtly tachycardic.

Coprine Ingestion

Coprinus atramentarius and *Clitocybe clavipes* contain coprine. Like disulfiram (Antabuse; Odyssey Pharmaceuticals, Inc.), coprine inhibits the metabolism of acetaldehyde after ethanol ingestion. The clinical manifestations result from accumulation of acetaldehyde.

Coprine intoxication becomes apparent after ethanol ingestion and may occur up to 5 days after consumption of the mushroom. Hyperemia of the face and trunk, tingling of the hands, metallic taste, tachycardia, and vomiting occur acutely. Hypotension may result from intense peripheral vasodilation.

The syndrome typically is self-limited and lasts only several hours. No specific antidote is available. If hypotension is severe, vascular reexpansion with isotonic parenteral solutions may be required. Small oral doses of propranolol have also been suggested.

CENTRAL NERVOUS SYSTEM: RAPID ONSET

Isoxazole Intoxication

Although *Amanita muscaria* and *Amanita pantherina* may contain muscarine, the toxins responsible for the CNS symptoms after ingestion of these mushrooms are muscimol and ibotenic acid, the heat-stable derivatives of the isoxazoles. Muscimol, a hallucinogen, and ibotenic acid, an insecticide, act as γ-aminobutyric acid agonists. From 30 min to 3 hr after ingestion, CNS symptoms appear: obtundation, alternating lethargy and agitation, and, occasionally, seizures. Nausea and vomiting are uncommon. If large amounts of muscarine are contained in the mushroom, symptoms of cholinergic crisis also may occur.

Specific therapy must be carefully selected. If an exaggerated cholinergic response is observed, atropine should be administered. Because ingestions of *A. muscaria* often are associated with anticholinergic findings, the acetylcholinesterase inhibitor physostigmine is often used to reverse the delirium and coma. Benzodiazepines also are used for the agitation and delirium. Seizures can be controlled with diazepam. In most cases, however, early treatment with ipecac (if the patient is conscious) and close observation are all that is required.

Indole Intoxication

Mushrooms belonging to the genus *Psilocybe* ("magic mushrooms") contain psilocybin and psilocin, 2 psychotropic compounds. Within 30 min after ingestion, patients experience euphoria and hallucinations, often accompanied by tachycardia and mydriasis. Fever and seizures have also been observed in children with psilocybin poisoning. These symptoms are short lived, usually lasting for 6 hr after consumption of the mushroom. Treatment consists of rest and observation in a quiet environment. Severely agitated patients may show response to diazepam.

GASTROINTESTINAL: RAPID ONSET

Many mushrooms from various genera produce local gastrointestinal manifestations. The causative toxins are diverse and largely unknown. Within 1 hr of ingestion, patients experience acute abdominal pain, nausea, vomiting, and diarrhea. Symptoms may last from hours to days, depending on the species of mushroom.

Treatment is mainly supportive. Children with large fluid losses may require parenteral fluid therapy. It is imperative to differentiate ingestion of mushrooms of this class from ingestion of *Amanita* and *Galerina* species containing cyclopeptide toxins.

Bibliography is available at Expert Consult.

722.2 Solanine Poisoning

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Potatoes exposed to light and allowed to turn green and/or sprout produce a number of alkaloid glycosides containing the cholesterol derivative solanidine. Two of these glycosides, α-solanine and α-chaconine, are found in highest concentration in the peels of greened potatoes and in the sprouts. Some solanine can be removed by boiling but not by baking. The major effect of α-solanine and α-chaconine is the reversible inhibition of cholinesterase. Cardiotoxic and teratogenic effects have also been reported.

Clinical manifestations of solanine and chaconine poisoning intoxication occur within 7-19 hr after ingestion. The most common symptoms are vomiting, abdominal pain, and diarrhea; in more severe instances of poisoning, neurologic symptoms, including drowsiness, apathy, confusion, weakness, and vision disturbances, are rarely followed by coma or death.

Treatment of solanine poisoning is largely supportive. In the most severe cases, symptoms resolve within 11 days.

Bibliography is available at Expert Consult.

722.3 Seafood Poisoning

Denise A. Salerno and Stephen C. Aronoff

CIGUATERA FISH POISONING

The most frequently reported seafood-toxin illness in the world, ciguatera fish poisoning, has been reported in Florida, Hawaii, French Polynesia, the Marshall Islands, Caribbean and South Pacific islands, and the Virgin Islands. With modern methods of transportation, the illness now occurs worldwide. Grouper is the most commonly identified source of the toxin, followed by snapper, kingfish, amberjack, dolphin, eel, and barracuda. Poisoning has also been associated with farm-raised salmon.

The dinoflagellate *Gambierdiscus toxicus,* a microscopic unicellular organism found along coral reefs, produces high concentrations of ciguatoxin and maitotoxin. The toxins are passed along the food chain

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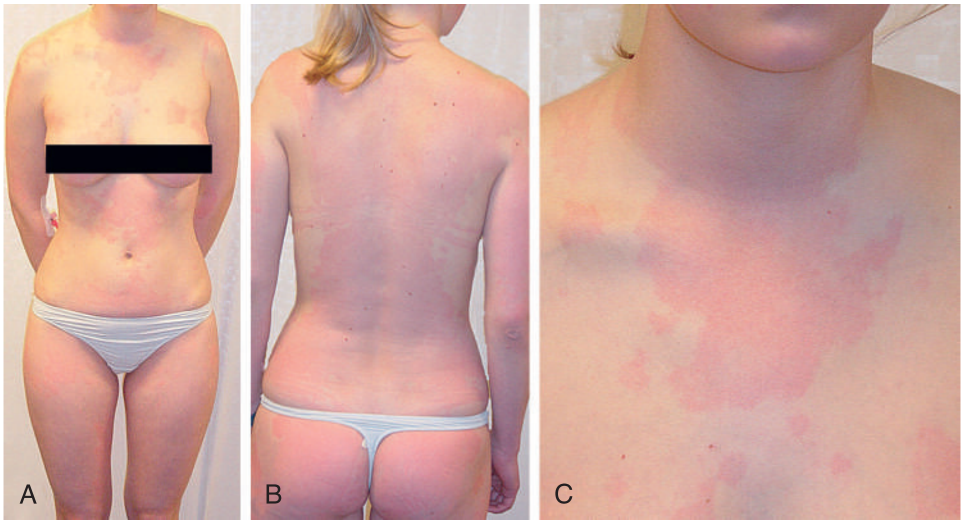

Figure 722-1 **A** and **B,** Widespread erythematous rash predominantly on the face (not shown) and trunk of patient 1. **C,** Close-up view of the upper chest area. Note the absence of wheals. *(From Jantschitsch C, Kinaciyan T, Manafi M, Safer M, Tanew A. Severe scombroid fish poisoning: an underrecognized dermatologic emergency.* J Am Acad Dermatol *65(1):246–247, 2011, Fig. 1.)*

from small herbivorous fish that consume the dinoflagellate to larger predatory fish and then to humans. These toxins are harmless in fish but produce distinct clinical symptoms in humans.

The lipid ciguatoxin-1 is odorless, colorless, and tasteless and is not destroyed by cooking or freezing. Ciguatoxin-1 increases the sodium ion permeability of excitable membranes and depolarizes nerve cells, actions that are inhibited by calcium and tetrodotoxin.

Between 2 and 30 hr after ingestion, ciguatoxin poisoning typically produces a biphasic illness. The initial symptoms are not specific and are of gastrointestinal origin (diarrhea, vomiting, nausea, and abdominal pain). The second phase occurs within a few days of ingestion and consists of intense itching, anxiety, myalgias, painful intercourse, and rash on palms and soles; the neurologic symptoms of circumoral or extremity dysesthesias (characterized by reversal of hot and cold sensation) are characteristic of this disease and may last for months. Tachycardia, bradycardia, hypotension, and death occur infrequently. Eating fish organs, roe, or viscera is associated with greater symptom severity. The diagnosis of ciguatera fish poisoning is based on clinical presentation and a compatible epidemiologic history; the diagnosis is confirmed by testing the ingested fish for toxin. There is no human biomarker to confirm ciguatera fish poisoning.

Treatment

Treatment of ciguatera fish poisoning is supportive. Gastric lavage is recommended to remove any remaining toxin. Intravenous fluids may be required for severe diarrhea, and parenteral administration of calcium can be used to treat hypotension. Once adequate hydration is established, mannitol (0.5-1.0 g/kg, IV over 30-45 min) given within 48-72 hr of the toxic fish ingestion is recommended for reduction of acute symptoms (especially neurologic symptoms) and possible prevention of chronic neurologic symptoms. Various other medications and herbal remedies have been tried, with variable results. Most cases are self-limited, and death occurs in less than 0.1% of cases.

SCOMBROID (PSEUDOALLERGIC) FISH POISONING

Ingestion of members of the Scomberesocidae and Scombridae families, including albacore, mackerel, tuna, bonita, and kingfish, have been linked to major outbreaks of pseudoallergy fish poisoning. Nonscombroid fish and marine mammals, such as mahi-mahi (dolphin fish), swordfish, and bluefish, also are associated with poisoning.

Scombrotoxin, either histamine or the product of the action of the toxin on fish flesh, is responsible for the clinical syndrome. Histidine is found in high concentrations in the flesh of scombroid fish; the action of bacterial decarboxylases during putrification converts the histidine to histamine. Fish containing more than 20 mg of histamine per 100 g of flesh are toxic. In patients receiving isoniazid, a potent histaminase blocker, ingestion of fish flesh containing a lower concentration of histamine may be toxic.

The onset of **clinical manifestations** is acute and occurs within 10 min to 2 hr of ingestion. The most common symptoms and signs are diarrhea, erythema, sweating, flushing, diaphoresis, urticaria, nausea, and headache (Fig. 722-1). Abdominal pain, tachycardia, oral burning or numbness, dizziness, respiratory distress, hives, and facial swelling also occur. The illness is usually self-limited, terminating within 8-24 hr.

Treatment

Treatment is mainly supportive. Gastric lavage decreases continued absorption of histamine. With severe diarrhea, fluid replacement may be necessary. Antihistamines have been variably successful. Four patients with severe toxicity treated with cimetidine (a histamine blocker) showed rapid response. Because data on these possible treatments are limited, cimetidine or ranitidine should be reserved for severe cases.

PARALYTIC SHELLFISH POISONING

Mussels, clams, oysters, scallops, and other filter-feeding mollusks may become contaminated during dinoflagellate blooms or “red tides.” During periods of contamination, water in coastal areas can be colored red by the algae; this sign is the origin of the term *red tide*. (Such discoloration does not necessarily indicate the presence of toxin, and toxin may be present in high quantities without discoloration. Nonetheless, discolored water should be regarded with suspicion.) The dinoflagellates *Alexandrium* spp. and *Gymnodinium catenatum* often are responsible for these red tides and contain several potent neurotoxins. Paralytic shellfish poisoning is a distinctive neurologic illness caused by 20 closely related heat-stable paralytic shellfish toxins. Saxitoxin is the most potent of the neurotoxins responsible for paralytic shellfish poisoning. This toxin prevents nerve conduction by inhibiting the sodium–potassium pump. Other toxins may be bioconverted to less toxic compounds. Consumption of bivalves, such as mussels, scallops, and clams, is the usual pathway of intoxication, although crustaceans and fish have been implicated as well.

The onset of **clinical manifestations** of paralytic shellfish poisoning occurs rapidly, 30 min to 2 hr after ingestion. Abdominal pain and

nausea are common. Paresthesias are common and occur circumorally or in a stocking–glove distribution, or both. Perioral numbness or tingling, diplopia, ataxia, dysarthria, and the sensation of floating are seen less commonly. Hot-cold reversal in temperature sensation is not unusual. In severe cases, respiratory failure from diaphragmatic paralysis may result. Swimming in the water during a red tide episode does not appear to have neurologic sequalae, although skin or mucosal irritation may result.

Treatment

No antidote for paralytic shellfish poisoning is known. Supportive care, including mechanical ventilation, may be needed. Although the symptoms are usually self-limited and short-lived, weakness and malaise may persist for weeks after ingestion.

NEUROTOXIC SHELLFISH POISONING

Neurotoxic shellfish poisoning is a rare disease caused by molluscan shellfish contaminated with brevetoxins. Shellfish harvested along the Gulf of Mexico during or right after a red tide are at risk of contamination with brevetoxins produced by the dinoflagellate *Karenia brevis*. There has also been recent evidence of brevetoxin production by raphidophytes (*Chattonella* spp.). Brevetoxins are a group of more than 10 lipid-soluble neurotoxins that activate sodium ion channels, causing nerve membrane depolarization. Shellfish are not affected by the brevetoxins. Rinsing, cleaning, cooking, and freezing do not destroy the toxins. Consumption of contaminated shellfish goes unnoticed because the brevetoxins cannot be detected by taste or smell.

The onset of **clinical manifestations** of neurotoxic shellfish poisoning occurs from within a few min up to 18 hr after consumption. The majority of symptoms are gastrointestinal (nausea, vomiting, and diarrhea) or neurologic (numbness and tingling of the lips, mouth, face, and extremities, ataxia, partial limb paralysis, reversal of hot and cold sensation, slurred speech, headache, and fatigue). Neurotoxic shellfish poisoning is similar to a mild case of paralytic shellfish poisoning.

Treatment

There are no specific antidotes for brevetoxins. Treatment involves mostly supportive care. Brevenal, a natural antagonist of brevetoxin produced by *K. brevis*, may be used as a form of treatment in the future.

DIARRHETIC SHELLFISH POISONING

Several outbreaks of diarrhetic shellfish poisoning have been reported in Europe after consumption of mussels, cockles, and other shellfish. The dinoflagellates *Dinophysis* and *Prorocentrum* produce okadaic acid and its derivatives, the dinophysistoxins. These compounds inhibit protein phosphatases. The intracellular accumulation of phosphorylated proteins causes increased fluid secretion by gut cells via calcium influx, which is mediated by cyclic adenosine monophosphate and prostaglandins.

Patients have severe diarrhea. Care is supportive and directed at rehydration. The illness is self-limited, and recovery occurs in 3-4 days; few patients require hospitalization.

AMNESIC SHELLFISH POISONING

Amnesic shellfish poisoning was first reported in 1987 in Canada when a group of people demonstrated severe gastroenteritis as well as neurologic symptoms, including memory loss, after eating mussels from Prince Edward Island. Subsequent cases have been identified after consumption of shellfish from the United States, Spain, and the United Kingdom. The responsible toxin, domoic acid, comes from a diatom, *Pseudonitzschia multiseries,* and is a potent glutamate agonist, disrupting neurochemical transmission in the brain. It also binds to glutamate receptors, which increase calcium influx, producing neuronal swelling in the hippocampal area of the brain and death.

The initial **clinical manifestations** are gastrointestinal. Memory loss is closely related to advanced age. Those patients <40 yr are more likely to suffer only from diarrhea, whereas those >50 yr suffer from short-term memory loss lasting months to years.

AZASPIRACID POISONING

The azaspiracids are a class of algal toxins. Azaspiracid poisoning results from ingestion of contaminated bivalve shellfish, especially mussels. Azaspiracid toxins are distributed throughout the muscle tissue in the shellfish. Azaspiracid is cytotoxic to cells and an inhibitor of Ca^{++} channels in plasma membranes. Symptoms start 6-18 hr after ingestion and include nausea, vomiting, severe stomach cramps, and diarrhea, which often persist up to 5 days.

Bibliography is available at Expert Consult.

722.4 Melamine Poisoning

Denise A. Salerno and Stephen C. Aronoff

Melamine (1,3,5-triazine-2,4,6-triamine, or $C_3H_6N_6$), a compound developed in the 1830s, is found in many plastics, adhesives, laminated products, cement, cleansers, fire retardant paint, and more. Melamine poisoning from food products was unheard of until 2007, when melamine-tainted pet food caused the death of many dogs and cats in the United States. In 2008, feeding of melamine-tainted infant formula to more than 300,000 children resulted in kidney injuries, 50,000 hospitalizations, and 6 deaths in China. This was the first reported epidemic of melamine-tainted milk products.

Melamine contains 66% nitrogen by mass. The illegal addition of melamine to infant formula can give the formula a milky appearance and falsely raise the protein content as measured by nitrogen testing.

Melamine, combined with cyanuric acid, forms cyanurate crystals in the kidneys. Along with protein, uric acid, and phosphate, melamine forms renal calculi.

Clinical manifestations are initially subtle and nonspecific. The severity is dose related. The first symptoms in affected infants are unexplained crying (especially when urinating), vomiting, and discolored urine caused by the formation of stones and gravel in the urinary tract. Urinary obstruction and acute renal failure follow. In the absence of a specific diagnosis, death from renal failure occurs. Whether children with melamine-induced renal failure will have chronic sequelae is currently unknown. Animal studies have shown that melamine may cause cognitive impairment but further investigation is needed.

The melamine stones and gravel can be treated with hydration, alkalinization, or lithotripsy. Acute renal failure requires supportive care and dialysis if needed.

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Chapter 723

Biologic and Chemical Terrorism

Theodore J. Cieslak and Frederick M. Henretig

Tragically, increasing numbers of children are being victimized by terrorist actions. Brought to the forefront of American consciousness by Timothy McVeigh's references to child fatalities as "collateral damage" during the Oklahoma City bombing in April 1995, the intentional targeting of children became firmly ensconced as a global reality with the attack upon a school in Beslan, Russia, in September 2004. The attack, which left 334 (Including 186 children) dead, presaged additional attacks specifically directed against children at an Amish School in Pennsylvania in 2006, at a camp for teenagers in Utoya, Norway, in

2011, and at Sandy Hook Elementary School in Connecticut in 2012, among others.

Paralleling the targeting of children is an apparent trend toward the use of "unconventional" weapons of terror. In 1984, members of the Rajneeshee cult employed *Salmonella typhi* in a wave of intentional poisonings that affected 751 persons, including 142 teenage patrons of a popular pizza parlor. In 1995, the Aum Shinrikyo cult killed 12 and sickened thousands by intentionally releasing sarin nerve agent in the Tokyo subway system. A disgruntled scientist deployed anthrax spores via the U.S. mail in October 2001, killing 5 and injuring 17 in an attack upon a nation already reeling in the wake of the 9/11 attacks.

These developments remind us that terrorists can strike at any time utilizing any number of unconventional weapons, including biologic and chemical agents. Children will not be spared in these attacks on civilians, and, indeed, schools and daycare sites may be the targets of these actions.

ETIOLOGY

Terrorists may choose to use **weapons of opportunity,** agents that for some reason are readily available to some member of the terrorist group. The motives of terrorists often are obscure and difficult to predict. Prevention and response strategies should thus concentrate not on those agents most likely to be used but, rather, on those agents that, if used, would constitute the gravest potential threats to public health and security.

Biologic threat agents, including pathogens and toxins, have been divided by the Centers for Disease Control and Prevention into 3 categories, with **category A** including diseases caused by those 6 agents posing the greatest threat: anthrax, plague (see Chapter 203.3), tularemia (see Chapter 206), smallpox, botulism (see Chapter 210), and the viral hemorrhagic fevers (see Chapter 271).

Terrorists could also procure and release a vast array of potentially harmful chemicals. Tank cars full of flammable industrial gases and liquids, corrosive industrial acids and bases, poisonous compounds such as cyanides and nitrites, pesticides, dioxins, and explosives traverse our railways and roads daily. Four classes of "military-grade" chemicals with a history of use in warfare or manufactured specifically for use as weapons include the organophosphate-based nerve agents, vesicants, "blood agents" (cyanides), and certain pulmonary irritants or "choking agents."

EPIDEMIOLOGY AND PEDIATRIC-SPECIFIC CONCERNS

Large-scale attacks on civilian targets will likely involve pediatric victims, and children may be more susceptible than adults to the effects of certain biologic and chemical agents (see Chapter 719). A thinner and less-keratinized epidermis makes dermally active chemical agents, such as mustard, a greater risk to children than adults. A larger surface area per unit volume further increases the problem. A small relative blood volume makes children more susceptible to the volume losses associated with enteric infections such as cholera and to gastrointestinal intoxications such as might be seen with exposure to the staphylococcal enterotoxins. Children's high minute ventilation, compared with that of adults, increases the threat of agents delivered via the inhalational route. The fact that children live "closer to the ground" compounds this effect when heavier-than-air chemicals are involved. An immature blood–brain barrier may heighten the risk of central nervous system toxicity from nerve agents. Developmental considerations make it less likely that a child would readily flee an area of danger, thereby increasing exposure to these various adverse effects.

Children appear to have a unique susceptibility to certain potential agents that might be used by terrorists. Although adults generally suffer only a brief, self-limited incapacitating illness after infection with Venezuelan equine encephalitis virus, young children are more likely to experience seizures, permanent neurologic sequelae, and death. In the case of smallpox, waning herd immunity may disproportionately affect children. Vaccine-induced immunity to smallpox probably diminishes significantly after ages 3-10 yr. Although most adults are considered susceptible to smallpox, given that routine civilian immunization ceased in the early 1970s, older adults may have some residual protection from death, if not from the development of disease. Today's children are among the first to grow up in a world without any individual or herd immunity to smallpox.

Children also may experience unique disease manifestations not seen in adults; suppurative parotitis is a common characteristic ring among children with melioidosis but is not generally seen in adults with *Burkholderia pseudomallei* infection (see Chapter 205.2).

Pediatricians are likely to experience unique problems in managing childhood victims of biologic or chemical attack. Many of the drugs useful in treating such casualties are unfamiliar to pediatricians or have relative contraindications in childhood. The fluoroquinolones and tetracyclines are commonly cited as agents of choice in the treatment and prophylaxis of anthrax, plague, tularemia, brucellosis, and Q fever. Both drug classes are often avoided in children, although the risk of morbidity and mortality from diseases induced by agents of bioterrorism far outweighs the minor risks associated with short-term use of these agents. Ciprofloxacin received, as its first licensed pediatric indication, FDA approval for use in the prophylaxis of anthrax after inhalational exposure during a terrorist attack. Doxycycline and levofloxacin are licensed specifically in children for the same indication and levofloxacin is also licensed for postexposure prophylaxis of children against plague. Immunizations potentially useful in preventing biologic agent–induced diseases are often not approved for use in pediatric patients. The available anthrax vaccine is licensed only for those between 18 and 65 yr of age. The plague vaccine, currently out of production and probably ineffective against inhalational exposures, was approved only for individuals ages 18-61 yr. The smallpox vaccine, a live vaccine employing vaccinia virus, can cause fetal vaccinia and demise when given to pregnant women.

Many otherwise useful pharmaceutical agents are not available in pediatric dosing regimens. The military distributes nerve agent antidote kits consisting of prefilled autoinjectors designed for the rapid administration of atropine and pralidoxime. Many emergency departments and some ambulances stock these kits. The doses of agents contained in the nerve agent antidote kit are calculated for soldiers and thus are far in excess of those appropriate for young children, and pediatric pralidoxime autoinjectors are not yet available. Atropine autoinjectors specifically formulated for children are approved by the FDA and are available.

Although physical protective measures and devices (e.g., "gas masks") are likely to be of little utility in a civilian terrorism setting, such commercially available devices are not often available in pediatric sizes. The Israeli experience during the first Gulf War suggests that frightened parents may improperly use such masks on their children, resulting in inadvertent suffocation.

In the event of a large-scale terrorist attack, there may be an insufficient number of pediatric hospital beds. In any large disaster, excess bed capacity might potentially be provided at civilian and veterans hospitals under the auspices of the National Disaster Medical System, but that system makes no specific provision for pediatric beds.

CLINICAL MANIFESTATIONS

Should a terrorist attack occur, clinicians may be called on to make prompt diagnoses and render rapid lifesaving treatments before the results of confirmatory diagnostic tests are available. Although each potential agent of terrorism produces its own unique clinical manifestations, it is useful to consider their effects in terms of a limited number of distinct clinical syndromes. This approach helps clinicians make prompt, rational decisions regarding empirical therapy. Casualties resulting from a terrorist attack would either experience symptoms immediately upon exposure to an agent (or within the 1st several hr after exposure) or, alternatively, would see their symptoms develop slowly over a period of days to weeks. In the former case, the sinister nature of the event is often obvious and the etiology more likely to be conventional or chemical in nature. Biologic agents differ from conventional, chemical (see Chapter 719), and nuclear (see Chapter 718) weapons in that they have inherent incubation periods. Consequently, patients are likely to present removed in time and place from the point

Table 723-1 Diseases Caused By Agents of Chemical and Biologic Terrorism, Classified By Syndrome

	NEUROMUSCULAR SYMPTOMS PROMINENT	RESPIRATORY SYMPTOMS PROMINENT	DERMATOLOGIC FINDINGS PROMINENT
Sudden-onset	Nerve agents	Chlorine Phosgene Cyanide	Mustard Lewisite
Delayed-onset	Botulism	Anthrax Plague Tularemia Ricin	Smallpox

of an unannounced and unnoticed exposure to a biologic agent. Whereas traditional first responders, such as firefighters and paramedics, may be at the forefront of a conventional or chemical terrorism response, the primary care physician is likely to constitute the first line of defense against the effects of a biologic agent.

Casualties can thus be categorized as either immediate or delayed in presentation. Within each of these categories, patients can be further classified as having primarily respiratory, neuromuscular, or dermatologic manifestations (Table 723-1). A limited number of agents may cause each particular syndrome, permitting institution of empiric therapy targeted at a short list of potential etiologies. The viral hemorrhagic fevers might manifest as fever and a bleeding diathesis; these agents are considered separately in Chapter 271. In most cases, supportive care is the mainstay of hemorrhagic fever treatment.

Sudden-Onset Neuromuscular Syndrome: Nerve Agents

The very rapid onset of neuromuscular symptoms after an exposure should lead the clinician to consider nerve agent intoxication. The nerve agents (*tabun, sarin, soman,* and *VX*) are **organophosphate** analogs of common pesticides that act as potent inhibitors of the enzyme acetylcholinesterase. They are hazardous via ingestion, inhalation, or cutaneous absorption (see Chapter 63).

The inhibition of cholinesterase by these compounds results in the accumulation of acetylcholine at neural and neuromuscular junctions, causing excess stimulation. The resultant **cholinergic syndrome** involves central, nicotinic, and muscarinic effects. Central effects include altered mental status progressing rapidly to lethargy and coma, as well as ataxia, convulsions, and respiratory depression. Studies on pesticide exposure suggest that children may be more prone to central neurologic dysfunction with organophosphate toxicity than adults. Nicotinic effects include muscle fasciculations and twitching, followed by weakness, which can progress to flaccid paralysis as muscles fatigue. Muscarinic effects include miosis, visual blurring, profuse lacrimation, and watery rhinorrhea. Bronchospasm and increased bronchial secretions lead to cough, wheezing, dyspnea, and cyanosis. Cardiovascular manifestations include bradycardia, hypotension, and atrioventricular block. Flushing, sweating, salivation, nausea, vomiting, diarrhea, abdominal cramps, and urinary incontinence are also seen. In the absence of prompt intervention, death can quickly result from a combination of central effects and respiratory muscle paralysis.

Delayed-Onset Neuromuscular Syndrome: Botulism

The delayed onset (hours to days after exposure) of neuromuscular symptoms is characteristic of botulism. Botulism occurs after exposure to 1 of 7 related neurotoxins produced by certain strains of *Clostridium botulinum,* a strictly anaerobic, spore-forming, Gram-positive bacillus commonly found in soil. Naturally occurring botulism (see Chapter 210) usually follows ingestion of preformed toxin (food poisoning) or results from intestinal toxin production (infantile botulism). An aerosol exposure would likely result in a case of clinical botulism indistinguishable from that caused by natural exposures.

Following exposure to botulinum toxin, clinical manifestations typically begin with bulbar palsies, causing patients to complain of ptosis, photophobia, and blurred vision resulting from difficulty in accommodation. Symptoms can progress to include dysarthria, dysphonia, and dysphagia and, finally, a descending symmetric paralysis. Sensation and sensorium are typically not affected. In the absence of intervention, death often results from respiratory muscle failure.

Sudden-Onset Respiratory Syndrome: Chlorine, Phosgene, and Cyanide

The acute onset of respiratory symptoms shortly after exposure should prompt the clinician to consider a range of potential chemical agents. Of note, nerve agents, discussed previously, may affect respiration via massive bronchial hypersecretion, bronchospasm, and respiratory muscle paresis. However, the nerve agent casualty will likely have generalized muscle involvement and central nervous system manifestations. In contrast, the toxic inhalants chlorine and phosgene produce respiratory distress without neuromuscular involvement.

Chlorine is a dense, acrid, yellow-green gas that is heavier than air. After mild to moderate exposure, ocular and nasal irritation occurs, followed by cough, a choking sensation, bronchospasm, and substernal chest tightness. Pulmonary edema, mediated by hydrochloric acid and free oxygen radical generation, follows moderate to severe exposures within 30 min to several hours. Hypoxemia and hypovolemia secondary to pulmonary edema are the factors responsible for death when it occurs.

Phosgene, like chlorine, is a common industrial compound that was used as a weapon on the battlefields of World War I. Its odor has been described as similar to "new-mown hay." Like chlorine, phosgene also is thought to result in the generation of hydrochloric acid, contributing particularly to upper airway, nasal, and conjunctival irritation. Acylation reactions caused by the effects of phosgene on the pulmonary alveolar-capillary membrane lead to pulmonary edema. Phosgene lung injury also may be mediated, in part, by an inflammatory reaction associated with leukotriene production. Patients with mild to moderate exposures to phosgene may be asymptomatic, a fact that may cause victims to remain in a contaminated area. Pulmonary edema occurs 4-24 hr after exposure and is dose dependent, with heavier exposures causing earlier symptoms. Dyspnea may precede radiologic findings. In severe exposures, pulmonary edema may be so marked as to result in hypovolemia and hypotension. As in the case of chlorine, death results from hypoxemia and asphyxia.

Cyanide is a cellular poison, with protean clinical manifestations. Initially, cyanide toxicity is most likely to manifest as tachypnea and hyperpnea, progressing rapidly to apnea in cases with significant exposure (see Chapter 63). The efficacy of cyanide as a chemical terrorism agent is limited by its volatility in open air and relatively low lethality in comparison with nerve agents. Released in a closed room, however, cyanide could have devastating effects, as evidenced by its use in the Nazi gas chambers during World War II. Cyanide inhibits cytochrome a_3, interfering with normal mitochondrial oxidative metabolism and leading to cellular anoxia and lactic acidosis. In addition to respiratory distress, early findings among cyanide victims include tachycardia, flushing, dizziness, headache, diaphoresis, nausea, and vomiting. With greater exposure, seizures, coma, apnea, and cardiac arrest may follow within min. An elevated anion gap metabolic acidosis is typically

present, and decreased peripheral oxygen utilization leads to an elevated mixed venous oxygen saturation value.

Delayed-Onset Respiratory Syndrome: Anthrax, Plague, Tularemia, and Ricin

A delayed onset of respiratory symptoms (days after exposure) is characteristic of several infectious diseases and 1 toxin that might be adapted for sinister purposes by terrorists. Among the most threatening and problematic of these are anthrax, plague, tularemia, and ricin, the latter having garnered considerable media attention in recent years.

Anthrax is caused by infection with the Gram-positive spore-forming rod *Bacillus anthracis.* Its ability to form a spore enables the anthrax bacillus to survive for long periods in the environment and enhances its potential as a weapon.

The vast majority of naturally occurring anthrax cases are cutaneous, acquired by close contact with the hides, wool, bone, and other by-products of infected ruminants (principally cattle, sheep, and goats). Cutaneous anthrax is amenable to therapy with a variety of antibiotics and is readily recognizable to experienced clinicians in endemic areas; consequently, it is rarely fatal. Although it is common in parts of Asia and sub-Saharan Africa, only 2 cases of cutaneous anthrax had occurred in the United States in the 9 yr that preceded the attacks of 2001 (when 11 cutaneous cases were seen). Gastrointestinal anthrax, which has never been described in the United States, can occur after the ingestion of contaminated meat. In the past, inhalational anthrax, or **woolsorters' disease**, was an occupational hazard of abattoir and textile workers. Now eliminated as a naturally occurring disease in the United States, it is this inhalational form of anthrax that poses the greatest terror threat. Following an inadvertent release in 1979 from a bioweapons facility at Sverdlovsk in the former Soviet Union, 66 of 77 (86%) known adult victims of inhalational anthrax died. In the 2001 attacks involving contaminated mail in the United States, 5 of 11 (46%) patients with inhalational anthrax died. Whether better intensive care modalities, changes in antibiotic therapy, or earlier recognition accounted for this improved mortality rate remains unknown.

Symptomatic inhalational anthrax typically begins 1-6 days after exposure, although incubation periods of up to several weeks have been reported. The disease begins as a flu-like illness, characterized by fever, myalgia, headache, and cough. A brief intervening period of improvement sometimes follows, but rapid deterioration then ensues; high fever, dyspnea, cyanosis, and shock mark this second phase. Hemorrhagic meningitis occurs in up to 50% of cases. Chest radiographs obtained late in the course of illness may reveal a widened mediastinum or prominent mediastinal lymphadenopathy; pleural effusions also may be seen. Bacteremia is often so profound that Gram stains of peripheral blood may demonstrate the organism at this stage. Prompt treatment is imperative; death occurs in as many as 95% of inhalational anthrax cases if such treatment is begun more than 48 hr after the onset of symptoms.

Whereas inhalational anthrax is a disease primarily of mediastinal lymphatic tissue, exposure to aerosolized plague bacilli typically leads to a primary pneumonia. Endemic **plague** is usually transmitted via the bites of fleas and is discussed in Chapter 203.3. The causative organism of all forms of human plague, *Yersinia pestis,* is a bipolar-staining, Gram-negative facultative intracellular bacillus. An ability to survive within the macrophage aids its dissemination to distant sites following inoculation or inhalation. "Buboes," markedly swollen, tender regional lymph nodes in the distribution of a bite, are the hallmark feature of bubonic plague. Fever and malaise are typically present, and septicemia often develops as bacteria gain access to the circulation. Petechiae, purpura, and overwhelming disseminated intravascular coagulopathy commonly occur, and 80% of bubonic plague victims ultimately have positive blood culture results. Plague is extremely infective and lethal, as illustrated by the fact that the "Black Death" eliminated one third of the population of Europe during the Middle Ages.

Intentional aerosol dissemination of *Y. pestis* would likely result in a preponderance of pneumonic plague cases. Pneumonic plague may also arise secondarily after seeding of the lungs of septicemic patients. Symptoms include fever, chills, malaise, headache, and cough. Chest radiographs may reveal a patchy consolidation, and the classic clinical finding is blood-streaked sputum. Disseminated intravascular coagulation and overwhelming sepsis typically develop as the disease progresses. Untreated pneumonic plague has a fatality rate approaching 100%.

Tularemia is a highly infectious disease caused by the Gram-negative coccobacillus *Francisella tularensis.* Naturally occurring tularemia is discussed in Chapter 206. The high degree of infectivity of *F. tularensis* (<10 organisms are thought to be necessary to produce infection via inhalation), as well as its survivability in the environment, contributes to its inclusion on the list of agents of concern. Several clinical forms of endemic tularemia are known, but inhalational exposure resulting from a terrorist attack would likely lead to a plague-like primary pneumonia or to typhoidal tularemia, manifesting as a variety of nonspecific symptoms including fever, malaise, and abdominal pain.

Ricin is a protein toxin derived from the castor bean plant (*Ricinus communis*) that inhibits ribosomal protein synthesis. It is highly toxic in animal studies when inhaled and may result in the delayed onset of respiratory distress, pulmonary edema, and acute respiratory failure. One case series of 8 persons from the 1940s described a febrile respiratory illness after inhalational exposure. If injected it may cause a sepsis-like syndrome that may progress to multiorgan system failure; ingestion can lead to severe gastroenteritis. Ricin-containing letters were mailed to a U.S. Senate office building in 2004, and again to President Obama and New York City Mayor Bloomberg in 2013, although no persons were sickened in either attack.

Sudden-Onset Dermatologic Syndrome: Mustard and Lewisite

The development of skin lesions shortly after exposure is characteristic of the chemical vesicants. These compounds, often referred to as *blistering agents*, are cellular poisons and include the alkylating agent mustard and the organic arsenical agent lewisite. Tissue injury to rapidly reproducing cells begins within minutes of contact with these agents. Clinical effects typically become evident several hours after exposure to mustard, whereas patients exposed to lewisite feel immediate pain. Both mustard and lewisite affect the eyes and respiratory tract and their inadvertent ingestion may produce significant gastrointestinal symptoms. Mustard exposure may lead to bone marrow suppression.

Delayed-Onset Dermatologic Syndrome: Smallpox

The appearance of an exanthem days to weeks after exposure is likely to be a presenting feature of smallpox. Caused by infection with variola virus, a member of the orthopoxvirus family, smallpox has an incubation period of 7-17 days. This would likely permit the wide dispersal of asymptomatic exposed persons, thus contributing to the spread of an outbreak. During the incubation period, virus replicates in the upper respiratory tract. A primary viremia ensues, during which time seeding of the liver and spleen occurs. A secondary viremia then develops, the skin is seeded, and the classic exanthem of smallpox appears.

Symptoms of smallpox begin abruptly during the phase of secondary viremia and include fever, rigors, vomiting, headache, backache, and extreme malaise. Within 2-4 days, macules appear on the face and extremities and then progress in synchronous fashion to papules, pustules, and finally scabs. As the scabs separate, survivors often are left with disfiguring, depigmented scars. The synchronous nature of the rash and its centrifugal distribution distinguish smallpox from chickenpox, which has a centripetal distribution. Historically, smallpox had a 30% mortality rate, with death typically resulting from visceral organ involvement.

DIAGNOSIS

In some cases, the terrorist nature of a chemical or biologic attack may be obvious, for example, a chemical attack in which victims succumb in close temporal and geographic proximity to a dispersal device or terrorists announce their attack. In other instances, the clinician may

need to rely on epidemiologic clues to suspect an intentional release of chemical or biologic agents. The presence of large numbers of victims clustered in time and space should raise the index of suspicion, as should cases of unexpected death or unexpectedly severe disease. Diseases unusual in a given locale, in a given age group, or during a certain season likewise may warrant further investigation. Simultaneous outbreaks of a disease in noncontiguous areas should cause one to consider an intentional release, as should outbreaks of multiple diseases in the same area. Even a single case of a rare disorder such as anthrax or certain viral hemorrhagic fevers would be suspicious, and a single case of smallpox would almost certainly be the result of an intentional dissemination. Large numbers of dying animals might provide evidence of an unnatural aerosol release, as would evidence of disparate attack rates between those known to be indoors and outdoors at a given time.

In a mass casualty setting, diagnoses may be made largely on clinical grounds. The diagnosis of nerve agent intoxication is based primarily on clinical recognition and patient response to antidotal therapy. Several simple rapid detection devices developed for military use can detect the presence of nerve agents. Some of these are now commercially available and are stocked in certain emergency departments and public safety vehicles. Measurements of acetylcholinesterase in plasma or erythrocytes of nerve agent victims may be helpful in long-term prognostication, but correlation between cholinesterase levels and clinical effects is often poor, and the test rarely is available on an emergency basis.

Botulism should be suspected clinically among patients presenting with a symmetric, descending, flaccid paralysis. Although the differential diagnosis of botulism includes other uncommon neurologic disorders, such as myasthenia gravis and the Guillain-Barré syndrome, the presence of multiple casualties with similar symptoms should aid in the determination of a botulism outbreak.

Initially, the diagnosis of **cyanide poisoning** also will likely be made on clinical grounds in the presence of the appropriate toxidrome. An unusually high anion gap metabolic acidosis with elevated serum lactate and an oxygen concentration greater than expected in mixed venous blood lend support to the clinical diagnosis. Elevated blood cyanide concentrations can confirm the clinical suspicion.

Anthrax should be suspected upon finding Gram-positive bacilli in skin biopsy material (in the case of cutaneous disease), blood smears, pleural fluid, or spinal fluid. Chest radiographs demonstrating a widened mediastinum in the context of fever and constitutional signs, and in the absence of another obvious explanation (e.g., blunt trauma or postsurgical infection), should also lead one to consider the diagnosis. Confirmation can be obtained by blood culture. State health laboratories and federal facilities at the U.S. Centers for Disease Control and Prevention and at the U.S. Army Medical Research Institute of Infectious Diseases can confirm a diagnosis of anthrax by polymerase chain reaction and immunohistochemical assay.

A diagnosis of **plague** can be suspected on finding bipolar "safety-pin"–staining bacilli in Gram or Wayson stains of sputum or aspirated lymph node material; confirmation is obtained by culturing *Y. pestis* from blood, sputum, or lymph node aspirate. The organism grows on standard blood or MacConkey TRA agars but it is often misidentified by automated systems. *F. tularensis* grows poorly on standard media; its growth is enhanced on media containing cysteine. Because of its extreme infectivity, however, many laboratories prefer to make a diagnosis via polymerase chain reaction or serologically using an enzyme-linked immunosorbent assay or serum agglutination assay.

Smallpox should be suspected on clinical grounds and can be confirmed by culture or electron microscopy of scabs or vesicular fluid, although the manipulation of clinical material from suspected smallpox victims should be attempted only at public health laboratories able to employ maximum biocontainment (Biosafety Level 4) precautions. Similar caution should be exercised with specimens from patients with various viral hemorrhagic fevers.

PREVENTION

Preventive measures can be considered in both a preexposure and a postexposure context. **Preexposure protection** against a chemical or biologic attack may consist of physical, chemical, or immunologic measures. **Physical protection** against primary attack often involves gas masks and protective suits; such equipment is used by the military and by certain hazardous materials response teams but it is unlikely to be available to civilians at the precise moment that a release occurs. Medical personnel need to understand the principles of physical protection as they apply to infection control and the spread of contamination.

Pneumonic plague is spread through respiratory droplets. Droplet precautions, including the use of simple surgical masks, are thus warranted for providers caring for patients with plague. Smallpox is transmitted by droplet nuclei. Airborne precautions, including (ideally) a high-efficiency particulate air filter mask, are thus warranted with smallpox victims. Similarly, patients with viral hemorrhagic fever should, in general, be managed with use of contact precautions. Most other biologic agent victims can be safely cared for with use of standard precautions. In the case of chemical agents, residual mustard or nerve agent on the skin or clothing of victims might potentially pose a hazard to medical personnel. For such victims, whenever possible, clothing should be removed and the patients decontaminated using copious amounts of water before extensive medical care is rendered. Most other chemical agents are volatile enough that spread of an agent among patients or from patient to caregiver is unlikely.

Preexposure chemical prophylaxis might be used on the basis of credible intelligence reports. Should officials deem that the threatened release of a specific biologic agent appears imminent, antibiotics might be distributed to a population preemptively. Opportunities to employ such a strategy are likely to be limited, although federal and state officials are examining various mechanisms for such employment.

Although licensed vaccines **(preexposure immunologic measures)** against anthrax and smallpox have been developed, widespread use of either vaccine is likely to be problematic, especially in children. The anthrax vaccine is licensed only for those persons age 18 yr and older, is given as a 5 dose series over 18 mo, and requires annual booster doses. These considerations make civilian employment of the current anthrax vaccine on a large scale unlikely, although a new recombinant anthrax vaccine is in development and being studied as a 3 dose series.

Significant obstacles to the widespread employment of smallpox vaccine also exist, although public health officials have contemplated the resumption of a smallpox vaccination campaign. Whereas in the past smallpox vaccine (prepared from vaccinia virus, an orthopoxvirus related to variola) was used safely and successfully in young infants, it has a relatively high rate of serious complications in certain patients. *Fetal vaccinia* and demise can occur when pregnant women are vaccinated. *Vaccinia gangrenosa,* an often fatal complication, can occur when immunocompromised persons are vaccinated. *Eczema vaccinatum* occurs in those with preexisting dermatoses (atopic dermatitis). Severe vaccine-related encephalitis was well known during the era of widespread vaccination; because it occurs only in primary vaccinees, it would disproportionately affect pediatric patients. Autoinoculation can occur when virus present at the site of vaccination is manually transferred to other areas of skin or to the eye. Young children would presumably be at greater risk for such inadvertent transmission. Myocarditis has been reported following vaccinations of military recruits.

To manage these complications, vaccinia immune globulin should be available when one is undertaking a vaccination campaign. Vaccinia immune globulin (0.6 mg/kg IM) may be given to vaccine recipients who experience severe complications or to significantly immunocompromised individuals exposed to smallpox and in whom vaccination would be unsafe. A compound, ST-246, has been used successfully under an Investigational New Drug permit to treat persons (including children) experiencing severe complications from vaccine. The current cell-culture–derived vaccine (ACAM2000), as well as vaccinia immune globulin and ST-246, can be obtained as needed upon consultation with officials at the Centers for Disease Control and Prevention. In addition to a potential role in preexposure prophylaxis, vaccination may be effective in postexposure prophylaxis if given within the 1st 4 days or so after exposure.

Table 723-2 Critical Biologic Agents of Terrorism

DISEASE	CLINICAL FINDINGS	INCUBATION PERIOD (DAYS)	ISOLATION PRECAUTIONS	INITIAL TREATMENT	PROPHYLAXIS
Anthrax (inhalational)* Patients who are clinically stable after 14 days can be switched to a single oral agent (ciprofloxacin or doxycycline) to complete a 60-days course†	Febrile prodrome with rapid progression to mediastinal lymphadenitis and mediastinitis, sepsis, shock, and meningitis	1-5	Standard	Ciprofloxacin‡ 10-15 mg/kg IV q12h *or* doxycycline 2.2 mg/kg IV q12h *and* clindamycin§ 10-15 mg/kg IV q8h *and* penicillin G‖ 400-600 kU/kg/day IV q4h plus raxibacumab	Ciprofloxacin 10-15 mg/kg PO q12h *or* doxycycline 2.2 mg/kg PO q12h
Plague (pneumonic)	Febrile prodrome with rapid progression to fulminant pneumonia, hemoptysis, sepsis, disseminated intravascular coagulation	2-3	Droplet (for 1st 3 days of therapy)	Gentamicin 2.5 mg/kg IV q8h *or* doxycycline 2.2 mg/kg IV q12h *or* ciprofloxacin 15 mg/kg IV q12h	Doxycycline 2.2 mg/kg PO q12h *or* ciprofloxacin 20 mg/kg PO q12h
Tularemia	Pneumonic: abrupt onset of fever with fulminant pneumonia Typhoidal: fever, malaise, abdominal pain	2-10	Standard	Same as for plague	Same as for plague
Smallpox	Febrile prodrome with synchronous, centrifugal, vesiculopustular exanthema	7-17	Airborne (+ contact)	Supportive care	Vaccination may be effective if given within the 1st several days after exposure
Botulism	Afebrile descending symmetric flaccid paralysis with cranial nerve palsies	1-5	Standard	Supportive care; antitoxin (see text) may halt the progression of symptoms but is unlikely to reverse them	None
Viral hemorrhagic fevers	Febrile prodrome with rapid progression to shock, purpura, and bleeding diatheses	4-21	Contact (consider airborne in cases of massive hemorrhage)	Supportive care; ribavirin may be beneficial in select cases	None

*In a mass casualty setting, in which resources are severely constrained, it may be necessary to substitute oral therapy for the preferred parenteral option.
†Assuming the organism is sensitive, children may be switched to oral amoxicillin (80 mg/kg/day ÷ q8h) to complete a 60-day course. We recommend that the 1st 14 days of therapy or postexposure prophylaxis, however, include ciprofloxacin and/or doxycycline regardless of age.
‡Levofloxacin or ofloxacin may be an acceptable alternative to ciprofloxacin.
§Rifampin or clarithromycin may be an acceptable alternative to clindamycin as a drug that targets bacterial protein synthesis. If ciprofloxacin or another quinolone is employed, doxycycline may be used as a second agent because it also targets protein synthesis.
‖Ampicillin, imipenem, meropenem, or chloramphenicol may be an acceptable alternative to penicillin as a drug with good central nervous system penetration.

Anthrax vaccine might similarly be employed in a postexposure setting. Some authorities recommend 3 doses of this vaccine as an adjunct to postexposure chemoprophylaxis after documented exposure to aerosolized anthrax spores. Nonetheless, postexposure administration of oral antibiotics constitutes the mainstay of management for asymptomatic victims believed to have been exposed to anthrax as well as to other bacterial agents such as plague and tularemia. Table 723-2 lists appropriate prophylactic regimens for various biologic exposures.

TREATMENT

Tables 723-2 and 723-3 provide recommended therapies for overt diseases caused by various chemical and biologic agents. It is likely that the clinician attending to victims will need to make therapeutic decisions before the results of confirmatory diagnostic tests are available and in situations in which the diagnosis is not known with certainty. In particular, decontamination by hospital personnel in appropriate personal protective equipment is required for patients exposed to chemical agents who have not been adequately decontaminated in the prehospital setting (see Table 723-3). In such cases, it is useful to note that many diseases and symptoms caused by chemical and biologic agents will resolve spontaneously, with only supportive care required. Most cases of chlorine or phosgene exposure can be successfully managed by providing meticulous attention to oxygenation and fluid balance. Mustard victims may require intensive multisystem support, but no specific antidote or therapy is available. Many viral diseases, such as smallpox, most viral hemorrhagic fevers, and the equine encephalitides, are also managed supportively.

In addition to ensuring adequate oxygenation, ventilation, and hydration, the clinician may need to provide specific empiric therapies on an urgent basis. Patients suffering from the sudden onset of severe neuromuscular symptoms may have nerve agent intoxication and should be given atropine (0.05 mg/kg) promptly for its antimuscarinic effects. Although atropine relieves bronchospasm and bradycardia, reduces bronchial secretions, and ameliorates the gastrointestinal effects of nausea, vomiting, and diarrhea, it does not improve skeletal muscle paralysis. Pralidoxime (also known as *2-PAM*) cleaves the organophosphate moiety from cholinesterase and regenerates intact enzyme if "aging" has not occurred. The effect is most prominent at the neuromuscular junction and leads to improved muscle strength. Its prompt use (at a dose of 25 mg/kg) as an adjunct to atropine is recommended in all serious cases.

Ideally, both atropine and pralidoxime should be administered intravenously in severe cases, although the intraosseous route may be acceptable. Some experts recommend that atropine be given intramuscularly in the presence of hypoxia to avoid arrhythmias associated with

Table 723-3 Critical Chemical Agents of Terrorism

AGENT	TOXICITY	CLINICAL FINDINGS	ONSET	DECONTAMINATION*	MANAGEMENT
NERVE AGENTS					
Tabun, sarin, soman, VX	Anticholinesterase: muscarinic, nicotinic, central nervous system effects	Vapor: miosis, rhinorrhea, dyspnea Liquid: diaphoresis, vomiting Both: coma, paralysis, seizures, apnea	Seconds: vapor Minutes to hours: liquid	Vapor: fresh air, remove clothes, wash hair Liquid: remove clothes, wash skin, hair with copious soap and water, ocular irrigation	ABCs. Atropine: 0.05 mg/kg IV†, IM‡ (min: 0.1 mg, max: 5 mg), repeat q2-5 min prn for marked secretions, bronchospasm Pralidoxime: 25 mg/kg IV, IM§ (max: 1 g IV; 2 g IM), may repeat within 30-60 min prn, then again q1h for 1 or 2 doses prn for persistent weakness, high atropine requirement Diazepam: 0.3 mg/kg (max: 10 mg) IV; lorazepam: 0.1 mg/kg IV, IM (max: 4 mg); midazolam: 0.2 mg/kg (max: 10 mg) IM prn for seizures or severe exposure
VESICANTS					
Mustard	Alkylation	Skin: erythema, vesicles Eye: inflammation Respiratory tract: inflammation	Hours	Skin: soap and water Eyes: water (effective only if done within minutes of exposure)	Symptomatic care
Lewisite	Arsenical		Immediate pain		Possibly British antilewisite (BAL) 3 mg/kg IM q4-6h for systemic effects of lewisite in severe cases
PULMONARY AGENTS					
Chlorine, phosgene	Liberate hydrochloric acid, alkylation	Eye, nose, and throat irritation (especially chlorine) Respiratory: bronchospasm, pulmonary edema (especially phosgene)	Minutes: eye, nose, and throat irritation, bronchospasm Hours: pulmonary edema	Fresh air Skin: water	Symptomatic care (see text)
CYANIDE					
	Cytochrome oxidase Inhibition: cellular anoxia, lactic acidosis	Tachypnea, coma, seizures, apnea	Seconds	Fresh air Skin: soap and water	ABCs, 100% oxygen Na bicarbonate prn metabolic acidosis; hydroxycobalamin 70 mg/kg IV (max: 5 g) *or* nitrite/thiosulfate, given as follows (see text): *Na nitrite (3%): dose (mL/kg) (max: 10 mL)* — *Estimated hemoglobin concentration (g/dL)* 0.27 — 10 0.33 — 12 (estimated for average child) 0.39 — 14 followed by Na thiosulfate (25%): 1.65 mL/kg (max: 50 mL)

*Decontamination, especially for patients with significant nerve agent or vesicant exposure, should be performed by healthcare providers garbed in adequate personal protective equipment. For emergency department staff, this equipment consists of a nonencapsulated, chemically resistant body suit, boots, and gloves with a full-face air-purifier mask/hood.

†Intraosseous route is likely equivalent to intravenous.

‡Atropine might have some benefit via endotracheal tube or inhalation, as might aerosolized ipratropium. See also Table 723-4.

§Pralidoxime is reconstituted to 50 mg/mL (1 g in 20 mL water) for IV administration, and the total dose infused over 30 min, or may be given by continuous infusion (loading dose 25 mg/kg over 30 min, and then 10 mg/kg/hr). For IM use, it might be diluted to a concentration of 300 mg/mL (1 g added to 3 mL water—by analogy to the U.S. Army's Mark 1 autoinjector concentration), to effect a reasonable volume for injection. See also Table 723-4.

ABCs, airway, breathing, and circulatory support; max, maximum; min, minimum; prn, as needed.

Adapted from Henretig FH, Cieslak TJ, Eitzen EM: Biological and chemical terrorism, J Pediatr *141:311–326, 2002.*

intravenous administration. Many emergency management services stock military-style autoinjector kits consisting of atropine and 2-PAM for intramuscular injection. Pediatric atropine autoinjectors are licensed, although kits intended for adults (with 2 mg of atropine and 600 mg of pralidoxime) might be used in children >2-3 yr (Table 723-4). Animal studies support the routine prophylactic administration of anticonvulsant doses of benzodiazepines, even in the absence of observable convulsive activity.

Delayed neuromuscular symptoms in the setting of terrorism might be due to botulism. Supportive care, with meticulous attention

Table 723-4 Pediatric Autoinjector Recommendations for Mass Casualties or Prehospital Care*

ATROPINE AUTOINJECTOR THERAPY			
APPROXIMATE AGE	**APPROXIMATE WEIGHT (kg)**	**AUTOINJECTOR SIZE (mg)**	
<6 mo	<7.5	0.25	
6 mo-4 yr	7.5-18	0.5	
5-10 yr	18-30	1.0	
>10 yr	>30	2.0	
PRALIDOXIME AUTOINJECTOR THERAPY			
APPROXIMATE AGE (yr)	**APPROXIMATE WEIGHT (kg)**	**NUMBER OF AUTOINJECTORS**	**PRALIDOXIME DOSE (mg/kg)**
3-7	13-25	1	24-46
8-14	26-50	2	24-46
>14	>50	3	<35

*Consider adult pralidoxime autoinjector use for severely affected mass casualties when IV access or more precise mg/kg IM dosing is logistically impractical. The initial dose using atropine autoinjectors is 1 autoinjector of each recommended size. The initial dose using pralidoxime autoinjectors is the recommended number of (adult-intended, 600 mg) autoinjectors. These latter may also be injected into an empty sterile vile; the contents redrawn through a filter needle into a small syringe may then provide a ready source of concentrated (300 mg/mL) pralidoxime solution for IM injection to infants. Autoinjectors may become available that provide adult doses of both atropine and pralidoxime in one injector; these could be used in children ≥3 yr in lieu of two individual injectors and dosed as noted above for pralidoxime alone.

to ventilatory support, is the mainstay of botulism treatment. Such support may be necessary for several mo, making the management of a large-scale botulism outbreak especially problematic in terms of medical resources. A licensed heptavalent antitoxin (types A-G) is available through the Centers for Disease Control (1-800-232-4636). Administration of this antitoxin is unlikely to reverse disease in symptomatic patients but may prevent further progression. In addition, a pentavalent (containing antibody against toxin types A to E; but licensed only for treatment of type A or B intoxication) product, Botulism Immune Globulin Intravenous (Human), BabyBIG, is available through the California Department of Health Services (1-916-327-1400) specifically for the treatment of infant botulism.

The **rapid onset of respiratory symptoms** may signal an exposure to chlorine, phosgene, cyanide, or a number of other toxic industrial chemicals. Although the mainstay of therapy in virtually all of these exposures consists of removal to fresh air and intensive supportive care, cyanide intoxication often requires the administration of specific antidotes.

The classic cyanide antidote utilizes a nitrite along with sodium thiosulfate and is given in 2 stages. The methemoglobin-forming agent (e.g., sodium nitrite) is administered first, because methemoglobin has a high affinity for cyanide and causes it to dissociate from cytochrome oxidase. Nitrite dosing in children should be based on body weight to avoid excessive methemoglobin formation and nitrite-induced hypotension. For the same reasons, nitrites should be infused slowly over 5-10 min. A sulfur donor, such as sodium thiosulfate, is given next. This compound is used as a substrate by the hepatic enzyme rhodanese, which converts cyanide to thiocyanate, a less toxic compound excreted in the urine. Thiosulfate treatment itself is efficacious and relatively benign and may be used alone for mild to moderate cases. Sodium nitrite and sodium thiosulfate are packaged together in standard antidote kits, along with amyl nitrite, a sodium nitrite substitute that can be inhaled in prehospital settings in which intravenous access is not available.

Another antidote available in the United States is hydroxocobalamin, which exchanges its hydroxy group for cyanide, forming harmless cyanocobalamin (vitamin B_{12}), which is subsequently excreted by the kidneys. Hydroxycobalamin use is not complicated by the potential for nitrite-induced hypotension or methemoglobinemia, and it has low toxicity. The recommended dose is 5 g in adults or 70 mg/kg in children, administered IV over 15 min. A second dose (2.5-5 g in adults; 35-70 mg/kg in children) may be repeated in severely affected patients. Side effects include modest hypertension and reddening of skin, mucous membranes, and urine that may last several days. Although no human controlled trials are currently available to compare hydroxocobalamin with nitrite/thiosulfate-based therapies, many authorities believe that hydroxocobalamin's efficacy and safety profile favor it as the cyanide antidote of choice, especially for children in the mass casualty context.

Animal research suggests a modest benefit of steroid therapy in mitigating lung injury after chlorine inhalation, and thus steroids may be considered for patients with chlorine exposure, especially as an adjunct to bronchodilators in those manifesting bronchospasm and/or a history of asthma. Further, symptomatic relief has also been reported following chlorine exposure with nebulized 3.75% sodium bicarbonate therapy, though the impact of this regimen on pulmonary damage is unknown. Animal models have also suggested a benefit from antiinflammatory agents, including ibuprofen and *N*-acetylcysteine, which appear to ameliorate phosgene-induced pulmonary edema, as well as the utilization of low tidal volume ventilation (protective ventilation), although the results of such interventions have not yet been reported in clinical trials.

In cases in which the **delayed onset of respiratory symptoms** may be the result of a terrorist attack, consideration should be given to the empirical administration of an antibiotic effective against anthrax, plague, and tularemia. Ciprofloxacin (10-15 mg/kg IV q12h), levofloxacin (8 mg/kg IV q12h), or doxycycline (2.2 mg/kg IV q12h) is a reasonable choice. Although naturally occurring strains of *B. anthracis* usually are quite sensitive to penicillin G, these agents are chosen because penicillin-resistant strains of *B. anthracis* exist. Moreover, ciprofloxacin and doxycycline are effective against almost all known strains of *Y. pestis* and *F. tularensis*. Concerns about inducible β-lactamases in *B. anthracis* have led some experts to recommend 1 or 2 additional antibiotics in patients with inhalational anthrax. Rifampin, vancomycin, penicillin or ampicillin, clindamycin, imipenem, and clarithromycin are reasonable choices based on in vitro sensitivity data. Because *B. anthracis* relies on the production of 2 protein toxins, edema toxin, and lethal toxin, for its virulence, drugs that act at the ribosome to disrupt protein synthesis (e.g., clindamycin, the macrolides) provide a theoretical advantage. Frequent meningeal involvement among inhalational anthrax victims makes agents with superior central nervous system penetration desirable. A combination of ciprofloxacin plus clindamycin plus penicillin G is a good initial empiric therapy for presumed inhalational anthrax. Ciprofloxacin, levofloxacin, or doxycycline monotherapy is probably adequate in cases of cutaneous anthrax, although patients with cutaneous disease resulting from a terrorist attack initially should receive multidrug therapy, because of the possibility of concomitant inhalational exposure.

Raxibacumab, a monoclonal antibody that inhibits anthrax antigen binding to cell receptors, thus preventing toxins from entering cells, is

approved for the treatment of inhalation anthrax in combination with antibodies. The adult dose is 40 mg/kg given IV over 2 hr and 15 min. The dose for children is weight based; ≤15 kg: 80 mg/kg; >15-50 kg: 60 mg/kg; >50 kg: 40 mg/kg. Premedication with diphenhydramine IV or PO is recommended 1 hr before the infusion.

In patients in whom a diagnosis of plague or tularemia is established, streptomycin (15 mg/kg IM q12h) has historically been considered the drug of choice. Because this drug is generally unavailable, many experts consider gentamicin (2.5 mg/kg IV/IM q8h) the preferred choice for therapy. In addition to ciprofloxacin, levofloxacin, or doxycycline, chloramphenicol (25 mg/kg IV q6h) should be employed in the 6% of pneumonic plague cases with concomitant meningitis. To be effective, therapy for pneumonic plague must be initiated within 24 hr of the onset of symptoms. There is little clinical experience with ricin-induced pulmonary injury. The mainstay of therapy is expected to be supportive care.

The management of **vesicant-induced injury** is similar to that for burn victims and is largely symptomatic (see Chapter 75). Mustard victims will benefit from the application of soothing skin lotions such as calamine and the administration of analgesics. Early intubation of severely exposed patients is warranted to guard against edematous airway compromise. Oxygen and mechanical ventilation may be needed, and meticulous attention to hydration is of paramount importance. Ongoing research suggests a role for oral *N*-acetylcysteine in mitigating chronic pulmonary effects due to mustard injury. Lewisite victims can be managed in much the same manner as mustard victims. In addition, dimercaprol (British antilewisite) in oil, given intramuscularly, may help ameliorate the systemic effects of lewisite.

The management of symptomatic smallpox victims also is largely supportive, with attention to pain control, hydration status, and respiratory sufficiency again of primary importance. The parenteral antiviral compound cidofovir, licensed for the treatment of cytomegalovirus retinitis in HIV-infected patients, has in vitro efficacy against variola and other orthopoxviruses. Its utility in treating smallpox victims is untested. Moreover, in the face of a large outbreak of disease, wide parenteral use of this drug would be problematic. ST-246, mentioned previously, demonstrates excellent in vitro activity against orthopoxviruses, but its utility in treating patients with smallpox is likewise untested.

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Chapter 724

Animal and Human Bites

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Many animals besides domestic and stray dogs and cats inflict bites on humans. The profile of such bites varies by country and region, based on living conditions, indigenous species, and opportunity for encounter.

EPIDEMIOLOGY

Worldwide there are tens of millions of **dog bites**, resulting in approximately 55,000 deaths from rabies (see Chapter 274). Dog bites represent approximately 80-90% of all bites in the United States; 5-15% are from cats, 2-5% from rodents, and the remainder from rabbits, ferrets, farm animals, monkeys, and reptiles. An estimated 4.5 million persons in the United States are bitten by dogs annually; approximately 885,000 of those bitten seek medical care. Bites from dogs are also most common in Bangladesh, India, Pakistan, and Myanmar, whereas in Nepal, cattle and buffalo account for more than half of bites, followed by dogs, pigs, and horses. Approximately 1% of dog bite wounds and 6% of cat bite wounds in the United States require hospitalization. During the past 3 decades, there have been approximately 20 deaths per year in the United States from dog-inflicted injuries; 65% of these occurred in children < age 11 yr. The breed of dog involved in attacks on children varies; Table 724-1 depicts the risk index of fatal dog bites by breed. Compared with other breeds, bites by pit bulls account for higher rates of hospital admission, higher Glasgow scores at admission, and an increased risk of death. Unaltered male dogs account for approximately 75% of attacks; nursing dams often inflict injury to humans when children attempt to handle their puppies.

The majority of dog attacks on children in the United States occur between the ages of 6 and 11 yr, with a slight predominance of males. Approximately 65% of the attacks occur around the home, 75% of the biting animals are known by the children, and almost 50% of the attacks are said to be unprovoked. Similar statistics apply in Canada, where 70% of all bites reported in 1 study were sustained by children between ages 2 and 14 yr; 65% of the dogs involved in the biting were part of the family or extended family, and the bite occurred in someone's home.

Of the approximately 450,000 reported **cat bites** per year occurring in the United States, nearly all are inflicted by known household animals. Because rodent bites (rat, mouse, gerbil) do not represent reportable conditions, little is known about the epidemiology of these injuries or the incidence of infection after rodent-inflicted bites or scratches.

Few data exist on the incidence and demographics of **human bite** injuries in pediatric patients; however, preschool and early school-age children appear to be at greatest risk of sustaining an injury from human bites, often in daycare or preschool settings. In some series, the proportion of human bites is highest among adolescents, an age group in which fist-to-tooth injuries (so-called fight bites) become more common.

CLINICAL MANIFESTATIONS

Dog bite–related injuries can be divided into 3 categories of almost equal incidence: abrasions, puncture wounds, and lacerations with or without an associated avulsion of tissue. Dog bites may also involve crush injury to tissues. In contrast, the most common type of injury from cat and rat bites is a puncture wound. Cat bites often penetrate to deep tissue. Human bite injuries are of 2 types: an occlusion injury that is incurred when the upper and lower teeth come together on a body part, or a clenched-fist injury that occurs when the injured fist, usually on the dominant hand, strikes the teeth of another individual.

DIAGNOSIS

Management of the bite victim should begin with a thorough history and physical examination. Careful attention should be paid to the circumstances surrounding the bite event (e.g., species and number of animals, type of animal [domestic or wild], whether the attack was provoked or unprovoked, location of the attack); a history of drug allergies; and the immunization status of the child (tetanus) and animal (rabies). During physical examination, meticulous attention should be paid to the type, size, and depth of the injury; the presence of any foreign material in the wound; the status of underlying structures; and, when the bite is on an extremity, the exact location of the injury, an assessment of possibly involved structures, and the range of motion of the affected area. A diagram of the injury should be recorded in the patient's medical record. Radiographs of the affected part should be considered if there is likelihood that a bone or joint was penetrated or fractured, or if foreign material is present. The possibility of a fracture or penetrating injury of the skull should particularly be considered in infants who have sustained dog bite injuries to the face or head.

COMPLICATIONS

Infection is the most common complication of bite injuries, regardless of the species of biting animal. The decision to obtain material for culture from a wound depends on the species of the biting animal, the

Table 724-1 Breed of Dog Associated with Involvement in Fatal Attacks, 2007 National Registration Data from the American Kennel Club, and Relative Risk of Fatal Attack

BREED*	NUMBER OF DOGS INVOLVED IN FATAL ATTACKS	NUMBER OF DOGS REGISTERED AKC	RELATIVE RISK OF FATAL ATTACK PER DOG‡
Pit Bull†	113	2239	2520
Neapolitan Mastiff	2	357	280
Chow Chow	2	1567	65
Rottweiler	18	14,211	65
Great Pyrenees	2	1916	50
Parson Russell Terrier	1	1096	45
Old English Sheepdog	1	1206	40
Siberian Husky	6	9048	35
Bullmastiff	1	3735	15
Doberman Pinscher	2	11,381	10
Australian Shepherd or Mix	1	6471	10
Mastiff Mix	1	7160	5
German Shepherd Dog	4	43,376	5
Boxer	1	33,548	1.5
Golden Retriever or Mix	1	39,659	1.5
Labrador Retriever or Mix	2	114,110	1
Total	**158**		

*Data presented only for dog breeds for which registration information is available from the American Kennel Club (AKC). The AKC does not register the Perro de Presa Canario, Wolf Hybrids, or dogs of unknown mixed breed.

†The term pit bull refers to dogs from the following breeds: American Pit Bull Terrier, American Staffordshire Terrier, and Staffordshire Bull Terrier.

‡Data for Labrador Retrievers and Labrador Mix are combined. Relative Risk is normalized to Labrador Retriever and Labrador Mix.

AKC, American Kennel Club.

From Bini JK, Cohn SM, Acosta SM, McFarland MJ, Muir MT, Michalek JE; TRISAT Clinical Trials Group. Mortality, mauling, and maiming by vicious dogs. Ann Surg *253(4):791–797, 2011, Table 2.*

length of time that has elapsed since the injury, the depth of the wound, the presence of foreign material contaminating the wound, and whether there is clinical evidence of infection. Although potentially pathogenic bacteria have been isolated from up to 80% of dog bite wounds that are brought to medical attention within 8 hr after the bite, the infection rate for wounds receiving medical attention in <8 hr is relatively low (2.5-20%). If the dog bite(s) is(are) not deep and/or extensive, wounds that are <8 hr old do not require cultures unless there are early signs of infection or the patient is immunocompromised. *Capnocytophaga canimorsus* is isolated from approximately 5% of infected wounds in immunocompromised patients and can cause serious systemic infection in these individuals. The infection rate in **cat bite** wounds, even those that receive prompt medical attention, is >50%; therefore, it is prudent to obtain material for culture from all but the most trivial cat-bite wounds. Cultures should be taken from **all** other animal bite wounds that are not brought to medical attention within 8 hr, regardless of species.

The rate of infection after **rodent bite** injuries is not known. Most of the oral flora of rats is similar to that of other mammals; however, approximately 50% and 25% of rats harbor strains of *Streptobacillus moniliformis* and *Spirillum minus,* respectively, both of which cause **rat bite fever** (see Chapter 724.1).

All human bite wounds, regardless of the mechanism of injury, should be regarded as carrying a high risk for infection and should be cultured. Because of the high incidence of anaerobic infection after bite wounds, it is important to obtain material for anaerobic as well as aerobic cultures.

Table 724-2 lists common causes of soft tissue bacterial infections after dog, cat, or human bites. Bites of humans or cats, those in which treatment is delayed, those in immunocompromised patients, and those associated with deep puncture wounds or significant crush injury carry higher risk for infection. An elevated risk for infection is also present if the bite is to certain anatomic regions (e.g., hand, foot, or genitals) or there is penetration of bone or tendons.

TREATMENT

Table 724-3 describes the prophylactic management of human or animal bite wounds to prevent infection.

After appropriate material has been obtained for culture, the wound should be anesthetized, cleaned, and vigorously irrigated with copious amounts of sterile saline. Irrigation with antibiotic-containing solutions provides no advantage over irrigation with saline alone and may cause local irritation of the tissues. Puncture wounds should be thoroughly cleansed and gently irrigated with a catheter or blunt-tipped needle; high-pressure irrigation should not be employed. Avulsed or devitalized tissue should be debrided and any fluctuant areas incised and drained.

Insufficient data exist to settle questions of whether bite wounds should undergo primary closure, delayed primary closure (3-5 days), or healing by secondary intention. Factors to be considered are the type, size, and depth of the wound; the anatomic location; the presence of infection; the time since the injury; and the potential for cosmetic disfigurement. Appropriate surgical consultation (e.g., general pediatric surgery; plastic, hand, or orthopedic surgery) should be obtained for all patients with deep or extensive wounds; wounds involving the hands, face, or bones and joints; and infected wounds that require open drainage. Although there is general agreement that **visibly infected wounds and those that are more than 24 hr old should not be sutured**, there is variation in practice regarding the efficacy and safety of closing wounds <8 hr old with no evidence of infection. Because all **hand wounds** are at high risk for infection, particularly if there has been disruption of the tendons or penetration of the bones, surgical

Table 724-2 Microorganisms Associated with Bites

DOG BITES *Staphylococcus* species *Streptococcus* species *Eikenella* species *Pasteurella* species *Proteus* species *Klebsiella* species *Haemophilus* species *Enterobacter* species *Capnocytophaga canimorsus* *Bacteroides* species *Moraxella* species *Corynebacterium* species *Neisseria* species *Fusobacterium* species *Prevotella* species *Porphyromonas* species	SWINE BITES *Pasteurella aerogenes* *Pasteurella multocida* *Bacteroides* species *Proteus* species *Actinobacillus suis* *Streptococcus* species *Flavobacterium* species *Mycoplasma* species RODENT BITES—RAT BITE FEVER *Streptobacillus moniliformis* *Spirillum minus*
CAT BITES *Pasteurella* species *Actinomyces* species *Propionibacterium* species *Bacteroides* species *Fusobacterium* species *Clostridium* species *Wolinella* species *Peptostreptococcus* species *Staphylococcus* species *Streptococcus* species	PRIMATE BITES *Bacteroides* species *Fusobacterium* species *Eikenella corrodens* *Streptococcus* species *Enterococcus* species *Staphylococcus* species *Enterobacteriaceae* Simian herpesvirus
HERBIVORE BITES *Actinobacillus lignieresii* *Actinobacillus suis* *Pasteurella multocida* *Pasteurella caballi* *Staphylococcus hyicus* subsp. *hyicus*	LARGE REPTILE (CROCODILE, ALLIGATOR) BITES *Aeromonas hydrophila* *Pseudomonas pseudomallei* *Pseudomonas aeruginosa* *Proteus* species *Enterococcus* species *Clostridium* species

Adapted from Perkins Garth A, Harris NS: Animal bites. Available at: http://emedicine.medscape.com/article/768875-overview. Reprinted with permission from eMedicine.com, 2009.

consultation is almost always indicated, and delayed primary closure is recommended for many bite wounds of the hands. **Facial lacerations** are at smaller risk for secondary infection because of the more luxuriant blood supply to this region. Given this fact and cosmetic considerations, many plastic surgeons advocate primary closure of facial bite wounds that have been brought to medical attention within 6 hr and after thorough irrigation and debridement.

Similarly, there are few studies addressing the efficacy and selection of antimicrobial agents for **prophylaxis** of bite injuries. The bacteriology of bite wound infections is primarily a reflection of the oral flora of the biting animal more than the skin flora of the victim (see Table 724-2). Because many of the aerobic and anaerobic bacterial species colonizing the oral cavity of the biting animal have the potential to invade local tissue, multiply, and cause tissue destruction, most bite wound infections are polymicrobial.

Despite the large degree of homology in the bacterial flora of the oral cavity among humans, dogs, and cats, important differences exist between the biting species, and they are reflected in the type of wound infections that occur. The predominant bacterial species isolated from infected dog bite wounds are *Staphylococcus aureus* (20-30%), *Pasteurella multocida* (20-30%), *Staphylococcus intermedius* (25%), and *C. canimorsus;* approximately one half of dog bite wound infections also contain mixed anaerobes. Similar species are isolated from infected cat bite wounds; however, *P. multocida* is the predominant species in at least 50% of cat bite wound infections. At least 50% of rats harbor strains of *S. moniliformis* in the oropharynx, and approximately 25% harbor *Spirillum minor,* an aerobic Gram-negative organism. In human bite wounds, nontypable strains of *Haemophilus influenzae, Eikenella corrodens, S. aureus,* α-hemolytic streptococci, and β-lactamase–producing aerobes (~50%) are the predominant species. Clenched-fist injuries are particularly prone to infection by *Eikenella* spp. (25%) and anaerobic bacteria (50%).

The choice between oral and parenteral antimicrobial agents should be based on the severity of the wound, the presence and degree of overt infection, signs of systemic toxicity, and the patient's immune status. Amoxicillin–clavulanate is an excellent choice for empirical oral

Table 724-3 Prophylactic Management of Human or Animal Bite Wounds to Prevent Infection

CATEGORY OF MANAGEMENT	MANAGEMENT
Cleansing	Remove visible dirt. Cleanse the wound surface with soap and water, saline, 1% povidone–iodine, or 1% benzalkonium chloride. Irrigate with a copious volume of sterile saline solution by high-pressure syringe irrigation.* Do not irrigate puncture wounds; Standard Precautions should be used.
Wound culture	No, for fresh wounds, unless signs of infection exist. Yes for wounds that appear infected.†
Diagnostic Imaging	Indicated for penetrating injuries overlying bones or joints, for suspected fracture, or to assess foreign body inoculation.
Debridement	Remove superficial devitalized tissue.
Operative debridement and exploration	Yes if any of the following: • Extensive wounds (devitalized tissue) • Involvement of the metacarpophalangeal joint (clenched-fist injury) • Cranial bites by large animal
Wound closure	Yes for selected fresh, nonpuncture bite wounds.
Assess tetanus immunization status	Yes.
Assess risk of rabies from animal bites	Yes.
Assess risk of hepatitis B virus infection from human bites	Yes.
Assess risk of human immunodeficiency virus from human bites	Yes.
Initiate antimicrobial therapy	Yes for: • Moderate or severe bite wounds, especially if edema or crush injury is present • Puncture wounds, especially if penetration of bone, tendon sheath, or joint has occurred • Face, hand, foot, and genital bites • Wounds in immunocompromised and asplenic persons • Wounds with signs of infection
Follow-up	Inspect wound for signs of infection within 48 hr

*Use of an 18-gauge needle with a large-volume syringe is effective. Antimicrobial or antiinfective solutions offer no advantage and may increase tissue irritation.

†Both aerobic and anaerobic bacterial culture should be performed.

From American Academy of Pediatrics: Red Book: 2012 report of the Committee on Infectious Diseases, *ed 29, Elk Grove Village, IL, 2012, American Academy of Pediatrics, Table 2-18.*

therapy for human and animal bite wounds, because of its activity against most bacteria that have been isolated from infected bites. Similarly, ticarcillin–clavulanate or ampicillin–sulbactam is preferred for patients who require empirical parenteral therapy. Penicillin G remains the drug of choice for prophylaxis and treatment of rat-inflicted injuries, as this agent has excellent activity against *S. moniliformis* and *S. minor*. Because 1st-generation cephalosporins have limited activity against *P. multocida* and *E. corrodens*, they should not be used for prophylaxis or empirical initial therapy of bite wound infections. Therapeutic alternatives for penicillin-allergic patients are limited, because the traditional alternative agents are generally inactive against 1 or more of the multiple pathogens that cause bite wound infections. Clindamycin plus trimethoprim–sulfamethoxazole is the most commonly suggested regimen for these patients. Tetracycline is the drug of choice for penicillin-allergic patients who have sustained rat bite injuries.

Although **tetanus** occurs only rarely after human or animal bite injuries, it is important to obtain a careful immunization history and to provide tetanus toxoid to all patients who are incompletely immunized or in whom it has been longer than 5 yr since the last tetanus immunization. The need for postexposure **rabies** vaccination in victims of dog and cat bites depends on whether the biting animal is known to have been vaccinated and, most importantly, on local experience with rabid animals in the community. Bites from bats, foxes, skunks, and raccoons should be considered to carry a high risk of rabies, and postexposure prophylaxis is indicated. For dogs, cats, and other animals that are known or can be captured, observation for 7-10 days by the local animal control department is indicated. If a biting dog or cat has escaped, a decision about rabies prophylaxis can be based on the circumstances surrounding the bite and advice from local infectious diseases specialists and/or health department officials. Annually worldwide, animal bites and contacts result in more than 10 million postexposure courses. Postexposure prophylaxis for hepatitis B should be considered in the rare instance in which a susceptible individual has sustained a human bite from an individual who is at high risk for hepatitis B.

Table 724-4 Measures for Preventing Dog Bites

- Realistically evaluate environment and lifestyle and consult with a professional (e.g., veterinarian, animal behaviorist, or responsible breeder) to determine suitable breeds of dogs for consideration.
- Dogs with histories of aggression are inappropriate in households with children.
- Be sensitive to cues that a child is fearful or apprehensive about a dog and, if so, delay acquiring a dog.
- Spend time with a dog before buying or adopting it. Use caution when bringing a dog or puppy into the home of an infant or toddler.
- Spay/neuter virtually all dogs (this frequently reduces aggressive tendencies).
- Never leave infants or young children alone with any dog.
- Properly socialize and train any dog entering the household. Teach the dog submissive behaviors (e.g., rolling over to expose abdomen and relinquishing food without growling).
- Immediately seek professional advice (e.g., from veterinarians, animal behaviorists, or responsible breeders) if the dog develops aggressive or undesirable behaviors.
- Do not play aggressive games with your dog (e.g., wrestling).
- Teach children basic safety around dogs and review regularly:
  - Never approach an unfamiliar dog.
  - Never run from a dog and scream.
  - Remain motionless when approached by an unfamiliar dog (e.g., "be still like a tree").
  - If knocked over by a dog, roll into a ball and lie still (e.g., "be still like a log").
  - Never play with a dog unless supervised by an adult.
  - Immediately report stray dogs or dogs displaying unusual behavior to an adult.
  - Avoid direct eye contact with a dog.
  - Do not disturb a dog who is sleeping, eating, or caring for puppies.
  - Do not pet a dog without allowing it to see and sniff you first.
  - If bitten, immediately report the bite to an adult.

From Centers for Disease Control and Prevention: Dog bite-related fatalities—United States, 1995-1996, MMWR Morb Mortal Wkly Rep *46:463–467, 1997.*

PREVENTION

It is possible to reduce the risk of animal bite injury with anticipatory guidance (Table 724-4). Parents should be routinely counseled during prenatal visits and routine health maintenance examinations about the risks of having potentially biting pets in the household. All patients should be cautioned against harboring exotic animals for pets. Additionally, parents should be made aware of the proclivity of certain breeds of dogs to inflict serious injuries and the protective instincts of nursing dams. All young children should be closely supervised, particularly when in the presence of animals, and from a very early age should be taught to respect animals and to be aware of their potential to inflict injury. Reduction of the rate of human bite injuries, particularly in daycare centers and schools, can be achieved by good surveillance of the children and adequate teacher : child ratios.

Bibliography is available at Expert Consult.

724.1 Rat Bite Fever

Charles M. Ginsburg and David A. Hunstad

ETIOLOGY

Rat bite fever is a generic term that has been applied to at least 2 distinct clinical syndromes, each caused by a different microbial agent. Rat bite fever caused by *S. moniliformis* is most commonly reported in the United States, as well as in Brazil, Canada, Mexico, Paraguay, Great Britain, and France; it has been identified elsewhere in Europe and in Australia. *S. moniliformis* is a Gram-negative bacillus that is present in the nasopharyngeal flora of many laboratory and wild rats. Infection with *S. moniliformis* most commonly occurs following the bite of a rat; however, infection has also been reported in individuals who have been scratched by rats, in those who have handled dead rats, and in those who have ingested milk contaminated with the bacterium (termed **Haverhill fever**). Rat bite fever may also be transmitted by bites from wild mice. Rat bite fever caused by *S. minus,* called **sodoku,** is most commonly reported in Asia. *S. minus* is a small, spiral, aerobic Gram-negative organism. Reports of rat bite fever from Africa are rare, suggesting underrecognition rather than absence of the disease.

CLINICAL COURSE

The incubation period for the streptobacillary form of rat bite fever is variable, ranging from 3-10 days. The illness is characterized by an abrupt onset of fever up to 41°C (105.8°F) (fever occurring in more than 90% of reported cases), severe throbbing headache, intense myalgia, chills, and vomiting. In virtually all instances, the lesion at the cutaneous inoculation site has healed by the time the systemic systems first appear. Shortly after the onset of the fever, a polymorphous rash occurs in up to 75% of patients. In most patients, the rash consists of blotchy, red maculopapular lesions that often have a petechial component; the distribution of the rash is variable but is typically most dense on the extremities. Hemorrhagic vesicles may develop on the hands and feet and are very tender to palpation (Fig. 724-1).

Approximately 50% of patients have arthritis, which first manifests toward the end of the 1st wk of disease; early on, the arthritis may be migratory. If untreated, fever, rash, and arthritis last from 14-21 days, often with a biphasic pattern to the fever and arthritis. A wide range of complications are reported in patients with rat bite fever, the most common being pneumonia, persistent arthritis, brain and soft tissue abscesses, and, less commonly, myocarditis or endocarditis. The mortality rate of untreated rat bite fever is estimated to be approximately 13%.

The incubation period of sodoku is longer (14-21 days) than that of the streptobacillary form of disease. The hallmark of *Spirillum*-induced

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Figure 724-1 Hemorrhagic vesicles on the 1st and 3rd toes of a patient with advanced rat bite fever. *(From Elliott SP: Rat bite fever and* Streptobacillus moniliformis. Clin Microbiol Rev *20:13–22, 2007, Fig. 3.)*

disease is fever associated with an indurated, often suppurative, nonhealing lesion at the bite site. Lymphadenitis and lymphadenopathy invariably are present in the regional nodes that drain the inoculation site, and many patients have a generalized macular rash most prominent when fever is present. In untreated patients, sodoku has a relapsing and remitting course; symptoms abate after 5-7 days of chills and fever but recur 7-10 days later. There may be multiple cycles if the disease is not recognized and treated.

DIAGNOSIS

Diagnosis of the streptobacillary form of rat bite fever is difficult, because the disease is uncommon and can be confused with Rocky Mountain spotted fever or (less commonly) meningococcemia. Furthermore, *S. moniliformis* is difficult both to isolate and to identify with classic bacteriologic techniques. The organism is fastidious, requires enriched media for growth, and is inhibited by sodium polyanethol sulfonate, an additive present in many commercial blood culture bottles. A definitive diagnosis is made when the organism is recovered from blood or joint fluid or is identified in human samples with molecular technology such as polymerase chain reaction analysis, which has been used successfully in humans and laboratory animals.

Diagnosis of sodoku is made on clinical grounds, because there are no diagnostic serologic tests and *S. minus* has not been cultured on artificial media. Rarely, the organism may be identified in Gram-stained smears of pus from the inoculation site.

TREATMENT

Penicillin is the drug of choice for both forms of rat bite fever. Intravenous penicillin G or intramuscular penicillin G procaine is recommended for 7-10 days; a regimen of IV penicillin G for 5-7 days followed by oral penicillin V for an additional 7 days has also been used. Doxycycline, gentamicin, or streptomycin represent effective alternatives for penicillin-allergic patients. Patients with endocarditis caused by *S. moniliformis* require high-dose penicillin G for 4 wk; the addition of streptomycin or gentamicin might be helpful.

Bibliography is available at Expert Consult.

724.2 Monkeypox

Charles M. Ginsburg and David A. Hunstad

ETIOLOGY

Monkeypox virus, causing the disease monkeypox, is the most important member for humans of the genus *Orthopoxvirus* since the eradication of smallpox (variola). Monkeys are the predominant host for the virus; however, it may be endemic in African rainforest squirrels and is present in African rats, mice, domestic pigs, hedgehogs, and opossums. It also has been identified in and transmitted by prairie dogs in the United States, and has affected elephants in zoos. Severity of infection varies by viral strain and by host; for example, disease is relatively mild in cynomolgus monkeys but severe in orangutans.

Monkeypox virus was first observed in humans from West and Central Africa in the 1970s at the time that smallpox had been eradicated from the area. In the 1970s, the secondary attack rate was around 3% (a stark comparison to the 80% seen in unvaccinated smallpox contacts). Few cases were observed over the next 2 decades; however, during a subsequent outbreak in the 1990s when immunity to smallpox was no longer prevalent in the population, the secondary attack rate exceeded 75%. Monkeypox outbreaks have also been reported in the Sudan. Monkeypox was inadvertently introduced into the United States in 2003, presumably through rodents from Ghana that infected prairie dogs who were distributed as pets; this outbreak affected more than 70 persons. Primary transmission of the disease from infected animal to human is by bite or by human contact with an infected animal's blood, wound discharge, or other body fluids. Human-to-human transmission of infection is uncommon but is believed to have been an important source for transmission of new cases during the United States outbreak.

CLINICAL COURSE

The clinical signs, symptoms, and course of monkeypox are similar to those of smallpox, although typically milder. After a 10-14 day incubation period during which the virus replicates in lymphoid tissues, humans experience an abrupt onset of malaise, fever, myalgia, headache, and severe backache. Nonproductive cough, nausea, vomiting, and abdominal pain may be present. Generalized lymphadenopathy, a finding unusual in smallpox, is invariably present during the acute stages of monkeypox illness. After a 2-4 day prodrome, an exanthem appears in cephalad-to-caudal progression. As the rash progresses, fevers begin to abate. The rash is initially macular, but transforms within hours to firm papules that rapidly vesiculate and become pustular over 2-3 days. Unlike smallpox lesions, but similar to chickenpox lesions, the lesions of monkeypox tend to occur in crops (Fig. 724-2). Late into the 2nd wk of illness, the lesions begin to desiccate, crust, scab, and fall off.

Monkeypox should be suspected in any child who has the characteristic prodrome associated with an atypical form of chickenpox and a history of contact with prairie dogs or exotic mammals such as Gambian rats and rope squirrels. Diagnosis is by isolation of monkeypox virus in culture, demonstration by polymerase chain reaction of viral DNA in a clinical specimen, or microscopic demonstration of an orthopoxvirus in a clinical specimen in the absence of other orthopoxvirus exposure.

TREATMENT

There is no proven effective therapy for monkeypox. Despite evidence that preexposure administration of smallpox vaccine is 85% effective in preventing or attenuating monkeypox disease, the rarity of monkeypox infection does not warrant universal vaccination. In instances of known exposure or in outbreak situations, there may be an indication

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Figure 724-2 **A,** Legs and feet of monkeypox patient. **B,** Legs and feet of smallpox patient at similar stage of rash (pustular). *(**A** courtesy of Joseph M. Harvey, MD; **B** courtesy of J. Nobel, Jr, MD, Centers for Disease Control and Prevention.)*

for administering smallpox vaccine. Consideration should be given to vaccinating close family contacts and health care workers who provide care to infected individuals. Vaccine is said to be preventive if given within 2 wk of exposure. Individuals with a compromised immune system and those with life-threatening allergies to latex or to smallpox vaccine or any of its components (polymyxin B, streptomycin, tetracycline, neomycin) also should not receive smallpox vaccine.

Although there are data indicating that cidofovir has in vitro activity against monkeypox virus and has been effective in preventing monkeypox infection in animals, there are no data to support its effectiveness in humans. Careful attention should be paid to skin hygiene, maintenance of adequate nutrition and hydration, and prompt implementation of local or systemic therapy of secondary bacterial infection that may occur. For prevention of human-to-human spread of disease, a combination of contact, droplet, and airborne infection control procedures should be implemented.

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Chapter 725

Envenomations

Bill J. Schroeder and Robert L. Norris

Being bitten or stung by a venomous animal or insect is frightening for an adult, a child, or a child's parent or care provider. Although most bites and stings by spiders, snakes, scorpions, and other venomous animals cause little more than local pain and do not require medical attention, there are thousands of species of potentially harmful or deadly venomous creatures worldwide. Each country/region has its own array of medically important organisms.

The terms *venomous* and *poisonous* are not synonymous. *Venom* is produced in specialized glands of the host and is usually injected by means of a bite or sting. *Poisonous* refers to detrimental effects from consuming or touching a plant, animal, or insect. Poison is generally found throughout the animal and venom is isolated to the specialized glands.

Not every bite from a venomous creature is harmful. In many cases no venom is injected, so-called dry bites. A dry bite may occur for many reasons, including failure of the venom delivery mechanism and depletion of venom. Up to 20% of pit viper, 80% of coral snake, and approximately 50% of all venomous snake bites are dry.

In the 2011 report of the American Association of Poison Control Centers, more than 60,000 consultations were related to bites and stings of various creatures, with approximately one third involving victims < age 19 yr. There were 2 deaths, both from snake bites in adult males, 1 from the genera *Crotalus* (rattlesnake) and 1 from the genera *Agkistrodon* (copperhead or cottonmouth).

GENERAL APPROACH TO THE ENVENOMATED CHILD

Children may be bitten or stung as they play and explore their environment. The evaluation may be hampered by an unclear history of the circumstances and the possible offending organism, particularly with preverbal children. The overall effects of some venomous bites and stings may be relatively more severe in children than in adults, because children generally receive a similar venom load from the offending animal yet have less circulating blood volume to dilute its effects.

General Management

When faced with an envenomated child, the treating physician should anticipate a dynamic clinical syndrome that may progress with time, with important, potentially subtle, findings. Treatment of an envenomated child should start with assessing and managing as necessary the airway, breathing, and circulation (ABCs). Most envenomations require little more than local wound care, pain control, reassurance, and possibly observation. The severely envenomated child may need airway and respiratory protection and support (e.g., high-concentration oxygen administration and endotracheal intubation) and adequate IV access in an unaffected extremity if possible (see Chapters 70 and 71). Early hypotension tends to be related to vasodilation and should be treated with volume expansion using appropriate infusion of physiologic saline solutions (normal saline boluses of 20 mL/kg body weight; repeated as needed up to 3 times). Shock unresponsive to volume repletion may require addition of a vasoactive pharmacologic agent such as epinephrine or dopamine (in addition to antivenom administration as appropriate). If the presentation is suspicious for an anaphylactic reaction to venom, appropriate treatment (including epinephrine) should be initiated as soon as possible (see Chapter 149). Occasionally,

it is difficult to determine the precise etiology for sudden collapse after a venomous bite or sting–venom toxicity vs anaphylaxis. In such cases, treatment for both should be started.

The affected body part should be immobilized in a position of function and any areas of edema should be marked, measured, and monitored. If antivenom (AV) is available for the envenomation, efforts should be initiated to locate and secure an adequate amount to treat the patient (at least a starting dose). In the United States, regional poison control centers can facilitate this effort and are especially helpful if the offending species is exotic. Guidance in dosing the appropriate AV can generally be found in the package insert that accompanies the agent, although the advice in inserts for some products from developing countries may contain inaccurate and incorrect recommendations. Physicians who do not regularly treat venomous bites and stings should consult local or regional experts for assistance.

Antivenom Administration

Specific AVs are available for many venomous creatures of the world, particularly snakes, spiders, and scorpions. These products essentially impart passive immunity to the victim and should be given in cases of significant envenomation as early in the process as possible, because AV is capable of neutralizing only circulating, unbound venom components in the blood.

AVs may be either in liquid form or lyophilized (requiring reconstitution prior to administration). Most AVs are given intravenously. *There is no benefit to giving any AV locally at the bite site*. As soon as the need for AV is established, it should be placed into solution (generally diluted in a quantity of normal saline equivalent to 20 mL/kg body weight, up to 250-1,000 mL total).

As heterologous serum products, AVs carry some variable risk of inducing nonallergic or allergic anaphylactic reactions. Therefore, the patient should be closely monitored, and a physician should be present during the infusion, with access to all the appropriate equipment and medications needed to reverse such a reaction. Skin tests, often recommended by AV manufacturers, are unreliable and should be omitted.

Intravenous AV should be started slowly, and the rate gradually increased as tolerated by the patient, with a goal to administer the entire dose in approximately 1 hr.

If the victim experiences a reaction to the product, it should be temporarily stopped. Intramuscular epinephrine and intravenous antihistamines and steroids should be given. Then the AV should be restarted, possibly at a slower rate and in a more dilute solution. If the reaction is severe, the decision must be made as to whether the benefits of AV outweigh the risks of anaphylaxis on the basis of the patient's clinical condition. If AV is deemed critical for the patient's survival despite the occurrence of anaphylaxis, the patient should be placed in an intensive care setting with close, possibly invasive, monitoring, and should receive simultaneous administration of AV and an epinephrine infusion.

AV can also cause delayed immunoglobulin G and M–mediated serum sickness in some patients (see Chapter 150). Serum sickness occurs 1-2 wk after AV administration, manifesting as fever, myalgias, arthralgias, urticaria, and potential renal and neurologic involvement. It is easily treated with oral steroids, antihistamines, and acetaminophen.

General Wound Care

Bites and stings require basic wound care, including copious tap water or normal saline irrigation under pressure when possible. For small puncture wounds this is impractical, but the skin should still be cleaned with soap and water. Tetanus immunization should be updated as needed. Intact blisters should be left to act as natural bandages and help prevent infection, whereas broken blisters should be debrided. Exposed tissue should be covered with wet to dry dressings. Necrotic wounds, such as those that might follow some snake and spider bites, should be judiciously debrided, with removal of only clearly necrotic tissue. Reconstructive surgery with skin grafts or muscle/tendon grafts may be necessary. Prophylactic antibiotics are not necessary except, perhaps, in cases in which an ill-informed "rescuer" cut into the bite and applied mouth suction. Antibiotics should generally be reserved for signs of established secondary infection.

SNAKE BITES

Most snake bites are inflicted by nonvenomous species and are of no more consequence than a potentially contaminated puncture wound (Fig. 725-1). Venomous snakes, however, kill many tens of thousands of people in the world each year. The precise number is difficult to ascertain, because the toll in human suffering is far greatest in developing nations. Developed nations, with established medical care systems, have relatively few fatalities each year.

Most of the world's medically significant venomous snakes belong to 1 of 2 families—Viperidae and Elapidae (Table 725-1). In developing nations, most snake envenomations occur in agricultural workers who inadvertently contact snakes while in the fields. Many victims of snake envenomation in developed nations are adolescent or young adult males, frequently intoxicated, who are attempting to handle or catch the snake. Bites are located on an extremity in more than 95% of cases. In the United States, approximately 98% of venomous snake bites are inflicted by pit vipers (family Viperidae; subfamily *Crotalinae*). A small fraction of bites are caused by coral snakes (family Elapidae) in the South and Southwest, and by exotic snakes that have been imported.

Venoms and Effects

Snake venoms are complex mixtures of proteins including large enzymes that cause local tissue destruction and low-molecular-weight polypeptides that have the more lethal systemic effects. The symptoms and severity of an envenomation vary according to the type of snake, the amount of venom injected, and the location of the bite. The fear caused by a snake bite can result in nausea, vomiting, diarrhea, cold/clammy skin, and even syncope regardless of whether or not venom was injected. In general, viper venoms can have deleterious effects on almost any organ system. Most viper bites cause significant local pain, swelling, and ecchymosis and may result in variable necrosis of the bitten extremity (Fig. 725-2). The pain and swelling typically begin quickly after the bite and progress over hours to days. Serious envenomations may result in a consumptive coagulopathy, hypotension, and respiratory distress. In contrast, venoms from the **Elapidae** tend to be more neurotoxic with little or no local tissue damage. These bites cause variable local pain and the onset of systemic effects can be delayed for hours. Manifestations of neurotoxicity generally are caused by curare-like blockade at the neuromuscular junction. Symptoms usually begin with cranial nerve palsies such as ptosis, dysarthria, and dysphagia and may progress to respiratory failure and complete paralysis. There are exceptions; some members of the Elapidae family cause little or no neurotoxicity but rather severe tissue necrosis (e.g., African spitting cobras). Some vipers, including the southern Pacific rattlesnake *(Crotalus oreganus helleri)*, western diamondback rattlesnake *(Crotalus atrox)*, timber rattlesnake *(Crotalus horridus horridus)*, and some populations of the Mohave rattlesnake *(Crotalus scutulatus)*, cause significant neurotoxicity. Physicians should proactively learn the important species in their regions, including how the species can be identified, the expected effects of their venoms, and proper approaches to management.

Management

Prehospital care should focus on rapid transport to the emergency department while supporting the victim's vital signs as needed. Constrictive clothing, jewelry, and watches should be removed, and the injured body part should be immobilized in a position of function at the level of the heart. *All proposed field treatments for snake bites, such as tourniquets, ice, electric shock, incision, and suction, have proven problematic, with most being ineffective and deleterious.*

At the hospital, attention is directed to the ABCs and supportive care as needed. An effort should be made to identify the offending snake and then to secure the appropriate AV. Intravenous access should be established in an unaffected extremity, and standard laboratory specimens should be obtained, including those for a complete blood count, coagulation studies, fibrinogen concentration, and serum chemistry

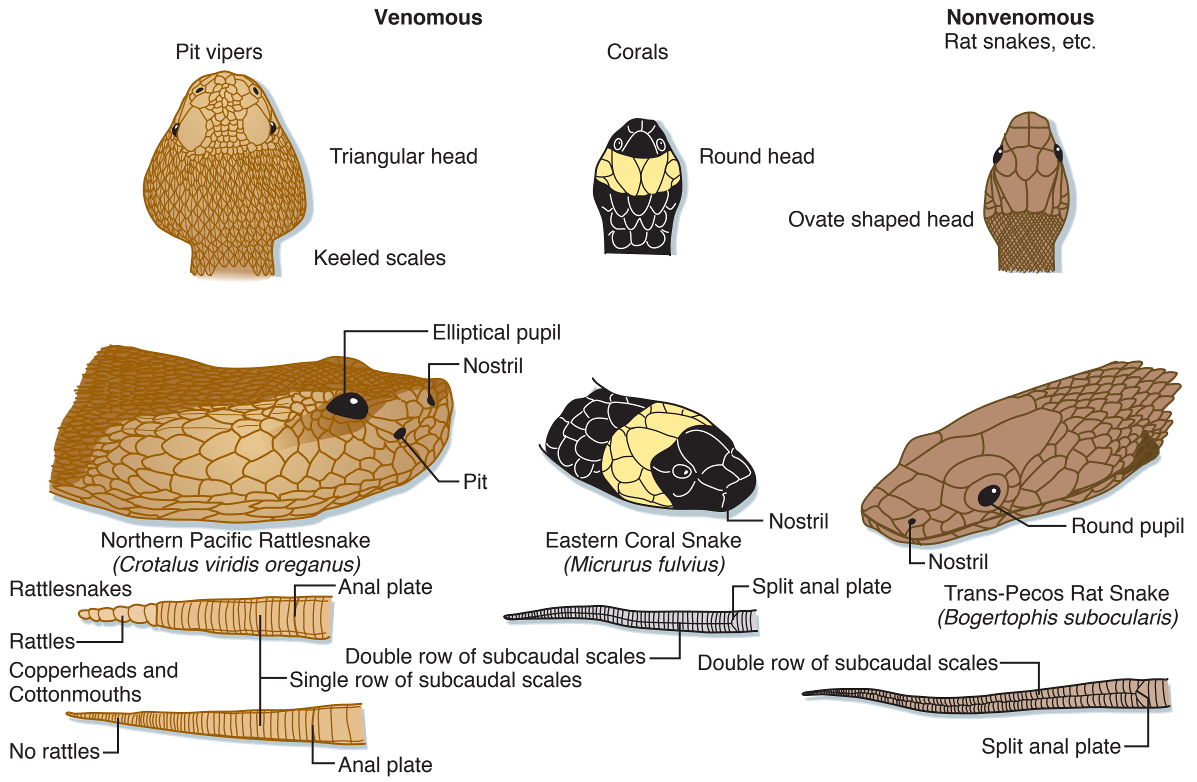

Figure 725-1 **Anatomic comparison of pit vipers, coral snakes, and nonvenomous snakes of the United States.** (Note: the northern Pacific rattlesnake is now classified as *Crotalus oreganus oreganus*.) *(Modified from Adams JG, et al, editors:* Emergency medicine, *Philadelphia, 2008, WB Saunders. Drawing by Marlin Sawyer.)*

Table 725-1 Medically Important Snake Families

FAMILY	VENOMOUS?	LOCATION	EXAMPLES	TOXIN EFFECTS/OTHER COMMENTS
Colubridae	Some species	Most parts of the world	Garter snakes (*Thamnophis* spp.), king snakes and milk snakes (*Lampropeltis* spp.)	Largest family of snakes; most are considered harmless to humans; a few species are dangerously toxic (e.g., African boomslang *[Dispholidus typus]*)
Boidae	None	Most parts of the world	*Boa* species, *Python* species	Constrictors; unsupervised children should not be allowed access to large constrictors
Viperidae				
Subfamily *Crotalinae* (pit vipers)	All	Americas, Asia	Rattlesnakes (*Crotalus* and *Sistrurus* spp.), cottonmouths and copperheads (*Agkistrodon* spp.), Lancehead pit vipers (*Bothrops* spp.)	Heat-sensing "pit" between each eye and nostril
Subfamily *Viperinae* (true vipers)	All	Europe, Africa, Middle East, Asia	Puff adder *(Bitis arietans)*, Gaboon viper *(Bitis gabonica)*	No heat-sensing pits
Elapidae	All	Americas, Africa, Middle East, Asia	Cobras (*Naja* spp.), mambas (*Dendroaspis* spp.), kraits (*Bungarus* spp.), coral snakes (*Micrurus* spp.), and the venomous snakes of Australia	Highly variable venom effects—some largely neurotoxic, others causing severe local tissue damage
Hydrophiidae	All	Warm waters of the Pacific Ocean, Indian Ocean, and Oceana (none in the Atlantic Ocean)	Sea snakes including the pelagic sea snake *(Pelamis platurus)*	Neurotoxins and myotoxins; rarely bite humans unless provoked

analysis including total creatine kinase. A blood sample should be sent for typing and screening, although blood products are rarely actually required in management of snake bite. Samples collected later in the clinical course may be hard to cross match because venom and AV can interfere with the testing. Tourniquets placed in the field by laypeople should be cautiously removed after venous access is obtained, to watch for and treat adverse effects that may follow a sudden bolus of acidotic, hyperkalemic blood mixed with venom into the systemic circulation. The bitten extremity should be marked at 2 or more sites proximal to the bite, and the circumferences at these locations should be assessed every 15 min to monitor for progressive edema—indicative of ongoing venom effects. Occasionally, the sharp, recurved teeth of snakes, including nonvenomous snakes, are left behind in wounds; they should be identified (using soft tissue radiographs or ultrasound as needed) and removed.

Assessing the severity of the envenomation in the field and at the hospital is essential (Table 725-2).

AVs are relatively specific for the snake species against which they are designed to protect. *There is no benefit to administering an AV for an unrelated species*, and doing so certainly involves unacceptable risk (e.g., anaphylaxis) and expense. If it is determined that the child requires AV, a search for the appropriate product should begin as soon as possible—checking the hospital pharmacy, regional poison control center, and perhaps local zoos and museums that keep captive snakes. Table 725-3 lists the indications for administering AV.

Figure 725-2 **Southern Pacific rattlesnake bite *(Crotalus oreganus helleri)* in a 2 yr old boy.** Note the fang marks, swelling, and bruising of the tissues (photograph taken 2 hr following the bite). *(Courtesy of Sean Bush, MD.)*

In October 2000, Crotalidae polyvalent immune Fab known as CroFab was approved by the FDA for use in crotaline envenomations. CroFab is derived from sheep (ovine) antibodies and replaces the previously used AV derived from horses (equine-derived AV). The most important advantage of this AV is fewer hypersensitivity reactions, including both immediate and delayed reactions. A metaanalysis showed only 8% immediate hypersensitivity reactions and 13% delayed or serum sickness reactions after administration of CroFab, compared to an estimated 23-56% from the previous equine-derived AV.

CroFab is derived from 4 snakes, 3 from the genera *Crotalus* (the eastern diamondback rattlesnake, the western diamondback rattlesnake, and the Mohave rattlesnake) and 1 from the genera *Agkistrodon* (the cottonmouth water moccasin). It is effective against the venoms of all pit vipers in the United States. There is controversy regarding the use of CroFab in bites from copperheads (*Agkistrodon contortrix*) because they tend to cause fewer systemic effects. Most copperhead envenomations cause only local tissue swelling, ecchymosis, and pain, and generally do well even without AV. Serious envenomations, including fatalities, have followed copperhead bites, and any child with evidence of systemic toxicity should receive CroFab.

The half-life of CroFab is considerably shorter than that of crotaline venom constituents, and redosing is frequently needed to prevent or treat recurrence of venom effects. Patients with significant envenomation should be followed for late hematologic abnormalities (coagulopathy) that can occur up to 2 weeks after the bite. Although these

Table 725-3 Indications for Snake Antivenom Administration

Evidence of systemic toxicity:	
Hemodynamic or respiratory instability	Hypotension, respiratory distress
Hemotoxicity	Clinically significant bleeding or abnormal coagulation studies
Neurotoxicity	Any evidence of toxicity: usually beginning with cranial nerve abnormalities and progressing to descending paralysis including the diaphragm
Evidence of worsening local toxicity	*Progressive* soft tissue swelling

Table 725-2 Crotaline Envenomation: Determining the Degree of Envenomation

DEGREE OF ENVENOMATION	CONTIGUOUS MANIFESTATIONS	SYSTEMIC MANIFESTATIONS	LABORATORY ABNORMALITIES
None or trivial ("dry bite")	Punctures or abrasions; pain and tenderness at bite	None	None
Mild or minimal	Punctures or abrasions; pain, tenderness, edema, and erythema at and adjacent to bite	None	None
Moderate	Punctures or abrasions; pain, tenderness, edema, and erythema beyond area adjacent to bite	Perioral paresthesias; peripheral paresthesias; gustatory changes; nausea; emesis; diarrhea; weakness; light-headedness; diaphoresis; chills	↑PT; ↑PTT; ↓platelets; ↓fibrinogen; ↑hemoglobin
Severe	Punctures or abrasions; pain, tenderness, edema, and erythema of entire extremity	Ventilatory insufficiency; hypotension; shock; bleeding; altered mental status; fasciculations; seizures	↑↑PT; ↑↑PTT; ↓↓platelets; ↓↓fibrinogen; ↑↓hemoglobin

↑, increased; ↑↑, very increased; ↑↓, increased or decreased; ↓, decreased; ↓↓, very decreased; PT, prothrombin time; PTT, partial thromboplastin time.

From Walter FG, Chase PB, Fernández MC, McNally J: Venomous snakes: North American Crotalinae envenomation. In Shannon MW, Borron SW, Burns MJ, editors: Haddad and Winchester's clinical management of poisoning and drug overdose, *ed 4, Philadelphia, 2007, WB Saunders, Table 21A-9.*

Table 725-4 Indications for Administration of Additional Antivenom in Patients with Recurrent Coagulopathy or Thrombocytopenia After Initial Control

- Evidence of clinically significant bleeding
- Platelet count below 25,000/cu mm
- International normalized ratio (INR) greater than 3
- Activated partial thromboplastin time (aPTT) greater than 50 sec
- Fibrinogen less than 50 mg/dL
- Presence of multicomponent coagulopathy
- Worsening trend in a patient with prior severe coagulopathy
- High-risk behavior for trauma
- Certain comorbid conditions (e.g., systemic vasculitis, seizure disorders, prior stroke)

From Norris RL, Bush SP, Smith J: Bites by venomous reptiles in Canada, the U.S. and Mexico. In Auerbach PS, editor: Wilderness medicine, *ed 6, Philadelphia, 2012, Elsevier.*

Figure 725-3 Female black widow spider (*Latrodectus mactans*). Note the red hourglass-shaped marking on the underside of her abdomen. *(From The Centers for Disease Control and Prevention Public Health Image Library, Image #5449.)*

tend to be mild laboratory coagulopathies without clinical bleeding, rare cases of intracranial bleeding have been reported. Further AV therapy should be considered for such delayed onset or recurrent coagulopathy as outlined in Table 725-4.

Disposition

Any child with a potential venomous snake bite should be admitted to a closely observed setting for at least 24 hr, regardless of whether evidence of envenomation exists or AV has been given. Children with evidence of systemic toxicity should initially be admitted to an intensive care setting until stabilized.

SPIDER BITES

More than 20,000 venomous spiders have been identified, but most lack either potent venom or fangs long enough to penetrate human skin, and are therefore of no medical significance. No spiders can be considered truly deadly, meaning that an untreated bite in a human would be expected to cause death. The spiders of medical significance can be broadly divided into 2 major groups: those that cause a neurotoxic syndrome and those that cause tissue necrosis. In the United States, the only significant morbidities are caused by 1 genus of spider from each group: *Latrodectus* (the widow spiders) and *Loxosceles* (the fiddleback or recluse spiders).

Neurotoxic Spiders

The major neurotoxic spiders are the widow spiders (*Latrodectus* spp.), the funnel web spiders (*Atrax* and *Hydronyche* spp.—found in Australia), and the banana spiders (*Phoneutria* spp.—indigenous to Latin America).

Venoms and Effects

Neurotoxic spiders all possess venoms that act at neural synapses, both at neuromuscular junctions and at autonomic nervous system junctions. All of the widow spiders (*Latrodectus* spp., including the well-studied black widow [*Latrodectus mactans;* Fig. 725-3)] and the Australian red-back spider [*Latrodectus hasselti*]) possess very similar venoms, with the most important neurotoxin being α-latrotoxin. The neurotoxin of the Sydney funnel web spider (*Atrax robustus*) is robustoxin.

Bites by the neurotoxic spiders tend to be very painful, and the offending spider is often seen. Systemic effects may include hypertension, tachycardia, bradycardia, hypersalivation, diaphoresis, and diffuse muscle spasms.

Management

Management of neurotoxic spider envenomation centers on sound supportive care. Several *Latrodectus* AVs are available, and each appears to be effective regardless of which species of widow spider was responsible for the bite. There is also an AV for the Sydney funnel web spider, the only species of funnel web that has caused human fatalities (none since the introduction of the AV), and a polyspecific AV for the banana spider in South America. These AVs should be used in significant bites with potentially serious systemic effects. The package insert for the appropriate product is used to guide therapy.

In the United States, *Latrodectus* AV is administered to reverse serious systemic effects of widow spider envenomation. One vial is given either intramuscularly (IM) or IV. Efficacy is usually noted within 1 hr of administration, reversal of systemic toxicity and relief of pain being noted. Occasionally, a second vial is necessary. There have been deaths related to acute nonallergic anaphylactic reactions to the U.S. AV, so its administration should be undertaken with due caution and close monitoring.

If AV is to be withheld or is not available, generous doses of opioid analgesics and benzodiazepines may be used to ease symptoms (although this may require up to 72 hr of therapy).

Disposition

Most neurotoxic spider bite victims, even those requiring AV, can be discharged from the emergency department if they have a satisfactory response to therapy. Parents should be warned to bring their child back for any reoccurrence of venom effects. Children with more-severe cases should be admitted for 24 hr of monitoring.

Necrotizing Spiders

Venoms and Effects

Although many spiders may cause a small amount of local tissue damage after their bites, the spiders most notorious for their dermonecrotic potential are the violin or recluse spiders of the genus *Loxosceles*. The best known member of this genus is the brown recluse (*Loxosceles reclusa*; Fig. 725-4), found in the midwestern and southern portions of the United States. The venom of *Loxosceles* spiders contains a phospholipase enzyme, sphingomyelinase D, which attacks cell membranes and can cause local tissue damage that can occasionally be severe. The bite of this spider, most common between April and October, is generally painless and initially goes unnoticed. A few hours after the bite, pain related to focal ischemia begins at the site. Within a day, the site may have a central clear or blood-filled vesicle with surrounding ecchymosis and a rim of pale ischemia. The lesion may gradually expand over a period of days to weeks until necrotic tissue sloughs and healing begins (Fig. 725-5).

Rare cases of systemic loxoscelism appear to be more common in young children than adults. Patients present with systemic toxicity, including fever, chills, nausea, malaise, diffuse macular rash, and petechiae, and may experience hemolysis, coagulopathy, and/or renal failure.

In cases of suspected necrotic arachnidism, when no spider was actually seen by the patient, a broad differential diagnosis must be considered to ensure appropriate management of the true etiology. The differential diagnosis includes skin infections (particularly methicillin-resistant *Staphylococcus aureus;* see Chapter 181), bites by other arthropods (e.g., fleas, ticks), pyoderma gangrenosum, or ecthyma gangrenosum.

Management

For necrotizing spider bites, management of the wound involves sound supportive care, including intermittent local ice therapy for the 1st 72 hr and administration of antibiotics if there is any question of secondary bacterial infection. Daily wound cleansings, combined with splinting of the bitten area, should be performed until the wound is healed.

Figure 725-4 Male recluse spider (*Loxosceles* spp.). Note the distinct violin-shaped marking on the dorsum of the cephalothorax. *(Courtesy of Michael Cardwell/Extreme Wildlife Photography.)*

Nothing has been definitively proven effective in limiting the extent of necrosis following a spider bite. There is no role for steroids in managing necrotic arachnidism. Dapsone, although used anecdotally in managing *Loxosceles* bites in adults, is not approved for use in children and should not be prescribed.

Children appearing systemically unwell should be admitted and undergo laboratory evaluation (complete blood count, coagulation studies, and urinalysis). Systemic loxoscelism is managed with intravenous hydration, management of renal failure as needed, and a brief course of systemic steroids to stabilize red blood cell membranes. Although there are documented fatalities following bites by the South American violin spider (*Loxosceles laeta*), there has never been a definitively proven fatality following a brown recluse bite in the United States. No AV is commercially available in the United States for management of necrotizing spider bites such as those from *Loxosceles* species.

Disposition

Victims with potentially necrotic bites should be monitored for a few days with daily wound checks. Local, intermittent cooling therapy should be continued for approximately 72 hr. Any child with a probable necrotizing spider bite and evidence of systemic involvement should be admitted to be watched for hemolysis and coagulopathy.

SCORPION STINGS

Of the more than 1,200 species of scorpions worldwide, only a few cause more than a painful sting. In the United States, there is 1 medically significant scorpion, the bark scorpion (*Centruroides sculpturatus* [formerly *Centruroides exilicauda*]). Although this scorpion has caused death in children in the past, such an outcome is exceedingly rare. It is found only in Arizona and small areas of immediately surrounding states. In other regions of the world, especially Latin America, Africa, the Middle East, and Asia, a number of scorpions regularly cause fatalities, particularly in small children.

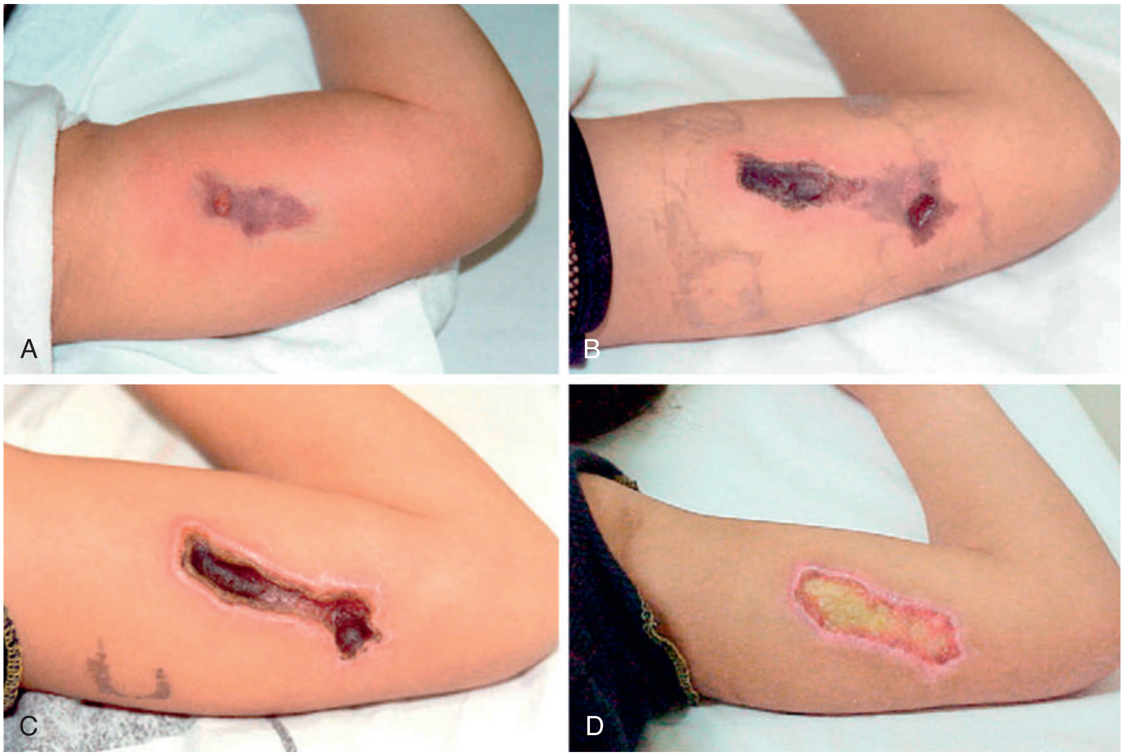

Figure 725-5 Progression of cutaneous loxoscelism in a Brazilian patient who was bitten inside a house while putting on a shirt. Ulceration and necrosis at day 1 **(A),** day 9 **(B),** day 16 **(C),** and day 25 **(D).** *(From Isbister G, Fan HW: Spider bite.* Lancet *378:2039–2046, 2011, Fig. 3. Photographs by Ceila MS Malaque.)*

Venoms and Effects

The major components of important scorpion venoms are neurotoxins that alter neural membrane ionic channels, causing autonomic and cardiovascular dysfunction through the release of acetylcholine and catecholamines. Manifestations of scorpion stings in children vary from mild to severe and may include pain, paresthesias, roving eye movements, cranial nerve dysfunction, opisthotonos/emprosthotonos, seizures, hypertensive crisis, cardiovascular collapse, and respiratory failure. Two important ingestions that can be confused with a bark scorpion envenomation are organophosphate poisoning (see Chapter 63) and methamphetamine intoxication (see Chapter 114). The opsoclonus-like roving eye movements seen in bark scorpion envenomations are not seen in the above ingestions and may help differentiate these conditions.

Management

Most stings require only pain control and respond well to ice, immobilization, and analgesics. Management of severe stings should begin with the ABCs. Opioid analgesics may have some synergy with scorpion neurotoxins and should be used with caution. Benzodiazepines may be more useful, especially for severe muscle spasms or sedation of the agitated child. Approximately 20 different scorpion AVs are available worldwide, but their use is controversial because of variable efficacy and the risk of potential nonallergic anaphylaxis. Practitioners should be familiar with the local standard of care for treating the stings of their indigenous scorpions and should consult a local or regional expert for assistance as necessary. In August 2011, the FDA approved a bark scorpion–specific AV, Anascorp, for use in the United States. It is manufactured in Mexico and marketed there under the name Alacramyn. The AV is generally given to any patient with cranial nerve or somatic skeletal neuromuscular dysfunction. The starting dose is 3 vials given IV, followed by another vial if symptoms still persist 30-60 min later and up to 5 vials were used in the initial study. Anascorp is currently only approved for IV administration; however, there are case reports of it being given IM and IO in children without IV access. *For more specific information about the administration of Anascorp, the practitioner should contact the Arizona Poison and Drug Information Center for details and assistance (800-222-1222).* In some regions of the world, prazosin is used in severe scorpion stings to ameliorate acute cardiovascular effects.

Disposition

The child with evidence of systemic toxicity following a scorpion sting should be admitted for at least 24 hr of monitoring (including cardiac monitoring) and, if envenomation is severe, should be monitored in a pediatric intensive care unit. In the absence of systemic toxicity and with adequate pain control, children >1 yr can be discharged to go home with a responsible adult.

HYMENOPTERA STINGS

The insect order Hymenoptera includes the stinging ants, bees, and wasps, which are characterized by the presence of a modified ovipositor (the "sting" or "stinger") at the end of the abdomen through which venom is injected. Various members of the order can be found throughout the world.

Venoms and Effects

Hymenoptera venoms, mixtures of proteins and vasoactive substances, are not very potent. Most stings result in only local pain, redness, and swelling, followed by itching and resolution. Some patients experience a large local reaction in which swelling progresses beyond the sting site, possibly involving the entire extremity. Approximately 0.4-0.8% of children are at risk for acute, life-threatening allergic reactions as a result of hymenoptera venom sensitivity. Each year, an estimated 50-150 people in the United States die of allergic anaphylaxis caused by hymenoptera stings (see Chapter 70). Rare cases of delayed serum sickness can follow hymenoptera stings (see Chapter 150). Finally, with the spread of Africanized honey bees *(Apis mellifera scutellata),* massive stinging episodes resulting in systemic venom toxicity (hypotension, respiratory failure, shock, hemolysis, and renal failure) appear to be increasing in Latin America and the southwestern U.S. states.

Management

Children with typical local reactions can be treated with application of cold compresses and with analgesics and antihistamines as needed. Children with large local reactions should also receive a 5 day course of oral corticosteroids and a prescription for an epinephrine autoinjection kit (and instructions in its use) prior to discharge. Patients presenting with urticaria, angioedema, wheezing, or hypotension should be treated aggressively for an immediate hypersensitivity reaction with intramuscular epinephrine (0.01 mg/kg, up to 0.3-0.5 mg of 1 : 1,000 formulation), airway management as needed, oxygen, intravenous fluids, antihistamines, and corticosteroids. Children suffering massive stinging episodes should undergo treatment similar to that for allergic anaphylaxis.

Disposition

Children with local reactions (limited or large local) can be discharged with continued care as outlined previously and instructions for wound precautions. More difficult disposition decisions are involved for children with systemic manifestations. Children with only diffuse urticaria, who are stable after a period of observation, can be discharged in the care of a responsible adult to continue antihistamines and steroids and to carry an epinephrine self-administration kit. These children seem to be at little risk for progressing to systemic anaphylaxis with future stings. Children suffering more than simple hives (e.g., wheezing, evidence of laryngeal edema or cardiovascular instability) should be admitted for 24 hr of observation and should receive a referral to an allergist for testing for hymenoptera venom sensitivity and possible immunotherapy. Immunotherapy reduces the risk of systemic anaphylaxis from future stings in high-risk patients from somewhere between 30% and 60% to less than 5%.

MARINE ENVENOMATION

The most commonly encountered venomous marine creatures are the jellyfish (Cnidaria), stingrays (Chondrichthyes), and members of the family Scorpaenidae—the lionfish, scorpionfish, and stonefish. Although most injuries occur when a child ventures into the animal's natural environment, lionfish (*Pterois* spp.) are commonly kept in private aquariums and children may be stung if they attempt to handle these beautiful fish.

Venoms and Effects

All jellyfish have unique stinging cells called **nematocysts**. These cells contain a highly folded tubule that everts on contact and injects venom. The venom is antigenic and can be dermonecrotic, hemolytic, cardiotoxic, or neuropathic, depending on the species. The nematocysts can sting even after the tentacle is severed from the body and after the jellyfish is dead. The Pacific box jellyfish *(Chironex fleckeri)* of Australia, with its cardiotoxic venom, is known to cause rapidly fatal stings. Although fatal anaphylaxis to jellyfish stings has been reported in coastal waters of the United States, these events are rare. For clinicians in the Americas, the primary concern with jellyfish stings is localized pain that may be associated with paresthesias or pruritus. Rarely, jellyfish victims may have systemic symptoms such as nausea, vomiting, headache, and chills.

Stingrays have a sharp, retroserrated spine and associated venom gland at the base of the tail. Stings tend to occur when the victim steps on the animal hidden in the surf. Injuries involve jagged lacerations from the spine, often with retained debris (spine fragments, glandular tissue, sand, etc.), and the venom has vasoconstrictive properties that can result in tissue necrosis and poor wound healing. Stingray envenomations are noteworthy for immediate and intense pain at the site of injury that lasts 24-48 hr. Some patients experience nausea, vomiting, and muscle cramps, and, rarely, hypotension or seizures.

The Scorpaenidae have venomous dorsal, pelvic, and anal spines that become erect when threatened. The glands associated with these spines contain venoms that result in direct myotoxicity leading to

paralysis of cardiac, involuntary, and skeletal muscles. Envenomation causes immediate pain that may persist for hours or days. Victims may experience intense local tissue destruction in which superinfections are common. Systemic symptoms include vomiting, abdominal pain, headache, delirium, seizures, and respiratory failure.

Management

Treatment of jellyfish stings begins in the ocean. The involved skin should be quickly rinsed *in seawater (fresh water may stimulate further nematocyst firing)*. Dousing the sting site with vinegar or rubbing alcohol can inhibit nematocyst discharge. Visible tentacle fragments should be removed with a gloved hand or forceps, and microscopic fragments may be removed by gently shaving the affected area. Folk remedies such as rubbing the sting with sand and applying urine are not helpful and cause more irritation. Meat tenderizer is not effective. Antihistamines and corticosteroids are indicated for swelling and urticaria. An apparent, acute allergic reaction should be treated with intramuscular epinephrine. Antibiotics are not needed.

Treatment of stingray and Scorpaenidae stings is similar. These toxins are heat labile, and immersion in hot water (approximately 42°C [107.6°F]) for 30-60 min denatures the protein constituents and decreases pain significantly. The wounds should be thoroughly cleaned and explored with use of local or regional anesthesia to rule out retention of spine or integument fragments. Stingray spines are radiopaque and may be seen on plain films of the wounded area or identified by ultrasonography. Lacerations should be treated with delayed primary closure or allowed to heal by secondary intention. Systemic analgesia should be provided as needed. Because of the risk of secondary bacterial infection, there should be a low threshold for administering prophylactic antibiotics to cover *Staphylococcus*, *Streptococcus,* and *Vibrio* species, and wounds should be rechecked daily for a few days.

Disposition

After wound care, most victims can be discharged home with responsible adults. If there are significant systemic effects after pain control is achieved, the child should be admitted for monitoring and further care as needed.

Bites and stings by venomous creatures are common occurrences in children, but they uncommonly cause major morbidity or mortality. The majority of such injuries do very well with sound supportive care. In serious cases, aggressive management of the ABCs combined with specific interventions (such as AVs when available) maximize the potential for an optimal outcome. A low threshold should be maintained for consulting specialists in envenomation medicine, available through regional poison control centers.

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Laboratory Medicine

PART XXXV

Chapter 726 Laboratory Testing in Infants and Children

Stanley F. Lo

"Normal values" (reference intervals) are difficult to establish within the pediatric population. Differences in genetic composition, physiologic development, environmental influences, and subclinical disease are variables that need to be considered when developing reference intervals. Other considerations for further defining reference intervals include partitioning based on sex and age. The most commonly used reference range is generally given as the mean of the reference population ±2 standard deviations (SD). This is acceptable when the distribution of results for the tested population is essentially gaussian. The serum sodium concentration in children, which is tightly controlled physiologically, has a distribution that is essentially gaussian; the mean value ±2 SD gives a range very close to that actually observed in 95% of children (Table 726-1). However, not all analytes have a gaussian distribution. The serum creatine kinase level, which is subject to diverse influences and is not actively controlled, does not show a gaussian distribution, as evidenced by the lack of agreement between the range actually observed and that predicted by the mean value ±2 SD. In these cases, a reference interval defining the 2.5-97.5 percentiles is typically used.

Reference cutoffs are typically established from large studies with a large reference population. Examples of these cutoffs are illustrated by reference cutoffs established for cholesterol, lipoproteins, and neonatal bilirubin. Patient results exceeding these cutoffs have a future risk of acquiring disease. A final modification needed for reporting reference intervals is referencing the Tanner stage of sexual maturation, which is most useful in assessing pituitary and gonadal function.

The establishment of common reference intervals remains an elusive target. Although some patient results are directly comparable between laboratories and methods, most are not. Careful interpretation of patient results must consider when testing was performed and what method was used. Higher-order methods, methods that are more accurate and precise, continue to be slowly developed. These will be critical to the standardization of tests and the establishment of common reference intervals.

ACCURACY AND PRECISION OF LABORATORY TESTS

Technical accuracy, or trueness, is an important consideration in interpreting the results of a laboratory test. Because of improvements in methods of analysis and elimination of analytic interference, the accuracy of most tests is limited primarily by their precision. **Accuracy** is a measure of the nearness of a test result to the actual value, whereas **precision** is a measure of the reproducibility of a result. No test can be more accurate than it is precise. Analysis of precision by repetitive measurements of a single sample gives rise to a gaussian distribution with a mean and an SD. The estimate of precision is the coefficient of variation (CV):

$$CV = \frac{SD}{Mean} \times 100$$

The CV is not likely to be constant over the full range of values obtained in clinical testing, but it is approximately 5% in the normal range. The CV is generally not reported, but is always known by the laboratory. It is particularly important in assessing the significance of changes in laboratory results. For example, a common situation is the need to assess hepatotoxicity incurred as a result of the administration of a therapeutic drug and reflected in the serum alanine aminotransferase (ALT) value. If serum ALT increases from 25 units/L to 40 units/L, is the change significant? The CV for ALT is 7%. Using the value obtained ±2 × CV to express the extremes of imprecision, it can be seen that a value of 25 units/L is unlikely to reflect an actual concentration of >29 units/L, and a value of 40 units/L is unlikely to reflect an actual concentration of <34 units/L. Therefore, the change in the value as obtained by testing is likely to reflect a real change in circulating ALT levels. Continued monitoring of serum ALT is indicated, even though both values for ALT are within normal limits. *Likely* in this case is only a probability. Inherent biologic variability is such that the results of 2 successive tests may suggest a trend that will disappear on further testing.

The precision of a test may also be indicated by providing confidence limits for a given result. Ordinarily, 95% confidence limits are used, indicating that it is 95% certain that the value obtained lies between the 2 limits reported. Confidence limits are calculated using the mean and SD of replicate determinations:

$$95\% \text{ confidence limits} = Mean \pm t \times SD$$

where t is a constant derived from the number of replications. In most cases, $t = 2$.

Accuracy is expressed by determining the difference, or bias, between results from a comparative method and a definitive or reference method. A definitive or reference method provides results with increased precision and accuracy compared to the clinical laboratory. When these methods are used, along with highly purified materials (i.e., Standard Reference Materials from the National Institute of Standards and Technology) to establish values for assay calibrators used in the clinical laboratory, the accuracy of patient results is improved. Creatinine, hemoglobin A_{1c}, and neonatal bilirubin are examples in which the accuracy of these tests has been improved.

SENSITIVITY, ACCURACY, AND ANALYTIC TESTING

In some circumstances, the sensitivity and accuracy of an analysis are reduced or increased as functions of clinical purpose. For example, ion exchange chromatography of plasma amino acids for the diagnosis of inborn errors of metabolism is usually performed at an analytic sensitivity that allows measurement of all of the amino acids with a single set of standards. The range of values is approximately 20-800 µmol/L, and accuracy is poor at values ≤20 µmol/L. The detection of homocysteine in this type of analysis suggests an inborn error of methionine metabolism. If the analysis is adjusted to achieve greater analytic sensitivity, it is possible to measure homocysteine accurately in normal plasma (3-12 µmol/L). This more sensitive test is used to assess cobalamin status and analyze risk factors for atherosclerotic cardiovascular disease.

PREDICTIVE VALUE OF LABORATORY TESTS

Predictive value (PV) theory deals with the usefulness of tests as defined by their clinical sensitivity (ability to detect a disease) and specificity (ability to define the absence of a disease).

$$Sensitivity = \frac{\text{Number positive by test}}{\text{Total number positive}} \times 100$$

Table 726-1 Gaussian and Nongaussian Laboratory Values in 458 Normal School Children 7-14 Yr of Age

	SERUM SODIUM (mmol/L)	SERUM CREATINE KINASE (units/L)
Mean	141	68
SD	1.7	34
Mean ±2 SD	138-144	0-136
Actual 95% range	137-144	24-162

$$\text{Specificity} = \frac{\text{Number negative by test}}{\text{Total number without disease}} \times 100$$

$$\text{PV of a positive test result} = \frac{\text{True-positive results}}{\text{Total positive results}} \times 100$$

$$\text{PV of a negative test result} = \frac{\text{True-negative results}}{\text{Total negative results}} \times 100$$

The problems addressed by PV theory are false-negative and false-positive test results. Both are major considerations in interpreting the results of screening tests in general and neonatal screening tests in particular.

Testing for HIV seroreactivity illustrates some of these considerations. If it is assumed that approximately 1,100,000 of 284,000,000 residents of the United States are infected with HIV (prevalence = 0.39%) and that 90% of those infected demonstrate antibodies to HIV, then we can consider the usefulness of a simple test with 99% sensitivity and 99.5% specificity (see Chapter 276). If the entire population of the United States were screened, it would be possible to identify most of those infected with HIV.

$$1{,}100{,}000 \times 0.9 \times 0.99 = 980{,}100\ (89.1\%)$$

However, there will be 119,900 false-negative test results. Even with 99.5% specificity, the number of false-positive test results would be larger than the number of true-positive results:

$$284{,}000{,}000 \times 0.0005 = 1{,}420{,}000$$

In addition, there will be 281,480,000 true-negative results:

$$\text{PV of positive test result} = \frac{980{,}100}{(980{,}100 + 1{,}420{,}000)} \times 100 = 41\%$$

$$\text{PV of negative test result} = \frac{281{,}480{,}000}{(281{,}480{,}000 + 119{,}900)} \times 100 = 99.96\%$$

Given the high cost associated with follow-up and the anguish produced by a false-positive result, it is easy to see why universal screening for HIV seropositivity received a low priority immediately after the introduction of testing for HIV infection.

By contrast, we can consider the screening of 100,000 individuals from groups at increased risk for HIV in whom the overall prevalence of disease is 10%, with all other considerations being unchanged.

$$\text{True-positive results} = 0.9 \times 0.99 \times 10{,}000 = 8{,}910$$

$$\text{False-positive results} = 0.005 \times 90{,}000 = 450$$

$$\text{False-negative results} = 10{,}000 - 8{,}910 = 1{,}090$$

$$\text{PV of positive test result} = \frac{8{,}910}{8{,}910 + 450} \times 100 = 95\%$$

$$\text{PV of negative test result} = \frac{89{,}500}{89{,}550 + 1{,}090} \times 100 = 99\%$$

These 2 hypothetical testing strategies show that the diagnostic efficiency of testing depends heavily on the prevalence of the disease being tested for, even with a superior test, such as the test for HIV antibodies. Because the treatment of pregnant women infected with HIV is effective in preventing vertical transmission of the infection, screening has now been expanded to all pregnant women. The proven effectiveness of current therapy in preventing neonatal infection has intensified screening for HIV early in pregnancy.

However, because of the long time needed to test for HIV antibodies, it was difficult to screen women during labor and provide the necessary therapy. Recently, rapid HIV antibody testing procedures using a fingerstick or venipuncture to obtain whole blood, plasma, or serum, and tests using oral fluid were approved (Table 726-2). The HIV test results are usually obtained in <20 min. The collection of oral fluid samples provides an alternative for individuals who avoid HIV testing because of their dislike of needlesticks. HIV testing using whole blood or oral fluid is classified as a waived test under the **Clinical Laboratory Improvement Amendments of 1988,** and these tests are allowed in a point-of-care setting. Waived tests are simple laboratory procedures that use methodologies that are so simple and accurate as to render the likelihood of an erroneous result by the user negligible. A positive rapid HIV test result is then confirmed by Western blot analysis or immunofluorescence assay.

According to the U.S. Centers for Disease Control and Prevention, 162 infants were born with HIV in 2010 in the United States. Rapid HIV testing during labor allows for implementation of antiretroviral therapy for HIV-infected women who have not been tested or are unaware of their HIV status. The initiation of therapy at the time of labor or within the 1st 12 hr of an infant's birth significantly reduces the risk of mother-to-child transmission. In the mother–infant rapid intervention at delivery study, it was shown that the sensitivity and specificity of a rapid whole blood test for HIV during labor were 100% and 99.9%, respectively, with a positive PV of 90%. The median turnaround time for obtaining results from blood collection to patient notification was only 66 min. The performance of the rapid blood test was better than that of the standard HIV enzyme immunoassay, which had sensitivity and specificity of 100% and 99.8%, respectively, with a positive PV of 76%. In addition, the median turnaround time from blood collection to patient notification was 28 hr. As a result, rapid whole blood HIV testing is now the standard of care for women in labor with undocumented HIV status.

Rapid HIV testing can also be used in developing countries. In resource-poor settings, because of the lack of properly equipped laboratories, skilled technologists, and basic resources, such as electricity and water, these self-contained, point-of-care HIV tests are very attractive. In areas of Asia and Africa in which HIV is epidemic, screening pregnant women with rapid HIV tests and offering antiretroviral therapy can significantly reduce the transmission of HIV to hundreds of thousands of infants.

NEONATAL SCREENING TESTS

Almost all of the diseases detected in neonatal screening programs have a very low prevalence, and for the most part, the tests are quantitative rather than qualitative. In general, the strategy is to use the initial screening test to separate a highly suspect group of patients from normal infants (i.e., to increase the prevalence) and then to follow this suspect group aggressively. There are 2 common strategies used to detect congenital hypothyroidism (see Chapter 568.2): 1 uses thyroid-stimulating hormone for the initial screen and the other uses thyroxine. In the thyroxine strategy for congenital hypothyroidism, which has a prevalence of 25 in 100,000 liveborn infants, the initial test performed is for thyroxine in whole blood. Infants with the lowest 10% of test results are considered suspect. If all infants with hypothyroidism were included in the suspect group, the prevalence of disease in this group would be 250 in 100,000 infants. The original samples obtained from the suspect group are retested for thyroxine and are tested for thyroid-stimulating hormone. This second round of testing results in an even more highly suspect group composed of 0.1% of the infants screened and having a prevalence of hypothyroidism of 25,000

Table 726-2 Rapid HIV Antibody Tests and Status Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA)

RAPID HIV TEST	SPECIMEN TYPE	CLIA CATEGORY	TIME FOR PERFORMING ASSAY	WAIT TIME TO READ RESULTS	MANUFACTURER
OraQuick ADVANCE Rapid HIV-1/2 Antibody Test	Oral fluid Whole blood (fingerstick or venipuncture) Plasma	Waived Waived Moderate complexity	<5 min	20-40 min	OraSure Technologies, Inc. www.orasure.com
Uni-Gold Recombigen HIV-1	Whole blood (fingerstick or venipuncture) Serum and plasma	Waived Moderate complexity	<5 min	10-12 min	Trinity Biotech www.unigoldhiv.com
Reveal G-2 Rapid HIV-1 Antibody Test	Serum and plasma	Moderate complexity	<5 min	Read result immediately	MedMira, Inc. www.medmira.com
MultiSpot HIV-1/HIV-2 Rapid Test	Serum and plasma	Moderate complexity	10-15 min	Result can be read immediately or up to 4 hr later	BioRad Laboratories www.bio-rad.com
Clearview HIV 1/2 STAT-PAK	Whole blood (fingerstick or venipuncture) Serum and plasma	Waived Waived	5 min 5 min	15-20 min 15-20 min	Chembio Diagnostic Systems, Inc; distributed by Alere www.alere.com Chembio Diagnostic Systems, Inc; distributed by Alere www.alere.com
Clearview COMPLETE HIV 1/2	Whole blood (fingerstick or venipuncture) Serum and plasma	Waived Waived	5 min 5 min	15-20 min 15-20 min	Chembio Diagnostic Systems, Inc; distributed by Alere www.alere.com Chembio Diagnostic Systems, Inc; distributed by Alere www.alere.com

in 100,000 subjects. This final group is aggressively pursued for further testing and treatment. Even with a 1,000-fold increase in prevalence, 75% of the aggressively tested population is euthyroid. The justifications advanced for the program are that treatment is easy and effective and that the alternative, if congenital hypothyroidism is undetected and untreated—long-term custodial care—is both unsatisfactory and expensive.

At its inception, newborn screening was driven by the selection of genetic diseases whose clinical manifestations developed postnatally, such as phenylketonuria, galactosemia, and hypothyroidism. Diseases selected for screening typically had to meet certain criteria. The prevalence of disease had to meet a minimum, typically 1 in 100,000. Disease selection required demonstrated reduction in morbidity and mortality in the neonatal period. Effective therapies needed to be available, and the cost of screening and the feasibility of laboratory testing were also considerations in this selection process.

More common diseases have also become targets for neonatal screening programs. Sickle cell disease (see Chapter 462.1), easily detected using liquid chromatography or isoelectric focusing, can be treated more effectively if it is diagnosed before clinical signs appear. In addition, the results of neonatal screening for cystic fibrosis (CF; see Chapter 403) show that there are clear benefits associated with preclinical diagnosis, but also that there are some inherent difficulties associated with genetic screening for complex autosomal recessive diseases that are common and are caused by a rather large number of mutations (>1,500) of a single gene. The definitive diagnostic test for CF is the measurement of concentrations of chloride in sweat, a test that is not practical during the 1st wk of life. Neonates with CF generally have elevations in whole blood trypsinogen. This test allows the identification of a group of neonates at risk for CF. Unfortunately, trypsinogen as an initial screening test has a high false-positive rate, an unfavorable characteristic that creates unnecessary anxiety among newborn parents and families, and is costly because of the time and expense for medical follow-up. Performing DNA analysis for common mutations that cause CF reduces the size of the suspect group and identifies neonates with a higher likelihood of disease. This 2-tiered strategy identifies a manageable number of infants on whom to perform sweat tests. Problems include the following: (1) Uncommon mutations are not included in the screening panel (thus, cases of CF caused by these mutations can be missed); (2) common mutations that cause clinically innocent elevations of whole blood trypsinogen in heterozygous neonates cause potentially alarming false-positive findings; and (3) CF in patients with normal sweat test results is rare but is likely to be missed.

Tandem mass spectrometry (MS/MS) is a technically advanced method in which many compounds are initially fragmented and separated by molecular weight. Each compound is then fragmented again. Identification of compounds is based upon characteristic fragments. The process requires roughly 2 min per sample and can detect 20 or more inborn errors of metabolism. The effects of prematurity, neonatal illness, and intensive neonatal management on metabolites in blood complicate the interpretation of results. The PV of a positive screening result is likely to be <10%; that is, 90% of positive results are not indicative of a genetic disorder of metabolism. Nonetheless, MS/MS permits a diagnosis to be made before clinical illness develops and has revolutionized the purpose and ability of newborn screening. MS/MS is not directed toward diseases defined as treatable, but it is directed toward all of the diseases, each of which is rare, that the technique can identify.

Electrospray MS/MS permits the detection of rare inborn errors of metabolism and has been introduced as a newborn screening tool all around the world. Since 1998, when mass spectrometry was implemented in Australia, the rate of detection per 100,000 births has been 15.7, significantly higher than the rate of 8.6-9.5 in the 6 preceding 4 yr periods. Disorders of fatty acid oxidation, particularly medium-chain acyl coenzyme A dehydrogenase deficiency (see Chapter 86), accounted for the majority of increased diagnoses.

Table 726-3	American College of Medical Genetics Core Panel
Isovalericacidemia	
Glutaric aciduria type 1	
3-Hydroxy-3-methylglutaricaciduria	
Multiple coenzyme A (CoA) carboxylase deficiency	
Methylmalonic acidemia (mutase deficiency)	
3-Methylcrotonyl CoA carboxylase deficiency	
Methylmalonic acidemia (cobalamin [Cbl] A, B)	
Propionicacidemia	
β-Ketothiolase deficiency	
Medium-chain acyl-CoA dehydrogenase deficiency	
Very-long-chain acyl-CoA dehydrogenase deficiency	
Long-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency	
Trifunctional protein deficiency	
Carnitine uptake deficiency	
Phenylketonuria	
Maple syrup urine disease	
Homocystinuria (because of cystathionine β-synthase deficiency)	
Citrullinemia	
Argininosuccinic acidemia	
Tyrosinemia type 1	
Sickle cell anemia (Hb SS disease)	
Hemoglobin (Hb) S/β-thalassemia	
Hb S/C disease	
Congenital hypothyroidism	
Biotinidase deficiency	
Congenital adrenal hyperplasia (21-hydroxylase deficiency)	
Classical galactosemia	
Hearing loss	
Cystic fibrosis	

Expanded newborn screening programs using MS/MS increase the detection of inherited metabolic disorders. All states in the United States use MS/MS in their neonatal screening programs. The metabolic conditions screened for by states using MS/MS vary, ranging from 31 to >50.

In an attempt to standardize newborn screening programs, the American College of Medical Genetics recommends that every baby born in the United States be screened for a core panel of 29 disorders (Table 726-3). An additional 25 conditions were recommended as secondary targets because they may be identified while screening for the core panel disorders. The March of Dimes and the American Academy of Pediatrics also endorse the recommendation by the American College of Medical Genetics. However, expansion of the screening test menu raises several issues. The cost of implementation can be significant because many states will need multiple MS/MS systems. Staffing the laboratory with qualified technical personnel to run the MS/MS system and qualified clinical scientists to interpret the profiles can be a challenge. A number of false-positive results will also be obtained with these newborn screening programs. Many of these findings are the result of parenteral nutrition, biologic variation, or treatment, and are not the result of an inborn error of metabolism. Consequently, qualified staff will be needed to ensure that patients with abnormal results are contacted and receive follow-up testing and counseling, if needed. Even with these concerns, the American College of Medical Genetics report is a step in the right direction toward standardizing guidelines for state newborn screening programs.

TESTING IN REFINING A DIFFERENTIAL DIAGNOSIS

The use of laboratory tests in refining a differential diagnosis satisfies PV theory because a correct differential diagnosis should result in a relatively high prevalence of the disease under consideration. An example of testing in refining a differential diagnosis is the measurement of urinary vanillylmandelic acid (VMA) for the diagnosis of neuroblastoma (see Chapter 498). A simple spot test for VMA is not useful in general screening programs because of the low prevalence of neuroblastoma (3 cases/100,000) and the low sensitivity of the test (69%). Even though the specificity of urinary VMA is 99.6%, testing of 100,000 children would produce 2 true-positive test results, 400 false-positive results, and 1 false-negative result. The PV of a positive result in this setting is 0.5%, and the PV of a negative result is 99.99%, not much different from the assumption that neuroblastoma is not present. Testing for urinary VMA in a 3 yr old child with an abdominal mass, however, gives a useful result because the prevalence of neuroblastoma is at least 50% in 3 yr old children with abdominal masses. If 100 such children are tested and the prevalence of neuroblastoma in the group is assumed to be 50%, then a satisfactory PV is obtained.

$$\text{PV of positive test result} = \frac{0.69 \times 50}{0.69 \times 50 + (0.004 \times 50)} \times 100 = 99\%$$

$$\text{PV of negative test result} = \frac{0.996 \times 50}{0.996 \times 50 + (0.31 \times 50)} \times 100 = 76\%$$

Thus, in this situation, a test with low sensitivity is powerful in refining the differential diagnosis because the PV of a positive result is almost 100% in the setting of high prevalence.

Serologic Testing

Using laboratory testing to refine a differential diagnosis poses problems, as exemplified by serologic testing for Lyme disease, which is a tick-borne infection by *Borrelia burgdorferi* that has various manifestations in both early and late stages of infection (see Chapter 222). Direct demonstration of the organism is difficult, and serologic test results for Lyme disease are not reliably positive in young patients presenting early with erythema chronicum migrans. These results become positive after a few weeks of infection and remain positive for a number of years. In an older population being evaluated for late-stage Lyme disease, some individuals will have recovered from either clinical or subclinical Lyme disease and some will have active Lyme disease, with both groups having true-positive serologic test results. Of individuals without Lyme disease, some will have true-negative serologic test results, but a significant percentage will have antibodies to other organisms that cross react with *B. burgdorferi* antigens.

This set of circumstances gives rise to a number of problems. First, the protean nature of Lyme disease makes it difficult to ensure a high prevalence of disease in subjects to be tested. Second, the most appropriate antibodies to be detected are imperfectly defined, leading to a wide variety of tests with varying false-positive and false-negative rates. Third, the natural history of the antibody response to infection and the difficulty of showing the causative organism directly combine to make laboratory diagnosis of early Lyme disease difficult. Fourth, in the diagnosis of late-stage Lyme disease in older subjects, the laboratory diagnosis is plagued by misleading positive (either false-positive or true-positive, but not clinically relevant) results, typically an enzyme-linked immunosorbent assay that uses whole *B. burgdorferi* organisms. In a review of 788 patients referred to a specialty clinic with the diagnosis of Lyme disease, the diagnosis was correct in 180 patients, 156 patients had true seropositivity without active Lyme disease, and 452 had never had Lyme disease, even though 45% of them were found to be seropositive by at least 1 test before referral.

A 2-step approach, similar to that used in HIV testing, is commonly used: a screening test that has high sensitivity (e.g., enzyme-linked immunosorbent assay) and excellent negative PV, followed by a very specific confirmatory test for verification of positive screening test results (e.g., Western blot to detect antibodies to selected bacterial antigens). Negative screening test results and negative verification test results are reported as negative. Positive verification test results are reported as positive. However, standardization of the testing procedures is difficult in North America, where only 1 pathogenic strain of *B. burgdorferi* is found, and is more difficult elsewhere in the Northern hemisphere, where as many as 3 pathogenic strains are present. Identification of microbial DNA in body fluids by polymerase chain reaction is definitive but invasive.

Table 726-4 Laboratory Profile as a Review of Systems

LABORATORY TEST	ASSESSMENT FACILITATED BY TESTS
Complete blood cell count and platelets	Nutrition, status of formed elements
Complete urinalysis	Renal function/genitourinary tract inflammation
Albumin and cholesterol	Nutrition
ALT, bilirubin, GGT	Liver function
BUN, creatinine	Renal function, nutrition
Sodium, potassium, chloride, bicarbonate	Electrolyte homeostasis
Calcium and phosphorus	Calcium homeostasis

ALT, alanine aminotransferase; BUN, blood urea nitrogen; GGT, γ-glutamyltransferase.

Laboratory Screening

Screening profiles (Table 726-4) are used as part of a complete review of systems, to establish a baseline value, or to facilitate patient care in specific circumstances, such as (1) when a patient clearly has an illness, but a specific diagnosis remains elusive; (2) when a patient requires intensive care; (3) for postmarketing surveillance and evaluation of a new drug; and (4) when a drug is used that is known to have systemic adverse effects. Laboratory screening tests should be used in a targeted manner to supplement, not supplant, a complete history and physical examination.

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Chapter **727**

Reference Intervals for Laboratory Tests and Procedures

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In Tables 727-1 through 727-5, the reference intervals apply to infants, children, and adolescents when possible. For many analyses, separate reference intervals for children and adolescents are not well delineated. When interpreting a test result, the reference interval supplied by the laboratory performing the test should always be used as these intervals are instrument and/or method dependent. Figures 727-1 and 727-2 provide estimations related to dosages. Figure 727-3 is a nomogram for risk assessment of hyperbilirubinemia.

Bibliography is available at Expert Consult.

Table 727-1 Prefixes Denoting Decimal Factors in Table 727-5

PREFIX	SYMBOL	FACTOR
Mega-	M	10^{6}
Kilo-	k	10^{3}
Hecto-	h	10^{2}
Deka-	da	10^{1}
Deci-	d	10^{-1}
Centi-	c	10^{-2}
Milli-	m	10^{-3}
Micro-	µ	10^{-6}
Nano-	n	10^{-9}
Pico-	p	10^{-12}
Femto-	f	10^{-15}

Table 727-2 Abbreviations Used in Table 727-5

Ab	Absorbance
AU	Arbitrary unit
BB	Brain isoenzyme of creatine kinase
cap	Capillary
CH_{50}	Dilution required to lyse 50% of indicator red blood cells; indicates complement activity
Cr	Creatinine
CSF	Cerebrospinal fluid
F	Female
g	Gram
Hb	Hemoglobin
HbCO	Carboxyhemoglobin
hpf	High-power field
hr	Hour, hours
IU	International unit of hormone activity
L	Liter
M	Male
MB	Heart isoenzyme of creatine kinase
mEq/L	Milliequivalents per liter
min	Minute, minutes
mm^3	Cubic millimeter, microliter (µL)
mm Hg	Millimeters of mercury
mmol	Millimole
mo	Month, months
mol	Mole
mOsm	Milliosmole
MW	Relative molecular weight
ND	Not detected
nm	Nanometer (wavelength)
Pa	Pascal
pc	Postprandial
RBC	Red blood cell(s), erythrocyte(s)
RT	Room temperature
SD	Standard deviation
sec	Second, seconds
Tr	Trace
U	International unit of enzyme activity
V	Volume
WBC	White blood cell(s)
WHO	World Health Organization
wk	Week, weeks
yr	Year, years

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Table 727-3 Abbreviations for Specimens in Table 727-5

S	Serum	(C)	Citrate
P	Plasma	(O)	Oxalate
(H)	Heparin	W	Whole blood
(LiH)	Lithium heparin	(NH_4H)	Ammonium heparinate
(E)	Ethylenediaminetetraacetic acid (EDTA)		

Table 727-4 Key to Comments Section of Table 727-5

30°C, 37°C	Temperature of enzymatic analysis (Celsius)	l	Fluorometric method
a	Values obtained are significantly method dependent	m	Fluorescence-activated cell sorting (FACS)
		n	Fluorescence polarization
b	Values in older males are higher than those in older females	o	Gas chromatography
c	Values in older females are higher than those in older males	p	High-performance liquid chromatography (HPLC)
		q	Indirect fluorescence antibody (IFA) assay
d	Atomic absorption	r	Ion-selective electrode
e	Borate affinity chromatography	s	Nephelometry
f	Cation-exchange chromatography	t	Optical density
g	Vitros, a proprietary analytic system of Ortho Clinical Diagnostics, Inc.	u	Radial immunodiffusion (RID)
		v	Radioimmunoassay (RIA)
i	Electrophoresis	w	Spectrophotometry
j	Enzymatic assay		
k	Enzyme-amplified immunoassay		

Table 727-5 Reference Intervals*

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (US)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
COMPLETE BLOOD COUNT						
Hematocrit (HCT, Hct)	W(E)		% of packed red cells (V red cells/V whole blood cells × 100)		Volume fraction (V red cells/V whole blood)	
Calculated from mean corpuscular volume (MCV) and RBC count (electronic displacement or laser)		0-30 days	44-70%	×0.01	0.44-0.70	
		1-23 mo	32-42%		0.32-0.42	
		2-9 yr	33-43%		0.33-0.43	
		10-17 yr M	36-47%		0.36-0.47	
		F	35-45%		0.35-0.45	
		>18-99 yr M	42-52%		0.42-0.52	
		F	37-47%		0.37-0.47	
Hemoglobin (Hb)	W(E)		g/dL		mmol/L	
		0-30 days	15.0-24.0	×0.155	2.32-3.72	MW Hb = 64,500
		1-23 mo	10.5-14.0		1.63-2.17	
		2-9 yr	11.5-14.5		1.78-2.25	
		10-17 yr M	12.5-16.1		1.93-2.50	
		F	12.0-15.0		1.86-2.32	
		>18-99 yr M	13.5-18.0		2.09-2.79	
		F	12.5-16.0		1.93-2.48	
	P(H)	See Chemical Elements				

Continued

Table 727-5 Reference Intervals—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (US)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Erythrocyte indices (RBC indices)						
Mean corpuscular hemoglobin (MCH)	W(E)		pg/cell		fmol/cell	
		0-30 days	33-39	×0.0155	0.51-0.60	
		1-23 mo	24-30		0.37-0.46	
		2-9 yr	25-31		0.39-0.48	
		10-17 yr M	26-32		0.26-0.32	
		F	26-32		0.26-0.32	
		>18-99 yr M	27-31		0.27-0.31	
		F	27-31		0.27-0.31	
Mean corpuscular hemoglobin concentration (MCHC)	W(E)		% Hb/cell or g Hb/dL RBC		mmol Hb/L RBC	
			32-36	×0.155	4.96-5.58	
Mean corpuscular volume (MCV)	W(E)		μm³		fL	
		0-30 days	99-115	×1	99-115	
		1-23 mo	72-88		72-88	
		2-9 yr	76-90		76-90	
		10-17 yr	78-95		78-95	
		>18-99 yr	78-100		78-100	
Leukocyte count (WBC count)	W(E)	×1,000 cells/mm³ (μL)			×109 cells/L	
		0-30 days	9.1-34.0	×1	9.1-34.0	
		1-23 mo	6.0-14.0		6.0-14.0	
		2-9 yr	4.0-12.0		45.0-12.0	
		10-17 yr	4.0-10.5		4.0-10.5	
		18-99 yr	4.0-10.5		4.0-10.5	
Leukocyte differential	W(E)	%			Number fraction	
Myelocytes		0%		×0.01	0	
Neutrophils ("bands")		3-5%			0.03-0.05	
Neutrophils ("segs")		54-62%			0.54-0.62	
Lymphocytes		25-33%			0.25-0.33	
Monocytes		3-7%			0.03-0.07	
Eosinophils		1-3%			0.01-0.03	
Basophils		0-0.75% Cells/mm³ (μL)			0-0.0075 ×106 cells/L	
Myelocytes		0		×1	0	
Neutrophils ("bands")		150-400			150-400	
Neutrophils ("segs")		3,000-5,800			3,000-5,800	
Lymphocytes		1,500-3,000			1,500-3,000	
Monocytes		285-500			285-500	
Eosinophils		50-250			50-250	
Basophils		15-50			15-50	
Platelet count (thrombocyte count)	W(E)	×103/mm³ (μL)			×109/L	
		Newborn 84-478 (after 1 wk, same as adult)		×106	84-478	(Buck, 1996)
		Adult 150-400			150-400	
Reticulocyte count	W(E,H,O)	Adults 0.5-1.5% of erythrocytes or 25,000-75,000/mm³ (μL)		×0.01 ×106	0.005-0.015 (number fraction) or 25,000-75,000 × 106/L	
			%		Number fraction	
	W(cap)	1 day	0.4-6.0	×0.01	0.004-0.060	
		7 days	<0.1-1.3		<0.001-0.013	
		1-4 wk	<1.0-1.2		<0.001-0.012	
		5-6 wk	<0.1-2.4		<0.001-0.024	
		7-8 wk	0.1-2.9		0.001-0.029	
		9-10 wk	<0.1-2.6		<0.001-0.026	
		11-12 wk	0.1-1.3		0.001-0.013	

Table 727-5 Reference Intervals—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (US)[†]		CONVERSION FACTOR	REFERENCE VALUES (SI)[†]	COMMENTS
Alanine aminotransferase (ALT, SGPT)	S	0-7 days 8-30 days M F 1-12 mo 1-19 yr	6-40 U/L 10-40 8-32 12-45 5-45	×1	6-40 U/L 10-40 8-32 12-45 5-45	37°C, bgw (Soldin, Savwoir, Guo, 1997) (Lockitch, Halstead, Albersheim, 1988)
Albumin (BCG)	P	Premature 1 day Full term <6 days 8 days-1 yr 1-3 yr 4-19 yr	1.8-3.0 g/dL 2.5-3.4 1.9-4.9 3.4-4.2 3.5-5.6	×10	18-30 g/dL 25-34 19-49 34-42 35-56	g (Meites, 1989) (Soldin Morse, 1998) (Lockitch, Halstead, Albersheim, 1988)
Ammonia	P		11-35 μmol/L	×1	11-35 μmol/L	g
Amylase	S,P	1-19 yr	30-100 U/L % pancreatic fraction	×1	30-100 U/L % pancreatic fraction	(Lockitch, Halstead, Albersheim et al, 1988; Gillard, Simbala, Goodglick, 1983)
Amylase isoenzymes	S,P(H)	Cord-8 mo 9 mo-4 yr 5-19 yr	0-34% 5-56% 23-59%	×0.01	0-0.34% 0.05-0.56% 0.23-0.59%	
Anion gap (sodium – [chloride + bicarbonate])	P(H)	7-16 mEq/L		×1	7-16 mEq/L	
Antideoxyribonuclease B titer (anti-DNase B titer)	S	Age 4-6 yr 7-12 yr	Upper limit of normal 240-480 U 480-800 U	×1	Upper limit of normal 240-480 U 480-800 U	(Kaplan, Rothermel, Johnson, 1998)
Antidiuretic hormone (hADH, vasopressin)	P(E)	Plasma osmolarity (mOsm/kg) 270-280 280-285 285-290 290-295 295-300	Plasma ADH (pg/mL) <1.5 <2.5 1-5 2-7 4-12	×1	Plasma ADH ng/L <1.5 <2.5 1-5 2-7 4-12	
Antistreptolysin-O titer (ASO titer)	S	Age 2-5 yr 6-9 yr 10-12 yr	Upper limit of normal 120-160 Todd units 240 Todd units 320 Todd units	×1	Upper limit of normal 120-160 Todd units 240 Todd units 320 Todd units	(Kaplan et al, 1998)
Aspartate aminotransferase (AST, SGOT)	S	0-7 days M F 8-30 days 1-12 mo 1-3 yr 3-9 yr 10-15 yr 16-19 yr M F	U/L 30-100 24-95 22-71 22-63 20-60 15-50 10-40 15-45 5-30	×1	U/L 35-100 24-95 22-71 22-63 20-60 15-50 10-40 15-45 5-30	37°C, g (Soldin, Savwoir, Guo, 1997) (Lockitch, Halstead, Albersheim, 1988)
Base excess	W(H)	Newborn Infant Child Thereafter	mmol/L (–10)-(–2) (–7)-(–1) (–4)-(+2) (–3)-(+3)	×1	mmol/L (–10)-(–2) (–7)-(–1) (–4)-(+2) (–3)-(–3)	
Bicarbonate	S,P	Arterial Venous	mmol/L 21-28 22-29	×1	mmol/L 21-28 22-29	

Continued

Table 727-5 Reference Intervals—cont'd

ANALYTE OR PROCEDURE	SPECIMEN		REFERENCE VALUES (US)[†]	CONVERSION FACTOR	REFERENCE VALUES (SI)[†]	COMMENTS
Bilirubin, total	S		mg/dL		μmol/L	
		Newborn	See Bhutani nomogram (Fig. 727-3)	×17.1		(Bhutani, Johnson, Sivieri, 1999)
		1 mo-adult	<1.0		<17	
C-reactive protein (high sensitivity)	S					(Soldin, et al, 2004)
			M (mg/dL)	F (mg/dL)	M (mg/L) F (mg/L)	
		0-90 days	0.08-1.58	0.09-1.58	×10 0.8-15.8 0.9-15.8	
		91 days-12 mo	0.08-1.12	0.05-0.79	0.8-11.2 0.5-7.9	
		13 mo-3 yr	0.08-1.12	0.08-0.79	0.8-11.2 0.8-7.9	
		4-10 yr	0.06-0.79	0.5-1.0	0.6-7.9 0.5-10.0	
		11-14 yr	0.08-0.76	0.06-0.81	0.8-7.6 0.6-8.1	
		15-18 yr	0.04-0.79	0.06-0.79	0.4-7.9 0.6-7.9	
Calcium, ionized (Ca)	S,P(H),W(H)		mg/dL		mmol/L	
		Cord blood	5.0-6.0	×0.25	1.25-1.50	
		Newborn, 3-24 hr	4.3-5.1		1.07-1.27	
		24-48 hr	4.0-4.7		1.00-1.17	
		Thereafter	4.8-4.92		1.12-1.23	
		or	2.24-2.46 Eq/L	×0.5	1.12-1.23	
Calcium, total	S		mg/dL		mmol/L	
		Cord blood	9.0-11.5	×0.25	2.25-2.88	
		Newborn, 3-24 hr	9.0-10.6		2.3-2.65	
		24-48 hr	7.0-12.0		1.75-3.00	
		4-7 days	9.0-10.9		2.25-2.73	
		Child	8.8-10.8		2.20-2.70	
		Thereafter	8.4-10.2		2.10-2.55	
Carbon dioxide, partial pressure (pCO_2)	W(H)		mm Hg		kPa	
		Newborn	27-40	×0.1333	3.6-5.3	
		Infant	27-41		3.6-5.5	
		Thereafter M	35-48		4.7-6.4	
		F	32-45		4.3-6.0	
Carbon monoxide (carboxyhemoglobin)	W(E)	Nonsmoker	<2% HbCO	×0.01	HbCO fraction <0.02	
		Smoker	<10%		<0.10	
		Lethal	>50%		>0.5	
Chloride	S,P(H)	Cord blood	96-104 mmol/L	×1	96-104 mmol/L	
		Newborn	97-110		97-110	
		Thereafter	98-106		98-106	
Chloride, sweat	Sweat		mmol/L			(Farrell, et al, 2008)
		0-5 mo	≤29	CF unlikely		
			30-59	intermediate		
			≥60	indicative of CF		
		≥6 mo	≤39	CF unlikely		
			40-60	intermediate		
			≥60	indicative of CF		
Cortisol	S,P(H)		μg/dL		nmol/L	
		Newborn	1-24	×27.59	28-662	
		Adults, 8:00 AM	5-23		138-635	
		4:00 PM	3-15		82-413	
		8:00 PM	<50% of 8:00 AM	×0.01	Fraction of 8:00 AM ≤0.50	
Creatine kinase	S	Cord blood	70-380 U/L	×1	70-380 U/L	30°C, b (Jedeikin, et al, 1982)
		5-8 hr	214-1,175		214-1,175	
		24-33 hr	130-1,200		130-1,200	
		72-100 hr	87-725		87-725	
		Adult	5-130		5-130	
Creatine kinase isoenzymes	S		% MB	% BB		
		Cord blood	0.3-3.1	0.3-10.5		
		5-8 hr	1.7-7.9	3.6-13.4		
		24-33 hr	1.8-5.0	2.3-8.6		
		72-100 hr	1.4-5.4	5.1-13.3		
		Adult	0-2	0		

Table 727-5 Reference Intervals—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (US)[†]	CONVERSION FACTOR	REFERENCE VALUES (SI)[†]	COMMENTS
Creatinine (IDMS)					
Enzymatic	S,P	mg/dL		μmol/L	g
		0-4 yr 0.03-0.50	×88.4	2.65-44.2	
		4-7 yr 0.03-0.59		2.65-52.2	
		7-10 yr 0.22-0.59		19.4-52.2	
		10-14 yr 0.31-0.88		27.4-77.8	
		>14 yr 0.50-1.06		44.2-93.7	
Creatinine clearance (endogenous)	S,P,U	Newborn 40-65 mL/min/1.73 m^2			
		<40 yr, M 97-137			
		F 88-128			
		Decreases <6.5 mL/min/decade			
Ferritin	S	ng/mL		μg/L	
		0-6 wk 0-400	×1	0-400	
		7 wk-365 days 10-95		10-95	
		1-9 yr 10-60		10-60	
		10-18 yr M 10-300		10-300	
		F 10-70		10-70	
Folate	S	Newborn 7.0-32 ng/mL	×2.265	15.9-72.4 nmol/L	
		Thereafter 1.8-9.0		4.1-20.4	
	W(E)	150-450 ng/mL RBCs		340-1,020 nmol/L cells	
Glucose	S	mg/dL		mmol/L	
		Cord blood 45-96	×0.0555	2.5-5.3	
		Premature 20-60		1.1-3.3	
		Neonate 30-60		1.7-3.3	
		Newborn			
		1 day 40-60		2.2-3.3	
		>1 day 50-90		2.8-5.0	
		Child 60-100		3.3-5.5	
		Adult 70-105		3.9-5.8	
	W(H)	Adult 65-95		3.6-5.3	
Glucose, 2 hr post	S	<120		<6.7	
Glucose tolerance test (GTT) (see Chapter 589)	S	mg/dL		mmol/L	
Oral dose					
Adult: 75 g		Normal / Diabetic		Normal / Diabetic	
Child: 1.75 g/kg of ideal weight, up to a maximum of 75 g		Fasting 70-105 / ≥126	×0.0555	3.9-5.8 / ≥7.0	(Diabetes Care, 2010)
		120 min 70-120 / ≥200		3.9-6.7 / ≥11	
Glucose-6-phosphate dehydrogenase (G6PD) in erythrocytes		W(E,H,C)			
Bishop, modified		Adult		Adult	
		3.4-8.0 U/g Hb	×0.0645	0.22-0.52 mU/mol Hb	
		98.6-232 U/1012 RBC	×10–3	0.10-0.23 nU/106 RBC	
		1.16-2.72 U/mL RBC	×1	1.16-2.72 kU/L RBC	
		Newborn: 50% higher		Newborn: 50% higher	
γ-Glutamyl transpeptidase (GGT, GGTP)	S	U/L		U/L	
		Cord blood 37-193	×1	37-193	37°C, b (Knight and Haymond, 1981)
		0-1 mo 13-147		13-147	
		1-2 mo 12-123		12-123	
		2-4 mo 8-90		8-90	
		4 mo-10 yr 5-32		5-32	
		10-15 yr 5-24		5-24	
Immunoglobulin A (IgA)	S	mg/dL		mg/L	
		Cord blood 1.4-3.6	×10	14-36	s (Meites, 1989)
		1-3 mo 1.3-53		13-530	
		4-6 mo 4.4-84		44-840	
		7 mo-1 yr 11-106		110-1,060	
		2-5 yr 14-159		140-1,590	
		6-10 yr 33-236		330-2,360	
		Adult 70-312		700-3,120	

Continued

Table 727-5 Reference Intervals—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (US)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Immunoglobulin D (IgD)	S	Newborn: none detected			None detected	
		Thereafter: 0-8 mg/dL		×10	0-80 mg/L	
Immunoglobulin E (IgE)	S	M 0-230 IU/mL		×1	0-230 kIU/L	
		F 0-170			0-170	
Immunoglobulin G (IgG)	S		mg/dL		g/L	
		Cord blood	636-1,606	×0.01	6.36-16.06	s (Meites, 1989)
		1 mo	251-906		2.51-9.06	
		2-4 mo	176-601		1.76-6.01	
		5-12 mo	172-1,069		1.72-10.69	
		1-5 yr	345-1,236		3.45-12.36	
		6-10 yr	608-1,572		6.08-15.72	
		Adult	639-1,349		6.39-13.49	
Immunoglobulin M (IgM)	S		mg/dL		mg/L	
		Cord blood	6.3-25	×10	63-250	s (Meites, 1989)
		1-4 mo	17-105		170-1,050	
		5-9 mo	33-126		330-1,260	
		10 mo-1 yr	41-173		410-1,730	
		2-8 yr	43-207		430-2,070	
		9-10 yr	52-242		520-2,420	
		Adult	56-352		560-3,520	
Iron	P	All ages	22-184 µg/dL	×0.1791	4-33 µmol/L	(Lockitch, Halstead, Wadsworth, et al, 1988)
Iron-binding capacity, total (TIBC)	S	Infant 100-400 µg/dL		×0.179	17.90-71.60 µmol/L	
		Thereafter 250-400			44.75-71.60	
L-lactate (perchloric acid)	W		mg/dL		mmol/L	
		1-12 mo	10-21	×1	1.1-2.3	(Bonnefont, et al, 1990)
		1-7 yr	7-14		0.8-1.5	
		7-15 yr	5-8		0.6-0.9	
D-lactate	P(H)					j (Rosenthal and Pesce, 1985)
		6 mo-3 yr	0.0-0.3	×1	0.0-0.3	
Lactate dehydrogenase	S		U/L		U/L	
		<1 yr	170-580	×1	170-580	37°C, a (Meites, 1989)
		1-9 yr	150-500		150-500	
		10-19 yr	120-330		120-330	
Isoenzymes	S		% of total activity			
			1-6 yr 7-19 yr			
		LD1	20-38 20-35			
		LD2	27-38 31-38			
		LD3	16-26 19-28			
		LD4	5-16 7-13			
		LD5	3-13 5-12			
Lead	W(H)		µg/dL		mmol/L	
		Child	<5	×0.0483	<0.0024	
		Toxic	≥70		≥3.38	
Lipase	P,S	1-18 yr	145-216 U/L	×1	145-216 U/L	(Ghoshal and Soldin, 2003)
Magnesium	P(H)		mg/dL		mmol/L	
		0-6 days	1.2-2.6	×0.411	0.48-1.05	w (Meites, 1989)
		7 days-2 yr	1.6-2.6		0.65-1.05	
		2-14 yr	1.5-2.3		0.60-0.95	
		0.78 ± 0.37% of total Hb		×0.01	0.0078 ± 0.0037 (mass fraction)	
Osmolality	S	Child, adult				
		275-295 mOsm/kg H_2O				
Phosphatase, alkaline	S		U/L		U/L	
		1-9 yr	145-420	×1	145-420	37°C, aw
		10-11 yr	140-560		140-560	
			M F		M F	
		12-13 yr	200-495 105-420		200-495 105-420	
		14-15 yr	130-525 70-230		130-525 70-230	
		16-19 yr	65-260 50-130		65-260 50-130	

Table 727-5 Reference Intervals—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (US)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Phosphorus, inorganic	S,P(H)		mg/dL		mmol/L	
		0-5 days	4.8-8.2	×0.3229	1.55-2.65	w (Meites, 1989)
		1-3 yr	3.8-6.5		1.25-2.10	
		4-11 yr	3.7-5.6		1.20-1.80	
		12-15 yr	2.9-5.4		0.95-1.75	
		16-19 yr	2.7-4.7		0.90-1.50	
Potassium	S		mmol/L		mmol/L	
		0-1 wk	3.2-5.5	×1	3.3-5.5	(Greeley, et al, 1993)
		1 wk-1 mo	3.4-6.0		3.4-6.0	Increased by hemolysis; serum values systematically higher than plasma values
		1-6 mo	3.5-5.6		3.5-5.6	
		6 mo-1 yr	3.5-6.1		3.5-6.1	
		>1 yr	3.3-4.6		3.3-4.6	
	P(H)	3.5-4.5 mmol/L			3.5-4.5 mmol/L	
Prealbumin (transthyretin)	S		mg/dL		mg/L	
		0-5 days	6.0-21.0	×10	60-210	s (Lockitch, Halstead, Quigley, et al, 1988)
		1-5 yr	14.0-30.0		140-300	
		6-9 yr	15.0-30.0		150-300	
		10-13 yr	20.0-36.0		200-360	
		14-19	22.0-45.0		220-450	
Protein, total	S		g/dL		g/L	
		Premature	4.3-7.6	×10	43-76	(Meites, 1989)
		Newborn	4.6-7.4		46-74	
		1-7 yr	6.1-7.9		61-79	
		8-12 yr	6.4-8.1		64-81	
		13-19 yr	6.6-8.2		66-82	
Pyruvate (perchloric acid)	W	7-17 yr	0.076 ± 0.026 mmol/L	×1	0.076 ± 0.026 mmol/L	(Pianosi, Seargeant, Haworth, 1995)
Sodium	S,P (LiH, NH_4H)		mmol/L		mmol/L	
		Newborn	133-146	×1	133-146	g (Greely, Snell, Colaco, 1993)
		Infant	134-144		134-144	
		Child	134-143		134-143	
		Thereafter	135-145		135-145	
Thyroid-stimulating hormone	S		µIU/L		µIU/L	
		0-3 days	1.00-20.00	×1	1.0-20.00	g (Dugaw, Jack, Rutledge, 2001)
		3-30 days	0.5-6.5		0.50-6.50	
		1-5 mo	0.5-6.0		0.5-6.0	
		6 mo-18 yr	0.5-4.5		0.5-4.5	
Thyroid uptake of radioactive iodine	Activity over thyroid gland	2 hr	<6%	×0.01	2 hr <0.06	
		6 hr	3-20%		6 hr 0.03-0.20	
		24 hr	8-30%		24 hr 0.08-0.30	
Thyroid uptake of technetium-99m	Activity over thyroid gland	After 24 hr	0.4-3.0%	×0.01	Fractional uptake 0.004-0.030	
Thyrotropin-releasing hormone (TRH)	P	5-60 pg/mL		×2.759	14-165 pmol/L	
Thyroxine-binding globulin (TBG)	S		mg/dL		mg/L	
		Cord blood	1.4-9.4	×10	14-94	
		1-4 wk	1.0-9.0		10-90	
		1-12 mo	2.0-7.6		20-76	
		1-5 yr	2.9-5.4		29-54	
		5-10 yr	2.5-5.0		25-50	
		10-15 yr	2.1-4.6		21-46	
		Adult	1.5-3.4		15-34	

Continued

Table 727-5 Reference Intervals—cont'd

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (US)†		CONVERSION FACTOR	REFERENCE VALUES (SI)†	COMMENTS
Thyroxine, total	S		μg/dL		nmol/L	
		0-3 days	8.0-20.0	×12.9	103-258	g (Dugaw, Jack, Rutledge, 2001)
		3-30 days	5.0-15.0		64-193	
		31-365 days	6.0-14.0		77-180	
		1-5 yr	4.5-11.0		58-142	
		6-18 yr	4.5-10.0		58-129	
Thyroxine, free	S		ng/dL		pmol/L	
		0-3 days	2.00-5.00	×12.9	25.7-64.3	g (Dugaw, Jack, Rutledge, 2001)
		3-30 days	0.90-2.20		11.6-28.3	
		31 days-18 yr	0.7-2.00		9.0-25.7	
Thyroxine, total	W	Newborn screen (filter paper) 6.2-22.0 μg/dL		×12.9	80-283 nmol/L	
Triiodothyronine, free	S		pg/dL		pmol/L	
		Cord blood	20-240	×0.01536	0.3-3.7	
		1-3 days	200-610		3.1-9.4	
		6 wk	240-560		3.7-8.6	
		Adult (20-50 yr)	230-660		3.5-10.0	
Triiodothyronine resin uptake test (T3RU)	S				Fractional uptake	
		Newborn 26-36%		×0.01	0.26-0.36	
		Thereafter 26-35%			0.26-0.35	
Triiodothyronine, total	S		ng/dL		nmol/L	
		0-3 days	60-300	×0.0154	0.9-4.7	g (Dugaw, Jack, Rutledge, 2001)
		4-365 days	90-260		1.4-4.0	
		1-6 yr	90-240		1.4-3.7	
		7-11 yr	90-230		1.4-3.6	
		12-18 yr	100-210		1.5-3.3	
Urea nitrogen	S,P		mg/dL		mmol/L	
		Cord blood	21-40	×0.357	7.5-14.3	
		Premature (1 wk)	3-25		1.1-9.0	
		Newborn	3-12		1.1-4.3	
		infant or child	5-18		1.8-6.4	
		Thereafter	7-18		2.5-6.4	
Uric acid	S		mg/dL		μmol/L	
		1-3 yr	1.8-5.0	×59.48	100-300	(Lockitch, Halstead, Albersheim, et al, 1988)
		4-6 yr	2.2-4.7		130-280	
		7-9 yr	2.0-5.0		120-295	
		10-11 yr M	2.3-5.4		135-320	
		10-11 yr F	3.0-4.7		180-280	
		12-13 yr M	2.7-6.7		160-400	
		14-15 yr M	2.4-7.8		140-465	
		12-15 yr F	3.0-5.8		180-345	
		16-19 yr M	4.0-8.6		235-510	
		16-19 yr F	3.0-5.9		180-350	

*In preparing the reference range listings, a number of abbreviations, symbols, and codes were used (see Table 727-2).
†Reference values are shown in SI units (International System of Units) and US units (Traditional Units).]

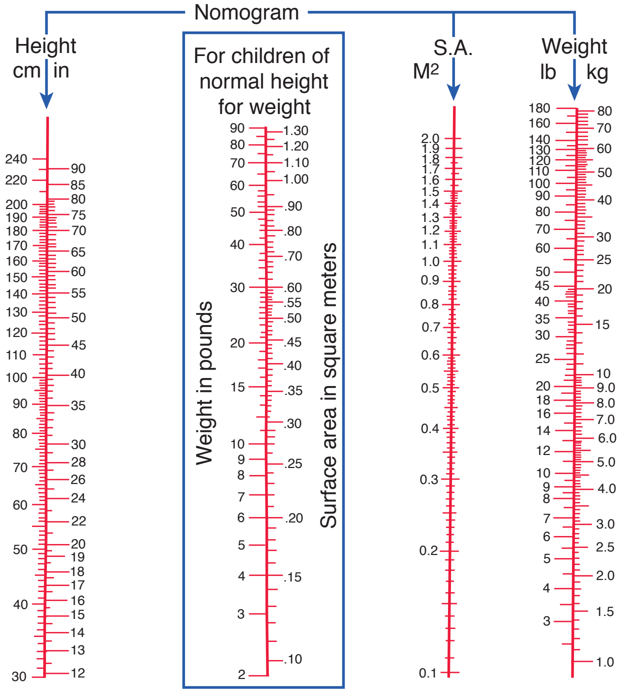

Alternative (Mosteller's formula):

$$\text{Surface area (m}^2\text{)} = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$$

Figure 727-1 **Nomogram for the estimation of surface area.** The surface area is indicated where a straight line that connects the height and weight levels intersects the surface area column, or if the patient is roughly of average size, from the weight alone *(enclosed area). (Nomogram modified from the data of E. Boyd by C.D. West. See also Briars GL, Bailey BJ: Surface area estimation: pocket calculator v nomogram,* Arch Dis Child *70:246–247, 1994.)*

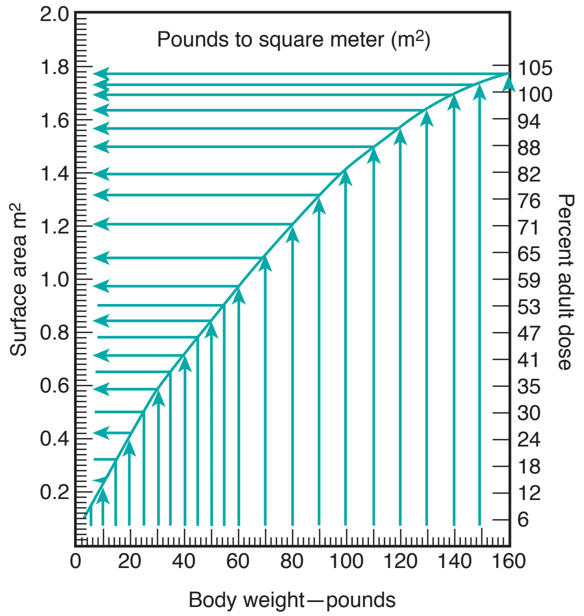

Figure 727-2 **Relationships among body weight (lb), body surface area, and adult dosage.** The surface area values correspond with those set forth by Crawford JD, Terry ME, Rourke GM: Simplification of drug dosage calculation by application of the surface area principle, *Pediatrics* 5:783–790, 1950. Note that the 100% adult dose is for a patient weighing approximately 140 lb and having a surface area of approximately 1.7 m^2. *(From Talbot NB, Richie RH, Crawford JH:* Metabolic homeostasis: a syllabus for those concerned with the care of patients, *Cambridge, MA, 1959, Harvard University Press.)*

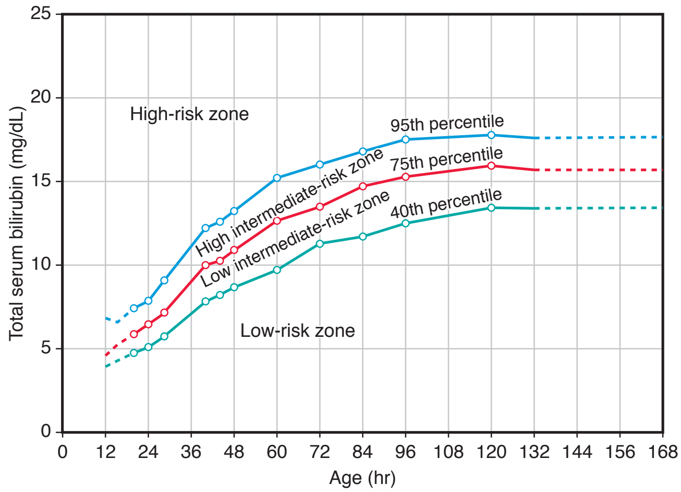

Figure 727-3 Nomogram for risk assessment of hyperbilirubinemia. *(From Bhutani VK, Johnson L, Sivieri EM: Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns,* Pediatrics *103:6–14, 1999, Fig. 2, p. 9.)*